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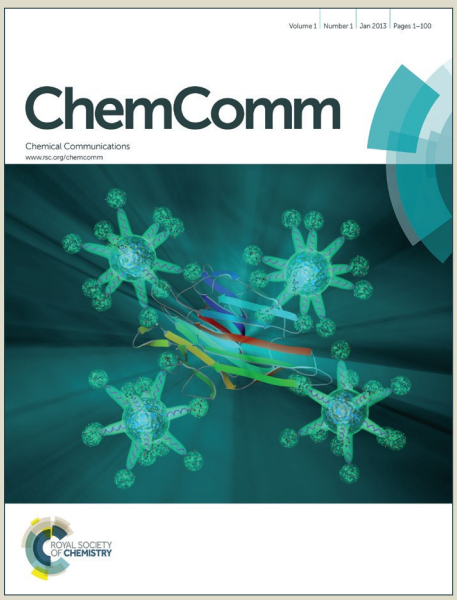

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Direct Heptafluoroisopropylation of Arylboronic Acids via Hexafluoropropene (HFP)

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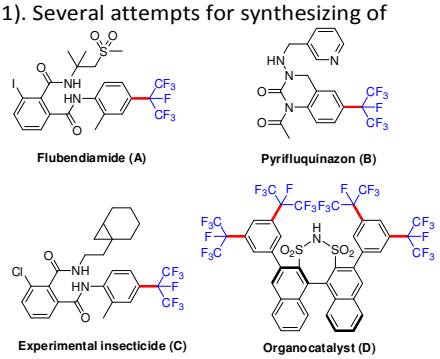
A novel and straightforward strategy for heptafluoroisopropylation of arylboronic acids at room temperature has been developed. This method, directly using commercial available hexafluoropropene (HFP) as the starting material, provides a new way to a variety of synthetically useful heptafluoroisopropylated arenes.

Perfluoroalkylated arenes play a unique role in the field of modern pharmaceuticals, agrochemicals and functional materials.[1] Among them, heptafluoroisopropylated arenes, in spite of showing better performances than trifluoromethylated arene in some cases[2], are still severely underexploited compared to their analogues. For instances, Flubendiamide (compound **A**)[2a] and Pyrifluquinazon (compound **B**)[2b] are commercial available insecticides with excellent activity against a broad-spectrum pests, and compound **C**[2c] is a potential insecticide. Meanwhile, heptafluoroisopropylated arenes can be applied to the development of organocatalysts with better selectivity and yield (compound **D**) [2d] and also have potential applications in the field of liquid crystal[2e].

Although many new methds for introducing triflromethyl group onto organic molecules are reported in recent years,[3] but the methods for heptafluoroisopropylation of organic compounds are rarely reported. The traditional means for introducing a heptafluoroisopropyl group (*i*-C_3F_7) onto an aromatic ring rely on Sulfinatodehalogenation reaction[4] and Ullmann reaction[5] using heptafluoroisopropyl iodide or bromide, which is synthesized from hexafluoropropene (HFP) (Scheme 1). Several attempts for synthesizing of



heptafluoroisopropylated arenes are repoeted. For instances, Burton et al. realized the synthesis of heptafluoroisopropyl copper(I) from heptafluoroisopropyl iodide with the assistance of cadmium.[6] But the copper species show no reactivity to halogenated arenes. Hu's group has described a method for trifluoromethylation–iodination of arynes promoted by silver.[7a] However, the intermediate heptafluoroisopropyl silver reagent decomposed when 1,10-phenanthroline was added as a ligand, even before the difunctionalization of arynes.[7b] Moreover, described by Hirano and Uchiyama, heptafluoroisopropyl zinc reagents failed in heptafluoroisopropylation of *ortho*-iodobenzoate.[8] Grushin's group reported great successes in cupration of CF_3H[9] and C_2F_5H[10]. But this method met its limitation when tried the cupration of *i*-C_3F_7H, which might be used to synthesize heptafluoroisopropylated arenes. There are only very few other successful examples to heptafluoroisopropylated arenes[11-15]. For examples, Ishikawa et al. described a method to form heptafluoroisopropylated arenes under ultrasonic irradiation condition from heptafluoroisopropylhalide.[11] Chen et al. reported a synthetic route to heptafluoroisopropylated arenes *via* pre-prepared copper complexes from heptafluoroisopropylhalide.[12]

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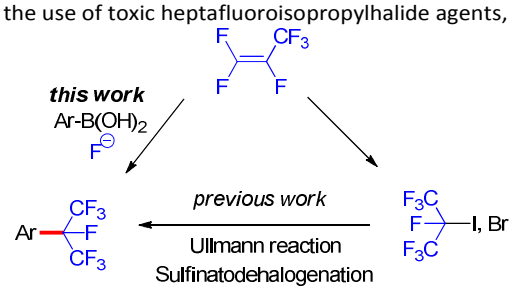
Despite the progress in the synthesis of heptafluoroisopropylated arenes, the known methods suffer from the use of toxic heptafluoroisopropylhalide agents,



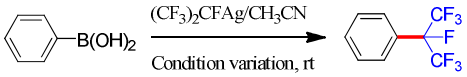
Scheme 1 Synthesis of Heptafluoroisopropylated Arenes Derived from Hexafluoropropene.

narrow substrate scope, poor regioselectivity, and harsh conditions. Therefore, it is urgent to develop new methods to address these problems. Herein, we report the facile synthesis of heptafluoroisopropylated arenes directly from inexpensive and readily available hexafluoropropene, *a fire fighting agent*.[16]

Hexafluoropropene and other fluorinated olefins can react with fluoride to form heptafluoroisopropyl carbanion directly.[1b,f-g] This is the most convenient and economical way to obtain heptafluoroisopropyl carbanion. Based on this unique reactivity, we consider developing a method to synthesize heptafluoroisopropylated arenes directly from hexafluoropropene. However, the stability of heptafluoroisopropyl carbanion reagent needs to be considered, because most heptafluoroisopropyl–metal species are very unstable, even at very low temperature.[17] To the best of our knowledge, only heptafluoroisopropyl silver[17e] and heptafluoroisopropyl mercury[17b] have been reported with relative stability from the reaction between hexafluoropropene and fluoride. A viable methodology will not use highly toxic mercury reagent. Thus, we envisioned that the heptafluoroisopropyl silver reagent would be a good choice for the synthesis of heptafluoroisopropylated arenes.

The reaction was initiated with phenylboronic acid[18], HFP and silver fluoride (Table 1, for details please see Supporting Information). Heptafluoroisopropyl silver reagent could be easily obtained by nucleophilic addition of silver fluoride to hexafluoropropene in acetonitrile and this reagent was relatively stable at room temperature.[17e] Thus, after the heptafluoroisopropyl silver reagent was generated in situ, phenylboronic acid was added to the reaction mixture at room temperature. But no heptafluoroisopropylbenzene was observed (Table 1, entry 1). It should be noted that no additional oxidant was used in this reaction because the silver species formed *in situ* may play as oxidants.[19] Trace amount of expected product was observed when CuI was added (Table 1, entry 2). This result indicated that the copper species might be the crucial to the success of the reaction. The addition of 1,10-Phen ligand however, didn't improve the yield (Table 1, entry 3).[7b] To our delight, when DMF (2 mL) was added, the desired heptafluoroisopropylated product was obtained in 25% yield based on ^{19}F NMR spectroscopy, implying that the use of DMF as a solvent is essential to this reaction (Table 1, entry 4). The product yield could be further improved to 50% by the removal of acetonitrile *via* evaporation before adding DMF (Table 1,

Table 1 Condition Optimization[a]



1a **2a**

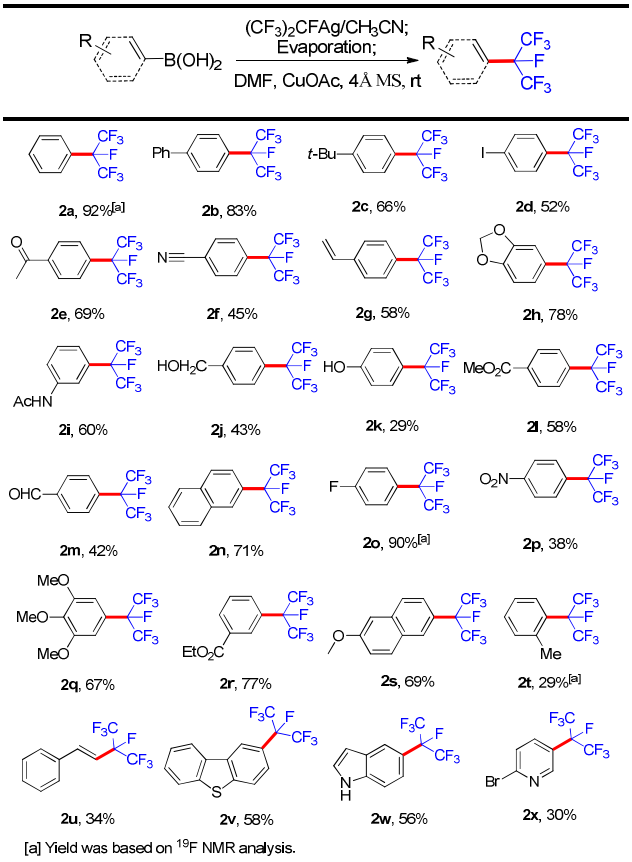
Entry	Condition Variation	Yield[b](%)
1	None	0
2	Addition of CuI[c]	Trace
3	Addition of CuI[c] and Phen[c]	Trace
4	Addition of DMF[d] and CuI[c]	25
5	Evaporation; Addition of DMF[d] and CuI[c]	50
6	Evaporation; Addition of DMF[d] and $[Cu(OTf)]_2{\cdot}PhH$[e]	18
7	Evaporation; Addition of DMF[d] and CuCl[c]	15
8	Evaporation; Addition of DMF[d] and $Cu(CH_3CN)_4BF_4$[c]	14
9	Evaporation; Addition of DMF[d] and CuOAc[c]	86
10	Evaporation; Addition of DMF[d], CuOAc[c] and 4Å MS[f]	92
11	Evaporation; Addition of DMF[d], CuOAc[c] and 4Å MS[f]	84[g]
12	Evaporation; Addition of DMF[d], CuOAc[c] and 4Å MS[f]	74[h]
13	Evaporation; Addition of DMF[d], CuOAc[c] and 4Å MS[f]	77[i]
14	Evaporation; Addition of DMF[d], CuOAc[j], TBAOAc[c] and 4Å MS[f]	Trace
15	Evaporation; Addition of DMF[d], CuOAc[c] and 4Å MS[f]	0[k]

[a] Reaction condition: at room temperature, 0.2 mmol of phenylboronic acid was added to 2.0 equiv. of silver reagent in 4 ml of CH_3CN. [b] Yields were based on ^{19}F NMR with $PhCF_3$ as an internal standard. [c] 1.0 equiv. [d] DMF (4 ml). [e] 0.5 equiv. [f] 50 mg. [g] The reaction was carried out at 0 °C. [h] The reaction was carried out at 35 °C. [i] Phenylboronic acid was added dropwise. [j] 0.2 equiv. [k] PhBpin was used instead of $PhB(OH)_2$.

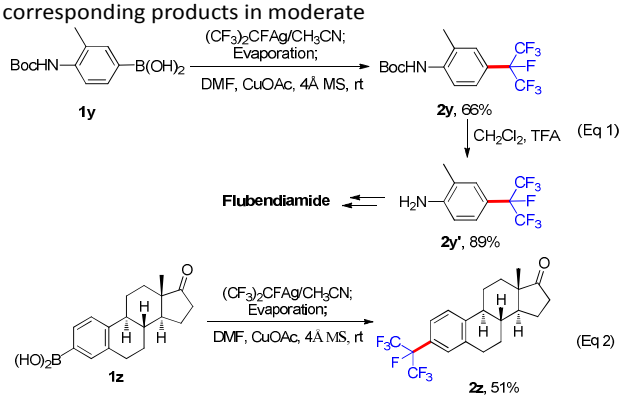
entry 5).[20] Several other copper species were also screened, such as $[Cu(OTf)]_2{\cdot}PhH$ (Table 1, entry 6), CuCl (Table 1, entry 7), $Cu(CH_3CN)_4BF_4$ (Table 1, entry 8), but none of them showed better performances than CuI. Surprisingly, when CuOAc was employed, the product yield was significantly improved to 86% yield (Table 1, entry 9). The yield was further improved to 92% when 4Å MS was used (Table 1, entry 10).[21] It was found that the reaction is favored at room temperature. When the reaction temperature was switched to either 0 °C or 35 °C, a slight drop of yield was observed (Table 1, entries 11 and 12).

Furthermore, slow addition of phenylboronic acid resulted in a descended yield (Table 1, entry 13).[19d] Trace amount of product was detected when catalytic amount of copper was used, even when DMF was used as the solvent (Table 1, entry 14). When phenylboronic acid pinacol ester was employed, instead of phenylboronic acid, no heptafluoroisopropylated product was detected (Table 1, entry 15).

Scheme 2 Heptafluoroisopropylation of Various Arylboronic Acid Derivatives.



With the optimal reaction conditions in hand, the substrate scope was then explored (Scheme 2). We were pleased to find that a series of arylboronic acid derivatives were heptafluoroisopropylated under this conditions. The arylboronic acid derivatives bearing either electron-donating or electron-withdrawing groups reacted smoothly to form the corresponding heptafluoroisopropylated arenes in moderate to good yields. Of note, the halides (**2d** and **2o**) were survived under the reaction conditions, which might be useful for further manipulations. The carbonyl group likely reacts with silver reagent directly to form heptafluoroisopropylated alcohol.[22] However, in this reaction the carbonyl functionalities could be tolerated, as indicated by the isolation of **2e** and **2m**, in good yields. Remarkably, reactions of substrates with unprotected hydroxyl group afforded the desired products **2j** and **2k** in acceptable yields, respectively. Notably, vinyl group that is prone to oxidation was compatible with the reaction conditions (**2g**). Substrate with an *ortho*-methyl group could give the desired product with a relatively low yield, presumably due to the steric effect (**2t**). Furthermore, vinylboronic acid could afford the desired product with a descended yield (**2u**). For heteroarylboronic acid substrates, benzothiophene (**2v**) and indole (**2w**) could give the corresponding products in moderate yields, respectively. Substrate with a pyridine moiety only offered a low yield of product **2x**, probably due to the coordination of the pyridine.

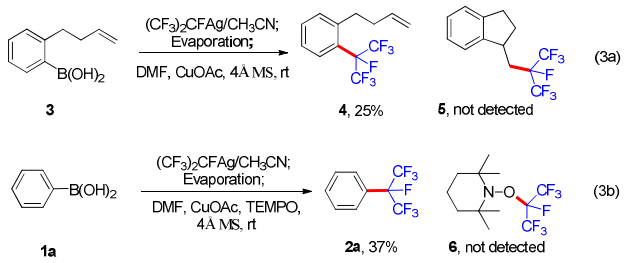


By our strategy, product **2y'**, an important intermediate for the synthesis of flubendiamide, could also be obtained in high yield by heptafluoroisopropylation of arylboronic acid **1y** and successive deprotection of the Boc group (Eq 1). Furthermore, substrate **1z** derived from estrone could also be converted to the heptafluoroisopropylated product with a moderate yield (Eq 2).

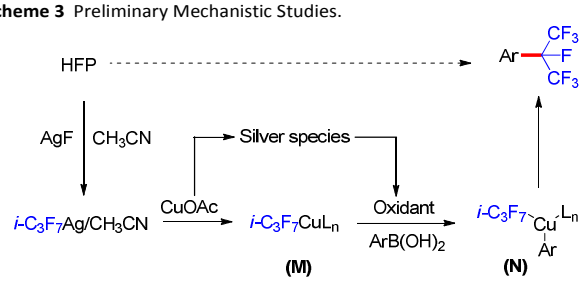
To demonstrate the practical utility of this heptafluoroisopropylation strategy, some enlarged reactions for substrate **1r** and **1y** were conducted, the corresponding products were obtained in satisfied yield (**2r**: 1.2 mmol, 232.8 mg, 74%; 6 mmol, 1.164g, 61%; **2y**: 0.97 mmol, 244 mg, 69%).

Preliminary studies have been conducted to elucidate the reaction mechanism. The reaction promoted by copper species might involve free radical pathways.[23] Thus, a radical clock substrate **3** was employed as a probe for the mechanism (Scheme **3a**).[24] Only normal heptafluoroisopropylated product **4** was isolated and the cyclized product **5** formed by radical pathway was not observed. The reaction proceeded smoothly when TEMPO (2,2,6,6-tetramethyl-1-piperidinyloxy) was added as a free radical scavenger (Scheme 3b).[25] And no heptafluoroisopropylated compound **6** was detected. These results suggest that a radical pathway may not be involved in the reaction.

On the basis of these mechanism studies and reported reference,[26] a plausible reaction mechanism was proposed as shown in Scheme 4. The reaction of HFP with AgF formed the heptafluoroisopropylated silver species, which underwent transmetalation to form the reactive heptafluoroisopropylated



Scheme 3 Preliminary Mechanistic Studies.



Scheme 4 Plausible Reaction Mechanism.

copper reagent (**M**) and silver species.[19] These silver species might serve as oxidants in the following step. Then, oxidized by silver species, copper reagent underwent transmetalation with arylboronic acid to form an intermediate **N**. Finally, reductive elimination released the heptafluoroisopropylated product.

In conclusion, we have developed the first heptafluoroisopropylation reaction of arylboronic acids utilizing hexafluoropropene (HFP), a fire fighting and readily available agent, directly. This reaction occurred at room temperature and tolerated a series of arylboronic acid derivatives bearing both electron-donating and electron-withdrawing groups. Further investigations on the synthetic application and the mechanism of this method are currently ongoing in our laboratory.

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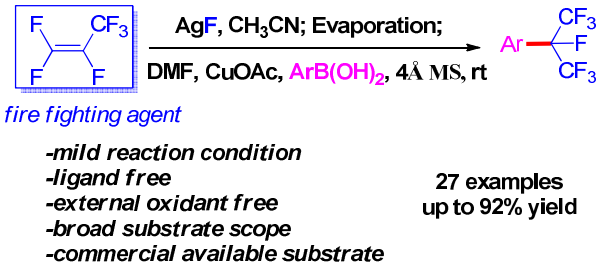
Graphical Abstract



ABSTRACT: A novel and straightforward strategy for heptafluoroisopropylation of arylboronic acids under mild reaction condition has been developed, directly using hexafluoropropene (HFP), a fire fighting and readily available agent. This method provides a new way to synthesize a variety of synthetically useful heptafluoroisopropylated arenes. No extra oxidant was used in this reaction.