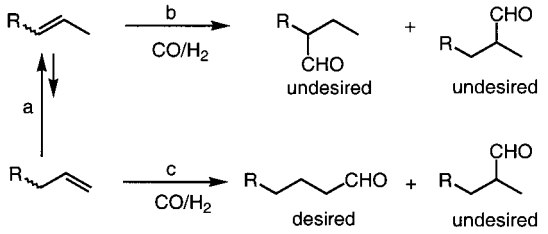
Highly Selective Catalyst Systems for the Hydroformylation of Internal Olefins to Linear Aldehydes**

Holger Klein, Ralf Jackstell, Klaus-Diether Wiese, Cornelia Borgmann, and Matthias Beller*

Dedicated to Professor Manfred Michalik on the occasion of his 60th birthday

The rhodium-catalyzed hydroformylation of aliphatic olefins to give linear aldehydes constitutes the most important homogeneously catalyzed process in industry today in terms of volume produced.[1] More than seven million tons of various aldehydes and alcohols are produced in this way each year. The hydroformylation of propene is especially important for the production of *n*-butyraldehyde, used as a valuable starting material for 2-ethylhexanol, which is currently the most important plasticizer alcohol in use. Recently there has been an increasing interest in the production of alternative plasticizer alcohols due to environmental concern about current products.[2] For economic reasons internal olefins or mixtures of internal and terminal olefins are the starting materials of choice for new plasticizer alcohols, yet peferably unbranched alcohols are the desired products due to better physical properties of the resulting plasticizers. However, the selective hydroformylation of internal olefins to give linear aldehydes (and subsequently linear alcohols) is difficult (Scheme 1). To obtain linear aldehydes from internal olefins



Scheme 1. Selective hydroformylation of internal olefins to give linear aldehydes: a) Isomerizaton, b) hydroformylation of internal olefin, c) hydroformylation of terminal olefin.

the catalyst has to perform a fast isomerization between the internal and terminal olefin (Scheme 1: reaction a). Unfortunately the thermodynamic equilibrium mixture contains in general less than 5% of the terminal olefin (for this reason isomerization should be avoided if terminal olefins are used as starting material). In addition the hydroformylation of the terminal olefin (Scheme 1, reaction c) must occur many times faster (and with high *n* selectivity) than that of the internal olefin (Scheme 1, reaction b).

To date only a limited number of rhodium catalysts[3] with sterically hindered phosphites[4] have been shown to be suitable for this purpose. Owing to the limited thermal stability and the ease of hydrolysis of these ligands there is considerable interest in new hydroformylation catalysts for the selective conversion of internal olefins.[5] Clearly phosphanes would offer advantages in terms of stability compared to phosphite ligands.[6] Regarding phosphane catalyst systems there has been only one recent development, which was described by van Leeuwen and co-workers, where modified xanthene ligands were used for the hydroformylation of 2- and 4-octene.[7] With these ligands linear:branched (*n*:*i*) ratios up to 90:10 and catalyst turnover frequencies (TOF)[8] of 112 h^{-1} were achieved for the hydroformylation of 2-octene.

Herein we report the development of new rhodium catalyst systems that enable the hydroformylation of different terminal and internal olefins in excellent selectivities, which represents a substantial improvement in efficiency of this industrially important reaction.

While studying the homogeneous and biphasic[9] hydroformylation of 1- and 2-pentene in the presence of phosphane-modified cobalt catalysts,[10] we became interested in similar reactions with more active rhodium catalysts. Among the various phosphanes tested for this reaction 2,2′-bis(diphenylphosphanylmethyl)-1,1′-binaphthyl (NAPHOS,[11] a structural variation of the 2,2′-bis(diphenylphosphanylmethyl)biphenyl (BISBI) ligand), which resembles the backbone of the sterically demanding phosphites, gave the best results (Table 1).

Table 1. Hydroformylation of 1- and 2-pentene with NAPHOS.[a]

Entry	Olefin	*p* [bar]	*T* [°C]	Yield [b] [%]	*n*:*i*	TOF [h^{-1}]
1	1-pentene	10	120	76	99:1	475
2	1-pentene	50	120	88	97:3	550
3	2-pentene	10	120	22	89:11	138
4	2-pentene	50	120	7	55:45	44

[a] Reaction conditions: olefin (70.0 mmol; 40 mL solution), [Rh(acac)-$(CO)_2$] (0.01 mol%; 20.7 ppm Rh), NAPHOS:Rh = 5:1, t = 16 h. [b] No significant amounts (>1%) of other products apart from isomerized olefin were detected.

As expected the rhodium-catalyzed hydroformylation of the terminal olefin proceeds in the presence of NAPHOS in good yields (76–88%) and excellent selectivities (*n*:*i* = 97:3–99:1). However, much to our surprise NAPHOS also gives a highly selective (*n*:*i* = 89:11) catalyst system for the reaction of 2-pentene at a low CO/H_2 pressure (10 bar). Although the yield (22%) is modest after 16 h (TOF = 138 h^{-1}),[12] it is important to note that this is only the second known phosphane that allows a selective synthesis of linear aldehydes from internal olefins. The even lower yield at 50 bar, can be explained by the fact that the isomerization step, which is necessary for the formation of the linear aldehyde from an internal olefin, is faster at a lower CO pressure.

In view of this promising result, we were interested in the synthesis of new substituted NAPHOS derivatives, especially

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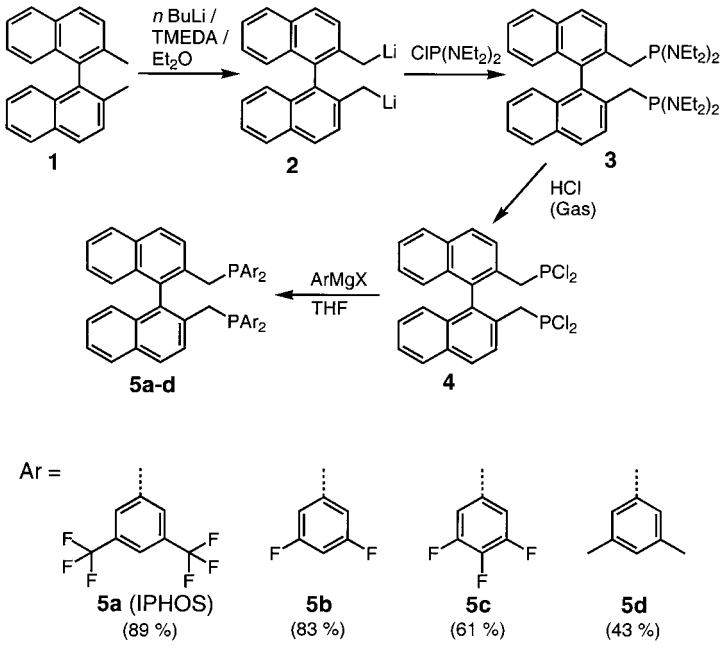
those with electron-withdrawing substituents on the aryl rings. After considerable experimentation we developed a simple and general synthesis for NAPHOS derivatives, which can be performed without problems on a multigram scale.[13] 2,2′-Dimethyl-1,1′-binaphthyl (**1**) is lithiated[14] with 2.5 equivalents of *n*-butyllithium to give the double lithiated derivative **2** (Scheme 2). Reaction of **2** with chlorobis(diethylamino)phosphane[15] in *n*-hexane at −70 °C yields 2,2′-bis[bis(diethylamino)phosphanylmethyl]-1,1′-binaphthyl (**3**), which is converted directly to 2,2′-bis(dichlorophosphanylmethyl)-1,1′-binaphthyl (**4**) with gaseous hydrogen chloride in 44% overall yield from **1**.



Scheme 2. Synthesis of substituted NAPHOS derivatives. The yield of the final step of **4** → **5** is given in parentheses below the Ar groups of **5a–d**.

Reaction of the new central building block **4** with Grignard reagents provides an efficient synthesis of a number of new NAPHOS derivatives. As shown in Scheme 2 mainly fluorinated ligands were synthesized due to the electron-withdrawing nature of the substituents. In general such electron-deficient substituents in aryl diphosphanes (with large bite angles) have a positive effect on the activity and the linear:branched selectivity of hydroformylation catalysts in case of primary olefins.[16] This can be explained by a preference for the diequatorial over the equatorial–apical binding mode of the ligand.[17]

The best yields in the Grignard coupling were obtained with 3,5-bis(trifluoromethyl)-1-bromobenzene and 1-bromo-3,5-difluorobenzene (89 and 83%, respectively), while 1-bromo-3,4,5-trifluorobenzene and 1-bromo-3,5-dimethylbenzene gave only moderate coupling yields (61 and 43, respectively; non-optimized).

The rhodium-catalyzed hydroformylation with the new ligands was performed at a synthesis gas pressure of 10 bar and 120 as well as 100 °C.[18] Apart from 1- and 2-pentene other internal olefins such as 2-butene, 2-octene, and 4-octene were used as starting materials. As shown in Table 2 ligands with electron-withdrawing substituents (**5a–c**) led to much more active and slightly more selective catalysts for the hydroformylation of internal olefins compared to NAPHOS and **5d**.

Table 2. Rhodium-catalyzed hydroformylation in the presence of substituted NAPHOS derivatives.[a]

Entry	Olefin	*p* [bar]	*T* [°C]	Yield [b] [%]	*n*:*i*	TOF [h^{-1}]
1	**5a**	1-pentene	120	82	96:4	512
2	**5a**	2-pentene	120	68	91:9	425
3	**5a**	2-pentene	100	52	89:11	325
4	**5a**	2-butene[b]	120	66	91:9	825
5	**5a**	2-octene[c]	120	51	86:14	319
6	**5b**	1-pentene	120	78	97:3	488
7	**5b**	2-pentene	120	59	94:6	369
8	**5b**	2-pentene	100	21	95:5	131
9	**5c**	1-pentene	120	83	97:3	519
10	**5c**	2-pentene	120	61	93:7	381
11	**5c**	2-pentene	100	24	94:6	150
12	**5c**	2-butene[b]	120	74	95:5	925
13	**5c**	2-octene[c]	120	48	91:9	300
				(64	88:12	114)[d]
14	**5c**	4-octene[e]	120	14	66:34	88
				(41	70:30	43)[f]
15	**5d**	1-pentene	120	76	81:19	475
16	**5d**	2-pentene	120	11	78:22	69

[a] Reaction conditions: pentene (73 mmol), solution (40 mL anisole + isooctane as internal standard), $p = 10$ bar, [Rh(acac)(CO)$_2$] (0.01 mol%; 20.7 ppm Rh), ligand:Rh = 5:1, $t = 16$ h. [b] 2-Butene (146 mmol), anisole (30 mL), [Rh(acac)(CO)$_2$] (0.005 mol%). [c] 2-Octene (73 mmol), solvent (28.5 mL; anisole + toluene). [d] After a reaction time of 56 h. [e] 4-Octene (73 mmol), solvent (10 mL; anisole + toluene). [f] After a reaction time of 96 h.

In the case of 2-pentene the ligand **5a** (IPHOS) led to the most active catalyst system, especially at 100 °C (Table 2, entry 3; TOF = 325 h^{-1}). The largest amount of *n*-aldehydes (Table 2, entries 7, 8; *n*/*i* = 94:6 (95:5); 120 (100) °C) was obtained in the presence of **5b**. Significantly higher catalyst activities but similar selectivities (up to 95:5) (Table 2, entries 4 and 12; TOF = 825 and 925 h^{-1}, respectively) were observed with the industrially important olefin 2-butene. These are the highest selectivities known so far for the hydroformylation of internal olefins to give linear aldehydes with phosphane ligands. Interestingly, the catalyst activities in the presence of **5a–c** do not significantly differ for 1- and 2-pentene (compare entries 1,2 or 6,7 or 9,10 in Table 2). Thus the isomerization of 1-pentene is most likely similar in rate or faster than the hydroformylation step.

In addition the new ligands **5a–c** also allow a selective hydroformylation of higher internal olefins. With 2-octene a *n*:*i* ratio of 91:9 was obtained in the presence of **5c** (Table 2, entry 13; TOF = 300 h^{-1}). However in the case of 4-octene the selectivity is comparably low (Table 2, entry 14; *n*:*i* = 66:34) after 16 h. To understand this different behavior the reactions of 2- and 4-octene in the presence of **5c** (Table 2, entries 13 and 14, respectively) were monitored by removing samples from the autoclave, which were taken during the reaction. The results are displayed in Figure 1 and 2. The conversion of 2- and 4-octene reveals significant differences. Utilizing 2-octene

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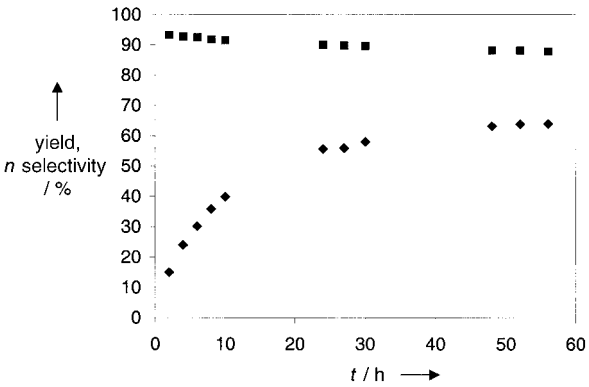

Figure 1. Yield (◆) and *n* selectivity (■) of the rhodium-catalyzed hydroformylation of 2-octene with **5c**.

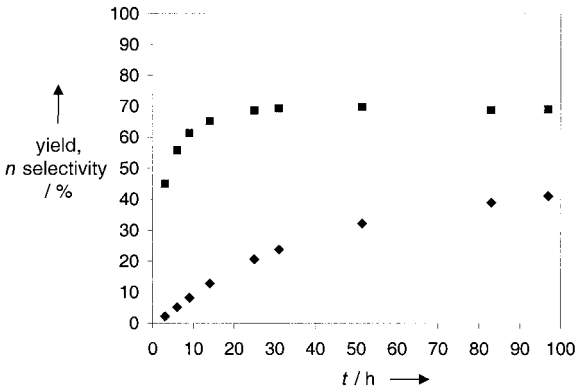

Figure 2. Yield (◆) and *n* selectivity (■) of the rhodium-catalyzed hydroformylation of 4-octene with **5c**.

the *n*:*i* ratio *decreases* from 94:6 after 2 h to 88:12 after 56 h. In contrast, with 4-octene the *n*:*i* ratio *increases* from 45:55 after 3 h to 70:30 after 31 h and then remains approximately constant. It seems that in case of 2-octene the isomerization towards the 1-octene is significantly faster than that to give 3-octene. The isomerization is much slower for 4-octene, hence hydroformylation of the internal double bond occurs preferentially. Interestingly, the hydroformylation of 4-octene still proceeds after 80 h, which underlines the high catalyst stability.

In conclusion we have shown that NAPHOS-type ligands induce excellent selectivities for the conversion of internal olefins to linear aldehydes. Based on our newly developed synthesis of **4**, variously substituted NAPHOS derivatives have been synthesized on a multigram scale. We believe the interesting features and the easy synthesis of this ligand class will lead to further applications for industrially important hydroformylation reactions, although for a practical application the activity and long-time stability still have to be improved.

Experimental Section

General: All reactions were carried out under an argon atmosphere. For the hydroformylation experiments a 100-mL stainless steel autoclave (Parr Co.) equipped with a magnet-driven propeller stirrer or a 160-mL stainless steel autoclave (Parr Co.) stirred magnetically were used.

Example of a typical hydroformylation experiment (Table 2, entry 1): A solution of [Rh(acac)(CO)$_2$] (7.3 μmol, 1.88 mg; acac = acetylacetonate) and ligand **5a** (M_r = 1194.73; 44 mg, 36.5 μmol) in anisole (30 mL) was treated with isooctane (2 mL as internal standard) and 1-pentene (8 mL, 73.0 mmol). This mixture was added to the autoclave, which was subsequently pressurized to 5 bar with synthesis gas (CO:H$_2$ = 1:1). The autoclave was then heated to 120 °C and the pressure adjusted to 10 bar. After 16 h the autoclave was cooled in an ice bath and the pressure was released. A sample was taken immediately and analyzed by GC.

All hydroformylation experiments were conducted under isobaric conditions. Synthesis gas (purity 99.97 – 99.997 %) was purchased from Aga Gas GmbH, Berlin (Germany).

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[6] Phosphites readily undergo side reactions with the produced aldehydes at the required reaction temperature. These side reactions are not observed with phosphanes.

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[8] Turnover frequencies (TOFs) are defined here as mol aldehyde per mol rhodium per hour after 20 – 30 % conversion. The concentration of alkene used in our work is about three times higher. Thus higher rates are expected and a good comparison with the values in reference [7] cannot be made yet.

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[12] Turnover frequencies (TOFs) are given as mol aldehyde per mol rhodium per hoour after 16 h conversion.

[13] Synthesis of **4** and **5a**: A solution of *n*BuLi in hexane (33.2 mL, 1.6 M, 53 mmol) was concentrated in vacuum. After the mixture had been cooled to 0 °C, diethyl ether (25 mL) and *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (7.9 mL) were added. A solution of **1** (5 g) in diethyl ether (30 mL) was then added slowly with stirring and cooling. The mixture was kept for 24 h at room temperature and for a further 4 h at 0 °C. The precipitate was filtered off and washed with hexane (2 × 25 mL). The product was treated with hexane (50 mL) and cooled to – 70 °C. A mixture of chlorobis(diethylamino)phosphane (7.5 mL, 35.4 mmol) and hexane (25 mL) was added dropwise to the stirred suspension. After slowly warming up to room temperature the mixture was stirred for a further 12 h (until the red color had completely disappeared). The solid was filtered off and extracted with toluene (2 × 50 mL). The solvents and excess of chlorobis(diethylamino)phosphane were then removed in vacuum. The residue was dissolved in hexane and HCl gas was bubbled through the solution with external ice cooling and stirring until saturation (about 1 h). The mixture was filtered and the precipitate washed with hexane (2 × 25 mL). The combined filtrates were concentrated to a volume of 50 mL and kept overnight at

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– 30 °C. The resulting crystals were collected, washed with a minimum amount of cold hexane, and dried in vacuum. Yield of **4**: 2.9 g (44 % related to **1**). Mg turnings (302 mg, 12.4 mmol) were placed in a three-necked flask (100 mL) and treated with diethyl ether (10 mL). A solution of 3,5-bis(trifluoromethyl)-1-bromobenzene (3.6 g, 12.4 mmol) in diethyl ether (10 mL) was added dropwise to the magnetically stirred mixture. After 1 h the solution was transferred into a dropping funnel and slowly added to a solution of **4** (1.5 g, 3.1 mmol) in THF (25 mL). The mixture was then heated at reflux until the reaction was complete (~2 h). After removal of the solvents in vacuum the residue was dissolved in toluene. The solution was washed with degassed water and dried with anhydrous Na_2SO_4. The toluene was removed in vacuum, and the residue was recrystallized from acetone/methanol. Yield of **5a**: 3.3 g (89 %).

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[18] Preformation of the rhodium/phosphane catalyst mixture does not lead to superior product yields.

Nucleophilic Trapping of π-Allylpalladium Intermediates Generated by Carbopalladation of Bicyclopropylidene: A Novel Three-Component Reaction**

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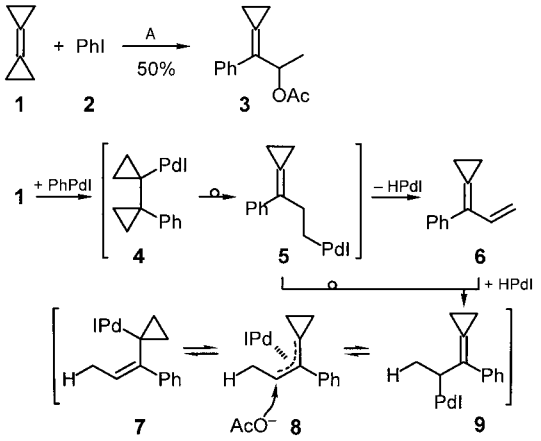
Dedicated to Professor Barry M. Trost on the occasion of his 60th birthday

The construction of complex molecules from simple starting materials is a challenging task for chemists. One of the most elegant ways to achieve this is by utilizing so-called domino reactions.[1] Multicomponent reactions such as the Mannich and the Ugi reaction are examples of all-intermolecular domino reactions. Recently, our group has published a new all-carbon-coupling three-component reaction, the domino Heck – Diels – Alder reaction of bicyclopropylidene (**1**).[2] This sequence involves the Heck-type coupling of bicyclopropylidene (**1**)[3] with haloarenes and -alkenes to form 1-substituted allylidenecyclopropanes which then undergo [4+2] cycloadditions with dienophiles yielding 7-substituted spiro[2.5]oct-7-enes in a one-pot operation. In the course of a more extensive study of this methodology we became aware of a new reaction mode through the isolation of the side product **3**, the formation of which can only be rationalized by an intermolecular nucleophilic attack of an acetate anion stemming from the catalyst precursor on an intermediate π-allylpalladium species **8** (Scheme 1).[4]



Scheme 1. Mechanism of the nucleophilic trapping of π-allylintermediate **8**. A) 5 mol % $Pd(OAc)_2$, 10 mol % TFP, 5.0 equiv LiOAc, K_2CO_3, Et_4NCl, MeCN, 80 °C, 24 h.

The π-allylpalladium intermediate **8** must be formed after the initial carbopalladation and *β*-hydride elimination by readdition of the hydridopalladium species onto the newly formed double bond[5] via a σ-allylpalladium complex **9**. The ligand tris-(*α*-furyl)phosphane (TFP), which is known to retard *β*-hydride elimination[6] and thus favor the readdition of the hydridopalladium complex onto the double bond, proved to be best for this reaction, and the yield of the allyl acetate **3** could be raised up to 50 % by using LiOAc as an additional source of acetate.

In view of previous observations on the nucleophilic substitution reactions on 1,1-dimethyleneallylpalladium intermediates,[7] stabilized enolates and other carbon nucleophiles were tested. These were generated by separately deprotonating malononitriles and diethyl malonates with sodium hydride and then adding to the reaction mixture from **1**, the palladium precatalyst, and iodobenzene (**2**) to give the malonic acid derivatives **11a – c** in up to 77 % yield.[8] In accordance with earlier findings,[7] only products of the nucleophilic attack at the sterically less encumbered terminus of the allyl moiety were obtained (Scheme 2).

Especially interesting is the possible preparation of amino acid derivatives by this method. With O'Donnell's nucleophilic glycine equivalent **12**[9] the methylenecyclopropane derivative **13**, a substituted isomer of hypoglycin A in a protected form,[10] was obtained in 76 % yield (Scheme 3). Glycine methyl ester **14a**, in the presence of triethylamine in

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