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Visible-Light Photocatalytic Aerobic Annulation for the Green Synthesis of Pyrazoles

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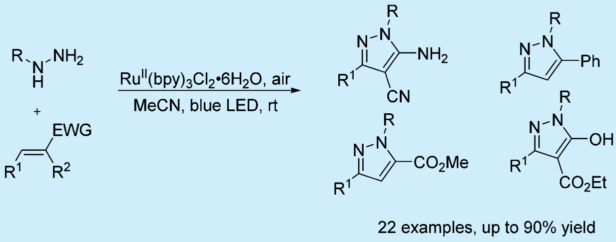
S *Supporting Information*

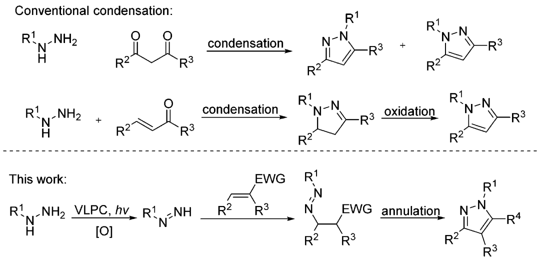
ABSTRACT: A selective and high yielding synthesis of polysubstituted pyrazoles through a VLPC (visible light photoredox catalysis)-promoted reaction of hydrazine with Michael acceptors is reported. The method employs very mild reaction conditions and uses air as the terminal oxidant, which makes the process environmentally benign. Different types of Michael acceptors with various substituents can undergo the reaction to afford corresponding pyrazoles in good to excellent yields. The reaction is proposed to go through VLPC-promoted oxidation of hydrazine to diazene followed by its addition to Michael acceptors, other than the conventional condensation of hydrazine with a carbonyl.



Pyrazoles and their derivatives represent an important framework in pharmaceutical and agrochemical sciences.[1] For example, a number of pyrazole-containing compounds have been successfully developed into commercial drugs including Celebrex,[2a,b] Acomplia,[2c] and Viagra,[1a] and the insecticide Fipronil.[2d] Additionally, substituted pyrazole derivatives have been employed as ligands for transition-metal-catalyzed cross-coupling reactions,[3] precursors to N-heterocyclic carbenes (NHCs),[4] and directing groups for C−H activations.[5] Due to the functional versatility of the pyrazole skeleton, their synthesis has been extensively explored.[6] By far the most prevalent strategies for constructing pyrazole rings are annulations initiated by the condensation of a monosubstituted hydrazine with a carbonyl, such as cyclocondensation of 1, 3-dicarbonyl or α,β-unsaturated carbonyl compounds with hydrazines.[7] However, these methods usually involve reaction conditions such as high reaction temperature, microwave irradiation, and hazard oxidants, which are contrary to the concept of green chemistry, and sometimes can lead to poor regioselectivity (Scheme 1). Accordingly, synthetic methods for polysubstituted pyrazoles with high selectivity employing mild and cheap conditions are still of current interest to the synthetic community.

Over the past decade, visible light photoredox catalysis has evolved to be a green synthetic strategy, as it uses visible light as a renewable energy source to promote chemical reactions involving electron transfers.[8] Since the independent seminal reports from the MacMillan, Yoon, and Stephenson groups almost a decade ago,[9] VLPC has already found major applications in enantioselective α-functionalization of carbonyl compounds,[10] [2 + 2] cycloadditions,[11] dehalogenationreactions,[12] decarboxylative couplings,[8e] radical C−H functionalization of aromatic compounds,[13] and the synergistic catalysis involving VLPC for oxidative couplings/annulations.[8n,14] For visible light photocatalytic oxidative couplings/annulations, VLPC usually serves as an oxidation promoter to generate reactive intermediates which can be utilized in further transformations to furnish complicated molecular structures. In this context, we envision that VLPC can promote transformation of substituted hydrazine to a diazene intermediate which could attack Michael acceptors and cyclize to pyrazoles (Scheme 1).

Scheme 1. Strategies for the Synthesis of Pyrazoles



To test this rationale, we started our investigation by studying the oxidative annulation between methyl hydrazine (**1a**) and 2-benzylidenemalononitrile (**2a**). The desired product, 5-amino-1-methyl-3-phenyl-1*H*-pyrazole-4-carbonitrile (**3a**), was furnished in 75% yield when the reaction proceeded at 25 °C in the presence of 2 mol % Ru^{II}(bpy)$_3$Cl$_2$·6H$_2$O irradiated with a 3 W blue LED in an open vial for 24 h in MeOH (entry 1, Table 1). Encouraged by the aforementioned result, other reaction conditions were investigated, and the results are summarized in Table 1. First, various solvents were

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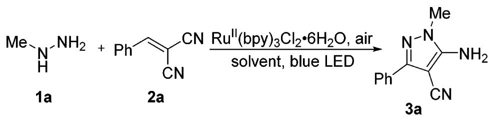
Table 1. Optimization of Reaction Conditions[a]



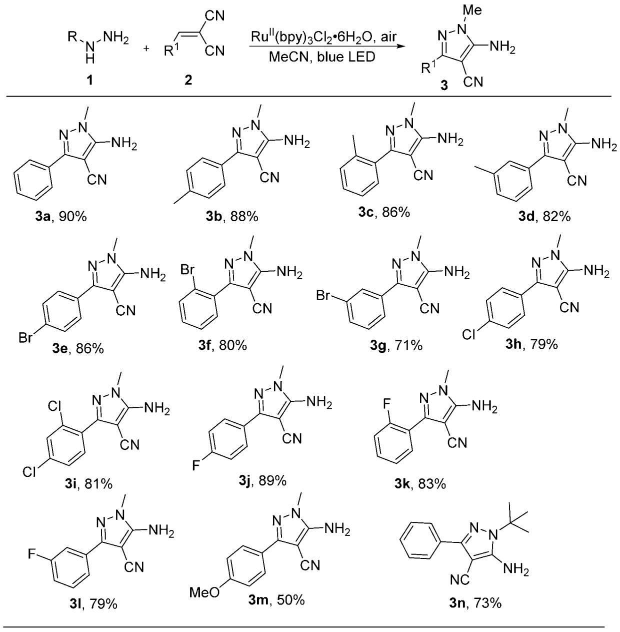
entry	solvent	temp (°C)	time (h)	yield[b] (%)
1	MeOH	25	24	75
2	DCM	25	24	78
3	EtOH	25	24	80
4	H_2O	25	24	81
5	**MeCN**	**25**	**24**	**90**
6	DMSO	25	24	70
7	DMF	25	24	65
8	THF	25	24	61
9	Et_2O	25	24	46
10	MeCN	25	12	60
11	MeCN	50	24	75

[a] 0.5 mmol of **2a**, 0.6 mmol of **1a**, 0.01 mmol of $Ru^{II}(bpy)_3Cl_2{\cdot}6H_2O$, 1.0 mL of solvents, with 3W blue LED, under air. [b] Isolated yield.

screened, revealing that CH_3CN was the best choice for the reaction, though other solvents such as EtOH, DCM, DMSO, DMF, THF, Et_2O, and even H_2O can also give decent yields (entries 1–9). Additionally, shortening the reaction time decreased the yield of **3a** (entry 10). Subsequently, varying the reaction temperature uncovered that higher temperature can jeopardize the reaction, leading to a lower yield (entry 11).

After optimizing the reaction conditions, we turned our attention to the generality and scope of the substrates for this transformation. A wide range of substituted olefins bearing two nitriles were first evaluated in the reaction with methyl hydrazine, as shown in Scheme 2. Nearly all substrates examined were found to undergo the desired transformation to give the corresponding products in good to excellent yields (71–90%), except for the one with an electron-donating group which could also be converted to the desired product but in moderate yield (4-OMe, **3m**, 50%). The presence of electron-neutral (4-H, 2-Me, 3-Me, 4-Me) and electron-deficient (2-F, 3-F, 4-F) groups attached to the phenyl ring had little effect on reactivity, and the corresponding pyrazoles were afforded in good to excellent yields (**3a–3d** and **3j–3l**). The steric nature of the substrates was shown to have little influence on the reaction efficiency, and substrates with ortho, meta, or para substituents on the phenyl group could be converted to the corresponding pyrazoles in good to excellent yields (**3b–3d**, **3e–3g**, and **3j–3l**); even the one with 2,4-dichloro substituents could also give 81% yield (**3i**). It is noteworthy that the all the substrates with halide substituents could be smoothly converted to corresponding pyrazoles which could be used for further functionalization through transition-metal-catalyzed cross-coupling (**3e–3l**). Furthermore, different hydrazines were examined for this reaction, and *tert*-butyl hydrazine reacted smoothly with **2a** to give corresponding pyrazole **3n** in good yield while $PhNHNH_2$ and $TsNHNH_2$ only led to other unexpected structures.[15]

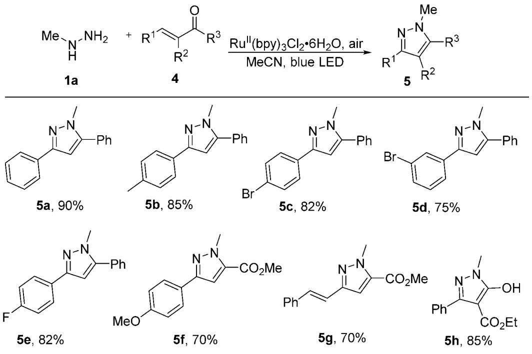
Scheme 2. Scope of Methylenemalononitriles Reacting with Hydrazine[a]



[a] 0.5 mmol of **2**, 0.6 mmol of **1**, 0.01 mmol of $Ru^{II}(bpy)_3Cl_2{\cdot}6H_2O$, 1.0 mL of MeCN, with 3W blue LED, under air, 24 h.

Encouraged by the exciting results obtained between the reactions of methyl hydrazine with different substituted methylenemalononitriles, application of this VLPC promoted aerobic annulation to other Michael acceptors was investigated next (Scheme 3). Substituted chalcones (**5a–5e**) turned out to be suitable substrates for this transformation, and they can be converted to corresponding 1,3,5-triubstituted pyrazoles in good to excellent yields (75–90%). Similarly α,β-unsaturated ketoesters also work well for the reaction to give the corresponding pyrazoles in good yields (**5f–5g**). To our delight, diethyl 2-benzylidenemalonate was found to undergo the desired transformation to give the corresponding 5-hydoxy pyrazole in 85% yield (**5h**).

Scheme 3. Scope of Different Michael Acceptors[a]



[a] 0.5 mmol of **4**, 0.6 mmol of **1a**, 0.01 mmol of $Ru^{II}(bpy)_3Cl_2{\cdot}6H_2O$, 1.0 mL of MeCN, with 3W blue LED, under air, 24 h.

During the study of the reaction between methyl hydrazine and Michael acceptor **2a** in Et_2O, an intermediate **6** was isolated and confirmed by ^1H NMR, ^{13}C NMR, MS, and IR (see Supporting Information), and **6** can be converted to corresponding pyrazole when subjected to standard conditions (eq 1, Scheme 4). This observation supports the idea that the reaction is initiated by a pathway other than the condensation of methyl hydrazine with the carbonyl. Another control reaction of **1a** with **2a** in the absence of a photocatalyst under a dark environment resulted in 77% starting material **2a** recovered (eq 2, Scheme 4). Also the luminescence of

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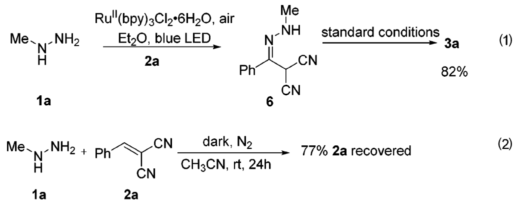
Scheme 4. Mechanistic Study



$Ru^{II}(bpy)_3Cl_2{\cdot}6H_2O$ with excitation at 493 nm could be readily quenched by **1a** following Stern–Volmer kinetics (Figure 1).

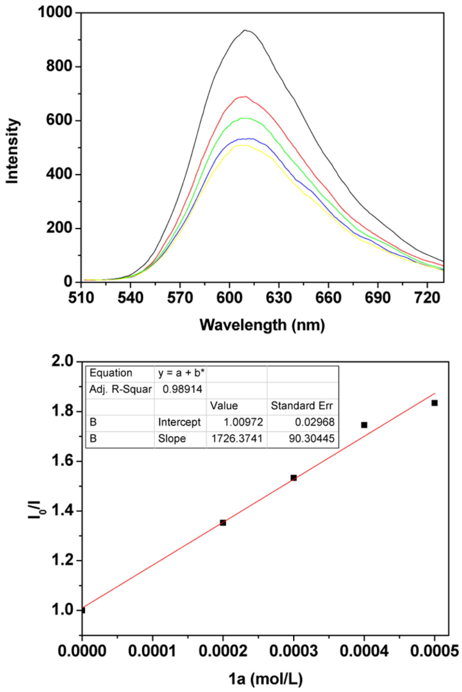
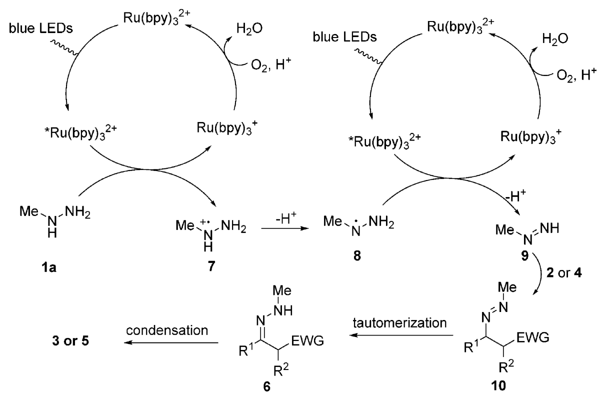


Figure 1. (up) Luminescence quenching of $Ru^{II}(bpy)_3Cl_2{\cdot}6H_2O$ with excitation at 493 nm by **1a**. (down) The Stern–Volmer plot.

This luminescence quenching is most likely due to photo-induced electron transfer. On the basis of these experimental observations, a plausible mechanism is proposed (Scheme 5). First, the Ru^{II} photocatalyst is irradiated to the excited state $Ru^{II}*$ using blue LEDs, and this excited state is then reductively quenched by **1a** with concomitant generation of radical anion **7** and Ru^{I}. Upon deprotonation, radical anion **7** is converted to radical **8**, which can also quench the excited state $Ru^{II}*$ and lose a proton to form diazene **9**. At the same time Ru^{I} is oxidized back to Ru^{II} by molecular oxygen. Then the addition of diazene **9** to the Michael acceptor and proton tautomerization furnish the intermediate **6** which undergoes intramolecular condensation to form the desired product.

Scheme 5. Proposed Mechanism



In conclusion, we have developed a selective and high yielding synthesis of polysubstituted pyrazoles through a VLPC-promoted reaction of hydrazine with Michael acceptors. The method employs very mild reaction conditions and uses air as the terminal oxidant, which makes the process environmentally benign. Different types of Michael acceptors with various substituents can undergo the reaction to afford corresponding pyrazoles in good to excellent yields. The reaction is proposed to go through VLPC-promoted oxidation of hydrazine to diazene followed by its addition to Michael acceptors, other than the conventional condensation of hydrazine with a carbonyl. Further study on the reactivity of diazene intermediate is ongoing in our laboratory.

■ ASSOCIATED CONTENT

S Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b01867.

> Experimental procedures and spectral data for all new compounds; mechanistic study, luminescence quenching experiment; and spectral data for intermediate **6** (PDF)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) (a) Terrett, N. K.; Bell, A. S.; Brown, D.; Ellis, P. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 1819. (b) Elguero, J.; Goya, P.; Jagerovic, N.; Silva, A. M. S. *Targets Heterocycl. Syst.* **2002**, *6*, 52. (c) Tracey, W. R.; Allen, M. C.; Frazier, D. E.; Fossa, A. A.; Johnson, C. G.; Marala, R. B.; Knight, D. R.; Guzman-Perez, A. *Cardiovasc. Drug Rev.* **2003**, *21*, 17. (d) Wyatt, P. G.; Woodhead, A. J.; Berdini, V.; Boulstridge, J. A.; Carr, M. G.; Cross, D. M.; Davis, D. J.; Devine, L. A.; Early, T. R.; Feltell, R. E.; Lewis, E. J.; McMenamin, R. L.; Navarro, E. F.; O'Brien, M. A.; O'Reilly, M.; Reule, M.; Saxty, G.; Seavers, L. A.; Smith, D. M.; Squires, M.; Trewartha, G.; Walker, M. T.; Woolford, A. J. A. *J. Med. Chem.* **2008**, *51*, 4986. (e) Keter, F. K.; Darkwa, J. *BioMetals* **2012**, *25*, 9. (f) Havrylyuk, D.; Zimenkovsky, B.; Vasylenko, O.; Gzella, A.; Lesyk, R. *J. Med. Chem.* **2012**, *55*, 8630.

(2) (a) Hwang, S. H.; Wagner, K. M.; Morisseau, C.; Liu, J. Y.; Dong, H.; Wecksler, A. T.; Hammock, B. D. *J. Med. Chem.* **2011**, *54*, 3037. (b) Dai, H. X.; Stepan, A. F.; Plummer, M. S.; Zhang, Y. H.; Yu, J. Q. *J. Am. Chem. Soc.* **2011**, *133*, 7222. (c) Donohue, S. R.; Halldin, C.; Pike, V. W. *Bioorg. Med. Chem.* **2006**, *14*, 3712. (d) Terçariol, P. R. G.; Godinho, A. F. *Pestic. Biochem. Physiol.* **2011**, *99*, 221.

(3) (a) Singer, R. A.; Caron, S.; McDermott, R. E.; Arpin, P.; Do, N. M. *Synthesis* **2003**, *2003*, 1727. (b) Singer, R. A.; Dore, M.; Sieser, J. E.; Berliner, M. A. *Tetrahedron Lett.* **2006**, *47*, 3727. (c) Kowalczyk, R.; Skarzewski, J. *Tetrahedron* **2005**, *61*, 623. (d) Ojwach, S. O.; Darkwa, J. *Inorg. Chim. Acta* **2010**, *363*, 1947.

(4) Schmidt, A.; Dreger, A. *Curr. Org. Chem.* **2011**, *15*, 2897.

(5) (a) Thirunavukkarasu, V. S.; Raghuvanshi, K.; Ackermann, L. *Org. Lett.* **2013**, *15*, 3286. (b) Liu, P. M.; Frost, C. G. *Org. Lett.* **2013**, *15*, 5862.

(6) For reviews: (a) Makino, K.; Kim, H. S.; Kurasawa, Y. *J. Heterocycl. Chem.* **1998**, *35*, 489. (b) Svete, J. *ARKIVOC* **2006**, *7*, 35. (c) Fustero, S.; Simón-Fuentes, A.; Sanz-Cervera, J. F. *Org. Prep. Proced. Int.* **2009**, *41*, 253. (d) Fustero, S.; Sánchez-Roselló, M.; Barrio, P.; Simón-Fuentes, A. *Chem. Rev.* **2011**, *111*, 6984. (e) Janin, Y. L. *Chem. Rev.* **2012**, *112*, 3924. For recent pyrazole syntheses, see, for example: (f) Neumann, J. J.; Suri, M.; Glorius, F. *Angew. Chem., Int. Ed.* **2010**, *49*, 7790. (g) Shan, G.; Liu, P.; Rao, Y. *Org. Lett.* **2011**, *13*, 1746. (h) Wang, Y.; Bi, X.; Li, W. Q.; Li, D.; Zhang, Q.; Liu, Q.; Ondon, B. S. *Org. Lett.* **2011**, *13*, 1722. (i) Qian, J.; Liu, Y.; Zhu, J.; Jiang, B.; Xu, Z. *Org. Lett.* **2011**, *13*, 4220. (j) Foster, R. S.; Jakobi, H.; Harrity, J. P. A. *Org. Lett.* **2012**, *14*, 4858. (k) Zhang, G.; Ni, H.; Chen, W.; Shao, J.; Liu, H.; Chen, B.; Yu, Y. *Org. Lett.* **2013**, *15*, 5967. (l) Zhu, X.; Wang, Y. F.; Ren, W.; Zhang, F. L.; Chiba, S. *Org. Lett.* **2013**, *15*, 3214. (m) Zhang, G.; Zhao, Y.; Ge, H. *Angew. Chem., Int. Ed.* **2013**, *52*, 2559. (n) Kong, Y.; Tang, M.; Wang, Y. *Org. Lett.* **2014**, *16*, 576. (o) Schneider, Y.; Prévost, J.; Gobin, M.; Legault, C. Y. *Org. Lett.* **2014**, *16*, 596. (p) Zhang, F. G.; Wei, Y.; Yi, Y. P.; Nie, J.; Ma, J. A. *Org. Lett.* **2014**, *16*, 3122. (q) Zhang, J.; Shao, Y.; Wang, H.; Luo, Q.; Chen, J.; Xu, D.; Wan, X. *Org. Lett.* **2014**, *16*, 3312. (r) Li, X.; He, L.; Chen, H.; Wu, W.; Jiang, H. *J. Org. Chem.* **2013**, *78*, 3636. (s) Zhang, T.; Bao, W. *J. Org. Chem.* **2013**, *78*, 1317. (t) Chen, J. R.; Dong, W. R.; Candy, M.; Pan, F. F.; Jorres, M.; Bolm, C. *J. Am. Chem. Soc.* **2012**, *134*, 6924. (u) Zhu, C.; Bi, B.; Yao, D.; Chen, Q. Y.; Luo, Z. B. *Synthesis* **2015**, *47*, 1877.

(7) (a) Lee, K. Y.; Kim, J. M.; Kim, J. N. *Tetrahedron Lett.* **2003**, *44*, 6737. (b) Gerstenberger, B. S.; Rauckhorst, M. R.; Starr, J. T. *Org. Lett.* **2009**, *11*, 2097. (c) Okitsu, T.; Sato, K.; Wada, A. *Org. Lett.* **2010**, *12*, 3506. (d) Zora, M.; Kivrak, A.; Yazici, C. *J. Org. Chem.* **2011**, *76*, 6726.

(8) For reviews: (a) Xuan, J.; Xiao, W. J. *Angew. Chem., Int. Ed.* **2012**, *51*, 6828. (b) Prier, C. K.; Rankic, D. A.; MacMillan, D. W. *Chem. Rev.* **2013**, *113*, 5322. (c) Schultz, D. M.; Yoon, T. P. *Science* **2014**, *343*, 1239176. (d) Angnes, R. A.; Li, Z.; Correia, C. R. D.; Hammond, G. B. *Org. Biomol. Chem.* **2015**, *13*, 9152. (e) Xuan, J.; Zhang, Z. G.; Xiao, W. J. *Angew. Chem., Int. Ed.* **2015**, *54*, 15632. (f) Luo, J.; Zhang, J. *ACS Catal.* **2016**, *6*, 873. (g) Chen, J. R.; Hu, X. Q.; Lu, L. Q.; Xiao, W. J. *Chem. Soc. Rev.* **2016**, *45*, 2044. (h) Lang, X.; Zhao, J.; Chen, X. *Chem. Soc. Rev.* **2016**, *45*, 3026. For recent examples: (i) Jeffrey, J. L.; Terrett, J. A.; MacMillan, D. W. C. *Science* **2015**, *349*, 1532−1536. (j) Douglas, J. J.; Albright, H.; Sevrin, M. J.; Cole, K. P.; Stephenson, C. R. J. *Angew. Chem., Int. Ed.* **2015**, *54*, 14898. (k) Zhang, G.; Liu, C.; Yi, H.; Meng, Q.; Bian, C.; Chen, H.; Jian, J. X.; Wu, L. Z.; Lei, A. *J. Am. Chem. Soc.* **2015**, *137*, 9273. (l) Jiang, H.; An, X.; Tong, K.; Zheng, T.; Zhang, Y.; Yu, S. *Angew. Chem., Int. Ed.* **2015**, *54*, 4055. (m) Liu, C.; Oblak, E. Z.; Vander Wal, M. N.; Dilger, A. K.; Almstead, D. K.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2016**, *138*, 2134−2137. (n) Hu, X. Q.; Qi, X. T.; Chen, J. R.; Zhao, Q. Q.; Wei, Q.; Lan, Y.; Xiao, W. J. *Nat. Commun.* **2016**, *7*, 11188. (o) Wei, Y.; Lu, L. Q.; Li, T. R.; Feng, B.; Wang, Q.; Xiao, W. J.; Alper, H. *Angew. Chem., Int. Ed.* **2016**, *55*, 2200. (p) Kainz, Q. M.; Matier, C. D.; Bartoszewicz, A.; Zultanski, S. L.; Peters, J. C.; Fu, G. C. *Science* **2016**, *351*, 681. (q) Yayla, H. G.; Peng, F.; Mangion, I. K.; McLaughlin, M. M.; Campeau, L. C.; Davies, I. W.; DiRocco, D. A.; Knowles, R. R. *Chem. Sci.* **2016**, *7*, 2066. (r) Zhong, J. J.; Liu, Q.; Wu, C. J.; Meng, Q. Y.; Gao, X. W.; Li, Z. J.; Chen, B.; Tung, C. H.; Wu, L. Z. *Chem. Commun.* **2016**, *52*, 1800. (s) Amador, A. G.; Yoon, T. P. *Angew. Chem., Int. Ed.* **2016**, *55*, 2304.

(9) (a) Nicewicz, D. A.; MacMillan, D. W. C. *Science* **2008**, *322*, 77. (b) Ischay, M. A.; Anzovino, M. E.; Du, J.; Yoon, T. P. *J. Am. Chem. Soc.* **2008**, *130*, 12886. (c) Narayanam, J. M. R.; Tucker, J. W.; Stephenson, C. R. J. *J. Am. Chem. Soc.* **2009**, *131*, 8756. (d) Nagib, D. A.; Scott, M. E.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2009**, *131*, 10875.

(10) (a) Zhu, Y.; Zhang, L.; Luo, S. *J. Am. Chem. Soc.* **2014**, *136*, 14642. (b) Cecere, G.; König, C. M.; Alleva, J. L.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2013**, *135*, 11521. (c) Riente, P.; Matas Adams, A.; Albero, J.; Palomares, E.; Pericàs, M. A. *Angew. Chem., Int. Ed.* **2014**, *53*, 9613. (d) Hong, B. C.; Lin, C. W.; Liao, W. K.; Lee, G. H. *Org. Lett.* **2013**, *15*, 6258.

(11) (a) Yoon, T. P. *ACS Catal.* **2013**, *3*, 895. (b) Du, J.; Skubi, K. L.; Schultz, D. M.; Yoon, T. P. *Science* **2014**, *344*, 392.

(12) (a) Ghosh, I.; Ghosh, T.; Bardagi, J. I.; König, B. *Science* **2014**, *346*, 725. (b) Beatty, J. W.; Stephenson, C. R. J. *Acc. Chem. Res.* **2015**, *48*, 1474.

(13) Jin, J.; MacMillan, D. W. C. *Nature* **2015**, *525*, 87.

(14) (a) Zoller, J.; Fabry, D. C.; Ronge, M. A.; Rueping, M. *Angew. Chem., Int. Ed.* **2014**, *53*, 13264. (b) Fabry, D. C.; Zoller, J.; Raja, S.; Rueping, M. *Angew. Chem., Int. Ed.* **2014**, *53*, 10228. (c) Fabry, D. C.; Ronge, M. A.; Zoller, J.; Rueping, M. *Angew. Chem., Int. Ed.* **2015**, *54*, 2801.

(15) Benzophenone/*p*-toluenesulfonate hydrazone of benzaldehyde were isolated as the major products from the reactions of $PhNHNH_2$/$TsNHNH_2$ with **2a** respectively. See Supporting Information for details.