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ARTICLE TYPE

A novel poly (*N*-isopropyl-acrylamine-*co*-*L*-proline) catalystfor aldol reaction: synthesis, catalytic performance and recyclability

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A novel homogeneous copolymer catalyst was synthesized via single step radical copolymerization and developed for aldol reaction. It was demonstrated that the catalyst possessed excellent activity and stereoselectivities. The secondary structureof copolymer catalyst was evaluated by circular dichroism. Furthermore, the catalyst was readily recovered withoutloss in conversion and stereoselectivitieseven after ten cycles.

L-Proline has been widely used as an organocatalyst for the construction of asymmetric carbon-carbon bonds, since 2000.[1, 2] Although *L*-proline and its derivatives are highly effective and metal-free used in many reactions such as Aldol reaction, Mannich reactions, Diels-Alder reactions and others,[2-5]there are two main issues that must be considered. The first one is the relative low activity of catalysts, which need further improve by choosing the appropriate functional groups or adjusting the structure of catalysts. The second one is the difficulty associated with recycling and reusing of the organocatalysts.To counterbalance these points, recent research efforts have been dedicated to immobilizing and recycling of *L*-proline and its derivatives. [6, 7] Among those immobilization methods, heterogeneous materials supported *L*-proline has generally reduced the catalytic activity and stereoselectivities, whereas homogeneous polymer-supported *L*-proline has emerged as a promising strategy due to the high catalytic activity and low cost. In homogeneous polymer-supported *L*-proline, the polymer skeleton can act as a natural part of the catalytic system and the amphipathic polymer provides a favourable catalytic microenvironment, like a pseudo-enzyme system.[8]

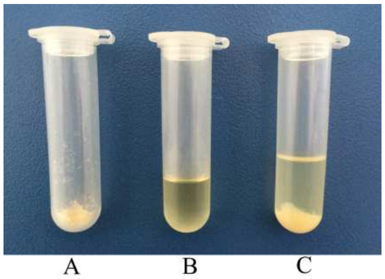
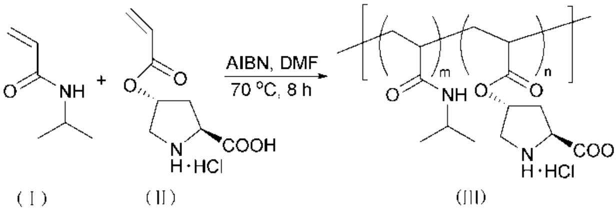


Fig. 1 (A) the copolymer catalyst, (B) the catalytic reaction carried out homogeneously, (C) the catalyst precipitated out of solution after reaction.

Herein, a novel homogeneous polymer-supported *L*-proline copolymer catalyst, poly (*N*-isopropyl-acrylamine-*co*-*L*-proline), which combines the merit of homogeneous and heterogeneous processes, is synthesized by radical copolymerization. The catalytic reaction carries out homogeneously and the catalyst can be easily recovered by precipitation (Fig 1).The secondary structure of copolymer catalyst is also evaluated to elucidate the relationship between secondary structure and selectivities in this study.

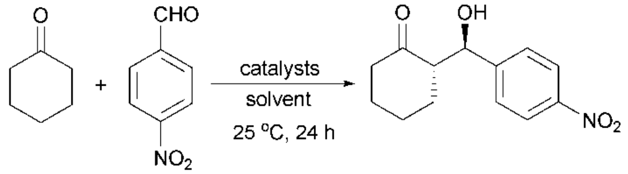
The synthesis of polymer-supported *L*-proline follows the outline shown in Scheme 1. In contrast to traditional postmodification scheme, radical copolymerization has many advantages, including high and controllable catalyst loading, and less synthetic steps. With the presence of azodiisobutyronitrile (AIBN) as radical initiator, the copolymerization of *N*-isopropylacrylamide (NIPAM) with *O*-acryloyl-*trans*-4-hydroxy-*L*-proline hydrochloride is carried out in *N, N*-dimethyl formamide (DMF) at 70 °C for 8 hwith a single synthetic step(Scheme 1). The proline compositions in the copolymers possessd different loading amounts were determined by ^{1}H NMR spectroscopy (Fig S1). Although the catalyst loading was 8.6 mol% lower than 10 mol% feed ratio, it was interesting to find the good linear relationship of feed ratio from 5 mol% to 20 mol% against catalyst loading (Fig S5). Therefore, it suggested that the catalyst loading could be adjusted by radical copolymerization.



Scheme 1 Polymer-supported *L*-proline by copolymerization

A model reaction, the asymmetric aldol addition of*p*-nitrobenzaldehyde to cyclohexanone, was chosen to evaluate thecopolymer catalyst (Table 1).[9-11] The aldoladditionwas typically carried out in polar aprotic solvents, dimethylformamide (DMF) or dimethyl sulfoxide (DMSO), which had proven to be the optimal media for the reaction.[12, 13] Thus, the reaction could be performed heterogeneously in H_2O, tetrahydrofuran (THF), $CHCl_3$, CH_3CN and $CH_3COOCH_2CH_3$, and homogeneously in CH_3OH, DMF, DMSO, DMF/H_2O and DMSO/H_2O. Although the heterogeneous catalyst system gave low conversion, the moderatestereoselectivities were observed (Table 1, entry 1-5), which could probably due to that the hydrophobic part of the copolymer backbone played an important role in the stereocontrol.[14, 15] Compared with the heterogeneous catalyst system, the homogeneous catalyst system exhibited better catalytic performance with high conversion (98-99%) and moderate to high stereoselectivities (*anti*/*syn* = 37-99/63-1, 48-99% ee) (Table 1, entry 6-10). Notably, the best result with respect to conversion, diastereo- and enantioselectivities (98-99% conversion, *anti*/*syn* = 96-99/4-1, 97% ee) were achieved in DMF/H_2O and DMSO/H_2O (Table 1, entry 9 and 10). However, both conversion and stereoselectivities decreased obviously as the content of water was increased, and enantioselectivities decreased slightly as the amount of water was reduced (Table 1, entry 11 and 12). This result provides evidence that appropriate amount of water could accelerate reactions and improve stereoselectivities, but the excess water resulted in low yields. [16-19]

Table 1 The model aldol reaction catalyzed bycopolymer catalyst, monomer and PNIPAM[a]



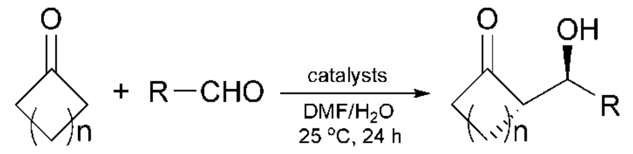
Entry	Catalyst	Solvent	Conversion[b] [mol%]	*anti:syn*[b]	ee[c] [%]
1	III	H_2O	63	86:14	79
2	III	THF	19	99:1	94
3	III	$CHCl_3$	60	99:1	90
4	III	CH_3CN	48	83:17	70
5	III	$CH_3COOCH_2CH_3$	17	80:20	85
6	III	CH_3OH	95	99:1	97
7	III	DMF	99	37:63	99
8	III	DMSO	99	74:26	48
9	III	DMSO/H_2O (3:1 v/v)	99	99:1	97
10	III	DMF/H_2O (3:1 v/v)	98	96:4	97
11	III	DMF/H_2O (1:3 v/v)	46	58:42	73
12	III	DMF/H_2O (10:1 v/v)	97	97:3	81
13	II	H_2O	74	83:17	65
14	II	CH_3OH	62	75:25	82
15	II	DMF/H_2O (3:1 v/v)	97	57:43	88
16	II	DMSO/H_2O (3:1 v/v)	99	40:60	73
17	PNIPAM	DMF/H_2O (3:1 v/v)	0	-	-

[a]Reaction conditions: *p*-nitrobenzaldehyde (0.0756 g, 0.50 mmol), cyclohexanone (2.0 mL), 0.5g 8.6 mol % loading of copolymer catalyst, 24 h, rt. [b]Determined by ^1H NMR. [c]Determined by chiral HPLC.

For comparison, the aldol addition was performed under the same conditions with monomer *O*-acryloyl-*trans*-4-hydroxy-*L*-proline hydrochloride and Poly (*N*-isopropylacrylamide) (PNIPAM) (Table 1, entry 13-17). Obviously, PNIPAM had no activity in the aldol reaction and the monomer exhibitedless stereoselectivities (*anti*/*syn* = 40-83/60-17, 73-88%ee) compared with the copolymer catalyst. Thus, the polymeric system is favorable to aldol reaction. The hydrophobic/hydrophilic balance of copolymer catalyst and the water are helpful to form hydrogen bonds, an ideal reaction microenvironment which often positively influences activity and stereoselectivities of the configurated catalyst.[8, 17, 18, 20]

It is noteworthy that all the catalytic reaction data was obtained without treating with triethylamine (Et_3N) to cause free amino acid polymer, which is different from the previous reports.[21, 22] Not only did itshorten the synthetic route, but alsoinfluenced the catalytic activity and stereoselectivities. It was also evident that the role of the HCl as acid additive was dual, orienting the substrate and facilitating the formation of enamine. The same phenomenon had been observed in aldol reaction with Brønsted acid as additive to improve the activity and stereoselectivity.[11, 23]

Table 2 Asymmetric aldol reaction in DMF/H_2O with copolymer catalyst



Entry	n	R	Conversion[a] [mol%]	*anti:syn*[a]	ee[b] [%]
1	3	*o*-NO_2Ph	97	97:3	96
2	3	*m*-NO_2Ph	94	99:1	91
3	3	*p*-ClPh	99	96:4	99
4	3	*p*-BrPh	99	99:1	94
5	3	*p*-MePh	58	56:44	95
6	3	*p*-MeOPh	7	53:47	94
7	3	*p*-pyridyl	99	81:19	97
8	0	*p*-NO_2Ph	33	99[c]	84
9	2	*p*-NO_2Ph	99	88:12	72

[a]Determined by ^1H NMR. [b]Determined by chiral HPLC. [c]Selectivity to 4-hydroxy-4-(4-nitrophenyl)-butan-2-one

In comparison, a series of aldehydes and ketones were also employed to explore the scope of the copolymer catalyst under the optimized reaction conditions (Table 2). Reaction between aldehydes with an electron-withdrawing group and cyclohexanone gave the corresponding products in high conversion (> 94%) and stereoselectivities (diastereoselectivity > 96%, ee > 91%) (entry 1-4). Electron-withdrawing groups (-NO_2, -Cl, -Br) at the aromatic portion were well tolerated, however, the electron-donating substituted aldehydes (-CH_3 or -OCH_3 substituted) resulted in low conversions， moderate diastereo-selectivities and high enantioselectivities (entry 5, 6).In fact, as previously reported,the aldehydes with electron-withdrawing groups showed much higher reactivity and enantioselectivity than those with electron-donating groups.[11,20,21] Moreover, the expected products inexcellentconversion (99%) and enantio-selectivity (97%) were observed when *p*-pyridinecarboxaldehyde, a heteroaromatic aldehyde, was used as the acceptor (entry 7).

Finally, other aldol donors, such as acetone and cyclopentanone, reacted with *p*-nitrobenzaldehyde (entry 8, 9). In the cases of cyclic ketones (cyclohexanone and cyclopentanone), the catalyst exhibited better catalytic performance than acetone.[11,18,20] When cyclopentanone was used as donor, high conversion (99%) and moderate stereoselectivity (88% *anti*, 72% ee) were obtained. However, only 33% conversion and 84% ee were obtained when acetone was used as substrate.

The circular dichroism (CD) and UV-vis spectroscopy of the copolymer catalyst and monomer have been investigated (Fig 2, Fig S6 and Fig S7). CD is a technique commonly used for probing the secondary structure and chiroptical properties of proteins, polymers and other compounds.[24-26]The CD spectra of the copolymer catalyst are significantly different from the monomer both in H_2O or MeOH. In H_2O, the molecular ellipticities are as follows: $[\theta]_{\lambda(\max)} = -8.03\times10^4$ (212 nm), $+2.21\times10^4$ (204 nm). Clearly, the copolymer catalyst exhibits CD signals with negative Cotton effects, which is similar to polyproline Ⅱ helix conformation,[27] while the monomer possess CD signal with positive Cotton effects, suggesting the noticeable secondary structure differences between them. In CH_3OH, the copolymer catalyst not only exhibits negative CD signal at 219 nm, but also has positive CD signal at 205 nm, while the CD signal monomer has no significant change compared with it in H_2O (Fig S6). These results suggest that secondary structure is related to the conformation of copolymer catalyst in solutions and there is a dramatic change of monomer and copolymer catalyst in secondary structure. Therefore, it is not difficult to explain that copolymer catalyst can increase the stereoselectivities and the solvents affect the stereoselectivities (Table 1, entry 1,6, 9,10 and 13-16).[25] The change of structure induced the change of stereoselectivities. In other words, the secondary structure of copolymer catalyst provides an advantage in improving the stereoselectivities and the appropriate solvent is also favorable toward increasing the stereoselectivities.

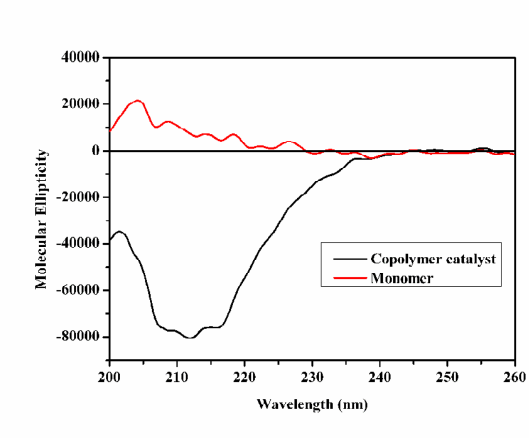


Fig. 2CD spectra of copolymer catalyst (1.0×10^{-5} mol • L^{-1}) and monomer (1.0×10^{-5} mol • L^{-1}) in H_2O

In order to further investigate the activity of copolymer catalyst, we turned attention to the kinetics for aldol reaction in polymer catalytic system (Fig 3). Gratifyingly, we found that the stereoselectivities was preserved at high level (diastereoselectivity > 95%, ee > 95%) after 5 h reaction. It was found that the stereoselectivities did not change over time. But importantly, at the initial stage, the conversion was very low (conversion < 10%); and after 5 h, with the subsequent increase in reaction time, the conversion increased from 56% to 99%. Obviously, there was a jump in conversion between 4 and 5 h. It was probably that the catalytic rate is associated with mass transferin the polymer catalytic system. After the polymer had dissolved, the viscosity of catalytic system increased distinctly, and thus, the reactants transfer rate decreased. It was universally accepted that the viscosity is inversely related to the mass transfer rate, which can well explain the low conversion at the beginning of reaction and abrupt change. This diffusion controlled process has been widely found in polymer catalytic system.[28]The limiting factors arise from mass transfer have always been and will continue to be one of the challenges to overcome for polymer catalytic system.[29]

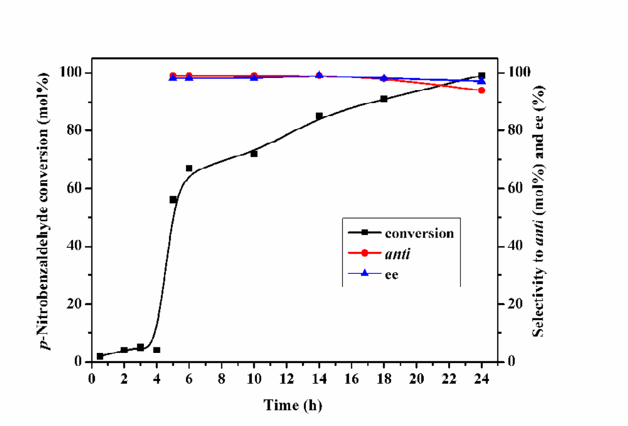


Fig. 3 The catalytic activity of the copolymer catalyst against time

As the catalyst is homogeneously mixed on a molecular scale within the reaction mixtures, recycling of the homogeneous catalysts is a problem that must be appropriately settled to date.[21, 30-32]In present work, we therefore investigated the recycling potential of copolymer catalyst using diethyl ether (Et_2O) or saturated brine as the precipitants. The catalyst was readily precipitated out of reaction mixture by addition of Et_2O. Then, the precipitated catalyst was isolated, washed, dried and reused in the following recycle experiments.

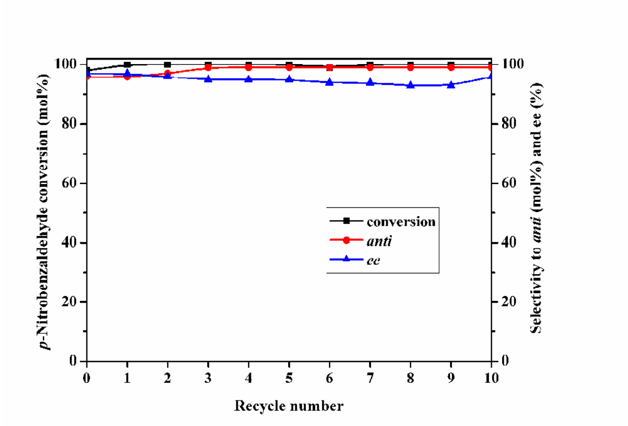


Fig. 4 Recyclability of the copolymer catalyst

As Fig 3 shown, the copolymer catalyst had excellent recyclability. Even in the tenth run, there was no loss in conversion (> 96%) and stereoselectivities (anti/syn = 99/1, 99% ee).

In addition, we also successfully recovered the copolymer catalyst by precipitation using saturated brine, which is a green recycling method. At the end of aldol reaction, the mixture was added saturated brine to form three phases: aqueous phase, organic phase and solid phase. The polymer was successfully isolated by centrifugation. The separated organic phase was dried over $MgSO_4$ and concentrated under vacuum. The aqueous phase was reused directly in the next recycling (Scheme S1). Under these conditions, the catalyst was used in 7 cycles without losing significantstereoselectivities (> 95%), but the conversion was decreased from 99% to nearly 80% after 2 cycles (Fig 4). Predicated on these data, the influence of salt on the conversion and stereoselectivity couldn't escape notice. Gallardo and co-workers suggested that the addition of salts promoted an appreciable increase of stereoselectivity at the expense of the conversion.[15] On the other hand, the reduction in copolymer solubility was related to the adsorption of salt on copolymer. Thus, due to the adsorption and subsequent adsorption saturation, the conversion was decreased significantly and subsequently retained at around 80%.

In summary, a novel homogeneous copolymer catalyst was synthesized by the simple radical copolymerization of the *L*-proline derivative with *N*-isopropylacrylamide. This copolymer catalyst offers several advantages, including single synthetic step, high catalytic activity and recyclability. It was demonstrated that the copolymer catalyst exhibited excellent catalytic properties, resulting in higher conversion (98-99%) and stereoselectivities (*anti/syn* = 96-99/4-1, 97% ee) in the model aldol reaction compared to unsupported *L*-proline derivative monomer. The CD spectra of the copolymer catalyst are apparently different from the corresponding monomer, which, from the point of secondary structure, suggested the supported catalyst by copolymerization benefited promoting the catalytic activity. Regarding to the affect of the solvent, two main issues have been raised: (1) the solubility of copolymer catalyst, and (2) the different secondary structure of copolymer catalyst in different solvents. The copolymer catalyst can be recovered and reused with the conversion keeping above 96% and high stereoselectivities (*anti/syn* = 99/1, 99% ee), even after ten cycles, allowing efficient recycle of the copolymer catalyst.Nevertheless, a more detailed study will be carried out on the relationship between secondary structure of copolymer catalyst and catalytic activity.

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Notes and references

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