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Polymer-Supported Chiral 1,2-Diamines by Radical Copolymerization with Vinyl Monomer for Asymmetric Hydrogenation of Aromatic Ketones

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Summary: Novel polymer-supported chiral 1,2-diamines have successfully synthesized by radical copolymerization of *N*-Boc protected enantiopure 1,2-diamine bearing two vinylphenyl moieties ((*S*,*S*)-**5**) with various achiral vinyl monomer including methyl methacrylate, 2-hydroxyethyl methacrylate, butyl acrylate, and *N*-isopropyl acrylamide, followed by deprotection of *N*-Boc moiety. Hydrogenation of acetophenone in 2-propanol/DMF mixed solvent was performed with use of polymeric catalyst system prepared from the polymer-supported chiral 1,2-diamine and $RuCl_2$/(*S*)-BINAP. The reaction proceeded smoothly to give 1-phenylethanol in quantitative yield with high level of enantioselectivity. In addition, various other aromatic ketones could be asymmetrically hydrogenated by the polymeric catalyst system. Furthermore, the polymeric catalyst could be reused several times in hydrogenation of aromatic ketones without loss of the enantioselectivity.

Keywords: catalysts; chiral; metal-polymer complexes; radical polymerization; supports

Introduction

Enantiomerically pure 1,2-diamines are widely used as chiral auxiliary in chiral catalysts and reagents for asymmetric synthesis.[1] Especially, C_2-symmetric chiral 1,2-diphenylethylenediamine (DPEN), 1,2-cyclohexanediamine, or their derivatives have been complexed with transition metal reagents and the resulting complexes are well known to be effective asymmetric catalysts for various asymmetric reactions.

Design and synthesis of polymer-supported asymmetric catalysts have also been developed by the progress of asymmetric catalysts. The polymer-supported catalysts have been used in various asymmetric reactions mainly for the purpose of their facilitated separation from the reaction mixture. In fact, a considerable number of papers on the immobilization of chiral catalyst to polymer have been reported.[2–6] When paying attention to chiral ligand of polymer-supported asymmetric catalysts, amino alcohol, diol, and amino acid have been reported vigorously so far. In contrast, immobilization of enantiopure 1,2-diphenylethylenediamine is quite limited, which is probably because of difficulty in its immobilization reaction with maintaining the primary amino groups.

We have recently designed and synthesized novel crosslinked polystyrene-supported chiral 1,2-diamines (Figure 1) by radical polymerization of styrene derivatives bearing *N*-Boc protected 1,2-diamine moieties, followed by deprotection of the *N*-Boc moiety.[7–9] The crosslinked polymers could be complexed with $RuCl_2$/(*S*)-BINAP[10] and the resulting polymeric catalysts were used for asymmetric hydrogenation of aromatic ketones. The aromatic ketones were hydrogenated quantitatively to give the corresponding chiral secondary alcohols in excellent yield with high level of enantioselectivity (Ee). Crosslinked

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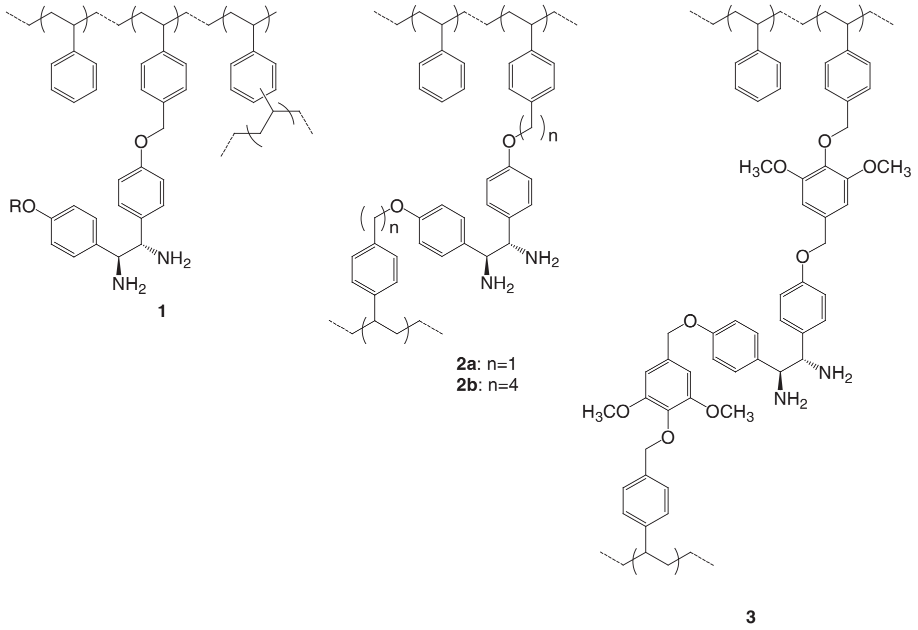


Figure 1.
Polystyrene-supported Chiral 1,2-Diamines.

polystyrene is presently the overwhelming choice as polymer-support because it fulfills many of the requirements such as mechanical, chemical, and thermal stability. In addition to the crosslinked polystyrene, various kinds of polymer-supports are required for diversification of the usage. Vinyl monomers that undergo radical polymerization can be one of the good candidates as monomers for polymer-support. Similar synthetic procedure to the preparation of crosslinked polystyrene can be applied. Furthermore, the property of polymer-support can be easily expected because most polymers obtained by radical polymerization of vinyl monomers have been well studied.

Herein, we report synthesis of novel polymer-supported chiral 1,2-diamine by radical polymerization of *N*-Boc protected 1,2-diphenylethylenediamine derivatives bearing two vinylphenyl groups ((*S*,*S*)-**5**) and various achiral vinyl monomers. The polymers were applied to asymmetric hydrogenation of aromatic ketones.

Experimental Part

Materials

N, *N*-Dimethylformamide (DMF), *p*-vinylbenzyl chloride, methyl methacrylate (MMA), isoproyl methacrylate (iPMA), butyl methacrylate (BMA), methyl acrylate (MA), butyl acrylate (BA), *N*, *N*-dimethyl acrylamide (DMAA), and *N*-isopropyl acrylamide (iPAA) were distilled from calcium hydride (CaH_2) under reduced pressure. 2-Hydroxyethyl methacrylate (HEMA) was dissolved in water and extracted with heptane and distilled twice under reduced pressure. All ketones used were distilled twice from CaH_2 under argon immediately before use.

Measurements

HPLC analyses were performed with a JASCO HPLC system composed of 3-line degasser DG-980-50, HPLC pump PV 980, column oven CO-965, equipped with a chiral column (CHIRALCEL OD or CHIRALCEL AD, Daicel) using hexane/

2-propanol as an eluent. A UV detector (JASCO UV-975) was used for the peak detection. GC analyses of reaction conversion were performed with a Shimadzu Capillary Gas Chromatograph 14B equipped with a capillary column (SPERCO β-DEX 325 or β-DEX 120, 30 m × 0.25 mm).

Synthesis of (*S,S*)-1,2-Diamine Monomer Bearing Two Vinylphenyl Moieties

A 30 mL round-bottom flask equipped with a magnetic stirring bar was charged with (*S,S*)-**4**[7] (0.50 g, 1.1 mmol), K_2CO_3 (0.93 g, 6.8 mmol), and 5.0 mL of dry DMF. *p*- Vinylbenzyl chloride 0.69 g (4.5 mmol) was then added to the mixture at 0 °C, and the mixture was stirred at rt for 24 h. The volatiles were completely removed with a vacuum pump, and 20 mL of water was added. The suspension was transferred to a glass filter and was washed with water and hexanes. Further purification by silica gel column chromatography with 8:1 (*v*/*v*) $CHCl_3/CH_3OH$ as an eluent yielded the 1,2-diamine monomer (*S,S*)-**5** (0.62 g, 83%).

General Procedure for Copolymerization of Chiral 1,2-Diamine Monomer (*S,S*)-5 with Achiral Vinyl Monomer

A 20 mL glass ampoule equipped with magnetic stirring bar was charged with (*S,S*)-**5** (0.295 mmol), achiral vinyl monomer (5.6 mmol), AIBN (13 mg, 80 µ mol), and 2.0 mL of DMF. After three cycles of freeze-thaw under liquid nitrogen, the ampoule was sealed and then heated at 70 °C. After 24h, the ampoule was opened and the resulting mixture was poured into methanol. The resulting polymer was washed with THF and methanol and dried at 40 °C under high vacuum. The resulting polymer was then transferred to a flask containing 15 mL of 4*N* HCl in THF solution at rt and stirred for 5 h. The insoluble polymer was filtered and washed with THF, water and THF again. The chiral 1,2-diamine hydrochloride polymer was then treated with THF (20 mL)/triethylamine (20 mL) mixture at rt for 12 h. The polymer was collected on a glass filter and washed with THF, water, and methanol and dried at 40 °C under high vacuum for 20 h. The polymer-supported 1,2-diamines were obtained in 75-99% yields.

Asymmetric Hydrogenation of Acetophenone by Using Polymer-supported Chiral 1,2-Diamine/$RuCl_2$/(*S*)-BINAP

A 20 mL Schlenk vessel equipped with a Teflon-coated magnetic stirring bar was charged with polymer-supported chiral 1,2-diamine (0.02 mmol), $RuCl_2$/(*S*)-BINAP[10] (0.01 mmol) and 2 mL of dry DMF. The above mixture was degassed and heated to 80 °C. After 2.5 h, DMF was removed under reduced pressure and the polymeric complex was obtained as red solid.

Air presented in a 100 mL glass autoclave equipped with a pressure gauge and a gas inlet tube attached to a hydrogen source was replaced with argon. A solution of acetophenone (0.85 mL, 5.0 mmol) in a 1:1 mixture of 2-propanol (2 mL) and DMF (2 mL), a 1.0 M *tert*-BuOK solution in *tert*-BuOH (0.1 mL), and the resulting polymeric complex were added to the autoclave. Hydrogen was then added to the autoclave and pressurized to 1 MPa. The reaction mixture was stirred at 30 °C for 5 h. After the venting of the hydrogen gas, the reaction mixture was diluted with ethyl acetate (10 mL) and filtered through a short silica gel column. The solvent was removed under reduced pressure, and the conversion was determined by GC analysis. The Ee was determined by HPLC analysis (CHIRALCEL OD, Daicel; hexanes/2-propanol = 20:1, 0.4 mL/min, 30 °C, $t_R(R) = 22.8$ min, $t_R(S) = 25.9$ min.). In case of reuse system, only solution of the reaction mixture was carefully taken out via gas-tight syringe and acetophenone, *tert*-BuOK, solvent, and hydrogen gas were newly added for the next reaction.

Asymmetric Hydrogenation of Other Aromatic Ketones

The procedures were as same as that of acetophenone. The conversion and enantiomeric excess of resulting alcohols were determined by GC and HPLC analysis, respectively.

Results and Discussion

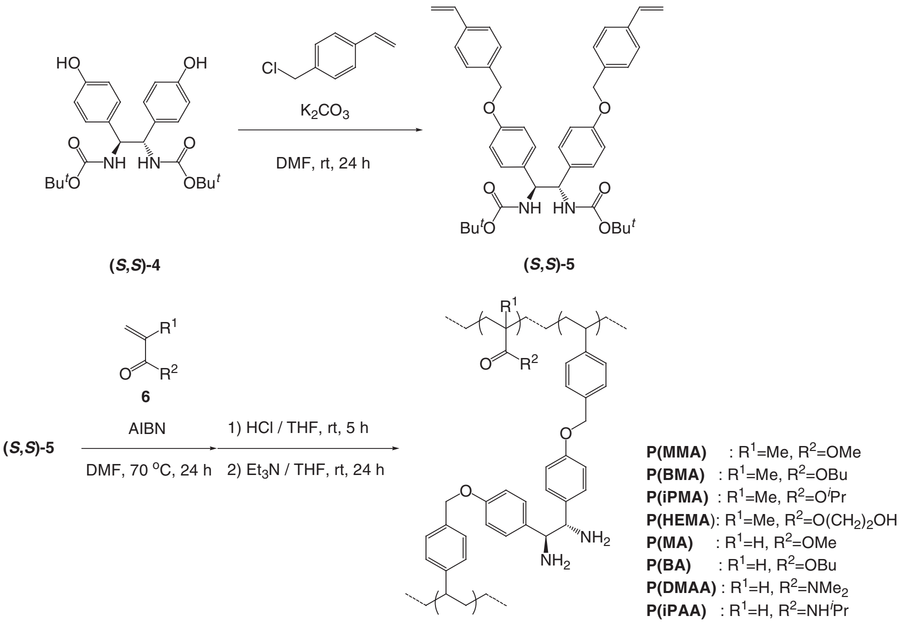
Synthesis of Polymer-supported 1,2-Diamine

The synthetic procedure of polymer-supported chiral 1,2-diamine is illustrated in Scheme 1. Introduction of vinylphenyl group was successfully carried out by a Williamson reaction of (*S*,*S*)-**4**[7] with *p*-vinylbenzyl chloride in DMF at room temperature for 24 h. The (*S*,*S*)-**5** was isolated by column chromatography on silica gel by using hexanes as an eluent in 83% yield.

(*S*,*S*)-**5** was then copolymerized with achiral vinyl monomer (**6**) such as methacrylate, acrylate, and acrylamide under general radical polymerization conditions. The solution became a gel after 1–5 h at 70 °C. *tert*-Butoxycarbonyl (*tert*-Boc) group of the resulting polymers were readily eliminated by a treatment with HCl in THF. In FT-IR spectrum, absorption of 1710 cm^{-1}, which was assigned to carbonyl of *tert*-Boc, completely disappeared with this treatment. After neutralization with triethylamine, free primary amino groups on the polymer were detected by a bromophenol blue test of the polymer. The 1, 2- diamine content, determined by the nitrogen analysis of polymer, was in fair agreement with that calculated. Final yields of these polymers are more than 75% up to 99%. These results indicated that a series of poly(methacrylate)-, poly(acrylate)-, and poly(acrylamide)-supported chiral 1,2-diamines were successfully synthesized by the radical polymerization and the following deprotection. Although these resulting polymers had network structures and were insoluble, they swelled well in $CHCl_3$, THF and DMF because of the flexible cross-linkages caused by (*S*,*S*)-**5**.

Preparation and NMR Analysis of Polymer-supported 1,2-Diamine/$RuCl_2$/(*S*)-BINAP Complex.

To apply the resulting polymers for asymmetric hydrogenation of aromatic ketones, polymer-supported (*S*,*S*)-1,2-diamines were



Scheme 1.
Synthesis of Polymer-supported 1,2-Diamines.

treated with $RuCl_2$/(*S*)-BINAP in DMF at 80 °C for 2 h. A reddish-brown DMF solution containing the $RuCl_2$/(*S*)-BINAP gradually became colorless as the complex formed on the polymer. We succeeded in ^{31}P NMR spectrum measurement of the resulting complex in $CDCl_3$, which indicated that complex was formed quantitatively on the polymer.

Asymmetric Hydrogenation of Acetophenone by the Polymer-supported Complex Prepared from Poly(methacrylate)s, Poly(acrylate)s, and Poly(acrylamide)s.

At first, asymmetric hydrogenation of acetophenone by using the **P(MMA)**/$RuCl_2$/(*S*)-BINAP complex was carried out. These results were summarized in Table 1. In general, 2-propanol is known to be the most suitable solvent for the hydrogenation using (*S*,*S*)-DPEN/$RuCl_2$/(*S*)-BINAP system to give high enantioselectivity with quantitative conversion for various kinds of aromatic ketones.[11] However, no reaction occurred in 2-propanol with the catalysts prepared from both **2a** and **P(MMA)**, which were thoroughly shrank in the solvent (entry 1).

In order to increase the affinity of the polymer with alcoholic solvent, a mixed solvent system was employed. We have found that a mixed solvent system (2-propanol/DMF = 1/1 (v/v)) worked very well in the case of polymeric catalyst derived from **2a**. Acetophenone was completely hydrogenated by using crosslinked PS-based complex within 5 h to give (*R*)-1-phenylethanol with 76% ee (entry 18). We have tested the asymmetric hydrogenation of acetophenone by using the catalyst prepared from **P(MMA)** in the 2-propanol/DMF mixed solvent. The reaction at 30 °C proceeded smoothly within 5 h in the mix solvent to afford (*R*)-1-phenylethanol in 78% ee (entry 2). Although lowering the

Table 1.
Asymmetric Hydrogenation of Acetophenone with Polymer-supported Chiral Catalyst.[a)]

Entry	Chiral 1,2-Diamine Polymer	Temp. (°C)	Time (h)	1-Phenylethanol		
				Conv. (%)	Ee (%)	*Config.*
1	**P(MMA)**[b)]	30	24	0	–	–
2	**P(MMA)**	30	5	>99	78	*R*
3	**P(MMA)**	10	24	96	80	*R*
4[c)]	**P(MMA)**	30	5	>99	97	*R*
5	**P(MMA)**[d)]	30	5	>99	77	*R*
6	**P(iPMA)**	15	24	>99	80	*R*
7	**P(BMA)**	30	5	>99	76	*R*
8	**P(BMA)**	15	36	>99	79	*R*
9	**P(BMA)**[d)]	30	5	>99	79	*R*
10	**P(HEMA)**	30	5	81	74	*R*
11	**P(HEMA)**	30	24	>99	65	*R*
12	**P(MA)**	30	5	81	73	*R*
13	**P(BA)**	30	5	>99	77	*R*
14	**P(BA)**[d)]	30	5	>99	78	*R*
15	**P(DMAA)**	30	5	>99	76	*R*
16	**P(DMAA)**[d)]	30	5	>99	78	*R*
17	**P(iPAA)**	30	5	80	72	*R*
18[e)]	**2a**	30	5	>99	76	*R*
19[f)]	**2b**[d)]	30	5	>99	77	*R*

[a)] Reactions were conducted at 1 MPa of H_2 using acetophenone (5.0 mmol), *tert*-BuOK (1.0 M in *tert*-BuOH, 100 μL), (S,S)-1,2-diamine polymer (0.02 mmol), and $RuCl_2$/(S)-BINAP (0.01 mmol) in 2-propanol (2.0 mL) and DMF (2.0 mL);

[b)] In 2-propanol;

[c)] (S)-Xyl-BINAP was used instead of (S)-BINAP;

[d)] Chiral 1,2-diamine monomer having longer methylene chain was used for the preparation of chiral 1,2-diamine polymers;

[e)] See ref [8];

[f)] See ref [14].

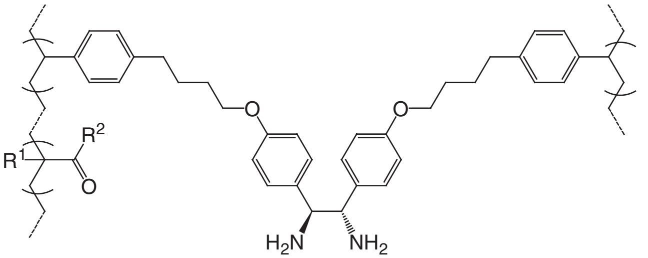


Figure 2.
Polymer-supported chiral 1,2-diamines having longer methylene chain.

reaction temperature to 10 °C decreased the reaction rate, slightly higher enantioselectivity (80% ee) was obtained after 24 h (entry 3). When (*S*)-Xyl-BINAP[12] was used instead of (*S*)-BINAP as diphosphine ligand, higher enantioselectivity (97% ee) was obtained as expected from the (*S*,*S*)-DPEN/RuCl$_2$/(*S*)-Xyl-BINAP developed by Noyori et al.[13] (entry 4). As the consequence, **P(MMA)**/RuCl$_2$/(*S*)-BINAP complex system worked well in the asymmetric hydrogenation of acetophenone.

Other polymer-supported (*S*,*S*)-1, 2-diamine/RuCl$_2$/(*S*)-BINAP complexs prepared from poly(methacrylate)s, poly(acrylate)s, and poly(acrylamide)s were then applied for the polymeric catalyst in asymmetric hydrogenation of acetophenone (Table 1). Acetophenone was asymmetrically hydrogenated by using the polymeric catalyst at 30 °C to give (*R*)-1-phenylethanol with a high level of enantioselectivity. Temperature effect was also observed in the reaction using the catalyst prepared from **P(BMA)** (entry 8). These results clearly show that poly(methacrylate)s, poly(acrylate)s and poly(acrylamide)s can be used as polymer-support for the asymmetric hydrogenation.

In order to increase conformational flexibility of chiral 1,2-diamine moiety, another chiral 1,2-diamine monomer having longer methylene chain between chiral 1,2-diamine and polymerizable group was prepared by the reaction of (*S*,*S*)-**4** with 4′-(4-bromobutyl)styrene. The monomer was copolymerized with achiral vinyl monomers under radical conditions followed by deprotection of *N*-Boc moieties to give polymer-supported chiral

Table 2.
Asymmetric Hydrogenation of Aromatic Ketones[a,b] with **P(MMA)**[c] and Low Molecular Weight Catalyst.[d]

Entry	Ketone	Ee(%)[e]	
		Polymer-supported Chiral Catalyst	Low Molecular Weight Catalyst
1	Acetophenone	78	80
2	Propiophenone	84	84
3	Butyrophenone	86	83
4	Valerophenone	87	91
5	4′-Methoxyacetophenone	79	76
6	4′-Bromoacetophenone	49	50
7	2′-Methylacetophenone	94[f]	94[f]
8	1′-Acetonaphthone	96	97

[a] Reactions were conducted at 1 MPa of H$_2$ using ketone (5.0 mmol) and *tert*-BuOK (1.0 M in *tert*-BuOH, 100 μL) in 2-propanol (2.0 mL) and DMF (2.0 mL);
[b] Conversions determined by GC were quantitative in all cases;
[c] Reactions were conducted at 30 °C for 12 h with **P(MMA)** (0.02 mmol) and RuCl$_2$/(S)-BINAP (0.01 mmol);
[d] Reactions were conducted at 30 °C for 4 h with (S,S)-DPEN (0.02 mmol) and RuCl$_2$/(S)-BINAP (0.01 mmol);
[e] Determined by HPLC using Chiralcel OD;
[f] Determined by HPLC using Chiralcel AD.

Table 3.
Recycle and Reuse of Polymeric Catalyst in Asymmetric Hydrogenation of Acetophenone at 30 °C.[a]

Chiral 1,2-Diamine Polymer	Diphosphine Ligand	Run	Time (h)	(*R*)-1-Phenylethanol	
				Conv. (%)[b]	Ee(%)[c]
2a	(*S*)-BINAP	1	12	>99	76
		2	12	>99	76
		3	12	>99	75
		4	12	>99	76
2b	(*S*)-Xyl-BINAP	1	18	>99	97
		2	18	>99	98
		3	18	>99	97
		4	18	>99	98
		5	18	>99	97
		6	18	>99	97
P(MMA)	(*S*)-BINAP	1	12	>99	78
		2	12	>99	78
		3	12	>99	78
		4	12	>99	78

[a] Reaction conditions; See footnote a) in Table 1;
[b] Determined by GC analysis;
[c] Determined by HPLC using Chiralcel OD.

1,2-diamines having longer methylene chain (Figure 2). These polymers were then reacted $RuCl_2$/(*S*)-BINAP to form the polymeric complexes. Entries 5, 9, 14, 16 and 19 in Table 1 show the results obtained from the polymer-supported catalysts derived from the methylene spacer type ligand. In most cases, slightly incresed enantioselectivities were obtained compared to those counterparts in the asymmetric hydrogenation of acetophenone.

Asymmetric Hydrogenation of Aromatic Ketones by the Polymer-supported Catalyst Prepared from P(MMA)

Not only acetophenone but various other aromatic ketones were also subjected to the asymmetric hydrogenation using polymeric catalyst derived from **P(MMA)** (Table 2). High level of asymmetric induction was observed in all cases. In order to compare these results and those obtained from the corresponding low molecular weight counterparts, the same ketones were hydrogenated by using (*S*,*S*)-DPEN/$RuCl_2$/(*S*)-BINAP in a mixed solvent of 2-propanol and DMF. The enantioselectivity values are found to be nearly equal to those from polymeric catalyst.

Recycle and Reuse of the Polymer-supported Catalyst

Separation of polymeric catalyst from resulting product in reaction mixture can be easily done by simple filtration. In addition, the separated polymeric catalyst is potentially able to be reused in the next reaction. Since the polymer-supported catalysts we have synthesized and used in this article are also insoluble polymer with crosslinkages, the recyclability of the polymer-supported catalysts was examined.

Table 3 shows the results of repeated use of the polymeric catalysts in the asymmetric hydrogenation of acetophenone. The polymeric catalysts could be reused several times without loss of the enantioselectivity. In case of **2b**/$RuCl_2$/(*S*)-Xyl-BINAP system, high level of enantioselectivity with quantitative conversion was maintained until six recycling.

Conclusions

We have successfully synthesized novel polymer-supported 1,2-diamines by radical polymerization of enantiopure 1,2-diamine derivative with various achiral vinyl monomers. The hydrogenation of aromatic ketones with the polymeric catalyst system prepared from the polymer-supported 1,2-diamine and $RuCl_2$/(*S*)-BINAP proceeded smoothly to give enantioenriched secondary alcohols in quantitative yield. The polymeric catalyst could be reused several times without loss of the enantioselectivity.

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