Asymmetric Synthesis Using Chirally Modified Borohydrides. Part 1. Enantioselective Reduction of Aromatic Ketones with the Reagent Prepared from Borane and (*S*)-Valinol

Shinichi Itsuno,* Akira Hirao, Seiichi Nakahama, and Noboru Yamazaki
Department of Polymer Science, Tokyo Institute of Technology, Ohokayama, Meguro-ku, Tokyo 152, Japan

The asymmetric reduction of aromatic ketones with the reagents prepared from borane and chiral amino-alcohols was studied under various conditions. The ratio of borane to (*S*)-valinol was found to be optimum at 2—3 : 1, when up to 65—73% selectivity was obtained in the reduction of n-propyl phenyl ketone. The amino-alkoxy-amine-boranes (2) and/or (3) were tentatively proposed as the reaction species responsible for asymmetric induction.

During the course of our studies on new chirally modified reducing agents, we have found that the reagents prepared from borane and optically active amino alcohols are efficient chiral reducing agents for ketones to alcohols.[1] In fact, contrary to the limited success (*ca.* 25% optical yield) of previous work on asymmetric reductions using similar kinds of chiral amine-borane complexes,[2a-e] the reagent prepared from (*S*)-(+)-2-amino-3-methylbutan-1-ol [(*S*)-valinol] and borane gave (*R*)-1-phenylpropan-1-ol in up to 60% stereoselectivity in the reduction of propiophenone.[1]

We report here a detailed study of the asymmetric reduction of aromatic ketones with the (*S*)-valinol–borane reagent to establish the optimum conditions for maximum stereoselectivity and discuss the structure of the reagent responsible for the asymmetric induction.

Results and Discussion

Upon addition of equimolar borane to (*S*)-valinol in tetrahydrofuran (THF) at −78 °C, hydrogen was liberated gradually at −60 °C and rapidly at −30 °C, and the evolution subsided within 1 h. Further addition of equimolar borane to the reaction mixture evolved hydrogen again. The total amount of hydrogen evolved was estimated to be 2.0 mol by hydrolysis of the resulting solution. This suggests that the initial reaction is that of borane with the hydroxylic group of (*S*)-valinol and then further borane reacts with the amino group. Amines are known to co-ordinate readily with borane to form stable amine-borane complexes,[3] and accordingly the reaction mixture may contain alkoxy-, amino-, and amine-borane derivatives. A detailed discussion of the structures of the reagents generated is given later.

Asymmetric reductions of n-propyl phenyl ketone were carried out with (*S*)-valinol to which varying quantities of borane had been added. The results, summarized in Table 1, showed that stereoselectivity depends critically upon the proportion of borane. The graphical representation shows that the stereoselectivity increases to a maximum, remaining almost constant at ratios of 2.0—3.0 : 1 of borane and (*S*)-valinol, and then decreases as more borane is added (Figure). Thus, the ratio of borane to (*S*)-valinol was found to be optimum at *ca.* 2—3 : 1, where up to 65—73% selectivity was obtained. At ratios higher than 3 : 1, excess of borane free from (*S*)-valinol may cause non-asymmetric reduction leading to lower stereoselectivity. This was confirmed by the following experiment. After treatment of (*S*)-valinol with 3.0—4.0 equimolar borane in THF, the excess of borane and solvent was evaporated off to give a white pasty solid; asymmetric reduction of n-propyl phenyl ketone with this compound afforded (*R*)-1-phenylbutan-1-ols in optical yields of 67—70%.

Table 1. Effect of the ratio [BH_3] : [(*S*)-valinol] on the optical yield in the reduction of n-propyl phenyl ketone in THF at 30 °C. The yield of the butanol was 100% unless stated otherwise

[BH_3] / [(*S*)-Valinol]	1-Phenylbutan-1-ol optical yield (%) [a]
0.5 [b]	0
0.9	0
1.0	3 (*R*)
1.1	13 (*R*)
1.7	47 (*R*)
2.0	68 (*R*) [69 (*R*)] [c]
2.2	69 (*R*) [67 (*R*)] [c]
2.5	73 (*R*)
3.0	65 (*R*) [70 (*R*)] [c]
4.0	45 (*R*) [69 (*R*)] [c]

[a] Values for maximum rotation and configuration taken from ref. 5f. [b] 99% Yield. [c] Yields were obtained with the reagent evaporated to dryness.

These results are in good agreement with those obtained at ratios of 2 : 1—3 : 1. Surprisingly, almost no asymmetric induction was observed with reagents prepared from 0.5—1.0 : 1 molar ratios of borane and (*S*)-valinol, although complex formation between borane and (*S*)-valinol was shown to occur by the evolution of hydrogen.

Reductions were fast and normally complete in 30 min at 30 °C with the ratios of borane to (*S*)-valinol in the range employed in this study. Consequently, the reagents involved must be highly reactive members of the general class of amine-borane complexes.[4]

The reagent prepared from a 2 : 1 ratio of borane to (*S*)-valinol was totally soluble in THF at a wide range of temperatures (50 to −78 °C). Lowering the reaction temperature to −30 °C unexpectedly gave slightly lower selectivities (Table 2).

A series of alkyl phenyl ketones were examined with the 2 : 1 reagent (Table 3). Increasing the length of the alkyl chains in the series led to higher stereoselectivities, as follows (% stereoselectivity in parentheses): methyl (49), ethyl (61), n-propyl (69), n-butyl (73). Substitution of the phenyl by a naphthyl group also gives higher selectivity as expected. In all instances, alcohols of predominantly *R* configuration were formed. Unfortunately, dialkyl ketones such as hexyl methyl ketone gave low optical yields.

A study of the effect of solvent on the reaction was carried out using the ' dried ' 2 : 1 reagent. The results are summarized in Table 4. This reagent was soluble in and unreactive towards a wide variety of protic and aprotic solvents, such as THF, diethyl ether, t-butyl alcohol, 1,4-dioxan, benzene, n-pentane,

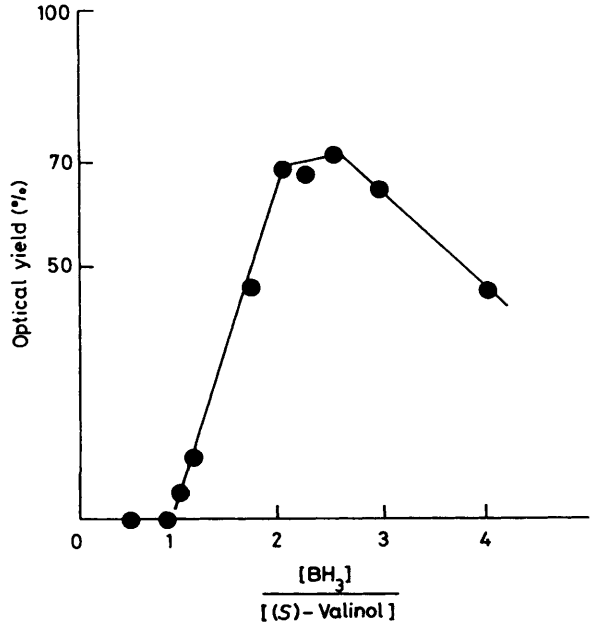


Figure. Effect of the ratio of borane : (*S*)-valinol on the optical yield in the reduction of n-propyl phenyl ketone in THF at 30 °C

Table 2. Effect of temperature on the optical yield for the reduction of n-propyl phenyl ketone with the reagent prepared from a 2 : 1 ratio of borane and (*S*)-valinol in THF.[a] The yield of butanol was 100% in each case

T (°C)	1-Phenylbutan-1-ol optical yield (%)
30	69 (*R*)
−30	62 (*R*)

[a] At −78 °C, the reaction was very sluggish and the amount of alcohol obtained was too small to measure optical yield.

Table 3. Asymmetric reduction of aromatic ketones with the reagent prepared from 2 : 1 borane and (*S*)-valinol in THF at 30 °C. The yield of alcohol was 100% in each case

	Alcohols produced		
Ketone	$[\alpha]_D^{25}$	Optical yield (%)	Absolute configuration
Methyl phenyl	+25.60 [a]	49	*R*
Ethyl phenyl	+28.48 [b]	61	*R*
Phenyl propyl	+29.90	69	*R*
Butyl phenyl	+22.78 [c]	73	*R*
Methyl β-naphthyl	+26.67 [d]	64	*R*
Hexyl methyl	−0.974 [e]	10	*R*

[a] In CH_2Cl_2 (U. Nagai, T. Shishido, R. Chiba, and H. Mitsuhashi, *Tetrahedron*, 1965, **21**, 1701). [b] In acetone (K. Kwart and D. P. Hoster, *J. Org. Chem.*, 1967, **32**, 1896). [c] In benzene (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). [d] In ethanol (S. R. Landor, B. J. Miller, and A. R. Tatchell, *J. Chem. Soc.*, 1966, 2282). [e] Neat (S. J. Cristol, B. Franzus, and A. Shadan, *J. Am. Chem. Soc.*, 1955, **77**, 2512.

chloroform, carbon tetrachloride, methanol, ethanol, and methanol–water (1 : 1, v/v). The reduction of n-propyl phenyl ketone in THF, benzene, n-pentane, and carbon tetrachloride led to (*R*)-1-phenylbutan-1-ols in reasonably high optical

Table 4. Effect of the solvent on the optical yield in the reduction of n-propyl phenyl ketone with the reagent from 2 : 1 borane and (*S*)-valinol at 30 °C. The yield of the butanol was 100% in each case

Solvent	1-Phenylbutan-1-ol optical yield %
THF	69 (*R*)
Benzene	54 (*R*)
Pentane	60 (*R*)
Carbon tetrachloride	55 (*R*)
t-Butyl alcohol	28 (*R*)

Table 5. Asymmetric reduction of n-propyl phenyl ketone with reagents from borane and various optically active amino alcohols in the ratio 2 : 1 in THF at 30 °C. The yield of the butanol was 100% in each case

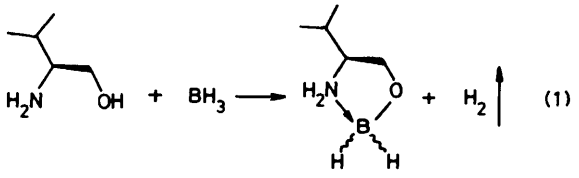
Amino alcohol	1-Phenylbutan-1-ol optical yield (%)
(*S*)-(+)-2-Amino-3-methylbutan-1-ol	69 (*R*)
(*S*)-(−)-2-Amino-3-methylpentan-1-ol	70 (*R*)
(*S*)-(−)-2-Amino-3-phenylpropan-1-ol	44 (*R*)
(*S*)-(+)-2-Amino-4-methylpentan-1-ol	49 (*R*)
(*S*)-(−)-2-Amino-3-methylthiopropan-1-ol	45 (*R*)
(*R*)-(−)-2-Amino-2-phenylethan-1-ol	32 (*S*)
(*S*)-(−)-2-Amino-3-benzylthiopropan-1-ol	57 (*R*)
(*S*)-(−)-2-Amino-3-[(*p*-benzyloxy)phenyl]propan-1-ol	68 (*R*)

yields (≥ 50%) whereas the reagent in t-butyl alcohol, although readily reduced, gave rather a low percentage asymmetric reduction.

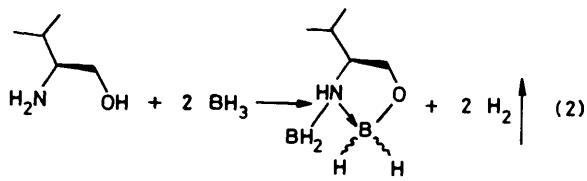
The effect of a chiral aminoalcohol on the selectivity in the present asymmetric reduction was examined using a 2 : 1 ratio of borane–aminoalcohol. The results are summarized in Table 5. Of the chiral aminoalcohols examined, (*S*)-(−)-2-amino-3-methylpentan-1-ol [(*S*)-isoleucinol] and (*S*)-(−)-2-amino-3-[(*p*-benzyloxy)phenyl]propan-1-ol [(*S*)-*O*-benzyltyrosinol] were most effective in asymmetric reduction as with (*S*)-valinol. An alcohol with the opposite configuration was obtained in the reduction with (*R*)-(−)-2-amino-2-phenylethan-1-ol [(*R*)-phenylglycinol]–borane.

Products from the Reaction of Borane and (S)-*Valinol in THF.*—Borane reacts readily with alcohols to give alkoxy-borane derivatives whereas it normally forms co-ordinated complexes with amines.[4] In the case of primary amines or unhindered secondary amines, however, complexation and a reaction involving liberation of hydrogen leading to amino-borane formation proceeded concurrently, but the latter reaction was usually slower. In the reaction of 1 : 1 borane with (*S*)-valinol, rapid evolution of hydrogen occurs at −50 to −30 °C and no further reaction is detected between −30 and 30 °C even after 24 h. The resulting solution was found to contain 2.0 equiv. of hydride by hydrolytic gasometry. It is reasonable to conclude that borane reacts preferentially with the hydroxy group of (*S*)-valinol, evolving 1 mol of hydrogen to afford alkoxy-borane co-ordinated with the amino group, *i.e.* the complex known as alkoxy-amine-borane (1), as shown in equation (1).

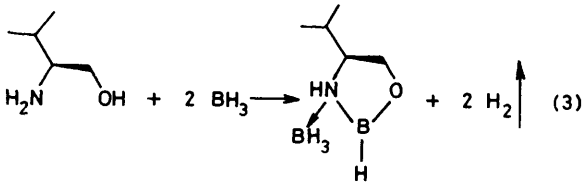
However, the reaction of n-propyl phenyl ketone with this reagent proceeded smoothly to give quantitative reduction in 30 min at 30 °C, but resulted in disappointingly low selectivity (*ca.* 3%). Consequently, complex (1), which was tentatively



(1)



(2)



(3)

proposed as the active agent,[1] is not responsible for the asymmetric reduction.

In the reaction of (*S*)-valinol with 2 equimolar borane in THF, hydrogen evolution was complete within 1 h at −50 to −30 °C, resulting in a solution which was estimated to contain 4.0 equimolar hydride by hydrolytic gasometry. This suggests that 2.0 mol of hydrogen were liberated through the following two reaction paths. The first one involves reaction of borane with the hydroxy group of (*S*)-valinol in a similar manner to that described for 1 : 1 (*S*)-valinol–borane, 1 mol of hydrogen thus being produced. The second one involves reaction of borane with the amino group to give the amino-borane, an additional 1 mol of hydrogen being evolved. Since no further uptake of hydrogen was observed after 24 h, the formation of $-B{=}N-$ or $-N(B\langle)_2$ bonds by the subsequent reaction might not occur. Since the amino group may co-ordinate to borane to form the amine-borane complex, possible candidates are species (2) and/or (3), as shown in equations (2) and (3). The structure of the reagent is now under investigation.

Experimental

All reactions were carried out under nitrogen. THF was dried over sodium wire and distilled over lithium aluminium hydride immediately before use. Benzene and n-pentane were washed with conc. H_2SO_4, dried over calcium chloride, and distilled over sodium wire. Carbon tetrachloride was distilled over phosphorus pentaoxide. t-Butyl alcohol was refluxed and distilled over potassium. Acetophenone, propiophenone, n-propyl phenyl ketone, n-butyl phenyl ketone, and n-hexyl methyl ketone were dried and distilled over calcium hydride. β-Naphthyl methyl ketone was obtained from Wako Pure Chemicals and used without purification. Borane was prepared by the reaction of sodium borohydride with trifluoroborane–diethyl ether according to the procedure of Brown.[5] The purities of all reagents were checked by g.l.c. or n.m.r. spectroscopy. All the materials described were stored under nitrogen prior to use.

G.l.c. was performed on a Simazu GC-6A instrument (injection port, TCD detector, and heated collector, temperature 250 °C; column temperature 150—230 °C) using a glass-coated analytical column (1.5 m × 3 mm) packed with PEG 20 M on Chromosorb. The ratios of alcohols and unchanged ketones were determined by their peak areas.

N.m.r. spectra were run on a Hitachi R-22 90-MHz spectrometer. Optical rotations were taken on a Zeiss visual polarimeter with readings to ±0.02 °C or on a JASCO DIPSL automatic electronic polarimeter using a 1-cm thermostatted microcell. I.r. spectra were measured with a JASCO IR-G instrument for Nujol mulls. T.l.c. was run on silica gel 60F-254 precoated plates with 9 : 1 (v/v) benzene–ethyl acetate or 1,2-dichloroethane as the mobile phase. Evolution of hydrogen was measured by Brown's method.[5]

(S)-(+)-2-*Amino*-3-*methylbutan*-1-*ol* [(S)-*Valinol*].—This compound was prepared by the reduction of (*S*)-valine (2-amino-3-methylbutyric acid) with lithium aluminium hydride in THF at reflux temperature for 3 h. After the usual work-up, (*S*)-valinol (70%) was obtained by fractional distillation under reduced pressure, b.p. 55—57 °C/2 mmHg, $[\alpha]_D^{25}$ +18.41° (*c*, 2.01 in ethanol) {lit.,[6] $[\alpha]_D^{25}$ +18.5° (*c*, 7.83 in ethanol)}.

Similarly, other chiral amino alcohols employed in this study were prepared in 50—90% yield by the reduction of the corresponding α-amino acids with lithium aluminium hydride in THF at reflux temperature for 3—10 h, followed by distillation or recrystallization. Their b.p.s, m.p.s, and $[\alpha]_D^{25}$ s are as follows. (*S*)-(−)-2-Amino-3-phenylpropan-1-ol, m.p. 91—93 °C, $[\alpha]_D^{25}$ −25.7° (*c*, 1.37 in ethanol) {lit.,[7] $[\alpha]_D^{25}$ −25.6° (*c*, 1.037 in ethanol)}.

(*R*)-(−)-2-Amino-2-phenylethan-1-ol, m.p. 75—76 °C, $[\alpha]_D^{25}$ −27.07° (*c*, 4.432 in methanol) {lit.,[7] $[\alpha]_D^{25}$ −27.1° (*c*, 5.36 in methanol)}.

(*S*)-(−)-2-Amino-3-methylpentan-1-ol, b.p. 56—57 °C/3 mmHg, $[\alpha]_D^{25}$ −3.62° (*c*, 3.35 in ethanol) {lit.,[8] $[\alpha]_D^{25}$ −3.6° (*c*, 1.776 in ethanol)}.

(*S*)-(−)-2-Amino-3-methylthiopropan-1-ol, b.p. 60—62 °C/3 mmHg, $[\alpha]_D^{25}$ −9.68° (*c*, 2.71 in ethanol) {lit.,[7] $[\alpha]_D^{25}$ −9.7° (*c*, 1.481 in ethanol)}.

(*S*)-(+)-2-Amino-4-methylpentan-1-ol, 64—65 °C/1.5 mmHg, $[\alpha]_D^{25}$ +1.27° (neat) {lit.,[6] $[\alpha]_D^{25}$ +1.21° (neat)}.

(*S*)-(−)-2-Amino-3-benzylthiopropan-1-ol, m.p. 31—33 °C, $[\alpha]_D^{25}$ −48.55° (*c*, 3.444 in chloroform).

(*S*)-(−)-2-Amino-3-[(p-benzyloxy)phenyl]propan-1-ol, b.p. 169—176 °C/0.5 mmHg, $[\alpha]_D^{29}$ −16.1° (*c*, 5.91 in ethanol).

General Procedure for Asymmetric Reduction of n-Propyl Phenyl Ketone with the Reagent Prepared from Borane and (S)-*Valinol in THF at* 20 °*C*.—A solution of borane (20 mmol) in THF (10 ml) was added dropwise to a stirred solution of (*S*)-valinol (10 mmol) in THF (5 ml) at −50 °C during *ca.* 20 min. The resulting solution was gradually warmed to 30 °C and stirring continued at 30 °C for 10 h; a solution of n-propyl phenyl ketone (8 mmol) in THF (5 ml) was then added dropwise during 5 min. The resulting mixture was stirred at 30 °C for 1 h, and then decomposed by the addition of 2M-HCl (10 min). The hydrolysed mixture was extracted with ethyl acetate (3 × 10 ml) and the extract was washed with saturated NaCl solution (2 × 10 ml), dried ($MgSO_4$), and evaporated to give a colourless oil. The ratio of alcohol to unchanged ketone was determined by g.l.c. The crude product was then chromatographed on silica gel, with 1,2-dichloroethane as eluant, and distilled (bulb-to-bulb) to give 1-phenylbutan-1-ol (1.12 g, 93% of isolated material) which was characterized by i.r. and n.m.r. spectroscopy and was homogeneous on g.l.c. and t.l.c. The optical rotation for the benzene solution was $[\alpha]_D^{25}$ +29.90° (*c*, 5.00 in benzene). The optical

yield (69%) was calculated by the observed optical rotation and the known maximum rotation of 1-phenylbutan-1-ol.

A number of other asymmetric reductions using different reagents such as ketones, other chiral amino alcohols, *etc.*, were performed under conditions similar to those described above. The results are summarized in Table 1—5.

References

1 A. Hirao, S. Itsuno, S. Nakahama, and N. Yamazaki, *J. Chem. Soc., Chem. Commun.*, 1981, 315.
2 (*a*) J. C. Fiaud and H. B. Kagan, *Bull. Soc. Chim. Fr.*, 1969, 2742; (*b*) R. F. Borch and S. R. Levitan, *J. Org. Chem.*, 1972, **37**, 2347; (*c*) M. F. Grundon, D. G. McCleery, and J. W. Wilson, *Tetrahedron Lett.*, 1976, 295; (*d*) T. Yamashita, H. Mitsui, H. Watanabe, and N. Nakamura, *Makromol. Chem.*, 1980, **181**, 2563; (*e*) M. F. Grundon, D. G. McCleery, and J. W. Wilson, *J. Chem. Soc., Perkin Trans. 1*, 1981, 231.
3 G. C. Andrews and T. C. Crawford, *Tetrahedron Lett.*, 1980, 693, 697.
4 A. Pelter and K. Smith in ' Comprehensive Organic Chemistry,' ed. D. N. Jones, Pergamon, Oxford, 1979, vol. 3, pp. 689—940.
5 ' Organic Syntheses *via* Boranes,' ed. H. C. Brown, John Wiley and Sons, New York, 1975.
6 A. I. Meyers, G. S. Poindexter, and Z. Brich, *J. Org. Chem.*, 1978, **43**, 892.
7 H. Seki, K. Koga, H. Matsuno, S. Ohki, I. Matsuno, and S. Yamada, *Chem. Pharm. Bull.*, 1965, **13**, 995.

Received 4*th October* 1982; *Paper* 2/1697