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Self-Assembled Nanoreactors as Highly Active Catalysts in the Hydrolytic Kinetic Resolution (HKR) of Epoxides in WaterBenjamin M. Rossbach, Kerstin Leopold, and
Ralf Weberskirch*

The synthesis of optically active organic compounds is a central research topic in chemistry because of their widespread use in the pharmaceutical industry as well as in the production of fine chemicals.^[1] Catalytic enantioselective organic reactions can be achieved by metal catalysis,^[2] by biocatalysis,^[3] and more recently also by organocatalysis.^[4] Despite the increased industrial demand for enantiomerically pure compounds, to date only a few catalytic asymmetric processes have found commercial application.^[5] One rare exception is the hydrolytic kinetic resolution (HKR) of terminal epoxides, which allows the production of enantiopure epoxides and diols from the racemic starting materials.^[6] These chiral compounds play a key role as intermediates in the production of pharmaceuticals and agricultural chemicals.^[7]

Studies of HKR of epoxides catalyzed by Co^{III}(salen) complexes ($H_2salen = N,N'$ -bis(salicylidene)ethylenediamine) support a cooperative mechanism involving two catalyst metal centers that leads to the dual activation of the epoxide as an electrophile and water as a nucleophile.^[6] This synergistic activation seems to be a common feature of Lewis acid catalysis in general and asymmetric catalysis in particular. Two discrete cobalt centers bring the nucleophilic and electrophilic reaction partners into proximity and with the correct relative geometry for the selective conversion of only one enantiomer, thus reducing the energetic barrier in a similar way to enzyme catalysis.^[8a] The asymmetric ring-opening reaction of epoxides by azide nucleophiles catalyzed by related Cr^{VI}(salen) complexes follows a similar mechanism.^[9] Also, Shibasaka and co-workers reported already in 1995 on the use of heterobimetallic binol complexes that

enable asymmetric Michael additions by a dual activation of the reagents (binol = 1,1'-bi-2-naphthol).^[8b,c]

Catalyst immobilization and environmentally benign solvents are important issues in the development of sustainable industrial processes. The use of water as a reaction medium has attracted increasing attention because it is economical and has no associated health and safety risks.^[10] In the past couple of years several groups have reported the application of polymer-supported catalysts in water without the use of any organic cosolvent.^[11] Water plays a particular role in the Co^{III}(salen)-catalyzed HKR in acting as reagent in the epoxide opening as well as a ligand for the Co(salen) complex.^[12] As a consequence the amount of water in the reaction mixture is a very sensitive factor. In general, 0.55–0.70 equivalents of water with respect to the racemic epoxides is employed to achieve high enantioselectivity, and residual water must be removed carefully before workup so as not to diminish the enantiomeric excess and yield of the chiral products. As the enantioselective kinetic resolution of the terminal epoxides is also exothermic, the addition of water must be continuous and at constant temperature.^[6,13] Therefore, carrying out HKR in water seems to be possible only if the amount of water in the immediate environment of catalyst and the racemic epoxides can be strictly controlled.

Jacobsen and co-workers utilized dendrimers as a support material for Co^{III}(salen) complexes and showed the beneficial effects of high local concentrations of catalyst on the activity without loss of enantioselectivity.^[14] Inspired by this work, we aimed to prepare a core-shell-type nanoreactor in which the hydrophobic core provides a favorable environment for the Co^{III}(salen) complex and the racemic epoxide, while the hydrophilic shell guarantees water-solubility of the nanoreactor. Several approaches can be used to prepare such amphiphilic structures, for example, with either core-shell-like dendrimers^[15] or by simple amphiphilic block copolymers that self-assemble in water to form micellar aggregates with a hydrophobic core and a water-soluble shell.^[16] Although dendrimers can enhance reaction rates and have therefore been regarded as “unimolecular micelles”,^[14,17] elaborate preparation of the functionalized dendrimers through multi-step synthesis is required. For that reason we decided to prepare amphiphilic block copolymers with pendant Co^{III}(salen) moieties covalently attached to the hydrophobic block. These functionalized block copolymers should form micellar aggregates in water, thereby creating a nanoenvironment with high local concentration of the Co^{III}(salen) complex in the hydrophobic core along with a hydrophilic shell ensuring the water-solubility of the whole aggregate. The approach was based on several considerations: Firstly, it was anticipated that the hydrophobic core would exclude any excess water from the catalyst and epoxides. Secondly, the high local concentration of catalyst should be beneficial for catalytic activity. Thirdly, covalent attachment of the catalyst to the polymer should also allow separation and recycling of the catalyst.

As the presence of functional moieties could disturb the polymerization of the 2-alkyl-2-oxaline-based monomers, the salen moiety was introduced in a polymer-analogous coupling reaction. In the first step, the amphiphilic block copolymer **1**

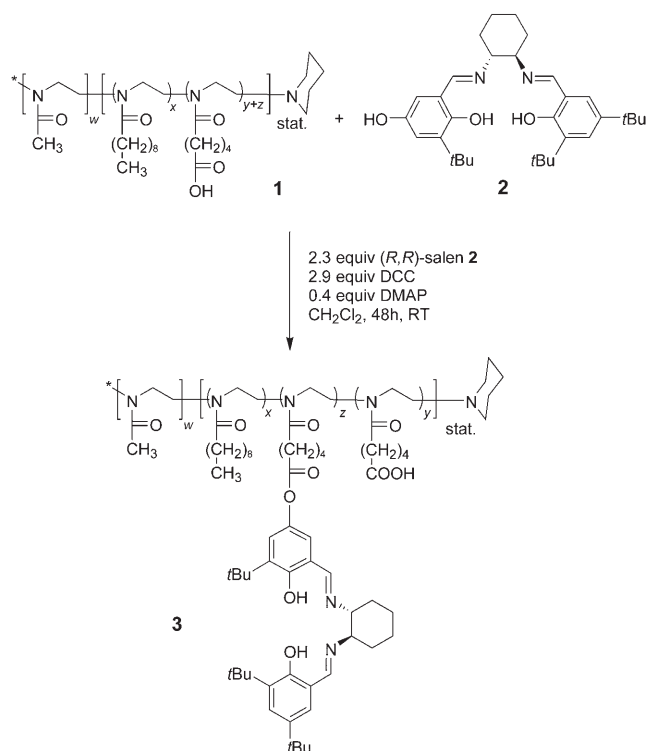
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with pendant carboxylic acid groups was prepared according to a literature procedure.^[18] Its structure and composition was confirmed by ¹H NMR spectroscopy, and size-exclusion chromatography (SEC) revealed a molar mass of 6153 g mol⁻¹ and a polydispersity of 1.12. The chiral salen ligand **2**, featuring a hydroxy group for covalent attachment to the polymer, was prepared in a three-step synthesis,^[13a,19] and its structure and purity were confirmed by ¹H NMR and ¹³C NMR spectroscopy as well as by elemental analysis. The precursor polymer **1** was treated with two equivalents of salen ligand **2** in the presence of *N,N'*-dicyclohexylcarbodiimide (DCC) as an activation reagent (Scheme 1).



Scheme 1. Synthesis of the amphiphilic (*R,R*)-macrosalen ligand **3** ($w = 41$, $x = 4.5$, $y = 2.8$, $z = 2.3$). DCC = *N,N'*-dicyclohexylcarbodiimide; DMAP = 4-dimethylaminopyridine; stat. = statistical.

An excess of the carboxylic acid groups in the polymer (2.1 equiv relative to the salen ligand) guaranteed quantitative binding. The immobilized salen ligand **3** was analyzed by ¹H and ¹³C NMR spectroscopy as well as by SEC. The ¹H NMR spectrum of macrosalen ligand **3** is depicted in Figure 1. The signals labeled 9 and 6,6' can be clearly assigned to the polymer backbone and the methyl or methylene group neighboring the amide in the side chain, respectively. Also, the salen ligand can be identified by the signals at $\delta = 1.25$ and 1.35 ppm corresponding to the *tert*-butyl groups and the signals between $\delta = 6.66$ and 7.32 ppm that belong to the aromatic salen protons. The broad signal at $\delta = 13.84$ ppm can be assigned to the internal hydroxy groups of the salen ligand. Quantitative NMR analysis revealed that approximately 2.3 ligand moieties were bound on average to each polymer chain. SEC measurements indicate an increase in molar mass

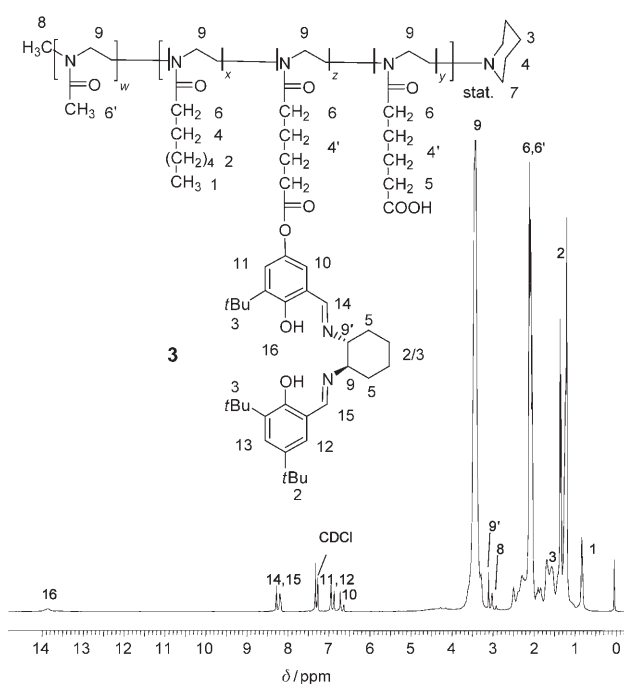
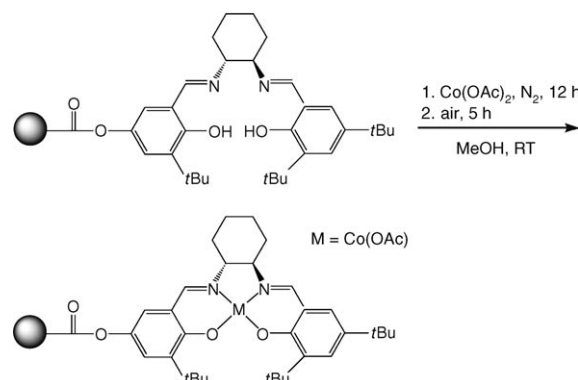


Figure 1. ¹H NMR spectrum of **3** (CDCl₃, 500.1 MHz, $T = 297.0$ K).

to 7667 g mol⁻¹ for the polymer-bound salen ligand **3** with a narrow polydispersity of 1.07.

The polymer-Co^{III}(salen) complex **4** was prepared by reaction of a solution of **3** in methanol with two equivalents of Co(OAc)₂·4H₂O under inert gas (Scheme 2). The typically



Scheme 2. Metalation followed by oxidation of (*R,R*)-**3** to give the polymeric Co^{III}(salen) complex **4**.

red Co^{II} complex immediately turned dark brown upon exposure to air. The metal content was determined by graphite-furnace atomic-absorption spectrometry (GFAAS) to be 0.0179 g Co per gram of polymer, which corresponds to one Co atom per polymer chain.

The aggregation behavior of **4** in water was studied by dynamic light scattering (DLS) and TEM analysis. The hydrodynamic radii of the particles measured at three different concentrations ($c_p = 1.0$, 2.0, and 4.0 mg mL⁻¹) were in the range of 10 to 12 nm. TEM analysis (Figure 2) revealed

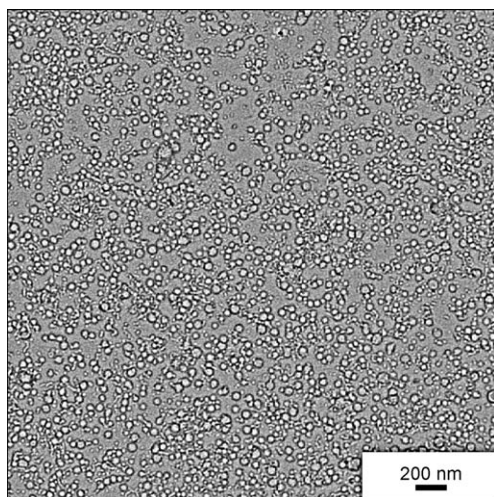


Figure 2. TEM micrograph of micellar aggregates of **4** ($c_p = 2 \text{ mg mL}^{-1}$, 0.31 mmol).

spherical aggregates with an average radius of 14.3 nm, which is in good agreement with the DLS data.

The activity and selectivity of the self-assembled aggregates were investigated with four different aromatic epoxides, chosen because they are known to require higher amounts of catalyst and longer reaction times than aliphatic epoxides for HKR. For these experiments, **4** was dissolved in degassed water in concentrations suitable for the formation of micellar aggregates ($1.2\text{--}2.6 \text{ mg mL}^{-1}$; $0.18\text{--}0.39 \text{ mmol L}^{-1}$). The racemic epoxide was then added, and the reaction mixture was stirred at room temperature. When the reaction was complete, as indicated by chiral gas chromatography (GC), the aqueous phase was extracted twice with ethyl acetate to separate the enantio-enriched epoxide and diol from the reduced catalyst, which remains completely in the aqueous phase. The aromatic diols precipitated upon addition of hexane to the organic extracts and were separated from the epoxides by filtration.

Following this procedure we first investigated the catalytic efficacy of **4** in HKR of ether-containing terminal epoxides (Table 1, entries 1–4). As an example, the reaction in water of 2-phenoxy-methyloxirane with **4** at room temperature gave an enantiomeric excess of 99.1% *ee* of (*S*)-phenoxy-methyloxirane after 4.5 h when a catalyst loading of 0.02 mol % was used, and 96.6% *ee* after a shorter reaction time of 1 h and with a catalyst loading of 0.08 mol % (Table 1, see entries 1 and 2). The enantiomeric excess of the diol fraction was determined to be at least 88.9% *ee* in the latter (entry 1) and 95.9% *ee* in the former experiment (entry 2). Most remarkable, however, is that the micellar catalytic approach allows the use of low amounts of catalyst (0.02–0.08 mol %) and shorter reaction times (1–4.5 h) than the homogeneous approach ($c_{\text{cat}} = 0.5 \text{ mol \%}$, $t = 16\text{--}18 \text{ h}$) to achieve the same enantioselectivity (> 99% *ee*).^[20]

Similar results were obtained with racemic 2-benzyloxy-methyloxirane under the same reaction conditions ($c_{\text{cat}} = 0.10 \text{ mol \%}$, $t = 1 \text{ h}$, $T = \text{room temperature}$): (*S*)-2-benzyloxy-methyloxirane was obtained with 95.6% *ee* and the diol derivative with 87.4% *ee* (Table 1, entry 3). Greater than

Table 1: Hydrolytic kinetic resolution (HKR) of aromatic terminal epoxides in water in the presence of catalyst **4**.^[a]

$(+/-) \text{ R} \begin{array}{c} \diagup \text{O} \diagdown \\ \text{C} \end{array} \xrightarrow[\text{H}_2\text{O}]{(R,R)\text{-4, N}_2, \text{RT}} \text{R} \begin{array}{c} \diagup \text{O} \diagdown \\ \text{C} \end{array} + \text{R} \begin{array}{c} \text{OH} \\ \\ \text{C} \end{array} \text{OH}$							
No.	R	c_{cat} ^[b] [mol %]	c_p [mmol L ⁻¹]	t ^[c] [h]	ee_{epox} ^[d] [%]	ee_{diol} ^[e] [%]	Conv. ^[f] [%]
1	CH ₂ OPh	0.08	0.177	1	96.6	88.9	52.2
2	CH ₂ OPh	0.02	0.168	4.5	99.1	95.9	51.1
3	CH ₂ OBn	0.10	0.220	1	95.6	87.4	52.3
4	CH ₂ OBn	0.02	0.178	4	> 99.9	86.9	53.5
5	Ph	0.09	0.331	6	91.3	91.3	50.0
6	Ph	0.06	0.229	24	98.1	91.5	51.8
7	<i>p</i> -ClC ₆ H ₄	0.10	0.265	6	> 99.9	95.1	51.2
8	<i>p</i> -ClC ₆ H ₄	0.06	0.393	7.5	97.8	95.1	50.9

[a] A detailed description of the catalysis is given in the Supporting Information. Bn = benzyl. [b] Ratio of Co to racemic epoxide. [c] The reaction was terminated by extraction of the diol and epoxides fraction. [d] Enantiomeric excess of the epoxides was determined by chiral GC or chiral HPLC immediately after the aliquot was removed. [e] Diols were treated with 2,2-dimethoxypropane and a catalytic amount of *p*-TsOH and the enantiomeric excess was determined by chiral GC. *p*-TsOH = *p*-toluenesulfonic acid. [f] Estimated on the basis of the *ee* value of the recovered epoxide and diol products (see the Supporting Information).

99.9% *ee* for the epoxide was achieved by reducing the cobalt loading to 0.02 mol % (Table 1, entry 4). The increased reaction time evidently led to a slight consumption of the less reactive enantiomer, which explains the relatively high overall yield and the low enantiomeric excess for the diol product (86.9% *ee*).

The effects of the nanoreactor in improving catalytic activity become even clearer with the less-reactive HKR substrates 2-phenyloxirane and 2-(4-chlorophenyl)oxirane. 2-Phenyloxirane could be isolated in up to 98% *ee* after 24 h with only 0.06–0.09 mol % catalyst (Table 1, entries 5 and 6), whereas similar *ee* values could be obtained from the homogeneous reaction only after 48 h and with 0.8 mol % catalyst.^[20] The results in Table 1 demonstrate the advantages of the nanoreactor approach. The high local concentration of catalyst leads to enhanced activity similar to that obtained by Jacobsen and co-workers with dendrimer and oligomeric salen systems. More important, however, is the fact that the hydrophobic core limits the penetration of water into the nanoreactors and thus prevents the early hydrolysis of the racemic and chiral epoxides.

For the complete characterization of (*R,R*)-**4**, we investigated its recycling and reuse in four consecutive cycles with the substrate 2-phenyloxirane. The catalyst was recovered from the aqueous phase and regenerated by treatment with diluted acetic acid and exposure to air. The results of the recycling experiments are summarized in Table 2. Although the reaction time had to be increased, *ee* values greater than 99.9% could still be obtained in the fourth run. We assume that the increased reaction times are due to partial oxidation of Co^{III} to give an unreactive Co^{IV} species and that acetic acid was sometimes difficult to remove completely (even by lyophilization) after the regeneration of the catalyst. The leaching of cobalt from **4** after isolation of the substrate by repeated extraction of the aqueous phase with ethyl acetate

Table 2: Catalyst recycling of **4** in the HKR of 2-phenyloxirane in water.

Cycle	$c_{\text{cat.}}^{\text{[a]}}$ [mol %]	t [h]	$ee_{\text{max,epox}}^{\text{[b]}}$ [%]	$ee_{\text{max,diol}}^{\text{[c]}}$ [%]	Conv. ^[d] [%]
1	0.06	24	98.1	91.5	51.8
2	0.29	20	97.6	72.6	57.9
3	0.30	44	> 99.9	80.9	54.7
4	0.12	96	> 99.9	87.5	53.3

[a] Ratio of Co to racemic epoxide. [b] The ee values of the *S* epoxide were determined by chiral GC or HPLC analysis after workup. [c] The ee values were determined by chiral GC after reaction of the diols with 2,2-dimethoxypropane and a catalytic amount of *p*-TsOH. [d] Estimated on the basis of the ee value of the recovered epoxide and diol products (see the Supporting Information).

and hexane was analyzed by GFAAS. The metal content of the product fraction was below the analytical detection limit (7.4 ppb), which suggests that the immobilization of the Co^{III}(salen) catalyst to the polymer is stable, even after extended reaction times.

In summary, we have demonstrated the first HKR of various racemic aromatic epoxides in pure water using a Co^{III}(salen) complex supported on an amphiphilic, water-soluble block copolymer. The aggregation of the polymer and the formation of micellar aggregates are key steps in the preparation of functional nanoreactors. The high local concentration of catalyst in the hydrophobic core and the limited amount of water that can penetrate into the micellar core during catalysis are crucial to achieving high activity while maintaining excellent enantioselectivity comparable to that obtained under homogeneous reaction conditions in organic media. Finally, the polymeric catalyst could be separated and reused in four consecutive cycles, without loss of enantioselectivity. Studies are continuing on the optimization of the catalyst regeneration.

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