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# Polymerization of L-proline functionalized styrene and its catalytic performance as a supported organocatalyst for direct enantioselective aldol reaction

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ABSTRACT

As an alternative approach to the graft modification of polymers to fabricate polymer-supported chiral organocatalysts in a bottom-up fashion, L-prolinamide functionalized polymers were prepared by general solution homopolymerization or copolymerization of L-proline functionalized styrene monomer in the presence of 1,4-divinylbenzene as the crosslinking agent. The catalytic performance of the as-prepared heterogeneous catalysts towards the direct enantioselective aldol reaction of ketones with a series of aromatic aldehydes was explored. Our findings indicate that the as-prepared heterogeneous catalysts can afford relevant aldol addition products with good yields (up to 96%), high diastereoselectivities (up to 8:92 dr) and excellent enantiomeric excess (up to 96%); they also exhibit good recyclability, retaining high yield and rate as well as good selectivity after several cycles.



## 1. Introduction

Direct enantioselective aldol reactions involving a non-activated ketone as the nucleophile, are an effective and straightforward route to provide C–C backbones. This reaction has been extensively used in the synthesis of a variety of natural products and non-natural drug molecules.[1,2]

Amongst a wide range of efficient chiral homogeneous organocatalysts for the direct enantioselective aldol reaction, L-proline and its derivatives[3,4] have attracted great attention from chemists since they are water and air tolerant and exhibit high efficiency.[5,6] However, the application of L-proline and its derivatives as organocatalysts is often limited by the difficulty of separating them from the reaction system. To facilitate the recyclability of L-proline and its derivatives as organocatalysts, many researchers[7] have made great efforts to immobilize L-proline with various polymer scaffolds via grafting modification reactions. The resultant polymer-supported heterogeneous catalysts[8,9] have many unique advantages such as easy purification, potential recyclability, enhanced catalytic activity and the absence of an organic solvent.[10,15] Unfortunately, polymer molecular chains are often susceptive to curling and twinning, which means that due to the embedding of the functional group, grafting modification reaction can only provide the target products with a low grafting ratio.[11] The low grafting ratio, undoubtedly, will further affect the catalytic performance of polymer-supported heterogeneous catalysts. Therefore, it remains a challenge to develop new polymer-supported organocatalysts, with good control of catalyst loading and simple work-up and purification.

In recent years, Pericàs et al. and Gruttadauria et al.[12] have reported the synthesis of cross-linked polystyrene anchored proline and especially good results have been obtained. Hansen et al.[13] have explored the incorporation of several L-proline functionalized monomers into polymers to substitute for grafting a chiral L-proline molecule onto polymer scaffolds directly, and a range of L-proline functionalized methacrylate monomers and several L-proline functionalized styrenic as well as methacrylic copolymer beads were synthesized. The as-prepared functional polymers showed good activities and high stereoselectivities as well as good recyclability. These researchers and more recently others[14] have provided a novel bottom-up fashion for synthesizing supported proline-derived chiral organocatalysts with good control of the catalyst loading and simple work-up.

Bearing those perspectives in mind, we chose styrenic L-prolinamide as the highly active and stereoselective monomer to synthesise the L-proline functionalized polymers via a general solution polymerization, hoping to explore a straightforward process for synthesizing new, robust, efficient and recyclable organocatalysts. In addition, according to the urgent need for a

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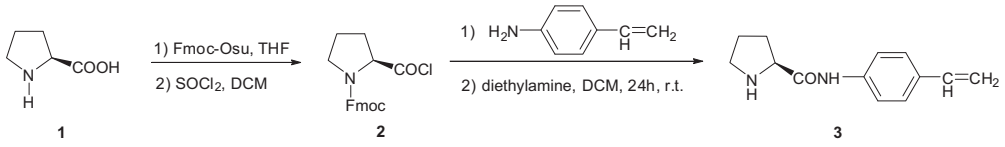
more environmentally responsible chemistry,[10,15] we tried to adopt ethanol as the solvent in the solution polymerization. Herein we report the synthesis of L-proline functionalized polymers and the application of these novel functional polymers as supported organocatalysts for a typical direct enantioselective aldol reaction between ketones and a series of aromatic aldehydes at room temperature. The recyclability of the aforementioned catalysts was also evaluated in the mixed solvent system with petroleum ether/water.

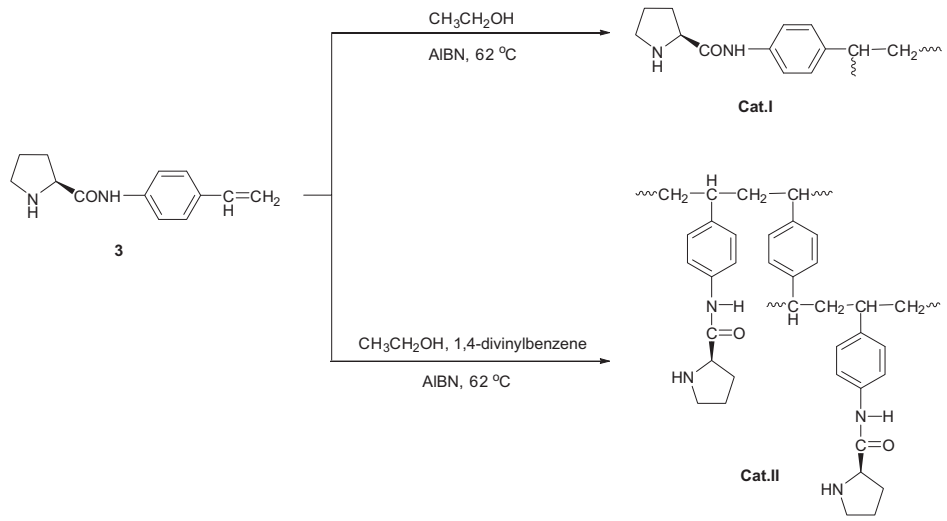
## 2. Results and discussion

Schemes 1 and 2 depict the procedures for preparing **Cat.I** and **Cat.II**, where three major steps are involved. Firstly, *N*-9-fluorenylmethyloxy-carbonyl protected L-proline (Fmoc-L-Pro) was reacted with $SOCl_2$ to give the target product acyl chloride **2**. Secondly, the acyl chloride **2** was modified by *p*-aminostyrene in the presence of pyridine as the acid binding agent, and the resultant product was further modified via one deprotection reaction to yield L-proline functionalized styrene monomer **3**. Finally, monomer **3** was initiated by azodiisobutyronitrile (AIBN) to homopolymerize and yield the functional polymer **Cat.I** or copolymerize with 1,4-divinylbenzene to give the cross-linked **Cat.II**.

For the evaluation of the catalytic properties of the synthesized L-proline functionalized polymers **Cat.I** and **Cat.II**, the representative aldol reaction between 4-nitrobenzaldehyde and cyclohexanone served as a model reaction. Table 1 summarizes the effects of catalyst dosage on the aqueous aldol reaction. It can be seen that high selectivity (87–95% ee) and high activity (up to 95% yield) were achieved in the tested range of catalyst dosage. When

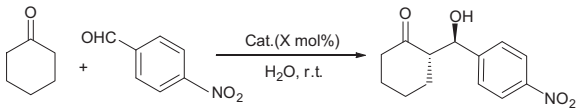



**Scheme 1.** The preparation of L-proline functionalized styrene monomer **3**.




**Scheme 2.** The polymerization of functionalized monomer **3** to afford **Cat.I** and **Cat.II**.

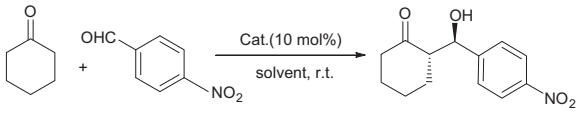
**Table 1**
Effect of catalyst dosage on the aldol reaction between *p*-nitrobenzaldehyde and cyclohexanone in a water medium[a]




| Entry | Catalyst | Mol % | Time (h) | Yield[b] (%) | dr[c] (*syn*/*anti*) | ee[c] (%; *anti*) |
|---|---|---|---|---|---|---|
| 1 | **Cat.I** | 5 | 24 | 81 | 20:80 | 89 |
| 2 | **Cat.I** | 10 | 24 | 94 | 19:81 | 95 |
| 3 | **Cat.I** | 15 | 15 | 89 | 20:80 | 95 |
| 4 | **Cat.I** | 20 | 15 | 96 | 23:77 | 94 |
| 5 | **Cat.II** | 5 | 24 | 72 | 29:71 | 87 |
| 6 | **Cat.II** | 10 | 24 | 87 | 26:74 | 95 |
| 7 | **Cat.II** | 15 | 15 | 91 | 28:72 | 92 |
| 8 | **Cat.II** | 20 | 15 | 92 | 25:75 | 94 |

[a] Reaction was carried out using 4-nitrobenzaldehyde (1 equiv, $1.98 \times 10^{-4}$ mol) and cyclohexanone (10 equiv, $1.98 \times 10^{-3}$ mol) in 0.5 mL of $H_2O$.
[b] Isolated yield.
[c] Determined by chiral-phase HPLC analysis (Chiralpak AD-H).

**Table 2**
Screening solvents for the organocatalytic enantioselective aldol reaction between p-nitrobenzaldehyde and cyclohexanone[a]




| Entry | Catalyst | Solvent (mL) | Time (h) | Yield[b] (%) | dr[c] (*syn*/*anti*) | ee[c] (%; *anti*) |
|---|---|---|---|---|---|---|
| 1 | **Cat.I** | $H_2O$ (0.01) | 24 | 86 | 21:79 | 90 |
| 2 | **Cat.II** | $H_2O$ (0.01) | 24 | 81 | 28:72 | 91 |
| 3 | **Cat.I** | $H_2O$ (0.20) | 24 | 89 | 22:78 | 94 |
| 4 | **Cat.II** | $H_2O$ (0.20) | 24 | 91 | 30:70 | 92 |
| 5 | **Cat.I** | $H_2O$ (0.50) | 24 | 90 | 19:81 | 95 |
| 6 | **Cat.II** | $H_2O$ (0.50) | 24 | 82 | 26:74 | 92 |
| 7 | **Cat.I** | Neat | 48 | 76 | 31:69 | 88 |
| 8 | **Cat.II** | Neat | 48 | 63 | 23:77 | 57 |
| 9 | **Cat.I** | Petroleum ether | 48 | 76 | 19:81 | 90 |
| 10 | **Cat.II** | Petroleum ether | 48 | 79 | 31:69 | 89 |
| 11 | **Cat.I** | Hexane | 48 | 91 | 27:73 | 90 |
| 12 | **Cat.II** | Hexane | 48 | 89 | 26:74 | 86 |
| 13 | **Cat.I** | $CH_3CN$ | 48 | 72 | 29:71 | 61 |
| 14 | **Cat.II** | $CH_3CN$ | 48 | 62 | 25:75 | 69 |
| 15 | **Cat.I** | Dimethylformamide (DMF) | 48 | 59 | 30:70 | 76 |
| 16 | **Cat.II** | Dimethylformamide (DMF) | 48 | 71 | 27:73 | 66 |

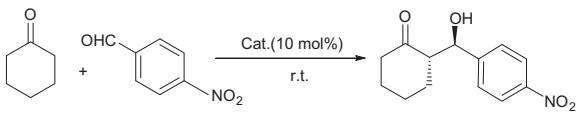
[a] Reaction was carried out with *p*-nitrobenzaldehyde (1 equiv, 0.030 g, $1.985 \times 10^{-4}$ mol) and cyclohexanone (10 equiv, 0.2 mL, $1.985 \times 10^{-3}$ mol) in 0.5 mL undistilled solvent.
[b] Isolated yield.
[c] Determined by chiral-phase HPLC analysis (Chiralpak AD-H).

10 mol % of catalyst was used, the best overall results were obtained after 24 h of reaction (Table 1, entries 2 and 6, 94–87% yield and 95% ee). When the catalyst dosage was fixed at 5 mol %, the yields and ee values decreased significantly (Table 1, entries 1 and 5). Moreover, when the reaction time was decreased to 15 h, an increased amount (15 –20 mol %) of the catalyst did not significantly change the diastereoselectivities but decreased the ee values. Thus the optimal catalyst dosage of either **Cat.I** or **Cat.II** is suggested to be 10 mol %.

Table 2 presents the catalytic activity of the synthesized polymer-supported organocatalysts for the above-mentioned aldol reaction in various solvent systems at 10 mol % catalyst dosage. It can be seen that the catalysts possess the best reactivities and stereoselectivities in the presence of 0.5 mL of water, and the reaction can be completed in only 24 h (Table 2, entries 5 and 6). However, less polar solvents are unfavorable for the catalytic efficiency and stereoselectivities of the as-synthesized polymer-supported organocatalysts, and an increased reaction time of 48 h was required in the less polar solvents (Table 2, entries 13–16). Moreover, high yields and ee values were obtained in non-polar organic solvents (Table 2, entries 9–12); and **Cat.I** and **Cat.II** exhibit decreased enantioselectivities in association with low yields under neat reaction conditions (Table 2, entries 7–8).

Furthermore, as shown in Table 2, the enantioselectivity of **Cat.I** and **Cat.II** depends greatly on the volume of water (entries 1–6). The ee values and yields rise significantly when increasing the water volume from 0.01 mL to 0.20 mL (Table 2, entries 1–4). When a large amount of water (0.50 mL) is employed, the relevant aldol products were obtained with good yields and near perfect ee values (Table 2, entries 5 and 6). According to these findings, in the presence of trace water, we speculate that the as-synthesized amphiphilic polymers could provide a hydrophobic microenvironment for the substrates and catalytic sites capable of efficiently catalyzing the aldol reaction between cyclohexanone and 4-

**Table 3**
Yield, final diastereomeric ratio (dr) and enantiomeric excess (ee) with 10 mol % as-synthesized catalysts in the mixed solvent system of petroleum ether/$H_2O$[a]




| Entry | Catalyst | % Water in petroleum ether | Time (h) | Yield[b] (%) | dr[c] (*syn*/*anti*) | ee[c] (%; *anti*) |
|---|---|---|---|---|---|---|
| 1 | **Cat.I** | 0 | 48 | 61 | 19:81 | 90 |
| 2 | **Cat.I** | 5 | 24 | 81 | 18:82 | 90 |
| 3 | **Cat.I** | 7.5 | 24 | 93 | 16:84 | 96 |
| 4 | **Cat.I** | 10 | 24 | 87 | 24:76 | 92 |
| 5 | **Cat.II** | 0 | 48 | 72 | 31:69 | 89 |
| 6 | **Cat.II** | 5 | 24 | 81 | 27:73 | 92 |
| 7 | **Cat.II** | 7.5 | 24 | 89 | 26:74 | 94 |
| 8 | **Cat.II** | 10 | 24 | 92 | 29:71 | 93 |

[a] Reaction was carried out with 4-nitrobenzaldehyde (1 equiv, 0.030 g, $1.985 \times 10^{-4}$ mol) and cyclohexanone (10 equiv, 0.2 mL, $1.985 \times 10^{-3}$ mol) under 10 mol % catalyst dosage in undistilled mixed solvent.
[b] Isolated yield.
[c] Determined by chiral-phase HPLC analysis (Chiralpak AD-H).

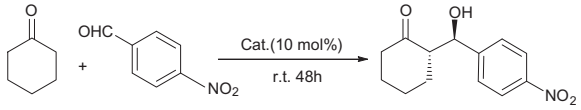
nitrobenzaldehyde to produce the product with excellent enantioselectivity (ee). The volume of the water medium, however, should be below 0.5 mL, because above this volume level, the catalysts tend to precipitate from the solution, due to the presence of a hydrophobic group in the as-synthesized polymer-supported catalysts.

To further investigate the potential of the synthesized polymer-supported organocatalysts, we also explored the effects of the mixed solvent system of petroleum ether/$H_2O$ in different ratios for the selected aldol reactions. The relevant results are summarized in Table 3. It can be seen that increasing the water content in petroleum ether to 7.5% (volume fraction) led to excellent yields and high ee values (Table 3, entries 3 and 7). When the water content in petroleum ether was fixed at 10 vol %, slightly decreased stereo- and enantioselectivities were obtained. Particularly, when petroleum ether alone was used as the reaction solvent, the corresponding aldol products were obtained with low yield and enantioselectivity, while the reaction time increased to 48 h (Table 3, entries 1 and 5). In combination with the results shown in Tables 1 and 2, the optimized catalyst dosage and solvent system for the title aldol reaction are suggested as 10 mol % and petroleum ether/$H_2O$ (volume ratio: 92.5/7.5).

The reactions of various aromatic aldehydes with cyclohexanone (cyclopentanone, and acetone) were studied under the optimized conditions [10 mol % of catalyst in petroleum ether/$H_2O$ (volume ratio: 92.5/7.5)]. The results are summarized in Table 4. It can be seen that a wide range of aromatic aldehydes can effectively participate in the aldol reactions. With regards to some benzaldehydes with electron-withdrawing substituents, the reaction was completed with good selectivity (anti/syn ratio and ee) and high yield; in particular, 2,4-dinitrobenzaldehyde and 4-nitrobenzaldehyde can provide relatively high selectivity and yield (Table 4, entries 1 and 3, 8/92 to 15/85 *syn*/*anti* ratio and 86–94% ee). In contrast, longer reaction times (72 h) were required for aromatic aldehydes containing an electron-donating group to provide medium diastereoselectivities and poor yields, but the enantioselectivities retain high (Table 4, entries 11–12). Moreover, the high diastereoselectivity was achieved with the participation of neutral aldehyde (Table 4, entry 10). To broaden the scope of the methodology, we also adopted polymer-supported catalysts to catalyze the direct enantioselective aldol reaction between cyclopentanone and benzaldehyde. We found that the aldol products were obtained with moderate yields and good stereoselectivity (Table 4, entries 13–14). In the presence of hydrophilic acetone as the donor, the aldol reaction furnished β-hydroxy carbonyl aldol products in medium ee values, but the yields were too low (41–52%) (Table 4, entries 15–16).

Table 5 shows the recovery and recycling of the synthesized catalysts towards the aldol reaction between cyclohexane and 4-nitrobenzaldehyde in a mixed solvent of petroleum ether/water (volume ratio: 92.5/7.5). It can be seen that the polymer-supported **Cat.I** retains almost unchanged reactivity and selectivity after three cycles. The cross-linked Cat.II exhibits better recyclability than **Cat.I.**, i.e., **Cat.II** retains high selectivity and a slightly decreased yield after five consecutive cycles, which indicates that

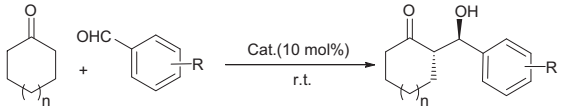
**Table 5**
Recyclability of polymer-supported catalysts under the optimized conditions[a]




| Entry | Catalyst | Yield[b] (%) | dr[c] (*syn*/*anti*) | ee[c] (%; *anti*) |
|---|---|---|---|---|
| 1 | **Cat.I** (cycle 1) | 93 | 19:81 | 95 |
| 2 | **Cat.I** (cycle 2) | 94 | 21:79 | 94 |
| 3 | **Cat.I** (cycle 3) | 87 | 25:75 | 92 |
| 4 | **Cat.II** (cycle 1) | 91 | 26:74 | 95 |
| 5 | **Cat.II** (cycle 2) | 95 | 29:71 | 92 |
| 6 | **Cat.II** (cycle 3) | 89 | 30:70 | 92 |
| 7 | **Cat.II** (cycle 4) | 90 | 23:77 | 94 |
| 8 | **Cat.II** (cycle 5) | 84 | 28:72 | 93 |

[a] Reaction performed at 0.2 mmol scale of aldehyde and 10 equiv of cyclohexanone in petroleum ether/water (volume ratio: 92.5/7.5) after 48 h.
[b] Isolated yield.
[c] Determined by chiral-phase HPLC analysis (Chiralpak AD-H).

**Table 4**
Asymmetric Aldol reactions catalyzed by polymer-supported catalysts[a]




| Entry | R | Catalyst | Time (h) | Yield[b] (%) | dr[c] (*syn*/*anti*) | ee[c] (%; *anti*) |
|---|---|---|---|---|---|---|
| 1 | 2,4-Dinitro | **Cat.I** | 48 | 89 | 8:92 | 86 |
| 2 | 2,4-Dinitro | **Cat.II** | 48 | 79 | 12:88 | 80 |
| 3 | 4-$NO_2$ | **Cat.I** | 48 | 92 | 15:85 | 94 |
| 4 | 4-$NO_2$ | **Cat.II** | 48 | 90 | 27:73 | 92 |
| 5 | 3-$NO_2$ | **Cat.I** | 48 | 85 | 11:89 | 80 |
| 6 | 3-$NO_2$ | **Cat.II** | 48 | 87 | 14:86 | 79 |
| 7 | 2-$NO_2$ | **Cat.I** | 48 | 73 | 10:90 | 84 |
| 8 | 4-CN | **Cat.I** | 72 | 52 | 25:75 | 69 |
| 9 | 4-F | **Cat.I** | 72 | 63 | 24:76 | 64 |
| 10 | 4-H | **Cat.I** | 72 | 69 | 17:83 | 76 |
| 11 | 4-$CH_3$ | **Cat.I** | 72 | 58 | 32:68 | 83 |
| 12 | 4-$OCH_3$ | **Cat.I** | 72 | 45 | 43:57 | 84 |
| 13[d] | 4-$NO_2$ | **Cat.I** | 48 | 72 | 39:61 | 69 |
| 14[d] | 2-$NO_2$ | **Cat.I** | 48 | 76 | 31:69 | 88 |
| 15[e] | 4-$NO_2$ | **Cat.I** | 60 | 41 | — | 67 |
| 16[e] | 3-$NO_2$ | **Cat.I** | 60 | 52 | — | 65 |

[a] Reaction performed at 0.2 mmol scale of aromatic aldehyde and 10 equiv of ketone in the presence of petroleum ether/water (volume ratio: 92.5/7.5).
[b] Isolated yield.
[c] Determined by chiral-phase HPLC analysis (Chiralpak AD-H).
[d] Cyclopentanone was used as the nucleophile.
[e] Acetone was used as the nucleophile.

the cross-linked **Cat.II** is superior to **Cat.I** in terms of the application in engineering.

## 3. Conclusions

Two L-proline functionalized polymer catalysts have been successfully prepared via a general solution polymerization in a bottom-up fashion, and the catalytic performance of the as-prepared polymer-supported organocatalysts for the aldol condensation reaction between ketones and aromatic aldehydes has been carefully evaluated. Our results indicate that the catalysts can catalyze the aldol reaction at rt in the presence of various solvent systems. Yields of up to 96%, *anti*/*syn* ratios of up to 8:92, and enantiomeric excesses of up to 96% were achieved when the aldol reaction was carried out in a mixed solvent of petroleum ether/water with a volume ratio of 92.5:7.5. The as-synthesized polymer-supported catalysts can be recovered and reused for several consecutive cycles while their reactivity and selectivity remained almost unchanged; the cross-linked **Cat.II** exhibited better recyclability than **Cat.I**. We have hopefully provided a novel method towards the development of new supports for chiral heterogeneous organocatalysts. Further work is intended to extend L-proline functionalized polymer catalysts for other asymmetric reactions and to reveal reaction mechanisms as well.

## 4. Experimental

### 4.1. General

Raw material 4-aminostyrene containing a small amount of quinone stabilizer was purchased from J&K Technology Company Ltd (Beijing, China) and used without further purification. The other chemicals were provided by various commercial suppliers and were used as-received.

Thin-layer chromatograph (TLC) analysis was performed with pre-coated silica gel GF254 plates. Infrared spectra were recorded with an Avatar360 Fourier transform infrared spectrometer (FTIR; Nicolet, Thermo Scientific, Pittsburgh, PA). Nuclear magnetic resonance (NMR) spectra were obtained from Bruker Avance 400 M system, and the chemical shifts of $^1$H NMR spectra were reported in relation to tetramethyl silane ($\delta = 0$). Thermal degradation behavior of the as-synthesized polymer-supported catalysts were analyzed by means of thermo gravimetric analyzer (TGA/SDTA851e, Mettler Toledo, Switzerland) at a heating rate of 10 °C min$^{-1}$ from 25 °C to 700 °C in nitrogen atmosphere. Column chromatograph was conducted to purify the aldol products; and the stereoselectivity was determined by a chiral high performance liquid chromatograph (HPLC) with Daicel Chiralpak AD-H chiral columns.

### 4.2. General procedure for the preparation of chiral organocatalysts

#### 4.2.1. Synthesis of *N*-Fmoc-L-proline, 2

L-Proline (1.5 g) was dissolved in 30 mL of aqueous $Na_2CO_3$ (mass fraction:10%) under stirring and mixed with 4.5 g of *N*-(9-fluorenylmethoxycarbonyloxy)succinimide (Fmoc-Osu) dissolved in THF (30 mL). After 48 h, water (40 mL) was added and the mixture extracted with ether (5 × 30 mL). The pH value of the aqueous phase was adjusted to 2–3 with aqueous HCl and extracted with ethyl acetate (5 × 30 mL), while the organic layer containing the target product was dried overnight with $Na_2SO_4$. Subsequently, the ethyl acetate was removed by decompression-evaporation to obtain 2.7 g of a white solid powder. $^1$H NMR (400 MHz, $CDCl_3$): 9.68 (s, 1H), 7.75–7.73 (m, 1H), 7.60–7.57 (m, 1H), 7.42–7.36 (m, 1H), 7.34–7.25 (m, 1H), 4.51–4.42 (m, 1H), 4.25–4.28 (d, 1H), 3.40 (s, 1H), 3.51 (m, 2H), 2.02–1.98 (m, 2H), 1.86 (m, 2H). $^{13}$C NMR (100 MHz, $CDCl_3$): 177.12, 175.50, 155.67, 153.48, 141.43, 142.60, 126.62, 126.13, 123.89, 118.92, 66.80, 66.52, 58.26, 57.42, 46.12, 45.63, 29.92, 28.34, 23.30, 22.31.

#### 4.2.2. Synthesis of functionalized monomer 3

Fmoc-L-Pro (1.49 g, 4.42 mmol) was dissolved with $CH_2Cl_2$ (3 mL) in a flask. To the resultant solution was slowly added 1 mL of $SOCl_2$ at 37 °C with 15 min of stirring. The mixture was stirred at 37 °C for 1.5 h to afford acyl chloride **2**. Next, *p*-aminostyrene was dissolved in pyridine and added to acyl chloride **2** in 30 min while the temperature was kept under 25 °C for 6 h. The resultant *N*-Fmoc was deprotected prior to polymerization with diethylamine with stirring overnight to give the functionalized monomer **3**. The product was characterized by FTIR and $^1$H NMR. FTIR (*m* = 3246, 2965, 1671, 1621, 1517, 1424, 988, 903 cm$^{-1}$).$^1$H NMR (400 MHz, $CDCl_3$): 9.82–9.80 (s, H), 7.52–7.46 (d, 2H), 7.36–7.28 (d = 2H), 6.63–6.58 (dd, 1H), 5.10–5.58 (m, 2H), 3.82–3.89 (m, 1H), 2.98–3.16 (m, 2H), 2.94–2.96(m, 1H), 1.95–2.11 (m, 2H), 1.72–1.74 (m, 2H).

#### 4.2.3. Synthesis of catalysts I–II

L-Proline functionalized monomer **3** (1.42 g, 6.6 mmol) was dissolved in 3 mL of $CH_3CH_2OH$ and sequentially mixed with 1,4-divinylbenzene (10%, 0.142 g, 1.091 mmol) and AIBN (2%, 0.028 g, 0.173 mmol). The resultant mixture was stirred at 62 °C for 12 h to allow for polymerization to yield a white powder precipitate. At the end of the polymerization, the crude product was washed sequentially with ethanol, acetone and water. The target product, cross-linked copolymer **Cat.II** was dried in vacuum oven until the weight remained constant. L-Proline functionalized homopolymer **Cat.I** was prepared in the same manner, except that crosslinking agent 1,4-DIVINYLBENZENE was not added. The products were characterized by means of Fourier transformation infrared (FTIR) spectrometry. The final target products **Cat.I** and **Cat.II** were used as novel catalysts for direct enantioselective aldol reactions. Gel permeation chromatograph (GPC) analysis showed that **Cat.I** has a weight-average molecular weight (Mw) of $1.42 \times 10^4$ and PDI value of 1.81. Proline loading of **I-II** was determined, by elemental analysis to be 2.10 and 2.01 mmol/g, respectively.

### 4.3. Recyclability of the as-synthesized polymer-supported catalysts

Upon completion of the reaction between cyclohexanone and the aromatic aldehyde, the catalyst was separated by centrifuging and washed with dichloromethane, followed by drying under 45 °C in an oven for 24 h. As-recovered catalysts can be reused directly without further purification.

### 4.4. General procedure for the aldol reaction

Substituted aromatic aldehyde (0.2 mmol) was added to cyclohexanone with stirring at room temperature. Into the resultant mixture were sequentially added a certain amount of catalyst and solvent. The resultant reaction system was stirred at room temperature for a certain period of time and monitored by TLC (ethyl acetate/petroleum ether = 1:2 (volume ratio)). The crude products were extracted with ethyl acetate (4 × 1 mL) once the reaction was completed, then the organic layers were dried ($Na_2SO_4$), vacuum filtered, concentrated and evaporated under reduced pressure. The crude products were purified by column chromatograph (eluted with ethyl acetate/petroleum ether (volume ratio: 10:20) to yield desired aldol products.

#### 4.4.1. (*S*)-2-[(*R*)-Hydroxy(4-nitrophenyl)methyl] cyclohexanone[5c,8b]

White powder; mp 129–130 °C; $[\alpha]_D^{20}$ = +12.8 (*c* 1.85, $CHCl_3$). Enantiomeric excess was determined by HPLC with a Chiralpak AD-H column (*n*-hexane/isopropanol, volume ratio 92:8), flow rate 1.0 mL/min, $\lambda$ = 268 nm; $t_R$(*anti*) = 40.25 min (major) and 29.86 min, $t_R$(*syn*) = 22.99 min and 26.25 min (major); $^1$H NMR (300 MHz, $CDCl_3$): 8.20–8.24 (m, 2H), 7.48–7.54 (m, 2H), 4.90 (d, *J* = 8.1 Hz, 1H), 4.09 (s, 1H), 2.32–2.64 (m, 3H), 2.08–2.16 (m, 1H), 1.82–1.86 (m, 1H), 1.35–1.73 (m, 4H).

#### 4.4.2. (*S*)-2-[(*R*)-Hydroxy(2,4-nitrophenyl)methyl] cyclohexanone[5c,8b]

Yellow oil. Enantiomeric excess was determined by HPLC with a Chiralpak AD-H column (*n*-hexane/isopropanol, volume ratio 92:8), flow rate 1.0 mL/min, $\lambda$ = 254 nm; $t_R$(*anti*) = 44.06 min and 39.37 min (major), $t_R$(*syn*) = 24.60 min and 32.95 min (major); $^1$H NMR (400 MHz, $CDCl_3$): 8.74–8.75 (d, *J* = 2.3 Hz, 1H), 8.45–8.49 (d, *J* = 8.7 Hz, *J* = 2.4 Hz, 1H), 8.06–8.08 (d, *J* = 8.7 Hz, 1H), 6.05–6.06 (d, *J* = 1.9 Hz, 1H), 5.51–5.53 (br s, 1H), 2.73–2.77 (m, 1H), 2.44–2.47 (m, 1H), 2.11–2.33 (m, 1H), 2.04–2.14 (m, 1H), 1.82–1.88 (m, 1H), 1.79–1.82 (m, 1H), 1.69–1.79 (m, 1H), 1.61–1.68 (m, 1H).

#### 4.4.3. (*S*)-2-[(*R*)-Hydroxy(2-nitrophenyl)methyl] cyclohexanone[5c,8b]

Yellow powder; mp 116–118 °C; $[\alpha]_D^{24}$ = +19.8 (*c* 1.60, $CHCl_3$). Enantiomeric excess was determined by HPLC with a Chiralpak AD-H column (*n*-hexane/isopropanol, volume ratio 92:8), flow rate 1.0 mL/min, $\lambda$ = 209 nm; $t_R$(*anti*) = 24.05 min and 22.53 min (major); $^1$H NMR (300 MHz, $CDCl_3$): 7.84 (d, *J* = 7.8 Hz, 1H), 7.77 (d, *J* = 7.8 Hz, 1H), 7.64 (t, *J* = 7.2 Hz, 1H), 7.40–7.46 (m, 1H), 5.44 (d, *J* = 7.2 Hz, 1H), 4.11 (br, 1H), 2.73–2.81 (m, 1H), 2.29–2.48 (m, 2H), 2.04–2.14 (m, 1H), 1.55–1.86 (m, 5H).

#### 4.4.4. (*S*)-2-[(*R*)-Hydroxy(3-nitrophenyl)methyl] cyclohexanone[5c,8b]

White powder; mp 69–71 °C; $[\alpha]_D^{24}$ = +32.5 (*c* 1.35, $CHCl_3$). Enantiomeric excess was determined by HPLC with a Chiralpak AD-H column (*n*-hexane/isopropanol, volume ratio 92:8), flow rate 1.0 mL/min, $\lambda$ = 263 nm; $t_R$(*anti*) = 33.94 min and 26.05 min (major), $t_R$(*syn*) = 23.10 min (major) and 22.08 min; $^1$H NMR (300 MHz, $CDCl_3$): 8.15–8.22 (m, 2H), 7.67 (d, *J* = 7.5 Hz, 1H), 7.53 (t, *J* = 7.8 Hz, 1H), 4.90 (d, *J* = 8.4 Hz, 1H), 4.14 (d, *J* = 2.4 Hz, 1H), 2.58–2.67 (m, 1H), 2.32–2.54 (m, 2H), 2.09–2.16 (m, 1H), 1.82–1.86 (m, 1H), 1.36–1.71 (m, 4H).

#### 4.4.5. (*S*)-2-[(*R*)-Hydroxy(4-cyanophenyl)methyl] cyclohexanone[5c,8b]

White powder; mp 82–83 °C; $[\alpha]_D^{22}$ = +23.3 (*c* 1.55, $CHCl_3$). Enantiomeric excess was determined by HPLC with a Chiralpak AD-H column (*n*-hexane/isopropanol, volume ratio 92:8), flow rate 1.0 mL/min, $\lambda$ = 267 nm; $t_R$(*anti*) = 40.88 min (major) and 31.98 min, $t_R$(*syn*) = 23.20 min and 27.33 min (major); $^1$H NMR (300 MHz, $CDCl_3$): 7.65 (d, *J* = 8.1 Hz, 2H), 7.43 (d, *J* = 8.1 Hz, 2H), 4.84 (d, *J* = 8.4 Hz, 1H), 4.07 (s, 1H), 2.47–2.62 (m, 2H), 2.31–2.41 (m, 1H), 2.08–2.15 (m, 1H), 1.81–1.83 (m, 1H), 1.49–1.73 (m, 3H), 1.32–1.41 (m, 1H).

#### 4.4.6. (*S*)-2-[(*R*)-Hydroxy(4-fluorophenyl)methyl] cyclohexanone[5c,8b]

$[\alpha]_D^{22}$ = +27.5 (*c* 0.35, $CHCl_3$). Enantiomeric excess was determined by HPLC with a Chiralpak AD-H column (*n*-hexane/isopropanol, volume ratio 90:10), flow rate 0.3 mL/min; $\lambda$ = 208 nm; $t_R$(*anti*) = 49.15 min and 44.19 min (major), $t_R$(*syn*) = 29.38 min (major) and 33.28 min; $^1$H NMR (300 MHz, $CDCl_3$):1.41–1.87 (m, 5H), 1.91–2.21 (m, 1H), 2.26–2.49 (m,3H), 3.01–3.20 (br s, 1H), 3.88–3.92 (br s, 1H), 4.70–4.73 (d, *J* = 9 Hz, 1H), 5.29 (s, 1H), 6.96–7.00 (m, 2H), 7.20–7.23 (br s, 2H).

#### 4.4.7. (*S*)-2-[(*R*)-Hydroxy(phenyl)methyl] cyclohexanone[14a]

Enantiomericexcess was determined by HPLC with a Chiralpak AS-H column (*n*-hexane/isopropanol = 95:5), flow rate 0.5 mL/min, $\lambda$ = 221 nm; $t_R$(*anti*) = 40.79 min (major) and 43.94 min, $t_R$(*syn*) = 29.19 min and 37.08 min (major); $^1$H NMR (300 MHz, CDCl3): $\delta$ 1.40–1.22 (m,1H), 1.72–1.50 (m, 3H), 1.87–1.73 (m, 1H), 2.16–2.03 (m, 1H), 2.34 (td, *J* = 12.3, 5.4 Hz, 1H), 2.55–2.44 (m, 1H), 2.70–2.56 (m,1H), 4.00(m, 1H), 4.80 (d, *J* = 9.0 Hz, 1H), 7.39–7.28 (m, 5H).

#### 4.4.8. (2*S*,10*R*)-2-(Hydroxy-(4-tolyl)methyl) cyclohexanone[1e]

Enantiomericexcess was determined by HPLC with a Chiralpak AD-H column (*n*-hexane/isopropanol = 90:10), flow rate 0.5 mL/min, $\lambda$ = 221 nm; $t_R$ = 32.8 min (*anti*, major), $t_R$ = 44.5 min (*anti*, minor). $^1$H NMR(300 MHz, CDCl3): $\delta$ 7.18 (dd, 4H, *J* = 17.1, 8.4 Hz), 4.75 (dd, 1H, *J* = 9.0, 2.7 Hz), 3.91 (d, 1H, *J* = 2.7 Hz), 2.66–2.54 (m, 1H), 2.51–2.43 (m, 1H), 2.35 (td, 1H, *J* = 13.2, 6.0 Hz), 2.34 (s, 3H), 2.14–2.03(m, 1H), 1.82–1.72 (m, 1H), 1.70–1.50 (m, 3H), 1.38–1.18 (m, 1H).

#### 4.4.9. 2-[Hydroxyl(4-methoxyphenyl)-methyl] cyclohexanone[5c,8b]

White powder; mp 74–76 °C; [Daicel Chiralpak AD-H column, *n*-hexane/isopropanol = 92: 8, flow rate 1.0 mL/min, $\lambda$ = 218 nm; $t_R$(*anti*) = 36.54 min and 29.20 min, $t_R$(*syn*) = 25.25 min (major) and 21.15 min]; $^1$H NMR (300 MHz, $CDCl_3$) d: 1.19–1.33 (m, 1H), 1.48–1.81 (m, 4H), 2.05–2.13 (m, 1H), 2.31–2.64 (m, 3H), 3.80 (s, 3H), 3.92 (s, 1H), 4.74 (d, *J* = 8.7 Hz, 1H), 6.86–6.90 (m, 2H), 7.22–7.26 (m, 2H).

#### 4.4.10. (*S*)-2-[(*R*)-hydroxyl(4-nitrophenyl)methyl] cyclopentanone[5c]

Light yellow powder; mp 88–90 °C; $[\alpha]_D^{22}$ = −30.6 (*c* 0.56, $CHCl_3$). Enantiomeric excess was determined by HPLC with a Chiralpak AD-H column (*n*-hexane/isopropanol = 90:10), 1.0 mL/min, $\lambda$ = 254 nm; $t_R$(*anti*) = 23.94 min (major) and 23.06 min, $t_R$(*syn*) = 13.95 min and 18.04 min (major); $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 8.20–8.24 (m, 2H), 7.51–7.56 (m, 2H), 4.78–5.43 (m, 1H), 1.52–2.62 (m, 7H).

#### 4.4.11. (*S*)-2-[(*R*)-Hydroxyl(2-nitrophenyl)methyl] cyclopentanone[5c]

Enantiomeric excess was determined by HPLC with a Chiralpak AS-H column (*n*-hexane/IPA, volume ratio 95:5), flow rate 1.0 mL/min, $\lambda$ = 225 nm; $t_R$(*anti*) = 28.22 min (major) and 31.09 min, $t_R$(*syn*) = 22.75 and 36.83 min (major);$^1$H NMR ($CDCl_3$, 300 MHz) $\delta$: 7.78 ~ 7.81 (m, 2H), 7.59 ~ 7.72 (m, 1H), 7.38 ~ 7.57 (m, 1H), 5.89 ~ 5.90 (d, *J* = 3 Hz, 1H), 5.41 ~ 5.44 (d, *J* = 8.4 Hz, 1H), 4.50 (br s, 1H), 2.65 ~ 2.85 (m, 1H), 2.26 ~ 2.60 (m, 2H), 1.95 ~ 2.26 (m, 2H), 1.69 ~ 1.8 (m, 2H); $^{13}$C NMR ($CDCl_3$, 300 MHz): $\delta$ 20.1, 20.4, 22.8, 26.5, 38.6, 54.7, 55.3, 66.4, 69.0, 123.9, 124.4, 127.9, 128.5, 128.6, 128.9, 133.1, 133.3, 138.6, 146.9, 219.1.

#### 4.4.12. 4-Hydroxyl-4-(4′-nitrophenyl)-butan-2-one[2d,5d]

[Daicel Chiralpak AS-H column, *n*-hexane/isopropanol = 70:30, flow rate 1.0 mL/min, flow rate 1.0 mL/min, $\lambda$ = 254 nm; $t_R$(*anti*) = 15.39 min and 12.08 min(major)]; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$: 2.21 (s, 3H), 2.80–2.85 (m,2H), 3.56 (br s, 1H), 5.20–5.30 (m, 1H), 7.52 (d, *J* = 7.0 Hz, 2H), 8.20 (d, *J* = 7.0 Hz, 2H).

#### 4.4.13. 4-Hydroxyl-4-(3′-nitrophenyl)-butan-2-one[2d,5d]

[Daicel Chiralpak AS-H column, *n*-hexane/isopropanol = 70:30, flow rate 1.0 mL/min, $\lambda$ = 254 nm; $t_R$ = 11.37 min and 9.74 min(major)]; $^1$H NMR (300 MHz, CDCl3) $\delta$: 2.23 (s, 3H), 2.82 (m, 2H), 3.50 (br s, 1H), 5.15–5.27 (m, 1H), 7.53 (t, *J* = 7.5 Hz, 1H), 7.71 (d, *J* = 7.5 Hz, 1H), 8.13 (d, *J* = 8.6 Hz, 1H), 8.24 (s, 1H).

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