Organic LETTERS

Letter

pubs.acs.org/OrgLett

Synthesis of Polycarbonyl Pyrroles via $K_2S_2O_8$-Mediated Oxidative Cyclization of Enamines

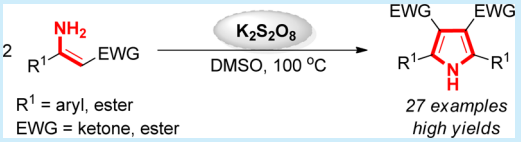
Peng Gao,*[,†,‡] Juan Wang,[†] Zi-Jing Bai,[†] Li Shen,[†] Yun-Yun Yan,[†] De-Suo Yang,[†] Ming-Jin Fan,[†] and Zheng-Hui Guan*[,‡]

[†]Shaanxi Key Laboratory of Phytochemistry, College of Chemistry and Chemical Engineering, Baoji University of Arts and Sciences, Baoji, Shaanxi 721013, P. R. China

[‡]Key Laboratory of Synthetic and Natural Functional Molecule Chemistry of Ministry of Education, Department of Chemistry & Materials Science, Northwest University, Xi'an 710127, P. R. China

Supporting Information

ABSTRACT: A novel $K_2S_2O_8$-promoted oxidative cyclization of enamines is described. A variety of enamines having diverse functional groups and substitution patterns react well using $K_2S_2O_8$ as the oxidant in the absence of catalyst. This protocol provides a very simple route for the synthesis of polycarbonyl pyrroles and has the advantages of readily available starting materials, mild reaction conditions, and a wide scope of substrates.



Polysubstituted pyrroles are an important class of five-membered heterocycles and exist in numerous natural products and bioactive molecules.[1] Carbonyl groups in these molecules are key moieties that are closely related to their biological activities (Figure 1). For example, ningalins A is

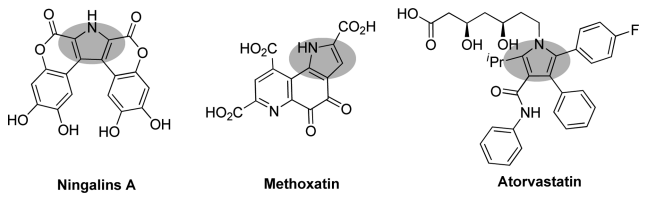


Figure 1. Selected examples of functional polycarbonyl pyrroles.

isolated from Western Australian ascidian,[1a] methoxatin acts as a bacterial coenzyme,[1b] and atorvastatin is used for the treatment of dyslipidemia.[1c] Thus, extensive attention has been paid to developing methods for the construction of pyrroles containing carbonyl groups. The classic Paal–Knorr[2] and Hantzsch[3] reactions have been frequently used to assemble pyrroles with a single carbonyl group on the ring. In the past several decades, novel methods such as transition-metal-catalyzed coupling[4] and multicomponent reactions[5] have been established for the synthesis of functional multicarbonyl pyrroles. Following these strategies, one or two carbonyl groups can be introduced into the pyrrole compound. In addition, oxidative cyclization of enamines using various oxidants,[6] including $Pb(OAc)_4$,[6a] $PhI(OAc)_2$,[6b] and CAN,[6c] has provided alternative approaches for the synthesis of dicarbonyl pyrroles. However, the development of novel and practical methods for the synthesis of multicarbonyl pyrroles, especially symmetrical multicarbonyl pyrroles, is still highly desirable.

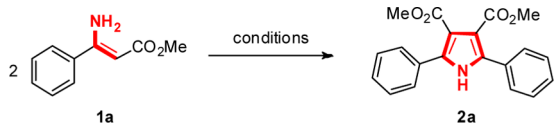
In recent years, radical reactions have attracted broad interest in organic synthesis and have been widely applied in medicinal and materials chemistry.[7−9] In this context, a variety of transition-metal-free radical cyclization processes have been successfully established for the synthesis of functional heterocyclic compounds via intra- or intermolecular carbon–carbon or carbon–heteroatom bond formations.[10] Despite considerable progress in this field, exploration of simpler and efficient methods are still highly appealing. Very recently, $K_2S_2O_8$ was found to be a useful oxidant in oxidative reactions because of its characteristics of easy availability, good stability, and low toxicity.[11] Thus, studies focusing on the development of $K_2S_2O_8$-mediated oxidative reactions meet the requirement of sustainable chemistry. In continuation of our efforts on the synthesis of pyrroles,[12] herein we report an efficient $K_2S_2O_8$-mediated oxidative cyclization of enamines for the synthesis of dicarbonyl or tetracarbonyl pyrroles.

In preliminary experiments, (*Z*)-methyl 3-amino-3-phenylacrylate (**1a**) was chosen as a model substrate to optimize the reaction conditions (Table 1). Treatment of **1a** with 1.0 equiv of *tert*-butyl hydroperoxide (TBHP) in DCE at 100 °C under air for 5 h afforded the desired pyrrole **2a** in 19% yield (Table 1, entry 1). Then various reaction parameters were screened, including the oxidant, solvent, and temperature. A range of oxidants such as $PhI(OAc)_2$, IBX, $NaBO_3{\cdot}4H_2O$, $(NH_4)_2S_2O_8$, $Na_2S_2O_8$, and $K_2S_2O_8$ were tested, and $K_2S_2O_8$ showed the highest efficiency (Table 1, entries 2–7). Increasing the loading of $K_2S_2O_8$ to 1.2 equiv improved the yield of **2a** to 87% (Table 1, entry 8), while the yield of **2a** was decreased when the loading of $K_2S_2O_8$ was further increased (Table 1, entry 9). The solvent also plays a key role in this transformation. The product yield decreased when DCE, CH_3CN, or toluene was used as the

Received: October 12, 2016

DOI: 10.1021/acs.orglett.6b03060
Org. Lett. XXXX, XXX, XXX–XXX

Table 1. Optimization of the Reaction Conditions[a]



1a 2a

entry	oxidant (equiv)	solvent	t (°C)	yield (%)[b]
1	TBHP (1)	DMSO	100	19
2	$PhI(OAc)_2$ (1)	DMSO	100	<5
3	IBX (1)	DMSO	100	<5
4	$NaBO_3{\cdot}4H_2O$ (1)	DMSO	100	0
5	$(NH_4)_2S_2O_8$ (1)	DMSO	100	54
6	$Na_2S_2O_8$ (1)	DMSO	100	64
7	$K_2S_2O_8$ (1)	DMSO	100	68
8	**$K_2S_2O_8$ (1.2)**	**DMSO**	**100**	**87**
9	$K_2S_2O_8$ (1.5)	DMSO	100	74
10	$K_2S_2O_8$ (1.2)	DCE	100	21
11	$K_2S_2O_8$ (1.2)	CH_3CN	100	26
12	$K_2S_2O_8$ (1.2)	toluene	100	23
13	$K_2S_2O_8$ (1.2)	DMSO	80	85
14	$K_2S_2O_8$ (1.2)	DMSO	120	84

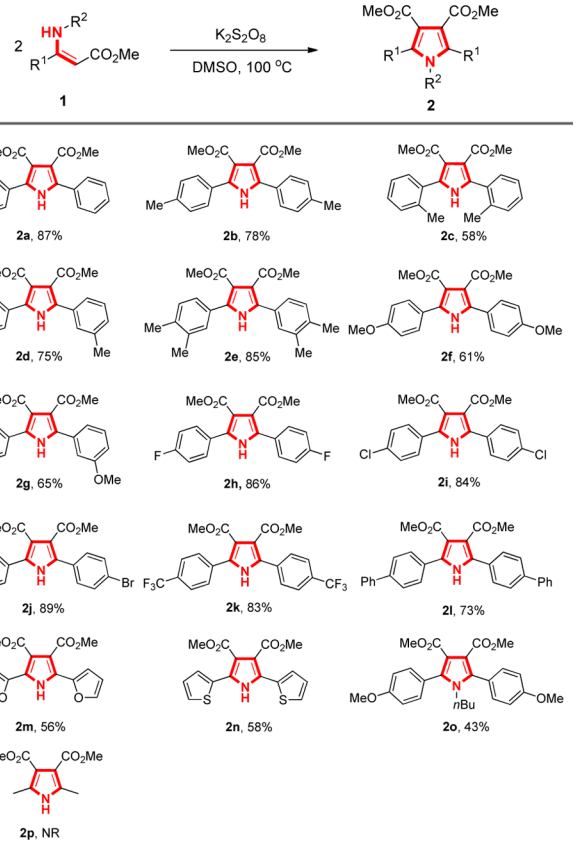
[a]Conditions: **1a** (0.5 mmol), oxidant, solvent (5 mL), 5 h. [b]Isolated yields.

solvent (Table 1, entries 10−12). The reaction temperature has little influence on the reaction efficiency, and 100 °C is still the best choice (Table 1, entries 13 and 14). Thus, the optimized procedure was chosen as follows: **1a** (0.5 mmol) and $K_2S_2O_8$ (0.6 mmol) in DMSO at 100 °C.

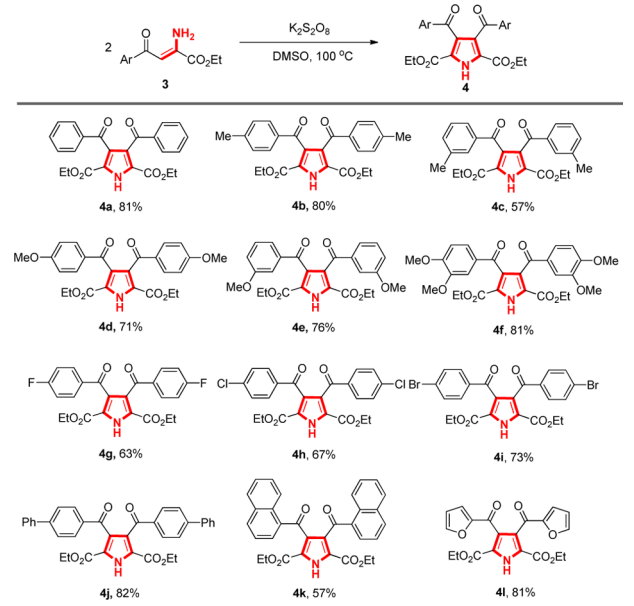
With optimized reaction conditions available, the scope of this oxidative cyclization reaction was then investigated. The reaction showed good functional group tolerance and proved to be a practical procedure for the synthesis of dicarbonyl pyrroles (Scheme 1). Enamines containing an electron-donating substituent such as a methyl or methoxyl group on the aryl ring furnished the corresponding products in 58−85% yield (**2b−g**). It should be noted that the lower yield of product **2c** might be due to the steric effect of the *o*-methyl group. Substituents such as F, Cl, and Br on the aryl ring of the enamine were smoothly tolerated in the reaction, and the desired products were obtained in good yields (**2h−j**) and could be derivatized to give various functionalized pyrrole compounds. Trifluoromethyl and phenyl groups also were compatible with the reaction and gave the corresponding products in 83% and 73% yield, respectively (**2k** and **2l**). It was remarkable that heterocyclic and *N*-butyl-substituted enamines were tolerated as well, providing the desired pyrroles in moderate yields (**2m−o**). However, alkyl-substituted enamine **1p** failed to yield the desired product **2p**.

To further demonstrate the synthetic practicality of this method, we next focused on the synthesis of tetracarbonyl pyrroles (Scheme 2). When enaminone **3a** was employed in the reaction, the desired tetracarbonyl pyrrole **4a** was obtained in 81% yield, and this was further proved by X-ray analysis (Figure 2). Encouraged by this result, we evaluated the scope and generality of this transformation. Aryl enaminones **3** with electron-donating substituents (−Me, −OMe) were well-

Scheme 1. Scope of the Synthesis of Dicarbonyl Pyrroles



Scheme 2. Scope of the Synthesis of Tetracarbonyl Pyrroles



tolerated, delivering the desired products in 57−80% yield (**4b−f**). Enaminones with electron-withdrawing substituents such as F, Cl, and Br all reacted well and were transformed into the corresponding tetracarbonyl pyrroles in moderate yields (**4g−i**). In addition, the biaryl and fused-ring substrates gave the products in 81% and 53% yield, respectively (**4j** and **4k**). The heteroaromatic substrate **3l** was also smoothly converted

DOI: 10.1021/acs.orglett.6b03060
Org. Lett. XXXX, XXX, XXX−XXX

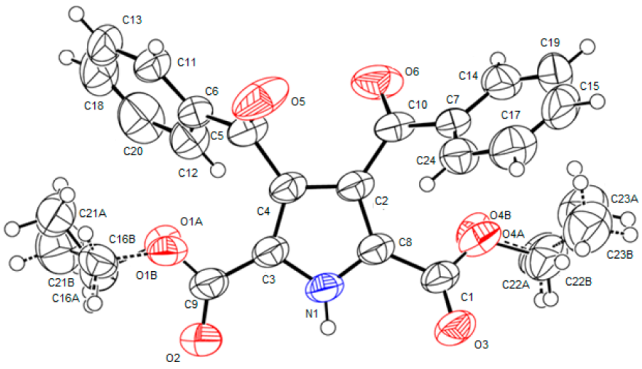
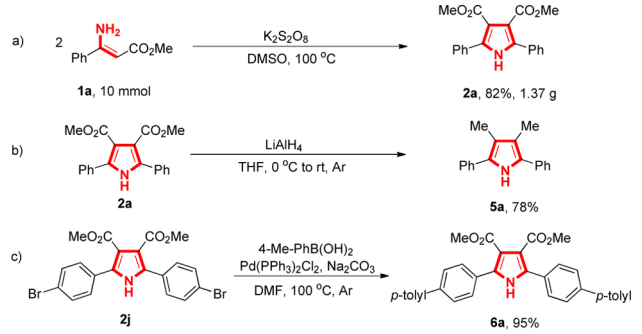


Figure 2. X-ray of structure of **4a**.

to the corresponding tetracarbonyl pyrrole **4l** in very good yield.

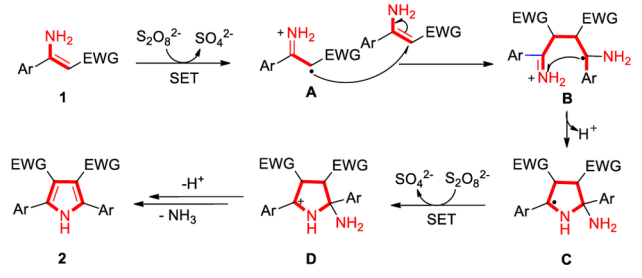
For practical purposes, we attempted the scaled-up synthesis of pyrrole **2a** (Scheme 3a). The reaction using 10 mmol of **1a** furnished **2a** in 82% yield without any significant decrease in its efficiency. Furthermore, to probe the utility of the reaction, several derivatization reactions were carried out. Reduction of **2a** with $LiAlH_4$ gave pyrrole derivative **5a** in 78% yield (Scheme 3b). On the other hand, Suzuki coupling of **2j** with *p*-tolylboronic acid afforded **6a** in 95% yield (Scheme 3c). These successful conversions of **2a** and **2j** illustrated that polycarbonly pyrroles are potential intermediates in organic synthesis.

Scheme 3. Gram-Scale Synthesis of 2a and Derivatization Reactions



We next focused on the mechanism of this reaction. A control experiment in which 2 equiv of 2,2,6,6-tetramethylpiperidin-1-oxyl (TEMPO) or 2,6-di-*tert*-butyl-4-methylphenol (BHT) was added to the model reaction failed to afford the pyrrole product **2a**, suggesting that the reaction may involve a radical process. On the basis of our experimental results and the literature,[6,13] a possible mechanism is proposed (Scheme 4).

Scheme 4. Possible Mechanism



Initially, oxidation of enamine **1** by $K_2S_2O_8$ generates amino radical cation **A**, which reacts with a second molecule of enamine **1** to form intermediate **B**. Then intramolecular C−N bond formation leads to intermediate **C**. Oxidation of **C** generates intermediate **D**. Finally, sequential elimination of H^+ and NH_3 from **D** produces the product **2**.

In summary, we have developed an efficient and practical oxidative cyclization of enamines for the synthesis of polycarbonyl pyrroles under transition-metal-free conditions. A range of functionalized dicarbonyl or tetracarbonyl pyrroles were obtained in high yields using inexpensive, stable, and commercially available $K_2S_2O_8$ as the sole oxidant. Moreover, the gram-scale reaction demonstrates the potential usefulness of this transformation in organic synthesis. Further studies of oxidative cyclization of enamines are ongoing in our group.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b03060.

Experimental procedures, analytical data, and NMR spectra of the products (PDF)
X-ray data for **2a** (CIF)
X-ray data for **4a** (CIF)

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: gaopeng_hx@bjwlxy.edu.cn.
*E-mail: guanzhh@nwu.edu.cn.

ORCID

Peng Gao: 0000-0003-1292-0691
Zheng-Hui Guan: 0000-0003-4901-5951

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We are grateful to the National Natural Science Foundation of China (21272183, 21472147, and 21622203), Shaanxi Provincial Key Laboratory Project (15JS004), Baoji University of Arts and Sciences (ZK15046), and Northwest University (334100038) for financial support.

■ REFERENCES

(1) (a) Fan, H.; Peng, J.; Hamann, M. T.; Hu, J.-F. *Chem. Rev.* **2008**, *108*, 264. (b) Young, I. S.; Thornton, P. D.; Thompson, A. *Nat. Prod. Rep.* **2010**, *27*, 1801. (c) Colhoun, H. M.; Betteridge, D. J.; Durrington, P. N.; Hitman, G. A.; Neil, H. A. W.; Livingstone, S. J.; Thomason, M. J.; Mackness, M. I.; Charlton-Menys, V.; Fuller, J. H. *Lancet* **2004**, *364*, 685. (d) Liu, R.; Liu, Y.; Zhou, Y.-D.; Nagle, D. G. *J. Nat. Prod.* **2007**, *70*, 1741. (e) Jansen, R.; Sood, S.; Mohr, K. I.; Kunze, B.; Irschik, H.; Stadler, M.; Müller, R. *J. Nat. Prod.* **2014**, *77*, 2545.

(2) (a) Chen, J.; Wu, H.; Zheng, Z.; Jin, C.; Zhang, X.; Su, W. *Tetrahedron Lett.* **2006**, *47*, 5383. (b) Cranwell, P. B.; O'Brien, M.; Browne, D.; Koos, P.; Polyzos, A.; Peña-López, M.; Ley, S. V. *Org. Biomol. Chem.* **2012**, *10*, 5774. (c) Handy, S.; Lavender, K. *Tetrahedron Lett.* **2013**, *54*, 4377. (d) Karami, B.; Khodabakhshi, S.; Jamshidi, M. *J. Chin. Chem. Soc.* **2013**, *60*, 1103. (e) Cho, H.; Madden, R.; Nisanci, B.; Török, B. *Green Chem.* **2015**, *17*, 1088.

(3) (a) Herath, A.; Cosford, N. D. P. *Org. Lett.* **2010**, *12*, 5182. (b) Moss, T. A.; Nowak, T. *Tetrahedron Lett.* **2012**, *53*, 3056.

DOI: 10.1021/acs.orglett.6b03060
Org. Lett. XXXX, XXX, XXX−XXX

(c) Estévez, V.; Villacampa, M.; Menéndez, J. C. *Chem. Commun.* **2013**, *49*, 591.
(4) (a) Seregin, I. V.; Gevorgyan, V. *Chem. Soc. Rev.* **2007**, *36*, 1173. (b) McMurray, L.; O'Hara, F.; Gaunt, M. J. *Chem. Soc. Rev.* **2011**, *40*, 1885. (c) Li, B.-J.; Shi, Z.-J. *Chem. Soc. Rev.* **2012**, *41*, 5588. (d) Wang, L.; Li, Z.; Qu, X.; Peng, W. *Chin. J. Chem.* **2015**, *33*, 1015. (e) Zhou, N.-N.; Zhu, H.-T.; Yang, D.-S.; Guan, Z.-H. *Org. Biomol. Chem.* **2016**, *14*, 7136.
(5) (a) Estévez, V.; Villacampa, M.; Menéndez, J. C. *Chem. Soc. Rev.* **2010**, *39*, 4402. (b) Estévez, V.; Villacampa, M.; Menéndez, J. C. *Chem. Soc. Rev.* **2014**, *43*, 4633. (c) Zhang, M.; Fang, X.; Neumann, H.; Beller, M. *J. Am. Chem. Soc.* **2013**, *135*, 11384. (d) Wang, X.; Xu, X.; Wang, S.-Y.; Zhou, W.; Ji, S.-J. *Org. Lett.* **2013**, *15*, 4246.
(6) (a) Sukari, M. A.; Vernon, J. M. *Tetrahedron* **1983**, *39*, 793. (b) Tsai, A.-I.; Chuang, C.-P. *Tetrahedron* **2006**, *62*, 2235. (c) Wang, J. Y.; Liu, S.-P.; Yu, W. *Synlett* **2009**, *2009*, 2529. (d) Rakshit, S.; Patureau, F. W.; Glorius, F. *J. Am. Chem. Soc.* **2010**, *132*, 9585. (e) Liu, W.; Jiang, H.; Huang, L. *Org. Lett.* **2010**, *12*, 312. (f) Zhao, M.; Wang, F.; Li, X. *Org. Lett.* **2012**, *14*, 1412. (g) Zhou, N.; Xie, T.; Liu, L.; Xie, Z. *J. Org. Chem.* **2014**, *79*, 6061.
(7) (a) Recupero, F.; Punta, C. *Chem. Rev.* **2007**, *107*, 3800. (b) Zard, S. Z. *Chem. Soc. Rev.* **2008**, *37*, 1603. (c) Wille, U. *Chem. Rev.* **2013**, *113*, 813. (d) Hoffmann, R. W. *Chem. Soc. Rev.* **2016**, *45*, 577. (e) Staveness, D.; Bosque, I.; Stephenson, C. R. J. *Acc. Chem. Res.* **2016**, *49*, 2295. (f) Matcha, K.; Narayan, R.; Antonchick, A. P. *Angew. Chem., Int. Ed.* **2013**, *52*, 7985. (g) Tang, S.; Liu, K.; Liu, C.; Lei, A. *Chem. Soc. Rev.* **2015**, *44*, 1070.
(8) (a) Caron, S.; Dugger, R. W.; Ruggeri, S. G.; Ragan, J. A.; Ripin, D. H. B. *Chem. Rev.* **2006**, *106*, 2943. (b) Xu, G.; Chance, M. R. *Chem. Rev.* **2007**, *107*, 3514. (c) Nicolaou, K. C.; Chen, J. S. *Chem. Soc. Rev.* **2009**, *38*, 2993. (d) Yu, L.-F.; Hu, H.-N.; Nan, F.-J. *J. Org. Chem.* **2011**, *76*, 1448. (e) Yin, J.; Kong, L.; Gao, S. *Youji Huaxue* **2013**, *33*, 259. (f) Newcomb, E. T.; Knutson, P. C.; Pedersen, B. A.; Ferreira, E. M. *J. Am. Chem. Soc.* **2016**, *138*, 108.
(9) (a) Satoh, K.; Kamigaito, M. *Chem. Rev.* **2009**, *109*, 5120. (b) Ratera, I.; Veciana, J. *Chem. Soc. Rev.* **2012**, *41*, 303. (c) Tzirakis, M. D.; Orfanopoulos, M. *Chem. Rev.* **2013**, *113*, 5262. (d) Zhang, N.; Samanta, S. R.; Rosen, B. M.; Percec, V. *Chem. Rev.* **2014**, *114*, 5848.
(10) (a) Majumdar, K. C.; Basu, P. K.; Mukhopadhyay, P. P. *Tetrahedron* **2005**, *61*, 10603. (b) Uyanik, M.; Ishihara, K. *ChemCatChem* **2012**, *4*, 177. (c) Sun, C.-L.; Shi, Z.-J. *Chem. Rev.* **2014**, *114*, 9219. (d) Merino, E.; Nevado, C. *Chem. Soc. Rev.* **2014**, *43*, 6598. (e) Shang, X.; Liu, Z. *Huaxue Xuebao* **2015**, *73*, 1275.
(11) (a) Yang, Z.; Chen, X.; Wang, S.; Liu, J.; Xie, K.; Wang, A.; Tan, Z. *J. Org. Chem.* **2012**, *77*, 7086. (b) Gary, J. B.; Cook, A. K.; Sanford, M. S. *ACS Catal.* **2013**, *3*, 700. (c) Wang, H.; Guo, L.-N.; Duan, X.-H. *Org. Lett.* **2013**, *15*, 5254. (d) Wang, S.; Guo, L.-N.; Wang, H.; Duan, X.-H. *Org. Lett.* **2015**, *17*, 4798. (e) Ma, D.; Chen, W.; Hu, G.; Zhang, Y.; Gao, Y.; Yin, Y.; Zhao, Y. *Green Chem.* **2016**, *18*, 3522.
(12) (a) Guan, Z.-H.; Li, L.; Ren, Z.-H.; Li, J.; Zhao, M.-N. *Green Chem.* **2011**, *13*, 1664. (b) Zhao, M.-N.; Liang, H.; Ren, Z.-H.; Guan, Z.-H. *Adv. Synth. Catal.* **2013**, *355*, 221. (c) Zhao, M.-N.; Ren, Z.-H.; Wang, Y.-Y.; Guan, Z.-H. *Org. Lett.* **2014**, *16*, 608. (d) Du, W.; Zhao, M.-N.; Ren, Z.-H.; Wang, Y.-Y.; Guan, Z.-H. *Chem. Commun.* **2014**, *50*, 7437. (e) Lian, X.-L.; Ren, Z.-H.; Wang, Y.-Y.; Guan, Z.-H. *Org. Lett.* **2014**, *16*, 3360. (f) Ran, L.-F.; Ren, Z.-H.; Wang, Y.-Y.; Guan, Z.-H. *Green Chem.* **2014**, *16*, 112.
(13) (a) Toh, K. K.; Wang, Y.-F.; Ng, E. P. J.; Chiba, S. *J. Am. Chem. Soc.* **2011**, *133*, 13942. (b) Wang, Y.-F.; Zhu, X.; Chiba, S. *J. Am. Chem. Soc.* **2012**, *134*, 3679. (c) Cheung, C. W.; Buchwald, S. L. *J. Org. Chem.* **2012**, *77*, 7526. (d) Zhang, Z.-J.; Ren, Z.-H; Wang, Y.-Y.; Guan, Z.-H. *Org. Lett.* **2013**, *15*, 4822.

DOI: 10.1021/acs.orglett.6b03060
Org. Lett. XXXX, XXX, XXX−XXX