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DOI
10.1002/chem.202000620

Publication date
2020

Document Version
Final published version

Published in
Chemistry-A European Journal

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Regioselective Hydroformylation of Internal and Terminal Alkenes via Remote Supramolecular Control

Pim R. Linnebank,[a] Stephan Falcão Ferreira,[a] Alexander M. Kluwer,[b] and Joost N. H. Reek*[a,b]

Abstract: Regioselective catalytic transformations using supramolecular directing groups are increasingly popular as it allows for control over challenging reactions that may otherwise be impossible. In most examples the reactive group and the directing group are close to each other and/or the linker between the directing group is very rigid. Achieving control over the regioselectivity using a remote directing group with a flexible linker is significantly more challenging due to the large conformational freedom of such substrates. Herein, we report the redesign of a supramolecular Rh–bisphosphite hydroformylation catalyst containing a neutral carboxylate receptor (DIM pocket) with a larger distance between the phosphite metal binding moieties and the DIM pocket. For the first time regioselective conversion of internal and terminal alkenes containing a remote carboxylate directing group is demonstrated. For carboxylate substrates that possess an internal double bond at the Δ-9 position regioselectivity is observed. As such, the catalyst was used to hydroformylate natural monounsaturated fatty acids (MUFA) in a regioselective fashion, forming an excess of the 10-formyl product (10-formyl/9-formyl product ratio of 2.51), which is the first report of a regioselective hydroformylation reaction of such substrates.

Supramolecular approaches in transition metal catalysis offer unique tools to achieve selectivity in transformations that are otherwise difficult to control.[11–14] Unrivalled selectivity by supramolecular strategies has been demonstrated for a wide array of organic and organometallic transformations.[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.[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.[28]

Toste et al. reported a transition metal catalyst encapsulated in a self-assembled cage that can be used for site selective hydrogenation of polyenes.[16] Moreover, the selectivity in hydroformylation 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 L1 (Figure 1a) 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 L1 in the hydroformylation of natural fatty acids with a double bond on the 9-position gives no regioselectivity (vide infra).[22] Currently there are no hydroformylation catalysts that convert natural monounsaturated fatty acids (MUFA) in a regioselective fashion, whereas such technologies may allow broader applicability of the biofeedstock.[30–42]

In this paper we report the redesign of DIMPhos ligand L1 to L2 in which the distance between the active metal and the binding site matches that of typical natural fatty acids (Figure 1a), 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.

The distance between rhodium and the 7,7’-diamido-2,2’-diindolylmethane anion receptor for L1 (the DIM pocket, 6.8 Å,
Indeed, DFT calculations (see Supporting Information).

It was hypothesized that an extended ligand binds substrates with large carboxyl-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 1a, L2) between the DIM pocket and the phosphite donor atoms, instead of the phenyl linker that is present in the original DIMPphos ligand (L1). DFT calculations of 9-decenoate di-catalyst and should react with lower regioselectivity. To a rhodium biphenyl complex provides the corresponding pentacoordinate [Rh(acac)(L1)] complex to match the distance between the acid directing group and as a result the directing group, the carboxylic acid, pocket preorganizes the two phosphorous moieties for the formation of mononuclear species.

A series of (deprotonated) ω-unsaturated carboxylic acids with varying length between the alkene reactive group and 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). Indeed, DFT calculations (BLYP,DZP,D3BJ) show that 9-decenoate, used as a model for natural fatty acids, needs to fold significantly to bind ditopically to [Rh(L1)(H)(CO)] (see Figure 1b). 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 1a, L2) between the DIM pocket and the phosphite donor atoms, instead of the phenyl linker that is present in the original DIMPphos ligand (L1). DFT calculations of 9-decenoate di-catalyst and should react with lower regioselectivity. To a rhodium biphenyl complex provides the corresponding pentacoordinate [Rh(acac)(L1)] complex to match the distance between the acid directing group and as a result the directing group, the carboxylic acid, pocket preorganizes the two phosphorous moieties for the formation of mononuclear species.

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tance. The highest l/b ratio of 27 is obtained for the 8-none- 
noate (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-decanoate: l/b of 7/1 for L1 and l/b 23/ 
1 for L2, see Figure S18 for full comparison of l/b ratios of L1 
and L2). [47]

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 Δ9-position. Initial investigations 
were conducted with 8-decanoate, which is the internal 
alkene analogue of the most selective terminal alkene sub-
strate (vide supra), and 9-undecenoate, which has the exact 
alkene-carboxylic acid distance as natural fatty acids 
(Table 1). [9, 10, 21]

When 8-decanoate 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 pre-
organizes the substrate leads to high conversion with a 
high regioselectivity to produce the 9-formyl product in excess (9-
formyl/8-formyl ratio is 8.8).

The linear aldehyde product is also observed under these 
conditions, which arises from an isomerization/hydroformyla-
tion 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 opti-
mized 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. Im-
portantly, 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 bind-
ing.

Having established our redesigned [Rh(L2)] catalyst is able 
to control the regioselectivity of remote internal alkenes on 
position Δ8 and Δ9 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 rh-
dium catalyst, equal amounts of the 10-formyl and the 9-
formyl products are formed, in line with previous reports. [39–41] 
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 con-

![Figure 2. Hydroformylation of n-unsaturated carboxylic acids using rhodium complexes based on L2.](image)

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Ligand</th>
<th>Conversion (%)</th>
<th>9-Formyl/8-Formyl</th>
<th>9-Formyl/10-Formyl</th>
</tr>
</thead>
<tbody>
<tr>
<td>8-decanoic acid</td>
<td>L1</td>
<td>74</td>
<td>2.6</td>
<td>1.9</td>
</tr>
<tr>
<td>8-decanoic acid</td>
<td>L2</td>
<td>97</td>
<td>8.8</td>
<td>5.8</td>
</tr>
<tr>
<td>8-decanoic acid</td>
<td>PPh₃</td>
<td>100</td>
<td>1.6</td>
<td>1.6</td>
</tr>
<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 (15 equiv), [Rh(acac)(CO)]_2 (1 mol %), L1 (1.1 mol %), 20 bar CO/H₂ (1:1), 40 °C, 24 h. Conversion and regioselectivity determined by ’H NMR analysis of the crude reaction mixture. For full experimental details, see the Supporting Information.

Table 1. Selective hydroformylation of 8-decanoic acid and 9-undecenoic acid
Increasing the rhodium:ligand ratio is capable of controlling the regioselectivity (10-formyl/9-formyl ratio is 1.5 for [Rh(acac)(CO)]_2/C, 96 h. Conversion determined by H NMR analysis of the reaction mixture and the regioselectivity was determined by GC analysis after methylation of the reaction mixture. [b] Methyl 9- and 10-formylpalmitate could not be baseline separated on GC, therefore a larger error in the determined regioselectivity is expected. [c] 9- and 10-formyl stearic acid were not separable after methylation on GC and therefore the regioselectivity was not determined (n.d.). For full experimental details, see the Supporting Information.

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 was 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.

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 ex-

### Table 2. Hydroformylation of natural fatty acids.

<table>
<thead>
<tr>
<th>L1</th>
<th>L2</th>
<th>n=3, myristoleic acid</th>
<th>n=5, palmitoleic acid</th>
<th>n=7, oleic acid</th>
</tr>
</thead>
<tbody>
<tr>
<td>[Rh(acac)(CO)]_2L1</td>
<td>27</td>
<td>1.03</td>
<td>0.79</td>
<td></td>
</tr>
<tr>
<td>[Rh(acac)(CO)]_2L2</td>
<td>69</td>
<td>1.61</td>
<td>1.23</td>
<td></td>
</tr>
<tr>
<td>[Rh(acac)(CO)]_2PPh_3</td>
<td>66</td>
<td>1.0</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>[Rh(acac)(CO)]_2L1</td>
<td>23</td>
<td>1.0</td>
<td>0.8</td>
<td></td>
</tr>
<tr>
<td>[Rh(acac)(CO)]_2L2</td>
<td>66</td>
<td>1.0</td>
<td>1.2</td>
<td></td>
</tr>
<tr>
<td>[Rh(acac)(CO)]_2PPh_3</td>
<td>100</td>
<td>1.0</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>[Rh(acac)(CO)]_2L1</td>
<td>76</td>
<td>n.d.</td>
<td>n.d.</td>
<td></td>
</tr>
<tr>
<td>[Rh(acac)(CO)]_2L2</td>
<td>76</td>
<td>n.d.</td>
<td>n.d.</td>
<td></td>
</tr>
<tr>
<td>[Rh(acac)(CO)]_2PPh_3</td>
<td>76</td>
<td>n.d.</td>
<td>n.d.</td>
<td></td>
</tr>
</tbody>
</table>

[a] Reagents and conditions: [substrate] = 0.2 M, DIPEA (1.5 equiv), [Rh(acac)(CO)]_2 (2 mol%), L1 and L2 (2.2 mol%), PPh_3 (6.6 mol%), 20 bar CO/H_2 (1:1), 60 °C, 96 h. Conversion determined by H NMR analysis of the reaction mixture and the regioselectivity was determined by GC analysis after methylation of the reaction mixture. [b] Methyl 9- and 10-formylpalmitate could not be baseline separated on GC, therefore a larger error in the determined regioselectivity is expected. [c] 9- and 10-formyl stearic acid were not separable after methylation on GC and therefore the regioselectivity was not determined (n.d.). For full experimental details, see the Supporting Information.

### Table 3. Optimization of regioselectivity of myristoleic acid.

<table>
<thead>
<tr>
<th>Entry</th>
<th>[Substrate] [%]</th>
<th>[Catalyst] [%]</th>
<th>Conversion of 10-formyl tetradecanoic acid</th>
<th>Conversion of 9-formyl tetradecanoic acid</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.2</td>
<td>4</td>
<td>33</td>
<td>1.87</td>
</tr>
<tr>
<td>2</td>
<td>0.1</td>
<td>4</td>
<td>66</td>
<td>1.99</td>
</tr>
<tr>
<td>3</td>
<td>0.02</td>
<td>4</td>
<td>85</td>
<td>2.20</td>
</tr>
<tr>
<td>4</td>
<td>0.02</td>
<td>0.4</td>
<td>76</td>
<td>2.31</td>
</tr>
<tr>
<td>5</td>
<td>0.02</td>
<td>0.4</td>
<td>77</td>
<td>2.43</td>
</tr>
<tr>
<td>6</td>
<td>0.02</td>
<td>0.4</td>
<td>77</td>
<td>2.43</td>
</tr>
<tr>
<td>7</td>
<td>0.02</td>
<td>0.4</td>
<td>77</td>
<td>2.43</td>
</tr>
<tr>
<td>8</td>
<td>0.02</td>
<td>0.4</td>
<td>77</td>
<td>2.43</td>
</tr>
<tr>
<td>9</td>
<td>0.02</td>
<td>0.4</td>
<td>77</td>
<td>2.43</td>
</tr>
<tr>
<td>10</td>
<td>0.02</td>
<td>0.4</td>
<td>63</td>
<td>2.51</td>
</tr>
</tbody>
</table>

[a] Reagents and conditions: DCM, DIPEA (1.5 equiv with respect to acid), catalyst = [Rh(acac)(CO)]_2/L2 in a 1:1.1 ratio, substrate = myristoleic acid, 20 bar CO/H_2 (1:1), 40 °C, 96 h. Conversion determined by 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 Supporting Information.

In an improvement of 10-formyl/9-formyl ratio from 1.61 to 1.67, 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 unsselective 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 was 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. [21, 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 ex-
plained by lower levels of isomerization of the alkene, commonly observed for hydroformylation reactions carried out at higher CO concentration.[10]

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 carbonylic directing group is remote from the alkene group, including monounsaturated fatty acids (MUFA's) and their model substrates. The [Rh(L2)] catalyst provides the hydroformylation product with a 10-formyl/9-formyl ratio of 2.51 for myristoleic acid, which represents the first selective catalyst for this biobased compound. These results show that catalysts that operate via supramolecular substrate preorganization can be redesigned to provide selective catalysts for substrates of different sizes, and as such we are able to make a catalyst that can convert fatty acids in a regioselective fashion. This paves the way for the design of other challenging conversions for which no catalysts exist yet.

Acknowledgements

NWO, the Dutch science foundation, is acknowledged for financial support. We also would like to thank InCatT for financial support and useful discussions.

Conflict of interest

The authors declare no conflict of interest.

Keywords: fatty acid functionalization · hydroformylation · regioselectivity · substrate preorganization · supramolecular chemistry

The effective concentration for substrate 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 $1.1 \times 10^{-8}$ dm$^3$. Which translates to $\frac{4/3 \pi (1.1 \times 10^{-8} \text{dm})^3}{0.5 \times 10^{-24} \text{dm}^3} = 5.5 \times 10^{-24} \text{dm}^3$. Of this spherical volume it was estimated the alkene could occupy 50%. This translates to an effective concentration of $\approx 0.06$ 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.