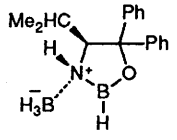
Asymmetric Reduction of *N*-Substituted Ketimines with the Reagent prepared from Borane and (*S*)-(−)-2-Amino-3-methyl-1,1-diphenylbutan-1-ol (Itsuno's Reagent): Enantioselective Synthesis of Optically Active Secondary Amines

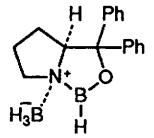
Byung Tae Cho * and Yu Sung Chun
Department of Chemistry, Hallym University, Chunchon 200–702, Republic of Korea

Itsuno's Reagent (**1**) reduced *N*-substituted ketimines in very high yields to the corresponding amines with high optical induction.

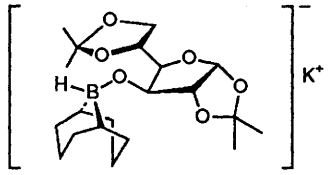
Although highly effective asymmetric reductions of carbonyl compounds have been extensively reported in recent years,[1] useful enantioselective conversions of imine derivatives into amines have been relatively neglected and only limited success has been achieved.[2] In the course of our study on asymmetric reduction of *N*-substituted ketimine derivatives with various chiral reducing agents, such as Itsuno's reagent (**1**),[2c] Corey's reagent (**2**),[1k] K glucoride (**3**),[1f] Sharpless' reagent (**4**),[3] and Mosher's reagent (**5**),[4] we found that complex (**1**) reduced the ketimines (**6**) in high yields to the corresponding optically active secondary amines (**7**) with high enantioselectivity. We now report our preliminary results for the reaction.



(1)

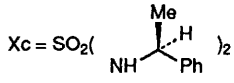


(2)

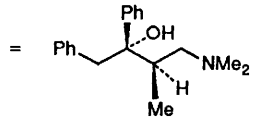


(3)

Chiral auxiliary (Xc) / $LiAlH_4$ Complex

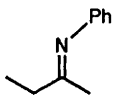


(4)

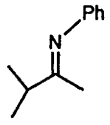


(5)

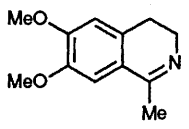
First, we compared the asymmetric reducing characteristics of compounds (**1**)–(**5**) for propiophenone *N*-phenylimine (**6b**) chosen as a representative *N*-substituted ketimine. The reductions were carried out under the same conditions as those found most successful for the corresponding studies with ketones. Among these reagents, (**1**), (**2**),[9] and (**4**) reduced (**6b**) smoothly to optically active *N*-phenyl-1-phenylpropylamine (**7b**) with 87, 78, and 66% ee, respectively. However, (**3**) and (**5**) did not reduce (**6b**). The results led us to investigate asymmetric reductions of the other ketimines (**6**) with (**1**). The reductions were carried out in THF at 30 °C.[2c] All the ketimines examined are reduced to the corresponding amines (**7**) in essentially quantitative yields. In the reduction of *N*-phenyl aromatic ketimines, consistently high optical yields, such as 73% ee for acetophenone *N*-phenylimine (**6a**), 71% ee for isobutyrophenone N-phenylimine (**6c**), and 88% ee for valerophenone *N*-phenylimine (**6d**) were obtained. To our knowledge, this is the first example that such high optical inductions have been achieved for the asymmetric reduction of *N*-phenyl ketimines. It is noteworthy that increasing the steric bulk of R group in (**6**) leads to higher optical induction. In contrast, the reduction of *N*-alkyl ketimines, such as (**6e**) and (**6f**) provided lower optical induction (46 and 52%, respectively). The results are summarized in Table 1. On the other hand, asymmetric reductions of *N*-substituted alkyl ketimines (**8**) and (**9**) with (**1**)



(8)



(9)



(10)

were less effective to give 9 and 14% *ee*, respectively. The cyclic imine (**10**) was not reduced by (**1**). The following procedure is representative. To a solution of (**1**) (3.3 mmol) in THF prepared from BH_3 (6.6 mmol) in THF (1M; 6.6 ml) and *S*-(−)-AMDPB[8] (3.3 mmol) in THF (2.4 ml) at 0 °C by the known method[2c] was

Table 1. Asymmetric reduction of *N*-substituted ketimines (**6**) with (**1**) in THF at 30 °C.

PhCR=NR′ $\xrightarrow{(1)}$ PhCHR–NHR′
(**6**) (**7**)

	R	R′	Time (h)	(7) Yield[a] (%)	(7) % ee[b]	Abs. config.
a	Me	Ph	20	98(87)	73	*R*-(−)[5]
b	Et	Ph	22	97(89)	87	*R*-(−)[c]
c	Pr^i	Ph	24	96(90)	71	(+)
d	Pr	Ph	24	97	88	*R*-(−)[c]
e	Me	$PhCH_2$	20	98	46	*R*-(−)[6]
f	Me	n-C_7H_{13}	20	96	52	*R*-(−)[c]

[a] GC yields. The figures in parentheses indicated isolated yields after column chromatography. [b] Determined by capillary GC analysis of their MTPA-amides.[7] [c] The absolute configuration is unknown, but probably R, based on the order of elution of MTPA derivatives and the sign of rotation.

added a solution of (**6b**) (627 mg, 3 mmol) in THF. The reaction mixture was stirred at 30 °C for 22 h and then excess of hydride was decomposed by the addition of 1M HCl solution. THF was removed *in vacuo* and deposited AMDPB-HCl was filtered off and washed with water. The filtrate was cooled to 0 °C, basified with 3M NaOH, and extracted with ether. The extract was washed with brine, dried (K_2CO_3), and evaporated to give an oily residue. Column chromatography on silica gel (eluant: $CHCl_3$) gave (**7b**) (564 mg, 89%) of a pale yellow syrup: $[\alpha]_D^{22}$ −7.61 (*c* 1.06 in MeOH): 87% ee by capillary GC analysis of the MTPA amide;[7] ν_{max} (liq. film) 3510 (NH), 3073 (ArH), 2959 (aliphatic CH), and 1601 cm^{-1}; δ_H(60 MHz; solvent $CDCl_3$; standard $MeSi_4$): 0.91 (3 H, t, *J* 7 Hz, CH_3), 1.61–2.02 (2 H, m, CH_2CH_3), 3.90 (1 H, br s, NH), 4.23 (1 H, t, *J* 7 Hz, CH) and 6.4–7.6 (10 H, m, Ph).

Acknowledgements

We are grateful to the Korea Research Foundation and the Organic Chemistry Research Center sponsored by the Korea Science and Engineering Foundation for financial support.

References

1 For a review of recent work, see: (*a*) M. M. Midland, 'Asymmetric Synthesis', J. D. Morrison, ed., Academic Press: New York 1983; vol. 2, ch. 2; (*b*) E. R. Grandbois, S. I. Howard and J. D. Morrison, ref. 1*a*, ch. 3; (*c*) H. Haubenstock, *Top. Stereochem.*, 1983, **14**, 231; (*d*) J. W. ApSimon and T. Lee Collier, *Tetrahedron*, 1986, **42**, 5157; recent additional studies include the following: (*e*) a comparative work: H. C. Brown, W. S. Park, B. T. Cho and P. V. Ramachandran, *J. Org. Chem.*, 1987, **52**, 5406; (*f*) K 9-O-DIPGF-9-BBNH (K glucoride): H. C. Brown, B. T. Cho and W. S. Park, *J. Org. Chem.*, 1988, **53**, 1231; (*g*) Ipc_2BCl: H. C. Brown, J. Chandrasekharan and P. V. Ramachandran, *J. Am. Chem. Soc.*, 1988, **110**, 1539; (*h*) IpcBRCl: H. C. Brown, M. Srebnik and P. V. Ramachandran, *J. Org. Chem.*, 1989, **54**, 1577; (*i*) Eap-Bu^{t}Cl: H. C. Brown and P. V. Ramachandran, *J. Org. Chem.*, 1989, **54**, 4504; (*j*) (*R,R*)-2,5-dimethylborolane: T. Imai, T. Tamura, A. Yamamura, T. Sato, T. A. Wollman, R. M. Kennedy and S. Masamune, *J. Am. Chem. Soc.*, 1986, **108**, 7402; (*k*) chiral oxazaborolidines: E. J. Corey, R. K. Bakshi and S. Shibita, *J. Am. Chem. Soc.*, 1987, **109**, 5551; E. J. Corey, R. K. Bakshi, C-P. Chen and V. K. Singh, *J. Am. Chem. Soc.*, 1987, **109**, 7925.

2 For cyclic imines: (*a*) lithium alkyldipan-3α-ylborate (4–25% ee): M. F. Grundon, W. A. Khan, D. R. Boyd and W. R. Jackson, *J. Chem. Soc. C*, 1971, 2557; (*b*) sodium acyloxyborohydrides (0–86% ee): M. Yamada, M. Takeda and T. Iwakuma, *J. Chem. Soc., Perkin Trans.*, 1, 1983, 265; for ketoxime derivatives: (*c*) amino alcohol (AMDPB)/BH_3 (8.7–99% ee): S. Itsuno, M. Nakano, K. Miyazaki, H. Masuda, K. Ito, A. Hirao and S. Nakahama, *J. Chem. Soc., Perkin Trans.*, 1, 1985, 2039. In this paper, a defined structure of the reagent was not reported, but the structure of (**1**) became apparent after Corey's work (ref. 1*k*); (*d*) glucofuranose/$LiAlH_4$ (9.5–56% ee): S. R. Landor, O. O. Sonola and A. R. Tatchell, *J. Chem. Soc., Perkin Trans. 1*, 1974, 1902; S. R. Landor, Y. M. Chan, O. O. Sonola and A. R. Tatchell, *J. Chem. Soc., Perkin Trans. 1*, 1984, 493; (*e*) $NaBH_4$-Lewis acid-amino alcohol (12–92% ee): S. Itsuno, Y. Sakurai, K. Shimizu and K. Itoh, *J. Chem. Soc., Perkin Trans. 1*, 1989, 1548; for *N*-phenylazomethines: (*f*) glucofuranose/$LiAlH_4$ (9.4–23.6% ee): S. R. Landor, O. O. Sonola and A. R. Tatchell, *J. Chem. Soc., Perkin Trans. 1*, 1978, 605; (*g*) homogeneous catalytic hydrogenation (4–84% ee): F. Spindler, B. Pugin and H-U. Blaser, *Angew. Chem., Int. Ed. Engl.*, 1990, **29**, 558; for *N*-phosphinylimines: (*h*) R. O. Hutchins, A. Abdel-Magid, Y. P. Sterecho and A. Wambsgan, *J. Org. Chem.*, 1987, **52**, 702; for *N*-benzylketimines: (*i*) homogeneous catalytic hydrogenation (2–91% ee): G-J. Kang, W. R. Cullen, M. D. Fryzuk, B. R. James and J. P. Kuteney, *J. Chem. Soc., Chem. Commun.*, 1988, 1466.

3 J. M. Hawkins and K. B. Sharpless, *J. Org. Chem.*, 1984, **49**, 3861.

4 S. Yamaguchi and H. Mosher, *J. Org. Chem.*, 1973, **38**, 1870.

5 G. Wittig and U. Thiele, *Liebigs Ann. Chem.*, 1969, **726**, 1.

6 S. Yamamoto, F. Yasuhara and K. Kabuto, *J. Org. Chem.*, 1978, **42**, 1578.

7 H. C. Brown, K-W. Kim, T. E. Cole and B. Singaram, *J. Am. Chem. Soc.*, 1986, **108**, 6761.

8 AMDPB = 2-amino-3-methyl-1,1-diphenylbutan-1-ol.

9 Using (**2**) prepared from 1 equiv. of the oxazaborolidine and 1.1 equiv. of BH_3·THF, the reduction was carried out in THF at 25 °C (ref. 1*k*).

Paper 0/02739A
Received 18*th June* 1990
Accepted 18*th August* 1990