Asymmetric Borane Reduction of Prochiral Ketones Using Aluminum Triethoxide and Chiral Amino Alcohols

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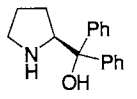
The asymmetric borane reduction of prochiral ketones with catalysts prepared *in situ* from aluminum triethoxide and chiral amino alcohols was examined, and the corresponding chiral alcohols were obtained in high optical purity.

Several asymmetric borane reductions of prochiral ketones using a chiral oxazaborolidine catalyst have been reported[1] after the original studies of Itsuno[2] and Corey.[3,4] Oxazaborolidine **2a** prepared from trimethyl boroxine or methylboronic acid and the chiral amino alcohol **1** is a very useful catalyst for the asymmetric reduction of prochiral ketones.[4,5] However, this method has not been satisfactory due to the necessity of using expensive boroxine or boronic acid and the preparation process of the catalyst. Recently, Masui and Shioiri reported an asymmetric borane reduction using an *in situ* generated catalyst from trimethyl borate and chiral amino alcohol **1**.[6] They proposed the formation of oxazaborolidine **2b**.



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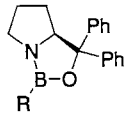
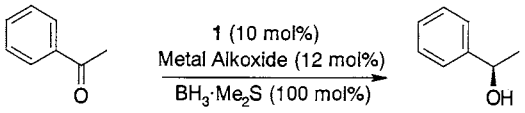


2a R=Me
2b R=OMe

On the other hand, so far as we know, there are no reports using metals except for boron in the asymmetric borane reduction. We were very interested in using other metals, because certain metal alkoxides (especially aluminum alkoxides) are easily obtainable and inexpensive. Furthermore, the coordination rate of the oxygen of the prochiral ketone to the metal of the catalyst may differ and influence the reaction rate and the enantioselectivity. During the course of our study to synthesize optically active pharmaceutical substances, we tried the asymmetric borane reductions of acetophenone using the catalysts generated *in situ* from several metal alkoxides and the amino alcohol **1**.[7] These results are shown in Table 1.

Trimethyl borate gave a good enantioselectivity within a short reaction time as already reported (entry 2).[6] Without the addition of a metal alkoxide (entry 1), the enantioselectivity was good (94.7% ee) but the reaction time became longer (1.5 h). The addition of tetraethyl orthosilicate gave a similar result (entry 5). We thought that tetraethyl orthosilicate could not generate the catalyst with the amino alcohol **1** and, as a result, a long reaction time was necessary. However, the addition of other metal alkoxides showed enantioselectivities in short reaction times (10 min). Especially, the addition of aluminum triethoxide produced an excellent enantioselectivity (97.5% ee) in a short reaction time (entry 4).

Table 1. Asymmetric reduction of acetophenone with metal alkoxide and **1**[a]

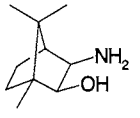


Entry	Metal Alkoxide	Time	ee/%[b]	Yield/%
1	none	1.5 h	94.7	98
2	$B(OMe)_3$[c]	10 min	98	>90
3	$Mg(OEt)_2$	10 min	75.8	80
4	$Al(OEt)_3$	10 min	97.5	100
5	$Si(OEt)_4$	1 h	92.0	99
6	$Sc(OPr^i)_3$	10 min	63.4	99
7	$Ti(OEt)_4$	10 min	37.0	95
8	$Ta(OMe)_5$	10 min	81.8	91

[a]The absolute configuration of the products was assigned by comparison of the retention time on an HPLC chiral column with the commercially available compound. [b]Determined by HPLC analysis using a chiral column (Chiralcel OJ). [c]Ref. 6.

The addition of these metal alkoxides influenced the enantioselectivities and the reaction times in the asymmetric borane reduction. Especially, the reaction using aluminum triethoxide and the amino alcohol **1** showed equally good enantioselectivity in a short reaction time for the reaction using oxazaborolidines. Furthermore, aluminum and boron are elements in Group 13 of the periodic table. Therefore, we supposed that during the reaction using aluminum triethoxide and the chiral amino alcohol **1**, the catalyst similar to oxazaborolidine **2b** was generated *in situ*.

We then tried the asymmetric reductions of several prochiral ketones using this catalyst, and these results are shown in Table 2. Phenacyl chloride and 1-tetralone gave the corresponding chiral alcohols in excellent optical purities of 98.9% ee and 98.6% ee, respectively. Propiophenone produced 1-phenyl-1-propanol in the good optical purity of 91.5% ee. During the reduction of the dialkyl ketones, 2-pentanone produced 2-pentanol in the moderate optical purity of 68.7% ee, though the highly hindered 3,3-dimethyl-2-butanone was reduced to 3,3-dimethyl-2-butanol in the high optical purity of 97.2% ee. These results indicate that the combination of aluminum triethoxide and the amino alcohol **1** is a potentially good catalyst for the asymmetric borane reduction of prochiral ketones.



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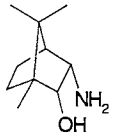

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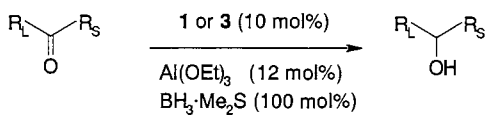
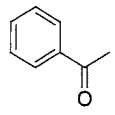
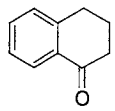
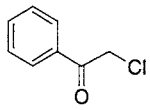
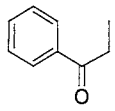
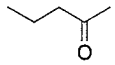
Table 2. Asymmetric reduction of prochiral ketones with aluminum triethoxide and amino alcohol **1** or **3**



Ketone	Amino Alcohol	Absolute Configuration[a]	ee/%[b]	Yield/%[d]
	**1**	*R*	97.5	100
	3	*S*	92.3	95
	**1**	*R*	98.6	93
	3	*S*	90.9	92
	**1**	*S*	98.9	98
	**1**	*R*	91.5	87
	**1**	*R*	68.7[c]	70
	**1**	*R*	97.2[c]	69

[a]The absolute configuration of the products was assigned by comparison of the sign of the specific rotation with the literature value or the retention time on an HPLC chiral column with the commercially available compound. [b]Determined by HPLC analysis using a chiral column (Chiralcel OJ). [c]Analytical samples were converted to 3,5-dinitrobenzoates. [d]Isolated yield by silica-gel column chromatography or distillation.

The asymmetric reduction using the catalysts prepared from aluminum alkoxide and some other chiral amino alcohols is also very interesting. Amino alcohols derived from camphor were reported as catalysts for the asymmetric borane reduction[8,9] and showed different enantioselectivities. Therefore, we tried the asymmetric borane reduction using aluminum triethoxide and the amino alcohol **3**.

(+)-Camphor was easily converted to the amino alcohol **3**, which included *ca.* 11% of the *endo* form **4**, and the intricate purification via the cyclic carbamate was reported.[11] We found that the crude amino alcohol (**3** + **4**) was readily purified by recrystallization of its methansulfonic acid salt.

The results of the asymmetric borane reduction of prochiral ketones using aluminum triethoxide and the amino alcohol **3** are shown in Table 2. Acetophenone and 1-tetralone gave chiral alcohols of the *S*-enantiomer type in good optical purities of 92.3% ee and 90.9% ee, respectively. These results show that the amino alcohol **3** had an enantioselectivity opposite to the amino alcohol **1**.

In summary, we report the asymmetric reduction of prochiral ketones using the catalysts prepared *in situ* from aluminum triethoxide and the amino alcohol **1** or **3**. These catalysts are easily prepared and show good enantioselectivity. We are now further examining the asymmetric borane reduction along these lines.

References and Notes

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7 Normal procedure for asymmetric reduction: Metal alkoxide (0.6 mmol) was added to a solution of a chiral amino alcohol (0.5 mmol) in 5 mL of dry THF, and the mixture was stirred at room temperature for 1 h under N_2. After a borane-dimethyl sulfide complex (5 mmol) was added, a solution of a ketone (5 mmol) in 10 mL of dry THF was added dropwise via a syringe pump over 1 h. The reaction mixture was stirred until the ketone disappeared on a TLC. The resulting mixture was quenched with 1M HCl or triethanolamine. The usual workup provided the chiral alcohol.
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