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A Self-Assembled Molecular Cage for Substrate-Selective Epoxidation Reactions in Aqueous Media

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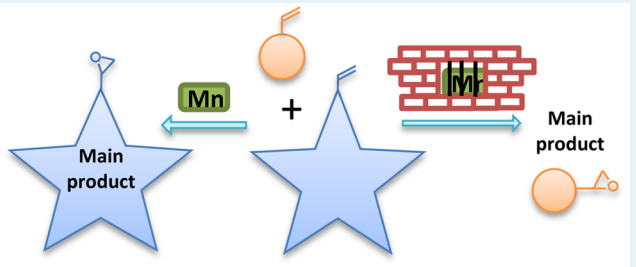
Supporting Information

ABSTRACT: Encapsulation of a manganese porphyrin in a self-assembled molecular cage allows catalytic epoxidation of various substrates in 1:1 water/acetonitrile mixtures. The cage acts as a phase-transfer catalyst and creates a protective environment for the catalyst improving the stability. The encapsulated catalyst also allows discrimination between styrene derivatives of various sizes. In a direct competition experiment, the selectivity of the epoxidation reaction could be inverted with respect to a benchmark catalyst.



KEYWORDS: *manganese, porphyrin, epoxidation, size-selective, supramolecular chemistry*

INTRODUCTION

Metallo-porphyrins are widely applied as synthetic models for Cytochrome P-450 enzymes.[1,2] Over the last decades, many systems have been reported describing both functional and structural analogues of this important class of natural catalysts.[3] The major drawback of most of these mimics is the fast deactivation of the catalyst due to two commonly encountered deactivation pathways.[4] The formation of μ-O-bridged dimers results in a significant decrease in the reaction rate, whereas ligand oxidation can result in complete loss of activity over time.[5] Several elegant approaches have been used to circumvent these problems by tuning of the electronics. For example, halogenated porphyrins suffer much less from deactivation via dimer formation.[6,7] In natural enzymes, such decomposition pathways are prevented by hosting the active site in a protective cavity of the protein matrix.[8] As such, "picket-fence" porphyrins have been developed in a bioinspired approach to protect the catalysts by increasing the steric bulk around the porphyrin ring.[9,10] Most of these systems are, however, not water-soluble or do not provide full cage-encapsulation of the catalyst. In addition, the size of the catalytic pocket is often greatly reduced, resulting in hindered substrate access to the active site.[11] Self-assembled supramolecular architectures have been used to improve the lifetime of the catalyst, thereby increasing the turnover numbers (TONs) of the manganese porphyrin oxidation systems.[12] Recently, encapsulation of catalysts in supramolecular containers have been described, resulting in an improved activity or selectivity compared to the free catalyst.[13−17] Transition-metal-catalyzed transformations with these capsules in aqueous media remains challenging. The use of aqueous media could create a driving force for organic substrate encapsulation and therefore lead to enhanced activity and substrate selectivity. We were therefore interested whether this approach would be viable in the epoxidation of alkenes in aqueous media to yield a more active and selective catalyst.

RESULTS AND DISCUSSION

We previously reported the synthesis and application of a molecular cage in polar reaction media.[18] The large 16+ charged molecular cage was obtained by self-assembly from the corresponding building blocks (Scheme 1, top). The pores of the capsule allow substrates to enter the molecular cage to reach the encapsulated catalyst. By using a similar procedure as previously reported for the encapsulation of cobalt and zinc porphyrins (**2-M**) in cage **1**, we now report the encapsulation of manganese chloride tetrapyridylporphyrin (Mn(TPyP) (Cl), **2-MnCl**) (Scheme 1, bottom). The supramolecular cage **2-MnCl@1** was characterized by ESI-MS (see Supporting Information for mass analysis) and NMR.

The manganese porphyrin **2-MnCl** is paramagnetic, which results in broadening of the ^{1}H NMR cage signals after encapsulation (Figure 1,b). Nevertheless, desymmetrization

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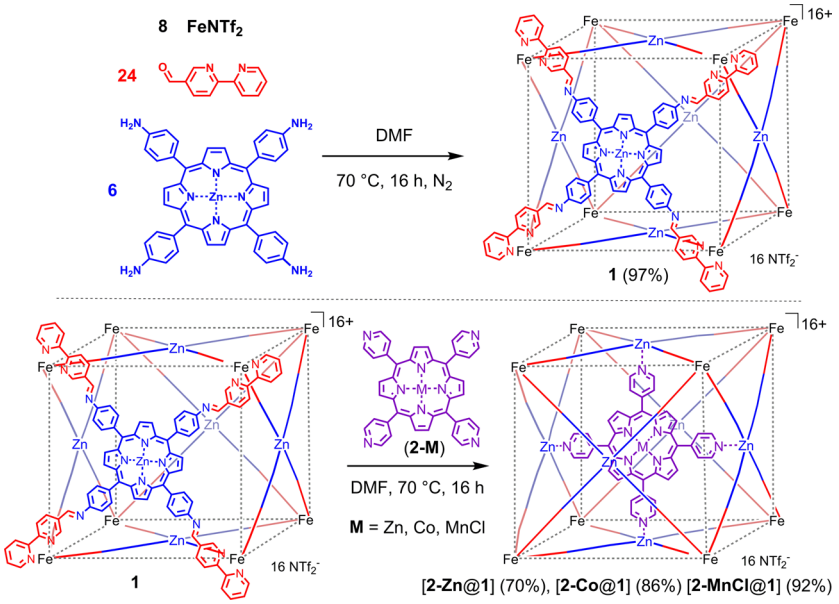
Scheme 1. Synthesis of Molecular Cage 1 (Top) and Encapsulation of 2-MnCl To Form 2-MnCl@1 (Bottom)[18]



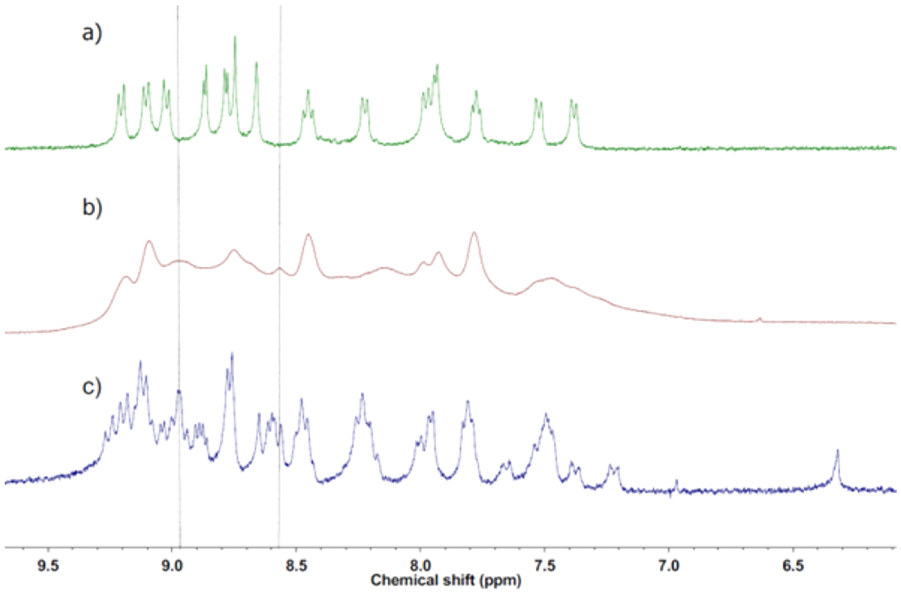
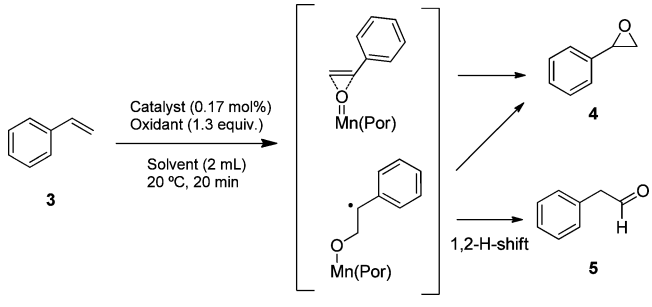


Figure 1. ^{1}H NMR spectra (acetone-d_6) of (a) empty supramolecular cage **1**, (b) encapsulated manganese porphyrin **2-MnCl@1**, and (c) encapsulated zinc porphyrin **2-Zn@1**.

was observed showing several signals which were also observed for the previously reported encapsulated zinc tetrapyridylporphyrin (ZnTPyP, **2-Zn**), as depicted in Figure 1c.[18]

It should be noted that these signals do not correspond to chemical shifts commonly observed for manganese porphyrins, and the signals are therefore ascribed to cage signals, which show reduced symmetry upon encapsulation of the guest. The upfield shifted signal (6.3 ppm) assigned to the zinc porphyrin guest (**2-Zn**) in Figure 1c could not be observed for the manganese porphyrin **2-MnCl@1** in Figure 1b due to its paramagnetic nature. We investigated the catalytic activity of **2-MnCl@1** in the epoxidation of styrene (**3**, Scheme 2). Iodosylbenzene is often employed as the oxidant in manganese-catalyzed epoxidation reactions but is not commercially available and can disproportionate to explosive iodylbenzene ($PhIO_2$) upon heating or prolonged storage.[5]

Scheme 2. Presumed Intermediates/Transition States Explaining Formation of Epoxide Product 4 (Stepwise and Concerted) and Aldehyde Product 5 (1,2-Hydrogen-Shift from the Radical Intermediate).[20]



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Therefore, we decided to use (diacetoxyiodo)benzene, a stable precursor to iodosylbenzene, as the oxidant in our studies.[19]

Initial experiments showed a low activity of the supramolecular catalyst **2-MnCl@1** in acetonitrile after 20 min (Table 1, entry 1). However, the activity was greatly increased by changing the solvent composition to a 1:1 mixture of acetonitrile and water (Table 1, entry 2). It should be noted that such large amounts of water have previously been reported to have a negative effect on the activity of similar catalytic systems.[19] The selectivity also changed to yield the epoxide **4** and aldehyde product **5** in a 2:1 ratio. The more polar solvent employed might facilitate the 1,2-hydrogen shift to yield the aldehyde product. Furthermore, water could be involved directly in facilitating the 1,2-hydrogen shift.

Table 1. Styrene Epoxidation Using Various Catalysts[a]

entry	solvent[b]	catalyst	4 (TON)[c]	5 (TON)[c]	ratio 4:5
1	MeCN	**2-MnCl@1**	11	1	92:8
2	MeCN:H_2O	**2-MnCl@1**	187	86	68:32
3[d]	MeCN	**2-MnCl@1**	98	33	75:25
4[d]	MeCN:H_2O	**2-MnCl@1**	235	99	70:30
5	MeCN:H_2O	MnTPP (**6**)[e]	16	6	71:29
6	MeCN:H_2O	MnTPPS (**7**)	10	2	81:19
7	MeCN:H_2O	**1**	1	2	33:67
8	MeCN:H_2O	**2-MnCl**[e]	99	48	67:33

[a]Reaction conditions: styrene (0.3 mmol), catalyst (0.5 μmol), solvent (2 mL), and iodobenzene diacetate (0.39 mmol) were stirred for 20 min under air. [b]When multiple solvents are listed, a ratio of 1:1 was used. [c]TON = turnover number, determined by ^{1}H NMR with triphenylmethane as external standard. Depicted values are averaged over two runs. [d]Iodosylbenzene was used as the oxidant. [e]The catalyst is poorly soluble in the used solvent system. Yield = TON/TON_{max} × 100% = TON/600 × 100%.

It can be expected that the addition of water to the solvent system allows significantly faster in situ formation of iodosylbenzene from the used precursor leading to a higher active oxidant concentration.[21,22] Indeed the use of iodosylbenzene as the oxidant in acetonitrile yielded a higher turnover number after 20 min for both the epoxide (**4**, TON: 98) and the aldehyde (**5**, TON: 33) using encapsulated porphyrin **2-MnCl@1** (Table 1, entry 3). However, also in this case, the results could be improved significantly by using water in the solvent mixture. A system containing a 1:1 acetonitrile/water mixture and iodosylbenzene as the oxidant resulted in over a 2-fold increase of the turnover numbers (235 and 99, respectively, for **4** and **5**, Table 1, entry 4). The addition of water in the solvent mixture likely results in a larger driving force for apolar substrates to enter the cage cavity and approach the catalytic center.

In order to investigate the effect of the catalyst encapsulation, we also studied manganese catalysts containing tetraphenylporphyrin ([Mn(TPP) (Cl)], **6**, Figure 2, left) and the water-soluble sodium tetrasulfonylporphyrin ([Mn(TPPS) (Cl)], **7**, Figure 2, right) ligands (Table 1, entries 5 and 6, respectively). During the reaction with water-soluble electron-withdrawing porphyrin **7**, the reaction mixture lost most of its typical purple/red color within the first 10 min of reaction. This indicates fast porphyrin ligand oxidation, thus explaining the low TONs obtained for this catalyst. In addition to rapid porphyrin oxidation, the poor solubility of **6** might also contribute to the very low TONs obtained for this benchmark catalyst. As expected, the empty molecular cage **1** showed only negligible activity in the epoxidation of styrene (Table 1, entry 7).

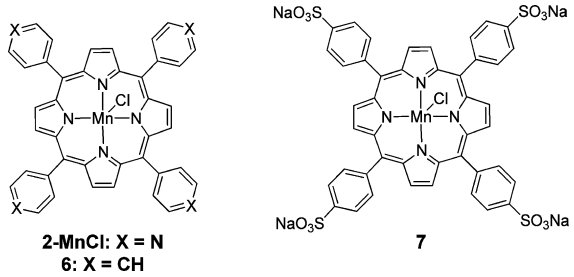

Figure 2. Manganese porphyrins used in this study. Left [Mn(TPP) (Cl)] **6**, and manganese chloride tetrapyridylporphyrin [Mn(TPyP) (Cl)] **2-MnCl**, right [Mn(TPPS) (Cl) 7.

The caged catalyst **2-MnCl@1** is clearly more stable than the nonencapsulated catalysts **6** and **7**. However, while much slower, some degradation of the cage structure does occur under the applied oxidative conditions. After 20 min, the reaction was stopped by extraction of the products. After this reaction time, some degradation of the cage structure 1 was detectable. A purple/red precipitate could be visually observed, and the 2,2′-bipyridine-5-carbaldehyde building block was detected with ^{1}H NMR. We speculate that cage degradation is caused by oxidation of the iron centers on the corners of capsule **1** by the oxidant used. Indeed, after the reaction with empty capsule **1**, some degradation of the cage is observed.

Due to the electron-deficient nature of tetrapyridyl porphyrin **2**, we expected a low activity of the nonencapsulated catalyst **2-MnCl** (Figure 2, left). Surprisingly, when we studied the nonencapsulated catalyst **2-MnCl**, we observed a dramatic increase in the activity compared to both **6** and **7** (Table 1, entry 8) even though the catalyst is poorly soluble in the reaction media. Such an effect was not observed for previously reported cobalt-porphyrin-catalyzed reactions.[18] However, it is important to note that the activity of the caged catalyst **2-MnCl@1** is substantially higher than that of nonencapsulated **2-MnCl**. When we monitored the reaction in time for both caged catalyst **2-MnCl@1** and free catalyst **2-MnCl**, we observed that the cage does indeed stabilize the catalyst, resulting in a higher TON for the epoxide after 20 min (Figure 3).

The increased activity of nonencapsulated **2-MnCl** compared to the free catalysts **6** and **7** is nonetheless interesting and can be ascribed partially to intermolecular pyridine coordination to manganese. It is well-known in the literature that additives such

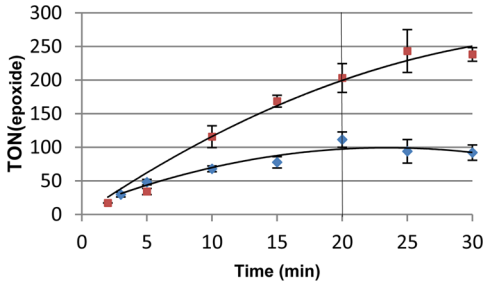

Figure 3. Following the styrene epoxidation reaction in time for caged catalyst **2-MnCl@1** (squares, red) and nonencapsulated catalyst **2-MnCl** (diamonds, blue). Vertical line: Some catalyst decomposition could be observed after 20 min of reaction.

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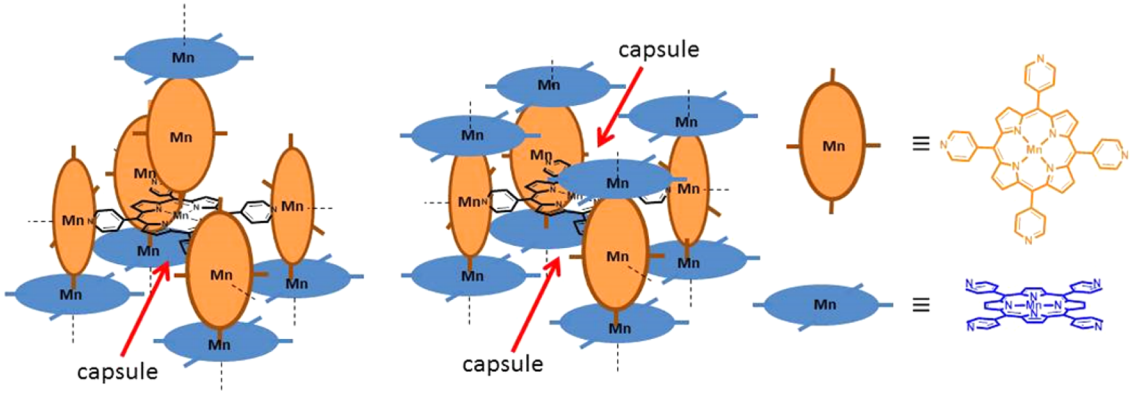


Figure 4. Schematic representations of porphyrin self-aggregation to form protective capsules.[27]

as pyridine[23] or imidazole[24,25] can increase the activity and stability of porphyrin-based epoxidation catalysts.[26] It can be expected that the catalyst **2-MnCl** has a pyridine ligand from an additional porphyrin molecule axially coordinated, thus influencing the electronic structure and thereby the reactivity.

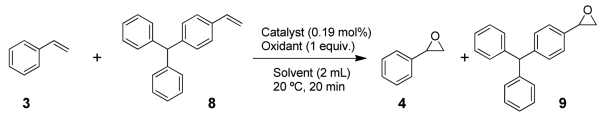
Indeed, when catalyst **6** was studied in the presence of 4 equiv of pyridine, the TONs for products **4** and **5** increased significantly to 33 and 14, respectively, after 20 min of reaction. Furthermore, the self-aggregation of catalyst **2-MnCl** by coordination of pyridine ligands to adjacent porphyrin molecules can be expected to create a protective site around the catalyst to further increase the TONs (Figure 4). This effect could also be achieved by addition of 4 equivalents of zinc tetraphenylporphyrin (ZnTPP) to the catalyst **2-MnCl** to increase the total turnover number (see Supporting Information).

Next to improving the stability of the catalyst **2-MnCl** by encapsulation, we were also interested in whether the selectivity can be influenced by cage **1**. Previously, we reported the competition between substrates of variable size in cyclopropanation to observe a clear preference for the smaller substrates in the presence of the cage **1**.[18] The required entrance of the substrate through the pores of the molecular cage **1** likely slows down the reactivity of larger substrates. As such, we expect that **2-MnCl@1** could be used as a size-selective epoxidation catalyst.

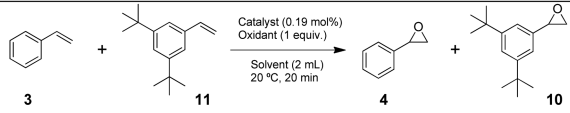
We started our investigation by performing a direct competition experiment (Table 2) between styrene (**3**) and 4-benzhydrylstyrene (**8**) using 300 equiv of each of these substrates with respect to the catalyst.

We initially performed the reaction with control catalyst **6**, which should not differentiate between the two substrates based on their respective size. We observed a ratio between the two products of 41:59 in favor of the more bulky epoxide **9** (Table 2, entry 1). Interestingly, applying our encapsulated catalyst **2-MnCl@1** for the same reaction resulted in a preference toward styrene, yielding the smaller and more bulky epoxide in a 65:35 ratio (Table 2, entry 2, TON = 204).[34] To our surprise, the nonencapsulated catalyst **2-MnCl** was even more selective for the smaller substrate (**4**:**9** ratio = 79:21). It should however be noted that the activity for the **2-MnCl** catalyst is also significantly lower compared to our encapsulated catalyst **2-MnCl@1**. The nonencapsulated catalyst **2-MnCl** most likely self-aggregates by coordination of the pyridine ligands to the manganese core of adjacent porphyrin molecules (Figure 4). This creates a steric confinement around the catalyst, thus explaining the observed size selectivity.[28] This is

Table 2. Competition Experiments for Size-Selective Catalysis[a]



Entry	Catalyst	Ratio product **4**:**9**	TON[b]
1	MnTPP **6**	41:59	65
2	**2-MnCl@1**	65:35	192
3	**2-MnCl**	79:21	61



Entry	Catalyst	Ratio product **4**:**10**	TON[b]
4	MnTPP **6**	40:60	41
5	**2-MnCl@1**	66:34	204
6	**2-MnCl**	77:23	67

[a]Reaction conditions: styrene (0.3 mmol), bulky styrene **8** or **11** (0.3 mmol), catalyst (0.5 μmol), solvent (2 mL), and iodobenzene diacetate (0.3 mmol) were stirred for 20 min under air. [b]TON = combined turnover number toward both expoxides, determined by ^{1}H NMR with triphenylmethane or anisole as external standard. Depicted values are averaged over two experiments.

also in agreement with the observed low TONs toward the bulky epoxides **9** and **10** in isolated experiments (TON = 16 and 14, respectively, see Scheme 3). The in situ-formed assembly likely has an even smaller cavity than the encapsulated catalyst **2-MnCl@1** (see Figure 4). Another possible explanation for the observed lower selectivity of **2-MnCl@1** as compared to **2-MnCl** could be that the binding affinity of cage **1** is higher for the more bulky substrates (due to favorable phenyl-porphyrin interactions or the higher hydrophobic nature) than for styrene. Substrate binding in general is probably stronger in cage **1** than in the partial capsules

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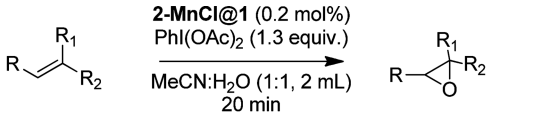
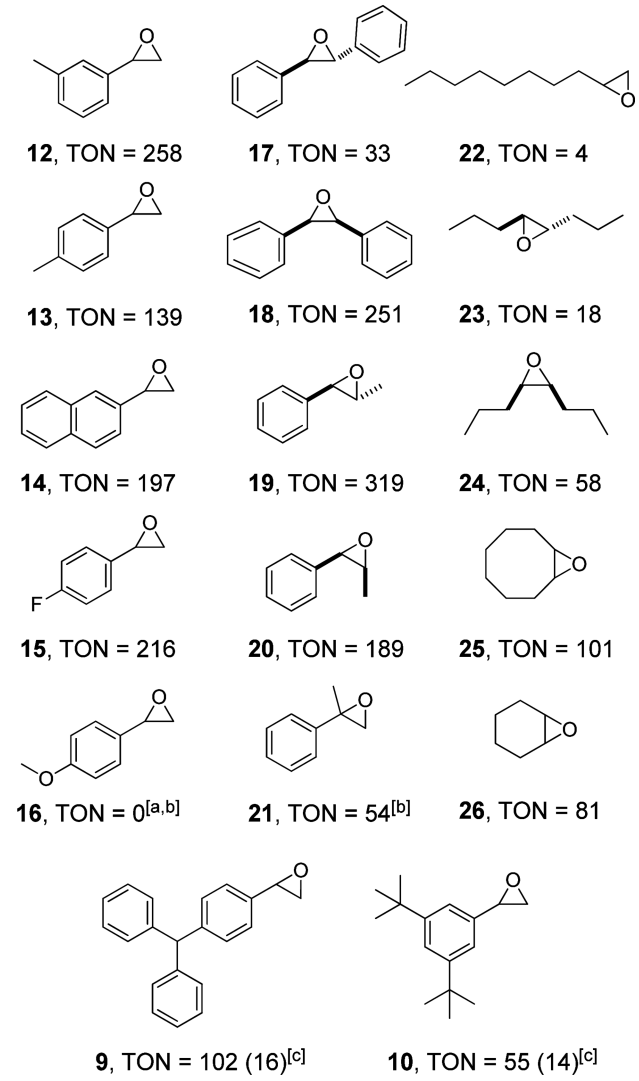
Scheme 3. Epoxides Obtained after Reaction of the Corresponding Alkene under the Optimized Reaction Conditions[a,b,c]





[a]Significant amounts of the corresponding aldehyde product were observed. . [b]Significant amounts of an oxidative cleavage product were observed. [c]**2-MnCl** was used as the catalyst for the TONs in brackets. Note: depicted TONs are toward the epoxide product and averaged over at least two runs.

constructed by self-assembly of **2-MnCl**. Combined, this may well cause an offset in the size-selectivity caused by a slower diffusion rate of bigger substrates (and products) through the pores of cage **1**.[29]

We continued to investigate the direct competition between styrene (**3**) and 3,5-di-*tert*-butylstyrene (**11**). As in the previous case, the control catalyst **6** showed preferred epoxidation of the bulky substrate **11** and a ratio of 40:60 was obtained (Table 2, entry 4). The encapsulated catalyst **2-MnCl@1** clearly favors styrene over the bulky substrate **11** (Table 2, entry 5; obtained ratio = 66:34), but the result is comparable to the previous competition experiment with styrene and **8**. As it appears, the pores of the cage around **2-MnCl** in the assembly **2-MnCl@1** are sufficiently large and flexible enough to allow both substrates to enter (partially) into the cavity, hereby leading to a clear but nonetheless moderate size-selectivity. Lastly, the most selective, though less active, system was once more obtained when **2-MnCl** was used as the catalyst (Table 2, entry 6; ratio = 77:23, TON = 67). This shows once more that the self-assembly of **2-MnCl** leads to smaller cavities around some remaining active manganese catalysts with an increased size-selectivity but lower activity.

To verify whether self-aggregation indeed results in the observed selectivity for the nonencapsulated catalyst **2-MnCl**, we decided to vary the concentration of catalyst **2-MnCl**. As expected, we observed a slight increase in the selectivity when a catalyst concentration of 1 mol % was used (ratio **4**:**10** = 82:18). Even more pronounced was the loss in selectivity when the catalyst concentration was decreased to 0.03 mol % (ratio **4**:**10** = 71:29). This effect of concentration was not observed for the encapsulated catalyst **2-MnCl@1**. A catalyst concentration of 0.03 mol % resulted in a comparable product ratio of 68:32 in favor of styrene oxide **4**. These results confirm that the size-selectivity observed in the competition experiments using the nonencapsulated catalyst **2-MnCl** are indeed caused by self-aggregation.

To obtain further insight into which substrates would still be accessible by the encapsulated catalyst **2-MnCl@1** we decided to screen various substrates in the epoxidation reaction under the optimized conditions. For several alkenes used in this study, the kinetic diameter has been reported.[30] The kinetic diameter varies from 5.5 Å for *cis*-cyclooctene to 7.8 Å for *cis*-stilbene. All substrates and products except for the very bulky substrates 4-benzhydrylstyrene **8** and 3,5-di-*tert*-butylstyrene **11** should therefore easily be able to pass through the pores of cage **1** (see Supporting Information). Hence, significant size-discrimination can only be expected when comparing the bulkiest substrates with smaller substrates.[31] The results from our screening are summarized in Scheme 3. We found that the system is applicable for the epoxidation of various substituted styrene derivatives (Scheme 3, products **12** to **15**). The system appears to be sensitive to small changes in the electronics.

Turnover numbers up to 258 toward the epoxide **12** were obtained, but no epoxide product **16** was formed in the oxidation of 4-methoxystyrene. Next, we examined the sensitivity of our systems toward substitutions on the alkene bond. The general reactivity trends of the various substrates **17** to **21** are in agreement with the activities reported previously for similar systems.[32,33] Remarkably in the reaction of α-methylstyrene **21** large amounts of acetophenone were obtained (2 equiv with respect to the epoxide **21**). Commonly this oxidative cleavage product is only observed after long reaction times in the presence of large amounts of the oxidant.[34] The substrate scope was further expanded to aliphatic alkenes (Scheme 3, products **22** to **26**), but the caged catalyst **2-MnCl@1** shows only poor reactivity in the epoxidation of both 1-decene and *trans*-4-octene (Scheme 3, products **22** and **23**). Only trace amounts of the epoxides were detected (TON = 4 and 18 for products **22** and **23** respectively). The reactivity of **2-MnCl@1** toward a terminal alkene is lower than a comparable internal aliphatic alkene.[35] When we used *cis*-4-octene as a substrate, a significantly higher reactivity toward the corresponding epoxide (Scheme 3, product **24** TON = 58) was obtained. No isomerization

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toward the *trans*-epoxide product was observed in this reaction. Cyclic alkenes can also be used under the applied conditions showing a TON of 101 in the epoxidation of *cis*-cyclooctene (Scheme 3, product **25**). Our system shows a decreased activity for the smaller *cis*-cyclohexene (Scheme 3, product **26**, TON = 81), as commonly found for related systems.[33,36]

As expected from the direct competition experiments, a decreased TON with respect to styrene for both product **9** (TON = 102) and **10** (TON = 50) was observed with our encapsulated catalyst **2-MnCl@1**. Also the nonencapsulated catalyst **2-MnCl** showed a very low activity for products **9** and **10** in isolated experiments (TON = 16 and 14, respectively). In general, the cage around the manganese catalyst seems to tolerate a wide range of differently substituted styrenes. However, apart from the above-mentioned size-selectivity, the pores of cubic cage 1 are likely too big to induce any further shape-selective effects between the substrates smaller than bulky styrene **8** and **11**.

CONCLUSIONS

In conclusion, we have shown that it is possible to encapsulate a manganese porphyrin catalyst in a cubic self-assembled molecular cage. The obtained catalyst is active in aqueous media for the epoxidation of a variety of alkenes to reach up to 319 turnover numbers toward the desired product. The surrounding cage functions as a phase-transfer catalyst and improves the stability of the encapsulated catalyst. Furthermore, the encapsulated catalysts show size-selectivity when mixtures of bulky and less bulky substrates are applied.

EXPERIMENTAL SECTION

General conditions for the epoxidation reactions: Substrate (0.3 mmol) and catalyst (0.5 μmol) were mixed in a 10 mL vial, and solvent was added (2 mL). After addition of the oxidant (0.4 mmol), the mixture was stirred at 600 rpm for 20 min under air. Products were extracted with *n*-pentane (3 × 10 mL), dried over $MgSO_4$, and filtered. Solvents were removed under reduced pressure (40 °C, 500 mbar). Triphenylmethane (60 μmol) was added as a reference, and the products were quantified by ^{1}H NMR spectroscopy ($CDCl_3$ was used as the solvent for analysis).

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acscatal.6b00283.

Rotatable model of the caged catalyst **2-MnCl@1** (PDB)
Synthesis and characterization data for **2-MnCl@1**; detailed conditions and ^{1}H NMR spectra for the performed reactions; an estimation of the pore size of **2-MnCl@1** (PDF)

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Notes

The authors declare no competing financial interest.

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