Supramolecular control of regioselectivity in the hydroformylation reaction

Substrate preorganization and second coordination sphere catalysis

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Chapter 3

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

Introduction

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

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

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

Our group reported the regioselective hydroformylation of unsaturated carboxylates using bisphosphine and bisphosphite ligands, which contained a neutral anion receptor based on 7,7′-diamido-2,2′-diindolylmethane (DIM pocket).\[20–23,29\] This class of ligands was coined DIMPhos. The rhodium–DIMPhos catalyst based on \textbf{L1} (Figure 1) hydroformylates internal alkenes such as 4-hexenoate with high regioselectivity (78:1 selectivity) but for longer substrates the regioselectivity is much lower and application of \textbf{L1} in the hydroformylation of natural fatty acids with a double bond on the 9-position gives no regioselectivity (\textit{vide infra}).\[22\] Currently there are no hydroformylation catalysts that convert natural monounsaturated fatty acids (MUFAs) in a regioselective fashion, whereas such technologies may allow broader applicability of the biofeedstock.\[30–42\] In this chapter we report the redesign of DIMPhos ligand \textbf{L1} to \textbf{L2} in which the distance between the active metal and the binding site matches that of typical natural fatty acids (Figure 1), and demonstrate that the concept of substrate orientation to control the regioselectivity in hydroformylation also works when the directing group is remote from the double bond.

\[
\text{[Rh(\(9\text{-decenoate}\) complexes L1)(CO)(H)]}
\]

\[
\text{[Rh(\(9\text{-decenoate}\) complexes L2)(CO)(H)]}
\]

Figure 2 Modeling (DFT) of 9-decanoate as a fatty acid model bound ditopically to [Rh(\textbf{L1})(H)(CO)] (left) and [Rh(\textbf{L2})(H)(CO)] (right). For clarity, the 9-decanoate substrate is shown in green.
Results and discussion

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

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

To investigate if ligand L2 formed a stable metal complex with rhodium it was mixed with \([\text{Rh}(\text{acac})(\text{CO})_2]\), which is the precursor complex of the hydroformylation catalyst, in a 1:1 ratio in CD\(_2\)Cl\(_2\). \(^{1}H\) NMR studies show a well-defined complex formed after mixing (Figure 4) and DOSY spectroscopy reveals the formation of a single species with a hydrodynamic radius of 7.9 Å in line with the size of a mononuclear complex (see Figure 5).\(^{[46]}\) Upon addition of 1.5 equivalents of tetrabutylammonium acetate, the N-H protons are downfield shifted, which shows the carboxylate group binds to the DIM pocket of the \([\text{Rh}(\text{acac})(\text{L}2)]\) species in a similar fashion as reported for the \([\text{Rh}(\text{acac})(\text{L}1)]\) complex (Figure 6).\(^{[21]}\) Pressurization with 5 bar of syngas (H\(_2\):CO (1:1)) to the solution of the \([\text{Rh}(\text{acac})(\text{L}2)]\) complex provides the corresponding pentacoordinate \([\text{Rh}(\text{L}2)(\text{CO})_2\text{H}]\) species as evidenced by the rhodium hydrido signal (\(\delta = -10.5\) ppm).\(^{[47]}\) Next to the well-defined signal, also a broad rhodium–hydrido signal (\(\delta = -10.7\) ppm) appears in the NMR spectrum, which becomes larger over time (see Figure 9). DOSY spectroscopy of the \([\text{Rh}(\text{L}2)(\text{CO})_2\text{H}]\) complex under 5 bar CO/H\(_2\) (1:1) in CD\(_2\)Cl\(_2\) gave a larger average hydrodynamic radius (12.1 Å) than for the \([\text{Rh}(\text{acac})(\text{L}2)]\) complex suggesting that the broad signal is due to formation of dinuclear and/or oligomeric species under these conditions (see Figure 7). However, under identical conditions but in the presence of 4 equivalents guest that binds in the DIM pocket (tetrabutylammonium acetate) the average
hydrodynamic radius (8.4 Å) (see Figure 8) is close to that of the [Rh(acac)(L2)] species, indicating that carboxylate binding in the DIM pocket preorganizes the two phosphorous moieties for the formation of a mononuclear species.[29] A series of (deprotonated) ω-unsaturated carboxylic acids with varying length between the alkene reactive group and the carboxylate directing group was hydroformylated using [Rh(L2)] as a catalyst (Figure 3). As substrates we reacted 4-pentenoic acid (n = 2) up to 10-undecenoic acid (n = 8) both in the presence and the absence of base. In the presence of base, the carboxylate functional group of the substrate binds in the DIM pocket and thus substrates long enough to span the DIM pocket-rhodium distance are expected to react with improved regioselectivity. In absence of base, the protonated carboxylic acids do not bind in the DIM pocket and as a result the directing group, the carboxylic acid, cannot be used for substrate preorganization with the [Rh(L2)] catalyst and should react with lower regioselectivity.[20,21] Because of this, the protonated substrates were used as control experiments. All substrates studied gave full conversion to the aldehyde and the linear/branched (l/b) ratios of the aldehyde products were determined by 1H-NMR spectroscopy (Figure 3).

Figure 3 Hydroformylation of ω-unsaturated carboxylic acids using rhodium complexes based on L2[6]

[a] Reagents and conditions: [substrate] = 0.2 M, DIPEA (15 equiv. (blue bars)), [Rh(CO)2(acac)] (1 mol %), L2 (1.1 mol %), 20 bar CO/H2 (1:1), 40°C, 24 h. Conversion and regioselectivity determined by 1H NMR analysis of the crude reaction mixture. For full experimental details, see the experimental details. The blue bars are experiments in presence of base, and the red bars are in absence of base as control experiment.
The catalytic results show that the long anionic substrates (with \( n > 4 \), 7-octenoate and longer) display much higher l/b ratios than the protonated analogues. The distance between the carboxylate and alkene function in these substrates is at least 9.7 Å, and this shows this catalyst is able to control the regioselectivity via substrate preorganization on remote distance. The highest l/b ratio of 27 is obtained for the 8-nonenolate (\( n = 6 \)), which is the substrate that binds strongest to the catalyst as it fits perfectly according to our modelling studies (vide supra). The longer substrates that easily span the distance between the DIM pocket and the rhodium center (\( n = 7 \) and 8) are also converted with improved regioselectivity when preorganized, albeit with a lower linear/branched ratio of 23 and 14 respectively. In line with the binding energy calculated for these substrates. The smaller substrates (\( n = 2 \) and 3) are not able to bind in a ditopic fashion to [Rh(L2)] and thus the difference in l/b ratios between the anionic and the protonated substrates is very small. Consistent with our design model, the L2 system is indeed more selective than the L1 system for long substrates (e.g. 9-decenoate: l/b of 7/1 for L1 and l/b 23/1 for L2, see Figure 10 for full comparison of l/b ratios of L1 and L2).[22]

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

When 8-decenolate was hydroformylated using the PPh3-based catalyst the two aldehyde products were formed with a small excess for the 9-formyl product.[9, 10, 21, 39] Performing the same reaction with the rhodium catalyst based on L2 that preorganizes the substrate leads to high conversion with a high regioselectivity to produce the 9-formyl product in excess (9-formyl/8-formyl ratio = 8.8). The linear aldehyde product is also observed under these conditions, which arises from an isomerization/hydroformylation sequence, which is not uncommon for bisphosphite-based catalysts.[47] When we applied the rhodium catalyst based on L1, the catalyst that can also pre-organize but is optimized for smaller substrates, only slightly better selectivities are obtained than with the PPh3-based catalysts. The same trend was observed in the hydroformylation of 9-undecenoic acid; only the [Rh(L2)] catalyst provides the product with high regioselectivity, yielding a 10-formyl/9-formyl ratio of 6.9. Importantly, the redesigned [Rh(L2)] catalyst clearly outcompetes [Rh(L1)] with respect to regioselectivity and conversion for the longer substrates, as a result of more favorable ditopic binding.
Regioselective Hydroformylation of Internal and Terminal Alkenes via Remote Supramolecular Control

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

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Ligan d</th>
<th>Conversion (%)</th>
<th>9-formyl/8-formyl</th>
<th>9-formyl/all other isomers</th>
</tr>
</thead>
<tbody>
<tr>
<td>8-decenoic acid</td>
<td>L1</td>
<td>74</td>
<td>2.6</td>
<td>1.9</td>
</tr>
<tr>
<td>8-decenoic acid</td>
<td>L2</td>
<td>97</td>
<td>8.8</td>
<td>5.8</td>
</tr>
<tr>
<td>8-decenoic acid</td>
<td>PPh₃</td>
<td>100</td>
<td>1.6</td>
<td>1.6</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Ligan d</th>
<th>Conversion (%)</th>
<th>10-formyl/9-formyl</th>
<th>10-formyl/all other isomers</th>
</tr>
</thead>
<tbody>
<tr>
<td>9-undecenoic acid</td>
<td>L1</td>
<td>70</td>
<td>2.2</td>
<td>1.7</td>
</tr>
<tr>
<td>9-undecenoic acid</td>
<td>L2</td>
<td>96</td>
<td>6.9</td>
<td>5.0</td>
</tr>
<tr>
<td>9-undecenoic acid</td>
<td>PPh₃</td>
<td>100</td>
<td>1.3</td>
<td>1.3</td>
</tr>
</tbody>
</table>

[a] Reagents and conditions: [substrate] = 0.2 M, DIPEA (1.5 equiv.), [Rh(acac)_2(CO)] (2 mol %), L1 and L2 (2.2 mol %), PPh₃ (6.6 mol%), 20 bar CO/H₂ (1:1), 60°C, 96 h. Conversion and regioselectivity determined by ¹H NMR analysis of the reaction mixture. For full experimental details, see the experimental details.

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

<table>
<thead>
<tr>
<th></th>
<th>Ligand</th>
<th>Conversion (%)</th>
<th>10-formyl/9-formyl</th>
<th>10-formyl /all other isomers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myristoleic acid</td>
<td>L1</td>
<td>27</td>
<td>1.03</td>
<td>0.79</td>
</tr>
<tr>
<td>Myristoleic acid</td>
<td>L2</td>
<td>69</td>
<td>1.61</td>
<td>1.23</td>
</tr>
<tr>
<td>Myristoleic acid</td>
<td>PPh\textsubscript{3}</td>
<td>100</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Palmitoleic acid\textsuperscript{b}</td>
<td>L1</td>
<td>23</td>
<td>~1.0</td>
<td>~0.8</td>
</tr>
<tr>
<td>Palmitoleic acid\textsuperscript{b}</td>
<td>L2</td>
<td>66</td>
<td>~1.5</td>
<td>~1.2</td>
</tr>
<tr>
<td>Palmitoleic acid\textsuperscript{b}</td>
<td>PPh\textsubscript{3}</td>
<td>100</td>
<td>~1.0</td>
<td>~1.0</td>
</tr>
<tr>
<td>Oleic acid\textsuperscript{c}</td>
<td>L1</td>
<td>21</td>
<td>n.d.</td>
<td>n.d.</td>
</tr>
<tr>
<td>Oleic acid\textsuperscript{c}</td>
<td>L2</td>
<td>76</td>
<td>n.d.</td>
<td>n.d.</td>
</tr>
<tr>
<td>Oleic acid\textsuperscript{c}</td>
<td>PPh\textsubscript{3}</td>
<td>100</td>
<td>n.d.</td>
<td>n.d.</td>
</tr>
</tbody>
</table>

\textsuperscript{[a]} Reagents and conditions: [substrate] = 0.2 M, DIPEA (1.5 equiv.), [Rh(CO)\textsubscript{2}(acac)] (2 mol %), L\textsubscript{1} and L\textsubscript{2} (2.2 mol %), PPh\textsubscript{3} (6.6 mol %), 20 bar CO/H\textsubscript{2} (1:1), 60\textdegreeC, 96 h. Conversion determined by \textsuperscript{1}H NMR analysis of the reaction mixture and the regioselectivity was determined by GC analysis after methylation of the reaction mixture.\textsuperscript{[b]} Methyl 9- and 10-formylpalmitate could not be baseline separated on GC, therefore a larger error in the determined regioselectivity is expected. For full experimental details, see the experimental details.\textsuperscript{[c]} Palmitoleic acid was converted with similar levels of regioselectivity as observed for myristoleic acid, with the [Rh(L\textsubscript{2})] catalyst being the only catalyst capable of controlling the regioselectivity (10-formyl/9-formyl ratio is 1.5 for [Rh(L\textsubscript{2})] and 1.0 for [Rh(L\textsubscript{1})] and [Rh(PPh\textsubscript{3})], Table 2). For the fatty acids also minor amounts of isomerization/hydroformylation products were observed with the [Rh(L\textsubscript{1})] and [Rh(L\textsubscript{2})] catalysts, lowering the overall selectivity. Palmitoleic acid was converted with similar levels of regioselectivity as observed for myristoleic acid, with the [Rh(L\textsubscript{2})] catalyst being the only catalyst capable of controlling the regioselectivity (10-formyl/9-formyl ratio is 1.5 for [Rh(L\textsubscript{2})] and 1.0 for [Rh(L\textsubscript{1})] and [Rh(PPh\textsubscript{3})])(Table 2). A major platform chemical, oleic acid, was also hydroformylated using these catalysts. Similar conversion was observed with oleic acid as with myristoleic acid and palmitoleic acid using the respective catalysts. However, the regioisomers could not be separated on GC and therefore the regioselectivity could not be determined.
Regioselective Hydroformylation of Internal and Terminal Alkenes via Remote Supramolecular Control

Table 3 Optimization of regioselectivity of myristoleic acid[^a]

<table>
<thead>
<tr>
<th>Entry</th>
<th>[substrate] (M)</th>
<th>[catalyst] (M)</th>
<th>Conversion (%)</th>
<th>10-/9-formyl tetradecanoic acid</th>
<th>10-formyl tetradecanoic acid /all other isomers</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.2M</td>
<td>4mM</td>
<td>33</td>
<td>1.87</td>
<td>1.58</td>
</tr>
<tr>
<td>2</td>
<td>0.1M</td>
<td>4mM</td>
<td>66</td>
<td>1.99</td>
<td>1.61</td>
</tr>
<tr>
<td>3[^b]</td>
<td>0.02M</td>
<td>4mM</td>
<td>85</td>
<td>2.20</td>
<td>1.72</td>
</tr>
<tr>
<td>4[^c]</td>
<td>0.02M</td>
<td>0.4mM</td>
<td>76</td>
<td>2.31</td>
<td>1.90</td>
</tr>
<tr>
<td>5[^b]</td>
<td>0.2M</td>
<td>4mM</td>
<td>35</td>
<td>1.82</td>
<td>1.63</td>
</tr>
<tr>
<td>6[^b]</td>
<td>0.02M</td>
<td>0.4mM</td>
<td>77</td>
<td>2.43</td>
<td>1.95</td>
</tr>
<tr>
<td>7[^c]</td>
<td>0.02M</td>
<td>0.4mM</td>
<td>20</td>
<td>1.42</td>
<td>1.42</td>
</tr>
<tr>
<td>8[^d]</td>
<td>0.02M</td>
<td>0.4mM</td>
<td>&gt;1</td>
<td>n.d.</td>
<td>n.d.</td>
</tr>
<tr>
<td>9[^e]</td>
<td>0.2M</td>
<td>4mM</td>
<td>32</td>
<td>2.10</td>
<td>1.91</td>
</tr>
<tr>
<td>10[^e]</td>
<td>0.02M</td>
<td>0.4mM</td>
<td>63</td>
<td>2.51</td>
<td>2.33</td>
</tr>
</tbody>
</table>

[^a] Reagents and conditions: DCM, DIPEA (1.5 equiv. with respect to acid), catalyst = [Rh(acac)\(_2\)(CO)/L2] in a 1:1.1 ratio, substrate = myristoleic acid, 20 bar CO/H\(_2\) (1:1), 40°C, 96 h. Conversion determined by \(^1\)H NMR analysis of the reaction mixture and the regioselectivity was determined via GC analysis following methylation of the reaction mixture. [^b] Rhodium:ligand ratio 1:2. [^c] THF used as solvent instead of DCM. [^d] DMF was used instead of DCM. For full experimental details, see the SI.[^e] 50 bar syngas (H\(_2\):CO) (1:1) was used instead of 20 bar of syngas.

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

Conclusions

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

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

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

Ligand Synthesis

4’-(Benzyloxy)-[1,1’-biphenyl]-4-carboxylic acid 4 was synthesized according to a literature procedure from 4’-Hydroxy-biphenyl-4-carboxylic acid.[52]

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

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

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

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

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

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

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

\(1,1\)-Bis-\{(3-methyl-7-amino-1H-indol-2-yl)propane\ 6\ \text{1,1-Bis-\{(3-methyl-7-nitro-1H-indol-2-yl)propane\ (0.60 g, 1.53 mmol)\ 5\) was added to a flame-dried Schlenk and dissolved in MeOH/THF (2:1) to give an orange solution. The addition of Pd/C yielded a black suspension with an orange glow. A balloon of H\(_2\) was added and the solution was flushed with hydrogen after which the solution was stirred vigorously for 2.5 hrs. After 2.5h, the black/orange suspension turned black/colorless. TLC showed complete conversion of starting material. Subsequently the reaction was filtered over celite filter aid and the solvents were removed in
vacuo. The resulting off-white/brownish solid was stripped with toluene (2x 15ml). Following evaporation, the product was immediately used without further purification.

**Bis-(4'-{benzyloxy}[1,1'-biphenyl]-4-carboxamide of 1,1-bis-(-7-amino-3-methyl-1H-indol-2-yl)-propane**  

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

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

**<sup>13</sup>C NMR** APT (101 MHz, DMSO-d<sub>6</sub>) δ 165.59, 158.85, 142.80, 137.23, 136.07, 133.88, 131.78, 130.67, 129.03, 128.87, 128.76, 128.24, 128.18, 127.95, 126.11, 123.05, 118.67, 115.67, 115.47, 115.19, 106.64, 69.69, 36.05, 26.95, 12.51, 8.91.

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

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

**13C NMR APT** (75 MHz, DMSO-d₆) δ 165.79, 158.24, 143.24, 136.17, 133.13, 130.80, 130.05, 129.08, 128.99, 128.37, 125.94, 123.24, 118.80, 116.33, 115.52, 115.26, 106.77, 36.23, 27.17, 12.67, 9.05.

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

(S)-1,1'-Binaphthyl-2,2-diyl phosphorochloridate, (S)-binol-PCl 9 Note: PCl₃ is extremely toxic and should be handled with extreme caution. All glassware was oven-dried or flame-dried under vacuum. All solvents and reagents were dried and degassed prior to use. (S)-binol ((S)-1,1'-Bis(2-naphthol)) was azeotropically dried prior to use by co-evaporation with dry toluene (3x 20 ml). (S)-binol (50 gram) was suspended in 84 ml PCl₃ in a three neck round bottom flask (500 ml) under an inert atmosphere (N₂). The suspension was heated to reflux (85°C) and stirred overnight. After overnight stirring, the PCl₃ was evaporated in vacuo and collected with a cold trap. The solid was subsequently stripped with toluene (3x20 ml). Subsequently the
reaction mixture was dissolved in DCM, followed by its evaporation to form a white solid which is the product.

\[ ^{31}P\text{(}^1H\text{) NMR (162 MHz, THF}-d_8\text{): } \delta = 177.9 \]

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

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

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

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

\[ ^{31}P\text{ NMR (162 MHz, DMSO}-d_6\text{)}\delta = 144.48.\]

HR MS (EI) calcd. for C\text{87}H\text{62}N\text{4}O\text{8}P\text{4} 1352.40429, found: 1352.40589.
Substrate Synthesis

8-Decenoic acid 12 8-bromo-octanoic acid 10 (3.01 g, 13.45 mmol) was dissolved in MeCN together with PPh₃ (3.53 g, 13.45 mmol) and refluxed for 168h. All volatiles were evaporated in vacuo. The intermediate phosphonium salt was washed with diethyl ether. $^{31}$P NMR showed full conversion of the PPh₃ and subsequently the product was used in the following reaction without further purification.

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

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

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

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

9-Undecenoic acid 15 9-bromononanoic acid 13 (3.00 g, 12.65 mmol) was dissolved (after heating for 20 min a clear solution was obtained) in MeCN together with PPh₃ (3.318 g, 12.65 mmol) and refluxed for 168h. All volatiles were evaporated in vacuo. The intermediate phosphonium salt was washed with diethyl ether. $^{31}$P NMR showed full conversion of the PPh₃ and subsequently the product was used in the following reaction without further purification.
Next, 14 was suspended in THF (20 ml), KOtBu (2.839 g, 25.3 mmol) in THF (20 ml) was added at -20 °C, and the reaction was stirred for 1h. Next, acetaldehyde (1.2 mL, 24.9 mmol) was added at room temperature and the reaction was stirred overnight. The THF was removed in vacuo and the reaction mixture was acidified with 1M HCl until the pH was ~2. The aqueous layer was next extracted with ethyl acetate (3 * 60 ml). The combined organic layers were dried over MgSO₄ and concentrated in vacuo. The product was purified with a silica gel plug with pentane/diethyl ether in a 1:1 ratio as an eluent to give a colorless oil. The THF was removed in vacuo and water (60 ml) was added to the residue, which was then extracted with diethyl ether (3 * 60 ml). The diethyl ether layers were discarded, while the aqueous layer was acidified with HCl. The aqueous layer was next extracted with ethyl acetate (3 * 60 ml). The combined organic layers were dried over MgSO₄ and concentrated in vacuo. The product was purified with a silica gel plug with pentane/diethyl ether in a 1:1 ratio as an eluent to give a colorless oil (450 mg, 20% yield).

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

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

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

Coordination and Anion Binding Studies

General comments.

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

NMR complexation experiments

[Rh(acac)(CO)₂] and ligand L₂ (1.1eq) were added to a flame-dried Schlenk equipped with a Teflon stirring bar followed by addition of CD₂Cl₂ (0.6 mL) to yield a solution with a 0.006 M Rh concentration. This mixture was stirred for several minutes before NMR analysis at room temperature was taken in a screw cap NMR tube under inert conditions. ³¹P and ¹H spectroscopy showed well defined spectra. Noteworthy is in the ¹H spectrum, the four NH protons become inequivalent on NMR due to binding of the (S)-binol moieties to rhodium. Furthermore, ¹H DOSY spectroscopy was conducted on the [Rh(L₂)(acac)] complex. From the
DOSY, the average hydrodynamic radius was calculated using a previously reported method.\textsuperscript{[46]} The hydrodynamic radius calculated (7.9 Å) matched the size of the mononuclear complex.

**Figure 4** \textsuperscript{1}H NMR (400MHz) spectrum of 0.006M [Rh(L2)(acac)] in CD\textsubscript{2}Cl\textsubscript{2}

**Figure 5** \textsuperscript{1}H DOSY(300MHz) of 0.006 M [Rh(L2)(acac)] in CD\textsubscript{2}Cl\textsubscript{2}, hydrodynamic radius determined at 7.9 Å.
Regioselective Hydroformylation of Internal and Terminal Alkenes via Remote Supramolecular Control

Figure 6 Binding study of 0.008 M [Rh(L2)(acac)] in CD₂Cl₂ with tetrabutyl ammonium acetate

NMR complexation experiments under CO/H₂ pressure

A flame-dried Schlenk flask equipped with a Teflon stirring bar was charged with L2 and with [Rh(acac)(CO)₂] (1:1 ratio), followed by addition of an appropriate amount of CD₂Cl₂ to obtain a desired concentration of the solution of a Rh-ligand complex. The solution was stirred at room temperature for approximately 10 minutes. Next, the solution was transferred to a high-pressure NMR tube, which was then purged at least three times with 5 bar of syngas (H₂:CO) and subsequently pressurized with 5 bar of syngas. The tube was shaken and an NMR spectrum was taken. Measurements were done at room temperature (rt) unless otherwise stated. In CD₂Cl₂, both the ¹H and the ³¹P-NMR spectra presented broad signals. The corresponding pentacoordinate [Rh(L2)(CO)₂H] complex which is characterized by the rhodium-hydrido signal at δ = -10.5 ppm which was identified as a triplet. Next to the triplet, we also observed a broad rhodium-hydrido signal at δ = -10.7 ppm. This broad signal was identified as oligomeric species. As a result DOSY spectroscopy of the complex under syngas conditions was measured(Figure 7), which showed a higher average hydrodynamic radius (12.4 Å) compared to the [Rh(L2)(acac)] (7.9Å) species. According to DOSY spectroscopy, the addition of 4 equivalents tetrabutylammonium acetate suppressed the formation of oligomers as the hydrodynamic radius was determined at 8.4 Å which is smaller than the same complex without tetrabutyl ammonium acetate.
Figure 7: \( ^1H \text{DOSY (300MHz)} \) of 0.008 M[Rh(L2)(acac)] in CD\(_2\)Cl\(_2\) under 5 bar H\(_2\):CO, hydrodynamic radius was determined at 12.4 Å

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

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

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

General procedure for preparation of NMR samples

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

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

\[
\text{RCO}_n\text{O} \quad \xrightarrow{\text{Rh(acac)[CO]}_2/\text{ligand} (1 \text{ mol%)}} \quad \text{O} \quad \text{RCO} \quad \text{OH} \\
\text{n=1-8} \quad \text{DCM, DIPEA} \quad \text{H}_2\text{CO} (20 \text{ bar}) \quad 40\,^\circ\text{C}, 24\,\text{hrs} \quad \text{linear(l)} \quad \text{branched(b)}
\]

Comparisson of L1 and L2

[a]: [Substrate] = 0.2 M, Rh: Ligand: Substrate: DIPEA = 1:1:100:150 in DCM. Experiment performed with 20 bar CO/H\(_2\) (1:1) for 24h at 40 °C. Conversion and regioselectivity determined via \(^1\text{H NMR}. l/b ratios of L1 reported in an earlier study.[21]

Hydroformylation of natural fatty acids

General procedure for preparation of GC samples

For the natural fatty acids, GC analysis was required to determine the regioselectivity. 50 µl of the reaction mixture sample was added to dimethylformamide (0.3 ml) saturated with KHCO\(_3\) in a Schlenk under a nitrogen flow. Methyl iodide (50 µl) was added to the Schlenk and the mixture was stirred overnight at 40°C. Then ethyl acetate (1 ml) and distilled water (1 ml) were added. The mixture was shaken, followed by separation of the layers. Next, the ethyl acetate layer was dried over MgSO\(_4\), filtered over a syringe HPLC filter, and transferred to a GC vial, followed by GC analysis.
To determine which peak was which in the GC, the methyl esters of the natural fatty acid, methyl palmitoleate and methyl myristoleate, were reacted with H₂:CO (20 bar) using a Rh/PPh₃ catalyst for 96 hrs at 60°C. After cooling down the autoclave, full conversion of the double bond was observed. Next, a sample was taken of the reaction mixture which was diluted with DCM, filtered and subsequently injected into the GC. Simultaneously the non-natural regioisomer of the fatty acid methyl ester with the double bond on the 10-position was synthesized according to a procedure reported by Vandenberg et al. This product was reacted under the same conditions and following sample preparation injected into the GC. For the hydroformylation products of methyl myristoleate, a GC-2010 Plus Capillary GC-MS containing the SH-Rtx-5 Amine column of 30 m x 0.25 mm, df 0.25 μm column was used to determine the regioselectivity. Both the chromatograms of the methyl myristoleate and the methyl tetradec-10-enolate hydroformylation products gave two peaks which integrated with equal areas, which were the two regioisomers formed. One of the two peaks overlapped in both chromatograms, which was identified as the methyl ester of 10-formyltetradecanoate. The regioisomers of methyl-formyl-tetradecanoate were separated by injecting the mixture at with an oven temperature of 50°C and heating for 30°C/min until 145°C was reached. Next the temperature was kept at 145°C for 20 min after which the oven was heated for 30°C/min until the temperature reached 300°C after which the temperature was kept at this temperature for 5 minutes. For the hydroformylated products of palmitoleic acid an Interscience Focus GC containing a Supelco SP®-2560 capillary GC Column 200 m x 0.25 mm df 0.20 μm was used. Both the chromatograms of the methyl oleate and the methyl hexadec-10-enolate hydroformylation products gave two peaks which integrated with equal areas, which were the two regioisomers formed. One of the two peaks overlapped in both chromatograms, which was identified as the methyl ester of 10-formylhexadecanoate. Following injection of the samples, the column was heated for 5 hours at 170°C after which the temperature was raised with 20°C/min until the temperature was 220°C where the temperature was kept at for 5 minutes. Separation of the hydroformylation products of oleic acid regioisomers were not successful and therefore most studies were conducted with palmitoleic acid and myristoleic acid.

DFT calculations

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

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

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<th>Rh(L1)(H)(CO)</th>
<th>Rh(L2)(H)(CO)</th>
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<td>9-decenoate</td>
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<td>-3676,9</td>
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</tbody>
</table>

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

![Diagram showing binding enthalpy of various acids](image)

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References

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[49] The effective concentration for substrate x bound in the DIM pocket was roughly estimated: The maximum radius between the rhodium center and the double bond of natural fatty acids is approximately 11 Å which is 1,1 x 10⁻₈dm³. Which translates to 4/3π(1,1 x 10⁻₈dm³)³ = 5,5 x 10⁻²₄ dm³. Of this spherical volume it was estimated the alkene could occupy 50%. This translates to an effective concentration of ≈ 0.6 M. Since the substrate concentration is 0.2 M for most experiments, non-bound substrates will likely compete and allow for a non-selective background reaction. This nicely explains why the regioselectivity increases upon lowering of the concentration as this background reaction is repressed.


