

Article

Bioinspired Polymer-Bound Organocatalysts for Direct Asymmetric Aldol Reaction: Experimental and Computational Studies

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Abstract: A series of poly(2-oxazoline) (POX) derivatives bearing prolinamide pendants were designed as organocatalysts and evaluated in the direct asymmetric aldol reaction between aromatic aldehydes and cyclic ketones. The structural variation of the alkyl spacer connecting the polymer backbone with the catalytic unit was applied so as to deduce structure–performance relationships combined with comparable experiments from model catalysts. Results showed that the POX-bound prolinamides can promote the aldol reaction more effectively as compared to their small-molecular and non-POX-bound analogs. The catalyst **P3** containing the pyrrolidine moiety closer to the tertiary amide backbone exhibited the overall best catalytic efficiency, affording *anti*-products in 84% yield with 89% *ee* in the representative aldol addition of cyclohexanone to 4-nitrobenzaldehyde at a 10 mol.% catalyst loading. Furthermore, the influence of trifluoroacetic acid as an additive on the asymmetric transformation was investigated. Theoretical calculations revealed that the protonation of the aldehyde carbonyl group switched the activation mode of the aldol acceptor through hydrogen bond interactions, thereby changing the relative energy barrier of the enamine/aldehyde reaction transition states, which accounted well for the significant improvement in the enantioselectivity of the acidic additives observed experimentally.

Keywords: aldol reaction; organocatalysis; stereoselectivity; acidic additives; DFT calculations

1. Introduction

Since List and co-workers reported asymmetric direct aldol reactions catalyzed by proline [1], immobilization of chiral organocatalysts on polymer matrices has attracted increasing interest in recent decades, owing to the advantages of easy product separation and catalyst recycling, as well as the possibility of mimicking the enzymatic systems [2–5]. However, the preparation of a polymeric analogue for an enzyme is not a simple task. The polymer matrix should be capable of providing a suitable chain architecture to locate the catalytic units for efficient chiral induction. In view of this, among a variety of polymeric catalysts [6–14] for asymmetric organic reactions, the synthetic polypeptides [11–14] show promise as an ideal scaffold to construct artificial enzymes because their structural components are similar to those of biological macromolecules.

In the past decade, poly(2-oxazoline)s (POXs), obtained using cationic ring-opening polymerization of 2-substituted 2-oxazoline monomers, have attracted considerable attention for their potential applications in biomedical areas [15–18]. These polymers are regarded as pseudopeptides, thus bioinspired polymers, due to their structural relation to polypeptides. Based on this unique polymer backbone, as well as a great deal of flexibility in molecular design and synthetic accessibility, we recently

developed a new type of organocatalysts by attaching L-proline to the poly(2-oxazoline) chain through an amide linkage [19]. As a proof of concept, the L-prolinamido-POX (**P1**, Figure 1) has demonstrated its potential to mimic some extent the aldolase biomimetic system. In the aldolisation of cyclic ketones with several aromatic aldehydes, moderate efficiency and high enantioselectivity have been achieved.

To further explore structure–property relationships present in the pseudopeptide-based organocatalysts, in this study we designed additional three analogs, **P2–P4**, as shown in Figure 1. The major difference between these species lies in the spacer length between the catalytic moiety and the polymer backbone. The second chiral subunit in the lateral group was introduced to test for possible effects of various configuration combinations on the stereoselectivity and whether the substituents at the stereogenic center affect the catalyst properties. We also synthesized a non-POX-anchored prolinamide derivative (**P5**) and two small-molecular counterparts (**MC1**, **MC2**) for comparable experiments to ascertain the role of the tertiary amide backbone in the asymmetric aldol reactions. In addition, using density functional methods we investigated the transition states associated with the carbon–carbon bond formation in the reaction with the intention to understand the effects of acidic additives on the stereochemical outcomes. To the best of our knowledge, although the external acid additive has previously been shown to achieve better yield and stereoselectivity for organocatalyzed aldolizations [20–22], the real mechanism has not yet been elucidated.

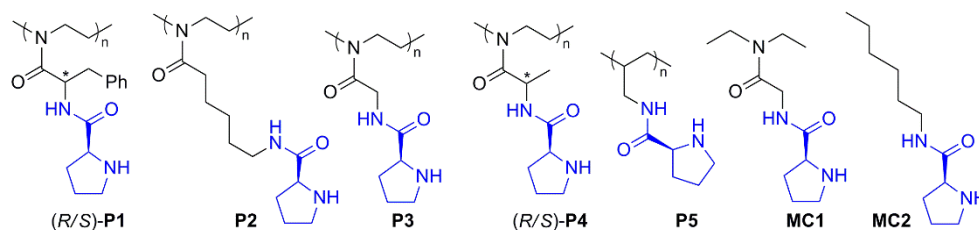
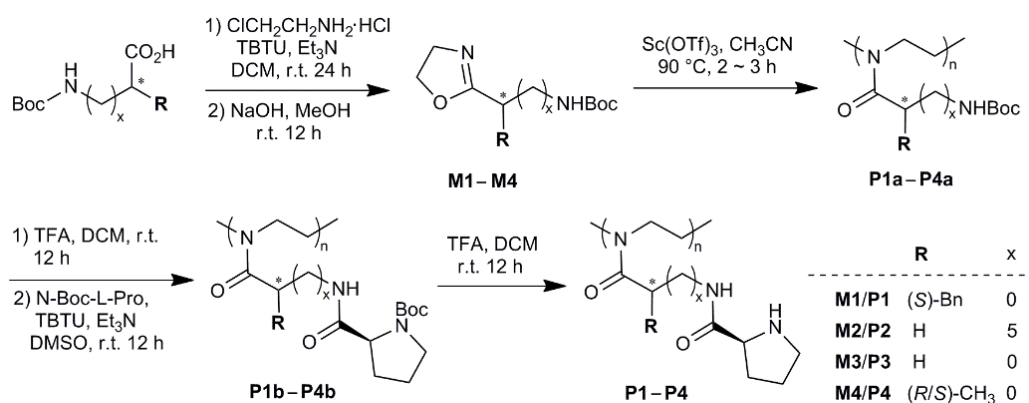


Figure 1. Structures of poly(2-oxazoline)-bound L-prolinamide catalysts (**P1–P4**), prolinamido-poly(allylamine) (**P5**), and small-molecular analogs (**MC1**, **MC2**).

2. Results and Discussion

2.1. Catalyst Synthesis and Structural Characterization

As depicted in Scheme 1, the employed protocol involves the synthesis of 2-oxazoline monomers, ring-opening polymerization, and post-modification of corresponding polymers. Monomers **M1–M3** were prepared readily from Boc-protected amino acids and 2-chloroethylamine *via* two-step reactions with a total yield of 65–80%, according to a generally adapted method [23,24]. (*R/S*)-**M4** were synthesized using a different method, described in the Supplementary Information (Scheme S1; Figures S1–S6).



Scheme 1. Synthesis of L-prolinamido-poly(2-oxazoline) (POXs).

On the basis of our previous work [19,25], the ring-opening polymerization was carried out in acetonitrile using $\text{Sc}(\text{OTf})_3$ as initiator. As evidenced by the linear first-order kinetics and the unimodal molecular-weight distribution for the resulted polymers with PDI values below 1.15 (Figures S7–S10), a good control of the polymerization process was achieved with this system. In all cases, the L-proline residue can be efficiently introduced into the polymer skeleton, with an amide coupling efficiency of the repeating monomeric units more than 95%. For the polymer catalyst **P5** for reference, synthesis began with the amidation of poly(allylamine) with *N*-Boc-L-proline, followed by global deprotection (Scheme S2). The synthesis of small-molecular catalysts **MC1** and **MC2** is similar to that of **P5** except for the use of Boc-amino-acetic acid diethylamide and 1-hexanamine as their respective starting materials. The experimental procedures and structural characterization data are provided in the Supporting Information (Table S1).

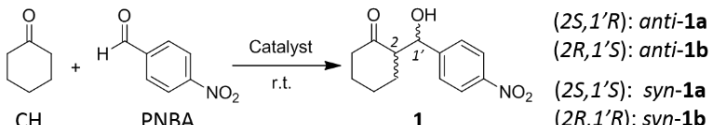
2.2. Evaluation of Catalytic Activity

First, the reaction optimized conditions were screened for the aldol reaction of cyclohexanone (0.4 mL, 14 eq) with 4-nitrobenzaldehyde (40.8 mg, 0.27 mmol, 1 eq) in the presence of **P3** (0.027 mmol, based on the prolinamide content in the polymer; 10 mol.% relative to the aldehyde) using an excess cyclohexanone as solvent (Table S2). As previously noted with **P1** [19], the reaction did not take place in the absence of water. However, the catalysis can be obviously initiated by the addition of some water. Upon introduction of 10 μL of water (accounted for 2.5% of cyclohexanone), the reaction afforded the desired *anti*-aldol products in 45% yield with enantioselectivity of 42% *ee*. It is generally to be understood that the essential role of water is due to significant promotion of the rate-determining proton transfer step since the iminium–enamine catalytic cycle is intrinsically a multiproton transfer process [26,27]. It was also found that trifluoroacetic acid (TFA) as an additive can further improve the catalyst activity and stereoselectivity. Thus, a combination of water (10 μL) with TFA (1.6 μL) led to a large increase in the yield and enantiomeric excess to 86% and 88%, respectively.

Employing the same benchmark test reaction as above, we subsequently evaluated the catalytic properties of various prolinamide derivatives shown in Figure 1. Under identical conditions, i.e., an excess of cyclohexanone as solvent and the catalyst loading of 10 mol.%, POX-bound prolinamides **P1**, **P3**, and **P4** are able to catalyze the aldol reaction more effectively with higher stereoselectivity (yield up to 94%, *anti/syn* up to 84:16, *ee* of the *anti*-isomer up to 91%, entries 1, 2 and 4–6 in Table 1) compared with their monomeric counterpart **MC1** and non-POX-conjugated catalyst **P5** (9–29% yield, 58–68% *ee*; entries 7–8). However, **P2** constitutes an exception to this general trend. With **P2** as a catalyst, almost no reaction occurred (~5% yield, entry 3), and its small-molecular analogue **MC2** led to a low yield but relatively high enantioselectivity (64% *ee*, Table 2, entry 9).

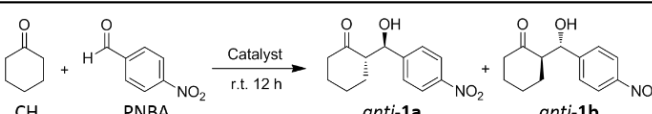
Notably, a comparison of **P3** and **P2**, which differ in the length of the alkyl spacer connecting the polymer backbone with the prolinamide moiety, shows a dramatic difference in catalytic activity (entries 3 vs. 4, Table 1). The former containing a methylene linkage proved to be a highly active catalyst for the aldolization, but the latter, with a longer spacer, afforded only a negligible yield (~5%) in the same reaction even after 48 h. This result is in sharp contrast to what observed for some polymer-supported L-proline catalysts, where they exhibited a poor catalytic proficiency and the variation of spacer length had a little effect on the stereochemical outcomes of the aldol reaction [28]. Based on these observations, we reasoned that the CH_2 linker in **P3** most likely forces both the tertiary amide and L-prolinamide moieties into such a close proximity that they act in concert to form a favorable microenvironment for the asymmetric induction. In other words, the tertiary amide backbone played a type of synergistic effect on the enantioselective transformation.

Table 1. Aldol reaction of cyclohexanone with 4-nitrobenzaldehyde catalyzed by various catalysts ^a.

						
Entry	Catalyst ^b	Loading (mol.%)	Time (h)	Yield (%) ^c	anti/syn ^d	% ee of anti-1 ^e
1 ^f	(R)-P1	10	24	44	80:20	91 (34)
2	(S)-P1	10	24	42	80:20	87 (16)
3	P2	10	48	~5	—	—
4	P3	10	12	86	84:16	88 (33)
5	(R)-P4	10	12	94	75:25	79 (11)
6	(S)-P4	10	12	91	79:21	71 (5)
7	P5	10	12	9	74:26	68 (26)
8	MC1	10	48	29	70:30	58 (6)
9	MC2	10	24	22	74:26	64 (8)
10	P3	5	24	54	82:18	89 (27)
11	P3	5	48	84	85:15	89 (27)

^a Reaction condition: PNBA (40.8 mg, 0.27 mmol, 1 equiv.), CH (0.4 mL, 14 equiv.), water (10 μ L), TFA (1.6 μ L, 0.8 equiv. relative to the catalyst loading). ^b Characterization data are provided in the Supporting Information (Table S1, Figures S11–S14). ^c Isolated yield. ^d Determined by ¹H NMR of the crude product. ^e Determined by chiral-phase HPLC analysis. Data in parenthesis represent % ee for syn-1. The absolute configuration of the aldol products was deduced by comparing the HPLC retention times with reported values (ref. [28,29]; see: Figures S15–S19). ^f Data taken from ref. [19].

Table 2. Effect of trifluoroacetic acid (TFA) on the aldol reaction of cyclohexanone with 4-nitrobenzaldehyde ^a.

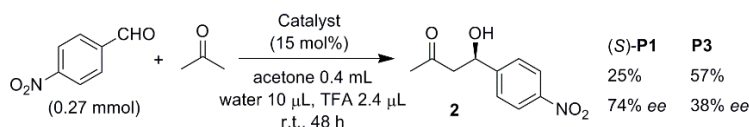
					
Entry	Catalyst (mol.%)	TFA (equiv.)	Yield (%) ^b	<i>anti/syn</i> ^c	% <i>ee</i> of <i>anti</i> -1 ^d
1	P3 (10)	0	40	72:28	42 (5)
2	P3 (10)	0.2	73	77:23	73 (48)
3	P3 (10)	0.4	79	79:21	77 (53)
4	P3 (10)	0.6	85	81:19	80 (38)
5	P3 (10)	0.8	86	84:16	88 (33)
6	P3 (10)	1	33	83:17	88 (39)
7 ^e	P3 (5)	0.8	84	85:15	89 (27)
8 ^e	P3 (5)	1.6	15	79:21	82 (17)
9	P5 (10)	0	77	79:21	47 (28)
10	P5 (10)	0.8	9	74:26	68 (26)

^a Reaction condition: PNBA (40.7 mg, 0.27 mmol, 1 equiv.), CH (0.4 mL, 14 equiv.), the catalyst loading was 10 mol.% or 5 mol.% with respect to PNBA (5.3 mg P3, or 4.2 mg P5), water (10 μ L) and TFA (relative to the catalyst loading).

^b Isolated yield. ^c Determined by ¹H NMR analysis of the crude product. ^d Determined by chiral-phase HPLC analysis. Data in parenthesis represent % ee of syn-1. ^e Reaction time was 48 h.

Contrastingly, the structural change introduced by the substituents at the alkyl spacer has a considerably large degree of influence on the stereochemical outcome. For example, higher enantioselectivity (87–91% ee) but with lower yield (42–45%) were noticed for P1 in comparison to P4 (71–79% ee, 91–94% yield; entries 1–2 vs. 5–6, Table 1). Similarly, for the reaction of acetone (a smaller aldol donor than cyclohexanone) with 4-nitrobenzaldehyde P1 also gave a much higher ee value (74%) and lower yield (25%) than P3 (38% ee, 57% yield), as shown in Scheme 2 (also see: Figures S20–S21). These findings indicated that the benzyl group in the side chain may provide P1 with a rigid environment that preferred the stereocontrol in enamine/aldehyde reaction transition by

steric hindrance, which could also be one of the factors responsible for the observed lower conversion because the bulky substituent prevents the access of substrates.



Scheme 2. Aldol reaction of acetone with 4-nitrobenzaldehyde catalyzed by POX-bound prolinamides.

A closer inspection of Table 1 reveals that there was some difference in the enantioselectivity between (*R*)-P1 and (*S*)-P1 (91% *ee* vs. 87% *ee*), especially for (*R*)-P4 and (*S*)-P4 (79% *ee* vs. 71% *ee*). That is, (*R*)-P1 and (*R*)-P4 offered better stereocontrol compared to their respective quasi-enantiomers (*S*)-P1 and (*S*)-P4 during the present aldol reaction. Such a matching effect of configuration between catalytic unit and chiral linker was also observed in other organocatalytic systems [30]. However, the configuration of the favored stereoisomer of the aldol products is dictated by the stereogenic center of L-prolinamide moiety rather than by that of the linker, as documented by Portnoy et al [31].

Of the synthesized prolinamide derivatives (Figure 1), P3 exhibited the overall best catalytic efficiency for the aldol reaction of cyclohexanone with 4-nitrobenzaldehyde. When reducing the catalyst loading to 5 mol.%, high *anti*-selectivity (85% *de*) and good enantioselectivity (89% *ee*) were still provided for the aldol products in decent yield (84%) despite requiring longer reaction times (Table 1, entries 10, 11). The results are comparable to those of L-prolyl dipeptides (72–98% *de*, 73–93% *ee*) reported in the literature [20,28,29], even superior to some silica- [32] and polystyrene-supported [33] analogs (76–87% *de*, 75–79% *ee*) in the same process.

Table 2 summarizes the influence of TFA additive on the P3-catalyzed aldol reaction in the case of keeping other parameters constant. The data show that the diastereoselectivity ranged from 72% to 84% for the aldol adducts while increasing the amount of TFA from 0 to 1 equiv. relative to the catalyst loading, and the *ee* of *anti*-1 improved from 42% to 88% (entries 1–6, Table 2). The yield reached a maximum (86%) at 0.8 equiv. of TFA addition and then dropped dramatically as more acid was introduced into the system. The decreased yield may be attributed to the hydrolysis of the iminium-ion intermediate in the catalytic cycle caused by excess acid [34] (see Figure S22). A similar trend was observed for P3 at a lower catalyst loading (5 mol.%), and also for P5 (entries 7–10).

2.3. Mechanistic Studies Based on DFT Calculations

Our results, in combination with previous studies in the literature [20–22], showed that addition of acidic additives can markedly promote the aldol reactions. However, this effect has not been well explained theoretically to date. To gain an insight into the specific role of external acids, interactions between the enamine intermediate and the aldehyde acceptor were investigated in the gas phase using density functional methods. In the mechanism hypothesis for pyrrolidine-catalyzed aldol reactions [34] (see Figure S22), the formation of C–C bond *via* the nucleophilic attack of enamine to aldehyde substrate is a stereoselectivity-determining step. Therefore, the favored stereoisomer of the aldol products could be predicted based on the relative energy barrier of the enamine/aldehyde reaction transition states [35–37].

Figures 2 and 3 present the optimized transition states for the aldol reaction of cyclohexanone with 4-nitrobenzaldehyde catalyzed by P3/P5 in the absence and presence of acidic protons, respectively. The relative energy barriers ($\Delta\Delta G$) of the TSs and the corresponding stereoisomers are summarized in Table 3. A survey of data in Table 3 revealed that TS_{a1}, TS_{c1}, TS_{b1} or TS_{d1} has the lowest energy barrier in their respective catalytic systems (entries 1, 5). This suggests both P3 and P5 would preferentially afford *anti*-1a regardless of the presence of acidic additives. The transition state leading to *anti*-1a is more stable than the transition state to *anti*-1b by 1.48 kcal/mol and 1.84 kcal/mol for P1 and P2 catalysis without TFA, respectively (entries 1 vs. 4, 5 vs. 8). In the absence of acidic protons, these prolinamide catalysts rely on hydrogen bonding from the secondary amide NH to activate the aldehyde partner in the transition state, as shown in Figure 2. Judging from the bond length (shown by arrow in

Figure 2), strong amide N–H···O hydrogen bonding between the catalyst and the aldehyde acceptor is primarily responsible for stabilizing the transition state TS_{a1} (or TS_{b1}) compared to TS_{a4} (or TS_{b4}). Thus, the preference for yielding *anti*-**1a** rather than *anti*-**1b** was predicted, which is in good agreement with experimental observations (See: Table 2, Figures S16 and S17).

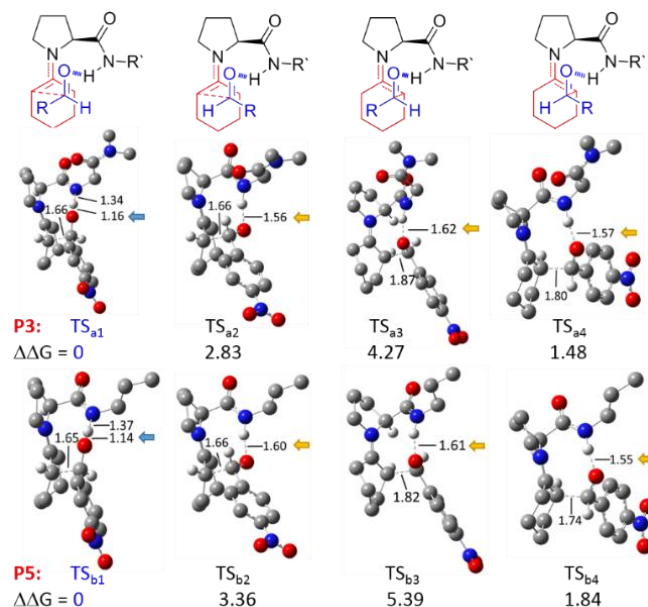


Figure 2. Optimized enamine/aldehyde reaction transition states in the **P3**–**P5**-catalyzed aldol addition of cyclohexanone to 4-nitrobenzaldehyde in the absence of acidic additives. Relative energy barriers (in kcal/mol) and relevant geometric parameters are shown (in Å). Partial hydrogen atoms are hidden for clarity.

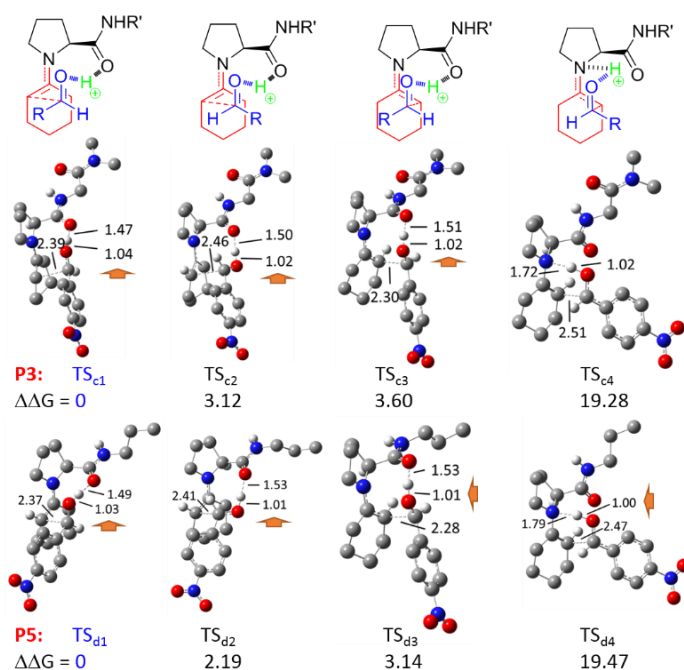


Figure 3. Optimized enamine/aldehyde reaction transition states in the **P3**–**P5**-catalyzed aldol addition of cyclohexanone to 4-nitrobenzaldehyde in the presence of acidic additives. Relative energy barriers (in kcal/mol) and relevant geometric parameters are shown (in Å). Partial hydrogen atoms are hidden for clarity.

Table 3. The calculated relative energy barriers ($\Delta\Delta G$) for the enamine/aldehyde reaction transition states in the aldol reaction of cyclohexanone with 4-nitrobenzaldehyde ^a.

Entry	Catalyst	Without TFA		With TFA		Product ^b
		TS	$\Delta\Delta G$ (kcal/mol)	TS	$\Delta\Delta G$ (kcal/mol)	
1	P3	TS _{a1}	0	TS _{c1}	0	<i>anti</i> - 1a
2		TS _{a2}	2.83	TS _{c2}	3.12	<i>syn</i> - 1a
3		TS _{a3}	4.27	TS _{c3}	3.60	<i>syn</i> - 1b
4		TS _{a4}	1.48	TS _{c4}	19.28	<i>anti</i> - 1b
5	P5	TS _{b1}	0	TS _{d1}	0	<i>anti</i> - 1a
6		TS _{b2}	3.66	TS _{d2}	2.19	<i>syn</i> - 1a
7		TS _{b3}	5.39	TS _{d3}	3.14	<i>syn</i> - 1b
8		TS _{b4}	1.84	TS _{d4}	19.47	<i>anti</i> - 1b

^a The energies of transition states were calculated in the gas phase at b3lyp/6-31g(d,p) level at 293K. ^b See Table 1 for the absolute configuration of products.

For the TFA-assisted **P3**/**P5**-catalyzed aldol reaction, the activation mode of aldehyde acceptor is different from that in the absence of acidic additives. In this case, the carbonyl oxygen atom of the aldehyde acceptor is protonated preferentially (indicated by arrow in Figure 3). In the transition states TS_{c1}–TS_{c3} and TS_{d1}–TS_{d3}, which leading respectively to *anti*-**1a**, *syn*-**1a**, and *syn*-**1b**, a hydrogen bonding network formed by the acidic proton connects the carbonyl oxygen atoms of the acceptor and the prolinamide unit, whereas in TS_{c4} or TS_{d4} for *anti*-**1b**, the proton bridges the aldehyde carbonyl oxygen and the enamine nitrogen atoms. Of these protonated transition states, TS_{c4} and TS_{d4} are unfavored due to nonbonding interactions between the aromatic ring of the acceptor and the amide moiety adjacent to the polymer backbone. Notably, in the TFA-assisted **P3** catalysis the energy difference of transition states for the enantiomer couples *anti*-**1a** and *anti*-**1b** is much greater than that observed for non-acid assisted system when compared pairwise (19.28 vs. 1.48 kcal/mol, entry 4 in Table 3). A similar situation also occurred in the **P5** catalytic system (19.47 vs. 1.84 kcal/mol, entry 8 in Table 3). This provides a rationale for the improvement of enantioselectivity in the aldol reaction by acidic additives (see: Table 2, Figures S18 and S19).

2.4. Substrate Scope of Aldol Reactions and Recycling Experiments

Finally, we examined the applicability of **P3** by the choice of aromatic aldehydes as aldol acceptors to respectively react with cyclohexanone, cyclopentanone, or 4-pyranone. As seen from Table 4, benzaldehydes bearing electron-withdrawing substituents can effectively participate in this reaction, affording *anti*-aldol products in excellent yields with high enantioselectivity, whereas the electron-rich substrates led to poor results. This trend is reasonable, because the aldehyde substrate acts as an electrophile in the reaction. Also, recycling of **P3** was demonstrated for five cycles in which the catalyst was readily isolated by precipitation in ether and reused without further addition of acid to afford reproducible stereoselectivities in the model aldol reaction of cyclohexanone with 4-nitrobenzaldehyde, as shown in Table 5.

Table 4. Aldol reaction of cyclic ketones with aromatic aldehydes catalyzed by **P3** ^a.

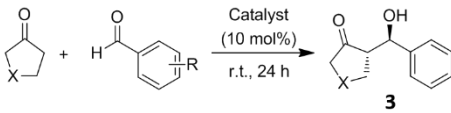
						
Entry	X	R	Product	Yield (%) ^b	<i>syn/anti</i> ^c	<i>ee</i> (%) ^d
1	–CH ₂ CH ₂ –	2-NO ₂	3a	86	15/85	90
2	–CH ₂ CH ₂ –	3-NO ₂	3b	96	18/82	91
3	–CH ₂ CH ₂ –	4-CN	3c	83	30/70	88
4	–CH ₂ CH ₂ –	4-CO ₂ CH ₃	3d	61	13/87	80

Table 4. Cont.

Entry	X	R	Product	Yield (%) ^b	syn/anti ^c	ee (%) ^d
5	–CH ₂ CH ₂ –	H	3e	<5	–	–
6	–CH ₂ CH ₂ –	4-OCH ₃	3f	<5	–	–
7	–CH ₂ O–	4-NO ₂	3g	97	15/85	94
8	–CH ₂ –	4-NO ₂	3h	70	25/75	72

^a Reaction condition: aldehyde (0.27 mmol, 1 equiv.), ketone (0.4 mL), water 10 µL, TFA 1.6 µL. ^b Isolated yield. ^c Determined by ¹H NMR of the crude product. ^d Determined by chiral-phase HPLC analysis for *anti*-product.

Table 5. Recycling **P3** in the aldol reaction of cyclohexanone with 4-nitrobenzaldehyde ^a.

Entry	Cycle	Yield (%) ^b	syn/anti ^c	ee (%) ^d
1	1	86	24:76	88
2	2	85	20:80	90
3	3	85	19:81	91
4	4	82	16:84	89
5	5	79	13:87	92

^a For cycle 1, the reaction condition was the same as depicted in Table 1 entry 4. ^b Isolated yield. ^c Determined by ¹H NMR of the crude product. ^d Determined by chiral-phase HPLC for *anti*-1.

3. Materials and Methods

3.1. Materials

N-Boc-glycine, *N*-Boc-L-alanine, *N*-Boc-L-proline, *O*-(1*H*-benzotriazol-1-yl)-*N,N,N',N'*-tetramethyluroniumtetrafluoroborate (TBTU), trifluoroacetic acid (TFA), and Boc anhydride were purchased from Qiude Chemical Co. (Shanghai, China). 4-Nitrobenzaldehyde (PNBA) was purchased from Acros (Shanghai, China). Poly(allyamine) hydrochloride (*M*_n = 10,000–15,000) was purchased from J&K Chemicals (Beijing, China). Dichloromethane (DCM), triethylamine (Et₃N), acetonitrile (CH₃CN), piperidine, and *N,N*-diisopropyl ethylamine (DIPEA, Acros, Shanghai, China) were distilled CaH₂ prior to use. Scandium triflate [Sc(OTf)₃] was prepared as reported [38] and dehydrated in vacuum at 200 °C for 48 h, then stored under nitrogen. Other chemicals were used as received.

3.2. Characterization

¹H NMR and ¹³C NMR spectra were measured on a Bruker (Karlsruhe, German) Avance DMX-500 spectrometer. Chemical shifts were reported in δ ppm relative to tetramethylsilane (TMS) as an internal standard. Size-exclusion chromatography (SEC) was measured on a Waters–150C (Milford, MA, USA) apparatus equipped with two PL gel 5 µm MIXED-C 300 × 7.5 mm columns and a differential refractometer detector using tetrahydrofuran (THF) as the eluent (flow rate 1 mL/min, 40 °C). The number-average molecular weight (*M*_n) and polydispersity index (PDI) of the polymers were calculated based on a polystyrene calibration. Electrospray ionization mass spectrometry (ESI-MS) measurements were performed on a Varian 500 mass spectrometer (Palo Alto, CA, USA). Chiral high-performance liquid chromatography (HPLC) data were collected on a Chromeleon® (Sunnyvale, CA, USA) apparatus equipped with a Chiralpak AD-H (4.6 mm × 250 mm) column (Shanghai, China) using a solution of *n*-hexane/2-propanol (90/10, *v/v*) as an eluent at a flow rate of 1.0 mL/min.

3.3. Computational Methods

All the transition states (TSs) were optimized by B3LYP/6-31G(d,p) methods. Frequency calculations and intrinsic reaction coordinate (IRC) calculations were conducted to confirm the calculated transition states. Results demonstrated that all TSs have only one imaginary frequency and the pathway for each TS connected the desired products with the reactants. Gibbs free energies

were obtained at 1 atm with the temperature set as 293 K. All calculations were performed using the Gaussian 03 program package [39].

4. Conclusions

In this research, a series of poly(2-oxazoline)s bearing L-proline residues as the pendants through an amide linkage have been synthesized and used as organocatalysts for the aldol reaction of cyclic ketones with aromatic aldehydes. Their catalytic activities were found to be sensitively influenced by the length of the alkyl linker and its substituent. In the representative aldol reaction of cyclohexanone with 4-nitrobenzaldehyde, the POX-bound prolinamide (**P1**) containing a benzyl group on the spacer provided higher enantioselectivity (87–91% *ee*) but lower yield (42–45%) than its analog **P4** with methyl substituent (71–79% *ee*, 91–94% yield). Of the prolinamide catalysts studied, **P3** featuring a short alkyl linker was the best performer, affording *anti*-aldol products with good yield (84%) and stereoselectivity (85:15 *anti:syn* ratio, 89% *ee*) at a 5 mol.% catalyst loading. Introduction of acidic protons has a beneficial to the enhancement of yield and enantioselectivity in the aldol reactions. On the basis of density functional theory calculation, the high reactivity and stereoselectivity could be described to the protonation of aldehyde acceptor as well as activation of the acceptor *via* a hydrogen bonding network with the carbonyl oxygen atom of the prolinamide moieties.

Supplementary Materials: The following are available online at <http://www.mdpi.com/2073-4344/9/5/398/s1>, Scheme S1: Synthesis route of 2-oxazoline monomers, Scheme S2: Synthesis of the reference catalyst **P5**, Table S1: Characterization data of prolinamide catalysts and their precursors, Table S2: Aldol reaction of cyclohexanone with 4-nitrobenzaldehyde catalyzed by **P3** in the presence of different amounts of water, Figure S1: ^1H NMR spectrum of **M2** in CDCl_3 , Figure S2: ^{13}C NMR spectrum of **M2** in CDCl_3 , Figure S3: ^1H NMR spectrum of **M3** in CDCl_3 , Figure S4: ^{13}C NMR spectrum of **M3** in CDCl_3 , Figure S5: ^1H NMR spectrum of (*S*)-**M4** in CDCl_3 , Figure S6: ^{13}C NMR spectrum of (*S*)-**M4** in CDCl_3 , Figure S7: (a) Kinetics plots for polymerizations of **M2** initiated with $\text{Sc}(\text{OTf})_3$ ($[\text{M}]_0/[\text{I}]_0 = 100$) in acetonitrile ($[\text{M}]_0 = 2.0 \text{ M}$) at 90°C . (b) Evolution of the molar mass (M_n) and the PDI value with monomer conversion (determined by SEC, RI detection, PS calibration, using THF as eluent), Figure S8: (a) Kinetics plots for polymerizations of (*S*)-**M4** initiated with $\text{Sc}(\text{OTf})_3$ ($[\text{M}]_0/[\text{I}]_0 = 100$) in acetonitrile ($[\text{M}]_0 = 2.0 \text{ M}$) at 90°C . (b) Evolution of the molar mass (M_n) and the PDI value with monomer conversion (determined by SEC, RI detection, PS calibration, using THF as eluent), Figure S9: GPC traces of **P2a** samples collected periodically from the polymerization kinetic experiments, PS standard, with THF as the eluent, Figure S10: GPC traces of (*S*)-**P4a** samples collected periodically from the polymerization kinetic experiments, PS standard, THF as the eluent, Figure S11: ^1H - and ^{13}C NMR spectra of **MC1** (top) and **MC2** (bottom) in CDCl_3 , Figure S12: ^1H NMR spectrum of **P3** in CDCl_3 (the grafting degree: $h/d \times 100\%$), Figure S13: ^1H NMR spectrum of (*S*)-**P4** in CDCl_3 (the grafting degree: $i/2d \times 100\%$), Figure S14: ^1H NMR spectrum of **P5** in D_2O (the grafting degree: $2e/d \times 100\%$), Figure S15: Determination of the *anti/syn* ratio (*dr*) of the aldol products by ^1H NMR, Figure S16: HPLC chart for the aldol products (Table 2 entry 1). Peaks 1# and 2# are assignable to *syn*-1, peaks 3# and 4# to *anti*-1, Chiralpak AD-H, *n*-hexane/*i*PrOH 1:9, 1.0 mL/min. The absolute configuration of the products was deduced by comparing the HPLC retention times with reported values (ref. 3 and 4), Figure S17: HPLC chart for the aldol products (Table 2 entry 9), Peaks 1# and 2# are assignable to *syn*-1, peaks 3# and 4# to *anti*-1, Chiralpak AD-H, *n*-hexane/*i*PrOH 1:9, 1.0 mL/min, Figure S18: HPLC chart for the aldol products (Table 2 entry 5). Peaks 1# and 2# are assignable to *syn*-1, peaks 3# and 4# to *anti*-1. Chiralpak AD-H, *n*-hexane/*i*PrOH 1:9, 1.0 mL/min, Figure S19: HPLC chart for the aldol products (Table 2 entry 10). Peaks 1# and 2# are assignable to *syn*-1, peaks 3# and 4# to *anti*-1. Chiralpak AD-H, *n*-hexane/*i*PrOH 1:9, 1.0 mL/min, Figure S20: ^1H NMR spectrum of the aldol adduct of acetone to 4-nitrobenzaldehyde, Figure S21: A representative HPLC chart for the aldol products of acetone and 4-nitrobenzaldehyde, Chiralpak AS-H, *n*-hexane/*i*PrOH 1:9, 1 mL/min, Figure S22: Pyrrolidine-catalyzed α -functionalization of aldehydes (Elec = electrophile). The cartesian coordinates of optimal structures in the DFT calculations are also included in the Supporting Information.

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References

1. List, B.; Lerner, R.A.; Barbas, C.F., III. Proline-catalyzed direct asymmetric aldol reactions. *J. Am. Chem. Soc.* **2000**, *122*, 2395–2396. [[CrossRef](#)]
2. Cozzi, F. Immobilization of organic catalysts: When, why, and how. *Adv. Synth. Catal.* **2006**, *348*, 1367–1390. [[CrossRef](#)]
3. Benaglia, M.; Puglisi, A.; Cozzi, F. Polymer-supported organic catalysts. *Chem. Rev.* **2003**, *103*, 3401–3430. [[CrossRef](#)]
4. Yin, Y.; Dong, Z.; Luo, Q.; Liu, J. Biomimetic catalysts designed on macromolecular scaffolds. *Prog. Polym. Sci.* **2012**, *37*, 1476–1509. [[CrossRef](#)]
5. Breslow, R.; Bandyopadhyay, S.; Levine, M.; Zhou, W. Water exclusion and enantioselectivity in catalysis. *ChemBiochem* **2006**, *7*, 1491–1496. [[CrossRef](#)]
6. Font, D.; Sayalero, S.; Bastero, A.; Jimeno, C.; Pericàs, M.A. Toward an artificial aldolase. *Org. Lett.* **2008**, *10*, 337–340. [[CrossRef](#)] [[PubMed](#)]
7. Benaglia, M.; Celentano, G.; Cozzi, F. Enantioselective aldol condensations catalyzed by poly(ethylene glycol)-supported proline. *Adv. Synth. Catal.* **2001**, *343*, 171–173. [[CrossRef](#)]
8. Akagawa, K.; Sakamoto, S.; Kudo, K. Direct asymmetric aldol reaction in aqueous media using polymer-supported peptide. *Tetrahedron Lett.* **2005**, *46*, 8185–8187. [[CrossRef](#)]
9. Tang, Z.; Iida, H.; Hu, H.Y.; Yashima, E. Remarkable enhancement of the enantioselectivity of an organocatalyzed asymmetric Henry reaction assisted by helical poly(phenylacetylene)s bearing cinchona alkaloid pendants via an amide linkage. *ACS Macro Lett.* **2012**, *1*, 261–265. [[CrossRef](#)]
10. Karjalainen, E.; Izquierdo, D.F.; Martí-Centelles, V.; Luis, S.V.; Tenhu, H.; García-Verdugo, E. An enzymatic biomimetic system: Enhancement of catalytic efficiency with new polymeric chiral ionic liquids synthesised by controlled radical polymerization. *Polym. Chem.* **2014**, *5*, 1437–1446. [[CrossRef](#)]
11. Julia, S.; Guixer, J.; Masana, J.; Rocas, J.; Colonna, S.; Annuziata, R.; Molinari, H. Synthetic enzymes part 2: Catalytic asymmetric epoxidation by means of polyamino-acids in a triphase system. *J. Chem. Soc. Perkin Trans. 1* **1982**, 1317–1324. [[CrossRef](#)]
12. Itsuno, S.; Sakakura, M.; Ito, K. Polymer-supported poly(amino acids) as new asymmetric epoxidation catalyst of α,β -unsaturated ketones. *J. Org. Chem.* **1990**, *55*, 6047–6049. [[CrossRef](#)]
13. Davie, E.A.C.; Mennen, S.M.; Xu, Y.; Miller, S.J. Asymmetric catalysis mediated by synthetic peptides. *Chem. Rev.* **2007**, *107*, 5759–5812. [[CrossRef](#)] [[PubMed](#)]
14. Kelly, D.R.; Roberts, S.M. Oligopeptides as catalysts for asymmetric epoxidation. *Pept. Sci.* **2006**, *84*, 74–89. [[CrossRef](#)] [[PubMed](#)]
15. Aoi, K.; Okada, M. Polymerization of oxazolines. *Prog. Polym. Sci.* **1996**, *21*, 151–208. [[CrossRef](#)]
16. Hoogenboom, R. Poly(2-oxazoline)s: A polymer class with numerous potential applications. *Angew. Chem. Int. Ed.* **2009**, *48*, 7978–7994. [[CrossRef](#)] [[PubMed](#)]
17. Schlaad, H.; Diehl, C.; Gress, A.; Meyer, M.; Demirel, A.L.; Nur, Y.; Bertin, A. Poly(2-oxazoline)s as smart bioinspired polymers. *Macromol. Rapid Commun.* **2010**, *31*, 511–525. [[CrossRef](#)] [[PubMed](#)]
18. Hoogenboom, R.; Schlaad, H. Bioinspired poly(2-oxazoline)s. *Polymers* **2011**, *3*, 467–488. [[CrossRef](#)]
19. Wang, Y.; Shen, H.; Zhou, L.; Hu, F.; Xie, S.; Jiang, L. Novel poly(2-oxazoline)s with pendant L-prolinamide moieties as efficient organocatalysts for direct asymmetric aldol reaction. *Catal. Sci. Technol.* **2016**, *6*, 6739–6749. [[CrossRef](#)]
20. Chen, F.; Huang, S.; Zhang, H.; Liu, F.; Peng, Y. Proline-based dipeptides with two amide units as organocatalyst for the asymmetric aldol reaction of cyclohexanone with aldehydes. *Tetrahedron* **2008**, *64*, 9585–9591. [[CrossRef](#)]
21. Miura, T.; Imai, K.; Ina, M.; Tada, N.; Imai, N.; Itoh, A. Direct asymmetric aldol reaction with recyclable fluorous organocatalyst. *Org. Lett.* **2010**, *12*, 1620–1623. [[CrossRef](#)]
22. Fuentes de Arriba, A.L.; Simon, L.; Raposo, C.; Alcazar, V.; Sanz, F.; Muniz, F.M.; Moran, J.R. Imidazolidinone intermediates in prolinamide-catalyzed aldol reactions. *Org. Biomol. Chem.* **2010**, *8*, 2979–2985. [[CrossRef](#)]
23. Kobayashi, S. Ethylenimine polymers. *Prog. Polym. Sci.* **1990**, *15*, 751–823. [[CrossRef](#)]
24. Wenker, H.J. Syntheses from ethanolamine V. synthesis of Δ^2 -oxazoline and of 2,2'- Δ^2 -dioxazoline. *J. Am. Chem. Soc.* **1938**, *60*, 2152–2153. [[CrossRef](#)]

25. Hu, F.; Xie, S.; Jiang, L.; Shen, Z. Living cationic ring-opening polymerization of 2-oxazolines initiated by rare-earth metal triflates. *RSC Adv.* **2014**, *4*, 59917–59926. [[CrossRef](#)]
26. Torii, H.; Nakadai, M.; Ishihara, K.; Susumu, S.; Yamamoto, H. Asymmetric direct aldol reaction assisted by water and a proline-derived tetrazole catalyst. *Angew. Chem. Int. Ed.* **2004**, *43*, 1983–1986. [[CrossRef](#)]
27. Yang, G.; Zhou, L. Mechanisms and reactivity differences of proline-mediated catalysis in water and organic solvents. *Catal. Sci. Technol.* **2016**, *6*, 3378–3385. [[CrossRef](#)]
28. Doyagüez, E.G.; Parra, F.; Corrales, G.; Fernández-Mayoralas, A.; Gallardo, A. New hydroxyproline based methacrylic polybetaines: Synthesis, pH sensitivity and catalytic activity. *Polymer* **2009**, *50*, 4438–4446. [[CrossRef](#)]
29. Lei, M.; Shi, L.; Li, G.; Chen, S.; Fang, W.; Ge, Z.; Cheng, T.; Li, R. Dipeptide-catalyzed direct asymmetric aldol reactions in the presence of water. *Tetrahedron* **2007**, *63*, 7892–7898. [[CrossRef](#)]
30. Haraguchi, N.; Kiyono, H.; Takemura, Y.; Itsuno, S. Design of main-chain polymers of chiral imidazolidinone for asymmetric organocatalysis application. *Chem. Commun.* **2012**, *48*, 4011–4013. [[CrossRef](#)]
31. Tuchman-Shukron, L.; Miller, S.J.; Portnoy, M. Polymer-supported enantioselective bifunctional catalysts for nitro-michael addition of ketones and aldehydes. *Chem. Eur. J.* **2012**, *18*, 2290–2296. [[CrossRef](#)] [[PubMed](#)]
32. Kong, Y.; Tan, R.; Zhao, L.; Yin, D. L-Proline supported on ionic liquid-modified magnetic nanoparticles as a highly efficient and reusable organocatalyst for direct asymmetric aldol reaction in water. *Green Chem.* **2013**, *15*, 2422–2433. [[CrossRef](#)]
33. Gruttadauria, M.; Salvo, A.M.P.; Giacalone, F.; Agrigento, P.; Noto, R. Enhanced activity and stereoselectivity of polystyrene-supported proline-based organic catalysts for direct asymmetric aldol reaction in water. *Eur. J. Org. Chem.* **2009**, 5437–5444. [[CrossRef](#)]
34. Bertelsen, S.; Jorgensen, K.A. Organocatalysis—After the gold rush. *Chem. Soc. Rev.* **2009**, *38*, 2178–2189. [[CrossRef](#)] [[PubMed](#)]
35. Bassan, A.; Zou, W.; Reyes, E.; Himo, F.; Cordova, A. The origin of stereoselectivity in primary amino acid catalyzed intermolecular aldol reactions. *Angew. Chem. Int. Ed.* **2005**, *44*, 7028–7032. [[CrossRef](#)] [[PubMed](#)]
36. Bahmanyar, S.; Houk, K.N. Transition states of amine-catalyzed aldol reactions involving enamine intermediates: Theoretical studies of mechanism, reactivity, and stereoselectivity. *J. Am. Chem. Soc.* **2001**, *123*, 11273–11283. [[CrossRef](#)] [[PubMed](#)]
37. Bahmanyar, S.; Houk, K.N.; Martin, H.J.; List, B. Quantum mechanical predictions of the stereoselectivities of proline-catalyzed asymmetric intermolecular aldol reactions. *J. Am. Chem. Soc.* **2003**, *125*, 2475–2479. [[CrossRef](#)]
38. Kobayashi, S.; Hachiya, I. Lanthanide triflates as water-tolerant lewis acids activation of commercial formaldehyde solution and use in the aldol reaction of silyl enol ethers with aldehydes in aqueous media. *J. Org. Chem.* **1994**, *59*, 3590–3596. [[CrossRef](#)]
39. Frisch, M.J.; Trucks, G.W.; Schlegel, H.B.; Scuseria, G.E.; Robb, M.A.; Cheeseman, J.R.; Montgomery, J.A.; Vreven, T.; Kudin, K.N.; Burant, J.C.; et al. *Gaussian 03, Revision E.01*; Gaussian, Inc.: Wallingford, CT, USA, 2004.



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