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Oxidative Cycloaddition Reactions of Arylboron Reagents via a One-pot Formal Dehydroboration Sequence

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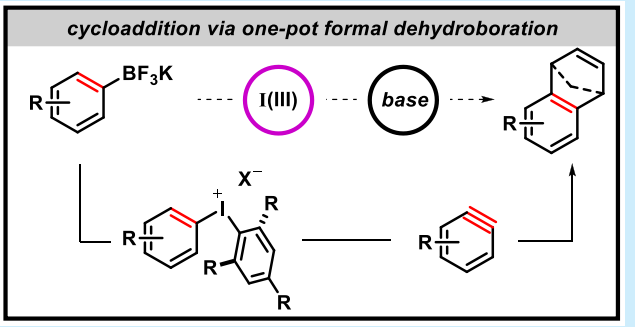
ABSTRACT: Arylboron compounds are widely available and synthetically useful reagents in which the boron group is typically substituted. Herein, we show that the boron group and *ortho*-hydrogen atom are substituted in a formal cycloaddition reaction. This transformation is enabled by a one-pot sequence involving diaryliodonium and aryne intermediates. The scope of arylboron reagents and arynophiles is demonstrated, and the method is applied to the formal synthesis of an investigational drug candidate.



Arylboron compounds are ideal reagents for the diversification of aromatic scaffolds because they are widely commercially available and bench-stable. As such, they are ubiquitous building blocks and act as nucleophilic components in a variety of useful metal-free and metal-catalyzed substitution reactions (Scheme 1a).[1−5] In most applications, boron-based functional groups act as an electrofuge departing without the C_{aryl}—B bonding pair of electrons (Scheme 1a),[6] which is consistent with their *C*-nucleophilic character and results in *ipso*-substitution. Herein, we demonstrate that arylboron reagents can be used as the starting point for oxidative cycloaddition reactions with dienes and 1,3-dipoles and thereby expand the value of arylboron reagents in synthesis by affording both *ipso*- and *ortho*-functionalization of the ring (Scheme 1b).[7] The key to developing a formal cycloaddition reaction of arylboron reagents is the intermediacy of a highly reactive aryne[8] via formal dehydroboration.

Arylboron reagents have indeed served as aryne precursors in the past (Scheme 1c).[9] In this context, a nucleofugal leaving group was required in the *ortho*-position to the electrofugal boron-based leaving group, and these are redox-neutral aryne formations (Scheme 1c).[6] Morrocchi et al. first described the activation of 2-triflylphenylboronic acid with organolithium reagents more than 50 years ago, and Wenger et al. pioneered stoichiometric studies to form metal−aryne complexes from the reaction of Pd(0) and Ni(0) with 2-bromophenylboronic esters.[9a,b] Hosoya et al. and Greaney et al. have since independently developed useful synthetic methods and expanded the scope of these reactions (Scheme 1c).[9c,d] The phenyliodonium group is well established as a hypernucleofugal leaving group, [10] and Zhdankin et al. discovered that the combination of the nucleofugal phenyliodonium group[10] and electrofugal $B(OH)_2$, leads to an aryne when activated by water at room temperature; this is likely the most mild method known to generate arynes.[9g] Notwithstanding these advances, the necessity to have a nucleofugal leaving group *ortho* to the electrofugal boron group limits the scope of substrates.

Like boron-based functional groups, the proton is an electrofugal leaving group.[6] Therefore, generating arynes by loss of a boron-based functional group and a proton is an oxidative process, and to the best of our knowledge, the generation of arynes directly by loss of these two groups is not known. Pilarski et al. has previously synthesized Kobayashi-type aryne precursors from arylboronic acids via a four-step sequence involving *ortho*-C−H silylation.[11] We have used a different approach to achieve a formal dehydroboration in one-pot[12] via the conversion of the electrofugal boron-based group into the nucleofugal aryliodonium leaving group (Scheme 1d). The resulting transformation allows for arylboron reagents devoid of *ortho* nucleofugal leaving groups to be used as substrates in Diels−Alder and other cycloaddition reactions.

We assessed the feasibility of coupling two stages, boron−iodane exchange and aryne formation/trapping, together in a one-pot formal dehydroboration reaction (Table 1). Although both stages have literature precedent,[13,14] there are several potential incompatibilities. For instance, in prior reports on the

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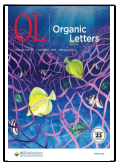

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Scheme 1. Reactivity of Arylboron Reagents

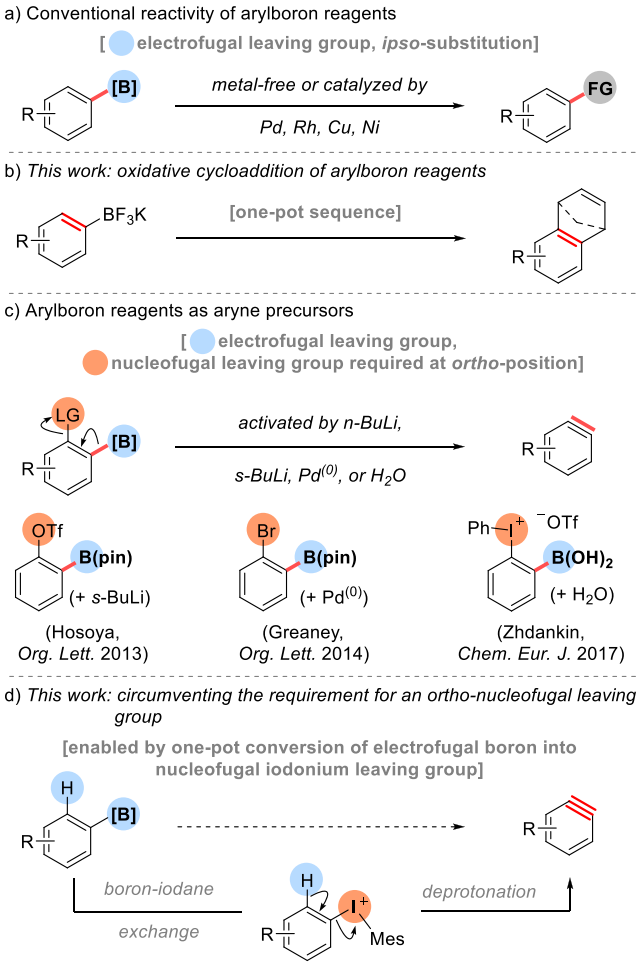
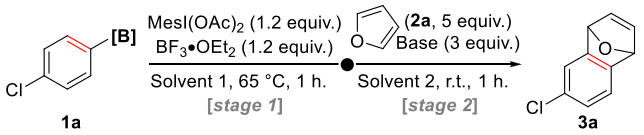


Table 1. Analysis of the Reaction Conditions



entry	[B]	solvent 1	solvent 2	base	yield[b]
1[c]	$B(OH)_2$	MeCN	TBME	NaO*t*-Bu	41%
2[c]	BF_3K	MeCN	TBME	NaO*t*-Bu	56%
3	BF_3K	MeCN	MeCN	NaO*t*-Bu	18%
4	BF_3K	TBME	TBME	NaO*t*-Bu	58%
5[c]	BF_3K	MeCN	toluene	NaO*t*-Bu	44%
6[c]	BF_3K	MeCN	toluene	LiHMDS	74%
7	BF_3K	MeCN	MeCN	LiHMDS	0%
8	BF_3K	toluene	toluene	LiHMDS	75%

[a]Conditions, Stage 1: **1a** (0.1 mmol, 1 equiv), $MesI(OAc)_2$ (0.12 mmol, 1.2 equiv), $BF_3{\cdot}OEt_2$ (0.12 mmol, 1.2 equiv), solvent (1 mL), 65 °C, 1 h. Stage 2: **2a** (0.5 mmol, 5 equiv), base (0.3 mmol, 3 equiv), rt, 1 h. [b]Yield determined by ^{1}H NMR spectroscopy with 1,3,5-trimethoxybenzene as an internal standard. [c]Solvent switch between stages; 1 mL of second solvent added.

individual stages, different solvents are used, and (Lewis or Bronsted) acid conditions are used in stage 1, whereas basic conditions are used in stage 2.[13,14] We first attempted to mitigate these incompatibilities by conducting a solvent swap between each stage without actually isolating the intermediate aryl(Mes)iodonium salt. By using *p*-chlorophenylboron **1a**, we observed higher yields with the potassium trifluoroborate salt relative to the boronic acid when MeCN was used for the first stage and TBME was used for the second stage (Table 1, entries 1 and 2).[13b,14i] We also attempted to conduct the entire telescoped reaction in the same solvent using either MeCN or TBME, and we found that TBME resulted in substantially higher yield than MeCN as solvent (Table 1, entries 3 and 4). Toluene has also been used as a solvent for generating arynes from diaryliodonium salts and is often paired with LiHMDS as a base.[14c,j] A comparison of NaO*t*Bu and LiHMDS as base revealed a substantial increase in yield with the latter (Table 1, entries 5 and 6). Using LiHMDS as base, we tested the possibility of conducting the entire sequence in the same solvent. Although no product **3a** was observed when LiHMDS was used as a base and MeCN was used as the solvent for both stages, a high yield of **3a** was observed when toluene was used for both stages (Table 1, entries 7 and 8). The conditions presented in Table 1, entry 8, represent a very practical approach to formal dehydroboration in which **1a** as the BF_3K salt is treated with $MesI(OAc)_2$ and $BF_3{\bullet}OEt_2$ in toluene at 65 °C for 1 h, and then, the reaction is cooled to room temperature for ∼10 min, followed by the direct addition of furan **2a** and LiHMDS, and is stirred for an additional 1 h.[15]

The scope of arylboron compounds **1a**−**m** and arynophiles **2a**−**h** that are compatible in this reaction is presented in Scheme 2, and the position originally occupied by the boron group is highlighted on the products **3a**−**t** (gray ball, Scheme 2). Boron−iodane exchange occurs by *ipso*-substitution of boron (stage 1), and deprotonation occurs at the *ortho*-position to the iodonium leaving group formerly occupied by boron (stage 2). The aryne intermediates derived from **1a**−**m** were trapped with furan in moderate (54%) to high (76%) yield of aryne−furan cycloadducts **3a**−**m**. The scope of arylboron compounds **1a**−**m** demonstrates two important points. (1) This is the shortest route that we are aware of to convert arylboron reagents, which lack an *ortho*-nucleofugal leaving group, into arynes,[15] as the total reaction time is approximately 2 hours.[11] (2) The boron group fills a strategic role to activate the arene for regiospecific installation of the nucleofugal iodine leaving group and, therefore, generates arynes at positions that would not be possible from the corresponding simple arene.[16] For instance, electron-deficient arenes with substituents found in **1b**−**e** are not nucleophilic enough for C−H thianthrenation and aryne formation.[16] Likewise, although bromobenzene is a compatible arene nucleophile for thianthrenation, the resulting aryne is formed at the 3,4-position relative to the bromine substituent.[16] Here, the aryne is formed at the 2,3-position as a result of regiospecific boron−iodane exchange and electronically controlled regioselective deprotonation (Scheme 2). All reactions of arylboron substrates were conducted in toluene as a solvent for both stages, though moderate yields were observed for those bearing electron-deficient rings (Scheme 2, **3b**−**d**, 36−52%). We attribute this to competitive iodination of toluene under the reaction conditions, which could be avoided by using MeCN as the solvent for the first stage and resulted in improved yields (Scheme 2, 54−76%). This strategy allows for the efficient inclusion of base-sensitive acyl groups that are challenging to include in the corresponding *o*-(trimethylsilyl)-aryl triflates (Scheme 2, **3e**).[17] In this case, we observed higher yields when we used an alternative protocol in which a Mes-

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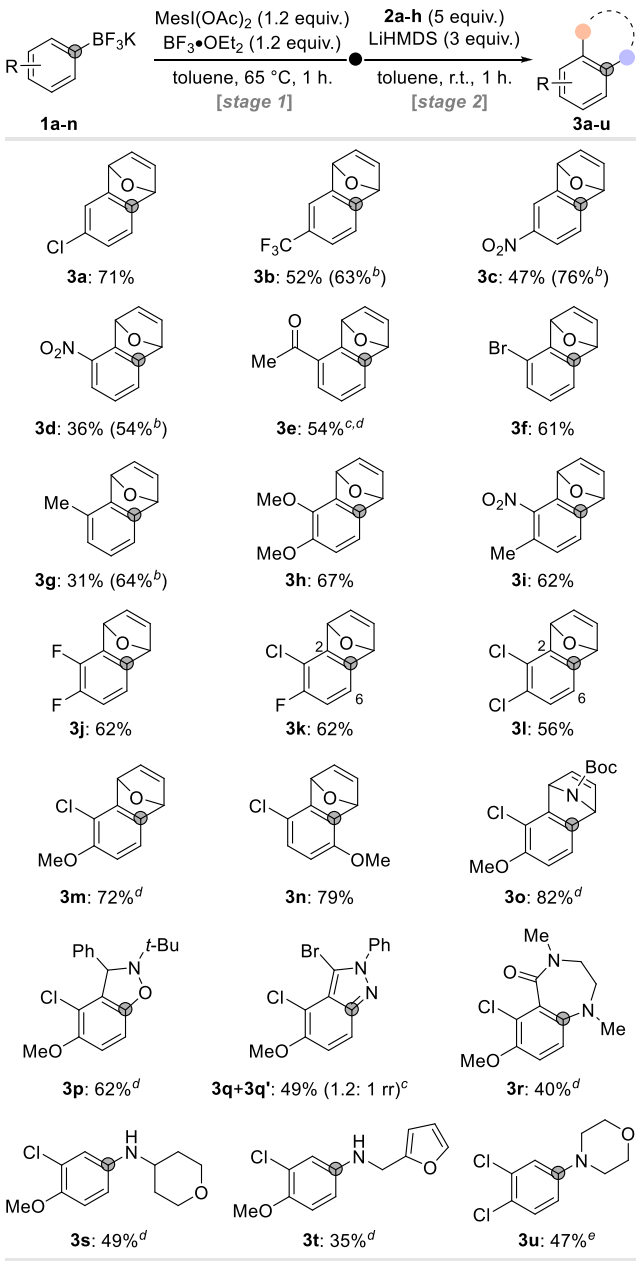
Scheme 2. Scope of the Arylboron Reagent and Arynophiles



[a]Conditions, Stage 1: **1** (1 mmol, 1 equiv), $MesI(OAc)_2$ (1.2 mmol, 1.2 equiv), $BF_3{\cdot}OEt_2$ (1.2 mmol, 1.2 equiv), toluene (10 mL), 65 °C, 1 h. Stage 2: arynophile (5 mmol, 5 equiv), LiHMDS [3 mL (1 M in toluene), 3 mmol, 3 equiv], rt, 1 h. See the Supporting Information for product **3a**–**t** structures. [b]Stage 1 conducted in MeCN, and solvent switch performed between stages (see the Supporting Information for details). [c]Stage 1: **1** (0.5 mmol, 1 equiv), MesI (0.6 mmol, 1.2 equiv), *N*-fluoro-2,6-dichloropyridinium tetrafluoroborate (0.6 mmol, 1.2 equiv), MeCN (5 mL), 65 °C, 1 h; solvent switch (see the Supporting Information). Stage 2: arynophile (2.5 mmol, 5 equiv), NaO*t*-Bu (1.5 mmol, 3 equiv), TBME (5 mL), rt, 1 h. [d]Stage 1: **1** (0.5 mmol, 1 equiv), $MesI(OAc)_2$ (0.6 mmol, 1.2 equiv), $BF_3{\cdot}OEt_2$ (0.6 mmol, 1.2 equiv), MeCN (5 mL), 65 °C, 1 h; solvent switch. Stage 2: arynophile (0.6–2.6 mmol, 1.2–5 equiv), NaO*t*-Bu (1.5 mmol, 3 equiv), TBME (5 mL), rt, 1 h. [e]Aryne derived from **1l**.

iodonium species is generated *in situ* with an F^+ oxidant, and the BF_3 Lewis acid is omitted (Scheme 2).[13b,18] For substrates in which the substituent is at the 3-position relative to the boron group (and therefore, the iodonium; **3d**–**3m**, Scheme 2), the regioselectivity for deprotonation in stage 2 is consistent with prior literature and occurs at the 2-position.[14] Incidentally, the regioselectivity of aryne formation in our transformation is complementary from that previously observed by Pilarski et al.[11] In the two examples where direct comparison can be made (**3k** and **3l**), C–H silylation previously reported occurs at position 6;[11] in our reaction, deprotonation occurs at position 2, and therefore, a distinct aryne is formed. Finally, for examples in which a direct comparison can be made, that is, **3b**, **3f**, and **3i**, higher yields are obtained from the one-pot method described here versus a stepwise approach in which the aryl(Mes)iodonium salts are isolated.[13b,14c,15]

A variety of arynophiles are also compatible in this reaction, in addition to furan, and we used the aryne derived from **1m** and **1l** to assess the arynophile scope (Scheme 2). The compatible arynophiles span several reaction classes, including [4 + 2] (furan **2a** and pyrrole **2b**) and [3 + 2] (nitrone **2c** and sydnone **2d**) cycloaddition, *σ*-bond insertion (*N*,*N*-dimethylpyrrolidinone **2e**), and nucleophilic addition (amines **2f**–**h**) (Scheme 2). In the case of **2g**, nucleophilic addition of the amine is preferred over cycloaddition with furan, which is consistent with the arynophilicity parameters derived for primary amines and furan (Scheme 2, **3t**).[19] Unsymmetrically substituted arynes, as is the case with the aryne derived from **1l** and **1m**, undergo addition consistent with the aryne distortion model in which the nucleophilic end of the arynophile attacks distal to the substituent.[20] The regioselectivity is generally high (>10:1) and the yield of the major regioisomer is presented in (Scheme 2, **3p**,**r**,**s**,**u**). In the case of **3q** and **3q′**, a 1.2:1 mixture of regioisomers was isolated because of similar nucleophilicity at each end of the sydnone 1,3-dipole.[15,21]

To demonstrate that this method provides efficient access to novel chemical space, we conducted a formal synthesis of PF-03814735, an investigational Aurora Kinase inhibitor.[22] PF-03814735 was previously synthesized in nine steps from commercially available *rac*-**4** via **5** (Scheme 3a).[22] As an alternative to nitration of *rac*-**4**,[22] we envisioned that *rac*-**5** could be obtained from *rac*-**6** already containing the appropriate nitrogen functionality (Scheme 3a). Moreover, *rac*-**6** could be efficiently obtained from a formal dehydroboration of **1c** and the aryne Diels–Alder with **2b** (Scheme 3a). The only prior literature synthesis of *rac*-**6** also uses an aryne Diels–Alder reaction with **2b** but uses the potentially explosive **7** as the aryne precursor and proceeds in 19% yield (Scheme 3a).[23,24] We synthesized *rac*-**5** in two steps and a 72% overall yield (Scheme 3b). The one-pot formal dehydroboration–aryne Diels–Alder sequence between **1c** and **2b** afforded *rac*-**6** in 74% yield over the two stages (Scheme 3b). In this case, we used a different solvent for each stage (Table 1, entry 6), as toluene competes with the electron-deficient **1c** as a nucleophile in the first stage. Hydrogenation of *rac*-**6** with Pd/C and an H_2 balloon reduced both the alkene and nitro functionality to deliver *rac*-**5** in 98% yield without the need for chromatography, which can be carried on to PF-03814735 (Scheme 3b).[22a]

In conclusion, we have developed a one-pot reaction in which arylboron compounds undergo a formal dehydroboration reaction via *in situ* generated aryl(Mes)iodonium salts, which lead to arynes. Our approach circumvents the need for a nucleofugal leaving group *ortho* to the boron substituent that is a structural characteristic of previous arylboron-derived aryne

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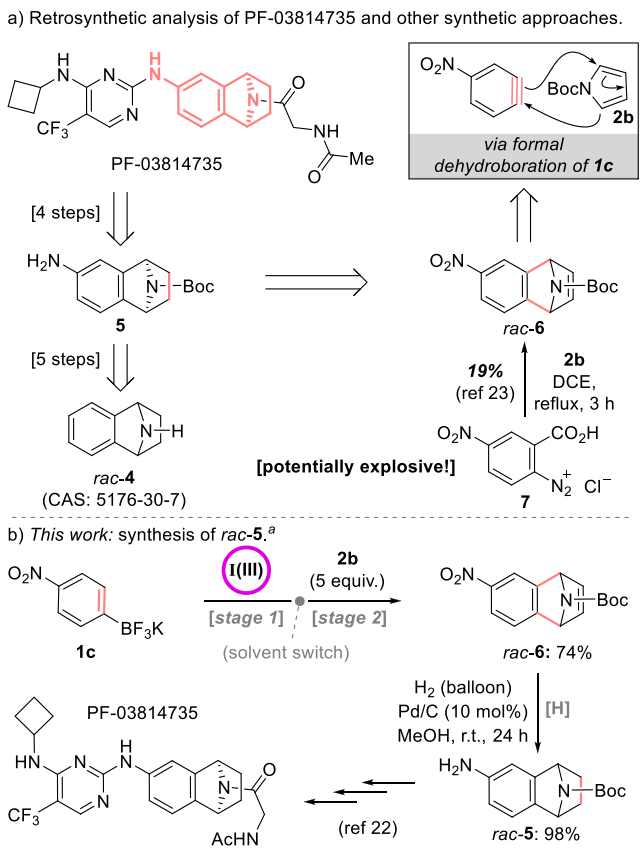
Scheme 3. Formal Synthesis of PF-03814735



[a]Conditions, Stage 1: **1c** (2 mmol, 1 equiv), $MesI(OAc)_2$ (2.4 mmol, 1.2 equiv), $BF_3{\cdot}OEt_2$ (2.4 mmol, 1.2 equiv), MeCN (20 mL), 65 °C, 1 h; solvent switch. Stage 2: **2b** (10 mmol, 5 equiv), LiHMDS [3 mL (1 M in toluene), 6 mmol, 3 equiv], rt, 1 h. [H]: *rac*-**4** (1 mmol, 1 equiv), Pd/C (0.05 mmol, 0.05 equiv), H_2 (balloon), MeOH, rt, 24 h.

precursors. This work adds to the already immense synthetic value of arylboron reagents by providing an avenue for oxidative cycloaddition reactions, and we have demonstrated this by the formal synthesis of the investigational drug candidate PF-03814735.

■ ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article and its Supporting Information.

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.3c02379.

Experimental procedures, characterization data, and copies of ^1H, ^{13}C, and ^{19}F NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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