Organic LETTERS

Letter

pubs.acs.org/OrgLett

Direct and Oxidant-Free Electron-Deficient Arylation of *N*-Acyl-Protected Tetrahydroisoquinolines

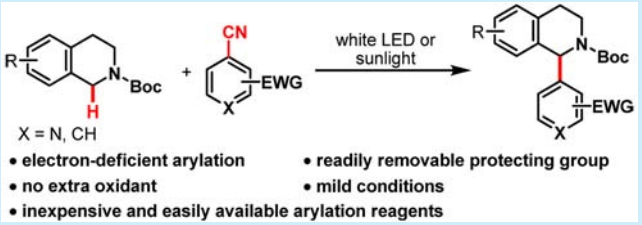
Changcun Yan,[†] Lili Li,[†] Yuxiu Liu,[†] and Qingmin Wang*[,†,‡]

[†]State Key Laboratory of Elemento-Organic Chemistry, Research Institute of Elemento-Organic Chemistry, Nankai University, Tianjin 300071, People's Republic of China

[‡]Collaborative Innovation Center of Chemical Science and Engineering (Tianjin), Tianjin 300071, People's Republic of China

Supporting Information

ABSTRACT: A direct α-C−H electron-deficient arylation reaction of *N*-acyl protected tetrahydroisoquinolines is developed via visible light photoredox catalysis. The reaction was performed under mild conditions without any extra oxidant and could also proceed smoothly when sunlight was used as the light source. The protecting group on the tetrahydroisoquinolines could be removed easily.



α-Aryl tetrahydroisoquinolines (THIQs) represent ubiquitous structural motifs in numerous biologically active natural products and synthetic pharmaceuticals (Figure 1).[1] Therefore,

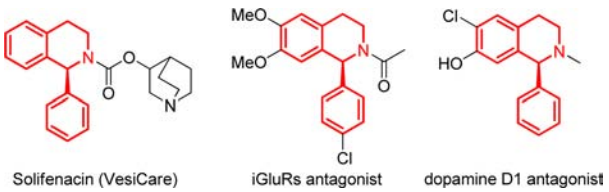


Figure 1. Representative α-Aryl THIQs.

a number of methodologies for the efficient preparation of such compounds have been developed,[2] such as the Pictet−Spengler condensation and the Bischler−Napieralski cyclization/reduction sequence which were mostly used. Direct oxidative α-C−H arylation of THIQs presents a new synthetic strategy since the past decade, which can avoid prior installation of activating groups.[3] However, the *N*-aryl group can only be removed under very harsh conditions resulting in poor functional group tolerance and, therefore, limits its synthetic utility.[4]

In recent years, direct arylation of readily removable acyl moieties protected THIQs has attracted the attention of organic chemists and several examples have been disclosed.[5] However, in the majority of them only highly electron-rich arenes or heteroarenes can be used as arylation reagents.[5a−d] Last year, the Liu group achieved asymmetric C−H arylation of *N*-acyl THIQs using arylboronic acids as the arylation reagent,[5e] but electron-deficient arylation reagents were still inapplicable. The root of the problem is that electron-deficient arylation reagents are not suitable for nucleophilic addition reactions with the unstable key *N*-acyliminium intermediate. This critical defect seriously hampers the application of these methods in medicinal development and structure−activity relationship study in which electronically varied substituents were needed. In addition, the formation of the *N*-acyliminium intermediate needs to consume stoichiometric oxidant, such as triphenylcarbenium perchlorate,[5d] DDQ,[5e] peroxide,[5a,b] or inorganic salts;[5c] beyond that, the generated nonvolatile reduced species increases the complexity of product purification. To solve these problems, we decided to develop an oxidant-free method for direct electron-deficient arylation of *N*-acyl-protected tetrahydroisoquinolines.

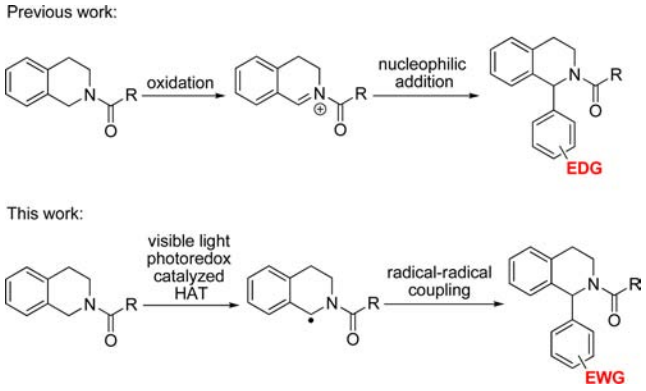
Our initial motivation stemmed from the notion that a radical−radical coupling reaction is rather insensitive to the electronic effect of reactants and that the emerging field of photoredox catalysis has recently provided an effective way of generating radicals from bench-stable precursors under mild conditions.[6] In 2011, the MacMillan group found, unexpectedly, that electron-deficient group substituted benzonitriles could be reduced by photoexcited tris(2-phenylpyridinato-C_2,*N*)iridium(III) ($Ir(ppy)_3$) to form the corresponding arene radical anion which would undergo a radical−radical coupling reaction with another radical.[7] So, we speculate that if the corresponding radical intermediates are generated from the *N*-acyl THIQs, the electron-deficient arylation will be realized (Scheme 1). The visible light photoredox catalyzed hydrogen atom transfer (HAT) reaction developed in 2014 gave us a chance. Namely, an HAT catalyst such as thiols (R−SH) can be oxidized by the photoredox catalyst to generate a thiyl radical (R−S·) which can further abstract a H· from certain substrates to give the corresponding radical intermediates.[8]

A detailed mechanism for the envisioned radical−radical coupling is depicted in Scheme 2 which contains two synergistic catalytic cycles. The photoredox catalytic cycle is initiated via excitation of photoredox catalyst $Ir^{III}(ppy)_3$ to give the excited state $*Ir^{III}(ppy)_3$.[9] Electron-deficient benzonitriles

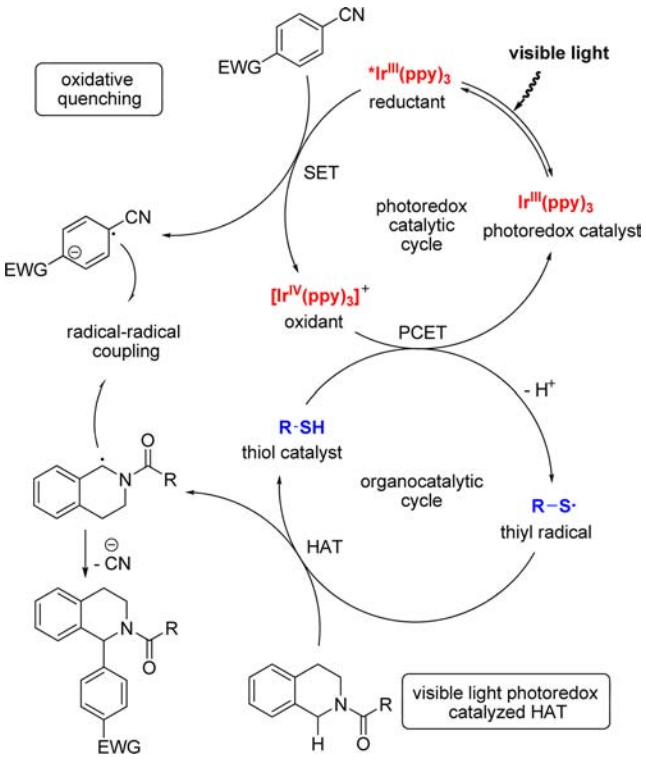
Received: August 5, 2016
Published: September 6, 2016

DOI: 10.1021/acs.orglett.6b02326
Org. Lett. 2016, 18, 4686−4689

Scheme 1. α-C−H Arylation of *N*-Acyl THIQs



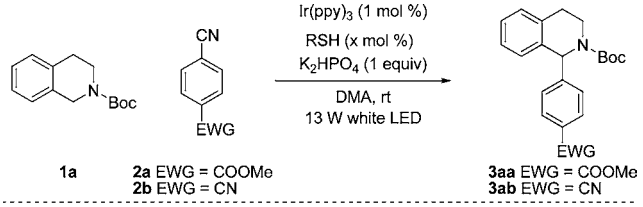
Scheme 2. Mechanism of the Arylation Reaction



(for example, reduction potential $E_{1/2}$ = −1.61 V vs SCE for 1,4-dicyanobenzene in CH_3CN)[10] can be reduced by $*Ir^{III}(ppy)_3$ [$E_{1/2}(Ir^{IV}/*Ir^{III})$ = −1.73 V vs SCE in CH_3CN][9] via SET to generate the corresponding radical anion along with oxidant $Ir^{IV}(ppy)_3$. In the presence of a base, the HAT catalytic cycle can be initiated via single-electron oxidation of the HAT catalyst thiol R−SH ($E_{1/2}$ = +1.12 V vs SCE for butanethiol and $E_{1/2}$ = −0.85 V vs SCE for butanethiolate in CH_3CN)[11] by $Ir^{IV}(ppy)_3$ [$E_{1/2}(Ir^{IV}/Ir^{III})$ = +0.77 V vs SCE in CH_3CN][9] via a PCET mechanism[12] to give the thiyl radical R−S· along with the regenerated $Ir^{III}(ppy)_3$ to complete the photoredox catalytic cycle. R−S· (S−H BDE = 365.7 kJ/mol)[13] would readily abstract an α-hydrogen atom from the *N*-acyl THIQs substrate (α-C−H BDE < 345.6 kJ/mol)[13] to provide the corresponding radical intermediates along with regenerated HAT catalyst R−SH to complete the HAT catalytic cycle.[14] At this time, an intermolecular radical−radical coupling would serve to forge the new C−C bond prior to rapid elimination of cyanide to form the desired product of electron-deficient arylated *N*-acyl THIQ. Homodimerization coupling would not happen because of the steric effect.

In our work, first, we used a commercially available 13 W white LED bulb as the light source for simulating sunlight and *N*-Boc THIQ (**1a**, 3 equiv) and methyl 4-cyanobenzoate (**2a**, 1 equiv) as the substrates to optimize the reaction conditions (Table 1). After a preliminary screening (see Supporting Information), a 69% yield was obtained when $Ir(ppy)_3$ (1 mol %), methyl thioglycolate (A, 20 mol %), K_2HPO_4 (1 equiv), and *N*,*N*-dimethylaniline (DMA) were used as the solvent (entry 1). Then, different thiols were examined. The results showed that 1-Dodecanethiol (B) and a type of 1-thio-glucose C gave lower yields of 14% and 51% respectively (entries 2 and 3). As in the case of A, triphenylsilanethiol (D) gave a 69% yield as well (entry 4). When terephthalonitrile (**2b**) was used as the substrate, D was better than A in catalyzing this reaction, and a high yield of 93% was obtained when D was used as the HAT catalyst (entries 5 and 6). Further screening indicated that just 2 equiv of **1a** were sufficient (entry 7 and Supporting Information). We also found that reducing the amount of D to 5 mol % even gave a high yield of 95% (entries 7−10). When the photoredox catalyst, HAT catalyst, or light was absent, the reaction could not occur or just gave trace product (entries 11−13). Base proved to be unnecessary, but a higher yield was obtained when K_2HPO_4 was added (entries 9 and 14). Finally, we found that the yield of the reaction was obviously reduced

Table 1. Optimization of Reaction Conditions[a]



entry	berizonitriles	RSH	*x*	yield (%)[b]
1	**2a**	A	20	69
2	**2a**	B	20	14
3	**2a**	C	20	51
4	**2a**	D	20	69
5	**2b**	A	20	75
6	**2b**	D	20	93
7[c]	**2b**	D	20	94
8[c]	**2b**	D	10	94
9[c]	**2b**	**D**	**5**	**95**
10[c]	**2b**	D	2	81
11[c,d]	**2b**	D	5	<5
12[c]	**2b**	none	–	NR
13[c,e]	**2b**	D	5	NR
14[c,f]	**2b**	D	5	78
15[c,g]	**2b**	D	5	37

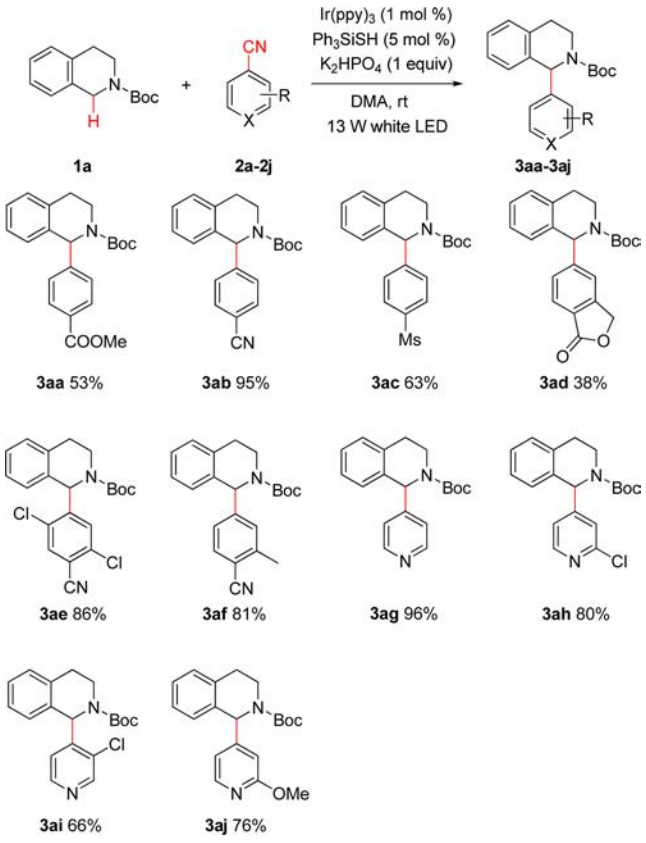
[a]Reaction conditions: **1a** (1.2 mmol, 3 equiv), **2a** or **2b** (1 equiv), $Ir(ppy)_3$ (1 mol %), RSH, K_2HPO_4 (1 equiv) in DMA (2 mL) irradiated by a 13 W white LED bulb at rt under Ar after being degassed unless otherwise noted. [b]Isolated yield; NR, no reaction. [c]**1a** (0.8 mmol, 2 equiv). [d]No $Ir(ppy)_3$. [e]No light. [f]No K_2HPO_4. [g]Not degassed.

DOI: 10.1021/acs.orglett.6b02326
Org. Lett. 2016, 18, 4686−4689

and complex products were obtained if the reaction system was not degassed (entry 15).

With the optimized conditions in hand, we then investigated the scope of the arene coupling partner of the reaction. As shown in Scheme 3, a range of benzonitriles were examined.

Scheme 3. Reaction Scope with Different Aryl Cyanides[a,b]

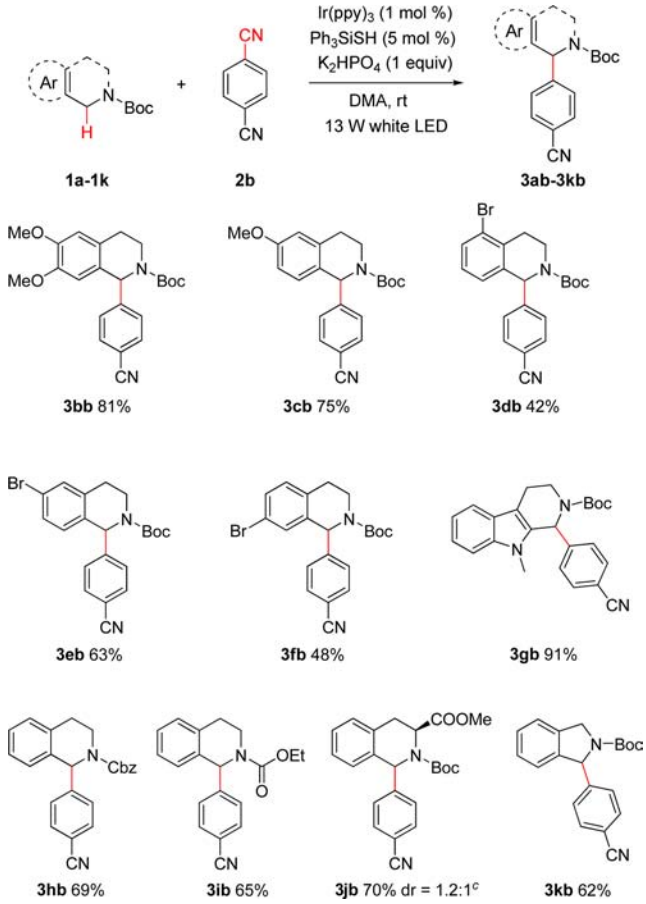


[a]Reaction conditions: **1a** (1.2 mmol, 2 equiv), **2** (1 equiv), $Ir(ppy)_3$ (1 mol %), Ph_3SiSH (5 mol %), K_2HPO_4 (1 equiv) in DMA (2 mL) irradiated by a 13 W white LED bulb at rt under Ar after degassed unless otherwise noted. [b]Isolated yield.

The reaction of acyl, cyano, and sulfonyl substituted benzonitriles all gave corresponding products in high or moderate yields (**3aa**−**3ac**, 53−95% yield). Moreover, the lactone group on the aryl ring could be accommodated by these mild reaction conditions as well but with a lower yield (**3ad**, 38% yield). As expected, polysubstituted benzonitriles, such as 2,5-dichloroterephthalonitrile, were viable arylation reagents (**3ae**, 86% yield). When unsymmetrical dicyanoarene **2f** was used, an excellent regioselectivity was observed because of the steric effect. In addition, a variety of heteroaromatic nitriles had also been found to be suitable substrates. 4-Cyanopyridyl, 2-chloro-4-cyanopyridyl, and 3-chloro-4-cyanopyridyl substituted products were obtained in good yields of 66−96% (**3ag**−**3ai**). An electron-donating methoxy group substituted 4-cyanopyridine underwent the reaction in good yield as well (**3aj**, 76% yield).

We next examined the structural diversity of *N*-acyl THIQs in our new protocol. As shown in Scheme 4, dimethoxy and monomethoxy substituted substrates were arylated smoothly in good yields (**3bb** and **3cb**, 81% and 75% yield). When *N*-Boc THIQs were substituted by bromo in different positions, the reactions could proceed well (**3db**−**3fb**, 42−63% yield). For

Scheme 4. Reaction Scope with Different N-Acyl THIQs[a,b]



[a]Reaction conditions: **1** (1.2 mmol, 2 equiv), **2b** (1 equiv), $Ir(ppy)_3$ (1 mol %), Ph_3SiSH (5 mol %), K_2HPO_4 (1 equiv) in DMA (2 mL) irradiated by a 13 W white LED bulb at rt under Ar after being degassed unless otherwise noted. [b]Isolated yield. [c]Diastereoisomer ratios (dr) determined by ^1H NMR.

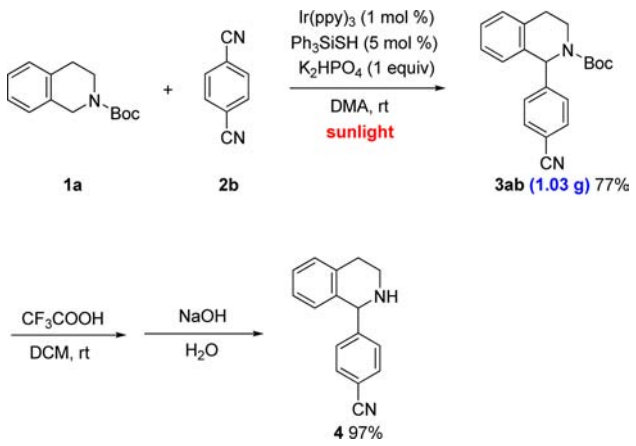
tetrahydro-*β*-carboline derivative **3g**, the arylated product **3gb** was obtained in a high yield of 91%. Other protecting groups such as carboxybenzyl and carbethoxy can be tolerated under the reaction conditions (**3hb** and **3ib**). At the C3 position, the ester group was also tolerated, and the corresponding product **3jb** was obtained as the only product, demonstrating the perfect regioselectivity of the reaction. In addition, the low diastereoselectivity of **3jb** (dr = 1.2:1) complied with the characteristic radical−radical coupling reaction. Besides *N*-acyl THIQs, *N*-acyl isoindolines can also be *α*-arylated under the reaction conditions (**3kb**, 62% yield).

To demonstrate the practicality of our method, we performed the electron-deficient arylation reaction under sunlight on a gram scale (Scheme 5). The product was obtained in 77% yield. Additionally, the Boc group could be easily removed in an acidic condition.

In conclusion, we have developed a visible light photoredox catalyzed direct *α*-C−H electron-deficient arylation reaction of N-acyl THIQs that proceed under mild conditions without any extra oxidant. A series of electron-deficient benzonitriles and heteroaromatic nitriles can be used as the arylation reagents. The reaction can also be performed under sunlight, and the protecting groups can be removed easily. We anticipate our

DOI: 10.1021/acs.orglett.6b02326
Org. Lett. 2016, 18, 4686−4689

Scheme 5. Large-Scale α-C−H Arylation of *N*-Boc THIQ under Sunlight and Deprotection of the Product



new method will find broad application in pharmaceutical and agricultural agent development.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b02326.

Detailed experimental procedures and characterization data of relevant compounds (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: wangqm@nankai.edu.cn, wang98@263.net

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We are grateful to the National Natural Science Foundation of China (21132003, 21421062, 21372131) and the Specialized Research Fund for the Doctoral Program of Higher Education (20130031110017) and the Tianjin Natural Science Foundation (16JCZDJC32400) for generous financial support for our programs.

■ REFERENCES

(1) (a) Shamma, M.; Moniot, J. T. *The Isoquinoline Alkaloids, Chemistry and Pharmacology*; Academic Press: New York and London, 1972. (b) Ohtake, A.; Ukai, M.; Hatanaka, T.; Kobayashi, S.; Ikeda, K.; Sato, S.; Miyata, K.; Sasamata, M. *Eur. J. Pharmacol.* **2004**, *492*, 243. (c) Cardozo, L.; Lisec, M.; Millard, R.; Trip, O. V.; Kuzmin, I.; Drogendijk, T. E.; Huang, M.; Ridder, A. M. *J. Urol.* **2004**, *172*, 1919. (d) Smulders, R. A.; Krauwinkel, W. J.; Swart, P. J.; Huang, M. *J. Clin. Pharmacol.* **2004**, *44*, 1023.

(2) (a) Chrzanowska, M.; Rozwadowska, M. D. *Chem. Rev.* **2004**, *104*, 3341. (b) Polniaszek, R. P.; Kaufman, C. R. *J. Am. Chem. Soc.* **1989**, *111*, 4859. (c) Fishlock, D.; Williams, R. M. *J. Org. Chem.* **2008**, *73*, 9594.

(3) For recent selected reviews and examples of oxidative C−H arylation of tetrahydroisoquinolines see: (a) Li, Z.; Bohle, D. S.; Li, C.-J. *Proc. Natl. Acad. Sci. U. S. A.* **2006**, *103*, 8928. (b) Li, C.-J. *Acc. Chem. Res.* **2009**, *42*, 335. (c) Scheuermann, C. J. *Chem. - Asian J.* **2010**, *5*, 436. (d) Li, Z. P.; Li, C.-J. *J. Am. Chem. Soc.* **2005**, *127*, 6968. (e) Baslé, O.; Li, C.-J. *Org. Lett.* **2008**, *10*, 3661. (f) Muramatsu, W.; Nakano, K.; Li, C.-J. *Org. Lett.* **2013**, *15*, 3650. (g) Muramatsu, W.; Nakano, K.; Li, C.-J. *Org. Biomol. Chem.* **2014**, *12*, 2189.

(4) (a) Girard, N.; Gautier, C.; Malassene, R.; Hurvois, J.-P.; Moinet, C. *Synlett* **2004**, 2005. (b) Girard, N.; Hurvois, J.-P.; Toupet, L.; Moinet, C. *Synth. Commun.* **2005**, *35*, 711. (c) Girard, N.; Hurvois, J.-P. *Tetrahedron Lett.* **2007**, *48*, 4097.

(5) For selected recent examples of α-C−H arylation reactions of *N*-acyl THIQs, see: (a) Ghobrial, M.; Harhammer, K.; Mihovilovic, M. D.; Schnurch, M. *Chem. Commun.* **2010**, *46*, 8836. (b) Ghobrial, M.; Schnurch, M.; Mihovilovic, M. D. *J. Org. Chem.* **2011**, *76*, 8781. (c) Chen, W. F.; Zheng, H. B.; Pan, X. H.; Xie, Z. Y.; Zan, X.; Sun, B.; Liu, L.; Lou, H. X. *Tetrahedron Lett.* **2014**, *55*, 2879. (d) Xie, Z. Y.; Liu, L.; Chen, W. F.; Zheng, H. B.; Xu, Q. Q.; Yuan, H. Q.; Lou, H. X. *Angew. Chem., Int. Ed.* **2014**, *53*, 3904. (e) Liu, X. G.; Sun, S. T.; Meng, Z. L.; Lou, H. X.; Liu, L. *Org. Lett.* **2015**, *17*, 2396. For selected recent examples of direct α-C−H functionalization of *N*-acyl heterocycles, see: (f) Richter, H.; Mancheno, O. G. *Eur. J. Org. Chem.* **2010**, 4460. (g) Richter, H.; Frohlich, R.; Daniliuc, C.-G.; Mancheno, O. G. *Angew. Chem., Int. Ed.* **2012**, *51*, 8656. (h) Schweitzer-Chaput, B.; Klussmann, M. *Eur. J. Org. Chem.* **2013**, *2013*, 666. (i) Liu, X. G.; Sun, B.; Xie, Z. Y.; Qin, X. J.; Liu, L.; Lou, H. X. *J. Org. Chem.* **2013**, *78*, 3104. (j) Yan, C. C.; Liu, Y. X.; Wang, Q. M. *RSC Adv.* **2014**, *4*, 60075. (k) Liu, X. G.; Meng, Z. L.; Li, C. K.; Lou, H. X.; Liu, L. *Angew. Chem., Int. Ed.* **2015**, *54*, 6012. (l) Sun, S. T.; Li, C. K.; Floreancig, P. E.; Lou, H. X.; Liu, L. *Org. Lett.* **2015**, *17*, 1684. (m) Yan, C. C.; Liu, Y. X.; Wang, Q. M. *Org. Lett.* **2015**, *17*, 5714. (n) Xie, Z. Y.; Zan, X.; Sun, S. T.; Pan, X. H.; Liu, L. *Org. Lett.* **2016**, *18*, 3944.

(6) For recent selected reviews of visible light photoredox catalysis, see: (a) Shi, L.; Xia, W. J. *Chem. Soc. Rev.* **2012**, *41*, 7687. (b) Xuan, J.; Xiao, W. J. *Angew. Chem., Int. Ed.* **2012**, *51*, 6828. (c) Prier, C. K.; Rankic, D. A.; MacMillan, D. W. C. *Chem. Rev.* **2013**, *113*, 5322. (d) Schultz, D. M.; Yoon, T. P. *Science* **2014**, *343*, 1239176. (e) Xie, J.; Jin, H. M.; Xu, P.; Zhu, C. J. *Tetrahedron Lett.* **2014**, *55*, 36. (f) Skubi, K. L.; Blum, T. R.; Yoon, T. P. *Chem. Rev.* **2016**, DOI: 10.1021/acs.chemrev.6b00018. (g) Romero, N. A.; Nicewicz, D. A. *Chem. Rev.* **2016**, DOI: 10.1021/acs.chemrev.6b00057.

(7) McNally, A.; Prier, C. K.; MacMillan, D. W. C. *Science* **2011**, *334*, 1114.

(8) (a) Qvortrup, K.; Rankic, D. A.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2014**, *136*, 626. (b) Hager, D.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2014**, *136*, 16986. (c) Cuthbertson, J. D.; MacMillan, D. W. C. *Nature* **2015**, *519*, 74.

(9) Flamigni, L.; Barbieri, A.; Sabatini, C.; Ventura, B.; Barigelletti, F. *Top. Curr. Chem.* **2007**, *281*, 143.

(10) Mori, Y.; Sakaguchi, W.; Hayashi, H. *J. Phys. Chem. A* **2000**, *104*, 4896.

(11) Ogawa, K. A.; Boydston, A. J. *Org. Lett.* **2014**, *16*, 1928.

(12) Tarantino, K. T.; Liu, P.; Knowles, R. R. *J. Am. Chem. Soc.* **2013**, *135*, 10022.

(13) Luo, Y. R. *Handbook of Bond Dissociation Energies in Organic Compounds*; CRC Press: Boca Raton, FL, 2003.

(14) Roberts, B. P. *Chem. Soc. Rev.* **1999**, *28*, 25.

DOI: 10.1021/acs.orglett.6b02326
Org. Lett. 2016, 18, 4686−4689