

# Copper(I)-Catalyzed Cyanoperfluoroalkylation of Alkynes

Muhammad Israr,<sup>†,‡</sup> Haigen Xiong,<sup>†,‡</sup> Yajun Li,<sup>†</sup><sup>®</sup> and Hongli Bao<sup>\*,†,‡</sup><sup>®</sup>

<sup>†</sup>State Key Laboratory of Structural Chemistry, Key Laboratory of Coal to Ethylene Glycol and Its Related Technology, Center for Excellence in Molecular Synthesis, Fujian Institute of Research on the Structure of Matter, University of Chinese Academy of Sciences, 155 Yangqiao Road West, Fuzhou, Fujian 350002, People's Republic of China

<sup>‡</sup>University of Chinese Academy of Sciences, Beijing 100049, People's Republic of China

Supporting Information

ABSTRACT: A highly chemoselective and regioselective coppercatalyzed radical cyanoperfluoroalkylation of alkynes is described. This three-component reaction directly uses commercially available alkynes, perfluoroalkyl iodides, and trimethylsilyl cyanide as the reaction partners and delivers a variety of perfluoroalkylated cyanoalkenes in good yields. Broad substrate scope and good functional group tolerance are observed. The perfluoroalkylated



cyanoalkenes that are produced can be readily transformed into useful fluoroalkylated derivatives.

ecause of the special properties of organofluorine B compounds,<sup>1</sup> the efficient introduction of fluoroalkyl moieties into generally used chemical building blocks has increasingly attracted the attention of chemists. Fluoroalkylated compounds are commonly used in medicinal chemistry, agrochemistry, and materials science.<sup>2,3</sup> To date, substantial efforts have been made to synthesize fluoroalkylated aromatic molecules.<sup>4</sup> Efficient approaches to fluoroalkylated alkenes are, however, less developed, presumably due to the lack of general and catalytic strategies. Commonly, fluoroalkylated alkenes can be achieved through Heck-type fluoroalkylation of alkenes<sup>5</sup> or cross-coupling of prefunctionalized fluoroalkyl species with alkenyl halides,6 but such processes can principally only introduce fluoroalkyl groups into the target molecules. In contrast, fluoroalkylative difunctionalization of alkynes possesses the fascinating capability to introduce both a fluoroalkyl group and an additional functionality, forming functionalized fluoroalkylated alkenes in a step-economic strategy.

In recent years, together with the progress on hydro-,<sup>7</sup> oxy-,<sup>8</sup> carbo-,<sup>8d,9</sup> or aminotrifluoromethylation<sup>10</sup> of alkynes with Togni or Umemoto reagents or others, several catalytic approaches for the synthesis of fluoroalkylated alkenes via an alkyne difunctionalization process have been explored.<sup>11</sup> In 2014, Hu et al. reported an iron-catalyzed atom-transfer radical addition (ATRA) reaction of alkynes with perfluoroalkyl iodides to afford  $\beta$ -fluoroalkyl vinyl iodides (Scheme 1a). These products are highly reactive and can be easily converted into other functionalized fluoroalkyl-containing motifs.<sup>12</sup> Subsequently, Nevado et al. and Liang et al. independently established excellent methods for the synthesis of fluoroalkylated alkenes through palladium-catalyzed three-component reactions with alkynes, perfluoroalkyl iodides or ethyl difluoroiodoacetate, and arylboronic acids (Scheme 1b).<sup>13,14</sup> Taking advantage of the palladium catalysis with fluoroalkyl iodides, the Wu group disclosed an interesting procedure for the synthesis of perfluoroalkylated enynes from perfluoroalkyl

Scheme 1. Perfluoroalkylative Difunctionalization of Alkynes with Perfluoroalkyl Iodides



iodides and alkynes (Scheme 1c).<sup>15</sup> In addition, cyanodifluoroalkylation of alkynes was explored. This reaction occurs in the presence of a stoichiometric amount of copper powder with only ethyl difluoroiodoacetate as the difluoroalkyl source.<sup>16</sup> Although some progress has been achieved, however, methods for perfluoroalkylative difunctionalization of alkynes are still limited. Recently, we reported an iron-catalyzed radical

Received: July 27, 2019

relay process for the carboazidation of alkenes and alkynes with fluoroalkyl iodides<sup>17</sup> as the fluoroalkyl source. With our interest in radical difunctionalization of alkenes as well as alkynes,<sup>18</sup> we were eager to explore the possibility of the fluoroalkylative difunctionalization of alkynes. Herein, we report a copper-catalyzed cyanoperfluoroalkylation of alkynes (Scheme 1d), providing facile and general access to a wide range of fluoroalkylated cyanoalkenes.

Our investigation started with phenylacetylene (1a, 1 equiv),  $C_4F_9I$  (2a, 2 equiv), and TMSCN (3a, 2 equiv) as model substrates, lauroyl peroxide (LPO, 4a, 2 equiv) as the radical initiator, anhydrous MeOH as the solvent, CuTc (copper thiophene carboxylate, 10 mol %) as the catalyst, and L1 (20 mol %) as the ligand (Table 1). In a preliminary experiment,

			-	
Ph	$$ + $^{9}C_{4}F_{9}I$ + TMSCN 1a 2a 3a	catalyst (10 r ligand (20 m LPO ( <b>4a</b> , 2 c solvent (1 70 °C, 5	nol%) iol%) equiv) mL) h	$ \begin{array}{c} CN \\ \stackrel{n}{\longrightarrow} \\ n_{C_4F_9} \\ 5a \\ 5a \\ 5a' \end{array} $
		Ph N L2	N=	
	Ph Ph			
entry	catalyst	ligand	solvent	yield <sup><math>b</math></sup> (%) of 5a/5a'
1	CuTc	L1	MeOH	75/14
2	CuBr	L1	MeOH	68/15
3	CuI	L1	MeOH	68/19
4	$Cu(CH_3CN)_4PF_6$	L1	MeOH	74/17
5	$Cu(CH_3CN)_4BF_4$	L1	MeOH	$80(76)^{c}/8$
6	CuBr <sub>2</sub>	L1	MeOH	67/24
7	CuCl <sub>2</sub>	L1	MeOH	66/22
8	$Cu(OAc)_2$	L1	MeOH	68/18
9	Cu powder	L1	MeOH	68/22
10	$Cu(CH_3CN)_4BF_4$	L2	MeOH	42/18
11	$Cu(CH_3CN)_4BF_4$	L3	MeOH	65/29
12	$Cu(CH_3CN)_4BF_4$	L4	MeOH	39/22
13	$Cu(CH_3CN)_4BF_4$	L5	MeOH	64/30
14	$Cu(CH_3CN)_4BF_4$	L6	MeOH	57/33
15	$Cu(CH_3CN)_4BF_4$	L1	$CH_2Cl_2$	58/21
16	$Cu(CH_3CN)_4BF_4$	L1	CH <sub>3</sub> CN	61/24
17	$Cu(CH_3CN)_4BF_4$	L1	THF	14/59
18	$Cu(CH_3CN)_4BF_4$	L1	EtOH	62/31
19		L1	MeOH	
20	$Cu(CH_3CN)_4BF_4$	-	MeOH	trace

 Table 1. Reaction Condition Optimization<sup>a</sup>

<sup>*a*</sup>Reaction conditions: **1a** (0.3 mmol, 1 equiv), **2a** (2 equiv), **3a** (2 equiv), **4a** (2 equiv), catalyst (10 mol %), ligand (20 mol %), solvent (1 mL), at 70 °C, 5 h. <sup>*b*</sup>Determined by <sup>1</sup>H NMR with 1,4-dimethoxybenzene as an internal standard. <sup>*c*</sup>Isolated yield in parentheses.

the desired cyanoperfluoroalkylation product (5a) was observed in 75% yield, determined from NMR data. However, an ATRA side product (5a') was also formed in 14% NMR yield (Table 1, entry 1). Production of 5a' is a process which is significantly competitive with the reaction producing the desired product. In order to improve the chemoselectivity and to exclude the generation of the ATRA product (5a'), the reaction conditions with respect to metal catalysts, ligands, solvents, temperature, and loadings of reagent and reactant were then screened (see Tables S1-S6 for details). First, a variety of copper salts and also copper powder were tested (Table 1, entries 2-9). Cu(I) salts, Cu(II) salts, and copper powder produced 5a and 5a' with similar selectivity, and  $Cu(CH_3CN)_4BF_4$  offered the best result, forming 5a in 80% NMR yield and 5a' in only 8% NMR yield (Table 1, entry 5). Examination of ligands L2-L6 (Table 1, entries 10–14) and changing the solvent (Table 1, entries 15-18) failed to show any improvement in the selectivity and the yield of **5a**. Without metal catalyst or ligand, both the desired product 5a and ARTA product 5a' were almost not formed (Table 1, entries 19 and 20). After considerable effort, the competitive chemoselectivity between 5a and 5a' was limited, and only a small amount of the ATRA side product 5a' was formed when using  $Cu(CH_3CN)_4BF_4$  as the catalyst and L1 as the ligand (Table 1, entry 5).

With the established procedure in hand, the scope of alkynes in their cyanoperfluoroalkylation was investigated. As described in Scheme 2, a series of terminal phenylacetylenes



<sup>a</sup>Reaction conditions: 1 (0.3 mmol, 1 equiv), 2a (2 equiv), 3a (2 equiv), 4a (2 equiv), Cu(CH<sub>3</sub>CN)<sub>4</sub>BF<sub>4</sub> (10 mol %), L1 (20 mol %), MeOH (1 mL), 70 °C, 5 h. <sup>b</sup>Isolated yields.

with various substituents on the aromatic ring were found to be appropriate candidates, affording the desired products (5a-5t) in good yields with excellent chemo-, regio-, and stereoselectivity. A range of functional groups, such as alkyl (5b-5g), halogen (5h-5l), an ether (5m-5o), a free aldehyde (5p), an ester (5q), and a ketone (5t), tolerated the reaction conditions. Generally, phenylacetylenes bearing an electron-donating group gave higher yields than those bearing an electron-withdrawing group, and the substituent can be attached on the *ortho-*, *meta-*, or *para*-position of the phenyl ring. Moreover, the thiophene ring, an example of a heterocyclic ring, was also tolerated (5u-5v). However, internal alkynes were not good reaction partners for this reaction, and in cases where the terminal was blocked by a methyl group, only 21% yield of 5w was obtained. It should be mentioned, in general, that substrates with an electron-donating group can only afford a trace amount of the side products, while other substrates provide the side products in approximately less than 10% yields. Notably, 1-octyne, as an alkyl acetylene, but-3-yn-1-ylbenzene, as an arylalkyl acetylene, 2-ethynylquinoline, and 3-ethynylpyridine all failed to provide the desired products.

Inspired by these results, we further investigated the scope of perfluoroalkyl iodides. As shown in Scheme 3, a variety of



"Reaction conditions: 1a (0.3 mmol, 1 equiv), 2 (2 equiv), 3a (2 equiv), 4a (2 equiv), Cu(CH<sub>3</sub>CN)<sub>4</sub>BF<sub>4</sub> (10 mol %), L1 (20 mol %), MeOH (1 mL), 70 °C, 5 h. <sup>b</sup>Isolated yields.

perfluoroalkyl iodides, including n-C<sub>3</sub>F<sub>7</sub>I, n-C<sub>6</sub>F<sub>13</sub>I, n-C<sub>8</sub>F<sub>17</sub>I, and n-C<sub>10</sub>F<sub>21</sub>I, and other fluoroalkyl iodides, such as C<sub>4</sub>F<sub>8</sub>I<sub>2</sub> and FSO<sub>2</sub>CF<sub>2</sub>CF<sub>2</sub>OCF<sub>2</sub>CF<sub>2</sub>I, all reacted smoothly to afford the corresponding products (**6a**-**6f**) with good yields and excellent regioselectivity. Interestingly, only one terminal of C<sub>4</sub>F<sub>8</sub>I<sub>2</sub> reacted to afford the corresponding product **6f**, leaving another one untouched. These results imply that the reaction generally tolerates various fluoroalkyl iodides which can be used directly as feedstock reagents for the radical cyanofluoroalkylation of alkynes. However, the reactions failed with CF<sub>3</sub>I (balloon) and ICF<sub>2</sub>COOEt as the fluoroalkyl iodides.

To demonstrate the potential of this alkyne cyanofluoroalkylation reaction, compound **5a** was transformed into many useful products (Scheme 4). Owing to the general capability of

#### Scheme 4. Synthetic Applications



the cyano group, product **5a** could be selectively transformed into a fluoroalkylated amide<sup>19</sup> (7) or a fluoroalkylated aldehyde<sup>20</sup> (8) in 80% and 78% yield, respectively. Upon treatment with sodium azide and ammonium chloride, the cyanofluoroalkylation product (**5a**) afforded in 69% yield a fluoroalkylated triazole<sup>21</sup> (9) which can be easily converted to *N*-methylated fluoroalkylated triazole<sup>21</sup> (10) in 74% yield. Moreover, the cyanofluoroalkylation product (**5a**) can react with methyl acrylate in the presence of a base and a reducing agent to afford a Michael addition product<sup>22</sup> (11) with a quaternary carbon center in 61% yield.

Preliminary experiments (Scheme 5) were performed to further understand the mechanism of this cyanofluoroalkyla-

Scheme 5. Preliminary Mechanistic Studies



tion reaction. When the radical scavenger TEMPO (2,2,6,6tetramethyl-1-piperidinyloxy) was added under the standard conditions, no product (5a) was formed and an adduct TEMPO- $C_{11}H_{23}$  (12) was detected by GC-MS analysis, suggesting a radical process (Scheme 5a). Upon the addition of BHT (butylated hydroxytoluene) to the reaction mixture under the standard conditions, the yield of product 5a fell sharply to 31% (Scheme 5b). Furthermore, a control experiment was carried out without the addition of LPO to the standard reaction conditions. No 5a was detected in this case, indicating that LPO is crucial for the cyanofluoroalkylation reaction (Scheme 5c). Finally, side product 5a' was supposed to be the reaction intermediate. However, upon treatment of 5a' under the standard reaction conditions, an almost quantitative yield of 5a' was recovered. This reaction excludes the possibility of 5a' as the reaction intermediate (Scheme 5d).

On the basis of these preliminary findings and previously reported papers,  $^{13,17d}$  a plausible mechanism was proposed and is shown in Scheme 6. First, the L1Cu(I) catalyst (A)

Scheme 6. Possible Radical Pathway



undergoes a SET process with LPO to deliver an undecyl radical, a molecule of  $CO_2$ , and a L1Cu(II) complex (B), which undergoes a ligand exchange with TMSCN to form a L1Cu(II)CN<sup>23</sup>/L1Cu(II)NC<sup>18h</sup> species (C). The undecyl radical reacts with a fluoroalkyl iodide via a radical relay process to provide a fluoroalkyl radical, which subsequently attacks an alkyne forming a vinyl radical intermediate. Then the vinyl radical reacts with the copper(II) species (C) to produce the desired cyanofluoroalkylation product and the regenerated active L1Cu(I) species (A). This procedure is expected to be much faster than I atom abstraction from the fluoroalkyl iodide, forming the ATRA type product.

In summary, we have reported a novel copper-catalyzed cyanofluoroalkylation of alkynes with perfluoroalkyl iodides and trimethylsilyl cyanide for the synthesis of fluoroalkylated cyanoalkenes. This protocol features a wide scope of alkynes and perfluoroalkyl iodides, excellent functional group tolerance, remarkable chemoselectivity and regioselectivity, and simple operation. Moreover, owing to the general capability of the cyano group, the fluoroalkylated cyanoalkenes could be further transformed into many useful derivatives, and this greatly extends the utility of this methodology.

# ASSOCIATED CONTENT

#### **S** Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.or-glett.9b02648.

General procedure, optimization of reaction conditions, characterization data, and copies of NMR spectra for all novel compounds (PDF)

# AUTHOR INFORMATION

### **Corresponding Author**

\*E-mail: hlbao@fjirsm.ac.cn. ORCID <sup>©</sup>

Yajun Li: 0000-0001-6690-2662 Hongli Bao: 0000-0003-1030-5089

# Notes

The authors declare no competing financial interest.

### ACKNOWLEDGMENTS

We thank the National Key R&D Program of China (Grant No. 2017YFA0700103), the NSFC (Grant Nos. 21672213, 21871258), the Strategic Priority Research Program of the Chinese Academy of Sciences (Grant No. XDB2000000), the Haixi Institute of CAS (Grant No. CXZX-2017-P01), the Natural Science Foundation of Fujian Province (Grant No. 2018J05037), and the CAS-TWAS president program of the UCAS for financial support.

## REFERENCES

(1) (a) Müller, K.; Faeh, C.; Diederich, F. Fluorine in pharmaceuticals: looking beyond intuition. *Science* 2007, 317, 1881–1886. (b) O'Hagan, D. Understanding organofluorine chemistry. An introduction to the C–F bond. *Chem. Soc. Rev.* 2008, 37, 308–319. (c) Purser, S.; Moore, P. R.; Swallow, S.; Gouverneur, V. Fluorine in medicinal chemistry. *Chem. Soc. Rev.* 2008, 37, 320–330.

(2) (a) Umemoto, T. Electrophilic Perfluoroalkylating Agents. *Chem. Rev.* **1996**, *96*, 1757–1778. (b) Ma, J. A.; Cahard, D.

Asymmetric fluorination, trifluoromethylation, and perfluoroalkylation reactions. *Chem. Rev.* **2004**, *104*, 6119–6146. (c) Liang, T.; Neumann, C. N.; Ritter, T. Introduction of fluorine and fluorinecontaining functional groups. *Angew. Chem., Int. Ed.* **2013**, *52*, 8214– 8264.

(3) (a) Uneyama, K. Organofluorine Chemistry; Blackwell Publishing: Oxford. 2006. (b) Bégué, J.-P.; Bonnet-Delpon, D. Bioorganic and medicinal chemistry of fluorine; John Wiley & Sons, 2008. (c) Ojima, I. Fluorine in medicinal chemistry and chemical biology; John Wiley & Sons, 2009. (d) Petrov, V. A. Fluorinated heterocyclic compounds: synthesis, chemistry, and applications; John Wiley & Sons, 2009.

(4) (a) Furuya, T.; Kamlet, A. S.; Ritter, T. Catalysis for fluorination and trifluoromethylation. Nature 2011, 473, 470-477. (b) Tomashenko, O. A.; Grushin, V. V. Aromatic trifluoromethylation with metal complexes. Chem. Rev. 2011, 111, 4475-4521. (c) Besset, T.; Schneider, C.; Cahard, D. Tamed arene and heteroarene trifluoromethylation. Angew. Chem., Int. Ed. 2012, 51, 5048-5050. (d) Wu, X.-F.; Neumann, H.; Beller, M. Recent developments on the trifluoromethylation of (hetero)arenes. Chem. - Asian J. 2012, 7, 1744-1754. (e) Barata-Vallejo, S.; Lantano, B.; Postigo, A. Recent advances in trifluoromethylation reactions with electrophilic trifluoromethylating reagents. Chem. - Eur. J. 2014, 20, 16806-16829. (f) Barata-Vallejo, S.; Bonesi, S. M.; Postigo, A. Perfluoroalkylation reactions of (hetero)arenes. RSC Adv. 2015, 5, 62498-62518. (g) Feng, Z.; Xiao, Y. L.; Zhang, X. Transition-Metal (Cu, Pd, Ni)-Catalyzed Difluoroalkylation via Cross-Coupling with Difluoroalkyl Halides. Acc. Chem. Res. 2018, 51, 2264-2278.

(5) (a) Murakami, S.; Ishii, H.; Tajima, T.; Fuchigami, T. Photochemical substitution of olefins and aromatic compounds with difluoromethyl radicals bearing ester and phosphonate groups. Tetrahedron 2006, 62, 3761-3769. (b) Li, Y.; Liu, J.; Zhang, L.; Zhu, L.; Hu, J. Radical (phenylsulfonyl)difluoromethylation with iododifluoromethyl phenyl sulfone. J. Org. Chem. 2007, 72, 5824-5827. (c) Surapanich, N.; Kuhakarn, C.; Pohmakotr, M.; Reutrakul, V. Palladium-Mediated Heck-Type Reactions of [(Bromodifluoromethyl)sulfonyl]benzene: Synthesis of  $\alpha$ -Alkenyland  $\alpha$ -Heteroaryl-Substituted  $\alpha, \alpha$ -Difluoromethyl Phenyl Sulfones. Eur. J. Org. Chem. 2012, 2012, 5943-5952. (d) Belhomme, M. C.; Poisson, T.; Pannecoucke, X. Copper catalyzed beta-difluoroacetylation of dihydropyrans and glycals by means of direct C-H functionalization. Org. Lett. 2013, 15, 3428-3431. (e) Yu, C.; Iqbal, N.; Park, S.; Cho, E. J. Selective difluoroalkylation of alkenes by using visible light photoredox catalysis. Chem. Commun. 2014, 50, 12884-12887. (f) Feng, Z.; Min, Q. Q.; Zhao, H. Y.; Gu, J. W.; Zhang, X. A general synthesis of fluoroalkylated alkenes by palladium-catalyzed Heck-type reaction of fluoroalkyl bromides. Angew. Chem., Int. Ed. 2015, 54, 1270-1274. (g) Zhang, X.; Zhang, F.; Min, Q.-Q. Palladium-Catalyzed Heck-Type Difluoroalkylation of Alkenes with Functionalized Difluoromethyl Bromides. Synthesis 2015, 47, 2912-2923. (h) Fan, T.; Meng, W. D.; Zhang, X. Palladium-catalyzed Hecktype reaction of secondary trifluoromethylated alkyl bromides. Beilstein J. Org. Chem. 2017, 13, 2610-2616. (i) Tiwari, D. P.; Dabral, S.; Wen, J.; Wiesenthal, J.; Terhorst, S.; Bolm, C. Organic Dye-Catalyzed Atom Transfer Radical Addition-Elimination (ATRE) Reaction for the Synthesis of Perfluoroalkylated Alkenes. Org. Lett. 2017, 19, 4295-4298. (j) Wang, X.; Zhao, S.; Liu, J.; Zhu, D.; Guo, M.; Tang, X.; Wang, G. Copper-Catalyzed C-H Difluoroalkylations and Perfluoroalkylations of Alkenes and (Hetero)arenes. Org. Lett. 2017, 19, 4187-4190.

(6) (a) Taguchi, T.; Kitagawa, O.; Morikawa, T.; Nishiwaki, T.; Uehara, H.; Endo, H.; Kobayashi, Y. Synthesis of 2,2-difluoroesters by iododifluoroacetate-copper with organic halides. *Tetrahedron Lett.* **1986**, 27, 6103–6106. (b) Yokomatsu, T.; Suemune, K.; Murano, T.; Shibuya, S. Synthesis of (alpha,alpha-Difluoroallyl)phosphonates from Alkenyl Halides or Acetylenes. *J. Org. Chem.* **1996**, *61*, 7207–7211. (c) Sato, K.; Kawata, R.; Ama, F.; Omote, M.; Ando, A.; Kumadaki, I. Synthesis of Alkenyl- and Aryldifluoroacetate Using a Copper Complex from Ethyl Bromodifluoroacetate. *Chem. Pharm. Bull.* **1999**, *47*, 1013–1016. (d) Schwaebe, M. K.; McCarthy, J. R.; Whitten, J. P. Nickel(0)-catalyzed coupling of vinylzirconiums to  $\alpha$ bromo- $\alpha$ , $\alpha$ -difluoro esters. Convenient generation of a functionalized allyldifluoro moiety. Tetrahedron Lett. 2000, 41, 791-794. (e) Prakash, G. K.; Ganesh, S. K.; Jones, J. P.; Kulkarni, A.; Masood, K.; Swabeck, J. K.; Olah, G. A. Copper-mediated difluoromethylation of (hetero)aryl iodides and beta-styryl halides with tributyl(difluoromethyl)stannane. Angew. Chem., Int. Ed. 2012, 51, 12090-12094. (f) Fier, P. S.; Hartwig, J. F. Copper-mediated difluoromethylation of aryl and vinyl iodides. J. Am. Chem. Soc. 2012, 134, 5524-5527. (g) Jiang, H.; Lu, W.; Yang, K.; Ma, G.; Xu, M.; Li, J.; Yao, J.; Wan, W.; Deng, H.; Wu, S.; Zhu, S.; Hao, J. Enhancement of neighbouring-group participation in Cu<sup>0</sup>-promoted cross-coupling gem-difluoromethylenation of aryl/alkenyl halides with 1,3-azolic difluoromethyl bromides. Chem. - Eur. J. 2014, 20, 10084-10092. (h) Aikawa, K.; Nakamura, Y.; Yokota, Y.; Toya, W.; Mikami, K. Stable but reactive perfluoroalkylzinc reagents: application in ligand-free coppercatalyzed perfluoroalkylation of aryl iodides. Chem. - Eur. J. 2015, 21, 96-100. (i) Chang, D.; Gu, Y.; Shen, Q. Pd-catalyzed difluoromethylation of vinyl bromides, triflates, tosylates, and nonaflates. Chem. - Eur. J. 2015, 21, 6074-6078. (j) Wu, C.; Huang, Y.; Zhang, Z.; Weng, Z. Decarboxylative Perfluoroalkylation of Vinyl Bromides with Copper(I) Perfluorocarboxylato Complexes. Asian J. Org. Chem. 2016, 5, 1406-1410. (k) Mestre, J.; Lishchynskyi, A.; Castillon, S.; Boutureira, O. Trifluoromethylation of Electron-Rich Alkenyl Iodides with Fluoroform-Derived "Ligandless" CuCF<sub>3</sub>. J. Org. Chem. 2018, 83, 8150-8160.

(7) (a) 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. (b) Iqbal, N.; Jung, J.; Park, S.; Cho, E. J. Controlled trifluoromethylation reactions of alkynes through visiblelight photoredox catalysis. Angew. Chem., Int. Ed. 2014, 53, 539-542. (c) Pitre, S. P.; McTiernan, C. D.; Ismaili, H.; Scaiano, J. C. Metal-Free Photocatalytic Radical Trifluoromethylation Utilizing Methylene Blue and Visible Light Irradiation. ACS Catal. 2014, 4, 2530-2535. (d) Cheng, Y.; Yu, S. Hydrotrifluoromethylation of Unactivated Alkenes and Alkynes Enabled by an Electron-Donor-Acceptor Complex of Togni's Reagent with a Tertiary Amine. Org. Lett. 2016, 18, 2962-2965. (e) Jacquet, J.; Blanchard, S.; Derat, E.; Desage-El Murr, M.; Fensterbank, L. Redox-ligand sustains controlled generation of CF<sub>3</sub> radicals by well-defined copper complex. Chem. Sci. 2016, 7, 2030-2036. (f) He, L.; Yang, X.; Tsui, G. C. Domino Hydroboration/Trifluoromethylation of Alkynes Using Fluoroform-Derived [CuCF<sub>3</sub>]. J. Org. Chem. 2017, 82, 6192-6201.

(8) (a) Janson, P. G.; Ghoneim, I.; Ilchenko, N. O.; Szabo, K. J. Electrophilic trifluoromethylation by copper-catalyzed addition of CF<sub>3</sub>-transfer reagents to alkenes and alkynes. Org. Lett. 2012, 14, 2882–2885. (b) Egami, H.; Shimizu, R.; Sodeoka, M. Oxy-trifluoromethylation of multiple bonds using copper catalyst under mild conditions. Tetrahedron Lett. 2012, 53, 5503–5506. (c) Wang, Y.; Jiang, M.; Liu, J.-T. Copper-catalyzed stereoselective oxy-trifluoromethylation of propargyl amides for the construction of oxazolines. Org. Chem. Front. 2015, 2, 542–547. (d) Zhang, S.-L.; Wan, H.-X.; Bie, W.-F. syn-Fluoro- and -Oxy-trifluoromethylation of Arylacetylenes. Org. Lett. 2017, 19, 6372–6375.

(9) (a) Wang, Y.; Jiang, M.; Liu, J.-T. Copper-Catalyzed Intramolecular Carbotrifluoromethylation of Alkynes for the Construction of Trifluoromethylated Heterocycles. *Chem. - Eur. J.* **2014**, 20, 15315–15319. (b) He, Y.-T.; Wang, Q.; Zhao, J.; Liu, X.-Y.; Xu, P.-F.; Liang, Y.-M. The copper-catalyzed synthesis of beta-trifluoromethylated acrylonitriles and trifluoromethyl-substituted 2*H*-azirines. *Chem. Commun.* **2015**, 51, 13209–13212.

(10) (a) Ge, G.-C.; Huang, X.-J.; Ding, C.-H.; Wan, S.-L.; Dai, L.-X.; Hou, X.-L. A new strategy to construct a  $C = C-CF_3$  subunit via CuBrcatalyzed domino reaction of homopropargyl amines: an efficient synthesis of trifluoromethyl containing building blocks 4-trifluoromethyl-2,3-dihydro-pyrroliums. *Chem. Commun.* **2014**, *50*, 3048– 3051. (b) Wang, F.; Zhu, N.; Chen, P.; Ye, J.; Liu, G. Copper-Catalyzed Trifluoromethylazidation of Alkynes: Efficient Access to CF<sub>3</sub>-Substituted Azirines and Aziridines. *Angew. Chem., Int. Ed.* **2015**, *54*, 9356–9360.

(11) Wallentin, C. J.; Nguyen, J. D.; Finkbeiner, P.; Stephenson, C. R. Visible light-mediated atom transfer radical addition via oxidative and reductive quenching of photocatalysts. *J. Am. Chem. Soc.* 2012, 134, 8875–8884.

(12) 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.

(13) Li, Z.; Garcia-Dominguez, A.; Nevado, C. Pd-Catalyzed Stereoselective Carboperfluoroalkylation of Alkynes. J. Am. Chem. Soc. 2015, 137, 11610–11613.

(14) (a) He, Y.-T.; Wang, Q.; Li, L.-H.; Liu, X.-Y.; Xu, P.-F.; Liang, Y.-M. Palladium-Catalyzed Intermolecular Aryldifluoroalkylation of Alkynes. Org. Lett. 2015, 17, 5188–5191. (b) Wang, Q.; Zheng, L.; He, Y.-T.; Liang, Y.-M. Regioselective Synthsis of Difluoroalkyl/ Perfluoroalkyl Enones via Pd-Catalyzed Four-component Carbonylative Coupling Reactions. Chem. Commun. 2017, 53, 2814–2817. (c) Wang, Q.; Yu, X.-W.; Jin, J.-N.; Wu, Y.; Liang, Y.-M. Difunctionalization of Alkynes: Synthesis of Novel Fluoropolymer Materials. Chin. J. Chem. 2018, 36, 223–226.

(15) Qi, X.; Ai, H.-J.; Cai, C.-X.; Peng, J.-B.; Zheng, F.; Wu, X.-F. Palladium-Catalyzed Selective Synthesis of Perfluoroalkylated Enynes from Perfluoroalkyl Iodides and Alkynes. *Eur. J. Org. Chem.* 2017, 2017, 2940–2943.

(16) He, Y.-T.; Li, L.-H.; Wang, Q.; Wu, W.; Liang, Y.-M. Synthesis of beta-Difluoroalkylated Acrylonitriles in the Presence of Copper Powder. *Org. Lett.* **2016**, *18*, 5158–5161.

(17) (a) Deng, W.; Ye, C.; Li, Y.; Li, D.; Bao, H. Iron-Catalyzed Oxyalkylation of Terminal Alkynes with Alkyl Iodides. Org. Lett. 2019, 21, 261-265. (b) Ge, L.; Li, Y.; Bao, H. Iron-Catalyzed Radical Acyl-Azidation of Alkenes with Aldehydes: Synthesis of Unsymmetrical beta-Azido Ketones. Org. Lett. 2019, 21, 256-260. (c) Xiong, H.; Li, Y.; Qian, B.; Wei, R.; Van der Eycken, E. V.; Bao, H. Iron(II)-Catalyzed Heck-Type Coupling of Vinylarenes with Alkyl Iodides. Org. Lett. 2019, 21, 776-779. (d) Xiong, H.; Ramkumar, N.; Chiou, M.-F.; Jian, W.; Li, Y.; Su, J. H.; Zhang, X.; Bao, H. Iron-catalyzed carboazidation of alkenes and alkynes. Nat. Commun. 2019, 10, 122. (18) (a) Zhu, N.; Wang, T.; Ge, L.; Li, Y.; Zhang, X.; Bao, H. gamma-Amino Butyric Acid (GABA) Synthesis Enabled by Copper-Catalyzed Carboamination of Alkenes. Org. Lett. 2017, 19, 4718-4721. (b) Jian, W.; Ge, L.; Jiao, Y.; Qian, B.; Bao, H. Iron-Catalyzed Decarboxylative Alkyl Etherification of Vinylarenes with Aliphatic Acids as the Alkyl Source. Angew. Chem., Int. Ed. 2017, 56, 3650-3654. (c) Li, Y.; Ge, L.; Muhammad, M.; Bao, H. Recent Progress on Radical Decarboxylative Alkylation for Csp<sup>3</sup>-C Bond Formation. Synthesis 2017, 49, 5263-5284. (d) Deng, W.; Feng, W.; Li, Y.; Bao, H. Merging Visible-Light Photocatalysis and Transition-Metal Catalysis in Three-Component Alkyl-Fluorination of Olefins with a Fluoride Ion. Org. Lett. 2018, 20, 4245-4249. (e) Jiao, Y.; Chiou, M.-F.; Li, Y.; Bao, H. Copper-Catalyzed Radical Acyl-Cyanation of Alkenes with Mechanistic Studies on the tert-Butoxy Radical. ACS Catal. 2019, 9, 5191-5197. (f) Qian, B.; Chen, S.; Wang, T.; Zhang, X.; Bao, H. Iron-Catalyzed Carboamination of Olefins: Synthesis of Amines and Disubstituted beta-Amino Acids. J. Am. Chem. Soc. 2017, 139, 13076-13082. (g) Ye, C.; Li, Y.; Zhu, X.; Hu, S.; Yuan, D.; Bao, H. Copper-catalyzed 1,4-alkylarylation of 1,3-enynes with masked alkyl electrophiles. Chem. Sci. 2019, 10, 3632-3636. (h) Zhu, X.; Deng, W.; Chiou, M. F.; Ye, C.; Jian, W.; Zeng, Y.; Jiao, Y.; Ge, L.; Li, Y.; Zhang, X.; Bao, H. Copper-Catalyzed Radical 1,4-Difunctionalization of 1,3-Enynes with Alkyl Diacyl Peroxides and N-Fluorobenzenesulfonimide. J. Am. Chem. Soc. 2019, 141, 548-559.

(19) Zhu, X.; Deng, W.; Chiou, M.-F.; Ye, C.; Jian, W.; Zeng, Y.; Jiao, Y.; Ge, L.; Li, Y.; Zhang, X.; Bao, H. Copper-Catalyzed Radical 1,4-Difunctionalization of 1,3-Enynes with Alkyl Diacyl Peroxides and N-Fluorobenzenesulfonimide. *J. Am. Chem. Soc.* **2019**, *141*, 548–559. (20) Campi, E.; Fitzmaurice, N. J.; Jackson, W. R.; Perlmutter, P.; Smallridge, A. J. A two-step hydroformylation of alkynes. *Synthesis* **1987**, 1987, 1032–1034.

(21) Madadi, N. R.; Penthala, N. R.; Song, L.; Hendrickson, H. P.; Crooks, P. A. Preparation of 4, 5 disubstituted-2H-1, 2, 3-triazoles from (Z)-2, 3-diaryl substituted acrylonitriles. *Tetrahedron Lett.* **2014**, 55, 4207–4211.

(22) Arai, S.; Sato, T.; Koike, Y.; Hayashi, M.; Nishida, A. Palladiumcatalyzed cyanation of carbon-carbon triple bonds under aerobic conditions. *Angew. Chem., Int. Ed.* **2009**, *48*, 4528–4531.

(23) (a) Wang, F.; Chen, P.; Liu, G. Copper-Catalyzed Radical Relay for Asymmetric Radical Transformations. *Acc. Chem. Res.* 2018, *51*, 2036–2046. (b) Zhang, W.; Wang, F.; McCann, S. D.; Wang, D.; Chen, P.; Stahl, S. S.; Liu, G. Enantioselective cyanation of benzylic C-H bonds via copper-catalyzed radical relay. *Science* 2016, 353, 1014–1018.