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Asymmetric Borane Reduction of Achiral Ketones Mediated by A Chiral Oxazaborolidine Derived from (-)-Ephedrine

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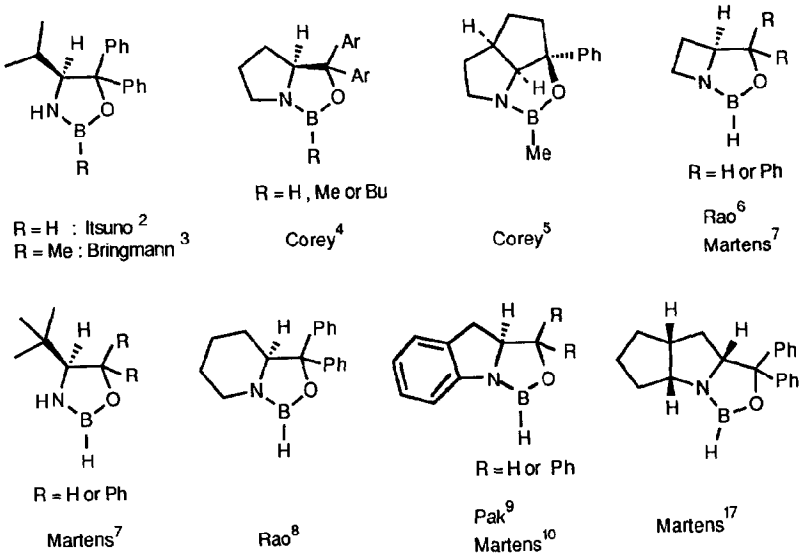
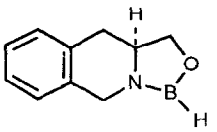
Abstract: Asymmetric borane reduction of achiral ketones in the presence of a chiral oxazaborolidine derived from (-)-ephedrine yielded the corresponding alcohols in optical yields of 41 - 83 % ee.

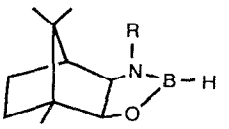
Asymmetric reduction of achiral ketones by chiral reducing agents has been extensively investigated.[1] Recently much attention has been focused on the asymmetric borane reduction of ketones catalyzed by a variety of chiral oxazaborolidines (scheme 1). However, these methods have been mainly applied to the

Scheme 1

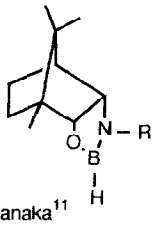




Martens[18]



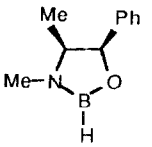
Tanaka[11]



Tanaka[11]

asymmetric reduction of aromatic ketones , whereas the applications for aliphatic ketones have been relatively neglected.

In continuation of our interest in the asymmetric reduction of achiral ketones with chiral hydride reagents,[12] we now wish to report that (4S,5R)-3,4-dimethyl-5-phenyl-1,3,2-oxazaborolidine (**1**) is useful for asymmetric reduction of ketones to the corresponding alcohols. The chiral oxazaborolidine was prepared



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from commercially available borane methyl sulfide (BMS) and (1R, 2S)-(-)-ephedrine by the literature procedures.[13] First, we examined the catalytic effect of **1** on the asymmetric borane reduction of representative achiral ketones, such as acetophenone (**2a**) and 3,3-dimetyl-2-butanone (**2i**). The optical purities were determined by capillary Gc analyses of MTPA esters of products alcohols (**3**).[14] Thus, the ketones were treated with 0.6 equiv of borane-THF in the presence of 0.1 equiv of **1** in THF at 0 °C. The reductions were complete within 10 min to give the corresponding alcohols in 96 - 100 % yields. As shown in Table 1, **1** showed a strong catalytic effect by influencing the chirality of the products alcohols, such as 70 % ee for **2a** and 59 % ee for **2i**. On the other hand, the reductions were also carried out with 1 equiv of a 1:1 mixture of **1** and borane-THF under the same reaction condition The noncatalyzed reduction afforded the corresponding alcohols with much improvement in optical inductions as compared to those obtained by the catalyzed reduction, such as 83 % ee for **2a** and 75 % ee for **2i**. The results led us to investigate the asymmetric reduction of the other achiral aromatic and aliphatic ketones by using the noncatalytic procedure. Thus, the reductions of aromatic ketones, such as propiophenone and butyrophenone provided similar optical inductions to that for **2a**, giving the corresponding alcohols in 79 % ee and 81 % ee, respectively. All of the products alcohols (**3a**-**3c**) obtained are enriched with the R enantiomers. In contrast, the reductions of isobutyrophenone and pivalophenone interestingly afforded the alcohols (**3d** and **3f**)

Table 1. Asymmetric borane reduction of achiral ketones mediated by chiral oxazaborolidine (**1**) in THF at 0 °C.[a]

		alcohols (**3**)	
	compounds (**2**)	% ee[b]	abs. config.[c]
a	acetophenone	83 (70)[d]	R
b	propiophenone	79	R
c	butyrophenone	81	R
d	isobutyrophenone	56	S
e	pivalophenone	74	S
f	2-heptanone	42	R
g	3-methyl-2-pentanone	41	R
h	3-methyl-2-butanone	63	R
i	3,3-dimethyl-2-butanone	75 (59)	R
j	2,2-dimethylcyclopentanone	76[e]	R

[a] The reductions were complete within 10 min to give the corresponding alcohols (**3**) in very high yields (96-100 %). Unless otherwise indicated, the concentration of compounds was 0.4 M and the mole ratio of compounds to borane-THF to **1** was 1 : 1 : 1. [b] Determined by capillary Gc analyses of MTPA esters. [c] The figures in parentheses indicated % ee obtained from an equimolar borane reduction in the presence of 0.1 equiv of **1**. [d] Determined by the elution orders of MTPA esters in Gc analyses and the sign of optical rotation of **3**. [e] Determined by Gc analysis of *l*-(-)-menthyl carbonate.[15]

with the opposite absolute configuration (S isomers), although somewhat low optical yields (56 % ee and 74 %ee, respectively) were obtained. The reason was not fully understood, but it seems to be attributed to the steric effects of isopropyl group and *tert*-butyl group of the ketones (**2d** and **2e**) in the transition state of the reduction. On the other hand, the reduction of unhindered aliphatic ketones, such as 2-heptanone and 3-methyl-2-pentanone yielded the corresponding alcohols (**3f** and **3g**) in 42 % ee and 41 % ee, respectively. For the relative hindered ketones, higher optical yields were obtained, such as 63 % ee for 3-methyl-2-butanone, 75 % ee for 3,3-dimethyl-2-butanone and 76 % ee for 2,2-dimethylcyclopentanone. All of the product aliphatic alcohols (**3f-3j**) obtained are consistently enriched with the R enantiomers. The results are summarized in Table 1. The following procedure is representative. To a solution of **1** (5 mmol; 1 M; 5 ml) in THF was added BH_3-THF (5 mmol; 1 M; 5 ml) in THF at 0 °C. After the reaction mixture was maintained for 0.5 h, acetophenone (**2a**; 5 mmol) in THF (2 ml) was added. The reaction mixture was stirred at 0 °C for 10 min and then excess hydride was decomposed by the addition of 1 M HCl solution. THF was removed in vacuo and the residue was extracted with ether. The extract was washed with brine and dried over anhydrous $MgSO_4$. Gc analysis showed the formation of 1-phenylethanol (**3a**) in 98 % yield. After **3a** was isolated by bulb-to-bulb distillation (94-100 °C / 18 mm Hg), the optical purity of **3a** (83 % ee, R) was determined by capillary Gc analysis of MTPA ester prepared by the reaction of **3a** and

(R)-(-)-MTPA acid chloride.[16]

In summary, asymmetric borane reductions mediated by the chiral oxazaborolidine (**1**) prepared from commercially available borane methyl sulfide and (-)-ephedrine provided good enantioselectivities for aromatic ketones with one exception (**2d**) and the relatively hindered aliphatic ketones.

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