Supramolecular control of regioselectivity in the hydroformylation reaction

Substrate preorganization and second coordination sphere catalysis

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Invitation to the public defense of my thesis

Supramolecular Control of Regioselectivity in the Hydroformylation reaction: Substrate Preorganization and Second Coordination Sphere Catalysis

On Wednesday the 31st of March at 11:00

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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*


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 H\textsubscript{2} and 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.\cite{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.\cite{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. n-butyraldehyde and iso-butyraldehyde, finding many industrial applications.\cite{3,5} For instance, n-butyraldehyde can be converted to 1-butanol, which is used for the production of 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.\cite{8}

Chiral products can also be synthesized 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.
Supramolecular Approaches to Control Activity and Selectivity in Hydroformylation Catalysis

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]

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

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.[326] 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](image)

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).[27–31]

![Scheme 4](image)

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.\cite{40, 41} The reactivity trends are established as:

$$\text{Ph}_3\text{P} > \text{Ph}_3\text{As} > \text{Ph}_3\text{N} > \text{P} \text{h}_3\text{Sb} > \text{Ph}_3\text{Bi}$$

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.

![Figure 2 Classes of substituted phosphorous atoms generally applied in the hydroformylation reaction.](image-url)
Replacement of one of the carbon atoms with an oxygen group results in the formation of phosphinites, two carbon atoms results 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.\textsuperscript{[26]} In contrast, the activity often increases following the addition of phosphines for rhodium.\textsuperscript{[3]}

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.\textsuperscript{[32,33]} 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 (\textit{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
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.

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[42,43] and Xantphos[44,45] 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.[46] 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.[47,48] 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.[49] 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.[50] 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.[51–53]
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).\textsuperscript{[54,55]} Later on, Clarke et al. reported BOBphos which is a chiral bidentate phosphite-phospholane ligand with a small bite angle.\textsuperscript{[56]} 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.\textsuperscript{[57]} To stabilize these CH−π interactions, the toluene solvent was replaced with an octafluorotoluene, which resulted in even higher levels of selectivity to the branched product.\textsuperscript{[58]} This high selectivity was also obtained for propene (l/b = 0.22), which demonstrates the potential of this ligand for industrial applications.
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-phosphoramidite 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 alkenes (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.[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).[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.[90–93] Alternatively, such substrates can be subjected to an isomerization-hydroformylation sequence, which yields the linear product in modest yields under optimized conditions.[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.
Supramolecular Approaches to Control Activity and Selectivity in Hydroformylation Catalysis

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 by 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 via a Zn-pyridine interaction forming a supramolecular bidentate (Figure 9).

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.
Supramolecular Approaches to Control Activity and Selectivity in Hydroformylation Catalysis

Scheme 8 6-diphenylphosphanyl-2-pyridone (6-DPOn) 12 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).[103] 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.[104,105] 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.[104] Also, another heterobidentate Supraphos catalyst delivered the linear product in the hydroformylation of styrene with 72% selectivity.[105]

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.

By introducing a recognition site in the backbone of the catalyst, no longer preorganization of the substrate is established \textit{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 \textit{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.](image)

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).](image)

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).

![Scheme 10. Selectivity for 4-pentenoic acid hydroformylation.](image)

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 triphenyl phosphine-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.
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(l:b = 32), compared to the alkene moiety that is further from the carboxylic acid (l:b = 3).\textsuperscript{[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.\textsuperscript{[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 \( \alpha,\beta \) unsaturated carboxylic acids.
The [Rh]/13 catalysts is also effective in a decarboxylative hydroformylation of α,β-unsaturated carboxylic acids (Scheme 11).\textsuperscript{112} In this cascade reaction the formyl group is introduced on the substrate, after which the carboxylate leaves the substrate as CO\textsubscript{2}. 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).\textsuperscript{113} These internal alkynes could be converted to obtain internal aliphatic aldehydes with high levels of regioselectivity and chemoselectivity.

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).\textsuperscript{114}

\[
\text{Scheme 13. Tandem processes using supramolecular substrate preorganization ligands.}
\]

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). 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. 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.

Regioslective hydroformylation of unsaturated acids can also be achieved with a series of bidentate phosphines and phosphite ligands, coined DIMPhos, functionalized with a highly selective anion receptor, 7,7-diamido-2,2-diindolylmethane (Figure 14).

Figure 14. Anion receptor functionalized bisphosphines (DIMPhos).
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.[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. [117,118].

An ortho analog of the DIMphos catalyst allowed for the selective hydroformylation of smaller substrates such as 3-butenoate.[120] Interestingly this ligand formed a dimer complex, that transformed into the monomer species in the presence of large amounts of carboxylates.[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.
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Figure 15. Substrate pre-organization in the selectivity determining hydride migration step (DFT study).

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.\(^{[118]}\) The CO inserts farthest from the carboxylate and exceptionally high selectivities are observed for internal alkenes (i.e. up to \(\alpha:i = 78\)) 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.

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].\(^{[122,123]}\) 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).\(^{[122-124]}\) 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).
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). The advantage is that branched aldehydes can be synthesized from inexpensive terminal alkenes in selectivities competitive to the highest direct branched selective hydroformylation catalyst.

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. 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.

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). 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,α-disubstituted alcohols to form quaternary carbon centers.
The same scaffolding strategy can also be applied to form quaternary carbon centers via a hydroformylolation reaction, which is considered as one of the most challenging reactions in hydroformylation.\textsuperscript{133,134} Hydroformylation to form quaternary carbon centers was achieved when $\alpha,\alpha$, disubstituted olefins were used with the previously discussed scaffolding ligands \textsuperscript{28} and \textsuperscript{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, \textsuperscript{35} and \textsuperscript{36}).\textsuperscript{34}

Scheme 21. Enantioselective hydroformylation of amine-based substrates.

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

Scheme 22. Directed hydroformylation of 2,5-cyclohexadienyl-1-carbinols.

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 $\alpha:1 = 19:1$ (Scheme 23, \textsuperscript{39}).\textsuperscript{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.
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 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.\footnote{[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.\footnote{[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.\footnote{[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 \footnote{[155]} (Scheme 25). 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. Branched selectivity was achieved using an encapsulated catalyst. The catalyst used was based on a self-assembled cage consisting of a \textit{meta}-trispyridyl phosphine \([P_{(m)Py_3}]\) 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.

This approach was coined the ligand-template approach. 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 \([P_{(m)Py_3}]\) can coordinate to rhodium. This encapsulated catalyst can form an excess of the branched product when reacted with 1-octene (l/b=
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 \([\text{P(n,P_3)}]\) 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 coordinated species.\(^{[158]}\)

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 $[P(mPy)_3]$ 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 $[Rh(P(mPy)_3)]$ (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 $[P(mPy)_3]$. 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 of \((P_{(pPy_3(ZnTPP))_3})\) 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 (I/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.\[169]\] 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 meta substituted pyridine analog of the aforementioned phosphoramidite ligand could also be used to generate caged structure when combined with two bis-[ZnII(salphen)] building blocks. This formed a “supramolecular box” 46 (Scheme 29).\[167,170] The pyridine functionalized phosphoramidite ligands formed the pillars of this box and this allowed for the formation of an encapsulated bisphosphorous coordinated rhodium complex. Due to confinement effects, the enantio- and regioselectivity could effectively be controlled for trans-2-octene, with the innermost aldehyde product being formed in excess with exceptionally high enantioselectivity.

![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.](image)

The same pyridine functionalized phosphoramidite ligand that was applied in the “supramolecular box” depicted in Scheme 29 was also encapsulated in a palladium based metalloccage that was reported by Costas et al.\[171] This metalloccaged 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(\textit{p}Py\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-butenolate 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 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 L1 and L2 based complexes are used.

Chapter 5 reports the investigation of the substrate scope using 41 terminal alkenes in the hydroformylation reaction using our previously reported encapsulated rhodium catalyst [Rh(\(\text{H}(\text{CO})_3\))\(\{\text{P}(_{m}\text{Py}_3\text{ZnTPP})_3\}\)]. 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 [Rh(\(\text{H}(\text{CO})_2\))\(\{\text{P}(_{n}\text{Py}_3)_2\}\)]. 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 ZnTPP building block for cage formation with an analog that contained OiPr substituents on one of the meta positions of the aryl rings of the porphyrin. The resulting caged catalyst could convert substrates with even higher branched selectivity.

In 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 chapter 5 for both the encapsulated [Rh(\(\text{H}(\text{CO})_3\))\(\{\text{P}(_{m}\text{Py}_3\text{ZnTPP})_3\}\)] catalyst as well as the unencapsulated [Rh(\(\text{H}(\text{CO})_2\))\(\{\text{P}(_{n}\text{Py}_3)_2\}\)] 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.
Supramolecular Approaches to Control Activity and Selectivity in Hydroformylation Catalysis

References


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Chapter 1


Supramolecular Approaches to Control Activity and Selectivity in Hydroformylation Catalysis


Chapter 2

Unraveling the Origin of the Regioselectivity of a Supramolecular Hydroformylation Catalyst
Introduction

Immense progress in the field of transition metal catalysis 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 important to also control the selectivity of the reaction, which nowadays has been achieved for numerous transformations.\cite{1,2} In general, the intrinsic reactivity of the substrate is exploited and the reaction conditions are optimized to achieve selective transformations. Exploiting this intrinsic reactivity of the substrate, however, becomes less effective when pathways leading to different products are very similar, or even worse, if the desired product is formed via a higher reaction barrier pathway compared to a side product forming pathway. In the past two decades, supramolecular strategies in transition metal catalysis have provided chemists a toolbox to obtain selectivity control for challenging substrates as these strategies allow for energetic differentiation among competing reaction pathways.\cite{3–13} Indeed, applying such supramolecular strategies has led to unique selectivity control complementary to traditional transition metal complexes.\cite{14–36}

![Schematic drawing of supramolecular substrate preorganization](image)

One commonly explored supramolecular strategy relies on the use of bifunctional ligands that, apart from the donor atoms for coordination to the metal center, possess a recognition site for a directing group located on the substrate.\cite{4,6,11} This strategy is commonly referred to as (supramolecular) substrate preorganization (or orientation) and is depicted schematically in Figure 1. Through binding of the directing group to the recognition site of the ligand, the selectivity can be controlled as the substrate is positioned in such a way that the reactive group is preorganized with respect to the catalytically active metal center.

A reaction in which this strategy has been applied successfully is the hydroformylation reaction, which is a transition metal catalyzed reaction where a double bond is reacted with a syngas mixture (H\textsubscript{2}:CO) to yield an aldehyde (Figure 2).\cite{37,38} As the aldehyde can be incorporated on both sides of the double bond, the regioselectivity of this reaction needs to be controlled as often multiple products are formed.
The generally accepted mechanism, which is displayed in Figure 3, commences with the dissociation of CO from the biscarbonyl complex (Resting state) to generate the 16-electron species (1). This is followed by alkene coordination (2). Subsequently, the hydride can migrate to either carbon atom of the alkene (ts3), leading to the formation of two possible rhodium-alkyl regioisomers, (4) after which CO coordinates to rhodium to form (5). Migratory insertion of the CO (ts6) generates an acyl species (7). Subsequent hydrogenolysis steps (ts9, 10 and 11) finally generates the aldehyde product (12) and regenerates (1) to close the catalytic cycle.

Figure 3 General hydroformylation catalytic cycle, hydride migration step controlled via supramolecular substrate preorganization.
For many substrates, the optimization of the catalyst and the reaction conditions, often by varying the syngas pressure and the ligand used, can lead to the formation of a large excess of a single regioisomer with high selectivity.\textsuperscript{[36,37,45–52]} However, this strategy falls short for substrates where the reactivity of the alkene is not biased to a single product or alternatively, the reactive alkene is biased to a product that is different from the desired product.\textsuperscript{[17,53–59]}

Using the supramolecular substrate preorganization strategy, our group and the group of Breit \textit{et al.} were able to control the regioselectivity of challenging substrates in the hydroformylation reaction using a carboxylate directing group.\textsuperscript{[18,20,25–29,35,60,61]} The selective catalysts reported by our group were based on bisphosphine or bisphosphite ligands, coined DIMPhos, which contain a neutral anion receptor based on 7,7'-diamido-2,2'-diindolylmethane (DIM pocket) in the backbone for carboxylate binding (Figure 4).\textsuperscript{[62]}

\begin{figure}
\centering
\includegraphics[width=\textwidth]{supramolecular_preorganization.png}
\caption{Supramolecular substrate preorganization hydroformylation catalysis yield the aldehyde product farthest from the carboxylic acid i.e. the linear product for terminal alkenes.}
\end{figure}

For all the DIMPhos based rhodium catalysts investigated so far, the aldehyde product that was formed was that with the aldehyde farthest from the directing group e.g. for terminal alkenes the linear aldehyde was the dominant product. This phenomenon was also exploited for 2-carboxyvinylarenes, which are converted to the linear (outermost) aldehyde product, overruling the typical natural branched selectivity of these compounds.\textsuperscript{[19,60]} Moreover, we recently reported the regioselective conversion of the internal double bond of natural fatty acids using this substrate preorganization approach,
in which the distance between the carboxylic acid directing group and the internal alkene reactive group was eight bonds.\textsuperscript{[25]}

Preliminary calculations combined with mechanistic studies show that the regioselectivity for these catalysts is determined in the hydride migration step of the catalytic cycle (Figure 3). Ditopic substrate binding restricts alkene rotation, which leads to the outermost product formation (Figure 5).\textsuperscript{[18,35]} However, the reason why the hydride migration transition state that leads to the outermost aldehyde product is significantly lower than the competing innermost hydride migration transition state is not well understood. For other hydroformylation catalysts, in-depth DFT calculations have resulted in improved understanding of these catalysts.\textsuperscript{[63–69]} In this chapter we report a theoretical study to pinpoint the mechanistic basis that explains the typical regioselectivity observed for the DIMPhos based rhodium catalysts.

Figure 5 Restricted rotation the controls selectivity determining hydride migration step

**Results and discussion**

To investigate the mechanistic basis for the observed regioselectivity, the reaction profile of the DIMPhos catalyst was analyzed using DFT calculations. The ADF modeling suite was used with BLYP-D3BJ as a functional, DZP as a basis set for all atoms apart from rhodium, for which a TZP basis set was used.\textsuperscript{[70]} Furthermore, we used ZORA to account for relativistic effects.\textsuperscript{[71]} The ligand system used was a simplified version of bis-(4-(diphenylphosphino)benzoamide) of 1,1-bis-(7-amino-3-methyl-1H-indol-2-yl)-propane), coined DIMPhos, (Figure 7).\textsuperscript{[18,35,60]} This simplification is justified as it involves alkyl groups remote from the catalyst. With the resultant [Rh (DIMPhos) (CO)\textsubscript{2}(H)] complex, we calculated the catalytic pathway of the hydroformylation reaction of 4-pentenoate, which is a substrate that is experimentally found to be converted with high
regioselectivity. The substrate exactly spans the distance between the carboxylate receptor and the rhodium metal center of this catalyst.

Figure 6 Catalytic [Rh(DIMPhos)] system studied; conversion of 4-pentenoate to 6-oxohexanoate and 4-methyl-5-oxopentanoate with [Rh (DIMphos) (CO)\(_2\)](H)]

Figure 7 Lowest energy pathway of the hydroformylation of 4-pentenoate to 6-oxohexanoate with [Rh (DIMphos) (CO)\(_2\)](H)]. In this figure, only the lowest observed energetic minima and relevant transition states are reported for clarity

The DFT calculated energy profile of the conversion of 4-pentenoate to 6-oxohexanoate is reported in Figure 7. The reaction commences with CO dissociation from [Rh ((4-pentanoate) ⊂ DIMPhos) (CO)\(_2\)](H)] directly followed by the alkene coordination (2) that
is already bound to the anion binding pocket. This is followed by a hydride migration step (TS3). The combination of these aforementioned steps (2 & 3) represents the highest energetic barrier for this reaction pathway, which identifies these steps as rate and selectivity determining. This is consistent with previously reported mechanistic studies on this system.[18,35] For the later steps, significantly lower energetic barriers are obtained and therefore these do not significantly affect the regioisomeric outcome (see experimental details).

Since the hydride migration step from 2 via transition state TS3 leading to the alkyl intermediate 4 determines the regioselectivity, more in-depth analyses were performed on the 1) alkene coordination 2, 2) hydride migration transition state TS3 and 3) the resultant alkyl intermediate 4. More specifically, we calculated both the diphosphine coordination modes equatorial-equatorial (EE) and equatorial-axial (EA) isomers, and the pathways from these complexes to the linear and branched alkyl intermediate 4. All the product forming pathways are represented in Figure 8.

![Figure 8 Overview of competing hydride migration pathways. Blue pathways are linear product forming. Red pathways are branched product forming. Energies normalized by subtracting the energy from the lowest energy [Rh(4-pentenoate)\(\subset\)DIMPhos)(CO)(H)] structure.](image)

The four alkene coordination geometries for intermediate (2) that were obtained from our calculations are displayed in Figure 9, and are indicated EE pre linear, EE pre branched (EE stands for equatorial-equatorial coordination of phosphorus) and EA pre linear, EA pre-branched (EA stands for equatorial-axial coordination of phosphorus). The coordination geometry (EE vs EA) in the ground state (2) stay the same in the associated transition states (3).[66] After hydride migration, three alkyl intermediates (4) are obtained. One linear alkyl intermediate and two branched alkyl intermediates. The two pre-linear transition states lead to an identical linear alkyl intermediate. The two branched transition states lead to two different alkyl intermediates, with the lowest energy branched transition state also leading to the lowest branched alkyl intermediate.
In line with the experimentally observed selectivity, the lowest energy pathway is the EE linear pathway that eventually leads to the linear aldehyde. The transition state barrier for formation of the linear aldehyde from the EA pre-linear intermediate is 3.3 kcal/mol higher in energy, and the barrier for formation of the branched aldehyde from EA pre-branched is 4.2 kcal/mol. The branched transition states are significantly higher than the lowest linear transition state (4.2 and 15.7 kcal/mol). Therefore, these pathways do not likely contribute to the catalytic outcome, in line with the experimentally observed selectivity. Interestingly, the energy differences in the selectivity determining transition states, are already present in the alkene coordination complexes 2. This shows that the energetic differentiation that are the origin of the high regioselectivity induced by substrate pre-organization is in the alkene coordination state 2. We therefore inspected the structures in more detail.

Figure 9: Four ground state geometries (2) of [Rh((4-pentenoate) ⊂ DIMPphos)(CO)(H)]. Energies normalized by subtracting the energy from the lowest energy [Rh((4-pentenoate) ⊂ DIMPphos)(CO)(H)] structure. Some hydrogens and phenyls are removed for clarity.
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studied in more detail. Inspection of the ground state energies 2 or transition states TS3 do not clearly show why the energies of the alkene geometries are higher for the branched forming structures. To get an insight in the contribution of strain in the structures that lead to the branched product [Rh((4-pentenoate) ⊂ DIMPhos)(CO)(H)], we optimized a model [Rh(PPh₃)₂(H)(CO)(C₂H₄)] complex as a reference (Figure 10) and compared the angles of the two complexes for both the EE and EA orientations. This model complex is not affected by ditopic binding of the alkene and therefore should adopt a non-strained geometry. If the angles of [Rh((4-pentenoate) ⊂ DIMPhos)(CO)(H)] are similar to [Rh(PPh₃)₂(H)(CO)(C₂H₄)] complex, this suggests that this complex is less strained. The normalized energies and three key angles are represented in Table 1.

![Figure 10](image-url)

Table 1 Crucial geometric parameters of the relevant alkene coordinating geometries 2 compared with a model [Rh(PPh₃)₂(H)(CO)(ethylene)] system. Key angles represented to provide insight in how strained the geometry is.  

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<td>108.2</td>
<td>100.7</td>
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The geometric analyses show that the angles of the EE and EA pre-linear geometries of the [Rh((4-pentenoate) ⊂ DIMPhos)(CO)(H)] species are more similar to the corresponding EE and EA [Rh(PPh₃)₂(H)(CO)(C₂H₄)] species than the pre-branched EE and EA [Rh(4-pentenoate) ⊂ DIMPhos)(CO)(H)] species. In particular, the P₁-Rh-P₂ angle is significantly larger for the EE pre-branched [Rh((4-pentenoate) ⊂ DIMPhos)(CO)(H)] species (160°) compared to the corresponding EE pre-linear [Rh((4-pentenoate) ⊂ DIMPhos)(CO)(H)] species (107°) and the EE [Rh(PPh₃)₂(H)(CO)(C₂H₄)] species (105°). This shows that the EE pre-branched species adopts rhodium geometry that is more similar to a square pyramidal species than to a trigonal bipyramidal geometry. Also for the EA pre-branched [Rh((4-pentenoate) ⊂ DIMPhos)(CO)(H)] structure the P₁-Rh-P₂ angle is larger (105°) than the corresponding EA pre-linear [Rh((4-pentenoate) ⊂ DIMPhos)(CO)(H)] species (100°) as well as the EA [Rh(PPh₃)₂(H)(CO)(C₂H₄)] species (100°). Thus, in the [Rh((4-pentenoate) ⊂ DIMPhos)(CO)(H)], the rhodium complex geometry is distorted when the catalyst adopts a pre-branched orientation.

Figure 11 [Rh (DIMPhos) (CO)₂(H)] (1) complex energies normalized against the lowest energy [Rh (DIMPhos) (CO)₂(H)] geometry. All energies in kcal/mol. Some hydrogens and phenyls are removed for clarity. Minor relative energy differences observed for different coordination modes.

We next calculated the different coordination modes of [Rh (DIMPhos) (CO)₂(H)] complex (EE vs EA) (Figure 11). This is the catalyst structure in absence of the 4-pentenoate substrate. Interestingly, the relative energies display minor energy differences (up to 1.4 kcal/mol). Furthermore, when the CO points to the DIM pocket (EE₂, see Figure 11), the energy is only 0.4 kcal/mol higher than the lowest energy geometry in which the hydride
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points to the pocket. This is in contrast to the large energy difference when 4-pentenoate is coordinated to the RhDIMPhos complex (Figure 9). These results suggest that the substrate binding event is responsible for the large differences in energy in the alkene coordination step 2 and transition state TS3, which in turn is the origin for the high regioselectivity (Figure 12). Next we looked in more detail to this substrate binding event.

The ditopic substrate binding event involves CO dissociation/alkene coordination to the rhodium center as well as carboxylate binding in the DIM pocket (Figure 12). To investigate the effect of both binding events on the energetic differentiation that is responsible for the regioselectivity control, we replaced the 4-pentenoate moiety with 1) a propene moiety that coordinates to rhodium, 2) an acetate moiety that binds in the DIM pocket, or 3) both moieties (Figure 12). This allows us to systemically study the effects of binding events on the relative energy of various systems with the ligand in the EE and EA coordination modes.

![Diagram showing ditopic binding](image)

Figure 12 Ditopic binding of 4-pentenoate to the RhDIMPhos binding in the DIM pocket appears responsible for the large energy differences between the different coordination modes. Inversion of the position of the CO and the hydride results in low energy differences (ΔE) in absence of 4-pentenoate and high energy differences in the presence of acetate. Propene and acetate moieties are used as model systems for ditopic binding of 4-pentenoate to study the origin of the energetic differentiation.

The complexes for which we calculated how the relative energies changed when the ligand orientations were varied were; [Rh (DIMPhos) (CO)(H)], [Rh ((acetate) ⊂ DIMPhos) (CO)(H)], [Rh (DIMPhos) (propene)(CO)(H)], [Rh ((acetate) ⊂ DIMPhos) (CO)2(H)] and [Rh ((acetate) ⊂ (DIMPhos) (propene)(CO)(H)] (Figure 13). We have compared the energy differences between the various coordination modes around rhodium. For all
structures where rhodium is four coordinate i.e. \([\text{Rh (DIMPhos)} \ (\text{CO})(\text{H})]\) and \([\text{Rh ((acetate) } \subset \text{DIMPhos)} \ (\text{CO})(\text{H})]\), the lowest energy structure was obtained when the phosphines adopt a cis conformation. For the lowest energy geometry where the phosphines adopt a trans conformation energy was higher (0.9 – 3.1 kcal/mol) the. Interestingly, small differences in energy are observed between the two trans coordination geometries around rhodium where the CO and hydride are inverted (0.1 – 0.6 kcal/mol).

For all pentacoordinate complexes various coordination modes were calculated where the phosphines adopted an EE geometry with CO and hydride at the axial positions as well as the structures where the phosphines adopted an EA conformation. For all calculated complexes, the lowest energy geometries were structures where the phosphines adopted
an EE conformation. For several complexes, this lowest energy orientation was where CO pointed to the DIM pocket whereas others the hydride pointed to the DIM pocket (see experimental details). The EA geometries were 1.4 - 3.4 kcal/mol higher than the lowest EE geometry, similar to what is observed with [Rh((4-pentenoate)⊂ DIMPhos)(CO)(H)] (vide supra). For two complexes i.e. [Rh ((acetate) ⊂ DIMPhos) (CO)2(H)] and [Rh ((acetate) ⊂(DIMPhos) (propene)(CO)(H))] also a high energy intermediate in which the CO points to the DIM pocket was obtained (11.4 -12.3 kcal/mol)(Figure 13). As a result these structures are indicated with red. The other structures display significantly lower energy differences between the EE structures when the position of the CO and the hydride is inverted (up to 2.2 kcal mol) and were therefore indicated in green.

For most complexes no large energy differences are obtained between the different coordination modes. Only when the acetate is bound in the pocket and the rhodium is pentacoordinate; i.e. for [Rh ((acetate) ⊂ DIMPhos) (CO)2(H)] and [Rh (acetate) ⊂ DIMPhos) (propene)(CO)(H)], a large energy difference was observed. In particular, a high energy ground state structure was obtained for the complex in which a CO moiety points to the DIM pocket and the phosphines adopt an EE conformation. The effect is similar to what is observed for the [Rh ((4-pentenoate) ⊂ DIMPhos)(CO)(H)] complex (Figure 14), in which case it blocks a low energy pathway to the branched aldehyde product. This shows the complexity of the system, as the carboxylate binding event has an influence on the different coordination geometries around the rhodium metal of the [Rh((4-pentenoate) ⊂ DIMPhos)(CO)(H)] complex, and these in turn lead to blockage of some of the competing pathways. It is important to note that for substrates that cannot bind ditopically, for example 1-octene, the selectivity is low also in the control experiment in the presence of acetate. In these cases more pathways to the branched product are available as substrate rotation is not inhibited by ditopic binding. The high energy intermediate of the [Rh ((acetate) ⊂ DIMPhos) (propene)(CO)(H)] (Figure 14, left) model complex is similar to the pre-branched EE structure of [Rh((4-pentenoate) ⊂ DIMPhos)(CO)(H)] complex (Figure 14, right). We also calculated a low energy intermediate in which the CO points to the DIM pocket (Figure 15, left). However, for this structure the acetate is oriented away from the propene moiety and such structure cannot be formed for ditopically bound substrates. When the acetate is placed in close proximity to the propene moiety (Figure 15, right), the energy is significantly higher (12.3 kcal/mol). Importantly, if the CO moiety points to the DIM pocket in these structures, it experiences steric hindrance with the acetate moiety which leads to the relative high energy of these structures.
Figure 14 Structural similarity between [Rh ((4-pentenoate) ⊂ DIMPhos) (CO) (H)] EE geometry where the CO points to the DIM pocket and the high energy [Rh ((acetate) ⊂ DIMPhos) (CO) (H) (propene)] where the CO adopts a similar orientation relative to rhodium and the carboxylate moiety. ΔΔEnergies determined by subtracting the energy outcome from the lowest energy [Rh((4-pentenoate) ⊂ DIMPhos)(CO)(H)] structure and [Rh ((acetate) ⊂ DIMPhos) (propene) (CO)(H)] structure.

The model structures of the [Rh (acetate) ⊂ DIMPhos (CO) (H) (propene)] with the acetate orientated in different manners, clearly show why the analogous structure of the EE pre-branched [Rh(4-pentenoate) ⊂ DIMPhos)(CO)(H)] complex is high in energy. With 4-pentenoate, the carboxylate and propene are covalently linked and therefore are in close proximity by default, which leads to steric hindrance between the 4-pentenoate moiety and the CO ligand. This steric hindrance forms the basis for the high energy of this pre-branched structure and as a result, the catalyst adopts a pre-linear EE structure upon ditopic substrate binding as this structure is significantly lower in energy and leads to the linear product.
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Figure 15 [Rh \((\text{acetate}) \subset \text{DIMPhos}\) \((\text{CO})\) \((\text{H})\) \((\text{propene})\)] identified EE ground state geometries. All energies were normalized to the lowest identified energetic \([\text{Rh} \((\text{acetate}) \subset \text{DIMPhos}\) \((\text{CO})\) \((\text{H})\) \((\text{propene})\)\) geometry. All energies in kcal/mol. Some hydrogens and phenyls are removed for clarity.

These results taken together show that the substrate binding event is responsible for the energy differences between the relative ligand orientations around rhodium, which forms the basis for the regioselectivity observed. To accommodate the substrate in a ditopic fashion, the catalyst predominantly adopts an orientation where the phosphines adopt an EE conformation that allows preorganization of the substrate to the linear/outermost product. The substrate hinders the EE branched pathway due to steric congestion between the substrate and the CO ligand (Figure 16). Furthermore, the substrate binding event also results in higher energy differences between the lowest energy EE orientation and the EA geometries in the selectivity determining step, as prior to substrate binding, only minor energy differences are observed between the complexes with different ligand geometries. By analogy, nature’s catalysts, which also preorganize the substrate to yield high degrees of control over the selectivity, also often rearrange to accommodate the substrate, commonly referred to as induced fit effects.
Conclusions and outlook

In summary, supramolecular substrate preorganization is an effective way to control the regioselectivity in the hydroformylation reaction. We previously introduced DIMPhos as a bifunctional ligand for regioselective rhodium catalyzed hydroformylation. A carboxylate functional group on the alkene substrate is used as a directing group. In these reported catalytic systems that operate using this strategy the aldehyde product with the carbonyl farthest from the carboxylate directing group is formed, i.e. the linear aldehyde for terminal alkenes. The mechanistic basis for why in all cases the same regioselectivity is observed is not known in detail and therefore DFT calculations were conducted on our previously reported DIMPhos phosphine based rhodium catalyst. These results, reported in this chapter, show that before substrate binding the rhodium complex exists in various coordination modes, with the phosphorus atoms in equatorial-equatorial (EE) or equatorial-axial (EA) position, which are all similar in energy. This however changes when the substrate binds. DFT calculations show that the EE complex with the alkene coordinated to form the linear product is lowest in energy. The EE complex that would lead to the branched aldehyde, that is the complex with the CO pointing to the DIM pocket (instead of the hydride) is 12 kcal/mol higher in energy. The calculations show that the substrate and the CO moiety experience steric hindrance within this structure. The lowest pathway to the branched product, starts from a complex in which the phosphines adopt an EA coordination geometry around rhodium, but the hydride migration TS is 4.2 kcal/mol higher in energy, in line with the observed selectivities found experimentally. Interestingly, the energy difference between the different complexes occurs only after the...
substrate binds, indicating a substrate induced catalyst rearrangement, similar to induced fit effects observed in enzymatic catalysis.

We anticipate that these results can be extended to other substrate preorganization hydroformylation catalysts. Therefore, we envision these results to pave the way for the design of new ligands that operate on the same principle, but are able to bind other directing groups in the backbone. Alternatively, preorganization hydroformylation catalysts can be designed with this knowledge that bind carboxylates but are easier to synthesize than the previously known DIMPhos ligands. These results show that to obtain supramolecular substrate preorganization hydroformylation catalysts that yield the aldehyde product closest to the directing group require a novel design, as the steric hindrance of the substrate with the CO moiety disfavors branched product formation. Therefore, ligand design strategies should circumvent such issues and favor the innermost product forming pathway. Using these insights, we are currently conducting experiments in our pursuit of novel catalysts that operate on the basis of substrate preorganization in our laboratories.
Experimental details

All DFT calculations were performed with the Amsterdam Density Functional (ADF) program. The BLYP-D3BJ functional was used together with a small core and a DZP basis set for all atoms apart from rhodium, for which a TZP basis set was used. Relativistic effects were accounted for by running calculations with zeroth-order regular approximation (ZORA).

Energetic details of catalytic cycle

\[
\begin{align*}
\text{4-pentenoate} & \quad \text{H}_2\text{CO} \quad \text{RhDIMPPhos} & \quad \text{6-oxohexanoate} & \quad \text{4-methyl-5-oxopentanoate} \\
\end{align*}
\]

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<th>Step</th>
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<th>Pre branched</th>
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<th>CO to DIM pocket</th>
<th>Alkyl species to DIM pocket</th>
<th>CO migration transition state (6)</th>
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</tbody>
</table>
Unraveling the Origin of the Regioselectivity of a Supramolecular Hydroformylation Catalyst

<table>
<thead>
<tr>
<th><a href="H">Rh(6-oxohexanoate)(DIMPhos)(CO)</a>₂</th>
<th>Transphosphines hydride to DIM pocket</th>
<th>Transphosphines CO to DIM pocket</th>
<th>Cisphosphines acyl to DIM pocket hydride away from DIM pocket</th>
<th>Cisphosphines acyl to DIM pocket CO away from DIM pocket</th>
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Table 1 Energies of catalytic conversion of 4-pentenoate to 6-oxohexanoate with [Rh(DIMPhos)(CO)](H). Lowest energies for all coordination modes presented.

**Energies of [Rh(PPh₃)₂(H)(CO)(C₂H₄)]**

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<thead>
<tr>
<th>[Rh(PPh₃)₂(H)(CO)(C₂H₄)]</th>
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<th>EA</th>
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Table 2 EE and EA energies of the ground state of [Rh(PPh₃)₂(H)(CO)(C₂H₄)]

**Model systems for substrate binding event**

<table>
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<tr>
<th><a href="H">Rh(DIMPhos)(CO)</a></th>
<th>Transphosphines Hydride to DIM pocket</th>
<th>Transphosphines CO to DIM pocket</th>
<th>Cisphosphines</th>
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</table>

<table>
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<th>Transphosphines Hydride to DIM pocket</th>
<th>Transphosphines CO to DIM pocket</th>
<th>Cisphosphines</th>
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<table>
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<table>
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<th>EE hydride to DIM pocket</th>
<th>EA</th>
<th>EE CO to DIM pocket acetatehinder</th>
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</table>
Table 3 Model studies for the substrate binding event. Lowest energies for all coordination modes presented.
References


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8559.


Chapter 3

Regioselective Hydroformylation of Internal and Terminal Alkenes via Remote Supramolecular Control*

Introduction

Supramolecular approaches in transition metal catalysis offer unique tools to achieve selectivity in transformations that are otherwise difficult to control.\cite{1-8} Unrivalled selectivity by supra-molecular strategies has been demonstrated for a wide array of organic and organometallic transformations.\cite{9-28} A frequently applied strategy involves the use of a functional group on a substrate that serves as a directing group to control the substrate coordination at the metal center, allowing for differentiation of reactive sites that are otherwise indistinguishable for transition metal catalysts. This strategy, coined substrate preorganization, has been broadly demonstrated for substrates in which the directing group is relatively close to the reactive group.\cite{13, 14, 22-26} It remains an open question if such a strategy can be extended to substrates in which the functional group is remote from the directing group, which may be especially challenging for long flexible alkyl chain type substrates due to the large conformational freedom of such compounds. Recently, Costas et al. reported a system in which protonated aliphatic amines were oxidized by a manganese catalyst functionalized with crown ether recognition sites, leading to selective oxidation of the C-H carbons to yield a mixture of position 8 and 9 oxidation products using substrate preorganization.\cite{28}

Figure 1 Redesign of a rhodium-monophenyl (L1) to a rhodium biphenyl (L2) DIMPhos complex to match the distance between the acid directing group and alkene functionality in typical fatty acids.

Toste et al. reported a transition metal catalyst encapsulated in a self-assembled cage that can be used for site selective hydrogenation of polyenes.\cite{16} Moreover, the selectivity in hydro-formylation reactions can also be controlled by substrate preorganization via
carboxylate directing groups. The guanidinium functionalized monodentate phosphine ligands introduced by Breit et al. convert terminal and internal alkenes to the outermost aldehyde with high regioselectivity, provided that the carboxylic acid and alkene are in close distance.\cite{24}

Our group reported the regioselective hydroformylation of unsaturated carboxylates using bisphosphate and bisphosphite ligands, which contained a neutral anion receptor based on 7,7’-diamido-2,2’-diindolylmethane (DIM pocket).\cite{20–23,29} This class of ligands was coined DIMPhos. The rhodium–DIMPhos catalyst based on $L_1$ (Figure 1) hydroformylates internal alkenes such as 4-hexenoate with high regioselectivity (78:1 selectivity) but for longer substrates the regioselectivity is much lower and application of $L_1$ in the hydroformylation of natural fatty acids with a double bond on the 9-position gives no regioselectivity (vide infra).\cite{22} Currently there are no hydroformylation catalysts that convert natural monounsaturated fatty acids (MUFAs) in a regioselective fashion, whereas such technologies may allow broader applicability of the biofeedstock.\cite{30–42} In this chapter we report the redesign of DIMPhos ligand $L_1$ to $L_2$ in which the distance between the active metal and the binding site matches that of typical natural fatty acids (Figure 1), and demonstrate that the concept of substrate orientation to control the regioselectivity in hydroformylation also works when the directing group is remote from the double bond.

![Figure 2 Model](image)

\[
[Rh((9-decenoate)\subset L_1)(CO)(H)] \\
[Rh((9-decenoate)\subset L_2)(CO)(H)]
\]

Figure 2 Modeling (DFT) of 9-decanoate as a fatty acid model bound ditopically to $[Rh(L_1)(H)(CO)]$ (left) and $[Rh(L_2)(H)(CO)]$ (right). For clarity, the 9-decanoate substrate is shown in green.
Results and discussion

The distance between rhodium and the 7,7'-diamido-2,2'-diindolylmethane anion receptor for L1 (the DIM pocket, 6.8 Å) is significantly shorter than the carboxylate-alkene distance of fatty acids (12.4 Å) and this mismatch was proposed to be the reason for the low selectivity observed for long substrates (vide infra).\[22\]

Indeed, DFT calculations (BLYP,DZP,D3BJ) show that 9-decenoate, used as a model for natural fatty acids, needs to fold significantly to bind ditopically to [Rh(L1)(H)(CO)] (see Figure 2).\[43–45\] It was hypothesized that an extended ligand binds substrates with large carboxylate-alkene distances in less folded manners and as a result leads to a higher control over the regioselectivity. To achieve this goal, we designed a ligand that has a biphenyl linker (Figure 1, L2) between the DIM pocket and the phosphite donor atoms, instead of the phenyl linker that is present in the original DIMphos phosphite ligand (L1). DFT calculations of 9-decenoate ditopically bound to [Rh(L2)(H)(CO)] (Figure 2) indeed shows less folding compared to binding to [Rh(L1)(H)(CO)]. This is also reflected in the lower folding energy of 9-decenoate bound to [Rh(L2)(H)(CO)] (9.4 kcal mol\(^{-1}\)) for [Rh((9-decenoate) L2)(CO)(H)] vs. 15.4 kcal mol\(^{-1}\) for [Rh((9-decenoate) L1)(CO)(H)] (Table 4). Also binding enthalpies of aliphatic deprotonated ω-unsaturated carboxylic acids with various lengths (3-butenoate to 10-undecenoate) to [Rh(L2)(H)(CO)] were calculated using DFT calculations (Figure 11). These studies show that 8-nonenoate fits best and has the highest binding enthalpy. In addition, 9-decenoate, which is a better model for natural fatty acids, also binds well to [Rh(L2)(H)(CO)]. Encouraged by these results, we synthesized the L2 ligand using a similar synthetic strategy as previously reported for L1 (see Experimental details).\[21\]

To investigate if ligand L2 formed a stable metal complex with rhodium it was mixed with [Rh(acac)(CO)\(_2\)], which is the precursor complex of the hydroformylation catalyst, in a 1:1 ratio in CD\(_2\)Cl\(_2\). \(^1\)H NMR studies show a well-defined complex formed after mixing (Figure 4) and DOSY spectroscopy reveals the formation of a single species with a hydrodynamic radius of 7.9 Å in line with the size of a mononuclear complex (see Figure 5).\[46\] Upon addition of 1.5 equivalents of tetrabutylammonium acetate, the \(\text{N}-\text{H}\) protons are downfield shifted, which shows the carboxylate group binds to the DIM pocket of the [Rh(acac)(L2)] species in a similar fashion as reported for the [Rh(acac)(L1)] complex (Figure 6).\[21\] Pressurization with 5 bar of syngas (H\(_2\):CO (1:1)) to the solution of the [Rh(acac)(L2)] complex provides the corresponding pentacoordinate [Rh(L2)(CO)\(_2\)H] species as evidenced by the rhodium hydrido signal (δ = -10.5 ppm).\[47\] Next to the well-defined signal, also a broad rhodium–hydrido signal (δ = -10.7 ppm) appears in the NMR spectrum, which becomes larger over time (see Figure 9). DOSY spectroscopy of the [Rh(L2)(CO)\(_2\)H] complex under 5 bar CO/H\(_2\) (1:1) in CD\(_2\)Cl\(_2\) gave a larger average hydrodynamic radius (12.1 Å) than for the [Rh(acac)(L2)] complex suggesting that the broad signal is due to formation of dinuclear and/or oligomeric species under these conditions (see Figure 7). However, under identical conditions but in the presence of 4 equivalents guest that binds in the DIMpocket (tetrabutylammonium acetate) the average
Regioselective Hydroformylation of Internal and Terminal Alkenes via Remote Supramolecular Control

hydrodynamic radius (8.4 Å) (see Figure 8) is close to that of the \([\text{Rh(acac)(L2)}]\) species, indicating that carboxylate binding in the DIM pocket preorganizes the two phosphorous moieties for the formation of a mononuclear species.\[^{29}\] A series of (deprotonated) \(\omega\)-unsaturated carboxylic acids with varying length between the alkene reactive group and the carboxylate directing group was hydroformylated using \([\text{Rh(L2)}]\) as a catalyst (Figure 3). As substrates we reacted 4-pentenoic acid \((n = 2)\) up to 10-undecenoic acid \((n = 8)\) both in the presence and the absence of base. In the presence of base, the carboxylate functional group of the substrate binds in the DIM pocket and thus substrates long enough to span the DIM pocket-rhodium distance are expected to react with improved regioselectivity. In absence of base, the protonated carboxylic acids do not bind in the DIM pocket and as a result the directing group, the carboxylic acid, cannot be used for substrate preorganization with the \([\text{Rh(L2)}]\) catalyst and should react with lower regioselectivity.\[^{20,21}\] Because of this, the protonated substrates were used as control experiments. All substrates studied gave full conversion to the aldehyde and the linear/branched (l/b) ratios of the aldehyde products were determined by \(^1\)H-NMR spectroscopy (Figure 3).

Figure 3 Hydroformylation of \(\omega\)-unsaturated carboxylic acids using rhodium complexes based on \(\text{L2}[^{a}]\)

[a] Reagents and conditions: [substrate] = 0.2 M, DIPEA (15 equiv. (blue bars)), \([\text{Rh(CO)}_2\text{(acac)}]\) (1 mol %), \(\text{L2}\) (1.1 mol %), 20 bar CO/H\(_2\) (1:1), 40°C, 24 h. Conversion and regioselectivity determined by \(^1\)H NMR analysis of the crude reaction mixture. For full experimental details, see the experimental details. The blue bars are experiments in presence of base, and the red bars are in absence of base as control experiment.
Chapter 3

The catalytic results show that the long anionic substrates (with \( n > 4 \), 7-octenoate and longer) display much higher \( l/b \) ratios than the protonated analogues. The distance between the carboxylate and alkene function in these substrates is at least 9.7 Å, and this shows this catalyst is able to control the regioselectivity via substrate preorganization on remote distance. The highest \( l/b \) ratio of 27 is obtained for the 8-nonenolate \((n = 6)\), which is the substrate that binds strongest to the catalyst as it fits perfectly according to our modelling studies (vide supra). The longer substrates that easily span the distance between the DIM pocket and the rhodium center \((n = 7 \text{ and } 8)\) are also converted with improved regioselectivity when preorganized, albeit with a lower linear/branched ratio of 23 and 14 respectively. In line with the binding energy calculated for these substrates. The smaller substrates \((n = 2 \text{ and } 3)\) are not able to bind in a ditopic fashion to \([\text{Rh(L2)}]\) and thus the difference in \( l/b \) ratios between the anionic and the protonated substrates is very small. Consistent with our design model, the \textbf{L2} system is indeed more selective than the \textbf{L1} system for long substrates (e.g. 9-decenoate: \( l/b \) of 7/1 for \textbf{L1} and \( l/b \) 23/1 for \textbf{L2}, see Figure 10 for full comparison of \( l/b \) ratios of \textbf{L1} and \textbf{L2}).[22]

We continued our catalytic studies using internal alkenes with a remote carboxylate group as substrates, which served as models for natural monounsaturated fatty acids that possess an internal double bond at the \( \Delta 9 \)-position. Initial investigations were conducted with 8-decenoate, which is the internal alkene analogue of the most selective terminal alkene substrate (vide supra), and 9-undecenoate, which has the exact alkene-carboxylic acid distance as natural fatty acids (Table 1).[9,10, 21]

When 8-decenoate was hydroformylated using the PPh\(_3\)-based catalyst the two aldehyde products were formed with a small excess for the 9-formyl product.[9, 10, 21, 39] Performing the same reaction with the rhodium catalyst based on \textbf{L2} that preorganizes the substrate leads to high conversion with a high regioselectivity to produce the 9-formyl product in excess (9-formyl/8-formyl ratio = 8.8). The linear aldehyde product is also observed under these conditions, which arises from an isomerization/hydroformylation sequence, which is not uncommon for bisphosphite-based catalysts.[47] When we applied the rhodium catalyst based on \textbf{L1}, the catalyst that can also pre-organize but is optimized for smaller substrates, only slightly better selectivities are obtained than with the PPh\(_3\)-based catalysts. The same trend was observed in the hydroformylation of 9-undecenoic acid; only the \([\text{Rh(L2)}]\) catalyst provides the product with high regioselectivity, yielding a 10-formyl/9-formyl ratio of 6.9. Importantly, the redesigned \([\text{Rh(L2)}]\) catalyst clearly outcompetes \([\text{Rh(L1)}]\) with respect to regioselectivity and conversion for the longer substrates, as a result of more favorable ditopic binding.
Regioselective Hydroformylation of Internal and Terminal Alkenes via Remote Supramolecular Control

### Table 1 Selective hydroformylation of 8-decenoic acid and 9-undecenoic acid

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Ligated</th>
<th>Conversion (%)</th>
<th>9-formyl/8-formyl</th>
<th>9-formyl/all other isomers</th>
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<tr>
<td>8-decenoic acid</td>
<td>L₁</td>
<td>74</td>
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<tr>
<td>8-decenoic acid</td>
<td>L₂</td>
<td>97</td>
<td>8.8</td>
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<tr>
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<td>PPh₃</td>
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</table>

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Ligated</th>
<th>Conversion (%)</th>
<th>10-formyl/9-formyl</th>
<th>10-formyl/all other isomers</th>
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<tbody>
<tr>
<td>9-undecenoic acid</td>
<td>L₁</td>
<td>70</td>
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<td>1.7</td>
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<tr>
<td>9-undecenoic acid</td>
<td>L₂</td>
<td>96</td>
<td>6.9</td>
<td>5.0</td>
</tr>
<tr>
<td>9-undecenoic acid</td>
<td>PPh₃</td>
<td>100</td>
<td>1.3</td>
<td>1.3</td>
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</table>

[a] Reagents and conditions: [substrate] = 0.2 M, DIPEA (1.5 equiv.), [Rh(acac)(CO)₂] (2 mol %), L₁ and L₂ (2.2 mol %), PPh₃ (6.6 mol%), 20 bar CO/H₂ (1:1), 60°C, 96 h. Conversion and regioselectivity determined by ¹H NMR analysis of the reaction mixture. For full experimental details, see the experimental details.

Having established our redesigned [Rh(L₂)] catalyst is able to control the regioselectivity of remote internal alkenes on position ∆8 and ∆9 through preorganization, we extended our system to naturally occurring monounsaturated fatty acids (oleic acid, palmitoleic acid and myristoleic acid, Table 2). When myristoleic acid is hydroformylated using the PPh₃-based rhodium catalyst, equal amounts of the 10-formyl and the 9-formyl products are formed, in line with previous reports. Furthermore, when the same reaction was carried out with the [Rh(L₁)] catalyst, also equal amounts of the two regioisomers are obtained. In contrast, the [Rh(L₂)] catalyst provides a 10-formyl/9-formyl ratio of 1.61 and shows this catalyst can control the regioselectivity of this substrate via substrate preorganization. For the fatty acids also minor amounts of isomerization/hydroformylation products were observed with the [Rh(L₁)] and [Rh(L₂)] catalysts, lowering the overall selectivity.
Table 2 Hydroformylation of natural fatty acids

<table>
<thead>
<tr>
<th>Ligand</th>
<th>Conversion (%)</th>
<th>10-formyl/ 9-formyl</th>
<th>10-formyl/all other isomers</th>
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<tr>
<td>Myristoleic acid</td>
<td>L1</td>
<td>27</td>
<td>1.03</td>
</tr>
<tr>
<td>Myristoleic acid</td>
<td>L2</td>
<td>69</td>
<td>1.61</td>
</tr>
<tr>
<td>Myristoleic acid</td>
<td>PPh₃</td>
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<td>1.0</td>
</tr>
<tr>
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<td>L1</td>
<td>23</td>
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</tr>
<tr>
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<td>L2</td>
<td>66</td>
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<tr>
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<td>PPh₃</td>
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<td>~1.0</td>
</tr>
<tr>
<td>Oleic acidᶜ</td>
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<td>n.d.</td>
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<tr>
<td>Oleic acidᶜ</td>
<td>L2</td>
<td>76</td>
<td>n.d.</td>
</tr>
<tr>
<td>Oleic acidᶜ</td>
<td>PPh₃</td>
<td>100</td>
<td>n.d.</td>
</tr>
</tbody>
</table>

[a] Reagents and conditions: [substrate] = 0.2 M, DIPEA (1.5 equiv.), [Rh(CO)₂(acac)] (2 mol %), L₁ and L₂ (2.2 mol %), PPh₃ (6.6 mol%), 20 bar CO/H₂ (1:1), 60°C, 96 h. Conversion determined by ¹H NMR analysis of the reaction mixture and the regioselectivity was determined by GC analysis after methylation of the reaction mixture. [b] Methyl 9- and 10-formyl palmitate could not be baseline separated on GC, therefore a larger error in the determined regioselectivity is expected. For full experimental details, see the experimental details.

Palmitoleic acid was converted with similar levels of regioselectivity as observed for myristoleic acid, with the [Rh(L₂)] catalyst being the only catalyst capable of controlling the regioselectivity (10-formyl/9-formyl ratio is 1.5 for [Rh(L₂)]) and 1.0 for [Rh(L₁)] and [Rh(PPh₃)]. Table 2). For the fatty acids also minor amounts of isomerization/hydroformylation products were observed with the [Rh(L₁)] and [Rh(L₂)] catalysts, lowering the overall selectivity. Palmitoleic acid was converted with similar levels of regioselectivity as observed for myristoleic acid, with the [Rh(L₂)] catalyst being the only catalyst capable of controlling the regioselectivity (10-formyl/9-formyl ratio is 1.5 for [Rh(L₂)] and 1.0 for [Rh(L₁)] and [Rh(PPh₃)]. Table 2). A major platform chemical, oleic acid, was also hydroformylated using these catalysts. Similar conversion was observed with oleic acid as with myristoleic acid and palmitoleic acid using the respective catalysts. However, the regioisomers could not be separated on GC and therefore the regioselectivity could not be determined.
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Table 3 Optimization of regioselectivity of myristoleic acid

<table>
<thead>
<tr>
<th>Entry</th>
<th>[substrate] (M)</th>
<th>[catalyst] (M)</th>
<th>Conversion (%)</th>
<th>10-/9-formyl tetradecanoic acid</th>
<th>10-formyl tetradecanoic acid/all other isomers</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.2M</td>
<td>4mM</td>
<td>33</td>
<td>1.87</td>
<td>1.58</td>
</tr>
<tr>
<td>2</td>
<td>0.1M</td>
<td>4mM</td>
<td>66</td>
<td>1.99</td>
<td>1.61</td>
</tr>
<tr>
<td>3</td>
<td>0.02M</td>
<td>4mM</td>
<td>85</td>
<td>2.20</td>
<td>1.72</td>
</tr>
<tr>
<td>4</td>
<td>0.02M</td>
<td>0.4mM</td>
<td>76</td>
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<tr>
<td>5b</td>
<td>0.2M</td>
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<td>1.82</td>
<td>1.63</td>
</tr>
<tr>
<td>6b</td>
<td>0.02M</td>
<td>0.4mM</td>
<td>77</td>
<td>2.43</td>
<td>1.95</td>
</tr>
<tr>
<td>7c</td>
<td>0.02M</td>
<td>0.4mM</td>
<td>20</td>
<td>1.42</td>
<td>1.42</td>
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<tr>
<td>8d</td>
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<td>0.4mM</td>
<td>&gt;1</td>
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<td>n.d.</td>
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<td>9e</td>
<td>0.2M</td>
<td>4mM</td>
<td>32</td>
<td>2.10</td>
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</tr>
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<td>10e</td>
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<td>0.4mM</td>
<td>63</td>
<td>2.51</td>
<td>2.33</td>
</tr>
</tbody>
</table>

[a] Reagents and conditions: DCM, DIPEA (1.5 equiv. with respect to acid), catalyst = [Rh(acac)\(_2\)]\(/L2\) in a 1:1:1 ratio, substrate = myristoleic acid, 20 bar CO/H\(_2\) (1:1), 40°C, 96 h. Conversion determined by \(^1\)H NMR analysis of the reaction mixture and the regioselectivity was determined via GC analysis following methylation of the reaction mixture. [b] Rhodium:ligand ratio 1:2. [c] THF used as solvent instead of DCM. [d] DMF was used instead of DCM. For full experimental details, see the SI. [e] 50 bar syngas (H\(_2\)::CO)(1:1) was used instead of 20 bar of syngas.

With a regioselective hydroformylation catalyst for monounsaturated fatty acids in hand, we optimized the reaction conditions using myristoleic acid as a substrate to further improve the selectivity (Table 3). We commenced our optimization studies by lowering the reaction temperature to 40°C. This resulted in an improvement of 10-formyl/9-formyl ratio from 1.61 to 1.87, although at a lower conversion (69 % vs. 33 %) (see entry 1 of Table 3). Under the same conditions (40 °C) but at lower substrate concentrations (compare entries 1–3) the re-gioselectivity was further enhanced yielding 10-formyl/9-formyl ratios of 1.99 and 2.20 at a substrate concentration of 0.1 M and 0.02 M, respectively. Most likely, the lower selectivity at higher substrate concentration results from unselective hydroformylation reactions in which the substrate is not ditopically bound, which is more dominant at higher substrate concentrations, especially for these longer substrates.\(^{[21, 48, 49]}\) In the experiment where the catalyst concentration was reduced by a factor 10 (entry 4) the regioselectivity further increased (10-formyl/9-formyl ratio
to 2.31). Somewhat counterintuitively, the conversion was also higher in the experiment, reflecting the complicated kinetics of the system. Such complicated kinetics are previously reported for [Rh(L1)], in which the catalytically active species is in equilibrium with dormant state complexes in which carboxylate groups of the substrate and product are directly coordinated to rhodium.\[^{23, 50}\] Increasing the rhodium:ligand ratio from 1:1.1 to 1:2 (entries 5 and 6) further improved the regioselectivity to yield a 10-formyl/9-formyl ratio of 2.43 under dilute conditions (entry 6). Changing the solvent from DCM to THF or DMF (entries 7 and 8) led to lower activity and selectivity. Experiments performed at syngas pressures of 50 bar instead of 20 bar (entries 9 and 10), but otherwise identical conditions, led to an improved regioselectivity of 2.10 and 2.51 for entries 9 and 10 respectively. Notably, also the overall selectivity improved to 1.91 and 2.33 respectively, which is explained by lower levels of isomerization of the alkene, commonly observed for hydroformylation reactions carried out at higher CO concentration.\[^{51}\]

**Conclusions**

In conclusion, supramolecular substrate orientation is a powerful tool to control selectivity in transition metal catalysis, which has been mainly demonstrated for substrates in which the supramolecular functional group is close to the reactive group. In this paper, we demonstrate that supramolecular substrate orientation can also work when this group is remote from the reactive group, thereby increasing the scope of the approach. In order to show this a previously reported hydroformylation catalyst with an integrated anion receptor, DIMPhos [Rh(L1)], was redesigned to accommodate larger substrates. This hydroformylation catalyst [Rh(L2)] converts substrates with high regioselectivity when the carboxylate directing group is remote from the alkene group, including monounsaturated fatty acids (MUFAs) and their model substrates. The [Rh(L2)] catalyst provides the hydroformylation product with a 10-formyl/9-formyl ratio of 2.51 for myristoleic acid, which represents the first selective catalyst for this biobased compound. These results show that catalysts that operate via supramolecular substrate preorganization can be redesigned to provide selective catalysts for substrates of different sizes, and as such we are able to make a catalyst that can convert fatty acids in a regioselective fashion. This paves the way for the design of other challenging conversions for which no catalysts exist yet.
Experimental details

Reactions were carried out under N₂ atmosphere using standard Schlenk techniques THF, pentane, hexane and diethyl ether were distilled from sodium benzophenone ketyl under nitrogen; CH₂Cl₂, methanol and Et₃N were distilled from CaH₂ under nitrogen and toluene was distilled from sodium under nitrogen. NMR spectra were measured on a Bruker DRX 300 or a Bruker AMX 400. Measurements were done at rt unless otherwise stated. High resolution mass spectrometry was carried out using the AccuTOF GC v 4g, JMS-T100GCV mass spectrometer (JEOL, Japan). CD₂Cl₂, CD₃CN, THF-D₈ and DIPEA were dried with activated molecular sieves and degassed using three freeze-pump thaw cycles and stored in young valve Schlecks. Syngas refers to a 1:1 mixture of CO/H₂, pressure stated refers the sum pressure of the two gasses. GC-MS measurements were conducted on GC-2010 Plus Capillary GC-MS containing a splitter to an MS detector and an FID detector with a SH-Rtx-5 Amine column of 30 m x 0.25 mm, df 0.25 μm or on an Interscience Focus GC containing a Supelco SP®-2560 capillary GC Column 200 m x 0.25 mm, df 0.20 μm.

All reagents were purchased from commercial suppliers and used without any further purification unless otherwise stated. Synthesis of ligand L1 was carried out according to a previous reported procedure[21]

**Ligand Synthesis**

4'-{Benzyl oxy}-[1,1'-biphenyl]-4-carboxylic acid 4 was synthesized according to a literature procedure from 4'-Hydroxy-biphenyl-4-carboxylic acid.[52]

4'-{Hydroxy}-[1,1'-biphenyl]-4-carboxylic acid methyl ester 2 A solution of 4'-Hydroxy-biphenyl-4-carboxylic acid (1) (5.0815 g, 23.7 mmol) of methanol (120 mL) and concentrated sulfuric acid (0.5 mL) was heated to reflux for 17h. The reaction was cooled and water (120 mL) was added forming a white precipitate. The precipitate was filtered and washed with water and methanol yielding 4.973 g (91.9%) of 2 as white solid.

$^1$H NMR (400 MHz, DMSO-d₆) δ = 9.74 (s, 1H), 7.99 (d, $\textit{j} = 8.4$ Hz, 2H), 7.75 (d, $\textit{j} = 8.5$ Hz, 2H), 7.60 (d, $\textit{j} = 8.6$ Hz, 2H), 6.88 (d, $\textit{j} = 8.6$ Hz, 2H), 3.87 (s, 3H).
4'-{Benzyloxy}-[1,1'-biphenyl]-4-carboxylic acid methyl ester 3 4'-{hydroxy}-[1,1'-biphenyl]-4-carboxylic acid methyl ester, 2 (2.0261 g, 8.88 mmol) is added to acetone (10 mL), together with potassium carbonate (3.71 g, 26.63 mmol) and benzyl chloride (2.55 mL, 22.19 mmol) in a pressure tube to give a light green suspension. The reaction is stirred for 18 h at 70 °C. The reaction was cooled and water (30 mL) was added. The resulting precipitate was filtered and washed with water and methanol. The white solid was suspended in chloroform and filtered again. 3 (2.64 g, 93.5%) was obtained by evaporation in vacuo.

$^1$H NMR (300 MHz, DMSO-d$_6$) $\delta$ = 8.01 (d, $J$ = 8.4 Hz, 2H), 7.80 (d, $J$ = 8.3 Hz, 2H), 7.72 (d, $J$ = 8.8 Hz, 2H), 7.51 – 7.30 (m, 5H), 7.15 (d, $J$ = 8.7 Hz, 2H), 5.19 (s, 2H), 3.87 (s, 3H).

4'-{Benzyloxy}-[1,1'-biphenyl]-4-carboxylic acid methyl ester 3 (2.6421 g, 8.30 mmol) was suspended in 1,4-dioxane (20 mL) and 1M sodium hydroxide (25 mL), and refluxed overnight. The reaction was cooled down and acidified. The precipitated white solid was filtered and washed with water and methanol yielding 4 quantitatively.

$^1$H NMR (300 MHz, DMSO-d$_6$) $\delta$ = 7.90 (d, $J$ = 8.2 Hz, 2H), 7.64 (d, $J$ = 8.6 Hz, 2H), 7.57 (d, $J$ = 7.9 Hz, 2H), 7.51 – 7.30 (m, 5H), 7.11 (d, $J$ = 8.7 Hz, 2H), 5.17 (s, 2H).

1,1-Bis{-3-methyl-7-nitro-1H-indol-2-yl}propane 5 was synthesized according to a literature procedure at to obtain the pure product in 28.1% yield.$^{[29]}$

$^1$H NMR (400 MHz, Chloroform-d) $\delta$ 9.61 (s, 2H), 8.12 (d, $J$ = 8.1 Hz, 2H), 7.86 (d, $J$ = 7.7 Hz, 2H), 7.21 (psr, $J$ = 7.9 Hz, 2H), 4.53 (t, $J$ = 8.0 Hz, 1H), 2.37 (m, 2H), 2.34 (s, 6H), 1.10 (t, $J$ = 7.3 Hz, 3H).

1,1-Bis{-3-methyl-7-amino-1H-indol-2-yl}propane 6 1,1-Bis{-3-methyl-7-nitro-1H-indol-2-yl}propane (0.60 g, 1.53 mmol) 5 was added to a flame-dried Schlenk and dissolved in MeOH/THF (2:1) to give an orange solution. The addition of Pd/C yielded a black suspension with an orange glow. A balloon of H$_2$ was added and the solution was flushed with hydrogen after which the solution was stirred vigorously for 2.5 hrs. After 2.5h, the black/orange suspension turned black/colorless. TLC showed complete conversion of starting material. Subsequently the reaction was filtered over celite filter aid and the solvents were removed in

80
vacuo. The resulting off-white/brownish solid was stripped with toluene (2x 15ml). Following evaporation, the product was immediately used without further purification.

Bis-(4’-{benzyloxy}[1,1’-biphenyl]-4-carboxamide of 1,1-bis-{7-amino-3-methyl-1H-indol-2-yl]-propane} 7 The crude diamine 6 (1.53 mmol from the previous step) and 4’-{benzyloxy}-[1,1’-biphenyl]-4-carboxylic acid (1.00 gram, 3.28 mmol) 4 and DMAP (100 mg) were added to a flame dried Schlenk and were dissolved/suspended in THF. Subsequently EDC-HCl (1.2 gram)) was added to the reaction mixture and the reaction was allowed to stir overnight at room temperature. The next day, a small amount of the reaction mixture was taken from the reaction. The solvent was evaporated and dissolved in DMSO-D_6 for crude nmr analysis. Nmr analysis revealed the appearance of amide protons. Subsequently the solids were filtered and the THF was evaporated. The residue was purified by column chromatography on silica gel with DCM/MeOH (199:1) as eluent. Finally, after combining the fractions with product and evaporating the solvent, the product was not pure and the solid was dissolved in a minimal amount of THF and precipitated by addition of hexane and was subsequently sonicated (2 min). After filtration the pure product was obtained as a yellow powder (856 mg, 60% yield).

**1H NMR** (300 MHz, DMSO-d_6) δ = 10.24 (s, 2H), 10.13 (s, 2H), 8.03 (d, J = 8.2 Hz, 4H), 7.68 (d, J = 8.1 Hz, 4H), 7.58 (d, J = 8.6 Hz, 4H), 7.49 – 7.25 (m, 14H), 7.08 (d, J = 8.7 Hz, 4H), 6.98 (t, J = 7.7 Hz, 2H), 4.53 (t, J = 8.1 Hz, 1H), 2.28 (s, 6H), 2.22 (m, 2H), 0.92 (t, J = 7.2 Hz, 3H).

**13C NMR APT** (101 MHz, DMSO-d_6) δ 165.59, 158.85, 142.80, 137.23, 136.07, 131.78, 130.67, 129.03, 128.87, 128.76, 128.24, 128.18, 127.95, 126.11, 123.05, 118.67, 115.67, 115.47, 115.19, 106.64, 69.69, 36.05, 26.95, 12.51, 8.91.

**HR MS (FD+)** calcld C_{61}H_{52}N_{4}O_{4}: 904.399 found: 904.325
Bis-{4′-(hydroxy)[1,1′-biphenyl]-4-carboxamide of 1,1-bis-{(-7 amino-3 methyl-1H indol-2-yl)[-propane]} 8 The benzyl protected 7 (0.856 g, 0.945 mmol) was dissolved in THF/MeOH (3:1) in a flame-dried Schlenk and Pd/C (0.274 g) was added to this mixture. A balloon of H₂ was connected to the Schlenk and the Schlenk was flushed with hydrogen. Subsequently the reaction mixture was heated to 40 °C and stirred vigorously. TLC showed completion after 5h and the mixture was filtered over celite. The solvents were evaporated. Next the product was dissolved in a minimum amount of THF and followed by precipitation with hexane. The precipitate was sonicated for 2 min. Filtration of the suspension yielded the pure product as a yellow powder (0.606 g, 88.5% yield).

¹H NMR (400 MHz, DMSO-d₆) δ = 10.26 (s, 2H), 10.11 (s, 2H), 9.72 (s, 2H), 8.00 (d, J = 7.8 Hz, 4H), 7.64 (d, J = 7.9 Hz, 4H), 7.48 (d, J = 8.4 Hz, 4H), 7.35 (d, J = 7.5 Hz, 2H), 7.27 (d, J = 7.7 Hz, 2H), 6.98 (t, J = 7.9 Hz, 2H), 6.85 (d, J = 8.5 Hz, 4H), 4.52 (t, J = 8.1 Hz, 1H), 2.26 (s, 6H), 2.18 (m, 2H), 0.91 (t, J = 7.1 Hz, 3H).

¹³C NMR APT (75 MHz, DMSO-d₆) δ 165.79, 158.24, 143.24, 130.84, 133.13, 133.17, 130.81, 130.05, 129.08, 128.99, 128.37, 125.94, 123.24, 118.80, 116.33, 115.52, 115.26, 106.77, 36.23, 27.17, 12.67, 9.05.

HR MS (FD+) calcd C₄₇H₄₀N₄O₄: 724.3050 found 724.3198

(S)-1,1′-Binaphthyl-2,2-diyl phosphorochloridate, (S)-binol-PCl 9 Note: PCl₃ is extremely toxic and should be handled with extreme caution. All glassware was oven-dried or flame-dried under vacuum. All solvents and reagents were dried and degassed prior to use. (S)-binol ((S)-1,1′-Bis(2-naphthol)) was azeotropically dried prior to use by co-evaporation with dry toluene (3x 20 ml). (S)-binol (50 gram) was suspended in 84 ml PCl₃ in a three neck round bottom flask (500 ml) under an inert atmosphere (N₂). The suspension was heated to reflux (85°C) and stirred overnight. After overnight stirring, the PCl₃ was evaporated in vacuo and collected with a cold trap. The solid was subsequently stripped with toluene (3x 20 ml). Subsequently the
reaction mixture was dissolved in DCM, followed by its evaporation to form a white solid which is the product.

\[31^P{\{^1H\}} \text{NMR (162 MHz, THF-d}_8)\]: \(\delta = 177.9\)

(bis-{4'[(S)-1,1'-binaphthyl-2,2-diyl phosphito] [1,1'-biphenyl]-4-carboxamide of 1,1-bis{-7-amino-3-methyl-1H-indol-2-yl]-propane)} \(\text{L}_2\)

Note: In order to achieve selective formation of the phosphite product \(\text{L}_2\), extreme caution needs to be taken to work water-free and all steps were carried out using Schlenk techniques. Furthermore, all glassware was flame-dried under vacuum or oven dried and strictly dry and degassed solvents were used. \(8\) (0.740 g, 1 mmol) was azeotropically dried with \((3 \times 10 \text{ mL})\) toluene. \(8\) was dissolved in 8.8 ml THF in a Schlenk, to which 1.0 ml of Et\(_3\)N was added. In another Schlenk \((S)\) -BinolPCl \(9\) (0.770 gram, 2.2 mmol) was dissolved in 10 mL THF. The solution of \(9\) in THF was added dropwise to the solution of \(8\) at -78 °C. After 30 min the reaction mixture was allowed to warm up until r.t. was reached. The reaction continued at room temperature overnight. Crude \(31^P\) NMR revealed product formation combined with hydrolysis products. The suspension was filtered over basic alumina (activated in the oven at 130 °C) to remove the salts and the hydrolysis product. Next, the product was purified dissolving the compound in a minimum of THF and subsequent precipitation with pentane to yield the pure product (220 mg, 14.7% yield).

\(^1H\text{ NMR (400 MHz, CD}_2\text{Cl}_2-d_2)\): \(\delta = 9.76 (s, 2H), 8.33 (s, 2H), 8.03 - 7.81 (m, 12H), 7.59 - 7.23 (m, 30H), 7.06 (m, J = 21.1, 7.6 Hz, 4H), 4.56 (t, J = 8.1 Hz, 1H), 2.39 (s, 7H), 2.25 (m, J = 14.4, 7.1 Hz, 1H), 1.06 (t, J = 7.3 Hz, 3H).

\(^{13}C\text{ NMR (101 MHz, CD}_2\text{Cl}_2-d_2)\): \(\delta = 165.30, 151.76, 147.35, 146.77, 143.15, 135.98, 135.67, 132.89, 132.64, 132.34, 131.78, 131.64, 131.17, 130.49, 129.87, 128.31, 127.80, 126.66, 126.56, 126.28, 125.20, 125.03, 124.10, 122.70, 121.99, 121.47, 120.68, 118.79, 115.75, 113.37, 107.59, 36.11, 27.64, 12.10, 8.36.

\(31^P\text{ NMR (162 MHz, DMSO-d}_6)\): \(\delta = 144.48.

HR MS (EI) calcd. for \(C_{87}H_{62}N_4O_8P_4\): 1352.40429, found: 1352.40589.
Substrate Synthesis

8-Decenoic acid 12, 8-bromoocatnoic acid 10 (3.01 g, 13.45 mmol) was dissolved in MeCN together with PPh₃ (3.53 g, 13.45 mmol) and refluxed for 168 h. All volatiles were evaporated in vacuo. The intermediate phosphonium salt was washed with diethyl ether. §P NMR showed full conversion of the PPh₃ and subsequently the product was used in the following reaction without further purification.

Next, the intermediates were suspended in THF (20 mL), KOTBu (3.019 g, 26.79 mmol) in THF (20 ml) was added at -20 °C, and the reaction was stirred for 1 h. Next, acetaldehyde (1.2 mL, 24.9 mmol) was added at room temperature and the reaction was stirred overnight. The THF was removed in vacuo and the reaction mixture was acidified with 1 M HCl until the pH was ~2. The aqueous layer was next extracted with ethyl acetate (3 * 60 ml). The combined organic layers were dried over MgSO₄ and concentrated in vacuo. The product was purified with a silica gel plug with pentane/diethyl ether in a 1:1 ratio as an eluent to give a colorless oil (610 mg, 25% yield) which was a mixture of the E and Z isomers.

1H NMR (400 MHz, CDCl₃-d) δ 11.97 (s, 1H), 5.48 – 5.33 (m, 2H), 2.20 (t, J = 7.3 Hz, 2H), 2.06 – 1.98 (m, 2H), 1.58 (d, J = 5.5 Hz, 3H), 1.56 – 1.44 (m, 2H), 1.37 – 1.25 (m, 8H).

13C NMR APT (75 MHz, CDCl₃-d) δ 178.87, 130.63, 123.82, 33.89, 32.49, 29.31, 28.96, 28.85, 26.73, 24.69, 12.76.

HR MS (EI) calcd. for C₁₀H₁₇O₂ 169.1234, found: 169.1153

9-Undecenoic acid 15, 9-bromononanoic acid 13 (3.00 g, 12.65 mmol) was dissolved (after heating for 20 min a clear solution was obtained) in MeCN together with PPh₃ (3.318 g, 12.65 mmol) and refluxed for 168 h. All volatiles were evaporated in vacuo. The intermediate phosphonium salt was washed with diethyl ether. §P NMR showed full conversion of the PPh₃ and subsequently the product was used in the following reaction without further purification.
Next, 14 was suspended in THF (20 ml), KOtBu (2.839 g, 25.3 mmol) in THF (20 ml) was added at -20 °C, and the reaction was stirred for 1h. Next, acetaldehyde (1.2 mL, 24.9 mmol) was added at room temperature and the reaction was stirred overnight. The THF was removed in vacuo and the reaction mixture was acidified with 1M HCl until the pH was ~2. The aqueous layer was next extracted with ethyl acetate (3 * 60 ml). The combined organic layers were dried over MgSO₄ and concentrated in vacuo. The product was purified with a silica gel plug with pentane/diethyl ether in a 1:1 ratio as an eluent to give a colorless oil. The THF was removed in vacuo and water (60 ml) was added to the residue, which was then extracted with diethyl ether (3 * 60 ml). The diethyl ether layers were discarded, while the aqueous layer was acidified with HCl. The aqueous layer was next extracted with ethyl acetate (3 * 60 ml). The combined organic layers were dried over MgSO₄ and concentrated in vacuo. The product was purified with a silica gel plug with pentane/diethyl ether in a 1:1 ratio as an eluent to give a colorless oil (450 mg, 20% yield).

**1H NMR** (400 MHz, CDCl₃-d) 5.50-5.30 (m, 2H), 2.38 (t, J = 7.3 Hz, 2H), 2.04 (m, 2H), 1.64 (m, 5H), 1.35-1.20 (m, 8H).

**13C NMR APT** (75 MHz, DMSO-d₆) δ 174.92, 130.91, 123.99, 29.35, 29.06, 28.99, 28.96, 26.71, 24.94.

**HR MS (EI)** calcd. for C₁₀H₁₇O₂ 183.1391, found: 183.1268

### Coordination and Anion Binding Studies

#### General comments.

All manipulations were conducted under inert atmosphere (argon or nitrogen) using oven-dried or flame dried glassware and pre-dried and degassed CD₂Cl₂ and CD₃CN as solvents. All NMR spectra were collected at 25ºC, unless stated otherwise. Tetrabutylammonium acetate was stored in a glovebox.

#### NMR complexation experiments

[Rh(acac)(CO)₂] and ligand L₂ (1.1eq) were added to a flame-dried Schlenk equipped with a Teflon stirring bar followed by addition of CD₂Cl₂ (0.6 mL) to yield a solution with a 0.006 M Rh concentration. This mixture was stirred for several minutes before NMR analysis at room temperature was taken in a screw cap NMR tube under inert conditions. ³¹P and ¹H spectroscopy showed well defined spectra. Noteworthy is in the ¹H spectrum, the four NH protons become inequivalent on NMR due to binding of the (S)-binol moieties to rhodium. Furthermore, ¹H DOSY spectroscopy was conducted on the [Rh(L₂)(acac)] complex. From the
DOSY, the average hydrodynamic radius was calculated using a previously reported method. The hydrodynamic radius calculated (7.9 Å) matched the size of the mononuclear complex.

Figure 4: $^1\text{H NMR (400MHz)}$ spectrum of 0.006M [Rh(L2)(acac)] in CD$_2$Cl$_2$

Figure 5: $^1\text{H DOSY(300MHz)}$ of 0.006 M [Rh(L2)(acac)] in CD$_2$Cl$_2$, hydrodynamic radius determined at 7.9 Å.
Regioselective Hydroformylation of Internal and Terminal Alkenes via Remote Supramolecular Control

Figure 6 Binding study of 0.008 M [Rh(L2)(acac)] in CD$_2$Cl$_2$ with tetrabutyl ammonium acetate

**NMR complexation experiments under CO/H$_2$ pressure**

A flame-dried Schlenk flask equipped with a Teflon stirring bar was charged with L2 and with [Rh(acac)(CO)$_2$] (1:1 ratio), followed by addition of an appropriate amount of CD$_2$Cl$_2$ to obtain a desired concentration of the solution of a Rh-ligand complex. The solution was stirred at room temperature for approximately 10 minutes. Next, the solution was transferred to a high-pressure NMR tube, which was then purged at least three times with 5 bar of syngas (H$_2$:CO) and subsequently pressurized with 5 bar of syngas. The tube was shaken and an NMR spectrum was taken. Measurements were done at room temperature (rt) unless otherwise stated. In CD$_2$Cl$_2$, both the $^1$H and the $^{31}$P-NMR spectra presented broad signals. The corresponding pentacoordinate [Rh(L2)(CO)$_2$H] complex which is characterized by the rhodium-hydrido signal at $\delta$ = -10.5 ppm which was identified as a triplet. Next to the triplet, we also observed a broad rhodium-hydrido signal at $\delta$ = -10.7 ppm. This broad signal was identified as oligomeric species. As a result DOSY spectroscopy of the complex under syngas conditions was measured (Figure 7), which showed a higher average hydrodynamic radius (12.4 Å) compared to the [Rh(L2)(acac)] (7.9 Å) species. According to DOSY spectroscopy, the addition of 4 equivalents tetrabutylammonium acetate suppressed the formation of oligomers as the hydrodynamic radius was determined at 8.4 Å which is smaller than the same complex without tetrabutyl ammonium acetate.
Figure 7 $^1$H DOSY (300MHz) of 0.008 M[Rh(L2)(acac)] in CD$_2$Cl$_2$ under 5 bar H$_2$:CO, hydrodynamic radius was determined at 12.4 Å

Figure 8 $^1$H DOSY (300MHz) of [Rh(L2)(CO)$_2$H] with 4 eq.TBA-OAc at 0.008 M Rh,L2:([Rh(acac)(CO)]$_2$) = 1.05:1 ratio in CD$_2$Cl$_2$, Hydrodynamic radius was determined at 8.4 Å
In CD$_2$Cl$_2$, both the $^1$H and the $^{31}$P-NMR spectra presented broad signals. Gratifyingly, changing the solvent to CD$_2$Cl$_2$:CD$_3$CN in a 2:1 ratio led to more defined spectra (Figure 9), which allowed for more straightforward analyses of the coupling constants. Similar to the spectra in CD$_2$Cl$_2$, also in the CD$_2$Cl$_2$:CD$_3$CN a defined rhodium hydrido signal is formed at $\delta = -10.53$ ppm, which is a triplet of doublets, together with a broad rhodium hydrido signal at $\delta = -10.7$ ppm. From the coupling constants ($^1J_{P-Rh} = 282.3$Hz $^2J_{H-P} = 21.0$ Hz $^1J_{H-Rh} = 4.7$ Hz) of the rhodium-hydrido signal on $^1$H-NMR ($\delta = -10.53$ppm) obtained from the phosphorous-rhodium signals on $^{31}$P-NMR ($\delta = 168.9$ppm) it can be inferred that the complex exists as a mixture of equatorial-equatorial (ee) and equatorial-axial (ea) isomers, which interconvert on NMR timescale. Since the rhodium hydrido signals were clearly visible in this solvent mixture, we conducted variable temperature NMR studies on this sample. These measurements showed the broad signal became larger over time upon heating (Figure 9). Subsequent cooling down of the sample showed this process was not reversible as the large broad signal persisted. Furthermore, $^{31}$P NMR was conducted before the variable temperature experiments. This spectrum revealed the presence of two defined peaks, which were attributed to the mononuclear complex. Also, similar to the $^1$H NMR spectra, the $^{31}$P spectrum showed broad signals that were attributed to oligomeric species.

![Figure 9 Variable temperature HP $^1$H NMR(500MHz) spectrum for [Rh(L2)(CO)$_2$H] at 0.02 M Rh, L2:([Rh(acac)(CO)$_2$] = 1.05:1 ratio, in CD$_2$Cl$_2$/CD$_3$CN (2:1) formed in situ with 5 bar syngas (CO/H$_2$, 1:1)](image-url)
Catalytic studies

A stock solution containing Rh(acac)(CO)$_2$, ligand, DIPEA, internal standard (1,3,5-trimethoxybenzene), and solvent (DCM) was prepared in a flame-dried Schlenk. The substrates are added to GC vials equipped with Teflon stirring bars, after which 1 mL of stock solution is added. The vials are placed in an insert capable of holding 8 vials. This insert is placed in a stainless-steel autoclave. The autoclave was purged three times with 20 bar syngas and then pressurized with 20 bar syngas. The autoclave was heated to the appropriate temperature and the reaction mixture were stirred for the necessary amount of time. After the required time, the pressure was released and the samples were analyzed to obtain the regioselectivity and (conversion) by NMR and/or GC. The terminal alkenes and the internal alkenes that contained a methyl group next to the double bond could be analyzed via $^1$H NMR. The aldehyde products of the natural fatty acids formed had the same chemical shift on $^1$H NMR and therefore required GC analysis.

General procedure for preparation of NMR samples

For $^1$H NMR analysis 75 µL from each sample was taken and the volatiles were evaporated using a rotary evaporator (400 mbar, 40 °C). The samples were then diluted with approximately 0.7 mL CDCl$_3$ in an NMR tube. For substrates with a double bond at position 4 from the carboxylate, DIPEA or triethylamine (TEA) (~50 µL) was added in order to allow for analysis of the branched aldehyde as this signal is broadened due to intermolecular interactions.
Hydroformylation of terminal alkenes

Figure 10 Comparison of L1 and L2 with the hydroformylation of deprotonated ω-unsaturated carboxylic acids[a]

[a]: [Substrate] = 0.2 M, Rh: Ligand: Substrate: DIPEA = 1:1.1:100:150 in DCM. Experiment performed with 20 bar CO/H2 (1:1) for 24h at 40 °C. Conversion and regioselectivity determined via 1H NMR. l/b ratios of L1 reported in an earlier study.[21]

Hydroformylation of natural fatty acids

General procedure for preparation of GC samples

For the natural fatty acids, GC analysis was required to determine the regioselectivity. 50 µl of the reaction mixture sample was added to dimethylformamide (0.3 ml) saturated with KHCO3 in a Schlenk under a nitrogen flow. Methyl iodide (50 µl) was added to the Schlenk and the mixture was stirred overnight at 40°C. Then ethyl acetate (1 ml) and distilled water (1 ml) were added. The mixture was shaken, followed by separation of the layers. Next, the ethyl acetate layer was dried over MgSO4, filtered over a syringe HPLC filter, and transferred to a GC vial, followed by GC analysis.
To determine which peak was which in the GC, the methyl esters of the natural fatty acid, methyl palmitoleate and methyl myristoleate, were reacted with H$_2$:CO (20 bar) using a Rh/PPh$_3$ catalyst for 96hrs at 60°C. After cooling down the autoclave, full conversion of the double bond was observed. Next, a sample was taken of the reaction mixture which was diluted with DCM, filtered and subsequently injected into the GC. Simultaneously the non-natural regioisomer of the fatty acid methyl ester with the double bond on the 10-position was synthesized according to a procedure reported by Vandenberg et al.$^{[53]}$ This product was reacted under the same conditions and following sample preparation injected into the GC. For the hydroformylation products of methyl myristoleate, a GC-2010 Plus Capillary GC-MS containing the SH-Rtx-5 Amine column of 30 m x 0,25 mm, d$_l$ 0.25 μm column was used to determine the regioselectivity. Both the chromatograms of the methyl myristoleate and the methyl tetradec-10-enoate hydroformylation products gave two peaks which integrated with equal areas, which were the two regioisomers formed. One of the two peaks overlapped in both chromatograms, which was identified as the methyl ester of 10-formyltetradecanoate. The regioisomers of methyl-formyl-tetradecanoate were separated by injecting the mixture at with an oven temperature of 50°C and heating for 30°C/min until 145°C was reached. Next the temperature was kept at 145°C for 20 min after which the oven was heated for 30°C/min until the temperature reached 300°C after which the temperature was kept at this temperature for 5 minutes. For the hydroformylated products of palmitoleic acid an Interscience Focus GC containing a Supelco SP®-2560 capillary GC Column 200 m x 0.25 mm d$_l$0.20 μm was used. Both the chromatograms of the methyl oleate and the methyl hexadec-10-enoate hydroformylation products gave two peaks which integrated with equal areas, which were the two regioisomers formed. One of the two peaks overlapped in both chromatograms, which was identified as the methyl ester of 10-formylhexadecanoate. Following injection of the samples, the column was heated for 5 hours at 170°C after which the temperature was raised with 20°C/min until the temperature was kept at 220°C where the temperature was kept at for 5 minutes. Separation of the hydroformylation products of oleic acid regioisomers were not successful and therefore most studies were conducted with palmitoleic acid and myristoleic acid.

**DFT calculations**

All DFT calculations were performed with the Amsterdam Density Functional (ADF) program$^{[43,44]}$. The BLYP-D3(BJ) density functional was used together with a small core DZP basis set. Relativistic effects were accounted for by running calculations with zeroth-order regular approximation (ZORA)$^{[45]}$. Binding enthalpies were calculated from the bond energies of the geometry optimized complexes minus the energies of the free [Rh(L2)(H)(CO)] complex and free substrate. The [Rh(L2)(H)(CO)] ligand having an energy of -23501.72 kcal/mol. Folding energies were determined by running a single point energy calculation of atoms of the substrate (9-decenoate) in the optimized geometry upon binding to the [Rh(L1)(H)(CO)] and [Rh(L2)(H)(CO)] and subtracting the energies with the optimized geometry.
Regioselective Hydroformylation of Internal and Terminal Alkenes via Remote Supramolecular Control

Folding energy determination

Table 4 Folding energy determination in kcal mol\(^{-1}\)

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Figure 11 Binding enthalpy of deprotonated \(\omega\)-unsaturated carboxylic acids to [Rh(L2)(H)(CO)]

Acknowledgements

NWO, the Dutch science foundation, is acknowledged for financial support. We also would like to thank InCatT for financial support and useful discussions. Stephan Falcao Ferreira is acknowledged for his contributions to this chapter. Ed Zuidinga is acknowledged for his high resolution mass spectrometry measurements.
References

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[49] The effective concentration for substrate x bound in the DIM pocket was roughly estimated: The maximum radius between the rhodium center and the double bond of natural fatty acids is approximately 11 Å which is 1.1 x 10^{-8} dm^3. Which translates to 4/3π(1,1 x 10^{-8} dm^3) = 5,5 x 10^{-24} dm^3. Of this spherical volume it was estimated the alkene could occupy 50%. This translates to an effective concentration of ≈ 0.6 M. Since the substrate concentration is 0.2 M for most experiments, non-bound substrates will likely compete and allow for a non-selective background reaction. This nicely explains why the regioselectivity increases upon lowering of the concentration as this background reaction is repressed.


Chapter 3

Chapter 4

Regioselective Hydroformylation of $\omega$-Unsaturated Acids via Supramolecular Control Using a 1,3,-Benzenedicarboxamide Receptor Functionalized Bidentate Ligand
Introduction

Achieving highly selective chemical transformations is one of the great challenges chemists face in order to use resources more efficiently and make processes more economically beneficial.\textsuperscript{[1,2]} One of the strategies to engineer highly selective catalysts that has recently gained considerable attention in the field of homogeneous catalysis relies on ditopic binding of substrates to the catalytic center, thereby pre-organizes the substrate by restricting the movement of the reactive group.\textsuperscript{[3–7]} This can be achieved using a supramolecular directing group that binds to a recognition site of the catalyst (Figure 1).

![Figure 1 Schematic drawing of the concept of supramolecular substrate preorganization, M = metal center, Do = donor atom, RS = Recognition site, DG = Directing group, RG = reactive group.](image)

Successful examples using the ditopic binding of a substrate shows that certain reaction pathways become inaccessible which is often the mechanism underlying the increase in selectivity. Using this strategy, selectivity control has been reported that would otherwise be impossible using traditional transition metal catalysts and has been applied successfully by various research groups for a variety of reactions. Examples include the asymmetric hydrogenation,\textsuperscript{[8,9]} epoxidation \textsuperscript{[10–12]}, enantioselective aziridination,\textsuperscript{[13]} sulfoxidation,\textsuperscript{[14]} C-H activation reactions\textsuperscript{[15–22]} as well as in the hydroformylation reaction.\textsuperscript{[23–31]}

In the hydroformylation reaction, a syngas mixture (H\textsubscript{2}:CO) is reacted with an alkene in the presence of a transition metal catalyst to form an aldehyde moiety (Figure 2).\textsuperscript{[32–34]}

![Figure 2 General scheme of the hydroformylation reaction.](image)

For a number of substrates, it is difficult to obtain a single aldehyde product under commonly used hydroformylation conditions.\textsuperscript{[33–36]} To control the regioselectivity, the aforementioned supramolecular substrate preorganization strategies can be used to
control the regioselectivity for substrates that contain a (supramolecular) directing group.\cite{3,4,6} Using carboxylic acids as supramolecular directing groups, our group and the group of Breit were able to control the regioselectivity of terminal and internal alkenes in the hydroformylation reaction.\cite{23–31,37}

Figure 3 a) Regioselectivity control in the hydroformylation reaction of unsaturated carboxylates using diaminodiindolyl methane anion receptor functionalized bisphosphines and phosphites (DIMPhos) b) Investigation into 1,3 benzenedicarboxamide functionalized bisphosphines and bisphosphites.

The substrate preorganization catalysts reported by our group were based on bisphosphine and bisphosphite bidentate ligands (DIMPhos) which contained a diaminodiindolyl methane anion receptor (the DIM pocket) in the backbone (Figure 3a).\cite{25–28,30,38} This diaminodiindolyl methane anion receptor strongly binds deprotonated carboxylic acids allowing for ditopic binding of the carboxylate containing alkenes.\cite{125,26} DFT calculations in Chapter 2 have established that the ditopic binding of the substrate hinders geometries leading to the aldehyde product closest to the directing group. This results in a selectivity enhancement to the outermost product.

The current DIMPhos catalysts are generally difficult to synthesize and require column chromatography steps which impairs the scalability of the synthesis of these ligands.
Therefore, it is desirable to investigate whether novel bidentate bisphosphine and bisphosphite hydroformylation catalysts containing an anion receptor in the backbone are also able to control the regioselectivity via ditopic substrate binding.

Indeed, many anion receptors have been published, of which several are easy to synthesize and can potentially be turned into a bisphosphorous ligand. The 1,3-benzenedicarboxamide carboxylate receptor, which was initially reported by Crabtree et al. (Figure 3, b)\cite{50,51} was chosen a platform for the synthesis of novel bisphosphine and bisphosphite ligands. This receptor motif finds widespread application in the field of supramolecular chemistry as an anion receptor and many variants are known.\cite{44,52–61} In DCM, these receptors have a binding constant for acetate of ~ 20000 M$^{-1}$. However, to the best of our knowledge, this anion receptor has not yet been converted into bisphosphorous ligands. The readily available building blocks and the facile synthesis result in a lower overall cost of the ligands, allowing for broader applicability of this type of ligands.

**Results and discussion**

**Ligand design, synthesis and anion binding studies**

![Figure 4](image_url) Novel designed bidentate ligands based on the 1,3 benzenedicarboxamide anion receptor.

To study if bisphosphine ligands with a 1,3-benzenedicarboxamide anion receptor in the backbone could form bidentate chelating coordination complexes with rhodium, DFT calculations were conducted with the ADF modeling suite (BLYP-D3, DZP, ZORA).\cite{62–65} These calculations resulted in the design of L1, L2 and L3 (Figure 4) as the catalytically relevant [Rh(H)(CO)$_2$(L1)], [Rh(H)(CO)$_2$(L2)] and [Rh(H)(CO)$_2$(L3)] species displayed a similar binding enthalpy as the previously reported [Rh(H)(CO)$_2$(DIMphos)] complexes (Figure 5).
Regioselective Hydroformylation of ω-Unsaturated Acids via Supramolecular Control Using a 1,3-Benzenedicarboxamide Receptor Functionalized Bidentate Ligand

All ligands could be prepared in high yields ranging from 60 to 92 % by reacting isophthaloyl chloride with the appropriate amine to form the 1,3-benzenedicarboxamide anion receptor motif. For the phosphine-based ligand, L1, 4-(diphenylphosphino)benzenemethanamine was used and directly yielded the ligand. To generate bidentate phosphite ligands L2 and L3, we first synthesized N1,N3-bis(4-hydroxyphenyl) 1,3-benzenedicarboxamide and N1,N3-bis(3-hydroxyphenyl) 1,3-benzenedicarboxamide. Subsequently, the alcohols were reacted with (S)-(binol)P-Cl to ultimately yield the novel bisphosphite ligands. All new ligands were fully characterized by 1H NMR, 31P NMR 13C NMR and high-resolution mass spectrometry (see experimental section).

Following the successful synthesis, binding studies were conducted in CD2Cl2 to investigate whether these ligands can still effectively bind carboxylates when functionalized when phosphorous moieties have been introduced. Titration of tetrabutylammonium acetate of a solution of L1 reveals the typical amide N-H peak shifts downfield (from 6.5 ppm to 10.0 ppm) in the 1H-NMR spectra. The binding isotherm was fitted assuming a 1:1 binding revealing an acetate binding constant of ~ 19000 M⁻¹ for L1 (see experimental section).[66] This shows the bisphosphine ligand displays a similar binding constant to the parent anion receptor. Analogous to L1, binding studies were conducted for L2 and L3 with tetrabutylammonium acetate in CD2Cl2, which gave binding constants of 16000 M⁻¹ and 14000 M⁻¹ for L2 and L3, respectively. This shows that these ligands bind acetate in a similar fashion to the parent the 1,3 benzenedicarboxamide core.

**Catalytic studies**

With these three new anion receptor functionalized ligands in hand, we investigated whether the novel phosphine and phosphites, L1-L3, can be used to control the regioselectivity in the hydroformylation reaction of unsaturated carboxylates. Previous studies have shown that DIMPPhos based rhodium complexes are able to control the
regioselectivity of deprotonated \( \omega \)-unsaturated carboxylic acids, forming predominantly the linear product, which is reflected in the high linear/branched ratios (l/b ratios)\[25,26\]. Control experiments showed that the selectivity for the linear product was significantly lower for the protonated analogs that do not bind in the receptor of the DIMPhos ligands. For the current catalytic experiments, using similar conditions, in which \textbf{L1}, \textbf{L2} and \textbf{L3} were mixed with [Rh(acac)(CO)\(_2\)] in separate vials in DCM, which under syngas pressure (20 bar) form the active hydroformylation catalysts. As substrates, the \( \omega \)-unsaturated carboxylic acids 3-butenolic acid (\( n = 1 \)) up to 7-octenoic acid (\( n = 5 \)) were hydroformylated in the presence and absence of the base, DIPEA. For \textbf{L1} and \textbf{L2} the obtained selectivities (l/b) are presented in Figure 6 and Figure 7 for each substrate in the presence (blue) and absence (orange) of the base DIPEA. Since the protonated acids cannot bind to the receptor, these entries serve as control experiments. The differences in selectivities observed in these experiments are reflecting the effect of substrate pre-organization by carboxylate binding. For \textbf{L1} and \textbf{L2}, the regioselectivity was similar for the protonated and the deprotonated entries, which shows that these ligands are not effective in controlling the regioselectivity \textit{via} ditopic substrate binding. Only for 3-butenolic acid, a significant regioselectivity difference was observed for the reactions carried out in the presence or absence of base. It should be noted that the deprotonated and protonated entries have an intrinsic difference in regioselectivity due to inductive effects\[26,30\].

![Regioselectivity of deprotonated omega-unsaturated carboxylic acids](image)

Figure 6 Hydroformylation of different omega-unsaturated acids using the [Rh(L1)]. Reagents and conditions: [substrate] = 0.2 M, DIPEA (1,5 equiv. (blue bars)), [Rh(CO)\(_2\)(acac)] (1 mol %), \textbf{L1} (1.1 mol %) or \textbf{L2} (1.1 mol%), 20 bar CO/H\(_2\) (1:1), 40°C, 24 h. Conversion and regioselectivity determined by \(^1H\) NMR analysis of the crude reaction mixture. For full experimental details, see the experimental section. The blue bars are experiments in presence of base, and the orange bars are in absence of base as control experiment.

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Regioselective Hydroformylation of ω-Unsaturated Acids via Supramolecular Control Using a 1,3-Benzenedicarboxamide Receptor Functionalized Bidentate Ligand

Figure 7 Hydroformylation of different ω-unsaturated acids using the [Rh(L2)] catalyst. Reagents and conditions: [substrate] = 0.2 M, DIPEA (1.5 equiv. (blue bars)), [Rh(CO)₂(acac)] (1 mol %), L₂ (1.1 mol%), 20 bar CO/H₂ (1:1), 40°C, 24 h. Conversion and regioselectivity determined by ¹H NMR analysis of the crude reaction mixture. For full experimental details, see the experimental section. The blue bars are experiments in presence of base, and the orange bars are in absence of base as control experiment.

Gratifyingly, for complexes based on L₃, the selectivity for the linear product is significantly higher for the deprotonated entries compared to the protonated entries (Figure 8). As a control experiment, the [RhL₃] catalyst was used to convert 1-octene in the presence and absence of DIPEA as the base. This was done to study the effect of DIPEA on the selectivity of this [RhL₃] hydroformylation catalyst for substrates that do not have a carboxylate function. Similar regioselectivities are observed for 1-octene in presence and absence of base. These results show the deprotonation of the 3-butenoate substrates to 7-octenoate is responsible for the selectivity enhancement observed. This shows [RhL₃] catalyst is able to control the regioselectivity via anion binding, which confirms our hypothesis that other anion receptor-based ligands can also control the regioselectivity of unsaturated carboxylates in the hydroformylation reaction.
Figure 8 Hydroformylation of different ω-unsaturated acids using the [Rh(L2)] catalyst. Reagents and conditions: [substrate] = 0.2 M, DIPEA (1.5 equiv. (blue bars)), [Rh(CO)$_2$(acac)] (1 mol %), L3 (1.1 mol %), 20 bar CO/H$_2$ (1:1), 40°C, 24 h. Conversion and regioselectivity determined by $^1$H NMR analysis of the crude reaction mixture. For full experimental details, see the experimental section. The blue bars are experiments in presence of base, and the orange bars are in absence of base as control experiment.

**Coordination studies**

To understand the catalytic behavior of these three catalysts, coordination and binding studies were conducted on rhodium complexes of L1, L2 and L3 (Figure 9). In separate experiments, these three ligands were mixed with [Rh(acac)(CO)$_2$] in a 1:1 ratio in CD$_2$Cl$_2$ using the same catalyst concentrations as during the catalytic experiments, and the $^1$H and $^{31}$P NMR spectra were measured to identify the complexes that were formed.
Regioselective Hydroformylation of ω-Unsaturated Acids via Supramolecular Control Using a 1,3-Benzenedicarboxamide Receptor Functionalized Bidentate Ligand

For the [Rh(acac)]/L1, [Rh(acac)]/L2 and [Rh(acac)]/L3 complexes, 1H NMR spectra displayed broader peaks compared to the respective free ligands L1-L3, complicating straightforward analysis of these complexes. The 31P NMR spectra of the solution containing [Rh(acac)]/L1 displayed a broad doublet with a coupling constant of 140 Hz and the [Rh(acac)]/L3 complex gave a similar doublet, but with a coupling constant of 293 Hz. In contrast, the solution containing the [Rh(L2)(acac)] complex displays no clear peaks in the 31P NMR spectra even when spectra were recorded with an increased number of scans, which suggests no single species is present in large quantities as this would be observable as a large peak. For all these complexes and their respective ligands, 2D DOSY NMR experiments were conducted to estimate their hydrodynamic size in solution (Table 1). These 2D DOSY experiments reveal stark differences between the [Rh(L1)(acac)], [Rh(L2)(acac)] and [Rh(L3)(acac)] complexes. DFT-optimized (BLYP, DZP) structures of the mononuclear [Rh(acac)(L1)], [Rh(acac)(L2)] and [Rh(acac)(L3)] species give a 5.7 Å, 9.0 Å and 8.3 Å radii for these complexes, respectively (see Table 1). For the [Rh(acac)]/L1 the measured hydrodynamic radius is slightly smaller than the free ligand and similar to the size of the calculated mononuclear [Rh(acac)(L1)] complex. This decrease in size measured is presumably caused by a conformational change of the ligand L1 following complexation with rhodium. In contrast, the [Rh(acac)]/L2 and [Rh(acac)]/L3 complexes display an increase in the average hydrodynamic radius compared to the respective free ligands. Also the average hydrodynamic radius is larger than the calculated hydrodynamic radii of [[Rh(acac)(L2)] and [Rh(acac)(L3)] suggesting that these complexes are likely to be dimeric/oligomeric species. When the dimeric complexes;[Rh(acac)(L1)]2, [Rh(acac)(L2)]2 and [Rh(acac)(L3)]2 are calculated, the hydrodynamic radius is calculated at 11.2 Å, 15.1 Å, and 14.6 Å, respectively. For the [Rh(acac)]/L2 complex, the measured average hydrodynamic radius on 2D DOSY is larger than both the monomer and the dimer with a hydrodynamic radius that is more than 200% than the measured radius of free ligand L2. Moreover, this [Rh(acac)]/L2 complex gave no well-defined peaks in 1H NMR. When 31P NMR was measured of the [Rh(acac)]/L2 complex, no peaks could be detected. These results show that most of the complex is not the monomeric M1L1 species. For the [Rh(acac)]/L3 complex, the 1H spectrum displayed
more defined peaks than the [Rh(acac)]/L2 complex and a hydrodynamic radius of [Rh(acac)]/L3 was determined to be 13.2 Å by 2D DOSY NMR spectroscopy that falls between the radius of the monomer and the dimer species (Table 1).

The addition of 5 equivalents of tetrabutylammonium acetate to [Rh(acac)]/L1 displays no shifts of the N-H protons in the 1H NMR spectra, suggesting that acetate is not strongly bound in the pocket of the ligand when it is coordinated to the rhodium. In contrast, the addition of tetrabutylammonium acetate to the [Rh(acac)]/L2 and [Rh(acac)]/L3 complexes leads to downfield N-H peaks in the 1H NMR spectra, characteristic for the binding of acetate. However, due to the broad peaks in the 1H NMR spectra a clear assessment of the binding constant could not be made for these complexes.

**Coordination studies of under syngas conditions**

Next the [Rh(acac)]/L1, [Rh(acac)]/L2 and [Rh(acac)]/L3 complexes were pressurized with syngas (5 bar, H2:CO) in CD2Cl2. Pressurization of these complexes leads to major changes in the 1H and 31P NMR spectra, which shows that the Rh(acac)/L1-L3 complexes are successfully activated by the syngas mixture, forming the catalytically active rhodium catalysts.69–73

![Figure 10 Conversion of [Rh(acac)]/L1, [Rh(acac)]/L2 and [Rh(acac)]/L3 complexes under syngas pressure in the absence or the presence of acetate.](image)

The signals of the [RhL1] complex change when it is under syngas pressure and two broad peaks appear in 31P NMR (28–29 ppm). Also, in the 1H NMR spectrum a rhodium-hydrido signal (δ= -9.5 ppm) is observable, providing further evidence for the successful conversion of the [Rh(acac)(L1)] complex to the catalytically active rhodium hydride complex (Figure 11, top). For the [RhL2] and [RhL3] syngas complexes, the 31P NMR spectra reveal no discernible peaks that could be analyzed. Additionally, for all three complexes, the hydrido signal is observed but the signal is not well-defined and therefore coupling constants could not be analyzed from these signals. Next, for these complexes that formed under syngas pressure, 2D DOSY measurements were conducted. These measurements reveal that for all three complexes, the average hydrodynamic radius is larger than observed for the respective free ligands. Additionally, the calculated radii of the mononuclear [Rh(H)(CO)2(L1)], [Rh(H)(CO)2(L2)] and [Rh(H)(CO)2(L3)] species give a 5.7, 0 Å, 9.0 Å and 8.3 Å radii for these complexes, respectively. The calculated dimeric complexes of [Rh(H)(CO)2(L1)]2, [Rh(H)(CO)2(L2)]2 and [Rh(H)(CO)2(L3)]2 are similar to the dimeric [Rh(acac)(Lx)]2 species with calculated radii of 11.2 Å, 15.1 Å and 14.6 Å respectively. For the [RhL1] and [RhL3] syngas complexes, the average hydrodynamic radius determined with 2D DOSY is between the calculated sizes of the monomeric
complex of the ligand and the dimeric rhodium complex of the ligand. For the [Rh\text{L}2] complex, the average hydrodynamic size is larger than the calculated dimer and monomer.

In the next series of experiments, solutions of the [Rh(acac)]/\text{L}1, [Rh(acac)]/\text{L}2 and [Rh(acac)]/\text{L}3 complexes were prepared to which 2 equivalents tetrabutylammonium acetate was added before converting the Rh(acac) species to the catalytically active species under syngas pressure. Interestingly, for the [Rh\text{L}1] syngas complex the addition of acetate resulted in appearance of downfield peaks that are characteristic of acetate binding by the 1,3 benzene dicarboxamide core. This is different from the non-pressurized [Rh(acac)]/\text{L}1 precursor complex, which does not display binding of acetate in CD\text{2}Cl\text{2} (\textit{vide supra}).

Moreover, a well-defined rhodium-hydrido species appears following the addition of acetate in the [Rh\text{L}1] complex (Figure 11, bottom). This effect is not observed with the [Rh\text{L}2] and [Rh\text{L}3] syngas complexes. Previous studies have shown that for DIMPhos phosphite ligands the carboxylate can coordinate to rhodium under catalytic conditions, whereas phosphine based DIMPhos ligands do not display carboxylate coordination, which forms an explanation for why the rhodium-hydrido signal does not become well defined following the addition of acetate for phosphite ligands.\textsuperscript{[26,28,74,75]}

Figure 11 Rhodium-hydride region of 1:1 mixture of \text{L}1 and [Rh(acac)(CO)\textsubscript{2}] under syngas pressure (H\textsubscript{2}: CO, 5 bar) in CD\text{2}Cl\text{2}(top) and with two equivalents of tetrabutylammonium acetate(bottom).

For all three [Rh\text{L}1], [Rh\text{L}2] and [Rh\text{L}3] complexes measured under syngas in the presence of acetate, more well defined peaks in the aromatic region of
the $^1$H NMR spectra were observed compared to the acetate free spectra under otherwise identical conditions. Also, the presence of acetate results in the appearance of multiple downfield peaks between 8-10 ppm, which is characteristic of carboxylate binding.\textsuperscript{[50,51]} The fact that there are multiple peaks present indicate the formation of multiple species, as for the parent ligands we only found one set of signals. The presence of multiple complexes is also in accordance with the 2D DOSY spectra of these complexes that reveal a higher average hydrodynamic radius than the free ligands $\mathbf{L1-L3}$ (Table 1). In particular, for the $[\text{RhL2}]$ complexes the measured average size was larger than the calculated dimeric and monomeric species, which shows most of this ligand is involved in complexes that are in the polymeric/oligomeric state.

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Table 1 Comparison of hydrodynamic radii of $\mathbf{L1}$, $\mathbf{L2}$ and $\mathbf{L3}$ and their respective rhodium complexes in CD$_2$Cl$_2$. Note: For the $[\text{RhL2}]$ complexes, a precipitate formed after several hours and 2D DOSY shift was broad, therefore the precise hydrodynamic radius was more difficult to determine than with the other two complexes.\textsuperscript{a} Hydrodynamic radius determined by performing a 2D DOSY and calculating the radius based on the Stokes-Einstein equation.\textsuperscript{[67]} \textsuperscript{b} increase in average hydrodynamic radius compared to the free ligand. \textsuperscript{c} Two equivalents acetate added to the reaction mixture prior to pressurization with syngas.

For the $[\text{RhL1}]$ and $[\text{RhL3}]$ complexes that form under syngas, the average hydrodynamic radius is between the size of the monomeric complex and the dimeric complex. In particular for the $[\text{RhL3}]$ complex in the presence of acetate the average hydrodynamic radius is $\sim$30 % larger than the measured free ligand size. If we assume that the $[\text{RhL3}]$ complex is only in the monomeric and dimeric state, we estimate that $\sim$60% of the complex is in the monomeric state. However, also larger species may be present, which have a greater impact on the average hydrodynamic radius. These results suggest that the monomeric $[\text{RhL3}]$ complex is actually more selective than what is currently observed with the catalytic experiments (\textit{vide supra}). Through optimization of the conditions the
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Regioselectivity control may be improved by ensuring a higher portion of the [RhL3] catalyst is in the monomeric state.

Since the regioselectivity in the hydroformylation reaction seems to be controlled by substrate pre-organization when complexes based on L3 are used, we conducted variable temperature studies with the complexes formed under syngas conditions, in presence and absence of acetate. In these experiments the temperature was varied from 40 °C to -40°C, however, in this temperature window only minor variations in the 1H NMR spectra were observed and well-defined peaks in both 31P NMR and 1H NMR were still lacking.[28]

Figure 12. Dimeric/oligomeric rhodium species cannot bind substrate in a ditopic fashion, leading to lower overall selectivity control.

Based on the 2D-DOSY spectra conducted with acetate under syngas conditions, we conclude a larger proportion of the rhodium catalyst based on L3 is in the monomeric state compared to the rhodium catalysts based on L1 and L2. The larger portion of this [RhL3] catalyst being in the monomeric state may explain why this catalyst is able to control the regioselectivity of unsaturated carboxylates, whereas the [RhL1] and [RhL2] catalysts do not convert the ω-unsaturated carboxylates with high levels of regioselectivity. For the [RhL1] and [RhL2] catalysts a large portion is in the dimeric/oligomeric state and such complexes cannot bind the substrates in a ditopic fashion. As a result, the regioselectivity is poorly controlled (Figure 12). Previous studies
have also shown that only when a large portion of the anion receptor functionalized rhodium catalyst is in the $M_1L_1$ state, a significant regioselectivity effect is observed.[31]

**Conclusions and outlook**

In conclusion, we report a new class of bidentate ligands based on a 1,3-benzenedicarboxamide anion receptor, $L_1-L_3$. We demonstrate that these ligands bind carboxylate substrates and that these can be used as ligands in the hydroformylation reaction. Complexes based on ligand $L_3$ show higher selectivity in in the rhodium catalyzed hydroformylation reaction of unsaturated carboxylates, leading to more linear aldehyde, as a result of substrate pre-organization. These results show the approach of controlling the regioselectivity in the hydroformylation reaction with a bidentate phosphorous ligand containing an anion receptor in the backbone can be extended from previously reported DIMPhos to other anion receptor-based ligands. Two other ligands $L_1$ and $L_2$, which also contained the 1,3-benzenedicarboxamide motif in the backbone were successfully synthesized and applied in the hydroformylation of $\omega$-unsaturated carboxylates. In contrast to $L_3$, the resultant rhodium complexes of $L_1$ and $L_2$ do not selectively convert $\omega$-unsaturated carboxylates with higher levels of regioselectivity than the control experiments. This shows these ligands cannot control the regioselectivity via ditopic substrate binding. Mechanistic studies show all three ligands do not selectively form mononuclear complexes and also dimeric/oligomeric complexes are formed under catalytic conditions. The more well-defined spectra observed combined with lower average hydrodynamic radii under of the spectra conducted with acetate under syngas conditions show that a larger portion of the $[\text{Rh}L_3]$ complex is in the monomeric state compared to the $[\text{Rh}L_1]$ and $[\text{Rh}L_2]$ complexes. This explains why the $[\text{Rh}L_3]$ catalyst displays higher regioselectivity than the control experiments. As dimeric/oligomeric transition metal complexes also convert the substrates and since these complexes cannot bind the substrates in a ditopic fashion, the regioselectivity is not controlled by the dimeric/oligomeric rhodium complexes. These insights provide further evidence that the selective formation of a $M_1L_1$ species is crucial for attaining high levels of regioselectivity in the hydroformylation for substrate preorganization catalysis. We are using these insights in our pursuit for novel catalysts that are both facile to synthesize and lead to high levels of regioselectivity control in the hydroformylation reaction.
Experimental section

Materials and Methods
All manipulations were conducted under inert atmosphere (argon or nitrogen) using oven-dried or flame dried glassware and pre-dried and degassed. Reactions were carried out under N₂ atmosphere using standard Schlenk techniques. THF, pentane, hexane and diethyl ether were distilled from sodium benzophenone ketyl under nitrogen; CH₂Cl₂, methanol and Et₃N were distilled from CaH₂ under nitrogen and toluene was distilled from sodium under nitrogen. NMR spectra were measured on a Bruker DRX 300 or a Bruker AMX 400. Measurements were done at room temperature (rt) unless otherwise stated. High resolution mass spectrometry was carried out using the AccuTOF GC v 4g, JMS-T100GCV mass spectrometer (JEOL, Japan). CD₂Cl₂, and DIPEA were dried with activated molecular sieves and degassed using three freeze-pump thaw cycles and stored in young valve Schlenks. All reagents were purchased from commercial suppliers and used without any further purification unless otherwise stated. Tetrabutylammonium acetate was stored in a glovebox.

Ligand Synthesis

![Diagram of ligand synthesis](image)

4-(diphenylphosphino)-benzenemethanamine 3

3 was synthesized according to a previously reported procedure.[76] A 100 ml Schlenk equipped with a reflux condenser was charged with 2.5 mL of 4-fluorobenzylamine and 44 mL of a 0.5 M solution of KPPh₂. The reaction mixture was refluxed overnight. After heating the reaction mixture overnight, the reaction was quenched with 2 ml of methanol. Next, the solvents were evaporated and redissolved in dry and degassed DCM (40 ml) and washed in with degassed water (2x 40 ml). Next the reaction mixture was washed 3 times with degassed water and dried with MgSO₄. After filtration, all solvents were evaporated and the reaction mixture was purified by column chromatography using a DCM:MeOH (19:1 → 9:1 ) to yield the pure product (2.68 g, 9.2 mmol, 42% yield).
N\textsuperscript{1},N\textsuperscript{3}-bis(4-(diphenylphosphanyl)benzyl)isophthalamide, L\textbf{1}

4-(diphenylphosphino)-benzenemethanamine 3 (0.291 g, 1 mmol) was dissolved in a CH\textsubscript{2}Cl\textsubscript{2} (15 ml) and Et\textsubscript{3}N (0.2 ml) mixture. Next, isophthaloyl chloride 4 (0.100 g, 0.5 mmol) was dissolved in a separate Schlenk in CH\textsubscript{2}Cl\textsubscript{2} (2 ml). The dissolved isophthaloyl chloride solution added dropwise to the phosphine mixture. After 1 hour, the full conversion of the starting material was observed with TLC. Following full conversion, the reaction mixture was washed with degassed water and dried with MgSO\textsubscript{4}. After filtration, all solvents were evaporated and the reaction mixture was purified using column chromatography DCM:MeOH (20:1) to yield the pure product (0.330 g, 0.46 mmol, 93% yield).

\textbf{1H NMR} (400 MHz, Chloroform-d) \(\delta\) 8.23 (s, 1H), 7.96 (d, \(J = 7.7\) Hz, 2H), 7.54 (t, \(J = 7.8\) Hz, 1H), 7.44 – 7.22 (m, 28H), 6.54 (t, \(J = 5.7\) Hz, 2H), 4.67 (d, \(J = 5.7\) Hz, 4H).

\textbf{13C NMR} (126 MHz, DMSO-d\textsubscript{6}) \(\delta\) 166.32, 141.04, 137.30, 137.20, 134.93, 134.00, 133.85, 133.68, 133.52, 130.38, 129.38, 129.18, 128.16, 42.92

\textbf{31P NMR} (162 MHz, Chloroform-d) \(\delta\) -6.01

Predicted mass: 712.24085 Measured mass: 712.24066

N\textsuperscript{1},N\textsuperscript{3}-bis(4-(benzyloxy)phenyl)isophthalamide 6

4-(Benzyloxy)aniline hydrochloride 5 (2.35 g, 1.0 mmol) was dissolved in a mixture of dry DCM (40 ml) and Et\textsubscript{3}N (5 ml). Next isophthaloyl chloride 4 (1.0 g, 0.5 mmol) was dissolved in 20 ml of dry DCM. Subsequently the solution of 4 was added to the solution of 5. After 10 minutes, a white solid crashed out of solution. The suspension was filtered using vacuum filtration and the solid was washed thoroughly with DCM, which was the pure product (2.45 g, 0.46 mmol, 95% yield).

\textbf{1H NMR} (400 MHz, DMSO-d\textsubscript{6}) \(\delta\) 10.32 (s, 2H), 8.53 (s, 1H), 8.12 (d, \(J = 7.8\) Hz, 2H), 7.88 – 7.56 (m, 6H), 7.51 – 7.28 (m, 10H), 7.07 – 6.96 (m, 5H), 5.11 (s, 4H).

\textbf{13C NMR} (126 MHz, DMSO-d\textsubscript{6}) \(\delta\) 165.10, 155.15, 137.64, 135.69, 132.80, 130.85, 129.35, 128.86, 128.66, 128.25, 128.15, 122.37, 115.23, 69.83
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Predicted mass: 528.20491 Measured mass: 528.20666

\[ \text{N}^1,\text{N}^3\text{-bis(4-hydroxyphenyl)}\text{isophthalamide 8} \]

7 (1.02 g, 0.2 mmol) was dissolved/suspended in a MeOH:THF 1:3 (150 ml) mixture. Next Pd/C (0.1 g) was added to the reaction mixture. A balloon of H\(_2\) was added and the solution was flushed with hydrogen after which the solution was heated to 40°C and the reaction mixture was stirred vigorously overnight. The next day, a small sample was taken from the crude reaction mixture which was evaporated and measured with NMR spectroscopy. This revealed full conversion of the starting material to the product. Next, the reaction mixture was filtered over celite and the solvents were evaporated to yield the pure product (0.66 g, 0.018 mmol, 94% yield).

\(^1\)H NMR (400 MHz, DMSO-\(d_6\)) \(\delta = 10.18\) (s, 2H), 9.27 (s, 2H), 8.48 (s, 1H), 8.09 (d, \(J = 7.6\) Hz, 2H), 7.65 (t, \(J = 7.6\) Hz, 1H), 7.56 (d, \(J = 8.4\) Hz, 4H), 6.76 (d, \(J = 8.4\) Hz, 4H).

\(^{13}\)C NMR (126 MHz, DMSO-\(d_6\)) \(\delta = 164.93, 154.25, 135.76, 131.08, 130.71, 128.90, 127.16, 122.65, 115.46\)

Predicted mass: 348.11101 Measured mass: 348.11121

\((S)\)-Binol PCl 10

10 was synthesized according to a previously reported procedure.\(^{[30]}\)
(bis-(4’((S)-1,1’-binaphthyl-2,2-diyl phosphito) 4-bisphenyl N₁,N₃ isophthalamide L₂

Note: In order to achieve selective formation of the phosphite product L₂, extreme caution needs to be taken to work water-free and all steps were carried out using Schlenk techniques. Furthermore, all glassware was flame-dried under vacuum or oven dried and strictly dry and degassed solvents were used. 9 (0.50 g, 1.43 mmol) was azeotropically dried with (3 x 10 mL) toluene. 9 was dissolved in 60 mL of THF, to which 2.0 mL Et₃N was added. In another Schlenk (S)-BinoIPCI 10 (1.02 gram, 2.88 mmol) was dissolved in 10 mL THF. The solution of 9 in THF was added dropwise to the solution of 10 at -78 °C. After 30 min the reaction mixture was allowed to warm up until room temperature was reached. The reaction continued at room temperature overnight. Crude 31P NMR revealed product formation combined with minor amounts of hydrolysis products. The suspension was filtered over basic alumina (activated in the oven at 130 °C) to remove the salts and the hydrolysis product. Next, the product was purified dissolving the compound in a minimum of THF and subsequent precipitation with pentane to yield the pure product (950 mg, 0.97 mmol, 67% yield).

¹H NMR (400 MHz, DMSO-d₆) δ = 10.53 (s, 2H), 8.55 (s, 1H), 8.32 – 8.04 (m, 10 H), 7.87 (d, J = 8.6 Hz, 4H), 7.75 (m, 4H), 7.55 (q, J = 7.0 Hz, 5H), 7.41 (t, J = 9.2 Hz, 4H), 7.27 (m, 8 H).

¹³C NMR (126 MHz, DMSO-d₆) δ = 165.42, 147.43, 147.07, 146.85, 136.44, 135.53, 132.48, 132.25, 131.85, 131.58, 131.41, 130.92, 129.14, 127.42, 126.07, 123.90, 122.20, 122.09, 121.12.

³¹P NMR (162 MHz, DMSO-d₆) δ = 144.87

Predicted mass: 976.21034 Measured mass: 976.21418

N₁,N₃-bis(3-(benzyloxy)phenyl)isophthalamide 12

11 (2.00 gram, 10 mmol) was dissolved in a mixture of dry DCM (20 ml) and dry Et₃N (2 ml). Next 4 (1.00 gram, 5 mmol) was dissolved in 10 mL of DCM. Subsequently the solution of 4 was added to the solution of 5. After 10 minutes, a white solid crashed out of solution. The
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Suspension was filtered using vacuum filtration and the solid was washed with DCM to yield the pure product (2.42 gram, 0.46 mmol, 92% yield).

\(^1\)H NMR (400 MHz, DMSO-\(d_6\)) \(\delta\) 10.39 (d, \(J = 3.9\) Hz, 2H), 8.51 (s, 1H), 8.13 (d, \(J = 7.8\) Hz, 2H), 7.70 (t, \(J = 7.7\) Hz, 1H), 7.59 (d, \(J = 2.3\) Hz, 2H), 7.51 - 7.18 (m, 14H), 6.79 (d, \(J = 8.1, 2.6\) Hz, 2H), 5.12 (s, 4H).

\(^1\)C NMR (126 MHz, DMSO-\(d_6\)) \(\delta\) 165.55, 159.00, 140.71, 137.51, 135.63, 131.13, 129.95, 129.10, 128.91, 128.29, 128.12, 127.42, 113.28, 110.56, 107.45, 69.62

Predicted mass: 528.20491 Measured mass: 528.20666

\(\text{N}^{1},\text{N}^{3}\)-bis(3-hydroxyphenyl)isophthalamide 13

\(\text{N}^{1},\text{N}^{3}\)-bis(3-(benzyloxy)phenyl)isophthalamide 12 (2.00 gram, 3.8 mmol) was dissolved/suspended in a MeOH:THF 1:3 (150 ml) mixture in a Schlenk. Next, Pd/C (0.2 gram) was added to the reaction mixture. A balloon of H\(_2\) was added and the solution was flushed with hydrogen after which the solution was heated to 40°C and the reaction mixture was stirred vigorously overnight. The next day, a small sample was taken from the reaction mixture for NMR analysis, which displayed full conversion to the alcohol product. The reaction mixture was subsequently filtered over celite and the solvents were evaporated to yield the pure product (1.23 gram, 3.5 mmol, 93% yield).

\(^1\)H NMR (400 MHz, DMSO-\(d_6\)) \(\delta\) 10.27 (s, 2H), 9.43 (s, 2H), 8.47 (s, 1H), 8.11 (d, \(J = 7.8\) Hz, 2H), 7.67 (t, \(J = 7.7\) Hz, 1H), 7.38 (s, 2H), 7.16 (dt, \(J = 15.7, 8.1\) Hz, 4H), 6.53 (d, \(J = 7.9\) Hz, 2H).

\(^1\)C NMR (101 MHz, DMSO-\(d_6\)) \(\delta\) 165.27, 157.82, 140.36, 135.56, 130.83, 129.55, 128.80, 127.25, 111.37, 111.22, 107.74

Predicted mass: 348.11101 Measured mass: 348.11020
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(bis-(4′((S)-1,1′-binaphthyl-2,2′-diyl phosphito)-3-bisphenyl N1,N3 isophthalamide L3

Note: In order to achieve selective formation of the phosphite product L3, extreme caution needs to be taken to work water-free and all steps were carried out using Schlenk techniques. Furthermore, all glassware was flame-dried under vacuum or oven dried and strictly dry and degassed solvents were used. 12 (1.00 g, 2.85 mmol) was azeotropically dried with (3 x 10 mL) toluene. 12 was dissolved in 60 ml of THF, to which 2.0 ml Et3N was added. In another Schlenk, (S)-BinolPCh 10 (2.1 gram, 5.8 mmol) was dissolved in 10 mL THF. The solution of 12 in THF was added dropwise to the solution of 10 at -78 °C. After 30 min the reaction mixture was allowed to warm up until r.t. was reached. The reaction continued at room temperature overnight. Crude 31P NMR revealed product formation combined with hydrolysis products. The suspension was filtered over basic alumina (activated in the oven at 130 °C) to remove the salts and the hydrolysis product. Next, the product was purified dissolving the compound in a minimum of THF and subsequent precipitation with pentane to yield the pure product (1.6 g, 1.8 mmol, 63% yield).

1H NMR (300 MHz, DMSO-d6) δ 10.64 (s, 2H), 8.59 (s, 1H), 8.33 – 7.92 (m, 10H), 7.91 (s, 2H), 7.80 – 7.14 (m, 21H), 7.04 (d, J = 4.0 Hz, 2H).
13C NMR (126 MHz, DMSO-d6) δ 165.76, 151.35, 147.40, 146.80, 141.19, 135.45, 132.49, 132.26, 131.87, 131.62, 131.42, 130.81, 129.24, 127.44, 126.50, 125.88, 123.93, 122.58, 122.07, 116.92, 112.44.
31P NMR (162 MHz, CD2Cl2) δ 145.44

Predicted mass: 976.21034 Measured mass: 976.21210

Coordination and Anion Binding Studies

Binding studies of free ligands L1 – L3

For the binding studies of the free ligands L1, L2 and L3, two solutions were made which contained a 0.002M concentration of the respective ligands in a Schlenk under nitrogen. To one of the two solutions, several equivalents of tetrabutyl ammonium acetate was added. Next, 0.5 ml of the solution without tetrabutyl ammonium acetate was transferred to a screw cap NMR tube under inert conditions and subsequently equivalents of tetrabutyl ammonium acetate were added until no shift of the N-H species was observed anymore.

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Figure 13 Binding constant determination of free \( L1 \) in \( CD_2Cl_2 \); fit based on the N-H proton

Figure 14 Binding constant determination of free \( L1 \) in \( CD_2Cl_2 \); fit based on the C-H proton

\[ K_a = 19000.00 \pm 3909.2 \text{ M}^{-1} \] (20.57%)

\[ r = 0.98090 \]

\[ K_a = 19000.00 \pm 4141.25 \text{ M}^{-1} \] (21.8%)

\[ r = 0.97833 \]
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Figure 15 Binding constant determination; fit based on the N-H proton of free L2

Figure 16 Binding constant determination; fit based on the C-H proton of free L2
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Figure 17 Binding constant determination in CD$_2$Cl$_2$; fit based on the N-H proton of free L3

$K_a = 14000.00 \pm 1060.77$ M$^{-1}$ (7.58%) $r = 0.99749$

Figure 18 Binding constant determination in CD$_2$Cl$_2$; fit based on the C-H proton of free L3

$K_a = 14000.00 \pm 1060.77$ M$^{-1}$ (7.58%) $r = 0.99749$
Catalytic studies

A stock solution containing [Rh(acac)(CO)₂], ligand, DIPEA, internal standard (1,3,5-trimethoxybenzene), and solvent (DCM) was prepared in a flame-dried Schlenk. The substrates are added to GC vials equipped with Teflon stirring bars, after which 1 mL of stock solution is added. The vials are placed in an insert capable of holding 8 vials. This insert is placed in a stainless-steel autoclave. The autoclave was purged three times with 20 bar syngas and then pressurized with 20 bar syngas. The autoclave was heated to the appropriate temperature and the reaction mixture were stirred for the necessary amount of time. After the required time, the pressure was released and the samples were analyzed to obtain the regioselectivity and (conversion) by NMR and/or GC. The terminal alkenes and the internal alkenes that contained a methyl group next to the double bond could be analyzed via ¹H NMR.

General procedure for preparation of NMR samples

For ¹H NMR analysis 75 µL from each sample was taken and the volatiles were evaporated using a rotary evaporator (400 mbar, 40 °C). The samples were then diluted with approximately 0.7 mL CDCl₃ in an NMR tube. For substrates with a double bond at position 4 from the carboxylate, DIPEA or triethylamine (TEA) (~50 µL) was added in order to allow for analysis of the branched aldehyde as this signal is broadened due to intermolecular interactions.

Coordination studies

For all three ligands, L₁ - L₃, coordination studies were conducted with rhodium. A flame-dried Schlenk flask equipped with a Teflon stirring bar was charged with a ligand and with [Rh(acac)(CO)₂] (1:1 ratio). This is followed by addition of an appropriate amount of CD₂Cl₂ to obtain a desired concentration of the solution of a Rh-ligand complex. The solution was stirred at room temperature for approximately 10 minutes. Next, ¹H and ³¹P NMR analysis at room temperature was performed in a screw cap NMR tube under inert conditions. Furthermore, ¹H 2D-DOSY spectroscopy was conducted on the [Rh(Lₓ)(acac)] complexes as well as the free ligands L₁-L₃. As an internal standard 1,3,5 trimethoxybenzene was added. From the 2D-DOSY, the average hydrodynamic radii were calculated using the Stokes–Einstein equation, \[ D = \frac{k \cdot T \cdot (6 \pi \eta \cdot r_H)^{-1}}{k} \] (k = the Boltzmann constant, T = the absolute temperature, η = the fluid viscosity, \( r_H \) = the hydrodynamic radius).\[^{67,68,77}\] Note: For the [RhL₂] complexes, a precipitate formed after several hours and 2D DOSY shift was broad, therefore the precise hydrodynamic radius was more difficult to determine than with the other two complexes.
Figure 19 $^1$H NMR spectra (400 MHz, CD$_2$Cl$_2$) of 1:1 mixture with [Rh(acac)(CO)$_2$] and L1 (top), L2 (middle) and L3 (bottom) (0.002M), aromatic region
Figure 20 2D DOSY of [Rh(acac)(CO)\(_2\)]: \textbf{L1} (1:1 ratio) reaction mixture (0.002M) in CD\(_2\)Cl\(_2\). Average hydrodynamic radius determined at 5.5 Å determined via Stokes–Einstein equation\(^{[67]}\)

Figure 21 2D DOSY of 1:1 mixture of \textbf{L2} and [Rh(acac)(CO)\(_2\)] (0.002 M) in CD\(_2\)Cl\(_2\). Average hydrodynamic radius determined at 26 Å determined via Stokes–Einstein equation\(^{[67]}\). Average hydrodynamic radius is larger than the free ligand, \textbf{L2}, which shows the oligomeric species are formed.
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Figure 22 2D DOSY of 1:1 mixture of [Rh(acac)(CO)]₂ and L₃ (0.002M) in CD₂Cl₂ Average hydrodynamic radius determined at 13.2 Å, determined via Stokes–Einstein equation[67]

Binding studies of [Rh(acac)]/L₁, [Rh(acac)]/L₂ and [Rh(acac)]/L₃

In order to confirm the anion binding properties of the [Rh(acac)]/Lₓ complexes, tetrabutylammonium acetate was added. For each rhodium complex, two stock solutions were prepared. One contained the rhodium complex in dry and degassed CD₂Cl₂ and the other solution contained the rhodium complex and 2.1 equivalents of tetrabutyl ammonium acetate. Several screw cap NMR tubes were prepared that contained several equivalents of acetate with respect to the ligand by mixing the appropriate amounts of the two stock solutions under inert conditions. Next, the NMR tubes were vigorously shaken before NMR analysis. Due to the presence of broad peaks, an accurate binding constant could not be assessed.

NMR complexation experiments under CO/H₂ pressure

Also, the [Rh(acac)]/Lₓ complexes were pressurized with H₂:CO in a high-pressure NMR tube and studied with NMR. In CD₂Cl₂, both the ¹H and the ³¹P-NMR spectra presented broad signals for all ligand complexes studied. Subsequently 2D DOSY spectroscopy was conducted for all three complexes, which displayed increased hydrodynamic radii compared to the [Rh(acac)]/Lₓ complexes, which indicates coordination polymers/oligomers are formed. Furthermore, also the complexes that contained two equivalents of acetate were pressurized and studied with NMR spectroscopy. These complexes displayed downfield NH shifts on ¹H NMR compared
to the complexes in absence of acetate, which is characteristic of acetate binding. The syngas complexes in the presence of acetate were studied with 2D DOSY spectroscopy. Note: For the [RhL2] complexes, a precipitate formed after several hours and 2D DOSY shift was broad, therefore the precise hydrodynamic radius was more difficult to determine than with the other two complexes.

Figure 23: **H NMR spectrum** (400 mHz, CD2Cl2) of top 1:1 mixture of L1 and [Rh(acac)CO2] (0.002M) 5 bar of syngas (CO/H2, 1:1) and bottom: 1:1 mixture of L1 and [Rh(acac)(CO)2] (0.002M) with 2 equivalents of tetrabutyl ammonium acetate 5 bar of syngas (CO/H2, 1:1)
Regioselective Hydroformylation of ω- Unsaturated Acids via Supramolecular Control Using a 1,3-Benzene dicarboxamide Receptor Functionalized Bidentate Ligand

Figure 24 2D DOSY of [RhL1] complex (0.002 M solution), formed in situ under 5 bar of syngas (CO/H₂, 1:1) measured in CD₂Cl₂ Average hydrodynamic radius determined at 9.3 Å. determined via Stokes–Einstein equation[67]

Figure 25 2D DOSY of 1:1 mixture of L1 and [Rh(acac)CO₂] (0.002M) under 5 bar syngas (H₂:CO, 1:1 ratio) in CD₂Cl₂ with 2 equivalents of tetrabutyl ammonium acetate. Average hydrodynamic radius determined at 8.7 Å. determined via Stokes–Einstein equation[67] Average hydrodynamic radius is larger than the free ligand, L1, indicating the formation of dimeric/oligomeric species
Figure 26 top: $^1$H NMR spectrum (400 mHz, CD$_2$Cl$_2$) of 1:1 mixture of L2 and [Rh(acac)(CO)$_2$](0.002M) under syngas conditions bottom: 1:1 mixture of L2 and [Rh(acac)(CO)$_2$](0.002M) with 2 equivalents of tetrabutyl ammonium acetate under syngas conditions.
Regioselective Hydroformylation of ω-Unsaturated Acids \textit{via} Supramolecular Control Using a 1,3-Benzenedicarboxamide Receptor Functionalized Bidentate Ligand

Figure 27 2D DOSY of [Rh(L2)(CO)2H] complex (0.002 M solution), formed in situ under 5 bar of syngas (CO/H2, 1:1) measured in CD2Cl2. Average hydrodynamic radius determined at 26 Å, determined via Stokes–Einstein equation\cite{67}. Average hydrodynamic radius is larger than the free ligand, L2, indicating the formation of oligomeric species. Note: due to the broadness of the peaks an accurate assessment of the average hydrodynamic radii could not be made.

Figure 28 2D DOSY of 1:1 mixture of L2 and [Rh(acac)(CO)2] with 2 equivalents of tetrabutylammonium acetate under syngas (CO/H2, 1:1) conditions. Average hydrodynamic radius determined at 42 Å, determined via Stokes–Einstein equation\cite{67}. Average hydrodynamic radius is larger than the free ligand, L2, indicating the formation of oligomeric species. Note: due to the broadness of the peaks an accurate assessment of the average hydrodynamic radii could not be made.
Figure 29 top: $^1$H NMR spectrum (400 mHz, CD$_2$Cl$_2$) of 1:1 mixture of L3 and [Rh(acac)(CO)$_2$](0,002M) under syngas conditions bottom: 1:1 mixture of L3 and [Rh(acac)(CO)$_2$] (0,002M) with 2 equivalents of tetrabutyl ammonium acetate under syngas conditions.
Figure S 1 2D DOSY of RhL3 complex (0.002 M solution), formed in situ under 5 bar of syngas (CO/H₂, 1:1) measured in CD₂Cl₂ Average hydrodynamic radius determined to be 12.9 Å. determined via Stokes–Einstein equation Average hydrodynamic radius is larger than the free ligand, L3, indicating the formation of dimeric/oligomeric species.

Figure 30 2D DOSY of RhL3 complex (0.002 M solution), formed in situ under 5 bar of syngas (CO/H₂, 1:1) with 2 equivalents of tetrabutylammonium acetate measured in CD₂Cl₂ Average hydrodynamic radius determined at 10.8 Å. determined via Stokes–Einstein equation Average hydrodynamic radius is larger, L3, which shows oligomeric/dimeric species are formed.
DFT calculations

All DFT calculations were performed with the Amsterdam Density Functional (ADF) program\textsuperscript{62,63,65}. The BLYP-D3(BJ) density functional was used together with a small core DZP basis set. Relativistic effects were accounted for by running calculations with zeroth-order regular approximation (ZORA).\textsuperscript{64} Complexation enthalpies were calculated from the geometry optimized \([\text{Rh(Lx)}(\text{H})(\text{CO})_2]\) complexes minus the energies of the free ligands and the \([\text{Rh(H)(CO)}_2]\) and these were compared to the complexation enthalpies of the DIMPhos phosphine and phosphite ligands. For all three ligands \textbf{L1-L3} the binding enthalpy was lower than the DIMPhos ligands.

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2015, 13, 3136–3143.


Chapter 5

A Substrate Scope Driven Optimization of an Encapsulated Hydroformylation Catalyst
Introduction

Catalysts encapsulated in supramolecular architectures offer unique levels of selectivity that are mostly unattainable for traditional transition metal catalysts.\(^{[1-10]}\) By encapsulating a transition metal in a cage, a microenvironment is created around the catalytically active transition metal and, analogous to enzymes, this allows for differentiation of reactive sites on the substrate that are otherwise indistinguishable for a traditional transition metal catalyst. Encapsulated catalysts have led to impressive control over the site-, regio-, enantio- and chemoselectivity for challenging substrates for several reactions such as the hydroformylation reaction,\(^{[11-20]}\) allylic alkylations,\(^{[21]}\) substrate selective isomerization reactions,\(^{[22]}\) C-H activations,\(^{[23]}\) site selective semihydrogenation reactions,\(^{[24]}\) cyclopropanations,\(^{[25,26]}\) epoxidations,\(^{[27-29]}\) hydroborations\(^{[30]}\) and gold-catalyzed cyclization reactions.\(^{[31-33]}\) A general strategy to encapsulate transition metals in an efficient manner is the ligand-template approach.\(^{[34,35]}\) In this approach, the ligand has a dual role as it coordinates the catalytically active metal while also operates as a template for the self-assembly of the capsule. One of the pioneering examples in this regard is the application of \([\text{Rh(H)(CO)}_3\text{P(mPy}_3\text{(ZnTPP)}_3\text{)}] (\text{CAT1})\) as a caged hydroformylation catalyst (Figure 1).\(^{[14,15]}\)

![Diagram of CAT1](image)

Figure 1 The ligand template approach for the formation of \([\text{Rh(H)(CO)}_3\text{P(mPy}_3\text{(ZnTPP)}_3\text{)}] (\text{CAT1})\) (DFT modeled structure). ZnTPP building blocks depicted in yellow for clarity.

\text{CAT1} is formed by self-assembly by combining tris(meta-pyridyl)phosphine \([\text{P(mPy}_3\text{)}]\) and three zinc meso-tetraphenylporphyrin (ZnTPP) units relying on the selective N–Zn coordination.\(^{[35]}\) The phosphine atom of the ligand-template \([\text{P(mPy}_3\text{)}]\) is coordinated to
rhodium when reacted with \([\text{Rh(acac)}(\text{CO})_2]\). By using syngas \((\text{H}_2:\text{CO})\), the encapsulated hydroformylation catalyst \text{CAT1} is formed as depicted in Figure 1.\(^{[35,36]}\)

Figure 2 General scheme of the hydroformylation reaction showing that two regio-isomers of the aldehyde product can be formed.

In a hydroformylation reaction an alkene substrate is reacted with a syngas mixture \((\text{H}_2:\text{CO})\) in the presence of a transition metal catalyst to form an aldehyde. Often two different regio-isomeric products are formed, for terminal alkenes usually referred to as the linear (l) and the branched (b) aldehyde (Figure 2).\(^{[37,38]}\)

Figure 3 The substrate rotation is blocked by the ZnTPP capsule for most of the catalytic pathways that lead to the outermost aldehyde.

It has previously been demonstrated that the application of \text{CAT1} in the hydroformylation of aliphatic alkenes leads to enhanced activity with higher regioselectivity to the innermost aldehyde.\(^{[14-17]}\) For instance, using \text{CAT1} in the hydroformylation of 1-octene an excess of the branched aldehyde product is obtained \((\text{linear/branched (l/b)} \text{ ratio} = 0.56, \text{Figure 5a})\). The selectivity for the formation of the branched product for terminal aliphatic alkenes is remarkable as most catalysts convert such substrates with an excess to the linear aldehyde.\(^{[37,39,40]}\) Mechanistic studies show that the selectivity provided by \text{CAT1} is achieved by blocking some of the hydride migration pathways that would lead to the linear aldehyde and thus an enhancement in the branched selectivity is observed (Figure 3).\(^{[17]}\) Only recently, two other catalysts have been reported that also convert unfunctionalized aliphatic alkenes to form mostly the branched product i.e. rhodium catalyst based on BOBphos and Triphos.\(^{[41-44]}\)
Next to the unusual selectivity, the application of CAT1 in the hydroformylation of 1-octene also leads to a 10-fold increase in the activity compared to the non-encapsulated analogue which is mostly the \([\text{Rh}(\text{H})(\text{CO})_2(\text{P}(\text{mPy})_3)]_2\) species (Figure 4, CAT2). This is, at least in part, explained by the number of phosphine ligands coordinated to the rhodium center, i.e. monophosphine coordinated rhodium complexes are more active and this species is enforced by encapsulation of the porphyrins. DFT calculations show indeed lower energy barriers to complete the hydroformylation pathway for monophosphine coordination complexes compared to the bisphosphine analogues.\(^{45}\)

![CAT2](image)

**Figure 4** Non-encapsulated reference catalyst \([\text{Rh}(\text{H})(\text{CO})_2(\text{P}(\text{mPy})_3)]_2\) CAT2 generated by combining \([\text{P}(\text{mPy})_3]\) and \([\text{Rh}(\text{acac})(\text{CO})_2]\) under syngas conditions

Next to terminal alkenes, the caged catalyst CAT1 can to convert internal aliphatic alkenes, again leading to unusual product selectivity. More specifically, it has been reported that

![Previous work](image)

**Figure 5** Previously reported substrate scope of aliphatic alkenes using CAT1.
an excess of the innermost aldehyde isomer for trans-2-octene (outermost (o): innermost (i) ratio = 1:9, Figure 5b) and for trans-3-octene (o:i = 1:4, Figure 5c)) is produced with this catalyst,[16,17] This is a remarkable selectivity as the carbon atoms in these alkene substrates are indistinguishable in terms of electronics and steric for a traditional hydroformylation catalysts. Furthermore, the substrate also does not contain a (supramolecular) directing group to allow substrate orientation at the metal center[46–54] Further improvements have been made by employing an analog of ZnTPP, a porpholactone, that displays a stronger zinc-pyridine interaction and forms an encapsulated rhodium catalyst similar to CAT1.[19] The stronger binding of the porphyrin to the ligand-template provides a cage that is also selective at higher temperatures and in more polar solvents (Figure 5d). Moreover, as the space around the metal center is slightly smaller, this cage can also be used for smaller alkenes, and even propene was converted to form mainly the branched product (l/b = 0.84).

Since the confinement of the Rh-catalyst in CAT1 plays a crucial role in the selectivity displayed, substrates with other shapes may experience different confinement effects. Therefore, the catalytic results observed for 1-octene cannot be extrapolated to other terminal alkenes and as a result these need to be established experimentally. We were interested in to what extent the encapsulated catalyst CAT1 can selectively convert aliphatic alkenes as well as other alkyl alkenes of type R-CH2-C=C. This was done to investigate if there are particular structural motifs on the substrate that affect the regioisomeric outcome in CAT1. The catalytic outcomes can provide mechanistic insights on how this caged catalyst operates. Using these insights, a roadmap can be provided to select substrates that can be converted with high regioselectivity. In this chapter, we report the evaluation of the substrate scope of terminal alkenes using both CAT1 as well as a nonencapsulated analogue as reference catalyst, CAT2.

Results and discussion

CAT1 has previously been studied in detail for the hydroformylation of 1-octene, providing conditions that ensure that catalysis is taking place in the capsule.[14–17] All reactions were conducted in toluene, at room temperature using 20 bar of syngas, similar to previously reported studies with CAT1.[16] For the investigation of our substrate scope we evaluated 41 substrates that are commercially available, using CAT1 as the encapsulated catalyst and CAT2 as reference catalyst that is formed under the same conditions in absence ZnTPP. Apart from the presence of ZnTPP, all conditions were the same for each catalytic entry and every reaction was run for 48 hrs.

Since the different alkenes have a non-identical inherent bias to either regioisomer, the absolute linear/branched ratio of the products when converted with CAT1 does not provide a comprehensive measure for how effective the cage is at enhancing branched product formation. To get a better insight in how effective CAT1 is at enhancing the branched product, we calculated the relative reaction barriers (∆∆E) based on the linear/branched ratio for every substrate with CAT1 and CAT2. For these calculations the
Boltzmann distribution was used with $k_B$ being the Boltzmann constant and $T$ being the temperature in Kelvin at which the reaction was carried out:

$$\Delta \Delta E = \ln \left( \frac{\text{linear ratio}}{\text{branched ratio}} \right) \times k_B T \quad (\text{eq } 1)$$

With this energy values we subtracted the $\Delta \Delta E$ with CAT 1 from the $\Delta \Delta E$ with CAT2 for every substrate investigated:

$$\text{Cage effect} = \Delta \Delta E \text{ CAT2} - \Delta \Delta E \text{ CAT1} \quad (\text{eq } 2)$$

This energy difference was coined "cage effect" and provides a measure for selectivity control of every substrate investigated. From initial evaluations it was clear that not all substrates displayed the same trends and hence we will discuss the results of the various sub classes of substrates in the next sections.

**Aliphatic alkenes with remote substituents**

First, we reacted the previously reported 1-octene and aliphatic alkenes with substitution patterns on position 4 and 5 and these catalytic results are presented in Table 1. For these aliphatic substrates (1a-1g), CAT1 gives full conversion after 48 hrs. In contrast, the conversion is lower when CAT2 is applied, which is in line with the higher activity of the caged catalyst that was previously reported for other substrates.[14,45] The selectivity obtained for 1-octene using CAT1 is similar as previously reported (l/b is 0.56), whereas the uncaged catalyst CAT2 provides the aldehydes with a typical regioselectivity of l/b 2.88. The regioselectivity obtained for 5-methylhexene 1b is similar to that for 1-octene 1a and thus this additional steric bulk has no effect on the regioselectivity. For the substrates with a substituent on position 4, 1c-1g, the branched selectivity was significantly higher with CAT 1 compared to 1-octene 1a with the l/b ranging between 0.44 and 0.27. In particular, the substrates that have a five or six membered ring on position 4, i.e. allylcyclohexane 1f and allylcyclopentane 1g are converted with high branched selectivity when using CAT1.
Table 1 Sub-class of aliphatic alkene substrates studied. Conditions \([\text{Rh(acac})(\text{CO})_2] = 0.70\) mmol/L in toluene, pressure (H\(_2\):CO) = 20 bar, substrate/rhodium = 1000, \([\text{P(nPy)}_3]\) = 6.4 mol/L and 19.2 mmol/l of zinc(II) tetraphenylporphyrin for CAT1.

<table>
<thead>
<tr>
<th>Substrate/catalyst</th>
<th>% conv(^a)</th>
<th>l:b(^b)</th>
<th>Cage effect(^c)</th>
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<tr>
<td>1g/CAT2</td>
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<td>2.55</td>
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\(^a\)Conversion determined by \(^1\)H NMR spectroscopy \(^b\)linear:branched ratio determined by GC \(^c\)Cage effect calculated by subtracting relative energy barriers of encapsulated reaction outcome (using CAT1) from unencapsulated reaction outcome (using CAT2).

For the substrates 1b-d the cage effect is similar to the parent 1a substrate (cage effect of 0.97 – 1.06 kcal/mol). For 4,4'-dimethyl pen-1-tene 1e, the cage effect is lower than for 1-octene 1a (cage effect 0.73 kcal/mol for 1e vs. 0.97 kcal/mol for 1a), which shows that the higher branched selectivity of 1e compared to 1a is mostly caused by the electronic bias of the substrate. Interestingly, the cage effects of substrates with a cyclic structure on position 4, i.e. 1f and 1g, are significantly higher than the parent alkene 1a (1.33 kcal/mol and 1.18 kcal/mol respectively), which shows that such a cyclic substrate moiety improves the branched selectivity with CAT1.
Aliphatic alkenes with substituents close to the alkene

The second set of substrates for the scope evaluation focused on substrates that contained an additional alkyl substituent on position 3 and the catalytic results of these substrates are presented in Table 2. When these substrates are hydroformylated using caged catalyst \( \text{CAT1} \), a large difference between the catalytic outcomes of these substrates is observed. Vinlycyclopentane \( 2\text{a} \) is converted with a high branched selectivity \( (l/b = 0.45) \) with \( \text{CAT1} \), whereas vinlycyclooctane \( 2\text{d} \) is converted to dominantly the linear product \( (l/b = 2.14) \). In contrast, the unencapsulated catalyst \( \text{CAT2} \) converts all these substrates with a comparable regioselectivity \( (l/b \text{ of around 5.5).} \)

Table 2 Sub class of aliphatic alkene substrates with substituents close to the alkene.

<table>
<thead>
<tr>
<th>Substrate/catalyst</th>
<th>% conv(^a)</th>
<th>l:b(^b)</th>
<th>Cage effect(^c)</th>
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<td>( 2\text{c}/\text{CAT2} )</td>
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<tr>
<td>( 2\text{d}/\text{CAT1} )</td>
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<td>5.75</td>
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</table>

\(^a\)Conversion determined by \(^1\text{H NMR spectroscopy}\) \(^b\)linear:branched ratio determined by GC \(^c\)Cage effect calculated by subtracting relative energy barriers of encapsulated reaction outcome (using \( \text{CAT1} \)) from unencapsulated reaction outcome (using \( \text{CAT2} \)).

These alkene substrates bearing an alkyl substituent at position 3 are converted to the aldehyde with significantly higher selectivity for the linear product than the parent 1-octene \( 1\text{a} \) with \( \text{CAT2} \) which is common for aliphatic alkenes bearing a substituent on position 3.\(^{55,56}\) The large selectivity difference between the substrates of this subset with \( \text{CAT1} \) is also reflected in the large discrepancy in the cage effects obtained. \( 2\text{a} \) displays the highest cage effect (1.38 kcal/mol) and \( 2\text{d} \) displaying the lowest cage effect (0.59 kcal/mol).
kcal/mol) with an overall relative energy difference of ~0.8 kcal/mol. Interestingly, the cage effect on 2a and 2b is higher than the parent 1a, showing that the presence of 5 and 6 membered rings close to the alkene increase the cage effect and result in higher selectivity control. In contrast, when the ring size increases further, as is the case for 2d, the effect of the cage on the regioselectivity is lower. Likely, a larger steric bulk at this position inhibits certain alkene rotations leading to the branched product, which is detrimental for the selectivity.

**Aliphatic alkenes with oxygen atoms in the chain**

We next evaluated how the cage controls the regioselectivity of aliphatic alkenes that contain an ether 3a-e, ester 3f-g or ketone 3h substituent (Table 3).

The catalytic results show that for the allylether type substrates, 3a-d, there is only a minor difference between the regioselectivity displayed by the encapsulated catalyst CAT1 and the unencapsulated catalyst CAT2, albeit that CAT1 converts these substrates with higher branched selectivity than CAT2. This is also reflected in the low cage effects obtained ranging between 0.24 kcal/mol and 0.52 kcal/mol. For these substrates, the branched selectivity is already high for the unencapsulated catalyst CAT2 due to the polarization of the C=C bond.[57,58] In contrast, 4-methoxybut-1-ene (3e), a substrate in which the ether moiety is one atom position farther away from the alkene, displays a higher cage effect of 1.21 kcal/mol. This substrate has a lower intrinsic bias to form the branched aldehyde due to a less polarized C=C bond than the allylethers. The cage effect being significantly higher than the aforementioned substrates 3a-d however shows that the precise position of an ether group has a large effect on the selectivity control of the cage (Figure 6).
Table 3 Subset of aliphatic alkenes with oxygen atoms in the chain. Conditions
[Rh(acac)(CO)]$_2$ = 0.70 mmol/L in toluene, pressure (H$_2$:CO) = 20 bar, substrate/rhodium = 1000, [P(mPy)$_3$] = 6.4 mol/L and 19.2 mmol/l of zinc(II) tetraphenylporphyrin for CAT1

<table>
<thead>
<tr>
<th>Substrate/catalyst</th>
<th>% conv$^a$</th>
<th>l:b$^b$</th>
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<td>3g/CAT2</td>
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$^a$Conversion determined by $^1$H NMR spectroscopy $^b$linear:branched ratio determined by GC $^c$Cage effect calculated by subtracting relative energy barriers of encapsulated reaction outcome (using CAT1) from unencapsulated reaction outcome (using CAT2).
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For the ketone and ester substrates 3f-h, the cage effects are similar to the parent 1-octene, 1a. For methyl 3-butenoate 3f, the regioselectivity for the branched aldehyde is relatively high (l/b = 0.21) when the substrate is converted using the cage catalyst CAT1. The control experiment using the uncaged catalyst CAT2 suggests that the high regioselectivity with CAT1 is in-part caused by the polarization of the alkene substrate.

**Allyl benzene derivatives**

Allylbenzene derivatives 4 is the next class of substrates that were investigated (Table 4). The parent allylbenzene, 4a, forms more branched product with the encapsulated CAT1 and reacts with a higher cage effect than 1-octene, 1a (1.13 kcal/mol vs. 0.97 kcal/mol). In contrast, homoallylbenzene, 4b, was converted with a similar regioselectivity as observed for 1-octene 1a showing that the distal phenyl group has little influence on the selectivity. Interestingly, the presence of a methyl group on the benzene ring significantly affects the regioselectivity with CAT1 which was observed for substrate 4c-4e. A methyl on the ortho 4c (l/b = 0.32), or the para 4e position of the allylbenzene derivatives results in an improved regioselectivity compared to the parent allylbenzene 4a when converted with CAT1. In contrast, when the methyl is present on the meta position, 4d, a lower regioselectivity (l/b = 0.5) is obtained. The control experiments with CAT2 display minor variations in the regioisomeric outcome for the allyltoluene substrates 4c-4e, which shows the variation in the regioselectivity is caused by stereoelectronic interactions between the phenyl rings of the substrates and the walls of the cage that either stabilize or destabilize the linear or branched product forming pathways.

Since the presence of one methyl group significantly affects the regioselectivity, we also explored allylbenzene derivatives with two methyl groups on the phenyl ring using substrate 4f-h. Analogous to the allyltoluene substrates 4c-4e, the presence of methyl groups on the ortho and/or para position gives higher regioselectivity for 4f-g than 4a. Two methyl groups on the meta position 4h provide lower regioselectivity when converted with CAT1 compared to 4a. Noteworthy is that the variations in the regioselectivity are more pronounced with two methyl groups than with a single methyl group.
Table 4 Allylbenzene, homoallylbenzene allylbenzene derivatives containing 1,2 or 3 methyl groups and allylnaphthalene substrates. Conditions [Rh(acac)(CO)$_2$] = 0.70 mmol/L in toluene, pressure (H$_2$:CO) = 20 bar, substrate/rhodium = 1000, [P(mPy)$_3$] = 6.4 mol/L and 19.2 mmol/l of zinc(II) tetraphenylporphyrin for CAT1

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<thead>
<tr>
<th>Substrate/catalyst</th>
<th>% conv$^a$</th>
<th>$k_b$$^b$</th>
<th>Cage effect$^c$</th>
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</table>

$^a$% conversion

$^b$k$_b$ is the rate constant

$^c$Cage effect is the difference in free energy between the transition state for the reaction with the substrate and that of the reaction with the model compound
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<table>
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<th>Substrate</th>
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<td>0.71</td>
<td>0.77 kcal/mol</td>
</tr>
<tr>
<td>4h/CAT2</td>
<td>62</td>
<td>2.62</td>
<td></td>
</tr>
<tr>
<td>4i/CAT1</td>
<td>100</td>
<td>0.12</td>
<td>1.83 kcal/mol</td>
</tr>
<tr>
<td>4i/CAT2</td>
<td>33</td>
<td>2.66</td>
<td></td>
</tr>
<tr>
<td>4j/CAT1</td>
<td>100</td>
<td>0.53</td>
<td>0.82 kcal/mol</td>
</tr>
<tr>
<td>4j/CAT2</td>
<td>41</td>
<td>2.11</td>
<td></td>
</tr>
<tr>
<td>4k/CAT1</td>
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<td>0.29</td>
<td>1.23 kcal/mol</td>
</tr>
<tr>
<td>4k/CAT2</td>
<td>83</td>
<td>2.30</td>
<td></td>
</tr>
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</table>

- Conversion determined by $^1$H NMR spectroscopy
- Linear:branched ratio determined by GC
- Cage effect calculated by subtracting relative energy barriers of encapsulated reaction outcome (using CAT1) from unencapsulated reaction outcome (using CAT2).

Since the presence of a second methyl group on the ortho and/or para position gives a larger cage effect, leading to higher regioselectivity, we next evaluated allylmesitilene 4i, which has two methyl groups on the ortho positions and one methyl group on the para position. Reacting this substrate with CAT1 leads to an exceptionally high branched selectivity of l/b = 0.12 and displays a cage effect of 1.83 kcal/mol. Noteworthy is that the branched selectivity for allylmesitilene 4i is even higher than the branched selectivity for allylbenzene derivatives previously reported. Next, allylnaphthalene substrates were investigated 4j and 4k. Similar to the methyl functionalized allylbenzene derivatives, also for these substrates the regioselectivity was significantly influenced by the relative orientation of the naphthalene group with respect to the allyl reactive group. 4k is converted with higher branched selectivity when reacted with CAT1 (l/b = 0.29), whereas 4j reacts with decreased regioselectivity (l/b = 0.53) compared to the parent allylbenzene 4a.

![Figure 7 Clear regioselectivity trends for allylbenzene derivatives results in the identification of privileged allylmesitilene substrate for CAT1](image)

Next, the substrate scope was extended to allylbenzene derivatives with heteroatom substituents. We commenced our investigations with the substrates 2-allylanisole, 3-allylanisole and 4-allylanisole 5a-c (Table 5). The substrate with the methoxy moiety on the ortho 5a or meta 5b position is converted by CAT1 with significantly lower regioselectivity (l/b = 0.53 and 0.49 respectively) than observed for the parent allylbenzene 4a (l/b = 0.36). In contrast, when the methoxy substituent is on the para position 5c, the regioselectivity achieved was higher (l/b = 0.29). Again, the control
experiments using unencapsulated catalysts CAT2 give comparable levels of regioselectivity for all three substrates investigated. The higher branched selectivity obtained for 4-allylanisole (5c) compared to 4a also results in an improved cage effect of 1.38 kcal/mol. In addition, the hydroformylation of 4-allyl-1,2-dimethoxybenzene, 5d, and 5-allyl-1,2,3-trimethoxybenzene, 5e, bearing two and three methoxy moieties on the phenyl ring respectively display only modest regioselectivity for the branched product (l/b = 0.53 5d and l/b = 0.53 5e).

Table 5 Subset of allylbenzene derivatives with 1,2 or 3 methoxy substituents on the phenyl ring. Conditions [Rh(acac)(CO)₂] = 0.70 mmol/L in toluene, pressure (H₂:CO) = 20 bar, substrate/rhodium = 1000, [P(3,Py₃)] = 6.4 mol/L and 19.2 mmol/l of zinc(II) tetraphenylporphyrin for CAT1.

<table>
<thead>
<tr>
<th>Substrate/catalyst</th>
<th>% conv^a</th>
<th>l/b^b</th>
<th>Cage effect^c</th>
</tr>
</thead>
<tbody>
<tr>
<td>5a/CAT1</td>
<td>100</td>
<td>0.53</td>
<td>0.97 kcal/mol</td>
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<tr>
<td>5a/CAT2</td>
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<td>2.73</td>
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<tr>
<td>5b/CAT1</td>
<td>58</td>
<td>0.49</td>
<td>0.93 kcal/mol</td>
</tr>
<tr>
<td>5b/CAT2</td>
<td>14</td>
<td>2.39</td>
<td></td>
</tr>
<tr>
<td>5c/CAT1</td>
<td>100</td>
<td>0.29</td>
<td>1.38 kcal/mol</td>
</tr>
<tr>
<td>5c/CAT2</td>
<td>47</td>
<td>2.96</td>
<td></td>
</tr>
<tr>
<td>5d/CAT1</td>
<td>100</td>
<td>0.53</td>
<td>0.96 kcal/mol</td>
</tr>
<tr>
<td>5d/CAT2</td>
<td>45</td>
<td>2.61</td>
<td></td>
</tr>
<tr>
<td>5e/CAT1</td>
<td>99</td>
<td>0.53</td>
<td>0.91 kcal/mol</td>
</tr>
<tr>
<td>5e/CAT2</td>
<td>25</td>
<td>2.46</td>
<td></td>
</tr>
</tbody>
</table>

^aConversion determined by ¹H NMR spectroscopy ^blinear:branched ratio determined by GC ^cCage effect calculated by subtracting relative energy barriers of encapsulated reaction outcome (using CAT1) from unencapsulated reaction outcome (using CAT2).

The final set of allylbenzene substrates that was explored for regioselective hydroformylation were derivatives with halogen atoms (Table 6). Both 1-allyl-4-
(trifluoromethyl)benzene 6a and 1-allyl-4-fluorobenzene 6b were converted by the caged catalyst CAT1 with high branched selectivity (l/b = 0.15 for 6a and l/b = 0.25 for 6b). These results show that a substituent on the para position of the allylbenzene derivative results in a more branched selective reaction, as improved branched selectivity is also observed for methyl groups 4c and methoxy groups 5c on the para position with CAT1 (vide supra).

Table 6 Allylbenzene derivatives with halogen atoms. Conditions \([\text{[Rh(acac)(CO)}_2]\) = 0.70 mmol/L in toluene, pressure (H\textsubscript{2}:CO) = 20 bar, substrate/rhodium = 1000, \([\text{P(5Py)}_3]\) = 6.4 mol/L and 19.2 mmol/l of zinc(II) tetraphenylporphyrin for CAT1.

<table>
<thead>
<tr>
<th>Substrate/catalyst</th>
<th>% conv\textsuperscript{a}</th>
<th>l:b\textsuperscript{b}</th>
<th>Cage effect\textsuperscript{c}</th>
</tr>
</thead>
<tbody>
<tr>
<td>6a/CAT1</td>
<td>100</td>
<td>0.15</td>
<td>1.46 kcal/mol</td>
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<tr>
<td>6a/CAT2</td>
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<td>1.76</td>
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</tr>
<tr>
<td>6b/CAT1</td>
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<td>0.25</td>
<td>1.32 kcal/mol</td>
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<td>6b/CAT2</td>
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<tr>
<td>6c/CAT1</td>
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<td>1.07 kcal/mol</td>
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<td>6c/CAT2</td>
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<td>6d/CAT1</td>
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<td>6d/CAT2</td>
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<td>1.08 kcal/mol</td>
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<td>6e/CAT2</td>
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<tr>
<td>6f/CAT1</td>
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</tr>
<tr>
<td>6f/CAT2</td>
<td>54</td>
<td>1.09</td>
<td></td>
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</tbody>
</table>

\textsuperscript{a} Conversion determined by \textsuperscript{1}H NMR spectroscopy \textsuperscript{b} linear:branched ratio determined by GC \textsuperscript{c} Cage effect calculated by subtracting relative energy barriers of encapsulated reaction outcome (using CAT1) from unencapsulated reaction outcome (using CAT2).
The allylbenzene derivatives that contained a halogen atom on the meta position reacts with a lower regioselectivity than allylbenzene 4a. In particular, 3-chloro-1-allylbenzene 6d gives a lower regioselectivity, whereas the corresponding fluorine analog, 3-fluoro-1-allylbenzene 6c gives a similar cage effect and regioselectivity compared to the parent allylbenzene 4a. Substrates that have a methyl or methoxy group on this position also display a lower cage effect compared to 4a (vide supra). The hydroformylation of 2-bromo-1-allylbenzene was also studied, and for substrate similar cage effects are observed as for allylbenzene 4a. Interestingly, a substrate with the perfluorinated aryl ring, allylpentafluorobenzene 6f, is converted with a branched selectivity comparable to allylbenzene 4a. However, the control experiment with CAT2 reveal that the C=C polarization of the substrate results in more branched product (l/b = 1.09) formation than for 4a, which is reflected in a significantly lower cage effect (0.56 kcal/mol). Likely, the lower cage effect is explained by the pentafluorobenzene group having different noncovalent interactions with the walls of the porphyrin cage compared to the phenyl group of allylbenzene.

**Optimization of reaction conditions**

The exploration of the large substrate scope shows that the regioselectivity control displayed by the caged catalysts CAT1 depends on steric parameters but also stereoelectronic interactions between the substrates and the encapsulated CAT1. For instance, the bulky vinylcyclooctane reacts with low regioselectivity with CAT1 (l/b = 2.14), whereas the bulky allylmesitilene reacts with exceptionally high regioselectivity with CAT1 (l/b = 0.12). To shed light on this, we conducted DFT calculations (ADF, BLYP-D3, DZP) with CAT1 and replaced one CO moiety with allylbenzene coordinated to rhodium prior to the selectivity determining hydride migration step (Figure 8). The lowest energy structures of the alkene coordination complex shows that the phenyl ring of the substrate is in close contact (2.6 Å) with a phenyl ring of the ZnTPP building block. Moreover, in previous DFT calculations on this system, remote substrate moieties display similar close contacts with the phenyl rings of the cage during selectivity determining transition states. This shows that such interactions play a role in determining the regiosomeric outcome by stabilizing certain product forming pathways over others. Moreover, for several other hydroformylation catalyst systems it has been established that CH-π interactions between the substrate and the catalysts play a crucial role in controlling the regioselectivity. With this in mind, we intended to further optimize the regioselectivity displayed by these type of caged catalysts by using analogues of the ZnTPP building block.
Previous studies have shown that the shape of the encapsulated CAT1 is crucial for obtaining high levels of branched selectivity.\cite{17,20,65–67} The shape of these cages is only preserved with ZnTPP building blocks that are functionalized with a single substituent at the meta position of the phenyl rings of the zinc-porphyrin. When the phenyls were functionalized with two meta substituents or with a substituent on the ortho or para position, steric hindrance disrupts crucial CH-π interactions between the different ZnTTP building blocks required for the formation of the cage. As a result, substrates are converted with lower regioselectivity for the branched product. Hence, analogues of the ZnTTP building block that contain a single substituent on the meta position of all the phenyl rings were used to generate novel caged catalysts.

Figure 8 DFT optimized structure of $[\text{Rh(H)(CO)}_2(\text{allylbenzene})(\text{P}(_m\text{Py}_3\text{ZnTPP})_3)]]$. ZnTPP building block colored yellow. Allylbenzene substrate colored red. Hydrogens removed for clarity apart from the relevant phenyl rings, which display CH-π interactions.

Figure 9 ZnTPP analogs with a single substituent on the meta position of all phenyl rings.
For the further optimization of the current caged catalyst, two porphyrins to form the cage were investigated; one that contains electron withdrawing substituents, CF$_3$, coined $m$CF$_3$ZnTPP (Figure 9, left)\[^{[68]}\] and one that contained an electron donating group, OiPr, on the meta position, coined $m$OiPrZnTPP (Figure 9, right).

Figure 10 DFT optimized structures of ([Rh(H)(CO)$_3$(P$(m$Py$_3$(m$CF$_3$ZnTPP)$_3$))] (CAT3) (left) and [Rh(H)(CO)$_3$(P$(m$Py$_3$(m$OiPrZnTPP)$_3$))] (CAT4) (right). Porphyrin building blocks were colored green and red for clarity.

Molecular modeling using DFT shows that capsules based on these building blocks ($m$CF$_3$ZnTPP and $m$OiPrZnTPP) provides cages CAT3 and CAT4 respectively (see Figure 10), with shapes that are similar in structure as the parent CAT1. The substituents on the phenyl rings point away from the capsule, such that the cage is not significantly distorted. We explored the hydroformylation reaction of several substrates using CAT3 and CAT4. The parent 1-octene 1a and allylbenzene 4a and several privileged substrates that display large cage effects with CAT1; allylcylohexane 1f, vinylcyclopentane 2a, 4-methoxybut-1-ene 3e, allylmesitilene 4i, 4-trifluoromethyl-1-allylbenzene 6a and 4-fluoro-1-allylbenzene 6b were all explored.

In general, CAT3 and CAT4 display the high branched selectivity characteristic for the caged catalyst for all the substrates investigated (Table 7), which confirms these porphyrins form cages away from the capsule, such that the cage is not significantly distorted. Importantly the branched selectivity was higher when CAT4 was used as catalyst compared to the results obtained with CAT1. Since DFT calculations show that the cage shape is not distorted by the functionalization of the OiPr substituents, this improved selectivity is most likely caused by optimized supramolecular interactions between the substrate moieties and the more electron rich phenyl ring of the $m$OiPrZnTPP building block. For allylmesitilene 4i and 4-
trifluoromethyl-1-allylbenzene 6a the branched selectivity is l/b = 0.11 with CAT4, which are the most branched selective reactions of allylbenzene derivatives to date.[41,44]

Table 7 Optimization of the regioselectivity by replacing the ZnTPP building block of CAT1 with mCF3ZnTPP (CAT3) or mOiPrZnTPP (CAT4) for a subset of substrates. Conditions [Rh(acac)(CO)2] = 0.70 mmol/L in toluene, pressure (H2:CO) = 20 bar, substrate/rhodium = 1000, [P(mPy3)] = 6.4 mol/L and 19.2 mmol/l of zinc(II) tetraphenylporphyrin for CAT1 or analogs mCF3ZnTPP for CAT3 and mOiPrZnTPP for CAT4.

<table>
<thead>
<tr>
<th>Substrate/catalyst</th>
<th>% conva</th>
<th>l:b b</th>
<th>Cage effectc in kcal/mol</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a/CAT1</td>
<td>100</td>
<td>0.56</td>
<td>0.97</td>
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<tr>
<td>1a/CAT3</td>
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<td>1.20</td>
</tr>
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<td>0.36</td>
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<td>4a/CAT3</td>
<td>99</td>
<td>0.31</td>
<td>1.24</td>
</tr>
<tr>
<td>4a/CAT4</td>
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<td>0.26</td>
<td>1.34</td>
</tr>
<tr>
<td>1f/CAT1</td>
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<td>0.27</td>
<td>1.33</td>
</tr>
<tr>
<td>1f/CAT3</td>
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<td>0.25</td>
<td>1.45</td>
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<td>1.19</td>
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<tr>
<td>3e/CAT4</td>
<td>100</td>
<td>0.29</td>
<td>1.30</td>
</tr>
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<td>4i/CAT1</td>
<td>100</td>
<td>0.12</td>
<td>1.83</td>
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<td>4i/CAT3</td>
<td>100</td>
<td>0.19</td>
<td>1.56</td>
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<tr>
<td>4i/CAT4</td>
<td>100</td>
<td>0.11</td>
<td>1.89</td>
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<td>6a/CAT1</td>
<td>100</td>
<td>0.16</td>
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<td>0.14</td>
<td>1.50</td>
</tr>
<tr>
<td>6a/CAT4</td>
<td>100</td>
<td>0.11</td>
<td>1.64</td>
</tr>
</tbody>
</table>
Conversion determined by $^1$H NMR spectroscopy. $^b$Linear:branched ratio determined by GC.

The higher selectivity obtained with CAT4, translates to a higher cage effect compared to that found for CAT1. In particular, the cage effect of 1-octene is 0.23 kcal/mol higher for CAT4. Interestingly, the substrates 1a, 2a, 4a, 1f and 6a also give a higher branched selectivity with CAT3, which shows that the branched selectivity of these substrates benefits from both an electron withdrawing and an electron donating substituent on the ZnTPP building block.

For several substrates CAT3 displayed lower conversions. Previous studies have shown that the presence of an electron withdrawing substituent (i.e. NO$_2$) on the meta position of the phenyl ring of the porphyrin lowers the conversion compared to CAT1 due to a lower dynamicity of the cage, similar to what is observed with CAT3.\textsuperscript{[17]} Also lower conversions are observed with a ruthenium porphyrin. This porphyrin forms a stronger metal-pyridine bond than ZnTPP and this results in the formation of a more tight capsule, which was hypothesized to hinder certain product forming rotations.\textsuperscript{[15]}

**Summary and Conclusion**

In summary, we have demonstrated that CAT1 is able to convert a wide range of substrates with increased regioselectivity to the branched product compared to the benchmark catalyst CAT2. Analysis of the substrate scope with CAT1 reveals a large variation in the catalytic outcome, also when corrected for inherent substrate bias that are determined from the control experiments with CAT2. This investigation identified privileged substrates that are converted with a high degree of selectivity enhancement to the branched product. For aliphatic substrates, allylcyclohexane, allylcyclopentane, vinylcyclopentane and vinylcyclohexane display higher cage effects than the parent 1-octene, which shows such cyclic shapes enhance the branched selectivity with CAT1. In contrast, allylether substrates react with remarkably low cage effects. When the position of the ether moiety is one carbon atom farther from the alkene moiety, the cage effects are restored. This shows that the precise position of the ether moiety is crucial for high regioselectivity control by the cage. Also, clear regioselectivity trends are established for allylbenzene derivatives. For these substrates, substituents on the ortho and para position improved branched product formation and substituents on the meta position lowered branched product formation compared to the unsubstituted analogue. These trends led us to identify an allylbenzene derivative that contain two methyl groups on the ortho position and a single methyl group on the para position, allylmesitilene, as a privileged substrate that reacts with exceptionally high regioselectivity when converted by the cage catalyst CAT1 ($l/b = 0.12$).
The large variation in the catalytic outcome between substrates obtained by CAT1 and CAT2, which could not solely be explained on the basis of steric or inherent substrate bias, suggests that the substrates have noncovalent interactions with the walls of the encapsulated CAT1 during the catalytic event. These interactions are relevant to obtain these high branched regioselectivities. This is also in agreement with DFT calculations, which indeed show that remote structural motifs of the substrates display CH-π interactions with the phenyl rings of CAT1. With this observation in mind, we modified the building blocks that form the cage, by modification of the phenyl rings of the porphyrin building blocks to optimize these CH-π interactions. ZnTPP analogs that have a single electron donating, (OiPr) or electron withdrawing (CF₃), substituent on the meta position of all phenyl rings of the porphyrin were used as cage building blocks to generate two new encapsulated catalysts: CAT3 and CAT4. Application of CAT3 and CAT4 in the hydroformylation of a subset of the substrate scope show that these catalysts generally convert the substrates with improved regioselectivity levels compared to CAT1. In particular, CAT4 gives even higher regioselectivity for the branched aldehyde for all substrates investigated than CAT1. This shows that the investigation of the substrate scope of an encapsulated catalyst provides new insights which leads to a redesign of the cage building blocks entries to optimize the regioselectivity displayed by encapsulated catalysts.
Experimental details

All manipulations were conducted under inert atmosphere (argon or nitrogen) using oven-dried or flame-dried glassware and pre-dried and degassed solvents. The solvent toluene was distilled from sodium prior to use. NMR spectra were measured on a Bruker DRX 300 or a Bruker AMX 400. All reagents were purchased from commercial suppliers.

The hydroformylation experiments were carried out in a stainless steel autoclave (volume 150 ml) charged with an insert suitable for 15 reaction vessels (including Teflon mini stirring bars) for conducting parallel reactions. The substrates were filtered over basic alumina to remove possible peroxide impurities. GC vials were charged with 0.35 µmol of [Rh(acac)(CO)₂], 3.2 µmol of phosphine, (if necessary) 9.6 µmol of zinc(II) tetraphenylporphyrin or an analog, 368 µmol of substrate and a known amount of 1,3,5 trimethoxybenzene in 0.50 ml of toluene. The autoclave was purged three times with 20 bar syngas (H₂:CO, 1:1) after which the autoclave was pressurized to 20 bar of syngas and the Teflon stirring bars were stirred vigorously for 48 hrs at 25°C. After 48 hrs the pressure was carefully released and ~0.05 ml of the reaction mixture was taken and diluted with 0.4 ml CDCl₃ for NMR analysis. Simultaneously ~0.03 ml of the reaction mixture was diluted with dichloromethane for GC-analysis. GC-MS and GC-FID measurements were conducted on a Shimadzu GC-2010 Plus Capillary GC-MS containing a splitter to an MS detector and an FID detector with a SH-Rtx-5 Amine column of 30 m x 0.25 mm, d½ 0.25. All reaction mixtures were separated by diluting the reaction mixture with DCM and injecting reaction mixtures at 50°C after which the temperature was increased at 10°C/min up to 300°C. The oven was kept at 300°C for 5 minutes. This method was applied to all reaction mixtures and gave successful separation for all the substrates apart from allylethyl ether and 4-methoxybut-1-ene. These reaction mixtures were injected at 30°C after which the temperature was increased at 10°C/min up to 300°C.

Note: for the branched products of 4- and 3- methyl hexene two different diastereoisomers are possible, which are also observed in the GC and ¹H-NMR spectra in nearly equal amounts under all catalytic conditions employed. The integrals of the two peaks were combined and reported together as the branched product.

DFT calculations

All DFT calculations were performed with the Amsterdam Density Functional[59,69] (ADF) program. The BLYP-D3BJ[70,71] functional was used together with a small core and a DZP basis set for all atoms apart from rhodium, for which a TZP basis set was used. Relativistic effects were accounted for by running calculations with zeroth-order regular approximation (ZORA).[72–74]

Acknowledgements

Bin Sun is kindly acknowledged for supplying the [P(mPy₃)] ligand used in this study. Dr. Rosalba Bellini is kindly acknowledged for supplying the mCF₃ZnP building block.[68] Dr. Xiaowu Wang is kindly acknowledged for supplying the mOIPrZnTPP building block. Ed Zuidinga is acknowledged for HR-NMR measurements.
Zinc-5,10,15,20-tetrakis(3-trifluoromethylphenyl)porphyrin

$^1$H NMR (400 MHz, Chloroform-$d$) $\delta$ 8.94 (s, 7H), 8.51 (s, 4H), 8.45 (d, $J = 7.6$ Hz, 5H), 8.11 (d, $J = 7.9$ Hz, 4H), 7.94 (t, $J = 7.8$ Hz, 4H).

Predicted mass: 948.1101  Measured mass: 948.1110

Zinc-5,10,15,20-tetrakis(3-isopropoxyphenyl)porphyrin

$^1$H NMR (400 MHz, Chloroform-$d$) $\delta$ 9.03 (s, 8H), 7.89 – 7.74 (m, 8H), 7.64 (t, $J = 7.9$ Hz, 4H), 7.39 – 7.29 (m, 4H), 1.48 (d, $J = 6.0$ Hz, 24H).

Predicted mass: 909.3358  Measured mass: 909.3206
References


A Substrate Scope Driven Optimization of an Encapsulated Hydroformylation Catalyst


[60] www.scm.com


Chapter 6

A Substrate Descriptor Based Approach for the prediction of the Regioselectivity of an Encapsulated Hydroformylation Catalyst

![Diagram of reactants and products with labels for regioselectivity prediction. Diagram includes chemical structures and labels for I_C=C stretch and Delta_13C shift.]
Introduction

The use of encapsulated transition metal catalysts has led to impressive examples of selectivity control for several reactions.\(^1\)\(^{-33}\) In chapter 5 of this thesis, the substrate scope was explored in the hydroformylation reaction using the encapsulated \([\text{Rh(H)(CO)}_3(\text{P}_{\text{mPy}}_3(\text{ZnTPP}))_3] (\text{CAT1})\) catalyst and compared these outcomes to an unencapsulated reference catalyst \([\text{Rh(H)(CO)}_2(\text{P}_{\text{mPy}}_3)_2] (\text{CAT2})\). In these investigations different substrate classes reveal regioselectivity trends when reacted in the presence of CAT1 and CAT2, which are currently not well understood. For all substrates investigated, CAT1 produces more branched product than with CAT2. However, the degree of branched selectivity enhancement significantly varies between substrates.

Scheme 1 Substrate scope investigation of \([\text{Rh(H)(CO)}_3(\text{P}_{\text{mPy}}_3(\text{ZnTPP}))_3]\) capsule (CAT1) in the hydroformylation reaction of terminal alkenes.

A common approach to understand the catalytic outcome for traditional transition metal catalysts is the use of DFT calculations combined with physical organic techniques to rationalize catalytic outcomes and predict the selectivity for novel substrates.\(^{34\text{-}41}\) Often, the evaluation of the catalytic cycle of a transition metal catalyst is conducted for a single substrate and these results are extended to other substrates. However, changing the substrate with encapsulated catalyst CAT1 leads to altered catalyst-substrate interactions, which leads to a significant variation in the regioisomeric outcome between electronically similar substrates. In theory, 4 alkene rhodium complexes can form with CAT1, leading to 8 hydride migration transition states, which are all relevant to the catalytic outcome.\(^{42,43}\) To explain the catalytic outcomes using DFT calculations all pathways need to be considered for every substrate, which is not feasible due to computational cost and computational resources required due to the size of CAT1. Therefore, it is desirable to find methods that circumvent elaborate DFT calculations for caged catalysts, while being able to predict the catalytic outcome with reasonable accuracy. This would provide an important tool for identifying substrates that can be converted with high selectivity with a chosen encapsulated transition metal catalyst.
Additionally, this could significantly reduce the amount of experiments required to identify reactions that are practically applicable.

Recently multivariate data driven approaches have been applied to predict the catalytic outcomes of catalyzed reactions.\textsuperscript{[44,45]} These methods have received considerable attention as these require less computational power while providing valuable information about catalytic systems studied. To be successful, these methods typically require large data sets. Most often catalyst descriptors are used to devise a mathematical model that accurately describes the catalytic outcome for such a data set, which subsequently can be used for predicting catalyst properties. For such a strategy, steric\textsuperscript{[46]} and electronic parameters\textsuperscript{[47–49]} as well as IR frequencies\textsuperscript{[50]} have been used as descriptors. These have been successfully applied to predict catalyst properties for several different reactions including as organocatalyzed\textsuperscript{[51–53]} and transition metal catalyzed reactions.\textsuperscript{[46–50,54]} Such models provided more insight as well as a platform for more focused investigations on how to optimize the selectivity of existing catalysts. In most examples reported to date, catalyst properties have been parametrized, usually for a single reaction. But such models can also be applied to a single catalyst that is reacted with a library of substrates.\textsuperscript{[46]} Based on a limited parameter set, a mathematical model can be constructed. This model shows which parameters largely affect the outcome of the reaction and this allows for the \textit{a priori} identification of substrates that react with high selectivity with a chosen catalyst.

The use of multivariate data driven approaches have not been reported yet to model the catalytic outcomes of encapsulated catalysts and it is therefore unknown whether such tools are applicable. In chapter 5 we reported a larger data set of 41 terminal alkene substrates that were hydroformylated by an encapsulated catalyst [Rh(H)(CO)$_3$($P(m$Py$_3$)(ZnTPP))$_2$] (CAT1) (Scheme 1) and an unencapsulated catalyst [Rh(H)(CO)$_2$($P(m$Py$_3$))$_2$] CAT2 (Figure 1). The catalytic outcomes with CAT1 and CAT2 show large variations in the regioselectivity between substrates, which are currently not well understood. As a result, we set out to delineate the factors that control the regioselectivity of both systems, which is reported in this chapter. In this study, catalytic outcomes of CAT1 and CAT2 were used to evaluate whether a descriptor-based approach provides practical models that can explain and/or predict the catalytic outcome of these hydroformylation catalysts. Since many steric as well as noncovalent interactions appear relevant for determining the catalytic outcome with the encapsulated CAT1, it is unknown
whether a descriptor-based approach can simplify these interactions leading to models that accurately predict the regioselectivity.

Results and discussion

The catalytic results of the hydroformylation of 41 terminal alkenes using the encapsulated \([\text{Rh(H)(CO)}_3\text{P(\text{mPy}{_3}ZnTPP)}_3]\) catalyst (CAT1) were reported in chapter 5 and are investigated in this chapter. As a reference, the catalytic results of unencapsulated \([\text{Rh(H)(CO)}_2\text{P(\text{mPy}{_3})}_2]\) (CAT2) catalyst that is formed under same conditions in absence of the Zn-porphyrin building blocks was also investigated. In all cases, two regioisomers were formed; the linear (l) and the branched (b) aldehyde product.

Using the linear/branched ratios of all entries, we calculated the relative reaction barriers (\(\Delta \Delta E\)) for CAT1 and CAT2 based on the Boltzmann distribution with \(k_B\) being the Boltzmann constant and \(T\) being the reaction temperature in Kelvin:

\[
\Delta \Delta E = \ln \left( \frac{\text{linear ratio}}{\text{branched ratio}} \right) \times k_B T \quad \text{(eq 1)}
\]

As substrates studied the encapsulated CAT1 provided more of the branched product than the unencapsulated CAT2, a lower \(\Delta \Delta E\) for all the reaction outcomes with CAT1 compared to CAT2 is obtained. With this energy values we subtracted the \(\Delta \Delta E\) with CAT1 from the \(\Delta \Delta E\) with CAT2 for every substrate which is a measure of the cage induced selectivity:

\[
\text{Cage effect} = \Delta \Delta E \text{ CAT2} - \Delta \Delta E \text{ CAT1} \quad \text{(eq2)}
\]

Since the CAT1 always provides a higher branched selectivity than CAT2 all cage effects were positive. These experimentally determined energies were used to find correlations between substrate properties and the cage induced selectivity (expressed in relative energies between the product forming pathways).
For the substrate parametrization, we commenced our investigations by correlating the catalytic outcomes of CAT1 and CAT2 against the polarization of the alkenes. It is well known that the polarization of the alkene plays a large role in determining the regioisomeric outcome in the hydroformylation reaction.\[55-59\] For this, the difference between the $^{13}$C shift of the two olefinic carbon atoms ($\Delta^{13}$C shift) was used as a descriptor, which was correlated to the selectivity of the hydroformylation reaction using CAT1 and CAT2. In previous olefin insertion reactions, this has been identified as a descriptor that strongly correlates with the regioisomeric outcome.\[48,49,59\] The experimental selectivity, expressed in $\Delta\Delta E$, are plotted against the $\Delta^{13}$C shift of all substrates for data sets obtained for both CAT1 and CAT2 (Figure 2).

Plotting the regioselectivity ($\Delta\Delta E$) against the $\Delta^{13}$C shift of all substrates evaluated shows a correlation with both catalysts CAT2 and CAT1. These results also show, however, that the correlation for CAT1 is weak with $R^2 = 0.35$. In contrast, the correlation is significantly stronger for CAT2 with an $R^2 = 0.74$. These results show that for the unencapsulated CAT2 the regioselectivity in the hydroformylation reaction can be predicted with a reasonable accuracy using the $\Delta^{13}$C shift as a substrate descriptor, in line with a previous report.\[59\] For the encapsulated CAT1, the correlation is much weaker, indicating that the selectivity displayed by this encapsulated catalysts is determined by more factors. We anticipate that the steric size of the substrate (that may deform the cage) and secondary interactions between the substrate and the cage may play a role, and as such further investigations of the models was directed to parameters that describe these.

To obtain models that account for the shape of the substrates, we extended the substrate descriptors investigated to Sterimol parameters, which are parameters that systematically account for the steric influence of the shape of the substrates as reported
by Verloop et al. Previous work reported by Sigman et al. has shown that for several reactions such descriptors are useful to account for steric effects of functional groups. Therefore it would be interesting to investigate whether such simple steric parameters can account for the many steric interactions such substrates display with the complicated shape of CAT1. Additionally, the C=C IR-stretch intensity \((I_{\text{C=C stretch}})\) was calculated for all substrates as this frequencies was proven to be an useful descriptor that accurately predicts the selectivity for some other reactions.

Figure 3 Substrate parameters acquired to find stronger correlations between substrate properties and selectivity in hydroformylation displayed by CAT1 and CAT2

The substrate parameters were extracted from DFT calculations by performing geometry optimizations and subsequent frequency calculations on all substrates. All DFT calculations were performed with the Amsterdam Density Functional (ADF) program. The B3LYP-D3(BJ) density functional was used together with a small core TZ2P basis set. With the obtained coordinates, the Sterimol parameters were determined. The Sterimol values consist of two width parameters \((B_1\) and \(B_5\)) and a length parameter \((L)\). The different width parameters were calculated according to the profile of the substituent when viewed down on the axis of the C=C bond. \(B_1\) is defined as the minimum width perpendicular to the primary bond axis. This value generally describes the extent of branching at the first carbon center next to the C=C bond. The \(B_5\) parameter describes the maximum width orthogonal to the same axis, which is a degree for how wide the substrate is. \(L\) is the total length of the substituent along the C=C axis.

In first instance, the substrate descriptor values were plotted against the regioselectivity (expressed in \(\Delta\Delta E\)) experimentally found when either CAT1 or CAT2 was used and the overall \(R^2\) values for every parameter are presented in Figure 4. From these values it appears that better correlations are observed for CAT2 than CAT1 for most substrate descriptors. Moreover, it appears that \(I_{\text{C=C stretch}}\) reasonably correlates with the selectivity for reference CAT2 as well as with the cage effect. \(B_1\) also appears to correlate with the regioselectivity displayed by the catalysts, however, closer inspection of the \(B_1\) values shows that this parameter is nearly equal for alkenes that are monosubstituted at the carbon atom next to the C=C bond \((B_1 = 1.8)\). In the substrate scope, also four substrates were investigated that are disubstituted at the carbon atom next to the C=C bond. For these latter substrates, the \(B_1\) value is almost equal \((B_1 = 2.4)\). The trendline suggests that the disubstituted substrates should give more of the linear product. Most likely, this is caused by the more electron rich nature of alkenes with a disubstituted carbon center. These substrates also have a larger \(\Delta^{13}\text{C}\) shift than the alkenes that have a monosubstituted carbon atom next to the C=C bond, and as such it is not an independent parameter.

Also, the substrate length parameter \((L)\) is nearly equal for all substrates. As expected, plotting this parameter to the cage effect reveals a poor correlation, which suggests that these parameters provide limited added value for predicting the regioselectivity compared to the \(\Delta^{13}\text{C}\) shift.
For B₅, the parameter that represents the maximum width of the substrate orthogonal to the C=C bond, also low correlation values were obtained for both catalysts. Apparently, the substrate width is not a useful substrate parameter to predict the regioselectivity displayed by these catalysts. Indeed, in our substrate scope investigation, some bulky substrates reacted with exceptionally high branched selectivity (e.g. allylmesitylene, l/b = 0.12) whereas other bulky substrates reacted with low branched selectivity (e.g. 3-(3,5-dimethylphenyl)-1-propene, l/b = 0.71) (Figure 5), which exemplifies the limitations of employing the Sterimol parameters for predicting the catalytic outcome with CAT1.

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Figure 4 Correlation between descriptors and experimental results (given as R² values) and a visual representation of parameters investigated.

![Descriptive image](image_url)

Figure 5 Bulky substrates both display high regioselectivity control as well as low regioselectivity control with CAT1 despite having similar Sterimol parameters.
The $I_{C=C}$ stretch correlates reasonably well with the selectivity displayed by the unencapsulated CAT2 ($R^2 = 0.57$) as well as with the cage effect ($R^2 = 0.43$), but interestingly, not with CAT1. Therefore, we combined this parameter with the $\Delta^{13}C$ shift to construct multiparameter formulas to predict the reaction selectivity obtained for CAT1 and CAT2 using linear regression analyses.

For CAT1, a formula was constructed based on these two parameters (eq 3). Although the correlation improved compared to the single parameter analysis, it is still relatively low ($R^2 = 0.52$). The results in chapter 5 show that also substituents remote from the alkene can interact with caged catalysts and that these interactions are relevant for regioselectivity displayed by CAT1. These types of interactions are not included in this model and this can be the cause of the weaker correlation.

$$\Delta\Delta E_{cat1} = 0.057\Delta^{13}C_{shift} - 0.031I_{C=C\ stretch} - 1.28 \text{ (eq 3)}$$

Figure 6 Moderate correlation for catalytic outcome with CAT1 and the $\Delta^{13}C$ shift and $I_{C=C\ stretch}$ substrate parameters

In contrast, the multiparameter formula constructed for prediction of the regioselectivity displayed by CAT2 (eq 4) displayed a relatively high accuracy ($R^2 = 0.86$) (Figure 7). Moreover, the accuracy of the formula significantly improved when the $I_{C=C\ stretch}$ was included to the formula compared to the correlation with solely the $\Delta^{13}C$ shift.
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\[ \Delta \Delta E_{cat2} = 0.038 \Delta^{13}C_{\text{shift}} + 0.021 I_{C=C\text{stretch}} - 0.70 \quad (\text{eq 4}) \]

Figure 7 Correlation plot of regioselectivity (\(\Delta \Delta E_{cat2}\)) predicted versus the experimentally obtained regioselectivity using the \(\Delta^{13}C\) shift and \(I_{C=C\text{stretch}}\) substrate parameters as indicated in equation 4.

The best fits obtained for \textbf{CAT1} and \textbf{CAT2}, were based on formulas (eq 3 and 4) that have an opposite sign for \(I_{C=C\text{stretch}}\). The correlation equation for \textbf{CAT1} shows that an increase in \(I_{C=C\text{stretch}}\) value enhances the selectivity for the branched product, whereas the correlation equation for \textbf{CAT2} indicates that a higher value for \(I_{C=C\text{stretch}}\) enhances the selectivity for the linear product. To identify a physical basis for the inversion of the sign in the formula is not straightforward. The IR intensity is mainly governed by the charge redistribution within the bond under specific vibrational transitions.\[^{[65]}\] Possibly, the \(I_{C=C\text{stretch}}\) of alkenes is altered by substrate moieties that affect the regioselectivity differently for \textbf{CAT1} and \textbf{CAT2}. In particular, allylether substrates generally have a low value for \(I_{C=C\text{stretch}}\) and generally react more linear selective with \textbf{CAT1} than what is expected on the basis of the \(\Delta^{13}C\) shift and generally react more branched selective with \textbf{CAT2} than what is expected on the \(\Delta^{13}C\) shift. Furthermore, the allylethers display comparable Sterimol values compared to the analogous substrates where the oxygen atom is replaced with a \(CH_2\) moiety, but the regioselectivity control is significantly lower than the aliphatic analogs as evidenced by the lower cage effects for allyl ethers (eq 2) (Figure 8). Therefore, we propose the ether moiety on this position is involved in noncovalent interactions with the walls of the cage of \textbf{CAT1}, which are rather different than the interactions displayed by the \(CH_2\) group present in the typical alkene substrates. These altered noncovalent interactions with the cage might explain why the regioselectivity control is lower with \textbf{CAT1} than with aliphatic substrates.

\[ \begin{align*}
R' & \text{O} \text{CH}_2 \\
\text{Low regioselectivity control}
\end{align*} \]

Figure 8 Allyl ethers display low regioselectivity control with \textbf{CAT1}
We also explored correlation equations that included the Sterimol parameters. However, these did not yield significantly better correlations to describe the regioselectivity observed by CAT1 and CAT2 than the equation based on solely the $\Delta^{13}C$ shift. For CAT1, this shows that the steric hindrance of the substrates with the cage cannot be simply accounted for with the Sterimol parameters. Most likely, due to the complicated shape of CAT1, the precise position of the steric bulk on the substrate plays a large role in determining the regioisomeric outcome. With the Sterimol substrate parameters this is not accounted for to a satisfactory level.

In a previous report and in chapter 5, DFT calculations show that certain alkene substrates display CH-π interactions with the porphyrin walls of the cage and these also differ between substrates.\textsuperscript{[9]} During the selectivity determining transition states both noncovalent and steric interactions with the cage affect the relative energies of the linear and branched product forming pathways. In the mathematical models studied in this chapter, a parameter that accounted for these noncovalent interactions was not included. This was because a parameter that accounts for such interactions for all substrates evaluated was not identified. To obtain accurate models, such noncovalent interactions between the substrate and the cage need to be understood more accurately between substrate classes. As these are most likely responsible for the large differences in selectivity control e.g., the regioselectivity differences between allylether substrates and analogous aliphatic substrates (vide supra). From these insights, correction factors can be added to the mathematical models, which should improve the accuracy.

Correlation equations have also been applied to a limited set of similar substrates in other reports.\textsuperscript{[46–48,61]} This is generally more facile as the catalyst-substrate interactions are generally more similar, making the construction of predictive formulas less complicated. Possibly, due to the diversity of the substrates investigated in this study, the construction of a general formula that accounts for all substrates evaluated is unsuccessful for CAT1. As too many factors appear relevant for the regioisomeric outcome that are currently not well understood. Therefore, better correlations might be obtained with models that only cover certain substrate classes. However, the added value of such models is lower as the formulas only apply to a single class of substrates.

Recently Norrby et al. reported a transition state force field (TSFF) using the quantum-guided molecular mechanics (Q2MM) method to predict the enantioselectivity with high accuracy by modeling the enantio-determining migratory insertion step.\textsuperscript{[66–68]} This method could account for noncovalent interactions while using significantly less computational time than with DFT techniques. Since noncovalent interactions are also accounted for in such methods, this technique is potentially a useful tool to predict the regioselectivity displayed for encapsulated hydroformylation catalysts. Since small energetic differences lead to large regioselectivity differences, it is important that the accuracy of such methods is satisfactory.
Conclusions

In this chapter we evaluated if correlation equations using multivariate linear regression analyses are helpful tools for the prediction of the selectivity in the hydroformylation reaction. The selectivity in the hydroformylation obtained from the substrate scope of terminal alkenes with both an encapsulated catalyst CAT1 and an unencapsulated reference catalyst CAT2 were used to correlate against equations based on different substrate descriptors. For the unencapsulated CAT2, a formula was constructed that described the catalytic outcome with high accuracy ($R^2 = 0.86$) using the $\Delta^{13}C$ shift of the alkenes and the $\text{I}_{\text{C=C stretch}}$ as substrate descriptors. This is in agreement with our assertion that the outcome is mostly determined by the alkene polarization parameters and remote substituents do not significantly affect the catalytic outcome with this catalyst.

A similar approach for the encapsulated catalyst CAT1 showed that the selectivity of the reaction was significantly more difficult to predict and it is clear that additional substrate parameters such as steric interactions between the substrates and the cage as well as noncovalent interactions may play a role in determining the overall regioselectivity. Sterimol parameters were investigated in order to improve the model by accounting for the substrate size. However, the use of such parameters does not lead to significantly better models for prediction of the selectivity of the reaction. The current models used do not account for the noncovalent interactions displayed between substrate moieties and the walls of the cages. The inclusion of descriptors that accurately account for such interactions, may lead to improved correlation between the predicted and experimentally determined selectivity. It may also well be that for complicated catalysts as studied here, the use of correlation equations only applies for very similar sets of substrates.
Experimental details

The catalytic results were used of Chapter 5 for these analyses. To construct the formulas that describe the catalytic outcomes using descriptors, the Origin program package was used.

Computational details

All DFT calculations were performed with the Amsterdam Density Functional (ADF) program. The BL3YP-D3(BJ) density functional was used together with a small core TZ2P basis set. For all substrates the lowest energy conformer was identified. Using these coordinates the alkene carbon atoms were defined and using this as a primary axis, the Sterimol parameters were determined. Moreover, frequency calculations were conducted and of these equations, the intensity of the C=C shift was determined.

$^{13}$C NMR spectra of substrates

$^{13}$C shifts of the substrates were taken from Spectral Database for Organic Compounds SDBS https://sdbs.db.aist.go.jp/sdbs/cgi-bin/cre_index.cgi and/or from other reports. If the $^{13}$C were not found in literature, we conducted $^{13}$C NMR measurements with of a concentrated sample of the substrates in CDCl$_3$ with a Bruker 400 or 300 MHz NMR spectrometer.

$^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 143.64, 112.08, 77.33, 77.01, 76.69, 44.36, 32.75, 25.15.

$^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 172.62, 129.41, 122.63, 77.48, 77.05, 76.63, 51.70, 37.85, 17.83.

$^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 145.86, 111.03, 77.44, 77.02, 76.59, 41.79, 31.42, 27.42, 25.98, 25.03.

Substrate details

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## Acknowledgements

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References

Chapter 6

10961–10965.

A Substrate Scope Driven Optimization of an Encapsulated Hydroformylation Catalyst

[63] www.SCM.com
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 (H₂: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.

![Supramolecular strategies](image.png)

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.

![DIMPhos](image)

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](image)

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 \([\text{Rh}(\text{H})(\text{CO})_3(\text{P}[n\text{Py}_3(\text{ZnTPP})_3])]\) 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$_{an}$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).
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 preorganizes 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 phosphate 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).
Rhodium biphenyl DIMPhos complex is able to regioselectively hydroformylate natural fatty acids \textit{via} supramolecular substrate preorganization.

In \textbf{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 \textit{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 \textit{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.
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 $[\text{Rh}(\text{H})(\text{CO})_3(P_{m\text{Py}_3}(\text{ZnTPP})_3))]$ (CAT1). For all substrates, the amount of branched hydroformylation product formed was higher with CAT1 than with the unencapsulated reference catalyst $[\text{Rh}(\text{H})(\text{CO})_2(P_{m\text{Py}_3})_2)]$ (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.
In Chapter 6, we investigated whether the catalytic outcomes of the encapsulated [Rh(H)(CO)$_2$($P_{m}$Py$_3$(ZnTPP)$_3$)] catalyst as well as the unencapsulated [Rh(H)(CO)$_2$($P_{m}$Py$_3$)$_2$] catalyst could be accounted for with correlation equations using multivariable linear regression. For the unencapsulated [Rh(H)(CO)$_2$($P_{m}$Py$_3$)$_2$] catalyst, using the Δ$^{13}$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(P₃Py₃(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.
Samenvatting

In dit proefschrift beschrijf ik mijn bijdragen aan het veld van de hydroformyleringskatalyse. Ik heb computer gebaseerde technieken gebruikt om bepaalde verschijnselen die zulke katalysatoren laten zien te begrijpen. Vervolgens heb ik deze inzichten gebruikt om nieuwe supramoleculaire hydroformyleringskatalysatoren te maken. Verder heb ik deze nieuwe en bestaande supramoleculaire katalysatoren gebruikt om de regioselectiviteit te sturen van interne en terminale alkenen in de hydroformylerings reactie. Met deze experimenten liet ik zien dat ik de selectiviteit van verbindingen kon controleren die niet mogelijk was met traditionele overgangsmetaal katalyse.

Voor het maken van chemische verbindingen is het gebruik van katalysatoren essentieel. In de afgelopen 50 jaar is er een gigantische vooruitgang geboekt op dit gebied en zijn er veel verschillende katalysatoren gerapporteerd. Een van de cruciale eigenschappen die een katalysator moet hebben is dat de katalysator in staat is de beginstof selectief kan omzetten in een eindstof. Een bekende homogeen gekatalyseerde reactie, is de hydroformyleringsreactie. Bij deze reactie wordt een alkeen gereageerd met een syngasmengsel (een mengsel van H₂ (waterstof) CO (koolstofmonoxide)) in de aanwezigheid van een overgangsmetaalkatalysator om zo de alkeen om te zetten tot een aldehyde. Wat deze reactie interessant maakt is dat er vele industriële toepassingen bekend zijn en hierdoor methodes om deze reactie efficiënter te maken ook vanuit een industrieel oogpunt interessant zijn. Op dit moment zijn veel de het omzetten van de beginstoffen naar het gewenste aldehyde niet altijd mogelijk voor deze reactie en daarom is het extreem interessant om nieuwe methodes te ontwikkelen om de selectiviteit te controleren.

In hoofdstuk 1 leg ik uit wat de huidige beperkingen zijn binnen het veld van de hydroformyleringskatalyse. Traditioneel gezien wordt de selectiviteit gecontroleerd door het liganden te coordineren aan het katalytisch actieve metalcentrum. Hierdoor kan een omgeving gecreëerd worden waar een stof gevormd is. Echter is deze strategie niet in elk geval succesvol. Een voorbeeld waar de selectiviteit lastig te controleren is zijn interne alkenen. In de afgelopen twintig jaar zijn supramoleculaire strategieën succesvol geïntroduceerd in de hydroformyleringsreactie. Doordat complexere structuren werden gebruikt om de reacties te katalyseren kon de regioselectiviteit worden op manieren die niet mogelijk zijn met traditionele overgangsmetaal katalysatoren. In dit hoofdstuk worden drie veelgebruikte supramoleculaire strategieën besproken: supramoleculaire bidentaten, supramoleculaire substraat preorganisatie en katalysatoren geëncapsuleerd in supramoleculaire kooien (Figuur 1). Vooral de substraat preorganisatie en de geëncapsuleerde katalysatoren worden toegepast in latere hoofdstukken en daarom worden deze uitgebreider besproken. Met behulp van substraat preorganisatie en met geëncapsuleerde katalysatoren kan de selectiviteit van lastige verbindingen, zoals interne alkenen, worden gecontroleerd.
Veelgebruikte supramoleculaire strategieën in de hydroformyleringsreactie

Links: Supramoleculaire zelf-assemblerende bidentaat liganden
Midden: Supramoleculaire substraat preorganisatie
Rechts: Katalysatoren geëncapsuleerd in supramoleculaire kooien.

M = Metaal centrum, FG = Functionele groep, DG = Directieve groep, RG = Reactieve groep, HP = Herkenningsplaats, Do = Donor atoom, ENC = Encapsulatie

Een ligand waar dit proefschrift zich op heeft gericht is een bidentaat ligand wat anionen kan binden: **DIMPhos** (Figuur 2). Dit ligand is gebaseerd op een $7,7'$-diamido-$2,2'$-diindolylmethane (DIM pocket) en het vormt een soort boog met aan de uiteinden twee plaatsen waar een metaal kan binden en in het middenstuk een bindingsplaats voor gedeprotoneerde carboxylzuren.

**DIMPhos**

Figure 1 Een anion receptor gefunctionaliseerd bisfosfor ligand gebaseerd op $7,7'$-diamido-$2,2'$-diindolylmethane: DIMPhos.

De uiteinden werden gebruikt om rhodium te binden en zo een katalysator van dit ligand te maken. Doordat verbindingen die zuren bevatten werden gebonden in het middenstuk, konden deze verbindingen als het ware vastgezet worden en daardoor reageerden ze op een heel andere manier dan als ze niet vast zouden zitten (Schema 1). Dit fenomeen heet supramoleculaire substraat preorganisatie. Door verbindingen vast te zetten kon ervoor gezorgd worden dat de uitkomst in de hydroformyleringsreactie significant selectiever verliep dan wanneer de carboxylzuur verbinding niet gebonden was (Schema 1).
Samenvatting

Schema 1 Regioselectieve hydroformylering van interne en terminale onverzadigde carboxylzuren met behulp van supramoleculaire substraat preorganisatie door RhDIMPPhos complexen.

Een andere onderzochte katalysator in dit proefschrift, is de geëncapsuleerde \([\text{Rh(H)(CO)}_3(\text{P(mPy}_3\text{ZnTPP)}_3))]\) hydroformylerings katalysator (Schema 2). Deze katalysator kan terminale alkenen omzetten naar hoofdzakelijk het vertakte of 'branched' aldehyde product. De meeste katalysatoren converteren zulke substraten hoofdzakelijk naar het lineaire product.

Schema 2 Branched selectieve hydroformylering van 1-octeen met \([\text{Rh(H)}(\text{CO})_3(\text{P(mPy}_3\text{ZnTPP)}_3))]\) (DFT gemodelleerde structuur). ZnTPP bouwstenen zijn geel gekleurd.
Ook kan deze katalysator ervoor zorgen dat als een intern alkeen wordt gereageerd in de hydroformylersingreactie, er hoofdzakelijk het binnenste product wordt gevormd. Voor verbindingen waar geen functionele groep aan zit, zoals alkenen gefunctionaliseerd met alifatische groepen, is dit de enige bekende katalysator die dit kan.

In Hoofdstuk 2 wordt uitgezocht waarom de gerapporteerde DIMPhos gebaseerde katalysatoren tot nu toe altijd hoofdzakelijk het aldehyde invoegen op de plaats die het verst van de zuurgroep ligt. Bij terminale alkenen is het lineaire aldehyde veruit het meest gevormde product. Dit fenomeen werd uitgezocht met behulp van kwantumchemische DFT berekeningen. Deze berekeningen laten zien dat er grote energieverschillen liggen tussen de verschillende hydride migratie paden. Deze verschillen vormen de basis voor de controle over de selectiviteit. Verder laten de berekeningen zien dat het binden van het substraat zelf een belangrijke rol in het veroorzaken van deze grote energieverschillen. Na het ditopisch binden van het substraat zijn de paden die leiden naar het minder gevormde product hoog in energie. Dit komt door het feit dat het substraat en het CO ligand sterische hindering ervaren van elkaar en hierdoor het koolstofmonoöxide ligand weggeduwd wordt van de zuur-bindingsplaats (Figuur 3). Het aanpassen van de homogene katalysator aan het substraat lijkt sterk op de ‘induced fit’ effecten die men ziet bij enzymen.

Figuur 3 conceptuele verklaring voor de grote energieverschillen tussen de rhodium geometrieën na het binden van de substraat. Het binden van het substraat zelf zorgt voor de energieverschillen, wat lijkt op de geïnduceerde fit effecten die vaak worden gezien bij enzymen. Dit zorgt ervoor dat CO van de DIM receptor af wijst. Hierdoor preorganiseert de katalysator het substraat richting het aldehyde product waar de aldehyde zo ver mogelijk weg van de carboxylzuur af staat.

In Hoofdstuk 3 laten wij zien dat wij de een katalysator zo kunnen aanpassen dat wij hem geschikt maken voor natuurlijke vetzuren. De supramoleculaire DIMPhos Rh-bisphosphiet hydroformylersings katalysator kan alkenen met carboxylzuur-bindingsplaats extreem selectief omzetten als de zuur-bindingsplaats afstand klein is. Als de afstand groot is, kan deze katalysator dit niet. In dit hoofdstuk hebben wij nieuwe
Samenvatting

katalysator gemaakt die een grotere afstand tussen de het metaal en zuur bindingsplaats heef (de DIM pocket). Hierdoor werd de selectiviteit voor substraten met een grote afstand tussen de bindingsplaats en de reactieve groep veel groter. Door deze aanpassing konden natuurlijke mono-onverzadigde vetzuren (MUFAs) op een regioselectieve manier omgezet en met deze katalysator werd een overmaat van het 10-formyl product gevormd (10-formyl/9-formyl product ratio van 2.51). Dit is de eerste keer dat zulke verbindingen regioselectief werden omgezet in de hydroformyleringsreactie (Schema 3).

Schema 3 Het rhodium DIMphos complex kan natuurlijke vetzuren regioselectief omzetten met behulp van supramoleculaire substraat preorganisatie.

In Hoofdstuk 4 zijn drie 1,3-benzeendicarboxamide anion receptor gefunctionaliseerde liganden gesynthetiseerd: Een bisfosfine ligand and twee bisfosfiet gebaseerde liganden. Dit werd gedaan om te onderzoeken of deze liganden ook de regioselectiviteit kunnen controleren in de hydroformyleringsreactie door middel van ditopisch binden van carboxyaat gefunctionaliseerde alkenen. Katalytische studies laten zien dat een van de twee ligand gebaseerde rhodium complexen 3-butenoaat tot 7-octenoaat kan converteren met een hogere selectiviteit (l/b tot 6.1) dan de controle experimenten. In de controle experimenten is het substraat niet gebonden is in de bindingsplaats (l/b tot 2.0)(Schema 4). De andere liganden gaven geen hogere selectiviteit dan de controle experimenten. 2D DOSY spectroscopie laat zien dat de rhodium complexen gebaseerd op deze liganden niet selectief mononucleaire complexen vormen en er ook dimere/oligomere complexen worden gevormd. Deze dimere/oligomere complexen zijn waarschijnlijk ook katalytisch actief en verlagen de selectiviteit van deze katalysatoren.
In **Hoofdstuk 5** onderzocht van hoe regioselectief de geëncapsuleerde rhodium katalysator \([\text{Rh(H)(CO)}_3\{\text{P(mPy}_3\text{(ZnTPP)3)}\}] (\text{CAT1})\) terminale alkenen omzet met veel verschillende vormen en veel verschillende functionele groepen. Voor deze studie zijn 41 terminale alkeen substraten gebruikt. Bij alle substraten werd er meer vertakt hydroformylerings product gevormd dan met de ongeëncapsuleerde referentiekatalysator \([\text{Rh(H)(CO)}_2\{\text{P(mPy}_3\}]_2\) (CAT2) (lineair/vertakt ratio tussen 2.14 en 0.12 met CAT1 en lineair/vertakt ratio tussen 6.22 en 0.59 met CAT2). Het effect van het encapsuleren van de katalysator op de selectiviteit van de reactie varieerde daarentegen sterk tussen substraten en dit liet zien dat de vorm en de functionele groepen sterk invloed hadden op de katalytische uitkomst. Uit de analyse van gereageerde substraten wat werd gecombineerd met computer berekeningen (op DFT niveau) blijkt dat zwakke, reversibele interacties tussen bepaalde gedeeltes van de reagentia en de muren van de kooi een belangrijke rol spelen in het controleren van de regioselectiviteit (Figuur 4). Deze zwakke interactie interacties (supramoleculaire interacties) werden geoptimaliseerd door de ZnTPP bouwsteen te vervangen met een porphyrine analoog met een enkele OiPr substituent op alle fenyl ringen. Deze substituent werd geplaatst op een van de twee *meta* posities van de fenyl. De daarop gevormde gekooide katalysator, CAT4, converteerde substraten met nog hogere selectiviteit naar het exotische, vertakte product dan de originele katalysator, CAT1.

**Schema 1** Regioselectivieve hydroformylering van terminale alkenen met behulp van supramoleculaire substraat preorganisatie met behulp van een 1,3 benzeendicarboxamide anion receptor gefunctionaliseerde bisfosfiet.
Figuur 2 DFT berekeningen laten zien dat de substraten CH-π interacties met de ZnTPP muren van de kooi vertonen. ZnTPP bouwstenen zijn geel gekleurd. Het allylbenzeen substraat is rood gekleurd. Waterstoffen zijn verwijderd voor de duidelijkheid behalve bij de relevante relevante fenyl ringen die de CH-π interacties laten zien.

In Hoofdstuk 6 werd onderzocht of de katalytische uitkomsten van de geëncapsuleerde [Rh(H)(CO)$_3$(P(mPy)$_3$(ZnTPP)$_3$)] katalysator en de niet geëncapsuleerde [Rh(H)(CO)$_2$(P(mPy)$_3$)$_2$] katalysator konden worden voorspeld op basis van multivariabele regressietechnieken. Bij de ongeëncapsuleerde [Rh(H)(CO)$_2$(P(mPy)$_3$)$_2$] hydroformylersingkatalysator werden de $\Delta^{13}$C shift van de twee koolstofatomen waaruit de reactieve alken bestaat in combinatie met de intensiteit van de C=C strek vibratie van de reactieve alken ($I_{C=C}$ stretch) gebruikt om een multiparameter formule te construeren die de regioselectiviteit voorspelde met een hoge precisie ($R^2 = 0.86$). Daartegenover was de multiparameter formule voor de gekooide katalysator significant minder goed in het nauwkeurig de regioselectiviteit voorspellen ($R = 0.52$). Dit laat zien dat andere factoren significant bijdrogen aan het bepalen van de regioselectiviteit van de kooi de kooi structureel significant complexer is dan de niet geëncapsuleerde referentiekatalysator. Ook zijn Sterimol parameters gebruikt om de een systematische waarde toe te kenen aan de sterische eigenschappen van alle substraten. De formules die de regioselectiviteit voorspelden met behulp van deze Sterimol waardes waren echter niet beter in het voorspellen van de regioselectiviteit dan de formule op basis van de $\Delta^{13}$C shift en $I_{C=C}$ stretch. De modellen die bestudeerd zijn in dit hoofdstuk gebruikten geen parameters die rekening hielden met niet-covalente interacties tussen de muren van de kooi en het substraat en dit is waarschijnlijk een van de redenen dat de nauwkeurigheid van deze modellen laag was voor de gekooide katalysator.
In dit proefschrift zijn twee klassen supramoleculaire katalysatoren bestudeerd in de hydroformylerings reactie; substraat preorganisatie katalysatoren en geëncapsuleerde katalysatoren. Theoretische en experimentele benaderingen zijn gebruikt om het begrip van deze systemen te vergroten. Met behulp van DFT berekeningen is de mechanistische basis van de geobserveerde regioselectiviteit onderzocht. Verder hebben wij een bestaande DIMPhos fosfiet katalysatoren om de katalysator geschikt voor natuurlijke vetzuren. Verder hebben wij laten zien dat 1,3 benzeen dicarboxamide receptor gebaseerde bisforfor liganden kunnen gebruikt worden voor substraat preorganisatie in de hydroformyleringsreactie. Ook hebben wij onderzocht hoe een geëncapsuleerde katalysator [Rh(H)(CO)3(P[mPy3{ZnTPP}3])] reageerde op structurele veranderingen van substraten in de hydroformylering van terminale alkenen. Hier laten wij zien dat bepaalde substraten met exceptioneel hoge regioselectiviteit reageren met deze katalysatoren. Deze inzichten van deze studie in acht nemend, liet ons de regioselectiviteit optimaliseren door de ZinkTPP bouwsteen te vervangen met een bouwsteen waarop elke fenylring een enkele OiPr substituent zit op de meta positie van de fenylring. Met de katalytische uitkomsten van de gekooid katalysator hebben wij data gedreven benaderingen onderzocht om te begrijpen wat de katalytische uitkomsten veroorzaakten. Met dit werk hebben wij de veelzijdigheid en effectiviteit van supramoleculaire strategieën in de hydroformyleringsreactie laten zien en wij hopen dat dit werk een platform biedt voor het vinden van nieuwe supramoleculaire katalysatoren die zullen leiden tot praktische toepassingen.
List of publications

Publications within this thesis


4. Regioselective Hydroformylation of ω- Unsaturated Acids via Supramolecular Control Using a 1,3-Benzenedicarboxamide Receptor Functionalized Bidentate Ligand, P. R. Linnebank, A. M. Kluwer, J. N. H. Reek, manuscript in preparation


6. A Substrate Descriptor Based Approach for the prediction of the Regioselectivity of an Encapsulated Hydroformylation Catalyst, P. R. Linnebank, A. M. Kluwer, J. N. H. Reek, manuscript in preparation

Publications outside of this thesis


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