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Controllable double CF₂-insertion into sp² 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 $TMSCF_3$ 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 aryl, heteroaryl 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.

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. Among various fluorinated functionalities, the tetrafluoroethylene motif (-CF₂CF₂-) has attracted considerable attention because of its applications in agrochemicals and liquid-crystalline materials. Moreover, the introduction of -CF₂CF₂- 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. 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 SF₄ and DeoxoFluor;⁹⁻¹¹ (2) fluorination of C-C triple bonds using F₂;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 ozone-depleting substances (ODS). As such, developing a new method to incorporate -CF₂CF₂- structure motif into organic

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 C₆F₅CF₂CF₂Cu, which can be applied to the preparation of a diverse range of tetrafluoroethylene-bridged compounds

Scheme 1 Fluorocarbon homologation with TMSCF $_3$. TMS = trimethylsilyl.

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a) Previous work: single CF_2 insertion into CF_3Cu with $TMSCF_3$ $CuCI + KF + TMSCF_3 \longrightarrow CuCF_2 \longrightarrow CuCF_2 CF_3$ b) **This work**: double CF_2 insertion into C_6F_5Cu with $TMSCF_3$ $CuCI + KF + TMSC_6F_5 \longrightarrow CuC_6F_5 \xrightarrow{TMSCF_3} CuCF_2 CF_2 C_6F_5$

Results and discussion

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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 CuCF₃ (16%) and CuC₂F₅ (12%) being formed; neither C₆F₅Cu 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 selec-

tivity 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 reac-

tivity than CuCF₃ because of its longer fluoroalkyl chain.^{24,25}

Therefore, even in the presence of excess of TMSCF₃, triple CF₂-

$$\begin{array}{c|c} \text{CuCF}_3 & \longrightarrow [\text{Cu=CF}_2] \xrightarrow{C_6F_5\text{CU}} & \text{C}_6F_5\text{CF}_2\text{Cu} & \xrightarrow{[\text{Cu=CF}_2]} & \text{C}_6F_5\text{CF}_2\text{CF}_2\text{Cu} \\ \hline & k_1 & \text{CuCF}_3 & k_4 & \text{|Cu=CF}_2 \\ & & \text{CuC}_2F_5 & \text{C}_6F_5\text{CF}_2\text{C$$

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 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=CF₂ 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 TMSCF₃ 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 CuCF₃ to Cu=CF₂ would release

Table 1 Optimization of reaction conditions for the double CF_2 insertion into C_6F_5Cu with TMSCF₃^a

$$\mathsf{TMSC}_6\mathsf{F}_5 + \mathsf{CuCl} + \mathsf{KF} \xrightarrow{\qquad \qquad \mathsf{DMF} \qquad \qquad } \mathsf{C}_6\mathsf{F}_5\mathsf{Cu} \xrightarrow{\qquad \qquad \mathsf{TMSCF}_3 \qquad \qquad } \mathsf{C}_6\mathsf{F}_5\mathsf{CF}_2\mathsf{CF}_2\mathsf{Cu}$$

Entry	$TMSC_{6}F_{5}:CuCl:KF:TMSCF_{3}$	<i>t</i> (h)	<i>T</i> (°C)	Yield (%)	
				$C_6F_5C_2F_4Cu$	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^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^{ef}	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 C_6F_5Cu . ^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 C₆F₅CF₂CF₂Cu. ^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 CuC₂F₅, we envisaged that adding TMSCF₃ in batches to decrease the concentration of CuCF₃ might be helpful. After some brief optimizations and decreasing the amount of TMSCF₃ to 1.9 equivalents (entries 9-11), C₆F₅CF₂CF₂Cu was formed in 92% yield, together with 2% of C₆F₅Cu and 4% of CuCF₃ 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 C₆F₅Cu and little amounts of CuCF₃ (1%) and CuC₂F₅ (2%) could be detected, with C₆F₅CF₂CF₂Cu 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 arvl 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.

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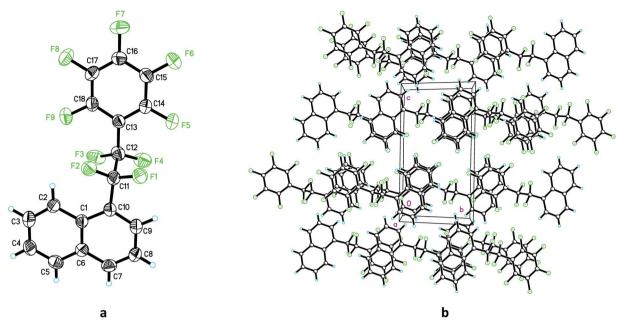


Fig. 1 (a) The single crystal structure and (b) packing diagram of 2n.36

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 -CF₂CF₂- bridged molecules.

The inherent value of our controllable double CF2-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 CF₂-insertion into C₆F₅Cu was realized using TMSCF₃ as the difluoromethylene source. The resulting C₆F₅CF₂CF₂Cu species showed high reactivity towards various (hetero)aryl iodides and alkenyl iodides,

providing an easy access to a variety of -CF2CF2- bridged molecules. Compared with previous methods for the construction of -CF₂CF₂- 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.

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- 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 **2n**.