Supramolecular Catalysis

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

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Dedicated to Professor Janusz Jurczak on the occasion of his 70th birthday

Immense progress in the field of transition-metal catalysis has been achieved over the past few decades, and the contributions of the ligands that are coordinated to the metals are now well understood.[1] Despite notable insights made into various reaction mechanisms, 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 that lead to the isomeric products are nearly identical in energy, or worse, if the pathway to 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.[2] Supramolecular ligands that form by self-assembly of 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, a great effort in catalyst development has been applied to the incorporation of cavitands that can bind guest molecules to an active site and promote reactions that are typically displayed by enzymes.[4] Remarkable examples of highly selective oxidation reactions catalyzed by metalloporphyrins, where hydrophobic interactions allow for substrate preorganization, have been developed by Breslow and co-workers.[5] However, simple hydrogen-bonding interactions between a substrate and the functional groups of a catalyst can also be used to greatly improve the selectivity of a reaction. This principle was elegantly demonstrated by Crabtree, Brudvig, and co-workers in a dimanganese catalyst for the highly selective functionalization of C–H bonds at sp^3-hybridized carbon atoms.[6] Recently, our research group showed that even a single hydrogen bond between a catalyst and a substrate leads to improved activities in cyclopropanation reactions,[7] and excellent enantioselectivity in the hydrogenation of the Roche ester precursor.[8] A similar supramolecular substrate preorganization 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 that operate predicatively. 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 noncovalent interactions that are more remote from the catalytic center. Herein we report a bisphosphine ligand based on an anion receptor backbone. As predicted, the ligand can be used in a 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 substrates with various anionic groups can be used. 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.

We anticipated that neutral anion receptors are excellent candidates for the design of substrate-directing motifs in supramolecular catalysts. The relatively strong and highly directional interactions of these receptors with anionic substrates[10] allow the predictable orientation of a reactive functionality close to a catalytic metal center. In this study, we fused a 7,7′-diamido-2,2′-diindolylmethane (DIM) scaffold—a tailor-made receptor[11] for carboxylate and phosphate anions—with two triphenylphosphine moieties to generate a 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.

The ligand DIMPhos (**1**) is prepared easily by hydrogenation of 7,7′-dinitro-2,2′-diindolomethane **2**[11] using H_2 and Pd/C and subsequent condensation with 4-(diphenylphosphino)benzoic acid by following a standard protocol,[12] which provided bisphospine **1** in an overall yield of 62% (Scheme 1).

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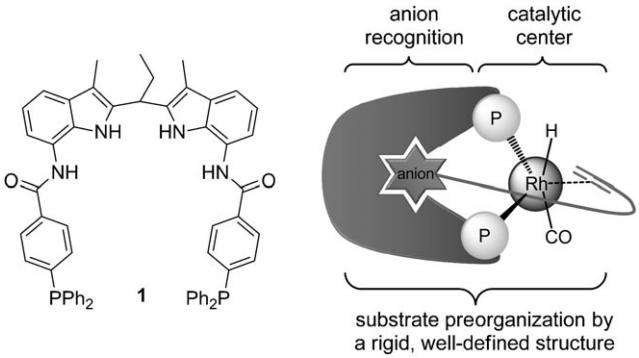
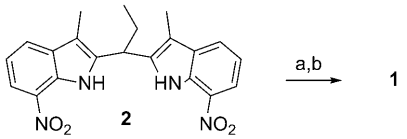


Figure 1. Structure of ligand **1** (left) and general concept of anionic substrate preorganization by a Rh catalyst that bears a ligand furnished with an anion-binding pocket (right).



Scheme 1. Synthesis of ligand **1**: a) H_2, Pd/C(10%), MeOH, RT; b) 4-(Ph_2P)PhCOOH, diisopropylcarbodiimide (DIC), 4-dimethylaminopyridine (DMAP), 4-pyrrolidinopyridine, CH_2Cl_2, RT.

Upon addition of $[RhCl(CO)_2]_2$ to a CH_2Cl_2 solution of **1**, which had an acetate ion bound in the DIM pocket, an Rh complex was formed with two P donors coordinated to the Rh center in a mutual trans orientation. This coordination geometry was further supported by the X-ray structure of TBA[Rh(**1**·AcO)(CO)Cl] (Figure 2; TBA = tetrabutylammonium).[13] Importantly, the acetate ion remains 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) and 3.006(3) Å, for the amide and indole N atoms, respectively). Importantly, the aliphatic

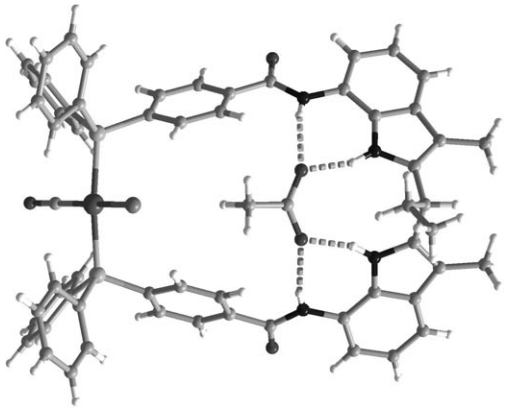


Figure 2. Crystal structure of the supramolecular complex [Rh(**1**·AcO)(CO)Cl]$^-$; TBA^+ counterion and disordered solvent molecules are omitted for clarity.

group of the anionic guest points towards the metal center, as is consistent with our design.

High-pressure (HP) NMR experiments show that a 1:1 mixture of ligand **1** and $[Rh(acac)(CO)_2]$ (acac = acetylacetonate) under hydroformylation conditions, 5 bar CO/H_2 (1:1), forms exclusively a mononuclear trigonal bipyramidal rhodium complex $[Rh(\mathbf{1})(CO)_2H]$.[14] Low-temperature NMR studies reveal that bisphosphine ligand **1** is coordinated predominantly in an equatorial–equatorial (ee) fashion. At room temperature, this complex is in fast equilibrium on the NMR timescale with the minor equatorial–apical (ea) isomer.[15] Indeed, high-pressure infrared (IR) spectra using either H_2/CO or D_2/CO (both 1:1) revealed four bands in the carbonyl region that correspond 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 $[Rh(\mathbf{1})(CO)_2H]$ takes less than 2 hours, even at room temperature. HP NMR experiments show that the coordination geometry around the Rh center does not change in the presence of carboxylate (acetate) or phosphate ions ($H_2PO_4^-$). Under these conditions, the signals of the NH groups are shifted towards lower fields in the ^1H NMR spectra ($\Delta\delta = 2.5$–3.1 ppm), thus signifying the formation of strong hydrogen bonds between the anion and the pocket.[11] The carbonyl bands in the HP IR spectra also show a small shift to lower wavenumbers ($\Delta\nu$ up to 5 cm^{-1}) upon anion binding, indicating an increased electron density at the phosphorus atoms.

The binding constants of carboxylate and phosphate anions in the DIM pocket of $[Rh(\mathbf{1})(CO)_2H]$ were determined from titration experiments carried out at 5 bar CO/H_2 (1:1) in CH_2Cl_2 by monitoring the chemical shift of various protons by using HP NMR spectroscopy. These titration studies reveal that only one anion is bound in the DIM receptor of $[Rh(\mathbf{1})(CO)_2H]$, and that the association constants for CH_3COO^- and $H_2PO_4^-$ are higher than 10^5 and around $10^{3.7}$, respectively. In contrast to these anionic species, non-deprotonated CH_3COOH and H_3PO_4, as well as their methyl and ethyl esters, are not bound in the pocket of ligand **1**.

Next, we applied ligand **1** in the rhodium-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, that is, from 3-butenoic to 8-nonenoic acid. Calculations show that 3-butenoate anion (C3-CO_2^-) is too small to bind in the pocket, while its double bond is coordinated to the metal center, but the 4-pentenoate anion (C4-CO_2^-) fits precisely, and the other substrates easily span the distance between metal and binding site. The neutral acids and methyl esters, that is, substrates that do not bind in the pocket, were used as control experiments. The linear/branched selectivity (l/b) determined by ^1H NMR spectroscopy is shown in Figure 3.[14] For the small substrates based on 3-butenoic acid, we hardly observe any difference between the anion and the acid and ester analogues, and the l/b ratio is in the expected range between 1.6 and 2.6. In contrast, the 4-pentenoate ion, which is the substrate that precisely spans the distance between the metal and the pocket, is hydroformylated with unprecedented selectivity for the linear aldehyde (l/b ratio of 40). If the

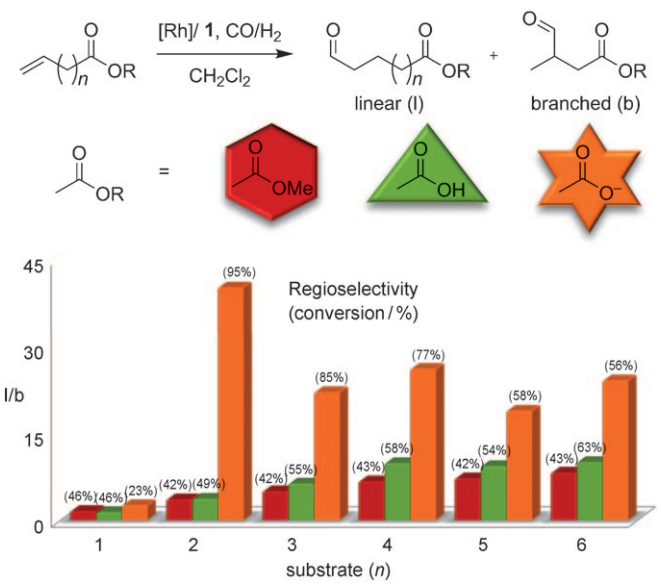
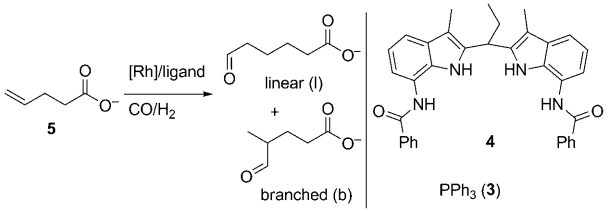


Figure 3. Hydroformylation of ω-unsaturated carboxylic acids and methyl esters. [Rh(acac)$(CO)_2$]/**1**/substrate = 1:3:100; c_0(substrate) = 0.2 M, 20 bar CO/H_2 (1:1), CH_2Cl_2, 40 °C, 24 h. *N*,*N*-diisopropylethylamine (DIPEA) was used as a base for anionic substrate generation (c_{DIPEA} = 0.3 M). Regioselectivity and conversion (%) were determined by analysis of the reaction mixture by ^{1}H NMR spectroscopy. No side reactions (isomerisation, hydrogenation, etc.) were observed.

reaction is carried out at room temperature (instead of 40 °C) the l/b ratio exceeds 50 (Table 1, entry 1). For the protonated or the methyl ester analogues, substrates of the same size that

Table 1: Hydroformylation of **5**.[a]



Entry	Ligand	Conversion [%]	Regioselectivity [l/b ratio]
1	**1**	95 (80)[b]	40 (> 50)[b]
2	**4**/**3** (1:2)	100	2.9
3[c]	**3**	100	3.1
4	–	13	1.8

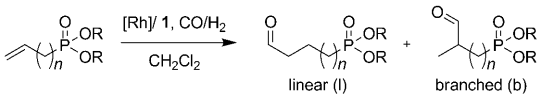
[a] [Rh(acac)$(CO)_2$]/**1**(**4** and/or **3**)/**5**/DIPEA = 1:3(3 and/or 6):100:150; c_0(**5**) = 0.2 M, 20 bar CO/H_2 (1:1), DCM, 40 °C, 24 h. Regioselectivity and conversion (%) were determined by ^{1}H NMR analysis of the reaction mixture. [b] Reaction at RT, 72 h. [c] The results for other studied acids (Figure 3 are similar to those (see the Supporting Information for details).

do not bind in the DIM pocket, typical low l/b values of around 3 are obtained, confirming the importance of the anion binding. Besides the higher selectivity, the conversion is also much higher when the substrate is bound in the pocket. This result suggests that the reaction barrier for formation of the linear aldehyde is lowered by the substrate-preorganizing 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, the 4-pentenoate ion (**5**) is hydroformylated with the typical selectivity displayed by catalysts based on triphenylphospine (**3**; Table 1, entries 2 and 3). In the absence of a phosphorus ligand, substrate **5** is hydroformylated with poor selectivity (l/b = 1.8) and low convrsion (Table 1, entry 4). Importantly, for non-anionic substrates, the addition of excess acetate ion that binds in the DIM pocket of [Rh(**1**)$(CO)_2$H] has no effect on the (low) regioselectivity.[17]

The substrates that are longer than the one that precisely fits between the metal and the binding site—5-hexenoate through 8-nonenoate anion—also experience an effect of binding in the DIM pocket. These substrates 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 the 4-pentenoate ion, which is the substrate that fits best in the catalytic pocket.

We extended the scope of substrates to alkenes functionalized with a phosphate group (Table 2). Again, we expected that 3-butenylphosphonate ion (C4-PO_3^{2-}) would be hydroformylated with the highest selectivity, as this substrate

Table 2: Hydroformylation of ω-unsaturated phosphonic acids and ethyl esters.[a]



Entry	Substrate [*n*]	Form (OR)	Conversion [%]	Regioselectivity [l/b ratio]
1	1	ester (OEt)	3	0.6
2	1	acid (OH)	–[b]	–
3	1	anion (O^-)	10 (69)[c]	– (1.6)[c]
4	2	ester (OEt)	12	4.0
5	2	acid (OH)	–[b]	–
6	2	anion (O^-)	100	> 40

[a] [Rh(acac)$(CO)_2$]/**1**/substrate = 1:3:100; c_0(substrate) = 0.2 M, 20 bar CO/H_2 (1:1), DCM, RT, 24 h, DIPEA used as a base for anionic substrate generation (c_{DIPEA} = 0.6 M). Regioselectivity and conversion (%) were determined by ^{1}H and ^{13}C NMR analysis of the reaction mixture. [b] Additional experiments with 1-octene showed that the catalyst is inactive under these strongly acidic conditions. [c] The conversion is too low at RT to determine the selectivity; values between parentheses are for the reaction at 40 °C.

exactly spans the distance between the binding site and the metal center. Indeed, this substrate is hydroformylated by [Rh(**1**)$(CO)_2$H] to form the linear aldehyde with excellent regioselectivity (l/b > 40). Again, the high selectivity and higher conversion are observed only when the anionic substrate is used (Table 2, entries 4–6). The shorter allyl-

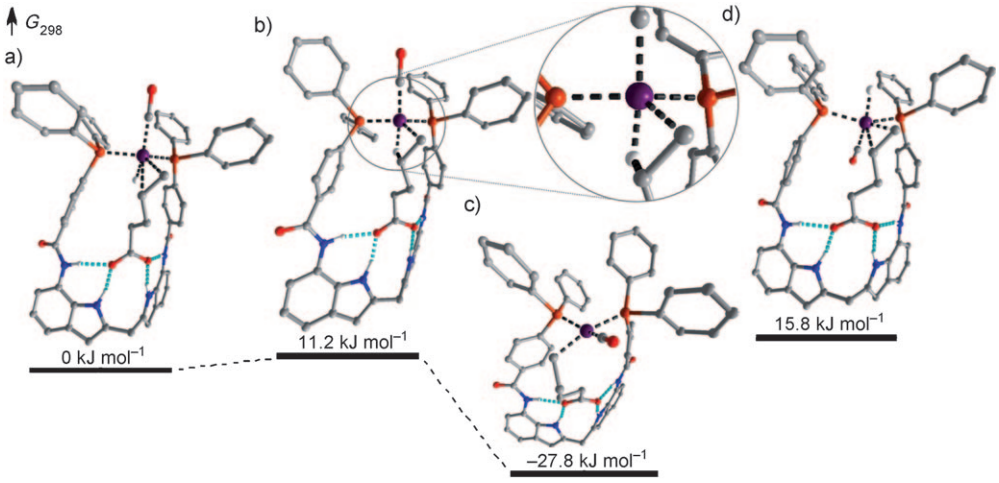


Figure 4. Calculated reaction pathway (DFT, BP86, SV(P)) of the regioselectivity-determining hydride-migration step in the hydroformylation of 4-pentenoate by Rh(**1**) catalyst; catalyst–substrate complex (a), transition state toward linear product (b) and linear alkyl Rh complex (c), and alternative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

phosphonate ion (C3-PO_3^{2-}) is hydroformylated with similar regioselectivity as the analogue that does not bind to the pocket (Table 2, entries 1 and 3).

To gain a deeper understanding of the origin of the high selectivity in the hydroformylation of anionic substrates, we studied the Rh(**1**) catalytic system with DFT calculations (BP86, SV(P)). Since, in the absence of isomerization, 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),[1c] this step was studied in detail. We first calculated several possible structures of the complex [RhH(CO)(**1**)]–(4-pentenoate), and found that the ee coordination geometry was favored for this complex. The energy-minimized structure shows that the carboxylate group of the substrate is strongly bound in the pocket by four hydrogen bonds ($d_{N-O} = 2.7$–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 arises as the carboxylate ion is anchored in the pocket, in addition severely restricting the movement of the coordinated double bond. However, the alkene 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 ($\Delta G^{\neq} = 11.2$ kJ mol^{-1}) is almost unperturbed (the Rh–H bond elongates by only 0.036 Å), with the alkene rotated only a little further out of the equatorial plane (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 carboxylate moiety being anchored within the pocket.[18] This result 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 modeled the conformer of the initial complex in which the carbonyl and hydride positions are inverted (Figure 4d), and which favors 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}), which is even higher than the transition state that leads to the linear product ($\Delta\Delta G^{\circ} = 4.6$ 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. Binding of the substrate in the pocket favors 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.

In summary, we have introduced DIMPhos (**1**), which is a new bidentate phosphorus ligand with an integral anion-recognition site. We have demonstrated that under hydroformylation conditions, well-defined Rh complexes are formed that strongly bind anionic substrate species. DFT calculations show that the 4-pentenoate ion exactly spans the distance between the rhodium center and the 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 ω-unsaturated carboxylic acids, that is, up to 8-nonenoic acid, and phosphonic acids, and thus provides 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 an advantage over functionalized mondentate ligands that the number of possible complexes that can be formed is significantly fewer, which may be important for the design of selective catalysts based on substrate orientation.[9] We are currently investigating optimization of the activity of this system, and are applying supramolecular ligands equipped with the anion binding pocket to other challenging transformations.

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[14] For details see the Supporting Information.

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[17] In control experiments, we investigated the influence of acetate ion 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 nonbinding substrate, methyl 4-pentenoate. In all cases, the influence on the selectivity, as compared with the reaction without additives, was negligible (see the Supporting Information).

[18] Despite 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.

