Tetrahedron Letters,Vol.29,No.35,pp 4453-4456,1988 0040-4039/88 $3.00 + .00
Printed in Great Britain Pergamon Press plc

ASYMMETRIC BORANE REDUCTION OF KETONES CATALYZED BY OXAZABOROLIDINE

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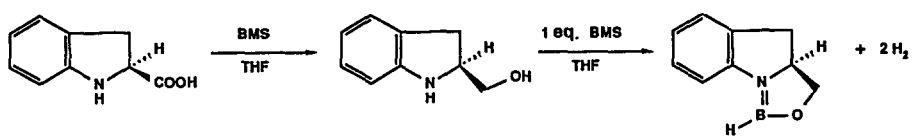
Abstract: Asymmetric reduction of prochiral ketones with borane-methyl sulfide (BMS) in the presence of chiral oxazaborolidine(3) afforded the corresponding secondary alcohols in moderate to high(46-97%) optical yields.

Asymmetric reduction of prochiral ketones with chiral hydride reagent has been intensively investigated[1]. Among the various chiral ligands for boron hydrides, vicinal amino alcohols derived from the corresponding amino acids exhibited diverse degrees of enantioselectivity when applied to aliphatic and aromatic ketones in the form of amino alcohol-borane complex[2].

After the recent report of Itsuno et al.[3] on the catalytic behavior of (S)-2-amino-3-methyl-1,1-diphenylbutan-1-ol and borane complex during enantioselective reduction, Corey et al.[4a] isolated and identified the catalyst as oxazaborolidine. They further developed another chiral oxazaborolidine using (S)-(-)-2-(diphenylhydroxymethyl)pyrrolidine as a ligand and applied this to the multistep synthesis[4b].

Herein, we report moderate to high enantioselectivity(46-97%) obtained in the reduction of aliphatic and aromatic ketones employing a new oxazaborolidine (3).



1 2 3

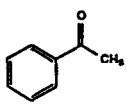
The crystalline oxazaborolidine[5](3) was prepared by sublimation of the residue obtained from a 1:1 equivalent mixture of BMS and (S)-2-hydroxymethylindoline(2) which was prepared by reduction of (S)-2-indoline carboxylic acid(1)[6,7].

When(2) was treated with one equivalent of BMS in THF, two equivalents of hydrogen evolution were measured by gasometry[8]. Further hydrolysis of(3) produced another one equivalent of hydrogen gas, indicating that one equivalent

of active hydride is incorporated in(3). However, (3) had no ability to reduce ketones by itself.

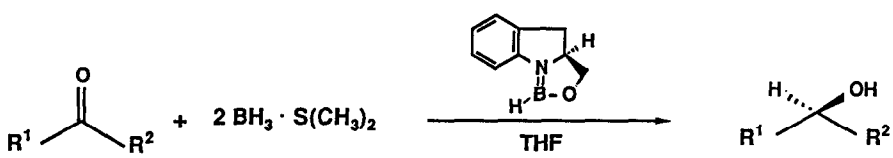
Thus the ratio of(3) to BMS was varied representatively in the case of acetophenone to evaluate the catalytic behavior of(3) (Table 1).

Table 1. Asymmetric Reduction of Acetophenone in the Presence of(3)

Ketone	BMS(eq.)	(3) (eq.)	Optical Yield(%)	Configuration
	5.0	1.0	88	R
	2.0	1.0	97	R
	1.0	1.0	92	R
	0	1.0	-	-
	1.1	0.1	59	R
	0.6	0.1	10	R
	1.2	0.025	5	R

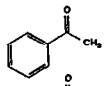
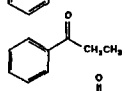
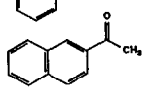
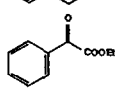
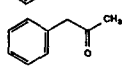
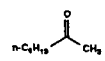
Apparently one equivalent of(3) was needed to get the maximum optical yield, whereas only one tenth equivalent was required to achieve the highest enantiomeric excess in the case of (S)-(-)-2-(diphenylhydroxymethyl)pyrrolidine[4]. Further, to check the catalytic effect of(3), each one equivalent of acetophenone and BMS was added further to the reaction mixture after the first reduction of acetophenone was completed by Method A (see Experimental). After work-up, 94% optical yield was obtained in 1-phenylethanol along with more than 90% recovery of(2) without any loss of original optical activity. Thus(3) must have served as a catalyst, not a reagent.

The optimum condition(Ketone:(3):BMS = 1:1:2) was applied to a series of ketones to get the corresponding optically active secondary alcohols. The results are summarized in Table 2.



Although high enantioselectivity was achieved in aromatic ketones (Entries 1-3) (87-97%), aliphatic ketones (Entries 6 and 7) (46-60%) gave lower values, as expected from previous reports[1,9]. For ethyl benzoylformate selectivity was sufficiently higher(64%) than that of methyl benzoylformate reported by Itsuno et al.(25%)[2]. On the other hand, α-tetralone gave lower value(68%) compared to that obtained by Corey(86%)[4b]. While external addition of(3) markedly enhanced reaction rate, enantioselectivity was little changed in comparison with when it was generated in situ. Thus it seems that the species in situ is quite similar to the structure of(3).

Table 2. Asymmetric Reduction of Ketones with Borane-methyl sulfide in the Presence of Oxazaborolidine(3)

Entry	Ketone	Method[a]	Chemical[b] Yield(%)	Optical[c] Yield(%)	Configuration	Reaction time(min)
1		A (B)	96 (98)	97 (93)	R (R)	10 (10)
2		A (B)	93 (86)	87 (84)	R (R)	10 (10)
3		A (B)	97 (97)	88 (89)	R (R)	10 (20)
4		A (B)	94 (96)	68 (71)	R (R)	10 (30)
5		A (B)	46 (43)[d]	64 (62)	S (S)	10 (20)
6		A (B)	95 (94)	60 (57)	R (R)	10 (20)
7		A (B)	94 (94)	46 (45)	R (R)	10(120)

a. Data in parenthesis were obtained by method B (see Experimental).
b. Isolated yields
c. Optical yields were calculated based upon the value reported.
d. Overreduction to diol was the major side reaction.

Further investigation of optically active oxazaborolidine of 2-hydroxymethylindoline skeleton is in progress.

Experimental

General Procedure for Method A: To a stirred solution of(3) (318mg, 2.0 mmol) in THF(4ml), BMS(10M, 4.0 mmol) and acetophenone(240mg, 2.0 mmol) were added consecutively at room temperature. The reaction mixture was stirred at room temperature for 10 min and then added with 2N hydrochloric acid at 0°C. The hydrolyzed mixture was extracted with diethyl ether (50mlx3) and the combined extract was washed with brine (30mlx2), and dried over anhydrous magnesium sulfate. After removal of the solvent, the residue was purified on silica gel column chromatography to give 1-phenylethanol (235mg, 96% yield) $[\alpha]_D^{25}$ +50.9 (c 2.30, CH_2Cl_2).

General procedure for Method B: To a stirred solution of(2) (298mg, 2.0 mmol) in THF(4ml) was added BMS (10M, 2 mmol) at -78°C. The resulting solution was gradually warmed up to 45°C and stirred for 3hrs. After cooling to room temperature, additional BMS (10M, 2 mmol) was added. Stirring was continued for 3hrs at room temperature. Then acetophenone (216mg, 1.8 mmol) was added. After stirring for 10 min at room temperature the reaction mixture was worked up as above. The crude product was column chromatographed

on silica gel to give 1-phenylethanol (215mg, 98% yield) $[\alpha]_D^{25}$ +48.9(c 2.27, CH_2Cl_2).

References and Notes

1. a) Asymmetric Synthesis, Vol 2, (ed. Morrison, J.D.) Chap. 2,3, Academic Press, New York 1983.
   b) H. Haubenstock, Top. Stereochem., 1983, 14, pp 231-300.
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2. S. Itsuno, M. Nakano, K. Miyazaki, H. Masuda, and K. Ito, J. Chem. Soc. Perkin Trans., 1, 2039(1985) and references cited therein.
3. S. Itsuno, Y. Sakurai, K. Ito, A. Hirao, and S. Nakahama, Bull. Chem. Soc., Jpn., 60, 395(1987).
4. a) E.J. Corey, R.K. Bakshi, and S. Shibata, J. Am. Chem. Soc., 109, 5551 (1987).
   b) E.J. Corey, R.K. Bakshi, S. Shibata, C.P. Chen and V.K. Singh, J. Am. Chem. Soc., 109 7925(1987).
5. Compound (3): After evaporation of the solvent, the residue was sublimed twice (0.6 Torr, 140°-150°C oil bath) to give approximately 10% wt white crystalline solid, the melting point of which was not clear (m.p. 140°-160°C) ^1H NMR (300 MHz, 0.04M in C_6D_6 + $CDCl_3$) δ 7.02-6.40(m, 4H, aromatic), 3.46 (m, 1H, N-CH), 3.15(m, 2H, O-CH_2), 2.70(dd, 1H, J=9.3, 15.6Hz, benzylic), 2.51(dd, 1H, J=7.6, 15.6Hz, benzylic). ^{11}B NMR(0.6M in THF, BF_3 OEt_2 as external standard) + 22.4 ppm broad single peak. mass spectra; m/e (relative intensity) 159(100, M^+), 158(96, M-1), 143(4), 130(36), 117(10), 103(7) high resolution mass spectra m/e obsvd 159.0851 (calcd for C_9H_{10} NOB 159.0857); IR(Nujol mull) 2487.5cm^{-1} (B-H stretching).
6. Compound (1)is available from Kawaken Fine Chemicals Co., Ltd, Japan in commercial quantity or can be prepared according to the known procedure in reference 7.
7. a) E.J. Corey, R.J. McCaully, and H.S. Sachdev, J. Am. Chem. Soc., 92, 2476 (1970).
   b) E.J. Corey, H.S. Sachdev, J.Z. Gougoutas, and W. Saenger, J. Am. Chem. Soc., 92, 2488(1970).
   c) I.K. Youn, G.H. Yon, and C.S. Pak, Tetrahedron Lett., 2409(1986)
   d) I.K. Youn, C.S. Pak, Bull. Chem. Soc., Korean 8, 434(1987)
8. Herbert C. Brown, Organic Synthesis via Boranes, Wiley-Interscience, 1975, pp 243.
9. S. Itsuno and K. Ito, J. Org. Chem., 49, 555(1984).

Caution: We observed that compound(3) was pyrophoric when the vacuum was released in the air after sublimation. But once isolated under argon it was stable enough to handle in the open air.

(Received in Japan 27 June 1988)