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Pd(II)-catalyzed oxidative alkoxycarbonylation of 2-phenoxypyridine derivatives with CO and alcohols†

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A Pd(II)-catalyzed oxidative alkoxycarbonylation of phenol derivatives with atmospheric pressure of CO–O_2 and alcohols has been achieved. The reaction provides an efficient strategy for the synthesis of carboxylic esters and can be applied to the late-stage modification of complex molecules.

Since the pioneering work of Heck and co-workers in the 1970s on palladium catalyzed carbonylation reactions, the application of CO as a cost-efficient C_1 building block to access carboxylic acid derivatives has attracted tremendous interest in the past 40 years.[1–3] However, this method necessitates the use of prefunctionalized starting materials, which require additional synthetic operation, and thus reduces the overall efficiency of this transformation. For this reason, transition-metal catalyzed direct carbonylation of relatively unactivated C–H bonds has emerged as an increasingly viable alternative to the traditional method.[4] Since the seminal work of Fujiwara in 1980,[5] direct oxidative carbonylation of C–H bonds with CO in the presence of various nucleophiles using palladium, ruthenium, and rhodium catalysts has undergone rapid development.[6–10] Amine derivatives have long been used as directing groups for the oxidative carbonylation. In 2004, Orito developed a Pd(II)-catalyzed direct aromatic carbonylation that affords benzolactams from secondary ω-phenylalkyl amines.[7a] In 2011, Zhu developed an efficient synthesis of quinazolin-4(3*H*)-ones from *N*-aryl amidines through palladium catalyzed intramolecular C(sp^2)–H carboxamidation.[7e] Later, Zhu and Zhang developed an unprecedented C–H aminocarbonylation reaction using unprotected aniline NH_2 as a directing group,[7j,k] and various free (NH) phenanthridinone derivatives were efficiently synthesized. Yu and coworkers developed the first palladium catalyzed carbonylation of aromatic C–H bonds directed by hydroxyl auxiliary using amino acid ligands to promote the reaction.[7l] Recently, Huang and co-workers reported an efficient method for the synthesis of phenylacetic acid esters from simple toluenes through Pd-catalyzed non-directed benzylic C–H bond activation in the presence of CO.[6] Beller and co-workers reported a ruthenium catalyzed carbonylative C–C bond formation by directed C–H functionalization.[8f] In these reports, however, nucleophiles are mainly restricted to heteroatoms in the directing groups with active protons (Fig. 1A), such as amines[7a–k,8a–c] or alcohol,[7l,m,9] or carbon nucleophiles (Fig. 1B), such as alkenes[8d,e] or arenes.[7o,8f]

Aromatic and heteroaromatic carbonyl compounds are vital intermediates in the manufacture of agrochemicals, dyes, pharmaceuticals, and other industrial products. Palladium-catalyzed coupling reactions have become a powerful tool in organic synthesis. Today, there are numerous applications of palladium-catalyzed carbonylation in the preparation of pharmaceuticals, agrochemicals, and advanced materials both on the laboratory and industrial scales. However, Pd(II)-catalyzed intermolecular alkoxycarbonylation of arenes with CO and alcohols remains a great challenge.[10] Shi reported a Pd(II)-catalyzed carbonylation of *N*,*N*-dimethylbenzylamines with the assistance of LiCl.[10b] Very recently, our group reported an

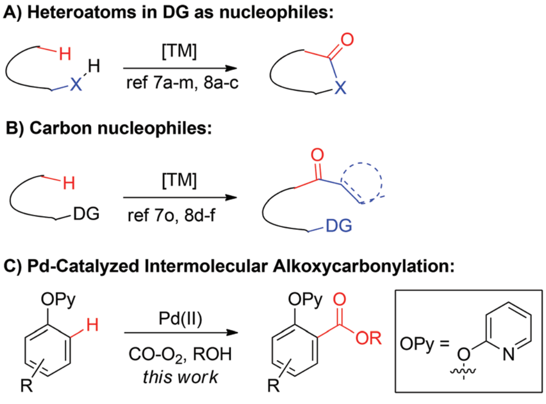

Fig. 1 Transition-metal-catalyzed C–H carbonylation.

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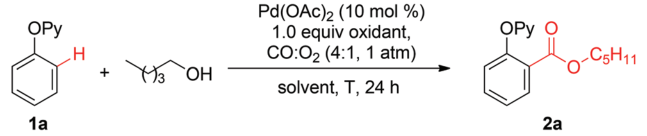
efficient protocol for the preparation of aryl carboxylic esters *via* palladium(II)-catalyzed alkoxycarbonylation of arenes and heteroarenes with atmospheric pressure of CO and alcohols.[10c] In our continuous studies of the synthesis of bioactive molecules *via* C–H functionalization, we are particularly interested in C–H functionalization directed by removable directing groups.[11] Herein, we report an efficient protocol for the synthesis of carboxylic esters *via* Pd-catalyzed alkoxycarbonylation of 2-phenoxypyridines under atmospheric pressure of CO and O_2 (Fig. 1C).[12]

We commenced our studies by probing a variety of oxidants for the alkoxycarbonylation of **1a** with pentanol (15 equiv.) in the presence of a balloon pressure of CO/O_2 (4 : 1, v/v, Table 1). The use of $CuBr_2$ as an oxidant gave only unsatisfactory results (entries 1–4); unfortunately a number of solvents, such as DCE, DMF and toluene, were tested in the presence of $CuBr_2$: they were ineffective for the reaction (entries 2–4). To improve the reaction further, we evaluated the influence of other reaction parameters. As shown in Table 1, a more promising result was obtained using $CuSO_4$ as an oxidant and 1,4-dioxane as a solvent (entry 5, 55% yield). A variety of other oxidants, such as CuCl, $AgBF_4$, AgOTf, AgOAc and AgTFA, were then tested, and the desired product was obtained in 75% yield when AgTFA was used as the oxidant (entries 6–10). A reduced yield was obtained in the absence of O_2, since oxygen might be a co-oxidant in this reaction (entry 11, 41%). Among the reaction temperatures examined, it turned out that the yield decreased when the temperature was lower than 100 °C or higher than 100 °C (entries 12 and 13); at last it was revealed that the transformation was best conducted at 100 °C (entries 10 and 12–14).

Table 1 Optimization of the reaction conditions[a]



1a **2a**

Entry	Oxidant	T (°C)	Solvent	Yield[b] (%)
1	$CuBr_2$	100	1,4-Dioxane	10
2	$CuBr_2$	100	CH_2Cl_2	0
3	$CuBr_2$	100	Toluene	0
4	$CuBr_2$	100	$ClCH_2CH_2Cl$	0
5	$CuSO_4$	100	1,4-Dioxane	55
6	CuCl	100	1,4-Dioxane	31
7	$AgBF_4$	100	1,4-Dioxane	37
8	AgOTf	100	1,4-Dioxane	Trace
9	AgOAc	100	1,4-Dioxane	0
10	**AgTFA**	**100**	**1,4-Dioxane**	**75**
11[c]	AgTFA	100	1,4-Dioxane	41
12	AgTFA	80	1,4-Dioxane	47
13	AgTFA	90	1,4-Dioxane	66
14	AgTFA	110	1,4-Dioxane	70

[a] Reaction conditions: **1a** (0.4 mmol), $Pd(OAc)_2$ (10 mol%) and oxidant (0.4 mmol) in 2 mL solvent for 24 h. [b] Yields are given for isolated products after chromatography. [c] 1 atm CO only.

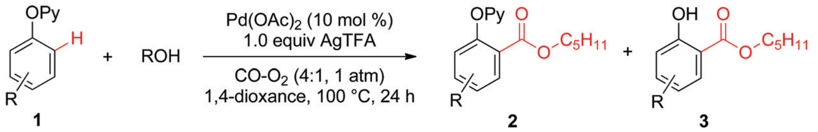
With the optimized conditions in hand, we examined the scope and limitations of the alkoxycarbonylation process (Table 2). We were pleased to find that a variety of phenol derivatives were compatible with the optimal conditions and could be converted to the desired carboxylic esters in modest to good yields (up to 92%). An *o*-methylphenol derivative gave a reduced yield (**2b**, 30%) due to the steric hindrance between the directing group and the methyl group in the *ortho*-position. Other methyl-substituted phenols gave reasonable yields as shown. Surprisingly, 3,5-dimethylphenol derivative **1e** reacted smoothly to give the desired product in 67% yield, regardless of the steric congestion in the *ortho*-position. Phenol derivatives containing electron-donating groups were generally more reactive and afforded higher yields (**2f**–**2h**). Fluoride is also compatible with the process, albeit affording the product in lower yield (**2i**, 37%). Primary alcohols, such as MeOH and EtOH, gave moderate yields (**2k** and **2l**, 64% and 67%, respectively). Notably, secondary alcohols, such as isopropanol, were also compatible with this protocol (**2m**, 71%). When CF_3CH_2OH and phenol were used, the *ortho*-alkoxycarbonylated products were hydrolyzed to phenols under the standard reaction conditions (**3n**, 50%, and **3o**, 48%). The same thing happened to *m*-methoxylphenol and 1-naphthol derivatives (**3g**, 73%, and **3j**, 84%). It is interesting to note that monocarbonylation products were obtained in all cases from the corresponding substrates.

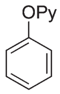
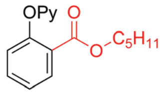
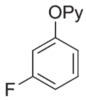
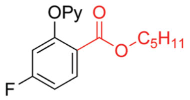
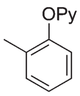
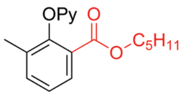
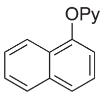
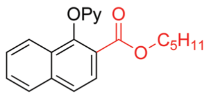
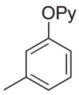
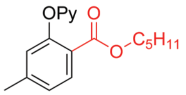
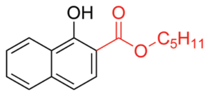
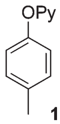
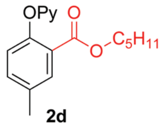
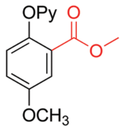
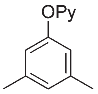
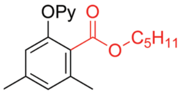
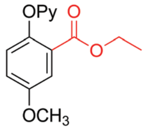
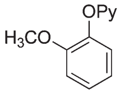
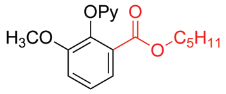
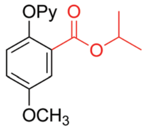
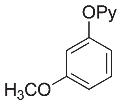
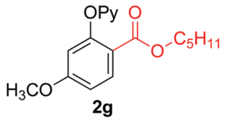
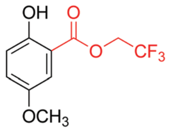
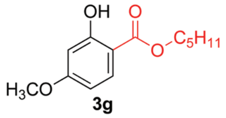
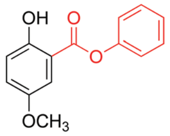
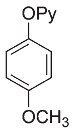
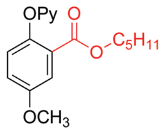
We were delighted to find that the palladium-catalyzed alkoxycarbonylation reaction was compatible with a natural-product-derived substrate, such as estrone, as shown in Scheme 2. The pyridyl auxiliary can be installed *via* a copper-catalyzed C–O bond formation of estrone (**4**).[13] Subsequently, the alkoxycarbonylation can be achieved selectively at the less sterically hindered C–H bond under our optimal reaction conditions (**5a**, 53% yield with phenol; **5b**, 52% yield with pentanol). This process highlights the potential utility of this reaction in the late-stage modification of complex molecules (Scheme 1). It is worth noting that the pyridine auxiliary can be removed as demonstrated by Ackermann and Wu.[12a–c]

To check the reversibility of the C–H activation step, a reaction using substrate **1h** was carried out in CD_3OD in the absence of CO (Scheme 2). No deuterium incorporation was detected even after 24 h. When the same reaction was conducted in the presence of CO and was stopped after 24 h, no deuterium incorporation was observed in the starting material **1h** or in the product. These deuterium experiments suggested that the C–H activation step was irreversible.

Although the details of the mechanism of this reaction remain to be elucidated, a plausible mechanism can be proposed on the basis of the above results and previous studies (Fig. 2).[12c] First, as reported previously, coordination of Pd(II) with 2-phenoxypyridine (**1**) triggers cyclopalladation to form the dimeric palladacycle **A**, which has been characterized by X-ray crystallographic analysis.[12c] Intermediate **B** is then formed *via* ligand exchange. Subsequently, 1,1-migratory insertion of CO into the Pd–C bond to a seven-membered cyclic

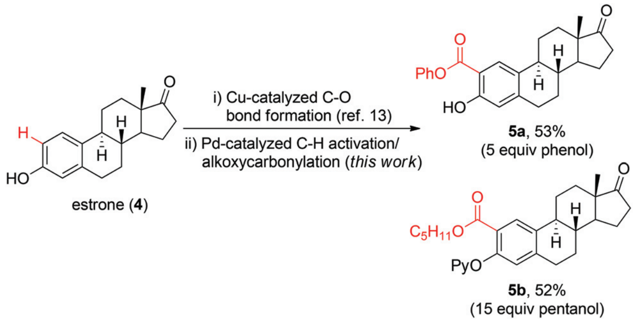
Table 2 The scope of olefins



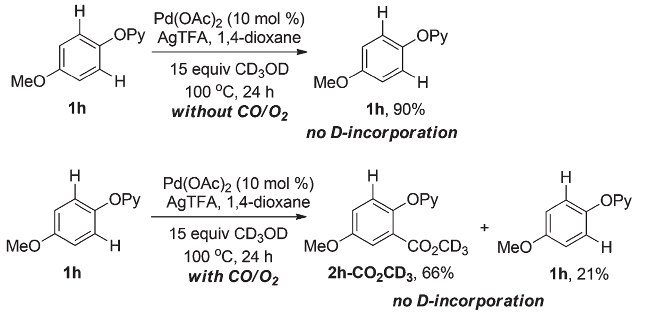
Entry	Substrate	Product	Yield[a] [%]	Entry	Substrate	Product	Yield[a] [%]
1	 **1a**	 **2a**	75	9	 **1i**	 **2i**	37
2	 **1b**	 **2b**	30	10	 **1j**	 **2j**	15
3	 **1c**	 **2c**	50			 **3j**	84[b]
4	 **1d**	 **2d**	50	11	**1h**	 **2k**	64
5	 **1e**	 **2e**	67	12	**1h**	 **2l**	67
6	 **1f**	 **2f**	44	13	**1h**	 **2m**	71
7	 **1g**	 **2g**	24[c]	14	**1h**	 **3n**	50
		 **3g**	73[b,c]	15	**1h**	 **3o**	48
8	 **1h**	 **2h**	92				

[a] Isolated yield. [b] Py was removed. [c] $CuSO_4$ was used as an oxidant.

intermediate **C** takes place, followed by C–O bond reductive elimination to afford the desired product (**2a**) and Pd(0). Finally, Pd(0) is oxidized by Ag(I)/O_2 to regenerate Pd(II), which would finish the catalytic cycle. However, an alternative route that involves the insertion of CO into the Pd–OR bond cannot be ruled out at this stage (Fig. 2).[10b,14]



Scheme 1 Derivatization of estrone.



Scheme 2 Deuteration experiments probing the reversibility of the C–H activation step.

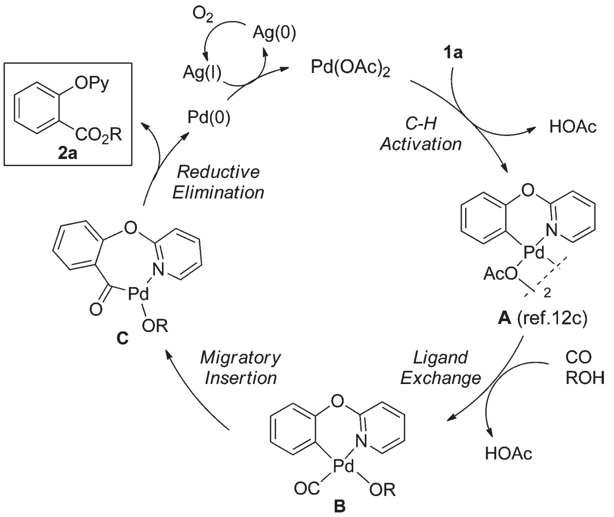


Fig. 2 Proposed mechanism of the Pd(II)-catalyzed alkoxycarbonylation reaction.

Conclusions

In conclusion, we have achieved a Pd(II)-catalyzed oxidative alkoxycarbonylation of phenol derivatives with atmospheric pressure of CO–O_2 and alcohols. This protocol obviates the need for pre-functionalization to generate aryl halide and utilize carbon monoxide, providing an efficient strategy for the synthesis of carboxylic esters. Furthermore, we demonstrate the utility of this protocol in the derivatization of a natural product, which showcases that this reaction could be applied in late stage total synthesis.

Acknowledgements

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