Summary

In this thesis I describe my contributions to the field of hydroformylation catalysis. I have used computational techniques to understand certain phenomena observed with such catalysts. Using these insights, I have developed novel supramolecular catalysts. Furthermore I have applied these catalysts as well as existing catalysts to control the regioselectivity of internal and terminal alkenes, demonstrating the utility of these catalysts.

Transition metal catalysis is a pivotal tool for the preparation of chemical compounds in a sustainable fashion. Immense progress in the field has been achieved in the past decades, and the number of active catalysts that have been reported is enormous. In the development of new catalysts, it is crucial to also control the selectivity and the activity of the reaction. An intensively investigated reaction in the field of homogeneous catalysis is the hydroformylation reaction and many industrial applications are known in the bulk chemical as well as the fine chemical industry. In this reaction, an alkene is reacted with a syngas mixture (H_2:CO) in the presence of a transition metal catalyst to produce aldehyde products. Currently, many selectivity issues have not been resolved yet for this reaction, and doing so expands the scope of this reaction.

In **chapter 1** I will explain the current challenges in the field of hydroformylation catalysis. Traditionally, the selectivity is controlled by the ligand that is coordinated to the active metal center. In the past 20 years, supramolecular strategies have been introduced successfully in the hydroformylation reaction and this has allowed for novel ways to control the regioselectivity that would be impossible using the traditional transition metal catalysts.

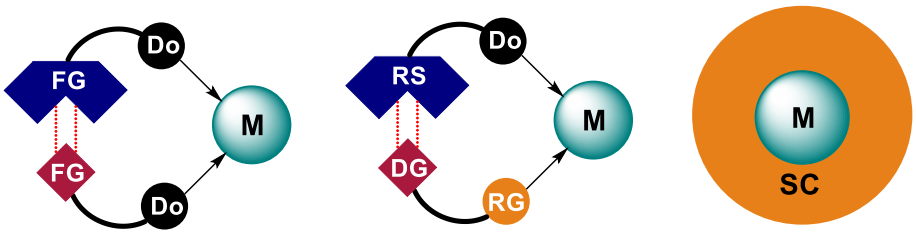


Figure 1 Supramolecular strategies commonly applied in the hydroformylation Left: supramolecular self-assembled bidentate ligands Middle: Supramolecular substrate preorganization, Right: Second coordination sphere catalysis. M = metal center, FG = Functional group, DG = directing group, RG = reactive group, RS = recognition site, Do = donor center, SC = Second coordination sphere

In this chapter, the use of supramolecular bidentate ligands, substrate preorganization as well as hydroformylation catalysis in cages are discussed (Figure 1). In particular, the substrate preorganization and encapsulated catalyst strategies are applied in later chapters and therefore these strategies are discussed more extensively.

One class of ligand systems that has been the focus of this thesis is the anion receptor functionalized bisphosphorous ligand: **DIMPhos** (Figure 2). The anion receptor based on 7,7'-diamido-2,2'- diindolylmethane (DIM pocket) in the backbone of the ligand was able to strongly bind deprotonated carboxylic acids.

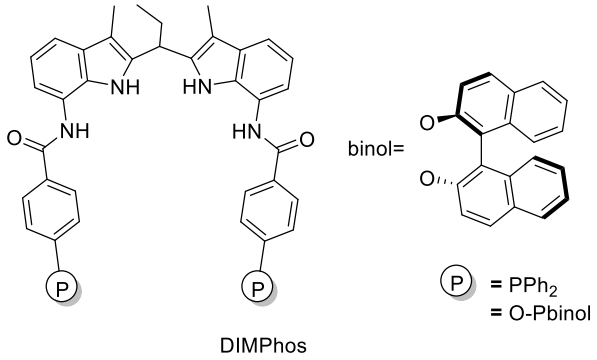
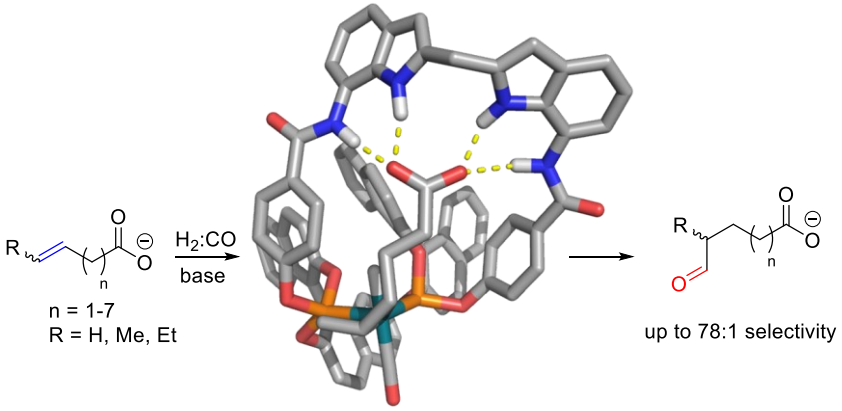


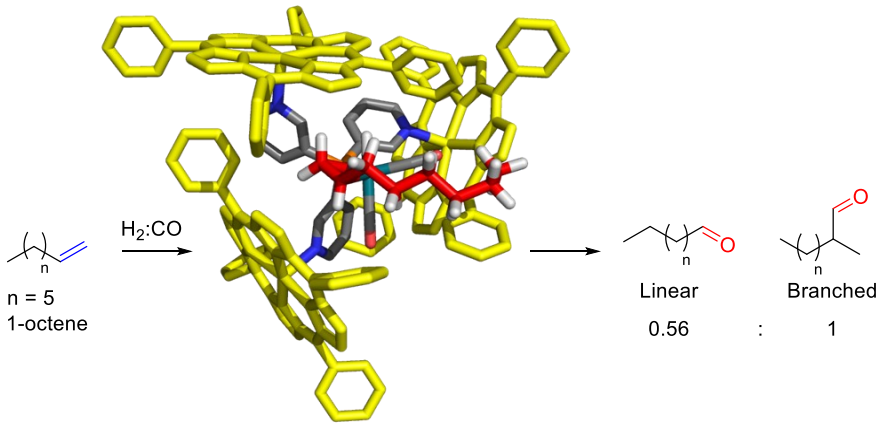
Figure 2 An anion receptor functionalized bisphosphorous ligand based on 7,7'-diamido-2,2'-diindolylmethane: DIMPhos.

The rhodium complexes based on these ligands are applicable in substrate preorganization of deprotonated unsaturated acids. Through ditopic binding of the unsaturated carboxylic acids exceptionally high levels of regioselectivity control was demonstrated (Scheme 1).



Scheme 1 Regioselective hydroformylation of internal and terminal unsaturated carboxylic acids *via* supramolecular substrate preorganization using RhDIMPhos complexes.

Another catalyst that has been studied is the encapsulated $[Rh(H)(CO)_3(P(_mPy_3(ZnTPP)_3))]$ hydroformylation catalyst. This catalyst is able to convert internal and terminal alkenes in the hydroformylation reaction. What is remarkable is that this catalyst can convert terminal aliphatic alkenes to the branched product in excess, whereas most catalysts convert such substrates with an excess to the linear aldehyde.



Scheme 2 Branched selective hydroformylation of 1-octene with [Rh(H)(CO)$_3$(P($_m$Py$_3$(ZnTPP)$_3$))] (DFT modeled structure). ZnTPP building blocks depicted in yellow for clarity.

In **Chapter 2**, the mechanistic basis behind the regioselectivity of **DIMPhos** is investigated using DFT calculations. For all the substrates converted with **DIMPhos** based rhodium catalysts investigated so far, the aldehyde product with the carbonyl farthest from the directing group was formed in excess as major product, e.g. for terminal alkenes the linear aldehyde was the dominant product. DFT calculations show large energy differences between the competing hydride migration steps and this forms the basis for the selectivity control. In depth calculations show that the substrate binding event itself plays an important role in determining these large energy differences. Following ditopic substrate binding, the product forming pathways that lead to the minor product are high in energy due to steric hindrance between the substrate and the CO ligand of the catalyst (Figure *3*).

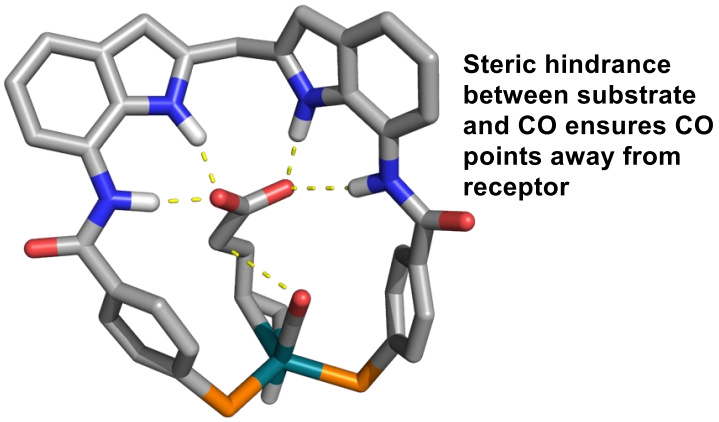
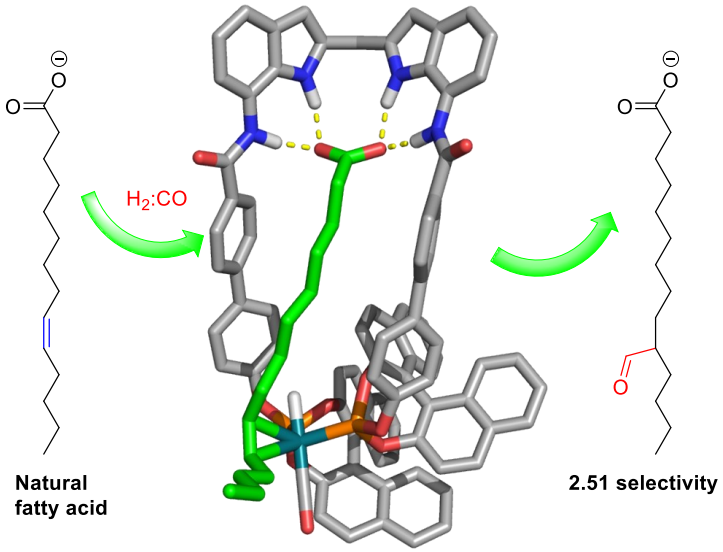


Figure 3 Conceptual explanation for large differences between rhodium geometries upon substrate binding. Energy differences caused by substrate binding, reminiscent of induced fit effects commonly observed in enzymatic catalysis ensures that CO points away from DIM receptor. As a result the catalyst preoraganizes the substrate to the aldehyde product farthest from the carboxylic acid.

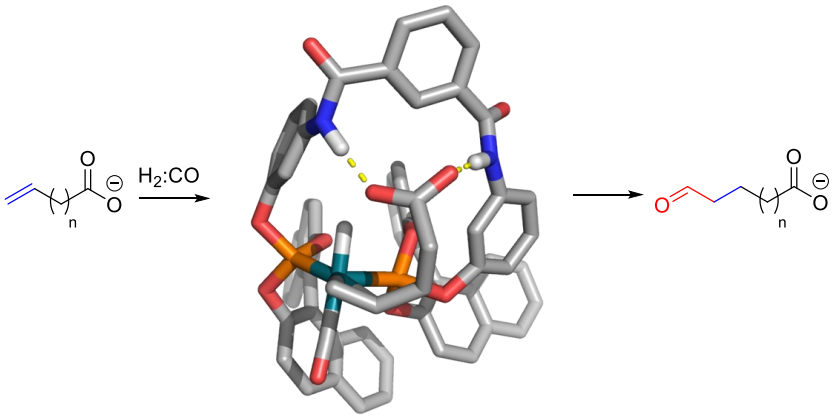
As a result, the catalyst adopts an orientation that preorganizes the alkene with respect to the hydride leading to a pathway that produces aldehyde product with the carbonyl farthest from the acid. The concept that the catalyst rearranges to accommodate the substrate, which forms the basis for the energetic differentiation of the hydride migration step in the current system, shares similarities with induced fit effects commonly observed in enzymatic catalysis.

In **Chapter 3**, we report the redesign of a supramolecular **DIMPhos** Rh-bisphosphite hydroformylation catalyst**.** With this novel catalyst, there is a larger distance between the phosphite metal binding moieties and the DIM pocket. This is achieved by replacing the phenyl linker in the original design with a biphenyl linker. For the first time, regioselective conversion of internal and terminal alkenes containing a remote carboxylate directing group is demonstrated. For carboxylate substrates that possess an internal double bond at the Δ9 position, regioselectivity control is observed. As such, the catalyst was used to hydroformylate natural monounsaturated fatty acids (MUFAs) in a regioselective fashion, forming of an excess of the 10-formyl product (10-formyl/9-formyl product ratio of 2.51), which is the first report of a regioselective hydroformylation reaction of such substrates (Scheme 3).



Scheme 3 Rhodium biphenyl DIMPhos complex is able to regioselectiviely hydroformylate natural fatty acids *via* supramolecular substrate preorganization.

In **Chapter 4**, three 1,3-benzenedicarboxamide anion receptor functionalized ligands were synthesized: one bisphosphine ligand and two bisphosphite ligands. This was done to investigate whether regioselectivity control *via* ditopic binding could also be achieved in the hydroformylation of carboxylate functionalized alkenes with other anion receptors than the aforementioned DIM pocket. Catalytic studies show that one of the two phosphite complexes is able to convert 3-butenoate to 7-octenoate with higher levels of regioselectivity (l/b up to 6.1) than the control experiments in which the substrate is not bound *via* supramolecular interactions (l/b up to 2.0) (Scheme 4). In contrast, the other two designed ligands do not give improved regioselectivity than the control experiments. 2D DOSY spectroscopy shows that the rhodium complexes based on these novel ligands do not behave as bidentate chelating ligands and also dimeric/oligomeric complexes are formed. Most likely, other catalytically active species that cannot bind the substrate in a ditopic fashion also contribute to the catalytic outcome, which lowers the overall regioselectivity of these catalysts.



Scheme 4 Regioselective hydroformylation of terminal alkenes *via* supramolecular substrate preorganization using a 1,3 benzenedicarboxamide anion receptor functionalized bisphosphite.

In **Chapter 5**, the substrate scope using 41 terminal alkene substrates is investigated in the hydroformylation reaction using the encapsulated rhodium catalyst [Rh(H)(CO)$_3$(P($_m$Py$_3$(ZnTPP)$_3$))] (**CAT1**). For all substrates, the amount of branched hydroformylation product formed was higher with **CAT1** than with the unencapsulated reference catalyst [Rh(H)(CO)$_2$(P($_m$Py$_3$))$_2$](**CAT2**) (linear/branched ratio between 2.14 and 0.12 for **CAT1** and linear/branched ratio between 6.22 and 0.59 for **CAT2**). The effect of caging the catalyst on the selectivity of the reaction strongly depends on the substrate. Analysis of the substrate scope combined with DFT calculations suggest that supramolecular interactions between certain moieties on the substrate with the walls of the cage play a key role in controlling the regioselectivity (Figure 4). These supramolecular interactions were further optimized by replacing the ZnTPP building block with an zinc porphyrin analog that contained OiPr substituents on the *meta* positions of the aryl rings. The resulting caged catalyst, **CAT4,** could convert substrates with even higher branched selectivity.

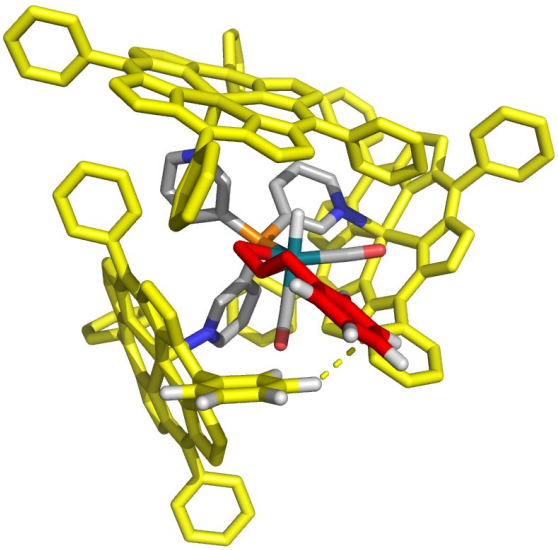


Figure 4 DFT calculations show the substrates display CH-π interactionswith the ZnTPP walls of the cage. ZnTPP building block colored yellow. Allylbenzene substrate colored red. Hydrogens removed for clarity apart from the relevant phenyl rings that display catalyst-substrate CH-π interactions.

In **Chapter 6**, we investigated whether the catalytic outcomes of the encapsulated $[Rh(H)(CO)_3(P(_mPy_3(ZnTPP)_3))]$ catalyst as well as the unencapsulated $[Rh(H)(CO)_2(P(_mPy_3)_2)]$ catalyst could be accounted for with correlation equations using multivariable linear regression. For the unencapsulated $[Rh(H)(CO)_2(P(_mPy_3)_2)]$ catalyst, using the $\Delta^{13}C$ shift of the olefinic carbon atoms and the intensity of the C=C alkene ($I_{C=C\ stretch}$) vibration as substrate descriptors were used to construct a multiparameter formula which predicted the regioselectivity with high accuracy (R^2 = 0.86). In contrast, the multiparameter formula constructed for the caged catalyst was significantly weaker (R^2 = 0.52). which shows that many other factors affect the regioisomeric outcome due to confinement effects. Also, Sterimol parameters of the substrate were employed to account for steric properties of the substrates. Unfortunately using these substrate descriptors did not lead to models that improved reaction prediction. This shows that the steric interactions with the cage are too complicated to be accounted for with these parameters. Additionally, the models that were studied did not include parameters that account for noncovalent interactions of the substrates with the walls of the cage and this is the reason the predictability of the models was low.

In this thesis, two classes of supramolecular catalysts in the hydroformylation reaction were studied; substrate preorganization catalysts and encapsulated catalysts. Both theoretical and experimental approaches were used to improve the understanding of these systems. Using DFT calculations the mechanistic basis for the observed regioselectivity of DIMPhos

catalysts was unraveled. Next, we redesigned an existing DIMPhos phosphite catalyst to accommodate substrates with large carboxylate-alkene distances. Using these catalysts, we were able to selectively hydroformylate monounsaturated fatty acids (MUFAs) using substrate preorganization. Furthermore, we demonstrate that a 1,3 benzene dicarboxamide receptor based bisphosphorous ligand can also be used for substrate preorganization, albeit with lower regioselectivity than previously reported DIMphos based catalysts. Furthermore, we investigated the substrate scope of an encapsulated [Rh(H)$(CO)_3$(P($_m$Py$_3$(ZnTPP)$_3$))] catalyst in the hydroformylation of terminal alkenes. Here, we demonstrate that certain privileged substrates react with exceptional regioselectivity to the branched product. Using the insights of the substrate scope investigation, we were able to optimize the regioselectivity by replacing the ZnTPP building block of the catalyst with a zinc porphyrin analog that contained OiPr substituents on the *meta* positions of the aryl rings. Using the outcomes of the caged catalyst, we investigated data driven approaches to understand the outcomes of the caged catalyst. With this work, we have demonstrated the power of supramolecular transition metal catalysis and we envision that the strategies employed in this thesis provides a platform to find novel supramolecular catalysts that will lead to practical applications.