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Mild Silver(I)-Mediated Regioselective Iodination and Bromination of Arylboronic Acids

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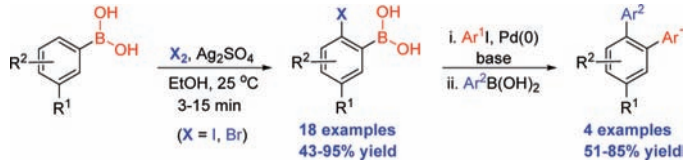
ABSTRACT



A convenient and regioselective silver(I)-mediated electrophilic iodination and bromination reaction of arylboronic acids has been developed. The boronic acid does not require protection prior to the reaction, which can be performed on a multigram scale with moderate to excellent yields. A mild, simple, and effective method is disclosed to provide *ortho*-haloarylboronic acids that can be used as useful intermediates in selective sequential Suzuki−Miyaura cross-coupling reactions to provide *ortho*-triaryl derivatives in good yields.

Boronic acids have become an increasingly important class of compounds for biological and synthetic applications[1] due to: (1) their interconvertibility between the sp^2 and sp^3 forms, (2) their strong interaction with diol-containing compounds, (3) their Lewis acidity, (4) their relatively low toxicity[2] [phenylboronic acid: LD_{50}, oral-rat = 740 mg/kg], and (5) their stability and commercial availability.

For these unique properties, boronic acids have been used as pharmaceuticals,[1−3] receptors in carbohydrate recognition,[1,2] boron neutron capture therapy agents,[1,2] catalysts,[4] and synthetic reagents.[5]

For instance, AN-2690 (**1**, Figure 1) is a fluoroarene boroxole-based broad-spectrum antifungal agent developed specifically for the treatment of onychomycosis, a fungal infection that affects fingers and toes, causing the nails to become brittle and discolored with soreness of the surrounding skin.[6a] AN-2690 has retention of antifungal activity and a nail penetration efficiency coefficient 50-fold higher than that of topical ciclopirox.[6b] It is currently in phase II/III clinical trials by the U.S. Food and Drug Administration. This compound and other boronic acids such as bortezomib have initiated significant interest in boron-based small molecules in drug discovery.

Furthermore, boronic acids and their esters have been used extensively not only as versatile intermediates in organic synthetic transformations such as Suzuki−Miyaura[5,7a] and Chan−Lam[7b] couplings, allylborations,[7c,d] and multicomponent reactions for the synthesis of various amino acids[7e,f] but also as efficient catalysts for cycloaddition, aldol, and amidation reactions.[4]

Direct amide bond formation is one of the few reactions catalyzed by boronic acids. A recent survey revealed that amide bond formation was not only one of the top 15 reactions currently used in the drug discovery industry but

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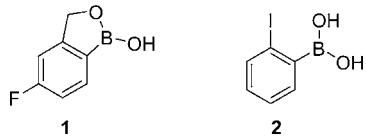

Figure 1. Structure of AN-2690 (5-fluoro-1,3-dihydro-1-hydroxy-2,1-benzoxaborole) (**1**) and *ortho*-iodophenylboronic acid (**2**).

also identified as a priority research area by the American Chemical Society (ACS) Green Chemistry Institute (GCI) and several leading global pharmaceutical corporations.[8] Consequently, the development of efficient amidation methods with high atom economy continues to be an important scientific pursuit. In 2008, Hall and co-workers described the remarkable activity of *ortho*-halophenylboronic acids as very active and mild catalysts toward cycloaddition reactions and direct amide bond formation at ambient temperature.[4c] *ortho*-Iodophenylboronic acid **2** (Figure 1) is the most active of the *ortho*-haloarylboronic acids. With an aim toward optimizing this catalyst, we sought to develop new methods that would provide a variety of substituted *ortho*-iodoarylboronic acids.

Even though arylboronic acids have been available for several years, are easy to handle, and are relatively stable, they are susceptible to chemoselectivity issues that render them difficult to further derivatization after introduction of the boronic acid. Their Lewis acidic nature makes them prone to react with commonly used organic reagents such as strong acids, bases, oxidants, and metal salts. This reactivity typically causes a simple protodeboronation or an ipso substitution of the boronic acid group, thus forming other products such as haloarenes,[9] amidoarenes,[10] and nitroarenes.[11] These transformations are believed to proceed via boron activation followed by an *ipso* displacement mechanism. As a result of this reactivity, boronic acids are rarely left intact after being carried through a number of synthetic chemical reactions.[12] Although direct bromination and chlorination of arylboronic acids have been reported by Kuivila and co-workers in 1962,[13] their direct iodination was not successful. The reaction was hampered by the formation of HI, which causes cleavage of the $B(OH)_2$ group to provide the iodoarene. While the halogenation of aromatic compounds is one of the most widely studied reactions in the literature,[14] a practical iodination of arylboronic acids to access iodinated arylboronic acids has not been reported. Herein, we report a convenient and effective method for mild and regioselective iodination and bromination of free arylboronic acids. This method provides the *ortho*-halogenated products in moderate to high yield (43%−95%). The reaction is operationally simple, requires no heating or cooling, and is easy to workup to provide crude products in high purity. Moreover, the silver reagent can easily be recycled from the reaction mixture as AgI or AgBr, which can be used for other reactions.[15]

We initiated this project by looking for a mild and convenient iodination agent. There have been a number of reports on direct aromatic iodination;[16] however, few Lewis acids have been examined. The most common Lewis acids are silver and mercuric salts in combination with I_2 due to the fact that silver and mercury can remove iodide efficiently from solution by precipitation. We decided to explore conditions with different solvents using 3-methoxyphenylboronic acid as a model substrate. First, a combination of silver sulfate and iodine was utilized as an iodinating agent at room temperature. A brief optimization of solvent revealed that ethanol and 1,2-ethanediol were the most suitable solvents for the desired transformation. The iodine color disappeared within a few minutes to provide the desired product without *ipso* deboronation side product (Table 1, entries 4 and 5). All other solvents were found to be unsuitable for this reaction (Table 1, entries 1−3). Using ethanol as a solvent, we examined the influence of different reagents on iodination of 3-methoxyphenylboronic acid to further establish the reaction conditions. We found that when a mixture of $Hg(OAc)_2/I_2$ was used instead of Ag_2SO_4/I_2 the yield of *ortho*-iodination product **3** decreased and formation of 10−15% of the *ipso*-iodination was observed (Table 1, entry 7). Using $AgNO_3/I_2$ led to a similar result as Ag_2SO_4/I_2 (Table 1, entry 6). No *ortho*-iodination was observed with NIS (Table 1, entry 8), while NIS in acetonitrile gave only the *ipso*-iododeboronation product in excellent yield (Table 1, entry 9). Furthermore, when the reaction times exceed 3 min, further decomposition occurred, and less *ortho*-iodination product **3** was observed.

The best yield of *ortho*-iodination product was obtained when 1.1 equiv of Ag_2SO_4 or $AgNO_3$ was used with 1.0 equiv of I_2 (Table 1, entry 10). The reaction also worked well on a multigram scale (Table 1, entry 12). Although the stoichiometric use of metal salts should be avoided as much as possible, it is tolerable for transformations that provide

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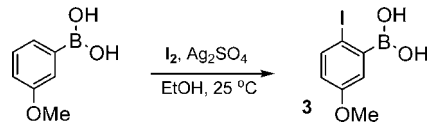
Table 1. Effect of Different Iodinating Agents in the Direct *ortho*-Iodination of 3-Methoxyphenylboronic Acid[a]



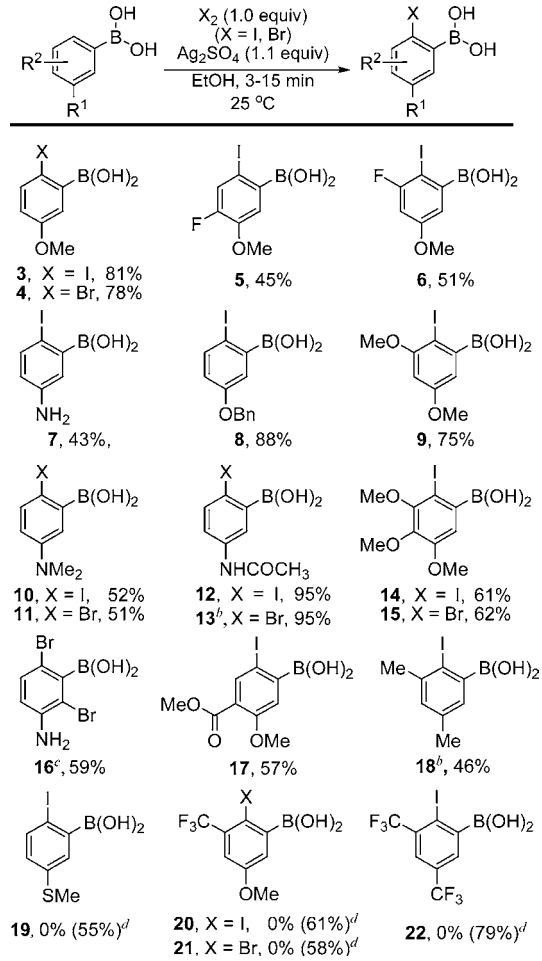
entry	solvent	iodinating agent	t (min)	yield (%)[b]
1	CH_2Cl_2	Ag_2SO_4/I_2	2.5	0[c]
2	THF	Ag_2SO_4/I_2	2	0[c]
3	CH_3CN	Ag_2SO_4/I_2	2	27[d]
4	$HOCH_2CH_2OH$	Ag_2SO_4/I_2	3	77
5	EtOH	Ag_2SO_4/I_2	2.5	79
6	EtOH	$AgNO_3/I_2$	3	75
7	EtOH	$Hg(OAc)_2/I_2$	20	40[e]
8	EtOH	NIS	>15	0[f]
9	CH_3CN	NIS	2	0[g]
10	**EtOH**	**Ag_2SO_4/I_2**[h]	**2.5**	**81**
11	EtOH	Ag_2SO_4/I_2[i]	2.5	82
12[j]	EtOH	Ag_2SO_4/I_2[h]	2.5	78

[a] Conditions: All the reactions were carried out using 1 equiv of iodinating agent and stirred at 25 °C for the time specified. [b] Isolated yield. [c] No reaction was observed. [d] Inseparable mixture of regioisomers along with *ipso*-iodinated product (~40%) was isolated. [e] *ipso*-Iodinated product (~15%) was also isolated. [f] No desired product was observed. [g] 97% yield of *ipso*-iodinated product. [h] Ag_2SO_4 (1.1 equiv of Ag). [i] Ag_2SO_4 (1.5 equiv of Ag). [j] 5 g scale (32.9 mmol).

products that are difficult or impossible to access by any other means. In this regard, we evaluated the substrate scope of the Ag(I)-mediated direct iodinaton of boronic acids using the optimized reaction conditions (Scheme 1). Different electron-rich, neutral, and electron-poor arylboronic acids bearing protic, basic, electrophilic, or nucleophilic functional groups were subjected to the optimal reaction conditions to provide the *ortho*-halogentaed products without any traces of other regioisomers. Substrates with electron-donating substituents such as a methoxy, amido, or amino provided the desired products in higher yield and shorter reaction times of 2−5 min (Scheme 1: **3**, **4**, **7**−**16**), whereas those bearing electron-withdrawing substituents decreased the reaction efficiency and increased the required reaction time to 10−15 min (Scheme 1: **5**, **6**, and **17**). The neutral substrate 3,5-dimethylphenylboronic acid was also subjected to the same reaction conditions to provide the desired iodinated product within 10 min (Scheme 1: **18**). Substrates with methylthio and trifluoromethyl substituents did not provide the desired products (Scheme 1: **19**−**22**).

Electron-rich substituents with their ability for conjugation enhance the reactivity of *ortho* and *para* positions toward electrophilic substitution reactions. The iodination of highly activated aromatic compounds like aniline provides the *para*-iodinated product in 66% yield as well as *ortho*- and *para*-diiodinated products in 13% yield at room temperature.[14] Using our conditions, the fact that the substitution occurs only *ortho* to the $B(OH)_2$ group and *para* to the electron-donating group even with multiple electron-donating groups

Scheme 1. Direct *ortho*-Iodination and Bromination of Arylboronic Acids[a]



[a] Yields are given for isolated compounds (reaction scale: 3.29 mmol). 1.1 equiv of Br_2 was used in case of bromination [b] $AgNO_3$ was used (1 equiv of Ag). [c] 2 equiv of Br_2 was used. An inseparable mixture of regioisomers was isolated when 1.1 equiv of Br_2 was used. [d] Recovered starting material in brackets.

(Scheme 1: **9**) indicates that electronic effects are not the only significant factor in these reactions. Indeed, the observed regioselectivity suggests that a strong *ortho* directing group effect from the $B(OH)_2$ is operative. Moreover, when there are two distinct *ortho* positions available for iodination, the site which is the least sterically hindered and *para* to the electron-donating group is iodinated (Scheme 1: **3**−**8**, **10**−**13**).

The regiochemistry in these examples is supported by X-ray crystallographic analyses of several products,[17] which clearly indicate the position of the electrophilic iodination. For example, the precursor to 2-iodo-3,5-dimethoxyphenyl boronic acid (Figure 2, **9**) has two positions available for iodination, *ortho* and *para* to the boronic acid group. The *ortho* position is iodinated exclusively under the optimized reaction conditions.

(17) CCDC-767421 and 767422 contain the supplementary crystallographic data for compounds **9** and **14**, respectively. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

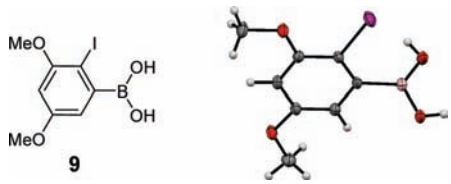
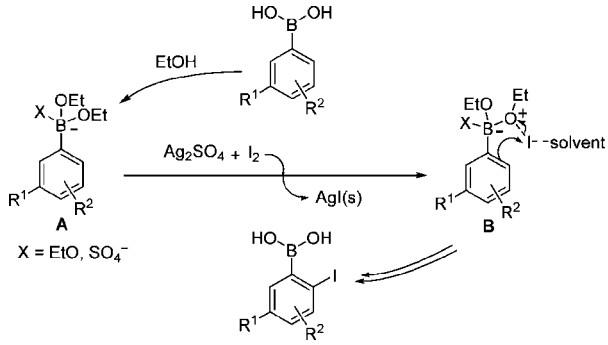


Figure 2. ORTEP view of 2-iodo-3,5-dimethoxyphenylboronic acid (**9**). Thermal Gaussian ellipsoids at the 20% probability level.

Since we have not observed other regioisomers in the reaction, it is likely that there exists a prominent interaction between the boronyl group and the active iodonium intermediate as shown in the proposed mechanism (Scheme 2).

Scheme 2. Proposed Mechanism for Direct *ortho*-Iodination of Arylboronic Acid

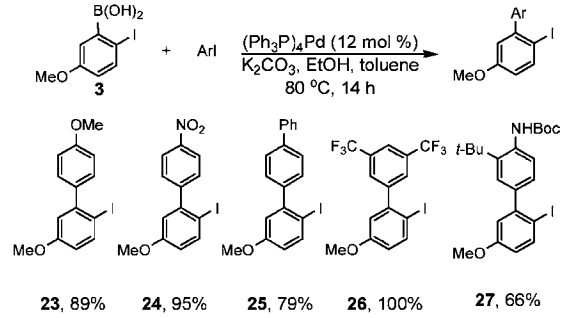


In ethanol, in the presence of anionic species, the formation of borate intermediate A is likely. Formation of this boronate anion activates the ring for electrophilic iodination while fostering electrostatic attraction with the iodonium reagent. This directing effect leads iodination to occur at the *ortho* position to the boronic acid as depicted in intermediate B.

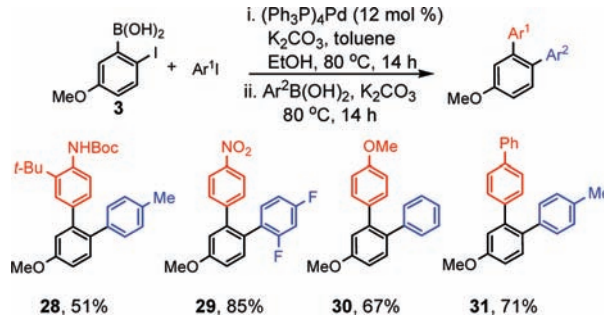
To demonstrate the utility of these *ortho*-iodoarylboronic acids as useful intermediates, different synthetic transformations were performed. For example, 5-methoxy-2-iodophenylboronic acid **3** was converted into biaryl derivatives by a highly chemoselective Suzuki−Miyaura coupling reaction with good to excellent yields (Scheme 3: **23**−**27**). Furthermore, one-pot double Suzuki−Miyaura couplings were also successful at providing the expected *ortho*-triaryl derivatives in good yields (Scheme 4: **28**−**31**).

In conclusion, we have developed the first mild and regioselective direct iodination of arylboronic acids. The

Scheme 3. Chemoselective Suzuki−Miyaura Coupling for *ortho*-Iodoarylboronic Acid



Scheme 4. One-Pot Chemoselective Double Suzuki−Miyaura Coupling of 2-Iodo 5-Methoxyphenylboronic Acid



functional group tolerance, broad substrate scope, and regioselectivity of the reaction provide a general method for halogenated arylboronic acids that are difficult to access otherwise. Remarkably, the resulting *ortho*-iodoarylboronic acids can be cross-coupled chemoselectively with other aryl iodides.

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Supporting Information Available: Detailed experimental procedures and spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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