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Copper-mediated trifluoromethylation of propiolic acids: facile synthesis of α-trifluoromethyl ketones†

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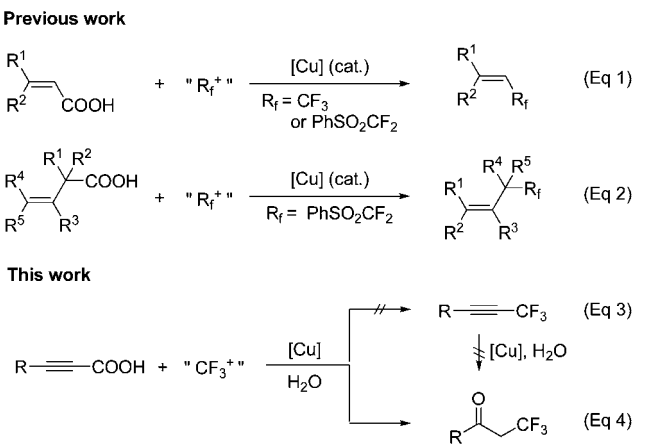
Copper-mediated decarboxylative trifluoromethylation provides a new protocol for the efficient preparation of α-trifluoromethyl ketones from propiolic acids. It was found that water is involved as a reactant in the reaction, which is significantly different from the previously reported decarboxylative fluoroalkylation reactions.

Trifluoromethylated compounds are of particular interest in the fields of materials, agrochemicals and pharmaceuticals owing to the unique characteristics of the trifluoromethyl (CF_3) group.[1] In drug design, for instance, incorporation of CF_3 group(s) into a lead molecule can dramatically alter the latter's metabolic stability, lipophilicity, and bioavailability.[1b,c,2] Hence, it has been of great synthetic interest to develop new efficient methods for the incorporation of CF_3 group(s) into organic molecules.[3] α-Trifluoromethyl ketones are useful starting materials for the synthesis of a wide range of fluorinated building blocks and complex trifluoromethylated compounds.[4] The most commonly used methods to prepare α-trifluoromethyl ketones are based on the electrophilic and radical trifluoromethylation of enolates or their equivalents.[5–8] Other methods based on the transformation of carbonyl compounds include the homologation of aldehydes and ketones using trifluoromethyl diazomethane (F_3CCHN_2),[9] and trifluoromethylation of α-haloketones using trifluoromethylcopper reagent.[10] Recently, Xiao and co-workers reported that α-trifluoromethyl ketones could be obtained from the reactions between alkenes and trifluoromethyl radical species in the presence of air; however, the yields were usually low.[11] In conjunction with our interest in synthesizing α-trifluoromethyl carbonyl compounds,[12] we have been interested in seeking new efficient methods to synthesize α-trifluoromethyl ketones with metal-mediated trifluoromethylations. In this communication, we wish to report a new protocol for the efficient synthesis of α-trifluoromethyl ketones through the copper-mediated decarboxylative trifluoromethylation of propiolic acids with Togni's electrophilic trifluoromethylating agent.

Very recently, we reported that Cu(II)-catalyzed decarboxylative fluoroalkylation reactions between α,β- or β,γ-unsaturated carboxylic acids and electrophilic fluoroalkylating agents could provide fluoroalkylated alkenes in high yields (Scheme 1, eqn (1) and (2)).[13] In our effort to explore the synthetic application of other unsaturated carboxylic acids, we initially surmised that Cu(II)-catalyzed or mediated reaction between propiolic acids and electrophilic trifluoromethylating agents[14] should give CF_3-substituted alkynes (Scheme 1, eqn (3)). However, it turned out that the decarboxylative trifluoromethylation of propiolic acids gave α-trifluoromethyl ketones (rather than the expected CF_3-substituted alkynes) as the major products (Scheme 1, eqn (4)). Not only does this serendipitous discovery provide a convenient method to prepare various α-trifluoromethyl ketones, it also demonstrates a new reaction mode of copper-mediated decarboxylative fluoroalkylation of unsaturated carboxylic acids (eqn (1)–(4)).[13]

At the outset of our investigation, we chose the reaction between Togni's electrophilic trifluoromethylating agent **1** and 3-phenylpropiolic acid **2a** as a model reaction to survey the reaction conditions. When a mixture of **1** (1.5 equiv.), **2a** (1.0 equiv.) and $Cu(OAc)_2 \cdot H_2O$ (1.5 equiv.) in CCl_4 was heated to reflux temperature under air for 12 h (Table 1, entry 1), reagent **1** decomposed completely and a complicated mixture was generated without any identifiable product. When water was added as a co-solvent,



Scheme 1 Copper-catalyzed or mediated decarboxylative fluoroalkylation reaction of unsaturated carboxylic acids.

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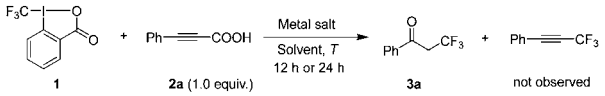
Table 1 Survey of reaction conditions



Entry[a]	**1** (equiv.)	Solvent[b]	Metal salt (equiv.)	Additive (equiv.)	T [°C]	Yield[c] [%]
1	1.5	CCl_4	$Cu(OAc)_2\cdot H_2O$ (1.5)	—	Reflux	0
2	1.5	H_2O–CCl_4 (3 : 2)	$Cu(OAc)_2\cdot H_2O$ (1.5)	—	Reflux	70
3	1.5	H_2O–CCl_4 (3 : 2)	$Zn(OAc)_2\cdot 2H_2O$ (1.5)	—	Reflux	0
4	1.5	H_2O–CCl_4 (3 : 2)	$Ni(OAc)_2\cdot 4H_2O$ (1.5)	—	Reflux	0
5	1.5	H_2O–CCl_4 (3 : 2)	$Pd(OAc)_2\cdot$ (1.5)	—	Reflux	0
6	1.5	H_2O–CCl_4 (3 : 2)	$Cu(OAc)_2\cdot H_2O$ (1.5)	—	RT	15
7	1.5	H_2O–CCl_4 (3 : 2)	$Cu(OAc)_2\cdot H_2O$ (1.5)	TMEDA (1.0)	RT	34
8	1.5	H_2O–DCM (3 : 2)	$Cu(OAc)_2\cdot H_2O$ (1.5)	TMEDA (1.0)	RT	70
9	1.5	H_2O–DCM (3 : 2)	$Cu(OAc)_2\cdot H_2O$ (1.5)	TMEDA (2.0)	RT	80
10	1.5	H_2O–DCM (3 : 2)	$Cu(OAc)_2\cdot H_2O$ (2.0)	TMEDA (2.0)	RT	85
11	2.0	H_2O–DCM (3 : 2)	$Cu(OAc)_2\cdot H_2O$ (2.0)	TMEDA (2.0)	RT	89
12	2.0	H_2O–DCM (3 : 2)	$Cu(OAc)_2\cdot H_2O$ (2.0)	TMEDA (2.5)	RT	93
13	1.0	H_2O–DCM (3 : 2)	$Cu(OAc)_2\cdot H_2O$ (2.0)	TMEDA (2.5)	RT	60
14	0.5	H_2O–DCM (3 : 2)	$Cu(OAc)_2\cdot H_2O$ (2.0)	TMEDA (2.5)	RT	58
15	2.0	H_2O–DCE (3 : 2)	$Cu(OAc)_2\cdot H_2O$ (2.0)	TMEDA (2.5)	RT	81
16	2.0	H_2O–CCl_4 (3 : 2)	$Cu(OAc)_2\cdot H_2O$ (2.0)	TMEDA (2.5)	RT	77
17	2.0	H_2O–DCM (3 : 2)	$CuF_2\cdot H_2O$ (2.0)	TMEDA (2.5)	RT	69
18	2.0	H_2O–DCM (3 : 2)	CuOAc (2.0)	TMEDA (2.5)	RT	28
19	2.0	H_2O–DCM (3 : 2)	CuCl (2.0)	TMEDA (2.5)	RT	Trace
20	1.5	H_2O–CCl_4 (3 : 2)	$Cu(OAc)_2\cdot H_2O$ (0.3)	TMEDA (0.5)	40	65
21	3.0	H_2O–DCE (3 : 2)	$Cu(OAc)_2\cdot H_2O$ (0.2)	TMEDA (2.0)	40	71

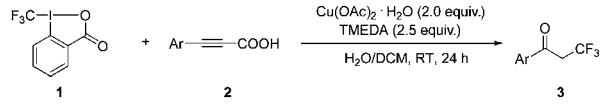
[a] For entries 1–5, reaction time is 12 h; for entries 6–21, reaction time is 24 h. [b] The data in the parentheses refer to the volume ratio. [c] Determined by ^{19}F NMR spectroscopy using $PhCF_3$ as an internal standard.

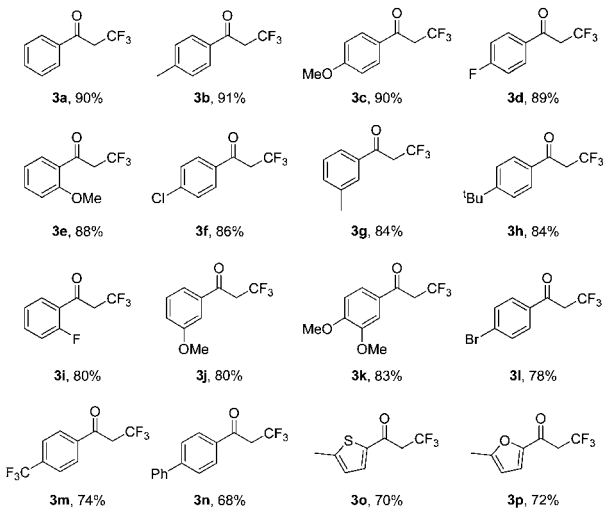
although no decarboxylative cross-coupling product (3,3,3-trifluoroprop-1-ynyl)benzene ($PhC{\equiv}CCF_3$) was detected, to our surprise and delight, trifluoromethyl ketone **3a** was formed in 70% yield as the major product (Table 1, entry 2). After a careful screening of the reaction conditions, we found that the selection of the appropriate metal salt, solvent, additive, and temperature was crucial for the formation of **3a**. Among several divalent metal salts that were tested, salts of metals other than copper, such as $Ni(OAc)_2\cdot 4H_2O$, $Zn(OAc)_2\cdot 2H_2O$, and $Pd(OAc)_2$, were unable to promote the formation of **3a** or $PhC{\equiv}CCF_3$, and a complete decomposition of reagent **1** was observed (Table 1, entries 2–5). When the reaction was performed at room temperature, a rather low yield of **3a** was obtained (Table 1, entry 6); however, using *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA) as an additive (for details, see Table S-1 in ESI†) and changing the solvent from CCl_4 to CH_2Cl_2 were found to be highly beneficial for this reaction (Table 1, entries 7 and 8). Further optimization of the reactant ratio (Table 1, entries 9–16) revealed that an excellent yield (93%) of **3a** was obtained when **1**, **2a**, $Cu(OAc)_2\cdot H_2O$, and TMEDA in a molar ratio of 2.0 : 1.0 : 2.0 : 2.5 were stirred in H_2O–DCM (3 : 2 v/v) at room temperature for 24 h (Table 1, entry 12); meanwhile, trace amount of phenylacetylene ($PhC{\equiv}CH$) was observed as a side product by GC-MS. As for the valence of copper, the divalent copper salts such as $Cu(OAc)_2\cdot H_2O$ and $CuF_2\cdot H_2O$ were superior to the monovalent ones such as CuOAc and CuCl (Table 1, entries 12 and 17–19). When the amount of $Cu(OAc)_2\cdot H_2O$ was reduced to a substoichiometric amount, the yield of **3a** dropped significantly, albeit two-fold excess of reagent **1** was used (Table 1, entries 20–21).

By using the optimized reaction conditions (Table 1, entry 12) as standard, we examined the substrate scope of the present trifluoromethylation reaction. The results are summarized in Table 2. The reaction proved to be general and amenable to a range of structurally diverse substrates **2a–p**, and the desired products **3a–p** were produced in high yields. We found that these reactions are not sensitive to the electronic nature of the aryl (or heteroaryl) groups in propiolic acids, that is, both electron-rich and electron-poor aryl-substituted propiolic acids could react with **1** to give products in high yields (see **3b–m**). However, the alkyl-substituted propiolic acids were not suitable substrates under the aforementioned reaction conditions. For example, when alkyl-substituted propiolic acid **4a** was subjected to the reaction conditions, the desired product **5a** was observed in only 10% yield (determined by ^{19}F NMR), and 83% of reagent **1** remained unreacted (^{19}F NMR) and 80% of the **4a** was recovered (Scheme 2). The sluggishness of the reaction is probably due to the low reactivity of alkyl-substituted propiolic acids at room temperature. Therefore, the development of new reaction conditions that are applicable for the transformation of alkyl-substituted propiolic acids is necessary.

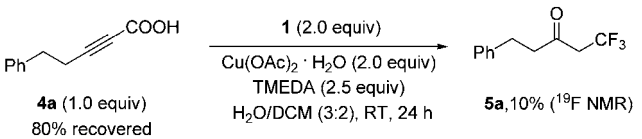
Subsequently, we chose 5-phenylpent-2-ynoic acid (**4a**) as a model substrate to further survey the reaction conditions using

Table 2 Trifluoromethylation of aryl-substituted propiolic acids **2**[a,b]



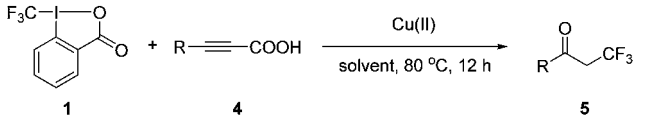


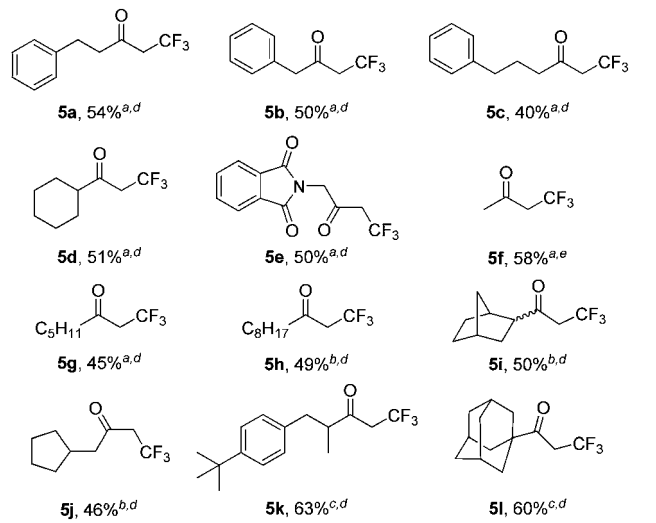
[a] The reaction conditions are as follows: **1** (0.8 mmol), **2** (0.4 mmol), $Cu(OAc)_2 \cdot H_2O$ (0.8 mmol), TMEDA (1.0 mmol), DCM (3 mL), and H_2O (4.5 mL) were stirred at room temperature for 24 h. [b] Isolated yield.



Scheme 2 Attempted trifluoromethylation of **4a** under the optimized conditions for aryl-substituted propiolic acids.

Table 3 Trifluoromethylation of alkyl-substituted propiolic acids **4**

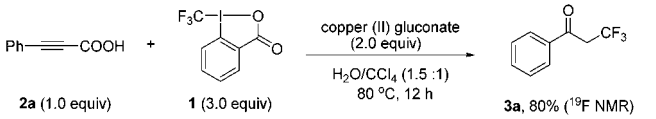




[a] The reaction conditions are as follows: **1** (2.4 mmol), **4** (0.8 mmol), copper(II) gluconate (1.6 mmol), CCl_4 (3.0 mL), and H_2O (4.5 mL) were stirred at 80 °C for 12 h. [b] The reaction conditions are as follows: **1** (2.4 mmol), **4** (0.8 mmol), copper(II) gluconate (1.6 mmol), DMSO (3.0 mL), and H_2O (4.5 mL) were stirred at 80 °C for 12 h. [c] The reaction conditions are as follows: **1** (0.6 mmol), **4** (0.2 mmol), copper(II) tartrate trihydrate (0.2 mmol), DMSO (2.0 mL), and H_2O (3.0 mL) were stirred at 80 °C for 12 h. [d] Isolated yield. [e] Determined by ^{19}F NMR spectroscopy using $PhOCF_3$ as an internal standard.

a variety of copper(II) salts at elevated temperatures (for details, see Table S-2 in the ESI†). We found that when copper(II) gluconate (2.0 equiv.) was used as a promoter and H_2O–CCl_4 (3 : 2 v/v) was used as a mixed solvent system, the reaction could proceed smoothly at 80 °C for 12 h, and the desired products were obtained in moderate yields (see Table 3, **5a–g**). Notably, it was found that the use of H_2O–DMSO (3 : 2 v/v) as mixed solvent resulted in the trifluoromethylation of substrates **4h–j** in higher yields than using H_2O–CCl_4 (3 : 2 v/v). Moreover, we found that copper(II) tartrate behaved as a better catalyst (compared to copper(II) gluconate) for reaction with substrates **4k** and **4l** in H_2O–DMSO (3 : 2 v/v), and products **5k** and **5l** were obtained in 63% and 60% yields, respectively. After examining the scope of alkyl-substituted propiolic acids, the aryl-substituted propiolic acid **2a** was subjected to these new reaction conditions, and the desired product **3a** was obtained in 80% yield (^{19}F NMR) (Scheme 3). In general, the trifluoromethylation with alkyl-substituted propiolic acids **4** (see Table 3) gave relatively lower yields than those for aryl-substituted ones **2** (as shown in Table 2). Similar to what we discovered previously,[13] the current trifluoromethylation system tolerates water and air, which makes the reaction easy to handle.

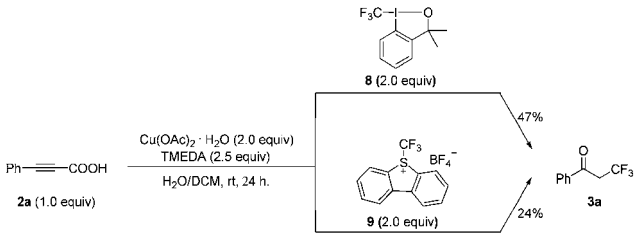
To elucidate whether the products obtained in this reaction and the reported trifluoromethylation of acrylic acids[13a] are substrate-dependent or condition-dependent, the decarboxylative trifluoromethylation of acrylic acids using the conditions of decarboxylative oxytrifluoromethylation of propiolic acids, and *vice versa*, were investigated. In the reaction between 3-(4-methoxyphenyl)acrylic acid (**6**) and reagent **1** under the reaction conditions as shown in Table 2, only vinylic trifluoromethylation product **7** was observed in 39% yield (determined by ^{19}F NMR). On the other hand, when 3-(4-methoxyphenyl)propiolic acid (**2c**) was subjected to the reported conditions for trifluoromethylation of acrylic acids, only α-trifluoromethyl ketone **3c** was obtained in 59% yield (Scheme 4). These results suggest that the propiolic acids are more reactive



Scheme 3 Trifluoromethylation of **2a** using the reaction conditions for alkyl-substituted propiolic acids.

than the acrylic acids and that the products observed in these decarboxylative trifluoromethylations were dependent on the structures of substrates rather than the reaction conditions.

To compare the influence of different electrophilic trifluoromethylating agents on this reaction, we investigated the trifluoromethylation of aryl-substituted propiolic acid **2a** with reagent **8** and Umemoto's reagent **9** as the CF_3^+ source under the similar conditions as shown in Table 1, entry 12 (Scheme 2). After 24 h, the reactions with reagent **8** and **9** afforded **3a** in 47% and 24% yields, respectively. These results suggest that reagent **1** (in the presence of copper acetate) is a much more effective CF_3^+ source than reagents **8** and **9** (Scheme 5).

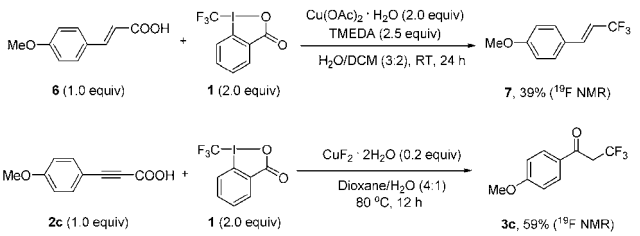


Scheme 5 The effect of different CF_3^+ sources.

To gain more mechanistic insights into this decarboxylative trifluoromethylation of propiolic acids, several experiments were conducted to figure out the possible pathways (see eqn (5)–(9)).

Firstly, the trifluoromethylation of acetylenes substituted with a trimethylsilyl group, which was known to be a good leaving group in electrophilic fluorination of alkenes,[15] was tested. The reaction between 1-phenyl-2-(trimethylsilyl)acetylene (**10**) and reagent **1** gave neither CF_3-substituted alkyne **11** nor α-trifluoromethyl ketone **3a** (eqn (5)). This result indicates that the COOH group in propiolic acids plays an important role in promoting the trifluoromethylation reaction; presumably the chelation of COOH with copper can facilitate the interaction of the trifluoromethylating reagent with the triple bond.

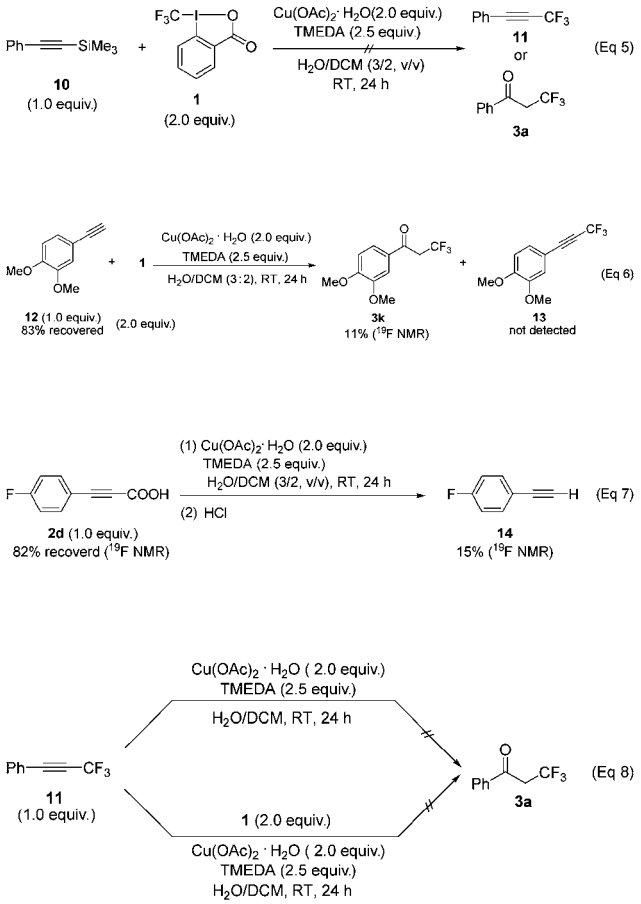
Secondly, because aryl or alkyl acetylenes were detected as the side products in this trifluoromethylation reaction, we investigated the feasibility of hydrodecarboxylation of propiolic acids followed by trifluoromethylation of the acetylenes. On one hand, exposing **2d** to the otherwise same trifluoromethylation conditions except that the reagent **1** was not added showed that the acetylene **14** could be formed in only 15% yield (determined by ^{19}F NMR) after 24 h, whereas 82% (determined by ^{19}F NMR) of the starting material **2d** was recovered (eqn (7)). On the other hand, the trifluoromethylation of 4-ethynyl-1,2-dimethoxybenzene (**12**) with reagent **1** could lead to the formation of **3k**; however, the yield of **3k** (11% based on ^{19}F NMR) was much lower than that (83% based on ^{19}F NMR) in the trifluoromethylation of **2k** under similar conditions, and 83% of the starting material **12** was recovered (eqn (6)). The sluggishness of these two reactions indicates that hydrodecarboxylation of propiolic acids followed by electrophilic trifluoromethylation of acetylenes is less likely to be a major pathway for the current transformation.

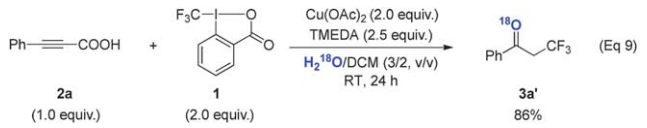


Scheme 4 The different reactivity of propiolic acids and α,β-unsaturated carboxylic acids.

Thirdly, although no trifluoromethyl-substituted alkynes were detected in these reactions, the possibility of involvement of CF_3-substituted alkynes as the intermediate species in the formation of α-trifluoromethyl ketones was investigated. When trifluoromethyl alkyne **11** was subjected to the reaction conditions in the presence and absence of reagent **1**, α-trifluoromethyl ketone **3a** was not observed in both cases (eqn (8)), suggesting that trifluoromethyl alkynes were not involved in the process of trifluoromethylation of propiolic acids.

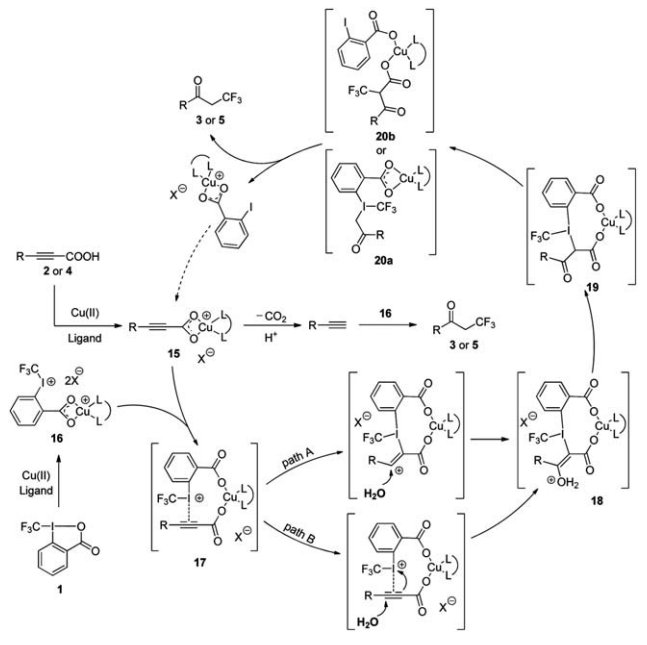
Finally, the isotopic labeling experiment was carried out in the reaction between **1** and substrate **2a**. When [^{18}O]-water with 97% abundance of ^{18}O was used as a co-solvent instead of normal water, the ^{18}O-labelled product **3a′** (with 89% abundance of ^{18}O) was obtained in 86% yield (eqn (9)). This result clearly illustrates that water was involved as a reactant (oxygen donor) in the present trifluoromethylation process.





Based on these experimental results, we propose that the copper(II)-mediated trifluoromethylation of substituted propiolic acids might proceed *via* the mechanism as depicted in Scheme 6. Initially, a substituted propiolic acid **2** or **4** coordinates with copper(II) to generate species **15**, and at the same time copper(II) activates **1**, leading to CF_3-containing intermediate **16**. Subsequently, transmetallation of the species **15** with CF_3-containing intermediate **16** generates intermediate **17**. A water-involved reaction with **17** affords intermediate **18.** It is worth emphasizing that there are two possible pathways (path A or B) in the process of forming intermediate **18**. In path A, the triple bond in intermediate **17** firstly attacks the intramolecular iodine atom to form an alkenyl carbocation intermediate, then water attacks the alkenyl carbocation intermediate to give the intermediate **18**; and in Path B, water attacks the triple bond at the same time as the intramolecular attacking of the triple bond with the iodine atom to form intermediate **18**. The latter species undergoes isomerization to give intermediate **19**. Then, the intermediate **19** undergoes decarboxylation to form intermediate **20a** or reductive elimination to give intermediate **20b**. Finally, **20a** or **20b** undergoes hydrodecarboxylation or reductive elimination to give α-trifluoromethyl ketone **3** or **5**. In addition, hydrodecarboxylation of species **15** followed by electrophilic trifluoromethylation with intermediate **16** may constitute a minor pathway for the formation of **3** and **5**.

In summary, we have described a new reaction mode of metal-mediated decarboxylative fluoroalkylation, that is, Cu(II)-mediated (or catalyzed) trifluoromethylation of substituted propiolic acids using Togni's reagent **1** in the presence of water to give α-trifluoromethyl ketone products in moderate to high yields. The mechanistic study shows that water is involved in the reaction as an oxygen donor and the reaction mechanism of the present trifluoromethylation is different from those of the previously reported trifluoromethylation of α,β- or β,γ-unsaturated carboxylic acids,[13] which is fundamentally very intriguing. The present trifluoromethylation method provides a new protocol for the efficient preparation of α-trifluoromethyl ketones from readily available propiolic acids and promises to find synthetic applications in many fields.



Scheme 6 Proposed reaction mechanism.

Acknowledgements

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Notes and references

1 (*a*) M. Shimizu and T. Hiyama, *Angew. Chem., Int. Ed.*, 2005, **44**, 214; (*b*) K. Müller, C. Faeh and F. Diederich, *Science*, 2007, **317**, 1881; (*c*) W. K. Hagmann, *J. Med. Chem.*, 2008, **51**, 4359–4369; (*d*) K. L. Kirk, *Org. Process Res. Dev.*, 2008, **12**, 305–321; (*e*) *Fluorine in Medicinal Chemistry and Chemical Biology*, ed. I. Ojima, Wiley, Chichester, 2009; (*f*) J.-P. Bégué and D. Bonnet-Delpon, *Bioorganic and Medicinal Chemistry of Fluorine*, Wiley-VCH, Weinheim, 2008; (*g*) *Organofluorine Compounds: Chemistry and Application*, ed. T. Hiyama, Springer, Berlin, 2000, pp. 183–234; (*h*) *Organofluorine Chemistry: Principles and Commercial Applications*, ed. R. E. Banks, B. E. Smart and C. J. Tatlow, Springer, New York, 1994, pp. 237–262.

2 (*a*) S. Purser, P. R. Moore, S. Swallow and V. Gouverneur, *Chem. Soc. Rev.*, 2008, **37**, 320; (*b*) *Organofluorine Compounds in Medicinal Chemistry & Biomedical Applications*, ed. R. Filler, Y. Kobayashi and L. M. Yagupolskii, Elserbier, Amsterdam, 1993.

3 For reviews on trifluoromethylation, see: (*a*) M. Schlosser, *Angew. Chem., Int. Ed.*, 2006, **45**, 5432; (*b*) J.-A. Ma and D. Cahard, *J. Fluorine Chem.*, 2007, **128**, 975; (*c*) J.-A. Ma and D. Cahard, *Chem. Rev.*, 2008, **108**, PR1; (*d*) G. K. S. Prakash and S. Chacko, *Curr. Opin. Drug Discovery Dev.*, 2008, **11**, 793; (*e*) O. A. Tomashenko and V. V. Grushin, *Chem. Rev.*, 2011, **111**, 4475; (*f*) T. Besset, C. Schneider and D. Cahard, *Angew. Chem., Int. Ed.*, 2012, **51**, 5048; (*g*) Z. Jin, G. B. Hammond and B. Xu, *Aldrichimica Acta*, 2012, **45**, 67.

4 (*a*) A. B. Ash, M. P. L. Montagne and A. Markovac, US 3,940,404, 1976; (*b*) G. Alvernhe, B. Langlois, A. Laurent, I. Le Drean, A. Selmi and M. Weissenfels, *Tetrahedron Lett.*, 1991, **32**, 643; (*c*) N. A. Petasis and M. Myslinska, US Patent Appl. 20090247766; (*d*) P. F. Wang, N. Li, W. M. Liu, S. T. Lee and C. S. Lee, US Patent Appl. 20090102356; (*e*) I. C. Mukhejee, S. H. Ko, J. P. Stables, M. K. Patel and M. L. Brown, *Bioorg. Med. Chem.*, 2004, **12**, 979.

5 (*a*) G. Q. Shi, X. H. Huang and F. Hong, *J. Chem. Soc., Perkin Trans. 1*, 1996, 763; (*b*) K. Sato, M. Higashinagata, T. Yuki, A. Tarui, M. Omote, I. Kumadaki and A. Ando, *J. Fluorine Chem.*, 2008, **129**, 51; (*c*) H. Rudler, A. Parlier, C. Denneval and P. Herson, *J. Fluorine Chem.*, 2010, **131**, 738; (*d*) V. M. Muzalevskiy, V. G. Nenajdenko, A. Y. Rulev, I. A. Ushakov, G. V. Romanenko, A. V. Shastin, E. S. Balenkova and G. Haufe, *Tetrahedron*, 2009, **65**, 6991; (*e*) R. A. Cox, E. Grant, T. Whitaker and T. Tidwell, *Can. J. Chem.*, 1990, **68**, 1876; (*f*) N. Yoneda, S. Matsuoka, N. Miyaura, T. Fukuhara and A. Suzuki, *Bull. Chem. Soc. Jpn.*, 1990, **63**, 2124; (*g*) N. Kamigata, K. Udodaira and T. Shimizu, *Phosphorus, Sulfur Silicon Relat. Elem.*, 1997, **129**, 155.

6 For examples of electrophilic α-trifluoromethylation methods, see: (*a*) T. Umemoto and S. Ishihara, *J. Am. Chem. Soc.*, 1993, **115**, 2156; (*b*) T. Umemoto and K. Adachi, *J. Org. Chem.*, 1994, **59**, 5692; (*c*) A. Togni, *Chimia*, 2008, **62**, 261; (*d*) A. E. Allen and D. W. C. MacMillan, *J. Am. Chem. Soc.*, 2010, **132**, 4986.

7 For examples of radical α-trifluoromethylation methods, see: (*a*) Y. Itoh and K. Mikami, *Org. Lett.*, 2005, **7**, 4883; (*b*) Y. Itoh and K. Mikami, *Tetrahedron*, 2006, **62**, 7199; (*c*) K. Miura, M. Taniguchi, K. Nozaki, K. Oshima and K. Utimoto, *Tetrahedron Lett.*, 1990, **31**, 6391; (*d*) P. V. Pham, D. A. Nagib and D. W. C. MacMillan, *Angew. Chem., Int. Ed.*, 2011, **50**, 6119; (*e*) D. A. Nagib, M. E. Scott and D. W. C. MacMillan, *J. Am. Chem. Soc.*, 2009, **131**, 10875.

8 For examples of organometallic α-trifluoromethylation methods, see: (*a*) K. Sato, T. Yuki, R. Yamaguchi, T. Hamano, A. Tarui, M. Omote, I. Kumadaki and A. Ando, *J. Org. Chem.*, 2009, **74**, 3815; (*b*) K. Sato, A. Tarui, M. Omote, A. Ando and I. Kumadaki, *Synthesis*, 2010, 1865.

9 B. Morandi and E. K. Carreira, *Angew. Chem., Int. Ed.*, 2011, **50**, 9085; and references therein.

10 P. Novak, A. Lishchynskyi and V. V. Grushin, *J. Am. Chem. Soc.*, 2012, **134**, 16167.

11 C. P. Zhang, Z. L. Wang, Q. Y. Chen, C. T. Zhang, Y. C. Gu and J. C. Xiao, *Chem. Commun.*, 2011, **47**, 6632.

12 M. Hu, C. Ni and J. Hu, *J. Am. Chem. Soc.*, 2012, **134**, 15257.

13 (*a*) Z. He, T. Luo, M. Hu, Y. Cao and J. Hu, *Angew. Chem., Int. Ed.*, 2012, **51**, 3944; (*b*) Z. He, M. Hu, T. Luo and L. Li, *Angew. Chem., Int. Ed.*, 2012, **51**, 11545.

14 (*a*) R. Koller, K. Stanek, D. Stolz, R. Aardoom, K. Niedermann and A. Togni, *Angew. Chem., Int. Ed.*, 2009, **48**, 4332; (*b*) A. E. Allen and D. W. C. MacMillan, *J. Am. Chem. Soc.*, 2010, **132**, 4986; (*c*) K. Niedermann, N. Frueh, E. Vinogradova, M. S. Wiehn, A. Moreno and A. Togni, *Angew. Chem., Int. Ed.*, 2011, **50**, 1059; (*d*) R. Koller, Q. Huchet, P. Battaglia, J. M. Welch and A. Togni, *Chem. Commun.*, 2009, 5993; (*e*) S. Fantasia, J. M. Welch and A. Togni, *J. Org. Chem.*, 2010, **75**, 1779.

15 B. Greedy and V. Gouverneur, *Chem. Commun.*, 2001, 233.