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# **Copper-Mediated Trifluoromethylation of α-Diazo Esters with TMSCF<sub>3</sub>: The Important Role of Water as a Promoter**

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Supporting Information Placeholder

**ABSTRACT:** A copper-mediated trifluoromethylation of  $\alpha$ -diazo esters with TMSCF<sub>3</sub> reagent has been developed, which serves as a new method for the preparation of  $\alpha$ -trifluoromethyl esters. This trifluoromethylation reaction represents the first example of fluoroalkylation of a non-fluorinated carbene precursor. It was found that water plays an important role in promoting the reaction by activating the "CuCF<sub>3</sub>" species prepared from CuI/TMSCF<sub>3</sub>/CsF (1:1.1:1.1). The scope of this trifluoromethylation reaction is broad, and the efficiency of the reaction is demonstrated in the synthesis of a variety of aryl-, benzyl-, and alkyl-substituted 3,3,3-trifluoropropanoates.

Trifluoromethylated compounds have attracted increasing attention in pharmaceutical and agrochemical research because of the unique role of  $CF_3$  group in the enhancement of the bioactivity of organic molecules.<sup>1</sup> Among various transition-metal-assisted methods for the incorporation of CF<sub>3</sub> group(s) into arenes or alkenes,<sup>2</sup> the copper-mediated trifluoromethylation is most extensively studied due to the high efficiency of the reaction and the relatively low cost of copper.2c And importantly, the copper-involved trifluoromethylation of aryl or vinyl halides often proceeds smoothly in the absence of an exogenous ligand.<sup>3</sup> On the other hand, the copper-based trifluoromethylation of sp<sup>3</sup> carbon atoms is much less explored,<sup>4-7</sup> among which, most work focus on the construction of CF<sub>3</sub>-bearing secondary or tertiary carbon centers via allylic or benzylic trifluoromethylation reactions,<sup>4,5</sup> with only very few examples of α-trifluoromethylation of ketones and aldehydes being available.<sup>6</sup> To date, a general method for the introduction of  $CF_3$  group(s) into the  $\alpha$ -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 for the construction of structurally diverse molecules.<sup>9</sup> Among many unique transformations based on these metal carbene species, the migratory insertion of a carbene ligand into a transition metal–carbon bond is a useful tool for the construction of a functionalized anionic carbon center for further transformations (eq. 1).<sup>9a,e</sup> Although carbene insertion into palladium–carbon bonds has been exploited for various cross-coupling reactions,<sup>9a,e</sup> carbene insertion.<sup>10,11</sup> The

available examples in the latter case using diazo compounds as carbene sources include copper-catalyzed polymerization of diazoalkenes,<sup>10a</sup> the stoichiometric reaction between diazoacetate,<sup>10b</sup> pentafluorophenylcopper and and copper-catalyzed reactions between alkynes (or heteroarenes) and N-tosylhydrazones (precursors for diazo compounds).<sup>10c-e</sup> Moreover, Burton and co-workers reported the CF<sub>2</sub>-homologation reactions of perfluorinated organocoppers (R<sub>f</sub>Cu) using trifluoromethylcopper species ("CuCF<sub>3</sub>") as the difluorocarbene source,<sup>11</sup> which was believed to proceed through the insertion of difluoromethylene into the R<sub>t</sub>-Cu bond.<sup>11b</sup> However, to the best of our knowledge, there has been no report on the insertion of a non-fluorinated carbene into a R<sub>t</sub>-Cu bond. Considering that diazo compounds have been widely used as the carbene precursors,<sup>12</sup> we envisioned that copper-mediated (or catalyzed) cross-coupling of  $\alpha$ -diazo esters and Ruppert-Prakash reagent (TMSCF<sub>3</sub>)<sup>13</sup> could result in a facile formation of  $\alpha$ -trifluoromethyl esters. Since various  $\alpha$ -diazo esters can be easily prepared by diazo-transfer reaction of the corresponding esters,<sup>12</sup> the overall process is the equivalent to the trifluoromethylation of  $\alpha$ -C-H bond of an ester with TMSCF<sub>3</sub> reagent (eq. 2).

### Scheme 1. Speculated Copper-Catalyzed Trifluoromethylation of α-Diazo Esters with TMSCF<sub>3</sub>



Initially, we speculated that "CuCF<sub>3</sub>" generated from TMSCF<sub>3</sub> and a Cu(I) salt could react with  $\alpha$ -diazo esters leading to the formation of a trifluoromethyl copper carbene species, which would undergo CF<sub>3</sub>-migratory insertion and subsequent protonation to afford  $\alpha$ -trifluoromethyl esters (Scheme 1). However, the attempted reaction between  $\alpha$ -diazo ester 1a and TMSCF<sub>3</sub> with a catalytic amount of copper(I) salt in the presences of a proton source (to regenerate the copper catalyst) failed due to the quick formation of undesired CF<sub>3</sub>H. Realizing that the pre-generated "CuCF<sub>3</sub>" could be used as a relatively stable "CF<sub>3</sub>" reservoir,<sup>2c</sup> we focused on the trifluoromethylation of 1a using a stoichiometric amount of copper salt and TMSCF<sub>3</sub>. However, when **1a** was added to the pre-generated "CuCF<sub>3</sub>" (from CuI, TMSCF<sub>3</sub> and CsF), only a trace amount of product 2a was detected after acidic workup (Table 1, entry 1). Considering that CsI was formed during the preparation of "CuCF<sub>3</sub>", the coordination of iodide ion ( $\Gamma$ ) to copper may retard the reaction between "CuCF<sub>3</sub>" and  $1a_{14}^{14}$ Furthermore, we found that the addition of another portion of CuI after 1a could significantly promote the reaction and the yield of 2a increased to 77% when 1.2 equiv of CuI was used

Table 1. Screening of the Reaction Conditions<sup>a</sup>

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	Ph <sup>L</sup> COOEt – <b>1a</b>		<ol> <li>Cul (x equiv), TMSCF<sub>3</sub> (y equiv), CsF (y equiv), RT, 30 min</li> <li>1a (1 equiv) and additive</li> </ol>		→ CF <sub>3</sub> Ph COOEt 2a	
	Entry <sup>b</sup>	Solvent	Additive (equiv)	Temp ( <sup>o</sup> C)	Time (h)	Yield (%) <sup>c</sup>
	1	DMF	none	rt	9	< 5
	2	DMF	Cul (0.05)	rt	9	17
	3	DMF	Cul (0.2)	rt	9	29
	4	DMF	Cul (0.5)	rt	9	37
	5	DMF	Cul (1.2)	rt	9	77
	6	NMP	Cul (1.2)	rt	13	88
	7	NMP	Cul (1.2) + H <sub>2</sub> O (1)	rt	13	90
	8	NMP	H <sub>2</sub> O (1)	rt	65	31
	9	NMP	H <sub>2</sub> O (10)	rt	65	36
	10	NMP	H <sub>2</sub> O (20)	40	10	69
	11	NMP	H <sub>2</sub> O (44)	40	10	80
	12	NMP	H <sub>2</sub> O (66)	40	10	77
	13	NMP	H <sub>2</sub> O (44)	rt	20	83
	14	NMP	H <sub>2</sub> O (44)	50	20	72
	15 <sup>d</sup>	NMP	H <sub>2</sub> O (44)	rt	20	69
	16 <sup>e</sup>	NMP	H <sub>2</sub> O (44)	rt	20	85
	17	NMP	<i>t</i> 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

<sup>*a*</sup>All reactions were performed by adding **1a** and additive into the pre-generated "CuCF<sub>3</sub>". <sup>*b*</sup>For entries 1-6, reactions were performed on 0.2 mmol sacle (x = 1.5, y = 1.8) in DMF or NMP (3 mL + 3 mL) under N<sub>2</sub> atmosphere, and no difluoroolefin **4a** was detected. For entries 7-19, reactions were performed on 0.5 mmol sacle (x = 1.5, y = 1.65) in NMP (3 mL + 3 mL) under N<sub>2</sub> atmosphere. <sup>*c*</sup> The yields were determined by <sup>19</sup>F NMR with PhCF<sub>3</sub> as an internal standard. <sup>*d*</sup> x = 1.2, y = 1.32. <sup>*e*</sup> x = 2.0, y = 2.2.

(Table 1, entries 2–5). When NMP (1-methylpyrrolidin-2-one) was used instead of DMF as solvent, a higher yield (88%) of 2a was obtained (Table 1, entry 6). It is interesting that when reaction was performed in a sealed the tube. gem-difluoroolefin 4a was formed as the major product and 2a as the minor product (Scheme 2). Furthermore, prolonged reaction time did not significantly increase the yield of 2a after the initial 20 minutes (Scheme 2), which demonstrates that 2a resulted from the quenching of the labile copper 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,  $\beta$ -elimination of fluoride from **3a** would lead to difluoroolefin **4**a

#### Scheme 2. Formation of Difluoroolefin<sup>a</sup>



<sup>a</sup> Reaction was performed in a sealed NMR tube in NMP (0.6 mL). "CuCF<sub>3</sub>" was prepared from Cul, TMSCF<sub>3</sub> and CsF in a molar ratio of 1:1:1.3. Yields were determined by <sup>19</sup>F NMR with PhCF<sub>3</sub> as an internal standard.

Next, we examined the influence of protic additives on the reaction. Although it has been known that long-chain perfluoroalkylcoppers are not so sensitive towards water,<sup>3a</sup> the similar data for trifluoromethylcopper species are not available. Indeed, we found that "CuCF<sub>3</sub>" (prepared from CuI/TMSCF<sub>3</sub>/CsF, in a ratio of 1:1.1:1.1) in NMP (1.0 M) in the presence of 66 equiv of water was hardly transformed into CF<sub>3</sub>H at low temperatures, and only ~5% of "CuCF<sub>3</sub>" was decomposed at room temperature in 5 hours (see section 6.1 in Supporting Information). When 1.0 equiv of water and 1.2 equiv of CuI were added into the reaction mixture of "CuCF<sub>3</sub>"

and 1a at room temperature, to our delight, the reaction proceeded smoothly to give 2a in excellent yield with good reproducibility (Table 1, entry 7). It is much impressive that *water itself could promote the reaction* and **2a** was obtained in 31% yield when 1.0 equiv of water was added (Table 1, entry 8). When less than 10 equiv of water was used, there was no substantial improvement of the yield (Table 1, entry 9). Notably, when the amount of water was increased to 20 equiv, the yield was strikingly improved to 69% (Table 1, entry 10). Further optimization indicated that the use of 44 equiv of water at room temperature gave the best result (Table 1, entries 11–14). As for the amount of copper reagent, "CuCF<sub>3</sub>" prepared from 1.5 equiv of CuI gave better results than those with 1.2 equiv or less, and more excessive amount of CuI could not further improve the yield significantly (Table 1, entries 15-16). Among several protic additives that were tested, tBuOH, EtOH, MeOH, and PhOH were found to be inferior to water (Table 1, entries 17-20).

#### Table 2. Trifluoromethylation of Various α-Diazo Esters<sup>a</sup>



<sup>a</sup> Unless otherwise noted, reactions were performed on 0.5 mmol scale by adding **1a** and water into the pre-generated "CuCF<sub>3</sub>". Yields refer to isolated yields of the analytically pure products. <sup>b</sup> The reaction was performed at 35 °C. <sup>c</sup> The yield of the reaction performed on 0.2 mmol scale at 60 °C using "CuCF<sub>3</sub>" (2.0 equiv) as trifluoromethylation reagent, Cul (1.2 equiv) and H<sub>2</sub>O (1 equiv) as additives was given in the parenthesis. <sup>d</sup> The reaction was performed at 40 °C. <sup>e</sup> The number in the parenthesis refers to <sup>19</sup>F NMR yield with PhCF<sub>3</sub> as an internal standard.

Having identified the optimal reaction conditions (Table 1, entry 13), we further examined the scope of this trifluoromethylation reaction (Table 2). Generally, both aryl-, benzyl- and other alkyl-substituted  $\alpha$ -diazo esters reacted smoothly to give  $\alpha$ -trifluoromethyl esters 2 in moderate to excellent yields, and no aromatic trifluoromethylation occurred in the cases of haloaryl-substituted  $\alpha$ -diazo esters (2j-2p and 2y-2zb). Moreover, the reaction also tolerates C=C bonds and no intramolecular cyclopropanation product was detected in the case of 2r. The aryl  $\alpha$ -diazo esters with electron-donating substituent such as methyl, methoxy and ethoxy groups on the aromatic ring gave  $\alpha$ -trifluoromethyl esters 2 in excellent yields (2c-2i), while those with weak

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electron-withdrawing substituent such as Cl and Br at the aromatic rings gave slightly decreased yields (2k-2p). α-diazo However. the ester **1q** with a strong electron-withdrawing substituent (NO<sub>2</sub>) 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, ethyl, to isopropyl esters caused no significant drop of yield (2g-2i). For the benzyl-substituted  $\alpha$ -diazo esters (2s-2za), the yields were generally lower than the normal alkyl-substituted ones (2zb-2zd), probably due to the occurrence of 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 also detected as the byproduct (6% by GC-MS). α-Trifluoromethyl carboxylic esters are key intermediates for the synthesis of non-ester pyrethroids insecticides such as flufenprox<sup>15a</sup> (for its concise synthesis from 2e, see sections 5.1-5.3 in Supporting Information) and fluorinated analogues of non-steroidal anti-inflammatory drugs<sup>15b</sup>.



**Figure 1.** Monitoring of the CuI-promoted trifluoromethylation of  $\alpha$ -diazo ester **1a** with <sup>19</sup>F NMR spectroscopy at rt (the chemical shifts were determined relative to PhCF<sub>3</sub> at -63.0 ppm). (A) "CuCF<sub>3</sub>" prepared from CuI, TMSCF<sub>3</sub> and CsF in 1:1.1:1.1 ratio; (B) 5 min after the addition of 2/3 equiv of CuI into sample A; (C) 10 min and (D) 60 min after the addition of 2/3 equiv of CuI and 2/3 equiv of **1a** into sample A.

To gain more insights into the present copper-mediated trifluoromethylation reaction, the composition of "CuCF<sub>3</sub>" and its reaction with **1a** and additional CuI were studied with <sup>19</sup>F NMR spectroscopy. When CuI, TMSCF<sub>3</sub> and CsF were mixed in a 1:1.1:1.1 ratio in NMP, apart from the two major trifluoromethylcopper species which were tentatively assigned as  $[Cu(CF_3)I]^-$  (5, -28.7 ppm) and  $[Cu(CF_3)_2]^-$  (6, -31.9 ppm) according to the reported NMR data<sup>16</sup> (neither of them is reactive towards 1a under this condition), a new species 7 at -26.9 ppm was also observed in small amount (Figure 1, A); and the species 7 became predominant when 2/3 more equiv of CuI was added into the mixture (Figure 1, B). By comparison with the <sup>19</sup>F NMR data (-27.2 ppm in DMF, -27.8 ppm in NMP) of "ligandless" CuCF<sub>3</sub><sup>3c</sup> prepared from CF<sub>3</sub>H and its reactivity with diazo ester 1a (see section 6.3 in Supporting Information), the species 7 was tentatively assigned as solvent-stabilized CuCF<sub>3</sub>, in which the solvent molecule NMP acted as a ligand. It is likely that the abstraction of iodide ion 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<sub>3</sub>", a new peak at -26.5 ppm appeared (in

addition to the species 7) (Figure 1, C), and the consumption of **8a** is much slower than its formation (Figure 1, C and D). Moreover, the N<sub>2</sub> evolution experiment showed that the decomposition of diazo compound **1a** was a slow process (see section 6.4 in Supporting Information). Based on these results, the species **8a** was tentatively identified as the complex CuCF<sub>3</sub>•**1a** rather than a carbene-ligated trifluoromethylcopper species **9**.<sup>17</sup>

Although it is difficult to identify the reactive intermediate with <sup>19</sup>F NMR spectroscopy when the reaction was performed in the presence of water (only two trifluoromethylcopper species assigned as 5 and 6 were observed, see section 6.1 in Supporting Information), we conjecture that water serves as the "scavenger" of iodide ion (by the formation of hydrated iodide ion)<sup>I8</sup> to promote the ligand exchange of copper complexes affording the reactive species 8 (see Scheme 3) at a low concentration. If water is used in a relatively small amount (less than 10 equiv), the saturation of the mixed solvent by iodide ion makes the formation of 8 (and the less efficient. subsequent trifluoromethylation) The assumption of water-promoted iodide complex dissociation was further supported by our observation that the yield of 2a decreased significantly with the addition of external KI into the reaction mixture (see section 6.5 in Supporting Information).

#### **Scheme 3. Proposed Mechanism**



Based on aforementioned results and discussion, we propose a mechanism for the current CuI-mediated, water-promoted trifluoromethylation of 1 with TMSCF<sub>3</sub> reagent (Scheme 3). Firstly, the reaction of CuI, TMSCF<sub>3</sub> and CsF (in a 1:1.1:1.1 ratio) gives the dicoordinated trifluoromethylcopper species 5, which is in equilibrium with bis(trifluoromethyl)copper species 6 and  $[CuI_2]^-$  via ligand redistribution on copper (eq. 3).<sup>19</sup> After the addition of  $\alpha$ -diazo ester 1 and water, a small amount of reactive intermediate complex 8 is formed from 5 by water-promoted  $\alpha$ -diazo ester-iodide ion exchange reaction (eq. 4). The extrusion of N<sub>2</sub> from 8 affords trifluoromethyl copper carbene species 9 and the subsequent migration of CF<sub>3</sub> group to the carbenic carbon atom of 9 results in  $\alpha$ -CF<sub>3</sub>-substituted copper species 3. The final hydrolysis of 3 by water gives product 2 and the unreactive Cu2O.20 Alternatively, based on the known copper-catalyzed cyclopropanation between diazo compounds and alkenes,<sup>21</sup> the complex 10 generated from  $[CuI_2]^-$  by a similar ligand-exchange reaction is also a possible intermediate. The extrusion of  $N_2$  from 10 affords copper carbene species 11. Both 10 and 11 can undergo ligand redistribution reaction with 5 to give 8 and 9, respectively. Although we could not rule out the formation of complex 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  $\alpha$ -diazo ester 1r.

In summary, we disclosed a mild copper-mediated trifluoromethylation of  $\alpha$ -diazo esters with TMSCF<sub>3</sub> to give  $\alpha$ -trifluoromethyl esters, which represents the first fluoroalkylation of a non-fluorinated carbene precursor. Water acts as an efficient activating agent in promoting the reaction with trifluoromethylcopper species prepared from CuI/TMSCF<sub>3</sub>/CsF (1:1.1:1.1). We propose that the hydration of iodide ion facilitates the formation of the intermediate  $\alpha$ -diazo ester-coordinated trifluoromethylcopper 8, and then the reaction occurs via N<sub>2</sub>-extrusion and subsequent migratory insertion of the carbene ligand into the Cu-CF<sub>3</sub> bond. This reaction is applicable for  $\alpha$ -aryl,  $\alpha$ -benzyl, and  $\alpha$ -alkyl diazo esters and tolerates bromo, chloro, fluoro, ether and double bond functionalities. Not only does our present work offer a simple and general way to introduce CF<sub>3</sub> group into α-position of structurally diverse carboxylic esters, it also provides fundamentally important insights into the reactivity of the elusive trifluoromethylcopper species. Further investigation of the more detailed reaction mechanism as well as the synthetic applications of the reaction are currently underway in our laboratory.

## ASSOCIATED CONTENT

## SUPPORTING INFORMATION

Experimental procedures and characterization for all new compounds, including  $^1\text{H},\,^{13}\text{C},\,\text{and}\,\,^{19}\text{F}\,\text{NMR}$  spectra.

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## REFERENCES

 (a) Fluorine in Medicinal Chemistry and Chemical Biology (Ed.: Ojima, I.), 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) For recent reviews, see: (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) For examples, see: (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) For examples of Cu-mediated/catalyzed allylic trifluoromethylation, see: (a) Andrew T. Parsons and Stephen L. Buchwald, *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 references therein.

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

(6) For examples on Cu-mediated/catalyzed  $\alpha$ -trifluoromethylation of aldehydes and ketones, see: (a) Bernard R. Langlois, Eliane Laurent, Nathalie Roidot *Tetrahedron Lett.* **1992**, *33*, 1291. (b) Kirij, N.V.; Pasenok, S.V.; Yagupolskii, Yu. 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) Very recently, a Cu-catalyzed electrophilic trifluoromethylation of  $\beta$ -ketoesters for the construction of quaternary carbon centers was reported, see: 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 references 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 references 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) For examples of ligands associating with copper to retard the decomposition of diazo compounds, see: (a) Wulfmanb, D. S.; W. Peace, W.; Stefeen, E. K. *Chem. Commun.* **1971**, 1360. (b) Salomon, R. G.; Kochi, J. K.; *J. Am. Chem. Soc.***1973**, *93*, 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 (Ed.: Tressaud, A.), 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 <sup>19</sup>F NMR chemical shift difference of  $[Cu(CF_3)I]^-$  in our cases, see section 6.2 in Supporting Information.

(17) For an example of well-defined  $\alpha$ -carbonyl diazoalkane complex of copper(I), see: Straub, B. F.; Rominger, F.; Hofmann, P. *Organometallics* **2000**, *19*, 4305.

(18) For water-promoted dissociation of [CuI<sub>2</sub>]<sup>-</sup>, see: Kauffman, G. B.; Fang, L. Y. *Inorg. Synth.* **1983**, *22*, 101.

(19) According to the overall yield (70–80%) of the "CuCF<sub>3</sub>" species, the solution maybe also contain some other copper species such as CuI, which can promote the trifluoromethylation. However, as shown in Table 1, entries 1-4, its contribution to the final yield is limited because it may transform into the unreactive species such as  $[CuI_2]$  in the absence of water.

(20) CuOH is a very elusive species due to its instability, and the theoretical study shows that it readily decomposes into stable substances  $Cu_2O$  and  $H_2O$ . (See: Korzhavyi, P. A.; Soroka I. L.; Isaev,

E. I.; Lijia, C.; Johansson, B. *Proc. Natl. Acad. Sci. USA.* **2012**, *109*, 686). In our case, red precipitate (that is assumed to be Cu<sub>2</sub>O) was observed after the completion of the reaction. We also tried the trifluoromethylation of **1a** with "CuCF<sub>3</sub>" using Cu<sub>2</sub>O instead of CuI as the additive, and only a trace amount of product **2a** was detected. (21) (a) Salomon, R. G.; Kochi, J. K. *J. Am. Chem. Soc.* **1973**, *95*, 3300. (b) Lebel, H.; Marcoux, J.-F.; Molinaro, C.; Charette, A. B. *Chem. Rev.* **2003**, *103*, 977.

