

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

Xiu Wang, Shitao Pan, Qinyu Luo, Qian Wang, Chuanfa Ni, and Jinbo Hu*

Cite This: *J. Am. Chem. Soc.* 2022, 144, 12202–12211

Read Online

ACCESS |



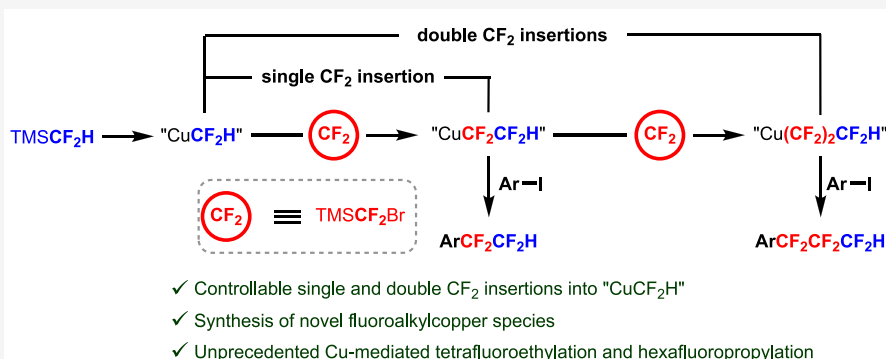
Metrics & More



Article Recommendations



Supporting Information



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)- $\text{CF}_3\text{CF}=\text{CFCu}$). 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 " $\text{Cu}(\text{CF}_2)_n\text{CF}_2\text{H}$ " ($n = 1$ 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 " $\text{Cu}(\text{CF}_2)_n\text{CF}_2\text{H}$ " ($n = 1$ 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 $\text{HCF}_2\text{CF}_2\text{CF}_2$ 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 " $\text{Cu}(\text{CF}_2)_n\text{CF}_2\text{H}$ " species ($n = 0, 1, 2$ and 3) and the loading of the TMSCF_2Br reagent.

INTRODUCTION

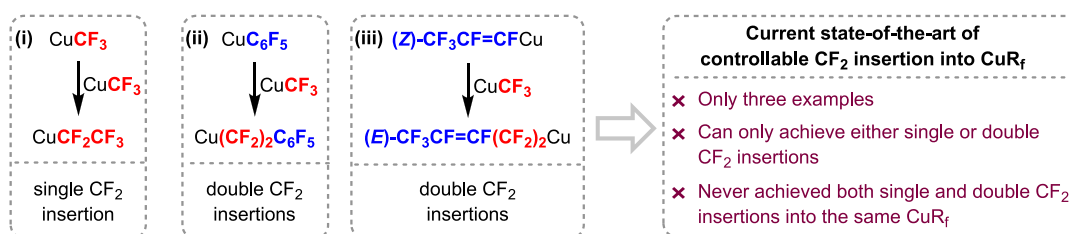
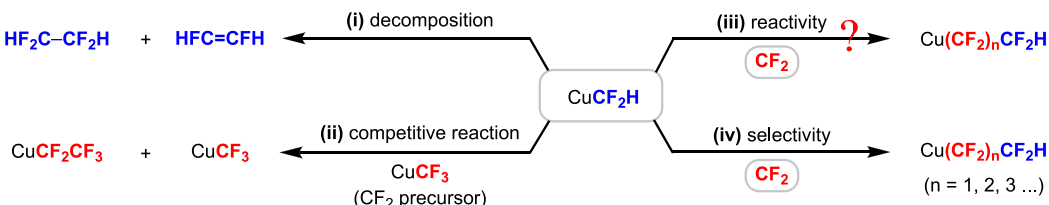
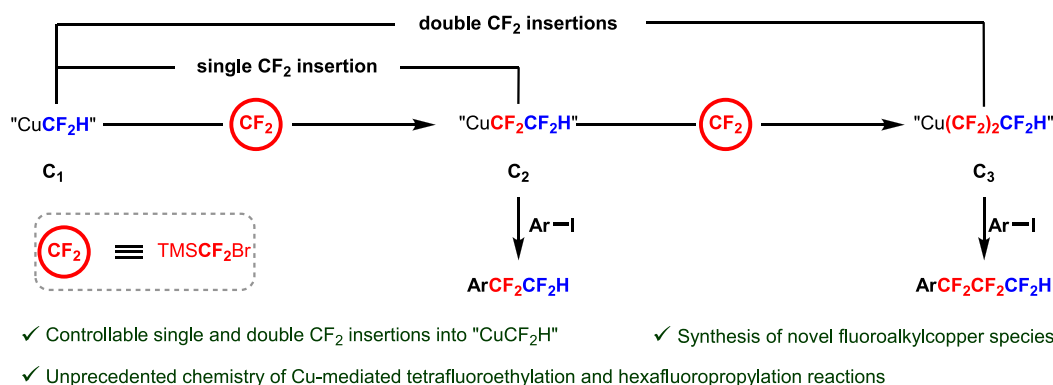
Organofluorine compounds have been widely used in pharmaceuticals, agrochemicals, and advanced materials due to their unique physicochemical properties.¹ In this context, the selective introduction of fluoromethyl groups into organic molecules has attracted much attention over the past decades, such 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 ($\text{HCF}_2\text{CF}_2\text{CF}_2$) 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 Hexa-

flumuron (a termite bait).¹² Despite the potential applications of HCF_2CF_2 - or $\text{HCF}_2\text{CF}_2\text{CF}_2$ -containing compounds, their synthetic methods are scarce. Conventionally, tetrafluoroethylated molecules are prepared by the deoxyfluorination of glyoxal hydrates¹³ 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-

Received: March 22, 2022

Published: July 5, 2022



Scheme 1. Controllable CF₂ Insertion into CuR_f Speciesa) Previous work: single reaction mode for one particular CuR_fb) Challenges in controllable CF₂ insertions into CuCF₂Hc) This work: double reaction modes for "CuCF₂H"

fluoroethane. As for hexafluoropropylated compounds, to our knowledge, their efficient and practical synthesis has never been reported, probably owing to the unavailability of HCF₂CF₂CF₂-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 (CF₂) insertion has been considered as a feasible strategy for fluorocarbon chain elongation. Some remarkable CF₂ carbene homologation reactions using TMSCF₃ have been reported recently.^{19,20c,22c,24} Indeed, single CF₂ insertion into trifluoromethylcopper was reported in 1986;²⁰ however, controllable double CF₂ insertions into trifluoromethylcopper failed, with a complex mixture of oligomers being obtained (Scheme 1a-i).²¹ Furthermore, double CF₂ insertions into perfluorophenyl/vinylcopper were subsequently realized, whereas their single CF₂ 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 CF₂ insertion processes are only limited to CuCF₃, CuC₆F₅, and (Z)-CF₃CF=CF-Cu (Scheme 1),^{20,22} and, more remarkably, achieving both controllable single and double CF₂ 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 (CuCF₂H) as a starting material and subject it to both single and double difluoromethylene insertions under different reaction conditions, both CuCF₂CF₂H and CuCF₂CF₂CF₂H 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 CF₂ insertions into CuCF₂H, several issues have to be considered: (1) CuCF₂H is less stable than CuCF₃ and has a tendency to decompose (Scheme 1b-i);²³ (2) when CuCF₃ 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 CuCF₂H 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 CF₂ insertions into "CuCF₂H", providing an access to scarcely

Table 1. Optimization of Reaction Conditions for Single CF₂ Insertion into “CuCF₂H”

(1) TMSCF₂H , CsF, DMF, 50 °C, 1 h									
CuX							"Cu(CF₂) _n CF₂H "		
(2) TMSCF₂Br (x equiv), NaOAc (x equiv), temp., t									
entry	x (equiv)	CuX (equiv)	TMSCF ₂ H (equiv)	CsF (equiv)	temp. (°C)	t (h)	"Cu(CF₂) _n CF₂H " (%) ^a		
							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

^aReactions were performed on a 0.200 mmol scale. Yields were determined by ¹⁹F NMR using PhCF₃ 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](#)). ^bReactions were performed on a 5.000 mmol scale. ^cWithout NaOAc.

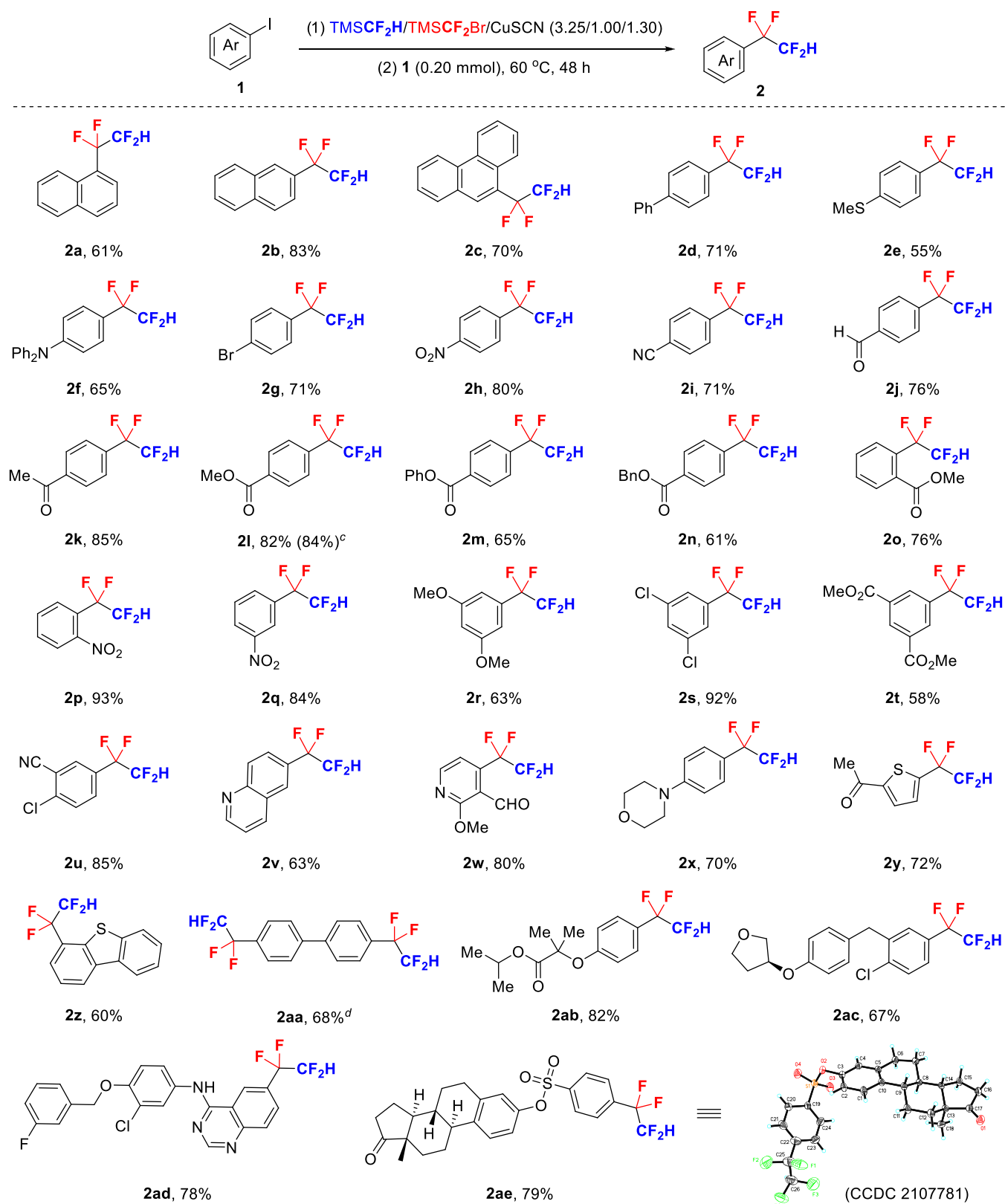
studied tetrafluoroethylcopper²⁵ and previously unknown hexafluoropropylcopper. With two fluoroalkylcopper species in hand, we successfully investigated the unprecedented copper-mediated tetrafluoroethylation and hexafluoropropylation reactions (Scheme 1c).

RESULTS AND DISCUSSION

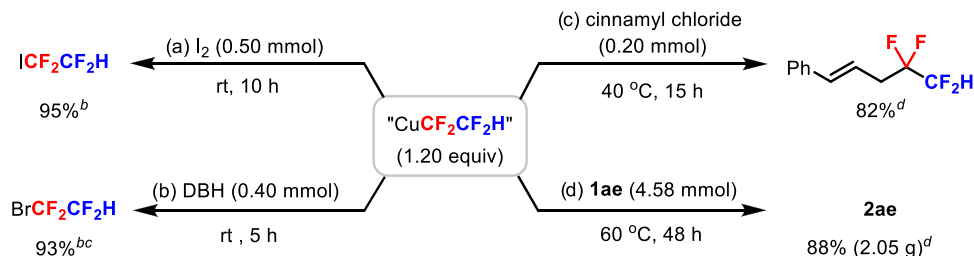
Since our first report of TMSCF₂Br in the [2 + 1] cycloaddition with alkynes in 2011,^{26a} TMSCF₂Br has been widely used as a powerful difluorocarbene source by us²⁶ and others.²⁷ Given its highly tunable characteristic in releasing difluorocarbene under a variety of mild conditions, TMSCF₂Br was chosen by us as a CF₂ source (instead of CuCF₃) in this study. In pilot experiments [see [Tables 1](#) and [S1–S4](#)], a mixture of CuI, CsF, and commercially available TMSCF₂H in DMF was stirred at 50 °C for 1 h to produce “CuCF₂H”, and then, the reaction conditions of controllable single CF₂ (from TMSCF₂Br) insertion into the formed “CuCF₂H” were systematically screened. Notably, adding no more than the necessary amount of TMSCF₂Br is the key to diminishing multiple CF₂ insertions into “CuCF₂H” (entries 1–4). The ratios among CuI, CsF, and TMSCF₂H were found to affect not only the yield and composition of “CuCF₂H” but also the selectivity of the single CF₂ insertion process (entries 4–7). With the optimized ratios of CuI, CsF, and TMSCF₂H (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 CF₂ 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-2H-imidazol-2-ylidene] inhibited the desired CF₂ 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 CF₂ insertion product “CuCF₂CF₂H” was obtained in 96% yield, with 3% yield of “Cu(CF₂)₂CF₂H” 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 “CuCF₂CF₂H” were observed in the absence of NaOAc (entry 18), which suggests that NaOAc could facilitate the activation of TMSCF₂Br and therefore promote the single CF₂ insertion into “CuCF₂H”. The thermal stability of “CuCF₂CF₂H” species was monitored by ¹⁹F NMR spectroscopy at the ambient temperature under an inert atmosphere, and it was found that only 6% of “CuCF₂CF₂H” decomposed even after 6 days (for details, see [SI](#)).

With the single CF₂ insertion product “CuCF₂CF₂H” 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 “CuCF₂CF₂H” species was able to efficiently tetrafluoroethylate a wide range of aryl iodides, yielding the corresponding HCF₂CF₂-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

Scheme 2. Tetrafluoroethylation of Aryl Iodides and “CuCF₂CF₂H”^{a,b}

^aPreparation of “CuCF₂CF₂H”: CuSCN (6.50 mmol), CsF (16.25 mmol), DMF (25 mL), TMSCF₂H (16.25 mmol), 50 °C, 1 h. Then, TMSCF₂Br (5.00 mmol), NaOAc (5.00 mmol), 30 °C, 50 min. The DMF solution of “CuCF₂CF₂H” was used after filtration. ^bPrepared “CuCF₂CF₂H” (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). ^cReaction conditions: CuSCN (0.33 mmol), CsF (0.81 mmol), DMF (1.25 mL), TMSCF₂H (0.81 mmol), 50 °C, 1 h. Then, TMSCF₂Br (0.25 mmol), NaOAc (0.25 mmol), 30 °C, 50 min. Then, 1l (0.20 mmol), 60 °C, 48 h. ¹⁹F NMR yield of 2l based on the loading of 1l (0.20 mmol) using PhCF₃ as an internal standard. ^d“CuCF₂CF₂H” (2.40 equiv) was added.

Scheme 3. Synthetic Applications of “CuCF₂CF₂H”^a

^aPreparation of “CuCF₂CF₂H”: CuSCN (6.50 mmol), CsF (16.25 mmol), DMF (25 mL), TMSCF₂H (16.25 mmol), 50 °C, 1 h. Then, TMSCF₂Br (5.00 mmol), NaOAc (5.00 mmol), 30 °C, 50 min. The DMF solution of “CuCF₂CF₂H” was used after filtration. ^b¹⁹F NMR yield using PhCF₃ as an internal standard. “CuCF₂CF₂H” (0.20 mmol, 1.00 equiv) was added. ^dIsolated yields.

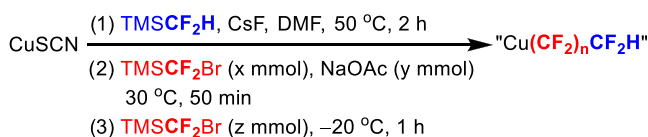
desired products **2r–2u** in 58–92% yields. Medicinally relevant heterocycles including quinoline (**1v**), pyridine (**1w**), morpholine (**1x**), thiophene (**1y**), and dibenzothio-
phene (**1z**) were competent in this coupling reaction, as demonstrated by the formation of the corresponding tetrafluoroethylation products **2v–2z** in moderate-to-good yields. Double-tetrafluoroethylation of 4,4'-diiodobiphenyl with 2.4 equivalents of “CuCF₂CF₂H” was also found to be possible, affording the product **2aa** in 68% yield. Notably, the potential use of this protocol for the late-stage functionaliza-
tion of bioactive molecules was demonstrated by tetrafluor-
oethylation 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 Lapatinib³⁰) 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 “CuCF₂CF₂H” was further
demonstrated by its tetrafluoroethylation of other electrophiles
(Scheme 3). Halogenations of “CuCF₂CF₂H” by I₂ and DBH
(1,3-dibromo-5,5-dimethylhydantoin) at room temperature
proceeded smoothly, affording the corresponding products
ICF₂CF₂H and BrCF₂CF₂H 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
“CuCF₂CF₂H”, we wondered whether the controllable double
CF₂ insertion product “Cu(CF₂)₂CF₂H” could be formed by
the addition of the appropriate amount of TMSCF₂Br. However,
the double CF₂ insertion product “Cu(CF₂)₂CF₂H” was
obtained with poor selectivity (Table S6 in SI). Under these
reaction conditions, with a ratio of CuSCN/TMSCF₂H/
CsF of 1:2.5:2.5, the excess difluoromethyl anion probably
interfered with the further CF₂ insertion process via ligand
exchange with the formed “CuCF₂CF₂H”. To overcome this
dilemma, we planned to use [XCuCF₂H][−] species as the
starting material and reduce the presence of other anions
(especially the difluoromethyl anion) to improve the selectivity
of double CF₂ insertions. After extensive screening of the
reaction parameters, to our delight, the selectivity and yield of
“Cu(CF₂)₂CF₂H” were drastically improved when the ratio of

CuSCN/TMSCF₂H/CsF was set as 1/2.5/2.5, but adding
CuSCN in two portions (Table 2, entry 1). Either adding

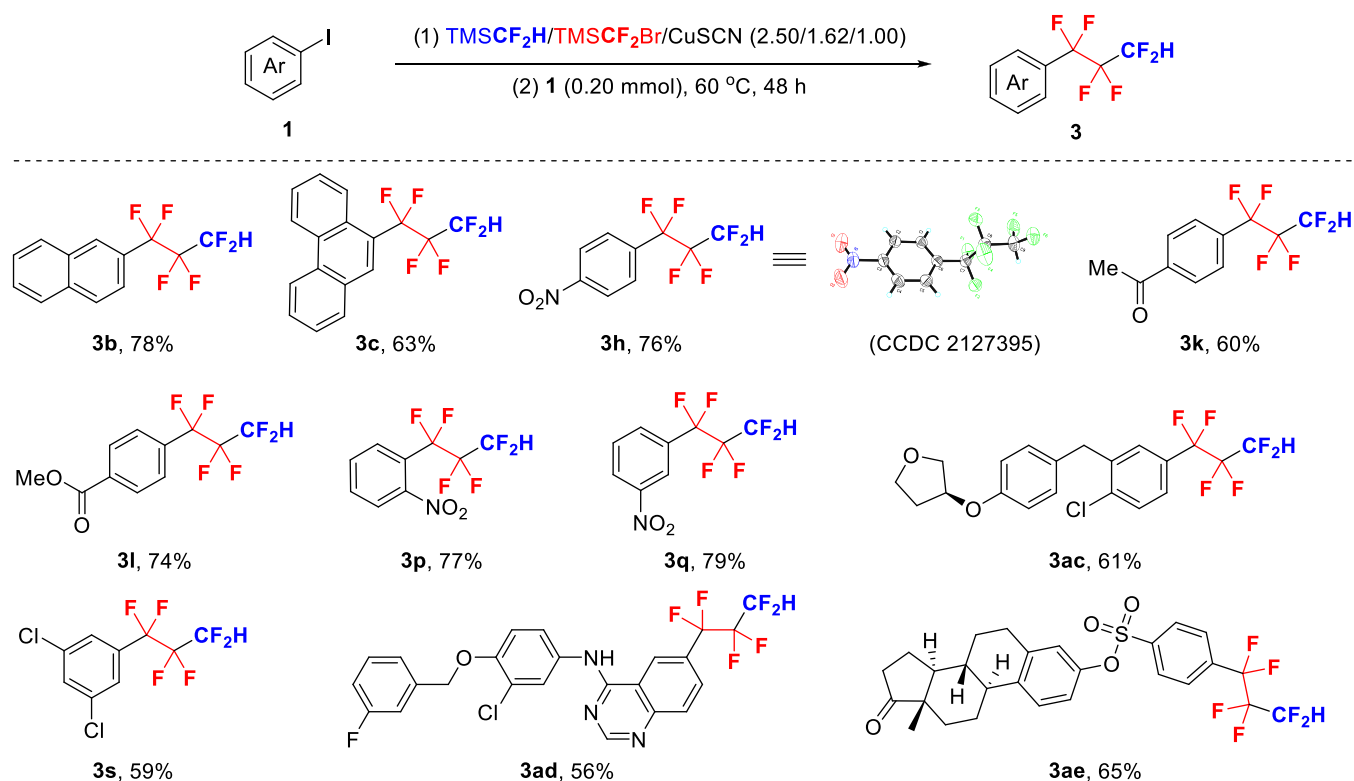
Table 2. Optimization of the Reaction Conditions for the Double CF₂ Insertions into “CuCF₂H”



entry ^a	x	y	z	“Cu(CF ₂) _n CF ₂ H” (%) ^b		
				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

^aReaction conditions: CuSCN (0.26 mmol), CsF (1.30 mmol), DMF (1 mL), TMSCF₂H (1.30 mmol), 50 °C, 1 h. CuSCN (0.26 mmol), 50 °C, 1 h. TMSCF₂Br (x mmol), NaOAc (y mmol), 30 °C, 50 min. TMSCF₂Br (z mmol), −20 °C, 1 h. ^bYields were determined by ¹⁹F NMR using PhCF₃ 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). ^cNaOAc (0.4 mmol) was added in the last step. ^dSecond portion of TMSCF₂Br was added at −20 °C.

another portion of NaOAc (entry 2) or reducing the loading of
TMSCF₂Br at the last step could not result in the highly
selective formation of “Cu(CF₂)₂CF₂H” (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 TMSCF₂Br at −20 °C (entry 5), higher yields of
single- and double CF₂ insertion products and a lower yield of
the triple CF₂ insertion product were afforded compared with
that obtained when adding it at room temperature (entry 4).
We also changed the amount of TMSCF₂Br to 0.42 mmol and
added the second portion of TMSCF₂Br at −20 °C; it was
found that the single CF₂ insertion product “CuCF₂CF₂H” was
almost consumed, and the target product “Cu(CF₂)₂CF₂H”
was delivered in 62% yield, along with a 2% yield of
“Cu(CF₂)₃CF₂H” (entry 6). The thermal stability of “Cu-
(CF₂)₂CF₂H” was monitored by ¹⁹F NMR spectroscopy under

Scheme 4. Hexafluoropropylation of Aryl Iodides and “Cu(CF₂)₂CF₂H”^{a,b}

^aReaction conditions: CuSCN (0.26 mmol), CsF (1.30 mmol), DMF (1 mL), TMSCF₂H (1.30 mmol), 50 °C, 1 h. CuSCN (0.26 mmol), 50 °C, 1 h. TMSCF₂Br (0.42 mmol), 30 °C, 50 min. TMSCF₂Br (0.42 mmol), −20 °C, 1 h. 1 (0.20 mmol), 60 °C, 48 h. ^bIsolated 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 S1).

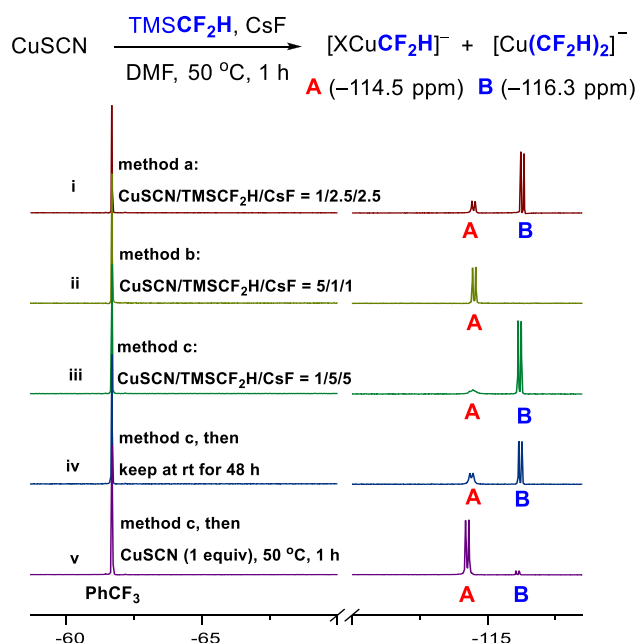
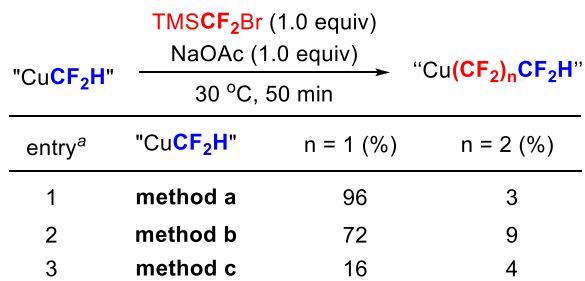
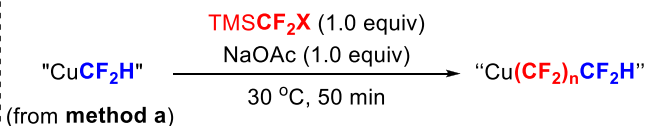
With “Cu(CF₂)₂CF₂H” (Table 2, entry 6) in hand, we assessed its synthetic value by couplings with aryl iodides (Scheme 4). It was found that 2-iodonaphthalene and 9-iodophenanthrene were viable in this reaction, yielding the corresponding products (3b and 3c) in 78 and 63% yields, respectively. The hexafluoropropylation 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(CF₂)₂CF₂H” 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 “CuCF₂H”, the active species, and the reaction pathway in a controllable CF₂ insertion process (Scheme 5). Initially, the reaction of 0.26 mmol of CuSCN, 0.65 mmol of CsF, and TMSCF₂H in DMF at 50 °C for 1 h was conducted (a method for the preparation of “CuCF₂H”). Analysis of this solution by ¹⁹F NMR spectroscopy indicated two “CuCF₂H” species at −114.5 ppm (species A) and −116.3 ppm (species B) (relative to CFCl₃) (Schemes 5(1-i) and S1). Interestingly, on changing the ratio of CuSCN/CsF/TMSCF₂H from 1:2.5:2.5 (method a) to 5:1:1 (method b), only species A was detected (Schemes

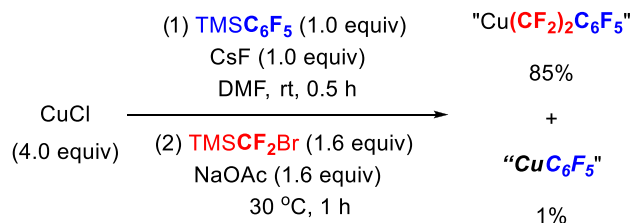
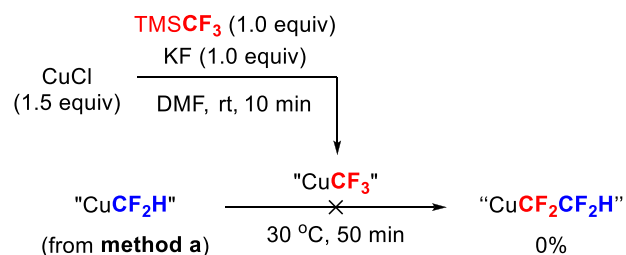
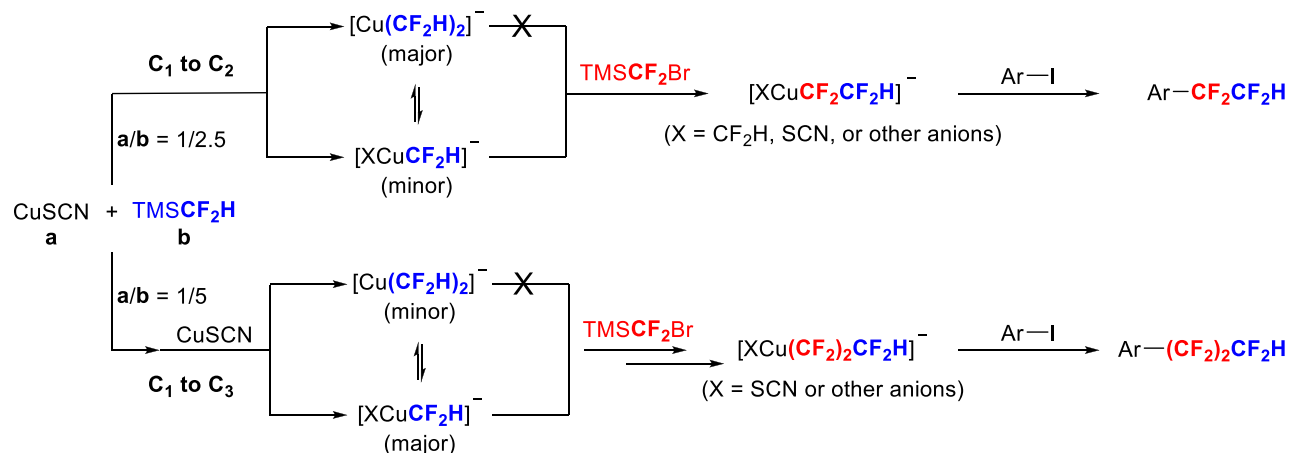
5(1-ii) and S2); however, species B was formed as the dominant species when the ratio of CuSCN/CsF/TMSCF₂H was 1:5:5 (method c; Schemes 5(1-iii) and S3). During the continuous monitoring of the mixture prepared by method c, species A began to grow slowly with a diminution of species B upon prolonging 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(CF₂H)][−] (X = SCN or other anions), and species B at −116.3 ppm in DMF was identified as [Cu(CF₂H)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/TMSCF₂H (1:2.5:2.5) but adding CuSCN under different conditions. Unfortunately, our attempts to synthesize [Ph₄P]⁺[XCu(CF₂H)][−] and [Ph₄P]⁺[Cu(CF₂H)₂][−] by treating the mixture (prepared by method b or c) with Ph₄P₄Cl at room temperature for 30 minutes failed.³²

To elucidate the active species in the single CF₂ insertion process, the treatment of “CuCF₂H” prepared by different methods with TMSCF₂Br activated by NaOAc at 30 °C for 50 min were tested (Scheme 5(4(2)) and Table S9). Notably, the single CF₂ insertion product “CuCF₂CF₂H” was obtained in 96 and 72% yields using “CuCF₂H” prepared by methods a and b, respectively (entries 1 and 2). Meanwhile, 16% yield of the single CF₂ insertion product was observed using “CuCF₂H” prepared by method c, in which species B was the dominant

Scheme 5. Mechanistic Studies

1. Identification of "CuCF₂H"2. Active species in single CF₂ insertion process3. Fluorocarbon chain elongation with different CF₂ 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. "CuCF₃" vs TMSCF₂Br in fluorocarbon chain elongation5. Proposed pathways for controllable single and double CF₂ insertions into CuCF₂H

component (entry 3). These results suggest that the $[\text{XCu}(\text{CF}_2\text{H})]^-$ species is more likely to be the major active species in the single CF₂ insertion process (rather than the $[\text{Cu}(\text{CF}_2\text{H})_2]^-$ species).

In addition, we screened different halodifluoromethyltrimethylsilanes TMSCF₂X (X = F, Cl, Br) as CF₂ sources for this

CF₂ insertion reaction (Scheme 5(3) and Table S10). The employment of TMSCF₂Cl and TMSCF₂Br yielded the desired product "CuCF₂CF₂H" in 45% and 96% yields, respectively (entries 2 and 3), whereas no desired product was generated using TMSCF₃ (entry 1). Their reactivity in this

process was in agreement with their ability to release the difluorocarbene ($\text{TMSCF}_3 \ll \text{TMSCF}_2\text{Cl} < \text{TMSCF}_2\text{Br}$).

To illustrate the superiority of TMSCF_2Br reagent in fluorocarbon chain elongation, we compared two controllable difluoromethylene (CF_2) insertion processes with (difluoromethyl)copper [$[\text{CuCF}_2\text{H}]^-$] and (pentafluorophenyl)copper [$[\text{CuC}_6\text{F}_5]^-$] as substrates using TMSCF_2Br or (trifluoromethyl)copper [$[\text{CuCF}_3]^-$] 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 [$[\text{CuCF}_2\text{CF}_2\text{H}]^-$] 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 [$[\text{Cu}(\text{CF}_2)_2\text{C}_6\text{F}_5]^-$] 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 [$[\text{CuC}_2\text{F}_5]^-$] 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 ", $[\text{XCu}(\text{CF}_2\text{H})]^-$ ($\text{X} = \text{SCN}$ or other anions; as the minor component) and $[\text{Cu}(\text{CF}_2\text{H})_2]^-$ (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 $[\text{XCu}(\text{CF}_2\text{H})]^-$ occurs with the appropriate loading of TMSCF_2Br . The relatively inert species $[\text{Cu}(\text{CF}_2\text{H})_2]^-$ participates in this reaction by converting to $[\text{XCu}(\text{CF}_2\text{H})]^-$. During double CF_2 insertions into " CuCF_2H ", $[\text{XCu}(\text{CF}_2\text{H})]^-$ as the dominant species is readily formed when the ratio of $\text{CuSCN}/\text{TMSCF}_2\text{H}$ 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 $[\text{XCu}(\text{CF}_2\text{H})]^-$ affords the double CF_2 insertion product $[\text{XCu}(\text{CF}_2)_2\text{CF}_2\text{H}]^-$ in a selective manner. Finally, the tetrafluoroethylation and hexafluoropropylation reactions with aryl iodides successfully proceed with the pregenerated $[\text{XCuCF}_2\text{CF}_2\text{H}]^-$ and $[\text{XCu}(\text{CF}_2)_2\text{CF}_2\text{H}]^-$ 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 " $\text{CuCF}_2\text{CF}_2\text{H}$ " and " $\text{CuCF}_2\text{CF}_2\text{CF}_2\text{H}$ ", 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 " $\text{Cu}(\text{CF}_2)_n\text{CF}_2\text{H}$ " and by the appropriate loading of TMSCF_2Br . The formation of relatively active $[\text{XCuCF}_2\text{H}]^-$ 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.

AUTHOR INFORMATION

Corresponding Author

Jinbo Hu – Key Laboratory of Organofluorine Chemistry, Center for Excellence in Molecular Synthesis, Shanghai Institute of Organic Chemistry, University of Chinese Academy of Sciences, Chinese Academy of Sciences, Shanghai 200032, China; orcid.org/0000-0003-3537-0207; Email: jinbohu@sioc.ac.cn

Authors

Xiu Wang – Key Laboratory of Organofluorine Chemistry, Center for Excellence in Molecular Synthesis, Shanghai Institute of Organic Chemistry, University of Chinese Academy of Sciences, Chinese Academy of Sciences, Shanghai 200032, China

Shitao Pan – Key Laboratory of Organofluorine Chemistry, Center for Excellence in Molecular Synthesis, Shanghai Institute of Organic Chemistry, University of Chinese Academy of Sciences, Chinese Academy of Sciences, Shanghai 200032, China

Qinyu Luo – Key Laboratory of Organofluorine Chemistry, Center for Excellence in Molecular Synthesis, Shanghai Institute of Organic Chemistry, University of Chinese Academy of Sciences, Chinese Academy of Sciences, Shanghai 200032, China

Qian Wang – Key Laboratory of Organofluorine Chemistry, Center for Excellence in Molecular Synthesis, Shanghai Institute of Organic Chemistry, University of Chinese Academy of Sciences, Chinese Academy of Sciences, Shanghai 200032, China

Chuanfa Ni – Key Laboratory of Organofluorine Chemistry, Center for Excellence in Molecular Synthesis, Shanghai Institute of Organic Chemistry, University of Chinese Academy of Sciences, Chinese Academy of Sciences, Shanghai 200032, China

Complete contact information is available at: <https://pubs.acs.org/doi/10.1021/jacs.2c03104>

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported by the National Key Research and Development Program of China (2021YFF0701700), the National Natural Science Foundation of China (21632009), the Key Programs of the Chinese Academy of Sciences (KGZD-EW-T08), the Key Research Program of Frontier Sciences of CAS (QYZDJ-SSW-SLH049) and the fellowship of China Postdoctoral Science Foundation 2020M671273. We thank Wei Du and Yangfan Liu (Shanghai Institute of Organic Chemistry) for their assistance in testing the stability of compound **2ae**.

■ REFERENCES

- (1) (a) Zhou, Y.; Wang, J.; Gu, Z.; Wang, S.; Zhu, W.; Aceña, J. L.; Soloshonok, V. A.; Izawa, K.; Liu, H. Next generation of fluorine-containing pharmaceuticals, compounds currently in phase II–III clinical trials of major pharmaceutical companies: new structural trends and therapeutic areas. *Chem. Rev.* **2016**, *116*, 422–518. (b) Meanwell, N. A. Fluorine and Fluorinated Motifs in the Design and Application of Bioisosteres for Drug Design. *J. Med. Chem.* **2018**, *61*, 5822–5880. (c) Mei, H.; Han, J.; Klika, K. D.; Izawa, K.; Sato, T.; Meanwell, N. A.; Soloshonok, V. A. Applications of fluorine-containing amino acids for drug design. *Eur. J. Med. Chem.* **2020**, *186*, No. 111826. (d) Caron, S. Where Does the Fluorine Come From? A Review on the Challenges Associated with the Synthesis of Organofluorine Compounds. *Org. Process Res. Dev.* **2020**, *24*, 470–480. (e) Ogawa, Y.; Tokunaga, E.; Kobayashi, O.; Hirai, K.; Shibata, N. Current Contributions of Organofluorine Compounds to the Agrochemical Industry. *iScience* **2020**, *23*, No. 101467. (f) Britton, R.; Gouverneur, V.; Lin, J.-H.; Meanwell, M.; Ni, C.; Pupo, G.; Xiao, J.-C.; Hu, J. Contemporary Synthetic Strategies in Organofluorine Chemistry. *Nat. Rev. Methods Primers* **2021**, *1*, No. 47.
- (2) (a) Wang, S.; Wang, W. Recent Advances of the Construction of Trifluoromethylated Quaternary Carbon Center. *Chin. J. Org. Chem.* **2020**, *40*, 1901–1911. (b) Xiao, H.; Zhang, Z.; Fang, Y.; Zhu, L.; Li, C. Radical trifluoromethylation. *Chem. Soc. Rev.* **2021**, *50*, 6308–6319. (c) Fernandes, A. J.; Panossian, A.; Michelet, B.; Martin-Mingot, A.; Leroux, F. R.; Thibaudau, S. CF₃-substituted Carbocations: Underexploited Intermediates with Great Potential in Modern Synthetic Chemistry. *Beilstein J. Org. Chem.* **2021**, *17*, 343–378.
- (3) Sap, J. B. I.; Meyer, C. F.; Straathof, N. J. W.; Iwumene, N.; Am Ende, C. W.; Trabanco, A. A.; Gouverneur, V. Late-stage difluoromethylation: concepts, developments and perspective. *Chem. Soc. Rev.* **2021**, *50*, 8214–8247.
- (4) Xie, Q.; Hu, J. Monofluoromethylation Reactions of Aliphatic Substrates and (Hetero)Arenes. In *Emerging Fluorinated Motifs*; Cahard, D.; Ma, J. A., Eds.; Synthesis, Properties, and Applications, Weinheim: Wiley-VCH, 2020; pp 119–133.
- (5) (a) Martínez, M. D.; Luna, L.; Tesio, A. Y.; Feresin, G. E.; Duran, F. J.; Burton, G. Antioxidant properties in a non-polar environment of difluoromethyl bioisosteres of methyl hydroxycinnamates. *J. Pharm. Pharmacol.* **2016**, *68*, 233–244. (b) Zafrani, Y.; Yeffet, D.; Sod-Moriah, G.; Berliner, A.; Amir, D.; Marciano, D.; Gershonov, E.; Saphier, S. Difluoromethyl bioisostere: examining the “lipophilic hydrogen bond donor” concept. *J. Med. Chem.* **2017**, *60*, 797–804. (c) Sessler, C. D.; Rahm, M.; Becker, S.; Goldberg, J. M.; Wang, F.; Lippard, S. J. CF₂H, a Hydrogen Bond Donor. *J. Am. Chem. Soc.* **2017**, *139*, 9325–9332. (d) Zafrani, Y.; Sod-Moriah, G.; Yeffet, D.; Berliner, A.; Amir, D.; Marciano, D.; Elias, S.; Katalan, S.; Ashkenazi, N.; Madmon, M.; Gershonov, E.; Saphier, S. CF₂H, a functional group-dependent hydrogen-bond donor: is it a more or less lipophilic bioisostere of OH, SH, and CH₃? *J. Med. Chem.* **2019**, *62*, 5628–5637.
- (6) Kaneko, S.; Yamazaki, T.; Kitazume, T. A remarkably simple route to versatile difluoromethylated molecules. *J. Org. Chem.* **1993**, *58*, 2302–2312.
- (7) (a) Meanwell, N. A. Synopsis of Some Recent Tactical Application of Bioisosteres in Drug Design. *J. Med. Chem.* **2011**, *54*, 2529–2591. (b) Wang, J.; Sánchez-Roselló, M.; Aceña, J. L.; del Pozo, C.; Sorochinsky, A. E.; Fustero, S.; Soloshonok, V. A.; Liu, H. Fluorine in Pharmaceutical Industry: Fluorine-Containing Drugs Introduced to the Market in the Last Decade (2001–2011). *Chem. Rev.* **2014**, *114*, 2432–2506.
- (8) Goure, W. F.; Leschinsky, K. L.; Wratten, S. J.; Chupp, J. P. Synthesis and herbicidal activity of N-substituted 2,6-bis-(polyfluoromethyl)dihydropyridine-3,5-dicarboxylates. *J. Agric. Food Chem.* **1991**, *39*, 981–986.
- (9) Václavík, J.; Klimankova, I.; Budinska, A.; Beier, P. Advances in the synthesis and application of tetrafluoroethylene- and 1,1,2,2-tetrafluoroethylcontaining compounds. *Eur. J. Org. Chem.* **2018**, *2018*, 3554–3593.
- (10) Bianchi, D.; Cesti, P.; Spezia, S.; Garavaglia, C.; Mirennat, L.; Donegani, I. G. Chemoenzymatic Synthesis and Biological Activity of Both Enantiomeric Forms of Tetraconazole, a New Antifungal Triazole. *J. Agric. Food Chem.* **1991**, *39*, 197–201.
- (11) Boisvenue, R. J.; O'Doherty, G. O. P. Systemic animal external parasiticide activity of perfluoroalkylbenzimidazoles and their amino-anilide Precursors. *Experientia* **1980**, *36*, 189–190.
- (12) Evans, T. A.; Iqbal, N. Termite (order Blattodea, infraorder Isoptera) baiting 20 years after commercial release. *Pest Manage. Sci.* **2015**, *71*, 897–906.
- (13) (a) Singh, R. P.; Shreeve, J. M. Concentration-Dependent Reactions of Deoxofluor with Arylglyoxal Hydrates: A New Route to Polyfluoro Ethers. *Org. Lett.* **2001**, *3*, 2713–2714. (b) Singh, R. P.; Twamley, B.; Shreeve, J. M. Polyfluoroether Derivatives via Nucleophilic Fluorination of Glyoxal Hydrates with Deoxofluor. *J. Org. Chem.* **2002**, *67*, 1918–1924.
- (14) (a) Petrov, V. A.; Swearingen, S.; Hong, W.; Petersen, W. C. 1,1,2,2-Tetrafluoroethyl-N,N-dimethylamine: a new selective fluorinating agent. *J. Fluorine Chem.* **2001**, *109*, 25–31. (b) Sokolenko, T. M.; Davydova, Y. A.; Yagupolskii, Y. L. Polyfluoroethoxy derivatives of malonic aldehyde acetal in the synthesis of heterocyclic compounds. *Chem. Heterocycl. Compd.* **2015**, *51*, 324–326. (c) Petko, K. I.; Vlasenko, Y. G.; Kachkovskii, O. D. Unexpected “reverse” cyclization of 2-mercaptopbenzimidazole with chlorotri-fluoroethylene and hexafluoropropene. *J. Fluorine Chem.* **2016**, *185*, 168–172.
- (15) Tichý, D.; Košťál, V.; Motornov, V.; Klimánková, I.; Beier, P. Preparation of 1-Azido-2-Bromo-1,1,2,2-Tetrafluoroethane and Its Use in the Synthesis of N-Fluoroalkylated Nitrogen Heterocycles. *J. Org. Chem.* **2020**, *85*, 11482–11489.
- (16) Fu, X.-P.; Xue, X.-S.; Zhang, X.-Y.; Xiao, Y.-L.; Zhang, S.; Guo, Y.-L.; Leng, X.; Houk, K. N.; Zhang, X. Controllable catalytic difluorocarbene transfer enables access to diversified fluoroalkylated arenes. *Nat. Chem.* **2019**, *11*, 948–956.
- (17) McLoughlin, V. C. R.; Thrower, J. A route to fluoroalkyl-substituted aromatic compounds involving fluoroalkylcopper intermediates. *Tetrahedron* **1969**, *25*, 5921–5940.
- (18) Tsyrlunikova, A. S.; Vershilov, S. V.; Popova, L. M.; Lebedev, N. V.; Litvinenko, E. V.; Ismagilov, N. G. Synthesis and study of amphiphilic properties of polyfluoroalkylethyl ethers. *J. Fluorine Chem.* **2022**, *257–258*, No. 109972.
- (19) García-Domínguez, A.; West, T. H.; Primozic, J. J.; Grant, K. M.; Johnston, C. P.; Cumming, G. G.; Leach, A. G.; Lloyd-Jones, G. C. Difluorocarbene Generation from TMSCF₃: Kinetics and Mechanism of NaI-Mediated and Si-Induced Anionic Chain Reactions. *J. Am. Chem. Soc.* **2020**, *142*, 14649–14663.
- (20) (a) Wiemers, D. M.; Burton, D. J. Pregeneration, Spectroscopic Detection, and Chemical Reactivity of (Trifluoromethyl) copper, an Elusive and Complex Species. *J. Am. Chem. Soc.* **1986**, *108*, 832–834. (b) Kremlev, M. M.; Tyrra, W.; Mushta, A. I.; Naumann, D.; Yagupolskii, Y. L. The solid complex Zn(CF₃)Br•2DMF as an alternative reagent for the preparation of both, trifluoromethyl and pentafluoroethyl copper, CuCF₃ and CuC₂F₅. *J. Fluorine Chem.* **2010**, *131*, 212–216. (c) Xie, Q.; Li, L.; Zhu, Z.; Zhang, R.; Ni, C.; Hu, J.

From C1 to C2: TMSCF_3 as a Precursor for Pentafluoroethylation. *Angew. Chem., Int. Ed.* **2018**, *57*, 13211–13215. (d) Mestre, J.; Castillon, S.; Bouteira, O. "Ligandless" Pentafluoroethylation of Unactivated (Hetero)aryl and Alkenyl Halides Enabled by the Controlled Self-Condensation of TMSCF_3 -Derived CuCF_3 . *J. Org. Chem.* **2019**, *84*, 15087–15097.

(21) (a) Burton, D. J.; Choukoun, H. P.; Easdon, J. C. Chain-extension reactions of F-alkyl copper reagents via insertions of difluorocarbene. *J. Fluorine Chem.* **1989**, *45*, No. 151. (b) Su, D.-B.; Duan, J.-X.; Yu, A.-J.; Chen, Q.-Y. Synthesis of functionalized long-chain perfluoroalkanes from methylhalodifluoroacetates: a process of difluorocarbene insertion into copper-carbon bonds. *J. Fluorine Chem.* **1993**, *65*, 11–14.

(22) (a) Yang, Z.-Y.; Wiemers, D. M.; Burton, D. J. (Trifluoromethyl)copper: A Useful CF_2 Transfer Reagent. A Novel Double Insertion of Difluoromethylene into (Pentafluorophenyl)-copper. *J. Am. Chem. Soc.* **1992**, *114*, 4402–4403. (b) Yang, Z.-Y.; Burton, D. J. A novel double insertion of the difluoromethylene unit from trifluoromethylcopper into the carbon–copper bond of perfluoroaryl- and perfluorovinylcopper reagents: preparation, mechanism and applications of new fluorinated copper reagents. *J. Fluorine Chem.* **2000**, *102*, 89–103. (c) Xie, Q.; Zhu, Z.; Li, L.; Ni, C.; Hu, J. Controllable double CF_2 -insertion into sp^2 C–Cu bond using TMSCF_3 : a facile access to tetrafluoroethylene-bridged structures. *Chem. Sci.* **2020**, *11*, 276–280.

(23) (a) Eujen, R.; Hoge, B.; Brauer, D. J. Synthesis and properties of donor-free bis(difluoromethyl) cadmium, $(\text{CF}_2\text{H})_2\text{Cd}$ NMR spectroscopic detection and structure of tetrakis(difluoromethyl) cuprate (III) and related compounds. *J. Organomet. Chem.* **1996**, *519*, 7–20. (b) Burton, D. J.; Hartgraves, G. A. The preparation of HCF_2CdX and HCF_2ZnX via direct insertion into the carbon halogen bond of CF_2HY ($\text{Y} = \text{Br}, \text{I}$). *J. Fluorine Chem.* **2007**, *128*, 1198–1215. (c) Fier, P. S.; Hartwig, J. F. Copper-Mediated Difluoromethylation of Aryl and Vinyl Iodides. *J. Am. Chem. Soc.* **2012**, *134*, 5524–5527. (d) Hu, J.; Zhang, W.; Wang, F. Selective difluoromethylation and monofluoromethylation reactions. *Chem. Commun.* **2009**, 7465–7478. (e) Jiang, X.-L.; Chen, Z.-H.; Xu, X.-H.; Qing, F.-L. Copper-mediated difluoromethylation of electron-poor aryl iodides at room temperature. *Org. Chem. Front.* **2014**, *1*, 774–776. (f) Bour, J. R.; Kariofillis, S. K.; Sanford, M. S. Synthesis, Reactivity, and Catalytic Applications of Isolable $(\text{NHC})\text{Cu}(\text{CHF}_2)$ Complexes. *Organometallics* **2017**, *36*, 1220–1223.

(24) (a) Li, L.; Ni, C.; Xie, Q.; Hu, M.; Wang, F.; Hu, J. TMSCF_3 as a Convenient Source of $\text{CF}_2=\text{CF}_2$ for Pentafluoroethylation, (Aryloxy)tetrafluoroethylation, and Tetrafluoroethylation. *Angew. Chem., Int. Ed.* **2017**, *56*, 9971–9975. (b) Wang, Q.; Ni, C.; Hu, M.; Xie, Q.; Liu, Q.; Pan, S.; Hu, J. From C₁ to C₃: Copper-Catalyzed gem-Bis(trifluoromethyl)olefination of α -Diazo Esters with TMSCF_3 . *Angew. Chem., Int. Ed.* **2020**, *59*, 8507–8511.

(25) Andrella, N. O.; Xu, N.; Ghabidullin, B. M.; Ehm, C.; Baker, R. T. Selective Copper Complex-Catalyzed Hydrodefluorination of Fluoroalkenes and Allyl Fluorides: A Tale of Two Mechanisms. *J. Am. Chem. Soc.* **2019**, *141*, 11506–11521.

(26) Selected work with TMSCF_2Br reported by us: (a) Wang, F.; Zhang, W.; Zhu, J.; Li, H.; Huang, K.-W.; Hu, J. Chloride ion-catalyzed generation of difluorocarbene for efficient preparation of gem-difluorinated cyclopropanes and cyclopropanes. *Chem. Commun.* **2011**, *47*, 2411–2413. (b) Xie, Q.; Ni, C.; Zhang, R.; Li, L.; Rong, J.; Hu, J. Efficient Difluoromethylation of Alcohols Using TMSCF_2Br as a Unique and Practical Difluorocarbene Reagent under Mild Conditions. *Angew. Chem., Int. Ed.* **2017**, *56*, 3206–3210. (c) Xie, Q.; Zhu, Z.; Li, L.; Ni, C.; Hu, J. A General Protocol for C–H Difluoromethylation of Carbon Acids with TMSCF_2Br . *Angew. Chem., Int. Ed.* **2019**, *58*, 6405–6410. (d) Xie, Q.; Zhu, Z.; Ni, C.; Hu, J. Nucleophilic (Phenylsulfonyl/arylthio)-difluoromethylation of Aldehydes with TMSCF_2Br : A Three-Component Strategy. *Org. Lett.* **2019**, *21*, 9138–9141. (e) Zhang, R.; Li, Q.; Xie, Q.; Ni, C.; Hu, J. Difluorocarbene-Induced Ring-Opening Difluoromethylation-Halogenation of Cyclic (Thio)Ethers with TMSCF_2X ($\text{X} = \text{Br}, \text{Cl}$).

Chem. - Eur. J. **2021**, *27*, 17773–17779. (f) Liu, A.; Ni, C.; Xie, Q.; Hu, J. TMSCF_2Br -Enabled Fluorination-Aminocarbonylation of Aldehydes: Modular Access to α -Fluoroamides. *Angew. Chem., Int. Ed.* **2022**, *61*, e202115467.

(27) Recent examples with TMSCF_2Br reported by others: (a) Wang, J.; Tokunaga, E.; Shibata, N. Highly C-selective difluoromethylation of β -ketoesters by using TMSCF_2Br /lithium hydroxide/ N,N,N -trimethylhexadecan-1-ammonium bromide. *Chem. Commun.* **2018**, *54*, 8881–8884. (b) Zhang, R.; Zhang, Z.; Zhou, Q.; Yu, L.; Wang, J. The Generation of Difluoroketenimine and Its Application in the Synthesis of α,α -Difluoro- β -amino Amides. *Angew. Chem., Int. Ed.* **2019**, *58*, 5744–5748. (c) Mita, T.; Harabuchi, Y.; Maeda, S. Discovery of a synthesis method for a difluoroglycine derivative based on a path generated by quantum chemical calculations. *Chem. Sci.* **2020**, *11*, 7569–7577. (d) Liu, X.; Du, D.; Li, S.; Wang, X.; Xu, C.; Wang, M. Defluorinative Ring-Opening Indolylolation of Siloxydifluorocyclopropanes: Controlled Synthesis of α -Fluoro- β -Indolyl-Propanones for Carbazole Construction. *Adv. Synth. Catal.* **2020**, *362*, 5135–5140. (e) Zhang, R.; Zhang, Z.; Wang, K.; Wang, J. Difluoroketenimine: Generation from Difluorocarbene and Isocyanide and Its [3+2] Cycloadditions with Alkenes or Alkynes. *J. Org. Chem.* **2020**, *85*, 9791–9800. (f) Kim, Y.; Heo, J.; Kim, D.; Chang, S.; Seo, S. Ring-opening functionalizations of unstrained cyclic amines enabled by difluorocarbene transfer. *Nat. Commun.* **2020**, *11*, No. 4761. (g) Trifonov, A. L.; Dilman, A. D. Synthesis of Difluoroalkylated Heteroarenes via Difluorocarbene. *Org. Lett.* **2021**, *23*, 6977–6981. (h) Jia, Y.; Yuan, Y.; Huang, J.; Jiang, Z.-X.; Yang, Z. Synthesis of Difluorinated Heterocyclics through Metal-Free [8+1] and [4+1] Cycloaddition of Difluorocarbene. *Org. Lett.* **2021**, *23*, 2670–2675. (i) Yang, R.-Y.; Wang, H.; Xu, B. Base promoted gem-difluoroolefination of alkyl triflones. *Chem. Commun.* **2021**, *57*, 4831–4834.

(28) Keating, G. M.; Croom, K. F. A Review of its Use in Primary Dyslipidaemia, the Metabolic Syndrome and Type 2 Diabetes Mellitus. *Drugs* **2007**, *67*, 121–153.

(29) Wang, X. J.; Zhang, L.; Byrne, D.; Nummy, L.; Weber, D.; Krisnamurthy, D.; Yee, N.; Senanayake, C. H. Efficient Synthesis of Empagliflozin, an Inhibitor of SGLT-2, Utilizing an AlCl_3 -Promoted Silane Reduction of a β -Glycopyranoside. *Org. Lett.* **2014**, *16*, 4090–4093.

(30) Burris, H. A., III Dual Kinase Inhibition in the Treatment of Breast Cancer: Initial Experience with the EGFR/ErbB-2 Inhibitor Lapatinib. *Oncologist* **2004**, *9*, 10–15.

(31) Zhu, S.-Q.; Xu, X.-H.; Qing, F.-L. Copper-mediated oxidative difluoromethylation of terminal alkynes with TMSCF_2H . *Org. Chem. Front.* **2015**, *2*, 1022–1025.

(32) (a) Liu, H.; Shen, Q. Bistrifluoromethylated Organocuprate $[\text{Ph}_4\text{P}]^+[\text{Cu}(\text{CF}_3)_2]^-$: Synthesis, Characterization and Its Application for Trifluoromethylation of Activated Heteroaryl Bromides, Chlorides and Iodides. *Org. Chem. Front.* **2019**, *6*, 2324–2328. (b) Liu, H.; Wu, J.; Jin, Y.; Leng, X.; Shen, Q. Mechanistic Insight into Copper-Mediated Trifluoromethylation of Aryl Halides: The Role of CuI . *J. Am. Chem. Soc.* **2021**, *143*, 14367–14378.