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Novel poly(2-oxazoline)s with pendant L-prolinamide moieties as efficient organocatalysts for direct asymmetric aldol reaction

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Abstract:

Poly(2-oxazoline)-supported bifunctional organocatalysts have been prepared through a bottom-up protocol, which involves synthesis of well-defined poly(2-oxazoline) precursors bearing amino groups in the side-chains followed by amide coupling with *N*-Boc-L-proline then deprotection. The resultant L-prolinamido-functionalized polymers have proven to be significantly more active than their monomeric counterpart for the aldolisation of cyclic ketones with several substituted benzaldehydes under neat conditions. By using 15 mol% of the polymer as catalyst, the direct aldol reaction products were isolated in high yields and with good diastereo- and enantioselectivity. Based on the circular dichroism spectrum analysis, the enhancement in catalytic activity is probably related to the conformational changes of the pseudo-peptide scaffold of poly(2-oxazoline)s. In addition, these soluble polymeric catalysts can be recovered and reused by precipitation in ether for five catalytic cycles without significantly diminishing its efficiency.

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Introduction

As interest in asymmetric organocatalysis is on the increase, the immobilization of organic catalysts, especially their polymeric immobilization has also attracted much attention.[1] Undoubtedly, the use of solid supports usually facilitates the isolation of the reaction products, the catalyst recovery and recycling.[2] For polymer-supported chiral organocatalysts, however, the polymer matrix seems to integrate itself as a more natural part of the overall catalytic system, influencing both catalyst activity and stereoselectivity.[3] Unlike what traditionally has been the case, the polymer scaffolds could even enhance catalyst performance by providing a favorable microenvironment around the catalytic active sites as is the case for enzymatic catalysis.[1,3] For example, Pericàs and coworkers constructed an artificial aldolase by bonding proline to polystyrene through a 1,2,3-triazole linker.[3a] The artificial aldolase with the optimum linker shows a high activity and enantioselectivity toward the direct aldol condensation in water. To mimic the property of type I aldolase enzyme, Cozzi et al.[3b] synthesized a soluble polymer-based biomimetic catalyst by anchoring (2*S*, 4*R*)-4-hydroxyproline to the monomethyl ether of PEG5000. Deng's group pioneered in creating artificial enzymes using optically active polyacetylene derivatives as scaffolds.[3c] They found that the helical chirality of the main chain plays a crucial role in the asymmetric aldol reaction of cyclohexanone with 4-nitrobenzaldehyde. Recently, Tenhu and coworkers reported new polymeric chiral ionic liquids prepared by controlled radical polymerization.[3d] The polymeric catalyst is able to promote the consecutive aldol-dehydration process behaving as a synthetic mimic of the

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aldolase-dehydrogenase enzymatic system.

Among the enormous amount of publications on organocatalysts for transformations of carbonyl compounds *via* enamine or iminium activation, the bifunctional aminocatalysts such as prolinamide derivatives are probably a kind of interesting candidate for polymeric immobilization owing to their powerful catalytic capability and stereoselectivity in a wide range of asymmetric bond forming organic reactions.[4] In this regard, Gruttadauria and co-workers conducted thorough investigations.[5] They synthesized a series of polymer-supported prolinamides and dipeptides through the thiol–ene coupling of styrenic derivatives onto the mercapto-functionalized Merrifield resin and subsequent deprotection. It was proven that these polymeric catalysts could give better selectivity compared to their small molecule counterparts, indicating the existence of a cooperative effect between the polymer matrices and catalytic units. Hansen et al.[6] applied an acrylic copolymerization strategy to immobilize L-proline moiety through an ester linkage. The resulted heterogeneous acrylic resins exhibited excellent catalytic properties in water and lead to aldol products in high yields and stereoselectivity. In addition to styrenic and acrylic resins, other types of polymer, such as dendrimer[7] and hyperbranched polymers,[8] were also employed as supports to bind prolinamide-based catalysts for the asymmetric aldol condensation and its variants.

Compared with the post-modification approach based on the commercial resins, the bottom-up methodology is generally more flexible within the design of polymeric catalysts to enable the catalyst loading and swelling characteristics to be tuned easily.

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This synthetic scheme would allow construction of new polymeric architectures for organocatalytic systems when combining with refined synthetic techniques, although such examples have scarcely been reported so far.[3d,6–9] On the other hand, we thought that it is still very interesting to explore different types of polymer scaffolds to link an ever-widening assortment of organocatalysts besides styrenic and acrylic polymers.

Herein, we describe a bottom-up strategy to synthesize novel polymer-bound L-prolinamide catalysts *via* the cationic ring-opening polymerization (CROP) of 2-oxazoline monomers with a protected amine functionality followed by subsequent post-modifications. Notably, poly(2-oxazoline) (POX) was chosen as a scaffold is due to its plenty of chemistry that would offer a great deal of flexibility with respect to the molecular design and polymer synthesis. The CROP of 2-oxazolines usually exhibits controlled/"living" character, which provides ready access to various well-defined POXs, whereby the end-group functionality can be controlled during initiation and termination, and side-chain functionalities can be introduced by the copolymerization with a (protected) functional monomer.[10] More importantly, the pseudo-peptide backbone[10a,b] of POXs is expected to confer a good compatibility on the polymer matrices with the anchored active moieties and thereby to produce a synergistic effect on the outcome of the catalytic transformation. As a proof of concept, we investigated the catalytic performance of the prolinamido-POX derivatives in the asymmetric aldol addition of cyclohexanone to various substituted benzaldehydes and the recyclability. Furthermore, to gain some additional insight into the specific role of the polymer backbone on the catalytic property, the chiroptical properties in solution of the

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polymer catalysts have been examined by circular dichroism and compared with those of the corresponding low molecular weight model compound. To the best of our knowledge, the construction of organocatalytic systems based on poly(2-oxazoline) scaffolds has remained unexplored, although the potential of this kind of polymers in biomedical applications has been reported in the literature.[10b,c]

Results and Discussion

In the present work, we designed a series of poly(2-oxazoline)s bearing L-proline residues as the pendants through an amide linkage. As shown in Fig. 1, an interesting feature of these polymers is the presence of a tertiary amide backbone and a hydrogen-donating prolinamide moiety in the side chains. Introduction of the second chiral subunit in the lateral group was to test for possible effect of the various configuration combinations on the stereoselectivity and whether catalyst activity is affected by the substituents at the stereogenic center.

<Figure 1 here>

Scheme 1 illustrates the employed protocol, which involving synthesis of the monomers (step i–ii), ring-opening polymerization (step iii), and post-modification of the corresponding polymers (step iv–vi). 2-Oxazoline monomers, (*S*/*R*)-PheOX, (*RS*)-PheOX, and (*R*/*S*)-PhgOX, were prepared easily from 2-chloroethylamine and Boc-phenylalanine or Boc-phenylglycine *via* two-step reactions in a total yield of 65~80% according to a general adapted method.[11] The chemical structure of monomers was confirmed by NMR and mass spectral analyses (see Experimental part and the ESI).

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<Scheme 1 here>

Taking the synthesis of (*S*)-PPheOX$_{NHPro}$ as an example, we examined the cationic ring-opening polymerization features of (*S*)-PheOX and the feasibility of post-modification for the resulted polymers. On the basis of our previous work,[12] the polymerization was allowed to conduct in CH_3CN using $Sc(OTf)_3$ as initiator. The data summarized in Table 1 showed that the polymerization leads to the corresponding polymers ((*S*)-PPheOX$_{NHBoc}$) with fairly narrow PDIs (M_w/M_n = 1.21–1.39) when it is carried out at 80–90°C. Performing the polymerization at higher temperature (100°C) or at a higher monomer concentration gave rise to higher yields, albeit with a slightly broad polydispersity in the latter case (entries 3, 5 and 6, 7; Fig. S6). Also observed were increasing the molar ratio of monomer-to-initiator in the range of 60–400 results in an increase in the molar mass of the polymers (entries 1–4).

The polymerization kinetics was studied under the optimized conditions. As can be seen from Figure 2, the polymerization process reveals a first-order kinetic behavior within 3 h and the M_n values increased linearly in proportion to the monomer conversion in the range of 60–95%. The results indicate that a good control of polymerization was achieved with this system, which was also supported by the unimodel molar mass distribution for the resultant polymers. Related SEC analysis data are provided in ESI (Fig. S15–16).

<Table 1 here>

<Figure 2 here>

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The as-synthesized poly(2-oxazoline)s represent an ideal substrate for preparing functional materials since the Boc protecting group can be easily hydrolyzed exposing a pendant amino group that is readily functionalized. To this end, the parent polymers (**POX$_{NHBoc}$**'s) were first deprotected using mildly acidic conditions according to well-established procedures (see Experimental Section). Fig. 3a–b plots as an example the changes in the ^{1}H NMR spectra of (*S*)-PPheOX$_{NHBoc}$ before and after treatment with trifluoroacetic acid (TFA) in CH_2Cl_2 at ambient temperature. We can see that the characteristic signal of the Boc protons (~1.45 ppm) disappeared fully in the spectrum of the deprotected product, and the methine peak labeled "*a*" has now shifted from δ 4.9 to ~4.1 ppm as a result of the removal of Boc groups. The results suggest that the deprotection process is finished almost quantitatively. Moreover, the tertiary amide linkages in the backbone remained intact during the acidic treatment, which could be deduced from the synthesis of the model compound.[13]

Afterwards, the resultant polymer with free amino groups ((*S*)-PPheOX$_{NH2}$) was converted to its L-prolinamide derivative, (*S*)-PPheOX$_{NHProBoc}$, followed by eliminating Boc groups from the proline ring to afford the goal product (*S*)-PPheOX$_{NHPro}$ in ~86% yield. ^{1}H NMR spectroscopic monitoring of the post-modification revealed that new proton signals assignable to the pyrrolidine unit can be observed at 4.10 ppm (*b*) and around 1.5–2 ppm (*c*, *d*) in the spectrum of (*S*)-PPheOX$_{NHProBoc}$ (Fig. 3a and 3b), whereas the signals of another methylene protons labeled "*e*" merged with that of the CH_2 backbone (δ: 2.5–3.5 ppm). At the last step, the hydrolytic detachment of Boc groups was also nearly quantitative.

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Judged from the relative peak integrations, i.e., "*a*" *vs*. "*b*" in Fig. 3c or "*a*" *vs*. "*c* + *d*" in Fig. 3d, the degree of incorporation of L-prolinamide moiety was estimated to be 94%. By using the same route, other **POX$_{NHPro}$**'s were also prepared for comparison and evaluation of the possible presence of structural effects. In all cases, L-proline residue can be efficiently introduced into the POX scaffolds, the amide coupling efficiency of the repeating monomeric units being more than 92% (see: Table 1 and Table S1).

<Figure 3 here>

The presence of a plenty of polar functionalities in the side chains enables **POX$_{NHPro}$** to be easily soluble in the polar solvents including methanol, but it leads to difficulties in the SEC measurements due to their strong interaction with column fillers. Accordingly, their molecular weights were characterized in the protected form (**POX$_{NHProBoc}$**). As shown in Fig. 4 and Fig. S17, SEC analyses of **POX$_{NHProBoc}$** gave unimodal traces with a longer retention time than **POX$_{NHBoc}$**. In fact, **POX$_{NHProBoc}$** has a larger molecular weight when compared to its precursors, as evident from the MALDI-TOF mass spectra (Fig. 5). It can be seen that the spacing between major peaks for (*S*)-PPheOX$_{NHBoc}$ and (*S*)-PPheOX$_{NHProBoc}$ agrees reasonably well with the mass of their respective repeating units (*m/z* 290.4, 387.4). Furthermore, the difference in the *m/z* values for both samples roughly corresponds to the mass of the coupled prolinamide moiety (~97 Da), confirming the near-quantitative attachment of the active group onto each repeat unit (Table 1 and Fig. S9).

<Figure 4 here>

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<Figure 5 here>

To evaluate the catalytic activity of the L-prolinamido-functionalized POXs, the aldolisation of cyclohexanone with 4-nitrobenzaldehyde to give *anti*/*syn* diastereomers of 2-[hydroxyl(4-nitrophenyl)methyl]cyclohexanone was chosen the benchmark reaction as often reported in the literature.[3d,14] Taking (*S*)-PPheOX$_{NHPro}$ as an example, we started the preliminary optimization of reaction conditions focusing on the solvent effect in the presence of an excess of the aldol donor (Table S2, ESI). The results showed that in only water the reaction produced *anti*-aldol in a moderate stereoselectivity (65% ee) at 20 mol% of catalyst loading, and the presence of water as cosolvent is essential to obtain a higher catalytic efficiency. Considering the good solubility of the polymers in cyclohexanone, we decided to perform the aldol reactions under neat conditions, which might be highly desirable because this process is more economic and environment-friendly.

Typically, the bulk reactions were performed in cyclohexanone of 0.516 mL (5 mmol) with 0.05 equivalent of 4-nitrobenzaldehyde (0.25 mmol) at 10°C. As anticipated, a very small amount of water has a significant effect on the catalytic transformation (Table 2). For example, at a catalyst loading of 20 mol% the addition of water (9 μL, ~1.7% relative to cyclohexanone in volume) led to a high conversion of the aldehyde in a shorter time, affording the product with 91% yield and 63% ee (entries 2 vs. 1). When decreasing the catalyst loading to 15 mol%, the highest ee value (78%) was obtained with the amount of water fixed, and the further increase or decrease in water content resulted in a lower enantioselectivity although somewhat

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higher *anti/syn* ratios occurred in some cases (entries 4–6). The accelerating effect of water on both the catalytic rate and/or stereoselectivity has been well documented in many aldolase-type organocatalytic reactions.[4g–h,14–15]

<Table 2 here>

At the same time, we noted that trifluoroacetic acid (TFA) as an additive also exhibited a remarkable acceleration on the aldol reaction (Table 2, entry 7). Further careful optimization revealed that an adequate combination of water (9 μL) with TFA (2 μL, 0.8 equiv. relative to the catalytic unit) can greatly promote the catalytic conversion, leading to the formation of aldol with high *trans*-selectivity (80% de) and good enantioselectivity (91% ee) in 96% yield (Table 2, entries 7–12).[17] Examination of the effect of the reactant ratio on the reaction indicated that 20 equiv of donor cyclohexanone to 1 equiv of the aldehyde gave the best results (entries 10 and 13–15). By holding H_2O/TFA at 9:2 and modulating the temperature from 10°C to 25°C the reaction resulted in an increased diastereoselectivity (88% de) at the cost of a small drop in the ee value to 87% (entry 16). Decreasing or increasing the catalyst loading would deviate from the optimal outcomes in terms of both the selectivity and/or yield (entries 17–18). Also, for the polymer catalysts the variation in the molecular weight (M_n 4 000~10 400) does not seem to have a large influence on the catalytic activity (Table S3).

With the optimal reaction parameters in hand, the further extension of the scope of the aldol reaction was investigated by the choice of aromatic aldehydes as aldol acceptors to react with cyclic ketones using (*S*)-PPheO X_{NHPro} as the catalyst (Table 3).

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When cyclohexanone was used as a pronucleophile, the reaction of benzaldehydes bearing electron-withdrawing substituents, such as nitro, cyano, and methoxycarbonyl, proceeded smoothly to afford the corresponding *anti*-aldol products in excellent yields with high enantioselectivities (entries 1–5, yield 85–96% and ee 79–91%). The aldehyde substituted by a nitro group at the *ortho* position gave a lower ee value (81%) than its *para*-/*meta*-substituted counterparts; however, a higher diastereoselectivity (85:15) was observed in this case (entry 3). For the neutral and electron-rich aromatic aldehydes the poor results were obtained (entries 6–8), giving low yields (< 20%) despite the longer reaction time. Similar phenomena were also observed by other groups, which may be related to the electronic and steric effects of aromatic aldehydes.[18]

Entries 9–10 in Table 3 show that the reaction of 4-nitrobenzaldehyde with 4-pyranone was remarkably fast, providing the corresponding *anti*-aldol product in very high yield and good stereoselectivity even in the absence of acid additive. Interestingly, the aldol reactions using a cyclopentanone donor with the aldehyde led to the preferential formation of *syn*-adducts in excellent yields (entries 11–12). However, the observed ee of the *syn*-aldol leaves much to be desired, reaching only 23–41%. Also, when (*S*)-PPheOX$_{NHPro}$ was used in the aldol reactions of cyclic ketones with aliphatic aldehydes, such as propanal and isobutyraldehyde, under the same conditions, very low conversions (<5%) were recorded after 24 h.

<Table 3 here>

Subsequently, the polymers (*R*)-PPheOX$_{NHPro}$ and (*RS*)-PPheOX$_{NHPro}$ were tested

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as reference catalysts for the standard aldol reaction under the previously optimized conditions. Compared with (*S*)-PPheOX$_{NHPro}$, the former afforded a slightly poorer enantioselectivity (86% ee), whereas the latter led to an ee value identical to and *trans/cis* ratio only 4% higher than those obtained with its (*S*)-counterpart (Table 4, entries 1, 3, and Table 2, entry 10). As was the case for the quasi-enantiomeric pair (*S*)-/(*R*)-PPheOX$_{NHPro}$, two additional polymers (*S*)- and (*R*)-PPhgOX$_{NHPro}$ gave comparable trends with respect to the catalytic activity and stereoselectivity in the aldolisation (Table 4, entries 3–4). In all cases, the configuration of the favored stereoisomer of the aldol adduct was dictated by the chiral center of L-prolinamide moiety, rather than by that of the spacer, as previously reported by Portnoy et al.[20] This indicates that there did not appear to be a clear match/mismatch effect of configuration between the L-proline ring and chiral linker, and the substituents at the linker had a minor influence on the catalytic outcomes only. Nonetheless, these POX-bound L-prolinamides could indeed exhibit a significant improvement in catalytic efficiency as compared to the non-supported compound (*S*)-**M1** (entry 5), implicating the existence of a fortunate symbiosis between the polymer scaffolds and catalytic sites. In terms of the aldol reaction between 4-nitrobenzaldehyde and cyclohexanone, the POX-supported prolinamides as a homogeneous catalyst performed not only comparable to L-prolyl dipeptides described earlier,[16] but also better than some silica-[18b] and PS-supported[5d] analogues under similar reaction conditions.

<Table 4 here>

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It is widely accepted that the aldol reaction of unactivated ketones follow an acid assisted enamine mechanism.[21] For the polymer catalyst under study, however, the catalyst activation observed upon addition of acid additives may be partly associated with the conformational mobility of the polymer chains originating from the reorganization of intra- and intermolecular hydrogen bonding responsive to the solvent environment. To clarify this point, we undertook circular dichroism (CD) titrations with TFA under such conditions almost identical to those for the catalytic reaction. The spectroscopic measurements were performed in the transparent CH_2Cl_2 containing trace amounts of water in an effort to exclude the influence of solvent composition on spectroscopy.

By way of example, the results of CD titration of (*S*)-PPheOX$_{NHPro}$ with TFA are shown in Figure 6. It can be seen that the polymer itself displays an intense CD signal at the positions almost completely corresponding to the UV-vis absorption peaks. Upon addition of TFA, the negative Cotton effect around 222 nm gradually decreases and nearly vanishes when about 0.3 equiv of TFA is added. With the incremental addition of the acid, a positive CD band emerges and finally reaches a maximum upon introduction of 0.8~1.0 equiv of TFA. Similar spectral response was also observed upon titration of (*RS*)-PPheOX$_{NHPro}$ with TFA (Fig. S22). For the model compound (*S*)-**M1**, however, addition of TFA did not lead to a noticeable change in CD spectra as in the case of the polymers (Fig. S23). These observations seem to suggest a close relationship with the outcomes of aldol reaction observed above, where the optimal results in terms of both the yield and enantioselectivity were

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obtained in the presence of catalytic amounts of water and TFA (~0.8 equiv.; in Table 2, entries 10–11). Therefore, we hypothesize that upon complexation with the acidic additives the polymer scaffolds, residing in the proximity of the active site, presumably create an appropriate microenvironment *via* the conformational transition for the hydrogen bond-based asymmetric induction.

<Figure 6 here>

Finally, we investigated re-use of the catalyst (*S*)-PPheOX$_{NHPro}$ in the benchmark reaction in an aqueous medium (MeOH/H_2O) and neat ketone as well. At the end of each reaction cycle, the polymer could be precipitated out by addition of ethyl ether into the reaction mixture followed by centrifugation and reused for next catalytic cycle. As shown in Table 5, the polymer catalyst was used five times with reproducible anti/syn and ee values. However, the activity of the recycled catalyst was somewhat lower than that of the previous one and a ~5% weight loss of catalyst for each recovery was unavoidable.

<Table 5 here>

In conclusion, we developed a class of novel poly(2-oxazoline)-supported L-prolinamide catalysts that are able to imitate to some extent the aldolase biomimetic system. The polymer catalysts proved to be highly efficient for the asymmetric aldolisation of cyclohexanone with several aromatic aldehydes. When the reaction was performed neat using 15 mol% of catalyst loading, the *anti*-aldol products could be obtained in excellent isolated yields with a 95:5 anti/syn ratio and 93% ee in the presence of H_2O/TFA as additive. Moreover, product isolation and catalyst recycling

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can be easily accomplished by precipitation several times without noticeable loss of stereoselectivity. The present work offers proof-of-principle and indicates that high asymmetric induction may be profit from the peculiar pseudo-peptide scaffold of poly(2-oxazoline)s, in which it would provide a suitable chain architecture for locating the chiral catalytic groups.

Experimental

Materials

Boc-L-proline, Boc-L/D-phenylalanine, Boc-L/D-phenylglycine, 2-chloroethylamine hydrochloride, trifluoroacetic acid (TFA), and *O*-(1*H*-benzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium tetrafluoroborate (TBTU) were used as received from Acros. Dichloromethane, triethylamine, acetonitrile and piperidine were distilled from calcium hydride and stored under dry nitrogen atmosphere before use. Scandium triflate [$Sc(OTf)_3$] was prepared as the reported method[22] and used after drying in vacuum at 200°C for 48 h.

Instrumentation

^1H and ^{13}C NMR spectra were recorded on a Bruker Avance III 400 spectrometer with DMSO-d_6 or $CDCl_3$ as solvent. The chemical shifts were reported in ppm relative to tetramethylsilane (TMS) as an internal standard. Size exclusion chromatography (SEC) data were acquired on a Waters−150C apparatus equipped with two PLgel 5 μm MIXED-C (300 mm × 7.5 mm) columns and a differential refractometer detector using tetrahydrofuran (THF) or DMF as the eluent (flow rate 1 mL min^{-1}, 40°C). The number-average molecular weight (M_n) and polydispersity index (PDI) of the

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polymers were calculated on the basis of a polystyrene (PS) or PMMA calibration. MALDI-TOF mass spectra were obtained on a Bruker Ultraflextreme mass spectrometer in the positive reflector mode with an acceleration voltage of 25 kV, using sodium iodide (10 mg mL^{-1} in THF) as ionization salt and dithranol (20 mg mL^{-1} in THF) as matrix. Electrospray ionization-mass spectrometry (ESI-MS) measurements were performed with a Varian 500 mass spectrometer. CD spectra were recorded on a Biologic MOS-450 CD spectropolarimeter (France) at ambient temperature (cell length: 1 cm, scanning speed: 10 nm sec^{-1}). Chiral high-performance liquid chromatography (HPLC) data were collected on a Chromeleon® apparatus equipped with a Chiralpak AD-H (4.6 mm × 250 mm) column using a solution of hexane/2-propanol (90:10, *v/v*) as an eluent at a flow rate of 0.8 mL min^{-1}.

Synthesis of 2-oxazoline monomers (Scheme 1), general procedure

Synthesis of (*S*)-2-(1-Boc-amino-2-phenyl)ethyl-2-oxazoline ((*S*)-PheOX) is described as an example. Boc-L-Phenylalanine (5.3 g, 20 mmol), 2-chloroethylamine hydrochloride (2.55 g, 22 mmol), and *O*-(1*H*-benzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium tetrafluoroborate (TBTU, 7.06 g, 22 mmol) were placed in a 100 mL oven dried 2-neck round bottom flask, followed by adding 50 mL of dichloromethane. To the solution was added dropwise triethylamine of 5.5 mL (40 mmol) at 0°C and then the mixture was allowed to stir for 4 h at ambient temperature under N_2 atmosphere. After removal of solvent under reduced pressure, the resultant residue was purified *via* column chromatography using a 1/2 EtOAc/petroleum ether

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eluent to give the intermediate **1** as a white solid (5.88 g, 90%).

To a solution of NaOH (1.2 g) in methanol (20 mL) was added **1** (3.268 g, 10 mmol) and then the mixture was stirred at 40°C in a N_2 atmosphere. After stirring the mixture for 6 h, the solvent was removed under reduced pressure. The resulted residue was dissolved in 30 mL of dichloromethane (DCM), followed by washing with deionized water (3 × 40 mL). The aqueous phase was extracted with DCM (2 × 20 mL). The collected organic phase was dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The obtained crude product was recrystallized from ethyl acetate to afford (*S*)-PheOX as a white solid in 81% yield (2.35 g).

Other 2-oxazoline monomers, *i.e.*, (*R*)-2-(1-Boc-amino-2-phenyl)ethyl-2-oxazoline ((*R*)-PheOX), (*RS*)-PheOX, (*S*)-2-(1-Boc-amino)benzyl-2-oxazoline ((*S*)-PhgOX), and (*R*)-2-(1-Boc-amino)benzyl-2-oxazoline ((*R*)-PhgOX), were prepared in a similar procedure to that described for (*S*)-PheOX, except for the use of Boc-D-phenyl-alanine, (±)-Boc-phenylalanine, or Boc-L/D-phenylglycine as their respective chiral materials.

Characterization data of monomers

(*S*)-PheOX. White solid; total yield 73%; m.p. = 128.5–129.6°C; $[\alpha]_D^{20}$ = +8° (*c* 0.01, MeOH); ^{1}H NMR ($CDCl_3$, 400 MHz, TMS): δ = 7.38–7.04 (m, 5H), 5.10 (d, J = 7.4 Hz, 1H), 4.67 (d, J = 6.6 Hz, 1H), 4.38–4.18 (m, 2H), 3.92–3.66 (m, 2H), 3.28–2.90 (m, 2H), 1.41 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 167.09, 154.9, 136.31, 129.50, 128.30, 126.79, 79.66, 68.11, 54.09, 49.74, 38.78, 28.31 ppm. MS (ESI+): *m/z*

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(%) = 290.9 (8.8) $[M + H]^+$, 312.9 (10) $[M + Na]^+$, 602.9 (100) $[2M + Na]^+$.

(*R*)-PheOX. White solid; total yield 80%; m.p. = 128.1–128.9°C; $[\alpha]_D^{20}$ = –8° (*c* 0.01, MeOH); ^{1}H NMR ($CDCl_3$, 400 MHz, TMS): δ = 7.35–7.09 (m, 5H), 5.11 (d, *J* = 7.6 Hz, 1H), 4.67 (d, *J* = 6.8 Hz, 1H), 4.37–4.23 (m, 2H), 3.88–3.68 (m, 2H), 3.09 (dd, *J* = 48.7, 13.7, 5.7 Hz, 2H), 1.41 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 167.10, 154.95, 136.31, 129.50, 128.30, 126.78, 79.65, 77.04, 76.72, 68.11, 54.08, 49.73, 38.76, 28.30 ppm. MS (ESI+): *m/z* (%) = 291.2 (100) $[M + H]^+$, 313.1 (51) $[M + Na]^+$.

(*RS*)-PheOX. White solid; total yield 82 %; m.p. = 127.81–28.6°C; ^{1}H NMR ($CDCl_3$, 400 MHz, TMS): δ = 7.43–7.07 (m, 5H), 5.15 (d, *J* = 7.9 Hz, 1H), 4.80–4.57 (m, 1H), 4.42–4.18 (m, 2H), 3.97–3.62 (m, 2H), 3.28–2.93 (m, 2H), 1.39 (d, *J* = 15.6 Hz, 9H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 167.11 , 154.98 , 136.32, 129.51, 128.31, 126.80, 79.65, 77.40, 77.08, 76.76, 68.13, 54.09, 49.74, 38.76, 28.32 ppm. MS (ESI+): *m/z* (%) = 291.2 (56) $[M + H]^+$, 603.2 (100) $[2M + Na]^+$.

(*S*)-PhgOX. Solid; m.p. = 112.5–113.4°C; $[\alpha]_D^{20}$ = +6° (*c* 0.01, MeOH); ^{1}H NMR ($CDCl_3$, 400 MHz, TMS): δ = 7.44–7.27 (m, 5H), 5.78 (s, 1H), 5.42 (d, *J* = 7.3 Hz, 1H), 4.28 (dq, *J* = 17.8, 8.6 Hz, 2H), 3.94–3.81 (m, 2H), 1.48–1.29 (m, 9H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 166.99, 154.74, 138.20, 128.74, 128.17, 127.00, 79.93, 76.72, 68.50, 54.00, 52.91, 28.31 ppm. MS (ESI+): *m/z* (%) = 299.1 (23) $[M + Na]^+$, 575.0 (100) $[2M + Na]^+$.

(*R*)-PhgOX. Solid; m.p. = 112.3–113.1°C, $[\alpha]_D^{20}$ = –6° (*c* 0.01, MeOH); ^{1}H NMR ($CDCl_3$, 400 MHz, TMS): δ = 7.51–7.27 (m, 5H), 5.71 (d, *J* = 5.32 Hz, 1H), 5.42 (d, *J*

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= 7.3 Hz, 1H), 4.46–4.09 (m, 2H), 3.98–3.73 (m, 2H), 1.37 (d, J = 41.0 Hz, 9H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 166.99, 154.73, 138.20, 128.73, 128.17, 127.00, 79.92, 77.04 (s), 76.73, 68.50, 54.00, 52.91, 28.31 ppm. MS (ESI+): m/z (%) = 299.1 (30) [M + Na]$^+$, 575.0 (100) [2M + Na]$^+$.

Synthesis of the model compound (*S*)-M1 (Scheme 2)

Boc-L-Phenylalanine (2.65 g, 10 mmol), TBTU (3.852 g, 12 mmol) were dissolved in CH_2Cl_2 of 50 mL, followed by adding diethylamine (3.1 g, 30 mmol) with stirring at ambient temperature in a nitrogen atmosphere. The resultant mixture was allowed to stir for 12 h and then washed with deionized water (3 × 40 mL), and the layers were separated. The aqueous layer was extracted several times with CH_2Cl_2, and the combined organic layers were dried (anhydrous $MgSO_4$), filtered, and concentrated under reduced pressure. The resulted residue was chromatographed over silica gel with 1/3 EtOAc/petroleum ether eluent to produce **3** (4.59 g, 70%) as a powder matter.

To a solution of **3** (3 g) in 15 mL CH_2Cl_2 was added TFA (15 mL) and then the mixture was stirred at room temperature for 4 h. The solvent was removed under reduced pressure, the residue was dissolved in CH_2Cl_2 (25 mL) and the resultant solution was successively washed by a saturated sodium bicarbonate aqueous solution and water. The organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give **4** as a pale-yellow liquid in 83% yield.

TBTU (6.42 g, 20 mmol), Boc-L-proline (4.3 g, 20 mmol), and **4** (3.6 g, 16.7 mmol) were dissolved in CH_2Cl_2 (50 mL), and then to the resultant mixture was added

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triethylamine (4.8 mL, 33 mmol) with stirring at 0°C. After stirring at room temperature for 12 h, the reaction mixture was washed by saturated aq. $NaHCO_3$ (3 × 60 mL). The aqueous layer was extracted several times with dichloromethane, and the combined organic layers were dried (anhydrous Na_2SO_4), filtered, and concentrated under reduced pressure to afford **5** as a white solid (72%). To obtain the unprotected model compound (*S*)-**M1**, **5** was treated with TFA/CH_2Cl_2 (2:3) solution for 6 h at room temperature. Then CH_2Cl_2 was added to the reaction mixture, the resulting solution was washed three times with saturated sodium bicarbonate solution. The organic extracts were dried (Na_2SO_4) and the solvent were evaporated under vacuum to give (2*S*)-2-L-prolinamido-3-phenyl-*N,N*-diethylpropanamide as a waxy solid ((*S*)-**M1**, yield 70%). $[\alpha]_D^{20}$ = +34° (*c* 0.01g/mL, CH_3OH); ^{1}H NMR ($CDCl_3$, 400 MHz, TMS): δ = 8.11 (d, *J* = 8.8 Hz, 1H), 7.30–7.03 (m, 5H), 4.97 (dd, *J* = 15.8, 8.0 Hz, 1H), 3.64 (dd, *J* = 9.2, 5.1 Hz, 1H), 3.47 (dq, *J* = 14.2, 7.2 Hz, 1H), 3.11–2.74 (m, 7H), 2.06–1.89 (m, 3H), 1.67 (tt, *J* = 9.0, 4.7 Hz, 1H), 1.04–0.91 (m, 6H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 173.14, 169.59, 135.48, 128.52, 127.31, 125.84, 76.33, 76.02, 75.70, 59.32, 48.39, 46.14, 40.70, 39.48, 38.81, 29.66, 24.96, 13.21 ppm. MS (ESI+): *m*/*z* (%) = 318 (66) $[M + H]^+$, 635 (100) $[2M + H]^+$, 657 (79) $[2M + Na]^+$.

<Scheme 2 here>

Synthesis of poly(2-oxazoline)-bound L-prolinamide catalysts (POX_{NHPro})

The preparation of polymer catalysts includes the polymerization of 2-oxazolines and post-modification of the corresponding polymers. Taking the synthesis of (*S*)-$PPheOX_{NHPro}$ as an example, a typical experimental procedure is as follows. To a

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flame-dried Schlenk tube (*S*)-PheOX (1.00 g, 3.45 mmol), 0.8 mL of a solution of $Sc(OTf)_3$ in acetonitrile (4.18×10^{-2} M) and additional solvent (0.925 mL) were successively added under N_2 atmosphere. After being heated at 90°C for a definite period of time with magnetic stirring, the reaction was quenched by the addition of deionized water. The resulting mixture was left to stir at ambient temperature for 1 h and the crude product was precipitated out by the addition of Et_2O. To completely remove the catalyst residue and unreacted monomer, the collected powder matter was redissolved in CH_3CN and then precipitated again from Et_2O. This process was repeated three times to give the desired product (*S*)-PPheOX$_{NHBoc}$ (0.896 g, yield 90%).

The obtained polymer (1.0 g) was treated with a 1:1 TFA/CH_2Cl_2 solution (10 mL) for 12 h at room temperature. After evaporation of the solvent and addition of MeOH (10 mL) and saturated aq. $NaHCO_3$ (~2 mL) the product was dialyzed against water using 1 kDa cut-off tubes, and it was finally freeze-dried to yield the deprotected polymer (*S*)-PPheOX$_{NH2}$ (quantitative). The intermediate (1 g) was dissolved in DMSO (~2 mL) and to the resulting solution was added Boc-L-proline (0.88 g, 4 mmol), TBTU (1.3 g, 4 mmol), and Et_3N (0.97 mL, 6.67 mmol) in turn. The mixture was allowed to react for 24 h at room temperature and mixed with water of ~15 mL. Then, the mixture was extracted with CH_2Cl_2 (3 × 5 mL), dried ($MgSO_4$), filtered, and concentrated. The residue was subject to the deprotection and dialysis purification in a similar way to that described for (*S*)-PPheOX$_{NH2}$, affording the target product (*S*)-PPheOX$_{NHPro}$ (yield 98%).

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General procedure for the direct asymmetric aldol reaction

The selected catalyst (15 mol %, based on the repeating unit in the polymer), aldehyde (0.25 mmol), cyclohexanone (0.526 mL, 5 mmol) and an appropriate amount of additives were added in a 10 mL round-bottom flask in turn under an atmosphere of air. The reaction mixture was stirred at ambient temperature (10~25°C) in a closed system for an appropriate time until the reaction was complete, as monitored by TLC. Then, to the mixture was added saturated ammonium chloride solution (~2 mL) and extracted with ethyl acetate (3 × 5 mL). The combined organic layer was dried anhydrous $MgSO_4$, filtered, and concentrated. The residue was purified by flash column chromatography on silica (*n*-hexane/EtOAc = 4:1) to obtain the aldol product as mixtures of *anti* and *syn* diastereomers. The diastereomeric ratio was determined by ^1H NMR spectroscopy on the crude samples. The enantiomeric excess was determined by HPLC on a chiral stationary phase (1:5 EtOAc/petroleum ether eluent).

The recyclability of the polymer catalyst

After carrying out the reaction, the mixture was poured into ethyl ether (~10 mL) followed by centrifugation to separate the polymer. After washing with Et_2O and drying, the catalyst can be reused directly without further purification.

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Captions:

Figure 1 The structural feature of POX-bound L-prolinamide catalysts (collectively referred to as **POX$_{NHPro}$**) and a monomeric counterpart (*S*)-**M1** in this study.

Scheme 1 Synthetic route for the preparation of polymer-supported organocatalysts using enantiopure, racemic Boc-phenylalanine or Boc-phenylglycine as starting materials. (i) $ClCH_2CH_2NH_2 \cdot HCl$, TBTU, Et_3N, 0°C~r.t. (ii) NaOH, CH_3OH, 40°C. (iii) $Sc(OTf)_3$, CH_3CN, 90°C. (iv) TFA, CH_2Cl_2, r.t. (v) Boc-L-proline, TBTU, Et_3N, DMSO, r.t. (vi) TFA, CH_2Cl_2, r.t.

Figure 2 (a) Kinetic plots for the cationic ring-opening polymerization of (*S*)-PheOX using $Sc(OTf)_3$ as initiator in acetonitrile at 90°C. $[M]_0/[I]_0 = 100$, $[M]_0 = 2$ M. (b) Evolution of the molar mass (M_n) and the PDI values with the monomer conversion (determined by SEC, PS calibration, THF as the eluent).

Figure 3 ^{1}H NMR spectra of (a) (*S*)-PPheOX$_{NHBoc}$ ($CDCl_3$), (b) (*S*)-PPheOX$_{NH2}$ (DMSO-d_6), (c) (*S*)-PPheOX$_{NHProBoc}$ (DMSO-d_6), and (d) (*S*)-PPheOX$_{NHPro}$ ($CDCl_3$).

Figure 4 Typical SEC traces of (*S*)-PPheOX$_{NHBoc}$ (blue) and (*S*)-PPheOX$_{NHProBoc}$ (red) showing a longer retention time for the latter (the molecular weight values are based on calibration against PMMA in DMF with 50 mM LiBr; see: Table 1, entry 1).

Figure 5 Typical MALDI-TOF mass spectra of (A) (*S*)-PPheOX$_{NHBoc}$ ($M_{n,SEC}$ = 5 500, PDI = 1.21) and (B) (*S*)-PPheOX$_{NHProBoc}$ ($M_{n,SEC}$ = 4 100, PDI = 1.20). See: Fig. 4.

Figure 6 CD spectral evolution of (*S*)-PPheOX$_{NHPro}$ (10^{-3} M) upon addition of TFA (0 ~ 1 equiv., relative to the active units in the catalyst) in CH_2Cl_2 containing ~1% water at 25°C.

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Scheme 2 Synthesis of model compound (*S*)-**M1**. (i) L-Boc-Phe-OH (10 mmol), TBTU (12 mmol), Et_2NH (30 mmol), CH_2Cl_2 ~50 mL, r.t., N_2 atmosphere; (ii) TFA/CH_2Cl_2 (1:1), r.t., 4 h; (iii) **4** (16.7 mmol), Boc-L-proline (20 mmol), TBTU, Et_3N, (iv) TFA/CH_2Cl_2 (2:3), r.t., 6 h.

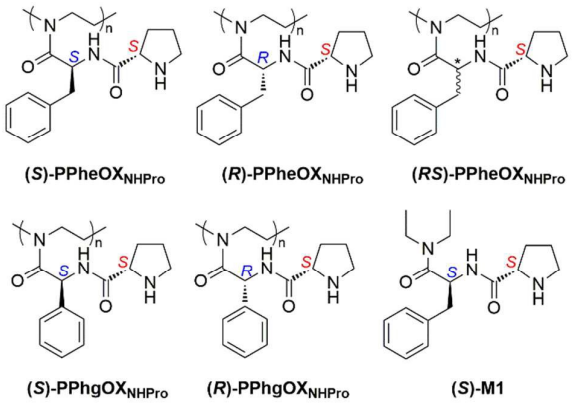
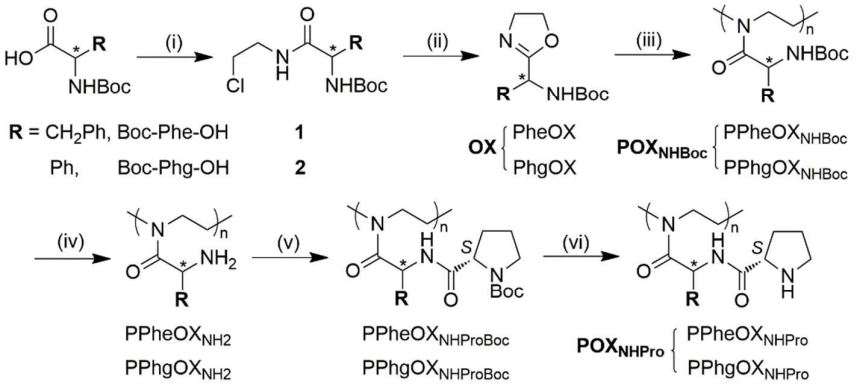


Figure 1



Scheme 1

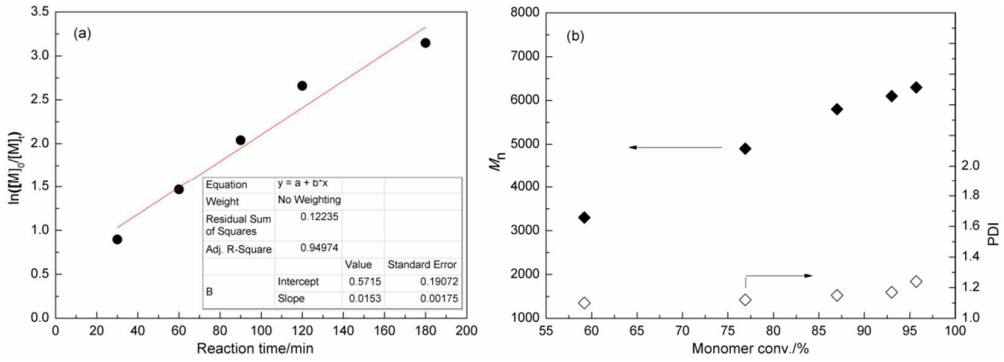


Figure 2

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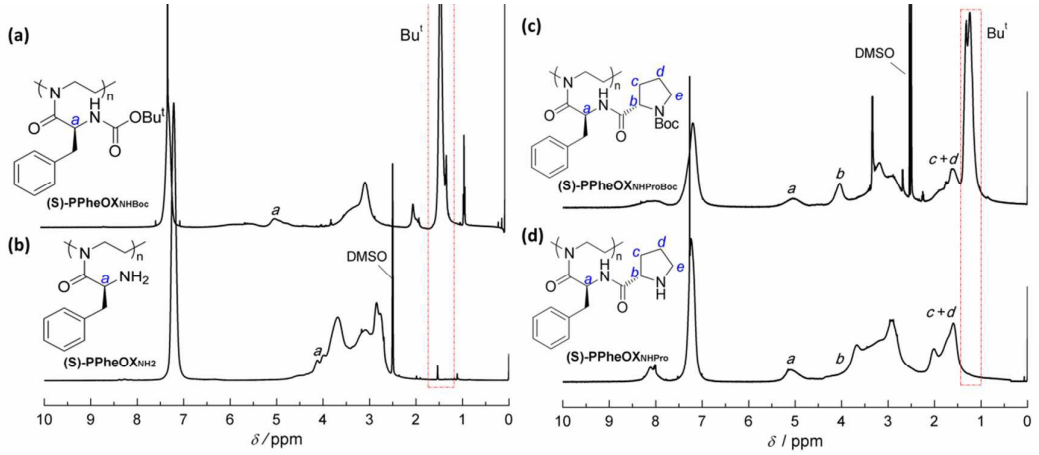

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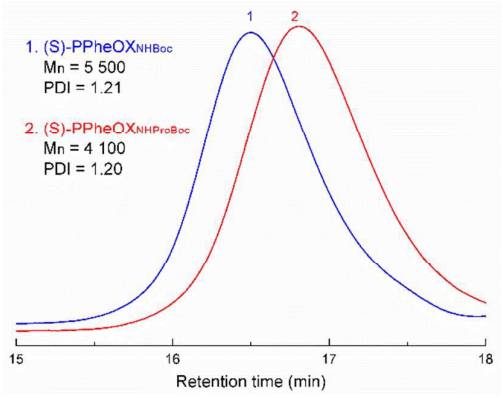

Figure 4

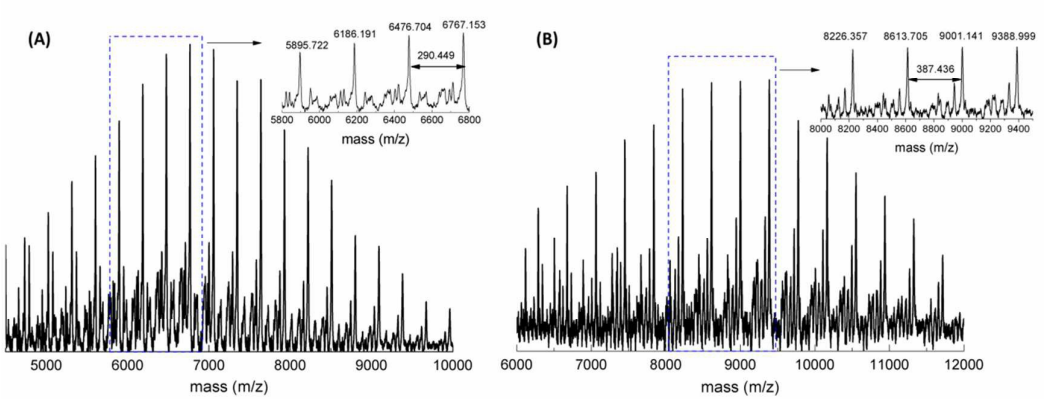

Figure 5

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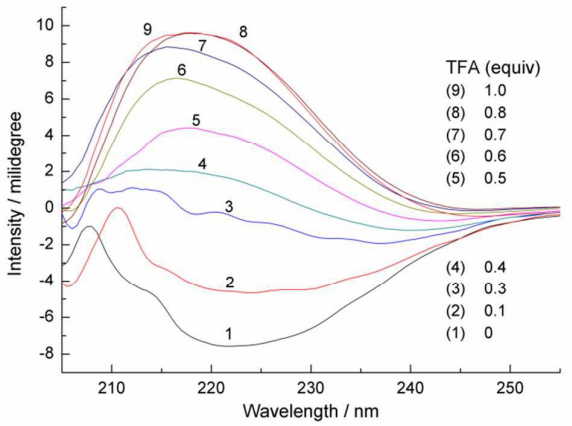
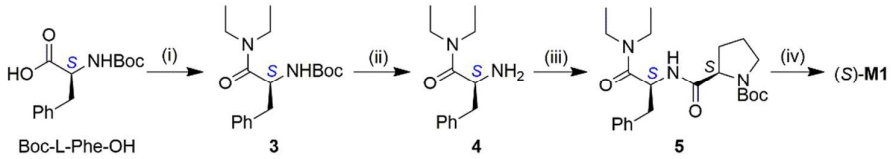


Figure 6



Scheme 2

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Table 1 Results on the polymerization of (*S*)-PheOX with $Sc(OTf)_3$ as initiator and post-modification for the resulting polymers [a]

Entry	[M]/[I]	T/°C	(*S*)-PPheOX$_{NHBoc}$			(*S*)-PPheOX$_{NHPro}$			
			Yield (%)[b]	M_n[c] (10^3)	PDI[c]	M_n[d] (10^3)	PDI[d]	E_{NHPro}[e] (%)	$[\alpha]_D^{20}$[f]
1	60	90	95	5.5	1.21	4.1	1.20	94	–24
2	100	90	90	7.5	1.28	5.8	1.28	98	–25
3	200	90	77	10.2	1.31	7.6	1.32	96	–27
4	400	90	59	10.5	1.36	8.0	1.37	93	–26
5[g]	200	90	82	11.2	1.39	8.6	1.41	92	–27
6	100	100	96	7.9	1.32	–	–	–	–
7	100	80	63	5.9	1.20	–	–	–	–

[a] Polymerization conditions: [M] = 2 mol L^{-1}, CH_3CN, 90°C, 3 h. [b] Isolated yield. [c] Determined by SEC measurements, PMMA calibration, DMF with 50 mM LiBr as the eluent. [f] c = 10 mg mL^{-1}, MeOH. [d] Determined by SEC in the protected form (i.e., (*S*)-PPheOX$_{NHProBoc}$), PMMA calibration, DMF with 50 mM LiBr as the eluent. [e] Amide coupling efficiency of repeating monomeric units was measured by ^1H NMR integration ($CDCl_3$). [g] [M] = 3 M.

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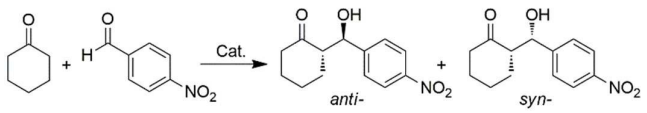
Table 2 The aldol reaction of cyclohexanone with 4-nitrobenzaldehyde at neat conditions catalyzed by (*S*)-PPheOX$_{NHPro}$[a]



Entry	Loading[b] (mol%)	CHO/*p*-NBA[c]	H_2O/TFA (μL)	Time[d] (h)	Yield[e] (%)	anti:syn[f]	ee[g]
1	20	20	–	48	<5	–	–
2	20	20	9:0	12	91	86:14	63
3	15	20	9:0	12	86	71:29	78
4	15	20	4.5:0	24	80	90:10	62
5	15	20	25:0	12	89	70:30	70
6	15	20	50:0	12	87	81:19	73
7	15	20	0:1.5	24	96	72:28	60
8	15	20	9:0.75	12	97	72:28	75
9	15	20	9:1.5	12	98	75:25	87
10	15	20	9:2	12	96	80:20	91
11	15	20	9:2.6	24	97	71:29	93
12	15	20	9:3.1	24	37	86:14	83
13	15	15	9:2	12	93	75:25	88
14	15	10	9:2	12	85	70:30	87
15	15	5	9:2	12	86	60:40	77
16[h]	15	20	9:2	12	99	88:12	87
17	10	20	9:2	24	42	80:20	87
18	20	20	9:2	12	98	71:29	84

[a] The polymer catalyst had a number average molecular weight (M_n) of 6 700 (PDI = 1.12). [b] Relative to 4-nitrobenzaldehyde, in monomeric units. [c] Cyclohexanone/4-nitrobenzaldehyde molar ratio. [d] Monitored by TLC. [e] Combined yield of the isolated diastereomers. [f] By ^{1}H NMR spectroscopic analysis of the crude product. [g] Determined by chiral HPLC analysis of the *anti* product. [h] Reaction temperature = 25°C. The absolute configurations of the aldol products were deduced by comparing the HPLC retention times with reported values (ref 16, also see: Fig. S19).

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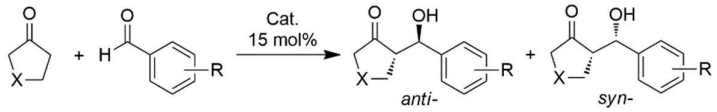
Table 3 Substrate scope of direct asymmetric aldol reactions catalyzed by (*S*)-PPheO X_{NHPro} [a]



Entry	R	X	Yield[b] (%)	anti/syn[c]	ee[d] (%)
1	4-NO_2	–CH_2CH_2–	96	80:20	91
2	3-NO_2	–CH_2CH_2–	92	72:28	90
3	2-NO_2	–CH_2CH_2–	93	85:15	81
4	4-CN	–CH_2CH_2–	91	75:25	83
5	4-CO_2CH_3	–CH_2CH_2–	85	76:24	79
6[e]	4-Br	–CH_2CH_2–	20	66:34	60
7[e]	4-CH_3	–CH_2CH_2–	<5	–	–
8[e]	H	–CH_2CH_2–	<5	–	–
9	4-NO_2	–CH_2O–	99	87:13[f]	82
10[g]	4-NO_2	–CH_2O–	97	73:27	80
11	4-NO_2	–CH_2–	91	42:58[f]	41[h]
12[g]	4-NO_2	–CH_2–	96	28:72	23[h]

[a] Reactions were performed at 15 mol% of catalyst loading in the presence of H_2O/TFA (9:2, μL), 12 h, other parameters are the same as those gave in Table 2. [b] Combined yield of the isolated diastereomers. [c] Determined by ^1H NMR. [d] Determined by chiral HPLC analysis of the *anti* product. [e] Reaction time = 48 h. [f] The absolute configurations of the aldol products were deduced by comparing the HPLC retention times with reported values (ref. 4g and 19, also see: Fig. S20–21). [g] In water (0.5 mL) without additional TFA. [h] Determined by chiral HPLC analysis of the *syn* product.

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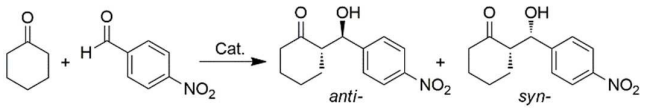
Table 4 Aldol reaction of cyclohexanone with 4-nitrobenzaldehyde by various catalysts under neat conditions[a]



Entry	Polymer catalysts (M_n, PDI)[b]	H_2O/TFA (μL)	Time[c] (h)	Yield[d] (%)	anti:syn[e]	ee[f]
1	(*R*)-PPheOX$_{NHPro}$	9:2	12	96	80:20	86
	(5 700, 1.28)	9:2.6	24	64	79:21	88
2	(*RS*)-PPheOX$_{NHPro}$	9:2	12	98	82:18	91
	(5 000, 1.25)	9:2.6	24	60	77:23	91
3	(*S*)-PPhgOX$_{NHPro}$	9:2	12	99	77:23	89
	(4 300, 1.29)	9:2.6	24	65	78:22	91
4	(*R*)-PPhgOX$_{NHPro}$	9:2	12	97	81:19	87
	(4 400, 1.25)	9:2.6	24	68	79:21	89
5	(*S*)-**M1**	9:2	12	80	63:37	60
		9:2.6	24	60	60:40	44

[a] Reaction conditions are the same as those described in Table 2. [b] Determined by SEC in its Boc-protected form. [c] Catalyst loading 15 mol%, relative to 4-nitrobenzaldehyde. [d] Monitored by TLC. [e] Combined yield of the isolated diastereomers. [f] Determined by ^{1}H NMR spectroscopic analysis of the crude product. [f] Determined by chiral-phase HPLC analysis of the *anti* product.

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Table 5 Recycling of (*S*)-PPheOX$_{NHPro}$ in the aldol reaction between cyclohexanone and 4-nitrobenzaldehye [a]

Entry[b]	Cycle	Yield[c] (%)	anti/syn[d]	ee[e] (%)
1	1	92	85:15	81
2	2	89	76:24	80
3	3	88	75:25	78
4	4	84	86:14	80
5	5	79	77:23	78
6	1	96	84:16	90
7	2	88	88:12	89
8	3	85	90:10	90
9	4	81	84:16	91
10	5	70	90:10	91

[a] Reaction was performed under the optimized conditions as shown in Table 2 (entry 10). [b] Entries 1–5, CH_3OH/H_2O (1:1) of 1 mL was used as reaction medium without TFA as additive, while for entries 6–10 the reaction was carried out in neat cyclohexanone (0.516 mL) in the presence of H_2O (9 μL) and TFA (2 μL) for the first cycle. The amount of reagents was calculated on the basis of the amount of recovered catalyst for successive cycles. [c] Combined yield of the isolated diastereoisomers. [d] Determined by ^1H NMR spectroscopy of the crude product. [e] Determined by chiral-phase HPLC analysis of the *anti* product.

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Graphical abstract:

A novel poly(2-oxazoline)-bound L-prolinamides has been developed as an aldolase biomimetic system for the direct aldol reaction with high stereoselectivity.