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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.

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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 researchers⁷ 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 susceptible 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 others¹⁴ 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 synthesize 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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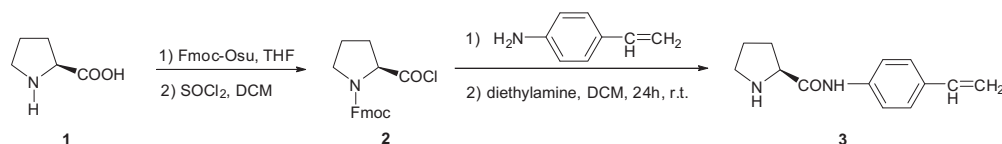
more environmentally responsible chemistry,^{10,15} we tried to adopt ethanol as the solvent in the solution polymerization. Herein we report the synthesis of L-proline functionalized polymers and the application of these novel functional polymers as supported organocatalysts for a typical direct enantioselective 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

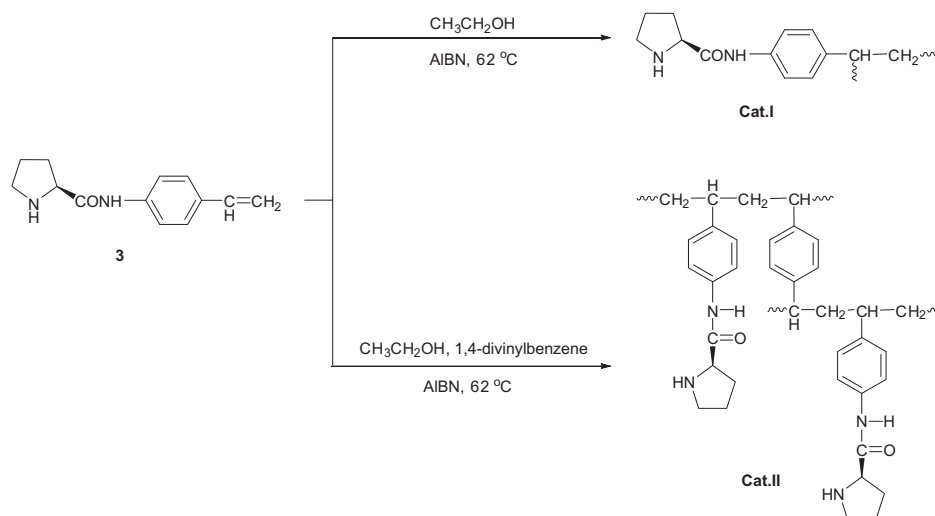
Schemes 1 and 2 depict the procedures for preparing **Cat.I** and **Cat.II**, where three major steps are involved. Firstly, *N*-9-fluorenylmethyloxy-carbonyl protected L-proline (Fmoc-L-Pro) was reacted

with SOCl₂ 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



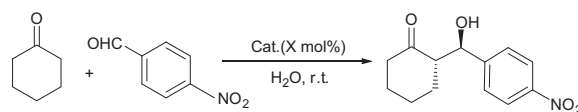
Scheme 1. The preparation of L-proline functionalized styrene monomer **3**.



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 (<i>syn/anti</i>)	ee ^c (%; <i>anti</i>)
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, 1.98×10^{-4} mol) and cyclohexanone (10 equiv, 1.98×10^{-3} mol) in 0.5 mL of H₂O.

^b Isolated yield.

^c Determined by chiral-phase HPLC analysis (Chiralpak AD-H).

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