OL | Organic Letters

Letter

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

pubs.acs.org/OrgLett

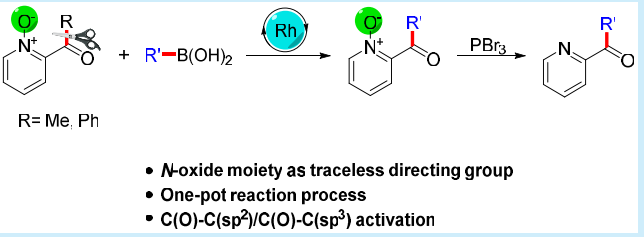
Rhodium-Catalyzed Pyridine *N*-Oxide Assisted Suzuki−Miyaura Coupling Reaction via C(O)−C Bond Activation

Jing Zhong, Yang Long, Xufei Yan, Shiyu He, Runyou Ye, Haifeng Xiang, and Xiangge Zhou*

College of Chemistry, Sichuan University, 29 Wangjiang Road, Chengdu 610064, P.R. China

Supporting Information

ABSTRACT: A rhodium-catalyzed Suzuki−Miyaura coupling reaction via C(O)-C bond activation to form 2-benzoylpyridine *N*-oxide derivatives is reported. Both the C(O)−C(sp^2) and C(O)−C(sp^3) bond could be activated during the reaction with yields up to 92%. The *N*-oxide moiety could be employed as a traceless directing group, leading to free pyridine ketones.

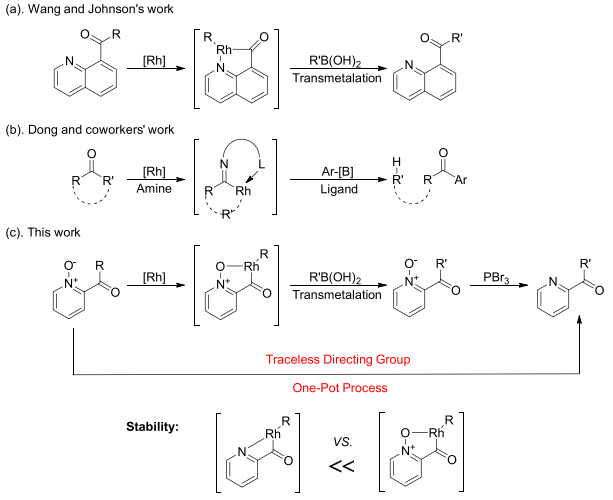


The Suzuki−Miyaura coupling reaction was first discovered by Suzuki and co-workers to achieve a C(sp^2)−C(sp^2) single bond in the presence of palladium catalyst in 1979.[1a] It has become one of the most general and straightforward synthetic methods to form carbon−carbon bonds as well as new functional groups in organic synthesis.[1] Several transition-metal catalysts including palladium,[2a] rhodium,[2b] nickel,[2c] iron,[2d] or cobalt[2e] have been applied in this transformation during the past decades.

On the other hand, it is well-known that the C−C bond of three- or four-membered ring molecules can be successfully activated, accompanyed by the release of ring strain.[3] In the case of unstrained molecules, special driving forces are usually required to overcome the high kinetic barriers associated with the activation step of generating stable intermediates.[4,5] Among various unstrained C−C bond activations, the cleavage of C−C bonds adjacent to the carbonyl group (C(O)−C bond cleavage) has been extensively investigated due to its weakness and wide availability of ketone derivatives. Pioneering works have been reported by Jun,[5a] Lee,[5b] Murai,[5c] Douglas,[5d] Shi,[5e] Dong,[5f] Johnson,[5g] Wei,[5h] and Chatani[5i] and other groups.

Furthermore, *N*-heteroaryl ketones are important structural units usually found in drug molecules, natural products, and functional materials. However, the functionalization of pyridines is quite difficult due to its electron-poor nature. Wang and co-workers reported a rhodium(I)-catalyzed cross-coupling reaction of 8-quinolinyl ketones with a broad scope of boronic acid reagents.[6] Johnson further proved that the reaction could be tolerant to a variety of electron-deficient aryl boronic reagents (Scheme 1a).[7] Utilizing a similar strategy, Dong and co-workers merged the imine-directed C−C activation in one-pot transmetalation process (Scheme 1b).[8] However, the direct pyridine assisted *ortho* position C(O)−C bond activation has not been reported, which might be caused by the difficulty in forming a stable four-membered ring intermediate (Scheme 1c). Meanwhile, pyridine *N*-oxides have been reported as activated starting substances for versatile derivations and also as the directing groups for selective C−H or C−C bond activation.[10] In continuation of our work on C−H bond activation[11] and C−C bond activation,[12] herein is reported the development of a rhodium-catalyzed Suzuki−Miyaura-type coupling reaction of 2-benzoylpyridine *N*-oxides with boronic acids (Scheme 1c). This work reported the first example of utilization of *N*-oxide moiety as a traceless directing group to achieve C−C bond activation, which could be subsequently easily removed in a one-pot process.[13]

Scheme 1. Examples of Suzuki−Miyaura Coupling via C(O)−C Bond Activation

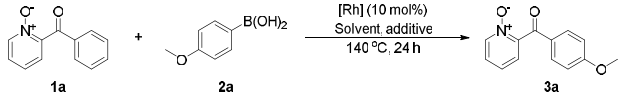


Initially, 2-benzoylpyridine 1-oxide (**1a**) was chosen as a model substrate to be coupled with 4-methoxyphenylboronic acid (**2a**) in the presence of 10 mol % of [$Rh(CO)_2(acac)$] as catalyst in toluene at 140 °C under N_2 atmosphere. As shown in Table 1, 23% yield of the desired product **3a** was detected (Table 1, entry 1). Then the solvent effect studies showed that

Received: November 13, 2019

DOI: 10.1021/acs.orglett.9b04068
Org. Lett. XXXX, XXX, XXX−XXX

Table 1. Screening for Optimal Catalytic System[a]



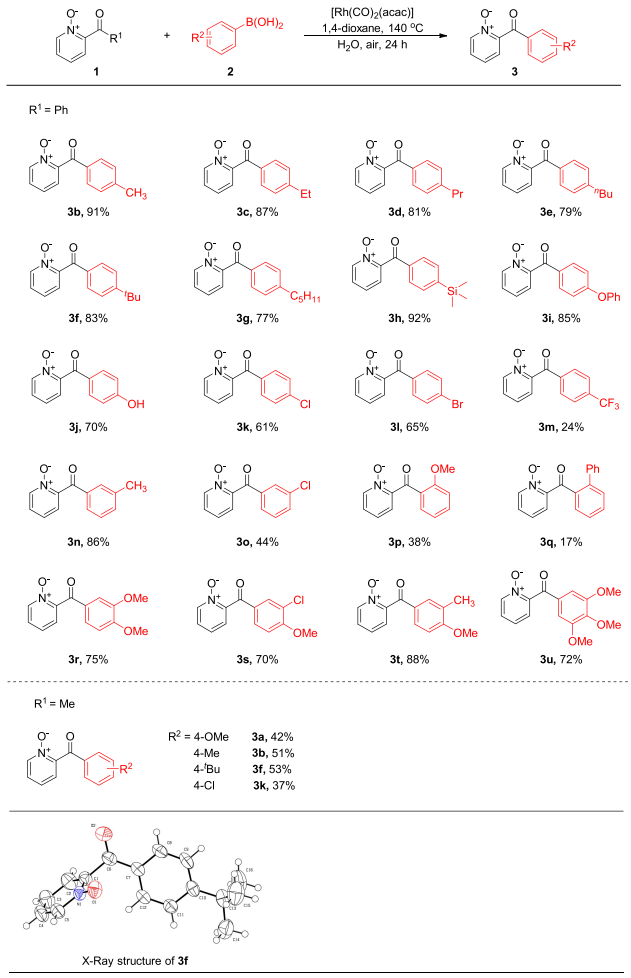
entry	[Rh][c]	additive (mol %)[d]	solvent	yield[b] (%)
1[e]	$[Rh(CO)_2(acac)]$		toluene	23
2[e]	$[Rh(CO)_2(acac)]$		DMSO	17
3[e]	$[Rh(CO)_2(acac)]$		PhCl	27
4[e]	$[Rh(CO)_2(acac)]$		1,4-dioxane	34
5	$[Rh(CO)_2(acac)]$		1,4-dioxane	53
6[f]	$[Rh(CO)_2(acac)]$		1,4-dioxane	55
7	$[Rh(CO)_2(acac)]$	K_2CO_3 (120)	1,4-dioxane	51
8	$[Rh(CO)_2(acac)]$	NaOAc (120)	1,4-dioxane	32
9	$[Rh(CO)_2(acac)]$	NaF (120)	1,4-dioxane	42
10	$[Rh(CO)_2(acac)]$	K_3PO_4 (120)	1,4-dioxane	50
11	$[Rh(CO)_2(acac)]$	dppb (20)	1,4-dioxane	36
12	$[Rh(CO)_2(acac)]$	dppp (20)	1,4-dioxane	NR
13	$[Rh(CO)_2(acac)]$	X-phos (20)	1,4-dioxane	25
14	$[Rh(CO)_2(acac)]$	ICy (20)	1,4-dioxane	NR
15	$[Rh(CO)_2Cl]_2$		1,4-dioxane	55
16	$[Rh(PPh_3)_3Cl]_2$		1,4-dioxane	35
17	$[Rh(C_2H_4)_2Cl]_2$		1,4-dioxane	27
18[g]	$[Rh(CO)_2(acac)]$		1,4-dioxane	65
19[g]	$[Rh(CO)_2(acac)]$	H_2O (250)	1,4-dioxane	75
20[g]	$[Rh(CO)_2(acac)]$	H_2O (500)	1,4-dioxane	77
21[g]	$[Rh(CO)_2(acac)]$	H_2O (750)	1,4-dioxane	82

[a]General conditions: **1a** (0.2 mmol), **2a** (0.5 mmol), [Rh] (10 mol %), additive, and solvent (1.0 mL) were stirred at 140 °C for 24 h in air. [b]Isolated yields. [c]acac: acetylacetonato. [d]dppb: 1,4-bis(diphenylphosphino)butane. dppp: 1,3-bis(diphenylphosphino)propane. X-phos: 2-dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl. ICy: 1,3-dicyclohexylimidazolium chloride. [e]Under N_2. [f]Under O_2. [g]1,4-Dioxane (2.0 mL).

1,4-dioxane was better than others including toluene, DMSO, and PhCl (Table 1, entries 2−4). It is worth noting that the *N*-oxide compound (**1a**) was found to be partially reduced under N_2 atmosphere, which would cause the decreased yields (Table 1, entry 4). Therefore, air and oxygen atmosphere were tried in the reaction, and air atmosphere was proved to be enough to suppress the reduction with yield of 53% (Table 1, entries 5 and 6). Different bases including K_2CO_3, NaOAc, NaF, K_3PO_4, and ligands including phosphine and NHC were also tested, resulting in similar or inferior effects (Table 1, entries 7−14).[14,15] With regard to the rhodium salts, $[Rh(CO)_2(acac)]$ was the best one (Table 1, entries 15−17). After extensive screening of the reaction parameters, addition of a small amount of H_2O was found to be beneficial to the reaction,[8,16] and the desired coupling product (**3a**) was ultimately obtained in 82% yield in the presence of 7.5 equiv of H_2O (Table 1, entry 21).

With the optimized reaction conditions in hand, the scope of arylboronic acids was then explored (Scheme 2). In general, electron-rich substituents were found to be beneficial to the reactions, which was probably due to a faster transmetalation process.[1e] For example, arylboronic acid with a *p*-methyl or chloro group resulted in yields of 91% and 61%, respectively (**3b** and **3k**). Meanwhile, steric effects seemed to be an important factor for the results. The arylboronic acid with a substituent at the *ortho* position gave low yields (**3p** and **3q**). Polysubstituted arylboronic acids also smoothly delivered the corresponding products in moderate to good yields (**3r**−**3u**).

Scheme 2. Scope of Arylboronic Acids[a,b]



[a]**1** (0.2 mmol), **2** (0.5 mmol), $[Rh(CO)_2(acac)]$ (10 mol %), H_2O (7.5 equiv), and 1,4-dioxane (2.0 mL) were stirred at 140 °C for 24 h in air. [b]Isolated yields.

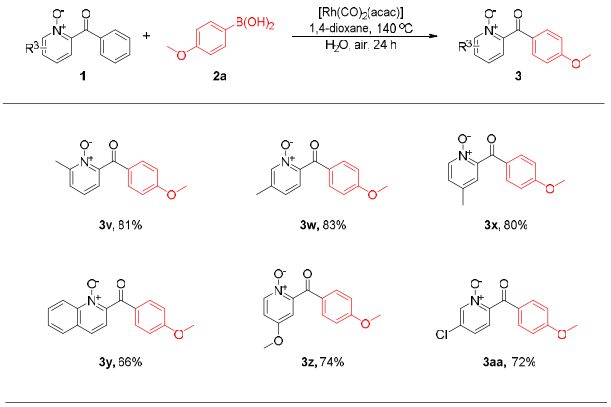
Further studies showed that 2-acetylpyridine *N*-oxide, which contains a $C(sp^3)-C(O)$ bond, could undergo similar conversions when it was reacted with an array of electron-rich and electron-deficient aryl boronic acid moieties under the standard conditions albeit in decreased yields (37%−53%), indicating that $C(O)-C(sp^2)$ activation might be easier than $C(O)-C(sp^3)$ activation. The structure of **3f** was confirmed via X-ray single-crystal determination.

Next, the limitation and generality of the pyridine *N*-oxides was examined. As shown in Scheme 3, the electronic and steric effects of some substituents were studied and seemed to have few effects on the results. For example, the *o*-, *m*-, and *p*-methyl-substituted substrates gave similar results around 80% yields (**3v**−**3x**). Meanwhile, methoxy- or chloro-substituted substrates also afforded the desired products in yields around 70% (**3z** and **3aa**). Additionally, 2-benzoylquinoline 1-oxide was applied as substrate to form the corresponding product **3y** in 66% yield.

To gain insight into the possible catalytic pathway, a series of control experiments were carried out as shown in Scheme 4. At first, no product was detected in the reaction between 2-benzoylpyridine (**4**) and 4-methoxyphenylboronic acid (**2a**) (Scheme 4a) under the standard conditions, indicating the

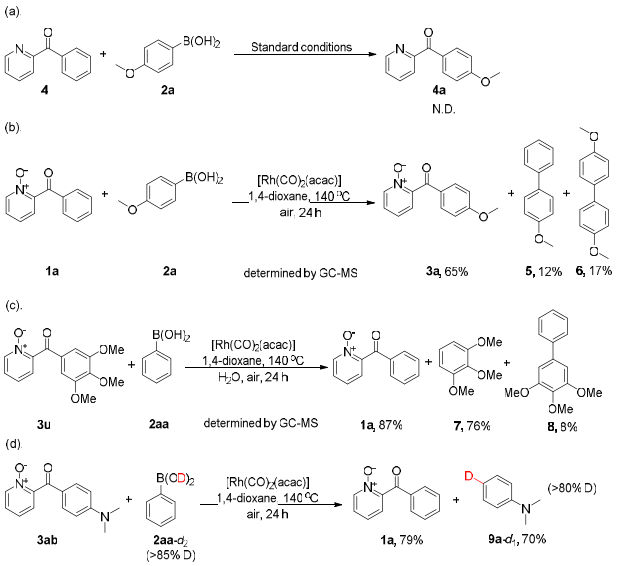
DOI: 10.1021/acs.orglett.9b04068
Org. Lett. XXXX, XXX, XXX−XXX

Scheme 3. Scope of 2-Benzoylpyridine *N*-Oxides[a,b]



[a]**1** (0.2 mmol), **2a** (0.5 mmol), [$Rh(CO)_2(acac)$] (10 mol %), H_2O (7.5 equiv), and 1,4-dioxane (2.0 mL) were stirred at 140 °C for 24 h in air. [b]Isolated yields.

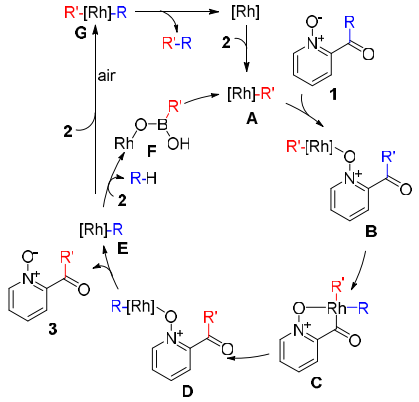
Scheme 4. Mechanistic Studies



pyridine *N*-oxides to be crucial for the reaction as a directing group. Then, analysis of the crude product mixture of the reaction between **1a** and **2a** by GC−MS and NMR revealed the existence of 4-methoxyl-1,1′-biphenyl (**5**), which proved the possibility of involvement of carbon−carbon activation and transmetalation steps during the reaction (Scheme 4b). Furthermore, a certain amount of protonated aryl product **7** from the starting substrate **3u** was detected by GC−MS (Scheme 4c). According to Hartwig's work,[17] the deuterium-labeling experiments have also been performed, indicating the source of proton might come from arylboronic acid (Scheme 4d). When the deuterated (at the 85% D level) phenylboronic acid (**2aa**-d_2) and **3ab** were subjected to the standard reaction conditions, more than 80% deuterium incorporation was observed at the C4 position of *N*,*N*-dimethylaniline (**9a**-d_1).

On the basis of the experimental results and literature precedence,[6,7,17] a plausible catalytic cycle for the rhodium-catalyzed C(O)−C activation was proposed as depicted in Scheme 5. Initial transmetalation of the boronic acid **2** with rhodium catalyst forms rhodium(I) aryl intermediate **A**. Next, coordination of substrate **1** through the oxygen atom of *N*-

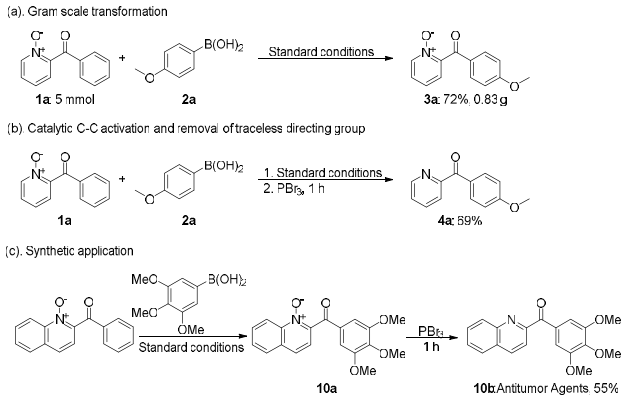
Scheme 5. Plausible Mechanistic Pathway



oxide with rhodium(I) and a formal oxidative addition process generates a five-membered rhodacyclic **C** and thereby sets the stage for the key C−C activation. Reductive elimination can form intermediate **D**, and subsequent dissociation would generate the desired product **3** and rhodium(I) complex **E**. Proton exchange of intermediate **E** with arylboronic **2** is feasible to give the intermediate **F** and R-H,[17] from which *β*-aryl elimination might take place to regenerate intermediate **A**. On the other hand, partial intermediate **E** would also be reacted with another arylboronic acid **2** in the presence of oxygen to generate Rh(III) complex **G**, releasing Rh(I) and the byproduct R-R′ by reductive elimination to complete the catalytic cycle.

To explore the efficiency and practical utility of this method, the scale-up experiment and synthetic transformation reactions were carried out. As shown in Scheme 6a, the gram-scale

Scheme 6. Gram-Scale Experiment and Synthetic Transformations



experiment (5 mmol) was conducted by using **1a** and **2a** as substrates, and **3a** was obtained in 72% yield. More importantly, after addition of PBr_3 into the reaction mixture, the free pyridine ketone (**4a**) could be obtained in a total yield of 69% in one-pot reaction (Scheme 6b), indicating that *N*-oxide moiety could be removed as a traceless directing group in the reaction. At last, this protocol could be successfully applied in the synthesis of 2-(3,4,5-trimethoxybenzoyl)-quinolone (**10b**), which was reported to show potent antiproliferative activity against various human cancer cells (Scheme 6c).[18]

DOI: 10.1021/acs.orglett.9b04068
Org. Lett. XXXX, XXX, XXX−XXX

In summary, a protocol of efficient cross-coupling of alkyl and 2-benzoylpyridine *N*-oxides with boronic acids via C(O)−C(sp^3) or C(O)−C(sp^2) activation was developed. The pyridine *N*-oxides proved to be crucial to realize the reaction, which was used as a traceless directing group and could be removed under PBr_3 conditions in one-pot reaction. The development of new reactions based on this strategy is currently in progress.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.9b04068.

Experimental procedures; crystallographic data; spectral data (PDF)

Accession Codes

CCDC 1956268 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 Author

*E-mail: zhouxiangge@scu.edu.cn.

ORCID

Haifeng Xiang: 0000-0002-4778-2455

Xiangge Zhou: 0000-0001-5327-6674

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We are grateful to the National Natural Science Foundation of China (Grant No. 21472128) and Sichuan Science and Technology Program (No. 2018JY560) for financial support. We also acknowledge the Comprehensive Training Platform of Specialized Laboratory, College of Chemistry, Sichuan University, for HRMS analysis.

■ REFERENCES

(1) (a) Miyaura, N.; Yamada, K.; Suzuki, A. *Tetrahedron Lett.* **1979**, *20*, 3437. (b) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457. (c) Blakey, S. B.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2003**, *125*, 6046. (d) Schaub, T.; Backes, M.; Radius, U. *J. Am. Chem. Soc.* **2006**, *128*, 15964. (e) Han, F.-S. *Chem. Soc. Rev.* **2013**, *42*, 5270. (f) Muto, K.; Yamaguchi, J.; Musaev, D. G.; Itami, K. *Nat. Commun.* **2015**, *6*, 7508. (g) Yadav, M. R.; Nagaoka, M.; Kashihara, M.; Zhong, R. L.; Miyazaki, T.; Sakaki, S.; Nakao, Y. *J. Am. Chem. Soc.* **2017**, *139*, 9423.

(2) (a) Sawai, K.; Tatumi, R.; Nakahodo, T.; Fujihara, H. *Angew. Chem., Int. Ed.* **2008**, *47*, 6917. (b) Wang, H.; Grohmann, C.; Nimphius, C.; Glorius, F. *J. Am. Chem. Soc.* **2012**, *134*, 19592. (c) Tobisu, M.; Xu, T.; Shimasaki, T.; Chatani, N. *J. Am. Chem. Soc.* **2011**, *133*, 19505. (d) Iwamoto, T.; Okuzono, C.; Adak, L.; Jin, M.; Nakamura, M. *Chem. Commun.* **2019**, *55*, 1128. (e) Verma, P. K.; Mandal, S.; Geetharani, K. *ACS Catal.* **2018**, *8*, 4049.

(3) (a) Periana, R. A.; Bergman, R. G. *J. Am. Chem. Soc.* **1986**, *108*, 7346. (b) Murakami, M.; Matsuda, T. *Chem. Commun.* **2011**, *47*, 1100. (c) Marek, I.; Masarwa, A.; Delaye, P. O.; Leibeling, M. *Angew. Chem., Int. Ed.* **2015**, *54*, 414. (d) Souillart, L.; Cramer, N. *Chem. Rev.* **2015**, *115*, 9410. (e) Shaw, M.; Bower, J. *Chem. Commun.* **2016**, *52*, 10817. (f) Chen, P. H.; Billett, B. A.; Tsukamoto, T.; Dong, G. *ACS Catal.* **2017**, *7*, 1340. (g) Fumagalli, G.; Stanton, S.; Bower, J. F. *Chem. Rev.* **2017**, *117*, 9404.

(4) (a) Havens, S.; Hergenrother, P. *J. Org. Chem.* **1985**, *50*, 1763. (b) Funayama, A.; Satoh, T.; Miura, M. *J. Am. Chem. Soc.* **2005**, *127*, 15354. (c) Shintani, R.; Takatsu, K.; Katoh, T.; Nishimura, T.; Hayashi, T. *Angew. Chem., Int. Ed.* **2008**, *47*, 1447. (d) Waibel, M.; Cramer, N. *Chem. Commun.* **2011**, *47*, 346. (e) Chen, K.; Li, H.; Li, Y.; Zhang, X.-S.; Lei, Z.-Q.; Shi, Z.-J. *Chem. Sci.* **2012**, *3*, 1645. (f) Engle, K.; Mei, T.-S.; Wasa, M.; Yu, J.-Q. *Acc. Chem. Res.* **2012**, *45*, 788. (g) Wang, Y.; Kang, Q. *Org. Lett.* **2014**, *16*, 4190. (h) Ozkal, E.; Cacherat, B.; Morandi, B. *ACS Catal.* **2015**, *5*, 6458. (i) Huang, Z.; Lim, H. N.; Mo, F.; Young, M. C.; Dong, G. *Chem. Soc. Rev.* **2015**, *44*, 7764. (j) Zhu, R.-Y.; Farmer, M. E.; Chen, Y.-Q.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2016**, *55*, 10578. (k) Zhi, Y.; Huang, J.; Liu, N.; Lu, T.; Dou, X. *Org. Lett.* **2017**, *19*, 2378. (l) Dou, X.; Liu, N.; Lu, T. *Org. Lett.* **2018**, *20*, 272. (m) Song, F.; Gou, T.; Wang, B.-Q.; Shi, Z.-J. *Chem. Soc. Rev.* **2018**, *47*, 7078. (n) Qiu, Y.; Scheremetjew, A.; Ackermann, L. *J. Am. Chem. Soc.* **2019**, *141*, 2731.

(5) (a) Suggs, J. W.; Jun, C.-H. *J. Am. Chem. Soc.* **1984**, *106*, 3054. (b) Jun, C.-H.; Lee, H. *J. Am. Chem. Soc.* **1999**, *121*, 880. (c) Chatani, N.; Ie, Y.; Kakiuchi, F.; Murai, S. *J. Am. Chem. Soc.* **1999**, *121*, 8645. (d) Wentzel, M. T.; Reddy, V. J.; Hyster, T. K.; Douglas, C. J. *Angew. Chem., Int. Ed.* **2009**, *48*, 6121. (e) Lei, Z.-Q.; Li, H.; Li, Y.; Zhang, X.-S.; Chen, K.; Wang, X.; Sun, J.; Shi, Z.-J. *Angew. Chem., Int. Ed.* **2012**, *51*, 2690. (f) Rong, Z.-Q.; Lim, H. N.; Dong, G. *Angew. Chem., Int. Ed.* **2018**, *57*, 475. (g) Lutz, J. K.; Rathbun, C. M.; Stevenson, S. M.; Powell, B. M.; Boman, T. S.; Baxter, C. E.; Zona, J. M.; Johnson, J. B. *J. Am. Chem. Soc.* **2012**, *134*, 715. (h) Zhao, T.-T.; Xu, W.-H.; Zheng, Z.-J.; Xu, P.-F.; Wei, H. *J. Am. Chem. Soc.* **2018**, *140*, 586. (i) Morioka, T.; Nishizawa, A.; Furukawa, T.; Tobisu, M.; Chatani, N. *J. Am. Chem. Soc.* **2017**, *139*, 1416. (j) Whittaker, R. E.; Dong, G. *Org. Lett.* **2015**, *17*, 5504. (k) Dermenci, A.; Whittaker, R. E.; Gao, Y.; Cruz, F. A.; Yu, Z.-X.; Dong, G. *Chem. Sci.* **2015**, *6*, 3201. (l) Onodera, S.; Ishikawa, S.; Kochi, T.; Kakiuchi, F. *J. Am. Chem. Soc.* **2018**, *140*, 9788. (m) Zeng, R.; Chen, P. H.; Dong, G. *ACS Catal.* **2016**, *6*, 969. (n) Sumida, Y.; Yorimitsu, H.; Oshima, K. *Org. Lett.* **2010**, *12*, 2254. (o) Arisawa, M.; Kuwajima, M.; Toriyama, F.; Li, G.; Yamaguchi, M. *Org. Lett.* **2012**, *14*, 3804. (p) Zhou, T.; Ji, C.-L.; Hong, X.; Szostak, M. *Chem. Sci.* **2019**, *10*, 9865.

(6) Wang, J.; Chen, W.; Zuo, S.; Liu, L.; Zhang, X.; Wang, J. *Angew. Chem., Int. Ed.* **2012**, *51*, 12334.

(7) Dennis, J. M.; Compagner, C. T.; Dorn, S. K.; Johnson, J. B. *Org. Lett.* **2016**, *18*, 3334.

(8) Xia, Y.; Wang, J.; Dong, G. *J. Am. Chem. Soc.* **2018**, *140*, 5347.

(9) (a) Yan, G.; Borah, A. J.; Yang, M. *Adv. Synth. Catal.* **2014**, *356*, 2375. (b) Zhou, W.; Miura, T.; Murakami, M. *Angew. Chem., Int. Ed.* **2018**, *57*, 5139. (c) Guo, L.; Tang, B.; Nei, R.; Liu, Y.; Lv, S.; Wang, H.; Guo, L.; Hai, L.; Wu, Y. *Chem. Commun.* **2019**, *55*, 10623. (d) Keerthi Krishnan, K.; Ujwaldev, S. M.; Saranya, S.; Anilkumar, G.; Beller, M. *Adv. Synth. Catal.* **2019**, *361*, 382.

(10) Suehiro, T.; Niwa, T.; Yorimitsu, H.; Oshima, K. *Chem. - Asian J.* **2009**, *4*, 1217.

(11) (a) Wu, Z.; Chen, S.; Li, Z.; Xiang, H.; Zhou, X. *ChemCatChem* **2013**, *5*, 2839. (b) Luo, F.; Yang, J.; Li, Z.; Xiang, H.; Zhou, X. *Adv. Synth. Catal.* **2016**, *358*, 887. (c) Yao, X.; Weng, X.; Wang, K.; Xiang, H.; Zhou, X. *Green Chem.* **2018**, *20*, 2472. (d) Long, Y.; Pan, L.; Zhou, X. *Molecules* **2019**, *24*, 535. (e) Yang, J.; Ji, D.-W.; Hu, Y.-C.; Min, X.-T.; Zhou, X.; Chen, Q.-A. *Chem. Sci.* **2019**, *10*, 9560.

(12) (a) Yan, X.; Sun, H.; Xiang, H.; Yu, D.-G.; Luo, D.; Zhou, X. *Chem. Commun.* **2018**, *54*, 8606. (b) Yan, X.; Ye, R.; Sun, H.; Zhong, J.; Xiang, H.; Zhou, X. *Org. Lett.* **2019**, *21*, 7455.

(13) Johnston, A.; Ling, K. B.; Sale, D.; Lebrasseur, N.; Larrosa, I. *Org. Lett.* **2016**, *18*, 6094.

(14) (a) Lennox, A.-J.; Lloyd-Jones, G. *Angew. Chem., Int. Ed.* **2013**, *52*, 7362. (b) Cox, P. A.; Reid, M.; Leach, A. G.; Campbell, A. D.; King, E. J.; Lloyd-Jones, G. *J. Am. Chem. Soc.* **2017**, *139*, 13156. (c) Malapit, C. A.; Bour, J. R.; Brigham, C. E.; Sanford, M. S. *Nature* **2018**, *563*, 100.

DOI: 10.1021/acs.orglett.9b04068
Org. Lett. XXXX, XXX, XXX−XXX

(15) (a) Lapointe, D.; Fagnou, K. *Chem. Lett.* **2010**, *39*, 1118. (b) Xia, Y.; Wang, J.; Dong, G. *Angew. Chem., Int. Ed.* **2017**, *56*, 2376.
(16) (a) Jun, C. H.; Chung, K.-Y.; Hong, J.-B. *Org. Lett.* **2001**, *3*, 785. (b) Jun, C.-H.; Lee, H.; Lim, S.-G. *J. Am. Chem. Soc.* **2001**, *123*, 751. (c) Xia, Y.; Lu, G.; Liu, P.; Dong, G. *Nature* **2016**, *539*, 546.
(17) Zhao, P.; Incarvito, C. D.; Hartwig, J. F. *J. Am. Chem. Soc.* **2007**, *129*, 1876.
(18) Nien, C.-Y.; Chen, Y.-C.; Kuo, C.-C.; Hsieh, H.-P.; Chang, C.-Y.; Wu, J.-S.; Wu, S.-Y.; Liou, J.-P.; Chang, J.-Y. *J. Med. Chem.* **2010**, *53*, 2309.

DOI: 10.1021/acs.orglett.9b04068
Org. Lett. XXXX, XXX, XXX−XXX