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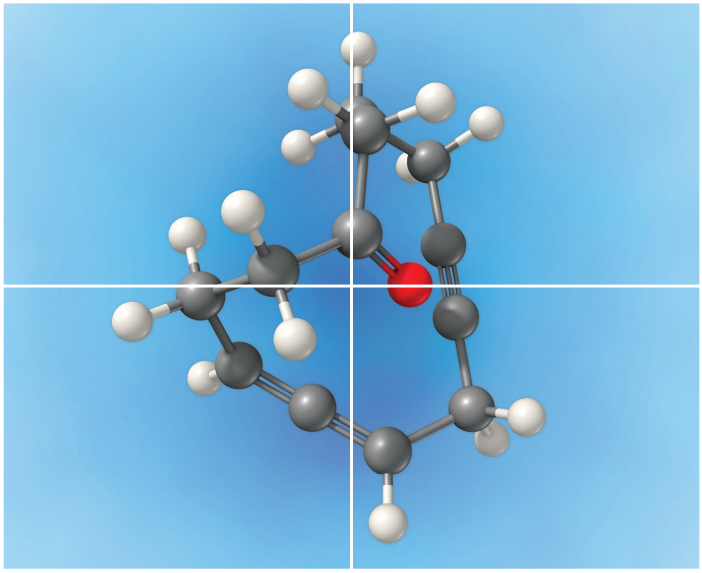

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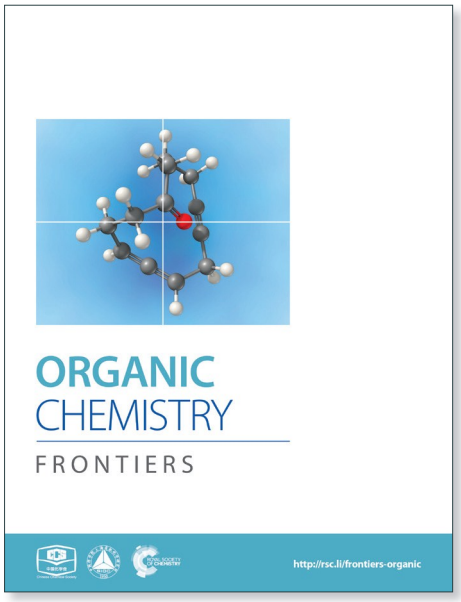

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Pd-Catalyzed Cross-Coupling of Aromatic Compounds with Carboxylic Acids via C-H Bond Activation

Cite this: DOI: 10.1039/xoxxoooooox

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Received ooth January 2012,
Accepted ooth January 2012

DOI: 10.1039/xoxxoooooox

www.rsc.org/

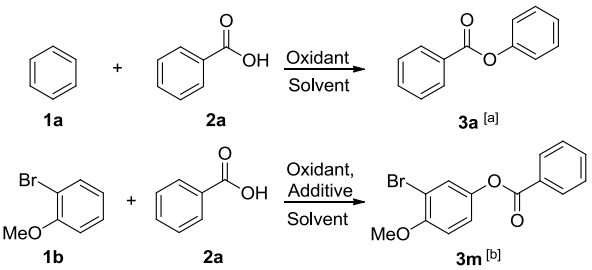
An efficient synthesis for an oxidative coupling of aromatic compounds with carboxylic acids *via* Pd-catalyzed C-H bond activation and C-O bond formation has been developed. This catalytic system works in a simple and efficient manner, by simply using aromatic compounds and carboxylic acids as coupling partners for C-O bond formation to synthesize esters with good to excellent yields.

In the past few decades, transition-metal-catalyzed functionalization of C-H bond is emerging as a versatile strategy for chemical synthesis.[1] A great number of novel organic reactions via C-H cleavage have been developed, and a variety of chemical bonds can be formed through this efficient manner, including carbon-carbon[2] and carbon-heteroatom[3-8] bond formation. Among them, C-O bond formation is quite challenging and less reported in the literature. This is probably due to high electronegativity of the element and may also be due to the metal-oxygen bond strength. To achieve the purpose for coupling an acid with arenes, Crabtree and co-worker[9] developed a strategy that employed iodosobenzenediacetate as the carboxylate source. Since then, a variety of C-H acetoxylation reactions have been developed. Concurrently, peroxide has also proven to be an effective promoter in Pd(II)-catalyzed C-H acetoxylation.[10] It is noted that direct acyloxylation of C-H bonds was realized with the assistance of directing groups recently,[11] while these reactions are limited to acetoxylation.

Recently, Yu[12] and Shi[13] first reported a Pd-catalyzed cyclization approach to form the benzofuranone through the C-H activation via intramolecular C-O formation sequence. However, report on catalyzation of intermolecular formation of ester by coupling of aromatic compounds with variety of acids via C-H bond activation has not been well developed.[14] Herein, we report a successful example of a straightforward and versatile method to obtain a variety of ester structure through palladium catalysed intermolecular oxidative coupling of simple aromatic compounds with readily available carboxylic acids.

Conditions were set up to facilitate high-yielding and direct coupling of aromatic compounds with carboxylic acids using $Pd(OAc)_2$ as the catalyst. Key development of this reaction involved using 1) commercially available iodosobenzene and carboxylic acids. 2) Iodosobenzene as an oxidant while the reaction was conducted under mild carboxylic acids condition in order to form the active coupling partner *in situ*. In these reactions, two general sets of conditions, **A** and **B**, were identified to the substrates of the arenes. Condition **A** was meant for simple and cheap benzene substrates where benzene was used as a solvent. Optimization was obtained when benzene **1a** reacted with benzoic acid **2a** (Table 1, entries 1-10). The reaction gave phenyl benzoate **3a** in 82% yield as the main product by employing $Pd(OAc)_2$ as the catalyst and iodosobenzene as the oxidant (Table 1, entry 6). However, when iodosobenzene diacetate was used instead of iodosobenzene, the product yield decreased to 42% (Table 1, entry 5). Utilization of other oxidants, such as $Na_2S_2O_8$, oxone, Ag_2O, and $Cu(OAc)_2$ did not favor the reaction (Table 1, entries 1-4), neither did other solvents yield a better result (Table 1, entries 7-10). In contrast, condition **B** was established for heavily functionalized or valuable arenes in which dichloroethane (DCE) was used as the solvent. Optimization was also obtained when 2-bromoanisole **1b** react with benzoic acid **2a** (Table 1, entries 11-18). 3-Bromo-4-methoxyphenyl benzoate **3m** was obtained in 88% of the yield in DCE at 120 ℃ when iodosobenzene and camphorsulfonic acid (CSA) were used as an oxidant and additive respectively (Table 1, entry 14). Other additives such as *p*-toluenesulfonic acid (TsOH), trifluoroacetic acid (TFA), trifluoromethylsulfonic acid (TfOH) did not improve the reaction (Table 1, entries 16-18). The screening of solvents showed that DCE was the most effective solvent for this reaction as compared to chloroform, dimethylformamide, dimethylsulfoxide and acetonitrile(Table 1, entries 11-13, 15).

Table 1 Optimization of reaction conditions.

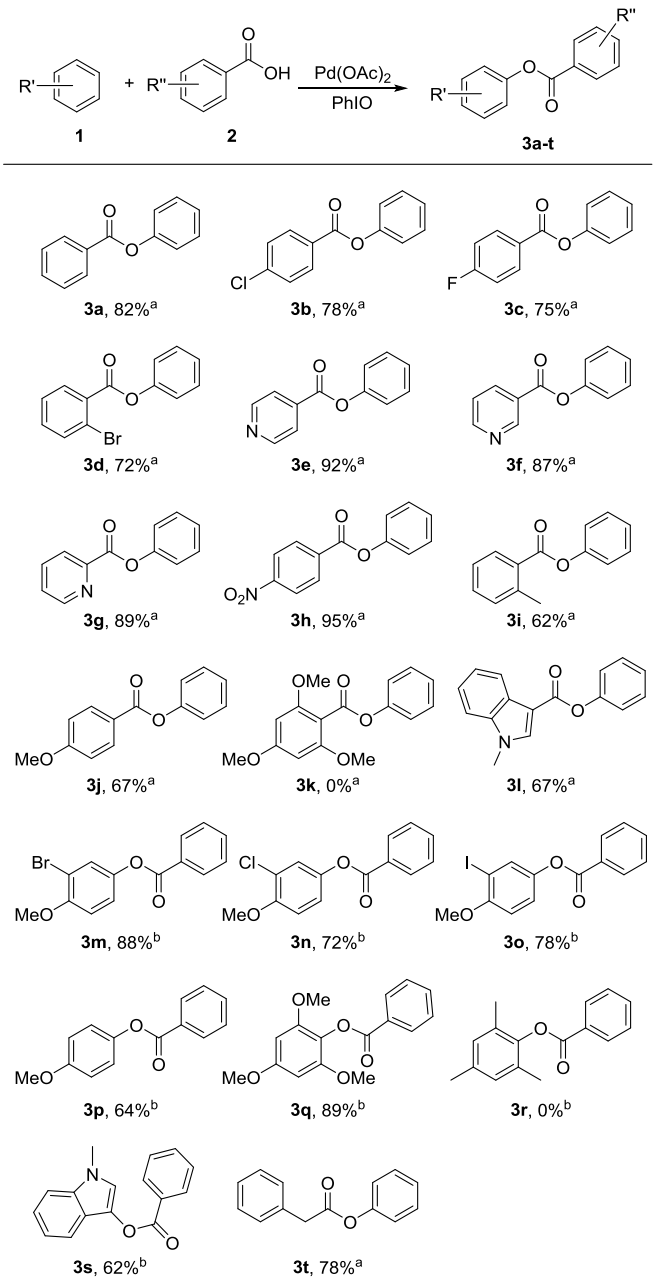


Entry	Solvent	Oxidant,	Product	Yield[c]
1[a]	Benzene	$Na_2S_2O_8$	**3a**	Trace
2[a]	Benzene	Oxone	**3a**	NR
3[a]	Benzene	Ag_2O	**3a**	NR
4[a]	Benzene	$Cu(OAc)_2$	**3a**	NR
5[a]	Benzene	$PhI(OAc)_2$	**3a**	42
6[a]	Benzene	PhIO	**3a**	82
7[a]	ACN	PhIO	**3a**	NR
8[a]	DCE	PhIO	**3a**	Trace
9[a]	DMF	PhIO	**3a**	NR
10[a]	1, 4-dioxane	PhIO	**3a**	NR
11[b]	ACN	PhIO, CSA	**3m**	Trace
12[b]	DMF	PhIO, CSA	**3m**	NR
13[b]	$CHCl_3$	PhIO, CSA	**3m**	78
14[b]	DCE	PhIO, CSA	**3m**	88
15[b]	DMSO	PhIO, CSA	**3m**	NR
16[b]	DCE	PhIO,TsOH•H_2O	**3m**	30
17[b]	DCE	PhIO, TFA	**3m**	Trace
18[b]	DCE	PhIO, TfOH	**3m**	Trace

[a]Condition **A**: Benzoic acid **2a** (0.5 mmol), $Pd(OAc)_2$ (5 mol%), oxidant (2.0 mmol), solvent (2 mL), 120 ℃, 40 h.
[b]Condition **B**: 2-bromoanisole **1b** (1.0 mmol), Benzoic acid **2a** (0.5 mmol), $Pd(OAc)_2$ (5 mol%), iodosobenzene (1.5 mmol), additive (1.5 mmol), solvent (2 mL), 120 ℃, 40 h.
[c]Isolated yields.

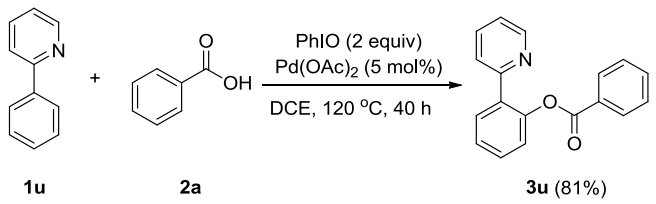
Under the optimized conditions, the substrates scope was examined as shown in **Table 2**. A variety of carboxylic acid reagents were used and they reacted with various aromatic compounds to afford the corresponding esters in moderate to good yields (**3a-3t**). Electron-donating, electron-withdrawing, and potentially sensitive functional groups including fluoro (**3c**), chloro (**3b**, **3n**), bromo (**3d**, **3m**), iodo (**3o**), nitro (**3h**), methyl (**3i**) and methoxy (**3j**, **3m**, **3n**, **3o**, **3p**, **3q**) groups as well as heterocycles, such as pyridyl (**3e**, **3f**, **3g**) and indolyl groups (**3l**, **3s**) were tolerated. The results in **Table 2** revealed that this procedure exhibited electronic dependence. Electron-deficient carboxylic acids exhibited higher reactivity than those of electron-rich substrates. Carboxylic acids substituted with electron-withdrawing group, such as chloro (**3b**), fluoro (**3c**), bromo (**3d**) and nitro (**3h**) were converted into the desired products smoothly in good to excellent yields, whereas only moderate yields were obtained for electron rich carboxylic acids, e.g. *o*-toluic acid (**3i**), anisic acid (**3j**) and *N*-methyl-3-indolecarboxylic acid (**3l**). Furthermore, no desired product was observed when employing 2,4,6-trimethoxybenzoic acid (**3k**) as the substrate. The substituents on the aromatic substrates also influenced the efficiency of the coupling reaction significantly. It was noted that only electron rich aromatic compounds can be employed for our procedure. In addition, aliphatic carboxylic acid can also be subjected to the reaction, with

Table 2 Palladium catalyzed direct coupling of aromatic compounds **1** with carboxylic acids **2**.



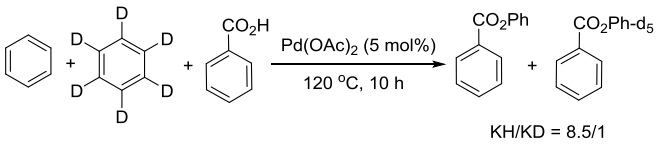
[a]Condition **A**: Carboxylic acid **2** (0.5 mmol), $Pd(OAc)_2$ (5 mol%), iodosobenzene(1.0 mmol), benzene **1a** (2 mL), 120 ℃, 40 h.
[b]Condition **B**: Aromatic compound **1** (1.0 mmol), benzoic acid **2a** (0.5 mmol), $Pd(OAc)_2$ (5 mol%), iodosobenzene (1.0 mmol), camphorsulfonic acid (0.75 mmol), DCE (2 mL), 120 ℃, 40 h.
[c]Isolated yields.

product (**3t**) obtained in good yield when phenyl-acetic acid was employed as the substrate.The present catalytic systems are also applicable to the chelation assisted C-H bond functionalization reaction. Under the optimized condition **B**, product (**3u**) was obtained in 81% yield when 2-phenylpyridine and benzoic acid was used as the coupling partners in the absence of additive CSA (**Scheme 1**).



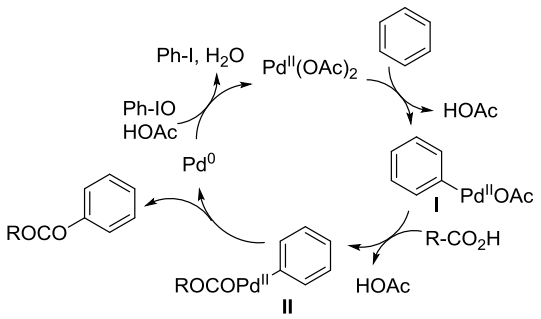
Scheme 1 Chelation assisted C-H bond functionalization.

To investigate the mechanism, competitive reaction was carried out using 1:1 ratio of benzene and benzene-d_6. The KIE was determined to be kH/kD = 8.5/1, indicating that the C−H bond cleavage process should be the rate-determining step.



Scheme 2 KIE competitive reaction.

A mechanism for the C-O bond formation reaction could involve Pd(II)-catalyzed C-H cleavage of the C-H bond of arene to form an Ar-Pd(II) intermediate **I** (**Scheme 3**). Intermediate **II** was formed by a ligand exchange process of intermediate **I** with carboxylic acid, followed by C-O reductive elimination to give out the ester product and Pd(0) species. Oxidation of Pd(0) to Pd(II) by iodosobenzene in the presence of acid to complete the catalytic cycle.



Scheme 3 Plausible Mechanism.

Conclusions

In summary, we have developed a versatile strategy for C-O bond formation by coupling aromatic compounds with carboxylic acids *via* Pd-catalyzed C-H bond activation. The present method not only serves as a practical, versatile, and atom-economical alternative to existing synthetic methods, but it also allows facile construction of ester skeletons that have not been easily accessible. Further synthetic exploration of the Pd-catalyzed C-H bond activation and C-O bond formation reaction is currently underway.

Experimental Section

General procedure for Condition A

Carboxylic acid (0.5 mmol), iodosobenzene (1 mmol) and $Pd(OAc)_2$ (5 mol%) and 2 mL benzene were added into the Schlenk tube. The mixture was stirred at 120 ℃ for 40 h and cooled down to room temperature, quenched with 50 mL saturated sodium bicarbonate solution and extracted thrice with ethyl acetate (30mL) and the combined organic phase was dried over Na_2SO_4. After evaporation of the solvents the residue was purified by silica gel chromatography or thin layer chromatography (TLC).

General procedure for Condition B

Benzoic acid (0.5 mmol), aromatic compound (1 mmol), iodosobenzene (1 mmol) and CSA (0.75 mmol) in 2 mL DCE were added into the Schlenk tube. The mixture was heated at 120 ℃for 40 h and cooled down to room temperature, quenched with 50 mL saturated sodium bicarbonate solution and extracted thrice with ethyl acetate (30 mL) and the combined organic phase was dried over Na_2SO_4. After evaporation of the solvents the residue was purified by silica gel chromatography or thin layer chromatography (TLC).

Acknowledgments

We gratefully acknowledge the support by Nanyang Technological University (RG6/13), Singaporefor financial support.

Notes and references

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Electronic Supplementary Information (ESI) available: [Experimental procedures and spectral data for all new compounds]. See DOI: 10.1039/c000000x/

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