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Synthesis of enantiopure 1,2-diamine attached to cross-linked polystyrene and its application to an insoluble catalyst for asymmetric hydrogenation

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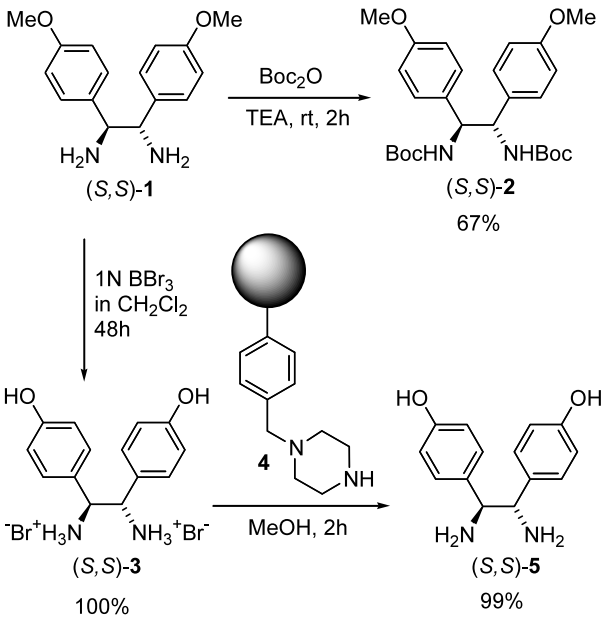
Abstract—A novel enantiopure 1,2-diamine (**5**) having two phenolic hydroxy groups was attached into chloromethylated polystyrene through benzyl ether linkage, which was used as a chiral ligand of the catalyst in asymmetric hydrogenation of acetophenone.

Enantiopure 1,2-diamines have recently been known as an efficient chiral auxiliary in various kinds of chiral catalysts and reagents.[1] Although a variety of 1,2-diamine structures have been designed and synthesized, no attention has been paid to preparation of the 1,2-diamines possessing phenolic hydroxy groups such as **5**. The phenol groups would be a very useful functionality to attach the chiral 1,2-diamine moiety into solid support materials. Supported catalysts have found increasing use in synthesis since they have inherent operational and economical advantages.[2] Surprisingly, it appears that there is no report up until now on the immobilization of chiral 1,2-diamine.[3] We now report the first preparation of a polymer-supported chiral 1,2-diamine **5P** by means of the reaction between **5** and chloromethylated polystyrene **6**. We also demonstrate the asymmetric hydrogenation of acetophenone as a test reaction using **5P** complexed with $RuCl_2$ and BINAP.[4]

According to Corey's method,[5] racemic 1,2-diamine **1** was readily prepared from 4,4′-dimethoxybenzil as a starting material. Optical resolution of racemic **1** was successfully achieved with (L)-(+)-tartaric acid.[6] Enantiomeric purity of the obtained chiral 1,2-diamine (*S*,*S*)-**1** was determined by HPLC analysis of its di(*t*-butyloxycarbonyl) derivative (*S*,*S*)-**2**. After optical resolution (*S*,*S*)-**1** was treated with BBr_3 in CH_2Cl_2 to cleave its methyl ether linkage to yield dihydroxydiamine dihydrobromide (*S*,*S*)-**3**. Once the usual aqueous alkaline treatment was undertaken for (*S*,*S*)-**3**, extraction of the desired chiral 1,2-diamine having phenol groups resulted in failure due to its solubility problem. We found that the use of polymer-supported piperazine **4**[7] as a scavenger resin was quite effective to remove boron derivatives and neutralize the HBr salt to afford (*S*,*S*)-**5** in quantitative yield (Scheme 1).



Scheme 1. Preparation of chiral 1,2-diamine **5**.

Keywords: 1,2-diamine; cross-linked polystyrene; asymmetric hydrogenation.

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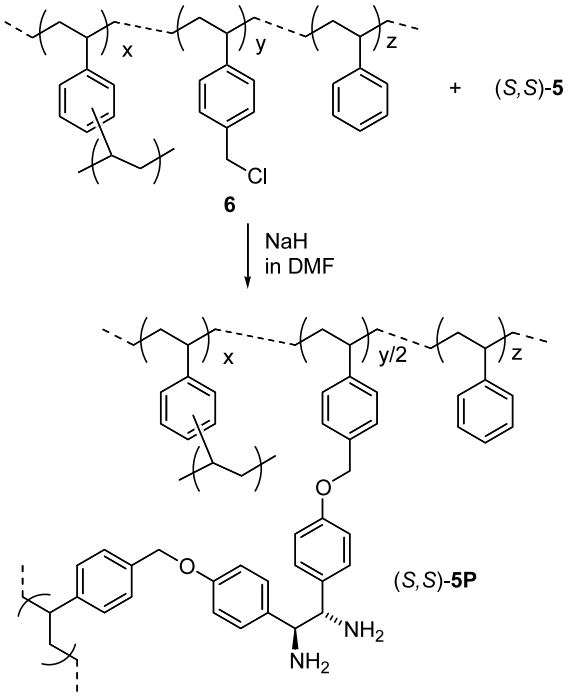
Our previous study revealed that a phenolic functionality is quite suitable for immobilization reaction to chloromethylated polystyrenes.[8] Thus, the sodium phenoxide derived from (*S*,*S*)-**5** was allowed to react with 1% cross-linked chloromethylated polystyrene to give polymer-supported diamine (*S*,*S*)-**5P**, as shown in Scheme 2. In this immobilization reaction, both hydroxy groups of (*S*,*S*)-**5** seem to react with the chloromethyl groups of **6** based on the diamine loading of **5P** calculated by nitrogen analysis. Under the same reaction conditions, 1,2-diphenylethylenediamine (DPEN) was not incorporated to the polymer, which means that no nucleophilic substitution reaction between the primary amino groups of 1,2-diamine and the chloromethyl groups in **6** took place. In the cases of higher content of the chloromethyl group (**5Pg**, **5Ph**) and a higher degree of crosslinking (**5Pe**), some unreacted chloromethyl groups remained.

One of the most important asymmetric reactions using enantiopure 1,2-diamine as a chiral ligand is hydrogenation of simple ketones developed by Noyori et al.[9] Although Noyori reported the use of a polymeric catalyst prepared from polymer-supported BINAP, $RuCl_2$ and DPEN for the same reaction,[10] no example has been reported on the use of polymeric 1,2-diamine. In order to demonstrate the efficiency of the polymer-supported chiral 1,2-diamine **5P**, we performed the asymmetric hydrogenation of acetophenone using the polymer-supported Ru complex derived from (*S*)-BINAP, $RuCl_2$ and (*S*,*S*)-**5P**. The results are summarized in Table 1. In most cases 2-propanol is the choice of solvent for the hydrogenation using this catalyst system.[9] Unfortunately, no reaction was achieved by using the polymer-supported complex in pure 2-propanol as a solvent (run 5). Styrene-based crosslinked polymers show little swelling in an alcoholic solvent which thus may prevent accessibility to the catalyst site in the polymer network. Addition of DMF as a co-solvent remarkably improved the reactivity of the hydrogenation using the polymeric catalyst. Acetophenone was smoothly hydrogenated with the polymer-supported Ru complex derived from (*S*,*S*)-**5P** and (*S*)-BINAP–$RuCl_2$ in a 1:1 2-propanol/DMF mixture to give the *R* alcohol with 73% ee in 100% yield (run 7).[11] This result strongly supported that the active complex was formed in the polymer since BINAP–$RuCl_2$ alone gives no reaction.[12] Pure DMF retarded the reaction with the polymeric catalyst (run 10). In a 1:1 2-propanol/DMF mixture a homogeneous catalyst derived from DPEN yielded the same alcohol with 81% ee in 92% yield (run 1). In DMF the ee decreased to 72% (run 2). Instead of BINAP the use of xylBINAP produced the same product in higher enantioselectivity as expected from the asymmetric hydrogenation data reported by Noyori (run 11).[13] The degree of crosslinking and loading influenced both the reactivity and the enantioselectivity. A lower degree of crosslinking gave better reactivity. Higher ees and conversions were obtained when **5Pc** was used.



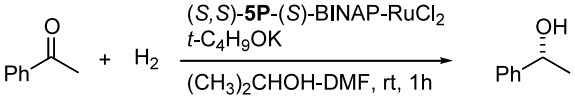
(*S*,*S*)-**5P**	x	y	z
(*S*,*S*)-**5Pa**	0.01	0.05	0.94
(*S*,*S*)-**5Pb**	0.01	0.10	0.89
(*S*,*S*)-**5Pc**	0.01	0.20	0.79
(*S*,*S*)-**5Pd**	0.02	0.20	0.78
(*S*,*S*)-**5Pe**	0.05	0.20	0.75
(*S*,*S*)-**5Pf**	0.01	0.30	0.69
(*S*,*S*)-**5Pg**	0.01	0.40	0.59
(*S*,*S*)-**5Ph**	0.01	0.50	0.49

Scheme 2. Preparation of polymer-supported chiral 1,2-diamine.

Isolation of the product by simple filtration was quite easy when the polymer-supported chiral catalyst was used. The recycling experiments were also readily performed. After a reaction was completed and the polymer-supported catalyst was allowed to settle, the solution containing the product was removed through a syringe. A further amount of acetophenone in 2-propanol/DMF was injected and the reaction was repeated. When (*R*,*R*)-**5Pc**–(*R*)-BINAP–$RuCl_2$ was employed, quantitative yields were obtained in the four continuous recycling experiments and the ee values of the chiral product were 73, 73, 73, and 74% ee, respectively.

In summary, we have shown an efficient preparative route to the polymer-supported chiral 1,2-diamine **5P**. Asymmetric hydrogenation of acetophenone smoothly occurred by using the **5P**–BINAP–$RuCl_2$ system in 2-propanol/DMF. We have shown that the immobilized catalyst can be reused at least four times without loss of activity. Studies of other asymmetric reactions using the polymeric chiral 1,2-diamine are currently under way.

Table 1. Asymmetric hydrogenation of acetophenone using the (*S*,*S*)-**5P**–(*S*)-BINAP–$RuCl_2$ complex[a]



Run	(*S*,*S*)-**5P**	Solvent (2-propanol:DMF)	1-Phenylethanol		
			Yield (%)[b]	Ee (%)[c]	Config.
1	(*R*,*R*)-DPEN[d]	1:1	92	81	*S*
2	(*R*,*R*)-DPEN[d]	DMF	100	72	*S*
3	(*S*,*S*)-**5Pa**	1:1	87	73	*R*
4	(*S*,*S*)-**5Pb**	1:1	86	74	*R*
5	(*S*,*S*)-**5Pc**	2-Propanol	0	–	–
6	(*S*,*S*)-**5Pc**	2:1	46	71	*R*
7	(*S*,*S*)-**5Pc**	1:1	100	73	*R*
8	(*R*,*R*)-**5Pc**[d]	1:1	100	73	*S*
9	(*S*,*S*)-**5Pc**	1:2	100	70	*R*
10	(*S*,*S*)-**5Pc**	DMF	38	75	*R*
11	(*S*,*S*)-**5Pc**[e]	1:1	100	93	*R*
12	(*S*,*S*)-**5Pd**	1:1	69	73	*R*
13	(*S*,*S*)-**5Pe**[f]	1:1	39	68	*R*
14	(*S*,*S*)-**5Pf**	1:1	91	69	*R*
15	(*S*,*S*)-**5Pg**[f]	1:1	78	67	*R*
16	(*S*,*S*)-**5Ph**[f]	1:1	43	63	*R*

[a] Reactions were conducted at 1 MPa of H_2 and at room temperature for 1 h using acetophenone (5 mmol), *t*-BuOK (1 M *t*-BuOH soln. 100 μL), 1,2-diamine (0.025 mmol) and BINAP–$RuCl_2$ (0.025 mmol).
[b] Determined by GC.
[c] Determined by HPLC using Chiralcel OD.
[d] (*R*)-BINAP was used.
[e] (*S*)-xylBINAP (2,2′-bis(di-3,5-xylylphosphino)-1,1′-binaphthyl) was used.
[f] Contains unreacted chloromethyl groups.

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11. Representative procedure for asymmetric hydrogenation of acetophenone: polymer-supported chiral 1,2-diamine ((*S*,*S*)-**5Pc**, 2.9 mg, 0.025 mmol) and (*S*)-BINAP[$RuCl_2$](dmf)$_n$ (23 mg, 0.025 mmol) were added to dry DMF (2 mL) in a dry, degassed 100-mL glass autoclave. To this suspension was added a degassed mixture of acetophenone (0.58 mL, 5 mmol) and a 1.0 M 2-

propanol solution of *t*-BuOK (100 μL, 0.1 mmol) in 2-propanol (2 mL), and then, hydrogen was pressurized to 1 MPa. The suspension was stirred at room temperature for 1 h. After the reaction, the mixture was filtered and concentrated. The yield determined by GC was 100%. The enantioselectivity was determined by HPLC analysis using a Daicel Chiralcel OD column (eluent, 1:20 2-propanol–hexane; flow rate, 0.4 mL/min).

12. After the complex formation of the polymer-supported 1,2-diamine with BINAP, some amount of free BINAP–$RuCl_2$ was detected in the solution part by NMR analysis. Based on the NMR analysis of the solution part, we can estimate that at least 85% of the polymeric 1,2-diamine forms the complex with BINAP–$RuCl_2$.
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