

RESEARCH ARTICLE

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Cite this: *Org. Chem. Front.*, 2015, 2, 1379

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 of the synthesis of a terbinafine analogue is shown. Some mechanistic experiments including deuterated reagents and radical/SET inhibitors are described.

Received 2nd July 2015,
Accepted 13th August 2015

DOI: 10.1039/c5qo00210a

rsc.li/frontiers-organic

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 used in the synthesis of agrochemicals, such as pyrethroid insecticides.^{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 CF₃CH₂Cl (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 has 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.*, CF₃CH₂I, BrCF₂P(O)OR, BrCF₂CH=CH₂, C₄F₉I and CF₃I) 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 hydrogen⁵ 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.

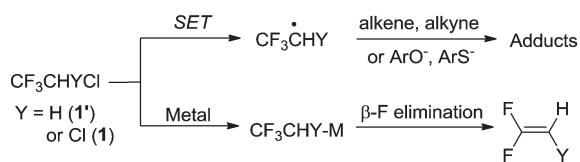
In 2011, Shibata reported the first example of trifluoromethylation of propargyl halides by a trifluoromethylation of 1-(3-bromoprop-1-ynyl)-4-nitrobenzene using the electrophilic trifluoromethylation reagent [*S*-(trifluoromethyl)diphenylsulfonium salt].^{11a} In 2012, Szabó reported the trifluoromethylation of propargylic halides and trifluoroacetates using the

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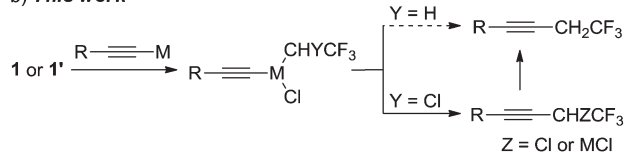
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[†]Electronic supplementary information (ESI) available: Details for experimental conditions, copies of ¹⁹F NMR, ¹H NMR and ¹³C NMR spectra for isolated compounds. See DOI: 10.1039/c5qo00210a

a) Previous work



b) This work



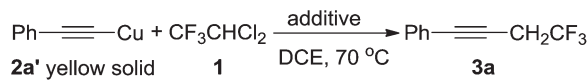
Scheme 1 (a) A graphic summary of previous work related to the C–Cl activation of HCFC-133a and HCFC-123. (b) A novel transition metal mediated C–C cross-coupling method using HCFCs.

(Ph₃P)₃Cu(CF₃) reagent to give the selective formation of allenyl or propargylic trifluoromethyl derivatives.^{11b} These methodologies gave trifluoroethylated alkynes with the requirement of a stoichiometric amount of copper metal. In 2013, Cu-catalyzed trifluoromethylation of primary propargylic chlorides with trifluoromethyl 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 copper-catalyzed coupling reactions of terminal alkynes with 2,2,2-trifluorodiazoethane.^{11e} Later, Xu^{11f} and Lee^{11g} independently disclosed the Pd-catalyzed 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 coupling¹² and Castro–Stephens coupling¹³). 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 and 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, and unfortunately no reac-



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

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

tion occurred (Scheme 2, 1). However, on addition of 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 2, 2). The addition of one equivalent of copper powder increased the yield from 40% to 61% (Scheme 2, 3). Further increasing the equivalents of copper powder and diethylamine did not improve the reaction yield (Scheme 2, 4). Considering that copper acetylide was synthesized from phenylacetylene **2a**, we studied a one-step reaction using acetylene **2a** as the substrate.

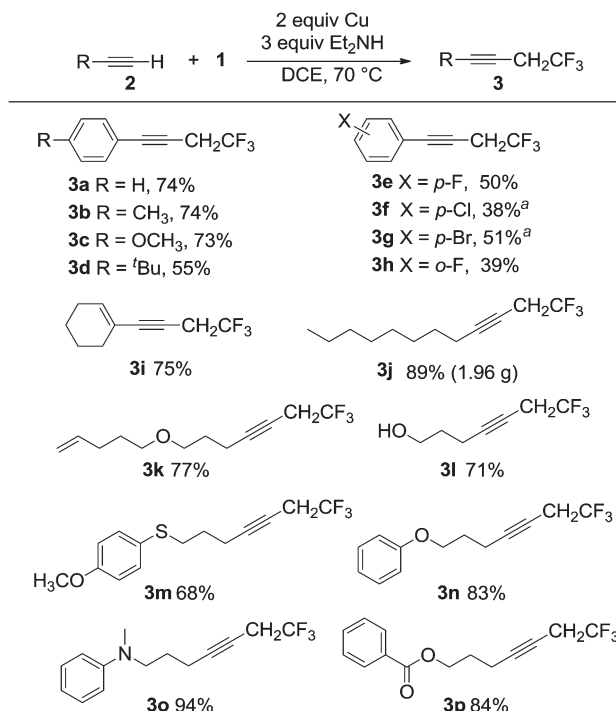
To our delight, a one-pot reaction including acetylene **2a**, HCFC-123, copper and diethylamine gave the desired product **3a** in 77% yield (Scheme 3, entry 1). To further increase the yield we examined a range of amines. The reaction yields decreased slightly when using di-*n*-propylamine and di-*n*-butylamine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

Ph-C≡C-H + **1** $\xrightarrow[\text{DCE, 70 °C}]{\text{Cu, amine}}$ Ph-C≡C-CH₂CF₃

2a **3a**

Entry	Amine	Yield (%) ^a	Entry	Amine	Yield (%) ^a
1	Et ₂ NH	77(74)	8	ⁱ Pr ₂ NH	N.R. ^c
2	ⁿ Pr ₂ NH	64	9	Ph ₂ NH	N.R.
3	ⁿ Bu ₂ NH	63	10	EtNH ₂	N.R.
4	diallylamine	30	11	Et ₃ N	N.R.
5	DMEDA	44 ^b	12	TEDA	N.R.
6	piperidine	7	13 ^d	Et ₂ NH	N.R.
7	azolidine	trace			

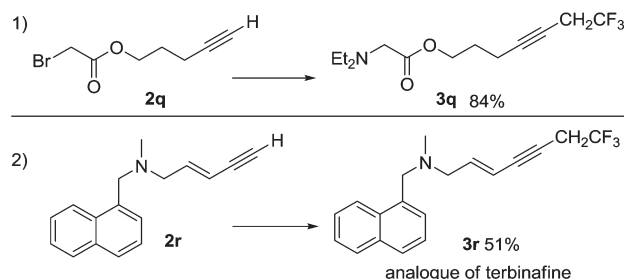
Scheme 3 Effect of amines in the reaction between phenylacetylene with **1**. The reactions were carried out with **2** (1 mmol) and **1** (2 mmol) in the presence of Cu powder (2 mmol) and amine (3 mmol) in 2 mL DCE at 70 °C in a Schlenk tube under a nitrogen atmosphere for 6 hours. ^aYields were determined by ¹⁹F NMR spectroscopy using benzo-trifluoride as an internal standard and an isolated yield is in parentheses. ^b(4,4,4-Trifluorobuta-1,2-dien-1-yl)benzene (20% yield according to ¹⁹F NMR spectroscopy) was found with **3a**. ^cN.R. = no reaction. ^d**1** was used instead of **1**.



Scheme 4 Scope of 2,2,2-trifluoroethylation of various alkynes with 1. 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. ^aUsing 1 as the sole solvent.

N,N-dimethyl-1,2-ethanediamine (DMEDA) also gave product **3a** in 44% yield, however a side-product (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 reactions (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 screened can be found in the ESI.[†] We have examined other solvents, such as DMF, THF, CH₃NO₂ and CH₃CN (Table S1[†]). Those solvents were not effective.

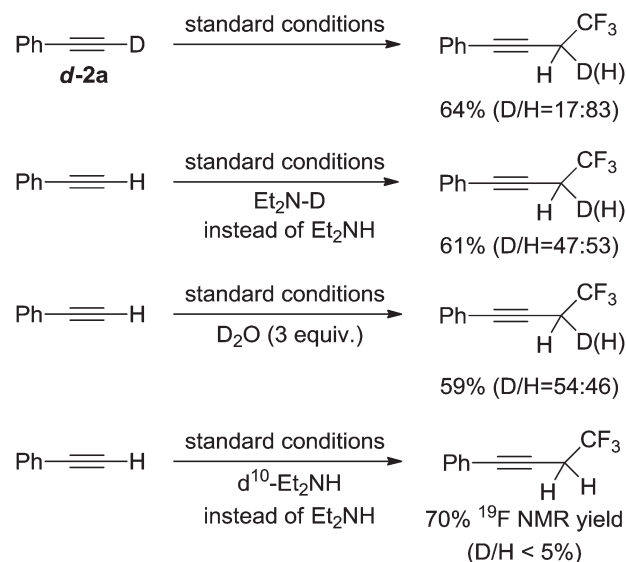
Reactions involving a series of related electron-rich and electron-poor aromatic alkynes gave products **3a–3h** in isolated yields between 38% and 74%, as shown in Scheme 4. The conjugated alkyne **3i** and the aliphatic alkyne **3j** were obtained in 75% and 89% yields, respectively. The coupling reaction occurred selectively at the alkyne in the presence of a terminal alkene giving product **3k** in 77% yield. The reaction was also



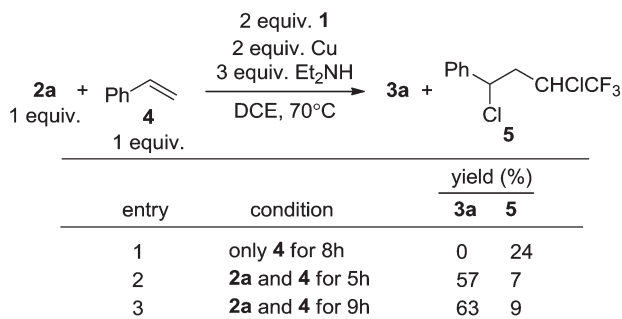
Scheme 5 Some special alkyne substrates in the reactions with 1. Reaction conditions as Scheme 4.

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% yield (Scheme 5). The reaction is not compatible with aryl alkynes bearing electron-deficient functional groups and heteroaryl alkynes bearing nitrogen and sulfur. For example, reactions with 4-acetylphenylacetylene, 2-ethynylpyridine and 2-ethynylthiophene gave no products. In spite of the very small substrate limitation, the reactions are scalable, which makes the reaction practical for further industry application. We were able to synthesize **3a** in a 100 mL autoclave, which gave 5 grams of the alkyne product in one pot. In a 20 mL Schlenk tube, **3j** could be obtained on a multi-gram scale.

To determine the source of protons in the final products we conducted a series of experiments using deuterated materials (Scheme 6). The reaction in which the deuterated alkyne **d-2a**



Scheme 6 Deuterated experiments for determination of H-sources.

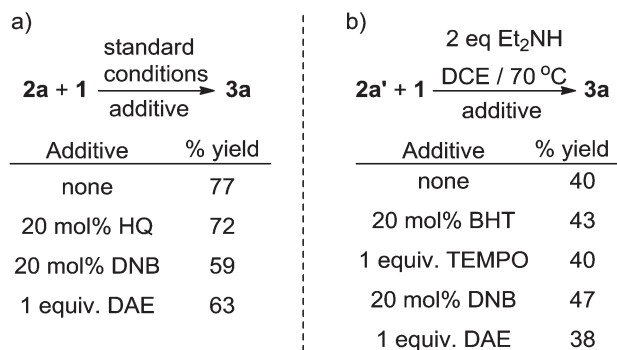
Scheme 7 Relative rate between alkyne **2a** and alkene **4**.

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 D₂O 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 the 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 is 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-oxyl (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 that fluorinated-alkyl free radicals may not be involved in the reaction.

Therefore, an outer-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.



Scheme 8 Mechanism experiments with radical scavengers.

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 outer-sphere radical process is unlikely to be the predominating pathway. This study has revealed the first C_{sp}³–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 in our laboratory.

Experimental section

General information

NMR spectra were obtained on 300 or 400 MHz spectrometers and recorded at 25 °C. Chemical shifts for ¹H NMR spectra are reported in ppm downfield from TMS, chemical shifts for ¹³C NMR spectra are recorded in ppm relative to internal chloroform (δ 77.0 ppm for ¹³C), and chemical shifts for ¹⁹F NMR are reported in ppm downfield from fluorotrichloromethane (CFCl₃). 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. ¹³C NMR was broadband 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 HRMS is time-of-flight mass spectrometer (TOF-MS) or Fourier transform ion cyclotron resonance mass spectrometer (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 2a¹⁴

CuI (2.02 g, 10.5 mmol) was dissolved in NH₃·H₂O (28% NH₃ 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 NH₃·H₂O (10% NH₃ solution, 3 × 25 mL), H₂O (3 × 25 mL), EtOH (3 × 25 mL), and Et₂O (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 Schlenk tube were added (phenylethynyl)copper 2a' (165 mg, 1 mmol) and copper powder (0 to 2 mmol). The tube was then evacuated and backfilled with N₂ (3 times). HCFC-123 (2 mmol), Et₂NH (0 to 3 mmol) and DCE (2 mL) were added into this Schlenk tube subsequently under N₂. 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 ¹⁹F NMR spectroscopy using benzotrifluoride as an internal standard before working up the reaction. If necessary, the reaction mixture was diluted with petroleum ether (PE, 10 mL) and the precipitate was removed by filtration. The filtrate was concentrated and the residue was purified with silica gel chromatography (petroleum ether as the eluent) to give the 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 (Tables 1S and 2S†)

To a 5 mL Schlenk tube was added metal powder (x mmol). The tube was then evacuated and backfilled with N₂ (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 N₂. 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 ¹⁹F NMR spectroscopy using benzotrifluoride as an internal standard before working up the reaction. If necessary, the reaction mixture was diluted with PE (10 mL) and the precipitate was removed by filtration. The filtrate was concentrated in a vacuum and the residue was purified with silica gel chromatography (petroleum ether as the eluent) and concentrated in a vacuum to give the 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 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), alkyne (1 mmol), Et₂NH (219 mg, 3 mmol) and DCE (2 mL) were added into this Schlenk tube subsequently under N₂. 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 precipitate was removed by filtration. The solvent was removed in a vacuum and the residue was purified with silica gel chromatography (petroleum ether as the eluent) to provide the pure product.

(4,4,4-Trifluorobut-1-yn-1-yl)benzene (3a).^{11e} The reaction was run as per the general procedure. Yield: 74%; 136 mg; colorless oil. ¹H NMR (300 MHz, CDCl₃) δ 7.43–7.47 (m, 2H), 7.25–7.33 (m, 3H), 3.27 (q, *J* = 10.0 Hz, 2H); ¹⁹F NMR (376 MHz, CDCl₃) δ –66.5 (t, *J* = 9.6 Hz).

Autoclave procedure: Cu powder (3.8 g, 60 mmol), phenylacetylene (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 °C for 7 h. The reaction was stopped and allowed to stand overnight. The solid was removed by filtration and rinsed with ethyl acetate. The organic phase was washed with deionized water (50 mL) and a 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 °C/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 CF₃CHCl₂ instead of DCE as the solvent); 146 mg; yellow oil. ¹H NMR (300 MHz, CDCl₃) 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); ¹⁹F NMR (282 MHz, CDCl₃) 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, CDCl₃) 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); ¹⁹F NMR (282 MHz, CDCl₃) 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, CDCl₃) δ 7.37 (m, 4H), 3.26 (q, *J* = 9.5 Hz, 2H), 1.32 (s, 9H); ¹⁹F NMR (282 MHz, CDCl₃) 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, CDCl₃) δ 7.40–7.45 (m, 2H), 6.97–7.03 (m, 2H), 3.25 (q, *J* = 9.0 Hz, 2H); ¹⁹F NMR (282 MHz, CDCl₃) 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 CF₃CHCl₂ instead of DCE as the solvent); 82 mg; colorless oil. ¹H NMR (300 MHz, CDCl₃) 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); ¹⁹F NMR (282 MHz, CDCl₃) 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 CF₃CHCl₂ instead of DCE as the solvent); 134 mg; yellow oil. ¹H NMR (300 MHz, CDCl₃) 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) $\delta -66.7$ (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) $\delta -66.8$ (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 $\text{C}_{10}\text{H}_6\text{F}_4$: 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) $\delta -67.3$ (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 $\text{C}_{10}\text{H}_{11}\text{F}_3$: 188.0813; found: 188.0817.

1,1,1-Trifluorododec-3-yne (3j). To a 20 mL Schlenk tube was added Cu powder (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_3NH (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 precipitate was removed by filtration. The solvent was removed in a vacuum and the residue was purified with silica gel chromatography (petroleum ether as the eluent) to provide the pure product.

Yield: 89%; 1.96 g; yellow oil. ^1H 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) $\delta -67.5$ (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 $\text{C}_{12}\text{H}_{19}\text{F}_3$: 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. ^1H 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) $\delta -67.2$ (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 $\text{C}_{12}\text{H}_{17}\text{F}_3\text{O}$: 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. ^1H 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) $\delta -67.4$ (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 $\text{C}_7\text{H}_8\text{OF}_3$: 165.0527; found: 165.0522.

(4-Methoxyphenyl)(7,7,7-trifluorohept-4-yn-1-yl)sulfane (3m). Yield: 68%; 196 mg; yellow oil. ^1H 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) $\delta -66.9$ (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 $\text{C}_{14}\text{H}_{15}\text{OF}_3\text{S}$: 288.0796; found: 288.0797.

((7,7,7-Trifluorohept-4-yn-1-yl)oxy)benzene (3n). Yield: 83%; 200 mg; yellow oil. ^1H 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) $\delta -66.9$ (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 $\text{C}_{13}\text{H}_{13}\text{OF}_3$: 242.0918; found: 242.0914.

N-Methyl-N-(7,7,7-trifluorohept-4-yn-1-yl)aniline (3o). Yield: 94%; 240 mg; yellow oil. ^1H 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) $\delta -66.9$ (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 $\text{C}_{14}\text{H}_{17}\text{NF}_3$: 256.1308; found: 256.1314.

7,7,7-Trifluorohept-4-yn-1-yl benzoate (3p). Yield: 84%; 225 mg; yellow oil. ^1H 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) $\delta -67.3$

($t, J = 9.8$ 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 $\text{C}_{14}\text{H}_{12}\text{O}_2\text{F}_3$: 269.0789; found: 269.0790.

7,7,7-Trifluorohept-4-yn-1-yl 2-(diethylamino)acetate (3q). Yield: 64%; 178 mg; yellow oil. ^1H 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 $\text{C}_{13}\text{H}_{20}\text{NO}_2\text{F}_3$: 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. ^1H 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 $\text{C}_{19}\text{H}_{18}\text{NF}_3$: 317.1391; found: 317.1385. as appropriate.

Isotopic labeling experiments

(1) To a 5 mL 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), 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 precipitate was removed by filtration. The solvent was removed and the residue was purified with silica gel chromatography (PE) and concentrated in a vacuum to provide the pure product.

(2) To a 5 mL 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), *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 precipitate was removed by filtration. The solvent was removed

and the residue was purified with silica gel chromatography (PE) to provide the pure product.

(3) To a 5 mL 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 precipitate was removed by filtration. The solvent was removed and the residue was purified with silica gel chromatography (PE) to provide the pure product.

(4) To a 5 mL 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), $d^{10}\text{-Et}_2\text{NH}$ (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 precipitate was removed by filtration. The solvent was removed and the residue was purified with silica gel chromatography (PE) and concentrated in a vacuum to provide the pure product.

Relative rate between alkyne **2a** and alkene **4**: to a 5 mL 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 precipitate was removed by filtration. The filtrate was concentrated and the residue was purified with silica gel chromatography (PE) and concentrated in a vacuum to give the pure product. Product **5** is a known compound.^{7a}

Mechanism experiments with radical scavengers

Inhibition experiments for Cu-mediated reactions of **1 with **2a'**.** Method A: to a 5 mL 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 Schlenk tube was 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.

Inhibition experiments for Cu-mediated reactions of 1 with 2a. Method A: to a 5 mL Schlenk tube were added Cu powder (128 mg, 2 mmol) and additive [HQ (22 mg, 0.2 mmol) or DNB (33.6 mg, 0.2 mmol)]. The tube was then evacuated and back-filled 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 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.

Acknowledgements

Support of our work by the National Basic Research Program of China (973 Program) (no. 2012CB821600), the National Natural Science Foundation of China (no. 21421002, 21032006, 21172241) and the Chinese Academy of Sciences is gratefully acknowledged.

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