Novel Polycarbonate Copolymer as Organocatalyst for Aldol and Michael Reaction

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GRAPHICAL ABSTRACT
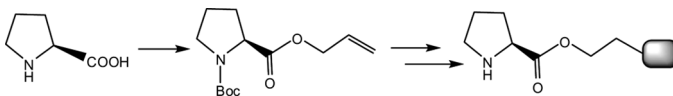
Abstract *A new polymeric organocatalyst is prepared by free radical copolymerization of allyl diglycol carbonate (ADC) and Boc-protected allyl prolinate and evaluated as a chiral catalyst for aldol and Michael reaction.*

INTRODUCTION

Asymmetric organocatalysis,[1] the area of metal-free catalysis, has developed tremendously ever since List et al. reported the first direct intermolecular asymmetric aldol reaction.[2] The high selectivity, atom efficiency, and environmental and experimental friendliness make it a more alluring alternative for providing chiral compounds.[3] There is continuing demand for the design and development of new effective catalysts for organic transformations because of their utility in cascade synthesis of complex skeleton. Immobilization of organic catalyst is an active field of research.[4] Immobilization by covalentl linking of 4-hydroxy proline has been effected to different supports such as polystyrene,[5] polyethyleneglycol,[6] ionic liquid,[7] silica,[8] dendrimer,[9] and acrylic polymer,[10] either directly or through a spacer. Likewise 4-hydroxyprolinamides,[10b,11] 4-aminoproline,[12] prolinamide,[13] and prolinamine derivatives[14] have also been effectively immobilized.

Most of the immobilization strategies give excellent yields, enantioselectivities, and recyclability results, while a few give moderate to poor results. Though effective, some of these strategies are very expensive. For more effective and environmental sustainability, new materials and ways for immobilization are required. The easy

degradation of polycarbonate-based polymers compared to hydrocarbon polymers, and our experience in developing solid-state nuclear track detectors (SSNTD) based on allyl diglycol carbonate (ADC) by casting homo- and copolymer films,[15] coupled with our interest in asymmetric synthesis,[16] prompted us to design a copolymer of pyrrolidine unit with ADC by radical copolymerization. Also to our knowledge there are no studies for effectiveness of a chiral catalyst when it is embedded in a polymer matrix. Herein, we report our efforts in designing and synthesis of a copolymer of ADC with allyl-N-Boc prolinate as an organocatalyst and its studies in aldol and Michael reactions.

RESULTS AND DISCUSSION

Our strategy for designing the polymeric material is based on radical copolymerization of easily accessible allyl containing proline derivative **1** with readily available ADC monomer **2** to make pyrrolidine-derived polycarbonate resin. Though all types of derivatives of proline are found to be effective as organocatalyst, proline esters are seldom used. This may be due to the self-condensation problems associated with amine esters. We thought that if such esters are immobilized in a polymer matrix then the self-condensation problem would be diminished because of fever intermolecular collisions. Further it was thought that the ADC backbone at the terminal end of the pyrrolidine moiety could act as a steric bulk and control the orientation of the intermediate enamine by efficient face shielding, and also the approach of the aldehyde, to influence the stereochemical outcome of the aldol reaction.

Thus, L-proline was treated with $SOCl_2$/allyl alcohol, wherein the salt of allyl prolinate was obtained, which was directly subjected to N-protection using Boc_2O to give the corresponding allyl-N-Boc prolinate **1** in 69% yield. The requisite ADC **2** was synthesized using the literature procedure.[15a] The allyl-N-Boc prolinate–ADC (1:4 w/w) copolymer was prepared by using an isopropyl peroxydicarbonate (IPP) initiator.

Allyl-N-Boc prolinate monomer **1** was mixed with ADC monomer **2** (1:4 w/w). This mixture was stirred under a nitrogen atmosphere to remove any dissolved air or oxygen. IPP initiator (4% w/w) and dioctyl phthalate plasticizer (1% w/w) were mixed and carefully injected in a previously assembled mold using a syringe. The mold was sealed, kept in the pressurizing assembly,[15b,c] and polymerized using 12 h constant rate of polymerization cycle devised for ADC as per its polymerization kinetics (Fig. 1). The copolymer **3** obtained was a brittle and glassy material. Finally, the deprotection of the Boc group from the prolinate unit of polymer **3** was carried with trifluoroacetic acid (TFA) solution in dichloromethane, followed by neutralization with aqueous NH_3, releasing the corresponding supported amine polymer **4** (Scheme 1). The infrared (IR) spectrum of polymer **3** and **4** shown in Fig. 2 confirms deprotection of Boc group. The loading of the catalyst in polymer was determined by CHN analysis and found to be 0.64 mmol/g.

The aldol reaction between 2-nitrobenzaldehyde and acetone was chosen to evaluate the polymeric catalyst. Initially the catalytic effect of the catalyst **4** for aldol reaction of acetone (10 equiv) and 2-nitrobenzaldehyde (1 equiv) in chloroform was studied by using 10, 20, and 30 mol% of catalyst (the percentage of allyl prolinate to the polymer was calculated based on percentage of nitrogen present on the polymer),
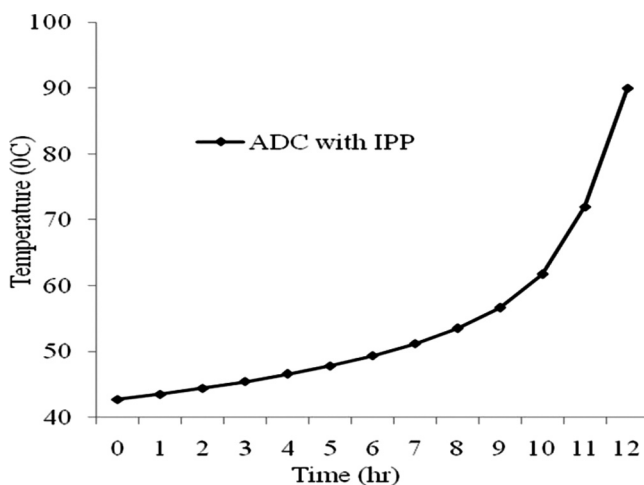
Figure 1. Constant rate polymerization cycle used for synthesis of the copolymer poly(ABP-co-ADC).

and the aldol product was obtained in 56%, 74%, and 74%, yield respectively with 68% *ee* values in all cases. Hence, the use of 20 mol% of catalyst was selected for further studies. Further the ee obtained were comparable to the most of the reported oganocatalyzed reaction.

   As the polymer swelling is also a key factor for catalysis reaction, studies were made to resolve the optimal solvent system for the reaction (Table 1). Interestingly, the reaction worked nicely in water, yielding aldol product in good yield (92%) after 4 h but imparted less asymmetric induction (entry 2). On the other hand, the
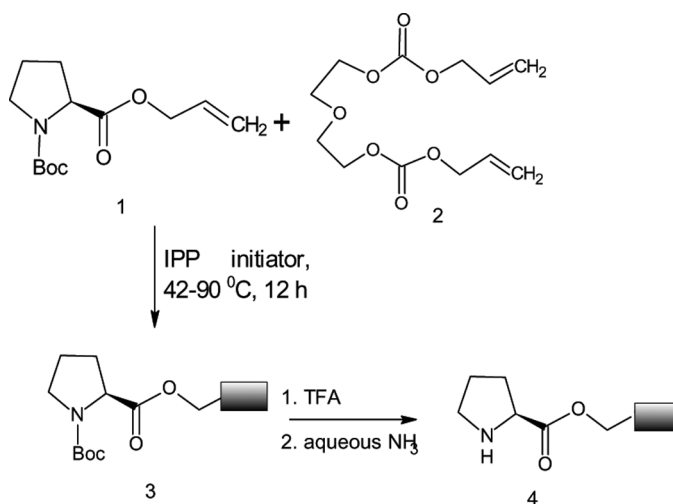
Scheme 1. Synthesis of polymer **4** by copolymerization.
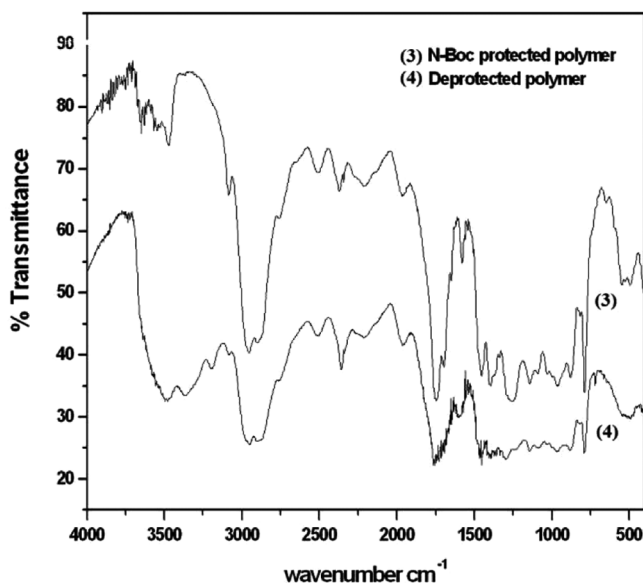
Figure 2. Comparison of IR spectra of polymer **3** and **4**.

enantiomeric excess was enhanced when good polymer-swelling solvents such as acetonitrile and dimethylsulfoxide (DMSO) were used; however, there was a decrease in the yield (entries 6, and 7). The solvents $CHCl_3$ and CH_2Cl_2 were found to be most satisfactory, which provided the aldol product in 74% and 69% yield and 68% and 72% ee respectively (entries 3 and 4). Furthermore, the neat reaction furnished the product with 88% yield and 41% ee (entry 1).

Table 1. Solvent effect on aldol reaction
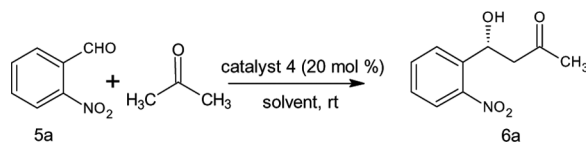
Entry	Solvent	Time (h)	Yield[a] (%)	Ee[b]
1	Acetone	24	88	41
2	Water	4	92	17
3	$CHCl_3$	24	74	68
4	CH_2Cl_2	24	69	72
5	THF	24	83	32
6	CH_3CN	24	68	45
7	DMSO	24	67	68
8	$CHCl_3$[c]	24	61	31

[a]Isolated yield.
[b]The ee values were determined by HPLC, using Chiralpak IC column.
[c]With 10 mol% of benzoic acid as additive.

Brønsted acids such as benzoic acid are known to accelerate both the activity and stereoselectivity of asymmetric aldol reaction catalyzed by pyrrolidine-based catalyst.[17] Hence, to check the effect of additives on the yield and stereoselectivity, the aldol reaction was carried out in the presence of catalyst **4** (20 mol%) and benzoic acid (10 mol%) in CHCl$_3$ (entry 8). However, the effect of benzoic acid as cocatalyst did not significantly improve either activity or selectivity.

The catalyst was further checked for its reaction with a set of different substituted benzaldehydes at optimal conditions. 4-Substituted benzaldehydes gave lower yields, whereas 2- and 3- substituted ones gave better yields with moderate *ee* for all the aldehydes (Table 2)

Having evaluated the reactivity and selectivity of the catalyst, reusability of the catalyst was also studied after a simple filtration from the reaction mixture without any further treatment. Our results of reuse of catalyst are summarized in Table 3. The catalyst gave gradual decrease in the yield as well as in the *ee* with increase in number of cycles.

The catalyst was also evaluated for Michael addition reaction, and the reaction between cyclohexanone (10 equiv) and nitrostyrene (1 equiv) was chosen as a model reaction. Introduction of 20 mol% catalyst gave 58% yield, but when catalyst

Table 2. Aldol reaction of acetone with substituted benzaldehydes
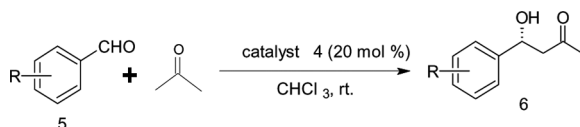
Entry	Product	Yield^a (%)	Time (h)	Ee^b
1(6b)		71	24	50
2(6c)		49	24	24
3(6d)		64	24	56
4(6e)		30	24	57
5(6f)		62	24	49

^{a}Isolated yield.
^{b}*Ee* values were obtained by using optical rotation values.

Table 3. Reuse of catalyst **4**

Entry	Reused catalyst	Time (h)	Yield[a] (%)	Ee[b] (%)
1	Cycle 1	24	69	52
2	Cycle 2	24	58	22
3	Cycle 3	24	55	17
4	Cycle 4	24	39	13

[a]Isolated yield.
[b]The *ee* values were determined by HPLC, using Chiralpak IC column.

Table 4. Solvent effect on Michael reaction

Entry	Solvent	Yield (%)[a]	Ee (%)[b]	Dr
1	Neat	97	18	94:6
2	CHCl$_3$	88	9	97:3
3	CH$_2$Cl$_2$	79	16	95:5
4	Ethanol	74	11	97:3
5	THF	86	8	91:9
6	DMSO	80	6	96:4
7	CH$_3$CN	79	18	94:6
8	CHCl$_3$[c]	42	4	94:6

[a]Isolated yield.
[b]The *ee* values were determined by HPLC, using Chiralpak AD and IC columns.
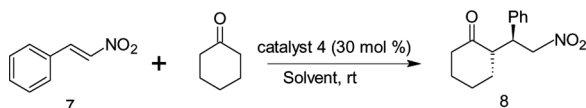[c]10 mol% *o*-nitrophenol as an additive.

quantity was increased to 30 mol%, yield further increased to 88% with 9% *ee* and 97:3 *dr*. Screening of solvents was carried out with 30 mol% catalyst at rt, and results shown in Table 4.

These studies indicated the Michael adduct is formed in good yield and *dr* in all organic solvents. However, *ee* obtained was insignificant. The use of additives such as *o*-nitrophenol did not improve the activity and enantioselectivity.

CONCLUSION

In conclusion, a novel copolymer of ADC and allyl-*N*-Boc prolinate was developed using free radical copolymerization. The polymeric catalyst promotes asymmetric aldol reaction in good yields and moderate enantioselectivities in organic solvents. Furthermore, the catalyst was studied for its reusability. In addition, catalyst also promotes Michael addition reaction of cyclohexanone and nitrostyrene in good yield and diastereomeric ratios. Further modifications are required for structural motifs of this class of catalyst to improve the overall efficacy.

EXPERIMENTAL

Chemicals and solvents were purchased from commercial suppliers and purified by standard techniques whenever necessary. Flash chromatography was performed on Combiflash. ^{1}H (300 MHz) and ^{13}C (75 MHz) NMR spectra were recorded on a Bruker Avance 300 instrument, and ^{1}H (400 MHz) and ^{13}C (100 MHz) NMR spectra were recorded on a Bruker Avance 400 instrument. Chemical shifts are expressed in δ relative to tetramethylsilane (TMS), and the coupling constant J are given in hertz (Hz). The spectra were recorded in CDCl$_3$ as solvent (δ = 7.28 ppm for ^{1}H, δ = 77.0 ppm for ^{13}C). Chemical shifts within square brackets give the values of amide torsion isomer. The multiplicities of carbon signals were obtained from the distortionless enhancement by polarization transfer (DEPT) 135 experiment. Optical rotations (concentration in grams/100 mL solvent) were measured using sodium D line on ADP220 polarimeter. Infrared (IR) spectra were recorded on a Shimadzu FTIR instrument. High-resolution mass spectrometry (HRMS) was recorded on a MicroMass ES-QTOF. Chiral high-performance liquid chromatographic (HPLC) analysis was executed using a Jasco HPLC model MX-2080-31 instrument. Elemental analysis was done using a CHNS Elementar Vario micro. Optical glass plates from Schott, Germany, and Teflon sheets were used for preparation of polymer molds. Polymerization was carried using a polymerization bath controlled using microprocessor-based electronic temperature controller F25 HP from M/s Julabo, Germany.

General Procedure for Aldol Reaction

Polymer **4** (20 mol% based on benzaldehyde) was added to a stirred solution of anhydrous acetone (3.330 mmol) and benzaldehyde (0.330 mmol) in appropriate solvent (2 mL). The reaction mixture was stirred at room temperature for 24 h, filtered through a sintered glass funnel, and washed with CHCl$_3$ (4 × 15 mL). The catalyst was recovered for reuse. The combined filtrate was dried over anhydrous Na$_2$SO$_4$ and concentrated under reduced pressure, and the residue was purified using flash column chromatography on silica gel (hexanes–EtOAc = 8:2) to give the pure product.

General Procedure for Michael Reaction

Catalyst **4** (30 mol% based on nitrostyrene) was added to a stirred solution of cyclohexanone (3.330 mmol) and nitrostyrene (0.330 mmol) in 2 mL of solvent. The reaction mixture was stirred at rt for 24 h, filtered through a sintered glass, and washed with CHCl$_3$ (3 × 10 mL). The combined filtrate was dried over anhydrous Na$_2$SO$_4$ and concentrated under reduced pressure, and the residue was purified using flash column chromatography on silica gel (hexanes–EtOAc = 8:2) to give the pure product.

SUPPORTING INFORMATION

Full experimental details, ^{1}H and ^{13}C NMR spectra, and high-performance liquid chromatography traces can be found online.

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