Organic LETTERS

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Access to Different Isomeric Dibenzoxazepinones through Copper-Catalyzed C−H Etherification and C−N Bond Construction with Controllable Smiles Rearrangement

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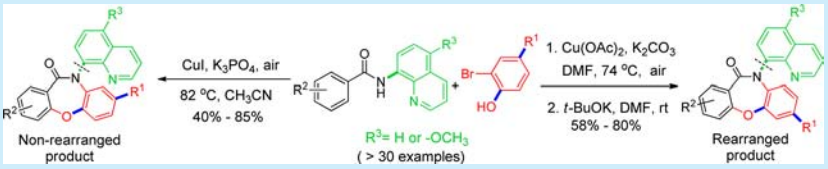
Supporting Information



ABSTRACT: An efficient new way to access two regio-isomeric dibenzoxazepinones is reported from 8-aminoquinoline benzamides and 2-bromophenols. Through choice of conditions, the reaction proceeds either through a sequential C−H etherification and subsequent Goldberg reaction, both controlled by the aminoquinoline group and Cu(I), or via a C−H etherification and subsequent Smiles rearrangement promoted by Cu(II) and *t*-BuOK. The 8-aminoquinoline moiety, e.g., 8-amino-5-methoxyquinoline, is readily removable from the structures of dibenzoxazepinones under moderate conditions.

Over the past two decades, metal-catalyzed carbon−hydrogen bond functionalization has attracted a lot of attention due to its ability to enable the direct introduction of functionality to organic molecules, in an economical and efficient manner.[1] Recently, copper has been shown to play an increasingly important role in this field, owing to its low-cost, abundance, and environmentally benign nature.[2] Combined with aromatic *ortho*-C−H activation via a bidentate directing group strategy,[3] copper has demonstrated a wide range of applications in the construction of C−O,[4] C−S,[5] and C−N[6] bonds.

The dibenzoxazepinone scaffold is a promising bioactive structure,[7] and considerable effort has been expended on its synthesis.[8] One approach to construct the seven-membered ring of the dibenzoxazepinone employs the domino C−O coupling and C−N bond formation via Smiles rearrangement (Scheme 1, eqs 1−3). In addition, Du recently employed hypervalent iodine(III)-mediated oxidative cyclization to access dibenzoxazepinone from 2-(aryloxy)benzamides (Scheme 1, eq 4).[8k] However, all of these strategies require the β-sp^2 C−H bond of the benzoic acid derivatives to be prefunctionalized with hydroxy[8a] or halide[8b,c,k] (Scheme 1, eqs 1−4). Herein, we disclose a copper-initiated aerobic oxidative C−H etherification[4a] assisted by the removable directing group 8-aminoquinoline followed by C−N bond formation to access different isomeric dibenzoxazepinones. The formation of the different isomers, i.e., with or without a Smiles rearrangement (Scheme 1, eqs 5 and 6), can be controlled by choice of reaction conditions. The 8-aminoquinoline moiety was found to be essential to enable the Goldberg reaction (Scheme 1, eq 5), which is a further distinction to the work of Snieckus[8c] (eq 3). Thus, this new methodology allows access to differently substituted dibenzoxazepinones from the same starting materials, simply by modifying the reaction conditions.

We initiated our studies by screening the reaction of benzamides containing different directing groups (Table 1, A, B, C, D, and E) with 2-bromo-4-chlorophenol in the presence of $Cu_2(OH)_2CO_3$ as catalyst, K_2CO_3 as base, and DMF as solvent. To our surprise, the 8-aminoquinoline directing group gave not only the expected Goldberg arylation product **7a** but also the rearranged compound **8a**, in which the oxygen and chlorine atoms have a *meta*-relationship (Table 1, entry 1). The structures of **7a** and **8a** were unambiguously confirmed by X-ray crystallography (Supporting Information). However, alternative directing groups (substrates **B**, **C**, and **D**) gave unsatisfied results. No reaction took place when naphthalene derivative (substrate **E**) was used, indicating that coordination in an *N*,*N*′-fashion is essential to this reaction. Cu(I) catalysts (Table 1, entries 3−5) showed exclusive formation of **7a**, and CuI (entry 5) gave a superior yield over other Cu(I) catalysts (entries 3 and 4). Evaluation of the bases (entries 5−8) revealed that K_3PO_4 (entry 8) was optimal. Different solvents had an appreciable impact on reaction yield. Toluene (entry 9), a nonpolar solvent, gave a poor yield, while acetonitrile (entry 12) gave a much higher yield (82%) than other polar solvents (entry 8, 10, 11). Further attempts to improve the

Received: November 25, 2015
Published: January 15, 2016

DOI: 10.1021/acs.orglett.5b03378
Org. Lett. 2016, 18, 380−383

Scheme 1. Synthetic Strategies for Dibenzoxazepinone

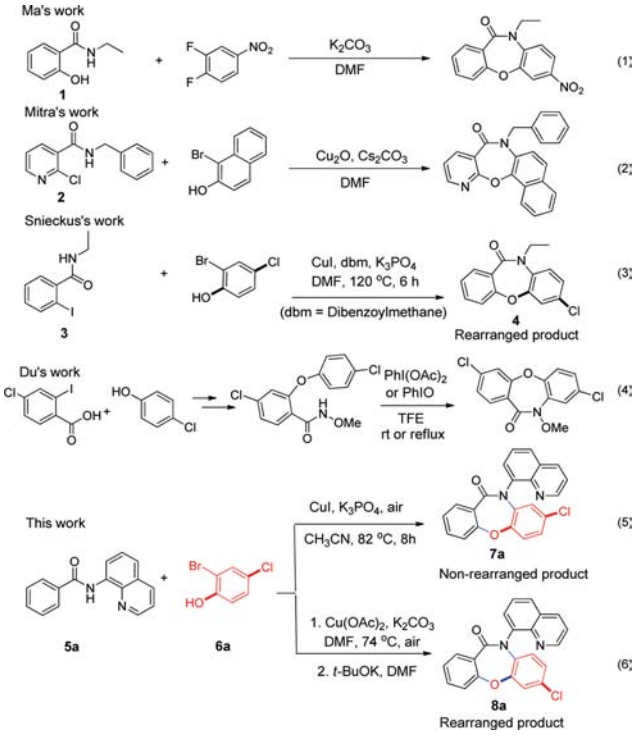
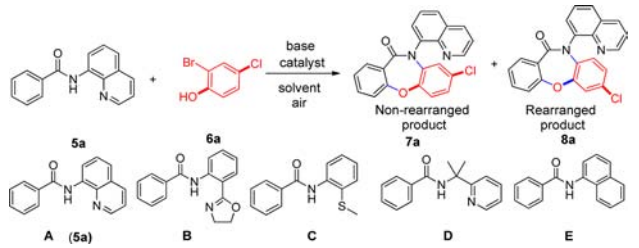


Table 1. Optimization of the Reaction Conditions[a]



				yield (%)[b]	
entry	catalyst	base	solvent	7a	8a
1	$Cu_2(OH)_2CO_3$	K_2CO_3	DMF	10	15
2	$Cu(OAc)_2$	K_2CO_3	DMF	5	25
3	Cu_2O	K_2CO_3	DMF	6	0
4	CuBr	K_2CO_3	DMF	9	0
5	CuI	K_2CO_3	DMF	25	0
6	CuI	Cs_2CO_3	DMF	28	0
7	CuI	Na_2CO_3	DMF	4	0
8	CuI	K_3PO_4	DMF	55	0
9	CuI	K_3PO_4	toluene	10	0
10	CuI	K_3PO_4	1,4-dioxane	40	0
11	CuI	K_3PO_4	DMSO	35	0
12[c]	**CuI**	**K_3PO_4**	**CH_3CN**	**82**	**0**
13[d]	**$Cu(OAc)_2$**	**K_2CO_3**	**DMF**	**0**	73

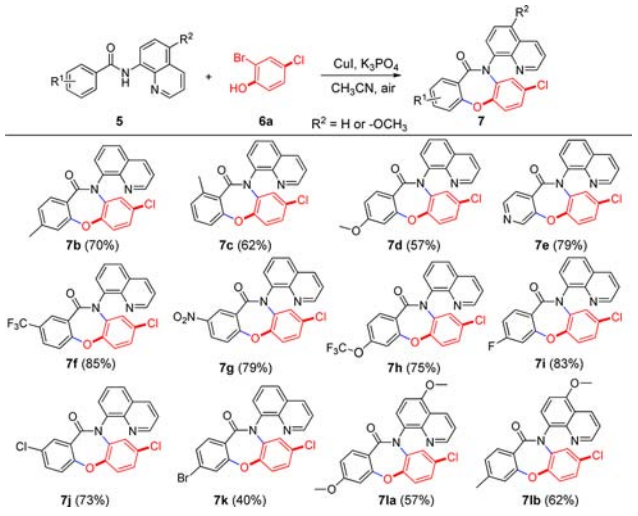
[a]Reaction conditions: **5a** (0.2 mmol), **6a** (0.2 mmol), copper salts (20 mol %), base (0.6 mmol), 100 °C, 7−12 h, open air. [b]Isolated yield. [c]74 °C for 0.5 h then reflux under 1 atm for 4−8 h. [d]74 °C for 5−10 h. After **5a** was consumed, *t*-BuOK was added.

reaction yield by adding ligands to chelate the copper failed (Table S1, Supporting Information). It is noteworthy that DMEDA (*N*,*N*′-dimethyl-1,2-ethanediamine) and picolinic acid, the classic ligands in amidation, failed to yield any products. This may be attributed to their ability to prevent the copper catalyst from binding to the 8-aminoquinoline directing group, thereby interrupting the process of aerobic oxidative C−H etherification. Thus, these results support the quinoline N atom of the 8-aminoquinoline playing an essential role as a ligand to assist the Goldberg amidation reaction. The optimal reaction conditions to furnish the nonrearranged product **7a** utilized 1 equiv of phenol **6a** and benzamide **5a**, 3 equiv of K_3PO_4 as base, and 20 mol % of CuI catalyst in refluxing acetonitrile with air as oxidant.

Given the reversal in selectivity highlighted in entry 2 (Table 1), we deduced that a strong base should be necessary for the Smiles rearrangement reaction to occur (refer to Supporting Information for the optimization of the rearrangement reaction conditions). Thus, at the end of the process of copper-catalyzed aerobic oxidative C−H etherification (DMF as solvent, K_2CO_3 as base, copper acetate as catalyst, 74 °C), i.e., when the starting materials were consumed, *t*-BuOK was added to facilitate the rearrangement. These conditions led to exclusive formation of **8a** in 73% yield (Table 1, entry 13).

Returning to the nonrearranged product, to study the effect of substitution on the benzamide moiety, we explored the derivatives as shown in the Scheme 2. Introduction of electron-

Scheme 2. Copper-Catalyzed Nonrearrangement Reaction of 2-Bromo-4-chlorophenol with 8-Aminoquinoline Benzamides[a,b]



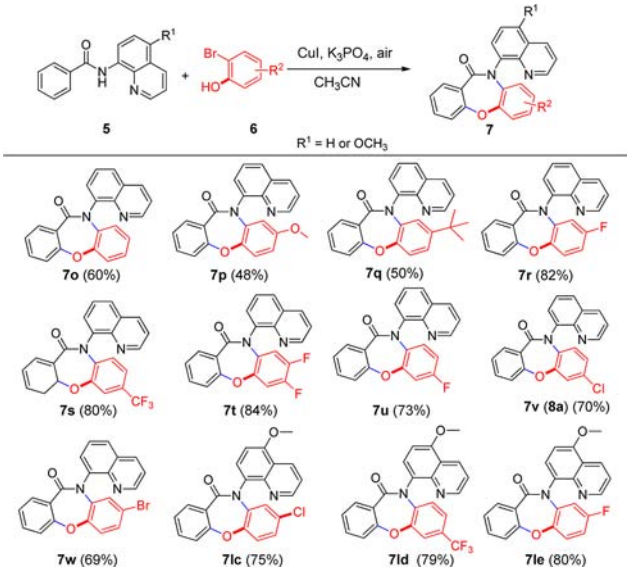
[a]Reaction conditions: **5** (0.2 mmol), **6a** (0.2 mmol), copper iodide (20 mol %), base (0.6 mmol), 74 °C for 0.5 h then reflux under 1 atm for 4−8 h, open air. [b]Isolated yield.

donating groups (−Me, −OMe) made the yield of the target products **7b**−**7d** slightly lower than that of the derivatives **7f**−**7h** with election-withdrawing groups (−CF_3, −NO_2, −OCF_3), demonstrating good substrate scope. Notably, an isonicotinamide derivative was compatible with the reaction conditions, yielding pyridyl amide derivative **7e**. Substitution *ortho* to the benzamide group, e.g., methyl, to give **7c** was tolerated. Halides (fluorine, chloride, and bromide) derivatives **7i**−**7k** worked well. With regard to the *meta*-substituted benzamides, cleavage of C−H bond occurred *para* to the substituent to yield single regioisomers **7f**, **7g**, and **7j**. It is noteworthy that the 8-aminoquinoline group could be replaced by a 5-methoxy-8-amoinoquinoline, to afford **7la**−**7le** in good yields (Schemes 2 and 3).

We also investigated the substrate scope with respect to 2-bromophenols (Scheme 3). The reaction showed a broad scope, electron donating (Scheme 3, **7p** and **7q**) and withdrawing groups

DOI: 10.1021/acs.orglett.5b03378
Org. Lett. 2016, 18, 380−383

Scheme 3. Copper-Catalyzed Nonrearrangement Reaction of *N*-(Quinolin-8-yl)benzamide with 2-Bromophenols[a,b]

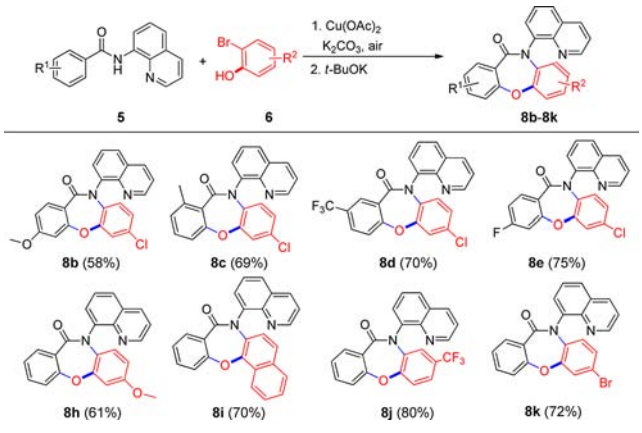


[a]Reaction conditions: **5** (0.2 mmol), **6a** (0.2 mmol), copper iodide (20 mol %), base (0.6 mmol), 74 °C for 0.5 h then reflux under 1 atm for 4−8 h, open air. [b]Isolated yield.

(Scheme 3, **7r**−**7w**) were both tolerated. In terms of regiochemistry, substitution was acceptable in both the *meta* and *para* positions relative to the phenolic oxygen. Notably **7v**, formed from 2-bromo-5-chlorophenol under nonrearrangement reaction conditions, is identical to the rearranged product **8a** from 2-bromo-4-chlorophenol (Scheme 1, eq 6), which further confirms the regioselectivity of this reaction.

The scope of the rearrangement reaction was also studied, both by varying the benzamide moiety, products **8b**−**8e**, and the 2-bromophenol moiety, products **8h**−**8k** (Scheme 4). These results further highlight the scope and utility of this methodology. Of particular note is the naphthyl product **8i**, the regioisomeric derivative of which failed to be detected from nonrearrangement

Scheme 4. Copper-Catalyzed Rearrangement Reaction of 8-Aminoquinoline Benzamides with 2-Bromophenols[a,b]

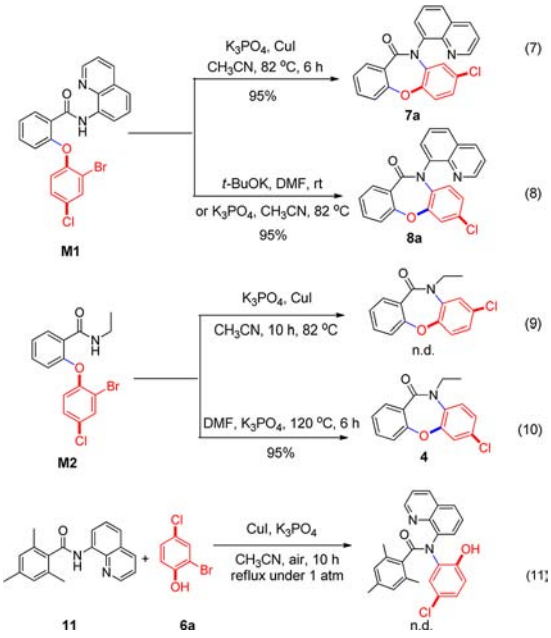


[a]Reaction conditions: **5** (0.2 mmol), **6** (0.2 mmol), copper acetate (20 mol %), K_2CO_3 base (0.4 mmol), open air, DMF solvent (5 mL), 74 °C. After **5** was consumed, *t*-BuOK (0.2 mmol) was added to the mixture at room temperature. [b]Isolated yield.

reaction conditions, potentially due to steric hindrance of the phenol.

To gain further insights into the mechanism of the reaction, controlled experiments were performed (Scheme 5). We

Scheme 5. Controlled Experiments to Validate the Proposed Mechanism



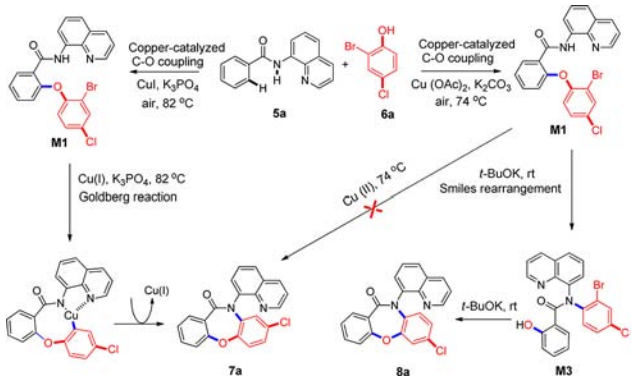
successfully isolated and identified the postulated intermediate **M1** (Supporting Information). The assumption that **M1** is an intermediate was further supported by the fact that it could be transformed into **7a** in quantitative yield under the optimized nonrearrangement reaction conditions (Scheme 5, eq 7).To investigate the role of the 8-aminoquinoline moiety, we prepared the ethylbenzamide analogue **M2**. Subjecting **M2** to the optimal nonrearrangement conditions failed to yield any nonrearranged product (Scheme 5, eq 9). Under base-mediated copper-free conditions (Scheme 5, eqs 8 and 10), M1 and M2 could be transformed into the rearranged product respectively in quantitative yield, which is consistent with Snieckus's work.[8c] These results show that copper and 8-aminoquinoline are not prerequisite for the rearrangement ring-closing reaction but are essential to the nonrearrangement reaction. The *ortho*-blocked benzamide **11** failed to generate Goldberg amidation product (Scheme 5, eq 11), supporting the hypothesis that the aerobic oxidative C−H etherification should take place first in this reaction.

Accordingly, the proposed mechanism of the reaction is outlined in Scheme 6. The first step in both mechanisms is the aerobic oxidative C−H etherification to form intermediate **M1**.[4a] Nonrearranged product **7a** is then formed from **M1** via a Goldberg reaction assisted with 8-aminoquinoline chelating Cu(I) at a higher temperature (82 °C). Alternatively, a moderate temperature (74 °C) and Cu(II) guarantee the yield of **M1** and inhibit the cascade transformation of **M1** into **7a**. Then **M1** is converted to **M3** through a base-mediated Smiles rearrangement reaction, followed by cyclization to produce the rearranged product **8a**.[8c]

Previous work has reported a modified 8-aminoquinoline auxiliary, 8-amino-5-methoxyquinoline, which can be easily removed.[3e] Thus, we sought to ascertain if these derivatives

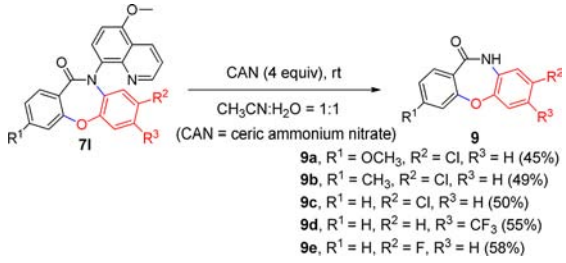
DOI: 10.1021/acs.orglett.5b03378
Org. Lett. 2016, 18, 380−383

Scheme 6. Plausible Reaction Mechanism



could also work. Treatment of **7l** with CAN (ceric ammonium nitrate) resulted in a facile cleavage of the directing group to afford dibenzoxazepinone **9** in a moderate yield (Scheme 7). It is

Scheme 7. Removable Directing Group[a,b]



[a]Reaction conditions: **7l** (0.08 mmol), CAN (0.32 mmol), room temperature, 16−48 h. [b]Isolated yield.

noteworthy that the derivatives **9a**, **9b** with electron donating groups (−OCH_3, −CH_3) and **9c**, **9d**, **9e** with withdrawing groups (−Cl, −CF_3, −F,) were tolerated well. Hence, this result may serve to further expand the application of this methodology.

In summary, we have discovered a copper-initiated highly regioselective reaction that provides a general route to two isomeric dibenzoxazepinones. The 8-aminoquinoline moiety is found to actually play a double role to facilitate the reactions, not only for C−H activation but also for the Goldberg coupling as a ligand to ensure the nonrearrangement transformation. This methodology has the advantage of wide generality, steric and functional group tolerance, and environmental friendliness. Finally, using the 8-amino-5-methoxyquinoline analogue allows for the facile removal of the auxiliary group, thus further expanding the application of the methodology.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b03378.

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

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported by NNSF (81273435 and 81302699), National Science & Technology Major Project (2013ZX0910-3001-001), Ministry of Science and Technology (2012AA-01A305), Natural Science Foundation of Shanghai, China (14ZR1447800), and The State Key Laboratory of Natural and Biomimetic Drugs (K20150205).

■ REFERENCES

(1) Reviews: (a) Chen, X.; Engle, K. M.; Wang, D.-H.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2009**, *48*, 5094. (b) Daugulis, O.; Do, H.-Q.; Shabashov, D. *Acc. Chem. Res.* **2009**, *42*, 1074. (c) Colby, D. A.; Bergman, R. G.; Ellman, J. A. *Chem. Rev.* **2010**, *110*, 624. (d) Lyons, T. W.; Sanford, M. S. *Chem. Rev.* **2010**, *110*, 1147. (e) Ackermann, L. *Chem. Rev.* **2011**, *111*, 1315. (f) Colby, D. A.; Bergman, R. G.; Ellman, J. A. *Chem. Rev.* **2010**, *110*, 624. (g) Alberico, D.; Scott, M. E.; Lautens, M. *Chem. Rev.* **2007**, *107*, 174. (h) Nakamura, E.; Yoshikai, N. *J. Org. Chem.* **2010**, *75*, 6061. (i) Yeung, C. S.; Dong, V. M. *Chem. Rev.* **2011**, *111*, 1215. (j) Sun, C.-L.; Li, B.-J.; Shi, Z.-J. *Chem. Commun.* **2010**, *46*, 677. (k) Li, C.-J. *Acc. Chem. Res.* **2009**, *42*, 335.

(2) (a) Guo, X.-X.; Gu, D.-W.; Wu, Z.; Zhang, W. *Chem. Rev.* **2015**, *115*, 1622. (b) Hickman, A. J.; Sanford, M. S. *Nature* **2012**, *484*, 177.

(3) (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) Corbet, M.; De Campo, F. *Angew. Chem., Int. Ed.* **2013**, *52*, 9896. (d) Rouquet, G.; Chatani, N. *Angew. Chem., Int. Ed.* **2013**, *52*, 11726. (e) He, G.; Zhang, S.-Y.; Nack, W. A.; Li, Q.; Chen, G. *Angew. Chem., Int. Ed.* **2013**, *52*, 11124.

(4) (a) Roane, J.; Daugulis, O. *Org. Lett.* **2013**, *15*, 5842. (b) Hao, X.-Q.; Chen, L.-J.; Ren, B.; Li, L.-Y.; Yang, X.-Y.; Gong, J.-F.; Niu, J.-L.; Song, M.-P. *Org. Lett.* **2014**, *16*, 1104. (c) Wang, Z.; Kuninobu, Y.; Kanai, M. *Org. Lett.* **2014**, *16*, 4790.

(5) (a) Tran, L. D.; Popov, I.; Daugulis, O. *J. Am. Chem. Soc.* **2012**, *134*, 18237. (b) Liu, J.; Yu, L.; Zhuang, S.; Gui, Q.; Chen, X.; Wang, W.; Tan, Z. *Chem. Commun.* **2015**, *51*, 6418.

(6) Tran, L. D.; Roane, J.; Daugulis, O. *Angew. Chem., Int. Ed.* **2013**, *52*, 6043.

(7) (a) Allen, R. C.; Reitano, P. A.; Urbach, H. *J. Med. Chem.* **1978**, *21*, 838. (b) Binaschi, M.; Boldetti, A.; Gianni, M.; Maggi, C. A.; Gensini, M.; Bigioni, M.; Parlani, M.; Giolitti, A.; Fratelli, M.; Valli, C.; Terao, M.; Garattini, E. *ACS Med. Chem. Lett.* **2010**, *1*, 411. (c) Deraeve, C.; Guo, Z.; Bon, R. S.; Blankenfeldt, W.; DiLucrezia, R.; Wolf, A.; Menninger, S.; Stigter, E. A.; Wetzel, S.; Choidas, A.; Alexandrov, K.; Waldmann, H.; Goody, R. S.; Wu, Y.-W. *J. Am. Chem. Soc.* **2012**, *134*, 7384. (d) Gijsen, H. J. M.; Berthelot, D.; Zaja, M.; Brone, B.; Geuens, I.; Mercken, M. *J. Med. Chem.* **2010**, *53*, 7011.

(8) (a) Liu, Y.; Chu, C.; Huang, A.; Zhan, C.; Ma, Y.; Ma, C. *ACS Comb. Sci.* **2011**, *13*, 547. (b) Ganguly, N. C.; Mondal, P.; Roy, S.; Mitra, P. *RSC Adv.* **2014**, *4*, 55640. (c) Kitching, M. O.; Hurst, T. E.; Snieckus, V. *Angew. Chem., Int. Ed.* **2012**, *51*, 2925. (d) Hone, N. D.; Salter, J. I.; Reader, J. C. *Tetrahedron Lett.* **2003**, *44*, 8169. (e) Lu, S.-M.; Alper, H. *J. Am. Chem. Soc.* **2005**, *127*, 14776. (f) Samet, A. V.; Marshalkin, V. N.; Kislyi, K. A.; Chernysheva, N. B.; Strelenko, Y. A.; Semenov, V. V. *J. Org. Chem.* **2005**, *70*, 9371. (g) Shen, C.; Neumann, H.; Wu, X.-F. *Green Chem.* **2015**, *17*, 2994. (h) Tsvelikhovsky, D.; Buchwald, S. L. *J. Am. Chem. Soc.* **2011**, *133*, 14228. (i) Xing, X.; Wu, J.; Luo, J.; Dai, W.-M. *Synlett* **2006**, *2006*, 2099. (j) Yang, Q.; Cao, H.; Robertson, A.; Alper, H. *J. Org. Chem.* **2010**, *75*, 6297. (k) Guo, X.; Zhang-Negrerie, D.; Du, Y. *RSC Adv.* **2015**, *5*, 94732.

DOI: 10.1021/acs.orglett.5b03378
Org. Lett. 2016, 18, 380−383