Summary

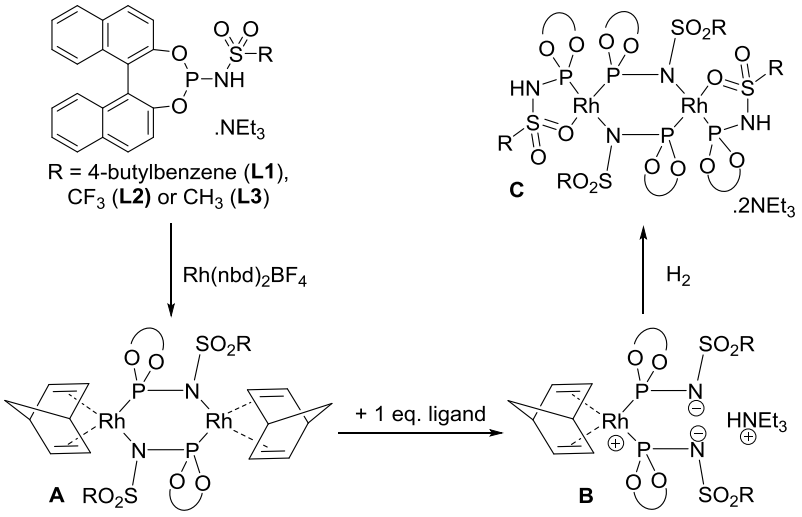
The manufacturing of most man-made goods involves the use of chemicals or chemical processes. Approximately 80 to 90% of all industrial chemical transformations include at least one catalytic step, as catalysis allows the reduction of waste and reduces the energy consumption. Driven by economic and environmental concerns, academic and industrial chemists are making constant efforts to develop ever-more efficient catalytic systems. Enzymes, catalysts found in living organisms, are great sources of inspiration for scientists as they are able to catalyze chemical reactions in a clean way at ambient temperature and pressure, using directly or indirectly solar energy. Many efforts have been devoted to the mimic of certain aspects of enzyme catalyzed transformations. For example, catalysis in confined spaces, substrate pre-orientation or redox non-innocent ligands are successful approaches derived from the imitation of enzymes. Recently, Complexity has emerged as a new subject for scientists. By understanding how the relationships between components of a given system give rise to a collective behaviour, it becomes possible to design new Complex system with useful features. Contrary to "traditional" synthetic catalysts, natural enzymes are not isolated molecules, but they are elements of Complex Systems, namely, living organisms. Each part of a biologic Complex System has a well-defined role and interacts with other parts in a well-defined way. The challenge for synthetic chemists is to mimic this high level of organization, in order to achieve the emergence of new properties or of new catalytic reactions that would be otherwise impossible, or to improve known catalyzed transformation.

Chapter 1 gives an overview of the different interpretations which can be given to "synthetic mimics of enzymes": from duplicates, to structural and functional imitations, to the design of artificial Complex Catalytic Systems.

The research described in this thesis deals with several Nature-inspired catalytic systems, and focuses on the understanding of the mechanisms and on the identification of interactions between the different components of those systems.

In **Chapter 2**, we described in detail a catalytic system for asymmetric hydrogenation based on racemic and scalemic METAMORPhos ligands, which form various complexes: mononuclear complexes [Rh**L**$_2$(nbd)] and dinuclear complexes [Rh$_2$**L**$_2$(nbd)$_2$] and [Rh$_2$**L**$_4$].

The coordination studies of these complexes, under various conditions, revealed self-sorting of the ligands at dinuclear complexes [Rh$_2$**L**$_2$(nbd)$_2$] and [Rh$_2$**L**$_4$], leading to homochiral complexes. In contrast, such behaviour is not observed for mononuclear complexes [Rh**L**$_2$(nbd)]. We confirmed the nature of each species by X-ray crystallography. Unusual lone-pair-π interactions between neighbouring binaphthol (BINOL) moieties were observed in the crystal structures of [Rh$_2$(**L2**)$_4$]. Together with steric effects, these supramolecular interactions seem to contribute to the observed self-sorting phenomenon. Furthermore, experimental work and computational modelling suggest that the self-sorting of the dinuclear complexes is thermodynamically driven.



Scheme 1. Coordination of the METAMORPhos ligands to rhodium in three steps to form the final dinuclear complex.

The *racemate* of the self-sorted homochiral complex [Rh_2(**L2**)$_4$] was found to be poorly soluble. This property leads to a very strong positive non-linear effect (NLE) in asymmetric hydrogenation, with a high ee obtained for the product while the ligand is present in low enantiopurity (e.g. 90% of ee of product at 40% ee of the ligand). This is, however, only observed when the substrate is introduced after an incubation time during which the self-sorting occurs. If the substrates are added from the beginning of the experiment, a (moderate) negative NLE is obtained. This behaviour shows that non-self-sorted monomeric intermediate complexes, which form before the thermodynamic equilibrium of the ligand-metal system is reached, are also catalytically active. Besides this, the substrate influences the solubility of [Rh_2(**L2**)$_4$], which has consequences on the nonlinear effects observed: the dimethyl itaconate substrate lowers the solubility of the racemate, increasing the strength of the positive NLE, while methyl 2-acetamido acrylate has the reverse effect. Since the substrate has an influence on its own catalyst, this behaviour constitutes a feedback loop.

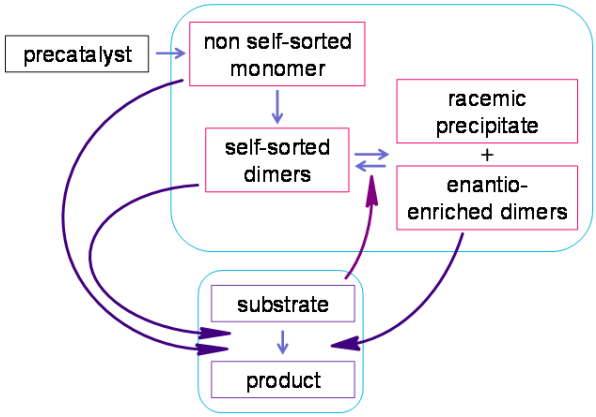


Figure 1. Schematic representation of the system studied in Chapter 2.

In **Chapter 3**, the influence of its ionic environment on the performance of a dianionic binuclear Rh complex [Rh_2(**L2**)$_4$] is reported. The counterion of the anionic METAMORPhos ligand **1** can be modified without changing its coordination mode. Importantly, the catalytic activity of the resulting complexes is highly dependent on the protic (or aprotic) character of

the cations in solution. When aprotic counterions like PPh_4^+ are used, the TOF decreases significantly, while the reaction is significantly faster when protic ammonium salts are used as counterions. The highest rates were obtained when an excess of mildly protic ammonium salt is added to the reaction mixture. When more acidic lutidinium or anilinium salts are used, the complex is deactivated by irreversible protonation of the metals as evidenced by NMR spectroscopy. DFT calculations suggest that temporary protonation of the chelating ligands of the dimer by mild acids moderately affects the energy of the transition states and significantly destabilizes the last catalytic intermediate.

Since protic cations enhance the properties of the catalyst and change the outcome of the reaction by interacting with a moiety different from the active site of the complex, they follow the definition of an effector, a molecule that triggers allosteric response of enzymes. With this approach, the difficult tetra-substituted enamide **2** could be quantitatively hydrogenated for the first time, with 99% enantiomeric excess.

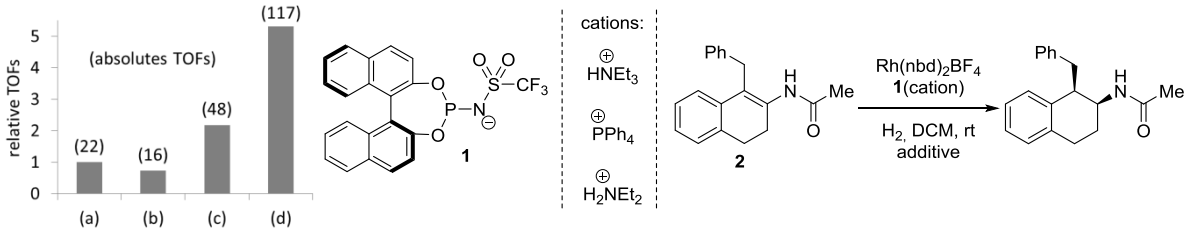


Figure 2. Relative and absolute Turnover Frequencies (in $mol_{substrate}/mol_{Rh}/h$) for the hydrogenation reaction (depicted on the right) with (a) $HNEt_3$.**1** as a ligand and no additive, (b) PPh_4.**1** as a ligand and no additive, (c) $HNEt_3$.**1** as a ligand and $HNEt_3.BF_4$ as additive and (d) $HNEt_3$.**1** as a ligand and $H_2NEt_2.BF_4$ as additive.

In **Chapter 4**, a new approach for combinatorial catalysis has been proposed. Anionic METAMORPhos ligands and neutral amino-acid based ligands were used separately and as a mixture for rhodium catalyzed asymmetric hydrogenation of eight industrially relevant substrates. Spectroscopic studies show that under catalytic conditions, the mononuclear heterocombination is the main complex in solution when both anionic and neutral ligands have the same chirality. When the neutral ligand and the anionic ligand bear opposite chirality on the phosphorus atom, monomeric and dimeric heterocomplexes could be detected by NMR and mass spectrometry.

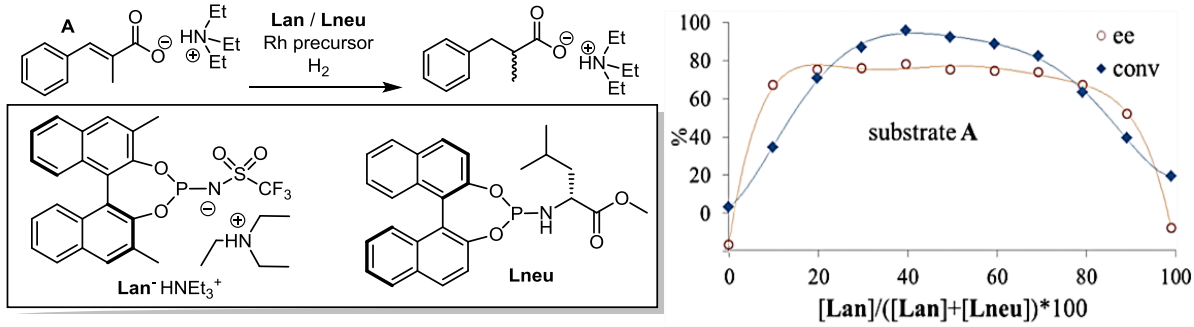
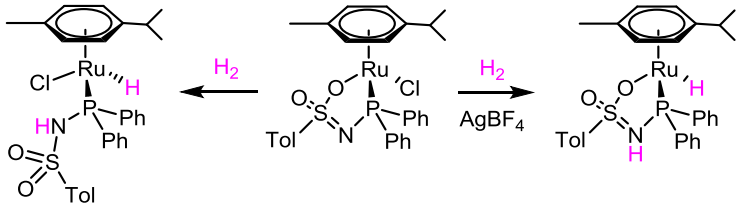


Figure 3. Hydrogenation of olefins using various ratio of anionic and neutral ligands.

For the majority of the substrates evaluated, higher enantioselectivities were obtained with complexes resulting from the heterocombination of an anionic and a neutral ligand compared to respective homocombinations. Higher TON and enantioselectivities could be easily

obtained by focussed ligand optimization. The superior properties of the hetero system are highlighted by its robustness: significant divergence from a 1:1 ratio between the ligands does not lower the selectivity of the catalyst. As our approach allows the easy preparation of highly diverse sets of catalysts - monometallic or bimetallic, anionic, cationic or neutral - it establishes a new dimension in the search for the best catalysts.

In **Chapter 5**, the synthetic scope of sulfonamidophosphorus ligands is expanded and design principles for the selective formation of particular tautomers, ion pairs, or double condensation products are elucidated. These ligands have been introduced in the coordination sphere of the ruthenium metal for the first time, thereby enabling their coordination as monoanionic P,O chelates. Depending on the ruthenium precursor employed, halide-bridged dinuclear species or cymene-derived piano-stool complexes are isolated and characterized. The METAMORPhos framework is shown to play a role in the heterolytic cleavage of H_2, since piano-stool complexes can be converted into neutral monohydrides upon exposure to hydrogen. Substitution chemistry with cymene complexes has also been examined, thereby giving rise to tetrakis(acetonitrile) adducts. Solid-state structures of four ruthenium-METAMORPhos complexes establish the precise bonding mode of the inorganic PNSO framework. This study enables the development of further catalytic systems which could take advantage of the proton-responsive nature of the METAMORPhos ligand.



Scheme 2. Heterolytic activation of H_2 by a piano-stool complex of METAMORPhos.

The contributions reported in this thesis represent further steps towards the mimicking of some aspects of natural catalytic systems, especially their Complex behaviors. This work shows that by embracing the notion of Complexity, new approaches can be defined which results exceed those of traditional approaches. As the subject of Complexity barely overlaps with chemistry yet, we believe this thesis will contribute to the establishment of a better defined conceptual framework for Complexity in catalysis. It is anticipated that in the future, a bigger importance will be given to the understanding and the design of increasingly Complex synthetic catalytic systems enabling cleaner technologies for a sustainable industry.