Asymmetric reduction of acetophenone *O*-methyloxime with the reagent prepared from borane and polymer-supported (*S*)-(−)-2-amino-3-(4-hydroxyphenyl)-1,1-diphenylpropan-1-ol

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Copolymerization of a new optically active amino alcohol monomer, (*S*)-(−)-2-amino-1,1-diphenyl-3-[4-(4-vinylphenylmethoxy)phenyl]propan-1-ol (**2**), with styrene provided a linear copolymer (LC) containing 33 mol% of **2**. The suspension copolymerization of **2** with styrene and divinylbenzene (DVB) provided crosslinked insoluble polymers (gel **2**) containing 10 mol% of **2** which swelled in THF. Another polystyrene-supported chiral amino alcohol (gel **1**) was also prepared from chloromethylated 2% crosslinked polystyrene gel and (*S*)-(−)-2-amino-3-(4-hydroxy)-1,1-diphenylpropan-1-ol (**1**). Addition of borane to the polymer-supported optically active amino alcohols gave the polymeric chiral reducing agents. Acetophenone *O*-methyloxime was reduced asymmetrically with the polymer reagent prepared from well swollen gel **2** at room temperature to yield the optically active 1-phenylethylamine in very high enantioselectivity (~99% *ee*).

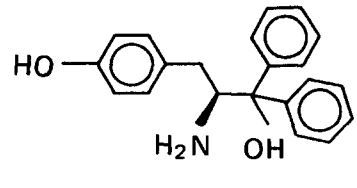
(Keywords: asymmetric reduction; polymer-supported chiral amino alcohol; acetophenone *O*-methyloxime; amino alcohol–borane complex)

INTRODUCTION

Although optically active amines are of importance for the preparation of synthetic drugs, resolving agents and natural compounds, there are few examples of asymmetric synthesis to yield optically active amines. Optically active amines are generally obtained either by optical resolution of racemic amines with chiral carboxylic acids or by complicated derivatization from natural products. One of the easiest methods of obtaining optically active amine is considered to be an asymmetric reduction of the oxime ether, which is easily prepared from ketones and known to be reduced easily with borane (BH_3·THF) to afford primary amines in good yield. We have previously reported that the asymmetric reduction of oxime ethers with the reagents prepared from chiral amino alcohols and borane gave optically active primary amines with high enantioselectivity (~99% *ee*)[1-3].

Many significant advantages have been pointed out when performing the asymmetric induction with polymer supports, particularly because the expensive chiral auxiliary reagents can generally be recovered by simple filtration[4-7]. Thus far, only a few studies concerning the polymeric reducing agents have been reported. On the basis of the above results, polymer-supported chiral amino alcohol–borane reagents have also been prepared and used for the asymmetric reduction of oxime ethers. Unfortunately, only low enantioselectivities (17–26% *ee*) resulted from the use of polymer-supported **1** (gel **1**)–borane complex, which was prepared by chemical modification of crosslinked polystyrene gel[3].

We report here the preparation of a new chiral monomer and its linear and crosslinked copolymers, which were used as a chiral auxiliary for asymmetric reduction of the oxime ether. The effect of the preparation method of polystyrene-supported chiral amino alcohol **2** on optical yield of amine was also investigated. The polymer-supported chiral amino alcohol (gel **2**) obtained by the copolymerization of the chiral monomer, styrene and divinylbenzene (DVB) gave much higher *ee* values (~99% *ee*) than gel **1** in the asymmetric reduction of acetophenone *O*-methyloxime, in spite of the fact that gel **2** should have apparently the same chemical structure as that of gel **1**. The polymer-supported reagents achieved the same enantioselectivity as their homogeneous counterparts, and they were able to be recycled by simple filtration and reused without a significant loss of activity.



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(*S*)-(−)-2-amino-3-(4-hydroxy)-1,1-diphenylpropan-1-ol

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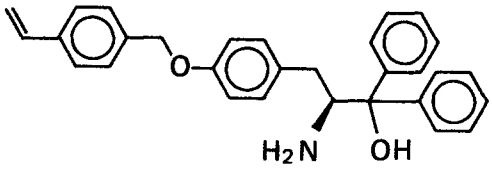


2

(*S*)-(−)-2-amino-1,1-diphenyl-3-[4-(4-vinylphenylmethoxy)phenyl] propan-1-ol

EXPERIMENTAL

Tetrahydrofuran (THF) was distilled over sodium wire and over lithium aluminium hydride immediately before use. *N,N*-Dimethylformamide (DMF) and 4-vinylbenzyl chloride were distilled over calcium hydride under reduced pressure. Sodium hydride, α,α'-azobisisobutyronitrile (AIBN) and benzoyl peroxide were used as supplied commercially. Styrene and divinylbenzene (DVB) were treated with aqueous sodium thiosulphate solution. Acetophenone *O*-methyloxime was prepared by the reaction of acetophenone oxime and methyl iodide[8]. Borane was prepared by the reaction of sodium borohydride with boron trifluoride–diethyl ether complex according to the procedure of Brown[9].

N.m.r. spectra were taken on a Jeol JNM-GX270 spectrometer. Melting points were determined on a Yanagimoto micro-melting-point apparatus. Optical rotations were taken on a Jasco DIP-140 digital polarimeter using a 1 cm or 10 cm thermostatted microcell.

(S)-(−)-2-Amino-3-(4-hydroxyphenyl)-1,1-diphenylpropan-1-ol(**1**)

1 was prepared from L-tyrosine according to the routes described previously[3].

(S)-(−)-2-Amino-1,1-diphenyl-3-[4-(4-vinylphenylmethoxy)phenyl]propan-1-ol (**2**)

1 (5.0 g, 15.7 mmol) and 50 ml of dry DMF were placed in a 200 ml round-bottomed flask under nitrogen. Sodium hydride (0.38 g, 15.7 mmol) was added slowly with stirring. After evolution of hydrogen was completed, 4-vinylbenzyl chloride (2.52 g) in dry DMF (20 ml) was added and the resulting mixture was stirred at room temperature for 5 h under nitrogen. The water layer was extracted with ethyl acetate (3 × 30 ml) and the extract was dried ($MgSO_4$) and evaporated to give a pale yellow solid. The crude product was recrystallized from ethanol–ethyl acetate–H_2O (80/10/10 vol%) to give white needles. Yield, 5.5 g, 80%. M.p., 160–163°C. ^1H n.m.r., δ ($CDCl_3$), 7.68–6.76 (18H, m), 6.71 (1H, q), 5.74 (1H, d), 5.24 (1H, d), 5.01 (2H, s), 4.51 (1H, s), 4.11 (1H, dd), 2.38 (2H, dd), 1.22 (2H, s). $[\alpha]_D^{25}$, −45.14° (*c*, 0.607 in THF). Elemental analysis: found, C 82.2, H 6.55, N 3.11; $C_{30}H_{29}NO_2$ requires C 82.7, H 6.7, N 3.2.

Linear copolymer (LC)

Radical copolymerization of **2** (4.36 g) with styrene (3.13 g) using AIBN (67 mg) as initiator was carried out in THF for 70 h at 60°C in an evacuated tube. The polymer was precipitated into methanol, reprecipitated from THF into methanol, washed with methanol and dried under reduced pressure. The linear copolymer (yield, 6.0 g; $[\alpha]_D^{25}$, −27.04° (*c*, 0.652 in THF)) thus obtained was confirmed to have been satisfactorily purified by the fact that g.p.c. showed no peak due to monomers. According to elemental analysis (C 87.1, H 7.0, N 2.2) the polymer contains 33 mol% amino alcohol unit.

Gel **1**

Gel **1** was prepared from **1** and 2% crosslinked chloromethylated polystyrene gel according to the routes described previously[3].

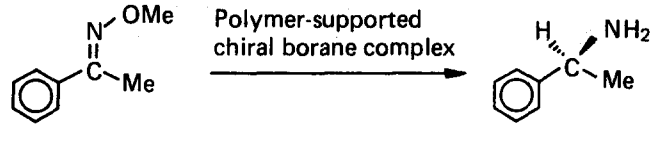
Gel **2**

To a well stirred solution of 0.4 g of poly(vinyl alcohol) in 230 ml of water heated to 50°C was added a solution of 6.54 g of **2**, 10.9 g of styrene, 3.9 g of DVB and 0.5 g of benzoyl peroxide in 50 ml of THF and 50 ml of benzene. The temperature was raised to 80°C and the reaction mixture was stirred vigorously for 18 h. The resulting beads were filtered and washed with water. Further washing with 50 ml each of water–methanol, methanol, THF and methanol followed by drying under reduced pressure at 40°C afforded the desired copolymer (yield, 19.5 g). Elemental analysis (C 89.1, H 7.4, N 1.1) showed that the polymer contained 10 mol% amino alcohol unit.

Gel **3**

Styrene (7.62 g), DVB (2.4 g) and **2** (0.24 g) were copolymerized in the presence of gel **2** (19.0 g) in a similar manner as gel **2**. The resulting polymer was washed and dried under reduced pressure at 40°C. Yield, 28.5 g. Elemental analysis: C 90.1, H 7.5, N 0.75.

Asymmetric reduction of acetophenone O-methyloxime



These reactions were carried out as previously described[3]. The product 1-phenylethylamine was characterized by i.r. and n.m.r. spectroscopy. The optical yield was calculated by the observed optical rotation and the known maximum rotation ($[\alpha]_D^{22}$, −40.3° (neat)) of (*S*)-1-phenylethylamine[10].

RESULTS AND DISCUSSION

Preparation of polymer-supported chiral amino alcohols

The required chiral auxiliary reagent can be introduced onto a polystyrene support in two ways. One process involves functionalization of polystyrene gel followed by supporting reaction. Another method involves copolymerization of substituted styrene monomers plus styrene and DVB to give the chiral polymer directly. We have prepared three types of polymer-supported chiral amino alcohols including the linear copolymer for application to the asymmetric synthesis (*Figure 1*). Gel **1** was easily prepared from chloromethylated polystyrene gel with the chiral amino alcohol **1** containing a hydroxyphenyl group[3].

Linear copolymer (LC) was obtained by radical copolymerization of styrene and **2**. The new optically active monomer **2** was prepared by the reaction between

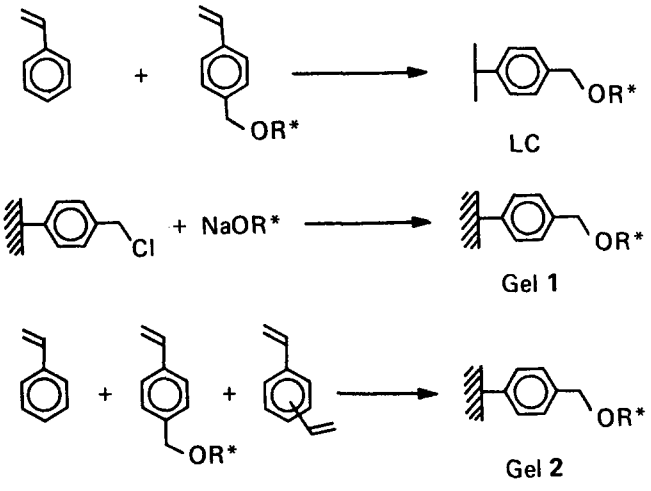


Figure 1 Preparation of polymer-supported chiral amino alcohols

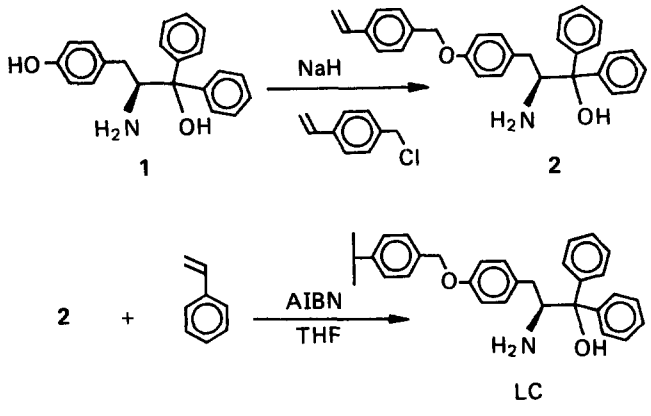


Figure 2 Preparation of chiral linear copolymer (LC)

4-vinylbenzyl chloride and **1** derived from L-tyrosine (*Figure 2*).

Gel **2** was prepared by copolymerization of the chiral monomer **2** and styrene in the presence of DVB (*Figure 3*).

(*S*)-(−)-2-Amino-3-(4-benzyloxyphenyl)-1,1-diphenylpropan-1-ol (**3**), the monomeric model chiral auxiliary, was also prepared by the same method as that of **2** (*Figure 4*).

Asymmetric reduction of acetophenone O-methyloxime with the polymer-supported chiral amino alcohol–borane complex

We have previously reported that the chiral reducing agent prepared from borane and optically active amino alcohol could reduce oxime ethers to give chiral primary amines with very high enantioselectivity[1,2]. In the first place, the chiral linear copolymer (LC) was used as chiral auxiliary reagent in the asymmetric reduction of acetophenone *O*-methyloxime. Asymmetric reductions of the oxime ether were carried out by using a procedure similar to that in a previous paper[2]. Although LC was very soluble in THF, the borane complex could not be dissolved at the same concentration level as that of the monomeric complex. As shown in *Table 1*, when 9 ml of THF per gram of polymer was used (runs 2 and 3), after addition of borane the resulting complex became a gel, which could not be stirred effectively by a magnetic stirring bar. This gelation served to slow down the rate of reaction and lowered enantioselectivity (58–69% *ee*) compared with the monomeric model reagent (run 1). Both homogeneity and optical yield increased with the amount of THF. More than 15 ml of THF per gram of LC gave a clear solution of the chiral polymer–borane complex. Indeed, the use of 18 ml of THF per gram of LC made the chiral polymeric borane complex homogeneous and gave the chiral product 1-phenylethylamine in a high optical purity equivalent to the results of monomeric model reagent (runs 5–7). The chiral linear copolymer (LC) was easily recovered and regenerated by precipitation. The regenerated polymer could be used for the same reaction to give the chiral product without significant loss of activity.

Results of the asymmetric reduction using crosslinked polymers are summarized in *Table 2*. As previously reported, asymmetric reduction of the oxime ether by the use of gel **1** prepared by chemical modification of polystyrene gel gave (*S*)-1-phenylethylamine in low optical yield (17–26% *ee*)[3]. Since high enantioselectivity was obtained by use of LC in a clear solution, a crosslinked but highly swellable polymer reagent also should realize the same selectivity as the monomeric reagent. This was indeed found with gel **2** prepared by suspension copolymerization. This gel, containing only 10 mol% of the chiral amino alcohol, swelled very well in

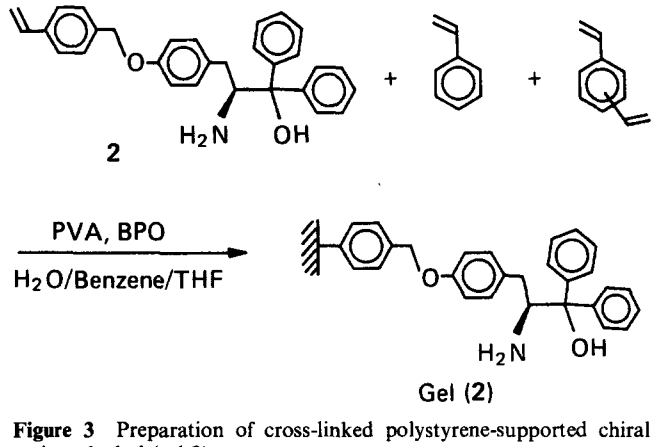


Figure 3 Preparation of cross-linked polystyrene-supported chiral amino alcohol (gel **2**)

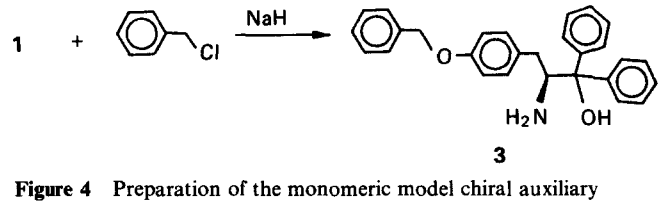


Figure 4 Preparation of the monomeric model chiral auxiliary

Table 1 Asymmetric reduction of acetophenone *O*-methyloxime with LC–borane complex in THF

Run	Concentration, THF/polymer (ml/g)	1-Phenylethylamine[a]		Solubility of the complex
		% *ee*	Config.	
1[b]	7.5	94	*S*	Clear soln
2	9.0	60	*S*	Gel
3[c]	9.0	58	*S*	Gel
4	13.5	81	*S*	Viscous soln
5	18.0	95	*S*	Clear soln
6[c]	18.0	89	*S*	Clear soln
7[c]	18.0	93	*S*	Clear soln

[a] Isolated yields were 85–95% in all cases
[b] Monomeric model reagent (**3**) was used
[c] Recovered polymer was used

Table 2 Asymmetric reduction of acetophenone *O*-methyloxime with crosslinked polymer-supported amino alcohol–borane complex

Run	Polymer-supported chiral amino alcohol	Concentration THF/Polymer (ml/g)	1-Phenylethylamine[a]		Swellability[b] in THF
			% *ee*	Config.	
1	Gel **1**	5.5	18	*S*	2.5
2	Gel **1**	16.5	18	*S*	2.5
3	Gel **2**	7.1	99	*S*	3.7
4[c]	Gel **2**	7.1	98	*S*	3.7
5	Gel **3**	2.3	58	*S*	1.5

[a] Isolated yields were 85–95% in all cases
[b] Ratio of the volume of dried gel and in THF
[c] Recovered gel was used

THF so that their active sites should show behaviour similar to that in LC, as observed. Importantly, gel **2** was recovered quantitatively by simple filtration and regenerated without appreciable loss of activity (*Table 2*, run 4).

The only defect in the asymmetric reduction using gel **2** is that well swollen gel **2** becomes fragile by vigorous stirring for a long time. That would cause some difficulties in handling. In such a case, slow stirring by mechanical stirrer is recommended. Increasing mechanical strength of the gel could also remove the above defect. Gel **3** prepared by copolymerization of styrene, DVB and **2** in the presence of gel **2** was less fragile and required less care in handling. Asymmetric reduction of the oxime ether with gel **3**–borane complex, however, gave the chiral amine with somewhat low enantioselectivity (*Table 2*). A low degree of swelling may have brought about lowering the selectivity. Another improvement of the polymer-supported chiral auxiliary may be introduction of the spacer chain, which would be suitable for the asymmetric reduction in this system because a linear polymer-like behaviour may be expected.

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