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Asymmetric Aldol Reaction Catalyzed by New Recyclable Polystyrene-supported L-proline in the Presence of Water

Yu-Xia Liu · Ya-Nan Sun · Hao-Han Tan · Jing-Chao Tao

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Abstract Two L-proline-based linear polystyrene anchored catalysts (**1a**–**b**) have been efficiently synthesized. By using only 5 mol% of catalysts, the corresponding products of the aldol reaction were obtained in good yields (up to 91%) with excellent *anti* diastereoselectivity (up to 93:7) and enantioselectivity (up to 98% ee) in DMF in the presence of water. The yields of these reactions in the ketone/water mixture were lower than those in wet DMF (up to 84%). However, the stereoselectivity was comparable (up to 92:8 *anti/syn* ratio and 96% ee, respectively). In addition, catalysts **1a**–**b** could be recovered by a simple precipitation and filtration process. They can also be re-used for at least five times without obvious loss of catalytic efficiency.

Keywords Aldol reaction · Asymmetric catalysis · Recyclable catalyst · Linear polystyrene · L-proline

1 Introduction

Asymmetric reactions using organocatalysts have attracted great attention in recent years. Researchers have focused on the new catalyst design to avoid the use of expensive transition metals [1]. The asymmetric aldol reaction, one of the most important carbon–carbon bond-forming reactions in synthetic organic chemistry, has been intensively studied [2]. Its products, enantiomerically pure β-hydroxy ketones, are important building blocks for the synthesis of polyfunctional compounds and natural products [3]. Since List reported the direct aldol reaction catalyzed by L-proline under mild reaction condition in 2000, much effort has been made to improve the catalytic performance [4]. Most effort has been devoted to the preparation of new small molecular L-proline derivatives as stereoselective catalysts [5]. Several methods have been studied for the recovery of the L-Proline-based organocatalysts. Some of them were based on the immobilization of L-proline on polymers [6]. Noto and co-workers recently utilized ionic liquids for the recovery of organocatalysts [7]. Different types of polymers have also been the subjects of attention in connection with catalysis chemistry for decades. Especially, the soluble polymer-supported organocatalysts not only secure the advantages of homogeneous process, easy characterization, high reactivity and best enantioselectivity, but also allow simple product purification and catalyst recovery and recycling.

Stereoselective reaction in water/aqueous media is another important research area because water is an environmentally safe media, which avoids the problems of pollution that are inherent with organic solvents [8]. Some organocatalysts for the direct aldol reaction in water/aqueous media have been developed in recent years [9]. However, the asymmetric aldol reaction in water has been proved to be very difficult although a small amount of water is somewhat beneficial in some L-proline derivative-mediated aldol reaction. Hayashi [10], as well as our group [11], have found that the long chain alkyl substituted L-proline is capable of catalyzing the direct aldol reaction in aqueous media at high diastereoselectivity and enantioseletivity. The findings induced our further interests in exploring new classes of amphiphilic catalysts for the C–C formation reactions.

Herein, we report the synthesis of L-proline-based linear polystyrene-supported catalysts **1a**–**b** (M_w = ca. 5,000)

Y.-X. Liu · Y.-N. Sun · H.-H. Tan · J.-C. Tao (✉)
Department of Chemistry, New Drug Research and Development Center, Zhengzhou University, Zhengzhou 450052, P.R. China
e-mail: jctao@zzu.edu.cn

with a rigid spacer. Their catalytic efficiency for the asymmetric aldol reaction was evaluated in wet DMF and ketone/water mixture. These catalysts are capable of catalyzing direct aldol reaction in the presence of water at high stereoselectivity (up to 98 and 96% ee, respectively).

2 Experimental

2.1 Materials and Methods

All chemicals were used as received unless otherwise noted. Reagent grade solvents were redistilled prior to use. All ^{1}H NMR spectra were collected on a Bruker DPX 400 NMR spectrometer with TMS as an internal reference. FT-IR spectra were determined on a Thermo Nicolet IR200 unit. High resolution mass spectra (HR-MS) were obtained on a Waters Micromass Q-Tof Micro^{TM} instrument using the ESI technique. Chromatography was performed on silica gel (200–300 mesh). Melting points were determined on a XT5A apparatus and uncorrected. Optical rotations were determined on a Perkin Elmer 341 polarimeter. Element analysis was determined on Flash EA1112 apparatus. Enantiomer excess was measured by chiral HPLC at room temperature using JASCO PU-1580 pump equipped with JASCO UV-1575 ultra detector (or Syltech 500 pump equipped with an UV 500 version 4.1 ultra-violet detector) with Chiralcel OD-H (4.6 × 250 mm^2) columns.

2.2 Preparation of Supported Catalysts **1a-b**

*2.2.1 (2S, 4S)-4-Aminoproline (**2**)*

Compound **2** was prepared from *trans*-4-hydroxy-L-proline as reported in literature [12] with overall yield up to 72%. $[\alpha]_D^{20}$ = –23.2° (*c* 1.18, EtOH); ^{1}H NMR (CDCl$_3$, ppm): δ = 1.83–1.89 (1 H, m, H-3), 2.42–2.48 (1 H, m, H-3), 3.31–3.37 (1 H, m, H-5), 3.56–3.57 (1 H, m, H-5), 3.70–3.79 (1 H, m, H-4), 3.59 and 3.77 (3 H, s, –OCH$_3$), 4.33–4.41 (1 H, m, H-2), 5.02–5.20 (2 H, m, –OCH$_2$Ph), 7.28–7.37 (5 H, m, Ph); IR (KBr, cm^{-1}): 3,374, 3,386, 3,033, 2,952, 2,886, 1,747, 1,704, 1,498, 1,418, 1,356, 1,204, 1,170, 1,112, 769, 751, 699; HR-MS *m/z*: calcd. For $C_{14}H_{18}N_2O_4$ (M + H)$^+$ 279.1345, found 279.1333.

*2.2.2 (2S, 4S)-1-Benzyloxycarbonyl-2-Methoxycarbonyl-4-(4′-Hydroxylbenzamido)-pyrrolidine (**3**)*

To a stirred solution of compound **2** (0.56 g, 2.0 mmol) and 4-hydroxy benzoic acid (0.28 g, 2.0 mmol) in anhydrous CH$_2$Cl$_2$ (15 mL) was added dicyclohexylcarbodiimide (DCC, 0.44 g, 2.1 mmol) and catalytic quantities of DMAP at room temperature. After stirring for about 6 h, the reaction mixture was filtered, and the filtrate was concentrated. The residue was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 1:1, v/v) to give 0.42 g (53%) of white solid product. $[\alpha]_D^{20}$ = –8.2° (*c* 1.24, EtOH); ^{1}H NMR (CDCl$_3$, ppm): δ 2.08–2.14 (1 H, m, H-3), 2.48–2.45 (1 H, m, H-3), 3.59, 3.77 (3 H, s, OCH$_3$), 3.72 (2 H, m, H-5), 4.42–4.49 (1 H, m, H-2), 4.89 (1 H, m, H-4), 5.06–5.22 (2 H, m, –OCH$_2$Ph), 6.87–6.89 (2 H, d, *J* = 8.2 Hz, Ar′–H), 7.70–7.71 (2 H, d, *J* = 8.4 Hz, Ar′–H), 7.31–7.35 (5 H, m, OCH$_2$Ph); ^{13}C NMR (CDCl$_3$): δ 36.8, 49.0, 53.1, 53.6, 57.9, 67.7, 115.6, 122.2, 128.1, 128.3, 128.5, 128.6, 129.1, 130.8, 154.3, 161.5, 165.2; IR (KBr, cm^{-1}): 3,401, 2,954, 2,924, 2,852, 1,735, 1,704, 1,638, 1,609, 1,544, 1,506, 1,425, 1,357, 1,277, 1,212, 1,175, 1,123, 851, 769, 699; HR-MS *m/z*: calcd. For $C_{14}H_{18}N_2O_4$ (M + Na)$^+$ 421.1376, found 421.1366.

*2.2.3 Preparation of Polymer **4***

A mixture of **3** (0.42 g, 1.1 mmol), K$_2$CO$_3$ (0.28 g, 2.0 mmol) and chlorolmethyl polystyrene (0.5 g) in DMF (20 mL) was heated at 65 °C for 6 h. The mixture was concentrated under reduced pressure, and the residue was washed with methanol (15 mL × 3) to give 0.63 g white powder. ^{1}H NMR (CDCl$_3$, ppm): δ 1.25–1.68 (2.0 H, br, PS–CH$_2$–), 1.68–2.04 (1.0 H, br, PS–CH–), 2.07–2.10 (0.2 H, m, H-3), 3.57–3.77 (0.4 H, H-5 and –OCH$_3$), 4.42–4.50 (0.08 H, m, H-2), 4.92 (0.24 H, br, –CH$_2$NH and H-4), 5.07–5.23 (0.17 H, m, –OCH$_2$Ph), 6.46–6.57 (2.0 H, br, PS), 7.21–7.23 (3.14 H, br, PS and –OAr), 7.32–7.34 (0.4 H, m,–OCH$_2$Ph), 7.79 (0.16 H, m, –OAr); IR (KBr, cm^{-1}): 3,408, 3,059, 3,026, 2,924, 2,852, 1,713, 1,662, 1,604, 1,496, 1,451, 1,415, 1,354, 1,250, 1,209, 1,175, 1,116, 1,025, 761, 700.

*2.2.4 Preparation of Polymer **6***

A solution of compound **2** (0.74 g, 3.0 mmol) and triethylamine (0.7 mL) in anhydrous CH$_2$Cl$_2$ (35 mL) was added dropwise to a stirred solution of terephthaloyl dichloride (0.61 g, 3.0 mmol) in anhydrous CH$_2$Cl$_2$ (35 mL) at 0 °C. Aminomethyl polystyrene (0.5 g) was added to the reaction mixture. The mixture was stirred for 4 h at room temperature. An appropriate amount of compound **2** was added to the mixture until the disappearance of the absorption at 1,790 cm^{-1} (–COCl) as detected by infrared spectrogram. The mixture was concentrated under reduced pressure, and the residue was washed with methanol (15 mL × 3) to give 0.58 g white powder. ^{1}H NMR (CDCl$_3$, ppm): δ 1.16–2.05 (3.3 H, br, PS–CH$_2$–,PS–CH–, and H-2), 3.48–3.74 (0.4 H, m, H-5 and –OCH_3), 4.43–4.46 (3 H, m, H-2 and PS–CH_2NH), 4.75 (0.08 H, m, H-4), 5.07–5.17 (0.15 H, m, –OCH_2Ph), 6.46–6.57 (2.0 H, br, PS), 7.03–7.25 (3.0 H, br, PS), 7.30–7.33 (0.40 H, m, OCH_2*Ph*), 7.44–7.51 (0.28 H, m, Ar′); IR (KBr, cm^{-1}): 3,424, 3,059, 3,026, 2,922, 2,850, 1,718, 1,667, 1,602, 1,515, 1,493, 1,450, 1,368, 1,277, 1,027, 758, 700.

2.2.5 *General Procedure for the Preparation of Catalysts **1a-b***

Polymer **4** or **6** was dissolved in 20 mL of THF, and 7 mL of 25% NaOH aqueous solution was then added. The reaction mixture was refluxed for 12 h and acidified to pH < 3 with 1 N hydrochloric acid. The aqueous layer was extracted with $CHCl_3$ (25 mL × 3). The organic layer was washed with Et_3N/H_2O 2/98 (30 mL × 3), and then concentrated under reduced pressure. The residue was washed with methanol (15 mL × 3) to give white powder **1**.

*Compound **1a***: ^1H NMR ($CDCl_3$, ppm): δ 1.18–1.63 (2.0 H, br, PS–CH_2–), 1.64–2.05 (1.0 H, br, PS–CH–), 2.09–2.22 (0.15 H, m, H-3), 3.57–3.88 (0.16 H, m, H-5), 4.50–4.92 (0.26 H, br, –CH_2NH and H-4), 6.55–6.63 (2.0 H, br, PS), 7.21–7.23 (3.14 H, br, PS and –OAr), 7.79 (0.15 H, m, –OAr); IR (KBr, cm^{-1}): 3,407, 3,058, 3,026, 2,925, 2,853, 1,709, 1,658, 1,605, 1,497, 1,450, 1,417, 1,358, 1,248, 1,177, 1,024, 845, 761, 701; Elemental analysis: N% 1.55, C% 85.6, H% 7.8. Loading: 0.55 mmol/g.

*Compound **1b***: ^1H NMR ($CDCl_3$, ppm): δ 1.14–1.68 (2.0 H, br, PS–CH_2–), 1.64–2.32 (1.2 H, br, PS–CH–), 3.48–3.75 (0.14 H, m, H-5), 4.39 (0.16 H, m, PS–CH_2NH) 4.67–4.73 (0.22 H, m, H-2 and H-4), 6.46–6.6.57 (2.0 H, br, PS), 7.04–7.08 (3.0 H, br, PS), 7.46–7.52 (0.3 H, m, –OAr); IR (KBr, cm^{-1}): 3,414, 3,059, 3,025, 2,923, 2,850, 1,712, 1,664, 1,601, 1,582, 1,513, 1,493, 1,452, 1,369, 1,278, 1,068, 1,028, 758, 699; Elemental analysis: N% 2.1, C% 86.2, H% 7.4. Loading: 0.50 mmol/g.

2.2.6 *Preparation of Polystyrene*

A solution of styrene (5.2 g, 5 mmol) and AIBN (16 mg, 0.1 mmol) in anhydrous toluene (15 mL) was stirred at 75 °C in an argon atmosphere for 5 h. The reaction mixture was concentrated under reduced pressure to give 4.1 g (80%) white powder product. ^1H NMR ($CDCl_3$, ppm): δ 0.90–0.95 (0.17 H, m, terminal methyl), 1.09–1.16 (0.14 H, m, terminal methyl), 1.26–1.54 (2.0 H, br, –CH_2–), 1.72–2.04 (1.1 H, br, –CH–), 6.46–7.08 (5.0 H, m, Ar–H); IR (KBr, cm^{-1}): 3,441, 3,059, 3,026, 2,922, 2,850, 1,601, 1,492, 1,448, 1,370, 1,256, 1,052, 843, 756, 698.

2.2.7 *Preparation of Chloromethyl Polystyrene*

A mixture of polystyrene (3 g), paraformaldehyde (3 g), trimethylchlorosilane (2.8 mL) and tin tetrachloride (0.25 mL) in anhydrous chloroform (30 mL) was stirred at 0 °C for 0.5 h, and then at room temperature for 2.5 h. The reaction mixture was filtered. The product was precipitated out by addition of 30 mL of methanol into the filtrate. The precipitate was filtered to give a white power which was washed with methanol (15 mL × 3) and then dried in the vacuum shelf dryer overnight to afford 2.8 g white powder. ^1H NMR ($CDCl_3$, ppm): δ 0.89–0.93 (0.12 H, m, terminal methyl), 1.09–1.13 (0.09 H, m, terminal methyl), 1.22–1.54 (2.1 H, br, –CH_2–), 1.72–2.05 (1.2 H, br, –CH–), 4.50 (0.18 H, m, –CH_2Cl), 6.45–7.08 (5.1 H, br, Ar–H); IR (KBr, cm^{-1}): 3,449, 3,059, 3,025, 2,921, 2,848, 1,601, 1,493, 1,451, 1,371, 1,265, 1,029, 840, 757, 699.

2.2.8 *Preparation of Aminomethyl Polystyrene*

Aminomethyl polystyrene was prepared from chloromethyl polystyrene as reported in literature [13]. ^1H NMR ($CDCl_3$, ppm): δ 0.88–0.93 (0.12 H, m, terminal methyl), 1.09–1.14 (0.09 H, m, terminal methyl), 1.26–1.5443 (2.0 H, br, –CH_2–), 1.85–2.46 (1.3 H, br, –CH–), 3.74–3.76 (0.19 H, m, –CH_2NH_2), 6.51–7.24 (5.1 H, br, Ar–H); IR (KBr, cm^{-1}): 3,385, 3,059, 3,025, 2,921, 2,848, 1,601, 1,493, 1,451, 1,372, 1,068, 1,028, 845, 757, 6,998.

2.3 General Procedure for the Asymmetric Aldol Reaction

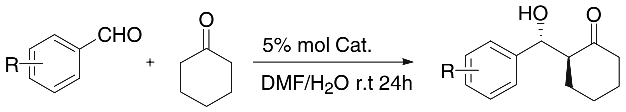
2.3.1 *Reaction in Wet DMF*

To a stirred mixture of an aldehyde (0.33 mmol), 1.5 mL of DMF, 0.1 mL of water and 0.5 mL of the corresponding ketone was added catalysts (0.016 mmol) at the indicated temperature (see Table 1). The mixture was stirred for the indicated period of time (see Table 1). The catalyst was precipitated out by the addition of diethyl ether and then filtered off. The filtrate was purified by thin layer chromatography on a silica gel plate (petroleum ether/ethyl acetate).

2.3.2 *Reaction in Ketone/Water Mixture*

About 0.33 mmol of an aldehyde was added to a mixture of 1.2 mL of a ketone, 0.8 mL of water and 0.016 mmol of catalyst. After being stirred at room temperature for the indicated time (see Table 2), the mixture was treated as described above for the reaction in DMF.

Table 1 Direct aldol reaction of aromatic aldehydes with cyclohexanone catalyzed by **1a–b** in aqueous DMF[a]



Entry	R	Cat	Yield (%)[b]	anti/syn	ee (%) (anti)[c]
1	*o*-NO_2	**1a**	35	87:13	89[d]
2	*o*-NO_2	**1a**	63	91:9	93
3	*o*-NO_2	**1a**	58	91:9	94[e]
4	*o*-NO_2	**1a**	45	93:7	93[f]
5	*o*-NO_2	**1a**	23	92:8	95[g]
6	*o*-NO_2	**1a**	10	92:8	95[h]
7	*m*-NO_2	**1a**	80	89:11	93
8	*p*-NO_2	**1a**	91	92:8	98
9	*o*-Cl	**1a**	72	91:9	89
10	*m*-Cl	**1a**	62	87:13	86
11	*p*-Cl	**1a**	69	89:11	90
12	*m*-Br	**1a**	65	92:8	96
13	*o*-NO_2	**1b**	62	91:9	93
14	*m*-NO_2	**1b**	81	87:13	90
15	*p*-NO_2	**1b**	90	93:7	95
16	*o*-Cl	**1b**	62	80:20	89
17	*m*-Cl	**1b**	66	79:21	82
18	*p*-Cl	**1b**	60	84:16	88
19	*m*-Br	**1b**	72	83:17	94
20	*o*-NO_2	Entry 2. Cycle 1	61	92:8	93
21	*o*-NO_2	Cycle 2	60	92:8	92
22	*o*-NO_2	Cycle 3	61	91:9	93
23	*o*-NO_2	Cycle 4	58	90:10	90
24	*o*-NO_2	Cycle 5	56	92:8	88

[a] The reaction of cyclehexanone (0.5 mL, 15.0 equiv. to aldehyde), aldehyde (50 mg, 0.33 mmol) and **1** (0.016 mmol) was performed in DMF/H_2O (15:1, 1.5 mL)

[b] Isolated yield after thin layer chromatography on silica gel

[c] Determined by HPLC using a chiral column (Daicel OD–H)

[d] In neat DMF

[e] 10.0 equivalent of cyclohexanone to aldehyde

[f] 5.0 equivalent of cyclohexanone to aldehyde

[g] 1.5 equivalent of cyclohexanone to aldehyde

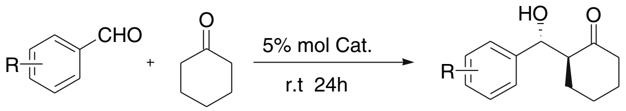
[h] 1.0 equivalent of cyclohexanone to aldehyde

3 Results and Discussion

3.1 Synthesis and Characterization of Polymer-supported Catalysts **1a-b**

(2*S*, 4*S*)-4-Aminoproline (**2**) was synthesized from the commercially available *trans*-4-hydroxy-L-proline in an overall yield of up to 72% [12]. Compound **2** was reacted with 4-hydroxy benzoic acid and terephthaloyl dichloride to give compounds **3** and **5**. These compounds were immobilized onto the linear polystyrene (M_w = ca. 5000, $f = 0.60$ mmol/g) to give compounds **4** and **6**, respectively (see Scheme 1). The molecular weight of these polymers was estimated by NMR spectroscopy according to the terminal methyl group. The degree of substitution (f) was determined by NMR spectroscopy according to the methylene group ($–CH_2NH_2$). The deprotection of the proline moiety was performed in the refluxing 25% aq. NaOH/THF (v/v 10/30) for 6 h to remove the Cbz and methyl groups simultaneously. The reaction mixture was treated with 1 M

Table 2 Direct aldol reaction of aromatic aldehydes with cyclohexanone catalyzed by **1a–b** in ketone/water mixture[a]



Entry	R	Cat	Yield (%)[b]	anti/syn[c]	ee (%) (anti)[c]
1	*o*-NO_2	**1a**	48	88:12	95
2	*o*-NO_2	**1b**	56	92:8	93
3	*m*-NO_2	**1a**	65	89:11	94
4	*p*-NO_2	**1a**	84	90:10	96
5	*o*-Cl	**1a**	59	85:15	84
6	*m*-Cl	**1a**	56	83:17	85
7	*p*-Cl	**1a**	63	90:10	94
8	*m*-Br	**1a**	62	86:14	94

[a] The reaction of cyclohexanone (1.2 mL), *o*-nitrobenzaldehyde (50 mg, 0.33 mmol) and **1** (0.016 mmol) was performed in water (0.8 mL)

[b] Isolated yield after thin layer chromatography on silica gel

[c] Determined by HPLC using a chiral column (Daicel OD–H)

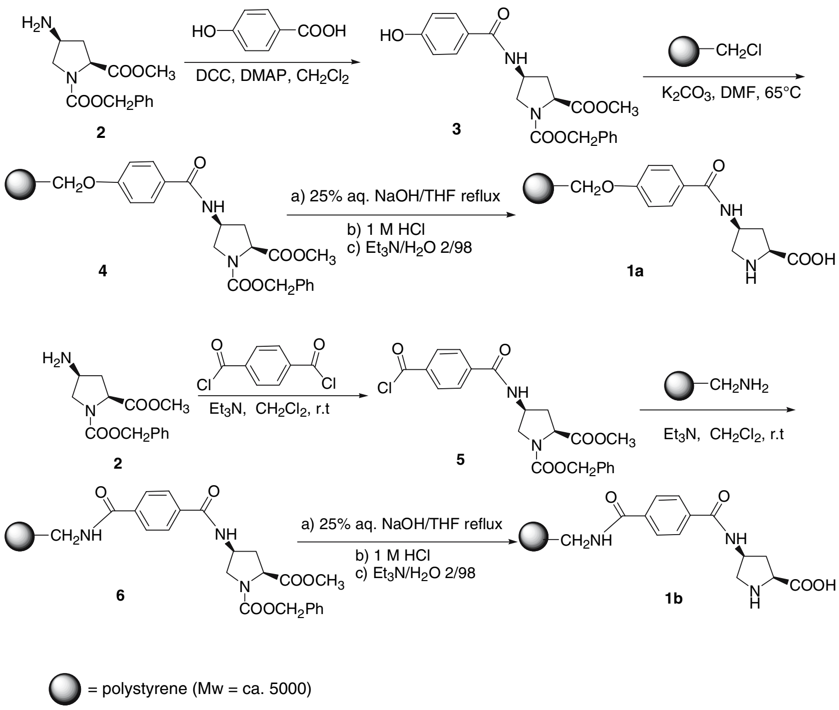
HCl followed by treatment with Et_3N/H_2O (2/98). The structures of the two catalysts were established by IR, NMR spectroscopic and elemental analyses. Their IR spectra showed two characteristic carbonyl absorptions at around 1,710 cm^{-1} (–COOH) and 1,660 cm^{-1} (–CONH). The strong absorption at 1,177 cm^{-1} in the IR spectrum of compound **1a** indicated the formation of the new C–O–C bond. Its NMR spectrum showed signals of proline backbone. The methylene signals of aminomethyl polystyrene (3.75 ppm) shift to downfield (4.92 ppm). This approach is proved to be available allowing the synthesis of polystyrene-supported L-proline possessing different linkers and can be used for the immobilization of different organic molecules.

3.2 Aldol Condensations

To evaluate the catalytic efficiency of the new polystyrene-supported catalysts **1a–b**, the condensation of various aromatic aldehydes with cyclohexanone was first performed in DMF/H_2O (v/v 15:1) which demonstrated to be the best ratio for other L-proline based polymer-supported catalysts [6i]. The results, as listed in Table 1, indicated that the yields of the aldol reactions are moderate to good, which are lower than those obtained with small molecule L-proline derivatives in the presence of water. However, the diastereoselectivity and the ee value are comparable to those of the unsupported small molecule catalysts [5, 8–11]. The supported catalysts can be re-used for at least five times without obvious loss of catalytic efficiency. In addition, the catalytic efficiency and selectivity observed are comparable or better than those obtained with other supported L-proline catalysts [6–7].

A comparative study was first performed in neat DMF in the absence of water (entry 1). It was known that the presence of water promoted the catalytic reaction in both activity and stereoselectivity. We presume that a possible interaction between water and the hydrophilic proline moiety may increase the amphiphilic property of the catalysts. Therefore, the hydrophilic catalytic moiety could stay away from the hydrophobic main chains, and may contact with substrates more efficiently. The improvement of the diastereoselectivity and enantioselectivity in the presence of small amount of water may attribute to the participation of water in the transition state during the catalytic aldol condensation. The results (entries 2–6) also showed that the smaller excess of cyclohexanone was used, the lower yields were obtained though the dia- and enantioselectivity were comparable. Catalysts **1a** and **b** have the similar catalytic efficiency. When nitrobenzaldehydes were used as aldol acceptors, *p*-nitrobenzaldehyde showed higher activity and stereoselectivity than *o*-nitro- and *m*-nitrobenzaldehydes (entries 2, 7, 8, 13–15). However, when chlorobenzaldehydes were used as aldol acceptors, there were no obvious differences among the three benzaldehydes not only in reactivity but also in anti/syn ratio and ee value (entries 9–11 and 16–18). *m*-Bromobenzadehyde showed similar activity and diastereoselectivity to chlorobenzaldehydes but much higher enantioselectivity (entries 12 and 19). Additionally, the nitrobenzaldehydes afforded higher reactivity, diastereo- and enantioselectivity than the chlorobenzaldehydes. Moreover, the performance of the recovered catalyst was also evaluated after a simple separation from the

Scheme 1 Synthesis of polystyrene-supported catalysts **1a** and **b**



reaction mixture without any further treatment. It indicated that the catalyst could be re-used at least five times without obvious decrease of anti/syn ratio and ee value although the reactivity decreased somewhat after using four times (entries 20–24).

It has been shown that water could play a special role in the catalyzed aldol reaction in aqueous (homogeneous) media. The direct aldol reaction in water/aqueous media has been developed in recent years [9]. We also tested the catalytic effect of **1a**–**b** in ketone/water mixture. Dickerson and coworkers [14] and Hayashi [10] revealed that the reaction under this condition was not really performed in water. We studied the catalytic effects of **1a**–**b** in cyclohexanone/H_2O (1.5:1 v/v) which turned out to be the best cyclohexanone/H_2O ratio for other L-proline based polymer-supported catalysts [6i]. The results are showed in Table 2. Although only moderate to good yields were obtained, good to excellent diastereoselectivity (entry 2, *anti*/*syn* ratio up to 92:8) and enantioselectivity (entry 1, up to 95% ee) were observed. It was comparable to the results observed in wet DMF. Individually, when using *p*-nitro or *p*-chlorobenzaldehyde as an aldol acceptor, the yield and ee value of the aldol products were much higher than that of the corresponding *o*- or *m*-isomers (entries 2–7).

4 Conclusions

In conclusion, two efficient linear polystyrene anchored L-proline catalysts have been synthesized for asymmetric direct aldol reaction. The catalytic effect of these catalysts for the aldol reaction was evaluated in wet DMF and ketone/water mixture. Good yields and high stereoselectivity (91% yield, 93:7 *anti/syn* ratio, 98% ee in wet DMF and 84% yield, 92:8 *anti/syn* ratio, 96% ee in ketone/water mixture) were obtained for the reactions of aromatic aldehydes with cyclohexanone. It was also found that water could play a special role to improve the reactivity and stereoselectivity in the aldol reaction catalyzed by the polymer-supported L-proline. Additionally, the polymer-supported catalysts could be recovered and re-used giving virtually unchanged stereoselectivity though slowly diminishing yields after four cycles. These results expand the scope of organic catalysts in the field of enantioselective synthesis, making the search for these reagents more appealing.

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