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Palladium-Catalyzed Hydroformylation of Terminal Arylacetylenes with Glyoxylic Acid

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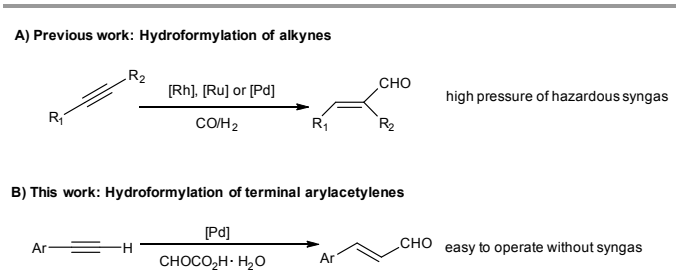
A simply practical and governable palladium-catalyzed hydroformylation of terminal arylacetylenes has been disclosed. The reaction processes under a syngas free condition, using readily available glyoxylic acid as formyl source, featured with mild conditions, giving arise to a broad way of α,β-unsaturated aldehydes.

With the development of transition metal catalysis, hydroformylation has become a significant method for the preparation of aldehydes. In the past few decades, the hydroformylation of alkenes catalyzed by transition metals reacted with syngas to form the corresponding aldehyde products has been widely reported.[1] In contrast to facile hydroformylation of alkenes, few successful examples of hydroformylation of alkynes have been reported, despite the resulting α,β-unsaturated aldehydes are valuable in synthesis. The hydroformylation of alkynes suffers with poor chemoselectivity, and low yields due to the undesired reduced side reaction via the formation of corresponding alkenes and saturated aldehydes byproduct.[2] During the past two decades, some effective catalysts such as $[Rh(CO)_2(acac)]$/Biphephos,[3] the heterobimetallic catalyst $[PdCl_2(PCy_3)_2]/[Co_2(CO)_8]$[4] and a zwitterionic rhodium complex[5] were developed to address these problems. Recently, some effective Rh or Pd catalyst with specific phosphine ligands[6] have been successively reported (Scheme 1 A). However, terminal alkynes are more easily hydrogenated than di-substituted alkynes under syngas condition, and so only a few successful examples has been reported[7].

Generally, hydroformylation reactions involving syngas must be carried out under high pressures, so the special pressurization equipment is indispensable. In the meanwhile, the application of syngas based hydroformylation in the laboratory is limited by the toxic CO and dangerous H_2. Fortunately, in recent years, some new formyl reagents such as formaldehyde,[8] alcohols,[9] formic acid[10] and 2,2-diethoxyglyoxylic acid[11] have been developed as alternative resources of syngas in the hydroformylation of olefins. Actually, there are few reports about the hydroformylation of alkynes without syngas. Herein, we use the glyoxylic acid as the formyl source and $PdCl_2(PPh_3)_2$ as the catalyst with the very common ligand 1,3-bis(diphenylphosphino)propane (dppp) and PPh_3 to achieve the hydroformylation of terminal arylacetylenes. This reaction featured with high stereoselectivity that only E-enals can be obtained (Scheme 1 B).



Scheme 1. Overview of transition metal catalyzed hydroformylation of alkynes.

Phenylacetylene was exploited as the model substrate for the studies. Here, 6 mol % or 12 mol % phosphine ligands, 3 mol % of $PdCl_2(PPh_3)_2$ and 5.0 equivalents of glyoxylic acid were added in DMF and heated to 80 °C for 2 hours with intense stirring. As shown in (Table 1), the yield was greatly influenced by ligand, solvent and Pd catalyst. Few aldehydes were observed without ligand (entry 3). Most of the bidentate phosphine ligands such as dppe, dppp and dppb are favorable for this reaction (entries 4-6). Instead, dppf and monodentate ligands give low yields (entries 7-10). The screening of solvent effect reveals that the larger polar amide is more favorable

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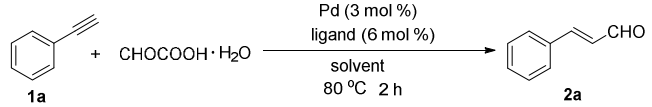
for the reaction, and DMF is superior to other solvents (entries 11-16). The choice of Pd catalysts is also crucial. $PdCl_2(PPh_3)_2$ was the best catalyst and the yield dropped down when it was replaced by $Pd(OAc)_2$ or $Pd(PPh_3)_4$ (entries 17,18). We found that additional 6 mol % PPh_3 would provide high yield during substrate scope studies. (entry 20)[12].

Table 1. Studies of the Reaction conditions[a]



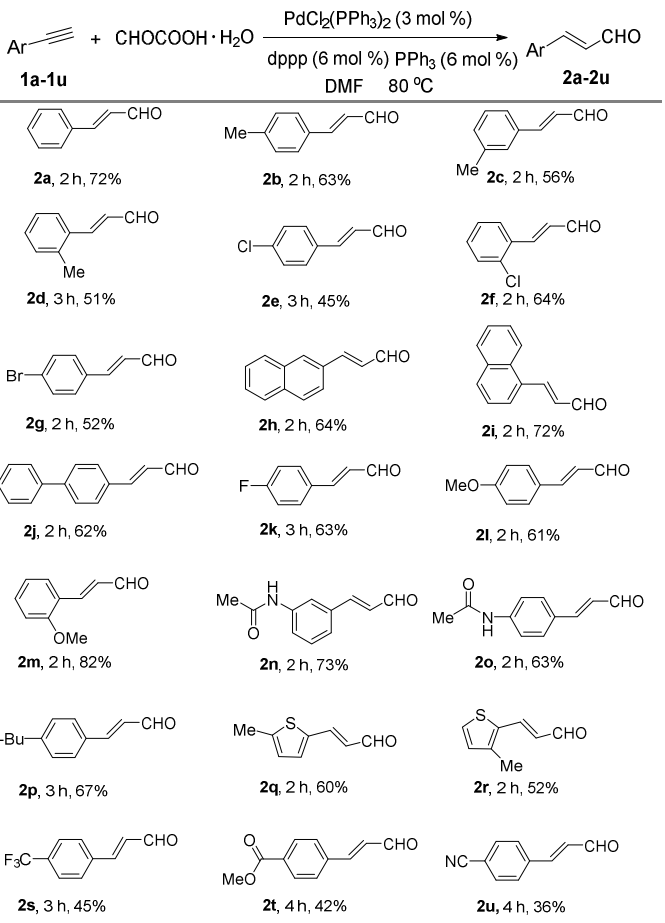
Entry	Ligand	Catalyst	Solvent	Yield[%][b]
1	—	$Pd(PPh_3)_4$	DMF	13
2	—	$PdCl_2(PPh_3)_2$	DMF	28
3	—	$Pd(OAc)_2$	DMF	2
4	dppb	$PdCl_2(PPh_3)_2$	DMF	72
5	dppe	$PdCl_2(PPh_3)_2$	DMF	79
6	dppp	$PdCl_2(PPh_3)_2$	DMF	81
7	dppf	$PdCl_2(PPh_3)_2$	DMF	15
8	PCy_3	$PdCl_2(PPh_3)_2$	DMF	11
9	Xphos	$PdCl_2(PPh_3)_2$	DMF	9
10	P(*o*-Tol)$_3$	$PdCl_2(PPh_3)_2$	DMF	8
11	dppp	$PdCl_2(PPh_3)_2$	DMAc	65
12	dppp	$PdCl_2(PPh_3)_2$	NMP	32
13	dppp	$PdCl_2(PPh_3)_2$	THF	trace
14	dppp	$PdCl_2(PPh_3)_2$	Toluene	0
15	dppp	$PdCl_2(PPh_3)_2$	DCE	0
16	dppp	$PdCl_2(PPh_3)_2$	t-BuOH	0
17	dppp	Pd $(OAc)_2$	DMF	12
18	dppp	$Pd(PPh_3)_4$	DMF	20
19	—	—	DMF	0
20[c]	dppp+PPh_3	$PdCl_2(PPh_3)_2$	DMF	86 (72)[d]

[a] The reactions were carried out with **1a** (1 mmol), catalyst (0.03 mmol), ligand (0.06 or 0.12 mmol, P:Pd = 4:1), and CHOCOOH·H_2O (5 mmol) in solvent (2 ml) at 80 □ for 2 h. [b] Determined by HPLC analysis. [c] 0.06 mmol dppp and 0.06 mmol PPh_3 was added. [d] Isolated yield.

With these optimized reaction conditions in hands (Table 1, entry 20), we investigated the general scope and the limitations of this synthetic protocol. As shown in Table 2, the hydroformylation can be extended to a variety of terminal alkynes, and the corresponding α,β-unsaturated aldehydes were isolated in 36-82% yield. It is found that the substrates with electron-donating substituents are beneficial to high product yields as well as the reducing time of reaction. Comparatively, the electron-withdrawing substituents such as CF_3, COOMe and CN led to the low yields (**2s**, **2t** and **2u**), and the reaction achieved maximum yields in about three hours.

The position of the substituent on the aryl ring also has a great influence on the reaction. The hydroformylation yields of *o*-methoxyphenylacetylene (**2m**) and *o*-chlorophenylacetylene (**2f**) are higher than the corresponding *p*-substituted substrates (**2l**, **2e**). Exceptionally, aldehydes **2n** and **2o** can be obtained in higher yields from their alkynyl substrates, but the corresponding hydration product N-(2-acetylphenyl) acetamide[13] was obtained when N-(2-ethynylphenyl)acetamide is used.

Table 2. Substrate scope[a,b]



[a] The reactions were carried out with **1** (2 mmol), $PdCl_2(PPh_3)_2$ (0.06 mmol), PPh_3 (0.12 mmol), dppp (0.12 mmol), and CHOCOOH·H_2O (10 mmol) in DMF (4 ml) at 80 □ for 2-4 h. [b] Isolated yields.

A precise reaction mechanism is not clear at this moment, one plausible catalytic cycle is depicted in Scheme 2. Initially, the reaction of palladium complex **4** and CHOCOOH (**3**) lead to the palladium species **5**. The active cationic palladium hydride species **6**[6b] can be formed in situ via the releasing of CO_2, which coordinate with alkyne (**1**), followed by the insertion reaction and the vinyl palladium intermediate **7** was formed, then insertion of CO into the palladium-vinyl bond would provide acyl palladium complex **8**. Subsequently, the hydrogenolysis reaction with glyoxylic acid should afford the desired aldehyde **2** and regenerate the palladium species **5**.

In order to gain more insight of the reaction mechanism, the deuterium labeling experiments were carried out with 1-ethynyl-4-methoxybenzene (**1l**), 3 mol % $PdCl_2(PPh_3)_2$, 6 mol % dppp, 6 mol % PPh_3 , 5 equivalent CHOCOOD, and shown in reaction A (Scheme 3). Aldehyde (**2l'**) was isolated in 20% yield with 72% D, 50% D and 56% D at carbons 1, 2, 3 respectively, and there was 61% D at the terminal carbon of the alkyne which was not fully converted. Reaction B was carried out with the same condition as reaction A

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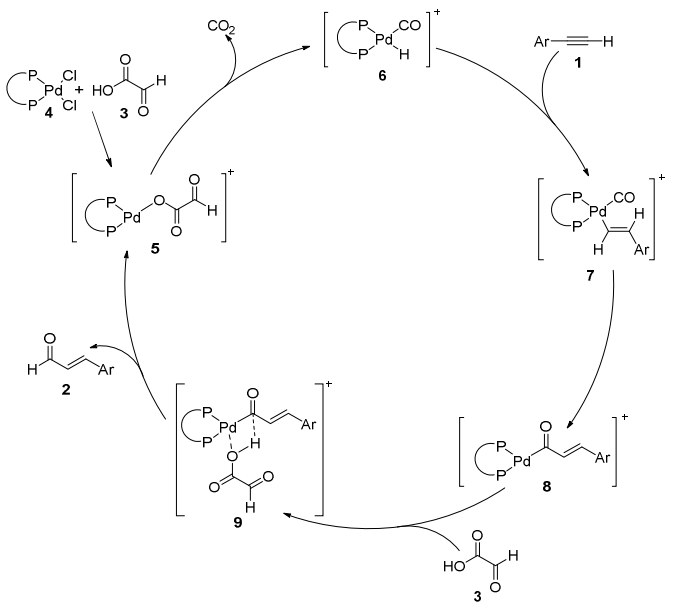
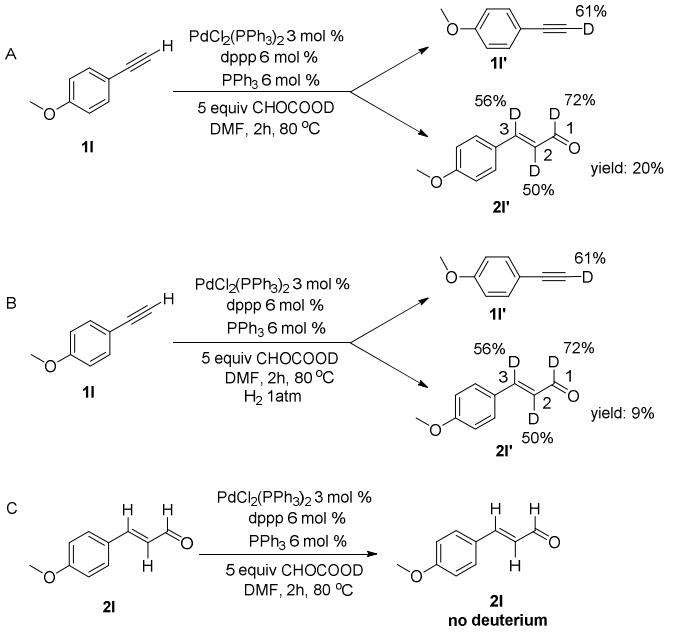
except H_2 atmosphere, the yield was 9% and the distribution of deuterium had



Scheme 2. Proposed catalytic cycle for this reaction.

not changed. In reaction C, the alkyne was replaced by hydroformylation product (**2l**), other conditions were the same as reaction A, and there was no deuterium in the product. More details are available in the ESI†.



Scheme 3. Deuterium-Labelling experiments.

The deuterium at each carbon on aldehyde (**2l'**) can be explained by the proposed catalytic cycle. When the reaction was carried out in the presence of CHOCOOD, the hydrogen on the active cationic palladium hydride species **6** can be exchanged by deuterium, which leads to the deuterium at carbon 3 via insertion reaction. The hydrogen of the alkyne was exchanged in deuterium-labelling experiments. The deuterium at carbon 2 of aldehyde (**2l'**) should come from the alkyne. And then, the hydrogenolysis reaction of acyl palladium complex **8** with CHOCOOD should afford the deuterium at carbon 1. When the reaction was carried out under H_2 atmosphere, the coordinated CO on the active cationic palladium hydride species **6** and the vinyl palladium intermediate **7** should be hindered and the yield was reduced.

In conclusion, an effective palladium-catalyzed hydroformylation of terminal alkynes with glyoxylic acid has been developed, affording the synthetically valuable α,β-unsaturated aldehydes with exclusive E-selectivity and wide functional tolerence. Future work will focus on extension substrate scope of alkylated alkyne and detailed mechanism studies. Advantageously, the reactions can be performed easily in the laboratory with glassware instead of high-pressure equipment.

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Conflicts of interest

There are no conflicts to declare.

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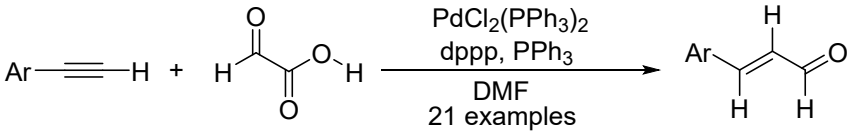

- Syngas-free reaction condition
- Use common ligands
- Terminal alkyne substrates
- Some researches for mechanism