Organic LETTERS

Letter

pubs.acs.org/OrgLett

Visible-Light-Driven, Radical-Triggered Tandem Cyclization of *o*-Hydroxyaryl Enaminones: Facile Access to 3-CF_2 /CF_3-Containing Chromones

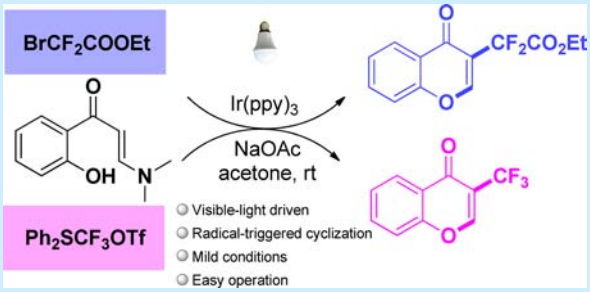
Haoyue Xiang,[†] Qinglan Zhao,[†] Zhenyu Tang,[†] Junan Xiao,[†] Pengju Xia,[†] Chaoming Wang,[†] Chunhao Yang,[‡] Xiaoqing Chen,*[,†] and Hua Yang*[,†]

[†]College of Chemistry and Chemical Engineering, Central South University, Changsha 410083, P. R. China

[‡]State Key Laboratory of Drug Research, Shanghai Institute of Materia Medica, Chinese Academy of Sciences, Shanghai 201203, P. R. China

Supporting Information

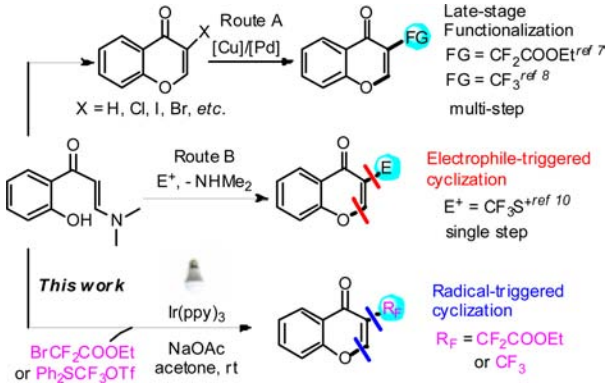
ABSTRACT: A practical and straightforward synthetic route to construct a variety of 3-CF_2/CF_3-containing chromones via photoredox catalysis was developed. This novel protocol features a visible-light-induced radical-triggered tandem cyclization.



Fluorinated organic molecules, frequently found in a number of biologically active natural products, pharmaceuticals, agrochemical reagents, and functional materials, have attracted enormous interest.[1] It is well-known that fluorinated analogues of pharmaceutically relevant compounds often possess interesting properties conducive to drug development, such as improved lipophilicity, electronegativity, bioavailability, and metabolic stability.[2] At present, approximately 30% of all agrochemicals and 20% of all pharmaceuticals contain fluorine, including best-selling drugs such as Lipitor, Lexapro, and Prozac.[3] Among various fluorinated moieties, difluoromethylene (−CF_2−) and trifluoromethyl (CF_3−) groups are specifically appealing. For instance, the CF_2 group is usually considered as a bioisostere for oxygen or carbonyl groups, which leads to increased dipole moments, enhanced acidity of its neighboring group, and conformational changes.[4] Accordingly, substantial efforts have been made toward the incorporation of fluorinated functional groups into organic molecules to modulate their biological activities.[5]

Chromones, widely found in many natural products and pharmaceuticals with a variety of physiological and biological activities, are versatile building blocks for constructing diversely featured heterocycles.[6] Consequently, the preparation of functionalized chromones, especially C3-functionalized analogues, has received considerable synthetic attention. In general, there are two major strategies for accessing 3-functionalized chromones (Scheme 1). The first choice relies on the late-stage functionalization of the C3-position of the preformed chromone core structure, in which multiple synthetic steps are requisite. Not surprisingly, this method was employed for incorporating fluorinated functional groups into chromone scaffolds (Scheme 1, route A). In 2013, Yang's group first synthesized 3-CF_2-containing chromones via copper/palladium-mediated cross-coupling of 3-iodochromones with ethyl bromodifluoroacetate.[7] However, the use of excessive copper reagent and the necessity for preforming 3-iodochromones imposed restrictions on its synthetic application. Afterward, a copper-catalyzed, regioselective C−H α-trifluoromethylation of α,β-unsaturated carbonyl compounds using Togni's reagent was developed by Bi et al., in which only one chromone substrate was explored and the reaction was carried out at 80 °C under argon atmosphere.[8] Alternatively, tandem cyclization reactions

Scheme 1. Synthetic Profiles Accessing 3-Fluorinated Chromones



Received: November 17, 2016
Published: December 12, 2016

DOI: 10.1021/acs.orglett.6b03441
Org. Lett. 2017, 19, 146−149

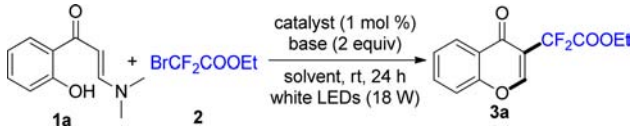
of *o*-hydroxyaryl enaminone afforded 3-functionalized chromone in a more step-economic manner.[9] This pathway was mostly initiated by the attack of electrophiles, such as halogens, acyl, and −SMe. Recently, we developed a method to synthesize SCF_3-containing chromones by using stoichiometric amounts of $AgSCF_3$ and trichloroisocyanuric acid (TCCA) (Scheme 1, route B).[10] Considering the importance and impact of CF_2/CF_3 groups in drug discovery, developing practical and step-economic approaches to synthesize the 3-CF_2/CF_3-incorporated chromones is highly desirable, which would enrich the library of fluorinated chromones and provide valuable synthons for the synthesis of diverse fluorine-containing heterocyclic scaffolds.

In recent years, photoredox catalysis has experienced a resurgence in interest as a powerful synthetic tool for easily promoting radical reactions.[11] In particular, it was found that, in the presence of photoredox catalysts, a variety of fluorinating reagents, including $BrCF_2COR$ and Langlois/Togni/Umemoto reagents, could effectively generate CF_2 and CF_3 radicals, respectively, under visible light.[12] Driven by our continued interest in fluorination of chromones,[13] we herein report a visible-light driven, radical-triggered cyclization of *o*-hydroxyarylenaminones to easily assemble 3-CF_2/CF_3-containing chromones. Prominently, in contrast to all of the previous pathways, this developed reaction proceeds under mild conditions upon irradiation with household LEDs, avoiding heating and the protection of inert atmosphere.

Initially, commercially available $BrCF_2COOEt$ was chosen to generate active CF_2 radical species via visible-light photoredox catalysis. We commenced our exploration with the reaction of (*E*)-3-(dimethylamino)-1-(2-hydroxyphenyl)prop-2-en-1-one (**1a**) with $BrCF_2COOEt$ (**2**) under irradiation of white LEDs (18 W) (Table 1). Catalyst screening demonstrated that $Ir(ppy)_3$ was the best choice, while eosin B and rhodamine B were found to be ineffective in promoting this reaction (Table 1, entries 1−5). Subsequently, various solvents were screened (Table 1, entries 6−12), and acetone was the optimal choice with a slightly improved yield (45%, entry 9). Interestingly, only 4*H*-chromen-4-one was obtained in MeCN and MeOH (entries 11 and 12). In addition, several bases were also evaluated in the reaction, of which NaOAc provided the highest yield (Table 1, entries 13−18). A decrease in the amount of $BrCF_2COOEt$ (2.5 equiv) further improved the corresponding yield to 68% (Table 1, entry 19). However, further reduction of the amount of $BrCF_2COOEt$ (1.2 equiv) obviously sabotaged the yield of **3a** (Table 1, entry 20).

To evaluate the substrate scope of this approach, various (*E*)-3-(dimethylamino)-1-(2-hydroxyphenyl)prop-2-en-1-ones **1** were prepared and subjected to the optimized reaction conditions. Generally, regardles of the electron-donating or electron-withdrawing substituent on the benzene moiety, the title reaction proceeded smoothly and consistently provided the corresponding products **3a−k** in moderate to good yields. It was found that the substrate with substituents at the *para*-position of phenol groups in compounds **1** gave lower yields than those substituted at the *meta*-position (Scheme 2, **3b** vs **3g** and **3j** vs **3c**). Meanwhile, aryl substituents were also suitable substrates, though the corresponding yields were relatively lower (**3h** and **3i**). Interestingly, the introduction of a fluorine substituent at the *meta*-position of the phenol moiety in **1** gave the desired product in better yield than a methoxy group (Scheme 2, **3j** vs **3k**). The practicality and scalability of this protocol was successfully demonstrated by performing the

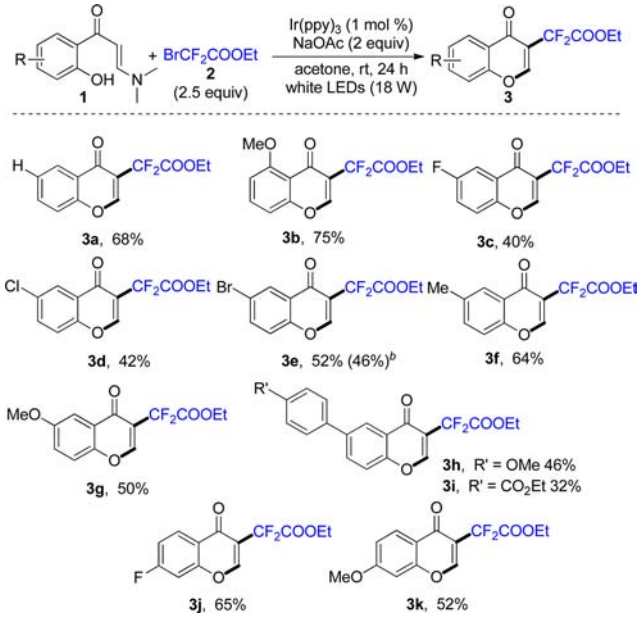
Table 1. Investigation of Reaction Conditions[a]



entry	catalyst	solvent	base	yield[b] (%)
1	eosin Y	CH_2Cl_2	Me_3N	–
2	rhodamine B	CH_2Cl_2	Me_3N	–
3	Ir(dtbbpy) $(bpy)_2PF_6$	CH_2Cl_2	Me_3N	26
4	$Ir(ppy)_3$	CH_2Cl_2	Me_3N	40
5	$Ru(bpy)_3PF_6$	CH_2Cl_2	Me_3N	trace
6	$Ir(ppy)_3$	MeCN	Me_3N	trace
7	$Ir(ppy)_3$	THF	Me_3N	23
8	$Ir(ppy)_3$	DCE	Me_3N	34
9	$Ir(ppy)_3$	acetone	Me_3N	45
10	$Ir(ppy)_3$	DMSO	Me_3N	20
11	$Ir(ppy)_3$	MeCN	Me_3N	trace[c]
12	$Ir(ppy)_3$	MeOH	Me_3N	–[c]
13	$Ir(ppy)_3$	acetone	–	18
14	$Ir(ppy)_3$	acetone	Et_3N	30
15	$Ir(ppy)_3$	acetone	DBU	trace
16	$Ir(ppy)_3$	acetone	NaOAc	53
17	$Ir(ppy)_3$	acetone	K_2CO_3	trace
18	$Ir(ppy)_3$	acetone	KH_2PO_4	37
19[d]	**$Ir(ppy)_3$**	acetone	**NaOAc**	**68**
20[e]	$Ir(ppy)_3$	acetone	NaOAc	46

[a]Reaction conditions: **1a** (0.2 mmol), $BrCF_2COOEt$ (**2**) (5 equiv), base (2 equiv), catalyst (1 mol %), solvent (2 mL), irradiation with white LEDs (18 W), rt, 24 h. [b]Isolated yields. [c]The major product was 4*H*-chromen-4-one. [d]2.5 equiv of $BrCF_2COOEt$ was used. [e]1.2 equiv of $BrCF_2COOEt$ was used.

Scheme 2. Substrate Scope for the Synthesis of 3-CF_2-Containing Chromones[a]



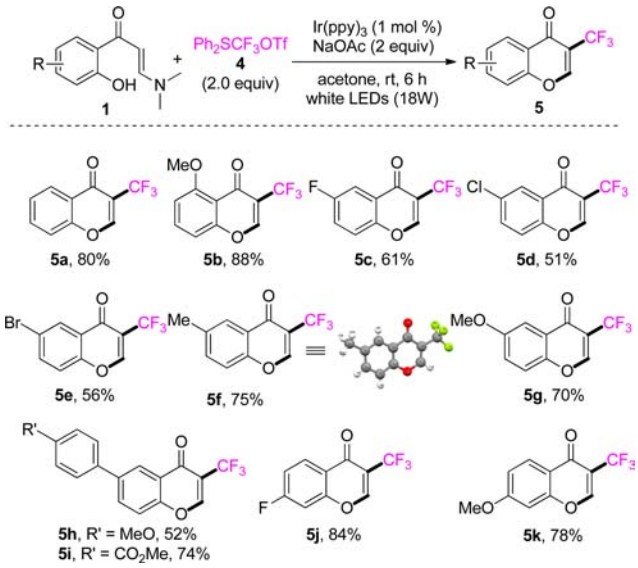
[a]Reaction conditions: **1** (0.2 mmol, 1 equiv), $BrCF_2COOEt$ (**2**) (0.5 mmol, 2.5 equiv), NaOAc (0.4 mmol, 2 equiv), $Ir(ppy)_3$ (1 mol %), acetone (2 mL), irradiation with white LEDs (18 W), rt, 24 h, isolated yields. [b]Performed at 1 g scale.

DOI: 10.1021/acs.orglett.6b03441
Org. Lett. 2017, 19, 146−149

reaction for **3e** on a gram scale under standard reaction conditions to give a similar yield (46%).

Subsequently, we extended this newly developed radical-triggered cyclization to install 3-CF_3-substituted chromones by simply replacing $BrCF_2COOEt$ with various CF_3 radical resources. In the model reaction using **1a**, it was found that Ph_2SCF_3OTf was the optimum CF_3 source, giving the desired 3-CF_3-substituted chromone **5a** in a good yield (80%) under standard conditions. As summarized in Scheme 3, the substrate

Scheme 3. Substrate Scope for the Synthesis of 3-CF_3-Containing Chromones[a]



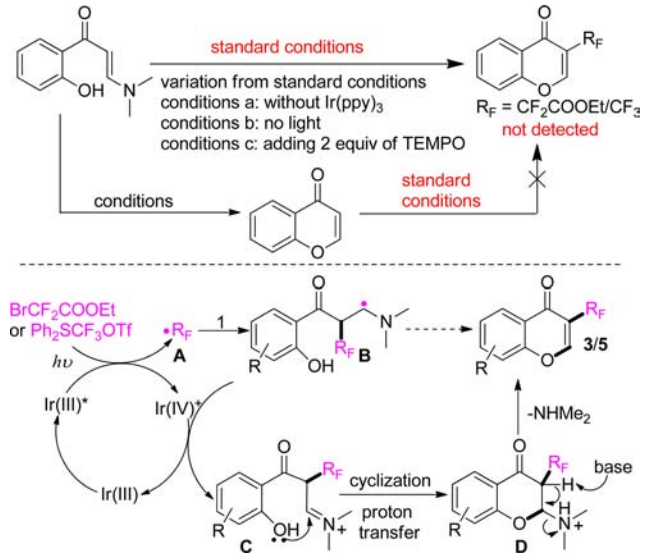
[a]Reaction conditions: **1** (0.2 mmol, 1 equiv), Ph_2SCF_3OTf (**4**) (0.4 mmol, 2 equiv), NaOAc (0.4 mmol, 2 equiv), $Ir(ppy)_3$ (1 mol %), acetone (2 mL), irradiation with white LEDs (18 W), rt, 6 h, isolated yields.

scope of this reaction was quickly investigated. In general, the yields for CF_3 radical-triggered cyclization product **5** are superior to those of CF_2-containing analogues **3**. Notably, the introduction of a halogen substituent at the *para*-position of the phenol moiety in **1** led to a significant decrease in the corresponding yields (Scheme 3, **5c**–**e**). Otherwise, good yields were generally achieved, and diverse functional groups were well tolerated. Additionally, the structure of **5f** was confirmed by X-ray crystallographic analysis.[14]

To gain mechanistic insight into the reaction, several control experiments were carried out. The desired products were not obtainable in the absence of photocatalyst or light (Scheme 4, conditions a/b), revealing that this transformation is a photocatalytic process. When 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO), as a radical inhibitor, was added into the reaction under standard conditions, no desired product was detected (Scheme 4, conditions c). This result indicates that a radical pathway may be involved in this transformation. Moreover, when 4*H*-chromen-4-one was subjected to the standard conditions, the desired products still could not be achieved.

On the basis of the obtained results, a plausible mechanism is proposed in Scheme 4. Initially, the excited state $[Ir(ppy)_3]^*$ was generated under visible light irradiation and then oxidized by $BrCF_2COOEt$ or Ph_2SCF_3OTf to generate $[Ir(IV)(ppy)_3]^+$ complex and R_F radical species **A**. Subsequently, the R_F radical

Scheme 4. Control Experiments and Plausible Mechanism



attacked the C═C of substrate **1** regioselectively to give radical intermediate **B**. It was then quickly oxidized by $[Ir(IV)(ppy)_3]^+$ to form iminium intermediate **C** with the concurrent regeneration of $[Ir(ppy)_3]$, which presumably contributed to the excellent regioselectivity in the process of the insertion of radical **A**. Subsequent cyclization of intermediate **C** gave di/trifluoromethylated intermediates **D**. Ultimately, the *N*,*N*-dimethyl group of intermediates **D** was eliminated to furnish the desired products **3** or **5**.

In conclusion, we successfully developed a facile and general synthetic route accessing a range of 3-CF_2/CF_3-containing chromones via visible-light photoredox catalysis under mild conditions. Preliminary mechanistic investigations indicated that a radical-triggered tandem cyclization was involved in this transformation. More importantly, this photoredox catalytic, radical-triggered cyclization would offer a novel pathway to access diverse fluorinated heterocycles.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b03441.

X-ray data for compound **5f** (CIF)

General experimental information and ^1H and ^{13}C NMR of new compounds (PDF)

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: xqchen@csu.edu.cn.

*E-mail: hyangchem@csu.edu.cn.

ORCID

Hua Yang: 0000-0002-7404-4247

Notes

The authors declare no competing financial interest.

DOI: 10.1021/acs.orglett.6b03441
Org. Lett. 2017, 19, 146–149

■ ACKNOWLEDGMENTS

We gratefully acknowledge financial support from the National Natural Science Foundation of China (Nos. 21576296 and 21676302) and Central South University.

■ REFERENCES

(1) (a) O'Hagan, D. *Chem. Soc. Rev.* **2008**, *37*, 308. (b) Gouverneur, V.; Seppelt, K. *Chem. Rev.* **2015**, *115*, 563.

(2) (a) Hagmann, W. K. *J. Med. Chem.* **2008**, *51*, 4359. (b) Purser, S.; Moore, P. R.; Swallow, S.; Gouverneur, V. *Chem. Soc. Rev.* **2008**, *37*, 320. (c) Wang, J.; Sanchez-Rosello, M.; Acena, J. L.; del Pozo; Sorochinsky, C. A.; Fustero, E. S.; Soloshonok, V. A.; Liu, H. *Chem. Rev.* **2014**, *114*, 2432. (d) Yerien, D. E.; Bonesi, S.; Postigo, A. *Org. Biomol. Chem.* **2016**, *14*, 8398.

(3) Furuya, T.; Kamlet, A. S.; Ritter, T. *Nature* **2011**, *473*, 470.

(4) (a) Blackburn, G. M.; England, D. A.; Kolkmann, F. *J. Chem. Soc., Chem. Commun.* **1981**, 930. (b) Hakogi, T.; Yamamoto, T.; Fujii, S.; Ikeda, K.; Katsumura, S. *Tetrahedron Lett.* **2006**, *47*, 2627.

(5) For selected reviews and reports on the incorporation of CF_2/CF_3 groups, see: (a) Uneyama, K.; Katagiri, T.; Amii, H. *Acc. Chem. Res.* **2008**, *41*, 817. (b) Ma, J. A.; Cahard, D. *Chem. Rev.* **2008**, *108*, Pr1. (c) Zhang, C. P.; Wang, Z. L.; Chen, Q. Y.; Zhang, C. T.; Gu, Y. C.; Xiao, J. C. *Angew. Chem., Int. Ed.* **2011**, *50*, 1896. (d) Mizuta, S.; Verhoog, S.; Engle, K. M.; Khotavivattana, T.; O'Duill, M.; Wheelhouse, K.; Rassias, G.; Medebielle, M.; Gouverneur, V. *J. Am. Chem. Soc.* **2013**, *135*, 2505. (e) Wang, J. Y.; Su, Y. M.; Yin, F.; Bao, Y.; Zhang, X.; Xu, Y. M.; Wang, X. S. *Chem. Commun.* **2014**, *50*, 4108. (f) Ni, C.; Hu, J. *Synthesis* **2014**, *46*, 842. (g) Besset, T.; Poisson, T.; Pannecoucke, X. *Chem. - Eur. J.* **2014**, *20*, 16830. (h) Xiao, Y. L.; Guo, W. H.; He, G. Z.; Pan, Q.; Zhang, X. *Angew. Chem., Int. Ed.* **2014**, *53*, 9909. (i) Chu, L.; Qing, F. L. *Acc. Chem. Res.* **2014**, *47*, 1513. (j) Hu, M.; Ni, C.; Li, L.; Han, Y.; Hu, J. *J. Am. Chem. Soc.* **2015**, *137*, 14496. (k) Matoušek, V.; Pietrasiak, E.; Sigrist, L.; Czarniecki, B.; Togni, A. *Eur. J. Org. Chem.* **2014**, *2014*, 3087. (l) Lin, J. H.; Xiao, J. C. *Tetrahedron Lett.* **2014**, *55*, 6147. (m) Gu, Y.; Chang, D.; Leng, X.; Gu, Y.; Shen, Q. *Organometallics* **2015**, *34*, 3065. (n) Alonso, C.; Martinez de Marigorta, E.; Rubiales, G.; Palacios, F. *Chem. Rev.* **2015**, *115*, 1847. (o) Liu, X.; Xu, C.; Wang, M.; Liu, Q. *Chem. Rev.* **2015**, *115*, 683. (p) Tarui, A.; Shinohara, S.; Sato, K.; Omote, M.; Ando, A. *Org. Lett.* **2016**, *18*, 1128.

(6) For selected reviews on chromones, see: (a) Plaskon, A. S.; Grygorenko, O. O.; Ryabukhin, S. V. *Tetrahedron* **2012**, *68*, 2743. (b) Gaspar, A.; Matos, M. J.; Garrido, J.; Uriarte, E.; Borges, F. *Chem. Rev.* **2014**, *114*, 4960. (c) Keri, R. S.; Budagumpi, S.; Pai, R. K.; Balakrishna, R. G. *Eur. J. Med. Chem.* **2014**, *78*, 340.

(7) Han, X.; Yue, Z.; Zhang, X.; He, Q.; Yang, C. *J. Org. Chem.* **2013**, *78*, 4850.

(8) Fang, Z.; Ning, Y.; Mi, P.; Liao, P.; Bi, X. *Org. Lett.* **2014**, *16*, 1522.

(9) (a) Gammill, R. B. *Synthesis* **1979**, *1979*, 901. (b) Vasselin, D. A. A.; Westwell, D.; Matthews, C. S.; Bradshaw, T. D.; Stevens, M. F. G. *J. Med. Chem.* **2006**, *49*, 3973. (c) Akram, M. O.; Bera, S.; Patil, N. T. *Chem. Commun.* **2016**, *52*, 12306. (d) Zhang, X.; Ge, D.; Chen, S.; Yu, X. *RSC Adv.* **2016**, *6*, 66320.

(10) Xiang, H.; Yang, C. *Org. Lett.* **2014**, *16*, 5686.

(11) For selected reviews on photoredox catalysis, see: (a) Ravelli, D.; Dondi, D.; Fagnoni, M.; Albini, A. *Chem. Soc. Rev.* **2009**, *38*, 1999. (b) Narayanam, J. M.; Stephenson, C. R. *Chem. Soc. Rev.* **2011**, *40*, 102. (c) Xuan, J.; Xiao, W. J. *Angew. Chem., Int. Ed.* **2012**, *51*, 6828. (d) Prier, C. K.; Rankic, D. A.; MacMillan, D. W. *Chem. Rev.* **2013**, *113*, 5322. (e) Ravelli, D.; Fagnoni, M.; Albini, A. *Chem. Soc. Rev.* **2013**, *42*, 97. (f) Karkas, M. D.; Porco, J. A., Jr.; Stephenson, C. R. *Chem. Rev.* **2016**, *116*, 9683. (g) Lang, X.; Zhao, J.; Chen, X. *Chem. Soc. Rev.* **2016**, *45*, 3026. (h) Shaw, M. H.; Twilton, J.; MacMillan, D. W. *J. Org. Chem.* **2016**, *81*, 6898. (i) Skubi, K. L.; Blum, T. R.; Yoon, T. P. *Chem. Rev.* **2016**, *116*, 10035. (j) Ravelli, D.; Protti, S.; Fagnoni, M. *Chem. Rev.* **2016**, *116*, 9850.

(12) For selected reviews and reported on fluoroalkylation reactions by visible-light photoredox: Catalysis: (a) Nagib, D. A.; Scott, M. E.; MacMillan, D. W. *J. Am. Chem. Soc.* **2009**, *131*, 10875. (b) Nagib, D. A.; MacMillan, D. W. *Nature* **2011**, *480*, 224. (c) Xu, P.; Xie, J.; Xue, Q.; Pan, C.; Cheng, Y.; Zhu, C. *Chem. - Eur. J.* **2013**, *19*, 14039. (d) Xie, J.; Yuan, X.; Abdukader, A.; Zhu, C.; Ma, J. *Org. Lett.* **2014**, *16*, 1768. (e) Yu, C.; Iqbal, N.; Park, S.; Cho, E. J. *Chem. Commun.* **2014**, *50*, 12884. (f) Barata-Vallejo, S.; Bonesi, S. M.; Postigo, A. *Org. Biomol. Chem.* **2015**, *13*, 11153. (g) Douglas, J. J.; Albright, H.; Sevrin, M. J.; Cole, K. P.; Stephenson, C. R. J. *Angew. Chem., Int. Ed.* **2015**, *54*, 14898. (h) Fu, W.; Han, X.; Zhu, M.; Xu, C.; Wang, Z.; Ji, B.; Hao, X. Q.; Song, M. P. *Chem. Commun.* **2016**, *52*, 13413. (i) Koike, T.; Akita, M. *Acc. Chem. Res.* **2016**, *49*, 1937. (j) Li, L.; Mu, X.; Liu, W.; Wang, Y.; Mi, Z.; Li, C. J. *J. Am. Chem. Soc.* **2016**, *138*, 5809. (k) Lin, Q. Y.; Ran, Y.; Xu, X. H.; Qing, F. L. *Org. Lett.* **2016**, *18*, 2419. (l) Rong, J.; Deng, L.; Tan, P.; Ni, C.; Gu, Y.; Hu, J. *Angew. Chem., Int. Ed.* **2016**, *55*, 2743. (m) Yu, W.; Xu, X. H.; Qing, F. L. *Org. Lett.* **2016**, *18*, 5130. (n) Zhang, M.; Li, W.; Duan, Y.; Xu, P.; Zhang, S.; Zhu, C. *Org. Lett.* **2016**, *18*, 3266. (o) Zhang, H. R.; Chen, D. Q.; Han, Y. P.; Qiu, Y. F.; Jin, D. P.; Liu, X. Y. *Chem. Commun.* **2016**, *52*, 11827. (p) Zhu, L.; Wang, L. S.; Li, B.; Fu, B.; Zhang, C. P.; Li, W. *Chem. Commun.* **2016**, *52*, 6371. (q) Chatterjee, T.; Iqbal, N.; You, Y.; Cho, E. J. *Acc. Chem. Res.* **2016**, *49*, 2284.

(13) (a) Qi, X.; Xiang, H.; He, Q.; Yang, C. *Org. Lett.* **2014**, *16*, 4186. (b) Qi, X.; Xiang, H.; Yang, C. *Org. Lett.* **2015**, *17*, 5590.

(14) CCDC-1515972 contains the supplementary crystallographic data for compound **5f**. Copies of these data can be obtained free of charge via www.ccdc.cam.ac.uk.

DOI: 10.1021/acs.orglett.6b03441
Org. Lett. 2017, 19, 146−149