Transition metal catalysis in confined spaces

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Citation for published version (APA):
Chapter 1:
An Introduction to Transition Metal Catalysis in Confined Spaces*

Abstract:
Transition metal catalysis plays an important role in both industry and in academia where selectivity, activity and stability are crucial parameters to control. Next to changing the structure of the ligand, introducing a confined space as second coordination sphere around a metal catalyst has recently been shown to be a viable method to induce new selectivity and activity in transition metal catalysis. This chapter discusses supramolecular strategies to encapsulate transition metal complexes with the aim of controlling the selectivity via the second coordination sphere. Examples will be shown where catalyst confinement can result in selective processes that are impossible or difficult to achieve by traditional methods.

Chapter 1

1.1 Introduction

Catalysis has grown to play a prominent role in science as it enables the preparation of chemicals and materials in an atom economical and efficient manner. As a consequence, far less waste is produced in catalytic processes compared to reactions that use stoichiometric reagents. In addition, new selective catalytic processes facilitate short-cuts in total synthesis, which again is favorable in terms of efficiencies. These benefits translate in overall more economical processes and as such, catalysis is well-implemented in the bulk and fine chemical industry. Homogeneous transition metal catalysis has been well developed over the past decades and is nowadays applied in both the bulk and fine chemical industry. One of the advantages over heterogeneous catalysts is that the properties of transition metal complexes can be tuned by changing the ligands that are coordinated to the metal. This is especially important for reactions for which it is difficult to achieve (high) selectivities. However, despite substantial progress in the field, there are still many reactions for which the selectivity and activity cannot be controlled to a useful extent. Consequently, new tools that allow to control the selectivity of a reaction are more than welcome. In that perspective, it is interesting to look at enzymes, nature’s catalysts, which typically show a superb selectivity and reactivity. Their mode of function is complex, multiple and far from completely understood. However, by now we have sufficient knowledge on the working mechanisms of enzymes to formulate some general principles that may be translated to synthetic systems. One of the most obvious differences between enzymes and transition metal catalysts is their size. Enzymes are generally 50-100 times larger than metal complexes, and the large protein surrounding the active site often provides a well-defined confined space (second coordination sphere) around the active center. This can be mimicked with bio-inspired supramolecular chemistry. Indeed, the field of supramolecular chemistry has now evolved to such an extent that it becomes an accessible tool for the formation of synthetic ‘caged catalysts’, and encapsulating a metal complex in a supramolecular container within the confined space can impose steric restrictions on the catalyst-bound substrate to mimic the second coordination sphere effects of a protein matrix around the active site of a metallo-enzyme. This can result in reaction pathways that are different from those of the free catalyst, leading to remarkably enhanced selectivities of the caged catalysts compared to their non-encapsulated analogs. So far, research has been mostly focused on the development of new cage-like structures that have an interior that can be utilized for purely cage-catalyzed chemical transformations (i.e. a cage-shaped ‘organic catalyst’ without a catalytically active transition metal included in the cage cavity). A given substrate that is brought into a confined space of this ‘cavity’ experiences a series of ‘confinement effects’, creating a
different environment around the substrate than in the bulk solvent. Often the encapsulated substrate molecule can only adapt certain specific conformations as it has to adjust to the size and shape of the cavity. This also limits its motion, and restricts the number of possible reaction pathways. Usually it also results in a reduced activation entropy of the reaction. The proximity and orientation of the reactive groups can be restricted, which affects the selectivity of a reaction (e.g. formation of low-entropy products, such as ring-compounds). In some cases, the substrate or the reaction intermediate is forced to adopt a high-energy (and low entropy) conformation leading to increased reactivity, which can effectively lower the free-energy reaction barrier, thus accelerating the reaction. Furthermore, the transition state of the effective reaction pathway can be stabilized by attractive interactions between the catalyst and the surrounding cavity, decreasing the overall energy barrier of the reaction. A number of elegant capsular catalysts that display unusual capsule-driven selectivity and/or enhanced activity in catalyzed reactions have been reported. For example, the Diels-Alder reactions within the octahedral coordination capsules, developed by Fujita and co-workers, led to products that are not formed in the bulk, demonstrating the capsule-directed selectivity effect. Raymond and co-workers showed that the rate of the acid-catalyzed hydrolysis reaction of orthoesters is dramatically increased by the microenvironment of the cage, and occurs even in a basic reaction medium, demonstrating the potential of the strategy to enhance rates.

In this chapter we focus on transition metal catalyzed transformations that take place in molecular containers. Similar to purely cage-catalyzed chemical transformations mediated by cage-shaped ‘organic catalysts’, substrate pre-organization is expected to be of crucial relevance for such encapsulated transition metal catalysts. In addition, the confined space can have an effect on certain specific reaction steps that occur at the metal site. In many reactions the transition metal shuttles through various oxidation states, thereby changing their coordination environment and geometry. For example, in a typical palladium catalyzed cross coupling, the metal cycles via square planar Pd(II) and tetrahedral Pd(0). Constraints imposed by the second coordination sphere could lead to (de-)stabilization of either one of these states. In addition, substrate coordination to the metal, as well as the rotational freedom of the substrate could also be controlled by encapsulation, leading to new tools to control the selectivity of a transition metal catalyzed reaction.

First we will show some examples of supramolecular assemblies in section 1.2. This highlights some of the possibilities in terms of making the confined space. Then, in section 1.3 some examples are shown involving a ligand and its metal complex covalently bound to the molecular container. These examples illustrate the benefits of having a capsule surrounding a transition metal catalysts. Section 1.4 discusses the
ligand-template approach, in which a ligand not only coordinates to the active metal center, but is also used as the template to form a cage-shaped second coordination sphere around the metal complex. The advantages of encapsulating metalloporphyrins in catalysis are described in section 5, and examples of the host-guest approach in which a catalyst is confined in a preformed cavity-shaped container are discussed in section 6. Finally a conclusion and an outline with project aims are given.

1.2 Formation of confined spaces through self-assembly

Nanocavities, or confined spaces can be formed through various ways. Covalently attaching different monomeric units to form a confined space is one of the earliest examples to make a confined space. Molecules like crown ethers form a confined space to embed ions. Larger systems like cavitands, cyclodextrins and cucurbit[6]urils have proven to form a void for the encapsulation of guests. Although the confined spaces of these molecules are well defined, catalysis can only be achieved by covalent attachment of the catalytic center (see section 1.3). Another way to form nanocavities is through self-assembly. By using supramolecular chemistry, multiple small building blocks can be used to form a larger structure. The amount of building blocks and the interactions that hold the monomers together can be varied. For example, the group of Rebek, Jr. has reported the assembly of cylindrical capsules (see Figure 1) leading to the formation of so called ‘softball’ structures. These structures are made through the hydrogen bonding of monomers and can accommodate various guests in the so formed cavity.

Figure 1: Two resorcinarene subunits can form a cylindrical capsule through hydrogen bonding.
The multiple weak hydrogen bonds that hold these structures together give them their stability and make them form spontaneously in solution. Both sides of the cylindrical capsule can host a different guest and due to formation of the capsule, pairwise encapsulation can be observed. When choosing the right guests, both guests can be brought together and forced to react with each other. In this way the group of Rebek, Jr. demonstrated that the capsule can facilitate a 1,3-dipolar cycloaddition of an alkyne and an azide.\textsuperscript{12}

The stability of these systems depend on the amount of hydrogen bonds and these bonds are therefore not always the preferred type of interactions to form the assembly. By using metal-ligand interactions, more strong and also directional assemblies can be formed. Depending on the coordination number of the metal that is used, and the type of ligand, different shapes of assemblies can be formed. Different shapes, ranging from tetrahedrons, octahedrons, cubes and polyhedrons can be designed. In these capsules the ligand can function as the strut of the assembly or occupy the vertices. For example, Nitschke \textit{et al.} have demonstrated that four iron centers can be held together by six bis-bidentate ligands\textsuperscript{13} forming an anionic tetrahedral cage (see Figure 2). The formed confined space can be fine-tuned by changing the ligand and can host different hydrophobic guests. These guests are then protected in the cavity. As demonstrated by the group of Nitschke, pyrophoric white phosphorus was prevented from oxidation in the cavity and furan can be protected from undergoing a Diels-Alder reaction.

\textbf{Figure 2:} Tetrahedral shaped cage formed via metal ligand interactions as designed by Nitschke and co-workers. The six bidentate ligands function as struts of the tetrahedron which are held together by four iron centers.

Octahedral and larger polyhedral structures have been shown to be formed when palladium pyridine bonds are used as demonstrated by Fujita and co-workers. When a tris-pyridine building block is used in combination with a \textit{cis}-capped palladium
species an octahedral cage consisting of six metals and four ligands is formed (see Figure 3a).\textsuperscript{14}

**Figure 3:** Octahedral shaped cage held together by pyridine-palladium bonds. The four tris-pyridine ligands occupy the vertices leaving four open windows for guests to enter. On the right some applications of the cage are depicted.

Due to the electron-deficient hydrophobic cavity a large variety of guests can be encapsulated.\textsuperscript{15} While transition metal catalysis has not yet been demonstrated inside the void of this M\textsubscript{6}L\textsubscript{4} capsule, organic transformations like [2+2] cycloadditions,\textsuperscript{16} Diels-Alder\textsuperscript{17} and Knoevenagel reactions\textsuperscript{18} have been shown to be facilitated by this assembly. In these examples the supramolecular assembly bring the components close together and forces the reaction to proceed because of the confined space. It even forces new reactivity due to the steric restrictions of the substrates in a Diels-Alder reaction (Figure 3b).\textsuperscript{17a} Furthermore, metal complexes can be encapsulated inside the octahedral cage. When a binuclear ruthenium complex is captured in the void, it is forced to adapt a cis-conformation of the indene ligands due to the steric restrictions (Figure 3c).\textsuperscript{19} By changing the indene ligands to a smaller tetramethylcyclopentadiene ligand, more free space is available for the binuclear system in the cavity. Fujita *et al.* demonstrated that, when this smaller metal complex is encapsulated, the cage can stabilize an intermediate species in the reaction of the complex with alkynes (Figure 3d).\textsuperscript{20} Furthermore, when a square planar palladium complex was encapsulated in the confined space together with an alkyne, C-H activation of the alkyne was observed (Figure 3e).\textsuperscript{21} Hence, the tight fit inside the capsule demonstrates that stabilization of intermediate species in a confined space is possible.
The group of Fujita furthermore demonstrated that pyridine-palladium interactions can also be used to form larger structures. When employing bent bispyridine building blocks (L) in combination with square planar non-ligated palladium complexes (M), hollow spherical structures are obtained of the formula $M_nL_{2n}$ ($n = 6, 12, 24$). Fujita and co-workers demonstrated that, depending on the bent angle of the pyridine building blocks, different spherical assemblies are formed. In this way, when the angle between the pyridines is smaller than $131^\circ$ a cuboctahedron or $M_{12}L_{24}$ species is formed, as is the case with a furan moiety (see Figure 4). When this bent angle is made bigger, for example by employing a pyrrole ring, a rhombi-cuboctahedron ($M_{24}L_{48}$) is formed as is displayed in Figure 4 on the right.

![Figure 4:](image)

Large spherical cages can be formed by using bis-pyridine ligands with different bent angles. Depending on the angle between the pyridines, either a $M_{12}L_{24}$ or a $M_{24}L_{48}$ species is formed when the pyridine is ligated to square planar palladium(II) species (Figure is partially adapted from reference [22]).

The confined space and structure formed by the building blocks is dependent on the structure of the building block itself. By modification of the building block, also more elaborated structures can be obtained, derived from the $M_{12}L_{24}$. Among the possibilities demonstrated are stellated cuboctahedrons, cantellated tetrahedrons and even a sphere-in-a-sphere. Interestingly, the spheres can also be decorated through functionalization of the building block. Because of the bent angle of the building block, one part of the backbone is pointing towards the inside and one part towards the outside. Through various synthetic routes the backbone can be functionalized to force functional groups point towards the outside of the sphere (exohedral functionalization, Figure 5, top) or the inside (endohedral functionalization, Figure 5, bottom).
Figure 5: Bis-pyridine ligands can form spheres which are either functionalized on the outside or inside, depending on the location of the synthetic modification of the building block. The exohedrally functionalized spheres are visualized on the top while the endohedrally functionalization is shown in the bottom (Figure is partially adapted from reference [22]).

The exohedral functionalization has been used to decorate the outside of the $\text{M}_{12}\text{L}_{24}$ spheres with various functional groups to interact with other molecules. For example, saccharide exohedral functionalized spheres have been shown to interact with proteins. More interestingly, in terms of confined spaces, is the endohedral functionalization of the spheres. The acetylene linked spacer is mostly used forming an endohedrally functionalized nanosphere with a size between 3.5 to 4.6 nm. Through the use of different building blocks, the inside has been shown to host, among others, polyethylene glycol tails, fluor tails to form a fluorous nanodroplet or coronene groups to form an aromatic cavity. The possibility to functionalize the inside gives distinct nanophases in a confined space, therefore allowing the encapsulation of different moieties, depending on the type of phase that is made through assembly. Due to the close proximity of the endohedral functionalized building blocks, the confined space can also be used to form well defined silica nanoparticles by embedding them in a saccharide functionalized sphere. A catalytically active cavity was designed by Reek et al. who embedded 24 gold chloride moieties inside the sphere. As a result of the confined space, a high local concentration of gold was formed inside the nanocapsule. This resulted in activity of the normally inactive gold chloride complex. Thus the spheres were able to cyclize an allenol substrate while the building block itself could not. More properties of the reactivity of this gold functionalized sphere are extensively discussed in chapter 3.
The structures of the systems discussed here are only a small fraction of all reported ones. As this thesis mostly concerns transition metal catalysis in confined spaces, the next sections only discuss capsules or cages which have been shown to be compatible with transition metal catalysis. Supramolecular assemblies are the preferred choice to make the confined space due to their ease of formation. We will also provide a few examples in which the catalyst is covalently attached to a host.

1.3 Metal encapsulation by covalent anchoring

Locating an active metal center in, or close to a molecular cavity can provide benefits in terms of activity and selectivity. First approaches in creating such systems dealt with covalent anchoring of metal complexes to synthetic receptors. The synthesis of such species is generally time-consuming and mostly limited to the molecular cavities that are readily available, such as resorcin[\(n\)]arenes, calix[\(n\)]arenes or cyclodextrins. There are some interesting examples that clearly show how the environment of a catalytic system can discriminate between different pathways occurring within the catalytic cycle. The group of Rebek, Jr. reported an example of a palladium complex attached to a cavitand, which is able to distinguish between different substrates in allylic alkylation (Figure 6). In the presence of a 1:1 mixture of two substrates that differ in size, the catalyst-cavitand system preferably forms one of the two corresponding palladium allyl species, which was proven by mass spectroscopy. This indicates that the capsular catalyst is already selective during the oxidative addition of the substrate, something that is not observed for the non-capsular catalyst studied in control reactions. Upon nucleophilic attack, the conventional palladium catalyst gives rise to a statistical mixture of products whereas the capsular catalyst produces the smallest product with a 9:1 selectivity.
Figure 6: Nucleophilic attack on the Pd-allylic species yielded new substrate selectivity when a cavitand was used to create a second coordination sphere around the catalyst (BSA: N,O-bis(trimethylsilyl)acetamide).

In a similar way, Sollogoub and co-workers nicely showed a gold-carbene catalyst in which the selectivity was controlled by the α- and β-cyclodextrin cavities attached to the catalyst (see Figure 7).\(^\text{32}\) Whereas the smaller α-cyclodextrin gold-carbene catalyst gives a 1:0.65 (1:2) ratio of both five-membered ring products, the bigger β-cyclodextrin analogue yielded the six-membered cyclic product as the major one (1:0:3.3, 1:2:3). Clearly, the selectivity of the reaction is controlled by the second coordination sphere that is surrounding the catalyst.
More recently, Matt and co-workers described the use of monophosphine-rhodium complexes embedded in α- and β-cyclodextrin cavities in the asymmetric hydroformylation of styrene (Figure 8). The cavity-functionalized ligands are bulky, thus enforcing formation of encapsulated complexes that only are coordinated to a single phosphine ligand. The shape and bulk of the ligand prevents coordination of a second phosphine ligand to the rhodium center. Interestingly, both a high regioselectivity (98%) and high enantiomeric excess (ee up to 95%) could be achieved with this capsular catalyst. The enantioselectivity is controlled by the chiral cyclodextrin environment around the rhodium complex. While detailed insight is currently lacking, these examples clearly demonstrate that the covalent attachment of a cavity-shaped host to a metal complex can be effectively used to tune the selectivity of a catalytic reaction.
Figure 8: Monophosphine-rhodium complex confined in a cyclodextrin, applied in the asymmetric hydroformylation of styrene.

As an alternative approach to the above described covalent attachment of cavities and catalysts, self-assembly can commendably be used to construct catalysts embedded in a host, thus providing a well-defined surrounding or second coordination sphere. Examples of such a self-assembly approach for second sphere formation are described in the following sections.

1.4 Ligand-template approach to transition metal complex encapsulation

Reek and co-workers have introduced the ligand-template approach as a new strategy that leads to catalyst encapsulation. In this approach a ligand-template has a dual function: (1) it coordinates to the transition metal that is the active site, and (2) it functions as a template for the assembly of the cage around the active site.$^{6i,34-35}$ The most successful example of a ligand-template is meta-tris-pyridylphosphine (4) that coordinates via its phosphorus atom to the catalytic active metal complex (e.g. $[\text{RhH(CO)}_3]$) and via its pyridine groups to three zinc(II)-porphyrin building blocks (Figure 9). As such, a narrow cavity is obtained via self-assembly, surrounding the catalytically active metal complex and enforcing mono-phosphorus coordination. With this approach in hand, different building blocks were studied to investigate how the size and shape of the generated cavity influences the reactivity and selectivity of the catalyst. If ligand 4 is used in combination with smaller building blocks such as zinc(II)salen, zinc(II)salphen and bis-(thiosemicarbazonato)zinc(II) complexes, the conformational flexibility is too large to enforce exclusive formation of well-defined encapsulated species.$^{34c,e,f}$ Also, if instead of meta-tris-pyridylphosphine ligand (4) the para-analogue is used as the template ligand, the formation of bis-phosphorus coordinated complexes are formed as a result of the open structure of the assembly.$^{34d}$ The second coordination sphere formed via the coordination of zinc-porphyrins (e.g. 5) leads to the proper cavity, allowing fine tuning via the phenyl groups of the porphyrin. The application of zinc-phthalocyanines results in spacious cages,
imposing little restriction on the active site in the cavity. This ligand-template strategy has been mainly exploited in the rhodium-catalyzed hydroformylation reaction of non-substituted alkenes.

![Ligand-template approach for the encapsulation of hydroformylation catalysts. The solid pink arrows indicate the major products obtained with the encapsulated rhodium catalyst 6.](image)

When 6 was employed as a catalyst in the hydroformylation of alkenes, it gave rise to unusual selectivities. For 1-octene the branched aldehyde was the main product formed, which is difficult to obtain with traditional ligands. For internal alkenes the main product formed was the one with the formyl group at the inner carbon atom of the C=C double bond (e.g. in case of 1-octene, 2-octene and 3-octene the major aldehyde formed is the one where the CHO group is located at the C2, C3 and C4 position, respectively; See Figure 9, bottom). Molecular modeling using density functional theory (DFT) together with detailed experimental studies revealed that the selectivity is determined during the hydride migration step (depicted in Figure 10). Some of the pathways are effectively blocked as the transition state for the inserted alkene requires substantial reorganization of the capsule, which has a high energy penalty. Thus the formation of the C3-alkyl species is favored (Figure 10c), leading to a higher selectivity towards the C3-aldehyde.
Figure 10: Energy profiles for the hydride migration step (a) that leads towards the more stable C3-alkylrhodium species (c) vs. the C2-alkylrhodium species (b). Reprinted with permission from reference [36]. Copyright © 2013, Nature Publishing Group.

This example shows that substrate rotation at the active site is controlled by the second coordination sphere and evidences a substrate preorganization feature, which is quite similar to substrate preorganization imposed by the hydrophobic cavity of an enzyme. Interestingly, the X-ray structure of 4•5₃ shows C-H⋯π interactions between adjacent porphyrin building blocks in the assembly, which are disrupted to accommodate the transition state that leads to the minor product. As a consequence, small changes to the porphyrin building block can lead to large changes in selectivity. Importantly, by using zinc-phthalocyanines as building blocks instead of porphyrins, the cavity generated around the rhodium active site is much larger, and this leads to a reversal of the selectivity from C3 to C2 aldehydes (Figure 11). This represents the first example in which the catalyst is the same, and where the selectivity is completely controlled by a synthetic second coordination sphere around it. In addition, the selectivity in the hydroformylation of internal alkenes is extremely difficult to control by traditional ligand design strategies. As such, this supramolecular tool adds new opportunities in transition metal catalysis. It is noteworthy to mention, that the selectivity of the encapsulated hydroformylation catalyst 6 can be maintained at high temperatures (75-80 °C) by changing the syngas ratio from 1:1 (H₂:CO) to 1:2 (high partial CO pressure), which is important when considering industrial applications.³⁷
This strategy can be further applied to other metal-catalyzed transformations. For example, $4\cdot 5$$_3$ was used in the palladium catalyzed Heck reaction, which appeared faster compared to classical triphenylphosphine systems, although this was mainly due to shorter incubation times.$^{34a}$

To extend the ligand-template approach to asymmetric hydroformylation of internal alkenes, Reek and co-workers reported the use of bulky chiral pyridine-based phosphoramidite ligands in combination with zinc(II)-templates for the encapsulation of transition metal catalysts.$^{38}$ These monodentate ligands showed an exceptional supramolecular control of the ligand coordination in a rhodium hydrido complex for hydroformylation. Upon addition of a zinc template, in situ high-pressure NMR and IR studies revealed a change in coordination mode of the ligand from an equatorial to an axial position, trans to the hydride (Figure 12). Application of these supramolecular ligands in asymmetric hydroformylation of challenging internal non-functionalized alkenes proved that this unusual coordination, induced by the supramolecular capsule is reflected in higher activity and enantioselectivity. The non-supramolecular cis-complex gives a poor conversion of 2-octene of only 12% and a moderate enantiomeric excess ($ee\%$) of only 25% of the C3-aldehyde. The supramolecular system, which enforces formation of the trans-complex, has a clearly enhanced performance: a conversion of 56% and $ee\%$ of 45%. The stereoselectivities obtained with this system left room for improvement, and hence it was anticipated that higher selectivities should be attainable when using a more rigid self-assembled system.
This led the authors to design a new chiral, box-shaped catalyst (7, Figure 13), which is based on a similar chiral pyridylphosphoramidite template ligand building block. By employing bis-zinc-salphens platforms, rigid molecular boxes are formed with a specific chiral second coordination sphere around the bis-chelated rhodium catalyst. The fact that the active species is spatially confined in a chiral cavity leads to high regioselectivity towards the formation of the internal aldehydes and results in high enantioselectivities (e.g. enantiomeric ratio up to 93:7 for the C3 aldehyde was obtained from cis-2-octene).

**Figure 12:** Phosphoramidite ligands used in combination with porphyrins to induce enantioselectivity in the hydroformylation of internal alkenes.
Figure 13: A self-assembled chiral rhodium catalyst employed in the asymmetric hydroformylation of internal alkenes.

The ligand template approach has been further extended to functionalized hybrid bidentate ligands, BIAN ligands and to xanthene based phosphorus ligands. It resulted in interesting new ways of controlling the selectivity in gold-catalyzed coupling reactions, palladium catalyzed co-polymerization and in asymmetric hydroformylation, but in these cases the effects were probably more due to changes in the steric properties of the ligand rather than to encapsulation effects. Overall, these examples show that the ligand-template approach is a very powerful strategy that leads to new ways of controlling reactions that are difficult to control otherwise. In the current examples the strategy uses the orthogonal binding properties of the soft phosphine donor and the hard pyridine donor, but many other interactions could be used for this. The next section will discuss different orthogonal approaches for capsule formation around porphyrin based catalysts.
1.5 Confined metalloporphyrins in catalysis

Inspired by enzymes containing metalloporphyrins, such as cytochrome P450, synthetic metalloporphyrins behaving as catalysts for transition metal catalysis have attracted a lot of attention. Metallo-porphyrins are active catalysts for a variety of reactions, and substitutions on the porphyrin backbone can be used for electronic fine-tuning. The incorporation of different metals in the central core makes them suitable for different reactions, for example epoxidation of alkenes. Manganese(III) porphyrin (or salen) catalysts have been thoroughly investigated as epoxidation catalysts, and the active species is believed to be a mononuclear manganese(V)-oxo species. However, the catalytic productivity is hampered due to the formation of $\mu$-oxo-bridged dimeric porphyrin species, leading to a loss of activity. Therefore formation of supramolecular assemblies to prevent dimer formation by site-isolation of a single metallo-porphyrin is an interesting strategy to increase the stability and the turnover number (TON) of the catalyst.

The group of Nolte reported on the confinement of an active and selective manganese catalyst in a cavity by capping a porphyrin scaffold with a glycoluril clip (Figure 14). The resulting cavity with a diameter of 9 Å is able to bind nitrogen-donors in an axial fashion; which induces catalysis at the opposite site, in the binding cavity. This does require the use of a bulky nitrogen donor. When using a small pyridine (py) donor, pyridine binding to manganese actually occurs inside the cavity, so that catalysis occurs at the outside where inactive dimeric species can still be formed during the reaction. However, the bulkier tert-butylpyridine (tbpy) binds from the outside, and hence the vacant site for catalysis is fully isolated and protected towards formation of undesired $\mu$-oxo-bridged manganese(IV)-porphyrin dimeric structures. This feature dramatically increases the catalyst activity and stability when applied in the oxidation of $\alpha$-pinene, cis-stilbene and trans-stilbene. Next to this, a remarkable cavity-induced selectivity towards cis-epoxide was observed for cis-stilbene. This approach was further intensively exploited in the epoxidation of polybutadiene where the catalyst moves along the polymer. Further catalyst development has been explored by introducing urea functionalities at the outside of the cage. In this system the epoxidation takes place in the cavity, regardless which pyridine is added. Consequently, higher activities and selectivities in the cis-epoxidation of polybutadiene were achieved.
Preventing formation of unreactive dimeric manganese(IV)-porphyrin species during the catalysis can also be achieved by encapsulating pyridine-functionalized metalloporphyrins in self-assembled molecular squares, as was reported by Nguyen, Hupp and co-workers (Figure 15). The metallo-supramolecular square 8, constructed from four zinc-porphyrins at the sides and four rhenium complexes at the corners, is able to bind the manganese(III)-porphyrin 8 with a high association constant (ca. $10^6$ M$^{-1}$). Encapsulated catalyst 8•10 was used in the epoxidation of styrene showing a tenfold increase in stability (turnover number) extending its lifetime from ten minutes to more than three hours. Such numbers can be even surpassed if the metallo-supramolecular square is used to bind the tetra-pyridine-manganese(III)-porphyrin 9, which displays an even higher binding constant (ca. $10^7$ M$^{-1}$). It was noticed that upon dilution of the manganese catalyst (which should further inhibit bimolecular degradation pathways), TON values up to 7000 and 21000 for 8•10 and 8•9, respectively, were reached.
The environment around the catalyst inside the cavity could be further confined by pairwise embedding chiral pyridylester 11 in the metallo-supramolecular square 8 as depicted in Figure 16. The binding of these guests restricts the cavity size and influences the substrate selectivity in the catalytic epoxidation of olefins. In this manner, 8•10•11₂ reacts with the smaller substrate, cis-stilbene (12) seven times faster compared to the larger substrate 13 and four times faster than 14. Unfortunately, no enantioselectivity was observed due to free rotation of the zinc panels, indicating that the additional guests in the cavity do not influence the transition states of the catalyst. It, however, does impose a stabilizing factor on the catalyst. This demonstrates that different reactivity for different substrate sizes can be imposed on the catalyst due to a restriction of space.

**Figure 15:** Metallo-supramolecular square 8 as designed by Hupp et al. (top). Through pyridine-zinc interactions, 9 and 10 are embedded in the square (bottom).
The same groups demonstrated the control of substrate- and enantio-selectivity via the utilization of a rigid, metallo-supramolecular box composed of twelve zinc-porphyrins, held together by four tin-porphyrins. In this assembly two catalytically active manganese-porphyrins were embedded. The self-assembled molecular box could be formed by stepwise addition of the components or by mixing all building blocks in one pot. The axial ligands of the tin porphyrin building blocks give the ability to fine-tune the second coordination sphere around the manganese catalyst in the cavity. Catalyst encapsulation proved to invoke substrate selectivity and cis-stilbene (12) was shown to be converted to its corresponding epoxide more than five times faster than the sterically larger tetra(tert-butyl)stilbene 13 (Figure 17). In this case the porphyrin planes cannot freely rotate anymore, (in contrast to metallo-supramolecular square 8) and the tin-porphyrins can bear chiral ligands. These features enabled enantioselective transformations with this system demonstrated by the oxidation of thioether 15. This yielded the corresponding sulfoxide with an enantiomeric excess of 12%. Despite the poor enantioselectivity, which is probably due to the small size of the axial chiral ligand on the tin-porphyrin, these results prove that chirality transfer via a second coordination sphere is feasible. Furthermore, this enantiomeric excess was only observed when the catalyst was embedded in the self-assembled supramolecular box and could be reversed by changing the chirality of the ligand attached to the tin-porphyrin that is located in the box. Although no detailed mechanistic studies for these systems have been reported, in the commonly accepted olefin epoxidation mechanism the selectivity is believed to
be determined by the approach of the alkene to the active manganese(-salen) catalyst.\textsuperscript{47} It is therefore likely that such approach is controlled to some extent by cage effect imposed by these supramolecular systems, which explains the selectivity observed.

![Figure 17](image)

**Figure 17:** Multi-component assembly based on various porphyrin blocks. Chiral ligands attached to the tin porphyrin (depicted in green), lead to chiral induction in the oxidation of sulfide 15.

Bimetallic deactivation pathways are also very common in radical-type transition metal catalysis, and therefore site isolation of such catalysts may lead to enhanced lifetimes. For example, cyclopropanation reactions mediated by cobalt(II) catalysts proceed via carbene-radical species, stabilized on a cobalt(II)-porphyrin scaffold, which reacts with alkenes to form the product. However, depending on the nature of the substrate that is used, the radical can become delocalized. As a result of having discrete spin density at a more remote carbon atom, partial loss of the ‘steric’ control of the catalysts over the substrate radical can lead to undesired radical-radical
coupling leading to C-C bond formation, thus leading to catalyst deactivation (Figure 18).48,49

![Figure 18: Dimerization pathway that leads to an inactive intermediate during the metalloradical-mediated catalysis.](image)

To prevent such dimerization to occur, supramolecular encapsulation of a cobalt-porphyrin catalyst was studied by de Bruin and co-workers. Inspired by Nitschke’s cubes, formed by a self-assembly process of six zinc-porphyrins held together by eight iron complexes at the corners,50 de Bruin and co-workers managed to prepare a larger analogue by using bigger zinc-porphyrin scaffolds. This resulted in a molecular flask (16) that is able to encapsulate a single catalytically active tetra-pyridyl-cobalt(II)-porphyrin 17 (16•17, Figure 19).51 Interestingly, metallo-radical-trapping experiments performed with an encapsulated Co(II)-porphyrin catalyst and EDA (18, EDA = ethyl diazoacetate; one of the reagents in cyclopropanation catalysis) in the presence of 1,4-cyclohexadiene (19, a hydrogen-atom-transfer reagent) indicate that EDA indeed reacts within the self-assembled cube leading to 16•20. Thus, molecular flask 16•17 represents an improved catalyst that prevents unreactive dimerization pathways by site-isolation and as such displays longer life times compared to the non-encapsulated version.
Indeed, in the cobalt-catalyzed cyclopropanation of styrene with diazo compounds (Figure 15) the encapsulated cobalt(II)-porphyrin catalyst 16•17 is active even after four hours and reaches comparable activity to the best cobalt(II)-porphyrin used for such transformations to date (Zhang’s catalyst), whereas the non-encapsulated catalysts showed only short life times (conversions stopped after one hour). In addition, the trans-cis selectivity for such transformation is different when performed inside the cage: 63:37 (16•17) vs. 75:25 (17). The encapsulated catalyst was also studied in the intramolecular reaction of 21 giving rise to a mixture of isomers 22-E and 22-Z. For this reaction 16•17 produces the highest yields of all available non-encapsulated Co(II)-porphyrin catalysts, and encapsulation also resulted in altered regioselectivity. For example, when using conventional cobalt(II)-tetraphenylporphyrin as catalyst the E:Z ratio is close to 40:60 whereas upon catalyst encapsulation there is an improved preference for the Z isomer (E:Z ratio of 16:84).

Figure 19: Cobalt encapsulated catalyst 16-17 (top) and radical-trapping experiments. The cage prevents binuclear radical-type deactivation processes (bottom).
By changing the anion of the molecular container from triflate (OTf) to triflimide (NTf₂), the system could be dissolved in water/acetone (5:1) mixtures. In this reaction medium TON values of more than 300 for the cyclopropanation of styrene with EDA were obtained with the confined catalyst, which outperformed non-encapsulated cobalt(II)-porphyrins. The supramolecular encapsulated catalyst was compatible with different alkenes, giving high yields for styrene analogues with electron-donating or electron-withdrawing substituents. Limited reactivity was observed with methacrylates, bulky alkenes and bulky diazo substrates. The restricted space inside the molecular container was further exploited by studying size-selective transformations via competitive experiments. In these experiments, styrene and a bulky alkene were competing for the reaction with a diazo-reagent (Figure 21). Interestingly, the encapsulated cobalt(II)-porphyrin catalyst 16•17 preferentially cyclopropanates the smaller styrene substrate, whereas non-encapsulated catalysts give an equal distribution of the small and large products. This shows that the second coordination sphere gives rise to size selectivity, which is difficult to achieve by modifications to the first coordination sphere around a catalyst. Although this confinement around the catalytic center shows substrate selectivity, the current system cannot control the cis/trans selectivity. The two zinc porphyrin building blocks still available for coordination of axial ligands, may provide a supramolecular handle to further confine the catalyst such that it becomes even more selective.
1.6 Catalytically active host-guest complexes

In the examples shown in the previous section the catalyst was incorporated in capsules and containers by self-assembly, leading to well-defined systems in which the orientation of the catalyst is fixed by specific metal-ligand coordination bonds between the catalyst and the cage. An alternative approach is the preparation of a preformed self-assembled host in which the catalyst can be bound as a guest, using weak interactions such as π-π stacking, hydrogen bonding, ionic and dipolar interactions, the ‘hydrophobic effect’, and entropic binding based on the replacement of multiple solvent molecules by a single guest in the cavity (i.e. the catalyst). It is of course of key importance that the catalyst remains bound inside the molecular container during catalysis. Furthermore, the system should be capable to co-encapsulate the catalyst and the substrate(s). Self-assembled supramolecular flasks formed in aqueous media are a particular promising class of systems enabling encapsulation of different chemical entities due to a combination of hydrophobic and ionic effects. In recent years, many water-soluble supramolecular flasks have been reported, but only few of them have been employed in metal complex encapsulation aiming for catalysis. The groups of Raymond and Bergman explored the use of an M₄L₆ anionic tetrahedral capsule (23), which is formed by six bis-catecholamide struts and four octahedral gallium(III) centers. The highly negatively charged (−12) and homochiral (ΔΔΔΔ and ΛΛΛΛ) capsule accommodates positively charged organometallic guests (Figure 22), and as such, the capsule can be used to bind cationic metal complexes. For example, it has been used as mediator for stoichiometric C-H activation using an encapsulated cationic iridium complex.54
The application of this capsule in controlling the properties of transition-metal catalysts was proven with different types of metal complexes. A series of bisphosphine rhodium-diene cations were encapsulated and the hydrogenation of the cyclooctadiene ligand yielded the active catalyst in the form of a hydrated bisphosphine complex (Rh(PMe$_3$)$_2$(D$_2$O)$_2$, 24).$^{55}$ Whereas the hydrated complex itself was not encapsulated because it has a too large solubility in water, *in situ* hydrogenation of the cyclooctadiene ligand yielded the kinetically trapped active catalyst 23•24. This active species is fully ejected from the cavity after twelve hours and the system should therefore be used within this timeframe, for example for fast isomerization reactions of allylic substrates (Figure 23). While the free catalyst showed conversion of different allylic alcohols and ethers to their corresponding aldehydes or enol ethers, the encapsulated catalyst 23•24 showed substrate selectivity, controlled by the aperture of the container. Based on the size of the substrate, only prop-2-en-1-ol (25) and its methyl ether (26) were isomerized by the encapsulated catalyst. This contrasts with the non-encapsulated catalyst that is able to isomerize larger and sterically more hindered substrates. It was furthermore shown that the capsule also protects the catalyst. For instance, while crotyl alcohol usually inhibits the free catalyst, the encapsulated rhodium-catalyst (23•24) is still able to convert allyl alcohols to the aldehydes in the presence of this inhibitor.
[RuCp(PMe$_3$)(MeCN)$_2$]$^+$ (28) was also sequestrated within the M$_4$L$_6$ tetrahedral cage (23•28, Figure 24). Within the assembly, a water-solvated ruthenium species was expected to form in D$_2$O, however no exchange of acetonitrile with water occurred and the ruthenium complex was bound quantitatively inside the cavity of 23. Such ruthenium complexes are known to isomerize allylic alcohols towards the corresponding aldehydes or ketones. In fact, the supramolecular ruthenium catalyst 23•28 provides TON > 1000 and a very long lifetime in the isomerization of 3-buten-2-ol (27), values that are much higher than those obtained for the non-encapsulated ruthenium catalyst, even if the latter is applied in organic media. Kinetic studies were performed, revealing that the encapsulated ruthenium catalyst does not display product inhibition. In fact, the system seems to accelerate as the reaction reaches completion. This also results in an increase in the pseudo-first-order rate constant near the end of the reaction. Based on kinetic analysis and competition experiments with an additional allyl ether, it was suggested that substrate-inhibition occurs due to the binding of a second olefin to the catalyst-substrate complex during the catalysis. It is speculated that, as substrate concentration lowers, less of this olefin inhibition occurs and thus the rate constant slightly increases. Although no intermediates were observed, this example clearly shows that catalyst encapsulation alters the kinetics for the formation of some intermediates during the catalytic cycle. Similar to the encapsulated rhodium catalyst 23•24, the supramolecular ruthenium catalyst 23•28 also showed substrate selectivity (Figure 24). For instance, the larger 1-phenylprop-2-en-1-ol does not react with the encapsulated 23•28, likely because of its big size. Noteworthy, 3-buten-2-ol (27) can now be isomerized to the ketone which was not possible with the rhodium analogue (23•24, Figure 23). This indicates that the aperture of the cage itself plays no role with this substrate and that it is more likely that the catalyst has a different orientation inside the capsule. Importantly, these

![Figure 23: Rhodium encapsulated catalyst 23-24 and its catalytic behavior in allylic isomerization compared to non-encapsulated rhodium catalyst.](image)
experiments show that the cage still allows small substrates to come in contact with the catalyst.\textsuperscript{55,56}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure24.png}
\caption{ Allylic isomerization within 23-28 compared to non-encapsulated ruthenium catalyst showing substrate selectivity.}
\end{figure}

The supramolecular capsule 23 was also used in intramolecular cyclization reactions when monophosphine gold complexes were encapsulated leading to 23•29.\textsuperscript{57} The supramolecular cage 23 drives the equilibrium of the gold complexes to the cationic form and thus (Me$_3$P)Au\textsuperscript{+} is encapsulated, regardless of the anion (Cl\textsuperscript{-}, Br\textsuperscript{-} or NTf$_2$\textsuperscript{-}) present in solution. The encapsulated gold(I) complex 23•29 was applied in the hydroalkoxylation of allenol 30 (Figure 25). The various free (non-encapsulated) gold(I) complexes showed different yields (11-87\%) depending on the gold-anion bond strengths (Me$_3$PAuBr gave the poorest yield); whereas the encapsulated gold catalyst 23•29 gave a reasonable yield (48\%) for the \textit{exo}-hydroalkoxylated product, regardless of the counterion used. The M$_4$L$_6$ tetrahedron itself does not catalyze the reaction. Also, performing the reaction while the pocket is blocked with a strong binding guest (PEt$_4$\textsuperscript{+}), resulted in a yield similar to the control reaction indicating that an encapsulated gold(I) species is the active catalyst. Further comparison of the encapsulated gold complex 23•29 with Me$_3$PAuBr showed that the reaction rate is accelerated by a factor of eight and the TON is increased to 67. Comparable to the case with the encapsulated 23•24 and 23•28 catalysts, this is not an example in which the fundamental transformations at the metal center are controlled by the confined space, as the same products are seen without the capsule. These systems, however, show that the supramolecular cage controls the coordination sphere around the gold(I) complex, and can act as a phase transfer reagent to enhance the reaction rate.
Interestingly, the gold-encapsulated catalyst $23\cdot 29$ did provide a different product distribution compared to the free complex when applied in the cyclo-isomerization of enyne $31$. With $23\cdot 29$ a remarkable change in product distribution was observed (Figure 26). It is believed that, if the reaction takes place outside the cage, the well solvated gold carbene species $32^{59,60}$ undergoes a nucleophilic attack of water to form the hydroalkoxylated species $34$. However, when the reaction takes place inside the cage, less water is available due to the hydrophobic cavity, and the activated species has time to undergo a cyclo-isomerization to form product $33$. Although the transition state leading to both products is probably the same, the hydrophobic environment within the capsule makes the nucleophilic attack of water energetically less favored compared to the non-encapsulated system. Hence, the pathway towards the intramolecular rearrangement is more accessible within the encapsulated gold(I) catalyst $23\cdot 29$. Furthermore, the selectivity of the reaction remained the same, independent of the gold precursor used (Me$_3$PAuCl or Me$_3$PAuBr), indicating that the encapsulated cationic Me$_3$PAu$^+$ complex is the active species.
Metal complex encapsulation can lead to protection of the catalyst from degradation. This was nicely demonstrated by combining the previously discussed encapsulated $\text{23\cdot28}$ (and $\text{23\cdot29}$) catalyst with enzymes such as esterases, lipases and alcohol dehydrogenases (ADH and FDH) to perform cascade reactions. In an one-pot reaction the ruthenium-encapsulated catalyst $\text{23\cdot28}$ was used in combination with ADH and FDH, enabling the conversion of an allylic alcohol to the aliphatic alcohol (Figure 27, top).\textsuperscript{61} In this reaction the metal catalyzed reaction precedes the enzyme catalyzed transformation. Alternatively, when the gold encapsulated catalyst $\text{23\cdot29}$ was used in a tandem reaction with an esterase, the enzymatic reaction takes place before the metal catalyzed reaction.\textsuperscript{61} The protection of the cationic gold complex in the supramolecular container is crucial as the free gold complex inhibits the esterase. In the overall reaction an ester was hydrolyzed by an esterase or lipase to give the allenol, which was subsequently cyclized by the encapsulated $\text{23\cdot29}$ catalyst (Figure 27, bottom). These examples further illustrate the potential of metal encapsulation as
it allows the combination of different catalysts for cascade transformations that cannot be combined otherwise.

Reek, Scarso and co-workers explored the use of water-hydrogen-bonded hexameric capsules (35) based on readily available resorcin[4]arenes. These resorcin[4]arene building blocks form self-assembled hexameric capsules in water-saturated organic solvents and have been demonstrated to encapsulate a variety of neutral and cationic guests. Reek and Scarso demonstrated that these capsules can also be used to encapsulate gold complexes (Figure 28). Upon encapsulation of the cationic gold(I) carbene complex, the triflate anion was separated and not bound in the cavity. The confined gold(I) catalyst 35•36 was explored in the hydration of butyne 37, which normally gives Markovnikov addition of water (38), or forms 1,2-dihydronaphthalene 40 under anhydrous conditions. Thus, the non-encapsulated (i-Pr-NHC)Au(OTf) gave almost quantitative formation of the Markovnikov product 38 within 30 min. Although the encapsulation of the gold catalyst slowed down the reaction (5% conversion after 30 min, 28% after 400 min), a new interesting distribution of products was observed. In contrast to the free gold catalyst, the encapsulated analogue yielded a small amount of linear aldehyde 39 (4%), next to 12% of 38 and, interestingly, the formation of 1,2-dihydronaphthalene 40 (12%) was observed. Thus far the origin of the change in selectivity remained somewhat unclear. Probably, the molecular container may impose a reaction barrier for water to enter the cavity,
hence slowing down the Markovnikov addition, or the capsule could force an unusual geometry of the substrate-metal complex inside the container, thus favoring the intramolecular reaction. In the latter case, the second coordination sphere disfavors certain reaction pathways, which may suggest that it should be possible to force the formation of other products, like the 5-membered ring (5-exo-dig product), by changing the shape of the cavity in which the metal catalyzed reaction takes place.

Figure 28: Capsule 35 and implications in catalysis of encapsulated 35-36.

Also other substrates were used for the hydration reaction, and a decrease in reaction rate was noted when the catalyst was enclosed in the hexameric cage. The difference in rate of various substrates that differ in size was translated in substrate-selectivity controlled by the cage. An interesting rate increase was observed when aliphatic cyclic functionalized alkyne (ethynylcyclohexane) was compared to linear alkynes (1-octyne and 1-dodecyne). A plausible explanation is that, due to its smaller and more rigid shape, the cyclohexane moiety fits better in the void of the container than the linear alkynes. The better fit results in a shift of the equilibrium to the substrate bound species, giving rise to a higher rate. The effect of the host on the guest is more clear when aromatic alkynes are used (41-43, Figure 29). In these cases, the non-encapsulated gold catalyst shows higher reactivity for the larger substituted (and more electron rich) alkynes following the order 41 < 42 < 43. The host-guest
complex shows the reverse substrate selectivity. The second coordination sphere
gives rise to a relative higher rate for the smaller and non-substituted aromatic
substrate overruling the natural selectivity that was based on the electronic properties
of the substrate.

![Figure 29](image)

**Figure 29:** Substrate-selectivity observed in the hydration of alkynes with encapsulated 35·36 catalyst.

In contrast to the hexameric cage, a self-folding cavitand forms when an amide-
functionalized resorcin[4]arene (44) is used. As demonstrated by Ballester and co-
workers, this cavitand is able to bind a [Rh(nbd)_2]^+ (nbd = norbornadiene) complex
which was studied in the catalytic hydrogenation of 46 (Figure 30). Due to the size
and shape of the cavitand 44 and the rhodium complex, only one part of the
encapsulated catalyst 44·45 is exposed to the outside forming a dichloromethane-
solvated species in solution. This partial exposure stabilizes the rhodium complex
when pressurized with hydrogen and prevents the formation of rhodium(0)-black
which is typically observed with non-encapsulated rhodium(I) complexes. Cavitand
44 stabilizes intermediates that are not present when the metal complex is free in
solution. In the hydrogenation of 46, the non-encapsulated [Rh(nbd)_2]^+ provides
dimeric product 47 in more than 80% yield. In contrast, the encapsulated rhodium
catalyst 44·45 results in a different product distribution, namely 47, 48 and 49 in a
39:58:3 ratio (Figure 30, bottom). A plausible explanation for the formation of the
dimeric product 47 is leaching of the catalyst from the cavity. However, the major
product 48 is likely formed because the transition state of the dimerization is
hampered by the molecular container.
Clearly, all these examples show that the formation of host-guest complexes are a viable method to control the second coordination sphere around metal complex and can be used in catalysis. However, finding the proper fit for a guest inside the host still remains a challenge. Furthermore it requires that a substrate can be co-encapsulated with the active site in the cavity.

**Figure 30**: Encapsulated 44-45 catalyst and its performance in hydrogenation of norbornadiene.
1.7 Conclusions and Perspectives

Activity, selectivity and stability are crucial parameters of a transition metal catalyst that are traditionally controlled by the ligands directly bound to a catalytically active metal, \textit{i.e.} the first coordination sphere. Metal catalysts can, however, be encapsulated in various types of molecular containers, providing tools to control these parameters via the second coordination sphere. Here, we have summarized different ways to encapsulate catalysts in well-defined, homogeneous confined spaces. Encapsulation through covalent linkage, the template-ligand approach or hosting the catalyst as a guest in a molecular container or protein-cavity are all demonstrated methods. As discussed in the various examples given in this chapter, such strategies can change certain steps in the catalytic cycle, giving rise to new kinetic profiles and altered selectivities. One of the main features observed in the examples discussed here is a higher stability of the encapsulated catalyst as the molecular container protects the active site from decomposition pathways, like self-deactivation through bridged species in epoxidation and cyclopropanation reactions. Furthermore, the capsular environment can induce substrate selectivity based on the size of the substrate and the aperture of the container, thus yielding high selectivity for the conversion of one substrate in a mixture of substrates. Although we are just at the beginning of exploring the possibilities in this area, it is clear that a molecular container can affect new regio- and enantio-selectivities in catalysis, which can sometimes be difficult to achieve by traditional means. Concluding from the examples provided in this chapter, the confinement of the catalyst has a clear and positive effect on the catalytic activities and/or selectivities. However, while these approaches are promising, the precise mode of operation is frequently poorly understood, while this understanding is essential for the future development of new capsules by rational design. It is relevant to note that microporous materials like metal-organic frameworks (MOFs)\textsuperscript{68} or Porous Organic Polymers (POPs)\textsuperscript{69} have also been demonstrated to be excellent hosts for the confinement of catalysts. One of the challenges in this field is to predict the selectivity displayed by a predesigned encapsulated catalyst, be it in solution or in the solid state in the form of a MOF. This prediction requires detailed knowledge of the effects prompted by a confined space imposed by a capsule around a catalyst on its elementary reaction steps, such as oxidative addition, migratory insertion and reductive elimination. Obviously, understanding how these elementary steps are influenced by a surrounding cage is important in order to predict how cage effects can be exploited to increase the activity and selectivity of a catalyst, and may allow us to affect the rate determining steps at will. With this in mind, the next generation of confined catalysts should become a well-accepted new tool to arrive at transition metal catalysts with superior properties.
1.8 **Research Aim and Outline of this Manuscript.**

Catalysis in a confined space is an interesting new strategy to induce new selectivity, reactivity and stability in known transformations. Many viable routes are possible to embed the metal catalyst in a confined space. This thesis utilizes assemblies that are held together by palladium-pyridine or platinum-pyridine interactions. By employing strategies developed by the group of Fujita and co-workers we designed and synthesized new systems in which different metal complexes are encapsulated in a well-defined confined space. Due to the pre-organization in the sphere, a high local concentration of metal complexes is obtained. Effects of this high local concentration and the ability to control the environment around the active metal species in catalysis are reported in this thesis.

In **chapter 2** the techniques to analyze supramolecular cages are discussed. The limitations and possibilities of diffusion NMR (DOSY) and mass spectrometry applied to spheres based on palladium-pyridine interactions, will be discussed. Spectra of spheres with different sizes in a mixture are separated with DOSY. When spheres are prepared by using a mixture of different building blocks, statistical mixtures of spheres form, which can be analyzed with high resolution mass spectrometry. In **chapter 3** the enhanced stability and change of reactivity will be demonstrated of encapsulated phosphine gold(I) catalysts via the ligand-template effect. The higher stability of the platinum spheres compared to the palladium analogues makes it possible to convert allene, alkyne and acid functionalities without decomposition of the spheres being observed. Cationic gold complexes could be obtained by addition of a silver salt and the resulting spheres have been applied in different gold catalyzed cyclization reactions. In **chapter 4**, the formation of spheres functionalized with cationic rhodium(I) N-heterocyclic carbenes is reported. The environment of the rhodium catalyst can be changed by the formation of statistical mixtures using different bispyridine building blocks. By simple mixing of different functionalized building blocks the local concentration of the metal complex can be controlled. In addition, the local environment can be altered by using building blocks with different polar or steric groups. The formed local environment around the rhodium catalysts is shown to influence the reaction profile in the cyclization of an alkynoic acid. **Chapter 5** showcases spheres functionalized with iridium(I) complexes. These complexes are pre-organized in the sphere and, upon reduction, well-defined small sized nanoparticles are formed. These nanoparticles are trapped in a confined space, thus preventing them from forming larger particles, which are thermodynamically more stable. The nanoparticles are more active catalysts than the mononuclear complexes and can be applied in the hydrogenation of various substrates. We move away from the ligand-template encapsulation methodology in
Chapter 6. Herein, we use the host-guest approach to selectively co-encapsulate various metal complexes with aromatic compounds. Due to the formation of a ternary complex, charge-transfer bands are observed in UV-Vis spectroscopy. The obtained charge transfer band is facilitated by the cage and can be fine-tuned, based on the redox properties of the metal complex.

1.9 References


An Introduction to Transition Metal Catalysis in Confined Spaces


Chapter 1

An Introduction to Transition Metal Catalysis in Confined Spaces


