Organic LETTERS

Letter

pubs.acs.org/OrgLett

Copper-Promoted Tandem Reaction of Azobenzenes with Allyl Bromides via N═N Bond Cleavage for the Regioselective Synthesis of Quinolines

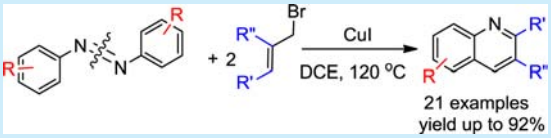
Xiangli Yi[†] and Chanjuan Xi*[,†,‡]

[†]Key Laboratory of Bioorganic Phosphorus Chemistry & Chemical Biology (Ministry of Education), Department of Chemistry, Tsinghua University, Beijing 100084, China

[‡]State Key Laboratory of Elemento-Organic Chemistry, Nankai University, Tianjin 300071, China

Supporting Information

ABSTRACT: A copper-promoted tandem reaction of a variety of azobenzenes and allyl bromides via N═N bond cleavage to regioselectively construct quinoline derivatives has been developed. The azobenzenes act as not only construction units but also an oxidant for quinoline formation.



RN═NR bond cleavage is of interest to understand the mechanisms of dinitrogen fixation. Moreover, RN═NR bond cleavage also offers potential value in catalytic and stoichiometric transformations involving [NR] transfer. Recently, the systematic cleavage of the N═N bond of azoarenes has been extensively investigated with metal complexes, in which the N═N bond was cleaved to give imido metal complexes or azametallocycles.[1] In addition, the transition-metal-catalyzed reduction of azoarenes also lead to the N═N bond cleavage to afford anilines.[2] Nevertheless, the well-defined N═N bond cleavage reactions of azoarenes have rarely been reported to directly form C−N bond in the construction of nitrogen-containing heterocycles,[3] to the best of our knowledge.

Quinoline is a class of nitrogen-containing heterocycles present in many biologically active compounds, including natural products and synthetic drugs.[4] Over the years, many strategies for the preparation of quinolines have been developed. Classical methods such as Skraup syntheses mainly employ condensation and Friedel−Crafts type reactions for ring construction.[5] Methods developed more recently tend to utilize transition metals to assist annulation via cycloaddition,[6] cationic cyclization,[7] and C−H or C−X functionalization.[8] Most of these existing methods employ substrates limited to anilines or prefunctionalized anilines, and many suffer from complicated multistep procedures and low regioselectivity. As a part of our ongoing projects on the formation of heterocycles using various substrates,[9] we herein report a new one-pot method for the regioselective synthesis of quinolines from azobenzenes and allyl bromides via N═N bond cleavage in the presence of CuI. In this reaction, the azobenzenes acted as both construction units and an oxidant.

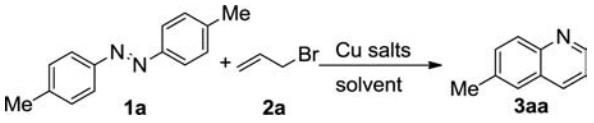
Initially, 1,2-bis(*p*-tolyl)diazene **1a** and allyl bromide **2a** were chosen as the model substrates to optimize the reaction conditions. As shown in Table 1, we first tested various copper salts in dichloroethane (DCE) at 120 °C for 6 h. When the reaction was attempted with CuI as a promoter, the product **3aa** was obtained in 35% yield (entry 1). CuBr, CuCl, and $CuBr_2$ were less effective, while $Cu(OTf)_2$ was inactive (entries 2−5). The product yield was considerably affected by the molar ratio of **1a** to **2a** (entries 6 and 9−11). The optimal ratio of **1a** to **2a** was found to be 1:2, which afforded an excellent yield (entry 10, 92% yield of **3aa**). The yield of product **3aa** did not improve when the molar ratio of **1a** to **2a** was increased into 1:3. When replacing **2a** with allyl choloride, no conversion of **1a** was observed (entry 12), while allyl iodide led to an 89% yield of **3aa** (entry 13). Then, the effect of solvents was also investigated (entries 10 and 17−19). The use of $CHCl_3$ and CH_3CN afforded product **3aa** in 61% and 70% yield, respectively. However, no product **3aa** was detected when the reaction was performed in toluene (entry 19). The decrease of reaction temperature to 110 °C resulted in a 65% yield (entry 16). In addition, when the amount of CuI was reduced to 0.5 equiv, the product **3aa** was obtained in only 66% yield (entry 14), and the reaction did not proceed at all without CuI (entry 15). Notably, reaction under air could give product **3aa**, albeit in relatively lower yield (entry 20). On the basis of the above-mentioned results, the optimal conditions are shown in entry 10.

Under the optimized reaction conditions, a study on the substrate scope was carried out. Some results are summarized in Scheme 1. First, a variety of symmetric azobenzenes **1** with a range of substituents, including *p*-Me, *o*-Me, *p*-OMe, *m*-^{t}Bu, and *m*-Me groups, were used in the reaction with allyl bromide **2a**. The corresponding quinolines were obtained in 58%−92% yields (**3aa**−**3ea**). When 1,2-bis(*m*-tolyl)diazene **1e** was used in this reaction, the products were obtained as two isomers in 58% yield in a 5:1 ratio. It should be noted that 7-(*tert*-butyl)quinoline **3da** as the sole regioisomer was obtained using 1,2-bis(*m*-*tert*-butylphenyl)diazene **1d** as the reactant, which may be attributed to bulky effect. When 1,2-bis(3,5-dimethylphenyl)diazene **1g** was used, we also obtained

Received: October 17, 2015
Published: November 18, 2015

DOI: 10.1021/acs.orglett.5b03009
Org. Lett. 2015, 17, 5836−5839

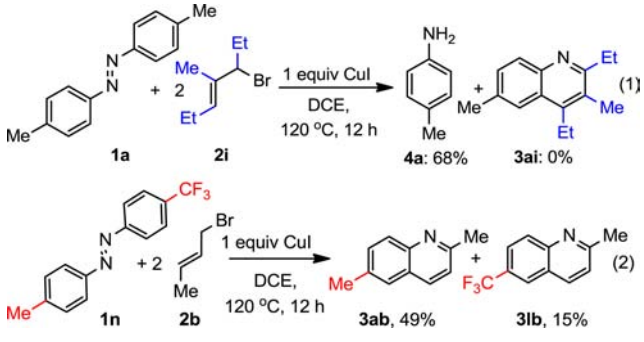
Table 1. Reaction Optimization of 1, 2-Bis(*p*-tolyl)diazene 1a with Allyl Bromide 2a[a]



entry	*t*/°C	solvent	Cu salts	time/h	ratio of **1a** to **2a**	yield[b]/% (conversion[c]/%)
1	120	DCE	CuI	6	1:1	35(59)
2	120	DCE	CuBr	6	1:1	25(65)
3	120	DCE	CuCl	6	1:1	11(23)
4	120	DCE	$CuBr_2$	6	1:1	19(44)
5	120	DCE	$Cu(OTf)_2$	6	1:1	0(76)
6	120	DCE	CuI	12	1:1	40(72)
7	120	DCE	CuI	24	1:1	45(83)
8	120	DCE	CuI	36	1:1	43
9	120	DCE	CuI	12	1:1.5	64
10	**120**	**DCE**	**CuI**	**12**	**1:2**	**92,82[d]**
11	120	DCE	CuI	12	1:3	84
12[e]	120	DCE	CuI	12	1:2	0
13[f]	120	DCE	CuI	12	1:2	89
14[g]	120	DCE	CuI	12	1:2	66
15[h]	120	DCE	–	12	1:2	0
16	110	DCE	CuI	12	1:2	65
17	120	$CHCl_3$	CuI	12	1:2	61
18	120	CH_3CN	CuI	12	1:2	70
19	120	toluene	CuI	12	1:2	0
20[i]	120	DCE	CuI	12	1:2	65

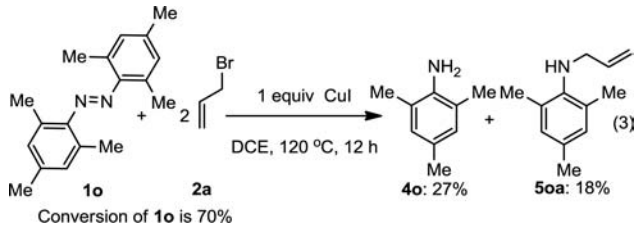
[a]Reaction condition: 0.2 mmol of **1a**, 0.2 mmol of Cu salt, 2 mL of solvent, under N_2, in a sealed tube. All chemical yields are calculated on the basis of **1a**. [b]^{1}H NMR yield. [c]^{1}H NMR conversion of **1a**. [d]Isolated yield. [e]Allyl choloride as substrate. [f]Allyl iodide as substrate. [g]0.1 mmol of CuI; when reaction time was prolonged to 36 h, the yield of **3aa** reached 78%. [h]Without CuI. [i]Under air.

5,7-dimethylquinoline **3ga** in 66% yield. While azobenzenes with substituents such as *p*-Cl, *p*-F, and *p*-CF_3 were tolerated, the reactions did not proceed and starting materials remained. To further demonstrate the scope of the reaction, crotyl bromide **2b** was chosen as a substrate and we were gratified to find the scope of substrates extended to less electron-rich azobenzenes. As shown in Scheme 1, a series of substituents on symmetric azobenzenes, including *p*-Me, *m*-OMe, *p*-Cl, *m*-Cl, *p*-F, *p*-CF_3, and *m*-CF_3 groups, were tolerated and the corresponding quinolines were obtained in moderate to good yields (**3ab**−**3mb**). Furthermore, some other substituted allyl bromides were examined (**2c**−**2h**) and the corresponding products were obtained in 28−72% yields with high regioselectivity (**3ac**−**3ah**). *β*- or *γ*-Monosubstituted and *β*,*γ*-disubstituted allyl bromides could be all tolerated in the reaction (**3ab**−**3af** and **3ag**−**3ah**). However, when 5-bromo-4-methylhept-3-ene **2i** (an *α*,*β*,*γ*-trisubstituted allyl bromide) was employed, the desired quinoline **3ai** was not observed and only *p*-toluidine **4a** was obtained in 68% yield (eq 1). Notably,



when asymmetric azobenzene 1-(*p*-tolyl)-2-(*p*-(trifluoromethyl)phenyl)-diazene **1n** was employed, products **3ab** and **3lb** were obtained in 49% and 15% yield, respectively (eq 2). This result means that the formation of quinoline is favored on the more electron-rich benzene ring.

To probe the reaction mechanism, additional experiments were performed. First, we tried 1,2-dimesityldiazene **1o** as the substrate, which in principle does not cyclize to afford quinoline, to react with **2a**, and **4o** and **5oa** were obtained respectively in 27% and 18% yield with 30% of **1o** remaining (eq 3).



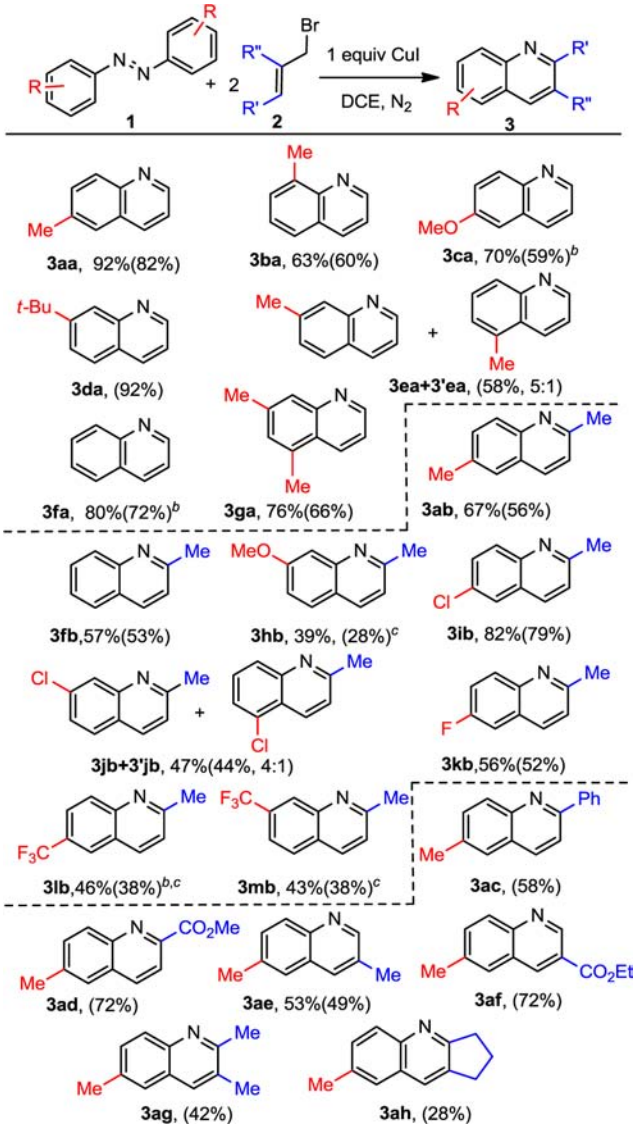
This reaction suggests conversion of azobenzene to aniline, and meanwhile allylation of the generated aniline could occur under this condition.

Then, by respectively adding one equivalent of aniline **4f** and **5fa** to the reaction system as shown in eq 3, we found quinoline **3fa** formed in 45% (eq 4) and 27% (eq 5) yield, respectively. These results indicated aniline and *N*-allylaniline could be intermidiates in the formation of quinoline.

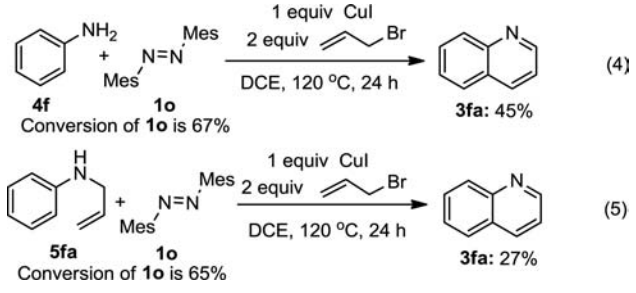
When the reaction of cinnamyl bromide **2c** and **1a** was subjected to a lower temperature, i.e. 80 °C, cinnamaldehyde anil **7ac** was obtained in 16% yield (eq 6). To prove the possible intermediate of this compound, cinnamaldehyde anil **7ac**

DOI: 10.1021/acs.orglett.5b03009
Org. Lett. 2015, 17, 5836−5839

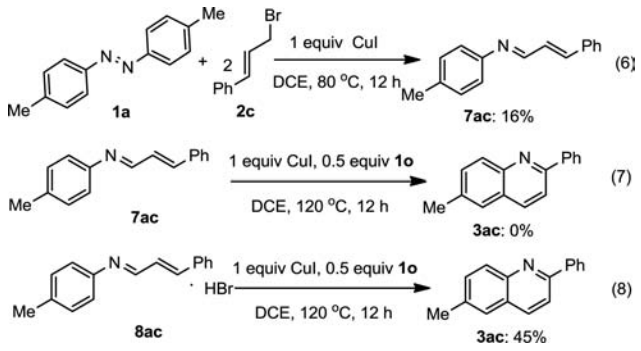
Scheme 1. CuI-Promoted Reaction of Symmetric Azobenzenes 1 with Allyl Bromides 2 for Synthesis of Quinolines 3[a]



[a]Reaction conditions: 0.2 mmol of **1**, 0.4 mmol of **2**, 0.2 mmol of CuI, 2 mL of DCE, 12 h, 120 °C. ^{1}H NMR yields (%) and isolated yields (%, in bracket) are displayed; all chemical yields are calculated on the basis of **1**. [b]130 °C. [c]Reaction for 24 h.

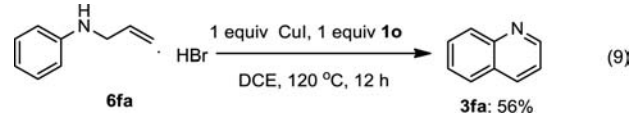


was synthesized and reacted with **1o** in the presence of CuI, but no formation of quinoline **3ac** was observed (eq 7). According to precedent literature, acrolein anils **7** cyclize to dihydroquinolines and subsequently become oxidized under acidic conditions to afford quinolines, which is a plausible pathway



for the Skraup reaction.[10] In our reaction, hydrogen bromide is formed when aniline **4** reacts with allyl bromide, which might be important to assist the cyclization of **7ac**. Thus, the hydrobromide of **7ac** (**8ac**) was synthesized and reacted with **1o** in the presence of CuI, and **3ac** was obtained in 45% yield (eq 8). Notably, the regioselectivity of cyclization in our reaction, i.e. forming 2-substituted instead of 4-substituted quinoline, is identical with that reported.[10] Therefore, we believe the intermediate acrolein anil **7** transforms into **3** with the assistance of HBr in a pathway consistent with what was reported.[10]

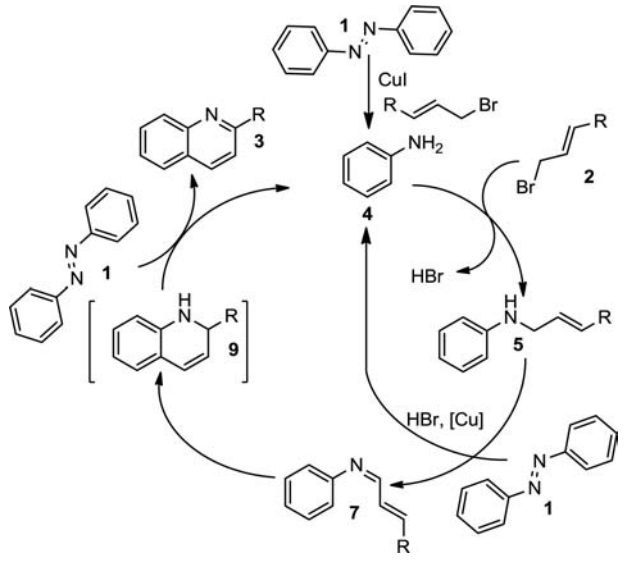
Additionally, it has been reported that *N*-allyl aniline could be oxidized to acrolein anil **7** with metal as the catalyst.[11] Under our reaction conditions, CuI and azobenzene could work together to transform **6fa** into quinoline **3fa** (eq 9), which very



possibly invovled oxidation of *N*-allyl aniline to acrolein anil **7** as the first step. It should be noted that both CuI and acidic conditions are necessary.

Based on the aforementioned results, a plausible reaction mechanism is proposed in Scheme 2. First, reduction of

Scheme 2. A Plausible Mechanism

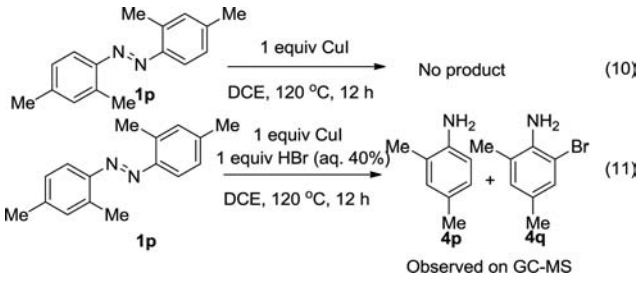


azobenzene **1** in the presence of CuI and allyl bromide **2** affords aniline **4** to initiate the reaction. Then, **4** undergoes nucleophilic substitution to generate *N*-allyl aniline **5** and HBr. The

DOI: 10.1021/acs.orglett.5b03009
Org. Lett. 2015, 17, 5836−5839

obtained *N*-allyl aniline **5** undergoes oxidation to furnish acrolein anil **7**, subsequently cyclizing to furnish intermediate **9** under acidic conditions.[10] Finally, the desired quinoline **3** was generated through dehydrogenation of the dihydroquinoline **9**. The oxidative processes, i.e. **5** to **7** and **9** to **3**, are accompanied by reduction of azobenzene **1** to aniline **4**, which ends up as starting material for another quinoline molecule formation.

Although how aniline was initially generated is still not clear, comparison of the following two reactions may give us some indications (eqs 10−11). Treatment of (*E*)-1,2-bis(2,4-dimethylphenyl)diazene



1p under the conditions without employing allyl bromide did not afford any products and **1p** remained (eq 10). When 1 equiv of hydrogen bromide (aqueous solution) was added (eq 11), anilines **4p** and **4q** were observed by GC-MS (see details in Supporting Information). This reduction very possibly involves a proton as a hydrogen source and Cu(I) as an electron source. Aniline **4q** could have been produced by bromination of **4p** with a combination of Br^- and the generated Cu(II).[12] In the reaction with allyl bromide, we believe it is possible that HBr may first be produced by hydrolysis (with a trace amount of H_2O in DCE) or pyrolysis of allyl bromide. Then, a similar electron transfer and proton transfer process results in the initial reduction of azobenzene.

In summary, we have developed a copper-promoted reaction of azobenzenes with allyl bromides via N═N bond cleavage to construct quinoline derivatives. The reaction conditions and the scope of this process were examined. The procedure is simple, the substrates are readily available, and no external oxidant is needed for quinoline formation. Mechanistic studies indicated a multistep domino reaction as a reasonable process. Further investigations to elucidate the interesting initial reduction of azobenzene are still in progress.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b03009.

Full experiment procedure, spectra data, and NMR charts for all new products (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: cjxi@tsinghua.edu.cn.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported by the National Natural Science Foundation of China (21272132 and 21472106) and the National Key Basic Research Program of China (973 program) (2012CB933402).

■ REFERENCES

(1) (a) Evans, W. J.; Kozimor, S. A.; Ziller, J. W. *Chem. Commun.* **2005**, 4681. (b) Warner, B. P.; Scott, B. L.; Burns, C. J. *Angew. Chem., Int. Ed.* **1998**, *37*, 959. (c) Tsai, Y.; Wang, P.; Chen, S.; Chen, J. *J. Am. Chem. Soc.* **2007**, *129*, 8066. (d) Kaleta, K.; Arndt, P.; Beweries, T.; Spannenberg, A.; Theilmann, O.; Rosenthal, U. *Organometallics* **2010**, *29*, 2604. (e) Milsmann, C.; Turner, Z. R.; Semproni, S. P.; Chirik, P. J. *Angew. Chem., Int. Ed.* **2012**, *51*, 5386. (f) Cladis, D. P.; Kiernicki, J. J.; Fanwick, P. E.; Bart, S. C. *Chem. Commun.* **2013**, *49*, 4169.

(2) (a) Schabel, T.; Belger, C.; Plietker, B. *Org. Lett.* **2013**, *15*, 2858. (b) Jagadeesh, R. V.; Wienhöfer, G.; Westerhaus, F. A.; Surkus, A.-E.; Junge, H.; Junge, K.; Beller, M. *Chem. - Eur. J.* **2011**, *17*, 14375. (c) Li, B.; Xu, Z. *J. Am. Chem. Soc.* **2009**, *131*, 16380.

(3) (a) Spencer, A. *J. Organomet. Chem.* **1985**, *295*, 199. (b) Yan, X.; Yi, X.; Xi, C. *Org. Chem. Front.* **2014**, *1*, 657. (c) Hong, G.; Mao, D.; Zhu, X.; Wu, S.; Wang, L. *Org. Chem. Front.* **2015**, *2*, 985.

(4) (a) Michael, J. P. *Nat. Prod. Rep.* **2008**, *25*, 166. (b) Balasubramanian, M.; Keay, J. G. In *Comprehensive Heterocyclic Chemistry II*; McKillop, A. E., Katrizky, A. R., Rees, C. W., Scrivem, E. F. V., Eds.; Elsevier: Oxford, 1996; Vol. 5, p 245. (c) Gorka, A. P.; de Dios, A.; Roepe, P. D. *J. Med. Chem.* **2013**, *56*, 5231. (d) Kaur, K.; Jain, M.; Reddy, R. P.; Jain, R. *Eur. J. Med. Chem.* **2010**, *45*, 3245.

(5) (a) Li, J. *Name Reactions in Heterocyclic Chemistry*; Wiley Interscience: Chichester, 2004; p 375. (b) Yamashkin, S. A.; Oreshkina, E. A. *Chem. Heterocycl. Compd.* **2006**, *42*, 701. (c) Zong, R.; Zhou, H.; Thummel, R. P. *J. Org. Chem.* **2008**, *73*, 4334. (d) Riesgo, E. C.; Jin, X.; Thummel, R. P. *J. Org. Chem.* **1996**, *61*, 3017. (e) Wu, Y.; Liu, L.; Li, H.; Wang, D.; Chen, Y. *J. Org. Chem.* **2006**, *71*, 6592.

(6) (a) Cao, K.; Zhang, F. M.; Tu, Y. Q.; Zhuo, X. T.; Fan, C. A. *Chem. - Eur. J.* **2009**, *15*, 6332. (b) Desrat, S.; van de Weghe, P. *J. Org. Chem.* **2009**, *74*, 6728. (c) Kulkarni, A.; Török, B. *Green Chem.* **2010**, *12*, 875. (d) Gao, G.; Niu, Y.; Yan, Z.; Wang, H.; Wang, G.; Shaukat, A.; Liang, Y. *J. Org. Chem.* **2010**, *75*, 1305. (e) Basuli, F.; Aneetha, H.; Huffman, J. C.; Mindiola, D. J. *J. Am. Chem. Soc.* **2005**, *127*, 17992.

(7) (a) Zhu, S.; Wu, L.; Huang, X. *J. Org. Chem.* **2013**, *78*, 9120. (b) Wang, Y.; Chen, C.; Peng, J.; Li, M. *Angew. Chem., Int. Ed.* **2013**, *52*, 5323. (c) Wang, Y.; Chen, C.; Zhang, S.; Lou, Z.; Su, X.; Wen, L.; Li, M. *Org. Lett.* **2013**, *15*, 4794. (d) Wang, Z.; Li, S.; Yu, B.; Wu, H.; Wang, Y.; Sun, X. *J. Org. Chem.* **2012**, *77*, 8615.

(8) (a) Matsubara, Y.; Hirakawa, S.; Yamaguchi, Y.; Yoshida, Z. *Angew. Chem., Int. Ed.* **2011**, *50*, 7670. (b) Korivi, R. P.; Cheng, C. H. *J. Org. Chem.* **2006**, *71*, 7079. (c) Wang, Y.; Liao, Q.; Zhao, P.; Xi, C. *Adv. Synth. Catal.* **2011**, *353*, 2659. (d) Li, L.; Jones, W. D. *J. Am. Chem. Soc.* **2007**, *129*, 10707.

(9) (a) Liao, Q.; Yang, X.; Xi, C. *J. Org. Chem.* **2014**, *79*, 8507. (b) Cai, S.; Chen, C.; Shao, P.; Xi, C. *Org. Lett.* **2014**, *16*, 3142. (c) Zhao, P.; Yan, X.; Yin, H.; Xi, C. *Org. Lett.* **2014**, *16*, 1120. (d) Liao, Q.; Zhang, L.; Li, S.; Xi, C. *Org. Lett.* **2011**, *13*, 228. (e) Wang, F.; Cai, S.; Wang, Z.; Xi, C. *Org. Lett.* **2011**, *13*, 3202. (f) Wang, F.; Cai, S.; Liao, Q.; Xi, C. *J. Org. Chem.* **2011**, *76*, 3174. (g) You, W.; Yan, X.; Liao, Q.; Xi, C. *Org. Lett.* **2010**, *12*, 3930. (h) Liao, Q.; Zhang, L.; Wang, F.; Li, S.; Xi, C. *Eur. J. Org. Chem.* **2010**, *2010*, 5426.

(10) Eisch, J. J.; Dluzniewski, T. *J. Org. Chem.* **1989**, *54*, 1269.

(11) (a) Choi, H.; Doyle, M. P. *Chem. Commun.* **2007**, 745. (b) Yamaguchi, K.; Mizuno, N. *Angew. Chem., Int. Ed.* **2003**, *42*, 1480.

(12) Bhatt, S.; Nayak, S. K. *Synth. Commun.* **2007**, *37*, 1381.

DOI: 10.1021/acs.orglett.5b03009
Org. Lett. 2015, 17, 5836−5839