Controlling radical-type reactivity with transition metals and supramolecular cages

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Chapter 4:

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

Abstract: Encapsulation of a manganese porphyrin in a self-assembled molecular cage allows catalytic epoxidation of various substrates in a 1:1 water/acetonitrile mixture. The cage acts as a phase-transfer catalyst and creates a protective environment for the catalyst improving the stability. Furthermore, the encapsulated catalyst 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.

4.1 Introduction

Metallo-porphyrins are widely applied as synthetic models for Cytochrome P-450 enzymes.\textsuperscript{1,2} Over the last decades many systems have been reported describing both functional and structural analogues of this important class of natural catalysts.\textsuperscript{3} The major drawback of most of these mimics is the fast deactivation of the catalyst due to two commonly encountered deactivation pathways.\textsuperscript{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.\textsuperscript{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.\textsuperscript{6,7} In natural enzymes such decomposition pathways are prevented by hosting the active site in a protective cavity of the protein matrix.\textsuperscript{8} As such, “picket-fence” porphyrins have been developed in a bio-inspired approach to protect the catalysts by increasing the steric bulk around the porphyrin ring.\textsuperscript{9,10} Most of these systems, however, do not provide full cage-encapsulation of the catalyst. In addition, the limited size of the catalytic pocket is often greatly reduced resulting in hindered substrate access to the active site.\textsuperscript{11}

Self-assembled supramolecular architectures have been used to improve the life-time of the catalyst, thereby increasing the turnover numbers (TONs) of the manganese porphyrin oxidation systems.\textsuperscript{12-16} In a more recently described approach, the encapsulation of catalysts in supramolecular containers has been introduced as a concept to reach improved activities and selectivities as compared to the free catalyst. This is an active research field which is attracting substantial attention in the catalysis community (see also Chapter 1).\textsuperscript{17-27} When a porphyrin catalyst is tightly bound inside a supramolecular cage, bimetallic deactivation pathways cannot occur. Furthermore, the substrate still has sufficient space near the active site to react unhindered. Transition metal catalyzed transformations with capsules soluble in aqueous media remains
however challenging. Yet, 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 for the epoxidation of alkenes in aqueous media to yield a more active and selective catalyst. The results of our investigations along this line are described in this chapter.

### 4.2 Results and Discussion

The synthesis and application of molecular cage 1 in polar reaction media was discussed in Chapter 3. 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 reported in Chapter 3 for the encapsulation of cobalt and zinc porphyrins (2-M) in cage 1, we report in this chapter the encapsulation of manganese chloride tetrakis(4-pyridyl)porphyrin ([Mn(TPyP)(Cl)], 2-MnCl) (Scheme 1, bottom).

**Scheme 1:** Synthesis of molecular cage 1 (top) and encapsulation of 2-MnCl to form 2-MnCl@1 (bottom).
The supramolecular cage 2-MnCl@1 was characterized by ESI-MS (Figure 1) and 1H-NMR spectroscopy (Figure 2). The mass spectrum shows a characteristic mass pattern for the supramolecular cage with exactly one equivalent of the manganese porphyrin. Signals are observed for the encapsulated complex after loss of up to 8 triflimide ions to yield signals ranging from 8+ to 14+. In addition a signal for the free manganese porphyrin complex (m/z = 671) was observed under the conditions of the mass spectrometry.

The manganese porphyrin 2-MnCl is paramagnetic which results in broadening of the 1H-NMR cage signals after encapsulation (Figure 2,b). Nevertheless the general pattern was observed which was also observed for the previously reported encapsulated zinc tetrakis(4-pyridyl)-porphyrin ([Zn(TPyP)], 2-Zn), as depicted in Figure 2c.28 The characteristic encapsulation peak for 2-Zn@1 (~6.3 ppm) was not observed in 2-MnCl@1. Most likely the paramagnetic manganese center has most effect on the
directly coordinated tetrakis(4-pyridyl)porphyrin ligand resulting in shifted and broadened signals in $^1$H-NMR.

Figure 2: $^1$H-NMR spectra (acetone-d$_6$) of a) Empty supramolecular cage 1. b) Encapsulated manganese porphyrin 2-MnCl@1. c) Encapsulated zinc porphyrin 2-Zn@1.

We investigated the catalytic activity of 2-MnCl@1 in the epoxidation of styrene (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.$^5$ Therefore we decided to use (diacetoxyiodo)benzene, a stable precursor to iodosylbenzene, as the oxidant in our studies.$^{29}$
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).\textsuperscript{30}

Initial experiments showed that the supramolecular catalyst 2-MnCl@1 produced limited turnovers in acetonitrile within 20 minutes (Table 1, entry 1). However, the conversion 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.\textsuperscript{29} 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.

It can be expected that the addition of water to the solvent system allows significantly faster \textit{in situ} formation of iodosylbenzene from the used precursor leading to a higher concentration of the active oxidant.\textsuperscript{31,32} Indeed the use of iodosylbenzene as the oxidant in acetonitrile yielded a higher turnover number after 20 minutes 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 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.
Table 1: Styrene epoxidation using various catalysts

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<td>2-MnCl</td>
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a) Reaction conditions: Styrene (0.3 mmol), catalyst (0.5 µmol), solvent (2 mL) and iodobenzene diacetate (0.39 mmol) were stirred for 20 minutes under air. (b) When multiple solvents are listed a ratio of 1:1 was used. (c) TON = Turn over number, determined by ¹H-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%.

In order to investigate the effect of the catalyst encapsulation we also studied manganese catalysts containing tetraphenylporphyrin ([Mn(TPP)(Cl)], 6, Figure 3, left) and the water-soluble sodium tetrakis(4-sulfonatophenyl)porphyrin ([Mn(TPPS)(Cl)], 7, Figure 3, right) based catalysts (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 ten minutes of reaction. This indicates fast porphyrin ligand oxidation, thus explaining the low TONs obtained for this catalyst. The poor solubility of 6 might also contribute to the very low TONs obtained for this benchmark catalyst, in addition to rapid porphyrin oxidation. As expected the empty molecular cage 1 shows only negligible activity in the epoxidation of styrene (Table 1, entry 7).
The caged catalyst \textit{2-MnCl@1} is clearly more stable than the non-encapsulated catalysts 6 and 7. However, while much slower, some degradation of the cage structure does occur under the applied oxidative conditions. After 20 minutes 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 spectroscopy. We speculate that cage degradation is caused by oxidation of the iron centers on the corners of capsule 1 by the oxidant used. Indeed also 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 non-encapsulated catalyst \textit{2-MnCl} (Figure 3, left). Surprisingly, however, when we studied the non-encapsulated catalyst \textit{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 the previously described cobalt porphyrin catalyzed reactions (see Chapter 3).\textsuperscript{18} However, it is important to note that the activity of the caged catalyst \textit{2-MnCl@1} is substantially higher than that of non-encapsulated \textit{2-MnCl}. When we monitored the reaction of caged catalyst \textit{2-MnCl@1} in time (Figure 4) we noticed that the conversion of the styrene substrate did not result in the same amount of products formed.
Figure 4: Stacked $^1$H-NMR spectra for the epoxidation of styrene with 2-MnCl@1 over time. a) styrene (3), b) triphenylmethane, c) styrene oxide (4), d) phenylacetaldehyde (5).

Under the applied conditions some styrene oligomerization occurs due to the removal of the stabilizer form the substrate. In addition, the epoxide is not completely stable which results in a decrease of the product yield upon prolonged reaction times (>20 minutes) as observed for the free catalyst 2-MnCl (Figure 5). Nevertheless, the encapsulated catalyst 2-MnCl@1 does indeed result in a higher TON for the epoxide after 20 minutes which, in contrast to 2-MnCl, remains active for over 20 minutes. The increased activity of non-encapsulated 2-MnCl compared to the free catalysts 6 and 7 is nonetheless interesting and can partially be ascribed to intermolecular pyridine coordination to manganese. It is well known in literature that additives such as pyridine$^{33}$ or imidazole$^{34,35}$ can increase the activity and stability of porphyrin based epoxidation catalysts.$^{36}$ 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.
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Figure 5: Following the reaction in time for caged catalyst 2-MnCl@1 (squares, red) and non-encapsulated catalyst 2-MnCl (diamonds, blue). Vertical line: Some catalyst decomposition could be observed after 20 minutes of reaction.

Indeed when catalyst 6 was studied in the presence of 4 equivalents of pyridine the TONs for products 4 and 5 increased significantly to 33 and 14 respectively after 20 minutes 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 6). This effect could also be achieved by addition of 4 equivalents of zinc tetraphenylporphyrin (ZnTPP) to the catalyst 2-MnCl to increase the turnover number to 154 and 108 for the products 4 and 5 respectively (41% and 21% yield respectively). The schematic representation depicted in Figure 6 is just one of the various possible aggregate structures that could be formed by self-assembly of 2-MnCl. Furthermore, in polar media it is unknown whether the axial chloride ligand is still coordinated.
In addition to improving the stability of the catalyst 2-MnCl by encapsulation we were also interested in whether the substrate selectivity can be influenced by cage 1. In Chapter 3 the competition between substrates of variable sizes in cyclopropanation reactions was described. A clear preference for the smaller substrates in presence of the cage 1 was observed. 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 expected that 2-MnCl@1 can 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 equivalents 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, hence slightly 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 for the smaller styrene substrate 3, yielding the smaller and more bulky epoxide in a 65:35 ratio (Table 2, entry 2, TON = 204). To our surprise the non-encapsulated catalyst 2-MnCl was even more selective for the smaller substrate (4:9 ratio = 79:21). The non-encapsulated catalyst 2-MnCl most likely self-aggregates by coordination of the pyridine ligands to the manganese core of adjacent porphyrin molecules (Figure 6). This creates a steric confinement around the catalyst, this explains the observed size selectivity. In addition, this leads to a limited amount of available catalytically active sites. As a result, the activity for the 2-MnCl catalyst is lower compared to our encapsulated catalyst 2-MnCl@1. This is also
in agreement with the observed low TONs in the formation of bulky epoxides 9 and 10 in separated 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 6).

Table 2: Competition experiments for size-selective catalysis

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<td>2-MnCl</td>
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<tr>
<td>6</td>
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<td>77:23</td>
<td>67</td>
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*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 minutes under air. b) TON = combined turnover number towards both epoxides, determined by ¹H-NMR with triphenylmethane or anisole as external standard. Depicted values are averaged over two experiments.*
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 to allow both substrates to enter (partially) into the cavity, leading to moderate size-selectivity. Finally the most selective, although 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 suggests that the self-assembly of 2-MnCl leads to smaller cavities around the 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 non-encapsulated 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 non-encapsulated 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 study various substrates in the epoxidation reaction under the optimized conditions. The results from these experiments 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 for formation of 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 towards 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.38,39
Remarkably in the reaction of α-methylstyrene 21 large amounts of acetophenone were obtained (2 equivalents with respect to the epoxide 21). Usually, this oxidative cleavage product is only observed after long reaction times in presence of large amounts of the oxidant.40

![Scheme 3: Epoxides obtained after reaction of the corresponding alkene under the optimized reaction conditions. Depicted TONs are towards the epoxide product and averaged over at least two runs.]

[Scheme 3

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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 towards a terminal alkene is lower than a comparable internal aliphatic alkene.41 When we used cis-4-octene as a substrate a significantly amount of the corresponding epoxide (Scheme 3, product 24 TON = 58) was observed. No isomerization towards the trans-epoxide product was detected 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.39,42

As expected based on the information gathered by 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 non-encapsulated catalyst 2-MnCl showed a very low activity for the formation of products 9 and 10 in separated experiments (TON = 16 and 14 respectively). For several alkenes used in this study the kinetic diameter has been reported.43 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 be able to easily pass through the pores of cage 1 (Figure 7).

Figure 7: Molecular model (Spartan ’08, MM SYBYL FF) (left) and space filling model (right) with the estimated size of the pores.
Based on the estimated sizes, the substrates 8 and 11 only barely fit through the pores of the cage. Hence, significant size-discrimination can only be expected when comparing the bulkiest substrates with smaller substrates. It cannot be fully excluded that during the catalysis reversible imine hydrolysis or bipyridine dissociation occurs. This would increase the pore-size of the capsule and therefore allow also some bigger molecules to enter and leave the cage cavity. 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.

4.3 Conclusions

In conclusion we have shown that it is possible to stabilize the 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 towards the desired product. Unfortunately the stability of the catalyst is still an issue which needs to be addressed in the future to obtain even higher turnover numbers. Furthermore the encapsulated catalysts could be used as a size-selective epoxidation catalyst for a mixture of bulky and less bulky substrates. Additionally the free 2-MnCl catalyst self-aggregates to form even more size-selective assemblies. Unfortunately less active catalytic centers are accessible leading to a decrease in the activity. Future research could however benefit from the easy self-assembly under the applied conditions.

4.4 Experimental Section

4.4.1 General information

All reactions involving air- or moisture sensitive compounds were carried out under nitrogen using standard Schlenk and vacuum line techniques. Dimethylformamide (DMF) was purchased from Aldrich and was used without further purification prior to use. Acetone-d₆ was purchased from Euriso-Top without purification before use. Deionized water was used without further purification. Styrene, 4-methylstyrene, 3-methylstyrene, α-methylstyrene and cis-β-methylstyrene were filtered over basic alumina prior to use. All other chemicals were purchased from Alfa Aesar, Acros, Fluka and Aldrich without additional purification before use.
$^1$H-NMR and $^{13}$C-NMR spectra were measured on Mercury Varian 300 MHz, Bruker 400 MHz or Bruker 500 MHz spectrometer. $^1$H-NMR chemical shifts are given in ppm, and were calibrated by using the residual non-deuterated solvent as internal reference (CHCl$_3$ (7.26 ppm), Acetone-$d_6$ (2.05 ppm)). $^{13}$C-NMR chemical shifts were recorded in ppm from the solvent peak employed as internal reference (CDCl$_3$ (77.0 ppm)). IR spectra were measured on a Bruker Alpha-P instrument as neat film. UV-vis spectra were measured on a Hewlett Packard 8453. MS measurements were performed on a UHR-ToF Bruker Daltonik (Bremen, Germany) maXis, which was coupled to a Bruker cryospray unit, an ESI-ToF MS capable of resolution of at least 40.000 FWHM. Detection was in positive-ion mode and the source voltage was 5 kV. The flow rates were 500 μL/hour. The drying gas (N$_2$), was held at -35 °C and the spray gas was held at -40 °C. The machine was calibrated prior to every experiment via direct infusion of the Agilent ESI-ToF low concentration tuning mixture, which provided an m/z range of singly charged peaks up to 2700 Da in both ion modes.

4.4.2 Synthesis of described compounds

Compounds 1, 28 2-Zn@1, 28 2-Co@1, 28 2-MnCl, 44 6, 45 7 45 and 28 46 were synthesized as described in literature.

Synthesis of supramolecular host-guest complex 2-MnCl@1.

To a flame dried schlenk flask were added cage 1 (482 mg, 36.1 μmol) and 2-MnCl (25.6 mg, 36.2 μmol). Deoxygenated DMF (10.0 mL) was added under an N$_2$ atmosphere and the resulting solution was degassed three times by freeze-pump-thaw and subsequently heated to 70 °C for 16 h. After cooling the reaction to room temperature, diethylether (100 mL) was added and the precipitate was collected by filtration. The purple residue was washed with diethylether (2 x 50 mL) and collected with acetone (200 mL). Removal of the solvents resulted in a purple powder (467 mg , 33.2 μmol, 92%). Exact mass ESI-MS see: Table 3.
Table 3: Exact mass ESI-MS signals of host-guest complex 2-MnCl@1.

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</table>
**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 minutes under air. Products were extracted with n-pentane (3 x 10 mL), dried over MgSO$_4$ and filtered. Solvents were removed under reduced pressure (40 ºC, 500 mbar). Triphenylmethane (60 µmol) was added as a reference and the products quantified by $^1$H-NMR spectroscopy (CDCl$_3$ was used as the solvent for analysis).

**Monitoring the epoxidation reaction over time**

![Reaction schematic](image)

$\text{2-MnCl@1 (15.0 mg; 1.1 µmol), 3 (63.3 mg; 0.661 mmol), acetonitrile (2.0 mL), water (2.0 mL) and 27 (233 mg; 0.72 mmol; 1.2 equivalents) were handled according to the generalized epoxidation procedure. After 2, 5, 10, 15, 20, 25 and 30 minutes a sample (0.25 mL) was taken from the reaction mixture and added to n-pentane (10 mL). The solution was dried over MgSO$_4$, filtered and solvent removed up to 500 mbar at 40 ºC. triphenylmethane (25 µmol) was added as standard and the reaction mixture was analyzed by $^1$H-NMR (CDCl$_3$). The results from two separate experiments were averaged to give the depicted turnover numbers towards epoxide 4 for both encapsulated 2-MnCl@1 and 2-MnCl (Table 4).}

<table>
<thead>
<tr>
<th>Time</th>
<th>2-MnCl@1 (TON)</th>
<th>2-MnCl (TON)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>17 ± 1</td>
<td>30 ± 3$^a$</td>
</tr>
<tr>
<td>5</td>
<td>34 ± 5</td>
<td>48 ± 4</td>
</tr>
<tr>
<td>10</td>
<td>116 ± 16</td>
<td>64 ± 4</td>
</tr>
<tr>
<td>15</td>
<td>169 ± 9</td>
<td>78 ± 8</td>
</tr>
<tr>
<td>20</td>
<td>203 ± 21</td>
<td>111 ± 11</td>
</tr>
<tr>
<td>25</td>
<td>243 ± 31</td>
<td>94 ± 18</td>
</tr>
<tr>
<td>30</td>
<td>238 ± 10</td>
<td>92 ± 11</td>
</tr>
</tbody>
</table>

$^a$The sample was taken after 3 minutes instead of 2 minutes.
Synthesis of styrene oxide (4) with idosylbenzene (28) as oxidant and catalyst 2-MnCl@1

2-MnCl@1 (6.8 mg; 0.48 µmol), 3 (28.3 mg; 0.27 mmol), acetonitrile (2.0 mL) and 28 (79.7 mg; 0.36 mmol; 1,3 equivalents) were handled according to the generalized epoxidation procedure to give 4 (47 µmol; 17%; TON = 98) and 5 (15.7 µmol; 6%; TON = 33). Repeating the reaction with a 1:1 acetonitrile/water mixture resulted in an increased yield of product 4 (112.8 µmol; 37%; TON = 235) and product 5 (47.6 µmol; 16%; TON = 99).

5. Synthesis of styrene oxide (4) with 2-MnCl and 4 equivalents ZnTPP

2-MnCl (0.5 mg; 0.71 µmol) and zinc tetraphenylporphyrin (ZnTPP; 2.3 mg; 3.4 µmol; 4.8 equivalents) were dissolved in dichloromethane (2.0 mL) and stirred for 15 minutes. Solvent was removed under vacuum and 3 (27.9 mg; 0.27 mmol), acetonitrile (1.0 mL), water (1.0 mL) and 27 (115 mg; 0.36 mmol; 1,3 equivalents) were added. After 20 minutes of reaction products were extracted with pentane (3 x 10 mL). The combined organic fractions were dried over MgSO₄, filtered and solvent removed under reduced pressure (40 ºC, 500 mbar). Triphenylmethane (13.3 mg; 54.5 µmol) was added as a reference. Products were redissolved in CDCl₃ and quantified by ¹H-NMR spectroscopy to give styrene oxide 4 (109.3 µmol; 41%; TON = 154) and phenylacetaldehyde 5 (57.1 µmol; 21%; TON = 108).

Synthesis of styrene oxide (4) with [MnTPP][Cl] (6) and 4 equivalents pyridine

A stock solution of pyridine in water (2.4 mM; 50 mL) was prepared. 6 (0.4 mg; 0.57 µmol), 3 (27.4 mg; 0.26 mmol), acetonitrile (1.0 mL), stock solution (1.0 mL) and 27 (116 mg; 0.36 mmol;
1,4 equivalents) were handled according to the generalized epoxidation procedure to give 4 (16 µmol; 6%; TON = 28) and 5 (5.6 µmol; 2%; TON = 10).

**Competition experiment between Styrene (3) and 4-benzhydrylstyrene (8) with Mn(TPP)Cl (6)**

![Chemical structure](image1)

Mn(TPP)Cl (6, 0.4 mg; 0.57 µmol), 3 (30.3 mg; 0.29 mmol), 8 (80.2 mg; 0.30 mmol), acetonitrile (1.0 mL), water (1.0 mL) and 27 (94.2 mg; 0.29 mmol) were handled according to the generalized epoxidation procedure to give 9 and 4. The ratio between the two products was analyzed by ^1^H-NMR (300 MHz, CDCl3) for the epoxide C-H signals which resulted in a ratio of 1.59:1 (61:39). Anisole was added to the sample (16.6 mg; 0.15 mmol) as external standard to determine the total epoxide yield (36.8 µmol; TTON = 65).

**Competition experiment between Styrene (3) and 4-benzhydrylstyrene (8) with 2-MnCl@1**

![Chemical structure](image2)

2-MnCl@1 (7.3 mg; 0.52 µmol), 3 (27.9 mg; 0.27 mmol), 8 (74.1 mg; 0.27 mmol), acetonitrile (1.0 mL), water (1.0 mL) and 27 (93.2 mg; 0.29 mmol) were handled according to the generalized epoxidation procedure to give 9 and 4. The ratio between the two products was analyzed by ^1^H-NMR (300 MHz, CDCl3) for the epoxide C-H signals which resulted in a ratio of 0.56:1 (36:64). Anisole was added to the sample (8.9 mg; 82.3 µmol) as external standard to determine the total epoxide yield (106 µmol; TTON = 204).

**Competition experiment between Styrene (3) and 4-benzhydrylstyrene (8) with 2-MnCl**

![Chemical structure](image3)
2-MnCl (0.5 mg; 0.71 µmol), 3 (31.8 mg; 0.31 mmol), 8 (80.5 mg; 0.30 mmol), acetonitrile (1.0 mL), water (1.0 mL) and 27 (96.0 mg; 0.30 mmol) were handled according to the generalized epoxidation procedure to give 9 and 4. The ratio between the two products was analyzed by $^1$H-NMR (300 MHz, CDCl$_3$) for the epoxide C-H signals which resulted in a ratio of 0.27:1 (21:79). Anisole was added to the sample (8.6 mg; 80 µmol) as external standard to determine the total epoxide yield (47.7 µmol; TTON = 67).

**Competition experiment between Styrene (3) and 3,4-di-tert-butylstyrene (11) with Mn(TPP)Cl (6)**

![Chemical diagram]

6 (0.4 mg; 0.57 µmol), 3 (31.0 mg; 0.30 mmol), 11 (68.3 mg; 0.32 mmol), acetonitrile (1.0 mL), water (1.0 mL) and 27 (96.2 mg; 0.30 mmol) were handled according to the generalized epoxidation procedure to give 10 and 4. Triphenylmethane was added to the sample (7.3 mg; 30 µmol) as external standard and the ratio between the two products was analyzed by $^1$H-NMR (300 MHz, CDCl$_3$) for the epoxide C-H signals which resulted in a ratio of 1.64:1 (62:38) and total epoxide yield (23.3 µmol; TTON = 41).

**Competition experiment between Styrene (3) and 3,4-di-tert-butylstyrene (11) with 2-MnCl@1**

![Chemical diagram]

2-MnCl@1 (7.0 mg; 0.50 µmol), 3 (28.7 mg; 0.28 mmol), 11 (61.6 mg; 0.28 mmol), acetonitrile (1.0 mL), water (1.0 mL) and 27 (94.6 mg; 0.29 mmol) were handled according to the generalized epoxidation procedure to give 10 and 4. Triphenylmethane was added to the sample (9.8 mg; 40.1 µmol) as external standard and the ratio between the two products was analyzed by $^1$H-NMR (300 MHz, CDCl$_3$) for the epoxide C-H signals which resulted in a ratio of 0.51:1 (66:34) and total epoxide yield (87.8 µmol; TTON = 176).
Competition experiment between Styrene (3) and 3,4-di-tert-butylstyrene (11) with 2-MnCl

![Chemical reaction diagram]

2-MnCl (0.4 mg; 0.57 µmol), 3 (36.2 mg; 0.35 mmol), 11 (67.2 mg; 0.31 mmol), acetonitrile (1.0 mL), water (1.0 mL) and 27 (98.3 mg; 0.31 mmol) were handled according to the generalized epoxidation procedure to give 10 and 4. Triphenylmethane was added to the sample (9.1 mg; 37.2 µmol) as external standard and the ratio between the two products was analyzed by $^1$H-NMR (300 MHz, CDCl$_3$) for the epoxide C-H signals which resulted in a ratio of 0.27:1 (21:79) and total epoxide yield (39.4 µmol; TTON = 69).

Competition experiment between Styrene (3) and 3,4-di-tert-butylstyrene (11) with varying catalyst concentration

![Chemical reaction diagram]

3 (0.3 mmol), 26 (0.3 mmol), catalyst (see Table 5), 27 (0.3 mmol), acetonitrile (1.0 mL) and water (1.0 mL) were handled analogously to the previous competition experiments although the amount of the catalyst was varied. The product ratio was determined from the $^1$H-NMR spectrum. The results are summarized in Table 5.

**Table 5: Catalyst concentration dependence on size-selectivity**

<table>
<thead>
<tr>
<th>Catalyst</th>
<th>Catalyst loading</th>
<th>Ratio 4:24</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-MnCl</td>
<td>0.03 mol%</td>
<td>71:29</td>
</tr>
<tr>
<td>2-MnCl</td>
<td>0.2 mol%</td>
<td>78:22</td>
</tr>
<tr>
<td>2-MnCl</td>
<td>1.0 mol%</td>
<td>82:18</td>
</tr>
<tr>
<td>2-MnCl@I</td>
<td>0.03 mol%</td>
<td>68:32</td>
</tr>
<tr>
<td>2-MnCl@I</td>
<td>0.2 mol%</td>
<td>66:34</td>
</tr>
</tbody>
</table>
Synthesis of 2-(m-tolyl)oxirane (12)

2-MnCl@1 (6.8 mg; 0.48 µmol), 29 (34.4 mg; 0.27 mmol), acetonitrile (1.0 mL), water (1.0 mL) and 27 (108 mg; 0.34 mmol; 1.2 equivalents) were handled according to the generalized epoxidation procedure to give 12 (141 µmol; 48%; TON = 299). Data for epoxide 12 were in agreement with published data.\(^{47}\)

Synthesis of 2-(p-tolyl)oxirane (13)

2-MnCl@1 (7.1 mg; 0.51 µmol), 30 (32.4 mg; 0.27 mmol), acetonitrile (1.0 mL), water (1.0 mL) and 27 (110 mg; 0.34 mmol; 1.3 equivalents) were handled according to the generalized epoxidation procedure to give 13 (78 µmol; 28%; TON = 153). Data for epoxide 13 were in agreement with published data.\(^{48}\)

Synthesis of 2-(naphthalene-2-yl)oxirane (14)

2-MnCl@1 (6.8 mg; 0.48 µmol), 31 (42.1 mg; 0.27 mmol), acetonitrile (1.0 mL), water (1.0 mL) and 27 (116 mg; 0.36 mmol; 1.3 equivalents) were handled according to the generalized epoxidation procedure to give 14 (78 µmol; 29%; TON = 163. Data for epoxide 14 were in agreement with published data.\(^{49}\)
Synthesis of 2-(4-fluorophenyl)oxirane (15)

\[
\begin{array}{c}
\text{F} \\
\text{O} \\
\text{O}
\end{array} + \begin{array}{c}
\text{O} \\
\text{O} \\
\text{O}
\end{array} \rightarrow \begin{array}{c}
\text{F} \\
\text{O} \\
\text{O}
\end{array}
\]

\[2\text{-MnCl}@1 \text{ (0.2 mol\%)}\]

\[\text{H}_2\text{O}/\text{CH}_3\text{CN 1:1} \text{ rt, 20 min}\]

2-MnCl@1 (6.9 mg; 0.49 µmol), 32 (40.5 mg; 0.33 mmol), acetonitrile (1.0 mL), water (1.0 mL) and 27 (124 mg; 0.39 mmol; 1.2 equivalents) were handled according to the generalized epoxidation procedure to give 15 (106 µmol; 32%; TON = 216). Data for epoxide 15 were in agreement with published data.50

Synthesis of 2-(4-methoxyphenyl)acetaldehyde (34) and 4-methoxybenzaldehyde (35)

\[
\begin{array}{c}
\text{O} \\
\text{O} \\
\text{O}
\end{array} + \begin{array}{c}
\text{O} \\
\text{O} \\
\text{O}
\end{array} \rightarrow \begin{array}{c}
\text{O} \\
\text{O}
\end{array} + \begin{array}{c}
\text{O}
\end{array}
\]

\[2\text{-MnCl}@1 \text{ (0.2 mol\%)}\]

\[\text{H}_2\text{O}/\text{CH}_3\text{CN 1:1} \text{ rt, 20 min}\]

2-MnCl@1 (7.0 mg; 0.50 µmol), 33 (43.6 mg; 0.31 mmol), acetonitrile (1.0 mL), water (1.0 mL) and 27 (129 mg; 0.40 mmol; 1.3 equivalents) were handled according to the generalized epoxidation procedure to give 34 (59 µmol; 19%; TON = 118) and 35 (27 µmol; 9%; 53 TON). Data for aldehydes 3451 and 3552 were in agreement with published data.

Synthesis of trans-stilbene oxide (17)

\[
\begin{array}{c}
\text{O} \\
\text{O} \\
\text{O}
\end{array} + \begin{array}{c}
\text{O} \\
\text{O} \\
\text{O}
\end{array} \rightarrow \begin{array}{c}
\text{O} \\
\text{O}
\end{array}
\]

\[2\text{-MnCl}@1 \text{ (0.2 mol\%)}\]

\[\text{H}_2\text{O}/\text{CH}_3\text{CN 1:1} \text{ rt, 20 min}\]

2-MnCl@1 (7.2 mg; 0.52 µmol), 36 (47.8 mg; 0.27 mmol), acetonitrile (1.0 mL), water (1.0 mL) and 27 (110 mg; 0.34 mmol; 1.3 equivalents) were handled according to the generalized epoxidation procedure to give 17 (18 µmol; 7%; TON = 34). Data for epoxide 17 were in agreement with published data.53
Synthesis of *cis*-stilbene oxide (18)

![Chemical Structure](image)

2-MnCl@1 (7.2 mg; 0.51 µmol), 37 (53.4 mg; 0.30 mmol), acetonitrile (1.0 mL), water (1.0 mL) and 27 (122 mg; 0.38 mmol; 1.3 equivalents) were handled according to the generalized epoxidation procedure to give 18 (138 µmol; 47%; TON = 271). Data for epoxide 18 were in agreement with published data.54

Synthesis of *trans*-1-phenyl-1,2-epoxypropane (19)

![Chemical Structure](image)

2-MnCl@1 (6.7 mg; 0.48 µmol), 38 (28.8 mg; 0.24 mmol), acetonitrile (1.0 mL), water (1.0 mL) and 27 (112 mg; 0.35 mmol; 1.4 equivalents) were handled according to the generalized epoxidation procedure to give 19 (163 µmol; 67%; TON = 339). Data for epoxide 19 were in agreement with published data.53

Synthesis of *cis*-1-phenyl-1,2-epoxypropane (20)

![Chemical Structure](image)

2-MnCl@1 (6.9 mg; 0.49 µmol), 39 (34.4 mg; 0.29 mmol), acetonitrile (1.0 mL), water (1.0 mL) and 27 (120 mg; 0.37 mmol; 1.3 equivalents) were handled according to the generalized epoxidation procedure to give 20 (90 µmol; 31%; TON = 184). Data for epoxide 20 were in agreement with published data.55
Synthesis of 2-methyl-2-phenyloxirane (21) and acetophenone (41)

\[
\begin{align*}
\text{2-MnCl@1} \quad & (7.2 \text{ mg; } 0.52 \mu\text{mol}), \quad 40 \quad (33.7 \text{ mg; } 0.29 \text{ mmol}), \quad \text{acetonitrile} \quad (1.0 \text{ mL}), \quad \text{water} \quad (1.0 \text{ mL}) \\
\text{and} \quad & 27 \quad (119 \text{ mg; } 0.037 \text{ mmol; } 1.3 \text{ equivalents}) \\
\text{were handled according to the generalized epoxidation procedure to give} \quad & 21 \quad (30 \mu\text{mol; } 10\%; \text{ TON} = 57) \quad \text{and} \quad 41 \quad (52 \mu\text{mol; } 18\%; \text{ TON} = 101). \text{ Data for epoxide} \quad 21^{54} \quad \text{and acetophenone} \quad 41^{53} \quad \text{were in agreement with published data.}
\end{align*}
\]

Synthesis of 1,2-epoxydecane (22)

\[
\begin{align*}
\text{2-MnCl@1} \quad & (7.0 \text{ mg; } 0.50 \mu\text{mol}), \quad 42 \quad (48.1 \text{ mg; } 0.34 \text{ mmol}), \quad \text{acetonitrile} \quad (1.0 \text{ mL}), \quad \text{water} \quad (1.0 \text{ mL}) \\
\text{and} \quad & 27 \quad (126 \text{ mg; } 0.39 \text{ mmol; } 1.1 \text{ equivalents}) \\
\text{were handled according to the generalized epoxidation procedure to give} \quad & 22 \quad (2 \mu\text{mol; } 1\%; \text{ TON} = 3). \text{ Data for epoxide} \quad 22 \quad \text{were in agreement with published data.}^{53}
\end{align*}
\]

Synthesis of trans-4,5-epoxyoctane (23)

\[
\begin{align*}
\text{2-MnCl@1} \quad & (6.8 \text{ mg; } 0.48 \mu\text{mol}), \quad 43 \quad (30.5 \text{ mg; } 0.27 \text{ mmol}), \quad \text{acetonitrile} \quad (1.0 \text{ mL}), \quad \text{water} \quad (1.0 \text{ mL}) \\
\text{and} \quad & 27 \quad (107 \text{ mg; } 0.33 \text{ mmol; } 1.2 \text{ equivalents}) \\
\text{were handled according to the generalized epoxidation procedure to give} \quad & 23 \quad (9 \mu\text{mol; } 3\%; \text{ TON} = 19). \text{ Data for epoxide} \quad 23 \quad \text{were in agreement with published data.}^{53}
\end{align*}
\]
Synthesis of *cis*-4,5-epoxyoctane (24)

\[
\begin{align*}
\text{2-MnCl@1} & \ (6.7 \text{ mg; } 0.48 \mu\text{mol}), \ 44 \ (26.5 \text{ mg; } 0.24 \text{ mmol}), \ \text{acetonitrile} \ (1.0 \text{ mL}), \ \text{water} \ (1.0 \text{ mL}) \ \text{and} \ 27 \ (113 \text{ mg; } 0.35 \text{ mmol; 1.5 equivalents}) \ \text{were handled according to the generalized epoxidation procedure to give} \ 24 \ (29 \mu\text{mol; 12%; TON = 60}). \ \text{Data for epoxide} \ 24 \ \text{were in agreement with published data.}^{56}
\end{align*}
\]

Synthesis of 2,3-epoxycyclooctane (25)

\[
\begin{align*}
\text{2-MnCl@1} & \ (7.3 \text{ mg; } 0.52 \mu\text{mol}), \ 45 \ (30.7 \text{ mg; } 0.28 \text{ mmol}), \ \text{acetonitrile} \ (1.0 \text{ mL}), \ \text{water} \ (1.0 \text{ mL}) \ \text{and} \ 27 \ (118 \text{ mg; } 0.37 \text{ mmol; 1.3 equivalents}) \ \text{were handled according to the generalized epoxidation procedure to give} \ 25 \ (54 \mu\text{mol; 19%; TON = 103}). \ \text{Data for epoxide} \ 25 \ \text{were in agreement with published data.}^{53}
\end{align*}
\]

Synthesis of 2,3-epoxycyclohexane (26)

\[
\begin{align*}
\text{2-MnCl@1} & \ (7.1 \text{ mg; } 0.51 \mu\text{mol}), \ 46 \ (24.4 \text{ mg; } 0.29 \text{ mmol}), \ \text{acetonitrile} \ (1.0 \text{ mL}), \ \text{water} \ (1.0 \text{ mL}) \ \text{and} \ 27 \ (115 \text{ mg; } 0.36 \text{ mmol; 1.2 equivalents}) \ \text{were handled according to the generalized epoxidation procedure to give} \ 26 \ (44 \mu\text{mol; 15%; TON = 86}). \ \text{Data for epoxide} \ 26 \ \text{were in agreement with published data.}^{56}
\end{align*}
\]
Synthesis of 2-(4-benzhydrylphenyl)oxirane (9)

![Chemical structure](image)

2-MnCl₂ (7.0 mg; 0.50 µmol), 8 (80.2 mg; 0.30 mmol), acetonitrile (1.0 mL), water (1.0 mL) and 27 (118 mg; 0.37 mmol; 1,2 equivalents) were handled according to the generalized epoxidation procedure to give 9 (56 µmol; 19%; TON = 112). Methoxybenzene (14.2 mg; 131 µmol) was used as the standard for ¹H-NMR to avoid overlapping signals of the substrate and product with triphenylmethane.

2-MnCl₂ (0.4 mg; 0.57 µmol), 8 (79.8 mg; 0.30 mmol), acetonitrile (1.0 mL), water (1.0 mL) and 27 (114 mg; 0.35 mmol; 1,2 equivalents) were handled according to the generalized epoxidation procedure to give 9 (6 µmol; 2%; TON = 10). Methoxybenzene (9.3 mg; 86 µmol) was used as the standard for ¹H-NMR to avoid overlapping signals of the substrate and product with triphenylmethane.

Synthesis of 2-(4-benzhydrylphenyl)oxirane (9) with 3-chloroperbenzoic acid (47) as oxidant

![Chemical structure](image)

To a solution of 4-benzhydrylstyrene (8; 135 mg; 0.5 mmol) in dichloromethane (5 mL) was slowly added under continuous stirring 3-chloroperbenzoic acid (47, 129 mg; 70 wt% solution; 0.52 mmol). After 30 minutes additional 3-chloroperbenzoic acid (120 mg; 0.49 mmol) was added. The progress of the reaction was monitored by TLC (SiO₂; hexanes:Ethyl acetate 98:2). Upon full conversion of the substrate the mixture was poured in a saturated aqueous solution of sodium thiosulfate (50 mL) and the products extracted with dichloromethane (20 mL). The organic fraction was separated, washed with saturated aqueous sodium thiosulfate solution (20 mL) and a saturated aqueous solution of sodium bicarbonate (20 mL). The organic fraction was dried over anhydrous magnesium sulfate, filtered and solvents removed under reduced pressure. The crude product was purified by column chromatography (SiO₂) using a gradient from 2% ethylacetate in hexanes to 10% to yield the product 9 as a colorless oil (39 mg; 0.14 mmol; 27%)
\(^{1}\)H-NMR (400 MHz, CDCl\(_3\)): 7.19-7.31 (m, 8H), 7.10-7.12 (m, 6H), 5.55 (s, 1H), 3.84 (dd, J = 4.1 Hz, J = 2.6 Hz, 1H), 3.13 (dd, J = 5.5 Hz, J = 4.1 Hz, 1H), 2.81 (dd, J = 5.5 Hz, J = 2.6 Hz, 1H); \(^{13}\)C-NMR (MHz, CDCl\(_3\)): 144.2, 143.8, 143.8, 135.7, 129.7, 129.5, 128.5, 126.5, 125.7, 56.7, 52.4, 51.3; IR (neat): 3024, 1599, 1494, 1449, 873, 746, 699, 607 cm\(^{-1}\); Exact mass GC-EI: C\(_{21}\)H\(_{18}\)O calculated: 286.1358 found: 286.1353.

**Synthesis of 2-(3,5-di-tert-butylphenyl)oxirane (10) with 2-MnCl@1**

\[ \text{11} + \text{27} \xrightarrow{\text{catalyst (0.2 mol%)}} \text{10} \]

2-MnCl@1 (6.9 mg; 0.49 µmol), 11 (64.8 mg; 0.30 mmol), acetonitrile (1.0 mL), water (1.0 mL) and 27 (117 mg; 0.36 mmol; 1.2 equivalents) were handled according to the generalized epoxidation procedure to give 10 (24 µmol; 8%; TON = 49). Data for epoxide 10 were in agreement with published data.\(^{57}\)

2-MnCl (0.4 mg; 0.57 µmol), 11 (61.3 mg; 0.28 mmol), acetonitrile (1.0 mL), water (1.0 mL) and 27 (114 mg; 0.35 mmol; 1.3 equivalents) were handled according to the generalized epoxidation procedure to give 10 (10 µmol; 3%; TON = 17). Data for epoxide 10 were in agreement with published data.\(^{57}\)

### 4.5 Acknowledgement

Financial support from the Netherlands Organization for Scientific Research (NWO-CW VICI project 016.122.613) is gratefully acknowledged. Maximilian Dürr is thanked for mass analysis of the 2-MnCl@1 assembly.
4.6 References