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Ni/Cu-Catalyzed Defluoroborylation of Fluoroarenes for Diverse C−F Bond Functionalizations

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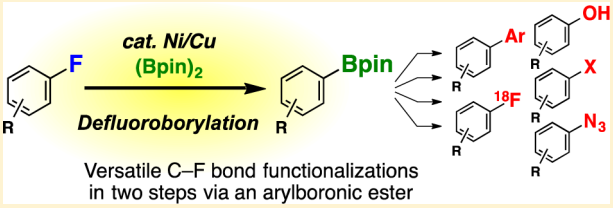
Supporting Information

ABSTRACT: Ni/Cu-catalyzed transformation of fluoroarenes to arylboronic acid pinacol esters via C−F bond cleavage has been achieved. Further versatile derivatization of an arylboronic ester has allowed for the facile two-step conversion of a fluoroarene to diverse functionalized arenes, demonstrating the synthetic utility of the method.

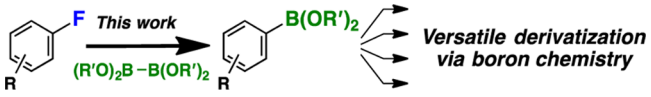


INTRODUCTION

Carbon−fluorine (C−F) bonds are found in a broad range of organic molecules, including pharmaceuticals, agrochemicals, and organic materials.[1] Recent advances in late-stage fluorination reactions have enabled the facile construction of C−F bonds, significantly expanding the diversity of available fluorine-containing compounds.[2] In light of the growing importance of C−F bond formation, C−F bond functionalization has also been attracting considerable interest.[3] This is because transformation through cleavage of significantly stable C−F bonds is challenging.[4] Furthermore, the ready availability of fluorine-containing molecules renders them a favorable platform for further diversification of synthesizable compounds through various derivatizations.[3,5] As such, fluorine-containing compounds are preferred over other halogenated compounds, as a wider range of potential compounds are available due to the chemical stability of C−F bonds, which can tolerate various synthetic transformations.

To achieve a flexible C−F bond functionalization, we developed a method to transform fluoroarenes into arylboronic esters that serve as versatile synthetic intermediates applicable to a wide spectrum of reliable derivatizations (Scheme 1).[6]

Scheme 1. Proposed Strategy: Versatile Derivatization of Fluoroarenes via Defluoroborylation



Recently reported copper-mediated *ipso*-[^{18}F]fluorination of arylboronic esters[7] also encouraged us to realize the defluoroborylation of fluoroarenes. Sequential use of these reactions was anticipated to greatly expedite the development of ^{18}F-labeled probes for positron emission tomography (PET) imaging.[8] We describe herein the transition metal-catalyzed *ipso*-borylation of fluoroarenes via C−F bond cleavage, which has enabled the facile diversification of fluoroarenes.[9]

The challenge of this method was to cleave a stable C−F bond while simultaneously forming an easily transformable C−B bond. When we started working on this project, the defluoroborylation was limited to reactive fluoroarenes such as polyfluorinated substrates.[3b,10,11] Conversely, C−F bond cleavage of simple fluoroarenes has often been observed in cross-coupling reactions using highly reactive nucleophiles, such as organomagnesium[12] or organozinc reagents,[13] in the presence of a nickel catalyst. Moreover, Tobisu, Chatani, and co-workers achieved a nickel-catalyzed cross-coupling reaction of monofluoroarenes with arylboronic esters through the addition of a Lewis acid to enhance the leaving group ability of the fluoride.[14] These reports suggested that using a nickel catalyst in combination with a highly nucleophilic boron reagent is a promising approach for achieving the desired defluoroborylation of fluoroarenes. We envisioned that a borylcopper species, which has previously been used for several nucleophilic borylative reactions and demonstrates a broad functional group tolerance, could serve as an efficient boron source.[15]

RESULTS AND DISCUSSION

After extensive screening of reaction conditions using 4-fluorobiphenyl (**1a**) as a model substrate, we discovered an efficient nickel and copper cocatalyst system[16] that suited our purpose (Tables 1 and S1−S6[17]). Heating the mixture of **1a**, bis(pinacolato)diboron (**2a**, $(Bpin)_2$, 2.0 equiv), $Ni(cod)_2$ (10 mol %), PCy_3 (50 mol %), CuI (20 mol %), and CsF (2.4 equiv) in toluene at 80 °C for 20 h afforded the desired defluoroborylated product **3a** in high yield (entry 1). The use of copper sources other than CuI led to poor results (entries 2−5 and 11). Using 3.0 equiv of CsF provided the best result

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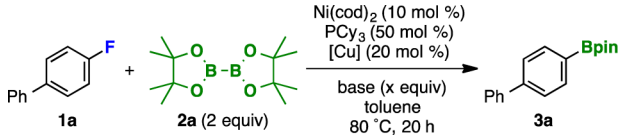
Table 1. Optimization of Reaction Conditions



entry	[Cu]	base	x	yield **3a** (%)[a]
1	CuI	CsF	2.4	89
2	CuBr	CsF	2.4	5
3	CuCl	CsF	2.4	1
4	CuOAc	CsF	2.4	<1
5	CuF_2	CsF	2.4	4
6	CuI	CsF	3.0	>99 (99)[b]
7	CuI	KF	3.0	0
8	CuI	TBAF	3.0	0
9	CuI	KO*t*-Bu	3.0	<1
10	CuI	Cs_2CO_3	3.0	0
11	none	CsF	3.0	3
12	CuI	none		0
13[c]	CuI	CsF	3.0	0

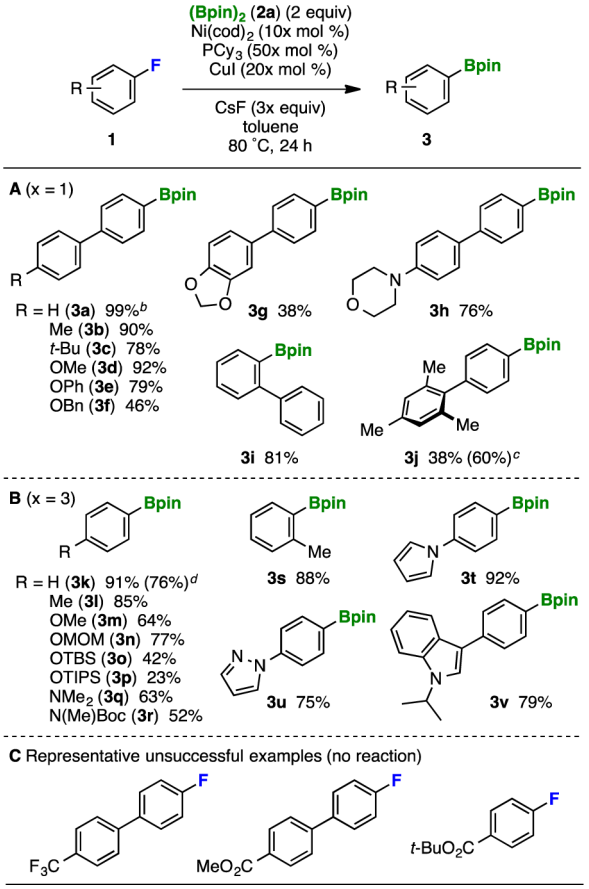
[a]Yields determined by GC analysis, unless otherwise noted. [b]Isolated yield in parentheses. [c]Reaction performed without PCy_3.

(entry 6), and the choice of CsF as the base was also crucial (entries 7−10 and 12). Performing the reaction without PCy_3 or using other ligands instead resulted in poor yields of **3a** (entry 13 and Table S1[17]). Furthermore, defluoroborylation of **1a** using bis(neopentyl glycolato)diboron (**2b**) instead of $(Bpin)_2$ (**2a**) under the optimal conditions did not afford the borylated product, which is in stark contrast to a related Ni(0)-catalyzed borylation of fluoroarenes recently reported by Martin and co-workers.[9]

The optimal conditions were applicable to other fluoroarenes (Table 2). Substituted 4-fluorobiaryls, bearing an electron-donating group at the 4′-position, participated in the reaction to afford defluoroborylated products **3b−h** in moderate to high yields (Table 2, condition A). Although the C−O bond in aryl ethers[18] or the C−N bond in aniline derivatives[19] can potentially be cleaved by Ni(0) complexes, borylation via C−F bond cleavage proceeded faster in our case, demonstrating high chemoselectivities. Defluoroborylation of 2-fluorobiphenyl efficiently provided product **3i**, irrespective of the steric hindrance of the 2-phenyl group. The reaction of 4-mesitylphenyl fluoride afforded desired product **3j** in a lower yield than other biaryl fluorides, indicating that substrates with extended π-systems are favorable for this transformation. A similar trend was reported for nickel-catalyzed transformations via cleavage of chemically stable bonds, such as C−O bonds.[14,18e,20]

A threefold increase in the amounts of the catalysts and base enabled expansion of the method to monoaryl fluorides (Table 2, condition B and Table S7[17]). Under the modified conditions, a variety of fluoroarenes, including 2- or 4-fluorotoluene, protected 4-fluorophenols, and 4-fluoroaniline derivatives, underwent defluoroborylation, providing borylarenes **3k−s** in moderate to high yields. The yield of **3j** was also largely improved. Notably, fluoroarenes bearing a pyrrole, pyrazole, or indole ring, which are often found in bioactive compounds, also participated in the reaction, affording boronates **3t**, **3u**, and **3v**, respectively, in high yields. Unexpectedly, substrates with an electron-withdrawing group, such as a trifluoromethyl or ester

Table 2. Defluoroborylation of Fluoroarenes[a]



[a]Isolated yields are shown. [b]Reaction time was 20 h. [c]The yield of **3j** under condition B (x = 3) in parentheses. [d]The yield of **3k** under condition A (x = 1) in parentheses.

group, showed unusually low reactivity without producing the desired defluoroborylated product (Table 2C and Figure S1[17]).

Since oxidative addition of electron-deficient haloarenes to Ni(0) complexes generally proceeds faster than that for electron-rich haloarenes,[21] we currently anticipate that the active catalyst contributing to the C−F bond cleavage is not a simple Ni(0)-phosphine complex, but a Ni(I) complex,[20c] which must have been generated via oxidation of Ni(0) with Cu(I) (Scheme 2a). In this mechanism, Ni(I) fluoride **B** is generated via the one-electron oxidation of Ni(0) complex **A** with CuI.[22] Subsequently, transmetalation of **B** with borylcopper complex **C**, which is formed in situ, affords borylnickel(I) complex **E**, which cleaves the C−F bond of fluoroarene **1** to form arylnickel(I) complex **F**. Finally, borylation of **F** with $(Bpin)_2$ (**2a**) affords desired product **3** with regeneration of **E**. This Ni(I)-catalyzed mechanism was also supported by other experimental results and some preliminary attempts to gain insight into the reaction mechanism. For example, we observed that **3a** was not produced at all for the first few hours under the optimized conditions for defluoroborylation of **1a** with **2a** (Table 3). The observed induction period possibly results from the time required for the generation of **E**. Indeed, a cocktail prepared separately by heating a mixture of $Ni(cod)_2$, PCy_3, CuI, and CsF in toluene at 80 °C for 20 h effectively promoted the defluoroborylation of **1a** with **2a** to afford **3a** after stirring at 80 °C for several hours (Table 4). These results demonstrate that

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Scheme 2. Possible Reaction Mechanisms

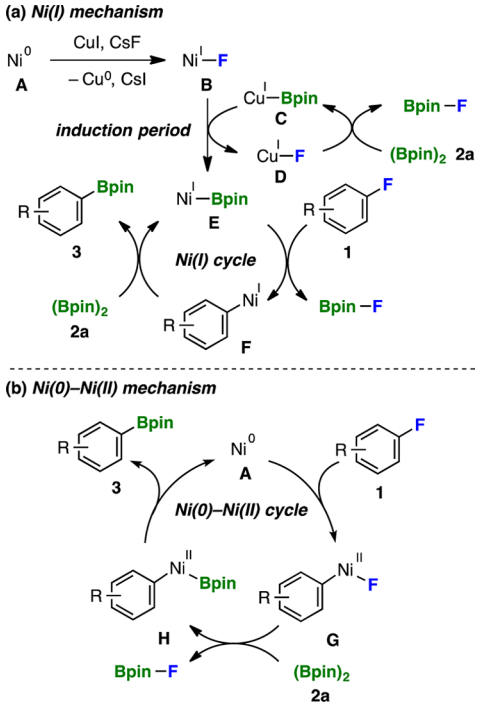
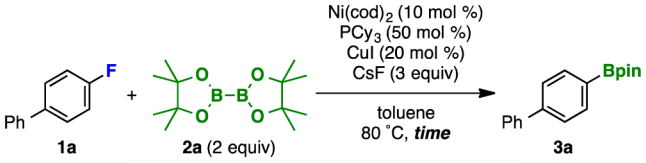


Table 3. Time Course of the Yield of 3a



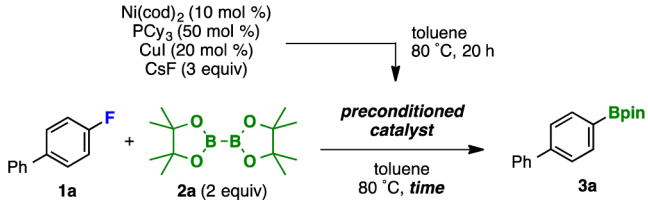
entry	time (h)	yield **3a** (%)[a]
1	2	0
2	4.5	0
3	6	0
4	9	0
5	10	4
6	20	>99

[a]Yields determined by GC analysis.

preheating of the catalyst is effective for eliminating the induction period by generating the active catalyst.

We also observed that defluoroborylation of **1a** efficiently proceeded using a preconditioned Ni catalyst, which was separately prepared as a "Ni(I) complex" by mixing Ni(0) and Ni(II) complexes with PCy_3 in THF at room temperature, followed by evaporation of the solvent (Table 5, entry 5).[23] The reaction using this separately prepared catalyst showed an induction period (entries 1–4) similar to that for the reaction under the standard conditions, indicating that the ligand exchange step (**B** to **E** in Scheme 2a) to afford borylnickel(I) complex **E**, which we consider to be the active catalyst, requires a high activation energy for its generation. Furthermore, even using this separately prepared Ni catalyst, CuI was essential for the successful defluoroborylation, which agreed with our hypothesis assuming the Cu-mediated generation of borylnickel(I) complex **E** (Table 5, entry 6). Although we cannot currently provide the direct evidence for the involvement of borylnickel(I) complex **E** in the C–F bond cleavage of **1** (**1** to **F** in Scheme 2a), a similar transformation,

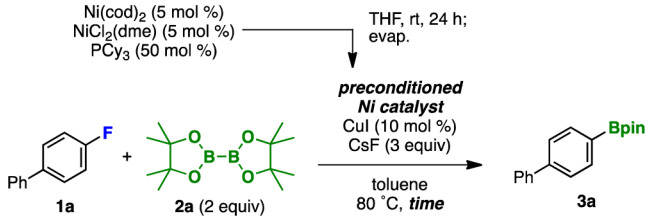
Table 4. Time Course of the Yield of 3a Using the Preconditioned Catalyst



entry	time (h)	yield **3a** (%)[a]
1	2	1
2	4	23
3	6	34
4	8	71

[a]Yields determined by GC analysis.

Table 5. Defluoroborylation Using the Ni Catalyst Prepared Separately from Ni(0) and Ni(II)



entry	time (h)	yield **3a** (%)[a]
1	1	0
2	2	0
3	6	0
4	7.5	27
5	24	71
6[b]	24	1

[a]Yields determined by GC analysis. [b]Reaction performed without CuI.

cleavage of the stable Ar–OMe bonds with a silylnickel(I) complex to afford arylnickel(I) compounds, was proposed with support from experimental and theoretical studies.[20c] Additionally, we could not disregard the contribution of Cu(I) to the Ni cycle after initiation.

A conventional cross-coupling mechanism involving C–F bond cleavage via oxidative addition of **1** to Ni(0) is also possible (Scheme 2b).[9] In this mechanism, the oxidative addition step (**A** + **1** to **G**) would have to overcome a high barrier in order to proceed, whereas the subsequent transmetalation (**G** + **2a** to **H**)[24] and reductive elimination (**H** to **A** + **3**) could occur much more easily. However, our results showed that the defluoroborylation did not proceed with electron-deficient arenes (Table 2C and Figure S1[17]), which are generally the preferred substrates for oxidative addition of C–X bonds.[21] Although we could not explain the exact role of CuI in this mechanism, these results indicate that the simple oxidative addition step is unlikely to contribute to the C–F bond cleavage.

Alternatively, a radical mechanism involving a single-electron transfer (SET) from Ni(0) complex **A** to **1** to afford a radical anion species is conceivable (Scheme S1[17]). In this scheme, cleavage of the C–F bond occurs to generate aryl radical, followed by borylation with **2a** to give desired product **3**.[25] To evaluate the probability of this mechanism, we conducted the defluoroborylation in the presence of radical scavengers.

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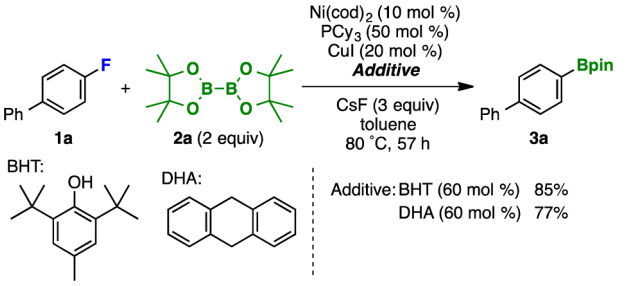
Consequently, the reaction in the presence of 60 mol % of 2,6-di-*tert*-butyl-4-methylphenol (BHT) or 9,10-dihydroanthracene (DHA) proceeded with comparable efficiency to that without radical scavengers (Scheme 3),[26] suggesting that a mechanism

Scheme 3. Defluoroborylation in the Presence of Radical Scavengers



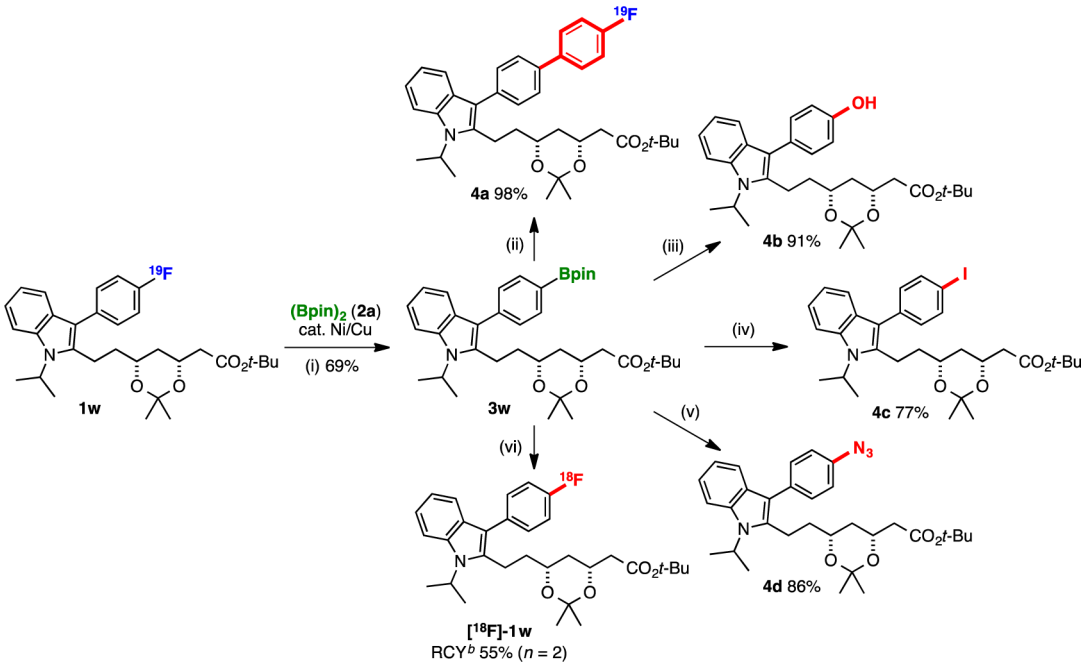
involving the free radical species is improbable. Although further mechanistic studies are required, these experimental results suggested that the defluoroborylation proceeds via C−F bond cleavage by a Ni(I) complex.

The synthetic utility of the defluoroborylation reaction was considerably enhanced by organoboron chemistry, as demonstrated by several formal C−F bond functionalizations of dihydrofluvastatin derivative **1w** (Scheme 4). Thus, Ni/Cu-catalyzed defluoroborylation of **1w** proceeded efficiently under the standard conditions to afford boronic ester **3w** in 69% isolated yield,[27] which served as a common intermediate for further transformations. For example, Suzuki−Miyaura cross-coupling[28] of **3w** with 1-fluoro-4-iodobenzene afforded phenylogous fluoroarene **4a** in excellent yield. Transformations of the C−B bond of **3w** into various C−heteroatom bonds, such as C−O,[29] C−I,[30] and C−N[31] were also achieved efficiently under oxidative conditions to afford hydroxy-, iodo-, and azido-functionalized derivatives **4b**, **4c**, and **4d**, respectively. The two-step conversion of a fluoroarene to an azidoarene would be a useful method for the development of photoaffinity labeling probes for identification of target proteins,[32] as well as further diversification through the use of click chemistry.[33] Moreover, using the recently reported copper-mediated method,[7] boronate **3w** was successfully transformed into ^{18}F-labeled compound [^{18}F]-**1w**.[34,35] Because short-lived ^{18}F ($t_{1/2}$ = 110 min) must be introduced in the last stage of synthesis, precursors of ^{18}F-labeled PET probes are generally prepared via a different synthetic route from that of the nonradioactive ^{19}F-containing compounds. Our defluoroborylation approach that enables the two-step preparation of precursors will facilitate the development of useful ^{18}F-labeled PET probes for the diagnosis of various diseases and evaluation of drug candidates in the early stages of drug development.[1c,8,36]

CONCLUSIONS

We have developed an efficient synthetic method for borylarenes from fluoroarenes via Ni/Cu-catalyzed C−F bond cleavage. In combination with versatile borylarene transformations, this method has enabled a variety of formal C−F bond functionalizations of a fluoroarene, involving formation of C−C, C−O, C−I, and C−N bonds. The two-step isotope-exchange of ^{19}F- to ^{18}F-fluoroarene has also been achieved, enabling expeditious preparation of ^{18}F-labeled PET probes. Further investigations, including detailed mechanistic studies, expansion of the substrate scope, and application to PET imaging research, are currently underway in our group.

Scheme 4. Versatile C−F Bond Functionalizations of Dihydrofluvastatin Derivative 1w via Defluoroborylation[a]



[a]Reagents and conditions: (i) condition B (Table 2); (ii) 1-fluoro-4-iodobenzene, $Pd(PPh_3)_4$, Cs_2CO_3, toluene, H_2O, 100 °C, 12 h; (iii) H_2O_2, NaOH, H_2O, rt, 50 min; (iv) NaI, chloramine-T, THF, H_2O, 70 °C, 3 h; (v) NaN_3, $Cu(OAc)_2$, MeOH, 50 °C, 8 h; (vi) $Py_4Cu(OTf)_2$, [^{18}F]KF/K_{222}, 110 °C, 20 min. For details, see the Supporting Information. [b]RCY indicates the radiochemical yield calculated via radio-TLC of the reaction mixture.

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■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.5b10119.

Experimental procedures, characterization for new compounds including copies of NMR spectra, and HPLC chromatograms for characterization of [^{18}F]-**1w** (PDF)

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Notes

The authors declare no competing financial interest.

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