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Copper-catalyzed trifluoromethylation of organic zinc reagents with an electrophilic trifluoromethylating reagent†

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A copper-catalyzed trifluoromethylation of aryl, vinyl and alkyl zinc reagents with Togni's reagent was described. Mechanistic studies indicated that the aryl group is initially transferred from the zinc reagent to hypervalent iodine to form a tri-substituted hypervalent iodine intermediate. Consequent reductive-elimination *via* a concerted bond-forming step and/or radical pathway from this intermediate generates the trifluoromethylated arenes.

It is widely recognized and accepted that the introduction of fluorine into small molecules will bring significant beneficial effects such as improved pharmacokinetics, increased binding selectivity and enhanced metabolic stability.[1] Thus, incorporation of fluorine into drug-like molecules has become an indispensible strategy for medicinal chemists in drug design and a daily routine practice for the discovery of new lead compounds.[2] Among many fluorinated functional groups, the trifluoromethyl group (CF_3–) is highly valuable because it might improve the drug's cellular membrane permeability, and thus its bioavailability.[3] As a result, in the past five years, tremendous efforts have been directed towards the development of efficient methods for the formation of C–CF_3 bonds. Consequently, significant advances have been achieved in transition metal-catalyzed direct trifluoromethylation of aryl halides, aryl boronic acids or arenes.[4,5]

In 2011, Shen's group reported a copper-catalyzed trifluoromethylation of aryl boronic acids using Togni's reagent **1** as the trifluoromethyl source.[4] The reaction was conducted under mild conditions and was compatible with a variety of functional groups. Inspired by this investigation, we envisaged that an efficient trifluoromethylation method would be developed if a zinc reagent could be employed as the nucleophile since zinc reagent has been demonstrated to be an effective coupling partner in a number of transition metal-catalyzed cross-coupling reactions.[6] Herein, we disclose a copper-catalyzed trifluoromethylation of aryl, vinyl and alkyl zinc reagents using Togni's reagent **2** as the trifluoromethyl source. Mechanistic studies indicated that the aryl group from the zinc reagent is initially transferred to hypervalent iodine to form a tri-substituted hypervalent iodine intermediate. Consequent reductive-elimination *via* a concerted bond-forming step and/or trifluoromethyl radical pathway from this intermediate generates the trifluoromethylated arenes.

We began our study with the reaction of 4-biphenyl zinc reagent **3** with Togni's reagent **1** (ref. 7 and 8) in the presence of a catalytic amount of CuI/1,10-phenanthroline (Phen) in different solvents.

To our surprise, the formation of trifluoromethylated biphenyl was observed in less than 10% yield in solvents such as THF, diethyl ether, diglyme, dioxane, 1,2-dichloroethane or DMF (Table 1, entries 1–6). Interestingly, when Togni's reagent **2** was used, reaction of 4-biphenyl zinc reagent **3** occurred smoothly at room temperature to give the desired product in 13% yield after 12 h at room temperature (Table 1, entry 7). The yield was improved to 42% when the reaction was conducted in the absence of 1,10-phenanthroline (Table 1, entry 8). The effect of the copper salts was then investigated. Nevertheless, the yield of the desired product did not increased significantly when other copper salts such as CuCN, CuCl, CuBr, $Cu(MeCN)_4PF_6$ or $Cu(OAc)_2$ were used (Table 1, entries 9–13). Since it was observed that side products such as trifluoromethane and iodotrifluoromethane were formed in the reaction mixture, it is likely only part of the Togni's reagent was converted to the final product. We then studied the effect of the amount of the Togni's reagent. The yield was improved to 50% and 61%, respectively, when 2.0 or 3.0 equivalents of reagent **2** was used (Table 1, entries 14–15). Furthermore, when 30 mol% of CuI was used, the yield was further increased to 90% (Table 1, entry 17). Carefully monitoring of the reaction showed that the reaction was completed within 20 min at room temperature (Table 1,

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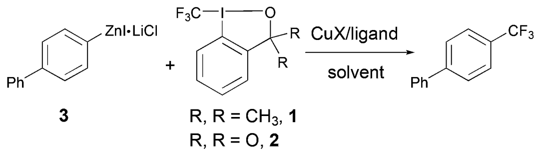
Table 1 Optimization of conditions for copper-catalyzed trifluoromethylation of aryl zinc reagent[a]



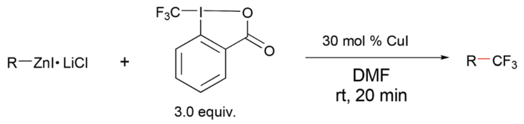
3

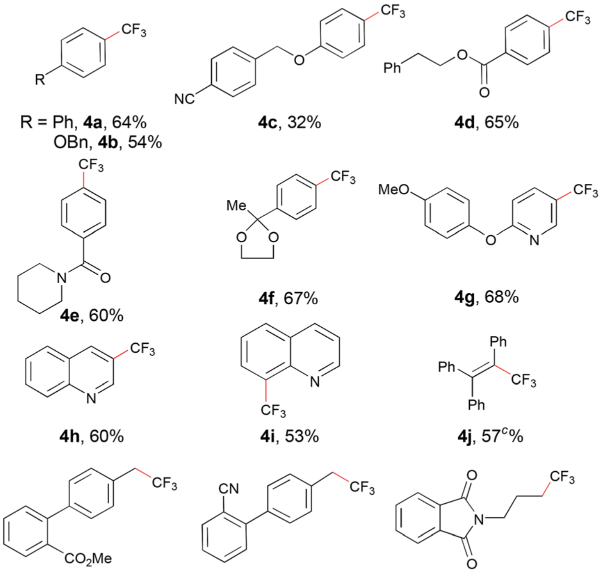
R, R = CH_3, **1**
R, R = O, **2**

Entry	CF_3 reagent	CuX	Ligand	Solvent	Yield[b] (%)
1	**1**	CuI	Phen	THF	—
2	**1**	CuI	Phen	Et_2O	—
3	**1**	CuI	Phen	Diglyme	—
4	**1**	CuI	Phen	1,4-Dioxane	—
5	**1**	CuI	Phen	$ClCH_2CH_2Cl$	—
6	**1**	CuI	Phen	DMF	—
7	**2**	CuI	Phen	DMF	13
8	**2**	CuI	—	DMF	42
9	**2**	CuCN	—	DMF	42
10	**2**	CuCl	—	DMF	24
11	**2**	CuBr	—	DMF	36
12	**2**	$Cu(MeCN)_4PF_6$	—	DMF	35
13	**2**	$Cu(OAc)_2$	—	DMF	—
14	**2**	CuI	—	DMF	50[c]
15	**2**	CuI	—	DMF	61[d]
16	**2**	CuI	—	DMF	72[e]
17	**2**	CuI	—	DMF	90[f]
18	**2**	CuI	—	DMF	90[g] (64)
19	**2**	CuI	—	DMF	90[h]
20	**2**	CuI	—	DMF	65[i]

[a] Reaction conditions: 4-biphenyl zinc reagent (0.1 mmol), Togni's reagent (0.1 mmol), CuX (10 mol%), ligand (20 mol%), solvent (1.0 mL) at room temperature for 12 h. [b] Yields were determined by ^{19}F NMR analysis of the crude product using *p*-fluorotoluene as an internal standard. [c] 2.0 equivalents of reagent **2** was used. [d] 3.0 equivalents of reagent **2** was used. [e] 3.0 equivalents of reagent **2** and 20 mol% of CuI were used. [f] 3.0 equivalents of reagent **2** and 30 mol% of CuI were used. [g] Reaction was conducted for 20 min; isolated in parentheses. [h] Reaction was conducted at 0 °C. [i] Reaction was conducted at 40 °C.

Table 2 Scope of copper-catalyzed trifluoromethylation of zinc reagents with Togni's reagent[a,b]





R = Ph, **4a**, 64%
OBn, **4b**, 54%

4c, 32%

4d, 65%

4e, 60%

4f, 67%

4g, 68%

4h, 60%

4i, 53%

4j, 57[c]%

4k, 56%

4l, 48%

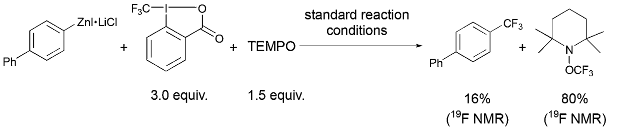
4m, 49%

[a] Reaction conditions: zinc reagent (0.5 mmol), Togni's reagent (1.5 mmol), CuI (30 mol%), DMF (5.0 mL) at room temperature for 20 min. [b] Isolated yields. [c] Yields were determined by ^{19}F NMR analysis of the crude product using *p*-fluorotoluene as an internal standard.

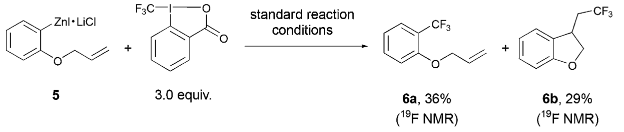
entry 18). Higher temperature was detrimental to the reaction. The yield dropped to 65% when the reaction was conducted at 40 °C (Table 1, entry 20).

With a relied procedure in hand, we then examined the scope of the copper-catalyzed trifluoromethylation of the zinc reagents, and the results were summarized in Table 2. In general, reactions of both electron-rich and electron-poor aryl zinc reagents occurred in good yields (Table 2, **4a–f**). Heteroaryl zinc reagents such as pyridyl and quinolinyl zinc reagents also reacted under the optimized conditions to give the corresponding trifluoromethylated heteroarenes in good yields (Table 2, **4g–i**). Likewise, reaction of vinyl zinc reagent **3j** also afforded the trifluoromethylated alkene in 57% yield (Table 2 and **4j**). Similarly, alkyl zinc reagents could also be trifluoromethylated under the optimized reaction conditions (Table 1, entry **4k–m**). One advantage of using zinc reagents is its tolerance of functional groups. As illustrated in Table 2, various functional groups such as ester, cyano, protected ketone and amide were compatible.

Typically, reaction of Togni's reagent **2** was proposed to proceed *via* a pathway involving an *in situ* generated CF_3 radical species.[8] To probe if the copper-catalyzed trifluoromethylation of zinc reagents proceeds *via* a radical mechanism, we conducted two sets of different experiments. In the first experiment, 1.5 equivalents of TEMPO, a radical trap, was added to the reaction mixture of 4-biphenyl zinc reagent with Togni's reagent **2** in the presence of 30 mol% CuI. The reaction was monitored by ^{19}F NMR spectroscopy and it showed the formation of trifluoromethylated TEMPO in 80% yield and the trifluoromethylated biphenyl in 16% yield, respectively (eqn (1)). This result indicated that the copper-catalyzed trifluoromethylation reaction was only partially inhibited by TEMPO. In the second experiment, we synthesized a zinc reagent **5** to probe if the radical is indeed involved under the standard reaction conditions. Both directed trifluoromethylated product **6a** and cyclized trifluoromethylated products **6b** were observed after 20 min at room temperature in 36% and 29% yields, respectively (eqn (2)). These results suggest that the copper-catalyzed trifluoromethylation of aryl zinc reagent might proceed *via* two parallel mechanisms: one involved a radical pathway and the other involved a non-radical pathway.

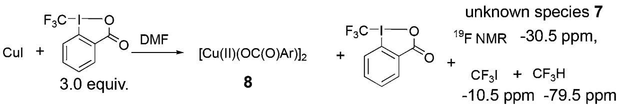


(1)



(2)

To gain more insight about the mechanism of the reaction, we conducted a stoichiometric reaction of CuI with Togni's reagent **2** (eqn (3)). A clear blue solution was formed within 1.0 min at room temperature upon mixing 19 mg of CuI with 3.0 equivalents of Togni's reagent **2** in 1.0 mL of DMF. The reaction was monitored by ^{19}F NMR spectroscopy and it showed the formation of CF_3I (resonated at $\delta = -10.5$ ppm in ^{19}F NMR), CF_3H (resonated at $\delta = -79.5$ ppm in ^{19}F NMR), unreacted reagent **2** and an unknown species **7** (resonated at $\delta = -30.5$ ppm in ^{19}F NMR).



(3)

Addition of 10 mL of diethyl ether precipitated a blue solid which was characterized to be bimetallic copper(II) species **8**, as determined by X-ray diffraction of its single crystals. This is consistent with previously reported observation by Xi and coworkers.[8] After the diethyl ether was removed under vacuum, the DMF solution of the reaction mixture was treated with 1.0 equivalent of 4-biphenyl zinc reagent. After 20 min, the peak at −30.5 ppm disappeared and a new peak at −62.6 ppm which corresponds to the trifluoromethylated biphenyl formed in 47% yield, as determined by ^{19}F NMR spectroscopy (Fig. 1).

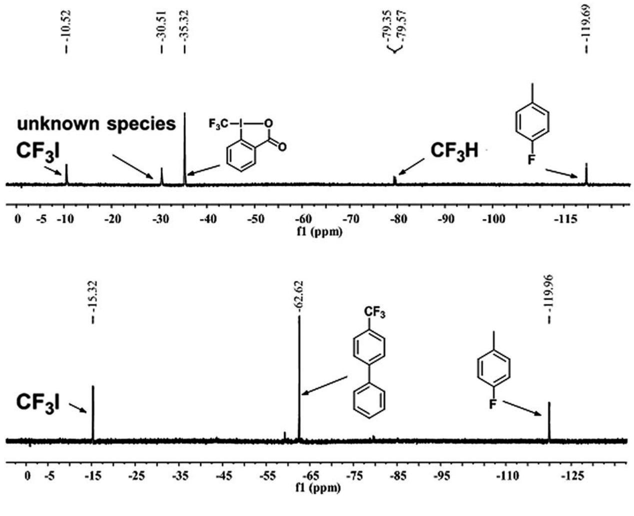


Fig. 1 ^{19}F NMR spectroscopy for reaction of CuI with 3.0 equivalents of Togni's reagent **2** in DMF at room temperature for 5 min; ^{19}F NMR spectroscopy for reaction of the DMF solution of above solution after removing the copper(II) salts with aryl zinc reagent **2** after 20 min at room temperature.

We speculated that the unknown species at −30.5 ppm might be [CF_3Cu]. To probe if this is the case, we independently prepared [CF_3Cu] by a method reported by Grushin.[9] Interestingly, stoichiometric reactions of independently prepared [CF_3Cu] with 1.0 equivalent of 4-biphenyl zinc reagent **3** in DMF in the presence of oxidants such as air, Ag_2CO_3, $K_2S_2O_8$ or AgOTf did not generate the coupled product. When $PhI(OAc)_2$ was used as the oxidant, the trifluoromethylated biphenyl was formed in 20% yield. These experiments suggest that the unknown species at −30.5 ppm might not be [CF_3Cu].

Togni reported that reaction of Togni's reagent **2** with $Zn(NTf)_2$ resulted in the formation of $[Zn(\mathbf{2})_2(NTf)_2]^+$, which showed a shift of the CF_3 signal of the hypervalent iodine species from −33.0 ppm to −26.9 ppm in the ^{19}F NMR spectroscopy. We think that a similar complex might be formed when Togni's reagent **2** was reacted with CuI in DMF. To figure out structural information of this transient reactive species at −30.5 ppm, we carefully monitored the diluted reaction mixture of CuI with Togni's reagent **2** in DMF by electrospray ionization tandem Mass spectroscopy (ESI-MS). The typical isotopic distributions of the ion species containing copper helped us the screen the reactive Cu-complexes from the ESI-MS spectra at different time.[10] The ESI-MS experimental results revealed that after adding CuI, Togni's reagent **2** to DMF solution, the major peak in the ESI-MS spectrum was the signal of Cu(II) with 2-iodobenzoic acid, which remained inert through the ESI-MS experiments. Interestingly, a new signal with a $m/z = 451.6$, which was assigned as the signal of $[\mathbf{2}\cdot\mathrm{Cu(I)}\cdot\mathrm{DMF}]^+$, appeared two minutes after addition of CuI, Togni's reagent **2** to DMF solution. This peak slowly increased and finally disappeared after nearly 2.5 h (Fig. 2). These results indicated that this species might be the active transient species that was observed in the ^{19}F NMR spectroscopy, which is consistent with Togni's observation for the formation of $[Zn(\mathbf{2})_2(NTf)_2]^+$.

Based on these preliminary results, we propose the reaction mechanism for copper-catalyzed trifluoromethylation of organic zinc reagent with Togni's reagent **2**, as outlined in Fig. 3. Reaction of CuI with Togni's reagent **2** formed an intermediate **7** and bimetallic copper(II) species **8**. Transmetallation of the aryl group from organic zinc reagent to intermediate **7** generated intermediate **9**. Directed reductive-elimination from this hypervalent iodine species affords the trifluoromethylated arene (pathway A). Alternatively, intermediate **9** may undergo a homolytic C–I bond scission to form a $CF_3^{\bullet}$, which will recombine with aryl group to form trifluoromethylated arene (pathway B) or a hemolytic C–I bond scission to form a $R^{\bullet}$, which then recombine with the trifluoromethyl group to form the final product (pathway B′). However, the detailed mechanism for the formation of the final product is more complicated and more experiments are required to elucidate this process.

In summary, a copper-catalyzed efficient trifluoromethylation of organic zinc reagents is developed. The reaction conditions

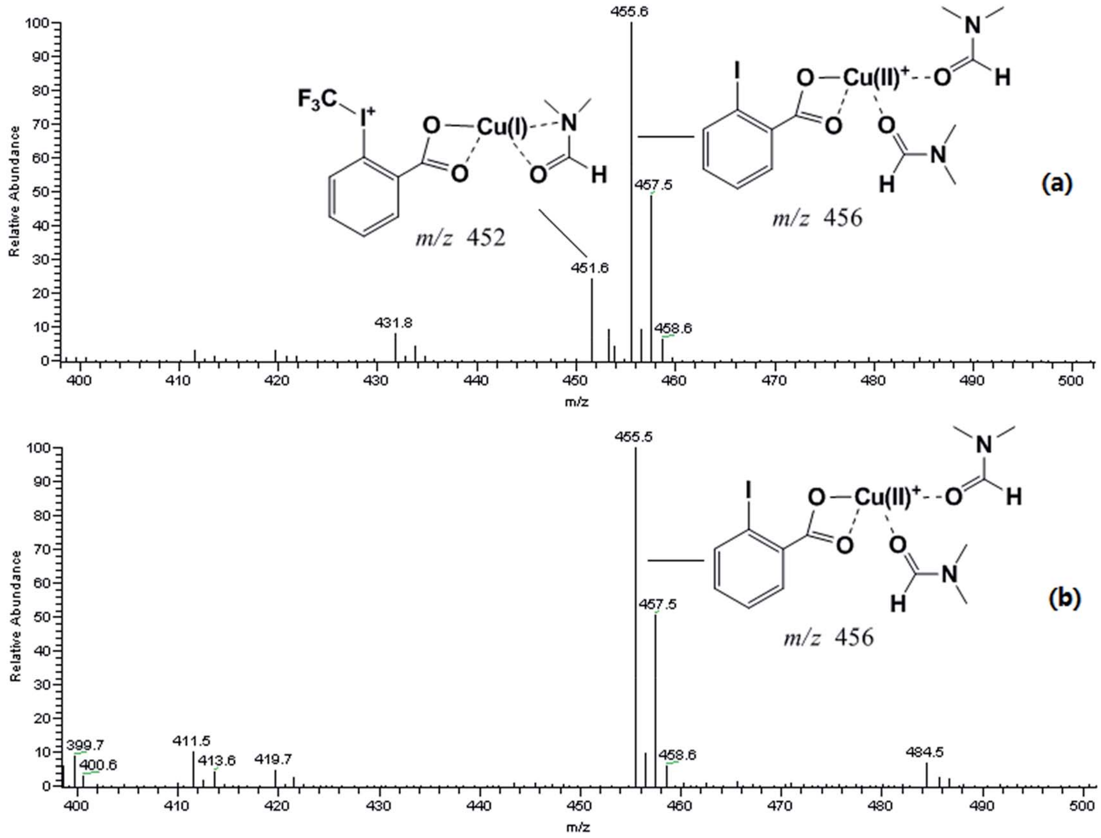


Fig. 2 The expanded ESI-MS spectra of: (a) the diluted reaction solution at reaction time 10 min; (b) the diluted reaction solution after 3 hour, in positive ion mode.

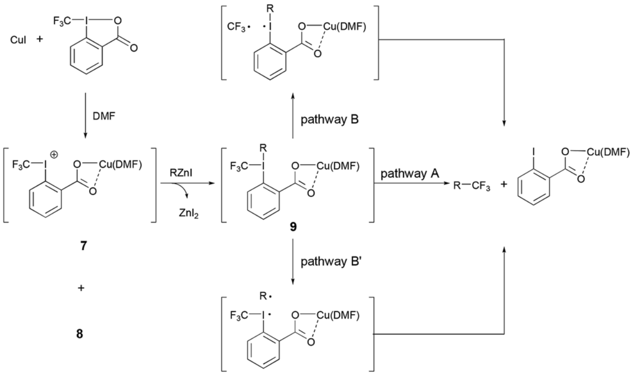


Fig. 3 Proposed mechanism for copper-catalyzed trifluoromethylation of organic zinc reagents with Togni's reagent **2**.

are mild and various functional groups such as ester, cyano, protected ketone and amide were compatible. Initial mechanistic studies indicated that the aryl group from the zinc reagent is transferred to hypervalent iodine to form a tri-substituted hypervalent iodine intermediate. Consequent reductive-elimination *via* a concerted bond-forming step and/or trifluoromethyl radical pathway from this intermediate generates the trifluoromethylated arenes. Further investigation to expand the scope of the substrates and clarify the reaction mechanism are currently undergoing in our laboratory.

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