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ARTICLE

Titanium(IV)-Folded Single-Chain Polymeric Nanoparticle as Artificial Metalloenzyme for Asymmetric Sulfoxidation in Water

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Intrachain Ti^{IV}-oxazoline complexation together with hydrophobic interaction triggered the self-folding of oxazoline-containing single polymeric chain in water. The formed Ti^{IV}-folded single-chain polymeric nanoparticle (SCPNs) exhibited metalloenzyme-mimetic catalysts in asymmetric sulfoxidation in water owing to their organized, compartmentalized structure, effective site isolation, and also secondary coordination sphere provided by copolymer backbone. In addition, they also could be facily recovered for steady reuse by simple thermo-controlled separation.

Enzymes are the efficient biocatalysts that regulate a broad variety of biochemical reactions in aqueous environment in nature. The catalytic properties result from a guided three-dimensional folding of single protein chain, which gives a compartmentalized structure with hydrophobic cores surrounded by hydrophilic shells.¹ Amino acid residues are brought together upon the single-chain folding, forming the inner compartment that act as an 'active site'. The intriguing enzyme catalysis inspires chemists to mimic these natural catalytic compartments where the catalytic active cores are isolated from the outer environment, so as to realize efficient organic reactions in water.² Folding of a single linear polymer chain into a hydrophobic cavity-containing SCPN, has been regarded as a feasible approach for constructing the enzyme-like compartment.³ The obtained SCPNs often exhibit some features that resemble natural enzymes. In particular, water-soluble SCPNs which contain active metal center in a hydrophobic cavity have demonstrated metalloenzyme-mimetic activity and selectivity in aqueous catalysis.⁴

In nature, metal coordination provides an excellent tool to direct protein self-assembly and often allows for the regulation of enzyme-catalyzed pathways during dynamic cellular processes.⁵ Intramolecular metal-ligand coordination which controls the folding of single-chain linear polymers offers a feasible way to prepare synthetic mimics of metalloenzymes.⁶ The formed metal complexes not only lock the chain-collapse, but also function as catalytic centers for confined catalysis. These fascinating features inspired us to reason that the coordination-driven self-folding strategy could be used to construct Ti^{IV}-folded SCPNs and allowed for metalloenzyme catalysis of asymmetric sulfoxidation in water. Herein, we reported

the design of Ti^{IV}-folded SCPNs as artificial metalloenzyme for enantioselective sulfoxidation in water. Since oxazoline are the attractive ligands suitable for the coordination of titanium(IV),⁷ we decided to append multiple chiral oxazolines as the structure-forming element to an amphiphilic random copolymer. We expected that the chiral oxazoline ligand would undergo intramolecular chelation with titanium(IV) ion, triggering self-folding of the copolymer into water-soluble SCPNs. Unfortunately, it is often troublesome to recover water-soluble SCPNs from water. The problem can be circumvented by developing "thermo-responsive" SCPNs that undergo inverse hydrophilic-to-hydrophobic switch in response to local temperature changes.⁸

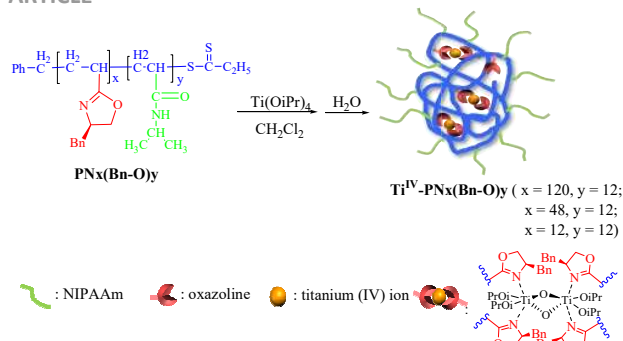
The parent thermoresponsive amphiphilic random copolymers of poly(NIPAAm-co-oxazoline) (NIPAAm, N-isopropylacrylamide) were synthesized *via* reversible addition-fragmentation chain transfer polymerization⁹ (Scheme 1, PN_x(Bn-O)_y). The copolymers were composed of two functional units: NIPAAm side chain to impart inverse temperature-dependent water-solubility and hydrophobic chiral oxazoline side chain to bind titanium(IV) ion. Polymerization degree was verified by ¹H NMR in CDCl₃ by comparing the signals attributable to individual blocks (NIPAAm at *ca.* 6.15-6.96 ppm assigned to O=C-NH-CH, and oxazoline at *ca.* 3.56-3.78 ppm assigned to -O-CH₂-CH-N-) with that of an end methylene group (S=C-CH₂-CH₃ at *ca.* 3.23 ppm) (see the corresponding ¹H NMR spectra in ESI[†]). Number average molecular weight (*M*_n) and polydispersity index (PDI, *M*_w/*M*_n) of PN_x(Bn-O)_y were determined by gel permeation chromatograph (GPC) (Section S1.3 in ESI[†]). Low PDI values (<1.10) suggested good control of the copolymer molecular weight distribution.¹⁰ Ti^{IV}-folded SCPNs (Scheme 1, Ti^{IV}-PN_x(Bn-O)_y) formation was carried out in dichloromethane at room temperature by using Ti(OⁱPr)₄ as reagent at high dilution conditions (1 mg/mL) to minimize unwanted interparticle coupling events. The resultant Ti^{IV}-PN_x(Bn-O)_y showed switchable temperature-dependent solubility in water. LCST of Ti^{IV}-PN₁₂₀(Bn-O)₁₂, Ti^{IV}-PN₄₈(Bn-O)₁₂, and Ti^{IV}-PN₁₂(Bn-O)₁₂ was *ca.* 27, 29 and 31 °C, respectively, which was determined by UV-vis (Fig. S12).

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ARTICLE

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Scheme 1. Schematic representations and chemical structures of $\text{Ti}^{\text{IV}}\text{-PN}_x(\text{Bn-O})_y$ ($\text{Ti}^{\text{IV}}\text{-PN}_{120}(\text{Bn-O})_{12}$, $\text{Ti}^{\text{IV}}\text{-PN}_{48}(\text{Bn-O})_{12}$, and $\text{Ti}^{\text{IV}}\text{-PN}_{12}(\text{Bn-O})_{12}$).

The Ti^{IV} -oxazoline coordination was examined using ^1H NMR spectroscopy (Fig. 1). $\text{PN}_{48}(\text{Bn-O})_{12}$ showed distinct protons signals of PNIPAAm units ($\delta = 3.91\text{--}4.16$ ppm, $\text{O}=\text{CNHCH}(\text{CH}_3)_2$) and oxazoline groups ($\delta = 3.56\text{--}3.78$ ppm, $-\text{O}-\text{CH}_2-\text{CH}-\text{N}-$, and $\delta = 7.10\text{--}7.73$ ppm, $\text{Ph}-\text{CH}_2\text{-oxazoline}$) in CDCl_3 (Fig. 1a). Although CDCl_3 was good solvent, resonance feature of oxazoline side chains almost disappeared after the addition of Ti^{IV} ions (Fig. 1b). It suggested the intramolecular Ti^{IV} -oxazoline coordination in $\text{PN}_{48}(\text{Bn-O})_{12}$. Similar discussion was reported in reference.^{6c} To confirm the coordinate ability of oxazoline group, oxazoline in $\text{PN}_{48}(\text{Bn-O})_{12}$ was protonated with HCl before it was exposed to titanium(IV) ion. Indeed, protonated $\text{PN}_{48}(\text{Bn-O})_{12}$ failed to fold, as evident from the appearance of resonance peak of oxazoline group (Fig. 1c vs. 1a). Therefore, the chiral oxazoline pendant served as a handle for binding titanium(IV) ion and folding the polymer chain.

Notably, the peaks corresponding to methylene (2.13–2.45, $-\text{CH}-\text{CH}_2-$) and methenyl (2.89–3.12, $-\text{CH}-\text{CH}_2-$) groups on the backbone showed clear broadening when $\text{Ti}^{\text{IV}}\text{-PN}_{48}(\text{Bn-O})_{12}$ was dissolved in D_2O . This is attributed to the presence of intramolecular hydrophobic interaction, which decreased chain mobility of copolymer.^{6c} The intramolecular hydrophobic interaction should further compact the SCPN in water, giving more compartmentalized structure for aqueous catalysis.

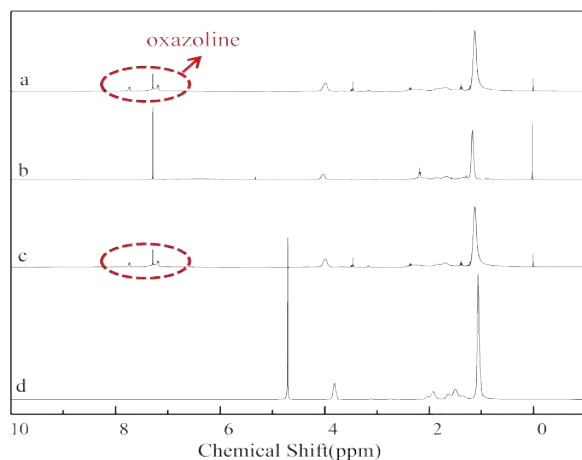


Fig. 1 ^1H NMR spectra of $\text{PN}_{48}(\text{Bn-O})_{12}$ (a), $\text{Ti}^{\text{IV}}\text{-PN}_{48}(\text{Bn-O})_{12}$ (b), and HCl treated $\text{PN}_{48}(\text{Bn-O})_{12}$ (c) in CDCl_3 ; and the $\text{Ti}^{\text{IV}}\text{-PN}_{48}(\text{Bn-O})_{12}$ in D_2O (d).

Self-folding was also evidenced by TEM. As shown in Fig. 2, $\text{PN}_{48}(\text{Bn-O})_{12}$ precursor was unfolded in methanol, a good solvent for the copolymer, adopting a random coil conformation in TEM image (Fig. 2a). Being treated with titanium(IV) ion, it coiled into spherical nanoparticles with an average size of *ca.* 5.0 nm (Fig. 2b). Ultrasmall size suggested intramolecular folding of $\text{PN}_{48}(\text{Bn-O})_{12}$ upon Ti^{IV} -oxazoline coordination. The SCPNs size further decreased to *ca.* 1.0 nm when water was used as the solvent (Fig. 2d). It was indicative of the intramolecular hydrophobic interaction which made the SCPNs more compact, as confirmed by ^1H NMR. Indeed, hydrodynamic diameter (D_h) of $\text{Ti}^{\text{IV}}\text{-PN}_{48}(\text{Bn-O})_{12}$ was 20.8 nm in methanol, while it reduced to 6.5 nm in water (Fig. S14). Therefore, amphiphilic $\text{PN}_x(\text{Bn-O})_y$ self-folded in aqueous media as a result of intrachain metal complexation and hydrophobic force of the oxazoline pendant groups, giving uniform, ultrasmall nanoparticles of $\text{Ti}^{\text{IV}}\text{-PN}_x(\text{Bn-O})_y$ (Fig. 2c–e).

The self-folding process was further probed by temperature-dependent circular dichroism (CD) spectroscopy (Fig. 3). Obviously, all $\text{Ti}^{\text{IV}}\text{-PN}_x(\text{Bn-O})_y$ exhibited negative Cotton effect at 258 nm in corresponding CD spectra. The Cotton effect gradually decreased with increasing local temperature, and almost disappeared above 40 °C. In fact, the solution turned turbid above 30 °C, and the copolymers were finally precipitated out of water due to their LCST. Dramatic decrease in Cotton effect above 30 °C should be related to

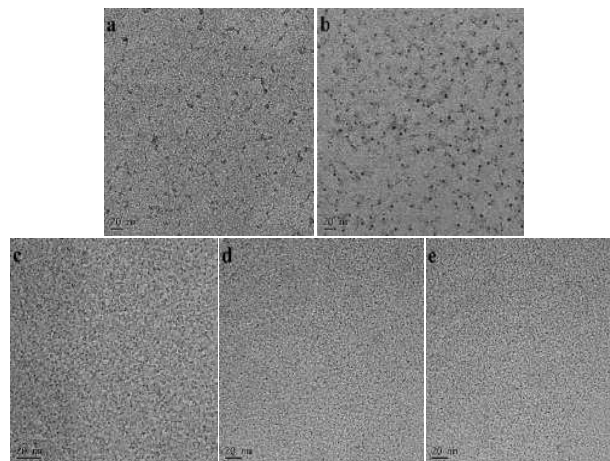


Fig. 2 TEM micrograph of $\text{PN}_{48}(\text{Bn-O})_{12}$ (a) and $\text{Ti}^{\text{IV}}\text{-PN}_{48}(\text{Bn-O})_{12}$ (b) in methanol, $\text{Ti}^{\text{IV}}\text{-PN}_{120}(\text{Bn-O})_{12}$ (c), $\text{Ti}^{\text{IV}}\text{-PN}_{48}(\text{Bn-O})_{12}$ (d) and $\text{Ti}^{\text{IV}}\text{-PN}_{12}(\text{Bn-O})_{12}$ (e) in water at room temperature. (Enlarged TEM images are provided in Fig. S14 in ESI[†]).

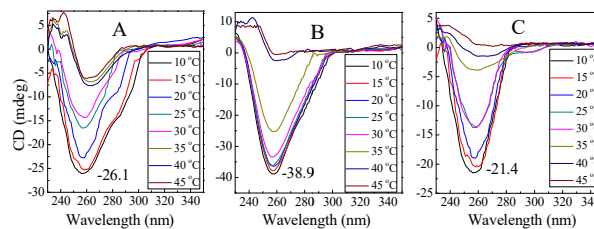


Fig. 3 The CD spectra of $\text{Ti}^{\text{IV}}\text{-PN}_{120}(\text{Bn-O})_{12}$ (A), $\text{Ti}^{\text{IV}}\text{-PN}_{48}(\text{Bn-O})_{12}$ (B), and $\text{Ti}^{\text{IV}}\text{-PN}_{12}(\text{Bn-O})_{12}$ (C) in water from 10 °C to 45 °C with 5 °C intervals (concentration = 0.5 $\text{mg}\cdot\text{ml}^{-1}$).















the “thermo-controlled” collapse of $\text{Ti}^{\text{IV}}\text{-PN}_x(\text{Bn-O})_y$ in water. The maximum molar CD values of $\text{Ti}^{\text{IV}}\text{-PN}_{120}(\text{Bn-O})_{12}$, $\text{Ti}^{\text{IV}}\text{-PN}_{48}(\text{Bn-O})_{12}$ and $\text{Ti}^{\text{IV}}\text{-PN}_{12}(\text{Bn-O})_{12}$ were 8.21, 5.08, and 1.24, respectively. Curiously, higher amount of CD active chromophores (Ti(salen)) decreased the Cotton effect of $\text{Ti}^{\text{IV}}\text{-PN}_x(\text{Bn-O})_y$. It was probably due to that too dense packing of oxazoline content in $\text{Ti}^{\text{IV}}\text{-PN}_{12}(\text{Bn-O})_{12}$ limit the flexibility of folded polymer chains through intrachain coordination. The observation indicated that the local Ti(oxazoline) concentration was responsible for the self-assembly occurred within a single chain. The self-folding of Ti(oxazoline) created hydrophobic compartment with a chiral internal secondary structure.

As expected, the Ti-containing SCPNs exhibited excellent activity and selectivity in asymmetric sulfoxidation of methyl phenyl sulfide with aqueous (aq.) H_2O_2 in water, especially, making the reaction highly enantioselective, as shown in Table 1. Only 0.1 mol% of $\text{Ti}^{\text{IV}}\text{-PN}_{48}(\text{Bn-O})_{12}$ was sufficient for affording an almost quantitative yield (97%) of (*R*)-methyl phenyl sulfoxide with unprecedented enantioselectivity (>99%) in water within 60 min (Table 1, entry 2). However, extremely low conversion (8%) with disappointing chemoselectivity (69%) and ee value (60%) was observed when neat Ti(oxazoline) complex (see Scheme S1 in Supporting Information) was used as a catalyst under identical conditions (Table 1, entry 5). Therefore, a hydrophobic, structured compartment provided by copolymer was a requirement to achieve efficient catalysis. Actually, midway addition of $\text{PN}_{48}(\text{Bn-O})_{12}$ copolymer (equivalent to the $\text{PN}_{48}(\text{Bn-O})_{12}$ amount in $\text{Ti}^{\text{IV}}\text{-PN}_{48}(\text{Bn-O})_{12}$) into the neat complex-catalyzed system dramatically increased the conversion (51%) and selectivity (75% chemoselectivity and 81% ee value) (Table 1, entry 6 vs. 5). Apart from shielding catalytic sites, the hydrophobic compartment effectively concentrated sulfides from the surrounding aqueous environment through hydrophobic affinity, resulting in a high local concentration of substrate around the confined catalytic sites for fast reactions,¹¹ as shown by the notably high TOF value in Table 1. The hydrophobic environment reaction space excluded excess aqueous H_2O_2 , hereby minimizing the undesired over-oxidation of sulfoxide to sulfone. More intriguingly, the internal chirality of hydrophobic pocket should further induce the confined asymmetric catalysis, introducing highly enantioselective effects. For this reason, it was not surprising that $\text{Ti}^{\text{IV}}\text{-PN}_{48}(\text{Bn-O})_{12}$ was universal for a wide range of sulfides (Table 1, entries 8, 10, 12, 14, and 16). In particular, more hydrophobic sulfides were more favorable for the aqueous catalysis (Table 1, entry 12 vs. 10 vs. 8 vs. 4). But the reactivity was not satisfied for methyl *p*-bromophenyl sulfide, although the selectivity was encouraging (Table 1, entry 18). Probably, it was solid and insoluble in water, which was unfavorable for permeation in hydrophobic pocket for smooth catalysis. The $\text{Ti}^{\text{IV}}\text{-PN}_{48}(\text{Bn-O})_{12}$ was far less efficient in dichloromethane than in water due to the absence of hydrophobic cavity (Table 1, entry 3 vs. 2).

Notably, the $\text{Ti}^{\text{IV}}\text{-PN}_{48}(\text{Bn-O})_{12}$ was even more efficient than our reported chiral salen Ti^{IV} -containing SCPNs of PN_{66}S_4 ,¹² as shown by TOF value (Table 1, entry 2 vs. 7), although the chiral salen Ti^{IV} -containing system also provided a hydrophobic compartment. Higher efficiency should benefit from more organized architecture of the metal-directed SCPNs than the previous chiral salen Ti^{IV} -containing system which was just regulated by nondirectional and

relatively flexible intramolecular hydrophobic interactions.¹² Furthermore, intramolecular chelation of $\text{Ti}^{\text{IV}}\text{-PN}_{48}(\text{Bn-O})_{12}$ should provide a more stable hydrophobic environment facilitating the encapsulation of substrate for efficient catalysis.

Table 1. Results of asymmetric sulfoxidation over different Ti(oxazoline) complexes^a

Entry	Catalyst	Substrate	T (min)	Conv. ^b (%)	Sel. ^b (%)	ee ^c (%)	TOF ^d (h ⁻¹)
1	$\text{Ti}^{\text{IV}}\text{-PN}_{120}(\text{Bn-O})_{12}$		60	89	93	92	890
2	$\text{Ti}^{\text{IV}}\text{-PN}_{48}(\text{Bn-O})_{12}$		60	>99	97	>99	990
3	$\text{Ti}^{\text{IV}}\text{-PN}_{48}(\text{Bn-O})_{12}$ ^e		60	21	72	62	210
4	$\text{Ti}^{\text{IV}}\text{-PN}_{12}(\text{Bn-O})_{12}$		60	73	90	89	730
5	Ti(oxazoline)		60	8	69	60	80
6	Ti(oxazoline) ^f		60	51	75	81	510
7	PN_{66}S_4		60	89	92	95	178 ^g
8	$\text{Ti}^{\text{IV}}\text{-PN}_{48}(\text{Bn-O})_{12}$		55	>99	97	>99	1080
9	Ti(oxazoline)		60	8	65	15	80
10	$\text{Ti}^{\text{IV}}\text{-PN}_{48}(\text{Bn-O})_{12}$		52	>99	>99	>99	1142
11	Ti(oxazoline)		60	6	66	9	60
12	$\text{Ti}^{\text{IV}}\text{-PN}_{48}(\text{Bn-O})_{12}$		50	>99	>99	>99	1188
13	Ti(oxazoline)		60	4	60	65	40
14	$\text{Ti}^{\text{IV}}\text{-PN}_{48}(\text{Bn-O})_{12}$		55	>99	95	>99	1080
15	Ti(oxazoline)		60	19	77	37	190
16	$\text{Ti}^{\text{IV}}\text{-PN}_{48}(\text{Bn-O})_{12}$		57	>99	98	97	1042
17	Ti(oxazoline)		60	15	81	71	150
18	$\text{Ti}^{\text{IV}}\text{-PN}_{48}(\text{Bn-O})_{12}$		60	41	93	90	410
19	Ti(oxazoline)		60	8	78	81	80

^a Catalyst (0.1 mol% of substrate, based on titanium content), substrate (1.0 mmol), H_2O_2 (1.2 mmol, added in 15 min), solvent (1 mL), 25 °C. ^b Determined by GC. ^c Determined by HPLC (Daicel chiralpak AD column). ^d Turnover frequency (TOF) is calculated by the expression of [product]/[catalyst] × time (h⁻¹). ^e Solvent was CH_2Cl_2 . ^f Ti(oxazoline) (0.1 mol% of substrate, based on titanium content), $\text{PN}_{48}(\text{Bn-O})_{12}$ (0.046 g, equivalent to the amount of $\text{PN}_{48}(\text{Bn-O})_{12}$ in $\text{Ti}^{\text{IV}}\text{-PN}_{48}(\text{Bn-O})_{12}$), methyl phenyl sulfide (1.0 mmol), H_2O_2 (1.2 mmol, added in 15 min), deionized water (1 mL), 25 °C. ^g Data from ref.¹³

Despite having similar organized, compartmentalized structure, the catalytic activity of $\text{Ti}^{\text{IV}}\text{-PN}_x(\text{Bn-O})_y$ was closely related with the local concentration of Ti(oxazoline) units. $\text{Ti}^{\text{IV}}\text{-PN}_{48}(\text{Bn-O})_{12}$ showed the highest catalytic efficiency in aqueous asymmetric oxidation of methyl phenyl sulfide (Table 1, entry 2). Reduced local concentration of catalytic Ti(oxazoline) units per polymer chain ($\text{Ti}^{\text{IV}}\text{-PN}_{120}(\text{Bn-O})_{12}$) was unfavorable for the transformation (Table 1, entry 1), logically due to the insufficient catalytic sites confined in SCPNs. While, too dense packing of Ti(oxazoline) per-polymer chain was also detrimental to the catalysis, as in the case of $\text{Ti}^{\text{IV}}\text{-PN}_{12}(\text{Bn-O})_{12}$.

O_{12} (Table 1, entry 4). It was likely due to the difference in flexibility of folded polymer chains that was largely limited in the presence of Ti(oxazoline) complexes. Since $\text{Ti}^{\text{IV}}\text{-PN}_{12}(\text{Bn-O})_{12}$ has a higher content of titanium(IV) ion, it became less flexible compared to $\text{Ti}^{\text{IV}}\text{-PN}_{48}(\text{Bn-O})_{12}$.^{6c} The stiffness of $\text{Ti}^{\text{IV}}\text{-PN}_{12}(\text{Bn-O})_{12}$ chains possibly limited the dynamic properties of adjacent Ti(oxazoline) complexes to cooperatively catalyze the sulfoxidation.

After reaction, $\text{Ti}^{\text{IV}}\text{-PN}_x(\text{Bn-O})_y$ turned to hydrophobic upon heating above their corresponding LCST (Figure S12-c'). It allowed for separation of them from aqueous phase by decantation. To our delight, the catalysts of $\text{Ti}^{\text{IV}}\text{-PN}_{120}(\text{Bn-O})_{12}$ (Figure 4A), $\text{Ti}^{\text{IV}}\text{-PN}_{48}(\text{Bn-O})_{12}$ (Figure 4B) and $\text{Ti}^{\text{IV}}\text{-PN}_{12}(\text{Bn-O})_{12}$ (Figure 4C) could be reused up to seven times without significant loss in activity and selectivity in asymmetric oxidation of methyl phenyl sulfide in water. Oxidative decomposition of the $\text{Ti}^{\text{IV}}\text{-PN}_x(\text{Bn-O})_y$ in H_2O_2 -based oxidation did not occur during the reaction, as proved by FT-IR spectrum of typical $\text{Ti}^{\text{IV}}\text{-PN}_{48}(\text{Bn-O})_{12}$ (Figure S13-d vs. S13-d'). The excellent stability of catalysts should arise from the hydrophobic shielding of chiral Ti(oxazoline) complex in a compartment, which protected the chiral Ti(oxazoline) complex from oxidative decomposition by excluding excess H_2O_2 from the hydrophobic pocket. The perfect stability together with efficient reusability of $\text{Ti}^{\text{IV}}\text{-PN}_x(\text{Bn-O})_y$ overcame the inherent poor stability of natural metalloenzyme, making the catalysts highly promising in industrial application.

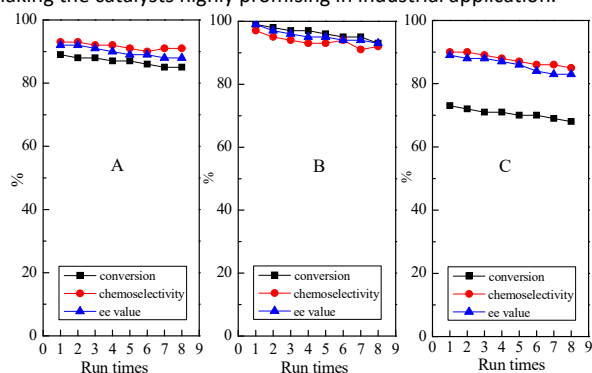


Fig. 4 Reuse of $\text{Ti}^{\text{IV}}\text{-PN}_{120}(\text{Bn-O})_{12}$ (A), $\text{Ti}^{\text{IV}}\text{-PN}_{48}(\text{Bn-O})_{12}$ (B) and $\text{Ti}^{\text{IV}}\text{-PN}_{12}(\text{Bn-O})_{12}$ (C) in asymmetric sulfoxidation of methyl phenyl sulfide in water.

Conclusions

In summary, we showed the use of Ti^{IV} -oxazoline coordination to trigger the efficient and reversible self-folding of chiral oxazoline-containing amphiphilic random copolymers. These synthetic soft nanoentities exhibited metalloenzyme-mimetic activity and selectivity in asymmetric sulfoxidation in water due to their organized, compartmentalized structure, effective site isolation, and also secondary coordination sphere provided by copolymer backbone. And they could be facilely recovered from the aqueous system for efficient reuse by simply adjusting the local temperature. This work inspired researchers to develop other metallo-folded SCPNs for a much wider range of application, and also offered a facile way to prepare "smart" synthetic mimics of metalloenzymes.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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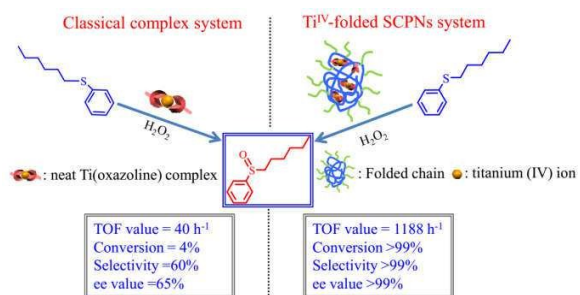
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TOC Graphic:

**Text:**

Bio-inspired Ti^{IV}-folded SCPNs exhibited metalloenzyme-mimetic activity, selectivity, and especially, facile reusability in asymmetric sulfoxidation in water.