SUMMARY

Confinement Effects in Homogeneous Catalysis using Well-defined Supramolecular Architectures

Nature has been a great source of inspiration for the development of new technologies and the improvement of existing chemical processes. The continuation of this pursue for the efficient use of natural resources and the minimization of waste production is pivotal for sustainable-oriented applications. For these reasons, advances in catalysis are central to the development of efficient chemical processes for the sustainable manufacturing of valuable chemicals. For homogeneous (transition) metal catalysts it is now well-recognized that the use of electronically and/or sterically tuned ligands can lead to enhanced catalytic performance of the corresponding metal complexes (Figure 1, left). Despite significant progress in the field of catalysis, there are still many reactions for which high catalytic efficiency cannot be achieved, and development of new approaches that lead to catalyst improvement are therefore important. In recent years, great efforts have been devoted to the development of supramolecular strategies as complementary approach to control catalytic performance. Within this field, 'caged catalysts' have shown interesting prospects. A catalyst under confinement conditions often imposes reactivity and selectivity not observed in the bulk. Thus far, many self-assembled capsules have been developed as supramolecular catalysts, where catalytic activity and/or selectivity are controlled by the second coordination sphere (Figure 1, right).
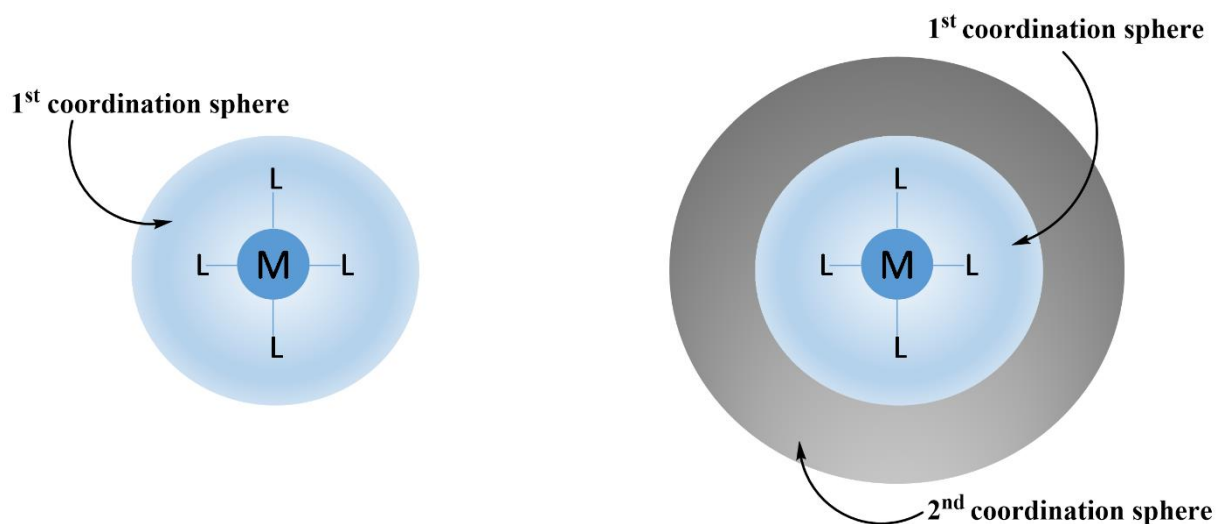

Figure 1. First coordination sphere (left) and second coordination sphere (right) of a catalyst.

Several studies have been reported in which coordination cages with well-defined confined spaces impose so-called second coordination sphere effects around the active metal center, thereby influencing the activity and selectivity of the catalytic reaction. An interesting feature of a reaction taking place in a confined space is the increased proximity of substrate(s) and the catalyst active site, thereby enhancing overall reaction rates by pre-organization. Secondly, selective substrate binding can lead to substrate selectivity and selective conversion of one of the substrates present in a mixture. Thirdly, the pre-organization of a substrate in a higher energy conformation can accelerate the reaction and promote reactivity. Most importantly, the stabilization of a transition state or intermediate can alter reaction mechanisms and lead to reactivity not observed in the bulk. The focus of this thesis is the design and synthesis of new supramolecular caged catalysts that can be used

to study various confinement effects in homogeneous transition metal catalysis. Emphasis is put on the effect of confinement on the catalytic performance in cobalt catalyzed cyclopropanation of alkenes and gold catalyzed cyclization reactions with the aim to demonstrate the importance of second coordination sphere effects in catalysis.

The first part of this thesis describes the investigations concerning the use a covalent cage as host for the encapsulation of cobalt(II)-tetrapyridylporphyrin (chapter 2). The formation of the host-guest complex was studied via two approaches: (1) the encapsulation of the diamagnetic analaogue zinc(II)- tetrapyridylporphyrin in the zincated box and (2) the use of the guest as a template for the formation of the desired supramolecule. We concluded that both the encapsulation and the template approach only lead to the formation of insoluble material. Stepwise formation was also problematic. While in-situ preparation of a 4:1 complex was successful, the next step in the anticipated sequential approach again resulted in undesired formation of an insoluble precipitate. Additionally, we have developed a robust and facile synthetic methodology for the synthesis of one of the building blocks (meso-tetrakis(4-formyl-phenyl)porphyrin) needed for the preparation of a reported covalent cage. This synthetic approach involves the reduction of the easily synthesized *meso*-tetrakis(4-carboxylphenyl)porphyrin followed by Parikh–Doering oxidation affording the desired tetra(formyl) product. This highly valuable building block for supramolecular chemistry was obtained in good yields and high purity without the use of any extensive purification method. Not only the overall yield is improved compared to the already reported methodologies, but also the complexity of the synthetic procedure has been significantly decreased, making this method suitable for gram-scale synthesis. Easy access to this symmetrical square-shaped building block facilitated further chemical investigations for the preparation of desirable caged catalysts.

In chapter 3 we have developed a novel and catalytically active caged-system **Co-G@Fe$_8$(Zn-L·1)$_6$**, soluble in both polar and apolar solvents without the necessity of any post-functionalization. This is a rare example of a large cage able to encapsulate catalytically active porphyrins soluble in several solvents of different polarity. The synthesis is based on the self-assembly of subcomponents **1** and **Zn-L** in which the catalyst acts as a template for the formation of an octahedral iron-iminopyridine coordination complex. Moreover, we demonstrate that DMF has a protective influence on the catalysts, slowing down deactivation of both **[Co(TPP)]** and **Co-G@Fe$_8$(Zn-L·1)$_6$** during radical-cyclopropanation of styrene (Figure 2). DFT studies reveal similar energy barriers for the rate-determining step of this reaction for **[Co(TPP)]** and **[Co(TPP)(L)]**, with DMF acting as an axial ligand **L**, thus showing that the observed higher TONs in DMF are not due to an intrinsic higher activity caused by axial ligand binding. Kinetic studies confirm that initial rates in toluene and DMF are similar, but that catalyst deactivation is faster in toluene than in DMF or toluene:DMF (100:1) mixtures. The combined effects of the solvent and the cage on the activity and stability of the **Co-G@Fe$_8$(Zn-L·1)$_6$** catalyst were investigated. Interestingly, encapsulation of **Co-G** led to a three times more active catalyst than **[Co(TPP)]** (TOF$_{ini}$) and a substantially increased TON compared to both **[Co(TPP)]** and free **Co-G**. The enhanced performance of the catalyst upon encapsulation demonstrates

the effect of the cage. We infer that the increased local concentration of ethyl diazoacetate and styrene in the hydrophobic cage compared to the bulk leads to higher catalytic activities.
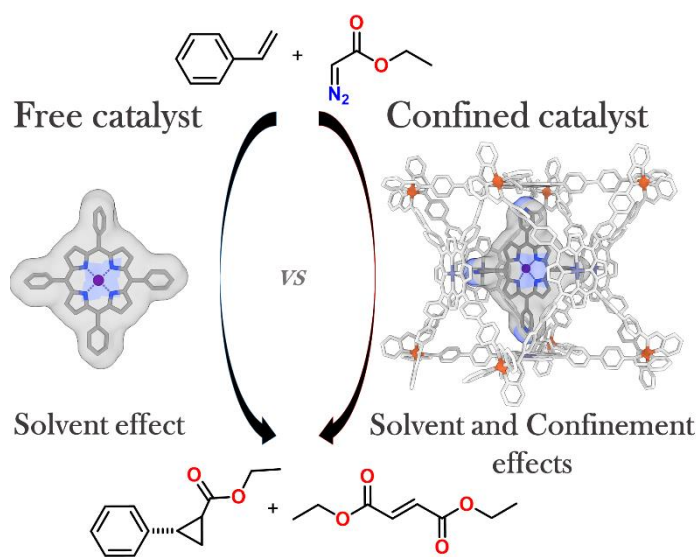

Figure 2. Solvent and confinement effects in radical-cyclopropanation of styrene.

In chapter 4 we describe computational studies of the reaction pathway of the cobalt-catalyzed cyclopropanation of styrene using **[Co(TPP)]**. This was done by DFT methods which reveal that the axial donor ligand does not have a significant influence on the relative free energy barriers. This contrasts with a previous theoretical study involving cyclopropanation of ethene by a Co-aldiminato complex, wherein the energy for the formation of the cobalt carbene complex was reduced upon axial ligand binding. The different outcome of these studies is likely due to the different ligand system and the use of a simplified model system and substrates in the earlier studies reported by Yamada. The computational results are in line with the kinetic experiments that showed no difference in reaction rate (TOF) in the presence of axial ligand binding to the cobalt center **[Co(TPP)(L)]**. The results presented herein clearly show that the experimentally observed improved catalytic performance of **[Co(TPP)]** in cyclopropanation of styrenes with EDA in the presence of DMF stem from a stabilizing effect of DMF. Computational investigations of the effect of axial ligand coordination on deactivation of the catalyst via HAT from toluene, EDA or DMF to the carbene radical intermediate revealed somewhat higher barriers when DMF or other axial donors are coordinated to the cobalt center. This, in combination with the similar barriers of the rate-limiting step of **[Co(TPP)]** and **[Co(TPP)(L)]**, provides theoretical support for our hypothesis (and experimental results; see chapter 3) that the observed improved catalytic performance in DMF or toluene/DMF mixtures compared to pure toluene is a result of slower catalyst deactivation in the presence of axial donors. This was confirmed by additional computational studies, showing that HAT barriers are indeed higher for species containing axial ligand donors.

In chapter 5 we reported the preparation of three novel cubic cages that can bind catalytically active cobalt(II) meso-tetra(4-pyridyl)porphyrin. The cages differ in exo-decoration with polar or apolar tails. By encapsulation of cobalt porphyrins as catalysts, this

strategy provides three supramolecular caged catalyst systems with only different peripheral environments, which effect was probed in catalysis (Figure 3). For the cyclopropanation of styrene with ethyl diazoacetate, we observed an effect of these peripheral groups on the catalytic activity, with the exo-functionalized cage catalyst with apolar icosyl groups providing a higher activity (TOF_{ini}) compared to the free bulk catalyst and cages with no or polar exo-functionalization (**Co-G@Fe$_8$(Zn-L·2)$_6$** and **Co-G@Fe$_8$(Zn-L·3)$_6$**). The catalytic activity of the non exo-functionalized cage catalysts (**Co-G@Fe$_8$(Zn-L·2)$_6$**) was nearly two times lower than that of **Co-G@Fe$_8$(Zn-L·1)$_6$** and three times higher than that of **Co-G@Fe$_8$(Zn-L·3)$_6$**. Remarkably, the peripheral modification of the cage catalysts from polar to apolar increases the catalytic activities in the cyclopropanation reaction and dimerization. We ascribe this effect to different (relative) substrate affinities to the cage that lead to different substrate local concentrations and thus to altered catalytic activities. The affinity of the substrates proved to be the highest when the apolar decorated cage (**Co-G@Fe$_8$(Zn-L·1)$_6$**) is used and the lowest for the polar analog (**Co-G@Fe$_8$(Zn-L·3)$_6$**).
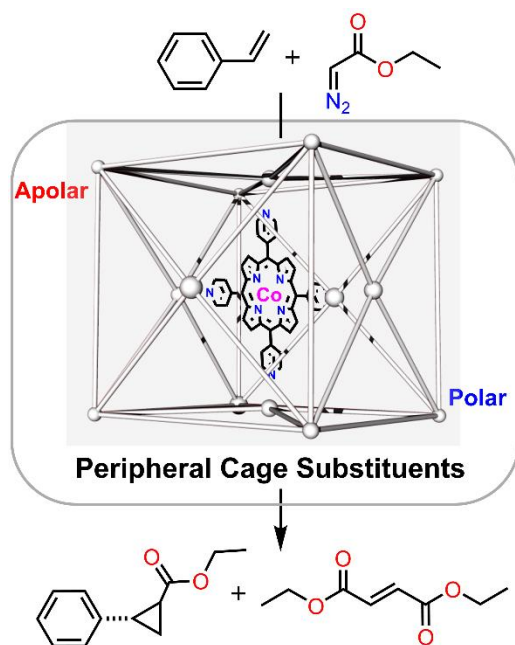

Figure 3. Controlling the activity of a caged cobalt–porphyrin-catalyst in cyclopropanation reactions with peripheral cage substituents

Chapter 6 elaborates on the preparation of two novel tetrahedral cages that differ in size and cavity space. This was done by using two building blocks that differ in size, specifically have different distances between the amines that are used for subcomponent supramolecular assembly of the cages. Post-assembly functionalization led to the selective formation of the corresponding Au^{I}Cl-phosphine cages (**[Fe$_4$(BB·1)$_6$(AuCl)$_{12}$]** and **[Fe$_4$(BB·2)$_6$(AuCl)$_{12}$]**) containing 12 Au atoms per cage. We utilized these newly developed catalyst systems in gold(I)-catalyzed cyclization reactions. This was done by the use of the AuCl-containing cages (**[Fe$_4$(BB·1)$_6$(AuCl)$_{12}$]** and **[Fe$_4$(BB·2)$_6$(AuCl)$_{12}$]**) and the activated analogues (**[Fe$_4$(BB·1)$_6$Au$_{12}$](BF$_4$)$_{12}$** and **[Fe$_4$(BB·2)$_6$Au$_{12}$](BF$_4$)$_{12}$**). Additionally, the catalytic performance of two bulk catalysts (**[((R)-BINAP)Au$_2$](BF$_4$)$_2$** and **[((R)-BB·1)Au$_2$](BF$_4$)$_2$**) was investigated and compared to that of the caged catalysts (Figure 4). Interestingly, **[((R)-**

BB·1)(AuCl)₂] was the most active catalyst before chloride abstraction, while the rest (**[((R)-BINAP)(AuCl)₂]**, **[Fe₄(BB·1)₆(AuCl)₁₂]** and **[Fe₄(BB·2)₆(AuCl)₁₂]**) led only to minor conversions. Compared to the bulk activated catalysts (**[((R)-BINAP)Au₂](BF₄)₂** and **[((R)-BB·1)Au₂](BF₄)₂**), **[Fe₄(BB·2)₆Au₁₂](BF₄)₁₂** results in slightly higher yields and conversion, whereas **[Fe₄(BB·1)₆Au₁₂](BF₄)₁₂** led to the formation of product **P1** in lower yields. While the differences were small in terms of the obtained yields for the formation of **P1**, there was a minor enhancement when the cage with the larger cavity space was used compared to the smaller analogue (Figure 4). Furthermore, we investigated the effect of the cavity space on the selectivity in the gold(I)-catalyzed cyclization of hex-4-ynoic acid. The obtained results of the non-activated catalyst were similar with the lactonization of 4-pentynoic acid. When the chloride was abstracted the difference in terms of selectivity is minor between the smaller (**[Fe₄(BB·1)₆Au₁₂](BF₄)₁₂**) and the larger analogue (**[Fe₄(BB·2)₆Au₁₂](BF₄)₁₂**), although there is an increased preference for the formation of the six-membered ring product when **[Fe₄(BB·2)₆Au₁₂](BF₄)₁₂** was used as the catalyst. The two bulk catalysts performed very similar and the **P2/P3** product selectivity was slightly lower compared to that when **[Fe₄(BB·2)₆Au₁₂](BF₄)₁₂** was used as the catalyst. These results show that chiral molecular cages functionalized with catalysts can be easily synthesized by a post-modification strategy, laying the foundation for further exploration of cage catalysis.
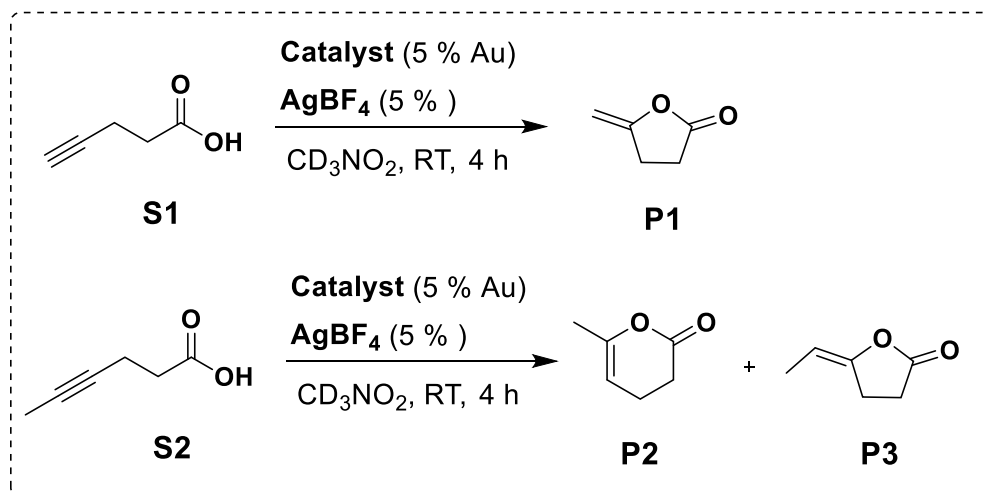

Figure 4. Gold(I)-catalyzed lactonization of 4-pentynoic acid (top) and of hex-4-ynoic acid (bottom).

This research shows the synthesis and catalytic application of several metal-coordination caged catalyst in cobalt-catalyzed cyclopropanation of alkenes and gold-cyclizations. The combined results from the various chapters show that metal-coordination cages offer several advantages compared to purely organic cages as a result of the ease of synthesis and increase dynamicity for the formation of inclusion complexes. Importantly, the confinement of a catalyst around catalytically active cobalt-porphyrin can alter the catalytic performance in the cobalt-catalyzed cyclopropanation of alkenes. The optimization and mechanistic understanding of the cobalt-catalyzed cyclopropanation of alkenes (experimentally and theoretically) by using the bulk catalyst allowed us to directly compared the performance of the caged and bulk catalyst and clearly showed the advantage of performing a reaction in a confined space. Moreover, the effect of high local concentration was demonstrated where higher activities and altered selectivities were obtained when the caged-catalyst was used as

the catalyst compared to the bulk catalyst. In addition, we were able to control the catalytic activity in cobalt-catalyzed cyclopropanation of alkenes by changing the polarity of the peripheral cage substitutents. These results illustrate how the introduction of a second- and third-coordination sphere can influence catalytic performance. The strategy of the third-coordination sphere controlling the catalytic activity can be further expanded to different catalytic systems where selectivity based on polarity of the substrate and/or product can be achieved. Lastly, we utilized two newly developed cage catalyst systems in gold(I)-catalyzed cyclization reactions. We initiated preliminary investigations of the catalytic activity of these cage catalyst systems in gold(I)-catalysis and explored the effect of having different cavity spaces on catalyst performance. While the differences are small in terms of the obtained yields these systems set the stage for gold(I)-catalyzed cyclization reactions by utilizing supramolecular cages as the catalysts.