Copper-Catalyzed Perfluoroalkylation of Alkynyl Bromides and Terminal Alkynes

Shilu Fan,* Chenggong Zheng, Kaiting Zheng, Junlan Li, Yaomei Liu, Fangpei Yan, Hua Xiao, Yi-Si Feng,* and Yuan-Yuan Zhu*



ABSTRACT: A copper-catalyzed one-pot perfluoroalkylation of alkynyl bromides and terminal alkynes has been disclosed, and the corresponding perfluoroalkylated alkynes could be attained in good to excellent yields. The new straightforward transformation shows high efficiency (0.01–0.5 mol % catalyst loading), broad substrate scope, and remarkable functional group tolerance and provides a facile approach for useful application in life and material sciences.

Perfluoroalkyl compounds have been the object of increasing attention in the fields of pharmaceutical, agrochemical, and material sciences since the incorporation of perfluoroalkyl groups (R_F) into organic molecules brings significant changes in their physical, chemical, and biological properties owing to the unique properties of the perfluoroalkyl group.^{1,2} Consequently, C-R_F bond formation has attracted considerable research interest in recent years. In the past decades, the rapid development of new perfluoroalkylation methods has been witnessed after arduous efforts of organic chemists. In comparison with the advances achieved in the formation of $C(sp^3)-R_F$ bonds and $C(sp^2)-R_F$ bonds, the construction of $C(sp)-R_F$ bonds by direct perfluoroalkylation of terminal alkynes (C-H) or alkyne derivatives (C-X) is still suffering from many limitations, notwithstanding the potentially booming demand of perfluoroalkylated acetylenes.³ In 2010, Qing and co-workers reported a copper-mediated oxidative trifluoromethylation of terminal alkynes with nucleophilic trifluoromethylating reagent (TMSCF₃),⁴ which provided a new approach for $C(sp)-CF_3$ bond formation (Scheme 1a).⁵ Soon afterward, the copper-mediated direct conversion of C(sp)-H bonds to C(sp)-CF₃ bonds has also been discovered by using CuCF₃,⁶ Ph₃P⁺CF₂CO₂⁻ (PDFA),⁷ and PhSOCF₃⁸ as CF₃ sources. Alkyne derivatives such as copper alkynes,⁹ potassium alkynyltrifluoroborates,¹⁰ arylpropiolic acids,¹¹ and TMS-protected alkynes¹² were smoothly employed in similar copper-mediated processes. Although the above approaches are attractive, the copper-catalyzed methods for preparation of perfluoroalkyl alkynes remain highly desirable in view of the requirement of a stoichiometric metal catalyst. To attain the goal, Qing, Huang, Weng, and Fu and Guo described the copper-catalyzed trifluoromethylation of terminal alkynes or potassium alkynyltrifluoroborates with nucleophilic⁵ or electrophilic¹³ trifluoromethylating reagents

Scheme 1. Perfluoroalkylation of Terminal Alkynes and Its Derivatives

(a) Copper-mediated methods for C(sp)-CF₃ bonds formation

Ar——X	Copper-mediated CF ₃ source	Ar — CF ₃				
X = H, Cu, BF ₃ K, CO ₂ H, T CF ₃ source = TMSCF ₃ , CF	MS F ₃ Cu, Ph ₃ ⁺ CF ₂ CO ₂ ⁻ , PhS	SOCF ₃ , NaSO ₂ CF ₃				
(b) Copper-catalyzed methods for C(sp)-CF ₃ bonds formation						
Ar———X	Copper-catalyzed CF ₃ source	Ar — CF ₃				
X = H, BF ₃ K CF ₃ source = TMSCF ₃ , To	ngi's reagent, Umemoto	reagent				
(c) Radical addition-elimination process for C(sp)-R _F bonds formation						
ArX	Photocatalyzed or Silver-mediated R _F -I	Ar — — R _F				
X = H, Br						
(d) High efficient copper-catalyzed method for C(sp)-R _F bonds formation						
Ar/Alkyl———Br/H	Copper-catalyzed R _F -I/(R _F) ₂ Zn(DMPU) ₂	Ar/Alkyl— — R _F				
		$R_F = C_3 F_7, C_4 F_9, C_6 F_{13}$				

(Scheme 1b). Unfortunately, the reported copper-catalyzed pathways did not show a high efficiency, and 20–30 mol % catalysts were required. In these cases, several kind of

Received: March 16, 2021 Published: April 1, 2021





perfluoroalkyl reagents have been utilized for the synthesis of alkynyl- R_F compounds, and only CF_3 sources are, however, commercially available, which limits the incorporation of other perfluoroalkyl substituent into organic molecule.

Perfluoroalkyl iodides (R_EI) are commercially available, inexpensive, low toxic, easily operated, and thereby, would be the very appealing R_F sources in the preparation of perfluoroalkylated compounds. Whereas the formation of alkyl-R_F and alkenyl-R_F bonds have been extensively studied through radical addition reaction of alkenes¹⁴ and alkynes¹⁵ with perfluoroalkyl radicals, respectively, perfluoroalkylation reactions for the construction of alkynyl- \hat{R}_F bonds by using R_FI are rather underdeveloped. Blancou described the earlier addition-elimination process for perfluoroalkylation of terminal propargyl alcohol.¹⁶ Cho and co-workers reported on the visible-light photoredox-catalyzed perfluoroalkylation of terminal alkynes¹⁷ and alkynyl bromides¹⁸ with R_FI as the ultimate R_F source, in which several perfluoroalkylated arylacetylenes were obtained in good to high yields (Scheme 1c). Very recently, we accomplished a silver-mediated perfluoroalkylation reaction for $C(sp)-R_F$ bond formation, which showed a good reactivity toward arylacetylenes.¹⁹ Notably, the available studies paid more attention to reactions with aromatic alkynes rather than those of aliphatic alkynes. Herein, we describe a practical protocol of copper-catalyzed one-pot perfluoroalkylation of alkynyl bromides and terminal alkynes (Scheme 1d). The distinct characteristics of this method are its high efficiency, low catalyst loading (0.5 mol %), broad substrate scope (both aromatic and aliphatic alkynes), outstanding functional group tolerance, and applicability for large-scale production.

Our studies began with the perfluoroalkylation reaction for the formation of 6a by using 1-(bromoethynyl)-4-propylbenzene 1a and perfluoroalkylzinc reagent 3^{20} as the model substrates (Table 1). In our initial efforts, we found that desired product 6a was produced in 72% isolated yield when the reaction was conducted with 1a (0.2 mmol), 3 (1.0 equiv), and Cu(acac)₂ (10 mol %) in THF at 100 °C (Table 1, entry 1). The nature of solvents is the critical factor for the reaction (Table 1, entries 2-6). When the polar solvents (such as DMSO, DMPU, and DMF) were employed, the unsatisfactory results were exhibited. Numerous copper(II) and copper(I) salts in toluene at 100 °C were able to afford the desired product 6a (Table 1, entries 7-10), with CuI serving as the most effective catalyst with a yield of 94% (Table 1, entry 9). The decrease of temperature (80 °C) was favorable to the transformation (Table 1, entry 11). However, the yields decreased with further decreasing temperature (Table 1, entries 12 and 13). To our surprise, this reaction condition showed a powerful catalytic efficiency at a low catalyst loading of CuI (0.5 mol %) (Table 1, entry 14). Of particular interest, no obvious impact on the reaction efficiency has been found by decreasing the catalyst loading to 0.01 mol %, and a high yield of 6a was still afforded (Table 1, entry 16). In addition, the formation of desired product was not observed in the absence of copper sources, which implies that the copper intermediate plays a crucial role in the promotion of the reaction (Table 1, entry 17).

With the optimal conditions established, a variety of alkynyl bromides were examined and a wide range of perfluorobuthyl acetylene derivatives 6 were furnished in good to excellent yields (Scheme 2). Substituted ethynylphenyl rings bearing both electron-donating and phenyl groups were well tolerated

Table 1. Optimization of the Reaction Conditions^a

nPr-	Br + (DMPU) ₂ Z	n(C ₄ F ₉) ₂ [Cu] so solven	nPr-	C4F9
1	a 3			6a
entry	[Cu] (mol %)	solvent	$T(^{\circ}C)$	yield ^b (%)
1	$Cu(acac)_2$ (10)	THF	100	(72)
2	$Cu(acac)_2$ (10)	dioxane	100	88
3	$Cu(acac)_2$ (10)	toluene	100	(90)
4	$Cu(acac)_2$ (10)	DMSO	100	40
5	$Cu(acac)_2$ (10)	DMPU	100	47
6	$Cu(acac)_2$ (10)	DMF	100	23
7	$Cu(OAc)_2$ (10)	toluene	100	(91)
8	$Cu(OTf)_2$ (10)	toluene	100	(90)
9	CuI (10)	toluene	100	(94)
10	CuCN (10)	toluene	100	72
11	CuI (10)	toluene	80	(95)
12	CuI (10)	toluene	60	(88)
13	CuI (10)	toluene	40	(78)
14	CuI (0.5)	toluene	80	(92)
15 [°]	CuI (0.1)	toluene	80	(85)
16 ^d	CuI (0.01)	toluene	80	(73)
17		toluene	80	ND

^{*a*}Reaction conditions: **1a** (0.2 mmol, 1.0 equiv), **3** (1.0 equiv), solvent (2 mL). ^{*b*}NMR yield determined by ¹⁹F NMR using fluorobenzene as an internal standard; the number in parentheses is the isolated yield. ^{*c*}With 0.1 mol % phen and 20 μ L of DMF. ^{*d*}With 0.01 mol % phen and 20 μ L of DMF. not enter the and 20 μ L of DMF. ND = not detected.

Scheme 2. Alkynyl Bromide Scope in Copper-Catalyzed Perfluoroalkylation Reaction"



"Reaction conditions: 1 (0.2 mmol, 1.0 equiv), 3 (1.0 equiv), CuI (0.5 mol %), toluene (2 mL), 80 °C, 12 h. ^bThis reaction was operated under air.

by the robust catalytic system, and excellent yields were realized under standard conditions (6a-g). The robust reactivity was illustrated with an open air operated reaction. To our delight, electron-deficiency alkynyl bromides could be smoothly perfluoroalkylated to give the desired products (6h, 6i) in 73% and 90% yields, respectively. Additionally, reactions with heteroaryl-substituted alkynyl bromides also gave the corresponding products 6j and 6k in good yields. While aliphatic alkynyl bromides were not suitable coupling partners in the reported studies,^{17–19} our copper-catalyzed system enables these substrates to be useful coupling partners, which offered the aliphatic perfluoroalkylated acetylenes in high yields (61-r). The presence of a wide range of functional groups, such as ether, halides, alkoxycarbonyl, heteroaryl, silyl ether, acetate, cyano, nitryl, phosphate, and sulfonyl, was tolerated by the process. Moreover, the steady formation of 6h, 6n, and 6r in high yields with intact chloride, acetate, and *p*-methylbenzenesulfonyl groups would facilitate further transformations of the target molecules without protection/ deprotection processes.

To demonstrate whether this method could be extended to perfluoroalkylating reagents other than 3, we examined 2 and 4 as the perfluoroalkylator (Scheme 3). Generally, good to

Scheme 3. Perfluoroalkylzinc Reagents Scope in Copper-Catalyzed Perfluoroalkylation Reaction⁴



^aReaction conditions: 1 (0.2 mmol, 1.0 equiv), 2, 4 (1.0 equiv), CuI (0.5 mol %), toluene (2 mL), 80 °C, 12 h.

excellent yields of desired products 5 and 7 were furnished under the standard conditions, respectively. To our excitement, substrates bearing functional groups which were employed above all showed good tolerance to the reaction conditions. Thienyl and pyridyl groups were compatible with the coupling reaction, providing high yields (7j and 7k). We were glad to find that the length of perfluoroalkyl chain does not impact reaction efficiency evidently, which implies that transmetalation is not the turnover-limiting step in the overall catalytic cycle.²⁰

In view of the above encouraging results, alkynyl bromides and terminal alkynes were employed as starting materials to check the Cu-catalyzed perfluoroalkylation reaction under a one-pot strategy.²¹ As demonstrated in Scheme 4, we were pleased to observe that the desired products were obtained from both of the raw materials with high yields under these one-step methods, even at the same low catalytic loading (0.5 mol %), which indicates that the strong practicability of the process. The reaction of substituted phenylacetylene and substituted alkynyl bromides all proceeded well and afforded the perfluoroalkylated acetylenes in good yields. To our delight, the heterocyclic substrates were shown acceptable activity, furnishing the desired products in moderate to high yields. At the same time, the terminal aliphatic alkynes and its derivatives were also suitable with high efficiency in this reaction system.

The desired product also could be accessed on gram-scale with high efficiency through a one-pot process (Scheme 5). For instance, **6a** was generated in 89% yield under the one-pot gram-scale operation. In respect to the advantages of R_F –I, we believe that perfluoroalkylation reactions will be prompted by this process with R_F I.

Scheme 4. One-Pot Reaction^a



^{*a*}Method A: R_FI (3.2 equiv) and Et_2Zn (1.5 equiv) in toluene (2 mL) were stirred at -41 to -5 °C for 4 h. Then 1 (0.2 mmol, 1.0 equiv) and CuI (0.5 mol %) were added, and the reaction was run at 80 °C for 12 h. Method B: terminal alkynes (0.2 mmol, 1.0 equiv), AgNO₃(0.1 equiv), and NBS (1.1 equiv) in toluene (4 mL) were stirred at rt for 3 h. Then (DMPU)₂Zn(R_F)₂ (1.0 equiv) and CuI (0.5 mol %) were added, and the reaction was run at 80 °C for 12 h. ^bNumbers in parentheses are yields from method B. Otherwise, yields are from method A. NBS = *N*-bromosuccinimide.

Scheme 5. One-Pot Gram-Scale Reaction

C_4F_9I	ZnEt ₂ , DMPU, toluene	$(DMPU)_2Zn(C_4F_9)_2$	Cul (0.5 mol%) 1a, 80°C	R- ≕− C ₄ F ₉
4.42 g	(12.8 mmol, 3.2 eq)	3		R = <i>pn</i> PrPh 6a , 1.28 g, 89%

To further showcase the importance and utility of this protocol, the late-stage perfluoroalkylation of biologically active molecules was performed (Scheme 6). The perfluor-

Scheme 6. Late-Stage Perfluoroalkylation in Synthesis of Biologically Active Molecules



oalkylated estrone derivative **6s** was obtained in excellent yield, thus offering a facile access to perfluoroalkylated natural product estrone derivatives, which are of great interest in the life sciences. The treatment of menthol-based substrate **1t** afforded perfluoroalkylated compound **6t** in excellent yield, which further highlights the significance of this protocol.

To gain further insight into the perfluoroalkylation, mechanism studies were conducted (see the Supporting Information). When the stoichiometric CuI was subjected to the treatment with 3 in toluene at 80 °C, a cuprates species was produced (as determined by ¹⁹F NMR) and used as an R_F source for subsequent transformation. These experiments lend strong credence for the proposed mechanism of transmetalation.

On the basis of these results and previous reports, $^{20-22}$ a plausible reaction mechanism involving a Cu^I/Cu^{III} catalytic cycle is proposed (Scheme 7). The reaction begins with the transmetalation between perfluoroalkylzinc reagent 3 and

Scheme 7. Proposed Mechanism



 $[\mathrm{Cu}^{I}\mathrm{L}_{n}]$ (I) which may be generated through the in situ formation. Subsequently, oxidative addition of alkynyl bromides 1 with $[(\mathrm{R}_{F})_{m}\mathrm{Cu}^{I}]\mathrm{L}_{n}$ (II) would provide the key copper intermediate III, which undergoes a reductive elimination to afford the desired product 6 and regenerate the $[\mathrm{Cu}^{I}\mathrm{L}_{n}]$ species simultaneously.

In summary, we have successfully established a one-pot perfluoroalkylation reaction of alkynyl bromides and terminal alkynes by using perfluoroalkyl iodides as an R_F source through an extremely low copper catalytic loading under mild reaction conditions, providing practical access to R_F -containing alkynes. Furthermore, various functional groups were well tolerated in the reaction affording the corresponding perfluoroalkylated products in good to excellent yields. These reactions proceed in good yields on both small and large scales.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c00906.

Experimental details, characterization data, and NMR spectra (PDF)

AUTHOR INFORMATION

Corresponding Authors

- Shilu Fan School of Chemistry and Chemical Engineering, Hefei University of Technology, Anhui 230000, China; Key Laboratory of Organofluorine Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, Shanghai 200032, China; orcid.org/0000-0003-0315-7874; Email: shilu.fan@hfut.edu.cn
- Yi-Si Feng School of Chemistry and Chemical Engineering, Hefei University of Technology, Anhui 230000, China;
 orcid.org/0000-0002-1646-0955; Email: fengyisi@ hfut.edu.cn
- Yuan-Yuan Zhu School of Chemistry and Chemical Engineering, Hefei University of Technology, Anhui 230000, China; orcid.org/0000-0002-3142-0396; Email: yyzhu@hfut.edu.cn

Authors

- **Chenggong Zheng** School of Chemistry and Chemical Engineering, Hefei University of Technology, Anhui 230000, China
- Kaiting Zheng School of Chemistry and Chemical Engineering, Hefei University of Technology, Anhui 230000, China

- Junlan Li School of Chemistry and Chemical Engineering, Hefei University of Technology, Anhui 230000, China
- Yaomei Liu School of Chemistry and Chemical Engineering, Hefei University of Technology, Anhui 230000, China
- Fangpei Yan School of Chemistry and Chemical Engineering, Hefei University of Technology, Anhui 230000, China
- Hua Xiao School of Food and Biological Engineering, Hefei University of Technology, Anhui 230000, China

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.orglett.1c00906

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

This work was financially supported by the Fundamental Research Funds for the Central Universities (JZ2020HGTB0018 and PA2020GDSK0067), the National Natural Science Foundation of China (Grant No. 21971050), and the Start-up Foundation of Hefei University of Technology. We are also grateful to Dr. Yanbo Yu for his generous help in revising the manuscript..

REFERENCES

(1) For selected reviews, see: (a) Kirsch, P. Modern Fluoroorganic Chemistry; Wiley-VCH: Weinheim, 2004. (b) Uneyama, K. Organofluorine Chemistry; Blackwell: Oxford, U.K., 2006. (c) Schlosser, M. CF(3)-bearing aromatic and heterocyclic building blocks. Angew. Chem., Int. Ed. 2006, 45, 5432-5446. (d) Muller, K.; Faeh, C.; Diederich, F. Fluorine in pharmaceuticals: looking beyond intuition. Science 2007, 317, 1881-1886. (e) Hird, M. Fluorinated liquid crystals-properties and applications. Chem. Soc. Rev. 2007, 36, 2070-2095. (f) Ma, J.-A.; Cahard, D. Update 1 of: Asymmetric Fluorination, Trifluoromethylation, and Perfluoroalkylation Reactions. Chem. Rev. 2008, 108, PR1-PR43. (g) Kirk, K. L. Fluorination in Medicinal Chemistry: Methods, Strategies, and Recent Developments. Org. Process Res. Dev. 2008, 12, 305-321. (h) Ojima, I. Fluorine in Medicinal Chemistry and Chemical Biology; Wiley-Blackwell: Chichester, U.K., 2009. (i) O'Hagan, D. Understanding organofluorine chemistry. An introduction to the C-F bond. Chem. Soc. Rev. 2008, 37, 308-319. (j) Lundgren, R. J.; Stradiotto, M. Transition-Metal-Catalyzed Trifluoromethylation of Aryl Halides. Angew. Chem., Int. Ed. 2010, 49, 9322-9324.

(2) For selected reviews, see: (a) McClinton, M. A.; McClinton, D. A. Trifluoromethylations and related reactions in organic chemistry. Tetrahedron 1992, 48, 6555-6666. (b) Shimizu, M.; Hiyama, T. Modern synthetic methods for fluorine-substituted target molecules. Angew. Chem., Int. Ed. 2005, 44, 214-231. (c) Grushin, V. V. The organometallic fluorine chemistry of palladium and rhodium: studies toward aromatic fluorination. Acc. Chem. Res. 2010, 43, 160-171. (d) Roy, S.; Gregg, B. T.; Gribble, G. W.; Le, V.-D.; Roy, S. Trifluoromethylation of aryl and heteroaryl halides. Tetrahedron 2011, 67, 2161-2195. (e) Furuya, T.; Kamlet, A. S.; Ritter, T. Catalysis for fluorination and trifluoromethylation. Nature 2011, 473, 470-477. (f) Tomashenko, O. A.; Grushin, V. V. Aromatic trifluoromethylation with metal complexes. Chem. Rev. 2011, 111, 4475-4521. (g) Chu, L.; Qing, F. L. Oxidative trifluoromethylation and trifluoromethylthiolation reactions using (trifluoromethyl)trimethylsilane as a nucleophilic CF3 source. Acc. Chem. Res. 2014, 47, 1513-1522.

(3) For selected examples, see: (a) Brisdon, A. K.; Crossley, I. R. Hydrofluorocarbon 245fa: a versatile new synthon in alkyne chemistry. *Chem. Commun.* 2002, 2420–2421. (b) Konno, T.; Daitoh, T.; Noiri, A.; Chae, J.; Ishihara, T.; Yamanaka, H. A highly regio- and stereoselective carbocupration of fluoroalkylated internal alkynes: a short total synthesis of the antiestrogenic drug panomifene. *Org. Lett.* 2004, *6*, 933–936. (c) Zhang, X.-G.; Chen, M.-W.; Zhong,

P.; Hu, M.-L. Regio- and stereo-specific preparation of (E)-1-aryl-3,3,3-trifluoro-1-iodo-propenes and their palladium-catalyzed reaction with terminal alkynes. J. Fluorine Chem. 2008, 129, 335-342. (d) Konno, T.; Kinugawa, R.; Morigaki, A.; Ishihara, T. An Efficient Protocol for the Stereoselective Construction of Multisubstituted Fluorine-Containing Alkenes. A Palladium-Catalyzed Bisstannylation of Fluorinated Internal Alkynes. J. Org. Chem. 2009, 74, 8456-8459. (e) Shimizu, M.; Higashi, M.; Takeda, Y.; Murai, M.; Jiang, G.; Asai, Y.; Nakao, Y.; Shirakawa, E.; Hiyama, T. New preparation and synthetic reactions of 3,3,3-trifluoropropynyllithium, -borate and -stannane: facile synthesis of trifluoromethylated allenes, arylacetylenes and envnes. Future Med. Chem. 2009, 1, 921-945. (f) Kawatsura, M.; Namioka, J.; Kajita, K.; Yamamoto, M.; Tsuji, H.; Itoh, T. Ruthenium-Catalyzed Regio- and Stereoselective Addition of Carboxylic Acids to Aryl and Trifluoromethyl Group Substituted Unsymmetrical Internal Alkynes. Org. Lett. 2011, 13, 3285-3287. (g) Daglar, O.; Cakmakci, E.; Gunay, U. S.; Hizal, G.; Tunca, U.; Durmaz, H. A Straightforward Method for Fluorinated Polythioether Synthesis. Macromolecules 2020, 53, 2965-2975.

(4) Chu, L.; Qing, F. L. Copper-mediated aerobic oxidative trifluoromethylation of terminal alkynes with Me3SiCF3. *J. Am. Chem. Soc.* **2010**, *132*, 7262–7263.

(5) Jiang, X.; Chu, L.; Qing, F. L. Copper-catalyzed oxidative trifluoromethylation of terminal alkynes and aryl boronic acids using (trifluoromethyl)trimethylsilane. *J. Org. Chem.* **2012**, *77*, 1251–1257.

(6) Serizawa, H.; Aikawa, K.; Mikami, K. Direct synthesis of a trifluoromethyl copper reagent from trifluoromethyl ketones: application to trifluoromethylation. *Chem. - Eur. J.* **2013**, *19*, 17692–17697.

(7) Deng, X.; Lin, J.; Zheng, J.; Xiao, J. Cu-Promoted Oxidative Trifluoromethylation of Terminal Alkynes with Difluoromethylene Phosphobetaine. *Chin. J. Chem.* **2014**, *32*, 689–693.

(8) Li, X.; Zhao, J.; Zhang, L.; Hu, M.; Wang, L.; Hu, J. Coppermediated trifluoromethylation using phenyl trifluoromethyl sulfoxide. *Org. Lett.* **2015**, *17*, 298–301.

(9) Tresse, C.; Guissart, C.; Schweizer, S.; Bouhoute, Y.; Chany, A.-C.; Goddard, M.-L.; Blanchard, N.; Evano, G. Practical Methods for the Synthesis of Trifluoromethylated Alkynes: Oxidative Trifluoromethylation of Copper Acetylides and Alkynes. *Adv. Synth. Catal.* **2014**, 356, 2051–2060.

(10) (a) Presset, M.; Oehlrich, D.; Rombouts, F.; Molander, G. A. Copper-mediated radical trifluoromethylation of unsaturated potassium organotrifluoroborates. J. Org. Chem. 2013, 78, 12837–12843.
(b) Dubbaka, S. R.; Nizalapur, S.; Atthunuri, A. R.; Salla, M.; Mathew, T. Copper-mediated trifluoromethylation of potassium alkynyltrifluoroborates with Langlois' reagent. Tetrahedron 2014, 70, 2118–2121.

(11) Yang, L.; Jiang, L.; Li, Y.; Fu, X.; Zhang, R.; Jin, K.; Duan, C. Cu(I)/Ag(I)-mediated decarboxylative trifluoromethylation of arylpropiolic acids with Me 3 SiCF 3 at room temperature. *Tetrahedron* **2016**, 72, 3858–3862.

(12) He, L.; Tsui, G. C. Fluoroform-Derived CuCF3 for Trifluoromethylation of Terminal and TMS-Protected Alkynes. *Org. Lett.* **2016**, *18*, 2800–2803.

(13) (a) Luo, D.-F.; Xu, J.; Fu, Y.; Guo, Q.-X. Copper-catalyzed trifluoromethylation of terminal alkynes using Umemoto's reagent. *Tetrahedron Lett.* **2012**, *53*, 2769–2772. (b) Weng, Z.; Li, H.; He, W.; Yao, L.-F.; Tan, J.; Chen, J.; Yuan, Y.; Huang, K.-W. Mild copper-catalyzed trifluoromethylation of terminal alkynes using an electro-philic trifluoromethylating reagent. *Tetrahedron* **2012**, *68*, 2527–2531. (c) Zheng, H.; Huang, Y.; Wang, Z.; Li, H.; Huang, K.-W.; Yuan, Y.; Weng, Z. Synthesis of trifluoromethylated acetylenes via copper-catalyzed trifluoromethylation of alkynyltrifluoroborates. *Tetrahedron Lett.* **2012**, *53*, 6646–6649.

(14) (a) Geng, X.; Lin, F.; Wang, X.; Jiao, N. Azidofluoroalkylation of Alkenes with Simple Fluoroalkyl Iodides Enabled by Photoredox Catalysis. Org. Lett. 2017, 19, 4738–4741. (b) Helmecke, L.; Spittler, M.; Baumgarten, K.; Czekelius, C. Metal-Free Activation of C-I Bonds and Perfluoroalkylation of Alkenes with Visible Light Using

Phosphine Catalysts. Org. Lett. 2019, 21, 7823–7827. (c) Moon, J.; Moon, Y. K.; Park, D. D.; Choi, S.; You, Y.; Cho, E. J. Visible-Light-Induced Trifluoromethylation of Unactivated Alkenes with Tri(9anthryl)borane as an Organophotocatalyst. J. Org. Chem. 2019, 84, 12925–12932. (d) Rosso, C.; Williams, J. D.; Filippini, G.; Prato, M.; Kappe, C. O. Visible-Light-Mediated Iodoperfluoroalkylation of Alkenes in Flow and Its Application to the Synthesis of a Key Fulvestrant Intermediate. Org. Lett. 2019, 21, 5341–5345. (e) Yajima, T.; Shigenaga, S. Metal-Free Visible Light Hydroperfluoroalkylation of Unactivated Alkenes Using Perfluoroalkyl Bromides. Org. Lett. 2019, 21, 138–141.

(15) (a) El Soueni, A.; Tedder, J. M.; Walton, J. C. Free-radical addition to olefins. Part 26.—Kinetics of the addition of trifluoromethyl radicals to acetylene and substituted acetylenes. J. Chem. Soc., Faraday Trans. 1 1981, 77, 89. (b) Kitazume, T.; Ishikawa, N. Ultrasound-promoted selective perfluoroalkylation on the desired position of organic molecules. J. Am. Chem. Soc. 1985, 107, 5186–5191. (c) Kitazume, T.; Ikeya, T. A remarkably simple route to perfluoroalkylated olefins and perfluoroalkanoic acids. J. Org. Chem. 1988, 53, 2350–2352. (d) Choi, S.; Kim, Y. J.; Kim, S. M.; Yang, J. W.; Kim, S. W.; Cho, E. J. Hydrotrifluoromethylation and iodotrifluoromethylation of alkenes and alkynes using an inorganic electride as a radical generator. Nat. Commun. 2014, 5, 4881. (e) Xu, T.; Cheung, C. W.; Hu, X. Iron-Catalyzed 1,2-Addition of Perfluoroalkyl Iodides to Alkynes and Alkenes. Angew. Chem., Int. Ed. 2014, 53, 4910–4914.

(16) (a) Blancou, H.; Calleja-Rubio, S.; Crette, S. An Improved Procedure for the Synthesis of Perfluoroalkylacetylenes. *Synthesis* **2003**, 2003, 0361–0364. (b) Konno, T.; Chae, J.; Kanda, M.; Nagai, G.; Tamura, K.; Ishihara, T.; Yamanaka, H. Facile syntheses of various per- or polyfluoroalkylated internal acetylene derivatives. *Tetrahedron* **2003**, *59*, 7571–7580.

(17) Iqbal, N.; Jung, J.; Park, S.; Cho, E. J. Controlled trifluoromethylation reactions of alkynes through visible-light photoredox catalysis. *Angew. Chem., Int. Ed.* **2014**, *53*, 539–542.

(18) Iqbal, N.; Iqbal, N.; Han, S. S.; Cho, E. J. Synthesis of fluoroalkylated alkynes via visible-light photocatalysis. *Org. Biomol. Chem.* **2019**, *17*, 1758–1762.

(19) Li, J.; Liu, L.; Zheng, K.; Zheng, C.; Xiao, H.; Fan, S. Silver-Mediated Perfluoroalkylation of Terminal Alkynes with Perfluoroalkyl Iodides. J. Org. Chem. **2020**, *85*, 8723–8731.

(20) Aikawa, K.; Nakamura, Y.; Yokota, Y.; Toya, W.; Mikami, K. Stable but reactive perfluoroalkylzinc reagents: application in ligand-free copper-catalyzed perfluoroalkylation of aryl iodides. *Chem. - Eur. J.* **2015**, *21*, 96–100.

(21) Kato, H.; Hirano, K.; Kurauchi, D.; Toriumi, N.; Uchiyama, M. Dialkylzinc-mediated cross-coupling reactions of perfluoroalkyl and perfluoroaryl halides with aryl halides. *Chem. - Eur. J.* **2015**, *21*, 3895–3900.

(22) (a) Bao, X.; Liu, L.; Li, J.; Fan, S. Copper-Catalyzed Oxidative Perfluoroalkylation of Aryl Boronic Acids Using Perfluoroalkylzinc Reagents. J. Org. Chem. 2018, 83, 463–468. (b) Liu, L.; Bao, X.; Xiao, H.; Li, J.; Ye, F.; Wang, C.; Cai, Q.; Fan, S. Copper-Catalyzed Perfluoroalkylation of Allyl Phosphates with Stable Perfluoroalkylzinc Reagents. J. Org. Chem. 2019, 84, 423–434.