Organic & Biomolecular Chemistry

Accepted Manuscript

This article can be cited before page numbers have been issued, to do this please use: X. Feng, X. Wang, H. Chen, X. Tang, M. Guo, W. Zhao and G. Wang, *Org. Biomol. Chem.*, 2018, DOI: 10.1039/C8OB00256H.

ROYAL SOCIETY OF CHEMISTRY

rsc.li/obc

View Article Online
DOI: 10.1039/C8OB00256H

Journal Name

COMMUNICATION

Copper-Mediated Regioselective Hydrodifluoroalkylation of Alkynes

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

www.rsc.org

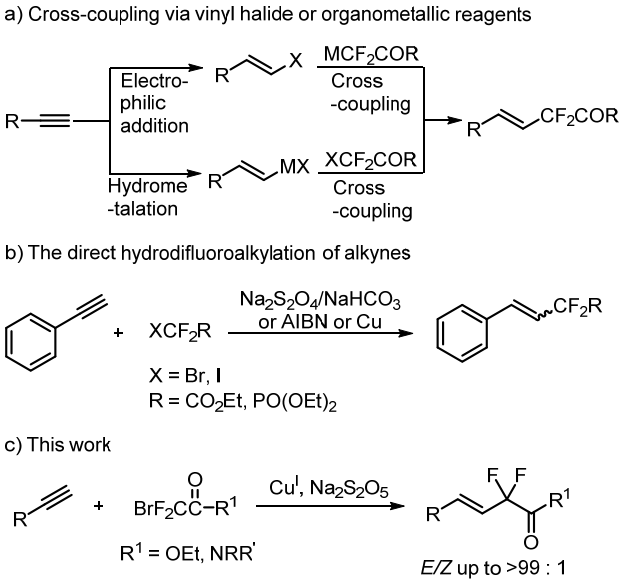
Xiaorui Feng,[a] Xiaoyang Wang,[a] Hongtai Chen,[a] Xiangyang Tang,[a] Minjie Guo,[b] Wentao Zhao,[a]* and Guangwei Wang[a]*

A highly regioselective copper-mediated hydrodifluoroalkylation of alkynes with ethyl bromodifluoroacetate or bromodifluoroacetamides has been developed. This strategy provides a straightforward access to a variety of difluoroalkylated alkenes under mild reaction conditions with low-cost cuprous bromide and metabisulfite as reduction agent. A wide range of alkynes are applicable with these reaction conditions. The excellent functional-group compatibility and good regio- and stereoselectivities are the notable features of this transformation.

Fluorine atom is generally considered as an extraordinary atom due to its small atomic radius and high electronegativity. Introduction of fluorine can generally enhance the lipophilicity, bioavailability, and metabolic stability of their parent molecules.[1] However, only a very limited number of fluorine-containing compounds, which can be used as potential starting fluorinated material, has been produced by nature. Due to the ubiquity of fluorine-containing molecules in the fields of materials, pesticides, and pharmaceuticals, the increasing demand for fluorine-containing organic compounds has made them urgent synthetic targets in organic chemistry.[2] Consequently, incorporation of fluorine and fluorine-containing groups has been an intensive topic of organofluorine synthetic chemistry.

Recently, the synthesis of difluoromethylene-containing compounds has attracted considerable attention.[3] Difluoromethylene (-CF_2-) is regarded as a bioisostere for oxygen atom, carbonyl, and methylene,[4] and it can affect the electronic properties, chemical properties, and reactivities of the adjacent functional group.[5] During the last decades, the synthesis of difluoroalkylated alkenes have been accomplished by direct C–H difluoroalkylation of alkenes,[6] decarboxylative cross-coupling of α,β-unsaturated carboxylic acids,[7] and transition metal-catalyzed cross-coupling reactions involving alkenyl metals[8] or halides.[9]

Scheme 1. Synthesis of difluoroalkylated alkenes from terminal alkynes



Traditionally, the alkenyl metals or alkenyl halides are derived from alkynes through hydrometalation or electrophilic addition reactions (Scheme 1a). Therefore, the direct addition of difluoroalkyl groups to alkynes to generate difluoroalkylated alkenes in a regio- and stereo-controlled fashion would prevent additional steps for the preparation of alkenylmetal species or alkenyl halides, thus improving their synthetic efficiency and applicability. However, it is challenging due to the difficulty in control of stereoselectivity (Scheme 1b).[10-13] For instance, Chen *et al*. and Piettre *et al*. respectively reported the transition metal-free hydrodifluoroalkylations of alkynes with $Na_2S_2O_4$[11] or AIBN[12] as a radical initiator, and Shibuya *et al*. reported a Cu-mediated hydrodifluoroalkylation of alkynes.[13] However, only low to moderate yields and poor stereoselectivities have been acheived. Recently, Song and co-

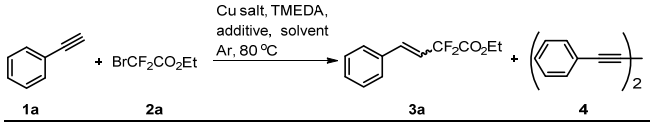
[a] *Tianjin Key Laboratory of Molecular Optoelectronic Science, Department of Chemistry, School of Science, Tianjin University, Tianjin 300072, P. R. China.*
[b] *Institute for Molecular Design and Synthesis, School of Pharmaceutical Science and Technology, Tianjin University, Tianjin 300072, P. R. China*
† Footnotes relating to the title and/or authors should appear here.
Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/x0xx00000x

workers reported the reaction of ethyl bromodifluoroacetate and alkynes in the presence of B_2pin_2.[14] Although good *cis*-hydrodifluoroalkylation have been realized for aromatic alkynes bearing an electron-donating group, the stereoselectivities are lower for aliphatic alkynes. Furthermore, stoichiometric amount of bis(pinacolato)diboron has been employed as reductant which is expensive, thus limiting its application in scaled up industrial synthesis. Herein, we report our results of direct hydrodifluoroalkylation of alkynes in the presence of low-cost copper(I) and sodium metabisulfite, undergoing different reaction pathway. Through this strategy, *trans*-fluoroalkylated alkenes could be accessed with good to excellent yields and high *E*-stereoselectivities for both aromatic and aliphatic alkynes (Scheme 1d).

RESULTS AND DISCUSSION

Initially, the radical addition of phenylacetylene (**1a**) with ethyl bromodifluoroacetate (**2a**) was chosen as a model reaction to optimize the reaction conditions. When using TMEDA (2.0 equiv) as base in the presence of CuBr (1.5 equiv) in DMF, the desired product **3a** was obtained in only 19% yield along with the homo-coupling byproduct **4** (75%) (Table 1, entry 1). When KF (1.5 equiv) was added, the yield of **3a** was improved to 74% (Table 1, entry 2) and the yield of byproduct **4** dropped to 21%. It is noteworthy that in the presence of $Na_2S_2O_5$ (1.5 equiv), the desired product **3a** can be obtained with an excellent yield of 97%, with the generation of **4** being sufficiently suppressed (entry 3). Various copper salts were subsequently screened (entries 3 to 6), which implied that copper(I) was more efficient than copper(II) (entry 3 vs 6), and CuBr gave the best yield and stereoselectivity. Next, a number of other additives were investigated (entry 7 vs 8) and $Na_2S_2O_5$ proved the most efficient additive in this reaction. Moreover, various solvents were screened (entries 9−12) and DMF was found to be the best option. However, our attempt to decrease the amount of copper to a catalytic amount (0.2 equiv) failed due to the decrease of yield to 23% (entry 13). A control experiment in the absence of TMEDA only gave the desired product **3a** in 6% yield (entry 14). Consequently, $Na_2S_2O_5$ as additive, TMEDA as base, and DMF as solvent in the presence of CuBr were chosen as the optimized conditions.

Table 1. Optimization of reaction conditions[a]



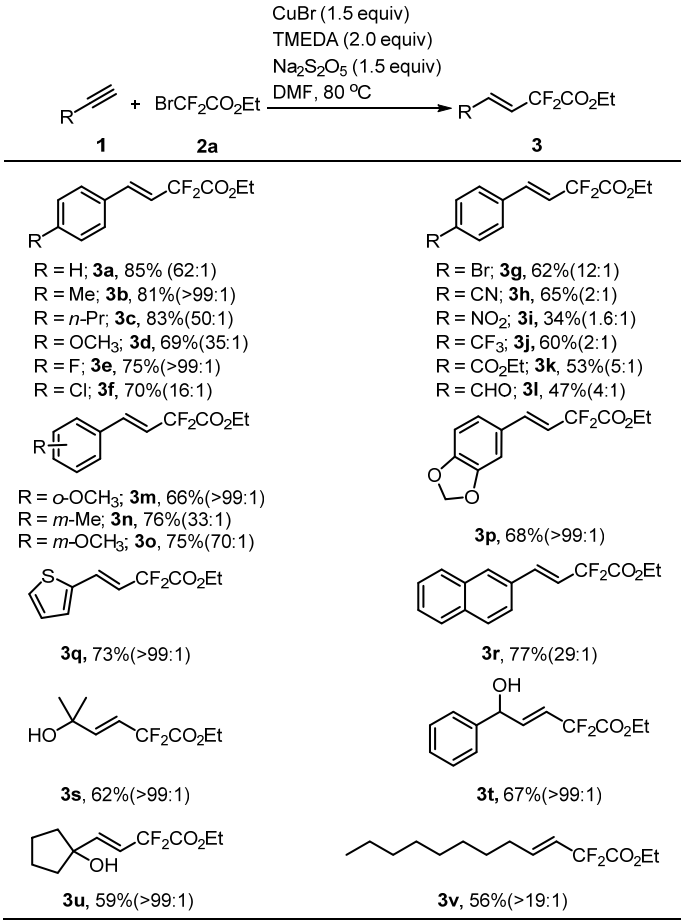
1a 2a 3a 4

Entry	Cu salt	additive	Solvent	yield[b] (%)	
				3a (*E*/*Z*)	**4**
1	CuBr	none	DMF	19(>99:1)	75
2	CuBr	KF	DMF	74(21:1)	21
3	CuBr	$Na_2S_2O_5$	DMF	97(96:1)	0
4	CuCl	$Na_2S_2O_5$	DMF	95(94:1)	0
5	CuI	$Na_2S_2O_5$	DMF	94(46:1)	0
6	$CuBr_2$	$Na_2S_2O_5$	DMF	53(>99:1)	33
7	CuBr	Na_2SO_3	DMF	71(22:1)	30
8	CuBr	$NaHSO_3$	DMF	62(8:1)	35
9	CuBr	$Na_2S_2O_5$	THF	22(10:1)	73
10	CuBr	$Na_2S_2O_5$	toluene	43(13:1)	51
11	CuBr	$Na_2S_2O_5$	1,4-dioxane	41(7:1)	49
12	CuBr	$Na_2S_2O_5$	CH_3CN	55(54:1)	36
13[c]	CuBr	$Na_2S_2O_5$	DMF	23(>99:1)	0
14[d]	CuBr	$Na_2S_2O_5$	DMF	6(>99:1)	0

[a]Reaction conditions: **1a** (0.3 mmol, 1.0 equiv), **2a** (0.45 mmol, 1.5 equiv), Cu salt (0.45 mmol, 1.5 equiv), TMEDA (0.6 mmol, 2.0 equiv), additive (0.45 mmol, 1.5 equiv), DMF (3 mL), 80 °C, under argon. [b]The yield was determined by HPLC analysis. TMEDA = *N, N, N', N'*-tetramethylethane-1,2-diamine. [c]Catalytic amount (0.2 equiv) of CuBr was used. [d]Without the addition of TMEDA.

With the optimal reaction conditions in hand, the substrate scope of this hydrodifluoroalkylation reaction was explored. A wide range of alkynes, including both aromatic and aliphatic ones, were examined and the results were depicted in Table 2. For the aromatic alkynes, diverse substituents on the aromatic ring were compatible under the standard conditions and gave moderate to high yields of the corresponding difluoroalkylated products (**3a**-**3o**). Both phenylacetylenes bearing an electron-

Scheme 2. Scope of alkynes[a,b]



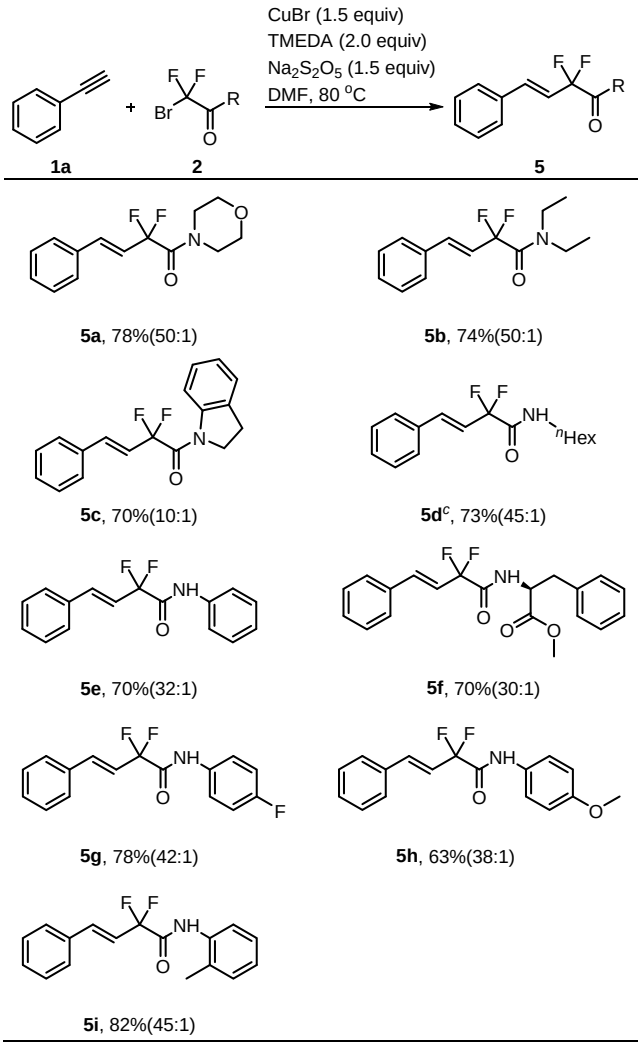
[a]Reaction conditions: **1** (0.5 mmol, 1.0 equiv), **2a** (0.75 mmol, 1.5 equiv), CuBr (0.75 mmol, 1.5 equiv), TMEDA (1.0 mmol, 2.0 equiv), $Na_2S_2O_5$ (0.75 mmol, 1.5 equiv), DMF (5 mL), 80 °C, under argon, 6-8 h. [b]Isolated yield. The ratios in parentheses are *E*/*Z* ratios, determined by ^{19}F NMR spectroscopy.

View Article Online DOI: 10.1039/C8OB00256H

donating group on the aryl ring (**3b**-**3d**, **3m**-**3p**) and halogen substituted phenylacetylenes (**3e**-**3g**) gave the desired products with high yields and excellent stereoselectivities. Meanwhile, for phenylacetylenes with strong electron-withdrawing groups (**3h**-**3l**), relatively lower yields and lower stereoselectivities were obtained, which might be due to the low isomerization barrier of alkenyl radicals.[15] Moreover, 2-ethynylthiophene (**3q**), 2-ethynylnaphthalene (**3r**), and aliphatic alkynes (**3s**-**3v**) also proceeded smoothly to afford the desired products with good yields and excellent stereoselectivities. It is noteworthy that various functional groups, such as cyano (**3h**), nitro (**3i**), alkoxycarbonyl (**3k**), formyl (**3l**), and hydroxyl (**3s**-**3v**) can be well tolerated.

To further demonstrate the generality of this method, different functionalized difluoromethyl bromides were also explored with the results being summarized in Table 3. As expected, a variety of bromodifluoroacetamides were compatible with the transformation and gave the desired products (**5a**-**5i**) with high yields and good stereoselectivities.

Scheme 3. Scope of bromodifluoroacetamides[a,b]

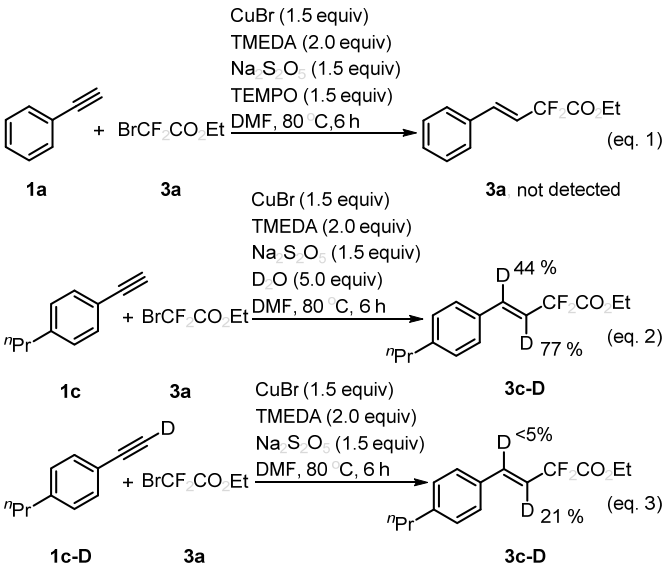


[a]Reaction Conditions: **1a** (0.5 mmol, 1.0 equiv), **2** (0.75 mmol, 1.5 equiv), CuBr (0.75 mmol, 1.5 equiv), TMEDA (1.0 mmol, 2.0 equiv), $Na_2S_2O_5$ (0.75 mmol, 1.5 equiv), DMF (5 mL), 80 °C, under argon, 6-8 h. [b]Isolated yield. The ratios in parentheses are *E*/*Z* ratios, determined by ^{19}F NMR spectroscopy.

It is remarkable that the amide containing compounds (**5e**-**5i**) cannot be accessed through previous reported difluoromethylation of alkenes[16] or hydrodifluoromethylation of alkynes,[17] both of which led to further cyclized products. Notably, reaction of phenylalanine derived bromodifluoroamide with phenylacetylene afforded the fluorinated alkene (**5f**) in good yield with an excellent functional group tolerance. Thus, unsaturated fluorinated amino acids can be efficiently accessed for further biologically active peptides and protein engineering studies.[18]

To exploit the reaction mechanism, several control experiments were carried out (for details, see the Supporting Information). When a radical inhibitor 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) was added into the reaction system, the reaction was quenched and thus implied that a radical pathway might be involved in this reaction (Scheme 4, eq. 1). To gain further insight into the source of the two protons in the desired product, two deuterium-labeling experiments were performed. When excessive amount of deuterated water was added to the reaction, the corresponding product **3c** was obtained with 77% deuterated at α-C and 44% deuterated at β-C (Scheme 4, eq. 2). When deuterated 4-propylphenylethylene was subjected to the reaction condition, the corresponding product **3c** was obtained with 21% deuterated at α-C and less than 5% deuterated at β-C (Scheme 4, eq. 3). When the reaction of **1a** with **2a** was run under anhydrous conditions, the yield dropped sharply. All above results indicate that water should be involved in this reaction as a hydrogen source.

Scheme 4. Control experiments for mechanism insight

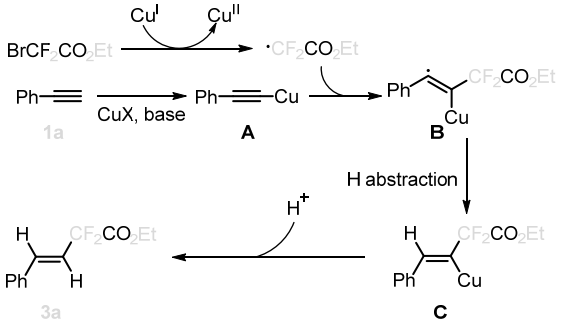


Based on the above experimental results and previous reports,[7,19] a plausible mechanism was proposed in Scheme 5. First, $BrCF_2CO_2Et$ is reduced by copper(I) salt via a single-electron transfer to afford the difluoroalkyl radical, which adds to the *in situ* formed (phenylethynyl)copper **A** to afford vinyl radical intermediate **B**. Subsequently, vinyl radical **B** could abstract the hydrogen from solvents and give vinyl-copper

View Article Online
DOI: 10.1039/C8OB00256H

intermediate **C**, which was quenched by proton from moisture in the reaction system, giving the desired product **3**. The diyne byproduct **4** might be derived from homocoupling of terminal alkynes in the presence of Cu(II) or Cu(III).[20] Therefore, $Na_2S_2O_5$ was applied as reductant to suppressed the side reaction.[21]

Scheme 5. Proposed mechanism



Conclusions

In summary, an economic copper/$Na_2S_2O_5$-mediated hydrodifluoroalkylation of alkynes with ethyl bromodifluoroacetate has been developed. Through this strategy, a number of difluroalkylated alkenes can be obtained in good yields and stereoselectivities. Further explorations to reveal the reaction mechanism are currently underway in our laboratory.

Conflicts of interest

There are no conflicts to declare.

Acknowledgment

We thank the National Basic Research Program of China (No. 2015CB856500) and the Natural Science Foundation of Tianjin (No. 16JCYBJC20100) for support of this research.

Notes and references

1 (a) B. E. Smart, *J. Fluorine Chem.*, 2001, **109**, 3; (b) P. Kirsch, *Modern Fluoroorganic Chemistry: Synthesis, Reactivity, Applications*, Wiley-VCH, Weinheim, 2013. (c) K. Müller, C. Faeh, F. Diederich, *Science*, 2007, **317**, 1881; (d) T. Besset, T. Poisson, X. Pannecoucke, *Chem. Eur. J.*, 2014, **20**, 16830.

2 (a) M. Schlosser, *Angew. Chem. Int. Ed.*, 2006, **45**, 5432; (b) S. Purser, P. R. Moore, S. Swallow, V. Gouverneur, *Chem. Soc. Rev.*, 2008, **37**, 320; (c) W. K. Hagmann, *J. Med. Chem.*, 2008, **51**, 4359; (d) K. L. Kirk, *Org. Process Res. Dev.*, 2008, **12**, 305; (e) J. Wang, H. Liu, *Chin. J. Org. Chem.*, 2011, **31**, 1785. (f) O. A. Tomashenko, V. V. Grushin, *Chem. Rev.*, 2011, **111**, 4475; (g) X.-F. Wu, H. Neumann, M. Beller, *Chem. Asian J.*, 2012, **7**, 1744; (h) J. Zhang, C. Jin, Y. Zhang, *Chin. J. Org. Chem.*, 2014, **34**, 662; (i) C. Ni, L. Zhu, J. Hu, *Acta Chim. Sinica*, 2015, **73**, 90.

3 (a) T. Besset, T. Poisson, X. Pannecoucke, *Eur. J. Org. Chem.*, 2015, **2015**, 2765; (b) M.-C. Belhomme, T. Besset, T. Poisson, X. Pannecoucke, *Chem. Eur. J.*, 2015, **21**, 12836.

4 (a) J. A. Erickson, J. I. McLoughlin, *J. Org. Chem.*, 1995, **60**, 1626; (b) N. A. Meanwell, *J. Med. Chem.*, 2011, **54**, 2529; (c) F.-L. Qing, F. Zheng, *Synlett*, 2011, **8**, 1052. (d) C. Ni, J. Hu, *Synthesis*, 2014, **46**, 842; (e) J. Xie, T. Zhang, F. Chen, N. Mehrkens, F. Rominger, M. Rudolph, A. S. K. Hashmi, *Angew. Chem. Int. Ed.*, 2016, **55**, 2934.

5 (a) D. O'Hagan, H. S. Rzepa, *Chem. Commun.,* 1997, **0**, 645; (b) D. O'Hagan, Y. Wang, M. Skibinski, A. M. Z. Slawin, *Pure Appl. Chem.*, 2012, **84**, 1587; (c) Q. Wang, L. Zheng, Y.-T. He, Y.-M. Liang, *Chem. Commun.*, 2017, **53**, 2814.

6 (a) X. Wang, S. Zhao, J. Liu, D. Zhu, M. Guo, X. Tang, G. Wang, *Org. Lett.*, 2017, **19**, 4187. (b) Y. Li, J. Liu, S. Zhao, X. Du, M. Guo, W. Zhao, X. Tang, G. Wang, *Org. Lett.* 2018, **20**, 917; (c) Z. Feng, Q.-Q. Min, H.-Y. Zhao, J.-W. Gu, X. Zhang, *Angew. Chem., Int. Ed.*, 2015, **54**, 1270; (d) Z. Feng, Y.-L. Xiao, X. Zhang, *Org. Chem. Front.,* 2016, **3**, 466.

7 (a) G. Li, Y.-X. Cao, C.-G. Luo, Y.-M. Su, Y. Li, Q. Lan, X.-S. Wang, *Org. Lett.*, 2016, **18**, 4806; (b) G. Li, T. Wang, F. Fei, Y.-M. Su, Y. Li, Q. Lan, X.-S. Wang, *Angew. Chem. Int. Ed.*, 2016, **55**, 3491; (c) Z. He, T. Luo, M. Hu, Y. Cao, J. Hu, *Angew. Chem. Int. Ed.*, 2012, **51**, 3944; (d) Q. Chen, C. Wang, J. Zhou, Y. Wang, Z. Xu, R. Wang, *J. Org. Chem.*, 2016, **81**, 2639; (e) H.-R. Zhang, D.-Q. Chen, Y.-P. Han, Y.-F. Qiu, D.-P. Jin, X.-Y. Liu, *Chem. Commun.*, 2016, **52**, 11827.

8 M. K. Schwaebe, J. R. McCarthy, J. P. Whitten, *Tetrahedron Lett.*, 2000, **41**, 791.

9 (a) T. Taguchi, O. Kitagawa, T. Morikawa, T. Nishiwaki, H. Uehara, H. Endo, Y. Kobayashi, *Tetrahedron Lett.*, 1986, **27**, 6103; (b) K. Sato, R. Kawata, F. Ama, M. Omote, A. Ando, I. Kumadaki, *Chem. Pharm. Bull.*, 1999, **47**, 1013; (c) J. Zhu, W. Zhang, L. Zhang, J. Liu, J. Zheng, J. Hu, *J. Org. Chem.*, 2010, **75**, 5505; (d) P. S. Fier, J. F. Hartwig, *J. Am. Chem. Soc.*, 2012, **134**, 5524; (e) G. K. S. Prakash, S. K. Ganesh, J.-P. Jones, A. Kulkarni, K. Masood, J. K. Swabeck, G. A. Olah, *Angew. Chem. Int. Ed.*, 2012, **51**, 12090; (f) D. Chang, Y. Gu, Q. Shen, *Chem. Eur. J.*, 2015, **21**, 6074.

10 (a) K. Nakamura, T. Nishikata, *ACS Catal.*, 2017, **7**, 1049; (b) J.-J. Ma, W.-B. Yi, *Org. Biomol. Chem.*, 2017, **15**, 4295.

11 Z.-Y. Long, Q.-Y. Chen, *J. Org. Chem.*, 1999, **64**, 4775.

12 S. Pignard, C. Lopin, G. Gouhier, S. R. Piettre, *J. Org. Chem.*, 2006, **71**, 31.

13 T. Yokomatsu, K. Suemune, T. Murano, S. Shibuya, *J. Org. Chem.*, 1996, **61**, 7207.

14 M. Ke, Q. Feng, K. Yang, Q. Song, *Org. Chem. Front.*, 2016, **3**, 150.

15 The reaction might proceed through vinyl radical B, which is prone to isomerize due to its a low isomerization barrier. When its lifetime increases, it would have more chance to isomerize. Since lifetime of the vinyl radical B is elongated by stabilizing effect of the electron-withdrawing substituent on phenyl ring (see ref. 11), *E*/*Z* ratio of the corresponding product will decrease.

16 H. Chen, X. Wang, M. Guo, W. Zhao, X. Tang, G. Wang, *Org. Chem. Front.*, 2017, **4**, 2403.

17 Y. Lv, W. Pu, Q. Chen, Q. Wang, J. Niu, Q. Zhang, *J. Org. Chem.*, 2017, **82**, 8282.

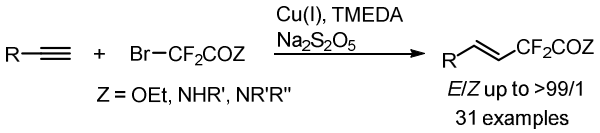
18 F. Zhang, Q.-Q. Min, X. Zhang, *Synthesis*, 2015, **47**, 2912.

19 M.-C. Belhomme, D. Dru, H.-Y. Xiong, D. Cahard, T. Besset, T. Poisson, X. Pannecoucke, *Synthesis*, 2014, **46**, 1859.

20 G. Zhang, H. Yi, G. Zhang, Y. Deng, R. Bai, H. Zhang, J. T. Miller, A. J. Kropf, E. E. Bunel, A. Lei, *J. Am. Chem. Soc.*, 2014, **136**, 924.

21 (a) C. M. R. Abreu, P. V. Mendonça, A. C. Serra, A. V. Popov, K. Matyjaszewski, T. Guliashvili, J. F. J. Coelho, *ACS Macro Lett.*, 2012, **1**, 1308; (b) C. M. R. Abreu, A. C. Serra, A. V. Popov, K. Matyjaszewski, T. Guliashvili, J. F. J. Coelho, *Polym. Chem.*, 2013, **4**, 5629.

View Article Online
DOI: 10.1039/C8OB00256H



A highly regioselective copper-mediated hydrodifluoroalkylation of alkynes with ethyl bromodifluoroacetate or bromodifluoroacetamides has been developed.