Supramolecular control of selectivity in transition metal catalysis: Substrate preorganization & cofactor-steered catalysis

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Chapter 3

Precise Supramolecular Control of Selectivity in the Rh-catalyzed Hydroformylation of Terminal and Internal Alkenes*

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3.1 Introduction

Transition metal catalysis is a powerful enabling technology for the sustainable preparation of chemical compounds. However, the value of the individual catalytic transformations depends largely on the access to catalysts displaying the required selectivity, activity and stability. Various tools to control these decisive features by modification of ligands coordinated to the catalytically active metal centers have been introduced. The traditional approach to catalyst development involves knowledge-supported trial-and-error protocol, for which combinatorial and high-throughput screening methods of putative catalysts have demonstrated their added value. If the required selectivity is not obtained using these strategies, “directing groups” (DGs) can be used. Such groups should be introduced to the substrate molecules, and during the reaction they steer the selectivity by coordination to the metal center, directing the reaction toward the desired product. Although effective, this method is limited to substrates with DGs spatially close to the reactive functionality, imposing limitations. Moreover, the reaction occurring at the metal center should be compatible with the DGs, further limiting its potential. For these reasons it is highly interesting to develop alternative methodologies with directing groups that operate via interactions between the functional groups of the substrate and the ligand of the catalyst. This can be achieved by using bifunctional ligands that can coordinate to the metal center and bind non-covalently to a substrate molecule. This supramolecular substrate binding can in principle pre-organize the reactive functionality at the catalytic center (Figure 1) such that one of the competitive reaction pathways is favored over the competing ones, controlling the overall selectivity. This principle was demonstrated in selective oxidation reactions catalyzed by metalloporphyrins by Breslow and coworkers, using hydrophobic or coordination interactions as the driving force. Hydrogen bonding is highly directional and can lead to relatively strong interactions, hence it provides a powerful tool for the rational design of selective catalysts that operate via substrate orientation. As such, it was elegantly used for controlling the regioselectivity in the Ru-catalyzed hydration of alkenes, the Mn-catalyzed C-H oxidation at sp^3-carbon atoms, and the Rh-catalyzed hydroformylation of β,γ-unsaturated carboxylic acids. A two-point hydrogen bonding interaction allowed also to control regio- and enantioselectivity in the Ru-catalyzed epoxidation of olefinic double bonds, and a simple single hydrogen bond was shown to improve the selectivity in the Co-catalyzed cyclopropanation and the enantioselectivity in the Rh-catalyzed hydrogenation of olefins.

Figure 1. General concept of substrate preorganization by a catalyst with a bifunctional ligand - equipped with a donating function for a catalytic center coordination and a specific recognition site for binding to a functional group of a substrate.
The examples reported so far,\textsuperscript{9-14} addressed successfully quite small or rigid substrate molecules of rather limited scope. We anticipated that the ‘remote control’ for more flexible and bigger substrates requires catalytic systems based on well-defined, rigid complex structures, in which the positions of the controlling unit and the catalytic centers are precisely defined. In this respect, the use of functionalized bidentate ligands has an advantage over functionalized mondentate ligands\textsuperscript{11} as the number of possible complexes that can be formed is significantly lower. We considered that neutral anion receptors\textsuperscript{15} that operate with hydrogen bonding are excellent candidates for the substrate-directing motifs for supramolecular catalysts, as they can interact with one of the most common functional groups in organic compounds, i.e. carboxylic moiety. Therefore we chose the 7,7’-diamido-2,2’-diindolylmethane (the DIM pocket)\textsuperscript{16} - a tailor-made receptor for carboxylate and phosphate anions, as a scaffold to prepare new bidentate DIMPhos ligands L1-L3 (Figure 2). In this chapter we report in depth studies that demonstrate that these new ligands can control the regioselectivity in hydroformylation of alkenes by substrate orientation in the binding site. Especially, control over selectivity in the hydroformylation of internal alkenes is challenging\textsuperscript{17} and there are only a few literature precedence of precise selectivity control.\textsuperscript{11,18,19} DFT calculations of the decisive intermediates reveal the mode of operation of this new catalyst. The anion binding in the DIM pocket restricts the rotational freedom of the reactive double bound required during the hydride migration step. As a result, the pathway to the undesired product is strongly hindered, whereas that for the desired product is lowered in energy. The kinetic studies and the \textit{in situ} spectroscopic measurements support this mechanism, and reveal that the system follows Michaelis–Menten kinetics. Full details of these studies are presented in the following sections of this chapter.\textsuperscript{20}

\section*{3.2 Results and discussion}

\subsection*{3.2.1 Coordination and Anion Binding Properties}

We first investigated the anion binding and coordination properties of the DIMPhos ligands. Strong anion binding of L1 was apparent as the presence of acetate anions triggered a significant downfield shift of the NH signals ($\Delta \sigma = 2.4-3.9$ ppm) on $^1$H NMR spectra in CD$_2$Cl$_2$. Further, the titration studies revealed the high association constant, $K_a >> 10^5$ M$^{-1}$, for the formation of a 1 : 1 ligand – acetate anion complex. Upon the addition of the rhodium precursor, [Rh(acac)(C$_2$H$_4$)$_2$] (acac=acetylacetonate), the rhodium – ligand complex, the precursor of the active hydroformylation catalyst\textsuperscript{17a} with the acetate remained bound in the DIM pocket, [Rh(L1·AcO)(acac)], was formed. Also the addition of [RhCl(CO)$_2$)$_2$ as metal precursor led to the formation of the complex with both phosphorus atoms coordinated to the rhodium center in a trans mutual orientation, with the acetate anion bound in the DIM pocket. The structure of this complex was also elucidated by the X-ray crystallography of TBA[Rh(L1·AcO)(CO)(Cl)] crystals (Figure 2 (right), TBA$^+$= tetrabutylammonium cation).\textsuperscript{20a} As anticipated, the acetate is bound in the binding site with 4 strong hydrogen bonds (the N–O distances are 2.737(3) and 3.006(3) Å, for the amide and indole N atoms, respectively), and importantly, its aliphatic group points toward the metal center.
Figure 2. Structure of DIMPhos ligands L1-L3 and DIM anion receptor R1 (left) and X-ray structure of the supramolecular complex [Rh(L1·AcO)(CO)Cl]- (right); TBA⁺ counterion, disordered solvent molecules and most hydrogen atoms are omitted for clarity.

High-pressure (HP) NMR studies reveal that a 1 : 1 mixture of ligand L1 and [Rh(acac)(CO)₂] under hydroformylation conditions, 5 bar CO/H₂ (1:1), results in exclusive formation of a trigonal bipyramidal hydrido complex [Rh(L1)(CO)₂H] – the catalytically active complex for hydroformylation. A typical doublet of triplets for the hydride signal at δ = −9.5 ppm in the $^1$H NMR spectrum indicates that the hydride has a coupling with both rhodium and the two phosphorous donor atoms. This signal simplifies in a phosphorous-decoupled $^1$H-$^31$P NMR experiment and the observed doublet is consistent with the hydride coupled to rhodium. The $^31$P-$^1$H NMR spectrum displays only one doublet at δ = 36.7 ppm, indicative of the phosphine coupling with rhodium and showing the equivalency of both phosphorous atoms. Upon lowering the temperature from 25°C to -95°C the signals in both $^1$H and $^31$P NMR spectra broaden and split into two sets. These experiments establish that the bidentate ligand L1 coordinates in both equatorial–equatorial (eq-eq) and equatorial–axial (eq-ax) fashions and that at room temperature these isomeric complexes are in fast equilibrium on the NMR timescale. The low value of the phosphorous-hydride coupling (4.0 Hz) indicates that the eq-eq isomer dominates the equilibrium. In line with this, high-pressure infrared (IR) studies using either H₂/CO or D₂/CO (both 1:1, 20bar) show absorption bands in the carbonyl region corresponding to both eq-eq and eq-ax isomeric complexes. Furthermore, DFT calculations (BP86, SV(P)) indicate that the complex can adopt both conformations, and that the eq-eq isomer is more favored by 11.4 kJ/mol.

Importantly, HP NMR studies show that the coordination geometry around the rhodium center does not change in the presence of anions (acetate or H₂PO₄⁻) that are bound in the binding site of the ligand. The signals of the NH groups of the ligand are
shifted towards lower fields in the $^1$H NMR spectra ($\Delta \delta = 2.5$–$3.1$ ppm), confirming the formation of strong hydrogen bonds between the anions and the binding site of the ligand. The carbonyl absorption bands of the rhodium complex show only a small shift in the HP IR spectra to lower wavenumbers ($\Delta v$ up to $5$ cm$^{-1}$) upon anion binding, indicating a slightly increased electron density at the metal complex. The binding constants for carboxylate and phosphate anions to the DIM binding site of [Rh(L1)(CO)$_2$H] were determined from titration experiments performed at $5$ bar CO/H$_2$ (1:1) in CD$_2$Cl$_2$ by using HP NMR spectroscopy. These studies reveal that only one anion is bound in the DIM pocket of [Rh(L1)(CO)$_2$H], and that the association constants for CH$_3$COO$^-$ and H$_2$PO$_4^-$ are higher than $10^5$ M$^{-1}$ and around $10^{3.7}$ M$^{-1}$, respectively. In contrast to these anionic species, the acidic (CH$_3$COOH and H$_3$PO$_4$) and the (alkyl) esters analogues are not bound in the DIM pocket of the ligand, and therefore they are well suited for control experiments.

### 3.2.2 Regioselective Hydroformylation of Terminally Unsaturated Aliphatic Acids

We next studied the performance of ligand L1 in the rhodium-catalyzed hydroformylation of a series of deprotonated $\omega$-unsaturated carboxylic acids 1a-8a, varying the aliphatic chain length between the carboxylic moiety and the double bond, that is, from $3$-butenoic to $10$-undecenoic acid (Table 1). Molecular modeling reveals that the shortest substrate 1a (3-butenoate anion) cannot simultaneously bind to the anion binding site and coordinate to the Rh center with its double bond. The homologue substrate 2a that is one carbon longer (4-pentenoate anion) can precisely span the distance between the metal and the binding site of the catalyst, whereas the other substrates 3a-8a fit easily. To verify the influence of the anion binding on the reaction selectivity, we performed control experiments with the neutral acids 1b-8b and their methyl esters 1c-8c (Table 1 and Table 5), substrates that do not bind in the DIM pocket of the catalyst (vide supra). As anticipated, the shortest substrate 1a is hydroformylated with poor selectivity, and hardly any difference in reactivity is observed between this anionic substrate and its acid (1b) and ester (1c) analogues. The linear/branched selectivity (l/b product ratio) is in the expected range for these substrates, between 1.6 and 2.6. In sharp contrast, substrate 2a (4-pentenoate anion) that precisely spans the distance between the metal and the DIM pocket, is hydroformylated with unprecedented selectivity for the linear aldehyde (l/b ratio of 40). If the reaction is carried out at room temperature (instead of $40^\circ$C) the l/b ratio reaches 66. In contrast, the neutral acid (2b) and the methyl ester (2c) analogues of 2a, substrates of the same size that do not bind to the DIM binding site of the ligand, form the aldehyde with the typical low selectivity (l/b ratios of ca. 3), verifying the importance of the anion binding. These results demonstrate that for anionic 2a the reaction barrier for the formation of the linear aldehyde is effectively lowered, with respect to that for the branched product, by the substrate binding event. Interestingly, along with the higher selectivity, the conversion is also much higher when the substrate binds in the DIM pocket of the ligand. The observed rate acceleration can result from the overall lowered reaction barrier due to the substrate pre-organization, as well as, from the higher concentration of the olefin near the metal center due to substrate pre-binding to the DIM pocket of the ligand – that is the so called effective concentration of the olefin is substantially higher than the actual concentration of the olefin in solution. Obviously, both effects can contribute simultaneously to the overall increase in rate.
Scheme 1

![Scheme 1](image)

Table 1. Hydroformylation of anionic substrates 1a-8a and control experiments.$^a$

<table>
<thead>
<tr>
<th>#</th>
<th>ligand</th>
<th>substrate</th>
<th>n</th>
<th>conversion (%)</th>
<th>regioselectivity (l/b ratio)</th>
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<td>1a</td>
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<td>8a</td>
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<td>42</td>
<td>15</td>
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<td>L1</td>
<td>1b</td>
<td>1</td>
<td>46</td>
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<tr>
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<td>L1</td>
<td>1c</td>
<td>1</td>
<td>46</td>
<td>1.6</td>
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<tr>
<td>11</td>
<td>L1</td>
<td>2b</td>
<td>2</td>
<td>49</td>
<td>3.7</td>
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<tr>
<td>12</td>
<td>L1</td>
<td>2c</td>
<td>2</td>
<td>42</td>
<td>3.6</td>
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<td>13$^c$</td>
<td>L1</td>
<td>2c</td>
<td>2</td>
<td>43</td>
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<td>L1</td>
<td>2c</td>
<td>2</td>
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<td>16</td>
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<td></td>
<td>2a</td>
<td>2</td>
<td>13</td>
<td>1.8</td>
</tr>
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</table>

$^a$ Reagents and conditions: [Rh(acac)(CO)$_2$/L1(R1 and/or L4)/substrate = 1 : 3 (and/or 6) : 100; c(Rh) = 2 mmol, 20 bar CO/H$_2$ (1 : 1), CH$_2$Cl$_2$, 40°C, 24h, N,N-diisopropylethylamine (DIPEA, 1.5 equiv.) was used as a base for anionic substrate generation; triethylamine (TEA) can be used alternatively. Regioselectivity and conversion (%) were determined by $^1$H NMR analysis of the reaction mixture. Isomerization and hydrogenation side reactions were not observed. $^b$ Values between parentheses are for the reaction at room temperature for 72h. $^c$ Reaction in the presence of DIPEA (0.3 M). $^d$ Reaction in the presence of acetic acid (0.2 M). $^e$ Reaction in the presence of a mixture of acetic acid and DIPEA (0.2 and 0.3 M, respectively). For full experimental details see the experimental section.

Control experiments confirmed that the presence of acetate ions has negligible effect on the regioselectivity and activity of the Rh(L1) catalyst for non-anionic substrates, e.g. methyl 4-pentenoate (2c) (Table 1, entries 12-15). To further verify that the anion binding site and the catalytic center must be present as an integrated system, we performed a control experiment using a mixture of the anion receptor R1 (Figure 2) and triphenylphosphine (L4). In this case substrate 2a (4-pentenoate anion) is hydroformylated with low selectivity, nearly the same as displayed by the catalyst based on only triphenylphosphine (Table 1, entries 16 and 17). In the absence of any phosphorus ligand, substrate 2a is also hydroformylated with poor selectivity (l/b=1.8) and low conversion (Table 1, entry 18).
Table 2. Hydroformylation of substrates 9-13.  

<table>
<thead>
<tr>
<th>#</th>
<th>substrate</th>
<th>n</th>
<th>conversion (%)</th>
<th>regioselectivity (l/b ratio)</th>
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<td>-</td>
<td>79</td>
<td>&gt; 100</td>
</tr>
<tr>
<td>2</td>
<td>10</td>
<td>-</td>
<td>84</td>
<td>28</td>
</tr>
<tr>
<td>3</td>
<td>11</td>
<td>-</td>
<td>22</td>
<td>13</td>
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<tr>
<td>4</td>
<td>12a</td>
<td>1</td>
<td>10 (69)</td>
<td>- (1.6)</td>
</tr>
<tr>
<td>5</td>
<td>12b</td>
<td>1</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>6</td>
<td>12c</td>
<td>1</td>
<td>3</td>
<td>0.6</td>
</tr>
<tr>
<td>7</td>
<td>13a</td>
<td>2</td>
<td>100</td>
<td>&gt; 40</td>
</tr>
<tr>
<td>8</td>
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</tr>
<tr>
<td>9</td>
<td>13c</td>
<td>2</td>
<td>12</td>
<td>4.0</td>
</tr>
</tbody>
</table>

* Reagents and conditions: [Rh(acac)(CO)$_2$/L1]/substrate = 1 : 3 : 100; c(Rh) = 2 mmol, 20 bar CO/H$_2$ (1 : 1), CH$_2$Cl$_2$, 40°C for entries 1-3 and room temperature (RT) for entries 4-9, 24h, N,N-disopropylethylamine (DIPEA, 1.5 equiv. for entries 1-3; 3 equiv. for entries 4-9) was used as a base for anionic substrate generation. Regioselectivity and conversion (%) were determined by $^1$H and/or $^{13}$C NMR analysis of the reaction mixture. Isomerization and hydrogenation side reactions were not observed. At RT the conversion is too low to determine the selectivity; values between parentheses are for the reaction at 40°C. Additional experiments with 1-octene showed that under these strongly acidic conditions the catalyst is inactive. For full experimental details see the experimental section.

Substrates 3a-8a (5-hexenoate through 10-undecenoate anions) that are longer homologues of optimal substrate 2a also experience an effect of binding in the DIM pocket of the ligand (Table 1). These substrates are hydroformylated with higher selectivity for linear products than their acid 3b-8b or ester analogues 3c-8c. In these reactions, the l/b ratios are larger than 15 and therefore all considerably higher than that for the substrates that do not bind to the DIM pocket of the ligand (Table 5). Notably, both the regioselectivity and the rate enhancement (based on conversion) gradually drop with the increasing distance between the anion and the alkene of the substrate (i.e., from 2a to 8a). This trend can be explained by the aforementioned effective concentration once the alkene is bound in the DIM pocket of the catalyst, which depends on the
inverse cube of the linker length. Consequently, with larger substrates the effective concentration of alkene is lower, hence the reaction is slower, and the alternative pathway via the non-bound species (that is the non-selective “background reaction”) contributes effectively, lowering to some extent the overall selectivity of the reaction. Also, the longer substrates lead to complexes with less perturbed alkene coordination, which could affect their reactivity (vide infra). Interestingly, for the longest substrate 8a the conversion is alike for ester 8c, however, the selectivity is still enhanced. Notably, among the series of substrates 1a-8a, the highest regioselectivity and the highest rate enhancement was achieved for substrate 2a, 4-pentenoate anion that fits precisely in the catalytic cavity, that is between the DIM pocket and the rhodium center.

To further investigate the substrate scope, we also evaluated a small series of (deprotonated) substituted 4-pentenoate acids 9-11 (Table 2). These experiments show that the Rh(L1) catalyst stays highly selective as long as the substituents introduced do not hamper the bifunctional substrate binding (Table 2, entries 1-2 vs. entry 3).

In view of the high affinity of the DIM binding site for phosphate anions (vide supra), we next extended the scope of substrates to alkenes functionalized with the phosphate group (Table 2). One might expect that substrate 13a, 3-butenylphosphonate anion that is a phosphate analogue of 2a, would react with similar high selectivity. Indeed, substrate 13a is hydroformylated by the Rh(L1) catalyst to form the linear aldehyde with excellent regioselectivity (l/b>40). Again, the high selectivity and higher conversion are observed only when the anionic substrate is used (Table 2, entries 7–9). As expected, the homologue 12a, allyl-phosphonate anion that is too short to span the distance between catalyst and binding site is converted with low regioselectivity (Table 2, entries 4 and 6).

3.2.3 Kinetic Studies and Mode of Action

To gain a deeper insight into the reaction mechanism we studied the hydroformylation of substrate 2a by Rh(L1) in more details. In situ HP IR spectroscopy identifies the hydrido complex [Rh(L1)(CO)2H] as the resting state of the catalyst throughout the whole catalytic experiment. Monitoring reaction progress by the gas-uptake for experiments with different partial pressures of CO and H2 reveals the (nearly) zero order dependence of the reaction rate (Turnover Frequency, TOF, consumed substrate/catalyst/time in mol·mol⁻¹h⁻¹) on the hydrogen pressure and the negative dependence of the TOF on the pressure of CO (Table 3). Furthermore, experiments with different substrate concentrations reveal the positive dependency of the TOF on the alkene concentration (Table 3). Thus, both in situ HP IR spectroscopy and gas-uptake experiments are in agreement with a rate-determining step early in the catalytic cycle (Scheme 4), being either alkene coordination or hydride migration.

Table 3. Hydroformylation of substrate 2a by Rh(L1).a

<table>
<thead>
<tr>
<th>#</th>
<th>c(2a) (M)</th>
<th>P(H2) (bar)</th>
<th>P(CO) (bar)</th>
<th>TOF</th>
</tr>
</thead>
<tbody>
<tr>
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<td>2</td>
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</tr>
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<td>7</td>
<td>0.1</td>
<td>10</td>
<td>10</td>
<td>13</td>
</tr>
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</table>

a Reagents and conditions: [Rh(acac)(CO)2]L1 = 1 : 1.5; c(Rh) = 2 mmol, CH2Cl2, 40°C, triethylamine (TEA, 1.5 equiv.) was used as a base for anionic substrate generation. Turnover Frequency, TOF (mol·mol⁻¹h⁻¹) determined from gas-uptake profiles at 10% conversion.
Scheme 4. General catalytic cycle of the rhodium catalyzed hydroformylation

Reaction progress kinetic analysis\(^{26}\) for experiments under the standard conditions (CO/H\(_2\) 1:1, 20bar (constant pressure), 40°C) provides further insight in the reaction mechanism. The initial studies were performed for ester 2c (methyl 4-pentenoate), that is the substrate, which does not bind in the DIM pocket of the Rh(L1) catalyst. These experiments reveal, common for hydroformylation\(^{3b}\) the first-order dependence of the reaction rate on the substrate concentration (the first-order constant, \(k_1=0.0458\) h\(^{-1}\); equation 1). Furthermore, no catalyst inhibition by the product was observed, as indicated by the overlying curves, in Figure 3a.\(^{26}\)

\[
V = k_1 \cdot [S] \quad \text{(eq. 1)}
\]

Additionally, this analysis shows that the catalyst activation period is negligible and that there is no catalyst deactivation occurring during the reaction triggered by the substrate or the product. Both of these findings stay in agreement with the \textit{in situ} HP IR and HP NMR studies, which showed the fast catalyst activation (< 15 min at 40°C) and no catalyst decomposition within at least 48h.

In contrast, the reaction progress kinetic analysis for the hydroformylation of anionic alkene 2a (4-pentenoate), which is the substrate that does bind in the binding site of the Rh(L1) catalyst, demonstrates a different kinetic behavior (under otherwise identical conditions, Figure 3b). Experiments at different initial substrate concentrations (0.1 – 1.0 M of 2a) reveal a linear dependence of rate on substrate concentration for an individual experiment yet the reaction kinetics is also strongly dependent on the initial substrate concentration (non-overlying blue, red, orange and green curves, Figure 3b). This observation could indicate either slow catalyst deactivation in the course of the reaction or catalyst inhibition by the product formed.\(^{26}\) To discriminate between these scenarios, we performed an additional experiment using a mixture of 0.5 M of the substrate and 0.5 M of the product, simulating the reaction with the initial substrate concentration of 1M at 50% conversion. As is clear from Figure 3b, the reaction rate versus substrate concentration plots from these experiments overlay perfectly (green and black curves, Figure 3b), in contrast to that for the experiment with the initial substrate concentration of 0.5 M (orange curve, Figure 3b). These experiments indicate that the catalyst is stable and that the reaction is inhibited to some extent by the product that is formed. Such behavior is in line with a mechanism in which the substrate is pre-organized in the binding site of the catalyst prior the conversion. Such system should
follow Michaelis-Menten kinetics with a competitive product inhibition (equation 2; \( V \) = reaction rate (in M·h\(^{-1}\)), \( V_{\text{max}} \) = maximum reaction rate (in M·h\(^{-1}\)), \( K_{\text{mm}} \) = Michaelis constant (in M), \( K_i \) = product inhibition constant (in M), \([S]\) = substrate concentration (in M), and \([P]\) = product concentration (in M)). \(^{27}\)

\[
V = \frac{V_{\text{max}}[S]}{K_{\text{mm}}+[S]+K_i[P]}
\]  
(eq. 2)

**Figure 3.** Graphical representation of the kinetic profiles: reaction rate vs. substrate concentration plots from reaction at different initial substrate concentration for hydroformylation of ester 2c (a) and anionic 2a (b) using Rh(L1) as the catalyst, determined by gas uptake methods. Reagents and conditions: 20 bar CO/H\(_2\) (1 : 1), CH\(_2\)Cl\(_2\), 40\(^\circ\)C, [Rh(acac)(CO)\(_2\)]/L1 = 1 : 1.5; c(Rh) = 2 mmol, triethylamine (TEA, 1.5 equiv.) was used as a base for anionic substrate generation, pentanoic acid was used to mimic the product (the aldehyde group is proven not to affect the kinetics). (* = repeated experiment with a longer reaction time); for full experimental details see the experimental section.
Precise Supramolecular Control of Selectivity

Indeed, the reaction progress data gave a good fit to equation 2, revealing the following kinetic parameters: \( V_{\text{max}} = 0.063 \ \text{M} \cdot \text{h}^{-1} \), \( K_{\text{mm}} = 0.168 \pm 0.05 \ \text{M} \) and \( K_i = 0.158 \pm 4 \ \text{M} \). Nearly equal values of the Michaelis constant and the product inhibition constant show that both the substrate and the product interact with the catalyst with a similar fashion. This indicates that they compete for the binding in the DIM pocket (rather than for the metal center). Thus the product inhibits the reaction via partial expelling the substrate from the DIM pocket, hence lowering its ‘effective concentration’. In view of nearly equal values of \( K_{\text{mm}} \) and \( K_i \), and the stoichiometry of the reaction (one molecule of the product formed for one molecule of the substrate reacted, hence the sum of \([S]\) and \([P]\) being equal to the initial substrate concentration \(c_0\)), equation 2 can be simplified:

\[
K_{\text{mm}} \approx K_i
\]

and

\[
[S] + [P] = c_0
\]

Thus in this case equation 2 simplifies to:

\[
V = \frac{V_{\text{max}} [S]}{K_{\text{mm}} + c_0} \quad (\text{eq. 3})
\]

Equation 3 shows and rationalizes the pseudo-first order dependence of the reaction rate on the substrate concentration observed experimentally for individual experiments (Figure 3b) and shows the influence of the initial substrate concentration on the reaction kinetics.

The evaluation of the influence of the concentration of substrate \(2a\) on its hydroformylation reveals that the selectivity gradually drops with higher initial concentrations, however, it does not change during the single experiment (the \(l/b\) ratio = 52, 44, 22 and 15, at 0.1, 0.2, 0.5 and 1.0 M solution of \(2a\), respectively, and the \(l/b = 15\) at 0.5 M solution of \(2a\) in the presence of 0.5 M of the product). This shows that at higher concentrations a greater part of the reaction occurs along a non-selective pathway with more substrate molecules involved. Higher concentrations favor a scenario, in which the anionic functionality of the reactive substrate is not bound in the DIM binding site, because the latter is already occupied by another molecule (substrate or product formed). Thus, this transformation does not experience any substrate preorganization and leads to a mixture of both products (in analogy to reaction with non-anionic substrates). This stays in agreement with DFT calculations, which suggest that the branched aldehyde cannot be formed when the anionic moiety is bound in the DIM binding site of the catalyst (\textit{vide infra}).

To investigate the relative substrate selectivity, we next performed competition experiments with mixtures of substrates. Competitive hydroformylation of substrate \(2a\) that precisely fits to the Rh(\text{L1}) system, and of its methyl ester analogue \(2c\) shows that at first mostly anionic substrate is consumed, while during that reaction period ester \(2c\) reacts slowly (Figure 4a). During the course of the reaction, when a greater part of \(2a\) is consumed (and the anionic product formed competes for the binding to the DIM binding site with remaining substrate \(2a\) (\textit{vide supra})), ester substrate \(2c\) is converted more quickly (Figure 4a). Kinetic analysis shows that anion \(2a\) reacts with the overall first order kinetics, despite the competition with ester \(2c\), as in the single substrate experiments (\textit{vide supra}). Interestingly, ester \(2c\) reacts at first with the seeming negative order kinetics that during the course of the reaction (conversion of \(2a > 60\%\)) switches to the expected first order kinetics. This indicates that initially the pre-association of \(2a\) with the DIM pocket of the Rh(\text{L1}) increases its ‘effective concentration’ around the
catalytic metal center, allowing to outcompete substrate \(2c\), but in the final phase of the reaction this effect is attenuated due to the product inhibition (\textit{vide supra}).

Figure 4. Substrate competition experiments: hydroformylation of a (1:1) mixture of substrates \(2a\) and \(2c\) (a) and \(1a\) and \(1c\) (b) by Rh(L1). Reagents and conditions: 20 bar CO/H\(_2\) (1:1), CH\(_2\)Cl\(_2\), 40°C, [Rh(acac)(CO)\(_2\)]/L1/substrate I/substrate II = 1:3:100:100; c(Rh) = 2 mmol, N,N-diisopropylethylamine (DIPEA, 1.5 equiv.) was used as a base for anionic substrate generation; for full experimental details see the experimental section.
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In contrast, the competition experiment with the shortest substrate 1a, which is too short for bifunctional binding to Rh(L1), and with its methyl ester 1c, shows that both substrates react rather independently of each other (Figure 4b), and both follow the first order kinetics. Interestingly, in this case ester 1c reacts a bit faster than anionic 1a. Presumably, the latter being bound in the anion binding site needs to dissociate prior to reacting on the metal center, resulting in its lower reactivity. Furthermore, the competition experiment between anionic substrates 1a and 2a shows similar reactivity trends (Figure 5), with the first order kinetics, demonstrating that both compete for the binding site equally. However, substrate 2a reacts faster, since it can react more easily on the metal center when its anionic group is bound in the DIM pocket, while substrate 1a needs to dissociate from the DIM binding site prior to reacting on the metal center, lowering its reactivity. Additionally, the competition experiment between the longest anionic substrate 8a and ester 1c shows that both substrates seem to react independently of one another, both following first order kinetics.

This reveals that, at the concentrations used, the effective concentration of the long substrate 8a is comparable to the actual concentration in solution. Therefore, the substrate pre-binding does not lead to the effective competition with the non-binding substrate 1c, and hence does not inhibit the intermolecular hydroformylation. This confirms that the effective concentration that depends inversely on the linker length is of crucial importance in determining the (relative) reaction rate, which is found both in the competition experiment, as well as in the rate enhancement for shorter substrate 2a compared to 8a.

![Figure 5](image_url)

**Figure 5.** Competitive hydroformylation of a (1:1) mixture of substrates 1a and 2a by Rh(L1). Reagents and conditions: 20 bar CO/H₂ (1:1), CH₂Cl₂, 40°C, [Rh(acac)(CO)₂]/L₁/1a/2a = 1 : 3 : 100 : 100; c(Rh) = 2 mmol, triethylamine (TEA, 1.5 equiv.) was used as a base for anionic substrate generation; for full experimental details see the experimental section.
Taken all these results together these experiments reveal the order of the events taking place on the catalyst. First, the substrate molecule is bound via the anionic group to the binding site of the catalyst (rather than the double bond coordinates first). Then, if the CO dissociates from the rhodium center, the double bond can coordinate to it and follow the catalytic cycle (Scheme 4), that is finished by the product release. Otherwise, the substrate can leave the DIM pocket of the catalyst, with which it is in fast equilibrium.

### 3.2.4 DFT Calculations and Origin of Selectivity

To gain deeper understanding of the origin of the selectivity, we studied the Rh(L1) catalytic system with DFT (BP86, SV(P)). Both in situ IR and kinetic studies (vide supra) show that the rate-determining step is early in the catalytic cycle, which in combination with the absence of double bond isomerization indicates that the regioselectivity for this catalytic system is defined during insertion of the olefin into the Rh–H bond. We additionally confirmed this by performing experiments using D2/CO. Under these conditions deuterium scrambling was not observed (see Figure 11), which indicates that the hydride migration step is indeed irreversible. Consequently, this selectivity determining hydride migration step was further studied in detail.

![Diagram](image)

**Figure 6.** Calculated reaction pathway (DFT, BP86, SV(P)) of the regioselectivity-determining hydride migration step in the hydroformylation of substrate 2a by the Rh(L1) catalyst. Notation: catalyst–substrate complex I, transition state toward linear product II and linear alkyl Rh complex III, alternative structures of the catalyst–substrate complex IV and V. $G^{298}$: Gibbs free energy at 298 K (relative to the catalyst-substrate complex I) in kJ·mol$^{-1}$; for full computational details, see the experimental section.
We first calculated several possible structures of the substrate-catalyst complex [RhH(CO)(L1)]–(2a) with different geometries around the metal center. We found that the eq-eq coordination geometry is preferred over the eq-ax isomeric complex by 17.7 kJ/mol (I and V in Figure 6). The optimal eq-eq complex structure shows that the carboxylate group of the substrate is strongly bound in the DIM pocket of the ligand with 4 hydrogen bonds (d_{N-O}=2.7–2.9 Å), and the coordinated alkene moiety is tilted out of the P-Rh-P plane of the trigonal bipyramidal rhodium complex (I in Figure 6). This perturbation results from the carboxylate moiety being anchored in the binding site of the ligand. Importantly, the anionic group binding severely restricts the movement of the coordinated double bond. However, the double bond can easily rotate towards the transition state, leading to the linear alkyl Rh complex, and hence to the linear aldehyde product. In fact, the geometry of the complex in the calculated early transition state (ΔG°‡=11.2 kJ·mol⁻¹) is almost unperturbed (the Rh–H bond elongates by only 0.036 Å), with the alkene rotated only a little further out of the equatorial plane (II in Figure 6). Restrictions on the movement of the double bond imposed by the bifunctional substrate binding block its rotation in the direction necessary for the reaction pathway towards the branched alkyl Rh, hence the branched aldehyde product cannot be formed from this complex conformer. The alternative conformer of the substrate-catalyst complex in which the carbonyl and hydride positions are inverted (IV in Figure 6), hence for which the favored rotation of the alkene would direct the reaction toward the branched product, was also evaluated. This conformation has a much higher energy (15.8 kJ·mol⁻¹) that is even higher than the transition state leading to the linear product from the former substrate-catalyst conformer (ΔΔG = 4.6 kJ·mol⁻¹). These calculations suggest that the branched aldehyde product that is formed during the reaction follows a pathway in which the anion moiety of the substrate is not bound in the DIM pocket of the ligand (e.g. the anion binding site is occupied by another substrate molecule or by the product formed, vide supra).

Calculations for reactions with longer substrates 3a and 4a reveal similar trends for the hydride migration step (Figure 7). The main difference is that the longer aliphatic linkers between the double bond and the carboxylic moiety allow to more easily span the distance between the metal center and the anion binding site, resulting in the less perturbed coordination of the alkene moiety in the equatorial plane of the Rh(L1) complex. Thus, the double bond needs to rotate a bit further to reach the transition state leading to the linear product. However, this is still the privileged direction of the alkene rotation, due to restrictions imposed by the substrate anchoring in the DIM pocket. Moreover, the lower perturbation of the alkene coordination for longer substrates results in the greater difference between the substrate-catalyst complex and the decisive transition state. This in turn results in a higher energy barrier. This, together with the change in the effective concentration, explains why the longer anionic substrates have a lower rate enhancement with respect to their ester analogues in comparison to the substrate 2a that fits best (vide supra).

This DFT studies corroborate our assertion that the high regioselectivity obtained for size-matching substrates with the Rh(L1) catalyst originates from substrate pre-orientation imposed by the hydrogen bonds between the anionic functionality and the DIM pocket. This interaction highly restricts the movement of the reactive double bond during the decisive selectivity-determining step. Pre-organization favors the reaction pathway that leads to the linear aldehyde and hinders the competing pathway that would lead to the isomeric product.
3.2.5 Regioselective Hydroformylation of Internally Unsaturated Aliphatic Acids

Selective hydroformylation of internal alkenes is highly challenging, as it involves an internal double bond with inherent lower reactivity. More forcing conditions in turn lead to possible isomerization side reactions,\(^2\) which are deteriorating the selectivity.\(^{33}\)

Moreover, to be selective, the catalyst needs to precisely differentiate between carbon atoms of the double bond whose electronic properties are nearly identical. Importantly, analysis of the mechanism controlling the regioselectivity for hydroformylation of terminal olefins \(1a-8a\) with the Rh(L1) catalyst (Figures 6-7) allows to postulate that the approach should be also operative for substrates with internal double bonds. In principle, one may expect that the restricted movement of the reactive functionality should allow for selective introduction of the aldehyde moiety on the carbon atom of the double bond, which is more distant from the carboxylic group. Unfortunately, our initial hydroformylation experiments proved that the Rh(L1) catalyst is not active enough for substrates with internal double bonds. Therefore, we next investigated the optimization of the activity for this catalytic system by modifying the DIMPPhos ligand.

---

**Figure 7.** Calculated reaction pathway (DFT, BP86, SV(P)) of the regioselectivity-determining hydride migration step in the hydroformylation of substrate 3a (a) and 4a (b) by the Rh(L1) catalyst. Notation: catalyst–substrate complex I, transition state toward linear product II and linear alkyl Rh complex III. \(G^{298}\): Gibbs free energy at 298 K (relative to the catalyst-substrate complex I) in kJ·mol\(^{-1}\); for full computational details, see the experimental section.
Less basic phosphine and more π-accepting phosphite ligands are known to afford more active rhodium complexes for hydroformylation.\textsuperscript{34,35} We therefore designed and prepared ligand \textbf{L2}, a close analogue of \textbf{L1} functionalized with 2 strongly electron withdrawing trifluoromethyl groups on each of 4 phenyl rings (Figure 2). We also obtained ligand \textbf{L3}, equipped with phosphite donor atoms (Figure 2), which are known to lead to highly reactive hydroformylation catalysts.\textsuperscript{35a}

To evaluate the influence of the modifications introduced, ligands \textbf{L2} and \textbf{L3} were first studied in the hydroformylation of anionic terminal olefins \textbf{1a-8a} (under otherwise identical conditions). In general, ligands \textbf{L1-L3} allow for hydroformylation of all substrates \textbf{1a-8a} with remarkable regioselectivities, with the l/b ratios all above 38. The trends of relative selectivity are somewhat different (Figure 8), and they cannot be fully rationalized at this point. Interestingly, when phosphite ligand \textbf{L3} was applied, also the shortest substrate \textbf{1a} reacts with very high selectivity (l/b = 38), in contrast to results for catalysts with phosphine ligands \textbf{L1-L2}. To rationalize this, we performed DFT studies for the Rh(\textbf{L3})–(\textbf{1a}) complex. The molecular modeling shows that the higher flexibility of this phosphite-based ligand allows to reduce the distance between the metal center and the anion binding site such that the Rh(\textbf{L3}) can adjust for bifunctional binding to substrate \textbf{1a} (Figure 9). Again, the double bond can rotate more easily in one direction, leading to regioselective hydroformylation of the bound substrate (see the experimental section - Figures 13). The activities displayed by catalysts with all DIMPPhos ligands \textbf{L1-L3} were further compared quantitatively in hydroformylation of model substrate \textbf{2a}, revealing TOFs: 24, 86 and 100 mol·mol\textsuperscript{-1}·h\textsuperscript{-1}, for \textbf{L1}, \textbf{L2} and \textbf{L3}, respectively, proving the successful design of new ligands.

\begin{figure}[h]
\centering
\includegraphics[width=0.5\textwidth]{figure8.png}
\caption{Hydroformylation of anionic substrates 1a-8a using Rh–ligands L1-L3 catalysts. Full conversion in all cases for catalysts with ligands L2-L3, for conversion with ligand L1, see Table 1. Conditions as described at the footnote to Table 1, with L2/Rh = L3/Rh = 1.1. For full experimental details see the experimental section.}
\end{figure}

\begin{figure}[h]
\centering
\includegraphics[width=0.5\textwidth]{figure9.png}
\caption{Calculated structure (DFT, BP86, SV(P)) of the catalyst–substrate complex [RhH(CO)(L3)]–(1a). For reaction pathways of the regioselectivity-determining hydride migration step in the hydroformylation of substrate 1a by the Rh(L3) catalyst, see Figure 13.}
\end{figure}
Table 4. Hydroformylation of internal alkenes 14-19.

<table>
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* Reagents and conditions: [Rh(acac)(CO)₂]L3/substrate = 1 : 1.1 : 100; [Rh] = 2 mmol, 20 bar CO/H₂ (1 : 1), CH₂Cl₂, 40°C, 72h, triethylamine (TEA, 1.5 equiv.) was used as a base for anionic substrate generation. Regioselectivity and conversion (%) were determined by ¹H NMR analysis of the reaction mixture. For full experimental details see the experimental section.

With more active catalysts in hand, we evaluated the hydroformylation of aliphatic carboxylates with internal double bonds. Although more reactive than Rh(L1), the catalyst with phosphine ligand L2 did not afford sufficient activity to convert internal alkenes. Fortunately, the catalyst based on phosphite L3 proved to be active toward these substrates, providing close to full conversion for most of reactions (Table 4). Interestingly, the catalyst is highly precise, presenting unprecedented regioselectivities for the whole range of substrates that differ in the positions of the reactive double bond with respect to the carboxylic functionality and in size of the substituents (Table 4). In addition, both E and Z isomers of the substrates are converted with high selectivity. The analysis of the isolated products show that, as anticipated, in all cases the major product has the aldehyde functionality on the carbon atom of the double bond more distant from the carboxylate group (Table 4). The relative selectivity of addition of the aldehyde group across the double bond is above 23 in all cases, hence the major product is formed.
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with regioselectivity above 95% \[^{36}\] For comparison, typical catalysts provide close to equimolar mixtures of alternative products. For example, for Rh-PPh\(_3\) catalyst, the ratio between products is in the range 0.8 and 1.7 (under otherwise identical conditions). \[^{24}\] Importantly, for reactions with Rh(L3) at higher temperatures, the regioselectivity is retained at a similar level, allowing for greater catalyst activity, however, at the expense of some side/consecutive reactions. \[^{25}\] These results further confirm the general operational model of the Rh-DIMPhos catalysts.

3.3 Conclusions

In summary, we have reported a series of DIMPhos ligands L1-L3, which are bidentate phosphorous ligands equipped with an integral anion binding site (the DIM pocket). We have shown that these bifunctional ligands form well-defined rhodium complexes that can bind anionic species in the binding site of the ligand. This interaction can be used to preorganize a substrate molecule, i.e. an alkene with an anionic group that can be remote from the reactive double bond (even 10 bonds!), which leads to its highly selective hydroformylation. For the hydroformylation of substrates with internal double bonds the current system gives the highest selectivity reported in the literature, \[^{27}\] clearly demonstrating the power of supramolecular control of the selectivity for catalysis. Importantly, the mode of operation is well understood by the detailed studies provided in this paper. This enables rational design of selective catalysts for desired reactions, clearly complementing trial-and-error approaches in the field of transition metal catalysis. In principle it should be possible to transmit the current system to other transition metal catalyzed processes involving a migration in the selectivity-determining step, giving rise to other selective transformations in chemical catalysis.

3.4 Experimental section

General Procedures

All reactions were carried out under an argon atmosphere using standard Schlenk techniques. THF, pentane, hexane and diethyl ether were distilled from sodium benzophenone ketyl under nitrogen; CH\(_2\)Cl\(_2\), isopropanol and methanol were distilled from CaH\(_2\) under nitrogen; toluene was distilled from sodium under nitrogen and triethylamine was distilled from KOH pellets under nitrogen. NMR spectra were measured on a Bruker AMX 400 (400.1MHz, 100.6MHz and 162.0 for \(^1\)H, \(^13\)C and \(^31\)P respectively). Infrared spectra were recorded on a Thermo Nicolet NEXUS 670 FT-IR. Elemental analyses were carried out on a Carlo Erba NCSO-analyzer. High resolution mass spectra were recorded on a JEOL JMS SX/SX102A four sector mass spectrometer; for FAB-MS 3-nitrobenzyl alcohol was used as matrix. ESI-MS measurements were recorded on a Shimadzu LCMS-2010A liquid chromatography mass spectrometer by direct injection of the sample to the ESI probe. CD\(_2\)Cl\(_2\) and DIPEA were dried over molecular sieves (3Å) and degassed by 3 freeze-pump-thaw cycles. If not stated otherwise, syngas refers to a 1 : 1 mixture of H\(_2\) and CO, and the pressure refers to a sum pressure of both.

Materials

All reagents were purchased from commercial suppliers and used without further purification, with the exception of a ligand building block – 1,1-bis-(3-methyl-7-nitro-1H-indol-2-yl)-propane, \[^{16}\] receptor R1, \[^{16}\] which were synthesized according to the published procedures. The synthesis procedures for ligands L1\[^{20}\] and L3\[^{20}\] and substrates 6c-7c, 12a-13a\[^{20}\] were reported previously (see also Chapters 2 and 5).
Synthesis of ligand L2

4-(bis(3,5-di(trifluoromethyl)phenylphosphino)benzoic acid; 4-iodobenzoic acid (822mg, 3.3 mmol), bis(3,5-di(trifluoromethyl)phenyl)phosphine (1.52g, 3.3 mmol), triethylamine (0.93ml) and palladium (II) acetate (2mg), were dissolved in acetonitrile (25 ml) under argon, brought to reflux and continued overnight. The next day, the volatiles were evaporated under reduced pressure, and to the residue water (40ml) and potassium hydroxide (0.45g) were added. Then, the water phase was washed with diethyl ether (3·50ml), acidified with 1M HCl to pH ~ 3, and extracted with DCM (3·50 ml). The combined organic layers were dried over MgSO₄, and the solvent was removed under vacuum. The solid residue was crystallized from hot C₂H₂Cl₂ (20ml), adding a hexane layer on the top (15ml), yielding 1.57g (82%) of the product.

1H NMR (400 Mhz, DMSO-d₆): δ = 13.25 (bs, 1H), 8.20 (s, 2H), 8.00 (d, J₁ = 8.0 Hz, 2H), 7.93 (d, J₂ = 6.3 Hz, 4H), 7.53 (dd, J₁ = J₂ = 8.0 Hz, 2H);

13C NMR (100Mhz, DMSO-d₆): δ = 166.7 (s), 139.3 (d, J₁ = 18.8 Hz), 133.8 (d, J₁ = 13.2 Hz), 134.0 (d, J₁ = 20.9 Hz), 133.6 (d, J₁ = 19.7 Hz), 132.4 (s), 130.8 (qd, J₁ = 30.2 Hz, J₂ = 6.2 Hz), 129.9 (d, J₁ = 7.3 Hz), 123.6 (m), 123.0 (q, J₁ = 272.0 Hz);

19F NMR (31Mhz, DMSO-d₆): δ = -5.28.

Bis-(4-(bis(3,5-di(trifluoromethyl)phenylphosphino)benzoamide) of 1,1-bis-(7-amino-3-methyl-1H-indol-2-yl-propane)): 1,1-Bis-(3-methyl-7-nitro-1H-indol-2-yi)propane (392mg, 1mmol) was suspended in methanol (20 ml) and 10% palladium on charcoal was added (0.1g). The reaction mixture was flushed with hydrogen, and then vigorously stirred under a hydrogen atmosphere (balloon). The progress of the reaction was monitored by TLC, and after completion (~hour), the catalyst was filtered off over Celite®. The solvent was evaporated, and the crude diamine was immediately used in the subsequent reaction without further purification.

To the solution of crude diamine (1mmol), 4-(bis(3,5-di(trifluoromethyl)phenylphosphino)benzoic acid (1.45g, 2.5mmol), 4-dimethylaminopyridine (60mg, 0.5mmol) and DIPEA, with the 3 : 100 : 150 ratio, respectively; before the addition of the ligand di(trifluoromethyl)phenyl)phosphino)benzoic acid: 1,1-diamino-4-methyl-1H-indol (0.45g) were added. Then, the water phase was washed with diethyl ether (3·50ml), acidified with 1M HCl to pH ~ 3, and extracted with DCM (3·50 ml). The combined organic layers were dried over MgSO₄, and the solvent was removed under vacuum. The solid residue was purified by column chromatography on silica gel (60g), with a hexane : chloroform (2:1 → 1:1) mixture as an eluent. Fractions of the product were combined, and the solvent evaporated off, and pure product was obtained by recrystallization from methanol.

The solid was dissolved in a minimum amount of dichloromethane and precipitated by the addition of hexane, followed by the cooling (~20°C), and the powder was isolated by the filtration of the cold suspension, yielding 0.94g (64%) of L2.H₂O.

1H NMR (400Mhz, CD₂Cl₂): δ = 9.45 (s, 2H, NH-indole). 8.25 (s, 2H, NH-amide), 7.98 (s, 4H), 7.90-7.70 (m, 12H), 7.41-7.29 (m, 6H), 7.03 (dd, J₁ = J₂ = 7.5Hz, 2H), 6.92 (d, J₁ = 7.5Hz, 2H), 4.49 (t, J₁ = 7.9Hz, 1H, CH₂CH₂NH₂), 2.30 (s, 6H, ArCH₂), 2.23 (m, 2H, CH₂CH₂NH₂), 1.01 (t, J₁ = 7.3Hz, 3H, CH₂CH₂);

13C({¹H} NMR (100Mhz, CD₂Cl₂): δ = 165.1 (s), 139.2 (dd, J₁ = 18.2Hz, J₂ = 3.4Hz), 138.1 (d, J₁ = 13.4Hz), 136.5 (d, J₁ = 26.0Hz), 134.2 (d, J₁ = 20.9Hz), 133.9 (d, J₁ = 21.5Hz), 132.6 (qd, J₁ = 33.6Hz, J₂ = 7.2Hz), 132.5 (s), 128.5 (d, J₁ = 7.7Hz), 128.1 (s), 124.3 (m), 123.2 (q, J₁ = 273.1Hz), 122.0 (s), 119.3 (s), 116.6 (s), 114.0 (s), 108.5 (s), 37.3 (s), 27.6 (s), 12.5 (s), 8.9 (s);

31P({¹H} NMR (162Mhz, CD₂Cl₂): δ = -4.45 (s); HR MS (FAB): calcd. for C₉H₉N₆O₃P₂F₂ [M⁺]: 1452.2400, found: 1452.2390;

Elemental analysis (% calcd.) for C₉H₉N₆O₃P₂F₂: C 54.71, H 3.01, N 3.81, F 31.00, P 4.21, found: C 55.01, H 3.29, N 3.62, F 29.76, P 4.61.

Coordination and titration studies

For details concerning coordination and titration studies, see the experimental section of Chapter 2. The details concerning the in situ HP IR studies are provided below.

The in situ HP IR experiments in the presence of substrate were analogous to the above described coordination experiments, with the following exceptions: the autoclave was initially charged with the solution of ligand L1, substrate 2a and DIPEA, with the 3 : 100 : 150 ratio, respectively; before the addition of the rhodium precursor solution (from the reservoir) the autoclave was equilibrated at 40°C, which was the temperature of the actual measurement.

The experiments revealed the fast catalyst activation under the actual hydroformylation conditions. The full activation was reached before the first spectrum was recorded (at 15min), and the metal carbonyl region of the spectrum did not change further in the course of the experiment. The spectrum presents the same signals as the rhodium hydride observed before, revealing that the Rh(L1)(CO)₂H complex is the resting state of the catalyst. Furthermore, the consumption of the substrate and the formation of the product can be observed, respectively, at 1639 cm⁻¹ (corresponding to the terminal double bond signal) and at 1728 cm⁻¹.
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Catalysis studies

General procedure for the hydroformylation experiments

A stock solution for the hydroformylation experiments was prepared by charging a flame-dried Schlenk flask with Rh(acac)(CO)$_2$, ligand, DIPEA or TEA (if appropriate), internal standard (1,3,5-trimethoxybenzene) and solvent (DCM). The solution was stirred for several minutes and then transferred into 1.5ml reaction vessels equipped with mini Teflon stir bars (under inert conditions), followed by substrate addition. The vessels were placed in a stainless steel autoclave (250 mL) charged with an insert suitable for 15 reaction vessels for conducting parallel reactions. Before starting the catalytic reactions, the charged autoclave was purged three times with 20 bar of syngas and then pressurized at 20 bar of syngas. The reaction mixtures were stirred at the appropriate temperature for the required reaction time, after which the pressure was released and the regioselectivity and the conversion determined by NMR. Additionally, the reaction mixtures were analyzed by electrospray ionization mass spectrometry (ESI MS).

For NMR analysis, usually two small portions (75 μl) of each reaction mixture were taken. From one of them, the solvent was evaporated (400 mbar, 40ºC). Then, both samples were diluted to 0.7ml with CDCl$_3$ and $^1$H NMR spectra were recorded and compared with a $^1$H NMR spectrum of the initial reaction mixture (before hydroformylation). Analyses of characteristic signals in the aliphatic and aldehyde regions were in agreement in all cases. No by-products (hydrogenation, double bond isomerization) were observed in all runs.

When 3-butenolic or 4-pentenolic acid, or substrates with the internal double bond in positions 3 or 4 form the carboxylic group, were used as substrates, the characteristic aldehyde signal for the branched product was not observed or was broadened (due to intramolecular interactions). Thus, a small amount (~50 μl) of DIPEA or TEA was added to the sample, and the $^1$H NMR spectrum was collected once more, which enabled direct integration of both aldehyde signals. Furthermore, alternative straightforward analysis conducted in more polar solvents (DMSO-$d_6$ or MeOD-$d_4$) gave the same results.

When phosphonic acids were used as substrates, the characteristic aldehyde signal for the branched product was also not observed (due to intramolecular interactions), both after addition of DIPEA and in more polar solvents (DMSO-$d_6$ or MeOD-$d_4$). The aldehyde signal was only observed after esterification of the phosphonic group. For straightforward analysis, larger portions (700 μl) of each reaction mixture were taken and the residue was diluted to 0.7ml with CD$_2$Cl$_2$ and $^{13}$C NMR spectrum was recorded, which allowed the determination of the ratio between both products. No by-products were observed.

For ESI MS analysis, a small portion (10 μl) of each reaction mixture was taken and diluted with MeOH (1 ml). Samples prepared in this way were analyzed by ESI-MS (negative ions). No by-products (hydrogenation of double bond or aldehyde group) were observed.

For more details concerning the hydroformylation of the terminal alkenes, including images of NMR and ESI-MS spectra, see the supporting information of the preliminary report (http://onlinelibrary.wiley.com/doi/10.1002/anie.201005173/suppinfo) and Chapter 2.

Table 5. Hydroformylation of 1b-8b and 1c-8c with the Rh(L1) – control experiments.$^a$

<table>
<thead>
<tr>
<th>#</th>
<th>substrate</th>
<th>n</th>
<th>conversion (%)</th>
<th>regioselectivity (l/b ratio)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1b</td>
<td>1</td>
<td>46</td>
<td>1.4</td>
</tr>
<tr>
<td>2</td>
<td>2b</td>
<td>2</td>
<td>49</td>
<td>3.7</td>
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<td>3</td>
<td>3b</td>
<td>3</td>
<td>55</td>
<td>6.3</td>
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<td>4b</td>
<td>4</td>
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<td>9.8</td>
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<td>5b</td>
<td>5</td>
<td>54</td>
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<tr>
<td>7</td>
<td>7b</td>
<td>7</td>
<td>77</td>
<td>12</td>
</tr>
<tr>
<td>8</td>
<td>8b</td>
<td>8</td>
<td>76</td>
<td>10.6</td>
</tr>
<tr>
<td>9</td>
<td>1c</td>
<td>1</td>
<td>46</td>
<td>1.6</td>
</tr>
<tr>
<td>10</td>
<td>2c</td>
<td>2</td>
<td>42</td>
<td>3.6</td>
</tr>
<tr>
<td>11</td>
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<tr>
<td>13</td>
<td>5c</td>
<td>5</td>
<td>42</td>
<td>7.2</td>
</tr>
<tr>
<td>14</td>
<td>6c</td>
<td>6</td>
<td>43</td>
<td>8.2</td>
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<tr>
<td>15</td>
<td>7c</td>
<td>7</td>
<td>38</td>
<td>9.7</td>
</tr>
<tr>
<td>16</td>
<td>8c</td>
<td>8</td>
<td>39</td>
<td>9.9</td>
</tr>
</tbody>
</table>

$^a$ Reagents and conditions: Rh(CO)$_2$(acac) as a rhodium source, [substrate] = 0.2 M, Rh : ligand L1 : substrate, 1/3/100, CO/H$_2$ = 1/1 (20bar), 24h, 40ºC, CH$_2$Cl$_2$ as a solvent; acac = acetylacetonate.
Table 6. Hydroformylation of 14-19 with the Rh-PPh₃ catalyst – control experiments. *

<table>
<thead>
<tr>
<th>#</th>
<th>substrate</th>
<th>conversion (%)</th>
<th>regioselectivity (o/i ratio)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>14</td>
<td>26</td>
<td>1.1</td>
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<tr>
<td>2</td>
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<td>40</td>
<td>1.0</td>
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<td>16</td>
<td>23</td>
<td>0.9</td>
</tr>
<tr>
<td>4</td>
<td>17</td>
<td>28</td>
<td>0.8</td>
</tr>
<tr>
<td>5</td>
<td>18</td>
<td>24</td>
<td>1.2</td>
</tr>
<tr>
<td>6</td>
<td>19</td>
<td>23</td>
<td>1.7</td>
</tr>
</tbody>
</table>

*Reagents and conditions: Rh(CO)₂(acac) as a rhodium source, [substrate] = 0.2 M, Rh : PPh₃ : substrate, 1/6/100, CO/H₂ = 1/1 (20bar), 72h, 40°C, CH₂Cl₂ as a solvent; acac = acetylacetonate.

Isolation of products:

General procedure: A stainless steel autoclave equipped with an oven-dried glass insert (15 mL) was charged with a solution of a substrate (0.2M), dry triethylamine (0.2M), Rh(CO)₂(acac) (0.002M), ligand L₃ (0.0022M) in dry DCM. The charged autoclave was carefully purged three times with 20 bar of syngas and then pressurized at 20 bar of syngas, followed by stirring at 40°C for 96h. Afterwards the pressure was carefully released, the reaction mixture was evaporated with ~1g of silica gel, the residue was charged onto a chromatography column (20-30g SiO₂) and eluted with a hexane : diethyl ether : acetic acid mixture (200 : 100 :1). Fractions of the pure product were combined, and the solvent evaporated off (the traces of acetic acid were co-evaporated with toluene), yielding the product.

4-Methyl-5-oxopentanoic acid:

(E)-3-Pentenoic acid 14 (100mg, 1mmol) was used as the starting material, yielding 103mg (80%) of the product.

1H NMR (400 Mhz, CDCl₃): δ = 10.00 (vbs, 1H, COO⁻), 9.63 (d, J₁ = 1.5 Hz, 1H, CHO), 2.50-2.40 (m, 3H, CH₂-COO+CHCHO), 2.11-2.01 (m, 1H, CH₂-CHCHO), 1.74-1.64 (m, 1H, CH₂-CHCHO), 1.14 (d, J₁ = 7.1 Hz, 3H, CH₃);

13C NMR (100MHz, CDCl₃): δ = 204.2, 179.2, 45.4, 31.3, 25.1, 13.4;


4-Formylhexanoic acid:

(E)-3-Hexenoic acid 15 (114mg, 1mmol) was used as the starting material, yielding 123mg (86%) of the product.

1H NMR (400 Mhz, CDCl₃): δ = 10.40 (bs, 1H, COO⁻), 9.59 (bs, 1H, CHO), 2.48-2.23 (m, 3H, CH₂-COO+CHCHO), 2.01-1.90 (m, 1H, CH₂-CH₂-COOH), 1.83-1.63 (m, 2H, CH₂CH₂+CH₂-COOH), 1.61-1.49 (m, 1H, CH₂CH₂), 0.93 (t, J₁ = 7.5 Hz, 3H, CH₃);

13C NMR (100MHz, CDCl₃): δ = 204.6, 179.4, 52.3, 31.5, 22.8, 21.9, 11.3;


4-Formylheptanoic acid:

(E/Z)-3-Heptenoic acid 16 (128mg, 1mmol) was used as the starting material, yielding 115mg (73%) of the product.

1H NMR (400 Mhz, CDCl₃): δ = 10.80 (bs, 1H, COO⁻), 9.60 (bs, 1H, CHO), 2.48-2.28 (m, 3H, CH₂-COO+CHCHO), 2.03-1.89 (m, 1H, CH₂-CH₂-COOH), 1.85-1.72 (m, 1H, CH₂-CH₂-COOH), 1.72-1.59 (m, 1H, CH₂-CH₂-CH₂), 1.52-1.27 (m, 3H, 1H of CH₂-CH₂-CH₂+CH₂-CH₂-CH₂), 0.93 (t, J₁ = 7.2 Hz, 3H, CH₃);

13C NMR (100MHz, CDCl₃): δ = 204.5, 179.0, 50.9, 31.4, 31.1, 23.3, 20.2, 14.2;
Precise Supramolecular Control of Selectivity

4-Formyloctanoic acid:
(E/Z)-3-Octenoic acid 17 (142mg, 1mmol) was used as the starting material, yielding 122mg (71%) of the product.

\[ {\text{HR MS (FAB): calcd. for C}_{13}\text{H}_{23}\text{O}_{3} [M+H]^+: 159.1021, found: 159.1025.} \]

5-Methyl-6-oxohexanoic acid:
(E/Z)-4-Hexenoic acid 18 (114mg, 1mmol) was used as the starting material, yielding 108mg (75%) of the product.

\[ {\text{HR MS (FAB): calcd. for C}_{15}\text{H}_{25}\text{O}_{3} [M+H]^+: 173.1178, found: 173.1175.} \]

Gas uptake experiments
The experiments were carried out in the AMTEC SPR16 equipment consisting of 16 parallel reactors equipped with internal temperature and pressure sensors, and a mass flow controller. The apparatus is suited for monitoring gas uptake profiles during the catalytic reactions. Prior to catalytic experiments, the autoclaves were heated to 110°C and flushed with argon (22 bar) five times. Next the reactors were cooled to room temperature and flushed again with argon (22 bar) five times. Then, the autoclaves were charged with solutions of the rhodium precursor [Rh(acac)(CO)\(_2\)], ligand, substrate, base (if desired) and internal standard (1,3,5-trimethoxybenzene) in CH\(_2\)Cl\(_2\) (8ml). The reactors were pressurized with syngas (CO/H\(_2\), appropriate ratio and pressure) and heated up to 40°C. The pressure was kept constant during the whole reaction, and the gas uptake was monitored and recorded for every reactor. After catalysis the pressure was reduced to 2.0 bar, the reactor was flushed with argon, and samples were taken for further analysis.

Conversions were determined by NMR analysis of the final reaction mixtures (in respect to the internal standard). Initially, the measured data of the gas consumption in time (attributed quantitatively to the conversion in time) were smoothed, to minimize the noise inherent in the integral measurements (to capture important patterns in the data, while leaving out noise), with the Origin 8.0 software, applying the Boltzmann model or similar. To avoid artefacts, the correctness of the model used was evaluated and confirmed by the analysis of the regular residuals of the fitting. The smoothed data were used to determine initial TOFs, reported in Table 4 and in the main text. Furthermore, as presented in Figure 3, the analysis revealed the linear dependency of the reaction rate of the Rh(L1) catalyst on the substrate concentration (for both, substrate 2a and 2c) in every separate experiment followed in time, as well as, showed the product inhibition in case of anionic substrate 2a, and no product inhibition in case of substrate 2c.

Testing the Michaelis-Menten kinetic model with a competitive product inhibition (equation 1) for experiments with different initial substrate 2a concentrations (under otherwise identical conditions of pressure, temperature and catalyst concentration), the initial data (without smoothing) were used, to avoid the data deflection due to amplifying of the fitting errors. The numerical differentiation was performed, and all datasets from 5 independent experiments were simultaneously fitted to the equation:

\[ V = \frac{[S]}{V_{\text{max}} / (K_{\text{mn}} + [S]) + (C_{\text{c}} - [S]) / K_{\text{c}}} \]
Chapter 3

The global fitting with parameter sharing method was applied, using the data fitting software package Origin 8.0. The maximum reaction rate $V_{\text{max}}$, the Michaelis constant $K_{\text{mm}}$ and the inhibition constant $K_i$ were set as shared free parameters for fitting, while the initial substrate concentration (or if applied, the sum of the initial substrate and the initial product concentrations) $C_0$ was set as a fixed parameter, defined separately for each dataset. The goodness of fit was evaluated by the analysis of the regular residuals of the fitting. For comparison, the processed data (after smoothing) were also fitted to the above described model, giving essentially the same results. Finally, the model and the quality of the obtained parameters were evaluated by a comparison of the measured to the simulated conversion in function of time for each dataset. The conversion in function of time can be described as:

$$\text{Conversion } \% = (1-\exp(-V_{\text{max}}*t/(K_{\text{mm}}+C_0)))*100 \%$$

For experiments with different initial substrate 2c concentrations, similarly to the experiments with substrate 2a, the global fitting of all initial datasets was applied. For the kinetic model $V = k_1*[$S$]$, the conversion in function of time can be described as:

$$\text{Conversion } \% = (1-\exp(-k_1*t)))*100 \%$$

Again, the global fitting with parameter sharing method was used, setting the first-order rate constant $k_1$ as a shared free parameter for fitting. The goodness of fit was evaluated by the analysis of the regular residuals of the fitting.

**Hydroformylation of substrate 2a by the Rh(L1) catalyst – different initial substrate concentration:**

**global data fitting:**

The parameters estimated during the fitting procedure: the maximum reaction rate $V_{\text{max}}= 0.06301(47)$ M*h$^{-1}$, the Michaelis constant $K_{\text{mm}}= 0.1688(46)$ M, and the inhibition constant $K_i = 0.1575(44)$ M. Global correlation coefficient value is 0.90; correlation coefficient values for each dataset in range of 0.78-0.91. For detailed analysis, see:


**Hydroformylation of substrate 2c by the Rh(L1) catalyst – different initial substrate concentration:**

**global data fitting:**

The estimated value of the first-order rate constant $k_1 = 0.04578(3)$ h$^{-1}$. Global correlation coefficient value is 0.998; correlation coefficient values for each dataset in range of 0.994-0.999. For detailed analysis, see:


**Hydroformylation of mixture of two substrates**

The substrate competition studies were conducted analogously to the above described hydroformylation experiments in an autoclave equipped with a sampling outlet. The sampled in time aliquots of the reaction mixture were analyzed immediately (to avoid further reactions), following the typical procedure. For detailed analysis, see: http://pubs.acs.org/doi/suppl/10.1021/ja4046235/suppl_file/ja4046235_si_001.pdf

![Figure 10](http://pubs.acs.org/doi/suppl/10.1021/ja4046235/suppl_file/ja4046235_si_001.pdf)

**Figure 10.** Competitive hydroformylation of a (1 : 1) mixture of substrates 8a and 1c by Rh(L1) - conversion of both substrates 8a and 1c versus time. Reagents and conditions: 20 bar CO/H$_2$ (1 : 1), CH$_2$Cl$_2$, 40°C, [Rh(acac)(CO)$_2$/L1]/8a/1c = 1 : 1.5 : 100 : 100; c(Rh) = 2 mmol, N,N-diisopropylethylamine (DIPEA, 1.5 equiv.) was used as a base for anionic substrate generation.
Isotope labeling studies - deuterioformylation

The deuterioformylation study was conducted analogously to the hydroformylation experiments, using a 1:1 mixture of D₂ and CO in place of H₂ and CO. The conversion was determined by the standard ¹H NMR analysis. The reaction time was adjusted to reach a medial conversion, so that there is still a high substrate concentration, yet the reaction time allows for a significant level of, if possible, deuterium incorporation to the substrate molecules via the reversible hydride migration – beta-hydride elimination mechanism. The crude reaction mixture was investigated by ²H NMR spectroscopic analysis (no other solvents were added). No deuterium incorporation into the substrate molecules was observed.

**Figure 11.** ²H NMR spectrum of the substrate 2a deuterioformylation reaction mixture by the Rh(L1) catalyst. Reagents and conditions: Rh(CO)₃(acac) as a rhodium source, [substrate 2a] = 0.2 M, Rh : ligand L1 : substrate 2a : TEA, 1/1.5/100/150, CO/D₂ = 1/1 (20bar), 5h, 40°C, CH₂Cl₂ as a solvent; acac = acetylacetonate, TEA = triethylamine. Conversion = 42%.

DFT calculations

The isomeric complexes of the active catalyst ([Rh(L1)(CO)₂H]) and the mechanisms of the regioselectivity-determining hydrometalation step for the anionic substrates by Rh(L1) or Rh(L3) were studied with DFT. The geometry optimizations were carried out with the Turbomole program coupled to the PQS Baker optimizer at the ri-DFT level using the BP86 functional and the resolution-of-identity (ri) method. We used the SV(P) basis set for the geometry optimizations of all stationary points. All minima (no imaginary frequencies) and transition states (one imaginary frequency) were characterized by numerically calculating the Hessian matrix. ZPE and gas-phase thermal corrections (entropy and enthalpy, 298 K, 1 bar) from these analyses were calculated. The thus obtained energies in kJ mol⁻¹ are reported.

**Figure 12.** Calculated isomeric equatorial-equatorial (eq-eq) and equatorial-apical (eq-ap) structures of [Rh(L1)(CO)₂H] complex, the active form of the hydroformylation catalyst (DFT, BP86, SV(P)), and the Gibbs free energy (ΔG°) difference at 298K.
Figure 13. Calculated alternative reaction pathways (DFT, BP86, SV(P)) of the regioselectivity-determining hydride migration step in the hydroformylation of substrate 1a by the Rh(L3) catalyst. Notation: catalyst–substrate complex I, transition state toward linear product II and linear alkyl Rh complex III, and alternative transition state toward branched product IV and branched alkyl Rh complex V. $G^{298}$: Gibbs free energy at 298 K (relative to the catalyst-substrate complex I) in kJ mol$^{-1}$.

3.5. Acknowledgements

We kindly acknowledge the NRSC-C for generous financial support, Prof. Bas de Bruin and Dr. Jarl Ivar van der Vlugt for helpful discussions, Dr. Wojciech I. Dzik and Dr. Tendai Gadzikwa for critical comments and valuable suggestions, and Dr. Remko J. Detz for assistance with the gas-uptake experiments.

3.6 References

Precise Supramolecular Control of Selectivity


Preliminary results of this study have been communicated: (a) Dydio, P.; Dzik, W. I.; Lutz, M.; de Bruin, B.; Reek, J. H. N. *Angew. Chem., Int. Ed.* 2011, 50, 396–400, and are presented in Chapter 2 of this thesis. For application of ligand L3 in β-selectivity hydroformylation of vinyl arenes, see Chapters 5 and 6 of this thesis, and: (b) Dydio, P.; Reek, J. H. N. *Angew. Chem., Int. Ed.* 2013, 52, 3878–3882.


For details see the experimental section.


The effective concentration for substrate 8a bound to the DIM pocket of the catalyst can be roughly estimated: (i) for the initial concentrations used and the association constant of Ks >10^5 M^{-1}, the DIM pocket is nearly fully occupied by the substrate (> 99.995%); (ii) the maximal distance between the Rh center and the alkene in the supramolecular complexes is about 15Å, thus the ‘probing volume’ is about 1.7·10^{-24} dm^3, which translates to the effective concentration C_{eq} = 0.9 M. With this rough estimate one can understand that the non-bound substrate present in 0.2 M, will considerably compete with the bound substrate. For comparison, for substrate 2a, with the maximal Rh-alkene distance of 8Å, the effective concentration is estimated to C_{eq} ≈ 6 M, which is substantially higher than the actual alkene concentration in solution (0.2 M), hence allowing for the effective competition. For detailed discussion on the influence of the effective concentrations, see ref. 25.


We started a search for possible conformations of the substrate-catalyst complex for both eq-eq and eq-ax coordination geometries, using a simplified model with a ligand in which the 4 phenyl rings were removed from the phosphine. Subsequently, the structures lowest in energy were supplemented with the phenyl rings and optimized again. (The geometries with much higher energies, >16 kJ mol^{-1}, were omitted).

Despite many attempts, we were not able to find a transition state for the formation of the branched alkyl complex from this substrate-catalyst complex conformer.

The complex structure is distorted from the ideal coordination geometry (a trigonal bipyramid or a square pyramid) due to the geometrical constrains imposed by the ligand and by the substrate bound to the phosphorus ligand (the virtually tridentate L1-2a ligand). Consequently, the two axial positions occupied by the hydrde and CO are electronically different. Therefore, the changing their positions leads to a complex with different energy, and also modifies the coordination geometry around the rhodium center.
As indicated by the change of the \( \tau \) parameter value from 0.39 to 0.27, for geometry I and IV, respectively, the CO and H ligands inversion pushes the geometry of the metal center to a structure closer to a square pyramid and results in its destabilization. (The \( \tau \) value indicates the idealized square pyramid with \( \tau = 0 \), and the trigonal bipyramid with \( \tau = 1 \)). For the description of the \( \tau \) parameter, see: Addison, A. W.; Rao, T. N.; Reedijk, J.; van Rijn, J.; Verschoor, G. C. J. Chem. Soc., Dalton Trans. 1984, 1349-1356.


Although, both ligand \( L_3 \) and the aldehyde products are chiral, there was no enantioselectivity observed in these reactions.

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