DOI: 10.1002/adsc.200505174

Bidentate Ligands by Self-Assembly through Hydrogen Bonding: A General Room Temperature/Ambient Pressure Regioselective Hydroformylation of Terminal Alkenes

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Received: April 24, 2005; Accepted: June 3, 2005

Abstract: The 6-DPPon (**1**)/rhodium catalyst allows for the first time a room temperature/ambient pressure regioselective hydroformylation of terminal alkenes with low catalyst loadings in good activity. The generality of this catalyst under these conditions was demonstrated for a wide range of structurally diverse alkenes equipped with many important functional groups. Thus, this practical and highly selective hydroformylation protocol, which omits the need for special pressure equipment, should find wide application in organic synthesis.

Keywords: aldehydes; hydroformylation; regioselectivity; self-assembly; synthetic methods

Hydroformylation of alkenes refers to the addition of hydrogen and carbon monoxide across the carbon-carbon double bond of an alkene.[1] A new carbon-carbon bond is formed with concomitant introduction of the aldehyde function which is synthetically most useful for further skeleton expansions.[2] Hence, the hydroformylation meets all criteria of an atom economic reaction.[3] It is thus not surprising that it has developed as one of the industrially most important processes relying on homogeneous catalysis.[4] On the other hand and despite its synthetic attractiveness, the reaction has not been of frequent use in organic synthesis.[2] One of the reasons for this discrepancy is certainly associated with the difficulty to control all aspects of selectivity in the course of this catalytic carbon-carbon bond forming reaction.[5] Another reason may be that the reaction has usually to be run in a pressure range which requires special pressure equipment, not available in most organic synthesis laboratories.

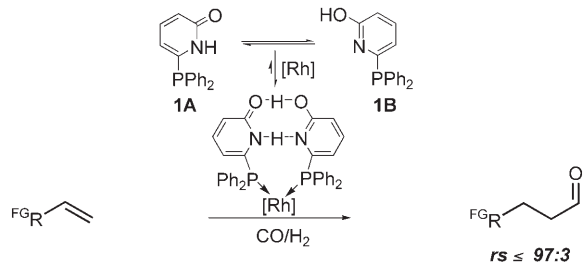
Hence, a hydroformylation which is both selective and proceeds at room temperature under atmospheric pressure, thus omitting the use of autoclaves, would be most desirable for use in organic synthesis. We herein report on the first regioselective hydroformylation of a wide range of functionalized terminal alkenes, which proceeds at room temperature employing atmospheric pressure of synthesis gas with low catalyst loadings.

We recently showed that 6-(diphenylphosphino)pyridin-2(1*H*)-one (6-DPPon; **1**) self-assembles through hydrogen bonding of the pyridone **1A** with its hydroxypyridine tautomer **1B** in the coordination sphere of a late transition metal center such as platinum(II) and rhodium(I) and displays the typical behavior of a bidentate ligand.[6] Rhodium(I) complexes derived from this ligand have proven to be very active and highly regioselective catalysts for the rhodium-catalyzed hydroformylation of *n*-alkenes (Scheme 1).[6,7]

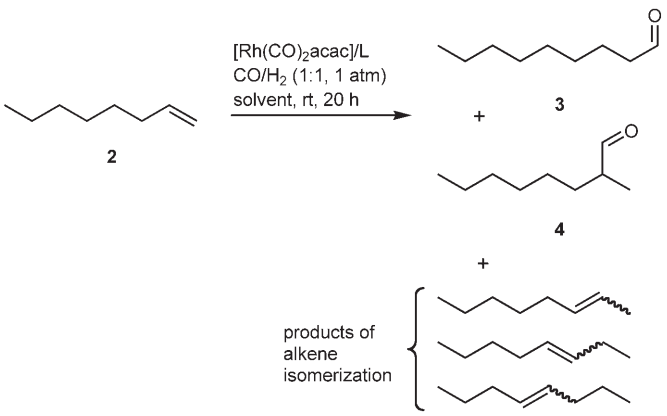
The observation that this catalyst was significantly more active than known bidentate phosphine ligands developed for linear selective hydroformylations induced us to develop a hydroformylation reaction which could be run at room temperature and ambient pressure of synthesis gas.

To identify optimal reaction parameters initial experiments focused on the hydroformylation of the unfunctionalized substrate 1-octene. Expected reaction products were the aldehydes **3** and **4** and internal octenes which could result from an undesired alkene isomerization (Scheme 2).

Hydroformylation was performed in a Schlenk tube which was equipped with a cross-type magnetic stirring



Scheme 1.

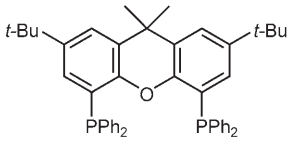


Scheme 2.

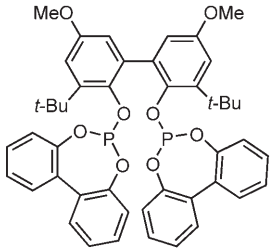
bar and was connected to a synthesis gas reservoir (see Experimental Section). In a first series of hydroformylation experiments (Table 1) we were looking for the best catalyst with respect to activity, chemo- and regioselectivitiy for the hydroformylation of terminal alkenes at room temperature and ambient pressure of synthesis gas. The *t*-Bu-XANTPHOS/rhodium catalyst,[8] which is known as one of the best catalysts for linear regioselective hydroformylation of terminal alkenes, showed a reasonable conversion of 68% during 20 h concomitant with excellent regioselectivity under these conditions (Table 1, entry 1). However, significant alkene isomerization was observed which limits the synthetic utility severely in the case of valuable functionalized alkenic substrates. Diphosphite/rhodium catalysts such as those derived from BIPHEPHOS are alternative catalysts for the regioselective hydroformylation of terminal alkenes.[9] These systems have frequently been used for linear selective hydroformylation of terminal alkenes.[10] When the BIPHEPHOS rhodium catalyst was subjected to our room temperature/ambient pressure conditions a complete consumption of 1-octene was noted. However, the majority of product was a mixture of internal octenes (Table 1, entry 2). On the other hand, when the monodentate triphenylphosphine was used as the modifying ligand, alkene isomerization was largely suppressed but regioselectivity was low (Table 1, entry 3). It is known that a large triphenylphosphine excess in the course of the rhodium-catalyzed hydroformylation can lead to a significantly higher regioselectivity.[11] We made a similar observation under our reaction conditions (Table 1, entry 4). Unfortunately, the increase of regioselectivity with increasing triphenylphosphine ligand loadings occurs at the expense of catalyst activity. The best catalyst for room temperature/ambient pressure hydroformylation of 1-octene was in fact the rhodium/6-DPPon (**1**) system. Complete conversion of 1-octene towards *n*-nonanal in perfect regioselectivity ($>99:1$) was observed (Table 1, entry 5).

In order to identify the optimal reaction parameters, four different solvent systems were monitored. Although in all cases regioselectivities were high, optimal catalyst activity was observed in THF. The low conversion observed in diethyl ether may be subscribed to the low solubility of the catalyst in this solvent. The order of reactivity in toluene and THF reflects the differences in CO solubility.[12]

Table 1. Identification of the optimal catalyst for linear selective hydroformylation of 1-octene (**2**) at room temperature and one atmosphere pressure of synthesis gas.



t-Bu-XANTPHOS



BIPHEPHOS

Entry[a]	Ligand	Rh:L:**2**	Conversion [%][b]	Isomerization [%][c]	**3**:**4**[b]
1	*t*-Bu-XANTPHOS	1:3:150	68	26	>99:1
2	BIPHEPHOS	1:3:150	99	54	>99:1
3	PPh_3	1:6:150	69	4	87:13
4	PPh_3	1:50:150	18	1	95:5
5	**6-DPPon (1)**	**1:6:150**	**99**	**8**	**>99:1**

[a] Conditions: [$Rh(CO)_2acac$]/Ligand/1-octene (Rh:L:**2**), 1 atm CO/H_2 (1:1), solvent [c_0(1-octene) = 0.97 M; C_M = 6.5 mM], 22 °C, 20 h.
[b] Determined by GC analysis.
[c] Isomerization to internal alkenes, determined by GC analysis.

Table 2. Solvent dependence of the linear selective hydroformylation of 1-octene (**2**) with rhodium/6-DPPon (**1**) at room temperature and atmospheric pressure of synthesis gas.

Entry[a]	Solvent	Conversion [%][b]	Isomerization [%][c]	**3**:**4**[b]
1	THF	99	6	>99:1
2	Toluene	19	2	>99:1
3	CH_2Cl_2	45	2.8	>99:1
4	Et_2O	0.4	0.3	>99:1

[a] Conditions: [Rh(CO)$_2$acac]/6-DPPon (**1**)/1-octene (1:5:150), 1 atm CO/H_2 (1:1), solvent [c_0(1-octene) = 0.97 M; C_M = 6.5 mM], 22 °C, 20 h.
[b] Determined by GC analysis.
[c] Isomerization to internal alkenes, determined by GC analysis.

Table 3. Determination of the optimal rhodium:ligand:substrate ratio (Rh:**1**:**2**) for the linear selective hydroformylation of 1-octene (**2**) with rhodium/6-DPPon (**1**) at room temperature and ambient pressure of synthesis gas.

Entry[a]	Rh:**1**:**2**	c_{Rh} [mM]	Conversion [%][b]	Isomerization [%][c]	**3**:**4**[b]
1	1:2:150	6.5	99	24	96:4
2	1:5:150	6.5	99	6	>99:1
3	1:10:150	6.5	72	6	>99:1
4	1:15:150	6.5	51	5	>99:1
5	1:5:100	9.7	92	6	>99:1
6	1:5:150	6.5	99	6	>99:1
7	1:5:200	4.8	95	7	>99:1
8	1:5:250	3.9	94	7	>99:1

[a] Conditions: 1 atm CO/H_2 (1:1), THF [c_0(1-octene) = 0.97 M], 22 °C, 20 h.
[b] Determined by GC analysis.
[c] Isomerization to internal alkenes, determined by GC analysis.

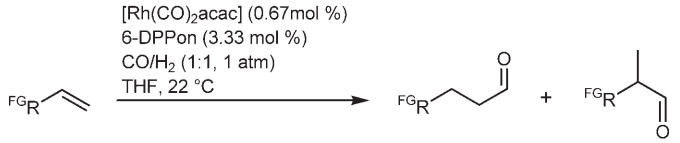
Next, experiments were undertaken to identify the optimal rhodium to ligand to substrate ratio. Table 3 summarizes some of these experiments. Thus, from entries 1–4 it is obvious that a metal to ligand ratio of 1:5 gives optimal conversion, low isomerization and high regioselectivity. Lower ligand loadings favor the undesired alkene isomerization and higher ligand loadings result in reduced catalyst activity. As the optimal catalyst to substrate ratio 1:150 was selected (entry 6, Table 3). In this case quantitative conversion was reached after 20 h of reaction time. Even though entries 7 and 8 of Table 3 clearly show that even lower catalyst loadings may be sufficient, the 1:150 ratio (0.67 mol % of catalyst) proved most general for a wide range of alkenic substrates (*vide infra*).

With optimal hydroformylation conditions in hand we focused on the functional group compatibility and generality of this process. Our results are summarized in Table 4.

Thus, linear unfunctionalized alkenes (entries 1 and 2) as well as terminal alkenes with α-branching gave excellent results. However, a quaternary carbon atom next to the reacting alkene function decreased the reaction rate. Similar observations were made for a tertiary allyl ether and a related acetal (entries 11 and 10). Arene substituents which are remote of the reaction center do not interfere with hydroformylation selectivity. However, the closer the phenyl substituent moves to the reacting alkene unit, the lower becomes the regioselectivity in favor of the linear isomer (entries 5–7). For styrene hydroformylation the branched isomer is usually formed in high selectivity which is substrate-inherent due to electronic reasons and the ability to pass a η^3-benzyl type coordination mode.[13,14] Although synthetically not useful, the 23:77 ratio observed for styrene hydroformylation with the rhodium/6-DPPon (**1**) system is indicative for the bidentate nature of the ligand system. This can easily be shown by changing the solvent from THF to methanol. In this case the hydrogen bonding backbone of the 6-DPPon ligand is disrupted and the 6-DPPon thus should behave as a monodentate ligand comparable to triphenylphosphine.[6] In fact, under these conditions (Table 3, entry 8) the room temperature/ambient pressure hydroformylation provided the branched aldehyde **4** selectively (96:4 in methanol) which is comparable to the triphenylphosphine result.[14]

A wide range of functional groups was investigated and found to be compatible with this room temperature/ambient pressure regioselective hydroformylation of terminal alkenes. Among them were ethers (entries

Table 4. Results of room temperature/ambient pressure hydroformylation of functionalized terminal alkenes with the rhodium/6-DPPon (**1**) catalyst.



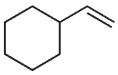
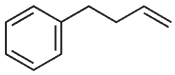
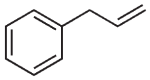
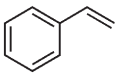
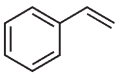
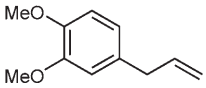
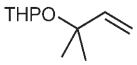
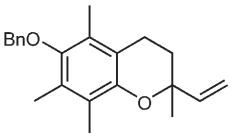
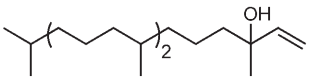
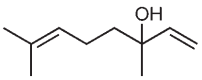
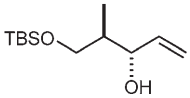
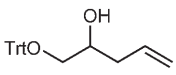
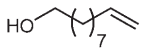
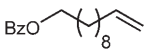
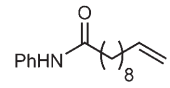
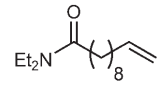
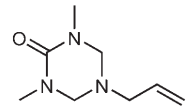
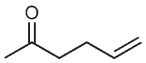
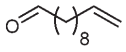
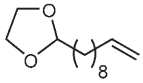
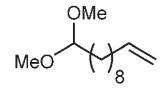
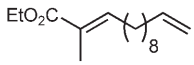
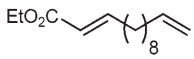
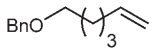
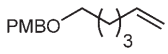
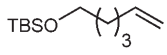
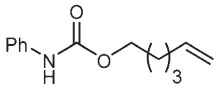
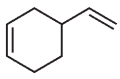
Entry[a]	Substrate	**3**:**4**[b]	Isomerization [%][c]	Time [h]	Yield [%]
1		99:1	5	20	quant.[d]
2		97:3	10	20	85[d]
3		>99:1	–	20	84[d]
4		>99:1	–	44	91[e]
5		96:4	<2	20	85[d]
6		91:9	<4	20	90[d]
7		23:77	–	20	quant.[d]
8	 solvent: MeOH	4:96	–	37	quant.[d]
9		90:10	<5	20	98[d]
10		>99:1	–	90	89[d]
11		99:1	–	63	90[f]
12		99:1	–	20	quant.[d, g]
13		99:1	–	20	quant.[d, g]
14		95:5	–	44	90[d, g]
15		99:1	<3	20	95[f]
16		96:4	5	20	98[d]
17		96:4	5	20	97[d]

Table 4 (cont.)

Entry[a]	Substrate	3:4[b]	Isomerization [%][c]	Time [h]	Yield [%]
18		99:1	5	20	65[e]
19		99:1	5	20	36[e]
20		92:8	5	20	82[d]
21		99:1	5	20	88[e]
22		99:1	<4	20	quant.[d]
23		97:3	5	20	98[d]
24		97:3	5	20	quant.[d]
25		97:3	5	20	97[d]
26		91:9	9	85	88[d, h]
27		97:3	5	20	99[d]
28		98:2	5	20	quant.[d]
29		96:4	5	20	97[d]
30		98:2	4	20	98[d]
31		99:1	–	20	95[d]

[a] Conditions: [Rh(CO)$_2$acac]/6-DPPon(**1**)/alkene (1:5:150), 1 atm CO/H$_2$ (1:1), THF [c_0(alkene) = 0.97 M; C_M = 6.5 mM], 22 °C.
[b] Determined by GC analysis.
[c] Isomerization to internal alkenes, determined by NMR analysis.
[d] Isolated yield after bulb-to-bulb distillation.
[e] Conversion.
[f] Isolated yield after chromatographic work-up.
[g] Isolated as lactols.

9, 11, 14, 15, 27, 28, 29), acetals (entries 10, 23, 24), ketones and aldehydes (entries 21, 22), esters (entries 17, 25, 26) and amides (entries 18, 19). A number of standard protecting groups for alcohols (entries 9, 10, 11, 14, 15, 17, 27, 28, 29, 30), aldehydes (entries 23, 24) and amines (entry 20) proved completely compatible with these hydroformylation conditions. Importantly, functional groups which themselves can be involved in hydrogen bonding such as free alcohol functions (entries 12–16), secondary amides (entry 18) and a carbamate

(entry 30) did not disturb the ligand's hydrogen bonding system as reflected in the high regioselectivity found for these systems. The chemoselectivity profile of the rhodium/6-DPPon (**1**) catalyst allows the regioselective hydroformylation of a terminal alkene in the presence of a 1,2-disubstituted alkene function (entry 31). However, if the internal alkene is part of an α,β-unsaturated ester a competing hydrogenation reaction is observed which leads after prolonged reaction time to the product arising from a tandem hydroformylation-hydrogenation reaction (entry 26). On the other hand, a trisubstituted enoate function is neither hydrogenated nor hydroformylated under these hydroformylation conditions (entry 25).

In summary, the rhodium/6-DPPon (**1**) catalyst allows for the first time a room temperature/ambient pressure regioselective hydroformylation of terminal alkenes with low catalyst loadings in good activity. The generality of this catalyst under these conditions was demonstrated for a wide range of structurally diverse alkenes equipped with many important functional groups. Thus, this practical and highly selective hydroformylation protocol, which omits the need for special pressure equipment, should find wide application in organic synthesis.

Experimental Section

General Procedure for the Room Temperature/ Ambient Pressure (RTAP) Hydroformylation

A Schlenk tube (10 to 15 mL volume) connected to the *RTAP hydroformylation apparatus* (see Figure 1) was loaded with [$Rh(CO)_2$acac] (2.5 mg, 9.7 μmol) and 6-DPPon (**1**) (13.5 mg, 48.4 μmol) under an atmosphere of argon. Then THF (1.5 mL) and after 5 min the alkene (1.45 mmol) were added.

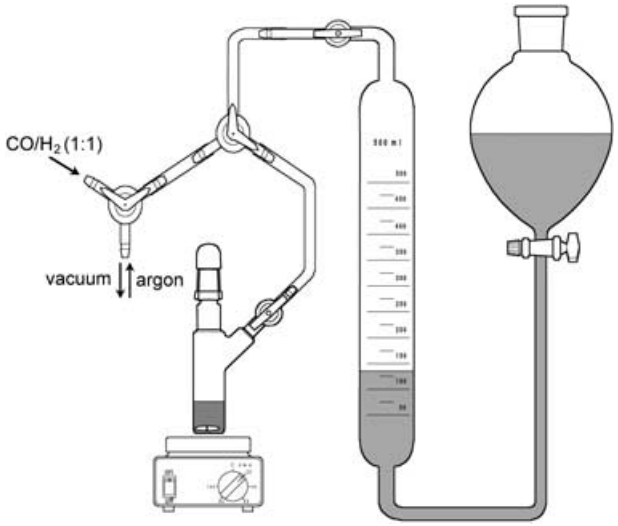


Figure 1. RTAP hydroformylation apparatus.

The reaction mixture was saturated with synthesis gas applying three cycles of careful evacuation and refilling with synthesis gas [CO/H_2 (1:1)]. The solution was magnetically stirred employing a cross-type stirring bar for 20 h [22 °C, approx. 1 bar CO/H_2 (1:1)]. Reaction progress (conversion) can be monitored by following the gas consumption. After full conversion (in most cases after 20 h) the solution was concentrated and the resulting crude product was purified by bulb-to-bulb distillation.

Caution: Synthesis gas is toxic and explosive, all operations should be performed in a well-ventilated fume hood!

Acknowledgements

This work was supported by the Fonds der Chemischen Industrie, the Alfried Krupp Award for young university teachers of the Krupp foundation (to BB) and BASF AG.

References and Notes

[1] O. Roelen, Chemische Verwertungsgesellschaft mbH, Oberhausen, *German Patent DE* 849,548, **1938/1952**; O. Roelen, Chemische Verwertungsgesellschaft mbH, Oberhausen, *U. S. Patent* 2,327,066, **1943**; *Chem. Abstr.* **1944**, *38*, 5501.

[2] a) B. Breit, W. Seiche, *Synthesis* **2001**, 1–36; b) I. Ojima, C.-Y. Tsai, M. Tzamarioudaki, D. Bonafoux, *Org. React.* **2000**, *56*, 1–354.

[3] a) B. M. Trost, *Science* **1991**, *254*, 1471–1477; b) B. M. Trost, *Angew. Chem.* **1995**, *107*, 285–307; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 259–281.

[4] K. Weissermel, H.-J. Arpe, *Industrial Organic Chemistry*; Wiley-VCH, Weinheim, **2003**, pp. 127–141.

[5] B. Breit, *Acc. Chem. Res.* **2003**, *36*, 264–275.

[6] B. Breit, W. Seiche, *J. Am. Chem. Soc.* **2003**, *125*, 6608–6609.

[7] B. Breit, W. Seiche, *Angew. Chem.* **2005**, *117*, 1666–1669; *Angew. Chem. Int. Ed.* **2005**, *44*, 1640–1643.

[8] a) XANTPHOS: M. Kranenbourg, Y. E. M. van der Burgt, P. C. J. Kamer, P. W. N. M. van Leeuwen, K. Goubitz, J. Fraanje, *Organometallics* **1995**, *14*, 3081–3089; b) *t*-Bu-XANTPHOS: L. A. van derVeen, P. C. J. Kamer, P. W. N. M. van Leeuwen, *Organometallics* **1999**, *18*, 4765–4777.

[9] E. Billig, A. G. Abatjoglou, D. R. Bryant, (UCC), *US Patent* 4,769,498, **1988**; *Chem. Abstr.* **1989**, *111*, 117287.

[10] a) G. D. Cuny, S. L. Buchwald, *J. Am. Chem. Soc.* **1993**, *115*, 2066–2068; b) G. D. Cuny, S. L. Buchwald, *Synlett* **1995**, 519–522; c) I. Ojima, D. M. Iula, M. Tzamarioudaki, *Tetrahedron Lett.* **1998**, *39*, 4599–4602; d) I. Ojima, M. Tzamarioudaki, M. Eguchi, *J. Org. Chem.* **1995**, *60*, 7078–7079.

[11] P. Cavalieri d'Oro, L. Raimondi, G. Pagani, G. Montrasi, G. Gregorio, A. Andreetta, *Chim. Ind.* **1980**, *62*, 572–579.

[12] M. P. Magee, H.-Q. Li, O. Morgan, W. H. Hersh, *Dalton Trans.* **2004**, 387–394.

[13] a) M. Tanaka, Y. Watanabe, T. Mitsudo, Y. Takegami, *Bull. Chem. Soc. Jpn.* **1974**, *74,* 1698–1703; b) C. O'Connor, *J. Inorg. Nucl. Chem.* **1970**, *32*, 2299–2302.
[14] The hydroformylation of styrene with the rhodium/triphenylphosphine catalyst at 20 bar syngas pressure (CO/H_2 1:1) at 25 °C, gave a 96:4 ratio of branched (**4**) to linear (**3**) aldehyde: B. Breit, R. Winde, K. Harms, *J. Chem. Soc. Perkin Trans. 1* **1997**, 2681–2682.

