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Communication

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Additive- and Metal-Free, Predictably 1,2- and 1,3-Regioselective, Photoinduced Dual C–H/C–X-Borylation of Haloarenes

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Supporting Information Placeholder

ABSTRACT: We report herein a simple, additive- and metal-free, photoinduced, dual C–H/C–X-borylation of chloro-, bromo-, and iodoarenes. The reaction produces 1,2- and 1,3-diborylarenes on gram scales under batch and continuous flow conditions. The regioselectivity of the dual C–H/C–X-borylation is determined by the solvent and the substituents in the parent haloarenes.

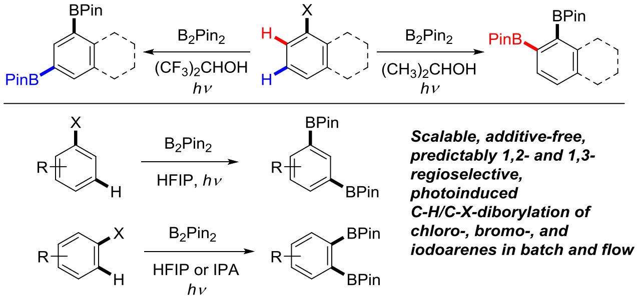
Aromatic di- and polyboronic acids (PBAs) are valuable organoboron materials with important roles in synthetic organic chemistry,[1] molecular self-assembly,[2] anion recognition,[3] molecular optoelectronics,[4] and materials science.[5] Regioselective installation of two boryl groups in the aromatic ring is challenging and is usually accomplished by borylation of the preinstalled C–X bonds using transition metal catalysis[6,7] or by generating dimagnesiated or dilithiated intermediates.[8] Alternatively, Rh- and Ir-catalyzed C–H-borylation[9] has also been used to prepare diborylarenes and related PBAs.[10] Other methods include the Zn-catalyzed 1,2-selective dual C–H/C–X-borylation of iodo- and bromoarenes described by Marder,[11] and the Pt- and Cu-catalyzed 1,2-diborylation of in situ-generated arynes developed by Yoshida.[12] However, the use of highly reactive, air- and moisture- sensitive reagents, expensive ligands and catalysts based on heavy metals, in addition to low regioselectivity and low yields limit the synthetic scope, practicality, and scalability of these methods.

Photoinduced dissociation of Ar–X bonds is an efficient method of generation of reactive intermediates that are typically inaccessible from the ground state.[13] In addition to homolytic cleavage of the Ar–X bond, photoheterolysis of haloarenes produces $\pi^5\sigma^1$ triplet aryl cations. Due to the combined radical and cationic character of these species, their reactivity is distinctively different from the reactivity of the ground state aryl cations and aryl radicals.[14] The multitude of reactivity patterns available after photoactivation of haloarenes has enabled a number of important carbon–heteroatom and carbon–carbon bond-forming reactions, including photoinduced nucleophilic substitution,[15] alkylation,[16] arylation,[17] and photocyclization[18] reactions.

We report herein that haloarenes undergo a photoinduced regioselective 1,2- and 1,3-C–H/C–X-diborylation that is enabled by a remarkable solvent effect. The diborylation reaction proceeds on preparative scales without removal of air or moisture in batch and flow and does not require catalysts or additives (Scheme 1).

We recently reported that haloarenes, including fluoroarenes, as well as quaternary arylammonium salts can be converted to the corresponding boronic acids and esters by a photoinduced borylation in the absence of additives and catalysts.[19,20] Homolytic and heterolytic cleavage of the Ar–X bond followed by the homolytic substitution at boron[21] in $B_2(OR)_4$ were proposed as key steps in this process.

Scheme 1. Photoinduced 1,2- and 1,3-Selective Dual C–H/C–X Borylation Reaction of Haloarenes



Scalable, additive-free, predictably 1,2- and 1,3-regioselective, photoinduced C-H/C-X-diborylation of chloro-, bromo-, and iodoarenes in batch and flow

A photoinduced diamine-mediated borylation of (pseudo)haloarenes was also reported by Li.[22] Computational studies by Li and Lin support involvement of aryl radicals and triplet aryl cations in the homolytic substitution step.[22b] Further investigation of the additive-free borylation reaction showed that small amounts of 1,2- and 1,3-C–H/C–X diborylation products **1** and **2** (Scheme 2) were formed from iodobenzene in acetonitrile. Additional studies identified isopropanol as the optimal solvent for the 1,2-selective dual C–H/C–X borylation. The ratio of 1,2- and 1,3-isomers **1** and **2** was 5.3:1. The 1,4-isomer was not observed in this case. Monoborylation and unselective diborylation were observed in a number of other solvents (see Table S1 in SI).

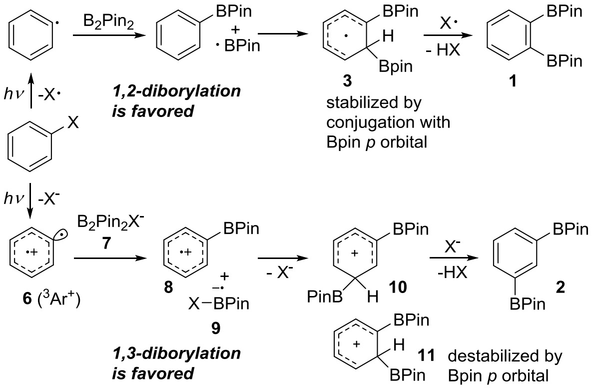
Remarkably, the regioselectivity of the reaction switched in favor of the 1,3-isomer **2**, when the borylation was carried out in hexafluoroisopropanol (HFIP). The diborylation products were isolated in 85% yield. The 1,3- 1,2-, and 1,4-isomers were formed in a ratio of 29:4:1. The reaction proceeded with a good photochemical quantum yield (Φ = 0.18, λ = 254 nm).

The experimental and computational data available for the photoinduced Ar–X monoborylation,[19,22] point to a solvent-cage-assisted radical pathway (Scheme 2) for the dual 1,2-C–H/C–X borylation reaction in isopropanol. Photoinduced homolysis is very efficient for bromo- and iodoarenes in low- and medium polarity solvents.[13,14] Following the initial homolytic substitution at B_2pin_2 with the photogenerated aryl radical,[19,22] addition of the Bpin radical to PhBpin may be enabled by the cage effect of the more confining medium (e.g. compare viscosities of acetonitrile

0.377 cP,[23] and isopropanol 2.859 cP,[24] at 15 °C). The 1,2-regioselectivity of the diborylation process is determined by the stabilization of the radical intermediate **3** by the conjugation with the boryl group.[25] Use of solvents with higher viscosity to suppress out-of-cage crossover reactions has previously been reported for other photoinduced radical processes.[26]

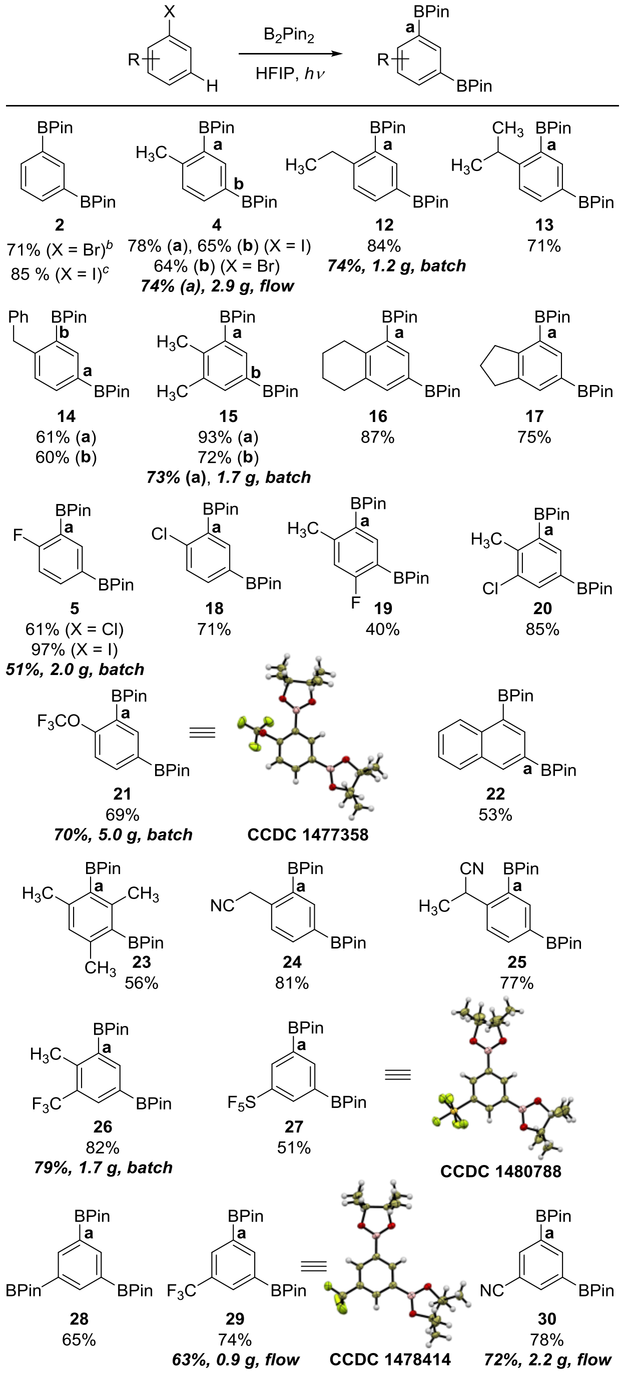
Hexafluoroisopropanol has found use in organic chemistry and electrochemistry, especially as a solvent for processes that involve arene cation radical intermediates, due to a combination of high polarity (E^{N}_{T} = 1.068), high ionizing power (Y_{OTs} = 3.79), and very low nucleophilicity (N_{OTs} = –4.23).[27] Additionally, as a weak hydrogen-bond acceptor and a strong hydrogen-bond donor, hexafluoroisopropanol has a strong propensity to solvate anions, further increasing the kinetic stability of cationic and cation radical species.[27a,b]

Scheme 2. Plausible Reaction Pathways for the Photoinduced Dual C–H/C–X-Borylation



Several experiments were performed to test the hypothesis that the reaction in HFIP proceeds via an electrophilic borylation of the intermediate ArBpin with pinB–X. First, the dual C–H/C–X borylation of iodobenzene was carried out in the presence of 2-tolylBpin (4 equiv.). A crossover reaction of pinB–I was expected to produce 1,3-diborylarene **4** (Table 1 and SI) in the case of the electrophilic borylation. However, the crossover product **4** was not formed. Further, since chloroarenes also undergo the dual C–H/C–X borylation, in the case of electrophilic borylation of ArBpin, addition of pinB–Cl was expected to increase the yield of the corresponding 1,3-diborylation product. However, addition of pinB–Cl (2 equiv.) to the diborylation reaction of 1-chloro-2-fluorobenzene did not lead to an increase in the yield of 1,3-diborylation product **5** (Table 1). Additionally, no accumulation of the monoborylation product (PhBpin) was observed at the early stages of the diborylation of iodobenzene (See Figure S1 in the SI). Taken together, these results indicate that electrophilic borylation of ArBpin with pinB–X may not be involved in the photoinduced dual C–H/C–X borylation process. In addition to homolysis, photoinduced heterolytic cleavage of C–X bonds to give the $\pi^5\sigma^1$ triplet aryl cations can take place in polar solvents, both directly, and by a homolysis followed by a charge transfer.[14] Formation of allylbenzene in the photolysis of ArX in the presence of allyltrimethylsilane has been used to detect involvement of photoheterolytic Ar–X bond dissociation pathways.[14b] In preliminary experiments, photolysis of iodo- and bromobenzene in HFIP in the presence of allyltrimethylsilane led to formation of allylbenzene that was not observed in isopropanol, pointing to the potential involvement of the heterolysis of haloarenes in HFIP. It is possible that heterolytic cleavage of the C–X bond in the very polar HFIP leads to the generation of the triplet aryl cation **6** that can react with the sp^2-sp^3 diboron anion **7**.[19,22,28] Subsequent recombination of the intermediates (**8** and **9**) will favor the 1,3-addition (**10**), since the 1,2- and 1,4-addition will produce cationic intermediates that are destabilized by the π-acceptor boryl group[29] (e.g. as in **11**). On the other hand, if a stronger electron-withdrawing group is present in the para position of the haloarene, the diborylation pattern in HFIP is expected to switch to the 1,2-diborylation. Similarly, if a strongly electron-releasing substituent is present in the meta position of the haloarene, 1,2-diborylation is also expected to become predominant. Since the boryl group is a relatively weak electron-acceptor (σ_p = 0.12 for $B(OH)_2$[30]), the substitution pattern can change from 1,3 to 1,2, depending on the position of other substituents in the haloarene, and it can be predicted from their electronic properties.

Table 1. Scope of the Photoinduced 1,3-Selective Dual C–H/C–X-Borylation Reaction of Haloarenes.[a]



[a] Iodoarenes were used unless specified otherwise; **a** and **b** denote the position of the C–X bond in the parent haloarene. Reaction conditions for small scale experiments: haloarene (0.6 mmol), B_2Pin_2 (1.2 mmol), HFIP (6 mL), 15 °C, UV lamp (254 nm, 4.5 mW/cm^2). [b] Ratio of 1,3/1,2/1,4-isomers: 42:5:1. [c] Ratio of 1,3/1,2/1,4-isomers: 29:4:1.

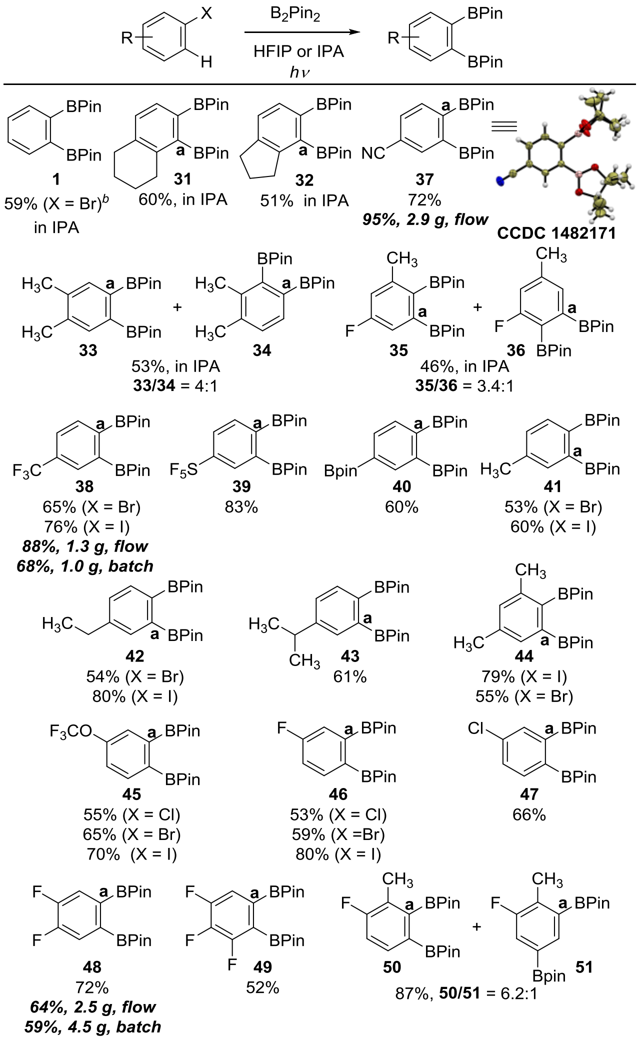
The scope and the influence of substituents on the regioselectivity were investigated next (Table 1). 2- and 4-alkyliodobenzenes afforded the 1,3-products in excellent yields (**4, 12-14**) and as single diastereomers, indicating that the 2- and 4-alkyl groups reinforce the 1,3-regioselectivity determined by the Bpin group. Similarly, high yields were observed for haloarenes with the 2,3-dialkyl substitution pattern (**15-17**). Benzylic positions in these substrates were not affected. 2- and 4-Fluoro and chloro groups were also tolerated (**5**, **18**, and **19**). 1,3-Diborylation products were formed in these cases, indicating that halogens serve as π-donor groups in the diborylation reaction. Methyl group in the ortho position proved to have a stronger effect than a chloro group in the meta position of the haloarene (product **20**). 2-Trifluoromethoxy group also showed good directing ability, reinforcing the 1,3-diborylation pattern (product **21**). The photoinduced diborylation also afforded the 1,3-diborylnaphthalene **22** and the sterically encumbered 1,3-diboryl derivative of mesitylene **23**. In addition, a cyano group in the benzylic position is also well-tolerated (**24** and **25**). An electron acceptor group in the meta position in haloarenes was expected to reinforce the 1,3-diborylation pattern. Indeed, several iodoarenes bearing electron-acceptor groups were tested, including the medicinally relevant pentafluorosulfanyl[31] and trifluoromethyl groups, as well as Bpin, and cyano groups. In all cases, the expected 1,3,5-trisubstituted products **26-30** were formed as single regioisomers. The reaction produced the less sterically hindered of the two possible electronically-favored 1,3-regioisomers. For example, for 2-substituted iodoarenes, only the hydrogen that is para to the substituent was displaced by the Bpin group (e.g. as in 1,3-diborylarene **4**). Bromo- and chloroarenes can also participate in the diborylation reaction, giving rise to 1,3-diborylarene products **2**, **4**, and **5** in good yields. The diborylation products were purified by evaporating the more volatile components of the reaction mixture (typically, B_2pin_2, ArBpin, and pinacolone) on a rotary evaporator equipped with an electrothermal vacuum oven.

The scope of the 1,2-diborylation was investigated next (Table 2). Diborylation in isopropyl alcohol proceeded with high 1,2-selectivity, and the corresponding products **31** and **32** were obtained in good yields. Two 1,2-diboronates **33** and **34** were formed in a ratio of 4:1 with 4-iodo-*o*-xylene, indicating that the second Bpin addition occurs preferably away from the present substituents. Interestingly, when both meta positions in the iodoarene were substituted with a methyl and a fluoro substituent, the diborylation in isopropyl alcohol produced 1,2-isomers **35** and **36** in a 3.4:1 ratio. In this case, substitution of the hydrogen para to the fluoro group was the more favored pathway.

Following the general mechanistic blueprint, the diborylation in HFIP was expected to produce 1,2-diborylarenes from haloarenes bearing electron-withdrawing groups (EWG) in the para position, and from haloarenes with electron-releasing substituents in the meta position. When *para*-EWG-substituted iodoarenes were subjected to the dual C–H/C–X borylation reaction, 1,2-diborylarenes **37-40** were obtained in excellent yields as single regioisomers. Similarly, 3-alkyl-substituted iodoarenes produced the corresponding 1,2-diborylarenes **41-44** as single regioisomers and in good yields. Haloarenes bearing heteroatom substituents (fluoro, chloro, trifluoromethoxy groups) also produced 1,2-diborylarenes (**45-47**). In addition, difluoro- and trifluoro-substituted 1,2-diborylarenes **48** and **49** were prepared in good yields. Interestingly, 1,2-diborylation was favored, when the fluoro group was in the meta position with respect to the iodide in the haloarene, while the ortho position was occupied by a methyl group. In this case regioisomers **50** and **51** were obtained in a ratio of 6.2:1. Chloro- and bromoarenes can also be successfully converted to the corresponding 1,2-diboryl derivatives (e.g. **38, 41, 42, 44-46**).

The structures of diborylarenes **21**, **27**, **29**, and **37** were confirmed by X-ray crystallography. The diborylation reactions were successfully carried out on gram scales in quartz test-tubes and FEP plasticware without prior deoxygenation of reaction mixtures. Diborylation products **5**, **12**, **15**, **21**, **26** (Table 1), as well as **38** and **48** (Table 2) were prepared in 1.1–5.0 g quantities. Further experiments showed that the dual C–H/C–X borylation reaction can also be translated to a continuous flow process, and several 1,3- and 1,2-diborylarenes were synthesized in flow on preparative scales (**4**, **29**, **30**, **37**, **38**, and **48**, 0.9–2.9 g). Importantly, hexafluoroisopropanol can be efficiently recovered by distillation (95% recovery) from the reaction mixture and reused in another diborylation reaction.

Table 2. Scope of the Photoinduced 1,2-Selective Dual C–H/C–X Borylation Reaction of Haloarenes.[a]



[a] Reaction conditions: see footnote for Table 1, IPA = isopropyl alcohol. The reactions were carried out in HFIP unless specified otherwise. [b] Ratio of 1,2/1,3-isomers: 5.3:1.

In conclusion, this paper describes a simple, scalable, additive- and heavy metal-free method of photoinduced dual C–H/C–X borylation of haloarenes. The reaction produces 1,2- and 1,3-diborylarenes regioselectively and in good to excellent yields under mild conditions from chloro-, bromo-, and iodoarenes. The regioselectivity of the reaction is determined by the solvent (hexafluoroisopropanol or isopropanol) and the substituents in the aromatic ring, and it can be readily predicted from the electronic properties of the substituents.

ASSOCIATED CONTENT

Supporting Information

Experimental and spectral details for all new compounds and all reactions reported. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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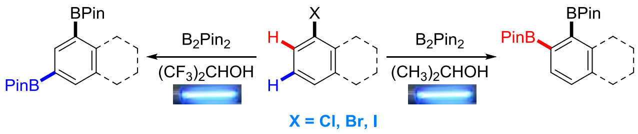
TOC Graphic



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solvent effect-enabled regioselectivity
metal- and additive-free borylation
practical gram-scale synthesis