Summary

Control over the selectivity and reactivity in transition metal catalysis is a major challenge and important for applications in both fine and bulk chemical industries. Traditionally, variation of ligands that coordinate to the metal center has been widely applied and explored to optimize the properties of transition metal catalysts. Despite many breakthroughs, the selectivity and reactivity that are generally dictated by the intrinsic properties of the substrate cannot always meet the requirements for applications. Nature serves as the master of making superior catalysts for versatile transformations. Inspired by nature, we explored supramolecular tools, i.e. effector controlled catalysis and supramolecular substrate preorganization, to control the selectivities and reactivities in hydroformylation reactions, asymmetric hydrogenation reactions and C-H activation reactions. These achievements reported in this thesis demonstrate the power of supramolecular interactions in controlling challenging selectivity and reactivity in transition metal-catalyzed transformations.

Hydroformylation, also known as the oxo-process, enables the addition of a formyl group and a hydrogen atom to a C=C double bond using syngas (H_2/CO) to produce aldehydes with 100% atom economy. Hydroformylation is one of the largest industrially applied homogeneous catalytic transformations with a total production capacity of 107 ton/year. Therefore, developing catalysts for regio- and enantioselective hydroformylation has received considerable attention over the past decades. Previously, our group reported a supramolecular catalyst that controls the regioselectivity by substrate orientation, reminiscent of enzymes, which was based on ParaDIMphos (**L1**). Using this catalyst system, carboxylate containing alkene substrates with a suitable span were pre-organized at the metal center via the DIM-receptor for linear selective hydroformylation. However, 3-butenoic acid that cannot be preorganized by the ParaDIMphos-Rh complex showed poor selectivity, indicating the limitation of substrate scope. Inspired by re-engineering of the enzyme to adapt its cavity for new substrates, we report in **Chapter 2** the rational redesign of a rhodium catalyst for selective conversion of shorter substrates via supramolecular substrate preorganization (**Fig. 1**). For this purpose, we developed a new ligand coined OrthoDIMphos (**L2**). DFT calculations show that the OrthoDIMphos (**L2**) based rhodium catalyst has a shorter distance between the DIM-receptor and the Rh center for 3-butenoate ditopic binding, as well as well-defined Rh-hydride coordination geometry. As expected, under optimized conditions, the new catalyst displayed the highest regioselectivity in the hydroformylation of 3-butenoic acid reported to date (l/b up to 84, TON up to 630). Furthermore, the internal alkene analogue, 3-pentenoic acid, was also converted with high

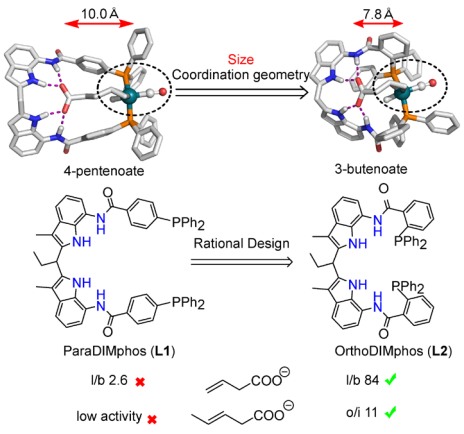

Fig. 1. Rational design of OrthoDIMphos (**L2**) for regioselective hydroformylation of 3-butenoic acid and its derivatives via substrate preorganization by changing the distance between the Rh-complex and the DIM-receptor (in blue color).

regioselectivity (o/i 11) whereas without substrate preorganization a 1:1 mixture of these products is obtained. Detailed *in situ* High-Pressure (HP) spectroscopy characterization of the active species, kinetic studies, and DFT calculations on the selectivity determining step also show the hydride migration towards the linear product is more favourable than the branched product via substrate preorganization in the DIM-receptor.

The mechanistic studies of **Chapter 2** reveal that the dimeric rhodium complexes formed are converted to the monomeric complexes for selective hydroformylation reaction via substrate binding to the DIM-receptor. On that basis, we report in **Chapter 3** the first supramolecular rhodium catalyst that form dimeric or monomeric Rh-complexes, controlled by the binding of effectors within the integrated DIM-receptor using hydrogen bonding (**Fig. 2-3**). X-ray crystal structures, *in situ* (high-pressure (HP)) spectroscopy studies, and molecular modelling studies show that in the absence of effectors, the preferred Rh-species formed is the dimer, in which two ligands coordinate to two rhodium metals. Importantly, the dimeric structures under hydroformylation conditions are stabilized by hydrogen bonding interactions between the carbonyl-O groups of the ligand and the DIM-receptors. As effector binding competes with this hydrogen bonding, the presence of carboxylate containing effectors in solution results in the formation of monomeric complexes with the effector bound in the DIM-receptor. As a consequence, the equilibrium between the dimeric and monomeric rhodium complexes of this [Rh(**L2**)]n catalyst system can be regulated by binding of effectors in the DIM-receptor. Furthermore, as the monomeric complex has different catalytic properties from the dimeric complex, we effectively generate a catalytic system of which the properties respond to the presence of effectors. Indeed, catalytic and kinetic experiments show that both the selectivity and activity of this supramolecular catalytic system can be regulated in the hydroformylation of 1-octene using acetates as effectors to shift the equilibrium from the dimeric to monomeric species.

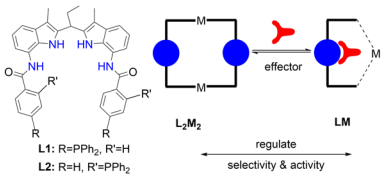

Fig. 2. The general concept of supramolecular tuning of the selectivity and activity via the regulation of the monomer-dimer catalyst equilibrium using an effector based on a hydrogen bonding approach

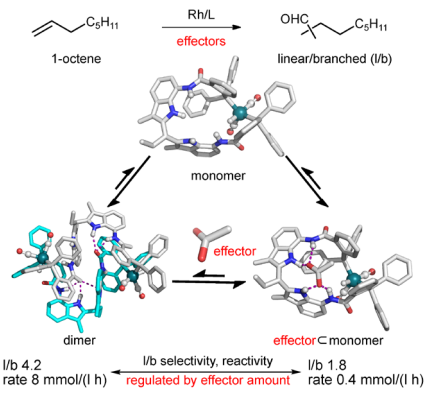

Fig. 3. Control over the selectivity and activity via the regulation of the monomer-dimer catalyst equilibrium using effectors

Control over the enantioselectivity is extremely challenging in the hydroformylation reaction. Binaphos, Yangphos and bis-3,4-Diazaphospholane are few representative chiral ligands that are successfully used for the enantioselective hydroformylation reaction. However, these ligands are generally tedious to synthesis, and variations of the ligands can be limited. Also, in some reactions the regioselectivity is too low for practical application. Therefore, we report

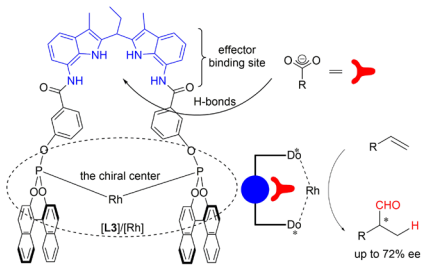

Fig. 4. An effector enhanced regio- and enantioselective hydroformylation reaction via tuning the surrounding environment around the chiral metal center.

in **Chapter 4** a series of supramolecular rhodium catalysts, of which the DIM-receptor can bind carboxylate containing effectors, thereby controlling the enantioselectivity (**Fig. 4**). In this case, both chiral and achiral effectors can be bound to modify the coordination environment of the rhodium center. The optimized supramolecular catalyst with an effector bound in the DIM-receptor displayed high regio- and enantioselectivity in the hydroformylation of vinyl acetate and its derivatives. The enantioselectivities increase up to Δ55% ee (from 17% ee to 72% ee for vinyl acetate). Control experiments with chiral enantiomerically pure effectors and achiral effectors show that both chiral and achiral effectors can enhance the enantioselectivity induced by the rhodium metal. Further catalytic experiments show that many of the complexes based on simple amino acids based effectors displayed decent enantioselectivity and excellent regioselectivity in the hydroformylation of vinyl acetate (up to 68% ee, b/l >99).

The rhodium catalyzed enantioselective hydrogenation reaction is a highly efficient and atom economic transformation, and as such it is often used in the production of enantiopure pharmaceuticals and agrochemicals. For this reason, it has received considerable attention both from academia and industry. Over the past decades, many ligands, including diphosphine ligands with a chiral backbone, P-stereogenic diphosphine ligands, and chiral mono-phosphite or phosphoramidite ligands, have been reported for rhodium catalyzed asymmetric hydrogenation reactions. Note that the enantioselectivity is generally controlled by the steric interactions between the catalyst and the substrate. Recently, our group reported an achiral supramolecular rhodium catalyst controlled by a chiral thiourea based effector for enantioselective hydrogenation (up to 99% ee). Importantly, this supramolecular catalyst can also be optimized via a deconvolution approach by the evolution of mixtures of effectors. In **Chapter 5**, we studied this supramolecular catalyst system in detail and demonstrate that multiple supramolecular interactions between the effector and the complex are required to obtain high enantioselectivity (**Fig. 5**). And, it also explains why this effector dominates in the presence of a mixture of competing effectors. *In situ* VCD, NMR spectroscopy and DFT modelling reveal multiple weak interactions form between the effector and the achiral rhodium complex. These weak interactions include the expected four hydrogen bonds between the carboxylate

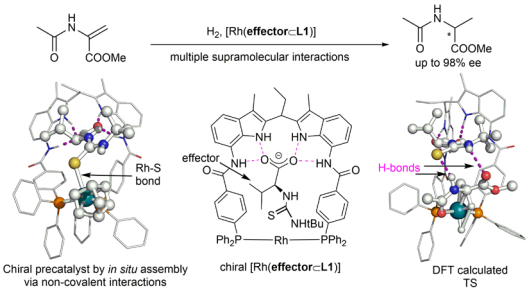

Fig. 5. Multiple supramolecular interactions are involved in an effector controlled enantioselective hydrogenation

group and the DIM-receptor, and an Rh-S bond between the thiocarbonyl group of the effector and the Rh center in the precatalyst, the rhodium-substrate and dihydride complexes. It is important to mention that the extra Rh-S bond results in the formation of well-defined supramolecular assembly in contrast to other effectors. Furthermore, DFT calculations on the four unsaturated catalytic pathways show that the H-bond interactions between the substrate and the effector controls the enantioselection step at the octahedral stage by stabilizing the transition state intermediates. DFT calculations also reveal the possible resting state complexes, which are stabilized by the Rh-S bond, formed in the early stage of the unsaturated mechanism, in line with *in situ* spectroscopy. Finally, control and competition experiments with new effectors and substrates confirm the two crucial factors important for achieving highly enantioselective catalysis. These two factors are: 1) A combination of the S-Rh bond and the four H-bonds leads to the formation of the well-defined supramolecular assembly for enhanced chirality transfer; 2) The hydrogen bonding interactions between the effector and the substrate stabilize the catalytic intermediates.

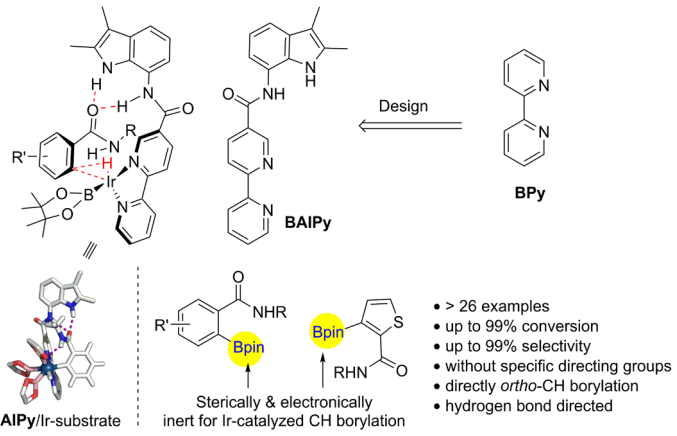

Fig. 6 Direct *ortho*-selective CH borylation of unactivated secondary aromatic amides via hydrogen bonds.

C-H bond activation and subsequent functionalization with transition metal catalysts is undoubtedly one of the most powerful catalytic transformations. As catalytic C-H functionalization directly converts the inert C-H bond to value added moieties, this technology provides endless opportunities for modern synthetic chemistry. Particularly, Iridium-catalyzed C-H borylation is a state-of-art transformation as the boron group installed can be easily converted to a variety of functional groups leading to value added compounds using known chemistry, such as Suzuki coupling, amination, hydroxylation and halogenation. However, the selectivity and reactivity are generally ruled by the substrates in terms of electronic and steric factors, limiting its potential application. As secondary aromatic amides are widely distributed structures among the chemical kingdoms, such as pharmaceuticals, agrichemicals and other high value intermediates, design of catalyst for *ortho*-selective CH-borylation of this class of compound is of high value. Therefore, we report in **Chapter 6** the first example of iridium catalyzed direct *ortho*-selective C-H borylation of challenging secondary aromatic amides in which the regioselectivity is controlled by hydrogen bond interactions (**Fig. 6**). The new iridium catalyst displays unprecedented *ortho*-selectivities for a wide variety of secondary amide substrates that differ in electronic and steric properties. Also, the catalyst tolerates various functional groups. The regioselective C-H borylation catalyst is readily accessible and demonstrated

to convert substrates at gram scale with high selectivity and conversion. These experiments show that supramolecular substrate orientation is a powerful approach to control the regioselectivity in challenging C-H borylation reactions.

In conclusion, the successful control over the challenging selectivity and reactivity in hydroformylation reactions, asymmetric hydrogenation reactions and C-H activation reactions using supramolecular tools demonstrate the power of effector controlled catalysis and supramolecular substrate preorganization concepts in transition metal catalysis. Moreover, beyond traditional approaches, new concepts based on supramolecular tools are envisioned to achieve more challenging goals in the future.