ORGANIC CHEMISTRY

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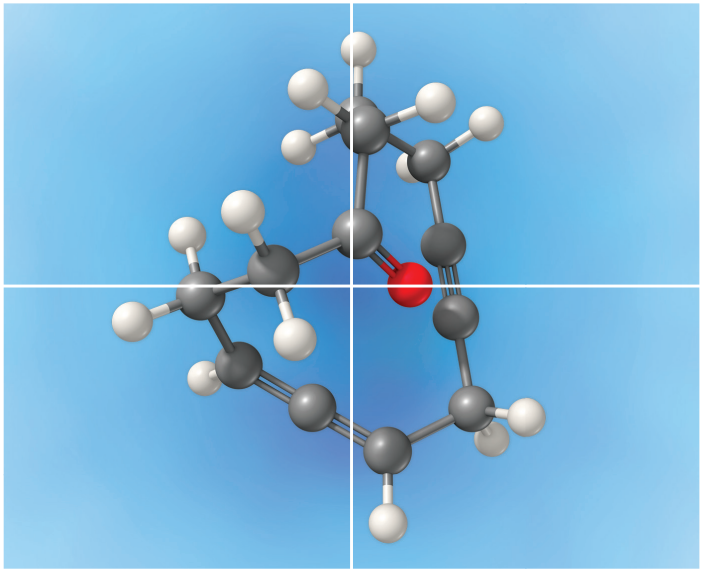

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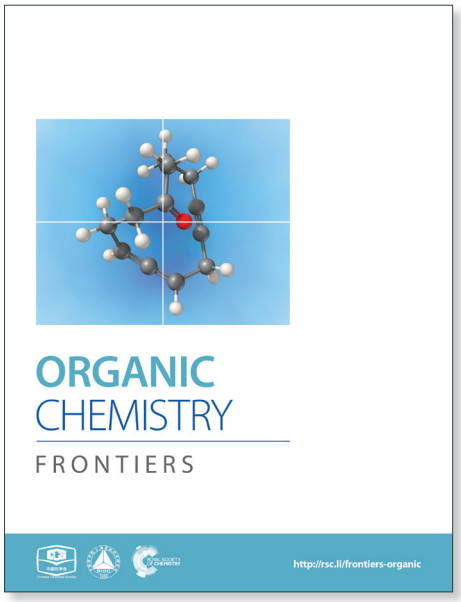

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Organic Chemistry Frontiers

RESEARCH ARTICAL

Cu-mediated 2,2,2-Trifluoroethylation of Terminal Alkynes using 1,1-Dichloro-2,2,2-trifluoroethane (HCFC-123)

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The title reaction provides a novel utilization of ozone-depleting/global-warming HCFCs as a new carbon-carbon cross-coupling model of various terminal alkynes by activating two inert C-Cl bonds successively. This protocol provided trifluoroethylated alkynes efficiently under mild reaction conditions and was compatible with a broad range of functional groups. An example for synthesis of a terbinafine analogue is shown. Some mechanistic experiments including deuterated reagents and radical/SET inhibitors are described.

Introduction

The strategic incorporation of fluorine or fluorinated moieties into organic substrates imparts useful properties to these molecules.[1a] Hydrofluorochlorocarbons (HCFCs) are essential materials for the fluorine industry. They are indispensable for the production of a variety of useful fluorinated compounds, although HCFCs cause ozone depletion and global warming.[1] An example of the sustainable use of HCFCs involves the synthesis of a very useful polymer polytetrafluoroethylene (PTFE) from the chemical precursor chlorodifluoromethane (HCFC-22) via tetrafluoroethylene. Besides the application in fluorinated materials, HCFCs are also be used in synthesis for agrochemicals, such as pyrethroid insecticide.[1d]

The challenge in using HCFC molecules in chemical synthesis is activating the inert C-Cl bond without influencing the fluorine moiety. Reported methods which use HCFCs in chemical synthesis typically cause C-F bond cleavage which yields fluoroalkenes. Burton and others have reported the transformation of CF_3CH_2Cl (HCFC-133a) to a fluoroalkene for further functionalization using dehydrofluorination.[2] Chen and Wu have reported reactions between nucleophiles and HCFC-133a under basic and supercritical conditions which gave fluorochlorovinyl derivatives and defluorinated ethers.[3] Nucleophilic addition of 1,1-dichloro-2,2,2-trifluoroethane (HCFC-123, **1**) to a variety of aldehydes in the presence of Zn have been reported to yield difluoropropenol.[4] HCFC-133a can generate either 1,1,1-trifluoroethane or 1,1-difluoroethylene depending on the activation method used.[5] Methods to activate the C-Cl bonds of HCFCs which do not affect the fluorine groups via radical intermediates have been developed.[5-7] Nevertheless, the reaction partners are limited to alkenes/alkynes,[6a,7a] phenols/thiophenols,[7] and secondary amines.[8] To the best of our knowledge, metal-mediated carbon-carbon cross-coupling reactions using HCFCs without defluorination have not been discovered.

Polyfluoro and perfluoroalkyl iodides/bromides (e.g., CF_3CH_2I, $BrCF_2P(O)OR$, $BrCF_2CH{=}CH_2$, C_4F_9I and CF_3I) are suitable coupling partners in metal-mediated C-C cross-coupling reactions.[9] However, there are few reports of C-C cross-coupling reactions involving fluorinated alkyl chlorides. In addition to the large C-Cl bond energy, the challenges involved in using HCFCs include (Scheme 1a): 1) the cleavage of the C-Cl bond commonly generates a fluoroalkyl radical via a single-electron transfer (SET) process, which can abstract a hydrogen[5] or add to unsaturated substrates;[6a,7a] 2) β-defluorination[5,10] is a predominating reaction pathway if an organometallic species is generated after the oxidative addition of a metal to the C-Cl bond.

In 2011, Shibata reported the first example trifluoromethylation of propargyl halides by a trifluoromethylation of 1-(3-bromoprop-1-ynyl)-4-nitrobenzene using electrophilic trifluoromethylation reagent [S-(trifluoromethyl)diphenylsulfoniumsalt].[11a] In 2012, Szabó reported the trifluoromethylation of propagylic halides and trifluoroacetates using $(Ph_3P)_3Cu(CF_3)$ reagent to give the selective formation of allenylic or propargylic trifluoromethyl derivatives.[11b] These methodologies gave trifluoroethylated alkynes with a requirement of a stoichiometric amount of copper metal. In 2013, Cu-catalyzed trifluoromethylation of primary propargylic chlorides with trifluomethyl trimethylsilane was reported by Nishibayashi.[11c] A specialized trifluoroethylated alkyne for biological research was synthesized in a good yield by the use of 1,1,1-trifluoro-2-iodoethane and a lithium reagent at an extremely low temperature.[11d] Some coupling approaches to trifluoromethylated alkynes have also been researched. Ma and his coworkers prepared trifluoromethylated alkynes in a copper-catalyzed coupling reactions of terminal alkynes with 2,2,2-trifluorodiazoethane.[11e] Later, Xu[11f] and Lee[11g] independently disclosed the Pd-catlayzed

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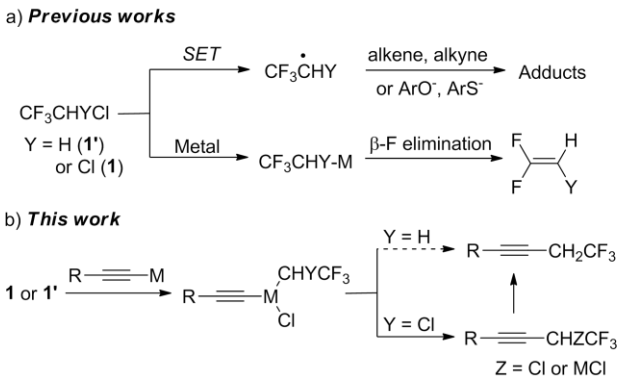
Electronic Supplementary Information (ESI) available: *details for experiments conditions, copies of ^{19}F NMR, ^{1}H NMR and ^{13}C NMR spectra for isolated compounds.* See DOI: 10.1039/x0xx00000x



Scheme 1. a) A graphic summary of previous works relating to the C-Cl activation of HCFC-133a and HCFC-123. b) A novel transition metal mediated C-C cross-coupling method using HCFCs.

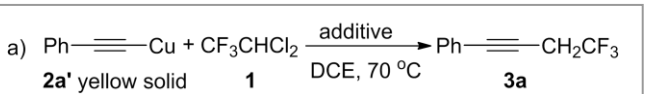
coupling reaction of 1,1,1-trifluoro-2-iodoethane with terminal alkynes or aryl alkynyl carboxylic acids.

Herein, we report a novel cross-coupling method in which two distinct steps occur to synthesize trifluoroethylated alkynes (Scheme 1b) inspired by two classical cross-coupling reactions (Cadiot-Chodkiewicz coupling[12] and Castro-Stephens coupling[13]). The first step is a generation of a transition-metal acetylide from the alkyne before the C-Cl activation. The second step is oxidative addition of the organometallic species to the C-Cl bond of a HCFC then reductive elimination which yields the desired coupling product. This method is a practical and efficient way to trifluoromethylated alkynes by using a cheap metal copper, an ordinary amine and a low-cost chlorofluorohydrocarbon as a fluorinated building block.

Results and discussion

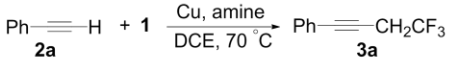
To test our hypothesis, we carried out the reaction between an isolated copper phenyl acetylide (**2a'**)[14] and compound **1** in 1,2-dichloroethane (DCE) at 70 °C, unfortunately no reaction occured (Scheme 2a, 1). However, when added two equivalents of diethylamine to the reaction, which was used to increase the solubility of the copper acetylide, the desired trifluoroethylated acetylene **3a** was obtained in 40% yield (Scheme 2a, 2). The addition of one equivalent of copper powder increased the yield from 40% to 61% (Scheme 2a, 3). Further increasing the equivalents of copper powder and diethylamine did not improve the reaction yield (Scheme 2, 4). Considering copper acetylide was synthesized from phenyl acetylene **2a**, we studied a one-step reaction using acetylene **2a** as substrate.

To our delight, a one-pot reaction including acetylene **2a**, HCFC-123, copper and diethylamine gave the desired product **3a** in 77% yield (Scheme 3, entry 1). To further increase the yield we examined a range of amines. The reaction yields decreased slightly when using di-*n*-propylamine and di-*n*-butylamine (Scheme 3, entries 2 and 3). Using diallylamine gave **3a** in a 30% yield (Scheme 3, entry 4). The secondary diamine N,N'-dimethyl-1,2-ethanediamine (DMEDA) also gave product **3a** in 44% yield, however a side-product



	Additive	% yield of **3a**
1)	no additive	0
2)	Et_2NH (2 equiv.)	40
3)	Cu (1 equiv.), Et_2NH (2 equiv.)	61
4)	Cu (2 equiv.), Et_2NH (3 equiv.)	60

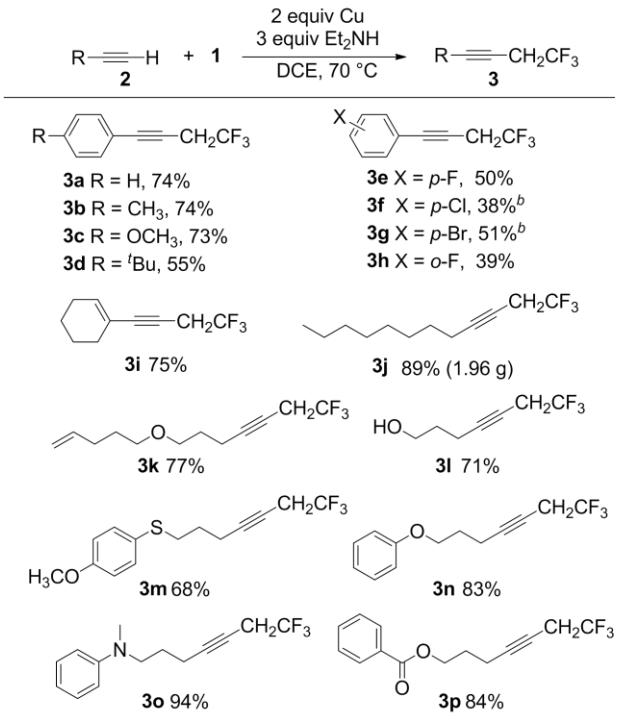
Scheme 2. Reactions between the isolated copper acetylide **2a'**, compound **1** and varying amounts of copper and diethylamine.



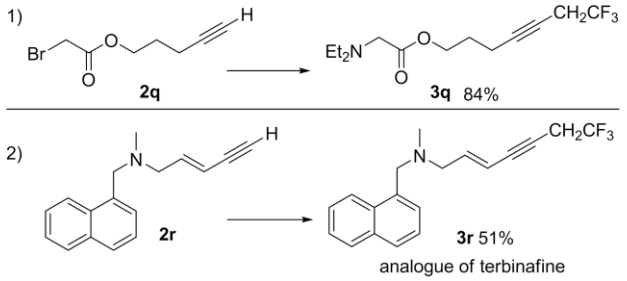
Entry	Amine	Yield (%)[b]	Entry	Amine	Yield (%)[b]
1	**Et_2NH**	**77(74)**	8	$^{i}Pr_2NH$	N.R.[d]
2	$^{n}Pr_2NH$	64	9	Ph_2NH	N.R.
3	$^{n}Bu_2NH$	63	10	$EtNH_2$	N.R.
4	diallylamine	30	11	Et_3N	N.R.
5	DMEDA	44[c]	12	TEDA	N.R.
6	piperidine	7	13[e]	Et_2NH	N.R.
7	azolidine	trace			

Scheme 3. Effect of amines in the reaction between phenyl acetylene with **1**.[a]
[a]The reactions were carried out with **2** (1 mmol) and **1** (2 mmol) in the presence of Cu powder (2 mmol) and amine (3 mmol) in 2 mL DCE at 70 °C in a Schlenk tube under a nitrogen atmosphere for 6 hours. [b]Yields were determined by ^{19}F NMR spectroscopy using benzotrifluoride as an internal standard and an isolated yield was in parentheses. [c](4,4,4-trifluorobuta-1,2-dien-1-yl)benzene (20% yield according to ^{19}F NMR spectroscopy) was found with **3a**. [d]N.R. = no reaction. [e]**1'** was used instead of **1**.

(4,4,4-trifluorobuta-1,2-dien-1-yl)benzene was detected (Scheme 3, entry 5). Moreover, the reactions using cyclic or aromatic secondary amines, sterically hindered secondary amines, primary amines, tertiary amines and tertiary diamines, all resulted in low-yielding or no reaction (Scheme 3, entries 6–12). These results suggested that electron-rich secondary linear amines, which are not sterically hindered, facilitated the reaction. What's more, the reaction did not occur when we replaced compound **1** with 2-chloro-1,1,1-trifluoroethane (HCFC-133a, **1'**) (Scheme 3, Entry 13). Plausibly, the second chlorine atom in compound **1** is required to activate the other C-Cl bond. Therefore, we used the optimal conditions described in Scheme 3 (entry 1) to test the scope of the reaction with a series of alkyne coupling partners (Scheme 4). Other conditions screening can be found in supporting information. We have examined other solvents, such as DMF, THF, CH_3NO_2 and CH_3CN (Table S1). Those solvents were not effective.

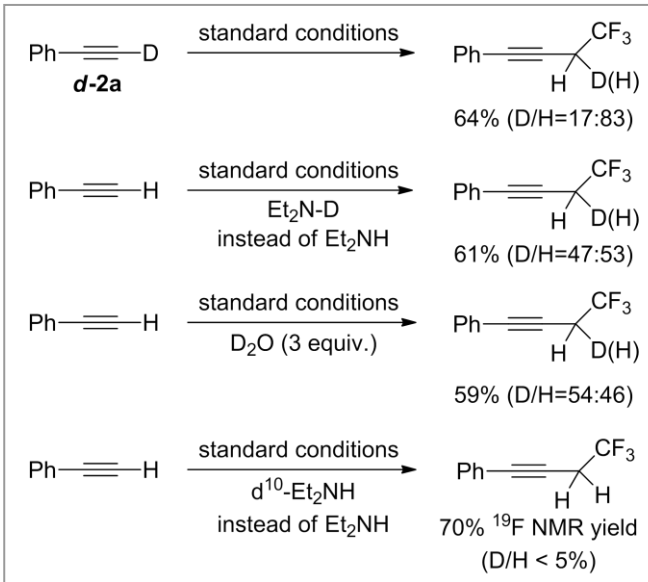


Scheme 4. Scope of 2,2,2-trifluoroethylation of various alkynes with **1**. [a]
[a]Reaction was carried out by using alkyne (1 mmol) and **1** (2 mmol) in the presence of Cu (2 mmol) and diethylamine (3 mmol) in DCE (2 mL) at 70 °C under a nitrogen atmosphere in a Schlenk tube for 6-8 hours and isolated yields are shown. [b]Using **1** as sole solvent.

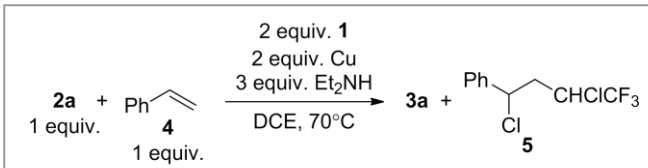


Scheme 5. Some special alkyne substrates in the reactions with **1**. Reaction conditions as Scheme 4.

Reactions involving a series of related electron-rich and electron-poor aromatic alkynes gave products **3a**–**3h** in isolated yields between 38% and 74%, as shown in Scheme 4. The conjugated alkyne **3i** and the aliphatic alkyne **3j** were obtained in 75% and 89% yields, respectively. The coupling reaction occurred selectively at the alkyne in the presence of a terminal alkene giving



Scheme 6. Deuterated experiments for determination of H-sources.



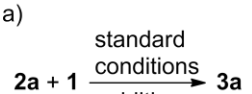
entry	condition	yield (%) 3a	5
1	only **4** for 8h	0	24
2	**2a** and **4** for 5h	57	7
3	**2a** and **4** for 9h	63	9

Scheme 7. Relative rate between alkyne **2a** and alkene **4**.

product **3k** in 77% yield. The reaction was also tolerant of a variety of functional groups, including hydroxyl (**3l**, 71%), ether and thioether (**3m**, 68%; **3n**, 83% and **3k**, 77%), tertiary amine (**3o**, 94%) and ester groups (**3p**, 84%). The C-C coupling reaction using the α-bromo carbonyl compound **2q** was successful, however the amine substituted compound **3q** was the major product isolated (Scheme 5). The functional group compatibility of the reaction allowed us to synthesize a fluorinated analogue of terbinafine **3r** in 51% (Scheme 5). The reaction is not compatible with aryl alkynes bearing with electron-deficient functional groups and heteroaryl alkynes bearing with nitrogen and sulfur. For examples, reactions with 4-acetylphenylacetylene, 2-ethynylpyridine and 2-ethynylthiophene gave no products. In spite of the tiny substrate limitation, the reactions are scalable, which make the reaction practical for further industry application. We were able to synthezie **3a** in a 100 mL autoclave, which gave 5 grams of alkyne proudct in one pot. In a 20 mL Shlenck tube, **3j** could be obtained in a multi-gram scale.

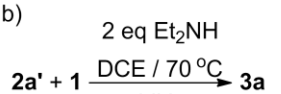
To determine the source of protons in the final products we conducted a series of experiments using deuterated materials

a)



Additive	% yield
none	77
20 mol% HQ	72
20 mol% DNB	59
1 equiv. DAE	63

b)



Additive	% yield
none	40
20 mol% BHT	43
1 equiv. TEMPO	40
20 mol% DNB	47
1 equiv. DAE	38

Scheme 8. Mechanism Experiments with radical scavengers.

(Scheme 6). The reaction in which the deuterated alkyne **d-2a** was used gave the desired product in 64% total yield, of which 17% was the deuterated product. Similar total yields were obtained when using either N-deuterated diethylamine or adding three equivalents of D_2O to the reaction mixture, however both gave the deuterated product in an approximately 50% ratio. These results indicated that the protons in the products originated from acidic protons within the reagents or water in solvents. The reaction in which ethyl-deuterated *d*[10]-diethylamine was used did not yield any deuterated products suggesting that redox reactions of diethylamine might not occur. These experiments don't support a carbenoid species because the ratio of deuterium to hydrogen at the propargyl positions in the corresponding products should be identical to that in the starting alkyne substrates if a carbenoid mechanism is involved.[11e]

Copper in known to initiate the cleavage of the C-Cl bond in compound **1** via a SET in reactions involving phenols, thiophenols and styrene.[7a] However, we found that the reactions with terminal alkynes were highly tolerant of aromatic rings, conjugated double bonds (**3i**) and even terminal double bonds (**3k**) (Scheme 4). Contrast experiments showed that in the absence of an alkyne, styrene (4, Scheme 7) could indeed react with **1** via a radical addition.[7a] However, the reactions between compounds **1**, **2a** and **4** found that the generation of the radical adduct **5** was much less than that of **3a** (Scheme 7). This indicated that the generation of radicals under these reaction conditions was not favorable.

Control experiments including electron transfer and radical inhibitors, including hydroquinone (HQ), 1,4-dinitrobenzene (DNB), 2,6-di-*tert*-butyl-4-methylphenol (BHT) and 2,2,6,6-tetramethylpiperidin-1-oxy (TEMPO), showed no significant influence on the reaction yields (Scheme 8a/b). Importantly, when the radical trap diallyl ether (DAE) was added to the reaction no radical addition products were detected (Scheme 8), suggesting fluorinated-alkyl free radicals may not be involved in the reaction.

Therefore, an out-sphere radical process is unlikely to be the predominating pathway and an oxidative addition mechanism may be involved.[15] However, rigorous investigations are necessary to unambiguously elucidate the detailed mechanism.

Conclusions

We have successfully developed a Cu-mediated 2,2,2-trifluoroethylation of a series of terminal alkynes using HCFC-123. These reactions are compatible with a range of functional groups and can be performed on a gram scale in an efficient and economic manner. Mechanistic experiments indicate that an out-sphere radical process is unlikely to be the predominating pathway. This study has revealed the first C_{sp3}-C_{sp} cross-coupling reaction using a commonly available HCFC, providing a profitable way to utilize the ozone-depleting and globe-warming chemicals to generate valuable fluorinated molecules. Detailed mechanistic studies and further applications of this reaction are in progress on our laboratory.

Experimental Section

General information: NMR spectra were obtained on 300 or 400 MHz spectrometers and recorded at 25 °C. Chemical shifts for ^{1}H NMR spectra are reported in ppm downfield from TMS, chemical shifts for ^{13}C NMR spectra are recorded in ppm relative to internal chloroform (δ 77.0 ppm for ^{13}C), and chemical shifts for ^{19}F NMR are reported in ppm downfield from fluorotrichloromethane ($CFCl_3$). Coupling constants (*J*) are reported in hertz. The terms m, s, d, t, q and br refer to multiplet, singlet, doublet, triplet, quartet and broad, respectively. ^{13}C NMR was broad-band decoupled from hydrogen nuclei. ^{1}Absorbance frequencies in infrared spectra (IR) are given at maximum intensity in cm^{-1}. The mass analyzer type used for the HRMS is time-of-flight mass spectrometry (TOF-MS) or Fourier transform ion cyclotron resonance mass spectrometry (FTICR-MS). Column chromatography was performed using silica gel (mesh 300−400).

All reagents were used as received from commercial sources or prepared as described in references. All reagents were weighed and handled in air. Substrates **1** and **1'** were purchased from commercial sources and used as received. Substrates **2k**[16], **2m**[17], **2n**[17], **2o**[18], **2p**[19], **2q**[19] and **2r**[20] were prepared according to literature procedures.

Preparation of (phenylethynyl)copper 2a'.[14] CuI (2.02 g, 10.5 mmol) was dissolved in $NH_3{\cdot}H_2O$ (28% NH_3 solution, 25 mL) and EtOH (15 mL) to form a blue solution. While stirring, phenylacetylene (1.02 g, 10.0 mmol) was added dropwise to the solution. The system was allowed to stand for 2 h to form a yellow precipitate. The precipitate was filtered out and successively washed with $NH_3{\cdot}H_2O$ (10% NH_3 solution, 3 × 25 mL), H_2O (3 × 25 mL), EtOH (3 × 25 mL), and Et_2O (3 × 25 mL). The bright yellow solid was then dried under high vacuum to afford the desired polymeric copper acetylide **2a'**, which was used without further purification.

General procedure for the reaction of (phenylethynyl)copper 2a' with 1,1-dichloro-2,2,2-trifluoroethane (HCFC-123). To a 5 mL of Schlenk tube were added with (phenylethynyl)copper **2a'** (165 mg, 1 mmol) and copper powder (0 to 2 mmol). The tube was then evacuated and backfilled with N_2 (3 times). HCFC-123 (2 mmol), Et_2NH (0 to 3 mmol) and DCE (2 mL) were added into this Schlenk tube subsequently under N_2. The tube was sealed and heated to 70 °C (oil bath). After stirring for 8 h, the reaction mixture was cooled to room temperature and benzotrifluoride was added. The yield was determined by ^{19}F NMR spectroscopy using

benzotrifluoride as an internal standard before working up the reaction before working up. If necessary, the reaction mixture was diluted with petroleum ether (PE, 10 mL) and the precipitation was removed with filtration. The filtrate was concentrated and the residue was purified with silica gel chromatography (petroleum ether as the eluent) to give pure product **3a**.

Screening conditions for reactions of phenylacetylene 2a with 1,1-Dichloro-2,2,2-trifluoroethane (HCFC-123) in the presence of various metals and salts (Table 1S and 2S). To a 5 mL of Schlenk tube were added with metal powder (x mmol). The tube was then evacuated and backfilled with N_2 (3 times). HCFC-123 (y mmol), phenylacetylene **2a** (102 mg, 1 mmol), amine (z mmol) and solvent (2 mL) were added into this Schlenk tube subsequently under N_2. The Schlenk tube was sealed and heated to 60-80 °C (oil bath). After stirring for 8 h, the reaction mixture was cooled to room temperature and benzotrifluoride was added. The yield was determined by ^{19}F NMR spectroscopy using benzotrifluoride as an internal standard before working up the reaction before working up. If necessary, the reaction mixture was diluted with PE (10 mL) and the precipitation was removed with filtration. The filtrate was concentrated in vacuum and the residue was purified with silica gel chromatography (petroleum ether as the eluent) and concentrated in vacuum to give pure product **3a**.

General procedure for the copper-mediated 2,2,2-trifluoroethylation of 2,2-dichloro-1,1,1-trifluoroethane (HCFC-123) with various alkynes. To a 5 mL of Schlenk tube was added Cu power (128 mg, 2 mmol). The tube was then evacuated and backfilled with N_2 (3 times). HCFC-123 (306 mg, 2 mmol), alkyne (1 mmol), Et_2NH (219 mg, 3 mmol) and DCE (2 mL) were added into this Schlenk tube subsequently under N_2. The Schlenk tube was sealed and heated to 70 °C (oil bath). After stirring for 8 h, the reaction mixture was cooled to room temperature and diluted with PE (10 mL). The precipitation was removed with filtration. The solvent was removed in vacuum and the residue was purified with silica gel chromatography (petroleum ether as the eluent) to provide pure product.

(4,4,4-Trifluorobut-1-yn-1-yl)benzene (3a)[11e]

The reaction was run as general procedure. Yield: 74%; 136 mg; colorless oil. ^1H NMR (300 MHz, $CDCl_3$) δ 7.43-7.47 (m, 2H), 7.25-7.33 (m, 3H), 3.27 (q, *J* = 10.0 Hz, 2H); ^{19}F NMR (376 MHz, $CDCl_3$) δ -66.5 (t, *J* = 9.6 Hz).

Autoclave procedure: Cu powder (3.8 g, 60 mmol), phenyl acetylene (4.1 g, 40 mmol), diethylamine (8.8 g, 120 mmol), 1,1-dichloro-2,2,2-trifluoroethane (12.2 g, 80 mmol) and 1,2-dichloroethane (40 mL) were added to an autoclave (0.1 L). After removal of air in the autoclave under vacuum, the reaction was run at 70 ^oC for 7 h. Stopped reaction and let it stand overnight. The solid was removed by filtration and rinsed with ethyl acetate. The organic phase was washed with deionized water (50 mL) and saturated solution of sodium chloride (50 mL). The organic phase was dried over anhydrous sodium sulfate. After removal of the solvent, the residue was distilled under vacuum to give the product as a colorless liquid (oil bath 120 ^oC/2 mmHg, 5.2 g, 28 mmol, 70%).

4-Methyl-1-(4,4,4-trifluorobut-1-yn-1-yl)benzene (3b)[11e]

Yield: 74% (using three equivalents of Cu powder and using CF_3CHCl_2 instead of DCE as the solvent); 146 mg; yellow oil. ^1H NMR (300 MHz, $CDCl_3$) δ 7.33 (d, *J* = 7.8 Hz, 2H), 7.11 (d, *J* = 7.8 Hz, 2H); 3.25 (q, *J* = 9.6 Hz, 2H), 2.34 (s, 3H); ^{19}F NMR (282 MHz, $CDCl_3$) δ -66.9 (t, *J* = 9.8 Hz).

1-Methoxy-4-(4,4,4-trifluorobut-1-yn-1-yl)benzene (3c)[11e]

Yield: 73%; 156 mg; yellow oil. ^1H NMR (300 MHz, $CDCl_3$) δ 7.37 (d, *J* = 9.0 Hz, 2H), 6.82 (d, J = 9.0 Hz, 2H), 3.78 (s, 3H), 3.24 (q, *J* = 9.6 Hz, 2H); ^{19}F NMR (282 MHz, $CDCl_3$) δ -66.9 (t, *J* = 10.0 Hz).

4-(tert-Butyl)-1-(4,4,4-trifluorobut-1-yn-1-yl)benzene (3d)[11b]

Yield: 55%; 132 mg; colorless oil. ^1H NMR (300 MHz, $CDCl_3$) δ 7.37 (m, 4H), 3.26 (q, *J* = 9.5 Hz, 2H), 1.32 (s, 9H); ^{19}F NMR (282 MHz, $CDCl_3$) δ -66.9 (t, *J* = 9.8 Hz).

1-Fluoro-4-(4,4,4-trifluorobut-1-yn-1-yl)benzene (3e)[11e]

Yield: 50%; 101 mg; yellow oil. ^1H NMR (300 MHz, $CDCl_3$) δ 7.40-7.45 (m, 2H), 6.97-7.03 (m, 2H), 3.25 (q, *J* = 9.0 Hz, 2H); ^{19}F NMR (282 MHz, $CDCl_3$) δ -66.8 (t, *J* = 8.5 Hz, 3F), -110.6 (m, 1F).

1-Chloro-4-(4,4,4-trifluorobut-1-yn-1-yl)benzene (3f)[11c]

Yield: 38% (using CF_3CHCl_2 instead of DCE as the solvent); 82 mg; colorless oil. ^1H NMR (300 MHz, $CDCl_3$) δ 7.37 (d, *J* = 9.0 Hz, 2H), 7.28 (d, *J* = 9.0 Hz, 2H), 3.26 (q, *J* = 9.4 Hz, 2H); ^{19}F NMR (282 MHz, $CDCl_3$) δ -66.8 (t, *J* = 8.8 Hz).

1-Bromo-4-(4,4,4-trifluorobut-1-yn-1-yl)benzene (3g)[11b]

Yield: 51% (using CF_3CHCl_2 instead of DCE as the solvent); 134 mg; yellow oil. ^1H NMR (300 MHz, $CDCl_3$) δ 7.44 (d, *J* = 9.0 Hz, 2H), 7.30 (d, *J* = 9.0 Hz, 2H), 3.25 (q, *J* = 9.0 Hz, 2H); ^{19}F NMR (282 MHz, $CDCl_3$) δ -66.7 (t, *J* = 9.8 Hz).

1-Fluoro-2-(4,4,4-trifluorobut-1-yn-1-yl)benzene (3h)

Yield: 39%; 82 mg; yellow oil. ^1H NMR (300 MHz, $CDCl_3$) δ 7.43 (m, 1H), 7.31 (m, 1H), 7.07 (m, 2H), 3.31 (q, *J* = 10.0 Hz, 2H); ^{19}F NMR (282 MHz, $CDCl_3$) δ -66.8 (t, *J* = 9.8 Hz, 3F), -110.6 (m, 1F); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.0 (d, *J* = 251 Hz), 133.7, 130.5 (d, *J* = 8 Hz), 124.1 (q, *J* = 275 Hz), 123.9, 115.5 (d, *J* = 21 Hz), 110.7 (d, *J* = 16 Hz), 82.7 (m), 77.9, 26.9 (q, *J* = 34 Hz); IR (neat) ν/cm^{-1}: 2936.3, 2230.0, 1614.0, 1578.8, 1493.9, 1450.7, 1419.7, 1366.1, 1281.7, 1259.7, 1219.6, 1150.7, 1111.4, 1032.3, 906.6, 822.4, 756.9, 659.2; EI-MS m/z (%): 107 (3), 133 (63), 134 (6), 151 (8), 182 (17), 183 (12), 202 (100), 203 (11). HRMS-EI (M) Calcd for $C_{10}H_6F_4$: 202.0406; found: 202.0407.

1-(4,4,4-Trifluorobut-1-yn-1-yl)cyclohex-1-ene (3i)

Yield: 75%; 141 mg; yellow oil. ^1H NMR (300 MHz, $CDCl_3$) δ 6.13 (m, 1H), 3.14 (q, *J* = 10.0 Hz, 2H), 2.08-2.10 (m, 4H), 1.55-1.64 (m, 4H); ^{19}F NMR (282 MHz, $CDCl_3$) δ -67.3 (t, *J* = 8.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.9, 125.0 (q, *J* = 275 Hz), 119.9, 86.1, 74.6 (q, *J* = 5 Hz), 29.0, 26.7 (q, *J* = 34 Hz), 25.6, 22.2, 21.4; IR (neat) ν/cm^{-1}: 2934.1, 2862.5, 2236.9, 1650.5, 1450.1, 1370.4, 1254.9, 1146.7, 1111.1, 906.9, 841.5, 671.3, 589.7; EI-MS m/z (%): 77 (26), 91 (90), 105 (66), 109 (23), 119 (24), 173 (41), 174 (30), 188 (100). HRMS-EI (M) Calcd for $C_{10}H_{11}F_3$: 188.0813; found: 188.0817.

1,1,1-Trifluorododec-3-yne (3j)

To a 20 mL of Schlenk tube was added Cu power (1.28 g, 20 mmol). The tube was then evacuated and backfilled with N_2 (3 times). HCFC-123 (3.06 g, 20 mmol), alkyne (10 mmol), Et_2NH (2.19 g, 30 mmol) and DCE (20 mL) were added into this Schlenk tube subsequently under N_2. The Schlenk tube was sealed and heated to 70 °C (oil bath). After stirring for 8 h, the reaction mixture was cooled to room temperature and diluted with PE (100 mL). The precipitation was removed with filtration. The solvent was removed in vacuum and the residue was purified with silica gel chromatography (petroleum ether as the eluent) to provide pure product.

Yield: 89%; 1.96 g; yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.00 (qm, *J* = 9.0 Hz, 2H), 2.13-2.19 (m, 2H), 1.47-1.52 (m, 2H), 1.27-1.35 (m, 10H), 0.88 (t, J = 9.0 Hz, 3H); ^{19}F NMR (282 MHz, $CDCl_3$) δ -67.5 (t, *J* = 9.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 124.5 (q, *J* = 275 Hz), 85.0, 68.1 (q, *J* = 5 Hz), 29.2, 29.1, 28.8, 28.4, 26.1 (q, *J* = 34 Hz), 22.7, 18.6, 14.1; IR (neat) ν/cm^{-1}: 2930.6, 2858.4, 2119.9, 1642.8, 1493.9, 1468.4, 1422.0, 1357.2, 1257.8, 1157.9, 1139.6, 1112.9, 908.8, 834.4, 656.3. Anal. calcd for $C_{12}H_{19}F_3$: C 65.43, H 8.69; found: C 65.50, H 8.70.

1,1,1-Trifluoro-7-(pent-4-en-1-yloxy)hept-3-yne (3k)

Yield: 77%; 180 mg; yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.79-5.84 (m, 1H), 4.95-5.05 (m, 2H), 3.49 (t, *J* = 8.0 Hz, 2H), 3.44 (t, *J* = 8.0 Hz, 2H), 3.00 (qm, *J* = 9.4 Hz, 2H), 2.28-2.30 (m, 2H), 2.12 (m, 2H), 1.75-1.79 (m, 2H), 1.65-1.69 (m, 2H); ^{19}F NMR (376 MHz, $CDCl_3$) δ -67.2 (t, *J* = 9.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.3, 124.9 (q, *J* = 275 Hz), 114.6, 84.3, 70.2, 68.9, 68.4 (q, *J* = 5 Hz), 30.3, 28.8, 28.6, 26.1 (q, *J* = 34 Hz), 16.3; IR (neat) ν/cm^{-1}: 2936.9, 2863.9, 2230.0, 1456.6, 1436.6, 1423.1, 1367.6, 1282.6, 1258.9, 1157.8, 1113.7, 909.9, 656.9; Anal. calcd for $C_{12}H_{17}F_3O$: C 61.53, H 7.31, F 24.33; found: C 61.51, H 7.30, F 24.05.

7,7,7-Trifluorohept-4-yn-1-ol (3l)

Yield: 71%; 117 mg; yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.74 (t, *J* = 6.0 Hz, 2H), 3.00 (qm, *J* = 9.4 Hz, 2H), 2.29-2.35 (m, 2H), 1.91 (br, 1H), 1.72-1.81 (m, 2H); ^{19}F NMR (282 MHz, $CDCl_3$) δ -67.4 (m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 124.3 (q, *J* = 275 Hz), 84.1, 68.8 (q, *J* = 5 Hz), 61.4, 31.0, 26.0 (q, *J* = 34 Hz), 15.0; IR (neat) ν/cm^{-1}: 3364.8, 2939.7, 2246.0, 1423.8, 1368.4, 1282.4, 1158.6, 1056.2, 931.6, 833.7, 657.0; EI-MS m/z (%): 69 (14), 79 (34), 97 (22), 83 (23), 101 (15), 127 (12), 148(100), 165 (6). HRMS-EI (M-1) Calcd for $C_7H_8OF_3$: 165.0527; found: 165.0522.

(4-Methoxyphenyl)(7,7,7-trifluorohept-4-yn-1-yl)sulfane (3m)

Yield: 68%; 196 mg; yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 (d, *J* = 8.0 Hz, 2H), 6.87 (d, *J* = 8.0 Hz, 2H), 3.82 (s, 2H), 3.01 (qm, *J* = 9.4 Hz, 2H), 2.93 (t, *J* = 8.0 Hz, 2H), 2.33-2.37 (m, 2H), 1.77-1.80 (m, 2H); ^{19}F NMR (376 MHz, $CDCl_3$) δ -66.9 (t, *J* = 9.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.0, 133.2, 126.1, 124.4 (q, *J* = 275 Hz), 114.6, 83.7, 69.0 (q, *J* = 5 Hz), 55.3, 34.6, 27.9, 26.1 (q, *J* = 34 Hz), 17.4; IR (neat) ν/cm^{-1}: 3003.5, 2940.0, 2837.8, 2220.0, 1593.4, 1494.5, 1441.8, 1366.8, 1283.1, 1140.8, 1032.3, 908.0, 828.4, 798.9; EI-MS m/z (%): 95 (17), 108 (18), 109 (19), 125 (34), 139 (64), 140 (100), 153 (17), 288 (32). HRMS-EI (M) Calcd for $C_{14}H_{15}OF_3S$: 288.0796; found: 288.0797.

((7,7,7-Trifluorohept-4-yn-1-yl)oxy)benzene (3n)

Yield: 83%; 200 mg; yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 (t, *J* = 8.0 Hz, 2H), 6.92-6.99 (m, 3H), 4.07 (t, *J* = 8.0 Hz, 2H), 2.99-3.06 (qm, *J* = 9.4 Hz, 2H), 2.41-2.45 (m, 2H), 1.98-2.05 (m, 2H); ^{19}F NMR (376 MHz, $CDCl_3$) δ -66.9 (t, *J* = 9.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.9, 129.4, 124.4 (q, *J* = 275 Hz), 120.7, 114.5, 83.9, 68.9 (q, *J* = 5 Hz), 66.0, 28.2, 26.1 (q, *J* = 34 Hz), 15.3; IR (neat) ν/cm^{-1}: 3063.8, 2937.2, 2220.0, 1600.8, 1497.8, 1367.0, 1246.9, 1138.7, 1053.8, 946.9, 908.1, 832.8; EI-MS m/z (%): 51 (6), 65 (10), 77 (15), 85 (6), 94 (100), 95 (9), 101 (6), 242 (14). HRMS-EI (M) Calcd for $C_{13}H_{13}OF_3$: 242.0918; found: 242.0914.

N-Methyl-N-(7,7,7-trifluorohept-4-yn-1-yl)aniline (3o)

Yield: 94%; 240 mg; yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.19-7.23 (m, 2H), 6.66-6.72 (m, 3H), 3.41 (t, *J* = 8.0 Hz, 2H), 3.01 (qm, *J* = 9.4 Hz, 2H), 2.92 (s, 3H), 2.20-2.24 (m, 2H), 1.73-1.80 (m, 2H); ^{19}F NMR (376 MHz, $CDCl_3$) δ -66.9 (t, *J* = 9.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.2, 129.1, 124.4 (q, *J* = 275 Hz), 116.2, 112.2, 84.2, 68.9 (q, *J* = 5 Hz), 51.4, 38.3, 26.1 (q, *J* = 34 Hz), 25.5, 16.1; IR (neat) ν/cm^{-1}: 3094.3, 3062.4, 2936.7, 2243.6, 1600.5, 1506.2, 1450.9, 1366.3, 1280.5, 1138.4, 1034.0, 991.5, 907.7, 832.9. ESI-MS m/z (%): 255.9 (M+1). HRMS-ESI (M+H) Calcd for $C_{14}H_{17}NF_3$: 256.1308; found: 256.1314.

7,7,7-Trifluorohept-4-yn-1-yl benzoate (3p)

Yield: 84%; 225 mg; yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.05 (d, *J* = 6.0 Hz, 2H), 7.56 (t, *J* = 7.5 Hz, 1H), 7.44 (t, *J* = 7.5 Hz, 2H), 4.41 (t, *J* = 6.0 Hz, 2H), 3.00 (qm, *J* = 10.0 Hz, 2H), 2.36-2.42 (m, 2H), 1.94-2.04 (m, 2H); ^{19}F NMR (282 MHz, $CDCl_3$) δ -67.3 (t, *J* = 9.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.4, 132.9, 130.2, 129.5, 128.3, 124.3 (q, *J* = 275 Hz), 83.4, 69.1 (q, *J* = 5 Hz), 63.5, 27.6, 26.0 (q, *J* = 34 Hz), 15.5; IR (neat) ν/cm^{-1}: 3064.7, 2963.7, 2247.0, 1720.6, 1602.5, 1452.4, 1388.5, 1274.0, 1111.6, 1027.6, 908.4, 833.1, 712.1; EI-MS m/z (%): 51 (12), 77 (43), 79 (17), 105 (100), 106 (8), 123 (9), 148 (29), 269 (7). HRMS-EI (M-1) Calcd for $C_{14}H_{12}O_2F_3$: 269.0789; found: 269.0790.

7,7,7-Trifluorohept-4-yn-1-yl 2-(diethylamino)acetate (3q)

Yield: 64%; 178 mg; yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.20 (t, *J* = 6.0 Hz, 2H), 3.33 (s, 2H), 2.99 (qm, *J* = 9.4 Hz, 2H), 2.66 (q, *J* = 8.0 Hz, 4H), 2.27-2.32 (m, 2H), 1.83-1.90 (m, 2H), 1.07 (t, *J* = 8.0 Hz, 6H); ^{19}F NMR (376 MHz, $CDCl_3$) δ -67.0 (t, *J* = 9.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.5, 124.3 (q, *J* = 275 Hz), 83.3, 69.1 (q, *J* = 5 Hz), 62.8, 54.1, 47.7, 27.5, 26.1 (q, *J* = 34 Hz), 15.3, 12.2; IR (neat) ν/cm^{-1}: 2971.6, 2360.0, 2244.9, 1739.0, 1455.3, 1367.7, 1282.2, 1139.3, 1030.2, 987.9, 908.5, 833.6; EI-MS m/z (%): 42 (2), 56 (2), 57 (1), 58 (5), 86 (100), 87 (6), 101 (1), 279 (1). HRMS-EI (M) Calcd for $C_{13}H_{20}NO_2F_3$: 279.1446; found: 279.1448.

(E)-7,7,7-Trifluoro-N-methyl-N-(naphthalen-1-ylmethyl)hept-2-en-4-yn-1-amine (3r)

Yield: 51%; 162 mg; yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.27 (d, J = 8.0 Hz, 1H), 7.86 (d, J = 8.0 Hz, 1H), 7.79 (d, J = 8.0 Hz, 1H), 7.48-7.55 (m, 2H), 7.40-7.43 (m, 2H), 6.28-6.35 (m, 1H), 5.69 (d, *J* = 12.0 Hz, 1H), 3.92 (s, 2H), 3.13-3.20 (m, 4H), 2.26 (s, 3H); ^{19}F NMR (376 MHz, $CDCl_3$) δ -66.5 (t, *J* = 11.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.6, 134.5, 133.8, 132.3, 128.4, 128.0, 127.2, 125.8, 125.6, 125.0, 124.5, 124.1 (q, *J* = 275 Hz), 111.1, 81.5, 77.1 (q, *J* = 5 Hz), 60.1, 59.3, 42.3, 26.6 (q, *J* = 34 Hz); IR (neat) ν/cm^{-1}: 3045.6, 2927.6, 2790.3,

2233.5, 1597.0, 1509.8, 1461.5, 1365.7, 1279.4, 1254.8, 1144.0, 1110.0, 1017.4, 963.0, 906.1, 791.7; EI-MS m/z (%): 127 (8), 141 (100), 142 (19), 176 (11), 234 (8), 236 (8), 302 (13), 317 (1). HRMS-EI (M) Calcd for $C_{19}H18NF_3$: 317.1391; found: 317.1385. as appropriate.

Isotopic labeling experiments.

(1) To a 5 mL of Schlenk tube was added Cu powder (128 mg, 2 mmol). The tube was then evacuated and backfilled with N2 (3 times). HCFC-123 (306 mg, 2 mmol), terminal deuterated alkyne (103 mg, 1 mmol), Et_2NH (219 mg, 3 mmol) and DCE (2 mL) were added into this Schlenk tube subsequently under N_2. The Schlenk tube was sealed and heated to 70 °C (oil bath). After stirring for 8 h, the reaction mixture was cooled to room temperature and diluted with PE (10 mL). The precipitation was removed with filtration. The solvent was removed and the residue was purified with silica gel chromatography (PE) and concentrated in vacuum to provide pure product.

(2) To a 5 mL of Schlenk tube was added Cu power (128 mg, 2 mmol). The tube was then evacuated and backfilled with N_2 (3 times). HCFC-123 (306 mg, 2 mmol), alkyne (102 mg, 1 mmol), N-deuterated diethylamine (222 mg, 3 mmol) and DCE (2 mL) were added into this Schlenk tube subsequently under N_2. The Schlenk tube was sealed and heated to 70 °C (oil bath). After stirring for 8 h, the reaction mixture was cooled to room temperature and diluted with PE (10 mL). The precipitation was removed with filtration. The solvent was removed and the residue was purified with silica gel chromatography (PE) to provide pure product.

(3) To a 5 mL of Schlenk tube was added Cu powder (128 mg, 2 mmol). The tube was then evacuated and backfilled with N_2 (3 times). HCFC-123 (306 mg, 2 mmol), alkyne (102 mg, 1 mmol), Et_2NH (219 mg, 3 mmol), D_2O (57 mg, 3 mmol) and DCE (2 mL) were added into this Schlenk tube subsequently under N_2. The Schlenk tube was sealed and heated to 70 °C (oil bath). After stirring for 8 h, the reaction mixture was cooled to room temperature and diluted with PE (10 mL). The precipitation was removed with filtration. The solvent was removed and the residue was purified with silica gel chromatography (PE) to provide pure product.

(4) To a 5 mL of Schlenk tube was added Cu power (128 mg, 2 mmol). The tube was then evacuated and backfilled with N_2 (3 times). HCFC-123 (306 mg, 2 mmol), alkyne (102 mg, 1 mmol), d^{10}-Et_2NH (249 mg, 3 mmol) and DCE (2 mL) were added into this Schlenk tube subsequently under N_2. The Schlenk tube was sealed and heated to 70 °C (oil bath). After stirring for 8 h, the reaction mixture was cooled to room temperature and diluted with PE (10 mL). The precipitation was removed with filtration. The solvent was removed and the residue was purified with silica gel chromatography (PE) and concentrated in vacuum to provide pure product.

Relative rate between alkyne 2a and alkene 4. To a 5 mL of Schlenk tube was added Cu powder (102 mg, 2 mmol). The tube was then evacuated and backfilled with N_2 (3 times). HCFC-123 (382 mg, 2.5 mmol), alkyne **2a** (102 mg, 1 mmol), styrene **4** (104 mg, 1 mmol), Et_2NH (219 mg, 3 mmol) and DCE (2 mL) were added into this Schlenk tube subsequently under N_2. The Schlenk tube was sealed and heated to 70°C (oil bath). After stirring for 5-9 h, the reaction mixture was cooled to room temperature and benzotrifluoride was added. The yield was determined by ^{19}F NMR before working up. If necessary, the reaction mixture was diluted with PE (10 mL) and the precipitation was removed with filtration. The filtrate was concentrated and the residue was purified with silica gel chromatography (PE) and concentrated in vacuum to give pure product. Product **5** is a known compound.[7a]

Mechanism Experiments with radical scavengers

a) Inhibition experiments for Cu-mediated reactions of **1** with **2a'**: **Method A:** To a 5 mL of Schlenk tube were added (phenylethynyl)copper **2a'** (165 mg, 1 mmol) and additive [BHT (44 mg, 0.2 mmol) or DNB (33.6 mg, 0.2 mmol) or TEMPO (156 mg, 1.0 mmol)]. The tube was then evacuated and backfilled with N_2 (3 times). HCFC-123 (306 mg, 2 mmol), Et_2NH (219 mg, 3 mmol) and DCE (2 mL) were added into this Schlenk tube subsequently under N_2. The Schlenk tube was sealed and heated to 70 °C (oil bath). After stirring for 8 h, the reaction mixture was cooled to room temperature and benzotrifluoride was added. The yield was determined by ^{19}F NMR. **Method B:** To a 5 mL of Schlenk tube were added (phenylethynyl)copper **2a'** (1 mmol). The tube was then evacuated and backfilled with N_2 (3 times). HCFC-123 (306 mg, 2 mmol), Et_2NH (219 mg, 3 mmol), additive [DAE (98 mg, 1.0 mmol)] and DCE (2 mL) were added into this Schlenk tube subsequently under N_2. The Schlenk tube was sealed and heated to 70 °C (oil bath). After stirring for 8 h, the reaction mixture was cooled to room temperature and benzotrifluoride was added. The yield was determined by ^{19}F NMR.

b) Inhibition experiments for Cu-mediated reaction of **1** with **2a**: **Method A:** To a 5 mL of Schlenk tube were added Cu powder (128 mg, 2 mmol), additive [HQ (22 mg, 0.2 mmol) or DNB (33.6 mg, 0.2 mmol)]. The tube was then evacuated and backfilled with N_2 (3 times). HCFC-123 (306 mg, 2 mmol), alkyne (102 mg, 1 mmol), Et_2NH (219 mg, 3 mmol) and DCE (2 mL) were added into this Schlenk tube subsequently under N_2. The Schlenk tube was sealed and heated to 70 °C (oil bath). After stirring for 8 h, the reaction mixture was cooled to room temperature and benzotrifluoride was added. The yield was determined by ^{19}F NMR. **Method B:** To a 5 mL of Schlenk tube was added Cu powder (128 mg, 2 mmol). The tube was then evacuated and backfilled with N_2 (3 times). HCFC-123 (306 mg, 2 mmol), alkyne (102 mg, 1 mmol), Et_2NH (219 mg, 3 mmol), additive [DAE (98 mg, 1.0 mmol)], and DCE (2 mL) were added into this Schlenk tube subsequently under N_2. The Schlenk tube was sealed and heated to 70 °C (oil bath). After stirring for 8 h, the reaction mixture was cooled to room temperature and benzotrifluoride was added. The yield was determined by ^{19}F NMR.

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