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Practical enantioselective reduction of ketones using oxazaborolidine catalyst generated in situ from chiral lactam alcohol and borane

Yasuhiro Kawanami,[a,*] Shinichi Murao,[b] Takahiko Ohga[a] and Nobuyo Kobayashi[a]

[a]*Department of Biochemistry and Food Science, Faculty of Agriculture, Kagawa University, Miki-cho, Kagawa 761-0795, Japan*
[b]*Department of Chemistry, Faculty of Education, Kagawa University, Takamatsu, Kagawa 760-8522, Japan*

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Abstract—Reduction intermediate prepared in situ from chiral lactam alcohol **3** and borane at room temperature was found to catalyze the borane reduction of various prochiral ketones with high enantioselectivity up to 98% ee.

1. Introduction

Since Itsuno et al.[1] and Corey et al.[2] reported oxazaborolidine-catalyzed asymmetric borane reduction of achiral ketones (CBS reduction), an enormous number of borane reduction using β-amino alcohol have been extensively investigated.[3] The most effective chiral amino alcohol was reported to be **1** derived from (*S*)-proline, providing the efficient method for the synthesis of optically active secondary alcohols with predictable absolute stereochemistry. However, the preparation of oxazaborolidine **2a** requires extended heating with excess BH_3 under increased pressure due to ring strain in the [3.3.0] ring system.[4] To overcome this disadvantage, the B–Me oxazaborolidine **2b** formed by reaction of **1** with methylboronic acid has been developed as an easily prepared and stable catalyst which mediates the borane reduction of ketones with excellent enantioselectivity.[5] Quallich et al.[4] described that the reaction of **1** with excess borane–methyl sulfide complex (BMS) generated the oxazaborolidine **2a** at room temperature for 10 h (Scheme 1). Shioiri et al.[6] also reported that trimethyl borate could improve the reactivity and enantioselectivity of BMS reduction using **1** via the B–OMe oxazaborolidine **2d** (Fig. 1).

As an alternative method, we suppose that chiral lactam alcohol **3**,[7] (*S*)-5-(diphenylhydroxymethyl) pyrrolidin-2-one, should be easily reduced with borane to the corresponding imine and would be further reduced by the neighboring alkoxyborane to generate the oxazaborolidine **2a** (Scheme 2). This is suggested by the fact that racemic **1** was synthesized from racemic **3** by reduction with borane in THF.[5] Therefore, we expected that the reduction intermediate generated in situ from **3** and borane would comparably catalyze borane reduction of prochiral ketones with high enantioselectivity. In this communication, we report a

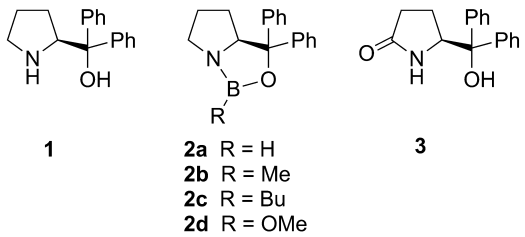
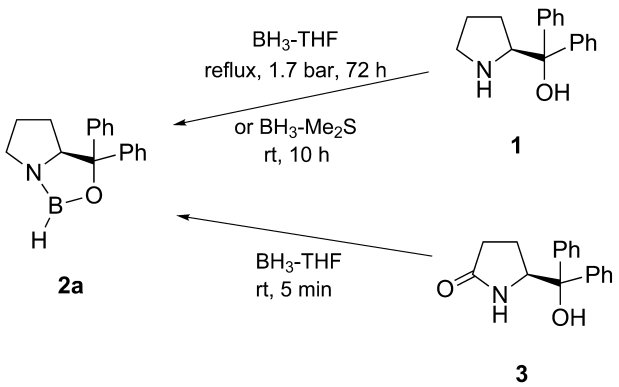


Figure 1.



Scheme 1. Preparation of oxazaborolidine.

Keywords: borane; reduction; asymmetric synthesis; enantioselective; lactam alcohol.
* Corresponding author. Tel.: +81-87-891-3088; fax: +81-87-891-3021; e-mail: kawanami@ag.kagawa-u.ac.jp

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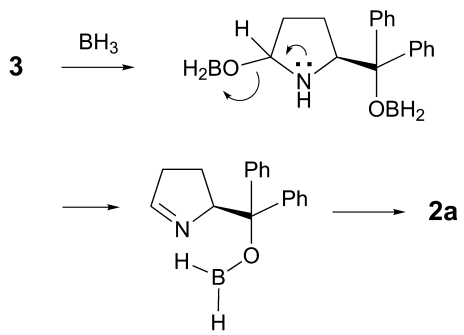


Scheme 2. A possible pathway to the oxazaborolidine **2a**.

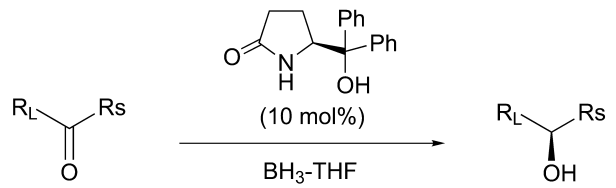
practical and excellent method for the enantioselective borane reduction of ketones using chiral lactam alcohol **3**.

2. Results and discussion

The lactam alcohol **3** was easily prepared by Grignard reaction (PhMgBr) of methyl (*S*)-pyroglutamate which was formed via esterification of inexpensive (*S*)-pyogultamic acid, as described previously.[7] The reduction of chiral lactam alcohol **3** (10 mol%) with 1 equiv. of BH_3–THF smoothly proceeded at room temperature within 5 min. The resulting oxazaborolidine catalyst was found to catalyze the borane reduction of a variety of ketones, providing chiral secondary alcohols in high enantiomeric excess (ee) and good yield. The results are summarized in Table 1 (Scheme 3).

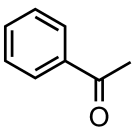
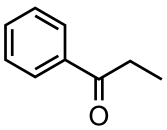
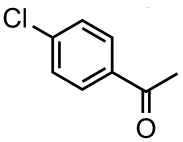
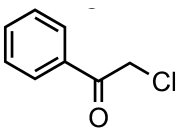
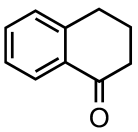
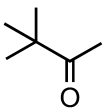
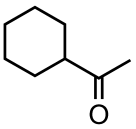
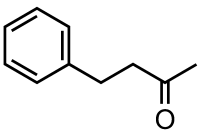
Reduction of aryl methyl, ethyl, and chloromethyl ketone with borane and 10 mol% of **3** proceeded with excellent enantioselectivity (91–98% ee, entries 1–4). Reduction of cyclic aryl ketone, α-tetralone afforded the corresponding (*R*)-alcohol with slightly lower enantioselectivity (85% ee, entry 5). Alkyl methyl ketones having a tertiary, secondary, and primary alkyl group were reduced with good to moderate ee (entries 6–8). Thus, the enantioselectivities of borane reduction using the lactam alcohol **3** were comparable to those reported in the literature for the isolated **2a** (entries 1, 2, 4–6). These results suggest that the lactam alcohol **3** was actually reduced by borane to generate the oxazaborolidine **2a** in situ at room temperature for a short time. Furthermore, 2-(diphenylhydroxymethyl)pyrrolidine **1** was recovered in good yield by neutralization and extraction from aqueous acidic solution after quenching. This result also supports the generation of oxazaborolidine **2a** as shown in Scheme 2, although the isolation of **2a** from the reaction mixture of **3** and borane and the NMR analysis have not been succeeded yet may be due to its instability.

To improve the enantioselectivity in reduction of aliphatic ketones with moderate enantioselectivities, we investigated the temperature effect on the enantioselectivity. The results are summarized in Table 2. When the reaction temperature was increased from −10 to 60°C, ee of the resulting alcohol produced from aliphatic ketones gradually increased up to 94% ee (entries 2–4), while that of aromatic ketone slightly decreased (entry 1). This is in agreement with the observations reported in the borane reduction catalyzed by B–Bu oxazaborolidine **2c**[8] (50°C), 1,3-amino alcohol derived from ketopinic acid[9] (50°C), and (*S*)-proline[10] (110°C).



Scheme 3.

Table 1. Asymmetric reduction of ketones using chiral lactam alcohol **3**

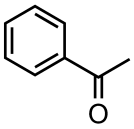
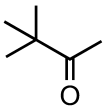
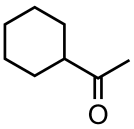
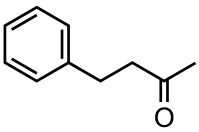
Entry	Ketone	Yield (%)	% ee[a]		Configuration[b]
1		97	97	(97)[c]	*R*
2		80	91	(90)[c]	*R*
3		96	97	–	*R*
4		82	98	(97)[c]	*S*
5		84	85	(89)[c]	*R*
6		86	89[d]	(92)[c]	*R*
7		87	81[d]	–	*R*
8		89	50	–	*R*

All reactions were carried out with 10 mol% of **3** at room temperature.
[a] Determined by HPLC analysis using chiralcel OD column.
[b] Determined by comparison of the sign of specific rotation with the literature value.
[c] Isolated oxazaborolidine catalyst **2a**.[2]
[d] Determined by HPLC analysis using chiralcel OD column after 4-nitrobenzoylation.

3. Conclusion

We have demonstrated that the chiral oxazaborolidine catalyst generated in situ from the lactam alcohol **3** and borane catalyzed the enantioselective reduction of ketones

Table 2. Temperature effect on the enantioselectivity of asymmetric reduction

Entry	Ketone	Temperature (°C)	% ee
1		−10	97
		25	97
		60	95
2		−10	88
		25	89
		60	94
3		−10	64
		25	81
		60	82
4		−10	28
		25	50
		60	64

with high enantioselectivity. Thus the new methodology made the enantioselective reduction more practical because it is easier to handle, the preparation of catalyst is less time consuming, and no expensive reagents are involved. Further study of this asymmetric catalytic reduction is now in progress.

4. Experimental

4.1. General

IR spectra were determined using a Shimadzu IR-435 spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were recorded at 400 and 100 MHz using JNM-A400 spectrometer, respectively. Mass spectra were recorded on a JEOL JMS-SX102A mass spectrometer. Optical rotations were taken with a JASCO P-1010 polarimeter. The HPLC analysis was carried out using a DAICEL Chiralcel OD column (0.46×25 cm) with a Shimadzu LC6A. Tetrahydrofurane (THF) was distilled from sodium benzophenone ketyl before use. TLC was carried out on Merck glass plates precoated with silica gel 60F-254 (0.25 mm) and column chromatography was performed using Merck 23–400 mesh silica gel. BH_3–THF solution was purchased from the Aldrich Chemical.

4.1.1. (*S*)-5-(Diphenylhydroxymethyl)pyrrolidin-2-one 3. This preparation has already reported.[7] Slight modification was carried out to improve the yield. A solution of methyl (*S*)-pyroglutamate (573 mg, 4.0 mmol) in THF (1 ml) was added dropwise to phenylmagnesium bromide (16 mmol) in THF (8 ml) at 0°C and the reaction mixture was stirred at room temperature for 12 h. The reaction was quenched with saturated aqueous NH_4Cl solution and extracted with ethyl acetate. The combined organic layer was dried over $MgSO_4$ and concentrated. The residue was washed with hexane–ethyl acetate (50/1) and then chromatographed (hexane–AcOEt, 4/1) to give a white solid (695 mg, 65%); mp 194–195°C, $[\alpha]_D^{25}=-86.8$ (*c* 0.74, $CHCl_3$); IR (KBr) 3300, 1680 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.94–2.05 (1H, m), 2.09–2.18 (1H, m), 2.23–2.38 (2H, m), 2.66 (1H, s), 4.75 (1H, dd, *J*=5.4, 8.3 Hz), 5.41 (1H, br s), 7.21–7.52 (10H, m); ^{13}C NMR ($CDCl_3$) δ 21.6, 30.2, 60.6, 78.7, 125.6, 125.8, 127.1, 127.5, 128.3, 128.8, 143.2, 145.2, 179.3; EI MS (M^+) 267.

4.2. Typical procedure for enantioselective reduction of ketones: (*R*)-1-phenylethanol

To a solution of chiral lactam alcohol **3** (26.6 mg, 0.1 mmol, 10 mol%) in THF (2 ml) was added 1 M BH_3–THF solution (1 ml, 1 mmol) and the mixture was stirred under Ar at room temperature for 5 min. A solution of acetophenone (116.6 μl, 1 mmol) in THF (1.5 ml) was added dropwise. The reaction mixture was stirred until the ketone was disappeared on a TLC (10 min). The reaction was quenched with 2N HCl (4 ml), extracted with ether, and dried over $MgSO_4$. Flash-chromatography of the crude mixture (hexane–AcOEt, 4/1) provided (*R*)-1-phenylethanol (119 mg, 97%); $[\alpha]_D^{25}=+49.8$ (*c*, 2.10, CH_2Cl_2) (lit.,[11] $[\alpha]_D^{23}=-52.5$ (*c*, 2.27, CH_2Cl_2) for *S*-isomer). The ee was determined to be 97% by HPLC analysis using a Chiralcel OD column, hexane–*i*-PrOH=97/3, 0.8 ml/min. For 1-phenylpropan-1-ol, 1-(4-chlorophenyl)ethan-1-ol, 2-chloro-1-phenylethan-1-ol, 1,2,3,4-tetrahydronapht-1-ol, 4-phenylbutan-2-ol, hexane–*i*-PrOH=97/3, 0.8 ml/min. For 4-nitrobenzoate of 1-cyclohexylethan-1-ol, 3,3-dimethylbutan-2-ol, hexane–*i*-PrOH=200/1, 0.3 ml/min.

To establish the absolute configuration of the produced alcohol, its sign of optical rotation was compared with the reported value; (*S*)-(−)-1-phenylpropan-1-ol,[12] (*R*)-(+)-1-(4-chlorophenyl)ethan-1-ol,[13] (*R*)-(−)-2-chloro-1-phenylethan-1-ol,[14] (*R*)-(−)-1,2,3,4-tetrahydronapht-1-ol,[15] (*R*)-(−)-1-cyclohexylethan-1-ol,[16] (*R*)-(−)-3,3-dimethylbutan-2-ol,[16] (*R*)-(−)-4-phenylbutan-2-ol.[17]

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References

1. Hirao, A.; Itsuno, S.; Nakahama, S.; Yamazaki, N. *J. Chem. Soc., Chem. Commun.* **1981**, 315. Itsuno, S.; Hirao, A.; Nakahama, S.; Yamazaki, N. *J. Chem. Soc., Perkin Trans. 1* **1983**, 1673. Itsuno, S.; Ito, K.; Hirao, A.; Nakahama, S. *J. Org. Chem.* **1984**, *49*, 555. Itsuno, S.; Nakano, M.; Miyazaki, K.; Masuda, H.; Ito, K.; Hirao, A.; Nakahama, S. *J. Chem. Soc., Perkin Trans. 1* **1985**, 2039. Itsuno, S.; Sakurai, Y.; Ito, K.; Hirao, A.; Nakahama, S. *Bull. Chem. Soc. Jpn* **1987**, *60*, 395.
2. Corey, E. J.; Bakshi, R. K.; Shibata, S. *J. Am. Chem. Soc.* **1987**, *109*, 5551.
3. For review, see: (a) Wallbaum, S.; Martens, J. *Tetrahedron: Asymmetry* **1992**, *3*, 1475. (b) Singh, V. K. *Synthesis* **1992**, 605.

(c) Deloux, L.; Srebnik, M. *Chem. Rev.* **1993**, *93*, 763. (d) Corey, E. J.; Helal, C. J. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 1986.
4. Qualich, G.; Woodall, T. M. *Synlett* **1993**, 929. Ganem, B. *Chemtracts-Org. Chem.* **1988**, 40.
5. Corey, E. J.; Bakshi, R. K.; Shibata, S.; Chen, C.-P.; Singh, V. K. *J. Am. Chem. Soc.* **1987**, *109*, 7925. Corey, E. J.; Bakshi, R. K. *Tetrahedron Lett.* **1990**, *31*, 611. Corey, E. J.; Link, J. O. *J. Am. Chem. Soc.* **1992**, *114*, 1906. Corey, E. J.; Link, J. O. *Tetrahedron Lett.* **1992**, *33*, 3431. Corey, E. J.; Cimprich, K. A. *Tetrahedron Lett.* **1992**, *33*, 4099.
6. Masui, M.; Shioiri, T. *Synlett* **1997**, 273.
7. Fujihara, H.; Tomioka, K. *J. Chem. Soc., Perkin Trans. 1* **1999**, 2377.
8. Stone, G. *Tetrahedron: Asymmetry* **1994**, *5*, 465.
9. Li, X.; Yeung, C.-H.; Chan, A. S. C.; Yang, T.-K. *Tetrahedron: Asymmetry* **1999**, *10*, 759.
10. Brunel, J. M.; Maffei, M.; Buono, G. *Tetrahedron: Asymmetry* **1993**, *4*, 2255.
11. Nagai, U.; Shishido, T.; Chiba, R. Mitsuhashi. *Tetrahedron* **1965**, *21*, 1701.
12. Kitamura, M.; Suga, S.; Kawai, K.; Noyori, R. *J. Am. Chem. Soc.* **1986**, *108*, 6071.
13. Polavarapu, P. L.; Fontana, L. P.; Smith, H. E. *J. Am. Chem. Soc.* **1986**, *108*, 94.
14. Hartgerink, J. W.; van der Laan, L. C. J.; Engberts, J. B. F. N.; de Boer, T. J. *Tetrahedron* **1971**, *27*, 4323.
15. Kim, Y. H.; Park, D. H.; Byun, S. *J. Org. Chem.* **1993**, *58*, 4511.
16. Brown, H. C.; Cho, B. T.; Park, W. S. *J. Org. Chem.* **1988**, *53*, 1231.
17. Nakamura, K.; Fujii, M.; Ida, Y. *Tetrahedron: Asymmetry* **2001**, *12*, 3147.