Organic LETTERS

Letter

pubs.acs.org/OrgLett

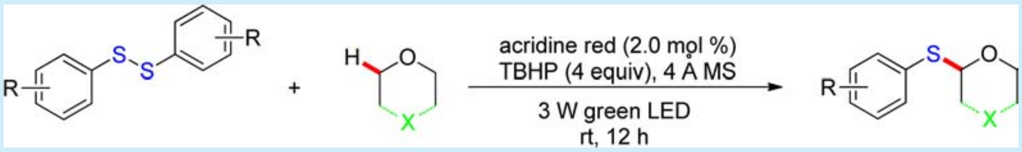
# Visible-Light-Induced Direct Thiolation at α-C($sp^3$)−H of Ethers with Disulfides Using Acridine Red as Photocatalyst

Xianjin Zhu,[†] Xiaoyu Xie, Pinhua Li,*[,†] Jianqi Guo,[†] and Lei Wang*[,†,‡]

[†]Department of Chemistry, Huaibei Normal University, Huaibei, Anhui 235000, P.R. China

[‡]State Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, Shanghai 200032, P.R. China

S *Supporting Information*



**ABSTRACT:** A simple and efficient method for the preparation of α-arylthioethers through a visible-light-induced direct thiolation at α-C($sp^3$)−H of ethers with diaryl disulfides was developed using acridine red as a novel photocatalyst. The reactions occurred at ambient conditions and generated the corresponding products in good to excellent yields, ignoring steric effect of disulfides.

The development of mild and efficient methods for the formation of C−S bonds has received significant attention because these bonds are widely found in many important biological and pharmaceutical compounds.[1] The classical constructions of C−S bonds include direct coupling of organic halides with thiols, and addition of thiols to unsaturated carbon−carbon bonds.[2] Recently, the direct C−H functionalization[3] and decarboxylative C−S coupling reactions[4] for their construction have been developed. However, the synthesis of C−S bonds through C($sp^3$)−H functionalization has been less explored. It is well-known that transformation of the inert C($sp^3$)−H bond into more useful molecules has attracted much attention in the past years. Notably, great progress has been achieved in the functionalization of α-C($sp^3$)−H bonds of ethers, alcohols,[5] and amines.[6] In general, tetrahydrofuran (THF) and its derivatives are usually accessible through their α-C($sp^3$)−H functionalization, such as Fe-catalyzed CDC reaction of THF with malonates,[7] Ni-catalyzed arylation of THF,[8] TBHP-promoted reaction of phenylacetylene with THF,[9] and others.[10] It was worth noting that the thiolation of α-C($sp^3$)−H bond of ethers and amines has also been achieved. Xiang and co-workers reported a TBHP-mediated oxidative thiolation of α-C($sp^3$)−H bond of amide with disulfides in 2011,[11] and an oxidative α-C($sp^3$)−H thiolation of ethers with disulfides under metal free conditions in 2013.[12] However, harsh reaction conditions, overstoichiometric amounts of oxidants, and high reaction temperature are required in the most cases. It is desirable to develop more practical methods for the synthesis of α-arylthioethers from simple and readily available precursors under mild reaction conditions.

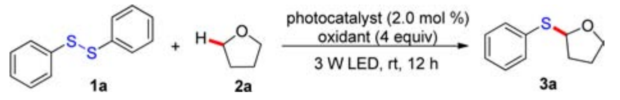
Sunlight is a unique natural resource. Early in 1912, a pioneering chemist Ciamician published a perspective of converting solar energy into chemical energy for chemical transformations by using sunlight as a safe, abundant, inexpensive, and renewable energy source.[13] Since the disclosure of visible-light-induced organic reactions by MacMillan,[14] extensive efforts have been made, and it has emerged as one of the most active research topics in organic synthesis. After that, a number of efficient and versatile protocols have been explored.[15] More recently, Wang and co-workers realized a relatively long-lived α-oxy radical species via external oxidation of α-C($sp^3$)−H of ethers by visible light stimulation and organic dye sensitization, subsequent radical addition to alkyne.[16] On the basis of our exploration in photocatalysis and inspired by reported results,[17] herein we report a simple and efficient protocol to access α-arylthioethers via visible-light-induced direct thiolation at α-C($sp^3$)−H of ethers with diaryl disulfides in the presence of acridine red. To the best of our knowledge, it is the first example of coupling reaction through energy transfer pathway using acridine red as photocatalyst under visible light irradiation and ambient conditions.

Initially, diphenyl disulfide (**1a**) and THF (**2a**) were chosen as substrates for the optimization of reaction conditions. It was found that the reaction afforded the corresponding product **3a** in 18% yield in the presence of Ru(bpy)$_3$Cl$_2$ as photocatalyst, and TBHP as oxidant under 3 W blue LED (530−535 nm) irradiation for 12 h, but Ru(phen)$_3$Cl$_2$ failed (Table 1, entries 1 and 2). Organic dyes including eosin Y, rose bengal, fluorescein, rhodamine B, and acridine red were employed in the reaction, as shown in Table 1. Most of the selected organic dyes showed catalytic reactivity, while rose bengal did not (entries 3−7). Among the tested organic dyes, acridine red exhibited the highest activity. Comparing with eosin Y, rose bengal, fluorescein, and rhodamine B, the advantages of acridine red

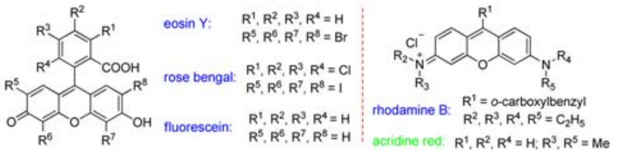
**Received:** January 29, 2016
**Published:** March 22, 2016

DOI: 10.1021/acs.orglett.6b00304
*Org. Lett.* 2016, 18, 1546−1549

**Table 1. Optimization of the Reaction Conditions**[a]



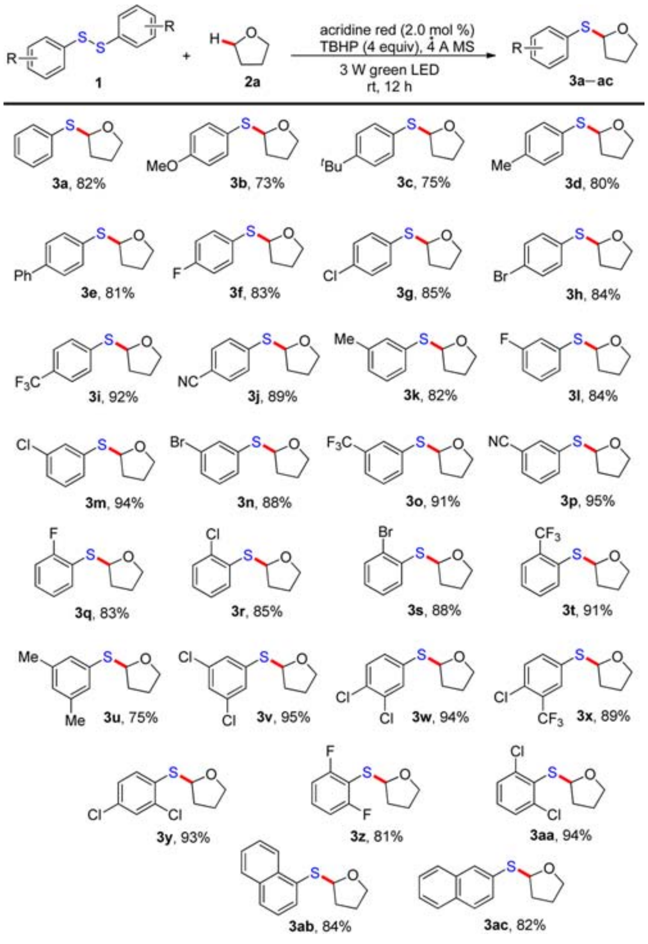
| entry | photocatalyst | light source | oxidant | yield[b] (%) |
|---|---|---|---|---|
| 1 | $Ru(bpy)_3Cl_2$ | blue LED | TBHP | 18 |
| 2 | $Ru(phen)_3Cl_2$ | blue LED | TBHP | trace |
| 3 | eosin Y | green LED | TBHP | 55, 65[c] |
| 4 | rose bengal | green LED | TBHP | trace |
| 5 | fluorescein | green LED | TBHP | 60, 72[c] |
| 6 | rhodamine B | green LED | TBHP | 50, 61[c] |
| 7 | acridine red | green LED | TBHP | 70 |
| 8 | – | green LED | TBHP | n.r. |
| 9 | acridine red | dark | TBHP | n.r. |
| 10 | acridine red | green LED | TBHP | 82[c] |
| 11 | acridine red | green LED | TBHP | 65[d] |
| 12 | acridine red | green LED | DTBP | 20 |
| 13 | acridine red | green LED | $H_2O_2$ | n.r. |
| 14 | acridine red | green LED | $Bz_2O_2$ | n.r. |
| 15 | acridine red | green LED | $CH_3COOH$ | n.r. |
| 16 | acridine red | green LED | TBHP | 60[e] |
| 17 | acridine red | green LED | TBHP | 76[f] |
| 18 | acridine red | green LED | TBHP | n.r.[g] |
| 19 | acridine red | green LED | TBHP | 22[h] |
| 20 | acridine red | green LED | TBHP | 34[i] |
| 21 | acridine red | green LED | TBHP | 70[j], 81[k] |
| 22 | acridine red | green LED | TBHP | 72[l], 83[m] |



[a] Reaction conditions: **1a** (0.25 mmol), THF (**2a**, 2.0 mL), photocatalyst (2.0 mol %), oxidant (1.0 mmol), rt, 3 W LED for 12 h. [b] Isolated yield. n.r. = no reaction. [c] Addition of 4 Å MS (80 mg). [d] TBHP (0.2 mL, 5.5 mol/L in decane). [e] THF/$CH_3CN$ (1:1, 2.0 mL). [f] THF/acetone (1:1, 2.0 mL). [g] THF/DMSO (1:1, 2.0 mL). [h] THF/PhMe (1:1, 2.0 mL). [i] THF/PhCl (1:1, 2.0 mL). [j] Acridine red (1.0 mol %). [k] Acridine red (3.0 mol %). [l] 10 h. [m] 15 h.

as photocatalyst are highlighted in simple structure, novelty, and high efficiency. In the absence of photocatalyst or visible-light irradiation, no product was detected and the starting material was recovered (entries 8 and 9). To our delight, a significant improved yield (82%) of **3a** was obtained when 4 Å molecular sieve was added (entry 10). In addition, a variety of oxidants were subjected to the reaction; TBHP (70% solution in water) was the best one among the tested oxidants (entries 11−15). The effect of solvent was also examined, and THF (also as substrate) was the best of choice (entries 16−20). The loading of photocatalyst and the reaction time were also optimized, which are presented in Table 1, entries 21 and 22.

**Scheme 1. Reactivity Screening on Disulfides**[a,b]

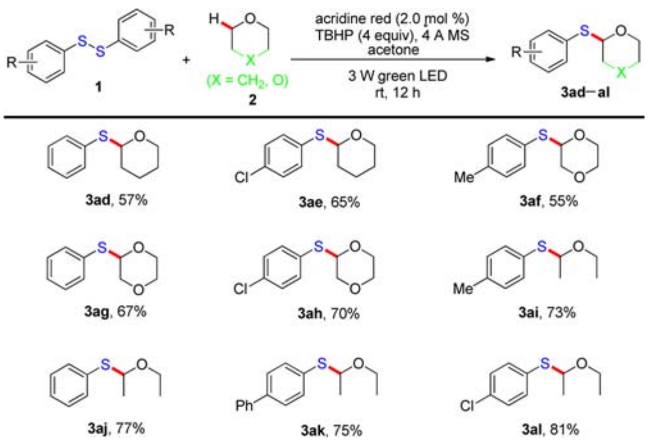


[a] Reaction conditions: **1** (0.25 mmol), THF (**2a**, 2.0 mL), acridine red (2.0 mol %), 4 Å MS (80 mg), TBHP (70% solution in water, 1.0 mmol), rt, 3 W green LED (530−535 nm) for 12 h. [b] Isolated yield.

Under the optimized reaction conditions, the generality of this direct thiolation of THF was investigated, as shown in Scheme 1. A variety of diaryl disulfides were subjected to the reaction, and the corresponding products were obtained in high yields with excellent functional group tolerance. Diaryl disulfides with an electron-rich group such as MeO, $^{t}$Bu, Me, and Ph on the *para*-positions of benzene rings reacted with THF to generate the corresponding products (**3b−e**) in 73−81% yields. Meanwhile, the reactions of THF with diaryl disulfides attached an electron-poor group including F, Cl, Br, $CF_3$, and CN on the *para*-positions of benzene rings afforded the corresponding products (**3f−j**) in excellent yields (83−92%). In addition, diaryl disulfides with an electron-donating or electron-withdrawing group on the *meta*-positions of benzene rings gave high yields (82−95%) of the desired products (**3k−p**). It should be noted that no *ortho*-position effect was observed when (2-substituted diphenyl)-disulfides reacted with THF, leading the products (**3q−t**) in 83−91% yields. Di(disubstituted)phenyl disulfides, such as di(3,5-dimethylphenyl)disulfide, di(3,5-dichlorophenyl)disulfide, di(3,4-dichlorophenyl)disulfide, di(3-trifluoromethyl-4-chlorophenyl)-disulfide, di(2,4-dichlorophenyl)disulfide, di(2,6-difluorophenyl)disulfide, and di(2,6-dichlorophenyl)disulfide were found to be applicable for this transformation (75−95% yields of **3u−aa**). It is important to note that diaryl disulfide with two *ortho*-substitutes on the benzene ring underwent the reaction smoothly to generate the anticipated products **3z** and **3aa** in 81% and 94% yields, respectively, ignoring steric effect. In addition, the reactions of dinaphthyl disulfides with THF also gave the desired products **3ab** and **3ac** in good yields. However, dialkyl disulfides, such as dibenzyl disulfide, di(*n*-butyl)disulfide failed under the present reaction conditions. The structure of product **3e** was further confirmed by X-ray single crystal analysis (Supporting Information).

On the other hand, the common used symmetrical ethers except THF were also examined in this transformation. As shown in Scheme 2, the direct thiolation at $\alpha$-C($sp^3$)−H of 1,4-dioxane and diethyl ether with diphenyl disulfide, di(4-chlorophenyl)disulfide, di(4-methylphenyl)disulfide, and di(4-phenylphenyl)disulfide proceeded to afford the desired products (**3ad**−**al**) in moderate to good yields (55−81%). The results indicated that the reactivity of ethers is THF > diethyl ether >1,4-dioxane > tetrahydropyran.

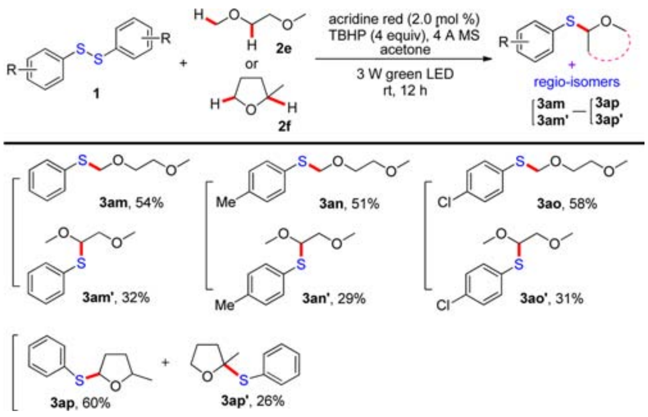
**Scheme 2. Reactivity Screening on Ethers**[a,b]



[a]Reaction conditions: **1** (0.25 mmol), **2** (1.0 mL), acetone (1.0 mL), acridine red (2.0 mol %), 4 Å MS (80 mg), TBHP (70% solution in water, 1.0 mmol), rt, 3 W green LED (530−535 nm) for 12 h. [b]Isolated yield.

Subsequently, the synthetic application of this methodology was further extended to unsymmetrical ethers, including 1,2-dimethoxyethane (**2e**) and 2-methyltetrahydrofuran (**2f**). As shown in Scheme 3, when 1,2-dimethoxyethane reacted with diphenyl disulfide, a couple of regioisomers **3am** and **3am′** were obtained in 54% and 32% isolated yields by column chromatography, showing a regioselectivity of 27/16. The reactions of other di(substituted phenyl)disulfides, such as di(*p*-tolyl)disulfide and di(*p*-chlorophenyl)disulfide with 1,2-dimethoxyethane proceeded smoothly to give **3an**/**3an′** (51/29, total 80% yield), **3ao**/**3ao′** (58/31, 89% of total yield). This protocol was further applied to 2-methyltetrahydrofuran with diphenyl disulfide; the corresponding isomers **3ap** and **3ap′** were isolated in 60% and 26% yields (total yield = 86%).

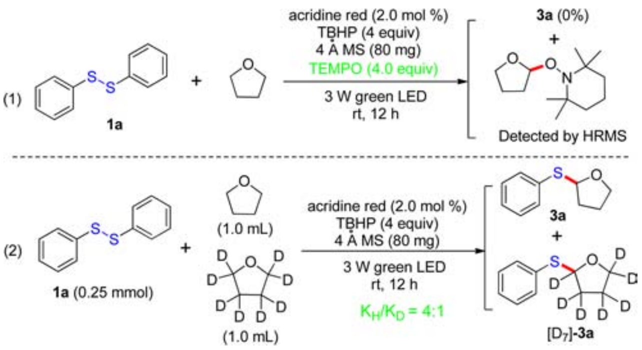
**Scheme 3. Regioselectivity of Unsymmetrical Ethers**[a,b]



[a]Reaction conditions: **1** (0.25 mmol), **4** (1.0 mL), acetone (1.0 mL), acridine red (2.0 mol %), 4 Å MS (80 mg), TBHP (70% solution in water, 1.0 mmol), rt, 3 W green LED (530−535 nm) for 12 h. [b]Isolated yield.

To elucidate the possible reaction mechanism, a series of experiments were performed, as summarized in Scheme 4.

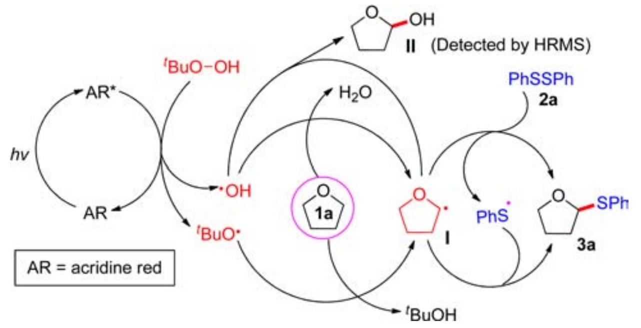
**Scheme 4. Control Experiment and KIE Determination**



When 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO), a radical scavenger, was added into the reaction of THF with diphenyl disulfide under the standard conditions, the reaction was inhibited completely. It is suggested that a radical pathway might be involved in this transformation. Moreover, a radical intermediate (**I**) formed in situ was captured by TEMPO and detected by high-resolution mass spectrum (HRMS) analysis. To further illustrate C−H bond cleavage of THF might be a rate-determining step, the kinetic isotope effect (KIE) was implemented, and a significant KIE ($K_H/K_D$) was found to be 4:1 (Scheme 4). Finally, an energy transfer process between acridine red and TBHP was confirmed by fluorescence quenching experiments (Support Information (SI) for detail).

On the basis of the above observation and previous literature, a proposed mechanism is shown in Scheme 5. At first, acridine red (AR) changed to its excited state (AR)* under green LED irradiation. Then, the formed (AR)* interacted with ${}^tBuOOH$ (TBHP) via an energy transfer to generate two crucial radical species, a hydroxyl radical ($HO^\bullet$) and a *tert*-butoxy radical (${}^tBuO^\bullet$) simultaneously, along with the formation of the ground state AR from (AR)*. Subsequently, $HO^\bullet$ or ${}^tBuO^\bullet$ abstracted hydrogen from $\alpha$-C($sp^3$)−H of THF (**1a**), giving a key alkoxyalkyl radical intermediate (**I**). The obtained **I** reacted with PhSSPh (**1a**) to afford the desired product 2-(phenylthio)-tetrahydrofuran (**3a**) and a new radical $PhS^\bullet$. On the other hand, the $PhS^\bullet$ would be trapped by another alkoxyalkyl radical. Moreover, a tetrahydrofuran-2-ol (**II**) was confirmed by HRMS

**Scheme 5. Plausible Mechanism**



analysis (SI for detail), which might be formed by the reaction of HO$^\bullet$ with alkoxyalkyl radical.

In summary, we have developed a simple and efficient method for the preparation of $\alpha$-arylthioethers through a visible-light-induced direct thiolation at $\alpha$-C(sp$^3$)−H of ethers with diaryl disulfides using acridine red as photocatalyst at ambient conditions. A number of disulfides reacted with various ethers to generate the corresponding 2-(arylthio)ethers in good to excellent yields, ignoring steric effect of disulfides. The reactions exhibited advantages including ambient conditions (room temperature and air atmosphere), eco-energy source, and good functional group compatibility. It is noteworthy that acridine red was first used as an energy transfer photocatalyst with inexpensive, commercially available, and easily degradable characteristics. Further applications of organic dyes in photochemical synthesis are under investigation 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.6b00304.

> Full experimental details and characterization data for all products (PDF)

## ■ AUTHOR INFORMATION

### Corresponding Authors

*E-mail: pphuali@126.com
*E-mail: leiwang88@hotmail.com

### Notes

The authors declare no competing financial interest.

## ■ ACKNOWLEDGMENTS

We gratefully acknowledge the National Natural Science Foundation of China (Nos. 21572078 and 21372095).

## ■ REFERENCES

(1) (a) Mitchell, S. C.; Nickson, R. M.; Waring, R. H. *Sulfur Rep.* **1993**, *13*, 279. (b) Liu, G.; Link, J. T.; Pei, Z.; Reilly, E. B.; Leitza, S.; Nguyen, B.; Marsh, K. C.; Okasinski, G. F.; Geldern, T. W.; Ormes, M.; Fowler, K.; Gallatin, M. *J. Med. Chem.* **2000**, *43*, 4025. (c) McReynolds, M. D.; Dougherty, J. M.; Hanson, P. R. *Chem. Rev.* **2004**, *104*, 2239. (d) Konaklieva, M. I.; Plotkin, B. J. *Recent Pat. Anti-Infect. Drug Discovery* **2006**, *1*, 177. (e) D'Angelo, N. D.; Kim, T.-S.; Andrews, K.; Booker, S. K.; Caenepeel, S.; Chen, K.; D'Amico, D.; Freeman, D.; Jiang, J.; Liu, L.; McCarter, J. D.; Miguel, T. S.; Mullady, E. L.; Schrag, M.; Subramanian, R.; Tang, J.; Wahl, R. C.; Wang, L.; Whittington, D. A.; Wu, T.; Xi, N.; Xu, Y.; Yakowec, P.; Yang, K.; Zalameda, L. P.; Zhang, N.; Hughes, P.; Norman, M. H. *J. Med. Chem.* **2011**, *54*, 1789. (f) Xu, X.-B.; Liu, J.; Zhang, J.-J.; Wang, Y.-W.; Peng, Y. *Org. Lett.* **2013**, *15*, 550.

(2) (a) Schaumann, E. *Top. Curr. Chem.* **2007**, *274*, 1. (b) Pan, X.-Q.; Zou, J.-P.; Yi, W.-B.; Zhang, W. *Tetrahedron* **2015**, *71*, 7481.

(3) Shen, C.; Zhang, P.; Sun, Q.; Bai, S.; Hor, T. S. A.; Liu, X. *Chem. Soc. Rev.* **2015**, *44*, 291 and references cited therein.

(4) (a) Duan, Z.; Ranjit, S.; Zhang, P.; Liu, X. *Chem. - Eur. J.* **2009**, *15*, 3666. (b) Ranjit, S.; Duan, Z.; Zhang, P.; Liu, X. *Org. Lett.* **2010**, *12*, 4134. (c) Becht, J.-M.; Drian, C. L. *J. Org. Chem.* **2011**, *76*, 6327. (d) Wang, P.-F.; Wang, X.-Q.; Dai, J.-J.; Feng, Y.-S.; Xu, H.-J. *Org. Lett.* **2014**, *16*, 4586.

(5) Zhang, S.-Y.; Zhang, F.-M.; Tu, Y.-Q. *Chem. Soc. Rev.* **2011**, *40*, 1937 and references citied therein.

(6) (a) Campos, K. R. *Chem. Soc. Rev.* **2007**, *36*, 1069. (b) Roesky, P. W. *Angew. Chem., Int. Ed.* **2009**, *48*, 4892. (c) Li, C.-J. *Acc. Chem. Res.* **2009**, *42*, 335. (d) Baudoin, O. *Chem. Soc. Rev.* **2011**, *40*, 4902.

(7) (a) Pan, S.; Liu, J.; Li, H.; Wang, Z.; Guo, X.; Li, Z. *Org. Lett.* **2010**, *12*, 1932. (b) Barve, B. D.; Wu, Y.-C.; El-Shazly, M.; Korinek, M.; Cheng, Y.-B.; Wang, J.-J.; Chang, F.-R. *Org. Lett.* **2014**, *16*, 1912. (c) Correa, A.; Fiser, B.; Gómez-Bengoa, E. *Chem. Commun.* **2015**, *51*, 13365.

(8) Liu, D.; Liu, C.; Li, H.; Lei, A. *Angew. Chem., Int. Ed.* **2013**, *52*, 4453.

(9) (a) Yang, Y.; Huang, H.; Zhang, X.; Zeng, W.; Liang, Y. *Synthesis* **2013**, *45*, 3137. (b) Zhang, R.-Y.; Xi, L.-Y.; Zhang, L.; Liang, S.; Chen, S.-Y.; Yu, X.-Q. *RSC Adv.* **2014**, *4*, 54349.

(10) (a) He, T.; Yu, L.; Zhang, L.; Wang, L.; Wang, M. *Org. Lett.* **2011**, *13*, 5016. (b) Liskey, C. W.; Hartwig, J. F. *J. Am. Chem. Soc.* **2012**, *134*, 12422. (c) Liu, D.; Liu, C.; Li, H.; Lei, A. *Chem. Commun.* **2014**, *50*, 3623. (d) Wan, M.; Meng, Z.; Lou, H.; Liu, L. *Angew. Chem., Int. Ed.* **2014**, *53*, 13845. (e) Aruri, H.; Singh, U.; Sharma, S.; Gudup, S.; Bhogal, M.; Kumar, S.; Singh, D.; Gupta, V. K.; Kant, R.; Vishwakarma, R. A.; Singh, P. P. *J. Org. Chem.* **2015**, *80*, 1929.

(11) Tang, R.-Y.; Xie, Y.-X.; Xie, Y.-L.; Xiang, J.-N.; Li, J.-H. *Chem. Commun.* **2011**, *47*, 12867.

(12) Guo, S.; Yuan, Y.; Xiang, J. *Org. Lett.* **2013**, *15*, 4654.

(13) Ciamician, G. *Science* **1912**, *36*, 385.

(14) Nicewicz, D. A.; MacMillan, D. W. C. *Science* **2008**, *322*, 77.

(15) For selected reviews and papers on visible-light photoredox catalysis, see: (a) Zeitler, K. *Angew. Chem., Int. Ed.* **2009**, *48*, 9785. (b) Yoon, T. P.; Ischay, M. A.; Du, J. *Nat. Chem.* **2010**, *2*, 527. (c) Narayanam, J. M. R.; Stephenson, C. R. J. *Chem. Soc. Rev.* **2011**, *40*, 102. (d) Allen, A. E.; MacMillan, D. W. C. *Chem. Sci.* **2012**, *3*, 633. (e) Shi, L.; Xia, W. *Chem. Soc. Rev.* **2012**, *41*, 7687. (f) Tucker, J. W.; Stephenson, C. R. J. *J. Org. Chem.* **2012**, *77*, 1617. (g) Xuan, J.; Xiao, W.-J. *Angew. Chem., Int. Ed.* **2012**, *51*, 6828. (h) Hari, D. P.; Koenig, B. *Angew. Chem., Int. Ed.* **2013**, *52*, 4734. (i) Deng, G.-B.; Wang, Z.-Q.; Xia, J.-D; Qian, P.-C.; Song, R.-J; Hu, M.; Gong, L.-B.; Li, J.-H. *Angew. Chem., Int. Ed.* **2013**, *52*, 1535. (j) Prier, C. K.; Rankic, D. A.; MacMillan, D. W. C. *Chem. Rev.* **2013**, *113*, 5322. (k) Zou, Y.-Q.; Chen, J.-R.; Xiao, W.-J. *Angew. Chem., Int. Ed.* **2013**, *52*, 11701. (l) Xie, J.; Jin, H.; Xu, P.; Zhu, C. *Tetrahedron Lett.* **2014**, *55*, 36. (m) Schultz, D. M.; Yoon, T. P. *Science* **2014**, *343*, 985. (n) Douglas, J. J.; Nguyen, J. D.; Cole, K. P.; Stephenson, C. R. J. *Aldrichimica Acta* **2014**, *47*, 15. (o) Nicewicz, D. A.; Nguyen, T. M. *ACS Catal.* **2014**, *4*, 355. (p) Jahn, E.; Jahn, U. *Angew. Chem., Int. Ed.* **2014**, *53*, 13326.

(16) Li, J.; Zhang, J.; Tan, H.; Wang, D.-Z. *Org. Lett.* **2015**, *17*, 2522.

(17) (a) Tan, H.; Li, H. J.; Ji, W.; Wang, L. *Angew. Chem., Int. Ed.* **2015**, *54*, 8374. (b) Yang, W.; Yang, S.; Li, P.; Wang, L. *Chem. Commun.* **2015**, *51*, 7520. (c) Xia, D.; Miao, T.; Li, P.; Wang, L. *Chem. - Asian J.* **2015**, *10*, 1919. (d) Zhou, C.; Li, P.; Zhu, X.; Wang, L. *Org. Lett.* **2015**, *17*, 6198. (e) Ji, W.; Tan, H.; Wang, M.; Li, P.; Wang, L. *Chem. Commun.* **2016**, *52*, 1462.