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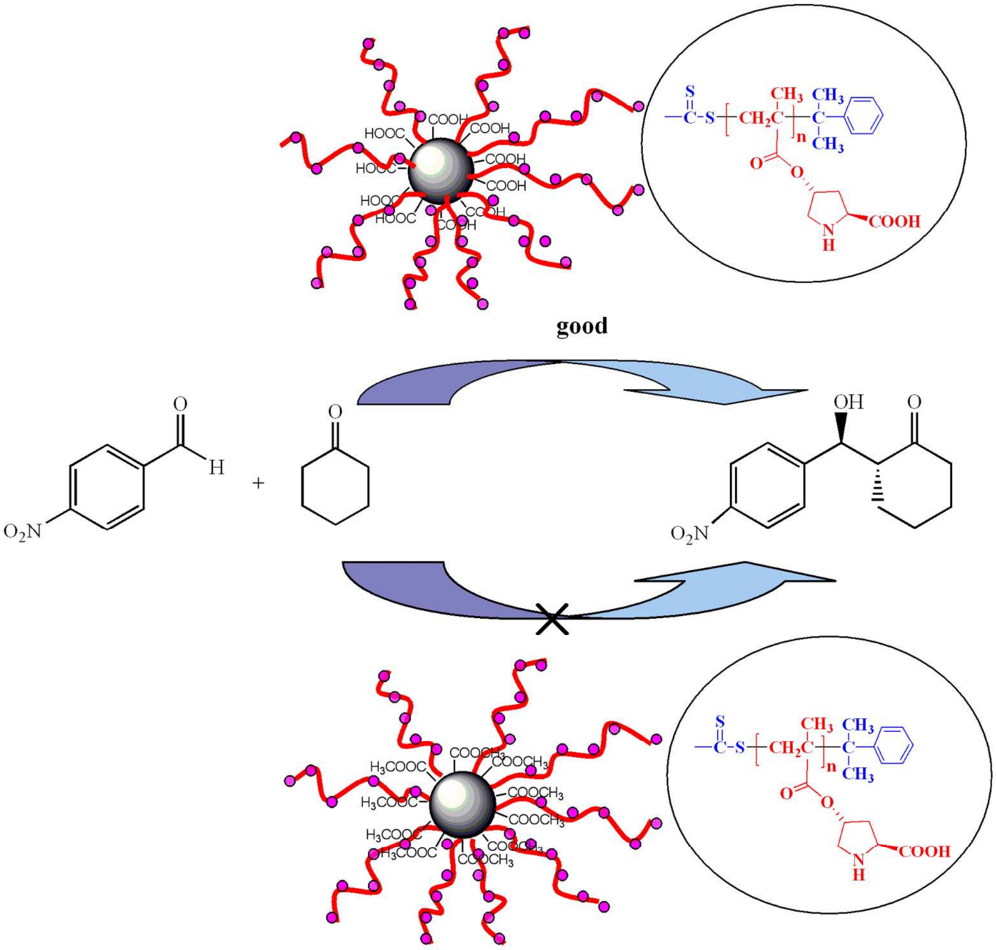

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Combining RAFT precipitation polymerization and Surface-initiated RAFT Polymerization: An Efficient Approach to Prepare Hairy Particles—supported Proline

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Abstract: In this paper, a simple and efficient approach to obtaining hairy particles supported proline system is described. The catalysts were synthesized by the modification of polymer microspheres via surface-initiated RAFT polymerization. The microspheres containing carboxyl or ester groups were respectively synthesized by RAFT precipitation copolymerization, and the functional groups affected the yield and asymmetric selectivity of chiral product in different DMF/H_2O solvent during a representative aldol reaction. Compared with the hairy particles 2 with ester group, the hairy particles 1 with carboxyl groups exhibited better catalytic activity and asymmetric selectivity, providing more suitable microenvironments for the aldol reaction. Importantly, the hairy particles 1 as catalyst can be easily recovered and recycled without losing significant activity and selectivity after 6 cycles. The application of RAFT precipitation polymerization, together with the facile surface-grafting approach provides a general and promising way for chiral catalyst load.

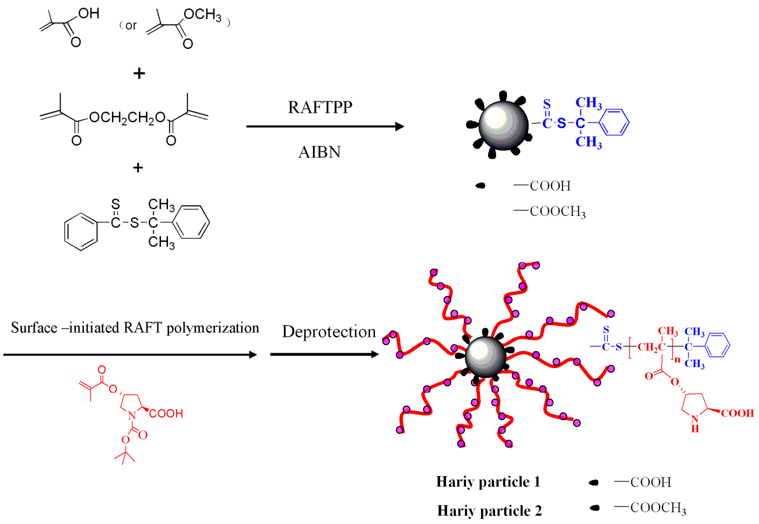
Keywords: hairy particle; polymer microsphere; RAFT polymerization; proline; asymmetric aldol reaction

1. Introduction

The asymmetric aldol reaction, one of the most important carbon–carbon bond forming reactions in synthetic organic chemistry, has been intensively studied. Since List reported the direct aldol reaction catalyzed by L-proline under mild reaction condition [1], L-proline and its derivatives have been widely used in asymmetric organic reactions [2-4]. Great deals of effort have been made to improve the catalytic performance and the recovery of proline [5]. A number of strategies have been used to immobilize proline such as polystyrene (beads) [6-9], merrifield resin[10], ionic liquids [11,12], dendrimers[13], and inorganic particles or crosslinked insoluble polymers [14, 15]. In general, the soluble polymer-supported catalysts have the advantages of homogeneous catalyst (high catalytic activity and high stereoselectivity), but recovery of the catalyst requires precipitation which may not be quantitative and simple. Ionic liquid as support for proline was effective for the reaction, but ionic liquids are still expensive and recovery of products by extraction is tedious. Inorganic particles or crosslinked insoluble polymers supported catalysts can be easily separated (e.g., by centrifugation or filtering), but the catalytic activities are lower than those of non-supported and linear soluble polymer-supported catalysts [15]. At present, the preparation of efficient and recoverable supports of the organocatalyst for direct asymmetric aldol reaction still remains challenging [17-20].

Hairy particles are a kind of core shell particles whose shell is composed of linear polymer chains having high affinity to the dispersion medium. Hairy particles have attracted ever increasing attention in the past decade due to a number of the possible applications such as bioscience, engineering, electronic and optical devices [21-24]. But there are very few examples of catalysts immobilized on hairy particles have been reported. Christopher et al synthesized a class of Fe_3O_4 nanoparticles supported Co(III)-salen by ATRP, the results proved the catalyst can catalyze ring-opening of epoxides efficiently and can be recovered and reused [25]. Also, they prepared the polymer-oxide hybrid materials based on nonporous silica-supported sulfonic acid, the polymer brushes supported sulfonic acid catalysts were used for the hydrolysis of ethyl lactate [26]. Zhao et al reported the synthesis of a hairy particle-supported DAAP catalyst, the hairy particles were found to efficiently catalyze the acylation of secondary alcohols and Baylis-Hillman reaction, and were recyclable [27]. The above results proved that unlike covalently immobilized small molecules which are completely fixed on the substrate, the polymer brushes on the surface of hairy particles are a dynamic system possessing a certain degree of mobility. Therefore, if organic catalysts are incorporated into the grafted polymer chains, hairy particles supported organocatalysts can combine the advantages of both homogeneous catalysts and heterogeneous catalysts, and provide a new and practical way for supporting catalysts. To our knowledge, the organocatalysts supported on hairy particles for asymmetric reaction have not been reported.

In this work, the hairy particles supported proline were designed and synthesized by grafting of chiral polymer brushes onto the preformed polymer microspheres via surface-initiated RAFT polymerization (Scheme 1). In comparison with the previously reported preparation methods (i.e., inorganic particles supported catalyst system), our approach should be more simple and efficient. One side, the polymer microspheres with surface-immobilized dithioester groups were synthesized by addition of the RAFT agent during the process of conventional precipitation polymerization, which needs only one step [28-29]. On the other hand, functional microspheres with various functional groups (such as hydroxyl, carboxylic and epoxy groups) can be prepared by RAFT precipitation co-polymerization of functional monomers (such as methyl methacrylate, hydroxylethyl methacrylate, 4-vinylpyridine) with a crosslinker [30]. The functional groups can adjust hydrophilic—hydrophobic balance of polymer microspheres, to offer suitable microenvironments for catalytic asymmetric reactions. In view of the versatility of RAFT polymerization, a large number of chiral polymer brushes with predetermined molecular weights, compositions and monomer sequences can be easily prepared. The presence of chiral polymer brushes on the obtained hairy particles was confirmed by Fourier transform infrared spectrum (FTIR), scanning electron microscope (SEM), field emission scanning electron microscopy (FESEM) and elemental analysis. Some quantitative information including the molecular weight and polydispersity of the grafted polymer brushes, and the catalyst loading were characterized in detail. Furthermore, the obtained catalysts were used in representative aldol reaction between cyclohexanone and 4-nitrobenzaldehyde. The catalytic activity, asymmetric selectivity and recyclability were further studied.



Scheme 1. Synthesis of hairy particles supported proline by the modification of polymer microspheres via surface-initiated RAFT polymerization.

2. Experimental

2.1 Materials

Methyl methacrylate (MMA, sinopharm chemical, China, AR), Methacrylic acid (MAA, Aladin, 98%), ethylene glycol dimethacrylate (EGDMA, Alfa Aesar, 98%), and N, N-dimethylformamide (DMF, Jiangtian Chemicals, China), were purified by distillation under vacuum. L-hydroxyproline was purchased from Biodee. Azobisisobutyronitrile (AIBN, Chemical Plant of Nankai University, AR) was recrystallized from ethanol. Cumyl dithiobenzoate (CDB) [31] and O-methyl acroloyl-L-hyp hydrochloride [32] were prepared following the literature procedure, and all the other chemicals were used as received.

2.2 Measurements

^{1}H NMR spectra were recorded on a Bruker AV-400 NMR spectrometer. FT-IR spectra were recorded on a Nicolet NEXUS Fourier transform infrared spectrometer using KBr pellets. Elemental analysis was performed on a Thermo FLASH 1112 elementar. MS analysis was recorded on Bruker mirOTOF II Focus mass spectrometry instrumentation. The morphologies and sizes of the samples were characterized using scanning electron microscopy (SEM, JSM-6390LV) and field-emitting scanning electron microscope (FESEM, JEOL-JSM-6700F). Molecular weights of the polymers were measured with GPC using PS as a standard, DMF as a mobile phase and RI detector was used. Two shodex LF-404 columns were conditioned at 35 □ and flow rate=0.3 mL/min. HPLC analysis was carried out on Agilent TM 1100 HPLC equipment using DAICEL Chiralpack AD-H chromatographic column, mobile phase: hexane/i-propanol=90/10 and flow rate=1.0 mL/min.

2.3 Preparation of the hairy particles supported catalyst

2.3.1 Preparation of Poly(MAA-co-EGDMA) Microspheres by RAFT

MAA (0.12 g, 1.50 mmol), CDB (18.2 mg, 0.66 mmol), EGDMA (1.41 mL, 7.50 mmol), a mixture of methanol and water (4/1, v/v, 120 mL) were added into a one-neck round bottom flask (250 mL) successively. After stirring of 30 min at room temperature, AIBN (54.1 mg, 0.33 mmol) were added. The reaction mixture was purged with nitrogen for 30 min and sealed. The flask was then attached to the rotor-arm of an evaporator, submerged in a 60□ oil bath and rotated slowly (ca. 20 rpm) for 24 h. The resulting polymer particles were collected by filtration and purified with methanol. After being dried at 40℃ under vacuum for 48 h, a light pink solid was obtained in a yield of 69%. ELEM. ANAL.: C, 58.74; H, 7.03; S, 2.48% (the CTA loading was 0.39 mmol/g).

2.3.2 Preparation of Poly(MMA-co-EGDMA) Microspheres by RAFT

Poly(MMA-co-EGDMA) microspheres (light pink solid) was prepared and purified under the identical conditions except the change of comonomer from MAA to MMA (yield:73%). ELEM. ANAL.: C, 58.71; H, 7.16; S, 3.08% (the CTA loading was 0.48 mmol/g).

2.3.3 Synthesis of chiral monomer (Boc-protected O-acrylic hydroxyproline)

O-methyl acroloyl-L-hyp hydrochloride (2.01 g, 8.50 mmol) and 50 mL CH_2Cl_2 were added in a round flask, 2.2 mL triethylamine was added to adjust the pH of the solution to about 9. Then di-tert butyl pyrocarbonate (4.61 g, 21.10mmol) was added in batch, stirred for 2 h under reflux. After reaction, apropriate amount $KHSO_4$ aqueous solution was added to adjust the pH of the solution to 2-3, and extracted with dichloromethane. The organic phase was washed with 50 mL×3 saturated NaCl solution, dried with $MgSO_4$, filtered and concentrated to give the crude product of yellow oil. The oil was further purified by silica flash column chloromatography using eluent of 4:1 petroleum ether/EtOAc, and obtained a yellow oil product in 78% isolated yield. ^{1}HNMR($CDCl_3$/TMS): δ1.44-1.48(d, 9H, -***(CH$_3$)$_3$***), 1.94(s, 3H, -***CH$_3$***), 2.24-2.54(m, 2H, -***CH$_2$***), 3.58-3.80(m, 2H, -***CH$_2$***CHCOOH), 4.35-4.52(t, 1H, -***CH***COOH), 5.35(m, 1H, -COO***CH***), 5.62(s, 1H, ***CH$_2$***=C), 6.11(s, 1H, ***CH$_2$***=C), MS(m/z): [M+H] $^+$ Calculated for $C_{14}H_{22}NO_6$: 300.32, Found: 300.24.

2.3.4 Grafting chiral polymer brushes onto polymer microspheres

The microspheres with grafted polymer brushes were prepared via surface-initiated RAFT polymerization according to the following procedure: poly(MMA-co-EGDMA) or poly(MAA-co-EGDMA) microspheres (the CTA loading 0.26 mmol), Boc-protected O-acrylic hydroxyproline (3.27 g, 10.89 mmol), CDB (30.4 mg, 0.11 mmol), AIBN (3.3 mg, 0.02 mmol), and DMF (5 mL) were added into a two-neck round-bottom flask (25 mL) successively. After being degassed with five freeze-pump-thaw cycles, the flask was sealed and immersed in a thermostated oil bath at 75℃ and stirred for 24 h. After centrifugation, the resulting solid products were thoroughly washed with DMF and methanol, and then dried at 30°C under vacuum to give a pale powder. The supernatant solutions were precipitated in ether, filtered and dried at 30°C under vacuum for 48 h, and obtained the free N-Boc protected polymer.

2.3.5 Deprotection of polymer brushes

The above hairy particles (1.00 g) were dispersed in dry CH_2Cl_2 (5 mL), and the solution of TFA (5 mL) and CH_2Cl_2 (5 mL) was dropwise added for 0.5 h at ice bath, then the mixture was stirred for 0.5 h at ambient temperature. After centrifugation, the solid products were thoroughly washed with water and methanol, then dried at 40°C under vacuum to obtain final particles (1) with carboxyl groups and (2) with ester groups.

The free polymer was also deprotected according to the above same way. After reaction, the free polymer solution was concentrated and purified by precipitation in diethyl ether, filtered and dried at 30°C under vacuum for 48 h, providing the homogeneous polymer supported proline.

ELEM. ANAL.of the hairy particles (1): C, 59.71; H, 7.17; N, 0.51; S, 1.79% (the proline loading was 0.36 mmol/g).

ELEM. ANAL.of the hairy particles (2): C, 59.69; H, 7.16; N, 0.47; S, 1.77% (the proline loading was 0.34 mmol/g).

2.4 General procedure for the asymmetric aldol reaction

4-nitrobenzaldehyde (38 mg, 0.25 mmol) and cyclohexanone (104 µL, 1.0 mmol) were dissolved in solvent (1 mL), and then the catalyst was added, the mixture was stirred at 0□ for 48 h. The reaction mixture was isolated by centrifugation, and the hairy particles were washed with dichloromethane and dried in a vacuum to use again.

The aqueous layer was extracted into ethyl acetate, and the organic layers were combined and dried over $MgSO_4$. The solvent was removed under vacuum, and the crude residue was purified by flash column chromatography on silica gel (petroleum ether / EtOAc = 4:1, v/v) and yielded the pure aldol product. The diastereomeric ratio (dr) was determined by ^1H NMR spectroscopy, and the enantiomeric excess (ee) was determined by chiral HPLC.

3. Results and discussion

3.1 Preparation of the hairy particles supported catalyst

3.1.1 Preparation of Poly(MAA-co-EGDMA) Microspheres by RAFT

The polymer microspheres with surface-immobilized dithioester groups were prepared via RAFT precipitation polymerization (RAFTPP) following the reference [28]. The incorporation of functional monomers (e g MAA) into the polymerization system can lead to copolymer microspheres with extra surface-immobilized functional groups [33], the functional groups can improve the stability of hairy particles in polar solvent. The polymerization was performed with CDB as the chain transfer agent and AIBN as the initiator at 60°C for 24 h with a reactant composition of MAA/EGDMA/AIBN/CDB being 4/20/0.88/1.76 (molar ratio). After being thoroughly purified by solvent washing, the light pink polymer microspheres were obtained, and the polymer microspheres showed high hydrophilicity. The above-obtained particles were characterized with SEM (Fig. 1a), and the result verified the formation of microspheres and their number-average diameters (Dn) being 2.46 μm. FT-IR spectra of the polymer microspheres revealed the presence of the characteristic peak corresponding to C=S stretching vibration (around 1048 cm^{-1}) (Fig. 2c), confirming the existence of dithioester group. The strong band at 3565 cm^{-1} was assigned to the OH of carboxyl group. The elemental analysis of the microspheres was carried out to determine the chemical composition and crosslinking density. If we assume that the obtained particles contain x moles of the bonded MAA unit (molecular formula: $C_4H_6O_2$) and y moles of the bonded EGDMA unit (molecular formula: $C_{10}H_{14}O_4$), the following equations can be obtained for the weight fractions of carbon (C_C) and hydrogen (C_H):

$$C_C = (4x + 10y)M_C/(xM_{MAA} + yM_{EGDMA})$$

$$C_H = (6x + 14y)M_H/(xM_{MAA} + yM_{EGDMA})$$

Where M_C is the atomic weight of carbon, M_H the atomic weight of hydrogen, M_{MAA} the molecular weight of MAA, and M_{EGDMA} the molecular weight of EGDMA. The molar fractions of the bonded EGDMA unit in the particles (i.e., y/(x+y), which can also be utilized to express the crosslinking density of the particles) can thus be obtained by introducing C_C and C_H values (determined by the elemental analysis). According to the elemental analysis, the crosslinking density of about 80% was obtained for the microspheres.

3.1.2 Preparation of Poly(MMA-co-EGDMA) Microspheres by RAFT.

In order to investigate the effect of the functional group in asymmetric reactions, we prepared poly(MMA-co-EGDMA) microspheres as reference. The synthesized method was same as the poly(MAA-co-EGDMA) microspheres. From SEM images (Fig. 1c), it is apparent that spherical microspheres were formed. The average diameter was 2.07 μm, which was smaller than poly(MAA-co-EGDMA) microspheres. The polymer microspheres showed hydrophobicity. From FTIR (Fig. 2a), the characteristic peak corresponding to C=S stretching vibration (around 1048 cm^{-1}) was also observed. According to the elemental analysis, the crosslinking density of about 75% was obtained for the microspheres.

3.1.3 Preparation of microspheres with surface-grafted chiral polymer brushes

Surface-initiated RAFT polymerization was then performed by using the polymer microsphere with surface-immobilized dithioester groups as the immobilized RAFT agent, AIBN as the initiator, and DMF as the solvent. A certain amount of CDB was also added into the reaction system as the sacrificial chain transfer agent in order to increase the control over the polymerization [28]. The polymerization was performed at 75°C with stirring for 24 h, and the resulting microspheres were thoroughly washed with DMF to remove the physically adsorbed chiral polymer. The weight increases of 12.5 wt% and 13.8 wt% were observed for microspheres. It is important to stress here that the increased weight of the modified particles should be mainly stemmed from the surface-grafted polymer brushes, because the rather high crosslinking density (around 80%) of the particles would prevent them from swelling in the reaction media and only allow the occurrence of surface polymerization, just as reported by Tirelli and coworkers [34]. FT-IR was also employed to characterize the grafted polymer microspheres (Fig. 2b and 2d). In addition to the peaks corresponding to the ungrafted one, some characteristic peaks such as the amide I band (1490 cm^{-1}, C=O stretching), amide II band (1394 cm^{-1}, C–N stretching) were also observed, further verifying the successful grafting of chiral polymer brushes. The average surface grafting density can be calculated according to the following method: by assuming the homogeneous grafting of polymer brushes on the microspheres and an average density ρ=1 g/cm^3 for the particle cores, the average surface grafting densities of polymer brushes (β) can be estimated by using the following equation:

$$\Delta \mathrm{W}(\%) = \frac{\mathrm{S} \times \beta \times M_{\mathrm{Polymer}}}{N_A \times V \times \rho}$$

Where △W refers to the increased weight percentage for the modified microspheres due to the surface-grafted polymer brushes (△W=12.5 and 13.8% for the grafted microspheres, respectively), the number-average molecular weight of the grafted chiral polymer brushes (Mn=58,300 and 55,300, respectively), N_A the Avogadro constant, S the average surface area of the particle core [S=4π(Dn/2)^2] is utilized here and V the average volume of the particle core [V=(4/3)×π(Dn/2)^3)]. An average surface grafting density of about 0.59 and 0.70 chains/nm^2 can be derived for the grafted polymer microspheres, respectively [28].

The free N-Boc protected polymer was further characterized with ^{1}H-NMR (Fig. 3b), it can be seen that the vinyl proton signals (at 5.62, 6.11 ppm) of methacryloyl group from the monomer have disappeared completely from the spectrum, further confirming that the unreacted monomer has been fully removed from the purified polymer. In addition, the chemical shifts and the peak integrations of all the protons in the polymer are consistent with its expected structure.

It is generally accepted that the component, molecular weight and polydispersity of the free polymer generated in the surface-initiated RAFT polymerization system (due to the addition of sacrificial chain transfer agent) are essentially identical to those of the grafted polymer brushes, so the free polymer can be utilized to represent those of the grafted polymer brushes [35]. Therefore, the obtained free polymers were characterized with GPC, from which the number-average molecular weights (Mn) of the grafted polymer brushes on the particles were evaluated to be 58,300 and 55,300 respectively, and their PDI were 1.35 and 1.10. The low polydispersity of the polymer brushes suggested that the surface-initiated RAFT polymerization took place in a well controlled way.

3.1.4 Preparation of the hairy particles (1) and (2)

The Boc protecting groups for the amine can be readily deprotected under acidic conditions [26]. Thus, the chiral polymer on the polymer microspheres was deprotected in dry CH_2Cl_2 in the presence of trifluoroacetic acid (TFA) to afford the final hairy particles. Successful deprotection was confirmed by comparing the ^1H NMR signals of the free polymer given in Figures 3b and 3c. The tBu signals (at 1.11-1.55 ppm) disappeared following deprotection, it turned out that the deprotection of hairy particles was successful. The morphology and particle size of the hairy particles supported proline were characterized with SEM (Fig. 1b and 1d), and the result clearly showed that the particles were still separate microspheres. The number-average diameters (Dn) of the hairy particles were determined to be 2.74 and 2.81 μm, an increases of 80 and 74 nm in Dn values were obtained for the grafted polymer microspheres, from which the layer thickness of 40 and 37 nm (i.e., $\triangle$Dn/2) could be derived for the grafted polymer brushes (in the dry state). The FESEM image (top right corner of Figure 1b and 1d) showed there exited polymer brushes on the surface of cores. The N contents of hairy particles from elemental analysis were 0.51 wt % and 0.47 wt %, corresponding to 0.36 mmol and 0.34 mmol catalyst/g particles.

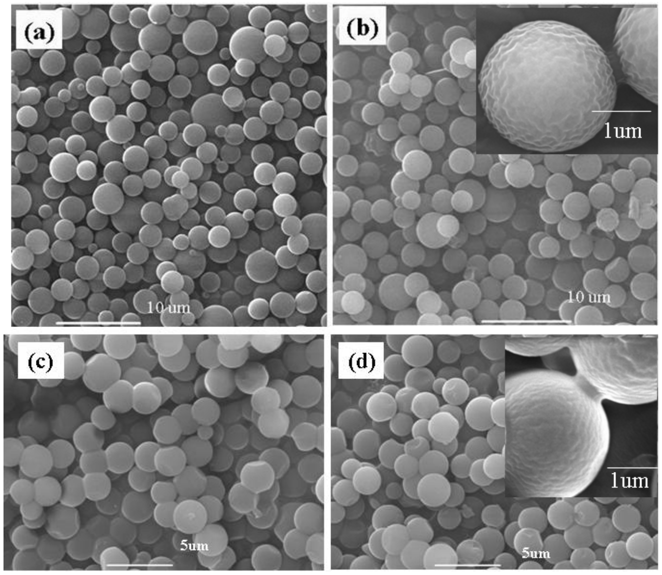


Figure 1. SEM images of no grafted poly(MAA-co-EGDMA) microspheres (a), hairy particles (1) (b), no grafted poly(MMA-co-EGDMA) microspheres (c) and hairy particles (2) (d).

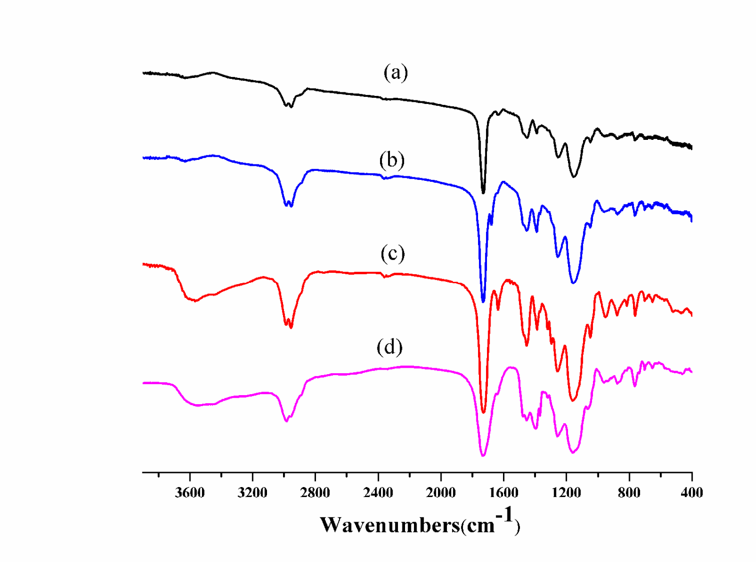


Figure 2. Fourier transform infrared (FT-IR) spectra of no grafted poly(MAA-co-EGDMA) microspheres (a), and the corresponding grafted ones before deprotection (c), no grafted poly(MMA-co-EGDMA) microspheres (b), and the corresponding grafted ones before deprotection (d).

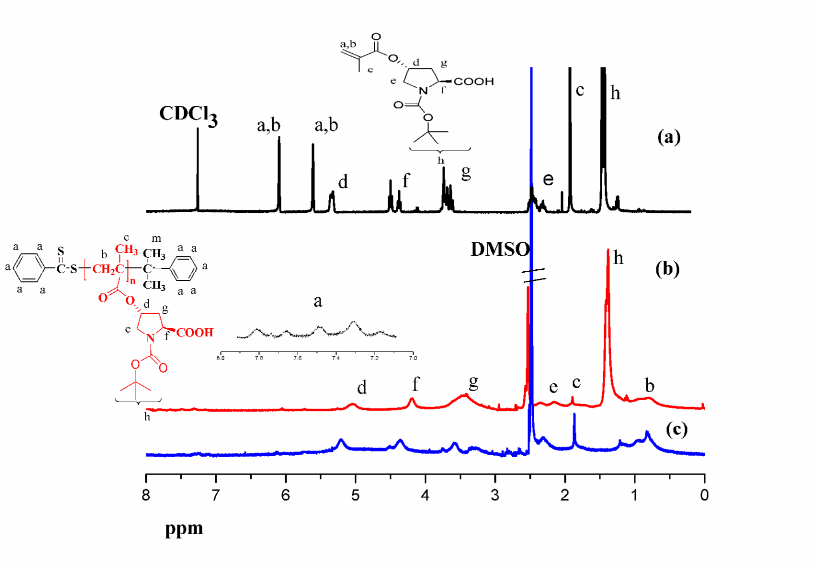
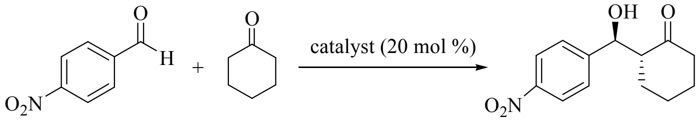


Figure 3. ^{1}H-NMR spectra of monomer Boc-protected O-acrylic hydroxyproline in $CDCl_3$ (a), the free polymer before deprotection in DMSO-d_6 (b), and the free polymer after deprotection in DMSO-d_6 (c).

3.2 The hairy particles supported organocatalyst for the asymmetric aldol reaction

The catalytic activity of the synthesized hairy particles supported L-proline was tested using a representative aldol reaction between cyclohexanone and 4-nitrobenzaldehyde. The reaction was first carried out at 20 mol % catalyst loading with different solvent at 0°C. Normally, L-proline reactions are performed in polar solvents to promote solubility of the organocatalyst, and frequently polar aprotic solvent such as DMF has proven to be the optimal media in which to conduct these reactions [36]. So the reaction was first carried out in DMF with the hairy particles (1) as catalyst, unfortunately the yield was very low (43%). Given the structure of the chiral polymer chains and the solubility of proline in water, it was postulated that a means toward optimizing solvent might be achieved by combining aqueous with organic solvent. Gratifyingly, when DMF and water as mixed solvent, better yields, diastereo- and enantioselectivities were observed, and the optimal solvent system was a 95/5 DMF/H_2O mixture, providing the desired aldol product with 99% yield, 98/2 dr (anti/syn) and 96% ee. When increasing the percentage of water in solvent (from 10% to 100 %), the reaction yield and regioselectivity (anti/syn) decreased obviously, but the ee values were still high. The adol reaction was also carried out at 20 mol% catalyst loading with hairy particles (2) as catalyst. Interestingly, the catalyst was not suitable for the reaction. The DMF/H_2O 95/5 mixture provided the optimal aldol product with 63% yield, 93/7 dr (anti/syn) and 95% ee. In the DMF/H_2O mixture solvent, the yield and asymmetric selectivity of hairy particles (2) were much worse than hairy particles (1). These results indicated that hairy particles (1) with carboxyl groups were more effective in the aldol reaction. Compared the dispersibility of hairy particles (1) with (2) in DMF/H_2O 95/5 mixture, hairy particles (1) was more dispersible than those of (2), the better dispersibility may be also the key factor affecting the catalytic activity. The carboxyl groups can adjust hydrophilic—hydrophobic balance of polymer microspheres in polar solvent, to offer more suitable microenvironments for catalytic asymmetric reactions. In pure water solvent, hairy particles (2) have little better catalytic activity. We hypothesize that the hydrophilic proline moiety and the hydrophobic surface of the particles provide a hydrophobic cavity, such a microenvironment promotes the aldol reaction with little high reaction yield in water [37].

Table 1. Solvent effects on the aldol reaction between cyclohexanone and 4-nitrobenzaldehyde.



entry	cat	solvent	% Yield [a]	Anti/syn [b]	% ee [c](Anti)
1	hairy particles (1)	DMF	43	82/18	89
2	hairy particles (1)	DMF/Water (95/5)	99	92/8	96
3	hairy particles (1)	DMF/Water (90/10)	89	90/10	95
4	hairy particles (1)	DMF/Water (80/20)	60	84/16	97
5	hairy particles (1)	Water	34	89/10	96
6	hairy particles (2)	DMF	25	85/15	87
7	hairy particles (2)	DMF/Water (95/5)	63	91/9	94
8	hairy particles (2)	DMF/Water (90/10)	42	90/10	95
9	hairy particles (2)	DMF/Water (80/20)	45	84/16	97
10	hairy particles (2)	Water	46	85/15	88

[a] Yield determined after chromatographic purification.

[b] Determined by ^{1}H NMR spectroscopic analysis of the product.

[c] Determined by HPLC using a chiral column.

To further investigate the activity and selectivity of the hairy particles 1, we compared the catalytic performance of the hairy particles (1) supported system with the unsupported L-proline and the corresponding free polymer supported proline system. All reactions were carried out using the same conditions in DMF with 5 vol % water at 0°C for 48 h, the results are detailed in Table 2. When lower catalyst loadings (i.e., 5 and 10 mol%) were used, yields and ee values of hairy particles 1 supported system were very close to that of the unsupported L-proline, but unsupported L-proline generated better regioselectivity (anti/syn). When increasing the catalyst loading (i.e., 20 mol%), the regioselectivity of hairy particles (1) increased obviously, the result demonstrates the similarity in both activity and selectivity between the hairy particles 1 (99% yield, 92:8 anti:syn, 96% ee) and unsupported L-proline (99% yield, 95:5 anti:syn, 95% ee).

Table 2. Comparison of the different catalyst system catalyzing the aldol reaction between cyclohexanone and 4-nitrobenzaldehyde at 0°C for 48 h.

entry	cat	mol %	Yield (%) [a]	Anti/syn [b]	% ee（Anti）[c]
1	no catalyst	-		no reaction	
2	poly(MAA-co-EGDMA) microspheres	-		no reaction	
3	L-proline	5	58	90/10	94
4	L-proline	10	99	90/10	94
5	L-proline	20	99	95/5	95
6	hairy particles (1)	5	67	74/26	94
7	hairy particles (1)	10	90	79/21	97
8	hairy particles (1)	20	99	92/8	96
9	homogeneous polymer	5	38	63/37	92
10	homogeneous polymer	10	43	65/35	92
11	homogeneous polymer	20	67	70/30	96

[a] Yield determined after chromatographic purification.

[b] Determined by ^{1}H NMR spectroscopic analysis of the product.

[c] Determined by HPLC using a chiral column.

The homogeneous polymer supported proline only generated 63/37 regioselectivity at 38% yield and 92% ee value with 5 mol % catalyst loading. Higher loading (10 mol%) catalyst slightly increased the yield (43%) and regioselectivity (65/35). When 20 mol% loading was used, the free polymer generated 70/30 regioselectivity with 67% yield and increasing ee value (96%). In contrast, the reaction catalyzed by the hairy particles supported system was more efficient than the free polymer. These results show the advantage of the hairy particles supported system. In order to investigate the reason of the excellent catalytic performance, the reaction was carried out with poly(MAA-co-EGDMA) microspheres in DMF with 5 vol % water at 0°C for 48 h. However, the reaction did not take place, which shows the carboxyl groups of polymer microsphere have no acid catalysis. The high catalytic activity may be due to the inherent cooperativity built into the polymer brush materials [38]. In addition, surface-grafting polymer brushes supported catalysts have proven to be highly efficient for improving the dispersion [27]. The hairy particles (1) in DMF/H_2O (95/5) had better dispersion than the ungrafted microspheres (Fig. 4). The good dispersion is very important for catalyst to have effective catalytic activity.

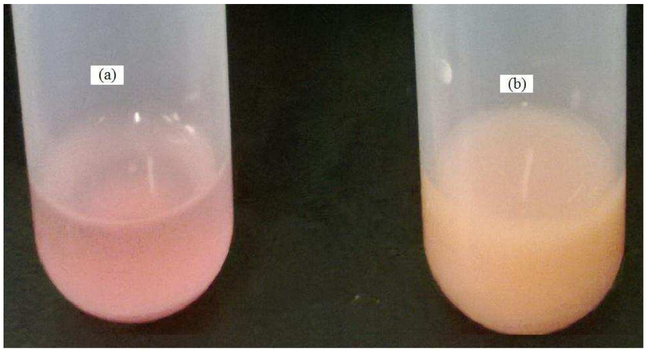


Figure 4. Images of poly(MAA-co-EGDMA) microspheres (a) and hairy particles (1) (b) in DMF/H_2O (95/5) at 0°C for 2 h.

The recycling potential of the hairy particles 1 supported catalytic system was studied using the same aldol reaction between 4-nitrobenzaldehyde and cyclohexanone, in the 5 vol % water/DMF solvent mixture. This adjustment was done to keep the aldol reaction at 20 mol % catalyst loading throughout the different cycles. Table 3 shows the recycling efficiency of the supported system. The catalyst was successfully used in 6 cycles without losing significant activity or selectivity.

Table 3. Recycle data for the aldol reaction using the hairy particles (1) supported catalyst at 0℃ for 48 h.

Cycle #	% Yield	Anti/syn	% ee
1	98	92/8	96
2	99	89/11	96
3	99	90/10	95
4	98	90/10	96
5	99	91/9	95
6	99	88/12	96

4. Conclusions

This paper proves that RAFT precipitation polymerization combining with surface-initiated RAFT polymerization is an efficient approach to obtain hairy particles supported proline system. The catalysts were used in representative aldol reaction between cyclohexanone and 4-nitrobenzaldehyde. The results proved that the hairy particles (1) with carboxyl groups were more effective than the hairy particles (2) with ester groups in the asymmetry aldol reaction. The results also proved the reaction catalyzed by the hairy particle (1) supported system was more efficient than the homogeneous polymer supported proline. When the catalyst loading increased to 20 mol%, the catalytic activity and selectivity of hairy particles supported system were very close to that of the unsupported L-proline. Importantly, the hairy particles (1) can be easily recovered and recycled without losing significant activity and selectivity after 6 cycles. The new catalyst system can combine the advantages of both homogeneous catalysts and heterogeneous catalysts, and provide a new and practical way for chiral catalyst load.

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