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Copper-mediated pentafluoroethylation of organoboronates and terminal alkynes with $TMSCF_3$†

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The $TMSCF_3$-derived $CuCF_2CF_3$ species has been successfully applied in pentafluoroethylation of organoboronates and terminal alkynes. By using 1,10-phenanthroline as a ligand, a broad range of (hetero)arylboronates and alkenylboronates were smoothly pentafluoroethylated under aerobic conditions. Furthermore, terminal alkynes can undergo aerobic cross-coupling with the $TMSCF_3$-derived $CuCF_2CF_3$ species in the absence of additional ligands.

Pentafluoroethyl-containing compounds have found applications in medicinal and pharmaceutical chemistry. For instance, Dup 532, which contains a pentafluoroethylated imidazole ring, is a more effective angiotensin II receptor antagonist than its nonfluorinated analogue Dup 753 when taken orally.[1] Moreover, pentafluoroethyl substituted compounds have demonstrated higher bioactivity and better lipophilicity than their trifluoromethylated analogues.[2] However, compared with extensively studied trifluoromethylation, the efficient synthesis of pentafluoroethylated compounds is still underexploited due to the limitation of available pentafluoroethyl sources. Nowadays, most commonly-used pentafluoroethylation methods are mainly derived from C2-building blocks, including (1) nucleophilic pentafluoroethyl anion equivalences, such as $Zn(CF_2CF_3)_2$,[3] $TMSCF_2CF_3$,[4] HCF_2CF_3,[5] and pentafluoropropionate acid derivatives;[6] (2) electrophilic pentafluoroethylation reagents, such as pentafluoroethyl hypervalent iodine reagents,[7] Umemoto type reagents,[8] CF_3CF_2I[3,9] and $CF_3CF_2SO_2Na$;[10] (3) the pentafluoroethyl anion *in situ* generated from fluoride ions and tetrafluoroethylene.[11] These reagents always suffer from limitations such as poor availability, high cost and/or difficulty in handling. Therefore, the development of a new pentafluoroethylation method using readily available reagents is highly desirable.

In 2018, our group reported the controllable generation of $CuCF_2CF_3$ species from readily available $TMSCF_3$, proceeding through *in situ* generation of $CuCF_3$ followed by selective insertion of one difluoromethylene into the Cu–C bond. The so-generated $CuCF_2CF_3$ species has been applied to cross-coupling reactions with a broad scope of aryl iodides in moderate to excellent yields.[12] In 2019, a similar pentafluoroethylation process was reported by Boutureira and coworkers.[13] In the past decade, oxidative fluoroalkylation has become an important strategy for the synthesis of organofluorine compounds.[14] However, oxidative pentafluoroethylation with $TMSCF_3$-derived $CuCF_2CF_3$ species has never been explored. Previously, copper-mediated oxidative pentafluoroethylation was mainly performed with arylboronates or arylboronic acids and various nucleophilic C2 reagents,[3b,4e,5a] and witnessed limited success on heteroaromatic substrates.[7a,15] Herein, as an extension of our interest in the chemistry of controllable fluorocarbon chain elongation,[12,16] we report copper-mediated oxidative pentafluoroethylation using $TMSCF_3$ as the sole fluorocarbon source (Scheme 1c), which is applicable to a broad variety of nucleophilic substrates including heteroaryl boronates, alkenylboronates, and acetylenes.

Initially, we evaluated the reactivity of DMF/pyridine solution of $TMSCF_3$-derived $CuCF_2CF_3$ ($CuCl/TMSCF_3/KF$)[12] in the coupling with arylboronate **1a** under aerobic conditions at 50 °C. In the absence of additional ligands and bases, the pentafluoroethylated product **2a** was obtained only in 29% yield along with diphenyl and 4-chlorobiphenyl as the major byproducts (Table 1, entry 1). Obviously, chloride ions introduced during the generation of $CuCF_2CF_3$ resulted in the formation of 4-chlorobiphenyl. Therefore, we tried to add AgF to abstract the chloride ions as well as the activator of the substrate (entry 2). To our delight, the yield was improved with the addition of AgF. Moreover, the ready oxidative chlorination of **1a** indicates that $TMSCF_3$-derived $CuCF_2CF_3$ is of relatively low reactivity, which probably arises from the inhibition effect of pyridine used in the

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† Electronic supplementary information (ESI) available: More detailed results of pentafluoroethylation of aryl/heteroaryl boronates and acetylenes, spectroscopic data and copies of ^1H, ^{13}C and ^{19}F NMR spectra. See DOI: 10.1039/d2cc00975g

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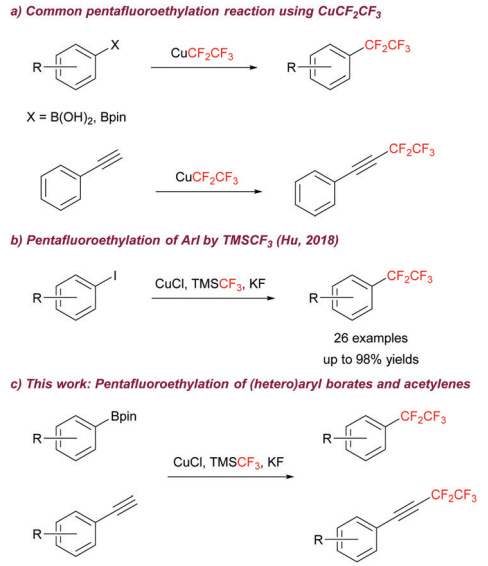
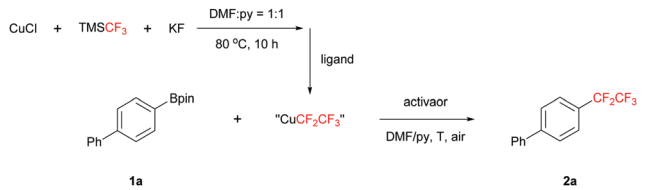


Scheme 1 Methods of realizing the pentafluoroethylation of aryl compounds and acetylenes.

Table 1 Survey of reaction conditions for pentafluoroethylation of arylboronate **1a**[a]



Entry	Ligand	Activator (equiv.)	T (°C)	**2a**[b] (%)
1[c]	—	—	50	29
2[c]	—	AgF (3.0)	50	45
3	phen	AgF (3.0)	50	69
4	2,2′-Bipyridine	AgF (3.0)	50	65
5	TMEDA	AgF (3.0)	50	39
6	BINAP	AgF (3.0)	50	31
7	phen	K_2CO_3 (3.0)	50	58
8	phen	NaO^{t}Bu (3.0)	50	22
9	phen	NaOAc (3.0)	50	58
10	phen	KF (3.0)	50	65
11	phen	AgF (4.0)	50	72
12[d]	phen	AgF (4.0)	50	70
13[d]	phen	AgF (4.0)	80	69
14[d]	phen	AgF (4.0)	30	58
15[de]	phen	AgF (4.0)	50	72
16[f]	phen	AgF (4.0)	50	70

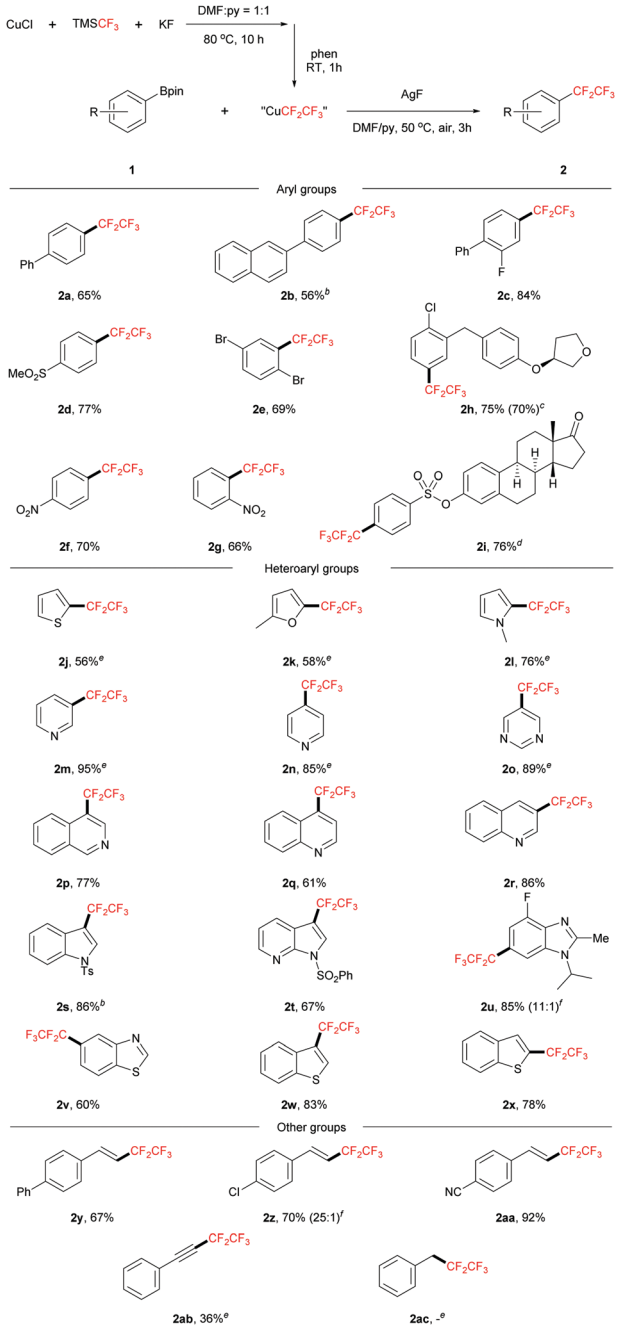
[a] Reaction conditions: $CuCF_2CF_3$ was prepared from $TMSCF_3$ (1.500 mmol), KF (1.500 mmol), CuCl (2.250 mmol), DMF (3.0 mL) and pyridine (3.0 mL) at 80 °C for 10 h, and used after filtration. Prepared $CuCF_2CF_3$ (2.4 equiv.), ligand (0.750 mmol, 11.2 equiv.), RT, 1 h. Then **1a** (0.067 mmol, 1.0 equiv.), 50 °C, 3 h, air. For details, see (ESI). [b] Yields were determined by ^{19}F NMR spectroscopy using $PhCF_3$ as the internal standard. [c] Without ligand. [d] 0.267 mmol of phen (4.0 equiv.) was used. [e] O_2 balloon was used. [f] $CuCF_2CF_3$ was prepared from CuCl (0.750 mmol), KF (0.500 mmol), $TMSCF_3$ (0.500 mmol), DMF (1.0 mL) and pyridine (1.0 mL) at 80 °C for 10 h, and used after filtration. Then adding the phen (0.267 mmol, 4.0 equiv.) at rt for 1 h, followed by reaction with **1a** (0.067 mmol, 1.0 equiv.) at 50 °C for 3 h under the air. phen = 1,10-phenanthroline; py = pyridine.

generation of $CuCF_2CF_3$. Thus, a series of additional ligands were scanned with AgF as both the activator of substrate **1a** and the abstractor of chloride ions (entries 3–6). Among the *N*,*N*- and *P*,*P*-bidentate ligands, 1,10-phenanthroline (phen) showed the highest improvement in yield (entry 3). The influence of other activators was also examined. The reaction proceeded well when K_2CO_3, NaOAc and KF were used (entries 7, 9 and 10), among which, KF gave the best result, with product **2a** being formed in only slightly lower yield than that of AgF. Further screening of the equivalents of phen revealed that AgF was more suitable for the reaction conditions (for details, see the ESI†). Moreover, increasing the equivalence of AgF led to the disappearance of a small amount of impurities in the ^{19}F NMR (entry 11). And the equivalence of phen could be reduced when preparing the solution of $CuCF_2CF_3$ (entry 12). Subsequently, we also examined the influence of the reaction temperature. Raising the temperature to 80 °C gave **2a** in 69% yield (entry 13), while the yield of **2a** decreased to 58% when conducting the reaction at 30 °C (entry 14). Then, we tried to use the O_2 balloon to provide the oxidative environment. However, only a slight improvement in yield was observed (entry 15). Finally, when we used the $CuCF_2CF_3$ solution prepared directly at the scale of 0.50 mmol, the yield of the product could be maintained well (entry 16).

After optimizing the reaction conditions, we tried to test the substrate limitations (Table 2). To our delight, this method tolerated diverse functional groups, such as sulfone (**2d**), nitro (**2f**, **2g**) and halogen atoms (**2c**, **2e**). Obviously, the electron-deficient substrates showed slightly higher yields than the electron-rich ones. The bromide group, which is likely to be pentafluoroethylated, was well retained and potentially useful for further modifications (**2e**). The comparison between the products **2f** and **2g** showed the small influence of the steric effect. As for the complex molecules, this pentafluoroethylation method also worked well as the desired products were obtained in satisfactory yields (**2h**, **2i**). Even when the scale of the substrate was raised to 2.0 mmol, the desired product could still be obtained in moderate yield (**2h**). Besides, the vinylboronates were also compatible in the reaction conditions. Similarly, the vinylboronates with electron-withdrawing groups also provided higher yields (**2z**, **2aa**) than the vinylboronate with an electron-donating group (**2y**). However, there was a little chlorinated byproduct in the product in which the molar ratio was 25 : 1 (**2z**). Additionally, the pentafluoroethylation of ethynyl boronate provided a low yield of product (**2ab**), and the pentafluoroethylation of benzyl boronate was not successful under the standard reaction conditions (**2ac**).

The heteroaryl boronates were also examined (Table 2). To our pleasure, diverse heterocycles all provided the corresponding products with moderate to good yields, respectively. The heteroaryl boronates with simple structures, such as thiophene (**2j**), furan (**2k**), pyrrole (**2l**) and pyridine (**2m**, **2n**), could be well tolerated in these reaction conditions. The electron effect was demonstrated by the comparison of different substituted positions in the quinoline rings. The substitution of a boronate group in the 3-position (**2m**, **2r**) gave higher yields as compared with the products of the substitution in the 4-position (**2n**, **2q**). Interestingly, the different substituted positions of boronate groups in the

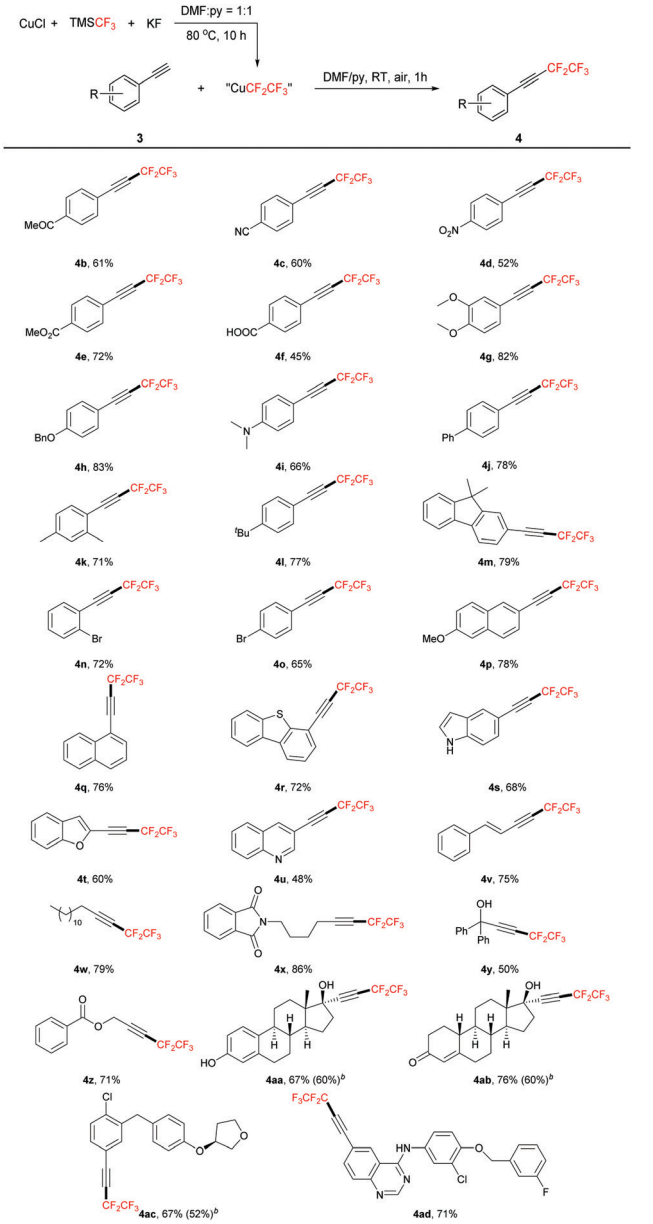
Table 2 Pentafluoroethylation of aryl/heteroaryl boronates with $TMSCF_3$-derived $CuCF_2CF_3$[a]



[a] Reaction conditions: **1** (0.4 mmol, 1.0 equiv.), CuCl (4.5 mmol, 11.2 equiv.), $TMSCF_3$ (3.0 mmol, 7.5 equiv.), KF (3.0 mmol, 7.5 equiv.), phen (1.6 mmol, 4.0 equiv.), AgF (1.6 mmol, 4.0 equiv.), air, 50 °C, 3 h. Isolated yields were given. [b] Reaction was conducted on 0.3 mmol scale. [c] When 2.0 mmol substrate was used, the isolated yield was given in the brackets. [d] Reaction was conducted on 0.2 mmol scale. [e] The yield was determined by ^{19}F NMR spectroscopy using $PhCF_3$ as an internal standard. [f] The molar ratio of the pentafluoroethylated product and the chlorinated byproduct is given in the brackets.

benzothiophenol showed limited influence (**2w**, **2x**). In addition, the reaction with a substrate bearing an isoquinoline cycle (**2p**) was also able to give the pentafluoroethylated product in good yield (77%). Besides, the substrates with pyrimidine (**2o**), indole (**2s**) and 7-azaindole (**2t**) also proceeded well to yield the desired products with moderate to good yields, respectively. The products bearing 1*H*-benzimidazole (**2u**) and benzothiazole (**2v**) moieties were also obtained in good yields despite the fact that the pentafluoroethyl groups were located in the aryl rings rather than the heterocycles.

Table 3 Pentafluoroethylation of terminal alkynes with $TMSCF_3$-derived $CuCF_2CF_3$[a]



[a] Reaction conditions: **3** (0.45 mmol, 1.0 equiv.), CuCl (2.25 mmol, 5.0 equiv.), $TMSCF_3$ (1.50 mmol, 3.3 equiv.), KF (1.50 mmol, 3.3 equiv.), air, RT, 1 h. Isolated yields are given. [b] Yields on the scale of 4.5 mmol are given in the brackets.

Considering the great importance of functionalized acetylenes,[17] we set out to examine the reaction conditions using phenylacetylene as the substrate after the pentafluoroethylation

of aryl/heteroaryl boronates. After the screening of a series of reaction conditions (for details, see the ESI†), the desired product could be obtained in 87% yield (Table 3).

With the optimized conditions in hand, we set out to examine the substrate scopes of this reaction. To our delight, diverse functional groups could be tolerated in this transformation due to the mild reaction conditions (room temperature, no strong base) and the corresponding products could be obtained in moderate to good yields, respectively. It is noteworthy that common functional groups, such as acetyl (**4b**), cyano (**4c**), nitro (**4d**), methyl ester (**4e**) and halogens (**4n**, **4o**) were all tolerated. The experimental results showed that the electronic effects of the substituents on the aromatic rings have small impacts on the pentafluoroethylation reactions. The corresponding products with electron-donating groups were obtained in moderate to excellent yields (**4g-4m**, **4p**, and **4q**), and the products with electron-withdrawing groups were obtained with similar yields (**4b-4f**, **4n**, **4o**). It should be noted that diverse kinds of heterocycles could be tolerated in the reaction conditions, such as benzothiophene (**4r**), unprotected indole (**4s**), benzofuran (**4t**) and quinoline (**4u**). Even the enyne was compatible in the reaction giving the corresponding product in 75% yield (**4v**). The reactions with diverse alkyl acetylenes (**4w-4z**) also showed the wide applicability of this pentafluoroethylation process. To our delight, substrates with active hydrogen, such as carboxyl (**4f**), secondary amine (**4s**, **4ad**), hydroxyl (**4aa**, **4ab**) or phenolic hydroxyl (**4y**), were compatible. This method could also be applied to the modification of substrates with complicated structures. For example, the pentafluoroethylation of the complex compound **4aa** could be achieved in 71% yield even though there is an unprotected –NH group and a heterocycle. Besides, the pharmaceutical molecules **4ac** and **4ad** were able to be pentafluoroethylated in the reaction conditions with 67% and 76% yields, respectively, which showed a potential application in the exploration of new drugs.

It is noteworthy that this pentafluoroethylation reaction proceeded well when applied to the gram-scale synthesis. For instance, when the substrates, **3aa**, **3ab** and **3ac**, were scaled up to 4.5 mmol, the corresponding products could all be obtained in good yields.

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Conflicts of interest

There are no conflicts to declare.

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