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

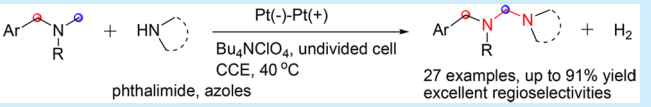
Electrochemical Dehydrogenative Imidation of *N*-Methyl-Substituted Benzylamines with Phthalimides for the Direct Synthesis of Phthalimide-Protected *gem*-Diamines

Fei Lian, Caocao Sun, Kun Xu, and Chengchu Zeng*

Beijing Key Laboratory of Environmental and Viral Oncology, College of Life Science & Bioengineering, Beijing University of Technology, Beijing 100124, China

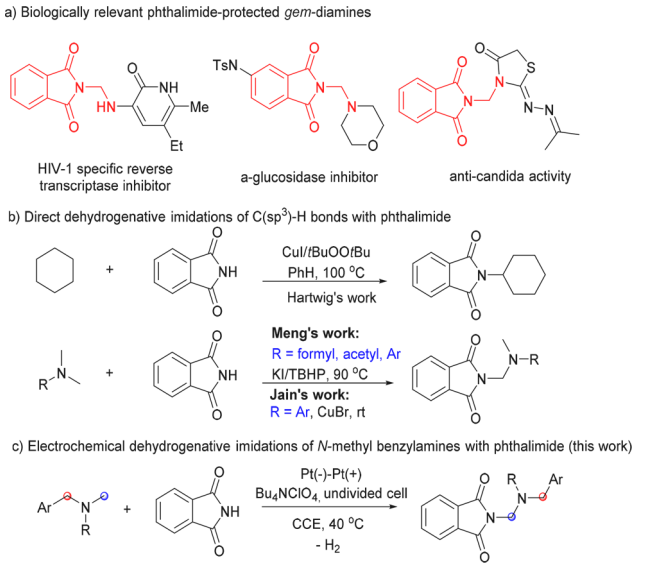
Supporting Information

ABSTRACT: A general and green electrochemical dehydrogenative method for the imidation of *N*-methyl benzylamines with phthalimides with excellent regioselectivities is reported for the first time. This operationally simple method offers a valuable tool to obtain structurally diverse phthalimide-protected *gem*-diamines.



Phthalimide-protected *gem*-diamines are an important class of core structures of biologically active molecules (Scheme 1a).[1] As such, there has been intensive efforts to identify convenient methods for phthalimide-protected *gem*-diamine synthesis.[2] In terms of synthetic efficiency and atom economy, dehydrogenative imidation of C(sp^3)−H bonds adjacent to a nitrogen atom with phthalimide would be an attractive strategy for the assembly of phthalimide-protected *gem*-diamines.[3] However, compared with imidation of C(sp^2)−H bonds,[4] direct imidation of C(sp^3)−H bonds with phthalimide is less explored (Scheme 1b).[5−7] In 2014, Hartwig and co-workers established a robust copper-catalyzed imidation of unactivated alkanes with phthalimide using *di-tert*-butyl peroxide as the oxidant.[5] The Meng and Jain groups realized the direct imidation of C(sp^3)−H bonds adjacent to a nitrogen atom with phthalimide under KI/TBHP or CuBr/air oxidative conditions, respectively.[6,7] Although significant progress has been made in the imidation of C(sp^3)−H bonds,[8] direct imidation of *N*-methyl-substituted benzylamines with phthalimide is still unexplored. Considering the importance of phthalimide-protected *gem*-diamines in medicinal chemistry, and that there are many existing methods for the deprotection of the benzyl group (Bn) in the resulting products for further derivatization, the realization of a dehydrogenative imidation of *N*-methyl substituted benzylamines with phthalimide for the construction of *N*-Bn-*N*′-phthalimido *gem*-diamines is highly desired.

Scheme 1. Biologically Relevant Phthalimide-Protected *gem*-Diamines and Imidation of C(sp^3)−H Bonds with Phthalimide



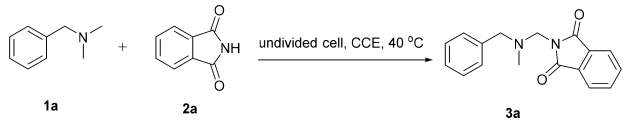
Organic electrosynthesis obviates the use of toxic chemical oxidants or reductants and thus provides a green strategy for organic synthesis.[9] Recent studies have demonstrated the power of organic electrosynthesis in dehydrogenative transformations.[10] In continuation of our interest in electrochemical dehydrogenative reactions,[11] we herein report the first example of an electrochemical dehydrogenative imidation of *N*-methyl-substituted benzylamines with phthalimide to afford phthalimide-protected *gem*-diamines with excellent regioselectivities (Scheme 1c). In addition, an electrochemical dehydrogenative amination of *N*-methyl-substituted benzylamines with azoles under the same reaction conditions is also described.

We initiated our studies by using *N*,*N*-dimethylbenzylamine **1a** and phthalimide **2a** as model substrates, platinum net as the anode, and a graphite plate as the cathode under constant current conditions to identify the optimal reaction conditions (Table 1). First, a series of electrolytes were examined, and the results showed that Bu_4NClO_4 was the optimal supporting electrolyte to give target product **3a** in 67% yield, while other

Received: November 13, 2018

DOI: 10.1021/acs.orglett.8b03624
Org. Lett. XXXX, XXX, XXX−XXX

Table 1. Optimization of Reaction Condition[a]



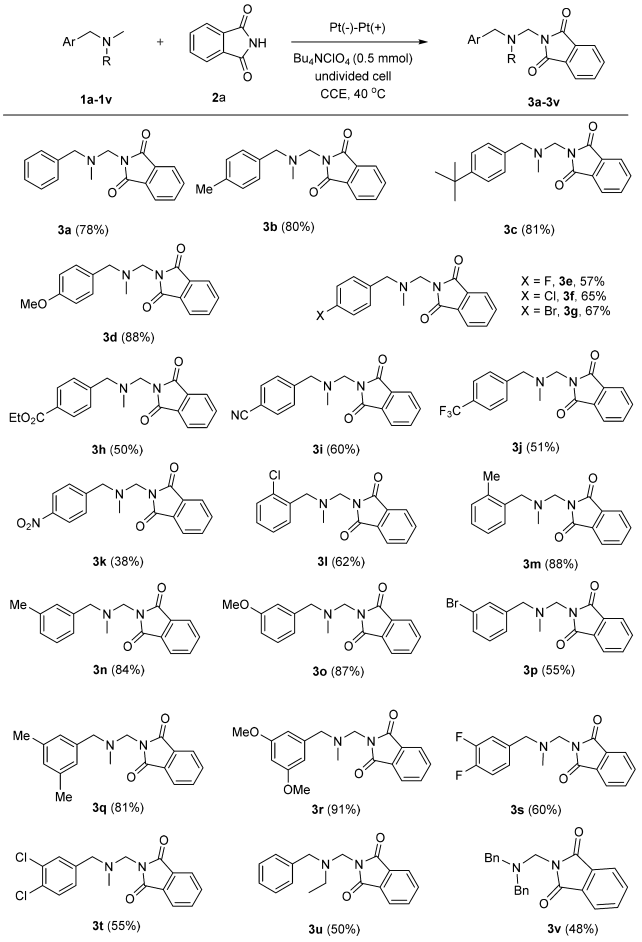
entry	electrolyte	solvent	anode/cathode	yield (%)[b]
1	$LiClO_4$	CH_3CN	Pt/C	32
2	Bu_4NPF_6	CH_3CN	Pt/C	55
3	Bu_4NBF_4	CH_3CN	Pt/C	32
4	Bu_4NClO_4	CH_3CN	Pt/C	67
5	$Bu_4NH_2PO_4$	CH_3CN	Pt/C	16
6	Et_4NOTs	CH_3CN	Pt/C	51
7	Et_4NOAc	CH_3CN	Pt/C	36
8	Et_4NClO_4	CH_3CN	Pt/C	61
9	Et_4NBF_4	CH_3CN	Pt/C	50
10	Bu_4NClO_4	CH_3CN	Pt/Ni	41
11	Bu_4NClO_4	CH_3CN	Pt/Fe	47
12	Bu_4NClO_4	CH_3CN	C/C	27
13	Bu_4NClO_4	CH_3CN	C/Pt	28
14	Bu_4NClO_4	CH_3CN	Pt/Pt	75
15	Bu_4NClO_4	MeOH	Pt/Pt	66
16	Bu_4NClO_4	DCE	Pt/Pt	32
17	Bu_4NClO_4	CH_3CN/MeOH = 8:2	Pt/Pt	78
18	Bu_4NClO_4	CH_3CN/MeOH = 6:4	Pt/Pt	75
19	Bu_4NClO_4	CH_3CN/MeOH = 4:6	Pt/Pt	63
20[c]	Bu_4NClO_4	CH_3CN/MeOH = 8:2	Pt/Pt	43
21[d]	Bu_4NClO_4	CH_3CN/MeOH = 8:2	Pt/Pt	66

[a]Reaction conditions: **1a** (2.0 mmol), **2a** (1.0 mmol), electrolyte (0.5 mmol), solvent (10 mL) as the mixed solvent, 40 °C, current density of 5 mA/cm^2, electrolyze in undivided cell for 5 h. [b]Isolated yield. [c]**1a** (1.0 mmol), **2a** (2.0 mmol). [d]Electrolyte (0.3 mmol).

commonly used electrolyte gave lower yields (entries 4 vs 1−3, 5−9). Further investigation of the electrode materials showed that when platinum net was used as the cathode and anode, the yield could be increased to 75% (entry 14). To improve the chemical yield of **3a**, a series of solvents were screened (entries 15−19). A satisfactory 78% yield of the desired product was obtained when the ratio of CH_3CN to MeOH by volume was 8:2 (entry 17), while other solvents such as MeOH or DCE (entries 15−16), or other ratios of CH_3CN to MeOH gave lower yields (entries 18−19). Notably, when the substrate ratio of **1a** to **2a** was inversed to 1:2, a lower yield (43%) of **3a** was obtained (entry 20). In addition, a 66% yield of product **3a** was isolated when the amount of the supporting electrolyte was decreased to 0.3 equiv (entry 21).

Under the optimized reaction conditions, we began to survey the scope and the generality of the protocol by examining the reactions of a variety of *N*-methylbenzylamines **1** with phthalimide **2a**. As shown in Scheme 2, the corresponding products **3a**−**3u** were obtained in up to 91% yield. Generally, excellent yields were obtained for **1** having electron-rich 4-aryl substituents (**3b**−**3d**). Substrates with electron-deficient 4-aryl substituents reacted with lower yields (**3e**−**3j**). The reaction of electron-deficient 4-nitrophenyl-substituted **1k** only gave the corresponding product **3k** in 38% yield. Altering the substituents to *ortho* or *meta* positions has little influence on the yield (**3l**−**3p**). Moreover, disubstituted substrates were also well tolerated under the conditions, giving the corresponding products **3r**−**3t** in up to 91% yield. Finally, *N*-methyl-*N*-ethyl benzylamine **1u** and *N*-benzyl-*N*-methyl-1-

Scheme 2. Substrate Scope with Respect to *N*-Methyl-Substituted Benzylamines[a]



[a]Reaction conditions: **1** (2.0 mmol), **2a** (1.0 mmol), Bu_4NClO_4 (0.5 mmol) in solvent of 8 mL of CH_3CN and 2 mL of MeOH, current 10 mA, platinum net anode and platinum net cathode (working area: 2 cm^2), undivided cell, 40 °C, 5 h, isolated yields.

phenylmethanamine **1v** were examined, which delivered the desired products **3u** and **3v** in 50% and 48% yields, respectively. It is noteworthy that the reactions of **1u** and **1v** showed regioselectivities, and the imidation of C(sp^3)−H bond of the methylene in ethyl and benzyl was not observed in the reactions. We speculate that it may be due to steric factors.

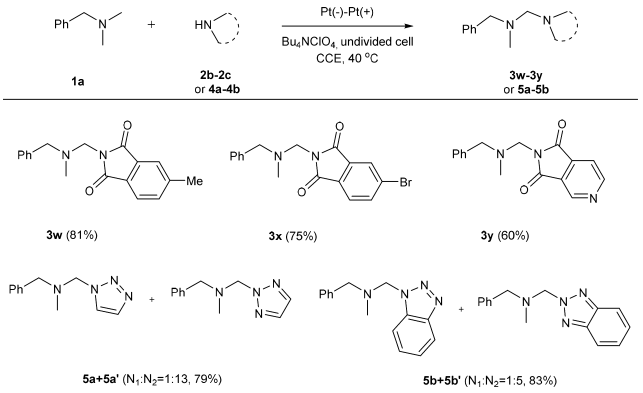
Having established the substrate scope of *N*-methyl-substituted benzylamines, the substrate scope of phthalimides **2** was then investigated, and the results are summarized in Scheme 3. First, for the imidation of *N*,*N*-dimethylbenzylamine **1a**, substituted phthalimides could also give the corresponding products **3w**−**3x** in excellent yields. When the phenyl moiety in the phthalimide was replaced by pyridyl, the corresponding product **3y** was also obtained in 60% yield.

To make this methodology more appealing, the amination reaction of *N*,*N*-dimethylbenzylamine **1a** with azoles **4** was also examined.[12] When triazole was employed as the substrate, the aminated products **5a**/**5a′** were obtained in 79% total yield with a ratio of 1:13; while the aminated products **5b**/**5b′** were obtained in 83% total yield with a ratio of 1:5 with benzotriazole as the substrate.

Our protocol proved to be practical and easily scalable. As shown in Scheme 4, when 20 mmol of *N*,*N*-dimethylbenzyl-

DOI: 10.1021/acs.orglett.8b03624
Org. Lett. XXXX, XXX, XXX−XXX

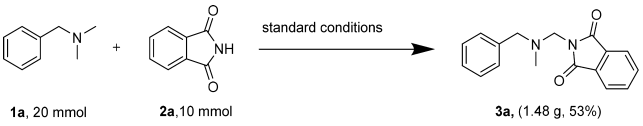
Scheme 3. Scope of Phthalimides and Azoles[a]



[a]Reaction conditions: **1a** (2.0 mmol), **2** (1.0 mmol), Bu_4NClO_4 (0.5 mmol) in solvent of 8 mL of CH_3CN and 2 mL of MeOH, current 10 mA, platinum net anode and platinum net cathode (working area: 2 cm^2), undivided cell, 40 °C, 5 h, isolated yields.

amine **1a** was treated with 10 mmol of phthalimide **2a** under standard conditions, a 53% yield of the desired adduct **3a** was obtained.

Scheme 4. Gram-Scale Experiment

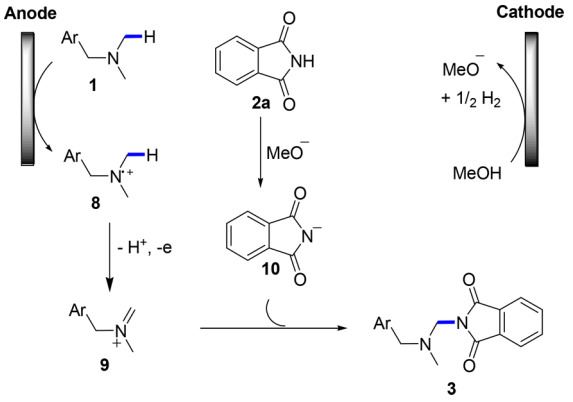


To gain more insight into the mechanism, cyclic voltammetry (CV) experiments were carried out (see SI for details). The results showed that substrate **1a** has two oxidation peaks at 0.8 and 1.0 V vs Ag/$AgNO_3$ (0.1 M in CH_3CN), respectively, whereas no obvious oxidation wave was observed for substrate **2a** within the potential window examined. In addition, the oxidation peak potential of phthalimide potassium salt was observed at 1.1 V vs Ag/$AgNO_3$ (0.1 M in CH_3CN). These results suggest that substrate **1a** is easier to be oxidized than substrate **2a**. Notably, the oxidation peak potential of the target product **3a** was observed at 1.1 V, higher than that of **1a**, thereby avoiding the overoxidation of **3a** in the electrolysis process.

Based on the above experiments, a possible mechanism for electrochemical dehydrogenative C−H imidation of *N*,*N*-dimethylbenzylamine is described in Scheme 5. The reaction sequence is initiated by anodic oxidation of *N*,*N*-dimethylbenzylamine **1** to give radical cation **8**, which undergoes deprotonation and further oxidation to generate iminium intermediate **9**. Meanwhile, MeOH is reduced at the cathode to give methoxide and H_2.[8] The formation of H_2 could be detected by GC (see SI for details). Phthalimide **2a** is deprotonated by methoxide to give intermediate **10**, which undergoes a Mannich-type addition to intermediate **9** to generate product **3**.

We have developed, for the first time, a general electrochemical dehydrogenative method for the imidation of *N*-methyl benzylamines with phthalimides with excellent regioselectivities. This operationally simple method proceeded with high substrate generality, offering a valuable tool to obtain structurally diverse phthalimide-protected *gem*-diamines.

Scheme 5. Proposed Mechanism



Moreover, the electrochemical dehydrogenative amination of *N*,*N*-dimethylbenzylamine with azoles was also realized.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b03624.

Experimental details, conditional optimization, control experiments, characterization data, NMR spectra, and HRMS of all new compounds (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: zengcc@bjut.edu.cn.

ORCID

Chengchu Zeng: 0000-0002-5659-291X

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported by grants from the National Key Technology R&D Program (2016YFD0400801) and the National Natural Science Foundation of China (No. 21871019). Z.C.C. is thankful for financial support from the Open Project Program of Beijing Key Laboratory of Flavor Chemistry, Beijing Technology and Business University (BTBU).

■ REFERENCES

(1) (a) Hoffman, J. M.; Wai, J. S.; Thomas, C. M.; Levin, R. B.; O'Brien, J. A.; Goldman, M. E. *J. Med. Chem.* **1992**, *35*, 3784−3791. (b) Bian, X.-L.; Wang, Q.; Ke, C.-H.; Zhao, G.-L.; Li, Y.-P. *Bioorg. Med. Chem. Lett.* **2013**, *23*, 2022−2026. (c) De Monte, C.; Carradori, S.; Bizzarri, B.; Bolasco, A.; Caprara, F.; Mollica, A.; Rivanera, D.; Mari, E.; Zicari, A.; Akdemir, A.; Secci, D. *Eur. J. Med. Chem.* **2016**, *107*, 82−96. (d) Zhou, W.; Li, S.-L.; Lu, W.-Q.; Yuan, J.; Xu, Y.-F.; Li, H.-L.; Huang, J.; Zhao, Z.-J. *Med. Chem. Commun.* **2016**, *7*, 292−296.

(2) For selected recent examples, see: (a) Sun, B.; Wang, Y.; Li, D.-Y.; Jin, C.; Su, W.-K. *Org. Biomol. Chem.* **2018**, *16*, 2902−2909. (b) Jin, Y.-H.; Yang, H.-J.; Fu, H. *Org. Lett.* **2016**, *18*, 6400−6403. (c) Kiyokawa, K.; Kosaka, T.; Kojima, T.; Minakata, S. *Angew. Chem., Int. Ed.* **2015**, *54*, 13719−13723.

(3) Selected reviews on dehydrogenative coupling, see: (a) Li, C.-J. *Acc. Chem. Res.* **2009**, *42*, 335−344. (b) Krylov, L. B.; Vil', V.-A.;

DOI: 10.1021/acs.orglett.8b03624
Org. Lett. XXXX, XXX, XXX−XXX

Terent'ev, A. O. *Beilstein J. Org. Chem.* **2015**, *11*, 92−146. (c) Lv, L.-Y.; Li, Z.-P. *Top. Curr. Chem.* **2016**, *374*, 1−39.
(4) Selected recent examples, see: (a) Xu, H.; Qiao, X.-X.; Yang, S.-P.; Shen, Z.-M. *J. Org. Chem.* **2014**, *79*, 4414−4422. (b) Yu, S.-J.; Wan, B.-S.; Li, X.-W. *Org. Lett.* **2013**, *15*, 3706−3709. (c) Yamaguchi, T.; Yamaguchi, E.; Itoh, A. *Org. Lett.* **2017**, *19*, 1282−1285. (d) Rit, R. K.; Shankar, M.; Sahoo, A. K. *Org. Biomol. Chem.* **2017**, *15*, 1282−1293. (e) Greulich, T. W.; Daniliuc, C. G.; Studer, A. *Org. Lett.* **2015**, *17*, 254−257.
(5) Tran, B. L.; Li, B.-J.; Driess, M.; Hartwig, J. *J. Am. Chem. Soc.* **2014**, *136*, 2555−2563.
(6) Lao, Z.-Q.; Zhong, W.-H.; Lou, Q.-H.; Li, Z.-J.; Meng, X.-B. *Org. Biomol. Chem.* **2012**, *10*, 7869−7871.
(7) Singh, S. K.; Chandna, N.; Jain, N. *Org. Lett.* **2017**, *19*, 1322−1325.
(8) Qiu, Y.-A.; Struwe, J.; Meyer, T. H.; Olivira, J. C. A.; Ackermann, L. *Chem. - Eur. J.* **2018**, *24*, 12784−12789.
(9) Selected recent reviews, see: (a) Yan, M.; Kawamata, Y.; Baran, P. S. *Chem. Rev.* **2017**, *117*, 13230−13319. (b) Jiang, Y.-Y.; Xu, K.; Zeng, C.-C. *Chem. Rev.* **2018**, *118*, 4485−4540. (c) Wiebe, A.; Gieshoff, T.; Möhle, S.; Rodrigo, E.; Zirbes, M.; Waldvogel, S. *Angew. Chem., Int. Ed.* **2018**, *57*, 5594−5619. (d) Kärkäs, M. D. *Chem. Soc. Rev.* **2018**, *47*, 5786−5865. (e) Ma, C.; Fang, P.; Mei, T.-S. *ACS Catal.* **2018**, *8*, 7179−7189. (f) Sauermann, N.; Meyer, T. H.; Qiu, Y.; Ackermann, L. *ACS Catal.* **2018**, *8*, 7086−7103. (g) Sauer, G. S.; Lin, S. *ACS Catal.* **2018**, *8*, 5175−5187. (h) Yoshida, J. I.; Shimizu, A.; Hayashi, R. *Chem. Rev.* **2018**, *118*, 4702−4730. (i) Okada, Y.; Chiba, K. *Chem. Rev.* **2018**, *118*, 4592−4630. (j) Cardoso, D. S. P.; Šljukic, B.; Santos, D. M. F.; Sequeira, C. A. C. *Org. Process Res. Dev.* **2017**, *21*, 1213−1226.
(10) (a) Wu, Z.-J.; Xu, H.-C. *Angew. Chem., Int. Ed.* **2017**, *56*, 4734−4738. (b) Wang, H.-Q.; Zhang, J.-J.; Tan, J.-J.; Xin, L.-L.; Li, Y.-P.; Zhang, S.; Xu, K. *Org. Lett.* **2018**, *20*, 2505−2508. (c) Wu, Z.-J.; Li, S. R.; Long, H.; Xu, H.-C. *Chem. Commun.* **2018**, *54*, 4601−4604. (d) Qiu, Y.-A.; Kong, W. J.; Struwe, J.; Sauermann, N.; Rogge, T.; Scheremetjew, A.; Ackermann, L. *Angew. Chem., Int. Ed.* **2018**, *57*, 5828−5832. (e) Zeng, L.; Li, H.-R.; Tang, S.; Gao, X.-L.; Deng, Y.; Zhang, G.; Pao, C.-W.; Chen, J.-L.; Lee, J.-F.; Lei, A.-W. *ACS Catal.* **2018**, *8*, 5448−5453.
(11) (a) Lin, M. Y.; Xu, K.; Jiang, Y. Y.; Liu, Y. G.; Sun, B.-G.; Zeng, C.-C. *Adv. Synth. Catal.* **2018**, *360*, 1665−1672. (b) Zhang, S.; Li, L.-J.; Wang, H.-Q.; Li, Q.; Liu, W.-M.; Xu, K.; Zeng, C.-C. *Org. Lett.* **2018**, *20*, 252−255. (c) Zhang, S.; Li, L.-J.; Xue, M.-Y.; Zhang, R.-K.; Xu, K.; Zeng, C.-C. *Org. Lett.* **2018**, *20*, 3443−3446.
(12) Gupta, S.; Chandna, N.; Singh, A. K.; Jain, N. *J. Org. Chem.* **2018**, *83*, 3226−3235.

DOI: 10.1021/acs.orglett.8b03624
Org. Lett. XXXX, XXX, XXX−XXX