OL | Organic Letters

pubs.acs.org/OrgLett

Letter

Starting from Styrene: A Unified Protocol for Hydrotrifluoromethylation of Diversified Alkenes

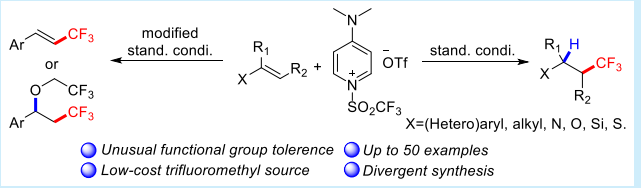
Yi-Fei Yang, Jin-Hong Lin,* and Ji-Chang Xiao*

Cite This: *Org. Lett.* 2021, 23, 9277–9282

Read Online

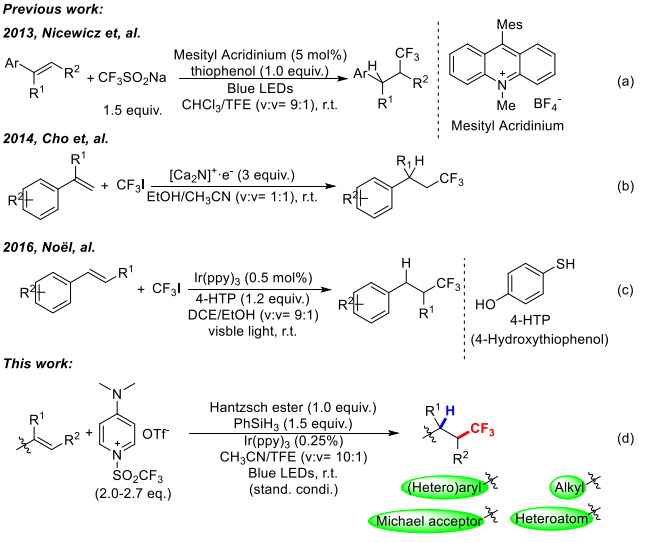
ACCESS | Metrics & More | Article Recommendations | Supporting Information

ABSTRACT: In contrast with unactivated alkenes, the corresponding hydrotrifluoromethylation of styrene has remained challenging due to the strong propensity of styrene for oligomerization and polymerization. On the basis of our newly developed trifluoromethylation reagent, TFSP, herein we present a general method for the hydrotrifluoromethylation of styrene under photoredox catalysis. The substrate scope was further extended to unactivated alkenes, acrylates, acrylamides, and vinyl-heteroatom-substituted alkenes. The tunability of this method was showcased via the relevant deprotonative trifluoromethylation and trifluoromethyltrifluoroethoxylation reactions.



Although the existence of fluoro-containing natural products is rare, fluoro-containing moieties are ubiquitously found in pharmaceutical, agrochemical, and material science.[1] The vast comparison has prompted the rapid development of fluorine chemistry in recent decades. Among the fluorine-containing pharmaceuticals, trifluoromethylated pharmaceuticals are found to be the most prevalent, except for fluorinated pharmaceuticals, which urges the development of new efficient, general, and tunable methods to incorporate the trifluoromethyl moiety.[2] In this context, the hydrotrifluoromethylation of olefins has emerged as a powerful strategy to introduce the trifluoromethyl moiety. Whereas a variety of methodologies have been reported to realize the hydrotrifluoromethylation of unactivated alkenes,[3] the hydrotrifluoromethylation of styrene has lagged behind due to the myriad side reactions including oligomerization, polymerization, and nucleophilic trapping.[4] In 2013, Nicewicz *et al.* reported for the first time the hydrotrifluoromethylation of styrene via an organic photoredox system (Scheme 1a).[4] Various vicinal-disubstituted styrenes were shown to be compatible. However, only one example of terminal styrene was reported, leaving the core problem still challenging. One year later, by means of a novel 2D electride dicalcium nitride ($[Ca_2N^+]\cdot e^-$), the hydrotrifluoromethylation of terminal styrene was realized (Scheme 1b).[5] Offering high reactivity, the active electride may at the same time result in restricted functional group tolerance. In 2016, the same transformation was smoothly conducted using 4-hydroxythiophenol as a stoichiometric hydrogen source in batch and flow (Scheme 1c).[6] Elegant as it is, the near-room-temperature melting point and offensive odor of the thiophenol used can reduce its practicability in certain circumstances. Meanwhile, despite the fact that several methods concerning the hydrotrifluoromethylation of acrylates,[7] acrylamides,[8] and vinyl phosphate esters[9] were reported,

Scheme 1. Hydrotrifluoromethylation of Styrene



a universal protocol that can break through the limits of the previously mentioned alkenes to realize hydrotrifluoromethylation has never been realized.

Our continuing interest in developing ionic-type fluoroalkylation reagents[10] and the recent concern about pyridinium

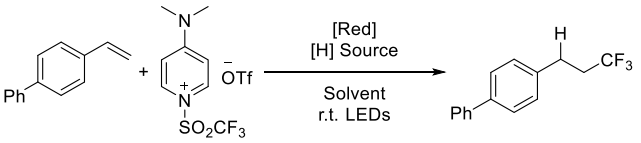
Received: October 26, 2021
Published: November 19, 2021

https://doi.org/10.1021/acs.orglett.1c03630
Org. Lett. 2021, 23, 9277–9282

salts[11] have led us to the development of TFSP, a readily available trifluoromethylation reagent prepared from the common base DMAP and the bulk chemical Tf_2O.[12] On the basis of this newly developed low-cost trifluoromethylation reagent, herein we present the hydrotrifluoromethylation of diversified olefins (Scheme 1d). The low catalyst and reactant loading rendered our protocol practical. The flexibility of our protocol was highlighted by the related deprotonative trifluoromethylation and trifluoromethyltrifluoroethoxylation reactions.

Our optimization began with 1-ethenyl-4-phenylbenzene (**1-1**) as a model substrate under photoredox catalysis (Table 1).

Table 1. Optimization of Reaction Conditions[a]



1-1 2 3-1

entry	[Red]	[H] source	solvent	yield (%)[b]
1	HEH		CH_3CN	14
2	BNAH		CH_3CN	trace
3	1,4-CHD		CH_3CN	trace
4	HEH	Et_3SiH	CH_3CN	21
5	HEH	$(TMS)_3SiH$	CH_3CN	12
6	HEH	$PhSiH_3$	CH_3CN	56
7	HEH	Ph_2SiH_2	CH_3CN	41
8[c]	HEH	$PhSiH_3$	CH_3CN	5
9	HEH	$PhSiH_3$	CH_3CN/MeOH	52
10	HEH	$PhSiH_3$	CH_3CN/*i*-PrOH	50
11	HEH	$PhSiH_3$	CH_3CN/TFE	66
12	HEH	$PhSiH_3$	DCM	48
13	HEH	$PhSiH_3$	EA	42
14[d]	HEH	$PhSiH_3$	CH_3CN/TFE	69
15[d,e]	HEH	$PhSiH_3$	CH_3CN/TFE	n.d.
16[d,f]	HEH	$PhSiH_3$	CH_3CN/TFE	n.d.

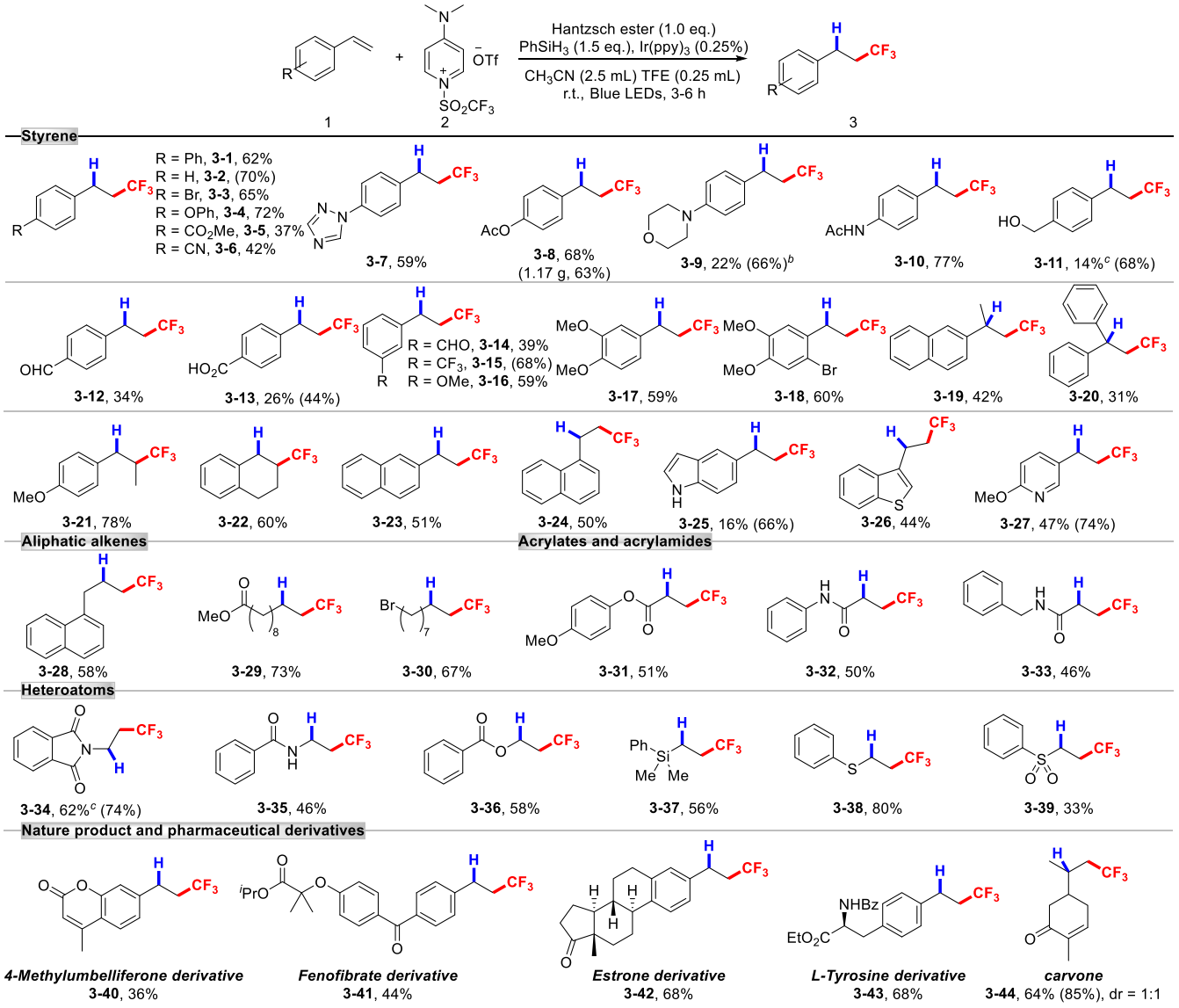
[a]Reaction conditions: Substrate **1-1** (0.2 mmol), **2** (2.0 equiv), [Red] (1.5 equiv), [H] source (1.0 equiv), and $Ir(ppy)_3$ (2.5 mol‰) in solvents (1 mL) were irradiated with 11.5 W blue LEDs at r.t. for 18 h under a N_2 atmosphere. When alcohols serving as a cosolvent were added, an additional 0.1 mL was charged. r.t., room temperature; [Red], reductant; BNAH, 1-benzyl-1,4-dihydronicotinamide; TFE, 2,2,2-trifluoroethanol; n.d., not detected; HEH, Hantzsch ester. [b]Yield was determined by ^{19}F NMR using $PhOCF_3$ as an internal standard. [c]$[RuCl_2(p\text{-cymene})]_2$ (5 mol %) was added. [d]HEH (1.0 equiv) and $PhSiH_3$ (1.5 equiv) were used instead for 3 h. [e]Without light irradiation. [f]Without $Ir(ppy)_3$.

Several difunctional reagents serving as both a hydrogen source and a reductant were investigated (entries 1−3). However, the desired product was obtained in only 14% yield when Hantzsch ester was used. We posited that the hydrogen transfer between two relatively low concentration species, that is, benzyl radicals and oxidized Hantzsch ester radical cations, was not competitive with the unproductive oligomerization side reaction. A thorough screening of stoichiometric silanes and other representative HAT catalysts to circumvent this obstacle revealed phenylsilane to be the best choice (entries 4−8). Thiols, another family of HAT catalysts,[13] were neglected on purpose to eliminate the disgusting nature attached to them. Subsequent attempts to activate the Si−H bond *via* transition-metal complexes or Lewis acids failed to improve the yield, which in one way excluded the possible radical−cation crossover mechanism (entry 8, *vide infra*, see the SI).[14] Alcohols, which have shown their potential in delivering a hydrogen atom, were then tested (entries 9−11).[3j] 2,2,2-Trifluoroethenol (TFE) emerged to fit in our protocol properly. A slight modification of loadings can give the optimized result in 3 h (entry 14). It is worth noting that the reaction can be smoothly conducted without super dry CH_3CN, an inert atmosphere, or stirring or even with 10 equiv of H_2O with only a slight decrease in yield. (See the SI.) Although the desired product was not observed without irradiation or a photocatalyst (entry 15−16), the reaction was insensitive to the wavelength, the power of light, and the type of photocatalysts (see the SI), which preliminary indicated the existence of a radical chain in our platform.

With the optimized conditions in hand, we next turned our attention to evaluate the substrate scope of our protocol (Scheme 2). An unexpected broad substrate scope was found during our investigation. Common functional groups and building blocks with different electronic effects including halide, (hetoro)aryl, tertiary amine, ether, ester, amide, imide, cyanide, alcohol, aldehyde, carboxylic acid, and CF_3, were well tolerated. Para-, meta-, and ortho-substituted styrene and di- and tri-substituted styrenes were all compatible in our platform, indicating the relative insensitivity to the steric effect. A wide range of substrates bearing active hydrogen such as amide, alcohol, carboxylic acid, and indole were shown to be suitable, which preliminarily suggested the robustness of our protocol. High regioselectivity was observed when geminal and E- and Z-disubstituted styrene was subjected to our reaction conditions. Subsequent exploration using fused aryl- and heteroaryl-containing substrates like naphthalene, benzothiophene, pyridine, and indole also delivered target products in moderate to good yield. Unactivated alkenes, with a reduced propensity of polymerization, reacted smoothly to deliver the desired products in high yields, further convincing us of the broad applicability of our platform. Another important kind of alkenes, α,β-unsaturated carboxylic acid derivatives, was then tested. The positive results given by acrylates and acrylamides again emphasize the universality of our protocol. Our curiosity regarding the location of the border of this conversion drove us to attempt α-heteroatom-substituted olefins. We were pleased that common heteroatoms involving N, O, Si, and S in different oxidation states with different electronic effects were shown to be applicable. In addition, the compatibility of different oxidation states showcased by OH, CHO, COOH, S, and SO_2 avoided the tedious modification of oxidation states, offering a practical tool for the key intermediate synthesis and late-stage functionalization. Because of their strong quenching ability, N-containing substrates were conventionally considered incompatible under photoredox conditions. However, a variety of N-containing functional groups and heteroaryls highlighted by tertiary amine, amide, imide, pyridine, and unprotected indole fit in with our platform. We regarded this observation as another indirect evidence of the existence of a radical chain. The application of our protocol to the late-stage functionalization of various natural products and pharmaceutical derivatives also proved to be efficient. Chemoselectivity between terminal alkenes and α,β-unsaturated ketones was observed during our investigation. The complete consumption of substrates was observed, but low yields were obtained in some cases, probably because of the oligomerization or polymerization of the benzyl radical (**Int 1** shown in the proposed mechanism). The

https://doi.org/10.1021/acs.orglett.1c03630
Org. Lett. 2021, 23, 9277−9282

Scheme 2. Substrate Scope of Hydrotrifluoromethylation[a]



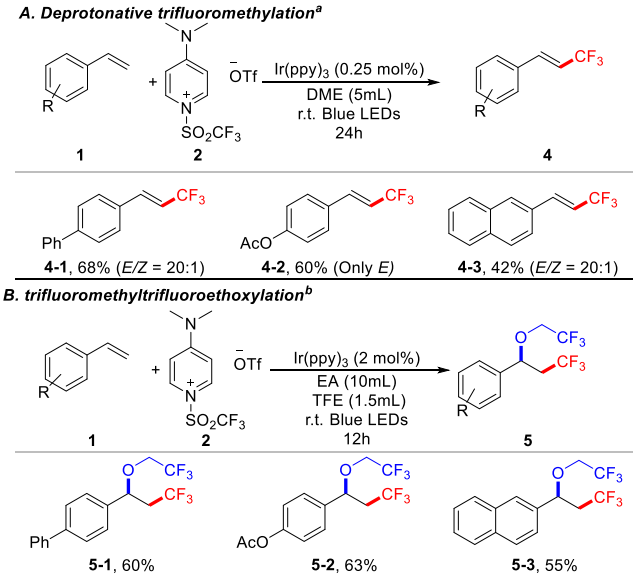
[a]Reaction conditions: Substrate **1** (0.5 mmol), **2** (2.0−2.7 equiv), HEH (1.0 equiv), $PhSiH_3$ (1.5 equiv), and $Ir(ppy)_3$ (2.5 mol‰) in CH_3CN/TFE (*v*/*v* 10:1, 2.75 mL) were irradiated with 11.5 W blue LEDs at r.t. for 3−6 h under a N_2 atmosphere. Isolated yields are shown. Yields in parentheses were determined by ^{19}F NMR using $PhOCF_3$ as an internal standard. [b]Low isolated yield was due to the close polarity between the major product and a side product. [c]Reaction was performed without HEH.

reaction can be smoothly conducted in a gram scale fashion (**3**−**8**), which further demonstrated its synthetic utility.

The unusual robustness has encouraged us to explore the potential tunability of our platform. We envisioned that by simply removing the hydrogen source added in the hydrotrifluoromethylation, a deprotonative trifluoromethylation procedure would occur though the radical addition elimination pathway. Gratifyingly, just reducing the equivalent of TFSP and altering the solvent were sufficient to deliver the target products with high stereoselectivity (Scheme 3A). Although various strategies have been developed to construct trifluoromethylated alkenes from unfunctionalized alkenes, external bases were frequently required to facilitate the elimination step.[3g,6,15] Featuring a pyridine core, our newly developed trifluoromethylation reagent, TFSP, can serve as both a trifluoromethyl radical source and a base, offering a simplified pathway compared with others. This result preliminary exhibited the dual-function character of TFSP. Furthermore, we wondered whether a trifluoromethyltrifluoroethoxylated product could be observed if TFE remained while other hydrogen sources (*i.e.*, $PhSiH_3$ and Hantzsch ester) were removed. We were pleased that with a slight modification, the expected products were detected in good yields (Scheme 3B). Although plenty of literature focused on the intermolecular trifluoromethylalkyloxylation reaction has been reported,[16] there is only one example concerning this particular trifluoromethyltrifluoroethoxylation reaction,[17] rendering our protocol valuable and complementary. A brief screening of the substrate scope revealed the promising value of these two conversions (Scheme 3). In short, three structurally diversified products were constructed under similar reaction conditions, which can be seen as an outstanding example of divergent synthesis. In addition, the robustness and tunability of our protocol render it competent in pharmaceutical development.

https://doi.org/10.1021/acs.orglett.1c03630
Org. Lett. 2021, 23, 9277−9282

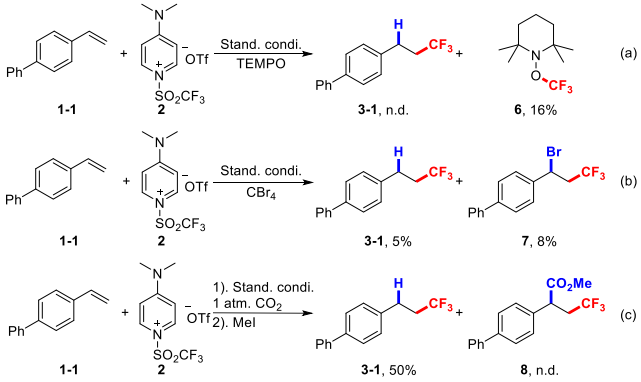
Scheme 3. Derivatized Reaction of Hydrotrifluoromethylation



[a]Reaction conditions: Substrate **1** (0.5 mmol), **2** (1.0 equiv), and $Ir(ppy)_3$ (2.5 mol‰) in DME (5 mL) were irradiated with 11.5 W blue LEDs at r.t. for 24 h under a N_2 atmosphere. [b]Reaction conditions: Substrate **1** (0.5 mmol), **2** (1.0 equiv), and $Ir(ppy)_3$ (2 mol %) in EA/TFE (*v*/*v* 10:1.5, 11.5 mL) were irradiated with 11.5 W blue LEDs at r.t. for 12 h under a N_2 atmosphere.

To shed light on the mechanism of our protocol, we conducted several preliminary mechanistic experiments. First, a radical scavenger (*i.e.*, TEMPO) was added to the system, and a total inhibition of hydrotrifluoromethylation along with a TEMPO adduct, TEMPO−CF_3, was observed (Scheme 4a).

Scheme 4. Preliminary Mechanistic Experiments

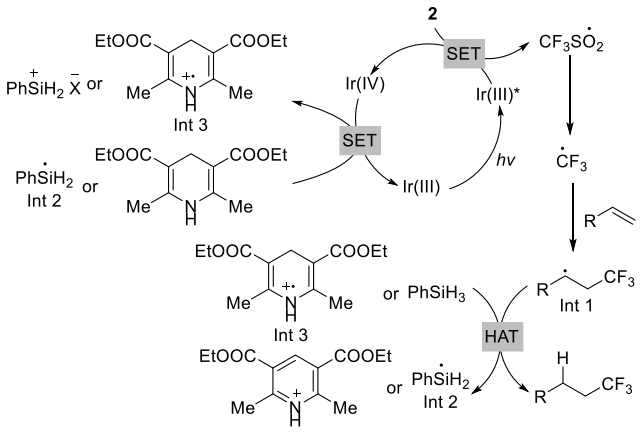


Second, a transient benzyl radical was identified based on the detected bromotrifluoromethylation product when CBr_4 was subjected to the reaction (Scheme 4b).[18] Third, when the reaction was conducted under a CO_2 atmosphere followed by treatment with MeI, the generation of **8** was not detected, and only a slight decrease in the yield of **3**−**1** was observed, which preliminarily excluded the carbon anion pathway. (Scheme 4c). The combination of the evidence suggested the radical nature of our protocol.

Despite our putting in much effort, the attempt to determine the quantum yield failed due to the notorious propensity for polymerization to dominate at the beginning of the reaction. However, a couple of pieces of evidence previously mentioned (*i.e.*, the low catalytic loading, fast reaction rate, insensitivity to the wavelength, power of light, and type of photocatalysts, and the compatibility of a variety of N-containing functional groups and the heteroaryl) still convinced us of the existence of a chain mechanism in addition to the closed catalytic cycle.[19]

On the basis of the above mechanistic investigation and reported literature,[12,20] a plausible mechanism is proposed (Scheme 5). An oxidative quench of the excited photocatalyst

Scheme 5. Plausible Reaction Mechanism



($E_{1/2}(Ir^{IV/III*})$ = −1.73 V vs SCE) by TFSP (E_p = −0.83 V vs SCE) releases a trifluoromethyl radical, which is subsequently trapped by styrene to generate a benzyl radical intermediate (Int 1). The desired product is delivered through a HAT between $PhSiH_3$ or Int 3 and Int 1. The oxidation of Hantzsch ester ($E_{1/2}^{ox}$ = +0.89 V vs SCE)[20d] or Int 2 by Ir(IV) ($E_{1/2}(Ir^{IV/III})$ = +0.77 V vs SCE) closes the photocatalytic cycle. In addition, we posit that a SET from Int 2 or Int 3 ($E_{1/2}^{ox}$ = +0.76 V vs SCE)[20d] to TFSP can release a trifluoromethyl radical and initiate a radical chain.

In conclusion, the divergent synthesis of three type of trifluoromethylated products was realized using our method. The potential value of our protocol in pharmaceutical development was showcased by the compatibility of a diversified structure of olefins. A preliminary mechanistic investigation indicated the existence of a radical chain.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c03630.

Materials and methods, experimental procedures, optimization studies, and ^1H NMR, ^{19}F NMR, ^{13}C NMR, IR, and MS data (PDF)

■ AUTHOR INFORMATION

Corresponding Authors

Jin-Hong Lin − *Key Laboratory of Organofluorine Chemistry, Shanghai Institute of Organic Chemistry, University of Chinese Academy of Science, Chinese Academy of Science, Shanghai 200032, China; Department of Chemistry, Innovative Drug Research Center, Shanghai University, Shanghai 200444, China;* orcid.org/0000-0002-7000-9540; Email: jlin@shu.edu.cn, jlin@sioc.ac.cn

https://doi.org/10.1021/acs.orglett.1c03630
Org. Lett. 2021, 23, 9277−9282

Ji-Chang Xiao − *Key Laboratory of Organofluorine Chemistry, Shanghai Institute of Organic Chemistry, University of Chinese Academy of Science, Chinese Academy of Science, Shanghai 200032, China;* orcid.org/0000-0001-8881-1796; Email: jchxiao@sioc.ac.cn

Author

Yi-Fei Yang − *Key Laboratory of Organofluorine Chemistry, Shanghai Institute of Organic Chemistry, University of Chinese Academy of Science, Chinese Academy of Science, Shanghai 200032, China*

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.orglett.1c03630

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank the National Natural Science Foundation (21971252, 21991122), the Key Research Program of Frontier Sciences, and the Chinese Academy of Sciences (CAS) (QYZDJSSWSLH049) for financial support.

■ REFERENCES

(1) (a) Wang, J.; Sánchez-Roselló, M.; Aceña, J. L.; del Pozo, C.; Sorochinsky, A. E.; Fustero, S.; Soloshonok, V. A.; Liu, H. Fluorine in Pharmaceutical Industry: Fluorine-Containing Drugs Introduced to the Market in the Last Decade (2001−2011). *Chem. Rev.* **2014**, *114*, 2432−2506. (b) Yale, H. L. The Trifluoromethyl Group in Medical Chemistry. *J. Med. Pharm. Chem.* **1959**, *1*, 121−133.

(2) (a) Ogawa, Y.; Tokunaga, E.; Kobayashi, O.; Hirai, K.; Shibata, N. Current Contributions of Organofluorine Compounds to the Agrochemical Industry. *iScience* **2020**, *23*, 101467. (b) Inoue, M.; Sumii, Y.; Shibata, N. Contribution of Organofluorine Compounds to Pharmaceuticals. *ACS Omega* **2020**, *5*, 10633−10640.

(3) (a) Barthelemy, A. L.; Dagousset, G.; Magnier, E. Metal-Free Visible-Light-Mediated Hydrotrifluoromethylation of Unactivated Alkenes and Alkynes in Continuous Flow. *Eur. J. Org. Chem.* **2020**, *2020*, 1429−1432. (b) Xiang, J. X.; Ouyang, Y.; Xu, X. H.; Qing, F. L. Argentination of Fluoroform: Preparation of a Stable AgCF3 Solution with Diverse Reactivities. *Angew. Chem., Int. Ed.* **2019**, *58*, 10320−10324. (c) Ren, Y. Y.; Zheng, X.; Zhang, X. G. Bromotrifluoromethane: A Useful Reagent for Hydrotrifluoro-methylation of Alkenes and Alkynes. *Synlett* **2018**, *29*, 1028−1032. (d) Cui, B.; Sun, H.; Xu, Y. B.; Li, L.; Duan, L. L.; Li, Y. M. $Mn(OAc)_3$-Mediated Hydrotrifluoromethylation of Unactivated Alkenes Using CF_3SO_2Na as the Trifluoromethyl Source. *J. Org. Chem.* **2018**, *83*, 6015−6024. (e) Zhu, L.; Wang, L. S.; Li, B. J.; Fu, B. Q.; Zhang, C. P.; Li, W. Operationally simple hydrotrifluoromethylation of alkenes with sodium triflinate enabled by Ir photoredox catalysis. *Chem. Commun.* **2016**, *52*, 6371−6374. (f) Cheng, Y. Z.; Yu, S. Y. Hydrotrifluoromethylation of Unactivated Alkenes and Alkynes Enabled by an Electron-Donor Acceptor Complex of Togni's Reagent with a Tertiary Amine. *Org. Lett.* **2016**, *18*, 2962−2965. (g) Egami, H.; Usui, Y.; Kawamura, S.; Nagashima, S.; Sodeoka, M. Product Control in Alkene Trifluoromethylation: Hydrotrifluoromethylation, Vinylic Trifluoromethylation, and Iodotrifluoromethylation using Togni Reagent. *Chem. - Asian J.* **2015**, *10*, 2190−2199. (h) Pitre, S. P.; McTiernan, C. D.; Ismaili, H.; Scaiano, J. C. Metal-Free Photocatalytic Radical Trifluoromethylation Utilizing Methylene Blue and Visible Light Irradiation. *ACS Catal.* **2014**, *4*, 2530−2535. (i) Wu, X. Y.; Chu, L. L.; Qing, F. L. Silver-Catalyzed Hydrotrifluoromethylation of Unactivated Alkenes with CF3SiMe3. *Angew. Chem., Int. Ed.* **2013**, *52*, 2198−2202. (j) Mizuta, S.; Verhoog, S.; Engle, K. M.; Khotavivattana, T.; O'Duill, M.; Wheelhouse, K.; Rassias, G.; Medebielle, M.; Gouverneur, V. Catalytic Hydrotrifluoromethylation of Unactivated Alkenes. *J. Am. Chem. Soc.* **2013**, *135*, 2505−2508.

(4) Wilger, D. J.; Gesmundo, N. J.; Nicewicz, D. A. Catalytic hydrotrifluoromethylation of styrenes and unactivated aliphatic alkenes via an organic photoredox system. *Chem. Sci.* **2013**, *4*, 3160−3165.

(5) Choi, S.; Kim, Y. J.; Kim, S. M.; Yang, J. W.; Kim, S. W.; Cho, E. J. Hydrotrifluoromethylation and iodotrifluoromethylation of alkenes and alkynes using an inorganic electride as a radical generator. *Nat. Commun.* **2014**, *5*, 7.

(6) Straathof, N. J. W.; Cramer, S. E.; Hessel, V.; Noel, T. Practical Photocatalytic Trifluoromethylation and Hydrotrifluoromethylation of Styrenes in Batch and Flow. *Angew. Chem., Int. Ed.* **2016**, *55*, 15549−15553.

(7) Batista, G. M. F.; de Castro, P. P.; Dos Santos, H. F.; de Oliveira, K. T.; Amarante, G. W. Electron-Donor-Acceptor Complex-Enabled Flow Methodology for the Hydrotrifluoromethylation of Unsaturated beta-Keto Esters. *Org. Lett.* **2020**, *22*, 8598−8602.

(8) Erdbrink, H.; Peuser, I.; Gerling, U. I. M.; Lentz, D.; Koksch, B.; Czekelius, C. Conjugate hydrotrifluoromethylation of α,β-unsaturated acyl-oxazolidinones: synthesis of chiral fluorinated amino acids. *Org. Biomol. Chem.* **2012**, *10*, 8583−8586.

(9) Yao, Q. L.; Ren, L. J.; Xiang, D.; Li, K. X.; Yan, B. Y.; Ran, M. G.; He, J. X.; Zhao, L. The Photoinduced Metal-Free Hydrotrifluoromethylation of Vinyl Phosphonates or Phosphine Oxides. *Eur. J. Org. Chem.* **2019**, *2019*, 7475−7482.

(10) Lin, J.-H.; Xiao, J.-C. Fluorinated Ylides/Carbenes and Related Intermediates from Phosphonium/Sulfonium Salts. *Acc. Chem. Res.* **2020**, *53*, 1498−1510.

(11) Rössler, S. L.; Jelier, B. J.; Magnier, E.; Dagousset, G.; Carreira, E. M.; Togni, A. Pyridinium Salts as Redox-Active Functional Group Transfer Reagents. *Angew. Chem., Int. Ed.* **2020**, *59*, 9264−9280.

(12) Zhang, M.; Lin, J.-H.; Xiao, J.-C. A Readily Available Trifluoromethylation Reagent and Its Difunctionalization of Alkenes. *Org. Lett.* **2021**, *23*, 6079−6083.

(13) (a) Lopp, J. M.; Schmidt, V. A. Intermolecular Phosphite-Mediated Radical Desulfurative Alkene Alkylation Using Thiols. *Org. Lett.* **2019**, *21*, 8031−8036. (b) Kawamoto, T.; Oritani, K.; Curran, D. P.; Kamimura, A. Thiol-Catalyzed Radical Decyanation of Aliphatic Nitriles with Sodium Borohydride. *Org. Lett.* **2018**, *20*, 2084−2087. (c) Musacchio, A. J.; Lainhart, B. C.; Zhang, X.; Naguib, S. G.; Sherwood, T. C.; Knowles, R. R. Catalytic intermolecular hydroaminations of unactivated olefins with secondary alkyl amines. *Science* **2017**, *355*, 727. (d) Miller, D. C.; Choi, G. J.; Orbe, H. S.; Knowles, R. R. Catalytic Olefin Hydroamidation Enabled by Proton-Coupled Electron Transfer. *J. Am. Chem. Soc.* **2015**, *137*, 13492−13495.

(14) (a) Ojima, Y.; Yamaguchi, K.; Mizuno, N. An Efficient Solvent-Free Route to Silyl Esters and Silyl Ethers. *Adv. Synth. Catal.* **2009**, *351*, 1405−1411. (b) Mori, K.; Tano, M.; Mizugaki, T.; Ebitani, K.; Kaneda, K. Efficient heterogeneous oxidation of organosilanes to silanols catalysed by a hydroxyapatite-bound Ru complex in the presence of water and molecular oxygen. *New J. Chem.* **2002**, *26*, 1536−1538. (c) Lee, M.; Ko, S.; Chang, S. Highly Selective and Practical Hydrolytic Oxidation of Organosilanes to Silanols Catalyzed by a Ruthenium Complex. *J. Am. Chem. Soc.* **2000**, *122*, 12011−12012.

(15) (a) Iqbal, N.; Choi, S.; Kim, E.; Cho, E. J. Trifluoromethylation of Alkenes by Visible Light Photoredox Catalysis. *J. Org. Chem.* **2012**, *77*, 11383−11387. (b) Lin, Q. Y.; Xu, X. H.; Qing, F. L. Chemo-, regio-, and stereoselective trifluoromethylation of styrenes via visible light-driven single-electron transfer (SET) and triplet-triplet energy transfer (TTET) processes. *J. Org. Chem.* **2014**, *79*, 10434−46. (c) Yang, X.; Tsui, G. C. Trifluoromethylation of Unactivated Alkenes with Me3SiCF3 and N-Iodosuccinimide. *Org. Lett.* **2019**, *21*, 1521−1525.

(16) (a) Jiang, X. Y.; Qing, F. L. Copper-catalyzed three-component oxytrifluoromethylation of alkenes with sodium trifluoromethanesulfinate and hydroxamic acid. *Angew. Chem., Int. Ed.* **2013**, *52*, 14177−80. (b) Yasu, Y.; Koike, T.; Akita, M. Three-component Oxy-

trifluoromethylation of Alkenes: Highly Efficient and Regioselective Difunctionalization of C = C Bonds Mediated by Photoredox Catalysts. *Angew. Chem., Int. Ed.* **2012**, *51*, 9567−9571. (c) Huang, L.; Zheng, S. C.; Tan, B.; Liu, X. Y. Metal-free direct 1,6- and 1,2-difunctionalization triggered by radical trifluoromethylation of alkenes. *Org. Lett.* **2015**, *17*, 1589−92. (d) Feng, C.; Loh, T.-P. Copper-catalyzed olefinic trifluoromethylation of enamides at room temperature. *Chem. Sci.* **2012**, *3*, 3458. (e) Egami, H.; Shimizu, R.; Sodeoka, M. Oxytrifluoromethylation of multiple bonds using copper catalyst under mild conditions. *Tetrahedron Lett.* **2012**, *53*, 5503−5506.

(17) Zhang, L. L.; Zhang, G. T.; Wang, P.; Li, Y. L.; Lei, A. W. Electrochemical Oxidation with Lewis-Acid Catalysis Leads to Trifluoromethylative Difunctionalization of Alkenes Using CF_3SO_2Na. *Org. Lett.* **2018**, *20*, 7396−7399.

(18) Mathew, L.; Warkentin, J. Rate constants for abstraction of bromine from bromotrichloromethane by butyl, cyclopropylmethyl, and phenyl radicals in solution. *Can. J. Chem.* **1988**, *66*, 11−16.

(19) Cismesia, M. A.; Yoon, T. P. Characterizing chain processes in visible light photoredox catalysis. *Chem. Sci.* **2015**, *6*, 5426−5434.

(20) (a) Park, G.; Yi, S. Y.; Jung, J.; Cho, E. J.; You, Y. Mechanism and Applications of the Photoredox Catalytic Coupling of Benzyl Bromides. *Chem. - Eur. J.* **2016**, *22*, 17790−17799. (b) Rono, L. J.; Yayla, H. G.; Wang, D. Y.; Armstrong, M. F.; Knowles, R. R. Enantioselective Photoredox Catalysis Enabled by Proton-Coupled Electron Transfer: Development of an Asymmetric Aza-Pinacol Cyclization. *J. Am. Chem. Soc.* **2013**, *135*, 17735−17738. (c) Wang, P.-Z.; Chen, J.-R.; Xiao, W.-J. Hantzsch esters: an emerging versatile class of reagents in photoredox catalyzed organic synthesis. *Org. Biomol. Chem.* **2019**, *17*, 6936−6951. (d) Zhu, X.-Q.; Li, H.-R.; Li, Q.; Ai, T.; Lu, J.-Y.; Yang, Y.; Cheng, J.-P. Determination of the C4-H Bond Dissociation Energies of NADH Models and Their Radical Cations in Acetonitrile. *Chem. - Eur. J.* **2003**, *9*, 871−880.

https://doi.org/10.1021/acs.orglett.1c03630
Org. Lett. 2021, 23, 9277−9282