Organic LETTERS
Letter
pubs.acs.org/OrgLett

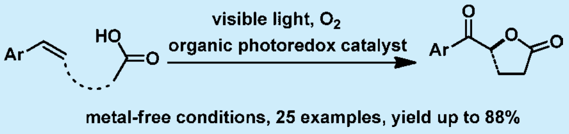
Preparation of α-Acyloxy Ketones via Visible-Light-Driven Aerobic Oxo-Acyloxylation of Olefins with Carboxylic Acids

Qing-Bao Zhang,[†] Yong-Liang Ban,[†] Da-Gang Zhou,[†] Pan-Pan Zhou,[†] Li-Zhu Wu,[‡] and Qiang Liu*,[†]

[†]State Key Laboratory of Applied Organic Chemistry, Lanzhou University, 222 South Tianshui Road, Lanzhou 730000, P. R. China
[‡]Key Laboratory of Photochemical Conversion and Optoelectronic Materials, Technical Institute of Physics and Chemistry, the Chinese Academy of Sciences, Beijing 100190, P. R. China

S *Supporting Information*

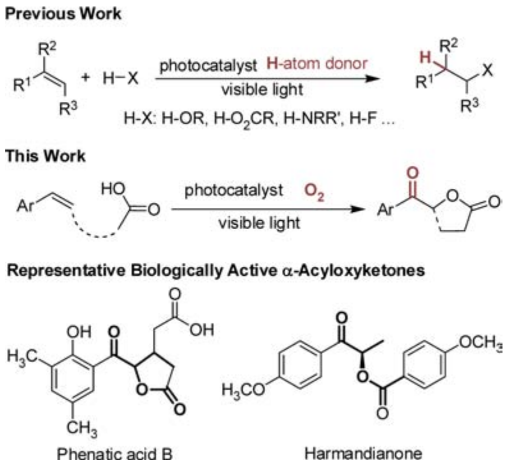
ABSTRACT: We developed a visible-light driven oxo-acyloxylation of aryl alkenes with carboxylic acids and molecular oxygen. A metal-free photoredox system, consisting of an acridinium photocatalyst, an organic base, and molecular sieve (MS) 4 Å, promotes chemoselective aerobic photooxidation of aryl alkenes. This approach may provide a green, practical, and metal-free protocol for a wide range of α-acyloxy ketones.



Selective aerobic oxidation is the most promising alternative approach to traditional oxidation processes.[1] However, numerous catalytic systems require expensive additives and/or harsh conditions to overcome the high energy barrier for the aerobic oxidation, thus diminishing the overall sustainability of these processes. Recently, visible-light photocatalysis has offered a technically attractive and energy-saving platform for the aerobic oxidation.[2a−l] With the aid of a photocatalyst excited by visible light, molecular oxygen can be activated to either a singlet oxygen or superoxide radical anion by an energy-transfer[2m,n] or electron-transfer process. Further reactions dominated by the reactive oxygen species (ROS) produced the meaningful transformations. For the visible-light-driven aerobic oxidations, the multiple parallel pathways of ROS give rise to the complexity of oxygenated products, which are obstacles to a more environmentally benign method. Therefore, new strategies to improve the chemoselectivity of visible-light-driven aerobic oxidation are highly desirable.

We have found that, for the compounds containing labile protons, the introduction of proper bases significantly contributes to the electron transfer from substrates to the excited organocatalysts, thereby suppressing the side reaction of singlet oxygen.[3] In continuation of our interest in the development of the chemoselective photocatalytic aerobic oxidation, we are intrigued by the unique property of 9-mesityl-10-methylacridinium perchlorate (Mes-Acr$^+$) as a photocatalyst. The mesityl group located at the 9-position of the acridinium ion dramatically increases the quantum yields for the formation of the electron-transfer state, which can inhibit the generation of singlet oxygen in the photocatalytic aerobic oxidation. Previous studies about Mes-Acr$^+$ demonstrated that the electron-transfer process dominates Mes-Acr$^+$ involved in photocatalytic aerobic oxidation.[4] Therefore, Mes-Acr$^+$ is a promising candidate for chemoselective photocatalytic aerobic oxidation of alkenes.

Scheme 1. Strategy for Biologically Active α-Acyloxyketones via Visible-Light Photocatalysis

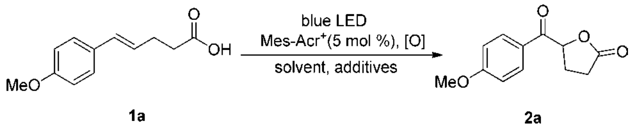


α-Acyloxyketones are basic structural elements in a variety of natural products and are prevalently used building blocks in synthetic organic chemistry (Scheme 1).[5] Besides, much effort has been devoted and valuable protocols have proven to be efficient for the preparation of α-acyloxyketones and their derivatives;[6] direct oxo-acyloxylation of alkenes with carboxylic acids is a potentially appealing method which provides a green approach toward the synthesis. It has been reported that α-acyloxyketones can be prepared by I_2-catalyzed oxo-acyloxylation of alkenes in the presence of stoichiometric amounts of *tert*-butyl hydroperoxide and Et_3N.[7] We envisioned that electron transfer from alkenes to the singlet electron-transfer state of Mes-Acr$^+$ can occur efficiently and generate the radical cation of alkenes under photocatalytic aerobic conditions.[8] Subsequent reaction of an alkene radical cation with carboxylic

Received: August 26, 2016
Published: September 29, 2016

acid and molecular oxygen should produce the desired α-acyloxyketones (Scheme 1).

Table 1. Optimization of Reaction Conditions



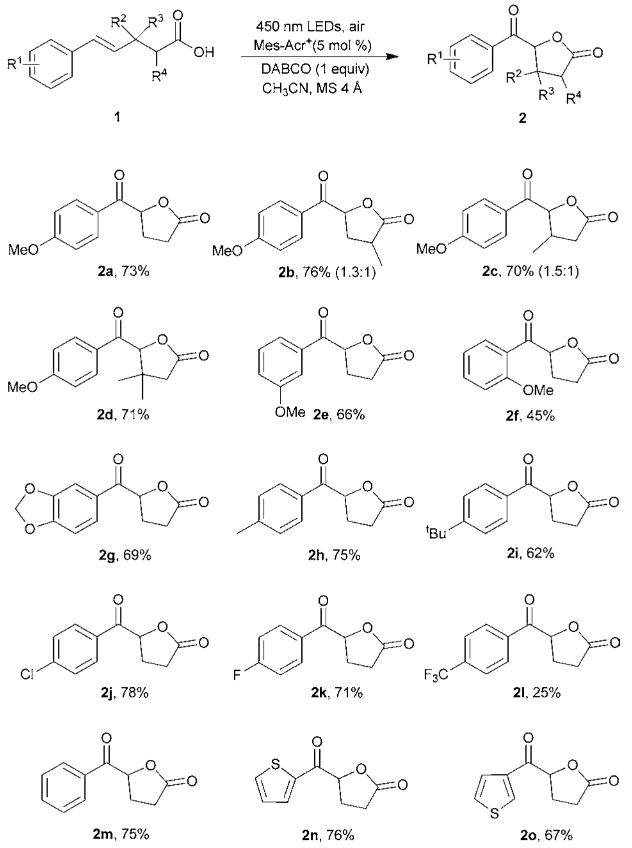
entry	solvent	additives	yield[b] (%)
1	CH_3CN	–	38
2	CH_3CN	K_2CO_3	42
3	CH_3CN	K_2HPO_4	45
4	CH_3CN	NaOH	50
5	CH_3CN	2,6-lutidine	62
6	CH_3CN	DABCO	67
7	DMF	DABCO	0
8	THF	DABCO	45
9	acetone	DABCO	57
10	DCE	DABCO	61
11[c]	CH_3CN	DABCO	62
12[d]	CH_3CN	DABCO	trace
13[e]	CH_3CN	DABCO, MS 4 Å	73
14[e,f]	CH_3CN	DABCO, MS 4 Å	0
15[g]	CH_3CN	DABCO, MS 4 Å	0

[a] Reaction conditions: **1a** (0.1 mmol), Mes-Acr$^+$ (5.0×10^{-3} mmol), additives (0.1 mmol without specially noted), solvent 3 mL, in air at room temperature, irradiated by 3 W blue LED for 48 h. [b] Isolated yield. [c] Pure O_2 was used instead of air. [d] 0.5 mmol of H_2O_2 was used instead of air. [e] 40 mg of MS 4 Å were added. [f] Reaction was carried out in the dark. [g] Reaction was carried out in the absence of Mes-Acr$^+$.

Thus, we chose 5-aryl-pent-4-enoic acid **1a** as the model substrate to explore the intramolecular aerobic oxo-acyloxylation. The results are listed in Table 1. An acetonitrile solution containing **1a** and Mes-Acr$^+$ (5 mol %) was irradiated by 3 W blue LEDs (λ = 450 nm) in an open vessel under ambient conditions for 48 h, and the desired oxolactone **2a** was obtained in 38% yield accompanied by the formation of 4-methoxybenzaldehyde and 4-methoxybenzoic acid, which may mainly be attributed to the decomposition of 1,2-dioxetane from the reaction between the **1a** radical cation and superoxide radical anion. Considering that a base might suppress the competing reaction by enhancing the nucleophilicity of the carboxylic acid moiety,[9] we tested a series of bases to initiate the reaction (entries 2–6). It was found that the yield of **2a** was improved in the presence of K_2CO_3, K_2HPO_4, NaOH, 2,6-lutidine, and DABCO (1,4-diazabicyclo[2.2.2]octane). After DABCO was chosen as the ideal base, several solvents, such as DMF, THF, acetone, and DCE were applied to this reaction to replace CH_3CN (entries 7–10). However, CH_3CN is still the best candidate solvent. Interestingly, the use of pure oxygen instead of air decreased the yield of the product (entry 11). Replacement of air by hydrogen peroxide failed to give the oxolactone (entry 12). Finally, it was found that the addition of molecular sieves (MS 4 Å) delivered **2a** in 73% yield (entry 13). A dark reaction and a reaction without the photocatalyst showed that both visible-light irradiation and Mes-Acr$^+$ are necessary for the desired reaction to proceed.

With optimized conditions in hand, we investigated the scope of the intramolecular olefin acids (Scheme 2). Thorpe–Ingold assistance is not required in the backbone of the molecule; **2a**–**2d** obtained nearly identical levels of reaction efficiency. For substrates bearing a methoxyl group at the aromatic ring, the order of the reactivity is para > meta > ortho in terms of yields (**2a**, **2e**, and **2f**). Electron-rich and halide substrates gave the corresponding oxolactones in good yields (**2g**–**2k** and **2m**). In contrast, the trifluoromethyl, a stronger electron-withdrawing group, retarded the reaction, and **2l** was obtained in low yield. We further probed the heteroaromatic carboxylic acid, and the corresponding oxolactones were acquired in good yields (**2n** and **2o**).

Scheme 2. . Oxylactonization of Olefin Acids[a]

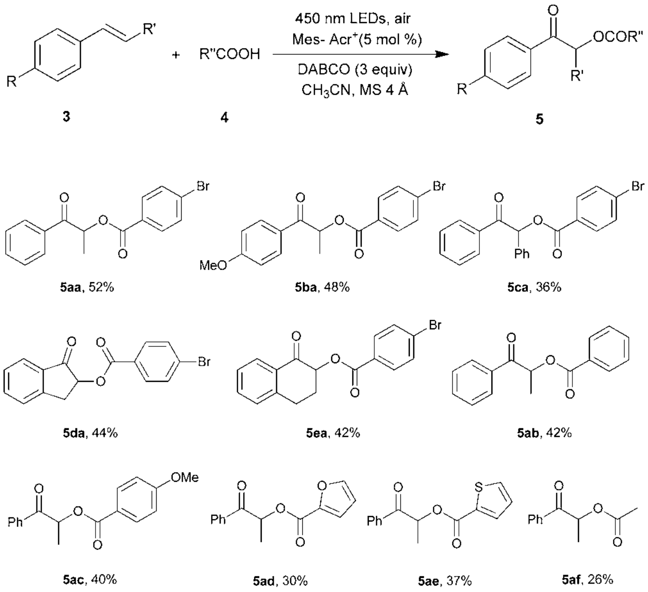


[a] Reaction conditions: a mixture of **1** (0.1 mmol), DABCO (0.1 mmol, 1.0 equiv), Acr$^+$-Mes (5.0 mol %) and MS 4 Å (40 mg) in dry CH_3CN (3.0 mL) was irradiated with a 3 W blue LED for 48 h at rt. [b] Isolated yield.

Next, we focused on the intermolecular oxo-acyloxylation of alkenes with carboxylic acids (Scheme 3). Initially, several different alkenes were examined. The less electron-rich β-methylstyrene (**3a**) resulted in similar yields, compared with electron-rich *p*-methoxy-β-methylstyrene (**3b**). Sterically hindered substrates gave the corresponding products, while slightly diminished yields were observed (**5ca**, **5da**, and **5ea**). We then turned to investigate the scope of carboxylic acids that could be employed. Aromatic carboxylic acids, which are substituted with electron-donating or electron-withdrawing groups, gave the desired products in moderate yield (**5aa**, **5ab**, and **5ac**). Heteroaromatic carboxylic acids and aliphatic carboxylic acids were poor substrates, and the corresponding products were in low yield (**5ad**, **5ae**, and **5af**).

It was found that arylaldehydes were formed as a byproduct in the lesser efficient oxo-acyloxylations. Fukuzumi et al. have reported that 1,2-dioxetane can be produced by the radical-coupling reaction between an alkene radical cation and a

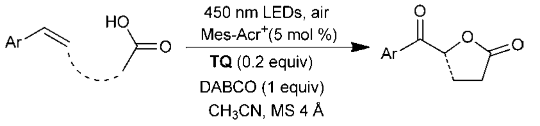
Scheme 3. **α-Oxo-acyloxylation of Olefins with Carboxylic Acids**[a]



[a] Reaction conditions: a mixture of **3** (0.2 mmol), **4** (2 mmol), DABCO (0.6 mmol, 3.0 equiv), Acr$^+$-Mes (5.0 mol %) and MS 4 Å (40 mg) in dry CH_3CN (3.0 mL) was irradiated with a 3 W blue LED for 48 h at rt. [b] Isolated yield.

superoxide radical anion.[10] The decomposition of 1,2-dioxetane will produce arylaldehyde and diminish the yield of the oxo-acyloxylated product. Therefore, if the generated superoxide radical anion during the photoreaction can be consumed, the yield of oxo-acyloxylation should be improved. We found that, under ambient air conditions, the addition of TQ (thymoquinone), a potent superoxide anion scavenger,[11] enhanced the yield of the oxo-acyloxylation remarkably. As shown in Scheme 4, for the substrates which were less efficient under standard conditions, the desired oxo-acyloxylated products were obtained in satisfactory yield except that the conversion was retarded.

Scheme 4. **Improved α-Oxo-acyloxylation with the Aid of Thymoquinone**



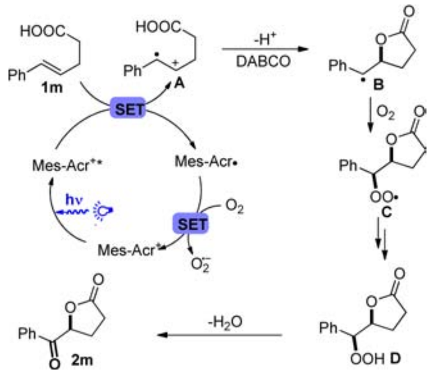
Product (conversion^b, yield^c): **2f** (65%, 82%); **2l** (47%, 88%); **5ab** (85%, 70%); **5ad** (81%, 62%); **5ae** (87%, 68%); **5af** (79%, 57%).

[a] Reaction conditions are similar to those mentioned in Schemes 2 and 3 except that 0.2 equiv of TQ was added. [b] The conversion of corresponding olefin acids or olefins. [c] Isolated yield based on the conversion.

The fluorescence of Mes-Acr$^+$ in air was quenched by 5-aryl-pent-4-enoic acid **1a** with a rate constant of 9.09×10^2 L·mol^{-1}, which is very close to the quenching rate constant of Mes-Acr$^+$ with **1a** under anaerobic conditions (1.05×10^3 L·mol^{-1}) (see Figure S2 in the Supporting Information (SI)). Recent mechanistic studies by Nicewicz et al. indicated that single electron transfer (SET) from alkenes (E_{ox} in the range +1.0 to +2.0 V) to the excited singlet state of Mes-Acr$^+$ (E^*_{red} = 2.08 V vs SCE) is thermodynamically feasible.[8] Therefore, the quenching should be attributed to the single electron transfer processes which generate an alkene radical cation. In addition, the adduct of 2,2,6,6-tetramethylpiperidine *N*-oxide (TEMPO) with the acyloxylated benzyl radical was detected when 2 equiv of TEMPO were introduced into the photocatalytic system (see SI for more details), indicating the nucleophilic attack of the alkene radical cation by the carboxyl moiety is plausible.

Our mechanistic hypothesis outlined in Scheme 5 proposes that, following addition of the alkene radical cation by the carboxyl anion with the aid of the base, the resulting radical **B** is captured by O_2 and populates peroxide radical **C**. Intermediate **C** further transforms into corresponding peroxide **D** through hydrogen atom abstraction or electron transfer following proton transfer.[12] Finally, the elimination of H_2O of **D** furnishes the desired product.[13] On the other hand, the reduced photocatalyst can be regenerated by molecular oxygen or peroxide radical **C** via SET. DFT calculations and photosensitizer experiments indicate that generation of **2m** from intermediate 1,2-dioxetane should not be mainly involved in the reaction (see SI for more details). For the substrates with less easily oxidized styrenes, a different pathway based on the formation of carboxyl radical seems also plausible.[14]

Scheme 5. **Proposed Mechanism**



In conclusion, we have developed a straightforward method for the synthesis of α-acyloxy ketones through oxo-acyloxylation of alkenes with carboxylic acids and molecular oxygen under visible-light irradiation. This protocol enables the conversion of a variety of readily available aryl alkenes in moderate to high yields. It is also recommended for its green and mild reaction conditions, such as the employment of metal-free catalyst Mes-Acr$^+$, ecologically benign oxidant molecular oxygen, and sustainable energy visible light. The further development of synthetically valuable visible-light-driven aerobic oxidations is a continuing effort in our laboratory.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b02560.

Experimental procedures and detailed characterization data of all compounds (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: liuqiang@lzu.edu.cn.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We are grateful for financial support from the Ministry of Science and Technology of China (2013CB834804), NSFC (21572090 and 21172102), and the fundamental research funds for the central universities (lzujbky-2015-49).

■ REFERENCES

(1) (a) Mallat, T.; Baiker, A. *Chem. Rev.* **2004**, *104*, 3037. (b) Shi, Z. Z.; Zhang, C.; Tang, C. C.; Jiao, N. *Chem. Soc. Rev.* **2012**, *41*, 3381. (c) Guo, Z.; Liu, B.; Zhang, Q. H.; Deng, W. P.; Wang, Y.; Yang, Y. H. *Chem. Soc. Rev.* **2014**, *43*, 3480. (d) Punniyamurthy, T.; Velusamy, S.; Iqbal, J. *Chem. Rev.* **2005**, *105*, 2329. (e) Stratakis, M.; Garcia, H. *Chem. Rev.* **2012**, *112*, 4469.

(2) (a) Fabry, D. C.; Ronge, M. A.; Zoller, J.; Rueping, M. *Angew. Chem., Int. Ed.* **2015**, *54*, 2801. (b) Zou, Y. − Q.; Lu, L.-Q.; Fu, L.; Chang, N. − J.; Rong, J.; Chen, J. − R.; Xiao, W. − J. *Angew. Chem., Int. Ed.* **2011**, *50*, 7171. (c) Su, F. Z.; Mathew, S. C.; Möhlmann, L.; Antonietti, M.; Wang, X. C.; Blechert, S. *Angew. Chem., Int. Ed.* **2011**, *50*, 657. (d) Lin, S. S.; Ischay, M. A.; Fry, G. C.; Yoon, T. P. *J. Am. Chem. Soc.* **2011**, *133*, 19350. (e) Maity, S.; Zheng, N. *Angew. Chem., Int. Ed.* **2012**, *51*, 9562. (f) Liu, Q.; Li, Y. − N.; Zhang, H. H.; Chen, B.; Tung, C. − H.; Wu, L. − Z. *Chem. - Eur. J.* **2012**, *18*, 620. (g) Yoo, W. − J.; Kobayashi, S. *Green Chem.* **2013**, *15*, 1844. (h) Pitre, S. P.; McTiernan, C. D.; Ismaili, H.; Scaiano, J. C. *J. Am. Chem. Soc.* **2013**, *135*, 13286. (i) Liu, J.; Liu, Q.; Yi, H.; Qin, C.; Bai, R. P.; Qi, X. T.; Lan, Y.; Lei, A. W. *Angew. Chem., Int. Ed.* **2014**, *53*, 502. (j) Zen, J. − M.; Liou, S. − L.; Kumar, A. S.; Hsia, M. − S. *Angew. Chem., Int. Ed.* **2003**, *42*, 577. (k) Xie, J.; Xue, Q. C.; Jin, H. M.; Li, H. M.; Cheng, Y. X.; Zhu, C. J. *Chem. Sci.* **2013**, *4*, 1281. (l) Romero, N. A.; Margrey, K. A.; Tay, N. E.; Nicewicz, D. A. *Science* **2015**, *349*, 1326. (m) Fan, W. G.; Li, P. X. *Angew. Chem., Int. Ed.* **2014**, *53*, 12201. (n) Meng, Q. − Y.; Lei, T.; Zhao, L. − M.; Wu, C. − J.; Zhong, J. − J.; Gao, X. − W.; Tung, C. − H.; Wu, L. − Z. *Org. Lett.* **2014**, *16*, 5968.

(3) (a) Song, T.; Zhou, B.; Peng, G. − W.; Zhang, Q. − B.; Wu, L. − Z.; Liu, Q.; Wang, Y. *Chem. - Eur. J.* **2014**, *20*, 678. (b) Wang, L.; Ma, Z. − G.; Wei, X. − J.; Meng, Q. − Y.; Yang, D. − T.; Du, S.-F.; Chen, Z. − F.; Wu, L. − Z.; Liu, Q. *Green Chem.* **2014**, *16*, 3752.

(4) (a) Fukuzumi, S.; Okamoto, K.; Tokuda, Y.; Gros, C. P.; Guilard, R. *J. Am. Chem. Soc.* **2004**, *126*, 17059. (b) Kotani, H.; Ohkubo, K.; Fukuzumi, S. *J. Am. Chem. Soc.* **2004**, *126*, 15999. (c) Griesbeck, A. G.; Cho, M. *Org. Lett.* **2007**, *9*, 611. (d) Fukuzumi, S.; Kotani, H.; Ohkubo, K.; Ogo, S.; Tkachenko, N. V.; Lemmetyinen, H. *J. Am. Chem. Soc.* **2004**, *126*, 1600. (e) Ohkubo, K.; Fujimoto, A.; Fukuzumi, S. *Chem. Commun.* **2011**, *47*, 8515.

(5) (a) Murahashi, S.; Saito, T.; Hanaoka, H.; Murakami, Y.; Naota, T.; Kumobayashi, H.; Akutagawa, S. *J. Org. Chem.* **1993**, *58*, 2929. (b) Akita, H.; Enoki, Y.; Yamada, Y.; Oishi, T. *Chem. Pharm. Bull.* **1989**, *37*, 2876. (c) Topczewski, J. J.; Neighbors, J. D.; Wiemer, D. F. *J. Org. Chem.* **2009**, *74*, 6965. (d) Kaila, N.; Janz, K.; DeBernardo, S.; Bedard, P. W.; Camphausen, R. T.; Tam, S.; Tsao, D. H.; Keith, J. C.; Nutter, C. N.; Shilling, A.; Sciame, R. Y.; Wang, Q. *J. Med. Chem.* **2007**, *50*, 21. (e) Ruiz, J. F. M.; Radics, G.; Windle, H.; Serra, H. O.; Simplício, A. L.; Kedziora, K.; Fallon, P. G.; Kelleher, D. P.; Gilmer, J. F. *J. Med. Chem.* **2009**, *52*, 3205. (f) Christoffers, J.; Baro, A.; Werner, T. *Adv. Synth. Catal.* **2004**, *346*, 143. (g) Fukuda, T.; Matsumoto, A.; Takahashi, Y.; Tomoda, H.; Ōmura, S. *J. Antibiot.* **2005**, *58*, 252. (h) Maneerat, W.; Phakhodee, W.; Ritthiwigrom, T.; Cheenpracha, S.; Deachathai, S.; Laphookhieo, S. *Phytochem. Lett.* **2013**, *6*, 18.

(6) (a) Uyanik, M.; Suzuki, D.; Yasui, T.; Ishihara, K. *Angew. Chem., Int. Ed.* **2011**, *50*, 5331. (b) Tada, N.; Cui, L.; Ishigami, T.; Ban, K.; Miura, T.; Uno, B.; Itoh, A. *Green Chem.* **2012**, *14*, 3007. (c) Reddi, R. N.; Malekar, P. V.; Sudalai, A. *Org. Biomol. Chem.* **2013**, *11*, 6477. (d) Guo, S. J.; Yu, J. − T.; Dai, Q.; Yang, H. T.; Cheng, J. *Chem. Commun.* **2014**, *50*, 6240. (e) Tellitu, I.; Serna, S.; Herrero, M. T.; Moreno, I.; Domínguez, E.; SanMartin, R. *J. Org. Chem.* **2007**, *72*, 1526.

(7) Reddi, R. N.; Prasad, P. K.; Sudalai, A. *Org. Lett.* **2014**, *16*, 5674.

(8) (a) Margrey, K. A.; Nicewicz, D. A. *Acc. Chem. Res.* **2016**, *49*, 1997. (b) Romero, N. A.; Nicewicz, D. A. *J. Am. Chem. Soc.* **2014**, *136*, 17024.

(9) (a) Zeller, M. A.; Riener, M.; Nicewicz, D. A. *Org. Lett.* **2014**, *16*, 4810. (b) Yasu, Y.; Arai, Y.; Tomita, R.; Koike, T.; Akita, M. *Org. Lett.* **2014**, *16*, 780.

(10) Ohkubo, K.; Nanjo, T.; Fukuzumi, S. *Org. Lett.* **2005**, *7*, 4265.

(11) Badary, O. A.; Taha, R. A.; El-Din, A. M. G.; Abdel-Wahab, M. H. *Drug Chem. Toxicol.* **2003**, *26*, 87.

(12) (a) Suga, K.; Ohkubo, K.; Fukuzumi, S. *J. Phys. Chem. A* **2003**, *107*, 4339. (b) Nobuta, T.; Hirashima, S. − I.; Tada, N.; Miura, T.; Itoh, A. *Org. Lett.* **2011**, *13*, 2576. (c) Sun, H. N.; Yang, C.; Gao, F.; Li, Z.; Xia, W. J. *Org. Lett.* **2013**, *15*, 624. (d) Keshari, T.; Yadav, V. K.; Srivastava, V. P.; Yadav, L. D. S. *Green Chem.* **2014**, *16*, 3986. (e) Yi, H.; Bian, C. J.; Hu, X.; Niu, L. B.; Lei, A. W. *Chem. Commun.* **2015**, *51*, 14046. (f) Wang, K.; Meng, L. G.; Zhang, Q.; Wang, L. *Green Chem.* **2016**, *18*, 2864. (g) Hering, T.; Slanina, T.; Hancock, A.; Wille, U.; König, B. *Chem. Commun.* **2015**, *51*, 6568. (h) Song, H. − T.; Ding, W.; Zhou, Q. Q.; Liu, J.; Lu, L. − Q.; Xiao, W. − J. *J. Org. Chem.* **2016**, *81*, 7250. (i) Zhang, M. L.; Duan, Y. Q.; Li, W. P.; Cheng, Y. X.; Zhu, C. J. *Chem. Commun.* **2016**, *52*, 4761. (j) Nair, V.; Nair, L. G.; Panicker, S. B.; Sheeba, V.; Augustine, A. *Chem. Lett.* **2000**, *29*, 584.

(13) Photoreduction of **D** following alkoxy radical rearrangement could also produce **2m**; see: Konya, K. G.; Paul, T.; Lin, S.; Lusztyk, J.; Ingold, K. U. *J. Am. Chem. Soc.* **2000**, *122*, 7518.

(14) (a) Cassani, C.; Bergonzini, G.; Wallentin, C.-J. *Org. Lett.* **2014**, *16*, 4228. (b) Noble, A.; McCarver, S. J.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2015**, *137*, 624. (c) Ramirez, N. P.; Bosque, I.; Gonzalez-Gomez, J. C. *Org. Lett.* **2015**, *17*, 4550.