Preparation of Immobilized L-Prolinamide Via Enzymatic Polymerization of Phenolic L-Prolinamide and Evaluation of Its Catalytic Performance for Direct Asymmetric Aldol Reaction

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ABSTRACT Phenolic L-prolinamide was allowed to participate in enzymatic polymerization with horseradish peroxidase as the catalyst, generating immobilized L-prolinamide. The catalytic performance of the resultant polymer-supported L-prolinamide for direct asymmetric aldol reaction between aromatic aldehyde and cyclohexanone was studied. The results show that as prepared L-prolinamide can catalyze the aldol reaction at room temperature in the presence of H_2O. Relevant aldol addition products are obtained with good yields (up to 91%), high diastereoselectivities (up to 6:94 dr), and medium enantioselectivities (up to 87% ee). Moreover, the title polymer-supported catalyst can be recovered and reused for at least five cycles while the activity remains almost unchanged. *Chirality 26:209–213, 2014.* © 2014 Wiley Periodicals, Inc.

KEY WORDS: L-prolinamide; polymerization; polymer-supported catalyst; asymmetric aldol reaction

INTRODUCTION

A direct asymmetric aldol reaction, involving a nonactivated ketone as nucleophile, is one of the most efficient reactions for affording C-C chains, and it has been extensively used in the synthesis of natural products and drug molecules.[1–7]

Among the various catalysts for direct asymmetric aldol reaction, a series of organocatalysts derived from L-proline[8] are of particular significance. This is why many efforts have been made to modify the structure of L-proline so as to improve selectivity and reusability, reduce load, and avoid the use of organic solvent.[9–14] To overcome these drawbacks, researchers also have made attempts to graft organocatalysts with suitable supports.[15–18] The resultant immobilized organocatalysts offer some advantages over small organic catalysts, such as recyclability, simple reaction set-up plus easy experimental procedure, and nontoxicity. In this sense, proline-derived organocatalysts, immobilized by polystyrene,[19–22] polyethyleneglycol,[23,24] chitosan,[25] silica,[26,27] and even ionic liquid,[28,29] may be particularly interesting. The synthesis of the supported proline catalysts via acrylic copolymerization[30,31] and the preparation of helical poly (phenylacetylene)s bearing cinchona alkaloid via the polymerization of corresponding phenylacetylenes[32,33] provide recent examples for synthesizing proline-derived organocatalysts.

In the present research, we chose phenolic L-prolinamide, while the prolinamide was considered as an active and highly stereoselective catalyst for the direct aldol reaction in the presence of water,[34–39] as a monomer to synthesize polymer-supported L-prolinamide via the enzymatic polymerization catalyzed by horseradish peroxidase (HRP).[40,41] Such an approach is facile and competitive. This paper reports the synthesis of polymer-supported L-prolinamide and the evaluation of its catalytic performance for direct asymmetric aldol reaction between aromatic aldehyde and cyclohexanone at room temperature in the presence of water. The recyclability of the catalyst was also evaluated carefully.

EXPERIMENTAL

General

Commercial-grade reagents and solvents were used as received excepting that a specific purification procedure was recommended. HRP (RZ = 2.5, activity = 200 U/mg) was purchased from Shanghai Guoyuan Biotechnology (China) and used without further purification. Thin-layer chromatograph (TLC) analysis was conducted with GF254 silica gel 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 with a Bruker Avance 400 M system, and the chemical shifts of ^{1}H-NMR spectra were reported in relation to tetramethyl silane ($\delta = 0$). Polymer molecular weight and the poly-dispersity index (PDI) were measured with a gel permeation chromatograph coupled with a static laser light scattering unit (GPC-SLS; DAWN EOS and OPTILAB rEX, Wyatt Technology, Santa Barbara, CA; flow rate of fluent tetrahydrofuran: 1.0 mL/min). Melting points (m.p.) were measured with an X-6 melting point apparatus. Analytical high-performance liquid chromatograph (HPLC) analysis was performed with an Agilent 1100 facility equipped with a diode array ultraviolet detector (Daicel, Tokyo, Japan, Chiralpak AD-H (AS-H) was used for HPLC analysis).

Preparation of the Catalysts

The procedures for preparing polymer-supported L-prolinamide **a** are outlined in Scheme 1, where three major steps are involved. First, acyl chloride **3** was synthesized by the reaction of Fmoc-L-Pro with $SOCl_2$; and then **3** was allowed to react with p-aminophenol to give Fmoc-protected phenolic L-prolinamide **2**. Second, the N-Fmoc protecting group of **2** was removed with diethylamine. Finally, phenolic L-prolinamide **1** (3.0 mmol) was dissolved in 3 mL buffer solution (phosphate, pH = 7) while 9 mL of dioxane was added as a cosolvent. Into the resultant solution was then added the enzyme solution of HRP (3.0 mg) in buffer (3 mL), followed by addition of 0.25 mL of 5% hydrogen peroxide every 5 min for a total cycles of 14. The resultant mixture was stirred at

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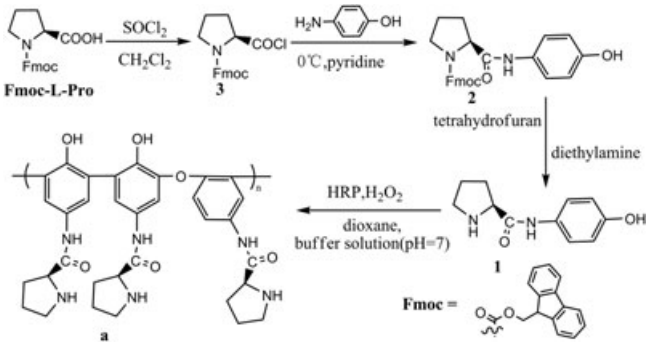


Scheme 1. Routes to synthesis of polymer-supported organocatalyst.

room temperature (r.t.) for 24 h to allow polymerization yielding brown powdery precipitates. At the end of the polymerization reaction, dioxane was evaporated in vacuo, and the crude product was collected by leaching and washing sequentially with water, petroleum ether, and ethylacetate. The target product, polymer-supported L-prolinamide catalyst **a**, was obtained after the washed product was dried in a vacuum oven until the weight remained constant. The functional groups were confirmed by the Fourier transform infrared (FT-IR) spectra. It can be seen from Figure 1 (m) that the broad band at around 3289 cm^{-1} was assigned to hydroxyl and amino of the polymer, the infrared absorption of 1674 cm^{-1} was assigned to the carbonyl of amido bond, and peaks of 1514 cm^{-1} and 1449 cm^{-1} were assigned to the benzene ring. The peaks at 1201 cm^{-1} and 1135 cm^{-1} were due to the C-O-C and C-OH linkage. Gel permeation chromatograph (GPC) analysis showed that L-prolinamide organocatalyst **a** has a weight-average molecular weight (M_w) of 15450 and PDI value of 1.84.

General Procedure for Direct Aldol Reaction

Substituted benzaldehyde (0.2 mmol) was added into the mixture of cyclohexanone, a certain amount of catalyst, and the solvent. The mixture was stirred at r.t., and the reaction system was detected by TLC (ethyl acetate/petroleum ether = 1:2 (volume ratio)). Upon completion of the reaction, the product was filtered and extracted with ethyl acetate; then the organic layer was dried over Na_2SO_4, filtered, concentrated, and purified by TLC on a silica gel (ethyl acetate/petroleum ether) giving pure aldol product.

Recyclability of Polymer-Supported L- Prolinamide Catalyst

At the end of the aldol reaction between cyclohexanone and 4-nitrobenzaldehyde, the catalyst was filtered in vacuum and washed with DCM. After being dried in an oven for 24 h, the catalyst could be reused directly without further purification.

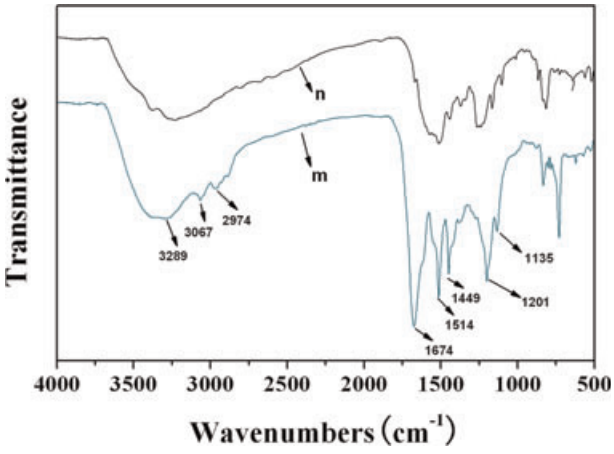


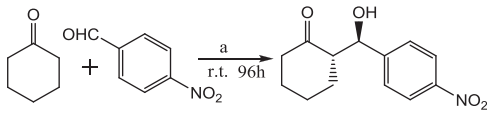
Fig. 1. FT-IR spectra of catalyst **a** (m) and poly(4-aminophenol) (n).

RESULTS AND DISCUSSION

The aldol reaction between 4-nitrobenzaldehyde and cyclohexanone was adopted as a model reaction to evaluate the catalytic performance of the synthesized polymer-supported L-prolinamide. Table 1 presents the catalytic performance of the synthesized L-prolinamide catalyst for the above-mentioned aldol reaction in various solvent systems. It could be seen that the synthesized L-prolinamide catalyst possessed the best catalytic efficiency in H_2O (Entry 1, 87% yield, 10:90 dr, and 83% ee), but it exhibited a reduced catalytic efficiency in organic solvents. Particularly, the aldol product was obtained with low yields (27%–43%) and poor stereoselectivities (43%–69% ee) in polar solvents or less polar solvents; what's more, the stereoselectivity of the catalyst remained almost unchanged in the aqueous solution of 2 mmol/L Tween-20 (Entry 8).

Table 2 shows the results of a series of reactions for optimizing the reaction conditions. Initial tests were conducted using different loading of cyclohexanone as nucleophile (Entries 1–4). When the dosage of cyclohexanone was fixed at 5 equivalent (equiv.), the aldol product was obtained with a higher ee value (83%); and lowering dosage of the nucleophile led to reduced reaction rate (Entry 4). Besides, the lower ee value was obtained for the reaction performed without H_2O (Entry 5), while the stereoselectivity of the catalyst was improved significantly when traces of H_2O were added into the reaction system (Entry 6). This might be because H_2O suppressed the formation of parasitic species, thereby decreasing the relative concentration of some intermediates like oxazolidinones and increasing the catalyst concentration.[20,42–44]

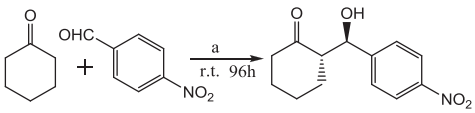
TABLE 1. Screening solvent for the asymmetric Aldol reaction between cyclohexanone and p-nitrobenzaldehyde[a]



Entry	Solvent	Yield[b] (%)	dr[c] (syn/anti)	ee[c] (%) (anti)
1	H_2O	87	10:90	83
2	Isopropanol	43	31:69	45
3	Dimethylformamide (DMF)	32	24:76	57
4	Dimethyl sulphoxide (DMSO)	27	27:73	43
5	CH_3CN	29	34:66	58
6	Petroleum ether	41	16:84	69
7	Toluene	35	40:60	51
8[d]	H_2O-Tween-20	89	12:88	78

[a]Reaction performed at 0.2 mmol scale of aldehyde and 5 equiv. of cyclohexanone in the presence of 10 mol% catalyst in 500 μL undistilled solvent.
[b]Isolated yield.
[c]Determined by chiral-phase HPLC analysis (Chiralpak AD-H).
[d]The aqueous solution of Tween-20 (2 mmol/L) was used as solvent.

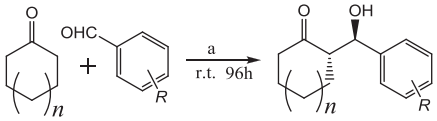
TABLE 2. Screening the amount of cyclohexanone, solvent and catalyst for the asymmetric Aldol reaction between cyclohexanone and 4-nitrobenzaldehyde[a]



Entry	Solvent (μL)	Cyclohexanoe (equiv.)	Yield[b] (%)	dr[c] (syn./anti.)	ee[c] (%) (anti.)
1	500	15	88	11:89	80
2	500	10	90	10:90	78
3	500	5	84	10:90	83
4[d]	500	2.5	67	10:90	78
5	neat	5	89	14:86	73
6	40	5	91	11:89	87
7	120	5	85	10:90	81
8[e]	500	5	86	8:92	78
9[f]	500	5	88	13:87	79
11[g]	40	5	89	12:88	76

[a]Reaction performed at 0.2 mmol scale of aldehyde and 5 equiv. of cyclohexanone in the presence of 10 mol% catalyst in 500 μL H_2O.
[b]Isolated yield.
[c]Determined by chiral-phase HPLC analysis (Chiralpak AD-H).
[d]The reaction time was 144 h.
[e]Reaction performed in the presence of 2.5 mol% catalyst.
[f]Reaction performed in the presence of 25 mol% catalyst.
[g]Reaction catalyzed by monomer **1**, and the reaction time was 24 h.

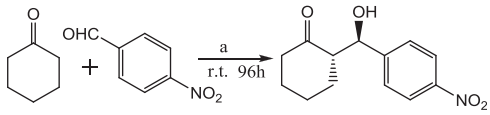
TABLE 3. Asymmetric Aldol reactions catalyzed by polymer-supported L-prolinamide[a]



Entry	*R*	Yield[b] (%)	dr[c] (syn/anti)	ee[c] (%) (anti)
1	4-NO_2	91	11:89	87
2	2,4-NO_2	90	9:91	82
3	2-NO_2	86	9:91	88
4	3-NO_2	83	6:94	87
5	4-CN	73	9:91	80
6	4-F	46	22:78	82
7	4-Cl	41	15:85	83
8	4-Br	43	16:84	80
9	4-H	27	39:61	67
10	4-OCH_3	25	22:78	75
11[d]	4-NO_2	68	—	32
12[e]	4-NO_2	89	40:60	87
13[e]	2-NO_2	87	17:83	86
14[e]	3-NO_2	73	33:67	80

[a]Reaction performed at 0.2 mmol scale of aldehyde and 5 equiv. of cyclohexanone (cyclopentanone) in the presence of 10 mol% catalyst in 40 μL of H_2O.
[b]Isolated yield.
[c]Determined by chiral-phase HPLC analysis (Chiralpak AD-H or AS-H).
[d]Acetone used as the nucleophile.
[e]Cyclopentanone used as the nucleophile.

TABLE 4. Recovery and reuse of polymer-supported L-prolinamide catalyst[a]



Entry	Cycle	Yield[b] (%)	dr[c] (syn./anti.)	ee[c] (%) (anti.)
1	1	91	11:89	87
2	2	90	9:91	84
3	3	92	8:92	86
4	4	83	10:90	82
5	5	89	11:89	85

[a]Reaction performed at 0.2 mmol scale of aldehyde and 5 equiv. of cyclohexanone (cyclopentanone) in the presence of 10 mol% catalyst in 40 μL of H_2O.
[b]Isolated yield.
[c]Determined by chiral-phase HPLC analysis (Chiralpak AD-H).

The effect of the amount of catalyst is summarized in Table 2. It can be seen that decreasing the amount of catalyst to 2.5 mol% led to a lower ee value, as did increasing the amount of catalyst to 25 mol% (Entries 3, 8–9). In combination with the results shown in Table 1, the optimized reaction conditions for the title aldol reaction were suggested as catalyst dosage of 10 mol% and 5 equiv. of cyclohexanone while H_2O was introduced into the reaction system. Moreover, by comparing with phenolic L-prolinamide **1** the catalyst tested under the optimized reaction conditions (Entry 11 in Table 2), we could draw a conclusion that the polymer-supported catalyst possesses better stereoselectivity but lower catalytic activity than the monomer **1**.

In the presence of cyclohexanone (cyclopentanone) as the donor, medium stereoselectivity was obtained with different aromatic aldehydes (Table 3). As to some benzaldehydes with strong electron-withdrawing substituents, the reaction was completed with good diastereoselectivity, moderate enantioselectivity, and high yield (Entries 1–4). However, a low diastereoselectivity was recorded for reactions involving benzaldehyde containing weak electron-withdrawing groups, and the reaction rate in these cases was also reduced (Entries 6–8). When benzaldehyde and 4-anisaldehyde were used as aldol acceptor, the enantioselectivity remained moderate, but the yield decreased significantly (Entries 9–10). To our disappointment, when the acetone was used as aldol donor the ee value just was 32% (Entry 11). To broaden the scope of the methodology, we also adopted polymer-supported L-prolinamide to catalyze the direct asymmetric aldol reaction between cyclopentanone and benzaldehyde, and we found that the aldol products were obtained with good yield (up to 89%) and enantioselectivity (up to 87%) in the presence of nitrobenzaldehydes as electrophile (Entries 12–14).

The recyclability of the polymer-supported L-prolinamide catalyst under the optimized reaction conditions was also evaluated and the results are listed in Table 4. It could be seen that the prepared polymer-supported L-prolinamide retained almost unchanged activity, enantioselectivity, and diastereoselectivity after it was used for at least five cycles, which indicates that the title catalyst was well reusable.

CONCLUSION

In summary, we have successfully designed a new strategy for the immobilization of L-prolinamide, which is based on the enzymatic polymerization of phenolic L-prolinamide in the presence of HRP as the catalyst. The resultant polymer-supported L-prolinamide was tested as an organocatalyst for direct asymmetric aldol reaction between aromatic aldehyde and cyclohexanone. The findings show that the synthesized polymer-supported L-prolinamide can catalyze the aldol reaction under investigation at r.t. in the presence of H_2O, giving good yield (up to 91%), high diastereoselectivity (up to 6:94 dr), and medium enantioselectivity (up to 87% ee) of the relevant aldol adducts. In addition, the prepared polymer-supported catalyst can be recovered and reused for at least five cycles while the activity remains almost unchanged, showing promising potential as a highly efficient organocatalyst for the aforementioned aldol reaction. Further studies on the influence for the catalytic performance of the copolymerization and other phenolic L-prolinamide like ortho-aminophenol-L-prolinamide are under way.

SUPPORTING INFORMATION

Additional supporting information may be found in the online version of this article at the publisher's web-site.

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