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Rhodium or Palladium-Catalyzed Cascade Aryl Addition/ Intramolecular Lactonization of Phthalaldehyde with Potassium Organotrifluoroborates to Access 3-Arylphthalides

Fang Luo,[a] Shen Pan,[a] Changduo Pan,[b] Pengcheng Qian,[a] and Jiang Cheng[a,*]

[a] College of Chemistry & Materials Engineering, Wenzhou University, Wenzhou 325000, People's Republic of China
Fax: (+86)-577-5699-8939; e-mail: jiangcheng@wzu.edu.cn
[b] Wenzhou Institute of Industry & Science, Wenzhou 325000, People's Republic of China

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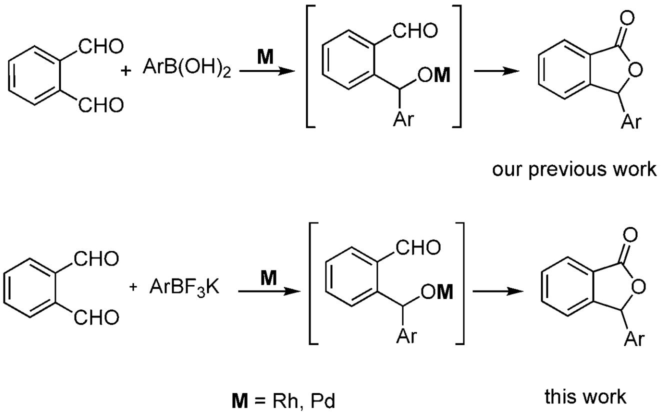
Abstract: An efficient rhodium-catalyzed lactonization of phthalaldehyde with potassium organotrifluoroborates to access 3-arylphthalides has been developed. Moreover, palladium is a also good catalyst for such transformation.

Keywords: 3-arylphthalides; palladium; phthalaldehyde; potassium organotrifluoroborates; rhodium

Phthalide (isobenzofuranone) frameworks are present in a large number of natural products and biologically active compounds.[1] Thus, significant efforts have been focused on synthesizing phthalides in the past few decades.[2] The transition metal-catalyzed carbon-carbon or carbon-heteroatom bond formation is a powerful tool in organic chemistry. However, less examples on the synthesis of 3-arylphthalides catalyzed by transition metals have been developed.[3] Recently, Onomura demonstrated the palladium-catalyzed arylation of methyl 2-formylbenzoate with organoboronic acids for the synthesis of 3-arylphthalides.[4] Subsequently, Hu demonstrated the rhodium-catalyzed addition of arylboronic acids to 2-formylbenzoates afforded 3-substituted phthalides.[5] Very recently, we developed a cascade aryl addition/intramolecular lactonization reaction of phthalaldehyde with boronic acids catalyzed by rhodium and palladium, respectively.[6] However, aryl-metal species were ultimately limited to boronic acids in the aforementioned transformations using the transition metal-catalyzed 1,2-addition of aldehyde as the key step. Thus, the discovery of more catalytically active and practically advantageous processes employing other reagents in such transformation is highly desirable.

Organoboron compounds and particularly boronic acids are known as useful reagents for carbon-carbon bond formation with various electrophiles in the presence of transition metals.[7] Although having advantages such as low toxicity and easy manipulation, boronic acids often dimerize and trimerize to form boronic acids anhydrides and boroxines,[8] which make difficulties in the direct purification and in the determination of the exact stoichiometry of the reactions. Recently, potassium organotrifluoroborates due to their superior features such as higher air- and moisture-stability,[9] have been focused as alternatives to boronic acid derivatives that easily undergo protodeboronation.[10] Over the past decade, the transition metal-catalyzed arylation reactions of aldehydes with organoboronic acids have attracted much attention.[11] Nevertheless, the employment of potassium organotrifluoroborates in transition metal-catalyzed 1,2-addition of aldehydes is rare.[12] Based on the aforementioned works, we envisioned to develop the reaction of phthalaldehyde with potassium organotrifluoroborates to access 3-substituted phthalides using the transition metal-catalyzed 1,2-addition of aldehyde as the key step (Scheme 1).

Initially, we chose phthalaldehyde **1** and potassium phenyltrifluoroborate **2a** as the model substrates for surveying the reaction parameters (Table 1). The choice of solvent had an important effect on the reaction. 1,2-Dichloroethane (DCE) turned out to be the best and the solvents such as DMF and DMSO which have high solubility with H_2O were totally ineffective. Bidentate phosphine ligands such as dppe and dppp, showed better catalytic reactivity. The influence of bases was also investigated, and Li_2CO_3 was found to be superior to some other bases such as K_2CO_3, Na_2CO_3, $NaHCO_3$, K_3PO_4 and CsF (Table 1, entries 13–19). Further study revealed that the source of Rh had also some effect on the reaction and



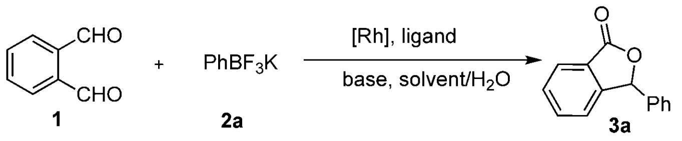
Scheme 1. The synthesis of 3-arylphthalides using phthaladehyde.

$[Rh(cod)Cl]_2$ was the best. After several rounds of optimization, we found that the best results were accomplished by using $[Rh(cod)Cl]_2$, dppe, and Li_2CO_3 in DCE/H_2O at 85 °C (Table 1, entry 20).

Next, we turned our attention to investigate the scope of the potassium aryltrifluoroborate (Table 2). As expected, various potassium aryltrifluoroborates worked well under the reaction conditions. The electronic properties of the substituents on the phenyl ring of the potassium aryltrifluoroborate had a dramatic effect on the reaction. Electron-donating substituents at the phenyl ring of boronic acids were beneficial for the transformation, whereas an electron-withdrawing group decreased the efficiency (Table 2, entries 2–7 *vs.* 8 and 9). The hindrance on the phenyl ring of the potassium aryltrifluoroborate had some effect on the reaction. For example, 93% of **3b** was isolated, while the yield of **3d** was slightly decreased to 84% (Table 2, entries 2 *vs.* 4). Under the standard reaction conditions, the reaction conducted on a 3-mmol scale formed the product **3a** in 84% yield. In comparison with our previous works, this procedure reduced the amount of Rh source and delivered the products in higher yields. Unfortunately, potassium methyltrifluoroborate failed to deliver the product under the standard procedure.

More experiments were carried out to gain a preliminary insight into reaction mechanism. When compound **4** was subjected to the standard reaction condition, **3** was isolated in 87% yield. We reasoned the rhodium species **A** was the key intermediate for the cascade reaction which was derived from the addition

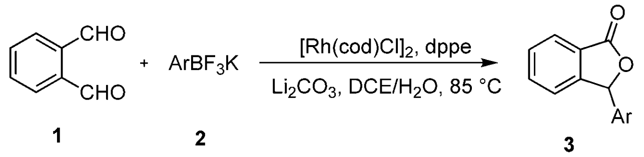
Table 1. Screening of conditions for the Rh-catalyzed lactonization of phthalaldehyde with potassium phenyltrifluoroborates.



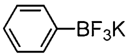
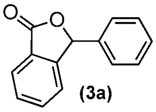
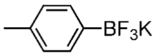
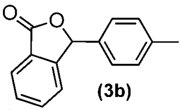
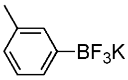
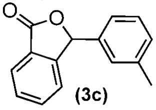
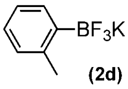
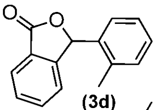
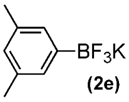
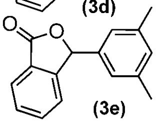
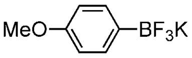
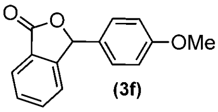
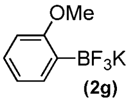
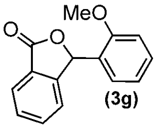
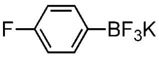
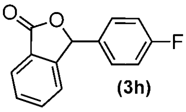
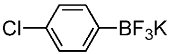
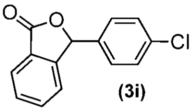
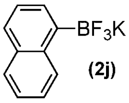
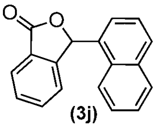
Entry	[Rh]	Ligand	Base	Solvent	Yield [%][a]
1	$[Rh(cod)OH]_2$	dppb	K_2CO_3	1,4-dioxane/H_2O	48
2	$[Rh(cod)OH]_2$	dppb	K_2CO_3	toluene/H_2O	48
3	$[Rh(cod)OH]_2$	dppb	K_2CO_3	xylene/H_2O	47
4	$[Rh(cod)OH]_2$	dppb	K_2CO_3	DME/H_2O	58
5	$[Rh(cod)OH]_2$	dppb	K_2CO_3	THF/H_2O	39
6	$[Rh(cod)OH]_2$	dppb	K_2CO_3	DCE/H_2O	69
7	$[Rh(cod)OH]_2$	dppb	K_2CO_3	CH_2Cl_2/H_2O	62
8	$[Rh(cod)OH]_2$	dppb	K_2CO_3	DMF/H_2O	<5
9	$[Rh(cod)OH]_2$	dppb	K_2CO_3	DMSO/H_2O	<5
10	$[Rh(cod)OH]_2$	dppp	K_2CO_3	DCE/H_2O	58
11	$[Rh(cod)OH]_2$	$P(1\text{-nap})_3$	K_2CO_3	DCE/H_2O	11
12	$[Rh(cod)OH]_2$	PPh_3	K_2CO_3	DCE/H_2O	10
13	$[Rh(cod)OH]_2$	dppe	K_2CO_3	DCE/H_2O	71
14	$[Rh(cod)OH]_2$	dppe	$KHCO_3$	DCE/H_2O	68
15	$[Rh(cod)OH]_2$	dppe	Na_2CO_3	DCE/H_2O	67
16	$[Rh(cod)OH]_2$	dppe	K_3PO_4	DCE/H_2O	52
17	$[Rh(cod)OH]_2$	dppe	$NaHCO_3$	DCE/H_2O	27
18	$[Rh(cod)OH]_2$	dppe	CsF	DCE/H_2O	<5
19	$[Rh(cod)OH]_2$	dppe	Li_2CO_3	DCE/H_2O	75
20	$[Rh(cod)Cl]_2$	dppe	Li_2CO_3	DCE/H_2O	86
21	$Rh(PPh_3)_3Cl$	dppe	Li_2CO_3	DCE/H_2O	54
22		dppe	Li_2CO_3	DCE/H_2O	<5

[a] *Reaction conditions:* **1** (0.2 mmol), **2a** (0.3 mmol), Rh source (2.5 mol%), ligand (5 mol%), base (2.0 equiv.) in solvent/H_2O (2 mL) at 85 °C for 12 h. Isolated yield.

Table 2. Rh-catalyzed lactonization of phthalaldehyde with potassium organotrifluoroborates.



1 **2** **3**

Entry	Substrate **2**	Product **3**	Yield [%][a]
1	 **(2a)**	 **(3a)**	86 (84)[b]
2	 **(2b)**	 **(3b)**	93
3	 **(2c)**	 **(3c)**	90
4	 **(2d)**	 **(3d)**	84
5	 **(2e)**	 **(3e)**	87
6	 **(2f)**	 **(3f)**	92
7	 **(2g)**	 **(3g)**	78
8	 **(2h)**	 **(3h)**	67
9	 **(2i)**	 **(3i)**	60
10	 **(2j)**	 **(3j)**	81

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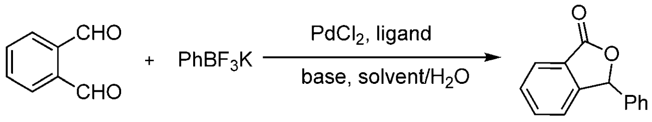
[a] *Reaction conditions:* **1** (0.2 mmol), **2** (0.3 mmol), [Rh(cod)Cl]$_2$ (2.5 mol%), dppe (5 mol%), Li_2CO_3 (2.0 equiv.) in $DCE/H_2O = 10/1$ (2 mL) at 85 °C for 12 h. Isolated yield.

[b] The reaction was run on a 3-mmol scale.

Table 3. Screening conditions for the Pd-catalyzed lactonization of phthalaldehyde with potassium phenyltrifluoroborates.



1 **2a** **3aa**

Entry	Ligand	Base	Solvent	Yield [%][a]
1	P(1-nap)$_3$	K_2CO_3	DCE/H_2O	<5
2	P(1-nap)$_3$	K_2CO_3	1,4-dioxane/H_2O	68
3	P(1-nap)$_3$	K_2CO_3	toluene/H_2O	68
4	P(1-nap)$_3$	K_2CO_3	DME/H_2O	69
5	P(1-nap)$_3$	K_2CO_3	THF/H_2O	80
6	dppe	K_2CO_3	THF/H_2O	<5
7	dppb	K_2CO_3	THF/H_2O	<5
8	dppp	K_2CO_3	THF/H_2O	<5
9	P(1-nap)$_3$	Li_2CO_3	THF/H_2O	80
10	P(1-nap)$_3$	Na_2CO_3	THF/H_2O	57
11	P(1-nap)$_3$	$KHCO_3$	THF/H_2O	34
12		K_2CO_3	THF/H_2O	<5

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[a] *Reaction conditions:* **1** (0.2 mmol), **2a** (0.4 mmol), $PdCl_2$ (5 mol%), ligand (5 mol%), base (2.0 equiv.) in solvent/H_2O (2 mL) at 65 °C for 12 h. Isolated yield.

of potassium aryltrifluoroborate to the C=O bond. Then, insertion of intermediate **A** to the second aldehyde carbonyl takes place to form the rhodium species **B**. Ultimately, β-H elimination of intermediate **B** delivers product **3** (Scheme 2).

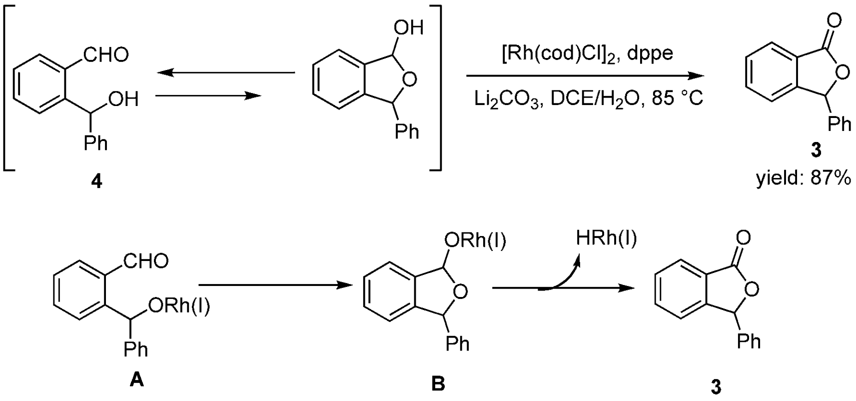
Next, we tried to develop a palladium-catalyzed lactonization of phthalaldehyde with potassium organotrifluoroborates. When $PdCl_2$ instead of [Rh(cod)Cl]$_2$ was subjected to the reaction, only 12% of the product **3a′** was isolated. Fortunately, after replacing dppe with the bulky and electron-rich P(1-nap)$_3$, **3a′** was isolated in 80% yield (Table 3). The results are shown in Table 4. Compared to the Rh-catalyzed lactonization of phthalaldehyde with potassium phenyltrifluoroborates, the yields were relatively lower. The effect of the electronic properties and the hindrance of the substituents on the phenyl ring of the potassium aryltrifluoroborate were consistent with those of the Rh-catalyzed procedure.

In summary, we have developed an efficient Rh-catalyzed lactonization of phthalaldehyde with potassium organotrifluoroborates to access 3-arylphthalides. Meanwhile, palladium was also a good catalyst for such transformation.

Experimental Section

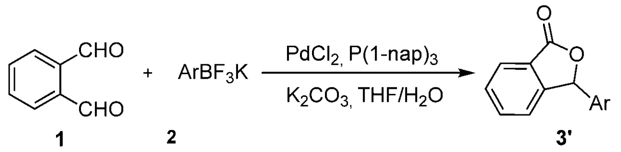
Typical Experimental Procedure for Rh-Catalyzed Lactonization of Phthalaldehyde with Potassium Organotrifluoroborates

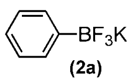
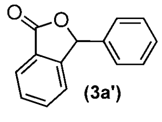
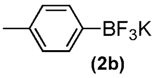
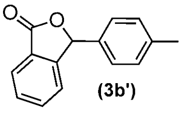
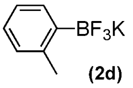
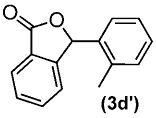
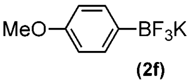
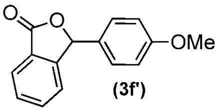
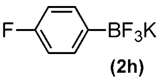
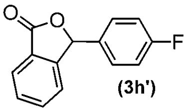
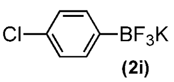
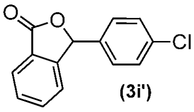
Under air atmosphere, a mixture of phthalaldehyde **1** (0.2 mmol), potassium organotrifluoroborate **2** (0.3 mmol),



Scheme 2. Possible mechanism.

Table 4. Pd-catalyzed lactonization of phthalaldehyde with potassium organotrifluoroborates.



Entry	Substrate **2**	Product **3**	Yield [%][a]
1	 **(2a)**	 **(3a')**	80
2	 **(2b)**	 **(3b')**	85
3	 **(2d)**	 **(3d')**	83
4	 **(2f)**	 **(3f')**	86
5	 **(2h)**	 **(3h')**	60
6	 **(2i)**	 **(3i')**	56

[a] *Reaction conditions:* **1** (0.2 mmol), **2** (0.4 mmol), $PdCl_2$ (5 mol%), $P(1\text{-nap})_3$ (5 mol%), K_2CO_3 (2.0 equiv.) in $THF/H_2O = 10/1$ (2 mL) at 65 °C for 12 h. Isolated yield.

$[Rh(cod)Cl]_2$ (2.5 mol%), dppe (5 mol%), Li_2CO_3 (2 equiv.) and $DCE/H_2O = 10/1$ (2 mL) was stirred in a reaction tube at 85 °C for 12 h. After the reaction was finished, the solvent was evaporated under reduced pressure and the residue was purified by flash column chromatography (petroleum ether/ethyl acetate) on silica gel to give the product.

3-Phenylisobenzofuran-1(3*H*)-one (3a):[6] ^1H NMR (500 MHz, $CDCl_3$): $\delta = 7.89$ (d, $J = 7.6$ Hz, 1 H), 7.59–7.56 (m, 1 H), 7.50–7.47 (m, 1 H), 7.32–7.29 (m, 3 H), 7.27–7.25 (m, 1 H), 7.21–7.18 (m, 2 H), 6.33 (s, 1 H); ^{13}C NMR (125 MH_Z, $CDCl_3$): $\delta = 170.5$, 149.7, 136.5, 134.3, 129.4, 129.3, 129.0, 127.0, 125.7, 125.6, 122.9, 82.7.

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