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Manganese Salen Compounds Embedded within Cross-Linked Chiral Polyethylenimine: Asymmetric Epoxidation in an Aqueous Biphasic Medium

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Polyethylenimine and derivative polymers have been used as enzyme mimics or surrogates, also called synzymes.[1] By attaching catalytic pyridoxamine and thiazolium moieties to the polymer backbone they have also been used to mimic enzyme-catalyzed transamination, and benzoin condensation reactions.[2] In the past our research group has embedded polyoxometalates and nanoparticles within alkylated polyethylenimine derivatives to catalyze aqueous biphasic epoxidation or carbon–carbon bond cleavage of alkenes, chemoselective hydrogenation of alkenes, and lipophiloselective oxidation of secondary alcohols.[3]

Conceptually our approach is based on a bottom-up preparation of an enzyme mimic with a metal-based active site. The first step is the synthesis of an alkylated polyethylenimine that assembles in water as globules with a hydrophilic surface and a hydrophobic core. Such globules, which incorporate known catalysts, can be considered primitive mimics of water-soluble metalloenzymes. Importantly, the catalysts or guests are not covalently attached to the polyethylenimine host, thus the approach is a general one, not requiring specific design of synthetic procedures for the preparation of each catalyst system.[3a,b] Similarly, more difficult to synthesize dendrimers and hyperbranched polymers have been used as vehicles for the incorporation of catalysts into their cores.[4] Chiral dendrimers have also been used in this context.[5] Because enzymes are often cross-linked by cysteine, the second step imparts some rigidity to the alkylated polyethylenimine constructs by the introduction of cross-linking moieties to yield hydrogel-like materials.[3c]

Herein, we proceeded to a third step through the relatively simple preparation of chiral polyethylenimine polymers[6] that can be cross-linked and then used to incorporate a Mn^{III}salen moiety as an active catalytic site.[7] In addition, we wished to test the hypothesis that a chiral polyethylenimine globule with a hydrophobic core can induce stereoselectivity to a catalytic center by weak van der Waals, hydrogen bonding, and/or π–π stacking interactions to lead to an enantioselective transformation. This is an approach that contrasts the one commonly used in asymmetric catalysis, where a chiral ligand is complexed to a catalytic center by strong interactions, such as covalent or coordination bonds, in order to give stereocontrolled access to the active catalytic site, and where stereoselectivity can also be augmented by template effects.[8] In addition, the hydrophilic surface of the constructs enables reactions in an aqueous biphasic mode, akin to a reaction catalyzed by a water-soluble enzyme with its inherent advantages,[9] obviating the need for an organic solvent.

The synthetic pathway for the preparation of amphiphilic cross-linked chiral polyethylenimines is presented in Scheme 1. Short polyamino acids were prepared by the *N*-carboxyanhydride (NCA) technique using a primary amine as a polymerization initiator.[10] The *N*-carboxy anhydrides of L-leucine (Leu) and L-phenylalanine (Phe) were polymerized in the presence of 2-aminoacetonitrile to yield polyLeu and polyPhe terminated by a cyanomethyl group. Simultaneous reduction of both the amide and nitrile units with BH_3 yielded a primary amine-terminated, chiral linear polyethylenimine with non-polar side chains, **1Leu** and **1Phe**. Cross-linked chiral linear polyethylenimines with hydrophilic units were then prepared in two ways. In method A, compound **1Leu** was cross-linked at the primary amine terminus with terephthaldehyde. The resulting Schiff base was reduced with $NaBH_4$ and then alkylated with 2-bromethanol to yield **2Leu**. The Mn^{III}salen catalyst, **4**, was introduced after formation of **2Leu** to yield the **MnSalen-2Leu** catalytic construct. Alternatively, in method B a cross-linker, **5**, was prepared by the reaction of 2-aminoethanol with two equivalents of epichlorohydrin that was then reacted with compounds **1** at the primary amine terminus in the presence of **4** to yield **MnSalen-3Leu** and **MnSalen-3Phe**.

Polymerization of the *N*-carboxyanhydride units of Leu and Phe at a 6:1 ratio per 2-aminoacetonitrile yielded polyLeu and polyPhe each terminated with one cyanomethyl group that was then reduced to give **1Leu** and **1Phe** as determined by ESI-MS (Figure 1). The spectrum of **1Leu** is easy to decipher with molecular peaks at *m/z* 458, 557, 656, 755, and 854 amu for four to eight repeating units. Fragments for the molecular peak minus the *iso*-butyl side chain were identified at *m/z* 500, 599, 698, and 797 amu. The spectrum of **1Phe** shows considerable fragmentation. Molecular peaks were observed at 726 and 859 amu for five and six repeating units. Fragments of the molecular peaks minus the benzyl side chain were observed at 635 and 768 amu and fragments for the molecular peaks minus the chain terminator $NH_2CH_2CH_2$ were obtained at 684 and 817 amu. Other fragments including molecular peaks plus Na^+ were also observed. It would appear from the ESI-MS that **1Leu** has a broader range of molecular weights ($n = 4$–8) relative to **1Phe** where mostly polymers of five and six repeating units were obtained.

Constructs, such as **MnSalen-3Leu** containing 6.8 wt% **MnSalen** are not freely soluble in water, but form a rather

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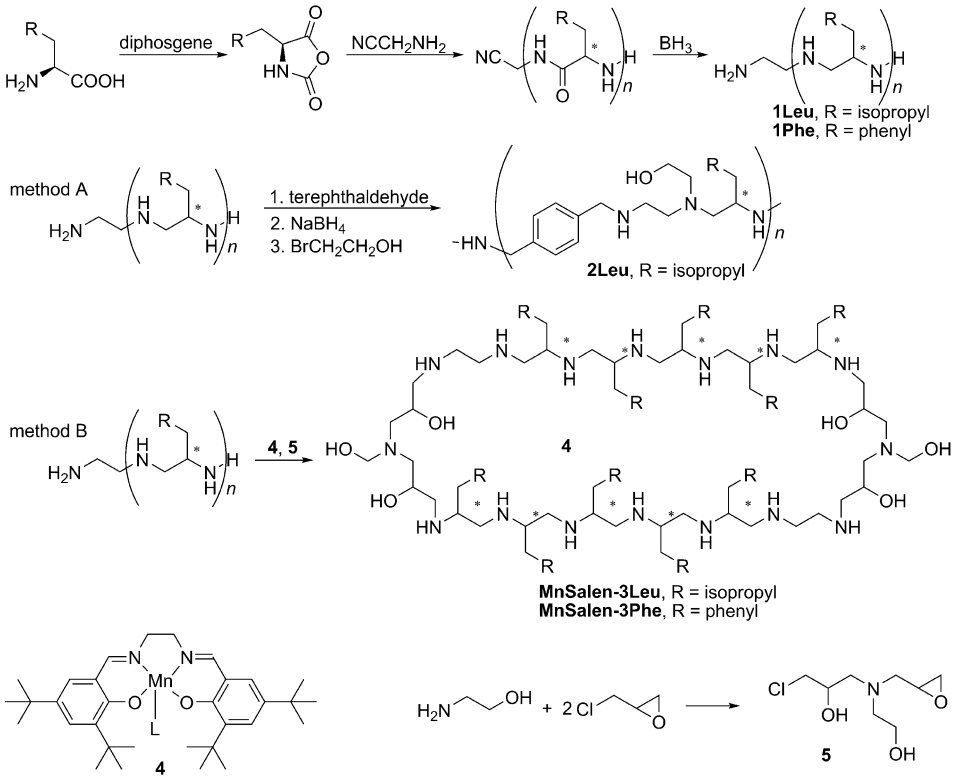


Scheme 1. Synthetic pathways for the preparation of **MnSalen** chiral polyethylenimine constructs. The constructs are shown as macrocycles, where two chiral **3Leu** or **3Phe** groups with five repeat units are linked by **5**. This is an inexact cartoon representation for simplicity. **3Leu** or **3Phe** have a distribution of repeat units and the cross linking procedure is random and will yield a complicated mixture. L = Cl, OAc.

well-dispersed hydrogel, especially if gently heated to 80-100 °C and then cooled. This was expected owing to their cross-linked nature as has been reported previously for another epichlorohydrin cross-linked polyethylenimine construct.[3c] The addition of a water-soluble co-solvent, such as THF, yielded a clear solution that enabled us to measure a circular dichroism (CD) spectrum of **MnSalen-3Leu** (Figure 2). As the **3Leu** framework does not absorb above 230 nm, the CD spectrum at longer wavelengths ($\lambda > 230$ nm) can only be attributed to the interactions of **MnSalen** with the chiral environment of the cross-linked **3Leu**. Indeed, the strong Cotton effects at 260 and 330 nm coincide with the absorption maximum of the **MnSalen** moiety (Figure 2, inset), indicating a close interaction between the achiral **MnSalen** catalytic center and the chiral cross-linked polyethylenimine.

The first catalytic tests to ascertain the ability of the chiral polymeric environment to induce an enantioselective transformation were performed using the epoxidation of 1,2-dihydronaphthalene catalyzed by **MnSalen-2Leu**, **MnSalen-3Leu**, and **MnSalen-3Phe** using a buffered hypochlorite solution as oxidant in the presence of *N*-methylmorpholine oxide (NMO) in an aqueous biphasic medium (Table 1). The catalyst construct **MnSalen-2** showed no stereoselective induction, whereas the catalyst constructs **MnSalen-3Leu** and **MnSalen-3Phe** showed a small, but consistent enantioselectivity towards the (1*R*,2*S*+)-tetralin oxide. One can suggest that the incorporation of the metal-centered catalyst during the cross-linking procedure is preferred for improved selectivity, as has been observed in the past.[3c] There was only a small difference between the catalysts with a benzylic versus *iso*-butyl side chain. Epoxidation of additional substrates (Table 2) showed that under the same conditions using **MnSalen-3Leu** as catalyst the enantioselectivity increased in the following order: styrene (0% *ee*) < *trans*-β-methylstyrene (7% *ee*) < 1,2-dihydronaphthalene (8% *ee*) < *cis*-β-methylstyrene (12% *ee*) < α-methyl-*trans*-stilbene (17% *ee*). Thus, the more sterically inhibited al-

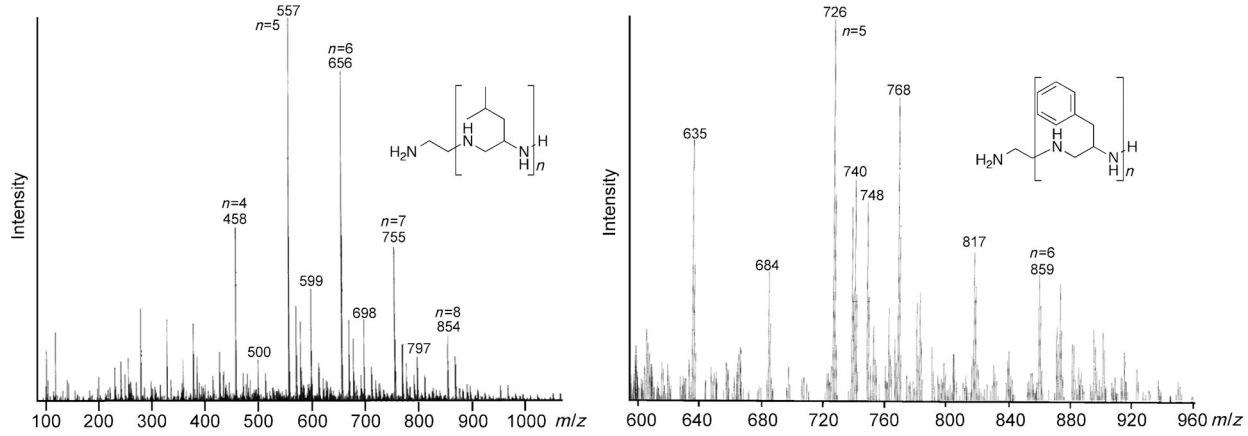


Figure 1. Electrospray ionization mass spectra of **1Leu** (above) and **1Phe** (below).

Table 1. Epoxidation of 1,2-dihydronaphthane catalyzed by **MnSalen-2** or **MnSalen-3** in water.[a]

Catalyst	Conversion [mol%]	Yield [mol%]	*ee* [%] (1*R*,2*S*)-(+)
MnSalen-2Leu	96	63	0
MnSalen-3Leu	64	45	8
MnSalen-3Phe	68	52	4

[a] Reaction conditions: 1 mmol 1,2-dihydronaphthalene, 32.8 mg catalyst, 0.5 mmol NMO, 1 mL water, 1.4 mL 0.55 M NaOCl buffered at pH 11.4 with Na_2HPO_4. $T = 3\,^{\circ}C$, time = 70 h. Conversion is mol% of 1,2-dihydrohaphthalene reacted, yield is mol% 1,2-dihydronaphthalene oxide formed.

Table 2. Epoxidation of various alkenes catalyzed by **MnSalen-3Leu** in water.[a]

Substrate	Conversion [mol%]	Yield [mol%]	*ee* [%]
styrene	80	64	0
trans-β-methylstyrene	74	48	7
1,2-dihydronaphthalene	64	45	8
cis-β-methylstyrene	39	15	12
α-methyl-*trans*-stilbene[b]	≈1	<1	17

[a] Reaction conditions: 1 mmol 1,2-dihydronaphthalene, 32.8 mg catalyst, 0.5 mmol NMO, 1 mL water, 1.4 mL 0.55 M NaOCl buffered at pH 11.4 with Na_2HPO_4. $T = 3\,^{\circ}C$, time = 70 h. [b] α-methyl-*trans*-stilbene is a solid at 3 °C therefore poorly soluble in the reaction mixture.

kenes yielded higher *ee* values, which was, however, inversely proportional to the total epoxide yield.

An asymmetric induction of the chiral polyethylenimine environment unto an achiral **MnSalen** catalyst was clearly observed. However, the absolute *ee* values obtained in these reactions was low despite what might have been expected from the interaction of the achiral catalyst with the chiral framework observed in the CD spectrum. To further understand the effect of the chiral polyethylenimine scaffold on the degree of enantioselectivity obtained in the epoxidation reaction, the *R,R*- and *S,S*-Jacobsen's catalysts (***RR*-MnSalen** and ***SS*-MnSalen**) were incorporated into **3Leu** according to method B and into an achiral cross-linked polyethylenimine to yield ***RR*-MnSalen-6** and ***SS*-MnSalen-6** as shown in Scheme 2.

A comparison of the epoxidation of 1,2-dihydronaphthalene as a model substrate using the chiral Jacobsen catalysts within

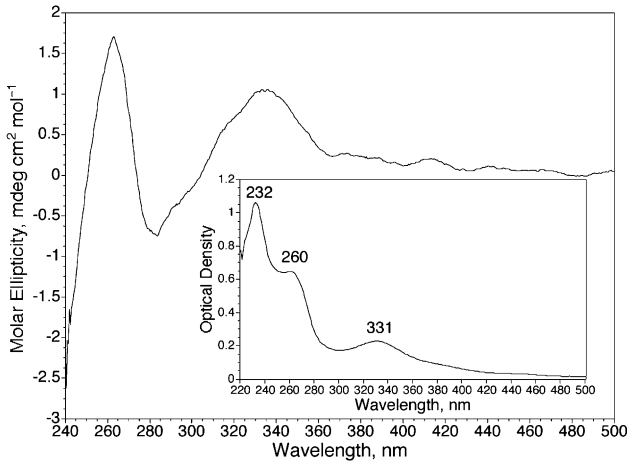
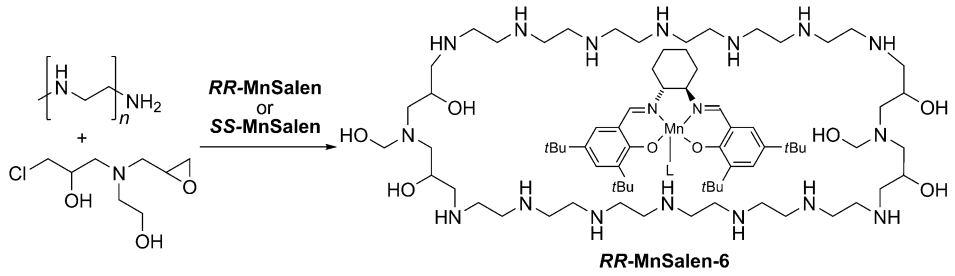


Figure 2. Circular dichroism spectra of **MnSalen-3Leu** in 40% THF/water and UV/Vis-spectrum of **MnSalen-3Leu** (0.2 mM **MnSalen**) in the same solvent. The molar absorptivities are: $\log\varepsilon_{232} = 4.01$, $\log\varepsilon_{260} = 3.82$, and $\log\varepsilon_{331} = 3.35$.

chiral and achiral polyethylenimine is presented in Table 3. Interestingly, we found that ***RR*-MnSalen-6** and ***SS*-MnSalen-6**, embedded within achiral cross-linked polyethylenimine yielded epoxide products with only low enantioselectivity (4–5% *ee*). This is similar to the enantioselectivity observed for achiral **MnSalen** within cross-linked **3Leu** (8% *ee*). Thus, the Jacobsen catalysts are surprisingly ineffective in these aqueous biphasic media. The results are significantly inferior to reactions carried out in an organic solvent, such as dichloromethane, where *ee* values of >80% have been observed with similar substrates.[11] On the other hand, when ***RR*-MnSalen** was embedded within **3Leu** there was a significant synergistic effect between the chiral catalyst and the chiral environment and 41% *ee* for the (1*R*,2*S*)-(+) epoxide was obtained. In contrast, when ***SS*-MnSalen-3Leu** was used a lower 27% *ee* of the opposite (1*S*,2*R*)-(−) enantiomer was obtained. It can be concluded that the handedness of the Jacobsen catalyst determines the enantiomer formed and the chiral cross-linked polyethylenimine significantly increases the enantiomeric excesses relative to those obtained in achiral cross-linked polyethylenimine. This observation requires some additional explanation.

As was discussed at length in the literature,[11,12] the enantioselectivity elicited by **MnSalen** complexes originates from the diimine bridge lying in the same plane of the aromatic system. Jacobsen proposed an attack of a *cis*-alkene on the Mn^{V}=O reactive intermediate from the direction of the diimine bridge, while Katsuki favors attack over the imine bond because of π–π interactions. The enhancement of enantioselectivity of the Jacobsen catalysts within the chiral polymeric framework requires consideration of a diastereomeric arrangement that will enhance the enantiosteric effect of the axial hydrogen at the diimine



Scheme 2. Synthetic pathway for the preparation of Jacobsen **MnSalen** achiral polyethylenimine (PEI) constructs. The constructs are shown as macrocycles, where PEI with six repeat units is linked by **5**. This is an inexact cartoon representation for simplicity. PEI has a distribution of repeat units and the cross linking procedure is random and will yield a complicated mixture.

Table 3. Comparison of the epoxidation of 1,2-dihydronaphthane catalyzed by ***RR***- or ***SS*-MnSalen-3Leu** and ***RR***- or ***SS*-MnSalen-6** in water.[a]

Catalyst	Conversion [mol%]	Yield [mol%]	*ee* [%]
***RR*-MnSalen-6**	47	30	5 (1*R*,2*S*)-(+)
***SS*-MnSalen-6**	43	31	4 (1*S*,2*R*)-(−)
MnSalen-3Leu	64	45	8 (1*R*,2*S*)-(+)
***RR*-MnSalen-3Leu**	78	51	41 (1*R*,2*S*)-(+)
***SS*-MnSalen-3Leu**	78	57	27 (1*S*,2*R*)-(−)

[a] Reaction conditions: 1 mmol 1,2-dihydronaphthalene, 32.8 mg catalyst, 0.5 mmol NMO, 1 mL water, 1.4 mL 0.55 M NaOCl buffered at pH 11.4 with Na_2HPO_4. $T = 3\,^{\circ}C$, time = 70 h. Conversion is mol% of 1,2-dihydrohaphthalene reacted, yield is mol% 1,2-dihydronaphthalene oxide formed.

bridge. As a model of such an arrangement, we considered the interaction between one of the secondary amines of the chiral polyethylenimine framework and the oxygen atom of the reactive intermediate Mn^{V}=O. A fragment of chiral **1Leu** with five repeating units was chosen as a representative model for such an interaction. The minimized energy arrangement of the **1Leu-Mn^{V}=O** complex was calculated by molecular mechanics using MM2 for ***RR*-MnSalen** and ***SS*-MnSalen** (Figure 3). For **1Leu-*RR*-MnSalen** the axial hydrogen atom (ax) is sterically hindered while the opposite face is open for an approach of the alkene (arrow), hence enhancing the enantioselectivity of the catalyst (Figure 3, top). For **1Leu-*SS*-MnSalen** the axial hydrogen (ax) is hindering the opposite enantioface, but the reactive face is more hindered (see arrow in Figure 3, bottom), than in the case of **1Leu-*RR*-MnSalen**. The more hindered reactive face for **1Leu-*SS*-MnSalen** lowers the enantioselectivity of the reaction, although the enantioface for the reaction is determined by the **MnSalen** catalyst and not the chiral polyethylenimine environment.

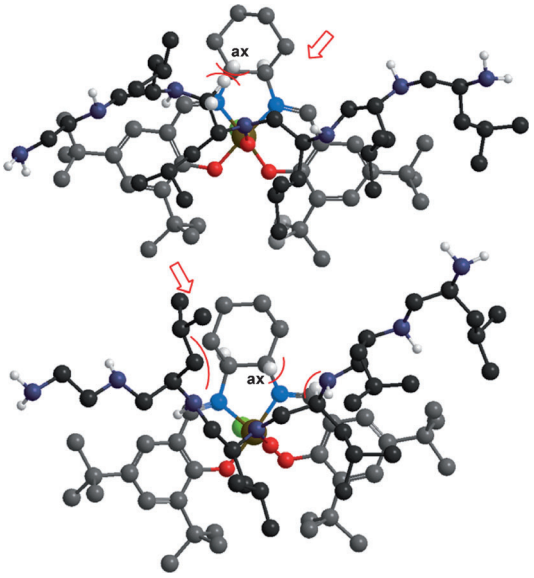


Figure 3. Minimal energy configuration for the diastereomeric interactions between **1Leu** and ***RR*-MnSalen** (top) and ***S,S*-MnSalen** (bottom). N (purple for **1Leu** blue for **MnSalen**); C (black for **1Leu** gray for **MnSalen**); O (red); Mn (brown); Cl (green); H (white, only N–H and H atoms involved in the stereo interactions are shown for clarity).

Several conclusions can be drawn from this research. 1) Easy to synthesize cross-linked chiral polyethylenimines can be used as a convenient aqueous biphasic reaction media for inducing enantioselectivity with an achiral catalyst. The method is a general one, and therefore, one can consider a multitude of catalysts and transformations that may be applicable. The present system showed a close interaction between the achiral catalysts and the cross-linked chiral polyethylenimine framework, but elicited only low *ee* values in a benchmark epoxidation reaction. Other systems may be more effective. 2) The significant synergistic effect obtained when using a chiral catalyst and a cross-linked chiral polyethylenimine has the potential for increasing enantioselectivities obtained in transformations with well-known chiral catalysts, provided they work well in these media, without the need for extensive and work-intensive ligand synthesis and optimization.

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Keywords: biphasic catalysis · enantioselectivity · enzyme mimics · epoxidation · polyethylenimine

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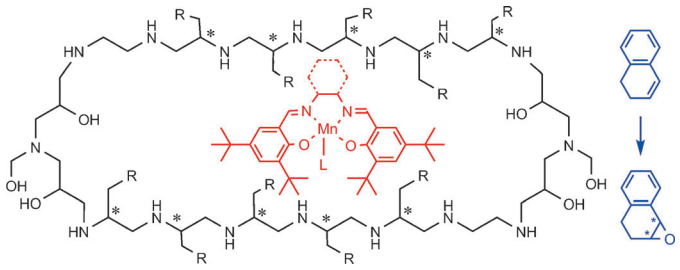

Chiral cross-linked polyethylenimines were used to intercalate Mn^{III} salen catalysts, thereby inducing a chiral environment upon an achiral metal complex. The synzyme, dispersed in water, catalyzes the aqueous biphasic asymmetric epoxidation of styrene derivatives (see structure; L = Cl, OAc, R = isopropyl, phenyl). In the presence of the chiral catalyst there is a significant synergistic effect that increases the enantioselectivity of epoxidation.

