Hydroformylation

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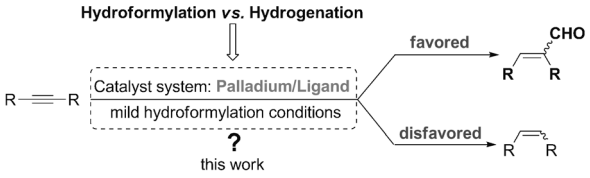
Selective Palladium-Catalyzed Hydroformylation of Alkynes to α,β-Unsaturated Aldehydes**

*Xianjie Fang, Min Zhang, Ralf Jackstell, and Matthias Beller**

The hydroformylation of olefins to give aldehydes as the predominant products, discovered by Otto Roelen in 1938, is an intriguing and extensively studied reaction.[1,2] Owing to its industrial importance, the hydroformylation of aliphatic olefins has been widely explored and these processes represent major applications of homogeneous catalysis for the production of bulk chemicals.[3] Most of the currently employed hydroformylation processes rely on rhodium- and cobalt-based catalysts.[4] Hence, still today the development of novel benign catalysts[5] and the extension of the basic methodology for new feedstocks are challenging and relevant topics for academic and industrial chemists.

Compared to the well-studied hydroformylation of olefins, the corresponding reaction of alkynes has received only scarce attention. This is somewhat surprising as such transformations provide in principle a 100% atom-efficient route for producing α,β-unsaturated aldehydes, which are important intermediates in organic synthesis,[6] particularly for the preparation of bioactive compounds, flavors, and fragrances.[7] In early studies, it was found that the hydroformylation of alkynes usually suffers from low chemoselectivity and/or low yield of the desired unsaturated aldehyde, primarily because the formation of the corresponding saturated aldehydes and alkenes is hardly suppressed.[8] However, during the past two decades, more effective catalysts such as $[Rh(CO)_2(acac)]$/Biphephos (acac = acetylacetonate, Biphephos = 6,6′-[(3,3′-di-*tert*-butyl-5,5′-dimethoxy-1,1′-biphenyl-2,2′-diyl)bis(oxy)]-bis(dibenzo[*d*,*f*][1,3,2]dioxaphosphepin)]),[9] the heterobimetallic catalyst $[PdCl_2(PCy_3)_2]/[Co_2(CO)_8]$,[10] and a zwitterionic rhodium complex with PPh_3 as a ligand[11] were developed. With these catalysts, the hydroformylation of some acetylenic substrates to produce α,β-unsaturated aldehydes with good selectivity is possible. Nevertheless, the efficient hydroformylation of easily accessible aryl alkynes and unsymmetrical alkynes was not possible and represents a challenging problem until today.

In the context of our ongoing research in the field of hydroformylation,[12] we recently set out to study less common hydroformylation catalysts. We demonstrated that metals besides rhodium and cobalt[12a,c] can be successfully applied in the hydroformylation of olefins. More specifically, we showed that palladium complexes with heterocyclic phosphine ligands are efficient and selective catalysts for the low-pressure hydroformylation of aromatic and aliphatic olefins.[12c] Therefore, we presumed that these complexes might be also suitable for the hydroformylation of alkynes to give selectively α,β-unsaturated aldehydes (Scheme 1).



Scheme 1. Hydroformylation and the competing hydrogenation of alkynes.

Herein, we present an efficient and selective palladium-based catalyst system for the general hydroformylation of alkynes under mild conditions. Notably, the enal products were obtained in high yields even from demanding substrates such as aryl alkynes since the unwanted hydrogenation side reactions were effectively suppressed.

It is well known that the influence of ligands on hydroformylation reactions is crucial. Thus, in our initial investigations we examined the effect of a series of phosphine ligands on the model reaction of diphenylacetylene (**1a**) with synthesis gas (Table 1). When monodentate ligands were used, no conversion was observed (Table 1, entries 1–4). However, the application of several commercially available bidentate ligands provided low to moderate yields of the desired product (Table 1, entries 5–9). Further investigations showed that bidentate ligands with larger bite angles (i.e. DPEphos, Naphos, and Xantphos) exhibited no activity in the formation of the desired product (Table 1, entries 10–12). Next, some of our own developed *N*-phenylpyrrole-based bisphosphine ligands[13] with different steric properties were tested (Table 1, entries 13–15). **L5** was identified as the most promising ligand and the reaction afforded the desired product **3a** in good yield with high stereoselectivity. Notably, the hydrogenated product **2a** formed in only 7% yield in this case (Table 1, entry 15). In order to improve the reaction further, we evaluated the influence of critical reaction parameters such as temperature, acid co-catalyst, and gas pressure in the presence of **L5** as the ligand. As shown in Table 1, the reaction temperature and the acid co-catalyst

[*] X. Fang, Dr. M. Zhang, Dr. R. Jackstell, Prof. Dr. M. Beller
Leibniz-Institut für Katalyse e. V. an der Universität Rostock
Albert-Einstein-Strasse 29a, 18059 Rostock (Germany)
E-mail: matthias.beller@catalysis.de
Homepage: http://www.catalysis.de

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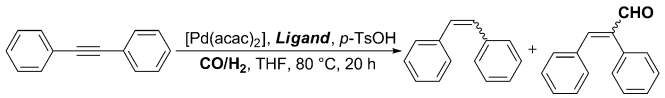
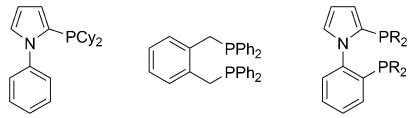
Table 1: Hydroformylation of diphenylacetylene (**1a**): Evaluation of reaction conditions.[a]





Entry	Ligand	CO/H_2 [bar]	Conv.	**2a** Yield[b] (*E*/*Z*)	**3a** Yield[b] (*E*/*Z*)
1	PPh_3	15:15		NR	
2	PCy_3	15:15		NR	
3	*n*BuPAd$_2$	15:15		NR	
4	L1	15:15		NR	
5	Dppp	15:15	23%	9% (71:29)	10% (96:4)
6	Dppb	15:15	37%	7% (59:41)	24% (96:4)
7	Dppf	15:15	45%	4% (54:46)	35% (96:4)
8	BINAP	15:15	45%	5% (37:63)	34% (95:5)
9	L2	15:15	21%	9% (88:12)	9% (>99:1)
10	DPEphos	15:15		NR	
11	Naphos	15:15		NR	
12	Xantphos	15:15		NR	
13	L3	15:15		NR	
14	L4	15:15		NR	
15	L5	15:15	100%	7% (76:24)	86% (96:4)
16[c]	L5	15:15	37%	1% (79:21)	30% (96:4)
17[d]	L5	15:15		NR	
18	L5	10:20	77%	13% (58:42)	59% (94:6)
19	L5	20:10	85%	7% (77:23)	73% (94:6)
20	L5	5:5	100%	9% (80:20)	84% (93:7)
21	***L5***	***25:25***	***100%***	***3% (79:21)***	***92% (95:5)***
22	L5	30:30	100%	3% (79:21)	92% (95:5)
23[e]	L5	25:25	100%	24% (17:83)	41% (98:2)

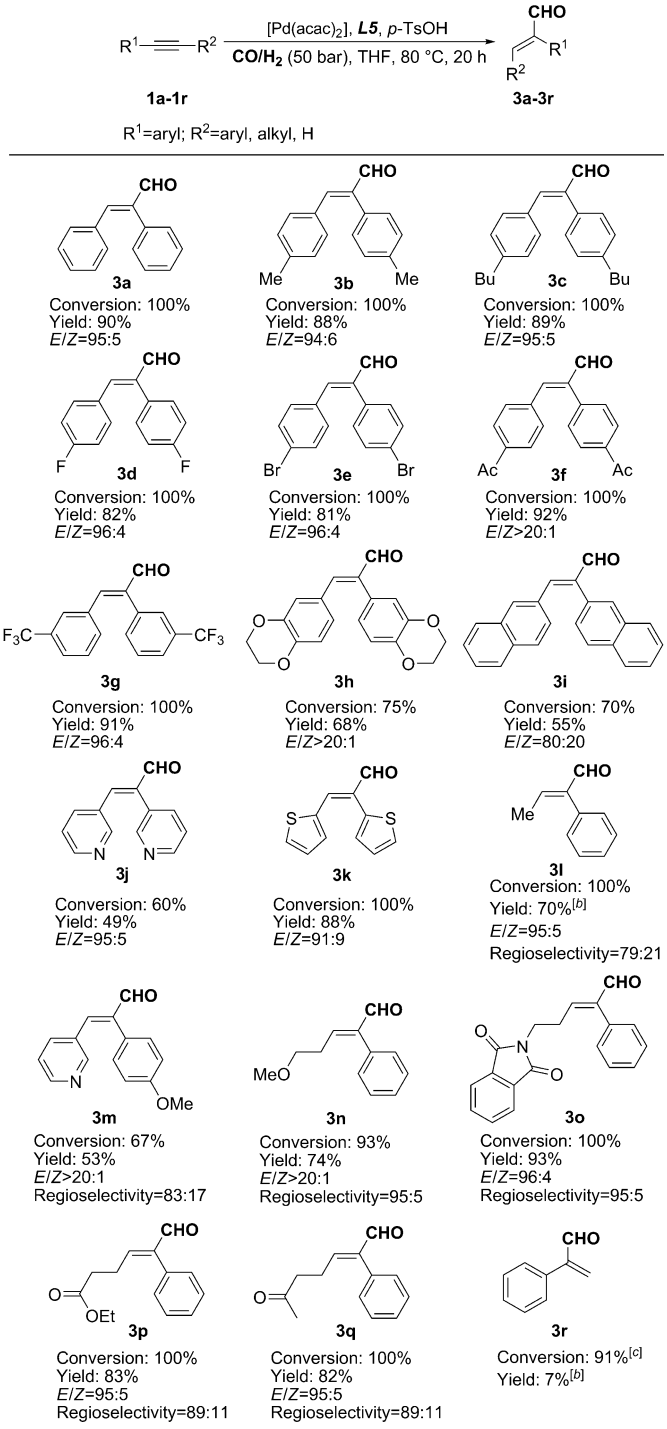
[a] Reaction conditions: **1a** (0.5 mmol), $[Pd(acac)_2]$ (0.5 mol%), monodentate ligand (2 mol%) or bidentate ligand (1 mol%), *p*-TsOH (2 mol%), THF (2 mL). [b] Yield determined by GC analysis using isooctane as the internal standard; the ratios of *E* to *Z* isomers were determined by GC–MS analysis; NR = no reaction. [c] Reaction temperature: 50 °C. [d] Without *p*-TsOH. [e] Using $[Rh(CO)_2(acac)]$ as catalyst, **2a′** = 2,3-diphenylpropanal (GC yield: 14%), **2a″** = 3,4-diphenylfuran-2(5*H*)-one (GC yield: 17%). Ad = adamantyl, DPEphos = bis(diphenylphosphinophenyl)ether; Naphos = 2,2-bis[(diphenylphosphino)methyl]-1,1-binaphthyl; Xantphos = 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene.

have a major influence on the product yields. For example, at 50 °C the conversion of **1a** decreased dramatically (Table 1, entry 16). No reaction occurred in the absence of *p*-toluenesulfonic acid monohydrate (*p*-TsOH), indicating the importance of the acid for the generation of the catalytically active Pd hydride species (Table 1, entry 17).[14] Furthermore, changing the ratio of CO/H_2 led to decreased conversion of **1a** (Table 1, entries 18 and 19). Lowering the syngas pressure resulted in full conversion of **1a** but increased the ratio of byproduct **2a** (Table 1, entry 20). In contrast, **2a** is obtained in only 3% yield when the pressure of syngas (Table 1, entries 21–22) is increased to 50 bar. Among the different metal catalysts tested, only $[Rh(CO)_2(acac)]$ gave the desired product **3a** in 41% yield (GC analysis) along with significant amount of the byproducts **2a** (yield: 24%), saturated aldehyde **2a′**, and lactone **2a″** (Table 1, entry 23). In contrast, other catalysts such as $[Co_2(CO)_8]$ [Ir(cod)(acac)], $[Ru_3(CO)_{12}]$, $[Fe_3(CO)_{12}]$, and $[Ni(acac)_2]$ led to the recovery of the starting materials under the reaction conditions.

Applying these optimized reaction conditions (Table 1, entry 21), we examined the general scope and the limitations of our synthetic protocol. As shown in Scheme 2, a variety of internal aryl alkynes underwent efficient hydroformylation to afford the corresponding α,β-unsaturated aldehydes in good to excellent yields. Various substrates with electron-neutral, electron-deficient, and electron-rich substituents led to good product yields and high *E* stereoselectivity (**3a**–**3i**). Substrates having different functional groups (i.e. -Br, -COMe, -NPhth, and -CO_2Et) were well tolerated, too (**3e**–**3g** and **3o**–**3q**). However, the use of the more bulky substrate **1i** gave product **3i** in moderate yield with decreased stereoselectivity, presumably due to steric effects. Moreover, substrates with heterocyclic substituents (such as pyridyl and thiophenenyl groups) proved also to be efficient coupling partners to generate the corresponding products in acceptable to good yields (**3j** and **3k**). From a synthetic point of view, it is important that reactions using unsymmetrical aryl alkynes (**1l**–**1q**) mainly occurred at the benzylic position. Thus, good regioselectivity is observed, which is attributed to the formation of the kinetically favored vinyl palladium species stabilized by aryl groups.[15] The reaction employing phenylacetylene **1r** resulted only in a low product yield, which is similar to reactions of the known rhodium-based catalysts.[16] All the yields of hydrogenation byproducts (alkenes) are less than 5% according to GC analysis.

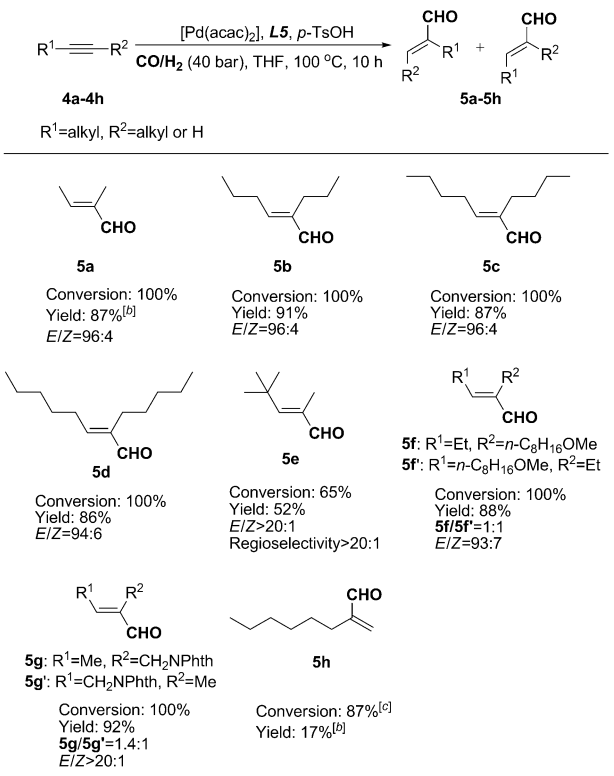
Next, we turned our attention to the hydroformylation of aliphatic alkynes, which is a class of less reactive substrates than aryl alkynes. When the catalyst loading was increased to 1 mol% $[Pd(acac)_2]$ and the reaction temperature to 100 °C, all the reactions proceeded smoothly and afforded the desired products in reasonable to excellent yields. As shown in Scheme 3, all the symmetrical alkyl alkynes were smoothly converted to the corresponding α,β-unsaturated aldehydes with high stereoselectivity (**5a**–**5d**). The hydroformylation of the unsymmetrical alkyl alkyne 4,4′-dimethylpent-2-yne (**4e**) gave the product **5e** exclusively in 65% yield. Here, the specific regioselectivity is attributed again to the steric effect. Alkynes **4f** and **4g** bearing different alkyl substituents resulted in mixed regioisomers in ratios of 1:1 and 1.4:1, respectively (**5f** and **5g**). The latter results clearly indicate that there is little differentiation between groups R^1 and R^2. Similar to the hydroformylation of phenylacetylene **1r** (Scheme 2), the terminal alkyl alkyne **4h** gave the desired product (**5h**) in lower yield (17%). It is noteworthy that alkene byproducts arising from hydrogenation of alkynes were not observed.

Finally, we were interested in demonstrating the usefulness of our procedure for the synthesis of bioactive compounds (Scheme 4). Hence, the synthesis of **3a** was scaled up

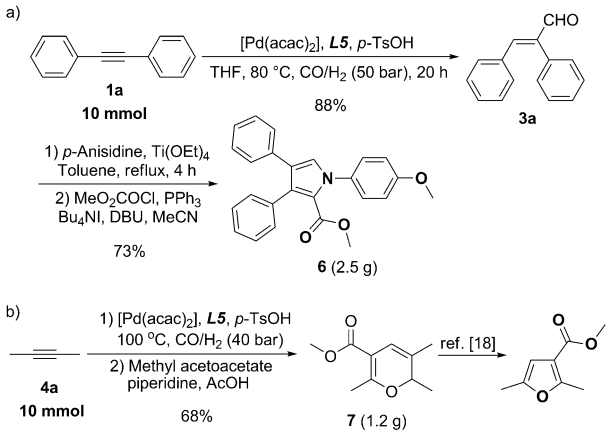


Scheme 2. Palladium-catalyzed hydroformylation of aryl alkynes. [a] Reaction conditions: **1** (0.5 mmol), $[Pd(acac)_2]$ (0.5 mol%), **L5** (1 mol%), *p*-TsOH (2 mol%), THF (2 mL); yield of isolated product after column chromatography; the ratios of *E* to *Z* isomers and the regioselectivity were determined by GC–MS analysis. [b] Yield determined by GC analysis using isooctane as the internal standard. [c] Reaction temperature: 120°C.

by using 10 mmol of substrate **1a** and gave 88% yield of the α,β-unsaturated aldehyde. Subsequently, **3a** was efficiently transformed into the tetrasubstituted pyrrole **6** in 73% yield by a multicomponent coupling reaction (Scheme 4a).[17]



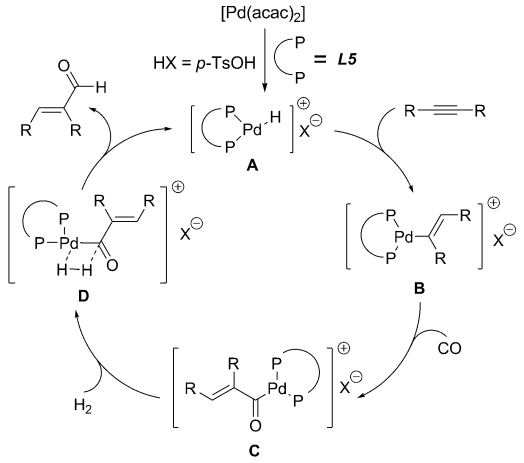
Scheme 3. Palladium-catalyzed hydroformylation of aliphatic alkynes. [a] Reaction conditions: **4** (7.5 mmol), $[Pd(acac)_2]$ (1 mol%), **L5** (4 mol%), *p*-TsOH (4 mol%), THF (30 mL); yield of isolated product after column chromatography; the ratios of *E* to *Z* isomers and the regioselectivity were determined by GC–MS analysis. [b] Yield determined by GC analysis using isooctane as the internal standard. [c] Reaction temperature: 130°C.



Scheme 4. Synthetic transformations of α,β-unsaturated aldehydes.

Moreover, a sequential one-pot methodology was applied for the preparation of the tetrasubstitued 2*H*-pyran **7**, which is easily accessible from the simple alkyne **4a** (yield: 68%) after successive hydroformylation and electrocyclization with methyl acetoacetate. Notably, product **7** proved to be a key intermediate for the preparation of various functionalized furans (Scheme 4b).[18]

Although the detailed mechanism of the palladium-catalyzed hydroformylation of alkynes is still under investigation, we suggest a simplified catalytic cycle based on the known palladium-catalyzed carbonylation of olefins and alkynes (Scheme 5).[5c,19] Initially, the active cationic palla-



Scheme 5. Proposed catalytic cycle for this reaction.

dium hydride species **A** is formed in situ from the reaction of $[Pd(acac)_2]$, **L5**, and *p*-TsOH.[14] Next, π-coordination of the carbon–carbon triple bond to the metal center, followed by the insertion of alkyne into the H–Pd bond, should afford the vinyl palladium intermediate **B**. Subsequent insertion of CO into the palladium–vinyl bond leads to the corresponding acyl palladium complex **C**. Finally, hydrogenolysis should afford the desired product and will regenerate the palladium hydride species **A**.

In summary, we have developed the first efficient palladium-based catalyst system for selective hydroformylation of alkynes to α,β-unsaturated aldehydes. Notably, competing hydrogenation side reactions can be almost completely suppressed. Compared to previously known catalyst systems a wider range of internal alkynes can be efficiently hydroformylated to α,β-unsaturated aldehydes in good yields with often high regio- and stereoselectivity.

Experimental Section

Typical procedure for the preparation of **3:** A 20 mL Schlenk flask was charged with $[Pd(acac)_2]$ (3.8 mg, 0.5 mol%), **L5** (13.4 mg, 1 mol%), *p*-TsOH (9.5 mg, 2 mol%), and THF (10 mL). Then, 2 mL of this clear light yellow solution was transferred into four vials (4 mL reaction volume) each equipped with a septum, a small cannula, a stirring bar, and 0.5 mmol of the corresponding alkynes **1**. The vials were placed in an alloy plate, which was transferred into a 600 mL autoclave under argon atmosphere. The autoclave was flushed with nitrogen, pressurized with 50 bar synthesis gas, and heated to 80 °C. The reaction was carried out for 20 h. Subsequently, the autoclave was cooled down to room temperature, the pressure was released, and isooctane (internal standard) was added to the solution. The conversion and regio- and stereoselectivity were measured by GC and GC–MS, respectively. After the solvent had been removed by vacuum, the residue was directly purified by flash chromatography on silica gel (eluent: heptane/ethyl acetate = 20:1) to give the desired product **3**.

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