J|A|C|S
COMMUNICATIONS

Main-Chain Ionic Chiral Polymers: Synthesis of Optically Active Quaternary Ammonium Sulfonate Polymers and Their Application in Asymmetric Catalysis

Shinichi Itsuno,* Devproshad K. Paul, M. A. Salam, and Naoki Haraguchi

Department of Materials Science, Toyohashi University of Technology, Toyohashi 441-8580, Japan

Received December 14, 2009; E-mail: itsuno@tutms.tut.ac.jp

Recently, polymer-immobilized asymmetric catalysts have attracted considerable attention. Although substantial research pertaining to the use of side-chain-functionalized polymers has been carried out, only a limited number of investigations to elucidate the use of main-chain-functionalized polymers have been performed. Some examples of main-chain-functionalized polymers include polymeric chiral salen ligand,[1] poly(amino acid),[2] poly(tartrate),[3] polybinaphthols,[4] and helical polymers.[5] These main-chain chiral polymers have been successfully used as chiral catalysts in various kinds of asymmetric reactions. The rigid and sterically regular polymer catalysts may have a better defined microenvironment at the catalytic sites and have allowed systematic modification of their catalytic properties.

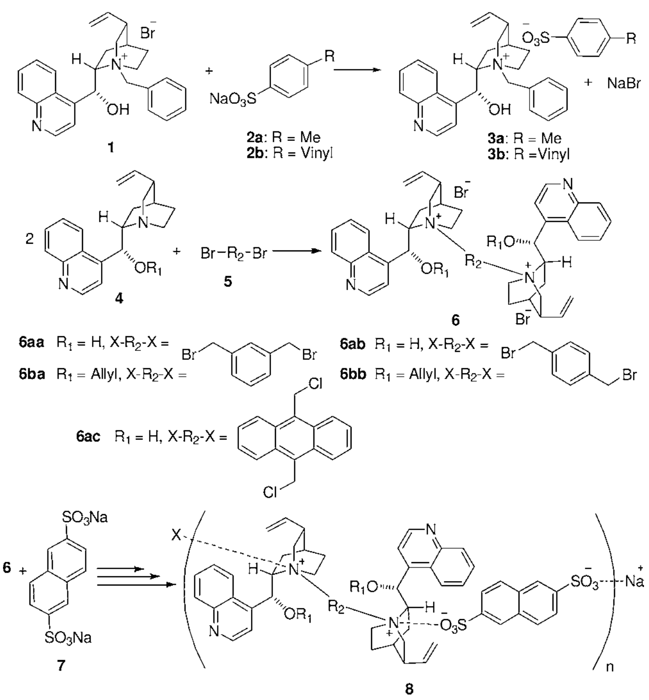
In asymmetric synthesis, chiral organocatalysts have received considerable attention in recent years, as asymmetric reactions with chiral organocatalysts satisfy green chemistry requirements.[6] One class of important chiral organocatalysts is optically active quaternary ammonium salts, which can be used in various kinds of asymmetric transformations. Polymer-immobilized versions of chiral organocatalysts have also been reported.[7] These chiral organocatalysts are all side-chain-modified polymer-immobilized ammonium salts, and the chiral quaternary ammonium salt is attached randomly as a pendant group of the polymer support.

We have found that quaternary ammonium sulfonates, such as **3**, can be prepared easily and are extremely stable in both aqueous and organic media.[8,9] We have recently reported polymer-immobilized chiral ammonium sulfonate obtained by radical polymerization of the chiral vinyl monomer **3b**. The obtained chiral polymer was successfully used as an asymmetric catalyst for an alkylation reaction.[10] This approach involved the attachment of the chiral catalyst moiety to an achiral and sterically irregular polymer backbone.

Because of the exceptional stability of quaternary ammonium sulfonates and their excellent catalytic activity, we used the quaternary ammonium sulfonate formation reaction for chiral polymer synthesis and employed the resulting chiral polymers as novel asymmetric catalysts. The reaction between chiral bis(quaternary ammonium salt) **6** and disulfonate **7** results in the formation of **8**, a main-chain chiral polymer of quaternary ammonium sulfonate that contains an ionic bond in the main chain. To the best of our knowledge, this is the first instance of the synthesis of chiral polymers that involve main-chain quaternary ammonium sulfonate bonding. In this study, we focused on the synthesis of the chiral quaternary ammonium sulfonate polymers and their use in the asymmetric benzylation of *N*-diphenylmethylidene glycine *tert*-butyl ester (**9**).

Synthesis of quaternary ammonium sulfonate is usually very simple and quantitative (Scheme 1). The ion-exchange reaction between quaternary ammonium halide and sodium sulfonate occurs readily to afford the corresponding quaternary ammonium sulfonate in quantitative conversion. For example, reaction of **1** and **2** occurred immediately to afford chiral sulfonates **3**, which could be easily extracted using an organic solvent.

Scheme 1



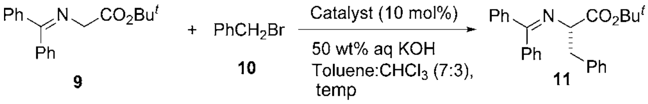
We then applied the quaternary ammonium sulfonate formation reaction to the polymer synthesis. First, we prepared chiral bis(quaternary ammonium salt) **6** containing the cinchonidine unit. Reaction of 2 equiv of cinchonidine derivative **4** with dihalide **5** afforded **6**, as shown in Scheme 1. The other monomer for this polymerization is a sodium disulfonate. We chose disodium 2,6-naphthalenedisulfonate (**7**) as the disulfonate monomer.

Disulfonate **7** is soluble only in water. Bis(quaternary ammonium halide) **6** is soluble in organic solvents, such as methanol, *N*,*N*-dimethylformamide (DMF), and dimethyl sulfoxide (DMSO). Our first polymerization attempt involved the reaction of an aqueous solution of **7** with a DMSO solution of **6**. In this homogeneous system, surprisingly, no reaction occurred after 3 h. The product solution contained a mixture of **7** and **6**. With the addition of chloroform to the reaction mixture, **7** completely precipitated out. Even when solid disulfonate **7** was added to the DMSO solution of **6**, no reaction occurred. Interestingly, when an aqueous solution of **7** was treated with powdered **6** without any organic solvent, we found a white precipitate of **8**. The precipitated product was

10.1021/ja909972d

thoroughly washed with dichloromethane and water to remove unreacted **6** and **7**, respectively. The obtained solid **8** was insoluble both in water and some organic solvents, such as toluene, chloroform, and ethanol, but was soluble in DMSO and DMF. The ^{1}H NMR spectrum of product **8** contained both the cinchonidine and naphthalene moieties. The inherent viscosity ($[\eta] = 0.1-0.2$) showed that product **8** is a polymeric material.

Table 1. Asymmetric Benzylation of *N*-Diphenylmethylidene Glycine *tert*-Butyl Ester[a]



entry	catalyst	temp. (°C)	11 time (h)	 yield (%)	 ee (%)[b]	 config.
1[c]	**1**	0	0.5	78	69	*S*
2[c]	**3a**	0	0.5	88	68	*S*
3[c]	**6aa**	rt	15	72	57	*S*
4[d]	**6ba**	0	2	91	90	*S*
5[d]	**6ba**	−20	5	94	95	*S*
6	**6ab**	0	12	91	80	*S*
7[d]	**6bb**	0	4	92	80	*S*
8[d]	**6bb**	−20	6	92	86	*S*
9[e]	**6ac**	0	6	88	86	*S*
10[e]	**6ac**	−20	12	75	86	*S*
11[c]	**8aa**	rt	12	75	60	*S*
12	**8ba**	0	15	86	92	*S*
13	**8ba**	−20	20	85	94	*S*
14	**8ab**	0	15	92	82	*S*
15	**8bb**	0	20	90	91	*S*
16	**8bb**	−20	20	93	94	*S*
17	**8bb**[f]	−20	20	91	93	*S*
18	**8bb**[g]	−20	20	90	93	*S*
19	**8ac**	0	48	83	87	*S*
20	**8ac**	−20	48	90	93	*S*

[a] The reaction was carried out with 1.2 equiv of benzyl bromide in the presence of 10 mol % catalyst in 50 wt % aqueous KOH/toluene/$CHCl_3$. [b] Enantiopurity was determined by HPLC analysis using a chiral column (Chiralcel OD-H) with 1:100 2-propanol/hexane as the eluent. [c] Toluene was used as an organic solvent. [d] See ref 11a. [e] See ref 12. [f] **8bb** used in entry 16 was reused. [g] **8bb** used in entry 17 was reused.

In order to investigate the catalytic activity of the chiral quaternary ammonium polymer **8**, we used chiral quaternary ammonium sulfonates as chiral organocatalysts for asymmetric benzylation of **9**. In a biphasic system of toluene and an aqueous alkaline solution, the reaction with monomeric quaternary ammonium sulfonate **3a** occurred smoothly to afford the corresponding chiral phenylalanine derivative in 88% yield and 68% ee (Table 1, entry 2). The catalytic activity of **3** was similar to that of the original chloride **1** (entry 1). Jew and co-workers[11] have systematically investigated the effectiveness of dimeric cinchonidinium salts for asymmetric alkylation. Najera et al. also reported dimeric cinchonidinium salts containing an anthracene moiety.[12] In most cases, the performance with the dimeric salt was better than that with the monomeric ones such as **1**. In the presence of chiral bis(quaternary ammonium bromide) **6ba**, they obtained 90% ee in the asymmetric benzylation of **9** to **11** (entry 4).[11a] Lowering the reaction temperature resulted in higher enantioselectivity (entry 5).[11a] We used chiral ionic polymer **8** as an organocatalyst in the same reaction. When polymer **8** was added in a biphasic system of aqueous KOH and toluene/chloroform, **8** was smoothly suspended in the organic phase. After the asymmetric benzylation of **9** was completed, product **11** was easily extracted from the organic phase. Even when the ionic polymer **8** was treated with a strong aqueous alkaline solution during the reaction, no destruction of its salt structure was detected. The polymeric catalyst **8** was easily separated from the reaction mixture. When **8ba** was used as a chiral organocatalyst, the reaction occurred smoothly to afford **11** in 92% ee (entry 12). In the presence of **8bb**, the same reaction occurred with a high yield and 91% ee. The enantioselectivity obtained from polymeric catalyst **8bb** was obviously higher than that obtained from model catalyst **6bb** (entry 15 vs 7). At −20 °C, a higher enantioselectivity of 94% ee was obtained using the same polymer (entry 16). Since the polymeric chiral catalyst was not soluble in the organic solvent used for the reaction, the polymer could be easily separated from the reaction mixture. The recovered polymer could be reused for the same reaction (entries 16−18). Although the reaction mechanism with the polymeric organocatalyst is not clear at this moment, the transition state should involve the polymeric ion complex to give the product.

In summary, we have prepared a novel type of main-chain chiral polymer that comprises a quaternary ammonium sulfonate repeating unit. This chiral polymer was successfully used as a catalyst for asymmetric alkylation of a glycine derivative. The use of chiral ionic polymers as organocatalysts may be extended to other types of asymmetric transformations.

Acknowledgment. This work was financially supported by a Grant-in-Aid from the Ministry of Education, Culture, Sports, Science and Technology (Japan).

Supporting Information Available: Details pertaining to the experimental procedure, NMR data, and viscosity data. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) (a) Pathak, K.; Bhatt, A. P.; Abdi, S. H. R.; Kureshy, R. I.; Khan, N.-U. H.; Ahmad, I.; Jasra, R. V. *Chirality* **2007**, *19*, 82. (b) Shin, C.-K.; Kim, S.-J.; Kim, G.-J. *Tetrahedron Lett.* **2004**, *45*, 7429.

(2) (a) Julia, S.; Masana, J.; Vega, J. C. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 929. (b) Julia, S.; Guixer, J.; Masana, J.; Rocas, J.; Colonna, S.; Annunziata, R.; Molinari, H. *J. Chem. Soc., Perkin Trans. 1* **1982**, 1317. (c) Itsuno, S.; Sakakura, M.; Ito, K. *J. Org. Chem.* **1990**, *55*, 6047.

(3) Canali, L.; Karjalainen, J. K.; Sherrington, D. C.; Hormi, O. *Chem. Commun.* **1997**, 123.

(4) Huang, W.; Hu, Q.; Zheng, X.; Anderson, J.; Pu, L. *J. Am. Chem. Soc.* **1997**, *119*, 4313. (b) Yu, H.-B.; Hu, Q.-S.; Pu, L. *Tetrahedron Lett.* **2000**, *41*, 1681. (d) Johannsen, M.; Jorgensen, K. A.; Zheng, X. F.; Hu, Q. S.; Pu, L. *J. Org. Chem.* **1999**, *64*, 299.

(5) (a) Hasegawa, T.; Furusho, Y.; Katagiri, H.; Yashima, E. *Angew. Chem., Int. Ed.* **2007**, *46*, 5885. (b) Matsumoto, K.; Yotuyanagi, H.; Namikoshi, T.; Teraguchi, M.; Marwanta, E.; Kaneko, T.; Aoki, T. *Polym. Prepr. Jpn.* **2008**, *57*, 4065.

(6) (a) Berkessel, A.; Groger, H. In *Asymmetric Organocatalysis: From Biomimetic Concepts to Applications in Asymmetric Synthesis*; Wiley-VCH: Weinheim, Germany, 2005. (b) *Enantioselective Organocatalysis*; Dalko, P. I., Ed.; Wiley-VCH: Weinheim, Germany, 2007.

(7) (a) Zhengpu, Z.; Yongmer, W.; Zhen, W.; Hodge, P. *React. Funct. Polym.* **1999**, *41*, 37. (b) Thierry, B.; Plaquevent, J. C.; Cahard, D. *Tetrahedron: Asymmetry* **2003**, *14*, 1671. (c) Chinchilla, R.; Mazon, P.; Najera, C. *Adv. Synth. Catal.* **2004**, *346*, 1186. (d) Danelli, T.; Annunziata, R.; Benaglia, M.; Cinquini, M.; Cozzi, F.; Tocco, G. *Tetrahedron: Asymmetry* **2003**, *14*, 461. (e) Wang, X.; Yin, L.; Wang, Y. *Tetrahedron: Asymmetry* **2007**, *18*, 108. (f) Shi, Q.; Lee, Y. J.; Cheng, M.; Jew, S. *Chem. Lett.* **2008**, *37*, 436.

(8) Itsuno, S.; Arakawa, Y.; Haraguchi, N. *J. Soc. Rubber Ind.* **2006**, *79*, 448.

(9) (a) Arakawa, Y.; Haraguchi, N.; Itsuno, S. *Tetrahedron Lett.* **2006**, *47*, 3239. (b) Arakawa, Y.; Chiba, A.; Haraguchi, N.; Itsuno, S. *Adv. Synth. Catal.* **2008**, *350*, 2295.

(10) Arakawa, Y.; Haraguchi, N.; Itsuno, S. *Angew. Chem., Int. Ed.* **2008**, *47*, 8232.

(11) (a) Jew, S.-s.; Jeong, B.-S.; Yoo, M.-S.; Huh, H.; Park, H.-g. *Chem. Commun.* **2001**, 1244. (b) Lee, J.-H.; Yoo, M.-S.; Jung, J.-H.; Jew, S.-s. *Tetrahedron* **2007**, *63*, 7906.

(12) Chinchilla, R.; Mazon, P.; Najera, C. *Tetrahedron: Asymmetry* **2002**, *13*, 927.

JA909972D