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Palladium-Catalyzed Cascade Aryl Addition/ Intramolecular Lactonization of Phthalaldehyde To Access 3-Aryl- and Alkenylphthalides

Zhishi Ye,[†] Pengcheng Qian,[†] Guanglei Lv,[†] Fang Luo,[†] and Jiang Cheng*[,†,‡]

[†]*College of Chemistry & Materials Engineering, Wenzhou University, Wenzhou 325027, People's Republic of China, and* [‡]*State Key Laboratory of Coordination Chemistry, Nanjing University, Nanjing 210093, People's Republic of China*

jiangcheng@wzu.edu.cn

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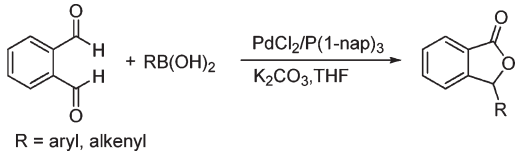

A palladium-catalyzed addition of arylboronic acids to phthalaldehyde, followed by an intramolecular lactonization to access 3-substituted phthalides, is described. The procedure tolerates a series of functional groups, such as methoxyl, fluoro, chloro, and trifluoromethyl groups. It represents a procedure for the synthesis of 3-substituted phthalides.

Phthalides are versatile building blocks for the synthesis of biologically active compounds and have been proven to be useful in the treatment of circulatory and heart diseases.[1] Especially, 3-arylphthalides are useful intermediates for the synthesis of tri- and tetracyclic natural products, such as anthracycline antibiotics.[2] Therefore, significant effort has been focused on synthesizing these organic skeletons.[3] However, few examples of transition-metal-catalyzed synthetic reactions to access 3-arylphthalides have been developed.[4] Stille and Larock described the tandem carbonylation of benzylic alcohol and *ortho*-halo benzylic alcohol followed by cyclization to access phthalides in the presence of palladium complexes, respectively.[5] In 2004, Cheng reported the nickel-catalyzed addition reaction of 2-halobenzoates with aldehydes to access 3-substituted phthalides.[6a] Subsequently, synthesis of phthalide derivatives using Co-catalyzed cyclization of *o*-halo esters with aldehydes was also developed by Cheng.[6b] Recently, Dong demonstrated an atom-economical approach to phthalides by enantioselective C−H functionalization.[7] Very recently, Hu demonstrated the rhodium-catalyzed addition of arylboronic acids to 2-formylbenzoates afforded 3-substituted phthalides.[8]

In recent years, palladium-catalyzed addition reactions of arylboronic acids with aldehydes have become useful tools to access carbinol derivatives.[9] We have also documented an effective catalysis system for the palladium-catalyzed 1,2-addition reaction of aryl- or heteroarylboronic acids to aldehydes.[9d] In 2009, Onomura demonstrated the palladium-catalyzed arylation of methyl 2-formylbenzoate with organoboronic acids for the synthesis of 3-arylphthalides.[10] Very recently, we developed a catalyzed system to access 3-aryl- and alkenylphthalides by rhodium-catalyzed cascade aryl addition/intramolecular esterification reaction (Scheme 1, eq 1).[11] On the basis of previous work, we envisioned developing the palladium-catalyzed reaction of phthalaldehyde with organoboronic acids to access 3-substituted phthalides (Scheme 1, eq 2). Herein, we

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SCHEME 1. Strategy To Access Phthalide

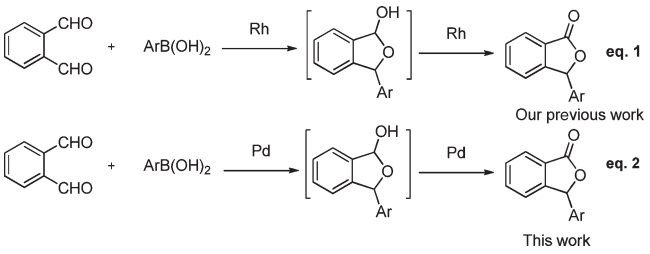
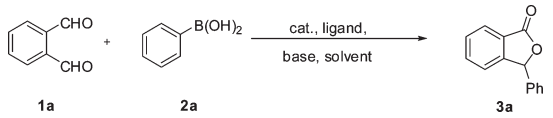


TABLE 1. Selected Results of Screening the Optimal Conditions



entry	Pd source	ligand	base	solvent	yield (%)[a]
1	$PdCl_2$	PPh_3	K_2CO_3	THF	< 5
2	$PdCl_2$	dppb	K_2CO_3	THF	< 5
3	$PdCl_2$	binap	K_2CO_3	THF	< 5
4	$PdCl_2$	dppe	K_2CO_3	THF	< 5
5	$PdCl_2$	dppf	K_2CO_3	THF	< 5
6	$PdCl_2$	$(1\text{-nap})_3P$	K_2CO_3	THF	78(66[b])
7	$PdCl_2$	$(1\text{-nap})_3P$	Na_2CO_3	THF	< 5
8	$PdCl_2$	$(1\text{-nap})_3P$	NaOMe	THF	66
9	$PdCl_2$	$(1\text{-nap})_3P$	$KHCO_3$	THF	< 5
10	$PdCl_2$	$(1\text{-nap})_3P$	Li_2CO_3	THF	< 5
11	$PdCl_2$	$(1\text{-nap})_3P$	NaOAc	THF	< 5
12	$PdCl_2$	$(1\text{-nap})_3P$	K_2CO_3	toluene	71
13	$PdCl_2$	$(1\text{-nap})_3P$	K_2CO_3	1,4-dioxane	77
14	$PdCl_2$	$(1\text{-nap})_3P$	K_2CO_3	$ClCH_2CH_2Cl$	< 5
15	$Pd(OAc)_2$	$(1\text{-nap})_3P$	K_2CO_3	THF	70
16	$Pd_2(dba)_3$	$(1\text{-nap})_3P$	K_2CO_3	THF	65

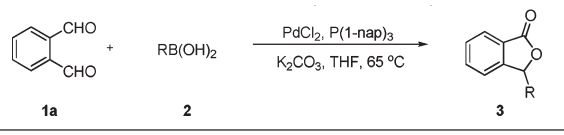
[a]Phthalaldehyde (26.8 mg, 0.2 mmol), phenylboronic acid (37 mg, 0.3 mmol), Pd source (5 mol %), ligand (5 mol %) with indicated base (3 equiv) in dry solvent (3 mL), 65 °C, 12 h, under air; nap = naphthyl. [b]Under N_2.

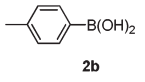
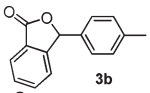
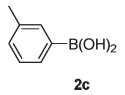
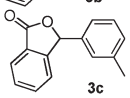
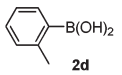
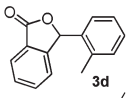
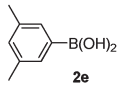
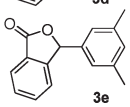
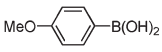
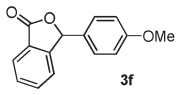
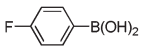
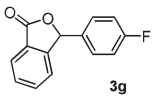
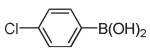
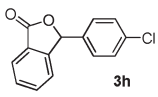
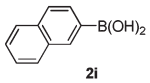
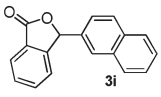
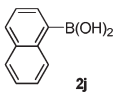
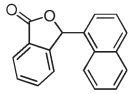
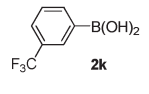
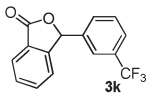
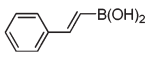
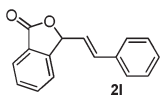
describe a palladium-catalyzed procedure for the aforementioned transformation.

Our investigation started with the reaction of phthalaldehyde and phenylboronic acid using $PdCl_2$ as catalyst (Table 1). The ligand effect was crucial to the model reaction. For example, dppb, which showed better catalytic reactivity in rhodium-catalyzed cascade reactions,[11] was ineffective at all (entry 2, Table 1). Remarkably, only when the bulky and electron-rich $P(1\text{-nap})_3$ was used, the product was obtained in 78% yield (entry 6, Table 1). The influence of bases was also investigated, and K_2CO_3 was found to be superior to some other bases such as Na_2CO_3, NaOMe, $KHCO_3$, Li_2CO_3, NaOAc (entries 7−11, Table 1). The choice of solvent had dramatic effect on the reaction. THF and 1,4-dioxane turned out to be the best (entries 6 and 13, Table 1). Next, we studied the effect of palladium sources and found that $PdCl_2$ showed better catalytic activity. Under N_2, a compatible yield was obtained (entry 15, Table 1). The reaction conducting on a 2 mmol scale produced **3a** in 75% yield.

With the optimal parameters established (under air, with 5 mol % of $PdCl_2$ and 5 mol % of $P(1\text{-nap})_3$ as the catalyst and K_2CO_3 (3 equiv) in dry THF at 65 °C), we turned our attention to investigate the scope of arylboronic acids. The results are summarized in Table 2. As expected, various

TABLE 2. Reaction of Phthalaldehyde with Arylboronic Acids



entry	substrate **2**	product **3**	yield[a] (%)
1	 **2b**	 **3b**	78
2	 **2c**	 **3c**	63
3	 **2d**	 **3d**	37(68[b])
4	 **2e**	 **3e**	82
5	 **2f**	 **3f**	73
6	 **2g**	 **3g**	82
7	 **2h**	 **3h**	66
8	 **2i**	 **3i**	72
9	 **2j**	 **3j**	66
10	 **2k**	 **3k**	42
11	 **2l**	 **3l**	24

[a]Phthalaldehyde (0.2 mmol), phenylboronic acid (0.3 mmol), $PdCl_2$ (5 mol %), $P(1\text{-nap})_3$ (5 mol %) with K_2CO_3 (3 equiv) in dry THF (3 mL), 65 °C, 12 h, under air. [b]Toluene, 110 °C.

arylboronic acids worked well under the reaction conditions. Functional groups, such as methoxy, trifluoromethyl, and chloro groups, were tolerated in this procedure. However, the hindrance on the phenyl ring of arylboronic acid inhibited the transformation. For example, 78% of **3b** was isolated, while the yield of **3d** was dramatically decreased to 37% (entries 1 vs 3, Table 2). Fortunately, replacing the THF with toluene and increasing the reaction temperature to 110 °C increased the yield of **3d** to 68%. The electron-donating substituents at the phenyl ring of boronic acids were beneficial for the transformation, whereas an electron-withdrawing group decreased the efficiency. Notably, **2h** underwent a cascade reaction, leaving

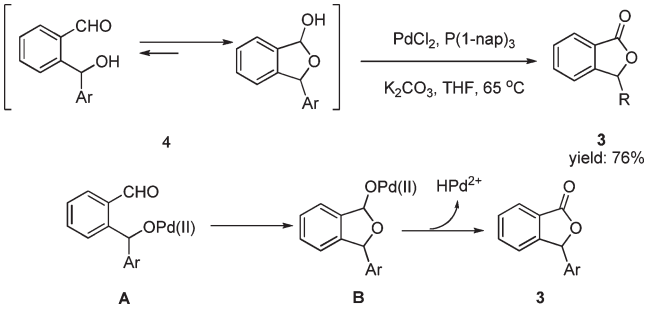


FIGURE 1. Proposed reaction intermediates.

the C−Cl bond intact, which is attractive for further synthetic elaboration (entry 7, Table 2). Disappointingly, under the standard procedure, the arylboronic acids bearing methoxycarbonyl and cyano groups and heteroaromatic boronic acids failed to deliver the product. Particularly, (*E*)-styrylboronic acid was subjected to the reaction procedure, albeit the product was isolated in low yield (entry 11, Table 2). Unfortunately, methylboronic acid failed to deliver the product under the standard procedure.

When compound **4** was subjected to the standard reaction condition, **3** was isolated in 76% yield. We reasoned the palladium species **A**, which was derived from the addition of arylboronic acid to the C═O, was the key intermediate for the cascade reaction (Figure 1). Then, insertion of intermediate **A** to the second aldehyde carbonyl takes place to form the palladium species **B**. Ultimately, β-H elimination of intermediate **B** delivers product **3**.

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In conclusion, we have developed a palladium-catalyzed cascade reaction of phthalaldehyde with arylboronic acids, affording the 3-aryl- and alkenylphthalides in moderate to good yields. The developed intramolecular lactonization provides a potential way to access chiral 3-aryl and other 3-substituted phthalides.

Experimental Section

General Procedure for Aryl Addition/Intramolecular Esterification Reaction. Under air, a reaction tube was charged with phthalaldehyde (26.8 mg, 0.2 mmol), boronic acids (0.3 mmol), $PdCl_2$ (1.7 mg, 5 mol %), $P(1\text{-nap})_3$ (4.2 mg, 5 mol %), K_2CO_3 (82.8 mg, 3 equiv), and dry THF (3 mL). The reaction tube was kept stirring at 65 °C for 12 h. After the completion of the reaction, as monitored by TLC, the solvent was evaporated under reduced pressure and the residue was purified by flash column chromatography on silica gel to give the product.

3-Phenylisobenzofuran-1-(3*H*)-one (3a):[12] ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.97 (d, J = 7.6 Hz, 1H), 7.68−7.63 (m, 1H), 7.58−7.53 (m, 1H), 7.38−7.26 (m, 6H), 6.41 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 170.7, 149.8, 136.6, 134.5, 129.5, 129.4, 129.1 127.1, 125.8, 123.0, 82.9.

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Supporting Information Available: Experimental procedures along with copies of spectroscopic data. This material is available free of charge via the Internet at http://pubs.acs.org.