Asymmetric Reduction of Aromatic Ketones with the Reagent prepared from (*S*)-(−)-2-Amino-3-methyl-1,1-diphenylbutan-1-ol and Borane

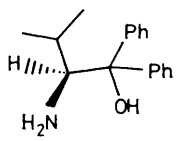
Shinichi Itsuno,*[a] Koichi Ito,[a] Akira Hirao,[b] and Seiichi Nakahama[b]

[a] *School of Materials Science, Toyohashi University of Technology, Tempaku-cho, Toyohashi 440, Japan*
[b] *Department of Polymer Science, Tokyo Institute of Technology, Ohokayama, Meguro-ku, Tokyo 152, Japan*

Asymmetric reduction of prochiral aromatic ketones with the reagent prepared from (*S*)-(−)-2-amino-3-methyl-1,1-diphenylbutan-1-ol [(*S*)-(**1**)] and borane afforded the corresponding aromatic secondary alcohols in high optical (94—100% enantiomeric excess) and chemical (100%) yields.

Many amine–borane complexes have practical advantages as reducing agents in organic synthesis,[1–3] owing to their selectivity, stability, and solubility in a wide variety of solvents. The application of chiral amine–borane complexes to the asymmetric reduction of ketones has been investigated, but it appears that little of preparative value has emerged yet because of the low stereoselectivity and the low ability of the chiral amine residue to be recycled.[4–8] We have recently reported the asymmetric reduction of aromatic ketones utilizing borane complexes with optically active β-aminoalcohols which give the corresponding secondary alcohols with up to 73% stereoselectivity.[9,10]

We now report that very high stereoselectivities (94—100%) are attained in the reduction of aromatic ketones by use of a new chiral borane complex with (*S*)-(−)-2-amino-3-methyl-1,1-diphenylbutan-1-ol [(*S*)-(**1**)], readily prepared in two steps from (*S*)-valine, in an experimentally convenient procedure.



(*S*)-(**1**)

(*S*)-Valine methyl ester hydrochloride was converted with excess of phenylmagnesium bromide into (*S*)-(**1**) in 56% overall yield: $[\alpha]_D^{25}$ −127.7° (*c* 0.693, $CHCl_3$), m.p. 94—95 °C. The same treatment of (*R*)-valine (93.4% optical purity) gave (*R*)-(**1**): $[\alpha]_D^{25}$ + 120.2° (*c* 0.272, $CHCl_3$), m.p. 94—95 °C. The optical purity of the (*R*)-isomer was tentatively determined to be 94% by comparison with the $[\alpha]_D^{25}$ value for (*S*)-(**1**).

In a typical asymmetric reduction the reagent, prepared from (*S*)-(**1**) (10 mmol) and borane (20 mmol), and the ketone

Table 1. Asymmetric reduction of aromatic ketones with the reagent prepared from (**1**) and borane in tetrahydrofuran at 30 °C for 2 h.[a]

Run	Amino-alcohol	Ketone	Alcohol produced[b] $[\alpha]_D^{20}$/°	Optical yield/%	Absolute configuration
1	(*S*)-(**1**)	MeCOPh	+49.1[e]	94	*R*
2	(*S*)-(**1**)	EtCOPh	+44.2[f]	94	*R*
3	(*S*)-(**1**)	Pr^{n}COPh	+43.4[g]	96	*R*
4[c]	(*S*)-(**1**)	Pr^{n}COPh	+42.9	95	*R*
5[d]	(*S*)-(**1**)	Pr^{n}COPh	+ 3.00	6.6	*R*
6	(*R*)-(**1**)	Pr^{n}COPh	+41.3	91 (97)[j]	*S*
7	(*S*)-(**1**)	Bu^{n}COPh	+31.9[h] (+20.0)[i]	100	*R*

[a] Conditions: amino-alcohol (**1**), 10 mmol; borane, 20 mmol; ketone, 8 mmol; total volume of solvent, 20 ml. The ratio of (**1**), borane, and ketone was 1 : 2.0 : 0.8. [b] Based on relative g.l.c. peak areas of alcohol and unchanged ketone, all yields were 100%. [c] Recovered (*S*)-(**1**) was used. [d] The reagent prepared from (*S*)-(**1**) and borane in a 1 : 1 molar ratio was used. [e] Maximum value for $[\alpha]_D^{23}$ is −52.5° (*c* 2.27, CH_2Cl_2) (see U. Nagai, T. Shishido, R. Chiba, and H. Mitsuhashi, *Tetrahedron*, 1965, **21**, 1701). [f] Maximum value for $[\alpha]_D^{20}$ is −47.03° (Me_2CO) (see H. Kwart and D. P. Hoster, *J. Org. Chem.*, 1967, **32**, 1867). [g] Maximum value for $[\alpha]_D^{22}$ is −45.2° (*c* 4.81, benzene) (see R. Noyori, I. Tomino, and Y. Tanimoto, *J. Am. Chem. Soc.*, 1979, **101**, 3129). [h] Maximum value for $[\alpha]_D^{20}$ is +31.3° (*c* 3, benzene) (see D. Seebach, H. O. Kalinowski, B. Bastani, G. Crass, H. Daum, H. Dörr, N. P. DuPreez, V. Ehrig, W. Langer, C. C. Nüssler, Hoc-An Oei, and M. Schmidt, *Helv. Chim. Acta*, 1977, **60**, 301). [i] Maximum value for α_D^{20} is +20° (neat) (see A. Horeau, J. P. Guette, and R. Weiolmann, *Bull. Soc. Chim. Fr.*, 1966, 3513). [j] Optical yield corrected for the optical purity of the (*R*)-(**1**) (94% enantiomeric excess).

(8 mmol) in tetrahydrofuran (THF) (20 ml) were kept for 2 h at 30 °C according to the published procedure.[10] After the usual work-up, the alcohol produced was purified by distillation and its optical rotation measured. (*S*)-(**1**) was first recovered by filtration as its hydrochloride salt after hydrolysis with 2M-HCl. Treatment with aqueous ammonia, extraction with ethyl acetate, drying ($MgSO_4$), filtration, and evaporation gave the crude crystalline (*S*)-(**1**) which was recrystallized from ethanol–water (10 : 1, v/v), leading to >80% recovery of (*S*)-(**1**) without racemization.

As can be seen from Table 1, the asymmetric reduction of aromatic ketones with the (*S*)-(**1**)–borane complex proceeded in a highly stereoselective manner, giving 94—100% optical yields in each case (runs 1—3, and 7). Both optical and chemical yields were reproducible when the reagent from the recovered (*S*)-(**1**) and borane was used (run 4). It is of particular interest that the reagent from (*S*)-(**1**) gives the (*R*)-alcohol while the reversed stereoselectivity with the same degree of asymmetric induction was achieved by use of the reagent from (*R*)-(**1**) (run 6). Since both (*S*)- and (*R*)-(**1**) are readily accessible, this method allows both enantiomers of secondary alcohols to be synthesised readily from aromatic ketones.

High stereoselectivity was always attained with the reagent prepared from a 1 : 2 molar ratio of (*S*)-(**1**) and borane, whereas the reduction with the reagent with a 1 : 1 ratio resulted in a disappointingly low selectivity (run 5). The effect of the molar ratio on asymmetric induction is thus critical, although the optimum ratio of the reducing reagent and modifier such as (*S*)-(**1**) might not be well defined in similar stereochemical reactions previously reported.[11–15] A similar phenomenon was observed in our previous work[10] on the asymmetric reduction of aromatic ketones by the same type of chiral borane reagents with optically active β-amino-alcohols.

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