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Copper-Catalyzed Trifluoromethylthiolation of Aryl Halides with Diverse Directing Groups

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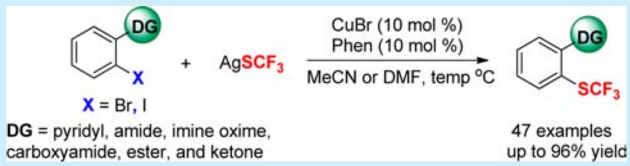
Supporting Information

ABSTRACT: The expansion of cross-coupling components in Cu-catalyzed C−X bond forming reactions have received much attention recently. A novel Cu-catalyzed trifluoromethylthiolation of aryl bromides and iodides with the assistance of versatile directing groups such as pyridyl, methyl ester, amide, imine and oxime was reported. CuBr was used as the catalyst, and 1,10-phenanthroline as the ligand. By changing the solvent from acetonitrile to DMF, the coupling process could even take place at room temperature.



Since the prominent breakthroughs on the catalytic Ullmann-type cross-coupling reactions,[1] much effort has been fulfilled to enrich the pool of coupling partners. The nucleophilic components have encompassed a variety of carbon, nitrogen, and oxygen sources with various chemical environments. These Cu-catalyzed reactions are robust to synthesize a variety of complex molecular architectures with a plethora of functional groups, making them highly attractive.[2] Quite recently, direct introduction of fluorine-containing moieties into arene rings using copper catalysts have received much attention due to far-reaching applications of organofluorines in pharmaceuticals and materials science.[3] For instance, some $CuCF_3$ complexes have been explored for the preparation of aryl-CF_3, and a number of copper-catalyzed trifluoromethylation reactions have been developed.[4]

Similar to the trifluoromethylation, related trifluoromethylthiolation of aryl halides for Ar−SCF_3 synthesis is also attractive, but far from successful.[4f] So far, only two catalytic systems were reported. Buchwald and co-workers reported a palladium-catalyzed trifluoromethylthiolation of aryl bromides using a sterically bulky phosphine ligand.[5] Vicic and co-workers later achieved a nickel-catalyzed trifluoromethylthiolation of aryl iodides and bromides.[6] For cheap metal catalysts, the $CuSCF_3$ complex, generated in situ, has been used to react with aryl halide (Br or I), but is less effective toward electron-rich substrates.[7] Until recently, Weng and Huang reported an (bpy)$CuSCF_3$ complex, which is effective for both electron-rich and -deficient substrates.[8] However, a stoichiometric amount copper−SCF_3 complex was required in those transformations, and catalytic trifluoromethylthiolation of aryl halides remained an underdeveloped issue.[9] Herein, we reported a novel copper-catalyzed trifluoromethylthiolation of aryl iodides and bromides in the presence of diverse *ortho*-directing groups including both strong and weak coordinating groups.

As part of our ongoing programs, we are interested in developing Cu-catalyzed fluorination methods to achieve the direct synthesis of arylfluorides and related organofluorines from arylhalides.[10] Recently, we reported a copper-catalyzed fluorination of aryl bromides in the presence of an *ortho*-pyridyl group; preliminary mechanistic studies indicated the precoordination of a pyridine group to a copper catalyst was essential for the success of catalytic transformation.[10a] Thus, we envisioned that *ortho*-directing groups, especially with more synthetic utility, could be introduced into arylhalide substrates to facilitate the copper-catalyzed trifluoromethylthiolation.

In order to test this possibility, an aryl bromide bearing an *ortho*-pyridyl group was first investigated in the presence of a copper catalyst. As shown in Table 1, substrate **1a** was treated with modified fluorination reaction conditions replacing AgF with $AgSCF_3$ at 120 °C. We were delighted to obtain the desired trifluoromethylthiolation product **2a** in 96% yield (entry 1). However, when the reaction temperature was lowered down to 80 °C, the yield was decreased to 38%, and no reaction occurred at room temperature (entries 2−3). Then, various Cu(I) catalysts were screened at room temperature, and CuBr was proven to be the most efficient catalyst (entries 4−6). Furthermore, the addition of bidentate nitrogen ligands was beneficial for this coupling reaction. For instance, the reaction with neocuproine provided **2a** in 88% yield, and 1,10-phenanthroline gave **2a** in 95% yield (entries 7−8). It is worth noting that no reaction occurred in the absence of a copper catalyst from room temperature to 120 °C (entry 9). In addition, phenyl bromide without a directing group was inert toward this trifluoromethylthiolation indicating that *ortho*-

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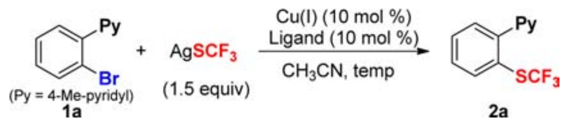
Table 1. Screening of Reaction Conditions[a]



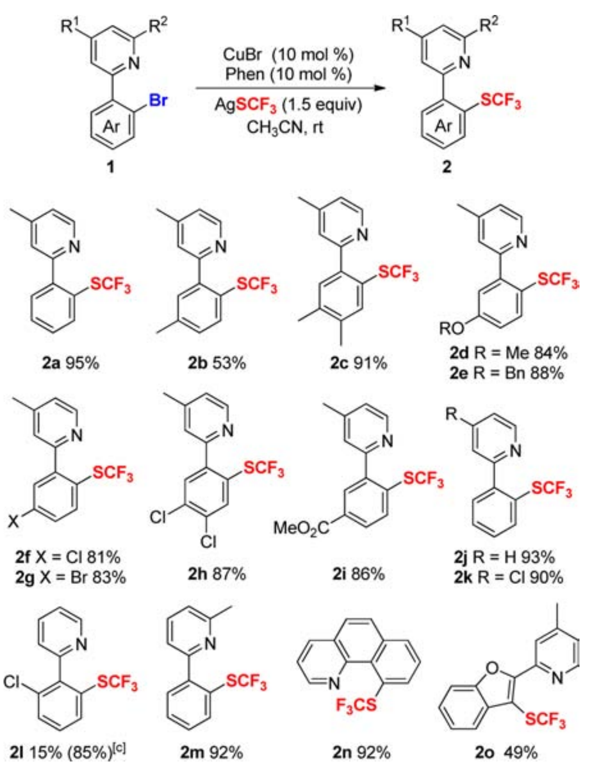
entry	Cu(I)	ligand	temp (°C)	yield (%)[b]
1	$Cu(MeCN)_4PF_6$	–	120	96
2	$Cu(MeCN)_4PF_6$	–	80	38
3	$Cu(MeCN)_4PF_6$	–	rt	0
4	CuOAc	–	rt	24
5	CuI	–	rt	5
6	CuBr	–	rt	80
7	CuBr	neocuproine	rt	88
8	CuBr	phenanthroline	rt	95
9	–	–	rt or 120	0
10[c]	CuBr	phenanthroline	rt or 120	0

[a]Reaction conditions: **1a** (0.1 mmol), $AgSCF_3$ (0.15 mmol), Cu(I) catalyst (0.01 mmol) in dry CH_3CN (1 mL) for 6 h. [b]^{19}F-NMR yield with CF_3–DMA as internal standard. [c]Phenyl bromide as substrate.

directing groups played an important role in this transformation (entry 10).

Having established the standard reaction conditions, we explored the scope of aryl bromides **1** with pyridyl groups (Scheme 1). A broad range of functional groups, such as alkyl, ether, halides, ester, etc., were tolerated under the standard reaction condition to provide the expected products **2a**–**2i** in good to excellent yields. Both electron-rich and -poor aryl bromides were proven to be good substrates. Furthermore,

Scheme 1. Substrate Scope of Arylbromides with Pyridyl Groups[a,b]

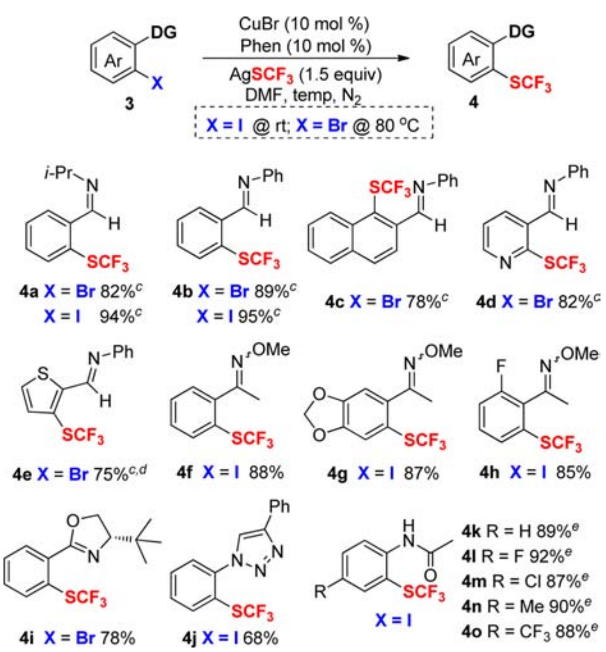


[a]All reactions were run in 0.2 mmol scale under N_2 at room temperature. [b] Isolated yield. [c] At 120 °C.

similar to the *para*-methylpyridyl group, pyridyl and *para*-chloropyridyl could promote this reaction to give desired products **2j**–**2k** in excellent yields. In addition, even as inert substrates toward Cu-catalyzed fluorination due to the steric effect,[10a] aryl bromides **1l** and **1m** were good substrates to give corresponding products **2l** and **2m** in excellent yields, in which the reaction of **1l** was conducted at elevated temperatures. This might be reasoned as the "softer" property with the "stronger" nucleophilicity of the SCF_3 anion compared to the fluoride anion which was less sensitive toward steric hindrance. Finally, other types of aryl bromides, such as benzo[*h*]quinoline bromide **1n** and benzofuran bromide **1o**, were also tested, and these reactions proceeded smoothly to give trifluoromethylthiolation products **2n** and **2o** in good and moderate yields. Unfortunately, *ortho*-pyridyl phenyl chloride was an inert substrate under the standard conditions.

Next, we sought to explore more synthetically useful coordinating groups which could be further converted to SCF_3-containing synthons. Aryl halides bearing an imine moiety were initially investigated (Scheme 2). We are delighted

Scheme 2. Substrate Scope of Arylhalides with Imine, Oxime, and Other Stronger Chelating Groups[a,b]



[a]All reactions were conducted in 0.2 mmol scale under N_2. [b] Isolated yield. [c] Isolated yield of aldehyde product hydrolysized from imine product. [d] 30 mol % of CuBr/Phen in CH_3CN at 140 °C. [e] In CH_3CN at 80 °C.

to find that, when solvent was switched from CH_3CN to DMF, the reaction of aryl iodides could be achieved under very mild reaction conditions (room temperature). For less active aryl bromides, reactions also proceeded very well with a slightly higher temperature (80 °C). For the *N*-aryl and alkyl imines, the reactions of aryl bromides and iodides could take place to give corresponding products **4a**–**4c** in high yields. It is worth noting that a series of heteroaromatic bromides, such as bromopyridine and bromothiophene, could also be converted to the SCF_3-substituted heteroaryl products **4d**–**4e** in good yields. For product **4e**, a higher catalyst and ligand loading with elevated temperature were required in acetonitrile. Further-

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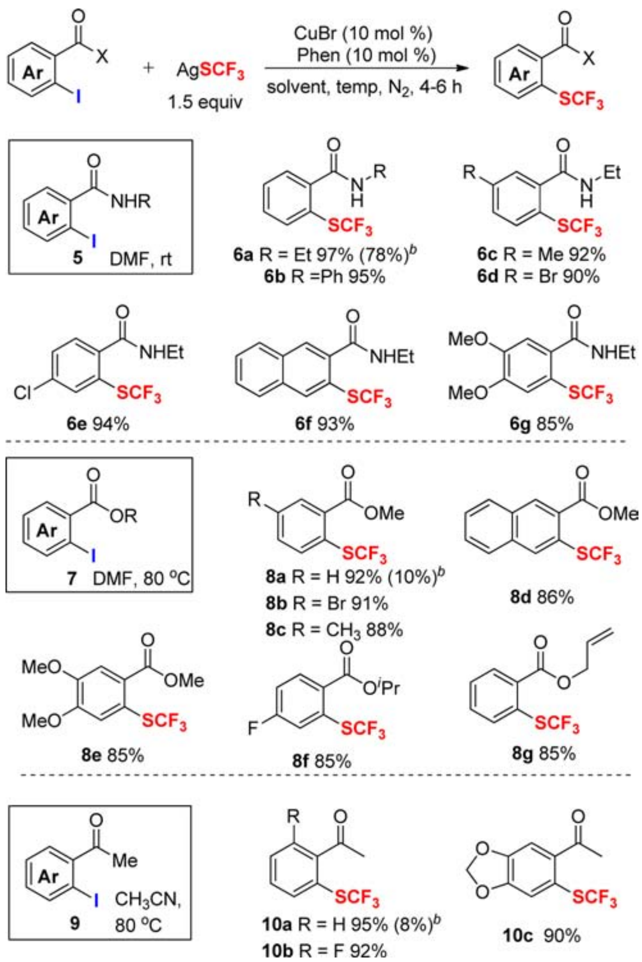
more, the oxime directing group is also eligible for this transformation to give related products **4f–4h** in excellent yields. For the other slightly stronger chelating groups, oxazoline and triazole groups were demonstrated as good directing groups to promote the coupling process (**4i–4j**). Finally, a range of acetyl protected 2-iodoanilines were also evaluated, and acetonitrile proved to be the best solvent. Both electron-rich and -poor substrates were operative under standard reaction conditions, and all of the reactions afforded the desired products **4k–4o** in excellent yields.

Additional chelating groups were also investigated for this transformation (Scheme 3). We were delighted to find that

Scheme 3. Cu-Catalyzed Thiotrifluoromethylation of Aryl Iodides Containing Amide and Ester Directing Groups[a]



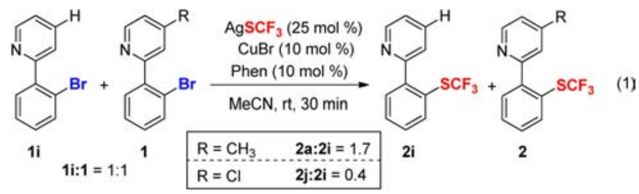
[a]Reaction conditions: 0.2 M arylhalides in 0.2 mmol scale, isolated yield. [b] Aryl bromide in CH_3CN at 120 °C

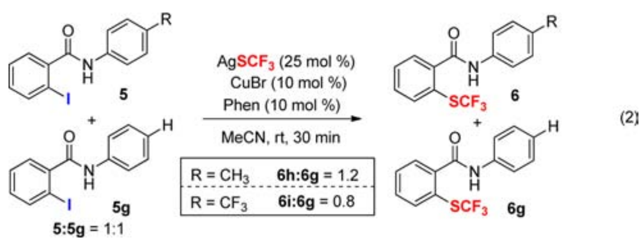
carboxamide was a good directing group to promote the desired trifluoromethylthiolation at room temperature in DMF, and a variety of functional groups, such as halide, ether, could be tolerated in the reaction conditions to provide products **6a–6g** in excellent yields. Further studies revealed that carboxylic ester groups were proven to be efficient in promoting the catalytic cross-coupling process, but with slightly lower reactivity. Aryl iodides bearing *ortho*-carboxylic ester groups could be efficiently coupled with $AgSCF_3$ to give products **8a–8g** in high yields at 80 °C. For substrate **7g**, the absence of any cyclization byproduct indicated the radical process was unlikely.

Finally, ketone as a directing group was also surveyed. As shown in Scheme 3, a related transformation did proceed very well in the acetonitrile at 80 °C. The *ortho*-SCF_3 arylketones **10a–10c** could be efficiently obtained in good yields. However, with these weak chelating groups, aryl bromides exhibited low reactivity. For instance, the trifluoromethylthiolation reaction of aryl bromide with the amide group was achieved at high temperature (120 °C) to give a good yield, but the reaction of *ortho*-ester and ketone aryl bromides exhibited poor reactivity even with higher temperatures.

To gain further insights into the reaction mechanisms of the Cu-catalyzed cross-coupling reactions, several radical scavengers, such as Tempo, BQ, and BHT, have been added to investigate the viability of the radical process (see Supporting Information (SI)). No suppressing effect was observed indicating that the involvement of the free radical process is unlikely.

In order to address the importance of directing groups in this reaction, competition experiments were conducted. For pyridyl directing groups, an electron-rich substituent will react faster than its electron-deficient counterpart (eq 1). Similar trends

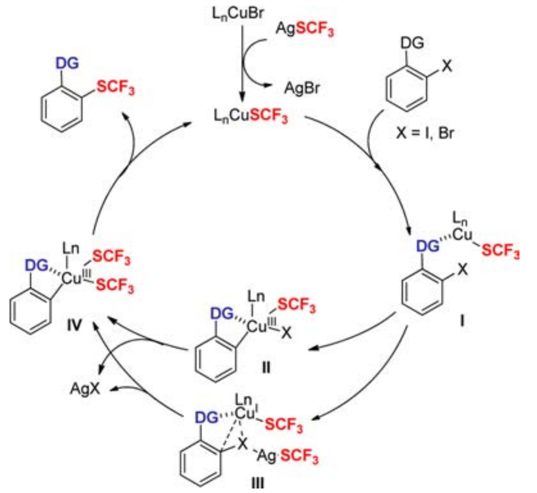




were discovered in benzamide substrates (eq 2). The more electron density that is within the directing group, the better the coordination ability with the copper catalyst to promote the oxidative addition toward the C–X bond.[11] Evaluation of the electronic properties on the aryl halide moiety suggested the electron-deficient aryl halide reacts faster than the electron-rich aryl halide substrates (see SI for details). This phenomenon is consistent with a previous report on the fluorination,[10a] which suggested a Cu(I/III) mechanism was involved in the catalytic cycle for the aryl-SCF_3 bond formation.

Based on the above results, a mechanism is proposed as shown in Scheme 4. The initial precoordination of arylhalides with Cu^ISCF_3 promotes an intramolecular oxidative addition to give the Cu(III) intermediate **II**. Subsequent ligand exchange with $AgSCF_3$ and reductive elimination of **IV** provided the desired trifluoromethylthiolation product. Alternatively, the oxidative addition of arylhalides to $CuSCF_3$ might also involve a complicated cooperative effect of silver as in the case of intermediate **III**, which could also release Cu(III) complex **IV** and AgX. Weng's study indicated that the stoichiometric trifluoromethylthiolation reaction can be achieved without a directing group, but with a higher temperature and slow reaction rate. The possible reason is that the oxidative addition

Scheme 4. Proposed Mechanism



of L_nCuSCF_3 with arylhalide is more difficult than CuSPh.[12] Thus, introducing a directing group could promote the oxidative addition, which resulted in the achievement of the catalytic reaction. In addition, silver also plays an important role for this transformation, because other SCF_3 sources, such as Me_4NSCF_3, exhibited much lower reactivity than that of $AgSCF_3$ (see SI).

In conclusion, we have developed the first Cu-catalyzed trifluoromethylthiolation of aryl bromides and iodides. Diverse coordinating groups have been identified that are very essential to promoting the catalytic reactions. For the strong coordinating pyridyl group, the cross-coupling reaction could take place even at room temperature. A detailed reaction mechanism is still under investigation.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental procedures, characterization, mechanistic study data, and additional data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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