Fluorine

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From C_1 to C_2: $TMSCF_3$ as a Precursor for Pentafluoroethylation

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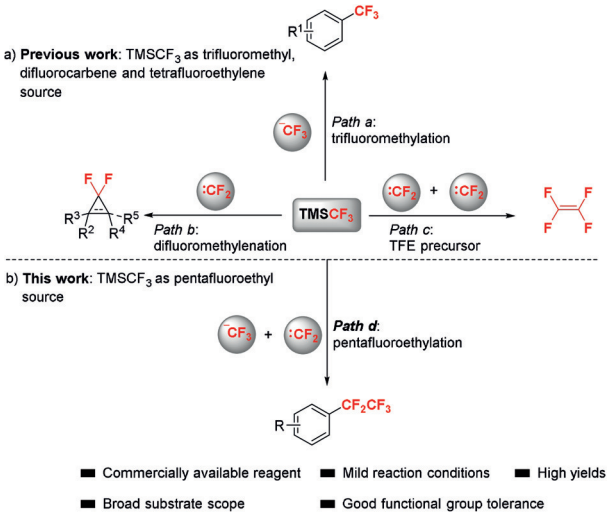
Abstract: *A highly efficient copper-mediated aromatic pentafluoroethylation method using $TMSCF_3$ as the sole fluoroalkyl source is described. The reaction proceeds by a key C_1 to C_2 process, that is, the generation of $CuCF_3$ from $TMSCF_3$, followed by a subsequent spontaneous transformation into CuC_2F_5. Various aryl iodides were pentafluoroethylated with the $TMSCF_3$-derived CuC_2F_5. This method represents the first practical and efficient method for pentafluoroethylation of aryl iodides using commercially available $TMSCF_3$ as a pentafluoroethyl precursor.*

The past decades have witnessed a boom in the introduction of fluorine-containing groups into organic molecules owing to the profound properties of fluorinated compounds compared with their nonfluorinated counterparts.[1] In this context, either transition metal catalyzed or mediated trifluoromethylation reactions of aromatic compounds have been extensively developed using various CF_3 sources.[2] But its analogue, the pentafluoroethyl (C_2F_5) group, has attracted less attention, although many bioactive molecules contain the C_2F_5 group.[3] For example, fulvestrant, an anticancer drug, approved by FDA in 2002, contains a C_2F_5 side chain and has been used to treat hormone receptor positive metastatic breast cancer in postmenopausal women with disease progression following antiestrogen therapy.[4] Dup 532, which contains a pentafluoroethylated imidazole ring, is a more potent angiotensin II receptor antagonist than nonfluorinated Dup 753 when given orally.[5]

Most of the current methods for the syntheses of pentafluoroethylated aromatic compounds use a certain C_2F_5 source, but these reactions suffer from the following drawbacks: 1) not readily available, expensive or hard to handle C_2F_5 sources; 2) harsh reaction conditions; 3) potentially explosive gaseous intermediate, and/or 4) low yields.[6–12] Owing to these problems, an efficient method for the synthesis of aromatic pentafluoroethyl compounds using a relatively inexpensive, commercially available, easy to handle reagent with simple manipulation is highly desired.

$TMSCF_3$, now known as the Ruppert–Prakash reagent, has been the most widely used and versatile trifluoromethylation reagent for various substrates[2d,h,13] since its preparation by Ruppert et al.[14] and application in nucleophilic trifluoromethylation by Prakash et al.[15] For a long time, $TMSCF_3$ was only considered a trifluoromethylation reagent (Scheme 1 a, path a). Recently, Hu, Prakash, and co-workers



Scheme 1. Synthetic application of $TMSCF_3$ as a versatile synthon. TMS = trimethylsilyl.

found that $TMSCF_3$ can also be used as a difluorocarbene reagent, thus *gem*-difluorocyclopropanes and difluorocyclopropenes can be synthesized from the corresponding alkenes and alkynes (Scheme 1 a, path b).[16] Very recently, Hu and coworkers found $TMSCF_3$ is also a convenient source of tetrafluoroethylene (TFE), which can be generated by dimerization of $TMSCF_3$-derived difluorocarbene[11,17] (Scheme 1 a, path c) and used for diverse polyfluoroalkylation reactions.[11] Inspired by these works, we hypothesized that $TMSCF_3$ might also be able to serve as both a trifluoromethyl and a difluorocarbene source in one-pot reaction, thus enabling a pentafluoroethylation. In fact, in copper-mediated or copper-catalyzed trifluoromethylation reactions with aryl halides, pentafluoroethylated compounds were sometimes observed as byproducts,[2d,8a,9,12,18] and further motivated us to pursue a new synthetic protocol using $TMSCF_3$ as an efficient pentafluoroethyl precursor (Scheme 1 b).

Our investigation started with the preparation of CuC_2F_5 by mixing CuI, KF, and $TMSCF_3$, a typical combination for $CuCF_3$ generation. Initially, we tried to add a Lewis acid or a difluorocarbene reagent to transform $CuCF_3$ into CuC_2F_5, but these strategies were not efficient in terms of the yield and selectivity (for details, see the Supporting Information). In

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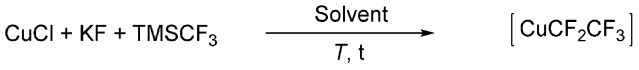
our attempts to monitor the yield of $CuCF_3$ by mixing CuCl, KF, and $TMSCF_3$, we were surprised to find CuC_2F_5 was formed in 4% yield after 30 minutes at room temperature (Table 1, entry 1). Encouraged by this result, we further

Table 1: Optimization of reaction conditions for preparation of CuC_2F_5 from $TMSCF_3$.[a]



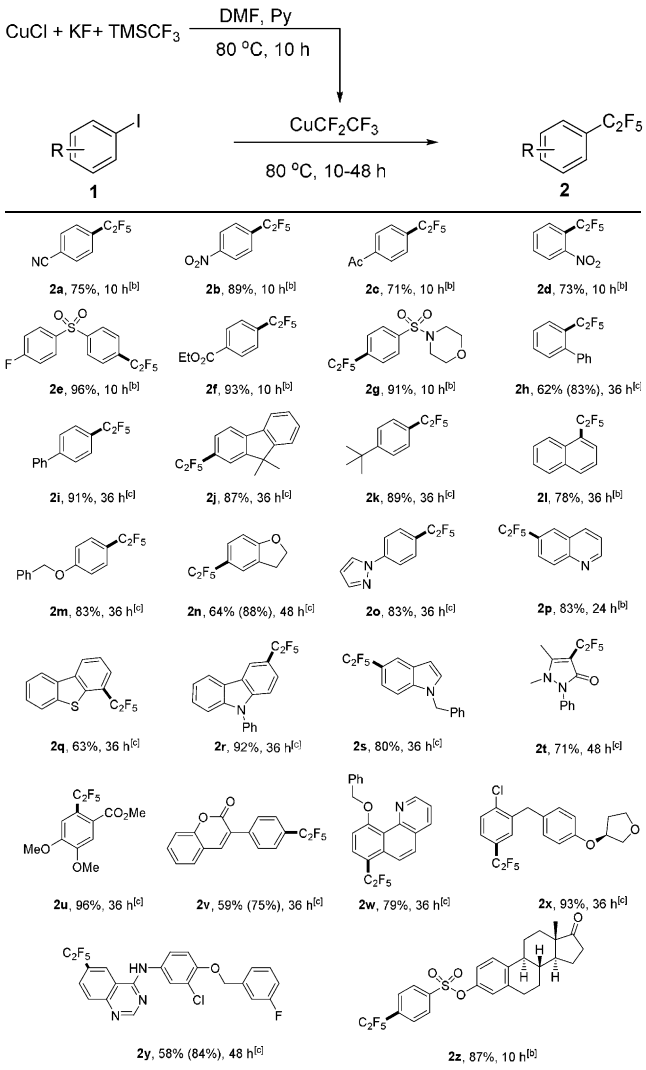
Entry	Solvent[f]	T [°C]	t [h]	Yield [%]			Selectivity[g]
				$CuCF_3$	CuC_2F_5	CuC_3F_7	
1[b]	DMF	RT	0.5	82	4	n.d.	–
2	DMF	RT	24	5	75	7.5	15
3	NMP	RT	24	14	52	4.5	17
4	Py	RT	26	4	33	n.d.	–
5	HMPA	RT	24	66	3	n.d.	–
6	DMF/THF (1:1)	50	15	n.d.	83	13.5	9
7[c]	DMF/THF (1:3)	50	18	n.d.	81	6	20
8[d]	DMF/THF (1:3)	50	16	n.d.	85	3	42
9	DMF/Py (1:1)	50	24	3	90	7.5	18
10	DMF/Py (1:1)	80	24	n.d.	71	2	47
11	DMF/Py (1:1)	80	12	n.d.	78	3	39
12	DMF/Py (1:1)	80	10	n.d.	86	3	43
13[e]	DMF/Py (1:1)	80	10	n.d.	80	3	40

[a] Unless otherwise noted, reactions were performed using KF (0.5 mmol), $TMSCF_3$ (0.5 mmol), CuCl (0.75 mmol), and solvent (2 mL). The yields of $CuCF_3$, CuC_2F_5, and CuC_3F_7 were calculated using 0.5, 0.25, and 0.167 mmol, respectively, as theoretical yields. All yields were determined by ^{19}F NMR spectroscopy using $PhOCF_3$ as an internal standard. [b] HMPA (0.8 equiv) was added, and the molar ratio of CuCl/KF/$TMSCF_3$ = 2:1:1. [c] Pyridine (0.2 mL) was added. [d] TMEDA (tetramethylethylenediamine, 0.2 mL) was added. [e] Reaction was performed using KF (1.5 mmol), $TMSCF_3$ (1.5 mmol), CuCl (2.25 mmol), and solvent (6 mL). The yields of CuC_2F_5 and CuC_3F_7 were calculated using 0.75 and 0.5 mmol as theoretical yields, respectively. [f] The data within parentheses refer to volume ratios. [g] The selectivity is the molar ratio of CuC_2F_5/CuC_3F_7. DMF = *N*,*N*-dimethylformamide, n.d. = not detected, NMP = 1-methyl-2-pyrrolidinone, Py = pyridine, HMPA = hexamethylphosphoramide, THF = tetrahydrofuran.

carried out detailed studies of this spontaneous transformation. When CuCl, KF, and $TMSCF_3$ (molar ratio = 1.5:1:1) were simply mixed in DMF for 24 hours at room temperature, CuC_2F_5 was formed in 75% yield, along with the formation of CuC_3F_7 (7.5%) and $CuCF_3$ (5%; entry 2). Changing solvent to NMP showed lower efficiency (entry 3). When pyridine was used as solvent, the yield of CuC_2F_5 was low, but no CuC_3F_7 could be detected (entry 4), which indicates that pyridine can somewhat inhibit the formation of the CuC_3F_7 species. When HMPA was used as solvent, $CuCF_3$ was formed predominantly (entry 5), and is in accordance with Burton's observation that the strong chelating solvent HMPA could stabilize $CuCF_3$.[19] Similarly, when CuI was used instead of CuCl, or the molar ratio of CuCl/KF/$TMSCF_3$ was 1:1.1:1.1, or excess KF was used, only $CuCF_3$ was observed (for details, see the Table S4 in the Supporting Information). In these cases, the formed $CuCF_3$ is relatively stabilized, so its transformation into CuC_2F_5 was not observed. These results suggest that, if we want to achieve an efficient formation of CuC_2F_5 from $TMSCF_3$, the destabilization of the initially formed $CuCF_3$ intermediate is a key issue. Next, various solvents were tested to destabilize $CuCF_3$ and promote its transformation into CuC_2F_5. After exhaustive solvent screening (for details, see the Supporting Information), we found that when DMF/THF (1:1 v/v) was used as solvent, after 15 hours at 50 °C, CuC_2F_5 was formed in 83% yield, together with 13.5% yield of CuC_3F_7 (entry 6). Although the yield of CuC_2F_5 was high, the selectivity of CuC_2F_5/CuC_3F_7 was only 9, which could not be used for coupling reactions because a mixture of pentafluoroethylated and heptafluoropropylated products would form, and the undesired heptafluoropropyl product would not be separated by ordinary column chromatography. Further exploration showed that if DMF/THF (1:3 v/v) was used, along with pyridine as a ligand, CuC_2F_5 was formed in 81% yield, together with 6% yield of CuC_3F_7 (entry 7). Furthermore, when TMEDA was used as a ligand, 85% yield of CuC_2F_5 was produced, along with only 3% of CuC_3F_7 (entry 8), and the selectivity reached up to 42. Unfortunately, when we used this CuC_2F_5 species (entry 8) to react with aryl iodide, only low yield of the pentafluoroethylation product was formed and the chlorination product was detected as the major byproduct. It seems that TMEDA strongly inhibits the reactivity of this CuC_2F_5 species for coupling reactions. Other ligands were also tried, however, neither yield nor selectivity was satisfactory (for details, see the Supporting Information). Being aware that pyridine could increase selectivity to some extent, we went back to study the influence of pyridine on this transformation. When we used DMF/Py (1:1) as the solvent, after 24 hours at 50 °C CuC_2F_5 was produced in 90% yield (entry 9), but the selectivity was only 18. To our surprise, when the reaction was conducted at 80 °C for 24 hours, the selectivity of CuC_2F_5/CuC_3F_7 was increased sharply to 47, with CuC_2F_5 being formed in 71% yield (entry 10). Screening of the reaction time showed that good yield of CuC_2F_5 and high selectivity could be achieved in 10 hours (entries 11 and 12). Finally, when the reaction was performed on 1.5 mmol ($TMSCF_3$) scale, the yield and selectivity were comparable to those on 0.5 mmol scale (entries 12 and 13).

With the optimized reaction conditions in hand (Table 1, entry 13), we then examined the reactivity of this $TMSCF_3$-derived CuC_2F_5 species by reaction with aryl iodides (Table 2). Satisfactorily, various aryl iodides could undergo coupling reactions with the in situ generated CuC_2F_5 to provide the desired pentafluoroethylation products. Typically, for electron-deficient arenes, reactions can be completed within 10 hours. For electron-rich arenes, because the oxidative addition step is slower, prolonged time is needed to achieve complete conversion. Functional groups such as cyano (**2a**), nitro (**2b**, **2d**; in *ortho* or *para* position), and acetyl (**2c**) were tolerated, and good yields of corresponding products were obtained. Substrates bearing sulfone, ester, and

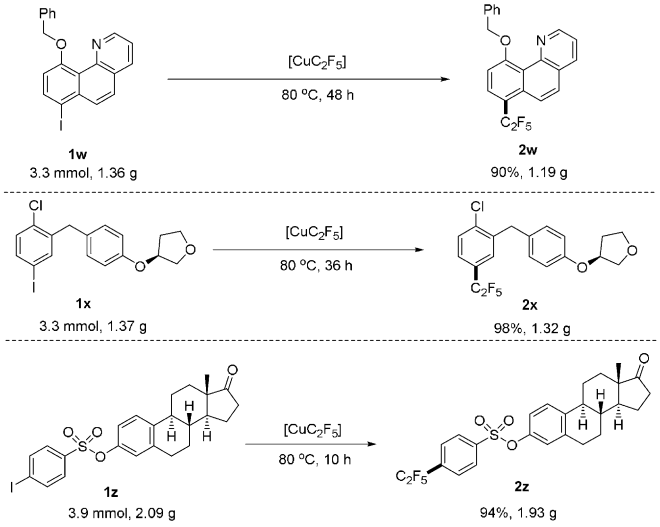
Table 2: Pentafluoroethylation of aryl iodides with $TMSCF_3$-derived CuC_2F_5.[a]



[a] Unless otherwise noted, reactions were performed using KF (1.5 mmol), $TMSCF_3$ (1.5 mmol), and CuCl (2.25 mmol). Yields given within parentheses were determined by ^{19}F NMR spectroscopy using $PhOCF_3$ as an internal standard. [b] 0.39 mmol of **1** was used. [c] 0.33 mmol of **1** was used.

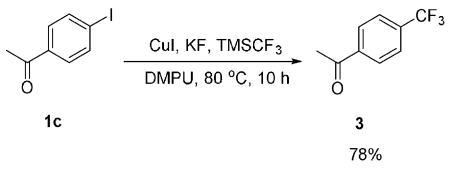
sulfonamide functionalities (**2e**–**g**) reacted smoothly in excellent yields. For an *ortho*-phenyl-substituted aryl iodide (**2h**), only moderate yield was achieved. However, a *para*-phenyl-substituted substrate (**2i**) showed excellent reactivity. This difference may be derived from the steric difference between **1h** and **1i**. For alkyl- or alkoxy-substituted electron-rich substrates (**2j**,**k**, **2m**,**n**), moderate to good yields were obtained. In addition to arenes, various heteroarenes such as pyrazole (**2o**), quinoline (**2p**), benzothiophene (**2q**), carbazole (**2r**), indole (**2s**), antipyrine (**2t**), and chromene (**2v**) were all compatible with this reaction, giving pentafluoroethylation products in moderate to excellent yields. Polysubstituted benzene (**2u**) and polycyclic aromatic hydrocarbon derivatives (**2l**, **2w**) also reacted smoothly. Notably, this protocol was also practical for pentafluoroethylation of relatively complex substrates and pharmaceutical intermediates, implying the potential use of this method for late-stage modification of bioactive molecules. The aryl iodide **1x**, an intermediate for the synthesis of the type II diabetes treatment drug Empagliflozin,[20] was successfully pentafluoroethylated in 93% yield. Another compound, **1y**, the intermediate to the antitumor drug Lapatinib,[21] reacted smoothly to afford the desired product in moderate yield. The derivative of estrone **1z** also showed high reactivity, giving the desired product **2z** in 87% yield.

To further demonstrate the practicability and effectiveness of this methodology, gram-scale syntheses were tested (Scheme 2). When the relatively complex substrates **1w**, **1x**, and **1z** were scaled up to 3.3 or 3.9 mmol, these reactions showed somewhat higher efficiency (the yields being slightly higher) and the desired products were all obtained on gram-scale.



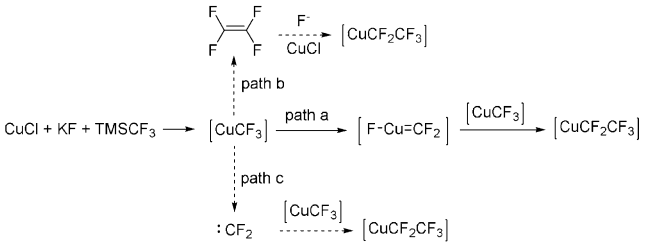
Scheme 2. Gram-scale syntheses of relatively complex pentafluoroethyl compounds. [CuC_2F_5] was prepared from CuCl (22.5 mmol), KF (15 mmol), $TMSCF_3$ (15 mmol).

Based on our understanding for CuC_2F_5 formation from $TMSCF_3$, if we want to achieve trifluoromethylation and avoid pentafluoroethylation, we need to stabilize the in situ formed $CuCF_3$.[18e] Indeed, when CuI was used instead of CuCl, excess KF and $TMSCF_3$ was used instead of excess CuCl and strong chelating DMPU was used as the solvent, the aryl iodide **1c** was completely trifluoromethylated to give **3**, and no pentafluoroethylation product **2c** could be detected (Scheme 3).



Scheme 3. Selective trifluoromethylation of aryl iodide. DMPU = 1,3-dimethyl-3,4,5,6-tetra-hydro-2(1*H*)-pyrimidinone.

To gain mechanistic insight into this selective formation of CuC_2F_5 from $TMSCF_3$, several experiments were conducted. According to our optimization of reaction conditions, it was obvious that $CuCF_3$ was formed firstly by mixing CuCl, KF, and $TMSCF_3$, and this $CuCF_3$ species could then transform into CuC_2F_5.[19] To probe whether the free difluorocarbene is involved in this C_1 to C_2 homologation reaction, various nucleophiles (that are known to have high reactivity towards difluorocarbene) were tested. It was found that electron-rich alkenes, phenols, and thiophenols all failed to give the desired difluoromethylation products (for details, see the Supporting Information), and indicates that the involvement of free difluorocarbene species in the formation of CuC_2F_5 from $CuCF_3$ is unlikely (Scheme 4, path c). In our attempts to



Scheme 4. Plausible mechanism for the formation of CuC_2F_5 from $TMSCF_3$.

prepare CuC_2F_5 from $TMSCF_3$, TFE was not observed in all cases, so the in situ generation of TFE can be excluded (Scheme 4, path b). As the transition-metal trifluoromethyl complexes (CF_3–M) can serve as precursors for metal difluorocarbenes (M=CF_2),[8e,22] we propose that copper difluorocarbene (Cu=CF_2) can be the possible intermediate in the transformation from $CuCF_3$ into CuC_2F_5 (Scheme 4, path a).[23]

In conclusion, a C_1 to C_2 process was achieved, using $TMSCF_3$ as a convenient pentafluoroethyl source. This reaction proceeds by in situ generation of $CuCF_3$, followed by spontaneous transformation into CuC_2F_5 in high yield and selectivity. This CuC_2F_5 species could undergo coupling reaction with aryl iodides to provide aromatic pentafluoroethyl products in moderate to excellent yields. This protocol not only represents the first practical and efficient pentafluoroethylation reaction of aryl iodides using $TMSCF_3$ reagent, it also opens a new door to the efficient homologation of fluorocarbon chains that has been previously believed to be challenging.[24] Further exploration in this direction is currently underway in our laboratory.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: arenes · carbenes · copper · fluorine · reaction mechanisms

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