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Synthesis of Novel Polymers with a Chiral 1,2-Diamine Moiety by Polycondensation and their Application to Catalyst for Asymmetric Hydrogenation of Aromatic Ketones

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Summary: Novel polymers with chiral 1,2-diamine moiety were successfully synthesized by polycondensation of *N*-Boc protected enantiopure 1,2-diamine bearing two phenol groups **(*S*,*S*)-4**, bisphenol derivatives, and dibromides, followed by deprotection of *N*-Boc moiety. Hydrogenation of acetophenone 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 even in 2-propanol to give 1-phenylethanol in quantitative yield with high level of enantioselectivity. Furthermore, various other aromatic ketones could be asymmetrically hydrogenated by the polymeric catalyst system.

Keywords: catalysts; chiral; metal-polymer complexes; polycondensation; supports

Introduction

Enantiomerically pure 1,2-diamines have been widely used as chiral auxiliary in various kinds of chiral catalysts and reagents in asymmetric synthesis.[1] Especially, C_2-symmetric chiral 1,2-diphenylethylenediamine, 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 such as hydrogenation,[2] epoxidation,[3,4] Diels-Alder reaction,[5] aldol reaction,[6] dihydroxylation of olefins,[7] nucleophilic addition of carbonyls,[8,9] conjugate addition,[10] protonation of enolates,[11] cyclopropanation,[12] and aziridination.[13,14]

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.[15–19] When paying attention to chiral ligand of polymer-supported asymmetric catalysts, amino alcohol, diol, and amino acid have been reported vigorously so far.

We have recently designed and synthesized novel crosslinked polystyrene-supported chiral 1,2-diamines by radical polymerization of some styrene derivatives bearing *N*-Boc protected 1,2-diamine moiety (**1** and **2**), followed by deprotection with HCl/THF treatment as illustrated in Scheme 1.[20–22] The radical polymerization and the following deprotection proceeded quantitatively to give crosslinked polystyrene-supported chiral 1,2-diamines (**P-1** and **P-2**). Coupling reaction of Merrifield-like resin with 1,2-diamine derivative (**3**) has also been utilized for the preparation of polymer-supported chiral 1,2-diamines

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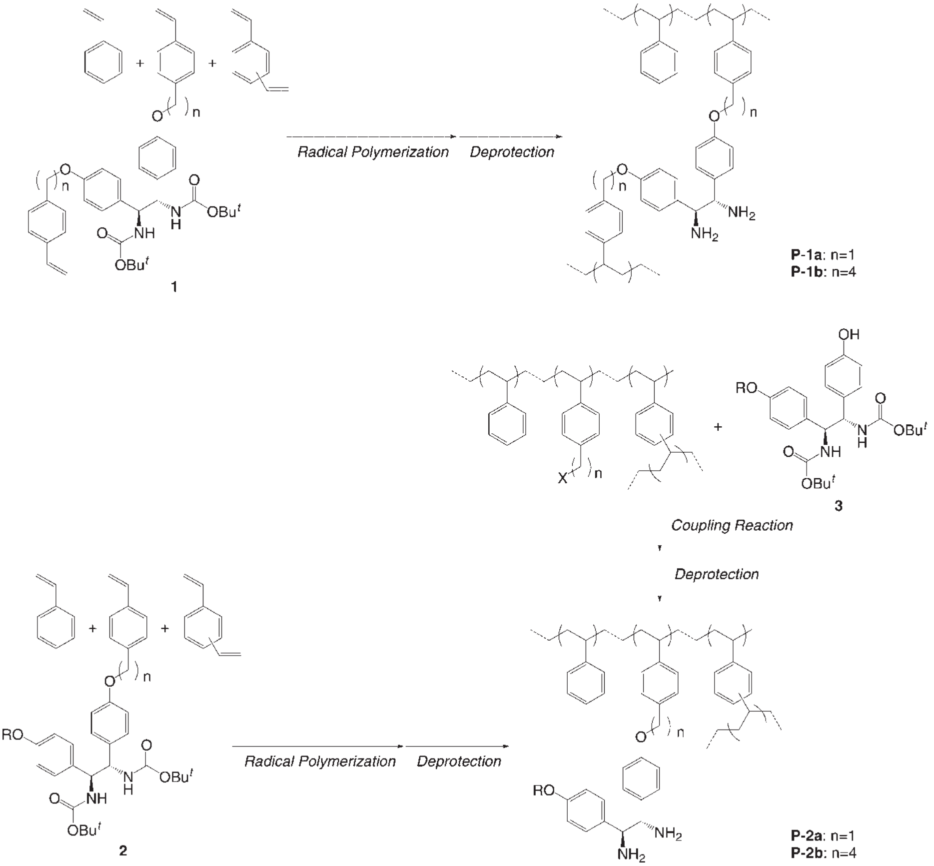


Scheme 1.
Synthesis of Polymer-supported Chiral 1,2-Diamines by Radical Polymerization and Coupling Reaction.

(**P-2**).[23–25] The resulting 1,2-diamine polymers could be complexed with $RuCl_2$/(*S*)-BINAP[26] 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).

The radical polymerization and coupling reaction techniques are presently the main choice for the synthesis of polymer supported catalyst, but the other preparation methods are worth utilizing to vary its property for requirement of diversification of the usage. Enantiopure 1,2-diamine derivative possessing two phenol groups **(*S*,*S*)-4** can be a suitable monomer of polycondensation with dibromides. In this article, we report synthesis of novel polymer-supported 1,2-diamines by polycondensation and their applications for chiral ligands for asymmetric hydrogenation of aromatic ketones. To our knowledge, this is the first report on preparation of polymer-supported chiral 1,2-diamine by polycondensation.

Experimental Part

Materials

N,*N*-Dimethylformamide (DMF) and 1,3-dibromopropane were distilled from calcium hydride (CaH_2) under reduced pressure. α,α'-Dibromo-*p*-xylene and bisphenol A were used as received. All ketones used were distilled twice from CaH_2 under argon immediately before use.

Measurements

^1H NMR (300 MHz) spectra were recorded on a Varian Mercury 300 spectrometer in $CDCl_3$ or $(CD_3)_2C{=}O$. ^{13}C and ^{31}P NMR spectra were recorded on a Varian Inova 400 spectrometer (100 MHz for ^{13}C and 162 MHz for ^{31}P) in $CDCl_3$ or $(CD_3)_2C{=}O$. Chemical shifts were reported in ppm relative to tetramethylsilane (δ 7.24 for ^1H NMR spectra) and chloroform (δ 77.1 for ^{13}C NMR spectra). FT-IR spectra were recorded with a JEOL JIR-700 Fourier transform infrared spectrometer and are reported in reciprocal centimeter (cm^{-1}). Elemental analyses were performed at the Microanalytical Center of Kyoto University. 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, 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 x 0.25 mm).

General Procedure for Preparation of Polymer-Supported 1,2-Dimamine by Polycondensation

A 50 mL round-bottom flask equipped with a magnetic stirring bar was charged with (*S*,*S*)-**4**[23] (1.000 g, 2.25 mmol), bisphenol A (2.055 g, 9.000 mmol), α,α'-dibromo-*p*-xylene (2.970 g, 11.25 mmol), and 25.0 mL of dry DMF. Cs_2CO_3 (14.66 g, 45.0 mmol) was then added to the mixture at room temperature, and the mixture was stirred at 50 °C. After 24 h, the volatiles were removed with a vacuum pump, and the residue was poured into water (200 mL) to precipitate the resulting polymer. The solid was washed with hexanes (20 mL) several times and dried at 40 °C under high vacuum to afford polymer-supported *N*-Boc protected 1,2-diamine as brown solid (3.49 g, 83%).

To a solution of THF-HCl (10 mL) at room temperature under nitrogen, 1.00 g of the *N*-Boc protected polymer was added. After being stirred for 24 h, another THF-HCl (2.5 mL) was added and stirred for additional 24 h. Triethylamine (7.5 mL) was then added and stirred for 24 h. The volatiles were removed with a vacuum pump, and the residue was poured into 200 mL of water. The precipitated solid was filtrated, washed with hexane (50 mL) several times, and dried at 40 °C under high vacuum to afford polymer-supported 1,2-diamine **P-6** as grayish solid (0.848 g, 95%).

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 (0.03 mmol), $RuCl_2$/(*S*)-BINAP (0.025 mmol) and 2 mL of dry DMF. The above mixture was degassed and heated to 80 °C. After 2 h, DMF was removed under reduced pressure and the polymeric complex was obtained as red or green solid.

Air present 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 2-propanol (4 mL) and a 1.0 M potassium *tert*-butoxide (*tert*-BuOK) solution in *tert*-BuOH (0.1 mL), which had been degassed, 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 room temperature for 24 h. After the careful venting of the hydrogen gas, the reaction mixture was diluted with ethyl acetate (10 mL) and filtered through a glass filter equipped with silica gel. The solvent was removed under reduced pressure, and the conversion was determined by GC analysis. The enantioselectivity 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.).

Asymmetric Hydrogenation of other Aromatic Ketones

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

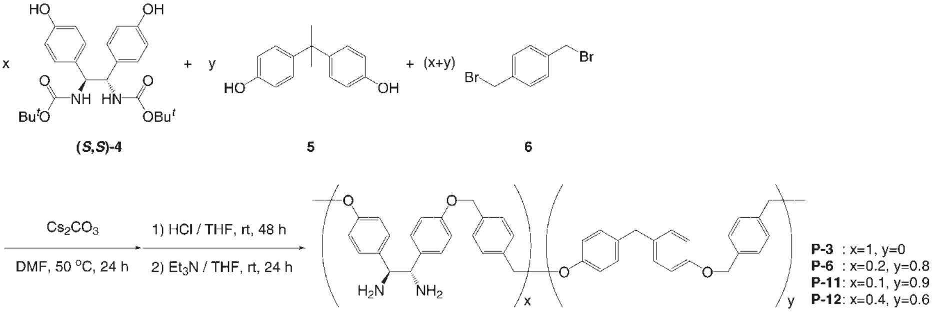
Results and Discussion

Synthesis of Polymer-Supported Chiral 1,2-Diamine by Polycondensation

The synthetic procedure of polymer-supported chiral 1,2-diamine **P-3** and **P-6** by polycondensation is illustrated in Scheme 2. At first, **(*S*,*S*)-4**[23] was reacted with α,α'-dibromo-*p*-xylene. The polycondensation proceeded smoothly to afford polymer-supported *N*-Boc-protected 1,2-diamine as the precursor of **P-3** in high yield. Other dibromides such as 1,3-dibromopropane and 1,12-dibromododecane were also used as monomer to give the precursors of **P-4** and **P-5** (see Figure 1). The other bisphenol-type monomers such as bisphenol A, 4,4′- (hexafluoroisopropylidene)-bisphenol, hydroquinone, and (*R*)- or (*S*)-BINOL[27] could be incorporated into the above polycondensation system, which led to the control of the 1,2-diamine content and the solubility (**P-6** – **P-12**). *tert*-Butoxycarbonyl (*tert*-Boc) groups of the resulting polymers were readily eliminated by a treatment with HCl in THF. In the FT-IR spectrum, the absorption at 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. Total yields of these polymers are more than 62% up to 99% (Table 1). These results indicated that polycondensation could be utilized for preparation of polymer- supported chiral 1,2-diamines.

Preparation and NMR Analysis of Polymer-Supported 1,2-Diamine/$RuCl_2$/(*S*)-BINAP Complexes

To apply the resulting polymers for asymmetric hydrogenation of aromatic ketones, polymer-supported (*S*,*S*)-1,2-diamines were treated with $RuCl_2$/(*S*)-BINAP in DMF at 80 °C for 2 h. A reddish-brown reaction mixture containing the $RuCl_2$/(*S*)-BINAP gradually turned to green 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 the complex was formed quantitatively on the polymer.



Scheme 2.

Synthesis of Polymer-supported Chiral 1,2-Diamine by Polycondensation.

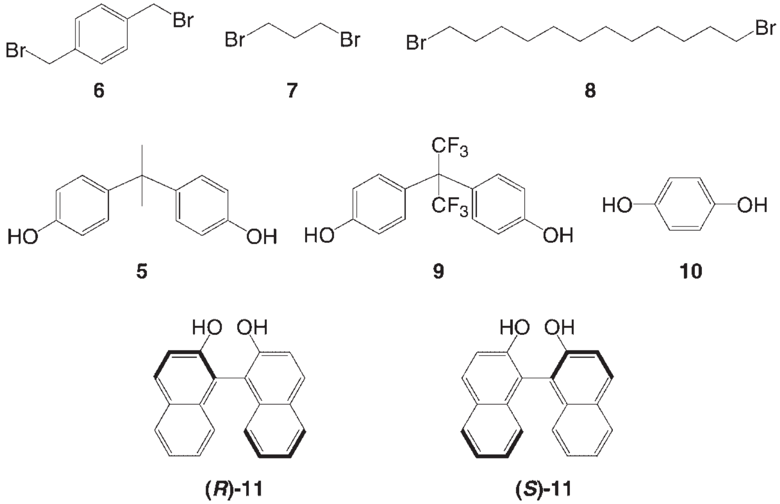


Figure 1.
Dibromides and Bisphenol Derivatives.

Asymmetric Hydrogenation of Acetophenone by the Polymer-Supported Complex Prepared from P-1, P-2, and P-3

At first, asymmetric hydrogenation of acetophenone by using the chiral 1,2-diamine polymer (**P-3**, **P-4**, or **P-5**)/RuCl$_2$/(*S*)-BINAP complex was carried out in DMF. The reactions proceeded quantitatively in DMF to afford (*R*)-1-phenylethanol in 70, 60, and 64% ee, respectively (Entries 1, 2, and 3 in Table 2). The Polymeric catalyst prepared from **P-1a** gave higher enantioselectivity in the reaction (Entry 4). A mixed solvent system (2-propanol/DMF = 1/1 (*v*/*v*)) in the hydrogenation reaction[22,23] was also utilized similar to the case of crosslinked polystyrene-supported chiral 1,2- diamine **P-1a** (Entries 5 and 6).

Table 1.
Polymer-supported Chiral 1,2-Diamine by Polycondensation.

Polymer	dibromide	bisphenol	x	y	Yield (%)
P-3	**6**	–	1	0	74
P-4	**7**	–	1	0	99
P-5	**8**	–	1	0	92
P-6	**6**	**5**	0.2	0.8	79
P-7	**6**	**9**	0.2	0.8	62
P-8	**6**	**10**	0.2	0.8	98
P-9	**6**	**(*R*)-11**	0.2	0.8	98
P-10	**6**	**(*S*)-11**	0.2	0.8	75
P-11	**6**	**5**	0.1	0.9	79
P-12	**6**	**5**	0.4	0.6	79

In general, 2-propanol is known to be the most suitable solvent for the hydrogenation using the (*S*,*S*)-DPEN/RuCl$_2$/(*S*)-BINAP system to give high enantioselectivity with quantitative conversion for various kinds of aromatic ketones.[28] Unfortunately, no reaction occurred in 2-propanol with the catalysts prepared from **P-1a**, which thoroughly shrunk in the solvent (Entry 8). We have tested the asymmetric hydrogenation of acetophenone by using the catalyst prepared from **P-3** in 2-propanol. Interestingly, the reaction proceeded smoothly within 24 h to afford (*R*)-1-phenylethanol in 78% ee (Entry 7). As the consequence, the **P-3**/RuCl$_2$/(*S*)-BINAP complex system worked well in the asymmetric hydrogenation of acetophenone.

Asymmetric Hydrogenation of Acetophenone by Various Polymer-supported Complexes

Other polymer-supported (*S*,*S*)-1,2-diamine/RuCl$_2$/(*S*)-BINAP complexes prepared from **P-6** to **P-12** were then applied for the polymeric catalyst in asymmetric hydrogenation of acetophenone in DMF and in 2-propanol. These results are summarized in Table 3. Acetophenone was asymmetrically hydrogenated by using the polymeric catalyst at room temperature to give

Table 2.
Asymmetric Hydrogenation of Acetophenone with Polymer-supported Chiral Catalyst.[a)]

Entry	Chiral 1,2-Diamine Polymer	Solvent	1-Phenylethanol		
			Conv. (%)	Ee (%)	*Config.*
1	**P-3**	DMF	>99	70	*R*
2	**P-4**	DMF	>99	60	*R*
3	**P-5**	DMF	>99	64	*R*
4[23]	**P-1a**	DMF	>99	69	*R*
5	**P-3**	DMF/2-Propanol = 1/1	>99	75	*R*
6[23]	**P-1a**	DMF/2-Propanol = 1/1	>99	76	*R*
7	**P-3**	2-Propanol	>99	78	*R*
8[23]	**P-1a**	2-Propanol	0	–	–

[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 (0.03 mmol), and $RuCl_2$/(*S*)-BINAP (0.025 mmol) in solvent (4.0 mL).

(*R*)-1-phenylethanol with a high level of enantioselectivity in most cases. The enantioselectivities obtained in 2-propanol are higher than in DMF. Comparing the effect of structure on the enantioselectivity, **P-3** and **P-6** gave the higher values both in DMF and in 2-propanol. A Slight difference in enantioselectivity was observed when using **P-9** and **P-10** in 2-propanol (Entries 15 and 16) but not in DMF. We have also prepared chiral 1,2-diamine polymers having different degrees of diamine content in the polymeric 1,2-diamine to investigate the effect of the diamine content of the polymeric catalyst (Entries 9, 10, 17, and 18). Lower loading of 1,2-diamine resulted in lower enantioselectivity. The rate of substrate to catalyst, S/C, could be gained to 1000 without loss of enantioselectivity (Entries 11 and 12). These results clearly show that polymer-supported chiral 1,2-diamine synthesized by polycondensation can be an useful polymeric chiral ligand of the asymmetric hydrogenation catalyst.

Not only acetophenone but various other aromatic ketones were also subjected to the asymmetric hydrogenation using the

Table 3.
Asymmetric Hydrogenation of Acetophenone with Polymer-supported Chiral Catalyst.[a)]

Entry	Chiral 1,2-Diamine Polymer	Solvent	1-Phenylethanol		
			Conv. (%)	Ee(%)	*Config.*
1	**P-3**	DMF	>99	70	*R*
2	**P-6**	DMF	>99	70	*R*
3	**P-7**	DMF	>99	68	*R*
4	**P-8**	DMF	>99	51	*R*
5	**P-9**	DMF	>99	65	*R*
6	**P-10**	DMF	>99	65	*R*
7	**P-11**	DMF	>99	67	*R*
8	**P-12**	DMF	>99	69	*R*
9	**P-3**	2-Propanol	>99	78	*R*
10	**P-6**	2-Propanol	>99	78	*R*
11[b)]	**P-6**	2-Propanol	>99	79	*R*
12[c)]	**P-6**	2-Propanol	>99	79	*R*
13	**P-7**	2-Propanol	28	71	*R*
14	**P-8**	2-Propanol	>99	62	*R*
15	**P-9**	2-Propanol	>99	71	*R*
16	**P-10**	2-Propanol	>99	76	*R*
17	**P-11**	2-Propanol	>99	73	*R*
18	**P-12**	2-Propanol	>99	79	*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 (0.03 mmol), and $RuCl_2$/(*S*)-BINAP (0.025 mmol) in solvent (4.0 mL).

[b)] S/C = 500. (*S*,*S*)-1,2-diamine polymer (0.012 mmol) and $RuCl_2$/(*S*)-BINAP (0.01 mmol) were used.

[c)] S/C = 1000. (*S*,*S*)-1,2-diamine polymer (0.006 mmol) and $RuCl_2$/(*S*)-BINAP (0.005 mmol) were used.

Table 4.
Asymmetric Hydrogenation of Aromatic Ketones with **P-6**.[a),b),c)]

Entry	Ketone	Ee (%)
1	Acetophenone	78
2	Propiophenone	82
3	Butyrophenone	88
4	1′-Acetonaphthone	88

[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 (4.0 mL).

[b)] Conversions determined by GC were quantitative in all cases.

[c)] Reactions were conducted at rt for 24 h with **P-6** (0.03 mmol) and $RuCl_2$/(S)-BINAP (0.025 mmol).

polymeric catalyst derived from **P-6**. As shown in Table 4, a high level of asymmetric induction was observed in all cases. The enantioselectivity values are found to be nearly equal to those from low-molecular catalysts.

Conclusions

We have successfully synthesized novel polymer-supported 1,2-diamines by polycondensation of *N*-Boc protected enantiopure 1,2-diamine bearing two phenol groups, bisphenol derivatives, and dibromides, followed by deprotection of the *N*-Boc moiety. 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 design of polymer-support is important because the asymmetric reaction is affected by substrate accessibility to the catalytic site at the polymer. Recyclability of the polymer-supported catalysts is now under investigation.

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