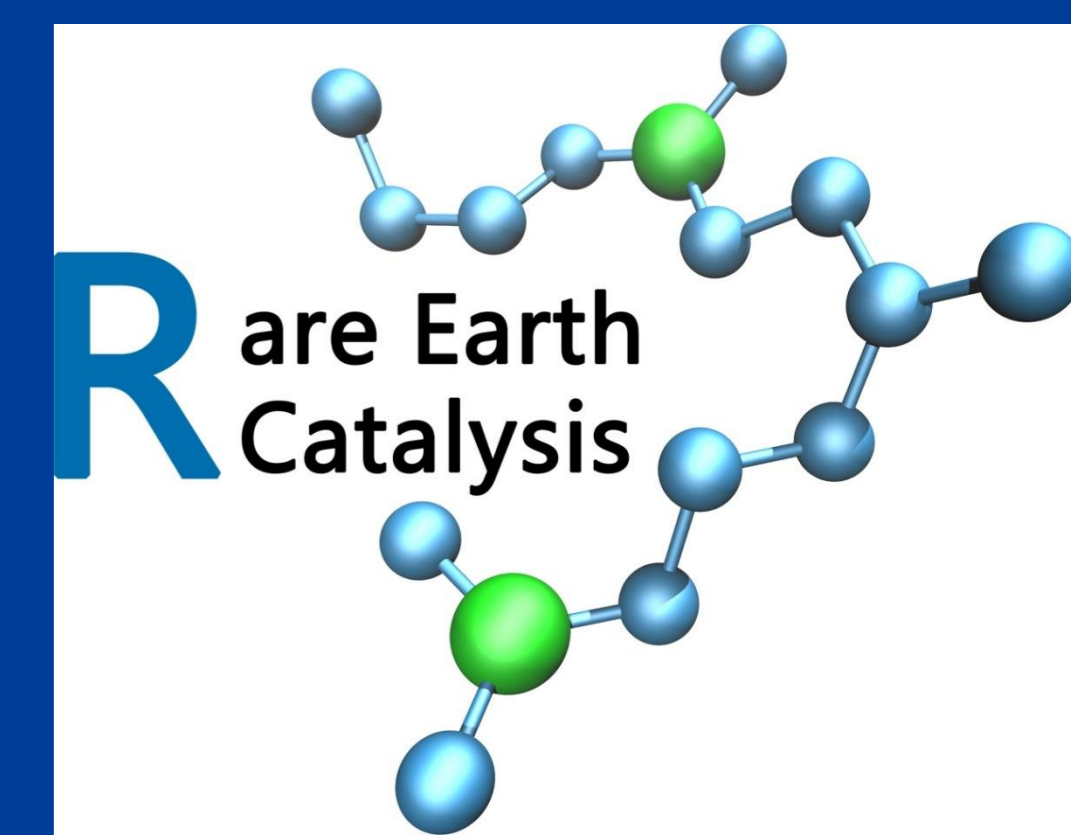


Novel poly(2-oxazoline)s with pendant L-prolinamide moieties as efficient organocatalysts for direct asymmetric aldol reaction

Yao Wang(21329021), Huifang Shen, Liming Jiang*

E-mail:cejlm@zju.edu.cn

MOE Key Laboratory of Macromolecular Synthesis and Functionalization; Department of Polymer Science and Engineering, Zhejiang University, Hangzhou 310027, China

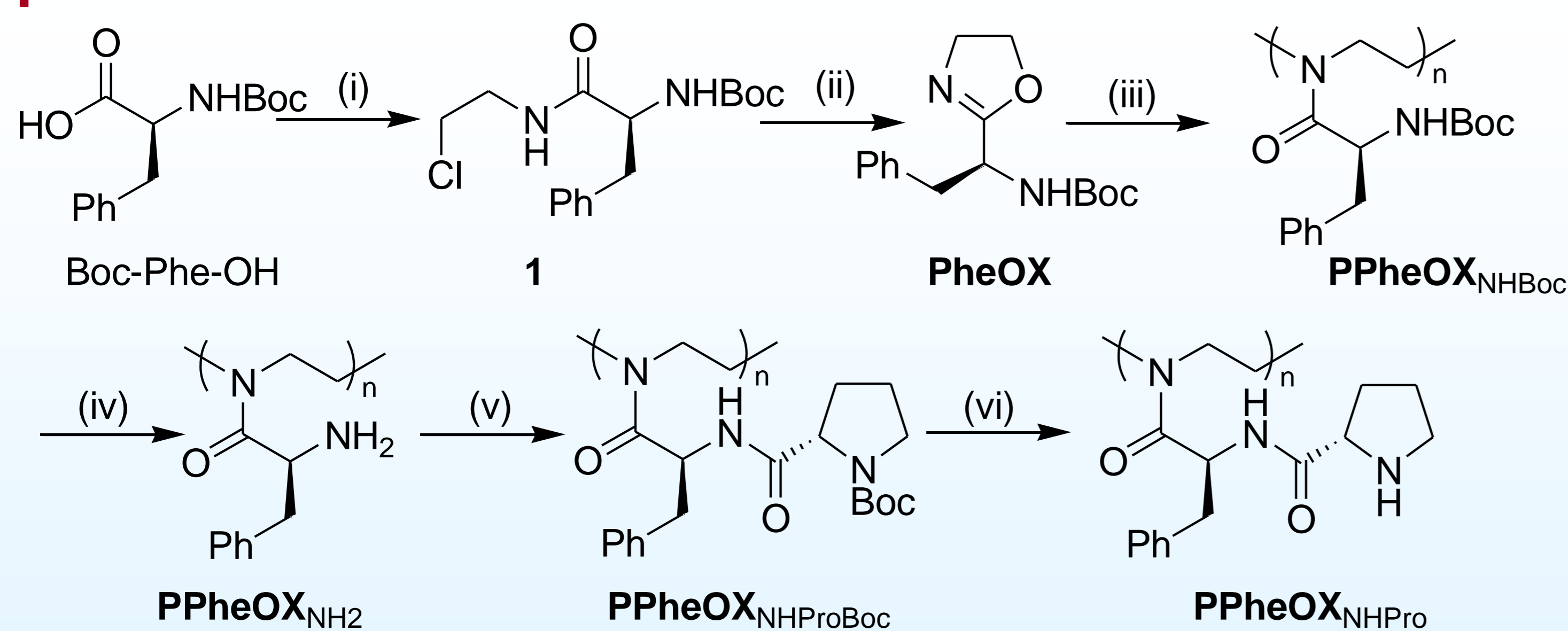


Introduction

During the last decade, as interest in asymmetric organocatalysis is on the increase, the immobilization of organic catalysts, especially their polymeric immobilization has also attracted much attention. The polymer matrix not only facilitates the isolation of the reaction products and the recycling of catalyst, but also seems to integrate itself as a more natural part of the overall catalytic system, influencing both catalyst activity and stereoselectivity.

Herein, we describe a novel bottom-up strategy to synthesize a series of L-prolinamido-functionalized poly(2-oxazoline) derivatives. These polymers have proven to be significantly more active than their monomeric counterpart for the aldolisation of cyclohexanone with several substituted benzaldehydes in neat ketone or in aqueous organic media.

Experimental



Scheme 1. Synthesis of poly(2-oxazoline)-bounded L-prolinamide catalyst using enantiopure Boc-phenylalanine as starting materials (Boc = tert-butyloxycarbonyl). (i) $\text{ClCH}_2\text{CH}_2\text{NH}_2 \cdot \text{HCl}$, TBTU, Et_3N , 0°C -r.t. (ii) NaOH , CH_3OH , 40°C . (iii) $\text{Sc}(\text{OTf})_3$, 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.

Results and Discussion

1. The cationic ring-opening polymerization of PheOX.

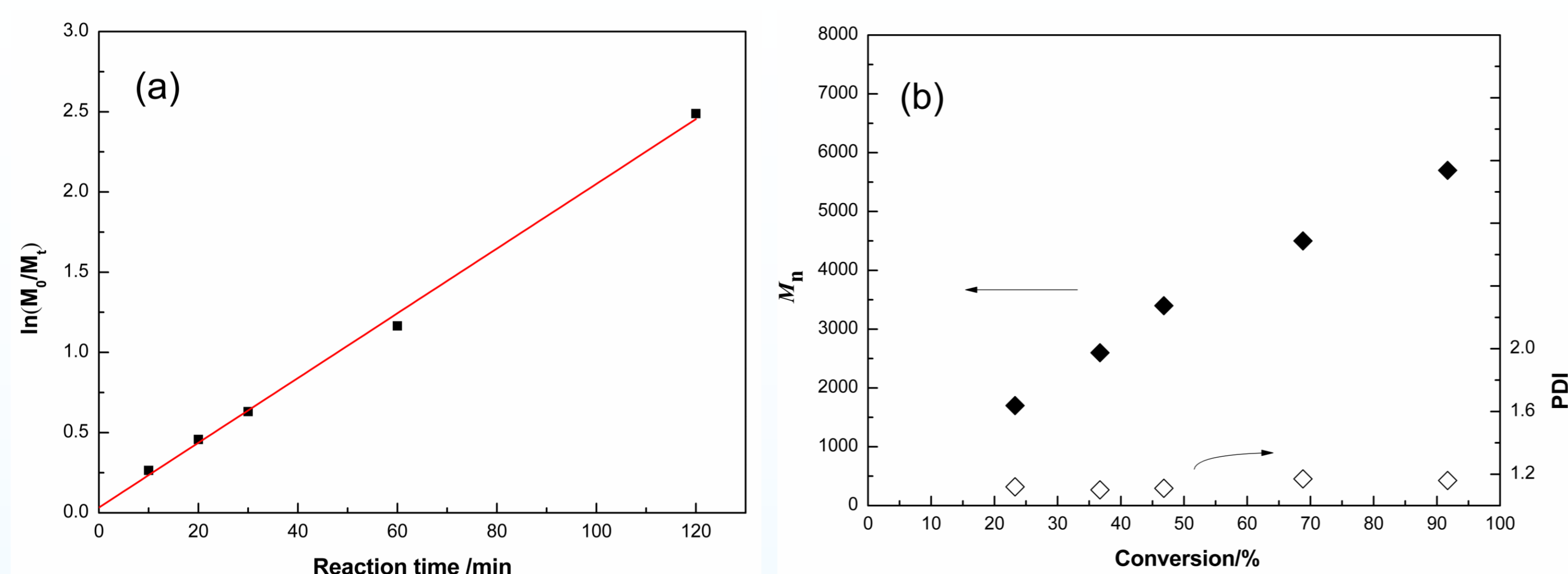


Figure 1. (a) Kinetic plot for **PheOX** polymerization initiated by $\text{Sc}(\text{OTf})_3$. (b) Evolution of M_n and the PDI value with monomer conversion (SEC, PS calibration, THF as the eluent).

2. The synthesis of organocatalysts.

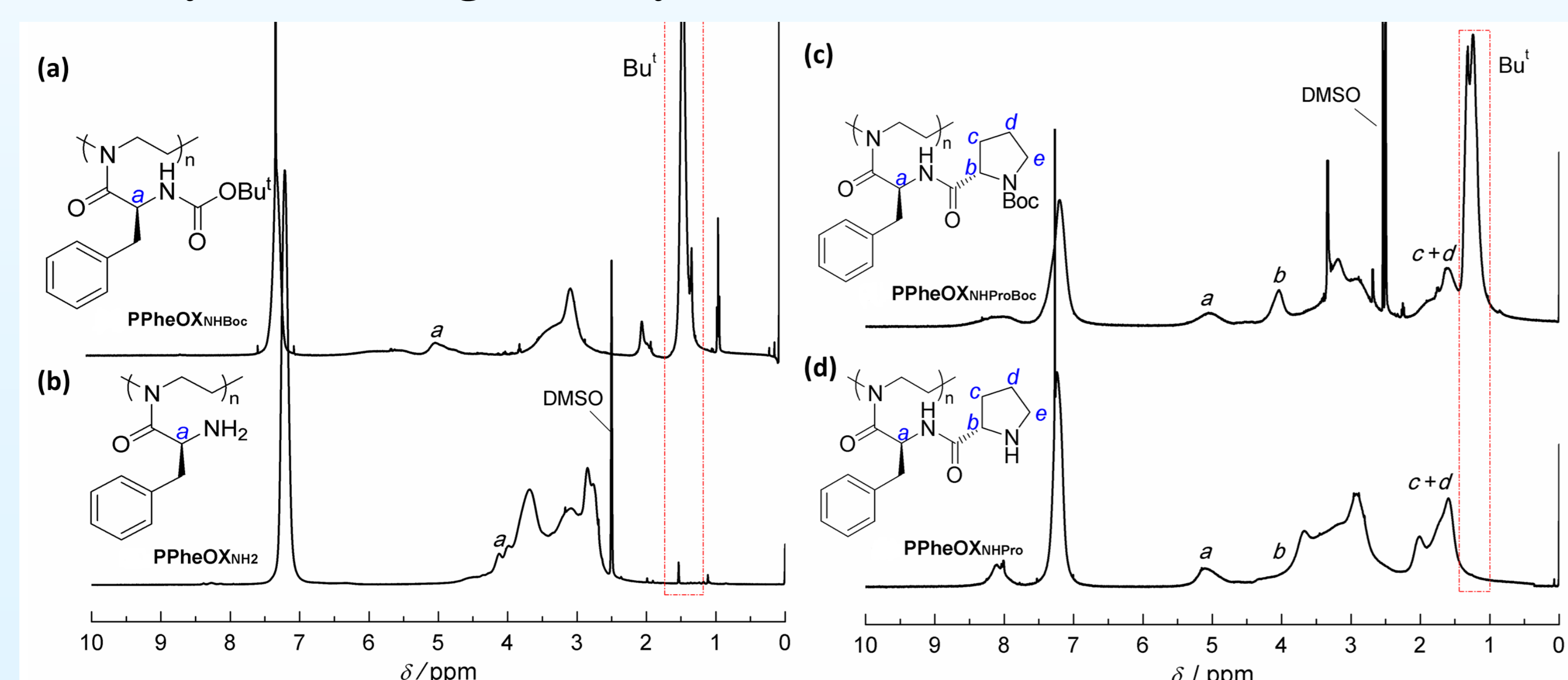


Figure 2. ^1H NMR spectra of (a) **PPheOX**_{NHBoc}, (b) **PPheOX**_{NH₂}, (c) **PPheOX**_{NHProBoc}, and (d) **PPheOX**_{NHPro}.

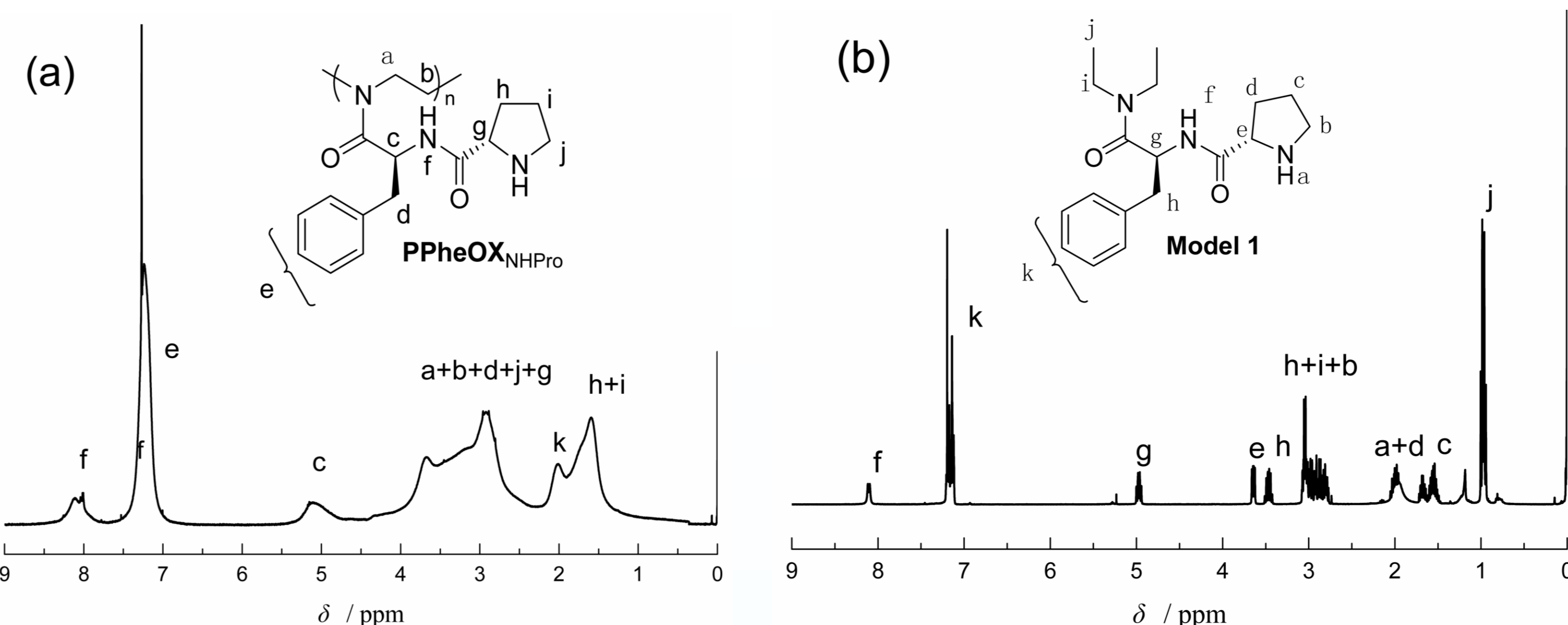


Figure 3. ^1H NMR spectra of (a) **PPheOX**_{NHPro} and (b) the monomeric counterpart **Model 1**.

3. The catalytic activity of the synthetic organocatalysts.

Table 1. The results of direct asymmetric aldol reaction. ^a

Entry	Catalyst	loading ^b (%)	Solvent/Additive	Time (h)	Yield ^c (%)	dr ^d (anti/syn)	ee ^e (%)
1	PPheOX _{NHPro}	15	H_2O 9 μL	12	86	71/29	78
2		15	H_2O 0.5mL	12	89	81/19	66
3		15	CH_3OH 0.5mL+ H_2O 0.5mL	24	97	8/15	84
4		15	H_2O 9 μL +TFA 1.5 μL	12	98	75/25	87
5		15	H_2O 9 μL +TFA 2 μL	12	96	78/22	91
6		15	H_2O 9 μL +TFA 2.6 μL	24	66	71/29	93
7 ^f		10	H_2O 9 μL +TFA 2 μL	36	42	80/20	87
8 ^g		20	H_2O 9 μL +TFA 2 μL	12	98	71/29	84
9	Model 1	15	H_2O 9 μL +TFA 1.5 μL	12	80	63/37	60
10		15	H_2O 9 μL +TFA 2 μL	24	60	60/40	44

^a Aldehyde 0.25 mmol, cyclohexanone 5 mmol, 10°C . ^b Catalyst loading: relative to the aldehyde. ^c Isolated yields. ^d determined by ^1H NMR. ^e Determined by HPLC using chiral column. ^f 10% catalyst loading. ^g 20%.

Table 2. Recovery and reuse of **PPheOX**_{NHPro} in the direct asymmetric aldol reaction. ^a

Entry	Cycle	Solvent/Additive	Yield ^b (%)	dr ^c (anti/syn)	ee ^d (%)
1	1	CH_3OH 0.5mL+ H_2O 0.5mL	92	85/15	81
2	3	CH_3OH 0.5mL+ H_2O 0.5mL	88	75/25	78
3	5	CH_3OH 0.5mL+ H_2O 0.5mL	79	77/23	73
4	1	H_2O 9 μL +TFA 2 μL	96	84/16	90
5	3	H_2O 9 μL +TFA 2 μL	85	90/10	90
6	5	H_2O 9 μL +TFA 2 μL	70	90/10	91

^a Aldehyde 0.25 mmol, cyclohexanone 5 mmol, 15 mol% **PPheOX**_{NHPro} loading, 10°C , 12h. ^b Isolated yields. ^c Diastereomeric ratio determined by ^1H NMR. ^d Determined by HPLC using chiral column.

Conclusion

In conclusion, we developed a kind of novel poly(2-oxazoline)-supported L-prolinamide catalyst that are able to imitate to some extent the aldolase biomimetic system. The polymer catalyst proved to be highly efficient for the asymmetric aldol reaction, high yield of up to 96% combined with excellent enantioselectivities of up to 91% ee have been achieved with 15 mol% of catalyst loading under the optimized condition. The polymer catalyst can be easily recovered and reused by precipitation in ethyl ether for five catalytic cycles without significantly diminishing its efficiency in the aldol addition of cyclohexanone to 4-nitrobenzaldehyde.

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