Organic LETTERS

Letter

pubs.acs.org/OrgLett

Nickel-Catalyzed Direct C (sp^3)–H Arylation of Aliphatic Amides with Thiophenes

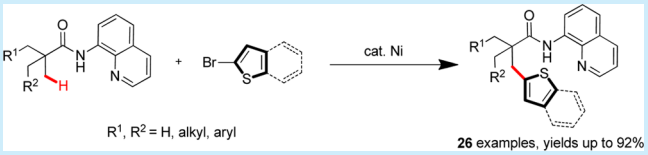
Xie Wang,[†] Longzhi Zhu,[†] Sihai Chen,[†] Xinhua Xu,*[,†] Chak-Tong Au,[†,‡] and Renhua Qiu*[,†]

[†]State Key Laboratory of Chemo/Biosensing and Chemometrics, College of Chemistry and Chemical Engineering, Hunan University, Changsha, 410082, P.R. China

[‡]Department of Chemistry, Hong Kong Baptist University, Hong Kong, P.R. China

Supporting Information

ABSTRACT: Nickel-catalyzed heteroarylation of the inactive methyl C(sp^3)–H bond of aliphatic amide with heteroarenes is described. The method takes advantage of chelation assistance by an 8-aminoquinolinyl moiety. The synthetic reaction has good tolerance toward functional groups, and it can be used in the construction of various kinds of alkyl-substituted heteroarenes.

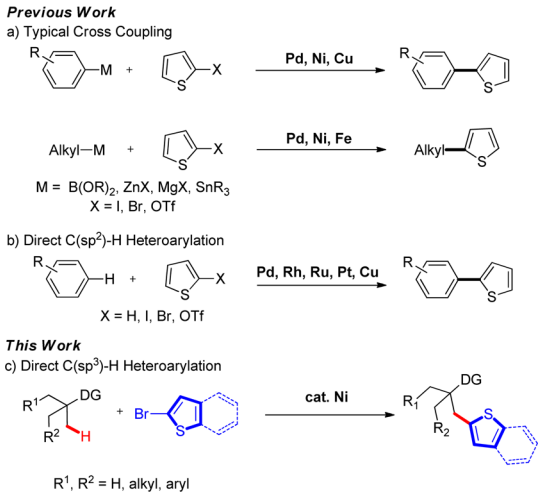


The thiophene structure has received much attention in organic synthesis because of its rigidity and distinct electronic nature that allow fine-tuning of its molecular properties.[1] Compared to other phenyl-type substituents, the thiophene structures often show higher bioactivity.[2] They are widely found in pharmaceuticals,[3] agrochemicals,[4] and organic catalysts.[5] Moreover, oligothiophenes make up a particularly important class of organic materials. They are components that are used in organic electronic devices for applications such as solar cells, field-effect transistors, and fluorescent biosensors.[6]

Starting from readily available (hetero)aromatic scaffolds, the coupling of two prefunctionalized substrates over a transition-metal catalyst is a typical method for the synthesis of substituted thiophenes (Scheme 1a).[7] However, the method has shortcomings because the prefunctionalization of substrate with organometallic reagents is tedious and the generation of metal halide as waste is undesirable.[8] As an alternative, the direct cross-coupling strategy is more promising (Scheme 1b). The method makes use of a prefunctionalized arene that bears a leaving group with a C–H bond, and the most used metal catalyst is palladium.[9] The method, however, is unselective and requires a directing group or large excess of arene to activate the relatively inert bonds.[10] Nonetheless, such limitations make the research challenging when the compatibility of the functional group is an issue of concern in the synthetic approach. Recently, there were the reports on the study of decarboxylative (hetero)-arylation catalyzed by transition metal.[11]

For the development of new material devices such as OLEDs (organic light-emitting diodes), alkyl-substituted heteroarenes bearing one or multiple alkyl components were aggressively pursued in the past decade,[6] and tremendous progress has been made to prepare these organic semiconductors (see the Supporting Information) that have flexible side chains, such as cross-coupling reactions,[6e,f] polymerization,[6g] and metalization[6h] with functionalized alkyl-substituted heteroarenes (Figure 1). Also, among pharmaceutical companies, there have been projects to collect heteroaromatic molecules that are decorated with branched alkyl chains into a medicinal compound database.[12] Consequently, extensive efforts were devoted to rapid and direct construction of C(sp^2)–C(sp^3) bonds.[13] In practice, intermolecular heteroarylation of alkanes catalyzed by a transition metal

Scheme 1. Types of Transition-Metal-Catalyzed Heteroarylation Using Thiophenes as Aryl Source



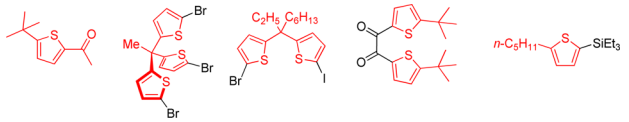


Figure 1. Functionalized alkyl-substituted heteroarenes.

Received: September 6, 2015

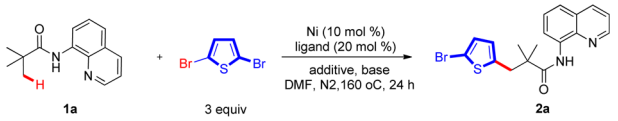
DOI: 10.1021/acs.orglett.5b02572
Org. Lett. XXXX, XXX, XXX–XXX

is a frequently used method. In the approach, the activated C(sp^3)−H bonds couple with aryl moieties to form alkyl-substituted heteroarenes scaffolds.[14] The method, however, is limited to relatively active aryl substrates such as iodoarenes,[15] hyperiodonium salts,[16] arylboron reagents,[17] and organozinc reagents.[12b,13,18]

As coupling partners in cross-coupling reactions, aryl bromides are more useful than aryl iodides or organometallic reagents because they are less expensive, nontoxic, and easy to handle. Despite reports on the arylation of the C(sp^3)−H bond with aromatic halide, such as the palladium-catalyzed intermolecular arylation with aryl bromides reported by Zeng,[19a] the use of aryl bromides to convert inactive C(sp^3)−H bonds to C(sp^3)−heteroaryl bonds via intermolecular coupling still remains to be explored.[19] Recently, the methods using removable directing groups for the formation of C(sp^2)−C(sp^3) bonds have made a significant impact on the field of organic chemistry.[15,20] Significant progress was first achieved via the chelation-assistance approach developed by Daugulis.[15c] A nickel-catalyzed system was also reported by Chatani[15a] in which phenyl bromide was used but there was no arylation product. Herein, we report the site-selective coupling of heteroaryl bromides with C(sp^3)−H bonds to achieve intermolecular heteroarylation. The reaction is conducted over a nickel-based catalyst and is assisted by a removable bidentate directing group. In general, the use of less reactive aryl bromides could enhance the practicality and hence broaden the applicability of the method.

We began our investigation by using aliphatic amides **1a** and 2,5-dibromothiophene as substrates for the optimization of reaction conditions (Table 1). After initial screening of catalysts, the heteroarylated product **2a** was obtained in 74% yield by using catalytic amounts of $NiBr_2$ and MesCOOH using excess Na_2CO_3 in DMF under an atmosphere of N_2 (entry 2). It was noticed that

Table 1. Optimization of Reaction Conditions[a]



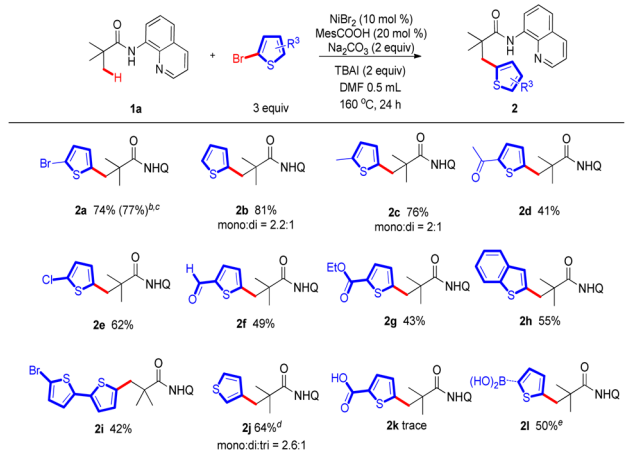
entry	catalyst	ligand	additive	yield[b] (%)
1	$NiBr_2$	MesCOOH		24
2	**$NiBr_2$**	**MesCOOH**	**TBAI**	**74**
3	$Ni(COD)_2$	MesCOOH	TBAI	64
4	$Ni(OTf)_2$	MesCOOH	TBAI	66
5	$NiCl_2$	MesCOOH	TBAI	62
6	NiF_2	MesCOOH	TBAI	67
7	$Ni(acac)_2$	MesCOOH	TBAI	69
8	$Ni(OAc)_2$	MesCOOH	TBAI	52
9	$NiBr_2$	PPh_3	TBAI	54
10	$NiBr_2$	PCy_3	TBAI	51
11	$NiBr_2$	*p*-HOC_6H_4COOH	TBAI	65
12	$NiBr_2$	PhCOOH	TBAI	58
13	$NiBr_2$	MesCOOH	TBAB	49
14	$NiBr_2$	MesCOOH	AgO	51
15	$NiBr_2$	MesCOOH	CuI	30
16	$NiBr_2$	MesCOOH	CuBr	37
17	$NiBr_2$	MesCOOH	$AgNO_3$	56

[a]Reaction conditions: amide (0.2 mmol), thiophene (0.6 mmol), catalyst (0.02 mmol), ligand (0.04 mmol), base (0.4 mmol), additive (0.4 mmol) in solvent (0.5 mL) at 160 °C for 24 h in 10 mL screw-capped vials. [b]Isolated yield.

without an additive such as TBAI there was poor yield of **2a** (entry 1). Further investigation showed that the reaction was improved by using benzoic acid as ligand (entries 9−12). The screening of additives showed that a change from TBAI to the others led to lower yields (entries 13−17). In the study, the use of base and solvent was also optimized (see the Supporting Information).

With the optimized conditions in hand, we studied the scope of thiophenes. As expected, thiophene bromides show great compatibility under the reaction conditions, and the reaction tolerates a variety of functional groups with both steric and electronic variations, such as the halides, methyl, acyl, aldehyde, ester, bithiophene, and benzothiophene. As shown in Scheme 2,

Scheme 2. Screening the Scope of Thiophenes[a]



[a]Reaction conditions: amide (0.2 mmol), thiophene (0.6 mmol), $NiBr_2$ (0.02 mmol), MesCOOH (0.04 mmol), Na_2CO_3 (0.4 mmol), TBAI (0.4 mmol) in DMF (0.5 mL) at 160 °C for 24 h in 10 mL screw-capped vials. [b]Isolated yields of major products. [c]The number in parentheses is the isolated yield when 6 equiv of 2,5-dibromothiophene was used. [d]Three equivalents of 3-bromothiophene was used. [e]The isolated product was **2b** when (5-bromothiophene-2-yl)boronic acid was used.

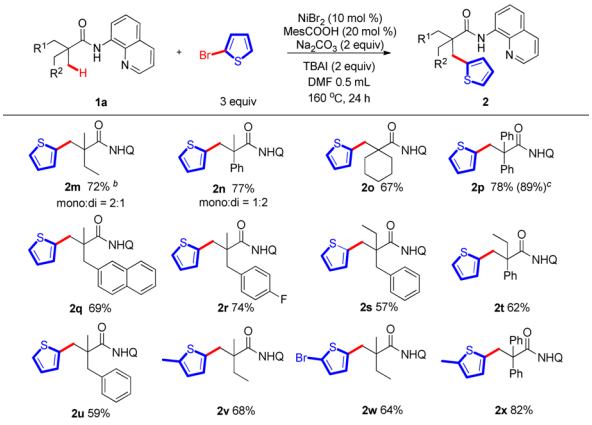
electron-deficient substrates are well tolerated, and the reaction shows a predominant preference for the generation of monoheteroarylated products (**2a**,**d**−**i**) with good yields (41−74%). The electron-rich thiophene substrate shows higher reactivity, giving higher yields of mono- and diheteroarylated products (**2b**,**c**). It is noted that steric hindrance only has a slight influence on the transformation (**2h**−**j**). In addition, an effort using (5-bromothiophene-2-yl)boronic acid as substrate only results in the heteroarylated product **2b**.

We then examined the scope of aliphatic amides under the optimized conditions. As shown in Scheme 3, the use of substituted propanamides bearing linear and cyclic chains results in a good yield of heteroarylated products (**2m**,**o**). Surprisingly, with a 2,2-diphenyl-substituted substrate, product **2p** is obtained in excellent yield (89%). Notably, there is difference in the mono-to-di (m:d) ratio between aliphatic amide **2m** (m:d = 2:1) and phenyl-substituted amide **2n** (m:d = 1:2). The observation suggests that the phenyl could benefit from activation of the inert C(sp^3)−H bond. The reactions show great regioselectivity that the methyl groups are preferred over the methylene and benzene groups, a phenomenon like that reported in our previous work.[21]

To further elucidate the viability of this C(sp^3)−H heteroarylation method, we studied the *N*-heteroaryl substrates

DOI: 10.1021/acs.orglett.5b02572
Org. Lett. XXXX, XXX, XXX−XXX

Scheme 3. Screening the Scope of Aliphatic Amides[a]



[a]Reaction conditions: amide (0.2 mmol), thiophene (0.6 mmol), $NiBr_2$ (0.02 mmol), MesCOOH (0.04 mmol), Na_2CO_3 (0.4 mmol), TBAI (0.4 mmol) in DMF (0.5 mL) at 160 °C for 24 h in 10 mL screw-capped vials. [b]Isolated yields of major products. [c]The number in parentheses is the isolated yield with time extended to 48 h.

that are closely related to thiophenes (Figure 2). Preliminary results indicated that the direct application of the method under

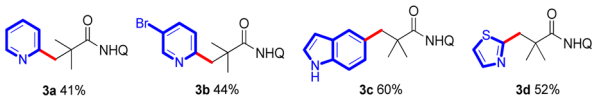
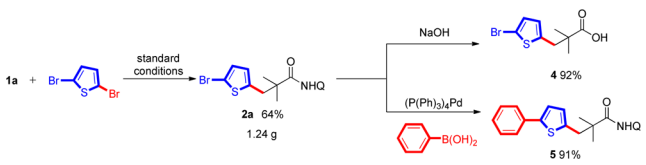


Figure 2. *N*-Heteroarylated products.

the optimized condition is successful, and the desired *N*-heteroarylated products are obtained in moderate yields (**3a**–**d**).

To further test the practicality of this method, the reaction was conducted on gram scale, and the desired product **2a** was obtained in 64% yield (Scheme 4). According to our previous

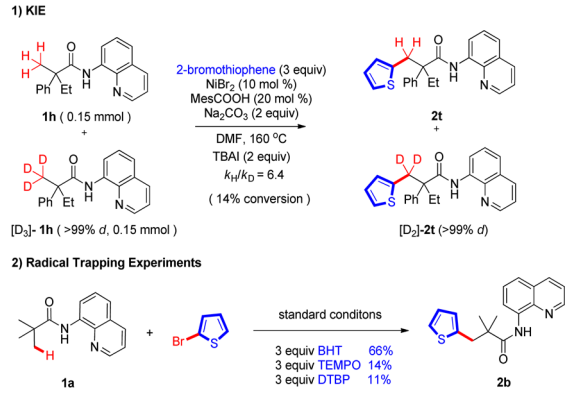
Scheme 4. Gram-Scale Synthesis and Removal of the Directing Group



work, the corresponding carboxylic acid **4** is easy to obtain[21] and can be readily transferred to the corresponding isocyanates as suggested by Fevig.[22a] Furthermore, the heteroarylated products can be used as substrates for the Suzuki or other cross-coupling reactions (Scheme 4). For example, the bromide thiophene products **2a** can undergo the Suzuki protocol to give the arylated product **6** with excellent yield (91%).[22b]

Several competition and radical-trapping experiments were carried out in an attempt to determine the reaction mechanism (Scheme 5). The intermolecular kinetic isotope effect for sp^3 C–H heteroarylation is 6.4, and the result indicates that the cleavage of C–H bond is a rate-determining step. The addition of 3 equiv of 2,6-di-*tert*-butyl-4-methylphenol (BHT) as radical scavenger does not inhibit the reaction. The addition of 3 equiv of 2,2,6,6-tetramethyl-1-piperidinoxyl (TEMPO); however, substantially reduces the yield but does not completely suppress the reaction, and there is no detection of 2,2,6,6-tetramethyl-1-(thiophene-2-

Scheme 5. Deuterium Labeling and Radical-Trapping Experiments



yloxy)piperidine by GC–MS. To verify whether the reaction activity was lowered by the oxidation property of TEMPO, and the cyclometalation process was hindered as such, we added di-*tert*-butyl peroxide (DTBP) under the standard conditions and observed that the reaction gives the product in a lower yield. According to the results, we deduce that the reaction does not proceed via a radical mechanism but via one that is similar to that proposed by Chatani and Ge.[15a,b,23]

In summary, we report the development of a low-cost nickel catalyst system that takes advantage of chelation assistance by an 8-aminoquinolinyl moiety. This method for the heteroarylation of the sp^3 C–H bond with aliphatic amides has good tolerance toward different functional groups and represents a facile alternative for the construction of alkyl-substituted heteroarenes.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b02572.

Experimental procedure, characterization data, and ^1H, ^{13}C and ^{19}F NMR spectra (PDF)

■ AUTHOR INFORMATION

Corresponding Authors

* E-mail: xhx1581@hnu.edu.cn.
* E-mail: renhuaqiu@hnu.edu.cn.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank the NSFC (Nos. 21373003, 21273068, J1210040) and the Fundamental Research Funds for the Central Universities for financial support. R.Q. thanks Prof. Nobuaki Kambe (Osaka University, Japan), Prof. Akihiro Orita (Okayama University of Science, Japan), and Prof. Li-Biao Han (AIST, Tsukuba, Japan) for helpful discussions. C.-T.A. thanks HNU for an adjunct professorship.

■ REFERENCES

(1) (a) *The Chemistry of Heterocyclic Compounds: Thiophene and Its Derivatives*; Weissberger, A., Taylor, E. C., Eds.; Wiley: New York, 1991; Vol. *44*, Parts 1–4. (b) Gronowitz, S.; Hornfeldt, A. B. *Thiophenes*; Elsevier: Oxford, 2004.

DOI: 10.1021/acs.orglett.5b02572
Org. Lett. XXXX, XXX, XXX–XXX

(2) Lamberth, C.; Jeanguenat, A.; Cederbaum, F.; De Mesmaeker, A.; Zeller, M.; Kempf, H. J.; Zeun, R. *Bioorg. Med. Chem.* **2008**, *16*, 1531.
(3) (a) Wang, W. L.; Chai, S. C.; Huang, M.; He, H. Z.; Hurley, T. D.; Ye, Q. Z. *J. Med. Chem.* **2008**, *51*, 6110. (b) Oberdorf, C.; Schepmann, D.; Vela, J. M.; Diaz, J. L.; Holenz, J.; Wunsch, B. *J. Med. Chem.* **2008**, *51*, 6531. (c) Junker, A.; Yamaguchi, J.; Itami, K.; Wunsch, B. *J. Org. Chem.* **2013**, *78*, 5579.
(4) Fokialakis, N.; Cantrell, C. L.; Duke, S. O.; Skaltsounis, A. L.; Wedge, D. E. *J. Agric. Food Chem.* **2006**, *54*, 1651.
(5) (a) Gao, J.; Martell, A. E. *Org. Biomol. Chem.* **2003**, *1*, 2801. (b) Bandini, M.; Benaglia, M.; Quinto, T.; Tommasi, S.; Umani-Ronchi, A. *Adv. Synth. Catal.* **2006**, *348*, 1521.
(6) (a) Henson, Z. B.; Mullen, K.; Bazan, G. C. *Nat. Chem.* **2012**, *4*, 699. (b) Saito, S.; Matsuo, K.; Yamaguchi, S. *J. Am. Chem. Soc.* **2012**, *134*, 9130. (c) Zhang, L.; Colella, N. S.; Cherniawski, B. P.; Mannsfeld, S. C. B.; Briseno, A. L. *ACS Appl. Mater. Interfaces* **2014**, *6*, 5327. (d) Dore, K.; Dubus, S.; Ho, H.-A.; Levesque, I.; Brunette, M.; Corbeil, G.; Boissinot, M.; Boivin, G.; Bergeron, M. G.; Boudreau, D.; Leclerc, M. *J. Am. Chem. Soc.* **2004**, *126*, 4240. (e) Wang, X.-Y.; Zhuang, F.-D.; Zhou, X.; Yang, D.-C.; Wang, J.-Y.; Pei, J. *J. Mater. Chem. C* **2014**, *2*, 8152. (f) Fan, L.; Cui, R.; Jiang, L.; Zou, Y.; Li, Y.; Qian, D. *Dyes Pigm.* **2015**, *113*, 458. (g) Wu, S.; Sun, Y.; Huang, L.; Wang, J.; Zhou, Y.; Geng, Y.; Wang, F. *Macromolecules* **2010**, *43*, 4438. (h) Toutov, A. A.; Liu, W.-B.; Betz, K. N.; Fedorov, A.; Stoltz, B. M.; Grubbs, R. H. *Nature* **2015**, *518*, 80. (i) Adachi, K.; Hirao, Y.; Matsumoto, K.; Kubo, T.; Kurata, H. *Org. Lett.* **2014**, *16*, 5870. (j) Chen, W.; Salim, T.; Fan, H.; James, L.; Lam, Y. M.; Zhang, Q. *RSC Adv.* **2014**, *4*, 25291.
(7) (a) Handy, S. T.; Mayi, D. *Tetrahedron Lett.* **2007**, *48*, 8108. (b) Beaumard, F.; Dauban, P.; Dodd, R. H. *Org. Lett.* **2009**, *11*, 1801. (c) Linshoeft, J.; Heinrich, A. C. J.; Segler, S. A. W.; Gates, P. J.; Staubitz, A. *Org. Lett.* **2012**, *14*, 5644. (d) Kadunce, N. T.; Reisman, S. E. *J. Am. Chem. Soc.* **2015**, *137*, 10480. (e) Molander, G. A.; Traister, K. M.; O'Neill, B. T. *J. Org. Chem.* **2015**, *80*, 2907.
(8) de Meijere, A.; Diederich, F. *Metal-Catalyzed Cross-Coupling Reactions*, 2nd ed.; Wiley-VCH: Weinheim, 2004.
(9) (a) Chen, X.; Engle, K. M.; Wang, D.-H.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2009**, *48*, 5094. (b) Qin, D.; Wang, J.; Qin, X.; Wang, C.; Gao, G.; You, J. *Chem. Commun.* **2015**, *51*, 6190. (c) Zhao, S.; Yuan, J.; Li, Y.-C.; Shi, B.-F. *Chem. Commun.* **2015**, *51*, 12823. (d) Matsumura, K.; Yoshizaki, S.; Maitani, M. M.; Wada, Y.; Ogomi, Y.; Hayase, S.; Kaiho, T.; Fuse, S.; Tanaka, H.; Takahashi, T. *Chem. - Eur. J.* **2015**, *21*, 9742. (e) Ashenhurst, J. A. *Chem. Soc. Rev.* **2010**, *39*, 540. (f) Malakar, C. C.; Schmidt, D.; Conrad, J.; Beifuss, U. *Org. Lett.* **2011**, *13*, 1378. (g) Xu, S.; Kim, E. H.; Wei, A.; Negishi, E. i. *Sci. Technol. Adv. Mater.* **2014**, *15*, 044201.
(10) (a) Lyons, T. W.; Sanford, M. S. *Chem. Rev.* **2010**, *110*, 1147. (b) Stuart, D. R.; Fagnou, K. *Science* **2007**, *316*, 1172. (c) Mercier, L. G.; Leclerc, M. *Acc. Chem. Res.* **2013**, *46*, 1597.
(11) (a) Zhao, S.; Liu, Y.-J.; Yan, S.-Y.; Chen, F.-J.; Zhang, Z.-Z.; Shi, B.-F. *Org. Lett.* **2015**, *17*, 3338. (b) Wang, C.; Piel, I.; Glorius, F. *J. Am. Chem. Soc.* **2009**, *131*, 4194. (c) Lu, Q.; Yu, H.; Fu, Y. *J. Am. Chem. Soc.* **2014**, *136*, 8252. (d) Zhang, Y.; Zhao, H.; Zhang, M.; Su, W. *Angew. Chem., Int. Ed.* **2015**, *54*, 3817.
(12) (a) Dandapani, S.; Marcaurelle, L. A. *Curr. Opin. Chem. Biol.* **2010**, *14*, 362. (b) Yang, Y.; Niedermann, K.; Han, C.; Buchwald, S. L. *Org. Lett.* **2014**, *16*, 4638.
(13) (a) Jana, R.; Pathak, T. P.; Sigman, M. S. *Chem. Rev.* **2011**, *111*, 1417. (b) Atwater, B.; Chandrasoma, N.; Mitchell, D.; Rodriguez, M. J.; Pompeo, M.; Froese, R. D. J.; Organ, M. G. *Angew. Chem., Int. Ed.* **2015**, *54*, 9502. (c) Thapa, S.; Kafle, A.; Gurung, S. K.; Montoya, A.; Riedel, P.; Giri, R. *Angew. Chem., Int. Ed.* **2015**, *54*, 8236.
(14) (a) Bellina, F.; Rossi, R. *Chem. Rev.* **2010**, *110*, 1082. (b) Hattori, K.; Ziadi, A.; Itami, K.; Yamaguchi, J. *Chem. Commun.* **2014**, *50*, 4105.
(15) (a) Aihara, Y.; Chatani, N. *J. Am. Chem. Soc.* **2014**, *136*, 898. (b) Wu, X.; Zhao, Y.; Ge, H. *J. Am. Chem. Soc.* **2014**, *136*, 1789. (c) Zaitsev, V. G.; Shabashov, D.; Daugulis, O. *J. Am. Chem. Soc.* **2005**, *127*, 13154. (d) Wasa, M.; Engle, K. M.; Yu, J. Q. *J. Am. Chem. Soc.* **2009**, *131*, 9886.
(16) (a) Gou, Q.; Zhang, Z. F.; Liu, Z. C.; Qin, J. *J. Org. Chem.* **2015**, *80*, 3176. (b) Iyanaga, M.; Aihara, Y.; Chatani, N. *J. Org. Chem.* **2014**, *79*, 11933.
(17) (a) Chan, K. S. L.; Wasa, M.; Chu, L.; Laforteza, B. N.; Miura, M.; Yu, J. Q. *Nat. Chem.* **2014**, *6*, 146. (b) Shang, M.; Sun, S.-Z.; Dai, H.-X.; Yu, J.-Q. *Org. Lett.* **2014**, *16*, 5666.
(18) Liang, Y.; Fu, G. C. *J. Am. Chem. Soc.* **2015**, *137*, 9523.
(19) (a) Wei, Y.; Tang, H.; Cong, X.; Rao, B.; Wu, C.; Zeng, X. *Org. Lett.* **2014**, *16*, 2248. (b) Li, M.; Dong, J.; Huang, X.; Li, K.; Wu, Q.; Song, F.; You, J. *Chem. Commun.* **2014**, *50*, 3944. (c) Zhang, Q.; Yin, X.-S.; Zhao, S.; Fang, S.-L.; Shi, B.-F. *Chem. Commun.* **2014**, *50*, 8353.
(20) (a) He, G.; Chen, G. *Angew. Chem., Int. Ed.* **2011**, *50*, 5192. (b) Zhang, S.-Y.; Li, Q.; He, G.; Nack, W. A.; Chen, G. *J. Am. Chem. Soc.* **2015**, *137*, 531.
(21) Wang, X.; Qiu, R.; Yan, C.; Reddy, V. P.; Zhu, L.; Xu, X.; Yin, S.-F. *Org. Lett.* **2015**, *17*, 1970.
(22) (a) Fevig, T. L.; Bowen, S. M.; Janowick, D. A.; Jones, B. K.; Munson, H. R.; Ohlweiler, D. F.; Thomas, C. E. *J. Med. Chem.* **1996**, *39*, 4988. (b) Lee, W.; Lee, D.-W.; Lee, M.; Hong, J.-I. *Chem. Commun.* **2014**, *50*, 14851.
(23) (a) Higgs, A. T.; Zinn, P. J.; Sanford, M. S. *Organometallics* **2010**, *29*, 5446. (b) Aihara, Y.; Chatani, N. *J. Am. Chem. Soc.* **2013**, *135*, 5308.

DOI: 10.1021/acs.orglett.5b02572
Org. Lett. XXXX, XXX, XXX−XXX