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Enhanced activity of enantioselective (salen)Mn(III) epoxidation catalysts through supramolecular complexation

Gregory A. Morris, SonBinh T. Nguyen*, Joseph T. Hupp[1]

Department of Chemistry and the Institute for Environmental Catalysis, Northwestern University, 2145 Sheridan Road, Evanston, IL 60208-3113, USA

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Abstract

(Salen)Mn(III) catalysts show increased turnover numbers in the catalytic asymmetric epoxidation of conjugated olefins upon addition of bulky Lewis acids (LA) such as zinc tetraphenylporphyrin (ZnTPP). Up to 3-fold increase in total catalytic activity and at least a 20-fold increase in catalyst stability was observed with a (salen)Mn catalyst bearing pendant 5,5′-bis-pyridyl groups. This latter enhancement is primarily attributed to formation of a coordination triad, which provides steric protection for the catalyst from bimolecular decomposition. Supramolecular complex formation enhanced the catalyst's stability without compromising its enantioselectivity.

Keywords: Catalytic epoxidation; Asymmetric epoxidation; Manganese; Salen; Supramolecular chemistry

1. Introduction

Asymmetric epoxidation of alkenes is a powerful method for the synthesis of chiral intermediates in the pharmaceutical and agrochemical fields [1]. Among the most useful systems for the asymmetric epoxidation of non-functionalized olefins is the Jacobsen–Katsuki Salen(Mn)–catalyzed reaction [2,3]. The (salen)Mn catalyst system has been shown to be effective for the epoxidation of an impressive variety of unfunctionalized conjugated olefins [4]. To date, however, the utility of these (salen)Mn catalysts has been limited by facile catalyst deactivation which is thought to occur primarily by Mn(IV) μ-oxo dimer formation [5] and irreversible ligand oxidation [6]. Recent efforts to circumvent this problem have centered around the site isolation of (salen)Mn catalysts through the use of cross-linked polymer supports [7–10] or immobilization in polysiloxane [11] and zeolite [12–14] matrices. We recently reported the success of a somewhat different, and potentially more versatile strategy for site isolation of porphyrin epoxidation catalysts via the formation of a coordination triad consisting of a pyridyl-substituted Mn(III) porphyrin complex and two zinc Lewis acids (LA) [15]. This approach is attractive because it allows for the efficient, non-covalent assembly of a sterically bulky complex structure designed to protect the Mn metal center from bimolecular deactivation pathways. Driven by our interest in expanding this methodology to asymmetric epoxidation, we decided to explore the ability of (salen)Mn supramolecular complex **1** to enhance catalyst stability without compromising enantioselectivity (Fig. 1). We were also interested in working with salen-type ligands because they

* Corresponding author.
E-mail addresses: stn@chem.nwu.edu (S.T. Nguyen), jthupp@chem.nwu.edu (J.T. Hupp).
[1] Co-corresponding author.

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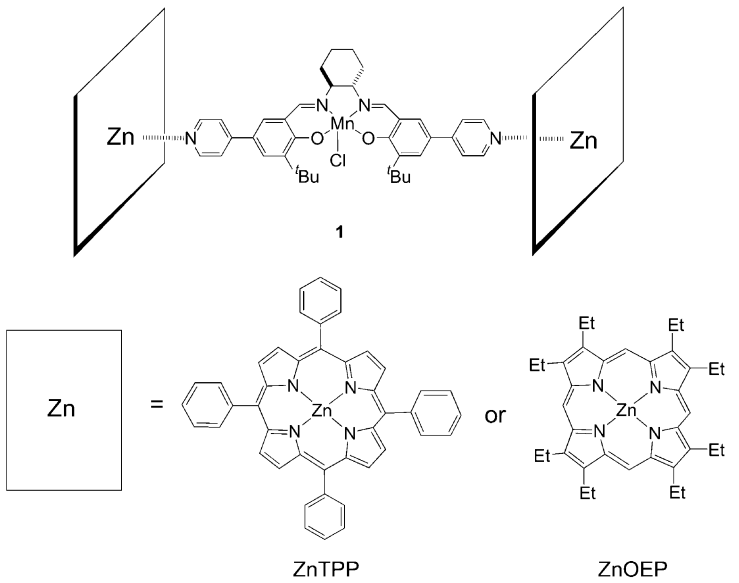


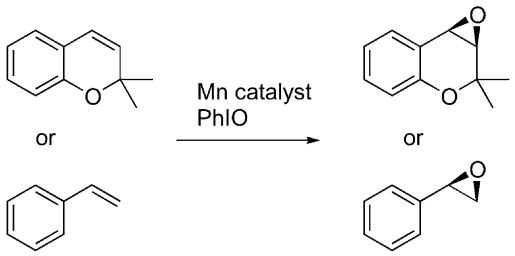
Fig. 1. ZnTPP-**2**-ZnTPP supramolecular complex **1**.

are often easier to synthesize than their porphyrin analogues, and their modular construction from salicylaldehydes and diamines permits the facile and convenient modification of steric and electronic properties. This paper describes the use of supramolecular complexation to enhance (salen)Mn catalyst stability in the asymmetric epoxidation of unfunctionalized conjugated olefins.

2. Results and Discussion

Since it has been observed that pyridines bind to zinc porphyrins with binding constants on the order of $3 \times 10^3\ M^{-1}$ [16–18], we reasoned that by combining one equivalent of (*R,R*)-(−)-1,2-cyclohexanediamino-*N,N′*-bis(3-*tert*-butyl- 5 - (4-pyridyl)-salicylidene)Mn-(III) chloride (**2**) and two equivalents of zinc tetraphenylporphyrin (ZnTPP), formation of supramolecular complex **1** would occur, thus, spatially isolating the (salen)Mn catalyst. The (salen)Mn complex **2** with pendant pyridyl groups was obtained from the corresponding ligand [19] and $Mn(OAc)_2$ following published procedures [20]. Formation of a manganese-free version of complex **1** can be conveniently monitored by ^1H NMR studies which showed the significant upfield shift (∼4 ppm) of the resonance for the 2,6-pyridyl protons of the Schiff base ligand (*R,R*)-(−)-*N,N′*-bis(3-*tert*-butyl-5-(4-pyridyl)-salicylidene)-1,2-diaminocyclohexane (**3**) upon addition of one equivalent of ZnTPP. A similar upfield shift of the resonances for the 2,6-pyridyl protons of dipyridyl and tetrapyridyl porphyrins has been observed upon formation of coordination triads with ZnTPP [15,21]. Unfortunately, our efforts to obtain a crystal structure of supramolecular complex **1** have not been successful to date, but a similar structure consisting of *meso*-tetra(4-pyridyl)porphyrin and two equivalents of ZnTPP has recently been characterized through X-ray crystallographic studies [22]. Coordination polymers of zinc [21] and other pyridine-functionalized transition-metal porphyrins, such as osmium [23] and ruthenium [24] have also been characterized in both solution and solid states.

To evaluate the utility of complex **1** as a catalyst for the asymmetric epoxidation reaction, we chose styrene and 2,2-dimethylchromene as substrates (Scheme 1). Since the latter olefin has been shown to give high enantiomeric excess (ee) with Jacobsen's catalyst [20], 1,2-cyclohexanediamino-*N,N′*-bis(3,5-di-*tert*-butylsalicylidene)Mn(III) chloride (**4**) (Fig. 2), it was envisioned that its use would yield information regarding



Scheme 1.

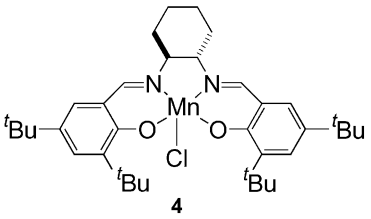


Fig. 2.

the effects of supramolecular complexation on enantioselectivity as well as catalyst stability. Epoxidation reactions were carried out at millimolar concentration of the catalyst in methylene chloride using iodosylbenzene as the oxidant. The epoxide products were quantified by GC and GC–MS using calibration curves that were established with pure standards, and the resulting data is listed in Table 1.

In a typical epoxidation procedure, the olefin (231 mg, 500 equivalents) and octane (22 μl as an internal GC standard) were added to a stirred solution

Table 1
Epoxidation activity of (salen)Mn(III) catalysts[a]

Entry	Catalyst	Additive	TON[b]	ee[c]	Epoxide product
1	**2**	None	51	23	Styrene oxide
2	**2**	1 ZnTPP	92	21	Styrene oxide
3	**2**	2 ZnTPP	133	22	Styrene oxide
4	**2**	3 ZnTPP	150	21	Styrene oxide
5	**2**	2 Zn(2-ethylhexanoate)$_2$	78	19	Styrene oxide
6	**2**	1 ZnOEP	104	21	Styrene oxide
7	**2**	2 ZnOEP	130	21	Styrene oxide
8	**2**	3 ZnOEP	155	22	Styrene oxide
9	**2**[d]	None	48	22	Styrene oxide
10	**2**[d]	2 ZnTPP	128	21	Styrene oxide
11	**2**	None	63	83	Chromene oxide
12	**2**	1 ZnTPP	123	80	Chromene oxide
13	**2**	2 ZnTPP	172	78	Chromene oxide
14	**2**	3 ZnTPP	181	78	Chromene oxide
15	**4**	None	37	19	Styrene oxide
16	**4**	2 ZnTPP	59	18	Styrene oxide
17	**4**	None	47	82	Chromene oxide
18	**4**	2 ZnTPP	76	84	Chromene oxide
19	**2**	None	51		Styrene oxide
		+(2 ZnTPP)[e]	+35		
		+(2 ZnTPP)[e]	+38		
20	**4**	None	37		Styrene oxide
		+(2 ZnTPP)[e]	+23		
		+(2 ZnTPP)[e]	+14		

[a] General experimental conditions: at 25°C, alkene (500 equivalents); catalyst (4.4 μmol, 1 equivalent); CH_2Cl_2 (4.4 ml); PhIO (100 equivalents) added at 0, 30, and 60 min. The reaction was monitored for 3 h.

[b] For consistency, the total turnover number is determined as the total concentration of oxidation products divided by the initial catalyst concentration at $t = 180$ min which is the point where no significant catalyst activity can be observed. In the case of styrene, TON was calculated with the inclusion of phenylacetaldehyde as an oxidation product.

[c] ee were determined by GC (Supelco β-Dex column (30 m × 0.25 mm, 0.25 μm film)).

[d] Styrene oxide (80 equivalents), phenylacetaldehyde (20 equivalents), and styrene (400 equivalents) added as substrate.

[e] ZnTPP (two equivalents) was added at 180 and 210 min. The catalyst was deactivated after less than 5 min.

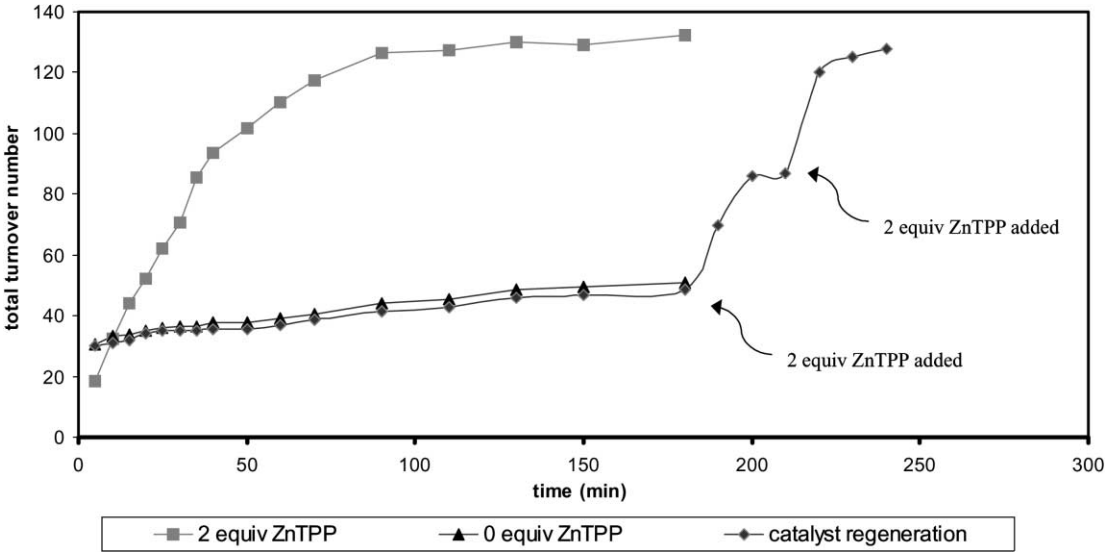


Fig. 3. Plot showing the enhancement of catalyst activity and stability in the epoxidation of styrene with **2** (in terms of TON) and the reactivation of deactivated catalyst by ZnTPP addition.

of **2** (3.0 mg) and ZnTPP (6.0 mg, 2 equivalents) in methylene chloride (4.4 ml). Solid iodosylbenzene (97 mg, 100 equivalents) was added at 0, 30, and 60 min. Samples (20 μl) were taken periodically over 3 h and filtered through a silica plug (60 mg) to remove any residual catalyst. The plug was then washed with methylene chloride (2× 1 ml). The filtrates were combined and analyzed quantitatively by GC.

The addition of ZnTPP to dipyridyl-substituted (salen)Mn catalyst **2** gave rise to a three-fold increase in total catalyst activity (Table 1, entries 1–4 and 11–14) and a significant increase in catalyst lifetime in the asymmetric epoxidation reactions of styrene (Fig. 3) and 2,2-dimethylchromene. A similar trend was observed for both substrates where the total turnover number (TON) increased substantially after the addition of one equivalent of ZnTPP and gave a smaller incremental increase in TON for each subsequent equivalent of ZnTPP added. This behavior is consistent with the formation of supramolecular complex **1** where the proportion of pyridyl groups bound to zinc is influenced by the concentration of ZnTPP in solution as is determined by the binding constant (dyad complexes, no doubt, are also present to varying degrees depending on the ZnTPP concentration). In reactions where ZnTPP was used as an additive, epoxide products with similar ee's to the corresponding control reactions (i.e. without additives) were obtained (Table 1, entries 1–4 and 11–14). In the epoxidation of 2,2-dimethylchromene with **2**, the addition of two equivalents of ZnTPP gave a three-fold enhancement in catalytic activity while the ee was reduced only slightly from 83 to 78%.

As was the case for our Mn dipyridyl porphyrin system [15], control experiments using a mixture of styrene, styrene oxide, and phenylacetaldehyde as the substrate have demonstrated that ZnTPP stabilizes catalyst **2** through a mechanism that is more complex than the exclusion of product inhibition by the LA Zn center (Table 1, entries 9 and 10). Reactions of ZnTPP, or the free base ligand **3** with styrene and iodosylbenzene also gave no epoxidation products, precluding the direct reaction of a Lewis-acid-activated iodosylbenzene complex with the olefin as a significant source of epoxide [25].

We were aware that favorable π-stacking interactions have been observed in the case of salen-capped porphyrins synthesized by intermolecular macrocyclization reactions [26]. Though the bulky *t*-Bu and cyclohexyl groups on **2** make this type of π-stacking interaction unlikely in our system, a series of experiments was carried out with zinc octaethylporphyrin

(ZnOEP) as the additive to rule out this possibility. It was reasoned that if π-stacking were to give rise to enhancement in catalytic activity, ZnOEP with flexible ethyl groups would be able to π-stack more efficiently than ZnTPP, thus, enhancing the catalyst activity to a greater degree. Asymmetric epoxidation reactions carried out with catalyst **2** on styrene showed no difference in stability enhancement in the presence of ZnOEP relative to ZnTPP (Table 1, entries 1–4 and 6–8). The ee's in the epoxidation of styrene with **2** were similar for the pair of additives.

As in the case of our Mn dipyridylporphyrin system [15], the enhancement of the catalytic epoxidation activity of **2** with zinc additives can be attributed to the formation of a supramolecular LA–LB (LB: Lewis base) complex. Similar to this earlier report, the addition of ZnTPP to the pyridine-less Jacobsen's catalyst **4** (Fig. 2) also slightly enhances the epoxidation activity (Table 1, entries 15–18) but not to the extent as that observed for **2**. Attempts to regenerate a deactivated solution of **4** by adding two equivalents of ZnTPP (at $t = 180$ and 210 min) led to only partial recovery of initial activity (Table 1, entry 20), in contrast to the full recovery obtained for **2** (Table 1, entry 19 and Fig. 3). In all cases where porphyrin-based LA were used, the epoxidation kinetics are significantly slower than those observed for the control experiments where no additive was present. That we were able to obtain a 3-fold enhancement in TON in the presence of the Zn porphyrins is largely due to the remarkable enhancement in catalyst stability (over 20-fold longer lifetime in reactive solution environments). For example, in the presence of ZnTPP catalytic activity of complex **2** persists for almost 90 min compared to that in the control experiment where the activity is lost within a couple of minutes (Fig. 3). In contrast to the all-porphyrin system [15], the use of the inexpensive LA Zn(2-ethylhexanoate)$_2$ in our system leads to a more modest enhancement of catalyst stability (Table 1, entry 5), presumably due to the more open and flexible framework of the salen ligand as compared to the close and rigid structure of the porphyrin macrocyle.

Taken together, these observations demonstrate the ability of bulky zinc porphyrin additives to play a role in the spatial isolation of pyridyl-substituted (salen)Mn epoxidation catalysts via supramolecular complex formation. LA–LB supramolecular assembly **1** has been shown to enhance the total turnover number of (salen)Mn catalysts while maintaining the high ee's that are intrinsic to the chiral (salen)Mn complexes. We have successfully combined the advantages of simple LA–LB coordination chemistry with proven chiral ligand frameworks to give enantioselective catalysts that are significantly more stable than conventional non-supramolecular systems. We are currently investigating a second generation of supramolecular catalysts that make use of a more advanced coordination motif that promises: (a) significantly stronger LA–LB association, and (b) catalyst encapsulation in addition to complexation.

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