Asymmetric Synthesis Using Chirally Modified Borohydrides. Part 2. Enantioselective Reduction of Ketones with Polymeric (*S*)-Prolinol–Borane Reagent

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Chiral polymeric reagents have been prepared from polymeric (*S*)-prolinols and borane and used in the enantioselective reduction of a series of prochiral ketones under various conditions. Reductions with these polymeric reagents are shown to give alcohols of reasonably good optical purity (up to 80%). The results are compared to those obtained with (*S*)-*N*-benzylprolinol–borane complex which is a soluble model reagent.

Polymer-supported reagents have a wide range of uses in organic chemistry owing to the ease of product isolation, the simple work-up procedures, and the fact they can be readily recovered and recycled. The increased interest in these reagents is exemplified by the numerous recent reviews.[1–3] However, only a few polymer-supported chiral reagents have been synthesized so that the full potential of these polymeric reagents for asymmetric synthesis has not been realized.[4–7]

We have already reported the asymmetric reduction of aromatic ketones using complexes of borane with optically active β-amino alcohols which gave the corresponding secondary alcohols with 73—95% stereoselectivity.[8–11] In an extension of this method, we synthesized a polymer-bound (*S*)-pyrrolidin-2-ylmethanol by the reaction of chloromethylated polystyrene gel with (*S*)-pyrrolidinylmethanol [(*S*)-prolinol], and then treated it with borane to give the polymeric chiral borane reagent. This reduced ethyl phenyl ketone enantioselectively to give (*R*)-1-phenylpropan-1-ol in an optical yield of 61%. The polymer reagent was easily recovered and re-used.[12]

In this paper, we describe further investigations of the synthesis of chiral polymeric reagents with various degrees of cross-linking and functionalization, and their application to the asymmetric reduction of prochiral ketones. We were interested in the effect of the polymer-attached reagent on the stereochemical course of the reaction and in the design of polymer reagents suitable for asymmetric synthesis.

Results and Discussion

Asymmetric Reduction of Propiophenone with Optically Active (S)-N-*Alkylprolinol–Borane Complexes.*—Before any detailed investigation of asymmetric reduction using polymer-bound prolinols was carried out, we examined the effectiveness of using *N*-substituted prolinol derivatives. The results are summarized in Table 1. The optical yield in the reduction of ethyl phenyl ketone was apparently affected by the *N*-substituent of the prolinol derivative. *N*-Benzylprolinol–borane reagent gave the highest optical yield, followed by the *N*-cyclohexyl derivative, with the *N*-hexyl and *N*-2-phenylethyl derivatives giving lower yields; the *N*-methylprolinol–borane reagent failed to induce asymmetric reduction, which may be partially due to the steric bulkiness of the *N*-substituent group. Thus it seems likely that the attachment of *N*-benzylprolinol onto the polymer backbone would give an effective polymeric reagent for asymmetric reduction.

Table 1. Asymmetric reduction of ethyl phenyl ketone with optically active (*S*)-1-alkylpyrrolidin-2-ylmethanol–borane complexes in THF at 30 °C. The alcohol was produced in 100% yield in each case

(*S*)-1-Alkylpyrrolidin-2-ylmethanol Alkyl	1-Phenylpropan-1-ol Optical yield (%)[a]
Methyl	0
Hexyl	16 (*R*)
Cyclohexyl	64 (*R*)
Benzyl	67 (*R*)
2-Phenylethyl	29 (*R*)

[a] Values for maximum rotation and configuration taken from K. Kwart and D. P. Hoster, *J. Org. Chem.*, 1967, **32**, 1896.

In the course of this reaction, we found that the stereoselectivity depends critically upon the ratio [borane]:[(*S*)-*N*-benzylprolinol]. When the reagent was prepared from a 1.0:1 molar ratio of these compounds, for example, almost no reduction occurred and the starting ketone was recovered. The reagent produced from a 2.0:1 ratio reduced ethyl phenyl ketone quantitatively to give the (*R*)-alcohol in only 17% optical yield. However, when the excess of borane was evaporated off after treatment of (*S*)-*N*-benzylprolinol with 2.0 mol equiv. of borane in tetrahydrofuran (THF), the asymmetric reduction of ethyl phenyl ketone with the resulting white pasty solid afforded (*R*)-1-phenylbutan-1-ol in an optical yield of 67%. To find the optimum conditions, the asymmetric reduction of ethyl phenyl ketone was repeated with (*S*)-*N*-benzylprolinol to which varying quantities of borane had been added. We found that the reagent prepared with a ratio of starting compounds of 2.0:1 and then evaporated to dryness gave the highest (67%) stereoselectivity. Similar results were obtained with the polymeric reagents in the same asymmetric reduction. Consequently, we used the 'dried' 2:1 reagent in all experiments unless stated otherwise.

The i.r. spectrum of the dried reagent showed that the hydroxy band disappeared in the course of the reduction and new bands at 2 376, 2 345, 1 311, and 1 169 cm^{-1} appeared; these are possibly due to the >B–H (2 376 and 2 345 cm^{-1}), >B–O (1 311 cm^{-1}), and ⩾B←N⩽ bonds (1 169 cm^{-1}), respectively, suggesting that the reagent contains the alkoxyborane (RO–B<) and amine–borane (⩾N→B⩽) moieties resulting from the reaction of the hydroxy group of (*S*)-*N*-benzylprolinol with borane and the co-ordination of the

amino group to borane. Some possible structures for the reagent (which could be a mixture of more than one of these) are shown in the Figure.

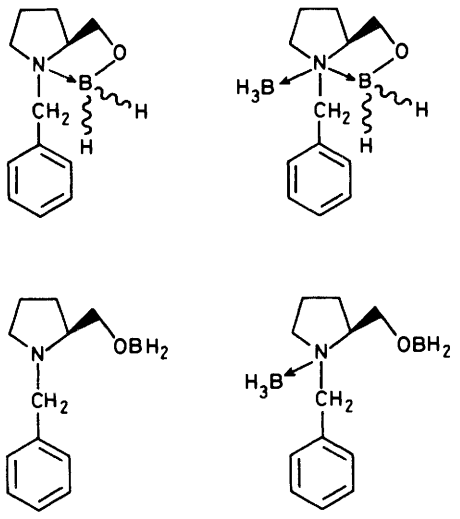
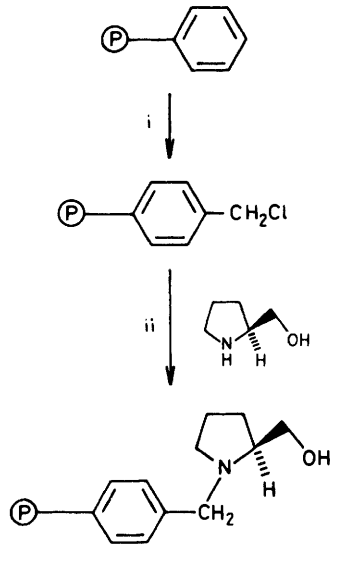


Figure. Possible structures for the (*S*)-*N*-benzylprolinol–borane reagents

The species responsible for the asymmetric reduction and the analogous chiral aminoalcohol–borane complexes, which reduce ketones asymmetrically in good to excellent optical yields (73—95%),[8–11] will be discussed in detail in a later publication.

Synthesis of the Polymeric Reagent from Polymer-bound (S)-*Pyrrolidin-2-ylmethanol and Borane.*—Polystyrene was treated with chloromethyl methyl ether and stannic chloride to introduce the *p*-chloromethyl group in the usual fashion.[13] Subsequent reaction with (*S*)-pyrrolidin-2-ylmethanol [(*S*)-prolinol] in the presence of anhydrous potassium carbonate in toluene gave the polymer-bound chiral aminoalcohol. The reaction proceeds as shown in Scheme 1, as confirmed by i.r.



(1)

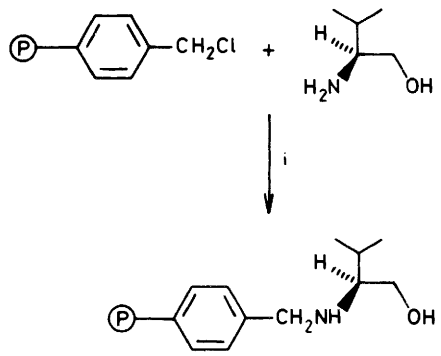
Scheme 1. *Reagents:* i, $MeOCH_2Cl$, $SnCl_4$; ii, K_2CO_3

spectroscopy, elemental analysis, and the model reaction of benzyl chloride and (*S*)-prolinol under the same conditions. These reactions were carried out with both swellable cross-linked (1, 2, 5, and 8%) and soluble polystyrene of molecular weight 100 000. Additionally, a macroporous polystyrene bead (non-swellable), highly cross-linked with 20% divinylbenzene, was used.

After several experiments we found that almost complete amination could be achieved by the use of an excess (1.6 times) of (*S*)-prolinol and K_2CO_3 in refluxing toluene for 20 h. The results are summarized in Table 2. The reaction was conveniently shown to be complete by the Beilstein test and by the disappearance of the characteristic i.r. absorption at 1 250 cm^{-1} attributed to the chloromethyl group, and the confirmation was given by elemental analysis.

This method gave a high degree of ring substitution (up to 82%), with the swellable 1% cross-linked polystyrene resin. Similarly, the use of a chiral prolinol-bound macroporous resin with a high degree of cross-linking (20%) gave quantitative conversion. With the soluble chloromethylated polystyrene, gelation occurred during the course of reaction under these conditions to produce a weakly cross-linked polymer, the chloromethyl group of which was almost converted into an (*S*)-prolinol group. Thus, this amination reaction enables a wide range of reasonably reproducible polymer attachments to be achieved.

(*S*)-(+)-2-Amino-3-methylbutan-1-ol [(*S*)-valinol] reacted less efficiently with the chloromethylated polystyrene under identical conditions (Scheme 2). In this case, the reaction was



Scheme 2. *Reagents:* i, K_2CO_3, toluene

much slower, only reaching completion after 72 h unless an excess (6 times) of (*S*)-valinol was used, as indicated in Table 3.

For comparison, both (*S*)-*N*-benzylprolinol and (*S*)-*N*-benzylvalinol were prepared, in excellent yields, as model compounds by treatment of (*S*)-prolinol or (*S*)-valinol with benzyl chloride under identical conditions. Their optical purities were confirmed by comparing the optical rotations with known values.[14,15] This suggests that the reactions proceed as shown in Schemes 1 and 2 and that no racemization takes place.

Each of the polymeric enantioselective reducing agents was then prepared by treatment of the polymer (**1**) with an excess (2 times) of borane in THF, followed by evaporation under reduced pressure to remove any unchanged borane. The i.r. spectra of the resulting polymers show characteristic >B–H (2 368 and 2 345 cm^{-1}), >B–O (1 319 cm^{-1}), and ⇒B←N⇐ (1 169 cm^{-1}) absorption bands which are not present in the starting polymers (**1**). The hydroxy absorption band disappeared in all cases. These absorptions are very similar to those observed in the (*S*)-*N*-benzylprolinol–borane complex, thus showing that the chirally modified borane complex could be supported on the solid phase.

Table 2. Results of the amination of chloromethylated polystyrenes with (*S*)-prolinol

Cross-linking in copolymer (%)	Chloromethylated ring substitution in the polystrene (%)	Ring substitution in the polystyrene-bound (*S*)-prolinol (**1**) (%)	Conversion (%)	Polymer yield (%)
0	97	98	101	99
1	14	15	107	90
1	69	68	99	90
1	81	82	101	92
2	50	51	102	95
2	56	56	100	100
2	79	81	103	91
5	41	41	100	90
8	73	68	93	92
20	27	27	100	98

Table 3. Results of the amination of 1% chloromethylated polystyrenes with (*S*)-valinol

Ring substitution in the chloromethylated polystyrene (%)	[(*S*)-Valinol]/[$-CH_2Cl$]	Reaction time (h)	Ring substitution in the polystyrene-bound (*S*)-valinol (%)	Conversion (%)	Polymer yield (%)
14	2.0	24	9.5	68	90
14	2.0	72	13.6	97	94
69	1.5	24	52	75	90
81	2.0	24	67	83	99
81	4.0	24	74	91	99
81	6.0	24	79	98	92

Table 4. Effect of degree of cross-linking and of the functionalization of the (*S*)-prolinol moiety on the asymmetric reduction of phenyl propyl ketone with various (**1**)–borane complexes in THF at 30 °C

		1-Phenylbutan-1-ol		
Degree of cross-linking (%)	Degree of functionalization (%)	Chemical yield (%)	Optical yield (%)	Absolute configuration
1	14	85	61	*R*
1	69	94	75	*R*
1	82	82	52	*R*
2	50	87	80	*R*
2	56	90	72	*R*
8	73	17	*a*	
20[b]	27	95	58	*R*

[a] The yield of alcohol was too small to permit measurement of the optical rotation. [b] Non-swellable macroporous polystyrene gel.

Asymmetric Reduction of Prochiral Ketones with Polymeric Chirally Modified Borane Complexes.—The stereoselectivity of reduction with the polymeric reagents may be influenced by the degree of ring functionalization and of cross-linking of the polymer support. To investigate these effects several different polymeric reagents of the type (**1**)–borane complex were prepared and used in the asymmetric reduction of prochiral ketones. Those investigated included a wide range of 1, 2, and 8% cross-linked swellable resins with varying degrees of functionalization from substitution of the (*S*)-prolinol moiety (14—82%), and the highly cross-linked (20%) macroporous non-swellable resin with 27% substitution. For comparison, the same reduction was carried out using the structural analogue, (*S*)-*N*-benzylprolinol–borane complex, as a soluble model reagent.

The results of the asymmetric reduction of phenyl propyl ketone with polymeric reagents are shown in Table 4. The most remarkable finding is that the optical yield of alcohol obtained is influenced by the degree of functionalization, and better optical yields are obtained with the polymeric reagents, in some cases 62% greater than from the corresponding soluble reagent. With a small degree of functionalization (14%), the selectivity from the polymeric reagent was comparable with that in solution. However, under the same conditions, polymeric reagents with a moderate degree of functionalization (50—69%) were notably more selective than the soluble reagent. The highest optical yield (80%) was obtained with the 1% cross-linked polymeric reagent with 50% functionalization. This was 20% higher than that obtained by the same reduction in solution. The selectivity, however, decreased when the degree of functionalization of the polymeric reagent was 82%. No appreciable difference in selectivity was observed between the 1 and 2% cross-linked polymer reagents.

The rates of reduction with polymeric reagents were generally slower than those with the soluble reagents and were affected significantly by the degree of cross-linking; the reductions reached completion in less than 20 h in solution, whereas the polymeric reagents with 1 or 2% cross-linking required 48—72 h to reach 70—100% conversion. 56% Conversion with the 5% cross-linked reagent was obtained in 72 h. When the 8% cross-linked polymer was used, the ketones were reduced much more slowly and the reductions were far from complete even after 170 h. The inefficiency is presumed to be due to poor transport of ketone into the rigid polymer matrices. Interestingly, the

Table 5. The asymmetric reduction of ketones with (**1**)–borane complex in THF at 30 °C

Ketone	Alcohol produced[a] Chemical yield (%)	Optical yield (%)	Absolute configuration
Methyl phenyl	99 (99)	23[b] (20)	*R* (*R*)
Ethyl phenyl	79 (100)	60[c] (67)	*R* (*R*)
Phenyl propyl	94 (98)	75[d] (59)	*R* (*R*)
Butyl phenyl	100	73[e]	*R*
Butyl methyl	100 (100)	0 (20)[f]	*R* (*R*)
Isobutyl methyl	100 (100)	9.8[f] (33)	*R* (*R*)
t-Butyl methyl	100 (100)	43[f] (44)	*R* (*R*)

[a] Values in parentheses were obtained from asymmetric reduction with (*S*)-*N*-benzylprolinol–borane complexes in THF at 30 °C. [b] In CH_2Cl_2 (U. Magai, T. Shishido, R. Chiba, and H. Mitsuhashi, *Tetrahedron*, 1965, **21**, 1701). [c] In acetone (K. Kwart and D. P. Hoster, *J. Org. Chem.*, 1967, **32**, 1896). [d] In benzene (R. Noyori, I. Tomino, and Y. Tanimoto, *J. Am. Chem. Soc.*, 1979, **101**, 3129). [e] In benzene (J. P. Mazaleyrat and D. J. Cram, *J. Am. Chem. Soc.*, 1981, **103**, 4585). [f] Neat (S. R. Landor, B. J. Miller, and A. R. Tatchell, *J. Chem. Soc. C*, 1966, 2280).

Table 6. The effect of the solvent on the optical yield from the asymmetric reduction of phenyl propyl ketone with (**1**)–borane complex at 30 °C

Solvent	1-Phenylbutan-1-ol[a] Chemical yield (%)	Optical yield (%)	Absolute configuration
THF	94 (98)	75 (59)	*R* (*R*)
1,4-Dioxane	16 (94)	(34)	(*R*)
1,2-Dimethoxyethane	5 (99)	(48)	(*R*)
Benzene	50 (70)	39 (40)	*R* (*R*)
Methanol–water (2:1)	36 (54)	0 (0)	

[a] Values in parentheses were obtained from asymmetric reduction with (*S*)-*N*-benzylprolinol–borane complex at 30 °C.

reagent prepared from macroporous resin, though highly cross-linked and non-swellable in THF, exhibited the same reactivity and selectivity as the swellable polymeric reagents with 1 and 2% cross-linking.

The reduction of a series of alkyl phenyl ketones and dialkyl ketones with the 1% cross-linked polymeric reagent with 69% (*S*)-prolinol substitution was investigated and the results compared with those obtained with (*S*)-*N*-benzylprolinol–borane complex in THF at 30 °C (Table 5). The relatively high optical yields obtained from the aromatic ketones with the polymeric reagent are comparable to those obtained with the soluble one. The same absolute configuration of the alcohols obtained is also observed. In the reduction of butyl methyl ketones it appears that the bulky substituent adjacent to the carbonyl group has a significant effect. Thus, in the butyl series, n-butyl, isobutyl, t-butyl, the maximum stereoselectivity is obtained with t-butyl which has the greatest steric hindrance. A similar trend was observed with the polymeric reagent, although it reduced the ketones less selectively.

A study of the solvent effect on the reduction was carried out using the same polymeric reagent. The results are summarized in Table 6. The (*S*)-*N*-benzylprolinol–borane complex, a soluble reagent, was found to be soluble in and unreactive towards a wide variety of protic and aprotic solvents. The reduction of phenyl propyl ketone in THF, 1,2-dimethoxyethane, 1,4-dioxane, or benzene gave the (*R*)-1-phenylbutan-1-ol in good optical yield (34—59%); however, no asymmetric reduction occurred in methanol–water (2:1). With the polymeric reagent, both chemical and optical yields were noticeably affected by changing the solvent. The optical yield of the alcohol obtained was highest in THF and moderate in benzene, while in 1,2-dimethoxyethane and 1,4-dioxane the reductions were very slow and the amounts of alcohol obtained were too small to permit measurement of the optical rotation. This is probably due to the slow diffusion of the ketone into the entangled polymer network, as the polymer appears to be much less swollen in the last two solvents. No asymmetric reduction occurred in methanol–water (2:1) with the polymeric reagent. The choice of solvent is thus very important with the polymer reagent.

Table 7. Recycling of the (**1**)–borane complex in the reduction of ethyl phenyl ketone in THF at 30 °C

(**1**)–Borane complex	1-Phenylpropan-1-ol Chemical yield (%)	Optical yield (%)	Absolute configuration
Original	79	57	*R*
1st Recycle	93	58	*R*
2nd Recycle	93	61	*R*

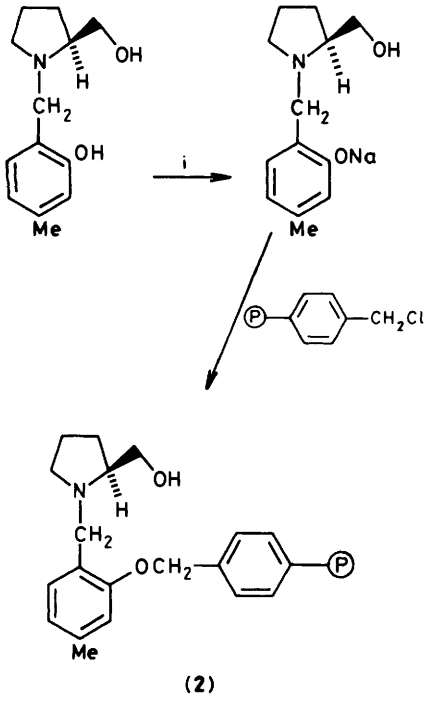
As pointed out in a number of studies, one of the major advantages of a polymeric reagent is the ease with which it can be worked up and recycled. The polymer-bound (*S*)-prolinol–borane reagents used could be conveniently separated from the reaction mixture by simple filtration and recycled after treatment with borane. The results are summarized in Table 7. Both optical and chemical yields gave reproducible values when re-used twice. However, the polymer support was ground to a fine powder by stirring after several runs. This made the work-up procedure very difficult to carry out and recycling of the polymer inefficient. The same problem was encountered even with the highly cross-linked macroporous resin. The polymer reagents therefore require very careful handling.

Asymmetric Reduction of Prochiral Ketones with the (**2**)*–Borane.*—As mentioned before, the rates of reduction with the polymeric reagents were slower than with the corresponding soluble reagents, and were significantly affected by the degree of cross-linking of the polymer supports. In particular, the reduction was very slow with the 8% cross-linked polymeric reagent with only 17% conversion after 170 h at 30 °C.

Recently, Montanari and co-workers[16] found that the rates of the reaction with polymer-bound phase transfer catalysts are markedly improved by inserting some suitable spacers between the catalytic function and the polymer backbone. To make use of this spacer effect, we synthesized another type of (*S*)-*N*-benzylprolinol-bound polymer support (**2**) in which the (*S*)-*N*-benzylprolinol moiety is separated from the polystyrene backbone by a benzylic ether linkage. It is proposed that this reaction proceeds as shown in Scheme 3 and this assumption was confirmed by i.r. spectroscopy and elemental analyses.

The polymeric reagent could then be prepared by treatment with an excess of borane, followed by evaporation. The results of the asymmetric reduction with the 2% cross-linked polymeric (**2**)–borane reagent are summarized in Table 8. The optical yields obtained with the polymeric reagent are comparable to those obtained with the (*S*)-*N*-benzylprolinol–borane reagent, although, strictly speaking, it is not an exact model in this case. In the reduction of acetophenone, a better optical yield was obtained with the polymeric reagent. The same absolute configuration of the products is also observed in all runs.

The polymeric reagent from the polymer (**2**) was found to reduce ketones somewhat faster than that from (**1**), the former



Scheme 3. *Reagents:* i, NaH, *N*-methylpyrrolidone

reduction, for example, reaching completion in 48 h, whereas the latter reagent requires 48—72 h to reach 70—100% conversion. The following result more clearly reveals the superiority of the polymeric reagent from (**2**) over that from (**1**) with respect to the reaction rate. With the 8% cross-linked polymeric reagent from (**2**), phenyl propyl and butyl phenyl ketones are reduced to the corresponding (*R*)-alcohols in 90 and 96% chemical and 56 and 68% optical yields, respectively. Under identical conditions, the reduction of both ketones with the 8% cross-linked polymeric (**1**)–borane reagent gives very poor yields (< 5%) of the desired alcohols. Thus, we are able to improve effectively the reduction yield by inserting a benzylic ether linkage as a spacer in the polymeric reagent. Finally, it should be noted that the 8% cross-linked polystyrene beads (swellable) are much stronger mechanically and easier to work with than the swellable 1 and 2% cross-linked and 20% cross-linked macroporous non-swellable polystyrene beads which proved to be rather fragile and were ground to a fine powder after several experiments.

Experimental

All reactions were carried out under nitrogen. THF, 1,4-dioxane, and 1,2-dimethoxyethane were dried over sodium wire and distilled over lithium aluminium hydride immediately before use. Benzene was washed with conc. H_2SO_4, dried over calcium chloride, and distilled over sodium wire. Acetophenone, ethyl phenyl ketone, phenyl n-propyl ketone, n-butyl phenyl ketone, methyl n-butyl ketone, isobutyl methyl ketone, and methyl t-butyl ketone were dried and distilled over calcium hydride. Borane was prepared by the reaction of sodium borohydride with trifluoroborane–diethyl ether complex according to the procedure of Brown.[17] The purities of all reagents were checked by g.l.c. or n.m.r. spectroscopy. All the materials described here 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 JEOL JNM-PMX 60 (60 MHz) spectrometer. Optical rotations were taken on a Zeiss visual polarimeter, reading 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 pre-coated plates with benzene–ethyl acetate (9:1 v/v) or 1,2-dichloroethane as the mobile phase. Evolution of hydrogen was measured by Browns method.[17]

Table 8. Asymmetric reduction of ketones with the (**2**)–borane[a] complex in THF at 30 °C

Ketone	Alcohols produced: Chemical yield (%)	Optical yield (%)	Absolute configuration
Methyl phenyl	100 (99)[b]	58 (20)	*R* (*R*)
Ethyl phenyl	100 (100)	49 (67)	*R* (*R*)
Phenyl propyl	100 (98)	58 (59)	*R* (*R*)
Butyl phenyl	100	71	*R*
Butyl methyl	100 (100)	25 (20)	*R* (*R*)
Isobutyl methyl	100 (100)	27 (33)	*R* (*R*)
t-Butyl methyl	100 (100)	44 (44)	*R* (*R*)

[a] 2% Cross-linking and 53% substitution of (*S*)-*N*-benzylprolinol. [b] Values in parentheses were obtained from asymmetric reductions with (*S*)-*N*-benzylprolinol–borane complex in THF at 30 °C.

(S)-(+)-*Pyrrolidin-2-ylmethanol* [(S)-*Prolinol*].—This compound was prepared by the reduction of (*S*)-proline (supplied by Kyowa Hakko Co.) with lithium aluminium hydride ($LiAlH_4$) in THF at reflux temperature for 3 h. After the usual work-up, (*S*)-prolinol was obtained in 54% yield by fractional distillation under reduced pressure, b.p. 64—66 °C/1 mmHg, $[\alpha]_D^{25}$ +31.00° (*c*, 1.5 in benzene) {lit.,[18] $[\alpha]_D^{20}$ +31.6° (*c*, 1.0 in benzene)}.

(S)-(+)-2-*Amino*-3-*methylbutan*-1-*ol* [(S)-*Valinol*].—This compound was similarly obtained in 70% yield from the reaction of (*S*)-valine with $LiAlH_4$ in THF; b.p. 55—57 °C/2 mmHg, $[\alpha]_D^{25}$ +18.41° (*c*, 2.01 in ethanol) {lit.,[15] $[\alpha]_D^{25}$ +18.5° (*c*, 7.83 in ethanol)}.

(S)-1-*Benzylpyrrolidin-2-ylmethanol* [(S)-*Benzylprolinol*].—This compound was prepared by the reaction of (*S*)-prolinol with benzyl chloride in the presence of anhydrous K_2CO_3 in refluxing toluene according to the previously reported procedure,[14] b.p. 90—92 °C/0.2mmHg, $[\alpha]_D^{25}$ −59.9° (*c*, 1.0 in chloroform) {lit.,[14] $[\alpha]_D^{25}$ −59.5° (*c*, 2.0 in chloroform)}.

(S)-2-*Benzylamino*-3-*methylbutan*-1-*ol* [(S)-*Benzylvalinol*].—This compound was similarly prepared by the reaction of (*S*)-valinol with benzyl chloride, according to the above procedure of (*S*)-benzylprolinol; b.p. 103—107 °C/0.2 mmHg, $[\alpha]_D^{25}$ +2.8° (*c*, 8.70 in ethanol) {lit.,[15] $[\alpha]_D^{25}$ +3.4° (*c*, 4.21 in ethanol)}.

(*S*)-1-Hexylpyrrolidin-2-ylmethanol and (*S*)-1-(2-phenylethyl)pyrrolidin-2-ylmethanol were similarly prepared by the reaction of (*S*)-prolinol with n-hexyl bromide and 2-phenylethyl bromide, respectively. Their b.p.s and $[\alpha]_D^{25}$ values are as follows. (S)-1-*Hexylpyrrolidin*-2-*ylmethanol*, b.p. 70—75 °C/1 mmHg, $[\alpha]_D^{25}$ −53.51° (*c*, 5.162 in dichloroethane) (Found: C, 70.8; H, 13.0; N, 7.5. $C_{11}H_{23}NO$ requires C, 71.2; H, 12.4;

N, 7.6%). (S)-1-(2-*Phenylethyl*)*pyrrolidin*-2-*ylmethanol*, b.p. 110 °C/4.5 mmHg, $[\alpha]_D^{25}$ −61.39° (*c*, 4.216 in chloroform). This compound is very hygroscopic and therefore satisfactory elemental analyses were not obtained. Both (*S*)-1-hexylpyrrolidin-2-ylmethanol and (*S*)-1-(2-phenylethyl)pyrrolidin-2-ylmethanol were characterized by n.m.r. spectroscopy.

(S)-1-*Cyclohexylpyrrolidin*-2-*ylmethanol* [(S)-*Cyclohexylprolinol*].—(*S*)-Prolinol (55 mmol) was added to 85% formic acid (55 mmol) rapidly with cooling with an ice-bath, and cyclohexanone (110 mmol) was added. The mixture was then refluxed for 5 h. After being cooled, the solution was poured into several volumes of water, acidified with 2M-HCl, and extracted with benzene to remove unchanged cyclohexanone. To the aqueous solution was added conc. aqueous NaOH (10 g). The resulting solution was extracted with chloroform (3 × 10 ml), dried ($MgSO_4$), and evaporated to give a colourless oil. (*S*)-Cyclohexylprolinol was obtained in 24% yield by fractional distillation under reduced pressure, and characterized by n.m.r., b.p. 40 °C/1 mmHg, $[\alpha]_D^{25}$ +73.92° (*c*, 3.118 in benzene).

(S)-1-(1-*Hydroxy*-3-*methylphenylmethyl*)*pyrrolidin*-2-*ylmethanol*.—Into a 500-ml baffled round-bottomed flask were placed (*S*)-prolinol (106 mmol), paraformaldehyde (106 mmol), and ethyl alcohol (100 ml). The resulting suspension was heated to reflux for 1 h until a homogeneous solution was obtained. *p*-Cresol (85 mmol) was then added and the resultant mixture was refluxed for 168 h. The desired *compound* was obtained in 90% yield by evaporation of solvent, followed by fractional distillation under reduced pressure, and was characterized by n.m.r.; δ($CDCl_3$) 7.0—6.0 (3 H, m, aromatic), 4.6—4.1 (2 H, m, OH), 4.0—2.4 (7 H, $-NCH(CH_2OH)CH_2CH_2CH_2$) 2.2 (3 H, s, CH_3), 2.1—1.4 (4 H, $NCHCH_2CH_2CH_2$), b.p. 130—140 °C/1 mmHg, $[\alpha]_D^{20}$ −53.07° (*c*, 2.516 in ethanol) (Found: C, 70.2; H, 9.1; N, 6.5. $C_{13}H_{19}NO_2$ requires C, 70.6; H, 8.6; N, 6.3%).

Polymer-bound (S)-*Prolinol* (**1**).—These were prepared from 1, 2, 5, or 8% cross-linked polystyrene resin, 200—400 mesh (Bio Beads S-X1, S-X2, S-5X, or S-X8 purchased from Bio Rad Laboratory) or 20% cross-linked macroporous polystyrene resin, 20—40 mesh (Mitsubishi Kasei Co.). These beads were chloromethylated as previously reported.[13] (*S*)-Prolinol (4.6 g, 46 mmol) was treated with chloromethylated polystyrene, 1% cross-linking (4.8 g, 28 mmol Cl) in the presence of anhydrous K_2CO_3 at reflux temperature (*ca.* 110 °C) in toluene for 20 h. After the polymer had been filtered off, the polymer bead was washed successively with water, methanol, THF, THF–water, THF, and methanol. It was vacuum dried at 40 °C to yield compound (**1**) (6.5 g) [Found: C, 79.0; H, 8.9; N, 5.95; Cl, 0.0. Calc. for polymer-bound (*S*)-prolinol with 84% substitution: C, 78.66; H, 8.67; N, 5.91; Cl, 0.00%]. All manipulations of the resin were carried out with care to avoid weight losses, as the change in weight was used to estimate the degree of substitution. The resulting polymer contained no chlorine and the nitrogen analysis showed that almost all the chloromethyl groups were converted into (*S*)-2-hydroxymethylpyrrolidin-1-yl groups. The degree of ring substitution was 82% in this case. The yield of the polymer seemed to be almost quantitative from the weight increase.

Polymer-bound (*S*)-valinol was similarly prepared from chloromethylated polystyrene gel and (*S*)-valinol.

Polymer-bound (S)-N-*Benzylprolinol* (**2**).—Into a 300-ml round-bottomed flask were placed (*S*)-1-(hydroxy-3-methylphenylmethyl)pyrrolidin-2-ylmethanol (18.6 g, 85 mmol) and dry *N*-methylpyrrolidone (100 ml) under nitrogen. Sodium hydride (2.04 g, 85 mmol) was added slowly with stirring. The resultant mixture was stirred until the evolution of hydrogen ceased. Chloromethylated polymer resin (2% cross-linking S-X2; 12.76 g, 52.6 mmol Cl) was added and the resultant mixture was stirred at 50 °C for 72 h under nitrogen. The polymer was collected by filtration, washed successively with water, methanol, THF, THF–water, THF, and methanol, and vacuum dried at 50 °C to yield the resin (20.6 g). The resulting polymer contained no chlorine and the nitrogen microanalysis showed that almost all the chloromethyl groups were converted into (*S*)-*N*-benzylprolinol moieties. The yield of the polymer was 92% based on weight increase.

General Procedure for the Asymmetric Reduction of Ketones with the Polymeric Reagent Prepared from the Polymer-bound (S)-*Prolinol* (**1**) *and Borane*.—Polymeric reagent was prepared by treatment of compound (**1**) (1.72 g, 10 mmol) with an excess of borane (20 mmol) in THF, initially at −60 °C and then at 30 °C overnight, followed by evaporation of the unchanged borane under reduced pressure (10^{-1} mmHg) for 5 h. The polymeric reagent thus formed was allowed to swell in THF (20 ml) under nitrogen. To this suspension was added a solution of phenyl propyl ketone (1.18 g, 8 mmol) in THF (5 ml) with stirring, and the resulting mixture was thermostatted at 30 ± 0.5 °C for 72 h. After hydrolysis with 2M-HCl, the polymer (**1**) was filtered off by suction, and was recovered almost quantitatively as its HCl salt. The resulting aqueous solution 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. (82% conversion). The crude product was then chromatographed on silica gel with 1,2-dichloroethane as eluant and distilled by bulb-to-bulb distillation to give 1-phenylbutan-1-ol (0.855 g, 71% of isolated material); it was characterized by i.r. and n.m.r. spectroscopy and was shown to be homogeneous by t.l.c. and g.l.c. analyses. The optical rotation for the benzene solution was $[\alpha]_D^{25}$ +23.50° (*c*, 2.00 in benzene). The optical yield, 52%, 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 polymeric reagents, ketones, solvents, *etc.*, were performed under conditions similar to those described above. The results are summarized in Tables 1—8.

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