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Introduction

Due to the unique physical, chemical and biological properties of organofluorine compounds, the introduction of fluorine atom(s) or fluorinated moieties into organic molecules has become a routine strategy in drug design and advanced material development.^{1–4} Among various fluorinated functionalities, the tetrafluoroethylene motif ($-\text{CF}_2\text{CF}_2-$) has attracted considerable attention because of its applications in agrochemicals⁵ and liquid-crystalline materials.^{6–8} Moreover, the introduction of $-\text{CF}_2\text{CF}_2-$ group into liquid crystals often results in highly advantageous properties such as high clearing temperature, broad nematic phase range, low rotational viscosity and high dielectric anisotropy.^{6–8} Therefore, it is of strong demand to access tetrafluoroethylene-bridged molecules.

Current methods for the syntheses of tetrafluoroethylene-bridged structures are mainly based on (1) deoxofluorination of 1,2-dicarbonyl compounds with SF_4 and DeoxoFluor;^{9–11} (2) fluorination of C–C triple bonds using F_2 ;^{12–14} (3) 1,2-difunctionalization of tetrafluoroethylene (TFE);^{15–23} (4) difluoromethylene insertion using CF_2Br_2 as the CF_2 source;^{24,25} and (5) using $\text{RCF}_2\text{CF}_2\text{Br}$ as the build block.⁵ However, these methods suffer from several drawbacks such as (1) using toxic, highly reactive or hazardous reagents; (2) low functional group tolerance and/or (3) using explosive gaseous reagents or ozone-depleting substances (ODS). As such, developing a new method to incorporate $-\text{CF}_2\text{CF}_2-$ structure motif into organic

molecules with readily available, easy to handle and environmentally benign reagents under mild conditions is highly desired.

(Trifluoromethyl)trimethylsilane (TMSCF_3), often called Ruppert–Prakash reagent, is arguably the most widely used trifluoromethylating agent.^{26–30} In 2011, our group, in collaboration with the Prakash group, revealed that TMSCF_3 is a good difluorocarbene precursor, which can be used in the $[2 + 1]$ cycloaddition reaction with alkenes and alkynes.³¹ Recently, our group reported that difluorocarbene generated from TMSCF_3 could undergo dimerization to give tetrafluoroethene (TFE),^{32,33} which can be used for a variety of transformations.³³ Very recently, our group demonstrated that, by using TMSCF_3 as the difluoromethylene source, controllable CF_2 -insertion into CuCF_3 to generate CuCF_2CF_3 could be realized.³⁴ Inspired by this C_1 to C_2 process, we envisioned that it might be possible to insert CF_2 into other C–M bonds. Herein, we report our latest progress in the fluorocarbon homologation reaction using TMSCF_3 as the difluoromethylene source. By carefully tuning the reaction conditions, controllable double insertion of CF_2 into $\text{C}_6\text{F}_5-\text{Cu}$ gives rise to $\text{C}_6\text{F}_5\text{CF}_2\text{CF}_2\text{Cu}$, which can be applied to the preparation of a diverse range of tetrafluoroethylene-bridged compounds (Scheme 1).

a) Previous work: single CF_2 insertion into CF_3Cu with TMSCF_3



b) This work: double CF_2 insertion into $\text{C}_6\text{F}_5\text{Cu}$ with TMSCF_3



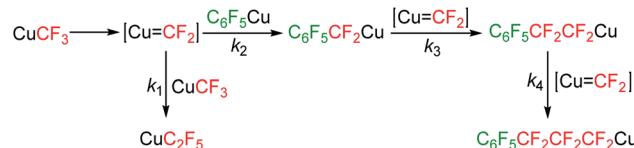
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Results and discussion

Our investigation commenced with the preparation of $C_6F_5-CF_2CF_2Cu$ from $TMSC_6F_5$ and $TMSCF_3$. Initially, we used 1 equivalent of $TMSC_6F_5$ as the C_6F_5Cu precursor, 1 equivalent of $TMSCF_3$ as the difluorocarbene precursor, 2 equivalents of KF as the desilylating reagent and 2.5 equivalents of CuCl as the copper source. All these components were added simultaneously with DMF as the solvent, and the resulting mixture was stirred at room temperature for 12 hours. Analysis of the mixture by ^{19}F NMR spectroscopy revealed that $C_6F_5CF_2CF_2Cu$ (21%), C_6F_5Cu (57%) and $CuCF_3$ (37%) were formed; no single CF_2 -insertion product $C_6F_5CF_2Cu$ could be detected (Table 1, entry 1). When adding 2 equivalents of difluorocarbene source $TMSCF_3$, we found that the desired product $C_6F_5CF_2CF_2Cu$ was formed in 79% yield, in conjunction with C_6F_5Cu (3%), $CuCF_3$ (10%) and CuC_2F_5 (5%) (entry 2).³⁵ If 3 equivalents of $TMSCF_3$ was used, $C_6F_5CF_2CF_2Cu$ was formed in 83% yield, along with $CuCF_3$ (16%) and CuC_2F_5 (12%) being formed; neither C_6F_5Cu nor triple CF_2 -insertion product $C_6F_5CF_2CF_2CF_2Cu$ could be detected (entry 3). These results (entries 1–3) clearly indicate that the $TMSCF_3$ -derived difluorocoppercarbene ($Cu=CF_2$) species³⁴ could selectively undergo double CF_2 -insertion into C_6F_5Cu , regardless of the amount of $TMSCF_3$ used. This behaviour is in accord with previous reports.²⁴ The high selectivity may be attributed to the intrinsic reactivity of different fluoroalkylcopper species toward $Cu=CF_2$ (Scheme 2). As to the possible intermediate, $C_6F_5CF_2Cu$, its benzylic C–Cu bond is highly reactive and tended to insert another CF_2 unit to give $C_6F_5CF_2CF_2Cu$,^{24,25} the resulting $C_6F_5CF_2CF_2Cu$ has lower reactivity than $CuCF_3$ because of its longer fluoroalkyl chain.^{24,25} Therefore, even in the presence of excess of $TMSCF_3$, triple CF_2 -



Scheme 2 Proposed reaction mechanism.

insertion into C_6F_5Cu could not be observed; in that case, the CF_2 -insertion into $CuCF_3$ to generate CuC_2F_5 would be favoured. Altogether, the relative reaction rate of each step is $k_3 > k_2 > k_1 > k_4$.

With this understanding in mind, we went on to optimize the reaction conditions in order to increase the yield of $C_6F_5-CF_2CF_2Cu$ and minimize those of $CuCF_3$ and CuC_2F_5 . By using 2 equivalents of $TMSCF_3$ and prolonging reaction time to 20 hours, $C_6F_5CF_2CF_2Cu$ was formed in 87% yield (entry 4). When we decreased the amount of CuCl from 4 equivalents to 3 equivalents, only trace of $C_6F_5CF_2CF_2Cu$ was observed, with >80% C_6F_5Cu and $CuCF_3$ being recovered (entry 5). This result revealed that the presence of excess amount of CuCl is crucial for the $Cu=CF_2$ generation, which is consistent with our previous report.³⁴ As $CuCF_3$ was always observed, we tried to speed up the decomposition of $CuCF_3$ at elevated temperatures. However, when the reaction was carried out at 50 °C, although no $CuCF_3$ was observed, a larger amount of CuC_2F_5 was detected, and $C_6F_5CF_2CF_2Cu$ was obtained in relatively lower yield (entry 6 vs. entry 4). Next, we attempted to add $TMSCF_3$ into the reaction mixture after the preparation of C_6F_5Cu . Gratifyingly, the yield of $C_6F_5CF_2CF_2Cu$ was increased slightly (entry 7). In light of the decomposition of $CuCF_3$ to $Cu=CF_2$ would release

Table 1 Optimization of reaction conditions for the double CF_2 insertion into C_6F_5Cu with $TMSCF_3$ ^a

Entry	$TMSC_6F_5 : CuCl : KF : TMSCF_3$	t (h)	T (°C)	Yield (%)	
				$C_6F_5C_2F_4Cu$	$C_6F_5Cu/CuCF_3/CuC_2F_5$
1 ^b	1 : 2.5 : 2 : 1	12	rt	21	57/37/n.d.
2 ^b	1 : 4 : 3 : 2	12	rt	79	3/10/5
3 ^b	1 : 5.5 : 4 : 3	12	rt	83	n.d./16/12
4 ^b	1 : 4 : 3 : 2	20	rt	87	4/2/4
5 ^b	1 : 3 : 3 : 2	20	rt	1	87/82/n.d.
6 ^b	1 : 4 : 3 : 2	10	50	75	1/n.d./23
7	1 : 4 : 3 : 2	28	rt	91	<1/<1/4
8	1 : 4 : 2 : 2	28	rt	76	n.d./2/5
9 ^c	1 : 4 : 3 : 2	28	rt	91	n.d./6/2
10 ^d	1 : 4 : 3 : 2	28	rt	93	n.d./8/2
11 ^e	1 : 4 : 3 : 1.9	28	rt	92	2/4/2
12 ^e	1 : 4 : 3 : 1.9	36	rt	86	3/4/2
13 ^{e,f}	1 : 4 : 3 : 1.9	28	rt	89	n.d./1/2

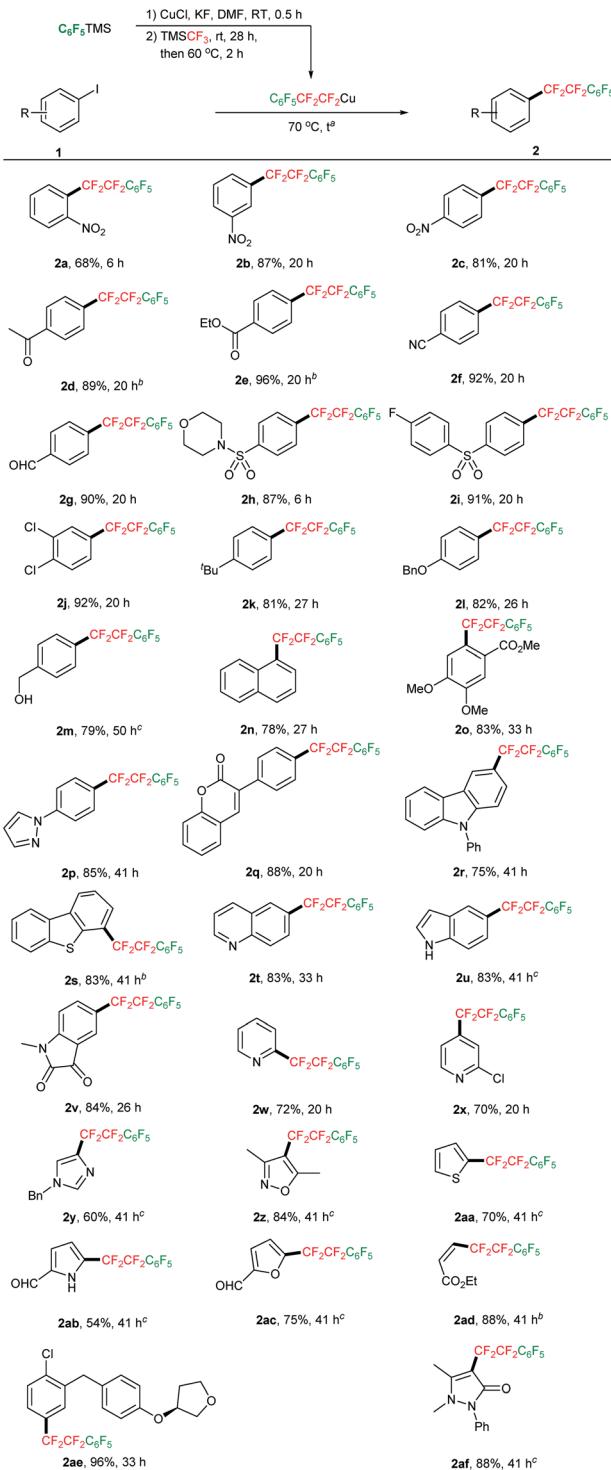
^a Reactions were performed on 0.2 mmol $TMSC_6F_5$ (1.0 equiv.) scale. Yields were determined by ^{19}F NMR spectroscopy using $PhOCF_3$ as an internal standard. n.d. = not detected. ^b $TMSC_6F_5$ and $TMSCF_3$ were added simultaneously without the pre-preparation of C_6F_5Cu . ^c $TMSCF_3$ was added in three portions for every 4 hours. ^d $TMSCF_3$ was added in three portions for every 6 hours. ^e $TMSCF_3$ was added in two portions for every 6 hours. ^f After reacted at rt for 28 hours, the reaction mixture was stirred at 60 °C for another 2 hours.



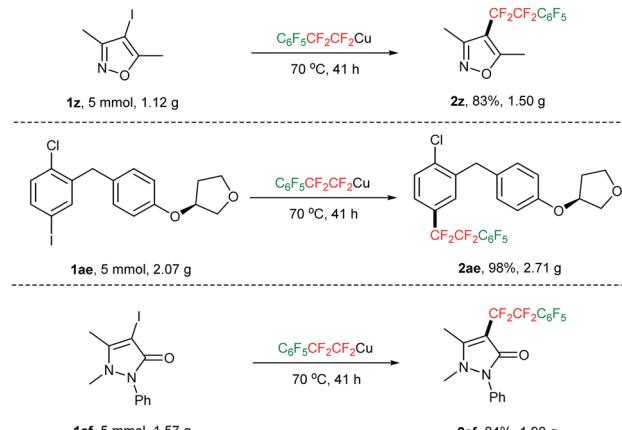
fluoride ions, we surmised that the amount of externally added KF could be reduced. However, lowering down KF to 2 equivalents gave inferior result (entry 8). To further decrease the yield

of CuC_2F_5 , we envisaged that adding TMSCF_3 in batches to decrease the concentration of CuCF_3 might be helpful. After some brief optimizations and decreasing the amount of TMSCF_3 to 1.9 equivalents (entries 9–11), $\text{C}_6\text{F}_5\text{CF}_2\text{CF}_2\text{Cu}$ was formed in 92% yield, together with 2% of $\text{C}_6\text{F}_5\text{Cu}$ and 4% of CuCF_3 being formed (entry 11). Prolonging the reaction time to 36 hours did not have any beneficial effect (entry 12). Finally, when the reaction was conducted at room temperature for 28 hours, then stirred at 60 °C for 2 hours, no $\text{C}_6\text{F}_5\text{Cu}$ and little amounts of CuCF_3 (1%) and CuC_2F_5 (2%) could be detected, with $\text{C}_6\text{F}_5\text{CF}_2\text{CF}_2\text{Cu}$ being formed in 89% yield (entry 13).

With the optimized conditions (Table 1, entry 13) in hand, the reactivity of this TMSCF_3 -derived $\text{C}_6\text{F}_5\text{CF}_2\text{CF}_2\text{Cu}$ towards aryl iodides was studied. A variety of structurally diverse (hetero)aryl and alkenyl iodides are all viable substrate, giving the desired tetrafluoroethylene-bridged products in moderate to good yields (Scheme 3). The electronic character of aryl iodides do not have obvious influence on the reaction efficiency, and both electron-deficient (2a–i) and electron-rich (2k–p, 2r–s) substrates were readily transformed to the desired products in good yields. Common functional groups such as nitro (2a–c, in *ortho*, *meta* and *para* positions), acetyl (2d), ester (2e), cyano (2f), sulfonamide (2h) and sulfone (2i) were compatible with the reaction conditions, and good yields of products were observed. Notably, because of the mildness of the reaction conditions, some sensitive functionalities including aldehyde (2g, 2ab–ac), alcohol (2m) and unprotected NH group (2u, 2ab), were also tolerated. Heterocycles, such as pyrazole (2p), coumarin (2q), carbazole (2r), benzothiophene (2s), quinoline (2t) and indole (2u) were competent under the reaction conditions, as demonstrated by the formation of tetrafluoroethylene-bridged products in high yields. Moreover, heteroaryl iodides, including iodopyridine (2w–x), iodoimidazole (2y), iodoisoxazole (2z), iodothiophene (2aa), iodothiophene (2ab) and iodothiophene (2ac), participated in this perfluorophenylethylation to afford corresponding products in moderate to good yields (54–84%). Iodoalkene 1ad also showed good reactivity towards $\text{C}_6\text{F}_5\text{CF}_2\text{CF}_2\text{Cu}$, furnishing the desired product 2ad in 88% yield. This protocol is also



Scheme 3 Perfluorophenylethylation of (hetero)aryl iodides with TMSCF_3 -derived $\text{C}_6\text{F}_5\text{CF}_2\text{CF}_2\text{Cu}$. ^a Unless otherwise noted, reactions were performed on 0.5 mmol of **1** (1.0 equiv.) scale, and TMSCF_3 was added in two portions every 6 h; 1.5 equivalents of TMSC_6F_5 was used; the molar ratio of TMSC_6F_5 : CuCl : KF : TMSCF_3 = 1 : 4 : 3 : 1.9. ^b 1.6 equivalent of TMSC_6F_5 was used. ^c 1.8 equivalent of TMSC_6F_5 was used.



Scheme 4 Gram-scale synthesis.



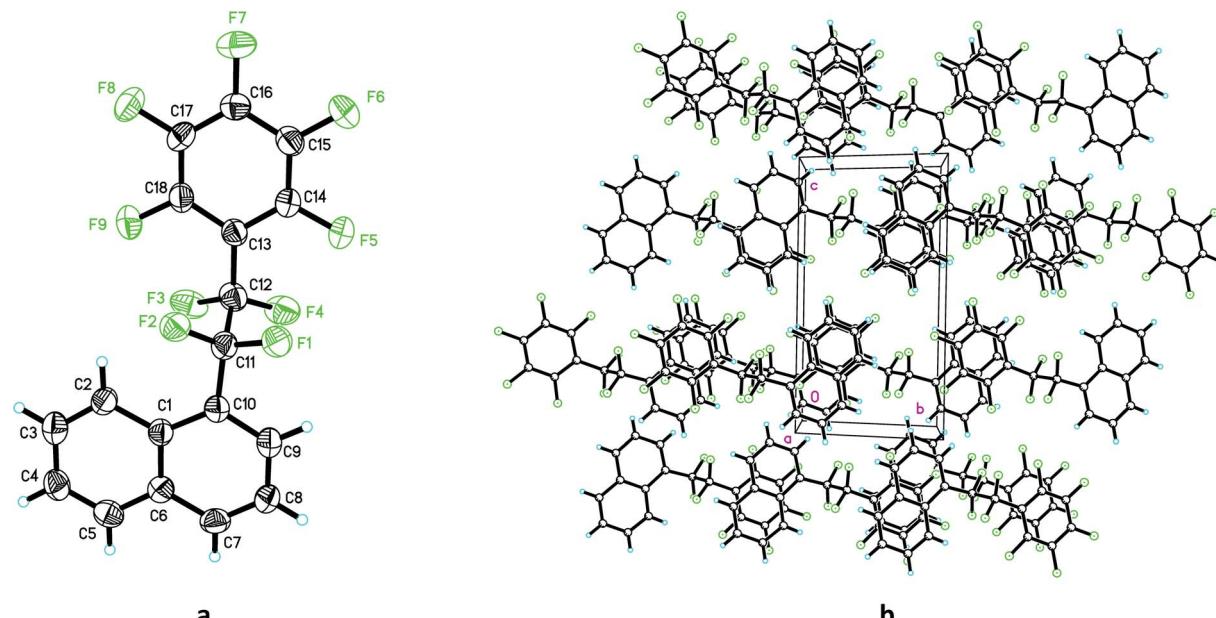


Fig. 1 (a) The single crystal structure and (b) packing diagram of **2n**.³⁶

effective for the perfluorophenylethylation of relatively complex compounds and pharmaceutical intermediates **1ae** and **1af**, giving the corresponding products **2ae** and **2af** in 96% and 88% yields, respectively. The broad scope of this reaction underscores the great potential of its application in the synthesis of a raft of valuable $-\text{CF}_2\text{CF}_2-$ bridged molecules.

The inherent value of our controllable double CF_2 -insertion strategy with TMSCF_3 for the introduction of tetrafluoroethylene bridge is further demonstrated by its applicability to gram-scale synthesis. For example, when iodoisoxazole **1z** was scaled up to 5 mmol (1.12 g), the desired product **2z** was obtained in 83% yield (1.50 g). Analogously, pharmaceutical intermediates **1ae** and **1af** were also successfully scaled up to 5 mmol, with the yields comparable to that on 0.5 mmol scale (Scheme 4).

It is worthwhile to note that the tetrafluoroethylene-bridged product **2n** possesses interesting conformation and intermolecular interaction. As shown in Fig. 1,³⁶ the single crystal structure of product **2n** shows that the dihedral angle of $\text{C10}-\text{C11}-\text{C12}-\text{C13}$ is 174.1° , and two aromatic (the naphthalenyl and pentafluorophenyl) rings in **2n** are almost parallel to each other (see Fig. 1a, also see ESI†). The packing diagram shows there are extensive intermolecular $\pi-\pi$ stackings between naphthalenyl and pentafluorophenyl rings of **2n** (Fig. 1b), which might find useful applications in crystal engineering and materials science.

Conclusions

In conclusion, a controllable double CF_2 -insertion into $\text{C}_6\text{F}_5\text{Cu}$ was realized using TMSCF_3 as the difluoromethylene source. The resulting $\text{C}_6\text{F}_5\text{CF}_2\text{CF}_2\text{Cu}$ species showed high reactivity towards various (hetero)aryl iodides and alkenyl iodides,

providing an easy access to a variety of $-\text{CF}_2\text{CF}_2-$ bridged molecules. Compared with previous methods for the construction of $-\text{CF}_2\text{CF}_2-$ unit, this approach owns several merits such as utilizing commercially available and environmentally benign reagents as the CF_2 source, easy to handle, broad substrate scope and mild conditions. This double CF_2 -insertion strategy represents the second generation of fluorocarbon homologation reactions *via* difluoromethylene insertion using TMSCF_3 (the first generation is single CF_2 -insertion into CuCF_3). Further efforts to seek after novel CF_2 -insertion reactions using TMSCF_3 are currently underway in our laboratory.

Conflicts of interest

There are no conflicts to declare.

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35 The chemical shifts of these fluoroalkylcopper/fluoroaryl copper species were assigned as follows (in ppm): C₆F₅CF₂CF₂Cu, –101.1 (t, 2F), –106.6 (s, 2F), –139.4 (m, 2F), –153.1 (t, 1F), –163.9 (t, 2F); C₆F₅Cu, –111.0 (d, 2F), –163.3 (t, 1F), –164.3 (t, 2F); CuCF₃, –26.7 (s, 3F); CuC₂F₅, –84.0 (s, 3F), –112.4 (s, 2F).

36 CCDC 1957757[†] contains the supplementary crystallographic data for compound 2n.

