Organic LETTERS

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

Letter

pubs.acs.org/OrgLett

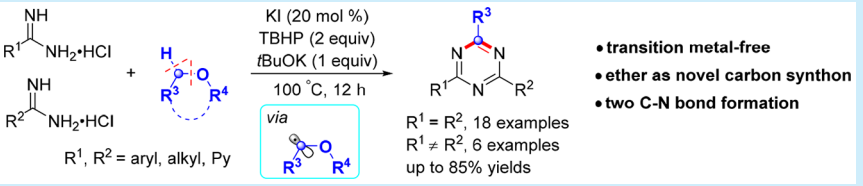
Alkyl Ether as a One-Carbon Synthon: Route to 2,4-Disubstituted 1,3,5-Triazines via C−H Amination/C−O Cleavage under Transition-Metal-Free Conditions

Yizhe Yan,*[†,‡] Zheng Li,[†] Hongyi Li,[†] Chang Cui,[†] Miaomiao Shi,[†] and Yanqi Liu*[†]

[†]School of Food and Biological Engineering, Zhengzhou University of Light Industry, Zhengzhou 450000, P. R. China

[‡]Collaborative Innovation Center of Food Production and Safety, Zhengzhou, Henan Province 450000, P. R. China

Supporting Information

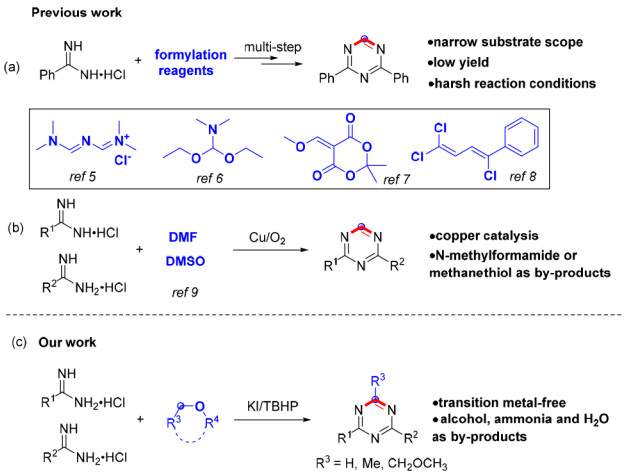


ABSTRACT: A transition-metal-free oxidative formal [3 + 2 + 1] cycloaddition for the synthesis of symmetrical and unsymmetrical 2,4-disubstituted 1,3,5-triazines has been first demonstrated. The reaction is involved in a domino C−H amination of alkyl ethers with amidines, C−O cleavage, nucleophilic addition, condensation, and an oxidative aromatization process. Notably, two C−N bonds were constructed in one pot, and alkyl ethers were employed as a novel carbon source of 1,3,5-triazines. The preliminary mechanistic studies revealed the reaction underwent a radical pathway.

1,3,5-Triazines represent an important and valuable class of nitrogen-containing heterocycles in natural products and medicinal chemistry.[1] In particular, a variety of 2,4-disubstituted 1,3,5-triazines exhibited good biological activities.[2] Furthermore, it was also a useful ligand in the preparation of organometallic materials[3] and transition-metal catalysis.[4] Over the past decades, symmetrical 2,4-disubstituted-1,3,5-triazines were mainly synthesized via the condensation and aromatization of two molecular amidines with formylation reagents such as (*E*)-*N*-((((dimethylamino)methylene)amino)methylene)-*N*-methylmethanaminium chloride,[5] 1,1-diethoxy-*N*,*N*-dimethylmethanamine,[6] 5-(methoxymethylene)-2,2-dimethyl-1,3-dioxane-4,6-dione,[7] and (*Z*)-(1,4,4-trichlorobuta-1,3-dien-1-yl)benzene[8] via multistep reactions (Scheme 1a). However, narrow substrate scope, low yield, and harsh reaction conditions limited their applications. Recently, copper-catalyzed oxidative cyclization of amidines with *N*,*N*-dimethylformamide or dimethyl sulfoxide has been developed for the synthesis of symmetrical and unsymmetrical 2,4-disubstituted 1,3,5-triazines (Scheme 1b).[9] The *N*-methyl group of DMF or *S*-methyl group of DMSO was used as the carbon source in these reactions. Although the reaction yield was good, transition metal was still required, and *N*-methylformamide or methanthiol was generated as environmentally unfriendly byproducts. Therefore, the development of a simple and environmentally friendly protocol for 2,4-disubstituted 1,3,5-triazines is highly desirable.

In recent years, transition-metal-catalyzed or metal-free direct α-C(sp^3)−H bond functionalization of ethers has emerged as an important tool for direct construction of the C−X bond.[10,11] However, to date, use of ethers as the carbon synthon of heterocycles has rarely been reported via C−H functionalization. In 2012, we developed an interesting metal-free α-C(sp^3)−H amination of ethers for the synthesis of quinazolines.[11] In the method, methyl *tert*-butyl ether was first employed as the carbon source of heterocycles. Inspired by this significant finding, herein we report a transition-metal-free oxidative formal [3 + 2 + 1] cycloaddition for the synthesis of 2,4-disubstituted 1,3,5-triazines from amidines and ethers (Scheme 1c). The extra carbon atom of 1,3,5-triazines

Scheme 1. Strategies for the Synthesis of 2,4-Disubstituted 1,3,5-Triazines



Received: October 11, 2017

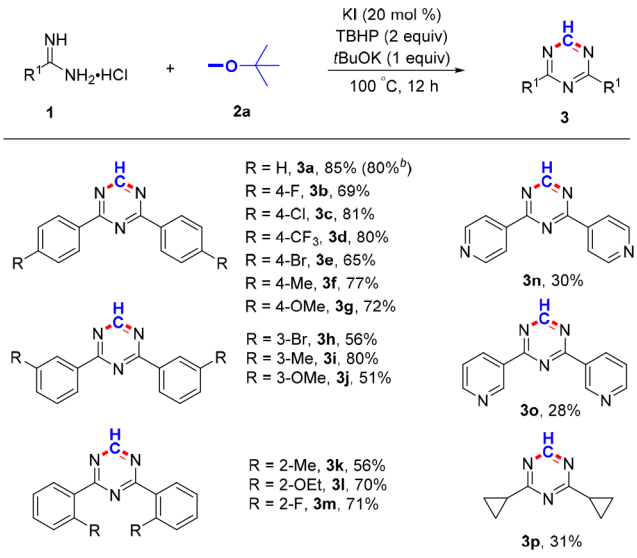
DOI: 10.1021/acs.orglett.7b03171
Org. Lett. XXXX, XXX, XXX−XXX

originates from ethers via oxidative C(sp^3)−H amination and C−O cleavage. A series of symmetrical and unsymmetrical 2,4-disubstituted 1,3,5-triazines were obtained in up to 85% yields with good functional group compatibility. Notably, the reaction is environmentally friendly because alcohol, ammonia, and water are the waste materials.

Initially, we began our study with the reaction of 1 equiv of benzamidine hydrochloride (**1a**), 1 equiv of K_2CO_3 as the base, 2 equiv of *tert*-butyl hydroperoxide (TBHP, 70% in aqueous) as the oxidant, and 20 mol % of KI as the catalyst. When the reaction mixture was heated in 1 mL of methyl *tert*-butyl ether (MTBE, **2a**) at 120 °C for 12 h, 2,4-diphenyl-1,3,5-triazine (**3a**) was obtained in 78% isolated yield (Table S1, entry 1). When various iodine reagents, such as tetrabutylammonium iodide (TBAI), I_2, and *N*-iodosuccinimide (NIS), were used as the catalyst, **3a** was obtained in slightly lower yields compared to KI (Table S1, entries 2−4). Among the examination of various bases, such as Na_2CO_3, Cs_2CO_3, KOH, and *t*BuOK, *t*BuOK afforded **3a** in the highest yield, 83% (Table S1, entries 5−8). Increasing the amount of *t*BuOK to 1.5 equiv or 2 equiv obviously decreased the reaction yield (Table S1, entries 9 and 10). To make the reaction conditions mild, the reaction temperature was decreased, which had a significant effect on the reaction yields. Notably, the desired product **3a** was obtained in excellent 85% yield at 100 °C (Table S1, entries 11−14). Therefore, the optimal conditions were established as described in entry 11.

Under the optimal reaction conditions, we then explored the generality of the synthetic protocol for various amidines **1** (Scheme 2). First, aryl amidines (**1a−m**) bearing electron-donating groups (Me and OMe) and electron-deficient groups (F, Cl, Br, and CF_3) could be employed in this reaction, giving the desired symmetrical 2,4-diaryl-1,3,5-triazines (**3a−m**) in moderate to good yields. It was noted that *ortho*-substituted aryl amidines (**1l** and **1m**) gave a yield similar to that of *para*-subsitituted ones (**1b** and **1g**) except for **1k**. To our delight, pyridyl-substituted amidines (**1n** and **1o**) also generated the desired 2,4-dipyridyl-1,3,5-triazines in 30% and 28% yields, respectively (Scheme 2, **2n** and **2o**). It is worth noting that the C−X bond on the phenyl ring and the C−H bond at the C6 position of 1,3,5-triazines in all of the obtained products provide the potential for further derivatization.

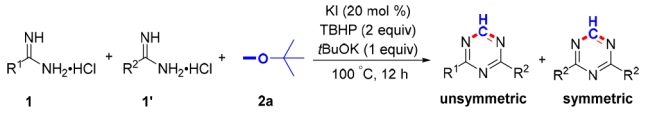
Scheme 2. Homocoupling Reactions of Amidines for the Synthesis of Symmetrical 2,4-Disubstituted 1,3,5-Triazines[a]



[a]Reaction conditions: **1** (0.4 mmol), KI (20 mol %), TBHP (2 equiv), *t*BuOK (1 equiv), MTBE (1 mL), 100 °C, 12 h; isolated yield. [b]10 mmol scale.

Subsequently, we expected to synthesize unsymmetrical 2,4-disubstituted 1,3,5-triazines with this synthetic protocol. Interestingly, the cross-coupling reactions occurred and afforded the desired unsymmetrical products by employing two different aryl amidines (Table 1). Initially, the reaction of 4-methoxybenzamidine (**1g**) and benzamidine (**1a**) in equimolar ratio could afford three products **3g**, **3ga**, and **3a** in 8%, 10%, and 28% yields, respectively. Due to the differences in reactivity, the yield of **3a** was higher than those of **3g** and **3ga**. To improve the yield of unsymmetrical product **3ga**, the reaction of **1g** and **1a** in a ratio of 4:1 was performed, giving **3g**, **3ga**, and **3a** in 13%, 12%, and 27% yields, respectively. To our delight, the reaction of **1g** and **1a** in a ratio of 1:4 could produce **3ga** in 29% yield with a 30% yield of **3a**, and another homocoupling product **3g** was not detected (Table 1, entry 1). Similarly, unsymmetrical products **3gc** and **3gd** could be obtained in 15 and 18% yields using **1c** and **1d** instead of **1a** (Table 1, entries 2 and 3). When **1g** was replaced with **1l**, **1q**, and **1p**, the unsymmetrical products **3la**, **3qa**, and **3pa** were also obtained in 17−27% yields (Table 1, entries 4−6).

Table 1. Cross-coupling Reactions of Two Different Amidines for the Synthesis of Unsymmetrical 2,4-Disubstituted 1,3,5-Triazines[a]



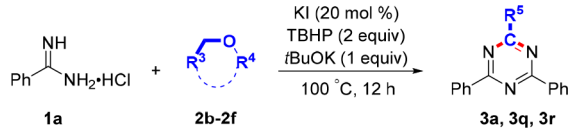
			product (yield, %)[b]	
entry	R^1 (**1**)	R^2 (**1′**)	unsymmetric	symmetric
1	4-OMePh (**1g**)	Ph (**1a**)	**3ga** (29)	**3a** (30)
2	4-OMePh (**1g**)	4-ClPh (**1c**)	**3gc** (15)	**3c** (25)
3	4-OMePh (**1g**)	4-CF_3Ph (**1d**)	**3gd** (18)	**3d** (19)
4	2-OEtPh (**1l**)	Ph (**1a**)	**3la** (27)	**3a** (23)
5	4-NO_2Ph (**1q**)	Ph (**1a**)	**3qa** (17)	**3a** (29)
6	cyclopropyl (**1p**)	Ph (**1a**)	**3pa** (17)	**3a** (34)

[a]Reaction conditions: **1** (0.2 mmol), **1′** (0.8 mmol), KI (20 mol %), TBHP (2 equiv), *t*BuOK (1 equiv), MTBE (1 mL), 100 °C, 12 h. [b]Isolated yield.

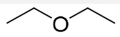
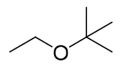
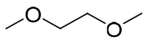
Then the substrate scope of ethers **2** was also investigated under the optimal reaction conditions (Table 2). When diethyl ether (**2b**) or ethyl *tert*-butyl ether (**2c**) was employed, the corresponding product **3q** was obtained in 63% or 67% yield, respectively (Table 2, entries 1 and 2). In addition, 1,2-dimethoxyethane, which has two types of C(sp^3)−H bonds adjacent to the oxygen atom, afforded **3a** and **3r** in 26% and 12% yields, respectively. Notably, the reaction with primary C−H bond gave products in higher yields than secondary C−H bond (Table 2, entry 3). Moreover, cyclic ethers were also examined in the reaction. For example, 1,3-dioxolane (**2d**) could give **3a** in 34% yield via a direct oxidative C(sp^3)−H amination and condensation process (Table 2, entry 4). Interestingly, **3a** was isolated in 13% yield via an unexpected C−C cleavage when 1,4-dioxane (**2e**) was used as the substrate (Table 2, entries 5).

DOI: 10.1021/acs.orglett.7b03171
Org. Lett. XXXX, XXX, XXX−XXX

Table 2. Substrate Scope of Ethers[a]



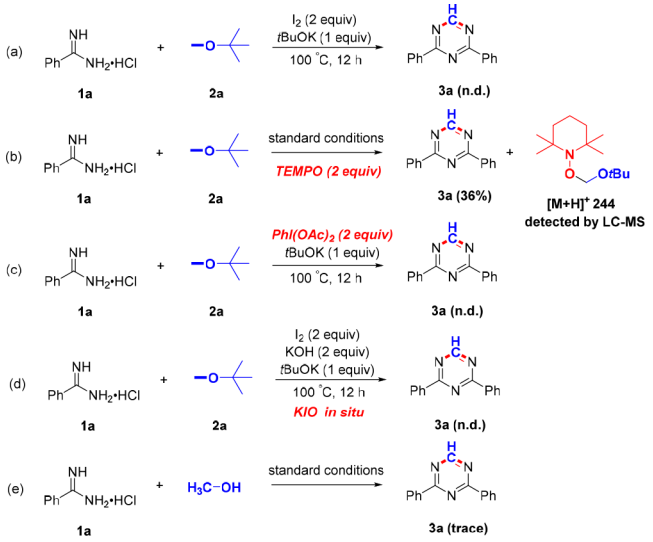
1a 2b-2f 3a, 3q, 3r

entry	ether		product	yield(%)[b]
1		2b	R^5 = Me, **3q**	63
2		2c	R^5 = Me, **3q**	67
3		2d	**3a**	26
			$R^5 = CH_2OCH_3$, **3r**	12
4		2e	**3a**	34
5		2f	**3a**	13

[a]Reaction conditions: **1a** (0.4 mmol), KI (20 mol %), TBHP (2 equiv), *t*BuOK (1 equiv), ether **2** (1 mL), 100 °C, 12 h. [b]Isolated yield.

To gain an insight into the mechanism, several control experiments were carried out (Scheme 3). First, the desired

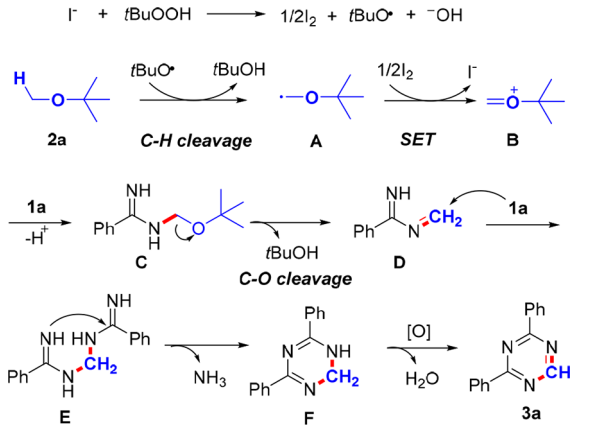
Scheme 3. Control Experiments for Mechanistic Studies



product was not detected in the presence of 2 equiv of iodine without TBHP, which indicated that TBHP should be necessary as the radical initiator (Scheme 3a). Moreover, it was observed that the reaction was obviously inhibited in the presence of 2 equiv of 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) as the radical inhibitor (Scheme 3b). Meanwhile, 1-(*tert*-butoxymethoxy)-2,2,6,6-tetramethylpiperidine was detected by LC–MS. This implied that *tert*-butoxymethyl radical was generated from MTBE via C–H cleavage. In addition, when 2 equiv of hypervalent iodine reagents, such as $PhI(OAc)_2$ or KIO, were employed instead of our catalytic system, no desired product was obtained (Scheme 3d). This result indicated that the reaction pathway was not involved in hypervalent iodine catalysis. In fact, the initial colorless solution was first changed to yellow and eventually colorless, indicating an I^-/I_2 redox process. Finally, when MTBE was replaced with methanol under standard conditions, only a trace amount of **3a** was detected (Scheme 3e). Therefore, a hydrolysis mechanism of MTBE should be excluded.

On the basis of the results reported above and previous reports,[10,11] a plausible mechanism was proposed (Scheme 4).

Scheme 4. Plausible Mechanism



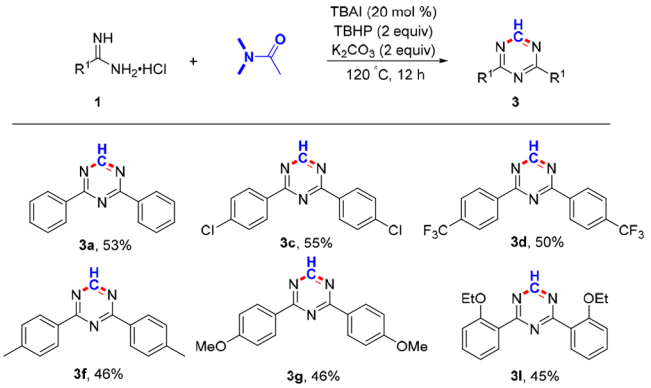
Initially, the decomposition of *tert*-butyl hydroperoxide generates a *tert*-butoxy radical in the presence of iodide, which was oxidized to molecular iodine. Then the *tert*-butoxy radical abstracts a hydrogen atom of $C(sp^3)$–H bond of MTBE to give a *tert*-butoxymethyl radical **A**, which could generate an oxonium ion **B** via a single-electron-transfer (SET) process in the presence of iodine. Subsequently, the nucleophilic addition of **1a** to **B** provides an intermediate **C**. A sequential C–O cleavage of **C** could generate an imine **D**, and then a nucleophilic addition of **1a** to **D** provides an intermediate **E**. Then **E** could be transformed to **F** by removal of one molecule of ammonia. Finally, **3a** could be formed through an oxidative aromatization. Overall, the I^-/I_2 catalytic cycle plays an important role in C–N bond formations.

Recently, we[12] and others[13] have also developed new strategies for the synthesis of heterocycles with *N,N*-dimethylacetamide (DMA) as the carbon synthon. In these reactions, an imine ion intermediate was usually generated in situ. According to our proposed mechanism above, the nucleophilic addition of **1** to the imine ion is expected to occur. After optimization (see Table S2 for details), the reaction of **1** with DMA afforded the desired products **3** in 45–55% yields in the presence of 20 mol % of TBAI as the catalyst (Scheme 5).

In summary, we have developed an oxidative annulation of amidines and ethers, affording a variety of symmetrical and unsymmetrical 2,4-disubstituted 1,3,5-triazines under transition-metal-free conditions. Compared to previous reports, this novel protocol is distinguished by (1) being transition-metal-free, (2) its operational simplicity, (3) the only wastes being alcohol, ammonia, and water, (4) its good functional group tolerance. The synthesis of valuable heterocycles using ethers as the carbon source is ongoing in our laboratory.

DOI: 10.1021/acs.orglett.7b03171
Org. Lett. XXXX, XXX, XXX–XXX

Scheme 5. Synthesis of Symmetrical 2,4-Diaryl-1,3,5-triazines Using DMA as the Carbon Synthon[a]



[a]Reaction conditions: **1** (0.4 mmol), TBAI (20 mol %), TBHP (2 equiv), K_2CO_3 (2 equiv), DMA (1 mL), 120 °C, 12 h; isolated yield.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b03171.

Experimental procedure and spectroscopic data for all compounds (PDF)

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: yanyizhe@mail.ustc.edu.cn.
*E-mail: liuyanqi@zzuli.edu.cn.

ORCID

Yizhe Yan: 0000-0003-0190-3474

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We are grateful to the National Natural Science Foundation of China (21502177), the Science and Technology Research Key Project of the Department of Education of Henan Province (15A150005), the Doctoral Research Foundation of Zhengzhou University of Light Industry (2014BSJJ032), and the Grants Program of Youth Backbone Teachers Training Object of Zhengzhou University of Light Industry.

■ REFERENCES

(1) (a) Kaminsky, R.; Brun, R. *Antimicrob. Agents Chemother.* **1998**, *42*, 2858. (b) Bacchi, C. J.; Vargas, M.; Rattendi, D.; Goldberg, B.; Zhou, W. *Antimicrob. Agents Chemother.* **1998**, *42*, 2718. (c) Iino, Y.; Karakida, T.; Sugamata, N.; Andoh, T.; Takei, H.; Takahashi, M.; Yaguchi, S.; Matsuno, T.; Takehara, M.; Sakato, M.; Kawashima, S.; Morishita, Y. *Anticancer Res.* **1998**, *18*, 171. (d) Irikura, T.; Abe, Y.; Okamura, K.; Higo, K.; Maeda, A.; Morinaga, F.; Shirai, G.; Hatae, S. *J. Med. Chem.* **1970**, *13*, 1081.

(2) (a) Suda, A.; Kawasaki, K.; Komiyama, S.; Isshiki, Y.; Yoon, D.-O.; Kim, S. J.; Na, Y.-J.; Hasegawa, K.; Fukami, T. A.; Sato, S. *Bioorg. Med. Chem.* **2014**, *22*, 892. (b) Klenke, B.; Stewart, M.; Barrett, M. P.; Brun, R.; Gilbert, I. H. *J. Med. Chem.* **2001**, *44*, 3440. (c) Katritzky, A. R.; Oniciu, D. C.; Ghiviriga, I.; Barcock, R. A. *J. Chem. Soc., Perkin Trans. 2* **1995**, *0*, 785. (d) Baker, B. R.; Ho, B.-T. *J. Heterocycl. Chem.* **1965**, *2*, 340.

(3) (a) Naik, S.; Kumaravel, M.; Mague, J. T.; Balakrishna, M. S. *Inorg. Chem.* **2014**, *53*, 1370. (b) Xiao, C.-Y.; Li, Y.-M.; Lun, H.-J.; Cui, C.-Y.; Xu, Y.-Q. *J. Solid State Chem.* **2013**, *208*, 127. (c) Gadekar, S. M.; Frederick, J. L. *J. Org. Chem.* **1962**, *27*, 1383.

(4) (a) Hernandez-Juarez, M.; Vaquero, M.; Alvarez, E.; Salazar, V.; Suarez, A. *Dalton Trans.* **2013**, *42*, 351. (b) Santra, P. K.; Sagar, P. *J. Mol. Catal. A: Chem.* **2003**, *197*, 37.

(5) Gold, H. *Angew. Chem.* **1960**, *72*, 956.

(6) Bredereck, H.; Effenberger, F.; Hofmann, A. *Chem. Ber.* **1963**, *96*, 3265.

(7) Wessig, P.; Schwarz, J. *Monatsh. Chem.* **1995**, *126*, 99.

(8) Popovich, T. P.; Drach, B. S. *Zh. Org. Khim.* **1987**, *23*, 2443.

(9) (a) Xu, X.; Zhang, M.; Jiang, H.; Zheng, J.; Li, Y. *Org. Lett.* **2014**, *16*, 3540. (b) Huang, H.; Guo, W.; Wu, W.; Li, C.-J.; Jiang, H. *Org. Lett.* **2015**, *17*, 2894.

(10) For reviews, see: (a) Guo, S.-R.; Kumar, P. S.; Yang, M. *Adv. Synth. Catal.* **2017**, *359*, 2. (b) Lakshman, M. K.; Vuram, P. K. *Chem. Sci.* **2017**, *8*, 5845. (c) Majji, G.; Rout, S. K.; Rajamanickam, S.; Guin, S.; Patel, B. K. *Org. Biomol. Chem.* **2016**, *14*, 8178.

(11) (a) Rout, S. K.; Guin, S.; Ali, W.; Gogoi, A.; Patel, B. K. *Org. Lett.* **2014**, *16*, 3086. (b) Majji, G.; Guin, S.; Rout, S. K.; Behera, A.; Patel, B. K. *Chem. Commun.* **2014**, *50*, 12193. (c) Majji, G.; Rajamanickam, S.; Khatun, N.; Santra, S. K.; Patel, B. K. *J. Org. Chem.* **2015**, *80*, 3440. (d) Rajamanickam, S.; Majji, G.; Santra, S. K.; Patel, B. K. *Org. Lett.* **2015**, *17*, 5586.

(12) (a) Yan, Y.; Zhang, Y.; Feng, C.; Zha, Z.; Wang, Z. *Angew. Chem., Int. Ed.* **2012**, *51*, 8077. (b) Yan, Y.; Li, H.; Li, Z.; Niu, B.; Shi, M.; Liu, Y. *J. Org. Chem.* **2017**, *82*, 8628.

(13) Modi, A.; Ali, W.; Patel, B. K. *Adv. Synth. Catal.* **2016**, *358*, 2100.

DOI: 10.1021/acs.orglett.7b03171
Org. Lett. XXXX, XXX, XXX−XXX