Organic LETTERS

Letter

Cite This: Org. Lett. XXXX, XXX, XXX−XXX

pubs.acs.org/OrgLett

Rapid Syntheses of Heteroaryl-Substituted Imidazo[1,5-*a*]indole and Pyrrolo[1,2-*c*]imidazole via Aerobic C2−H Functionalizations

Wei-Jun Kong,[†] Xingrong Chen,[†] Mingming Wang,[†] Hui-Xiong Dai,*[,†,‡] and Jin-Quan Yu*[,†,§]

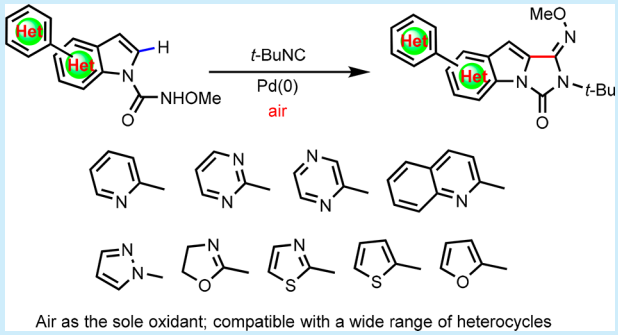
[†]State Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, Shanghai 200032, China

[‡]Department of Medicinal Chemistry, Shanghai Institute of Materia Medica, Chinese Academy of Sciences, 555 Road Zu Chong Zhi, Zhangjiang Hi-Tech Park, Shanghai, 201203, China

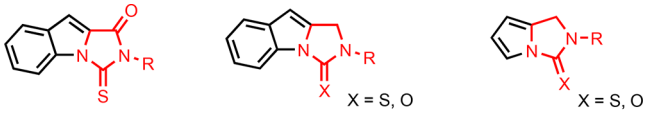
[§]Department of Chemistry, The Scripps Research Institute, 10550 North Torrey Pines Road, La Jolla, California 92037, United States

Supporting Information

ABSTRACT: Here we report an aerobic Pd(0) catalyzed C2−H functionalization of indoles and pyrroles with tethered *N*-methoxylamide as the directing group. A Pd(0)-initiated mechanism overcomes the directing or poisoning effect from a wide range of heterocycles including pyridine, pyrimidine, and thiazole. The imidazo[1,5-*a*]indole products are transformed to bioactive analogs after one-step manipulations, demonstrating the potential utility of this reaction in drug discovery.



Imidazo[1,5-*a*]indole and pyrrolo[1,2-*c*]imidazole derivatives have been found to possess a wide range of biological activities (Figure 1). A number of applications in medicinal



a: TNF-a antagonist and antifungals

b: CNS depressant, analgesics and 5-HT$_3$ receptor antagonists

c: Antidiabetic and aldose reductase inhibitor (ARI)

Figure 1. Representative bioactive compounds of imidazo[1,5-*a*]indole and pyrrolo[1,2-*c*]imidazole derivatives.

chemistry have been found by minor structural variations. For example, structure **a** could be used as light-dependent tumor necrosis factor-α (TNF-α) antagonists and antifungals.[1] Compounds containing structure **b** can serve as central nervous system (CNS) depressants, analgesics, and receptor antagonists.[2] Compounds **c** are aldose reductase inhibitors (ARI) and provide therapeutic possibility in the treatment of chronic complications in diabetes.[3] Directed C2−H functionalizations of indole or pyrrole have been successfully exploited to synthesize these polycyclic heterocycles.[4,5] Recently, Cui and others reported Rh(III)-catalyzed C2−H arylation using the CONHOMe directing group[5] previously developed in our laboratory.[6] However, substrates containing herteroaryls are not described, presumably due to incompatibility. Considering the importance of heterocycles in drug discovery,[7] it is crucial to develop catalytic systems that can functionalize heteroarylated indoles and pyrroles to provide synthetic routes for the preparation of heteroarylated imidazo[1,5-*a*]indole and pyrrolo[1,2-*c*]imidazoles.

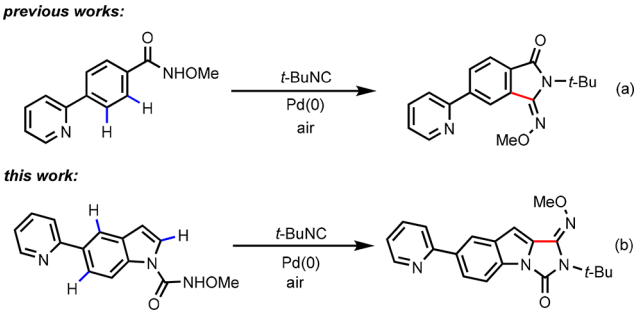
Poor compatibility with heterocycles is a widespread problem in Pd-catalyzed C−H functionalizations. First, heterocycles could direct C−H activation at the undesired position; second, heterocyles could sequester the Pd(II) catalyst via strong coordination and render them inactive. Three major approaches have been developed to overcome these undesired heterocycle effects. Masking the coordinating atom by strong acid or oxidizing the nitrogen to N-oxides has been employed for allylic C(sp^3)−H of acetoxylation.[8] Alternatively, the use of strongly coordinating bidentate directing groups can also circumvent this problem to some extent. Especially, the combination of a bidentate oxazoline-based directing group and copper catalysts has demonstrated exceptional compatibility.[9] The third approach involves design of directing groups that can coordinate with a metal catalyst and also participate in a subsequent bond forming event thereby outcompeting other heterocycles.[10]

We have previously developed a catalytic system in which Pd(0) is oxidized and sequestered by a *N*-methoxyl amide directing group using air as the sole oxidant.[10a] Pd(II) coordinated with the amide directing group is rapidly trapped by isocyanide thereby overcoming interference from a wide range of heterocycles (Scheme 1a). We wonder whether analogous transformation can be developed for C2−H functionalization of indole if the *N*-methoxylamide group is

Received: November 28, 2017

DOI: 10.1021/acs.orglett.7b03596
Org. Lett. XXXX, XXX, XXX−XXX

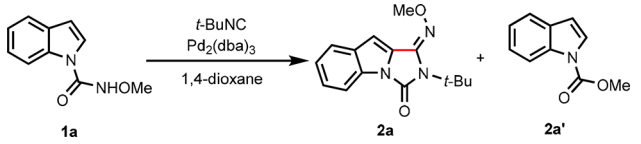
Scheme 1. Overcoming the Limitation of Heterocycle in Pd(0) Catalyzed C−H Functionalizations



tethered to indole via the urea linkage. If successful, a rapid synthetic route can be established for the imidzao[1,5-*a*]indole derivative (Scheme 1b). The anticipated compatibility of this reaction with heteroatoms might provide access to diverse imidzao[1,5-*a*]indole decorated with various heterocycles. Herein, we report an aerobic C2−H functionalization of indoles and pyrroles containing a wide range of heterocycles, which provides a new avenue to construct medicinally important imidazo[1,5-*a*]indole and pyrrolo[1,2-*c*]imidazole molecules.

We commenced the study with *N*-methoxy-1*H*-indole-1-carboxamide **1a** as the model substrate to explore the reaction conditions. The proposed reaction could take place at 50 °C, affording the desired product **2a** in 60% yield, and the C3−H is intact.[11] However, 10% of byproduct **2a′** was also observed (entries 2−4, Table 1). In order to improve the selectivity of **2a**

Table 1. Optimization of Reaction Conditions[a,b]



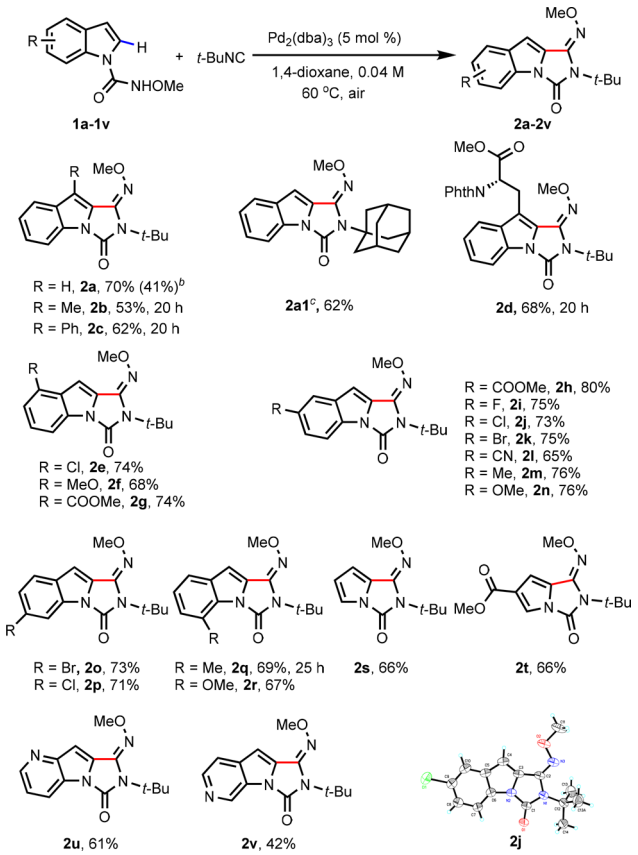
entry	temp (°C)	*V* (mL)	*M* (mol/L)	**2a**	**2a′**
1	rt	1	0.1	trace	trace
2	50	1	0.1	60%	10%
3	60	1	0.1	66%	10%
4	70	1	0.1	64%	10%
5	60	0.5	0.2	49%	12%
6	60	2	0.05	66%	5%
7	60	3	0.033	66%	4%
8	60	5	0.02	69%	4%
9[c]	**60**	**5**	**0.04**	**70%**[d]	–

[a]Reaction conditions: 0.1 mmol of **1a**, *t*-BuNC (2 equiv), $Pd_2(dba)_3$ (5 mol %), 15 mL sealed vial, 10 h. [b]Yield determined by ^1H NMR analysis of crude reaction mixture using CH_2Br_2 as an internal standard. [c]With 0.2 mmol of **1a**, 35 mL sealed vial. [d]Isolated yield.

to **2a′**, reaction conditions were screened and it was found that concentration played an important role in the formation of **2a′**. A lower concentration led to lower yields of **2a′** and a slight improvement in the production of **2a** (entries 5−8, Table 1). When the concentration was less than 0.05 M, the yield of **2a′** could be reduced to lower than 5%. For the reason for practicability, we chose 0.04 M as the optimal concentration for further study (entry 9, Table 1).

With the reaction conditions established, it is crucial to examine the scope of indoles, especially the compatibility with heteroaryl-substituted indoles and pyrroles (Scheme 2). *N*-methoxyl aminocarbonyl (MeONHCO−) protected 3-methyl-

Scheme 2. Scope of Indoles and Pyrroles[a]



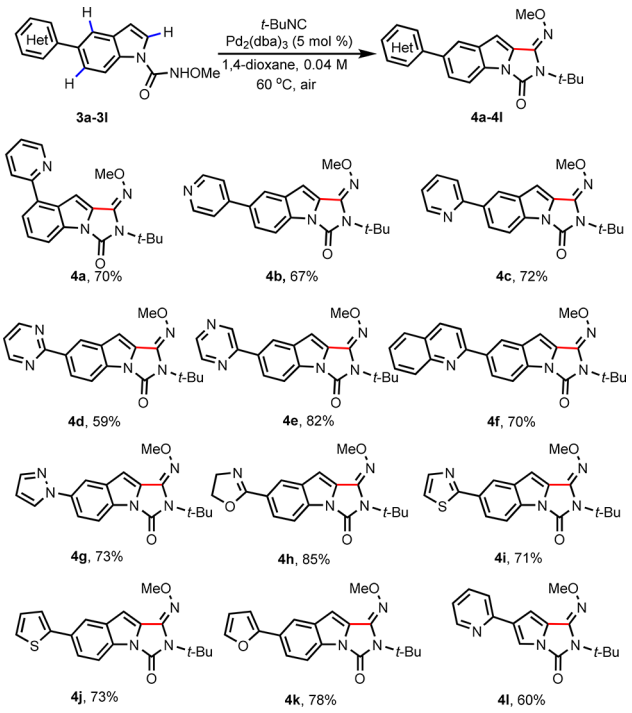
[a]Reaction conditions: 0.2 mmol **1a**−**1l**, *t*-BuNC (2 equiv), $Pd_2(dba)_3$ (5 mol %), 35 mL sealed vial, 60 °C, 10 h; isolated yields. [b]1.0 mmol scale. [c]With 1-adamantyl isocyanide (2 equiv).

indole **1b**, 3-phenylindole **1c**, and phthalimide protected L-phenylalanine methyl ester **1d** gave the corresponding products in moderate yields after a prolonged reaction time, which may be due to steric hindrance (**2b**−**2d**). Meanwhile, a moderate yield was obtained when the reaction was scaled up to 1.0 mmol (**2a**, conditions b). 1-Adamantyl isocyanide was also applicable in this reaction, affording **2a1** in 62% yield. Various electron-donating and -withdrawing substituents including methyl (**2m**, **2q**), methoxyl (**2g**, **2n**, and **2r**), fluoro (**2i**), chloro (**2e**, **2j** (confirmed by X-ray), and **2p**), cyano (**2l**), and ester (**2g**, **2h**) at the 4-, 5-, 6-, and 7- position on indole were tolerated in this reaction, affording the desired products in moderate to good yields and excellent regiosectivity at the C2 position (65%−80% yields). A relatively reactive bromo group was also well tolerated in this Pd(0) catalyzed reaction (**2k** and **2o**), which can serve as a handle for further synthetic elaborations. Pyrrole was applicable in this reaction as well, furnishing product **2s** in 66% yield. When the C3 position of pyrrole was substituted with a methoxycarbonyl group COOMe, C−H activation takes place at the less hindered C5 position exclusively in a yield of 66% (**2t**). It is worth noting that 4- and 6-azaindoles **1u** and **1v** gave the corresponding products **2u** and **2v** in 61% and 42% yields respectively, demonstrating the compatibility of heterocycles.

DOI: 10.1021/acs.orglett.7b03596
Org. Lett. XXXX, XXX, XXX−XXX

After exploring the generality with common indoles and pyrroles, we then extensively investigated the compatibility of heterocycles in this reaction (Scheme 3). In particular, we

Scheme 3. Overcome the Limitation of Heterocycles in C−H Functionalization of Indoles and Pyrroles[a]

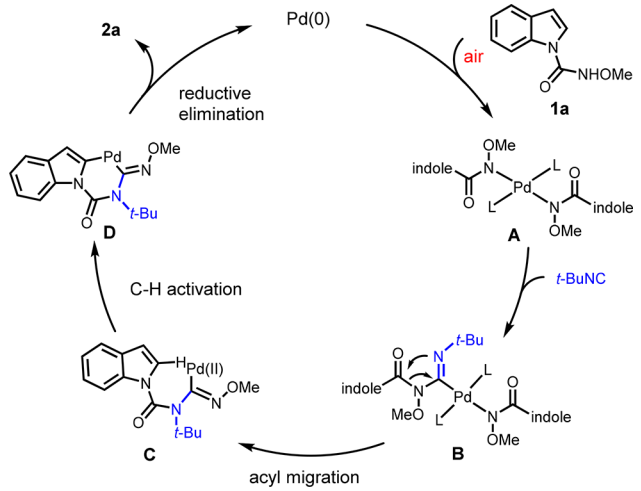


[a]Reaction conditions: 0.2 mmol of **3a−3l**, *t*-BuNC (2 equiv), $Pd_2(dba)_3$ (5 mol %), 35 mL sealed vial, 60 °C, 10 h; isolated yields.

examined the presence of heterocycles that can potentially direct C−H activation at other sites leading to scrambling of regioselectivity. When pyridine was installed at the C4 or C5 position of indoles, no detrimental effects were observed in this reaction. Importantly, no *ortho*-C−H activation directed by pyridine was observed with **3a−3c**. Pyrimidine, pyrazine, and quinoline tethered at the C5 position of indole were well tolerated, giving corresponding products in moderate to excellent yields (**4d−4f**). Substrates bearing five-membered nitrogen containing heterocycles including pyrazole, oxazoline, and thiazole at the C5 position were well tolerated (**3g−3i**). The C−H bonds of electron-rich furan and thiophene can potentially be activated by Pd(II) in a nondirected fashion to give undesired side products.[12] Under our standard conditions, the reaction produced the desired products **4j** and **4k** efficiently without side reactions occurring on the furan and thiophene rings. When the C3 position of pyrrole is substituted with a pyridyl group, C5−H was functionalized exclusively due to steric hindrance in 60% yield (**4l**). This result also suggests that the directing effect of pyridyl group is completely outcompeted.

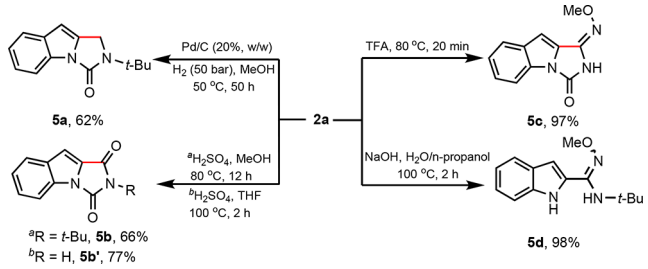
Based on our previous mechanistic study on this catalytic system,[10a] we propose a plausible mechanism for this reaction (Scheme 4). In the presence of air and **1a**, Pd(0) is oxidized to Pd(II) **A**, followed by 1,1-insertion of *t*-BuNC into the Pd−N bond to afford **B**. Acyl migration of **B** gives intermediate **C**, in which the C2−H is activated to give the six membered cyclopalladium(II) complex **D**. Reductive elimination of **D** furnishes the target product **2a** and releases active Pd(0).

Scheme 4. Proposed Mechanism for the Formation of 2a



To demonstrate the utility of the imidazo[1,5-*a*]indole products, a number of transformations were carried out. **2a** was converted to the aforementioned bioactive molecule analogs through simple manipulations (Scheme 5). The *N*-methoxyl

Scheme 5. Transformations of Product 2a



imido group of **2a** was reduced to afford analogous CNS depressant **5a** under hydrogen with Pd/C as catalyst. When treated with sulfuric acid in methanol, the *N*-methoxyl imido group could be hydrolyzed to give dicarboximide **5b** in 66% yield. Switching the solvent to tetrahydrofuran led to the removal of the *tert*-butyl group, affording 1*H*-imidazo[1,5-*a*]indole-1,3(2*H*)-dione **5b′**. Interestingly, reflux in trifluoroacetic acid can deprotect the *tert*-butyl group of **2a** selectively to give **5c** in 97% yield. Finally, treatment of **2a** with sodium hydroxide in mixed solvents of water and *n*-propanol furnished **5d** in nearly quantitative yield.

In summary, we have reported palladium(0) catalyzed isocyanide insertive C2−H functionalization of *N*-methoxylcarbonyl protected indoles and pyrroles to afford imidazo[1,5-*a*]indole and pyrrolo[1,2-*c*]imidazole derivatives. This reaction is compatible with various functional groups. The amide directing group overrides the directing or poisoning effect of diverse strongly coordinating heterocycles. The resulting imidazo[1,5-*a*]indoles could be transformed to bioactive analogs via simple synthetic manipulations.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b03596.

DOI: 10.1021/acs.orglett.7b03596
Org. Lett. XXXX, XXX, XXX−XXX

Experimental procedures and spectra data for all new compounds (PDF)

Accession Codes

CCDC 1573949 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

AUTHOR INFORMATION

Corresponding Authors

*E-mail: hxdai@simm.ac.cn (H.-X.D.).
*E-mail: yu200@scripps.edu (J.-Q.Y.)

ORCID

Hui-Xiong Dai: 0000-0002-2937-6146
Jin-Quan Yu: 0000-0003-3560-5774

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

We gratefully acknowledge Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, the CAS/SAFEA International Partnership Program for Creative Research Teams, NSFC-21121062, NSFC-21472211, NSFC-21421091, Youth Innovation Promotion Association CAS (No. 2014229), and The Recruitment Program of Global Experts for financial support. We gratefully acknowledge The Scripps Research Institute and the NIH (NIGMS, 1R01 GM102265) for their financial support.

REFERENCES

(1) (a) Voss, M. E.; Carter, P. H.; Tebben, A. J.; Scherle, P. A.; Brown, G. D.; Thompson, L. A.; Xu, M.; Lo, Y. C.; Yang, G.; Liu, R.-Q. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 533−538. (b) Kutschy, P.; Suchý, M.; Dzurilla, M.; Takasugi, M.; Kováčik, V. *Collect. Czech. Chem. Commun.* **2000**, *65*, 1163−1172.

(2) (a) Wright, W. B. US Patent, 3565902; *Chem. Abstr.* **1971**, *75*, 36033. (b) Varasi, M.; Heidempergher, F.; Caccia, C.; Salvati, P. PCT Int. Appl., WO 9532209; *Chem. Abstr.* **1995**, *124*, 232456.

(3) (a) Ogawa, K.; Yamawaki, I.; Matsushita, Y. *Jpn. Kokai.* Patent JP, 04297478; *Chem. Abstr.* **1992**, *118*, 234056. (b) Yamawaki, I.; Matsushita, Y.; Asaka, N.; Ohmori, K.; Nomura, N.; Ogawa, K. *Eur. J. Med. Chem.* **1993**, *28*, 481−498.

(4) Katritzky, A. R.; Singh, S. K.; Bobrov, S. *J. Org. Chem.* **2004**, *69*, 9313−9315.

(5) (a) Zheng, J.; Zhang, Y.; Cui, S. *Org. Lett.* **2014**, *16*, 3560−3563. (b) Wu, Z. J.; Li, Y. Q.; Huang, Z. Z. *Eur. J. Org. Chem.* **2016**, *2016*, 5399−5404. (c) Zhang, Y.; Zheng, J.; Cui, S. *J. Org. Chem.* **2014**, *79*, 6490−6500.

(6) (a) Wang, D.-H.; Wasa, M.; Giri, R.; Yu, J.-Q. *J. Am. Chem. Soc.* **2008**, *130*, 7190−7191. (b) Zhu, R.-Y.; Farmer, M. E.; Chen, Y.-Q.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2016**, *55*, 10578−10599; *Angew. Chem.* **2016**, *128*, 10734−10756.

(7) (a) Dalvie, D.; Kang, P.; Loi, C.-M.; Goulet, L.; Nair, S. *Metabolism, Pharmacokinetics and Toxicity of Functional Groups*; Royal Society of Chemistry: Cambridge, U.K., 2010; p 328. (b) Gibson, S.; McGuire, R.; Rees, D. C. *J. Med. Chem.* **1996**, *39*, 4065−4072. (c) Broughton, H. B.; Watson, I. A. *J. Mol. Graphics Modell.* **2004**, *23*, 51−58.

(8) Malik, H. A.; Taylor, B. L.; Kerrigan, J. R.; Grob, J. E.; Houk, K.; Du Bois, J.; Hamann, L. G.; Patterson, A. W. *Chem. Sci.* **2014**, *5*, 2352−2361.

(9) Shang, M.; Wang, M.-M.; Saint-Denis, T. G.; Li, M.-H.; Dai, H.-X.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2017**, *56*, 5317−5321.

(10) (a) Liu, Y.-J.; Xu, H.; Kong, W.-J.; Shang, M.; Dai, H.-X.; Yu, J.-Q. *Nature* **2014**, *515*, 389−393. (b) Kong, W.-J.; Liu, Y.-J.; Xu, H.; Chen, Y.-Q.; Dai, H.-X.; Yu, J.-Q. *J. Am. Chem. Soc.* **2016**, *138*, 2146−2149. (c) Wang, H.; Lorion, M. M.; Ackermann, L. *Angew. Chem., Int. Ed.* **2016**, *55*, 10386−10390.

(11) (a) Hu, Z.; Liang, D.; Zhao, J.; Huang, J.; Zhu, Q. *Chem. Commun.* **2012**, *48*, 7371−7373. (b) Xu, S.; Huang, X.; Hong, X.; Xu, B. *Org. Lett.* **2012**, *14*, 4614−4617.

(12) Yang, Y.; Lan, J.; You, J. *Chem. Rev.* **2017**, *117*, 8787−8863.

DOI: 10.1021/acs.orglett.7b03596
Org. Lett. XXXX, XXX, XXX−XXX