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Boron-Mediated Regioselective Aromatic C–H Functionalization via an Aryl BF₂ Complex

Ganesh H. Shinde^[a] and Henrik Sundén^{*[a, b]}

Abstract: An efficient regioselective functionalization of 2-aryl-heteroarenes and aryl aldehydes via an azaaryl BF₂ complex has been developed. Mechanistically the reaction comprises fluoride to bromide ligand exchange on an aryl boron species and consecutive C–B bond cleavage to deliver a broad range of functionalized products. The reaction is high

yielding, has a broad substrate scope where several different heteroarenes can be functionalized with chloro, bromo, iodo, hydroxyl, amine and BF₂ in a highly regioselective fashion. The method can be applied for late-stage functionalization or for rapid skeleton remodeling with for instance cross-couplings.

Introduction

To synthetically differentiate between similar aromatic C–H bonds is difficult but highly attractive. A regioselective C–H functionalization improves the synthetic efficiency, minimizes waste, and simplifies purification as regioisomeric mixtures can be avoided.^[1] In this work, we have focused our attention to the functionalization of the *ortho*-position of 2-aryl-*N*-heteroarenes and aryl aldehydes. The *ortho*-functionalized 2-aryl-*N*-heteroarenes can be found in several biologically active compounds (Figure 1A) and *ortho*-halogenated aldehydes are synthetically useful but difficult substrates to make and both substrate classes are therefore interesting to use as a starting point for synthetic methodology development.

Direct regioselective aromatic C–H functionalization of 2-aryl-*N*-heteroarenes can be performed with metal-based catalysts.^[2] However, these functionalizations mainly focused on pyridine-based *N*-heteroarenes via nitrogen chelation. Nevertheless, transition metal-free approaches for halogenations of aromatics does exist.^[3,4] For example, brominations can be performed, with a varying degree of selectivity, on substituted anilines,^[4a–c,e] anilides,^[4a,d,g] naphthols,^[4a–c] and, phenols.^[4a–c] but regioselective *ortho*-functionalization remain elusive.

Recently, metal-free carbon-boron bond formation using boron tribromide (BBr₃) via various directing groups has

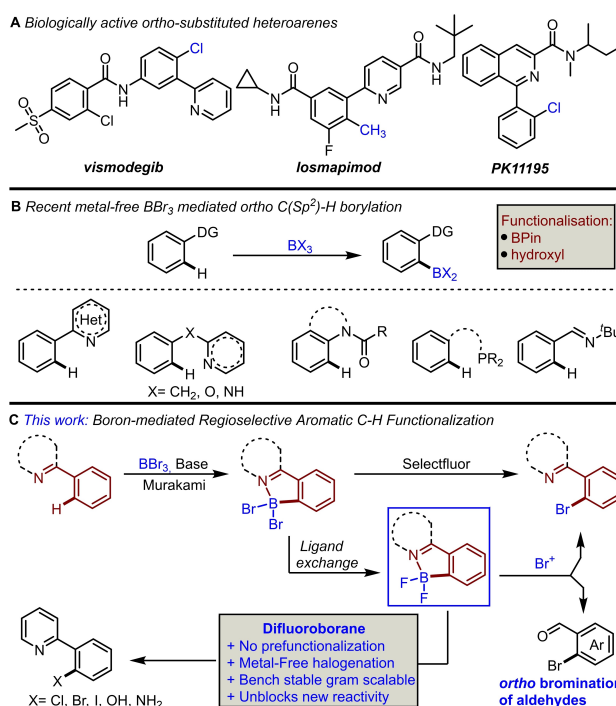


Figure 1. A) Examples of *ortho*-substituted heteroarenes. B) Literature survey of recent metal-free BBr₃ mediated *ortho* C(Sp²)-H borylation. C) Our work on boron-mediated regioselective aromatic C–H functionalization.

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attracted widespread attention in organic synthesis^[5] and materials chemistry as a direct way to introduce boron to the aromatic skeleton.^[6] The reactions generally proceed via a stable 5- or 6-membered boracycle^[7] that governs the regioselective functionalization of the aromatic or heteroaromatic system. These synthetic strategies have been used in borylative hydroxylation of *N*-heterocycles^[5d,m] and for installing boronic acid pinacol esters (Bpin) on aldehydes,^[5i] anilines,^[5b,e] alkenes,^[5g] indoles,^[5b,c] pyrroles,^[5h] phenoxypyridines,^[5a] pyrimidylanilines,^[5j] phosphines,^[5k,l] thiopyridines,^[5f] and are synthetically useful due to their widespread use in the Suzuki reaction (Figure 1B).

In the last few decades, Selectfluor (1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octanebis(tetrafluoroborate)) has emerged as a bench-top stable electrophilic fluorinating reagent.^[8] However, recent research has shown that Selectfluor is beyond just a fluorinating reagent, for instance, Curran and co-workers described the concept of ligand exchange on boron atoms using Selectfluor^[9a] and Xia and co-workers disclosed the Selectfluor-Eosin Y mediated regioselective bromination of aniline derivatives.^[9b] With these seminal advancements in mind, and our recent interest in BBr₃ mediated reactions,^[10] we argued that it would be possible to regioselectively introduce bromine to the *ortho* position of 2-aryl-heteroarenes through a five and six-membered dibromoboracycle via a Selectfluor mediated ligand exchange. The initial hypothesis was that the aromatic C–B bond would be activated by the introduction of a fluoro-ligand and thus facilitate an *ipso* attack at the C–B carbon^[11,12] by cationic bromine to provide the means for a regioselective bromination (Figure 1C).

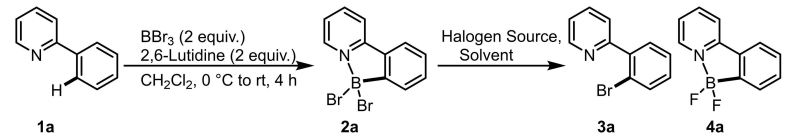
To the best of our knowledge, bromination of 2-aryl-heterocycles via in situ bromide to fluoride ion ligand exchange on boron using Selectfluor lacks precedence in the literature. Herein, we report an efficient method involving regioselective bromination of 2-aryl-heteroarenes and transient imines via C–B bond cleavage. Furthermore, the methodology can be extended to metal-free regioselective chlorination, iodination, hydroxylation, and copper-catalyzed amination using the bench stable difluoroborane (Figure 1C). Due to the synthetic utility of aryl-halogens and difluoroboranes, the methodology opens a completely new approach for the site-specific introduction of a wide array of functional groups that are useful for both material- and medicinal chemists.

Results and Discussion

To this end, we discovered that the use of 2.0 equiv. of BBr₃ and 2,6-lutidine in dichloromethane at room temperature for 4 h led to the full conversion of the starting material (**1a**) and formation of boron complex **2a**.^[7a] Having found our optimal conditions for the synthesis of **2a** we set out to explore the bromide to fluoride ligand exchange (Table 1). In our initial efforts, we observed that solubility and the source of fluorine play a crucial role in the ligand exchange and a switch from dichloromethane to acetonitrile was crucial. With 1 equiv. of Selectfluor and acetonitrile as solvent at room temperature, we observed the formation of the bisfluorinated product **4a** (Table 1, entry 1). Heating the reaction at 55 °C, gave approximately 10% of **3a** along with 81% of **4a** (Table 1, entry 2). With a higher loading of Selectfluor (2 equiv.) at 55 °C improved the yield of the halogenated product and **3a** could be isolated in 79% yield (Table 1, entry 3). Under these conditions, **4a** cannot be observed.

However, during the reaction, we observed the formation of a precipitate indicating that the solubility issue was not fully addressed. As it turns out, the use of an acetonitrile-water system makes the reaction mixture homogenous and the desired product could be isolated in 94% yield within 3 h at 55 °C (Table 1, entry 4). With the aqueous-based solvent system, the loading of Selectfluor could further be decreased to 1 equiv. to give the corresponding brominated product **3a** in 96% yield (Table 1, entry 5). When subjecting the reaction to another electrophilic fluorine source, NFSI, we isolated **3a** in 87% yield (Table 1, entry 6). A nucleophilic inorganic fluorine reagent such as KF was also investigated but provided only the bisfluorinated product **4a** in 63% yield (Table 1, entry 7). To run the reaction one-pot starting from **1a** required slight alterations of the

Table 1. Optimization of the reaction conditions.

						
Entry ^[a]	Halogen source (equiv.)	Solvent	Time [h]	Temperature [°C]	Yield [%] ^[b] 3a	Yield [%] ^[c] 4a
1	SF (1)	CH ₃ CN	1	rt	0	96
2	SF (1)	CH ₃ CN	6	55	> 10	81
3	SF (2)	CH ₃ CN	6	55	79	
4	SF (2)	CH ₃ CN:Water	3	55	94	
5	SF (1)	CH ₃ CN:Water	3	55	96	
6	NFSI (2)	CH ₃ CN:Water	6	55	87	
7	KF (2)	CH ₃ CN:Water	16	55	0	63
8 ^[d]	SF (1)	CH ₃ CN:Water	12	55	64	
9 ^[d]	SF (1.5)	CH ₃ CN:Water	12	55	80	
10 ^[d]	SF (2)	CH ₃ CN:Water	4	55	91	
11 ^[d]	NBS (2)	CH ₃ CN:Water	16	55	67	
12 ^[e,f]	SF (2)	CH ₃ CN:Water	4	55	0	
13 ^[g]	SF (2)	CH ₃ CN:Water	4	55	0	
14 ^[h]	–	CH ₃ CN:Water	12	55	0	

[a] Reaction conditions: i) **2a** (0.15 mmol), Selectfluor (SF) (0.15 mmol), in 1 mL CH₃CN and 0.5 mL water at rt to 55 °C, 3 h; [b] isolated yields; [c] crude yields, purified by pentane wash; [d] entries 8–12 one pot synthesis: i) **1a** (0.26 mmol), BBr₃ (0.52 mmol), and 2,6-lutidine (0.52 mmol), in 0.5 mL CH₂Cl₂ at 0 °C to rt, 4 h; ii) Selectfluor (0.52 mmol), in 1.5 mL CH₃CN and 1 mL water at rt to 55 °C, 4 h; [e] BCl₃ was used instead BBr₃; [f] starting material **1a** was recovered; [g] BF₃·OEt₂ was used instead BBr₃; [h] starting material **2a** was decomposed.

reaction conditions with the best results obtained with 2 equiv. of Selectfluor providing **3a** in 91 % yield (Table 1, entries 8 and 9 vs. 10). The need for higher loading of Selectfluor is most likely due to the presence of BBr₃ in the reaction mixture. An organic bromine source such as NBS is also compatible with the reaction delivering compound **3a** in 67 % yield (Table 1, entry 11). Furthermore, we tested the reactivity of **1a** under different boron sources (BCl₃ and BF₃) and it was observed that both of the reagents showed no reactivity, leaving a starting material unreacted (Table 1, entries 12 and 13). Running the reaction without Selectfluor gave no product and the starting material was decomposed (Table 1, entry 14).

Having established a protocol for the regioselective bromination of **1a**, the substrate scope was investigated. Different electron-donating and electron-withdrawing functional groups were well tolerated on the phenyl part of the substrates under optimal conditions. For example, substrates bearing electron-donating groups such as 4-methyl, 4-*t*-butyl, 2-methyl on the phenyl ring were compatible with the reaction condition giving the desired products **3a**, **3b**, **3c**, and **3d** in 91 %, 89 %, 87 %, and 84 % yield, respectively. However, a *meta*-substituted substrate such as **1e** gave two isomers **3e**:**3e'** in a 2.3:1 ratio with an excellent overall yield (81 %). Substrates with di-methyl substitution on the phenyl ring also gave the expected bromo derivatives in excellent yield (**3f** 89 % and **3g** 93 %). In the case of substrates bearing halogen atoms such as fluoro-, chloro-, and bromo-, we observed good to very good yields (**3h** 66 %, **3i** 80 %, and **3j** 81 %). A substrate with a halogen atom at the *meta* position showed the formation of two regioisomers in a (**3k**:**3k'** 3.5:1) ratio with a combined 86 % yield. Electron-withdrawing substituents are also tolerated by the reaction. For example, a CF₃ group in the *para* position on the phenyl ring delivered **3l** in a 33 % yield. However, in the case of cyano (**1m**) and nitro substrates (**1n**), product formation was not observed. However, strong electron-withdrawing groups such as cyano and nitro are similarly compatible on biphenyl rings with optimized reaction conditions to afford the desired product in moderate yield (**3o** 44 % and **3p** 63 %).

Regioselective monobromination was also observed on a substrate with a biphenyl ring and naphthyl ring furnishing **3q** in 46 % yield and **3r** in 86 % yield, respectively. We next explored the scope by substituting the pyridine ring. Methyl substitution at the 3, 5, and 6 positions of the pyridine ring underwent a smooth transformation with excellent yields (**3s** 89 %, **3t** 86 %, **3u** 88 %). Electron-rich substrates such as 2-(thiophen-2-yl)pyridine give a mixture of the products (**3v** 39 %) and (**3v'** 27 %) in an overall 66 % yield. However, one can also exclusively synthesize 3,5-dibrominated heteroaryl thiophenes (**3v'**) in 87 % yield using an altered protocol. Furthermore, exclusive monobromination was observed on the electronically rich (benzo[*b*]thiophen-2-yl)pyridine substrate **1w** providing **3w** in 41 % yield. The method is also compatible with other heteroaryls such as quinoline, isoquinolines, and benzo[*h*]quinoline and underwent a smooth reaction leading to products in excellent yields (**3x** 88 %, **3y** 89 %, **3z** 86 %, and **3aa** 82 %). Next, the generality of the established protocol was tested on pharmaceutically active cinchophen derivatives

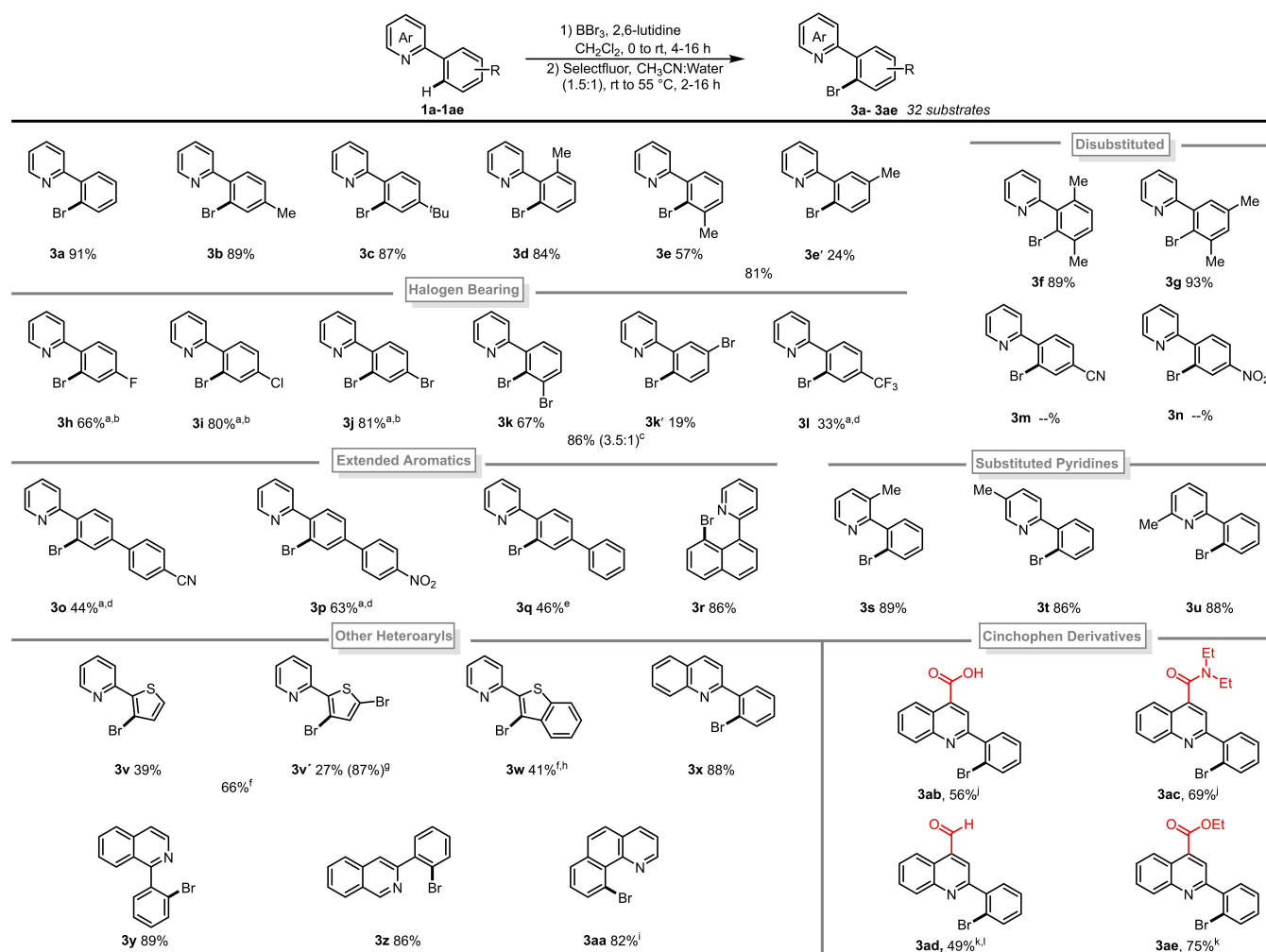
(Scheme 1). The results showed that the developed methodology could tolerate a series of functional groups such as acid, amide, aldehyde, and ester. The desired brominated products formed in 56 % (**3ab**, acid), 69 % (**3ac**, amide), 49 % (**3ad**, aldehyde), and 75 % (**3ae**, ester) yields, respectively (Scheme 1). The regioselective bromination of cinchophen showcases that the protocol can be used to engage pharmaceutically active N-heterocycles in skeleton diversification with for instance transition metal-based cross-couplings.

Next, we investigated transient arylimines as a substrate for our borylative halogenation. The transient imine serves as a masked form of an aldehyde consequently allowing for commercially available aromatic aldehydes to be used as substrates in the regioselective bromination.^[51] As it turns out the bromination works exceptionally well for a number of benzaldehyde derivatives exclusively providing the *ortho*-brominated aldehyde in excellent yields (Scheme 2, **6a–6e**).

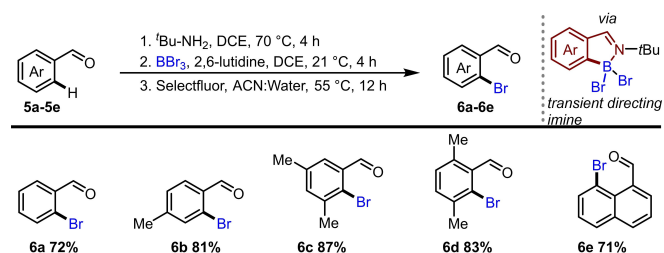
Seeking to gain mechanistic insight into the bromide to fluoride ion-exchange behavior and C–B bond cleavage, we conducted a few control experiments (Scheme 3). As it turns out, intermediate **4a** forms quantitatively already with 1 equiv. of Selectfluor suggesting that one fluorine comes from the F-NR₃⁺ in Selectfluor and one comes from BF₄[–] (Scheme 3A; Table 1, entry 1). This is corroborated by ¹¹B NMR which confirms that after the completion of the reaction both BF₃ and BF₄[–] are found in the reaction mixture (Scheme 3B and Supporting Information Section 4.2). After confirming the BF₃ species by ¹¹B NMR we investigated the role of water in the reaction mixture by subjecting **4a** to an aqueous reaction mixture. The results showed that boronic acid is not forming in the reaction leaving **4a** untouched (Scheme 3C). Next **4a** was subjected to bromine, however, the desired product was not observed which indicates that **4a** does not react with bromine which could potentially be generated in the reaction (Scheme 3D). To shed light on whether the reaction goes via a radical or cationic Br species we exposed **4a** to a preformed solution of Br^{+[13]} and could isolate **3a** in 96 % yield (Scheme 3E). Thus, confirming that the *ipso*-substitution occurs with cationic bromine.

To rationalize the observed reactivity, we propose a mechanism that starts with the formation of complex **A**.^[51] The highly electrophilic boron species **A** reacts with **1a** to form **B** via a regio-selective electrophilic aromatic substitution at the *ortho* position generating boracycle **B**. Boracycle **B** is converted to dibromoborane complex **2a** upon base promoted aromatization of intermediate **B**. Next, based on the control experiment's result, we propose that Selectfluor mediates a ligand exchange to generate **4a** (Scheme 3A) and the cationic^[119,13] bromide species (Scheme 3E) via **C**. Next, the *ipso* C–B carbon of **4a** reacts with the cationic bromide species to generate intermediate **D** that fragments to form **3a** and a BF₂X species (Scheme 4).

To confirm the scalability of the protocol, a scaled-up reaction of **2a** was carried out, and the corresponding brominated product **3a** was exclusively isolated in 88 % yield (Scheme 5a). This experiment reveals the synthetic utility of the present protocol and thus the method could be easily adapted for large-scale synthesis with high efficiency. Compound **4a** is



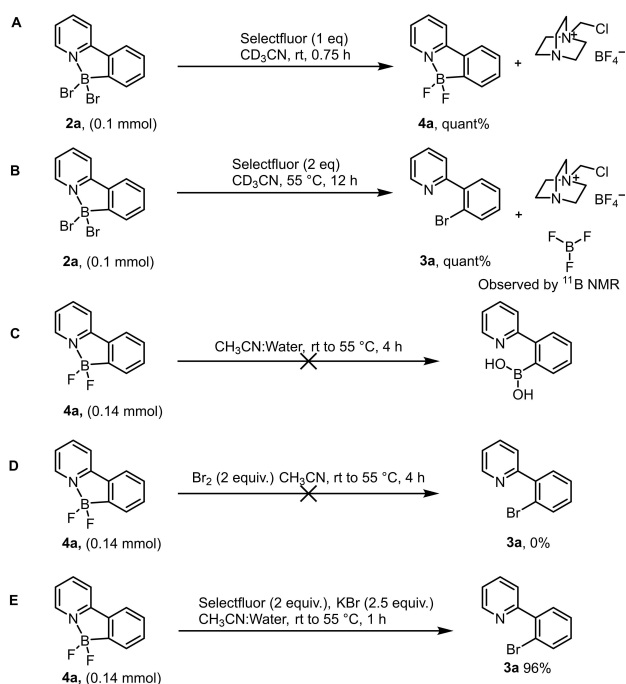
Scheme 1. Reaction conditions: i) **1a** (0.26 mmol), BBr₃ (0.52 mmol), 2,6-lutidine (0.52 mmol), CH₂Cl₂, 0 °C to rt 4 h; ii) Selectfluor (0.52 mmol), in 1.5 mL CH₃CN and 1 mL water, rt to 55 °C, 4 h; [a] 3 equiv. of BBr₃ and 3.5 equiv. of Selectfluor were used. [b] first step 6 h, second step 6 h. [c] 3 equiv. of BBr₃ and 3 equiv. of Selectfluor were used. [d] first step 16 h, second step 8 h. [e] 2 equiv. of BBr₃ and 1 equiv. of Selectfluor were used, first step 20 h, second step 16 h. [f] 2 equiv. of BBr₃ and 1 equiv. of Selectfluor were used, first step 3 h. [g] 2.5 equiv. of Selectfluor in 2 mL CH₃CN and 0.5 mL water, rt to 55 °C, 2 h. [h] second step 2 h. [i] First step 16 h. Functional group tolerance on pharmaceutically active cinchophen derivatives (**3ab**–**3ae**): Reaction conditions: [j] For acid- **2ab** (0.2 mmol), BBr₃ (0.8 mmol), 2,6-lutidine (0.5 mmol), CH₂Cl₂, 0 °C to rt 6 h; ii) Selectfluor (0.8 mmol), in 1.5 mL CH₃CN and 0.5 mL water, rt to 55 °C, 16 h; [j] For amide- **2ac** (0.2 mmol), BBr₃ (0.8 mmol), 2,6-lutidine (0.6 mmol), CH₂Cl₂, 0 °C to rt 16 h; ii) Selectfluor (0.8 mmol), in 1.5 mL CH₃CN and 1 mL water, rt to 55 °C, 8 h; [k] For aldehyde and ester- **2ad/2ae** (0.2 mmol), BBr₃ (0.6 mmol), 2,6-lutidine (0.6 mmol), CH₂Cl₂, 0 °C to rt 16 h; ii) Selectfluor (0.8 mmol), in 1.5 mL CH₃CN and 1 mL water, rt to 55 °C, 7 h. [l] Second step: 4 h.



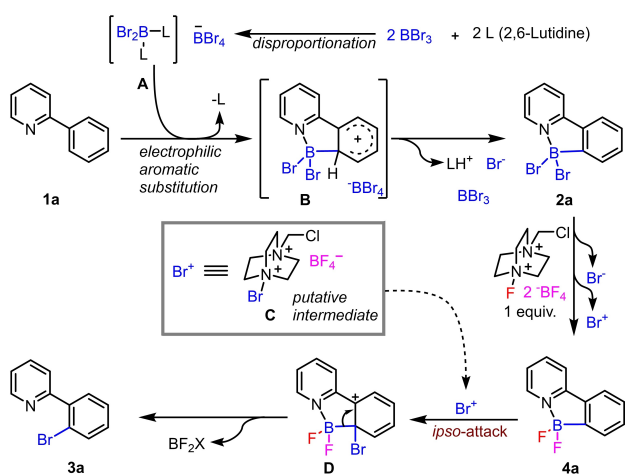
Scheme 2. Reaction conditions: step i) **5a** (0.26 mmol), 'Bu-NH₂ (1.04 mmol) in 0.5 mL DCE, 70 °C, 4 h; step ii) BBr₃ (0.65 mmol), 2,6-lutidine (0.65 mmol), DCE, 21 °C, 4 h; step iii) Selectfluor (0.65 mmol), in 1.5 mL CH₃CN and 1 mL water, 55 °C, 12 h.

also easily prepared on a gram scale with a very short reaction time (0.75 h) and swift purification by filtration only (Scheme 5b). Notably, this is the first straightforward, mild, and simple protocol to synthesize aryl-difluoroborane compounds.

Due to the very ease of preparing **4a**, we next examined its reactivity. We found that **4a** could be successfully functionalized in a multitude of reactions (Scheme 6). For example, difluoroborane **4a** is compatible with metal-free halogenations delivering chloro-, bromo-, and iodo- compounds, **7a**, **3a**, and **7b** in excellent yields. Treating **4a** with oxone delivered the hydroxylated congener **7c** in 87% yield^[5d] and copper-catalyzed amination of **4a** gave the corresponding amine **7d** in 76% yield.^[2d]



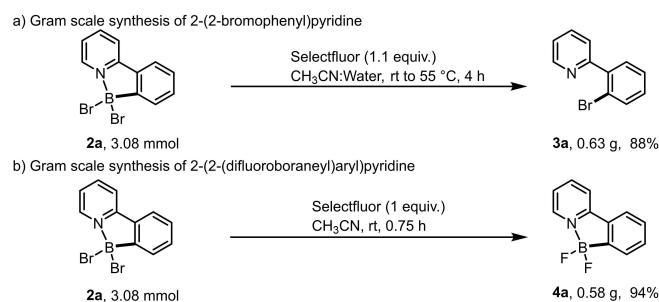
Scheme 3. Control experiments: Condition A: **2a** (0.1 mmol), Selectfluor (0.1 mmol), in 0.5 mL CD_3CN , rt, 0.75 h; Condition B: **2a** (0.1 mmol), Selectfluor (0.2 mmol), in 0.5 mL CD_3CN , rt to 55 °C, 12 h; Condition C: **4a** (0.14 mmol), in 0.5 mL CH_3CN and 0.5 mL Water, rt to 55 °C, 4 h; Condition D: **4a** (0.14 mmol), Br_2 (0.28 mmol) in 1 mL CH_3CN , rt to 55 °C, 4 h; Condition E: **4a** (0.14 mmol), Selectfluor (0.28 mmol), KBr (0.35 mmol), in 0.5 mL CH_3CN and 0.5 mL water, rt to 55 °C, 1 h.



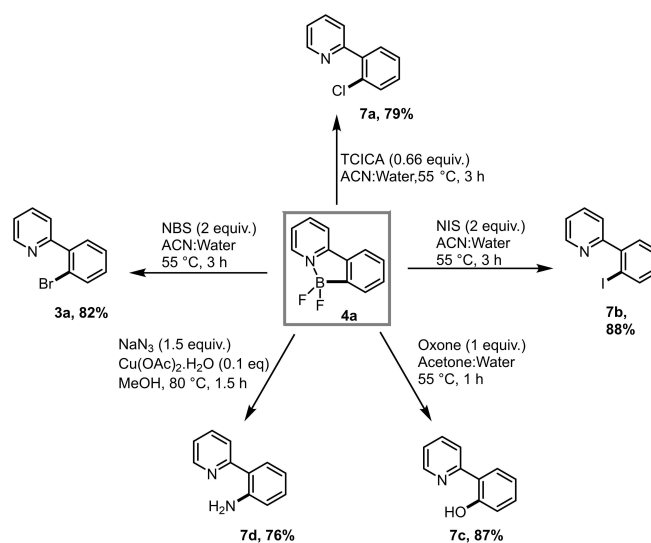
Scheme 4. Proposed mechanism.

Conclusion

In summary, we have demonstrated a regioselective, efficient, and practical BBR_3 mediated functionalization of 2-aryl-heteroarenes via an aryl BF_2 complex. A wide range of 2-aryl-*N*-heteroaryl substrates can be involved in the system under operationally facile conditions. Mechanistic studies showed that the reaction proceeds via a fluoride to bromide ligand exchange on the boracycle boron and subsequent cleavage of



Scheme 5. Gram scale experiments. Reaction conditions (a): i) **2a** (3.08 mmol), Selectfluor (3.38 mmol), in 20 mL CH_3CN and 10 mL water, rt to 55 °C, 4 h; Reaction conditions (b): **2a** (3.08 mmol), Selectfluor (3.08 mmol), in 20 mL dry CH_3CN , rt 0.75 h.



Scheme 6. Functionalization of 2-(2-(difluoroboraneyl)aryl)pyridine (**4a**): Reaction conditions (**3a**, **7a**, **7b**): i) **4a** (0.2 mmol), N-X (0.4 mmol), in 1 mL CH_3CN and 0.5 mL water, rt to 55 °C, 3 h; Reaction conditions (**7c**): **4a** (0.2 mmol), oxone (0.2 mmol), in 0.5 mL acetone and 0.5 mL water, rt to 55 °C, 1 h; Reaction conditions (**7d**): **4a** (0.2 mmol), NaN_3 (0.3 mmol), $\text{Cu}(\text{OAc})_2\cdot\text{H}_2\text{O}$ (0.02 mmol), in 1 mL MeOH, rt to 80 °C, 1.5 h.

the C–B bond with cationic bromine. The developed procedure is an attractive alternative to the state-of-the-art methods as it effectively mediates the regioselective introduction of halogens to a range of 2-aryl-heteroarenes and aldehydes which can, in turn, be utilized for installing a range of functional groups with modern cross-coupling techniques. As a result of our studies, we have also developed a synthesis of a scalable, bench stable difluoroboraneyl compound that can be used as a generic building block for regioselective functionalization of *N*-heterocycles. Further regioselective *ipso*-halogenations on various organic substrates are currently being investigated in our laboratory.

Experimental Section

General procedure for the bromination of N-heterocycles: To a dry 5 mL, screw-top V-Vial, equipped with a rubber septum, stir bar, under nitrogen atmosphere, the pyridine derivative (0.26 mmol, 1 equiv.), 2,6-lutidine (0.52 mmol, 2 equiv.), and anhydrous CH_2Cl_2 (0.5 mL) were added and the vial was placed in an ice bath. To this cool solution, BBr_3 (0.52 mmol, 2 equiv., 1 M solution in CH_2Cl_2), was added dropwise. After the complete addition of BBr_3 , the reaction mixture was stirred at room temperature until all starting material was consumed (as indicated by TLC analysis). The solvent was evaporated under reduced pressure. The solid containing the dibromoboron complex was dissolved in CH_3CN (1.5 mL) and water (1 mL). To this solution, Selectfluor (0.52 mmol, 2 equiv.) was added at room temperature, and the reaction mixture was heated at 55 °C until the dibromoboron complex was consumed. The reaction was quenched with sat. K_2CO_3 solution at room temperature and the crude mixture was purified by automated column chromatography on silica gel using pentane/EtOAc as the eluent to give the *ortho* halogenated product.

General procedure for the bromination of aryl-aldehydes: To an oven dried 5 mL, screw-top V-Vial in a glovebox, was added, the benzaldehyde derivative (0.26 mmol, 1 equiv.), *tert*-butyl amine (1.04 mmol, 4 equiv.), and DCE (0.5 mL), and the vial was placed in a heating block at 70 °C for 4 h outside the glovebox. The mixture was transferred to a rotary evaporator under nitrogen atmosphere and the solvent and excess of *tert*-butyl amine were removed under vacuum (keeping the water bath at lower temperature roughly 30 °C to prevent the low boiling substrate from evaporating). Next, the vial was placed in a glovebox and 2,6-lutidine (0.65 mmol, 2.5 equiv.) and DCE (0.5 mL) were added to the vial followed by the addition of BBr_3 (0.65 mmol, 2.5 equiv.; 1 M solution in CH_2Cl_2) that was added dropwise to the reaction mixture while stirring and the reaction vigorously at 21 °C for 4 h. After 4 h. the solvent was evaporated. To the vial was now added a solution of Selectfluor (0.65 mmol, 2.5 equiv.) in 1.5 mL CH_3CN and 1 mL distilled water, and the residual mixture was stirred at 55 °C for 12 h. The crude mixture was purified by automated column chromatography on silica gel (eluent: pentane/ CH_2Cl_2 , 100% pentane to 9:1) to give the *ortho*-bromo benzaldehyde derivative.

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Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Keywords: aryl-aldehydes • BBr_3 • N-heterocycles • *ortho* C–H halogenation • regioselective • Selectfluor

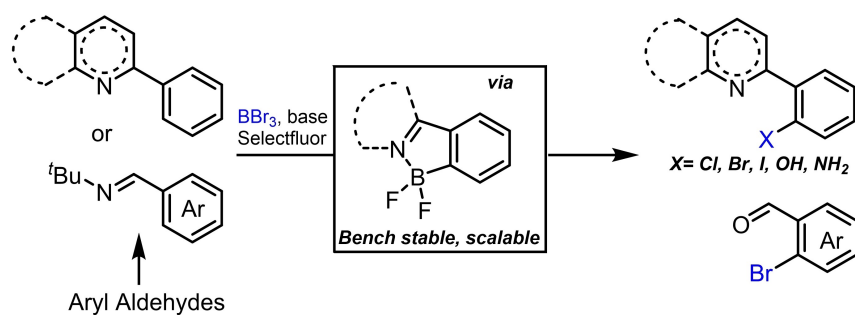
- [1] a) R. Rossi, M. Lessi, C. Manzini, G. Marianetti, F. Bellina, *Synthesis*. **2016**, 48, 3821–3862; b) T. Gensch, M. N. Hopkinson, F. Glorius, J. Wencel-Delord, *Chem. Soc. Rev.* **2016**, 45, 2900–2936; c) C. Sambaglio, D. Schönbauer, R. Blicke, T. Dao-Huy, G. Pototschnig, P. Schaaf, T. Wiesinger, M. F. Zia, J. Wencel-Delord, T. Besset, B. U. W. Maes, M. Schnürch, *Chem. Soc. Rev.* **2018**, 47, 6603–6743; d) P. Gandeepan, T. Müller, D. Zell, G. Cera, S. Warratz, L. Ackermann, *Chem. Rev.* **2019**, 119, 2192–2452; e) S. Rej, A. Das, N. Chatani, *Coord. Chem. Rev.* **2021**, 431, 213683.
- [2] Selected articles: a) D. Kalyani, A. R. Dick, W. Q. Anani, M. S. Sanford, *Org. Lett.* **2006**, 8, 2523–2526; b) X. Chen, X. S. Hao, C. E. Goodhue, J. Q. Yu, *J. Am. Chem. Soc.* **2006**, 128, 6790–6791; c) F. Kakiuchi, T. Kochi, H. Mutsutani, N. Kobayashi, S. Urano, M. Sato, S. Nishiyama, T. Tanabe, *J. Am. Chem. Soc.* **2009**, 131, 11310–11311; d) L. Niu, H. Yang, D. Yang, H. Fu, *Adv. Synth. Catal.* **2012**, 354, 2211–2217; e) S. Mo, Y. Zhu, Z. Shen, *Org. Biomol. Chem.* **2013**, 11, 2756–2760; f) Z. J. Du, L. X. Gao, Y. J. Lin, F. S. Han, *ChemCatChem* **2014**, 6, 123–126; g) P. Zhang, L. Hong, G. Li, R. Wang, *Adv. Synth. Catal.* **2015**, 357, 345–349; h) G. Zhang, S. Sun, F. Yang, Q. Zhang, J. Kang, Y. Wu, Y. Wu, *Adv. Synth. Catal.* **2015**, 357, 443–450; i) V. Pascanu, F. Carson, M. V. Solano, J. Su, X. Zou, M. J. Johansson, B. Martin-Matute, *Chem. Eur. J.* **2016**, 22, 3729–3737; j) P. C. Perumgani, S. P. Parvathaneni, G. V. Surendra Babu, K. Srinivas, M. R. Mandapati, *Catal. Lett.* **2018**, 148, 1067–1072; k) S. P. Parvathaneni, P. C. Perumgani, *Asian J. Org. Chem.* **2018**, 7, 324–327; l) Z. Zhu, C. Xu, Y. Wang, L. Zhao, *Synlett* **2018**, 29, 1122–1124; m) V. Botla, A. Akudari, C. Malapake, *Tetrahedron Lett.* **2019**, 60, 115–119; n) M. H. Majeed, P. Shayeesteh, P. Tunã, A. R. Persson, R. Gritcenko, L. R. Wallenberg, L. Ye, C. Hultberg, J. Schnadt, O. F. Wendt, *Chem. Eur. J.* **2019**, 25, 13591–13597; o) D. Meng, J. Bi, Y. Dong, B. Hao, K. Qin, T. Li, D. Zhu, *Chem. Commun.* **2020**, 56, 2889–2892; p) Y. Yuan, Y. Liang, S. Shi, Y. F. Liang, N. Jiao, *Chin. J. Chem.* **2020**, 38, 1245–1251.
- [3] For review: S. Mal, M. Jana, S. Sarkar, *ChemistrySelect* **2021**, 6, 11299–11330.
- [4] a) L. Kumar, T. Mahajan, D. D. Agarwal, *Green Chem.* **2011**, 13, 2187–2196; b) M. Naresh, M. Arun Kumar, M. Mahender Reddy, P. Swamy, J. B. Nanubolu, N. Narender, *Synthesis* **2013**, 45, 1497–1504; c) H. Veisi, A. Sedrpoushan, P. Mohammadi, A. R. Faraji, S. Sajjadifar, *RSC Adv.* **2014**, 4, 25898–25903; d) D. Liang, X. Li, C. Wang, Q. Dong, B. Wang, H. Wang, *Tetrahedron Lett.* **2016**, 57, 5390–5394; e) H. Kajita, A. Togni, *ChemistrySelect* **2017**, 2, 1117–1121; f) L. Li, Y. Li, Z. Zhao, H. Luo, Y. N. Ma, *Org. Lett.* **2019**, 21, 5995–5999; g) D. R. Motati, D. Uredi, A. G. Burra, J. P. Bowen, F. R. Fronczek, C. R. Smith, E. B. Watkins, *Org. Chem. Front.* **2020**, 7, 1095–1106.
- [5] a) L. Niu, H. Yang, R. Wang, H. Fu, *Org. Lett.* **2012**, 14, 2618–2621; b) S. A. Iqbal, J. Cid, R. J. Procter, M. Uzelac, K. Yuan, M. J. Ingleson, *Angew. Chem. Int. Ed.* **2019**, 58, 15381–15385; *Angew. Chem.* **2019**, 131, 15525–15529; c) J. Lv, X. Chen, X. S. Xue, B. Zhao, Y. Liang, M. Wang, L. Jin, Y. Yuan, Y. Han, Y. Zhao, Y. Lu, J. Zhao, W. Y. Sun, K. N. Houk, Z. Shi, *Nature* **2019**, 575, 336–340; d) J. Lv, B. Zhao, Y. Yuan, Y. Han, Z. Shi, *Nat. Commun.* **2020**, 11, 1316; e) G. Wu, X. Fu, Y. Wang, K. Deng, L. Zhang, T. Ma, Y. Ji, *Org. Lett.* **2020**, 22, 7003–7007; f) G. Wu, B. Pang, Y. Wang, L. Yan, L. Chen, T. Ma, Y. Ji, *J. Org. Chem.* **2021**, 86, 5933–5942; g) S. Li, C. Hu, X. Cui, J. Zhang, L. L. Liu, L. Wu, *Angew. Chem. Int. Ed.* **2021**, 60, 26238–26245; *Angew. Chem.* **2021**, 133, 26442–26449; h) Z. J. Wang, X. Chen, L. Wu, J. J. Wong, Y. Liang, Y. Zhao, K. N. Houk, Z. Shi, *Angew. Chem. Int. Ed.* **2021**, 60, 8500–8504; *Angew. Chem.* **2021**, 133, 8581–8585; i) S. Rej, N. Chatani, *J. Am. Chem. Soc.* **2021**, 143, 2920–2929; j) S. Rej, A. Das, N. Chatani, *Chem. Sci.* **2021**, 12, 11447–11454; k) J. Lv, X.-J. Zhang, M. Wang, Y. Zhao, Z. Shi, *Chem. Eur. J.* **2022**, 28, e202104100; l) O. Sadek, A. L. Gac, N. Hidalgo, S. Mallet-Ladeira, K. Miqueu, G. Bouhadir, D. Bourissou, *Angew. Chem. Int. Ed.* **2022**, 61, e202110102; *Angew. Chem.* **2022**, 134, e202110102; m) G. Wu, Z. Yang, X. Xu, L. Hao, L. Chen, Y. Wang, Y. Ji, *Org. Lett.* **2022**, 24, 3570–3575; n) X. Xu, G. Wu, Z. Yang, X. Liu, L. Hao, Y. Wang, Z. Ma, Y. Ji, *Org. Lett.* **2022**, 24, 7163–7167; o) For review: 1) S. Rej, N. Chatani, *Angew. Chem. Int. Ed.* **2022**, 61, e202209539; *Angew. Chem.* **2022**, 134, e202209539.
- [6] a) A. C. Shaikh, D. S. Ranade, S. Thorat, A. Maity, P. P. Kulkarni, R. G. Gonnade, P. Munshi, N. T. Patil, *Chem. Commun.* **2015**, 51, 16115–16118; b) D. L. Crossley, I. A. Cade, E. R. Clark, A. Escande, M. J. Humphries, S. M. King, I. Vitorica-Yrezabal, M. J. Ingleson, M. L. Turner, *Chem. Sci.* **2015**, 6, 5144–5151; c) D. L. Crossley, I. Vitorica-Yrezabal, M. J. Humphries, M. L. Turner, M. J. Ingleson, *Chem. Eur. J.* **2016**, 22, 12439–12448; d) M. Yusuf, K. Liu, F. Guo, R. A. Lalancette, F. Jäkle, *Dalton Trans.* **2016**, 45, 4580–4587; e) D. L. Crossley, L. Urbano, R. Neumann, S. Bourke, J. Jones, L. A. Dailey, M. Green, M. J. Humphries, S. M. King, M. L. Turner, M. J. Ingleson,

- ACS Appl. Mater. Interfaces **2017**, *9*, 28243–28249; f) K. Liu, R. A. Lalancette, F. Jäkle, *J. Am. Chem. Soc.* **2017**, *139*, 18170–18173; g) B. P. Dash, I. Hamilton, D. J. Tate, D. L. Crossley, J. S. Kim, M. J. Ingleson, M. L. Turner, *J. Mater. Chem. C* **2019**, *7*, 718–724; h) M. Shigeno, M. Imamatsu, Y. Kai, M. Kiriya, S. Ishida, K. Nozawa-Kumada, Y. Kondo, *Org. Lett.* **2021**, *23*, 8023–8027; i) L. Jiang, Y. Wang, D. Tan, X. Chen, T. Ma, B. Zhang, D. Yang, *Chem. Sci.* **2022**, *13*, 5597–5605; j) S. Oda, B. Kawakami, Y. Yamasaki, R. Matsumoto, M. Yoshioka, D. Fukushima, S. Nakatsuka, T. Hatakeyama, *J. Am. Chem. Soc.* **2022**, *144*, 106–112; k) K. Yuan, D. Volland, S. Kirschner, M. Uzelac, G. S. Nichol, A. Nowak-Król, M. J. Ingleson, *Chem. Sci.* **2022**, *13*, 1136–1145.
- [7] a) N. Ishida, T. Moriya, T. Goya, M. Murakami, *J. Org. Chem.* **2010**, *75*, 8709–8712S; b) M. Kondrashov, D. Provost, O. F. Wendt, *Dalton Trans.* **2016**, *45*, 525–531; c) A. Iqbal, K. Yuan, J. Cid, J. Pahl, M. J. Ingleson, *Org. Biomol. Chem.* **2021**, *19*, 2949–2958.
- [8] a) P. T. Nyffeler, S. G. Durón, M. D. Burkart, S. P. Vincent, C. H. Wong, *Angew. Chem. Int. Ed.* **2005**, *44*, 192–212; *Angew. Chem.* **2005**, *117*, 196–217; b) B. Lantaño, A. Postigo, *Org. Biomol. Chem.* **2017**, *15*, 9954–9973; c) F. J. Aguilar Troyano, K. Merken, A. Gómez-Suárez, *Asian J. Org. Chem.* **2020**, *9*, 992–1007.
- [9] a) S. Nerkar, D. P. Curran, *Org. Lett.* **2015**, *17*, 3394–3397; b) B. Huang, Y. Zhao, C. Yang, Y. Gao, W. Xia, *Org. Lett.* **2017**, *19*, 3799–3802.
- [10] a) M. Kamlar, A. Runemark, I. Cisařová, H. Sundén, *Org. Lett.* **2020**, *22*, 8387–8391; b) M. Kamlar, E. Henriksson, I. Cisařová, M. Malo, H. Sundén, *J. Org. Chem.* **2021**, *86*, 8660–8671.
- [11] a) H. G. Kuivila, E. K. Easterbrook, *J. Am. Chem. Soc.* **1951**, *73*, 4629–4632; b) H. C. Brown, R. Norman, D. Lue, G. W. Kabalka, H. C. Hedgecock, *J. Am. Chem. Soc.* **1976**, *98*, 1290–1291; c) H. C. Brown, C. F. Lane, *Tetrahedron* **1988**, *44*, 2763–2772; d) R. H. Szumigala, P. N. Devine, D. R. Gauthier, R. P. Volante, *J. Org. Chem.* **2004**, *69*, 566–569; e) C. Cazorla, E. Méta, B. Andrioletti, M. Lemaire, *Tetrahedron Lett.* **2009**, *50*, 3936–3938; f) M. L. Yao, M. S. Reddy, Y. Li, I. Walfish, D. W. Blevins, G. W. Kabalka, *Org. Lett.* **2010**, *12*, 700–703; g) G. A. Molander, L. N. Cavalcanti, *J. Org. Chem.* **2011**, *76*, 7195–7203; h) R. Larouche-Gauthier, T. G. Elford, V. K. Aggarwal, *J. Am. Chem. Soc.* **2011**, *133*, 16794–16797; i) M. L. Yao, G. W. Kabalka, D. W. Blevins, M. S. Reddy, L. Yong, *Tetrahedron* **2012**, *68*, 3738–3743; j) C. Sandford, R. Rasappan, V. K. Aggarwal, *J. Am. Chem. Soc.* **2015**, *137*, 10100–10103; k) R. J. Armstrong, C. Sandford, C. Garcia-Ruiz, V. K. Aggarwal, *Chem. Commun.* **2017**, *53*, 4922–4925; l) J. J. Molloy, K. M. O'Rourke, C. P. Frias, N. L. Sloan, M. J. West, S. L. Pimlott, A. Sutherland, A. J. B. Watson, *Org. Lett.* **2019**, *21*, 2488–2492.
- [12] For review: a) C. Zhu, J. R. Falck, *Adv. Synth. Catal.* **2014**, *356*, 2395–2410.
- [13] a) R. G. Syvret, K. M. Butt, T. P. Nguyen, V. L. Bullock, R. D. Rieth, *J. Org. Chem.* **2002**, *67*, 4487–4493; b) C. Ye, J. M. Shreeve, *J. Org. Chem.* **2004**, *69*, 8561–8563; c) S. Stavber, M. Zupan, *Acta Chim. Slov.* **2005**, *52*, 13–26; d) Z. Dağalan, R. Koçak, A. Daştan, B. Nişancı, *Org. Lett.* **2022**, 10.1021/acs.orglett.2c02627.

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Regioselective functionalization of 2-aryl-azaarenes *N*-heteroarenes and aryl aldehydes has been achieved. The reaction proceeds via a BBr_3 promoted 5 and 6-membered boracycle that undergoes a ligand

exchange promoted by Selectfluor to give a previously scarce aryl BF_2 species. The aryl BF_2 is a bench stable intermediate that can be used for the deborylative functionalization of the 2-aryl-azaarenes scaffold.

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Boron-Mediated Regioselective Aromatic C–H Functionalization via an Aryl BF_2 Complex

