# Summary

Catalysis is a powerful tool for selective transformations, and it has received a considerable attention in industry and academia. It is estimated that in 80–90% of all chemicals production processes worldwide, there is at least one step involving catalysis. At present, most of the bulk industrial processes utilise heterogeneous catalysts, while (transition metal) homogeneous catalysts are mostly applied in the fine chemicals industry. However, the recent Nobel Prize Awards for homogeneous catalysis[xxxi] indicate that homogeneous catalysis based on transition metal complexes will be gaining in importance in the future. The great advantage of the homogeneous systems is the excellent control of catalytic activity and selectivity, which is usually achieved by controlling the properties of the catalysts used in these reactions. The design of transition metal catalysts and control of their properties is traditionally done by modifications in the primary coordination sphere of the metal, *i.e.* by tuning the electronic and steric properties of the ligands that coordinate to the metal centre. Thus, ligand properties as electronic density on the donor atom, steric bulk (the cone angle), the number of binding sites, or the rigidity of the ligand backbone (the bite angle), are all relevant parameters for transition metal catalyst development and exploration. However, this approach has not yet resulted in a general strategy for design of catalysts suitable for selective transformations of non-functionalised and poorly reactive substrate molecules that do not possess any "handles"[xxxii] for steering the selectivity. The enzymes, however, are very efficient at exploiting subtle size differences and achieving high selectivities by providing binding pockets at their reactive sites, thereby constraining the motion of substrates and pre-orienting them for reaction. For the enhanced regio- and stereocontrol of chemical reactions for which the classical ligand design approach could not provide satisfactory solutions, more emphasis is being placed lately on the reactivity in confined nano-spaces, such as well-defined cavities of metal-organic frameworks, and (supra)molecular capsules, taking heavy inspiration from the biological systems. Catalysis in nano-spaces has the potential to produce sophisticated tools required to meet difficult synthetic challenges. Encapsulation imposes steric constraints within the capsule, decreasing the degrees of freedom of the reacting molecules and limiting the number of available conformations or relative orientations to one another. As a consequence, the reactions within the confined spaces are usually accelerated, and product distributions are often obtained, that are otherwise not accessible. Diels-Alder reactions in a spherical capsule of Rebek, or in an

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[xxxi]2001: William S. Knowles, Ryoji Noyori, and K. Barry Sharpless; 2005: Yves Chauvin, Robert H. Grubbs and Richard R. Schrock; 2010: Richard F. Heck, Ei-ichi Negishi and Akira Suzuki.

[xxxii]like acetamido functionality required in most asymmetric hydrogenation reactions, or electron-withdrawing groups next to the alkene double bond to direct the selectivity in the hydroformylation

octahedral metallocapsule of Fujita, as well as the acid-catalysed reaction within a tetrahedral metallocapsule of Raymond surrounded by a basic medium, are elegant examples of such reactions.

In our group, a ligand-templated strategy has been used to create cavities for the encapsulation of transition metal catalysts. We have specifically looked into hydroformylation of non-functionalised, linear internal alkenes, which are highly challenging substrates due to their poor reactivity and their lack of selectivity-steering handles. Their selective (isomerisation-free) functionalisation into either of the branched aldehydes is not yet possible. Free, or phosphine-modified rhodium catalysts typically produce a mixture of aldehydes and a considerable amount of isomerisation, while application of electron-poor ligands like phosphites leads to an isomerisation-hydroformylation sequence, producing mainly linear aldehydes. The branched aldehydes as potentially high added value products have remained inaccessible, due to the lack of catalysts able to produce them. However, the rhodium catalyst encapsulated using the ligand-template approach has displayed remarkable selectivity in this reaction. Moreover, this selectivity was possible to steer purely by using different building blocks for the encapsulation, as we have shown in this work.
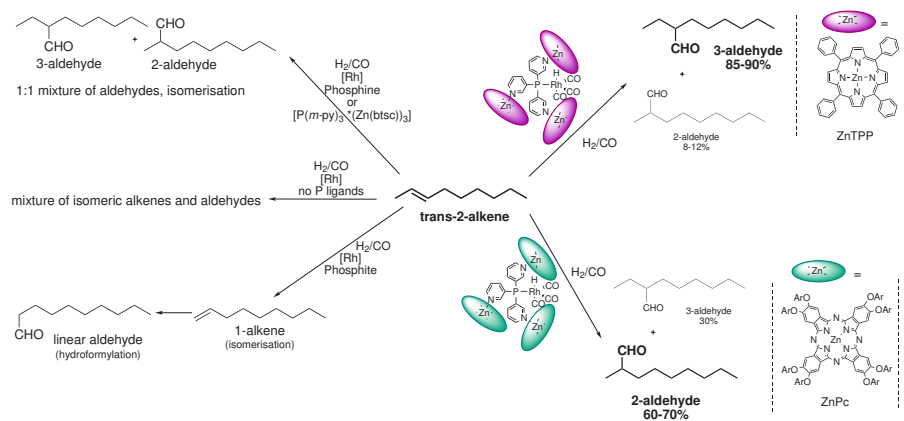
The DFT-study of the *trans*-2-octene hydroformylation by the non-encapsulated mono-phosphine rhodium catalyst, and the subsequent MATLAB simulation of the kinetics using the DFT-computed reaction constants, have shown that the major aldehyde product should be the 2-aldehyde (in ca. 80 %, Chapter 5). The mono-phosphine rhodium catalyst is not accessible using the conventional ligands, and our encapsulation approach (using large Zn^{II}complexes; application of smaller Zn^{II}complexes, like bis-(thiosemicarbazonato)Zn complexes leads to formation of bis-phosphine ligated rhodium catalysts, see Chapter 2) was a successful alternative to a clean formation of the monophosphine rhodium-hydrido species under hydroformylation conditions. The coordination of a Zn^{II}complex to the pyridyl groups of the template ligand tris-(*meta*-pyridyl)-phosphine ((m-py)$_3$P) creates a supramolecular capsule with the lone pair on the phosphorus atom free for coordination of a transition metal, as we have seen in the solid state structure of the supramolecular capsule formed using Zn^{II}(tetraphenylporphyrin) for the encapsulation (Chapter 4). The rhodium atom coordinated to phosphorus is thus situated

within the capsule, whose structure practically does not change upon formation of the catalytically active species. In order to simulate the non-encapsulated catalyst, a large cavity was created using a Zn^{II}(phthalocyanine) (ZnPc, Chapter 3) complex, a compound structurally related to porphyrins, without out-of-plane *meso*-substituents and with an extended planar surface around the Zn-centre. The volume of the cavity formed using ZnPc was about five times larger than the one formed using ZnTPP. The DFT-computed product ratio of the *trans*-2-octene hydroformylation using the catalyst encapsulated by a simplified ZnPc complex (without the peripheral aryloxy substituents) predicted the 2-aldehyde as the major product. Opposite to this, the DFT-predicted product ratio of the ZnTPP-encapsulated rhodium catalyst was 70 % 3-aldehyde (Chapter 5). These DFT-computed results are in an excellent agreement with the experiments, as the ZnPc-encapsulated catalyst led to a formation of 2-aldehyde as major product (60–70 %) when 2-alkenes (octene to decene) were used as substrates. The selectivity of the ZnTPP-encapsulated catalyst was opposite to this, as 3-aldehyde was obtained as the major product (85-91 %) from 2-alkenes.

Further detailed experimental and computational (DFT) studies of the the catalytic cycle have shown that the selectivity of the *trans*-2-octene hydroformylation by the ZnTPP-encapsulated catalyst is the transfer of the H atom from rhodium species to the coordinated alkene and formation of the alkylrhodium species (*i. e.*, the hydride migration step). We have found that for three of the four possible rhodium-alkene complexes, each with two reaction pathways (one to 2-, the other to 3-aldehyde), the hydride migration to form the 2-alkylrhodium species is greatly disfavoured, so that the formation of 3-aldehyde becomes the dominant process. During the hydride migration process, the supramolecular ZnTPP-based capsule needs to rearrange in order to accommodate the transition state, and the pathways leading to the minor product (2-aldehyde) are disfavoured since the substrate rotation in the respective transition states causes distortion of the capsule, which is associated with an energy penalty (Chapter 5). The distortion of the capsule disables the formation of the $CH–\pi$ attractive interactions between the adjacent porphyrin molecules, whose existence is suggested in the solid state, and in the solution as the origin of the cooperativity previously observed in the binding. In most of the pathways to the major product (3-aldehyde), the capsule distortion (and thus the rearrangement energy) is minimal, so that 3-aldehyde becomes the major product. Thus, the ZnTPP-based capsule represents an effective steric block for substrate rotation in the hydride migration step towards the 2-alkyl product, while the ZnPc-based one allows largely unhindered substrate motion during catalysis.

We have thus shown that the selectivity in the hydroformylation of 2-alkenes catalysed by the encapsulated rhodium catalyst can be steered by the size of the supramolecular capsule. Application of ZnPc in the encapsulation creates a spacious capsule that leads to formation of 2-aldehydes as major products. Opposite to this, the ZnTPP-capsule, whose shape is stabilised by the intra-supramolecular $CH–\pi$ attractive interactions, blocks most of the reaction pathways towards the 2-aldehyde, and leads to 3-aldehyde as the major product. In addition, we have demonstrated that the selectivity is dramatically influenced by modifications on sites remote from the catalytically active centre, which weaken the cooperative interactions between the adjacent porphyrins and/or distort the shape of the capsule (Chapter 4). This is a unique example of a transition metal catalyst that displays

significant selectivity in the hydroformylation of challenging 2-alkenes. Moreover, the selectivity could be steered by modifications in the secondary coordination sphere of the transition metal which change the capsule shape, a phenomenon observed in enzymatic catalysis and exploited in enzyme optimisation methodologies. The effects by which the enzymes are able to achieve high level of activity and selectivity strategies of catalyst control in transition metal catalysis are still scarce,[258] however, we believe that the future generations of sophisticated transition metal catalysts will include enzyme-like features in order to be able to achieve selective functionalisation of poorly reactive and challenging substrate molecules.