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Efficient Synthesis of 3-Arylphthalides using Palladium-Catalyzed Arylation of Aldehydes with Organoboronic Acids

Masami Kuriyama,*,† Natsuki Ishiyama,† Rumiko Shimazawa,‡ Ryuichi Shirai,‡ and Osamu Onomura*,†

†*Graduate School of Biomedical Sciences, Nagasaki University, 1-14 Bunkyo-machi, Nagasaki 852-8521, Japan, and* ‡*Faculty of Pharmaceutical Sciences, Doshisha Women's College of Liberal Arts, Kodo, Kyotanabe, Kyoto 610-0395, Japan*

mkuriyam@nagasaki-u.ac.jp; onomura@nagasaki-u.ac.jp

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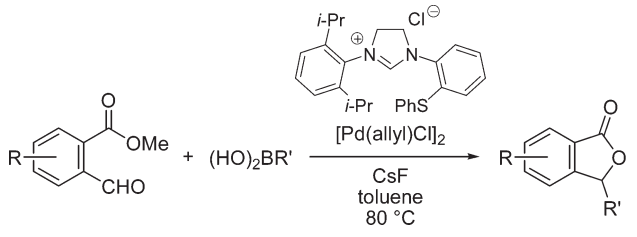

The synthesis of 3-arylphthalides via palladium-catalyzed arylation of aldehydes with organoboronic acids was achieved using the thioether-imidazolinium carbene ligand in good to excellent yields and was carried out using 1.0 mol % of the catalyst with high substrate tolerance.

Phthalides substituted at C-3 are important heterocycles possessing interesting biological activities and are found in various naturally occurring compounds,[1] such as alcyopterosin E,[2a] cytosporone E,[2b] fuscinarin,[2c] rubiginone H,[3a] isopestacin,[3b] and cryphonectric acid.[3c] Especially, 3-arylphthalides

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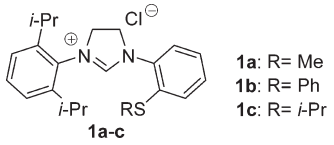


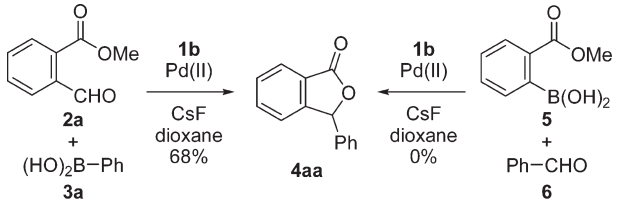
FIGURE 1. Precursors of *N*-heterocyclic carbene ligands.

are also known as useful intermediates for the synthesis of tri- and tetracyclic natural products, such as anthracycline antibiotics.[4] Because of their significance, various methods for the synthesis of 3-arylphthalides have been reported.[5] However, not many transition-metal-catalyzed synthetic reactions for 3-arylphthalides have been developed,[6,7d] although catalytic methods could be highly efficient processes.[7] In particular, there are only a few reports for the synthesis of 3-arylphthalides using transition-metal-catalyzed 1,2-addition as a key reaction,[8] and more catalytically active and practically advantageous processes are desirable.

Since Miyaura reported the rhodium-catalyzed 1,2-addition in 1998,[9] transition-metal-catalyzed arylation reactions of aldehydes with organoboronic acids have attracted much attention.[10] Because of the advantages of organoboronic acids such as low toxicity and easy manipulation,[11] several types of active catalysts have been reported for this kind of reaction.[12,13] We have already developed thioether-imidazolinium chlorides **1**[14] (Figure 1) as heterobidentate ligand precursors and found the palladium/thioether-imidazolinium chloride system achieved high catalyst performance in the 1,2-addition of organoboron reagents to aldehydes.[15] Herein, we would like to describe the efficient synthesis of 3-arylphthalides using the arylation of aldehydes with organoboronic acids catalyzed by the palladium/thioether-imidazolinium chloride system.

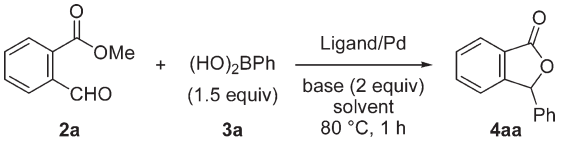
Initially, we examined two applicable synthetic methods for 3-arylphthalides using the palladium-catalyzed arylation of aldehydes with thioether-imidazolinium chloride **1b** (Scheme 1). Whereas the synthesis of 3-phenylphthalide **4aa** via the cyclization following addition of phenylboronic acid **3a** to methyl 2-formylbenzoate **2a** was carried out leading to 68% yield, the reaction of 2-methoxycarbonylphenylboronic acid **5** with benzaldehyde **6** gave no desired product, and the crude product after workup contained almost only benzaldehyde.[16]

SCHEME 1. Synthesis of 3-Phenylphthalide using Palladium-Catalyzed Arylation with Methyl Benzoates Substituted by Formyl or Boronic Acid Group at the Ortho Position[a]



[a]Reaction conditions: $ArB(OH)_2$ (1.5 equiv based on aldehyde), **1b** (1 mol %), $[Pd(allyl)Cl]_2$ (0.5 mol %), CsF (2 equiv), dioxane, 80 °C, 1 h.

TABLE 1. Synthesis of 3-Phenylphthalide using Palladium-Catalyzed Arylation of Methyl 2-Formylbenzoate with Phenylboronic Acid[a]



entry	ligand	Pd	base	solvent	yield (%)[b]
1	**1a**	$[Pd(allyl)Cl]_2$	CsF	dioxane	55
2	**1b**	$[Pd(allyl)Cl]_2$	CsF	dioxane	68
3	**1c**	$[Pd(allyl)Cl]_2$	CsF	dioxane	42
4	**1b**	$Pd(OAc)_2$	CsF	dioxane	34
5	**1b**	$Pd(acac)_2$	CsF	dioxane	0
6	**1b**	$Pd(dba)_2$	CsF	dioxane	32
7	**1b**	$Pd_2(dba)_3$	CsF	dioxane	31
8	**1b**	$[Pd(allyl)Cl]_2$	CsF	toluene	78
9	**1b**	$[Pd(allyl)Cl]_2$	CsF	DMA	0
10	**1b**	$[Pd(allyl)Cl]_2$	CsF	DMF	0
11	**1b**	$[Pd(allyl)Cl]_2$	CsF	DMSO	0
12	**1b**	$[Pd(allyl)Cl]_2$	KF	toluene	75
13	**1b**	$[Pd(allyl)Cl]_2$	NaF	toluene	0
14	**1b**	$[Pd(allyl)Cl]_2$	Cs_2CO_3	toluene	55
15	**1b**	$[Pd(allyl)Cl]_2$	K_3PO_4	toluene	63
16[c]	**1b**	$[Pd(allyl)Cl]_2$	CsF	toluene	97

[a]Reaction conditions: **2a** (0.75 mmol), **3a** (1.13 mmol), ligand (1 mol %), palladium (1 mol %), base (1.5 mmol), solvent (1.5 mL), 80 °C, 1 h. [b]Isolated yield. [c]2.5 equiv of **3a** was used.

On the basis of the results in Scheme 1, optimization of reaction conditions was conducted using methyl 2-formylbenzoate **2a** and phenylboronic acid **3a** (Table 1). The synthetic reactions for 3-phenylphthalide **4aa** using the arylation catalyzed by 1.0 mol % of the catalysts generated in situ from thioether-imidazolinium chlorides **1a**−**c** and

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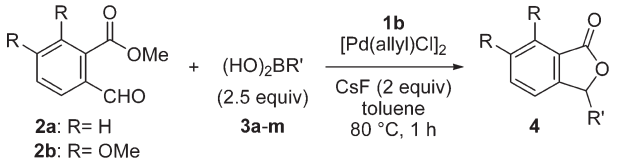
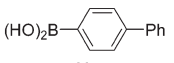
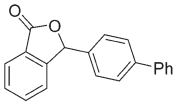
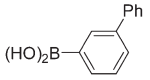
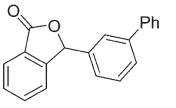
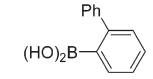
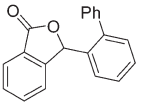
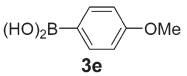
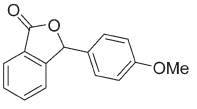
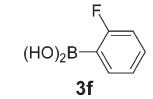
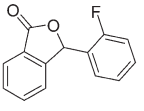
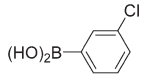
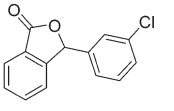
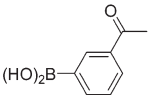
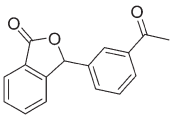
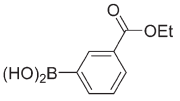
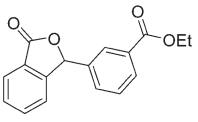
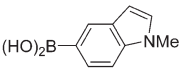
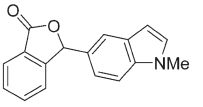
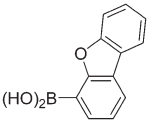
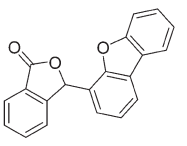
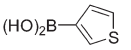
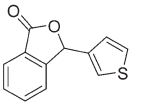
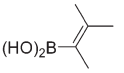
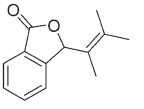
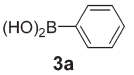
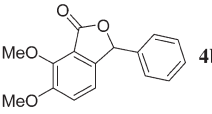
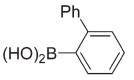
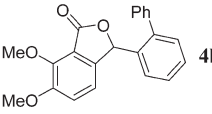
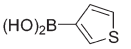
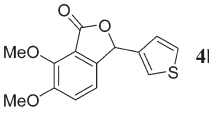
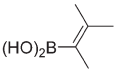
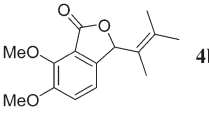
(16) There is a possibility that 2-methoxycarbonylphenylboronic acid **5** was decomposed through decarboxylation following transmetalation, which was similar to mechanisms in the following report: Kim, H. S.; Gowrisankar, S.; Kim, E. S.; Kim, J. N. *Tetrahedron Lett.* **2008**, *49*, 6569–6572. In 1,2-addition reactions of organoboron reagents catalyzed by rhodium or nickel, reaction mechanisms including transmetalation as a key step were proposed; see refs 10b, 13m, and 13r.

TABLE 2. Synthesis of 3-Arylphthalides using Palladium-Catalyzed Arylation of Aldehydes with Organoboronic Acids[a]



entry	$(HO)_2BR'$	product		yield (%)[b]
1	 **3b**		**4ab**	99
2	 **3c**		**4ac**	99
3	 **3d**		**4ad**	99
4[c]	 **3e**		**4ae**	99
5	 **3f**		**4af**	91
6	 **3g**		**4ag**	99
7	 **3h**		**4ah**	88
8	 **3i**		**4ai**	70
9[c]	 **3j**		**4aj**	87
10[c]	 **3k**		**4ak**	85
11[c]	 **3l**		**4al**	99
12	 **3m**		**4am**	99
13	 **3a**		**4ba**	85
14	 **3d**		**4bd**	75
15[c]	 **3l**		**4bl**	52
16[d]	 **3m**		**4bm**	88

[a]Reaction conditions: **2a** or **2b** (0.75 mmol), organoboronic acid (1.88 mmol), **1b** (1 mol %), $[Pd(allyl)Cl]_2$ (0.5 mol %), CsF (1.5 mmol), toluene (1.5 mL), 80 °C, 1 h. [b]Isolated yield. [c]Instead of toluene, dioxane was used as a solvent. [d]The uncyclized adduct was observed in the crude product (**4bm**/uncyclized adduct = 5/2), which was dissolved in chloroform and left at rt until the uncyclized adduct was converted into **4bm** completely.

$[Pd(allyl)Cl]_2$ in the presence of cesium fluoride were examined in dioxane at 80 °C for 1 h. Thioether-imidazolinium chloride **1b** was proven to be a superior heterobidentate carbene ligand precursor (entries 1−3). A series of palladium sources were screened, and $[Pd(allyl)Cl]_2$ gave the highest catalytic activity (entries 2 and 4−7). The influence of solvents was investigated, and toluene was most suitable, leading to 78% yield (entry 8). Highly polar solvents such as DMA, DMF, and DMSO afforded no desired product (entries 9−11). The exploration of bases revealed that cesium fluoride was the reagent of choice (entries 8 and 12−15). The increase in the equivalent of phenylboronic acid **3a** led to improvement in yield, giving 3-phenylphthalide **4aa** in 97% (entry 16).

Investigation of organoboronic acids in the synthesis of 3-subsituted phthalides using the arylation of methyl 2-formylbenzoate **2a** with 1.0 mol % of the catalyst was conducted (Table 2, entries 1−12). The sterically hindered 2-biphenylboronic acid **3d** as well as 4- and 3-biphenylboronic acids (**3b** and **3c**) reacted with the aldehyde **2a** efficiently to afford the cyclized products **4ab**−**4ad** in 99% yield (entries 1−3). Both the electron-rich and -poor arylboronic acids (**3e** and **3f**) led to excellent yields of the lactone products (entries 4 and 5). The reaction using 3-chlorophenylboronic acid **3g** proceeded smoothly without the generation of the uncyclized Suzuki−Miyaura coupling or dehalogenation products (entry 6). The ketone and ester groups in arylboronic acids were tolerated under the reaction conditions, giving the desired

products with 88% and 70% yields, respectively (entries 7 and 8). Then, heteroarylboronic acids bearing nitrogen, oxygen, and sulfur atoms were examined. The boronic acids **3j**−**l** proved to be good substrates, leading to high yields of the lactone products (entries 9−11). The synthesis of 3-alkenylphthalide using 1,2-dimethyl-1-propenylboronic acid **3m** was also achieved in excellent yield (entry 12).

Furthermore, the influence of the electron-rich aldehyde, methyl 6-formyl-2,3-dimethoxybenzoate **2b**, was investigated (Table 2, entries 13−16). No significant decrease in yield for the reaction of the aldehyde **2b** and phenylboronic acid **3a** was observed, affording the product **4ba** with 85% yield (entry 13). Although the reaction of sterically hindered 2-biphenylboronic acid **3d** proceeded with a good yield (entry 14), the reaction using 3-thiopheneboronic acid **3l** afforded the desired lactone product in moderate yield (entry 15). In the case of 3-alkenylphthalide **4bm**, the cyclization following addition was relatively slow. The crude product contained the uncyclized adduct, which was then dissolved in chloroform and converted to the cyclized product **4bm** in 88% yield (entry 16).

In summary, the synthesis of 3-arylphthalides via the arylation of aldehydes with organoboronic acids proceeded smoothly using 1.0 mol % of the catalyst generated from palladium and thioether-imidazolinium chloride. This process tolerated a diverse range of substrates, giving a variety of 3-substituted phthalides in good to excellent yields. Further efforts will be focused on the development of asymmetric versions in our research group.

Experimental Section

Typical Procedure for Synthesis of 3-Arylphthalides using Palladium-Catalyzed Arylation of Aldehydes with Organoboronic Acids. Under argon atmosphere, a reaction tube was charged with $[Pd(allyl)Cl]_2$ (1.37 mg, 3.75×10^{-3} mmol), imidazolinium chloride **1b** (3.38 mg, 7.5×10^{-3} mmol), and cesium fluoride (228 mg, 1.5 mmol). To this mixture was added dioxane (1.5 mL). The mixture was stirred for 15 min at 80 °C and cooled to room temperature. Then, methyl 2-formylbenzoate **2a** (123 mg, 0.75 mmol) and 3-thiopheneboronic acid **3l** (240 mg, 1.88 mmol) were added, and the reaction mixture was stirred at 80 °C for 1 h. The mixture was cooled to room temperature and stirred for 12 h. Water and saturated NH_4Cl were added, and the resulting mixture was extracted with CH_2Cl_2. The combined organic layers were washed with brine and then dried over $MgSO_4$. Concentration and purification through silica gel column chromatography (hexane/AcOEt = 5:1) gave 161 mg (0.74 mmol, 99% yield) of the product **4al**.

3-(3-Thienyl)-3*H*-isobenzofuran-1-one (4al) (Table 2, entry 11). Colorless solid of mp 86−87 °C. ^{1}H NMR ($CDCl_3$): δ 6.51 (1H, s), 6.95 (1H, dd, J = 2.0, 4.4 Hz), 7.33−7.35 (2H, m), 7.43 (1H, d, J = 7.3 Hz), 7.58 (1H, t, J = 7.3 Hz), 7.67 (1H, m), 7.97 (1H, d, J = 7.3 Hz). ^{13}C NMR ($CDCl_3$): δ 78.4, 122.8, 124.4, 125.7, 125.8, 125.9, 127.2, 129.4, 134.2, 137.2, 149.0, 170.1. IR (neat): 1780 cm^{-1}. HRMS (EI): m/z calcd for $C_{12}H_8O_2S$ (M^+) 216.0245, found 216.0231.

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Supporting Information Available: General procedure of the synthesis for 3-substituted phthalides **4**, spectral data of cyclized products **4**, and copies of ^{1}H and ^{13}C NMR spectra for cyclized products **4**. This material is available free of charge via the Internet at http://pubs.acs.org.