OL Organic Letters

pubs.acs.org/OrgLett

Letter

Oxidative Trifluoroacetoxylation of 1°, 2°, and 3° Benzylic C(sp^3)−H Bond Donors Using *N*-Trifluoroacetoxyquinuclidinium Salts under Photoredox Catalysis

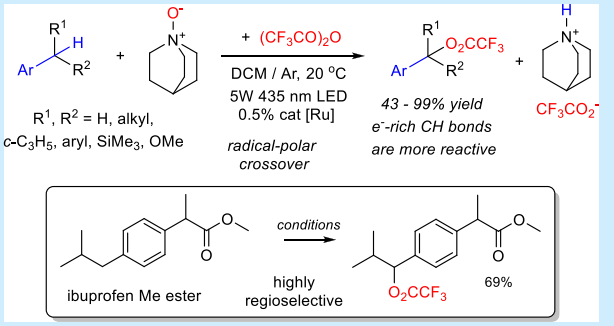
Michael Hitt and Andrei N. Vedernikov*

Cite This: *Org. Lett.* 2022, 24, 7737−7741

Read Online

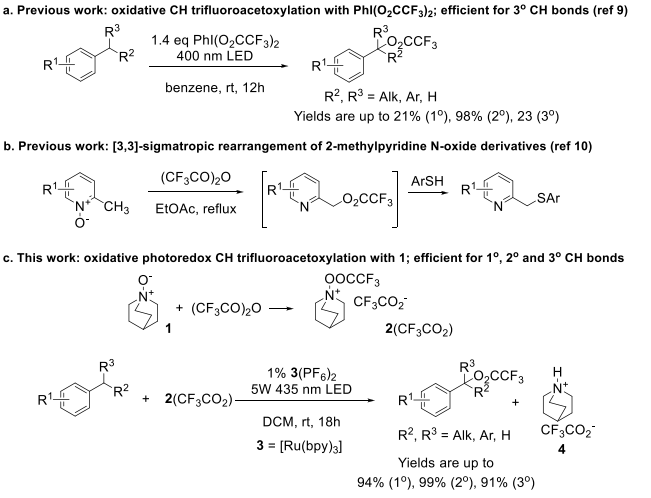
ACCESS | Metrics & More | Article Recommendations | Supporting Information

ABSTRACT: *N*-Trifluoroacetoxyquinuclidinium trifluoroacetate was prepared *in situ* from quinuclidine *N*-oxide and $(CF_3CO)_2O$. Except for some electron-poor substrates, this reagent allows for the high-yielding oxidative trifluoroacetoxylation of 1°, 2°, and 3° benzylic C−H bonds under photocatalytic conditions. The trifluoroacetoxylation of an ibuprofen methyl ester allowed the selective functionalization of a 2° benzylic C−H bond. For alkylbenzenes, hydrogen-atom transfer from a benzylic C−H bond to a quinuclidine cation radical was proposed to be the reaction-product-determining step.



Benzylic trifluoroacetates constitute an important group of reactive electrophiles that find various applications in organic synthesis.[1−5] A representative list of reactions where these reagents play a key role includes the transition-metal-free C(sp^3)−C(sp^2) cross-coupling of 2° benzylic trifluoroacetates with aryl zinc reagents,[1] the base-free Mizoroki−Heck reaction of olefins with 1° benzylic trifluoroacetates[2] and the asymmetric version,[3] the B(C$_6$F$_5$)$_3$-catalyzed allylation of 2° benzylic trifluoroacetates with allylsilanes,[4] and the conversion of aldehydes to dibenzyl acetals.[5] Remarkably, in a number of cases benzylic trifluoroacetates were the only efficient benzylic electrophiles while analogous and more common benzylic derivatives such as halides, mesylates, tosylates, benzoates, or acetates failed.[1,3] Typically, synthetic access to various types of benzylic trifluoroacetates is limited to the acylation of the corresponding benzylic alcohols.[6] The oxidative esterification of C−H bond donors has emerged as an efficient alternative method for the preparation of arene- and alkanecarboxylic acid-derived benzylic esters.[7,8] Still, there are only a few reports of efficient oxidative benzylic C−H trifluoroacetoxylation. In one report, PhI(O$_2$CCF$_3$)$_2$ serves as a trifluoroacetoxylation reagent under photochemical (400 nm) conditions (Scheme 1a).[9] Here the donors of 2° benzylic C−H bonds were most reactive, with product yields up to 98%, but substrates with 1° and 3° benzylic C−H bonds demonstrated yields that did not exceed 23%. Another work[10] reported the preparation of substituted 2-pyridylmethyl trifluoroacetates through a [3,3]-sigmatropic rearrangement starting from the corresponding 2-methylpyridine *N*-oxides and $(CF_3CO)_2O$ in refluxing ethyl acetate (Scheme 1b). The esters were used without isolation to synthesize derived sulfides. Examples of the oxidative trifluoroacetoxylation of nonbenzylic C(sp^3)−H bonds are rare.[11,12]

Scheme 1. Oxidative Trifluoroacetoxylation of Benzylic C−H Bond Donors



Received: August 30, 2022
Published: October 14, 2022

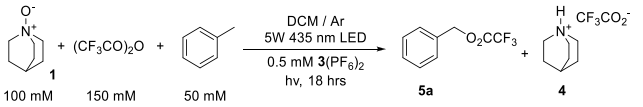
https://doi.org/10.1021/acs.orglett.2c02946
Org. Lett. 2022, 24, 7737−7741

In this work we disclose a protocol for the high-yielding selective oxidative trifluoroacetoxylation of donors of 1°, 2°, and 3° benzylic C−H bonds using a new reagent, *N*-trifluoroacetoxyquinuclidinium trifluoacetate ($\mathbf{2}(CF_3CO_2)$) (Scheme 1c), that acts in the presence of a suitable photoredox catalyst such as $[Ru(bpy)_3](PF_6)_2$ ($\mathbf{3}(PF_6)_2$). Compared to the use of $PhI(O_2CCF_3)_2$ as a trifluoroacetoxylation agent,[9] the use of $\mathbf{2}(CF_3CO_2)$ allowed high yields of both 1°, 2°, and 3° benzylic trifluoroacetates to be achieved. The difference in the reactions scope may be related to a different natures of the hydrogen atom transfer (HAT) agent and the oxidant involved. In our system the HAT agent is likely to be quinuclidine cation-radical, $\mathbf{Q}^{\bullet+}$, a powerful hydrogen-atom abstractor (HAA).[13] The use of $\mathbf{Q}^{\bullet+}$ in $C(sp^3)$−H bond functionalization received significant attention in electrocatalysis[14] and photoredox catalysis.[15−17] However, although some *N*-acyloxyquinuclidinium salts (acyl = Ac, Bz) are well-known,[18] to the best of our knowledge, any use of these salts as a source of quinuclidine cation radicals or their application in oxidative C−H bond functionalization has never been reported.

Our work started with the preparation of the reagent $\mathbf{2}(CF_3CO_2)$. The addition of 1.5 equiv of $(CF_3CO)_2O$ to a solution of quinuclidine *N*-oxide (**1**) in DCM-d_2 resulted in a complete consumption of **1** within 5 min and the formation of a single new species, $\mathbf{2}(CF_3CO_2)$, according to ^1H and ^{13}C NMR spectroscopy. The ^{19}F NMR spectrum of the reaction solution exhibited two broadened signals, one at −73.10 ppm assigned to the N-bound CF_3CO_2 group and another at −75.52 ppm assigned to the $CF_3CO_2^-$ counterion that existed in a fast exchange with excess $(CF_3CO)_2O$. The high hydrolytic reactivity of $\mathbf{2}(CF_3CO_2)$ made it difficult to isolate it as a pure compound. Removal of the solvent from the reaction mixture and subsequent ^1H NMR analysis in a fresh sample of DCM-d_2 revealed that some of $\mathbf{2}(CF_3CO_2)$ hydrolyzed to form $\mathbf{1}\cdot H^+$. As such, to simplify our CH functionalization experiments we prepared and used $\mathbf{2}(CF_3CO_2)$ *in situ* in the presence of an excess of $(CF_3CO)_2O$.

The optimization of the reaction conditions was carried out under an inert gas atmosphere using toluene as a substrate (Table 1). The highest yield of the derived benzyl trifluoroacetate **5a** (93%) was obtained when 2 equiv of **1** and 3 equiv of $(CF_3CO)_2O$ were used (entry 1). Quinuclidinium trifluoroacetate **4** was the reaction byproduct. Notably, CF_3H was not observed when the reaction was carried out in a Teflon-sealed NMR tube, which disproves the involvement of $CF_3^{\bullet}$ as a HAA. When all the reagents were taken in a 1:1:1 molar ratio, the yield of **5a** decreased to 32% (entry 2). Using 50% excesses of both **1** and $(CF_3CO)_2O$ increased the yield to 61% (entry 3). If both **1** and $(CF_3CO)_2O$ were used in twofold excess, the yield of **5a** increased to 76% (entry 4). The use of a 2.4-fold excess of $(CF_3CO)_2O$ led to an 84% yield of **5a** (entry 5), and the use of a 4-fold excess of $(CF_3CO)_2O$ did not improve the yield (entry 6) achieved under the optimized conditions. The use of a 10× higher concentration of the toluene substrate led to a lower yield of the ester (entry 7). Another photoredox catalyst, $\mathbf{6}(PF_6)$ (entry 8), led essentially to the same results. Finally, a series of control experiments (entries 9−12) showed that the presence of all the components of the reaction mixture, *i.e.*, **1**, $(CF_3CO)_2O$, $\mathbf{3}(PF_6)_2$, and LED light, was needed for the reaction to happen. The use of other solvents, such as 1,2-dichloroethane, DMF, or THF, led to inferior yields or a complete suppression of the reaction (entries 13−15, respectively).

Table 1. Optimization of Reaction Conditions

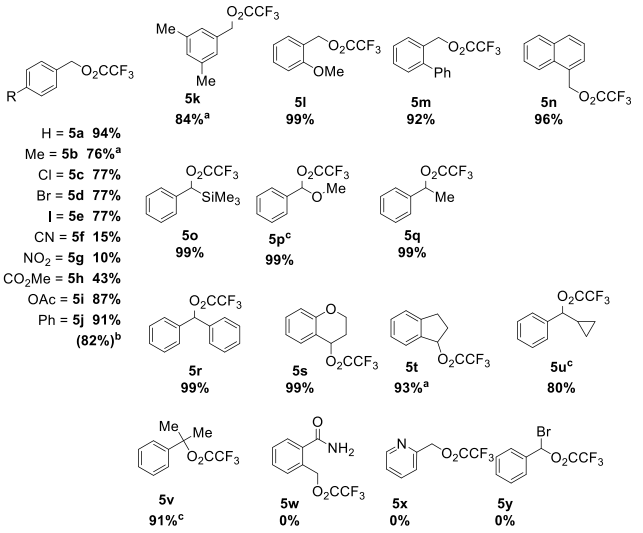


entry	deviation from conditions above	yield[a] of **5a** (%)
1	none	93
2	50 mM **1**, 50 mM $(CF_3CO)_2O$	32
3	75 mM **1**, 75 mM $(CF_3CO)_2O$	61
4	100 mM $(CF_3CO)_2O$	76
5	120 mM $(CF_3CO)_2O$	84
6	200 mM $(CF_3CO)_2O$	91
7	500 mM toluene	76
8	0.5 mM $\mathbf{6}(PF_6)$[b]	90
9−12	no light, catalyst, $(CF_3CO)_2O$, or **1**	0
13	1,2-dichloroethane as the solvent	42
14	DMF as the solvent	5
15	THF as the solvent	0

[a]NMR yields were calculated by ^1H NMR integration with 1,4-dioxane as an internal standard; all experiments were run in duplicate. [b]$\mathbf{6}(PF_6)$ is $[Ir(bpy)_2(^tBu_2bpy)](PF_6)$.

With the optimized reaction conditions in hand, we moved to exploring the reaction substrate scope. The results are summarized in Scheme 2. A large series of *para*-R-substituted toluenes produced good to excellent yields (76−91%) of the derived 1° benzyl trifluoroacetates **5b** − **5e**, **5i**, and **5j** bearing modestly electron-withdrawing halogen substituents, acetoxy and phenyl groups, respectively. The isolated yield of **5j** was 82% when the reaction was performed on a 1.0 mmol scale. More powerful electron-withdrawing substituents led to much

Scheme 2. Substrate Scope for the Oxidative Trifluoroacetoxylation of 1°, 2° and 3° Benzylic C−H Bond Donors Using $\mathbf{2}(CF_3CO_2)$[d,e]



[a]The reaction was performed using 500 mM substrate. [b]The reaction was performed on a 1.0 mmol scale; isolated yield. [c]The product was prepared and fully characterized by NMR in solution but decomposed upon attempted isolation.[19] [d]Prepared *in situ* under optimized conditions (Table 1). [e]NMR yields were calculated by ^1H NMR integration with 1,4-dioxane as an internal standard.

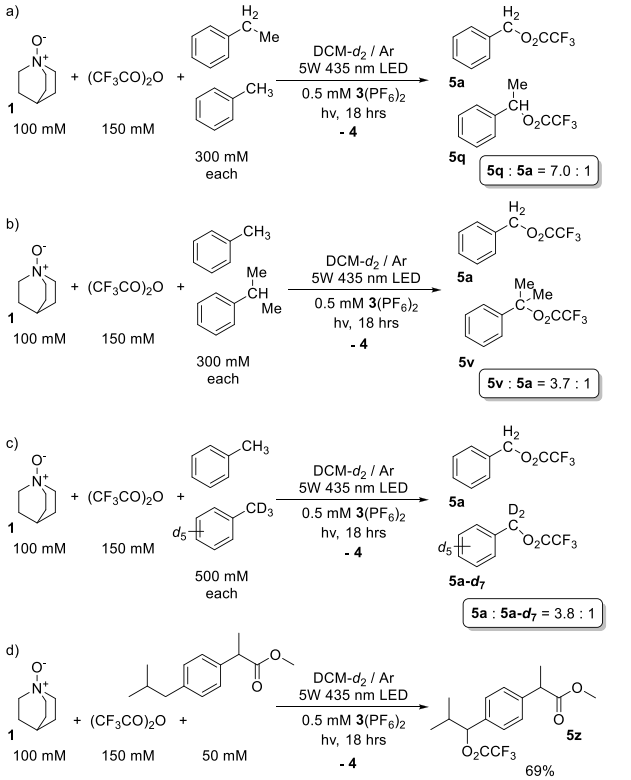
https://doi.org/10.1021/acs.orglett.2c02946
Org. Lett. 2022, 24, 7737−7741

lower yields of benzyl trifluoroacetates **5f** (15%, R = CN), **5g** (10%, R = NO_2), and **5h** (43%, R = CO_2Me). For substrates with several competing benzylic CH sites, *i.e.*, *p*-xylene, indene, mesitylene, we used a fivefold excess of the substrate (500 mM concentration) to avoid the formation of mixtures of polytrifluoroacetoxylated products. This modification resulted in acceptable (76−93%) yields of monofunctionalized derivatives with only trace amounts of bis-trifluoroacetates (<1%). Remarkably, in no case did we observe multiple trifluoroacetoxylation at the same carbon atom, suggesting a complete avoidance of overoxidation in this catalytic system. *meta*- and *ortho*-substituted toluenes with methyl (**5k**), methoxy (**5l**), and phenyl groups (**5m**) all reacted cleanly to produce the corresponding esters in high to virtually quantitative (**5l**) NMR yields. The reaction of 1-methylnaphthaline also led to an excellent yield of an ester **5n**. By contrast, *o*-amidocarbonyl (**5w**) and 2-picoline (**5x**) derivatives were not formed. For **5w**, this is related to incompatibility of the primary amide groups and $(CF_3CO)_2O$. Interestingly, the presence of a strongly electron-releasing or resonance-stabilizing group at a benzylic carbon, such as Me_3Si (**5o**) or MeO (**5p**), allowed the trifluoroacetoxylation to proceed in virtually quantitative NMR yields.[20] In turn, the presence of a bromine at the benzylic carbon atom would not allow for the formation of **5y**.[21] We then looked at the reactivity of some donors of 2° benzylic C−H bonds. Ethylbenzene reacted under standard conditions of Table 1 to afford **5q** in a > 99% NMR yield.

The reaction of diphenylmethane to afford **5r** was also effective. Chromane also reacted cleanly to afford **5s** in a quantitative NMR yield. To achieve a high 93% yield of indane derivative **5t**, a fivefold excess of indane was used to avoid 1,3-*bis*-trifluoroacetoxylation. Interestingly, the use of the "radical clock" substrate cyclopropylmethylbenzene led to an 80% yield of **5u** with no trace amounts of cyclopropane ring-opening derivatives.[22] Finally, the use of isopropylbenzene, a donor of 3° benzylic C−H bonds, as a substrate led to a 91% yield of the derived product **5v**. Consistent with a literature description,[19] the product was stable only in dilute solutions and decomposed upon the removal of solvent. Aside from highly reactive compounds **5p**, **5u**, and **5v**, trifluoroacetates **5a**−**5o** and **5q**−**5t**, were isolated as pure compounds and characterized by ^1H, ^{13}C, and ^{19}F NMR spectroscopy and HR DART-MS.

To explore the intermolecular selectivity of $\mathbf{2}(CF_3CO_2)$ with respect to 1°, 2°, and 3° benzylic C−H bonds, we performed competition experiments using excess substrates. These results are summarized in Scheme 3. Ethylbenzene was 7.0× more reactive than toluene (Scheme 3a), and isopropylbenzene outcompeted toluene in a 3.7:1 products ratio, suggesting the reactivity of 2° and 3° benzylic C−H bonds was about equal after a statistical correction. The latter fact may be due to the increased steric interference of 3 °C−H bond donors and the bulky quinuclidine cation-radical $\mathbf{Q}^{\bullet+}$ involved in the HAT step (*vide infra*). A deuterium kinetic isotope effect (k_H/k_D = 3.8 ± 0.1) was estimated by performing the competitive trifluoroacetoxylation of toluene and toluene-d_8 (Scheme 3c). The ^{19}F NMR signals of the products **5a** and **5a**-d_7 were readily resolved.[23] To explore the intramolecular selectivity of $\mathbf{2}(CF_3CO_2)$ with respect to 2° and 3° benzylic CH bonds, we used an ibuprofen methyl ester, a derivative of an anti-inflammatory drug. The substrate has two types of benzylic CH bonds, a relatively weak but electron-poor 3 °C−H bond adjacent to an electron-withdrawing methoxycarbonyl and

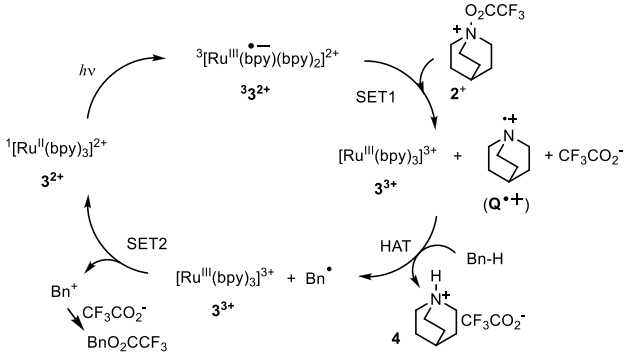
Scheme 3. Results of Inter- and Intramolecular Competition Experiments



stronger 2° C−H bonds adjacent to an electron-donating ^{i}Pr group. The reaction resulted in the selective formation of **5z** (Scheme 3d) in a 69% NMR yield,[24] a demonstration of the electrophilic polar character of $\mathbf{Q}^{\bullet+}$. A similar regioselectivity was observed in the fluorination,[25,26] hydroxylation, amidation,[28] and alkoxylation[27] of ibuprofen esters employing using electrophilic O-,[25,26] N-,[27] and I-centered[28] radicals as HAAs.

An additional mechanistic test was carried out using *p*-xylene as a substrate with O_2 in a reaction flask headspace. In this case, no derived trifluoroacetate **5b** was observed. Instead, *p*-methylbenzaldehyde was produced quantitatively. Based on our observations, we propose the following reaction mechanism (Scheme 4). A single-electron transfer from the catalyst's excited state, $^3[\mathbf{3}]^{2+}$,[29] to the electrophilic $\mathbf{2}^+$ (step SET1) would produce, along with a Ru^{III} species $\mathbf{3}^{3+}$, a derived

Scheme 4. Proposed Mechanism for the Oxidative Trifluoroacetoxylation of Benzylic C−H Donors Using $\mathbf{2}(CF_3CO_2)$ as an Oxidant under Photoredox Catalysis



https://doi.org/10.1021/acs.orglett.2c02946
Org. Lett. 2022, 24, 7737−7741

quinuclidine cation radical $\mathbf{Q}^{\bullet+}$ and a $CF_3CO_2^-$ anion. Next, $\mathbf{Q}^{\bullet+}$ would engage in HAT with a benzylic C−H bond donor, Bn−H. Subsequent oxidation of the transient benzyl radical $Bn^{\bullet}$ with $\mathbf{3}^{3+}$ (step SET2) would generate a carbocation Bn^+.[30−32] Finally, the carbocation is intercepted by a $CF_3CO_2^-$ anion to form the observed esters **5**. Based on the magnitude of the observed deuterium kinetic isotope effect for toluene, HAT may be the reaction product-determining step. Accordingly, the reactivity trend observed for alkylarenes, 2° ∼ 3° > 1°, reflects a combination of the C−H bond strength and the steric interference between the bulky $\mathbf{Q}^{\bullet+}$ and the C−H bond donor in the HAT transition state. In turn, more electron-poor C−H bond donors are expected to be less reactive.[33] As a consequence, multiple trifluoroacetoxylation at the same benzylic carbon is not observed. The proposed mechanism in Scheme 4 is in line with other recent reports disclosing the photoredox-catalyzed oxidative functionalization of benzylic CH bond donors.[25,28,27]

In summary, in this work we introduce a new reagent, *N*-acetoxyquinuclidinium trifluoroacetate **2**(CF_3CO_2), that can be readily prepared *in situ* from quinuclidine *N*-oxide and $(CF_3CO)_2O$. The reagent can be used for the high-yielding selective oxidative trifluoroacetoxylation of donors of 1°, 2°, and 3° benzylic C−H bonds under photoredox catalysis. Our observations suggest that a quinuclidine cation radical is responsible for HAT from benzylic C−H bonds.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.2c02946.

Description of all experimental procedures and NMR spectra (PDF)

■ AUTHOR INFORMATION

Corresponding Author

Andrei N. Vedernikov − *Department of Chemistry and Biochemistry, University of Maryland, College Park, Maryland 20742, United States;* orcid.org/0000-0002-7371-793X; Email: avederni@umd.edu

Author

Michael Hitt − *Department of Chemistry and Biochemistry, University of Maryland, College Park, Maryland 20742, United States*

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.orglett.2c02946

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported by the National Science Foundation (CHE-1800089). M.H. thanks the Department of Defence for a SMART Scholarship funded by OUSD/R&E (The Under Secretary of Defense-Research and Engineering), National Defense Education Program (NDEP)/BA-1, Basic Research. We thank Dr. Yue Li of the Department of Chemistry and Biochemistry of the University of Maryland for help running the DART-HRMS experiments.

■ REFERENCES

(1) Duan, H.; Meng, L.; Bao, D.; Zhang, H.; Li, Y.; Lei, A. Zinc Chloride Enhanced Arylations of Secondary Benzyl Trifluoroacetates in the Presence of β-Hydrogen Atoms. *Angew. Chem., Int. Ed.* **2010**, *49*, 6387−6390.

(2) Narahashi, H.; Shimizu, I.; Yamamoto, A. Synthesis of Benzylpalladium Complexes through C−O Bond Cleavage of Benzylic Carboxylates: Development of a Novel Palladium-Catalyzed Benzylation of Olefins. *J. Organomet. Chem.* **2008**, *693*, 283−296.

(3) Yang, Z.; Zhou, J. Palladium-Catalyzed, Asymmetric Mizoroki−Heck Reaction of Benzylic Electrophiles Using Phosphoramidites as Chiral Ligands. *J. Am. Chem. Soc.* **2012**, *134*, 11833−11835.

(4) Rubin, M.; Gevorgyan, V. $B(C_6F_5)_3$-Catalyzed Allylation of Secondary Benzyl Acetates with Allylsilanes. *Org. Lett.* **2001**, *3*, 2705−2707.

(5) Grabowski, J.; Granda, J. M.; Jurczak, J. Preparation of Acetals from Aldehydes and Alcohols under Basic Conditions. *Org. Biomol. Chem.* **2018**, *16*, 3114−3120.

(6) Riemenschneider, W.; Bolt, H. M. Esters, Organic. In *Ullmann's Encyclopedia of Industrial Chemistry*; Wiley-VCH: Weinheim, Germany, 2005. DOI: 10.1002/14356007.a09_565.pub2

(7) Liu, H.; Shi, G.; Pan, S.; Jiang, Y.; Zhang, Y. Palladium-Catalyzed Benzylation of Carboxylic Acids with Toluene via Benzylic C-H Activation. *Org. Lett.* **2013**, *15*, 4098−4101.

(8) (a) Lu, B.; Zhu, F.; Sun, H.-M.; Shen, Q. Esterification of the Primary Benzylic C−H Bonds with Carboxylic Acids Catalyzed by Ionic Iron(III) Complexes Containing an Imidazolinium Cation. *Org. Lett.* **2017**, *19*, 1132−1135. (b) Zhang, Y.; Jiang, Y.; Wang, Y.; Sun, T.; Meng, Y.; Huang, Y.; Lv, X.; Gao, J.; Zhang, X.; Zhang, S.; Liu, S. *Org. Lett.* **2022**, *24*, 2679−2683.

(9) Sakamoto, R.; Inada, T.; Selvakumar, S.; Moteki, S. A.; Maruoka, K. Efficient Photolytic C−H Bond Functionalization of Alkylbenzene with Hypervalent Iodine(III) reagent. *Chem. Commun.* **2016**, *52*, 3758−3761.

(10) Wang, D.; Liu, Z.; Wang, Z.; Ma, X.; Yu, P. Metal- and Base-Free Regioselective Thiolation of the Methyl $C(sp^3)$−H Bond in 2-Picoline N-Oxides. *Green Chem.* **2019**, *21*, 157−163.

(11) Tang, Y.; Qin, Y.; Meng, D.; Li, C.; Wei, J.; Yang, M. Diverse secondary $C(sp^3)$−H bond functionalization via site-selective trifluoroacetoxylation of aliphatic amines. *Chemical Science* **2018**, *9*, 6374−6378.

(12) Hou, X. F.; Wang, Y. N.; Göttker-Schnetmann, I. N-Heterocyclic Carbene Palladium Catalyzed Regioselective Oxidative Trifluoroacetoxylation of Unactivated Methylene sp^3 C-H Bonds in Linear Alkyl Esters. *Organometallics* **2011**, *30*, 6053−6056.

(13) Chan, A. Y.; Perry, I. B.; Bissonnette, N. B.; Buksh, B. F.; Edwards, G. A.; Frye, L. I.; Garry, O. L.; Lavagnino, M. N.; Li, B. X.; Liang, Y.; Mao, E.; Millet, A.; Oakley, J. V.; Reed, N. L.; Sakai, H. A.; Seath, C. P.; MacMillan, D. W. C. Metallaphotoredox: The Merger of Photoredox and Transition Metal Catalysis. *Chem. Rev.* **2022**, *122*, 1485−1542.

(14) Kawamata, Y.; Yan, M.; Liu, Z.; Bao, D.-H.; Chen, J.; Starr, J. T.; Baran, P. S. Scalable, Electrochemical Oxidation of Unactivated C−H Bonds. *J. Am. Chem. Soc.* **2017**, *139*, 7448−7451.

(15) Jeffrey, J. L.; Terrett, J. A.; MacMillan, D. W. O−H Hydrogen Bonding Promotes H-atom Transfer from α C−H Bonds for C-Alkylation of Alcohols. *Science* **2015**, *349*, 1532−1536.

(16) Ashley, M. A.; Yamauchi, C.; Chu, J. C.; Otsuka, S.; Yorimitsu, H.; Rovis, T. Photoredox-Catalyzed Site-Selective α-$C(sp^3)$-H Alkylation of Primary Amine Derivatives. *Angew. Chem., Int. Ed.* **2019**, *58*, 4002−4006.

(17) Shaw, M. H.; Shurtleff, V. W.; Terrett, J. A.; Cuthbertson, J. D.; MacMillan, D. W. Native Functionality in Triple Catalytic Cross-coupling: sp^3 C−H Bonds as Latent Nucleophiles. *Science* **2016**, *352*, 1304−1308.

(18) Huisgen, R.; Kolbeck, W. N-Acyloxy-Ammonium-Salze. *Tetrahedron Lett.* **1965**, *6*, 783−787.

(19) Creary, X.; Hatoum, H. N.; Barton, A.; Aldridge, T. E. Solvolytic Elimination Reactions of Tertiary α-CSNMe$_2$-Substituted Systems. *J. Org. Chem.* **1992**, *57*, 1887−1897.
(20) The product **5p** hydrolyzed easily to form the corresponding aldehyde upon attempted isolation.
(21) The lack of reactivity of benzyl bromide may be related to the polar effect of the bromine atom, similar to that observed for DCM (two chlorine atoms) used as an inert solvent in this work and for primary and secondary trifluoroacetates prepared in this work with an electron-withdrawing CF_3CO_2 group adjacent to a benzylic C−H bond.
(22) The compound decomposed only upon attempted isolation to give cyclopropane ring-opening products.
(23) See the Supporting Information for details.
(24) The yield is an average of three runs. On average, 25% of the ibuprofen methyl ester remained unreacted. The balance 6% corresponded to a few minor products that were unassigned.
(25) Leibler, I. N.-M.; Tekle-Smith, M. A.; Doyle, A. G. A general strategy for C(sp^3)−H functionalization with nucleophiles using methyl radical as a hydrogen atom abstractor. *Nature Commun.* **2021**, *12*, 6950.
(26) Huang, X.; Liu, W.; Ren, H.; Neelamegam, R.; Hooker, J. M.; Groves, J. T. Late stage benzylic C−H fluorination with [^{18}F] Fluoride for PET imaging. *J. Am. Chem. Soc.* **2014**, *136*, 6842−6845.
(27) Hu, H.; Chen, S.-J.; Mandal, M.; Pratik, S. M.; Buss, J. A.; Krska, S. W.; Cramer, C. J.; Stahl, S. S. Copper-catalyzed benzylic C−H coupling with alcohols via radical relay enabled by redox buffering. *Nat. Catal.* **2020**, *3*, 358−367.
(28) Li, G.-X.; Morales-Rivera, C. A.; Gao, F.; Wang, Y.; He, G.; Liu, P.; Chen, G. A unified photoredox-catalysis strategy for C(sp^3)−H hydroxylation and amidation using hypervalent iodine. *Chem. Sci.* **2017**, *8*, 7180−7185.
(29) Juris, A.; Balzani, V.; Barigelletti, F.; Campagna, S.; Belser, P.; von Zelewsky, A. Ru(II) Polypyridine Complexes: Photophysics, Photochemistry, Electrochemistry, and Chemiluminescence. *Coord. Chem. Rev.* **1988**, *84*, 85−277.
(30) In support of the hypothesis of carbocation involvement, we observed the competitive formation of Ritter-type reaction products when the reaction was run in MeCN as a solvent. See the SI for an example. A stoichiometric benzylic radical-to-carbocation oxidation by [$Ru^{III}(phen)_3$]$^{3+}$ and the formation of Ritter-type reaction products in wet MeCN was characterized previously, see: Rollick, K. L.; Kochi, J. K. Oxidation-Reduction Mechanisms. Inner-Sphere and Outer-Sphere Electron Transfer in the Reduction of Iron(III), Ruthenium(III), and Osmium(III) Complexes by Alkyl Radicals. *J. Am. Chem. Soc.* **1982**, *104*, 1319−1330.
(31) Such electron transfer is expected to be very fast. For example, our experiments with cyclopropylmethylbenzene resulted in a benzylic trifluoroacetate **5u** (Scheme 2) with no trace of an isomeric homoallylic ester. Hence, for this substrate the rate of the SET2 step should be much faster than the rate of the reversible ring-opening of the cyclopropylbenzyl radical, leading to an isomeric homoallyl radical (rate constant $k = 4.0 \times 10^4$ s^{-1} at 20 °C calculated from the reaction Arrhenius parameters found in ref 32).
(32) Beckwith, A. L. J.; Bowry, V. W. Kinetics of Reactions of Cyclopropylcarbinyl Radicals and Alkoxycarbonyl Radicals Containing Stabilizing Substituents: Implications for Their Use as Radical Clocks. *J. Am. Chem. Soc.* **1994**, *116*, 2710−2716.
(33) For substituted benzylic radicals bearing electron-withdrawing groups, *e.g.*, *p*-N≡C$C_6H_4CH_2^{\bullet}$ or *p*-$O_2NC_6H_4CH_2^{\bullet}$, the reaction with the oxidized form of the photocatalyst, *i.e.*, [$Ru(bpy)_3$]$^{3+}$, in the SET2 step may become product-determining.

https://doi.org/10.1021/acs.orglett.2c02946
Org. Lett. 2022, 24, 7737−7741