Communication

# Trifluoromethylation of Alkyl Radicals in Aqueous Solution

Haigen Shen, Zhonglin Liu, Pei Zhang, Xinqiang Tan, Zhenzhen Zhang, and Chaozhong Li

*J. Am. Chem. Soc.*, **Just Accepted Manuscript** • Publication Date (Web): 09 Jul 2017

# Trifluoromethylation of Alkyl Radicals in Aqueous Solution

Haigen Shen,[a] Zhonglin Liu,[a] Pei Zhang,[a] Xinqiang Tan,[a] Zhenzhen Zhang,[a] and Chaozhong Li*[a, b]

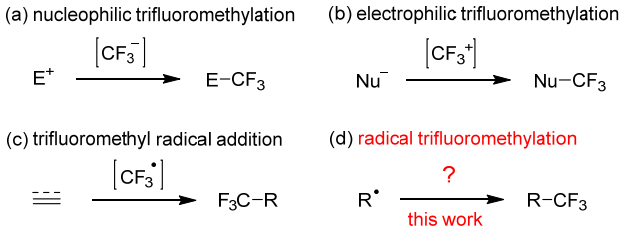
[a] Key Laboratory of Organofluorine Chemistry and Collaborative Innovation Center of Chemistry for Life Sciences, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 345 Lingling Road, Shanghai 200032, China, and [b] School of Materials and Chemical Engineering, Ningbo University of Technology, No. 201 Fenghua Road, Ningbo 315211, P. R. China.

*Supporting Information Placeholder*

**ABSTRACT:** The copper-mediated trifluoromethylation of alkyl radicals is described. The combination of $Et_3SiH$ and $K_2S_2O_8$ initiates the radical reactions of alkyl bromides or iodides with $BPyCu(CF_3)_3$ (BPy = 2,2'-bipyridine) in aqueous acetone at room temperature to afford the corresponding trifluoromethylation products in good yield. The protocol is applicable to various primary and secondary alkyl halides and exhibits wide functional group compatibility. A mechanism involving trifluoromethyl group transfer from Cu(II)–$CF_3$ intermediates to alkyl radicals is proposed.

Fluorine is recognized as a key element in pharmaceuticals, agrochemicals and materials. The incorporation of trifluoromethyl groups into organic molecules has a profound effect on their lipophilicity, permeability and metabolic stability. As a consequence, the development of new trifluoromethylation methods that involve mild conditions has received considerable attention and significant progress has been achieved in this area in the past decade.[1–3] In particular, a number of methods have been developed for C($sp^3$)–$CF_3$ bond formation. These methods generally fall into the following three categories based on the type of $CF_3$ intermediates involved: (a) nucleophilic trifluoromethylation with trifluoromethyl anions derived from reagents such as $Me_3SiCF_3$ (Ruppert–Prakash reagent),[4] $FSO_2CF_2CO_2Me$ (Chen reagent)[5] or $(Ph_3P)_3CuCF_3$ (Grushin reagent);[6] (b) electrophilic trifluoromethylation[2] of carbon-centered nucleophiles with electrophilic $CF_3$ reagents such as the Umemoto reagent,[7] Togni's reagent[8] or Shibata reagent;[9] (c) addition of trifluoromethyl radicals[3] to unsaturated moieties such as alkenes, alkynes or isonitriles (Scheme 1, a–c). Although the trifluoromethylation of carbon-centered nucleophiles and electrophiles is well documented, the trifluoromethylation of carbon-centered radicals remains largely unexplored (Scheme 1d). Of the few relevant reports, Gölitz and de Meijere reported that the decomposition of 1-alkyl-2-trifluoromethyldiazenes (R-N=N-$CF_3$) under UV irradiation in highly viscous solvents, such as *t*-butanol or hexadecane, led to products of radical coupling (R–$CF_3$) in low to moderate yield.[10] Furthermore, Qing and coworkers described the copper-mediated 1,2-bis(trifluoromethylation) of alkenes using $CF_3SO_2Na$ and *t*-BuOOH and involving the addition of $CF_3$ radical to alkenes followed by coupling of the resultant radical with another $CF_3$ radical.[11] Despite these reports, it is important to note that the cross coupling of two transient radicals is unlikely to be general and thus is of limited value in synthesis. Herein we describe a new protocol for the trifluoromethylation of alkyl radicals that involves $CF_3$ group transfer.

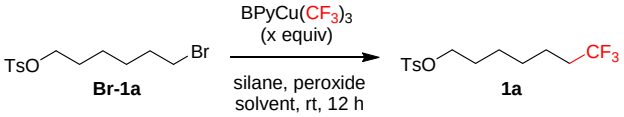
**Scheme 1. Trifluoromethylation for C($sp^3$)–$CF_3$ Fromation**




A common approach for the generation of alkyl radicals is the treatment of alkyl halides with reducing agents such as tin or silicon hydrides. Thus, we selected 6-bromohexyl tosylate (**Br-1a**) and triethylsilane as a model system to explore radical trifluoromethylation (Table 1). The use of **Br-1a** was also designed to help clarify the mechanism of substitution as the tosylate moiety should remain inert under radical trifluoromethylation but should be as reactive as the bromide under nucleophilic trifluoromethylation conditions.[12, 13] With regard to the $CF_3$ source, we chose to investigate the use of the complex $BPyCu(CF_3)_3$ (BPy = 2,2'-bipyridine), recently developed by Grushin et al.[14] Bromide **Br-1a** was treated with excess $Et_3SiH$ and $BPyCu(CF_3)_3$ in acetonitrile at room temperature in the presence of a peroxide initiator such as di-*tert*-butyl peroxyoxalate (DBPO), di-*tert*-butyl peroxide (DTBP), benzoyl peroxide (BPO) or $K_2S_2O_8$ (entries 1–6, Table 1). Pleasingly, the expected trifluoromethylation product **1a** was obtained in 11% yield when $K_2S_2O_8$ was used as the initiator. Switching the solvent to aqueous acetonitrile or acetone significantly increased the yield of the process (entries 7–10, Table 1) and an 80% yield of **1a** was obtained when acetone–water (2:1) was employed as solvent. The dramatic, beneficial effect of water may be attributed to the improved solubility of $K_2S_2O_8$ in aqueous solution. In contrast, no **1a** was detected when biphasic $CH_2Cl_2/H_2O$ was used as solvent (entry 11, Table 1). After further adjustment of the reagent ratios (entries 12–16, Table 1), the use of a stoichiometric amount of $BpyCu(CF_3)_3$ as the $CF_3$ source and $Et_3SiH$ (6 equiv)/$K_2S_2O_8$ (4 equiv) as the initiation system, gave **1a** in almost quantitative yield (entry 14, Table 1). Use of other silanes in place of $Et_3SiH$ led to lower yields of the product (entries 17–20, Table 1) and the product of direct reduction, *n*-hexyl tosylate, was obtained in 47%

when $(TMS)_3SiH$ was used. Finally, control experiments indicated that both $Et_3SiH$ and $K_2S_2O_8$ were required for the trifluoromethylation (entries 21 and 22, Table 1). Notably, **1a** was not formed when $Bu_4NCu(CF_3)_4$[14] or an electrophilic $CF_3$ reagent (*e.g.* Tongi's reagent, Umemoto reagent or Shibata reagent) was used in place of $BPyCu(CF_3)_3$.

**Table 1. Optimization of Reaction Conditions**



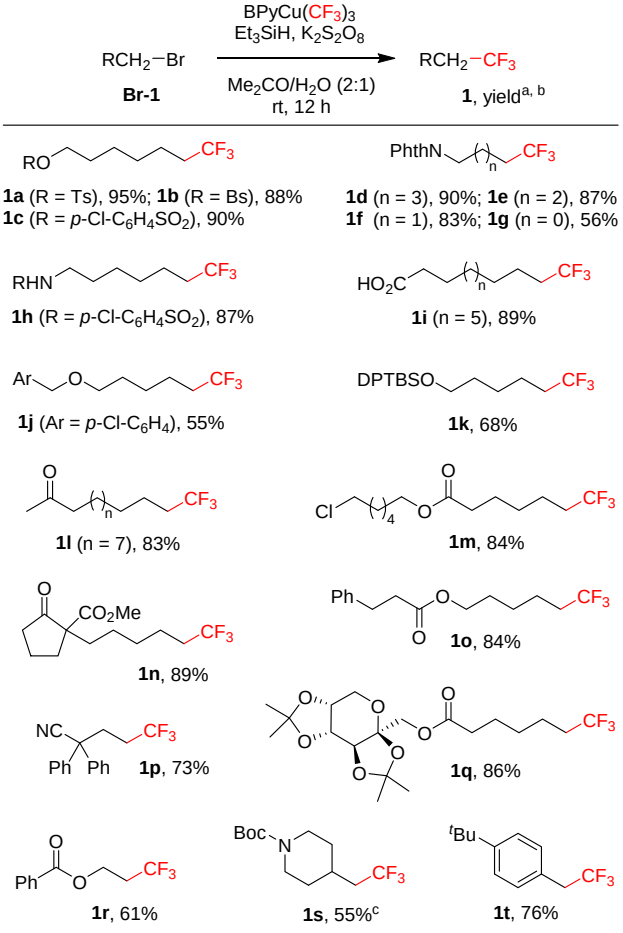

| entry[a] | x | silane (equiv) | peroxide (equiv) | solvent | yield (%)[b] |
|---|---|---|---|---|---|
| 1 | 2 | $Et_3SiH$ (5) | DBPO (3) | MeCN | 1 |
| 2 | 2 | $Et_3SiH$ (5) | DTBP (3) | MeCN | 4 |
| 3[c] | 2 | $Et_3SiH$ (5) | DTBP (3) | MeCN | 9 |
| 4 | 2 | $Et_3SiH$ (5) | BPO (3) | MeCN | 0 |
| 5[c] | 2 | $Et_3SiH$ (5) | BPO (3) | MeCN | 49 |
| 6 | 2 | $Et_3SiH$ (5) | $K_2S_2O_8$ (3) | MeCN | 11 |
| 7 | 2 | $Et_3SiH$ (5) | $K_2S_2O_8$ (3) | MeCN/$H_2O$ (2:1) | 65 |
| 8 | 2 | $Et_3SiH$ (5) | $K_2S_2O_8$ (3) | $Me_2CO/H_2O$ (2:1) | 80 |
| 9 | 2 | $Et_3SiH$ (5) | $K_2S_2O_8$ (3) | $Me_2CO/H_2O$ (4:1) | 75 |
| 10 | 2 | $Et_3SiH$ (5) | $K_2S_2O_8$ (3) | $Me_2CO/H_2O$ (1:1) | 30 |
| 11 | 2 | $Et_3SiH$ (5) | $K_2S_2O_8$ (3) | $CH_2Cl_2/H_2O$ (2:1) | 0 |
| 12 | 2 | $Et_3SiH$ (6) | $K_2S_2O_8$ (3) | $Me_2CO/H_2O$ (2:1) | 91 |
| 13 | 2 | $Et_3SiH$ (6) | $K_2S_2O_8$ (4) | $Me_2CO/H_2O$ (2:1) | 94 |
| **14** | **1** | **$Et_3SiH$ (6)** | **$K_2S_2O_8$ (4)** | **$Me_2CO/H_2O$ (2:1)** | **98[d]** |
| 15 | 0.8 | $Et_3SiH$ (6) | $K_2S_2O_8$ (4) | $Me_2CO/H_2O$ (2:1) | 90 |
| 16 | 0.6 | $Et_3SiH$ (6) | $K_2S_2O_8$ (4) | $Me_2CO/H_2O$ (2:1) | 80 |
| 17 | 1 | $Et_2SiH_2$ (6) | $K_2S_2O_8$ (4) | $Me_2CO/H_2O$ (2:1) | 76 |
| 18 | 1 | $(TMS)_3SiH$ (6) | $K_2S_2O_8$ (4) | $Me_2CO/H_2O$ (2:1) | 9[e] |
| 19 | 1 | $Ph_3SiH$ (6) | $K_2S_2O_8$ (4) | $Me_2CO/H_2O$ (2:1) | 0 |
| 20 | 1 | $(MeO)_3SiH$ (6) | $K_2S_2O_8$ (4) | $Me_2CO/H_2O$ (2:1) | 0 |
| 21 | 1 | none | $K_2S_2O_8$ (4) | $Me_2CO/H_2O$ (2:1) | 0 |
| 22 | 1 | $Et_3SiH$ (6) | none | $Me_2CO/H_2O$ (2:1) | 0 |

[a] Reaction conditions: **Br-1a** (0.1 mmol), $BPyCu(CF_3)_3$, silane, peroxide, solvent (3 mL), rt, 12 h. [b] $^{19}F$ NMR yield (with $PhCF_3$ as the internal standard) based on **Br-1a**. [c] The reaction was carried out under UV (365 nm) photolysis. [d] Isolated yield: 95%. [e] *n*-Hexyl tosylate was isolated in 47% yield.

With the optimized conditions in hand (entry 14, Table 1), we set out to explore the scope of the method. As shown in Scheme 2, the radical trifluoromethylation of various primary alkyl bromides **Br-1** proceeded smoothly in aqueous solution at room temperature and furnished products **1a–1t** in good to excellent yield. The presence of a wide range of functional groups was tolerated by the process. For example, ethers, silyl ethers, ketones, esters, nitriles, amides, imides, sulfonates, sulfonamides, free carboxylic acids, aryl and alkyl chlorides all proved to be compatible with the reaction. This excellent functional group compatibility allows the direct modification of complex molecules such as carbohydrates, as exemplified by the efficient preparation of **1q**. In contrast, primary alkyl chlorides were inert under the reaction conditions. For example, trifluoromethylated alkyl chloride **1m** was obtained in high yield.

We next extended the method to the trifluoromethylation of secondary alkyl bromides (Scheme 3). As for the reaction of primary alkyl bromides, secondary alkyl bromides **Br-2** underwent smooth trifluoromethylation under the optimized conditions and gave the expected products of trifluoromethylation **2a–2o** in satisfactory yield. Again, broad substrate scope and wide functional group compatibility was observed. Of particular note, trifluoromethylated alkyl azide (**2f**), amino acid derivative (**2j**), and steroid (**2n**) were obtained from the corresponding bromides, thus illustrating the suitability of this method for the late-stage modification of complex molecules. Moderate diastereocontrol was observed in the preparation of the trifluoromethylated products **2j**, **2l** and **2n**. Tertiary (*e.g.* **2m**) and primary alkyl chlorides (*e.g.* **2k**) were unreactive towards trifluoromethylation. Interestingly, when the *gem*-dibromide substrate (**Br-2o**) was employed, the corresponding mono-trifluoromethylation product **2o** was obtained in 83% yield with only a trace of bis-trifluoromethylation observed.

**Scheme 2. Trifluoromethylation of Primary Alkyl Bromides**

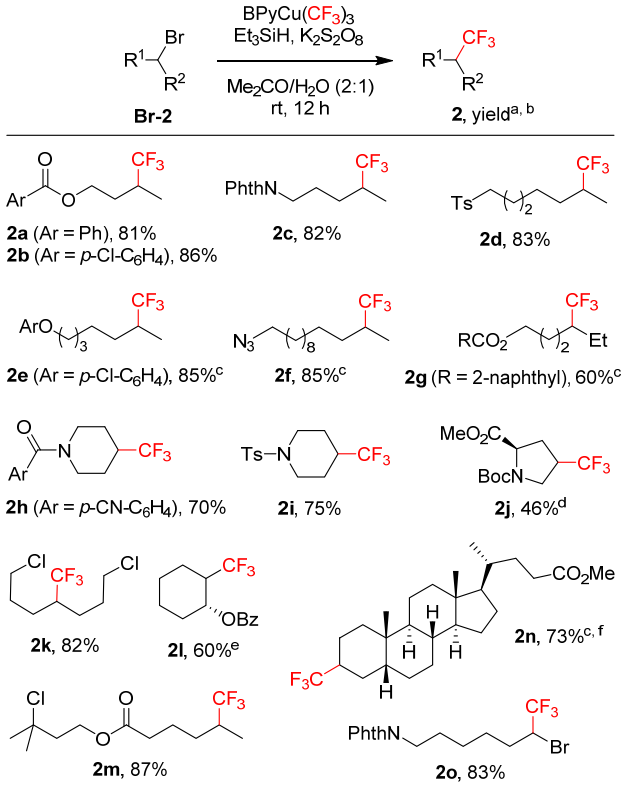



[a] Reaction conditions: **Br-1** (0.2 mmol), $BPyCu(CF_3)_3$ (0.2 mmol), $Et_3SiH$ (1.2 mmol), $K_2S_2O_8$ (0.8 mmol), acetone (4 mL), $H_2O$ (2 mL), rt, 12 h. [b] Isolated yield based on **Br-1**. [c] Solvent: acetone (4 mL), $H_2O$ (1 mL).

In addition to being general, the radical trifluoromethylation is operationally simple and the conditions used are extremely mild.

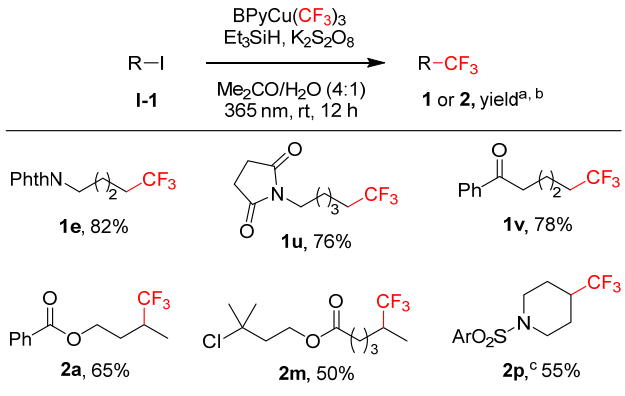
It is also important to note that the few reports of nucleophilic trifluoromethylation of simple alkyl halides either require harsh reaction conditions or suffer from limited substrate scope.[12] Thus, this radical trifluoromethylation approach complements known routes to related targets.

**Scheme 3. Trifluoromethylation of Secondary Alkyl Bromides**




[a] Reaction conditions: **Br-2** (0.2 mmol), $BPyCu(CF_3)_3$ (0.2 mmol), $Et_3SiH$ (1.2 mmol), $K_2S_2O_8$ (0.8 mmol), acetone (4 mL), $H_2O$ (2 mL), rt, 12 h. [b] Isolated yield based on **Br-2**. [c] Solvent: acetone (4 mL), $H_2O$ (1 mL). [d] *trans*/*cis* = 70:30. [e] *trans*/*cis* = 68:32. [f] dr = 80:20.

**Scheme 4. Trifluoromethylation of Alkyl Iodides**

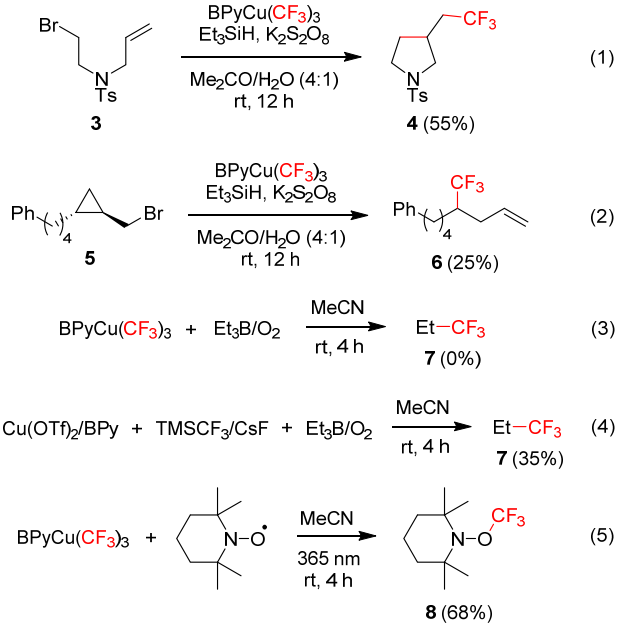



[a] Reaction conditions: **I-1** (0.2 mmol), $BPyCu(CF_3)_3$ (0.4 mmol), $Et_3SiH$ (1.2 mmol), $K_2S_2O_8$ (0.8 mmol), acetone (4 mL), $H_2O$ (1 mL), UV (365 nm), rt, 12 h. [b] Isolated yield based on **I-1**. [c] Ar = *p*-Cl-$C_6H_4$.

In contrast to primary and secondary alkyl bromides, tertiary alkyl bromides did not give the products of trifluoromethylation. Instead, byproducts presumably derived from the corresponding tertiary alkyl radicals were obtained (see the Supporting Information for details). It is likely that the trifluoromethylation of tertiary alkyl radicals is retarded by steric effects.

We then extended the method to alkyl iodides. Given that alkyl iodides are even more reactive than alkyl bromides towards triethylsilyl radicals,[15] it was surprising to find that the reaction of alkyl iodides under the above optimized conditions produced low yields of the expected trifluoromethylation products (20 ~ 30%) and the alkyl iodides (60 ~ 70%) were recovered. However, re-optimized reaction conditions, involving UV irradiation (365 nm), delivered the expected trifluoromethylation products **1** and **2** in satisfactory yields from the corresponding alkyl iodides **I-1**. This protocol is applicable to both primary and secondary alkyl iodides (Scheme 4).

**Scheme 5. Mechanistic Experiments**




To gain further insight into the trifluoromethylation, mechanistic studies were carried out (Scheme 5). The reaction of 2-(*N*-allyl-*N*-tosylamino)ethyl bromide (**3**) under the optimized conditions afforded the cyclized product **4** in 55% yield (Eq. 1). When cyclopropylmethyl bromide **5** was subjected to the optimized conditions for the trifluoromethylation of alkyl bromides, the ring-opening product **6** was isolated in 25% yield (**5** was recovered in 25% yield) (Eq. 2). These radical clock experiments[16] unambiguously demonstrated the intermediacy of alkyl radicals. To probe the identity of the species responsible for the trifluoromethylation of alkyl radicals, $BPyCu(CF_3)_3$ was directly treated with ethyl radicals formed from $Et_3B$ under an $O_2$ atmosphere. The formation of 1,1,1-trifluoropropane (**7**) was not detected (Eq. 3). In contrast, when a mixture of $Cu(OTf)_2$, BPy, $TMSCF_3$ and CsF in 1:1:2.5:2.5 ratio was treated with $Et_3B/O_2$ in acetonitrile at room temperature, the product **7** was formed (35% yield by $^{19}F$ NMR) (Eq. 4). These two experiments suggest that the active

trifluoromethylation agent is likely to be a Cu(II)–$CF_3$ complex rather than a Cu(III)–$CF_3$ complex. Finally, the role of UV irradiation in the reactions of alkyl iodides was also probed. As shown in Eq. 5, the photolysis of $BPyCu(CF_3)_3$ in the presence of an equimolar amount of TEMPO (2,2,6,6-tetramethylpiperidine-*N*-oxyl radical) afforded **8** in 68% yield, indicating that trifluoromethyl radicals are produced from $BPyCu(CF_3)_3$ upon photostimulation.[17]

A plausible mechanism for the trifluoromethylation is shown in Figure 1. Interaction of $Et_3SiH$ with persulfate generates the triethylsilyl radical that abstracts a bromine atom from alkyl bromide to produce the corresponding alkyl radical. Subsequent trifluoromethyl group transfer from a Cu(II)–$CF_3$ complex (such as **A**)[18] to the alkyl radical affords the trifluoromethylation product and a Cu(I) complex (such as **B**). Furthermore, complex **A** may be regenerated by comproportionation of **B** with $BPyCu(CF_3)_3$. In the reaction of alkyl iodides, $Et_3SiI$ generated by iodine atom abstraction by the triethylsilyl radical may undergo hydrolysis in aqueous solution to give HI. $I_2$ may then be produced by $K_2S_2O_8$ oxidation of HI, and $I_2$ may act as the radical chain suppressant.[19] Such a phenomenon is well documented in iodine atom transfer radical addition reactions.[19] Upon UV irradiation, the trifluoromethyl radical is generated and this may serve as a scavenger for $I_2$, forming $CF_3I$, thus allowing the radical trifluoromethylation to proceed smoothly. Further investigations on the mechanism of radical trifluoromethylation are certainly underway.

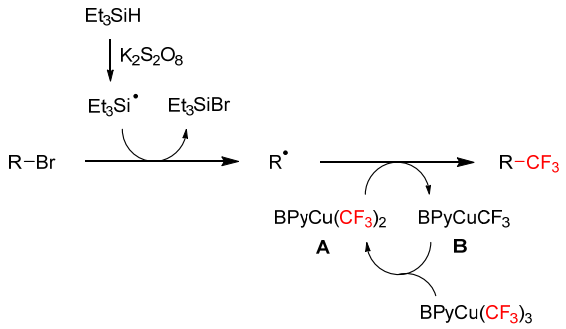



**Figure 1.** Proposed mechanism for the trifluoromethylation of alkyl radicals.

In conclusion, we have developed a practical protocol for the trifluoromethylation of alkyl halides formed *in situ* from alkyl halides. As the procedure is operationally simple, broad in scope, tolerant of sensitive functional groups, and utilizes the readily available Grushin reagent $BPyCu(CF_3)_3$, the method should find application in the synthesis of important trifluoromethylated molecules. A catalytic variant of the radical trifluoromethylation is currently under development in our laboratory.

## ASSOCIATED CONTENT

### Supporting Information

Full experimental details, characterizations of new compounds, and copies of $^1H$, $^{13}C$ and $^{19}F$ NMR spectra (PDF). The material is available free of charge on the ACS Publications website.

## AUTHOR INFORMATION

### Corresponding Author

* E-mail: clig@mail.sioc.ac.cn

### Notes

The authors declare no competing financial interests.

## ACKNOWLEDGMENT

This project was supported by the National Basic Research Program of China (973 Program) (Grant 2015CB931900), by the National Natural Science Foundation of China (Grants 21421002, 21472220, 21532008, and 21602239), and by the Strategic Priority Research Program of the Chinese Academy of Sciences (Grant XDB20020000). We thank Prof. David J. Procter of University of Manchester for his generous help in revising the manuscript.

## REFERENCES

(1) (a) Schlosser, M. *Angew. Chem., Int. Ed.* **2006**, *45*, 5432. (b) Ma, J.-A.; Cahard, D. *J. Fluorine Chem.* **2007**, *128*, 975. (c) Nie, J.; Guo, H.-C.; Cahard, D.; Ma, J.-A. *Chem. Rev.* **2011**, *111*, 455. (d) Egami, H.; Sodeoka, M. *Angew. Chem., Int. Ed.* **2014**, *53*, 8294. (e) Alonso, C.; de Marigorta, E. M.; Rubiales, G.; Palacios, F. *Chem. Rev.* **2015**, *115*, 1847. (f) Charpentier, J.; Fruh, N.; Togni, A. *Chem. Rev.* **2015**, *115*, 650. (g) Liang, T.; Neumann, C. N.; Ritter, T. *Angew. Chem., Int. Ed.* **2013**, *52*, 8214.

(2) (a) Shibata, N.; Matsnev, A.; Cahard, D. *Beilstein J. Org. Chem.* **2010**, *6*, 1860. (b) Umemoto, T. *Chem. Rev.* **1996**, *96*, 1757.

(3) (a) Studer, A. *Angew. Chem., Int. Ed.* **2012**, *51*, 8950. (b) Merino, E.; Nevado, C. *Chem. Soc. Rev.* **2014**, *43*, 6598. (c) Koike, T.; Akita, M. *Top. Catal.* **2014**, *57*, 967. (d) Koike, T.; Akita, M. *Acc. Chem. Res.* **2016**, *49*, 1937.

(4) (a) Ruppert, I.; Schlich, K.; Volbach, W. *Tetrahedron Lett.* **1984**, *25*, 2195. (b) Prakash, G. K. S.; Krishnamurti, R.; Olah, G. A. *J. Am. Chem. Soc.* **1989**, *111*, 393. (c) Shibata, N.; Mizuta, S.; Kawai, H. *Tetrahedron: Asymmetry* **2008**, *19*, 2633.

(5) Chen, Q.-Y.; Wu, S.-W. *J. Chem. Soc., Chem. Commun.* **1989**, 705.

(6) Tomashenko, O. A.; Escudero-Adan, E. C.; Martinez Belmonte, M.; Grushin, V. V. *Angew. Chem., Int. Ed.* **2011**, *50*, 7655.

(7) Umemoto, T.; Ishihara, S. *J. Am. Chem. Soc.* **1993**, *115*, 2156.

(8) Eisenberger, P.; Gischig, S.; Togni, A. *Chem. –Eur. J.* **2006**, *12*, 2579.

(9) Noritake, S.; Shibata, N.; Nakamura, S.; Toru, T.; Shiro, M. *Eur. J. Org. Chem.* **2008**, *2008*, 3465.

(10) Gölitz, P.; de Meijere, A. *Angew. Chem., Int. Ed. Engl.* **1977**, *16*, 854.

(11) Yang, B.; Xu, X.-H.; Qing, F.-L. *Org. Lett.* **2015**, *17*, 1906.

(12) (a) Kabayashi, Y.; Yamamoto, K.; Kumadaki, I. *Tetrahedron Lett.* **1979**, *20*, 4071. (b) Chen, Q.-Y.; Duan, J.-X. *Tetrahedron Lett.* **1993**, *34*, 4241. (c) Kim, J.; Shreeve, J. M. *Org. Biomol. Chem.* **2004**, *2*, 2728. (d) Tyrra, W.; Naumann, D.; Quadt, S.; Buslei, S.; Yagupolskii, Y. L.; Kremlev, M. M. *J. Fluorine Chem.* **2007**, *128*, 813. (e) Novák, P.; Lishchynskyi, A.; Grushin, V. V. *J. Am. Chem. Soc.* **2012**, *134*, 16167.

(13) Sevenard, D. V.; Kirsch, P.; Roschenthaler, G. V.; Movchun, V. N.; Kolomeitsev, A. A. *Synlett* **2001**, 379.

(14) Romine, A. M.; Nebra, N.; Konovalov, A. I.; Martin, E.; Benet-Buchholz, J.; Grushin, V. V. *Angew. Chem., Int. Ed.* **2015**, *54*, 2745.

(15) Chatgilialoglu, C.; Ingold, K. U.; Scaiano, J. C. *J. Am. Chem. Soc.* **1982**, *104*, 5123.

(16) Newcomb, M. In *Radicals in Organic Synthesis*; Renaud, P., Sibi, M. P., Eds.; Wiley-VCH: Weinheim, Germany, 2001; Vol.1, pp 317–336.

(17) Li, Y.; Studer, A. *Angew. Chem., Int. Ed.* **2012**, *51*, 8221.

(18) Nebra, N.; Grushin, V. V. *J. Am. Chem. Soc.* **2014**, *136*, 16998.

(19) (a) Curran, D. P. In *Free Radicals in Synthesis and Biology*; Minisci, F., Ed.; Kluwer: Dordrecht, the Netherlands, 1989; pp 37–51. (b) Byers, J. In *Radicals in Organic Synthesis*; Renaud, P., Sibi, M. P., Eds.; Wiley-VCH: Weinheim, Germany, 2001; Vol. 1, pp 72–89. (c) Li, C. In *Encyclopedia of Radicals in Chemistry, Biology and Materials*; Chatgilialoglu, C., Studer, A., Eds.; Wiley: Chichester, U.K., 2012; pp 943–964.

SYNOPSIS TOC.