OL Organic Letters

pubs.acs.org/OrgLett Letter

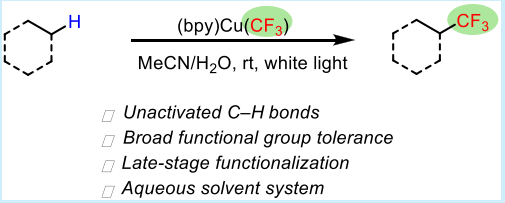
# Csp$^3$–H Trifluoromethylation of Unactivated Aliphatic Systems

Jiachen He, Truong N. Nguyen, Shuo Guo, and Silas P. Cook*

Cite This: *Org. Lett.* 2021, 23, 702–705 Read Online

ACCESS | Metrics & More | Article Recommendations | Supporting Information

**ABSTRACT:** A straightforward method for the undirected trifluoromethylation of unactivated methylene units was developed. The reaction proceeds in aqueous acetonitrile with Grushin's reagent, bpyCu(CF$_3$)$_3$, under broad-spectrum white-light irradiation. The trifluoromethylation tolerates a wide range of functional groups including ketones, esters, nitriles, amides, alcohols, and carboxylic acids. The C–H cleavage step is performed via intermolecular H atom abstraction, and the selectivities across a range of methylene units are reported. Mechanistic studies offer a general reaction coordinate for the overall transformation.

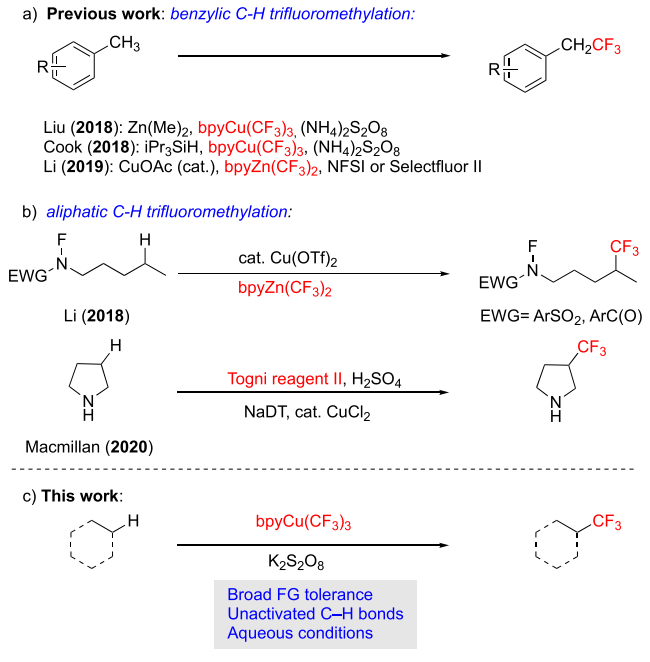





The introduction of fluorine atoms into small molecules selectively and safely has become of paramount importance across a range of industries. Numerous approved drugs and agrochemicals possess judiciously located fluorine atoms.[1] In general, the two most common fluorinated motifs in biologically active small molecules include simple monofluorinated motifs with a single C–F bond or the presence of the more electron-withdrawing trifluoromethyl group—CF$_3$.[2] The installation of such motifs is driven by a variety of reasons that range from modulating the p$K_a$ of nearby functionalities, dramatically changing the overall dipole of the target molecule, and even interrupting biological oxidation of the molecule to tune pharmacokinetics.[2] What is striking about a variety of these examples is the large percentage of aromatic C–F and C–CF$_3$ groups. Far more methods exist to target their installation relative to aliphatic fluorination.[3] This leads to a dearth of such compounds in typical screening libraries and underrepresentation in chemical campaigns.[4] By expending the toolbox for selective installation of aliphatic C–F-containing functionality, we can expand libraries and simplify potential chemical routes to hypothetical molecules of interest.

These issues have driven academic and industrial groups alike to focus on the problem of trifluoromethylation.[5] One strategy to generate aliphatic C(sp$^3$)–CF$_3$ bonds proceeds through carbon-based radicals generated from carboxylic acids[6,7] or halides;[8,9] however, the direct functionalization of carbon–hydrogen (C–H) bonds—the most abundant moiety in organic molecules—represents a more direct approach to trifluoromethylation.[10] In this context, a small number of recent publications have sought different approaches to convert Csp$^3$–H bonds into Csp$^3$–CF$_3$ systems. While somewhat limited at this time, the most common trifluoromethylation employs benzylic C–H substrates (Scheme 1a).[5a,11] Remarkably, similar conditions were reported near simultaneously by our group[5a] and the Liu group in 2018.[11a] Catalytic copper in combination with bpyZn(CF$_3$)$_2$ was accomplished by Li the following year.[11b] Fluoroamide-directed C–H functionalization, pioneered by our group in 2016,[12] has expanded beyond fluorination to include other functionalities, including trifluoromethylation (Scheme 1b).[13] Recently, Macmillan and co-workers demonstrated the trifluoromethylation of pyrrolidine using the electrophilic

**Scheme 1. Methods for Csp$^3$–H Trifluoromethylation**




**Received:** November 24, 2020
**Published:** January 14, 2021

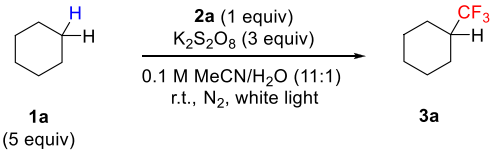



https://dx.doi.org/10.1021/acs.orglett.0c03891
*Org. Lett.* 2021, 23, 702–705

trifluoromethyl source of Togni's reagent II.[14] While these studies offer unique solutions to these specific substrates, we sought a more general trifluoromethylation reaction of unactivated, aliphatic C–H bonds (Scheme 1c).

To begin, we surveyed the reaction conditions for the trifluoromethylation of cyclohexane with Grushin's reagent, bpyCu($CF_3$)$_3$ (Table 1). The trifluoromethylation proceeded

**Table 1. Optimization of Pertinent Reaction Parameters**[a]



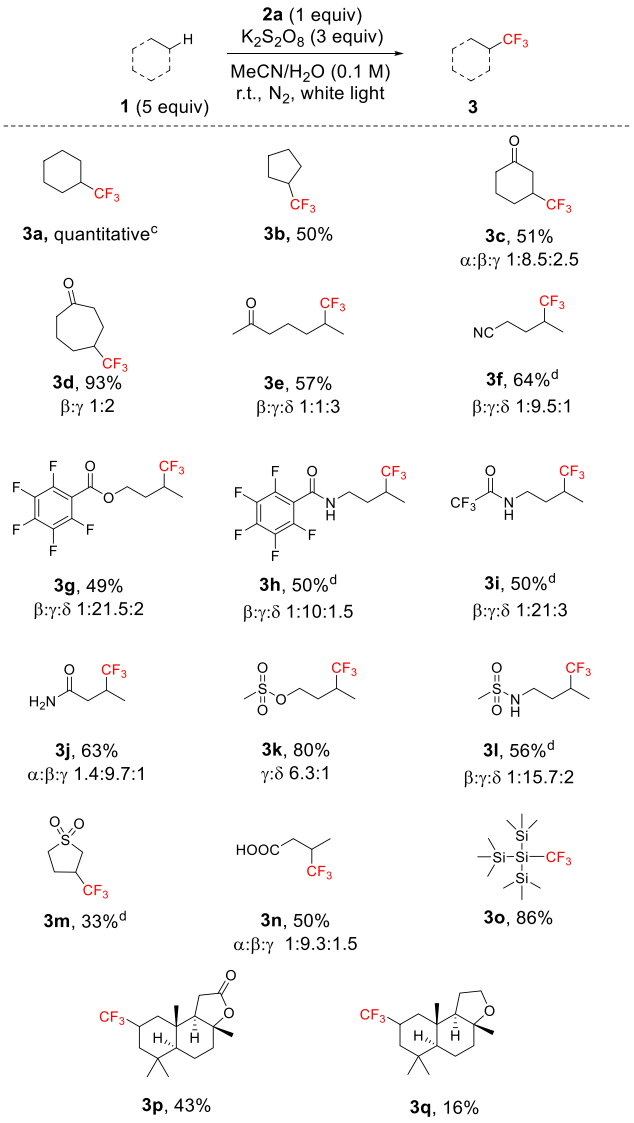

| entry | catalyst | yield[b] (%) |
|---|---|---|
| 1 | standard conditions | 110 |
| 2 | without $K_2S_2O_8$ | 47 |
| 3 | under air | 66 |
| 4 | no white LEDs | nd |
| 5 | 365 nm | 85 |
| 6 | 50 °C instead of white LEDs | trace |
| 7 | 0.05 M MeCN/$H_2O$ (11:1) | 62 |
| 8 | MeCN/$H_2O$ (1:5) | trace |
| 9 | MeCN/$H_2O$ (1:1) | 82 |
| 10 | MeCN/$H_2O$ (5:1) | 98 |
| 11 | acetone instead of MeCN | trace |
| 12 | $(CH_3)_3COH$ instead of MeCH | 23 |
| 13 | adding $(TMS)_3SiH$ | trace |

[a]Unless otherwise noted, all the reactions were run with **1a** (0.2 mmol) and **2a** (0.04 mmol) in 0.4 mL of solvent for 12 h. [b]Yields were determined by $^{19}F$ NMR spectroscopy with fluorobenzene as the internal standard.

well with or without persulfate present (Table 1, entries 1–3), but not without light irradiation (Table 1, entries 4–6). As Grushin's reagent can be excited by both longwave UV and blue light,[5a,b] the reaction proceeded well under 365 nm LED irradiation or with broad-spectrum white-light irradiation (Table 1, entries 1 and 5). While the trifluoromethylation proceeded in low yield in water, the addition of acetonitrile cosolvent dramatically increased the yield—presumably by solubilizing bpyCu($CF_3$)$_3$ (Table 1, entries 7–11). Supersilane inhibited the reaction,[5a] suggesting a critical role for the initial trifluoromethyl radical produced upon irradiation (Table 1, entry 13). With the optimal conditions, more than one trifluoromethyl from Grushin's reagent can produce the new carbon–carbon bond (Table 1, entry 1).

With suitable conditions for the trifluoromethylation of cyclohexane obtained, a variety of unactivated, aliphatic substrates were evaluated (Scheme 2). The reaction worked reasonably well across a range of methylene substrates to produce products **3a**–**3q**. Moreover, the exceptionally mild reaction conditions tolerated a number of commonly reactive functional groups such as ketones (**3c**–**3e**), ethers (**3q**), nitriles (**3f**), esters (**3g** and **3p**), a range of amide derivatives (**3h**–**3j**, **3l**), and even a free carboxylic acid (**3n**). The reaction could also provide Ruppert–Prakash derivative **3o**.[15] While the reaction performed reasonably well over a range of substrates, we were intrigued by the various selectivities observed in the reaction. While in some cases, trifluoromethylation $\alpha$ to an acidifying functional group was detected in small quantities (**3c**, **3f**, **3j** and **3n**), other systems provided no detectable a

**Scheme 2. Substrate Scope for Trifluoromethylation**[a]



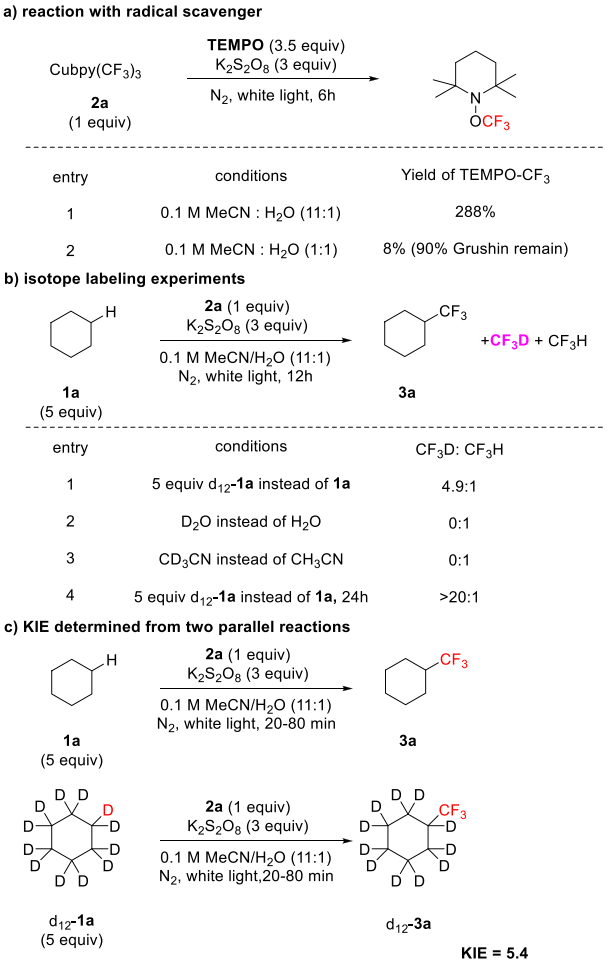

[a]All reactions were run on a 0.2 mmol scale with **1** (1 mmol) and **2a** (0.2 mmol) in 2 mL of solvent for 12 h unless otherwise noted. [b]Yields and regioselectivities determined by $^{19}F$ NMR analysis of the crude reaction mixtures with fluorobenzene as the internal standard. [c]90% in 1.0 mmol scale. [d]24 h.

trifluoromethylation (**3d**, **3e**, **3m**, and **3p**). Moreover, the yield of certain substrates could be improved by changing the ratio of MeCN/$H_2O$. For example, **3i** was produced in only 42% yield in 11:1 MeCN/$H_2O$, but trifluoromethylation improved to 56% in 1:1 MeCN/$H_2O$. Consequently, these conditions represent an operationally simple and convenient method for the trifluoromethylation of a wide range of substrate classes..

With access to this unique trifluoromethylation reaction, we sought to understand some of the fundamental steps involved in the reaction (Scheme 3). Based on previous work demonstrating the homolysis of Grushin's reagent under both long-wave UV and visible-spectrum light,[5a,b] we postulated the formation of trifluoromethyl-based radicals as key, long-lived species in the reaction. Interestingly, we found the combination of TEMPO and Grushin's reagent, lacking substrate **1**, produced TEMPO–$CF_3$ under the reaction conditions (Scheme 3a). Moreover, we found a positive


https://dx.doi.org/10.1021/acs.orglett.0c03891
Org. Lett. 2021, 23, 702–705

**Scheme 3. Key Mechanistic Experiments**




correlation between the amount of organic solvent in the reaction with the amount of TEMPO–$CF_3$ produced (entry 1 vs entry 2, Scheme 3a). We attribute this responsive photophysical behavior to the lack of aqueous solubility of bpyCu$(CF_3)_3$, but studies remain ongoing. Control reactions with deuterated substrate (entries 1 and 4, Scheme 3b) and deuterated reagents (entries 2 and 3, Scheme 3b) suggest that the C–H bond-cleaving step is performed by the trifluoromethyl-based radicals produced in the reaction. To examine whether C–H cleavage might be the slow step of the overall transformation, we conducted a parallel KIE study (Scheme 3c). Not surprisingly, a large, positive KIE of 5.4 was observed in this experiment. Taken together, these data enabled the formulation of a mechanistic hypothesis for the overall transformation (Figure 1).

The proposed roles for the reagents needed for the trifluoromethylation of unactivated methylene groups is delineated in Figure 1. The reaction likely proceeds through the homolysis of Grushin's reagent to generate an active, relatively long-lived trifluoromethyl-based radical. The newly formed trifluoromethyl-based radical can proceed through path b to abstract a C–H bond of the substrate, thereby generating a new carbon-based, secondary radical. This radical can recombine with the newly formed Cu(II) species to form a secondary alkyl copper species that undergoes rapid reductive elimination to give the desired products **3** and inactive Cu(I)$CF_3$. We cannot rule out a second path wherein

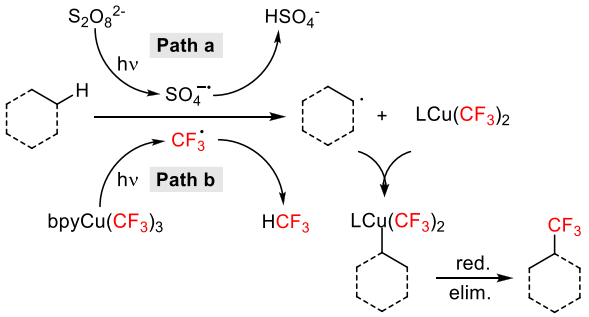



**Figure 1.** Proposed mechanism.

homolyzed persulfate represents an alternative C–H abstracting entity for the reaction (path a). That said, previous work by our group has also demonstrated that the role of persulfate may be more important for providing an ancillary ligand on copper intermediates to lower the activation barrier to radial recombination and reductive elimination.[5b]

In summary, we have developed an efficient copper-based system for the trifluoromethylation of unactivated methylenes in a wide range of chemical environments with interesting selectivities. Using simple, air- and moisture-tolerant reagents, the efficient construction of C–$CF_3$ and Si–$CF_3$ bonds can be accomplished under aqueous conditions. The reaction proved tolerant of a range of common functional groups that should provide a valuable transformation for practicing organic chemists. Mechanistic studies and experiments on the relative rates of Grushin's reagent homolysis in different solvents remain ongoing.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c03891.

Experimental details, compound characterization, and NMR data (PDF)

## ■ AUTHOR INFORMATION


### Corresponding Author

**Silas P. Cook** – *Department of Chemistry, Indiana University, Bloomington, Indiana 47405-7102, United States;* orcid.org/0000-0002-3363-4259; Email: sicook@indiana.edu

### Authors

**Jiachen He** – *Department of Chemistry, Indiana University, Bloomington, Indiana 47405-7102, United States*

**Truong N. Nguyen** – *Department of Chemistry, Indiana University, Bloomington, Indiana 47405-7102, United States*

**Shuo Guo** – *Department of Chemistry, Indiana University, Bloomington, Indiana 47405-7102, United States*

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.orglett.0c03891


### Notes

The authors declare no competing financial interest.

## ■ ACKNOWLEDGMENTS

We acknowledge funds from Indiana University in partial support of this work. We also gratefully acknowledge the NIH

(R01GM121668). Eli Lilly & Co. and Amgen supported this work through the Lilly Grantee Award and the Amgen Young Investigator Award. We thank IU mass spectrometry for HRMS spectra (NSF Grant No. CHE1726633).

## REFERENCES

(1) (a) Ma, J.-A.; Cahard, D. *J. Fluorine Chem.* **2007**, *128*, 975−996. (b) Wang, J.; Sánchez-Roselló, M.; Aceña, J. L.; del Pozo, C.; Sorochinsky, A. E.; Fustero, S.; Soloshonok, V. A.; Liu, H. *Chem. Rev.* **2014**, *114*, 2432−2506. (c) Nie, J.; Guo, H.-C.; Cahard, D.; Ma, J.-A. *Chem. Rev.* **2011**, *111*, 455−529. (d) Ilardi, E. A.; Vitaku, E.; Njardarson, J. T. *J. Med. Chem.* **2014**, *57*, 2832−2842. (e) Kirk, K. L. *Org. Process Res. Dev.* **2008**, *12*, 305−321. (f) Zhou, Y.; Wang, J.; Gu, Z.; Wang, S.; Zhu, W.; Aceñ a, J. L.; Soloshonok, V. A.; Izawa, K.; Liu, H. *Chem. Rev.* **2016**, *116*, 422−518.

(2) (a) Müller, K.; Faeh, C.; Diederich, F. *Science* **2007**, *317*, 1881−1886. (b) Studer, A. *Angew. Chem., Int. Ed.* **2012**, *51*, 8950−8958. (c) Meanwell, N. A. *J. Med. Chem.* **2018**, *61*, 5822−5880. (d) Shimizu, M.; Hiyama, T. *Angew. Chem., Int. Ed.* **2005**, *44*, 214−231. (e) Koike, T.; Akita, M. *Acc. Chem. Res.* **2016**, *49*, 1937−1945. (f) Furet, P.; Guagnano, V.; Fairhurst, R. A.; Imbach-Weese, P.; Bruce, I.; Knapp, M.; Fritsch, C.; Blasco, F.; Blanz, J.; Aichholz, R.; Hamon, J.; Fabbro, D.; Caravatti, G. *Bioorg. Med. Chem. Lett.* **2013**, *23*, 3741−3748.

(3) Bume, D. D.; Harry, S. A.; Lectka, T.; Pitts, C. R. *J. Org. Chem.* **2018**, *83*, 8803−8814.

(4) (a) Alonso, C.; Martínez de Marigorta, E.; Rubiales, G.; Palacios, F. *Chem. Rev.* **2015**, *115*, 1847−1935. (b) Inoue, M.; Sumii, Y.; Shibata, N. *ACS Omega* **2020**, *5*, 10633−10640.

(5) (a) Guo, S.; AbuSalim, D. I.; Cook, S. P. *J. Am. Chem. Soc.* **2018**, *140*, 12378−12382. (b) Guo, S.; AbuSalim, D. I.; Cook, S. P. *Angew. Chem., Int. Ed.* **2019**, *58*, 11704−11708. (c) Xiao, H.; Shen, H.; Zhu, L.; Li, C. *J. Am. Chem. Soc.* **2019**, *141*, 11440−11445. (d) Le, C.; Chen, T. Q.; Liang, T.; Zhang, P.; MacMillan, D. W. C. *Science* **2018**, *360*, 1010−1014.

(6) Tan, X.; Liu, Z.; Shen, H.; Zhang, P.; Zhang, Z.; Li, C. *J. Am. Chem. Soc.* **2017**, *139*, 12430−12433.

(7) Kautzky, J. A.; Wang, T.; Evans, R. W.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2018**, *140*, 6522−6526.

(8) Kornfilt, D. J. P.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2019**, *141*, 6853−6858.

(9) Shen, H.; Liu, Z.; Zhang, P.; Tan, X.; Zhang, Z.; Li, C. *J. Am. Chem. Soc.* **2017**, *139*, 9843−9846.

(10) Zhu, L.; Fang, Y.; Li, C. *Chin. J. Chem.* **2020**, *38*, 787−789.

(11) (a) Paeth, M.; Carson, W.; Luo, J.-H.; Tierney, D.; Cao, Z.; Cheng, M.-J.; Liu, W. *Chem. - Eur. J.* **2018**, *24*, 11559−11563. (b) Xiao, H.; Shen, H.; Zhu, L.; Li, C. *J. Am. Chem. Soc.* **2019**, *141*, 11440−11445.

(12) Groendyke, B. J.; AbuSalim, D. I.; Cook, S. P. *J. Am. Chem. Soc.* **2016**, *138*, 12771−12774.

(13) Liu, Z.; Xiao, H.; Zhang, B.; Shen, H.; Zhu, L.; Li, C. *Angew. Chem., Int. Ed.* **2019**, *58*, 2510−2513.

(14) Sarver, P. J.; Bacauanu, V.; Schultz, D. M.; DiRocco, D. A.; Lam, Y.-h.; Sherer, E. C.; MacMillan, D. W. C. *Nat. Chem.* **2020**, *12*, 459−467.

(15) (a) Prakash, G. K. S.; Mandal, M. *J. Fluorine Chem.* **2001**, *112*, 123−131. (b) Prakash, G. K. S.; Jog, P. V.; Batamack, P. T. D.; Olah, G. A. *Science* **2012**, *338*, 1324−1327.



https://dx.doi.org/10.1021/acs.orglett.0c03891
*Org. Lett.* 2021, 23, 702−705