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Shitao Pan, Qiqiang Xie, Xiu Wang, Qian Wang, Chuanfa Ni and Jinbo Hu*
The TMSCF₃-derived CuC₂F₆ species has been successfully applied in pentafluoroethylation of organoboronates and terminal alkynes.
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Copper-mediated pentafluoroethylation of organoboronates and terminal alkynes with TMSCF$_3$†

Shitao Pan,‡ Qiqiang Xie,‡ Xiu Wang,‡ Qian Wang, Chuanfa Ni and Jinbo Hu‡ *

The TMSCF$_3$-derived CuCF$_2$CF$_3$ 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$_2$CF$_3$ 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. Moreover, pentafluoroethyl substituted compounds have demonstrated higher bioactivity and better lipophilicity than their trifluoromethylated analogues. 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$_2$CF$_3$)$_2$, TMSCF$_3$, HCF$_2$CF$_3$, and pentafluoropropionate acid derivatives; (2) electrophilic pentafluoroethylation reagents, such as pentafluoroethyl hypervalent iodine reagents, Umemoto type reagents, CF$_3$CF$_2$I and CF$_3$CF$_2$SO$_2$Na; (3) the pentafluoroethyl anion in situ generated from fluoride ions and tetrafluoroethylene. 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$_2$CF$_3$ 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$_2$CF$_3$ species has been applied to cross-coupling reactions with a broad scope of aryl iodides in moderate to excellent yields. In 2019, a similar pentafluoroethylation process was reported by Boutureira and coworkers. In the past decade, oxidative fluoroalkylation has become an important strategy for the synthesis of organofluorine compounds. However, oxidative pentafluoroethylation with TMSCF$_3$-derived CuCF$_2$CF$_3$ species has never been explored. Previously, copper-mediated oxidative pentafluoroethylation was mainly performed with arylboronates or arylboronic acids and various nucleophilic C2 reagents, and witnessed limited success on heteroaromatic substrates.

Herein, as an extension of our interest in the chemistry of controllable fluorocarbon chain elongation, 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$_2$CF$_3$ (CuCl/TMSCF$_3$/KPF) 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 by-products (Table 1, entry 1). Obviously, chloride ions introduced during the generation of CuCF$_2$CF$_3$ 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$_2$CF$_3$ is of relatively low reactivity, which probably arises from the inhibition effect of pyridine used in...
the generation of CuCF$_2$CF$_3$. 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$_2$CO$_3$, 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$_2$CF$_3$ (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$_2$CF$_3$ solution prepared directly at the scale of 0.50 mmol, the yield of the product could be maintained well (entry 16) (Table 2).

After optimizing the reaction conditions, we tried to test the substrate limitations. 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 pentafluoroethylolation 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 pentafluoroethylolation of ethynyl boronate provided a low yield of product (2ab), and the pentafluoroethylolation of benzyl boronate was not successful under the standard reaction conditions (2ae).

The heteroaryl boronates were also examined. 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
Interestingly, the different substituted positions of boronate groups in the benzothiophenol showed limited influence. In addition, the reaction with a substrate bearing an isoquinoline cycle was also able to give the pentafluoroethylated product in good yield (77%). Besides, the substrates with pyrimidine, indole and 7-azaindole also proceeded well to yield the desired products with moderate to good yields, respectively. The products bearing 1H-benzo[d][1,2,3]triazole and benzothiazole moieties were also obtained in good yields despite the fact that the 3-position (2m, 2r) gave a higher yield as compared with the products of the substitution in the 4-position (2n, 2q).

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Table 2  Pentafluoroethylation of aryl/heteroaryl boronates with TMSCF₃-derived CuCF₂CF₃

| Reaction conditions: | CuCl (0.4 mmol, 1.0 equiv.), CuCl (4.5 mmol, 1.12 equiv.), TMSCF₃ (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. |  
| Reaction was conducted on 0.3 mmol scale. |  
| Reaction was conducted on 0.2 mmol scale. |  
| The yield was determined by ¹⁹F NMR spectroscopy using PhCF₃ as an internal standard. |  
| The molar ratio of the pentafluoroethylated product and the chlorinated byproduct is given in the brackets. |

Table 3  Pentafluoroethylation of terminal alkynes with TMSCF₃-derived CuCF₂CF₃

| Reaction conditions: | CuCl (0.45 mmol, 1.0 equiv.), CuCl (2.25 mmol, 5.0 equiv.), TMSCF₃ (1.50 mmol, 3.3 equiv.), KF (1.50 mmol, 3.3 equiv.), air, RT, 1 h. Isolated yields are given. |  
| Yields on the scale of 4.5 mmol are given in the brackets. |  
| The molar ratio of the pentafluoroethylated product and the chlorinated byproduct is given in the brackets. |
pentafluoroethyl groups were located in the aryl rings rather than the heterocycles.

Considering the great importance of functionalized acetylenes,\textsuperscript{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 strong base and the corresponding products could be obtained due to the mild reaction conditions (room temperature, no solvent). More importantly, diverse functional groups could be tolerated. The experimental results showed that the electronic impacts on the pentafluoroethylation reactions. The corresponding products with electron-donating groups were obtained in similar yields (4\textit{b}-4\textit{f}, 4\textit{n}, 4\textit{o}), and the products with electron-withdrawing groups were obtained with higher yields (4\textit{g}-4\textit{m}, 4\textit{p}, and 4\textit{q}).

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

In summary, we have successfully developed the pentafluoroethylation of aryl/heteroaryl boronates using the CuCF\textsubscript{2}CF\textsubscript{3} derived from commercially available TMSCF\textsubscript{3}. This method is amenable with a series of aryl boronates bearing different functional groups. More importantly, diverse heterocycles could be tolerated in the reaction conditions. Furthermore, the unexplored pentafluoroethylation of alkyl- and aryl-acetylenes with CuCF\textsubscript{2}CF\textsubscript{3} was also accomplished. This TMSCF\textsubscript{3}-based pentafluoroethylation reaction exhibited good compatibility with various functional groups and gave the corresponding products in moderate to excellent yields, which promises to find broad applications in the development of new pharmaceuticals, agrochemicals, and advanced materials.

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Conflicts of interest

There are no conflicts to declare.

Notes and references


