Efficient Synthesis of Carboxylic Esters via Palladium(II)-Catalyzed Direct Alkoxycarbonylation of Arenes with CO and Alcohols

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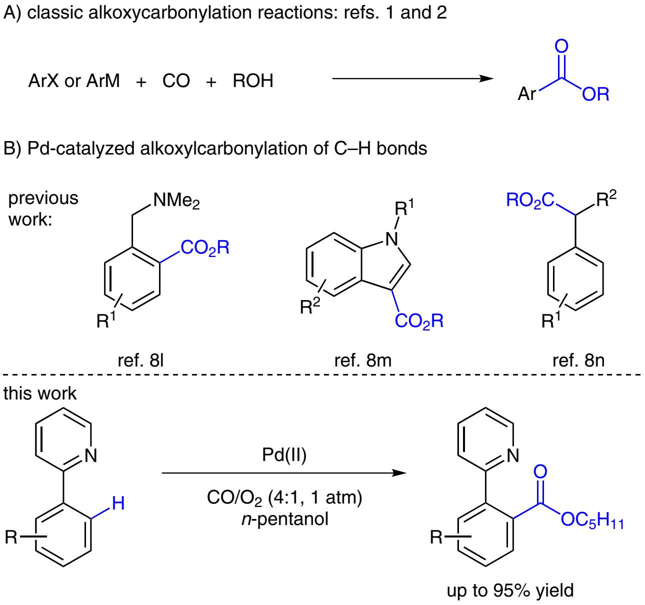
Abstract: An efficient palladium(II)-catalyzed procedure for the alkoxycarbonylation of arenes and heteroarenes with atmospheric pressure carbon monoxide and alcohols was developed to synthesize aryl carboxylic esters.

Key words: palladium, C–H activation, alkoxycarbonylation, CO, carboxylic esters

Aryl carboxylic esters are valuable commodity chemicals and useful synthetic building blocks for agrochemicals, active pharmaceutical ingredients, and process chemicals. Transition-metal-catalyzed carbonylation reactions involving the coupling of aryl halides (ArX) or arylmetallic compounds (ArM) with CO and various nucleophiles, such as alcohols, amines, and carbon nucleophiles, have been increasingly explored and received great success in both academia and industry in the last several decades (Scheme 1, A).[1,2] However, these reactions require multistep sequences to prepare the starting materials (ArX or ArM) and generate stoichimetric byproducts, which is not environmentally friendly and atom economic. Evidently, the direct C–H bond carbonylation of ArH would be an ideal method to construct aryl carboxylic acids and their derivatives in terms of atom- and step-economy.

Recently, great successes have been made in the palladium(II)-catalyzed direct transformation of unactivated C–H bonds into a variety of functional groups through the formation of C–C and C–X bonds.[3] However, palladium(II)-catalyzed direct carbonylation of C–H bonds remains an outstanding challenge.[4–9] Palladium(II)-catalyzed C–H carbonylation reactions were first reported by Fujiwara and co-workers in 1980, in which the substrate was used as the solvent and mixtures of regioisomeric products were obtained in the case of substituted arenes.[5] Little success has been made in this area, until 2004 Orito and co-workers demonstrated the *ortho*-selective carbonylation of *N*-alkyl-ω-arylalkylamines under atmospheric pressure CO to obtain benzolactams.[6] In 2008, the Yu group demonstrated the *ortho*-carbonylation of benzoic and phenylacetic acids.[7] Ever since then, the oxidative carbonylation of arenes with CO in the presence of nucleophiles has received tremendous interests, and various other directing groups have been reported.[8] However, despite of these successes, relatively few examples of the direct alkoxylcarbonylation of arenes with CO and alcohols to form carboxylic esters have been reported yet (Scheme 1, B).[8l–n] Herein, we describe a novel and efficient palladium-catalyzed oxidative alkoxycarbonylation to form esters with atmospheric pressure CO and alcohol coupled with an inexpensive terminal oxidant (Scheme 1, B).[9h]

Our studies commenced with examining the oxidative alkoxycarbonylation of 2-phenylpyridine (**1a**) with atmospheric pressure CO and *n*-pentanol in dioxane.[10] A variety of oxidants and additives were screened, and the results are shown in Table 1. Initially, we found that the alkoxycarbonylation proceeded in 12% yield in the presence of BQ and $NaHCO_3$ (Table 1, entry 1). Further optimization revealed that $CuBr_2$ is the ideal oxidant (Table 1, entry 3). The choice of additives is crucial for the success of this transformation, and NaOAc gave the best yield (Table 1, entries 4–7). After extensive screening, we were delighted to find that oxygen may promote the reaction.[6,8m,p] When the alkoxycarbonylation reaction was



Scheme 1 Palladium-catalyzed alkoxycarbonylation with CO and alcohols

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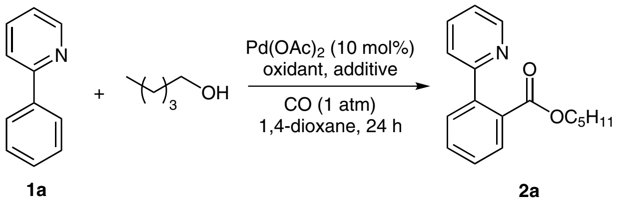
conducted under an atmospheric pressure of the mixture of CO and O_2 (about 4:1, v/v), the yield increased to 48% (Table 1, entry 8). Various reaction parameters were studied next, and we found that the aryl carboxylic ester **2a** could be afforded in 80% yield under our optimized conditions: 10 mol% $Pd(OAc)_2$, 1.0 equivalent $CuBr_2$, 1.0 equivalent NaOAc, and 15 equivalents *n*-pentanol in 1,4-dioxane under CO/O_2 (v/v, 4:1, 1 atm) at 100 °C (Table 1, entry 10).[11]

Table 1 Optimization of Reaction Conditions[a]



Entry	Oxidant	Additive	Alcohol (equiv)	Time (°C)	Yield (%)[b]
1	BQ	$NaHCO_3$	5.0	130	12
2	Oxone	$NaHCO_3$	5.0	130	10
3	$CuBr_2$	$NaHCO_3$	5.0	130	32
4	$CuBr_2$	$NaBF_4$	5.0	130	<5
5	$CuBr_2$	KOAc	5.0	130	20
6	$CuBr_2$	NaOAc	5.0	130	34
7	$CuBr_2$	K_3PO_4	5.0	130	18
8[c]	$CuBr_2$	NaOAc	10.0	130	48
9[c]	$CuBr_2$	NaOAc	15.0	130	66
10[c]	$CuBr_2$	NaOAc	15.0	100	80

[a] Reaction conditions: **1a** (0.2 mmol), $Pd(OAc)_2$ (10 mol%), oxidant (1.0 equiv), additive (1.0 equiv), and *n*-pentanol in 1,4-dioxane (2 mL) under CO (1 atm).

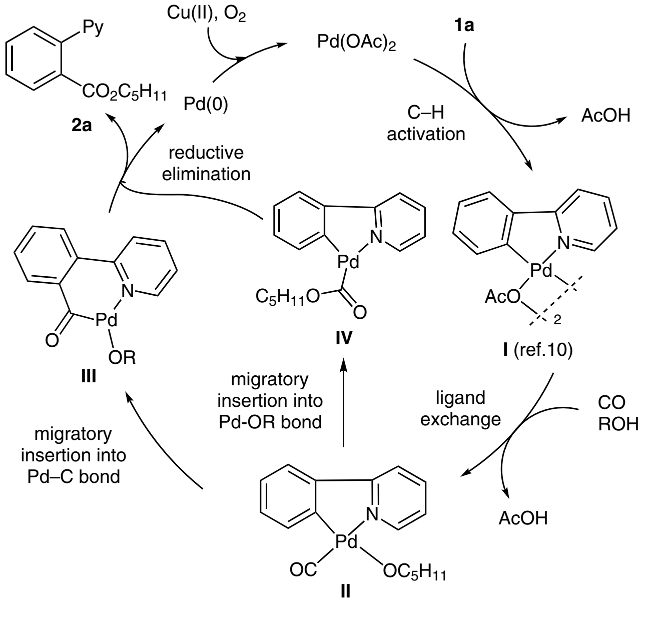
[b] Isolated yield.

[c] CO/O_2 = 4:1 (v/v, 1 atm).

With the optimized conditions in hand, we then explored the scope of pyridine derivatives. Generally, the reactions proceeded smoothly at 100 °C, and the yield of the alkoxycarbonylation product varied from 38% to 95%, depending on the nature of the pyridine derivatives (Table 2). The reaction delivered an array of carboxylic esters with various functional groups, such as carboxylic esters (Table 2, entries 4), methoxyl (Table 2, entries 5 and 10–12), chloride (Table 2, entry 6, and fluoride (Table 2, entry 10). Heteroarene is also tolerated, albeit affording the desired product in a reduced yield (Table 2, entry 9). Ethanol and *tert*-amyl alcohol exhibited no reactivity under the carbonylation reaction conditions. Under the optimal conditions, substrates containing different directing groups, including substituted pyridines and pyrimidine, were examined for this oxidative alkoxycarbonylation reaction. All of them generate the carbonylation products in moderate to good yields under this protocol (Table 2, entries 10–12). As mentioned previously, additives are crucial for this reaction and Li_2CO_3 was found to be a better additive than NaOAc in the reaction of **1i** (Table 2, entry 9). It is interesting to note that the monocarbonylation products were obtained in all cases. Even with pyrimidine as the directing group, the monocarbonylation product **2l** was formed exclusively (Table 2, entry 12). Furthermore, products **2b**,**d**–**2j**,**l** were all obtained with high regioselectivities. In these cases, the alkoxycarbonylation occurs selectively to the less sterically hindered site (Table 2, entries 2, 4–6, and 10–12).

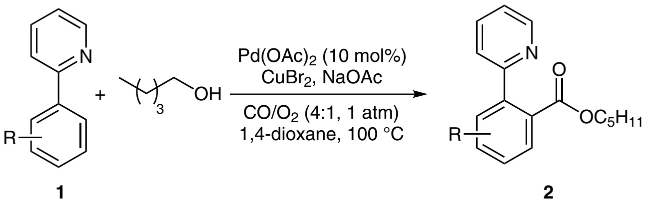
Finally, a plausible mechanism for the present palladium(II)-catalyzed alkoxycarbonylation of 2-phenylpyridine (**1a**) is proposed on the basis of previous studies (Scheme 2). Coordination of **1a** to palladium acetate is followed by C–H activation to form the dimeric palladacycle **I**.[10a] Subsequently, CO and alcohol coordinate to palladium via ligand exchange and release of AcOH. There are two possible pathways for the formation of carboxylic ester **2a** from intermediate **II**: 1) migration insertion of CO into the Pd–C bond to form intermediate **III**, followed by C–O bond reductive elimination; or 2) migration insertion of CO into the Pd–OR bond to form intermediate **IV**, followed by C–C bond reductive elimination. Although theoretical studies have shown that migration insertion of CO into Pd–OR bonds was preferred under certain conditions,[12] either of these pathways can be ruled out at this stage.

In conclusion, we have developed an efficient protocol for the preparation of aryl carboxylic esters via palladium(II)-catalyzed oxidative alkoxycarbonylation of arenes and heteroarenes with atmospheric pressure CO and alcohol.[13] The reaction shows high regioselectivity and reactivity (up to 95% yield). Moreover, this protocol might be further explored to the alkoxycarbonylation of other synthetically useful substrates.



Scheme 2 Plausible mechanism

Table 2 Palladium(II)-Catalyzed Alkoxycarbonylation of Aromatic C–H Bonds with CO and Alcohol[a]



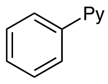
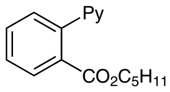
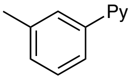
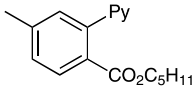
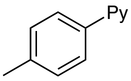
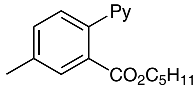
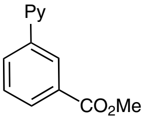
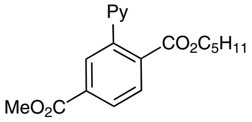
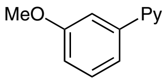
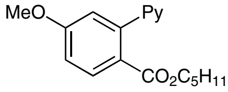
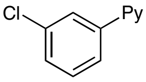
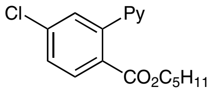
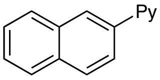
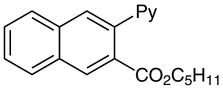
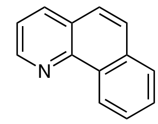
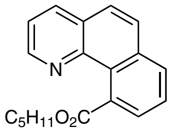
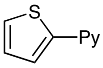
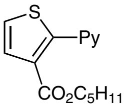
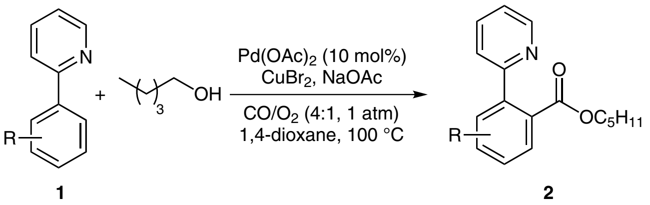
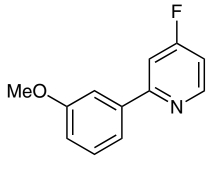
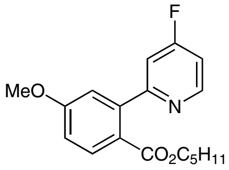
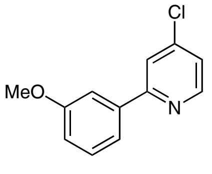
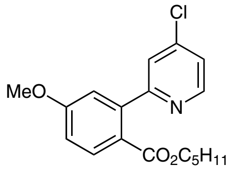
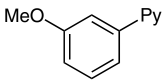
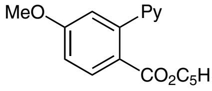
Entry	Substrate	Product	Time (h)	Yield (%)[b]
1	 **1a**	 **2a**	24	80
2	 **1b**	 **2b**	48	63
3	 **1c**	 **2c**	72	91
4	 **1d**	 **2d**	24	55
5	 **1e**	 **2e**	24	70
6	 **1f**	 **2f**	72	38
7	 **1g**	 **2g**	72	87
8	 **1h**	 **2h**	96	95
9	 **1i**	 **2i**	24	58[c]

Table 2 Palladium(II)-Catalyzed Alkoxycarbonylation of Aromatic C–H Bonds with CO and Alcohol[a] (continued)



Entry	Substrate	Product	Time (h)	Yield (%)[b]
10	 **1j**	 **2j**	48	76
11	 **1k**	 **2k**	48	70
12	 **1l**	 **2l**	24	77

[a] Reaction conditions: **1a** (0.2 mmol), Pd(OAc)$_2$ (0.02 mmol), CuBr$_2$ (0.2 mmol), NaOAc (0.2 mmol), and *n*-pentanol (3.0 mmol) in 1,4-dioxane (2 mL) under CO/O$_2$ (1 atm, v/v = 4:1) at 100 °C.
[b] Isolated yields.
[c] NaOAc was replaced by Li$_2$CO$_3$.

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Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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(11) **General Procedure for Alkoxycarbonylation of 1 with CO and Alcohols**

A mixture of substrate **1** (0.2 mmol), Pd(OAc)$_2$ (10 mmol%), CuBr$_2$ (0.2 mmol), NaOAc (0.3 mmol), alcohol (3.0 mmol), and dioxane (2.0 mL) in a 50 mL Schlenk tube (purged with CO/O$_2$ = 4:1) was heated at 100 °C for 24 h. The reaction mixture was cooled to r.t. and concentrated in vacuo. The residue was purified by chromatography on silica gel to afford the desired product **2**.

Pentyl 4-Methyl-2-(pyridin-2-yl)benzoate (2b)

Compound **2b** was prepared in 63% yield according to the general procedure as an oil. ^{1}H NMR (400 MHz, CDCl$_3$): δ = 8.64 (d, *J* = 4.8 Hz, 1 H), 7.77 (d, *J* = 7.6 Hz, 1 H), 7.72 (d, *J* = 7.6 Hz, 1 H), 7.41 (d, *J* = 7.6 Hz, 1 H), 7.34 (s, 1 H), 7.27 (d, *J* = 7.6 Hz, 2 H), 4.04 (t, *J* = 6.8 Hz, 2 H), 2.43 (s, 3 H), 1.41–1.35 (m, 2 H), 1.25–1.19 (m, 2 H), 1.11–1.04 (m, 2 H), 0.83 (t, *J* = 7.2 Hz, 3 H). ^{13}C NMR (100 MHz, CDCl$_3$): δ = 168.6, 159.2, 149.0, 141.6, 141.2, 135.9, 130.7, 130.1, 128.9, 123.0, 121.9, 55.0, 28.0, 22.3, 21.4, 13.9. HRMS (EI-TOF): *m/z* calcd for $C_{18}H_{21}NO_2$ [M$^+$]: 283.1572; found: 283.1573.

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