Enantioselective Reduction of Oxime Ethers with Borane Catalyzed by Polymer-Supported 2-Piperazinemethanol

Shinichi Itsuno,*,† Takeshi Matsumoto,†
Daisuke Sato,‡ and Tsutomu Inoue‡

Department of Materials Science, Toyohashi University of Technology, Toyohashi 441-8580, Japan, and Research & Planning Laboratory, Odawara Research Center, Nippon Soda Co., Ltd., 345 Takada, Odawara, Kanagawa 250-0280, Japan

itsuno@tutms.tut.ac.jp

Received May 22, 2000

Introduction

The enantioselective reduction of the C═N double bond is an important synthetic strategy for the preparation of optically active amines and has received much attention over the past few years, in both academic and industrial research.[1,2] Recently, we described new chiral ligands derived from enantiopure 2-piperazinemethanol, which are effectively used for the borane reduction of imines and oximes as well as ketones.[3] For example, by using (*S*)-4-(*p*-toluenesulfonyl)-2-piperazinemethanol as a chiral ligand, acetophenone *O*-methyloxime was reduced with borane to give (*S*)-1-phenylethylamine in 84% ee at 50 °C.

On the other hand, asymmetric syntheses achieved using polymer-supported chiral catalysts are a particularly attractive type of organic reaction.[4] Polymer-supported catalysis is receiving considerable and ever increasing interest as a useful tool for automated reactions with unique microenvironments for stereoselective reactions.[5] Because of the various advantages of supported catalysts, we have prepared a polymer-supported chiral ligand containing the 2-piperazinemethanol structure. We now report an enantioselective borane reduction of oxime ethers using the polymer-supported oxazaborolidine catalyst.[6] The reusability of the polymeric chiral ligand has also been demonstrated.

Results and Discussion

Based on the results using 4-(*p*-toluenesulfonyl)-2-piperazinemethanol as a chiral ligand in borane reduction of oxime ethers in homogeneous system,[3] we have designed a novel chiral monomer **1**. In the reaction of 4-vinylbenzenesulfonyl chloride with enantiopure O-protected 2-piperazinemethanol, the sulfonyl group was regioselectively introduced to the less hindered amino group of the piperazine to give (*R*)-**1**. This chiral monomer was then subjected to polymerization with styrene and divinylbenzene under the suspension polymerization condition in water to give the chiral polymer beads **2**, which were converted into **3** by treatment with tetrabutylammonium fluoride in THF (Scheme 1). By means of the polymerization method shown in Scheme 1, the loading of chiral ligand and the degree of cross-linking can be readily controlled by regulating the fractions of chiral monomer and divinylbenzene. To understand the effect of polymeric catalyst on the asymmetric reduction, we have prepared several chiral polymers (**3a**−**e**) containing different loadings and degrees of cross-linking.

In the first place, chiral polymer **3a** was suspended in THF, which was allowed to react with BH_3 to form the supported chiral oxazaborolidine.[7] The polymeric chiral oxazaborolidine was then used for the borane reduction of acetophenone *O*-methyloxime (**4a**) to give chiral primary amine **5** (Scheme 2). By using **3a**, the borane reduction occurred smoothly at 50 °C, the oxime ether being consumed completely in 24 h to afford the corresponding primary amine in 56% yield with 72% ee. The lower isolated yield of primary amine was caused by difficulties in the removal of byproducts including methoxyamine. Using the oxazaborolidine prepared from trimethyl borate,[8] a somewhat lower ee was obtained (entry 4, Table 1). Using polymeric chiral ligands **3a** and **3b** as well as model ligand in the homogeneous system, no reaction occurred below room temperature. Interestingly, when the polymer **3c** containing 20 mol % of chiral ligand was used, the reduction occurred even at room temperature to give the corresponding enantioenriched amine in 82% ee (entry 6). This polymeric oxazaborolidine showed apparently higher activity than that of the low molecular weight counterpart in the homogeneous system. In the case of lightly cross-linked polymer **3d** having the same content of chiral ligand, higher enantioselectivity (96% ee) was achieved at room temperature. Some other ketoxime *O*-methyl ethers were also asymmetrically reduced using **3d** to give the amines in high ees. Heavily loaded polymer **3e** gave poorer results probably due to the rigidity of the catalyst site (entry 14). Although no reaction took place at −78 °C with the polymeric oxazaborolidine **3d**, the reduction occurred at 0 °C. At this temperature almost perfect enantioselectivity was obtained (99% ee) in the reduction of **4a** (entry 12). Although it is not clear why high activity appears in these cross-linked polymeric oxazaborolidines, our discovery

* To whom corresponding should be addressed. Phone and fax: +81 532 44 6813.
† Toyohashi University of Technology.
‡ Nippon Soda Co.

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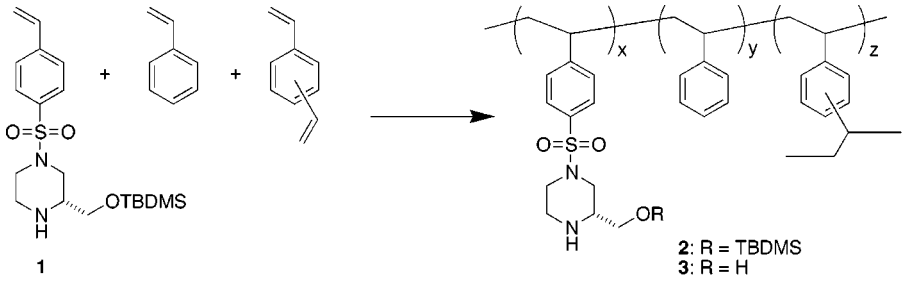
10.1021/jo0007837 CCC: $19.00
Published on Web 08/17/2000

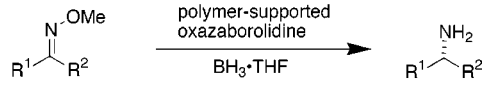
Scheme 1



x: mole fraction of chiral ligand
z: mole fraction of divinylbenzene

3a : x = 0.10, z = 0.10
3b : x = 0.10, z = 0.02
3c : x = 0.20, z = 0.10
3d : x = 0.20, z = 0.02
3e : x = 0.30, z = 0.02

Scheme 2



4a : R^1 = Ph, R^2 = Me
4b : R^1 = *p*-MeOPh, R^2 = Me
4c : R^1 = Ph, R^2 = Et
4d : R^1 = Ph, R^2 = *n*-Pr

Table 1. Enantioselective Reduction of Oxime Ether with BH_3·THF Catalyzed by Polymer-Supported Chiral Catalyst[a]

entry	oxime ether	polymeric ligand	*T* (°C)	time (h)	yield (%)	ee[b] (%)	config[c]
1	**4a**	*d*	50	6	61	84	*S*
2	**4a**	**3a**	50	12	56	72	*R*
3	**4a**	**3a**	rt	24	0		
4[e]	**4a**	**3a**	50	12	40	54	*R*
5	**4a**	**3b**	50	12	77	60	*R*
6	**4a**	**3c**	rt	24	60	82	*R*
7	**4a**	**3d**	rt	24	65	96	*R*
8	**4a**	(*S*)-**3d**[f]	rt	24	64	96	*S*
9	**4b**	**3d**	rt	24	75	86	*R*
10	**4c**	**3d**	rt	24	81	93	*R*
11	**4d**	**3d**	rt	24	63	88[g]	*R*
12	**4a**	**3d**	0	48	70	99	*R*
13	**4a**	**3d**	−78	48	0		
14	**4a**	**3e**	rt	36	37	90	*R*

[a] 2.23 equiv of the polymeric chiral ligand was used. [b] The enantiomeric excess of **5**. Determined by GC analysis with a chiral stationary phase column unless otherwise noted. See the Experimental Section. [c] The absolute configurations of **5a**,[10] **5c**,[11] and **5d**[12] were determined by the comparison of optical rotation with the literature values. The configuration of **5b** was assumed to be *R* from a similarity of the elution order in GC analysis. [d] (*S*)-4-(*p*-Toluenesulfonyl)-2-piperazinemethanol was used.[3] [e] Oxazaborolidine generated from trimethyl borate and **3a** was used. [f] (*S*)-**3d** was prepared from (*S*)-2-(*tert*-butyldimethylsilyloxy)methylpiperazine. [g] Determined by HPLC analysis with a chiral stationary phase column. See the Experimental Section.

belongs to the rare class of catalysts that are more active on support than in solution.

To show that the polymeric chiral ligand can be recycled a number of times, the borane reduction of **4a** using **3d** was repeated five times at room temperature (recycle method A in Experimental Section). The enantioselectivities remain around 95% ee (96, 93, 98, 95, and 96% ee, respectively) clearly illustrating the reusability of the chiral ligand. Polymer-supported oxazaborolidine could be reused even without its regeneration. In such a system, the chiral product in solution can be separated and remaining polymeric oxazaborolidine can be reused without regeneration in subsequent reactions (recycle method B in Experimental Section). The same level of enantioselectivities (94−96% ee) were achieved by this recycling method.

In summary, we have developed a polymer-supported version of 2-piperazinemethanol, which was efficiently used in the enantioselective borane reduction of oxime ethers to give enantioenriched primary amines. By appropriately balancing the content of the chiral ligand and the degree of cross-linking in the polymer support, it is possible to obtain a highly active catalyst. It is noteworthy that this chemistry shows a remarkable example of the polymer effect on catalysts to increase both reactivity and selectivity.

Experimental Section

General Procedures. All reactions were carried out under an atmosphere of dry nitrogen. Tetrahydrofuran (THF) and diethyl ether were freshly distilled from sodium benzophenone ketyl under nitrogen immediately before use. Flash column chromatography was performed over Wako silica gel (Wakogel C-200, 100−200 mesh). NMR spectra were obtained in $CDCl_3$ at 270 MHz for ^{1}H and 67.8 MHz for ^{13}C.

(*R*)-2-(*tert*-Butyldimethylsiloxy)methyl-4-(4-vinylbenzenesulfonyl)piperazine 1. To a solution of (*R*)-2-(*tert*-butyldimethylsiloxy)methylpiperazine (2.89 g, 12 mmol) and triethylamine (4.55 g, 45 mmol) in chloroform (15 mL) at 0 °C was added dropwise a chloroform (15 mL) solution of 4-vinylbenzenesulfonyl chloride[9] (2.42 g, 12 mmol) prepared from sodium 4-styrenesulfonate and thionyl chloride. The mixture was stirred at room temperature for 12 h. Water (40 mL) was then added, and the aqueous phase was extracted with chloroform. The organic layers were combined and dried over $MgSO_4$, filtered, and concentrated. Flash chromatography (hexane/ethyl acetate = 1:5) gave 3.40 g (70%) of **1** as colorless oil: $[\alpha]^{23}_D$ +41 (*c* 0.845, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.03 (s, 6H), 0.86 (s, 9H), 1.75 (br, 1H), 1.98−2.13 (m, 1H), 2.28−2.42 (m, 1H), 2.81−3.09 (m, 3H), 3.37−3.63 (m, 4H), 5.54 (*J* = 10.7 Hz, 1H), 5.88 (d, *J* = 17.6 Hz, 1H), 6.75 (dd, *J* = 10.7, *J* = 17.6 Hz, 1H), 7.53 (d, *J* = 8.5 Hz, 2H), 7.69 (d, *J* = 8.5 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ −5.0, 18.8, 26.4, 45.1, 47.1, 48.8, 56.3, 65.1, 117.9, 127.1, 128.6, 135.0, 135.8, 142 5; IR (neat) 1351, 1166 cm^{-1}. Anal. Calcd for $C_{19}H_{32}N_3O_3SSi$: C, 57.54; H, 8.13; N, 7.06. Found: C, 57.50; H, 8.09; N, 7.12.

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Polymer-Supported Chiral Ligand 3d. To a well-stirred solution of poly(vinyl alcohol) 0.6 g, degree of polymerization: 2000, 78−82% hydrolyzed) in 300 mL of water cooled to 0 °C was added a solution of **1** (3.25 g, 8.0 mmol), styrene (3.25 g, 31.2 mmol), divinylbenzene (0.10 g, 0.8 mmol), and 2,2′-azobis-(4-methoxy-2,4-dimethylvaleronitrile) (0.13 g, 0.5 mmol) in benzene (3 mL). After 1 h of stirring at 0 °C to homogenize the particle size, the temperature was raised to 80 °C and the reaction mixture was stirred vigorously (400 rpm) for 48 h at the same temperature. The resulting polymer beads were filtered and washed with water, methanol, THF−methanol, THF, and methanol, respectively. After the beads were dried in vacuo at 40 °C, 5.62 g (85%) of polymer **2d** was obtained: IR (KBr) 1352, 1166 cm^{-1}. Anal. Calcd for $(C_{19}H_{32}N_2O_3SSi)_{0.20}(C_8H_8)_{0.78}(C_{10}H_{10})_{0.02}$: C, 75.38; H, 7.93; N, 3.43. Found: C, 75.45; H, 8.01; N, 3.38.

2d was then suspended in THF (35 mL), and *n*-Bu_4NF (10.1 mL, 1.0 M) was added. The mixture was stirred at 50 °C for 20 h. The polymer beads were collected on the glass filter and washed with water, THF, and methanol. After the beads were dried in vacuo at 40 °C for 24 h, 4.75 g (100% from **2d**) of polymer **3d** was obtained. From the elemental analysis data shown below, the functional group substitution of **3d** was calculated to be 0.71 mmol/g: IR (KBr) 1331, 1164 cm^{-1}. Anal. Calcd for $(C_{13}H_{18}N_2O_3S)_{0.20}(C_8H_8)_{0.78}(C_{10}H_{10})_{0.02}$: C, 77.38; H, 7.21; N, 3.99. Found: C, 77.41; H, 7.19; N, 3.95.

General Procedure of Enantioselective Borane Reduction of Oxime Ether Using Polymer-Supported Catalyst. To a suspension of polymer-supported chiral ligand **3d** (4.79 g, 6.7 mmol) in 25 mL of dry THF was added dropwise BH_3·THF (9.0 mL, 1.0 M in THF). The reaction was stirred at 50 °C for 15 h. The excess borane and THF were removed in vacuo. The resulting polymeric oxazaborolidine was suspended in dry THF (25 mL), and acetophenone *O*-methyloxime (0.45 g, 3 mmol) was added. BH_3·THF (6.0 mL, 1.0 M) was then added to the above mixture and stirred at room temperature for 24 h. The reaction mixture was treated with 1 N HCl (15 mL) and filtered through a glass filter. The filtrate was washed with ether and neutralized with aqueous ammonia. The aqueous phase was extracted with ether, and then the combined organic layers were dried over $MgSO_4$, filtered, and concentrated. Flash chromatography (ether) gave 0.24 g (65%) of 1-phenylethylamine (**5a**) as a colorless oil. The enantioselectivity (96% ee) was determined for its trifluoroacetylated derivative by GC analysis using a chiral stationary-phase column (Astec Chiraldex G-TA, 30 m × 0.25 mm) at 110 °C; t_R = 25.3 min (*R*), t_R = 27.1 min (*S*). For **5b**: t_R = 44.9 min, t_R = 46.1 min at 130 °C. For **5c**: t_R = 36.3 min (*R*), t_R = 38.0 min (*S*) at 110 °C. The enantioselectivity of **5d** was determined for its trifluoroacetylated derivative by HPLC analysis using Chiralcel OD (flow rate 0.5 mL/min, hexane/2-propanol = 95:5, column temperature; 30 °C); t_R = 15.8 min (*R*), t_R = 17.1 min (*S*).

Recycle Method A. The polymeric chiral ligand **3d** separated through glass filter was neutralized with ammonia and washed with water, THF, and methanol. After being dried in vacuo at 40 °C for 24 h, **3d** was used for the second reaction.

Recycle Method B. A flask equipped with a glass frit was used for the recycle use of the polymeric oxazaborolidine without its regeneration. After the reaction was completed, the product in solution was separated by filtration through fritted glass attached to the flask. The second reaction was performed by using the polymeric oxazaborolidine left in the flask.

Acknowledgment. This work was supported in part by a Grant-in-Aid for Scientific Research from the Ministry of Education, Science, and Culture of Japan. Financial support from the Ogasawara Foundation for the Promotion of Science & Technology is also greatly acknowledged.

JO0007837