Supramolecular control of regioselectivity in the hydroformylation reaction

*Substrate preorganization and second coordination sphere catalysis*

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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.\textsuperscript{[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.\textsuperscript{[3–13]} Indeed, applying such supramolecular strategies has led to unique selectivity control complementary to traditional transition metal complexes.\textsuperscript{[14–36]}

![Figure 1 Schematic drawing of supramolecular substrate preorganization, M = metal center, Do = donor atom, RS = Recognition site, DG = Directing group, RG = reactive group](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.\textsuperscript{[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).\textsuperscript{[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.
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.\cite{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.\cite{17,53–59}

Using the supramolecular substrate preorganization strategy, our group and the group of Breit et al. were able to control the regioselectivity of challenging substrates in the hydroformylation reaction using a carboxylate directing group.\cite{18,20,25,27–29,35,60,61} 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).\cite{62}

![Supramolecular substrate preorganization hydroformylation catalysis](image)

**Figure 4** Supramolecular substrate preorganization hydroformylation catalysis yield the aldehyde product farthest from the carboxylic acid i.e. the linear product for terminal alkenes.

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.\cite{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).\textsuperscript{[25]}

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.

\begin{figure}
\centering
\includegraphics[width=\textwidth]{figure5.png}
\caption{Restricted rotation the controls selectivity determining hydride migration step}
\end{figure}

\textbf{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.

![Regioselectivity Diagram](image)

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

![Pathway Diagram](image)

Figure 7 Lowest energy pathway of the hydroformylation of 4-pentenoate to 6-oxohexanoate with \([\text{Rh(DIMphos)(CO)}_2(H)]\). 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 \([\text{Rh(4-pentanoate)\subset DIMPhos)(CO)}_2(H)]\) 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)⊂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.
Chapter 2

Figure 9 Four ground state geometries (2) of [Rh((4-pentenoate) ⊂ DIMPhos)(CO)(H)]. Energies normalized by subtracting the energy from the lowest energy [Rh((4-pentenoate) ⊂ DIMPhos)(CO)(H)] structure. Some hydrogens and phenyls are removed for clarity.

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.

The two EE geometries that lead to either the branched or the linear product differ in the position of the CO and hydride at the axial position, which are swapped. Just swapping the CO and hydride leads to a large energy difference of 12.0 kcal/mol. The EA geometries in the alkene coordination state are only slightly higher in energy than the lowest EE geometry (1.3 and 5 kcal/mol). The alkyl intermediate 4 that leads to the linear aldehyde is lowest in energy. From the two branched alkyl intermediates, which differ in the position of the CO, the one with the CO pointing to the DIM pocket is the highest in energy. This shows that for both intermediates 2 and 4 and transition state TS3 the structures with CO pointing to the DIM pocket are energetically unfavorable. This observation was
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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. a energies normalized by subtracting the energy outcome from the lowest energy [Rh((4-pentenoate) ⊂ DIMPhos)(CO)(H)] structure b energies normalized by subtracting the energy from the lowest [Rh(PPh₃)₂(H)(CO)] energy
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.[⁷²] 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)](100°) species 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.

![Diagram of complex energies](image)

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
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 \(\text{TS3}\), 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.

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 (\(\Delta E\)) 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; \([\text{Rh (DIMPhos)} \; (\text{CO})\; (\text{H})]\), \([\text{Rh ((acetate) \subset \text{DIMPhos})\; (\text{CO})\; (\text{H})]}\), \([\text{Rh (DIMPhos)\; (propene)}\; (\text{CO})\; (\text{H})]\), \([\text{Rh ((acetate) \subset \text{DIMPhos})\; (\text{CO})\; (\text{H})]}\) and \([\text{Rh ((acetate) \subset (DIMPhos)\; (propene)}\; (\text{CO})\; (\text{H})]\) (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. [Rh (DIMPhos) (CO)(H)] and [Rh ((acetate) ⊂ DIMPhos) (CO)(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).

Figure 13 Model systems studied. For all structures the EE geometries were calculated and the energy differences (∆E) are presented when the position of the hydride and CO ligands were inverted. Only when acetate is bound and rhodium is five coordinate, a high energy intermediate is obtained where the phosphines adopt an EE conformation and CO points to the DIM pocket, which is the case for [Rh ((acetate) ⊂ DIMPhos)(CO)₂(H)] and [Rh ((acetate) ⊂ DIMPhos)(propene)(CO)(H)] these high energy complexes were colored red for clarity.

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
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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 \([\text{Rh}((4\text{-pentenoate}) \subset \text{DIMPhos})(\text{CO})(\text{H})]\) \textit{(vide supra)}. For two complexes i.e. \([\text{Rh} ((\text{acetate}) \subset \text{DIMPhos}) (\text{CO})_2(\text{H})]\) and \([\text{Rh} ((\text{acetate}) \subset (\text{DIMPhos})(\text{propene})(\text{CO})(\text{H}))]\) also a high energy intermediate in which the CO points to the DIM pocket was obtained \((11.4 - 12.3 \text{ kcal/mol})(\text{Figure } 13)\). 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 \((\text{up to } 2.2 \text{ kcal mol})\) 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 \([\text{Rh} ((\text{acetate}) \subset \text{DIMPhos})(\text{CO})_2(\text{H})]\) and \([\text{Rh} (\text{acetate}) \subset (\text{DIMPhos})(\text{propene})(\text{CO})(\text{H}))]\), 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 \([\text{Rh}((4\text{-pentenoate}) \subset \text{DIMPhos})(\text{CO})(\text{H})]\) \textit{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 \([\text{Rh}((4\text{-pentenoate}) \subset \text{DIMPhos})(\text{CO})(\text{H})]\) \textit{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 \([\text{Rh} ((\text{acetate}) \subset \text{DIMPhos})(\text{propene})(\text{CO})(\text{H}))](\text{Figure } 14, \text{ left})\) model complex is similar to the pre-branched EE structure of \([\text{Rh}((4\text{-pentenoate}) \subset \text{DIMPhos})(\text{CO})(\text{H})]\) \textit{complex (Figure } 14, \text{ 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 \((12.3 \text{ kcal/mol})\). 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. ∆∆Energies 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 (acetate) $\subset$ DIMPhos) (CO) (H) (propene)] identified EE ground state geometries. All energies were normalized to the lowest identified energetic [(Rh (acetate) $\subset$ DIMPhos) (CO) (H) (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 in 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.
Chapter 2

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{array}{ccc}
\text{4-pentenoate} & \text{H}_2\text{CO} & \text{RhDIMPhos} \\
\text{6-oxohexanoate} & \text{4-methyl-5-oxopentanoate} \\
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<td>21</td>
<td>EE CO to DIM pocket</td>
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<tr>
<td>22</td>
<td>EA</td>
<td>-18903.55</td>
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<td>23</td>
<td>EE hydride to DIM pocket</td>
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<tr>
<td>24</td>
<td>Transphosphines hydrogen to DIM pocket Down</td>
<td>-18523.21</td>
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<td>25</td>
<td>Cisphosphines H2down</td>
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<td>26</td>
<td>Cisphosphines Codown</td>
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<td>27</td>
<td>H2 oxidative addition</td>
<td>-18539.7</td>
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</table>
Unraveling the Origin of the Regioselectivity of a Supramolecular Hydroformylation Catalyst

<table>
<thead>
<tr>
<th>System</th>
<th>Transphosphines</th>
<th>Transphosphines</th>
<th>Cisphosphines</th>
<th>Cisphosphines</th>
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</thead>
<tbody>
<tr>
<td>$\text{[Rh}((6\text{-oxohexanoate})\text{(DIMPhos})(\text{CO})(\text{H})\text{]}$</td>
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<td>hydride migration TS</td>
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<td>hydrogenolysis product</td>
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<td>$\text{[Rh}((6\text{-oxohexanoate})\text{(DIMPhos)}\text{(CO)}\text{2}(\text{H})\text{]}$</td>
<td>EE Coup</td>
<td>EA</td>
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<tr>
<td>$\text{[Rh(PPh}_3\text{)}\text{2}(\text{H})(\text{CO})(\text{C}_2\text{H}_4)$</td>
<td>-11067.77</td>
<td>-11065.09</td>
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</table>

Table 1: Energies of catalytic conversion of 4-pentenoate to 6-oxohexanoate with $\text{[Rh}((\text{DIMPhos})(\text{CO})\text{2}(\text{H})\text{]}$. Lowest energies for all coordination modes presented.

### Energies of $\text{[Rh(PPh}_3\text{)}\text{2}(\text{H})(\text{CO})(\text{C}_2\text{H}_4)$

<table>
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<tr>
<th>System</th>
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<th>EA</th>
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</thead>
<tbody>
<tr>
<td>$\text{[Rh(PPh}_3\text{)}\text{2}(\text{H})(\text{CO})(\text{C}_2\text{H}_4)$</td>
<td>-11067.77</td>
<td>-11065.09</td>
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</table>

Table 2: EE and EA energies of the ground state of $\text{[Rh(PPh}_3\text{)}\text{2}(\text{H})(\text{CO})(\text{C}_2\text{H}_4)$.

### Model systems for substrate binding event

<table>
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<th>Transphosphines</th>
<th>Cisphosphines</th>
<th>Cisphosphines</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\text{[Rh}((\text{acetate})\text{⊂ DIMPhos})(\text{CO})(\text{H})\text{]}$</td>
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</tr>
<tr>
<td>$\text{[Rh}((\text{acetate})\text{⊂ DIMPhos})(\text{CO})(\text{H})\text{]}$</td>
<td>EE hydride to DIM pocket</td>
<td>EE $\text{CO}$ to DIM pocket</td>
<td>EE hydride to DIM pocket</td>
<td>EE $\text{CO}$ to DIM pocket</td>
</tr>
<tr>
<td>$\text{[Rh}((\text{acetate})\text{⊂ DIMPhos})(\text{CO})(\text{H})\text{]}$</td>
<td>-17177.41</td>
<td>-17175.23</td>
<td>-17175.67</td>
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<tr>
<td>$\text{[Rh}((\text{acetate})\text{⊂ DIMPhos})(\text{CO})(\text{H})\text{]}$</td>
<td>EE hydride to DIM pocket</td>
<td>EE $\text{CO}$ to DIM pocket</td>
<td>EE hydride to DIM pocket</td>
<td>EE $\text{CO}$ to DIM pocket</td>
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<tr>
<td>$\text{[Rh}((\text{acetate})\text{⊂ DIMPhos})(\text{CO})(\text{H})\text{]}$</td>
<td>-17476.36</td>
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<tr>
<td>[Rh((acetate) ⊂ DIMPhos) (propene) (CO)(H)]</td>
<td>EE CO to DIM pocket</td>
<td>EE hydride to DIM pocket</td>
<td>EA</td>
<td>EE CO to DIM pocket acetatehinder</td>
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<tr>
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<td>-18212.59</td>
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<td>-18200.25</td>
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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.


