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C–H activation |*Hot Paper*|

Metal-Free C–H Borylation of N-Heteroarenes by Boron Trifluoride

Vladimir Iashin,[a] Dénes Berta,[b] Konstantin Chernichenko,[a, c] Martin Nieger,[a] Karina Moslova,[a] Imre Pápai,*[b] and Timo Repo*[a]

Abstract: Organoboron compounds are essential reagents in modern C–C coupling reactions. Their synthesis via catalytic C–H borylation by main group elements is emerging as a powerful tool alternative to transition metal based catalysis. Herein, a straightforward metal-free synthesis of aryldifluoroboranes from BF_3 and heteroarenes is reported. The reaction is assisted by sterically hindered amines and catalytic amounts of thioureas. According to computational studies the reaction proceeds via frustrated Lewis pair (FLP) mechanism. The obtained aryldifluoroboranes are further stabilized against destructive protodeborylation by converting them to the corresponding air stable tetramethylammonium organotrifluoroborates.

Introduction

Efficient C–C and C–X couplings in contemporary organic synthesis including Suzuki–Miyaura coupling, Petasis reaction, Chan–Lam coupling etc., are performed by utilizing various organoboron compounds.[1] Consequently, a ready access to initial organoboron reagents is prerequisite in such cross-coupling strategies. Among various organoboron compounds, organotrifluoroborates are widely used due to their increased stability under air and, especially, against protodeboronation. Generally, they are synthesized from boronic acids or their esters via fluorination with KHF_2.[2] In turn, synthesis of organoboronic acids and organoboronates is widely studied including both transition metal[3] and main group catalysis.[4] However, direct synthesis of organotrifluoroborates by C–H borylation is still underdeveloped.

Borylation of C(sp^2)–H bonds was traditionally performed by transition metal catalysts[5] until it was recently shown that geometrically arranged *ansa*-aminoboranes,[6] usually used for hydrogen activation and reductions, are also capable of activating certain electron-rich heteroarenes.[7] After that, substrate scope was notably expanded[6c] and several reports were published concerning the structure–activity correlation of such *ansa*-systems.[8] Beside *ansa*-aminoboranes, it is also possible to activate C(sp^2)–H bonds by strong Lewis acids such as $B(C_6F_5)_3$[9] or BX_3 (X = Cl, Br).[4c, 10] Depending on the conditions, reactions proceed either by direct electrophilic attack of the boron halide[10e] or by in situ generated borenium cations derived from BCl_3,[4c, 10b,b, 11] BBr_3,[10a,d,e, 11] or catecholborane.[12] Regardless of the mechanisms, such borylation reactions with BF_3, the weakest among boron halides Lewis acid, has not been reported to the best of our knowledge.

Recently, we reported that combination of $BF_3{\cdot}SMe_2$ with 1,2,2,6,6-pentamethylpiperidine (PMP, **4a**) borylates terminal alkynes forming tri- and tetraalkynyl borates.[13] Such approach avoids usage of precious metals and utilizes one of inexpensive boron reagents along with the recoverable base. Also, we found that $BF_3{\cdot}SMe_2$ adduct is very labile and can serve as the convenient alternative to reactive gaseous BF_3. In continuation of our efforts, we focused on extending developed methodology to the borylation of more challenging C(sp^2)–H bonds.

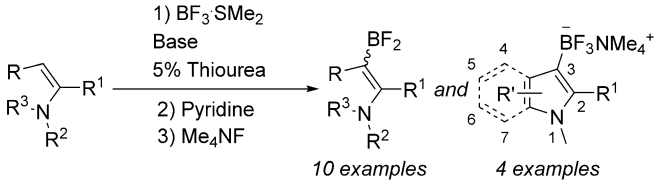
Herein, we present the direct C–H borylation of electron rich N-heterocycles such as indoles, pyrroles, and indolenines by $BF_3{\cdot}SMe_2$. These reactions are assisted by sterically hindered amines and promoted by catalytic amounts of various thioureas (Scheme 1). Borylation products, aryldifluoroboranes, are converted to organotrifluoroborates via complexation with pyridine and further fluorination by tetramethylammonium fluoride. Such procedure overcomes the problem of unwanted protodeboronation of organofluoroboranes and makes them practical starting materials for the C–C coupling reactions.

[a] *V. Iashin, K. Chernichenko, M. Nieger, K. Moslova, T. Repo*
Department of Chemistry, University of Helsinki
A. I. Virtasen aukio, 1 00014 Helsinki (Finland)
E-mail: timo.repo@helsinki.fi

[b] *D. Berta, I. Pápai*
Institute of Organic Chemistry, Research Centre for Natural Sciences
Magyar tudósok körútja 2, 1117 Budapest (Hungary)
E-mail: papai.imre@ttk.mta.hu

[c] *K. Chernichenko*
Present address: API Small Molecule Development
Janssen Pharmaceutica N.V., Turnhoutseweg 30, 2340 Beerse (Belgium)

Supporting information, including the Computational Methods and Experimental Section, as well as the ORCID identification number(s) for the author(s) of this article can be found under: https://doi.org/10.1002/chem.202001436.



Scheme 1. General pattern of N-heteroarenes borylation by boron trifluoride.

Results and Discussion

In our previous studies we showed that BF_3 together with sterically hindered base, **4a**, can borylate phenylacetylene quantitatively within 15 minutes.[13] The BF_3·SMe_2/**4a** pair was also proven efficient, yet full conversions were reached after 2 hours. When these Lewis pairs were applied to our model substrate, *N*-methylindole **1a**, we achieved 62–65% in situ yields of aryldifluoroborane **2a** and minor amounts of bis(indolyl) product **3a** (Scheme 2). Because of possibility of indole borylation to both 2nd and 3rd positions, regioselectivity of borylation was confirmed by X-ray diffraction and 2D NMR spectra of the corresponding trifluoroborate (see Supporting Information for details).

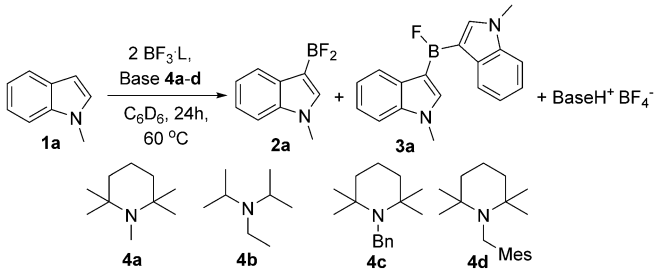
A mixture of BF_3·OEt_2 and PMP was shown to borylate terminal acetylenes to a remarkable degree,[13] whereas only traces of **2a** were observed with this reagent combination (entry 3). Addition of SMe_2 to the reaction mixture didn't enhance the reactivity of the BF_3·OEt_2/PMP system (entry 4). When the reaction temperature was raised to 120 °C, the in situ yield of **2a** raised to 30% (entry 5). According to the previous studies, a higher energetic penalty required for dissociation of BF_3·OEt_2 results in the poor reactivity of this adduct that sharply contrasts with labile and reactive BF_3·SMe_2 and BF_3·PMP (Table 1, column 4).[13]

We also explored the borylation of **1a** using other sterically hindered amines (Scheme 2, Table 1). Although **4a** is a sterically very demanding amine, it is capable of forming a weak Lewis adduct with BF_3 (Entry 1). When sterically less hindered and hence more strongly interacting with BF_3 *N*,*N*-diisopropylethylamine (DIPEA, **4b**) was applied in combination with BF_3·SMe_2, the yield of **2a** reached only 22% (entry 6). Moreover, when all the BF_3 in the solution was in the form of adduct with **4b**, not even traces of borylation products were found (entry 7). Sterically more hindered than **4a** bases **4c** and **4d** did not form stable adducts even with gaseous BF_3 (entries 8–9). However, borylation with **4c**–**d** was less effective as compared to **4a**, yet all the bases **4a**–**d** have similar Brønsted basicities. We hypothesized that **4c** and **4d** had stronger steric repulsive component in the borylation transitions states (vide infra) that conveyed into higher kinetic barriers in comparison to **4a**.

Table 1. In situ yields of the borylation product **2a** produced in the reactions of **1a**, BF_3·L, and sterically hindered amines **4a**–**d**[a]

Entry	Base	L	Strength of amine-BF_3 adduct, kcal mol^{-1}[b]	**1a**, %	**2a**, %[c,d]
1	**4a**	SMe_2	−1.9	28	62
2	**4a**	**4a**	−1.9	20	65
3	**4a**	OEt_2	−1.9	94	5
4[e]	**4a**	OEt_2	−1.9	83	3
5[f]	**4a**	OEt_2	−1.9	40	30
6	**4b**	SMe_2	−7.8	55	22
7	**4b**	**4b**	−7.8	100	0
8	**4c**	SMe_2	–[g]	55	35
9	**4d**	SMe_2	–[g]	43	47

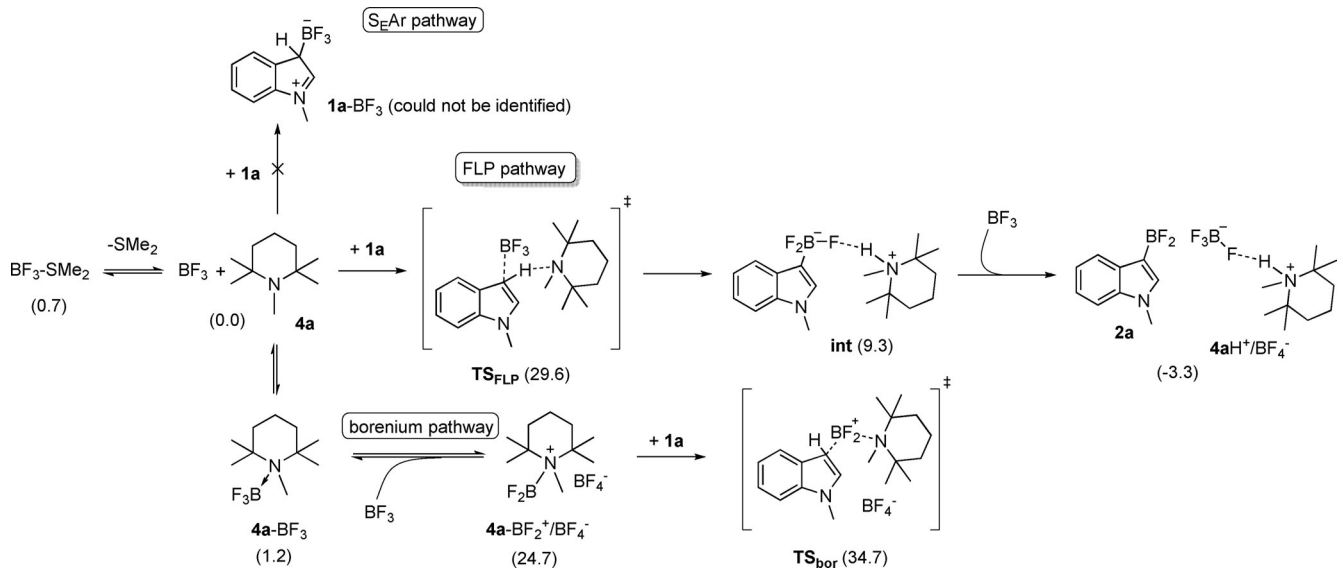
[a] Reactions were performed in the gas-tight NMR tubes for 24 h at 60 °C in the argon atmosphere; Yields were determined by the ^{1}H NMR spectroscopy against 1-bromo-3,5-difluorobenzene as the internal standard. [b] Defined as ΔG of amine + BF_3 → amine-BF_3 as obtained from ref. [13]. [c] Characteristic signal of **2a** in ^{11}B and ^{19}F NMR spectra was observed at +24 ppm and −94 ppm, respectively. [d] In addition to **1a** and **2a**, some amount of unidentified product with indole pattern was observed in ^{1}H NMR spectra (see Supporting Information for details). [e] 1 equiv. of SMe_2 was added to the reaction. [f] Reaction temperature 120 °C. [g] No adduct with gaseous BF_3 was detected.



Scheme 2. *N*-Methylindole **1a** borylation with BF_3·L and sterically hindered amines **4a**–**d** gives 3-difluoroborane **2a** and minor amounts of **3a**.

To gain mechanistic insight, computational studies of the borylation reaction of **1a** with BF_3·SMe_2/PMP pair were carried out. The mechanistic scenarios depicted in Scheme 3 were investigated via Density Functional Theory (DFT) calculations.[14] Despite the high nucleophilicity of indole, the **1a**-BF_3 adduct could not be identified computationally.[15] Therefore, the electrophilic substitution (S_EAr) pathway can be readily excluded as a viable mechanism. For the borenium mediated pathway, the formation of the borenium/BF_4^- species (**4a**-BF_2^+/BF_4^- ion pair) is thermodynamically uphill, but the relatively high barrier (34.7 kcal mol^{-1}) represented by the subsequent BF_2^+ transfer transition state (**TS$_{bor}$**) renders this pathway unlikely as well.

Hence our attention turned towards the FLP-type C–H activation mechanism, which has been described previously for *ansa*-aminoboranes.[7–9] This mechanism assumes the cooperative action of Lewis acid/base centers, which was confirmed computationally (see Figures 1 and 2).[16] The reactants (**1a**, **4a** and BF_3) form a transient weakly bound complex (**4a**·**1a**·BF_3), from which the C–H activation takes place concertedly via **TS$_{FLP}$**. The obtained free energy barrier (29.6 kcal mol^{-1}) is consistent with the reaction rate measured at elevated temperature. The concerted C–H activation leads to intermediate **int**, which is stabilized by N–H···F hydrogen bonding interactions. This species can favorably interact with an additional BF_3 molecule, and the (**int**-BF_3) adduct can easily furnish the borylated product **2a** via a fluoride transfer (**TS$_{Ftrans}$**). The dissociation of



Scheme 3. Computationally examined mechanistic pathways of **1a** borylation by a PMP/BF_3 Lewis pair. Free energy data (in kcal mol^{-1}) given in parentheses are with respect to the **1a** + **4a** + BF_3 reactant state.

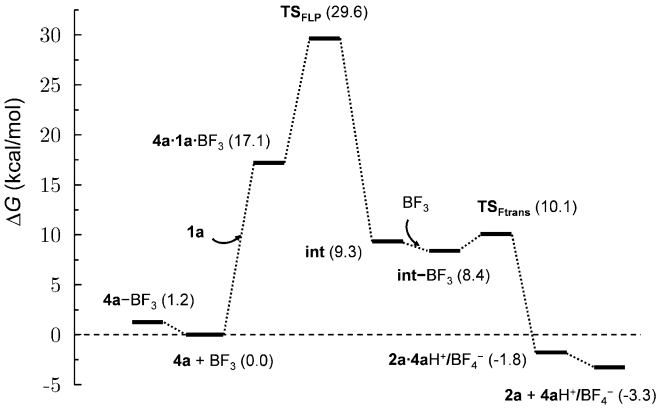


Figure 1. Free energy profile computed for the FLP-type C–H activation pathway for **1a** borylation by a PMP/BF_3 Lewis pair. Free energy data are given relative to the **1a** + **4a** + BF_3 reactant state.

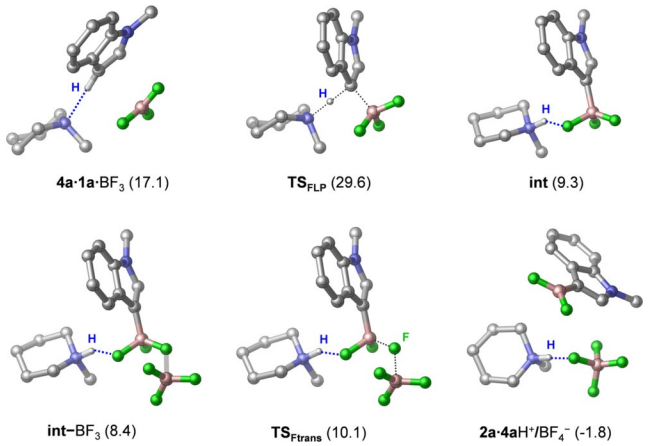


Figure 2. Structures of reaction intermediates and transition states identified computationally for the FLP-type C–H activation pathway for **1a** borylation by PMP·BF_3. H atoms (except that involved in the reaction) and the four methyl groups of PMP are omitted for clarity. Forming and breaking bonds are shown as black dotted lines in TS structures; H-bonds are highlighted by blue dotted lines. Free energy data are given relative to the **1a** + **4a** + BF_3 reactant state (in kcal mol^{-1}).

the weakly bound **2a·4a**H^+/BF_4^- species yield a more stable product state (**2a** + **4a**H^+/BF_4^-).

We carried out kinetic studies of the **1a** borylation in the presence of varying amounts of BF_3·SMe_2 and **4a**. Analysis of initial rates revealed that the reaction is first order in **1a** and a positive order in BF_3·SMe_2. At the same time, addition of over-stoichiometric 0.5 equivalents of **4a** resulted in a pronounced inhibiting effect (Figure 3). This effect was attributed to the zero kinetic order of the reaction in **4a** along with the positive order in free BF_3. Additional **4a** decreased the concentration of BF_3 and hence the reaction rate. Notwithstanding this explanation contrasted with the computationally found endergonicity of **4a**-BF_3 dissociation (Figure 1) it was known from our previous work[13] that this Lewis adduct was better stabilized in a more polar solvent, DCM. In the present work, the free energies were computed for benzene that was used as a solvent for borylation reaction. However, this might not be a completely adequate description of the real reaction mixture provided the presence of polar reactants (Me_2S-BF_3, **4a**-BF_3) and products ([**4a**-H^+][BF_4^-]) in high concentrations.

The ultimate picture of the kinetic processes seemed rather complex: apparently **4a**-BF_3 is generated in situ upon mixing of the reagents that discharged some amount of free Me_2S. In addition to that, more Me_2S was generated during the borylation, suppressing dissociation of the starting BF_3 adducts. In order to derive the quantitative model of the observed kinetics a numerical simulation was carried out. Two most likely models were compared, one that followed the k[**1a**][BF_3] rate law (model A) and the model B with the k[**1a**][BF_3]^2 law. Both

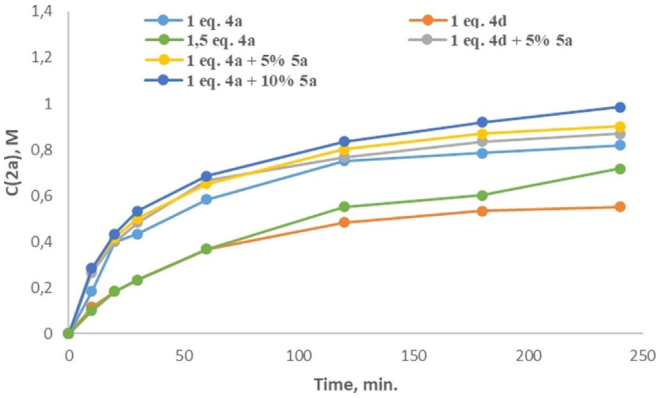
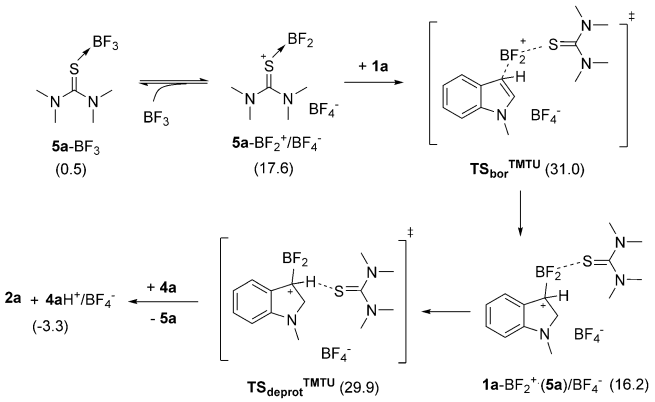


Figure 3. Kinetic profiles of **1a** borylation with BF_3·SMe_2, **4a**/**4d** and various amounts of **5a**.



Scheme 4. TMTU assisted borenium pathway examined computationally. Free energy data (in kcal mol^{-1}) given in parentheses are with respect to the **1a** + **5a** + BF_3 reactant state.

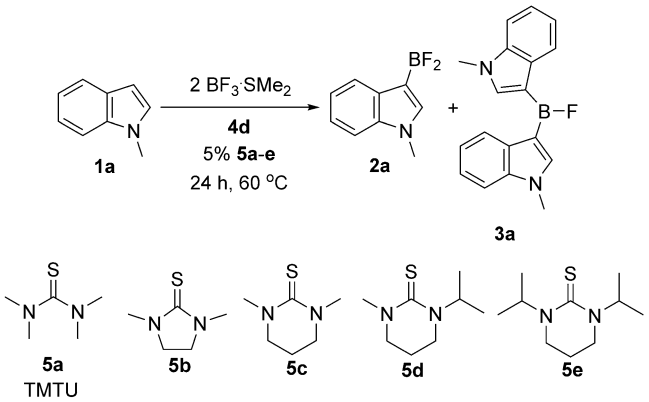
of them described high percentage of the total observed variability but statistically were quite comparable (see Supporting Information for details). We concluded that there is more than one mechanism in action including also the FLP mechanism that is expected to follow the *k*[**1a**][BF_3][PMP] kinetic law. Yet such a kinetic model alone would poorly agree with the collected kinetic data, it might in combination with the models A or B.

Although **4a** together with BF_3 gives the highest in situ yield in the borylation of **1a** among the bases **4a**–**d**, parallel decomposition of amine by Lewis acidic BF_3 is an unwanted side reaction.[13] This drawback can be overcome by using the most sterically hindered base **4d**, where formation of its BF_3 adduct is sterically unfavorable. However, borylation with **4d** proceeds much slower (Figure 3) and gives the lower yield of **2a** (Table 1). This inspired us to look for additives, which could promote the borylation reaction further. Considering that formation of borocations in benzene cannot be completely excluded (Scheme 3), we turned out attention to tetramethylthiourea (TMTU) that proved assisting the autoionization of BF_3.[17] Accordingly, we found that the addition of small (5 mol%) amounts TMTU (**5a**) to both BF_3·SMe_2/**4a** and BF_3·SMe_2/**4d** pairs increases the rate of **2a** formation (Figure 3). When stoichiometric amounts of **5a** were used in the absence of **4a** or **4d**, only **1a**, BF_3·**5a** adduct, some unidentified products but no traces of **2a** were detected by ^{1}H or ^{11}B NMR analysis.

Our computational analysis indicates that the formation of the borenium/BF_4^- species with TMTU (**5a**-BF_2^+/BF_4^- ion pair) as well the subsequent BF_2^+ transfer process is notably more favored as compared to the analogous borenium formation process with PMP (see Scheme 4).[18] The barrier computed for the formation of borenium **1a**-BF_2^+ is 31.0 kcal mol^{-1}, which is comparable to that of the FLP pathway with PMP (29.6 kcal mol^{-1}). Furthermore, the deprotonation of **1a**-BF_2^+ by TMTU takes place via a similar barrier (29.9 kcal mol^{-1}) and the proton is then delivered to the more basic PMP. Based on these results and considering the uncertainty in the computed barriers (a few kcal mol^{-1} at least), one possible explanation for the beneficial effect of TMTU is that it opens an alternative borylation pathway to the PMP assisted FLP mechanism. In this latter mechanism, TMTU acts as catalyst facilitating the formation and the deprotonation of the **1a**-BF_2^+ borenium intermediate. We have also explored the FLP pathway with TMTU acting as a base and we obtained a barrier of 31.7 kcal mol^{-1}, which is slightly higher than that of the TMTU promoted borenium pathway (31.0 kcal mol^{-1}), but still comparable to the most favored PMP assisted FLP pathway (29.6 kcal mol^{-1}). So an alternative explanation for the improved yields with TMTU is that it acts as a base in the FLP mechanism, which becomes important and beneficial at higher conversion rates, when most of the PMP is consumed.

To study the role of TMTU in more details, we introduced borylation of **1a** with other thioureas **5b**–**e** (Scheme 5). Among the series, cyclic thioureas **5b** and **5d** give the highest in situ yield of **2a**. Interestingly, in case of **5d** minor amounts of diarylfluoroborane **3a** were also found (Table 2).

We investigated the substrate scope of borylation with **5d**. In general, electron rich *N*-alkylindoles and -pyrroles were borylated with high to moderate yields (Scheme 6, examples **2a**–**d**). Moreover, *N*-allyl group remained untouched in the reaction conditions (entry **2e**). Incorporation of halogens atoms as electron withdrawing groups into the indole ring decreases

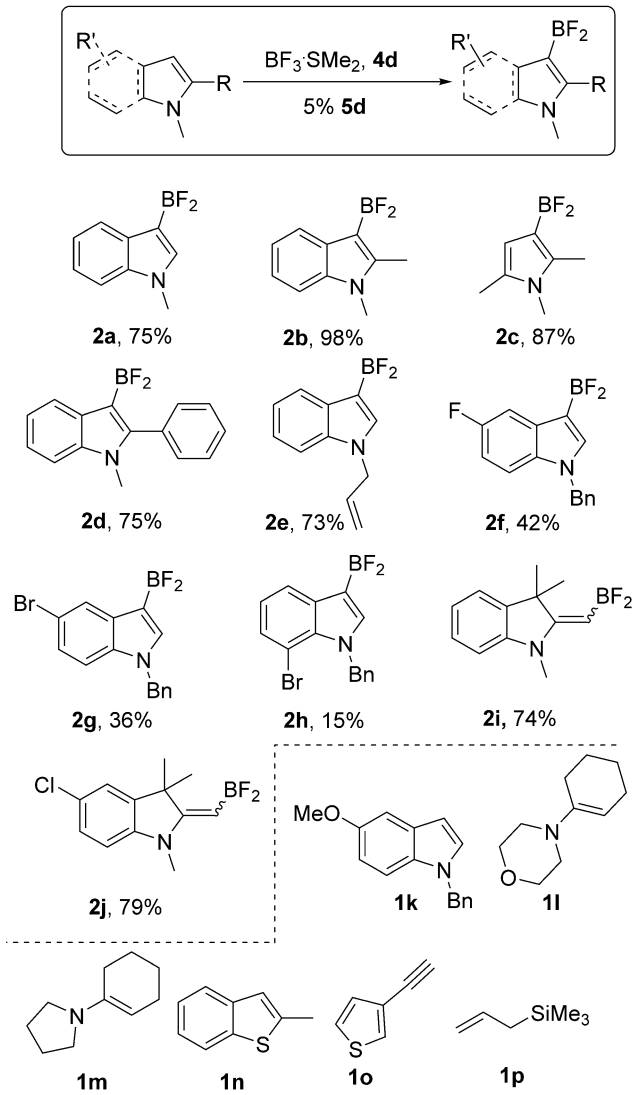


Scheme 5. Screening of various thioureas as catalysts for borylation of **1a**.

Table 2. In situ yields of products from the borylation of **1a** in the presence of thioureas **5a**–**5e**.[a]

Thiourea	1a	2a	3a
–	43	47	–
5a[b]	30	69	–
5b[b]	22	77	–
5c[b]	34	65	–
5d[b]	19	79	2
5e[b]	32	68	–

[a] Reactions were performed in the gas-tight NMR tubes for 24 h at 60 °C in the argon atmosphere; Yields were determined by the ^{1}H NMR spectroscopy against 1-bromo-3,5-difluorobenzene as the internal standard; see the Supporting Information for details; [b] 5 mol% of thiourea **5a**–**e** was used.

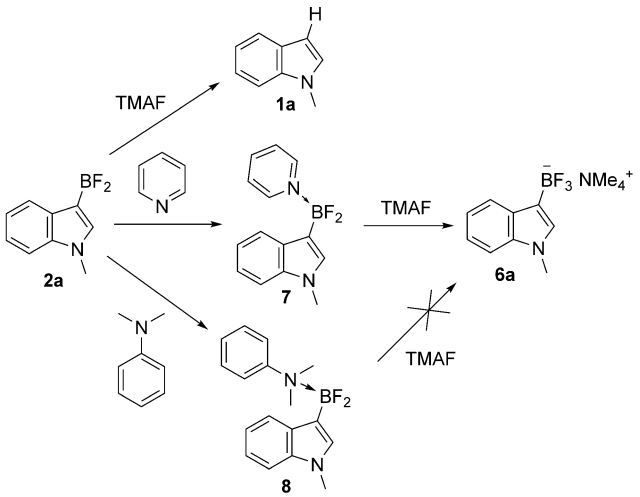


Scheme 6. Substrate scope of the reaction and NMR yields of the N-heteroarenes borylation products.

the conversion (examples **2f**–**h**). Interestingly, terminal double bond in indolenine ring (entry **2i,j**) can also be borylated with a high yield. In general, electron-rich alkyl- and halosubstituted N-heteroarenes we found to be the best substrates in the developed reaction conditions. Attempted borylation of other substrates was less successful: 5-Methoxy substituted indole **1k** produced complex mixture with no trace of borylation product. Set of signals around +15 ppm in the ^{11}B NMR spectrum indicated possible ether cleavage. Attempt to use conventional enamines **1l**–**m** led only to their BF_3 adducts whereas 2-methylbenzothiophene (**1n**) remained completely intact. Interestingly, 3-ethynylthiophene **1o** gave a complex product mixture, however, characteristic for hetarene-BF_2 peaks at 22.95 ppm (^{11}B NMR) and −84.96 (^{19}F NMR) were detected. Importantly, no evidence of terminal alkyne CH bond activation was found even though this substrate is known to form trialkynylborane SMe_2 adduct upon treatment with BF_3·SMe_2/**4a** system.[19] Allyltrimethylsilane **1p** gave traces of borylation products according to ^{11}B and ^{19}F spectra. At the same time, the characteristic peak for trimethylsilylfluoride multiplet found in the ^{19}F NMR spectrum at −157 ppm indicated TMS group cleavage.

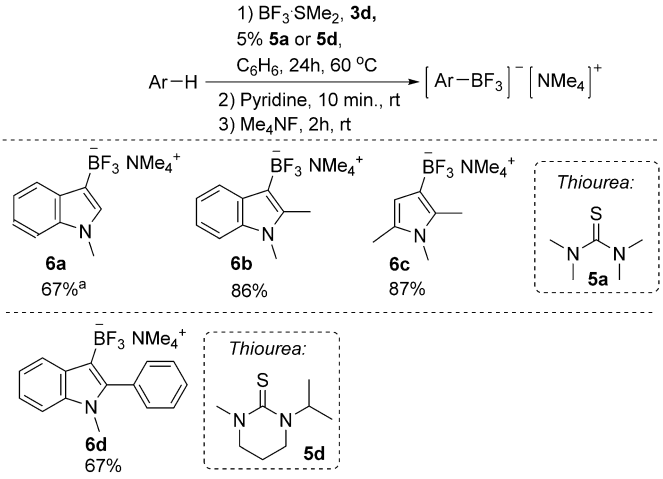
Aryldifluoroboranes **2a**–**j** were generated and partially characterized by the NMR spectroscopy in solution, however, attempted isolation of these compounds appeared to be unsuccessful due to high reactivity and reversibility of the borylation reaction (Figure 1). In line with the recent reports[15] we found protodeboronation to be the major decomposition pathway. Although only few 3-BF_3-substituted indoles, all stabilized by the strongly electron withdrawing groups on nitrogen, were known in the literature,[1g] we attempted conversion of in situ produced **2a** to the corresponding indolyltrifluoroborate (**6a**) (Scheme 7).

We reported previously that trialkynylboranes are converted to trialkynylfluoroborates by the treatment with tetramethylammonium fluoride (TMAF).[13] However, all attempts to perform direct fluorination of **2a** to **6a** with TMAF led to the complete protodeborylation, and starting material **1a** was ob-



Scheme 7. Aryldifluoroboranes are accessible with high reactivity and protodeboronation of 3-subsituted indole **2a** takes place in the presence of TMAF. However, **2a** forms pyridine (**7**) and *N*,*N*-dimethylaniline (**8**) adducts. The former can be further converted to trifluoroborate **11a** with TMAF.

served instead. The reason for instability of **2a** in the presence of TMAF is not clear, but to overcome this issue, we stabilized **2a** in the form of its pyridine or *N*,*N*-dimethylaniline adducts. Addition of any of these amines to the **2a** containing reaction mixture resulted in instantaneous formation of the corresponding adducts **7** and **8**. All further attempts to isolate them led to the decomposition to **1a**, but, to our delight, **7** produced trifluoroborate **6a** without noticeable protodeboronation upon treatment with TMAF. In contrast to **7**, reaction of adduct **8** with TMAF led to a complex mixture of unidentified products. To demonstrate generality of the developed two-step method, we applied it to other substrates and isolated the corresponding trifluoroborates with the overall yields equal or slightly lower than those measured in situ during the previous borylation experiments (Scheme 8). Although **5d** was found to be the most active additive for borylation in general, we found that commercially available **5a** gives similar yields with electron rich arenes (Scheme 8, substrates **6a**–**c**). Borylation of less active 1-methyl-2-phenylindole was successfully performed with bulky thiourea 5**d**, giving corresponding trifluoroborate **6d** in good yield.



Scheme 8. A one-pot thiourea-assisted synthesis of aryltrifluoroborates from heteroarenes. [a] compound **11a** was isolated along with 15% of tetramethyl-ammonium diindolyldifluoroborate (see Supporting Information for details).

Conclusions

In conclusion, we developed a straightforward method of N-heteroarenes C–H borylation by boron trifluoride and sterically hindered amines. Addition of thioureas as additives had a beneficial effect on the yield of borylation products. Indoles were selectively borylated into the 3-position and indolenines to the terminal position of the double bond. Borylation intermediates, aryldifluoroboranes, are very reactive and prone to protodeboronation in presence of Me_4NF. This problem was overcame by intermediate formation of their pyridine adducts prior to treatment with Me_4NF that furnished 3-substituted indolyl- and pyrrolyltrifluoroborates with high overall yields. Expansion of the reactivity of boron trifluoride towards other C–H bonds as well as studies towards avoiding protodeboronation in other organoboron compounds are subjects of ongoing studies in our groups.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: boron trifluoride · borylation · C–H activation · frustrated Lewis pairs · protodeboronation

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