Chiral Gating for Size- and Shape-Selective Asymmetric Catalysis

Xiaowei Li and Yan Zhao*

Department of Chemistry, Iowa State University, Ames, Iowa 50011-3111

Supporting Information Placeholder

ABSTRACT: A poor or mediocre stereoselectivity is a key roadblock for a chiral catalyst to find practical adoptions. We report a facile method to create a tunable chiral space near a chiral catalyst to augment its selectivity. The space was created rationally through templated polymerization within cross-linked micelles, using readily available amino acid derivatives. It provided gated entrance of reactants to the catalyst, enabling a mediocre prolinamide to catalyze aldol condensation in water with excellent yields and ee, in a size- and shape-selective manner.

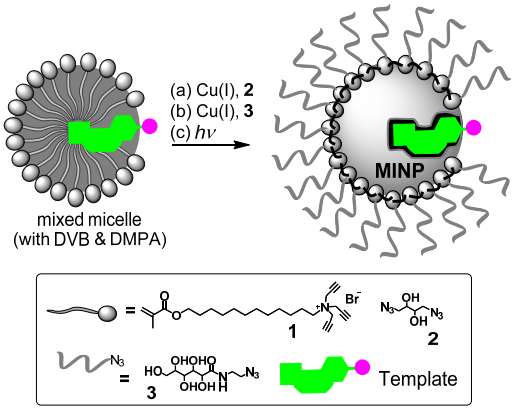
Asymmetric catalysis has become an indispensable tool in modern organic synthesis. An innumerable number of chiral ligands, metal complexes, and catalysts have been developed in last decades to control the stereoselectivity of chemical reactions. Very few of these made onto the privileged list with general applicability across different reaction types.[1,2] Tremendous research efforts went into their developments, sometimes aided by serendipity.

Most chiral catalysts failed to do so, however, either because their reaction scope was too narrow or their stereoselectivity just too low. If the highest ee delivered by an enantioselective catalyst only reaches <50%, it rarely impresses researchers in the field or finds practical applications. Unfortunately, this might represent the largest group of chiral catalysts synthesized, published or not.

Herein, we report a method to construct a chiral "gate" or nanospace near a chiral catalyst for direct aldol condensation in water as an example.[3-13] The gate controls the passage of reactants to the catalytic center to boost its enantioselectivity. In this way, even catalysts disqualified by traditional metrics might be useful, especially when highly selective catalysts are not available for an important reaction at the time.

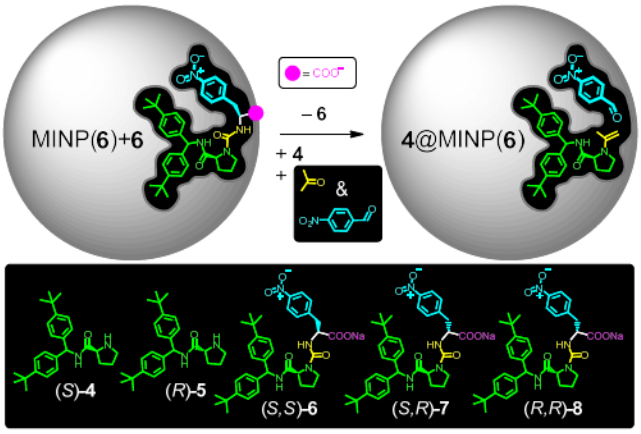
To use microenvironmental chirality to improve the performance of a chiral catalyst, we need to build a chiral space near the catalytic center and tune its chirality.[14,15] Although enzymes frequently use this approach to obtain nearly perfect selectivity, chemists cannot do so reliably. If synthesizing a chiral catalyst/ligand itself might require great synthetic efforts, building additional chiral space around the catalyst and influencing its stereoselectivity positively can be a more complicated task.

We recently developed a method to perform molecular imprinting[16-18] within the mixed micelle of **1** containing DVB, 2,2-dimethoxy-2-phenylacetophenone (DMPA, a photoinitiator), and a template molecule (Scheme 1).[19] The tripropargylammonium headgroup of the surfactant allows the micelle to be cross-linked on the surface with diazide **2** and functionalized with monoazide **3** by the Cu(I)-catalyzed click reaction. Free radical polymerization is then employed to cross-link the core, among DVB and the methacrylate of **1**, essentially to "solidify" the core around the template. The purple sphere in the template is normally a hydrophilic group that prefers to stay on the surface of the micelle, so that the binding site for the template would be close to the surface.[19] The molecularly imprinted nanoparticles (MINPs) obtained have remarkable abilities to replicate structural features of the template, and were shown to differentiate isoleucine and leucine in di- and tripeptides,[20] as well as mono- and oligosaccharides different in the stereochemistry of a single hydroxyl.[21,22] MINPs are typically 5 nm in size and soluble in water and selected organic solvents (DMF and DMSO). Since MINPs are estimated by dynamic light scattering to have ~50 cross-linked surfactants, their number of binding sites per particle averages 1 when the surfactant/template ratio is 50 in the MINP preparation.[19]



Scheme 1. Template polymerization within cross-linked micelle.

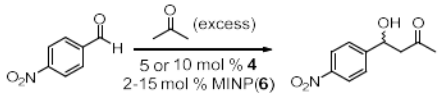
Although molecularly imprinted catalysts have been reported,[16,23-27] micellar imprinting, with its demonstrated high-fidelity and precision, provides us with a predicable way to construct a tunable nanospace around a catalyst.[28-30] Scheme 2 shows the design. Simple L-prolinamides such as **4** tend to have poor enantioselectivity for aldol condensation unless the amide proton is activated by electron-withdrawing groups.[4,31,32] Template **6** was prepared by standard peptide chemistry using commercially available (*S*)-*p*-nitrophenylalanine and (*S*)-L-proline. The template is color-coded to highlight different parts of its structure: the green moiety is the space holder for (*S*)-prolinamide catalyst **4**, yellow for the enamine derivative of acetone, and cyan for *p*-nitrobenzaldehyde, the electrophile in the aldol reaction. The two *p*-*t*-butylphenyl groups are included as hydrophobic anchors for **4** to have a strong driving force to enter the imprinted site.



Scheme 2. Preparation of chiral MINP for aldol reaction.

As expected, **4** performed poorly in the asymmetrical aldol reaction. Under typical literature conditions (10 mol % catalyst in DMSO), reaction between acetone and *p*-nitrobenzaldehyde gave a 64% yield and 42% ee for the *R*-enantiomer after 24 h at room temperature (Table 1, entry 1). When the reaction was performed in water, no product was obtained, possibly due to poor solubility of the catalyst in water (entry 2).

Table 1. Aldol reaction between acetone and *p*-nitrobenzaldehyde catalyzed by 4@MINP(6).[a]



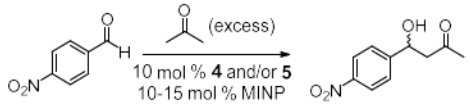
entry	mol % MINP(**6**)	mol % **4**	yield (%)	ee (%)
1	0[b]	10	64	42
2	0	10	0	0
3	2	5	42	14
4	5	5	48	32
5	10	5	67	80
6	5	10	57	53
7	10	10	84	91
8	15	10	99	96
9	10[c]	10	7	3

[a] The reactions were performed with 2 mM *p*-nitrobenzaldehyde and 50 μL acetone in 1 mL of water for 24 h unless otherwise indicated. [b] Solvent was DMSO. [c] Reaction was performed with nonimprinted nanoparticles (NINPs) prepared without any template.

To our delight, in the presence of 5 mol % **4**, an increasing amount of MINP(**6**) increased the yield steadily and the ee even more (entries 3–5). The same trend was observed with 10 mol % catalyst, allowing the reaction to proceed to practically completion with a measured ee of 96%. The imprinted binding site was clearly key to the improvement because nonimprinted nanoparticles, prepared without any template, gave little help to **4** (entry 9).

To probe the influence of the chiral gate on the reaction, we performed additional reactions using (*R*)-prolinamide **5** and MINPs prepared from two other stereoisomers of the template **7** & **8** (Table 2). As shown in entries 1&2, MINP(**6**) boosted the yield and enantioselectivity of (*S*)-prolinamide **4**. Not only so, it enabled the racemic mixture of **4**&**5** to give a remarkable 77% ee (entry 3). Inverting the chirality of the chiral gate through (*R*)-*p*-nitrophenylalanine diminished both the yield and ee (entry 4). When both the gate and the catalyst were inverted, an excellent yield and ee were obtained again, for the opposite enantiomer of the aldol product (entry 7). Consistent with the match–mismatch–match transition, both the yields and ee's in Table 2 were nearly symmetrical with respect to the center (entry 4), including those obtained from the racemic catalysts.

Table 2. Aldol reaction between acetone and *p*-nitrobenzaldehyde catalyzed by 4 and/or 5 with different MINPs.[a]



Entry	mol % MINP	template	catalyst	yield (%)	ee (%)
1	15	(*S*, *S*)-**6**	**4**	99	96 (*R*)
2	10	(*S*, *S*)-**6**	**4**	84	91 (*R*)
3	10	(*S*, *S*)-**6**	**4**&**5**[b]	69	77 (*R*)
4	10	(*S*, *R*)-**7**	**4**	47	40 (*R*)
5	10	(*R*, *R*)-**8**	**4**&**5**[c]	63	71 (*S*)
6	10	(*R*, *R*)-**8**	**5**	79	89 (*S*)
7	15	(*R*, *R*)-**8**	**5**	97	94 (*S*)

[a] The reactions were performed with 2 mM benzaldehyde, 10 mol % catalyst, and 50 μL acetone in 1 mL of water for 24 h. [b] The amount of catalyst was 10 mol %.

Performance of proline-derived catalysts in water can be improved significantly when they are attached to amphiphilic polymers or micelles.[33-37] Unusual hydration at the hydrophobic/hydrophilic interface has been postulated to impact the catalytic activities.[38] Although the same effect might have contributed to our improvement, it cannot explain the >70% ee obtained with the racemic catalysts.

To gain additional understanding of the catalysis, we measured the binding properties of MINP(**6**). The binding constant (K_a) for **4** and **5** was 20.4×10^4 and 0.18×10^4 M^{-1}, respectively (Table S1). The >100:1 enantioselectivity in the binding suggests that MINP(**6**) could easily pick out the correct catalyst (**4**) and perform asymmetric catalysis with the racemic catalysts, as shown above. Also, the 69% yield and 77% ee obtained with 10 mol % racemic catalysts (Table 2, entry 3) were experimentally the same as the 67% yield and 80% ee obtained with 5 mol % **4** (Table 1, entry 5). Since unbound catalyst was inactive according to Table 1, entry 2, the enantioselectivity of the racemic catalysts most likely came from the MINP-bound **4**.

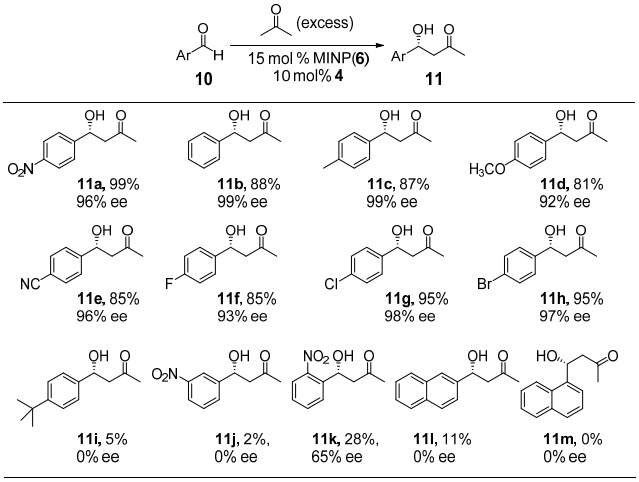
We could not study the binding of *p*-nitrobenzaldehyde (the limiting reagent in the reaction) directly because of its insolubility in water. Nonetheless, the chiral gate/space created from (*S*)-*p*-nitrophenylalanine was clearly present, as isothermal titration calorimetry (ITC) showed that the amino acid was bound by **4**@MINP(**6**) with $K_a = 4.51 \times 10^4$ M^{-1} and its enantiomer with $K_a = 0.59 \times 10^4$ M^{-1} (Table S1). The enantioselectivity of binding for the amino acids (~8:1) by the MINP thus was lower than that for the catalyst (>100:1). The result was consistent with our previous finding that chiral pockets near the surface of MINP had lower stereoselectivity than those deeper inside, due to strong hydrophobic contributions to the binding.[39]

Further insight into the catalysis was obtained from a kinetic study, which showed a zero-order dependence of the reaction rate on *p*-nitrobenzaldehyde (Figures S13 and S14). The result indicates that noncovalent binding of *p*-nitrobenzaldehyde by MINP(**6**) was much faster than the aldol reaction and the binding site was saturated under our reaction

conditions during the majority of the reaction time.

Table 3 shows the scope of the catalysis, keeping the reaction conditions the same while varying the aromatic aldehydes. Excellent yields and ee were obtained consistently when the *para* substituent was removed (R = H) or replaced with an electron-donating group (R = Me or OMe), an electron-withdrawing group (R = CN, NO_2), or halogens (R = F, Cl, Br). Hence, augmented enantioselectivity was obtained as long as the *para* substituent could fit reasonably well in the imprinted binding pocket created from the *p*-nitro group. The size- and shape-selectivity of **4**@MINP(**6**) was evident when a larger group such as *t*-butyl was placed at the *para* position, when the *para* nitro group was moved to other positions (*meta* or *ortho*), or when larger naphthaldehyde was used.

Table 3. Aldol reaction between acetone and aromatic aldehydes catalyzed by 4@MINP(6).[a]



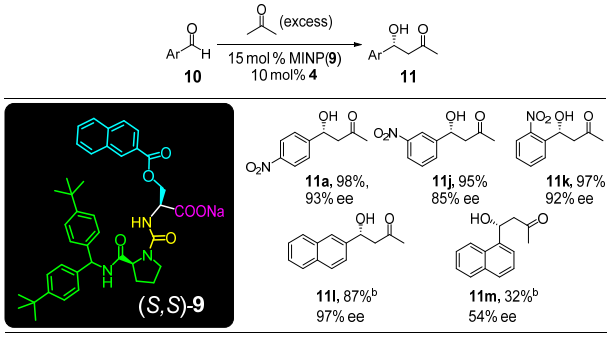
[a] The reaction was performed with 2 mM benzaldehyde and 50 μL acetone in 1 mL of water for 24 h.

Our **4**@MINP(**6**) thus mimicked enzymes in their ability to catalyze highly selective reactions for their targeted substrates: **4** being the catalytic co-factor and the MINP being an enzyme-mimic to provide a chiral, nanosized active site for the size- and shape-selectivity. Such catalysts can be extremely useful for applications such as converting a target reactant in a complex mixture or developing reaction-based sensors or signal-amplification systems. For common synthetic applications, however, it will be more desirable if the size of the chiral gate can be controlled so that the scope of the reaction can be tuned rationally.

Fortunately, to have a wider gate, so to speak, all we had to do was to use a larger group in place of the *p*-nitrobenzyl in the micellar imprinting. Template (*S*, *S*)-**9** was prepared in straightforward manners from natural L-serine and L-proline. Indeed, with a larger chiral space near the prolinamide, **4**@MINP(**9**) was able to catalyze the aldol reaction for all the nitrobenzaldehydes, *para*, *meta*, or *ortho* (Table 4). 2-Naphthaldehyde, with the right shape and size, was also let in, although the reaction took 48 instead of 24 h, possibly due to a different reactivity and/or a different turnover rate.[40] 1-Naphthaldehyde remained unreactive and gave poor selectivity, as anticipated from its wrong shape.

This work demonstrates the power of a rationally engineered chiral nanospace (i.e., "gate"), provided that the space can be tuned reliably in chirality, size, and shape. Not only could it endow a nearby chiral catalyst with size- and shape-selectivity, more importantly, it could also boost its performance in asymmetric catalysis, in yields and stereoselectivity. It is remarkable that chiral gating in the aldol reactions enabled racemic catalysts to afford >70% ee, when the MINP had high enantioselectivity in its binding.

Table 4. Aldol reaction between acetone and aromatic aldehydes catalyzed by 4@MINP(9).[a]



[a] The reaction was performed with 2 mM benzaldehyde and 50 μL acetone in 1 mL of water for 24 h unless indicated otherwise. [b] The reaction time was 48 h.

In a longer term, we envision to develop a predictable, convenient remedy to aid those catalysts that fail to "make the last few yards" in their asymmetric race. Although aldol reactions were studied as examples, the principle demonstrated should be general. MINPs can be prepared conveniently in a one-pot reaction in less than 2 days.[19] Their purification requires nothing other than precipitation and washing. With their ability to reproduce chiral nanospace faithfully from chiral templates, they have the potential to enable disqualified chiral catalysts to return to the asymmetric research field and find practical applications.

ASSOCIATED CONTENT

Supporting Information

Synthetic procedures, chromatographs, and NMR data. This material is available free of charge via the Internet at http://pubs.acs.org.

AUTHOR INFORMATION

Corresponding Author

zhaoy@iastate.edu

Notes

The authors declare no competing financial interests.

ACKNOWLEDGMENT

We thank NSF (CHE-1708526) for supporting the research.

REFERENCES

(1) Yoon, T. P.; Jacobsen, E. N. Privileged Chiral Catalysts. *Science* **2003**, *299*, 1691-1693.

(2) Zhou, Q.-L.: *Privileged Chiral Ligands and Catalysts*; Wiley-VCH: Weinheim, Germany, 2011.

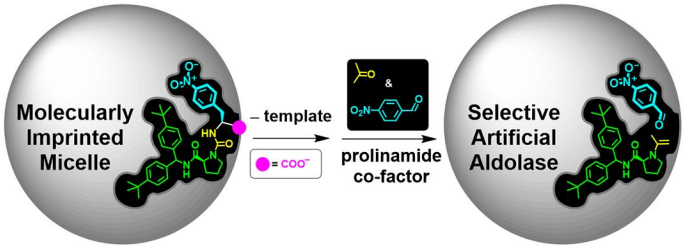
(3) Mlynarski, J.; Baś, S. Catalytic Asymmetric Aldol Reactions in Aqueous Media – a 5 Year Update. *Chem. Soc. Rev.* **2014**, *43*, 577-587.

(4) Yamashita, Y.; Yasukawa, T.; Yoo, W.-J.; Kitanosono, T.; Kobayashi, S. Catalytic Enantioselective Aldol Reactions. *Chem. Soc. Rev.* **2018**, *47*, 4388-4480.

(5) Mase, N.; Nakai, Y.; Ohara, N.; Yoda, H.; Takabe, K.; Tanaka, F.; Barbas, C. F. Organocatalytic Direct Asymmetric Aldol Reactions in Water. *J. Am. Chem. Soc.* **2006**, *128*, 734-735.

(6) Hayashi, Y.; Sumiya, T.; Takahashi, J.; Gotoh, H.; Urushima, T.; Shoji, M. Highly Diastereo- and Enantioselective Direct Aldol Reactions in Water. *Angew. Chem. Int. Ed.* **2006**, *45*, 958-961.

(7) Wu, Y.; Zhang, Y.; Yu, M.; Zhao, G.; Wang, S. Highly Efficient and Reusable Dendritic Catalysts Derived from N-Prolylsulfonamide for the Asymmetric Direct Aldol Reaction in Water. *Org. Lett.* **2006**, *8*, 4417-4420.
(8) Huang, J.; Zhang, X.; Armstrong, D. W. Highly Efficient Asymmetric Direct Stoichiometric Aldol Reactions on/in Water. *Angew. Chem. Int. Ed.* **2007**, *46*, 9073-9077.
(9) Rodríguez-Llansola, F.; Miravet, J. F.; Escuder, B. A Supramolecular Hydrogel as a Reusable Heterogeneous Catalyst for the Direct Aldol Reaction. *Chem. Commun.* **2009**, 7303-7305.
(10) Vishnumaya, M. R.; Singh, V. K. Highly Efficient Small Organic Molecules for Enantioselective Direct Aldol Reaction in Organic and Aqueous Media. *J. Org. Chem.* **2009**, *74*, 4289-4297.
(11) Qin, L.; Zhang, L.; Jin, Q.; Zhang, J.; Han, B.; Liu, M. Supramolecular Assemblies of Amphiphilic L-Proline Regulated by Compressed Co2 as a Recyclable Organocatalyst for the Asymmetric Aldol Reaction. *Angew. Chem. Int. Ed.* **2013**, *52*, 7761-7765.
(12) Huerta, E.; Stals, P. J. M.; Meijer, E. W.; Palmans, A. R. A. Consequences of Folding a Water-Soluble Polymer around an Organocatalyst. *Angew. Chem. Int. Ed.* **2013**, *52*, 2906-2910.
(13) Lee, K. S.; Parquette, J. R. A Self-Assembled Nanotube for the Direct Aldol Reaction in Water. *Chem. Commun.* **2015**, *51*, 15653-15656.
(14) Becker, J. J.; Gagné, M. R. Exploiting the Synergy between Coordination Chemistry and Molecular Imprinting in the Quest for New Catalysts. *Acc. Chem. Res.* **2004**, *37*, 798-804.
(15) Muratsugu, S.; Tada, M. Molecularly Imprinted Ru Complex Catalysts Integrated on Oxide Surfaces. *Acc. Chem. Res.* **2013**, *46*, 300-311.
(16) Wulff, G. Enzyme-Like Catalysis by Molecularly Imprinted Polymers. *Chem. Rev.* **2001**, *102*, 1-28.
(17) Haupt, K.; Mosbach, K. Molecularly Imprinted Polymers and Their Use in Biomimetic Sensors. *Chem. Rev.* **2000**, *100*, 2495-2504.
(18) Ye, L.; Mosbach, K. Molecular Imprinting: Synthetic Materials as Substitutes for Biological Antibodies and Receptors. *Chem. Mater.* **2008**, *20*, 859-868.
(19) Awino, J. K.; Zhao, Y. Protein-Mimetic, Molecularly Imprinted Nanoparticles for Selective Binding of Bile Salt Derivatives in Water. *J. Am. Chem. Soc.* **2013**, *135*, 12552-12555.
(20) Awino, J. K.; Gunasekara, R. W.; Zhao, Y. Sequence-Selective Binding of Oligopeptides in Water through Hydrophobic Coding. *J. Am. Chem. Soc.* **2017**, *139*, 2188-2191.
(21) Awino, J. K.; Gunasekara, R. W.; Zhao, Y. Selective Recognition of D-Aldohexoses in Water by Boronic Acid-Functionalized, Molecularly Imprinted Cross-Linked Micelles. *J. Am. Chem. Soc.* **2016**, *138*, 9759-9762.
(22) Gunasekara, R. W.; Zhao, Y. A General Method for Selective Recognition of Monosaccharides and Oligosaccharides in Water. *J. Am. Chem. Soc.* **2017**, *139*, 829-835.
(23) Wulff, G.; Liu, J. Design of Biomimetic Catalysts by Molecular Imprinting in Synthetic Polymers: The Role of Transition State Stabilization. *Acc. Chem. Res.* **2012**, *45*, 239-247.
(24) Sellergren, B.; Karmalkar, R. N.; Shea, K. J. Enantioselective Ester Hydrolysis Catalyzed by Imprinted Polymers. 2. *J. Org. Chem.* **2000**, *65*, 4009-4027.
(25) Carboni, D.; Flavin, K.; Servant, A.; Gouverneur, V.; Resmini, M. The First Example of Molecularly Imprinted Nanogels with Aldolase Type I Activity. *Chem. -Eur. J.* **2008**, *14*, 7059-7065.
(26) Shen, X.; Huang, C.; Shinde, S.; Jagadeesan, K. K.; Ekström, S.; Fritz, E.; Sellergren, B. Catalytic Formation of Disulfide Bonds in Peptides by Molecularly Imprinted Microgels at Oil/Water Interfaces. *ACS Appl. Mater. Interfaces* **2016**, *8*, 30484-30491.
(27) Zheng, A.-X.; Gong, C.-B.; Zhang, W.-J.; Tang, Q.; Huang, H.-R.; Chow, C.-F.; Tang, Q. An Amphiphilic and Photoswitchable Organocatalyst for the Aldol Reaction Based on a Product-Imprinted Polymer. *Mol. Catal.* **2017**, *442*, 115-125.
(28) Arifuzzaman, M.; Zhao, Y. Artificial Zinc Enzymes with Fine-Tuned Catalytic Active Sites for Highly Selective Hydrolysis of Activated Esters. *ACS Catal.* **2018**, *8*, 8154-8161.
(29) Hu, L.; Zhao, Y. A Bait-and-Switch Method for the Construction of Artificial Esterases for Substrate-Selective Hydrolysis. *Chem. -Eur. J.* **2019**, *25*, 7702-7710.
(30) Hu, L.; Arifuzzaman, M. D.; Zhao, Y. Controlling Product Inhibition through Substrate-Specific Active Sites in Nanoparticle-Based Phosphodiesterase and Esterase. *ACS Catal.* **2019**, *9*, 5019-5024.
(31) Notz, W.; Tanaka, F.; Barbas, C. F. Enamine-Based Organocatalysis with Proline and Diamines: The Development of Direct Catalytic Asymmetric Aldol, Mannich, Michael, and Diels-Alder Reactions. *Acc. Chem. Res.* **2004**, *37*, 580-591.
(32) Tang, Z.; Jiang, F.; Cui, X.; Gong, L.-Z.; Mi, A.-Q.; Jiang, Y.-Z.; Wu, Y.-D. Enantioselective Direct Aldol Reactions Catalyzed by L-Prolinamide Derivatives. *Proc. Natl. Acad. Sci. U. S. A.* **2004**, *101*, 5755-5760.
(33) Lipshutz, B. H.; Ghorai, S. Organocatalysis in Water at Room Temperature with in-Flask Catalyst Recycling. *Org. Lett.* **2012**, *14*, 422-425.
(34) Lu, A.; Moatsou, D.; Longbottom, D. A.; O'Reilly, R. K. Tuning the Catalytic Activity of L-Proline Functionalized Hydrophobic Nanogel Particles in Water. *Chem. Sci.* **2013**, *4*, 965-969.
(35) Neumann, L. N.; Baker, M. B.; Leenders, C. M. A.; Voets, I. K.; Lafleur, R. P. M.; Palmans, A. R. A.; Meijer, E. W. Supramolecular Polymers for Organocatalysis in Water. *Org. Biomol. Chem.* **2015**, *13*, 7711-7719.
(36) Huerta, E.; van Genabeek, B.; Lamers, B. A. G.; Koenigs, M. M. E.; Meijer, E. W.; Palmans, A. R. A. Triggering Activity of Catalytic Rod-Like Supramolecular Polymers. *Chem. -Eur. J.* **2015**, *21*, 3682-3690.
(37) Bhowmick, S.; Mondal, A.; Ghosh, A.; Bhowmick, K. C. Water: The Most Versatile and Nature's Friendly Media in Asymmetric Organocatalyzed Direct Aldol Reactions. *Tetrahedron Asymmetry* **2015**, *26*, 1215-1244.
(38) Stals, P. J. M.; Cheng, C.-Y.; van Beek, L.; Wauters, A. C.; Palmans, A. R. A.; Han, S.; Meijer, E. W. Surface Water Retardation around Single-Chain Polymeric Nanoparticles: Critical for Catalytic Function? *Chem. Sci.* **2016**, *7*, 2011-2015.
(39) Awino, J. K.; Zhao, Y. Imprinted Micelles for Chiral Recognition in Water: Shape, Depth, and Number of Recognition Sites. *Org. Biomol. Chem.* **2017**, *15*, 4851-4858.
(40) A low turnover rate could be caused by too strong a binding between the substrate and MINP, as suggested by our ITC data (Table S1, entry 7).


Molecularly
Imprinted
Micelle
– template
= COO⁻
&
prolinamide
co-factor
Selective
Artificial
Aldolase