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Hyperbranched Polyethylene-Supported L-Proline: A Highly Selective and Recyclable Organocatalyst for Asymmetric Aldol Reactions

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Abstract

A novel hyperbranched polyethylene (HBPE)-supported L-proline has been developed via a bottom-up copolymerization strategy. The copolymerization of ethylene and protected proline acrylate comonomer with cationic Pd-diimine catalysts was conducted, followed by de-protection of the proline groups. Well-defined HBPE copolymers having molecular weights (MWs) of 10.3-50.3 kDa and 3.2-15.6 L-proline molecules per HBPE polymer chain were synthesized. The effects of the L-proline amount and HBPE MW on the catalyst performance were studied. The HBPE catalysts were efficient in asymmetric Aldol reactions of p-nitrobenzaldehyde (p-NBA) or benzaldehyde derivatives with cyclohexanone. High p-NBA conversions of up to 98% and excellent product selectivities with anti/syn = 98/2 and ee>99% were achieved. Moreover, the HBPE catalysts could be easily reclaimed by adding water into the product. The reclaimed catalysts could be reused for multiple times with only a slight decline in reactivity and selectivity.

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Introduction

Organocatalysts have attracted increasing attention recently, mainly due to their capabilities in promoting asymmetric transformations to synthesize chiral compounds or pharmaceuticals with highly added values.[1] L-Proline is one of the representative examples of organocatalysts. L-Proline and their derivatives have been widely used in various important organic reactions, including Aldol, Mannich, Michael, and Baylis–Hillman reactions, Robinson annulation, and so on.[2] The proline molecules can be regarded as simple "enzymes", and they typically function in enzyme-mimetic ways.[2b] However, compared to the enzymes in nature, they often suffer such drawbacks as low catalytic activities, disappointing selectivities, and poor solubilities.[2g,3] Due to the low catalytic activities, high usage of catalyst, up to 30 mol % to substrate, is required. This in turn results in the need of intensive post-reaction separation process, elevating the manufacturing cost.

In attempts to resolve these issues, macromolecular scaffolds have been used to immobilize the organocatalysts.[2g,3-4] Such immobilization not only facilitates separation and the recyclability of the organocatalysts, but also improves the catalyst activity and selectivity and provides good control over the reaction pathways.[2g,4d,5] The polymer supports with designed compositions, topologies, and functionalities can offer prolines and their derivatives (or other organocatalysts) specific catalytic microenvironments, comparable to those found in natural enzymes. The design and synthesis of macromolecular scaffolds, while challenging, are thus of both fundamental importance and practical significance in the organocatalysis field.[5]

Numerous investigations have been reported in the preparation of polymer-supported L-prolines and their derivatives.[2g,4d] Polymeric scaffolds, including linear homopolymers[6,7], linear random[8] or block copolymers,[9] dendrimers,[10] and styrenic[11,12] or acrylic resins,[13] have been developed.

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Among these polymeric supports, dendrimers are particularly attractive because of their unique three-dimensional symmetrical structures, thus mimicking the globular structures of natural enzymes.[14] They are also nearly monodispersed with tailored internal microenvironments, control-dispersed functionalities, and good solubilities. These features endow the dendrimer-supported organocatalysts (or dendritic organocatalysts) with enzyme-mimic properties, such as selective binding and cooperative catalysis, rendering the catalysts to possess high activity and selectivity.[5,14a,14b] The use of dendrimers as scaffolds has been extensively studied and reported in the literature.[15] The synthesis of dendrimers, however, involves complicated and time-consuming iterative steps. On the other hand, hyperbranched polymers can be mass-produced using convenient one-pot, one-step procedures. Although their branching structures are not as well defined as dendrimers, hyperbranched polymers are analogues of dendrimers, thus they have majority of the desired properties of dendrimers.[16] Hyperbranched polymers are often ideal substitutes for dendrimers in practice and have great promise as platforms for the catalyst-support.[17]

To date, only a few examples have been reported on the use of hyperbranched polymers as the scaffolds for L-proline and their derivatives, as well as other organocatalysts.[5,17c] Fréchet and his coworkers[18] immobilized L-prolines onto propylene oxide-modified hyperbranched polyethyleneimine (HBPEI) via non-covalent electrostatic interactions. The polymeric scaffolds with hydrophobic pockets allowed the Aldol reactions of butanal and acetone to proceed in a kinetically unfavorable way under aqueous environment and produced α,β-unsaturated ketone with a yield > 90%. Breslow et al.[19] used lauryl-methylated HBPEI to covalently support pyridoxamines as polymeric transaminase mimics. The modified HBPEIs containing lauryl groups, e.g. 8.7% laurylation, significantly increased the transamination rates of the linked pyridoxamines due to a hydrophobic effect from the long lauryl chains. It was beneficial for selectively binding hydrophobic substrates. Such hydrophobic effect was also found in other supported L-prolines or their

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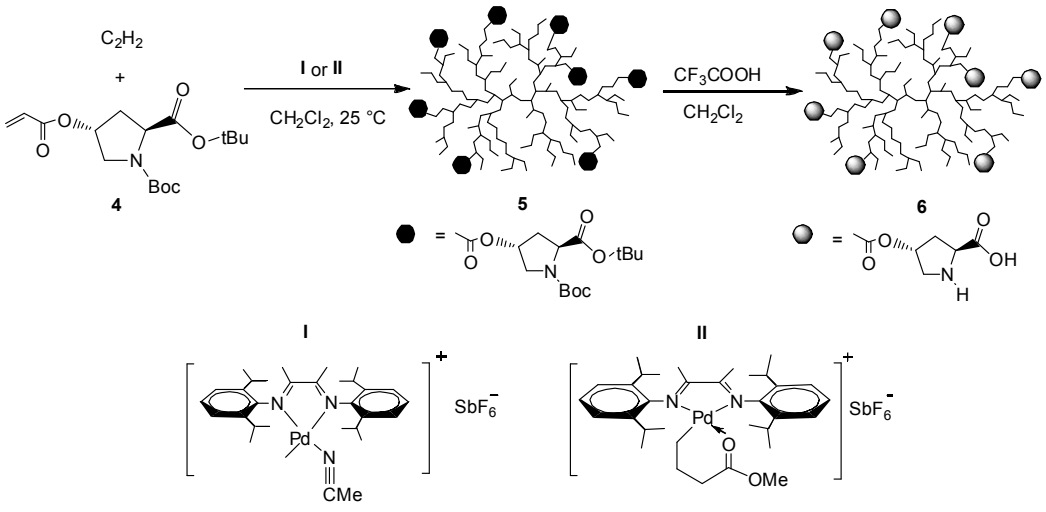
derivatives.[12]

In this work, a class of hyperbranched polyethylenes (HBPEs) containing pendant L-proline groups were developed. As shown in Scheme 1, the HBPE catalyst (**6**) can be facilely synthesized via a bottom-up strategy.[20,21] The hyperbranched copolymers (**5**) were synthesized by chain walking copolymerization (CWP) of ethylene and an acrylic comonomer (**4**), catalyzed by Pd−diimine compounds (**I** or **II**).[22] The protected L-proline groups in **5** were de-protected to consequently yield **6**. The structures and compositions of the HBPE catalysts were characterized by ^{1}H NMR, elemental analysis, infrared spectroscopy (IR), and triple-detector gel permeation chromatography (GPC). The catalytic performances in Aldol reactions of benzaldehyde derivatives and cyclohexanone in different solvents and the recyclability of the catalysts were investigated.



Scheme 1 Synthesis of hyperbranched polyethylene (HBPE) containing pendant L-proline functionalities via Pd-catalyzed chain walking copolymerization of ethylene and protected prolinecomonomer (**4**) followed by de-protection of the proline groups.

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Results and Discussion

Copolymerization of ethylene and the protected proline acrylates

The Pd−diimine catalyst is a class of late transition metal catalyst with distinctive features. It can catalyze chain walking polymerization of ethylene, readily producing HBPEs in one step. The branching density in the HBPEs decreases with increasing ethylene pressure. The catalyst has a remarkable tolerance to polar atoms such as oxygen, nitrogen, phosphorous, sulfone, etc., allowing convenient synthesis of functional HBPEs.[22] Under its catalysis, polar acrylic monomers bearing different functionalities can be used as comonomers to be copolymerized with ethylene to render HBPEs having various pendant functionalities,[22d,22e] and these groups are exclusively located at the end of branches due to the unique 2,1-insertion of the acrylates during the copolymerization.[22b,25] Proline acrylic comonomers (**4** in Scheme 1) with a protected secondary amine and carboxyl group (the active hydrogen is poison to the Pd−diimine catalyst) were thus copolymerized with ethylene. **Table 1** shows the chain walking polymerization results. Four HBPE copolymers (run P1–P4) were synthesized under different comonomer concentrations (0.2 or 0.4 M), ethylene pressures (0.45 or 1 atm), and Pd−diimine catalysts (I or II).

The acetonitrile ligated Pd-diimine complex **I** produced P1 and P2 with low molecular weight compared to the chelate Pd catalyst **II**. The nitrogen atom of comonomer **4** has binding affinity to the active Pd centers during the copolymerization, resulting in less monomer incorporation during copolymerization.[22e] This could be improved by using the chelate Pd catalyst **II** which has a higher copolymerization activity for ethylene and acrylates.[22b,25,26] It is evident that the polymer yield and molecular weight of P3 were higher than P2 at the same comonomer concentration and ethylene pressure.

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Table 1 Experiment conditions and results of Pd-catalyzed ethylene copolymerizations

Run	Cat	P (atm)[b]	$[4]_0$ (M)[c]	Yield (g)	F_4 (10^{-2})[d]	GPC [e]		N_4[f]	E_{DP}[g]	N_{pro}[g]	BD[h]
						Mn (kDa)	PDI				
P1	**I**	0.45	0.20	1.8	0.76	23.8	1.07	6.4	0.99	6.3	97
P2	**I**	0.45	0.40	0.9	0.89	10.3	1.27	3.2	0.99	3.2	98
P3	**II**	0.45	0.40	4.5	1.54	27.1	1.64	14.5	0.99	14.4	101
P4	**II**	1.00	0.40	10.0	0.89	50.3	1.49	15.6	0.99	15.5	98

[a] other conditions: Pd-diiminecatalyst loading 0.2 mmol, solvent CH_2Cl_2 10 mL, 25 ºC for 24 h; [b] ethylene pressure; [c] comonomer **4** concentration; [d] mole ratio of incorporated comonomer **4** determined by ^{1}H NMR; [e] absolute number-average molecular weight and PDI determined by GPC with light scattering detector; [f] N_4 is the average number of incorporated comonomer **4** per polymer chain; [g] E_{DP} is de-protection efficiency determined by ^{1}H NMR and N_{pro} is the average number of L-proline groups per polymer chain after de-protection; [h] branching density (BD) is the number of methyl groups per 1000 carbons determined by ^{1}H NMR.

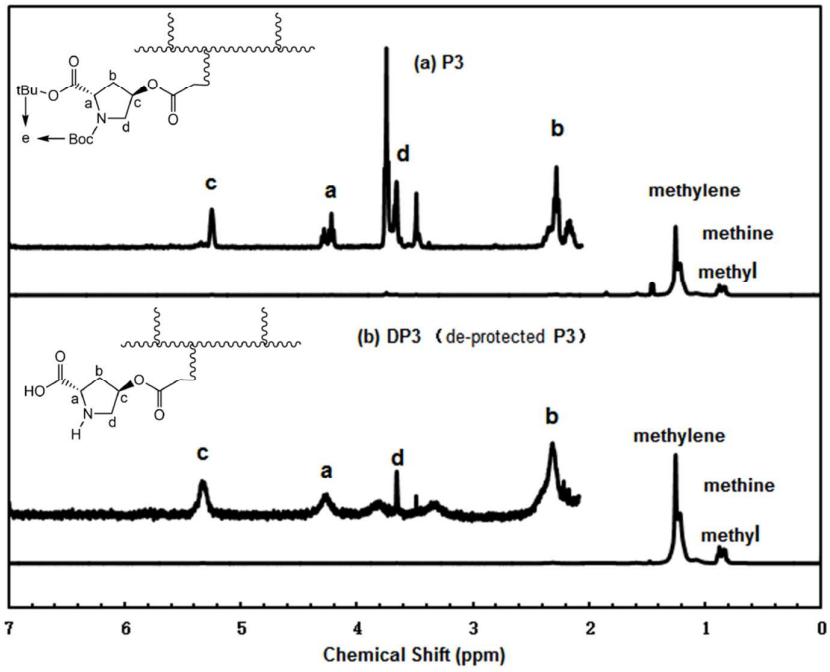

Fig. 1 ^{1}H NMR spectra of run P3 sample (a) before and (b) after de-protection with $CDCl_3$ as

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deuterated solvent.

Figure 1 (a) shows the ^{1}H NMR spectrum of run P3 sample. The corresponding signals of the protected L-proline groups and hyperbranched polyethylene scaffolds were identified. From the peak integrations, the contents of the incorporated comonomer **4** were estimated and included in Table 1. The comonomer **4** content in run P3 was further confirmed by the elemental analysis as shown in Table S1 in the Supporting Information. Run P2 sample only had a slightly higher comonomer content than P1, even with twice as much the comonomer concentration used in the synthesis of P2. This could be attributed to the lower copolymerization rate in P2. Run P3 had almost double incorporated comonomer amount than P4 by changing the ethylene pressure. Higher ethylene pressure resulted in higher polymerization rate, which was confirmed by the product weight (4.5g P3 and 10.0g P4) and molecular weight (27.1 kDa Mn P3 and 50.3 kDa Mn P4). The samples had PDIs of 1.07-1.64. The hyperbranched structures of run P1–P4 samples were also confirmed in the ^{1}H NMR spectra.[27] The branching densities were 97-101 branches per 1000 carbons.

De-protection of L-proline moieties in the copolymers

Run P1–P4 samples were treated with CF_3COOH to remove the -Boc and -tBu protections in the copolymers. Figure 1(b) shows the ^{1}H NMR spectrum of the de-protected P3 (DP3) with the identified groups. The signal peaks of protons from the pendant hydrophilic L-proline groups were blunt due to their reduced solubilities in $CDCl_3$. The de-protection efficiency was calculated through comparison of the peak **e** integrations of -Boc and -tBu groups at 1.42 ppm in Figure 1 (a) and (b), and was found to be over 99%. The completed de-protection was further confirmed by the IR spectra as shown in Figure S9 of the Supporting Information. The average number of the pendant L-proline groups (N_{pro}) per polymer chain was thus calculated and summarized in Table 1. The de-protected P4 (DP4) had the highest N_{pro} of 15.5, followed by DP3 of 14.4, DP1 of 6.3 and DP2 of 3.0. Upon

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de-protection, the liquid oil run P1–P3 samples became viscous jelly. Their thermal properties were also altered, as evident from the DSC thermograms in **Figure 2**. Run P3 sample had a T_g of -63.5 °C and a broad melting endotherm from -70 to 10 °C with a peak temperature of -37.3 °C, comparable to those HBPEs and functional HBPE copolymers in the previous studies.[24a,28] The de-protected P3 (DP3) had an increased T_g of -60.6 °C and T_m of -30.0 °C, suggesting enhanced entanglements of the polymer chains with reduced mobility. The hydrogen bond interactions between secondary amines and carboxylic acids in the pendant L-proline groups, both intramolecularly and intermolecularly, could exist.

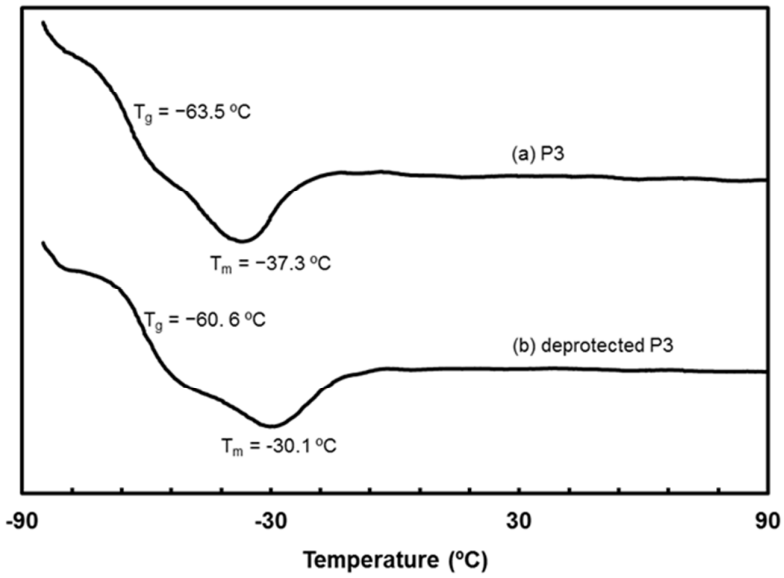


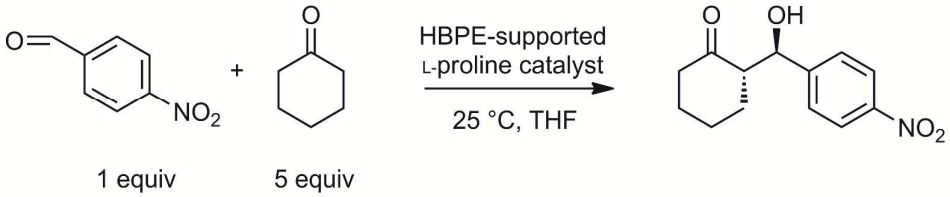
Fig. 2 The DSC thermograms of P3 and de-protected P3 (DP3).

HBPE-proline catalyzed Aldol reactions of benzaldehyde derivatives and cyclohexanone

The catalytic performance and recyclability of the hyperbranched organocatalysts were studied in the Aldol reactions of benzaldehyde derivatives and cyclohexanone. The p-NBA and cyclohexanone system as shown in **Scheme 2** was the main focus since it has been widely used as a model reaction to test the catalytic properties of various L-proline-functionalized polymer catalysts.[7,9a,12,29] The olefinic HBPE scaffold offers the hydrophilic prolines selective solubility in tetrahydrofuran (THF).

Catalysis Science & Technology Accepted Manuscript

THF was therefore used as solvent for the de-protected run P1–P4 samples (DP1-DP4) in the catalyzed reactions. A very small amount of water (1 vol. % of THF) was added because it is beneficial to the reaction rate and the stereoselectivity.[30] **Table 2** shows the reaction results of the HBPEs with varying L-proline to p-NBA molar ratios from 1 to 30 %.



Scheme 2 The Aldol reaction of p-NBA and cyclohexanone catalyzed by HBPE-supported L-prolines

Table 2 Catalytic performance of the HBPE-supported L-prolines in Aldol reaction of p-NBA and cyclohexanone [a]

Run	Catalyst	$[L\text{-proline}]_0/[p\text{-NBA}]_0$ (mol%)	Time (h)	x [b] (%)	anti/syn [c]	ee [d] (%)
1	DP1	1	48	30	88:12	67
2		10	24	69	96:4	94
3		30	24	96	98:2	>99
4	DP2	1	48	31	90:10	72
5		10	24	75	90:10	—
		10	48	83	96:4	97
6		30	24	98	96:4	>99
7	DP3	1	48	34	86:14	71
8		10	24	65	90:10	87
9		30	24	96	94:6	95
10	DP4	10	24	63	93:7	80
11		30	24	96	98:2	99

[a] other conditions: p-NBA (0.1mmol), cyclohexanone (0.5mmol), solvent 0.5 mL THF with 1 vol. % water, 25 °C; [b] conversion of p-NBA determined by ^{1}H NMR; [c] determined by ^{1}H NMR; [d]

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determined by the chiral HPLC.

The p-NBA conversions of 96-98% were achieved in 24 h with 30 mol % proline to p-NBA. The p-NBA conversion at a fixed reaction time increased with the proline amount, as expected. The activities of these supported L-prolines were comparable to the un-supported L-proline catalysts.[2g] In general, the transformation rate of p-NBA decreased with increasing DP molecular weight in comparison of DP2, DP1, and DP4 (having similar L-proline mole fraction in the HBPEs). This might be due to more steric hindrance and diffusion limitations that the reactants have to overcome to get to the catalytic sites in system with higher molecular weight polymer scaffold.

Selectivity is the most important parameter in the synthesis of chiral compounds. The selectivity results of the HBPE-proline catalyzed Aldol reaction of p-NBA and cyclohexanone are shown in Table 2. The HBPE-proline had the anti/syn value up to 98:2 and the ee value over 99%. The catalytic selectivity was comparable or superior to other supported prolines reported in literature with 30% L-proline to p-NBA.[2g,7,12,13a] Both hydrophobic HBPE chains and proline content in the polymer are speculated to have strong effect on the catalyst selectivity. While HBPE support is soluble in THF, hydrophilic proline is not, due to the –COOH group. The proline groups on HBPE could be wrapped by olefinic units of the support. The hydrophobic HBPE scaffolds thus provided the proline groups confined microenvironments or pockets in the catalysis, which is beneficial for the reaction selectivity.

The Aldol reaction of p-NBA and cyclohexanone in different solvents was conducted with DP4 as catalyst. **Table 3** gives the experimental results of DP4 with 30% L-proline to p-NBA conducted in various solvents. High catalytic activity and selectivity were achieved in using these solvent systems, which could be attributed to good solubility of the HBPEs in these solvents. The polarity

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of the solvents influenced the catalytic activity, with solvent having higher polarity favors the increase of transformation rate. The Aldol reactions of various benzaldehyde derivatives and cyclohexanone catalyzed by DP4 were also studied, with the results tabulated in **Table 4**. The HBPE-supported proline was efficient in catalyzing the Aldol reactions of cyclohexanone with the benzaldehyde derivatives, possessing good catalytic activity and selectivity.

Table 3 HBPE-supported L-proline catalyzed Aldol reaction of p-NBA and cyclohexanone in different solvents [a]

Run	Solvent	x [b] (%)	anti/syn [c]	ee [d] (%)
11	THF	96	98:2	99
12	Toluene	89	95:5	95
13	n-hexane	91	94:6	93
14	diethyl ether	98	90:10	94
15	dichloromethane	93	96:4	95

[a] other conditions: DP4 with 30% L-proline to p-NBA, p-NBA (0.1mmol), cyclohexanone (0.5mmol), solvent 0.5 mL, 25 °C for 24 h; [b] conversion of p-NBA determined by ^{1}H NMR; [c] determined by ^{1}H NMR; [d] determined by the chiral HPLC.

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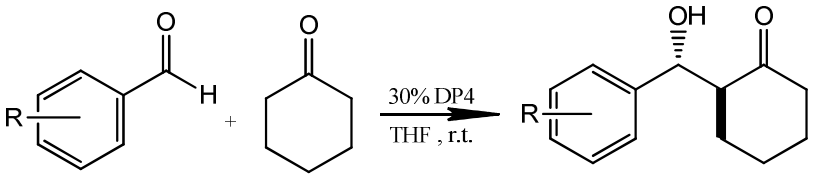
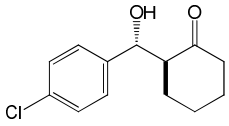
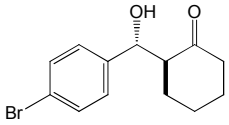
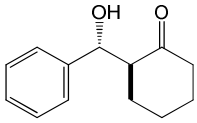
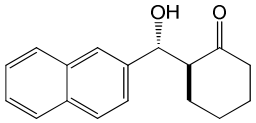
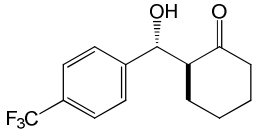
Table 4 HBPE-supported L-proline catalyzed Aldol reactions of benzaldehyde derivatives and cyclohexanone [a]



Run	Product	x (%) [b]	anti/syn [c]	ee (%) [d]
16		94	91:9	88
17		75	96:4	95
18		92	90:10	89
19		33	91:9	86
20		88	99:1	93

[a] other conditions: DP4 with 30% L-proline to benzaldehyde derivative, benzaldehyde derivative (0.1mmol), cyclohexanone (0.5mmol), solvent 0.5 mL THF with 1 vol. % water, 25 °C for 24 h; [b] conversion of benzaldehyde derivative determined by ^{1}H NMR; [c] determined by ^{1}H NMR; [d] determined by the chiral HPLC.

The HBPE-supported L-proline catalysts could be easily separated after reactions, to be reused for subsequent catalysis cycle. During the separation process, only addition of 3 mL water into the reaction solution (0.5 mL) was required to precipitate the catalyst. **Table 5** shows the results of using

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the recycled HBPE-supported L-proline catalyst DP4 in the Aldol reaction of p-NBA and cyclohexanone. It is evident that the reclaimed catalyst was efficient, showing only a slight decline in p-NBA conversion and selectivity.

Table 5 Performance of the recycled DP4 in Aldol reaction p-NBA and cyclohexanone [a]

Run	x (%) [b]	anti/syn [c]	ee (%) [d]
cycle 1	96	98: 2	99
cycle 2	98	98: 2	98
cycle 3	94	96: 4	99
cycle 4	88	96: 4	95
cycle 5	87	94: 6	94

[a] other conditions: DP4 with 30% L-proline to p-NBA, p-NBA (0.1mmol), cyclohexanone (0.5mmol), solvent 0.5 mL THF with 1 vol. % water, 25 °C for 24 h; [b] conversion of p-NBA determined by ^{1}H NMR; [c] determined by ^{1}H NMR; [d] determined by the chiral HPLC.

Experimental Section

Characterization

The ^{1}H-NMR characterization of small molecules and polymers were conducted on a Bruker Advance 2B 400 MHz spectrometer with CCl_3D or CD_3OD as deuterated solvent. The elemental analysis of polymers was carried out in a Flash EA 1112 elemental analyzer. The IR spectra were obtained from a Nicolet 5700 FT-IR. The polymer molecular weights and distributions were determined using a triple-detector gel permeation chromatography (PL-GPC50) equipped with differential refractive index (DRI), four-bridge capillary viscometer (IV), and light scattering (LS) detectors (45º and 90º).[23] One guard column (PL# 1110–1120) and three 30 cm columns (two PLgel 10 μm Mixed-B 300 × 7.5 mm and one PLgel 10 μm 500 Å 300 × 7.5 mm) were used. THF was

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used as eluent with a flow rate of 1.0 ml/min. The column temperature was set at 30 ºC. The signals collected by the laser detector were used to calculate the molecular weight via Cirrus software. A DRI increment (dn/dc) value of 0.078 mL/g was applied for the HBPE copolymers.[20a,23-24]

The thermal properties of the polymers were studied with a TA Instruments Q200 DSC equipped with refrigerated cooling system under N_2.[23,24b] The polymer was heated to 120 ºC at 10 ºC /min to eliminate the thermal history. It was then cooled down to −90 ºC at 10 ºC /min. The polymer was heated again from −90 ºC to 120 ºC at 10 ºC /min in the second cycle, and the data of this cycle was recorded for the analysis of glass transition temperature (T_g) and melting temperature (T_m).

The ee value was determined by a Fuli FL2200 HPLC equipped with a chiral HPLC column, CHIRALPAK® AD-H 250×4.6 mm. A solvent mixture of n-hexane and isopropanol (80/20 in vol.) was used as eluent at an inlet rate of 0.8 mL/min. The samples were dissolved in chromatographic grade ethanol to form solutions at approximately 1 wt.% concentration. The injection volume of the sample solutions was controlled at 80 μL. A UV detector with a wavelength number of 254 nm was used for the detection.

Materials

Experiments involving air- and/or moisture-sensitive compounds were conducted in a glove box or employing Schlenk techniques. Pd-diimine catalysts [(ArN=C(Me)-(Me)C=NAr)Pd(Me)(N≡CMe)]$^+SbF_6^-$ (Ar = 2,6–$(iPr)_2C_6H_3$) (I) and [(ArN=C(Me)-(Me)C=NAr)Pd$(CH_2)_3$C(O)OMe]$^+SbF_6^-$ (II) were synthesized following the reported procedure.[22a] Ultra-high purity N_2 and polymerization-grade ethylene (Sinopec China) were purified by passing through columns filled with CuO catalyst and 3-Å molecular sieve to remove oxygen and moisture, respectively. Chemicals including L-hydroxyproline (99%), trifluoromethane-sulfonic acid (98%), trifluoroacetic acid (AR, 99.0%), di-tert-butyl dicarbonate (99%), 6-dimethylaminopurine (DMAP) (98%),

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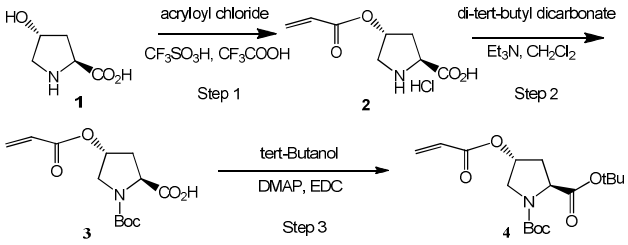
N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide (EDC) (98%), tert-butanol (99.5%), acryloyl chloride (96%), 4-chlorobenzaldehyde (98%), 4-(trifluoromethyl)-benzaldehyde (97%), and cyclohexanone (AR, 99.0%) from Aladdin, tetrahydrofuran (AR, 99.0%), triethylamine (AR,99.0%), and anhydrous methanol (AR, ≥ 99.5%) from Sinopharm, dichloromethane (anhydrous, 99.8%) from Acros, 4-bromobenzaldehyde (99%), 2-naphthaldehyde (98%) from J&K Scientific, 4-nitrobenzaldehyde (p-NBA, 98%), benzaldehyde (≥99%) from Sigma Aldrich were all used as received.

Synthesis of the acrylic proline comonomer 4

The procedure for synthesizing comonomer **4** is shown in Scheme 3.



Scheme 3 Synthesis of the acrylic proline comonomer **4**.

O-acryloyl-trans-4-hydroxy-L-proline hydrochloride (**2**) was synthesized following the reported procedure:[13a] Trifluoroacetic acid (55 mL) was added into a 250-mL round flask equipped with a magnetic stirrer under N_2 atmosphere. The flask was placed into an ice bath. 4-Hydroxy-L-proline (**1**, 0.11 mol, 15 g) was slowly charged within 5 mins. The flask was then taken out from the bath and stirred for another 5 mins at room temperature. Trifluoromethanesulfonic acid (1.8 mL) was added to the reaction mixture. After the solution was stirred for an additional 5 mins, acryloyl chloride (0.23 mol, 18.6 mL) was added into the reactor. The mixture was left to react for 3 hrs, after which the flask was placed back into the ice bath. Diethyl ether (100 mL) was slowly added into the solution within 15 mins. The products were precipitated out, filtrated, and washed with diethyl ether for three

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times, and dried at room temperature. A product of 11.3 g was collected and the yield was 54%. The ^{1}H and ^{13}C NMR spectra of the product are shown in the Supporting Information (Figure S1 and S2).

N-tert-butyloxycarbonyl-O-acryloyl-trans-4-hydroxy-L-proline (**3**) was synthesized as follow: Dichloromethane (150 mL), di-tert-butyl dicarbonate (0.065 mol, 11.3 g), and triethylamine (19.8 mL) were added into a 250 mL three-neck flask. Substance **2** (0.061 mol, 11.28 g) was then added slowly. After being refluxed for 30 mins, the solution was transferred into a 500-mL beaker in an ice bath. $KHSO_4$ solution (20.3 g in 156 mL water) was added to adjust the solution pH to 7 under stirring. The organic phase was separated and the aqueous phase was extracted with 100 mL dichloromethane twice. The organic phase was then collected and washed with saturated sodium chloride aqueous solution (100 mL × 2) and de-ionized water (100 mL × 3). The organic solution was separated and dried with anhydrous Na_2SO_4 for overnight. The solvent was then removed via evaporation. 12.8 g product **3** was obtained with a yield of 74%. The ^{1}H and ^{13}C NMR spectra of the product (**3**) are shown in the Supporting Information (Figure S3 and S4).

tert-Butyl-N-tert-Butyloxycarbonyl-O-acryloyl-trans-4-hydroxy-L-proline ester (**4**) was synthesized as follow: **3** (0.036 mmol, 10.37 g), DMAP (0.71 g), and tertiary butanol (0.074mol, 5.5 g) were added into a 250 mL three-neck flask with 50 mL dichloromethane. EDC (8.5 g) dissolved in CH_2Cl_2 (50 ml) was fed drop-wise into the flask in an ice-bath within 1 h. The reaction was conducted at room temperature for 18 h. The solution was then washed with hydrochloric acid (0.5 M, 100 mL) and sodium bicarbonate solution (5 wt. %, 100 mL) three times each, and dried with anhydrous Na_2SO_4 overnight. The solvent was removed under vacuum and the obtained product **4** (9.1 g, 73% yield) was characterized with ^{1}H and ^{13}C NMR (Figure S5 and S6 of Supporting Information).

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Copolymerization of ethylene and 4

All the copolymerization runs were carried out following a reported procedure.[20] The procedure is briefly described here by taking run P1 of Table 1 as an example. A 50-mL Schlenk flask was equipped with a magnetic stirrer and sealed with a rubber septum. The flask was flame-dried under vacuum and refilled with nitrogen. After additional three cycles of vacuum and ethylene-purging, the catalyst solution (0.2 mmol Pd-diimine catalyst **I** (0.16 g) in 10 mL CH_2Cl_2) was fed first, followed by the comonomer solution (2 mmol **4** (0.70 g) in 10 mL CH_2Cl_2). The ethylene pressure of 1 atm and temperature of 25 ºC were maintained. After 24 h reaction, the solution was poured into a large amount of methanol, followed by washing the precipitate with methanol three times and re-dissolving the precipitate in THF. The solution was filtered with a 0.45-μm Teflon syringe filter to remove the Pd black. Further precipitation with methanol and dissolution with THF were conducted for three times to purify the polymers. A polymer sample of 1.8 g was collected after three-day vacuum drying at 50 ºC.

De-protection of proline moieties in the copolymer 5

The de-protection was conducted in a mixture solvent of trifluoroacetic acid and dichloromethane (50 vol% each). Take run P1 as an example again, 0.75 g P1 was dissolved in 10 mL solvent mixture. The solution was stirred at room temperature for 24 h. The polymer was precipitated out with a large amount of methanol and was washed with methanol. Dissolution with CH_2Cl_2 and precipitation with methanol were repeated twice. The resulting polymers were dried at 60 ºC under vacuum for three days and 0.73 g of the final product was obtained.

Aldol reactions of cyclohexanone and benzaldehyde derivatives

The Aldol reactions catalyzed by the HBPE-supported L-proline **6** were carried out in a 10-mL tube reactor equipped with a magnetic stirrer at room temperature. In this description, run 9 in Table 2 is

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used as an example. De-protected P3 (60 mg, 0.03 mmol L-proline) was dissolved in THF (0.5 mL, containing 5.4 μL water). The p-NBA (0.1 mmol, 15 mg) and cyclohexanone (0.5 mmol, 47 mg) were then added into the solution. After 24 h reaction, 2 mL water was added to the solution to precipitate the HBPE catalyst. The aqueous phase was extracted for three times with 3 mL dichloromethane. Dichloromethane and THF were then removed under vacuum. The residual product was analyzed by ^{1}H NMR and chiral HPLC. The p-NBA conversion and the anti/syn value were estimated from the ^{1}H NMR data (Figure S7 in the Supporting Information). The ee value was determined from the chiral HPLC data (Figure S8 in the Supporting Information). During the recycling of the catalyst, the precipitated polymer was washed with 3 mL methanol three times and dried under vacuum oven at 60 ºC for 8 h. The polymer was then used as catalyst for the next run of Aldol reaction with the same recipe and experiment condition as employed in the previous run.

Conclusion

In this work, we developed a novel L-proline-based organocatalyst for Aldol reactions using hyperbranched polyethylene (HBPE) as support. An acrylic comonomer bearing protected proline functionality was synthesized and copolymerized with ethylene via a chain walking mechanism catalyzed by Pd-diimine to yield well-defined HBPEs with number-average molecular weights of 10.3-50.3 kg/mol and PDIs of 1.07-1.64. The proline moieties on copolymer were then de-protected to yield HBPE-supported catalyst, which contains 3.2-15.6 L-proline groups per HBPE molecule in average. The catalysts had high efficiencies and selectivities in catalyzing the Aldol reaction of p-nitrobenzaldehyde (p-NBA) and cyclohexanone, with p-NBA conversions up to 98%, anti/syn = 98/2, and ee > 99%. Steric effect and diffusion limitation imposed by the hydrophobic HBPE scaffolds on the reactants attributed to high selectivity of the catalyst. The HBPE-supported proline was also efficient in catalyzing the Aldol reactions of cyclohexanone with other benzaldehyde derivatives. The separation of the catalyst from the reactants could be achieved easily by adding

Catalysis Science & Technology Accepted Manuscript

water to precipitate the HBPE-supported proline. The reclaimed catalyst could be re-used for catalyzing subsequent Aldol reactions multiple times with only a slight decline in activity and selectivity.

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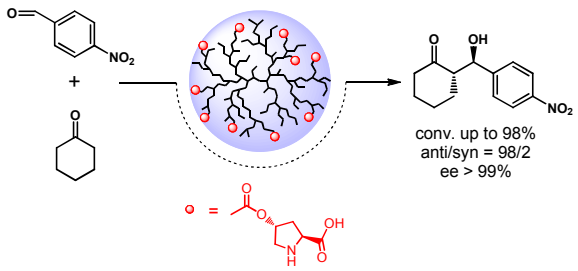
Table of contents entry

A recyclable L-proline-based organocatalyst system with a unique hyperbranched polyethylene as scaffold is prepared for highly stereoselective asymmetric Aldol reactions



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