Synthetic Methods

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Rhodium-Catalyzed Cascade Reaction: Aryl Addition/Intramolecular Esterification to Access 3-Aryl and 3-Alkenyl Phthalides**

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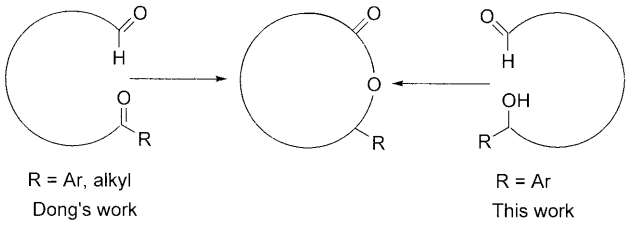
Phthalides (isobenzofuranone), a family of five-membered lactones in plants, are important building blocks in a large number of biologically active compounds.[1] 3-Arylphthalides, for example, are useful intermediates for the synthesis of tri- and tetracyclic natural products such as anthracycline antibiotics.[2] Approaches have been developed for the synthesis of these organic skeletons.[3] The tandem carbonylation of benzylic alcohol and *ortho*-halo benzylic alcohol with subsequent cyclization to access phthalides have been reported by Cowell and Stille, and Larock and Fellows, respectively.[4] In 2006, Chan and Scheidt described the NHC-catalyzed (NHC = N-heterocyclic carbene) intramolecular hydroacylation of 2-benzoylbenzaldehyde to afford phthalides in moderate yield.[5] Lin and co-workers reported the catalytic enantioselective synthesis of chiral phthalides by efficient reductive cyclization of 2-acylarylcarboxylates.[6] However, the development of a simple and efficient method to access 3-arylphthalide still remains a highly desirable goal in synthetic chemistry.

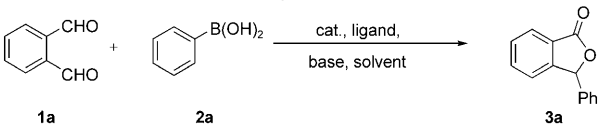
The transition metal catalyzed functionalization of the aldehyde C–H bond is a straightforward and atom-economical way to construct complex organic molecules.[7] In 2009, Onomura and co-workers reported a palladium-catalyzed arylation of methyl 2-formylbenzoate with organoboronic acids for the efficient synthesis of 3-arylphthalides.[8] Recently, Dong and co-workers demonstrated an elegant example of rhodium-catalyzed intramolecular ketone hydroacylation.[9a,b] Subsequently, Dong and co-workers reported an atom-economical approach to phthalides by enantioselective C–H functionalization.[9c] We envisioned a fundamentally different approach to lactonization based on this methodology (Scheme 1). Herein, we report a novel and facile strategy to obtain phthalide starting from commercially available phthalaldehyde and arylboronic acids based on the well-developed rhodium-catalyzed addition of arylboronic acids to aldehydes.[10]



Scheme 1. A novel strategy to phthalide.

We initiated our investigation by examining the reaction of phthalaldehyde and phenylboronic acid (Table 1). During the survey of rhodium sources, to our delight, phthalide was produced in 43% yield in the presence of [{Rh(cod)Cl}$_2$], dppb, and K_2CO_3 in THF (entry 3, Table 1). The influence of bases was investigated, and K_2CO_3 gave the best outcome (entries 3–6, Table 1). When we replaced THF with $ClCH_2CH_2Cl$, the yield dramatically increased to 83% (entry 10, Table 1). In addition to dppb, we compared the effects of several phosphino ligands, such as dppp, dppe, dppf, P(1-nap)$_3$ and PPh_3. Of these, dppb and P(1-nap)$_3$ showed the

Table 1: Selected results for the optimal reaction conditions.[a]



1a 2a 3a

Entry	Rh source	Ligand	Base	Solvent	Yield [%][b]
1	[Rh(PPh$_3$)$_3$Cl]	dppb	K_2CO_3	THF	< 5
2	[Rh(CO)$_2$(acac)]	dppb	K_2CO_3	THF	19
3	[{Rh(cod)Cl}$_2$]	dppb	K_2CO_3	THF	43
4	[{Rh(cod)Cl}$_2$]	dppb	$NaHCO_3$	THF	< 5
5	[{Rh(cod)Cl}$_2$]	dppb	K_3PO_4	THF	< 5
6	[{Rh(cod)Cl}$_2$]	dppb	CsF	THF	19
7	[{Rh(cod)Cl}$_2$]	dppb	K_2CO_3	DMF	< 5
8	[{Rh(cod)Cl}$_2$]	dppb	K_2CO_3	CH_3OH	< 5
9	[{Rh(cod)Cl}$_2$]	dppb	K_2CO_3	toluene	76
10	[{Rh(cod)Cl}$_2$]	dppb	K_2CO_3	$ClCH_2CH_2Cl$	83
11	[{Rh(cod)Cl}$_2$]	dppp	K_2CO_3	$ClCH_2CH_2Cl$	< 5
12	[{Rh(cod)Cl}$_2$]	dppe	K_2CO_3	$ClCH_2CH_2Cl$	< 5
13	[{Rh(cod)Cl}$_2$]	dppf	K_2CO_3	$ClCH_2CH_2Cl$	30
14	[{Rh(cod)Cl}$_2$]	PPh_3	K_2CO_3	$ClCH_2CH_2Cl$	24
15	[{Rh(cod)Cl}$_2$]	P(1-nap)$_3$	K_2CO_3	$ClCH_2CH_2Cl$	81
16	–	dppb	K_2CO_3	$ClCH_2CH_2Cl$	< 5

[a] Reaction conditions: Phthalaldehyde (0.2 mmol), phenylboronic acid (0.3 mmol), Rh source (10 mol%), ligand (10 mol% for monodentate ligand and 5 mol% for bidentate ligand) with indicated base (2 equiv) in dry solvent (3 mL), 65°C, 12 h, under air. [b] Yield of isolated product. cod = 1,5-cyclooctadiene, DCE = 1,2,-dichloroethane, dppb = 1,4-bis(diphenylphosphino)butane, nap = napthyl.

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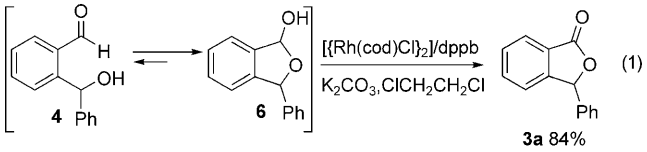
best catalytic reactivity (entries 10 and 15, Table 1). No desired product was formed in the absence of rhodium complex (entry 16, Table 1).

Having identified the optimal reaction parameters [under air, with $[\{Rh(cod)Cl\}_2]$ (5 mol%) and dppb (5 mol%) as the catalyst, and K_2CO_3 (2 equiv) in dry $ClCH_2CH_2Cl$ at 65°C], we turned our attention to an investigation of the scope of arylboronic acids (Table 2). The electronic properties of the substituents on the phenyl ring of the arylboronic acids had some effect on the reaction. Generally, the arylboronic acids possessing electron-donating groups produced 3-arylphthalides in higher yields (entries 1, 2, 5, and 8, Table 2). Notably, the procedure tolerated a range of functional groups, such as trifluoromethyl, nitro, chloro, and vinyl groups. The compatibility of vinyl and chloro groups is synthetically useful since the products could be additionally functionalized. Importantly, the hindrance of the phenyl ring of arylboronic acids had little effect on the reaction. For example, **2d** and **2e** produced **3d** and **3e** in 83% and 82% yields, respectively (entries 3 and 4, Table 2). Particularly, (*E*)-styrylboronic acid was also a good reaction partner and 3-alkenylphthalide **3n** was isolated in moderate yield (entry 13, Table 2). Replacing dppb with $P(1\text{-nap})_3$ increased the yields of **3j**, **3l**, and **3n** to some extent (entries 9, 11, and 13, Table 2). However, methylboronic acid failed to deliver the product. Under the optimized reaction conditions, the reaction conducted on 2 and 10 mmol scales formed the product **3a** in 81% and 70% yields, respectively. Thus, this transformation is very practical as it can be conducted in air and the rigorous exclusion of moisture is not required.

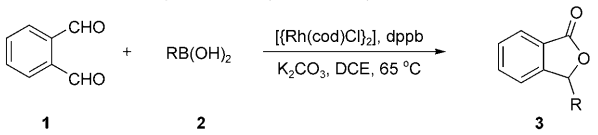
2-(Hydroxy(phenyl)methyl)benzaldehyde (**4**) is in equilibrium with **6**,[11] and when subjected to the reaction conditions **3a** was isolated in 84% yield [Eq. (1)]. This result indicated the arylation addition to **1a** could lead to product **4**, which may act as an intermediate.



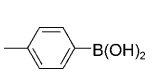
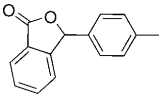
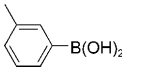
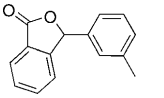
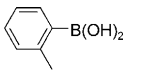
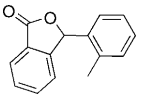
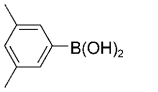
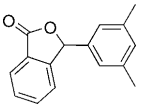
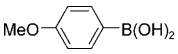
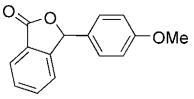
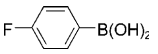
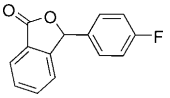
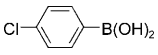
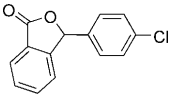
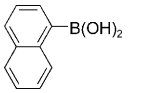
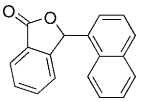
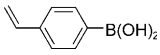
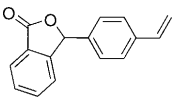
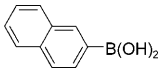
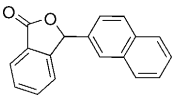
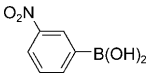
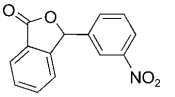
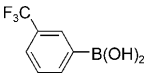
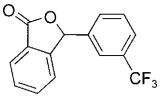
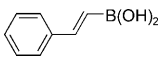
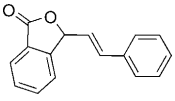
(1)

In principle, the intramolecular esterification reaction may involve three plausible pathways. As illustrated in path a of Scheme 2a, the first step involves the oxidative addition of the aldehydic C–H bond of **4** to Rh^I to produce the Rh^{III} intermediate **A**.[12] In the second step, the Rh^{III} intermediate **B** is formed by ligand exchange, and final reductive elimination of intermediate **B** delivers the product **3** and regenerates the Rh^I species. Recently, Krug and Hartwig reported the direct observation of aldehyde insertion into rhodium–alkoxide complexes.[13] As an alternative, path b begins with the rhodium-catalyzed addition of arylboronic acid **1** to the aldehydic carbonyl of **2** to produce the alkoxide intermediate **C**. Then, insertion of the intermediate **C** into the aldehyde C=O takes place to form the rhodium species **D**, and final β-hydride elimination of intermediate **D** delivers the product **3** and regenerates the rhodium species. Under this procedure, isobenzofuran-1(3*H*)-one (**5**), which is a Tishchenko reaction product, is sporadically isolated as a by-product [Eq. (2)]. The mechanism on the formation of **5** is proposed. The by-product

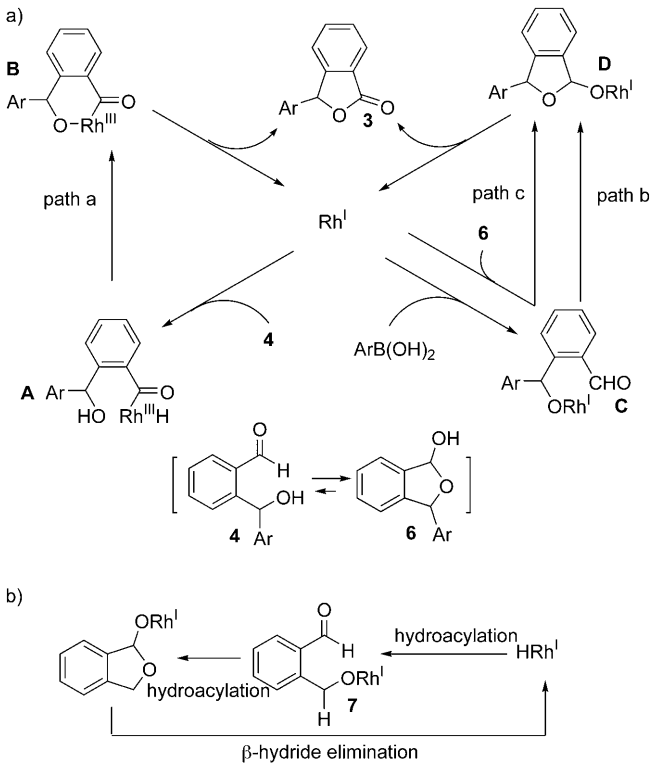
Table 2: Reaction of phthalaldehyde with arylboronic acids.[a]



1 2 3

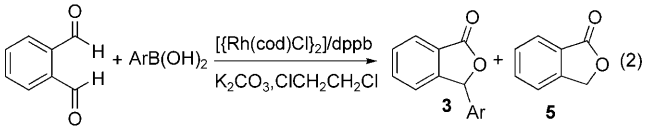
Entry	Substrate **2**	Product **3**	Yield [%][b]
1			85
2			82
3			83
4			82
5			84
6			84
7			77
8			90
9			43 (57)[c]
10			77
11			67[c]
12			64
13			50 (67)[c]

[a] Reaction conditions: Phthalaldehyde (0.2 mmol), phenylboronic acid (0.3 mmol), $[\{Rh(cod)Cl\}_2]$ (5 mol%), dppb (5 mol%) with K_2CO_3 (2 equiv) in dry $ClCH_2CH_2Cl$ (3 mL), 65°C, 12 h, under air. [b] Yield of isolated yield. [c] $P(1\text{-nap})_3$ (10 mol%).



Scheme 2. a) Plausible mechanism. b) Potential side reaction leading to product **5** [see Equation (2)].

5 may be derived from the HRh^I species (Scheme 2b), which results from either the main catalytic cycle or the β-hydride elimination of the aryl addition intermediate **C**.[14] The formation of **5** as the by-product indicates that the $RORh^I$ species **7** is reactive enough to insert into the second aldehydic carbonyl group. Therefore, path b is favored. However, path c, which involves a direct formation of the intermediate **D** from **6**, cannot be completely ruled out.



In conclusion, we have developed an efficient rhodium-catalyzed cascade aryl addition/intramolecular esterification of phthalaldehyde with arylboronic acids, affording the 3-aryl and alkenyl phthalides in moderate to good yields. The reaction showed remarkably broad substrate scope and good functional group tolerance. Efforts to expand the reaction to chiral 3-aryl and alkenyl phthalides and to elucidate the mechanism in detail are underway in our laboratory.

Experimental Section

Chemicals were either purchased or purified by standard techniques without special instructions. ^{1}H NMR and ^{13}C NMR spectra were measured on a 300 MHz or 500 MHz spectrometer (^{1}H 300 MHz, ^{13}C 75 MHz or ^{1}H 500 MHz, ^{13}C 125 MHz), using $CDCl_3$ as the solvent with tetramethylsilane (TMS) as the internal standard at room temperature. Chemical shifts are given in δ relative to TMS, the coupling constants J are given in Hz.

General procedure: Under air, a reaction tube was charged with phthalaldehyde (26.8 mg, 0.2 mmol), boronic acids (0.3 mmol), [{Rh-(cod)Cl}$_2$] (4.9 mg, 5 mol%), dppb (4.6 mg, 5 mol%), and dry $ClCH_2CH_2Cl$ (3 mL). The reaction tube was kept stirring at 65°C for 12 h. After the completion of the reaction, as monitored by TLC methods, the solvent was evaporated under reduced pressure and the residue was purified by flash column chromatography on silica gel to give the product.

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Keywords: arenes · boron · heterocycles · lactones · rhodium

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