J|A|C|S
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY

Communication
pubs.acs.org/JACS

Copper-Mediated Trifluoromethylation of α-Diazo Esters with $TMSCF_3$: The Important Role of Water as a Promoter

Mingyou Hu, Chuanfa Ni, and Jinbo Hu*

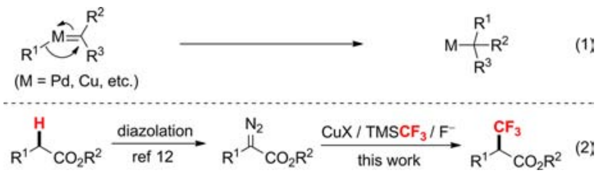
Key Laboratory of Organofluorine Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 345 Ling-Ling Road, Shanghai 200032, China

Ⓢ *Supporting Information*

ABSTRACT: Copper-mediated trifluoromethylation of α-diazo esters with $TMSCF_3$ reagent has been developed as a new method to prepare α-trifluoromethyl esters. This trifluoromethylation reaction represents the first example of fluoroalkylation of a non-fluorinated carbene precursor. Water plays an important role in promoting the reaction by activating the "$CuCF_3$" species prepared from CuI/$TMSCF_3$/CsF (1.0:1.1:1.1). The scope of this trifluoromethylation reaction is broad, and its efficiency is demonstrated in the synthesis of a variety of aryl-, benzyl-, and alkyl-substituted 3,3,3-trifluoropropanoates.

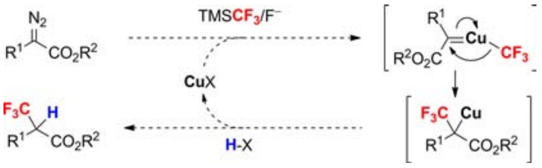
Trifluoromethylated compounds are of interest in pharmaceutical and agrochemical research because of the unique role of the CF_3 group in enhancing the bioactivity of organic molecules.[1] Among various transition-metal-assisted methods for incorporating CF_3 into arenes or alkenes,[2] copper-mediated trifluoromethylation is most extensively studied due to its high efficiency and the relatively low cost of Cu.[2c] Importantly, Cu-involved trifluoromethylation of aryl or vinyl halides often proceeds smoothly in the absence of an exogenous ligand.[3] On the other hand, Cu-based trifluoromethylation of sp^3 carbon atoms is much less explored,[4−7] most work focused on constructing CF_3-bearing secondary or tertiary carbon centers via allylic or benzylic trifluoromethylation reactions,[4,5] with only a very few examples of α-trifluoromethylation of ketones and aldehydes.[6] To date, a general method for introducing CF_3 group(s) into the α-position of aliphatic carboxylic esters is conspicuously missing.[7,8]

Transition-metal−carbene species possess remarkably versatile reactivity and have been widely used in organic synthesis to construct structurally diverse molecules.[9] Among many unique transformations based on these species, migratory insertion of a carbene ligand into a transition metal−carbon bond is useful for constructing a functionalized anionic carbon center for further transformations (eq 1).[9a,e] Although carbene insertion into Pd−C bonds has been exploited for various cross-coupling reactions,[9a,e] carbene insertion into Cu−C bonds has received less attention.[10,11] Examples in the latter case using diazo compounds as carbene sources include Cu-catalyzed polymerization of diazoalkenes,[10a] the stoichiometric reaction between pentafluorophenylcopper and diazoacetate,[10b] and Cu-catalyzed reactions between alkynes (or heteroarenes) and *N*-tosylhydrazones (precursors for diazo compounds).[10c−e] Burton et al. reported CF_2-homologation reactions of perfluorinated organocoppers (R_fCu) using trifluoromethylcopper species ("$CuCF_3$") as the difluorocarbene source,[11] which was believed to proceed through insertion of difluoromethylene into the R_f−Cu bond.[11b] However, to our knowledge, there has been no report on the insertion of a non-fluorinated carbene into a CF_3−Cu bond. Considering that diazo compounds have been widely used as carbene precursors,[12] we envisioned that Cu-mediated (or catalyzed) cross-coupling of α-diazo esters and Ruppert−Prakash reagent ($TMSCF_3$)[13] could result in facile formation of α-trifluoromethyl esters. Since various α-diazo esters can be easily prepared by diazo-transfer reaction of the corresponding esters,[12] the overall process is equivalent to the trifluoromethylation of an α-C−H bond of an ester with $TMSCF_3$ (eq 2).



Initially, we speculated that "$CuCF_3$" generated from $TMSCF_3$ and a Cu(I) salt could react with α-diazo esters, forming a trifluoromethylcopper−carbene species that would undergo CF_3-migratory insertion and subsequent protonation to afford α-trifluoromethyl esters (Scheme 1). However, the attempted reaction between α-diazo ester **1a** and $TMSCF_3$ with a catalytic amount of Cu(I) salt in the presence of a proton source (to regenerate the Cu catalyst) failed due to quick formation of undesired CF_3H. Realizing that the pre-generated "$CuCF_3$" could be used as a relatively stable "CF_3^-" reservoir,[2c] we focused on trifluoromethylation of **1a** using a stoichiometric amount of Cu salt and $TMSCF_3$. When **1a** was added to the pre-generated "$CuCF_3$" (from CuI, $TMSCF_3$, and CsF), only a trace amount of **2a** was detected after acidic workup (Table 1, entry 1).

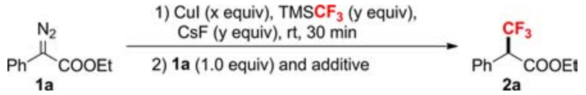
Scheme 1. Speculated Cu-Catalyzed Trifluoromethylation of α-Diazo Esters with $TMSCF_3$



Received: July 18, 2012
Published: August 22, 2012

dx.doi.org/10.1021/ja307058c | *J. Am. Chem. Soc.* 2012, 134, 15257−15260

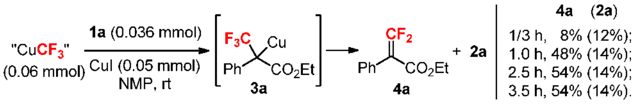
Table 1. Screening of the Reaction Conditions[a]



entry[b]	solvent	additive (equiv)	temp (°C)	time (h)	yield[c] (%)
1	DMF	none	rt	9	<5
2	DMF	CuI (0.05)	rt	9	17
3	DMF	CuI (0.2)	rt	9	29
4	DMF	CuI (0.5)	rt	9	37
5	DMF	CuI (1.2)	rt	9	77
6	NMP	CuI (1.2)	rt	13	88
7	NMP	CuI (1.2) + H_2O (1.0)	rt	13	90
8	NMP	H_2O (1.0)	rt	65	31
9	NMP	H_2O (10)	rt	65	36
10	NMP	H_2O (20)	40	10	69
11	NMP	H_2O (44)	40	10	80
14	NMP	H_2O (66)	40	10	77
13	**NMP**	**H_2O (44)**	**rt**	**20**	**83**
14	NMP	H_2O (44)	50	20	72
15[d]	NMP	H_2O (44)	rt	20	69
16[e]	NMP	H_2O (44)	rt	20	85
17	NMP	*t*BuOH (44)	rt	20	15
18	NMP	EtOH (44)	rt	20	19
19	NMP	MeOH (44)	rt	20	32
20	NMP	PhOH (44)	rt	20	49

[a] All reactions were performed by adding **1a** and additive into the pre-generated "$CuCF_3$". [b] For entries 1−6, reactions were performed on 0.2 mmol scale (x = 1.5, y = 1.8) in DMF or NMP (3 mL + 3 mL) under N_2 atmosphere, and no difluoroolefin **4a** was detected. For entries 7−20, reactions were performed on 0.5 mmol scale (x = 1.5, y = 1.65) in NMP (3 mL + 3 mL) under N_2 atmosphere. [c] Yields were determined by ^{19}F NMR with $PhCF_3$ as an internal standard. [d] x = 1.2, y = 1.32. [e] x = 2.0, y = 2.2.

Scheme 2. Formation of Difluoroolefin[a]



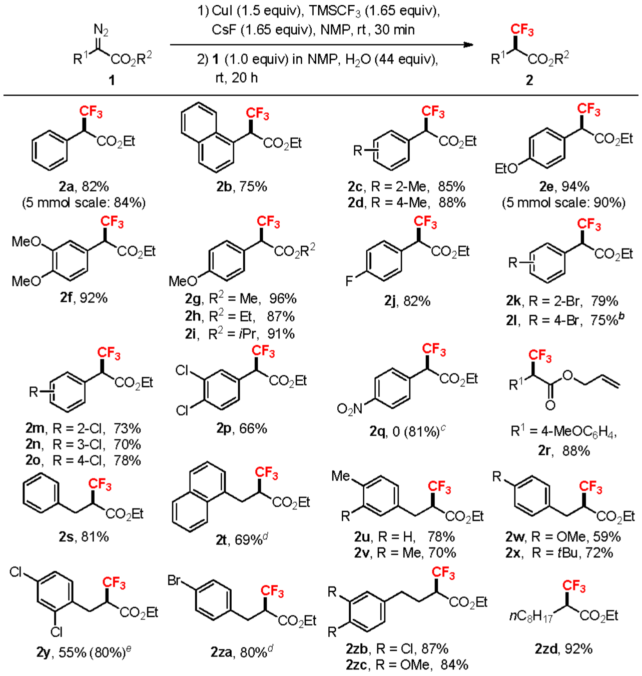
[a] Reaction performed in a sealed NMR tube in NMP (0.6 mL). "$CuCF_3$" was prepared from CuI, $TMSCF_3$, and CsF in a molar ratio of 1.0:1.0:1.3. Yields determined by ^{19}F NMR with $PhCF_3$ as internal standard.

Considering that CsI was formed during the preparation of "$CuCF_3$", coordination of iodide ion (I^-) to Cu may retard the reaction between "$CuCF_3$" and **1a**.[14] We found that adding another portion of CuI after **1a** could significantly promote the reaction; the yield of **2a** increased to 77% when 1.2 equiv of CuI was used (Table 1, entries 2−5). When 1-methylpyrrolidin-2-one (NMP) was used instead of DMF as solvent, an 88% yield of **2a** was obtained (Table 1, entry 6). Interestingly, when the reaction was performed in a sealed tube, *gem*-difluoroolefin **4a** was the major product and **2a** the minor product (Scheme 2). Prolonged reaction time did not significantly increase the yield of **2a** after the initial 20 min (Scheme 2), which demonstrates that **2a** resulted from the quenching of the labile Cu intermediate **3a** by a random proton source (most probably from adventitious water in the reaction system) (Table 1, entries 1−6). When the amount of proton source was insufficient, β-elimination of fluoride from **3a** would lead to difluoroolefin **4a**.

Next, we examined the influence of protic additives on the reaction. Although it is known that long-chain perfluoroalkylcoppers are not so sensitive toward water,[3a] similar data for trifluoromethylcopper species are not available. Indeed, we found that "$CuCF_3$" (prepared from CuI/$TMSCF_3$/CsF in a ratio of 1.0:1.1:1.1) in NMP (1.0 M) in the presence of 66 equiv of water was hardly transformed into CF_3H at low temperatures, and only ~5% of "$CuCF_3$" decomposed at room temperature (rt) in 5 h (see SI section 6.1). When 1.0 equiv of water and 1.2 equiv of CuI were added into the reaction mixture of "$CuCF_3$" and **1a** at rt, the reaction proceeded smoothly to give **2a** in excellent yield with good reproducibility (Table 1, entry 7). *It is quite impressive that water itself could promote the reaction.* **2a** was obtained in 31% yield when 1.0 equiv of water was added (Table 1, entry 8). When <10 equiv of water was used, there was no substantial improvement in the yield (Table 1, entry 9). Notably, when the amount of water was increased to 20 equiv, the yield strikingly improved to 69% (Table 1, entry 10). Further optimization indicated that 44 equiv of water at rt gave the best results (Table 1, entries 11−14). As for the amount of Cu reagent, "$CuCF_3$" prepared from 1.5 equiv of CuI gave better results than those with 1.2 equiv or less, and greater excesses of CuI did not improve the yield significantly (Table 1, entries 15 and 16). Among several protic additives that were tested, *t*BuOH, EtOH, MeOH, and PhOH were found to be inferior to water (Table 1, entries 17−20).

Having identified the optimal reaction conditions (Table 1, entry 13), we further examined the scope of this trifluoromethylation reaction (Table 2). Generally, aryl-, benzyl-, and

Table 2. Trifluoromethylation of Various α-Diazo Esters[a]



[a] Unless otherwise noted, reactions were performed on 0.5 mmol scale by adding **1a** and water into the pre-generated "$CuCF_3$". Yields refer to isolated yields of analytically pure products. [b] Reaction performed at 35 °C. [c] Yield of the reaction performed on 0.2 mmol scale at 60 °C using "$CuCF_3$" (2.0 equiv) as trifluoromethylation reagent, CuI (1.2 equiv), and H_2O (1.0 equiv) as additives is given in parentheses. [d] Reaction performed at 40 °C. [e] The number in the parentheses refers to ^{19}F NMR yield with $PhCF_3$ as an internal standard.

other alkyl-substituted α-diazo esters reacted smoothly to give α-trifluoromethyl esters **2** in moderate to excellent yields, and no aromatic trifluoromethylation occurred in the cases of haloaryl-substituted α-diazo esters (**2j**−**2p** and **2y**−**2zb**). The reaction also tolerates C═C bonds, and no intramolecular cyclopropanation product was detected in the case of **2r**. Aryl α-diazo esters with electron-donating substituents such as methyl, methoxy, and ethoxy groups on the aromatic ring gave **2c**−**2i** in excellent yields, while those with weak electron-withdrawing substituents such as Cl and Br on the aromatic ring gave slightly lower yields of **2k**−**2p**. However, the α-diazo ester **1q**, with a strong electron-withdrawing substituent (NO_2), is unreactive under the optimized conditions. Note that this reaction was not sensitive to the steric bulkiness of the ester group adjacent to the carbenoid carbon, and changing from the methyl to ethyl to isopropyl esters caused no significant drop of yield (**2g**−**2i**). For the benzyl-substituted α-diazo esters **2s**−**2za**, the yields were generally lower than for the normal alkyl-substituted **2zb**−**2zd**, probably due to the competitive 1,2-H shift of the copper−carbene intermediates. For example, in the case of **1y**, besides the desired product **2y**, (*E*)-ethyl 3-(2,4-dichlorophenyl)acrylate was detected as a byproduct (6% by GC-MS). α-Trifluoromethylcarboxylic esters are key intermediates for the synthesis of non-ester pyrethroid insecticides such as flufenprox[15a] (for its concise synthesis from **2e**, see SI sections 5.1−5.3) and fluorinated analogues of non-steroidal anti-inflammatory drugs.[15b]

To gain more insights into the present Cu-mediated trifluoromethylation reaction, the composition of "$CuCF_3$" and its reaction with **1a** and additional CuI were studied with ^{19}F NMR spectroscopy. When CuI, $TMSCF_3$, and CsF were mixed in a 1.0:1.1:1.1 ratio in NMP, apart from the two major trifluoromethylcopper species—tentatively assigned as $[Cu(CF_3)I]^-$ (**5**, −28.7 ppm) and $[Cu(CF_3)_2]^-$ (**6**, −31.9 ppm) according to reported NMR data[16] (neither of them is reactive toward **1a** under this condition)—a small amount of a new species **7** was also observed at −26.9 ppm (Figure 1A). **7** became predominant when 2/3 more equiv of CuI was added into the mixture (Figure 1B). By comparison with the ^{19}F NMR data (−27.2 ppm in DMF, −27.8 ppm in NMP) of "ligandless" $CuCF_3$[3c] prepared from CF_3H and its reactivity with diazo ester **1a** (see SI section 6.3), **7** was tentatively assigned as solvent-stabilized $CuCF_3$, in which the solvent molecule NMP acted as a ligand. *It is likely that the abstraction of* I^- *by CuI (to form* $[CuI_2]^-$*) promotes the formation of* **7**. When **1a** (2/3 equiv) and CuI (2/3 equiv) were added into the pre-generated "$CuCF_3$", a new peak at −26.5 ppm appeared (in addition to **7**) (Figure 1C), and consumption of **8a** was much slower than its formation (Figure 1C, D). Moreover, the N_2 evolution experiment showed that decomposition of diazo compound **1a** was slow (see SI section 6.4). Based on these results, **8a** was tentatively identified as the complex $CuCF_3 \cdot$**1a** rather than carbene-ligated trifluoromethylcopper species **9**.[17]

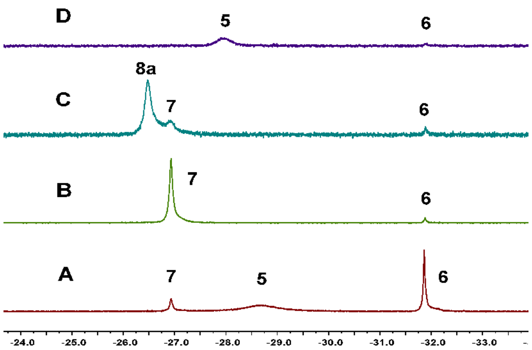
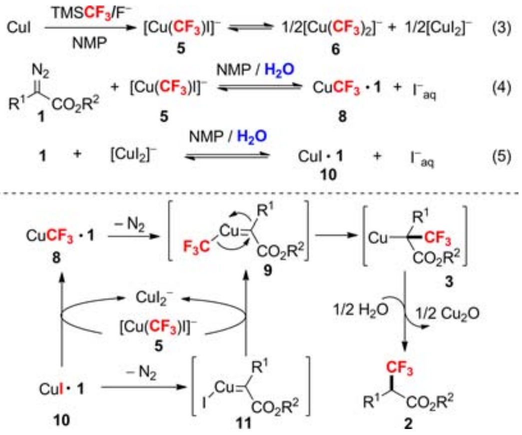


Figure 1. Monitoring CuI-promoted trifluoromethylation of α-diazo ester **1a** with ^{19}F NMR at rt; chemical shifts determined relative to $PhCF_3$ at −63.0 ppm: (A) "$CuCF_3$" prepared from CuI, $TMSCF_3$, and CsF (1.0:1.1:1.1); (B) 5 min after addition of 2/3 equiv of CuI into sample A; and (C) 10 and (D) 60 min after addition of 2/3 equiv of CuI and 2/3 equiv of **1a** into sample A.

Although it is difficult to identify the reactive intermediates by ^{19}F NMR when the reaction is performed in the presence of water (only two trifluoromethylcopper species, assigned as **5** and **6**, were observed; see SI section 6.1), we conjecture that *water serves as a "scavenger" of* I^- *(by the formation of hydrated iodide ion)*[18] *to promote ligand exchange of Cu complexes*, affording reactive species **8** (see Scheme 3) at a low concentration. If water is used in a relatively small amount (<10 equiv), saturation of the mixed solvent by I^- makes the formation of **8** (and subsequent trifluoromethylation) less efficient. Water-promoted iodide complex dissociation was further supported by our observation that the yield of **2a** decreased significantly with addition of external KI into the reaction mixture (see SI section 6.5).

Scheme 3. Proposed Mechanism



Based on our findings, we propose a mechanism for CuI-mediated, water-promoted trifluoromethylation of **1** with $TMSCF_3$ reagent (Scheme 3). First, reaction of CuI, $TMSCF_3$, and CsF (1.0:1.1:1.1) gives the di-coordinated trifluoromethylcopper species **5**, which is in equilibrium with bis(trifluoromethyl)copper species **6** and $[CuI_2]^-$ via ligand redistribution on Cu (eq 3).[19] After addition of α-diazo ester **1** and water, a small amount of reactive intermediate **8** is formed from **5** by water-promoted α-diazo ester−iodide ion exchange (eq 4). Extrusion of N_2 from **8** affords trifluoromethylcopper−carbene species **9**, and subsequent migration of CF_3 to the carbenic carbon atom of **9** results in α-CF_3-substituted Cu species **3**. Final hydrolysis of **3** by water gives **2** and the unreactive Cu_2O.[20] Alternatively, based on the known Cu-catalyzed cyclopropanation between diazo compounds and alkenes,[21] complex **10** generated from $[CuI_2]^-$ by a similar ligand-exchange reaction is also a possible intermediate. Extrusion of N_2 from **10** affords copper−carbene species **11**. Both **10** and **11** can undergo ligand redistribution reactions with **5** to give **8** and **9**, respectively. Although we could not rule out the formation of **10**, **11** is less likely involved in this water-promoted trifluoromethylation reaction, as we did not observe any intramolecular cyclopropanation byproduct in the case of C=C bond-containing α-diazo ester **1r**.

In summary, we disclose a mild Cu-mediated trifluoromethylation of α-diazo esters with $TMSCF_3$ to give α-trifluoromethyl esters, which represents the first fluoroalkylation of a nonfluorinated carbene precursor. Water acts as an efficient activating agent in promoting the reaction with trifluoromethylcopper species prepared from $CuI/TMSCF_3/CsF$ (1.0:1.1:1.1). We propose that hydration of iodide ion facilitates the formation of the intermediate α-diazo ester-coordinated trifluoromethylcopper **8**, and then the reaction occurs via N_2 extrusion and subsequent migratory insertion of the carbene ligand into the Cu−CF_3 bond. This reaction is applicable for α-aryl, α-benzyl, and α-alkyl diazo esters and tolerates bromo, chloro, fluoro, ether, and double bond functionalities. Our present work not only offers a simple and general way to introduce CF_3 group into the α-position of structurally diverse carboxylic esters but also provides fundamentally important insights into the reactivity of the elusive trifluoromethylcopper species. Further investigations of the more detailed reaction mechanism as well as synthetic applications of the reaction are currently underway in our laboratory.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental procedures and characterization for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

jinbohu@sioc.ac.cn

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported by the National Basic Research Program of China (2012CB821600, 2012CB215500) and the National Natural Science Foundation of China (20825209, 20832008).

■ REFERENCES

(1) (a) *Fluorine in Medicinal Chemistry and Chemical Biology* Ojima, I., Ed.; Wiley: Chichester, 2009. (b) Bégué, J.-P.; Bonnet-Delpon, D. *Bioorganic and Medicinal Chemistry of Fluorine*; Wiley-VCH: Weinheim, 2008. (c) Kirk, K. L. *Org. Process Res. Dev.* **2008**, *12*, 305. (d) Müller, K.; Faeh, C.; Diederich, F. *Science* **2007**, *317*, 1881. (e) Hagmann, W. K. *J. Med. Chem.* **2008**, *51*, 4359. (f) Filler, R; Saha, R. *Future Med. Chem.* **2009**, *1*, 777.

(2) Recent reviews: (a) Furuya, T.; Kamlet, A. S.; Ritter, T. *Nature* **2011**, *473*, 470. (b) Roy, S.; Gregg, B. T.; Gribble, G. W.; Le, V.-D.; Roy, S. *Tetrahedron* **2011**, *67*, 2161. (c) Tomashenko, O. A.; Grushin, V. V. *Chem. Rev.* **2011**, *111*, 4475. (d) Besset, T.; Schneider, C.; Cahard, D. *Angew. Chem., Int. Ed.* **2012**, *51*, 5048.

(3) Examples: (a) McLoughlin, V. C. R.; Thrower, J. *Tetrahedron* **1969**, *25*, 5921. (b) Urata, H.; Fuchikami, T. *Tetrahedron Lett.* **1991**, *32*, 91. (c) Zanardi, A.; Novikov, M. A.; Martin, E.; Benet-Buchholz, J.; Grushin, V. V. *J. Am. Chem. Soc.* **2011**, *133*, 20901. (d) Novák, P.; Lishchynskyi, A.; Grushin, V. V. *Angew. Chem., Int. Ed.* **2012**, *51*, 7767. (e) Chen, Q.; Wu, S. *J. Chem. Soc., Chem. Commun.* **1989**, 705.

(4) Cu-mediated/catalyzed allylic trifluoromethylation: (a) Parsons, A. T.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2011**, *50*, 9120. (b) Chu, L.; Qing, F.-L. *Org. Lett.* **2012**, *14*, 2106. (c) See ref 3e. For more examples, see: (d) Mizuta, S.; Galicia-López, O.; Engle, K. M.; Verhoog, S.; Wheelhouse, K.; Rassias, G.; Gouverneur, V. *Chem.—Eur. J.* **2012**, *51*, 8583 and refs therein.

(5) Cu-mediated/catalyzed benzylic trifluoromethylation: (a) Kawai, H.; Furukawa, T.; Nomura, Y.; Tokunaga, E.; Shibata, N. *Org. Lett.* **2011**, *13*, 3596 and refs therein. (b) See ref 3e.

(6) Cu-mediated/catalyzed α-trifluoromethylation of aldehydes and ketones: (a) Langlois, B. R.; Laurent, E.; Nathalie, R. *Tetrahedron Lett.* **1992**, *33*, 1291. (b) Kirij, N. V.; Pasenok, S. V.; Yagupolskii, Y. L.; Tyrra, W.; Naumann, D. *J. Fluorine Chem.* **2000**, *106*, 217. (c) Allen, A. E.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2010**, *132*, 4986.

(7) Cu-catalyzed electrophilic trifluoromethylation of β-ketoesters for construction of quaternary carbon centers was recently reported: Deng, Q.-H.; Wadepohl, H.; Gade, L. H. *J. Am. Chem. Soc.* **2012**, *134*, 10769.

(8) Hagooly, A.; Rozen, S. *J. Org. Chem.* **2004**, *69*, 7241 and refs therein.

(9) (a) Dörwald, F. Z. *Metal Carbenes in Organic Synthesis*; Wiley-VCH: Weinheim, 1999. (b) Kirmse, W. *Angew. Chem., Int. Ed.* **2003**, *42*, 1088. (c) de Frémont, P.; Marion, N.; Nolam, S. P. *Coord. Chem. Rev.* **2009**, *253*, 862. (d) Zhang, Y.; Wang, J. *Eur. J. Org. Chem.* **2011**, 1015. (e) Franssen, N. M. G.; Walters, A. J. C.; Reeka, J. N. H.; de Bruin, B. *Catal. Sci. Technol.* **2011**, *1*, 153.

(10) (a) Imoto, M.; Nakaya, T. *J. Macromol. Sci., Rev. Macromol. Chem.* **1972**, *7*, 1 and refs therein. (b) Cairncross, A.; Sheppard, W. A. *J. Am. Chem. Soc.* **1968**, *90*, 2186. (c) Zhao, X.; Wu, G.; Zhang, Y.; Wang, J. *J. Am. Chem. Soc.* **2011**, *133*, 3296. (d) Xiao, Q.; Xia, Y.; Li, H.; Zhang, Y.; Wang, J. *Angew. Chem., Int. Ed.* **2011**, *50*, 1114. (e) Ye, F.; Ma, X.; Xiao, Q.; Li, H.; Zhang, Y.; Wang, J. *J. Am. Chem. Soc.* **2012**, *134*, 5742.

(11) (a) Wiemers, D. M.; Burton, D. J. *J. Am. Chem. Soc.* **1986**, *108*, 832. (b) Yang, Z.-Y.; Wiemers, D. M.; Burton, D. J. *J. Am. Chem. Soc.* **1992**, *114*, 4402. (c) Nair, H. K.; Burton, D. J. *J. Am. Chem. Soc.* **1997**, *119*, 9137. (d) Yang, Z.-Y.; Burton, D. J. *J. Fluorine Chem.* **2000**, *102*, 89.

(12) Doyle, M. P.; Mckervey, M. A.; Ye, T. *Modern Catalytic Methods for Organic Synthesis with Diazo Compounds*; John Wiley & Sons: New York, 1998.

(13) Prakash, G. K. S.; Yudin, A. K. *Chem. Rev.* **1997**, *97*, 757.

(14) Ligands associating with Cu to retard the decomposition of diazo compounds: (a) Wulfmanb, D. S.; Peace, W.; Stefeen, E. K. *Chem. Commun.* **1971**, 1360. (b) Salomon, R. G.; Kochi, J. K. *J. Am. Chem. Soc.* **1973**, *95*, 3300. (c) Díaz-Requejo, M. M.; Belderrain, T. R.; Nicasio, M. C.; Prieto, F.; Pérez, P. J. *Organometallics* **1999**, *18*, 2601.

(15) (a) Theodoridis, G. Fluorine-Containing Agrochemicals: An Overview of Recent Developments. In *Fluorine and the Environment: Agrochemicals, Archaeology, Green Chemistry & Water*; Tressaud, A., Ed.; Elsevier: Amsterdam, 2006. (b) Yamauchi, Y.; Hara, S.; Senboku, H. *Tetrahedron* **2010**, *66*, 473.

(16) (a) Kuett, A.; Movchun, V.; Rodima, T.; et al. *J. Org. Chem.* **2008**, *73*, 2607. (b) Dubinina, G. G.; Ogikubo, J.; Vicic, D. A. *Organometallics* **2008**, *27*, 6233. (c) For a discussion on the ^{19}F NMR chemical shift difference of $[Cu(CF_3)I]^-$ in our cases, see SI section 6.2.

(17) A well-defined α-carbonyl diazoalkane complex of Cu(I): Straub, B. F.; Rominger, F.; Hofmann, P. *Organometallics* **2000**, *19*, 4305.

(18) Water-promoted dissociation of $[CuI_2]^-$: Kauffman, G. B.; Fang, L. Y. *Inorg. Synth.* **1983**, *22*, 101.

(19) According to the overall yield (70−80%) of the "$CuCF_3$" species, the solution may also contain some other copper species such as CuI, which can promote trifluoromethylation. However, as shown in Table 1, entries 1−4, its contribution to the final yield is limited because it may transform into unreactive species such as $[CuI_2]^-$ in the absence of water.

(20) CuOH is elusive due to its instability, and a theoretical study shows that it readily decomposes into stable Cu_2O and H_2O: Korzhavyi, P. A.; Soroka, I. L.; Isaev, E. I.; Lijia, C.; Johansson, B. *Proc. Natl. Acad. Sci. U.S.A.* **2012**, *109*, 686. In our case, a red precipitate (assumed to be Cu_2O) was observed at the completion of the reaction. We also tried trifluoromethylation of **1a** with "$CuCF_3$" using Cu_2O instead of CuI as the additive, and only a trace amount of **2a** was detected.

(21) (a) See ref 14b. (b) Lebel, H.; Marcoux, J.-F.; Molinaro, C.; Charette, A. B. *Chem. Rev.* **2003**, *103*, 977.