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ACS Catal., **Just Accepted Manuscript** • Publication Date (Web): 31 May 2017

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Copper-Catalyzed *ipso*-Borylation of Fluoroarenes

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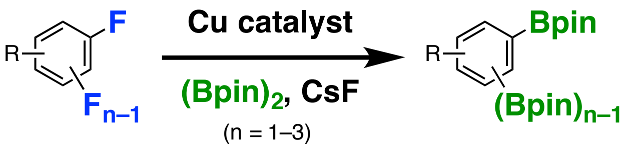
ABSTRACT: *ipso*-Borylation of fluoroarenes has been achieved using an air-stable copper complex as a catalyst. Mechanistic studies suggest that the reaction proceeds via an $S_{RN}1$ mechanism involving a single-electron transfer (SET) process and not via the typical S_NAr mechanism. This method differs the previously reported nickel/copper-cocatalyzed system in terms of scope of the substrate and has exhibited good scalability. Double and triple *ipso*-borylation of several di- and trifluoroarenes have been also achieved efficiently, enhancing the synthetic utility of this method.

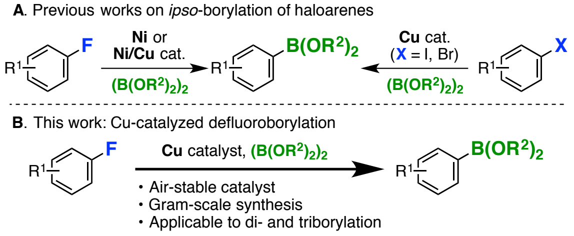


KEYWORDS: Copper, Defluoroborylation, Fluoroarene, Arylboron, Single-Electron Transfer, Air-Stable Catalyst

INTRODUCTION

Fluoroarene structures are frequently found in a broad range of molecules including drugs and organic materials.[1] Availability of fluoroarenes has been significantly expanding with recent advances in late-stage fluorination reactions.[2] The ready availability of fluoroarenes has stimulated considerable interest in their transformation via C–F bond cleavage.[3] This interest arises because cleaving the stable C–F bond is a challenging issue and late-stage C–F bond derivatization enables formation of a diverse range of molecules. In particular, *ipso*-borylation of fluoroarenes has been attracting much attention owing to the reliable and versatile organoboron chemistries[4] that enable facile diversification for obtaining valuable compounds such as new drug candidates and molecular probes.

Scheme 1. Catalytic *ipso*-Borylation of Haloarenes



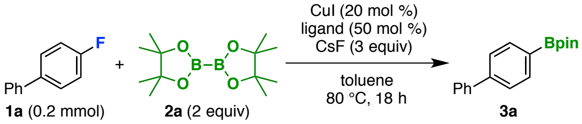
Recently, several groups, including ours, independently reported *ipso*-borylation reactions of fluoroarenes via C–F bond cleavage (Scheme 1A);[5,6] however, almost all of these methods utilize a severely air-sensitive low-valent nickel complex as a catalyst and the substrate scope is still limited. Herein, we report a novel method for *ipso*-borylation of fluoroarenes that is catalyzed by an air-stable copper complex (Scheme 1B).

During the course of our investigation on Ni/Cu-catalyzed defluoroborylation,[5b] we unexpectedly found that *ipso*-borylation of 4-fluorobiphenyl (**1a**) with bis(pinacolato)diboron ($(Bpin)_2$, **2a**) proceeded in the absence of the nickel reagent; heating a mixture of **1a** (0.2 mmol) and **2a** (2 equiv) in the presence of CuI (20 mol %), PCy_3 (50 mol %), and CsF (3 equiv) in deoxygenated toluene at 80 °C for 18 h afforded the desired arylboronic acid pinacol ester **3a** in 40% yield (Table 1, entry 1). This result indicated the possibility for achieving efficient defluoroborylation using a copper catalyst alone. Whereas copper-catalyzed *ipso*-borylation of haloarenes such as iodo- or bromoarenes has already been reported (Scheme 1A),[7] neither the borylation nor other transformation via C–F bond cleavage of fluoroarenes catalyzed by a copper complex has been reported.[8] As copper salts are generally air-stable and easy to handle, we embarked on an optimization study of this promising and mechanistically interesting transformation.

RESULTS AND DISCUSSION

Optimization Studies. Extensive screening of the conditions for the reaction between **1a** and **2a** significantly improved the yield of **3a** (Table 1). Whereas changing the phosphine ligand from PCy_3 to others were ineffective (entries 2–11), several copper salts, such as CuCl, CuBr, CuF_2, $CuCl_2$, $CuBr_2$, $Cu(OAc)_2$, and $Cu(OTf)_2$, efficiently catalyzed the defluoroborylation (entries 12–20). In contrast, using CsF as the base was crucial (entries 21–25 and Table S1). Nonpolar solvents, such as toluene, benzene, and cyclopentyl methyl ether, were preferred for this transformation (Table S2). The reaction did not proceed without either the copper salt, phosphine ligand, or base (Table 1, entries 26–28).

Table 1. Optimization of ligand, copper source and base

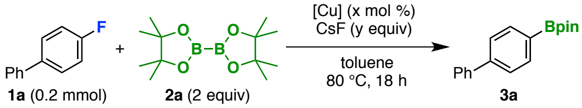


entry	[Cu]	ligand	base	yield **3a** (%)[a]
1	CuI	PCy$_3$	CsF	40
2	CuI	Ad$_2$P(*n*-Bu)	CsF	12
3	CuI	P(*t*-Bu)$_3$	CsF	0
4	CuI	P(*c*-C$_5$H$_9$)$_3$	CsF	0
5	CuI	Xphos	CsF	0
6	CuI	Davephos	CsF	6
7	CuI	P(*o*-tol)$_3$	CsF	0
8	CuI	PPh$_3$	CsF	<1
9[b]	CuI	dppf	CsF	<1
10[b]	CuI	dppbz	CsF	2
11	CuI	IPrAgCl	CsF	2
12	CuBr	PCy$_3$	CsF	>99
13	CuCl	PCy$_3$	CsF	>99 (95)[c]
14	CuOAc	PCy$_3$	CsF	37
15	CuPF$_6$(MeCN)$_4$	PCy$_3$	CsF	0
16	Cu(OTf)$_2$	PCy$_3$	CsF	>99
17	Cu(OAc)$_2$	PCy$_3$	CsF	83
18	CuBr$_2$	PCy$_3$	CsF	>99
19	CuCl$_2$	PCy$_3$	CsF	75
20	CuF$_2$	PCy$_3$	CsF	97
21	CuCl	PCy$_3$	RbF	0
22	CuCl	PCy$_3$	KF	0
23	CuCl	PCy$_3$	NaF	0
24	CuCl	PCy$_3$	Cs$_2$CO$_3$	0
25	CuCl	PCy$_3$	CsOPiv	1
26	–	PCy$_3$	CsF	0
27	CuCl	–	CsF	<1
28	CuCl	PCy$_3$	–	0

[a]Yields determined by GC analysis, unless otherwise noted. [b]Ligand (25 mol %) was used. [c]Isolated yield for the reaction using 5 mol % Cu of the copper complex with 2.97 mmol (511 mg) of **1a** in parentheses.

Efficient results were also obtained using pre-coordinated copper complexes, such as [CuCl(PCy$_3$)]$_2$ and CuCl(PCy$_3$)$_2$, instead of the CuCl/PCy$_3$ system (Table 2). These complexes were easily prepared on a gram-scale[9] and are practically active for more than a year without special care in storing, making this method more practical.[10] The use of 5 mol % of each complex afforded **3a** in excellent yields and reducing the amount of complex to 2 mol % was still sufficient to obtain **3a** in acceptable yields (entries 1–8). Furthermore, this reaction was scalable as demonstrated in a decagram scale borylation of **1a** using 5 mol % of CuCl(PCy$_3$)$_2$ with standard grade reagents such as undried CsF and non-deoxygenized toluene (entry 5).[11] Whereas the amount of CsF could be reduced to 1.2 equiv (entries 9–11), using an excess amount (3 equiv) showed excellent result with high reproducibility. In some cases during the optimization study, we observed generation of a small amount of hydrodefluorinated biphenyl as a byproduct; however, 3-borylbiphenyl, a regioisomer of **3a**, was not detected, indicating that a benzyne intermediate was not involved in this reaction.[12] Similar to the Ni/Cu-catalyzed system,[5b] bis(neopentyl glycolato)diboron (**2b**) was unsuitable as the boron source.

Table 2. Further Optimization Using Pre-coordinate complexes



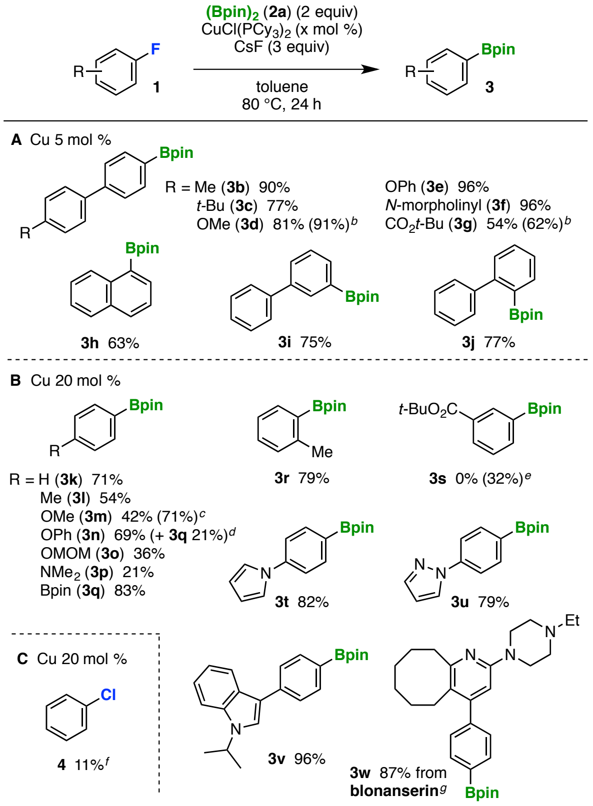
entry	[Cu]	x (mol %)	y (equiv)	yield **3a** (%)[a]
1	[CuCl(PCy$_3$)]$_2$	5	3	>99 (86[b])[c]
2	[CuCl(PCy$_3$)]$_2$	2	3	89
3	[CuCl(PCy$_3$)]$_2$	1	3	32
4	[CuCl(PCy$_3$)]$_2$	0.5	3	26
5	CuCl(PCy$_3$)$_2$	5	3	>99 (94, 97[b], 92[d])[c]
6	CuCl(PCy$_3$)$_2$	2	3	>99
7	CuCl(PCy$_3$)$_2$	1	3	69
8	CuCl(PCy$_3$)$_2$	0.5	3	33
9	CuCl(PCy$_3$)$_2$	2	2.4	>99
10	CuCl(PCy$_3$)$_2$	2	1.2	82
11	CuCl(PCy$_3$)$_2$	2	0.2	13

[a]Yields determined by GC analysis, unless otherwise noted. [b]Yields for the reaction using 2.97 mmol (511 mg) of **1a**. [c]Isolated yields in parentheses. [d]Yield for the reaction using 49.4 mmol (8.51 g) of **1a** with undried CsF in non-deoxygenated toluene.

Substrate Scope. *ipso*-Borylation of various fluoroarenes **1** were achieved based on the optimal conditions (Table 3). Under the standard conditions (Table 2, entry 5, using 0.200 mmol of **1**), 4-fluorobiphenyls **1b**–**f** bearing an electron-donating group at the 4′-position were transformed to the corresponding 4-borylbiphenyls **3b**–**f** in high yields (Table 3A). Notably, borylation of a 4-fluorobiphenyl bearing an electron-withdrawing group such as **1g**, to which the Ni/Cu system was inapplicable,[5b] also took place, affording the borylated product **3g** in good yield. 1-Fluoronaphthalene (**1h**), 3-fluorobiphenyl (**1i**), and sterically hindered 2-fluorobiphenyl (**1j**) also participated in this reaction to afford **3h**, **3i**, and **3j**, respectively.

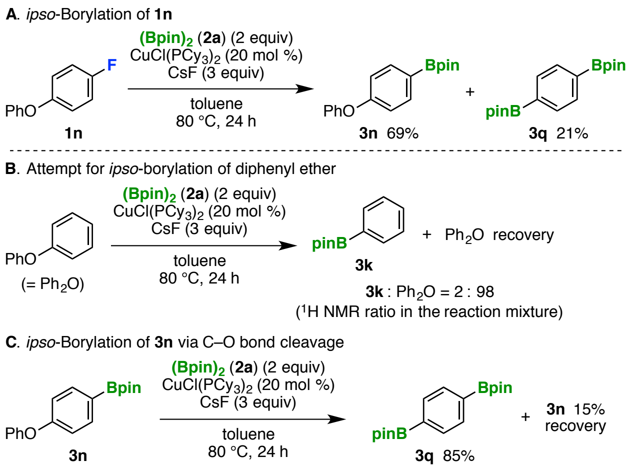
Monoaryl fluorides were also successfully defluoroborylated by increasing the amount of CuCl(PCy$_3$)$_2$ from 5 to 20 mol % (Table 3B). For example, fluorobenzene (**1k**) and its derivatives **1l**–**r** with an electron-donating group at the *para*- or *ortho*-position were borylated to afford **3k**–**r** in moderate to good yields. From the reaction of 4-fluorophenyl phenyl ether (**1n**), a small amount of *para*-diborylbenzene **3q** was also obtained, indicating that borylative C–O bond cleavage also took place. Since *para*-borylated fluorobenzene **1q** was not detected in this reaction mixture, we assumed that borylative cleavage of the C–F bond of **1n** proceeded faster than that of the C–O bond under these conditions. Indeed, diphenyl ether was almost inert under the same conditions, while borylative C–O bond cleavage of **3n** proceeded to afford *para*-diborylbenzene **3q** in high yield (Scheme 2). These results indicate that the boryl group at the 4′-position accelerated C–O bond cleavage. Similarly, defluoroborylation of **1q** took place smoothly to give *para*-diborylbenzene **3q** in high yield. An attempt to defluoroborylate *meta*-fluorobenzoate **1s**, which has an electron-withdrawing group directly attached to the fluoroarene ring, was unsuccessful, indicating the significantly low reactivity of electron-deficient fluoroarenes; however, performing the reaction of **1s** in toluene-d_8 using an equimolar amount of $CuCl(PCy_3)_2$ provided the borylated product **3s** in low yield (Table S3).[13] Whereas the borylation of fluoroarenes bearing a benzyl ether, allyl ether, acidic amide proton, or π-conjugated C–C multiple bond were unsuccessful (Figure S1), substrates **1t**–**v** with nitrogen-containing heterocycles, such as pyrrole, pyrazole, and indole, were smoothly borylated to afford **3t**–**v** in high yields. Furthermore, defluoroborylation of blonanserin (**1w**), a commercial a typical antipsychotic drug that contains a 2-piperazinylpyridine structure, afforded **3w** in high yield, demonstrating the practicality of this method. Moreover, other electrophilic (pseudo)halobenzenes such as chlorobenzene (**4**) were unfavorable substrates (Tables 3C and S4), indicating that the copper-catalyzed *ipso*-borylation of fluoroarenes proceeds via a different mechanism from the previously reported transition metal-catalyzed borylation of haloarenes.[5,7,14]

Table 3. *ipso*-Borylation of Various Fluoroarenes[a]

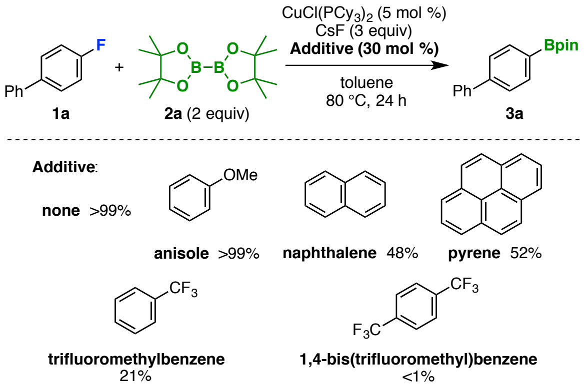


[a]Isolated yields are shown unless otherwise noted. [b]Yields for the reactions using 20 mol % of $CuCl(PCy_3)_2$ in parentheses. [c]Yield for the reaction using 60 mol % of $CuCl(PCy_3)_2$ in parentheses. [d]Yield of byproduct **3q** in parentheses. [e]Yield for the reaction performed in toluene-d_8 using 100 mol % of $CuCl(PCy_3)_2$ in parentheses. [f]Yield of **3k** was determined by GC analysis. [g]Reaction was conducted using 0.100 mmol of **1w**.

Scheme 2. *ipso*-Borylation of Aryl Phenyl Ethers via C–O Bond Cleavage

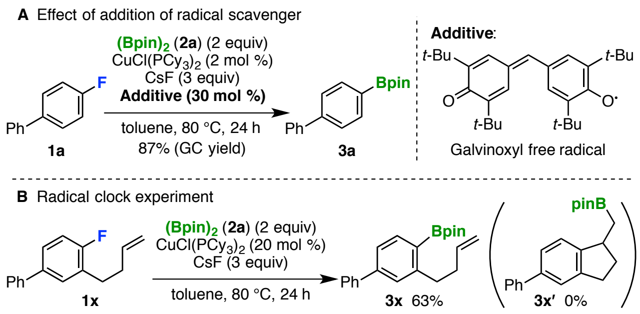


Scheme 3. *ipso*-Borylation of 1a in the Presence of Other Arenes

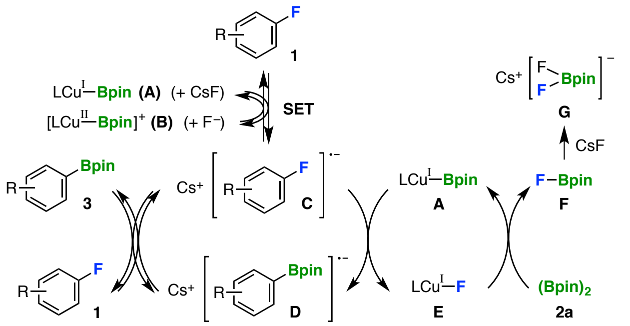


Mechanistic Considerations. Since *ipso*-borylation of electron-deficient fluoroarenes proceeds much slower than that of electron-neutral ones, the reaction is unlikely to occur via the typical S_NAr mechanism.[15] Other results obtained from experiments performed to gain insights into the reaction mechanism also support this idea. For example, defluoroborylation of **1a** was significantly inhibited by adding a catalytic amount of an extensively π-conjugated arene, such as naphthalene or pyrene, or an electron-deficient arene, such as benzotrifluoride and 1,4-bis(trifluoromethyl)benzene (Scheme 3), suggesting the involvement of single-electron transfer (SET) process.[16,17] This agrees with the high reactivity observed for fluoroarenes with an extended π-conjugated system such as biaryl fluorides. Furthermore, addition of Galvinoxyl free radical did not affect the borylation of **1a**, indicating that a free radical species was not generated throughout the transformation (Scheme 4A and Table S5). Indeed, a radical clock experiment using 3-(3-butenyl)-4-fluorobiphenyl (**1x**) did not afford an intramolecularly cyclized product such as **3x′** and instead borylarene **3x** was obtained in good yield (Scheme 4B).

Scheme 4. Mechanistic Experiments Conducted to Investigate the Involvement of Radical Intermediates



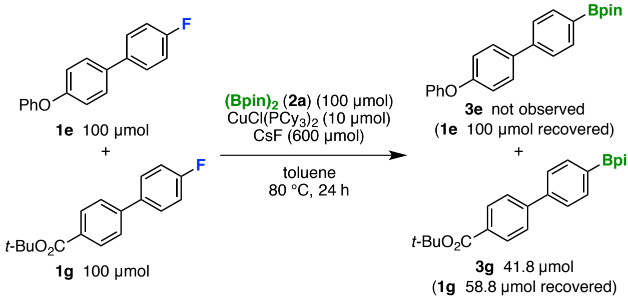
Scheme 5. Plausible Reaction Mechanism



On the basis of these results, we currently consider that the defluoroborylation proceeds via an $S_{RN}1$ mechanism (Scheme 5).[18,19] In this scheme, fluoroarene **1** reversibly accepts an electron, likely transferred from a borylcopper(I) species **A** generated in situ, to give an anion radical form of fluoroarene **C** with copper(II) complex **B**.[20] The subsequent nucleophilic substitution of **C** with a borylcopper(I) species **A** affords an anion radical of borylarene **D** via C–F bond cleavage, which then returns the electron to fluoroarene **1** to regenerate **C** and afford borylarene **3**. Borylcopper(I) **A** is catalytically generated via metathesis between a fluorocopper(I) complex **E** and diboron **2a** to afford fluoroboronate **F**, which in turn reacts with CsF to give cesium difluoroborate **G**. This agrees with the experimental result that a slightly excess amount of CsF is essential to achieve efficient borylation (Table 2, entries 10 and 11). The fluoride anion could also accelerate the SET process (**1** + **A** to **B** + **C**) by stabilizing the copper(II) species **B**.[21] Further, the ineffectiveness of metal fluorides other than CsF (Table 1) suggests partial contribution of the cesium cation because of its large size that is preferable to stabilize anion radical species such as **C** and **D**. Potential interaction between the boron atom of the borylcopper(I) species **A** and the fluorine atom of the substrates,[22] as well as significant electrophilicity of the *ipso*-carbon of fluoroarenes,[23] explains the superior reactivity of fluoroarenes when compared with that of chlorobenzene observed in this reaction. The considerably slow reaction observed in the borylation of electron-deficient fluoroarene **1s** indicated that the rate-determining step was involved in the C–F bond cleavage step (**C** + **A** to **D** + **E**), wherein the anion radical **C** was stabilized by the electron-withdrawing group.

To elucidate the involvement of the SET process, we conducted several experiments. For example, a competitive reaction between **1e** and **1g**, in which the preferential consumption of **1g** was observed, indicated that electron-deficient fluoroarenes are the favored substrates for this reaction (Scheme 6). This result is in stark contrast to that observed in the borylation for each substrate performed independently, wherein electron-rich **1e** reacted more smoothly than electron-deficient **1g** (Table 3A). These contradictory results can be explained by the hypothetical mechanism, where the reaction of fluoroarene **1** starts from the SET process; in the competitive reaction between **1e** and **1g**, more electron-deficient **1g** favorably accepts one electron from the borylcopper(I) **A** to generate the corresponding anion radical selectively, affording the defluoroborylated product **3g** and leaving **1e** untouched.

Scheme 6. Competition Experiment



A spectroscopic analysis of the reaction mixtures also offered us further insight into the reaction mechanism of defluoroborylation. We focused on the color of the reaction mixture; in the cases that the reaction proceeded successfully, the colorless suspension gradually turned to dark red when the reaction mixture was heated.[24] The UV-visible absorption analysis of a mixture of $CuCl(PCy_3)_2$ (1 equiv), $(Bpin)_2$ (4 equiv), CsF (6 equiv), and 4-fluorobiphenyl (**1a**, 1 equiv) in toluene, which was measured after heating for 3 h at 80 °C, gave a spectrum with a weak peak of λ_{max} at 572 nm (Figure 1, green line). We assumed that this peak corresponded to a copper(II) species, such as **B,** that was generated in the mixture via the oxidation of the borylcopper(I) species **A** (Scheme 5). The intensity of this peak observed at almost the same λ_{max} largely increased when 1,4-bis(trifluoromethyl)benzene was added to the mixture instead of **1a** (Figure 1, red line), indicating that a copper(II) species was generated more efficiently in this case. This result was consistent with the significant inhibitory effect of electron-deficient arenes on the defluoroborylation (Scheme 3), which was probably caused by the retardation of the SET process by irreversible oxidation of the borylcopper(I) species **A** that terminated or disabled the initiation of the catalytic cycle. A similar color change of the reaction mixture that showed a characteristic λ_{max} peak at 585 nm in the UV-visible absorption spectrum was observed when 2,2,6,6-tetramethylpiperidine 1-oxyl (TEMPO) was added instead of **1a** (Figure 1, yellow line). This result could be attributed to the generation of a piperidin-1-oxycopper(II) species via the oxidation of borylcopper(I) complex **A** by TEMPO. Although the small-intensity peak of λ_{max} at 572 nm was observed even in the absence of **1a** (Figure 1, blue line), indicating the generation of a copper(II) species via the disproportionation of the borylcopper(I) species **A**,[25] the increased intensity of the peak of λ_{max} at 572 nm in the presence of fluoroarene **1a** (Figure 1, green line) suggests the involvement of the SET process in the formation of a copper(II) species. Further, an electron paramagnetic resonance (EPR) analysis of several reaction mixtures resulted in the observation of no significant peak,[26] suggesting that a copper(II) species generated in the borylation reactions exists as a dimer or polymeric form in the reaction mixture.[27] We currently consider that these results suggest the generation of a copper(II) species in the reaction mixture and support the involvement of the SET process in the reaction mechanism.

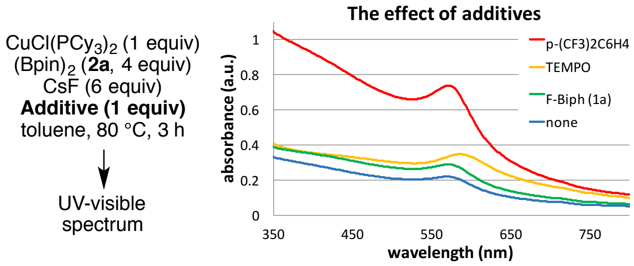
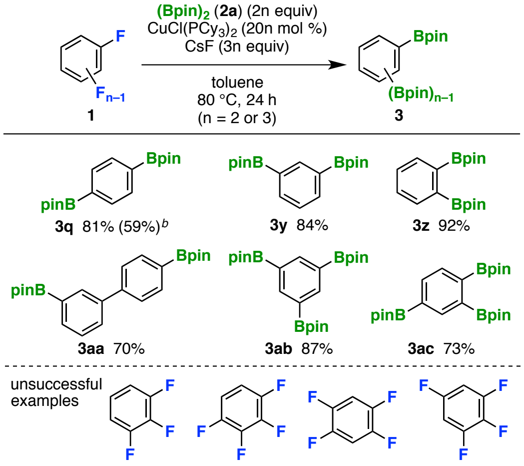


Figure 1. UV-Visible absorption spectra of the reaction mixtures containing various additives measured after toluene dilution (1 mM for copper).

Multi-*ipso*-Borylation of Di- and Trifluoroarenes. Copper-catalyzed defluoroborylation was applicable to the synthesis of di- and triborylated arenes from di- and trifluoroarenes (Table 4).[28] Encouraged by the successful result obtained from the *ipso*-borylation of *para*-borylated fluorobenzene **1q** (Table 3B), we examined the double borylation of 1,4-difluorobenzene using two times the amounts of the reagents, affording the desired 1,4-diborylbenzene **3q** in high yield. In this reaction, monoborylated product **1q** was not detected, even when the amount of (Bpin)$_2$ (**2a**) was reduced to 2 equiv. This result indicates that the second borylation took place faster than the first one, which can be explained by an increase in the electron density on the aromatic ring after the first C–F bond cleavage. This shows an opposite trend to the conventional methods for transition metal-catalyzed C–F bond functionalization of polyfluoroarenes, wherein the first C–F bond transformation proceeded fastest.[29] The utility of our method was further demonstrated in diborylation of *meta*- and *ortho*-difluorobenzene, **1y** and **1z**, and 3,4′-difluorobiphenyl (**1aa**), which smoothly afforded diborylarenes **3y**, **3z**, and **3aa**, respectively, in high yields. Similarly, 1,3,5- and 1,2,4-triborylbenzene, **3ab** and **3ac**, respectively, were efficiently prepared via the triple *ipso*-borylation of the corresponding trifluorobenzenes using three times the amounts of reagents. Multi-*ipso*-borylation was inapplicable to 1,2,3-trifluorobenzene or tetrafluorobenzenes, which resulted in no reaction. Nevertheless, because most of reported multi-defluorinative transformations of polyfluoroarenes are hydrodefluorination,[30] our result demonstrates a unique case for multifunctionalization of polyfluoroarenes via sequential C–F bond cleavage.[31]

Table 4. Double and Triple Defluoroborylations[a]



[a]Isolated yields are shown. [b]Yield for the reactions using 2 equiv of **2a** in parentheses.

CONCLUSIONS

We have demonstrated that *ipso*-borylation of fluoroarenes is efficiently catalyzed by an air-stable copper complex. Mechanistic studies suggest that the reaction proceeds via an S$_{RN}$1 mechanism involving the SET process and not via the typical S$_N$Ar mechanism. The method shows a different substrate scope with the previously reported nickel/copper-cocatalyzed system.[5b] Good scalability of the method has been also demonstrated, increasing the options of transformation via stable C–F bond cleavage. Furthermore, an unexpected gift has been brought to us; it has allowed for the efficient multi-*ipso*-borylation of di- and trifluoroarenes to afford di- and triborylarenes, which serve as useful building blocks for extended π-conjugated systems,[12a,32] versatile components for covalent organic frameworks,[33] and structural motifs that exhibit phosphorescence in the solid state.[34]

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: xxxxxx.

Experimental procedures, characterization for new compounds including copies of NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENT

The authors thank Mr. Natsuhiko Sugimura, Dr. Masahiro Uwamori, and Prof. Masahisa Nakada at Waseda University for their kind support for the EPR analysis. This research was supported by JSPS KAKENHI Grant Number 15K05509 (T.N.), the Project for Cancer Research And Therapeutic Evolution (P–CREATE) from AMED (T.N.), and Special Postdoctoral Researchers Program Fellowship from RIKEN (H.O.).

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(25) A UV-visible absorption analysis of a mixture containing a copper(I) complex, **2a**, and CsF in cyclopentyl methyl ether (CPME), which was measured after heating at 80 °C for 3 h, also gave a spectrum with the peak of λ_{max} at 572 nm having the same intensity as that

measured in toluene (Figure S2), suggesting that toluene did not serve as a key one-electron acceptor in this case.

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