Supramolecular control of regioselectivity in the hydroformylation reaction
Substrate preorganization and second coordination sphere catalysis
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Chapter 1

Supramolecular Approaches to Control Activity and Selectivity in Hydroformylation Catalysis*

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In this thesis I describe my contributions to the field of hydroformylation catalysis. I will start with a general introduction to exemplify the relevance of this research. I will explain the current challenges in the field of hydroformylation catalysis. Next, I will describe the added value of applying supramolecular concepts in hydroformylation catalysis. I will focus mostly on the supramolecular strategies and successful examples that served as an inspiration for this thesis.
The hydroformylation reaction

The hydroformylation reaction, also known as the “oxo” process, is the transition metal catalyzed addition of \( \text{H}_2 \) and \( \text{CO} \) to an alkene to yield an aldehyde (Scheme 1). The reaction was discovered serendipitously by Otto Roelen in 1938 while doing research on the Fischer–Tropsch process in 1938.[1,2]

![Scheme 1 General depiction of the hydroformylation reaction.](image)

The reaction is catalyzed by a homogeneous catalyst and finds widespread application in industry.[3-7] The hydroformylation reaction is the largest homogeneously catalyzed process in volume. Propene hydroformylation is responsible for most of this volume, with both regioisomeric products, i.e. \( \text{n-butyaldehyde} \) and \( \text{iso-butyaldehyde} \), finding many industrial applications.[3,5] For instance, \( \text{n-butyaldehyde} \) can be converted to \( \text{1-butanol} \), which is used for the production of \( \text{2-ethylhexanol} \) which is used to produce a plasticizer. Apart from the use of the hydroformylation reaction in the bulk chemical industry, this reaction also has many applications in the fine chemical industry. Due to the characteristic smell of aldehydes, it is applied in the flavor, fragrance and food industry, which has been summarized by Börner and coworkers.[8]

Chiral products can also be synthesized \textit{via} asymmetric hydroformylation, which leads to the formation of chiral aldehydes. These aldehydes are versatile and can be used for further functionalization, and as such provides an interesting entry for the pharmaceutical and chemical industry.

The aldehyde can be converted into numerous products (Scheme 2). For instance, the aldehyde can either be reduced with molecular hydrogen to form the alcohol, which is one of the main applications of this reaction in the bulk chemical industry. Additionally, the aldehyde can be reacted directly with an amine to form an imine that can be reduced to form amine products.
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Scheme 2 Aldehydes are versatile moieties that can be converted into alcohols, amines, acids, esters and amides.

The condensation of the aldehyde with an amine and subsequent reduction is often done as a tandem reaction using molecular hydrogen, which is referred to as a hydroaminomethylation sequence.\(^9\)–\(^12\) The alkene can also be converted to a carboxylic acid through an oxidation step. These acids can subsequently be converted *via* a condensation with an alcohol or amine to yield esters or amides, respectively.

The first catalyst used was a cobalt complex and also the first commercial plants operated using a cobalt catalyst. Later on, rhodium was found to offer superior performance, which resulted in higher activity and chemoselectivity to the aldehyde. This allowed hydroformylation plants to operate at lower temperatures and pressures. Additionally, the use of rhodium in combination with ligands leads to a high degree of selectivity control for many substrates. As a result, currently most plants use a rhodium catalyst, despite the significantly higher price of rhodium compared to cobalt. Several plants still operate using a cobalt catalyst as cobalt offers certain advantages over rhodium, such as a lower price and a higher tolerance towards poisons.\(^3\) For instance, the production of high boiling alcohols and aldehydes make use of a cobalt catalyst. Other transition metals, such as platinum, ruthenium, palladium and iridium have been investigated in the context of the hydroformylation reaction and typically displayed a lower activity.\(^13\) In general, the reactivity of transition metal salts is:\(^3\)

\[
\text{Rh} \gg \text{Co} > \text{Ir}, \text{Ru} > \text{Os} > \text{Pt} > \text{Pd} > \text{Fe, Ni}
\]

This reactivity trend has been established under specific conditions using metal salts. However, the presence of ligands and counterions also affects the activity and as such several active catalysts have been reported that use metals other than rhodium or cobalt.\(^10,14–25\) However, to the best of our knowledge, no commercial hydroformylation processes currently operate using a transition metal catalyst other than rhodium or cobalt.

The hydroformylation reaction has several inherent selectivity issues (Scheme 3). First of all, the aldehyde can add on both sides of the alkene, forming regioisomers for most
substrates employed. For most processes, the formation of a single isomer is desired and the catalyst used and reaction conditions often need to be optimized to control the regioselectivity. Additionally, since hydrogen is always present, both the alkene substrates as well as the aldehyde products can be hydrogenated forming alkanes and alcohols respectively, which is commonly observed with cobalt catalysts. Moreover, under catalytic conditions the alkene can isomerize leading to a mixture of internal and terminal alkenes, which in turn can be hydroformylated forming even more regioisomers.

Scheme 3 Inherent selectivity issues typically associated with the hydroformylation reaction.

Through optimization of the conditions the isomerization reaction can be used to the advantage by an isomerization-hydroformylation sequence, in which internal alkenes are converted to terminal aldehydes with high selectivity. This isomerization-hydroformylation sequence can also be used to convert a mixture of internal alkenes to a terminal product with high selectivity (Scheme 4).

Scheme 4 Isomerization-hydroformylation sequence can be optimized to obtain the linear aldehyde product selectively from a mixture of terminal and internal alkenes.

The selectivity to the linear aldehyde in a hydroformylation-isomerization sequence is caused by the fact that terminal alkenes react with higher activity than internal alkenes. When the isomerization process is operative, a dynamic mixture of isomeric alkenes is
produced. The ability of the catalyst to specifically hydroformylate only the terminal alkene gives rise to the high selectivity provided the isomerization activity is sufficiently fast.

In general, when the substitution pattern around the alkene increases, the reactivity decreases (Figure 1). Additionally, in general the aldehyde mostly adds to the least substituted side and almost always the aldehyde does not add on a disubstituted alkene forming tertiary aldehyde, which is known as "Keulemans rule", named after the author that reported this selectivity trend.

![Figure 1 General reactivity trend for substituted alkenes in the hydroformylation reaction. The higher the substitution, the lower the activity.](image)

The mechanism of the hydroformylation reaction was originally proposed by Heck and Breslow and still is the generally accepted mechanism. Since then, many groups have performed mechanistic studies on this reaction which has provided additional mechanistic insights.

![Scheme 5 Catalytic cycle of the hydroformylation reaction.](image)

The general mechanism is depicted in Scheme 5 and uses a rhodium monohydride bisphosphine biscarbonyl complex (1) as starting point. After the dissociation of one CO ligand from a rhodium hydrido complex (1) the catalytically active species (2), which has
a vacant site, is generated to which an alkene can coordinate to rhodium to give intermediate 3. This is followed by the migratory insertion in which the hydride can insert on both sides of the alkene, which either leads to the linear (4) or branched (8) alkyl species. These two species enter separate catalytic cycles. Following the formation of the alkyl species a CO molecule coordinates to rhodium (5 & 9). This is followed by migratory insertion to form a rhodium acyl species (6 & 10). These four coordinate rhodium species can either react directly with hydrogen to form the aldehyde and regenerate 2. Alternatively, the four coordinate acyl species (6 & 10) can react reversibly with CO to form a pentacoordinate rhodium acyl species (7 & 11). This pentacoordinate species is an off-cycle species that can be detected spectroscopically (for certain catalytic systems). It should be noted that the relative rate of all steps determine which step is rate and selectivity determining. These relative rates are affected by the type of metal used, ligand, solvent as well as the relative pressures of hydrogen and CO. As such variations of the conditions can allow for tuning of the selectivity.

The addition of ligands to the reaction mixture significantly impacts the activity as well as the regioisomeric outcome. Therefore, many studies focus on the variation of the ligands to optimize the regioselectivity. Furthermore, the addition of a chiral ligand can lead to enantioselective conversions when prochiral substrates are employed. As ligands phosphorous compounds are used almost exclusively as ligands in this reaction. Other types of ligands have also been studied in the context of the hydroformylation reaction such as amines and arsines, but such compounds display significantly lower activity than the phosphorous based rhodium complexes.\(^{40,41}\) The reactivity trends are established as:

\[
\text{Ph}_3\text{P} > \text{Ph}_3\text{As} > \text{Ph}_3\text{N} > \text{Ph}_3\text{Sb} > \text{Ph}_3\text{Bi}
\]

Of these phosphorous ligands, many variants are known (Figure 2). Often, the phosphorous has three carbon-based substituents. One of the most studied ligands, triphenylphosphine, belongs to this class as it is a cheap and readily available ligand (Figure 3). Also, water-soluble analogues of triphenylphosphine have been developed and these have been used for aqueous phase hydroformylation. Phosphorous ligands with other heteroatoms are also used in the hydroformylation reaction.
Replacement of one of the carbon atoms with an oxygen group results in the formation of phosphinites, two carbon atoms result in the formation of phosphonites, and the replacement of three carbon atoms with oxygen groups are referred to as phosphites. In particular, phosphites are frequently used as the increased electronegativity of the oxygen compared to carbon results in a more $\pi$-accepting ligand (Figure 3). This generally results in a higher activity in the rhodium catalyzed hydroformylation as CO dissociation is more facile. Alternatively, the carbon atoms can be replaced stepwise with nitrogen atoms, which produces aminophosphines, diaminophosphines, or triaminophosphines. Another class that should be highlighted are the commonly used phosphoramidites, which have a single N-atom and two oxygen substituents connected to phosphorous. For cobalt catalysts, the activity is (slightly) decreased in the presence of phosphines, but with higher selectivity to the linear aldehyde. In contrast, the activity often increases following the addition of phosphines for rhodium.

For most rhodium catalyzed systems studied the hydride migration ($3 \rightarrow 4$) is rate and selectivity determinizing and therefore the relative barriers of this step determine the overall regioselectivity. When the alkene coordination step and subsequent hydride migration step are rate determining this is generally referred to as type 1 kinetics. In particular, rhodium catalysts based on triarylphosphines mostly reveal type 1 kinetics. The application of more $\pi$-accepting phosphines leads to faster CO/substrate exchange and often to a reversible subsequent hydride migration step. When the hydride migration is reversible, all the steps up to the hydrogenolysis step are in fast equilibrium. Now, the intermediates $6$ and $10$ are in fast equilibrium and the hydrogenolysis rate of both intermediates determines the regioselectivity. When this is the case, this is generally referred to as type 2 kinetics. Since the hydride migration step is reversible in type 2 kinetics, this results in more isomerization side products. Under optimized conditions this isomerization pathway allows for selective isomerization-hydroformylation sequences (vide supra).

The size of the ligands also affects the overall activity. Rhodium complexes with only one phosphorous atom coordinated are generally the most active. Therefore, monodentate ligands that are too bulky to accommodate an additional phosphorus ligand generally give the most active complexes. Bidentate ligands are less active as they enforce biscoordination. However, bidentate ligands generally allow for better control over the regioselectivity and as such they are often studied in the context of rhodium catalyzed hydroformylation. For enantioselective hydroformylation bidentate ligands are most often used as they offer better control over the enantioselectivity.

Extensive research has been conducted to control the regioselectivity in the hydroformylation reaction. Due to the high market demand of the linear aldehyde for compounds such as propene and 1-octene, most research focuses on obtaining the linear aldehyde product of these compounds. It is well known that excess of triphenylphosphine gives a high level of selectivity for the linear product in the rhodium catalyzed
hydroformylation of 1-octene (Figure 3). The excess of phosphine enforces bisphosphine or even trisphosphine coordination around rhodium, which is more linear selective than monophosphine coordinated rhodium species. However, bisphosphine ligated systems are also generally lower in activity than their monophosphine ligated counterparts.

![PPh₃, TPPMS, triphenylphosphite]

Figure 3 Frequently applied monodentate phosphine ligands.

Bidentate ligands with a wide bite angle of around 120° are found to hydroformylate aliphatic alkenes with even higher linear regioselectivity than monophosphine based systems (Figure 4). In this regard, BISBI[^2,^3] and Xantphos[^4,^5] are frequently used as they allow for exceptionally high selectivities in the hydroformylation for 1-octene (l/b > 50). Several derivatives of these ligands have also been reported. In one example, phenyl groups of Xantphos were replaced with pyrrole groups[^6]. This led to even higher selectivity for the linear product in the hydroformylation of 1-octene. Also a naphthyl based ligand derivative of the BISBI ligand was reported, Naphos. This also resulted in high linear selectivities to the linear product[^7,^8]. Furthermore, this ligand was also active in the isomerization reaction and as such it was used to convert internal 2-alkenes to the linear aldehyde product with high levels of regioselectivity. Also, a BISBI analog that has four phosphorous coordination sites instead of two coordination sites has been reported[^9]. The presence of four coordination sites enforces more biscoordination over monocoordination under catalytic conditions, while retaining the wide bite angle required for high levels of linear selectivity. These tetraphosphorous ligands display even higher linear selectivity in the hydroformylation reaction of 1-octene (l/b = 50.5). Additionally the isomerization reaction, which lowers chemoselectivity, is also lower compared to the BISBI ligand under equivalent conditions. A pyrrole substituted tetraphosphorous ligand also gave high levels of linear selectivity in the hydroformylation of 1-octene[^10]. This ligand was also used in the hydroformylation of 2-alkenes, which were converted with high selectivity to the linear product via the aforementioned isomerization-hydroformylation sequence. Due to the allyl stabilization of the branched product forming pathway, vinyl acetate and styrene are generally hydroformylated with high selectivity to the branched product. Interestingly, rhodium complexes based on a pyrrole substituted tetraphosphorous ligand was also able to hydroformylate styrene and vinyl acetate derivatives to the linear product with high selectivity, whereas these substrates commonly convert to an excess of the branched product.[^11–^13]
Figure 4 Wide bite angle bidentate and tetraphosphorous ligands that deliver linear products with exceptionally high selectivity.

Obtaining high selectivity for the branched product for aliphatic alkenes, such as 1-octene, is significantly more challenging than obtaining high selectivity for the linear product. Currently only three ligand classes exist that give an excess of the branched product (Figure 5). The first report of a catalyst that converts 1-octene to predominantly the branched aldehyde was by Reek et al. and used an encapsulated ligand (vide infra). Later on, Clarke et al. reported BOBphos which is a chiral bidentate phosphite-phospholane ligand with a small bite angle. Rhodium complexes based on this ligand converted 1-hexene to form an excess of the branched product (l/b = 0.33). Furthermore, this system also displays high levels of enantioselectivity for such substrates. Mechanistic studies show that CH−π interactions between the ligand and substrate block certain linear forming pathways and as a result the branched product is formed in excess. To stabilize these CH−π interactions, the toluene solvent was replaced with a octafluorotoluene, which resulted in even higher levels of selectivity to the branched product. This high selectivity was also obtained for propene (l/b = 0.22), which demonstrates the potential of this ligand for industrial applications.
Chapter 1

Recently, Nozaki et al. identified the Triphos ligand as a ligand that is able to form a branched selective rhodium complex. The selectivity was found to be highly dependent on the CO pressure and only at high CO pressures, the selectivity was high for the branched product.

The generation of highly enantiomerically pure aldehyde products by hydroformylation catalysis is highly desired as this holds great potential for the fine chemical and pharmaceutical industry. This field has been reviewed extensively either in dedicated reviews and in reviews on asymmetric catalysis. As both the regioselectivity and the enantioselectivity needs to be controlled in the same reaction, this transformation is challenging. For this reason, the substrates investigated are those that typically give high branched selectivity, such as styrene derivatives and vinyl acetate. One exception is a branched selective hydroformylation of 1-butene using rhodium complexes of the aforementioned BOBphos (vide supra) which results in high enantio- and regioselectivity under optimized conditions (l/b = 0.16, e.r. = 96). Several ligand classes have been reported that yield moderate to high levels of enantioselectivity (Figure 6).

One phosphine-phosphite ligand that stands out, BINAPhOS, was reported by Nozaki et al. as it delivers high levels of enantioselectivity. The phosphine-phosphoramide analog of this ligand, YanPhos, was reported by Zhang et al, which also delivered high levels of enantioselectivity for several substrates. Landis reported a diazaphospholane ligand that delivered high levels of enantioselectivity.
Figure 6 Bidentate ligands that are frequently applied in enantioselective hydroformylation protocols.

Scheme 6 The regioselectivity of internal alkenes is difficult to control in the hydroformylation reaction.

One of the substrates for which the regioselectivity is currently difficult to control using traditional transition metal catalysts are internal alkene substrates (Scheme 6). Due to the lack of electronic bias to either product, internal alkenes are generally hydroformylated
with low regioselectivity. Isomerization-hydroformylation sequences have been employed to obtain selectivity to the linear aldehyde.\cite{28}

Scheme 7 Currently known strategies for fatty acid hydroformylation

Obtaining selectivity to a single aldehyde from an internal alkene is challenging. One frequently investigated class of internal alkene substrates is unsaturated fatty acids, as the feedstock is readily available, biobased and the double bond can be used for hydroformylation. Currently, fatty acids represent a challenge as the regioselectivity is not effectively controlled in the hydroformylation reaction (Scheme 7).\cite{87-89}

This class of substrates has at least one internal double bond. In reports where unsaturated fatty acids are hydroformylated, often a 50/50 mixture of both regioisomers was formed.\cite{90-93} Alternatively, such substrates can be subjected to an isomerization-hydroformylation sequence, which yields the linear product in modest yields under optimized conditions.\cite{27,29-31,89,94}

The aforementioned examples exemplify the complexity of the hydroformylation reaction. Since the discovery, many selectivity issues have been solved in this reaction by ligand optimization. However, to further unlock the potential of the hydroformylation reaction new concepts to control the regio- and enantioselectivity are required. In the past 20 years, supramolecular concepts 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 aforementioned traditional ligand design strategies. This has emerged in the field of transition metal catalysis and these concepts are found to be highly applicable (Figure 7).

In general, three strategies are applied in the hydroformylation reaction 1. Supramolecular bidentate ligands. 2. Supramolecular substrate preorganization, and 3. The use of a second coordination sphere to control the selectivity and activity.
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Figure 7 Supramolecular strategies commonly applied in the hydroformylation. Left: supramolecular 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

The use of supramolecular substrate preorganization and second coordination sphere catalysis have served as fundamental starting points for this thesis. Therefore, we will briefly outline the concept of supramolecular bidentate ligands and highlight some of the most important examples within this field. Next, we will cover the use of substrate preorganization strategies as well as second coordination sphere catalysts to obtain regio- and enantioselectivity in this reaction more extensively.

Supramolecular strategies in the hydroformylation reaction

1. Supramolecular bidentate ligands

Supramolecular bidentate ligands make up a class of ligands that has been introduced in the past 20 years. These ligands offer the synthetic accessibility of monodentate ligands. Due to self-assembly, these monodentate ligands however behave as bidentate ligands, which offer better control over the regio- and enantioselectivity. This concept has been reviewed by Reek et al.[95–97] and Breit et al.[98]

Figure 8 Schematic representation of the two strategies generally applied to generate supramolecular bidentate ligands. M = metal center, FG = functional group, Do = donor center.
Supramolecular bidentate ligands can be synthesized using a metal templated assembly (Figure 8, left). In this strategy, a template that contains two binding sites for the selective binding of two ligand building blocks. Alternatively, bidentate ligands can be formed by a direct supramolecular interaction between the two ligand building blocks (Figure 8, right).

The concept of a metal templated assembly to generate supramolecular bidentate ligands was introduced by Reek et al. \[99\] In this report, an assembly of two monomeric pyridine-phosphine ligands are bound to a dimeric zinc(II) porphyrin template \textit{via} a Zn-pyridine interaction forming a supramolecular bidentate (Figure 9).

![Figure 9](image-url) Supramolecular bidentate based on a metal-template assembly as reported by Reek et al.

Later on, two tris(zinc(II) porphyrin)-phosphite ligands were bridged by three DABCO units as ditopic template ligands to generate a rigid supramolecular bidentate ligand.\[100\] Rhodium complexes based on this self-assembled ligand resulted in high linear selectivities in the hydroformylation of 1-octene (l/b up to 22.8).

Hydrogen bonds are frequently used to generate supramolecular bidentate ligands.\[101\] A hydrogen donor-acceptor system is often applied to form supramolecular bidentate ligands (Figure 8). A pioneering system based on hydrogen bonds was reported by Breit et al.\[102\] The ligand used was 6-diphenylphosphanyl-2-pyridone (6-DPPon) (12). This ligand can exist both in a 2-pyridone and in a 2-hydroxypyridine tautomeric form. In absence of a metal center the ligand forms a self-complementary dimer and is in the 2-pyridone form. However, following the addition of a metal center, this resulted in a supramolecular bidentate, where the 2-pyridone/2-hydroxypyridine tautomer formed two hydrogen bonds necessary for the bidentate character of this ligand. The application of this 2-pyridone/2-hydroxypyridine supramolecular bidentate (6-DPPon) ligand 12 in the rhodium catalyzed hydroformylation of 1-octene resulted in the formation of high amounts of the linear product (l/b = 33), which are regioselectivity levels that are competitive with the best performing covalently synthesized bidentate catalysts.
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Scheme 8 6-diphenylphosphanyl-2-pyridone (6-DPPon) as building blocks to form a supramolecular bidentate ligand, used in the rhodium catalyzed hydroformylation reaction.

Figure 10 A supramolecular bidentate system based on a Zinc-pyridine coordination, coined Supraphos. Both components of the ligands could be modified in a straightforward fashion and as a result, a large pool of catalyst can be generated through mixing.

Another example of a supramolecular bidentate ligand based on a direct supramolecular interaction between the two monomers relies on a selective zinc-pyridine coordination and was introduced by Reek et al (Figure 10). In this example, a phosphorous moiety was functionalized with a ZnTPP moiety, which formed a Zinc-pyridine interaction with a nitrogen functionalized phosphorous ligand to generate heterobidentate ligands. Due to the highly modular nature of this supramolecular platform, coined Supraphos, both components of the ligand could be varied with relative ease and as a result, this resulted in the formation of 450 combinations. In combination with high throughput instrumentation this could be used to evaluate many catalysts to find the most selective catalysts from this pool. In the hydroformylation of styrene one catalyst delivered the branched product with 76% ee. Also, another heterobidentate Supraphos catalyst delivered the linear product in the hydroformylation of styrene with 72% selectivity.

2. Supramolecular substrate preorganization

Another recently introduced strategy for achieving selectivity in transition metal catalysis is through preorganization of the substrate with respect to the metal center. A commonly
explored way to achieve preorganization is through ditopic binding of the substrate to the catalytically active metal center, in which a second functional group controls the orientation of the substrate (Figure 11, left).\textsuperscript{106,107} Such a directing group can already be present on the substrate, or alternatively needs to be introduced temporarily to the substrate before it is subjected to the catalytic conversion. These strategies have been demonstrated to be very powerful in C-H activation and asymmetric hydrogenation, however, there are some limitations and drawbacks. For example, the strategies are limited to substrates that have a specific directing group next to the reactive bond, or additional synthesis steps are required for the introduction and removal of the directing group. Moreover, an additional vacant coordination site has to be present on the metal center for the coordination of the directing group. Using supramolecular chemistry, a recognition site can be introduced to the catalyst for substrate orientation.

Figure 11. Schematic representation of substrate pre-organization via traditional approaches or via supramolecular strategies. M = metal center, DG = directing group, RG = reactive group, RS = recognition site, Do = donor center.

By introducing a recognition site in the backbone of the catalyst, no longer preorganization of the substrate is established via ditopic binding to the catalytically active metal. Recently many groups have focused on catalysts containing an additional recognition site as a way to pre-organize the substrate with respect to the metal center (Figure 11, right). The structure of the bifunctional catalyst can be adjusted to the structure of the substrate. This can allow for remote selectivity control as well as catalyst design in a predictable fashion when combined with in-depth mechanistic knowledge. This is far more challenging using traditional approaches. Through supramolecular substrate pre-organization highly selective reactions have been engineered and this strategy was highlighted specifically in recent perspectives by Phipps et al.\textsuperscript{108} and Reek et al.\textsuperscript{109} In the rhodium catalyzed hydroformylation, the selectivity is typically determined during the hydride migration step. Generally, the alkene substrate can coordinate in various manners, and upon hydride migration the alkene rotates. By blocking certain rotations, substrate orientation via supramolecular interactions should be a viable strategy to control the selectivity and indeed this approach has been shown to
be very powerful in the hydroformylation reaction; in this section we will discuss the relevant examples reported so far.

Figure 12. Guanidinium functionalized phosphine ligands.

Hydrogen bonded systems have been exceptionally effective in the context of supramolecular substrate pre-organization, particularly in the hydroformylation reaction. Breit et al. reported a guanidinium functionalized phosphine ligand which acts as a receptor for unsaturated carboxylic acids (Figure 12). Hydrogen bonds between the guanidinium group of the ligand and the carboxylic acid moiety of the substrate pre-organize the alkene with respect to the metal center. When 3-butenolic acid is converted by a rhodium catalyst based on 13, a very high selectivity is achieved for the linear product (l:b = 41) (Scheme 9, 17a).

Scheme 9. Regioselective hydroformylation of unsaturated carboxylic acids (o = outermost; i = innermost).

This catalyst is also active for internal alkenes, which are generally less reactive. When 3-pentenoic acid is hydroformylated with this catalyst system, the product is formed in which the aldehyde is introduced at the unsaturated carbon atom furthest away from the carboxylate (Scheme 9, 17b).

The selectivity was found to be highly dependent on the distance between the acid moiety and the alkene function. 4-Pentenoic acid hydroformylation with the supramolecular system gave selectivity to levels typically found for triphenylphosphine-based catalysts, indicating that substrate pre-organization does not play a role for this particular substrate. This clearly shows that for this catalyst system the alkene-acid distance has to be precise in order to control the selectivity by supramolecular pre-organization. This can be exploited for substrates containing two alkenes at different distances from the carboxylate (Scheme 10, 18). The alkene with the proper carboxylic acid-olefin distance is converted at a higher rate (8.8:1) and with a higher selectivity for the linear aldehyde.
(l:b = 32), compared to the alkene moiety that is further from the carboxylic acid (l:b = 3).[111]

Scheme 10. Hydroformylation of a substrate containing multiple olefinic sites.

DFT calculations show that the lowest energy is obtained when two ligands are coordinated to the metal center and the carboxylic acid moiety of the substrate forms four hydrogen bonds with the two guanidine groups of the ligands (Figure 13). No substrate-ligand interaction can be observed when only one ligand coordinates to the metal center and as such the biscoordinated species is proposed to be the most likely intermediate responsible for the high selectivity.[111] Analysis of the calculated structures indicate that preceding the hydride migration step the alkene is rotated towards the hydride through the hydrogen bonds between the guanidinium moieties and carboxylic acid moiety of the substrate.

Figure 13. Substrate orientation in the selectivity determining hydride migration step (DFT study).

Scheme 11. Decarboxylative hydroformylation of α,β unsaturated carboxylic acids.
The [Rh]/13 catalysts is also effective in a decarboxylative hydroformylation of α,β-unsaturated carboxylic acids (Scheme 11).[112] In this cascade reaction the formyl group is introduced on the substrate, after which the carboxylate leaves the substrate as CO₂. Under similar conditions, but using triphenylphosphine as the ligand, the double bond is reduced instead of hydroformylated, which exemplifies the need of supramolecular interactions between the substrate and the catalyst to yield the terminal aldehyde product.

Later on, a more electron withdrawing guanidine functionalized phosphine ligand 14 was used and the conditions were optimized to obtain a selective hydroformylation-hydrogenation reaction sequence for carboxylate containing alkynes (Scheme 12).[113] These internal alkynes could be converted to obtain internal aliphatic aldehydes with high levels of regioselectivity and chemoselectivity.

![Scheme 12](image_url)

Scheme 12 Regioselective alkyne hydroformylation- hydrogenation to yield internal aldehydes.

When the pyridine moiety of the previously discussed ligand (Figure 12, 13) is replaced with a benzene moiety or a pyrrole moiety, aldehyde hydrogenation is observed (Figure 12, 15-16).[114]

**tandem hydroformylation-aldehyde hydrogenation reaction**

[Rh(l)]

![Reaction Diagram](image_url)

**tandem decarboxylative hydroformylation-aldehyde hydrogenation reaction**

![Reaction Diagram](image_url)

**tandem isomerization-hydroformylation reaction sequence**

![Reaction Diagram](image_url)

Scheme 13. Tandem processes using supramolecular substrate preorganization ligands.

As such, these ligands can be used in the context of a tandem hydroformylation-hydrogenation sequence converting 1-octene into 1-nonanol. The selectivity for the linear alcohol can be enhanced by combining the pyrrole (16) analogue of the guanidium
catalyst in combination with the 2-pyridone/2-hydroxypyridine supramolecular bidentate (6-DPPon) to yield a highly selective hydroformylation-hydrogenation reaction of 1-octene to 1-nonanol (Scheme 13).

Combining the decarboxylative hydroformylation approach of α,β-unsaturated acids with a supramolecular aldehyde hydrogenation catalyst yields a tandem decarboxylative hydroformylation-hydrogenation catalytic system (Scheme 13).[115] The system works most effectively when a mixture of the most active catalyst in decarboxylative (13) hydroformylation is used in combination with an analogue effective in the hydrogenation of aldehydes (15).

The alkene hydroformylation method was later applied to alkyne hydroformylation with substrates where the alkyne moiety is next to the carboxylate moiety.[116] In combination with a Michael addition, this resulted in decarboxylation of the substrate to yield aldehyde functionalized products that contained a nucleophile as is schematically represented in Scheme 14. The nucleophiles used were trimethoxybenzene and indole derivatives.

Scheme 14 domino hydroformylation-Michael addition-decarboxylation reaction.

Regioselective hydroformylation of unsaturated acids can also be achieved with a series of bidentate phosphines and phosphite ligands, coined DIMPphos, functionalized with a highly selective anion receptor, 7,7-diamido-2,2-diindolylmethane (Figure 14).[117–119]

Figure 14. Anion receptor functionalized bisphosphines (DIMPphos).
Terminal unsaturated carboxylates can be hydroformylated with a rhodium complex based on the phosphine analogue (Figure 14, 22) of the ligand. 4-Pentenoate up to 10-undecenoate are converted to the aldehyde with high selectivities for the linear product (Scheme 15, 24). 3-Butenoate is not converted selectively since the substrate is too short to bind to the receptor moiety and the metal center simultaneously. Unsaturated phosphate analogues are also converted in high selectivities. Upon protonation or methylation of the substrate, the selectivity is lost and the conversion is significantly lower. It is interesting to note that, contrary to the monodentate guanidinium ligands (Figure 12, 13-16) reported by Breit et al., the high selectivity for the linear product is obtained for a variety of substrates with different distances between the alkene and the carboxylate group.\cite{110,111}

Scheme 15. Regioselective hydroformylation of ω-unsaturated carboxylic acids.

In situ spectroscopy, kinetic data and DFT calculations show that the hydride migration step is selectivity determining. Similarly to the guanidinium phosphine systems, DFT data show that due to the binding of the substrate in the DIM pocket, the alkene is properly pre-organized with respect to the Rh-H bond for the hydride migration step leading to the linear rhodium alkyl species (Figure 15). The hydride migration to form the branched alkyl species cannot proceed without the carboxylate leaving the pocket, and also other competitive pathways leading to the branched product are significantly higher in energy.\cite{117,118}.

An ortho analog of the DIMphos catalyst allowed for the selective hydroformylation of smaller substrates such as 3-butenoate.\cite{120} Interestingly this ligand formed a dimer complex, that transformed into the monomer species in the presence of large amounts of carboxylates.\cite{121} The dimer and the monomer displayed different regioselectivities in the hydroformylation of 1-octene and thus by controlling the monomer-dimer equilibrium via the addition of acetate, the regioisomeric outcome could be controlled in the hydroformylation of 1-octene.
Phosphite analogues of the DIMPhos ligands (Figure 14, 23) give rhodium catalysts that are sufficiently active to hydroformylate internal aliphatic alkenes under mild conditions, which is not possible with the phosphine based systems.\textsuperscript{[118]} The CO inserts farthest from the carboxylate and exceptionally high selectivities are observed for internal alkenes (i.e. up to $\alpha:1 = 78$) using the substrate orientation strategy with 23 as the ligand. Again, a series of substrates with different distances between the alkene and the carboxylate were selectively converted with the highest selectivity obtained for the internal alkene on the 4-position. Experiments with terminal alkenes with various lengths did display that the selectivity lowered when the alkyl chain length was increased.

![Diagram of substrate pre-organization](image)

Figure 15. Substrate pre-organization in the selectivity determining hydride migration step (DFT study).

Scheme 16. Regioselective hydroformylation of internal unsaturated carboxylic acids.

Also, carboxy-vinylarenes are hydroformylated with the same system to form the linear product in the highest selectivities reported to date (more than 98\%) (Scheme 17, 26a).\textsuperscript{[122,123]} The branched aldehyde is not detected, whereas this is usually the dominant product as electronic factors dictate that these aromatic substrates mainly form branched aldehydes (Scheme 17, 26b).\textsuperscript{[122–124]} Remarkably, internal alkene and cyclic analogues were also converted with very high selectivity to the aldehyde farthest from the carboxylate directing group (Scheme 17, 27).
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Scheme 17. Regioselective hydroformylation of 2-carboxyvinylarenes and cyclic analogues.

When the phosphite based DIMPPhos hydroformylation system 23 is combined with a palladium isomerization catalyst, terminal alkenes are converted into α-branched methyl aldehydes (Scheme 13).\textsuperscript{[125]} The advantage is that branched aldehydes can be synthesized from inexpensive terminal alkenes in selectivities competitive to the highest direct branched selective hydroformylation catalyst.\textsuperscript{[58][54,56]}

A related strategy for selective hydroformylation catalysis relies on dynamic covalent chemistry. Instead of supramolecular interactions, the substrate is temporarily bound to a scaffolding ligand by reversible bond formation between the substrate and such a ligand.\textsuperscript{[126–128]} Via the scaffolding ligand the substrate binds in a ditopic fashion to the metal complex. The exchange process of the substrate with the scaffolding ligand should be compatible with the hydroformylation reaction.\textsuperscript{[129][130]}

Figure 16. Catalytic scaffolding ligands (reversible bond in red).

One scaffolding ligand that can be used in the context of regioselective hydroformylation is 28 and has a hemilabile C-O bond (Figure 16).\textsuperscript{[129]} Through reversible cleavage of the C-O bond the hydroxy group of the substrate can bind to the ligand.

Scheme 18. Regioselective hydroformylation employing catalytic scaffolding ligands.
Preorganization reverses the regioselectivity of substituted homoallylic alcohols to form the branched/innermost product in excess. After hydroformylation, an oxidation reaction yields five-membered ring lactones in good selectivities of up to 98:2 (Scheme 18, 32). The strategy is feasible for both internal and terminal alkenes. A control reaction using PPh₃ yields the six-membered ring lactone in excess (6-membered / 5-membered = 3:1). The same ligand is also successfully applied in the hydroformylation of substrates containing a sulfonamide as a directing group instead of an alcohol group.[131]

Scheme 19. Regioselective hydroformylation of homoallylic- and bishomoallylic alcohols employing catalytic scaffolding catalysts.

In a similar approach methyl diphenylphosphinite has been used as a scaffolding ligand (Figure 16, 29).[130] This ligand has a labile P-O bond and the methoxy moiety can exchange with hydroxy groups on the substrate. A catalytic amount of the ligand can be combined with homoallylic alcohols to yield the branched product (innermost for internal alkenes) in near perfect selectivities of <99% (Scheme 19, 33). A lactone is formed after oxidation of the formed lactol in this reaction. This ligand can also be applied in the regioselective hydroformylation of bishomoallylic alcohols to selectively yield six-membered lactones as a product (Scheme 19, 34).[132]

Scheme 20. Hydroformylation of α,α-,disubstituted alcohols to form quaternary carbon centers.
The same scaffolding strategy can also be applied to form quaternary carbon centers via a hydroformylation reaction, which is considered as one of the most challenging reactions in hydroformylation.\cite{133,134} Hydroformylation to form quaternary carbon centers was achieved when α,α-disubstituted olefins were used with the previously discussed scaffolding ligands $28$ and $29$. As the aldehyde inserts on the carbon center closest to the alcohol group, the “Keulemans’ rule” which dictates that addition of a formyl group never occurs at the tertiary position of the olefin in hydroformylation, is overruled (Scheme 20, 35 and 36).\cite{34}

![Scheme 21. Enantioselective hydroformylation of amine-based substrates.](image)

When amine-based substrates are hydroformylated in combination with an enantioenriched version of the previously discussed scaffolding ligand $30$ high enantioselectivities of up to 92% are obtained (Scheme 21, 37).\cite{135} Directed hydroformylation of 2,5-cyclohexadienyl-1-carbinols with diphenylphosphite as ligand allowed excellent regio- and diastereocontrol (Scheme 22, 38).\cite{136}

![Scheme 22. Directed hydroformylation of 2,5-cyclohexadienyl-1-carbinols.](image)

Remarkably, placement of the binding moiety of the scaffolding ligand at a larger distance from the phosphorus atom reverses the selectivity completely. Now preorganization leads to the insertion at the outermost carbon providing the product with selectivities of up to $\alpha: \omega = 19:1$ (Scheme 23, 39).\cite{137} Altering the distance between the alcohol and the olefinic moiety reveals that the homoallylic alcohols reacted with the highest selectivity using this system to form 6-membered lactols and lactones.
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Scheme 23. Divergent selectivity upon variation of the scaffolding ligand.

3. Hydroformylation in confined spaces

In the previous section, substrate preorganization using supramolecular directing groups was discussed. As can be seen, this strategy has allowed for impressive control over the regioselectivity for many substrates. However, this strategy requires a (supramolecular) directing group. As a result, this strategy is not applicable for unfunctionalized alkenes. Many substrates that are of interest do not possess such a directing group and therefore alternative strategies are required to control the selectivity. The use of encapsulated catalysts can provide an entry to control the selectivity of such substrates. As encapsulation creates a microenvironment around the transition metal center and due to this microenvironment certain reaction pathways become more accessible than others, which allows for selectivity control. For many types of reactions this strategy has proven effective to obtain selectivity control and this topic has been reviewed extensively by many groups.[138–146] In this section we will discuss the most important examples in the hydroformylation reaction.

One of the first examples of using confined spaces for hydroformylation catalysis was published by Monflier et al. A modified cyclodextrin was used to perform hydroformylation in a biphasic system with hydrophobic olefins (Scheme 24).[147] The water soluble triphenylphosphine analog was in the water layer and the hydrophobic pocket of the water soluble cyclodextrin 40 served as a phase transfer catalyst. In absence of the cyclodextrin moiety the activity was significantly lower and only the substrates that were water soluble were converted. Moreover, later studies with cyclodextrins and water soluble phosphines displayed that the phosphine ligand interacted with the cyclodextrin moiety and formed an inclusion complex.[148] The formation of an inclusion complex results that a single phosphine is coordinated to rhodium and these monophosphine ligated complexes react with lower linear selectivity for aliphatic alkenes. To increase the linear selectivity, more bulky sulfonated phosphines were synthesized to inhibit the formation of inclusion complexes inside the cyclodextrin moiety.[149–151] This modification did not only lead to higher linear selectivity with the cyclodextrin system, it also led to higher conversions. Which shows the inclusion complex is less catalytically active and/or
the inclusion of rhodium in the cyclodextrin competes with substrate transportation into
the water layer.

![Scheme 24](image)

Scheme 24 Cyclodextrin moieties as phase transfer catalysts for hydrophobic substrates in
aqueous hydroformylation

A water soluble sulfonated Xantphos ligand combined with a cyclodextrin moiety resulted
in a highly linear selective system in water.\[^{151}\] Interestingly in the presence of a
cyclodextrin, the linear selectivity was higher than in absence of the cyclodextrin, which
shows the inclusion of the substrate into the cyclodextrin moiety enhances the
regioselectivity under these conditions.

A recent example by Monflier et al. extended the cyclodextrin approach to fully solvent
free conditions.\[^{152}\] The rhodium phosphine catalyst and the substrate was immersed in
a mixture of acyclic saccharides and cyclodextrines. This resulted in complete dispersion
of the substrates in the solid. When the substrate allyl naphthalene was used in
combination with a larger cyclodextrin (n = 7), the alkene functional group was deeply
immersed in the cyclodextrin. This led to a selectivity enhancement to the outermost
aldehyde.

Other groups covalently functionalized cyclodextrins with phosphine ligands to control
the regioselectivity and enantioselectivity. Reetz et al. reported a cyclodextrin that was
covalently functionalized with a bisphosphorous moiety.\[^{153,154}\] The use of this
cyclodextrin moiety in the biphasic hydroformylation of 1-octene resulted in a significant
increase in the activity compared to analogous non-encapsulated ligands. Later on, Matt
and coworkers functionalized a cyclodextrin with a single phosphorous moiety 41
(Scheme 25).\[^{155}\] This catalyst was able to hydroformylate styrene derivatives with
exceptionally high enantioselectivities. Moreover, the cyclodextrin phosphine catalyst
also suppressed the formation of the linear aldehyde product, which is often difficult to
control with other enantioselective catalysts reported. What is remarkable is that the
chirality comes only from the cyclodextrin moiety, which is a nice example of the second
coordination sphere controlling the enantioselectivity.
Reek and coworkers reported the first example of branched selectivity for aliphatic alkenes in the hydroformylation reaction.\[54,55\] Branched selectivity was achieved using an encapsulated catalyst. The catalyst used based on a self-assembled cage consisting of a meta-trispyridyl phosphine \([\text{P(mPy}_3]]\) that was combined with three Zinc-tetraphenylporphyrin (ZnTPP) building blocks to form the caged structure (Scheme 26). This structure can be combined with a rhodium precursor to form the active catalyst under hydroformylation conditions 42.

Scheme 26 [Rh(H)(CO)\textsubscript{3}(P(mPy\textsubscript{3}(ZnTPP))\textsubscript{3})] hydroformylation cage assembly. ZnTPP building blocks yellow for clarity

This approach was coined the ligand-template approach.\[156,157\] In this approach the ligand also forms a template to form a supramolecular structure. This supramolecular structure can subsequently be used to induce confinement effects around the catalytically active center. The phosphine atom of \([\text{P(mPy}_3]]\) can coordinate to rhodium. This encapsulated catalyst 42 can form an excess of the branched product when reacted with 1-octene (l/b=...
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0.56) (Scheme 27a). Currently, only three catalyst classes are known that form branched aldehydes from terminal aliphatic alkenes despite the many research efforts conducted (vide supra). Following encapsulation of the \([P(nPy)_3]\) with three ZnTPP moieties, the activity increases a tenfold when compared to the same catalyst in absence of ZnTPP. This is, at least in part, explained by the monophosphine coordination that is enforced around rhodium, which are generally more active than the bisphosphine ligated analogs. Indeed, DFT calculations showed that catalytic pathway of the monophosphine coordinated species had lower overall barriers and as such is more reactive than the bisphosphine species.\(^{[158]}\)

![Diagram of catalytic species](image)

Scheme 27 Previously reported examples of selectivity with 42 and caged analogs based on 43 and 44. Encapsulation blocks certain reaction pathways to outermost aldehyde product.

What is remarkable, is that 42 can also convert internal aliphatic alkenes with selectivity to the innermost aldehyde. Due to the lack of both steric and electronic bias to either aldehyde product.\(^{[159]}\) Trans-2-octene (Scheme 27b) was converted with a 9:1 selectivity to the innermost aldehyde and trans-3-octene was converted with a selectivity of 4:1 (Scheme 27c), which demonstrates the power of second coordination sphere catalysis. DFT calculations on this system revealed that the porphyrin walls of the cage block alkene rotation in the hydride migration step to the outermost aldehyde product. As a result the innermost product is formed with high selectivity.\(^{[160]}\) To further optimize the system, the ZnTPP building block was replaced with several analogs. In one study, the ZnTPP was substituted with a ruthenium(II) carbonyl tetraphenyl porphyrin, which forms stronger
bonds with pyridine. This replacement resulted in a higher regioselectivity for the branched product (l/b = 0.4) under equivalent conditions, but at the cost of activity due to the formation of a more rigid capsule.[55]

Also substituted zinc porphyrins were studied and it was found that only when a single substituent was present on the meta position of all phenyl rings, successful cage formation and subsequent regioselectivity control was observed.[160] Mechanistic studies showed that the presence of substituents on the para or ortho position of the phenyl rings of the porphyrin disrupted crucial C-H-π interactions required for capsule formation. As a result, the use of such porphyrins did not result in the formation of branched selective capsules. Increased temperatures rapidly result in lower branched selectivities due to dissociation of the capsule since the capsule is held together by noncovalent interactions. Gratifyingly, it was shown that high pressures of CO allowed for branched product selectivity at higher temperatures of 75-80°C with 42, which was desirable for industrial applications.[161] Later on, it was found that a Zn-porpholactone 43, which is an oxidized analog of ZnTPP (Figure 17) formed a cage with $[P(\text{mPy})_3]$ with a similar shape as 42.[162] Due to a stronger Zn-pyridine interaction with 43 than with ZnTPP, this allows for selective catalysis at higher temperatures and/or in more coordinative solvents. Furthermore, the windows of the 43 based cage are slightly smaller which resulted in improved regioselectivity control of smaller substrates such as propene (Scheme 27d). With the 43 based cage an excess of the branched product was formed in the hydroformylation reaction (l/b = 0.84), which demonstrates its industrially relevance. In another study, ZnTPP porphyrins were functionalized with chiral groups 44 to obtain an enantioselective caged catalyst with [Rh($P(\text{mPy})_3$)] (Figure 17). Despite the fact that the chiral substituents were remote from the catalytically active rhodium center, the chirality could be transferred to the catalyst and enantiomeric excess was obtained in the hydroformylation of vinyl acetate (33% ee) (Scheme 27e). Similar to the work of Matt et al.[155] (vide supra), this is a nice example of where the enantioselectivity is obtained solely via the second coordination sphere. Also a molecular Zn(II) porphyrin clip that was reported by Nolte et al.[163] was found to form a self-assembled cage in combination with $[P(\text{mPy})_3]$. Again, the rhodium catalyst based on this cage formed an excess of the branched product in the hydroformylation of 1-octene.[164] Interestingly, only when a methyl viologen guest was added as a cofactor, selective cage formation was obtained, thereby paving the way for switchable catalysis.
Figure 17 Porpholactone (left) allows for capsule formation at higher temperatures and/or more coordinative solvents and chiral porphyrin (right) allows for second coordination sphere controlled chirality.

This ligand-template approach can be extended by replacing the meta substituted [P(mPy$_3$)] with the para substituted trispyridyl phosphine [P(pPy$_3$)].$^{[165]}$ In combination with three ZnTPP moieties and a rhodium precursor resulted in a more open structure than the [P(mPy$_3$)] ligand in combination with three equivalents of ZnTPP. A crystal structure of this ligand-template system was obtained, which displayed a rare hexacoordinate Zn species ligated by two pyridine moieties. The application the (P(pPy$_3$(ZnTPP))$_3$) based encapsulated catalyst in the rhodium catalyzed hydroformylation of 1-octene resulted in a product distribution typical for a bisphosphine ligated rhodium species. This shows the supramolecular complex does not enforce monophosphine coordination which was the case for the 42 catalyst.

[P(pPy$_3$)] and [P(mPy$_3$)] were also studied in combination with zinc salphens and zinc bis(thiosemicarbazonato) complexes to generate encapsulated rhodium complexes.$^{[166,167]}$ These zinc salphens and zinc bis(thiosemicarbazonato) complexes are significantly smaller than the aforementioned ZnTPP porphyrin. Due to the smaller size of the zinc salphen and zinc bis(thiosemicarbazonato) building blocks, these building blocks did not lead to the formation of a well-defined monocoordinated rhodium complex. For a Rhodium catalyst based on [P(mPy$_3$)] and a salphen complex an increase is observed in the branched selectivity (l/b = 0.8) compared to the non-encapsulated analog. However, the branched selectivity is lower than with the initially reported 42 caged catalyst.

The ligand-template approach was also applied in combination with a chiral ligand to enhance the enantioselectivity in several reports by Reek et al (Scheme 28)$^{[168–170]}$ To achieve high levels of enantioselectivity, phosphoramidite ligands are used that are functionalized with two pyridine moieties. These pyridine moieties are used to bind ZnTPP, which results in a confined structure around rhodium 45. The encapsulation of
this catalyst with ZnTPP results in a conformational change of the phosphorous ligand around rhodium. In absence of ZnTPP the phosphoramidite ligand adopts an equatorial orientation around rhodium. However, when ZnTPP is added, the phosphoramidite adopts an axial orientation.

Scheme 28 Ligand template assembly based on a chiral phosphoramidite ligand. Confinement with ZnTPP enhances the branched selectivity

This encapsulated catalyst 45 also leads to significantly higher levels of enantioselectivity in the hydroformylation of trans-2-octene compared to the unencapsulated phosphoramidite based catalyst. The binol motif that contained two pyridine coordination moieties that formed the basis of the aforementioned enantioselective catalyst, was also used to generate phosphine-phosphoramidite bidentate ligands. To these phosphine-phosphoramidite bidentate ligands ZnTPP as well as several ZnTPP analogs were added, which resulted in higher enantioselectivities in the hydroformylation of styrene derivatives compared to the same entries in absence of the ZnTPP derivatives.

The ligand-template approach was also applied in combination with a chiral ligand to enhance the enantioselectivity in several reports by Reek et al (Scheme 28). To achieve high levels of enantioselectivity, phosphoramidite ligands are used that are functionalized with two pyridine moieties. These pyridine moieties are used to bind ZnTPP, which results in a confined structure around rhodium 45. The encapsulation of this catalyst with ZnTPP results in a conformational change of the phosphorous ligand around rhodium. In absence of ZnTPP the phosphoramidite ligand adopts an equatorial
orientation around rhodium. However, when ZnTPP is added, the phosphoramidite adopts an axial orientation. This encapsulated catalyst 45 also leads to significantly higher levels of enantioselectivity in the hydroformylation of trans-2-octene compared to the unencapsulated phosphoramidite based catalyst. The binol motif that contained two pyridine coordination moieties that formed the basis of the aforementioned enantioselective catalyst, was also used to generate phosphine-phosphoramidite bidentate ligands.\textsuperscript{169} To these phosphine-phosphoramidite bidentate ligands ZnTPP as well as several ZnTPP analogs were added, which resulted in higher enantioselectivities in the hydroformylation of styrene derivatives compared to the same entries in absence of the ZnTPP derivatives.

A \textit{meta} substituted pyridine analog of the aforementioned phosphoramidite ligand could also be used to generate caged structure when combined with two bis-[Zn\textsuperscript{II}(salphen)] building blocks. This formed a “supramolecular box” 46 (Scheme 29).\textsuperscript{167,170} The pyridine functionalized phosphoramidite ligands formed the pillars of this box and this allowed for the formation of an encapsulated bisphosphorhorous coordinated rhodium complex. Due to confinement effects, the enantio- and regioselectivity could effectively be controlled for \textit{trans}-2-octene, with the innermost aldehyde product being formed in excess with exceptionally high enantioselectivity.

\begin{center}
 Scheme 29 Ligand template assembly to generate a chiral “supramolecular box”. Encapsulation results in regio- and enantioselectivity control for 2-octene in the hydroformylation reaction
\end{center}

The same pyridine functionalized phosphoramidite ligand that was applied in the “supramolecular box” depicted in Scheme 29 was also encapsulated in a palladium based metallocage that was reported by Costas et al.\textsuperscript{171} This metallocaged rhodium catalyst was
able to hydroformylate styrene type substrates with higher levels of enantioselectivity than the free phosphoramidite ligand due to confinement effects.\textsuperscript{[172]}

Scheme 30 Encapsulated bisphosphine catalyst in a Fe\textsubscript{4}L\textsubscript{6} cage as reported allows for the selective hydroformylation of mixtures with the smaller substrate being converted preferentially over the larger substrate.

Another example of selectivity control in the hydroformylation using the a Zn-pyridine interaction employs a Fe\textsubscript{4}L\textsubscript{6} Zn-porphyrin cage that was reported by Nitschke and coworkers to encapsulate two [P(pPy\textsubscript{3})] ligands via the a Zn-pyridine interaction with the Zinc porphyrin moieties present on the walls of the cage (Scheme 30).\textsuperscript{[173,174]} This led to the formation of an encapsulated rhodium catalyst ligated by two phosphine ligands. Due to the small windows of the cage, smaller substrates are converted with higher rates than larger substrates. This resulted in substrate selectivity for smaller substrates when competition experiments were conducted with both large and small substrates, which bears resemblance to the effects commonly observed in enzymatic catalysis where the enzyme selectively converts a single substrate from a large pool of substrates.
Thesis scope and outline

The work in this chapter discusses supramolecular concepts applied in the hydroformylation reaction and these concepts have served as an inspiration for this thesis. This thesis is the result of research efforts conducted to further expand the field of supramolecular approaches in the hydroformylation reaction. In particular, the substrate preorganization strategies as well as second coordination sphere catalysis have been applied in this thesis. These efforts have resulted in regioselective transformations for several substrates and novel mechanistic insights and are reported in the following chapters.

Chapter 2 focuses on the mechanistic understanding of why DIMPhos catalysts enhance the formation of the aldehyde product in which the carbonyl is farthest from the carboxylic acid directing group. To explain this phenomenon, DFT calculations were conducted on a DIMPhos phosphine system. These calculations show that the pathways leading to the aldehyde product that is closest to the carboxylic acid directing group are significantly higher in energy. Following ditopic substrate binding the competing, innermost product forming pathways, are blocked due to steric hindrance between the substrate and the CO ligand of the catalyst. As a result, the catalyst adopts an orientation that preorganizes to the migration step that leads to the product with the aldehyde farthest from the acid. The concept that the catalyst rearranges to accommodate the substrate, which forms the basis for selectivity control, shares similarities with induced fit effects commonly observed in enzymatic catalysis.

Chapter 3 reports the redesign of a supramolecular Rh–bisphosphite hydroformylation catalyst containing a neutral carboxylate receptor (DIM pocket) with a larger distance between the phosphite metal binding moieties and the DIM pocket. This was done to achieve regioselective hydroformylation of internal and terminal alkenes that are remote from the carboxylic acid directing group. 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 Δ-9 position regio-selectivity is observed. As such, the catalyst was used to hydroformylate natural monounsaturated fatty acids (MUFAs) in a regioselective fashion, forming 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 fatty acids.

Chapter 4 focuses on whether bisphosphines and bisphosphites functionalized with an anion receptor other than the previously reported diindolylmethane anion receptor (DIM pocket) in the backbone can be used to control the regioselectivity in the rhodium catalyzed hydroformylation reaction of unsaturated carboxylates. To investigate this, we synthesized three 1,3-benzenedicarboxamide anion receptor functionalized ligands: one bisphosphine ligand L1, and two bisphosphite ligands, L2 and L3. Catalytic studies show that the [RhL3] complex is able to convert 3-butenoate up to 7-octenoate with higher levels of regioselectivity than the control experiments. This shows that other anion
receptor functionalized bisphosphorous ligands can be used for regioselective hydroformylation reactions. In contrast, the other two designed ligands do not give higher regioselectivity than the control experiments. Mechanistic studies show that the rhodium complexes based on ligands \textbf{L1-L3} do not selectively 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 contribute to the catalytic outcome, which lowers the supramolecular control of the regioselectivity when these \textbf{L1} and \textbf{L2} based complexes are used.

\textbf{Chapter 5} reports the investigation of the substrate scope using 41 terminal alkenes in the hydroformylation reaction using our previously reported encapsulated rhodium catalyst \([\text{Rh(H)(CO)}_3\{\text{P}_{\text{mPy}}_3(\text{ZnTPP})_3\}]\). This was done as substrates with different sizes should experience different confinement effects with the encapsulated catalyst. In all reactions where the encapsulated catalyst was used the amount of branched hydroformylation product was higher with the encapsulated catalyst than with the unencapsulated reference catalyst \([\text{Rh(H)(CO)}_2\{\text{P}_{\text{mPy}}_2\}]\). However, the level of selectivity control with the encapsulated catalyst was found to strongly depend on the substrate and this investigation reveals privileged substrates that provide the aldehyde with exceptional branched selectivity with the encapsulated catalyst. Analysis of the substrate scope combined with DFT calculations suggest that supramolecular interactions between certain moieties of the substrate with the walls of the cage play a key role in controlling the regioselectivity. These supramolecular interactions were optimized by replacing the \textbf{ZnTPP} building block for cage formation with an analog that contained OiPr substituents on one of the \textit{meta} positions of the aryl rings of the porphyrin. The resulting caged catalyst could convert substrates with even higher branched selectivity.

In \textbf{chapter 6} reports if correlation equations using multivariate linear regression analyses are helpful tools for the prediction of the selectivity of the substrate scope reported in \textbf{chapter 5} for both the encapsulated \([\text{Rh(H)(CO)}_3\{\text{P}_{\text{mPy}}_3(\text{ZnTPP})_3\}]\) catalyst as well as the unencapsulated \([\text{Rh(H)(CO)}_2\{\text{P}_{\text{mPy}}_2\}]\) catalyst in the hydroformylation reaction. To understand the catalytic outcomes, several substrate descriptors were obtained from every substrate and such descriptors were used to find meaningful correlations between the energy difference and several substrate properties. For the unencapsulated catalyst, strong correlations were found for a formula that employs the \(\Delta^{13}\text{C}\) shift and the intensity of the C=C alkene vibration to predict the regioisomeric outcome, which shows that the regioisomeric outcome under these conditions used are mostly determined on the basis of electronic factors of the alkene site of the substrate. In contrast, the correlation was significantly weaker with the caged catalyst which shows many other factors affect the regioisomeric outcome due to confinement effects. Therefore, Sterimol parameters of the substrate were employed to account for steric effects. Unfortunately this did not lead to models that improved reaction prediction. Most likely, 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.
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