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Iron(II)-folded single-chain nanoparticle: a metalloenzyme mimicking sustainable catalyst for highly enantioselective sulfa-Michael addition in water

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Metalloenzyme is a source of inspiration for chemists who attempt to create versatile synthetic catalysts for aqueous catalysis. Herein, we impart metalloenzyme-like characteristics to chiral Fe^{II}-oxazoline complex by incorporating Fe(II) ion into chiral oxazoline-containing discrete self-folded polymer, to realize the highly enantioselective sulfa-Michael addition (SMA) in water. Intrachain Fe^{II}-

10 oxazoline complexation together with hydrophobic interaction triggers the self-folding of oxazoline-containing single polymeric chain in water. The formed Fe^{II}-folded single-chain polymeric nanoparticles (SCPNs) significantly accelerate the aqueous asymmetric SMA reaction *via* self-folded hydrophobic compartment around the catalytic sites, reminiscent of metalloenzymatic catalysis. In addition, they can be facilely recovered for reuse by simple thermo-controlled separation due to thermo-responsive properties. Such metallo-folded SCPNs combine the benefits of transition metal- and bio-catalyst, and avoid the tedious procedures for separation, which is a benefit for

15 energy-saving and industrial applications.

Introduction

Asymmetric sulfa-Michael addition (SMA) is of great importance in asymmetric synthesis, since it provides direct access to enantioenriched sulfides that are versatile precursors for

20 the synthesis of bioactive compounds.[1] Several catalytic systems, including cinchona alkaloid derivatives,[2] heterobimetallic complexes,[3] and organocatalysts,[1c,4] have been developed specifically for this transformation. In spite of impressive progress, most of them suffer from certain limitations, such as

25 low reaction temperatures (-10 to -60 ℃),[1d,2a,4a,4e] high catalyst loading (10-20 mol%),[1b,4a,4c,4e] use of harsh additives (strong acid),[4b] and the requirement of halogenated or aromatic solvents (dichloromethane or toluene),[2-4] which restrict the large-scale application in industry (Scheme 1). Recently, iron-based chiral

30 complex have emerged to catalyze the asymmetric conjugate additions at room temperature without the use of any additives.[5] Nonetheless, industrial practice is still limited by the use of halogenated solvents (dichloroethane) which often results in

environmental problems. Water undoubtedly is an ideal solvent

35 for the asymmetric SMA from economical and environmental points of view. More importantly, water was reported to stabilize the transition state of SMA *via* weak hydrogen bonding, which enhanced the enantioselectivity.[2c] Yet, few attempt has been made to efficiently perform the asymmetric SMA in water,

40 because of the poor water-solubility of substrates and/or catalysts, as well as the competitive complexation of water to metal center.

In nature, metalloenzymes regulate a broad variety of biochemical reactions efficiently in aqueous bioenvironment.[6] The high catalytic efficiency is a result of the guided three-

45 dimensional folding of a single polypeptide chain, which gives a compartmentalized structure with hydrophobic cores surrounded by hydrophilic shells.[7] Amino acid residues often act as ligands to coordinate with metal ions upon the single-chain folding, forming the inner compartment that acts as an 'active site'. The intriguing

50 metalloenzyme catalysis inspired us to mimic these natural catalytic compartments where the catalytically active cores are isolated from the surrounding aqueous environment, so as to realize efficient SMA reactions in water. Incorporating metal ions into discrete self-folded polymer chains through intramolecular

55 chelation offers a facile way to prepare synthetic mimics of metalloenzymes.[8] Apart from operating as triggers for the chain-collapse, the formed metal complex embedding into the compartmentalized SCNP structure allows them to function as isolated catalytic center. The unique structural features are highly

60 reminiscent of those contributing to the effectiveness of metalloenzymes. These fascinating features encouraged us to reason that coordination-driven self-folding strategy could be used to construct Fe^{II}-folded SCPNs and allowed for highly enantioselective SMA reaction in water.

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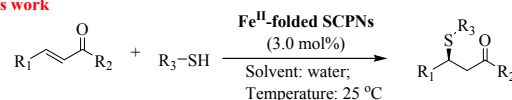
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a) Previous work
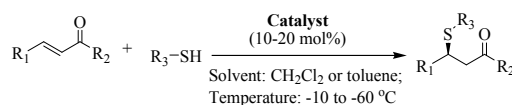
b) This work

Scheme 1 Asymmetric catalysis of SMA to α, β-unsaturated ketones

Since oxazolines are hydrophobic ligands suitable for the coordination of iron ion,[9] we appended multiple chiral oxazoline ligands as structure-forming elements on an amphiphilic random copolymer. It is expected that the chiral oxazoline ligands would undergo intrachain chelation with iron ion, triggering self-folding of the copolymer into water-soluble SCPNs. Hydrophobic compartment should be thus created around the catalytic iron centers, serving as a catalytic cavity for efficient asymmetric SMA in water. Water is strongly retarded into the hydrophobic compartment,[10] minimizing the undesired competitive complexation to Fe(II) center. Unfortunately, the hydrophilic shell may make the SCPNs difficult to be recovered from water. If the shell is thermo-sensitive, being able to undergo reversible hydrophilic/hydrophobic switch at its cloud-point, facile recovery of the SCPNs can be realized. Herein, the oxazoline-containing monomer was copolymerized with thermo-sensitive *N*-isopropylacrylamide (NIPAAm)[11] *via* reversible addition fragmentation chain transfer (RAFT) polymerization.[12] Treatment of the copolymers with FeCl₂ solution under highly diluted conditions gave the Fe^{II}-folded SCPNs with a hydrophobic Fe^{II}-oxazoline core surrounded by a thermosensitive NIPAAm shell. At the reaction temperature (25 °C), the SCPNs are water-soluble, and induced highly enantioselective SMA in water *via* the self-folded hydrophobic compartment around the catalytic sites, reminiscent of metalloenzymatic catalysis. Only 3.0 mol% of the Fe^{II}-folded SCPNs was sufficient to give almost quantitative yield (90-96%) of a wide range of chiral β-thioketones with high enantioselectivity (90–99%) in water without the use of any additives. After the reaction, the catalysts turned hydrophobic upon heating, allowing for the facile recovery of catalysts for steady reuse. More interestingly, the activity switching was repeatable even after seven heating/cooling cycles.

Results and Discussion

Preparation and Characterization of Catalysts

Metalloenzymes achieved efficient catalysis in aqueous bioenvironment *via* a hydrophobic compartment that isolates the active metal center.[6,7] It is a source of inspiration for chemists who sought to perform organic reactions in water. Folding of a single random copolymer chain into compartmentalized SCPNs is a simple and feasible approach for constructing the enzyme-like compartment.[7c,8] In particular, if active metal sites are isolated in their hydrophobic compartments, it endows the SCPNs with enzyme-mimetic activity and selectivity in aqueous catalysis.[8] Therefore, we decided to shield Fe(II) ion in a water-soluble SCPN compartment to fabricate a metalloenzyme-mimetic catalyst for highly enantioselective SMA in water. Intrachain

metal-coordination strategy has been employed to driven the single-chain folding. Given that chiral oxazoline is a suitable ligand for Fe(II) ion,[9] we thus prepared the random copolymers of poly(NIPAAm-*co*-oxazoline) (denoted as PN_xO_y) with NIPAAm and oxazoline pendants random distributed along the polymer backbone. The molar ration of NIPAAm/oxazoline per chain was adjusted elaborately to promote the self-folding of PN_xO_y. We envisioned that the hydrophobic oxazoline pendants would serve as handles for concurrent binding/folding *via* intrachain Fe(II) complexation. And the thermo-responsive NIPAAm side chains may impart inverse temperature-dependent water-solubility to the resulted SCPNs. The obtained Fe^{II}-PN_xO_y should not only achieve highly enantioselective SMA in water as a result of the "biomimetic catalysis", but also be facilely recovered by thermo-controlled separation. The synthesis of Fe^{II}-PN_xO_y was illustrated in Scheme 2.

Since reversible addition–fragmentation chain transfer (RAFT) polymerization provides fine control over the molar mass,[12] the parent random copolymers of PN_xO_y were synthesized *via* RAFT technology by using *N*, *N*-azobis(isobutyronitrile) (AIBN) and benzyl dithiopropionate as the radical initiator and chain transfer agent, respectively. Polymerization degrees of the NIPAAm and oxazoline monomers were verified by ^{1}H NMR in CDCl₃ by comparing the signals attributable to individual blocks (NIPAAm at *ca.* 6.78-6.04 ppm assigned to O=C-N*H*-CH-, and oxazoline at *ca.* 7.50-7.08 ppm assigned to *Ph*-CH₂-oxazoline) with that of an end methyl group (S=C–CH₂–C*H₃* at *ca.* 1.17-0.91 ppm) (see the corresponding ^{1}H NMR spectra in the ESI†). Number average molecular weight (*M*n) and polydispersity index (PDI, *M*w/*M*n) of PN_xO_y were determined by gel permeation chromatography (GPC). Low PDI values (<1.10) suggests the narrow molecular weight distribution of PN_xO_y, which is crucial for successful single-chain folding.[13] Fe^{II}-PN_xO_y formation was carried out in THF at 25 °C by using FeCl₂ as the iron(II) source. Feeding PN_xO_y precursor into the FeCl₂ solution at high dilution condition (0.16 mmol. mL^{-1}) prevented the unwanted interparticle coupling events during the single-chain folding.
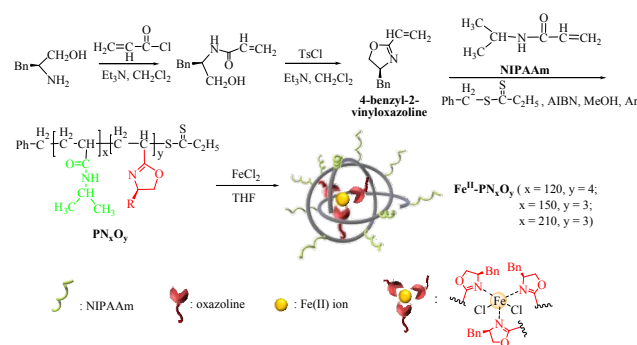
Scheme 2 Schematic representation of the synthesis of Fe^{II}-PN_xO_y (Fe^{II}-$PN_{120}O_4$, Fe^{II}-$PN_{150}O_3$, and Fe^{II}-$PN_{210}O_3$)
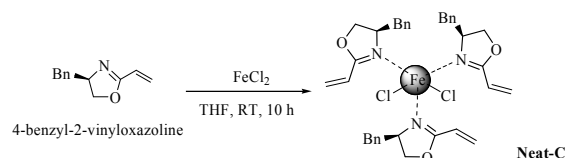
Scheme 3 Synthesis of Neat-C

To evaluate the importance of polymeric pockets around active sites, neat chiral Fe^{II}-oxazoline complex (denoted as Neat-C) was prepared as the control catalyst. As shown in Scheme 3, 4-benzyl-2-vinyloxazoline (5.0 mmol, 0.94 g) was dissolved in THF (20 mL). $FeCl_2$ (5.5 mmol, 0.70 g) in THF (50 mL) was added dropwise into the above solution under vigorous stirring. The mixture was stirred at room temperature for 10 h, and then concentrated in vacuum. Product was precipitated in cold *n*-pentane (100 mL). Filtration and drying in vacuum afforded the Neat-C as a brown powder.

Characterization of Samples

Cloud-point determination. Different from neat Fe^{II}-oxazoline complex (Neat-C) which is water-insoluble, **Fe^{II}-PN_xO_y** exhibits inverse temperature-dependent water-solubility due to the presence of thermosensitive NIPAAm unit. The cloud-point of **Fe^{II}-PN_xO_y** was measured by using UV-vis spectroscopy (Fig. 1A). It is the temperature at which the transmittance of corresponding aqueous solutions markedly decreased. Obviously, **Fe^{II}-$PN_{120}O_4$**, **Fe^{II}-$PN_{150}O_3$,** and **Fe^{II}-$PN_{210}O_3$** presented the cloud-point at *ca.* 26, 29 and 31°C, respectively (Fig. 1A). Indeed, the nanoobjects were soluble in water at 25 °C (room temperature, lower than their cloud-point), while became hydrophobic gradually as local temperature increased (Fig. 1B). When the local temperature was up to 36 °C, they were completely precipitated out of water, as shown by the typical **Fe^{II}-$PN_{150}O_3$** (Fig. 1B). Notably, the temperature for catalyst separation (36 °C) is slightly higher than room temperature (25 °C), which is a benefit for energy-saving in industrial applications. More interestingly, full reversibility without hysteresis was observed upon slow cooling (Fig. 1B). Such temperature-dependent dissolution-precipitation transitions behavior can be used to realize the coupling of the reaction and separation of **Fe^{II}-PN_xO_y** for asymmetric SMA in water.

UV-vis. The intramolecular Fe^{II}-oxazoline coordination in **Fe^{II}-PN_xO_y** was evaluated by UV-vis spectroscopy (Fig. 2A). Clearly, typical $PN_{150}O_3$ precursor exhibited a strong absorbed peak at 303 nm, which corresponded to $\pi \rightarrow \pi^*$ transitions of oxozaline group.[14] After $FeCl_2$ treatment, the characteristic peak shifted to 297 nm, along with the appearance of a new peak at 497 nm which were assigned to Fe^{II}-oxazoline charge-transfer (Fig. 2A-a *vs.* 2A-b). It is convincing proof for the coordination of oxazoline to Fe(II) ion. To confirm the coordinate ability of oxazoline

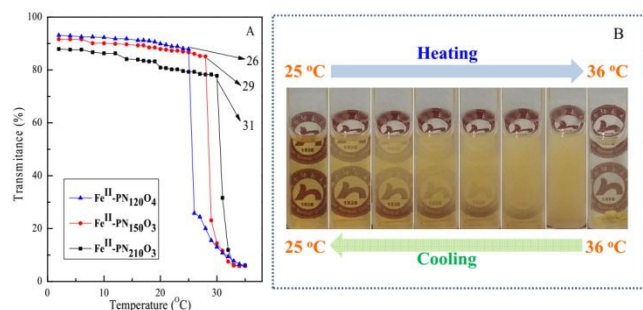**Fig. 1** (A) Transmittance curves of the **Fe^{II}-PN_xO_y** (**Fe^{II}-$PN_{120}O_4$**, **Fe^{II}-$PN_{150}O_3$**, and **Fe^{II}-$PN_{210}O_3$**) in aqueous solutions (concentration: 0.5 M); (B) aqueous solution of typical **Fe^{II}-$PN_{150}O_3$** at local temperature range from 25 to 36 °C

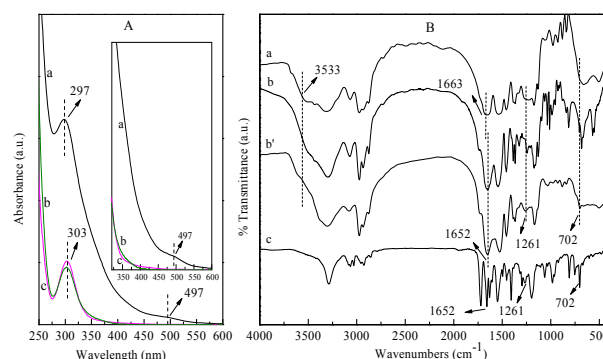**Fig. 2** (A) UV-vis spectra of $PN_{150}O_3$ (a), **Fe^{II}-$PN_{150}O_3$** (b) and HCl-treated **Fe^{II}-$PN_{150}O_3$** (c); (B) FT-IR spectra of $PN_{150}O_3$ (a), fresh **Fe^{II}-$PN_{150}O_3$** (b), recovered **Fe^{II}-$PN_{150}O_3$** after the 7th reuse (b') and Neat-C (c).

group, oxazoline in $PN_{150}O_3$ was protonated with HCl before it was exposed to Fe(II) ion. Indeed, the protonated $PN_{150}O_3$ failed to coordinate with Fe(II) ion, as evident from the absence of Fe^{II}-oxazoline charge-transfer peak (at 497 nm) (Fig. 2A-c).

FT-IR. Additional information on the metal coordination can be obtained from the FT-IR spectroscopy (Fig. 2B). Obviously, parent $PN_{150}O_3$ exhibited the characteristic C=N stretching vibration of oxazoline at 1663 cm^{-1} (Fig. 2B-a).[15] The stretching vibration shifted to 1652 cm^{-1} when $PN_{150}O_3$ was treated with $FeCl_2$ (Fig. 2B-b *vs.* 2B-a). It gives an evidence for the participation of C=N group in forming coordination bonds with Fe(II) ion. Indeed, a characteristic N-Fe stretching vibration was observed at 702 cm^{-1} in FT-IR spectrum of **Fe^{II}-$PN_{150}O_3$** (Fig. 2B-b).[16] The formation of N-Fe dative bonds should operate as triggers for the self-folding of $PN_{150}O_3$, enabling the creation of an enclosed polymeric pocket around Fe(II) ions. The heteroatom of oxygen in oxazoline don't take part in the coordination as evident from the intact C-O-C band (at 1261 cm^{-1}) during the treatment with Fe(II) ion (Fig. 2B-b *vs.* 2B-a).[15] Notably, the characteristic bands associated with Fe^{II}-oxazoline in **Fe^{II}-$PN_{150}O_3$** are similar to those of Neat-C (Fig. 2B-b *vs.* 2B-c). It suggests the identity of catalytic Fe^{II}-oxazoline sites in **Fe^{II}-PN_xO_y** with Neat-C. Apart from the characteristic vibration associated with Fe^{II}-oxazoline complex, additional band at around 3533 cm^{-1} was also obvious in the FT-IR spectrum of **Fe^{II}-$PN_{150}O_3$** (Fig. 2B-b *vs.* 2B-c). It is associated with stretching vibration mode of N–H of amide group in the thermo-responsive NIPAAm moiety.[17] Notably, no change in the amide band was observed during the incorporation of Fe(II) ion into $PN_{150}O_3$, which means that the thermo-sensitive NIPAAm remained intact during the coordination (Fig. 2B-b *vs.* 2B-a). Therefore, Fe(II) ions are only shielded in the oxozaline cavity *via* metal-coordination. The hydrophobic shielding of active site, together with the coordination sphere provided by folded copolymer, makes these Fe^{II}-containing SCPNs structurally similar to metalloenzyme.

Job's plot analysis. The binding stoichiometry of Fe(II) ion to oxozaline in **Fe^{II}-PN_xO_y** was determined by using Job's method, an approach that determined the stoichiometry of chemical equilibria (Fig. 3).[8c,18] In this method, UV-vis absorbance of Fe(II)-oxazoline complex which is proportional to the complex

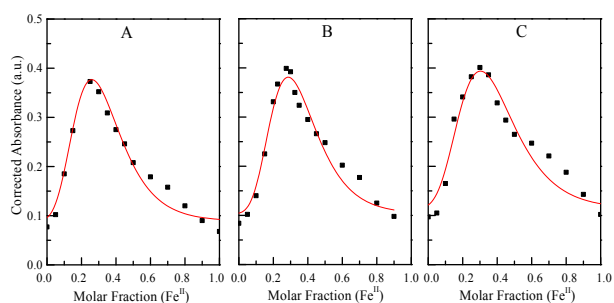**Fig. 3** Job's plot to determine the binding stoichiometry of Fe(II) ions. $PN_{120}O_4$ (A), $PN_{150}O_3$ (B) and $PN_{210}O_3$ (C) with Fe^{II} obtained from variations in absorption at 297 nm

concentration was plotted against the mole fraction of Fe(II) ion, while the total concentration of $FeCl_2$ and oxazoline was kept constant. The obtained Job's plots of Fe^{II}-$PN_{120}O_4$, Fe^{II}-$PN_{150}O_3$, and Fe^{II}-$PN_{210}O_3$ gave the maximum points at the Fe(II) mole fraction of 0.26, 0.29 and 0.3, respectively. Actually, the values represent mole fractions of Fe(II) ion in corresponding metal-coordination chemical equilibrium. According to the Job's plot, we estimated that the average coordination of oxozaline to Fe(II) ion in Fe^{II}-$PN_{120}O_4$, Fe^{II}-$PN_{150}O_3$, and Fe^{II}-$PN_{210}O_3$ was about 2.8, 2.4, and 2.3, respectively. The average coordination numbers are accorded with the numbers of oxozaline units per polymer chain. It suggests the intrachain metal coordination for Fe^{II}-PN_xO_y, rather than interchain coupling. Polymer backbone together with hydrophilic NIPAAm shell should isolate the oxozaline units, preventing interchain coupling events. Notably, the binding stoichiometry in Fe^{II}-PN_xO_y is less than the theoretical coordination number of Fe(II) ions (*i.e.*, 6 for an octahedron coordination). The unsaturated iron sites may favor the coordination of carbonyl oxygen in α,β-unsaturated ketones to Fe(II) center, which increases the electrophilicity of the β-carbon and assisted the conjugate addition.[19] Furthermore, the vacant coordination site on Fe(II) core should also benefit the formation of the Fe–thiol complex. This precoordinated thiol may play a role in orienting or activating the enone acceptor within the Fe–oxozaline complex through the known *trans* directing effect of sulfur ligands in metal complexes.[5,20]

TEM. The intrachain Fe^{II}-oxazoline coordination that triggers the self-folding of individual polymer chains simultaneously was further confirmed by TEM (Fig. 4). Clearly, $PN_{150}O_3$ precursor was unfolded in methanol, a good solvent for the both PNIPAAM and oxazoline segments, adopting a random coil conformation in the TEM image (Fig. 4a). Being treated with Fe(II) ion, the copolymer chain coiled into nanoparticles with an ultrasmall size in the range of 4-10 nm (Fig. 4b). This diameter value of obtained Fe^{II}-$PN_{150}O_3$ is consistent with that adopting a single-chain folded conformation in solution.[8c,21] Notably, HCl-treated $PN_{150}O_3$ failed to folded in methanol even through it was exposed to Fe(II) ions (Fig. 4c). This is attributed to the loss of coordinate ability of oxazoline group in $PN_{150}O_3$, as confirmed by UV-vis spectra (Fig. 2A-c). These observations confirms the intramolecular folding upon Fe^{II}-oxazoline coordination. Instead of the random coil morphologies in methanol, Fe^{II}-$PN_{150}O_3$ adopted more compact globule conformation in water (a good solvent for PNIPAAm, but bad solvent for oxazoline) at room

Fig. 4 TEM images of $PN_{150}O_3$ (a), Fe^{II}-$PN_{150}O_3$ (b), and HCl-treated Fe^{II}-$PN_{150}O_3$ (c) in methanol, as well as the Fe^{II}-$PN_{120}O_4$ (d), Fe^{II}-$PN_{150}O_3$ (e) and Fe^{II}-$PN_{210}O_3$ (f) in water at room temperature stained with phosphotungstic acid

temperature (Fig. 4e). The size of Fe^{II}-$PN_{150}O_3$ decreased to *ca.* 1.0 nm when water was used as the solvent. It is indicative of the intramolecular hydrophobic interaction which makes the SCPNs more compact. Similar morphologies were observed for the Fe^{II}-$PN_{120}O_4$ and Fe^{II}-$PN_{210}O_3$ in water (Fig. 4d and 4f). The observations confirms that amphiphilic PN_xO_y self-fold in water through the cooperation of intrachain metal coordination and hydrophobic interaction. The resulted Fe^{II}-PN_xO_y should adopt an individual core-shell nanostructure with the hydrophobic Fe^{II}-oxazoline core surrounded by hydrophilic PNIPAAm shell. Such morphology is akin to the globular, native conformation of enzymes which showed a hydrophobic core and a hydrophilic shell in aqueous media.[22]

Particle size distribution analysis. Dynamic light scattering (DLS) was employed to further determine the hydrodynamic diameter (D_h) and size distribution of $PN_{150}O_3$ and Fe^{II}-folded SCPNs in water at 25 ºC (Fig. 5). Clearly, the typical $PN_{150}O_3$ has a D_h of 15.9 nm in water, while the D_h of Fe^{II}-$PN_{150}O_3$ reduced to 8.7 nm. These findings confirm the intramolecular folding upon Fe-oxazoline coordination. Indeed, all Fe^{II}-PN_xO_y formed aggregates in water with D_h in the range of 7.5-13.5 nm, indicative of the intramolecular chain collapse. Interestingly, the size of Fe^{II}-PN_xO_y in water gradually decreased with increasing the hydrophobic oxazoline content. D_h of Fe^{II}-$PN_{210}O_3$, Fe^{II}-$PN_{150}O_3$, and Fe^{II}-$PN_{120}O_4$ were *ca.* 13.5, 8.7, and 7.5 nm, respectively. This tendency is fully consistent with the fact that intrachain hydrophobic interaction of oxazoline made the Fe^{II}-folded PN_xO_y compact. These observations give further evidence for the intramolecularly self-folding of Fe^{II}-PN_xO_y as a result of the cooperation of intrachain metal complexation and hydrophobic forces. The concurrent binding/folding strategy makes the Fe^{II}-containing SCPNs uniform and compact in water, as evidenced by the polydispersity indexes (PDI). Obviously, the hydrodynamic diameter analysis gave low PDI values for Fe^{II}-$PN_{120}O_4$, Fe^{II}-$PN_{150}O_3$, and Fe^{II}-$PN_{210}O_3$ (0.283, 0.312, and 0.275, respectively), suggesting the homogeneous distribution, spherical morphology, and uniform size of the corresponding SCPNs.[17,23] Aggregation of the resulting SCNPs should be prevented by the steric repulsion of multiple hydrophilic
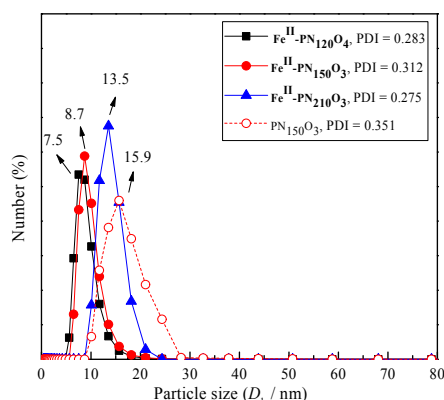
Fig. 5 Size distribution of **Fe^{II}-PN$_x$O$_y$** and PN$_{150}$O$_3$ in water at room temperature (concentration of 0.5 mg mL^{-1})

PNIPAAm chains which isolated a single main chain in water. The PDI value of PN$_{150}$O$_3$ in water was relatively higher (0.351), probably due to the sparse morphology. These observations are in complete agreement with the results obtained in TEM images.

Catalytic Performances

As expected, Fe^{II}-folded SCPNs provided the hydrophobic reaction spaces to accommodate asymmetric SMA of propanethiol to chalcone in water. As shown in Table 1, the asymmetric conjugation addition proceeded efficiently in water with the employment of **Fe^{II}-PN$_x$O$_y$** (Table 1, entries 1-4). In particular, only 3 mol% of **Fe^{II}-PN$_{150}$O$_3$** was sufficient to afford almost quantitative yield (95%) of the Michael adduct with excellent enantioselectivity (96%) (Table 1, entry 2). The absolute configuration of product was assigned to be (*S*) by comparing with the optical rotation value reported in the literature.[5a] However, in the absence of polymer frameworks, neat Fe^{II}-oxazoline complex (Neat-C) was far less active and selective for this transformation. Low yield (43%) with disappointing ee value (83%) was obtained under identical conditions (Table 1, entry 5). The discrepancy in catalytic efficiency emphasizes an importance of the catalytic, hydrophobic compartment for the aqueous catalysis. Apart from hydrophobic shielding of Fe^{II}-oxazoline from the aqueous environment, the hydrophobic compartment effectively sequestered substrates from the surrounding water through hydrophobic attractive forces.[8d,17,24] The high local concentration of substrates around catalytic sites in the interior of Fe^{II}-folded SCPNs allowed us to use low catalyst loading for efficient catalysis. More importantly, the internal chirality of hydrophobic compartment should further induce the confined asymmetric catalysis, introducing highly enantioselective effects.[22b] Interestingly, midway addition of PN$_{150}$O$_3$ copolymer (equivalent to the PN$_{150}$O$_3$ amount in **Fe^{II}-PN$_{150}$O$_3$**) into the Neat-C system failed to improve the catalytic efficiency (Table 1, entry 6 *vs.* 5). It is reasonable that unlike the organic substrates, the water-insoluble Neat-C is solid, and gives a small amount in solution, it is hard to be encapsulated in the hydrophobic domain along with substrates. The results are agree with our hypothesis that high local concentration of substrates around catalytic sites is crucial for this system to be active, and this is only achieved in the presence of hydrophobic, catalytic compartments.

Table 1 Results of asymmetric SMA of thiols to α, β-unsaturated ketones in water with chiral Fe^{II}-oxazoline catalysts [a]

Entry	Catalyst	R$_1$	R$_2$	R$_3$	Product	T (h)	Yield [b] (%)	ee [c] (%)
1	**Fe^{II}-PN$_{120}$O$_4$**					36	88	99
2	**Fe^{II}-PN$_{150}$O$_3$**					36	95	96
3	**Fe^{II}-PN$_{150}$O$_3$** [d]	Ph	Ph	n-C$_3$H$_7$	*1*	48	92	94
4	**Fe^{II}-PN$_{210}$O$_3$**					36	91	96
5	Neat-C					36	43	83
6	Neat-C [e]					36	47	82
7	**Fe^{II}-PN$_{150}$O$_3$**	Ph	CH$_3$	n-C$_3$H$_7$	*2*	24	96	99
8	Neat-C					24	59	70
9	**Fe^{II}-PN$_{150}$O$_3$**	4-OMePh	Ph	n-C$_3$H$_7$	*3*	48	92	98
10	Neat-C					48	46	60
11	**Fe^{II}-PN$_{150}$O$_3$**	4-OMePh	CH$_3$	n-C$_3$H$_7$	*4*	48	95	90
12	Neat-C					48	51	67
13	**Fe^{II}-PN$_{150}$O$_3$**	4-NO$_2$Ph	Ph	n-C$_3$H$_7$	*5*	48	10	89
14	Neat-C					48	3	59
15	**Fe^{II}-PN$_{150}$O$_3$**	Ph	Ph	4-Cl-C$_6$H$_4$-CH$_2$	*6*	36	93	95
16	Neat-C					36	56	87
17	**Fe^{II}-PN$_{150}$O$_3$**	4-OMePh	Ph	4-Cl-C$_6$H$_4$-CH$_2$	*7*	48	90	96
18	Neat-C					48	54	90
19	**Fe^{II}-PN$_{150}$O$_3$**	CH$_3$	CH$_3$	4-Cl-C$_6$H$_4$-CH$_2$	*8*	48	94	>99
20	Neat-C					48	52	69
21	**Fe^{II}-PN$_{150}$O$_3$**	Ph	Ph	4-Cl-C$_6$H$_4$	*9*	48	92	98
22	Neat-C					48	68	55

[a] Catalyst (3.0 mol% of ketones, based on iron content), α, β-unsaturated ketones (0.1 mmol), thiol (0.12 mmol), water (1.0 mL), 25 ºC.

[b] Isolated yield after column chromatography.

[c] Determined by HPLC (Daicel Chiralpak AD column). The absolute configuration of product was assigned to be (*S*) by comparing with the optical rotation value reported in the literature.[5a]

[d] Catalyst (3.0 mol% of ketones, based on iron content), α, β-unsaturated ketones (4.0 mmol), thiol (5.0 mmol), water (20 mL), 25 ºC.

[e] Neat-C (3.0 mol% of chalcone, based on iron content), PN$_{150}$O$_3$ (0.061 g, equivalent to the amount of PN$_{150}$O$_3$ in **Fe^{II}-PN$_{150}$O$_3$**), chalcone (0.1 mmol), propanethiol (0.12 mmol), water (1.0 mL), 25 ºC.

Since compartmentalized SCPNs behaved as a catalytic nanoreactor for asymmetric SMA reaction, morphology and microenvironment of the hydrophobic compartment directly affected the catalytic activity of **Fe^{II}-PN$_x$O$_y$**. Indeed, **Fe^{II}-PN$_{150}$O$_3$**-based SCPNs with D_h of 8.7 nm showed the highest catalytic efficiency in aqueous asymmetric SMA of propanethiol to chalcone (Table 1, entry 2). It could even mediate the gram-scale SMA reaction smoothly, yielding large quantity of (*S*)-3-(propylthio)-1,3-diphenylpropan-1-one (1.12 g, 92% yield) with excellent ee value (94% ee) (Table 1, entry 3). Reduced size of the SCPNs (**Fe^{II}-PN$_{120}$O$_4$**, D_h = 7.5 nm) was unfavorable for the transformation (Table 1, entry 1), probably due to the limited mobility of substrates in the catalytic pocket. Furthermore,

conformational freedom of Fe[II]-oxozaline complexes should be also limited in the smaller compartment, which was undesirable for the asymmetric catalysis. While, **Fe[II]-PN210O3** which folded into larger SCPNs (D_h = 13.5 nm) was also detrimental to the catalysis (Table 1, entry 4). Too dense chain loops around the metal-ions, which blocks access of substrate to the catalytic pockets, may result in the decline in activity.[8d] The observations provide further evidence for the confined catalysis in the SCPN compartment.

Different from natural metalloenzymes which often exhibits a narrow substrate range, the **Fe[II]-PN150O3** is universal in the aqueous asymmetric SMA. A wide range of α, β-unsaturated ketones, ethier aromatic or aliphatic, get almost quantitatively conjugate addition to yield the corresponding adducts (90-96%) with excellent enantioselectivity (90-99%) in water although they were water-incompatible (Table 1, entries 7, 9, 11, 15, 17, 19 and 21). Poor yield (10%) was observed over the nitro-substituted ketones, despite the encouraging enantioselectivity (89%) (Table 1, entry 13). The lower reactivity is probably due to undesirable competitive complexation of the nitro group to Fe(II) center,[25] which retards the precoordination of thiol to Fe(II) center for the conjugate addition. Furthermore, the nitro group in 4-nitrochalcone decreases the electron density at the carbonyl oxygen by inductive and resonance effects, which may further weaken the coordination between carbonyl oxygen and Fe(II) center. Interestingly, the use of benzyl mercaptan as sulfur source still provided the desired chiral β-thioketones with high yield (90-94%) and ee values (95-99%), although the nucleophile was more sterically demanding (Table 1, entries 15, 17 and 19). Furthermore, 4-chlorobenzenethiol, a less reactive nucleophile, also reacted with chalcone smoothly to afford the β-keto sulfide **9** in 92% yield and 98% ee value (Table 2, entry 21). In all cases, no disulfide formation was observed in water medium. Using the different alkyl thiols affords the access to optically active chiral sulfur compounds bearing removable S-protecting groups.[26]

Benefiting from the hydrophobic, catalytic compartment, the Fe[II]-folded SCPNs were superior to other reported catalytic systems either metallic or organic, such as per-6-amino-β-cyclodextrin,[27] Sc(OTf)3/bipyridine,[28] cinchona alkaloid-squaramide,[2b] and Fe[III]-salen complex,[5a] as seen in Table 2. At room temperature, only 3.0 mol% of **Fe[II]-PN150O3** was sufficient to efficiently catalyze the asymmetric SMA reaction in water without the use of any additives, due to the hydrophobic shielding effective and synergistic effect of metal center with polymeric framework (Table 2, entry 1). Despite possessing similar hydrophobic cavities, β-cyclodextrin was far less selective. Stoichiometric per-6-amino-b-cyclodextrin catalyst was insufficient to provide the β-adduct with satisfied ee value, although the yield was encouraging (Table 2, entry 2).[25] Sc(OTf)3/bipyridine, a Lewis acid catalytic system, could catalyze this transformation in an enantioselective fashion (Table 2, entry 3). But it suffered from low catalytic activity due to the poor water-solubility of catalysts and substrates. Furthermore, strong base of sodium hydroxide was required in the Sc(OTf)3/bipyridine system to ensure the conversion to Michael adduct, which was undesirable for industrial application (Table 2, entry 3).[27] Cinchona alkaloid-squaramide employing hydrogen bond for substrate activation circumvented the undesirable

Table 2 Asymmetric conjugate addition of various thiols to chalcone over different catalysts

Entry	Catalyst	Catalyst loading[f]	Nucleophile	Solvent	T (h)	Yield[b] (%)	ee[c] (%)
1	**Fe[II]-PN150O3**[a]	3.0 mol%	⌇SH	H2O	24	95	96
2	Per-6-amino-β-cyclodextrin[b]	100 mol%	⌇SH	H2O	36	100	23
3	Sc(OTf)3/bipyridine[c]	1.0 mol%	⌇SH	H2O	70	64	83
4	Cinchona alkaloid-squaramide[d]	1.0 mol%	⌇SH	Toluene	24	80	96
5	**Fe[II]-PN150O3**[a]	3.0 mol%	Cl—⬡—SH	H2O	36	93	95
6	Fe[III]-salen complex[e]	10 mol%	Cl—⬡—SH	CH2Cl2	36	68	84

[a] **Fe[II]-PN150O3** (0.003 mmol), chalcone (0.1 mmol), thiol (0.12 mmol), water (1.0 mL), 25 °C (In this work)

[b] Per-6-amino-β-cyclodextrin (0.1 mmol), chalcone (0.1 mmol), thiol (0.1 mmol), water (1.0 mL), 25 °C (Ref. 27).

[c] Sc(OTf)3 (0.005 mmol), bipyridine (0.01 mmol), chalcone (0.5 mmol), thiol (0.5 mmol), NaOH (3.0-20.0 mol %, the minimum quantity to reach pH = 7.0), water (1.0 mL), 30 °C (Ref. 28).

[d] Cinchona alkaloid-squaramide catalyst (0.0025 mmol), chalcones (0.25 mmol), thiol (0.375 mmol), toluene (1.0 mL), 25 °C (Ref. 2b) .

[e] Fe[III]-salen (0.01 mmol), chalcone (0.1 mmol), thiol (0.12 mmol), CH2Cl2 (1.0 mL), 25 °C (Ref. 5a) .

[f] The mol% of chalcone.

[g] Isolated yield after column chromatography.

[h] Determined by HPLC (Daicel Chiralpak AD column).

additives in the enantioselective SMA.[2b] Nevertheless, non-polar organic solvents, such as toluene and dichloromethane, were required to ensure the efficiency.[2b] If water is used as the reaction medium, low enantioselectivity or even racemic product should be detected due to the competition for the hydrogen bond of water with the catalyst (Table 2, entry 4).[2b] Furthermore, the **Fe[II]-PN150O3** in water was even more efficient than other reported iron-based complex in organic solvent (Table 2, entry 5 *vs.* 6). The 10 mol% of reported chiral Fe[III]-salen catalyst gave only 68 % yield of (*R*)-β-keto sulfide with low enantioselectivity (84%) even though the addition was performed in dichloromethane (Table 2, entry 6).[5a] The results demonstrate the advantages of metalloenzyme mimicking Fe[II]-folded SCPNs used for asymmetric SMA reaction in water.

Reusability

Apart from exhibiting superior activity and selectivity, **Fe[II]-PNxOy** exhibited the thermal driven ''smart'' recovery in the aqueous system due to the presence of thermo-sensitive PNIPAAm shell. After reaction, the Fe[II]-folded SCPNs turned hydrophobic upon heating above their corresponding cloud-point (Fig. 1). This allows for their separation from aqueous phase by decantation. To our delight, the recovered catalysts of **Fe[II]-PN120O4**, **Fe[II]-PN150O3** and **Fe[II]-PN210O3** could be reused up to seven times without significant loss in activity and selectivity in asymmetric SMA of propanethiol to chalcone in water (Fig. 6A). Leaching of Fe(II) species, a main reason for deactivation of the iron-containing catalyst, did not occur during the addition, as
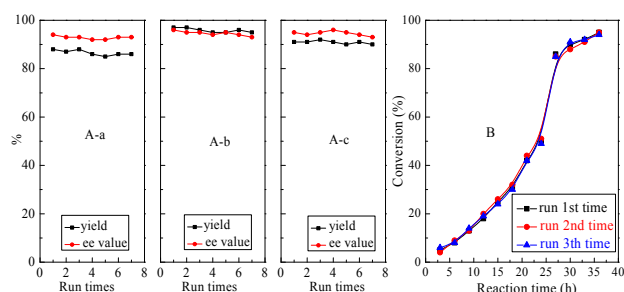
Fig. 6 (A) Reuse of **Fe^{II}-PN$_{120}$O$_4$** (a), **Fe^{II}-PN$_{150}$O$_3$** (b) and **Fe^{II}-PN$_{210}$O$_3$** (c) in asymmetric SMA reaction of propanethiol to chalcone in water, (B) kinetic curves of the consecutive experimental runs 1-3 over **Fe^{II}-PN$_{150}$O$_3$**

proved by the leaching tests of recovered catalysts by ICP. Indeed, chemical analysis of the recovered catalysts gave the iron content (0.089, 0.067, and 0.044 mmol g^{-1} for recovered **Fe^{II}-PN$_{120}$O$_4$**, **Fe^{II}-PN$_{150}$O$_3$** and **Fe^{II}-PN$_{210}$O$_3$**, respectively) almost identical to that of the corresponding fresh one. The negligible leaching of catalysts should arise from the hydrophobic shielding of Fe^{II}-oxazoline complex in a structured compartment which protected by PNIPAAm shell. Excellent stability of the **Fe^{II}-PN$_x$O$_y$** is also evident from the FT-IR spectra of typical **Fe^{II}-PN$_{150}$O$_3$** with fresh and reused seven times (Fig. 2b vs. b'). Kinetics study provided the other substantial proof for the stability of **Fe^{II}-PN$_x$O$_y$**, based on the fact that no significant change in the apparent rate constant occurred in the consecutive experimental runs 1-3 over typical **Fe^{II}-PN$_{150}$O$_3$** (Fig. 6B).[29] The facile recovery together with the perfect stability makes **Fe^{II}-PN$_x$O$_y$** highly promising in sustainable industrial applications.

Conclusions

In conclusion, Fe^{II}-folded SCPNs which shielded chiral Fe^{II}-oxazoline complex in a hydrophobic compartment have been constructed through the cooperation of intrachain Fe^{II}-oxazoline coordination and hydrophobic interaction. These synthetic soft nanoentities mimic the compartmentalized structure and catalytic function of metalloenzyme, allowing efficient asymmetric SMA of thiols to a wide range α, β-unsaturated ketones in water at room temperature without the need of any organic solvent or additional additives. In particular, they can be facilely recovered from the aqueous system for efficient reuse by simply adjusting the local temperature. The novel catalytic system offers several advantages, such as operational simplicity, mild reaction conditions, low catalyst loading, high efficiency, and facile reuse of catalyst. All these advantages make it a benign protocol from the sustainability point of view, and inspired us to design the other enzyme mimics for a wide range of sustainable industrial applications.

Experimental Section

Materials and Reagents

L-phenylalaninol, acryloylchloride and *p*-toluenesulfonyl chloride (TsCl) were brought from Aldrich. 4-(Dimethylamino) pyridine (DMAP) and *p*-anisaldehyde were purchased from MACKLIN. *P*-nitrobenzaldehyde, propanethiol, 4-chlorobenzylthiophenol, 4-chlorobenzenethiol, and 3-penten-2-one were obtained from J&K. AIBN,

FeCl$_2$ and acetophenone were brought from Alfa Aesar. NIPAAm was purchased from Acros. Other commercially available chemicals were laboratory grade reagents from local suppliers. AIBN was recrystallized from methanol. All reagents used for the monomer synthesis were stirred over CaH$_2$, freshly distilled under vacuum, and kept under a dry argon atmosphere until use.

Methods

FT-IR spectra were obtained as potassium bromide pellets with a resolution of 4 cm^{-1} and 64 scans in the range of 400-4000 cm^{-1} using an AVATAR 370 Thermo Nicolet spectrophotometer. NMR spectra were recorded on a BRUKER AVANCE-500 spectrometer with TMS as an internal standard. Iron contents in catalysts were determined by inductively coupled plasma mass spectrometry (ICP-MS) on a NexION 300X analyzer (Perkin-Elmer Corp.). Optical rotation of samples was measured on a WZZ-2A Automatic Polarimeter. Molecular weight and the molecular weight distribution of copolymers were obtained by GPC. Analyses were performed on an Alltech Instrument (Alltech, America) using THF as the solvent eluting at a flow of 1.0 mL. min^{-1} through a Jordi GPC 10000 A column (300 mm × 7.8 mm) equipped with an Alltech ELSD 800 detector. Cloud-point of catalysts in water was determined by measuring the transmittance of the corresponding aqueous solution (0.5 mg. mL^{-1}) using a UV-visible photometer. Morphologies of Fe^{II}-folded SCPNs were observed by TEM on a Microscope JEM-2100F at an accelerating voltage of 200 kV. Samples were prepared by depositing the aqueous solution (0.5 mg. mL^{-1}) onto an ultrathin carbon-coated copper grid, followed by removal of excess solution by blotting the grid with filter paper. The samples were dried for 48 h at room temperature in desiccators and were negatively stained by phosphotungstic acid. Hydrodynamic diameter (D_h) of Fe^{II}-folded SCPNs was determined by DLS using a MS2000 Laser Particle Size Analyzer (Malvern, U.K.). The aqueous solution of samples (0.5 M) was filtered through a 0.45 μm disposable polyamide membrane to free it from dust particles before measurement.

Preparation of Fe^{II}-PN$_x$O$_y$ (x=120, y=4; x=150, y=3; x=210, y=3)

Synthesis of 4-benzyl-2-vinyloxazoline: *L*-phenylalaninol (9.0 mmol, 1.36 g) and triethylamine (9.2 mmol, 0.93 g) were dissolved in dichloromethane (10 mL), and then cooled to 0 °C. Acryloyl chloride (9.2 mmol, 0.83 g) in dichloromethane (10 mL) was added dropwise over 1 h at 0 °C. The mixture was stirred at room temperature for 15 h, and then was extracted with saturated brine (3×15 mL). After being dried over anhydrous Na$_2$SO$_4$, organic phase was mixed with DMAP (0.8 mmol, 0.10 g) and triethylamine (8.2 mmol, 0.83 g) at 0 °C. TsCl (8.0 mmol, 1.53 g) in dichloromethane (10 ml) was then added. The mixture was stirred at room temperature for 12 h. The obtained solution was washed with saturated NH$_4$Cl (3×10 mL) to remove the DMAP, and further washed with saturated NaHCO$_3$ (3×10 mL) to remove the formed hydrochloric acid. Organic layer was dried over anhydrous Na$_2$SO$_4$. After being concentrated in vacuum, the residue was purified by chromatography on basic alumina with petroleum ether/ethyl acetate (v/v=1/1), giving 4-benzyl-2-vinyloxazoline as the white powder (0.88 g, yield: 59%). FT-IR (KBr): γ_{max}/cm^{-1} 3418, 3290, 3084, 3032, 2972, 2929, 2790, 1720, 1663, 1629, 1549, 1409, 1299, 1262, 1207, 1108, 1061, 1033, 983, 924, 885, 808, 752, 705, 603, 567, 477. ^{1}H NMR (500 MHz, CDCl$_3$): δ (ppm): 7.34-7.22 (m, 5 H, *Ph*-CH$_2$-oxazoline), 6.30-5.90 (m, 3 H, C*H$_2$*=C*H*-oxazoline), 4.25-4.23 (m, 1 H, O-CH$_2$-C*H*-N in oxazoline),

4.22-4.16 (m, 2 H, O-CH_2-CH-N in oxazoline), 3.03-2.86 (m, 2 H, Ph-CH_2-oxazoline).

Synthesis of PN$_x$O$_y$: A certain feed molar ratio of NIPAAm and oxazoline (10 mmol of NIPAAm and 0.33 mmol of oxazoline for PN$_{120}$O$_4$, 10 mmol of NIPAAm and 0.2 mmol of oxazoline for PN$_{150}$O$_3$, 10 mmol of NIPAAm and 0.14 mmol of oxazoline for PN$_{210}$O$_3$) were dissolved in anhydrous methanol (15 mL) in Schlenk tube. AIBN (1/80 of the total molar of monomers) and benzyl dithiopropionate (1/80 of the total molar of monomers) were then added as the radical initiator and chain transfer agent, respectively, for this copolymerization. The solutions were degassed by three freeze-pump-thaw cycles to remove oxygen completely. Polymerizations were carried out at 60 °C under dry argon atmosphere. After 24 h, the solutions were cooled with liquid nitrogen to cease the reactions, and then were concentrated in vacuo. Crude products were dissolved in THF (5.0 mL), and subsequently precipitated for three times from diethyl ether (100 mL). After being dried in vacuum, the copolymers were obtained as light yellow powder, which were denoted as PN$_x$O$_y$ (x=120, y= 4; x=150, y= 3; x= 210, y= 3, the numbers of NIPAAm and oxazoline units were determined by ¹H NMR spectra of corresponding copolymer).

PN$_{120}$O$_4$: FT-IR (KBr): γ$_{max}$/cm⁻¹ 3533, 3440, 3310, 3068, 2973, 2946, 2892, 1663, 1538, 1458, 1368, 1342, 1261, 1172, 1131, 1079, 977, 927, 880, 838, 660, 504. ¹H NMR (500 MHz, CDCl₃): δ (ppm): 7.39-7.08 (m, 25 H, *Ph*-CH₂-oxazoline and *Ph*-CH₂-CH₂-CH- in backbone chain), 6.59-6.27 (m, 120 H, O=C-N*H*-CH in NIPAAm), 4.01-3.89 (m, 126 H, -C*H*-CH₂- of backbone chain in NIPAAm, -C*H*-CH₂- of backbone chain in oxazoline and S=C-C*H₂*-CH₃ in backbone chain), 3.78-2.03 (m, 248 H, -CH-C*H₂*- of backbone chain in NIPAAm and -O-C*H₂*-CH-N- in oxazoline), 1.89-1.57 (m, 130 H, CH₃-C*H*-CH₃ in NIPAAm, Ph-C*H₂*-oxazoline, -O-C*H₂*-CH-N- in oxazoline and Ph-C*H₂*-CH₂-CH- in backbone chain), 1.45-1.38 (m, 8 H, -CH-C*H₂*- of backbone chain in oxazoline), 1.28-1.16 (m, 720 H, C*H₃*-CH-C*H₃* in NIPAAm), 0.91-0.88 (m, 3 H, S=C-CH₂-C*H₃* in backbone chain). GPC (THF): *M*n = 14456, *M*w = 15178, PDI = 1.05.

PN$_{150}$O$_3$: FT-IR (KBr): γ$_{max}$/cm⁻¹ 3533, 3438, 3312, 3068, 2974, 2945, 2897, 1663, 1542, 1460, 1367, 1340, 1261, 1172, 1129, 1068, 981, 934, 876, 838, 663, 505. ¹H NMR (500 MHz, CDCl₃): δ (ppm): 7.50-7.08 (m, 20 H, *Ph*-CH₂-oxazoline and *Ph*-CH₂-CH₂-CH- in backbone chain), 6.78-6.04 (m, 150 H, O=C-N*H*-CH in NIPAAm), 4.77-4.02 (m, 154 H, -C*H*-CH₂- of backbone chain in NIPAAm, -C*H*-CH₂- of backbone chain in oxazoline and S=C-C*H₂*-CH₃ in backbone chain), 2.97-2.55 (m, 306 H, -CH-C*H₂*- of backbone chain in NIPAAm and -O-C*H₂*-CH-N- in oxazoline), 2.23-2.17 (m, 158 H, CH₃-C*H*-CH₃ in NIPAAm, Ph-C*H₂*-oxazoline, -O-C*H₂*-CH-N- in oxazoline, and Ph-C*H₂*-CH₂-CH- in backbone chain), 2.08-1.88 (m, 6 H, -CH-C*H₂*- of backbone chain in oxazoline), 1.29-1.67 (m, 900 H, C*H₃*-CH-C*H₃* in NIPAAm), 1.17-0.91 (m, 3 H, S=C-CH₂-C*H₃* in backbone chain). GPC (THF): *M*n = 17328, *M*w = 18735, PDI =1.08.

PN$_{210}$O$_3$: FT-IR (KBr): γ$_{max}$/cm⁻¹ 3533, 3437, 3310, 3071, 2977, 2949, 2897, 1663, 1540, 1459, 1368, 1341, 1261, 1172, 1133, 1075, 979, 930, 879, 841, 662 504. ¹H NMR (500 MHz, CDCl₃): δ (ppm): 7.29-6.69 (m, 20 H, *Ph*-CH₂-oxazoline and *Ph*-CH₂-CH₂-CH- in backbone chain), 6.69-6.62 (m, 210 H, O=C-N*H*-CH in NIPAAm), 4.00-3.68 (m, 215 H, -C*H*-CH₂- of backbone chain in NIPAAm, -C*H*-CH₂- and S=C-C*H₂*-CH₃ in backbone chain), 3.58-3.49 (m, 426 H, -CH-C*H₂*- of backbone chain in NIPAAm and -O-C*H₂*-CH-N- in oxazoline), 2.05-1.82 (m, 218 H, CH₃-C*H*-CH₃ in NIPAAm, Ph-C*H₂*-oxazoline, -O-C*H₂*-CH-N- in oxazoline and Ph-C*H₂*-CH₂-CH- in

backbone chain), 1.73-1.43 (m, 6 H, -CH-C*H₂*- of backbone chain in oxazoline), 1.33-1.20 (m, 1260 H, C*H₃*-CH-C*H₃* in NIPAAm), 1.19-1.14 (m, 3 H, S=C-CH₂-C*H₃* in backbone chain). GPC (THF): *M*n = 24519, *M*w = 25499, PDI =1.04.

Synthesis of Fe^{II}-PN$_x$O$_y$ (x=120, y=4; x=150, y=3; x=210, y=3): A highly diluted solution of PN$_x$O$_y$ (x=120, y= 4; x=150, y= 3; x= 210, y= 3) (8.0 mmol) in THF (50 mL) was added dropwise to a stirred solution of FeCl₂ (8.8 mmol, 1.12 g) in THF (20 mL) at 25 °C. The mixtures were stirred at room temperature for 10 h and then were concentrated in vacuo. Crude products were subsequently precipitated in cold *n*-pentane (100 mL). Filtration and drying in vacuum afforded **Fe^{II}-PN$_x$O$_y$** as the brown powder. **Fe^{II}-PN$_{120}$O$_4$:** FT-IR (KBr): γ$_{max}$/cm⁻¹ 3533, 3302, 3080, 2973, 2931, 2877, 1727, 1652, 1526, 1457, 1380, 1368, 1334, 1261, 1167, 1031, 971, 917, 881, 840, 702, 671, 609, 509. α²⁰$_D$ = -32.9 (C = 0.005 g/mL, THF), iron content: 0.092 mmol/g. Cloud-point of **Fe^{II}-PN$_{120}$O$_4$** was *ca.* 26 °C. **Fe^{II}-PN$_{150}$O$_3$:** FT-IR (KBr): γ$_{max}$/cm⁻¹ 3533, 3300, 3082, 2975, 2934, 2878, 1725, 1652, 1524, 1455, 1377, 1367, 1335, 1261, 1172, 1031, 970, 916, 885, 841, 702, 673, 606, 507. α²⁰$_D$ = -29.6 (C = 0.005 g/mL, THF), iron content: 0.069 mmol/g. Cloud-point of **Fe^{II}-PN$_{150}$O$_3$** was *ca.* 29 °C. **Fe^{II}-PN$_{210}$O$_3$:** FT-IR (KBr): γ$_{max}$/cm⁻¹ 3533, 3302, 3083, 2974, 2937, 2875, 1729, 1652, 1527, 1456, 1381, 1368, 1335, 1261, 1172, 1030, 972, 919, 880, 843, 702, 673, 610, 509. α²⁰$_D$ = -37.8 (C = 0.005 g/mL, THF), iron content: 0.042 mmol/g. Cloud-point of **Fe^{II}-PN$_{210}$O$_3$** was *ca.* 31 °C.

Preparation of Neat-C

To evaluate the importance of polymeric pockets around active sites, Neat-C was prepared as the control catalyst. 4-benzyl-2-vinyloxazoline (5.0 mmol, 0.94 g) was dissolved in THF (20 mL). FeCl₂ (5.5 mmol, 0.70 g) in THF (50 mL) was added dropwise into the above solution under vigorous stirring. The mixture was stirred at room temperature for 10 h, and then concentrated in vacuum. Product was precipitated in cold *n*-pentane (100 mL). Filtration and drying in vacuum afforded the Neat-C as a brown powder. FT-IR (KBr): γ$_{max}$/cm⁻¹ 3264, 3150, 2946, 1959, 1916, 1726, 1652, 1574, 1494, 1447, 1402, 1158, 1033, 1007, 856, 815, 746, 702, 687, 572, 493. α²⁰$_D$ = -33.4 (C = 0.005 g/mL, THF), iron content: 1.41 mmol/g.

Job's plot to determine the stoichiometry of Fe(II) ion in Fe^{II}-PN$_x$O$_y$

Stoichiometry of Fe(II) ion in **Fe^{II}-PN$_x$O$_y$** was determined by Job's method. A series of solutions (3 mL) containing PN$_x$O$_y$ (x=120, y= 4; x=150, y= 3; x= 210, y= 3) and FeCl₂ with different molar ration were prepared in THF. The sum of the total concentration of oxazoline in PN$_x$O$_y$ and Fe(II) ion remained constant (0.01 mol.L⁻¹). Molar fraction of Fe(II) ion was varied from 0.1 to 1.0. The absorbance at 297 nm where the Fe^{II}-oxazoline complex shows a maximum absorbance was measured. The resultant absorbance was corrected to account for the absorbance of free Fe(II) ion. The corrected absorbance was plotted against the mole fraction of iron.

Asymmetric SMA of thiols to *α, β*-unsaturated ketones in water

Fe^{II}-PN$_x$O$_y$ (3 mol% of ketones based on iron content) and *α, β*-unsaturated ketones (0.1 mmol) were stirred in water (1.0 mL) for 5 min. Thiol (0.12 mmol) was then added. The resulting mixture was stirred at 25 °C until the reaction was judged to be complete based on TLC analysis. Then reaction mixture was heated to above 36 °C, and held at this temperature for 5 min to make catalyst completely precipitate from the

aqueous system. The precipitated catalyst was washed with ether (3 × 5.0 mL), dried at room temperature in vacuum, and finally recharged with fresh substrate for the next catalytic cycle. Supernatant separated from reaction system was extracted with dichloromethane (3 × 0.5 mL). Combined organic phase was dried with anhydrous Na_2SO_4 and concentrated in vacuum. Further purification of the residue by chromatography on silica gel (Acros, 40–60 μm, 60 Å, eluent: petroleum ether/ethyl acetate = 5/1 (v/v)) afforded the desired chiral adducts. All products of **1-7** were identified by ^1H NMR spectra. Their enantiomeric excess (ee) values were determined by high performance liquid chromatography (HPLC) analysis using the Daicel Chiralpak AD columns. Detailed NMR spectra and HPLC analysis for the products of **1-7** were available in the ESI.†

(S)-3-(Propylthio)-1,3-diphenylpropan-1-one *(1):* Yield: 95%, determined by isolated yield after column chromatography. Ee value: 96%, determined by HPLC (^{i}PrOH/*n*-hexane = 10:90 (v/v)), flow rate = 1.0 mL·min^{-1}, 25 °C, λ = 254 nm, major enantiomer t_S = 5.75 min, minor enantiomer t_R = 4.82 min. ^1H NMR (CDCl$_3$, 500 MHz): δ (ppm): 7.95-7.46 (m, 5 H, *Ph*-CO-CH$_2$-), 7.45-7.15 (m, 5 H, *Ph*-CH-S-), 4.59-4.56 (m, 1 H, C*H*-CH$_2$-CO-), 3.57-3.56 (d, 2 H, CH-C*H$_2$*-CO-), 2.41-2.23 (m, 2 H, -S-C*H$_2$*-CH$_2$-), 1.60-1.49 (m, 2 H, S-CH$_2$-C*H$_2$*-CH$_3$), 0.94-0.91 (m, 3 H, S-CH$_2$-CH$_2$-C*H$_3$*).

(S)-4-(Propylthio)-4-phenylbutan-2-one *(2):* Yield: 96%, determined by isolated yield after column chromatography. Ee value: 99%, determined by HPLC (^{i}PrOH/*n*-hexane = 20:80 (v/v)), flow rate = 1.0 mL·min^{-1}, 25 °C, λ = 254 nm, major enantiomer t_S = 6.12 min, minor enantiomer t_R = 4.74 min. ^1H NMR (CDCl$_3$, 500 MHz): δ (ppm): 7.55-7.31 (m, 5 H, *Ph*-CH-S-), 4.49-4.46 (m, 1 H, C*H*-CH$_2$-CO-), 3.25-3.24 (d, 2 H, CH-C*H$_2$*-CO-), 2.39-2.23 (m, 2 H, -S-C*H$_2$*-CH$_2$-CH$_3$), 1.57-1.53 (m, 2 H, -S-CH$_2$-C*H$_2$*-CH$_3$), 1.36 (s, 3 H, -CO-C*H$_3$*), 0.96-0.91 (m, 3 H, -S-CH$_2$-CH$_2$-C*H$_3$*).

(S)-3-(Propylthio)-3-(4-methoxyphenyl)-1-phenylpropan-1-one *(3):* Yield: 92%, determined by isolated yield after column chromatography. Ee value: 98%, determined by HPLC (^{i}PrOH/*n*-hexane = 20:80 (v/v)), flow rate = 1.0 mL·min^{-1}, 25 °C, λ = 254 nm, major enantiomer t_S = 12.32 min; minor enantiomer t_R = 10.08 min. ^1H NMR (CDCl$_3$, 500 MHz): δ (ppm): 7.94-7.43 (m, 5 H, *Ph*-CO-CH$_2$-), 7.39-6.82 (m, 4 H, CH$_3$O-*Ph*-CH-), 4.56-4.53 (m, 1 H, C*H*-CH$_2$-CO-), 3.81 (s, 3 H, C*H$_3$*O-Ph-CH-), 3.57-3.48 (d, 2 H, CH-C*H$_2$*-CO-), 2.38-2.23 (m, 2 H, -S-C*H$_2$*-CH$_2$-CH$_3$), 1.60-1.49 (m, 2 H, -S-CH$_2$-C*H$_2$*-CH$_3$), 0.97-0.88 (m, 3 H, -S-CH$_2$-CH$_2$-C*H$_3$*).

(S)-4-(Propylthio)-4-(4-methoxyphenyl) butan-2-one (4): Yield: 95%, determined by isolated yield after column chromatography. Ee value: 90%, determined by HPLC (^{i}PrOH/*n*-hexane = 10:90 (v/v)), flow rate = 1.0 mL·min^{-1}, 25 °C, λ = 254 nm, major enantiomer t_S = 11.04 min, minor enantiomer t_R = 8.11 min. ^1H NMR (CDCl$_3$, 500 MHz): δ (ppm): 7.75-6.91 (m, 4 H, CH$_3$O-*Ph*-CH-), 4.40-4.30 (m, 1 H, C*H*-CH$_2$-CO-), 3.92-3.87 (d, 2 H, CH-C*H$_2$*-CO-), 2.64 (s, 3 H, C*H$_3$*O-Ph-CH-), 2.28-2.23 (m, 2 H, -S-C*H$_2$*-CH$_2$-CH$_3$), 2.09-2.01 (m, 2 H, -S-CH$_2$-C*H$_2$*-CH$_3$), 1.40 (s, 3 H, -CO-C*H$_3$*), 0.92-0.85 (m, 2 H, -S-CH$_2$-C*H$_2$*-CH$_3$).

(S)-3-(Propylthio)-3-(4-nitrophenyl)-1-phenylpropan-1-one (5): Yield: 10%, determined by isolated yield after column chromatography. Ee value: 89%, determined by HPLC (^{i}PrOH/*n*-hexane = 30:70 (v/v)), flow rate = 1.0 mL·min^{-1}, 25 °C, λ = 254 nm, major enantiomer t_S = 11.78 min, minor enantiomer t_R = 10.01 min. ^1H NMR (CDCl$_3$, 500 MHz): δ (ppm): 8.20-7.81 (m, 4 H, NO$_2$-*Ph*-CH-), 7.75-7.46 (m, 5 H, *Ph*-CO-CH$_2$-), 4.79-4.50 (m, 1 H, C*H*-CH$_2$-CO-), 3.78-3.44 (d, 2 H, CH-C*H$_2$*-CO-), 2.50-2.18

(m, 2 H, -S-C*H$_2$*-CH$_2$-CH$_3$), 1.59-1.52 (m, 2 H, -S-CH$_2$-C*H$_2$*-CH$_3$), 0.95-0.89 (m, 3 H, -S-CH$_2$-CH$_2$-C*H$_3$*).

(S)-3-(4-Chlorobenzylthio)-1,3-diphenylpropan-1-one (6): Yield: 93%, determined by isolated yield after column chromatography. Ee value: 95%, determined by HPLC (^{i}PrOH/*n*-hexane = 20:80 (v/v)), flow rate = 1.0 mL·min^{-1}, 25 °C, λ = 254 nm, major enantiomer t_S = 8.51 min; minor enantiomer t_R = 6.42 min. ^1H NMR (CDCl$_3$, 500 MHz): δ (ppm): 7.89-7.42 (m, 5 H, *Ph*-CO-CH$_2$-), 7.40-7.35 (m, 4 H, Cl-*Ph*-CH$_2$-), 7.28-7.14 (m, 5 H, *Ph*-CH-S-), 4.17-4.12 (m, 1 H, -S-C*H*-Ph), 3.59-3.51 (m, 2 H, -S-C*H$_2$*-Ph), 3.51-3.44 (m, 2 H, CH-C*H$_2$*-CO-).

(S)-3-(4-Chlorobenzylthio)-3-(4-methoxyphenyl)-1-phenylpropan-1-one (7): Yield: 90%, determined by isolated yield after column chromatography. Ee value: 96%, determined by HPLC (^{i}PrOH/*n*-hexane = 3:97 (v/v)), flow rate = 1.0 mL·min^{-1}, 25 °C, λ = 254 nm, major enantiomer t_S = 20.15 min, minor enantiomer t_R = 17.48 min. ^1H NMR (CDCl$_3$, 500 MHz): δ (ppm): 7.33-7.17 (m, 13 H, Cl-*Ph*-CH$_2$-, CH$_3$O-*Ph*-CH-, and *Ph*-CO-CH$_2$-), 4.17-4.15 (m, 1 H, C*H*-CH$_2$-CO-), 4.14-4.13 (m, 2 H, Cl-Ph-C*H$_2$*-S-), 3.60 (s, 3 H, C*H$_3$*O-Ph-CH-), 2.99-2.91 (m, 2 H, CH-C*H$_2$*-CO-).

(S)-4-(4-Chlorobenzylthio)pentan-2-one (8): Yield: 94%, determined by isolated yield after column chromatography. Ee value: >99%, determined by HPLC (^{i}PrOH/*n*-hexane = 10:90 (v/v)), flow rate = 1.0 mL·min^{-1}, 25 °C, λ = 254 nm, major enantiomer t_S = 6.07 min, minor enantiomer t_R = 4.99 min. ^1H NMR (CDCl$_3$, 500 MHz): δ (ppm): ^1H NMR (CDCl$_3$, 500 MHz): δ (ppm): 7.33-7.27 (m, 4 H, Cl-*Ph*-CH$_2$-), 3.75-3.74 (m, 2 H, Cl-Ph-C*H$_2$*-), 3.20-3.13 (m, 1 H, -S-C*H*-CH$_3$), 2.73-2.64 (m, 2 H, CH-C*H$_2$*-CO-), 2.14 (s, 3 H, -CO-C*H$_3$*), 1.64-1.52 (m, 3 H, C*H$_3$*-CH-CH$_2$).

(S)-3-(4-Chlorophenylthio)-1,3-diphenylpropan-1-one (9): Yield: 92%, determined by isolated yield after column chromatography. Ee value: 98%, determined by HPLC (^{i}PrOH/*n*-hexane = 20: 80 (v/v)), flow rate = 1.0 mL·min^{-1}, 25 °C, λ = 254 nm, major enantiomer t_S = 10.34 min, minor enantiomer t_R = 8.34 min. ^1H NMR (CDCl$_3$, 500 MHz): δ (ppm): 7.44-7.41 (m, 5 H, *Ph*-CO-CH$_2$-), 7.32-7.29 (m, 9 H, *Ph*-CH-S- and Cl-*Ph*-S-), 2.05-2.03 (m, 1 H, C*H*-CH$_2$-CO-), 1.60-1.58 (d, 2 H, CH-C*H$_2$*-CO-).

Acknowledgements

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Graphical Abstract

Iron(II)-folded single-chain nanoparticle: a metalloenzyme mimicking sustainable catalyst for highly enantioselective sulfa-Michael addition in water

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Bio-inspired Fe^{II}-folded SCPNs enabled asymmetric sulfa-Michael addition to be performed in a green and efficient manner, using water as solvent.
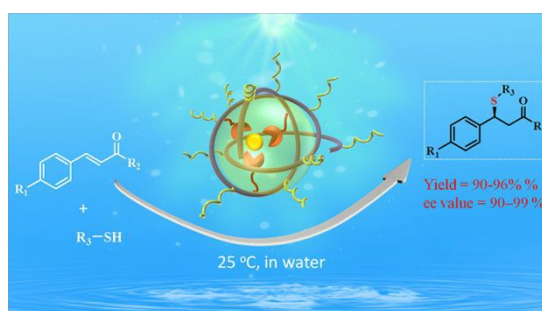
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