UPDATES

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Palladium-Catalyzed Oxidative Carbonylation of Aromatic C−H Bonds with Alcohols using Molybdenum Hexacarbonyl as the Carbon Monoxide Source

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Abstract: With molybdenum hexacarbonyl as the carbon monoxide source, a general palladium-catalyzed carbonylative transformation of the C−H bond on aromatic rings to produce esters has been developed. Good yields of the corresponding products have been obtained with wide functional group tolerance and excellent regioselectivity. A variety of aliphatic alcohols are suitable reactants here.

Keywords: carbonylation; C−H activation; molybdenum hexacarbonyl; palladium catalyst; 2-phenylpyridines

Carboxylic esters are important chemicals with wide applications in fine chemicals, natural products, and polymers.[1] Traditionally, esters are mainly prepared from the corresponding carboxylic acids or their derivatives and alcohols. Alternatively, direct oxidative esterifications of aldehydes, alcohols and arenes with alcohols have been investigated as well.[2]

On the other hand, transition metal-catalyzed carbonylation reactions have already become a powerful tool in modern organic synthesis.[3] By incorporating carbon monoxide as an inexpensive and abundant C_1 source, numerous carbonyl-containing compounds can be easily prepared. Depending on the nucleophiles, esters can be effectively produced when alcohols are added (called alkoxycarbonylation). However, most of the known alkoxycarbonylation procedures need aryl halides or analogues as the starting materials which require pre-activation steps.

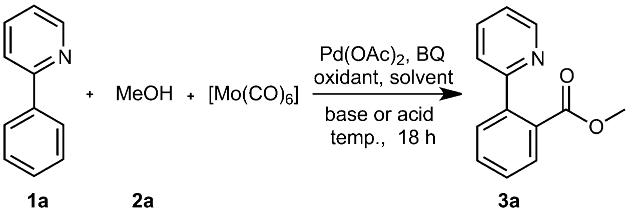
Based on the achievements in transition metal-catalyzed C−H activation reactions,[4] the merging of carbonylation and C−H bond activation in ester synthesis will be attractive. Indeed, some interesting transformations have been achieved recently. In 2009, a general rhodium-catalyzed carbonylation of arenes to produce esters was reported.[5] By using Oxone as the oxidant under a carbon monoxide (2 bar) atmosphere, the desired esters were formed in good to excellent yields with primary alcohols. Compared with expensive rhodium catalysts, palladium catalysts were explored in this topic as well. In 2010, Z. J. Shi and co-workers reported a novel palladium-catalyzed *ortho*-carbonylation of *N*,*N*-dimethylbenzylamines to produce the corresponding *ortho*-methyl benzoates.[6] With $Cu(OAc)_2$ as the oxidant, moderate to good yields of the desired products were isolated. LiCl was found to play an important role here. In 2013, B. F. Shi and co-workers reported an interesting palladium-catalyzed alkoxycarbonylation procedure for the synthesis of aryl carboxylic esters *via* C−H activation under an atmospheric pressure of carbon monoxide.[7] With oxygen as the co-oxidant, good yields of the desired products can be achieved with 2-arylpyridines and primary alcohols as the reactants. More recently, Lei[8] and Guan[9] reported their achievements on palladium-catalyzed carbonylative syntheses of *o*-aminobenzoates from *N*-alkylanilines *via* C−>H activation. With a copper(II) salt, KI and oxygen as the oxidation system, good yields of *o*-aminobenzoates can be isolated in both cases.

However, the above discussed procedures all require carbon monoxide gas as the CO source and primary or secondary alcohols as the reaction partner. Although carbon monoxide, as one of the cheapest C_1 sources, does hold a non-replaceable position in industrial scale applications, its high toxicity and odourless character limit its usage in laboratories. Hence, the development of new procedure based on CO surrogates will be interesting for the synthetic community.[10] Among all the candidates, $Mo(CO)_6$ as a non-toxic solid is an attractive CO source.[11] Against this background, we wish to report herein a general palladium-catalyzed oxidative carbonylation of aromatic C−H bonds with $Mo(CO)_6$ as the CO source. In the presence of only 0.4 equivalent of $Mo(CO)_6$, various kinds of alcohols were carbonylated in moderate to good yields. In addition to 2-arylpyridine derivatives, 1,2-diphenyldiazene, 1-phenyl-1*H*-pyrazole and 2-phenylpyrimidine are all suitable substrates here. Not only primary alcohols, but also secondary and tertiary alcohols are applicable as reaction partners.

Our initial investigation was started with 2-phenylpyridine (**1a**, 1 equiv.) and methanol (**2a**, 15 equiv.), $Pd(OAc)_2$,(10 mol%), $[Mo(CO)_6]$ (1 equiv.), BQ (benzoquinone, 2 equiv.), NaOAc (2 equiv.) and Ag_2CO_3 (3 equiv.) in chlorobenzene and, to our delight, a 45% yield of the desired carbonylation product **3a** was formed after 18 h at 130 °C (Table 1, entry 1). In our further optimization studies, we found that the use of BQ was essential for the formation of the carbonylation products **3**. Presumably, BQ can facilitate the reductive elimination step.[12] The yield of product **3a** was decreased when we changed the amounts of NaOAc or Ag_2CO_3 used (Table 1, entries 2–5). Various other oxidants such as Ag_2O, $AgNO_3$, $Cu(OAc)_2$, $CuCl_2$, CuO, $K_2S_2O_8$, and Oxone were tested in this reaction as well (Table 1, entries 6–12). However, none of them could give improved results.

Then the effects of other bases and acids were investigated (Table 1, entries 13–19). NaOAc was found to be the best base here, whereas Na_2CO_3, $NaHCO_3$,

Table 1. Optimization of the reaction conditions.[a]



Entry	Temp. [°C]	Base or Acid	Oxidant	Solvent	Yield [%][b]
1	130	NaOAc	Ag_2CO_3	PhCl	45
2	130	NaOAc	Ag_2CO_3 (2 equiv.)	PhCl	40
3	130	NaOAc	-	PhCl	23
4	130	-	Ag_2CO_3	PhCl	36
5	130	NaOAc (4 equiv.)	Ag_2CO_3	PhCl	41
6	130	NaOAc	Ag_2O	PhCl	trace
7	130	NaOAc	$AgNO_3$	PhCl	34
8	130	NaOAc	$Cu(OAc)_2$	PhCl	trace
9	130	NaOAc	$CuCl_2$	PhCl	trace
10	130	NaOAc	CuO	PhCl	20
11	130	NaOAc	$K_2S_2O_8$	PhCl	trace
12	130	NaOAc	oxone	PhCl	29
13	130	Na_2CO_3	Ag_2CO_3	PhCl	10
14	130	$NaHCO_3$	Ag_2CO_3	PhCl	12
15	130	KOAc	Ag_2CO_3	PhCl	8
16	130	K_2CO_3	Ag_2CO_3	PhCl	20
17	130	Cs_2CO_3	Ag_2CO_3	PhCl	trace
18	130	Li_2CO_3	Ag_2CO_3	PhCl	trace
19	130	DBU	Ag_2CO_3	PhCl	0
20	130	HOAc	Ag_2CO_3	PhCl	0
21	100	NaOAc	Ag_2CO_3	MeOH	43
22	100	NaOAc	Ag_2CO_3	DCE	81
23	130	NaOAc	Ag_2CO_3	DMSO	0
24	130	NaOAc	Ag_2CO_3	HOAc	0
25	80	NaOAc	Ag_2CO_3	DCE	56[c]
26	80	NaOAc	Ag_2CO_3	DCE	57[d]
27	**80**	**NaOAc**	**Ag_2CO_3**	**DCE**	**85 (80)[e]**
28	80	NaOAc	Ag_2CO_3	DCE	82[f]

[a] *Reaction conditions:* **1a** (0.5 mmol, 1 equiv.), **2a** (7.5 mmol, 15 equiv.), $[Mo(CO)_6]$ (0.5 mmol, 1 equiv.), $Pd(OAc)_2$ (0.05 mmol, 10 mol%), BQ (1 mmol, 2 equiv.), base or acid (1 mmol, 2 equiv.) and oxidant (1.5 mmol, 3 equiv.), solvent (2 mL) for 18 h in a sealed tube.

[b] Yields were determined by GC-MS. Isolated yield is given in parenthesis.

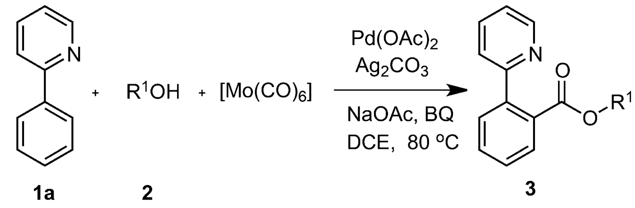
[c] $[Mo(CO)_6]$ (0.1 mmol, 0.2 equiv.).

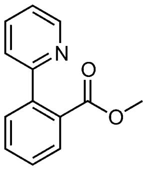
[d] $[Mo(CO)_6]$ (0.15 mmol, 0.3 equiv.).

[e] $[Mo(CO)_6]$ (0.2 mmol, 0.4 equiv.).

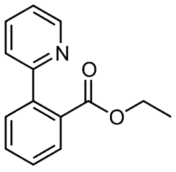
[f] $[Mo(CO)_6]$ (0.25 mmol, 0.5 equiv.).

Table 2. Carbonylation of 2-phenylpyridine with different alcohols.[a]

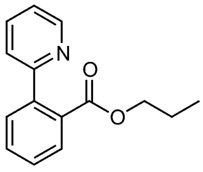




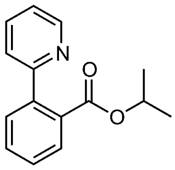
3a, 80%



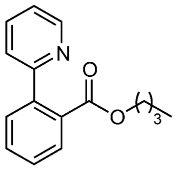
3b, 78%



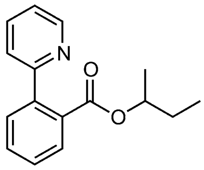
3c, 74%



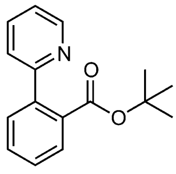
3d, 57%



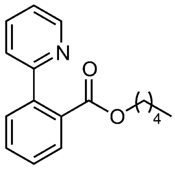
3e, 62%



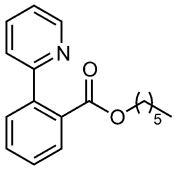
3f, 56%



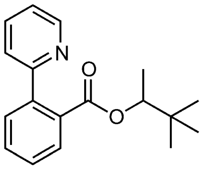
3g, 45%



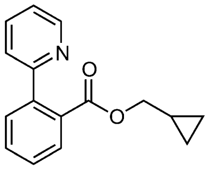
3h, 52%



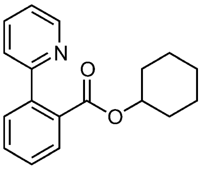
3i, 50%



3j, 41%



3k, 44%



3l, 43%

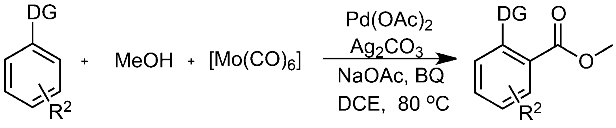
[a] 2-Phenylpyridine **1a** (0.5 mmol), alcohol **2** (7.5 mmol), $[Mo(CO)_6]$ (0.2 mmol), $Pd(OAc)_2$ (0.05 mmol), BQ (1 mmol), NaOAc (1 mmol) and Ag_2CO_3 (1.5 mmol) in DCE (2 mL) at 80 °C for 18 h, isolated yields.

KOAc, K_2CO_3, Cs_2CO_3, and Li_2CO_3 were all found to be inferior. DBU inhibited the reaction completely (Table 1, entry 19). No carbonylation product could be detected when AcOH was added (Table 1, entry 20). The solvent was found to function critically in this reaction. The yield decreased to 43% when MeOH was applied as the solvent (Table 1, entry 21) and no desired product can be observed when DMSO (dimethyl sulfoxide) or AcOH was used (Table 1, entries 23 and 24). However, 81% of the desired product **3a** can be formed when DCE (1,2-dichloroethane) was applied as the reaction medium (Table 1, entry 22). To our surprise, the yield can even be further improved by using 0.4 equiv. of $Mo(CO)_6$ (Table 1, entry 27).

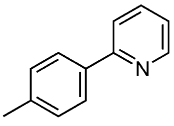
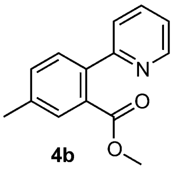
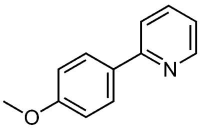
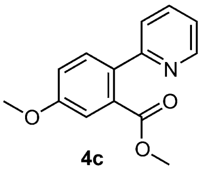
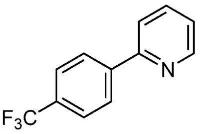
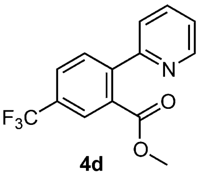
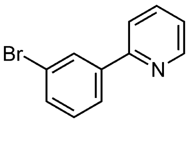
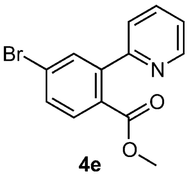
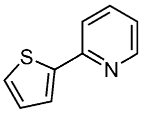
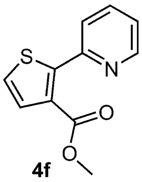
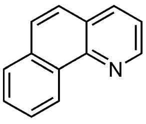
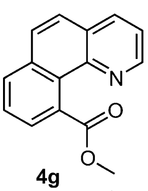
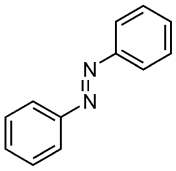
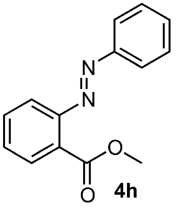
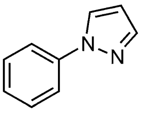
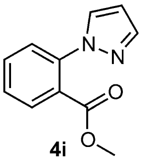
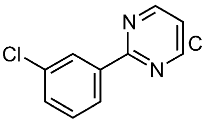
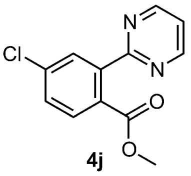
With the optimized conditions in hand (Table 1, entry 27), a screening of different alcohols was performed subsequently. As shown in Table 2, various primary, secondary and tertiary alcohols worked well under our reaction conditions and gave the corresponding esters in moderate to good yields. Nevertheless, no desired product could be detected when phenol, benzyl alcohol or amines was applied instead of aliphatic alcohols.

Successively, various directed arenes (**1b–j**) were screened with methanol (Table 3). Delightfully, a series of functional groups, such as Me, OMe, CF_3 and Br were compatible under our conditions, and gave the desired carbonylation products **4** in moderate to good isolated yields (Table 3, entries 1–4). In

Table 3. Carbonylation of arenes with methanol.[a]



1 **2a** **4**

Entry	Substrate	Product	Yield[b]
1	 **1b**	 **4b**	78%
2	 **1c**	 **4c**	76%
3	 **1d**	 **4d**	55%
4	 **1e**	 **4e**	48%
5	 **1f**	 **4f**	61%
6	 **1g**	 **4g**	64%
7	 **1h**	 **4h**	40%
8	 **1i**	 **4i**	61%
9	 **1j**	 **4j**	63%

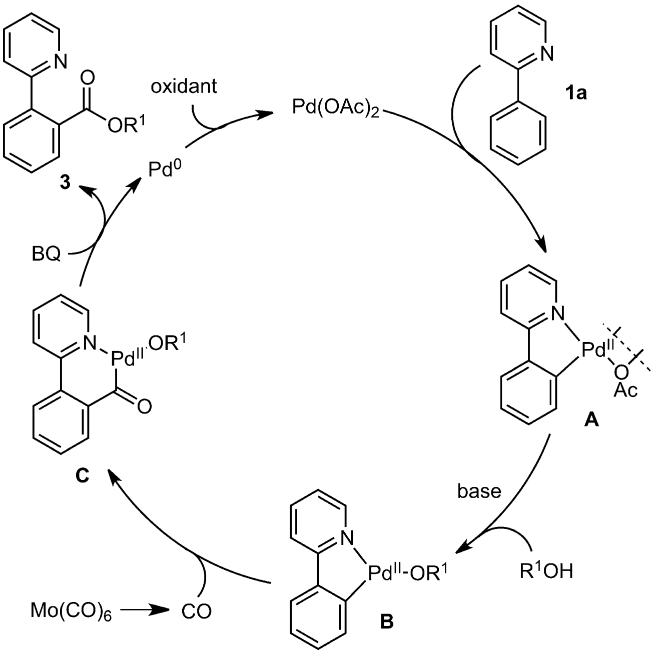
[a] *Reaction conditions:* **1** (0.5 mmol), methanol **2a** (7.5 mmol), BQ (1 mmol), $[Mo(CO)_6]$ (0.2 mmol), $Pd(OAc)_2$ (0.05 mmol), NaOAc (1 mmol) and Ag_2CO_3 (1.5 mmol) in DCE (2 mL) at 80 °C for 18 h.

[b] Isolated yields.

the case of the analogues **1f** and **1g**, the reaction worked efficiently and gave the corresponding carbonylation product **4f** and **4g** in 61% and 64% yields, respectively. Interestingly, 1,2-diphenyldiazene, 1-phenyl-1*H*-pyrazole and 2-phenylpyrimidine as examples of substrates with easily removable directing groups were found to be suitable substrates here as well (Table 3, entries 7–9).[13] Nitrogen heterocycles, such as pyrazole and pyrimidine, served as efficient directing groups and generated the carbonylation products in good yields under the optimal conditions (Table 3, entries 7 and 8). Good yields of the desired products were isolated (**4i–4j**; 40–63%). It's important to mention that 2-ethylpyridine, aniline, acetanilide, *N,N*-dimethylbenzylamine, and *N,N*-dimethylbenzamide were all tested under our standard conditions, but no carbonylation products could be observed.

A plausible reaction pathway is proposed on the basis of the above results and previous studies (Scheme 1).[14] The reaction started with C–H bond activation of 2-phenylpyridine **1a** which generates dimeric palladium intermediate **A**, that undergoes ligand exchange to provide intermediate **B**. Subsequently, a six-membered cyclic intermediate **C** is generated through the coordination and insertion of CO into the Pd–C bond. The final product will be eliminated after reductive elimination of intermediate **C** promoted by BQ which could also acts as a co-oxidant. The meanwhile formed Pd(0) will be re-oxidized to Pd(II) to complete the catalytic cycle.

In conclusion, we have developed a mild and general procedure for palladium-catalyzed alkoxycarbonylation of arenes with $Mo(CO)_6$ as the CO source. A variety of primary, secondary and tertiary alcohols can be applied as substrates here. Additionally, only 0.4 equivalent of $Mo(CO)_6$ as a solid and safe CO source is required for this new procedure. High regioselectivity and good functional group tolerance can be demonstrated, the desired carbonylation products were isolated in moderate to good yields.



Scheme 1. Proposed mechanism.

Experimental Section

General Procedure for Palladium-Catalyzed Oxidative Carbonylation

In a 25-mL sealed tube, a mixture of 2-substituted pyridine **1** (0.5 mmol, 1.0 equiv.), alcohol **2** (7.5 mmol, 15 equiv.), $Pd(OAc)_2$ (11.2 mg, 0.05 mmol, 10 mol%), Ag_2CO_3 (414 mg, 1.5 mmol, 3.0 equiv.), $Mo(CO)_6$ (52.8 mg, 0.2 mmol, 0.4 equiv.), BQ (108 mg, 1.0 mmol, 2 equiv.) and NaOAc (82 mg, 1.0 mmol, 2 equiv.) in DCE (2.0 mL) was stirred at 80 °C under air. After 18 h, the mixture was cooled to room temperature. The residue was diluted with H_2O (10 mL) and extracted with EtOAc (3 × 10 mL). The organic solvent was then evaporated under vacuum. The crude products were purified by using column chromatography on silica gel (pentane/ethyl acetate) to give the pure products.

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6 Palladium-Catalyzed Oxidative Carbonylation of Aromatic C–H Bonds with Alcohols using Molybdenum Hexacarbonyl as the Carbon Monoxide Source

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