Summary

Catalysis is a synthetic method for the fast production of chemicals in a selective way. The introduction of catalysis to the field of chemistry is a milestone in the industrial production of chemicals. Nowadays, the manufacturing processes of many pharmaceuticals, fragrances, plastics and agrochemicals are relying on catalysis as it is one of the best synthetic tools available in organic chemistry. The advantages of catalysis for the industry lie in the economic and environmental aspects that catalysis offers, enabling the synthesis of specific compounds in a smaller number of synthetic production steps reducing time and at lower costs. For these reasons, transition metals catalysis is a commonly applied methodology in industry and has been a growing research field in chemistry over the last decades. In transition metal catalysis, the metal is used as a reactive center where the reaction takes places by bringing the reactants together and by lowering reaction pathways for bond breaking and making. The coordination of ligands to the metal center can improve the performances of the metal in terms of activity and selectivity. As only a few transition metal elements can be used for catalysis in a particular reaction, the synthesis of new ligands that can confer new properties to the metal is at the center of attention in the search for new catalysts. Therefore, many families of ligands have been used in transition metal catalysis and intense searches are maintained in this area as new catalysts are often required for the synthesis of new products. However, the use of the classic transition metal catalysts cannot always supply the desired selectivity in the synthesis of particular compounds and new approaches have to be envisioned. Inspired by enzymes, supramolecular catalyst takes advantage of supramolecular interactions as an additional tool to control reactivity and selectivity. Weak interactions, like hydrogen bonds, are very convenient in chemistry as they can easily be used to create useful molecular architectures, like multi-components ligands or cages. They can also influence the reaction mechanism to provide uncommon reactivity or high selectivity. For instance, monodentate ligands functionalized with an appropriate hydrogen bond group can be used in the formation of bidentate ligands by self-assembly to form homobidentate ligands or by association to other functionalized ligand building blocks to form heterobidentate ligands.

This thesis describes a detailed study of a catalytic system in which hydrogen bonds are formed between two ligand building blocks as well as between the catalyst and the substrate during the asymmetric hydrogenation reaction catalyzed by rhodium complexes. The understanding of the mechanism involved in this transformation allowed us to design a second generation of catalyst that showed higher activity in the hydrogenation of functionalized substrates while excellent selectivity is maintained. Also, the same supramolecular strategy was applied for the formation

of iridium complexes. In **Chapter 1**, an overview of the asymmetric hydrogenation reaction rhodium-catalyzed is given and the mechanism is discussed. The search for new catalysts can be done using different approaches. The first method lies in a trial-and-error strategy using high throughput screening methods. Another strategy is based on the rational design of catalysts, using mechanistic considerations. Both of these strategies are discussed in this chapter. The emergence of supramolecular strategies in the design of catalytic systems has brought to light different classes of supramolecular systems. These different supramolecular concepts will also be presented in this introduction chapter.

In **Chapter 2**, we present detailed studies on the reaction mechanism of the asymmetric hydrogenation reaction catalyzed by a rhodium complex formed by the assembly of a urea-functionalized phosphine and a phosphoramidite (Figure 1). This complex is highly selective in the asymmetric hydrogenation of methyl 2-hydroxymethacrylate (ee up to 99%), which is a precursor of the so-called "roche ester", an important intermediate in the preparation of several biologically active compounds. Based on control experiments, it has been supposed that hydrogen bonds between the substrate and the catalyst are involved in the reaction mechanism.

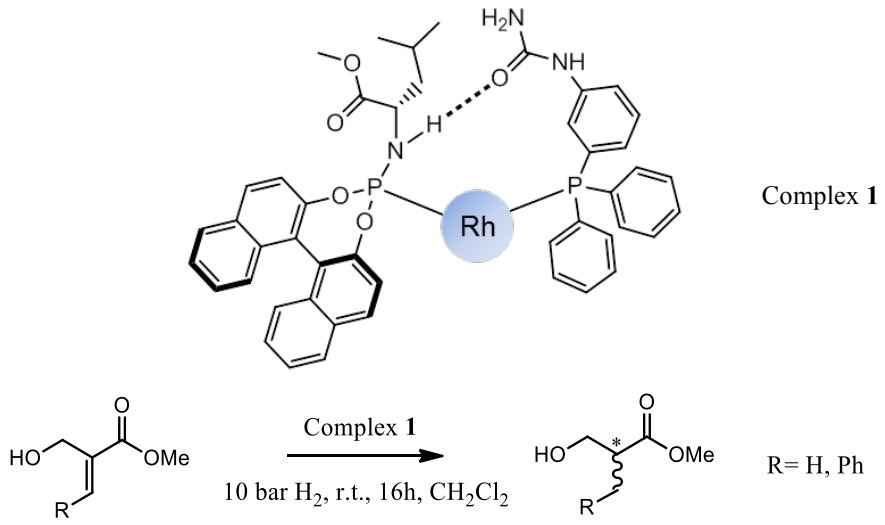


Figure 1. Top: supramolecular complex **1** studied in chapter 2 and 3 of this thesis. Bottom: asymmetric hydrogenation of methyl 2-hydroxymethacrylate and its phenyl derivative using complex **1**.

An in-depth study of the reaction mechanism has been carried out in order to detect if such interactions were actively involved during the reaction. The identification of several intermediates in the early stages of the reaction using NMR spectroscopy and X-ray crystallography revealed the involvement of hydrogen bonds at a key step of the reaction, i.e. the

coordination of the substrate to the catalyst. Two hydrogen bonds between the catalyst and the substrate were identified in the catalyst-substrate complex, which play a crucial role in the stabilization of this important intermediate in the early stages of the reaction. Gas uptake experiments together with *in situ* NMR spectroscopy elucidated the reaction mechanism of the reaction revealing that the catalytic cycle follows a lock-and-key mechanism in which the substrate coordinates prior to molecular hydrogen. Further kinetic experiments combining gas-uptake experiments and stopped-flow kinetics to evaluate the substrate coordination demonstrate that the rate determining step of the reaction is at the late stages of the reaction. Also, kinetic results based on the application of the Michaelis-Menten rate equation to describe this catalytic system highlighted the crucial role of the hydrogen bonding during catalysis at the late stages of the reaction. As more information was needed to fully understand the H-bond effect during the reaction, we performed a detailed computational study of the reaction mechanism, which is described in **Chapter 3**. By computing several possible pathways that can occur in the general reaction of asymmetric hydrogenation (the unsaturated pathway, the dihydride pathway and the semi-dihydride pathway), we demonstrate that the reaction follows an unsaturated pathway in which the hydride migration step is rate determining. Also, we compared the feasibility of several unsaturated pathways with and without the involvement of hydrogen bonds, revealing that the effective path is the one stemming from the diastereomer stabilized by two hydrogen bonds formed between the catalyst and the substrate (see Figure 2). The study of the different paths leading to products with opposite absolute configurations revealed that the hydrogen bonds between the catalyst and the substrate are also involved in the high selectivity observed experimentally.

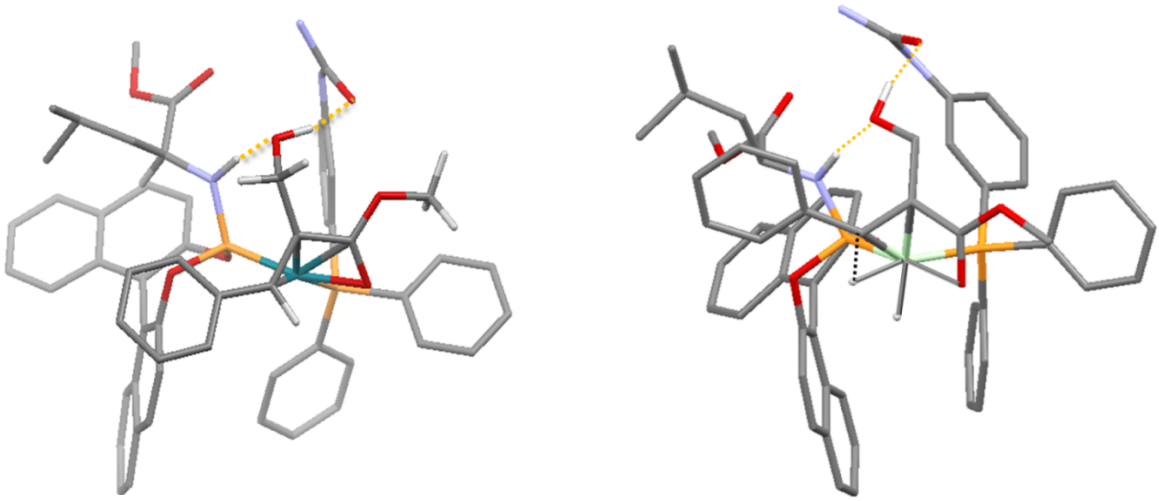
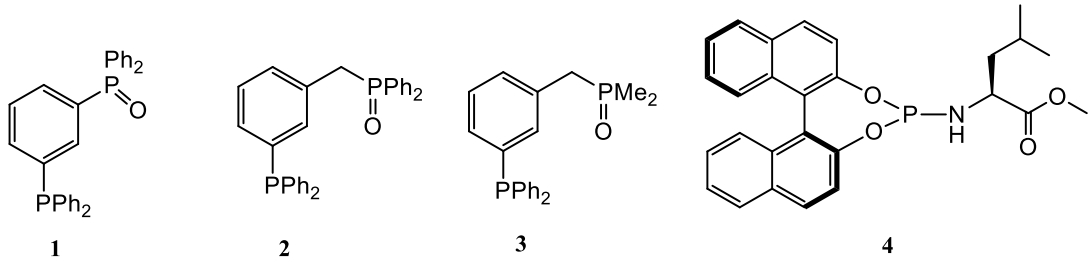


Figure 2. Left: catalyst substrate complex in which two hydrogen bonds are formed between the catalyst and the substrate. Right: hydride migration transition state in which two hydrogen bonds are formed between the catalyst and the substrate.

In **Chapter 4**, a new series of ligand building blocks for the formation of supramolecular rhodium complexes have been designed and evaluated in the asymmetric hydrogenation reaction (Figure 3). Based on the mechanistic understanding described chapters 2 and 3, we created a series of bisphosphine monoxide ligands that act as hydrogen bond acceptors to form hydrogen bonding with the PNH group of a phosphoramidite, resulting in the formation of new bidentate ligands. These supramolecular complexes based on phosphine oxides are very selective in the hydrogenation of several substrates bearing a hydroxyl group. NMR spectroscopy and DFT studies show that hydrogen bonds are responsible for the stabilization of a catalyst-substrate complex (Figure 4). Also, kinetics studies show that these supramolecular complexes display higher rates of hydrogenation and have an improved robustness toward the reaction conditions compared to the first generation of urea-based catalysts.



1 2 3 4

Figure 3. Building block ligands based on PO groups (ligands **1**, **2** and **3**) as hydrogen bond acceptors for the formation of supramolecular complexes Rh(**L**)(**4**) (**L**= **1**, **2**, **3**) using phosphoramidite **4** as a hydrogen bond donor buiding block ligand.

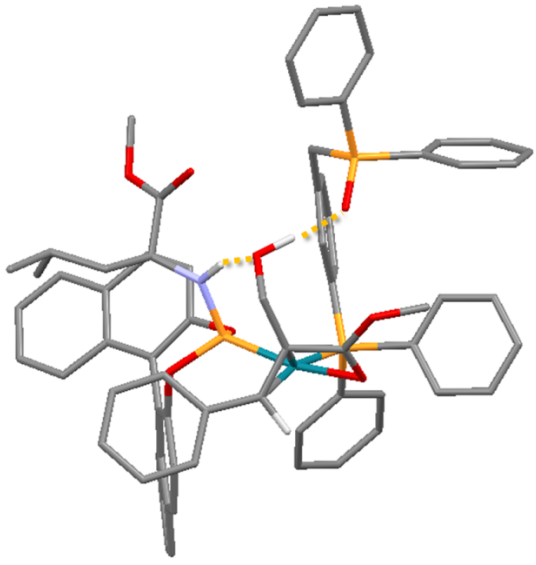


Figure 4. Catalyst substrate complex based on phosphine oxide ligand in which two hydrogen bonds are formed between the catalyst and the substrate.

Chapter 5 describes the formation of supramolecular iridium complexes. A series of iridium complexes has been made by using functionalized phosphines and phosphoramidite as building block ligands that interact together through hydrogen bonding. Coordination experiments supported by X-ray crystallography demonstrated the formation of the supramolecular bidentate ligands on the iridium metal center. Finally, the evaluation of these complexes in the hydrogenation of unfunctionalized alkenol substrates and their methoxy analogues revealed an increased activity for the substrate bearing a hydroxyl group.

The work described in this thesis gives detailed insights in how hydrogen bonds can be involved in the asymmetric hydrogenation reaction catalyzed by supramolecular rhodium complexes. The design of a traditional catalyst and its optimization is based on the modification of electronic and steric parameters that can be changed in the structure of the catalyst. The results stemming from the current study show that hydrogen bonds between the catalyst and the substrate can be an important factor to induce high rates of reactions and high selectivities. It remains to be seen if this concept can be used for other reactions.