Supramolecular control of selectivity in transition metal catalysis: Substrate preorganization & cofactor-steered catalysis
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Chapter 2

Remote Supramolecular Control of Catalyst Selectivity in the Hydroformylation of Alkenes*

Chapter 2

2.1 Introduction

Immense progress in the field of transition metal catalysis has been achieved over the past few decades, and the contributions of the ligands coordinated to the metals are now well-understood.\(^1\) Despite notable insights made into various reaction mechanisms over the years, the prediction of the selectivity that a new catalyst will display is still beyond our abilities. This becomes a particularly difficult issue when the reaction pathways leading to the isomeric products are nearly identical in energy, or worse, if the pathway for the desired isomer is higher in energy. For these challenging reactions, the trial-and-error approach is still dominant in the search for appropriate catalysts, and thus, combinatorial methods and high-throughput screening of ligands and catalysts have been developed in the past decades.\(^2\) Supramolecular ligands that form by self-assembly from smaller components appear suitable for this approach as the modular synthesis efficiently generates wide libraries of ligands.\(^3\)

Enzyme mimicry represents an alternative route to selective catalysts. Inspired by the properties and working principles of enzymes, great effort in catalyst development has been applied to the incorporation of cavitands that can bind guest molecules to an active site, promoting reactions typically displayed by enzymes.\(^4\) Remarkable examples of highly selective oxidation reactions catalyzed by metalloporphyrins, where hydrophobic interactions allow for substrate pre-organization, have been developed by Breslow and co-workers.\(^5\) However, simple hydrogen bond interactions between a substrate and the functional groups of a catalyst can also be used to greatly improve the selectivity of a reaction. This was elegantly demonstrated by Crabtree, Brudvig and co-workers in a dimanganese catalyst for the highly selective functionalization of sp\(^3\) C-H bonds.\(^6\) Recently, our research group showed that even a single hydrogen bond between a catalyst and a substrate leads to improved activities in cyclopropanation,\(^7\) and excellent enantioselectivity in the hydrogenation of the Roche ester precursor.\(^8\) A similar supramolecular substrate pre-organization strategy has been reported by Breit and co-workers, who applied guanidinium functionalized phosphines to the regioselective hydroformylation of vinylacetic acid and its analogues.\(^9\)

As supramolecular interactions can be arranged relatively easily, selective installation of functional groups can provide a powerful tool for the rational design of selective catalysts, which operate predicitively. The approach requires a set of receptors that can address a wide range of functional groups. In addition, the impact would be larger if the selectivity could also be controlled by non-covalent interactions that are more remote from the catalytic center. In this chapter we introduce the concept of selectivity control by supramolecular interactions between a substrate molecule and a catalyst, which is developed further in Chapters 3-6. We discuss here the principles of the catalyst design, and we present the initial results that provide the proof for the concept. We report here a bisphosphine ligand based on an anion receptor backbone that provides, as predicted, regioselective rhodium-based hydroformylation catalyst for substrates that have anionic groups. Remarkably high regioselectivities are obtained for those substrates that precisely span the distance between receptor and rhodium center, and various anions can be applied. DFT calculations of the essential intermediates show that the hydride migration pathway to the undesired product is blocked by the anion binding, whereas that for the desired product is lowered in energy. The full account of this study, including the initial results presented in this chapter, is presented in Chapter 3.
Remote Supramolecular Control of Catalyst Selectivity

2.2 Results and discussion

We anticipated that neutral anion receptors are excellent candidates for the design of substrate-directing motifs in supramolecular catalysts. Their relatively strong and highly directional interactions with anionic substrates allow for the predictable orientation of a reactive functionality close to a catalytic metal center. For the current study, we fused a 7,7’-diamido-2,2’-diindolylmethane (DIM) scaffold - a tailor-made receptor for carboxylate and phosphate anions - with two triphenylphosphine moieties, generating the new bidentate ligand (DIMPhos, 1, Figure 1). DFT calculations show that ligand 1 forms a rigid mononuclear Rh-complex, which can orient functionalized alkenes for selective hydride migration as a part of the hydroformylation cycle.

![Figure 1](image.png)

**Figure 1.** Structure of ligand 1 (left) and general concept of anionic substrate pre-organization by a Rh-catalyst with a ligand furnished with an anion-binding pocket (right).

The new ligand DIMPhos (1) is prepared easily by hydrogenation of 7,7’-dinitro-2,2’-diindolomethane 2 using H₂ and Pd/C and subsequent condensation with 4-(diphenylphosphino)benzoic acid using a standard protocol, providing bisphospine 1 with an overall yield of 62% (Scheme 1).

![Scheme 1](image.png)

**Scheme 1.** Synthesis of ligand 1: a) H₂, Pd/C(10%), MeOH, rt; b) 4-(Ph₂P)PhCOOH, DIC, DMAP, 4-Pyrrolidinopyridine, DCM, rt.

Upon the addition of [RhCl(CO)₂]₂ to a DCM solution of 1 with an acetate bound in the DIM pocket, a rhodium complex was formed with two P-donors in a mutual trans-orientation coordinated to Rh. This coordination geometry was further supported by the X-ray structure of [Rh(1·AcO)(CO)Cl]⁻TBA⁺ (Figure 2). Importantly, the acetate anion is still bound in the DIM pocket of the Rh complex of ligand 1. As anticipated, all four NH-groups are engaged in acetate binding and the relative short distances indicate that the hydrogen bonds formed are relatively strong (the N-O distances are 2.737(3) Å and 3.006(3) Å, for N-amide and N-indole, respectively). In line with our design, the aliphatic group of the anionic guest points towards the metal center.
Figure 2. Crystal structure of the supramolecular complex [Rh(1·AcO)(CO)Cl] ; TBA⁺ counterion and disordered solvent molecules are omitted for clarity.

High pressure (HP) NMR experiments show that a 1 : 1 mixture of ligand 1 and Rh(acac)(CO)₂ under hydroformylation conditions, 5 bar CO/H₂, forms a mononuclear trigonal bipyramidal rhodium complex, Rh(1)(CO)₂H exclusively.¹⁴ Low-temperature NMR studies reveal that bis-phosphine ligand 1 is coordinated predominantly in an equatorial-equatorial (ee) fashion. At room temperature this complex is in fast equilibrium on the NMR time-scale with the minor equatorial-apical (ea) isomer.¹⁵ Indeed, high pressure infrared (IR) spectra using H₂CO and D₂CO revealed four bands in the carbonyl region belonging to the ee and ea isomeric complexes.¹⁴,¹⁶ Moreover, HP IR studies indicate a fast catalyst activation process, the conversion of Rh(1)(acac) into Rh(1)(CO)₂H takes less than 2h even at room temperature. HP-NMR experiments show that the coordination geometry around rhodium does not change in the presence of carboxylate (acetate) or phosphate anions (H₂PO₄⁻). Under these conditions the signals of the NH groups are shifted towards low field in the ¹H NMR spectra (Δδ = 2.5 – 3.1 ppm), signifying the formation of strong hydrogen bonds involving the anion binding within the pocket.¹¹ The carbonyl bands in the HP IR spectra also show a small shift to lower wavenumbers (Δµ up to 5cm⁻¹) upon anion binding, indicating increased electron density at the phosphorous atoms.

The binding constants of carboxylate and phosphate anions in the DIM pocket of Rh(1)(CO)₂H were determined from titration experiments carried out at 5 bar CO/H₂ in DCM, monitoring the chemical shift of various protons using HP-NMR. These titration studies reveal that only one anion is bound in the DIM receptor of Rh(1)(CO)₂H, with the association constants for CH₃COO⁻ and H₂PO₄⁻ being higher than 10⁵ and ~ 10³⁺ respectively. In contrast to these anionic species, non-deprotonated CH₃COOH and H₃PO₄, as well as their methyl and ethyl esters, are not bound in the pocket of ligand 1.

Next, we applied ligand 1 in the Rh-catalyzed hydroformylation of a series of (deprotonated) ω-unsaturated carboxylic acids, with a range of aliphatic chain lengths between the carboxylic functionality and the double bond, i.e. from 3-butenolic to 8-nonenoic acid. Calculations show that 3-butenolate anion (C₃–CO₃⁻) is too small to bind in the pocket while coordinated to the rhodium metal, 4-pentenoate anion (C₄–CO₃⁻) fits precisely and the other substrates easily span the distance between metal and binding site. The neutral acids and methyl esters, substrates that do not bind in the pocket, were
used as control experiments. The linear/branched selectivity (l/b) determined by $^1$H NMR is displayed in Figure 3. For the small 3-butenolic-acid-based substrates we hardly observe any difference between the anion, the acid and ester analogues, and the l/b ratio is in the expected range between 1.6 and 2.6. In contrast, 4-pentenoate anion, the substrate that precisely fits, 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 40ºC) the l/b ratio even exceeds 50 (Table 1, Entry 1). For the protonated or the methyl ester analogues, substrates of the same size that do not bind in the DIM pocket, typical selectivities of l/b ratio around 3 are obtained, confirming the importance of the anion binding. Besides the higher selectivity, also the conversion is much higher when the substrate is bound in the pocket. This suggests that the reaction barrier to form the linear aldehyde is lowered by the substrate pre-organizing binding event, while the barrier to the branched aldehyde is increased. To further verify that the anion binding unit and the catalytic center must be present as an integrated system, we performed a control experiment using a mixture of the anion receptor (4) and triphenylphosphine (3). In this case, as expected, 4-pentenoate anion (5) is hydroformylated with the typical selectivity displayed by catalysts based on triphenylphosphine (3) (Table 1, Entry 2 and 3). In the absence of phosphorous ligand, substrate 5 is hydroformylated with poor selectivity (l/b=1.8) and low yield (Table 1, Entry 4). Importantly, for non-anionic substrates, the addition of excess acetate anion that binds in the DIM pocket of Rh(I)(CO)$_2$H has no effect on the (low) regioselectivity.\footnote{Reference 17}

\[ \text{Figure 3. Hydroformylation of } \omega\text{-unsaturated carboxylic acids and methyl esters. [Rh(acac)(CO)$_2$/I/substrate} \text{ = 1:3:100; } c_0(\text{substrate}) = 0.2 \text{ M, 20 bar CO/H}_2 \text{ (1:1), DCM, 40ºC, 24h. DIPEA used as a base for anionic substrate generation (C}_{\text{DIPEA}} = 0.3 \text{ M). Regioselectivity and conversion (\%)} \text{ were determined by } ^1\text{H NMR analysis of the reaction mixture. No side reactions (isomerisation, hydrogenation etc.) were observed.}} \]

The substrates that are longer than the one that precisely fits – 5-hexenoate through 8-nonenolate anion – also experience an effect of binding in the pocket; and they are hydroformylated with higher selectivity for linear products than their acid or ester analogues. The l/b factors are all greater than 20 for the anionic substrates, and between 5 and 10 for the substrates that do not bind to the DIM. Importantly, the highest regioselectivity is obtained for 4-pentenoate anion, the substrate that fits best.
Table 1. Hydroformylation of 5.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ligand</th>
<th>Conversion [%]</th>
<th>Regioselectivity (l/b ratio)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>95 (80)</td>
<td>40 (&gt; 50)</td>
</tr>
<tr>
<td>2</td>
<td>4/3 (1:2)</td>
<td>100</td>
<td>2.9</td>
</tr>
<tr>
<td>3</td>
<td>3</td>
<td>100</td>
<td>3.1</td>
</tr>
<tr>
<td>4</td>
<td>-</td>
<td>13</td>
<td>1.8</td>
</tr>
</tbody>
</table>

a [Rh(acac)(CO)2]/I(4 and/or 3)/5/DIPEA = 1:3(3 and/or 6):100:150; c0(5) = 0.2 M, 20 bar CO/H2 (1:1), DCM, 40°C, 24h. Regioselectivity and conversion (%) were determined by 1H NMR analysis of the reaction mixture. b Reaction at rt, 72h. c For other studied acids from Figure 3 the results are similar, for details see Supporting Information.

We extended the scope of substrates to alkenes functionalized with the phosphate group (Table 2). Again, we expected that 3-butenylphosphonate anion (C4-PO32-) would be hydroformylated with the highest selectivity as this substrate exactly spans the distance between binding site and metal center. Indeed this substrate is hydroformylated by Rh(I)(CO)2H to the linear aldehyde with excellent regioselectivity (the l/b factor is greater than 40). Again, the high selectivity and higher yield are observed only when the anionic substrate is used (Table 2, Entries 4-6). The shorter substrate, allylphosphonate anion (C3-PO32-), is hydroformylated with similar regioselectivity as the analogue that does not bind (Table 2, Entry 1 and 3).

Table 2. Hydroformylation of ω-unsaturated phosphonic acids and ethyl esters.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate (n)</th>
<th>Form (OR)</th>
<th>Conversion [%]</th>
<th>Regioselectivity (l/b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>ester (OEt)</td>
<td>3</td>
<td>0.6</td>
</tr>
<tr>
<td>2</td>
<td>1</td>
<td>acid (OH)</td>
<td>-b</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>1</td>
<td>anion (O-)</td>
<td>10 (69)c</td>
<td>- (1.6)c</td>
</tr>
<tr>
<td>4</td>
<td>2</td>
<td>ester (OEt)</td>
<td>12</td>
<td>4.0</td>
</tr>
<tr>
<td>5</td>
<td>2</td>
<td>acid (OH)</td>
<td>-b</td>
<td>-</td>
</tr>
<tr>
<td>6</td>
<td>2</td>
<td>anion (O-)</td>
<td>100</td>
<td>&gt;40</td>
</tr>
</tbody>
</table>

a [Rh(acac)(CO)2]/I/substrate = 1:3:100; c0(substrate) = 0.2 M, 20 bar CO/H2 (1:1), DCM, rt, 24h, DIPEA used as a base for anionic substrate generation (C0(DIPEA) = 0.6 M). Regioselectivity and conversion (%) were determined by 1H and 13C NMR analysis of the reaction mixture. b Additional experiments with 1-octene showed that under these strongly acidic conditions the catalyst is inactive. c At rt the conversion is too low to determine the selectivity; values between parentheses are for the reaction at 40°C.

To gain a deeper understanding of the origin of the high selectivity in the hydroformylation of anionic substrates we studied the Rh(I)-catalytic system with DFT
Since, in the absence of isomerisation, the regioselectivity of the rhodium/phosphine-catalyzed hydroformylation is defined by insertion of the olefin into the Rh–H bond to generate the Rh–alkyl complex (alkene hydrometalation), this step was studied in detail. We first calculated several possible structures of the complex [RhH(CO)(1)-(4-pentenoate), and found that for this complex the ee coordination geometry was favoured. The minimum-energy structure shows that the carboxylate group of the substrate is strongly bound in the pocket by four hydrogen bonds (d$_{N\cdots O}$ = 2.7-2.9 Å), and the coordinated alkene moiety is already tilted out of the P-Rh-P plane of the trigonal bipyramidal complex (Figure 4a). This perturbation results from anchoring of the carboxylate in the pocket, which severely restricts the movement of the coordinated double bond. The alkene, however, easily rotates towards the transition state leading to the linear alkyl–Rh complex. In fact, the geometry of the complex in the calculated early transition state (ΔG°$^\ddagger$ = 11.2 kJ mol$^{-1}$) is almost unperturbed (Rh–H bond elongates by only 0.036 Å), with the alkene rotated only a little further out of the equatorial plane (Figure 4b). There is no low-barrier reaction pathway towards the branched alkyl–Rh intermediate from this catalyst-substrate complex conformer, since the double bond cannot rotate in the necessary direction due to the anchoring of the carboxylate within the pocket. This indicates that the branched aldehyde that is formed during the reaction follows a pathway in which the anion is not bound in the receptor. We also modelled the conformer of the initial complex which has the carbonyl and hydride positions inverted (Figure 4d), and which favours the rotation of the alkene toward the transition state leading to the branched alkyl intermediate. However, this conformation has much higher energy (15.8 kJ mol$^{-1}$), even higher than the transition state leading to the linear product (ΔΔG = 4.6 kJ mol$^{-1}$). Thus, the calculations corroborate our assertion that the high regioselectivity obtained by the Rh(1)-catalyst stems from substrate orientation by the hydrogen bonds between the anionic functionality and the DIM pocket of the ligand. The substrate binding in the pocket favours one reaction pathway and hinders the competing pathway that would lead to the isomeric product by restricting the movements of the reactive functionality during the key selectivity-determining step.

Figure 4. Calculated reaction pathway (DFT, BP86, SV(P)) of the regioselectivity determining hydride migration step of hydroformylation of 4-pentenoate by Rh(1)-catalyst; catalyst-substrate complex (a), transition state toward linear product (b) and linear alkyl–Rh complex (c), alternative catalyst-substrate complex favoring formation of the branched product (d). G$_{298}$ - Gibbs free energy at 298K (relative to complex a) in kJ mol$^{-1}$. 
2.3 Conclusions

In summary, we have introduced DIMPhos (1), a new bidentate phosphorus ligand with an integral anion recognition site. We have demonstrated that under hydroformylation conditions well-defined rhodium complexes are formed that strongly bind anionic substrate species. DFT calculations show that 4-pentenoate exactly spans the distance between rhodium and receptor site, and this substrate orientation should lead to selective reactions. Indeed, high selectivity for the linear aldehyde is observed (l/b=40) for this substrate, in contrast to those that do not bind or are too small. The substrate scope can be extended to larger o-unsaturated carboxylic, up to 8-nonenolic acid, and phosphonic acids, providing the first example of wide-ranging remote control of catalyst selectivity by secondary substrate-ligand interactions. The use of functionalized bidentate ligands such as DIMPhos (1) has the advantage above functionalized mondentate ligands that the number of possible complexes that can be formed is significantly less, which may be important for the design of selective catalysts based on substrate orientation. Current efforts are focused on optimizing the activity of this system, and applying supramolecular ligands equipped with the anion binding pocket to other challenging transformations, and the results will be reported in due course.

2.4 Experimental section

General

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; CH₂Cl₂, isopropanol and methanol were distilled from CaH₂ and toluene was distilled from sodium under nitrogen. NMR spectra were measured on a Bruker AMX 400 (400.1MHz, 100.6MHz and 162.0 for ¹H, ¹³C and ³¹P 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. CD₂Cl₂ and DIPEA were dried over molecular sieves (4Å) and degassed by 3 freeze-pump-thaw cycles. If not stated otherwise, syngas refers to a 1 : 1 mixture of H₂ 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 compound 2 (1,1-bis-(3-methyl-7-nitro-1H-indol-2-yl)-propane) and anion receptor 4, which were synthesized according to the published procedures.

Synthesis of ligands and substrates

Ligand 1 - Bis-(4-(diphenylphosphino)benzoamide) of 1,1-bis-(7-amino-3-methyl-1H-indol-2-yl)-propane

1,1-Bis-(3-methyl-7-nitro-1H-indol-2-yl)propane (2) (784mg, 2mmol) was suspended in methanol (40 ml) and 10% palladium on charcoal was added (0.2g). 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 6 was immediately used in the subsequent reaction without further purification.

To the solution of crude diamine 6 (2mmol), 4-(diphenylphosphino)benzoic acid (1.286g, 4.2mmol), 4-dimethylaminopropidine (120mg, 1mmol) and 4-pyrrolidinopyridine (120mg, 0.8mmol) in dichloromethane (60ml), N,N′-disopropylcarbodiimide (1.63ml, 16.2mmol) was slowly added while stirring, and the mixture was allowed to continue stirring overnight. The precipitate was filtered off, the solvent was evaporated and the solid residue was purified by column chromatography on silica gel (100g), 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. 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 solution, yielding 1.15g (62%) of \( \text{H}_2\text{O} \).

\(^1\text{H} \text{ NMR} \) (400MHz, \( \text{CDCl}_3 \)); \( \delta = 9.45 \) (s, 2H, NH-indole), 8.20 (s, 2H, NH-amide), 7.81 (d, \( J = 7.3 \text{Hz} \), 4H), 7.63-7.49 (m, 22H), 7.30 (m, 4H), 7.22 (t, \( J = 7.7 \text{Hz} \), 2H), 7.15 (bd, \( J = 7.4 \text{Hz} \), 2H), 4.67 (t, \( J = 8 \text{Hz} \), 1H, \( \text{CH}_2\text{CH}_2\text{CH}_3 \)), 2.52 (s, 6H, \( \text{ArCH}_3 \)), 2.34 (m, 2H, \( \text{CHCH}_2\text{CH}_3 \)), 1.17 (t, \( J = 7.3 \text{Hz} \), 3H, \( \text{CHCH}_2\text{CH}_3 \)).

\(^{13}\text{C}[\text{H}] \text{ NMR} \) (100MHz, \( \text{CDCl}_3 \)); \( \delta = 165.6 \) (s, \( \text{CO}_2 \)), 143.0 (d, \( J = 14.8 \text{Hz} \)), 136.5 (dd, \( J = 11.3 \text{Hz} \), \( J = 3.0 \text{Hz} \)), 135.9 (s), 134.4 (s), 134.0 (dd, \( J = 20.0 \text{Hz} \), \( J = 6.1 \text{Hz} \)), 133.4 (d, \( J = 19.0 \text{Hz} \)), 132.0 (s), 129.3 (d, \( J = 2.9 \text{Hz} \)), 128.8 (d, \( J = 2.8 \text{Hz} \)), 127.7 (s), 127.2 (d, \( J = 6.4 \text{Hz} \)), 129.1 (s), 119.0 (s), 116.0 (s), 113.6 (s), 108 (s), 36.6 (s), 27.6 (s), 12.2 (s), 8.6 (s);

\( \text{HR MS (FAB)} \): calcld. for \( \text{C}_5\text{H}_9\text{N}_2\text{O}_2\cdot\text{P}[\text{M+H}^+]^+ \): 909.3487, found: 909.3497;

**Elemental analysis (%)** calcld. for \( \text{C}_5\text{H}_9\text{N}_2\text{O}_2\cdot\text{P}_2\cdot\text{H}_2\text{O} \): C 76.44, H 5.65, N 6.04, P 6.68, found: C 76.51, H 5.66, N 5.86, P 6.46.

**General procedure for preparation of \( \omega \)-unsaturated phosphonic acids**

To a solution of the diethyl ester of the \( \omega \)-unsaturated phosphonic acid (5mmol) in dichloromethane (40ml), bromotrimethylsilane (6.60ml, 50mmol) was added dropwise by syringe under a continuous flow of argon. After stirring with a constant flow of argon for 24 hours, the volatile reactants were removed under vacuum. To the residue, methanol (60ml) was added and stirring was continued under a continuous flow of argon for another 24 hours. Upon removal of the volatile reactants, the solid was washed with hexane and dried, yielding the product without further purification necessary.

**Allyl phosphonic acid**

Diethyl allylphosphonate (0.88ml, 5mmol) was used as the starting material, yielding 566mg (93%) of product.

\(^1\text{H} \text{ NMR} \) (400MHz, DMSO-\( \text{d}_6 \)); \( \delta = 9.38 \) (bs, 2H, OH), 5.75 (m, 1H, \( \text{PCH}_2\text{CH} \)), 5.11 (m, 2H, \( \text{PCH}_2\text{CHCH}_2\text{CH}_3 \)), 2.41 (dd, \( J = 21.6 \text{Hz} \), \( J = 7.4 \text{Hz} \), 2H, \( \text{PCH}_2\text{CH} \));

\(^{13}\text{C} \text{ NMR} \) (100MHz, DMSO-\( \text{d}_6 \)); \( \delta = 130.0 \) (d, \( J = 10.6 \text{Hz} \)), 118.3 (d, \( J = 13.9 \text{Hz} \)), 33.7 (d, \( J = 134.6 \text{Hz} \));

\(^{31}\text{P} \text{ NMR} \) (162MHz, DMSO-\( \text{d}_6 \)); \( \delta = 22.23 \);

**HR MS (FAB)**: calcld. for \( \text{C}_9\text{H}_8\text{O}_2\cdot\text{P}[\text{M+H}^+]^+ \): 123.0211, found 123.0217;

**Elemental analysis (%)** calcld. for \( 4 \cdot (\text{C}_3\text{H}_4\text{O}_2\cdot\text{P}) \cdot\text{H}_2\text{O} \): C 28.47, H 5.97, P 24.47, found: C 28.67, H 5.93, P 24.89.

**3-Butenylphosphonic acid**

Diethyl 3-butenylphosphonate (0.96ml, 5mmol) was used as the starting material, yielding 623mg (92%) of product.

\(^1\text{H} \text{ NMR} \) (400MHz, DMSO-\( \text{d}_6 \)); \( \delta = 10.13 \) (bs, 2H, OH), 5.87 (m, 1H, \( \text{PCH}_2\text{CHCH}_2\text{CH}_3 \)), 5.03 (dm, \( J = 17.2 \text{Hz} \), 1H, \( \text{PCH}_2\text{CHCH}_2\text{CH}_3 \)), 4.94 (dm, \( J = 10.2 \text{Hz} \), 1H, \( \text{PCH}_2\text{CHCH}_2\text{CH}_3 \)), 2.20 (m, 2H, \( \text{PCH}_2\text{CH} \)), 1.59 (m, 2H, \( \text{PCH}_2\text{CH} \));

\(^{13}\text{C} \text{ NMR} \) (100MHz, DMSO-\( \text{d}_6 \)); \( \delta = 138.4 \) (d, \( J = 17.3 \text{Hz} \)), 114.5 (s), 26.9 (d, \( J = 4.3 \text{Hz} \)), 26.8 (d, \( J = 136.4 \text{Hz} \));

\(^{31}\text{P} \text{ NMR} \) (162MHz, DMSO-\( \text{d}_6 \)); \( \delta = 26.39 \);

**HR MS (FAB)**: calcld. for \( \text{C}_9\text{H}_8\text{O}_2\cdot\text{P}[\text{M+H}^+]^+ \): 137.0368, found 137.0362;

**Elemental analysis (%)** calcld. for \( 3 \cdot (\text{C}_3\text{H}_4\text{O}_2\cdot\text{P}) \cdot\text{H}_2\text{O} \): C 33.81, H 6.86, P 21.80, found: C 33.77, H 6.83, P 20.82.

**General procedure for preparation of methyl ester of \( \omega \)-unsaturated carboxylic acids**

To a solution of the \( \omega \)-unsaturated carboxylic acid (2mmol) in toluene (10ml) and methanol (4ml), a solution of trimethylsilyldiazomethane in diethyl ether (1.3ml, 2M, 2.6mmol) was added dropwise while stirring, and stirring was continued for 2 hours. Upon removal of residual solvents and trimethylsilyl species, the product was obtained in quantitative yield without further purification necessary.

**Methyl 7-octenoate**

7-Octenoic acid was used as the starting material (0.30ml, 2mmol).

\(^1\text{H} \text{ NMR} \) (400MHz, \( \text{CDCl}_3 \)); \( \delta = 5.81 \) (m, 1H, \( \text{CH} \)), 4.96 (m, 2H, \( \text{CH}_2\text{CH} \)), 3.66 (s, 3H, \( \text{OCH}_3 \)), 2.30 (t, \( J = 7.5 \text{Hz} \), \( \text{COCH}_3 \)), 2.04 (m, 2H), 1.63 (m, 2H), 1.45-1.27 (m, 4H);

\(^{13}\text{C} \text{ NMR} \) (100MHz, \( \text{CDCl}_3 \)); \( \delta = 174.2, 138.8, 114.4, 51.4, 34.0, 33.5, 28.6, 28.5, 24.8 \);

**HR MS (FAB)**: calcld. for \( \text{C}_9\text{H}_8\text{O}_2 \cdot [\text{M+H}]^+ \): 157.1229, found: 157.1237.
Chapter 2

Methyl 8-nonenoate
8-Nonenoic acid was used as the substrate (0.33ml, 2mmol).

\(^1^H\) NMR (400MHz, CDCl\(_3\)): \(\delta = 5.80\) (dtt, \(J = 16.9\)Hz, \(J = 10.2\)Hz, \(J = 6.7\)Hz, 1H, CH\(_2\)), 4.95 (m, 2H, CH\(_2\)), 3.66 (s, 3H, OCH\(_3\)), 2.30 (t, \(J = 7.5\)Hz, COCH\(_3\)), 2.03 (m, 2H), 1.63 (m, 2H), 1.42-1.28 (m, 6H);

\(^{13}\)C NMR (100MHz, CDCl\(_3\)): \(\delta = 174.3, 139.0, 114.3, 51.4, 34.1, 33.7, 29.0, 28.69, 28.68, 24.9\);

HR MS (FAB): calcd. for C\(_{10}\)H\(_{19}\)O\(_2\) [M+H]: 171.1385, found: 171.1370.

Binding studies

General comments
Commercially available tetrabutylammonium (TBA) salts were used as the source of anions. All manipulations were conducted under inert atmosphere (argon or nitrogen). All NMR spectra, except where noted, were collected at 25°C.

NMR titration experiments under CO\(_2\)/H\(_2\) pressure
A flame-dried Schlenk flask equipped with a teflon stirring bar was charged with ligand 1 and with Rh(acac)(CO)\(_2\) (1:1 ratio), followed by addition of an appropriate amount of CD\(_2\)Cl\(_2\) to obtain a 0.004 M solution of the Rh(I) complex. The solution was stirred for 30 minutes at room temperature. In another flame-dried Schlenk flask a 0.05 M solution of the appropriate tetrabutylammonium salt was prepared. Under inert atmosphere (glove-box), aliquots (0.5ml) of the Rh(I) complex solution were transferred to high pressure reaction vessels, followed by addition of aliquots of the tetrabutylammonium salt solution. Next, the vessels were transferred to stainless steel mini-autoclaves, which were purged three times with 20 bar of syngas and then pressurized at 20 bar syngas overnight. Then the pressure was released and the solution was transferred immediately to the high pressure NMR tube, which was then purged three times with 10 bar of syngas and subsequently pressurized with 5 bar of syngas.

NMR titration experiments under inert gas
The inert gas NMR titration experiments were analogous to the experiments conducted under high pressure syngas, with the following exceptions: the ligand 1 solution was prepared without the rhodium precursor; both solutions, ligand 1 and TBA salt solutions, were transferred directly to the NMR tubes and both pressurization steps were omitted.

Experiments with tetrabutylammonium dihydrogen phosphate (TBA-H\(_2\)PO\(_4\))
The chemical shift of the ligand protons upon addition of different amounts of the anion were monitored. The largest changes were observed for both NH-indole and NH-amide protons in both cases studied (since they take part in hydrogen bond formation), and these signals were used to calculate the binding constants. Nonlinear curve fitting for 1:1 binding model was carried out with the WinEQNMR2 Version 2.00 program. In both experiments, with the Rh(I) complex under syngas pressure as well as with free ligand 1 under nitrogen, NH signals’ coalescence was observed between 0 and 1 equivalents of anion, and this phenomenon is common in anion binding chemistry.\(^{10}\)

The phosphine signal of ligand 1 on \(^{31}\)P NMR did not shift significantly upon anion addition.

Table 3. \(^1^H\) NMR titration experiments for the Rh(I) complex or free ligand 1 and TBA-H\(_2\)PO\(_4\).

<table>
<thead>
<tr>
<th></th>
<th>NH amide</th>
<th>NH indole</th>
<th></th>
<th>NH amide</th>
<th>NH indole</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rh-ligand 1 complex under syngas (5bar)</td>
<td></td>
<td></td>
<td>free ligand 1 under nitrogen (1 bar)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(K_a)</td>
<td>6445</td>
<td>4216</td>
<td>(K_a)</td>
<td>8740</td>
<td>3360</td>
</tr>
<tr>
<td>(\log K_a)</td>
<td>3.81</td>
<td>3.62</td>
<td>(\log K_a)</td>
<td>3.94</td>
<td>3.53</td>
</tr>
</tbody>
</table>
Experiments with tetrabutylammonium acetate (TBA-AcO)

The chemical shift of ligand protons upon addition of different amount of the anion was observed. The highest changes were observed for both NH-indole and NH-amide protons in both studied cases (as they take part in hydrogen bond formation).

Due to slow anion/receptor complex formation on the NMR timescale, there were two sets of broad NH signals observed between 0 and 1 equivalent of anion (other signals are significantly broaden, e.g. broad pseudo-singlet RhH hydride signal), and their ratio depends on the amount of anion added.

In the case of the Rh-complex under syngas (5bar), the spectrum was resolved, with all the signals sharpening (e.g. the RhH hydride signal is a clear doublet of triplets), when slightly more than a stoichiometric amount of anion is added (1.05 equiv.). At this point the anion binding pocket is saturated, and further addition of anion does not change the spectrum. Taking into account the complex concentration in this point (C_{Rh}= 0.003690 M), the association constant can be easily estimated: K_a = [CA]/([C][A]), with: [CA] = the concentration of the anion/receptor complex, [C] = the concentration of the free receptor, [A] = the concentration of the free anion. Based on analysis of the spectrum at 1.05 equivalents of anion: [CA] >> 0.95·C_{Rh}, [C] << 0.05·C_{Rh}, so then [A] ~ 0.05·C_{Rh}. After rearrangement: K_a >> 380·(C_{Rh})^{-1}, so then K_a >> 10^5.

Control experiments with acids and esters

Control titration experiments of ligand 1 with AcOH, AcOMe, H_3PO_4 and PO(OEt)_3 showed that non-deprotonated carboxylic and phosphonic acids as well as their esters are not bound in the binding pocket of ligand 1.

Low-temperature NMR studies under CO/H_2 pressure

The sample preparation for the low-temperature high pressure NMR studies was analogous to the procedure for the titration experiments under high pressure of syngas with the exception that the concentration of the Rh(I) complex was increased to 0.0143 M.

For the ^1H NMR spectra at −70°C and above, only one hydride signal for both ee and ea isomers of Rh(1)(CO)_2H was observed at an averaged chemical shift. At −80°C and below, one can see that there are two broad signals: a pseudo-singlet of the major ee isomer and a pseudo-doublet of the minor ea form, with an expected phosphorous-proton coupling constant (J_{PH}) of ca. 100Hz. As expected, the P–H coupling disappeared, when the phosphorous decoupling pulse was used (^1H[31P]) NMR study), and hydride signals for both ee and ee isomers overlapped.

For the ^31P[^1H] NMR spectra at −50°C and above, only one phosphorous signal for both ee and ea isomers of Rh(1)(CO)_2H was observed at an averaged chemical shift. At −60°C and −70°C, one can see that there are two signals: a doublet of the major ee isomer and a broad pseudo-singlet of the minor ea form.

High-pressure Infrared (HP IR) studies under CO/H_2 pressure

These experiments were performed in a stainless steel (SS 316) 50 mL autoclave equipped with IRTRAN windows (ZnS, transparent up to 700 cm\(^{-1}\), 10 mm i.d., optical path length 0.4 mm), a mechanical stirrer, a temperature controller, and a pressure transducer. The autoclave is equipped with a separately pressurized reservoir which allows for the addition of liquid or dissolved reagents to the main chamber, while it is pressurized. All HP IR experiments were performed at room temperature.

A flame-dried Schlenk flask equipped with a teflon stirring bar was charged with ligand 1 and DCM was added to obtain 0.00321 M (= 0.015 M of Rh(CO)(acac) solution in DCM was prepared. Under inert atmosphere (via syringe) the solution of ligand 1 (14ml) was transferred to the autoclave, which was subsequently purged with 20bar of CO/H_2 and then pressurized at 20 bar of syngas. After full equilibration (~15 minutes), a background spectrum was collected, the rhodium precursor solution (1ml) was added (from the reservoir) and a series of kinetic measurements was started. After 15 h (full catalyst activation was observed after less than 2h) the appropriate TBA salt solution (1ml, 0.009 M), the IR spectrum was collected. The effect of an anion addition was immediate and the spectrum did not change with time.

For the rhodium deuteride studies, Rh(I)(CO)H-D, deuterium-containing syngas (CO/D_2) was used (instead of CO/H_2) in both purging and pressurizing steps. After 15h, full catalyst activation time was shorter than 20 minutes. After 15h, the pressure was released, the autoclave was purged with 20bar of CO/H_2 and pressurized at 20bar of CO/H_2. The deuteride Rh(I)(CO)_2D was fully transformed to the hydride Rh(I)(CO)_2H immediately (<5 min).

High pressure infrared (IR) studies using H_2/CO and D_2/CO revealed four bands in the carbonyl region belonging to the ee and ea isomeric complexes. Upon H/D exchange, two bands shift significantly to lower
wavenumbers (both $\Delta v = 21\text{cm}^{-1}$), and therefore, they are assigned to the ee complex. The other two bands, which are less responsive to H/D exchange, belong to the ea isomer.\textsuperscript{16}

### 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 (if appropriate), internal standard (1,3,5-trimethoxybenzene) and solvent (DCM). The solution was stirred for 15 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, 40°C). 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 isomerisation) were observed in all runs.

When 3-butenolic or 4-pentenoic acid were used as substrates, the characteristic aldehyde signal for the branched product was not observed (due to intramolecular interactions).\textsuperscript{7} Thus, a small amount (50 μl) of DIPEA was added to the sample, and the $^1$H NMR spectrum was collected once more, which enabled direct integration of both aldehyde signals. Furthermore, straightforward analysis was conducted in more polar solvents (DMSO-$d_6$ or MeOD-$d_4$), giving 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), but 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 solvent was evaporated (50 mbar, 40°C). 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.

#### Table 4. Hydroformylation of $\omega$-unsaturated carboxylic acids and their esters by Rh(I).\textsuperscript{a}

<table>
<thead>
<tr>
<th>entry</th>
<th>substrate</th>
<th>form\textsuperscript{b}</th>
<th>regioselectivity (l/b ratio)</th>
<th>conversion (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>methyl 3-butenoate</td>
<td>ester</td>
<td>1.6</td>
<td>46</td>
</tr>
<tr>
<td>2</td>
<td>3-butenoic acid</td>
<td>acid</td>
<td>1.4</td>
<td>46</td>
</tr>
<tr>
<td>3</td>
<td>3-butenoic acid</td>
<td>anion</td>
<td>2.6</td>
<td>23</td>
</tr>
<tr>
<td>4</td>
<td>methyl 4-pentenoate</td>
<td>ester</td>
<td>3.6</td>
<td>42</td>
</tr>
<tr>
<td>5</td>
<td>4-pentenoic acid</td>
<td>acid</td>
<td>3.7</td>
<td>49</td>
</tr>
<tr>
<td>6</td>
<td>4-pentenoic acid</td>
<td>anion</td>
<td>40</td>
<td>95</td>
</tr>
<tr>
<td>7</td>
<td>methyl 5-hexenoate</td>
<td>ester</td>
<td>5.0</td>
<td>42</td>
</tr>
<tr>
<td>8</td>
<td>5-hexenoic acid</td>
<td>acid</td>
<td>6.3</td>
<td>55</td>
</tr>
<tr>
<td>9</td>
<td>5-hexenoic acid</td>
<td>anion</td>
<td>22</td>
<td>85</td>
</tr>
<tr>
<td>10</td>
<td>methyl 6-heptenoate</td>
<td>ester</td>
<td>6.7</td>
<td>43</td>
</tr>
<tr>
<td>11</td>
<td>6-heptenoic acid</td>
<td>acid</td>
<td>9.8</td>
<td>58</td>
</tr>
<tr>
<td>12</td>
<td>6-heptenoic acid</td>
<td>anion</td>
<td>26</td>
<td>77</td>
</tr>
<tr>
<td>13</td>
<td>methyl 7-octenoate</td>
<td>ester</td>
<td>7.2</td>
<td>42</td>
</tr>
<tr>
<td>14</td>
<td>7-octenoic acid</td>
<td>acid</td>
<td>9.3</td>
<td>54</td>
</tr>
<tr>
<td>15</td>
<td>7-octenoic acid</td>
<td>anion</td>
<td>19</td>
<td>58</td>
</tr>
<tr>
<td>16</td>
<td>methyl 8-nonenolate</td>
<td>ester</td>
<td>8.2</td>
<td>43</td>
</tr>
<tr>
<td>17</td>
<td>8-nonenolic acid</td>
<td>acid</td>
<td>10</td>
<td>63</td>
</tr>
<tr>
<td>18</td>
<td>8-nonenolic acid</td>
<td>anion</td>
<td>24</td>
<td>56</td>
</tr>
</tbody>
</table>

\textsuperscript{a} Reactions were performed in DCM, at 40°C, 24h; substrate/I/Rh(acac)(CO)$_2$ = 100:3:1; C$_{\text{substrate}}$ = 0.2 M. \textsuperscript{b} DIPEA was added to generate anionic forms of the substrates (C$_{\text{(DIPEA)}}$ = 0.3 M).
Remote Supramolecular Control of Catalyst Selectivity

Table 5. Control experiments - hydroformylation of ω-unsaturated carboxylic acids by Rh-PPh₃.a

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Regioselectivity (l/b ratio)</th>
<th>Conversion (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3-butanoic acid</td>
<td>3.1</td>
<td>100</td>
</tr>
<tr>
<td>2</td>
<td>4-pentenoic acid</td>
<td>3.1</td>
<td>100</td>
</tr>
<tr>
<td>3</td>
<td>5-hexenoic acid</td>
<td>3.0</td>
<td>100</td>
</tr>
<tr>
<td>4</td>
<td>6-heptenoic acid</td>
<td>3.1</td>
<td>100</td>
</tr>
<tr>
<td>5</td>
<td>7-octenoic acid</td>
<td>3.1</td>
<td>100</td>
</tr>
<tr>
<td>6</td>
<td>8-nonenonic acid</td>
<td>3.1</td>
<td>100</td>
</tr>
</tbody>
</table>

a Reactions were performed in DCM, at 40°C, 24h. substrate/DIPEA/PPh₃/Rh(acac)(CO)₂ = 100:150:6:1; C_{(substrate)} = 0.2 M; DIPEA was added to generate anionic forms of the substrates (C_{(DIPEA)} = 0.3 M).

Table 6. Control experiments.a

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>ligand</th>
<th>additivesb</th>
<th>Regioselectivity (l/b ratio)</th>
<th>Conversion (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4-pentenoic acid</td>
<td>4/3 (1:2)</td>
<td>DIPEA</td>
<td>2.9</td>
<td>100</td>
</tr>
<tr>
<td>2</td>
<td>4-pentenoic acid</td>
<td>-</td>
<td>DIPEA</td>
<td>1.8</td>
<td>13</td>
</tr>
<tr>
<td>3</td>
<td>1-octene</td>
<td>I</td>
<td>-</td>
<td>7.8</td>
<td>51</td>
</tr>
<tr>
<td>4</td>
<td>methyl 4-pentanoate</td>
<td>I</td>
<td>DIPEA</td>
<td>3.6</td>
<td>43</td>
</tr>
<tr>
<td>5</td>
<td>methyl 4-pentanoate</td>
<td>I</td>
<td>AcOH</td>
<td>3.9</td>
<td>34</td>
</tr>
<tr>
<td>6</td>
<td>methyl 4-pentanoate</td>
<td>I</td>
<td>DIPEA/AcOH</td>
<td>3.5</td>
<td>27</td>
</tr>
</tbody>
</table>

a Reactions were performed in DCM, at 40°C, 24h; substrate/ligand/Rh(acac)(CO)₂ = 100:3:1; C_{(substrate)} = 0.2 M. b Additives were used as noted (C_{(AcOH)} = 0.2 M and C_{(DIPEA)} = 0.3 M).

DFT calculations

The mechanism of the regioselectivity-determining hydrometalation step of 4-pentenoate by Rh(I) was studied with DFT. The geometry optimizations were carried out with the Turbomole program20 coupled to the PQS Baker optimizer11 at the r1-DFT level23 using the BP8624 functional and the resolution-of-identity (ri) method. We used the SV(P) basis set14 for the geometry optimizations of all stationary points. All mimima (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 in Table 7 (the values are relative to structure A). Structures A-D are presented in Figure 4. Structure E represents an alternative catalyst-substrate complex – the DIMPPhos ligand coordinated in the σ fashion.

Table 7. DFT calculated energies of structures A-E (relative to structure A).

<table>
<thead>
<tr>
<th>Structure</th>
<th>ΔE [kJ mol⁻¹]</th>
<th>ΔE ZPE [kJ mol⁻¹]</th>
<th>ΔG298K [kJ mol⁻¹]</th>
<th>ΔH298K [kJ mol⁻¹]</th>
<th>ΔS298K [J mol⁻¹ K⁻¹]</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>B (TS)</td>
<td>8.6</td>
<td>7.5</td>
<td>11.2</td>
<td>5.3</td>
<td>-19.7</td>
</tr>
<tr>
<td>C</td>
<td>-40.5</td>
<td>-29.3</td>
<td>-27.8</td>
<td>-30.6</td>
<td>-9.5</td>
</tr>
<tr>
<td>D</td>
<td>17.2</td>
<td>15.0</td>
<td>15.8</td>
<td>15.0</td>
<td>-2.7</td>
</tr>
<tr>
<td>E</td>
<td>6.7</td>
<td>10.8</td>
<td>17.8</td>
<td>8.6</td>
<td>-30.7</td>
</tr>
</tbody>
</table>

X-ray crystal structure: [Rh(1-AcO)(CO)Cl]²⁺ TBA⁺

CCDC 787323 [C_{60}H_{32}ClN_{2}O_{6}P_{2}Rh][C_{6}H_{18}N][C_{7}H_{12}O_{2}] + disordered solvent, Fw = 1376.84[1], yellow block, 0.36 x 0.21 x 0.21 mm², orthorhombic, Pmma (no. 62), a = 19.7962(3), b = 24.1139(5), c = 17.2646(3) Å, V = 8241.5(3) Å³, Z = 4, D_{r} = 1.110 g/cm³[1], μ = 0.33 mm⁻¹[1] (μ⁺ deriv values do not contain the contribution of the disordered solvent molecules). 86928 Reflections were measured on a Nonius KappaCCD diffractometer with rotating anode (graphite monochromator, λ = 0.71073 Å) up to a resolution of (sin θ/λ)max = 0.61 Å⁻¹ at a temperature of 150(2) K. Intensity integration was performed with HKL2000.25 The SORTAV program26 was used for scaling. An absorption correction was not considered necessary. 8024 Reflections were unique (Rint = 0.072), of which 6097 were observed [I>2σ(I)]. The structure was solved with Direct Methods using the program SHELXS-97.27 The structure was refined with SHELXL-97 against F² of all reflections. Non hydrogen atoms were refined with anisotropic displacement parameters. Hydrogen atoms were introduced in calculated positions and refined with a riding model. The crystal structure contains solvent accessible voids (1602 Å³ / unit cell) filled with disordered solvent molecules. Their contribution to the structure factors was secured by back-Fourier transformation using the SQUEEZE routine of PLATON28 resulting in 488 electrons / unit cell). 447 Parameters were refined with no restraints. R1/wR2 [I > 2σ(I)]:
Chapter 2

0.0446 / 0.1129. R1/wR2 [all refl.]: 0.0630 / 0.1212. S = 1.051. Residual electron density between −0.41 and
0.63 e Å⁻³. Geometry calculations and checking for higher symmetry was performed with the PLATON
program.

2.5 Acknowledgments

We kindly acknowledge the NRSC-C for generous financial support, Dr. Wojciech Dzik and Prof. Bas de Bruin for assistance with DFT calculations, Dr. Martin Lutz for the crystallographic measurements, Dr. Tendai Gadzikwa for fruitful discussions and creative ideas, Dr. Rosalba Bellini and Dr. M. Pilar del Rio Varea for assistance with the high pressure and low temperature NMR experiments.

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13 CCDC 787323 contains the supplementary crystallographic data for this paper. These data can be
obtained free of charge from The Cambridge Crystallographic Data Centre via
www.ccdc.cam.ac.uk/data_request/cif.

14 For details see the experimental section.

15 (a) The relatively small phosphorous-hydride coupling constant (2JPH = 4.0Hz) measured at room
temperature suggests predomination of the ee isomer over the ea form, see: (a) van der Veen, L. A.;

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Remote Supramolecular Control of Catalyst Selectivity


In control experiments, we investigated the influence of acetate binding within the DIM pocket of the catalyst, as well as the effect of base (DIPEA) and carboxylic acid (acetic acid), on the hydroformylation of a non-binding substrate, methyl 4-pentenoate. In all cases, the influence on the selectivity, as compared with the reaction without additives, was negligible.

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


