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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 ($-CF_2CF_2-$) has attracted considerable attention because of its applications in agrochemicals⁵ and liquid-crystalline materials.⁶⁻⁸ Moreover, the introduction of $-CF_2CF_2-$ 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 tetrafluoroethylenebridged structures are mainly based on (1) deoxofluorination of 1,2-dicarbonyl compounds with SF₄ 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 CF₂Br₂ as the CF₂ source;^{24,25} and (5) using RCF₂CF₂Br 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 ozonedepleting substances (ODS). As such, developing a new method to incorporate $-CF_2CF_2$ - structure motif into organic

Controllable double CF_2 -insertion into $sp^2 C-Cu$ bond using TMSCF₃: a facile access to tetrafluoroethylene-bridged structures[†]

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A highly efficient method for controllable double CF_2 -insertion into pentafluorophenylcopper species using TMSCF₃ as difluoromethylene source has been developed. The newly generated fluoroalkylcopper(I) species, $C_6F_5CF_2CF_2Cu$, shows good reactivity towards a myriad of structurally diverse and and alkenyl iodides. This protocol is easy to handle, ready to scale up and applicable for the synthesis of relative complex molecules, thus providing a convenient method for facile access to tetrafluoroethylene-bridged structures.

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

(Trifluoromethyl)trimethylsilane (TMSCF₃), often called Ruppet-Prakash reagent, is arguably the most widely used trifluoromethylating agent.²⁶⁻³⁰ In 2011, our group, in collaboration with the Prakash group, revealed that TMSCF₃ 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 TMSCF₃ 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 TMSCF₃ as the difluoromethylene source, controllable CF2-insertion into CuCF3 to generate CuCF2CF3 could be realized.³⁴ Inspired by this C1 to C2 process, we envisioned that it might be possible to insert CF₂ into other C-M bonds. Herein, we report our latest progress in the fluorocarbon homologation reaction using TMSCF₃ as the difluoromethylene source. By carefully tuning the reaction conditions, controllable double insertion of CF2 into C6F5-Cu gives rise to $C_6F_5CF_2CF_2Cu$, which can be applied to the preparation of a diverse range of tetrafluoroethylene-bridged compounds (Scheme 1).

a) Previous work: single CF₂ insertion into CF₃Cu with TMSCF₃

 $CuCl + KF + TMSCF_3 \longrightarrow CuCF_3 \longrightarrow CuCF_2CF_3$

b) This work: double CF₂ insertion into C₆F₅Cu with TMSCF₃

 $CuCl + KF + TMSC_6F_5 \longrightarrow CuC_6F_5$

Scheme 1 Fluorocarbon homologation with TMSCF_3 . TMS = trimethylsilyl.

TMSCF₃ CuCF₂CF₂C₆F₅

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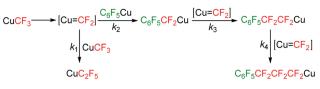
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Results and discussion

Our investigation commenced with the preparation of C₆F₅-CF₂CF₂Cu from TMSC₆F₅ and TMSCF₃. Initially, we used 1 equivalent of TMSC₆F₅ as the C₆F₅Cu precursor, 1 equivalent of TMSCF₃ 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 ¹⁹F NMR spectroscopy revealed that C₆F₅CF₂CF₂Cu (21%), C₆F₅Cu (57%) and CuCF₃ (37%) were formed; no single CF₂-insertion product C₆F₅CF₂Cu could be detected (Table 1, entry 1). When adding 2 equivalents of difluorocarbene source TMSCF₃, we found that the desired product C₆F₅CF₂CF₂Cu was formed in 79% yield, in conjunction with C₆F₅Cu (3%), CuCF₃ (10%) and CuC₂F₅ (5%) (entry 2).³⁵ If 3 equivalents of TMSCF₃ was used, C₆F₅CF₂CF₂Cu was formed in 83% yield, along with $CuCF_3$ (16%) and CuC_2F_5 (12%) being formed; neither C_6F_5Cu nor triple CF₂-insertion product C₆F₅CF₂CF₂CF₂Cu could be detected (entry 3). These results (entries 1-3) clearly indicate that the TMSCF₃-derived difluorocoppercarbene (Cu=CF₂) species³⁴ could selectively undergo double CF₂-insertion into C₆F₅Cu, regardless of the amount of TMSCF₃ 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=CF₂ (Scheme 2). As to the possible intermediate, C₆F₅CF₂Cu, its benzylic C-Cu bond is highly reactive and tended to insert another CF₂ unit to give C₆F₅CF₂CF₂Cu;^{24,25} the resulting C₆F₅CF₂CF₂Cu has lower reactivity than CuCF₃ because of its longer fluoroalkyl chain.^{24,25} Therefore, even in the presence of excess of TMSCF₃, triple CF₂-



Scheme 2 Proposed reaction mechanism.

insertion into C₆F₅Cu could not be observed; in that case, the CF₂-insertion into CuCF₃ to generate CuC₂F₅ would be favoured. Altogether, the relative reaction rate of each step is $k_3 > k_2 > k_1 > k_4$.

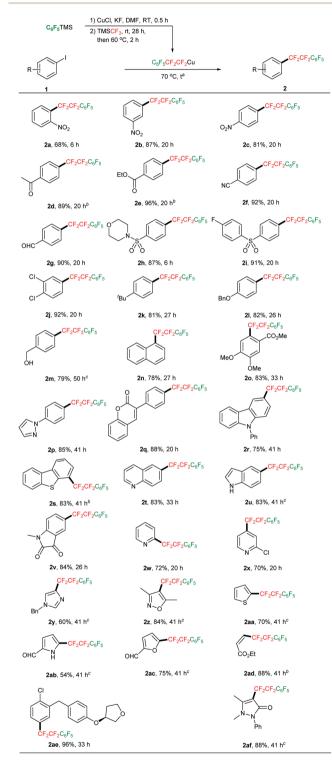
With this understanding in mind, we went on to optimize the reaction conditions in order to increase the yield of C₆F₅-CF₂CF₂Cu and minimize those of CuCF₃ and CuC₂F₅. By using 2 equivalents of TMSCF₃ and prolonging reaction time to 20 hours, C₆F₅CF₂CF₂Cu was formed in 87% yield (entry 4). When we decreased the amount of CuCl from 4 equivalents to 3 equivalents, only trace of C6F5CF2CF2Cu was observed, with >80% C₆F₅Cu and CuCF₃ 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 CuCF₃ was always observed, we tried to speed up the decomposition of CuCF₃ at elevated temperatures. However, when the reaction was carried out at 50 °C, although no CuCF3 was observed, a larger amount of CuC2F5 was detected, and C₆F₅CF₂CF₂Cu 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 C₆F₅Cu. Gratifyingly, the yield of C₆F₅CF₂CF₂Cu was increased slightly (entry 7). In light of the decomposition of $CuCF_3$ to $Cu=CF_2$ would release

	$TMSC_6F_5 + CuCl + KF \xrightarrow{DMF} C_6F_5Cu \xrightarrow{TMSCF_3} C_6F_5CF_2CF_2Cu$				
				Yield (%)	
Entry	$\mathrm{TMSC}_6\mathrm{F}_5:\mathrm{CuCl}:\mathrm{KF}:\mathrm{TMSCF}_3$	<i>t</i> (h)	$T(^{\circ}C)$	$C_6F_5C_2F_4Cu$	C ₆ F ₅ Cu/CuCF ₃ /CuC ₂ F 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 ^{<i>b</i>}	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 TMSC₆F₅ (1.0 equiv.) scale. Yields were determined by ¹⁹F NMR spectroscopy using PhOCF₃ as an internal standard. n.d. = not detected. ^{*b*} TMSC₆F₅ and TMSCF₃ were added simultaneously without the pre-preparation of C₆F₅Cu. ^{*c*} TMSCF₃ was added in three portions for every 4 hours. ^{*d*} TMSCF₃ was added in three portions for every 6 hours. ^{*e*} TMSCF₃ 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.

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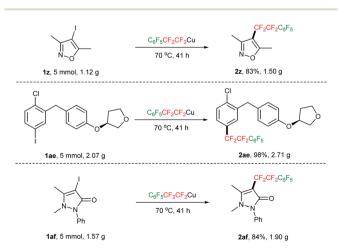
fluoride ions, we surmised that the amount of externally added KF could be reduced. However, lowering down KF to 2 equivalents gave inferior result (entry 8). To further decrease the yield



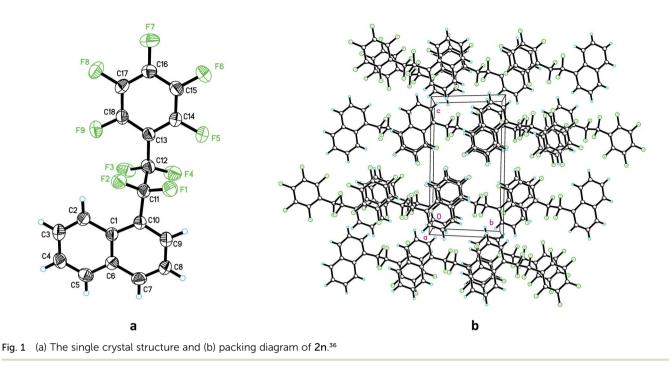
Scheme 3 Perfluorophenylethylation of (hetero)aryl iodides with TMSCF₃-derived C₆F₅CF₂CF₂CL. ^{*a*} Unless otherwise noted, reactions were performed on 0.5 mmol of **1** (1.0 equiv.) scale, and TMSCF₃ was added in two portions every 6 h; 1.5 equivalents of TMSC₆F₅ was used; the molar ratio of TMSC₆F₅ : CuCl : KF : TMSCF₃ = 1 : 4 : 3 : 1.9. ^{*b*} 1.6 equivalent of TMSC₆F₅ was used. ^{*c*} 1.8 equivalent of TMSC₆F₅ was used.

of CuC_2F_5 , we envisaged that adding TMSCF₃ in batches to decrease the concentration of $CuCF_3$ might be helpful. After some brief optimizations and decreasing the amount of TMSCF₃ to 1.9 equivalents (entries 9–11), $C_6F_5CF_2CF_2Cu$ was formed in 92% yield, together with 2% of C_6F_5Cu 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 C_6F_5Cu and little amounts of $CuCF_3$ (1%) and CuC_2F_5 (2%) could be detected, with $C_6F_5CF_2CF_2Cu$ being formed in 89% yield (entry 13).

With the optimized conditions (Table 1, entry 13) in hand, the reactivity of this TMSCF3-derived C6F5CF2CF2Cu 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), iodopyrrole (2ab) and iodofuran (2ac), participated in this perfluorophenylethylation to afford corresponding products in moderate to good yields (54-84%). Iodoalkene 1ad also showed good reactivity towards C₆F₅CF₂CF₂Cu, furnishing the desired product 2ad in 88% yield. This protocol is also



Scheme 4 Gram-scale synthesis.



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 $-CF_2CF_2$ - bridged molecules.

The inherent value of our controllable double CF_2 -insertion strategy with TMSCF₃ 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 C10–C11–C12–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 π – π 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 C_6F_5Cu was realized using TMSCF₃ as the diffuoromethylene source. The resulting $C_6F_5CF_2CF_2Cu$ species showed high reactivity towards various (hetero)aryl iodides and alkenyl iodides, providing an easy access to a variety of $-CF_2CF_2$ - bridged molecules. Compared with previous methods for the construction of $-CF_2CF_2$ - unit, this approach owns several merits such as utilizing commercially available and environmentally benign reagents as the CF₂ source, easy to handle, broad substrate scope and mild conditions. This double CF₂-insertion strategy represents the second generation of fluorocarbon homologation reactions *via* difluoromethylene insertion using TMSCF₃ (the first generation is single CF₂-insertion into CuCF₃). Further efforts to seek after novel CF₂-insertion reactions using TMSCF₃ are currently underway in our laboratory.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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- 34 Q. Xie, L. Li, Z. Zhu, R. Zhang, C. Ni and J. Hu, Angew. Chem., Int. Ed., 2018, 57, 13211–13215.
- 35 The chemical shifts of these fluoroalkylcopper/ fluoroarylcopper species were assigned as follows (in ppm): $C_6F_5CF_2CF_2Cu$, -101.1 (t, 2F), -106.6 (s, 2F), -139.4 (m, 2F), -153.1 (t, 1F), -163.9 (t, 2F); C_6F_5Cu , -111.0 (d, 2F), -163.3 (t, 1F), -164.3 (t, 2F); $CuCF_3$, -26.7 (s, 3F); CuC_2F_5 , -84.0 (s, 3F), -112.4 (s, 2F).
- 36 CCDC 1957757† contains the supplementary crystallographic data for compound 2**n**.