Catalytic Behavior of Optically Active Amino Alcohol-Borane Complex in the Enantioselective Reduction of Acetophenone Oxime *O*-Alkyl Ethers

Shinichi Itsuno,* Yoshiki Sakurai, Koichi Ito, Akira Hirao,† and Seiichi Nakahama†
School of Materials Science, Toyohashi University of Technology, Tempaku-cho, Toyohashi 440
†Department of Polymer Science, Tokyo Institute of Technology, Ohokayama, Meguro-ku, Tokyo 152
(Received July 7, 1986)

Synopsis. In the presence of the optically active amino alcohol-borane complex, an oxime ether was reduced with various hydride reducing agents to give a chiral primary amine of high optical purity. Catalytic use of the chiral complex was also investigated.

We have reported previously that a tetrahydrofuran (THF) solution of a chiral reducing agent prepared from an optically active amino alcohol and borane reduced ketones and ketone oxime *O*-alkyl ethers quantitatively with high enantioselectivity to give optically active secondary alcohols[1] and primary amines,[2] respectively. In most studies for asymmetric reduction, a stoichiometric amount of chiral metal hydrides has been required. For the practical purpose, catalytic use of the expensive chiral auxiliary has been intensely desired as well as high enantioselectivity of the reaction.[4] In this context, we studied the catalytic behaviour of the chiral amino alcohol-borane complex in the reduction of oxime ethers.

The optically active amino alcohol such as **1** reacted with an excess borane in THF to generate hydrogen. After evaporation of unreacted free borane and THF under reduced pressure at room temperature, chiral complex was obtained as a white powder. Although this chiral complex has a B–H bond which was easily detected by infra-red spectroscopy (2500 cm^{-1}) and hydrogen evolution by acid hydrolysis, a THF solution of this white powder could not reduce any oxime ether within one day at room temperature. However, interesingly, when THF–borane (1:1) was added to the mixture of a THF solution of the chiral complex and acetophenone *O*-methyl oxime, optically pure (*S*)-1-phenylethylamine was obtained quantitatively in 20 h at room temperature, after hydrolysis (Table 1, Run 1). In the presence of the above chiral complex prepared from **1** and borane, the oxime ether was reduced asymmetrically also with metal hydrides such as lithium alminum hydride ($LiAlH_4$) and aluminum hydride (AlH_3) in place of borane. The reduction with sodium borohydride did not proceed due to its low reactivity. Results are summarized in Table 1.

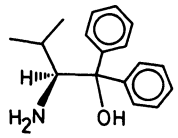
On the basis of these results, catalytic use of the chiral complex was investigated. For example, in the presence of 1 equiv of the chiral complex, 1 equiv of acetophenone *O*-benzyl oxime was reduced asymmetrically in a THF solution containing excess of free borane (4 equiv) to give (*S*)-1-phenylethylamine of 95% ee (see Experimental). Under the same conditions, 4 equiv of the oxime ether could also be reduced to give the chiral amine in 90% ee. These results show that the reduction is catalyzed by the chiral complex. The chiral complex would interact with the oxime ether to accelerate the borane reduction and induce asymmetry. Indeed, borane alone reduced the oxime ether slowly in THF at ambient temperatute. Even 10 equiv of the oxime ether was reduced quantitatively with 10 equiv of borane in the presence of only 1 equiv of the chiral complex to give the chiral amine (52%ee). This somewhat low enantioselectivity indicates that the reduction of the oxime ethers with free borane proceeded competitively when a small amount of the chiral complex was employed. To use the chiral complex more effectively, the following procedure was attempted. After asymmetric reduction of 5 mmol of acetophenone *O*-methyl oxime with borane in the presence of the chiral complex prepared from 5 mmol of the chiral amino alcohol, another 5 mmol of the oxime ether and borane was introduced again without work-up procedure. Overall, 10 mmol of the oxime ether may interact with the chiral complex successively. Isolated 9 mmol of the amine exhibited 85% of the optical purity. This result demonstrates that the chiral complex induces the asymmetric reduction also for the borane reduction of the second added substrate. The successive asymmetric reduction of the oxime ether was repeated five times. Total amount of the amine isolated was 43 mmol by use of only 5 mmol of the complex, optical purity of the amine being 67% ee. A gradual decrease of enantioselectivity would be caused by the accumulation of chiral amino borane after asymmetric reduction of the oxime ether.

Table 1. Enantioselective Reduction of Acetophenone *O*-Methyloxime in the Presence of Chiral Complex Prepared from **1** and Borane

Run	Reducing agent	I-Phenylethylamine			
		Yield/% (Isolated)	$[\alpha]_D^{22}$	%ee[a]	Config.[a]
1	BH_3	90	−40.3	100	S
2	$NaBH_4$	0	—	—	—
3	$LiAlH_4$	85	−30.6	76	S
4	AlH_3	79	−17.7	44	S

a) Values for maximum rotation and configuration taken from Ref. 7).

Although the exact structure of the chiral complex was not clear, this complex possessed interesting characteristics in the asymmetric reduction of oxime ethers; (1) The reduction with borane was accelerated by the presence of the complex. (2) The complex itself could not reduce oxime ether. (3) The high level of asymmetry was induced by the complex. (4) By the use of small amount of the complex, more than stoichiometric amount of the oxime ether was reduced asymmetrically. Consequently, we supposed tentatively that this chiral complex prepared from optcally active amino alcohol and borane may be a chiral catalyst, not a reagent, for asymmetric reduction of oxime ethers. The realization of higher efficiency of the chiral catalyst is now under investigation.



1

Experimental

All reactions were carried out under a nitrogen atmosphere. GLPC analyses were carried out on a Yanaco G180 gas chromatograph with a 3 m×3 mm column packed with PEG20 M on Diasolid L. Optical rotations were measured on a JASCO DIP-140 digital polarimeter using a 1 cm or 10 cm thermostated microcell. ^{1}H NMR spectra were taken in $CDCl_3$ (internal Me_4Si) on a JEOL JNM-PMX 60 or a JEOL JNM-GX 270 spectrometer. Melting points were determined on a Yanagimoto micromelting point apparatus.

Materials. Tetrahydrofuran (THF) was dried over sodium wire and distilled over $LiAlH_4$ and stored under nitrogen. AlH_3 was prepared by adding the theoretical quantity of 100% sulfuric acid to the standardized THF solution of $LiAlH_4$.[5] Borane was prepared by the reaction of $NaBH_4$ with diethyl ether–trifluoroborane (1:1) according to the procedure of Brown.[6] (*S*)-(−)-2-amino-3-methyl-1,1,-diphenyl-1-butanol (**1**) and acetophenone oxime *O*-alkyl ethers were prepared by previously described procedures.[2]

Enantioselective Reduction of Acetophenone *O*-Methyloxime with $LiAlH_4$ in the Presence of 1-Borane Complex. A solution of borane (20 mmol) in THF (10 ml) was added to a solution of **1** (10 mmol) at 0 °C during ca. 20 min. The resulting solution was stirred at 0 °C for 8 h. The excess of free borane and solvent were evaporated off in vac. at room temperature to give a white solid (the chiral complex). The chiral complex was dissolved in dry THF (20 ml) and acetophenone *O*-methyl oxime (10 mmol) in THF (5 ml) was then added dropwise at 0 °C. After addition was complete a THF solution of $LiAlH_4$ (10 mmol) was added at 0 °C. The reaction mixture was warmed to room temperature, stirred for 24 h, and then decomposed by the dropwise addition of Na_2SO_4 saturated water and 2M HCl(1 M=1 mol dm^{-3}). After hydrolysis, evaporation of THF deposited the **1**-HCl as a white solid, which was collected on a glass filter and washed with water. The aqueous acid extract was shaken with ether, cooled, made basic with aqueous ammonia, and extracted with ether. The ether layer was dried ($MgSO_4$) and evaporated to give a colorless oil which upon distillation (bulb-to-bulb) furnished 1-phenylethylamine: 85% yield. This was characterized by IR and ^{1}H NMR spectroscopy and shown to be homogeneous by GLPC analysis. The optical rotation was $[\alpha]_D^{22}$ −30.6° (neat)(lit,[7] $[\alpha]_D^{22}$ −40.3° (neat)). The optical yield, 76%, was calculated by the observed optical rotation and the kwown maximum rotation of 1-phenylethylamine.

Enantioselective Reduction of Acetophenone *O*-Benzyloxime with Borane in the Presence of 1-Borane Complex. A THF solution of the chiral complex was prepared from **1** (10 mmol) and borane (20 mmol) according to the above procedure. To the solution, a solution of acetophenone *O*-benzyl oxime (10 mmol) in THF (5 ml) was added and then borane (40 mmol) was added dropwise at 0 °C. The reaction mixture was warmed to room temperature and stirred for 24 h. After hydrolysis with 2M HCl, **1**-HCl was filtered off and benzyl alcohol was extracted. The aqueous layer was basified with aqueous ammonia and extracted with ether. The ether layer was dried ($MgSO_4$) and evaporated to give a colorless oil which upon distillation (bulb-to-bulb) furnished (*S*)-1-phenylethylamine: 80% yield, $[\alpha]_D^{22}$ −38.3°, 95% ee.

References

1) a) S. Itsuno, K. Ito, A. Hirao, and S. Nakahama, *J. Chem. Soc., Perkin Trans., 1*, **1984** 2887; b) S. Itsuno, K. Ito, A. Hirao, and S. Nakahama, *J. Org. Chem.* **49**, 555 (1984).

2) S. Itsuno, M. Nakano, K. Miyazaki, H. Masuda, K. Ito, A. Hirao, and S. Nakahama, *J. Chem. Soc., Perkin Trans., 1*, **1985**, 2039.

3) "Asymmetric Synthesis," ed by J. D. Morrison, Academic Press Inc., London (1983), Vol. 2.

4) a) "Asymmetric Synthesis," J. D. Morrison, Academic Press Inc., New York (1985), Vol. 5; b) I. Ojima, *Yuki Gosei Kagaku Kyokai Shi*, **44**, 499 (1986).

5) S. Krishnamurthy and H. C. Brown, *J. Org. Chem.* **45**, 849 (1980).

6) "Organic Syntheses via Boranes," ed by H. C. Brown Wiley, New York (1975).

7) W. Theilaker and H. G. Winkler, *Chem. Ber.* **87**, 691 (1954).