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Tetrahedron Letters 47 (2006) 3239–3243

Tetrahedron Letters

Design of novel polymer-supported chiral catalyst for asymmetric transfer hydrogenation in water

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Received 14 February 2006; revised 2 March 2006; accepted 8 March 2006
Available online 23 March 2006

Abstract—New polymer-supported chiral sulfonamides containing sulfonated pendant group have been synthesized. Chiral catalyst prepared from the new polymer-support is more effective for asymmetric transfer hydrogenation of aromatic ketones in water compared to that prepared from conventional polystyrene-support. Polymer-supported catalysts containing quaternary ammonium salt as a pendant increased not only the reactivity but also the enantioselectivity in asymmetric transfer hydrogenation in water. Moreover, this type of polymer can be reused without loss of the catalytic activity.

Asymmetric reaction in aqueous media has been energetically studied because water is a safe, cheap, and environmentally friendly media.[1] Number of water-soluble chiral catalysts have been developed and contributed to the growth of green chemistry.[2] From a viewpoint of efficiency in organic synthesis, polymer-supported chiral catalysts are extremely useful for asymmetric reaction mainly due to their easy separation from the reaction mixture.[3] Combination of these two important methodologies would provide a strong tool for efficient asymmetric synthesis. One seminal paper of asymmetric reaction using polymer-supported chiral catalyst in water was reported by Uozumi and Hayashi, which involved the use of Argogel type[4] amphiphilic polymer-support having oligo(oxyethylene) chains.[5] After their initial efforts on asymmetric polymeric catalyst in aqueous media, development in this area has been quite limited.[6] Only a few research groups have focused on the polymeric chiral catalysts in water and in aqueous/organic biphasic systems.[7] We have developed novel polymer-support consisting of polystyrene main chain and highly hydrophilic sulfonated pendant group. Hydrophilicity–hydrophobicity balance of the polymer-support may be one of the most important factors to be optimized for the reaction in aqueous media, which can be readily controlled by changing the pendant sulfonate structure in our polymer-support. Copolymerization of chiral ligand monomer with *p*-styrenesulfonate readily gave the polymeric chiral ligand suitable for their use in aqueous media. Although sulfonated catalysts have been frequently used in aqueous biphase system,[8] sulfonated polymer-support has not been applied to organic reaction in aqueous media. We have chosen asymmetric transfer hydrogenation as a model reaction since the reaction can be performed in water[9] and some polymeric catalysts were also developed for the reaction.[10] Among the various chiral catalysts reported for the asymmetric transfer hydrogenation the most significant to date is the ruthenium (II) complex with optically active *N*-toluenesulfonyl-1,2-diphenylethylenediamine (TsDPEN) developed by Ikariya and Noyori group.[11] Xiao and co-workers reported that the poly(ethylene glycol)-supported catalyst is highly effective for the same reaction in water.[6g] Silica supported catalyst has also been performed in water in the presence of SDS surfactant.[6d,k] In this communication we introduced novel sulfonated polymer-supported chiral catalysts and their use in asymmetric transfer hydrogenation in water (Fig. 1).

Chiral monomer (1*R*,2*R*)-*N*-(*p*-styrenesulfonyl)-1,2-diphenylethylenediamine (**1**) was easily prepared from commercially available chiral 1,2-diamine and *p*-styrenesulfonyl chloride.[10d] The first polystyrene-supported chiral 1,2-diamine monosulfonamide was reported by Lemaire and co-workers in 1997.[10d] The corresponding polymeric chiral ruthenium (II) complex in 2-propanol/triethylamine gave 84% ee with only 23% yield after two

Keywords: Water; Sulfonated polymer; Polymer-support; Chiral catalyst; Asymmetric transfer hydrogenation.

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doi:10.1016/j.tetlet.2006.03.041

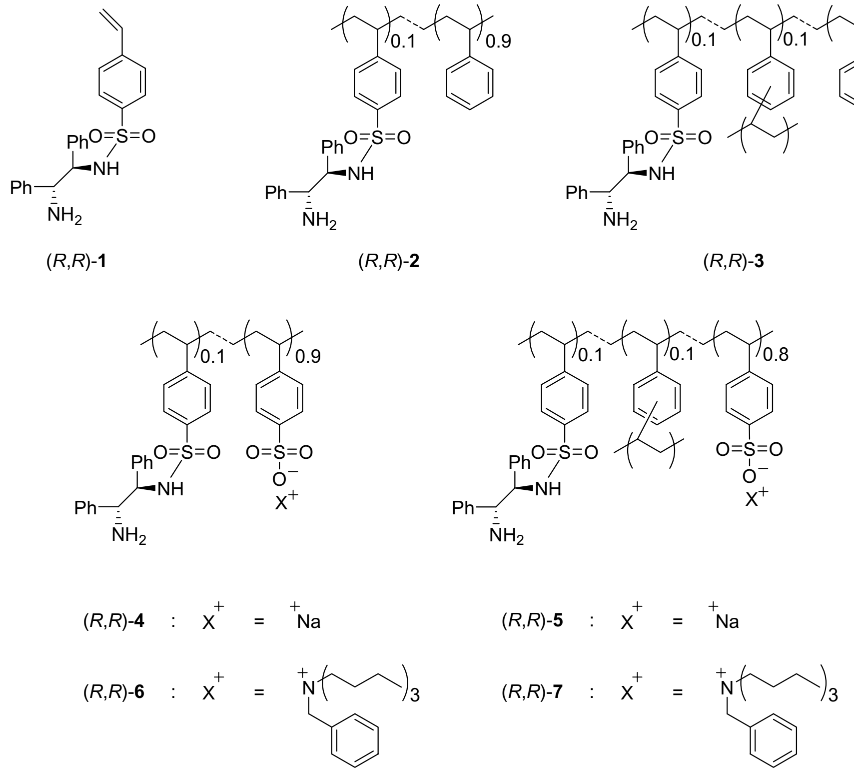


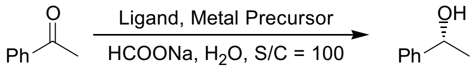
Figure 1. Polymer-supported chiral sulfonamides.

days at 70 °C. We synthesized the conventional polystyrene supported (*R*,*R*)-**2** and its crosslinked type (*R*,*R*)-**3**. Unfortunately, these polymers were severely shrunk in water. Sodium *p*-styrenesulfonate was copolymerized with the chiral monomer in DMF under radical polymerization condition to give the polymeric chiral ligand (*R*,*R*)-**4**. In the presence of divinylbenzene, (*R*,*R*)-**5** as an insoluble crosslinked polymer was obtained. Hydrophilicity–hydrophobicity balance of the polymer-support can be precisely controlled by changing the salt from Na^+ to quaternary ammonium. For example, benzyltributylammonium salt of *p*-styrenesulfonic acid was copolymerized with the chiral monomer in DMF to give (*R*,*R*)-**6** in 79% yield. Crosslinked polymer (*R*,*R*)-**7** was similarly prepared in high yield (94%).[12] In contrast with the conventional polystyrene supported (*R*,*R*)-**2** and (*R*,*R*)-**3**, these sulfonated polymers were nicely swelled in water.

We have then prepared polymer-supported chiral ligand–ruthenium (II) complex, which was used as a polymeric catalyst for asymmetric transfer hydrogenation of acetophenone in water. As reported in the literature,[9f] TsDPEN itself can be active enough even in water to afford the corresponding enantioenriched secondary alcohol in 94% ee (entry 1). However when conventional polystyrene-supported chiral ligands (*R*,*R*)-**2** and (*R*,*R*)-**3** were used, lower yields were obtained after longer reaction time as expected from their strong hydrophobicity (entries 2 and 3). In contrast to these polymers the sulfonated polymers (*R*,*R*)-**4** and (*R*,*R*)-**5** showed fairly higher activity in water (entries 4 and 5). Lowering the reaction temperature caused the decrease of the yield (entry 6). Surprisingly, the catalyst derived from (*R*,*R*)-**6** increased not only the reactivity but also the enantioselectivity in this reaction and gave **9a** in 98% ee with quantitative conversion (entry 7).[13] The reaction still occurred at room temperature with the catalyst derived from (*R*,*R*)-**6** to attain the quantitative conversion (entry 8). Crosslinked polymer (*R*,*R*)-**7** also performed well in water to give high level of enantioselectivity with quantitative yield within 3 h (entry 9). Even at lower temperature, quantitative conversion with 98% ee was obtained (entry 10). Since the polymeric chiral catalysts were insoluble in water the catalyst was easily separated from the reaction mixture and recycled several times (entry 11). Enantioselectivities of 97–98% ee were obtained in five recycle runs by using (*R*,*R*)-**7** derived catalyst. Transition metal precursors other than ruthenium (II) were also examined in the same reaction in water using the polymeric catalyst derived from (*R*,*R*)-**6**. Almost the same activity was observed with the catalyst prepared from $[RhCl_2Cp^*]_2$, while the catalyst from $[IrCl_2Cp^*]_2$ decreased both reactivity and enantioselectivity (entries 12 and 13).

In the heterogeneous reaction, stirring of the reaction mixture considerably influenced the reactivity. The catalyst prepared from TsDPEN required vigorous stirring to proceed the reaction (entry 1) and very low conversion was attained without stirring (entry 14), while the polymeric catalyst from (*R*,*R*)-**7** gave higher conversion and % ee under the same reaction condition (entry 15). Influence of surfactant is sometimes important to perform the organic reaction in aqueous media. Very recently, Wang et al. investigated the effect of surfactant in the asymmetric transfer hydrogenation in water.[9f] In our case, ammonium salt of sulfonic acid could be performed as a kind of phase transfer catalyst in water due to its amphiphilicity. This was confirmed by the same reaction with TsDPEN in the presence of BTBA salt (entry 16). However increase of enantioselectivity was only observed by using the polymeric catalyst. Although a clear explanation is not available for these results at the moment, it is obvious that polymeric sulfonates would form a special microenvironment within a polymer network structure that provides high enantioselectivity (Table 1).

Table 1. Asymmetric transfer hydrogenation of **8a** in water[a]



8a **9a**

Entry	Ligand	Metal precursor	Temp (°C)	Time (h)	Conv.[b] (%)	ee[c] (%)	Config.
1[d]	TsDPEN	$[\mathrm{RuCl_2}(p\text{-cymene})]_2$	28	1	52	94	*R*
2	(*R*,*R*)-**2**	$[\mathrm{RuCl_2}(p\text{-cymene})]_2$	40	13	34	92	*R*
3	(*R*,*R*)-**3**	$[\mathrm{RuCl_2}(p\text{-cymene})]_2$	40	17	7	86	*R*
4	(*R*,*R*)-**4**	$[\mathrm{RuCl_2}(p\text{-cymene})]_2$	40	15	97	92	*R*
5	(*R*,*R*)-**5**	$[\mathrm{RuCl_2}(p\text{-cymene})]_2$	40	15	92	91	*R*
6	(*R*,*R*)-**5**	$[\mathrm{RuCl_2}(p\text{-cymene})]_2$	18	15	10	91	*R*
7	(*R*,*R*)-**6**	$[\mathrm{RuCl_2}(p\text{-cymene})]_2$	40	3	100	98	*R*
8	(*R*,*R*)-**6**	$[\mathrm{RuCl_2}(p\text{-cymene})]_2$	25	18	100	98	*R*
9	(*R*,*R*)-**7**	$[\mathrm{RuCl_2}(p\text{-cymene})]_2$	40	3	100	98	*R*
10	(*R*,*R*)-**7**	$[\mathrm{RuCl_2}(p\text{-cymene})]_2$	18	18	100	98	*R*
11[e]	(*R*,*R*)-**7**	$[\mathrm{RuCl_2}(p\text{-cymene})]_2$	40	3	100	97	*R*
12	(*R*,*R*)-**6**	$[\mathrm{RhCl_2Cp^*}]_2$	40	10	99	98	*R*
13	(*R*,*R*)-**6**	$[\mathrm{IrCl_2Cp^*}]_2$	40	4	77	89	*R*
14[f]	TsDPEN	$[\mathrm{RuCl_2}(p\text{-cymene})]_2$	32	2	6	94	*R*
15[f]	(*R*,*R*)-**7**	$[\mathrm{RuCl_2}(p\text{-cymene})]_2$	32	2	38	98	*R*
16[g]	TsDPEN	$[\mathrm{RuCl_2}(p\text{-cymene})]_2$	40	0.5	84	95	*R*

[a] Reactions were carried out using 1 mmol of acetophenone, 5 equiv of HCOONa, and a S/C ratio of 100 in 2 mL of water.

[b] Determined by GC analysis.

[c] Determined by HPLC with Chiracel OD.

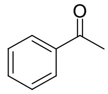
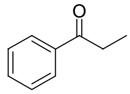
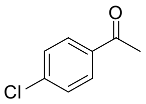
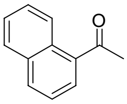
[d] Ref. 9f.

[e] The polymeric catalyst used in entry 9 was reused.

[f] Reaction was performed without stirring.

[g] The reaction was performed using benzyltributylammonium *p*-toluenesulfonate as an additive. [TsDPEN]:[Additive] = 1:9.

Table 2. Asymmetric transfer hydrogenation of ketones with the catalyst prepared from (*R*,*R*)-**6** in water[a]

Entry	Ketone	Time (h)	Conv.[b] (%)	ee[c] (%)		Config.
				Polymer	(Model)[d]	
1	 **8a**	3	100	98	(94)	*R*
2	 **8b**	2	91	96	(86)	*R*
3	 **8c**	2	90	99	(91)	*R*
4	 **8d**	13	97	97	(87)	*R*

[a] Reactions were carried out at 40 °C using 1 mmol of ketone, 5 equiv of HCOONa, and a S/C ratio of 100 in 2 mL of water.

[b] Determined by GC analysis.

[c] Determined by HPLC with Chiracel OD.

[d] Ref. 9a.

Encouraged by the results mentioned above, asymmetric transfer hydrogenation of various ketones by using the catalyst prepared from (*R*,*R*)-**6** were investigated (Table 2). Propiophenone (**8b**), *p*-chloroacetophenone (**8c**), and 1′-acetonaphthone (**8d**) are chosen as substrate, which are converted into the corresponding optically active secondary alcohols with excellent enantioselectivities, 96% ee (entry 2), 99% ee (entry 3), 97% ee (entry 4), respectively. As can be seen in Table 2, the enantioselectivities obtained in these reactions using polymeric catalyst are superior to that in the model reaction[9a] using monomeric one. To our knowledge, there have been only a few reports of polymeric chiral catalysts that exhibited higher enantioselectivity than that obtained from their low molecular weight counterparts.[14]

In summary, we have successfully synthesized new polymer-supported chiral 1,2-diamine monosulfonamides containing sulfonated pendant group. This is the first example of the use of sulfonated polymer-support for asymmetric catalyst in water. Chiral catalyst prepared from the new polymer-support is more effective for asymmetric transfer hydrogenation of aromatic ketones in water compared to that prepared from conventional polystyrene-support. We have also found that polystyrene-support containing quaternary ammonium salt of the pendant sulfonate was very important as a polymeric catalyst used in aqueous media, which increased not only the reactivity but also the enantioselectivity in this reaction. We are currently using this type of polymer-support for other organic reactions in aqueous media.

Acknowledgment

This work was partially supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Science, Sports and Culture of Japan.

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11. Hashiguchi, S.; Fujii, A.; Takehara, J.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1995**, *117*, 7562–7563.
12. Polymerization condition: Chiral monomer (*R*,*R*)-**1** (0.2 mmol), quaternary ammonium salt of *p*-styrenesulfonate (1.6 mmol), and divinlybenzene (0.2 mmol) were weighed into an ampoule with AIBN (2 mol % to the total monomer) and DMF. The ampoule was sealed after three cycles of freeze–thaw under liquid nitrogen. Copolymerization was carried out at 60 °C for 15 h to give (*R*,*R*)-**7** in 94% yield. Gel phase ^{1}H NMR (400 MHz, DMSO-d_6) of (*R*,*R*)-**7** showed peaks at $\delta = 0.8$ (br, CH_3), 1.1 (br, CH_2), 1.6 (br, CH_2), 3.1 (br, CH_2N) 4.5 (br, CH_2Ph), 6.4–7.1, 7.1–7.9 (br, Ar–H).

13. General procedure for the asymmetric transfer hydrogenation: $[RuCl_2(p\text{-cymene})]_2$ (3.0 mg, 0.005 mmol) and polymer-supported chiral sulfonamide (0.012 mmol) were added in water (2 mL). After the mixture was degassed and stirred at 40 °C for 1 h under an argon atmosphere, sodium formate (340 mg, 5 mmol) was introduced. Ketone (1 mmol) was then added and the mixture was stirred at 40 °C for a certain period of time. After cooling to room temperature, the organic compounds were extracted with ether. The conversion and enantioselectivity were determined by GC and HPLC analysis, respectively.
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