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Thermoresponsive Polymer-Supported L-Proline Micelle Catalysts for the Direct Asymmetric Aldol Reaction in Water

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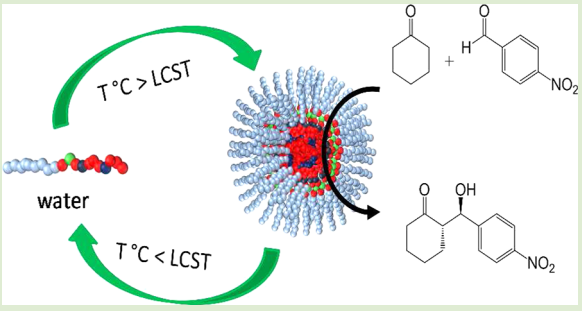
Supporting Information

ABSTRACT: L-Proline moieties bound to a thermoresponsive polymer nanoreactor efficiently directed the asymmetric aldol reaction in water with excellent yields and enantioselectivity (ee). The reactions were efficient at higher temperatures in direct contrast to the low yields and ee values found when the reaction was carried out in a DMF/water mixture due to the location of the L-proline moieties within the hydrophobic pocket inside the core of the nanoreactors. This ideal environment formed for catalysis allows control over the water content as well as enhancing interactions between the carboxylic acid of L-proline and the aldehyde substrate. The nanoreactors were disassembled to fully water-soluble polymers by lowering the temperature to below the lower critical solution temperature (LCST) of the polymer, resulting in precipitation of the product in near pure form. The product was isolated by centrifugation and the polymer/water solution reused in additional catalytic cycles by heating the polymer above its LCST and thus reforming the nanoreactors. Although a small decrease in yield after five cycles was observed, the selectivity (anti/syn ratio and ee) remained high.



Organocatalysts such as L-proline has become an important class of catalysts for C−C bond forming reactions with directed enantioselectivity[1−8] and represents the simplest chemical constituents found in type I aldolase enzyme.[9] The aldolase enzymes catalyze the aldol reaction via an enamine mechanism in a hydrophobic environment where the water content at the catalytic size is well controlled.[10−12] L-Proline has been reported to accelerate the reaction rate and improve enantioselectivity in the presence of a small amount of water,[13−15] but too much water resulted in low yields with little or no enantioselectivity.[7,14,16−19] There are many examples of L-proline catalyzed aldol reactions in organic solvents (e.g., DMSO, DMF, PEG, and in combination with varying water ratios).[7,20−23] Chemical modification of the catalyst with hydrophobic groups highlighted the importance of a hydrophobic environment for efficient catalyis in water.[24−27] Polymer-supported L-proline represent another approach to catalyze the aldol reaction in water, where the catalytic moiety is incorporated either on the exterior of the particles,[28−30] within the assembled polymer micelles[31] or single-chain polymer nanoparticles[32] or within cross-linked nanogels.[33] The generally low turnover number for organocatalysts requires high catalyst loadings, making catalyst recovery and recycling together with isolation of pure product in a one-pot reaction a challenge.

In this work, the desired hydrophobic environment[34] was created by designing a thermoresponsive[35,36] polymeric nanoreactor in water[23,37,38] capable of efficiently catalyzing the aldol reaction between cyclohexanone and *p*-nitrobenzaldehyde to produce the product in high yields with excellent enantioselectivity (ee), as depicted in Scheme 1. Cooling the reaction mixture below the lower critical solution temperature (LCST) of the polymer resulted in micelle dissociation to fully water-soluble polymer chains and precipitation of pure aldol product from the nanoreactors. The product was isolated and collected through centrifugation, and the nanoreactors reused by heating the remaining polymer/water solution above the LCST, giving excellent ee and good yields after five cycles. This process represents an elegant method to carry out catalytic asymmetric reactions in water in one-pot, improving on environmental concerns through the reduction of volatile organic compounds (VOCs) and cost, and increasing safety and scalability.[39] A thermoresponsive block copolymer with a permanently hydrophilic block (poly(dimethylacrylamide), PDMA) and a thermoresponsive block which above its LCST becomes hydrophobic (poly(*N*-isopropylacrylamide-*co*-butylacrylate-*co*-*N*-*tert*-butoxycarbonyl-*O*-acryloyl-*trans*-4-hydroxy-L-proline), P(NIPAM-*co*-BA-*co*-ProlA (Scheme 1) was designed.[37,38] At temperatures above the LCST (ranging from 25 to 40 °C; see Figure 1A), micelles were formed, approximately 15−20 nm in diameter with the catalytic L-proline moiety located within the hydrophobic NIPAM core. Upon cooling to temperatures

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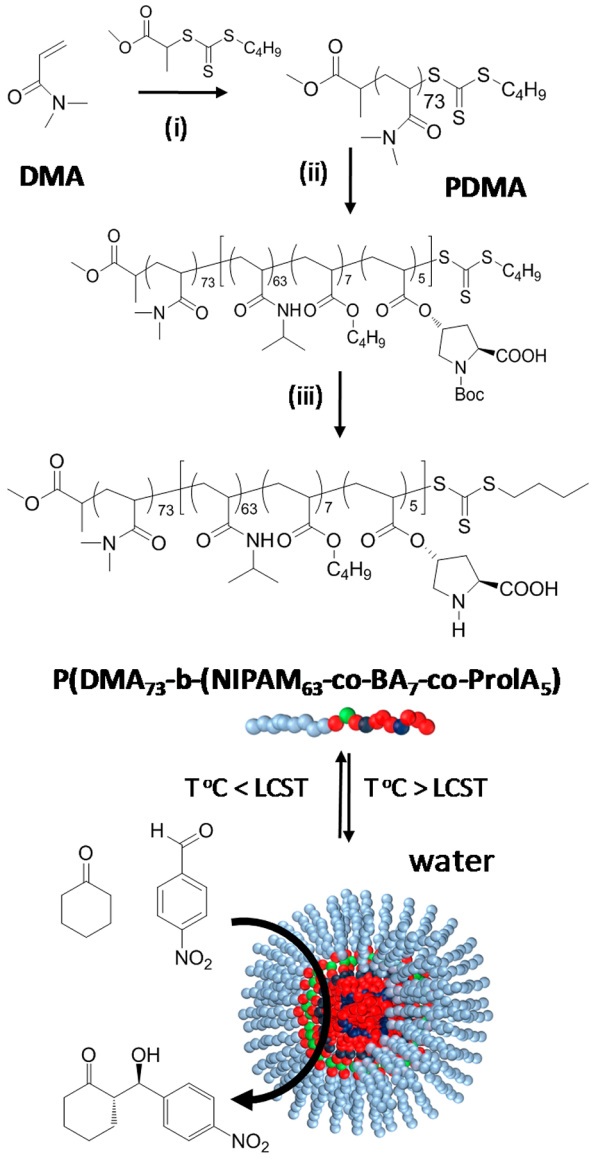
Scheme 1. General Mechanism for the Synthesis of the L-Proline Catalytic Polymer Nanoreactors[a]



[a](i) RAFT-mediated polymerization of DMA; (ii) block formation of macroCTA (i.e. PDMA-S(C═S)S-C_4H_9) with NIPAM, BA, and ProlA (protected with Boc), and (iii) deprotection of ProlA-Boc with TFA.

below the LCST, the block copolymer became fully water-soluble, allowing facile separation of the catalyst from the water insoluble aldol product (Figure 1B).

Using an unsupported L-proline catalyst (10 mol %) for the reaction between *p*-nitrobenzaldehyde (**2**, 1 equiv) and cyclohexanone (**1**, 7 equiv) in a homogeneous solvent mixture of DMF and water (95/5 vol%) resulted in a high conversion (99%), high anti/syn ratio (91/9) and ee (96%) at 25 °C after 24 h (Supporting Information, Table S1). Increasing the temperature from 25 to 50 °C resulted in a significant decrease in rate Supporting Information, Figure S1) and loss in both stereo- and enantioselectivity (Supporting Information, Table S1). This is consistent with the reaction equilibrium being driven toward the reactants over formation of enamine species (**4**; Scheme 2)[40,41] due to the higher water content inside the micelle core at higher temperatures. The mechanism given in

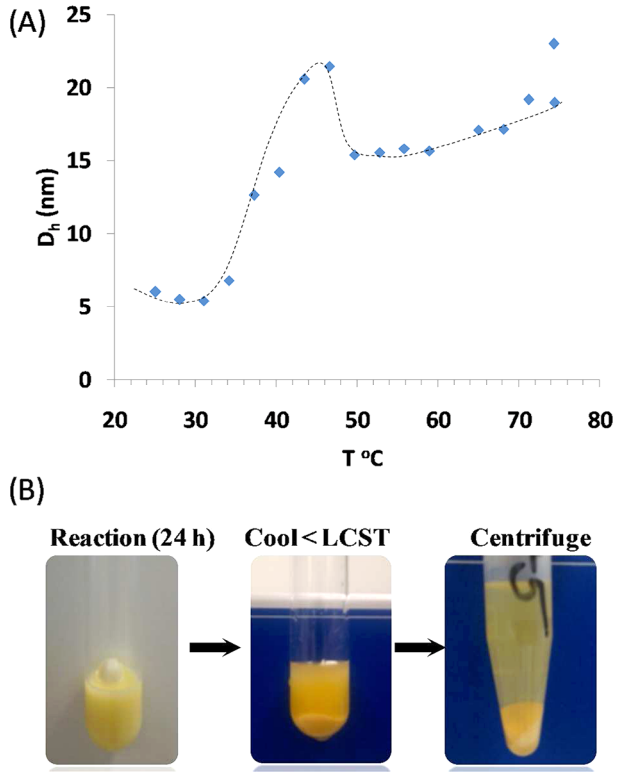
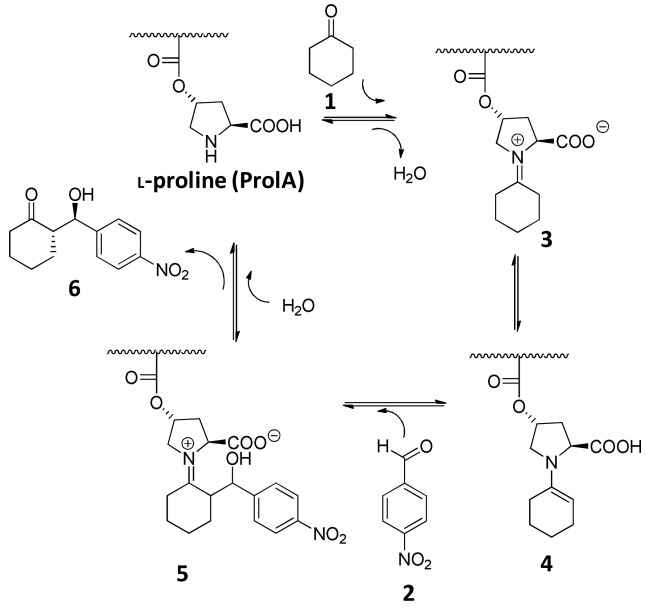


Figure 1. (A) Temperature dependence of $PDMA_{73}$-*b*-P($NIPAM_{63}$-*co*-BA_7-*co*-$ProlA_5$) on micelle formation, as determined by DLS. Determination of the lower critical solution temperature (LCST). (B) Photographs after the aldol reaction catalyzed by $PDMA_{73}$-*b*-P($NIPAM_{63}$-*co*-BA_7-*co*-$ProlA_5$) nanoreactors at 50 °C after 24 h, which was then cooled in an ice bath and further centrifuged to collect the product **6**.

Scheme 2. Kinetically Validated Mechanism for the L-Proline-Mediated Aldol Reaction in a Homogeneous Reaction Mixture[41]



Scheme 2 is generally accepted for solution reactions and has been kinetically validated.[40,41] The reduction in enantioselectivity with increasing temperature was likely to be due to

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Table 1. Kinetics Data for the Aldol Reaction of *p*-Nitrobenzaldehyde and Cyclohexanone in Water (1.0 mL) at Different Temperatures Catalyzed by $PDMA_{73}$-*b*-P($NIPAM_{63}$-*co*-BA_7-*co*-$ProlA_5$), 10 mol % Catalyst Loading

	50 °C[a]			40 °C[a]			35 °C[a]			25 °C[a]		
time (h)	% conv.[b]	*anti*/*syn*[c]	%ee[d]	% conv.[b]	*anti*/*syn*[c]	%ee[d]	% conv.[b]	*anti*/*syn*[c]	%ee[d]	% conv.[b]	*anti*/*syn*[c]	%ee[d]
3	44	96/4	98	26	97/3	94	23	100/0	89	11	100/0	63
6	66	95/5	97	47	96/4	98	37	100/0	91	17	100/0	89
9	76	95/5	97	59	96/4	98	43	96/4	95	26	92/8	80
12	86	95/5	97	72	96/4	98	57	97/3	98	32	95/5	79
24	95	94/6	96	89	96/4	96	80	96/4	96	53	97/3	96

[a]Reactions were carried out using *p*-nitrobenzaldehyde (1 equiv, 0.0232 g, 1.54×10^{-4} mol), cyclohexanone (7 equiv, 0.114 mL, 1.07×10^{-3} mol) and polymer-supported proline catalyst (10 mol %) in water (1.0 mL) at different temperatures for 24 h. [b]Conversion of *p*-nitrobenzaldehyde determined by ^{1}H NMR spectroscopy from crude reaction mixture. [c]Determined by ^{1}H NMR spectroscopy from crude reaction mixture. [d]Determined by HPLC.

Table 2. Recycling Data for the Aldol Reaction of *p*-Nitrobenzaldehdye and Cyclohexanone in Water at Different Temperatures Catalyzed by $PDMA_{73}$-*b*-P($NIPAM_{63}$-*co*-BA_7-*co*-$ProlA_5$), 10 mol % Catalyst Loading

	50 °C[a]			40 °C[a]			35 °C[a]		
cycle	conv.[b] %	*anti*/*syn*[c]	%ee[d]	conv.[b] %	*anti*/*syn*[c]	%ee[d]	% conv.[b]	*anti*/*syn*[c]	%ee[d]
1	96	92/8	95	91	96/4	94	85	97/3	95
2	86	95/5	97	85	93/7	96	81	96/4	96
3	78	93/7	96	78	95/5	96	78	97/3	97
4	66	92/8	98	67	95/5	98	70	95/5	91
5[e]	63	93/7	94	63	95/5	93	68	95/5	87

[a]Reactions were carried out using *p*-nitrobenzaldehyde (1 equiv, 0.0232 g, 1.54×10^{-4} mol), cyclohexanone (7 equiv, 0.114 mL, 1.07×10^{-3} mol), and polymer-supported proline catalyst (10 mol %) in water (1.0 mL) at different temperatures for 24 h. [b]Conversion of *p*-nitrobenzaldehyde determined by ^{1}H NMR spectroscopy from crude reaction mixture. [c]Determined by ^{1}H NMR spectroscopy from crude reaction mixture. [d]Determined by HPLC. [e]Additional water was added to the aqueous phase to make up a total volume of 1.0 mL due to the loss of volume after each catalytic cycle.

destabilization of the transition state between the carboxylic acid on the enamine species and the carbonyl group on the benzaldehyde through greater competitive hydrogen bonding with water.[42,43]

The polymer-supported L-proline catalytic nanoreactors gave enhanced rates of aldol formation with increasing temperature from 25 to 50 °C (Table 1), in direct contrast to the DMF/water homogeneous reaction. We chose this reaction temperature range to study the different possible states of the polymer/nanoreactor system (Figure 1A): (i) the absence of micelles at 25 °C (i.e., below the LCST), (ii) at the start of micellization at 35 °C, and (iii) above the LCST at 50 °C. Increased solubility of the reactants within the polymer nanoreactors at higher temperature is the most likely explanation to these higher reaction rates. The catalyst stereoselectivity was maintained over this temperature range as demonstrated by the excellent anti/syn ratio (>94% anti isomer) and ee (96%), suggesting that water is excluded from the transition state in forming **6**. The results for the reaction at 25 °C (i.e., below the LCST) suggested that the small amount of hydrophobic BA in the responsive block provided some control over the water content near the catalytic centers even in the absence of micelles, a process similar to that for single-chain polymer nanoparticles.[32] Decreasing the catalyst loading to 5 and 1 mol % resulted in a lower conversion from 83 to 31%, and a decrease in the anti/syn ratio and ee to 86% and 57%, respectively (Supporting Information, Table S2).

The results demonstrated that the hydrophobic environment within the nanoreactor controlled the water content at the active site allowing the reaction equilibrium to favor formation of the enamine species,[40] which then rapidly reacted with *p*-nitrobenzaldehyde to give the product, as depicted in Scheme 2.[41] The nanoreactor's mode of action was similar to that of enzymes, following the ping-pong model for enzymatic kinetics. First, L-proline reacted with cyclohexanone to form an enamine species (**4**), which was covalently bound to the polymer backbone (located within the core of the nanoreactor), releasing water to the aqueous phase. Second, *p*-nitrobenzaldehyde reacted with the enamine species to form a zwitterionic intermediate species (**5**), which allowed for a small but efficient partitioning of water into the core of the nanoreactors to complete the reaction and form the product (**6**). In the absence of a hydrophobic pocket by using a fully water-soluble polymer ($PDMA_{73}$-*b*-P(DMA_{70}-*co*-$ProlA_6$) at 10 mol % catalyst loading, the aldol reaction in water reached <6% conversion after 24 h (Table S3), supporting the effect of the hydrophobic pocket for efficient catalysis.

Recovery and recycling of the catalytic system was next investigated. The first cycle showed high conversions, anti/syn ratio, and ee after 24 h, comparable to those previously achieved (Table 1). After the first cycle, the reaction mixtures were cooled in an ice bath (below the LCST of the polymer), resulting in the disassembly of the nanoreactors into their water-soluble polymer chains. The product precipitated out of solution in a near pure form and was isolated by centrifugation (see Supporting Information, Figure S5 for a ^{1}H NMR spectrum of the crude product). The resulting supernatant (i.e., polymer in water) was recovered and reused in a second cycle via addition of a second batch of reagents and heating above the LCST of the polymer, reforming the nanoreactors. This polymer catalyst was successfully recycled using this procedure for five cycles (Table 2). A reduction in conversion after 24 h was observed for each cycle at all three temperatures, with the greatest reduction observed at 50 °C (96 to 63% after

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5 cycles) compared to 35 °C (85 to 68% after 5 cycles). However, there was no change in stereoselectivity for the reactions at 40 and 50 °C, and a small decrease in ee observed at 35 °C from 95% after the first cycle to 87% after the fifth cycle. These results suggest that the catalyst activity is being diminished with each cycle. We postulate that this could occur through cleavage of the ester groups covalently binding the L-proline to the polymer backbone at the higher temperatures, or that after each consecutive cycle the enamine intermediate species (**4**) may change the nature of the polymer and consequently change the amount of water within the nanoreactor core. However, the cumulative isolated yield after 5 cycles was 67, 80, and 78% at 35, 40, and 50 °C, respectively, suggesting good production of product (Supporting Information, Figure S9). Elucidation of the mechanism is quite complex, and relies on polymer interactions, transportation and solubility of reactants to the nanoreactor, and the amount of water within the nanoreactors. To account for the small loss of catalyst through loss of activation especially after the fourth and fifth cycle, a small amount of block copolymer catalyst (1 wt %) was added to the supernatant (Supporting Information, Table S4). The conversions of these recycling experiments after five cycles were slightly higher (70, 73, and 73% for 50, 40, and 35 °C, respectively) but more importantly high selectivity at 35 °C was conserved (ee 96%). Similar results were found if the recycling experiments were carried out using an initial catalyst loading of 20 mol % (Supporting Information, Table S5). The recovery and recycling of the catalyst, separation, and isolation of pure aldol product presented here represents an elegant solution to the use and reuse of organocatalysts in a purely aqueous system.

In summary, a catalytic thermoresponsive nanoreactor for the asymmetric aldol reaction in water without the need of additional organic solvents has been prepared. The efficiency of the nanoreactor system at high temperatures (above the LCST of the polymer) compared to unsupported catalytic reactions in DMF/water was demonstrated. The L-proline moieties located within the hydrophobic pocket of the nanoreactors provided an ideal environment for catalysis where the water content was controlled and further enhancing the interactions between the carboxylic acid of L-proline and the aldehyde substrate, mimicking the environment of enzymes. After the reaction was completed, the nanoreactors were disassembled to fully water-soluble polymers by decreasing the temperature below the LCST of the polymer, resulting in precipitation of the solid product in near pure form. The product was isolated by centrifugation and the polymer/water solution reused in additional catalytic cycles by heating the polymer above its LCST and, thus, reforming the nanoreactors. Although a small decrease in yield after five cycles was observed, the selectivity (anti/syn ratio and ee) remained high.

■ ASSOCIATED CONTENT

Supporting Information

Details describing synthetic methods, characterization, instrumentation, NMRs, and data for various reactions. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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