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From C1 to C2: $TMSCF_3$ as an Efficient Precursor for Pentafluoroethylation

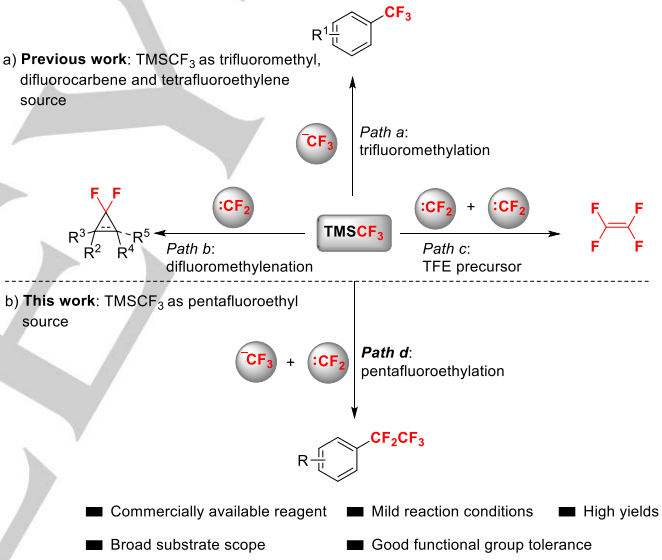
*Qiqiang Xie, Lingchun Li, Ziyue Zhu, Rongyi Zhang, Chuanfa Ni, and Jinbo Hu**

Abstract: A copper-mediated highly efficient aromatic pentafluoroethylation method using $TMSCF_3$ as the sole fluoroalkyl source is described. The reaction proceeds via a key C1 to C2 process; that is, the generation of $CuCF_3$ from $TMSCF_3$, followed by a subsequent spontaneous transformation to CuC_2F_5. Various aryl iodides could be smoothly pentafluoroethylated with the $TMSCF_3$-derived CuC_2F_5. This method represents the first practical and efficient method for pentafluoroethylation of aryl iodides through homologation reaction using commercially available $TMSCF_3$ as a pentafluoroethyl source.

The past decades have witnessed a boom of introduction of fluorine-containing groups into organic molecules owing to the profound property changes of fluorinated compounds compared with their non-fluorinated counterparts.[1] In this context, transition-metal catalyzed or mediated trifluoromethylation reactions of aromatic compounds have been extensively developed using various CF_3 sources.[2] But its analog, 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, which contains a C_2F_5 side chain, 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 Ruppert-Prakash reagent, is the most widely used, versatile trifluoromethylation reagent for various substrates,[2d,2h,13] since its preparation by Ruppert[14] and application in nucleophilic trifluoromethylation by Prakash[15]. For a long time, $TMSCF_3$ was only considered as a trifluoromethylation reagent (Scheme 1a, path a). Recently, Hu, Prakash and co-workers 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 1a, path b).[16] Very recently, Hu and co-workers found $TMSCF_3$ is also a convenient source of tetrafluoroethylene (TFE), which can be generated by dimerization of $TMSCF_3$-derived difluorocarbene[17] (Scheme 1a, 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 -catalyzed trifluoromethylation reactions with aryl halides, pentafluoroethylated compounds were sometimes observed as byproducts,[2d,8a,9,12,18] which further spurred us to pursue a new synthetic protocol using $TMSCF_3$ as an efficient pentafluoroethyl precursor (Scheme 1b).



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

Our investigation started with the preparation of CuC_2F_5 by mixing CuI, KF and $TMSCF_3$, which is a typical combination for $CuCF_3$ generation. Initially, we tried to add a Lewis acid or a difluorocarbene reagent to transform $CuCF_3$ to CuC_2F_5, but these strategies were not efficient in terms of the yield and selectivity (for details, see the Supporting Information). In 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 in 30 minutes at room temperature (Table 1, entry 1). Encouraged by this result, we further carried out detailed studies of this spontaneous transformation.

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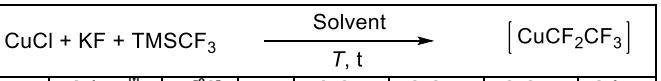
Table 1. Optimization of reaction conditions for preparation of CuC_2F_5 from $TMSCF_3$.[a]

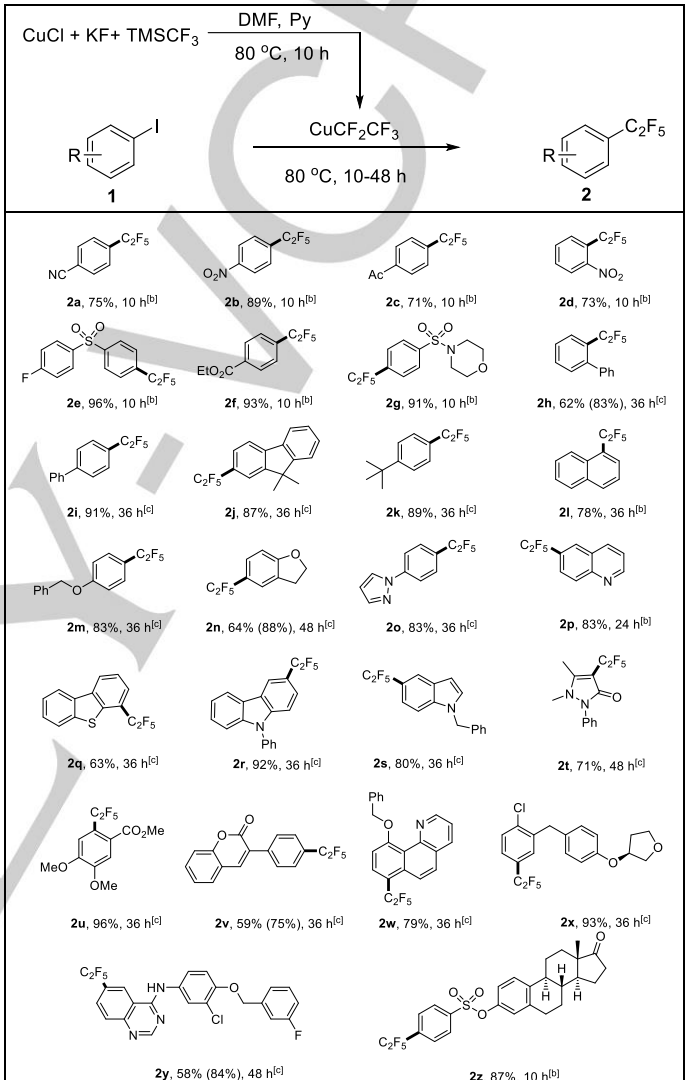


Entry	Solvent[f]	T [°C]	t [h]	$CuCF_3$ [%]	CuC_2F_5 [%]	CuC_3F_7 [%]	Selectivity[g]
1[b]	DMF	RT	0.5	82	4	N.D.	/
2	DMF	RT	24	5	75	7.5	15
3	NMP	RT	24	14	52	4.5	17
4	Py	RT	26	4	33	N.D.	/
5	HMPA	RT	24	66	3	N.D.	/
6	DMF/THF (1:1)	50	15	N.D.	83	13.5	9
7[c]	DMF/THF (1:3)	50	18	N.D.	81	6	20
8[d]	DMF/THF (1:3)	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 yield of $CuCF_3$, CuC_2F_5 and CuC_3F_7 were calculated using 0.5, 0.25, 0.167 mmol as theoretical yield, respectively. All yields were determined by ^{19}F NMR spectroscopy using $PhOCF_3$ as an internal standard. DMF = N,N-dimethylformamide, NMP = 1-methyl-2-pyrrolidinone, Py = pyridine, HMPA = hexamethylphosphoramide, THF = tetrahydrofuran. N.D. = not detected. [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 yield of CuC_2F_5 and CuC_3F_7 were calculated using 0.75 and 0.5 mmol as theoretical yield, respectively. [f] The data in parentheses refer to volume ratios. [g] The selectivity is the molar ratio of CuC_2F_5/CuC_3F_7.

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 CuC_3F_7 species. When HMPA was used as solvent, $CuCF_3$ was formed predominantly (entry 5), which is in accordance with Burton's observation that strong chelating solvent HMPA could stabilize $CuCF_3$.[19] Similarly, when CuI was used instead of CuCl, or the molar ratio of CuCl: KF: $TMSCF_3$ = 1: 1.1: 1.1, or excess amount of KF was used, only $CuCF_3$ was observed (for details, see the Supporting Information, Table S4). In these cases, the formed $CuCF_3$ is relatively stabilized, so its transformation to 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 to CuC_2F_5. After exhaustive solvent screening (for details, see the Supporting Information), we found 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 (Table 1, 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 could 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 (Table 1, 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 (Table 1, entry 8) to react with aryl iodide, only low yield of pentafluoroethylation product was formed and chlorination product was detected as the major by-product. 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 solvent, after 24 hours at 50 °C, CuC_2F_5 was produced in 90% yield (Table 1, 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 (Table 1, entry 10). Screening of the reaction time showed that good yield of CuC_2F_5 and high selectivity could be achieved in 10 hours (Table 1, entries 11-12). Finally, when the reaction was performed on 1.5 mmol ($TMSCF_3$)

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 in 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.

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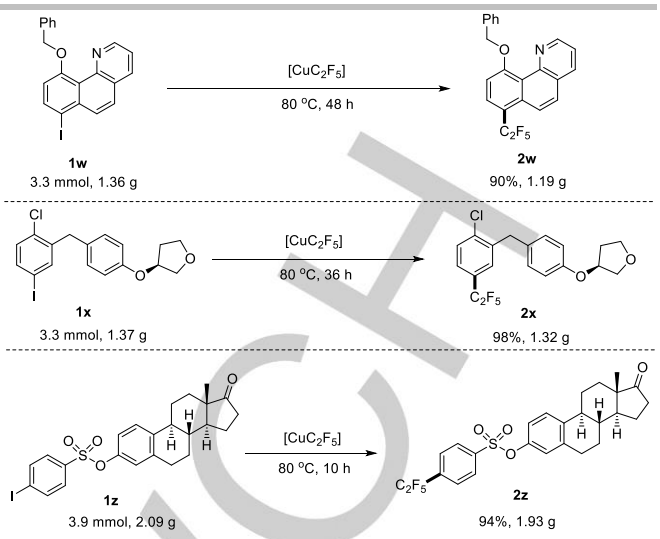
scale, the yield and selectivity was comparable to that on 0.5 mmol scale (Table 1, entries 12 and 13).

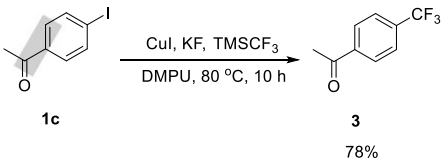
With the optimized conditions in hand (Table 1, entry 13), we then examined the reactivity of this $TMSCF_3$-derived CuC_2F_5 species by reacting with aryl iodides (Table 2). Satisfactorily, various aryl iodides could undergo coupling reactions with the in situ generated CuC_2F_5 to provide the desired 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 sulfonamide functionalities (**2e-g**) reacted smoothly in excellent yields. For ortho-phenyl substituted aryl iodide (**2h**), only moderate yield was achieved; however, para-phenyl substituted substrate (**2i**) showed excellent reactivity. This big difference may be derived from the intrinsic steric hindrance of **1h** and **1i**. For alkyl or alkoxyl-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 type II diabetes treatment drug, Empagliflozin[20], could be successfully pentafluoroethylated in 93% yield. Another compound **1y**, the intermediate to synthesize 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. 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 in gram-scale (Scheme 2).

Based on our understanding for CuC_2F_5 formation from $TMSCF_3$, if, on the other hand, 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 solvent, aryl iodide **1c** was completely trifluoromethylated to give **3**, and no pentafluoroethylation product **2c** could be detected (Scheme 3).

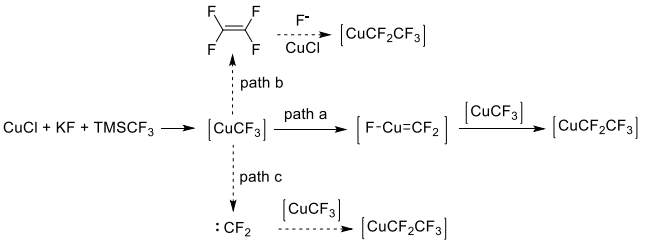


Scheme 2. Gram-scale syntheses of relatively complex pentafluoroethyl compounds. [CuC_2F_5] was prepared from CuCl (22.5 mmol), KF (15 mmol), $TMSCF_3$ (15 mmol).



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

To have a 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 to CuC_2F_5.[19] To probe whether the free difluorocarbene is involved in this C1 to C2 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), which



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

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 prepare CuC_2F_5 from $TMSCF_3$, no TFE was observed in all cases, so the in situ generation of TFE can be excluded (Scheme 4, path b). As the transition metal trifluoro-

methyl 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 $CuCF_3$ to CuC_2F_5 (Scheme 4, path a).[23]

In conclusion, a C1 to C2 process was achieved, using $TMSCF_3$ as a convenient pentafluoroethyl source. This reaction proceeds via in situ generation of $CuCF_3$, followed by spontaneous transformation to 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.

Acknowledgements

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Keywords: pentafluoroethylation • trifluoromethyltrimethyl silane • copper • difluorocarbene • homologation

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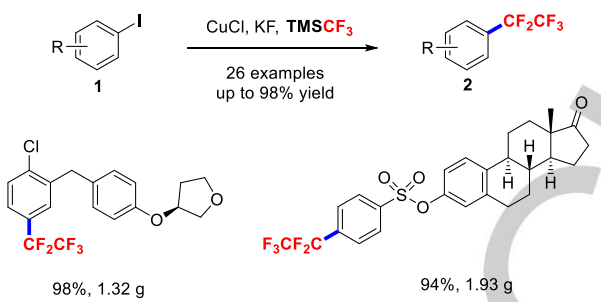
Chain grows! A highly efficient aromatic pentafluoroethylation using $TMSCF_3$ as the C_2F_5 source is developed. Various substituted aryl iodides were successfully pentafluoroethylated with simple manipulation. The homologation from CF_3 to C_2F_5 provides a new C1 to C2 synthetic strategy.



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