Supramolecular orientation of substrates in the transition metal catalyzed asymmetric hydrogenation reaction
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Chapter 1

Supramolecular Approaches in Asymmetric Hydrogenation

- A General Introduction
1.1. The role of catalysis

Over the past centuries, our society has been engaged in enhancing its life condition by mean of new technologies to satisfy our needs. Unfortunately, most of these technologies are relying on sources that are finite and often associated to environmental problems. As a consequence, the transformation to a world based on sustainable principles is imperative and must be achieved rapidly.\(^1\) Among the fields of science and technology involved in this evolution, chemistry has a central role. Indeed, its industrial importance in the production of agrochemicals, pharmaceuticals, materials and energies attests of the crucial role of chemistry in the development of our society.\(^2\) The Haber-Bosch process is an example underlining the major influence of chemistry as this has triggered the population explosion of the 20\(^{th}\) century due to its impact on the human ability to grow food. Most of these chemical processes are relying on catalysis as a first choice strategy for the production of chemicals. The term “catalysis” was coined by Berzelius in 1838 and refers to a process involving the use of a catalyst. A catalyst is a substance that increases the rate of a reaction by lowering the energy of activation required by the reaction, without being consumed itself. Catalysis enables chemical transformations in a very efficient way with high atom efficiency, energy economy, with very high selectivity in some cases and, consequently, with low production of waste. For these reasons, catalysis plays a key role in the transition leading to a sustainable world. In order to fit to the aims of this transition, new chemical technologies must be based on the principles of green chemistry aiming for environmentally friendly methods of production.

This introduction chapter will focus on homogeneous asymmetric catalysis and more particularly on the rhodium-catalyzed hydrogenation reaction. New advances in this field have enabled the emergence of new combinatorial strategies leading to very efficient catalysts for given substrates. The mechanistic insights of the asymmetric hydrogenation (AH) reaction will be discussed in detail. Also, an overview on the different approaches for discovering new catalysts (combinatorial screening vs. rational design) will be given This chapter will also give a brief description of supramolecular systems and the concept of enzyme mimicry, highlighting the importance of these new approaches in the development of catalytic technologies.

This introduction chapter gives an overview on the rhodium-catalyzed asymmetric hydrogenation and supramolecular catalysis. As the literature on these topics is very broad, this chapter should not be considered as a review and more details on the different topics can be found in the references.
1.2. The rhodium-catalyzed asymmetric hydrogenation

The preparation of enantiomerically enriched compounds is a long standing challenge that started in the middle of the nineteenth century with the contribution of the French scientist Louis Pasteur. In 1849, Pasteur made the discovery that the crystals of sodium ammonium tartrate could be manually separated into two optically active salts. This method allowed him to isolate the first asymmetric molecule. Remarkably, Pasteur was also the first one to understand that preparative chemistry needs chiral help to create dissymmetric compounds. After that, multiple techniques of synthesis and purification have been developed to produce chiral compounds. Among these techniques, the enantioselective catalytic hydrogenation reaction has many advantages and has already found its place in the industry, especially in the production of fine chemicals. Although early work reported the asymmetric hydrogenation of azlactone using heterogeneous catalysts, the poor selectivity and moderate enantioselectivities obtained shows the limited use of heterogeneous catalysts for practical applications. Since then, homogeneous catalysts for hydrogenation, which demonstrate much higher performances, have quickly become a powerful technology in this field.

The first example of a rhodium-catalyzed hydrogenation was reported by Wilkinson in 1965. Wilkinson discovered that the complex Rh(PPh₃)Cl was able to reduce unsaturated compound with dihydrogen and under mild conditions. However, it was not until 1968, that Knowles and Horner independently reported the preparation of a chiral version of the Wilkinson catalyst and its successful use in the asymmetric hydrogenation of prochiral alkenes. Although the enantioselectivity induced was low (Figure 1, ligands 1 and 2), it demonstrated for the first time that chiral phosphines were able to induce asymmetry in the hydrogenation of alkenes. This discovery was followed by a series of reports that showed that the enantioselectivity of the reaction could be increased (up to 90%) by modification of chiral monodentate phosphine. At that time the synthesis of P-chiral phosphine ligands was tedious, hindering further development of chiral monodentate phosphorus ligands.
A major breakthrough was accomplished by Kagan in 1971 when he discovered that a chiral diphosphine (Figure 1, ligand 3) gave a more selective catalyst for the asymmetric hydrogenation of alkenes than their monodentate analogues. Kagan had reported a 70% ee, which was at that time the highest ee obtained in the hydrogenation of 2-acetamidocinnamic acid.\textsuperscript{14} The high selectivity observed was attributed to the conformational rigidity of the diphosphine ligand compare to the monodentate phosphines that display many degrees of freedom. Knowles believed that the chirality of the diphosphine should be at the phosphorus atoms instead of being on the backbone of the ligand.\textsuperscript{15} As such, Knowles created DIPAMP (4, Figure 1), a bidentate analogue of PAMP, affording the highest ee obtained at that time (96% ee) in the hydrogenation of Z-methyl 2-acetamidocinnamate.\textsuperscript{16} Shortly after this discovery, DIPAMP was used in a commercial process for the synthesis of L-DOPA, replacing CAMP in the hydrogenation reaction.\textsuperscript{17} Later, Noyori reported the most generally used bidentate ligand, BINAP (5, Figure 1) which is successfully applied in hydrogenation reactions and many others transition-metal catalyzed transformations.\textsuperscript{18} These achievements highlighted the potential of the production of chiral compounds using asymmetric reactions and have significantly stimulated the research field. In 2001, Knowles and Noyori were awarded the Nobel Prize in chemistry for their research on asymmetric hydrogenation.\textsuperscript{19}
Molecular chirality plays a very important role in science and technology. Single enantiomers of the same molecule can interact very differently in natural systems (in the case of pesticides) or our body (in the case of drugs) resulting in different biological activities with possible harmful effects when the wrong isomer is used. For instance, Thalidomide is a drug that has been used by pregnant women as a sedative in the 1950’s. Commercialized as a racemic drug, the drug quickly presented serious side effects resulting in multiple birth defects. Investigations revealed that the S-enantiomer of Thalidomide is highly teratogenic, highlighting the importance of the enantiomeric composition of pharmaceuticals. This dramatic clinical case brought awareness of relevance of the application of enantiopure drugs. As a consequence, the pharmaceutical industry has now a considerable interest for chiral synthesis. The requirement of producing single enantiomers drugs has initiated the so-called “chiral switches”. In the pharmaceutical industry, a chiral switch is the development of a single enantiomer drug from a previously marketed racemate. Currently, 40 to 50% of the drugs that have been registered contain a chiral center and is applied as single enantiomer. Since catalysis is an excellent tool for the synthesis of chiral compounds, it plays a very important role in the production of single enantiomer drugs. Consequently, various studies on the discovery of new efficient chiral catalysts leading to the description of many families of new bidentate ligands have been carried out both in industry and academia (Figure 2). It was already noted in an early stage that for each substrates a different catalyst gave the best results in terms of enantiomeric excess.

![Image of bidentate phosphorus ligands](image)

**Figure 2.** Bidentate phosphorus ligands used in the industry of asymmetric hydrogenation reaction.
Numerous bidentate chelating phosphine ligands have been evaluated and demonstrated to successfully hydrogenate many prochiral substrates, implying that chelation of the ligand is a requisite to reach high enantioselectivity.\textsuperscript{22} It was suggested that the chelation of the ligand confers a high rigidity to the chiral environment around metal center, leading to a high facial discrimination of the prochiral olefin.

\textbf{1.3. Understanding the rhodium-catalyzed asymmetric hydrogenation of alkenes}

Next to developing new stereoselective catalysts, there was a considerable interest to elucidate the mechanism of the asymmetric hydrogenation. Also, the initial empirical rules for predicting the sense of enantioselection gave inconsistent results, stimulating the investigation in the origin of enantioselection.\textsuperscript{23,24,25} Structural characterization of intermediates and the kinetics of the hydrogenation of alkenes by the Wilkinson catalyst has been performed by Osborn\textsuperscript{26} and Halpern.\textsuperscript{27} Importantly, the remarkable advance in analytical techniques in the 70’s allowed the collection of structural information on key intermediates, which lead to detailed mechanistic insight.

The first initial results on the mechanism of asymmetric hydrogenation by rhodium (I) complexes bearing chelating diphosphine ligands were described by Halpern\textsuperscript{28} and Brown\textsuperscript{29} In a series of famous papers, Halpern and Brown reported the characterization of several intermediates of the catalytic cycle by NMR spectroscopy and X-ray crystallography. They postulated that the reaction follows an “unsaturated” mechanism (Figure 3) in which the alkene coordinates to the rhodium complex prior to oxidative addition of the molecular hydrogen. After hydrogenation of the coordinating diene on precatalyst A (i.e. the activation of the catalyst), the prochiral substrate coordinates reversibly to the solvate complex B, affording the catalyst-substrate complex C. In the next step, a molecule of dihydrogen coordinates to the catalyst-substrate complex to form a sigma hydrogen species D that undergoes the oxidative addition of hydrogen leading to an octahedral rhodium(III) species E. The migratory insertion of hydride on the double bond of the coordinated alkene affords an alkyl-hydride species H. The reductive elimination releases the product from the complex. This last step makes the solvate complex B available to go through the next turnover of catalytic cycle.
Figure 3. Intermediates involved in the catalytic hydrogenation of methyl-2-actemidoacrylate. Top part of the cycle: unsaturated pathway (B-C-D-E-H). Bottom part of the cycle: dihydride pathway (B-F-G-E-H).

The measurement of the rate constants for each individual step of the reaction showed that the oxidative addition of hydrogen to the catalyst-substrate complex is the rate determining step of the reaction. This step is followed by the irreversible hydride migration, determining the absolute configuration of the product. Upon coordination of the double bond of the prochiral alkene to the \( C_2 \)-symmetric catalyst, two diastereomeric complexes were observed and quantified. These diastereoisomers, which are in equilibrium, have a different energy and therefore are present in different concentrations, generally referred to as the major and the minor species. The difference in those complexes is that the double bond is coordinated either by the \( Si \) face or by the \( Re \) face (Figure 4). The detailed structural analysis of the major catalyst-substrate complex and the comparison to the product of the reaction revealed that the latter is produced by the minor diastereoisomer. To explain this phenomenon, Halpern measured the rate constants of the oxidative addition steps independently for the major and the minor diastereoisomers leading to the conclusion that the minor diastereoisomer in solution was in fact the most reactive in the activation of hydrogen (and consequently, affording the major product of the reaction). This mechanism is known as the “Halpern mechanism” (“anti-lock-and-key”) and holds for many \( C_2 \)-symmetric catalysts. These results were later supported by a detailed computational study reported by Felgus and Landis. More recently, several catalytic systems have been described.
that follow an anti-Halpern mechanism ("lock-and-key") in which the major diastereoisomer in solution is the one that forms the dominant product.\(^\text{31}\)

![Chemical Diagram](image)

**Figure 4.** Halpern mechanism, the minor diastereoisomer is the most active and forms the majority of the product.

In the light of the recent findings of Imamoto and Gridnev, enough reasons have been given to reconsider the stereodiscriminating step and the principles of enantioselection in the Rh-catalyzed asymmetric hydrogenation.\(^\text{32}\) Several solvate dihydrides species have been observed at low temperature using their rhodium complexes based on electron rich ligands and further detailed structural analysis was possible by means of HD isotopically labelling experiments.\(^\text{33}\) Their observations suggested a “dihydride mechanism” (Figure 3), especially when electron rich ligands are used. In the dihydride mechanism, molecular hydrogen coordinates to the solvate complex B to form a sigma hydrogen solvate complex F that evolves through oxidative addition into a solvate dihydrido complex G. Subsequent coordination of the substrate to the solvate dihydride complex G finally forms a Rh (III) octahedral species E. This species is a common intermediate of both the dihydride and the unsaturated pathway. As for the unsaturated route, the octahedral species E undergoes hydride migration, fixing irreversibly the chirality of the product.
Figure 5. Mechanism of stereoselection in Rh-catalyzed asymmetric hydrogenation taking place in the stage of association of the double bond in the non-chelating dihydride complex I.

Gridnev and Imamoto also conclude that the reversibility of the early stages of the cycle and the numerous possibilities of cross-over between the two reaction pathways imply that the sense and order of enantioselection is determined in the very late stage of the mechanism. As can be seen in Figure 5, both pathways lead to two common intermediates in equilibrium, the non-chelating dihydride intermediate I and the dihydride intermediate H. In the non-chelating dihydride intermediate I, the double bond is not coordinating the rhodium center. Prior to the hydride insertion, the double bond must recoordinate to the rhodium center by finding a path that is energetically favored in order to form the dihydride intermediate H. However, this mechanism has been described for a particular class of ligands and specific substrates and, thus, the Halpern mechanism may still hold for other catalytic systems. New reaction mechanisms are continuously discovered and for each new catalytic system the mechanism should be studied and confirmed. The exact mechanism of the reaction strongly depends on the ligands used and as such should be investigated when new ligands are applied. For instance, the recent emergence of new families of monodentate phosphorus ligand building blocks show additional important features of the catalysts such as hydrogen bonding, which are crucial in the reaction mechanism. For new catalytic systems, with functionalized ligands, hydrogen bond interactions between the catalyst and the substrate can occur, greatly influencing the outcome of the reaction.
1.4. Monodentate ligands in asymmetric hydrogenation

The recent evaluation of monodentate BINOL-based ligands has revealed that high rigidity and chelation of the ligand is not essential to arrive at highly selective catalysts. Following early work by Kagan, three research groups demonstrated that monophosphites, monophosphonites and monophosphoramidites are excellent ligands to form highly selective rhodium-based catalysts. Moreover, the ease of synthesis of these ligands makes them more attractive than bidentate ligands (Figure 6).

These classes of ligands form complexes that induce high selectivity but not much is known about the origin of the remarkable stereoselectivity. The monodentate character of these ligands increases the conformation flexibility of the complexes that are formed during the reaction mechanism. However, it is now accepted that, in most cases, the active species is a RhL$_2$ species in which two monodentate ligands are coordinated to the rhodium center. So called non-linear effects (first described by Kagan) have also been observed in asymmetric hydrogenation and used to obtain information about the nature of the complexes that are active in the reaction.

The observation of a non-linear effect when using non-enantiomercially pure ligands indicates that two (or more) chiral ligands are involved in the active species of the reaction. If enantiomerically impure ligands are used, homo and hetero complexes can be formed and a non-linear effect is observed if the R/S complex is less active or insoluble. As an example, it has been reported that the use of enantiomerically impure METAMORPhos ligand can produce non-linear effects that were attributed to the formation of insoluble racemic dimer species (pre-formed by incubation of the reaction) leaving in solution the homochiral complexes that catalyze the reaction (Figure 7).

Only a few experimental and theoretical studies have been reported on the mechanism by which complexes based on monophosphorus ligands catalyze the hydrogenation reaction. Pringle reported that bulky substituents on the phosphorus atom of monophosphines are crucial as it results in limited flexibility of the catalyst by constraining the rotation of the ligands around the
axis phosphorus-metal, improving the enantioselectivity of the reaction.\textsuperscript{46} Reetz also published a detailed study that is in line with this observation.\textsuperscript{43}

Figure 7. left: non-linear effect curves for the hydrogenation of dimethylitaconate. Right: crystal structure of the insoluble self-sorted homochiral complex.

The ease of synthesis of monodentate chiral ligands (compared to chiral diphosphines) gives these ligands a high versatility as many chiral groups can be easily introduced on the phosphorus atom within a few synthetic steps. For this reason, these classes of ligands are of interest in high throughput screening and combinatorial strategies. Next to the use of pure monodentate ligands, combinatorial screening of catalysts based on mixtures of monodentate ligands has given excellent results and even resulted in the development of an industrial process.\textsuperscript{47} The application of mixtures of monodentate phosphorus ligands has been independently described by Reetz,\textsuperscript{48a-c} Feringa and de Vries.\textsuperscript{48f-h} In such an approach, two different monodentate ligands, \(L^a\) and \(L^b\), are mixed with one equivalent of metal precursor, potentially leading to the formation of three catalysts that are in equilibrium in solution: two homocomplexes (\(ML^aL^a\) and \(ML^bL^b\)) and one heterocomplex (\(ML^aL^b\)) (Figure 8).

Figure 8. The concept of the use of mixtures of monodentate ligands
Figure 9. Example of an industrial process based on mixed-monodentate ligands.

The strategy only works if the heterocomplex has a higher activity and selectivity than the homocomplexes as only then it will be the dominant species performing more selective catalysis. Needless to say that this method can only work with catalytic systems that involve a transition state in which (at least) two ligands are coordinating the rhodium center. Fine tuning of the ratio of the two ligands may shift the equilibrium in favor of the heterocomplex and one of the homocomplexes, which is important if one of the homocomplexes is active but not selective. It was also demonstrated that the use of chiral phosphoramidites with achiral phosphine could remarkably increase the activity and the selectivity of a reaction. For a defined library of monodentate ligands, combinatorial screening based on this strategy considerably increases the number of catalytic systems that can be assessed. This approach has led to the discovery of catalyst “hits” for the synthesis of chiral intermediates and some processes based on mixed-monodentate ligands have been implemented at ton-scale (Figure 9).

1.5. The art of catalyst design: combinatorial screening vs. rational design

In this section, an overview of the different methods for discovering new catalysts is given. When a new catalyst is required for a particular reaction, two approaches are possible that are very different from a conceptual point of view. The first one is based on an empirical approach consisting of a trial-and-error development guided by intuition and serendipity. The second one requires the analysis and the understanding of the catalytic system in order to improve this one by rational approach. In both approaches (empirical and rational), the development of a catalyst is usually based on the modification of selected parameters that can influence the catalytic reaction. These parameters are determined by the nature of the components forming the catalytic system: the metal, the ligands and the solvent. For a selected metal source, variation of the ligand is a first choice strategy since the different contributions of phosphorus ligands to the catalyst
have been widely studied and are relatively well understood. These properties include mainly electronic ligand parameters, steric demand, bite angle effects and molecular electrostatic potential.\(^{52}\) However, more recently, other features of the ligand are taken in account as supramolecular effects. A combined strategy implies the use of the results of initial (high throughput) experiments and further optimization of the catalysts based on rational design and mechanistic considerations (Figure 10).

By combinatorial and high throughput screening several efficient catalysts have been identified.\(^{53}\) Such approach requires the synthesis of large libraries of chiral ligands and, therefore, can be very tedious especially in the synthesis of bidentate ligands. The development of a catalyst for a given reaction has to be a fast process, especially in the fine chemical and pharmaceutical industry in which time to market is decisive. For this reason, libraries of (monodentate) phosphorus ligands (and in particular privileged ligands)\(^{54}\) are generally used for the discovery of new efficient catalysts as they allow the screening of large libraries of catalysts using a combinatorial approach. In this context, parallel screening methods are now frequently applied.\(^{55}\) Also, numerous methods have been developed for the fast screening of reactions including the use of automated high throughput devices and parallel analytical devices for mass spectrometry, gas chromatography and liquid chromatography.\(^{56}\)

The level of understanding of many reactions has considerably increased during the past decades allowing catalyst development strategies based on rational design.\(^{57}\) The rational design of new catalysts relies on the understanding of the key steps of the reaction in order to judiciously modify the catalyst which will act in favor of the desired performances. This approach requires an in-depth study of the reaction mechanism and can be very difficult, even impossible in some cases. However, when the identification of the determining step(s) is possible, one can improve,
for instance, the rate or the selectivity of a reaction. In a reaction, the identification of the crucial transition states (TS) of the reaction is, in theory, the most powerful approach to modify the performances of a catalytic system.\textsuperscript{58} The evident instability of these TS and the resulting difficulty in detecting these species make this experimental study extremely difficult. However, major advances in computational sciences in the last decades enable nowadays to study the transitions states of reactions. In some recent cases, mechanistic understanding achieved by combining experimental data with modern computational chemistry has enabled encouraging results in the prediction of the selectivity observed experimentally.\textsuperscript{59}

### 1.6. Supramolecular systems

The concept of supramolecular chemistry refers to molecular systems in which two or several entities associate reversibly by self-assembly through non-covalent interactions.\textsuperscript{60} These weak molecular interactions can be, for instance, electrostatic forces, dispersions forces or hydrogen bonds and enable the organized association of building blocks into larger systems. This field has been inspired by Nature as many events in biology involve supramolecular interactions and self-assembly. For catalysis, the source of inspiration has been enzymes. As enzymes can catalyze reactions rapidly and in a very specific way, chemists tried to develop supramolecular systems that would mimic their catalytic principles.\textsuperscript{61} Reproducing the active site of an enzyme is currently impossible due to the complexity of such functionalized and dynamic structures, but the synthesis of systems that mimic certain principles is well documented.\textsuperscript{62} Supramolecular catalysis describes catalytic systems in which the activity and the selectivity are influenced by non-covalent interactions.\textsuperscript{63} Currently, the supramolecular tools can be divided into: 1) host-guest catalysis 2) catalysis in confined spaces 3) supramolecular bidentate ligands and 4) supramolecular substrate preorganization. Several of these strategies for supramolecular catalysis will be described in this section.

#### 1.6.1. Host-guest catalysis

The exceptional activity and selectivity of enzymes lies in several features among which molecular recognition plays an important role. The molecular complementarity between the host and the guest is driven by binding interactions (hydrophobic forces, ionic interactions, H-bonding) and have been a source of inspiration for chemists in the design of new catalytic systems. In this perspective, several groups have reported the use of host-guest systems in the design of catalytic systems. The first examples of host-guest catalysis were using crown ethers and cryptands as receptors that were functionalized with a catalytically active entity able to react with a complexed substrate.\textsuperscript{64} Other macrocycles have been used in host-guest catalysis such as
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cyclodextrins and cucurbituril. A typical example is the system developed by Mock et al. who used cucurbituril for the 1,3-dipolar cycloaddition reaction (Figure 11). As the cavity inside the cucurbituril macrocycle is large enough to receive aromatic five membered rings, this host was used as a nanoreactor catalyzing the reaction of 1,3-cycloaddition between propargylammonium and azidoethylammonium into a triazole adduct. Electrostatic interactions between the ammonium groups of the substrates and the urea group of the host ideally positioned the substrates in the cavity of the cucurbituril. The reaction catalyzed by the cucurbituril receptor is 55000 times fold faster than the uncatalyzed reaction. Also, only the 1,4-disubstituted product was formed since a 1:1 mixture of the two isomers triazole adducts and were formed under uncatalyzed conditions.

![Figure 11](image)

Figure 11. 1,3 dipolar cycloaddition between propargylammonium and azidoethylammonium catalyzed by cucurbit[6]uril.

The cucurbituril motif was used successfully in other reactions including the Diels-Alder reaction and the [2+2] photocycloaddition. The previous examples point out the efficiency of covalently assembled host as catalyst for certain reactions. However, as the structures of the desired products become more complex, the synthesis of covalent nanoreactors becomes more tedious and other adaptive synthetic strategies have to be applied.

1.6.2. Catalysis in confined spaces

Supramolecular chemistry offers ideal tools for the formation of non-covalent molecular structures. As hydrogen bonds and metal-ligand interactions possess valuable properties
(directionality of H-bonding and strength in the case of metal-ligand interactions) in the formation of non-covalently built structures, new capsules and cages were reported using multicomponent self-assembly of complementary building blocks. Encapsulation effects and catalysis in cages have been largely studied\textsuperscript{69} and several groups have reported the use of molecular cages that impose structural constraint as driving force to perform highly selective organocatalysis\textsuperscript{70} and transition metal catalysis.\textsuperscript{71,77} Also, new catalytic properties based on structural constraints emerge from the use of supramolecular cages. In an interesting related approach, Reek et al. have demonstrated that nanocapsules could serve as a micro-reactor in the formation of C-O and C-C bond-forming cyclisation reaction by increasing the local concentration of the gold catalyst.\textsuperscript{72} Based on nanosphere (a strategy previously developed by Fujita et al.),\textsuperscript{73} a self-assembled Pd\textsubscript{12}L\textsubscript{24} that was formed by assembly from two ditopic building blocks A and B, the local gold concentration could be tuned from 0.01M to 1M. Building block A is functionalized with a [R\textsubscript{3}PAuCl] (with R=aryl) unit whereas B just bears an acetate group. By mixing A and B in different ratios, nanospheres containing different concentration of gold catalyst could be formed, enabling the tuning of the local gold concentration. The hydroalkoxylation reaction was explored, revealing unprecedented activity of the gold catalyst due to unusual high local concentration (Figure 12).

**Figure 12.** a) building blocks A and B for the formation of nanosphere Pd\textsubscript{12}L\textsubscript{24} b) estimation of the local concentration for different ratio of A and B c) hydroalkoxylation of allenol into cyclic compound.
1.6.3 Supramolecular bidentate ligands

Recently, the synthesis of bidentate ligands using supramolecular ligands has been reported. In this approach, ligands building blocks are assembled through supramolecular interactions to form supramolecular bidentate ligands. The formation of supramolecular bidentate ligands can be achieved through different strategies. When using self-complementary binding motifs, homobidentate ligands can be formed by self-assembly. The use of two different building blocks allows the formation of heterobidentate ligands, increasing the diversity of the ligand library. Also, supramolecular bidentate ligands can be formed by the use of a template (Figure 13).

The strong, but dynamic, binding of pyridine groups to zinc-porphyrin building blocks make these building blocks interesting for supramolecular chemistry. Our group reported the use of metal-porphyrin-ligand interactions in the formation of supramolecular catalysts. We described the formation of rhodium complexes bearing phosphine ligands based on tripyridylphosphine-tertaphenylporphyrin complexes. Studies showed that the active catalyst is a mono-phosphine rhodium species in which the transition metal center is encapsulated in the ligand-porphyrin complex. This catalyst was evaluated in the hydroformylation of 1-octene, leading to a 10 fold increase in activity (compared to the non-encapsulated species) and an unusual preference for the branched aldehyde (Figure 14a).
Pyridine-zinc (II) porphyrin interactions have also been used in the formation of bidentate phosphite-phosphine ligands. Reek et al. reported the synthesis of SUPRAPhos in which a phosphite ligand functionalized with a zinc(II)-porphyrin moiety forms supramolecular bidentate ligand in combination with a pyridylphosphine. This new series of catalysts are very selective in the Pd-catalyzed asymmetric allylic alkylation, but also in the rhodium-catalyzed asymmetric hydrogenation of enamides substrates, and the kinetic resolution of racemic cyclohexenyl acetate. Several supramolecular bidentate ligands based on phosphoramidite functionalized with pyridyl moiety and zinc(II)-template (Figure 14c) were also reported. These ligands were applied in the asymmetric Rh-catalyzed hydroformylation of styrene.

Ionic interactions have been used by van Leeuwen et al. for the formation of supramolecular bidentate ligands. The ion-exchange reaction between a monosulfonated triphenylphosphine sodium salt and 3-(diphenylphosphanyl) aniline hydrochloride lead to the formation of a ion pair between the two ligands (Figure 15a). Cis and trans-complexes could be obtained by coordination of the supramolecular bidentate ligand with different transition metals (Pt, Pd and Rh) in an almost quantitative way (97% heterocomplex). The system is, however, strongly dependent on the solvent (polar, protic media), the concentrations and the experimental protocol. Similar ion-pair based ligands were explored by Gennari et al. and applied in the rhodium-catalyzed asymmetric hydrogenation of methyl-2-acetamidoacrylate (Figure 15b).
Hydrogen bonds are commonly applied in supramolecular chemistry. Several groups have reported the use of single (or multiple) hydrogen bonding for the formation of supramolecular bidentate ligands. In 2003, Breit et al. described for the first time the construction of bidentate ligands formed by self-assembly through hydrogen bonds. This system is based on the symmetric dimerization of 2-hydroxypyridine in aprotic solvent (structure 8, Figure 16). The tautomerisation of 2-hydroxypyridine into 2-pyridone (equilibrium 9, Figure 16) leads to the formation of an unsymmetrical dimer, which is less stable than the symmetric dimer (+4.8 kcal/mol). However, the phosphine functionalized analogue can coordinate to a metal center, pre-organizing the system for the formation of the unsymmetrical dimer, leading to the formation of a supramolecular bidentate ligand 10 (Figure 16).

The diversity of the available hydrogen bond donor and acceptor groups makes this strategy very appealing. Love and Reek described the use of urea-functionalized phosphines and phosphites as building blocks that can form supramolecular complexes by self-assembly. This strategy is very powerful and is now used commercially.

**Figure 15.** Ion-pair based bidentate ligands: a) van Leeuwen phosphine based ligand b) Gennari binol based ligand

**Figure 16.** First bidentate ligand formed by hydrogen bonding

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1.6.4 **Supramolecular substrate preorganization**

Another feature found in natural enzymes and a very attractive tool for catalysis is the preorganization of substrate using supramolecular interactions. The principle of this strategy is based on the use of secondary interactions between the catalyst and the substrate in order to give a precise orientation to the substrate and reducing its motions. These secondary interactions (H-bonding, ionic interactions) help in controlling the reactivity and can influence the selectivity and the activity of the reaction. In classic catalysis, the substrate is generally bound to the metal center via coordination of a directing group on the substrate in proximity of the reactive functionality. Beside the main directing group, other functionalities can be introduce temporarily or permanently on the substrate and able to interact with various functional groups on the catalyst. When judiciously positioned, these interactions can modify the geometry of the catalyst-substrate adduct and have an important effect on the selectivity and the activity of the reaction. This strategy has been used by Breslow et al. that reported the use manganese(III)-porphyrin functionalized with cyclodextrins 11 in the stereoselective hydroxylation of steroide derivatives (Figure 17).

![Figure 17](image.png)

**Figure 17.** Breslow’s supramolecular catalytic system for the selective hydroxylation of steroid derivatives catalyzed by 11.

The hydrophobic groups on the steroid derivative bind to the cyclodextrins (β groups, structure 11, Figure 17) and enable the substrate to be accurately positioned over the manganese center. The substrate being preorganized, only one CH group is hydroxylated with a regioselectivity over 90%.

Another interesting case of such supramolecular approach has been reported by Reek et al. in which an achiral bisphosphine ligand, DIMPPhos, acts as a receptor that binds strongly with chiral-cofactors, bringing the chiral information close to the substrate and allowing excellent selectivity in the hydrogenation of acetamido acrylate derivatives.\(^8^7\) It is suggested that the
cofactor plays an important role in the preorganization of the substrate by setting a hydrogen bond between a hydrogen bond acceptor group of the cofactor and a hydrogen bond donor on the substrate (Figure 18).

**Figure 18.** Molecular modelling of the structure of the rhodium-DIMPhos complex (violet framework) bearing a cofactor in the DIMPocket (turquoise) interacting via H-bonding with the NH group of methyl 2-acetamidoacrylate (grey) coordinated to the rhodium center (red sphere).

Complex 12 (Figure 19) has recently been introduced as a new supramolecular catalyst bearing a heterobidentate ligand formed by self-assembly through a single hydrogen bond between the NH group of a phosphoramidite and the urea carbonyl of a urea-functionalized phosphine (Figure 19). This complex affords the highest enantiomeric excess (>99% ee) reported up to now for the hydrogenation of methyl 2-hydroxymethacrylate, a precursor to the so-called “roche ester”, an important intermediate in the preparation of several biologically active compounds.

**Figure 19.** Formation of supramolecular complex 12 through a single hydrogen bond.
Based on control experiments, it was proposed that the high selectivity was a result of a hydrogen bond between the substrate and the functional group of the ligand. The role of this hydrogen bond, however, is unclear at this stage. Interestingly, there are a couple of articles reporting very high enantioselectivities in asymmetric hydrogenation that also proposed the involvement of hydrogen bonds between the substrate and the ligand. About the design of DIPAMP, one of the first successful ligands in asymmetric hydrogenation, Knowles stated: "Our first real variation was to introduce the o-anysyl group. This should provide some steric hindrance as well as a possible hydrogen bond site".

1.7 Aim and outline of the thesis

The emergence of supramolecular ligands for the asymmetric hydrogenation reaction requires the deeper understanding of these systems. In this thesis, we report on a detailed study of the supramolecular rhodium catalyst displayed in Figure 19 and the second generation thereof.

In chapter 2, we report an in-depth mechanistic study of this supramolecular system by means of different analytical techniques (characterization of intermediates, kinetic analysis) in order to highlight and understand the role of hydrogen bonds during the reaction.

In chapter 3, the mechanism of the reaction has been studied using computational chemistry methods. A DFT profile of the reaction has been calculated, by considering all the different pathways that can occur (unsaturated pathway, dihydride pathway and semi-hydride pathway).

In chapter 4, a new series of supramolecular ligands have been designed based on our previous mechanistic study. We synthesized a series of bisphosphine monoxide ligands and successfully used them in the formation of new supramolecular bidentate ligands. These catalysts gave very high selectivity in the asymmetric hydrogenation of functionalized substrates bearing a hydroxyl group. Also, kinetic studies revealed that some of these complexes gave higher rates than the first generation supramolecular catalyst while keeping excellent selectivity.

In chapter 5, we have extended this supramolecular strategy to form iridium complexes for the asymmetric hydrogenation of functionalized and non-functionalized alkenes. These complexes have been characterized by spectroscopic and crystallographic methods and evaluated in the asymmetric hydrogenation of functionalized and non-functionalized alkenes.

1.8 References

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19 The same year, Sharpless received the Nobel Prize in chemistry for his research on stereoselective reactions.
Chapter 1

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