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# Asymmetric Reduction of Imines with Chiral Dialkoxyboranes

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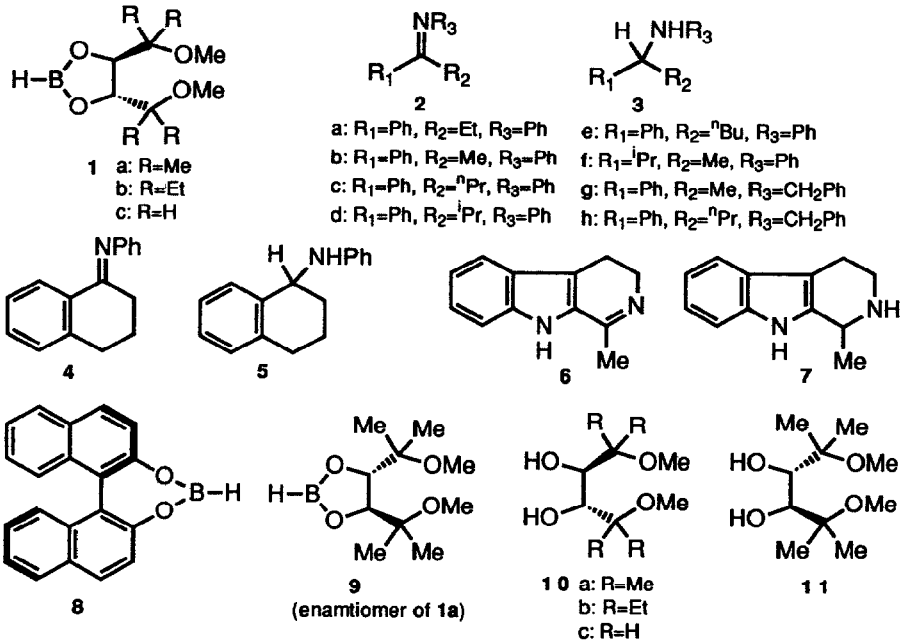
**Abstract:** The asymmetric reduction of imines with chiral dialkoxyboranes was investigated and gave an optically active amine up to 73%ee in the presence of $MgBr_2 \cdot OEt_2$.

The asymmetric reduction of C=N double bonds is a potentially important method for the preparation of enantiomerically pure amines and would provide a effective route to various optically active alkaloids. Although many examples of asymmetric reduction of prochiral ketones to chiral alcohols have been described,[1] only a little attention has been devoted to the asymmetric reduction of imine derivatives.[2]

In this communication, we would describe our preliminary results on the asymmetric reduction of prochiral *N*-phenyl imines, *N*-benzyl imines, and 1-methyl-3,4-dihydro-β-carboline with chiral dialkoxyborane reagents.

We found that the imine **2a** was readily reduced by a chiral borane **1a** (5 mol eq.) at room temperature in the presence of $MgBr_2 \cdot OEt_2$ (1.2 mol eq.) in THF to give the amine **3a** in 91% yield with 73%ee. Without $MgBr_2 \cdot OEt_2$, the reaction did not take place. The use of other additives such as $ZnCl_2$, $TiCl_4$, $ZrCl_4$, $CeCl_3$, and $Me_3SiOTf$ for this reaction reduced the chemical yield of **3a** (~ 30%), whereas $TiCl_4$, LiBr, $FeCl_3$, and $SnCl_4$ improved the yield but decreased the enantioselectivity (~ 36%ee). Other magnesium salts, $MgCl_2$, $MgI_2$, and $Mg(ClO_4)_2$, also gave less effective results (33 ~ 53%yields, 14 ~ 46%ee).

To improve the enantioselectivity, other borane reagents **1b**, **1c**, and **8** were examined, but proved to be less effective although the reduction proceeded in high yield. (Table, entries 1-4). Our attention was then focused on the asymmetric reduction of




various imines using **1a**. (Table) Treatment of the imines **2b**, **c**, and **e**, derived from phenyl primary alkyl ketones and aniline, with **1a** and $MgBr_2 \cdot OEt_2$ gave modest to good enantioselectivity with high chemical yield. (entries 5, 6, and 8) Better enantioselectivities were observed when an alkyl ketimine, 3-methyl-2-butanone anil **2f** and *N*-benzyl imine **2g** were reduced under similar condition. (entries 9 and 11) On the other hand, the reduction of imines such as **2d**, **4**, and **2h** gave only poor optical purity of the amines **3d**, **5**, and **3h**, respectively. (entries 7, 10, and 12) Although the stereochemical outcome of the present reduction is not clear, similar reduction of **2a** with **9**, the enantiomer of **1a**, cleanly produced (R)-**3a** in corresponding chemical and optical yields having the specific rotation opposite in sign. (entry 13) In contrast, the reduction of 1-methyl-3,4-dihydro-β-carboline **6** proceeded without $MgBr_2 \cdot OEt_2$ at low temperature (-78°C) within 10 min to give (R)-**7** in 98% yield and 42%ee.[4)]

In conclusion the chiral diol borane **1a** was found to be one candidate for the chiral reduction of imines such as **2**, although the enantioselectivity has room for improvement. One characteristic feature of **1a** was that this reagent has an ability for chiral reduction of the 3,4-dihydro-β-carboline **6**, while the Itsuno's reagent has been reported to reduce

Table : **Reduction of Imines with Chiral Dialkoxyboranes**[a)]

| entry | imines | $R_1$ | $R_2$ | $R_3$ | chiral borane | conditions temp(°C) | time(h) | results[b)] amine(%) | %ee | Abs.Config. |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | **2a** | Ph | Et | Ph | **1a** | rt | 23 | **3a** 91 | 73[c)] | S-(+) |
| 2 | **2a** | Ph | Et | Ph | **1b** | 0 | 1 | **3a** 73 | 41[c)] | S-(+) |
| | | | | | | rt | 23 | | | |
| 3 | **2a** | Ph | Et | Ph | **1c** | 0 | 0.5 | **3a** 96 | 15[c)] | S-(+) |
| 4 | **2a** | Ph | Et | Ph | **8** | 0 | 1 | **3a** 94 | 20[c)] | R-(-) |
| | | | | | | rt | 23 | | | |
| 5 | **2b** | Ph | Me | Ph | **1a** | 0 | 0.5 | **3b** 89 | 56 | R-(-) |
| | | | | | | rt | 15 | | | |
| 6 | **2c** | Ph | $^n$Pr | Ph | **1a** | 0 | 2 | **3c** 94 | 65 | S-(+) |
| | | | | | | rt | 14 | | | |
| 7 | **2d** | Ph | $^i$Pr | Ph | **1a** | 0 | 1 | **3d** 85 | 18 | (-)[d)] |
| | | | | | | rt | 24 | | | |
| 8 | **2e** | Ph | $^n$Bu | Ph | **1a** | 0 | 1 | **3e** 95 | 65 | (-)[d)] |
| | | | | | | rt | 25 | | | |
| 9 | **2f** | $^i$Pr | Me | Ph | **1a** | 0 | 1 | **3f** 75 | 71 | (-)[d)] |
| | | | | | | rt | 2 | | | |
| 10 | **4** | α-tetralone | | Ph | **1a** | 0 | 1 | **5** 79 | 12 | (+)[d)] |
| | | | | | | rt | 25 | | | |
| 11 | **2g** | Ph | Me | $CH_2Ph$ | **1a** | 0 | 1 | **3g** 70 | 72[c)] | R-(+) |
| | | | | | | rt | 23 | | | |
| 12 | **2h** | Ph | $^n$Pr | $CH_2Ph$ | **1a** | 0 | 1 | **3h** 81 | 36[e)] | (+)[d)] |
| | | | | | | rt | 23 | | | |
| 13 | **2a** | Ph | Et | Ph | **9** | 0 | 1 | **3a** 94 | 71[c)] | R-(-) |
| | | | | | | rt | 23 | | | |

a) Reaction was performed as described in note.[5)] b) Yields were referred to isolated material. Optical purities were determined by HPLC analysis using a chiral column (DAICEL, CHIRACEL OD, hexane:$^i$PrOH=95:5 or 98:2 as eluent). Absolute configurations were assigned as literature.[2a,3)] c) Optical purities were calculated from comparison of its optical rotation with reported value: **3a**, ref. 2a; **3g**, ref. 3. d) Absolute configuration was not determined. e) Determined by $^1$H-NMR using a chiral shift reagent, (R)-(-)-2,2,2-trifluoro-1-(9-anthranyl)ethanol.

imines enantioselectively, but not 1-methyl-6,7-dimethoxy-3,4-dihydro-isoquinoline.[2a)]

Further improvement in the enantioselectivity are now in progress.[7,8)]

**References and Note**

1) Reviews: (a) M. M. Midland, 'Asymmetric Synthesis', J. D. Morrison, ed., Academic Press: New York, 1983; vol. 2, chapter 2; (b) E. R. Grandbois, S. I. Howard and J. D. Morrison, ref. 1a, chapter 3; (c) H. Haubenstock, *Top. Stereochem.*, 1983, **14**, 231; (d) J. W. ApSimon and T. Lee Collier, *Tetrahedron*, 1986, **42**, 5157.

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3) A. I. Meyers and J. D. Brown, *Tetrahedron Lett.*, 1988, **29**, 5617.

4) H. Akimoto, K. Okamura, M. Yui, T. Shioiri, H. Kuramoto, Y. Kikugawa, and S. Yamada, *Chem. Pharm. Bull.*, 1974, **22**, 2614.

5) The chiral borane reagents were prepared as follow: (typically for **1a**): To a solution of 1.1 mol equivalent of chiral diol **10a**, obtained from dimethyl L-tartarate,[6] in THF, $BH_3$•THF (1M in THF) was added at 0°C. The reaction mixture was stirred for 2 h at the same temperature, then allowed to stand in refrigerator (ca. 4°C) for 22 h. And other reagents **1b**, **1c**, **8**, and **9** were also prepared by the same procedure from **10b**, **10c**, (R)-2,2'-binaphthol, and **11**,[6] respectively. For similar precedents, see : H.C. Brown, 'Organic Syntheses via Boranes', John Wiley & Sons: New York, 1975, p 44, 242 and references therein. The exact structures of **1** are not determined.

The reduction was typically performed as follow. (entry 1): To the mixture of *N*-phenyl imine **2a** (315 mg, 1.5 mmol) and $MgBr_2$•$OEt_2$ (1.2 mol eq.) in THF (20 ml), added **1a** (0.4M in THF, 18.8 ml, 7.52 mmol) at 0°C under Ar atmosphere. After stirred for 23 h at room temperature, saturated $NaHCO_3$ solution was added and concentrated *in vacuo*. The product was extracted with $CH_2Cl_2$ and the organic layers were washed, dried, and evaporated to gave a residue, which was chromatographed on silica gel to give the amine **3a** (289 mg, 91%, $[\alpha]_D^{25}$ +6.40 , 73%ee[2a]).

6) Preparation of chiral diols:**10a**: (a) I. Hoppe, U. Schüllkopf, M. Nieger, and E. Egert, *Angew. Chem., Int. Ed. Engl.*, 1985, **24**, 1067; (b) E. A. Mash, S. B. Hemperly, K. A. Nelson, P. C. Heidt, and S. Van Deusen, *J. Org. Chem.*, 1990, **55**, 2045; **10b** and **11** were prepared by similar method described for **10a**, for **10b** EtMgI was used instead of MeMgI, and for **11**, prepared from diethyl D-tartarate; **10c**: (c) M. Carmack and C. J. Kelley, *J. Org. Chem.*, 1968, **33**, 2127; (d) D. Seebach, H.-O. Kalinowski, B. Bastani, G. Crass, H. Daum, H. Dörr, N. P. DuPreez, V. Ehrig, W. Langer, C. Nüssler, H.-A. Oei, and M. Schmidt, *Helv. Chim. Acta*, 1977, **60**, 301; (R)-2,2'-binaphthol was purchased from Tokyo Kasei Kogyo Co. Ltd.

7) All new compounds described herein was characterized with NMR, IR, and mass spectra.

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