Supramolecular Catalysis

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A Supramolecular Catalyst for Regioselective Hydroformylation of Unsaturated Carboxylic Acids**

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Natural enzymes efficiently combine molecular recognition and catalysis in one functional assembly. Reactions within enzyme–substrate complexes have much higher rate constants than corresponding bimolecular reactions.[1] High degrees of regio- and stereoselectivity are achieved by orientation of the substrate and precise positioning of the reaction site in a favorable orientation relative to the catalytic center. Of particular importance for substrate binding by enzymes is the guanidine functional group of arginine. Over 70% of enzyme substrates and cofactors are anions, and the guanidinium group forms strong ion pairs with oxoanions, such as carboxylates and phosphates.[2] Through multiple noncovalent interactions within the active site, enzymes can achieve astonishing levels of substrate selectivity. This specificity, however, can also be a problem. Very often, enzymes have a narrow substrate specificity and lack the generality required for synthetic applications.

Homogeneous catalysis, especially with transition metals, is one of the key tools of modern synthetic chemistry. Traditionally, catalytic performance of an organometallic complex is tuned by variation of the steric bulk and electronic properties of the ligands. However, the emerging field of supramolecular catalysis seeks to produce efficient and selective catalysts by making use of specific molecular interactions and the principles of supramolecular chemistry.[3]

Many research groups have attempted to combine noncovalent substrate binding and transition-metal catalysis, thereby aiming at enzymelike behavior. However, only a few examples of successful catalysts showing selectivity and rate enhancement in synthetically useful transformations have been reported to date.[4,5] An early example came from Hayashi et al., who reported asymmetric hydrogenation of trisubstituted acrylic acids in the presence of a chiral (aminoalkyl)ferrocenylphosphine rhodium catalyst. The high enantioselectivity (greater than 97% *ee*) is ascribed mainly to the attractive interaction between the amino group on the ferrocenylphosphine ligand and the carboxyl group of the substrate.[6] Very prominent results were recently achieved in the design of oxidation catalysts. Breslow and co-workers prepared metalloporphyrin catalysts with attached cyclodextrin groups. Steroid derivatives were bound by hydrophobic interactions, and their regioselective hydroxylation was achieved.[7] Crabtree, Brudvig, and co-workers have recently reported a catalyst containing a dinuclear manganese core and a ligand based on Kemp's triacid. In this example, the carboxy group of the ligand can interact through hydrogen bonds with the carboxy group of the substrate, leading to specific substrate orientation and modified regioselectivity for oxidation.[8]

Reactions that build molecular skeletons belong to the most important in organic synthesis. Hydroformylation of alkenes represents an ideal example of an atom-economic[9] C–C bond-forming reaction and leads to products containing an aldehyde group, which is an ideal functionality for further synthetic transformations. At the same time, hydroformylation is one of the most important industrial processes relying on homogeneous catalysis.[10,11] Inspired by the selectivity of biological systems, we introduced the concept of a temporary substrate-bound catalyst-directing group. High regio- and stereoselectivity has been achieved in a number of catalytic transformations by equipping substrates with a covalently attached *ortho*-diphenylphosphinobenzoate group (*o*-dppb, Figure 1).[12] However, the requirement of a covalent ligand–substrate bond prevents the use of substoichiometric amounts of the ligand. Therefore, subsequent efforts have been directed towards the design of ligand moieties that can bind and orientate the substrate through noncovalent interactions.

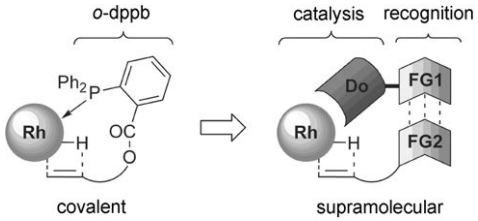

Figure 1. Concept of covalent and supramolecular catalyst-directing groups. Do = donor; FG1, 2 = complementary functional groups.

Herein, we report the synthesis of a new receptor-based phosphine ligand, which furnishes a highly reactive catalyst that leads to unusual regioselectivity in the rhodium-catalyzed hydroformylation of unsaturated carboxylic acids. Our strategy was to combine the structural features of phosphine ligands (catalyst binding unit) with a guanidinium-based recognition unit for carboxylic acids in one molecule.[13,14] The

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ligand architecture was designed employing molecular modeling. Thus, installation of the acylguanidinium functional group in the *meta* position with respect to the catalyst-binding phosphine unit should allow for two-point binding and thus conformational orientation of the substrate (Figure 2).

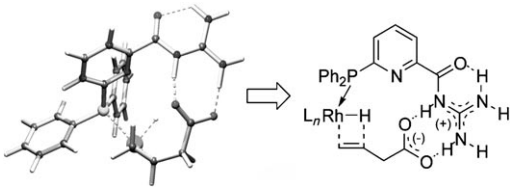
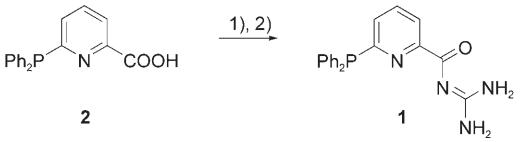


Figure 2. Catalyst design assisted by molecular modeling (Spartan Pro, molecular mechanics force field (MMFF); ligands not participating in the recognition are omitted for clarity) and hypothetical structure of the hydrometalation transition state.

Synthesis of the acylguanidine-functionalized phosphine ligand **1** (Scheme 1) was readily accomplished by coupling of the diphenylphosphinopyridine carboxylic acid **2**[15] with mono-Boc-protected guanidine and subsequent deprotection



Scheme 1. Synthesis of ligand **1**: 1) Boc-guanidine (Boc = *tert*-butoxycarbonyl), *N*-methylmorpholine, 1-benzotriazolyloxytris(dimethylamino)phosphonium hexafluorophosphate, DMF, RT (80%); 2) trifluoroacetic acid, RT, then Na_2CO_3, H_2O, CH_2Cl_2, 0°C (87%).

catalyzed by trifluoroacetic acid. After neutralization, ligand **1** precipitated as a dichloromethane adduct. X-ray diffraction analysis of the oxide of **1** confirmed the proposed conformation for the ligand (Figure 3).[16]

As a first test system, hydroformylation of vinylacetic acid **3** was studied (Figure 4). The industrially applied standard $[Rh(CO)_2acac]/PPh_3$ (**6**) system displayed rather low activity ($TOF = 30\ h^{-1}$, left graph, acac = acetylacetonate), and a typical regioselectivity (**4**/**5** = 1.3, right graph) was observed. Under the same conditions, the wide-bite-angle bisphosphine

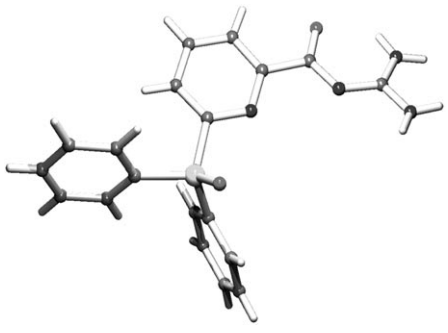


Figure 3. Crystal structure of ligand **1** oxide.

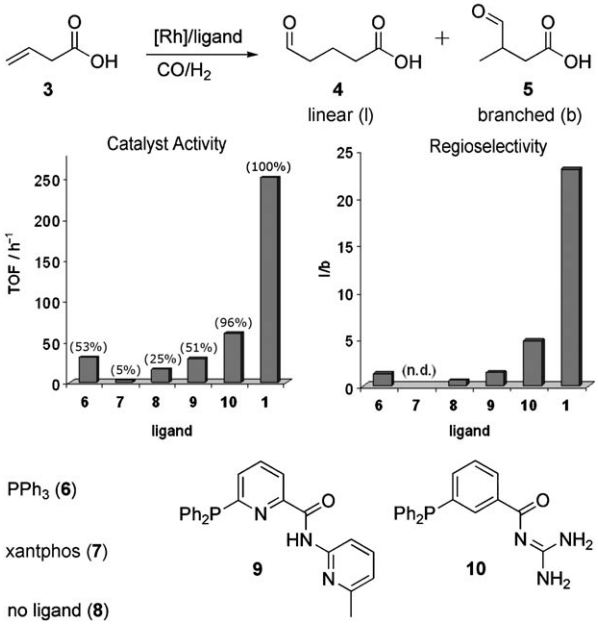


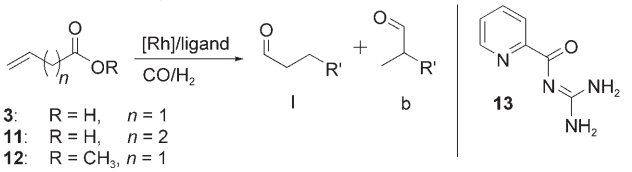
Figure 4. Hydroformylation of **3**; $[Rh(CO)_2acac]$/ligand/**3** = 1:10:200 (1:5:200 for ligand **7**); c_0(**3**) = 0.2 M, THF (2 mL), 10 bar CO/H_2 (1:1), 40°C, 4 h. TOF (mole aldehyde per mole catalyst per hour) determined from the gas consumption curve. Conversion (%) and regioselectivity (**4**/**5** ratio) was determined by ^1H NMR spectroscopic analysis of the reaction mixture. n.d. = not determined.

ligand xantphos (4,5-bis(diphenylphosphino)-9,9-dimethylxanthene, **7**)[17] showed very low activity (5% conversion).[18] When the reaction was conducted without ligand (**8**, unmodified rhodium catalyst), moderate activity and selectivity for the formation of the branched regioisomer (**4**/**5** = 0.59) was observed. With ligands **9** and **10**, which may allow for supramolecular substrate–ligand interactions, only minor improvements were seen. However, the pyridylacylguanidinium system **1** yielded an outstanding catalyst with excellent activity ($TOF = 250\ h^{-1}$) and regioselectivity (l/b > 23). Under optimized conditions, the linear aldehyde **4** was obtained in excellent yield (95%) and high regioselectivity (l/b>98:2).[19]

Obviously, the rhodium catalyst derived from ligand **1** is unique in that it yields both a significant rate enhancement (ca. eightfold compared to **6**) and high regioselectivity for hydroformylation. Both effects, however, are typical features of substrate-directed reactions.[20] Thus, to clarify the role of ligand **1** in this hydroformylation reaction, a number of control experiments were undertaken.

As can be seen from Table 1, γ,δ-unsaturated acids, such as pent-4-enoic acid (**11**), are hydroformylated much slower and with worse selectivities than β,γ-unsaturated acids (entry 2, Table 1). Hence, the distance between the carboxylic acid functionality and the reactive alkene group matters. Furthermore, the combination of acylguanidine **13** and triphenylphosphine **6** does not give the desired activity and selectivity (entry 3, Table 1). This finding suggests that the molecular-recognition unit and the catalytic unit must be an integral part of the same molecule to achieve the interesting catalytic activity and selectivity. Further evidence came from

Table 1: Control experiments.[a]



3: R = H, $n = 1$
11: R = H, $n = 2$
12: R = CH_3, $n = 1$

Entry	Ligand	Substrate	Conversion [%]	Regioselectivity (l/b ratio)	TOF [h^{-1}]
1	**1**	**3**	100	23	250
2	**1**	**11**	73	3.6	49
3	**6**/**13** (1:1)	**3**	20	1.5	12
4[b]	**1**	**12**	50	1.1	29
5	**1**	**12**/AcOH (1:1)	58	1.4	34

[a] $[Rh(CO)_2acac]$/ligand/substrate = 1:10:200, c_0(substrate) = 0.2 M, THF (2 mL), 10 bar CO/H_2 (1:1), 40 °C, 4 h, R′ = $(CH_2)_nCOOR$; [b] Suspension (ligand **1** is practically insoluble in the reaction medium without a carboxylic acid); all other runs were clear solutions.

the fact that methyl ester **12**, which lacks the complementary functionality, reacted slowly and with low selectivity (entries 4 and 5, Table 1).

If the interaction between the carboxylic acid and guanidine groups is important for catalyst performance, the addition of another carboxylic acid to the reaction medium should lead to competition for the recognition site. Indeed, when acetic or benzoic acid was added to the reaction mixture (1–5 equivalents relative to **3**), we observed inhibition and decreased selectivity (see the Supporting Information).[21] A mechanism in which the recognition event precedes the catalytic reaction implies that for high substrate concentrations, saturation should be achieved. Hydroformylation of **3** was therefore conducted at various substrate concentrations (0.05–0.4 M). Indeed, substrate saturation and even inhibition was observed (see the Supporting Information).

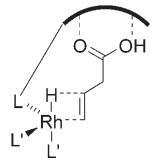
On the basis of these results, we propose a mechanism consisting of two consecutive steps analogous to enzyme catalysis:

a) binding of the substrate to the ligand(s) of the rhodium phosphine complex;
b) directed catalytic reaction within the supramolecular substrate–catalyst complex.

In this case, the rate- and selectivity-determining hydrometalation step[22,23] becomes intramolecular in nature, which accounts for both the observed rate acceleration and the unusual regioselectivity (Scheme 2).

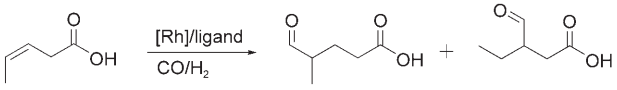
If this hypothesis is correct, it would be interesting to study the reactivity of internal alkenes, which under conventional hydroformylation conditions give nearly equimolar amounts of regioisomeric aldehydes. Thus, we investigated the hydroformylation of (*Z*)-pent-3-enoic acid (**14**).

Using triphenylphosphine (**6**) as a ligand, hydroformylation proceeded sluggishly, and formation of **16** over **15** was only slightly preferred (Table 2, entry 1). Using ligand **1**, unprecedented high selectivity in the hydroformylation of an internal alkene was achieved.[24] Branched aldehyde **15** was observed as the major reaction product together with an increased conversion (20→80%) and significantly lower amounts of side products (9→2.5%). The yield of isolated



Scheme 2. Proposed substrate binding in the rate- and selectivity-determining hydrometalation step. The bold curve represents the substrate binding site of ligand **1**.

Table 2: Hydroformylation of internal alkene **14**.[a]



Entry	Ligand	Conversion [%]	Regioselectivity (**15**/**16**)
1	**6**	20[b]	1:1.7
2	**1**	80.5[c]	11:1

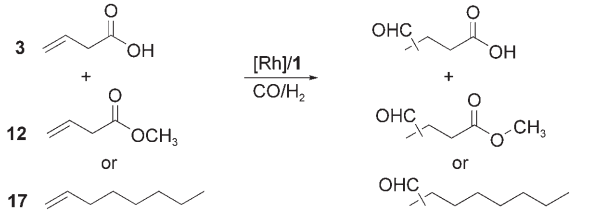
[a] $[Rh(CO)_2(acac)]$/ligand/**14** = 1:10:50, c_0(**14**) = 0.2 M, THF (4 mL), 6 bar CO/H_2 (1:1), RT, 68 h. [b] Yield determined by NMR spectroscopy: **15** (4%), **16** (7%). [c] Yield determined by NMR spectroscopy: **15** (71.5%), **16** (6.5%).

aldehydes **15** and **16** was 83% (based on conversion, **15**/**16** = 11:1). Interestingly, the preference for formyl addition at the 4-position is the same as that observed for substrate **3**, which is in agreement with a directed catalytic process.

Furthermore, using a catalyst containing a molecular-recognition unit should provide a possibility for substrate differentiation, which would be difficult to achieve with classical catalysts. Thus, we carried out a competition experiment in which a 1:1 mixture of terminal olefins of similar reactivity was hydroformylated in the presence of $[Rh(CO)_2acac]$/**1** catalyst (Table 3).

The ratio of products at low conversion indicates that the substrate selectivity was at least 9.7 for **3**/**12** and 7.3 for **3**/**17**. Thus, our supramolecular catalyst can carry out a chemical transformation selectively on a specific target in a mixture of chemical substances. It was also possible to achieve complete

Table 3: Hydroformylation of a 1:1 mixture of two substrates.[a]

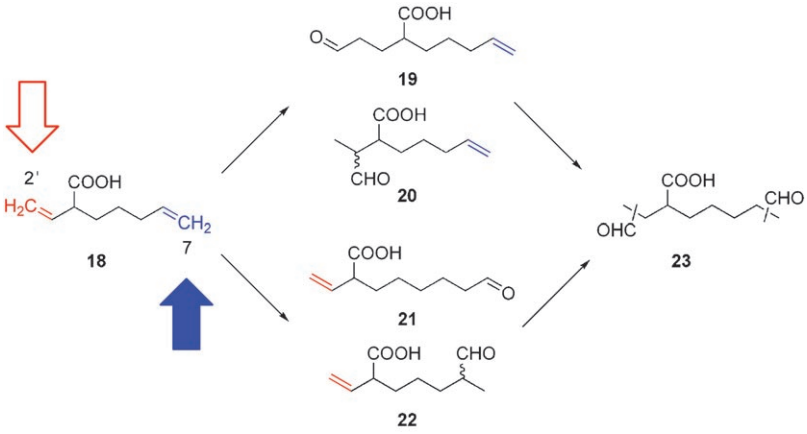


Entry	*t* [h]	Substrates	Conversion **3**/(**12** or **17**) [%]	Regioselectivity (l/b ratio) **3**, (**12** or **17**)
1	12	**3**, **12**	58:6	50, n.d.
2	20	**3**, **12**	100:28	50, 2.3
3	6	**3**, **17**	22:<3	50, n.d.
4	15.5	**3**, **17**	100:25	50, 3

[a] $[Rh(CO)_2(acac)]$/**1**/**3**/**12**(**17**) = 1:20:200:200, c_0(**3**) = c_0(**12** or **17**) = 0.13 M, THF (6 mL), 4 bar CO/H_2 (1:1), RT. n.d. = not determined.

conversion of substrate **3**; the conversion of the noncomplementary substrate was then as low as 28% (**12**) and 25% (**17**).

This unusual substrate selectivity might be used synthetically—a substrate molecule bearing several potential reaction sites could be selectively functionalized with the help of the directing effect. Substrate **18**, which bears two alkene functional groups at different distances from the acid moiety, was prepared and subjected to hydroformylation (Scheme 3). Using triphenylphosphine (**6**) as a ligand, rates of hydroformylation of the two alkene functionalities are very similar (see the Supporting Information). Regardless of when the reaction was stopped, we obtained an intractable mixture of several mono- and dihydroformylated products (**19**–**23**).



Scheme 3. Hydroformylation of **18**; [$Rh(CO)_2$acac]/ligand/**18** = 1:10:150; c_0(**18**) = 0.2 M, THF (8 mL), 4 bar CO/H_2 (1:1), 25 °C.

Using ligand **1**, the "blue" (remote) alkene functional group is hydroformylated with similar rate and selectivity (l/b) as with ligand **6**. Conversely, reaction of the "red" (β,γ-) alkene group is ten times faster (compared with **6**) and highly regioselective, which again is indicative of a directed process (see Figure 5, which displays ^{1}H NMR spectra of the reaction mixture taken at different reaction times and highlights the reaction-site selectivity). On a preparative scale, aldehyde **19** could be selectively prepared in high yield (80% as determined by NMR spectroscopy and 75% isolated product).

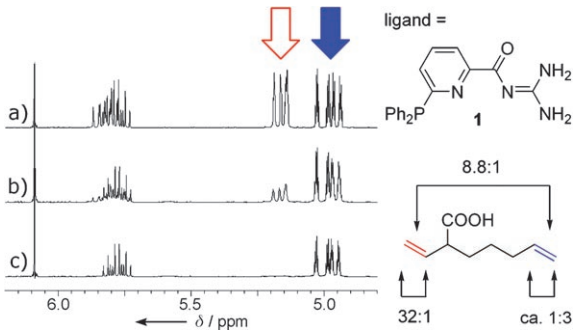


Figure 5. Hydroformylation of **18** using ligand **1**. ^{1}H NMR spectra (400 MHz, $CDCl_3$) of the double-bond region: a) 0 h, b) 4 h, c) 8.5 h. Signals from H2′ and H7 are marked with red and blue arrows, respectively. Reaction-site selectivity and regioselectivity was determined by ^{1}H NMR spectroscopic analysis of the reaction mixture.

In conclusion, we have developed a new supramolecular ligand system combining a guanidine receptor unit for carboxylates and a triarylphosphine group as the donor for a transition metal. For the first time we have shown that supramolecular interaction between ligand and substrate gives synthetically useful levels of selectivity and activity in a transition-metal catalyzed reaction. Our ligand proved to give superior activity, predictable regiocontrol, substrate selectivity, and reaction-site selectivity in the rhodium-catalyzed hydroformylation of β,γ-unsaturated acids. Future efforts will be devoted to gaining a deeper insight into the nature of the supramolecular interactions within our system. Furthermore, we propose that this general biomimetic supramolecular strategy can be applied to other catalytic reactions and classes of substrates. Additionally, a study of our catalyst may also contribute to the understanding of enzyme catalysis.

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[18] Using harsher conditions (80 °C, 20 h), complete conversion could be also achieved for the xantphos ligand (TOF = 50 h^{-1}, **4**/**5** = 15.5), although the yield (as determined by NMR spectroscopy) of aldehyde products (**4** + **5**) drops to 90% (the main byproduct is butyric acid (6%), probably formed by isomerization (→α,β) and hydrogenation).
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