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Facile benzofuran synthesis: Palladium-catalyzed carbonylative Suzuki coupling of methyl 2-(2-iodophenoxy)acetates under CO gas-free conditions

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ABSTRACT

A palladium-catalyzed carbonylative Suzuki coupling of methyl 2-(2-iodophenoxy)acetates with arylboronic acids has been developed. The reactions were performed under CO gas-free conditions and the obtained products act as a direct precursor for the synthesis of highly functionalized benzofuran derivatives.

Since the pioneering work by Heck and co-workers in the 1970s,[1] palladium-catalyzed carbonylation reaction has drawn increasing attention due to wide applications in both academic and industrial fields.[2] Carbonylation reactions represent a powerful method for the preparation of carbonyl-containing compounds, including ketones, aldehydes, carboxylic acids and their derivatives. Although significant progress has been made, some limitations still exist; for example reaction outcomes are typically worse with *ortho*-substituted substrates due to steric effects and carbon monoxide gas is usually needed which limits the application of the corresponding methods in laboratories.

On the other hand, diarylketones frequently appear in natural products, pharmaceuticals, and biologically active compounds.[3] Many synthetic methods have been developed for diarylketone synthesis, including the Friedel-Crafts acylation of arenes,[4] Fries-rearrangement,[5] and the acylation of benzoic acid derivatives with organometallic reagents.[6] Alternatively, the palladium-catalyzed carbonylative Suzuki coupling reaction offers another approach to construct diarylketones. Recently, we developed a practical and convenient synthetic method for diarylketone synthesis *via* the palladium-catalyzed carbonylative Suzuki coupling reactions of aryl halides with arylboronic acids, with formic acid as the CO source.[7] However, under these reaction conditions, dramatically decreased yields were obtained when a functional group was located at the *ortho* position of the aryl halides. Hence, this remains a challenge which needs to be solved.

Additionally, benzofuran derivatives have been applied in many areas and the development of new synthetic procedures is an attractive area of research.[8]

Herein, we report the continuation of our work on the preparation of diarylketones *via* palladium-catalyzed carbonylative Suzuki coupling reaction with formic acid as the CO source and the application of the obtained products as a direct precursor for the synthesis of highly functionalized benzofuran derivatives.

Initially, methyl 2-(2-iodophenoxy)acetate and phenyl boronic acid were used as model substrates, with formic acid as the CO source, $Pd(OAc)_2$ as the catalyst, PPh_3 as the ligand and K_2CO_3 as the base, in toluene at 100 °C for 16 h. Gratifyingly, the desired product was obtained in 43% yield (Table 1, entry 1). We then examined the efficiency of various ligands. Monodentate ligands PCy_3 and $BuPAd_2$ gave higher yields, while Xphos resulted in a lower yield (Entries 2–4). Bidentate ligands DPPF and DPPE also provided the desired product in decreased yields (Entries 5–6). Next, various bases including Cs_2CO_3, Ag_2CO_3, Et_3N, DIPEA, and DBU were investigated (Entries 7–11), where Cs_2CO_3 provided the best results. Solvent screening showed that toluene was the optimal solvent for

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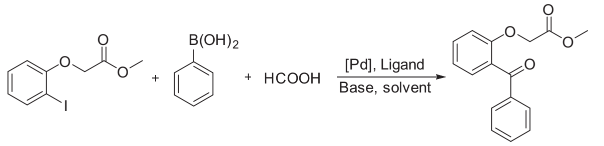
Table 1
Screening of the reaction conditions.[a]



Entry	Catalyst	Ligand	Base	Solvent	Yield (%)[b]
1	$Pd(OAc)_2$	PPh_3	K_2CO_3	Toluene	43
2	$Pd(OAc)_2$	PCy_3	K_2CO_3	Toluene	47
3	$Pd(OAc)_2$	$BuPAd_2$	K_2CO_3	Toluene	55
4	$Pd(OAc)_2$	XPhos	K_2CO_3	Toluene	13
5	$Pd(OAc)_2$	DPPF	K_2CO_3	Toluene	37
6	$Pd(OAc)_2$	DPPE	K_2CO_3	Toluene	34
7	$Pd(OAc)_2$	$BuPAd_2$	Cs_2CO_3	Toluene	67
8	$Pd(OAc)_2$	$BuPAd_2$	Ag_2CO_3	Toluene	23
9	$Pd(OAc)_2$	$BuPAd_2$	Et_3N	Toluene	61
10	$Pd(OAc)_2$	$BuPAd_2$	DIPEA	Toluene	52
11	$Pd(OAc)_2$	$BuPAd_2$	DBU	Toluene	47
12	$Pd(OAc)_2$	$BuPAd_2$	Cs_2CO_3	DMSO	0
13	$Pd(OAc)_2$	$BuPAd_2$	Cs_2CO_3	CH_3CN	Trace
14	$Pd(OAc)_2$	$BuPAd_2$	Cs_2CO_3	DCE	63
15	$Pd(OAc)_2$	$BuPAd_2$	Cs_2CO_3	1,4-Dioxane	55
16	$Pd_2(dba)_2$	$BuPAd_2$	Cs_2CO_3	Toluene	53
17	$PdCl_2(PPh_3)_4$	$BuPAd_2$	Cs_2CO_3	Toluene	0
18	$PdCl_2$	$BuPAd_2$	Cs_2CO_3	Toluene	51
19	$Pd(TFA)_2$	$BuPAd_2$	Cs_2CO_3	Toluene	62

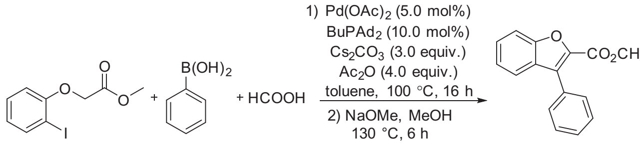
[a] Reagents and conditions: methyl 2-(2-iodophenoxy)acetate (0.5 mmol), phenyl boronic acid (1.0 mmol), catalyst (5.0 mol%), ligand (10.0 mol% for monodentate ligand; 5.0 mol% for bidentate ligand), base (1.5 mmol), formic acid (2.0 mmol), acetic anhydride (2.0 mmol), solvent (4.0 mL), 100 °C, 16 h.

[b] GC yield, with dodecane as an internal standard.

this transformation (Entries 12–15). Other palladium pre-catalysts, including $Pd_2(dba)_3$, $PdCl_2(PPh_3)_4$, $PdCl_2$, and $Pd(TFA)_2$ were also studied, however, no further improvement of the reaction outcome could be obtained (Entries 16–19).

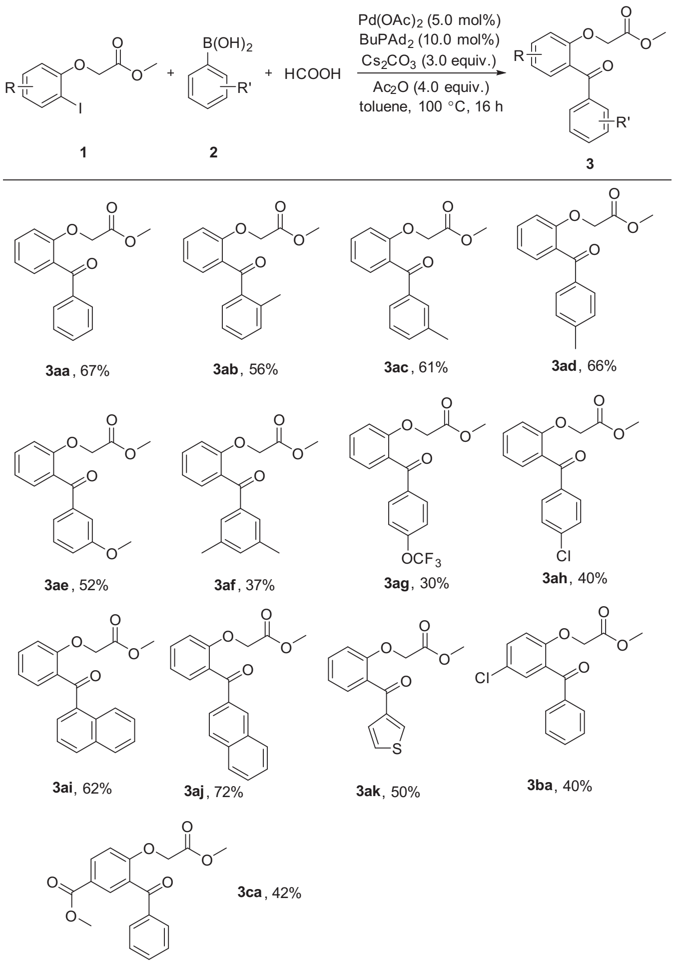
With the best reaction condition in hand, we then turned our attention to examining the substrate scope.[9] As shown in Scheme 1, aryl boronic acids with a single electron-donating group gave the corresponding products in good yields (**3ab**–**ae**), while the 3,5-dimethyl groups resulted in a lower yield (**3af**). Trifluoromethoxy substituted iodides gave the corresponding product in moderate yield (**3ag**). A moderate yield was also obtained with *para*-chloro substitution (**3ah**). Furthermore, 1-naphthyl and 2-naphthyl boronic acids were also studied; the corresponding products were isolated in 62% and 72% yield, respectively (**3ai**–**aj**). 3-Thiophenyl boronic acid was also tolerated and afforded the corresponding product in 50% yield (**3ak**). For aryl iodides, substitution at the *meta*-position to the iodo group with chloro and ester groups provided the corresponding products in 45% and 42% yields, respectively (**3ba**–**ca**).

Under our standard reaction conditions, we then explored a one-pot benzofuran synthesis reaction. After completion of the carbonylative Suzuki coupling reaction, sodium methoxide and methanol were added to the reaction mixture, affording benzofuran (**4**) in 40% yield after heating at 130 °C for 6 h.



4, 40% yield

In summary, we have disclosed a carbonylative Suzuki coupling of methyl 2-(2-iodophenoxy)acetates under gaseous CO-free conditions. Additionally, the one-pot reaction for benzofuran synthesis was also developed.



Scheme 1. Substrate scope for the carbonylative Suzuki coupling reaction. Reagents and conditions: aryl iodides (0.5 mmol), aryl boronic acid (1.0 mmol), $Pd(OAc)_2$ (5.0 mol%), $BuPAd_2$ (10.0 mol%), Cs_2CO_3 (1.5 mmol), formic acid (2.0 mmol), acetic anhydride (2.0 mmol), toluene (4.0 mL), 100 °C, 16 h, isolated yields.

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A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2017.09.063.

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9. General procedure: Pd(OAc)$_2$ (5 mol%), BuPAd$_2$ (10 mol%), phenylboronic acid (1.0 mmol, 2 equiv) and Cs$_2$CO$_3$ (1.5 mmol) were transferred into an oven-dried tube filled with nitrogen. Toluene (4.0 mL), acetic acid-2 (2-iodophenoxy)-methyl ester (0.5 mmol, 1 equiv) and Et$_3$N (4 mmol) were added into the reaction tube. Then a cooled mixture of formic acid (2.0 mmol) and acetic anhydride (2.0 mmol), which was stirred for 1.0 h at 60 °C, was rapidly added to the reaction tube and the reaction mixture stirred for 14–16 h at 100 °C. Upon completion, the reaction mixture was concentrated and purified by silica gel column chromatography.