Palladium-Catalyzed Cross-Coupling Reaction of Arylboronic Acids with Chloroformate or Carbamoyl Chloride

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Abstract: The first palladium-catalyzed cross-coupling reaction between substituted arylboronic acids and chloroformate or carbamoyl chloride is described. One-carbon homologation from arylboronic acids was achieved to give corresponding esters or amides in good yields.

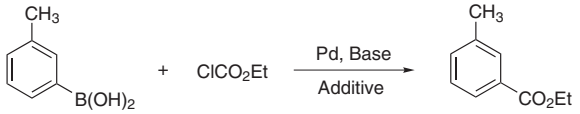
Key words: cross-coupling reaction, palladium, boronic acid, arylcarboxylic ester, arylcarboxamide

Arylcarboxylic esters and arylcarboxamides are useful building blocks both for laboratory synthesis as well as industrial manufacturing.[1] Among the methods for preparing these compounds, metal-catalyzed carbonylation of aryl halides using carbon monoxide as the carbonyl source in the presence of amines or alcohols is a popular way.[2] The toxicity of carbon monoxide and the troublesome gas handling procedures limit it for the high-throughput chemistry involved in pharmaceutical industry.[3] To avoid the use of gaseous carbon monoxide, modified processes appeared by using the solid carbon monoxide releasing reagents such as $Ni(CO)_4$,[4] and $Mo(CO)_6$,[5] and $Na_2Fe(CO)_4$.[6] Alternative ways to the above process are the carbamoylation of aryl halides with carbamoylstannanes,[7] carbamoylsilanes[8] or DMF.[9] But to the best of our knowledge, alkoxycarbonylation of aryl halides with alkoxycarbonylmetals has not yet been reported. Jousseaume and his coworkers reported a palladium-catalyzed carbamoylation and alkoxylcarbonylation process of organotin reagents to provide the corresponding esters or amides.[10] This method tolerates a range of functional groups because of the low polarity of the tin–carbon bond. However, it was limited by the toxicity of the organotin reagents.

In comparison with organotin and other organometallics, organoboron reagents are non-toxic, air-stable and readily available. Thus, the organoboron chemistry directed toward organic synthesis has been widely developed.[11] It is also well known that the palladium-catalyzed Suzuki-type reaction is an efficient method for the construction of carbon-carbon bonds. To expand the scope of Suzuki-type reaction, we investigated the cross-coupling reaction of arylboronic acids with chlorofomate or carbamoyl chloride. Herein, we report a convenient preparation of arylcarboxylic esters and arylcarboxamides from arylboronic acids and chloroformate or carbamoyl chloride under mild conditions.

The coupling reactions were carried out using 3-methylphenylboronic acid and ethyl chloroformate as starting materials to optimize the conditions (Table 1). Considering the property of chloroformate is similar to that of acid chloride, we initially tried to conduct the coupling reaction under our previous conditions for the Suzuki-type coupling reaction of cyclopropylboronic acids with acid chlorides.[12] But no desired cross-coupling product was observed (entry 1). When $Pd(PPh_3)_4$ was used instead of $PdCl_2(dppf)$, the expected product was obtained in a low yield (entry 2). Using $K_3PO_4{\cdot}3H_2O$ as the base and $Pd(PPh_3)_4$ as the catalyst, a moderate yield was obtained (entry 3). We had found that the addition of a catalytic amount of Cu_2O can promote the Suzuki-type coupling reactions of arylboronic acids with α-bromoacetates[13] or α-bromoacetamides.[14] When a catalytic amount of Cu_2O

Table 1 Effect of the Reaction Conditions on the Coupling Reaction of 3-Methylphenylboronic Acid and Ethyl Chloroformate[a]



Entry	Conditions	Yield (%)[b]
1[c]	Ag_2O, K_2CO_3, $PdCl_2(dppf)$	–
2[c]	Ag_2O, K_2CO_3, $Pd(PPh_3)_4$	37
3	$K_3PO_4{\cdot}3H_2O$, $Pd(PPh_3)_4$	54
4	Cu_2O, $K_3PO_4{\cdot}3H_2O$, $Pd(PPh_3)$	73
5	Cu_2O, K_2CO_3, $Pd(PPh_3)$	49
6	Cu_2O, $KF{\cdot}2H_2O$, $Pd(PPh_3)_4$	49
7	Cu_2O, KOH, $Pd(PPh_3)_4$	37

[a] All reactions were carried out using a mixture of 3-methylphenylboronic acid (0.6 mmol), ethyl chloroformate (0.5 mmol), Cu_2O (6 mol%), base (3.3 equiv) and catalyst (3 mol%) in 4 mL of toluene, for 24 h, at 80 °C, under Ar atmosphere (except for entries 1 and 2).
[b] Isolated yields.
[c] Ag_2O (2.0 equiv), K_2CO_3 (2.0 equiv) was used.

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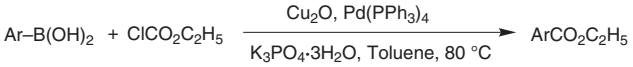
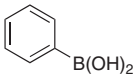
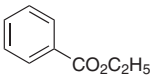
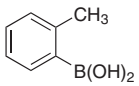
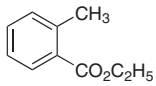
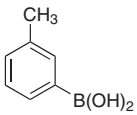
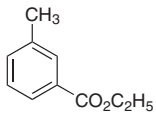
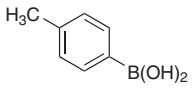
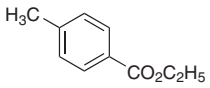
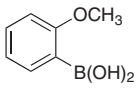
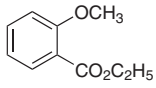
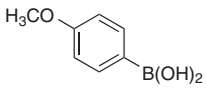
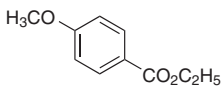
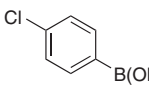
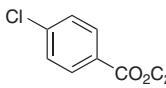
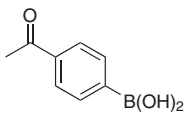
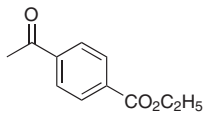
was used in this reaction, an improved yield was obtained (entry 4). Further studies on the effect of bases did not make any improvement (entries 5–7).

The reactions of various arylboronic acids with chloroformate were explored under the optimized conditions (Table 1, entry 4). The results are collected in Table 2.

As shown in Table 2, the cross-coupling reactions proceed readily to give the corresponding arylcarboxylic esters in good yields. The substituent at the *ortho* position of the arylboronic acid somewhat affects the reaction (entries 2 and 5). It is noticeable that electronic effect significantly influences the coupling reaction. The presence of an electron-donating group on the aromatic ring of aryl boronic acid benefits the reaction (entries 3, 4 and 6), while the presence of an electron-drawing group is unfavorable for the reaction (entry 8).

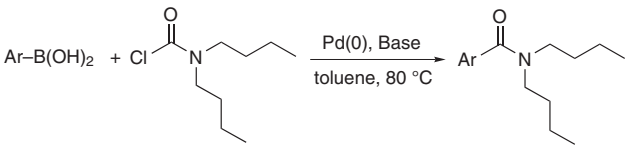
Table 2 Palladium-Catalyzed Cross-Coupling Reactions of Various Arylboronic Acids with Ethyl Chloroformate[a]

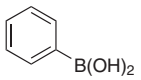
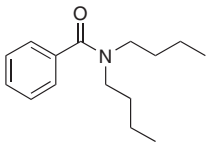
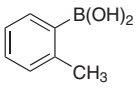
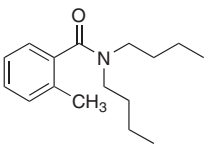
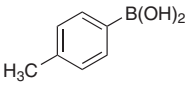
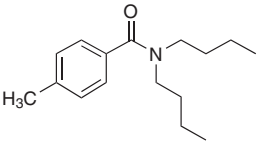
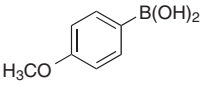
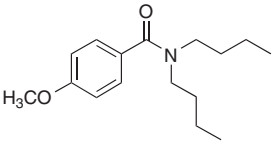
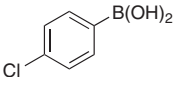
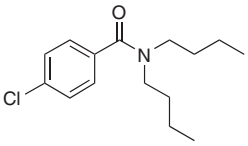
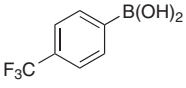
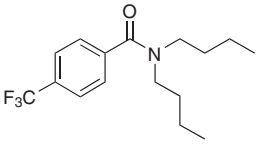
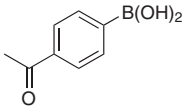
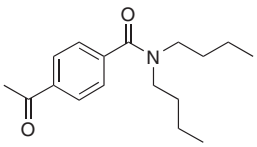


Entry	Arylboronic acid	Product (**a**)	Yield (%)[b]
1			59
2			60
3			73
4			73
5			36
6			78
7			54
8			21

[a] All reactions were carried out using a mixture of arylboronic acid (0.6 mmol), ethyl chloroformate (0.5 mmol), Cu_2O (6 mol%), $K_3PO_4·3H_2O$ (1.65 mmol) and $Pd(PPh_3)_4$ (3 mol%) in 4 mL of toluene, for 24 h, at 80 °C, under Ar atmosphere.
[b] Isolated yield.

Table 3 Palladium-Catalyzed Cross-Coupling Reactions of Various Arylboronic Acids with *N*,*N*-Dibutylcarbamoyl Chloride[a]



Entry	Arylboronic acid	Product (**b**)	Yield (%)[b]
1			93
2			60
3			93
4			86
5			87
6			87
7			89

[a] All the reactions were carried out using a mixture of the organic boronic acid (0.6 mmol), *N*,*N*-dibutyl chloroformamide (0.5 mmol), Cu_2O (6 mol%), $Pd(PPh_3)_4$ (3 mol%), and base (3.3 equiv) in 4 mL toluene, for 24 h, at 80 °C, under Ar atmosphere.
[b] Isolated yields.

The coupling reaction of arylboronic acids with *N*,*N*-dibutylcarbamoyl chloride was also investigated under the same conditions. The carbomylation proceeded smoothly for arylboronic acids bearing either electron-donating or electron-withdrawing groups with good to excellent yields (Table 3). The substituent at the *ortho* position

affects the reaction a little (entry 2). This process tolerates a number of functional groups on the aromatic ring (entries 4–7).

In summary, it was found that the Suzuki-type cross-coupling reactions of arylboronic acids with ethyl chloroformate or *N*,*N*-dibutylcarbamoyl chloride could readily take place to give the corresponding aryl esters and amides by using catalytic amounts of Cu_2O and $Pd(PPh_3)_4$.[15] This process is an efficient route to achieve aryl esters and amides with various functional groups from arylboronic acids. A detailed mechanistic study as well as an examination of the scope of the reaction is currently underway in our laboratory.

Acknowledgment

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(15) **General Procedure**: *m*-Tolylboronic acid (82 mg, 0.6 mmol), $Pd(PPh_3)_4$ (17 mg, 0.015 mmol), Cu_2O (4 mg, 0.028 mmol), $K_3PO_4 \cdot 3H_2O$ (439 mg, 1.65 mmol) were placed in a flask under Ar atmosphere. Toluene (4 mL) and ethyl chloroformate (50 μL, 0.5 mmol) were added and the reaction mixture was stirred at 80 °C for 24 h. The reaction mixture was allowed to cool to r.t., and H_2O (5 mL) was added. The mixture was then extracted with Et_2O (3 × 10 mL). The combined organic layer was washed with brine (3 × 10 mL), dried over $MgSO_4$ and concentrated. The residue was chromatographed on silica gel (elution with hexanes–EtOAc = 30:1) to afford the corresponding ethyl arylcarboxylic ester **3a**. ^1H NMR (300 MHz, $CDCl_3$–TMS): δ = 7.70–7.86 (m, 2 H), 7.30–7.35 (m, 2 H), 4.36 (q, *J* = 7.2 Hz, 2 H), 2.40 (s, 3 H), 1.39 (t, *J* = 7.2 Hz, 3 H) ppm. EIMS: *m/z* (%) = 164 (29) [M^+], 119 (100), 91 (51), 164 (29), 136 (26), 65 (23), 120 (16), 89 (12), 63 (10). IR (neat): 2983, 1719, 1280, 1201, 1107, 1084, 746, 684 cm^{-1}. Anal. Calcd for $C_{10}H_{12}O_2$: C, 73.17; H, 7.32; Found: C, 73.03; H, 7.45.