Organic LETTERS

Letter

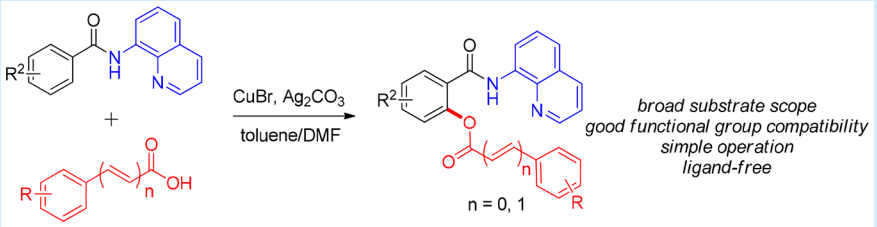
pubs.acs.org/OrgLett

Copper-Catalyzed Direct Acyloxylation of C(sp^2)–H Bonds in Aromatic Amides

Feifan Wang, Qiyan Hu, Chao Shu, Zhiyang Lin, Dewen Min, Tianchao Shi, and Wu Zhang*

Key Laboratory of Functional Molecular Solids, Ministry of Education, Anhui Laboratory of Molecule-Based Materials, College of Chemistry and Materials Science, Anhui Normal University, Wuhu 241000, China

Supporting Information

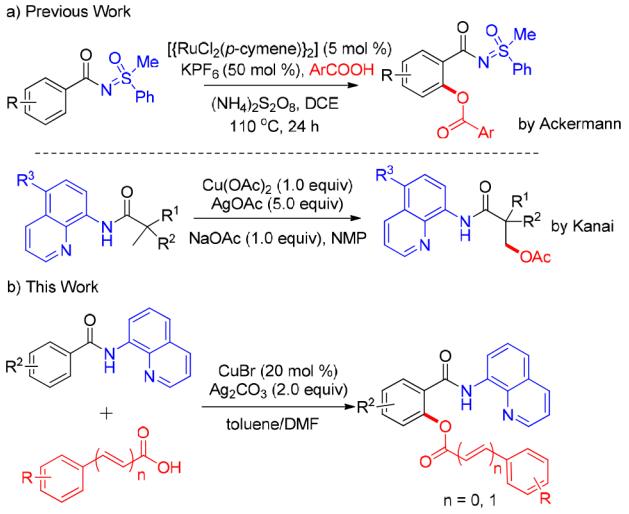


ABSTRACT: Copper-catalyzed *ortho*-acyloxylation of the sp^2 C–H bond of aryl amides with carboxylic acids is reported. Benzoic acids, cinnamic acids, and aliphatic acids can be involved, and the desired products were obtained in moderate to good yields. This procedure is compatible with a wide range of functional groups and heteroarenes without the use of any ligands or additives. This method provides an operationally simple approach for the synthesis of benzoate and cinnamate.

Over the last two decades, transition metal-catalyzed C–H bond activation has been extensively studied to enable the direct conversion of ubiquitous C–H bonds of organic molecules into diverse functional groups in a single synthetic operation.[1] Much attention has been focused on the development of regioselective C–O bond formation[2] via C–H bond functionalization because organic molecules containing C–O bonds have been widely found in numerous natural products, agricultural chemicals, drugs, and biologically active compounds.[3] Among these methods, directing group-assisted transition metal-catalyzed direct acyloxylation of C–H bonds has emerged as a powerful method for the synthesis of esters.[4] For example, Cheng[5] demonstrated the Rh-catalyzed *ortho*-benzoxylation of the sp^2 C–H bond of 2-arylpyridines and the transformation without any external oxidants. Xu,[6] Zhong,[7] Kantevari,[8] Kuang,[9] and Patel[10] have independently developed Pd-catalyzed direct acyloxylation of C(sp^2)–H bonds. Ackermann reported the Ru-catalyzed C–H oxygenation of reusable sulfoximine benzamides.[11] However, these transformations required precious metal catalysts, such as Rh, Pd, and Ru. Copper salts, which are abundant, relatively inexpensive, and possess low toxicity, have been the subject of extensive research.[12]

Although the 8-aminoquinoline-derived bidentate auxiliary has been widely used in direct C–H amination, arylation, and phenoxylation to facilitate the C–H bond activation and cyclometalation process,[13,14] 8-aminoquinoline-assisted acyloxylation has not been extensively explored. Kanai[15] and Ge[16] developed the copper-mediated direct acyloxylation of C(sp^3)–H bonds using 8-aminoquinoline as the bidentate directing group (Scheme 1). However, both reports are limited to acetoxylation using a combination of stoichiometric amounts of copper and silver salts. Herein, we report the copper-mediated

Scheme 1. Copper-Catalyzed Direct Acyloxylation of C(sp^2)–H bonds



direct acyloxylation of sp^2 C–H bonds using 8-aminoquinoline as the bidentate directing group (Scheme 1). This reaction exhibits wide substrate scope and is compatible with a variety of functional groups. More importantly, no external ligand or additive was required in this procedure.

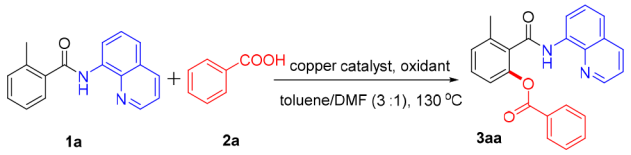
Our initial investigations started with the reaction of 2-methyl-*N*-(quinolin-8-yl)benzamide (**1a**, 1 equiv) and benzoic acid (**2a**, 1.5 equiv) in the presence of 10 mol % of Cu(OAc)$_2$·H$_2$O and 2

Received: May 30, 2017

DOI: 10.1021/acs.orglett.7b01559
Org. Lett. XXXX, XXX, XXX–XXX

equiv of Ag_2CO_3 in a mixed solvent consisting of toluene and DMF at 130 °C under air for 20 h. The product (i.e., 3-methyl-2-(quinolin-8-yl) phenyl benzoate (**3aa**)) was afforded in 57% yield (Table 1, entry 1). Various catalysts, oxidants, and reaction

Table 1. Optimization of the Reaction Conditions[a]



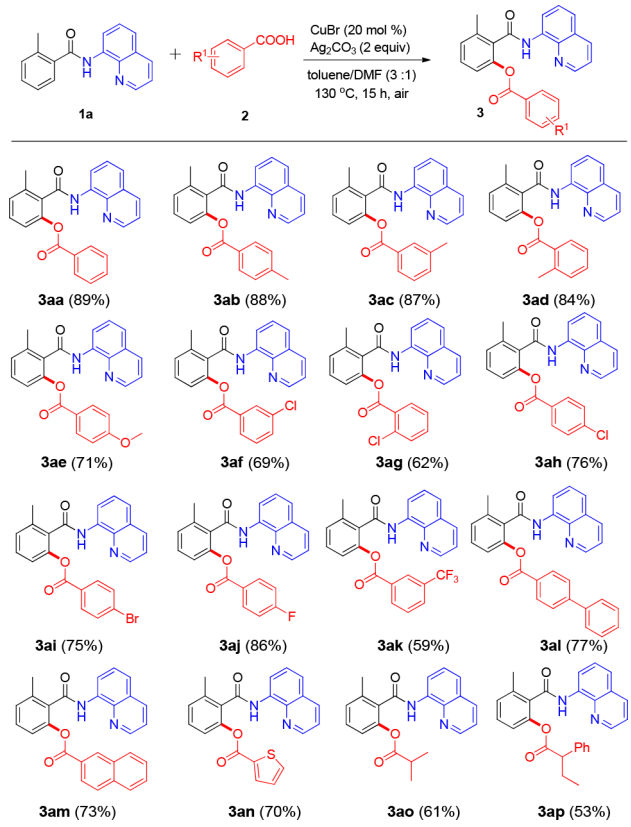
entry	catalyst (mol %)	oxidant	time (h)	yield (%)[b]
1	$Cu(OAc)_2·H_2O$ (10)	Ag_2CO_3	20	57
2	$CuCl_2·2H_2O$ (10)	Ag_2CO_3	20	61
3	$CuBr_2$ (10)	Ag_2CO_3	20	70
4	CuBr (10)	Ag_2CO_3	20	78
5	CuI (10)	Ag_2CO_3	20	56
6		Ag_2CO_3	20	NR
7	CuBr (10)		20	NR
8	CuBr (15)	Ag_2CO_3	20	81
9	CuBr (20)	Ag_2CO_3	20	89
10	CuBr (20)	Ag_2CO_3	15	89
11	CuBr (20)	AgOAc	15	39
12	CuBr (20)	BQ	15	NR
13	CuBr (20)	Ag_2CO_3	15	80[c]
14	CuBr (20)	Ag_2CO_3	15	75[d]

[a]Reaction conditions: **1a** (0.2 mmol), **2a** (0.3 mmol), oxidant (2 equiv), toluene/DMF (1.5 mL/0.5 mL) in air. [b]Isolated yield. [c]Ag_2CO_3 (1.5 equiv). [d]120 °C.

times were examined to determine the optimal reaction conditions as summarized in Table 1. The catalytic activity of the different copper sources, such as $Cu(OAc)_2$, $CuCl_2$, $CuBr_2$, CuBr, and CuI, was tested. Among these sources, CuBr was superior and resulted in a 78% yield (entry 4). The absence of either CuBr or Ag_2CO_3 failed to generate the desired products, and all the starting materials were recovered from the reaction system (entries 6 and 7), which indicated that both the copper catalyst and oxidant played indispensable roles in this reaction. The overall yield was improved to 89% when 20 mol % CuBr was used (entry 9). We were pleased to find that the reaction proceeded well when the reaction time was decreased from 20 to 15 h (entry 10). Various oxidants, such as Ag_2CO_3, AgOAc, and BQ (*p*-benzoquinone), were tested, and Ag_2CO_3 was determined to be especially effective (entries 11 and 12). A lower yield was observed when the amount of Ag_2CO_3 was decreased from 2 to 1.5 equiv (entry 13). When the temperature was decreased from 130 to 120 °C, the product yield decreased to 75% (entry 14).

With the optimized conditions in hand, we tested their versatility for C−H benzoxylation with diversely decorated benzoic acids. As shown in Scheme 2, this protocol was compatible with a wide range of functional groups, such as alkyl, methoxy, fluoro, chloro, bromo, aryl, and trifluoromethyl groups. No significant substitution effect was observed for the benzoic acids. Good yields were obtained for benzoic acids with both electron-donating and electron-withdrawing substituents on the *para*-position of aryl ring. Benzoic acid with chloro group at the *para*-position afforded better yields than those at the *ortho*- and *meta*-positions. 3-(Trifluoromethyl) benzoic acid also worked well and afforded product **3ak** in 59% yield. A thiophene-derived acid also reacted with **1a** to afford **3an** in good yield. More importantly, the acyloxylation of **1a** with isobutyric acid and 2-

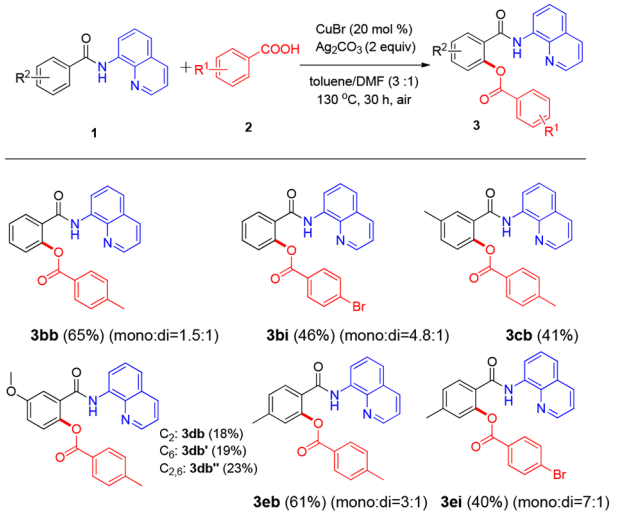
Scheme 2. *ortho*-Benzoxylation Reaction of 2-Methyl-*N*-(quinolin-8-yl)benzamide with Aromatic Acids



phenyl butyric acid provided desired products **3ao** and **3ap** in 61% and 53% yields, respectively, revealing the broad adaptability of this method.

Next, various benzamides **1** were used to further enrich the structural diversity of the acyloxylation products (Scheme 3). When *meta*-methylbenzamide **1c** was employed, the benzoxylation occurred predominantly at the sterically more accessible site to afford **3cb** in 41% yield. However, when *meta*-methoxybenzamide **1d** was subjected to benzoxylation, a mixture

Scheme 3. Scope of Benzamides

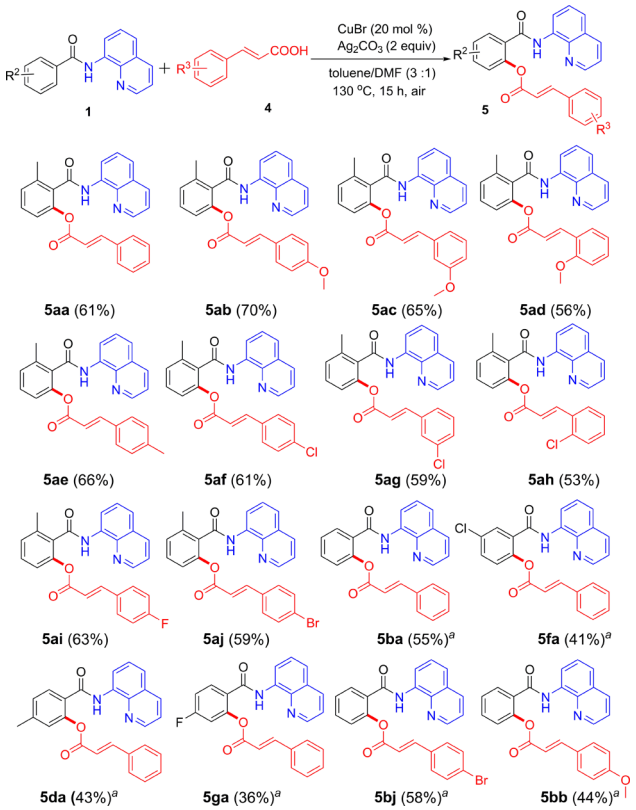


DOI: 10.1021/acs.orglett.7b01559
Org. Lett. XXXX, XXX, XXX−XXX

of **3db**, **3db′**, and **3db″** was obtained, which is most likely due to the coordination effect of the methoxy substituent that stabilized the aryl copper intermediate. Surprisingly, diacyloxylation products were obtained in moderate yields when an extended reaction time was used.

To further broaden the substrate scope of the copper-catalyzed acyloxylation of C (sp^2)−H, the reactions of cinnamic acids **4** with benzamide **1** were investigated, and the results are shown in Scheme 4. As expected, a wide range of cinnamic acid substrates

Scheme 4. Reaction Scope with Respect to Cinnamic Acids[a]

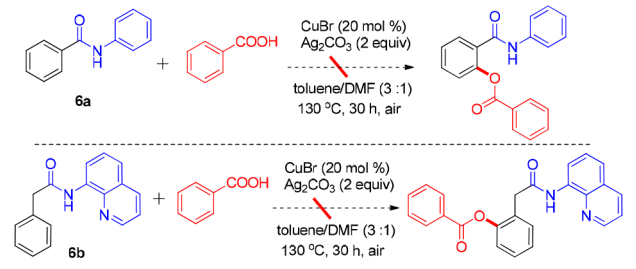


[a]Reaction time was extended to 30 h.

were compatible with this protocol. Products containing methyl, methoxy, fluoro, chloro, and bromo groups were obtained in good yields. As shown in Scheme 4, cinnamic acids exhibited lower reactivity than most of the benzoic acids, and the C−H acyloxylation of benzamides exhibited excellent monoselectivity despite extending the reaction time.

Then, we investigated the effects of the directing group on the efficiency of the acyloxylation reaction (Scheme 5). No reaction occurred when amide **6a** was used as the substrate, indicating that

Scheme 5. Effects of the Directing Group

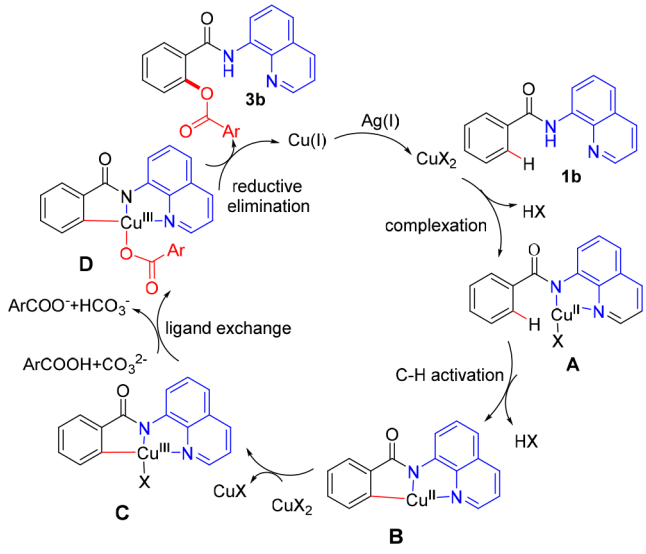


the presence of a bidentate directing group is crucial for the C−H bond activation and cyclometalation process. Additionally, 2-phenyl-*N*-(quinolin-8-yl)acetamide **6b** was not an effective substrate for this reaction, indicating that the formation of a six-membered ring intermediate is not favorable in the cyclometalation step when the directing group is far away from the benzene ring.

To gain additional insight into the mechanism of the C−H acyloxylation reactions, a series of controlled experiments was performed. The addition of 2,2,6,6-tetramethylpiperidine-*N*-oxide (TEMPO) as a radical quencher slightly inhibited the reaction (Scheme S2, eqs 1 and 2). The reaction proceeds well when sodium benzoate was used rather than benzoic acid (Scheme S2, eq 3), suggesting that the reaction does not involve a radical pathway. The intermolecular isotope kinetic effects of *N*-(quinolin-8-yl)benzamide and other experiments were studied (Figure S3). The kinetic isotope effect value (k_H/k_D) was calculated to be 1.4, indicating that the C−H cleavage was not involved in the rate-determining step of the reaction.

Based on these observations and earlier precedent,[17] a plausible mechanism for the current copper-catalyzed *ortho*-acyloxylation of *N*-(quinolin-8-yl)benzamide with benzoic acid is proposed in Scheme 6. The reaction was initiated by the

Scheme 6. Plausible Reaction Mechanism



complexation of benzamide **1b** with copper using the *N*,*N*-bidentate directing group to afford Cu(II)-complex **A**. Next, **A** involved chelate-directed C−H activation of the substrate to afford Cu(II) intermediate **B**. Then, intermediate **C** may be produced by disproportionation or oxidation. Finally, ligand exchange and reductive elimination from intermediate **C** delivered desired product **3b** with Cu(I). Based on this mechanism, we rationalize that Ag_2CO_3 may not only act as an oxidant but could also react with ArCOOH to generate $ArCOO^-$.

In summary, an efficient method for the *ortho*-acyloxylation of benzamides with an inexpensive copper catalyst has been developed to afford acyloxylation products in moderate to good yields. This protocol exhibits wide substrate scope and good functional group compatibility. The reaction can be conducted without using any ligands or additives, resulting in an operationally simple protocol for the synthesis of carboxylic esters.

DOI: 10.1021/acs.orglett.7b01559
Org. Lett. XXXX, XXX, XXX−XXX

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b01559.

Experimental details, characterization data, and ^{1}H NMR and ^{13}C NMR spectra of new compounds (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: zhangwu@mail.ahnu.edu.cn.

ORCID

Wu Zhang: 0000-0002-8327-3957

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We gratefully acknowledge the National Natural Science Foundation of China (21272006), which provided financial support.

■ REFERENCES

(1) (a) Lyons, T. W.; Sanford, M. S. *Chem. Rev.* **2010**, *110*, 1147. (b) Wencel-Delord, J.; Droge, T.; Liu, F.; Glorius, F. *Chem. Soc. Rev.* **2011**, *40*, 4740. (c) Ackermann, L. *Acc. Chem. Res.* **2014**, *47*, 281. (d) Tang, C.; Jiao, N. *J. Am. Chem. Soc.* **2012**, *134*, 18924. (e) Wang, C.; Chen, H.; Wang, Z.; Chen, J.; Huang, Y. *Angew. Chem., Int. Ed.* **2012**, *51*, 7242. (f) Rao, W. H.; Zhan, B. B.; Chen, K.; Ling, P. X.; Zhang, Z. Z.; Shi, B. F. *Org. Lett.* **2015**, *17*, 3552. (g) Wang, N. C.; Li, R. H.; Li, L. B.; Xu, S. S.; Song, H. B.; Wang, B. Q. *J. Org. Chem.* **2014**, *79*, 5379. (h) Li, G.; Leow, D. S.; Wan, L.; Yu, J. Q. *Angew. Chem., Int. Ed.* **2013**, *52*, 1245. (i) Wang, D. H.; Engle, K. M.; Shi, B. F.; Yu, J. Q. *Science* **2010**, *327*, 315. (j) Ackermann, L.; Vicente, R.; Kapdi, A. R. *Angew. Chem., Int. Ed.* **2009**, *48*, 9792. (k) Seregin, I. V.; Gevorgyan, V. *Chem. Soc. Rev.* **2007**, *36*, 1173. (l) Bergman, R. G. *Nature* **2007**, *446*, 391. (m) Pouliot, J.-R.; Grenier, F.; Blaskovits, J. T.; Beaupre, S.; Leclerc, M. *Chem. Rev.* **2016**, *116*, 14225. (n) Seki, M. *Org. Process Res. Dev.* **2016**, *20*, 867. (o) Ackermann, L. *Org. Process Res. Dev.* **2015**, *19*, 260.

(2) (a) Zhang, W.; Wang, F.; McCann, S. D.; Wang, D. H.; Chen, P. H.; Stahl, S. S.; Liu, G. S. *Science* **2016**, *353*, 1014. (b) Liu, B. X.; Zhou, T.; Xu, S. S.; Song, H. B.; Wang, B. Q. *Angew. Chem., Int. Ed.* **2014**, *53*, 4191. (c) Zhao, J. J.; Wang, Y.; He, Y. M.; Liu, L. Y.; Zhu, Q. *Org. Lett.* **2012**, *14*, 1078. (d) Roane, J.; Daugulis, O. *Org. Lett.* **2013**, *15*, 5842. (e) Li, S. J.; Zhu, W.; Gao, F.; Li, C. P.; Wang, J.; Liu, H. *J. Org. Chem.* **2017**, *82*, 126.

(3) (a) Roughley, S. D.; Jordan, A. M. *J. Med. Chem.* **2011**, *54*, 3451. (b) May, J. A.; Ratan, H.; Glenn, J. R.; Losche, W.; Spangenberg, P.; Heptinstall, S. *Platelets* **1998**, *9*, 227. (c) Fuerst, E. P.; Arntzen, C. J.; Pfister, K.; Penner, D. *Weed Sci.* **1986**, *34*, 344. (d) Wang, S.; Beck, R.; Blench, T.; Burd, A.; Buxton, S.; Malic, M.; Ayele, T.; Shaikh, S.; Chahwala, S.; Chander, C.; Holland, R.; Merette, S.; Zhao, L.; Blackney, M.; Watts, A. *J. Med. Chem.* **2010**, *53*, 1465. (e) Imramovsky, A.; Jorda, R.; Pauk, K.; Reznickova, E.; Dusek, J.; Hanusek, J.; Krystof, V. *Eur. J. Med. Chem.* **2013**, *68*, 253.

(4) (a) Moghimi, S.; Mahdavi, M.; Shafiee, A.; Foroumadi, A. *Eur. J. Org. Chem.* **2016**, *2016*, 3282. (b) Gou, F. R.; Wang, X. C.; Huo, P. F.; Bi, H. P.; Guan, Z. H.; Liang, Y. M. *Org. Lett.* **2009**, *11*, 5726.

(5) Ye, Z. S.; Wang, W. H.; Luo, F.; Zhang, S. H.; Cheng, J. *Org. Lett.* **2009**, *11*, 3974.

(6) Zheng, X. J.; Song, B. R.; Xu, B. *Eur. J. Org. Chem.* **2010**, *2010*, 4376.

(7) Hu, C. J.; Zhang, X. H.; Ding, Q. P.; Lv, T.; Ge, S. P.; Zhong, P. *Tetrahedron Lett.* **2012**, *53*, 2465.

(8) Patpi, S. R.; Sridhar, B.; Tadikamalla, P. R.; Kantevari, S. *RSC Adv.* **2013**, *3*, 10251.

(9) Wang, Z. C.; Kuang, C. X. *Adv. Synth. Catal.* **2014**, *356*, 1549.

(10) Santra, S. K.; Banerjee, A.; Khatun, N.; Patel, B. K. *Eur. J. Org. Chem.* **2015**, *2015*, 350.

(11) Raghuvanshi, K.; Zell, D.; Ackermann, L. *Org. Lett.* **2017**, *19*, 1278.

(12) Guo, X. X.; Gu, D. W.; Wu, Z. X.; Zhang, W. B. *Chem. Rev.* **2015**, *115*, 1622.

(13) Chen, Z. K.; Wang, B. J.; Zhang, J. T.; Yu, W. L.; Liu, Z. X.; Zhang, Y. H. *Org. Chem. Front.* **2015**, *2*, 1107.

(14) (a) Zaitsev, V. G.; Shabashov, D.; Daugulis, O. *J. Am. Chem. Soc.* **2005**, *127*, 13154. (b) Shabashov, D.; Daugulis, O. *J. Am. Chem. Soc.* **2010**, *132*, 3965. (c) Tran, L. D.; Popov, I.; Daugulis, O. *J. Am. Chem. Soc.* **2012**, *134*, 18237. (d) Truong, T.; Klimovica, K.; Daugulis, O. *J. Am. Chem. Soc.* **2013**, *135*, 9342. (e) Nishino, M.; Hirano, K.; Satoh, T.; Miura, M. *Angew. Chem., Int. Ed.* **2013**, *52*, 4457. (f) Suess, A. M.; Ertem, M. Z.; Cramer, C. J.; Stahl, S. S. *J. Am. Chem. Soc.* **2013**, *135*, 9797. (g) Wang, Z.; Ni, J. Z.; Kuninobu, Y.; Kanai, M. *Angew. Chem., Int. Ed.* **2014**, *53*, 3496. (h) Wu, X.; Zhao, Y.; Zhang, G.; Ge, H. *Angew. Chem., Int. Ed.* **2014**, *53*, 3706. (i) Li, Q.; Zhang, S. Y.; He, G.; Ai, Z.; Nack, W. A.; Chen, G. *Org. Lett.* **2014**, *16*, 1764. (j) Shang, M.; Sun, S. Z.; Dai, H. X.; Yu, J. Q. *J. Am. Chem. Soc.* **2014**, *136*, 3354. (k) Dong, J. X.; Wang, F.; You, J. S. *Org. Lett.* **2014**, *16*, 2884.

(15) Wang, Z.; Kuninobu, Y.; Kanai, M. *Org. Lett.* **2014**, *16*, 4790.

(16) Wu, X. S.; Zhao, Y.; Ge, H. B. *Chem. - Asian J.* **2014**, *9*, 2736.

(17) Li, X.; Liu, Y. H.; Gu, W. J.; Li, B.; Chen, F. J.; Shi, B. F. *Org. Lett.* **2014**, *16*, 3904.

DOI: 10.1021/acs.orglett.7b01559
Org. Lett. XXXX, XXX, XXX−XXX