



Cite this: *Polym. Chem.*, 2015, **6**, 5358

Received 8th June 2015,
Accepted 29th June 2015

DOI: 10.1039/c5py00872g

www.rsc.org/polymers

Aqueous asymmetric aldol reactions in polymersome membranes†

Matthijs C. M. van Oers, Wouter S. Veldmate, Jan C. M. van Hest* and Floris P. J. T. Rutjes*

L-Proline catalysts have been immobilised in the hydrophobic domain of a polymersome via a copper(i)-catalysed azide–alkyne cycloaddition (CuAAC) reaction. Utilisation of these nanoreactors in the asymmetric aldol reaction of cyclohexanone with 4-nitrobenzaldehyde afforded the corresponding β -hydroxyketones in quantitative yields and with excellent enantio- and diastereoselectivities. The polymersomes were recycled up to five times without any loss in activity or selectivity.

The field of asymmetric organocatalysis has witnessed a tremendous growth in the last decade. Ever since the pioneering work of List¹ and Macmillan,² chemists have been seeking novel applications to exploit the catalytic nature of small organic molecules. One emerging trend has been the utilisation of organocatalysts in aqueous media. Despite the apparent benefits of using water as a solvent, realisation of this concept has been far from trivial since the presence of water often hampers the formation of the intermediate in enamine-mediated organocatalytic reactions. For instance, in the L-proline-catalysed asymmetric aldol reaction of 4-nitrobenzaldehyde with ketone donors, yields and selectivities significantly drop when water is added to the reaction mixture.³ To overcome these incompatibility issues, the organocatalyst has to be effectively shielded from the aqueous environment. The research groups of Barbas,⁴ Hayashi⁵ and Noto⁶ solved this problem by adding a hydrophobic group to the proline catalyst which sequesters the enamine intermediate away from water. Armstrong and coworkers⁷ used a cyclodextrin that could bind a *tert*-butylphenoxyproline molecule to achieve a site-isolated catalytic system in water. Other strategies involve the immobilisation of organocatalysts on polystyrene resins,^{8,9} acrylic beads,^{10–12} micelles,^{13,14} and stimuli-responsive polymers.^{15–17} Most of these heterogeneous catalysts take advantage of a

confined hydrophobic microenvironment that maximises the substrate concentration around the catalyst.¹⁸ This often results in an increase in reaction rate compared to the activity of the homogeneous catalyst under non-aqueous conditions.

In a previous report¹⁹ we demonstrated the embedding of a chiral copper bis(oxazoline) catalyst inside the hydrophobic domain of a polymersome membrane via a copper(i)-catalysed azide–alkyne cycloaddition (CuAAC) reaction.^{20,21} By applying these polymersomes in an aqueous asymmetric cyclopropanation reaction between ethyl diazoacetate and styrene derivatives, we showed that the corresponding cyclopropane products were obtained in high yields and enantioselectivities. These results encouraged us to investigate the immobilisation of other catalysts inside the polymersome bilayer. Given the powerful nature of L-proline in catalysing asymmetric aldol reactions, we envisioned that affixation of this organocatalyst in the membrane of a polymersome would yield a catalytic system that could mimic the activity of an aldolase enzyme.²² Not only would this afford a novel catalytic nanoreactor for the synthesis of enantiopure aldol products, the presence of an inner aqueous cavity would potentially allow the encapsulation of a biocatalyst which could work in concert with the organocatalyst to enable one-pot aqueous cascade reactions. Additionally, we expected that the polymersomes could readily be separated from the products by extraction, which would allow them to be reused in subsequent aldol reactions.

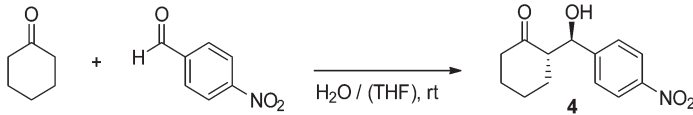
To allow the immobilisation of L-proline in the polymersome membrane, it had to be functionalised with an alkyne tail. This was achieved by alkylating *N*-Boc-*trans*-4-hydroxy-L-proline with propargyl bromide, followed by a subsequent deprotection step with HCl to provide catalyst **2** in 57% overall yield (Fig. 1).

Next we turned our attention to the synthesis of the block copolymers. Following the described conditions for the preparation of poly(ethylene glycol)-*b*-poly(styrene-*co*-4-vinylbenzyl azide) (PEG-*b*-P(S-*co*-4-VBA)) polymers, we obtained block copolymers **P1–P6** with varying azide contents, simply by changing the ratio between styrene and 4-vinylbenzyl chloride

Radboud University, Institute for Molecules and Materials, Heyendaalseweg 135, 6525 AJ Nijmegen, The Netherlands. E-mail: J.vanHest@science.ru.nl, F.Rutjes@science.ru.nl

† Electronic supplementary information (ESI) available. See DOI: 10.1039/c5py00872g



Table 1 Asymmetric aldol reaction of cyclohexanone and 4-nitrobenzaldehyde^a


Entry	Reaction time (h)	Conc. aldehyde (mM)	H ₂ O : THF	Polymer	Azide content (%)	Conversion ^{b,c} (%)	<i>anti/syn</i> ^c	ee <i>anti</i> ^d (%)
1	22	83	100 : 0	P1	18	9	87/13	88
2	22	83	90 : 10	P1	18	40	95/5	95
3	22	83	72 : 25	P1	18	29	95/5	96
4	22	120	90 : 10	P1	18	62	95/5	95
5	22	120	90 : 10	P2	22	60	96/4	98
6	22	120	90 : 10	P3	34	17	92/8	95
7	22	120	90 : 10	P4	42	21	95/5	94
8	22	120	90 : 10	P5	13	31	94/6	92
9	22	120	90 : 10	P6	5	16	89/11	89
10 ^e	22	120	90 : 10	—	—	4	71/29	1
11	72	120	90 : 10	P2	22	99	96/4	98

^a Reactions were carried out at room temperature using a 4 : 1 ratio between cyclohexanone and 4-nitrobenzaldehyde, a catalyst concentration of 30 mol% and a reaction volume of 1.0 mL. ^b Conversion of 4-nitrobenzaldehyde into β -hydroxyketone **4**. ^c Determined by ¹H-NMR spectroscopy of crude product. ^d Determined by chiral HPLC. ^e L-Proline was used as catalyst.

branes when using polymers with a high degree of functionalisation. As these membranes contain more catalysts, there is less room available to accommodate the substrates. This also results in a lower overall concentration of reactants accessible to the catalyst. It could well be that at an 18–22% functionalisation level the substrate concentration surrounding the catalyst is at a maximum which causes the reaction rate to peak. A similar effect was observed by Lu *et al.* when they investigated the aqueous asymmetric aldol reaction in PMMA nanogels.¹¹ At identical catalyst loadings the conversion reached an optimum when the nanogel was functionalised for 2 wt% with L-proline monomers.

Applying nanogels with higher or lower degrees of functionalisation led to a significant drop in reaction rate. The sequestering effect of the polymersome membrane was demonstrated when we employed L-proline as a catalyst in the aqueous asymmetric aldol reaction. Under identical circumstances we could now only recover 4% of product **4**. More compelling evidence was obtained when we measured the de and ee of the reaction. With an *anti/syn* ratio of 71/29 and an almost racemic mixture of enantiomers the control reaction could be considered as non-asymmetric. In a final attempt to improve the yield of the aldol reaction we extended the reaction time to 72 h (entry 11). Much to our satisfaction, β -hydroxyketone **4** was isolated nearly at full conversion while the diastereo- and enantioselectivity were preserved to an excellent degree.

With the optimised conditions established, we investigated the recyclability of the catalytic polymersomes. To ensure that all product after the first cycle was removed we decided to spin the polymersomes down after completion of the reaction. Next, we separated the aqueous supernatant, redispersed the polymersomes in ethyl acetate and centrifuged them again. After the organic phase was removed and combined with the

aqueous supernatant, the polymersomes were redispersed in a H₂O : THF mixture and new substrates were added to initiate the next reaction cycle.

Following this procedure we were able to reuse our catalytic polymersomes five consecutive times without noticeable deterioration of the catalyst or the interior structure of the polymersome membrane. More strikingly, both the yield and the de/ee did not show any decline over the course of the five cycles (Chart 1). This proves the robustness of our system and

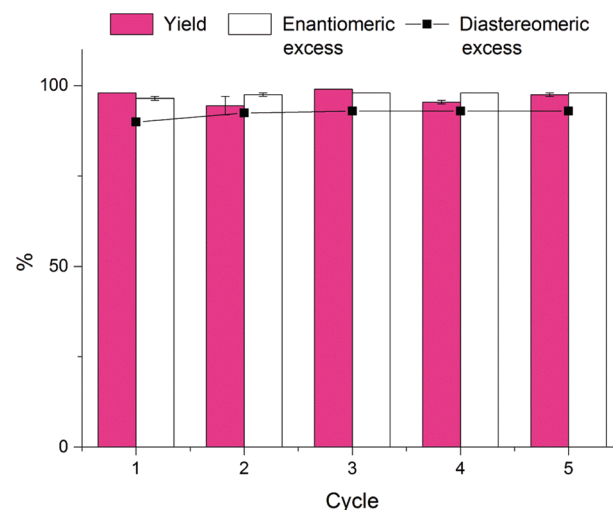


Chart 1 Diagram of the isolated yield, enantiomeric excess, and diastereomeric excess of the asymmetric aldol reaction of 4-nitrobenzaldehyde with cyclohexanone repeated over five cycles with L-proline-functionalised polymersomes. Reactions were carried out in *duplo* in a 1.0 mL MilliQ : THF (90 : 10) mixture at room temperature using 4-nitrobenzaldehyde (120 mM), cyclohexanone (480 mM) and a 30 mol% catalyst loading.



illustrates the potential of these polymersomes as green recyclable catalysts in aqueous asymmetric reactions.

Conclusions

In summary, we have designed a polymersome nanoreactor capable of catalysing asymmetric aldol reactions in water with excellent yields, diastereoselectivities, and enantioselectivities. The successful immobilisation of an L-proline catalyst in the polymersome membrane was achieved *via* a CuAAC reaction which provided a protective hydrophobic environment for the enamine intermediate. The rate of the aldol reaction turned out to be highly dependent on the substrate concentration, the catalyst loading per polymersome, and the amount of plasticiser present in the aqueous solution. Optimising these conditions allowed us to produce β -hydroxyketone **4** in almost quantitative yield and with high enantio- and diastereomeric purity. Furthermore, we managed to recycle the polymeric vesicles up to five times while preserving the excellent catalytic properties of the polymersomes. With the possibility to expand the catalytic system with a second site-isolated (bio)catalyst and driven by the increasing demand for green reusable catalysts, we foresee a promising future for these polymeric nanoreactors as versatile platforms for multistep asymmetric reactions in aqueous solutions.

Acknowledgements

We thank the Netherlands Research School Combination Catalysis (NRSCC) and the Ministry of Education, Culture and Science (Gravitation programme 024.001.035) for funding.

Notes and references

- 1 B. List, R. A. Lerner and C. F. Barbas, *J. Am. Chem. Soc.*, 2000, **122**, 2395.
- 2 K. A. Ahrendt, C. J. Borths and D. W. C. MacMillan, *J. Am. Chem. Soc.*, 2000, **122**, 4243.
- 3 A. Cordova, W. Notz and C. F. Barbas, *Chem. Commun.*, 2002, 3024.
- 4 N. Mase, Y. Nakai, N. Ohara, H. Yoda, K. Takabe, F. Tanaka and C. F. Barbas, *J. Am. Chem. Soc.*, 2006, **128**, 734.
- 5 Y. Hayashi, S. Aratake, T. Okano, J. Takahashi, T. Sumiya and M. Shoji, *Angew. Chem., Int. Ed.*, 2006, **45**, 5527.
- 6 F. Giacalone, M. Gruttadauria, P. Agrigento, P. Lo Meo and R. Noto, *Eur. J. Org. Chem.*, 2010, 5696.
- 7 J. Huang, X. Zhang and D. W. Armstrong, *Angew. Chem., Int. Ed.*, 2007, **46**, 9073.
- 8 M. Gruttadauria, F. Giacalone, A. M. Marculescu, P. Lo Meo, S. Riela and R. Noto, *Eur. J. Org. Chem.*, 2007, 4688.
- 9 D. Font, C. Jimeno and M. A. Pericas, *Org. Lett.*, 2006, **8**, 4653.
- 10 T. E. Kristensen, K. Vestli, K. A. Fredriksen, F. K. Hansen and T. Hansen, *Org. Lett.*, 2009, **11**, 2968.
- 11 A. Lu, D. Moatsou, D. A. Longbottom and R. K. O'Reilly, *Chem. Sci.*, 2013, **4**, 965.
- 12 A. Lu, D. Moatsou, I. Hands-Portman, D. A. Longbottom and R. K. O'Reilly, *ACS Macro Lett.*, 2014, **3**, 1235.
- 13 B. H. Lipshutz and S. Ghorai, *Org. Lett.*, 2012, **14**, 422.
- 14 A. Lu, P. Cotanda, J. P. Patterson, D. A. Longbottom and R. K. O'Reilly, *Chem. Commun.*, 2012, **48**, 9699.
- 15 E. Huerta, P. J. M. Stals, E. W. Meijer and A. R. A. Palmans, *Angew. Chem., Int. Ed.*, 2013, **52**, 2906.
- 16 A. Lu, T. P. Smart, T. H. Epps, D. A. Longbottom and R. K. O'Reilly, *Macromolecules*, 2011, **44**, 7233.
- 17 L. Qin, L. Zhang, Q. X. Jin, J. L. Zhang, B. X. Han and M. H. Liu, *Angew. Chem., Int. Ed.*, 2013, **52**, 7761.
- 18 J. L. Zhang, M. X. Zhang, K. J. Tang, F. Verpoort and T. L. Sun, *Small*, 2014, **10**, 32.
- 19 M. C. M. van Oers, L. K. E. A. Abdelmohsen, F. P. J. T. Rutjes and J. C. M. van Hest, *Chem. Commun.*, 2014, **50**, 4040.
- 20 H. C. Kolb, M. G. Finn and K. B. Sharpless, *Angew. Chem., Int. Ed.*, 2001, **40**, 2004.
- 21 V. V. Rostovtsev, L. G. Green, V. V. Fokin and K. B. Sharpless, *Angew. Chem., Int. Ed.*, 2002, **41**, 2596.
- 22 A. Heine, G. DeSantis, J. G. Luz, M. Mitchell, C. H. Wong and I. A. Wilson, *Science*, 2001, **294**, 369.
- 23 P. L. Soo and A. Eisenberg, *J. Polym. Sci., Part A: Polym. Chem.*, 2004, **42**, 923.
- 24 T. Azzam and A. Eisenberg, *Angew. Chem., Int. Ed.*, 2006, **45**, 7443.
- 25 N. Zotova, A. Franzke, A. Armstrong and D. G. Blackmond, *J. Am. Chem. Soc.*, 2007, **129**, 15100.

