

Shell Cross-Linked Micelle-Based Nanoreactors for the Substrate-Selective Hydrolytic Kinetic Resolution of Epoxides

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S Supporting Information

ABSTRACT: Shell cross-linked micelles (SCMs) containing Co(III)–salen cores were prepared from amphiphilic poly(2-oxazoline) triblock copolymers. The catalytic activity of these nanoreactors for the hydrolytic kinetic resolution of various terminal epoxides was investigated. The SCM catalysts showed high catalytic efficiency and, more significantly, substrate selectivity based on the hydrophobic nature of the epoxide. Moreover, because of the nanoscale particle size and the high stability, the catalyst could be recovered easily by ultrafiltration and reused with high activity for eight cycles.

Substrate selectivity remains one of the most intriguing research targets in catalysis. Nature has perfected substrate-selective catalysis, as exhibited by many enzymatic systems that can interact specifically with certain substrates on the basis of differences in size/shape, charge, and/or hydrophobicity/hydrophilicity. The development of substrate selectivity in synthetic systems is still at an early stage.¹ Several catalytic systems have been reported to achieve size/shape selectivity, including metal–organic frameworks (MOFs),^{2,3} zeolite-based catalysts,^{4,5} silica nanoparticle-based catalysts,⁶ polyoxometalates (POMs),⁷ and supramolecular nanocapsules.^{8,9} Synthetic systems can be endowed with hydrophilic/hydrophobic-based substrate selectivity through the use of biphasic media such as ionic liquids and fluoros and supercritical-fluid biphasic reaction media. The challenge is to realize substrate selectivity of nonbiological catalytic systems in homogeneous media, such as aqueous environments. Examples in the literature include the use of polymer-based hydrogels,^{10a} micellar structures,^{10b} and hydrophobic reagents.¹¹

Shell cross-linked micelles (SCMs) are unique and attractive functional nanoparticles for use in aqueous environments.¹² The micellar structure of SCMs is stabilized by a covalently cross-linked shell layer, rendering SCMs advantageous over conventional micelles. SCMs show high stability toward external stimuli such as temperature and solvents and have much lower critical micelle concentrations.^{13–17} SCMs have been reported as key materials in biomedical science, particularly in drug delivery and bioimaging.^{18–20} We view SCMs as a unique support structure for catalysis. The fixed microenvironment composed of the hydrophobic core, the cross-linked shell, and the hydrophilic corona has the potential to allow for programmed substrate selectivity. Additionally, catalysts confined in the core domain of SCMs can be forced into highly dense arrangements, leading to enhanced reaction rates for catalytic reactions that follow a

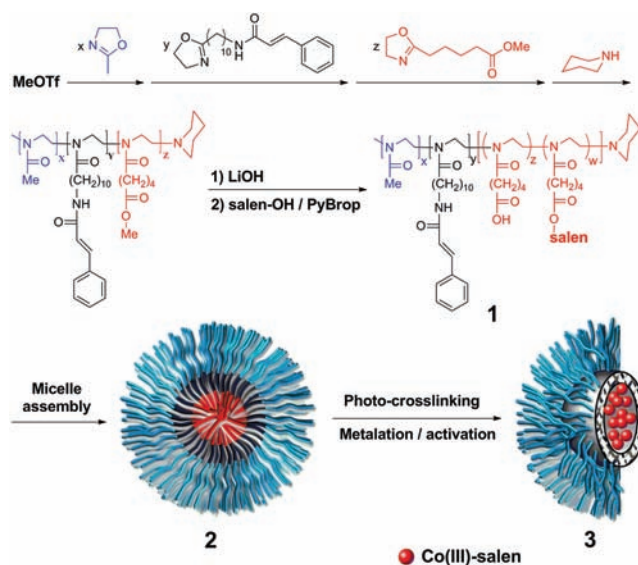


Figure 1. Schematic representation of the synthesis of poly(2-oxazoline) SCMs with Co(III)–salen-functionalized cores.

bimolecular mechanism. Furthermore, the cross-linked shell layer should provide an external shielding against metal leaching or catalyst poisoning, which could benefit catalyst recovery and recycling. To examine these hypotheses, we synthesized poly(2-oxazoline)-based SCMs containing Co(III)–salen complexes in the core and studied their use as catalysts for the hydrolytic kinetic resolution (HKR) of terminal epoxides (Figure 1). The catalysis results demonstrate that this novel support system is not only highly active but also displays unusual substrate selectivity.

Our SCM support structure is based on the work of Weberskirch and co-workers, who reported the synthesis and activity of Co(III)–salen micellar catalysts.²¹ The Weberskirch system uses conventional non-cross-linked micelles. Our design includes a cross-linkable layer decorated with cinnamate side chains. Cinnamates can undergo cross-linking via UV-activated [2 + 2] cycloaddition. The cinnamate-functionalized oxazoline monomer was synthesized in five steps in 69% overall yield. The hydrophilic and hydrophobic blocks were constructed from methyl 2-oxazoline and methyl 3-(oxazol-2-yl)pentanoate,²² respectively. Poly(2-oxazoline) triblock copolymers were synthesized via microwave-irradiated cationic living polymerization^{23,24} using methyl triflate as the initiator. The polymerization was

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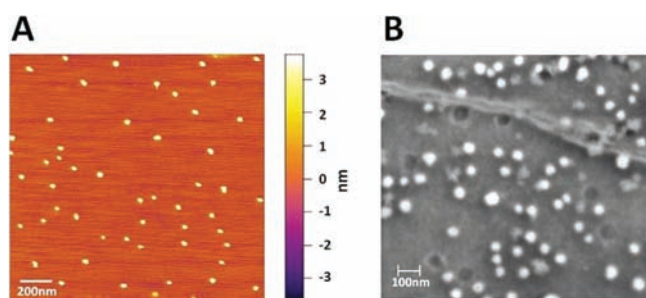


Figure 2. (A) AFM and (B) SEM images of **3**.

monitored by gel-permeation chromatography (GPC). Clear shifts of the GPC traces after each block formation indicated the stepwise growth of the block copolymer [see the Supporting Information (SI)]. The triblock copolymer was subjected to deprotection followed by esterification to introduce the salen ligand to repeating units of the hydrophobic block. The obtained triblock copolymer **1** was characterized by ^1H NMR and ^{13}C NMR spectroscopy and GPC. In CDCl_3 , the ^1H NMR spectrum of **1** showed degrees of polymerization of the individual blocks of $x:y:z:w = 39:3.3:2.2:3.4$ (see the SI). GPC analysis revealed a number-average molecular weight (M_n) of 6300 and a polydispersity index of 1.45. Micelle formation was induced by dissolving **1** in methanol and was proved by ^1H NMR spectroscopy in MeOD (see the SI). Only signals of the hydrophilic and cinnamate blocks were detected. The disappearance of the signals of the hydrophobic salen block is attributed to the motional restriction of the micelle core.^{25,26}

Cross-linking of **2** using UV irradiation was conducted in degassed methanol. The cross-linking progress was monitored by UV spectroscopy. The disappearance of the absorption at 270 nm indicated the full cross-linking of the cinnamates (see the SI).²⁶ The formation of the cross-linked shell was also proved by dynamic light scattering (DLS) analysis. In the nonselective solvent dichloromethane, only one signal for the SCMs was detected, corresponding to a hydrodynamic radius of 17.7 nm. This is in agreement with the hydrodynamic radius of 17.5 nm measured in methanol. In contrast, without cross-linking, the dichloromethane solution of **2** showed some large-size signals (51 and 2700 nm), suggesting the dissociation of micelles and the formation of large aggregates (see the SI).

The SCMs were metalated with Co(II) acetate under an inert atmosphere and then oxidized in air to produce micelle Co(III)–salen catalyst **3**. The cobalt content was determined by inductively coupled plasma mass spectrometry (ICP-MS) to be 0.24%, which corresponds to an 85% metalation yield. Catalyst **3** was characterized by DLS, atomic force microscopy (AFM), and scanning electron microscopy (SEM). The hydrodynamic radius determined via DLS was 18.2 nm, which is consistent with the radii of 20 ± 3 nm obtained by AFM (Figure 2A) and 24 ± 6 nm obtained by SEM (Figure 2B).

The catalytic activity and selectivity of **3** were examined for the HKR of a series of epoxides in water (Table 1). During the HKR of terminal epoxides using **3**, we observed substrate selectivity. With a catalyst loading of 0.05 mol %, **3** showed poor catalytic activities toward less hydrophobic as well as small-sized epoxides. After 24 h, epichlorohydrin (entry 1) was less than 5% resolved with 5% ee. During this time frame, allyl glycidyl ether was 4% resolved with only 3% ee (entry 2). We, and other groups, have reported that these epoxides can be resolved completely in 12 h

Table 1. HKR Tests of **3** with Various Terminal Epoxides^a

$$\text{R-epoxide} + \text{H}_2\text{O} \xrightarrow[\text{Excess}]{\text{SCM catalyst } \mathbf{3}} \text{R-epoxide} + \text{R-1,2-diol}$$

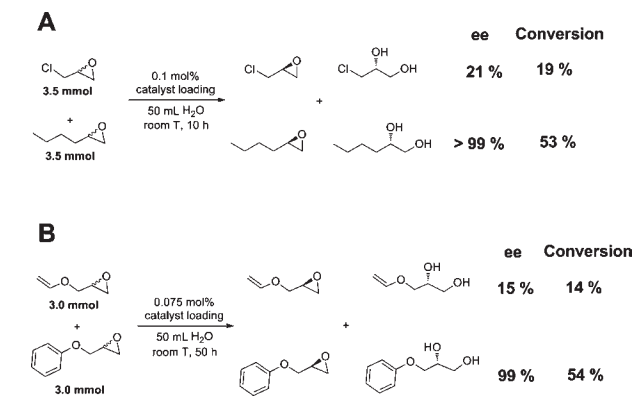
entry	R	loading (mol %) ^b	time (h)	ee (%) ^c	conv. (%) ^d
1	CH ₂ Cl	0.05	24	5	5
2	CH ₂ O–allyl	0.05	24	3	4
3	<i>n</i> -butyl	0.05	8	>99	52
4	<i>c</i> -hexyl	0.05	15	>99	52
5	CH ₂ OPh	0.05	5	>99	50
6	CH ₂ OBn	0.05	8	>99	51
7	Ph	0.15	24	95	53
8	CH ₂ O(CH ₂ CH ₂ O) ₃ CH ₃	0.05	24	<1	<1
9 ^e	<i>n</i> -dodecyl	0.05	24	>99	53

^a Reactions were carried out with 7 mmol of epoxide in 10 mL of water at room temperature. ^b Catalyst loading based on cobalt. ^c Determined by chiral GC or HPLC analyses. ^d Determined by GC or HPLC analyses with chlorobenzene as an internal standard. ^e 1,2-Hexanediol was added in a 1:1 ratio relative to the epoxide.

or less with 0.01–0.04 mol % Co(III)–salen supported on other polymer or oligomer systems,^{27–30} demonstrating the substrate inactivity of **3** toward these epoxides. Increasing the number of carbons in the side chain of the target epoxides resulted in a remarkable rate acceleration. The resolution of epoxyhexane was complete in 8 h (entry 3). For the more sterically hindered vinylcyclohexane oxide, the reaction was finished within 15 h (entry 4). Aromatic epoxides, such as phenyl glycidyl ether and benzyl glycidyl ether (entries 5 and 6) were fully resolved in 5 and 8 h, respectively. When the catalyst loading was increased to 0.15%, even the conjugated compound styrene oxide reached 95% ee after 24 h (entry 7). These results indicate that the HKR using **3** exhibits a substrate selectivity based on hydrophobicity: the more hydrophobic the epoxide, the better is the diffusion of the epoxide into the hydrophobic core of the SCM where the catalytic active centers are located.

To verify the reason for the substrate selectivity, water-soluble (2,5,8,11-tetraoxadodecyl)oxirane was synthesized and subjected to the HKR conditions (entry 8). No resolved product was formed after 24 h, indicating that the hydrophilic epoxide remained in the water solution instead of interacting with the SCM catalyst. We then explored the HKR of epoxytetradecane, a very hydrophobic epoxide, using **3**. Surprisingly, almost no resolution occurred (ee < 2%) after 24 h. Epoxytetradecane should be able to permeate easily into the hydrophobic SCM core. We hypothesized that the hydrolyzed product, the resolved diol, is too hydrophobic to diffuse through the SCM into the outside water solution, resulting in blockage of the catalytic cycle. To test this hypothesis, 1,2-hexanediol was added to the reaction mixture in a 1:1 ratio relative to epoxytetradecane to increase the water solubility of the product. Under these conditions, epoxytetradecane could be resolved completely and selectively in 24 h (entry 9). In all of the HKR experiments, although large amounts of water were applied, the product conversions were consistent with the ee values; reactions with high ee values showed ~50% conversions, and those with low ee were accompanied by poor conversions, which demonstrates the high enantioselectivity of **3**.

Scheme 1. One-Pot Competitive HKR Reactions To Test the Substrate Selectivity of 3: HKRs Using 1:1 Ratios of (A) Epichlorohydrin and Epoxyhexane and (B) Allyl Glycidyl Ether and Phenyl Glycidyl Ether



Our attention was then focused on the role played by the cross-linked shell layer in this substrate selectivity of the SCM catalyst. Non-cross-linked micellar catalysts obtained by direct metalation and oxidation of **2** were applied as controls. Although, at the same catalyst loading, the non-cross-linked catalyst showed a slightly higher catalytic activity by resolving epoxyhexane in 5 h, it exhibited almost no substrate selectivity by producing a 90% ee of epichlorohydrin in 48 h. In contrast, **3** afforded only a 7.7% ee of epichlorohydrin during the same reaction time (see the SI). The main difference between **2** and **3** is the fixed core–shell structure of **3**, which we suggest limits the substrate permeability.

To examine further the substrate selectivity of **3**, a one-pot competitive HKR experiment involving epoxyhexane and epichlorohydrin was performed (Scheme 1A). When epoxyhexane was fully resolved after 10 h of reaction, epichlorohydrin had reached only 21% ee. A similar result was obtained for the competitive reaction of phenyl glycidyl ether and allyl glycidyl ether (Scheme 1B): the resolution of phenyl glycidyl ether was complete in 50 h, whereas only 15% ee of allyl glycidyl ether was resolved. To our knowledge, the SCM catalyst is the first HKR catalytic system with substrate selectivity based on the hydrophobicity of epoxides.

We reasoned that SCM-supported catalysts stabilized by the cross-linked layer might have better recyclability than their conventional non-cross-linked analogues. We investigated the recovery and recycling of **3** using the HKR of epoxyhexane (Table 2). Because of its nanoscale size, the SCM catalyst could be recovered easily by passing the reaction solution through an ultrafiltration membrane with a molecular-weight cutoff of 30 000. For cycles 2–5, the recovered catalyst was used directly without reactivation. In the first five cycles, while a slow decrease in reaction rate was observed, the SCM catalysts were highly active, resolving epoxyhexane in 8–12 h. In cycles 6–8, acetic acid (0.01 equiv relative to epoxyhexane) was added to the reaction mixture to regenerate the Co(III)–salen complexes in situ with acetate as the counterion. Under these conditions, the catalyst maintained the high catalytic efficiency by completing the HKR in 11–12 h. For all of the HKR cycles, the catalyst loadings were kept at 0.05 mol %. Cobalt leaching was investigated by ICP-MS analyses of the filtrates for cycles 4 and 7. In both samples, the Co content was below the analytical detection limit (<1 ppm), proving the high stability of **3**. Comparisons of

Table 2. Recycling of 3 in the HKR of Epoxyhexane in Water^a

cycle ^b	time (h)	ee (%) ^c	conv. (%) ^d
1	8	>99	52
2	8.5	>99	53
3	10	>99	54
4	10.5	>99	54
5	12	98	55
6 ^e	11	>99	53
7 ^e	11	>99	54
8 ^e	12	99	55

^a Conditions: 0.05 mol % catalyst loading in 10 mL of water at room temperature. ^b The SCM catalyst was recovered by passing the reaction solution through an ultrafiltration membrane with a molecular-weight cutoff of 30 000. ^c Determined by chiral GC analyses. ^d Determined by GC analyses with chlorobenzene as an internal standard. ^e During these cycles, acetic acid (0.01 equiv relative to epoxyhexane) was added.

the catalyst stability and activity in the recycling tests showed that the SCM catalyst surpasses the conventional micellar catalyst²¹ and is comparable to the most recyclable homogeneous Co(III)–salen catalysts.^{31,32} However, the SCM catalyst holds the advantage of facile product separation and catalyst recovery.

In conclusion, we have synthesized a new class of supported Co(III)–salen complexes using shell cross-linked micelles as a support structure. These new supported Co(III)–salen catalyst complexes have high catalytic efficiencies and a very unique substrate selectivity. The high support stability resulted in outstanding recycling properties of the system.

■ ASSOCIATED CONTENT

S Supporting Information. Syntheses and characterizations of the cinnamate-containing monomer and triblock copolymer **1**, synthetic procedures and characterization of SCM catalyst **3**, experimental procedures for HKR tests and the catalyst recycling experiment, and crystallographic data (CIF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

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