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Palladium-Catalyzed Carbonylations of Arylboronic Acids: Synthesis of Arylcarboxylic Acid Ethyl Esters

Apeng Liang,[a,b,c] Shuaijun Han,[a] Liang Wang,[a] Jingya Li,[b,c] Dapeng Zou,[a,b,c] Yangjie Wu,[a,*] and Yusheng Wu[b,d,*]

[a] The College of Chemistry and Molecular Engineering, Zhengzhou University, Zhengzhou, People's Republic of China
E-mail: wyj@zzu.edu.cn
[b] Collaborative Innovation Center of New Drug Research and Safely Evaluation, Henan Province, People's Republic of China
[c] Tetranov Biopharm, LLC, No.75 Daxue Road, Zhengzhou, People's Republic of China
[d] Tetranov International, Inc., 100 Jersey Avenue, Suite A340, New Brunswick, NJ 08901, USA
Fax: (+1)-732-253-7327; phone: (+1)-732-253-7326120; e-mail: yusheng.wu@tetranovglobal.com

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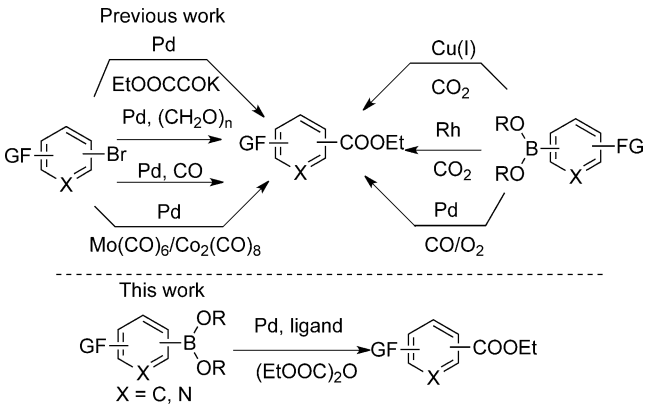
Abstract: An approach for the palladium-catalyzed ethoxycarbonylations of arylboronic acids using diethyl pyrocarbonate as carbon monoxide/carbon dioxide (CO/CO_2) surrogate in moderate to good yields has been investigated.

Keywords: arylboronic acids; arylcarboxylic acid ethyl esters; CO/CO_2 surrogate; diethyl pyrocarbonate; palladium-catalyzed carbonylation

Aryl(heteroaryl)carboxylic acid derivatives are not only important tools and structural elements in material sciences and chemical biology but also versatile building blocks in organic synthesis.[1] Ever since the pioneering work of Heck and Schoenberg in 1974, palladium-catalyzed carbonylations using CO and aryl halides have enabled the synthesis of a variety of carbonyl compounds.[2] Nowadays, these reactions are routinely applied for constructing carbonyl-containing compounds such as aldehydes, amides, esters etc, using carbon monoxide gas under high pressure and temperature for long durations.[3] Although Beller and Buchwald et al. reported relatively mild reaction conditions,[4] one of the raw materials for the carbonylation reaction is still the toxic carbon monoxide. Therefore, the search for some alternative sources of CO is underway to provide an effective supplement to the carbonylation reaction.[5] For example, Liu et al. successfully synthesized aromatic esters using oxalate monoester salts as carbonylation reagent.[6] As a CO surrogate, $Mo(CO)_6$ and $Co_2(CO)_8$ have been used extensively by Larhed and others.[7] In the meantime Skrydstrup et al. reported a series of CO-free carbonylation reactions using *ex situ* generated carbon monoxide.[8] In the last two years, Manabe and co-workers reported an interesting palladium-catalyzed reductive carbonylation of aryl halides using *N*-formylsaccharin and phenyl formate as an *in situ* CO source.[9] Recently, Beller et al. have also done a lot of excellent work in the utilization of CO surrogates like aryl formates and paraformaldehyde in carbonylation reactions.[10]

Arylboronic acids appeared to be the carbon nucleophiles of choice, as they are readily available,[11] nontoxic, air- and moisture-stable compounds that tolerate the presence of many sensitive functionalities. In 2001, Gooßen and co-workers successfully accomplished the acylation reaction of arylboronic acids using carboxylic acids or anhydrides as acylation reagent.[12] A few years later, the research groups of Iwasawa[13] and Hou[14] reported a nucleophilic addition of arylboronate esters toward CO_2 in the presence of rhodium or copper catalysts, respectively. Next, Lei et al. reported the oxidative carbonylation of arylboronic acid derivatives under balloon pressure of CO with air as the oxidant.[15] In 2014, the *tert*-butyl esters of (hetero)arylcarboxylic acid were synthesized using $(Boc)_2O$ as CO surrogate from (hetero)arylboronic acid derivatives by our groups.[16] At the same time, Xu et al. reported the ruthenium-catalyzed two-fold C–H tertiary alkoxycarbonylation of arenes using $(Boc)_2O$.[17] Compared to CO, CO_2 or other CO surrogates, diethyl pyrocarbonate is more desirable because it is a low toxic, stable, safe, widely available, and inexpensive CO/CO_2 surrogate. As yet there have been no reports of alkoxycarbonylation reactions using diethyl pyrocarbonate. Herein, we

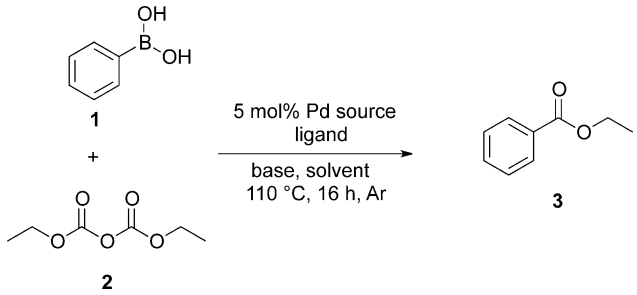


Scheme 1. Synthesis of aryl esters by palladium-catalyzed alkoxycarbonylation.

report the first example of the palladium-catalyzed carbonylation of aryl(heteroaryl)boronic acid derivatives to form various aryl(heteroaryl)carboxylic acid derivatives using diethyl pyrocarbonate as the carbonylation reagent (Scheme 1).

The reaction of phenylboronic acid (**1**) with diethyl pyrocarbonate (**2**) was chosen as model reaction and the results are summarized in Table 1. Initially, this reaction was carried out by using 2.0 equivalents of diethyl pyrocarbonate (**2**) as a CO/CO_2 surrogate, with 5 mol% $Pd(OAc)_2$ and 15 mol% PPh_3 as catalyst system in 3.0 mL of dioxane at 100 °C for 15 h. To our disappointment, only a moderate yield was observed (Table 1, entry 1). After increasing the loading of PPh_3 to 20 mol% and the reaction temperature to 110 °C, the yield of **3** increased to 75% (Table 1, entry 2). Next, various Pd sources and ligands were investigated (Table 1, entries 2–12). Obviously, when palladium acetate was used as catalyst in the presence of triphenylphosphine as ligand, the yield of the desired product was better (Table 1, entry 2). The reaction has also been carried out in different solvents (Table 1, entries 13–16). Based on the results obtained, we selected dioxane as the medium and 110 °C as the optimum temperature (Table 1, entry 2). Bases are very important in transition metal-catalyzed organic reactions to promote the reaction efficiency and increase the yields of products according to the literature.[18] Screening studies to find a suitable base for the ethoxycarbonylation of phenylboronic acid were carried out (Table 1, entries 17–21). The results indicated that Na_2CO_3 (Table 1, entry 20) to be a relatively good base. We also tested an oxygen atmosphere[15,19] in the reaction (Table 1, entry 22), and found that the yield was less than the result under an argon atmosphere (Table 1, entry 20). It was also found that the yield was lower in the presence of a certain amount of water[12] (Table 1, entry 23). Finally, the optimum reaction conditions were determined as the combination of 5 mol% $Pd(OAc)_2$, 20 mol% PPh_3, 2.0 equiv. Na_2CO_3, in anhydrous dioxane at 110 °C.

Table 1. Optimization of the reaction conditions.[a]

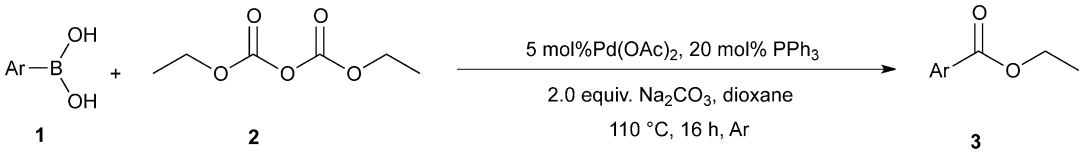


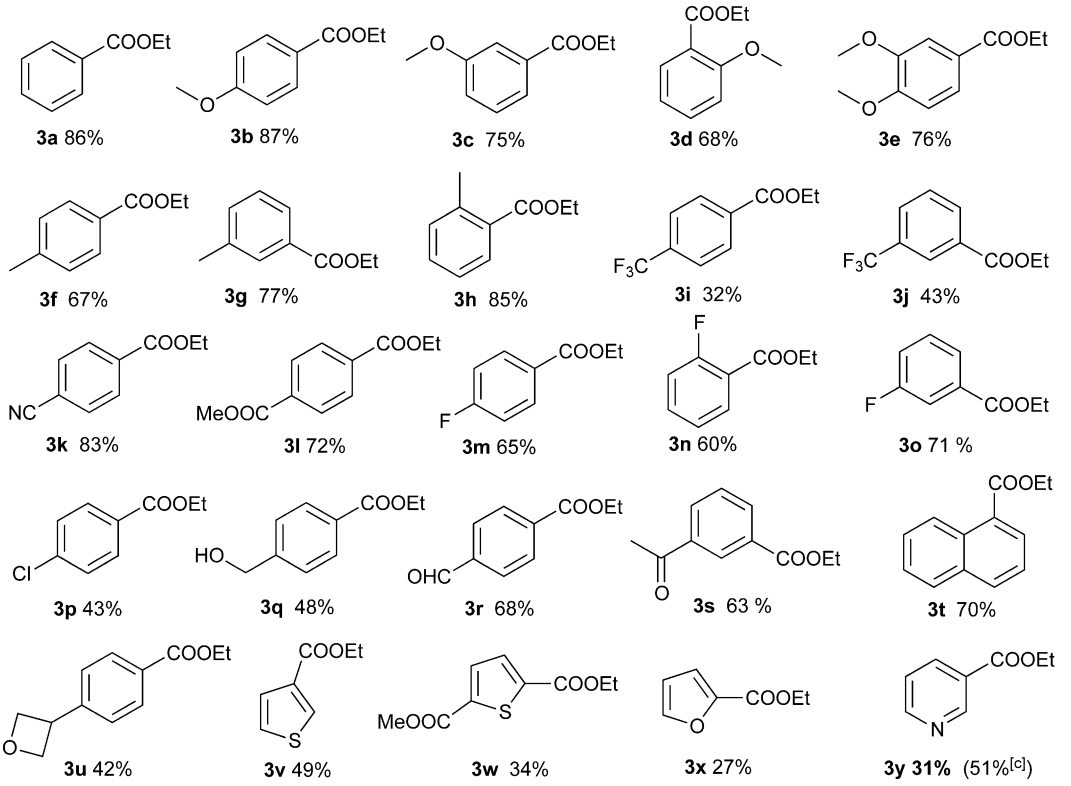
Entry	Catalyst	Ligand	Base	Solvent	Yield[c] [%]
1	$Pd(OAc)_2$	PPh_3	–	dioxane	46[b]
2	$Pd(OAc)_2$	PPh_3	–	dioxane	75
3	$PdCl_2$	PPh_3	–	dioxane	36
4	$Pd_2(dba)_3$	PPh_3	-	dioxane	42
5	$Pd(TFA)_2$	PPh_3	–	dioxane	68
6	$Pd(PPh_3)_4$	–	-	dioxane	63
7	$Pd(OAc)_2$	PCy_3	–	dioxane	33
8	$Pd(OAc)_2$	Dppf	–	dioxane	51
9	$Pd(OAc)_2$	S-Phos	–	dioxane	63
10	$Pd(OAc)_2$	Xantphos	–	dioxane	56
11	$Pd(OAc)_2$	Binap	–	dioxane	20
12	$Pd(OAc)_2$	DavePhos	–	dioxane	46
13	$Pd(OAc)_2$	PPh_3	–	DMSO	12
14	$Pd(OAc)_2$	PPh_3	-	toluene	64
15	$Pd(OAc)_2$	PPh_3	–	DMF	21
16	$Pd(OAc)_2$	PPh_3	–	EtOH	trace[e]
17	$Pd(OAc)_2$	PPh_3	Et_3N	dioxane	26
18	$Pd(OAc)_2$	PPh_3	DMAP	dioxane	32
19	$Pd(OAc)_2$	PPh_3	K_2CO_3	dioxane	87
20	$Pd(OAc)_2$	PPh_3	Na_2CO_3	dioxane	92/86[d]
21	$Pd(OAc)_2$	PPh_3	K_3PO_4	dioxane	78
22	$Pd(OAc)_2$	PPh_3	Na_2CO_3	dioxane	23[f]
23	$Pd(OAc)_2$	PPh_3	Na_2CO_3	dioxane	68[g]/NA[h]

[a] *Reaction conditions:* 1.0 mmol **1**, 2.0 mmol **2**, 5 mol% catalyst, 20 mol% ligand, no base or 2.0 mmol base, 3 mL solvent, 110 °C, 16 h, argon atmosphere.
[b] 15 mol% PPh_3, the reaction temperature was 100 °C.
[c] The yields were determined by using GC (average of two GC runs) using di-*n*-pentyl phthalate as an internal standard.
[d] Isolated yields based on **1**.
[e] The reaction temperature was 80 °C.
[f] Oxygen atmosphere.
[g] Reaction performed in the presence of H_2O (1.0 mmol, 1.0 equiv.).
[h] Reaction performed in the presence of H_2O (1.0 mL).

This transformation was next applied to a variety of different arylboronic acid derivatives. The representative examples shown in Table 2 were selected to highlight not only the broad scope but also the limitations of this method. Aromatic boronic acids bearing either electron-donating (methyl, methoxy) or electron-with-

Table 2. Palladium-catalyzed ethoxycarbonylation of arylboronic aicds with diethylpyrocarbonate.[a,b]



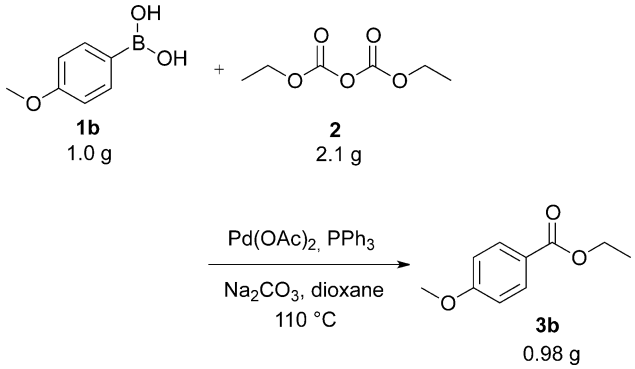


[a] *Reaction conditions:* 1.0 mmol **1**, 2.0 mmol **2**, 5 mol% $Pd(OAc)_2$, 20 mol% PPh_3, 2.0 mmol Na_2CO_3, 3 mL dioxane, 110 °C, 16 h, argon atmosphere.
[b] Isolated yields base on **1**.
[c] Using boronic acid pinacol ester as substrate.

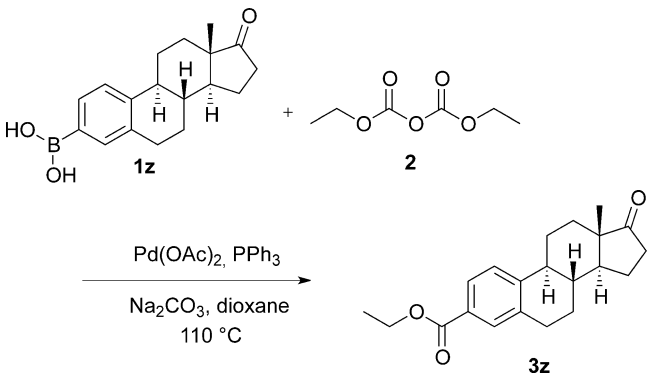
drawing (cyano, trifluoromethyl, fluoro, methyl ester) substituents underwent ethoxycarbonylation in moderate to high yields. While the conversion rates of **1i**, **1j**, **1m**, **1n** and **1o** were very good as detected by GC, the isolated yields of **3i**, **3j**, **3m**, **3n** and **3o** were relatively lower because the fluorinated organic compounds have high volatility. A variety of different potentially reactive functional groups which can be further functionalized (aromatic chloride, alcohol, ketone, aldehyde) were quite well-tolerated. Meanwhile, boronic acids derived from pyridine, furan, and thiophene all underwent the ethoxycarbonylation in middle yields.

To demonstrate the scalability of the reaction, we chose the ethoxycarbonylation of **1b** with **2** on a 1.0 g scale. The desired ethoxycarbonylated product **3b** was isolated in 83% yield (0.98 g) (Scheme 2).

Subsequently, the method was investigated in the synthesis of an estrone derivative (Scheme 3). The ethoxycarbonylation of **1z** with **2** provided **3z** in 76% yield. So, we have developed a new method for the synthesis of substituted estratriene analogues as 17ß-HSD inhibitors.[20] This result demonstrates that this



Scheme 2. Scalability of the ethoxycarbonylation of **1b**.



Scheme 3. The ethoxycarbonylation of an estrone derivative.

method is extendable to other pharmaceutically relevant molecules.

In summary, we have developed a mild and general CO/CO_2-free carbonylation protocol for the palladium-catalyzed ethoxycarbonylation of arylboronic acid derivatives. Notably, the advantage of this method is that diethyl pyrocarbonate is a readily available and an inexpensive carbonylation reagent. What is more, this method offers a convenient alternative for ethoxycarbonylation compared to conventional carbonylations using syngas or CO/CO_2 directly. Avoiding the use of high-pressure equipment is another merit of this method.

Experimental Section

Palladium-Catalyzed Carbonylations of Arylboronic acids with Diethyl Pyrocarbonate; Typical Reaction Procedure

$Pd(OAc)_2$ (11.2 mg, 0.05 mmol, 5 mol%), PPh_3 (52.4 mg, 0.20 mmol, 20 mol%), Na_2CO_3 (212 mg, 2.0 mmol, 2.0 equiv.), arylboronic acid (1.0 mmol, 1.0 equiv.), diethyl pyrocarbonate (324.0 mg, 2.0 mmol, 2.0 equiv.) and dioxane (3 mL) were placed in a dried glass reaction tube and the air was replaced three times with argon. The reaction mixture was stirred at 110 °C for 16 h. After the mixture had been cooled to room temperature it was extracted with EtOAc and H_2O. The combined organic layer was washed with brine, and then dried over anhydrous Na_2SO_4. The solvent was evaporated under vacuum to afford the crude reaction mixture, which was then purified on silica gel plates to produce the desired product. The products were characterized by ^1H NMR, ^{13}C NMR and LC-MS.

Acknowledgements

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