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Visible-Light-Mediated Synthesis of Unsymmetrical Diaryl Sulfides via Oxidative Coupling of Arylhydrazine with Thiol

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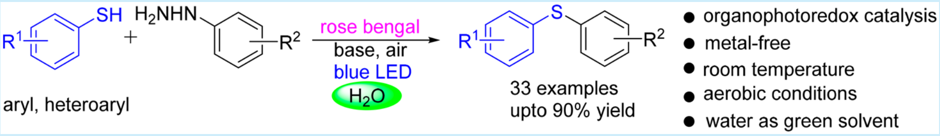
Supporting Information

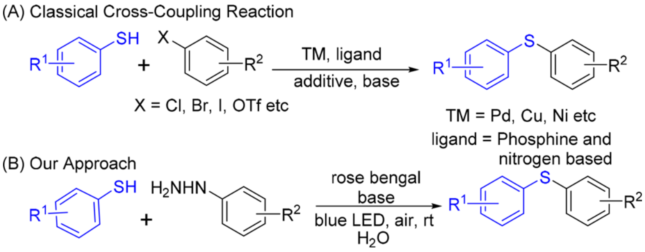


ABSTRACT: A metal-free visible-light-promoted oxidative coupling between thiols and arylhydrazines has been developed to afford diaryl sulfides using a catalytic amount of rose bengal as photocatalyst under aerobic conditions. A library of unsymmetrical diaryl sulfides with broad functionalities was synthesized in good yields at room temperature. The present methodology is also applicable to benzo[*d*]thiazole-2-thiols, benzo[*d*]oxazole-2-thiol, 1*H*-benzo[*d*]imidazole-2-thiols, and 1*H*-imidazole-2-thiol.

Sulfur-containing organic scaffolds, particularly diaryl sulfides, have a valuable impact in the biological as well as pharmaceutical field because of their immense response against cancer, malarial, Alzheimer's, Parkinson's, HIV, etc. diseases.[1] They serve as the building block of several natural products.[2] Besides, diaryl sulfides show various applications in material sciences.[3] Moreover, *ipso*-substitution reactions via C−S bond cleavage enhance the utility of aryl sulfides as synthetic intermediates.[4]

Over the past few decades, synthesis of organic sulfides has received considerable attention from synthetic organic chemists. The conventional methods for the synthesis of diaryl sulfides involve the cross-coupling reaction between prefunctionalized arenes with a suitable arylsulfur reagent (Scheme 1A).[5] Most of the reported methods require toxic and expensive transition metal (Pd, Cu, Ru, Ir, etc.) catalysts in the presence of ligands under harsh reaction conditions. Recently, arylhydrazine has emerged as an effective coupling partner in various carbon−carbon and carbon−heteroatom bond-forming cross-coupling reactions.[6] It is considered as an environmentally benign arylating agent for oxidative cross-coupling reactions, as it releases only nitrogen gas and water as byproducts during C−N bond cleavage. Very recently Zhao et al. reported a Pd(II)-catalyzed oxidative cross-coupling between phenylhydrazine and thioarenes for the synthesis of diaryl sulfides at 100 °C.[7] However, synthesis of unsymmetrical diayl sulfides via oxidative coupling at room temperature as well as in water is rare. Therefore, development of a simple and environmentally benign method for the formation of unsymmetrical diaryl sulfides is highly desirable in organic synthesis.

Scheme 1. Synthesis of Unsymmetrical Diaryl Sulfides



In recent years, visible-light-mediated photoredox catalysis becomes a powerful synthetic tool in organic synthesis.[8] Organic dyes are considered as alternatives of photoredox transition metal catalysts due to their inexpensiveness, synthetic versatility, nontoxicity, and better environmental perspective.[9] In continuation of our research interest in visible-light-promoted C−C and C−heteroatom bond forming reactions,[10] herein we report a visible-light-promoted C−S bond forming reaction for the synthesis of unsymmetrical diaryl sulfides using rose bengal as a photocatalyst under ambient air at room temperature in water (Scheme 1B).

We commenced our study using 4-methoxybenzenethiol (**1a**) and phenylhydrazine hydrochloride (**2a**) as model substrates employing Na_2CO_3 (2 equiv) as the base and rose bengal (2 mol %) as the photocatalyst in CH_3CN under 34 W blue LED at room temperature. Gratifyingly, the oxidative cross-coupling product (**3aa**) was obtained with a 58% yield within 8 h under aerobic conditions (Table 1, entry 1). Inspired by the initial result, we carried out the reaction under different conditions to optimize the yield and the results are summarized in Table 1. We first screened the effect of different solvents such as 1,2-DCE, DCM, THF, toluene, DMSO, DMF, EtOH, and H_2O (Table 1, entries 2−9). Among them, a high yield was obtained in H_2O (Table 1, entry 9). The effect of other organic dyes such as eosin Y, eosin B, and rhodamine 6G

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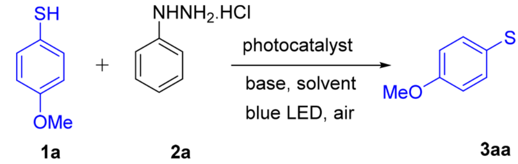
Table 1. Optimization of the Reaction Conditions[a]



entry	photocatalyst	base (equiv)	solvent	yield (%)
1	rose bengal	Na_2CO_3 (2)	CH_3CN	58
2	rose bengal	Na_2CO_3 (2)	1,2-DCE	45
3	rose bengal	Na_2CO_3 (2)	DCM	28
4	rose bengal	Na_2CO_3 (2)	THF	47
5	rose bengal	Na_2CO_3 (2)	toluene	35
6	rose bengal	Na_2CO_3 (2)	DMSO	65
7	rose bengal	Na_2CO_3 (2)	DMF	58
8	rose bengal	Na_2CO_3 (2)	EtOH	78
9	**rose bengal**	**Na_2CO_3 (2)**	**H_2O**	**85**
10	eosin Y	Na_2CO_3 (2)	H_2O	72
11	eosin B	Na_2CO_3 (2)	H_2O	69
12	rhodamine 6G	Na_2CO_3 (2)	H_2O	53
13	rose bengal	K_2CO_3 (2)	H_2O	81
14	rose bengal	Et_3N (2)	H_2O	64
15	rose bengal	DBU (2)	H_2O	71
16	rose bengal	Na_2CO_3 (3)	H_2O	84[b]
17	rose bengal	Na_2CO_3 (1)	H_2O	52,[c] 45
18	rose bengal	–	H_2O	trace
19	–	Na_2CO_3 (2)	H_2O	nr[d]
20	rose bengal	Na_2CO_3 (2)	H_2O	nr[e]
21	rose bengal	Na_2CO_3 (2)	H_2O	nr,[f] 37[g]

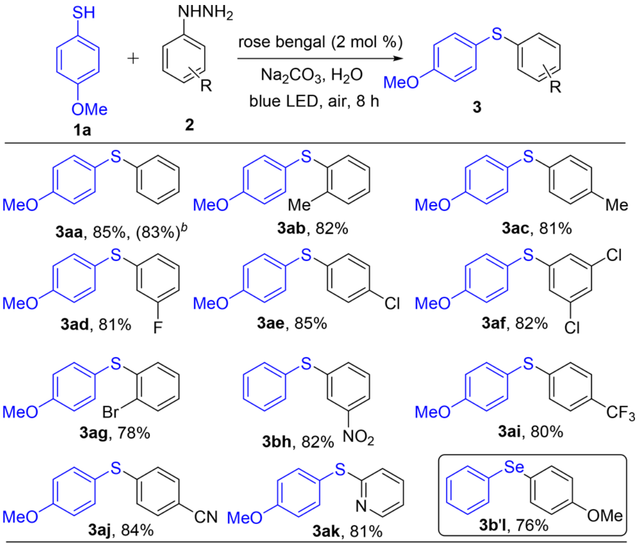
[a] Reaction conditions: **1a** (0.2 mmol), **2a** (0.4 mmol), photocatalyst (2 mol %), base, solvent (3 mL), 34 W blue LED for 8 h. [b] 3 mol % photocatalyst used. [c] 1.5 mol % photocatalyst and 2 equiv of Na_2CO_3 were used. [d] No reaction. [e] In the dark. [f] Under an argon atmosphere. [g] 5 W blue LED for 20 h.

were also studied (Table 1, entries 10–12). But all of them gave lower yields of the desired product. Then the reaction was carried out with different bases, but no improvement of yield was observed (Table 1, entries 13–15). No further improvement of the yield was observed with increasing the amount of both rose bengal (3 mol %) and Na_2CO_3 but decreased significantly with decreasing the loading of both photocatalyst (1.5 mol %) and base (Table 1, entries 16–17). Only a trace amount of product was obtained in the absence of base (Table 1, entry 18). No formation of product was observed in the absence of any photocatalyst (Table 1, entry 19). However, the reaction did not proceed in dark conditions and as well as under an argon atmosphere (Table 1, entries 20 and 21). A lower yield of the coupling product was obtained under irradiation with a 5 W blue LED for 20 h (Table 1, entry 21). Thus, the optimized yield was obtained using 2 mol % rose bengal and 2 equiv of Na_2CO_3 in H_2O under irradiation with a 34 W blue LED for 8 h in air (Table 1, entry 9).

After obtaining the optimized conditions, next we investigated the scope of this cross-coupling reaction exploring various arylhydrazines (Scheme 2). Arylhydrazines with an electron-donating substituent such as $-CH_3$ at the ortho- and para- position afforded the corresponding products with excellent yields (**3aa** and **3ab**). Halogen substituted arylhydrazines also successfully coupled with 4-methoxybenzenethiol to give the desired products in high yields (**3ad**–**3ag**). Strong electron-withdrawing groups ($-NO_2$, $-CF_3$, and $-CN$) substituted onto arylhydrazines also furnished the coupling products without any difficulties (**3bh**, **3ai**, and **3aj**). 2-Hydrazinopyridine also participated in this coupling reaction to afford the desired product in good yield (**3ak**). Diphenyldiselenide also reacted with 4-methoxy phenylhydrazine hydrochloride to give the coupling product (4-methoxyphenyl)(phenyl)selane (**3b′l**) in good yield. The gram-scale reaction of the present methodology was also performed in the usual laboratory setup by taking 4-methoxybenzenethiol (**1a**) and phenylhydrazine hydrocholoride (**2a**) on 6 mmol scale. The desired diaryl sulfide product (**3aa**) was obtained without a significant decrease in yield which implies the practical applicability of the present methodology.

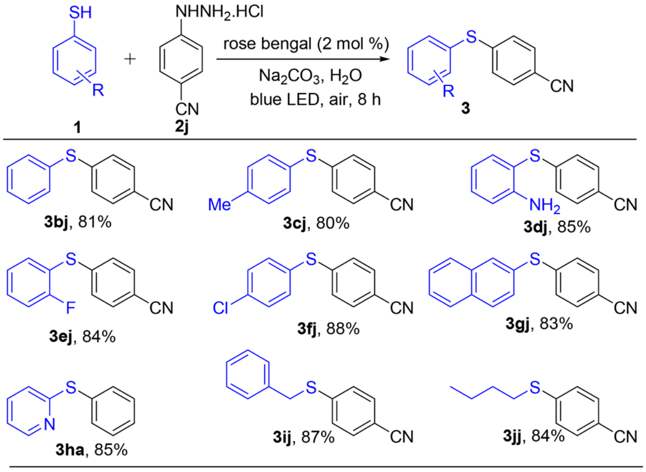
Next, to further expand the substrate scope, we carried out this coupling reaction with a variety of thiols and the results are summarized in Scheme 3. Arenethiols containing electron-donating groups, such as $-Me$ and $-NH_2$, successfully

Scheme 2. Substrate Scope of Arylhydrazines[a]



[a] Reaction conditions: **1a** (0.2 mmol), **2** (0.4 mmol), Na_2CO_3 (0.4 mmol), rose bengal (2 mol %) in 3 mL of H_2O, 34 W blue LED. [b] 6 mmol scale.

Scheme 3. Substrate Scope of Thiols[a]



[a] Reaction conditions: **1** (0.2 mmol), **2j** (0.4 mmol), Na_2CO_3 (0.4 mmol), rose bengal (2 mol %) in 3 mL of H_2O, 34 W blue LED.

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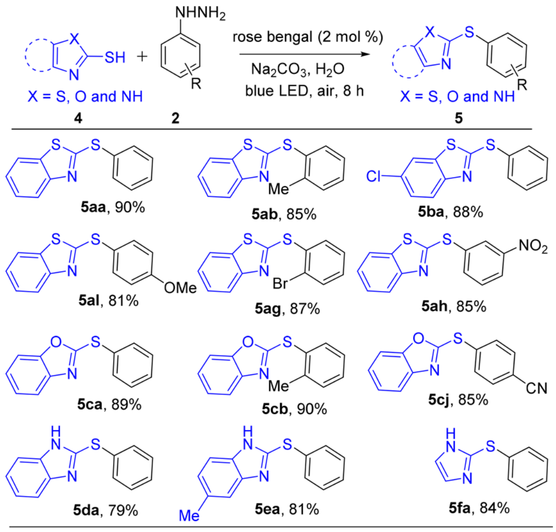
afforded the diaryl sulfide with excellent yields (**3cj** and **3dj**). Moreover, the halogen substituted (−F and −Cl) arenethiols also furnished the desired products in good yields (**3ej** and **3fj**). To our delight, naphthalene-2-thiol and pyridine-2-thiol were also well tolerable for such transformation (**3gj** and **3ha**). Benzyl mercaptan and butane-1-thiol also reacted well to afford the desired products in good yields (**3ij** and **3jj**).

The present protocol is also applicable to various heteroaryl thiols (Scheme 4). Benzo[*d*]thiazole-2-thiols, benzo[*d*]-oxazole-2-thiol, 1*H*-benzo[*d*]imidazole-2-thiols, and 1*H*-imidazole-2-thiol reacted with phenyl hydrazine derivatives to provide the diaryl sulfide products in high yields (**5aa−5fa**).

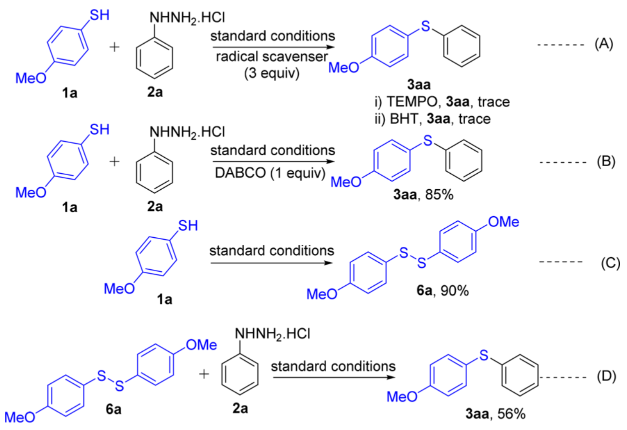
Scheme 4. Substrate Scope of Other Heteroarylthiols[a]



[a] Reaction conditions: **4** (0.2 mmol), **2** (0.4 mmol), Na_2CO_3 (0.4 mmol), rose bengal (2 mol %) in 3 mL of H_2O, 34 W blue LED.

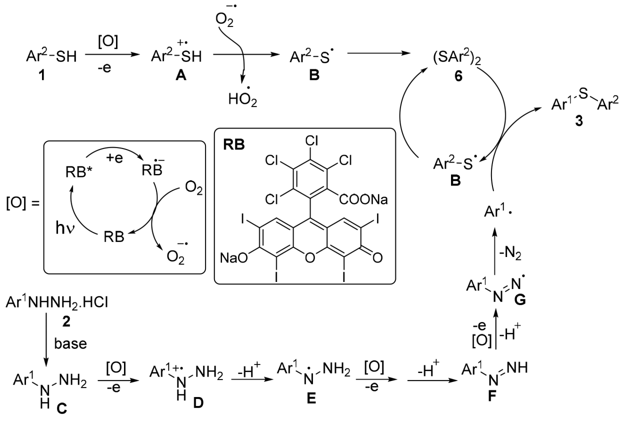
To understand the mechanistic pathway of this cross-coupling reaction, few control experiments were performed as shown in Scheme 5. The reaction was carried out in the presence of different radical scavengers such as 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO) (Scheme 5, eq A, (i)) and 2,6-di-*tert*-butyl-4-methylphenol (BHT) (Scheme 5, eq A (ii)). However, in both cases, only a trace amount of the product was obtained. These results suggest that the reaction possibly proceeds through a radical pathway. When the reaction was carried out in the presence of a singlet oxygen quencher such as 1,4-diazabicyclo[2.2.2]octane (DABCO),[11] the reaction proceeded with equal ease (Scheme 5, eq B). This result indicates that the singlet oxygen is not involved in this cross-coupling reaction. Disulfide (**6a**) was obtained from 4-methoxybenzenethiol (**1a**) in the absence of phenylhydazine hydrochloride under the standard reaction conditions (Scheme 5, eq C). In addition, 1,2-bis(4-methoxyphenyl)disulfane (**6a**) produced the desired coupling product **3aa** with phenylhydrazine hydrochloride in 56% yield under the optimized reaction conditions. These results indicate that the present reaction might proceed through the formation of disulfide (Scheme 5, eq D).

Scheme 5. Control Experiments



On the basis of control experiments and literature reports,[6f,g,9h] a plausible mechanistic pathway has been proposed in Scheme 6. First, the ground state of RB (rose bengal) is converted to its excited state RB* upon irradiation with blue LED light. RB* reacts with thiol to afford thiol radical cation **A** and $RB^{\bullet -}$ via single electron transfer (SET). Subsequently RB is regenerated through the reduction of O_2 to $O_2^{\bullet -}$ which abstracts a proton from **A** to produce thiyl radical **B**. Next thiyl radical **B** undergoes a homocoupling reaction to generate diaryl disulfide (**6**). On the other hand arylhydrazine **C** is oxidized by RB* to afford radical cation **D**. Upon deprotonation, radical cation **D** is converted to radical intermediate **E**. Radical intermediate **G** is formed from **E** through sequential SET and deprotonation. An aryl radical is generated from **G** by the elimination of nitrogen. Finally, the aryl radical is coupled with diaryl disulfide (**6**) to afford the desired coupling product (**3**) and thiyl radical **B** which again dimerizes to regenerate **6**.

Scheme 6. Plausible Mechanistic Pathway



In summary, we have developed a visible-light-promoted oxidative C−S cross-coupling reaction between arylhydrazine and thiol to synthesize unsymmetrical diaryl sulfides under organophotoredox catalysis. A library of diaryl sulfides with broad functionalities was synthesized at ambient temperature under aerobic conditions. Scalability, metal-free conditions, use of water as a green solvent, and ambient air as the oxidant make this method more practicable in organic synthesis. To the best of our knowledge, this is the first report of a visible-light-promoted synthesis of unsymmetrical diaryl sulfides in water at room temperature. We believe our present methodology becomes more interesting in organic synthesis as well as in medicinal chemistry.

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■ ASSOCIATED CONTENT

Supporting Information

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Experimental procedures and spectral data (PDF)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) (a) Marcincal-Lefebvre, A.; Gesquiere, J. C.; Lemer, C. *J. Med. Chem.* **1981**, *24*, 889. (b) McReynolds, M. D.; Dougherty, J. M.; Hanson, P. R. *Chem. Rev.* **2004**, *104*, 2239. (c) Gelb, M. H. *Science* **1997**, *275*, 1750. (d) Fraústo da Silva, J. J. R.; Williams, R. J. P. *The Biological Chemistry of the Elements*; Oxford University Press: New York, 2001. (e) McGarrigle, E. M.; Myers, E. L.; Illa, O.; Shaw, M. A.; Riches, S. L.; Aggarwal, V. K. *Chem. Rev.* **2007**, *107*, 5841.

(2) Tatsuta, T.; Hosono, M.; Rotinsulu, H.; Wewengkang, D. S.; Sumilat, D. A.; Namikoshi, M.; Yamazaki, H. *J. Nat. Prod.* **2017**, *80*, 499.

(3) Kondo, T.; Mitsudo, T. *Chem. Rev.* **2000**, *100*, 3205.

(4) (a) Wang, L.; He, W.; Yu, Z. *Chem. Soc. Rev.* **2013**, *42*, 599. (b) Lian, Z.; Bhawal, B. N.; Yu, P.; Morandi, B. *Science* **2017**, *356*, 1059. (c) Takahashi, F.; Nogi, K.; Yorimitsu, H. *Org. Lett.* **2018**, *20*, 6601.

(5) (a) Eichman, C. C.; Stambuli, J. P. *Molecules* **2011**, *16*, 590. (b) Fernandez-Rodriguez, M. A.; Shen, Q.; Hartwig, J. F. *J. Am. Chem. Soc.* **2006**, *128*, 2180. (c) Teverovskiy, G.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2011**, *50*, 7312. (d) Kwong, F. Y.; Buchwald, S. L. *Org. Lett.* **2002**, *4*, 3517. (e) Gan, J.; Ma, D. *Org. Lett.* **2009**, *11*, 2788. (f) Saha, A.; Saha, D.; Ranu, B. C. *Org. Biomol. Chem.* **2009**, *7*, 1652. (g) Jammi, S.; Barua, P.; Rout, L.; Saha, P.; Punniyamurthy, T. *Tetrahedron Lett.* **2008**, *49*, 1484. (h) Xu, X.-B.; Liu, J.; Zhang, J.-J.; Wang, Y.-W.; Peng, Y. *Org. Lett.* **2013**, *15*, 550. (i) Arisawa, M.; Suzuki, T.; Ishikawa, T.; Yamaguchi, M. *J. Am. Chem. Soc.* **2008**, *130*, 12214. (j) Correa, A.; Carril, M.; Bolm, C. *Angew. Chem., Int. Ed.* **2008**, *47*, 2880. (k) Wang, H.; Wang, L.; Shang, J.; Li, X.; Wang, H.; Gui, J.; Lei, A. *Chem. Commun.* **2012**, *48*, 76. (l) Xiao, X.; Feng, M.; Jiang, X. *Angew. Chem., Int. Ed.* **2016**, *55*, 14121. (m) Oderinde, M. S.; Frenette, M.; Robbins, D. W.; Aquila, B.; Johannes, J. W. *J. Am. Chem. Soc.* **2016**, *138*, 1760. (n) Jouffroy, M.; Kelly, C. B.; Molander, G. A. *Org. Lett.* **2016**, *18*, 876.

(6) (a) Zhu, M. K.; Zhao, J. F.; Loh, T. P. *Org. Lett.* **2011**, *13*, 6308. (b) Su, Y.; Sun, X.; Wu, G.; Jiao, N. *Angew. Chem., Int. Ed.* **2013**, *52*, 9808. (c) Xu, W.; Hu, G.; Xu, P.; Gao, Y.; Yin, Y.; Zhao, Y. *Adv. Synth. Catal.* **2014**, *356*, 2948. (d) Zhao, Y.; Song, Q. *Chem. Commun.* **2015**, *51*, 13272. (e) Hosseinian, A.; Mohammadi, R.; Ahmadi, S.; Monfared, A.; Rahmanic, Z. *RSC Adv.* **2018**, *8*, 33828. (f) Ding, Y.; Zhang, W.; Li, H.; Meng, Y.; Zhang, T.; Chen, Q.-Y.; Zhu, C. *Green Chem.* **2017**, *19*, 2941. (g) Taniguchi, T.; Murata, A.; Takeda, M.; Mizuno, T.; Nomoto, A.; Ogawa, A. *Eur. J. Org. Chem.* **2017**, *2017*, 4928.

(7) Wang, C.; Zhang, Z.; Tu, Y.; Li, Y.; Wu, J.; Zhao, J. *J. Org. Chem.* **2018**, *83*, 2389.

(8) (a) Prier, C. K.; Rankic, D. A.; MacMillan, D. W. C. *Chem. Rev.* **2013**, *113*, 5322. (b) Narayanam, J. M. R.; Stephenson, C. R. J. *Chem. Soc. Rev.* **2011**, *40*, 102. (c) Shaw, M. H.; Twilton, J.; MacMillan, D. W. C. *J. Org. Chem.* **2016**, *81*, 6898. (d) Sun, M.-J.; Liu, Y.; Yan, Y.; Li, R.; Shi, Q.; Zhao, Y. S.; Zhong, Y.-W.; Yao, J. *J. Am. Chem. Soc.* **2018**, *140*, 4269. (e) Zhou, Q.-Q.; Zou, Y.-Q.; Lu, L.-Q.; Xiao, W.-J. *Angew. Chem., Int. Ed.* **2018**, DOI: 10.1002/anie.201803102. (f) Kundu, D.; Ahammed, S.; Ranu, B. C. *Org. Lett.* **2014**, *16*, 1814.

(9) (a) Pan, Y.; Kee, C. W.; Chen, L.; Tan, C.-H. *Green Chem.* **2011**, *13*, 2682. (b) Ravelli, D.; Fagnoni, M. *ChemCatChem* **2012**, *4*, 169. (c) Fukuzumi, S.; Ohkubo, K. *Chem. Sci.* **2013**, *4*, 561. (d) Hari, D. P.; König, B. *Chem. Commun.* **2014**, *50*, 6688. (e) Sun, P.; Yang, D.; Wei, W.; Jiang, M.; Wang, Z.; Zhang, L.; Zhang, H.; Zhang, Z.; Wang, Y.; Wang, H. *Green Chem.* **2017**, *19*, 4785. Wei, W.; Wang, L.; Bao, P.; Shao, Y.; Yue, H.; Yang, D.; Yang, X.; Zhao, X.; Wang, H. *Org. Lett.* **2018**, *20*, 7125. (g) Romero, N. A.; Nicewicz, D. A. *Chem. Rev.* **2016**, *116*, 10075. (h) Hong, B.; Lee, J.; Lee, A. *Tetrahedron Lett.* **2017**, *58*, 2809.

(10) (a) Singsardar, M.; Dey, A.; Sarkar, R.; Hajra, A. *J. Org. Chem.* **2018**, *83*, 12694. (b) Kibriya, G.; Bagdi, A. K.; Hajra, A. *J. Org. Chem.* **2018**, *83*, 10619. (c) Kibriya, G.; Bagdi, A. K.; Hajra, A. *Org. Biomol. Chem.* **2018**, *16*, 3473. (d) Kibriya, G.; Samanta, S.; Jana, S.; Mondal, S.; Hajra, A. *J. Org. Chem.* **2017**, *82*, 13722. (e) Mitra, S.; Ghosh, M.; Mishra, S.; Hajra, A. *J. Org. Chem.* **2015**, *80*, 8275.

(11) Keshari, T.; Yadav, V. K.; Srivastava, V. P.; Yadav, L. D. S. *Green Chem.* **2014**, *16*, 3986.