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Visible-Light- and Oxygen-Promoted Direct Csp^2-H Radical Difluoromethylation of Coumarins and Antifungal Activities

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Supporting Information

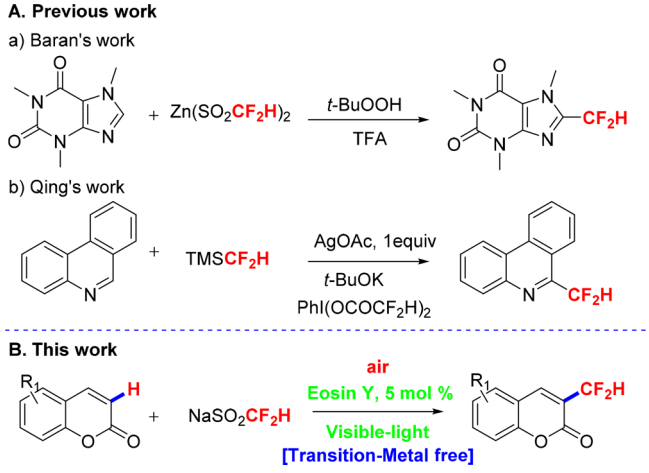
ABSTRACT: An efficient general method using a clean and transition-metal-free photochemical strategy for the direct Csp^2-H radical difluoromethylation of coumarins with HCF_2SO_2Na was developed. The visible-light-promoted strategy proceeds with 5 mol % Eosin Y under mild reaction conditions and showed excellent functional group compatibility. The control experiments illustrated that $O_2^{\bullet-}$ participated in this process and plays an important role in the reactions. Moreover, the representative products exhibited excellent antifungal activities in vitro. It was noted that the EC_{50} value of compound **3a** was determined to be as low as 1.5463 μg/mL against *Rhizoctorzia solani*, which was better than Boscalid (EC_{50} = 2.9767 μg/mL).

The incorporation of fluorine atoms in organic molecules has emerged as a widely employed strategy in pharmaceutical and agrochemical research. Due to lipophilic hydrogen bond donors and bioisosteres of alcohols and thiols for the difluoromethyl-containing molecules,[1] the difluoromethyl-containing compounds have gained considerable attention. For example, thiazopyr (herbicide),[2a] fluxapyroxad (fungicide),[2b] and deracoxib (anti-inflammatory drug)[2c] have shown promising biological activities. However, most of the previous methods for difluoromethylation required hazardous reagents or multistep sequences.[3] Compared with the CF_3 group, the CF_2H group is weakly acidic and is capable of hydrogen bonding interactions to improve the binding selectivity of biologically active compounds,[4] and the highly developed methods for the incorporation of the CF_3 group into organic molecules have been studied.[5] However, most of the previous methods for difluoromethylation required hazardous reagents or multistep sequences and are less than the methods for trifluoromethylation.

There are several methods for the fluorination of compounds; however, strategies for direct difluoromethylation are less common, especially in the context of heteroarenes.[6] Traditionally, difluoromethylation of organic compounds often uses *N*,*N*-dimethylaminosulfur trifluoride (DAST) and bis(2-methoxyethyl)aminosulfur trifluoride (Deoxo-Fluor).[7] However, these methods often suffer from the need of expensive and toxic fluorinating agents. In 2012, the Baran group published the direct C−H difluoromethylation of *N*-heteroarenes utilizing *tert*-butyl hydroperoxide (TBHP) and zinc sulfinate salts as difluoromethylation sources (Scheme 1a).[8] Then, the Qing group found a silver-mediated oxidative difluoromethylation of phenanthridines and 1,10-phenanthrolines with $TMSCF_2H$ to form Csp^2-H difluoromethylation products in 2017 (Scheme 1b).[9] However, most of the reaction systems involved transition metals, which were expensive,[10] toxic, and recognized as undesirable impurities in pharmaceuticals. After that, Maruoka realized the direct Csp^2-H difluoromethylation of *N*-heteroarenes with hypervalent iodine(III) reagents under UV radiation in 2017.[11] In 2018, Qing disclosed the direct introduction of the difluoromethyl group into heteroarenes via the copper-mediated C−H oxidative difluoromethylation of heteroarenes with $TMSCF_2H$.[12] Hence, it is very important to develop transition-metal-free and step-economical strategies for this transformation.

Intriguingly, practices in visible-light photocatalysis have actively responded to the demands of reaction economics, operational simplicity, and environmental friendliness. Many papers related to the direct C−H bond functionalization by photoredox catalysis were reported.[13] However, few examples

Scheme 1. Synthesis of 3-Difluoromethylated Coumarins



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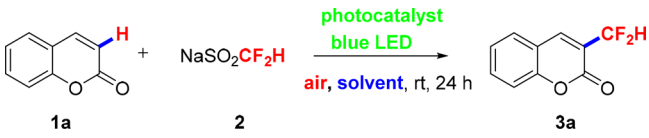
Org. Lett. XXXX, XXX, XXX−XXX

have been reported about the visible-light-induced radical difluoromethylation of heteroarenes,[10,11,14] especially the visible-light-induced direct Csp^2-H radical difluoromethylation of *O*-heteroarenes. Therefore, we focused our attention on developing an efficient and general method for the direct Csp^2-H radical difluoromethylation of *O*-heteroarenes; it has been proven much more challenging by visible light.

Coumarins are an important class of natural products, which exhibit a broad scope of biological activities and have been extensively investigated for their outstanding optimal properties.[15] In this research, we report an approach to the first direct Csp^2-H visible-light-mediated radical difluoromethylation of coumarins with sodium sulfinate (Scheme 1B).

Initially, HCF_2SO_2Na was used as a fluorine source and eosin Y as a photosensitizer under 12 W blue LEDs for the difluoromethylation of coumarin (**3a**). The desired product was obtained in 57% yield (Table 1, entry 1), and eosin B, rose

Table 1. Optimization of the Reaction Conditions[a]



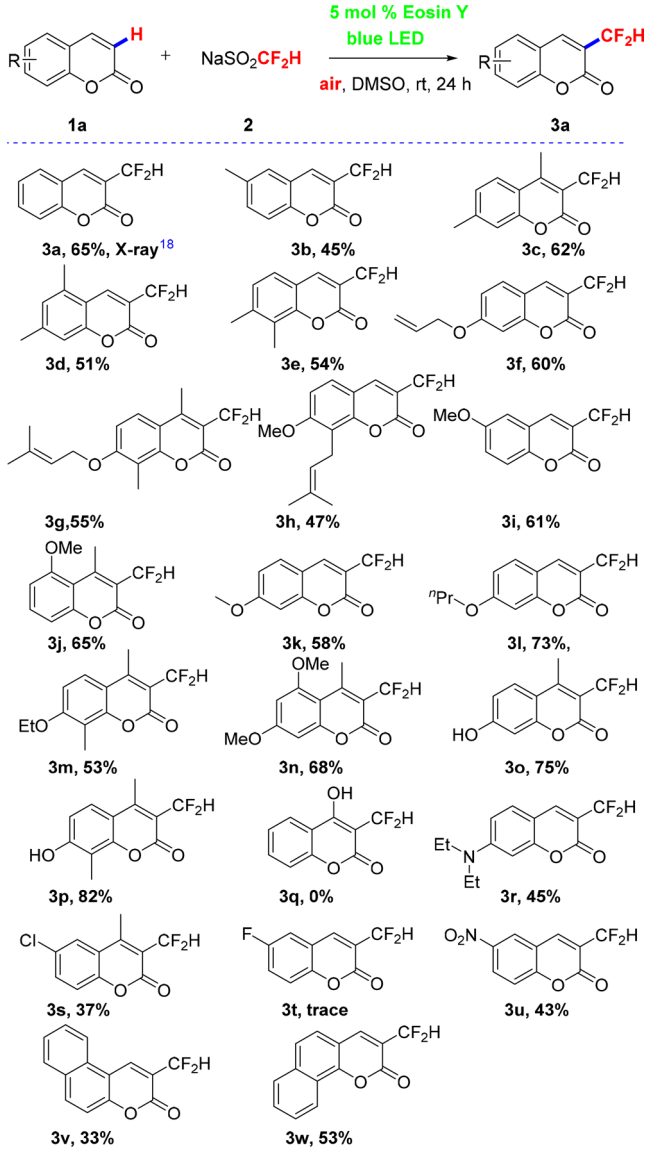
entry	photocatalyst (5 mol %)	solvent (2 mL)	additives (2 equiv)	yield[b] (%)
1	eosin Y	DMSO		57
2	rose bengal	DMSO		56
3	eosin B	DMSO		55
4	eosin Y	DMF		23
5	eosin Y	acetone		10
6	eosin Y	DMSO	pyridine	24
7	eosin Y	DMSO	AcOH	34
8[c]	eosin Y	DMSO		N.R.
9[d]	eosin Y	DMSO		20
10[e]	eosin Y	DMSO		65
11[f]	eosin Y	DMSO		5
12		DMSO		N.R.
13[g]	eosin Y	DMSO		N.R.

[a]Standard conditions: coumarins (**1a**, 0.3 mmol), HCF_2SO_2Na (**2a**, 0.6 mmol), and photocatalysts (0.015 mmol, 5.0 mol %), solvent (2.0 mL), 12 W blue LED, 24 h, rt; N.R. = no reaction. [b]Isolated yields. [c]HCF_2SO_2Ph instead of HCF_2SO_2Na. [d]HCF_2SO_2Py instead of HCF_2SO_2Na. [e]HCF_2SO_2Na (**2a**, 0.9 mmol). [f]In N_2. [g]In the dark.

bengal, riboflavin, and fluorescein did not improve the yield compared to eosin Y. Many solvents were studied (DMF, DMSO, acetone, MeOH, Et_2O, and H_2O). The results show that DMF was 23% yield (Table 1, entry 4), and acetone was 10% (Table 1, entry 5). MeOH did not give the desired product. Unfortunately, additives such as CH_3COOH, CF_3COOH, pyridine, benzoic acid, and other acids or bases did not promote the reaction. Using the pyridine condition, we obtained the product with 24% yield (entry 6) and 34% yield with glacial acetic acid (entry 7). When the reaction was performed with HCF_2SO_2Py or HCF_2SO_2Ph, there was no desired product. The reason for this phenomenon may be due to the decomposition of substrate (Table 1, entries 8 and 9). When **2** (3 equiv) was used as a substrate in this reaction, it gave a 65% yield (Table 1, entry 10). Meanwhile, without photocatalyst or light the desired product was not found (Table 1, entries 12 and 13). Eventually, the optimized conditions for this reaction were determined as **1a** (0.2 mmol) and **2** (3 equiv) in the presence of eosin Y (5 mol %) with DMSO as solvent at room temperature for 24 h (more details are shown in the Supporting Information (SI)).

With the optimized reaction conditions in hand, the scope of difluoromethylation of coumarins was examined (Scheme 2).

Scheme 2. Scope for Difluoromethylation of Coumarins[a]



[a]Reaction conditions: 0.3 mmol coumarin, 0.9 mmol HCF_2SO_2Na, 5 mol % photocatalyst, 2 mL of DMSO, 12 W blue LED, 24 h, rt; isolated yields.

Generally, a range of courmains, containing both electron-donating and electron-withdrawing groups, were tolerated under our reaction conditions. The reactions involving coumarins with electron-rich groups such as Me, OMe, and alkenyl proceeded well, affording the desired products **3b**−**3n** in 45−73% yields. Especially, Osthole (**1h**) led to a 47% yield of **3h**. Meanwhile, 7-hydroxyl coumarins were well tolerated. Reactions with **3o** and **3p** proceeded with yields up to 75% and 82%, and using 1 mmol scale of **1o** led to a 52% yield of **3o**; however, 4-hydroxyl-substituted coumarin (**1q**) did not lead to the desired product. The strong electron-donating group diethylamine led to lower reactivity, with a 45% yield of **3r**.

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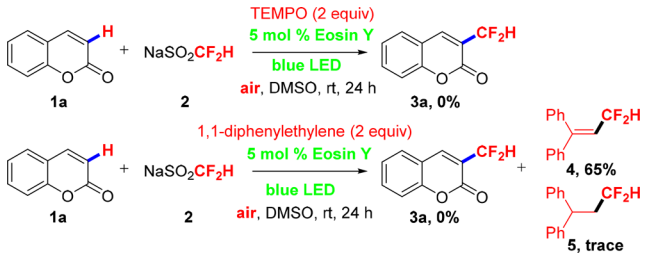
Org. Lett. XXXX, XXX, XXX−XXX

However, a 6-Cl-substituted compound provided a 37% yield, but 6-F coumarin only gave a trace of product (**3t**). The nitro group, strongly electron-withdrawing, led to a 43% yield of **3u**. The introduction of the difluoromethyl group on benzocoumarins afforded **3v** and **3w** with 33% and 53% yields.

To gain some mechanistic insight into the reaction, the radical scavenger 2,2,6,6-tetramethyl-1-piperidinoxyl (TEMPO, 2 equiv) was added to the standard reaction mixture of **1a** and **2** (Scheme 3). No desired product was

Scheme 3. Radical Trap Experiments



formed. When 1,1-diphenylethylene (2 equiv) was added to the standard reactions, the reaction provided the product **4** with 65% yield and a trace of **5** instead with forming **3a**. In addition, to determine the role of oxygen in the reaction, capturing agents such as 5,5-dimethyl-1-pyrroline-*N*-oxide (DMPO) were used to trap O_2. Peroxide radical anion ($O_2^{\bullet-}$) was trapped under standard reaction conditions by using the DMPO spin trapping (Figure 1).[16]

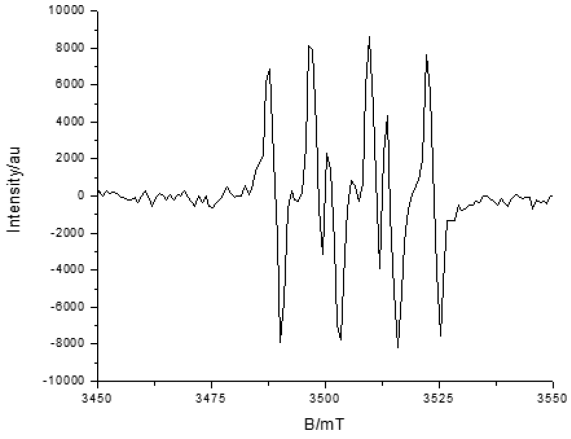
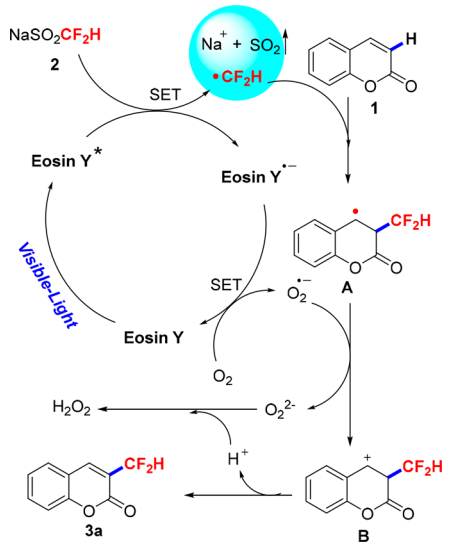


Figure 1. DMPO spin-trapping ESR spectra for peroxide radical anion ($O_2^{\bullet-}$) in standard reaction conditions.

Based on the previous control experiments, we propose the reaction mechanism in Scheme 4. First, the excited eosin Y* is formed under irradiation, and then a single electron is transferred from difluoromethylsulfone **2** to eosin Y*, which generates eosin$Y^{\bullet-}$ species and a highly reactive CF_2H radical. Subsequently, radical intermediate **A** was generated. Then one electron transfers from $Y^{\bullet-}$ to O_2 to give eosin Y and $O_2^{\bullet-}$, and eosin Y is regenerated. This is then further reacted with **A** to form O_2^{2-} and intermediate **B** through an electron transfer. Finally, deprotonation of this species furnishes the desired product **3a**.

The promising antifungal activities of the 3-difluoromethyl coumarins against phytopathogenic fungi were also tested. At first, the antifungal activities of **3a** were tested against five

Scheme 4. Proposed Reaction Mechanism



phytopathogenic fungi (*Botrytis cinerea*, *Alternaria solani*, *Gibberella zeae*, *Rhizoctorzia solani*, and *Alternaria* leaf spot) using mycelia growth inhibitory rate methods, with boscalid or carbendazim used as the positive control (Table 2).[17] The

Table 2. EC_{50} Values of Selected Compounds[a,b]

compounds	BOT	ALT	GIB	RHI	ALS
3a	7.0906	10.1533	23.7796	1.5463	11.8494
boscalid	0.5096	3.3253	—	2.9767	0.3445
carbendazim	—	—	0.4947	—	—

[a]EC_{50} values of **3a**. [b]BOT: *Botrytis cinerea*; ALT: *Alternaria solani*; GIB: *Gibberella zeae*; RHI: *Rhizoctorzia solani*; ALS: *Alternaria* leaf spot.

EC_{50} values of **3a**[18] possessing good activity were further evaluated using different concentrations by diluting the solution. Preliminary bioassay results indicate that 3-difluoromethylcoumarin exhibited potential antifungal activities at the concentration of 20 μg/mL. It is worth noting that the EC_{50} value of compound **3a** was determined as low as 1.5463 μg/mL against *Rhizoctorzia solani*, which exhibited competitive activity to that of the positive control (boscalid EC_{50} = 2.9767 μg/mL) (all of the above details are shown in the SI).

In summary, we have successfully developed a visible-light-promoted difluoromethylation of coumarins. Mechanistic investigations demonstrated that O_2 participated in this reaction as the oxidant. This reaction provided an efficient protocol for preparing useful 3-difluoromethylcoumarins that may be used as potential intermediates in organic synthesis and medicinal chemistry. This new method provided a green and operationally simple procedure of direct Csp^2-H bond functionalization. In addition, we evaluated preliminary bioactivity of a representative compound **3a** against five phytopathogenic fungi exemplified by their promising antifungal activities. Further synthetic applications and bioactivity tests are ongoing in our laboratory.

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■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b02965.

Experimental procedures, characterization data, and NMR spectra of products (PDF)

Accession Codes

CCDC 1844389 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) (a) Zafrani, Y.; Yeffet, D.; Sod-Moriah, G.; Berliner, A.; Amir, D.; Marciano, D.; Gershonov, E.; Saphier, S. Difluoromethyl Bioisostere: Examining the "Lipophilic Hydrogen Bond Donor" Concept. *J. Med. Chem.* **2017**, *60*, 797−804. (b) Fier, P. S.; Hartwig, J. F. Synthesis of Difluoromethyl Ethers with Difluoromethyltriflate. *Angew. Chem., Int. Ed.* **2013**, *52*, 2092−2095. (c) Zheng, J.; Li, Y.; Zhang, L.; Hu, J.; Meuzelaar, G. J.; Federsel, H. J. Chlorodifluoromethyl phenyl sulfone: a novel non-ozone-depleting substance-based difluorocarbene reagent for *O*- and *N*-difluoromethylations. *Chem. Commun.* **2007**, *0*, 5149−5151.

(2) (a) Fustero, S.; Sanchez-Rosello, M.; Barrio, P.; Simon-Fuentes, A. From 2000 to Mid-2010: A Fruitful Decade for the Synthesis of Pyrazoles. *Chem. Rev.* **2011**, *111*, 6984−7034. (b) Wang, J.; Sánchez-Roselló, M.; Aceña, J. L.; 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. (c) Vitale, A.; Bongiovanni, R.; Ameduri, B. Fluorinated Oligomers and Polymers in Photopolymerization. *Chem. Rev.* **2015**, *115*, 8835−8866.

(3) (a) Ran, Y.; Lin, Q. Y.; Xu, X. H.; Qing, F. L. Visible Light Induced Oxydifluoromethylation of Styrenes with Difluoromethyltriphenylphosphonium Bromide. *J. Org. Chem.* **2016**, *81*, 7001−7007. (b) Deng, Z.; Lin, J. H.; Cai, J.; Xiao, J. C. Direct Nucleophilic Difluoromethylation of Carbonyl Compounds. *Org. Lett.* **2016**, *18*, 3206−3209. (c) Thomoson, C. S.; Dolbier, W. R., Jr. Use of Fluoroform as a Source of Difluorocarbene in the Synthesis of Difluoromethoxy- and Difluorothiomethoxyarenes. *J. Org. Chem.* **2013**, *78*, 8904−8908. (d) Ge, S.; Chaladaj, W.; Hartwig, J. F. Pd-Catalyzed α-Arylation of α, α-Difluoroketones with Aryl Bromides and Chlorides. A Route to Difluoromethylarenes. *J. Am. Chem. Soc.* **2014**, *136*, 4149−4152. (e) Fujikawa, K.; Fujioka, Y.; Kobayashi, A.; Amii, H. A New Method for Aromatic Difluoromethylation: Copper-Catalyzed Cross-Coupling and Decarboxylation Sequence from Aryl Iodides. *Org. Lett.* **2011**, *13*, 5560−5563. (f) Schmitt, E.; Rugeri, B.; Panossian, A.; Vors, J. P.; Pazenok, S.; Leroux, F. R. In Situ Generated Fluorinated Iminium Salts for Difluoromethylation and Difluoroacetylation. *Org. Lett.* **2015**, *17*, 4510−4513. (g) Okusu, S.; Tokunaga, E.; Shibata, N. Difluoromethylation of Terminal Alkynes by Fluoroform. *Org. Lett.* **2015**, *17*, 3802−3805. (h) Prakash, G. K. S.; Yudin, A. K. Perfluoroalkylation with Organosilicon Reagents. *Chem. Rev.* **1997**, *97*, 757−786. (i) Li, L.; Wang, F.; Ni, C.; Hu, J. Synthesis of *gem*-Difluorocyclopropa(e)nes and O-, S-, N-, and P-Difluoromethylated Compounds with $TMSCF_2Br$. *Angew. Chem., Int. Ed.* **2013**, *52*, 12390−12394. (j) Ivanova, M. V.; Bayle, A.; Besset, T.; Poisson, T.; Pannecoucke, X. Copper-Mediated Formation of Aryl, Heteroaryl, Vinyl and Alkynyl Difluoromethylphosphonates: A General Approach to Fluorinated Phosphate Mimics. *Angew. Chem., Int. Ed.* **2015**, *54*, 13406−13410. (k) Zhang, B.; Studer, A. 6-Perfluoroalkylated Phenanthridines via Radical Perfluoroalkylation of Isonitriles. *Org. Lett.* **2014**, *16*, 3990−3993. (l) Gu, J. W.; Zhang, X. Palladium-Catalyzed Difluoroalkylation of Isocyanides: Access to Difluoroalkylated Phenanthridine Derivatives. *Org. Lett.* **2015**, *17*, 5384−5387. (m) 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.

(4) (a) Erickson, J. A.; McLoughlin, J. I. Hydrogen Bond Donor Properties of the Difluoromethyl Group. *J. Org. Chem.* **1995**, *60*, 1626−1631. (b) Meanwell, N. A. Synopsis of Some Recent Tactical Application of Bioisosteres in Drug Design. *J. Med. Chem.* **2011**, *54*, 2529−2591.

(5) (a) Nie, J.; Guo, H.-C.; Cahard, D.; Ma, J.-A. Asymmetric Construction of Stereogenic Carbon Centers Featuring a Trifluoromethyl Group from Prochiral Trifluoromethylated Substrates. *Chem. Rev.* **2011**, *111*, 455−529. (b) Tomashenko, O. A.; Grushin, V. V. Aromatic Trifluoromethylation with Metal Complexes. *Chem. Rev.* **2011**, *111*, 4475−4521. (c) He, Z.; Luo, T.; Hu, M.; Cao, Y.; Hu, J. Copper-Catalyzed Di- and Trifluoromethylation of α, β-Unsaturated Carboxylic Acids: A Protocol for Vinylic Fluoroalkylations. *Angew. Chem., Int. Ed.* **2012**, *51*, 3944−3947. (d) Chu, L.; Qing, F.-L. Acc. Oxidative Trifluoromethylation and Trifluoromethylthiolation Reactions Using (Trifluoromethyl)trimethylsilane as a Nucleophilic CF3 Source. *Acc. Chem. Res.* **2014**, *47*, 1513−1522. (e) Charpentier, J.; Freh, N.; Togni, A. Electrophilic Trifluoromethylation by Use of Hypervalent Iodine Reagents. *Chem. Rev.* **2015**, *115*, 650−682. (f) Liu, X.; Xu, C.; Wang, M.; Liu, Q. Trifluoromethyltrimethylsilane: Nucleophilic Trifluoromethylation and Beyond. *Chem. Rev.* **2015**, *115*, 683−730. (g) Ni, C.; Hu, M.; Hu, J. Good Partnership between Sulfur and Fluorine: Sulfur-Based Fluorination and Fluoroalkylation Reagents for Organic Synthesis. *Chem. Rev.* **2015**, *115*, 765−825. Yu, X.; Dai, P.; Zhu, Y.-C.; Teng, P.; Zhang, W.-H.; Deng, C. Metal-free, Visible-Light-Mediated Direct Csp2−H Radical Mono- and Bis-trifluoromethylation of Coumarins and Bioactivity Evaluation. *ChemCatChem* **2018**, DOI: 10.1002/cctc.201801332.

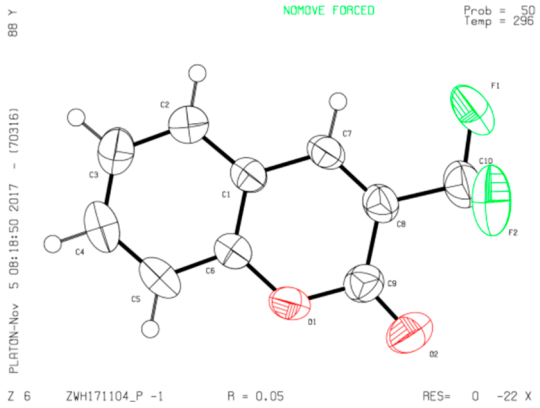
(6) (a) Tomashenko, O. A.; Grushin, V. V. Aromatic trifluoromethylation with metal complexes. *Chem. Rev.* **2011**, *111*, 4475−4521. (b) Rong, J.; Ni, C.; Hu, J. Metal-Catalyzed Direct Difluoromethylation Reactions. *Asian J. Org. Chem.* **2017**, *6*, 139−152.

(7) (a) Middleton, W. J. New fluorinating reagents. Dialkylaminosulfur fluorides. *J. Org. Chem.* **1975**, *40*, 574−578. (b) Lal, G. S.; Pez, G. P.; Pesaresi, R. J.; Prozonic, F. M.; Cheng, H. J. Bis(2-methoxyethyl)aminosulfur Trifluoride: A New Broad-Spectrum Deoxofluorinating Agent with Enhanced Thermal Stability. *J. Org. Chem.* **1999**, *64*, 7048−7054. (c) Yerien, D. E.; Vallejo, S. B.; Postigo, A. Difluoromethylation Reactions of Organic Compounds. *Chem. - Eur. J.* **2017**, *23*, 14676−14701.

(8) 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.

DOI: 10.1021/acs.orglett.8b02965
Org. Lett. XXXX, XXX, XXX−XXX

(9) Zhu, S. Q.; Xu, X. H.; Qing, F. L. Silver-mediated oxidative C-H difluoromethylation of phenanthridines and 1,10-phenanthrolines. *Chem. Commun.* **2017**, *53*, 11484−11487.
(10) Zhu, M.; Fu, W.; Wang, Z.; Xu, C.; Ji, B. Visible-light-mediated direct difluoromethylation of alkynoates: synthesis of 3-difluoromethylated coumarins. *Org. Biomol. Chem.* **2017**, *15*, 9057−9060.
(11) Sakamoto, R.; Kashiwagi, H.; Maruoka, K. The Direct C-H Difluoromethylation of Heteroarenes Based on the Photolysis of Hypervalent Iodine(III) Reagents That Contain Difluoroacetoxy Ligands. *Org. Lett.* **2017**, *19*, 5126−5129.
(12) Zhu, S.-Q.; Liu, Y.-L.; Li, H.; Xu, X.-H.; Qing, F.-L. Direct and Regioselective C-H Oxidative Difluoromethylation of Heteroarenes. *J. Am. Chem. Soc.* **2018**, *140*, 11613.
(13) (a) Yoon, T. P.; Ischay, M. A.; Du, J. Visible light photocatalysis as a greener approach to photochemical synthesis. *Nat. Chem.* **2010**, *2*, 527−532. (b) Narayanam, J. M. R.; Stephenson, C. R. Visible light photoredox catalysis: applications in organic synthesis. *Chem. Soc. Rev.* **2011**, *40*, 102−113. (c) Xuan, J.; Xiao, W. J. Visible-Light Photoredox Catalysis. *Angew. Chem., Int. Ed.* **2012**, *51*, 6828−6838. (d) Shi, L.; Xia, W. J. *Chem. Soc. Rev.* **2012**, *41*, 7687−7697. (e) Prier, C. K.; Rankic, D. A.; Macmillan, D. W. C. Visible Light Photoredox Catalysis with Transition Metal Complexes: Applications in Organic Synthesis. *Chem. Rev.* **2013**, *113*, 5322−5363. (f) Hari, D. P.; König, B. The Photocatalyzed Meerwein Arylation: Classic Reaction of Aryl Diazonium Salts in a New Light. *Angew. Chem., Int. Ed.* **2013**, *52*, 4734−4743. (g) Sun, C. L.; Shi, Z. J. Transition-Metal-Free Coupling Reactions. *Chem. Rev.* **2014**, *114*, 9219−9280. (h) Schultz, D. M.; Yoon, T. P. Solar Synthesis: Prospects in Visible Light Photocatalysis. *Science* **2014**, *343*, 1239176. (i) Beatty, J. W.; Stephenson, C. R. J. Amine Functionalization via Oxidative Photoredox Catalysis: Methodology Development and Complex Molecule Synthesis. *Acc. Chem. Res.* **2015**, *48*, 1474−1484.
(14) (a) Sun, X.; Yu, S. Visible-Light-Mediated Fluoroalkylation of Isocyanides with Ethyl Bromofluoroacetates: Unified Synthesis of Mono- and Difluoromethylated Phenanthridine Derivatives. *Org. Lett.* **2014**, *16*, 2938−2941. (b) Zhang, Z.; Tang, X.; Dolbier, W. R., Jr. Photoredox-Catalyzed Tandem Insertion/Cyclization Reactions of Difluoromethyl and 1, 1-Difluoroalkyl Radicals with Biphenyl Isocyanides. *Org. Lett.* **2015**, *17*, 4401−4403. (c) Lin, Q. Y.; Xu, X. H.; Zhang, K.; Qing, F. L. Visible-Light-Induced Hydrodifluoromethylation of Alkenes with a Bromodifluoromethylphosphonium Bromide. *Angew. Chem., Int. Ed.* **2016**, *55*, 1479−1483. (d) 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. (e) Noto, N.; Koike, T.; Akita, M. Diastereoselective Synthesis of CF_3- and CF_2H-Substituted Spiroethers from Aryl-Fused Cycloalkenylalkanols by Photoredox Catalysis. *J. Org. Chem.* **2016**, *81*, 7064−7071. (f) Fu, W.; Han, X.; Zhu, M.; Xu, C.; Wang, Z.; Ji, B.; Hao, X. Q.; Song, M. P. Visible-light-mediated radical oxydifluoromethylation of olefinic amides for the synthesis of CF_2H-containing heterocycles. *Chem. Commun.* **2016**, *52*, 13413−13416. (g) 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.
(15) (a) Wang, C. J.; Hsieh, Y. J.; Chu, C. Y.; Lin, Y. Y.; Tseng, T. H. Inhibition of cell cycle progression in human leukemia HL-60 cells by esculetin. *Cancer Lett.* **2002**, *183*, 163−168. (b) Zhao, Y.; Zheng, Q.; Dakin, K.; Xu, K.; Martinez, M. L.; Li, W. H. New Caged Coumarin Fluorophores with Extraordinary Uncaging Cross Sections Suitable for Biological Imaging Applications. *J. Am. Chem. Soc.* **2004**, *126*, 4653−4663. (c) Signore, G.; Nifosi, R.; Albertazzi, L.; Storti, B.; Bizzarri, R. Polarity-Sensitive Coumarins Tailored to Live Cell Imaging. *J. Am. Chem. Soc.* **2010**, *132*, 1276−1288. (d) Wang, C.; Wu, C.; Zhu, J.; Miller, R. H.; Wang, Y. Design, Synthesis, and Evaluation of Coumarin-Based Molecular Probes for Imaging of Myelination. *J. Med. Chem.* **2011**, *54*, 2331−2340. (e) Devji, T.; Reddy, C.; Woo, C.; Awale, S.; Kadota, S.; Carrico-Moniz, D. Pancreatic anticancer activity of a novel geranylgeranylated coumarin derivative. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 5770−5773.
(16) (a) Ben-Hur, E.; Carmichael, A.; Riesz, P.; Rosenthal, I. Photochemical generation of superoxide radical and the cytotoxicity of phthalocyanines. *Int. J. Radiat. Biol. Relat. Stud. Phys., Chem. Med.* **1985**, *48*, 837−846. (b) Ji, W.; Li, P.; Yang, S.; Wang, L. Visible-light-induced oxidative formylation of *N*-alkyl-*N*-(prop-2-yn-1-yl)anilines with molecular oxygen in the absence of an external photosensitizer. *Chem. Commun.* **2017**, *53*, 8482−8485. (c) Zhao, L.; Li, P.; Xie, X.; Wang, L. Selective remote C−H trifluoromethylation of aminoquinolines with CF_3SO_2Na under visible light irradiation in the absence of external photocatalyst. *Org. Chem. Front.* **2018**, *5*, 1689.
(17) (a) Liu, Y. F.; Chen, Z. Y.; Ng, T. B.; Zhang, J.; Zhou, M. G.; Song, F. P.; Lu, F.; Liu, Y. Z. Bacisubin, an antifungal protein with ribonuclease and hemagglutinating activities from *Bacillus subtilis* strain B-916. *Peptides* **2007**, *28*, 553−559. (b) Yu, X.; Wen, Y.; Liang, C. G.; Liu, J.; Ding, Y. B.; Zhang, W. H. Design, Synthesis and Antifungal Activity of Psoralen Derivatives. *Molecules* **2017**, *22*, 1672. (c) Dai, P.; Luo, K.; Yu, X.; Yang, W. C.; Wu, L.; Zhang, W. H. Tert-Butyl Nitrite Mediated Expeditious Methylsulfoxidation of Tetrazole-amines with DMSO: Metal-free Synthesis of Antifungal Active Methylsulfinyl-1*H*-tetrazole Derivatives. *Adv. Synth. Catal.* **2018**, *360*, 468−473.
(18) X-ray of **3a**.



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