Supramolecular Catalysis

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A Supramolecular Catalyst for the Decarboxylative Hydroformylation of α,β-Unsaturated Carboxylic Acids**

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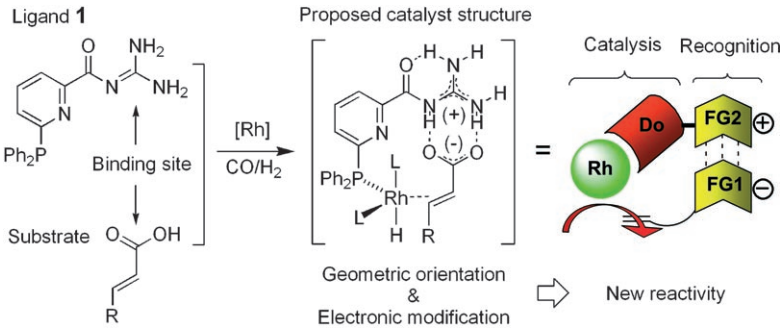
The design of new catalyst systems that allow for rapid, selective, and clean chemical transformations is of immense scientific importance.[1] Recently, a new biomimetic strategy for selectivity control in transition-metal catalysis has emerged. Hydrogen-bonding interactions between a substrate and metal-bound ligands have been used to position a substrate precisely relative to the catalytic metal center. Selectivity control has been achieved in hydroformylation of β,γ-unsaturated acids[2] and oxygenation of saturated C–H bond in some cyclohexylacetic acids.[3] In these examples, the binding site in the substrate molecule (carboxylic function) is remote from the reaction site. Accordingly the supramolecular effect is believed to be purely geometric.[4] Correspondingly, enzymes can achieve astonishing levels of selectivity through multiple noncovalent interactions with the substrate regions distant from the reaction site. However, this geometric preorganization alone is insufficient to explain the enormous acceleration in reaction rate observed for some enzymes.[5] Moreover, this rate enhancement has been suggested to be the result of transition-state stabilization,[6] which is mainly achieved by direct interaction with the substrate reaction site (hydrogen bonding, ion–ion and ion–dipole interactions) and change of the electron distribution in the reacting system (e.g. by substrate protonation/deprotonation).[7,8]

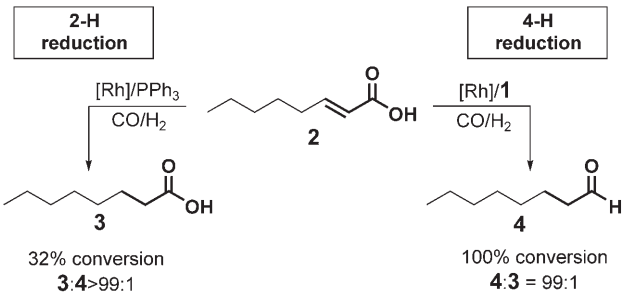


Scheme 1. Structure of ligand **1**, substrate (α,β-unsaturated acid), proposed structure of the active catalyst complex (L = **1** or CO), and generalized concept of the substrate activation by the formation of the receptor–substrate complex (Do = donor, FG1,2 = complementary functional groups).

In continuation of our efforts to develop efficient supramolecular catalysts, we attempted to alter the substrate reactivity by direct supramolecular interaction with the substrate reaction site.[9] We anticipated that the flexibility of our system (receptor-based monophosphine ligands assembled on a metal center, Scheme 1) should also allow the catalyst to accommodate α,β-unsaturated acids as substrates. In this class of substrates, the reaction site (alkene function) is in direct connection to the binding site (carboxylic function). Besides the geometric orientation, the formation of a receptor–substrate complex is presumed to modify the electron distribution of the bound substrate and may lead to unusual chemical reactivity (Scheme 1).

Aldehydes are key functional groups in synthetic chemistry and new reactions leading to the introduction of this functionality are highly desirable. Herein, we present a new methodology for the synthesis of aliphatic aldehydes by catalytic transformation of the corresponding α,β-unsaturated acids.[10] The α,β-unsaturated carboxylic acid function is a frequently encountered structural motif in many natural products and synthetic molecules. However, to the best of our knowledge there is currently no general catalytic method for the reduction of α,β-unsaturated acids to saturated aldehydes.

First, we examined the reaction of oct-2-enoic acid (**2**) under hydroformylation conditions (10 bar CO/H_2) using the standard $[Rh(CO)_2(acac)]/PPh_3$ catalyst (Scheme 2). Moder-



Scheme 2. Reduction of oct-2-enoic acid (**2**). Conditions: $[Rh(CO)_2(acac)]$/ligand/**2** = 1:10:200, c_0(**2**) = 0.2 M, CH_2Cl_2 (4 mL), 10 bar CO/H_2 (1:1), 25 °C, 24 h.

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ate activity for the hydrogenation of the carbon–carbon double bond of **2** was observed, whereas no aldehyde product could be detected. Competing hydrogenation presents the major limitation during hydroformylation of α,β-unsaturated aldehydes, ketones, or esters.[11,12] However, changing to ligand **1** completely switched the course of the reaction. Surprisingly, oct-2-enoic acid (**2**) was selectively transformed to octanal (**4**) (Scheme 2).

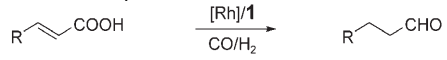
Then, we investigated the influence of various reaction parameters in more detail (Table 1). Under relatively mild conditions (10 bar CO/H_2, 25 °C; Table 1, entry 1), complete conversion of **2** had occurred after 24 hours and nearly perfect selectivity for the formation of **4** (94% yield; GC) was observed.[13] Reactions conducted in THF or toluene also proceeded selectively, but the catalyst activity was lower (Table 1, entries 2 and 3). When a lower ligand loading was used, a small amount of the undesired hydrogenation product **3** appeared (Table 1, entry 4). The optimal ratio of rhodium to ligand to substrate was identified to be $[Rh(CO)_2(acac)]$/**1**/**2** = 1:10:200. Increasing the synthesis gas pressure led to an increased reaction rate, but this was accompanied by the formation of the undesired "over-hydrogenated" alcohol product **5**. In one experiment the partial pressure of hydrogen was further increased and octanol **5** was obtained in 23.5% yield after 48 hours (Table 1, entry 7).

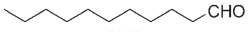
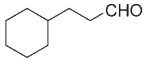
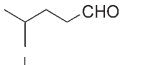
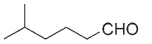
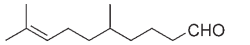
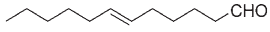
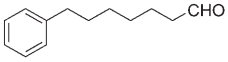
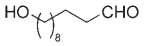
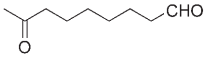
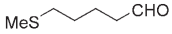
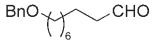
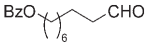
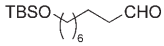
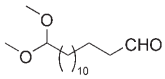
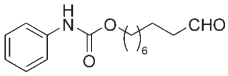
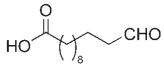
With the optimal reaction conditions in hand, we focused on the functional group compatibility and generality of this reduction process for various 3-substituted alk-2-enoic acids. In general, a slightly higher synthesis gas pressure (13 bar) was applied to make sure that full conversion was reached after 24 hours.

Thus, linear unfunctionalized alk-2-enoic acids (Table 2, entry 1) as well as substrates with an alkyl substitution in 4- and 5-positions (Table 2, entries 2, 3, 4) gave excellent results. Interestingly, other internal double bonds included in the substrate molecule are not affected at all (Table 2, entries 5 and 6). A wide range of functional groups including hydroxy, ketone, dialkylsulfide, ether, ester, and acetal functions (Table 2, entries 7–14) were found to be compatible with the optimized reaction conditions. Slightly lower reactivity under standard conditions was observed for substrates equipped with carbamate (Table 2, entry 15) and carboxylate (Table 2, entry 16) functions, but also in these cases practical yields of aldehyde could be obtained. A number of standard protecting groups for alcohols and aldehydes (Table 2, entries 11–14) displayed complete compatibility. However, more importantly, unprotected alcohol, oxo, or carboxylic acid functions were also tolerated (Table 2, entries 8, 9, 16).

To clarify the role of ligand **1** in the course of this reaction, a number of control experiments were undertaken. Unmodified rhodium catalyst (Table 3, entry 2)

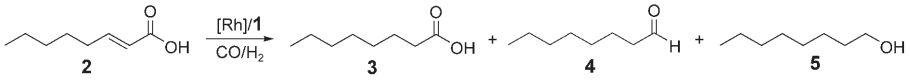
Table 2: Reduction of α,β-unsaturated acids.[a]



Entry	Product	Yield [%][b]
1		91
2		74, 97[c]
3		47, 98[c]
4		92[c]
5		94
6		97
7		94
8		87
9		91
10		74
11		75
12		96
13		95
14		68[d]
15[e]		77
16		50[f]

[a] Conditions: $[Rh(CO)_2(acac)]$/**1**/substrate = 1:10:200, c_0(substrate) = 0.2 M, CH_2Cl_2 (8 mL), 13 bar CO/H_2 (1:1), 25 °C, 24 h; Bn = benzyl, Bz = benzoyl, TBS = *tert*-butyldimethylsilyl. [b] Yields of isolated products. [c] Yield determined by NMR spectroscopy. [d] 93% conversion. [e] $[Rh(CO)_2(acac)]$/**1**/substrate = 1:10:100, 20 bar CO/H_2 (1:1), c_0(substrate) = 0.1 M, 20 h. [f] 75% conversion (low solubility of the substrate in CH_2Cl_2).

Table 1: Influence of reaction conditions on the reduction of **2**.[a]

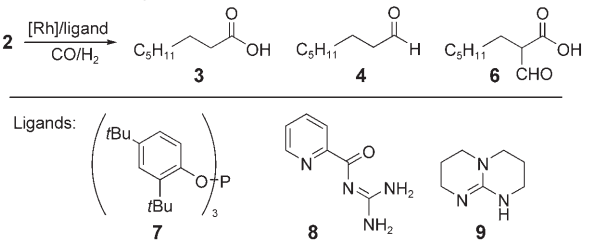


2 **3** **4** **5**

Entry	Solvent	Pressure (CO/H_2)	$[Rh(CO)_2(acac)]$/**1**/**2**	t [h]	**3** [%][b]	**4** [%][c]	**5** [%][c]	TOF [h^{-1}][d]
1	CH_2Cl_2	5/5	1:10:200	24	<1	94	0.3	8.8
2[e]	THF	5/5	1:10:200	20	<1	17	–	1.9
3[e]	toluene	5/5	1:10:200	20	<1	14	–	1.9
4	CH_2Cl_2	5/5	1:5:200	20.5	4.5	91	0.8	9.2
5	CH_2Cl_2	7.5/7.5	1:10:200	23	<1	91.5	2.8	15.8
6	CH_2Cl_2	10/10	1:10:200	18.7	<1	89	3.1	23.6
7	CH_2Cl_2	5/35	1:10:200	48	<1	67	23.5	42

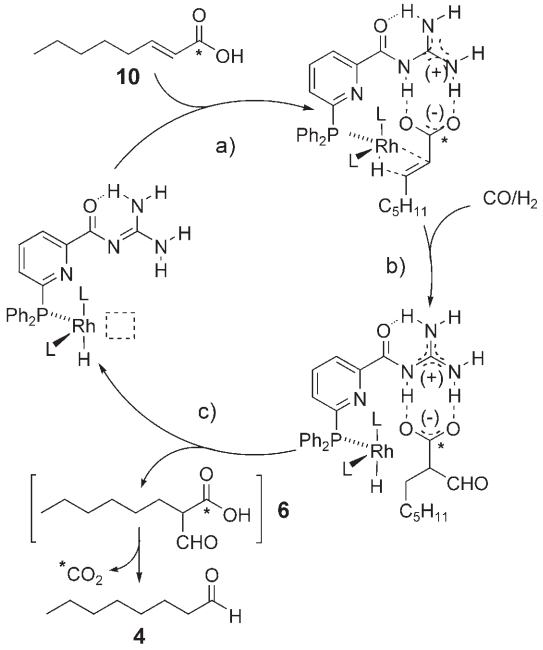
[a] Conditions: c_0(**2**) = 0.2 M, solvent (4 or 8 mL), 25 °C. [b] Determined by NMR spectroscopy. [c] Determined by GC analysis. [d] Turnover frequency (mol **4** per mol catalyst) h^{-1} determined by GC analysis. [e] Reaction performed at 40 °C.

Table 3: Control experiments.[a]



Entry	Ligand	Conversion [%]	Yield [%]
1	**1**	100	**3**(<1), **4**(94)
2	no ligand	<1	**3**(<1)
3	PPh_3	32	**3**(32)
4[b]	PPh_3	33	**3**(26), **4**(3), **6**(4)
5	**7**	68	**3**(33), **4**(23), **6**(12)
6[c]	PPh_3/**8** (1:1)	8	**3**(8)
7	PPh_3/Et_3N (1:1)	42	**3**(42)
8	PPh_3/**9** (1:1)	<1	**3**(<1)
9	PPh_3/Et_3N (1:20)	25	**3**(8), **4**(17)

[a] Conditions: $[Rh(CO)_2(acac)]$/ligand/**2** = 1:10:200, c_0(**2**) = 0.2 M, CH_2Cl_2 (4 mL), 10 bar CO/H_2 (1:1), 25 °C, 24 h. [b] THF(4 mL), 40 bar CO/H_2 (1:1). [c] Formation of a suspension was observed.



Scheme 3. The catalytic cycle proposed for decarboxylative hydroformylation catalyzed by $[Rh(CO)_2(acac)]$/**1**. For reaction with isotopically labeled substrate, asterisks indicate the ^{13}C-labeled positions.

showed very low activity (< 1% conversion). Triphenylphosphine (Table 3, entries 3 and 4) gave mainly the hydrogenation product **3** under the conditions optimal for ligand **1** as well as under typical hydroformylation conditions (THF, 40 bar).[14] Using a rhodium catalyst derived from the bulky monophosphite ligand **7** did not lead to better results and a mixture of products **3**, **4**, and **6** was obtained (Table 3, entry 5). Furthermore, the combination of triphenylphosphine and either acylguanidine **8**, or 1 equivalent of Et_3N did not lead to better selectivity, whereas the more basic guanidine **9** inhibited the reaction completely (Table 3, entries 6, 7, 8). With an excess (20 equiv) of Et_3N, a mixture of **3** and the desired product **4** was obtained albeit with low conversion (Table 3, entry 9). This result suggests that the deprotonation of the substrate during the course of the reaction may be important, but that the guanidine and the catalytic unit must be an integral part of the same molecule to achieve the observed high activity and selectivity.

Further evidence came from the fact that the absence of one of the complementary functionalities hampers the reaction.[15] These results suggest that the interaction of the guanidine with the carboxylic acid function is crucial for the catalyst performance. Furthermore, the reaction was carried out at various substrate concentrations (0.03–0.4 M), which revealed that the kinetics obeys the Michaelis–Menten equation ($K_M = 0.03$ M and $V_{max} = 8.2\ h^{-1}$).[15]

Finally, the isotopically labeled substrate [1-^{13}C]-oct-2-enoic acid **10** was subjected to the reaction conditions. Interestingly, aldehyde product **4** did not have any isotopic label (Scheme 3).

On the basis of the above results and the generally accepted mechanism of hydroformylation catalyzed by rhodium triarylphosphine complexes we propose a mechanism consisting of three consecutive steps, analogous to enzyme catalysis (Scheme 3):

a) binding of the substrate to the ligand(s) of the rhodium complex (accompanied by substrate deprotonation), which activates the substrate;
b) α-selective hydroformylation within the supramolecular substrate–catalyst complex;[16]
c) decarboxylation of α-formyl intermediate **6** to give aldehyde **4**.[17]

Hence, the reaction proceeds as a decarboxylative hydroformylation.

In conclusion, we have developed a catalytic reduction of α,β-unsaturated carboxylic acid to aldehydes. This previously unknown, environmentally benign reaction proceeds under mild conditions, tolerates a variety of functional groups and liberates CO_2 as the only stoichiometric by-product. Following the mechanism of this reaction the carboxy function is used as a temporary directing group for the introduction of the aldehyde function in the α-position and is subsequently removed (traceless) by decarboxylation. For the first time we have shown that supramolecular interaction between ligand and substrate may completely change the course of a catalytic reaction and give new reactivity that has not been observed before. Further studies of this basic principle may reveal important factors contributing to enzyme catalysis and may also provide useful synthetic tools for selective chemical transformations.

Experimental Section

General procedure for the decarboxylative hydroformylation of α,β-unsaturated carboxylic acids (Table 2): The hydroformylation solution was prepared by charging a Schlenk flask with $[Rh(CO)_2(acac)]$

(2.1 mg, 0.008 mmol), ligand **1** (31.2 mg, 0.08 mmol), and CH_2Cl_2 (8 mL) under argon. Then, the substrate (1.6 mmol) was added, and the mixture was stirred for 5 min under argon. The solution was transferred to the autoclave with a syringe under an argon atmosphere. The autoclave was purged three times with synthesis gas CO/H_2 (1:1). The reaction was conducted under 13 bar CO/H_2 (1:1) at 25 °C for 24 h in a Premex stainless steel autoclave Medimex (100 mL) equipped with a glass liner and containing a magnetic stirring bar (1000 rpm). Then, the reaction mixture was concentrated in vacuo and the crude product was purified by using flash column chromatography on silica gel to give the aldehyde product.

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Keywords: enzyme mimics · homogeneous catalysis · hydroformylation · molecular recognition · reduction

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[13] Similar results (TOF = 16 h^{-1}, **4**:**3** = 98:2) were obtained also at higher temperature (60 °C/10 bar). For the influence of the substrate concentration, see Supporting Information.
[14] For the mechanism of hydrogenation of 3-buten-2-on using the same catalyst see: E. B. Walczuk, P. C. J. Kamer, P. W. N. M. van Leeuwen, *Angew. Chem.* **2003**, *115*, 4813 – 4817; *Angew. Chem. Int. Ed.* **2003**, *42*, 4665 – 4669.
[15] For details see the Supporting Information.
[16] The perfect α-selectivity of the hydroformylation may partly be caused by the favorable orientation of the substrate within the supramolecular assembly; however, a directing effect of the carboxylate functionality may also be significant.
[17] The proposed α-formyl carboxylic acid intermediate **6** has never been observed during reactions catalyzed by **1**, but it was identified in reaction mixtures when PPh_3 or **7** were used as ligands (Table 3). This result suggests that also the decarboxylation reaction may be catalyzed by the ligand **1**. For an example of decarboxylation mediated by hydrogen-bonding interactions see: J. J. Almrud, G. J. Poelarends, W. H. Johnson, Jr., H. Serrano, M. L. Hackert, C. P. Whitman, *Biochemistry* **2005**, *44*, 14818 – 14827.

