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Controllable Single and Double Difluoromethylene Insertions into C−Cu Bonds: Copper-Mediated Tetrafluoroethylation and Hexafluoropropylation of Aryl Iodides with $TMSCF_2H$ and $TMSCF_2Br$

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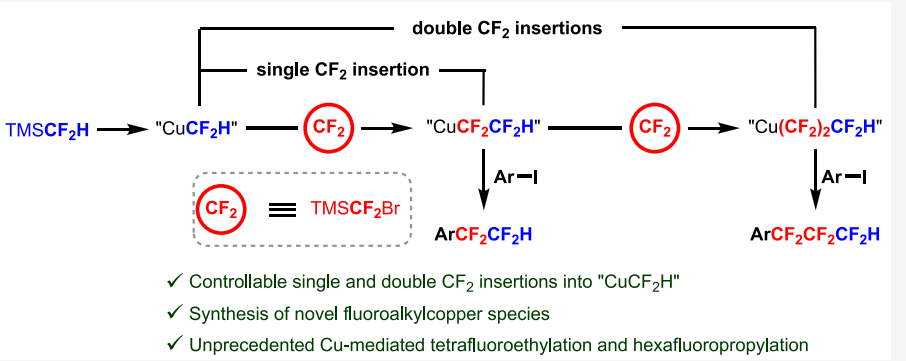

ABSTRACT: The selective difluoromethylene insertion into a C−Cu bond is a challenging task and is currently limited to either a single CF_2 insertion into $CuCF_3$ or double CF_2 insertions into CuC_6F_5 (or (*Z*)-CF_3CF = $CFCu$). Achieving both selective single and double CF_2 insertions into the same C−Cu bond is even more difficult. Herein, highly controllable single and double CF_2 insertions into $CuCF_2H$ species with a $TMSCF_2Br$ reagent have been described, affording two previously unknown fluoroalkylcopper species "$Cu(CF_2)_nCF_2H$" (n = 1 and 2) independently under different reaction conditions. This work represents the first example of both single and double CF_2 insertions into the same C−Cu bond in a highly selective manner. The synthetic value of the obtained "$Cu(CF_2)_nCF_2H$" (n = 1 and 2) species is demonstrated by their reactions with aryl iodides, halogenation agents, and cinnamyl chloride, which enables the direct transfer of HCF_2CF_2 and $HCF_2CF_2CF_2$ moieties into organic molecules. The key to controllable fluorocarbon chain elongation from C_1 to C_2 and from C_1 to C_3 is presumably attributed to the different reactivities of "$Cu(CF_2)_nCF_2H$" species (n = 0, 1, 2 and 3) and the loading of the $TMSCF_2Br$ reagent.

INTRODUCTION

Organofluorine compounds have been widely used in pharmaceuticals, agrochemicals, and advanced materials due to their unique physicochemical properties.[1] In this context, the selective introduction of fluoromethyl groups into organic molecules has attracted much attention over the past decades, such as trifluoromethylation,[2] difluoromethylation,[3] and monofluoromethylation.[4] In particular, the difluoromethyl functionality (CF_2H) is known as a bioisostere of OH and SH groups and as a lipophilic hydrogen bond donor,[5] which has been frequently used in the design of new pharmaceuticals[6,7] and agrochemicals.[8] As homologs of the CF_2H group, 1,1,2,2-tetrafluoroethyl (HCF_2CF_2) and 1,1,2,2,3,3-hexafluoropropyl ($HCF_2CF_2CF_2$) groups possess the combined physicochemical properties of difluoromethyl and perfluoroalkyl groups. For instance, HCF_2CF_2-containing compounds exhibit high antiparasitic activity and have been applied in agrochemicals,[9] such as Tetraconazole (a fungicide),[10] Nifluridide (an animal systemic insecticide),[11] and Hexaflumuron (a termite bait).[12] Despite the potential applications of HCF_2CF_2- or $HCF_2CF_2CF_2$-containing compounds, their synthetic methods are scarce. Conventionally, tetrafluoroethylated molecules are prepared by the deoxyfluorination of glyoxal hydrates[13] or by transferring the CF_2CF_2 fragment (derived from tetrafluoroethylene or 1,2-dibromotetrafluoroethane) into N-, O-, and S-nucleophiles.[14,15] Recently, a palladium-catalyzed difluorocarbene transfer reaction was developed to afford tetrafluoroethylated arenes as major products.[16] However, these methods suffer from the narrow substrate scope, or the requirement of either the explosive tetrafluoroethylene or the ozone-depleting 1,2-dibromotetra-

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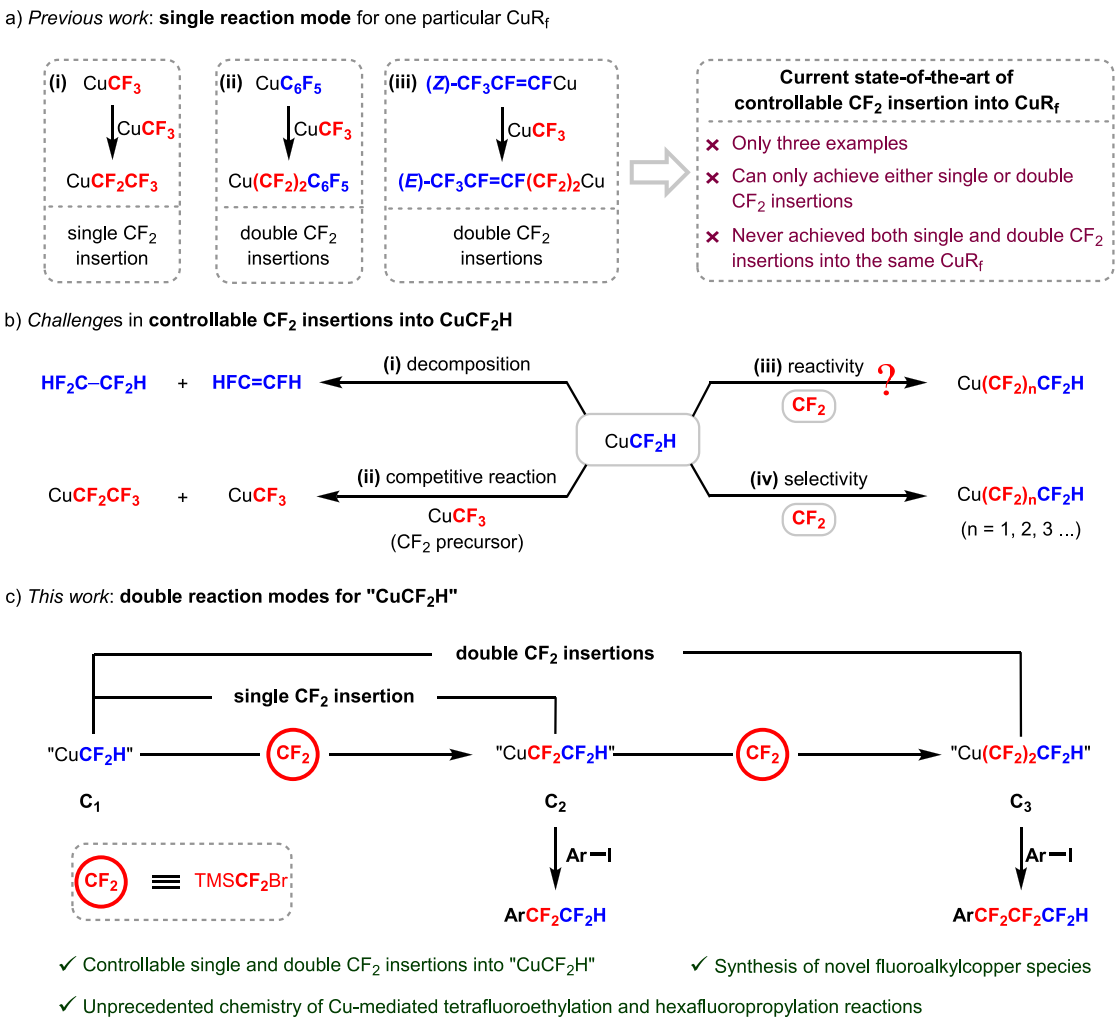
Scheme 1. Controllable CF_2 Insertion into CuR_f Species



fluoroethane. As for hexafluoropropylated compounds, to our knowledge, their efficient and practical synthesis has never been reported, probably owing to the unavailability of $HCF_2CF_2CF_2$-containing starting materials.[17] Furthermore, the terminal hydrogen in the tetrafluoroethyl or hexafluoropropyl group increases the polarity of these products (compared with those of their perfluoroethylated and perfluoropropylated analogs),[18] which may offer a weak point for biodegradation, making these products more acceptable environmentally. With these considerations, we envisaged that the development of efficient 1,1,2,2-tetrafluoroethylation and 1,1,2,2,3,3-hexafluoropropylation methods using readily available starting materials could be desirable for many applications.

On the other hand, controllable difluoromethylene (CF_2) insertion has been considered as a feasible strategy for fluorocarbon chain elongation. Some remarkable CF_2 carbene homologation reactions using $TMSCF_3$ have been reported recently.[19,20c,22c,24] Indeed, single CF_2 insertion into trifluoromethylcopper was reported in 1986;[20] however, controllable double CF_2 insertions into trifluoromethylcopper failed, with a complex mixture of oligomers being obtained (Scheme 1a-i).[21] Furthermore, double CF_2 insertions into perfluorophenyl/vinylcopper were subsequently realized, whereas their single CF_2 insertion products were very reactive to be secured (Scheme 1a-ii,a-iii).[22] To the best of our knowledge, over the past 30 years, fluoroalkylcopper species that are able to participate in controllable CF_2 insertion processes are only limited to $CuCF_3$, CuC_6F_5, and (*Z*)-CF_3CF=$CFCu$ (Scheme 1),[20,22] and, more remarkably, achieving both controllable single and double CF_2 insertions into the same fluoroalkylcopper species under different conditions still remains a formidable challenge.

To tackle this challenge, we envisioned that if we chose difluoromethylcopper ($CuCF_2H$) as a starting material and subject it to both single and double difluoromethylene insertions under different reaction conditions, both $CuCF_2CF_2H$ and $CuCF_2CF_2CF_2H$ species might be selectively formed for the desired 1,1,2,2-tetrafluoroethylation and 1,1,2,2,3,3-hexafluoropropylation. However, to achieve controllable CF_2 insertions into $CuCF_2H$, several issues have to be considered: (1) $CuCF_2H$ is less stable than $CuCF_3$ and has a tendency to decompose (Scheme 1b-i);[23] (2) when $CuCF_3$ is used as the difluoromethylene source, it will also undergo a difluoromethylene insertion reaction (Scheme 1b-ii);[22c] (3) the reactivity (Scheme 1b-iii) and selectivity (Scheme 1b-iv) of $CuCF_2H$ should be well tuned (Scheme 1b-iv).[21] In alignment with our continuing efforts in fluorocarbon-chain elongation,[20c,22c,24] we have investigated both single and double CF_2 insertions into "$CuCF_2H$", providing an access to scarcely

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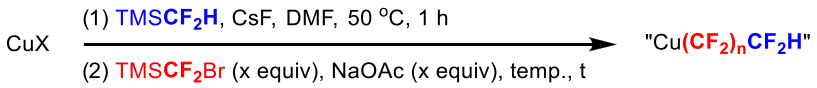
Table 1. Optimization of Reaction Conditions for Single CF_2 Insertion into "$CuCF_2H$"



							"Cu$(CF_2)_nCF_2H$" (%)[a]		
entry	x (equiv)	CuX (equiv)	$TMSCF_2H$ (equiv)	CsF (equiv)	temp. (°C)	t (h)	n = 1	n = 2	n = 3
1	2.50	CuI (1.00)	2.00	2.50	rt	9.0	0	27	21
2	1.50	CuI (1.00)	2.00	2.50	rt	9.0	0	35	8
3	1.20	CuI (1.00)	2.00	2.50	rt	9.0	25	23	0
4	1.00	CuI (1.00)	1.00	2.50	rt	9.0	62	14	0
5	1.00	CuI (1.30)	2.60	3.25	rt	9.0	69	10	0
6	1.00	CuI (1.50)	3.00	3.75	rt	9.0	59	28	6
7	1.00	CuI (1.30)	3.25	3.25	rt	8.0	77	10	0
8	1.00	CuBr (1.30)	3.25	3.25	rt	8.0	67	16	0
9	1.00	CuCl (1.30)	3.25	3.25	rt	8.0	50	24	0
10	1.00	CuOAc (1.30)	3.25	3.25	rt	8.0	0	0	0
11	1.00	IPrCuO^{t}Bu (1.30)	3.25	3.25	rt	8.0	0	0	0
12	1.00	IPrCuCl (1.30)	3.25	3.25	rt	8.0	0	0	0
13	1.00	CuSCN (1.30)	3.25	3.25	rt	8.0	80	trace	0
14	1.00	CuSCN (1.30)	3.25	3.25	50	4.0	75	6	0
15	1.00	CuSCN (1.30)	3.25	3.25	30	4.0	81	4	0
16	1.00	CuSCN (1.30)	3.25	3.25	30	0.8	96	3	0
17[b]	1.00	CuSCN (1.30)	3.25	3.25	30	0.8	94	5	0
18[c]	1.00	CuSCN (1.30)	3.25	3.25	30	1.0	71	3	0

[a]Reactions were performed on a 0.200 mmol scale. Yields were determined by ^{19}F NMR using $PhCF_3$ as an internal standard. Yields of all products were calculated with the following equation: yield = amount of the formed product/theoretical amount of the product (for details, see Supporting Information). [b]Reactions were performed on a 5.000 mmol scale. [c]Without NaOAc.

studied tetrafluoroethylcopper[25] and previously unknown hexafluoropropylcopper. With two fluoroalkycopper species in hand, we successfully investigated the unprecedented copper-mediated tetrafluoroethylation and hexafluoropropylation reactions (Scheme 1c).

RESULTS AND DISCUSSION

Since our first report of $TMSCF_2Br$ in the [2 + 1] cycloaddition with alkynes in 2011,[26a] $TMSCF_2Br$ has been widely used as a powerful difluorocarbene source by us[26] and others.[27] Given its highly tunable characteristic in releasing difluorocarbene under a variety of mild conditions, $TMSCF_2Br$ was chosen by us as a CF_2 source (instead of $CuCF_3$) in this study. In pilot experiments [see Tables 1 and S1–S4], a mixture of CuI, CsF, and commercially available $TMSCF_2H$ in DMF was stirred at 50 °C for 1 h to produce "$CuCF_2H$", and then, the reaction conditions of controllable single CF_2 (from $TMSCF_2Br$) insertion into the formed "$CuCF_2H$" were systematically screened. Notably, adding no more than the necessary amount of $TMSCF_2Br$ is the key to diminishing multiple CF_2 insertions into "$CuCF_2H$" (entries 1–4). The ratios among CuI, CsF, and $TMSCF_2H$ were found to affect not only the yield and composition of "$CuCF_2H$" but also the selectivity of the single CF_2 insertion process (entries 4–7). With the optimized ratios of CuI, CsF, and $TMSCF_2H$ (1.30:3.25:3.25, entry 7), other cuprous salts were examined (entries 8–13). Among the copper halides, CuI showed a superior result in single CF_2 insertion compared with CuBr and CuCl (entries 8–9). The addition of an ancillary ligand such as OAc and the sterically bulky *N*-heterocyclic carbene IPr [1,3-bis(2,6-diisopropylphenyl)-1,3-dihydro-2*H*-imidazol-2-ylidene] inhibited the desired CF_2 insertion process (entries 10–12). However, the use of CuSCN resulted in good yield and excellent selectivity (entry 13). After further screenings of the reaction temperature and time (entries 14–16), the single CF_2 insertion product "$CuCF_2CF_2H$" was obtained in 96% yield, with 3% yield of "$Cu(CF_2)_2CF_2H$" at 30 °C within 50 min (entry 16). The good reproducibility was demonstrated by the scale-up reaction (entry 17). A lower selectivity and yield of "$CuCF_2CF_2H$" were observed in the absence of NaOAc (entry 18), which suggests that NaOAc could facilitate the activation of $TMSCF_2Br$ and therefore promote the single CF_2 insertion into "$CuCF_2H$". The thermal stability of "$CuCF_2CF_2H$" species was monitored by ^{19}F NMR spectroscopy at the ambient temperature under an inert atmosphere, and it was found that only 6% of "$CuCF_2CF_2H$" decomposed even after 6 days (for details, see SI).

With the single CF_2 insertion product "$CuCF_2CF_2H$" in hand, we turned to investigate its synthetic power in coupling reactions with aryl iodides. The results are shown in Scheme 2. To our delight, the pregenerated "$CuCF_2CF_2H$" species was able to efficiently tetrafluoroethylate a wide range of aryl iodides, yielding the corresponding HCF_2CF_2-containing arenes in high yields. For the π-extended aromatic rings (**1a–c**), the corresponding tetrafluoroethylated products were afforded in moderate-to-good yields. Aryl iodides bearing electron-donating groups such as phenyl (**1d**), methylthiol (**1e**), and diphenylamine (**1f**) could deliver products **2d–2f** in 55–71% yields. The bromo-substituted aryl iodide at the *para* position was also tolerated with the product **2g** in 71% yield. Aryl iodides with the electron-deficient groups including nitro (**1h**, **1p**, and **1q** in *para*, *ortho*, and *meta* positions) and cyano (**1i**) groups afforded the corresponding tetrafluoroethylated products in 71–93% yields. Furthermore, the present tetrafluoroethylation reaction could tolerate various functional groups such as aldehyde (**1j**), ketone (**1k**), and ester (**1l–1o**). In addition, structurally diverse aryl iodides with two substituents were also viable in this reaction, yielding the

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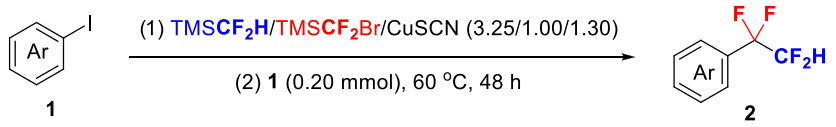
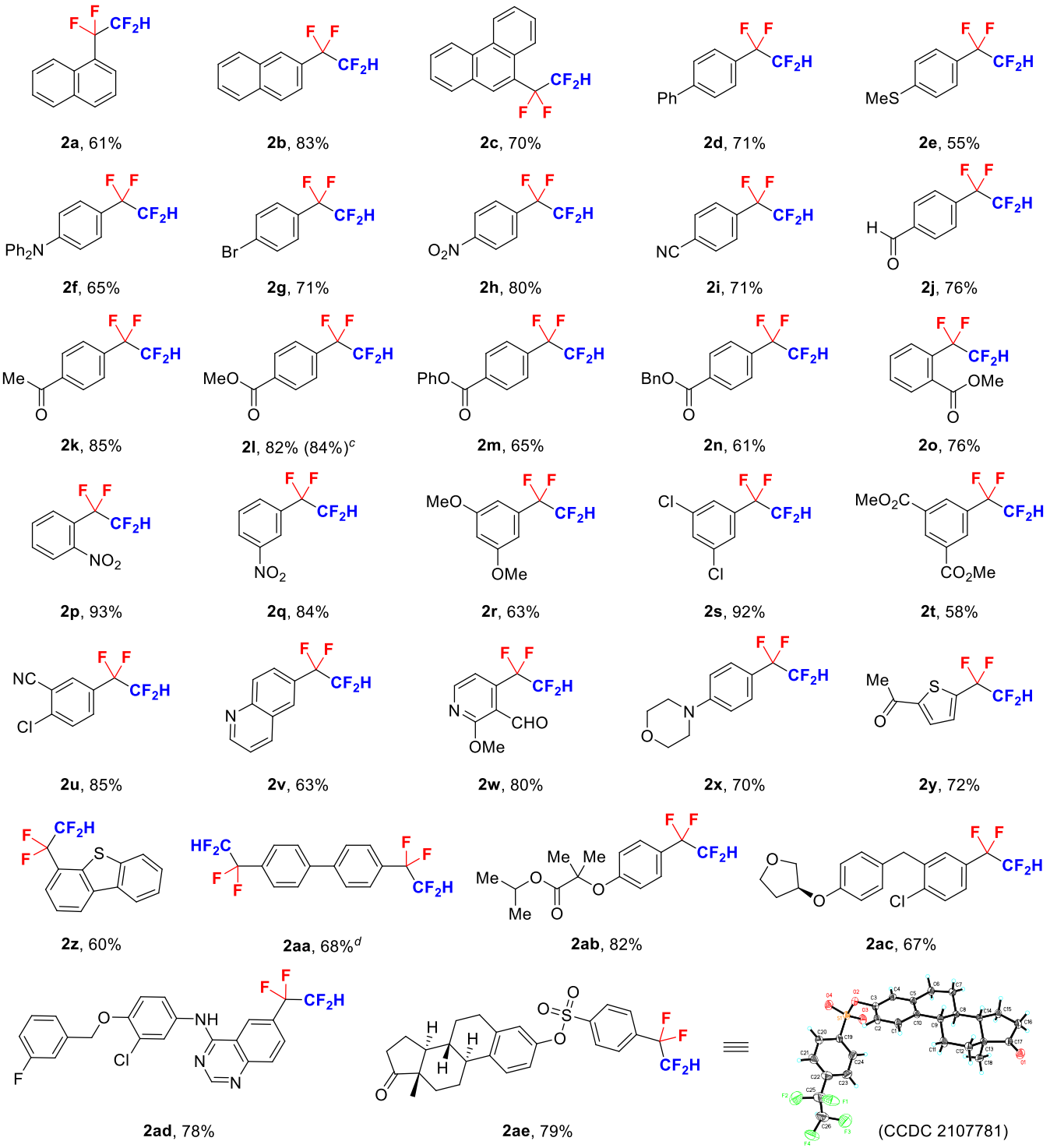
Scheme 2. Tetrafluoroethylation of Aryl Iodides and "$CuCF_2CF_2H$"[a,b]





[a]Preparation of "$CuCF_2CF_2H$": CuSCN (6.50 mmol), CsF (16.25 mmol), DMF (25 mL), $TMSCF_2H$ (16.25 mmol), 50 °C, 1 h. Then, $TMSCF_2Br$ (5.00 mmol), NaOAc (5.00 mmol), 30 °C, 50 min. The DMF solution of "$CuCF_2CF_2H$" was used after filtration. [b]Prepared "$CuCF_2CF_2H$" (1.20 equiv), **1** (0.20 mmol), 60 °C, 48 h. Isolated yields of **2** based on the loading of aryl iodides **1** (0.20 mmol). [c]Reaction conditions: CuSCN (0.33 mmol), CsF (0.81 mmol), DMF (1.25 mL), $TMSCF_2H$ (0.81 mmol), 50 °C, 1 h. Then, $TMSCF_2Br$ (0.25 mmol), NaOAc (0.25 mmol), 30 °C, 50 min. Then, **1l** (0.20 mmol), 60 °C, 48 h. ^{19}F NMR yield of **2l** based on the loading of **1l** (0.20 mmol) using $PhCF_3$ as an internal standard. [d]"$CuCF_2CF_2H$" (2.40 equiv) was added.

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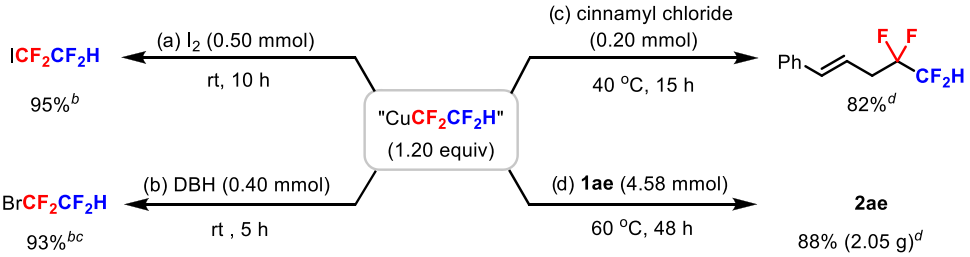
Scheme 3. Synthetic Applications of "$CuCF_2CF_2H$"[a]



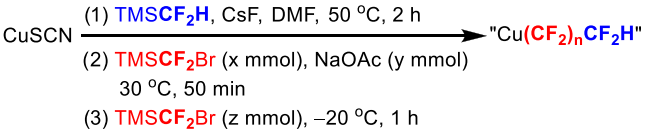
[a]Preparation of "$CuCF_2CF_2H$": CuSCN (6.50 mmol), CsF (16.25 mmol), DMF (25 mL), $TMSCF_2H$ (16.25 mmol), 50 °C, 1 h. Then, $TMSCF_2Br$ (5.00 mmol), NaOAc (5.00 mmol), 30 °C, 50 min. The DMF solution of "$CuCF_2CF_2H$" was used after filtration. [b]^{19}F NMR yield using $PhCF_3$ as an internal standard. [c]"$CuCF_2CF_2H$" (0.20 mmol, 1.00 equiv) was added. [d]Isolated yields.

desired products **2r**−**2u** in 58−92% yields. Medicinally relevant heterocycles including quinoline (**1v**), pyridine (**1w**), morpholine (**1x**), thiophene (**1y**), and dibenzothiophene (**1z**) were competent in this coupling reaction, as demonstrated by the formation of the corresponding tetrafluoroethylation products **2v**−**2z** in moderate-to-good yields. Double-tetrafluoroethylation of 4,4′-diiodobiphenyl with 2.4 equivalents of "$CuCF_2CF_2H$" was also found to be possible, affording the product **2aa** in 68% yield. Notably, the potential use of this protocol for the late-stage functionalization of bioactive molecules was demonstrated by tetrafluoroethylation of four pharmaceutical intermediates, and aryl iodides **1ab**−**1ad** (as the intermediates of antilipidemic drug fenfibrate,[28] SGLT-2 inhibitor Empagliflozin,[29] and antitumor drug Lapatinib[30]) were smoothly transformed into products **2ab**−**2ad** in 67−82% yields. Moreover, the estrone derivative **1ae** could be readily converted to the product **2ae** in 79% yield, and its structure was confirmed by single-crystal X-ray analysis.

The synthetic potency of "$CuCF_2CF_2H$" was further demonstrated by its tetrafluoroethylation of other electrophiles (Scheme 3). Halogenations of "$CuCF_2CF_2H$" by I_2 and DBH (1,3-dibromo-5,5-dimethylhydantoin) at room temperature proceeded smoothly, affording the corresponding products ICF_2CF_2H and $BrCF_2CF_2H$ in excellent NMR yields (Scheme 3a,3b). Cinnamyl chloride was also proved to be a good coupling partner (Scheme 3c). Furthermore, the present synthetic protocol was successfully applied in the gram-scale synthesis of tetrafluoroethylated estrone derivative **2ae** (88% yield; see Scheme 3d).

Encouraged by our success in the selective formation of "$CuCF_2CF_2H$", we wondered whether the controllable double CF_2 insertion product "$Cu(CF_2)_2CF_2H$" could be formed by the addition of the appropriate amount of $TMSCF_2Br$. However, the double CF_2 insertion product "$Cu(CF_2)_2CF_2H$" was obtained with poor selectivity (Table S6 in SI). Under these reaction conditions, with a ratio of CuSCN/$TMSCF_2H$/CsF of 1:2.5:2.5, the excess difluoromethyl anion probably interfered with the further CF_2 insertion process via ligand exchange with the formed "$CuCF_2CF_2H$". To overcome this dilemma, we planned to use $[XCuCF_2H]^-$ species as the starting material and reduce the presence of other anions (especially the difluoromethyl anion) to improve the selectivity of double CF_2 insertions. After extensive screening of the reaction parameters, to our delight, the selectivity and yield of "$Cu(CF_2)_2CF_2H$" were drastically improved when the ratio of CuSCN/$TMSCF_2H$/CsF was set as 1/2.5/2.5, but adding CuSCN in two portions (Table 2, entry 1). Either adding another portion of NaOAc (entry 2) or reducing the loading of $TMSCF_2Br$ at the last step could not result in the highly selective formation of "$Cu(CF_2)_2CF_2H$" (entry 3). An equally good result was obtained in the absence of NaOAc during the whole process, which largely simplified the synthetic procedure (entry 4 vs entry 1). Interestingly, by adding the second portion of $TMSCF_2Br$ at −20 °C (entry 5), higher yields of single- and double CF_2 insertion products and a lower yield of the triple CF_2 insertion product were afforded compared with that obtained when adding it at room temperature (entry 4). We also changed the amount of $TMSCF_2Br$ to 0.42 mmol and added the second portion of $TMSCF_2Br$ at −20 °C; it was found that the single CF_2 insertion product "$CuCF_2CF_2H$" was almost consumed, and the target product "$Cu(CF_2)_2CF_2H$" was delivered in 62% yield, along with a 2% yield of "$Cu(CF_2)_3CF_2H$" (entry 6). The thermal stability of "$Cu(CF_2)_2CF_2H$" was monitored by ^{19}F NMR spectroscopy under

Table 2. Optimization of the Reaction Conditions for the Double CF_2 Insertions into "$CuCF_2H$"



				"$Cu(CF_2)_nCF_2H$" (%)[b]		
entry[a]	x	y	z	n = 1	n = 2	n = 3
1	0.40	0.4	0.40	9	51	6
2[c]	0.40	0.4	0.40	1	38	7
3	0.40	0.4	0.30	24	48	3
4	0.40	0	0.40	4	52	5
5[d]	0.40	0	0.40	17	56	3
6[d]	0.42	0	0.42	<1	62	2

[a]Reaction conditions: CuSCN (0.26 mmol), CsF (1.30 mmol), DMF (1 mL), $TMSCF_2H$ (1.30 mmol), 50 °C, 1 h. CuSCN (0.26 mmol), 50 °C, 1 h. $TMSCF_2Br$ (*x* mmol), NaOAc (*y* mmol), 30 °C, 50 min. $TMSCF_2Br$ (*z* mmol), −20 °C, 1 h. [b]Yields were determined by ^{19}F NMR using $PhCF_3$ as an internal standard. Yields of all products were calculated with the following equation: yield = amount of formed product/theoretical amount of product (for details, see Supporting Information). [c]NaOAc (0.4 mmol) was added in the last step. [d]Second portion of $TMSCF_2Br$ was added at −20 °C.

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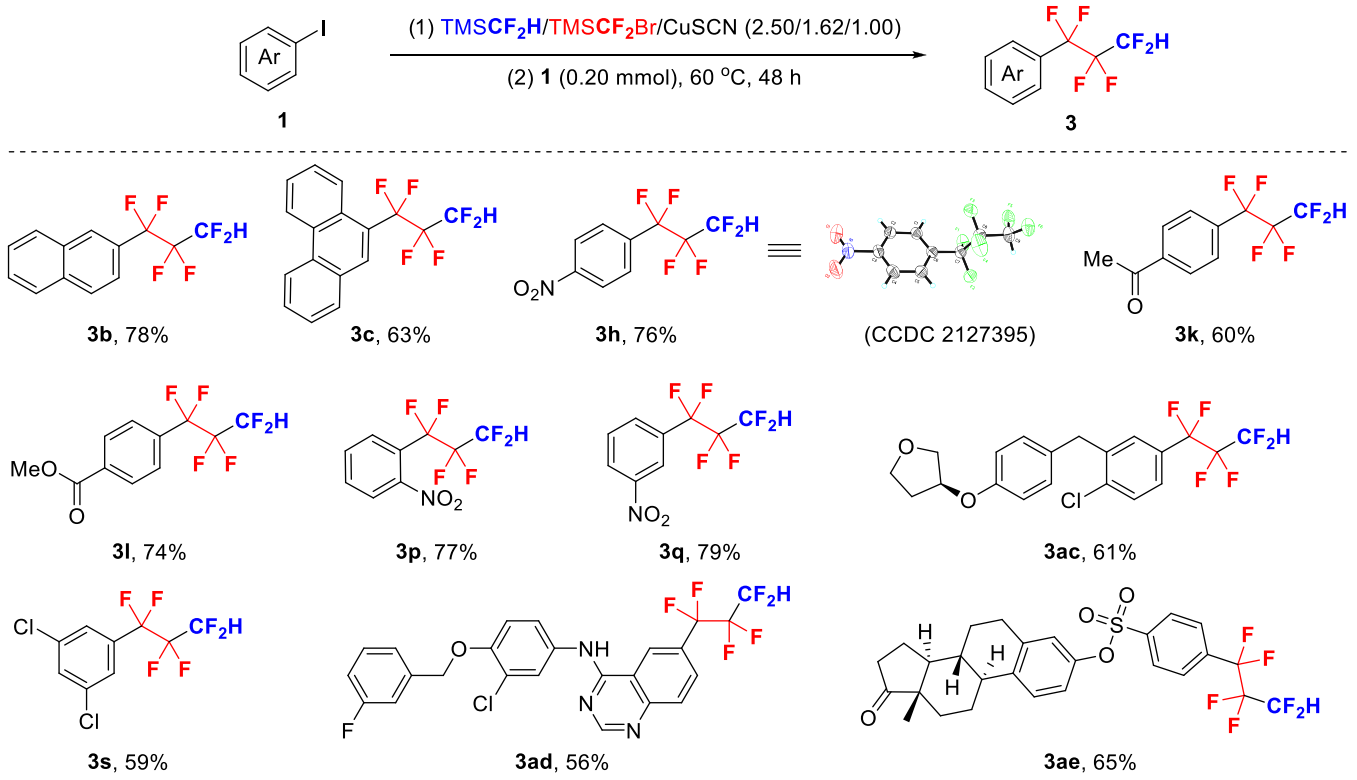
Scheme 4. Hexafluoropropylation of Aryl Iodides and "Cu$(CF_2)_2CF_2H$"[a,b]



[a]Reaction conditions: CuSCN (0.26 mmol), CsF (1.30 mmol), DMF (1 mL), $TMSCF_2H$ (1.30 mmol), 50 °C, 1 h. CuSCN (0.26 mmol), 50 °C, 1 h. $TMSCF_2Br$ (0.42 mmol), 30 °C, 50 min. $TMSCF_2Br$ (0.42 mmol), −20 °C, 1 h. **1** (0.20 mmol), 60 °C, 48 h. [b]Isolated yields of **3** based on the loading of aryl iodides **1** (0.20 mmol).

an inert atmosphere, and only 6% was decomposed even after 12 days (for details, see SI).

With "Cu$(CF_2)_2CF_2H$" (Table 2, entry 6) in hand, we assessed its synthetic value by couplings with aryl iodides (Scheme 4). It was found that 2-iodonaphthalene and 9-iodophenanthrene were viable in this reaction, yielding the corresponding products (**3b** and **3c**) in 78 and 63% yields, respectively. The hexafluoropropylation of 4-iodonitrobenzene also proceeded smoothly to yield the product **3h**, whose structure was confirmed by single-crystal X-ray analysis. Notably, this transformation was insensitive to the position of substituents (see **3h**, **3p**, and **3q**), and functionalities including acyl (**3k**), ester (**3l**), and chlorine (**3s**) were well tolerated. The synthetic potency of "Cu$(CF_2)_2CF_2H$" was further illustrated by the synthesis of hexafluoropropylated analogs of bioactive compounds such as SGLT-2 inhibitor Empagliflozin (**3ac**) and antitumor drug Lapatinib (**3ad**) as well as the late-stage modification of an estrone derivative (**3ae**).

To gain insights into the reaction, a set of experiments were conducted to explore the identity of "$CuCF_2H$", the active species, and the reaction pathway in a controllable CF_2 insertion process (Scheme 5). Initially, the reaction of 0.26 mmol of CuSCN, 0.65 mmol of CsF, and $TMSCF_2H$ in DMF at 50 °C for 1 h was conducted (a method for the preparation of "$CuCF_2H$"). Analysis of this solution by ^{19}F NMR spectroscopy indicated two "$CuCF_2H$" species at −114.5 ppm (species **A**) and −116.3 ppm (species **B**) (relative to $CFCl_3$) (Schemes 5(1-i) and S1). Interestingly, on changing the ratio of CuSCN/CsF/$TMSCF_2H$ from 1:2.5:2.5 (method a) to 5:1:1 (method b), only species **A** was detected (Schemes 5(1-ii) and S2); however, species **B** was formed as the dominant species when the ratio of CuSCN/CsF/$TMSCF_2H$ was 1:5:5 (method c; Schemes 5(1-iii) and S3). During the continuous monitoring of the mixture prepared by method c, species **A** began to grow slowly with a diminution of species **B** upon prolonging the time at room temperature (Schemes 5(1-iv) and S3). This result suggests that species **B** could be converted into species **A**. The remarkable conversion of species **B** to species **A** was found by the addition of another equivalent of CuSCN to the mixture (prepared by method c) at 50 °C within 1 h (Schemes 5(1-v)). Consistent with previous reports[23,31] species **A** at −114.5 ppm in DMF was identified as $[XCu(CF_2H)]^-$ (X = SCN or other anions), and species **B** at −116.3 ppm in DMF was identified as $[Cu(CF_2H)_2]^-$. Notably, compared with spectra i and v, completely different concentrations of species **A** and **B** were observed when retaining the same ratio of CuSCN/CsF/$TMSCF_2H$ (1:2.5:2.5) but adding CuSCN under different conditions. Unfortunately, our attempts to synthesize $[Ph_4P]^+[XCu(CF_2H)]^-$ and $[Ph_4P]^+[Cu(CF_2H)_2]^-$ by treating the mixture (prepared by method b or c) with Ph_4PCl at room temperature for 30 minutes failed.[32]

To elucidate the active species in the single CF_2 insertion process, the treatment of "$CuCF_2H$" prepared by different methods with $TMSCF_2Br$ activated by NaOAc at 30 °C for 50 min were tested (Scheme 5(4(2)) and Table S9). Notably, the single CF_2 insertion product "$CuCF_2CF_2H$" was obtained in 96 and 72% yields using "$CuCF_2H$" prepared by methods a and b, respectively (entries 1 and 2). Meanwhile, 16% yield of the single CF_2 insertion product was observed using "$CuCF_2H$" prepared by method c, in which species **B** was the dominant

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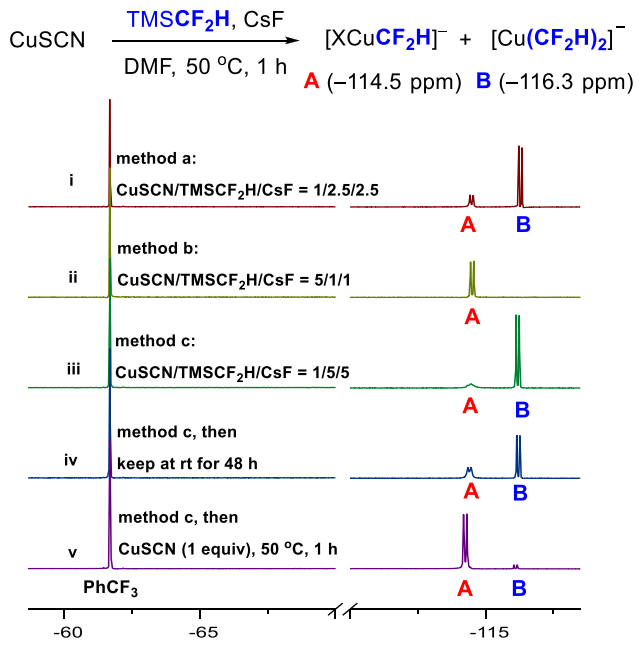
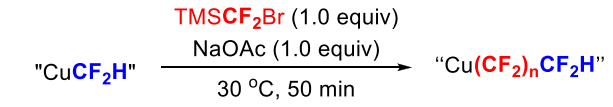
Scheme 5. Mechanistic Studies

1. Identification of "CuCF$_2$H"

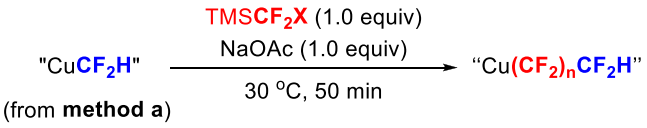


2. Active species in single CF$_2$ insertion process



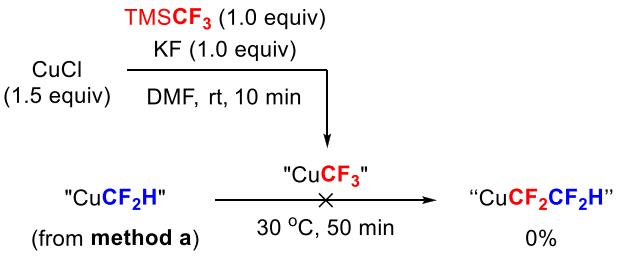
entry[a]	"CuCF$_2$H"	n = 1 (%)	n = 2 (%)
1	**method a**	96	3
2	**method b**	72	9
3	**method c**	16	4

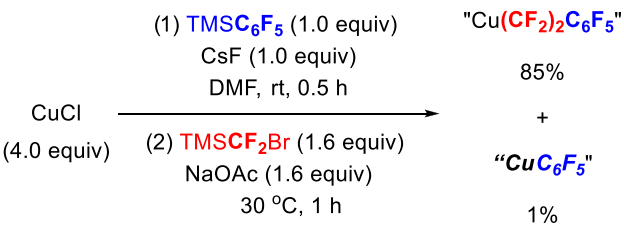
3. Fluorocarbon chain elongation with different CF$_2$ sources



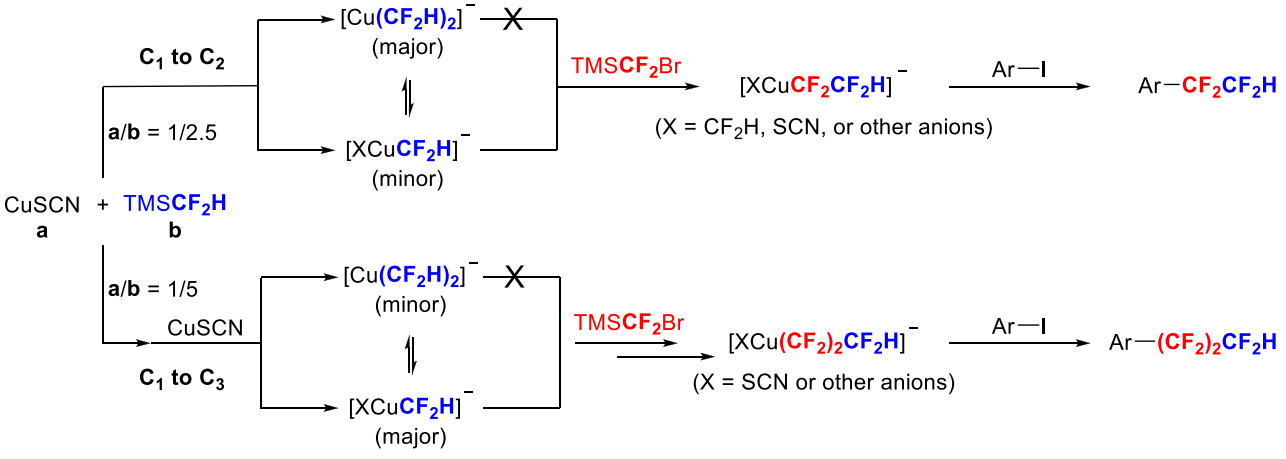
entry[a]	TMSCF$_2$X	n = 1 (%)	n = 2 (%)
1	TMSCF$_3$	0	0
2	TMSCF$_2$Cl	45	2
3	TMSCF$_2$Br	96	3

4. "CuCF$_3$" vs TMSCF$_2$Br in fluorocarbon chain elongation





5. Proposed pathways for controllable single and double CF$_2$ insertions into CuCF$_2$H



component (entry 3). These results suggest that the [XCu(CF$_2$H)]$^-$ species is more likely to be the major active species in the single CF$_2$ insertion process (rather than the [Cu(CF$_2$H)$_2$]$^-$ species).

In addition, we screened different halodifluoromethyltrimethylsilanes TMSCF$_2$X (X = F, Cl, Br) as CF$_2$ sources for this CF$_2$ insertion reaction (Scheme 5(3) and Table S10). The employment of TMSCF$_2$Cl and TMSCF$_2$Br yielded the desired product "CuCF$_2$CF$_2$H" in 45% and 96% yields, respectively (entries 2 and 3), whereas no desired product was generated using TMSCF$_3$ (entry 1). Their reactivity in this

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process was in agreement with their ability to release the difluorocarbene ($TMSCF_3 \ll TMSCF_2Cl < TMSCF_2Br$).

To illustrate the superiority of $TMSCF_2Br$ reagent in fluorocarbon chain elongation, we compared two controllable difluoromethylene (CF_2) insertion processes with (difluoromethyl)copper ["$CuCF_2H$"] and (pentafluoroohenyl)copper ["CuC_6F_5"] as substrates using $TMSCF_2Br$ or (trifluoromethyl)copper ["$CuCF_3$"] as the difluoromethylene source (Schemes 1a-ii and 5(4)). Indeed, when (trifluoromethyl) copper was employed as the difluoromethylene source and (difluoromethyl)copper as a substrate, no difluoromethylene insertion product (tetrafluoroethyl)copper ["$CuCF_2CF_2H$"] was detected (Schemes 5(4) and S4). However, when $TMSCF_2Br$ was employed as the difluoromethylene source and (pentafluorophenyl)copper as a substrate, the double difluoromethylene insertion product (perfluorophenylethyl) copper ["$Cu(CF_2)_2C_6F_5$"] was obtained in 85% yield (Schemes 5(4) and S5). Based on our previous work on controllable double difluoromethylene insertions into (pentafluorophenyl)copper using (trifluoromethyl)copper as the difluoromethylene source,[21] the byproduct (pentafluoroethyl)copper ["CuC_2F_5"] was detected; however, when $TMSCF_2Br$ was used to replace (trifluoromethyl)copper, no (pentafluoroethyl)copper was observed.

On the basis of these results, the possible pathways of the controllable single and double CF_2 insertions into "$CuCF_2H$" are proposed (Scheme 5(5)). On single CF_2 insertion into "$CuCF_2H$", $[XCu(CF_2H)]^-$ (X = SCN or other anions; as the minor component) and $[Cu(CF_2H)_2]^-$ (as the major component) are generated when adding CuSCN and $TMSCF_2H$ in the ratio of 1:2.5 (Scheme 5(1-i)). Then, the controllable single CF_2 insertion into the relatively active species $[XCu(CF_2H)]^-$ occurs with the appropriate loading of $TMSCF_2Br$. The relatively inert species $[Cu(CF_2H)_2]^-$ participates in this reaction by converting to $[XCu(CF_2H)]^-$. During double CF_2 insertions into "$CuCF_2H$", $[XCu(CF_2H)]^-$ as the dominant species is readily formed when the ratio of CuSCN/$TMSCF_2H$ is set as 1/2.5 and CuSCN is added in two portions (Scheme 5(1-v)). Subsequently, the portion-wise addition of $TMSCF_2Br$ to the active species $[XCu(CF_2H)]^-$ affords the double CF_2 insertion product $[XCu(CF_2)_2CF_2H)]^-$ in a selective manner. Finally, the tetrafluoroethylation and hexafluoropropylation reactions with aryl iodides successfully proceed with the pregenerated $[XCuCF_2CF_2H)]^-$ and $[XCu(CF_2)_2CF_2H)]^-$ species, respectively.

CONCLUSIONS

In summary, we successfully developed controllable CF_2 insertion into "$CuCF_2H$" with $TMSCF_2Br$, wherein controllable fluorocarbon chain elongation from C_1 to C_2 and from C_1 to C_3 were realized under different reaction conditions in selective manners. This strategy offered two fluoroalkylcopper species "$CuCF_2CF_2H$" and "$CuCF_2CF_2CF_2H$", which enabled the unprecedented tetrafluoroethylation and hexafluoropropylation reactions with different electrophiles, including a wide range of aryl iodides, halogenation sources, and cinnamyl chloride. Selective single CF_2 insertion into "$CuCF_2H$" was controlled both by the different reactivity of "$Cu(CF_2)_nCF_2H$" and by the appropriate loading of $TMSCF_2Br$. The formation of relatively active $[XCuCF_2H]^-$ species at the beginning ensured the high selectivity of fluorocarbon chain elongation from C_1 to C_3. Further investigations on controllable CF_2 insertion into structurally diverse C−Cu bonds are currently underway in our laboratory.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.2c03104.

Experimental details, optimization of the reaction conditions, procedures for the synthesis of substrates and products, X-ray structures of compounds **2ae** and **3h**, and spectroscopic data of the corresponding compounds (PDF)

Accession Codes

CCDC 2107781 and 2127395 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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