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Asymmetric reduction of prochiral ketones using in situ generated oxazaborolidines derived from amino alcohols of (1*R*)-camphor as catalysts

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Abstract

Chiral oxazaborolidines generated in situ from 1,2-amino alcohols and amino alcohol derivatives derived from (1*R*)-(+)-camphor and borane or trimethyl borate were used as catalysts for the enantioselective reduction of prochiral ketones. © 2000 Published by Elsevier Science Ltd.

1. Introduction

Enantioselective reduction of prochiral ketones to enantiomerically pure secondary alcohols is an important reaction in asymmetric synthesis. Many methods are available in the literature for the enantioselective reduction of ketones.[1,2] Although the catalytic asymmetric reduction using 1,3,2-oxazaborolidines as catalyst and borane as the reducing agent has received much attention[3] since the initial reports by Itsuno et al.,[4] there are only a few isolated reports on the use of borane complexes of 1,2-amino alcohols derived from (1*R*)-(+)-camphor in the asymmetric reduction of prochiral ketones.[5–8]

Herein we report the results obtained by an indepth study of the enantioselective reduction of prochiral ketones catalyzed by in situ generated oxazaborolidines. Oxazaborolidines were generated from the reaction of 1,2-amino alcohols synthesized from (1*R*)-(+)-camphor with borane or trimethyl borate.

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2. Results and discussion

2.1. Enantioselectivity

1,2-Amino alcohols derived from (1*R*)-(+)-camphor with different orientations of the –OH and $-NH_2$ groups provide opportunities to study the effect of the structure of the catalyst precursor on the enantioselectivity of the reduction. There are eight possible isomers that can be prepared from camphor. Pavia et al.[9] and Chittenden et al.[10] synthesized seven of these isomers. We prepared three isomers, *cis-endo-endo* and *cis-exo-exo* amino alcohols (**1**, **2** and **3**) using modified reported procedures (Fig. 1).

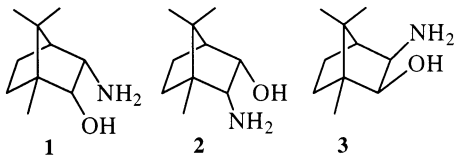
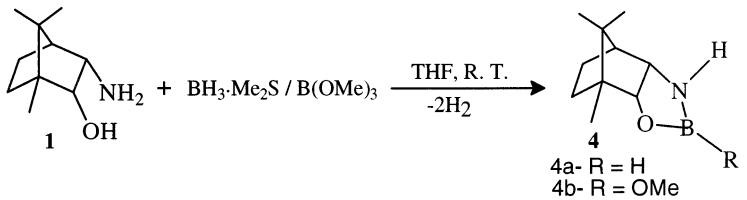


Figure 1.

These were treated with borane or trimethyl borate to generate the catalysts. The borane reductions were performed as described in Section 4 (Scheme 1).



Scheme 1.

Similarly, catalysts from other isomers were also prepared (Fig. 2).

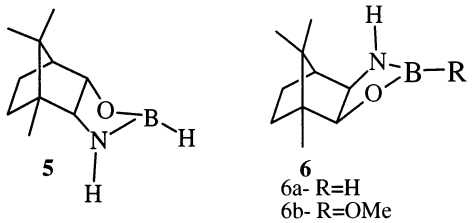
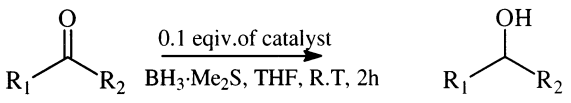


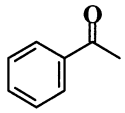
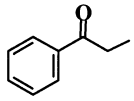
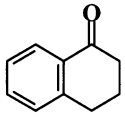
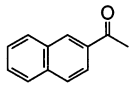
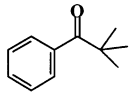
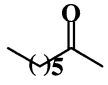
Figure 2.

The results obtained for the asymmetric reduction of prochiral ketones (Scheme 2) are summarized in Tables 1 and 2.



Scheme 2.

Table 1
Results of enantioselective reduction of prochiral ketones using *cis-endo-endo* amino alcohol derived oxazaborolidines as catalysts

Entry	Ketone	Catalyst	ee (%)[a]	Configuration	Yield (%)[b]
1		4(a)	93	R	84
2		4(b)	78	R	86
3		5	2	S	71
4		4a	86	R	93
5		4b	43	R	90
6		5	0.7	R	88
7		4a	74	R	95
8		4b	71	R	97
9		5	8	S	81
10		4a	90	R	78
11		4b	68	R	74
12		5	0.9	S	81
13		4a	59	R	84
14		4b	49	R	80
15		4a	85	R	73
16		4b	58	R	70
17		5	9	S	69

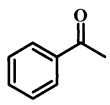
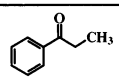
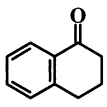
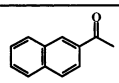
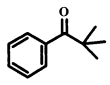
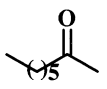
[a] determined by comparison with standard specific rotation values.
[b] isolated yield.

It is evident from the above results that the *cis*-3-*endo*-amino-2-*endo*-hydroxybornane and borane derived oxazaborolidine is an efficient catalyst for the asymmetric reduction of ketones. The very low value of enantioselectivity observed for *cis*-2-*endo*-amino-3-*endo*-hydroxybornane can be explained on the basis of steric factors. The free borane cannot coordinate with the nitrogen atom of the oxazaborolidine moiety because of the steric repulsion of the methyl group on the camphor skeleton thus facilitating free borane reduction.

The configuration of the products was found to be *S* when *cis-exo-exo* amino alcohol derived oxazaborolidines were used as catalysts.

As expected, with the substituted amino alcohols low *ee*'s were obtained for the products.[11]

Table 2
Results of enantioselective reduction of prochiral ketones using *cis-exo-exo* amino alcohol derived oxazaborolidines as catalysts

Entry	Ketone	Catalyst	ee (%)[a]	Yield (%)[b]
1		6a	79	94
2		6b	56	70
3		6a	68	70
4		6b	41	83
5		6a	63	98
6		6b	47	91
7		6a	78	85
8		6b	50	63
9		6a	74	79
10		6b	59	70
11		6a	69	88
12		6b	62	79

[a] determined by comparison with standard specific rotation values.
[b] isolated yield.

2.2. Effect of other factors on the enantioselectivity of asymmetric reduction

After carrying out these reductions, we were interested in studying the effect of various parameters on the enantioselectivity of asymmetric ketone reduction. The catalyst **4a** was taken as the standard and acetophenone was taken as the model substrate for these studies.

2.2.1. Temperature

Early reports on the effect of temperature on oxazaborolidine catalyzed reductions show a decrease in the enantioselectivity of the product with a decrease of temperature.[12] We carried out the oxazaborolidine reduction of acetophenone at various temperature and the results are summarized in Table 3.

It is evident from the study that good enantioselectivity is obtained only at room temperature. At −78 and 65°C reaction leads to low *ee* of the product. The catalyst may not be stable at 65°C and at −78°C the catalyst formation may be slow. In both cases free borane reduction may occur at a faster rate leading to low enantioselectivity of the product.

Table 3
Effect of temperature on enantioselectivity of reduction

Entry	Temperature (°C)	*ee* (%)[a]	Yield (%)[b]
1	−78	50	45
2	0 to −10	65	76
3	rt (25)	93	84
4	45	25	80
5	65	6	80

[a] Determined by comparison with standard specific rotation values.
[b] Isolated yield.

2.2.2. Catalyst–substrate ratio

Increase in concentration of the catalyst to substrate is known to increase the asymmetric induction in some cases. The effect of catalyst concentration on the enantioselectivity of the acetophenone reduction was studied by using 1, 5, 10 and 20 mol% of the catalyst. The results are tabulated in Table 4.

Table 4
Effect of catalyst concentration on the enantioselectivity of reduction

Entry	Catalyst mol (%)	*ee* (%)[a]	Yield (%)[b]
1	0	0	99
2	1	79	78
3	5	80	69
4	10	90	87
5	20	76	86

[a] Determined by comparison with standard specific rotation values.
[b] Isolated yield.

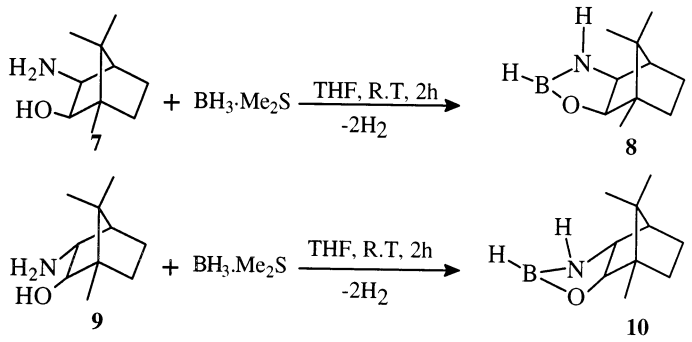
It can be concluded from the study that good *ee* is obtained using 10 mol% of the catalyst. When we carried out the reaction, adding the ketone to the catalyst borane complex,[13] we obtained a racemic secondary alcohol.

2.2.3. Chirality of the catalyst precursor

To study the effect of chirality of the catalyst precursor on the asymmetric reduction of acetophenone, the amino alcohols were prepared from (1*S*)-(−)-camphor according to a reported procedure.[5] Oxazaborolidines were generated from these amino alcohols by treatment with borane and the reduction of acetophenone was carried out in situ (Scheme 3).

The results are summarized in Table 5.

From Table 5 it is clear that chirality of the starting material also plays an important role in the enantioselectivity of the reduction product.



Scheme 3.

Table 5
Effect of chirality of starting material on enantioselectivity

Entry	Catalyst	*ee* (%)[a]	Configuration	Yield (%)[b]
1	8	42	*R*	78
2	10	46	*S*	76

[a] Determined by comparison with standard specific rotation values.
[b] Isolated yield.

3. Conclusion

This paper gives the results of our investigation into the catalytic enantioselective reduction of prochiral ketones catalyzed by the in situ generated oxazaborolidines generated from 1,2-amino alcohols and substituted amino alcohols derived from (1*R*)-(+)-camphor. The effect of various parameters such as temperature, catalyst–substrate ratio and chirality of the catalyst precursor on the enantioselectivity of the reduction were also studied.

4. Experimental

4.1. General experimental details

(1*R*)-(+)-Camphor was purchased from M/S Fluka. 1,2-Amino alcohols of (1*R*)-(+)-camphor were prepared according to the reported procedure.[5,9,10] $BH_3{\cdot}Me_2S$ was purchased from Aldrich Chemical Company, and made up to 2 M in dry THF and used for the reactions. All reactions were carried out under anhydrous conditions. Optical rotations were recorded on a Jasco DIP 370 digital polarimeter at ambient temperature (24–27°C). ^{1}H NMR spectra were recorded on a Bruker 300 MHz instrument using $CDCl_3$ as the solvent and TMS as the internal standard. All secondary alcohols were identified by spectral analysis. Enantiomeric excesses and configurations of secondary alcohols were determined by optical rotation measurements. The *ee* values obtained were further confirmed by studying the NMR spectra of (*R*)-MTPA esters of the secondary alcohols.[14]

A typical procedure for the asymmetric reduction using oxazaborolidines is described with *cis* 3-*endo*-amino-2-*endo*-hydroxybornane **1** as the starting material.

The amino alcohol (0.034 g, 0.2 mmol) was dissolved in 3 mL of dry THF in a three necked RB flask fitted with a septum, an argon source and a pressure equalizing funnel. To this 0.3 mmol of 2 M $BH_3 \cdot Me_2S$ in THF was added and the mixture stirred for one hour at room temperature. After the amino alcohol was fully consumed (monitored by TLC) another 1.4 mmol of 2 M $BH_3 \cdot Me_2S$ was added and the reaction mixture was stirred for a further 10 minutes. To this acetophenone (0.240 g, 2 mmol) in 4 mL THF was added dropwise. On completion of the reaction (2 h) the excess borane was destroyed by dropwise addition of cold water (2 mL). The reaction mixture was extracted with ether (4×5 mL). The organic layers were pooled together, washed with distilled water, brine, dried over anhydrous Na_2SO_4 and concentrated. The crude product was purified by column chromatography with silica gel (100–200 mesh) using a hexane–EtOAc mixture as the eluent to afford the alcohol in 85% yield $[\alpha]_D^{25} = +39.9$ (literature value +42.9). This was again confirmed by the NMR spectra of the MTPA ester of the alcohol.[14]

4.2. Reaction with trimethyl borate

The amino alcohol (0.034 g, 0.2 mmol) was dissolved in 3 mL of dry THF in a three necked RB flask fitted with a septum, an argon source and a pressure equalizing funnel. To this 0.26 mmol of trimethyl borate was added and the mixture stirred for one hour at room temperature. After the amino alcohol was fully consumed (monitored by TLC), the excess trimethyl borate was evaporated off, 1.4 mmol of 2 M $BH_3 \cdot Me_2S$ was added and the reaction mixture was stirred for a further 10 minutes. To this acetophenone (0.240 g, 2 mmol) in 4 mL THF was added dropwise. On completion of the reaction (2 h) the reaction mixture was worked up as described in the above experiment.

Acknowledgements

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