Aromatic trifluoromethylation catalytic in copper†

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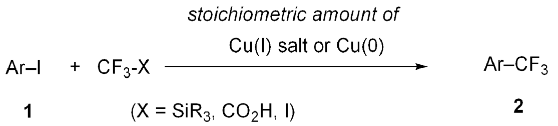
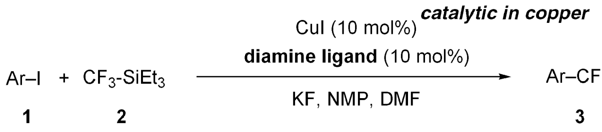
Cu(I)-diamine complexes were found to catalyse the trifluoromethylation of aryl iodides. In the presence of a small amount of CuX (X = Cl, Br, I) and 1,10-phenanthroline (phen), the cross-coupling reactions of iodoarenes with trifluoromethylsilanes proceeded smoothly to afford trifluoromethylated aromatics in good yields.

The cross-coupling reaction of organometallic reagents with aromatic halides in the presence of group 8–11 metal catalysts, notably nickel and palladium complexes, is the method of choice for wide range of aromatic C–C, C–N, C–O, C–S, C–P, or C–M bond-forming process.[1] Selective introduction of trifluoromethyl groups into aromatic compounds is of great importance in the medicinal, agricultural, and material sciences.[2,3] Fluoroalkyl cross-coupling is one of the most versatile methods to construct trifluoromethylated aromatics.[4,5] However, the progress of fluoroalkyl cross-coupling reactions has been much slower than that of general (non-fluorinated) cross-coupling reactions. Among aromatic trifluoromethylation reactions, the most promise has been demonstrated by the use of copper (Scheme 1).[6–9]



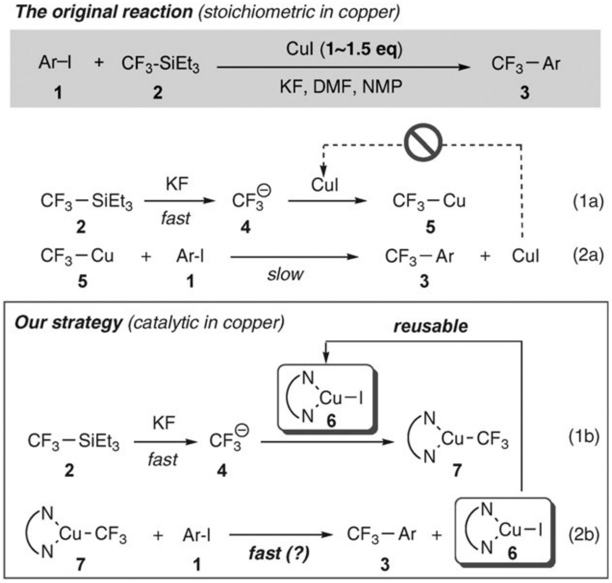
Scheme 1

Despite such synthetic utility, stoichiometric (sometimes, excess) amounts of copper reagents are required to complete these cross-coupling reactions. For the development of new practical and environmentally benign processes, it is desirable to reduce the quantity of heavy metal reagents employed in these transformations. Herein, we disclose an efficient procedure of aromatic trifluoromethylation using a diamine ligand, which makes possible a reaction using catalytic copper (Scheme 2).



Scheme 2

The propitious candidate for aromatic trifluoromethylation promoted by a small amount of copper is cross-coupling of aryl iodides with fluoroalkyl silanes.[7–9] Originally, Urata and Fuchikami reported the CuI-mediated cross-coupling protocols using CF_3SiEt_3, $C_2F_5SiMe_3$, and $C_3F_7SiMe_3$ as convenient fluoroalkyl sources under mild reaction conditions.[7] In spite of their operational simplicity, the singular, but significant drawback of the protocols is the loading of CuI (1–1.5 equiv.) to complete the desired reactions. The cross-coupling of aryl iodides **1** with trifluoromethyl silane **2** can be explained by assuming the pathway pictured in Scheme 3. First, a fluoride ion reacts with CF_3SiEt_3 (**2**) to give a trifluoromethyl anion species (**4**),[10] which readily undergoes generation of trifluoromethylcopper (**5**) (eqn (1a)) in Scheme 3). Next, σ-bond metathesis between CF_3Cu (**5**) and Ar–I (**1**) yields trifluoromethyl arenes **3** and CuI (eqn (2a)). The regenerated CuI in the second step would be reused to form CF_3Cu (**5**) in the first step again. However, the reaction rate of the first step leading to **4** seems to be much higher than that of second step affording **3** and CuI. Due to the sluggish regeneration of CuI in the second step, the net transformation cannot supply sufficient amount of CuI which reacts with trifluoromethyl anion **4** before its decomposition. This is the reason why a stoichiometric amount of CuI is needed for the cross-coupling process. Actually, Urata and Fuchikami reported that the use of a decreased amount (0.5 equiv.) of CuI resulted in the formation of the desired products **3** in less than 50% yields.[7a]



Scheme 3

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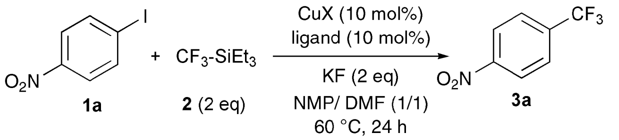
To overcome this shortcoming, we conceived a strategy to utilize copper (I)-diamine complexes **6** for the catalytic version of aromatic trifluoromethylation (eqn (1b) and (2b) in Scheme 3). Diamine ligands in trifluoromethylated complexes **7** would increase electron density at the metal centers by coordination and improve the nucleophilicity of the CF_3 moieties in **7** in the second step (eqn (2b)). Moreover, bidentate ligands are able to stabilize the soluble Cu(I) complexes by chelation. Thus, the use of diamine ligands is expected to accelerate the second step to regenerate sufficient amount of reusable complexes **6**. By this means, aromatic trifluoromethylation catalytic in copper would be accomplished.

Table 1



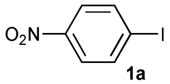
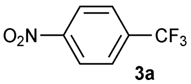
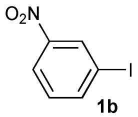
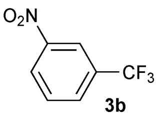
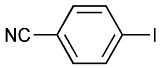
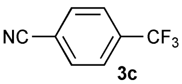
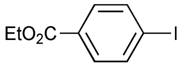
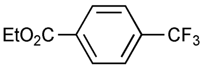
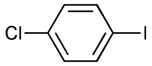
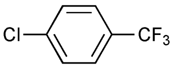
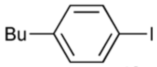
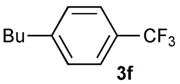
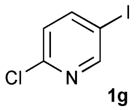
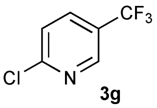
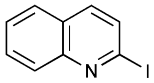
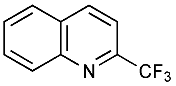
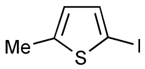
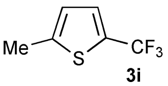
Entry	CuX	Ligand	%Yield of **3a**[a]
1	CuI	TMEDA[b]	40
2	CuI	bipy[c]	50
3	CuI	phen[d]	90
4	CuBr	phen	68
5	CuCl	phen	71

[a] NMR yield, which was calculated by ^{19}F NMR integration of product **3a** relative to the 2,2,2-trifluoroethanol internal standard. [b] *N*,*N*,*N*′,*N*′-Tetramethylethylenediamine. [c] 2,2′-Bipyridine. [d] 1,10-Phenanthroline.

In order to test our proposed methodology, catalytic amounts (10 mol%) of CuI and *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA) were added to a mixture containing 4-iodonitrobenzene, triethyl(trifluoromethyl)silane and KF in DMF/ NMP (entry 1 in Table 1). After 24 h at 60 °C, we were pleased to obtain 4-(trifluoromethyl)nitrobenzene (**3a**) in 40% NMR yield. The use of 2,2′-bipyridine (bipy) as a diamine ligand was found to be also effective for the cross-coupling reaction (entry 2). In particular, when 1,10-phenanthroline (phen) was employed as a catalyst ligand,[11] a significant increase of the product yield (90% NMR yield, 70% isolated yield) was observed (entry 3). Utilizing the phenanthroline ligand, CuBr and CuCl were applicable to the present trifluoromethylation to give **3a** in 68% and 71% yield, respectively (entries 4, 5).

Table 2

$$\underset{\mathbf{1}}{\text{Ar-I}} + \underset{\mathbf{2}\ (2\ \text{eq})}{CF_3\text{-}SiEt_3} \xrightarrow[\text{KF (2 eq), NMP/ DMF (1/1)} \\ 60\ ^\circ\text{C, 24 h}]{\text{CuI (10 mol\%)} \\ \text{phen (10 mol\%)}} \underset{\mathbf{3}}{Ar\text{-}CF_3}$$

Entry	Iodoarene **1**	Product **3**	%Yield of **3a**[ab]
1	 **1a**	 **3a**	90 (70)
2			54[c]
3			16[d]
4	 **1b**	 **3b**	90(63)
5	 **1c**	 **3c**	80
6[e]	 **1d**	 **3d**	89
7	 **1e**	 **3e**	63
8	 **1f**	 **3f**	44
9	 **1g**	 **3g**	69
10	 **1h**	 **3h**	99 (95)
11	 **1i**	 **3i**	63

[a] NMR yield, which were calculated by ^{19}F NMR integration of products **3** relative to the 2,2,2-trifluoroethanol internal standard. [b] The values in parentheses indicate the isolated yields of **3**. [c] The reaction was carried out in the presence of CuI (5 mol%) and phen (5 mol%). [d] The reaction was carried out in the presence of CuI (1 mol%) and phen (1 mol%). [e] CF_3SiEt_3 (1.2 eq) and KF (1.2 eq) were used.

Representative examples of the formation of trifluoromethyl arenes **2** are summarized in Table 2. Using 10 mol% of the copper(I) complex prepared *in situ* from CuI and phen in a molar ratio of 1 : 1[12] worked well for the cross-coupling of aryl iodides **1** with CF_3SiEt_3 (**2**) to afford the corresponding trifluoromethylated arenes **3** (entries 1, 4–11). In each case, selective aromatic trifluoromethylation was achieved; less than 3% yield of pentafluoroethylated by-product[6h,7] was observed. Even at 5 mol% and 1 mol% catalyst loading, 54% and 16% yields of **3a** were observed, respectively (entries 2, 3). Iodobenzenes **1a–e** endowed with electron-withdrawing groups on the aryl rings underwent catalytic trifluoromethylation smoothly to provide the desired cross-coupling products in high yields (entries 1, 4–7). The reaction of **1f** possessing a butyl group (an electron-donating group) with trifluoromethylsilane **2** delivered *p*-butyl(trifluoromethyl)benzene (**3f**) in 44% yield (entry 8). Furthermore, heteroaromatic iodides **1g–i** participated in cross-coupling reactions smoothly to yield the corresponding trifluoromethylated heteroaromatics **3g–i**. (entries 9–11).

In conclusion, we have demonstrated that a small amount of the CuI–phenanthroline complex engenders the cross-coupling reactions of aryl/heteroaryl iodides with CF_3SiEt_3 to give trifluoromethylated arenes in moderate to high yield. The substrate scope of the present methodology is broad and a variety of functional groups are tolerated. The catalyst design based on fine-tuning of ligand is essential to the development of efficient fluoroalkylation reactions.[13]

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