Controlling radical-type reactivity with transition metals and supramolecular cages

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Future Radical-type Reactivity with transition metals and Supramolecular Assemblies.¹
In this thesis, approaches to gain control over radical-type reactivity are described. Through encapsulation of metallo-radical catalysts in a supramolecular cage the lifetime of the catalysts could be improved. Furthermore, the encapsulated catalysts show size-selective reactions with electronically similar substrates. An important issue still encountered under catalytic conditions is the deactivation of the catalyst over time. Cage decomposition results in loss of the protective environment which subsequently leads to a decreased turnover number (TON). Additionally, the application of the described cages is limited due to their poor solubility in apolar solvents commonly used in radical-type reactions. This leaves room for improvement. It could have been useful to perform the C–H amination reactions as described in Chapter 5 and 6 with the encapsulated catalysts described in Chapter 2 and 3, as this could potentially slow-down unwanted amine or imine formation (see Chapter 5).

For substrates with high bond dissociation energies (BDE)$^2$ we noticed that intermolecular reactions leading to amine and imine formation become competitive under the reaction conditions described in Chapter 5 and 6. As such, these processes could be decelerated by performing the C–H amination reaction in a supramolecular cage. Some attempts to use the caged catalysts described in Chapter 2 and 3 for these reactions were already explored, but failed, most likely due to the use of polar solvents to dissolve the 16+ charged cages. Indeed, attempts to perform these same reactions with [Co(TMP)] or [Co(TPP)] catalysts in polar solvents or solvent mixtures such as acetone, acetone/water, acetonitrile and DMF also resulted in very low conversion of the azide substrate in all cases. Hence, the poor solubility of the cages described in this thesis in apolar solvents leads to solvent incompatibility in using the caged-catalysts for C–H amination. This is unfortunate, as encapsulation of chiral catalysts in a supramolecular cage would also be an interesting approach to obtain higher enantioselectivities. After all, the local chiral environment should be more rigid in the cage, and thus, more efficient chirality transfer can be expected.$^3$

As such, increasing the stability and solubility of the cages described in Chapter 2–4 would be highly desirable. Apart from these obvious challenges, the investigations described in this thesis actually call for several additional experiments in future studies. An outlook towards such future investigations, involving radical-type reactivity with both transition metals and supramolecular cages, is provided here.
Cage instability and decomposition.

After prolonged reaction times of the supramolecular cages described in this thesis, free aldehyde could be observed, indicative of cage decomposition. Furthermore, size-selectivities are moderate, which could be caused by reversible cage-opening and/or (partial) loss of the protective environment over time. To determine whether cage decomposition is responsible for selectivity loss, direct competition experiments should be monitored over time. In the manganese catalyzed oxidation reactions described in Chapter 4 we also observed a decrease in product formation after approximately 30 minutes of reaction. If strong encapsulation was indeed achieved for the manganese porphyrin, bimetallic deactivation pathways should be blocked resulting in much larger TON enhancements than observed in our systems. Therefore, it seems clear that significant cage decomposition occurs under the applied reaction conditions, and this issue should be addressed in future research. The instability of the cage could be caused by either hydrolysis of the imine functionalities and/or oxidation of the iron corners in presence of a strong oxidant. To avoid problems with cage decomposition due to hydrolysis of the imine functionalities in the cage structure, the imine linker could be replaced by other, more stable, linkers in future studies.

Replacing the imine linker by an amine linker

The imine linker could directly be changed to an amine linker by hydrogenation or reduction of the imines in the cage planes. This approach has the advantage that the cage formation step is not changed, which would most likely result in the same geometry of the cage (Figure 1, top pathway). The obtained amine linkers are no longer sensitive towards hydrolysis.

Unfortunately, initial attempts to reduce the imine linkers using sodium borohydride as a reducing agent resulted in zinc demetallation from the cage planes. Additionally, the fluoride signals from the counter ions could no longer be observed in $^{19}$F-NMR. An alternative route (Figure 1, bottom route) involving reductive amination might enable subsequent cage formation from the reduced plane precursor. Zinc could be introduced after reductive amination to circumvent the previously observed demetallation reaction.
Figure 1: Synthetic approaches to replace the imine linker by an amine linker in the cage structure.

The reduced plane precursors are obtained, however, they appear very insoluble in common organic solvents, which resulted in troublesome purification and low-yielding synthesis steps. Functionalization of the building blocks with aliphatic chains or tert-butyl groups will likely solve these solubility issues. In addition to the previously discussed routes to increase the stability of the cage (Figure 1) several alternative building blocks could be constructed to obtain new, potentially more stable cages (Figure 2).
Figure 2: Approaches to replace the imine linker by other linkers in the supramolecular cage.

To obtain a similar size and geometry of the current cage structure, an amide linker could be used to synthesize the cage, which could be prepared from the original zinc tetrakis(4-aminophenyl)porphyrin building block and a bipyridine functionalized carboxylic acid. Other stable connections (depending on the conditions for the catalytic reactions) might be obtained through a C–C linker using a Wittig reaction or a palladium catalyzed cross-coupling reaction (i.e. Heck, Suzuki or Sonogashira coupling). Although the length and the exact geometry differs between the various linkers, initial molecular modelling studies suggest that the corresponding cages should still allow encapsulation of tetrakis(4-pyridyl)porphyrin guests.

Solubility of the supramolecular cage

Apart from increasing the stability of the supramolecular cage, it will also be important to enhance the solubility of the cage in organic solvents for future application in catalysis. In Chapter 2 we described the influence of the counter ion on the solubility of our cages. However, using other metal precursors such as iron(II) tetrafluoroborate or iron(II) sulfate only yielded insoluble material or very broad $^1$H-NMR signals after cage forming conditions. The highly charged nature of the cage results in poor solubility in apolar solvents commonly employed for radical reactions. The overall charge of the cage could be reduced by replacing the bipyridine or iminopyridine ligands for monoanionic ligands. For instance, phenylpyridine complexes of iridium(III) or rhodium(III) would result in the formation of neutral capsules (Figure 3, top middle). Procedures for preparing the *facial* cyclometallated iridium complex selectively have been reported previously.
Also the use of picolinate complexes of iridium(III), cobalt(III) and iron(III) could result in neutral supramolecular cages (Figure 3, top right). To prepare the facial complex selectively might be more challenging in this case, which perhaps requires additional studies.\textsuperscript{12}

\textbf{Figure 3: Approaches to replace the iron bipyridine corners by other corners in the supramolecular cage.}

Alternatively, organic cages of similar size that are soluble in apolar solvents such as toluene or dichloromethane could be prepared, to expand the scope of encapsulated catalysts.\textsuperscript{13,14} Removing the metal from the corners of the supramolecular cage has the additional advantage that oxidation of the corner metal is no longer a decomposition pathway and potential metal catalyzed background reactions can also not occur. The solubility of the cages could further be increased through the introduction of aliphatic side-chains or tert-butyl groups at the linkers and/or corners.\textsuperscript{10} Once these issues of stability and solubility are solved, the obtained supramolecular cages can be used in the reported reactions to achieve more active and selective catalysts. Furthermore the catalytic assemblies could also be tuned further through additives to influence the encapsulated catalysts.
Tuning reactivity inside the supramolecular assembly

The supramolecular cages discussed in this thesis contain six zinc porphyrin planes in the cubic cage structure of which four are used for encapsulation of the pyridyl porphyrins. This leaves two additional zinc centers with an open coordination site available. In future studies this can be exploited to change the environment around the catalytically active site in the supramolecular cage. For example, the addition of functionalized pyridines will place the functionality close to the catalytically active metal center. This could lead to efficient chiral induction using chiral additives inside the supramolecular assembly (Figure 4, left). As such, investigations along these lines in future studies might result in interesting new applications of these supramolecular cages.

![Supramolecular Cage Diagrams](image)

**Figure 4:** Tuning of the encapsulated metal complex by coordination of additives.

Zinc porphyrins generally prefer to obtain a 5-coordinate geometry. Therefore, competition between coordination of the functionalized pyridine inside and outside the supramolecular cage is expected. To circumvent this issue, it might be possible to replace two of the zinc porphyrin planes for tin porphyrins which selectively bind carboxylates. Tin porphyrins are capable of forming 6-coordinate complexes, which would avoid the competition between outside and inside coordination (Figure 4, right).

The most interesting application of this intriguing possibility is probably to induce chiral induction by employing chiral additives in the second coordination sphere of the encapsulated catalyst. This approach provides a new strategy to provide chiral information to the catalyst, and therefore delivers complementary tools to arrive at selective catalysis.
Exploiting self-organization of tetrakis(4-pyridyl)porphyrins

Tetrakis(4-pyridyl) porphyrin (TPyP) complexes of both cobalt (Chapter 2) and manganese (Chapter 4) showed self-assembly behavior. The cobalt complex \([\text{Co(TPyP)}]\) displayed a broad featureless EPR spectrum, which is indicative for axial coordination of pyridines. The complex, however, showed only marginal activity in the cyclopropanation reactions as reported in Chapters 2 and 3. On the contrary, the manganese complex \([\text{Mn(TPyP)Cl}]\) showed a remarkably high activity and even size-selectivity in epoxidation reactions. It would be interesting to further study the structure of these self-assembled structures to understand their catalytic behavior (Figure 5).

Figure 5: Possible self-assembled structures for tetrakis(4-pyridyl)porphyrins.¹⁷

By determining the structure of the assembly it might be possible to increase the amount of accessible catalytic centers.¹⁸ In Figure 5 the central porphyrin is accessible for catalysis however the orange and/or blue ones are only used for protection of the active site. When more complex manganese porphyrins are used it is undesired to only use a fraction of the porphyrins in catalysis. Therefore, replacing the porphyrins labeled in orange with zinc or ruthenium porphyrins (which can form six-coordinate species) could lead to efficient assemblies in which all manganese porphyrins are catalytically accessible. Also the application in other catalytic transformations is interesting to determine why the cobalt assembly is inactive whereas the manganese assembly shows activity and selectivity enhancements.
Further developments for our direct C–H amination protocol

In Chapter 5 and 6 we developed a new direct C–H amination protocol starting from aliphatic azides. Initial optimization studies (Chapter 5) and mechanistic investigation (Chapter 6) revealed that electron donating substituents on the porphyrin resulted in more efficient catalysts for this reaction. Other electron-rich cobalt porphyrins could therefore be evaluated in the reaction (Figure 6).

![Alternative porphyrin and nitrogen-heterocycle complexes for C–H amination.](image)

The electron-donating ability of the ligand could be further tuned by the use of octaethylporphyrin and/or a para-methoxy substituted porphyrin complex (Figure 6, top left and middle respectively). The steric nature around the metal center could further be evaluated by changing the substituents on the ortho substituents on the phenyl groups (Figure 6, top right). In addition, several alternative macrocycles have been reported in literature which could be used to further improve the reported reaction (i.e. phthalocyanines, N-confused porphyrins or subporphyrins) (Figure 6, bottom). More active catalysts, especially at lower temperatures, could lead to more efficient chirality transfer for chiral analogs. Finally, the currently reported chiral catalyst could be improved through evaluation of various chiral groups at the porphyrin (Figure 7).
Various chiral acids are commercially available and could be evaluated in the synthesis of new chiral catalysts for application in enantioselective C–H amination reactions. Alternatively chiral catalysts based on phosphoric acids could be interesting to study due to the additional hydrogen bonding moiety available. The remaining two meso-positions could be used to further control the electronic and steric properties of the obtained catalysts (Figure 7).

Finally the obtained cobalt catalysts could be used in late stage functionalization of pharmaceuticals and to develop more challenging enantioselective intermolecular C–H amination reactions from aliphatic azides. Also the synthesis of C–C bonds through selective direct C–H activation with aliphatic diazo compounds might be accessible. As such, the investigations described in this Thesis call for several follow-up studies, and hopefully form the basis for several breakthrough studies in (enantioselective) catalytic radical-type reactions in the near future.

Figure 7: Chiral catalysts for the chiral C–H amination reaction.
References


