Radical borylation of aryl sulfones with 1,3-dimethylimidazol-2-ylidene borane leading to aryl boranes

Ryo Komatsu[1], Tsubasa Morioka[1], Akio Kamimura[1], Hiroshi Matsubara[2], Dennis P. Curran[3], Takuji Kawamoto[1]*

[1]Department of Applied Chemistry, Yamaguchi University, Ube, Yamaguchi 755-8611, Japan

[2]Department of Chemistry, Graduate School of Science, Osaka Metropolitan University, Sakai, Osaka 599-8531, Japan

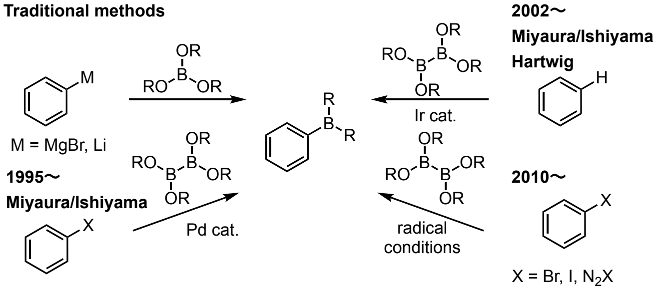
[3]Department of Chemistry, University of Pittsburgh, Pittsburgh, Pennsylvania 15260, United States

* tak102@yamaguchi-u.ac.jp

ABSTRACT: We have found that aryl boranes can be obtained from aryl sulfones, including phenyl methyl sulfone, 1,3-dimethylimidazol-2-ylidene borane (diMeImd-BH_3) in the presence of a radical initiator. The reaction proceeds via the addition of a boryl radical to an aryl sulfone, followed by β-cleavage to give an aryl borane and a sulfonyl radical. The generated aryl boranes can be applied for Suzuki-Miyaura coupling with 4-bromophenyl methyl sulfone.

The applications of aryl boron compounds have been steadily increasing over the past decades. For instance, they are widely regarded as important synthetic intermediates, serving as starting materials for various functional group transformation reactions, including the Suzuki-Miyaura coupling reaction.[1,2] Additionally, aryl boron compounds are directly used as pharmaceuticals[3] and functional materials.[4]

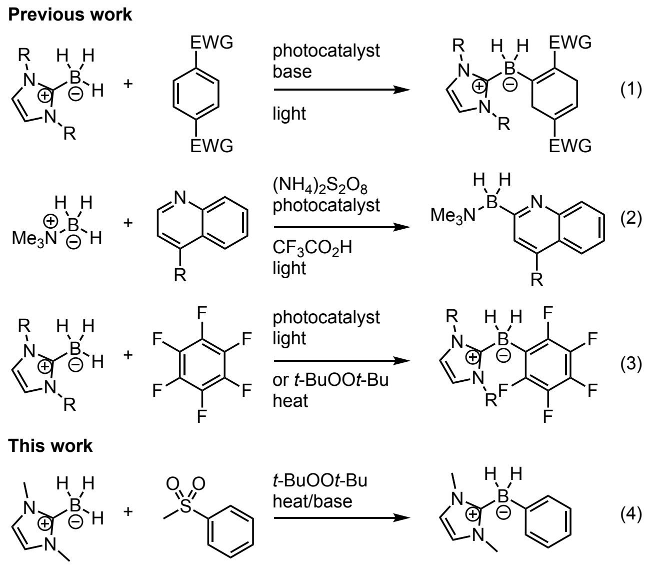
Classically, aryl boron compounds have been synthesized via reactions that exploit the electrophilicity of boron, arising from its empty p orbital. For instance, aryl boron compounds can be prepared by reacting aryl lithium species or Grignard reagents with $B(OR)_3$ (Scheme 1).[5] In recent decades, transition metal-catalyzed borylation reactions have been developed. Notable examples include Pd-catalyzed borylation of aryl halides[6,7] and Ir-catalyzed C-H borylation of arenes.[8–12] In the past decades, the borylations of aryl radicals have been also developed.[13–15] However, the borylation of aryl sulfones was scarcely reported. In 2022, Hu et al. disclosed a copper-catalyzed borylation of aryl sulfones.[16]



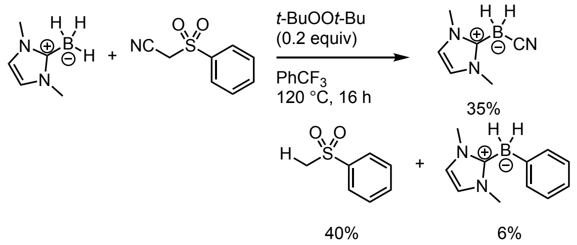
Scheme 1. Synthesis of aryl boranes.

In 2015, we reported radical cyanation of *N*-heterocyclic carbene boranes (NHC-boranes) via nucleophilic addition to the cyano group followed by β-cleavage.[17–19] After this work, various groups have since developed borylation reactions involving nucleophilic boryl radicals.[20–23] One of us reported 1,4-hydroboration of electron-deficient arenes such as 1,4-dicyanobenzene (eq. 1).[24] Recently, Leoroni et al. reported the oxidative C-H borylation of quinolines (eq. 2).[25–27] Additionally, nucleophilic borylation reactions of perfluoroarenes have been developed by many research groups and flourished (eq. 3).[28–32] However, to the best of our knowledge, no method has yet been established for the synthesis of simple aryl boranes via nucleophilic radical borylation (eq. 4).[33]

https://doi.org/10.26434/chemrxiv-2024-zbfbj **ORCID:** https://orcid.org/0000-0002-1845-4700

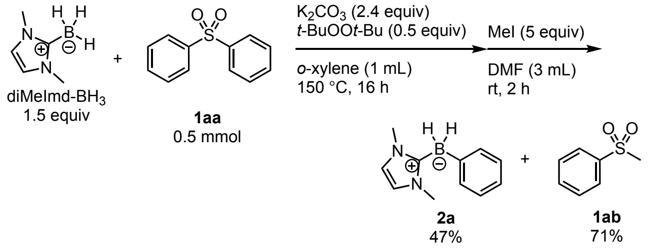


In our previous report on radical cyanation reaction, NHC-boryl radicals prefer to add electron-deficient nitriles such as malononitrile due to the nucleophilicity of a boryl radical.[17] When phenyl sulfonyl acetonitrile was used as a cyano source, we found that cyano borane was obtained along with phenyl borane (Scheme 2). In this study, we found radial borylation of diMeImd-BH$_3$[34] with simple aryl sulfones. The obtained aryl boranes were used for the Suzuki-Miyaura reaction with 4-bromophenyl methyl sulfone followed by radical borylation to achieve iterative coupling.



Scheme 2. Unexpected borylation of sulfone.

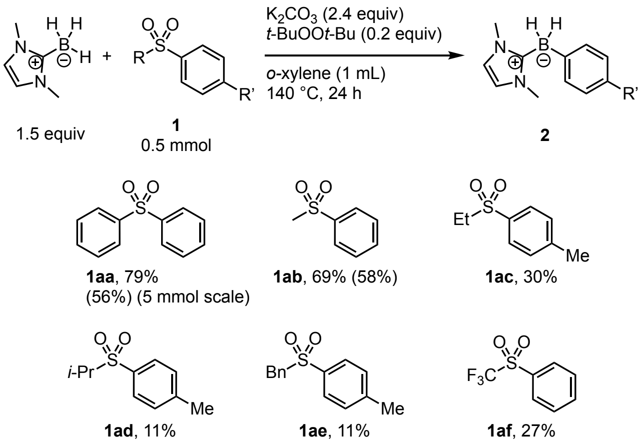
Preliminary investigations of the borylation reaction were conducted using diMeImd-BH$_3$ with diphenyl sulfone (**1aa**) as a model substrate (Scheme 3). Since sulfinic acid was expected to form as a byproduct in this borylation reaction, various bases were tested to optimize the conditions (see SI). Among the bases evaluated, K$_2$CO$_3$ was found to be the most effective. Furthermore, the reaction mixture, after borylation, was treated with methyl iodide to trap the benzene sulfinate, yielding methyl phenyl sulfone (**1ab**). For instance, when *t*-BuOO*t*-Bu was used as a radical initiator and K$_2$CO$_3$, the corresponding borylated product **2a** was obtained in 47% yield with **1ab** in 71% yield. However, the yield of **2a** was significantly lower compared to the yield of methyl phenyl sulfone (**1ab**).



Scheme 3. Initial study

Next, the equivalents of the radical initiator and reaction time were optimized. By using 0.2 equivalents of *t*-BuOO*t*-Bu and heating at 140 °C (bath temp.) for 24 hours, **2a** was obtained in a 79% yield (Table 1). When methyl phenyl sulfone (**1ab**) was used instead of **1aa**, **2a** was obtained in a comparable yield. However, when other sulfones (R = Et, *i*-Pr, Bn, CF$_3$; **1ac**–**1af**) were used, the yield of **2a** decreased significantly. Additionally, scaling up the reaction to 5 mmol using diphenyl sulfone (**1aa**) afforded **2a** in a 56% yield.

Table 1. Optimization [a,b]



1.5 equiv

1
0.5 mmol

2

1aa, 79%
(56%) (5 mmol scale)

1ab, 69% (58%)

1ac, 30%

1ad, 11%

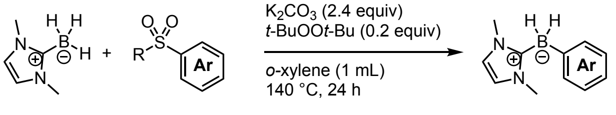
1ae, 11%

1af, 27%

[a] Determined by ^{1}H NMR using CH_2Br_2 as an internal standard. [b] Yield of product, isolated after flash column chromatography on SiO_2, is given in parentheses. [c] **1aa** (5 mmol)

Using the optimized conditions, the substrate scope of methyl aryl sulfones was investigated (Table 2). For substrate **1b**, substituted with a methyl group at the para position, the corresponding product **2b** was obtained in moderate yields (entry 1). When sulfone **1c** bearing an electron-donating (OMe) was used, the yield of the borylated product **2c** significantly decreased (entry 2). In contrast, methyl aryl sulfone **1d** with an electron-withdrawing CF_3 group provided the borylated product **2d** in good yield (entry 3). The reaction of methyl 4-(methylsulfonyl)benzoate (**1e**) gave **2e** in low yield (entry 4). Decreasing the reaction temperature to 120 °C improved the yield to 73% (entry 5). On the other hand, sulfones **1f** and **1g**, bearing cyano or nitro groups, respectively, afforded either low yields or no detectable borylated products (entries 6 and 7). For substrates **1h**–**1j**, substituted with Me or Ph groups at the *meta* or *ortho* positions, the corresponding products were obtained in moderate yields (entries 8–10). Similarly, 2-naphthyl substrates **1k** provided the desired product **2k** in moderate yields. When 4-bromophenyl methyl sulfone (**1l**) was used, the desired product **2l** was not obtained. Instead, **1ab**, resulting from debromination, was isolated in 62% yield, along with debrominated and borylated product **2a** in 12% yield.

Table 2. Substrate Scope of Sulfones



1.5 equiv

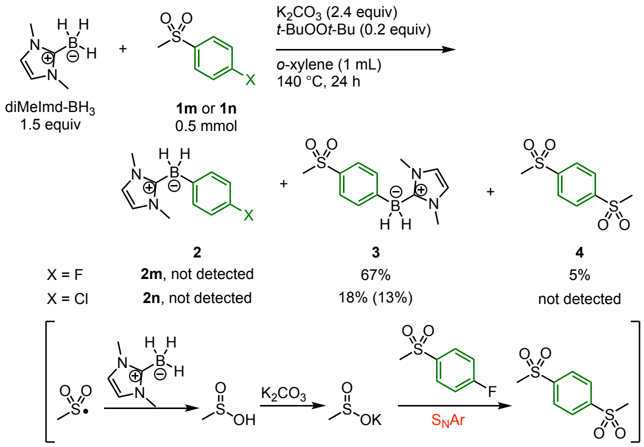
1
0.5 mmol

2

	entry	Ar	1	2	Yield [b,c]
135	1	4-$C_6H_4CH_3$	**1b**	**2b**	53% (45%)
191	2	4-$C_6H_4OCH_3$	**1c**	**2c**	37%
107	3 [d]	4-$C_6H_4CF_3$	**1d**	**2d**	89% (74%)
138	4	4-$C_6H_4CO_2Me$	**1e**	**2e**	62%
194	5 [e]	4-$C_6H_4CO_2Me$	**1e**	**2e**	73%
192	6	4-C_6H_4CN	**1f**	**2f**[e]	36% (20%)
105	7	4-$C_6H_4NO_2$	**1g**	**2g**[e]	0%
232	8	3-$C_6H_4CH_3$	**1h**	**2h**	65% (56%)
186	9	2-$C_6H_4CH_3$	**1i**	**2i**	74% (57%)
200	10	2-C_6H_4Ph	**1j**	**2j**	68% (58%)
190	11	2-naphthyl	**1k**	**2k**	74% (58%)
119	12	4-C_6H_4Br	**1l**	**2l**	0% [f]

[a] NHC borane (0.75 mmol), **1** (0.5 mmol), K_2CO_3 (1.2 mmol), *t*-BuOO*t*-Bu (0.1 mmol), *o*-xylene (1 mL), 24 h. [b] Determined by ^{1}H NMR spectroscopy using CH_2Br_2 as an internal standard. [c] yield of product, isolated after flash column chromatography on SiO_2, is given in parentheses. [d] 0.1 mmol scale, [e] 120 °C [f] **1ab** and **2a** were formed in 62% and 12% yields, respectively.

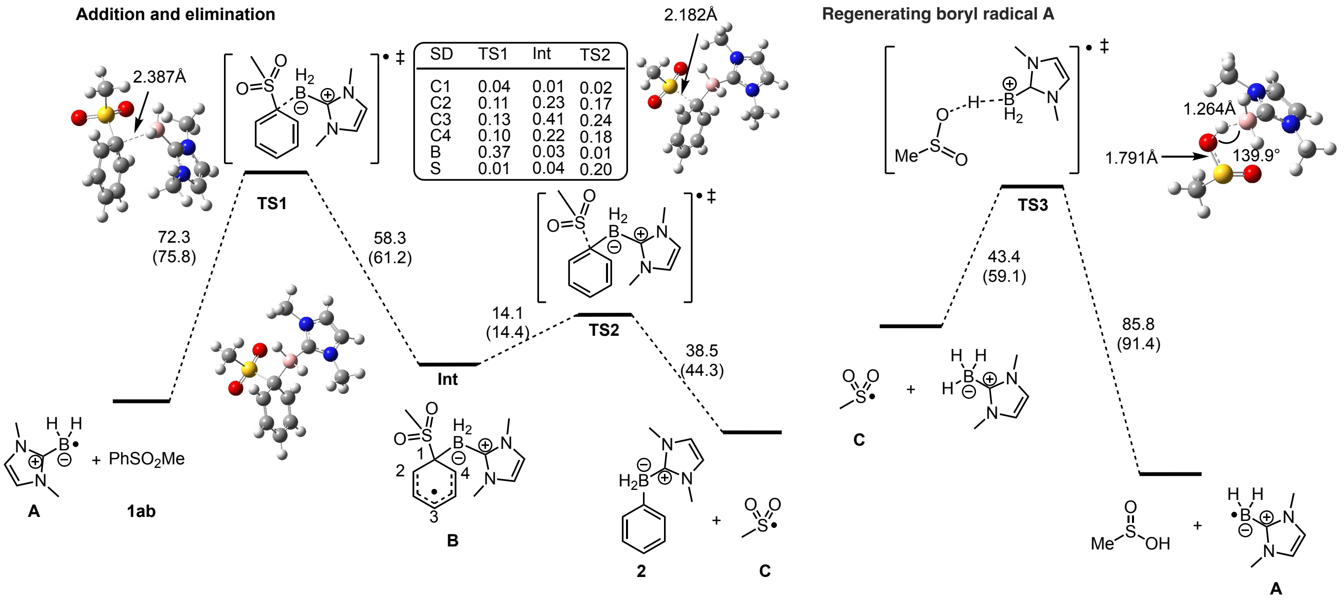
The reaction of 4-chlorophenyl methyl sulfone (**1m**) and 4-fluorophenyl methyl sulfone (**1n**) with NHC-borane gave the 4-methyl sulfonyl phenyl borane **3** in 18% and 67% NMR yields, respectively (Scheme 4). For the reaction of **1n** gave bis sulfones **4** in 5% yield. These results indicated that generated sulfinate attacks aryl fluoride via S$_N$Ar reaction to form the aryl sulfone.[35]



Scheme 4. Radical borylation of 4-chlorophenyl methyl sulfone (1m) and 4-fluorophenyl methyl sulfone (1n)

To elucidate the reaction mechanism, DFT calculations were performed (Figure 1). NHC boryl radical **A** attacks at the *ipso* position of the benzene ring of a methyl phenyl sulfone **(1ab)**, forming cyclohexadienyl radical **B**. The activation energy for this step is calculated to be 72.3 kJ/mol using the ROBHandHLYP/6-311G(d,p)//BHandHLYP/6-311(d,p) level of theory. Following this, β-cleavege occurs, leading to the expulsion of sulfonyl radical **C** and the formation of borylated product **2a**. This overall addition–elimination process is predicted to be exothermic (-10.4 kJ/mol). The generated sulfonyl radical **C** then abstracts a hydrogen atom from NHC-borane with a 43.4 kJ/mol of activation energy, regenerating the boryl radical **A** exothermically, thus keeping a radical chain mechanism. Energies including solvent effects were calculated using the PCM method. As shown in the profile, solvent effects increase all energy barriers in this study. Interestingly, a significant solvent effect (15.7 kJ/mol) is observed on the forward process of attacking NHC-BH2 radical to PhSO2Me, while smaller solvent effects (0.3–5.8 kJ/mol) are found on the other energy barriers.

Figure 1. Reaction profile for borylation of PhSO$_2$Me with NHC-BH$_2$ radical

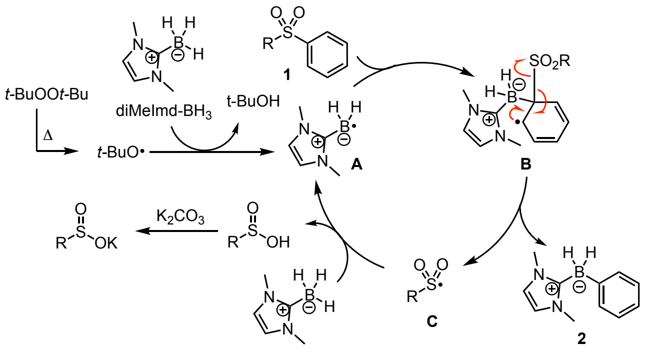


SD	TS1	Int	TS2
C1	0.04	0.01	0.02
C2	0.11	0.23	0.17
C3	0.13	0.41	0.24
C4	0.10	0.22	0.18
B	0.37	0.03	0.01
S	0.01	0.04	0.20

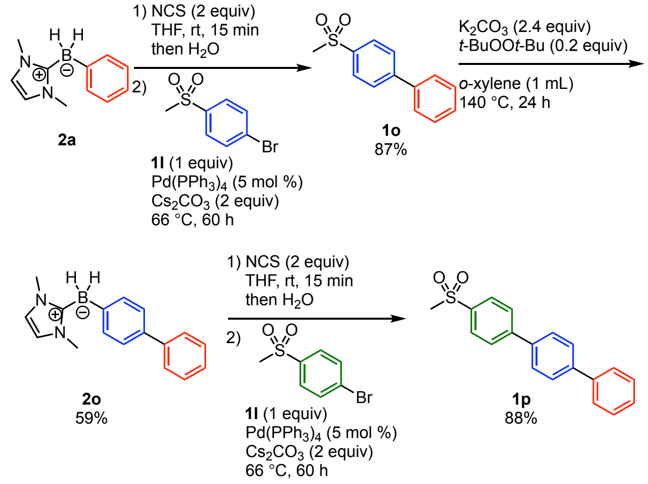
Energies (in kJ/mol) were calculated on the ROB-HandHLYP/$_{6\text{-}311}$G(d,p)//BHandHLYP/$_{6\text{-}311}$G(d,p) level. Energies with solvent effect (in o-xylene) are shown in paren-thesis.

The proposed reaction mechanism is shown in Figure 2. Initially, *t*-BuOO*t*-Bu undergoes homolytic cleavage upon heating, generating *t*-BuO radicals. These radicals abstract a hydrogen atom from diMeImd-BH$_3$, leading to the formation of an NHC boryl radical **A**. Subsequently, **A** adds to an aryl sulfone, and a subsequent cleavage reaction produces the desired product **2** along with the formation of a sulfonyl radical **C**. The sulfonyl radical **C** then abstracts a hydrogen atom from NHC borane, regenerating the boryl radical **A**. The sulfinic acid generated earlier reacts with a base to form the sulfinic salt.

Figure 2. Possible mechanism



The applications of the aryl boranes synthesized in this reaction are demonstrated (Scheme 5). The reaction of **2a** with *N*-chlorosuccinimide (NCS) followed by hydrolysis to form the corresponding boronic acid. Without purification, a Suzuki–Miyaura cross-coupling reaction with 4-bromophenyl methyl sulfone (**1l**) was performed, yielding 4-(methylsulfonyl)biphenyl (**1o**) in 87% yield.[36] Subsequently, **1o** was treated under standard borylation conditions to synthesize **2o** in 59% yield. After further formation of the boronic acid and performing a one-pot Suzuki–Miyaura cross-coupling reaction, 4-(methylsulfonyl)terphenyl **1p** was obtained in 88% yield.



Scheme 5. Suzuki-Miyaura reaction followed by borylation

In summary, we discovered that when NHC borane and aryl sulfone are reacted in the presence of a radical initiator, NHC-aryl substituted boranes are obtained. The aryl boranes synthesized in this reaction can be applied to functional group transformation reactions such as the Suzuki–Miyaura cross-coupling reaction. Furthermore, repeated cross-coupling reactions are possible, making this approach highly valuable in synthetic chemistry.

AUTHOR INFORMATION

Corresponding Author

* **Takuji Kawamoto** – Department of Applied Chemistry, Yamaguchi University, Ube, Yamaguchi 755-8611, Japan

Authors

Ryo Komatsu – Department of Applied Chemistry, Yamaguchi University, Ube, Yamaguchi 755-8611, Japan

Tsubasa Morioka – Department of Applied Chemistry, Yamaguchi University, Ube, Yamaguchi 755-8611, Japan

Akio Kamimura – Department of Applied Chemistry, Yamaguchi University, Ube, Yamaguchi 755-8611, Japan

Hiroshi Matsubara – Department of Chemistry, Graduate School of Science, Osaka Metropolitan University, Sakai, Osaka 599-8531, Japan

Dennis P. Curran – Department of Chemistry, University of Pittsburgh, Pittsburgh, Pennsylvania 15260, United States

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Notes

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