Effector enhanced enantioselective hydroformylation

Bai, S.-T.; Kluwer, A.M.; Reek, J.N.H.

DOI
10.1039/c9cc07327b

Publication date
2019

Document Version
Final published version

Published in
Chemical Communications

License
Article 25fa Dutch Copyright Act (https://www.openaccess.nl/en/in-the-netherlands/you-share-we-take-care)

Citation for published version (APA):
In this communication, we report rhodium DIMPhos complexes with an integrated DIM-receptor that can bind carboxylate-containing effectors and their application in the rhodium catalyzed hydroformylation reaction. The binding of chiral effectors in non-chiral [Rh(DIMPhos)] catalysts does not lead to enantioselective hydroformylation, but the binding of either achiral or chiral effectors can significantly enhance the enantioselectivity induced by the chiral Rh-metal complexes. For example, the supramolecular complex [Rh]/[1S = L3] displays high regio- and enantioselectivity in the hydroformylation of vinyl acetate (72% ee, and b/l > 99), whereas in absence of this effector the ee is around 17%.

The hydroformylation reaction, also known as the oxo-process, enables the addition of a formyl group and a hydrogen atom to a C=C double bond using syngas (H2/CO) to produce aldehydes with 100% atom economy.1 Hydroformylation is one of the largest industrially applied homogeneous catalytic reactions, with applications in both bulk and fine chemical industry.1 A lot of research focuses on achieving sufficient regio- and/or enantioselectivity for the hydroformylation of a wide variety of substrates, which is also important for commercial applications. Particularly, the enantioselective hydroformylation is challenging but provides interesting entries to make fine chemicals, agrochemicals, fragrance and pharmaceuticals when a proper process can be found.2-7 Next to the traditional ligand modification, we are interested in exploring alternative protocols8 and were fully characterized by NMR and HR-MS spectroscopy (see ESI†). We initially applied these rhodium catalysts in the hydroformylation reaction in the presence and absence of effector 1S, which was the effector that gave the best results in the asymmetric hydrogenation reaction.9 The selectivity and conversion were determined by GC and 1H NMR analysis. In the hydroformylation of styrene in the presence of 1S, all three catalysts [Rh]/[1S = L1-3] produce the aldehydes in close to racemic form. The branched aldehyde is the dominant product (b/l ratio around 15), which is typical in the hydroformylation of styrene (Table 1, entries 1-3). We next performed the hydroformylation of vinyl acetate, which has a functional group that can form hydrogen bonds with effector 1S (carbonyl-O hydrogen bonding with thiourea-NH), which was demonstrated to be important for the high enantioselectivity in effector controlled enantioselective hydrogenation reactions.9 ParaDIMPhos (L1)-rhodium and DIMPhosphite (L2)-rhodium catalysts also gave racemic aldehydes when performing the hydroformylation of vinyl acetate in the presence of 1S (Table 1, entries 4 and 5). Interestingly, DIMPhosphite (L3)-rhodium catalyst displayed...
pronounced enantioselectivity and regioselectivity in the presence of \textbf{1S}, whereas in the absence of \textbf{1S} the product is formed in almost racemic form (65 vs. 1% ee and b/l > 99 vs. 27, Table 1, entries 6 and 7). These results reveal that effector binding can indeed enhance the enantioselectivity and regioselectivity in the hydroformylation reaction. Importantly, even a higher enantioselectivity (72 vs. 63% ee, Table 1, entries 6 and 8) was achieved when the reaction was performed at room temperature instead of 40 °C.

Next, we extended the substrate scope to other vinyl derivatives using the supramolecular catalyst \([\text{Rh}]/[\text{L}]=\text{1S}\L3]. This catalyst displayed decent enantio- and regioselectivity in the hydroformylation of vinyl benzoate and vinyl pivalate (59 and 45% ee, respectively), and the regioselectivity was high for all substrates (b/l > 99%). In the absence of an effector, the DIMPhosphite-rhodium catalyst ([\text{Rh}]/[\text{L}]) provided the products in a much lower ee (7–24% ee, Table 2, entries 2, 4 and 6). Also, [\text{Rh}]/\text{1S}L3 displayed much higher enantioselectivity than [\text{Rh}]/\text{L3} in the hydroformylation of \(N\)-vinyl phthalimide (25 vs. 1% ee, Table 2, entries 7 and 8). These experiments show that the effector has an effect on the catalyst properties when converting various substrates with different size and electronic properties.

We then performed catalytic experiments using a variety of both chiral and achiral effectors in the hydroformylation of vinyl acetate (Table 3). The catalyst in the presence of \textbf{1R}, which is the opposite enantiomer of \textbf{1S}, displayed the same stereochemistry and gave similar ee (72 vs. 68% ee, Table 3, entries 1 and 2), indicating that the chirality of the effector has little influence on the enantiomeric excess of the products. Interestingly, the reactivity is different when the effectors with \(R\) or \(S\) configuration are applied (conversion 72 vs. 37%, Table 3, entries 1 and 2), revealing that the effectors do affect the overall process via matched/mismatched effects. In line with this, control experiments in the presence of racemic effectors \textbf{1R/S} displayed the same stereo-outcome and intermediate activity (71% ee, conversion 56%, Table 3, entry 3). Interestingly, the catalyst system in the presence of achiral Fmoc-glycine increased the ee of the products formed, resulting in decent enantioselectivity (40% ee, Table 3, entry 4). Even the catalyst in the presence of a simple acetate as an effector gave much higher enantioselectivity than that in the absence of an effector (37 vs. 17% ee, Table 3, entry 5 and Table 2, entry 2). The catalyst in the presence of benzoate as an effector showed even higher enantioselectivity (58 vs. 37% ee,

![Fig. 1](a) General concept of effector enhanced enantioselective hydroformylation; (b) DIM-type ligands studied in this contribution. The DIM-receptor is colored in blue.

**Table 1** Asymmetric hydroformylation using DIM-ligands L1–L3 and effector \textbf{1S}.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Ligand</th>
<th>Effectors</th>
<th>Conv./%</th>
<th>ee/%</th>
<th>b/l</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Styrene</td>
<td>L1</td>
<td>1S</td>
<td>70</td>
<td>0</td>
<td>13</td>
</tr>
<tr>
<td>2</td>
<td>Styrene</td>
<td>L2</td>
<td>1S</td>
<td>100</td>
<td>1</td>
<td>15</td>
</tr>
<tr>
<td>3</td>
<td>Styrene</td>
<td>L3</td>
<td>1S</td>
<td>100</td>
<td>3</td>
<td>15</td>
</tr>
<tr>
<td>4</td>
<td>Vinyl acetate</td>
<td>L1</td>
<td>1S</td>
<td>16</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>5</td>
<td>Vinyl acetate</td>
<td>L2</td>
<td>1S</td>
<td>98</td>
<td>0</td>
<td>15</td>
</tr>
<tr>
<td>6</td>
<td>Vinyl acetate</td>
<td>L3</td>
<td>1S</td>
<td>55</td>
<td>65(R)</td>
<td>&gt;99</td>
</tr>
<tr>
<td>7</td>
<td>Vinyl acetate</td>
<td>L3</td>
<td>—</td>
<td>100</td>
<td>1</td>
<td>&gt;27</td>
</tr>
<tr>
<td>8&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Vinyl acetate</td>
<td>L3</td>
<td>1S</td>
<td>72</td>
<td>72(R)</td>
<td>&gt;99</td>
</tr>
<tr>
<td>9&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Vinyl acetate</td>
<td>L3</td>
<td>—</td>
<td>26</td>
<td>17(R)</td>
<td>&gt;99</td>
</tr>
</tbody>
</table>

<sup>a</sup> Conditions: 0.5% cat. \([\text{Rh}]/[\text{acac}]/[\text{CO}]_2]/[\text{L}]=1/1.3, 0.2 M substrate, 10 mol% effector, 8 mol% DIPEA, 1 ml toluene as the solvent, 40 bar syngas, 40 °C, 96 hours. Conversion and regioselectivity were determined by <sup>1</sup>H NMR analysis. ee was determined by chiral-GC analysis. <sup>b</sup> Reaction was performed at room temperature, 120 hours. <sup>c</sup> Reported stereo-configurations were referred to the literature. 6<sup>12</sup>

**Table 2** The substrate scope using \([\text{Rh}]/[\text{L}]=\text{1S}\L3] as the catalyst and effector \textbf{1S}.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Ligand</th>
<th>Effectors</th>
<th>Conv./%</th>
<th>ee/%</th>
<th>b/l</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Vinyl acetate</td>
<td>L3</td>
<td>1S</td>
<td>72</td>
<td>72(R)</td>
<td>&gt;99</td>
</tr>
<tr>
<td>2</td>
<td>Vinyl acetate</td>
<td>L3</td>
<td>No</td>
<td>26</td>
<td>17(R)</td>
<td>&gt;99</td>
</tr>
<tr>
<td>3</td>
<td>Vinyl benzoate</td>
<td>L3</td>
<td>1S</td>
<td>69</td>
<td>59(S)</td>
<td>&gt;99</td>
</tr>
<tr>
<td>4</td>
<td>Vinyl benzoate</td>
<td>L3</td>
<td>No</td>
<td>31</td>
<td>24(S)</td>
<td>&gt;99</td>
</tr>
<tr>
<td>5</td>
<td>Vinyl pivalate</td>
<td>L3</td>
<td>1S</td>
<td>36</td>
<td>45(R)</td>
<td>&gt;99</td>
</tr>
<tr>
<td>6</td>
<td>Vinyl pivalate</td>
<td>L3</td>
<td>No</td>
<td>71</td>
<td>7(R)</td>
<td>&gt;99</td>
</tr>
<tr>
<td>7</td>
<td>N-Vinyl phthalimide</td>
<td>L3</td>
<td>1S</td>
<td>74</td>
<td>25</td>
<td>&gt;99</td>
</tr>
<tr>
<td>8</td>
<td>N-Vinyl phthalimide</td>
<td>L3</td>
<td>No</td>
<td>74</td>
<td>1</td>
<td>&gt;99</td>
</tr>
</tbody>
</table>

<sup>a</sup> Conditions: 0.5% cat. \([\text{Rh}]/[\text{acac}]/[\text{CO}]_2]/[\text{L}]=1/1.3, 0.2 M substrate, 10 mol% effector, 8 mol% DIPEA, 1 ml toluene as the solvent, 40 bar syngas, room temperature, 96–120 hours. Conversion and regioselectivity were determined by <sup>1</sup>H NMR analysis. ee was determined by chiral-GC and HPLC analysis. <sup>b</sup> Reported stereo-configurations were referred to the literature. 6<sup>12</sup>
In conclusion, we explored the binding of effectors to DIM-receptor based ligands and the properties in rhodium catalysed asymmetric hydroformylation. The use of non-chiral catalyst in combination with chiral effectors did give the aldehyde product in racemic form. The chiral catalyst in presence of an effector [Rh][1S-L3] displayed highly increased enantioselectivity (up to 72% ee) in the hydroformylation of N-vinyl phthalimide, vinyl acetate and its derivatives compared to catalyst systems in the absence of an effector. Also the use of non-chiral effectors and amino acids based effectors were shown to be effective leading to enantioselective hydroformylation of vinyl acetate with selectivities up to 68% ee. The in situ assembly of supra-molecular catalysts using an effector approach provides a new tool which may be used to solve challenging selectivity issues in the field of transition metal catalysis.

S.-T. Bai thanks the China Scholarship Council for a PhD fellowship (CSC student number 201506010269) and University of Amsterdam for financial support.

**Conflicts of interest**

There are no conflicts to declare.

**Notes and references**

For other examples on effector (cofactor) controlled catalysis see:
(a) C. G. Oliveri, P. A. Ulmann, M. J. Wiester and C. A. Mirkin, Acc.
Chem. Res., 2008, 41, 1618–1629; (b) A. M. Lifschitz, R. M. Young, J.
Mendez-Arroyo, C. L. Stern, C. M. McGuirk, M. R. Wastelewski and C. A.
Mirkin, Nat. Commun., 2015, 6, 6341; (c) H. J. Yoon, J. Kowalak, J.-H.
Kim and C. A. Mirkin, Science, 2010, 330, 66–69; (d) L. O. Fritsly, R.
N. M. van Leeuwen, D. Rivillo, M. Raynal and Z. Freixa, J. Am.
Chem. Soc., 2011, 133, 18562–18565; (f) G.-H. Ouyang, Y.-M. He, Y. Li,
(g) M. Vaquero, L. Rivara and A. Vidal-Ferran, Chem. Commun., 2016,
52, 11038–11041; (h) A. Vidal-Ferran, I. Mon, A. Bauza, A. Frontera and
L. Rivara, Chem. – Eur. J., 2015, 21, 14117–14126; (i) I. Mon, A. A. Jose and
A. Vidal-Ferran, Chem. – Eur. J., 2013, 19, 2720–2725; (j) L. Rivara,
(k) S.-T. Bai, V. Sinha, A. M. Kluver, P. R. Linnebank, Z. Abiri, P. Dydio,
Int. Ed., 2019, 58, 2696–2699; (m) C. M. McGuirk, C. L. Stern and C. A.
D’Elia, M. Fochi and L. Bernardi, RSC Adv., 2016, 6, 66490–66494; (o) V.
(p) N. Ma, Z. Chen, J. Chen, J. Chen, C. Wang, H. Zhou, L. Yao, O. Shoji,

12 X. Zhang, B. Cao, Y. Yan, S. Yu, B. Ji and X. Zhang, Chem. – Eur. J.,
2010, 16, 871–877.