Organic LETTERS

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# Copper-Mediated Trifluoromethylthiolation of $\alpha$-Diazoesters

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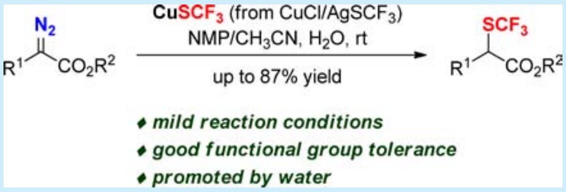
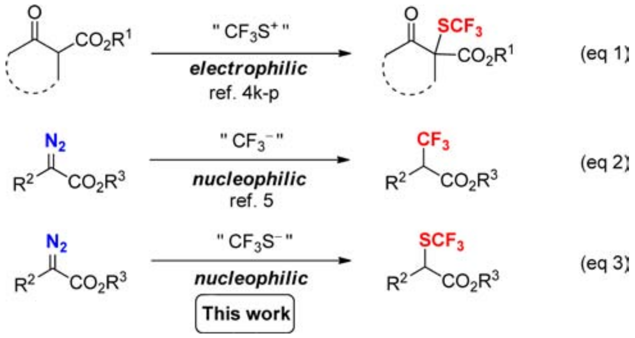
*Supporting Information*

**ABSTRACT:** A novel Cu-mediated trifluoromethylthiolation of diazo compounds has been developed that provides a convenient synthetic route for the efficient $\alpha$-trifluoromethylthiolation of simple esters under mild reaction conditions. The reaction is typically carried out at room temperature, and water could be used to promote the reaction.



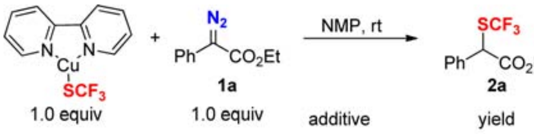
The introduction of an organic moiety that increases the lipophilicity of a drug candidate has become an important strategy in drug design because the lipophilicity parameter greatly contributes to the enhanced transmembrane permeation and the overall potency of the drug molecule.[1] In this context, the trifluoromethylthio ($CF_3S$) group has attracted much attention since it possesses admirable lipophilicity (Hansch–Leo $\pi$ value = 1.44).[2] Although the $CF_3S$ group has fascinated researchers for decades, the past five years have witnessed a "renaissance" of $CF_3S$-related chemistry, and a rapid progress in the development of new synthetic methods for efficient and direct trifluoromethylthiolation has emerged.[3,4] Among many transition-metal-free or -mediated trifluoromethylthiolation reactions, the selective introduction of the $CF_3S$ group into the $\alpha$-position of $\beta$-ketoesters has been intensively studied by using *electrophilic* trifluoromethylthiolating agents (Scheme 1, eq 1).[4k−p] However, the $\alpha$-trifluoromethylthiolation of simple carboxylic esters still remains an unsolved problem. Previously, we developed a general procedure for the $\alpha$-trifluoromethylation of carboxylic esters via Cu(I)-mediated trifluoromethylation of $\alpha$-diazoesters (Scheme 1, eq 2).[5] It was found that the pregenerated "$CuCF_3$" species (from $TMSCF_3$/CsF/CuI) is sluggish in the reaction with $\alpha$-diazoesters, but the addition of water or CuI could significantly promote the trifluoromethylation reaction presumably by activating the "$CuCF_3$" species.[5] We envisioned that a similar protocol might also be amenable to the installation of a $CF_3S$ group at the $\alpha$-position of a carboxylic ester by using a *nucleophilic* trifluoromethylthiolating agent ($CuSCF_3$)[3] (Scheme 1, eq 3).

**Scheme 1. Electrophilic and Nucleophilic Trifluoromethylthiolation and Trifluoromethylation of Esters**



Initially, a structurally well-defined $CF_3S$-transferring agent [(bpy)$CuSCF_3$][4i] was chosen to test the trifluoromethylthiolation reaction with diazo compound **1a**. However, it was found that the reaction was sluggish, and the desired product **2a** was obtained only in 13% yield (Scheme 2). It is possible that the strongly coordinating ligand 2,2-bipyridine in [(bpy)-$CuSCF_3$] presumably decreases its reactivity toward **1a**. When CuI or water was added to promote the reaction,[5] the yields were only slightly improved (Scheme 2).

**Scheme 2. Trifluoromethylthiolation of $\alpha$-Diazoester 1a with [(bpy)$CuSCF_3$]**



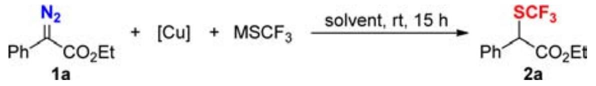
| additive | yield |
|---|---|
| none | 13% |
| CuI (1.0 equiv) | 38% |
| $H_2O$ (100 equiv) | 27% |

We then turned our attention to using a ligand-free $CuSCF_3$ species.[6] Initially, we tried to use $Me_4NSCF_3$ as a $CF_3S$ source[6a] and CuI as a copper source to in situ generate the $CuSCF_3$ species. However, the subsequent reaction with substrate **1a** was not successful (Table 1, entry 1). When CuI or water was added as promoter,[5] only a trace amount of desired product **2a** was detected (Table 1, entries 2 and 3). Thereafter, $AgSCF_3$[6b,c]

**Received:** February 26, 2014
**Published:** March 24, 2014

dx.doi.org/10.1021/ol500612n | *Org. Lett.* 2014, 16, 2030−2033

**Table 1. Survey of Reaction Conditions**



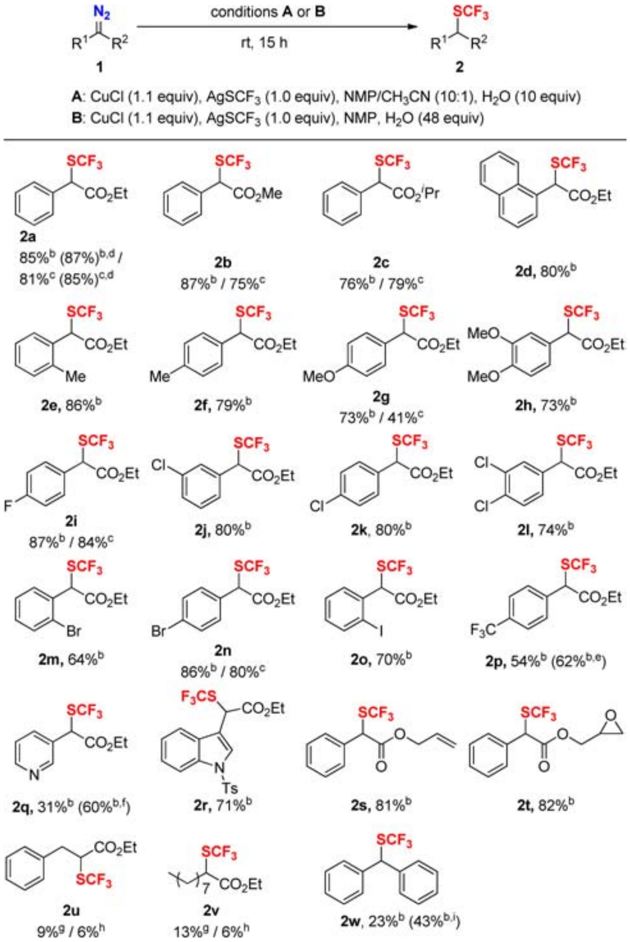
| entry | [Cu] (equiv) | $MSCF_3$ (equiv) | solvent | additive (equiv) | yield[a] (%) |
|---|---|---|---|---|---|
| 1 | CuI (1.0) | $Me_4NSCF_3$ (1.0) | NMP | | 0 |
| 2 | CuI (2.0) | $Me_4NSCF_3$ (1.0) | NMP | | <5 |
| 3 | CuI (1.0) | $Me_4NSCF_3$ (1.0) | NMP | $H_2O$ (40) | <5 |
| 4 | CuI (1.0) | $AgSCF_3$ (1.5) | NMP | | 41 |
| 5 | CuI (0.2) | $AgSCF_3$ (1.0) | NMP | | 27 |
| 6 | $CuF_2$ (1.0) | $AgSCF_3$ (1.0) | NMP | | 0 |
| 7 | CuCl (1.0) | $AgSCF_3$ (1.5) | NMP | | 60 |
| 8 | | $AgSCF_3$ (1.0) | NMP | | 0 |
| 9 | CuCl (1.0) | $AgSCF_3$ (1.0) | NMP | | 38 |
| 10 | CuCl (1.0) | $AgSCF_3$ (1.0) | NMP | $H_2O$ (10) | 59 |
| 11 | CuCl (1.0) | $AgSCF_3$ (1.0) | NMP | $H_2O$ (40) | 81 |
| 12 | CuCl (1.0) | $AgSCF_3$ (1.0) | NMP | $H_2O$ (48) | 84 |
| 13 | CuCl (1.0) | $AgSCF_3$ (1.0) | NMP | $H_2O$ (60) | 73 |
| **14** | **CuCl (1.1)** | **$AgSCF_3$(1.0)** | **NMP** | **$H_2O$ (48)** | **86** |
| 15 | CuCl (1.2) | $AgSCF_3$ (1.0) | NMP | $H_2O$ (48) | 85 |
| 16 | CuCl (1.32) | $AgSCF_3$ (1.1) | NMP | $H_2O$ (48) | 86 |
| 17 | CuCl (1.1) | $AgSCF_3$ (1.0) | NMP/$CH_3CN$ (10:1) | $H_2O$ (1) | 79 |
| **18** | **CuCl (1.1)** | **$AgSCF_3$(1.0)** | **NMP/$CH_3CN$ (10:1)** | **$H_2O$ (10)** | **89** |
| 19 | CuCl (1.1) | $AgSCF_3$ (1.0) | NMP/$CH_3CN$ (10:1) | $H_2O$ (40) | 84 |
| 20 | CuCl (1.1) | $AgSCF_3$ (1.0) | $CH_3CN$ | $H_2O$ (10) | 82 |

[a] All reactions were performed by mixing a Cu(I) salt and $MSCF_3$ in NMP (2 mL) or $CH_3CN$ (if used) and stirring for 5 min (for entries 1–3, 30 min), and then **1a** in NMP (3 mL) was added, followed by the addition of an additives (if used). Yields were determined by $^{19}F$ NMR spectroscopy with $PhCF_3$ as an internal standard. For entries 1–3 and 9–20, 0.5 mmol of **1a** was used. For entries 4–8, 0.2 mmol of **1a** was used. NMP = 1-methylpyrrolidin-2-one.

was chosen as the $CF_3S$ source, and the yield of product **2a** was significantly improved (Table 1, entry 4). However, when a catalytic amount of CuI was used, the yield was significantly decreased (Table 1, entry 5). It is noteworthy that no desired product **2a** could be detected when either Cu(II) or no copper was added (Table 1, entries 6 and 8). CuCl showed better activity than CuI in the reaction (Table 1, entries 4 and 7). It was encouraging to find that when water was added as an additive, the yield was remarkably improved (Table 1, entries 10–20)! After a careful screening, we found that a very good yield (86%) of product was obtained when water was used as a promoter (the volume ratio of NMP/$H_2O$ = 11.5:1) (Table 1, entries 10–16). We also found that acetonitrile had a similar effect as water to promote the reaction; thus, the addition of acetonitrile significantly reduced the amount of water used (Table 1, entries 17–20; for more details, see the Supporting Information).

With the optimized reaction conditions in hand (Table 1, entries 14 and 18), we further examined the substrate scope of the reaction. The results are shown in Scheme 3. For most of the α-diazo arylacetates **1**, the reaction proceeded smoothly to give the corresponding products **2** in moderate to excellent yields. When the ester group adjacent to the carbenic carbon was changed from methyl to ethyl to isopropyl esters, there was no significant drop of the product yield (Scheme 3, **2a–c**). Furthermore, the yields were not affected when the substituents were on the *ortho*-, *meta*-, and *para*-positions of the phenyl ring (Scheme 3, **2d–p**). Both moderately electron-donating or -withdrawing substituents on the phenyl ring had no significant

**Scheme 3. Trifluoromethylthiolation of Diazo Compounds**[a]



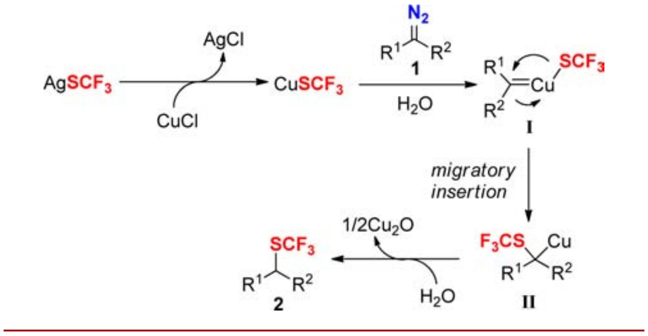
[a] Unless otherwise mentioned, all reactions were performed by mixing CuCl and $AgSCF_3$ in $CH_3CN$ (0.5 mL) + NMP (2 mL) (for conditions **A**) or NMP (2 mL, for conditions **B**) and stirring for 5 min, and then **1** in NMP (3 mL) was added followed by water. [b] Yields were of isolated products by using **1** (0.5 mmol) under conditions **A**. [c] Yields are of isolated products, by using **1** (0.5 mmol) under conditions **B**. [d] Yields for reactions with compound **1a** (5 mmol), $AgSCF_3$ (5 mmol), and CuCl (5.5 mmol). [e] The reaction temperature was 70 °C. [f] The reaction temperature was 60 °C. [g] The reactions were performed under conditions **A**, and the yields were determined by $^{19}F$ NMR spectroscopy using $PhCF_3$ as an internal standard. [h] The reactions were performed under conditions **B**, and the yields were determined by $^{19}F$ NMR spectroscopy using $PhCF_3$ as an internal standard. [i] 0.5 equiv of CuCl was used.

influence on the yields of trifluoromethylthiolated products (Scheme 3, **2e**,**f**,**i**−**o**). However, the strong electron-donating or -withdrawing substituents could resulted in a drop in reaction yields (Scheme 3, **2g**,**h**,**p**,**q**). It was found that heating was needed to obtain higher yields in the case of 4-trifluoromethylphenyl- and 3-pyridyl-substituted *α*-diazo acetates (Scheme 3, **2p**,**q**). Note that no aromatic trifluoromethylthiolation occurred when the substrates bore halogen atoms (F, Cl, Br, and I) on the aryl ring (Scheme 3, **2i**−**o**). Pyridyl and indolyl derivatives are well-tolerant in this trifluoromethylthiolation reaction (Scheme 3, **2q**,**r**). The reaction also tolerates vinyl and epoxy moieties, and no intramolecular cascade reactions occurred in the case of **2s** and **2t**. However, when alkyl-substituted *α*-diazoesters were used, the yields dropped sharply (Scheme 3, **2u**-**2v**), which might be due to the fact that migratory insertion of $CF_3S$ group to the carbenic carbon from Cu center is slower than 1,2-H shifts.[7] When more reactive diazo compound **1w** was used, the trifluoromethylthiolation reaction became less efficient. The yield was slightly improved when a substoichiometric amount of CuCl was used (Scheme 3, **2w**). It is noteworthy that under both optimized conditions, the reaction can be easily scaled up; for example, when 5 mmol of **1a** (0.95 g) was used, there was no appreciable drop of yield (Scheme 3, **2a**).

To gain more insight into this Cu-mediated trifluoromethylthiolation reaction, we carried out some control experiments. A mixture of CuCl and $AgSCF_3$ ($CuCl/AgSCF_3 = 1:1$) in NMP was stirred at room temperature for 5 min, and a sample from this mixture was characterized by $^{19}F$ NMR spectroscopy (using $PhCF_3$ at −63.0 ppm as an internal standard). A new peak at −25.8 ppm was observed, which was assigned as the "$CuSCF_3$" species.[8] Unlike the "$CuCF_3$" species,[9] there was only one single peak in $^{19}F$ NMR spectra even when the ratio of $CuCl/AgSCF_3$ was changed. For example, the $^{19}F$ NMR spectroscopy chemical shifts (in ppm) were −23.7 ($CuCl/AgSCF_3 = 1:2$), −25.2 ($CuCl/AgSCF_3 = 1:1.5$), −26.4 ($CuCl/AgSCF_3 = 1.1:1$), and −27.0 ($CuCl/AgSCF_3 = 1.5:1$), indicating that $AgSCF_3$ (or CuCl) has a fast equilibrium with $CuSCF_3$ (for details, see the Supporting Information).

Based on the aforementioned results, we propose a plausible reaction mechanism as described in Scheme 4. First, $AgSCF_3$ is rapidly converted to "$CuSCF_3$" by metathesis with CuCl in $CH_3CN$ or NMP.[6b,c] Then, $CuSCF_3$ reacts with diazo compound **1** to form Cu-carbene intermediates **I** (the addition of water could significantly activate "$CuSCF_3$" species and accelerate the reaction), which quickly undergo migratory insertion to give intermediates **II**, and **II** is converted to the final products in the presence of water.

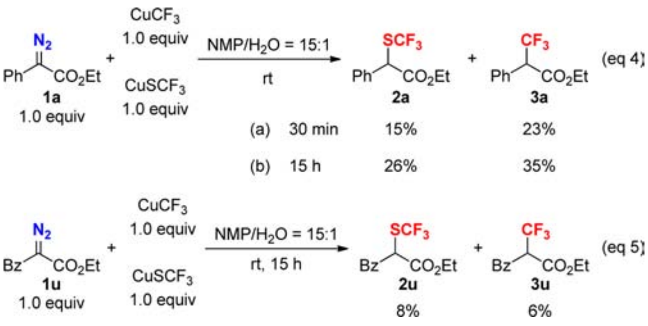
**Scheme 4. Plausible Reaction Mechanism**



As the mechanism of this trifluoromethylthiolation reaction is very similar to that of a trifluoromethylation reaction,[5] it provides an opportunity to compare these two reactions. (i) Both $CuCF_3$ and $CuSCF_3$ are stable in the presence of a certain amount of water. (ii) There are similar ligand effects of the two reactions; the spare ligand (e.g., $I^-$ and bipyridine) may attenuate the reactivity of Cu toward *α*-diazoesters, while the addition of water could promote the reactions.[5] (iii) The in situ generated "$CuCF_3$" (from $TMSCF_3/CsF/CuI$) usually contains $[(CF_3)_2Cu]^-$, $[ICuCF_3]^-$, and solvent-coordinated $CuCF_3$ species,[9] and these species can be detected by $^{19}F$ NMR spectroscopy, which indicates that they exist in relatively *slow* equilibriums; however, as described above, there is a *fast* equilibrium between $CuSCF_3$ and $AgSCF_3$ (or CuCl).

On the other hand, a competitive reaction of $CuCF_3$ and $CuSCF_3$ with diazo compound **1a** in one pot was carried out. The results demonstrated that the reaction of $CuCF_3$ with diazo compound **1a** was slightly faster than $CuSCF_3$ (Scheme 5, eq 4), which may provide some explanation to the low yields of trifluoromethylthiolation when *α*-H-containing substrates **2u** and **2v** were used. However, when the same experiment was conducted with substrate **2u**, the yields of both reactions were decreased (Scheme 5, eq 5).

**Scheme 5. Competitive Reaction of *α*-Diazoesters with $CuCF_3$ and $CuSCF_3$**



In summary, we have developed a novel Cu-mediated trifluoromethylthiolation of diazo compounds that provides a convenient synthetic route for the efficient *α*-trifluoromethylthiolation of simple esters. This reaction tolerates many functional groups and is not susceptible to the steric hindrance. The results indicate that similar to the $CF_3Cu$-carbene,[5] the $CF_3SCu$-carbene species can undergo migratory insertion to form a $C-SCF_3$ bond.[10] Further exploration of this chemistry is currently underway in our laboratory.

## ■ ASSOCIATED CONTENT

### Ⓢ Supporting Information

Experimental procedures and characterization data for all new compounds. 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.

## ■ ACKNOWLEDGMENTS

This work was supported by the National Basic Research Program of China (2012CB215500 and 2012CB821600), the National Natural Science Foundation of China (21372246 and 21202189), Shanghai QMX program (13QH1402400), and MSD China R&D Postdoc Fellowship (M.H.). We thank Professor Zhiqiang Weng (Fuzhou University) for providing us a sample of [(bpy)CuSCF$_3$].

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(8) The reported $^{19}$F NMR spectroscopy chemical shift of CuSCF$_3$ (prepared from Cu$^0$ + CF$_3$SSCF$_3$) in acetone-$d_6$ was −28.20 ppm; see: Kondratenko, N. V.; Kolomeytsev, A. A.; Popov, V. I.; Yagupolskii, L. M. *Synthesis* **1985**, 667. Tyrra et al. reported that the chemical shift of CuSCF$_3$ (prepared from CuCl + Me$_4$NSCF$_3$ or CsSCF$_3$) in CH$_3$CN was −16.6 ppm; see ref 6a. When we carried out the experiment with CuCl/CsSCF$_3$ = 1:1 in CH$_3$CN, the $^{19}$F NMR spectroscopy chemical shift was −25.3 ppm. When CuCl/CsSCF$_3$ = 1:2 in CH$_3$CN, we found that the $^{19}$F NMR spectroscopy chemical shift was −17.6 ppm, which was in accordance with Tyrra's report. We tentatively assigned it as CsCu(SCF$_3$)$_2$. (We also found that the $^{19}$F NMR spectroscopy chemical shift of AgSCF$_3$ in NMP was −20.8 ppm using PhCF$_3$ at −63 ppm as an internal standard.)

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