Organic LETTERS
Letter
Cite This: Org. Lett. XXXX, XXX, XXX−XXX
pubs.acs.org/OrgLett

Visible-Light-Enabled Construction of Thiocarbamates from Isocyanides, Thiols, and Water at Room Temperature

Wei Wei,*,†,§ Pengli Bao,§ Huilan Yue,*,‡ Sitong Liu,§ Leilei Wang,§ Yudong Li,§ and Daoshan Yang†,§

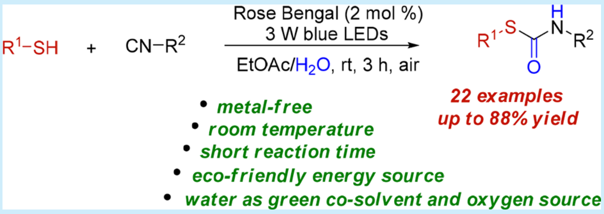
†State Key Laboratory Base of Eco-Chemical Engineering, College of Chemistry and Molecular Engineering, Qingdao University of Science and Technology, Qingdao 266042, P. R. China

‡Key Laboratory of Tibetan Medicine Research, Northwest Institute of Plateau Biology, Chinese Academy of Sciences and Qinghai Provincial Key Laboratory of Tibetan Medicine Research, Qinghai 810008, China

§School of Chemistry and Chemical Engineering, Qufu Normal University, Qufu 273165, Shandong, China

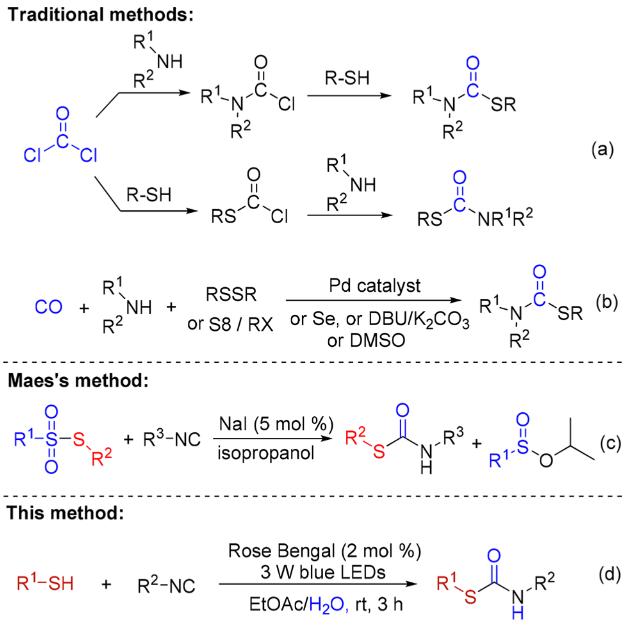
Supporting Information

ABSTRACT: A convenient visible-light-induced method for the synthesis of thiocarbamates from isocyanides, thiols, and water has been developed under mild reaction conditions. The present protocol offers a cost-effective and operationally straightforward approach to the various thiocarbamates in moderate to good yields by simple use of cheap Rose Bengal as the photocatalyst and water as the reaction reagent as well as an environmentally benign cosolvent.



As an important class of organosulfur compounds, thiocarbamates are ubiquitously found in various pharmaceutical molecules that possess a broad spectrum of biological properties such as antiviral,[1] fungicidal,[2] bactericidal,[3] anesthetic,[4] herbicidal,[5] and pesticidal[6] activities. Owing to their important biological activity and pharmacological value, thiocarbamates have attracted much attention from chemists in both academic and industrial communities.[7−17] Generally, thiocarbamates are prepared by the reaction of carbamoyl chlorides with thiols in the presence of base (Scheme 1a),[7] the reaction of alkyl chlorothioformate (RSCOCl) with amines (Scheme 1a),[8] the nucleophilic addition of thiols to isocyanates,[9] and the reactions of amines, thiols with phosgene derived carbonyldiimidazoles,[10] and di-*tert*-butyl dicarbonate.[11] Alternative methods for construction of thiocarbamates through direct carbonylation of amines with carbon monoxide (CO) and RSSR or S_8/RX have also been developed (Scheme 1b).[12] These reactions, although effective, usually involve the use of toxic phosgene/triphosgene reagents to prepare the starting materials or hazardous carbon monoxide as a C_1-reagent.[13] To avoid the use of hazardous reagents, other methods have also been reported. For example, Lee developed a one-pot synthesis of thiocarbamates from CBZ(Boc)-protected amines and thiophenols.[14] Mandal and co-workers described Boc-Oxyma mediated synthesis of thiocarbamates from hydroxamic acids via Lossen rearrangement.[15] Tang presented the thiocarbamation of imidazopyridines with carbamoyl chloride and elemental sulfur leading to imidazopyridines-thiocarbamates.[16] Very recently, Maes's group also reported an elegant iodine-catalyzed method for the synthesis of secondary thiocarbamates from thiosulfonates and isocyanides in isopropanol (Scheme 1c).[17] Nevertheless, most of these methodologies still suffer some limitations, such as the need for prefunctionalized starting materials, a narrow substrate scope, relatively harsh or complex reaction conditions, poor atom economy, or low yields. Therefore, the development of simple, mild, straightforward, and

Scheme 1. Methods for the Synthesis of Thiocarbamates



Received: July 17, 2018

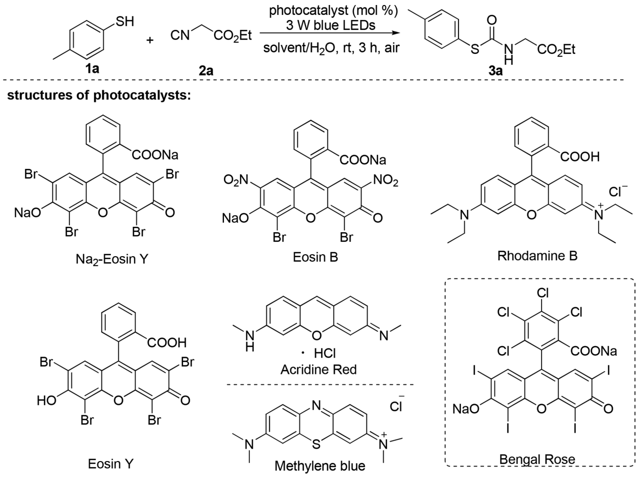
DOI: 10.1021/acs.orglett.8b02231
Org. Lett. XXXX, XXX, XXX−XXX

environmentally friendly approach to access thiocarbamates is still greatly desired.

In recent years, visible-light-initiated photoredox catalysis has become a fascinating and practical tool to develop sustainable synthetic processes under very mild conditions due to its economic and environmentally benign features.[18,19] Organic dyes have proven to be efficient catalysts in visible-light-mediated organic transformations and show the advantages of nontoxicity and cheapness compared with metal-based photoredox catalysts.[20,21] With our continued interest in the construction of sulfur-containing compounds,[22] herein, we wish to report a facile and efficient visible-light-induced protocol for the direct construction of thiocarbamates from isocyanides, thiols, and water at room temperature (Scheme 1d). This photocatalytic protocol, which utilized inexpensive Rose Bengal as a photocatalyst and water as the reaction reagent as well as an environmentally benign cosolvent, provided a new strategy for the synthesis of thiocarbamates.

Initially, the model reaction of 4-methylbenzenethiol (**1a**) with ethyl isocyanoacetate (**2a**) was performed in the presence of Na_2-Eosin Y (2 mol %) in CH_3CN/H_2O (1/1) at room temperature under air (Table 1, entry 1). The reaction was conducted under irradiation with 3 W blue LEDs lamp. Gratifyingly, the desired product **3a** was isolated in 62% yield after 3 h (Table 1, entry 1). Furthermore, a series of photocatalysts including Eosin B, Rhodamine B, Acridine Red, Eosin Y, Methylene blue, and Bengal Rose were explored (Table 1, entries 1−7). Among the above photocatalysts examined, Bengal Rose was found to be the most effective one to give the desired product **3a** in 74% yield (Table 1, entry 7). Next, a range of mixed solvents were screened (Table 1, entries 8−14), with $EtOAc/H_2O$ (1:1) being superior for the formation of product **3a** in 83% yield (Table 1, entry 14). It is noteworthy that the desired product could also be obtained in a moderate yield when the reaction was carried out in water (Table 1, entry 17). Increasing or decreasing the amount of Bengal Rose did not improve the reaction efficiency (Table 1, entries 18−19). The desired product **3a** was only obtained in 21% yield under visible-light irradiation in the absence of the photocatalyst (Table 1, entry 20). In contrast, no product was detected when the reaction was performed in the dark (Table 1, entry 21).

Table 1. Optimization of the Reaction Conditions[a]



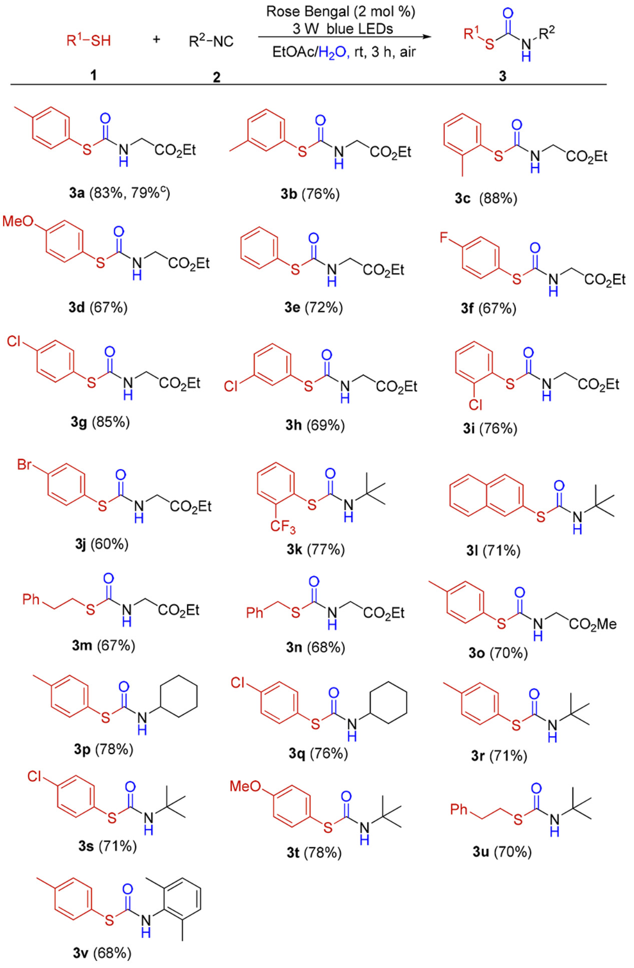
entry	photocatalyst (mol %)	solvent	yield (%)[b]
1	Na_2-Eosin Y (2)	CH_3CN/H_2O (1/1)	62
2	Eosin B (2)	CH_3CN/H_2O (1/1)	42
3	Rhodamine B (2)	CH_3CN/H_2O (1/1)	58
4	Eosin Y (2)	CH_3CN/H_2O (1/1)	43
5	Acridine Red (2)	CH_3CN/H_2O (1/1)	39
6	Methylene blue (2)	CH_3CN/H_2O (1/1)	trace
7	Rose Bengal (2)	CH_3CN/H_2O (1/1)	74
8	Rose Bengal (2)	DMF/H_2O (1/1)	46
9	Rose Bengal (2)	$DMSO/H_2O$ (1/1)	trace
10	Rose Bengal (2)	1,4-dioxane/H_2O (1/1)	51
11	Rose Bengal (2)	THF/H_2O (1/1)	53
12	Rose Bengal (2)	DCE/H_2O (1/1)	55
13	Rose Bengal (2)	CH_2Cl_2/H_2O (1/1)	70
14	Rose Bengal (2)	$EtOAc/H_2O$ (1/1)	83
15	Rose Bengal (2)	$EtOAc/H_2O$ (5/1)	65
16	Rose Bengal (2)	$EtOAc/H_2O$ (1/2)	60
17	Rose Bengal (2)	H_2O	50
18	Rose Bengal (1)	$EtOAc/H_2O$ (1/1)	69
19	Rose Bengal (5)	$EtOAc/H_2O$ (1/1)	59
20	–	$EtOAc/H_2O$ (1/1)	21
21	Rose Bengal (2)	$EtOAc/H_2O$ (1/1)	0[c]

[a] Reaction conditions: **1a** (0.2 mmol), **2a** (0.5 mmol), photocatalyst (1−5 mol %), solvent (1 mL), 3 W blue LED lamps, air, rt, 3 h. [b] Isolated yields based on **1**. [c] Without light irradiation.

With the optimized reaction conditions in hand, the generality of this reaction was further examined using different thiols and isocyanides (Scheme 2). Generally, aryl thiols with a wide range of substituents including electron-rich substituents and electron-poor substituents all generated the desired products in good yields (**3a**−**3k**). Halogen moieties were well compatible with this reaction leading to the desired products in satisfied yields (**3f**−**3j**), opening the door for further structural transformation. It was found that the steric effect has no obvious effect on the reaction efficiency. The steric encumbered substrates such as *ortho*-methyl, chloro and trifluoromethyl substituted aryl thiols still showed good activities (**3c**, **3i**, and **3k**). Naphthalene-2-thiol could be used in the reaction to produce the corresponding product **3l** in 71% yield. Notably, aliphatic thiols such as 2-phenylethanethiol and phenylmethanethiol were also well tolerated in the present reaction system, affording the expected products **3m** and **3n** in 67% and 68% yields, respectively. Nevertheless, when heterocyclic thiols such as pyridine-4-thiol and thiophene-2-thiol were investigated in the present reaction system, none of the desired product was detected. In addition to ethyl isocyanoacetate, aliphatic isocyanides such as methyl isocyanoacetate, *tert*-butyl isocyanide, and cyclohexyl isocyanide in our cases were also well compatible with this reaction leading to the desired products in good yields (**3o**−**3u**). In addition, aromatic isocyanide such as 2,6-dimethylphenyl isocyanide could also serve as a suitable substrate in this reaction system, providing the corresponding product **3v** in 68% yield.

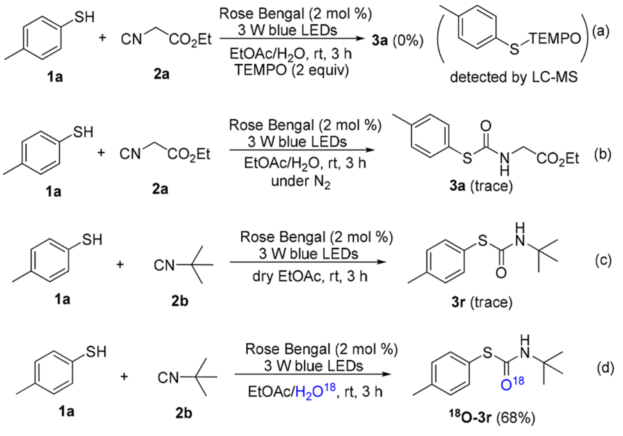
In order to elucidate the reaction mechanism, a series of control experiments were performed. Initially, the present transformation was completely inhibited when TEMPO (2,2,6,6-tetramethyl-1-piperidinyloxy, a well-known radical-capturing species) was added into reaction system under the standard conditions and a TEMPO-trapped complex (4-MePhS-TEMPO) was detected by LC-MS analysis (see Supporting Information (SI)), thus suggesting that this transformation might involve a radical process (Scheme 3a). When the model reaction of **1a** and **2a** was carried out under N_2, only a trace amount of product **3a** was detected. This result

Scheme 2. Visible-Light-Induced Method for the Synthesis of Thiocarbamates from Isocyanides, Thiols, and Water[a,b]



[a]Reaction conditions: **1** (0.2 mmol), **2** (0.5 mmol), Rose Bengal (2 mol %), EtOAc/H_2O (1/1) (1 mL), 3 W blue LEDs, air, rt, 3 h. [b]Isolated yields based on **1**. [c]**1a** (2 mmol), **2a** (5 mmol), 6 h.

Scheme 3. Control Experiments



indicated that air (O_2) is essential for the present transformation (Scheme 3b). Furthermore, only a trace amount of product **3r** was detected when the reaction of **1a** with **2b** was conducted in dry EtOAc (Scheme 3c). Also, ^{18}O-labeling experiment was performed to determine the source of oxygen in thiocarbamates. The corresponding O^{18}-**3r** was isolated in 68% yield when the reaction of **1a** and **2b** was carried out in the presence of EtOAc/H_2O^{18}, indicating that the oxygen atom of thiocarbamate came from water (Scheme 3d).

In addition, to prove an energy transfer process between Rose Bengal and 4-methylbenzenethiol **1a**, fluorescence quenching (Stern−Volmer) experiments were performed under visible-light irradiation. As demonstrated in Figures 1 and 2, the emission intensity of excited Rose Bengal was gradually diminished with increasing concentration of **1a**. In contrast, when Rose Bengal was separately mixed with ethyl isocyanoacetate (**2a**), such a phenomenon was not observed (see SI). The above results suggest that an electron transfer reaction actually occurred between Rose Bengal and thiol under visible-light irradiation.

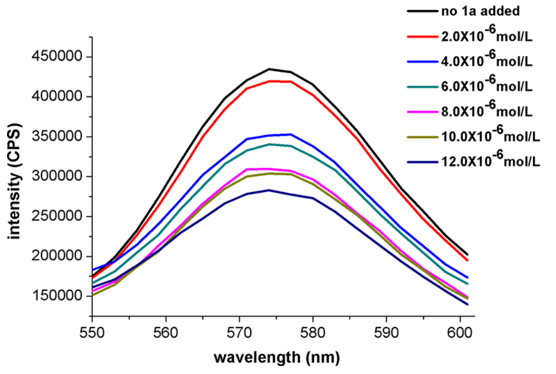


Figure 1. Quenching of Rose Bengal fluorescence emission in the presence of **1a**.

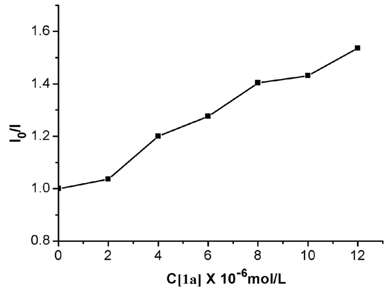
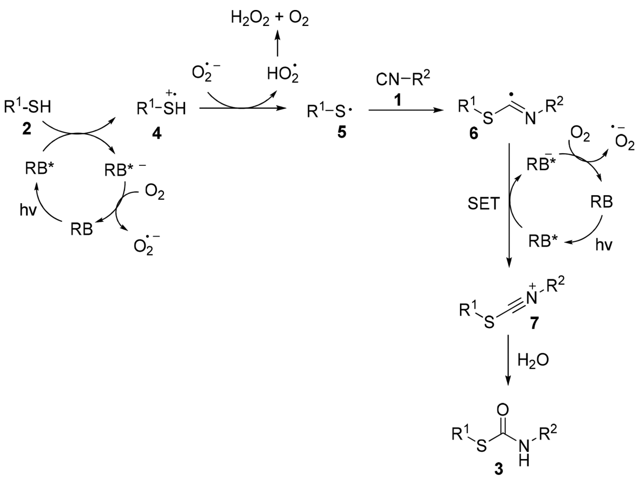


Figure 2. Stern−Volmer plots. I_0 is the inherent fluorescence intensity of Rose Bengal. I is the fluorescence intensity of Rose Bengal in the presence of **1a**.

On the basis of the above experimental results and previous reports,[17,21−26] a plausible mechanism for this reaction was proposed as shown in Scheme 4. Initially, the excited state RB* was produced from Rose Bengal under visible-light irradiation.[21] A single-electron transfer (SET) from the excited state of RB* to thiol **1** gave the radical cation **4** and $RB^{\bullet -}$ radical anion. The oxidation of $RB^{\bullet -}$ by oxygen (air) would lead to the formation of the ground state Rose Bengal and $O_2^{\bullet -}$.[22c] Subsequently, the deprotonation of the radical cation **4** by $O_2^{\bullet -}$ produced the thiyl radical **5** and hydroperoxide radical species. The disproportionation of the hydroperoxide radical would generate O_2 and H_2O_2.[24] Next, the addition of thiyl radical[25c] **5** to isocyanide **2** gave C-radical intermediate **6**,[25] which was oxidized by the excited state RB* through a single-electron transfer (SET) process leading to nitrilium

Scheme 4. Possible Reaction Pathway



intermediate 7. Finally, the addition of H_2O to nitrilium intermediate 7 produced the desired product 3.[26]

In summary, we have successfully developed a visible-light-promoted protocol for the synthesis of thiocarbamates from isocyanides, thiols, and water at room temperature. The present protocol, which utilizes a simple and cheap photocatalyst, readily available starting materials, and environmentally benign conditions, provides an attractive approach to various thiocarbamates in moderate to good yields. Further investigation of the detailed reaction mechanism and synthetic application are currently being pursued 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.8b02231.

Experimental details and compound characterization (PDF)

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: weiweiqfnu@163.com.
*E-mail: hlyue@nwipb.cas.cn.

ORCID

Wei Wei: 0000-0002-0015-7636
Daoshan Yang: 0000-0002-3047-5416

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported by the Natural Science Foundation of Shandong Province (ZR2018MB009 and ZR2016JL012), the International Cooperation Project of Qinghai Province (2018-HZ-806; 2017-HZ-806), Qinghai Key Laboratory of Tibetan Medicine Research (2017-ZJ-Y11), and the National Natural Science Foundation of China (Nos. 21302109 and 21302110).

■ REFERENCES

(1) Wood, T. F.; Gardner, J. H. *J. Am. Chem. Soc.* **1941**, *63*, 2741.

(2) (a) Heyns, A. J.; Carter, G. A.; Rothwell, K.; Wain, R. L. *Ann. Appl. Biol.* **1966**, *57*, 33. (b) Erian, A. W.; Sherif, S. M. *Tetrahedron* **1999**, *55*, 7957.

(3) (a) Bowden, K.; Chana, R. S. *J. Chem. Soc., Perkin Trans. 2* **1990**, 2163. (b) Beji, M.; Sbihi, H.; Baklouti, A.; Cambon, A. *J. Fluorine Chem.* **1999**, *99*, 17.

(4) Goel, A.; Mazur, S. J.; Fattah, R. J.; Hartman, T. L.; Turpin, J. A.; Huang, M.; Rice, W. G.; Appella, E.; Inman, J. K. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 767.

(5) (a) Chen, Y. S.; Schuphan, I.; Casida, J. E. *J. Agric. Food Chem.* **1979**, 27, 709. (b) Mizuno, T.; Nishiguchi, I.; Okushi, T.; Hirashima, T. *Tetrahedron Lett.* **1991**, *32*, 6867.

(6) (a) *The Pesticide Manual*, 9th ed.; Worthing, C. R., Ed.; British Crop Protection Council: London, 1991. (b) Chin-Hsien, W. *Synthesis* **1981**, *1981*, 622.

(7) (a) Weijlard, J.; Tishler, M. *J. Am. Chem. Soc.* **1951**, *73*, 1497. (b) Evans, T. W.; Dehn, W. M. *J. Am. Chem. Soc.* **1930**, *52*, 3645. (c) Tilles, H. *J. Am. Chem. Soc.* **1959**, *81*, 714.

(8) Riemschneider, R.; Kühl, A. *Monatsh. Chem.* **1953**, *84*, 1238.

(9) Movassagh, B.; Soleiman-Beigi, M. *Monatsh. Chem.* **2008**, *139*, 137.

(10) Padiya, K. J.; Gavade, S.; Kardile, B.; Tiwari, M.; Bajare, S.; Mane, M.; Gaware, V.; Varghese, S.; Harel, D.; Kurhade, S. *Org. Lett.* **2012**, *14*, 2814.

(11) Knölker, H.-J.; Braxmeier, T.; Schlechtingen, G. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2497.

(12) (a) Sugiyama, H. J. *Yuki Gosei Kagaku Kyokaishi* **1980**, *38*, 555. (b) Mizuno, T.; Nishiguchi, I.; Sonoda, N. *Tetrahedron* **1994**, *50*, 5669. (c) Mizuno, T.; Iwai, T.; Ito, T. *Tetrahedron* **2004**, *60*, 2869. (d) Mizuno, T.; Iwai, T.; Ishino, Y. *Tetrahedron* **2005**, *61*, 9157. (e) Nishiyama, Y.; Kawamatsu, H.; Sonoda, N. *J. Org. Chem.* **2005**, *70*, 2551.

(13) Health (H) rating of CO (H = 3), $COCl_2$ (H = 4), and isocyanates (e.g., *t*BuNCO (H = 3)) shows high toxicity. Scale from 0 (low) to 4 (high).

(14) (a) Kim, H.-K.; Lee, A. *Org. Biomol. Chem.* **2016**, *14*, 7345. (b) Kim, H.-K.; Lee, A. *Tetrahedron Lett.* **2016**, *57*, 4890.

(15) Manne, S. R.; Thalluri, K.; Giri, R. S.; Chandra, J.; Mandal, B. *Adv. Synth. Catal.* **2017**, *359*, 168.

(16) Deng, J.-C.; Zhuang, S.-B.; Liu, Q.-Z.; Lin, Z.-W.; Su, Y.-L.; Chen, J.-H.; Tang, R.-Y. *RSC Adv.* **2017**, *7*, 54013.

(17) Mampuys, P.; Zhu, Y.; Sergeyev, S.; Ruijter, E.; Orru, R. V. A.; Van Doorslaer, S. V.; Maes, B. U. W. *Org. Lett.* **2016**, *18*, 2808.

(18) Selective examples: (a) Zou, Y.-Q.; Chen, J.-R.; Liu, X.-P.; Lu, L.-Q.; Davis, R. L.; Jørgensen, K. A.; Xiao, W.-J. *Angew. Chem., Int. Ed.* **2012**, *51*, 784. (b) Ravelli, D.; Fagnoni, M.; Albini, A. *Chem. Soc. Rev.* **2013**, *42*, 97. (c) Keshari, T.; Yadav, V. K.; Srivastava, V. P.; Yadav, L. D. S. *Green Chem.* **2014**, *16*, 3986. (d) Ortgies, S.; Depken, C.; Breder, A. *Org. Lett.* **2016**, *18*, 2856. (e) Wei, W.; Cui, H.; Yang, D.; Yue, H.; He, C.; Zhang, Y.; Wang, H. *Green Chem.* **2017**, *19*, 5608. (f) Yang, S.; Li, P.; Wang, Z.; Wang, L. *Org. Lett.* **2017**, *19*, 3386.

(19) Selective reviews: (a) Prier, C. K.; Rankic, D. A.; MacMillan, D. W. C. *Chem. Rev.* **2013**, *113*, 5322. (b) Skubi, K. L.; Blum, T. R.; Yoon, T. P. *Chem. Rev.* **2016**, *116*, 10035. (c) Shaw, M. H.; Twilton, J.; MacMillan, D. W. C. *J. Org. Chem.* **2016**, *81*, 6898. (d) Staveness, D.; Bosque, I.; Stephenson, C. R. J. *Acc. Chem. Res.* **2016**, *49*, 2295. (e) Kärkäs, M. D.; Porco, J. A., Jr.; Stephenson, C. R. J. *Chem. Rev.* **2016**, *116*, 9683. (f) Ghogare, A. A.; Greer, A. *Chem. Rev.* **2016**, *116*, 9994.

(20) (a) Shi, Q.; Li, P.; Zhu, X.; Wang, L. *Green Chem.* **2016**, *18*, 4916. (b) Zhang, L.; Yi, H.; Wang, J.; Lei, A. *Green Chem.* **2016**, *18*, 5122. (c) Hu, X.; Zhang, G.; Bu, F.; Lei, A. *ACS Catal.* **2017**, *7*, 1432. (d) Li, X.; Fang, X.; Zhuang, S.; Liu, P.; Sun, P. *Org. Lett.* **2017**, *19*, 3580. (e) Wei, W.; Cui, H.; Yue, H.; Yang, D. *Green Chem.* **2018**, *20*, 3197. (f) Srivastava, V.; Singh, P. P. *RSC Adv.* **2017**, *7*, 31377.

(21) Romero, N. A.; Nicewicz, D. A. *Chem. Rev.* **2016**, *116*, 10075.

(22) (a) Wei, W.; Liu, C.; Yang, D.; Wen, J.; You, J.; Suo, Y.; Wang, H. *Chem. Commun.* **2013**, *49*, 10239. (b) Wei, W.; Li, J.; Yang, D.; Wen, J.; Jiao, Y.; You, J.; Wang, H. *Org. Biomol. Chem.* **2014**, *12*, 1861.

(c) Cui, H.; Wei, W.; Yang, D.; Zhang, Y.; Zhao, H.; Wang, L.; Wang, H. *Green Chem.* **2017**, *19*, 3520. (d) Wen, J.; Wei, W.; Xue, S.; Yang, D.; Lou, Y.; Gao, C.; Wang, H. *J. Org. Chem.* **2015**, *80*, 4966. (e) Wei, W.; Wen, J.; Yang, D.; Du, J.; You, J.; Wang, H. *Green Chem.* **2014**, *16*, 2988. (f) Wei, W.; Wen, J.; Yang, D.; Guo, M.; Wang, Y.; You, J.; Wang, H. *Chem. Commun.* **2015**, *51*, 768. (g) Wei, W.; Liu, C.; Yang, D.; Wen, J.; You, J.; Wang, H. *Adv. Synth. Catal.* **2015**, *357*, 987.

(23) (a) Fan, W.; Yang, Q.; Xu, F.; Li, P. *J. Org. Chem.* **2014**, *79*, 10588. (b) Sun, J.-G.; Yang, H.; Li, P.; Zhang, B. *Org. Lett.* **2016**, *18*, 5114. (c) Cao, S.; Zhong, S.; Xin, L.; Wan, J.-P.; Wen, C. *ChemCatChem* **2015**, *7*, 1478. (d) Pan, Y.; Kee, C. W.; Chen, L.; Tan, C.-H. *Green Chem.* **2011**, *13*, 2682.

(24) (a) Ohkubo, K.; Mizushima, K.; Iwata, R.; Souma, K.; Suzuki, N.; Fukuzumi, S. *Chem. Commun.* **2010**, *46*, 601. (b) Sawyer, D. T.; Calderwood, T. S.; Yamaguchi, K.; Angelis, C. T. *Inorg. Chem.* **1983**, *22*, 2577. (c) Ravelli, D.; Fagnoni, M.; Albini, A. *Chem. Soc. Rev.* **2013**, *42*, 97.

(25) (a) Bachi, M. D.; Balanov, A.; Bar-Ner, N. *J. Org. Chem.* **1994**, *59*, 7752. (b) Tsuchii, K.; Tsuboi, Y.; Kawaguchi, S-i.; Takahashi, J.; Sonoda, N.; Nomoto, A.; Ogawa, A. *J. Org. Chem.* **2007**, *72*, 415. (c) Dénès, F.; Pichowicz, M.; Povie, G.; Renaud, P. *Chem. Rev.* **2014**, *114*, 2587. (d) Saegusa, T.; Kobayashi, S.; Hirota, K.; Okumura, Y.; Ito, Y. *Bull. Chem. Soc. Jpn.* **1968**, *41*, 1638.

(26) Chen, M.; Li, Y.; Tang, H.; Ding, H.; Wang, K.; Yang, L.; Li, C.; Gao, M.; Lei, A. *Org. Lett.* **2017**, *19*, 3147.