DOI: 10.1002/cjoc.201700311

Copper-Promoted Conversion of Aromatic Amines into Trifluoromethylated Arenes: One-Pot Sandmeyer Trifluoromethylation

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A simple copper-promoted one-pot Sandmeyer trifluoromethylation of aromatic amines with Langlois' reagent has been demonstrated. The reaction is performed in mild reaction conditions under an air atmosphere with good substrate scope and functional group compatibility. It provides an alternative and straightforward synthetic approach to access a variety of trifluoromethylated arenes.

Keywords copper, sandmeyer trifluoromethylation, aromatic amine, langlois' reagent, trifluoromethylated arene

Introduction

Organofluorine compounds are biologically important due to their ubiquity in many top-selling pharmaceuticals, agrochemicals and functional materials.[1] Among the commonly familiar fluoroalkyl groups, the trifluoromethyl (CF_3) group has occupied a significant segment, because CF_3 group could enhance the metabolic stability, lipophilicity and bioavailability of the parent molecules.[2] However, CF_3-containing compounds are absent in nature, which accounts for the vital importance of developing efficient methods to introduce CF_3 group into parent structures.[1-3] The traditional methods for incorporation of CF_3 group into aromatic backbones are Swarts-type reactions. However, this reaction requires chlorine-fluorine exchange in the presence of HF under harsh conditions and has a relatively narrow substrate scope (Figure 1a).[4] Such process is not appropriate for late-stage incorporation of a CF_3 group into an aromatic structure. To solve the problem, methods for direct trifluoromethylation of aromatic compounds have been developed. A commonly applied approach is transition-metal-promoted or transition-metal-catalyzed trifluoromethylation of aryl halides with CF_3 reagents (Figure 1b),[5] most of which involve an MCF_3 intermediate that is generated in situ or preisolated. Meanwhile, closely related methods for conversion of boron group into a CF_3 group have also been disclosed (Figure 1c).[6] This transformation is usually accomplished by cross-coupling of aryl anion with electrophilic CF_3 sources (CF_3^+) or oxidative Chan-Lam-type coupling of aryl anion with nucleophilic CF_3 reagents (CF_3^-). Moreover, a distinct approach to incorporate the CF_3 group is the radical trifluoromethylation of an aromatic C—H bond via transition-metal-catalyzed/promoted or transition-metal-free procedure (Figure 1d).[7] Although significant advances in aromatic trifluoromethylation have been made, for fur-

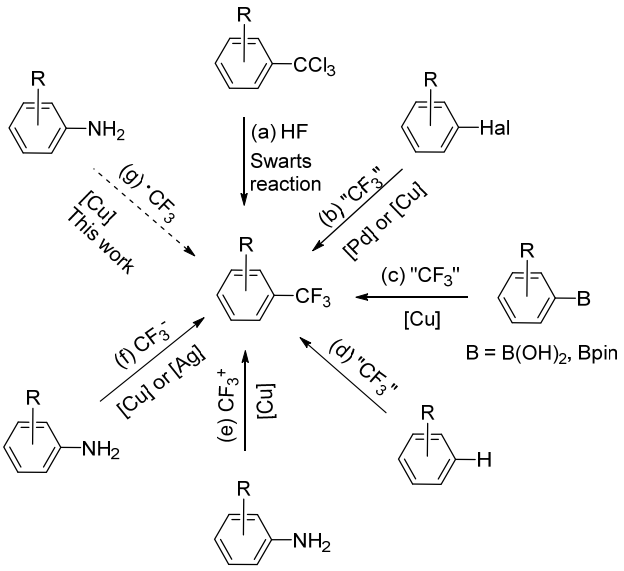

Figure 1 Methods for aryl trifluoromethylation.

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Received May 3, 2017; accepted June 25, 2017; published online XXXX, 2017.
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/cjoc.201700311 or from the author.

ther improvement of the flexibility and selectivity of the trifluoromethylation process, it remains important to explore the conversion of other functional groups into CF_3 group.

Aromatic amines are inexpensive and readily available substrates. It is well known that the aromatic amino group can be easily converted into various functional groups such as hydroxyl, halogen, cyano, borate, and azido groups.[8] This transformation usually goes through two reaction steps. The first one is the diazotization of aromatic amines with nitrous acid or alkyl nitrite, generating the aryl diazonium salts which are important intermediates in organic synthesis. The second step is the conversion of diazonium group into target functional groups. Since the first discovery by Griess in 1858,[9] aryl diazonium salts have been extensively studied and widely used for the preparation of functionalized arenes.[8,10] The conversion of anilines into aryl halides or pseudohalides, known as the Sandmeyer reaction,[11] is the most prominent method for functional group transformation. This classic transformation is not only routinely practiced in research laboratories but also widely applied in chemical industry. The conversion of anilines into trifluoromethylated arenes, recently called the Sandmeyer trifluoromethylation, has been witnessed as an efficient strategy for incorporation of CF_3 into an aromatic ring.[12] Examples are one pot trifluoromethylations of aromatic amines with CF_3^+ reagent (Umemoto's reagent) disclosed by Fu's group (Figure 1e),[12a] and with CF_3^- species (Ruppert's reagent (CF_3SiMe_3) and CHF_3) developed by Wang *et al*.,[12b,12f] Goossen *et al*.[12e,12g] and Grushin's group[12d] (Figure 1f). Another slightly cumbersome approach to access trifluoromethylated arenes is trifluoromethylation of arenediazonium tetrafluoroborates preisolated from reaction of anilines and *t*-BuONO/HBF_4. Examples of this methodolog are developed by Goossen *et al*.[12c] and Qing's group.[12h] Although the Sandmeyer trifluoromethylations have been reported independently by the aforementioned groups, method to access trifluoromethylated arenes by one pot manner in combination with the empolyment of $\bullet CF_3$ species hasn't been revealed yet.

Herein, we want to report the copper-promoted trifluoromethylation of aromatic amines, which can proceed via the reaction of active $\bullet CF_3$ species with aryl diazonium salts generated in situ from the reaction of aniline derivatives and $NaNO_2$/HCl. To establish this protocol, we pay attention to search for a practical potential source of $\bullet CF_3$. Several documents have shown that the incorporation of $NaSO_2CF_3$ (Langlois' reagent) and TBHP (*t*-BuOOH) can generate trifluoromethyl radical at room temperature under ambient air and moisture.[7c,13] We reason that trifluoromethylation of anilines could achieve selectively in the presence of Cu salt, $NaSO_2CF_3$ and TBHP (Figure 1g).

Experimental

General information

All reagents were obtained commercially and used without further purification. Column chromatography was carried out on silica gel (200−300 mesh). ^{1}H NMR spectra were recorded on 400 MHz in $CDCl_3$ or DMSO. ^{19}F spectra were recorded on 376 MHz in $CDCl_3$ or DMSO. ^{13}C NMR spectra were recorded on 101 MHz in $CDCl_3$ or DMSO. Chemical shifts (δ) were recorded with tetramethylsilane (TMS) as the internal reference standard. Multiplicities are given as: s (singlet), d (doublet), t (triplet), dd (doublet of doublets), dq (doublet of quartets), q (quartet) or m (multiplet).

General procedure for the synthesis of the products

Aromatic amine (0.5 mmol) and aq. HCl (28% in water, 1.0 mmol) were placed in a round-bottom flask equipped with a stirring bar at 0 ℃. A minute later, $NaNO_2$ (0.55 mmol) was added to the reaction flask and continued to react for 20 min. To this solution were added $NaHCO_3$ (0.4 mmol), $NaSO_2CF_3$ (1.5 mmol), CuCl (0.3 mmol), TBHP (2.5 mmol) and CH_3CN (5 mL) in turn. The reaction mixture was stirred at ambient temperature for 20 h. Then the resulting mixture was filtered through a short pad of celite and rinsed with diethyl ether (15 mL). The filtrate was washed with water (3×10 mL) and brine (10 mL). The organic layer was dried over Na_2SO_4, filtered and concentrated under vacuum (low temperature). The residue was further purified by flash chromatography (silica gel, petroleum ether/ethyl acetate gradient) to give the pure products.

4-(Trifluoromethyl)biphenyl (3a)[14] Colorless solid, 0.090 g, 81%. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.75 (d, J=8.4 Hz, 4H), 7.64 (d, J=7.7 Hz, 2H), 7.52 (t, J=7.6 Hz, 2H), 7.48−7.42 (m, 1H); ^{19}F NMR (376 MHz, $CDCl_3$) δ: −62.38 (s, 3F); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 144.77 (s), 139.79 (s), 129.38 (q, J=32.5 Hz), 128.21 (s), 127.44 (s), 127.30 (s), 125.73 (q, J=3.8 Hz), 124.3 (q, J=272.0 Hz).

4-Chlorobenzotrifluoride (3b)[14] Colorless liquid, 55% (Yield determined by ^{19}F NMR spectroscopy using 1,3,5-trifluorobenzene as an internal standard). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.59 (d, J=8.4 Hz, 2H), 7.47 (d, J=8.5 Hz, 2H); ^{19}F NMR (376 MHz, $CDCl_3$) δ: −62.84 (s, 3F); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 138.1 (s), 129.0 (s), 129.1 (q, J=32.5 Hz), 126.6 (q, J=3.8 Hz), 123.8 (q, J=272.0 Hz).

4-Bromobenzotrifluoride (3c)[15] Colorless liquid, 61% (Yield determined by ^{19}F NMR spectroscopy using 1,3,5-trifluorobenzene as an internal standard). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.68−7.60 (m, 2H), 7.51 (d, J=8.4 Hz, 2H); ^{19}F NMR (376 MHz, $CDCl_3$) δ: −63.00 (s, 3F); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 132.0 (s), 129.6 (q, J=32.5 Hz), 126.8 (m), 126.4 (m), 123.9 (q, J=272.0 Hz).

4-Trifluoromethyltoluene (3d)[14] Colorless liquid, 75% (Yield determined by ^{19}F NMR spectroscopy using

1,3,5-trifluorobenzene as an internal standard). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.58 (d, J=8.0 Hz, 2H), 7.33 (d, J=8.0 Hz, 2H), 2.47 (s, 3H); ^{19}F NMR (376 MHz, $CDCl_3$) δ: −62.38 (s, 3F); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 142.1 (s), 129.3 (s), 127.9 (q, J=32.5 Hz), 125.1 (q, J=3.8 Hz), 124.5 (q, J=272.0 Hz).

4-Trifluoromethylanisole (3e)[14] Colorless liquid, 67% (Yield determined by ^{19}F NMR spectroscopy using 1,3,5-trifluorobenzene as an internal standard). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.60 (d, J=8.8 Hz, 2H), 7.00 (d, J=8.7 Hz, 2H), 3.87 (s, 3H); ^{19}F NMR (376 MHz, $CDCl_3$) δ: −61.56 (s, 3F); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 162.1 (s), 126.8 (q, J=3.8 Hz), 124.6 (q, J=272.0 Hz), 122.8 (q, J=32.5 Hz), 113.9 (s), 55.1 (s).

4-(Trifluoromethyl)benzonitrile (3f)[15] White solid, 0.039 g, 46%. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.83 (d, J=8.2 Hz, 2H), 7.78 (d, J=8.3 Hz, 2H); ^{19}F NMR (376 MHz, $CDCl_3$) δ: −63.55 (s, 3F); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 134.5 (q, J=32.5 Hz), 132.7 (s), 126.2 (q, J=3.8 Hz), 123.1 (q, J=272.0 Hz), 117.4 (s), 116.1 (s).

1-Nitro-4-(trifluoromethyl)benzene (3g)[14] White solid, 0.030 g, 32%. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.37 (d, J=8.7 Hz, 2H), 7.86 (d, J=8.8 Hz, 2H); ^{19}F NMR (376 MHz, $CDCl_3$) δ: −63.31 (s, 3F); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 150.0 (s), 136.0 (q, J=32.5 Hz), 126.7 (q, J=3.8 Hz), 124.0 (s), 127.3 (q, J=272.0 Hz).

1-(4-(Trifluoromethyl)phenyl)ethanone (3h)[14] Colorless solid, 0.069 g; 73%. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.00 (d, J=7.9 Hz, 2H), 7.66 (d, J=8.1 Hz, 2H), 2.66−2.58 (m, 3H); ^{19}F NMR (376 MHz, $CDCl_3$) δ: −63.18 (s, 3F); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 196.8 (s), 139.6 (s), 134.2 (q, J=32.5 Hz), 128.5 (s), 125.5 (q, J=3.8 Hz), 123.5 (q, J=272.0 Hz), 26.5 (s).

3-Trifluoromethylpyridine (3i)[15] Colorless liquid, 19% (Yield determined by ^{19}F NMR spectroscopy using 1,3,5-trifluorobenzene as an internal standard). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.88−8.65 (m, 2H), 7.90−7.79 (m, 1H), 7.39−7.30 (m, 1H); ^{19}F NMR (376 MHz, $CDCl_3$) δ: −63.03 (s, 3F); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 152.8 (s), 146.5 (q, J=3.8 Hz), 132.9 (m), 126.6 (q, J=32.5 Hz), 123.3 (q, J=272.0 Hz), 123.2 (s).

Trifluoromethylbenzene (3j)[14] Colorless liquid, 83% (Yield determined by ^{19}F NMR spectroscopy using 1,3,5-trifluorobenzene as an internal standard). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.76 (d, J=7.7 Hz, 2H), 7.64 (t, J=7.4 Hz, 1H), 7.57 (t, J=7.5 Hz, 2H); ^{19}F NMR (376 MHz, $CDCl_3$) δ: −62.91 (s, 3F); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 131.7 (s), 130.8 (q, J=32.5 Hz), 128.7 (s), 125.1 (q, J=3.8 Hz), 124.4 (q, J=272.0 Hz).

1,4-Bis(trifluoromethyl)benzene (3k)[16] Colorless liquid, 0.040 g, 37%. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.17 (s, 4H); ^{19}F NMR (376 MHz, $CDCl_3$) δ: −63.00 (s).

2-(Trifluoromethyl)naphthalene (3l)[17] White solid, 0.058 g, 59%. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.19 (s, 1H), 8.06−7.90 (m, 3H), 7.77−7.57 (m, 3H); ^{19}F NMR (376 MHz, $CDCl_3$) δ: −62.24 (s, 3F); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 134.6 (q, J=0.9 Hz), 132.20 (s), 129.0 (s), 128.8 (s), 128.0 (s), 127.9 (s), 127.7 (q, J=32.5 Hz), 127.1 (s), 125.6 (q, J=4.6 Hz), 124.4 (q, J=272.0 Hz), 121.4 (q, J=3.8 Hz).

6-(Trifluoromethyl)quinolone (3m)[12c] White solid, 0.050 g, 46%. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.91 (s, 1H), 8.06 (d, J=8.5 Hz, 2H), 7.79 (s, 1H), 7.66 (s, 1H), 7.43 (s, 1H); ^{19}F NMR (376 MHz, $CDCl_3$) δ: −62.32 (s).

4-(Trifluoromethyl)benzoic acid (3n)[12d] White solid, 0.067 g, 70%. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 13.47 (s, 1H), 8.13 (d, J=8.1 Hz, 2H), 7.89−7.82 (m, 2H); ^{19}F NMR (376 MHz, DMSO-d_6) δ: −61.72 (s, 3F); ^{13}C NMR (101 MHz, DMSO-d_6) δ: 166.6 (s), 135.0 (s), 133.0 (q, J=32.5 Hz), 130.5 (s), 126.0 (s), 124.2 (q, J=272.0 Hz).

3-(Trifluoromethyl)benzoic acid (3o)[12d] White solid, 0.054 g, 57%. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 12.22 (br s, 1H), 8.60−8.23 (m, 2H), 7.91 (d, J=7.8 Hz, 1H), 7.67 (t, J=7.8 Hz, 1H); ^{19}F NMR (376 MHz, $CDCl_3$) δ: −62.91 (s, 3F); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 171.1 (s), 133.4 (s), 131.3 (q, J=32.5 Hz), 130.4 (q, J=3.6 Hz), 130.1 (s), 129.2 (s), 127.2 (q, J=3.8 Hz), 123.6 (q, J=272.0 Hz).

2-(Trifluoromethyl)benzoic acid (3p)[10d] White solid, 0.061 g, 64%. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 10.86 (br s, 1H), 8.02 (br s, 1H), 7.83 (br s, 1H), 7.70 (br s, 2H); ^{19}F NMR (376 MHz, $CDCl_3$) δ: −59.32 (s, 3F); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 172.1 (s), 132.2 (s), 131.8 (s), 131.2 (s), 129.6 (q, J=1.8 Hz), 129.5 (q, J=32.5 Hz), 127.0 (q, J=5.6 Hz), 123.2 (q, J=272.0 Hz).

Methyl 4-(trifluoromethyl)benzoate (3q)[12d] Colorless liquid, 0.069 g, 68%. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.06 (d, J=7.1 Hz, 2H), 7.62 (d, J=7.1 Hz, 2H), 3.89 (ddd, J=6.8, 5.3, 3.6 Hz, 3H); ^{19}F NMR (376 MHz, $CDCl_3$) δ: −63.55 (s, 3F); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 165.5 (s), 134.2 (q, J=32.5 Hz), 133.3 (s), 129.8 (s), 125.2 (q, J=3.8 Hz), 123.6 (q, J=272.0 Hz), 52.1 (s).

Ethyl 4-(trifluoromethyl)benzoate (3r)[15] Light yellow liquid, 0.067 g, 61%. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.22−8.11 (m, 2H), 7.67 (t, J=5.4 Hz, 2H), 4.45−4.37 (m, 2H), 1.44−1.37 (m, 3H); ^{19}F NMR (376 MHz, $CDCl_3$) δ: −63.33 (s, 3F); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 165.2 (s), 134.3 (q, J=32.5 Hz), 133.7 (s), 129.8 (s), 125.2 (m), 123.6 (q, J=272.0 Hz), 61.41 (s), 14.03 (s).

1-Ethynyl-4-(trifluoromethyl)benzene (3s)[12d] Colorless liquid, 0.030 g, 36%. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.61 (s, 4H), 3.22 (s, 1H); ^{19}F NMR (376 MHz, $CDCl_3$) δ: −63.01 (s, 3F); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 132.4 (s), 130.8 (q, J=32.5 Hz), 125.2 (q, J=3.8 Hz), 124.5 (q, J=272.0 Hz), 82.2 (s), 79.6 (s).

1-(Trifluoromethyl)-4-vinylbenzene (3t)[12b] Volatile compound, 0.005g, 6%. ^{19}F NMR (376 MHz, $CDCl_3$) δ: −62.06 (s, 3F). EI-MS (m/z): 172 (M^+).

3-Bromobenzotrifluoride (3v)[12h] Colorless oil, 0.024 g, 22%. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.65 (s, 1H), 7.58−7.52 (m, 2H), 7.45 (t, J=7.9 Hz, 1H); ^{19}F

NMR (376 MHz, $CDCl_3$) δ: −62.98 (s, 3F); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 134.9 (s), 132.3 (q, J=32.5 Hz), 132.0 (s), 130.2 (s), 125.6 (q, J=3.8 Hz), 123.4 (q, J=3.8 Hz), 123.3 (q, J=272.0 Hz).

3-Trifluoromethyltoluene (3w)[12c] Colorless liquid, 0.059 g, 74%. ^1H NMR (400 MHz, $CDCl_3$) δ: 7.48−7.37 (m, 4H), 2.44 (s, 3H); ^{19}F NMR (376 MHz, $CDCl_3$) δ: −62.64 (s, 3F); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 138.7 (s), 132.4 (s), 130.5 (q, J=32.5 Hz), 128.6 (s), 125.7 (q, J=3.8 Hz), 124.4 (q, J=272.0 Hz), 122.3 (q, J=3.8 Hz), 21.3 (s).

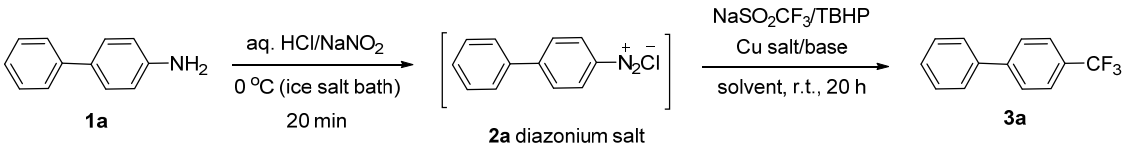
Methyl-3-(trifluoromethyl)benzene (3x)[12c] Colorless liquid, 0.060 g, 68%. ^1H NMR (400 MHz, $CDCl_3$) δ: 7.42 (t, J=8.0 Hz, 1H), 7.25 (d, J=7.7 Hz, 1H), 7.18 (s, 1H), 7.11 (d, J=8.3 Hz, 1H), 3.87 (s, 3H); ^{19}F NMR (376 MHz, $CDCl_3$) δ: −62.76 (s, 3F); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 159.8 (s), 131.8 (q, J=32.5 Hz), 129.9 (s), 124.1 (q, J=272.0 Hz), 117.5 (s), 117.3 (q, J=3.8 Hz), 110.7 (q, J=3.8 Hz), 55.3 (s).

Results and Discussion

We initiated our study on the model reaction of $NaSO_2CF_3$ with biphenyl diazonium salt generated in situ by treatment of 4-biphenylamine and $NaNO_2$/HCl at 0 ℃. To our delight, the trifluoromethylated product **3a** was obtained in 33% yield when the reaction was carried out in DMSO in the presence of CuCl and TBHP. Inspired by this result, we further tested the effect of different solvents, copper salts, and additives. As presented in Table 1, the conversion worked in a range of solvents such as toluene, DMSO, DMF and CH_3CN, and afforded the desired product in 19%−69% isolated yields based on the aromatic amine (Table 1, Entries 1−5). Significantly, employment of CH_3CN as reaction solvent gave a best yield for this transformation. In further screening the effect of different promoters, CuCl was proved to be more efficient comparing with other copper salts such as CuBr, $Cu(OTf)_2$, $CuCl_2$, $CuBr_2$, CuO, and $Cu(OAc)_2$ (Table 1, Entries 6−11). Examining the effect of inorganic base led to arriving at much improved condition in which **3a** was obtained in 79% yield when the reaction was carried out using $NaHCO_3$ as additive (Table 1, Entry 14). After screening of $NaSO_2CF_3$, TBHP and $NaHCO_3$ loading, the best outcome was found when 4-biphenylamine reacted with 3 equiv. of $NaSO_2CF_3$, 5 equiv. of TBHP, and 0.8 equiv. of $NaHCO_3$ using CuCl as a promoter in CH_3CN (Table 1, Entry 23). It is worth mentioning that no desired product was observed in the absence of copper salts (Table 1, Entry 24). Some important features of this protocol should be demonstrated here. Firstly, the reaction was performed under an air atmosphere without any purification of the commercial solvents and reagents. Moreover, the transformation was conducted under mild reaction conditions and gave 4-(trifluoromethyl)-1,1'-biphenyl in good yield.

With optimized conditions established (Table 1, Entry 23) for the Sandmeyer trifluoromethylation, we subsequently investigated the scope of aromatic amine

Table 1 Optimization of reaction conditions for the trifluoromethylation of **1a**[a]



1a **2a** diazonium salt **3a**

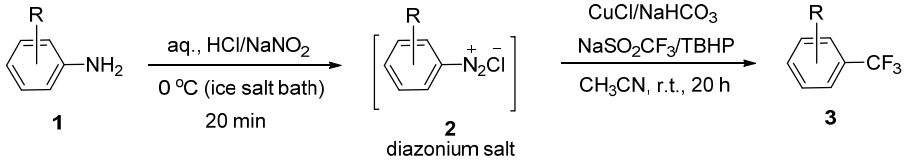
Entry	Cu salt	Base	Solvent	T/℃	Yield/%	Entry	Cu salt	Base	Solvent	T/℃	Yield/%
1	CuCl	—	DMSO	0−r.t.	33	13	CuCl	K_2CO_3	CH_3CN	0−r.t.	46
2	CuCl	—	DMF	0−r.t.	46	14	CuCl	$NaHCO_3$	CH_3CN	0−r.t.	79
3	CuCl	—	CH_3CN	0−r.t.	69	15	CuCl	$KHCO_3$	CH_3CN	0−r.t.	57
4	CuCl	—	Toluene	0−r.t.	19	16	CuCl	NaOH	CH_3CN	0−r.t.	27
5	CuCl	—	CH_3CN	0−40C	54	17	CuCl	KOH	CH_3CN	0−r.t.	29
6	CuBr	—	CH_3CN	0−r.t.	14	18[c]	CuCl	$NaHCO_3$	CH_3CN	0−r.t.	67
7	$Cu(OTf)_2$	—	CH_3CN	0−r.t.	39	19[d]	CuCl	$NaHCO_3$	CH_3CN	0−r.t.	78
8	$CuCl_2$	—	CH_3CN	0−r.t.	47	20[e]	CuCl	$NaHCO_3$	CH_3CN	0−r.t.	75
9	$CuBr_2$	—	CH_3CN	0−r.t.	25	21[f]	CuCl	$NaHCO_3$	CH_3CN	0−r.t.	79
10	CuO	—	CH_3CN	0−r.t.	31	22[g]	CuCl	$NaHCO_3$	CH_3CN	0−r.t.	70
11	$Cu(OAc)_2$	—	CH_3CN	0−r.t.	33	**23[h]**	**CuCl**	**$NaHCO_3$**	**CH_3CN**	**0−r.t.**	**81**
12	CuCl	Na_2CO_3	CH_3CN	0−r.t.	61	24	none	$NaHCO_3$	CH_3CN	0−r.t.	0

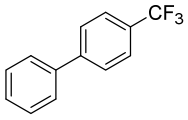
[a] Conditions: preparation of the diazonium salt: 4-biphenylamine **1a** (0.5 mmol), aq. HCl (28% in water, 1.0 mmol), $NaNO_2$ (0.55 mmol), solvent, 0 ℃ (ice salt bath), 20 min; Cu salt (0.6 mmol), base (0.6 mmol, 1.0 mL H_2O), $NaSO_2CF_3$ (1.5 mmol), TBHP (2.5 mmol), solvent, temp., 20 h under an air atmosphere. [b] Yields of isolated pure products. [c] 1.0 mmol $NaSO_2CF_3$ was used. [d] 2.0 mmol $NaSO_2CF_3$ was used. [e] 2.0 mmol TBHP was added. [f] 3.0 mmol TBHP was added. [g] 0.3 mmol $NaHCO_3$ was used. [h] 0.4 mmol $NaHCO_3$ was used.

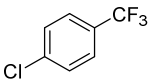
derivatives (Table 2). It was found that aromatic amines bearing electron-withdrawing groups such as halogens, cyano, nitro, acyl, trifluoromethyl, esters, and even carboxyl worked well under standard reaction conditions, giving the corresponding trifluoromethylated products (**3b**—**3c**, **3f**—**3h**, **3k**, **3n**—**3r** and **3v**) in modest to good yields. Meanwhile, trifluoromethylation of aniline derivatives containing electron-donating groups including aryl, alkyl and alkoxy afforded the desired trifluoromethylated products (**3a**, **3d**—**3e**, **3l** and **3w**—**3x**) in 59%—81% yields. In some previous reports, $NaSO_2CF_3$ in combination with TBHP was proven to be capable of trifluoromethylating the aromatic or heteroaromatic C—H bond under transition-metal-catalyzed/promoted or transition-metal-free conditions.[7c,13a,13b] However, under the present condition, all the C—H bonds were inert to the trifluoromethylation process. The reaction also tolerated well multiple bond such as C≡C triple bond, giving the trifluoromethylated product **3s** in modest yields. In regard to 4-vinylaniline **1t**, the trifluoromethylated products were very complicated (The formation of compound **3t** was confirmed by ^{19}F NMR comparing with the previously reported data).[12b] This may be due to the competitive substitution of $-N_2^+$ and radical addition to C=C double bond in the vinylbenzenediazonium. In the case of heteroaromatic amines (including 3-aminopyridine **2i** and 6-aminoquinoline **2m**), the transformation was still efficient to produce the corresponding trifluoromethylated products in spite of a decrease in the reaction yield, presumably attributed to the protonation of the nitrogen heteroatom during the diazotization. For heteroaromatic amine such as adenine **1u**, the trifluoromethylation process was completely shut down as a result of the strong protonation of heterocyclic nitrogen atoms. All the products were obtained in sufficiently pure form. Only for some simple, low-boiling substrates, the yields of the products were determined by ^{19}F NMR spectroscopy using 1,3,5-trifluorobenzene as an internal standard.

To shed light on the mechanism of the reaction, the following experiments were performed (Figure 2). Firstly, 4 equiv. of radical scavenger TEMPO was introduced to standard trifluoromethylation reaction (Figure 2a), no desired product **3j** was detected in ^{19}F NMR spectroscopy. Meanwhile, a signal at δ –56.18 ascribing to TEMPO-CF_3 **4** was observed.[12b] This result indicates CF_3 radical should be a key species for the trifluoromethylation of aromatic amine. On the other hand, the reaction of Langlois' reagent, TBHP and CuCl in addition of TEMPO was examined (Figure 2c). The

Table 2 Substrate scope of copper-promoted trifluoromethylation of aromatic amines[a]




3a, 81%[b]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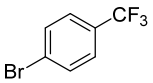
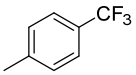
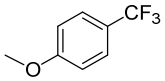

3c, 61%[c]


3d, 75%[c]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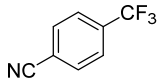
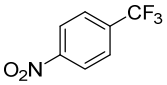
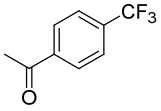

3f, 46%[b]


3g, 32%[b]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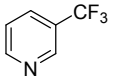
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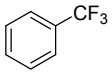
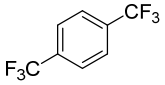
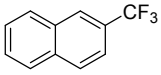

3j, 83%[c]


3k, 37%[b]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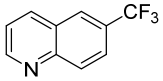
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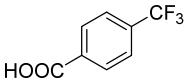
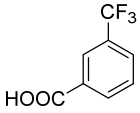

3n, 70%[b]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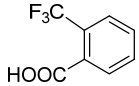
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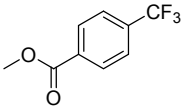
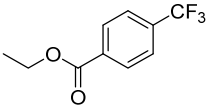
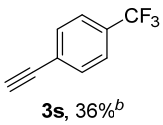
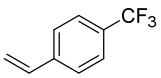
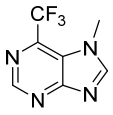
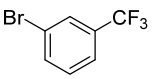

3q, 68%[b]

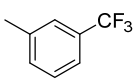

3r, 61%[b]

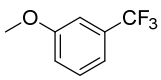

3s, 36%[b]


3t, 6%[c]


3u, 0%


3v, 22%[b]


3w, 74%[b]


3x, 68%[b]

[a] Conditions: preparation of the diazonium salts: aromatic amines (0.5 mmol), aq. HCl (28% in water, 1.0 mmol), $NaNO_2$ (0.55 mmol), CH_3CN, 0 ℃ (ice salt bath), 20 min; CuCl (0.6 mmol), $NaHCO_3$ (0.4 mmol, 1.0 mL H_2O), $NaSO_2CF_3$ (1.5 mmol), TBHP (2.5 mmol) and CH_3CN, at room temperature, 20 h under an air atmosphere. [b] Yields of isolated pure products. [c] Yields determined by ^{19}F NMR spectroscopy using 1,3,5-trifluorobenzene as an internal standard.

generation of TEMPO-CF_3 **4** was also confirmed by ^{19}F NMR. However, when treating Langlois' reagent with TBHP and TEMPO without addition of CuCl (Figure 2b), no reaction was observed. Thus, these experiments imply the generation of CF_3 radical when Langlois' reagent is treated with TBHP in the presence of CuCl.

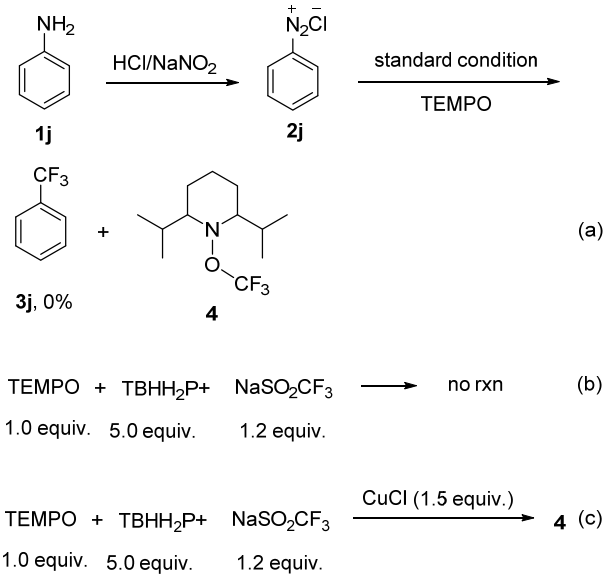


Figure 2 Trapping of CF_3 radical with TEMPO.

Based on the results described above and the previous documents,[12a,13] a plausible mechanism for the copper(I)-promoted Sandmeyer trifluoromethylation was illustrated in Figure 3. Firstly, the diazotization of aromatic amines afforded the diazonium salts **2**. Then Cu(I)-mediated single electron transfer (SET) with **2** generated the diazo radical, which released nitrogen gas to form the aryl radical. On the other hand, the reaction of $NaSO_2CF_3$ and TBHP released the CF_3 radical, which subsequently reacted with Cu(I) species to generate the corresponding Cu(II)CF_3 species. Finally, abstraction of the trifluoromethyl group from the copper(II) intermediate by aryl radical gave the desired products along with a copper(I) species.

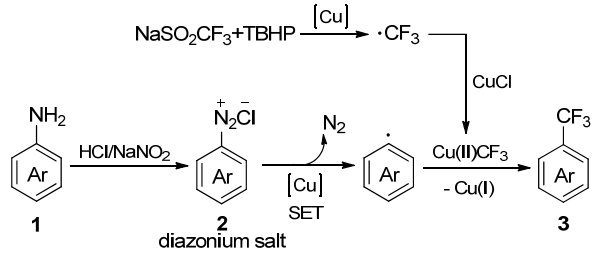


Figure 3 Proposed mechanism for aryl trifluoromethylation.

Conclusions

In summary, we have developed a simple CuCl-promoted one-pot Sandmeyer trifluoromethylation reaction of aromatic amines with Langlois' reagent. The reaction is operationally simple and proceeds well for a range of different aromatic amine substrates with electron-donating groups as well as electron-withdrawing groups in mild reaction conditions under an air atmosphere. Thus, this transformation is a valuable complement to the previously established Sandmeyer trifluoromethylation methods.

Acknowledgement

We acknowledge the financial support for this work from the National Natural Science Foundation of China (Nos. 21502070 and 21562041) and the Fundamental Research Funds for the Central Universities (No. JUSRP51626B).

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