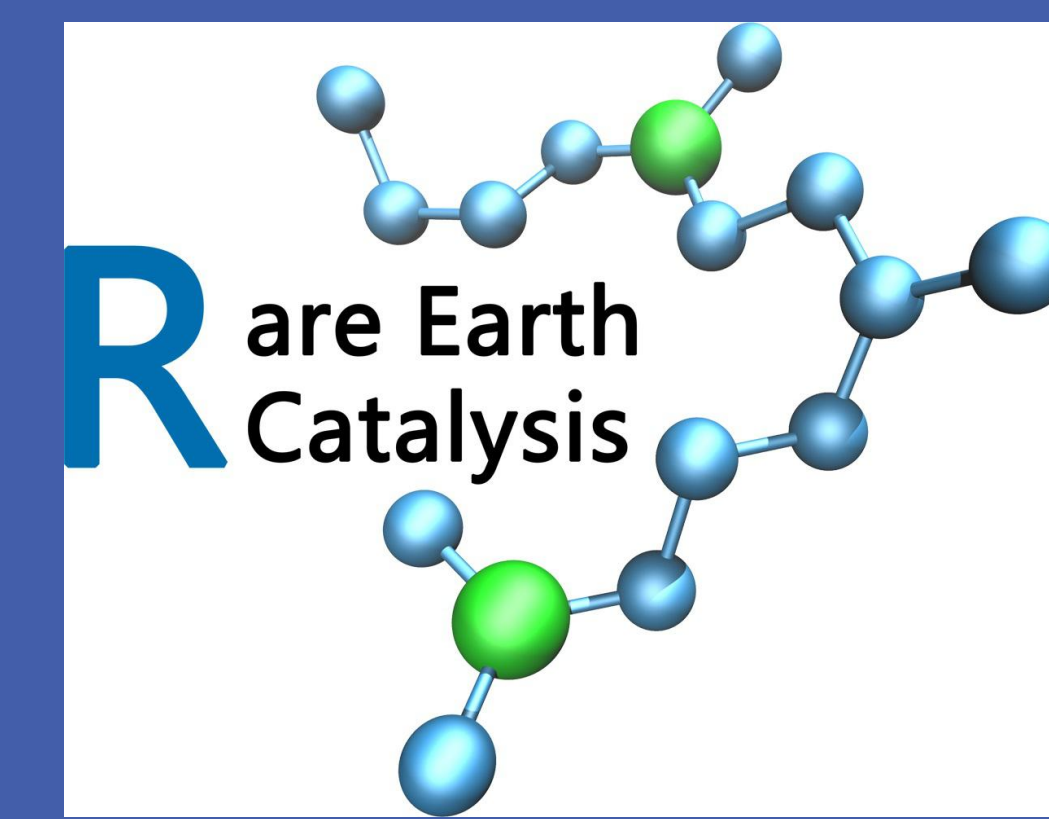




Asymmetric Aldol Reactions Catalyzed by *L*-Prolinamide Functionalized Poly(2-oxazoline) Derivatives in Aqueous Media

Long Ye, Ganhong Du, Le Zhou, Yao Wang, Liming Jiang* and Zhiquan Shen

Key Laboratory of Macromolecular Synthesis and Functionalization, Ministry of Education;
Department of Polymer Science and Engineering, Zhejiang University, Hangzhou, 310027, China
E-mail: cejlm@zju.edu.cn



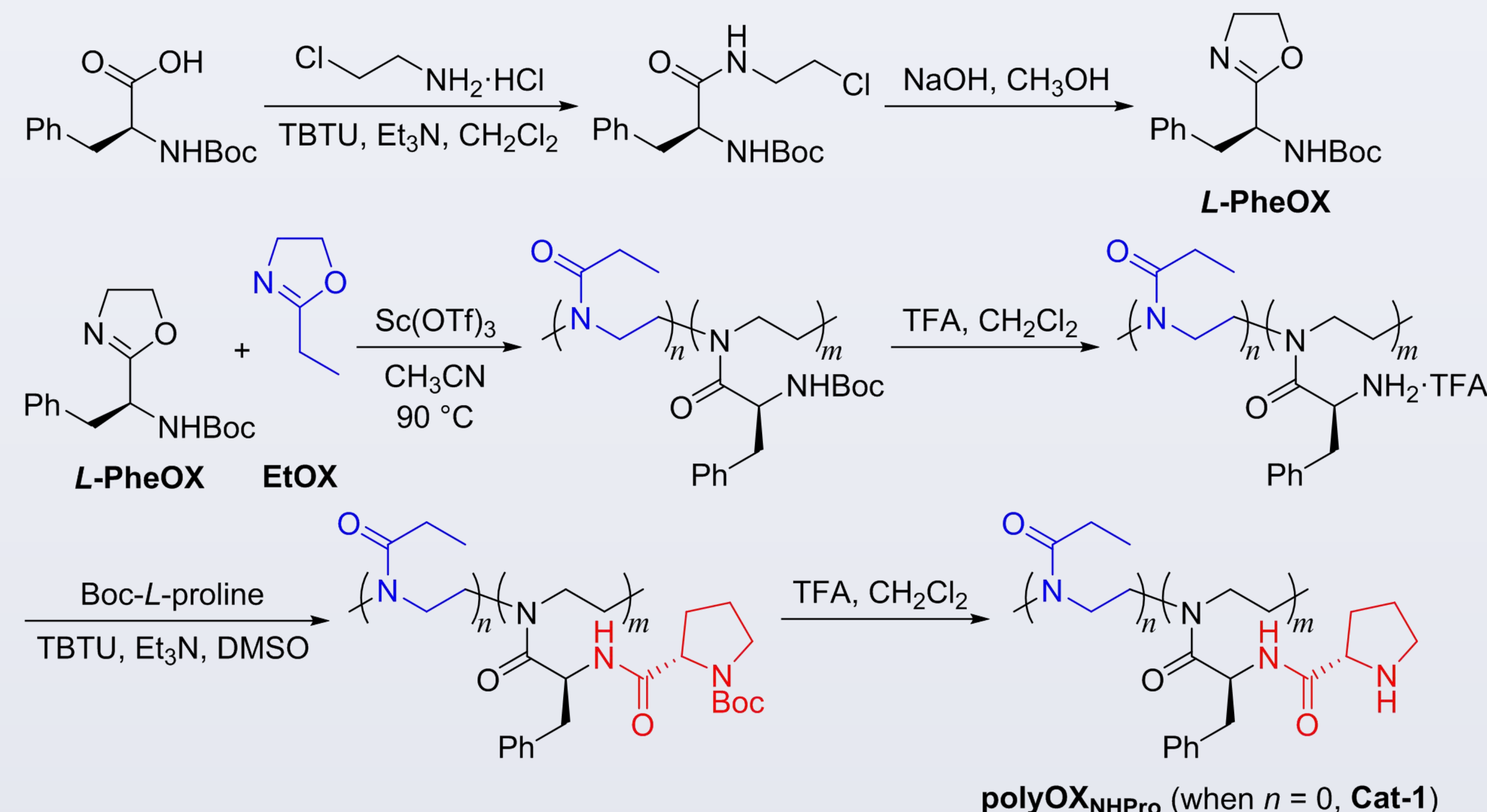
Introduction

In previous study, we have developed a class of novel poly(2-oxazoline)-supported *L*-prolinamide catalysts which proved to be highly efficient for the asymmetric aldolisation of cyclohexanone with several aromatic aldehydes under neat conditions.

With the objective of constructing biomimetic catalytic system capable of operating in aqueous media, we report herein the synthesis of novel amphiphilic copolymers by incorporating water-soluble 2-ethyl-2-oxazoline (EtOX) segment into polymer matrices. We investigated the catalytic performance of these copolymers in the asymmetric aldol addition of cyclohexanone to various substituted benzaldehydes and the recyclability.

Experimental

L-prolinamide containing amphiphilic poly(2-oxazoline)s were synthesized from commercially available starting materials by facile functional group transformations in high yield (Scheme 1).



Scheme 1 Synthetic route of *L*-prolinamide containing amphiphilic copolymers.

Results and discussion

In aqueous media, *L*-prolinamide functionalized amphiphilic poly(2-oxazoline)s catalyze the aldolisation of cyclohexanone and 4-nitrobenzaldehyde with good diastereo- and enantioselectivity compared to their homopolymeric counterpart (Table 1, entries 1, 3 and 5). A small amount of trifluoroacetic acid significantly improve the catalytic performance (Table 1, entries 2, 4 and 6). We hypothesize that the poly(2-oxazoline) scaffold could create an appropriate microenvironment around the active site *via* conformational transition for hydrogen bond-based asymmetric induction.

Figure 1 shows DLS measurements of these amphiphilic copolymers. As anticipated, they can self-assemble into nano-size aggregates in water, providing a concentrated hydrophobic core for aldol reaction with enhanced catalytic performance.

Moreover, product isolation and catalyst recycling can be easily accomplished by precipitation several times without noticeable loss of stereoselectivity.

Table 1 Aldol reaction of cyclohexanone and 4-nitrobenzaldehyde mediated by polyOX_{NHPro}.^a

Entry	polyOX _{NHPro} code	<i>m/n</i>	Additive	Yield (%)	anti/syn ^d	ee ^e (%)
1	Cat-1	20/0	—	97	77/23	52
2			TFA (1 μ L)	96	81/19	80
3	Cat-2^b	27/27	—	89	86/14	70
4			TFA (1 μ L)	93	87/13	82
5	Cat-3^c	44/11	—	93	87/13	63
6			TFA (1 μ L)	96	90/10	86

^a 0.25 mmol of 4-nitrobenzaldehyde, 20 equiv. of cyclohexanone.

^b Random copolymer. ^c Block copolymer. ^d By ¹H NMR analysis of the crude product. ^e By chiral HPLC analysis of the *anti*- product.

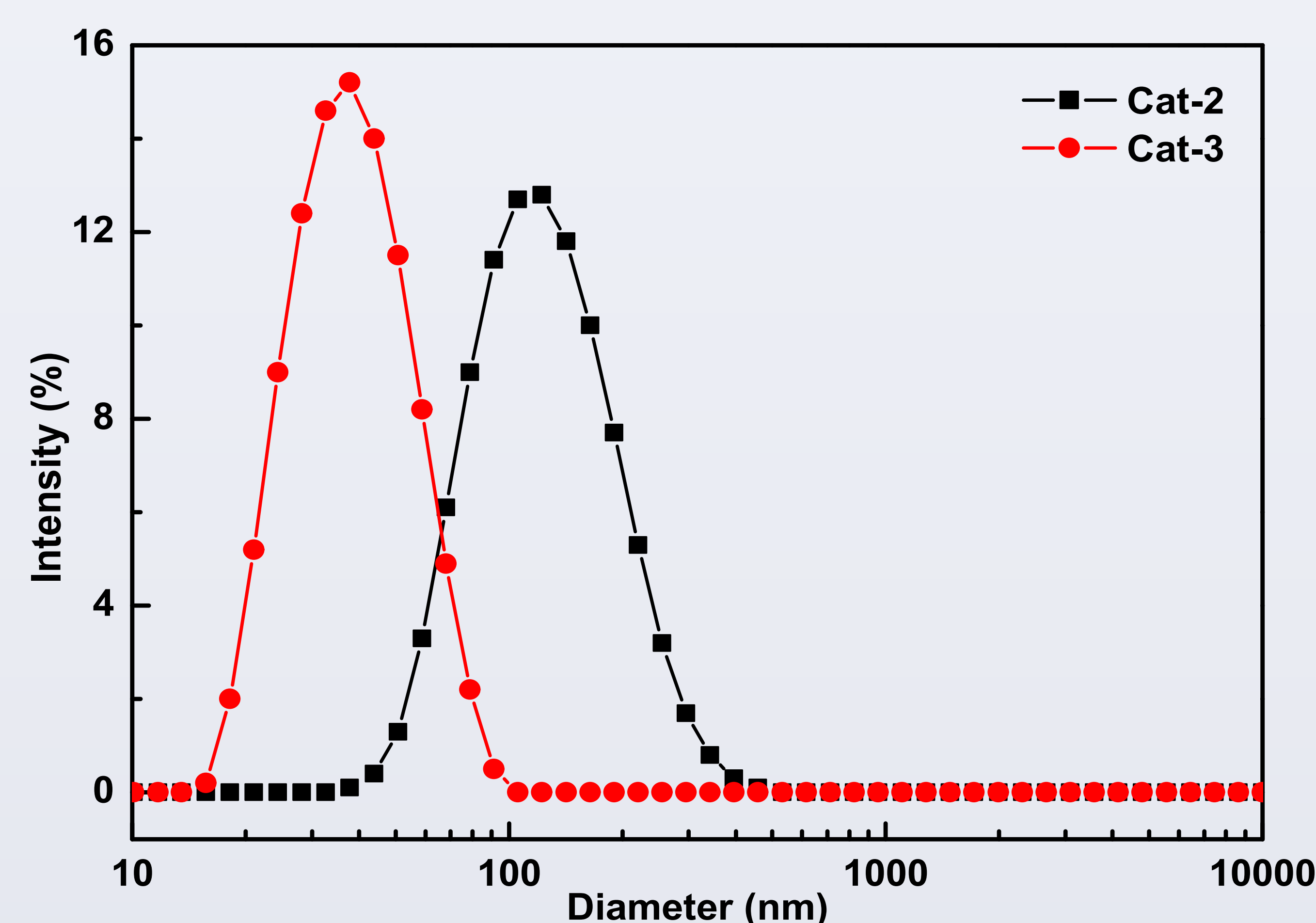


Figure 1 DLS measurements of **Cat-2** and **Cat-3** in water (1 mg/mL).

Conclusions

We have demonstrated that *L*-prolinamide functionalized amphiphilic poly(2-oxazoline) derivatives can self-assemble into micellar aggregates in water, in which higher diastereo- and enantioselectivities have been achieved in the aldolisation of cyclohexanone to 4-nitrobenzaldehyde. Catalyst recovery and reuse is convenient by simple centrifugation after each cycle. Further research on the detailed mechanism of acid-induced catalytic enhancement is in progress.

Acknowledgements

The authors gratefully acknowledge the National Natural Science Foundation of China (Grant No. 21274122) for financial support.

References

- [1] Y. Wang, H. Shen, L. Zhou, F. Hu, S. Xie, L. Jiang, *Catal. Sci. Technol.* **2016**, 6, 6739.
- [2] A. Lu, P. Cotanda, J. P. Patterson, D. A. Longbottom, R. K. O'Reilly, *Chem. Commun.* **2012**, 48, 9699.