Organic LETTERS

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Regioselective Synthesis of *o*-Benzenediboronic Acids via Ir-Catalyzed *o*-C−H Borylation Directed by a Pyrazolylaniline-Modified Boronyl Group

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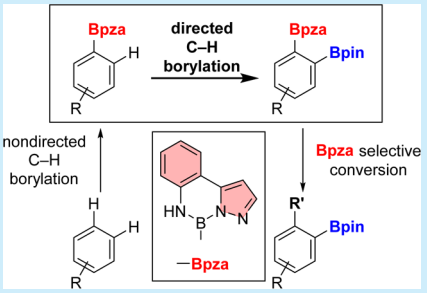
Supporting Information

ABSTRACT: Ir-catalyzed *ortho*-directed C−H borylation of pyrazolylaniline (PZA)-modified arylboronic acids with bis(pinacolate)diboron afforded *o*-benzenediboronic acids in which two boronyl groups are differentially modified by pinacol (PIN) and PZA. By using this borylation after nondirected Ir-catalyzed C−H borylation, *o*-benzenediboronic acids are conveniently synthesized from unfunctionalized arenes. The differentially modified *o*-benzenediboronic acids undergo selective oxidation and Suzuki−Miyaura cross-coupling at the PZA-modified boronyl groups, affording *o*-functionalized arylboronic acids selectively.

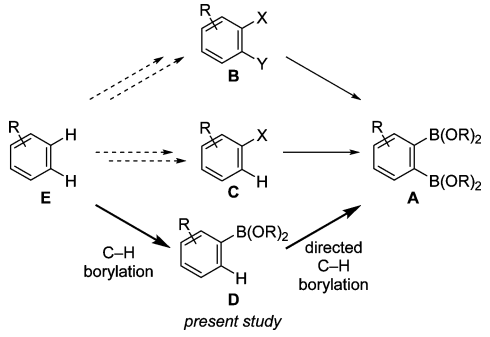


o-Benzenediboronic acid is an attractive structural motif not only as a building block and synthetic intermediate for the synthesis of natural products,[1] polycyclic aromatic hydrocarbons,[2] and oligoarene derivatives[3] but also as a bidentate Lewis acid[4] and key organic component of hydrogen-bonded organic frameworks.[5] In view of the rapid expansion of the utilization of functionalized boronic acid derivatives in various research fields including material science and organocatalysis, it is important to develop efficient and convenient synthetic access to *o*-benzenediboronic acids.

The synthesis of *o*-benzenediboronic acids **A** has generally relied on the use of 1,2-difunctionalized benzene derivatives **B** as starting materials (Scheme 1).[4−6] In typical cases, *o*-halobenzeneboronic acids or 1,2-dihalobenzenes are converted into *o*-benzenediboronic acids through halogen−metal (Li or Mg) exchange[5,6d−g] or palladium-catalyzed Miyaura borylation.[1,2b,c,3a,7] Recently, catalytic diborylation of arynes generated from 1,2-difunctionalized benzene derivatives has attracted much attention as a convenient route to *o*-benzenediboronic acids.[3b,c,8] Although these synthetic protocols are highly efficient and selective, the requirement for 1,2-difunctionalized arenes as starting material detracts much from the synthetic efficacy of the approach.[2a,b,9] Notably, high-yielding, photoinduced dual C−H/C−X borylation of monohaloarenes **C** has been reported quite recently.[10,11] However, although predictable, the selectivity for the formation of 1,2-diborylated products over 1,3-diborylated products depends to a significant degree on the electronic effect of substituents on the aromatic group. Furthermore, it is highly desirable to utilize simple arylboronic acids **D** or even nonfunctionalized arenes **E** as starting materials in the synthesis of *o*-benzenediboronic acids through C−H activation without using functionalized arenes bearing halogen or pseudohalogen leaving groups.

We previously reported Ru-catalyzed *o*-C−H silylation of arylboronic acids by attaching a temporary directing group on the boron atom of arylboronic acids.[12] Modification of the boronyl group with pyrazolylaniline or anthranilamide, which leads to the formation of the Bpza or Baam group, respectively, was found to be critical for the success of the highly selective directed transformation. In this paper, we describe the use of the PZA-modified boronyl groups as a temporary directing group in Ir-catalyzed *o*-C−H borylation. Although *o*-C−H borylation directed by several heteroatom functional groups was achieved by using Ir[13] and other transition-metal catalysts,[14] to our knowledge, boronyl-group-directed *o*-C−H borylation has not been reported. By utilizing the directed borylation, nonfunctionalized arenes are transformed into 1,2-

Scheme 1. Preparation of *o*-Benzenediboronic Acids



Received: January 5, 2017

DOI: 10.1021/acs.orglett.7b00041
Org. Lett. XXXX, XXX, XXX−XXX

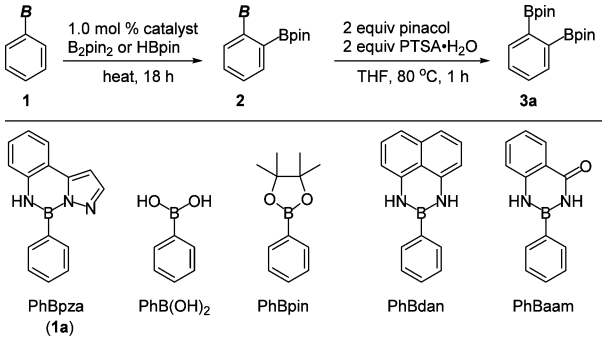
benzenediboronic acid derivatives through nondirected C−H borylation followed by Bpza-directed *o*-C−H borylation.

PZA-modified phenylboronic acid **1a**, synthesized by condensation of phenylboronic acid and 2-pyrazol-3-ylaniline,[12a] reacted with diboron in the presence of catalytic amounts of transition-metal complexes (Table 1). The resultant reaction mixture was treated with pinacol for detection and quantification of borylation product **2** in the form of pinacol ester (**3a**). In the presence of 1.0 mol % $[Ir(OMe)(cod)]_2$, *o*-C−H borylation proceeded at 80 °C for 18 h, giving **3a** in 85% yield (entry 1). Notably, unreacted **1a** and double borylated product were recovered as PhBpin (10%) and 1,2,3-benzenetriboronic acid pinacol ester (**5a**, 5%), respectively. Addition of 4,4′-di-*tert*-butyl-2,2′-bipyridyl (dtbpy), which is recognized as the most effective ligand in nondirected C−H borylation, resulted in *m*- or *p*-C−H borylation preferentially (15%, *m*:*p* = 1:2) (entry 2). The reaction with $[IrCl(cod)]_2$ afforded **3a** in 59% yield (entry 3). Although $[RhCl(cod)]_2$ and $[RhOH(cod)]_2$ showed low catalyst activities, C−H borylation proceeded at the *o*-position selectively (entries 4 and 5). The use of cyclohexane, toluene, 1,4-dioxane, or 1,2-dimethoxyethane as solvent resulted in lower yields, with recovery of unreacted **1a** as PhBpin (entries 6−9). Performing the reaction at 110 °C gave **3a** in lower yield and with a larger amount of **5a** (14%) (entry 10). The requirement for the *ortho*-directing group was confirmed by the observation that no product was formed in the reactions of $PhB(OH)_2$ or PhBpin under the same reaction conditions (entries 11 and 12). Furthermore, the use of PhBdan bearing a 1,8-diaminonaphthalene (DAN)-masked boronyl group afforded no desired product (entry 13). PhBaam underwent C−H borylation mainly at the anthranilamide group rather than at the *o*-C−H bond (entry 14). It was also found that use of HBpin instead of B_2pin_2 as a boron source successfully gave the *o*-borylation product in good yield (entry 15). In this case, a higher yield was obtained by raising the reaction temperature to 110 °C (entry 16). The primary product **2**, bearing Bpza and Bpin groups, was isolated by crystallization, albeit in moderate yield, and found to be hydrolytically unstable.

Under the optimized reaction conditions, various PZA-modified arylboronic acids were subjected to the directed C−H borylation (Scheme 2). All the products were isolated after conversion into the corresponding bispinacolates after treatment of the reaction mixtures with pinacol. The reaction of *p*-substituted compounds bearing methoxy, trifluoromethyl, and methyl groups afforded 4-substituted 1,2-diborylbenzenes **3b**−**d**. The directed C−H borylation of *m*-substituted arenes proceeded at the less hindered *o*-positions, giving 4-substituted 1,2-diborylbenzenes **3b**−**g** selectively. *o*-Substituted compounds could also be employed in the C−H borylation, giving the corresponding 3-substituted 1,2-benzenediboronates **3h**−**j** in high yields. 1-Naphthyl- and 2-naphthylboronic acids gave 1,2- and 2,3-diborylnaphthalenes **3k** and **3l**, respectively, in high yield and with excellent selectivity.

The Bpza-directed *o*-borylation, in combination with nondirected C−H borylation,[15] allowed the synthesis of 1,2-benzenediboronic acids from nonfunctionalized arenes (Scheme 3). 1-Chloro-2-methoxybenzene was subjected to Ir-catalyzed C−H borylation with B_2pin_2 in the presence of $[Ir(OMe)(cod)]_2$, giving a mixture of two regioisomers in a 1:1 ratio.[16] The mixture was treated with 2-pyrazol-3-ylaniline and subjected to the directed C−H borylation under the standard reaction conditions. After treatment with pinacol, 3-chloro-4-

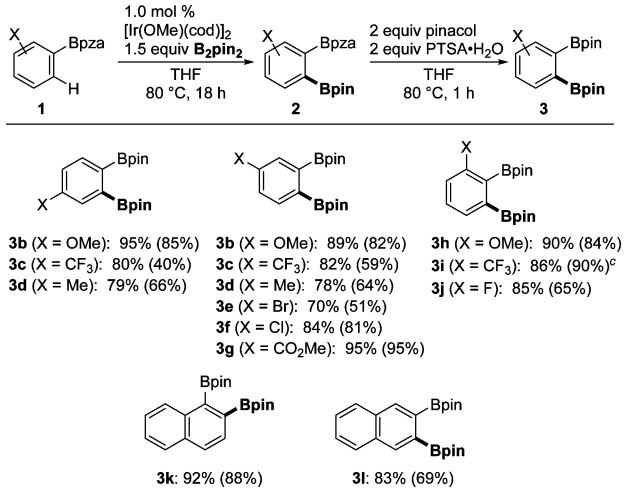
Table 1. *o*-C−H Functionalization of Phenylboronic Acid Derivatives[a]



entry	substrate (**1**)	catalyst	solvent	yield (%) of **3a**[b]
1	PhBpza (**1a**)	$[Ir(OMe)(cod)]_2$ (**4**)	THF	85
2	**1a**	**4**, dtbpy	THF	<1 (15)[c]
3	**1a**	$[IrCl(cod)]_2$	THF	59
4	**1a**	$[RhCl(cod)]_2$	THF	5
5	**1a**	$[RhOH(cod)]_2$	THF	2
6	**1a**	**4**	cyclohexane	60
7	**1a**	**4**	toluene	57
8	**1a**	**4**	1,4-dioxane	67
9	**1a**	**4**	1,2-DME[d]	68
10[e]	**1a**	**4**	THF	74
11	$PhB(OH)_2$	**4**	THF	0
12	PhBpin	**4**	THF	0
13	PhBdan	**4**	THF	0
14	PhBaam	**4**	THF	0
15[f]	**1a**	**4**	THF	70
16[e,f]	**1a**	**4**	THF	86

[a]Reaction conditions: **1** (0.10 mmol), B_2pin_2 (0.15 mmol), and catalyst (1.0 μmol), THF (1.0 mL), 80 °C, 18 h. [b]GC yield. [c]NMR yield of *m*- and *p*-diborylbenzenes. [d]1,2-Dimethoxyethane. [e]Reaction at 110 °C. [f]HBpin (0.30 mmol) instead of B_2pin_2.

Scheme 2. Substrate Scope[a,b]



[a]Reaction conditions: **1** (0.30 mmol), B_2pin_2 (0.45 mmol), $[Ir(OMe)(cod)]_2$ (3.0 μmol), THF (3.0 mL), 80 °C, 18 h. [b]NMR yield. Isolated yields in parentheses. [c]$[Ir(OMe)(cod)]_2$ (7.5 μmol).

DOI: 10.1021/acs.orglett.7b00041
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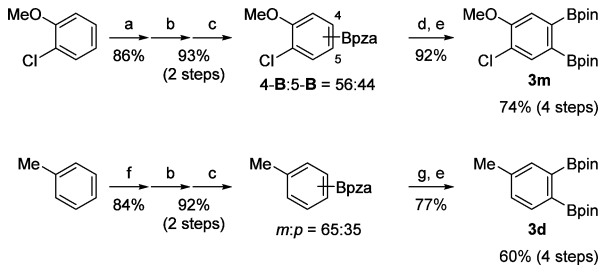
Scheme 3. Synthesis of *o*-Benzenediboronic Acid Derivatives from Nonfunctionalized Arenes[a]

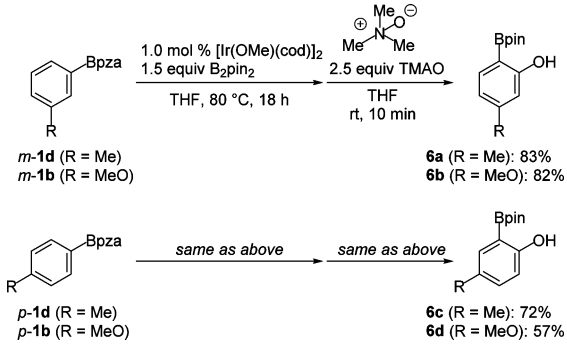


[a]Reaction conditions: (a) $[Ir(OMe)(cod)]_2$ (1.5 mol %), dtbpy (3.0 mol %), B_2pin_2 (1.2 equiv), THF, rt, 18 h; (b) $NaIO_4$ (3 equiv), THF, H_2O, 30 min, then HCl aq, 4 h; (c) H_2pza, toluene, reflux; (d) $[Ir(OMe)(cod)]_2$ (1.0 mol %), B_2pin_2 (1.5 equiv), THF, 80 °C, 18 h; (e) pinacol (2.0 equiv), PTSA·H_2O (2.0 equiv), THF, 80 °C, 1 h; (f) $[Ir(OMe)(cod)]_2$ (0.5 mol %), dtbpy (1.0 mol %), B_2pin_2 (1.0 equiv), toluene (30 equiv), rt, 30 h; (g) $[Ir(OMe)(cod)]_2$ (2.0 mol %), B_2pin_2 (1.5 equiv), THF, 80 °C, 18 h.

methoxy-1,2-benzenediboronate (**3m**) was isolated in good overall yield as a single regioisomer. This four-step protocol was also applicable to monosubstituted benzenes, as demonstrated by the conversion of toluene into 4-methyl-1,2-benzenediboronic acid (**3d**) (Scheme 2).

Our attention then turned to the reactivities of **2**, bearing two different masking groups, namely, PIN and PZA, on the boron atoms. When *m*-TolBpza (*m*-**1d**) was subjected to the directed C−H borylation and subsequent oxidation with trimethylamine oxide (TMAO, 2.5 equiv), we observed selective oxidation of one of the two different boron functional groups. The reaction gave *o*-hydroxyarylboronic acid **6**, which has been reported to be an important coupling building block in iterative cross-coupling for the synthesis of oligoarene derivatives, in a highly chemoselective manner (Scheme 4).[17,18] It is interesting to

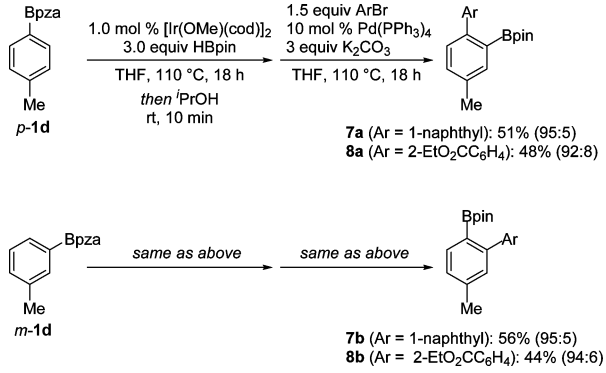
Scheme 4. One-Pot Synthesis of *o*-Hydroxyarylboronic Acid Derivatives



note that the Bpza group was oxidized selectively over the Bpin group. When *m*-TolBpza and *m*-TolBpin were separately treated with TMAO, we found that Bpza was more prone to oxidation (see Supporting Information). Use of regioisomeric TolBpza as a starting material allowed the synthesis of regioisomeric products **6a** and **6c** with high selectivity. Similarly, a pair of regioisomeric methoxy-substituted *o*-hydroxyarylboronic acid derivatives (**6b** and **6d**) was prepared selectively.

The Bpza selective conversion was also observed in Suzuki−Miyaura cross-coupling (Scheme 5). After the directed *o*-C−H

Scheme 5. One-Pot Synthesis of *o*-Borylated Biaryls



borylation of *p*-TolBpza (*p*-**1d**) using 3 equiv of HBpin, the reaction mixture was treated with isopropyl alcohol to decompose the remaining HBpin. Suzuki−Miyaura cross-coupling of the obtained crude product bearing Bpza and Bpin groups with 1-bromonaphthalene or ethyl 2-bromobenzoate proceeded at the Bpza group with high selectivity, giving biaryls **7a** and **8a**, bearing a Bpin group, along with the formation of a small amount of regioisomers **7b** and **8b**. Under the same reaction conditions, *m*-TolBpza (*m*-**1d**) was converted into methyl-substituted biaryls **7b** and **8b**, bearing a Bpin group, with high regioselectivity, in one-pot.

In conclusion, we have demonstrated a new Ir-catalyzed directed C−H borylation of arylboronic acid derivatives by attaching a removable directing group on the boron atoms. By combining with the nondirected C−H borylation, the reaction provides a new, convenient access to *o*-benzenediboronic acids from nonfunctionalized arenes through conversion of the two adjacent aromatic C−H bonds on the aromatic rings. The unsymmetrically modified *o*-benzenediboronic acids with PZA and PIN undergo selective conversion at the Bpza group in the TMAO oxidation and Suzuki−Miyaura cross-coupling.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b00041.

Detailed experimental procedures and compound characterization data (PDF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported by JSPS KAKENHI Grant Number JP15H05811 in Precisely Designed Catalysts with Customized Scaffolding and JP24750105 in Grant-in-Aid for Young Scientists (B).

DOI: 10.1021/acs.orglett.7b00041
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DOI: 10.1021/acs.orglett.7b00041
Org. Lett. XXXX, XXX, XXX−XXX