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Polymer-Immobilized Catalyst for Asymmetric Hydrogenation of Racemic α-(*N*-Benzoyl-*N*-methylamino)propiophenone

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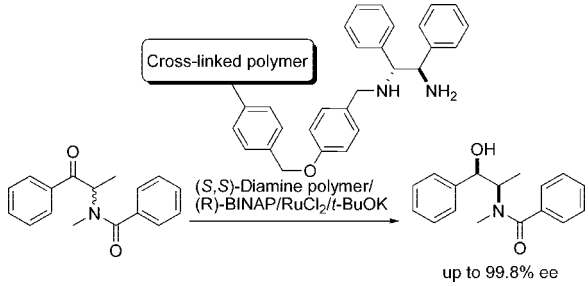
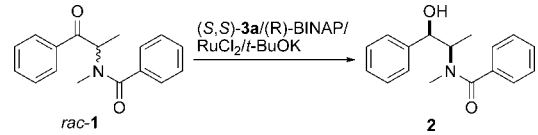


Asymmetric hydrogenation of α-(*N*-benzoyl-*N*-methylamino)propiophenone through dynamic kinetic resolution was performed by using a polymer-immobilized chiral diamine−ruthenium−BINAP−*t*-BuOK system in order to yield *syn*-β-amide alcohol exclusively with nearly perfect enantioselectivity.

Certain β-amino alcohols such as pseudoephedrine and its derivatives (**2**) are valuable constituents of a variety of biologically active products and medicinally important compounds.[1] In addition, pseudoephedrine has been used as an efficient chiral auxiliary for asymmetric reactions.[2] Such optically active β-amino alcohols having two adjacent stereogenic centers have been synthesized by using several methods, including the diastereoselective addition of organometallic reagents to α-amino aldehydes,[3] diastereoselective reduction of α-amino ketones,[4] and diastereoselective reduction of α-alkoxy imines.[5] In these reactions, the corresponding enantiopure starting materials produce optically active products. Moreover, these reactions preferentially produce *anti* isomers, and pseudoephedrine possesses a *syn*-β-amino alcohol structure.

An alternative method to obtain chiral β-amino alcohol involves the stereoselective hydrogenation of racemic α-nitrogen substituted ketones that contain configurational labile α-stereogenic centers. The dynamic kinetic discrimination[6] of the stereoisomers for such a racemic ketone is achievable. Although asymmetric hydrogenation under the conditions of dynamic kinetic resolution has been applied to some types of racemic ketones such as α-alkylcyclohexanone[7] and α-ketoethers,[8] the reaction involving α-nitrogen substituted ketones has not been studied extensively. A few examples of such a system have been reported. Noyori et al. and Hamada et al. reported on the hydrogenation of α-amino-β-keto ester involving the use of BINAP[9]−Ru complex.[10,11] The carbonyl group in the substrate structure is necessary for attaining high diastereoselectivity in the reaction. Ohkuma recently reported on the asymmetric hydrogenation of α-branched aromatic ketones with TolBINAP[12]/DMAPEN[13]−Ru(II) complex.[14] The dynamic kinetic resolution of racemic 2-*tert*-butoxycarbonylaminocyclohexanone by hydrogenation to produce 1,2-*cis*-configurated 2-*tert*-butoxycarbonylaminocyclohexanol in 82% ee was described.[15] In our study, to synthesize enantiopure pseudoephedrine derivatives, we focused on the asymmetric hydrogenation of racemic α-amide ketone *rac*-**1** by utilizing dynamic kinetic resolution (Scheme 1).

SCHEME 1. Asymmetric Hydrogenation of Racemic α-Amide Ketone 1



From the perspective of employing a green, sustainable synthetic method, the use of polymer-immobilized catalysts should be considered always mainly because they can easily be separated from the reaction mixture and because of their recyclability.[16] However, the dynamic kinetic resolution of α-amide ketone by using a polymer-immobilized chiral catalyst has not yet been reported. We developed a polymer-immobilized

(1) Sweetman, S. C.; Martindale. In *W. Martindale: the Complete Drug Reference*, 35th ed.; Pharmaceutical Press: London, UK, 2007.
(2) Myers, A. G.; Yang, B. H.; Chen, H.; McKinstry, L.; Kopecky, D. J.; Gleason, J. L. *J. Am. Chem. Soc.* **1997**, *119*, 6496–6511.
(3) Dondoni, A.; Fantin, G.; Fogagnolo, M.; Pedrini, P. *J. Org. Chem.* **1990**, *55*, 1439–1446.
(4) Lagu, B. R.; Liotta, D. C. *Tetrahedron Lett.* **1994**, *35*, 547–550.
(5) Lida, H.; Yamazaki, N.; Kibayashi, C. *J. Chem. Soc., Chem. Commun.* **1987**, 746–748.
(6) (a) Noyori, R.; Tokunaga, M.; Kitamura, M. *Bull. Chem. Soc. Jpn.* **1995**, *68*, 36–55. (b) Robinson, D. E. J. E.; Bull, S. D. *Tetrahedron: Asymmetry* **2003**, *14*, 1407–1446. (c) Noyori, R.; Ohkuma, T. *Pure Appl. Chem.* **1999**, *71*, 1493–1501. (d) Noyori, R.; Ohkuma, T. *Angew. Chem., Int. Ed.* **2001**, *40*, 40–73.
(7) Ohkuma, T.; Ooka, H.; Yamakawa, M.; Ikariya, T.; Noyori, R. *J. Org. Chem.* **1996**, *61*, 4872–4873.
(8) (a) Matsumoto, T.; Murayama, T.; Mitsuhashi, S.; Miura, T. *Tetrahedron Lett.* **1999**, *40*, 5043–5046. (b) Studer, M.; Blaser, H. U.; Burkhardt, S. *Adv. Synth. Catal.* **2002**, *344*, 511–515.
(9) BINAP = 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl.
(10) (a) Noyori, R.; Ikeda, T.; Ohkuma, T.; Widhalm, M.; Kitamura, M.; Takaya, H.; Akutagawa, S.; Sayo, N.; Saito, T.; Taketomi, T.; Kumobayashi, H. *J. Am. Chem. Soc.* **1989**, *111*, 9134–9135. (b) Kitamura, M.; Tokunaga, M.; Noyori, R. *J. Am. Chem. Soc.* **1993**, *115*, 144–152. (c) Noyori, R.; Tokunaga, M; Kitamura, M. *Bull. Chem. Soc. Jpn.* **1995**, *68*, 36–56.
(11) (a) Makino, K.; Okamoto, N.; Hara, O.; Hamada, Y. *Tetrahedron: Asymmetry* **2001**, *1*, 1757–1762. (b) Makino, K.; Goto, T.; Hiroki, Y.; Hamada, Y. *Angew. Chem., Int. Ed.* **2004**, *43*, 882–884. (c) Makino, K.; Hiroki, Y.; Hamada, Y. *J. Am. Chem. Soc.* **2005**, *127*, 5784–5785.
(12) TolBINAP = 2,2′-bis(di-4-tolylphosphino)-1,1′-binaphthyl.
(13) DMAPEN = 2-dimethylamino-1-phenyethylamine.
(14) Arai, N.; Ooka, H.; Azuma, K.; Yabuuchi, T.; Kurono, N.; Inoue, T.; Ohkuma, T. *Org. Lett.* **2007**, *9*, 939–941.
(15) Ohkuma, T.; Ishii, D.; Takeno, H.; Noyori, R. *J. Am. Chem. Soc.* **2000**, *122*, 6510–6511.
(16) (a) Itsuno, S. In *Handbook of Asymmetric Heterogeneous Catalysis*; Ding, K., Uozumi, Y., Eds.; Wiley-VCH: Weinheim, Germany, 2008; Chapter 3. (b) Itsuno, S. In *Acid Catalysis in Modern Organic Synthesis*; Yamamoto, H., Ishihara, K., Eds.; Wiley-VCH: Weinheim, Germany, 2008; Vol. 2, pp 1019−1060. (c) El-Shehawy, A. A.; Itsuno, S. In *Current Topics in Polymer Research*; Bress, R. K., Ed.; Nova Science Publisher: New York, 2005, pp 1−69.

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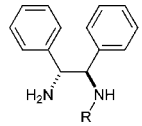
TABLE 1. Asymmetric Hydrogenation of *rac*-1 by Using *N*-Substituted Diamine−$RuCl_2$−BINAP in 2-Propanol[a]

				N-benzoyl pseudoephedrine			
entry	diamine	BINAP	time, h	conv. %[b]	de %[b]	ee %[c]	config.
1	(*S*,*S*)-**3a**	*S*	17	100	>99	72	*S*,*S*
2	(*R*,*R*)-**3b**	*S*	1	100	>99	91	*R*,*R*
3	(*R*,*R*)-**3b**	*R*	17	100	>99	42	*R*,*R*
4	(*R*,*R*)-**3c**	*S*	2	100	>99	99.4	*S*,*S*

[a] Reactions conducted at room temperature in 2-propanol. [Diamine]:[$RuCl_2$]:[(*S*)-BINAP] = 2:1:1, S/C = 500. [b] Determined by HPLC and ^{1}H NMR analysis. [c] Determined by chiral HPLC analysis.

CHART 1. Chiral 1,2-Diamine Ligand



(*R*,*R*)-**3**

3a: R = H

3b: R = benzyl

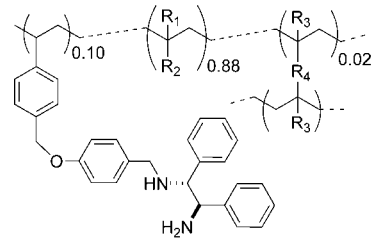
3c: R = 4-(4-vinylbenzyloxy)benzyl

chiral 1,2-diamine as a polymeric chiral ligand for the Noyori−Ohkuma-type catalyst. The polymeric chiral precatalyst was efficiently used for the asymmetric hydrogenation of *rac*-**1** via dynamic kinetic resolution.

Because the catalytic system prepared from BINAP−$RuCl_2$−DPEN[17] (**3a**)−*t*-BuOK in 2-propanol, which was originally developed by Noyori and Ohkuma, provides one of the most efficient hydrogenation activities for simple ketone reduction to a secondary alcohol,[18] we apply this system to the dynamic kinetic resolution of *rac*-**1**.[19] The racemic α-amide ketone is smoothly hydrogenated with (*S*,*S*)-**3a**−(*R*)-BINAP−$RuCl_2$−*t*-BuOK in 2-propanol to produce the corresponding *syn*-*β*-amide alcohol (*S*,*S*)-**2** in a quantitative yield with 72% ee (Table 1, entry 1).[20] In the hydrogenation of simple ketones, the use of *N*-substituted 1,2-diamine ligand decreases the catalytic activity. However, in the case of the dynamic kinetic resolution of *rac*-**1**, we observe that mono *N*-benzyl DPEN (*R*,*R*)-**3b** (Chart 1) is a rather effective chiral ligand for the catalyst system, as shown in Table 1. By using the precatalyst containing (*R*,*R*)-**3b** and (*S*)-BINAP/$RuCl_2$, the asymmetric hydrogenation of *rac*-**1** produces *syn*-*β*-amide alcohol (*R*,*R*)-**2** in quantitative conversion with 91% ee (entry 2). When (*R*)-BINAP is used instead of (*S*)-BINAP, both the reactivity and enantioselectivity decrease (entry 3). A combination of (*S*)-BINAP and (*R*,*R*)-*N*-substituted DPEN appears to be the matched pair required to produce (*R*,*R*)-*β*-amide alcohol. The mono *N*-benzylated DPEN ligand **3b** is readily prepared by the reaction between 3 equiv of DPEN and benzylic bromide. Under such reaction conditions, **3b** is exclusively obtained and the insoluble hydrobromide can easily be separated from the reaction mixture.

To prepare the polymer-immobilized version of mono *N*-benzylated DPEN ligand, we synthesized 4-(4-vinylbenzyloxy-)benzyl DPEN **3c** as a chiral ligand monomer by using the same method employed for the preparation of **3b**. The precatalyst prepared from (*R*,*R*)-**3c** exhibited a high level of enantioselectivity (99.4% ee), as shown in Table 1. The results obtained encouraged us to prepare the polymer-immobilized chiral ligand. Because the chiral monomer (*R*,*R*)-**3c** contains styrenic double bonds, various types of vinyl monomers can be copolymerized with **3c**. The properties of the chiral copolymers often influence the catalytic activity in the asymmetric reaction. We selected styrene, 2-hydroxyethyl methacrylate, methyl methacrylate, *N*-isopropylacrylamide, and 4-hydroxymethylstyrene as achiral vinyl monomers. In many cases of using the polymer-immobilized catalyst, the degree of cross-linking and the structure of the cross-linking agent affect the catalytic activity of the polymeric catalyst. Divinylbenzene (DVB) and ethyleneglycol dimethacrylate (EGDMA) were used as cross-linking agents. The terpolymerization of the chiral ligand monomer **3c** (10 mol %), achiral monomer (88 mol %), and cross-linking agent (2 mol %) smoothly proceeded under radical polymerization conditions in DMF to produce various types of the corresponding polymer-immobilized chiral 1,2-diamine ligands **4** (Chart 2). The insoluble cross-linked polymers **4** were used as the chiral polymeric ligand of the $RuCl_2$−BINAP complex.

CHART 2. Polymer-Immobilized Chiral 1,2-Diamine Ligand



(*R*,*R*)-**4**

4a: R_1=H, R_2=Ph, R_3=H, R_4=C_6H_4
4b: R_1=H, R_2=Ph, R_3=Me, R_4=$CO_2CH_2CH_2OCO$
4c: R_1=Me, R_2=$CO_2CH_2CH_2OH$, R_3=Me, R_4=$CO_2CH_2CH_2OCO$
4d: R_1=Me, R_2=$CO_2CH_2CH_2OH$, R_3=H, R_4=C_6H_4
4e: R_1=Me, R_2=CO_2Me, R_3=Me, R_4=$CO_2CH_2CH_2OCO$
4f: R_1=H, R_2=$CONH^iPr$, R_3=Me, R_4=$CO_2CH_2CH_2OCO$
4g: R_1=H, R_2=$C_6H_4CH_2OH$, R_3=Me, R_4=$CO_2CH_2CH_2OCO$

TABLE 2. Asymmetric Hydrogenation of *rac*-1 by Using Polymer-Immobilized Complex[a]

		N-benzoyl pseudoephedrine			
entry	polymeric diamine	conv,[b] %	de,[b] %	ee,[c] %	config.
1[d]	**4a**	0			
2[e]	**4a**	7	>99	61.7	*R*,*R*
3[e]	**4b**	10	>99	88.5	*R*,*R*
4[e]	**4c**	100	>99	99.8	*R*,*R*
5[d]	**4c**	0			
6[f]	**4c**	100	>99	90.0	*R*,*R*
7	**4d**	100	>99	99.5	*R*,*R*
8	**4e**	81.5	>99	99.6	*R*,*R*
9	**4f**	100	>99	92.0	*R*,*R*
10	**4g**	100	>99	95.5	*R*,*R*

[a] Reactions conducted at room temperature in 2-propanol/DMF (1:1) for 2 h. [Diamine]:[$RuCl_2$]:[(*S*)-BINAP] = 2:1:1, S/C = 500. [b] Determined by HPLC and ^{1}H NMR analysis. [c] Determined by chiral HPLC analysis. [d] Reaction carried out in 2-propanol. [e] 24 h. [f] Reaction carried out in DMF.

Table 2 shows the results obtained from the dynamic kinetic resolution of *rac*-**1** via hydrogenation by using the polymeric catalyst. First, we used the polystyrene-based polymeric chiral ligand **4a** in 2-propanol. Unfortunately, no reaction occurred in this solvent (Table 2, entry 1), mainly due to the strong

(17) DPEN = 1,2-diphenylethylenediamine.

(18) Ohkuma, T.; Ooka, H.; Hashiguchi, S.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1995**, *117*, 2675–2676.

(19) Racemic α-(*N*-benzoyl-*N*-methylamino)propiophenone **1** was obtained from Nippon Soda Co. Ltd.

(20) Obtained amide alcohol **2** was treated with 20% NaOH aqueous solution in reflux ethanol for 2 h to give the *syn* amino alcohol, (−)-(*R*,*R*)-pseudoephedrine. Methyl protons of the *syn* isomer appeared at 0.94 ppm in ^{1}H NMR spectra of the amino alcohol with no peak at 0.88 ppm for the anti isomer.

hydrophobicity of the polymer support. The polymeric complex prepared from **4a** shrunk in the alcoholic solvent and this prevented the catalytic activity (entry 1). We encountered the same problem when we developed the different types of polymeric catalysts that were applied to the asymmetric hydrogenation of simple ketones.[21] We used a mixed solvent of 2-propanol and DMF to solve this problem.[22] However, the precatalyst prepared from **4a** produced a very low conversion with 61.7% ee (entry 2) in the mixed solvent of 2-propanol and DMF. By using the polar cross-linking agent (EGDMA), a slight improvement was observed (entry 3). When the hydrophilic achiral monomer, hydroxyethyl methacrylate, was incorporated (**4c**) into the polymer support, the reactivity of the polymeric precatalyst prepared from **4c** dramatically increased to yield *syn*-β-amide alcohol exclusively. The enantioselectivity obtained approached 100% ee (entry 4) in 2-propanol/DMF. The solvent used in this system strongly influenced both the reactivity and enantioselectivity. The repeated use of a single solvent of 2-propanol showed no conversion with this catalyst (entry 5). On the other hand, the same reaction smoothly occurred in DMF alone with lowering of the enantioselectivity (entry 6). In the case of 2-hydroxyethyl methacrylate used as an achiral monomer in the polymer-support preparation, the influence of the cross-linking structure was not so important. The DVB cross-linkage significantly promoted the asymmetric hydrogenation (entry 7). Although the use of poly(methyl methacrylate) as a polymer support showed excellent enantioselectivity in the same reaction, the polymeric catalyst yielded slightly lower conversion under the same reaction conditions (entry 8). Other hydrophilic polymer supports such as poly(acrylamide) and poly(4-hydroxymethylstyrene) yielded the corresponding chiral β-amide alcohol (*R*,*R*)-**2** in quantitative conversion with high enantioselectivities (entries 9 and 10).

One of the important advantages of using polymer-immobilized catalysts is the recyclability of the catalyst. The polymeric chiral complex could be easily separated from the reaction mixture and then recovered by filtration after the hydrogenation was completed. Thus, we studied the recycle experiment by using the polymeric precatalyst prepared from **4c**. We confirmed that recycling can be carried out at least five times without any loss of catalytic activity of the polymeric catalyst. Under the reaction conditions for entry 4 using the catalyst derived from **4c**, we obtained (*R*,*R*)-**2** in the quantitative yield with 99.8%, 99.8%, 99.8%, 99.8%, and 99.8% ee values for five recycling experiments.

In conclusion, we successfully prepared various types of polymer-immobilized chiral 1,2-diamine **4**. The polymeric precatalyst prepared from hydrophilic polymer support such as poly(hydroxyethyl methacrylate) exhibited excellent performance in the dynamic kinetic resolution of racemic α-amide ketone *rac*-**1** via hydrogenation to yield the corresponding *syn*-β-amide alcohol (*R*,*R*)-**2** in quantitative conversion with nearly perfect enantioselectivity. In addition, the polymer-immobilized catalyst could be reused several times without loss of catalytic activity.

(21) (a) Itsuno, S.; Tsuji, A.; Takahashi, M. *J. Polym. Sci., Part A: Polym. Chem.* **2004**, *42*, 4556–4562. (b) Takahashi, M.; Haraguchi, N.; Itsuno, S. *Tetrahedron: Asymmetry* **2008**, *19*, 60–66.

(22) Ohkuma, T.; Takeno, H.; Honda, Y.; Noyori, R. *Adv. Synth. Catal.* **2001**, *343*, 369–375.

Experimental Section

General Procedure for Preparation of Polymers 4a−g by Radical Polymerization. A glass ampule equipped with a magnetic stirrer chip was charged with **3d** (0.23 mmol, 0.1 g), comonomer (2.02 mmol), cross-linking agent (0.046 mmol), AIBN (97 μmol), and DMF (1 mL). After three vacuum freeze−thaw cycles, the ampule was sealed under liquid nitrogen. Polymerization was performed at 70 °C for 48 h. The ampule was opened and the resulting mixture was poured into methanol. The polymer afforded was collected over a glass filter, washed with THF and methanol, and dried in vacuo at 40 °C.

Asymmetric Hydrogenation of α-Amide Ketone. A 20-mL Schlenk vessel equipped with a Teflon-coated magnetic stirrer bar was charged with a polymer-supported chiral diamine ligand (0.015 mmol), $RuCl_2$/(*S*)-BINAP(dmf)$_n$ (0.007 g, 0.0075 mmol), and dry DMF (1 mL). The mixture was degassed and heated at 80 °C for 2 h. The DMF was removed under reduced pressure, and the solid obtained was transferred together with α-amide ketone (0.2 g, 0.75 mmol) to a 100-mL autoclave equipped with a pressure gauge and hydrogen gas inlet tube. The autoclave was flushed with argon to replace air after which a degassed solution of a 1:1 mixture of 2-propanol (1 mL)/DMF (1 mL) and 1.0 M *t*-BuOK solution in *t*-BuOH (0.075 mL) was added. Hydrogen was then introduced into the autoclave and then it was pressurized up to 1 MPa. The reaction mixture was stirred at room temperature for 2 h. After carefully venting the hydrogen gas, the reaction mixture was filtered through a silica gel column (ethyl acetate/methanol as eluent) to remove the insoluble polymeric catalyst. The purified product was further concentrated and dried under reduced pressure. The conversion was determined by using ^{1}H NMR, and the enantioselectivity was determined by using HPLC analysis (Chiralcel OJ-H, Daicel; hexane/2-propanol/ethanol = 8:1:1, 0.3 mL/min, rt, t_R(*R*,*R*) = 27.35 min, t_R(*S*,*S*) = 23.80 min). (1*R*,2*R*)-**2**: ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.97 (d, J = 6.9 Hz), 2.89 (s, 3H), 4.58 (br, 1H), 5.26 (br, 1H), 7.23−7.40 (m, 10H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 15.0, 26.8, 59.2, 73.5, 126.7, 127.4, 128.1, 128.6, 137.7, 143.4, 171.4.

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Supporting Information Available: Details on the experiment and the ^{1}H and ^{13}C NMR spectra of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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