Summary

Transition metal catalysis is a powerful enabling technology for the sustainable preparation of chemical compounds, given the desired selectivity can be reached. The selectivity (together with the activity and stability) of a transition metal catalyst is highly dependent on the ligands coordinated to the catalytic metal center. Despite insights in various reaction mechanisms and good understanding of the role of the ligands in these reactions, design of a new selective catalyst for a reaction of interest is still highly challenging. Therefore, catalyst development usually involves the classic knowledge-supported trial-and-error screening of putative catalysts. This approach provided many successes, but is not optimal as selectivity issues for many reactions cannot be solved in this way. Therefore, complementary approaches that allow for a more rational catalyst design for those challenging reactions would be of high value.

Supramolecular chemistry uses reversible relatively weak interactions to create higher-order chemical architectures by a self-assembly of a number of molecular building blocks. As we discuss in Chapter 1, supramolecular chemistry provides new various tools for catalyst development. Among the described different strategies, supramolecular substrate preorganization via reversible substrate-ligand interactions is of high potential for controlling the selectivity for challenging reaction. In principle, rational design of catalyst system that includes reversible interactions to control the position of a substrate near the metal center is possible. In this thesis we demonstrate the power of this concept and we reveal its mechanistic aspects, using the industrially relevant hydroformylation of alkenes as a key reaction.

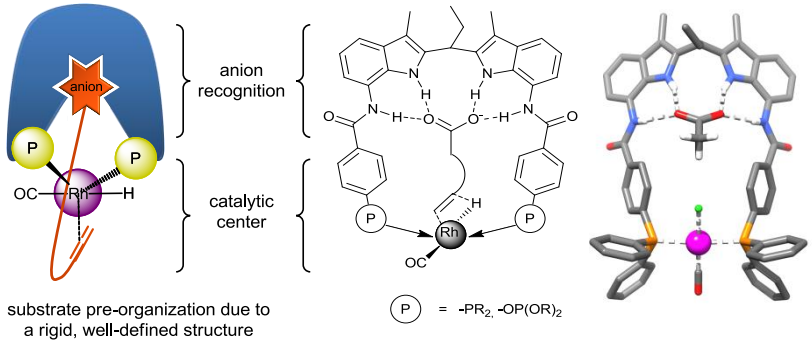
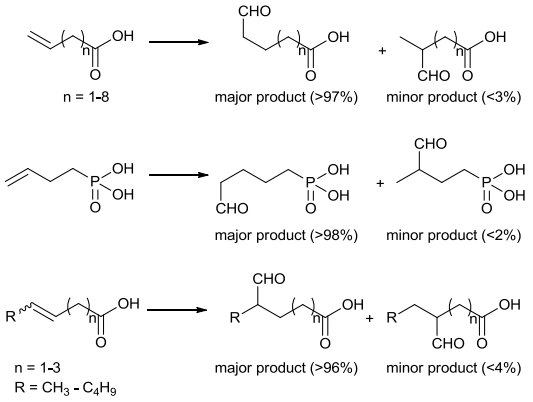


Figure 1. General concept of anionic substrate preorganization by a Rh catalyst that bears a ligand furnished with an anion-binding pocket (left), schematic structure of DIMPhos ligands (middle), and a X-ray structure of the supramolecular complex of acetate anion binding to a Rh-DIMPhos complex (right).

In Chapter 2, we introduce a new class of bifunctional ligands, coined DIMPhos, which consist of two phosphorus atoms for coordination to a catalytic metal center and a specific recognition site – DIM pocket – for binding to a carboxylate functional group of a substrate (Figure 1). Coordination studies show that these ligands bind to a rhodium center in a bidentate fashion. Experiments under hydroformylation conditions confirm the formation of the mononuclear hydridobiscarbonyl rhodium complexes that are generally assumed to be active in hydroformylation. The metal complexes formed still strongly bind the anionic species in the binding site of the ligand, without affecting the metal coordination sphere. These bifunctional properties of DIMPhos are further demonstrated by the crystal structure of the rhodium complex with acetate anion bound in the binding site of the ligand (Figure 1). The catalytic studies demonstrate that

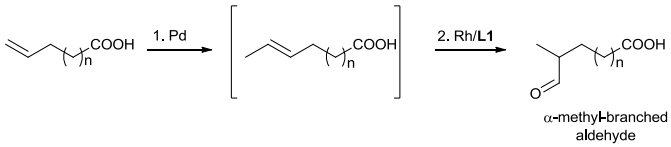
substrate preorganization by binding in the DIM pocket of the ligand results in unprecedented selectivities in hydroformylation of terminal alkenes functionalized with an anionic group (Scheme 1). Remarkably, the selectivity controlling anionic group can be even ten bonds away from the reactive double bond, demonstrating the potential of this supramolecular approach. This illustrates the first example of wide-ranging remote control of catalyst selectivity by secondary substrate-ligand interactions.



Scheme 1. Highly selective hydroformylation of terminal and internal alkenes catalyzed by Rh-DIMPhos catalysts.

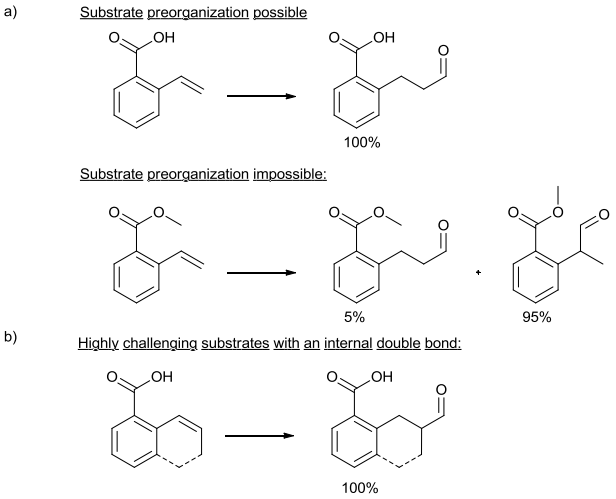
In Chapter 3, we show that extending the class of DIMPhos ligands also allows for the precise control of the selectivity in the hydroformylation of challenging internal alkenes functionalized with a carboxyl group (Scheme 1). Detailed experimental and computational studies reveal the precise operational mode of the catalyst. DFT studies on the decisive intermediates reveal that the anion binding in the DIM pocket restricts the rotational freedom of the reactive double bound. As a consequence, the pathway to the undesired product is strongly hindered, whereas that for the desired product is lowered in energy. Detailed kinetic studies, together with the in situ spectroscopic measurements and isotope-labeling studies, support this mode of operation and reveal that these supramolecular systems follow enzymatic-type Michaelis–Menten kinetics, with competitive product inhibition. This indicates that the substrate molecule is first bound to the DIM pocket of the catalyst, which is followed by the catalytic reaction at the metal center.

In Chapter 4, we apply a new cascade isomerization-hydroformylation reaction to convert linear alkenes to branched aldehydes. We show that a palladium isomerization catalyst can be combined with a DIMPhos-based rhodium catalyst in a two step one pot process, converting terminal olefins to α-methyl-branched aldehydes with unprecedented selectivities (Scheme 2). In view of the increasing interest to use bio-based feed stock to produce chemicals, this transformation is important as it allows to convert fatty acid-based materials to valuable intermediates for fine chemical synthesis.

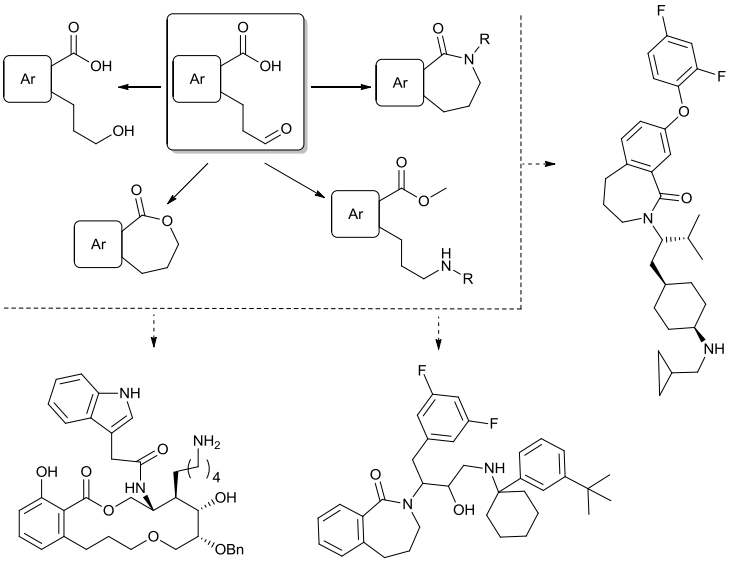


Scheme 2. Selective isomerization-hydroformylation sequence for terminal olefins toward valuable α-methyl-branched aldehydes catalyzed by a Pd-PPh_3 – Rh-DIMPhos catalyst combination.

To demonstrate the full potential of the catalytic system, we show in Chapter 5 that the precise supramolecular substrate preorganization for vinyl arene derivatives allows for the unprecedented full reversal of selectivity from the typical α-aldehyde to the otherwise unfavored β-aldehyde product (Scheme 3a). The preorganization of the substrate also results in very high activities (TOF > 6000 mol mol^{-1} h^{-1}) and the catalyst proves to be selective for a wide scope of substrates, including the most challenging substrates with an internal double bond (Scheme 3b). The substrate scope spans also to the allyl analogues. It is worth noting that these classes of compounds represent important intermediates for the fine-chemical industry. Therefore, this catalytic system that operates under mild reaction conditions opens up new pathways to current industrially relevant synthetic schemes of bioactive compounds. Towards this goal, we demonstrate several easy post-modification steps of the acid-aldehyde intermediate (Scheme 4).



Scheme 3. (a) Full reversal of regioselectivity in hydroformylation of vinyl arene derivatives controlled by supramolecular substrate preorganization, and (b) unprecedented selectivities in the hydroformylation of challenging β-substituted vinyl arenes catalyzed by the Rh-DIMPhos catalysts.



Scheme 4. Potential application for the developed β-regioselective hydroformylation of vinyl arene derivatives: easy transformation of the aldehyde products into other valuable building blocks for synthesis of bio-relevant compounds.

In Chapter 6, we extend the approach to related classes of substrates and we provide mechanistic insight by combining kinetic studies with DFT calculations and spectroscopic studies. Kinetic studies and *in situ* IR spectroscopy on the most active and selective DIMPhos phosphite-based catalyst reveal that the active species are involved in complex equilibria with other dormant (reversibly inactivated) species. In principle, the kinetics involve competitive inhibition by the product, explained by competitive binding in the DIM pocket. In addition, substrate inhibition is observed, which is explained by reversible coordination of the carboxylate to the active metal center leading to a dormant state, which involve both the substrate and the product. Overall, this results in the (expected) product and the (unusual) substrate inhibition effects as is clear from the reaction progress analysis of the kinetic data. Next to these effects, the catalyst is also slowly and irreversibly deactivated in a different reaction. Importantly, despite these inhibition effects, the catalyst is highly active (TOF > 6000 mol $mol^{-1}h^{-1}$) and performs many turnovers before final irreversible deactivation has occurred (TON up to 44 000), which is crucial for commercial applications.

Aside from supramolecular substrate preorganization, the recognition site of DIMPhos ligands has also been used to control catalyst properties by binding cofactors in the pocket, the principles of which are discussed in Chapter 7 (Figure 2). We show that an achiral catalyst with a chiral cofactor noncovalently bound in the DIM pocket gives high enantioselectivities (e.e.'s up to 99%) in the hydrogenation reaction of alkenes. Remarkably, in a catalysis experiment with a mixture of 12 cofactors in which they compete for the binding site, still high (85%) ee was obtained, indicating that the cofactor that binds the strongest also induces the highest ee, thus dominates the reaction. This feature provides a basis for smart screening strategies based on deconvolution, which allow to identify the best catalyst with a limited number of experiments. Interestingly, from DFT calculations and control experiments it is clear that additional

hydrogen bonding between the cofactor and the substrate that is bound to the metal is possible, which is proposed to be important for both the selection in the competition experiment as well as efficient transfer of chiral information from the cofactor to the metal complex.

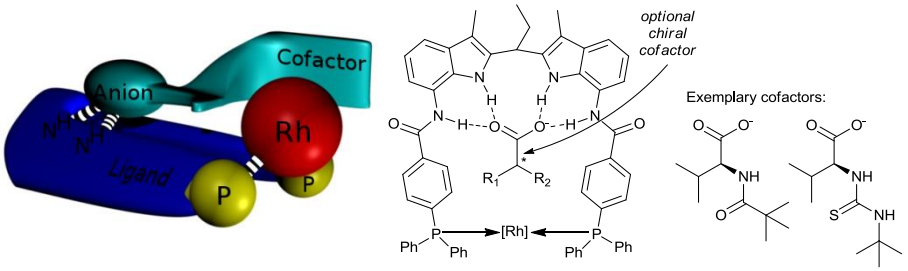


Figure 2. General concept of cofactor-controlled catalysis using a catalyst that bears a ligand furnished with an anion-binding pocket (left); and a chemical model of Rh-DIMPhos complex binding a chirality inducing cofactor (right).

Considering that many transition metal catalyzed processes involve elementary steps similar to those in the reactions studied in this thesis, the supramolecular methodologies outlined here should be more generally applicable. It is therefore anticipated that this work will have an impact on the future development of selective transformations in chemical catalysis. This should help to bring the field closer to the goal of fully sustainable synthesis. Furthermore, the first example of cofactor-steered catalysis, presented in this thesis, opens new attractive opportunities to control the selectivity of a transition metal catalyst. It is expected that this concept, together with smart screening methodologies, will lead to more efficient catalyst development for practical applications.