Organic LETTERS

Letter

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Direct *ortho*-Arylation of Pyridinecarboxylic Acids: Overcoming the Deactivating Effect of sp^2-Nitrogen

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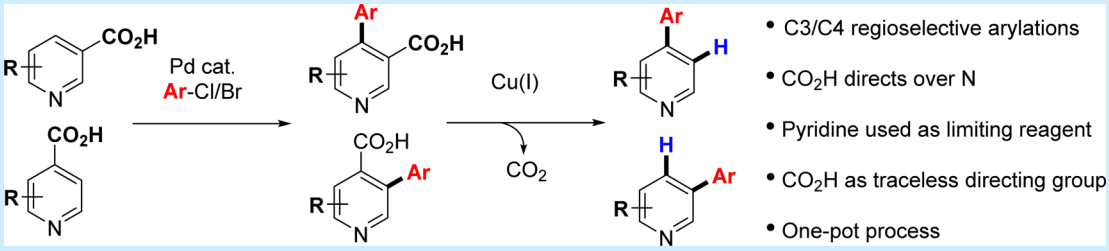
Supporting Information



ABSTRACT: Direct arylations of pyridines are challenging transformations due to the high Lewis basicity of the sp^2-nitrogen. The use of carboxylates as directing groups is reported, facilitating the Pd-catalyzed C−H arylation of this difficult class of substrates. This methodology allows regioselective C3/C4 arylation, without the need to use solvent quantities of the pyridine, and using low-cost chloro- and bromoarenes as coupling partners. Furthermore, carboxylates could be employed as traceless directing groups through a one-pot C−H arylation/Cu(I)-mediated decarboxylation sequence, thereby accessing directing-group-free pyridine biaryls.

Over the past decade, transition metal-catalyzed C−H arylation of aromatic and heteroaromatic rings has emerged as an effective method to access functionalized biaryls from simple starting materials.[1] Key challenges that arise when developing such methodologies lie in the control of the regioselectivity of the reaction, and for less reactive arenes, the need to use them in large excess.[2] Methodologies targeting arylation of pyridines[3,4] are of particular interest as these compounds often possess properties of substantial practical utility including their use as ligands for transition metals[5] and as functional materials,[6] along with remarkable biological activity.[7] The challenging nature of the direct arylation of pyridines stems from the high Lewis basicity of the sp^2-nitrogen, which often results in catalyst coordination and poisoning and/or in side reactions. Although significant progress has been made toward developing C2 arylation protocols,[3] the selective C−H arylation of the C3 and C4 positions is much less developed.[4] Common protocols for direct arylation of pyridines require the use of large excess of the pyridine substrate (often as solvent),[4f,h,q] or the prefunctionalization of the pyridine core to install activating or directing groups.[4a,e,i,k] However, such directing groups are often difficult to remove or transform, limiting applicability.

In the past few years, the use of carboxylic acids as directing groups has been under intense development.[8] Their ready availability as starting materials combined with an array of catalytic methods for their removal or subsequent functionalization[9] have made carboxylic acids the ideal directing groups for a variety of functionalizations. However, despite its appeal, a methodology able to harness the potential of carboxylic acids for the regioselective C−H arylation of pyridines has never been reported. Developing such an approach would require overcoming the strong coordination of pyridine, a common strong directing group for C−H arylation,[10] in favor of the often considered weaker coordination of the carboxylic acid.[8e] Previous approaches by the groups of Yu[4e] and Su[4k] involved the derivatization of the carboxylic acid into more coordinating amides (Scheme 1a). In this letter, we report a Pd-catalyzed system that can directly *utilize carboxylic acids as directing groups* for arylation at C3 or C4 of pyridines in preference to coordination at the pyridine nitrogen (Scheme 1b). Thus, readily available substituted nicotinic acids, used as limiting reagents, can be directly and selectively arylated. Furthermore, the carboxylic acid group can be subsequently removed in a one-pot process, acting as a traceless directing group.[11]

Working on the hypothesis that *N*-coordination is detrimental to any active catalyst species, we choose **1a** as our initial substrate (Table 1) since the large and strongly electron-withdrawing trifluoromethyl group should disfavor such coordination. A variety of C−H arylation methods based either on proposed Pd(II)/Pd(IV) or Pd(0)/Pd(II) catalytic cycles were assessed. While the former methods proved inactive, we were delighted to observe that $Pd(OAc)_2/PAd_2(n\text{-}Bu)$, a system previously reported by Daugulis et al. for the arylation of benzoic acids,[8a]

Received: October 13, 2016

DOI: 10.1021/acs.orglett.6b03085
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Scheme 1. Carboxylic Acids as Traceless Directing Groups for C3 and C4 Regioselective Pyridine Direct Arylation

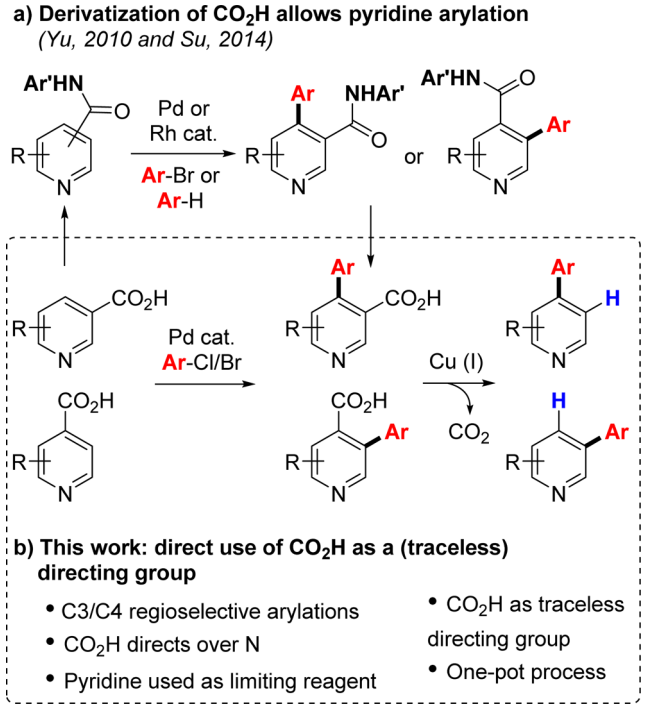
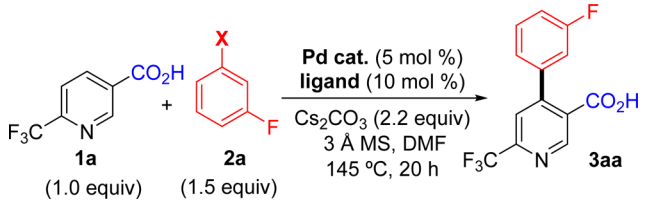
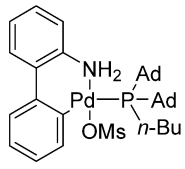


Table 1. Selected Optimization Results[a]



				yield (%)	
entry	X	Pd cat.	ligand	1a	3aa
1	Cl	$Pd(OAc)_2$	$PAd_2(n\text{-Bu})$	19	65
2	Cl	$Pd(OAc)_2$	$[PAd_2(n\text{-Bu})H]I$	25	66
3	Br	$Pd(OAc)_2$	$[PAd_2(n\text{-Bu})H]I$	20	64
4	Cl	cataCXium A-Pd-G3[b]		6	73
5	Br	cataCXium A-Pd-G3[b]		26	63

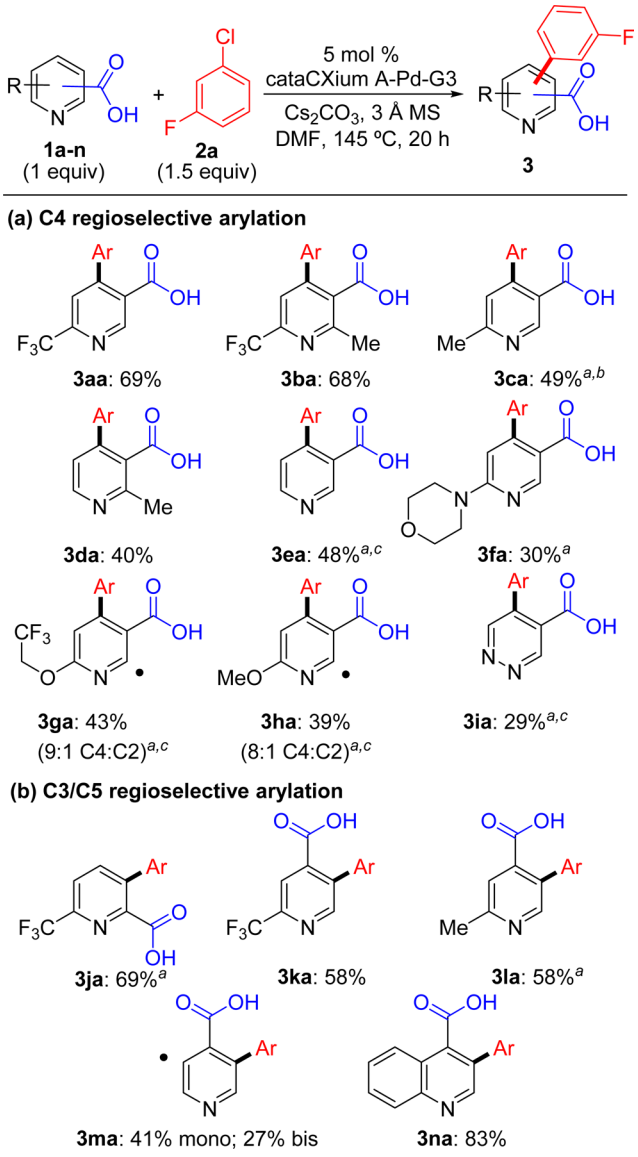
[a]Reactions were performed under Ar atmosphere. Yields were determined by ^1H NMR analysis using mesitylene or CH_2Br_2 as an internal standard. [b]



cataCXium® A-Pd-G3

was able to efficiently catalyze the arylation of **1a** with chloroarene **2a** with complete C4 regioselectivity (entry 1). Remarkably, the pyridine substrate can be the limiting reagent under these conditions. Conveniently, the free phosphine can be replaced by its air stable hydroiodide salt without any drop in yield and selectivity (entry 2), removing the need for the use of a glovebox. Along with chloroarenes, bromoarenes are also effective coupling partners under these reaction conditions, thus broadening the scope of this new methodology (entry 3).

Scheme 2. Scope of the Arylation of Pyridinecarboxylic Acids (1a−n) with Chloroarene 2a



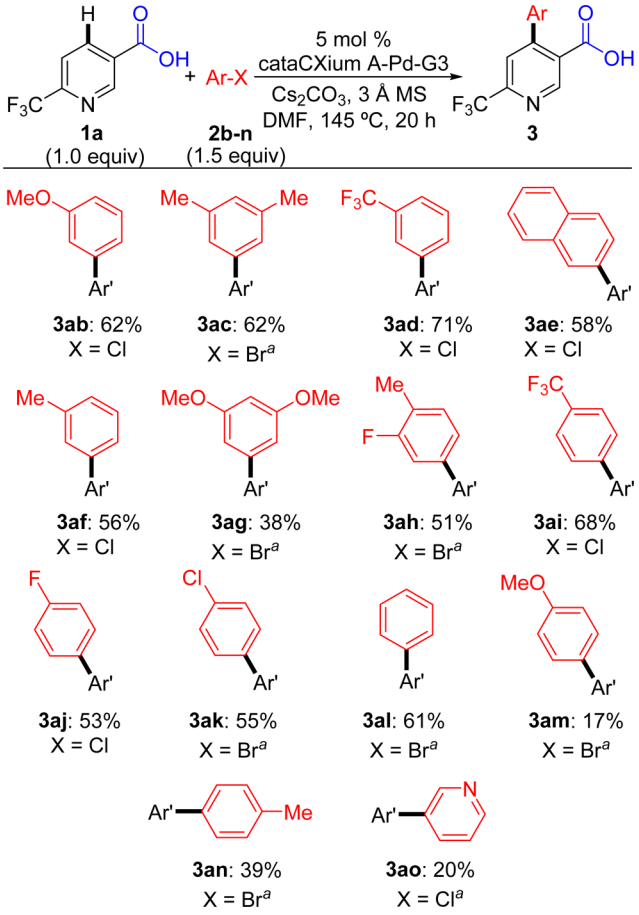
Reactions carried out on a 0.5 mmol scale. Yields are of pure isolated material. [a]Reactions performed with 5 mol % $Pd(OAc)_2$ and 10 mol % $[PAd_2(n\text{-Bu})H]I$. [b]After 20 h 5 mol % $Pd(OAc)_2$, 10 mol % $[PAd_2(n\text{-Bu})H]I$ in 0.5 mL of DMF was added and the reaction stirred for further 20 h. [c]The reaction for 48 h.

Further optimization showed that the yield of **3aa** could be increased to 73% by using the Buchwald third generation precatalyst cataCXium A-Pd-G3 (entries 4 and 5).[12]

With optimized conditions in hand the scope of the pyridinecarboxylic acids was next investigated (Scheme 2). We were delighted to find that, in addition to C4-selective arylation (Scheme 2a, **3aa**−**3ia**), C3/5-arylated pyridines could also be efficiently accessed by employing C2 or C4-pyridinecarboxylic acids (Scheme 2b, **3ja**−**3na**). Replacing the α-CF_3 substituent with a methyl still led to good reactivity (**3ca**, **3da**, and **3la**). Gratifyingly, both nicotinic (**1e**) and isonicotinic (**1m**) acids, despite their poor solubility and lack of α-substitution, were also arylated under the reaction conditions (**3ea** and **3ma**, respectively) showing that blocking *N*-coordination with an α-substituent is not necessary. 4-Quinolinecarboxylic acid **1n** led to

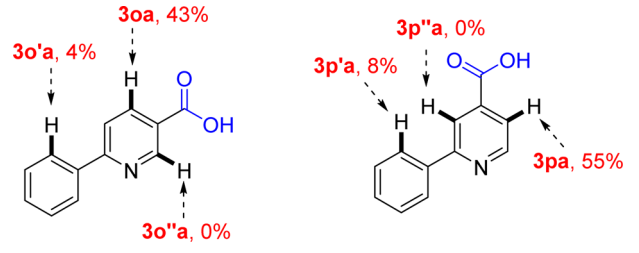
DOI: 10.1021/acs.orglett.6b03085
Org. Lett. XXXX, XXX, XXX−XXX

Scheme 3. Scope of the Arylation of Nicotinic Acid 1a with Haloarenes (2b–n)



Reactions carried out on a 0.5 mmol scale. Yields are of pure isolated material. [a]Reactions performed with 5 mol % $Pd(OAc)_2$ and 10 mol % $[PAd_2(n\text{-Bu})H]I$.

Scheme 4. Regioselectivity in the Arylation of Phenyl Pyridinecarboxylic Acids with 2a

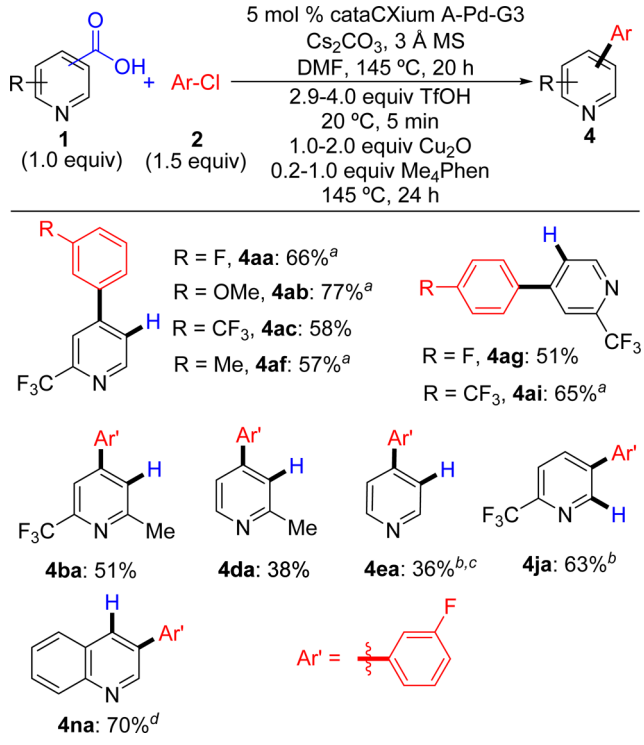


Reaction conditions: 5 mol % $Pd(OAc)_2$, 10 mol % $PAd_2(n\text{-Bu})$, 1 equiv of **1o** or **1p**, 1.5 equiv of **2a**, 2.2 equiv of Cs_2CO_3, 3 Å MS, DMF (0.2 M), 145 °C, 20 h. Yields were determined by ^1H NMR analysis of the crude mixture using CH_2Br_2 as an internal standard.

the desired arylated product (**3na**) in an excellent 83% yield. Pyridinecarboxylic acids bearing α-heteroatoms were also tolerated in this reaction (**3fa–ha**), although a small amount of the α-arylation product was also observed in this case. Pleasingly this protocol could be extended to a pyridazine, albeit in reduced yield (**3ia**).

We next examined the scope of the arylation with respect to the haloarene coupling partner (Scheme 3). Gratifyingly, a variety of substituents could be tolerated in both the meta (**3ab–ag**) and para (**3ag–an**) positions, although we found that ortho substituents were not tolerated. Electron-poor or neutral haloarenes generally gave higher yields than electron-rich haloarenes (**3am**). Even more challenging coupling partners such as 3-chloropyridine (**2o**) showed reactivity under these conditions, albeit in reduced yield (**3ao**). When 1-bromo-4-chlorobenzene (**2k**) was used as the coupling partner the reaction showed complete chemoselectivity for arylation of the C–Br bond leaving the C–Cl bond intact for further functionalization (**3ak**).

Scheme 5. Carboxylic Acids as Traceless Directing Groups for C–H Arylation of Pyridines via a One-Pot Arylation/Protodecarboxylation Process



Reactions carried out on a 0.5 mmol scale. Yields are of pure isolated material. [a]1,10-Phen used instead of Me_4Phen. [b]Reactions performed with 5 mol % $Pd(OAc)_2$ and 10 mol % $[PAd_2(n\text{-Bu})H]I$. [c]40 h arylation time. [d]48 h decarboxylation time.

The reaction is amenable to scaleup: **1n** reacted with **2a** in a 5 mmol scale without any modifications to the general protocol leading to 0.93 g of **3na** in 70% isolated yield.

Since pyridines are extremely efficient *N*-directing groups for *ortho*-arylation of adjacent arenes,[10] we were interested to examine the regioselectivity of C–H arylation when both competing pathways are available (Scheme 4). Accordingly, 6-phenylnicotinic acid **1o** and 2-phenylisonicotinic acid **1p** were tested, as *N*-directed C–H arylation would occur on the phenyl ring (**3′oa** and **3′pa**), whereas the desired CO_2H-directed arylation would occur on the pyridine ring (**3oa** and **3pa**). Remarkably, the system displayed high selectivity for arylation controlled by the often considered weaker CO_2H directing group with only a small amount of *N*-directed arylation obtained in both cases.

Having successfully achieved the direct arylation of pyridinecarboxylic acids we next turned our attention toward developing a one-pot arylation/decarboxylation process providing direct access to arylated pyridines. After careful optimization

DOI: 10.1021/acs.orglett.6b03085
Org. Lett. XXXX, XXX, XXX–XXX

of the reaction conditions, we were pleased to find that arylated pyridines **4** could be obtained in good yields via a C−H arylation/copper(I) mediated decarboxylation sequence (Scheme 5). The decarboxylation proceeded equally well at C3 (**4aa**−**4ea**), C2 (**4ja**), and C4 (**4na**). To the best of our knowledge, this represents the first strategy for the one-pot formation of directing-group-free, C4-arylated pyridines as single regioisomers.

In conclusion, we have demonstrated that the directing power of carboxylic acids could be successfully harnessed to regioselectively C−H arylate pyridines at the C3 and C4 positions. Starting from simple pyridinecarboxylic acids and inexpensive chloro- and bromoarenes, a variety of pyridine biaryls could be accessed with high regioselectivity and good yields. Furthermore, the carboxylic acids can be used as traceless directing groups via an efficient one-pot C−H arylation/copper(I)-mediated decarboxylation sequence allowing the formation of directing group free pyridine biaryls.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b03085.

Experimental procedures as well as characterization of all previously unknown compounds (PDF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We gratefully acknowledge the Engineering and Physical Sciences Research Council and Syngenta for a CASE studentship (to A.J.), and the EPSRC National Mass Spectrometry Service (Swansea).

■ REFERENCES

(1) (a) Alberico, D.; Scott, M. E.; Lautens, M. *Chem. Rev.* **2007**, *107*, 174. (b) Giri, R.; Shi, B. F.; Engle, K. M.; Maugel, N.; Yu, J. Q. *Chem. Soc. Rev.* **2009**, *38*, 3242. (c) Lyons, T. W.; Sanford, M. S. *Chem. Rev.* **2010**, *110*, 1147. (d) Ackermann, L. *Chem. Rev.* **2011**, *111*, 1315. (e) Sun, C.-L.; Li, B.-J.; Shi, Z.-J. *Chem. Rev.* **2011**, *111*, 1293. (f) Yamaguchi, J.; Yamaguchi, A. D.; Itami, K. *Angew. Chem., Int. Ed.* **2012**, *51*, 8960. (g) Wencel-Delord, J.; Glorius, F. *Nat. Chem.* **2013**, *5*, 369.

(2) (a) Roger, J.; Gottumukkala, A. L.; Doucet, H. *ChemCatChem* **2010**, *2*, 20. (b) Nakao, Y. *Synthesis* **2011**, *2011*, 3209. (c) Zhao, D.; You, J.; Hu, C. *Chem. - Eur. J.* **2011**, *17*, 5466. (d) Stephens, D. E.; Larionov, O. V. *Tetrahedron* **2015**, *71*, 8683.

(3) (a) Seiple, I. B.; Su, S.; Rodriguez, R. a.; Gianatassio, R.; Fujiwara, Y.; Sobel, A. L.; Baran, P. S. *J. Am. Chem. Soc.* **2010**, *132*, 13194. (b) Wen, J.; Qin, S.; Ma, L.-F.; Dong, L.; Zhang, J.; Liu, S.-S.; Duan, Y.-S.; Chen, S.-Y.; Hu, C.-W.; Yu, X.-Q. *Org. Lett.* **2010**, *12*, 2694. (c) Wang, J.; Wang, S.; Wang, G.; Zhang, J.; Yu, X.-Q. *Chem. Commun.* **2012**, *48*, 11769. (d) Liu, B.; Huang, Y.; Lan, J.; Song, F.; You, J. *Chem. Sci.* **2013**, *4*, 2163. (e) Patel, N. R.; Flowers, R. A. *J. Am. Chem. Soc.* **2013**, *135*, 4672. (f) Singh, P. P.; Aithagani, S. K.; Yadav, M.; Singh, V. P.; Vishwakarma, R. A. *J. Org. Chem.* **2013**, *78*, 2639. (g) Ren, X.; Wen, P.; Shi, X.; Wang, Y.; Li, J.; Yang, S.; Yan, H.; Huang, G. *Org. Lett.* **2013**, *15*, 5194. (h) Deb, A.; Manna, S.; Maji, A.; Dutta, U.; Maiti, D. *Eur. J. Org. Chem.* **2013**, *2013*, 5251. (i) Xue, D.; Jia, Z.-H.; Zhao, C.-J.; Zhang, Y.-Y.; Wang, C.; Xiao, J. *Chem. - Eur. J.* **2014**, *20*, 2960. (j) Ma, Z.; Liu, H.; Zhang, C.; Zheng, X.; Yuan, M.; Fu, H.; Li, R.; Chen, H. *Adv. Synth. Catal.* **2015**, *357*, 1143. (k) Kan, J.; Huang, S.; Lin, J.; Zhang, M.; Su, W. *Angew. Chem., Int. Ed.* **2015**, *54*, 2199.

(4) (a) Gürbüz, N.; Özdemir, I.; Çetinkaya, B. *Tetrahedron Lett.* **2005**, *46*, 2273. (b) Lafrance, M.; Rowley, C. N.; Woo, T. K.; Fagnou, K. *J. Am. Chem. Soc.* **2006**, *128*, 8754. (c) Lafrance, M.; Shore, D.; Fagnou, K. *Org. Lett.* **2006**, *8*, 5097. (d) Do, H.-Q.; Daugulis, O. *J. Am. Chem. Soc.* **2008**, *130*, 1128. (e) Wasa, M.; Worrell, B. T.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2010**, *49*, 1275. (f) Ye, M.; Gao, G.-L.; Edmunds, A. J. F.; Worthington, P. A.; Morris, J. A.; Yu, J.-Q. *J. Am. Chem. Soc.* **2011**, *133*, 19090. (g) Guo, P.; Joo, J. M.; Rakshit, S.; Sames, D. *J. Am. Chem. Soc.* **2011**, *133*, 16338. (h) Dai, F.; Gui, Q.; Liu, J.; Yang, Z.; Chen, X.; Guo, R.; Tan, Z. *Chem. Commun.* **2013**, *49*, 4634. (i) Aihara, Y.; Chatani, N. *Chem. Sci.* **2013**, *4*, 664. (j) Sirois, J. J.; Davis, R.; DeBoef, B. *Org. Lett.* **2014**, *16*, 868. (k) Shang, Y.; Jie, X.; Zhao, H.; Hu, P.; Su, W. *Org. Lett.* **2014**, *16*, 416. (l) Iaroshenko, V. O.; Gevorgyan, A.; Mkrtchyan, S.; Grigoryan, T.; Movsisyan, E.; Villinger, A.; Langer, P. *ChemCatChem* **2015**, *7*, 316. (m) Cambeiro, X. C.; Ahlsten, N.; Larrosa, I. *J. Am. Chem. Soc.* **2015**, *137*, 15636. (n) He, Y.; Wu, Z.; Ma, C.; Zhou, X.; Liu, X.; Wang, X.; Huang, G. *Adv. Synth. Catal.* **2016**, *358*, 375. (o) Senaweera, S.; Weaver, J. D. *J. Am. Chem. Soc.* **2016**, *138*, 2520. (p) Yamada, S.; Murakami, K.; Itami, K. *Org. Lett.* **2016**, *18*, 2415. (q) Jiao, J.; Murakami, K.; Itami, K. *Chem. Lett.* **2016**, *45*, 529.

(5) (a) Graber, S.; Doyle, K.; Neuburger, M.; Housecroft, C. E.; Constable, E. C.; Costa, R. D.; Ortí, E.; Repetto, D.; Bolink, H. J. *J. Am. Chem. Soc.* **2008**, *130*, 14944. (b) Wong, W.-Y.; Ho, C.-L. *Coord. Chem. Rev.* **2009**, *253*, 1709. (c) Robson, K. C.; Koivisto, B. D.; Berlinguette, C. P. *Inorg. Chem.* **2012**, *51*, 1501.

(6) (a) Vetrichelvan, M.; Valiyaveettil, S. *Chem. - Eur. J.* **2005**, *11*, 5889. (b) Oyston, S.; Wang, C.; Perepichka, I. F.; Batsanov, A. S.; Bryce, M. R.; Ahn, J. H.; Petty, M. C. *J. Mater. Chem.* **2005**, *15*, 5164.

(7) (a) Michael, J. P. *Nat. Prod. Rep.* **2005**, *22*, 627. (b) Kassis, P.; Brzeszcz, J.; Bénéteau, V.; Lozach, O.; Meijer, L.; Le Guével, R.; Guillouzo, C.; Lewiński, K.; Bourg, S.; Colliandre, L.; Routier, S.; Mérour, J.-Y. *Eur. J. Med. Chem.* **2011**, *46*, 5416. (c) O'Neill, P. M.; Ward, S. A. *Angew. Chem., Int. Ed.* **2015**, *54*, 13504. (d) Xie, Y.; Chi, H.-W.; Guan, A.-Y.; Liu, C.-L.; Ma, H.-J.; Cui, D.-L. *J. Agric. Food Chem.* **2014**, *62*, 12491. (e) Xie, Y.; Chi, H.-W.; Guan, A.-Y.; Liu, C.-L.; Ma, H.-J.; Cui, D.-L. *Bioorg. Med. Chem.* **2016**, *24*, 428. (f) Epp, J. B.; et al. *Bioorg. Med. Chem.* **2016**, *24*, 362.

(8) (a) Chiong, H. A.; Pham, Q.-N.; Daugulis, O. *J. Am. Chem. Soc.* **2007**, *129*, 9879. (b) Miura, M.; Satoh, T. *Synthesis* **2010**, *2010*, 3395. (c) Engle, K. M.; Mei, T.-S.; Wasa, M.; Yu, J.-Q. *Acc. Chem. Res.* **2012**, *45*, 788. (d) Wu, Z.; Chen, S.; Hu, C.; Li, Z.; Xiang, H.; Zhou, X. *ChemCatChem* **2013**, *5*, 2839. (e) Liu, Y.-J.; Xu, H.; Kong, W.-J.; Shang, M.; Dai, H.-X.; Yu, J.-Q. *Nature* **2014**, *515*, 389. (f) Zhu, C.; Zhang, Y.; Kan, J.; Zhao, H.; Su, W. *Org. Lett.* **2015**, *17*, 3418. (g) Xu, Z.; Yang, T.; Lin, X.; Elliott, J. D.; Ren, F. *Tetrahedron Lett.* **2015**, *56*, 475.

(9) (a) Gooßen, L. J.; Rodríguez, N.; Linder, C.; Lange, P. P.; Fromm, A. *ChemCatChem* **2010**, *2*, 430. (b) Grainger, R.; Nikmal, A.; Cornella, J.; Larrosa, I. *Org. Biomol. Chem.* **2012**, *10*, 3172. (d) Dzik, W. I.; Lange, P. P.; Gooßen, L. J. *Chem. Sci.* **2012**, *3*, 2671. (e) Grainger, R.; Cornella, J.; Blakemore, D. C.; Larrosa, I.; Campanera, J. M. *Chem. - Eur. J.* **2014**, *20*, 16680.

(10) (a) Ackermann, L.; Vicente, R.; Althammer, A. *Org. Lett.* **2008**, *10*, 2299. (b) Kitahara, M.; Umeda, N.; Hirano, K.; Satoh, T.; Miura, M. *J. Am. Chem. Soc.* **2011**, *133*, 2160. (c) Li, W.; Yin, Z.; Jiang, X.; Sun, P. *J. Org. Chem.* **2011**, *76*, 8543. (d) Zhang, X.; Wang, F.; Qi, Z.; Yu, S.; Li, X. *Org. Lett.* **2014**, *16*, 1586.

(11) (a) Cornella, J.; Righi, M.; Larrosa, I. *Angew. Chem., Int. Ed.* **2011**, *50*, 9429. (b) Luo, J.; Preciado, S.; Larrosa, I. *J. Am. Chem. Soc.* **2014**, *136*, 4109. (c) Luo, J.; Preciado, S.; Larrosa, I. *Chem. Commun.* **2015**, *51*, 3127.

(12) Bruno, N. C.; Tudge, M. T.; Buchwald, S. L. *Chem. Sci.* **2013**, *4*, 916.

DOI: 10.1021/acs.orglett.6b03085
Org. Lett. XXXX, XXX, XXX−XXX