OL Organic Letters

pubs.acs.org/OrgLett Letter

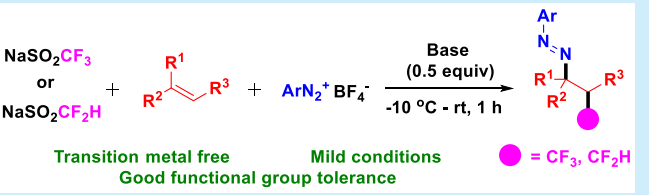
Base-Promoted Radical Azofluoromethylation of Unactivated Alkenes

Zhichao Lu, Olivia Hennis, Joseph Gentry, Bo Xu,* and Gerald B. Hammond*

Cite This: https://dx.doi.org/10.1021/acs.orglett.0c01395 Read Online

ACCESS | Metrics & More | Article Recommendations | Supporting Information

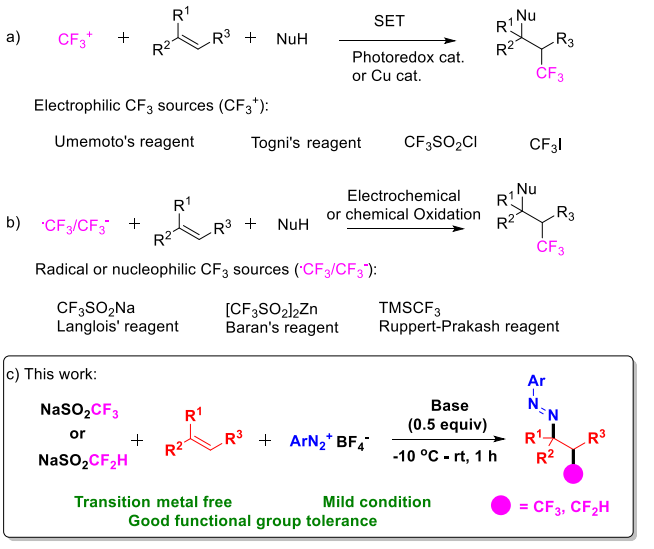
ABSTRACT: The base-induced reaction of aryl diazonium salts with commercially available CF_3SO_2Na/CF_2HSO_2Na allows for the generation of the corresponding diazene radicals along with fluoromethyl radicals. The addition of fluoromethyl radicals to alkenes with subsequent diazene trapping provides the azofluoromethylation products in good to excellent yields. This metal-free method under mild reaction conditions has broad functional group compatibility and is applicable in the late-stage modification of various natural products and bioactive molecules.



The selective installation of fluoroalkyl groups (such as CF_3 and CF_2H) into pharmaceutical and agrochemical compounds, as well as functional organic materials, often delivers compounds with unique physicochemical and biological properties.[1−8] Therefore, new methodologies for the efficient selective incorporation of these substituents into diverse molecular structures have received increasing attention.[9−15] Notably, radical fluoromethylation of alkenes using fluoromethyl radical precursors (electrophilic or nucleophilic) has been extensively studied and proven highly useful.[16] Alkenes are privileged chemicals because of their feedstock accessibility and versatile carbon−carbon double bonds.[17,18] Arguably, fluoromethylative difunctionalization of alkenes is one of the most straightforward strategies for the synthesis of the fluoromethylated building blocks.[19,20] Furthermore, the simultaneous introduction of the fluoromethyl group and another functional group is step-economical.

There are two popular strategies to generate fluoromethyl radicals. One strategy uses electrophilic fluoromethylating reagents, such as Umemoto's reagent, Togni's reagents, or triflyl chloride, that generate the CF_3 radical from SET reduction processes in the presence of photoredox catalysts[21,22] or copper catalysts[23−28] (Scheme 1a). The other strategy employs chemical/electrochemical oxidation[29−38] of radical/nucleophilic trifluoromethylation reagents (e.g., Langlois or Baran reagents) (Scheme 1b). Despite their synthetic utility, those methods have drawbacks, chief among them, expensive noble metal catalysts, complicated reaction setups, electrolytes, or the use of an excessive amount of oxidants, which inevitably generate environmentally hazardous waste or significantly reduce functional group compatibility. In addition, the majority of these studies have focused on styrene and other activated alkenes. Developing a sustainable and practical approach for the fluoroalkylation functionalization of unactivated alkenes is still an unmet challenge. We are glad to report a base-induced three-component radical azo-tri(di)fluoromethylation of alkenes under mild reaction conditions using easily accessible diazonium salts and commercially available, inexpensive CF_3SO_2Na/CF_2HSO_2Na as CF_3/CF_2H sources (Scheme 1c).

Scheme 1. Previous Work on Radical Fluoromethylative Difunctionalization of Alkenes



Received: April 22, 2020

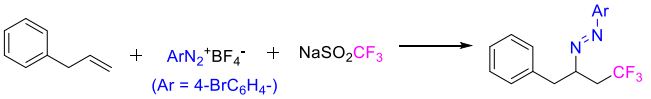
Our method does not require an external oxidant because the diazonium salt plays a dual role as a diazene source and oxidant. It is worth noting that diazenes are used as dyes,[39] pharmaceuticals,[40−42] and photoswitches.[43,44] The catalytic synthesis of diazenes by diazonium salt trapping of alkyl radicals is underexplored.[45−48] Our mild protocol offers the first metal-free azotrifluoromethylation of olefins without the use of stoichiometric oxidants, with broad functional group compatibility.

Several reports have indicated that diazonium salt could generate aryl or diazene radicals with a base.[49−52] Because this process involves an electron absorption by a diazonium salt, we speculated that the Langlois' reagent could serve as an electron donor that can be oxidized to a trifluoromethyl radical, which may further react with an alkene and produce an azotrifluoromethylated product. To prove our hypothesis, we chose allylbenzene **1a**, 4-bromophenyldiazonium tetrafluoroborate **2a**, and CF_3SO_2Na (Langlois' reagent) to test a base-catalyzed three-component azotrifluoromethylation. The results are summarized in Table 1. We screened different organic and inorganic bases and found that the reaction indeed generated the azotrifluoromethylation product, that tetrabutylammonium acetate (TBAOAc) gave the highest yield (entries 1−9), and that acetonitrile and DMF were superior solvents. The addition of water was conducive to the reaction (entries 9−17). The amount of TBAOAc was also crucial because the reaction gave lower yields with either higher or lower molar equivalent of TBAOAc (entries 11−13).

The temperature during the diazonium salt addition also impacted the reaction efficiency. At room temperature, the reaction produced fierce bubbling and lower yields. In contrast, if the reaction mixture was kept at −10 °C during the diazonium addition, the reaction was smoother and the yield higher (entry 18 vs entry 9). Further, two equivalents of both diazonium salt and Langlois' reagent were required (entry 9 vs entries 19, 20). Remarkably, increasing the reaction concentration to 0.5 M increased the reaction yield to 78% (entry 22).

With optimized reaction conditions in hand, we explored the reaction scope. As shown in Scheme 2, all the monosubstituted, disubstituted, and trisubstituted alkenes showed good to excellent yields of the corresponding products. Linear (**4d** and **4t**) and cyclic (**4u** and **4v**) internal alkenes also displayed good yields of the corresponding azo compounds, albeit with varying degrees of diastereoselectivity. A wide range of functional groups such as esters (**4b**, **4g**−**4i**, **4q**, **4r**, and **4z**), ethers (**4f**, **4j**−**4n**, **4p**, **4s**, and **4y**), nitro (**4g** and **4k**), nitriles (**4c** and **4j**), aldehydes (**4f** and **4m**), ketones (**4n** and **4x**), alcohol (**4w**), and sulfonate (**4e**, **4o**, and **4z**) were tolerated in this protocol. Acceptable to good yields were also obtained with heterocyclic substrates like thiophene (**4q**) and furan (**4h**). We then explored late-stage azotrifluoromethylation of natural products (**4w** and **4x**) and biologically active molecule derivatives (**4y**, **4z**). We found that the natural products (−)-ß-citronellol (**4w**) and nootkatone gave excellent yields. Methyl eugenol (**4y**), an active natural ingredient pollinator attractant, furnished the azotrifluoromethylation product in an acceptable yield. Our protocol provides an easy-to-use synthetic tool for the modification of drug molecules. For example, we obtained a derivative of Probenecid (**4z**) in 85% yield. Probenecid is a prototypical uricosuric agent used to treat patients with renal impairment. These examples further demonstrate that our azotrifluoromethylation protocol is suitable for the late-stage, protecting-group-free modification of biologically interesting molecules.

Table 1. Reaction Conditions for the Optimization of the Azotrifluoromethylation of Alkenes[a]



1a 2a 3 4a

entry	solvent	base	conc.	yield[b]
1	DMF/H_2O = 3/1	LiOAc	0.2 M	35%
2	DMF/H_2O = 3/1	kOAc	0.2 M	46%
3	DMF/H_2O = 3/1	CsOAc	0.2 M	34%
4	DMF/H_2O = 3/1	K_2CO_3	0.2 M	37%
5	DMF/H_2O = 3/1	Py	0.2 M	21%
6	DMF/H_2O = 3/1	Et_3N	0.2 M	54%
7	DMF/H_2O = 3/1	DIPEA	0.2 M	20%
8	DMF/H_2O = 3/1	DBU	0.2 M	48%
9	DMF/H_2O = 3/1	TBAOAc	0.2 M	61%
10	DMF	TBAOAc	0.2 M	55%
11	MeCN/H_2O = 3/1	TBAOAc	0.2 M	58%
12[c]	MeCN/H_2O = 3/1	TBAOAc	0.2 M	31%
13[d]	MeCN/H_2O = 3/1	TBAOAc	0.2 M	44%
14	MeCN	TBAOAc	0.2 M	54%
15	Acetone/H_2O=3/1	TBAOAc	0.2 M	54%
16	Acetone	TBAOAc	0.2 M	46%
17	DCM/H_2O = 3/1	TBAOAc	0.2 M	30%
18[e]	DMF/H_2O = 3/1	TBAOAc	0.2 M	28%
19[f]	DMF/H_2O = 3/1	TBAOAc	0.2 M	17%
20[g]	DMF/H_2O = 3/1	TBAOAc	0.2 M	26%
21	DMF/H_2O = 3/1	TBAOAc	0.1 M	14%
22	DMF/H_2O = 3/1	TBAOAc	0.5 M	78%

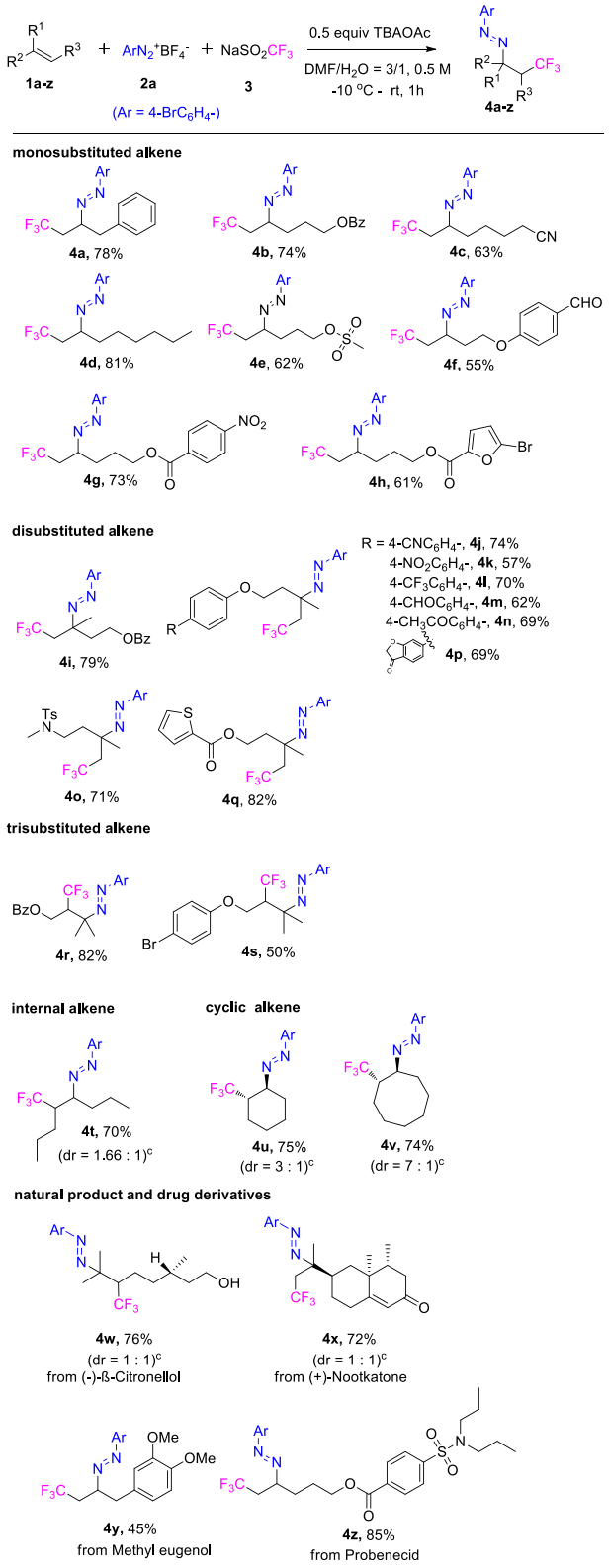
[a]Unless otherwise noted, reactions were conducted with a solution of **2a** (2 equiv) in 200 μL of mixed solvent (DMF/H_2O = 3/1) added dropwise to the mixture **1a** (0.2 mmol), base (0.5 equiv), and **3** (2 equiv) in 800 μL mixed solvent (DMF/H_2O = 3/1) at −10 °C; the reaction was then stirred at rt for 1 h. [b]Yields were determined by ^{19}F NMR using 4-fluoroanisole as an internal standard. [c]0.1 equiv of TBAOAc. [d]1 equiv of TBAOAc. [e]Room temperature. [f]**3** (1.5 equiv) and **2a** (1.5 equiv) were used. [g]**3** (2 equiv) and **2a** (1.5 equiv) were used.

Encouraged by these results, we explored the scope of diazonium salts under the standard conditions (Scheme 3). It was found that aryldiazonium salts **2b**−**2k** bearing electron-withdrawing or -donating groups at the *para*-, *meta*-, or *ortho*-positions were well tolerated, affording the corresponding products **5b**−**5k** in moderate to good yields. However, electron-rich diazonium salt gave a lower yield than the electron-deficient diazonium salts (**5g** vs **5d**−**5f**). The reason for this result could be attributed to electron-rich diazonium salts being less stable under basic conditions.

In contrast to various methods for the synthesis of trifluoromethylated organic substrates, direct difluoromethylation is still underdeveloped,[53−63] albeit the difluoromethyl group (CF_2H) is an intriguing structural motif in drug design.[64,65] We are glad to find that our protocol can also be applied to the azodifluoromethylation of alkenes by just switching the Langlois' reagent with the commercially available

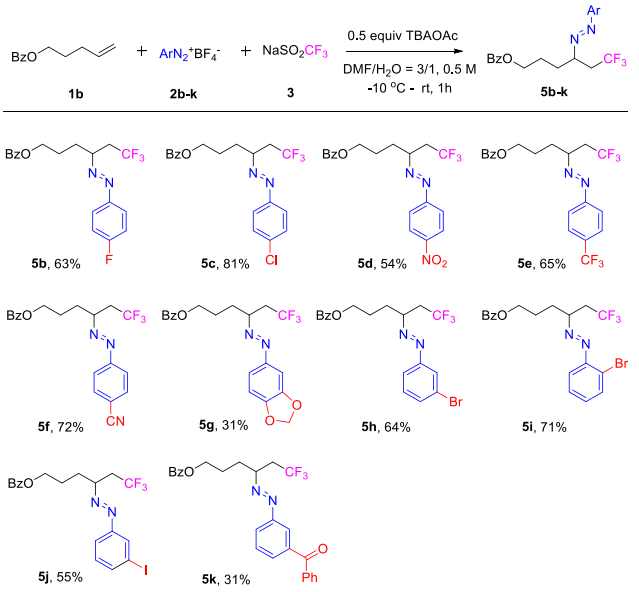
https://dx.doi.org/10.1021/acs.orglett.0c01395
Org. Lett. XXXX, XXX, XXX−XXX

Scheme 2. Substrate Scope of Alkenes[a,b]



[a]Reaction conditions: A solution of diazonium salt **2a** (2 equiv) in 200 μL of mixed solvent (DMF/H_2O = 3/1) was added dropwise to the mixture of alkene **1** (0.2 mmol), TBAOAc (0.5 equiv), and **3** (2 equiv) in 200 μL of mixed solvent (DMF/H_2O = 3/1) at −10 °C; the reaction was then stirred at rt for 1 h. [b]Isolated yield. [c]Diastereomeric ratios were determined by ^{19}F NMR analysis of the crude mixture.

Scheme 3. Substrate Scope of Diazonium Salts[a,b]



[a]Reaction conditions: A solution of diazonium salt **2** (2 equiv) in 200 μL of mixed solvent (DMF/H_2O = 3/1) was added dropwise to the mixture of alkene **1b** (0.2 mmol), TBAOAc (0.5 equiv), and **3** (2 equiv) in 200 μL of mixed solvent (DMF/H_2O = 3/1) at −10 °C; the mixture was then stirred at rt for 1 h. [b]Isolated yield.

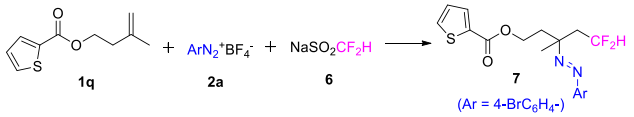
CF_2HSO_2Na. A simple reaction condition optimization showed that using CF_2HSO_2Na as CF_2H source, MeCN/H_2O = 3/1 as the solvent, and KOAc as the base at 0.5 M concentration delivered the azodifluoromethylated product at an acceptable 53% yield (Table 2).

The azodifluoromethylation protocol was less efficient than azotrifluoromethylation, but still showed good substrate scope and functional group compatibility. As illustrated in Scheme 4, monosubstituted (**7b**, **7l**), disubstituted (**7a**, **7c**−**7j**) and trisubstituted alkenes (**7k**) were amenable substrates. A wide range of functional groups such as esters (**7a**−**7c**, **7j**, and **7l**), ethers (**7d**−**7h**), nitro (**7e**), nitrile (**7d**), aldehyde (**7h**), ketone (**7f**), sulfonamide (**7i**), alcohol (**7k**), and alkyne (**7j**) were compatible with our protocol. We also applied this protocol to the late-stage azodifluoromethylation of a natural product (**7k**) and a biologically active molecule derivative (**7l**). Both compounds afforded the corresponding azodifluoromethylation products in acceptable yields.

To gain more insight into the reaction mechanism, we added TEMPO, a radical scavenger, to the reaction mixture (Scheme 5). As expected, the reaction led to a trace amount of the product (<2%), and TEMPO−CF_3 was observed (8%), which indicated a radical pathway. We postulated a mechanism initiated by the homolysis of the initially formed diazoacetate **A** (Scheme 6).[50,52] The resulting acetyloxy radical oxidizes the Langlois' reagent and delivers the trifluoromethyl radical and acetate. The addition of the CF_3 radical to an alkene affords the β-CF_3-substituted radical intermediate **C**; SET reduction of cation radical **D** by $NaSO_2CF_3$ affords product **4** and the CF_3 radical, which could initiate the radical chain propagation (pathway I).[46,52,66] Alternatively, the trapping of the intermediate **C** by diazoacetate **A** (pathway II) could provide the azofluoromethylation product **4** and the acetyloxy radical. The resulting acetyloxy radical oxidizes the Langlois' reagent and delivers the trifluoromethyl radical and acetate. The highly regioselective

https://dx.doi.org/10.1021/acs.orglett.0c01395
Org. Lett. XXXX, XXX, XXX−XXX

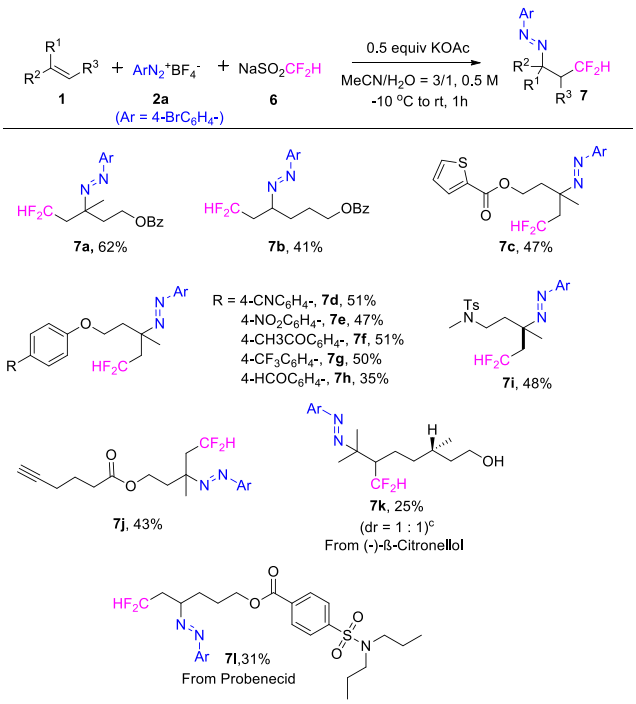
Table 2. Reaction Conditions for the Optimizations of the Azodifluoromethylation of Alkenes[a]



Entry	Base	Solvent	Conc.	Yield (%)[b]
1	TBAOAc	CH_3NO_2 / H_2O = 3/1	0.5 M	27
2	TBAOAc	Acetone / H_2O = 3/1	0.5 M	45
3	TBAOAc	DMF/ H_2O = 3/1	0.5 M	33
4	TBAOAc	MeCN / H_2O = 3/1	0.5 M	45
5	TBAOAc	MeCN / H_2O = 3/1	0.1 M	51
6	TBAOAc	MeCN / H_2O = 3/1	0.2 M	36
7	KOAc	MeCN / H_2O = 3/1	0.5 M	53
8	LiOAc	MeCN / H_2O = 3/1	0.5 M	34
9	Et_3N	MeCN / H_2O = 3/1	0.5 M	30
10	DBU	MeCN / H_2O = 3/1	0.5 M	41

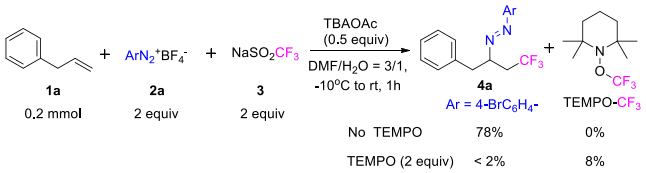
[a]Unless otherwise noted, reactions were conducted with a solution of **2a** (2 equiv) in 200 μL of mixed solvent (MeCN/H_2O = 3/1) added dropwise to the mixture of **1q** (0.2 mmol), base (0.5 equiv), and **6** (2 equiv) in 200 μL of mixed solvent (MeCN/H_2O = 3/1) at −10 °C; the reaction was then stirred at rt for 1 h. [b]Yields were determined by ^{19}F NMR using 4-fluoroanisole as an internal standard.

Scheme 4. Substrate Scope of Azodifluoromethylation of Alkene Using Various Alkenes[a,b]

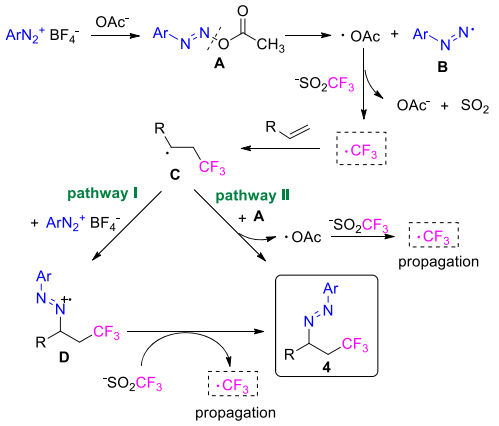


[a]Reaction conditions: A solution of diazonium salt (2 equiv) in 200 μL of mixed solvent (MeCN/H_2O = 3/1) was added dropwise to the mixture of alkene (0.2 mmol), KOAc (0.5 equiv), and **6** (2 equiv) in 200 μL of mixed solvent (MeCN/H_2O = 3/1) at −10 °C; the reaction was then stirred at rt for 1 h. [b]Isolated yield. [c]Diastereomeric ratios were determined by ^{19}F NMR analysis of the crude mixture.

Scheme 5. Control Experiments



Scheme 6. Plausible Mechanism for the Azotrifluoromethylation of Alkenes



formation of the terminal fluoromethylated product implied that the addition of the CF_3 radical occurred first as it delivered a more stable β-CF_3-substituted radical intermediate.

In summary, we have developed a base-induced three-component radical azo-tri(di)-fluoromethylation of alkenes under mild conditions, using easily accessible diazonium salts and commercially available, inexpensive CF_3SO_2Na/CF_2HSO_2Na. This transition-metal-free protocol is operationally simple, avoids the use of external stoichiometric chemical oxidants, and exhibits a broad substrate scope for the difunctionalization of a broad range of alkenes.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c01395.

NMR data and characterization (PDF)

■ AUTHOR INFORMATION

Corresponding Authors

Bo Xu − *College of Chemistry, Chemical Engineering and Biotechnology, Donghua University, Shanghai 201620, China;* orcid.org/0000-0001-8702-1872; Email: bo.xu@dhu.edu.cn

Gerald B. Hammond − *Department of Chemistry, University of Louisville, Louisville, Kentucky 40292, United States;* orcid.org/0000-0002-9814-5536; Email: gb.hammond@louisville.edu

Authors

Zhichao Lu − *Department of Chemistry, University of Louisville, Louisville, Kentucky 40292, United States;* orcid.org/0000-0002-4746-7543

Olivia Hennis − *Department of Chemistry, University of Louisville, Louisville, Kentucky 40292, United States*

https://dx.doi.org/10.1021/acs.orglett.0c01395
Org. Lett. XXXX, XXX, XXX−XXX

Joseph Gentry − *Williams College, Williamstown, Massachusetts 01267, United States*

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.orglett.0c01395

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We are grateful to the National Institutes of Health for financial support (R01GM121660). B.X. is grateful to the National Science Foundation of China (NSFC-21672035) for financial support. O.H. acknowledges with gratitude a Moissan Summer Undergraduate Research Fellowship, awarded by the Division of Fluorine Chemistry of the American Chemical Society.

■ REFERENCES

(1) Uneyama, K. *Organofluorine chemistry*; Blackwell Pub.: Ames, IA, 2006.
(2) Kirsch, P. *Modern fluoroorganic chemistry: synthesis, reactivity, applications*; 2nd ed.; Wiley-VCH, Verlag GmbH & Co. KGaA: Weinheim, Germany, 2013.
(3) Muller, K.; Faeh, C.; Diederich, F. Fluorine in pharmaceuticals: Looking beyond intuition. *Science* **2007**, *317*, 1881−1886.
(4) O'Hagan, D. Understanding organofluorine chemistry. An introduction to the C−F bond. *Chem. Soc. Rev.* **2008**, *37*, 308−319.
(5) Champagne, P. A.; Desroches, J.; Hamel, J.-D.; Vandamme, M.; Paquin, J.-F. Monofluorination of Organic Compounds: 10 Years of Innovation. *Chem. Rev.* **2015**, *115*, 9073−9174.
(6) Gillis, E. P.; Eastman, K. J.; Hill, M. D.; Donnelly, D. J.; Meanwell, N. A. Applications of Fluorine in Medicinal Chemistry. *J. Med. Chem.* **2015**, *58*, 8315−8359.
(7) Campbell, M. G.; Ritter, T. Modern Carbon−Fluorine Bond Forming Reactions for Aryl Fluoride Synthesis. *Chem. Rev.* **2015**, *115*, 612−633.
(8) Zhu, Y.; Han, J.; Wang, J.; Shibata, N.; Sodeoka, M.; Soloshonok, V. A.; Coelho, J. A. S.; Toste, F. D. Modern Approaches for Asymmetric Construction of Carbon−Fluorine Quaternary Stereogenic Centers: Synthetic Challenges and Pharmaceutical Needs. *Chem. Rev.* **2018**, *118*, 3887−3964.
(9) Besset, T.; Poisson, T.; Pannecoucke, X. Recent Progress in Direct Introduction of Fluorinated Groups on Alkenes and Alkynes by means of C−H Bond Functionalization. *Chem. - Eur. J.* **2014**, *20*, 16830−16845.
(10) Alonso, C.; Martínez de Marigorta, E.; Rubiales, G.; Palacios, F. Carbon Trifluoromethylation Reactions of Hydrocarbon Derivatives and Heteroarenes. *Chem. Rev.* **2015**, *115*, 1847−1935.
(11) Tomashenko, O. A.; Grushin, V. V. Aromatic Trifluoromethylation with Metal Complexes. *Chem. Rev.* **2011**, *111*, 4475−4521.
(12) Chu, L.; Qing, F.-L. Oxidative Trifluoromethylation and Trifluoromethylthiolation Reactions Using (Trifluoromethyl)-trimethylsilane as a Nucleophilic CF_3 Source. *Acc. Chem. Res.* **2014**, *47*, 1513−1522.
(13) Liu, X.; Xu, C.; Wang, M.; Liu, Q. Trifluoromethyltrimethylsilane: Nucleophilic Trifluoromethylation and Beyond. *Chem. Rev.* **2015**, *115*, 683−730.
(14) Yang, X.; Wu, T.; Phipps, R. J.; Toste, F. D. Advances in Catalytic Enantioselective Fluorination, Mono-, Di-, and Trifluoromethylation, and Trifluoromethylthiolation Reactions. *Chem. Rev.* **2015**, *115*, 826−870.
(15) Charpentier, J.; Früh, N.; Togni, A. Electrophilic Trifluoromethylation by Use of Hypervalent Iodine Reagents. *Chem. Rev.* **2015**, *115*, 650−682.
(16) Studer, A. A "Renaissance" in Radical Trifluoromethylation. *Angew. Chem., Int. Ed.* **2012**, *51*, 8950−8958.
(17) Tang, S.; Liu, K.; Liu, C.; Lei, A. Olefinic C−H functionalization through radical alkenylation. *Chem. Soc. Rev.* **2015**, *44*, 1070−1082.
(18) Huang, L.; Arndt, M.; Gooßen, K.; Heydt, H.; Gooßen, L. J. Late Transition Metal-Catalyzed Hydroamination and Hydroamidation. *Chem. Rev.* **2015**, *115*, 2596−2697.
(19) Egami, H.; Sodeoka, M. Trifluoromethylation of Alkenes with Concomitant Introduction of Additional Functional Groups. *Angew. Chem., Int. Ed.* **2014**, *53*, 8294−8308.
(20) Merino, E.; Nevado, C. Addition of CF_3 across unsaturated moieties: a powerful functionalization tool. *Chem. Soc. Rev.* **2014**, *43*, 6598−6608.
(21) Lemos, A.; Lemaire, C.; Luxen, A. Progress in Difluoroalkylation of Organic Substrates by Visible Light Photoredox Catalysis. *Adv. Synth. Catal.* **2019**, *361*, 1500−1537.
(22) Koike, T.; Akita, M. New Horizons of Photocatalytic Fluoromethylative Difunctionalization of Alkenes. *Chem.* **2018**, *4*, 409−437.
(23) Xiao, H.; Shen, H.; Zhu, L.; Li, C. Copper-Catalyzed Radical Aminotrifluoromethylation of Alkenes. *J. Am. Chem. Soc.* **2019**, *141*, 11440−11445.
(24) Wang, F.; Wang, D.; Wan, X.; Wu, L.; Chen, P.; Liu, G. Enantioselective Copper-Catalyzed Intermolecular Cyanotrifluoromethylation of Alkenes via Radical Process. *J. Am. Chem. Soc.* **2016**, *138*, 15547−15550.
(25) Zhu, Y.; Tian, J.; Gu, X.; Wang, Y. Free-Radical-Promoted Copper-Catalyzed Intermolecular Cyanosulfonylation and Cyanotrifluoromethylation of Unactivated Alkenes in Water-Containing Solvents. *J. Org. Chem.* **2018**, *83*, 13267−13275.
(26) Wang, F.; Wang, D.; Mu, X.; Chen, P.; Liu, G. Copper-Catalyzed Intermolecular Trifluoromethylarylation of Alkenes: Mutual Activation of Arylboronic Acid and CF_3^+ Reagent. *J. Am. Chem. Soc.* **2014**, *136*, 10202−10205.
(27) Zhang, Z.; Tang, X.; Thomoson, C. S.; Dolbier, W. R. Photoredox-Catalyzed Intramolecular Aminodifluoromethylation of Unactivated Alkenes. *Org. Lett.* **2015**, *17*, 3528−3531.
(28) Tang, X.-J.; Thomoson, C. S.; Dolbier, W. R. Photoredox-Catalyzed Tandem Radical Cyclization of N-Arylacrylamides: General Methods To Construct Fluorinated 3,3-Disubstituted 2-Oxindoles Using Fluoroalkylsulfonyl Chlorides. *Org. Lett.* **2014**, *16*, 4594−4597.
(29) Ruan, Z.; Huang, Z.; Xu, Z.; Mo, G.; Tian, X.; Yu, X.-Y.; Ackermann, L. Catalyst-Free, Direct Electrochemical Tri- and Difluoroalkylation/Cyclization: Access to Functionalized Oxindoles and Quinolinones. *Org. Lett.* **2019**, *21*, 1237−1240.
(30) Jiang, Y.-Y.; Dou, G.-Y.; Xu, K.; Zeng, C.-C. Bromide-catalyzed electrochemical trifluoromethylation/cyclization of *N*-arylacrylamides with low catalyst loading. *Org. Chem. Front.* **2018**, *5*, 2573−2577.
(31) Zou, Z.; Zhang, W.; Wang, Y.; Kong, L.; Karotsis, G.; Wang, Y.; Pan, Y. Electrochemically Promoted Fluoroalkylation−Distal Functionalization of Unactivated Alkenes. *Org. Lett.* **2019**, *21*, 1857−1862.
(32) Ye, K.-Y.; Pombar, G.; Fu, N.; Sauer, G. S.; Keresztes, I.; Lin, S. Anodically Coupled Electrolysis for the Heterodifunctionalization of Alkenes. *J. Am. Chem. Soc.* **2018**, *140*, 2438−2441.
(33) Jud, W.; Kappe, C. O.; Cantillo, D. Catalyst-Free Oxytrifluoromethylation of Alkenes through Paired Electrolysis in Organic-Aqueous Media. *Chem. - Eur. J.* **2018**, *24*, 17234−17238.
(34) Tommasino, J.-B.; Brondex, A.; Médebielle, M.; Thomalla, M.; Langlois, B. R.; Billard, T. Trifluoromethylation Reactions with Potassium Trifluoromethanesulfinate under Electrochemical Oxidation. *Synlett* **2002**, *2002*, 1697−1699.
(35) Sun, X.; Ma, H.-X.; Mei, T.-S.; Fang, P.; Hu, Y. Electrochemical Radical Formyloxylation−Bromination, − Chlorination, and − Trifluoromethylation of Alkenes. *Org. Lett.* **2019**, *21*, 3167−3171.
(36) Zhang, Z.; Zhang, L.; Cao, Y.; Li, F.; Bai, G.; Liu, G.; Yang, Y.; Mo, F. Mn-Mediated Electrochemical Trifluoromethylation/C(sp^2)−H Functionalization Cascade for the Synthesis of Azaheterocycles. *Org. Lett.* **2019**, *21*, 762−766.
(37) Zhang, S.; Li, L.; Zhang, J.; Zhang, J.; Xue, M.; Xu, K. Electrochemical fluoromethylation triggered lactonizations of alkenes under semi-aqueous conditions. *Chem. Sci.* **2019**, *10*, 3181−3185.

(38) Zhang, L.; Zhang, G.; Wang, P.; Li, Y.; Lei, A. Electrochemical Oxidation with Lewis-Acid Catalysis Leads to Trifluoromethylative Difunctionalization of Alkenes Using CF_3SO_2Na. *Org. Lett.* **2018**, *20*, 7396−7399.
(39) Zollinger, H. *Color Chemistry: Syntheses, Properties, and Applications of Organic Dyes and Pigments*; John Wiley & Sons, 2003.
(40) Velema, W. A.; van der Toorn, M.; Szymanski, W.; Feringa, B. L. Design, Synthesis, and Inhibitory Activity of Potent, Photoswitchable Mast Cell Activation Inhibitors. *J. Med. Chem.* **2013**, *56*, 4456−4464.
(41) Ferreira, R.; Nilsson, J. R.; Solano, C.; Andréasson, J.; Grøtli, M. Design, Synthesis and Inhibitory Activity of Photoswitchable RET Kinase Inhibitors. *Sci. Rep.* **2015**, *5*, 9769.
(42) Polanc, S. New synthetic applications and biological activity of diazenes. *J. Heterocycl. Chem.* **2005**, *42*, 401−412.
(43) Simeth, N. A.; Bellisario, A.; Crespi, S.; Fagnoni, M.; König, B. Substituent Effects on 3-Arylazoindole Photoswitches. *J. Org. Chem.* **2019**, *84*, 6565−6575.
(44) Crespi, S.; Simeth, N. A.; König, B. Heteroaryl azo dyes as molecular photoswitches. *Nat. Rev. Chem.* **2019**, *3*, 133−146.
(45) Abrams, R.; Lefebvre, Q.; Clayden, J. Transition Metal Free Cycloamination of Prenyl Carbamates and Ureas Promoted by Aryldiazonium Salts. *Angew. Chem., Int. Ed.* **2018**, *57*, 13587−13591.
(46) Yu, X.-L.; Chen, J.-R.; Chen, D.-Z.; Xiao, W.-J. Visible-light-induced photocatalytic azotrifluoromethylation of alkenes with aryldiazonium salts and sodium triflinate. *Chem. Commun.* **2016**, *52*, 8275−8278.
(47) Monge, D.; Daza, S.; Bernal, P.; Fernández, R.; Lassaletta, J. M. Synthesis of enantioenriched azo compounds: organocatalytic Michael addition of formaldehyde *N*-tert-butyl hydrazone to nitroalkenes. *Org. Biomol. Chem.* **2013**, *11*, 326−335.
(48) Zhang, Y.; Huang, C.; Lin, X.; Hu, Q.; Hu, B.; Zhou, Y.; Zhu, G. Modular Synthesis of Alkylarylazo Compounds via Iron(III)-Catalyzed Olefin Hydroamination. *Org. Lett.* **2019**, *21*, 2261−2264.
(49) Hartmann, M.; Li, Y.; Studer, A. Transition-Metal-Free Oxyarylation of Alkenes with Aryl Diazonium Salts and TEMPONa. *J. Am. Chem. Soc.* **2012**, *134*, 16516−16519.
(50) Koziakov, D.; Majek, M.; Jacobi von Wangelin, A. Metal-free radical thiolations mediated by very weak bases. *Org. Biomol. Chem.* **2016**, *14*, 11347−11352.
(51) Dong, B.; Peng, H.; Motika, S. E.; Shi, X. Gold Redox Catalysis through Base-Initiated Diazonium Decomposition toward Alkene, Alkyne, and Allene Activation. *Chem. - Eur. J.* **2017**, *23*, 11093−11099.
(52) Kindt, S.; Wicht, K.; Heinrich, M. R. Base-Induced Radical Carboamination of Nonactivated Alkenes with Aryldiazonium Salts. *Org. Lett.* **2015**, *17*, 6122−6125.
(53) Rong, J.; Deng, L.; Tan, P.; Ni, C.; Gu, Y.; Hu, J. Radical Fluoroalkylation of Isocyanides with Fluorinated Sulfones by Visible-Light Photoredox Catalysis. *Angew. Chem., Int. Ed.* **2016**, *55*, 2743−2747.
(54) Arai, Y.; Tomita, R.; Ando, G.; Koike, T.; Akita, M. Oxydifluoromethylation of Alkenes by Photoredox Catalysis: Simple Synthesis of CF_2H-Containing Alcohols. *Chem. - Eur. J.* **2016**, *22*, 1262−1265.
(55) Tang, X.-J.; Dolbier, W. R., Jr Efficient Cu-catalyzed Atom Transfer Radical Addition Reactions of Fluoroalkylsulfonyl Chlorides with Electron-deficient Alkenes Induced by Visible Light. *Angew. Chem., Int. Ed.* **2015**, *54*, 4246−4249.
(56) He, Z.; Tan, P.; Ni, C.; Hu, J. Fluoroalkylative Aryl Migration of Conjugated *N*-Arylsulfonylated Amides Using Easily Accessible Sodium Di- and Monofluoroalkanesulfinates. *Org. Lett.* **2015**, *17*, 1838−1841.
(57) Li, Z.; Cui, Z.; Liu, Z.-Q. Copper- and Iron-Catalyzed Decarboxylative Tri- and Difluoromethylation of α,β-Unsaturated Carboxylic Acids with CF_3SO_2Na and $(CF_2HSO_2)_2Zn$ via a Radical Process. *Org. Lett.* **2013**, *15*, 406−409.
(58) O'Brien, A. G.; Maruyama, A.; Inokuma, Y.; Fujita, M.; Baran, P. S.; Blackmond, D. G. Radical C−H Functionalization of Heteroarenes under Electrochemical Control. *Angew. Chem., Int. Ed.* **2014**, *53*, 11868−11871.
(59) Fujiwara, Y.; Dixon, J. A.; Rodriguez, R. A.; Baxter, R. D.; Dixon, D. D.; Collins, M. R.; Blackmond, D. G.; Baran, P. S. A New Reagent for Direct Difluoromethylation. *J. Am. Chem. Soc.* **2012**, *134*, 1494−1497.
(60) Cao, P.; Duan, J.-X.; Chen, Q.-Y. Difluoroiodomethane: practical synthesis and reaction with alkenes. *J. Chem. Soc., Chem. Commun.* **1994**, 737−738.
(61) Lin, Q.-Y.; Ran, Y.; Xu, X.-H.; Qing, F.-L. Photoredox-Catalyzed Bromodifluoromethylation of Alkenes with (Difluoromethyl)-triphenylphosphonium Bromide. *Org. Lett.* **2016**, *18*, 2419−2422.
(62) Zeng, X.; Yan, W.; Zacate, S. B.; Chao, T.-H.; Sun, X.; Cao, Z.; Bradford, K. G. E.; Paeth, M.; Tyndall, S. B.; Yang, K.; Kuo, T.-C.; Cheng, M.-J.; Liu, W. Copper-Catalyzed Decarboxylative Difluoromethylation. *J. Am. Chem. Soc.* **2019**, *141*, 11398−11403.
(63) Xu, L.; Vicic, D. A. Direct Difluoromethylation of Aryl Halides via Base Metal Catalysis at Room Temperature. *J. Am. Chem. Soc.* **2016**, *138*, 2536−2539.
(64) Rewcastle, G. W.; Gamage, S. A.; Flanagan, J. U.; Frederick, R.; Denny, W. A.; Baguley, B. C.; Kestell, P.; Singh, R.; Kendall, J. D.; Marshall, E. S.; Lill, C. L.; Lee, W.-J.; Kolekar, S.; Buchanan, C. M.; Jamieson, S. M. F.; Shepherd, P. R. Synthesis and Biological Evaluation of Novel Analogues of the Pan Class I Phosphatidylinositol 3-Kinase (PI3K) Inhibitor 2-(Difluoromethyl)-1-[4,6-di(4-morpholinyl)-1,3,5-triazin-2-yl]-1H-benzimidazole (ZSTK474). *J. Med. Chem.* **2011**, *54*, 7105−7126.
(65) Martínez, M. D.; Luna, L.; Tesio, A. Y.; Feresin, G. E.; Durán, F. J.; Burton, G. Antioxidant properties in a non-polar environment of difluoromethyl bioisosteres of methyl hydroxycinnamates. *J. Pharm. Pharmacol.* **2016**, *68*, 233−244.
(66) Kindt, S.; Wicht, K.; Heinrich, M. R. Thermally Induced Carbohydroxylation of Styrenes with Aryldiazonium Salts. *Angew. Chem., Int. Ed.* **2016**, *55*, 8744−8747.

https://dx.doi.org/10.1021/acs.orglett.0c01395
Org. Lett. XXXX, XXX, XXX−XXX