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Linear polystyrene anchored L-proline, new recyclable organocatalysts for the aldol reaction in the presence of water

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Abstract—Two L-proline-based linear polystyrene anchored catalysts **1a** and **1b** have been synthesized efficiently. The catalytic activities and stereoselectivity of these readily tunable and amphiphilic organocatalysts were evaluated in the direct asymmetric aldol reaction of various aromatic aldehydes and ketones. By using 5 mol % of the catalysts, the corresponding products of the aldol reaction were obtained in good yields (up to 94%) and with excellent *anti* diastereoselectivities (up to 96:4) and enantioselectivities (up to 96% ee) in DMF in the presence of water. The yields of these reactions in a ketone/water mixture were lower than those in wet DMF (up to 76%). However, the stereoselectivity was comparable (up to 93:7 *anti*/*syn* ratio and 95% ee, respectively). In addition, catalysts **1a** and **1b** could be recovered by a simple precipitation and filtration process. They could also be re-used for at least five times without obvious loss of catalytic efficiency.

1. Introduction

Asymmetric catalysis has witnessed a tremendous growth in recent years. Since List et al. reported the direct aldol reaction catalyzed by L-proline under a mild reaction condition in 2000,[1] asymmetric reaction catalyzed by organocatalysts has received great attention.[2] The direct asymmetric aldol reaction (DAAR), one of the most powerful C–C bond forming reactions, has been intensively studied in recent years.[3] The advantages of using an organocatalyst would be higher if an efficient recovery and reuse of the catalyst could be accomplished. From a practical point of view, it would be desirable to have the catalyst immobilized so that the product purification can be facilitated and the catalyst recycled. Since Benaglia et al. utilized poly(ethylene glycol)-supported L-proline catalyzing asymmetric aldol condensations,[4] much effort has been devoted to the recovery of the L-proline-based organocatalysts.[5] Different types of polymers have been the subject of attention in connection with organocatalysts recovery, for example, cross-linked polystyrene anchored L-proline,[5b–e] mesoporous MCM-41 supported L-proline,[5f] and dendrimers supported L-proline.[5a,g] Noto et al. recently utilized ionic liquids for the recovery of organocatalysts.[6] Soluble polymer-supported organocatalysts not only secure the advantages of homogeneous process, easy characterization, high reactivity and good enantioselectivity, but also allow simple product purification and catalyst recovery and recycling.

The 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.[7] Therefore, reactions in aqueous media have received a great deal of attention. Some organocatalysts for the direct aldol reaction in water/aqueous media have been developed in recent years.[5f,8] However, the asymmetric aldol reaction in water has proven to be very difficult although a small amount of water is somewhat beneficial in some proline derivative mediated aldol reactions. Hayashi,[9a] as well as our group,[9b] has found that the long chain alkyl substituted proline is capable of catalyzing the direct aldol reaction in aqueous media with high diastereoselectivity and enantioselectivity. These findings induced our further interest in exploring new classes of amphiphilic catalysts for the C–C formation reactions.

Herein, we reported the synthesis of L-proline-based linear polystyrene-supported catalysts **1a** and **1b** (M_w = ca. 5000) with a flexible spacer. Their catalytic efficiency for the asymmetric aldol reaction was evaluated in wet DMF and ketone/water mixture. These catalysts are capable of

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catalyzing the direct aldol reaction in the presence of water at high enantioselectivity (up to 96% and 93% ee, respectively).

2. Results and discussion

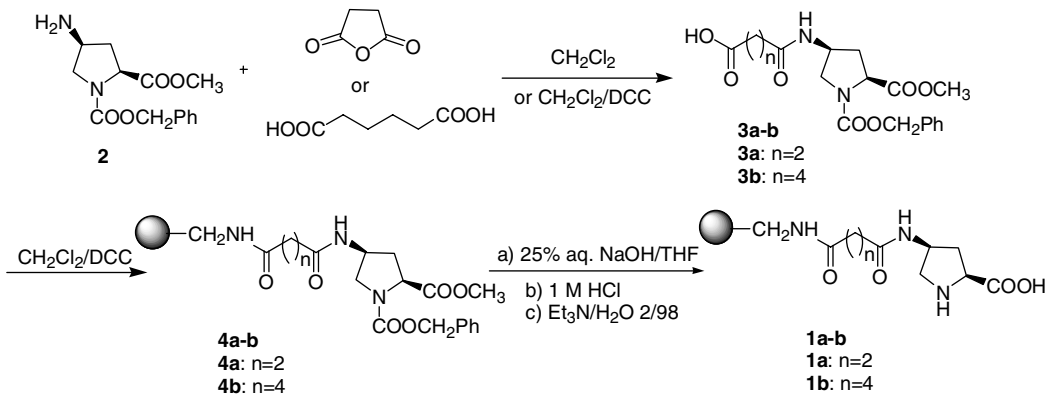
2.1. Synthesis of the catalysts 1a and 1b

(2*S*,4*S*)-*N*-Cbz-4-aminoproline methyl ester **2** was easily synthesized from the commercially available *trans*-4-hydroxy-L-proline with an overall yield of up to 72%.[10] Compound **2** was reacted with succinic anhydride (or hexanedioic acid) in anhydrous CH_2Cl_2 at room temperature to give the compounds **3a** and **3b**. These compounds were immobilized onto the linear aminomethyl polystyrene (M_w = ca. 5000, f = 0.56 mmol/g) to give compounds **4a** and **4b** (Scheme 1). The molecular weights of these polymers were 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 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 HCl followed by treatment with Et_3N/H_2O (2:98). The structures of the two catalysts were established by IR, NMR spectroscopy and elemental analyses. Their IR spectra showed two characteristic carbonyl absorptions at around 1707 cm^{-1} (–COOH) and 1675 cm^{-1} (–CONH); their NMR spectra showed signals of the proline backbone. The methylene signals of aminomethyl polystyrene (3.75 ppm) shifted downfield (4.92 ppm). This approach has been proven to be available to allow the synthesis of polystyrene-supported L-proline possessing different linkers and can be used for the immobilization of different organic molecules.

2.2. Aldol condensations

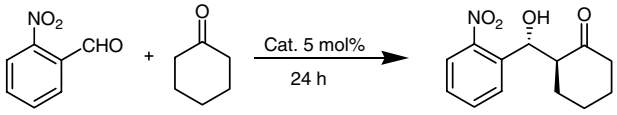
Initially, the catalytic effect of **1a** was tested in the model reaction of *o*-nitrobenzaldehyde with cyclohexanone in the presence of 5 mol % catalyst. The results are shown in Table 1. It was indicated in the literature[11] that the presence of water promoted the catalytic reaction in both activity and stereoselectivity. Therefore, the reaction was performed in DMF in the presence of different amounts of water (entries 2–6). A comparative study was first performed in DMF in the absence of water (entry 1). The results (entries 1–6) indicated that the activity and stereoselectivity were all improved significantly and the best ratio of DMF/H_2O was 15:1. 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 interact with the substrates more efficiently. The improvement of the diastereoselectivity and enantioselectivity in the presence of small amounts of water may be attributed to the participation of water in the transition state during the catalytic aldol condensation. The results (entries 7–10) showed that when a smaller excess of cyclohexanone was used, the lower yields were obtained, although the diastereo- and enantioselectivity were comparable. The temperature had some effect on the reactivity but almost no effect on the diastereo- and enantioselectivity (entries 4, 11 and 12). Moreover, the performance of the recovered catalyst was also evaluated after a simple separation from the reaction mixture without any further treatment. It was seen that the catalyst could be re-used at least five times without an obvious decrease of *anti*/*syn* ratio and ee value; although the reactivity decreased somewhat after using four times (entries 13–17).

To check the versatility of catalysts **1a** and **1b**, the reaction between cyclohexanone and several other substituted benzaldehydes was investigated in DMF/H_2O (15:1) at room temperature. The results, as listed in Table 2, indicate that the yields of the aldol reactions are good to excellent, which are a little lower than those obtained with small molecule L-proline derivatives in the presence of water. However, the diastereoselectivities and the ee values are comparable to those of the unsupported small molecule catalysts.[8,9] In addition, the catalytic efficiency and selectivity observed are comparable or better than those obtained with other supported L-proline catalysts.[5,6] The results also showed that catalysts **1a** and **1b** have a similar catalytic efficiency. When nitrobenzaldehydes were used as aldol acceptors, *o*-nitrobenzaldehyde showed a lower activity than *m*- and *p*-nitrobenzaldehyde, however, the diastereoselectivities



Scheme 1. Synthesis of linear polystyrene anchored catalysts **1a** and **1b**.

Table 1. The direct aldol reaction of *o*-nitrobenzaldehyde and cyclohexanone catalyzed by **1a** in wet DMF[a]

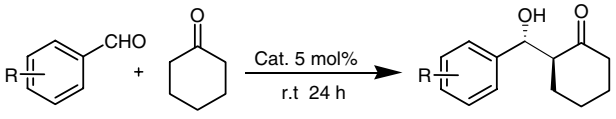


Entry	Solvent	Cat	*T* (°C)	Yield[b] (%)	*anti*/*syn*[c]	ee[c] (*anti*) (%)
1	DMF	**1a**	rt	30	88:12	87
2	DMF/H_2O (100:1)	**1a**	rt	51	90:10	89
3	DMF/H_2O (30:1)	**1a**	rt	65	95:5	95
4	DMF/H_2O (15:1)	**1a**	rt	73	95:5	95
5	DMF/H_2O (10:1)	**1a**	rt	55	93:7	95
6	DMF/H_2O (7.5:1)	**1a**	rt	51	95:5	96
7	DMF/H_2O (15:1)	**1a**	rt	71	94:6	96[d]
8	DMF/H_2O (15:1)	**1a**	rt	65	96:4	94[e]
9	DMF/H_2O (15:1)	**1a**	rt	43	95:5	95[f]
10	DMF/H_2O (15:1)	**1a**	rt	32	95:5	96[g]
11	DMF/H_2O (15:1)	**1a**	0	62	96:4	96
12	DMF/H_2O (15:1)	**1a**	30	78	92:8	94
13	DMF/H_2O (15:1)	Entry 4, cycle 1	rt	70	92:8	95
14	DMF/H_2O (15:1)	Cycle 2	rt	66	92:8	95
15	DMF/H_2O (15:1)	Cycle 3	rt	69	92:8	94
16	DMF/H_2O (15:1)	Cycle 4	rt	64	91:9	92
17	DMF/H_2O (15:1)	Cycle 5	rt	59	92:8	89

[a] The reaction of cyclohexanone (0.5 mL, 15.0 equiv to aldehyde), *o*-nitrobenzaldehyde (50 mg, 0.33 mmol) and **1a** (0.016 mmol) was performed in wet DMF (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] 10.0 equiv of cyclohexanone to aldehyde.
[e] 5.0 equiv of cyclohexanone to aldehyde.
[f] 1.5 equiv of cyclohexanone to aldehyde.
[g] 1.0 equiv of cyclohexanone to aldehyde.

and the ee values were comparable (entries 1–3 and 8–10). When chlorobenzaldehydes were used as aldol acceptors, there were no obvious differences among the three benzaldehydes not only in reactivity but also as the *anti*/*syn* ratio and ee value (entries 4–6 and 11–13). *m*-Bromobenzaldehyde showed a similar activity and diastereoselectivity to chlorobenzaldehydes but with much higher enantioselectivity (entries 7 and 14). Additionally, the nitrobenzaldehydes afforded higher reactivities, diastereo- and enantioselectivities than the chlorobenzaldehydes.

Table 2. The aldol reaction of aromatic aldehydes with cyclohexanone catalyzed by **1a**–**b** in wet DMF[a]

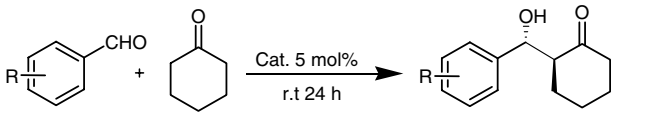


Entry	R	Cat	Yield[b] (%)	*anti*/*syn*[c]	ee[c] (*anti*) (%)
1	*o*-NO_2	**1a**	73	95:5	95
2	*m*-NO_2	**1a**	82	92:8	95
3	*p*-NO_2	**1a**	91	91:9	94
4	*o*-Cl	**1a**	72	87:13	86
5	*m*-Cl	**1a**	68	86:14	87
6	*p*-Cl	**1a**	77	86:14	90
7	*m*-Br	**1a**	46	89:11	96
8	*o*-NO_2	**1b**	76	93:7	92
9	*m*-NO_2	**1b**	85	92:8	93
10	*p*-NO_2	**1b**	94	92:8	91
11	*o*-Cl	**1b**	73	90:10	88
12	*m*-Cl	**1b**	69	83:17	84
13	*p*-Cl	**1b**	76	84:16	86
14	*m*-Br	**1b**	78	90:10	94

[a] The reaction of cyclohexanone (0.5 mL, 15.0 equiv to aldehyde), aldehyde (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).

It has been shown that water can 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.[8] We also tested the catalytic effect of **1a** and **1b** in a ketone/water mixture. Dickerson[12] and Hayashi[9a] revealed that the reaction under these conditions was not really performed in water. The results are shown in Table 3. The reactions between cyclohexanone and *o*-nitrobenzaldehyde were performed in the presence of different amount of water. The reaction progressed very slowly in the absence of water. Therefore, diastereo- and enantioselectivity were not detected (entry 1). When different amounts of water was added into the reaction mixture, the reactivity was improved evidently. However, there were no obvious differences in reactivity and stereoselectivity among the different cyclohexanone/H_2O ratios. Considering that cyclohexanone and water have an azeotropic point at 1.5:1, we studied the catalytic effects of **1a** and **1b** in ketone/water mixture (1.5:1 v/v). Although only moderate to good yields were obtained, good to excellent diastereoselectivities (entry 3, *anti*/*syn* ratio up to 93:7) and enantioselectivities (entries 4 and 11, up to 95% ee) were observed.

Table 3. The aldol reaction of aromatic aldehydes with cyclohexanone catalyzed by **1a**–**b** in ketone/water mixture[a]



Entry	Solvent	R	Cat	Yield[b] (%)	*anti*/*syn*[c]	ee[c] (*anti*) (%)
1	None H_2O	*o*-NO_2	**1a**	<5	nd	nd
2	0.8 mL H_2O	*o*-NO_2	**1a**	45	90:10	94
3	1.2 mL H_2O	*o*-NO_2	**1a**	37	93:7	94
4	1.8 mL H_2O	*o*-NO_2	**1a**	43	92:8	95
5	0.8 mL H_2O	*o*-NO_2	**1b**	51	92:8	91
6	0.8 mL H_2O	*m*-NO_2	**1a**	65	90:10	92
7	0.8 mL H_2O	*p*-NO_2	**1a**	76	91:9	93
8	0.8 mL H_2O	*o*-Cl	**1a**	39	90:10	89
9	0.8 mL H_2O	*m*-Cl	**1a**	47	86:14	83
10	0.8 mL H_2O	*p*-Cl	**1a**	64	87:13	90
11	0.8 mL H_2O	*m*-Br	**1a**	33	88:12	95

[a] The reaction of cyclohexanone (1.2 mL), aldehyde (0.33 mmol) and **1** (0.016 mmol) was performed in ketone/water mixture.
[b] Isolated yield after thin layer chromatography on silica gel.
[c] Determined by HPLC using a chiral column (Daicel OD-H).

These results are comparable to the results observed in wet DMF. Individually, when using *p*-nitro or *p*-chlorobenzaldehyde as an aldol acceptor, the yields of the aldol products were much higher than that of the corresponding *o*- or *m*-isomers (entries 2 and 6–10).

Cyclopentanone and acetone were finally explored as aldol donors. The results are listed in Table 4. When cyclopentanone was taken as the aldol donor, moderate to good yields were observed with moderate diastereoselectivities and excellent enantioselectivities (entries 1 and 3) in wet DMF. When the reaction was performed in ketone/water mixture, lower catalytic activities were obtained without any loss of stereoselectivity (entries 2 and 4). When acetone was used as the aldol donor, only moderate yields and good enantioselectivities were obtained (entries 5 and 7). When a small amounts of water were added into the reaction mixture of *o*-nitrobenzaldehyde and acetone, a much lower yield was obtained with comparable enantioselectivity (entry 6).

3. Conclusions

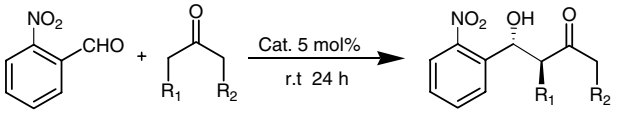
In conclusion, a new type of amphiphilic and recyclable catalysts **1a** and **1b** has been synthesized for the asymmetric direct aldol reaction. The catalytic effect of these catalysts for the aldol reaction was evaluated in wet DMF and a ketone/water mixture. Good yields and high stereoselectivities (94% yield, 96:4 *anti*/*syn* ratio, 96% ee in wet DMF and 76% yield, 93:7 *anti*/*syn* ratio, 95% ee in ketone/water mixture) were obtained for the reactions of aromatic aldehydes with ketones. It was also found that water could play a special role in improving the reactivity and stereoselectivity in the aldol reaction catalyzed by the linear polystyrene anchored L-proline. Additionally, the polymer-supported catalysts could be recovered and re-used giving virtually unchanged stereoselectivity although slowly diminishing yields were obtained 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.

4. Experimental

4.1. General

All chemicals were used as received unless otherwise noted. Reagent grade solvents were redistilled prior to use. All ^1H 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™ instrument using the ESI technique. Chromatography was performed on silica gel (200–300 mesh). Melting points were determined by a XT5A apparatus and uncorrected. Optical rotations were determined on a Perkin–Elmer 341 polarimeter. Element analysis was determined on Flash EA1112. Enantiomeric

Table 4. The aldol reaction of *o*-nitrobenzaldehyde with cyclopentanone or acetone catalyzed by **1a**–**b**



Entry	R_1, R_2	Solvent	Cat	Yield[d] (%)	*anti*/*syn*[e]	ee[e] (*anti*) (%)
1	CH_2, CH_2	DMF/H_2O (15:1)[a]	**1a**	55	75:25	94
2	CH_2, CH_2	Ketone/water[b]	**1a**	42	75:25	93
3	CH_2, CH_2	DMF/H_2O (15:1)[a]	**1b**	86	70:30	92
4	CH_2, CH_2	Ketone/water[b]	**1b**	47	80:20	92
5	H, H	DMF[c]	**1a**	61		78
6	H, H	DMF/H_2O (100:1)[c]	**1a**	40		76
7	H, H	DMF[c]	**1b**	72		76

[a] The reaction of cyclopentanone (0.5 mL), *o*-nitrobenzaldehyde (50 mg, 0.33 mmol) and **1** (0.016 mmol) was performed in DMF/H_2O (15:1, 1.5 mL).
[b] The reaction of cyclopentanone (1.2 mL), *o*-nitrobenzaldehyde (50 mg, 0.33 mmol) and **1** (0.016 mmol) was performed in water (0.8 mL).
[c] The reaction of acetone (0.5 mL), *o*-nitrobenzaldehyde (50 mg, 0.33 mmol) and **1** (0.013 mmol) was performed in DMF (1.5 mL).
[d] Isolated yield after thin layer chromatography on silica gel.
[e] Determined by HPLC using a chiral column (Daicel OD-H).

excesses were 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 a UV 500 version 4.1 ultra-violet detector) with Chiralcel OD-H (4.6 mm × 250 mm) columns.

4.2. Preparation of the catalysts 1a and 1b

4.2.1. (2*S*,4*S*)-*N*-Cbz-4-aminoproline methyl ester 2. Compound **2** was prepared from *trans*-4-hydroxy-L-proline as reported in the literature[10] with an overall yield of up to 72%. $[\alpha]_D^{20} = -23.2$ (*c* 1.18, EtOH); IR (KBr, cm^{-1}): 3374, 3386, 3033, 2952, 2886, 1747, 1704, 1498, 1418, 1356, 1204, 1170, 1112, 769, 751, 699; ^1H NMR ($CDCl_3$, ppm): $\delta = 1.83–1.89$ (1H, m, H-3), 2.42–2.48 (1H, m, H-3), 3.31–3.37 (1H, m, H-5), 3.56–3.57 (1H, m, H-5), 3.70–3.79 (1H, m, H-4), 3.59 and 3.77 (3H, s, $–OCH_3$), 4.33–4.41 (1H, m, H-2), 5.02–5.20 (2H, m, $–OCH_2Ph$), 7.28–7.37 (5H, m, Ph); HR-MS *m*/*z*: calcd for $C_{14}H_{18}N_2O_4$ $(M+H)^+$ 279.1345, found 279.1333.

4.2.2. (2*S*,4*S*)-1-Benzyloxycarbonyl-2-methoxycarbonyl-4-(3′-carboxyl-propanoyl)amino-pyrrolidine 3a. A solution of compound **2** (0.56 g, 2.0 mmol) and succinic anhydride (0.2 g, 2.0 mmol) in anhydrous CH_2Cl_2 (15 mL) was stirred at room temperature for 2 h. The reaction mixture was concentrated under reduced pressure. The residue was used without any further purification. $[\alpha]_D^{20} = -9.2$ (*c* 1.50, EtOH); IR (KBr, cm^{-1}): 3339, 3065, 3033, 2955, 1735, 1709, 1678, 1656, 1543, 1421, 1356, 1209, 1171, 770, 751, 699; ^1H NMR ($CDCl_3$, ppm): $\delta = 1.99–2.02$ (2H, m, H-3), 2.43–2.48 (6H, m, H-3 and $–CH_2CONH–$), 2.62–2.68 (4H, m, $–CH_2COOH$), 3.60 and 3.79 (6H, s, $–OCH_3$), 3.50–3.60 (2H, m, H-5), 3.67–3.71 (2H, m, H-5), 4.35–4.42 (2H, m, H-2), 4.61–4.62 (2H, m, H-4), 5.02–5.20 (4H, m, $–OCH_2Ph$), 7.28–7.36 (10H, m, Ph); ^{13}C NMR ($CDCl_3$) δ: 29.3, 30.7, 36.0, 48.0, 52.7, 53.1, 57.8, 67.5, 127.9, 128.1, 128.2, 128.5, 136.0, 154.4, 173.0, 175.5; HR-MS *m*/*z*: calcd for $C_{18}H_{22}N_2O_7$ $(M+H)^+$ 379.1505, found 379.1522.

4.2.3. (2*S*,4*S*)-1-Benzyloxycarbonyl-2-methoxycarbonyl-4-(5′-carboxyl-valeryl)amino-pyrrolidine 3b. To a stirred solution of compound **2** (0.56 g, 2.0 mmol) and hexanedioic acid (0.28 g, 2.0 mmol) in anhydrous CH_2Cl_2 (15 mL) was added *N*,*N*-dicyclohexylcarbodiimine (DCC, 0.44 g, 2.1 mmol) and catalytic quanties of DMAP at room temperature. After stirring for 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 0.36 g (45%) of semi-solid product. $[\alpha]_D^{20} = -13.8$ (*c* 0.65, EtOH); IR (KBr, cm^{-1}): 3374, 3065, 3033, 2951, 1747, 1709, 1672, 1653, 1543, 1420, 1356, 1208, 1170, 770, 751, 699; ^1H NMR ($CDCl_3$, ppm): $\delta = 1.64–1.66$ (4H, m, $–CH_2CH_2–$), 1.95–2.01 (1H, m, H-3), 2.45–2.48 (1H, m, H-3), 2.17–2.20 (2H, t, $–CH_2CONH–$), 2.34–2.37 (2H, t, $–CH_2COOH$), 3.59, 3.79 (3H, s, $–O\ CH_3$), 3.48–3.69 (2H, m, H-5), 4.35–4.42 (1H, m, H-2), 4.66 (1H, m, H-4), 5.03–5.21 (2H, m, $–OCH_2Ph$), 7.28–7.35 (5H, m, –Ph). ^{13}C NMR ($CDCl_3$) δ: 24.5, 25.3, 33.6, 35.6, 36.6, 48.0, 52.6, 53.3, 57.7, 67.5, 127.9, 128.1, 128.2, 128.5, 136.1, 154.3, 172.1, 174.6; HR-MS *m*/*z*: calcd for $C_{20}H_{26}N_2O_7$ $(M+H)^+$ 407.1818, found 407.1819.

4.2.4. General procedure for the preparation of 4a and 4b. To a stirred mixture of **3** (1.1 mmol) and aminopolystyrene (0.5 g) in anhydrous CH_2Cl_2 (25 mL) was added DCC (0.32 g, 1.5 mmol) and catalytic quantities of DMAP at room temperature. After stirring for about 12 h, the reaction mixture was filtered, and the filtrate was concentrated. The residue was washed with methanol (15 mL × 3) to give white powder **4**.

Compound **4a**: IR (KBr, cm^{-1}): 3401, 3058, 3025, 2921, 2849, 1744, 1711, 1661, 1598, 1535, 1493, 1450, 1415, 1354, 1207, 1172, 757, 699; ^1H NMR ($CDCl_3$, ppm): $\delta = 1.22–1.68$ (2.0H, br, PS–CH_2–), 1.68–2.05 (1.2H, br, PS–CH– and H-3), 2.05–2.17 (0.4H, m, NHC-OCH_2CH_2CONH), 3.58–3.78 (0.5H, m, $–OCH_3$ and H-5), 4.42–4.49 (0.1H, m, H-2), 4.92 (0.3H, br, H-4 and PS–CH_2NH), 4.58 5.10–5.23 (0.2H, m, $–OCH_2Ph$), 6.50–6.58 (2.0H, br, PS), 7.05–7.08 (3.0H, br, PS), 7.32–7.34 (0.5H, m, $–OCH_2Ph$).

Compound **4b**: IR (KBr, cm^{-1}): 3413, 3059, 3026, 2923, 2851, 1741, 1713, 1674, 1601, 1515, 1494, 1450, 1417, 1355, 1207, 1179, 758, 700; ^1H NMR ($CDCl_3$, ppm): $\delta = 1.13–1.65$ (2.4H, br, PS–CH_2– and $–CH_2CH_2–$), 1.65–2.04 (1.3H, br, PS–CH– and H-3), 2.50 (0.4H, m, NHC-OCH_2, CH_2CONH), 3.58–3.78 (0.5H, m, $–OCH_3$ and H-5), 4.32–4.60 (0.4H, m, H-2, H-4 and PS–CH_2NH), 5.06–5.20 (0.2H, m, $–OCH_2Ph$), 6.47–6.57 (2.0H, br, PS), 7.04–7.08 (3.0H, br, PS), 7.30–7.34 (0.5H, m, $–OCH_2Ph$).

4.2.5. General procedure for the preparation of 1a and 1b. Polymer **4** was dissolved in 20 mL of THF, after which 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 M 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**: IR (KBr, cm^{-1}): 3405, 3336, 3059, 3026, 2923, 2851, 1707, 1662, 1602, 1538, 1516, 1494, 1450, 1419, 1358, 1208, 1027, 758, 700; ^1H NMR ($CDCl_3$, ppm): $\delta = 1.25–1.68$ (2.0H, br, PS–CH_2–), 1.68–2.10 (1.2H, br, PS–CH– and H-3), 2.05–2.43 (0.4H, m, NHC-OCH_2CH_2CONH), 3.50 (0.2H, m, H-5), 4.40 (0.3H, m, H-2 and PS–CH_2NH), 5.0 (0.1H, m, H-4), 6.51–6.58 (2.0H, br, PS), 7.09 (3.0H, br, PS); Elemental Anal.: N, 2.3; C, 84.2; H, 7.6. Loading: 0.55 mmol/g.

Compound **1b**: IR (KBr, cm^{-1}): 3399, 3059, 3026, 2924, 2852, 1711, 1656, 1603, 1538, 1516, 1494, 1450, 1420, 1358, 1207, 1073, 1028, 759, 700; ^1H NMR ($CDCl_3$, ppm): $\delta = 1.11–1.68$ (2.0H, br, PS–CH_2–), 1.68–2.41 (2.0H, br, PS–CH–, H-3 and $NHCOCH_2CH_2CH_2$-CH_2CONH), 3.50 (0.2H, m, H-5), 4.0–5.0 (0.4H, m, H-2, H-4 and PS–CH_2NH), 6.51–6.59 (2.0H, br, PS), 7.06

(3.0H, br, PS); Elemental Anal.: N, 2.2; C, 84.5; H, 7.6. Loading: 0.52 mmol/g.

4.2.6. 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. IR (KBr, cm^{-1}): 3441, 3059, 3026, 2922, 2850, 1601, 1492, 1448, 1370, 1256, 1052, 843, 756, 698; ^1H NMR ($CDCl_3$, ppm): δ 0.90–0.95 (0.17H, m, terminal methyl), 1.09–1.16 (0.14H, m, terminal methyl), 1.26–1.54 (2.0H, br, $–CH_2–$), 1.72–2.04 (1.1H, br, –CH–), 6.46–7.08 (5.0H, m, Ar-H).

4.2.7. 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 then filtered. The product was precipitated out by addition of 30 mL of methanol into the filtrate. The precipitate was filtered to give a white powder, which was washed with methanol (15 mL × 3) and then dried in a vacuum shelf dryer overnight to afford 2.8 g of a white powder. IR (KBr, cm^{-1}): 3449, 3059, 3025, 2921, 2848, 1601, 1493, 1451, 1371, 1265, 1029, 840, 757, 699; ^1H NMR ($CDCl_3$, ppm): δ 0.89–0.93 (0.12H, m, terminal methyl), 1.09–1.13 (0.09H, m, terminal methyl), 1.22–1.54 (2.1H, br, $–CH_2–$), 1.72–2.05 (1.2H, br, –CH–), 4.50 (0.18H, m, $–CH_2Cl$), 6.45–7.08 (5.1H, br, Ar-H).

4.2.8. Aminomethyl polystyrene. Aminomethyl polystyrene was prepared from chloromethyl polystyrene as reported in the literature.[13] IR (KBr, cm^{-1}): 3385, 3059, 3025, 2921, 2848, 1601, 1493, 1451, 1372, 1068, 1028, 845, 757, 6998; ^1H NMR ($CDCl_3$, ppm): δ 0.88–0.93 (0.12H, m, terminal methyl), 1.09–1.14 (0.09H, m, terminal methyl), 1.26–1.5443 (2.0H, br, $–CH_2–$), 1.85–2.46 (1.3H, br, –CH–), 3.74–3.76 (0.19H, m, $–CH_2NH_2$), 6.51–7.24 (5.1H, br, Ar-H).

4.3. General procedure for the aldol condensations

4.3.1. 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). The mixture was stirred for 24 h. 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).

4.3.2. Reaction in ketone/water mixture. 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 24 h, the mixture was treated as described above for the reaction in DMF.

4.3.3. 2-(Hydroxyl(4-nitrophenyl)methyl)cyclohexanone. ^1H NMR ($CDCl_3$) δ: *syn*-isomer: 1.50–1.88 (m, 5H), 2.09–2.15 (m, 1H), 2.37–2.52 (m, 2H), 2.62–2.66 (m, 1H), 3.10 (s, 1H), 5.49 (d, $J = 1.6$ Hz, 1H), 7.49 (d, $J = 8.4$ Hz, 2H), 8.22 (d, $J = 8.4$ Hz, 2H); *anti*-isomer: 1.36–1.44 (m, 1H), 1.51–1.73 (m, 3H), 1.83 (m, 1H), 2.10–2.15 (m, 1H), 2.33–2.46 (m, 1H), 2.50 (m, 1H), 2.57–2.63 (m, 1H), 3.80 (s, 1H), 4.90 (d, $J = 8.4$ Hz, 1H), 7.51 (d, $J = 8.4$ Hz, 2H), 7.22 (d, $J = 8.4$ Hz, 2H); HPLC (for *anti*-isomer): Chiralcel OD-H, UV 254, *i*-PrOH/hexane = 5:95, flow rate 1.0 mL/min, t_R 29 min (major), t_R 45 min (minor).

4.3.4. 2-(Hydroxyl(2-nitrophenyl)methyl)cyclohexanone. ^1H NMR ($CDCl_3$) δ: *syn*-isomer: 1.53–1.87 (m, 5H), 2.10 (m, 1H), 2.42–2.47 (*m*, 2H), 2.90 (dd, $J = 13.2$, 4.8 Hz, 1H), 3.15 (s, 1H), 5.96 (d, $J = 1.6$ Hz, 1H), 7.46 (dt, $J = 0.8$, 8.0 Hz, 1H), 7.66 (dt, $J = 0.8$, 8.0 Hz, 1H), 7.84 (dd, $J = 8.0$, 0.8 Hz, 1H), 8.02 (dd, $J = 8.0$, 0.8 Hz, 1H); *anti*-isomer: 1.61–1.87 (m, 5H), 2.10 (m, 1H), 2.34–2.47 (m, 2H), 2.77 (m, 1H), 3.95 (s, 1H), 5.45 (d, $J = 7.2$ Hz, 1H), 7.44 (dt, $J = 0.8$, 8.0 Hz, 1H), 7.66 (dt, $J = 0.8$, 8.0 Hz, 1H), 7.78 (dd, $J = 8.0$, 0.8 Hz, 1H), 7.86 (dd, $J = 8.0$, 0.8 Hz, 1H); HPLC (for *anti*-isomer): Chiralcel OD-H, UV 254, *i*-PrOH/hexane = 5:95, flow rate 1.0 mL/min, t_R 17 min (major), t_R 21 min (minor).

4.3.5. 2-(Hydroxyl(2-chlorophenyl)methyl)cyclohexanone. ^1H NMR ($CDCl_3$) δ: *syn*-isomer: 1.53–1.71 (m, 4H), 1.81–1.84 (m, 1H), 2.08 (m, 1H), 2.33–2.42 (m, 1H), 2.48 (m, 1H), 2.81 (m, 1H), 3.95 (s, 1H), 5.72 (d, $J = 2.0$ Hz, 1H), 7.20–7.34 (m, 3H), 7.56 (d, $J = 8.0$ Hz, 1H); *anti*-isomer: 1.53–1.84 (m, 5H), 2.05–2.13 (m, 1H), 2.31–2.39 (m, 1H), 2.46–2.49 (m, 1H), 2.65–2.71 (*m*, 1H), 3.88 (s, 1H), 5.35 (d, $J = 8.0$ Hz, 1H), 7.20–7.34 (m, 3H), 7.56 (d, $J = 8.4$ Hz, 1H); HPLC (for *anti*-isomer): Chiralcel OD-H, UV 220, *i*-PrOH/hexane = 5:95, flow rate 1.0 mL/min, t_R 10 min (major), t_R 13 min (minor).

4.3.6. 2-(Hydroxyl(4-chlorophenyl)methyl)cyclohexanone. ^1H NMR ($CDCl_3$) δ: *syn*-isomer: 1.42–2.11 (m, 6H), 2.32–2.45 (m, 2H), 2.53–2.56 (m, 1H), 3.05 (s, 1H), 5.36 (d, $J = 2.0$ Hz, 1H), 7.24 (d, $J = 8.4$ Hz, 2H), 7.32 (d, $J = 8.4$ Hz, 2H); *anti*-isomer: 1.27–1.31 (m, 1H), 1.53–1.82 (m, 4H), 2.07–2.11 (m, 1H), 2.35–2.56 (m, 3H), 4.76 (d, $J = 8.8$ Hz, 1H), 7.26 (d, $J = 8.0$ Hz, 2H), 7.32 (d, $J = 8.0$ Hz, 2H); HPLC (for *anti*-isomer): Chiralcel OD-H, UV 220, *i*-PrOH/hexane = 5:95, flow rate 1.0 mL/min, t_R 14 min (major), t_R 22 min (minor).

4.3.7. 2-(Hydroxyl(3-nitrophenyl)methyl)cyclohexanone. ^1H NMR ($CDCl_3$) δ: *syn*-isomer: 1.48–2.10 (m, 6H), 2.33–2.48 (m, 2H), 2.62–2.66 (m, 1H), 3.16 (s, 1H), 5.48 (d, $J = 2.0$ Hz, 1H), 7.52 (t, $J = 8.0$ Hz, 1H), 7.66 (d, $J = 1.4$ Hz, 1H), 8.11 (d, $J = 8.0$ Hz, 1H), 8.20 (d, $J = 8.0$ Hz, 1H); *anti*-isomer: 1.33–2.10 (m, 6H), 2.32–2.48 (m, 2H), 2.70 (m, 1H), 3.16 (s, 1H), 4.91 (d, $J = 8.4$ Hz, 1H), 7.54 (t, $J = 8.0$ Hz, 1H), 7.68 (d, $J = 0.8$ Hz, 1H), 8.15 (m, $J = 8.0$ Hz, 1H), 8.20 (d, $J = 8.0$ Hz, 1H); HPLC (for *anti*-isomer): Chiralcel OD-H, UV 254, *i*-PrOH/hexane = 5:95, flow rate 1.0 mL/min, t_R 24 min (major), t_R 36 min (minor).

4.3.8. 2-(Hydroxyl(3-chlorophenyl)methyl)cyclohexanone. ^1H NMR ($CDCl_3$) δ: *syn*-isomer: 1.45–2.11 (m, 6H), 2.32–2.45 (m, 2H), 2.53–2.56 (m, 1H), 3.05 (s, 1H), 5.50 (d, $J = 2.0$ Hz, 1H), 7.21–7.30 (m, 3H, Ar), 7.37 (s, 1H,

Ar); *anti*-isomer: 1.31–2.08 (m, 6H), 2.30–2.45 (m, 3H), 4.80 (d, $J = 8.8$ Hz, 1H), 7.20–7.29 (m, 3H, Ar), 7.37 (s, 1H, Ar); HPLC (for *anti*-isomer): Chiralcel OD-H, UV 220, *i*-PrOH/hexane = 5:95, flow rate 1.0 mL/min, t_R 13 min (major), t_R 18 min (minor).

4.3.9. 2-(Hydroxyl(3-bromophenyl)methyl)cyclohexanone. ^{1}H NMR ($CDCl_3$) δ: *syn*-isomer: 1.50–2.08 (m, 6H), 2.31–2.61 (m, 3H), 5.36 (d, $J = 2.0$ Hz, 1H), 7.20–7.23 (m, 2H), 7.39–7.50 (m, 2H); *anti*-isomer: 1.30–2.08 (m, 6H), 2.30–2.45 (m, 3H), 4.74 (d, $J = 8.8$ Hz, 1H), 7.20–7.23 (m, 2H), 7.39–7.50 (m, 2H). HPLC (for *anti*-isomer): Chiralcel OD-H, UV 220, *i*-PrOH/Hexane = 5:95, flow rate 1.0 mL/min, t_R 14 min (major), t_R 19 min (minor).

4.3.10. 2-(Hydroxyl(2-nitrophenyl)methyl) cyclopentanone. ^{1}H NMR ($CDCl_3$) δ: *syn*-isomer: 1.70–1.78 (m, 2H), 2.03–2.19 (m, 3H), 2.37 (dd, $J = 8.0$, 1.6 Hz, 1H), 2.60 (br, 1H), 2.74 (m, 1H), 5.92 (d, $J = 2.4$ Hz, 1H) 7.44 (td, $J = 8.0$, 0.8 Hz, 1H, Ar-H), 7.66 (t, $J = 8.0$ Hz, 1H, Ar-H), 7.89 (d, $J = 8.0$ Hz, 1H, Ar), 8.02 (d, $J = 8.0$ Hz, 1H, Ar-H); *anti*-isomer: 1.70–2.03 (m, 4H), 2.19–2.38 (m, 2H), 2.68 (d, $J = 7.6$ Hz, 1H), 2.90 (br, 1H), 5.21 (d, $J = 7.2$ Hz, 1H), 7.44 (t, $J = 8.0$ Hz, 1H, Ar-H), 7.66 (t, $J = 8.0$ Hz, 1H, Ar-H), 7.89 (d, $J = 8.0$ Hz, 1H), 8.00 (dd, $J = 8.0$, 0.8 Hz, 1H); HPLC: *syn*-isomer: Chiralcel OD-H, UV 254, *i*-PrOH/Hexane = 5:95, flow rate 1.0 mL/min, t_R 17 min (major), t_R 13 min (minor); *anti*-isomer: Chiralcel OD-H, UV 254, *i*-PrOH/hexane = 5:95, flow rate 1.0 mL/min, t_R 23 min (major), t_R 26 min (minor).

4.3.11. 4-Hydroxyl-4-(2′-nitrophenyl)-butan-2-one. ^{1}H NMR ($CDCl_3$) δ: 2.24 (s, 3H), 2.74 (dd, $J = 17.8$, 9.4 Hz, 1H), 3.13 (dd, $J = 17.8$, 1.8 Hz, 1H), 3.89 (s, 1H), 5.68 (dd, $J = 9.4$, 1.8 Hz, 1H), 7.44 (t, $J = 8.0$ Hz, 1H), 7.67 (t, $J = 8.0$ Hz, 1H), 7.80 (d, $J = 8.0$ Hz, 1H), 7.96 (d, $J = 8.0$ Hz, 1H); HPLC: Chiralcel OD-H, UV 254, *i*-PrOH/hexane = 5:95, flow rate 1.0 mL/min, *S*-isomer, t_R 18 min, *R*-isomer, t_R 21 min.

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