Polymeric Catalysts

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An Immobilization Method of Chiral Quaternary Ammonium Salts onto Polymer Supports**

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Asymmetric transformations by means of a chiral quaternary ammonium salt acting as the organocatalyst have been extensively studied. Since the pioneering work by a research group at Merck in 1984,[1] cinchona-alkaloid-derived quaternary ammonium salts have been widely used as chiral organocatalyst in various asymmetric reactions.[2] The enantioselective alkylation of glycinate Shiff base in the presence of an enantiopure quaternary ammonium salt is a typical asymmetric synthesis of chiral α-amino acids.[3] From the viewpoint of reaction efficiency, polymer-immobilized chiral catalysts which have been used for asymmetric reactions are of considerable interest in organic synthesis. Although numerous polymer-immobilized chiral catalysts have been developed, but so far, there have been limited reports on polymer-immobilized chiral quaternary ammonium salts.[4] First examples were reported by Chiellini and Solaro in 1977[5] and Colonna et al. in 1978.[6] In 1981, Kobayashi and Iwai reported asymmetric catalysis by quinium salts immobilized onto polystyrene.[7] Hodge et al. also reported the quaternary ammonium salts of polymer-immobilized cinchona alkaloids [8] where the polymers were simply prepared through quaternarization of the cinchona alkaloid with partially chloromethylated cross-linked polystyrene. Najera and co-workers used the same type of polymeric cinchona-alkaloid quaternary ammonium salt for the enantioselective alkylation of *N*-diphenylmethylene glycine esters.[9] Cahard and co-workers have developed a similar type of polystyrene-immobilized chiral quaternary ammonium salts that have a spacer arm.[10] Furthermore, hydrocinchonidinium salts were immobilized onto Merrifield resin and used for the same alkylation reaction.[11] Poly(ethylene glycol) was also utilized as a polymer support of a chiral quaternary ammonium salt.[12–14] All of the above examples involve a covalent bond between the polymer and the chiral quaternary ammonium salt. We have found that quaternary ammonium sulfonate is quite stable and that polymers possessing sulfonate groups can immobilize quaternary ammonium cations through ionic bonding. [15] To our knowledge, this is a new type of immobilization comprising of an ionic bond between a chiral catalyst and a polymer. We have developed two methods of the ionic immobilization: the first involves the polymerization of a chiral quaternary ammonium sulfonate monomer, and the second is the immobilization of a chiral quaternary ammonium salt onto a sulfonated polymer through an ion exchange reaction. These polymeric chiral quaternary ammonium salts were successfully used as polymeric organocatalysts in the asymmetric alkylation of a glycine derivative. This is the first example of the immobilization of quaternary ammonium salt through an ionic interaction.

As chiral quaternary ammonium sulfonates can be easily prepared from cinchonidine, we have prepared our styrene sulfonate monomers from this substrate (Scheme 1). *N*-Benzylcinchonidinium chloride (**1a**) was treated with sodium *p*-styrene sulfonate (**2b**) in water, and subsequent extraction with dichloromethane gave the chiral quaternary ammonium monomer **3b**. The chiral monomer was copolymerized with styrene and divinylbenzene under radical condition to give the corresponding polymeric chiral quaternary ammonium salt **4aA**. By using this method, any type of chiral quaternary ammonium salt can be transformed into its corresponding monomer. This method is an easier way to obtain the chiral quaternary ammonium salt polymers in comparison to the conventional covalent bonding method. By means of this method, the original chiral quaternary ammonium structure can always be maintained in the polymer, as no chemical modification on the chiral ammonium moiety is required.

On the other hand, the same polymeric chiral quaternary ammonium salts can be readily prepared from polymers having sulfonate pendant groups (Scheme 1). An ion exchange reaction of **8** with a chiral quaternary ammonium salt gave the polymeric ammonium salts **4**. If difficulty in the chiral monomer synthesis is encountered or if functionalities contained in the quaternary ammonium moiety hinder the polymerization reaction, then the ion exchange reaction of polymeric sulfonate is a suitable method for the preparation of these polymers.

The chiral polymers mentioned above were then used as a catalysts for the asymmetric alkylation of *N*-diphenylmethylene glycine *tert*-butyl ester (**5**; Scheme 2). In the presence of **4aA**, prepared by polymerization, benzylation smoothly afforded the corresponding phenylalanine derivative with 78 % *ee* (Table 1, entry 3). Under the same reaction conditions, the unsupported catalyst **3a** showed 68 % *ee* (Table 1, entry 2) and the original chloride catalyst **1a** gave 69 % *ee* (Table 1, entry 1). The enantioselectivity obtained by using

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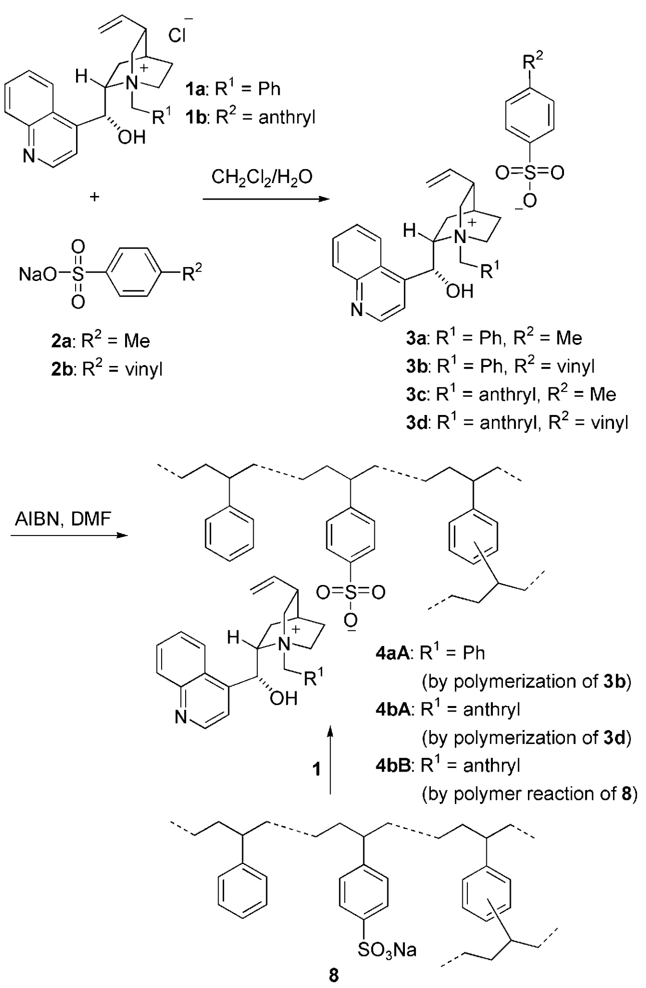
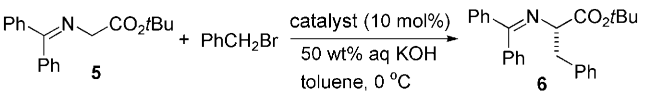


Scheme 1. Preparation of the polymer-supported chiral quaternary ammonium catalysts. AIBN = 2,2′-azobisisobutyronitrile, DMF = *N*,*N*-dimethylformamide.



Scheme 2. Asymmetric benzylation of *N*-diphenylmethylene glycine *tert*-butyl ester (**5**).

Table 1: Asymmetric benzylation of *N*-diphenylmethylene glycine *tert*-butyl ester (**5**).[a]

Entry	Catalyst	*t* [h]	Yield [%][b]	*ee* [%][c,d]
1	**1a**	0.5	78	69
2	**3a**	0.5	88	68
3	**4aA**	15	66	78
4[e]	**4aA**	15	66	79
5[f]	**4aA**	15	65	80
6	**7**	24	72	75
7[g]	**7**	24	0	–
8	**3c**	0.5	86	93
9	**4bA**	10	84	94
10[h]	**4bB**	24	73	95
11[i]	**4bB**	22	74	95
12[j,k]	**4bB**	24	70	96
13[j,k]	**4bB**	24	70	96
14[h,j]	**4bB**	24	61	96

[a] The reaction was carried out with benzyl bromide (1.2 equiv) in the presence of catalyst (10 mol%) in 50 wt% aqueous KOH/toluene at 0 °C. [b] The yields were determined by ^1H NMR spectroscopy. [c] The *ee* values were determined by HPLC on a chiral stationary phase using a Chiralcel OD-H column; eluent: 2-propanol/*n*-hexane(1:100). [d] All products have *S* configuration. [e] The polymer recovered from entry 3 was reused. [f] The polymer recovered from entry 4 was reused. [g] The polymer recovered from entry 6 was reused. [h] The polymer recovered from entry 10 was reused. [i] The reaction was carried out at −20 °C. [j] The polymer recovered from entry 12 was reused. [k] The polymer recovered from entry 13 was reused.

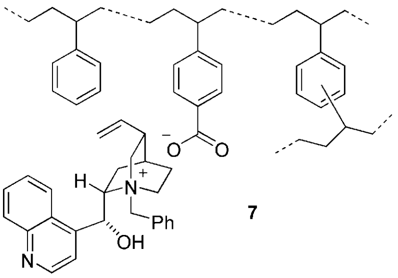


Figure 1. Polymer-supported chiral quaternary ammonium carboxylate catalyst **7**.

the polymeric catalyst was higher than those obtained from the unsupported catalyst **1a** and **3a**. Interestingly, the polymeric catalyst immobilized through the quaternary ammonium sulfonate substrate was unexpectedly stable. After the reaction the polymeric catalyst was easily separated and quantitatively recovered. No elimination of the chiral quaternary ammonium moiety was observed in solution. The recovered polymeric catalyst was successfully used again for the same reaction (Table 1, entries 4 and 5). Next, the carboxylate polymer **7** (Figure 1) was prepared by polymerization from the corresponding chiral monomer. The carboxylate counter anion of **7** had no obvious influence on the reactivity and enantioselectivity on the asymmetric benzylation reaction (Table 1, entry 6). However, in contrast to the sulfonated polymeric catalysts, **7** thoroughly released the chiral quaternary salt into the solution during the asymmetric reaction and could not be reused (Table 1, entry 7). This result shows that the sulfonate group gives considerable stability and is essential as a counter anion for the polymeric ammonium salt.

The 9-anthracenemethyl derivative of the cinchonidine-based quaternary ammonium salt **1b** was originally introduced by Lygo and co-workers as a powerful catalyst for the above mentioned asymmetric alkylation.[16] Enantioselectivity increased to 91 % using **1b**[16] and the sulfonated catalyst **3c** was also active for the same reaction to give 93 % *ee* (Table 1, entry 8). When the polymer-immobilized version of the catalyst **4bA** was employed a similar enantioselectivity (94 % *ee*) was obtained (Table 1, entry 9). Other alkyl halides were used as alkylating agent, and in all cases somewhat higher enantioselectivities were obtained with the polymer-supported catalyst (Table 2).

Table 2: Asymmetric alkylation of *N*-diphenylmethylene glycine *tert*-butyl ester (**5**) using polymeric catalyst **4bA**.[a]

Entry	Alkyl halide	*t* [h]	Yield [%][b,c]	*ee* [%][c,d]
1	benzyl bromide	10	84 (86)	94 (93)
2	4-methyl-benzyl bromide	5	90 (90)	97 (96)
3	4-bromo-benzyl bromide	12	95 (92)	91 (87)
4	allyl bromide	6	85 (85)	98 (95)
5	allyl iodide	16	74 (89)	80 (91)
6[e]	methyl iodide	19	45 (53)	70 (85)

[a] See Table 1 for reaction conditions. [b] The yields were determined by ^{1}H NMR spectroscopy. [c] Data in parenthesis were obtained using **3c**. [d] All products have *S* configuration. [e] Polymeric catalyst **4bB** was used.

Polymer-supported quaternary ammonium salts were also prepared by reaction of the sulfonated polymer **8** with a chiral quaternary ammonium salt. By using this method, any kind of chiral quaternary ammonium salt can be attached onto a polymer. The polymeric sulfonate catalyst **4bB** was used for the asymmetric benzylation to give the product with 95 % *ee* (Table 1, entry 10). This polymeric catalyst was recycled and reused and it showed the same catalytic activity (Table 1, entry 11).

Since this immobilization method can be applied to any kind of chiral ammonium salt, we chose to look at the excellent catalyst developed by Maruoka.[17] The chiral quaternary ammonium salt of polymer **9** (Figure 2) is one of the most effective catalysts for the asymmetric alkylation reaction. Our method is the only the way to prepare the polymer-supported Maruoka catalyst without modification of its original structure. By using 1 mol % of **9** in the reaction of **5** with benzyl bromide, the chiral product **6** was obtained in 84 % yield with 98 % *ee*. The polymer was fully recovered after the reaction and reused twice to give the same yields and enantioselectivities (for the second and third uses: 84 % yield, 98 % *ee*).

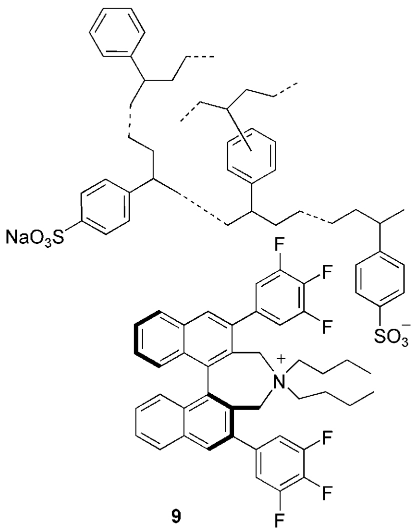


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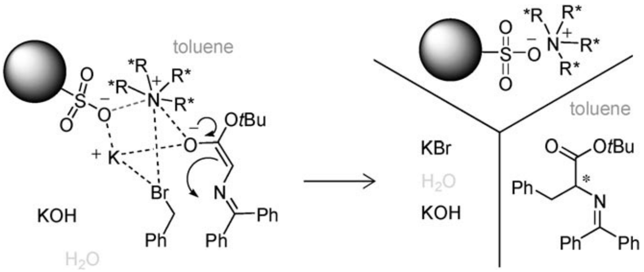
Figure 2. Polymer-supported Maruoka catalyst **9**.

Although the reaction mechanism is not clear at this moment, we believe that aggregated ion pairs seem to be involved (Scheme 3; see the Supporting Information). The results obtained from the polymer-immobilized catalysts leads to the assumption that the polymeric sulfonate must be closely involved in the transition state. Owing to the strong affinity between the sulfonate anion and ammonium cation, the polymeric quaternary ammonium sulfonate catalyst is always recovered.[18]



Scheme 3. A proposed reaction mechanism.

In conclusion, we have developed a novel immobilization method for chiral organocatalysts onto a polymer through ionic bonds to sulfonate groups. By using this method, any type of chiral quaternary ammonium organocatalyst can be easily immobilized onto a polymer support. Somewhat higher enantioselectivities were obtained in most cases by using this type of polymeric catalyst compared to the unsupported catalysts in homogeneous solution systems. The polymeric catalyst can be reused without the need for the regeneration of the catalyst.

Experimental Section

Preparation of **4aA**: A glass ampoule equipped with a magnetic stirring bar was charged with DMF (0.62 g), **3b** (228 mg, 0.4 mmol), styrene (366 mg, 3.52 mmol), divinylbenzene (10.4 mg, 0.08 mmol), and AIBN (13.2 mg, 80 μmol). The ampoule was sealed after three freeze-pump-thaw cycles. Copolymerization was carried out at 60 °C for 4 days. The ampoule was opened and the resulting mixture was poured into methanol (50 mL). The polymer was then collected and washed with dichloromethane and methanol, then dried in vacuo (93 %, 0.66 mol equiv nitrogen per gram of polymer). Elemental analysis calcd for $C_{10.6}H_{10.8}N_{0.2}O_{0.4}S_{0.1}$: C 84.56 %, H 7.23 %, N 1.85 %: found: C 84.38 %, H 7.09 %, N 2.03 %.

Preparation of **9**: A biphasic water (2 mL) and dichloromethane (5 mL) solution of (*S*)-4,4-dibutyl-2,6-bis(3,4,5-trifluorophenyl)-4,5-dihydro-3*H*-dinaphtho[2,1-c:1′,2′-e]azepinium bromide (0.1 g, 0.13 mmol) and **8** (128 mg, 0.11 mmol) was stirred at room temperature for 22 h. The resulting polymer was collected and washed with dichloromethane, water, and methanol, then dried in vacuo (166 mg, 56 % conversion, 0.38 mol equiv nitrogen per gram of polymer). Elemental analysis found C 82.55 %, H 6.70 %, N 0.52 %.

Asymmetric benzylation of **5**: A mixture of *N*-diphenylmethylene glycine *tert*-butyl ester (**5**; 0.53 g, 1.78 mmol), **9** (47 mg, 17.8 μmol), 50 wt % aqueous KOH solution (2.5 mL), and toluene (10.5 mL) was cooled to 0 °C. After stirring for 15 min, benzyl bromide (0.37 g, 2.14 mmol) was added and the reaction mixture stirred vigorously for 21 h. Saturated sodium chloride solution was then added, and the mixture was subsequently filtered to recover **9**, which was washed with water and dichloromethane several times. The organic phase was separated and concentrated in vacuo to give a colorless liquid **6**. The yield was determined by ^{1}H NMR spectroscopy (84%). The *ee* value (98%) was determined by HPLC on a chiral stationary phase using a Chiralcel OD-H column; eluent: 2-propanol/*n*-hexane (1:100); flow rate: 0.3 mL min^{-1}, $\lambda = 254$ nm, 22 °C; retention times: *R* enantiomer = 27.6 min, *S* enantiomer = 47.9 min.

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