Organic LETTERS

Letter

pubs.acs.org/OrgLett

Copper(I)-Catalyzed Sulfonylation of 8-Aminoquinoline Amides with Sulfonyl Chlorides in Air

Huijie Qiao,[†] Suyan Sun,[†] Fan Yang,*[,†] Yu Zhu,[†] Weiguo Zhu,[†] Yaxi Dong,[†] Yusheng Wu,*[,‡] Xiangtao Kong,[§] Ling Jiang,[§] and Yangjie Wu*[,†]

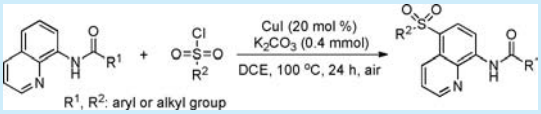
[†]The College of Chemistry and Molecular Engineering, Henan Key Laboratory of Chemical Biology and Organic Chemistry, Key Laboratory of Applied Chemistry of Henan Universities, Zhengzhou University, Zhengzhou 450052, People's Republic of China

[‡]Tetranov Biopharm, LLC., 75 Daxue Road, Zhengzhou, 450052, People's Republic of China

[§]State Key Laboratory of Molecular Reaction Dynamics, Dalian Institute of Chemical Physics, Chinese Academy of Sciences, 457 Zhongshan Road, Dalian 116023, Liaoning, People's Republic of China

Supporting Information

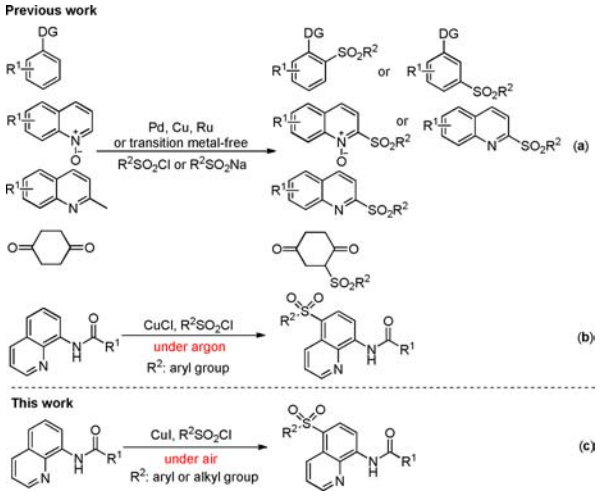
ABSTRACT: A simple and mild protocol for copper(I)-mediated sulfonylation of 8-aminoquinoline amides with sulfonyl chlorides was developed, affording desired products in moderate to good yields. This reaction proceeds in air and features excellent substrate tolerance, especially for aliphatic sulfonyl chlorides.



Sulfones have been extensively proven to possess a variety of bioactivities, such as anticancer, anti-HIV, and antibacterial activities.[1] Among them, heterocyclic aromatic sulfones have aroused great interest due to their wide application in organic synthesis, pharmaceutical chemistry, biological chemistry, and material sciences.[2] The most conventional synthetic routes to sulfones are the oxidation of sulfides and Friedel−Crafts sulfonylation.[3] However, these classic methods usually involve harsh reaction conditions (e.g., strong oxidants, strong acids) or are limited by the electronic effect. To cope with the above-mentioned limitation and satisfy the increasing synthetic demands of sulfones, developing new synthetic methodologies of these compounds is urgent and challenging.

During the past decades, transition-metal-catalyzed C−H functionalization has become a facile and robust tool in organic synthesis, and a series of transformations from C−H to C−C and C−heteroatom bonds have been demonstrated.[4−6] Particularly, sulfonylation of the C−H bond has been realized under transition metal catalysis (e.g., palladium,[7] copper,[8] and ruthenium[9]) or even transition-metal-free conditions[10] (Scheme 1a). Just recently, the Wei group reported a copper-catalyzed direct C−H bond sulfonylation of aminoquinolines with arylsulfonyl chlorides, and sulfonylation took place exclusively at the C5−H position of the quinoline ring (Scheme 1b).[8d] However, this reaction proceeded under an argon atmosphere and could not tolerate aliphatic sulfonyl chlorides. Our research interest is to demonstrate a simple and mild sulfonylation at the C5−H position of 8-aminoquinoline amides and a broader substrate scope such as aromatic and aliphatic sulfonyl chlorides. To this end, we envisioned developing a green reaction pattern for this C5−H sulfonylation of 8-aminoquinoline amides with sulfonyl chlorides, possibly in a different single electron transfer process (Scheme 1c).

Scheme 1. Direct Sulfonylation of C−H Bond

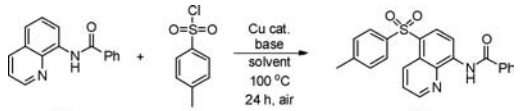


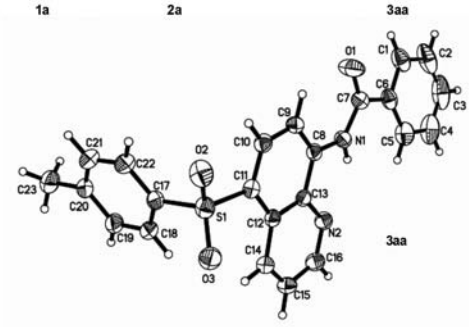
Initially, the sulfonylation of *N*-(quinolin-8-yl)benzamide (**1a**) with *p*-tolysulfonyl chloride (**2a**) (2.0 equiv) was chosen as a model reaction for optimization of the reaction parameters, and the results are displayed in Table 1. After the catalytic activity of various copper salts was checked, CuI (20 mol %) as a catalyst gave the desired product **3aa** in 80% yield in the presence of K_2CO_3 (2.0 equiv) under air for 24 h (Table 1, entry 3). However, CuCl, CuBr, CuSCN, and $CuBF_4$ showed lower catalytic activity (Table 1, entries 1−2, 4−5) as well as other copper(II) species (e.g., $Cu(OAc)_2$, $CuCl_2$, $CuBr_2$, $Cu(CF_3SO_3)_2$, and CuO) (<30%; see Supporting Information (SI)). The reaction did not occur at all under the copper-

Received: October 27, 2015
Published: December 2, 2015

DOI: 10.1021/acs.orglett.5b03114
Org. Lett. 2015, 17, 6086−6089

Table 1. Screening of Reaction Conditions[a]





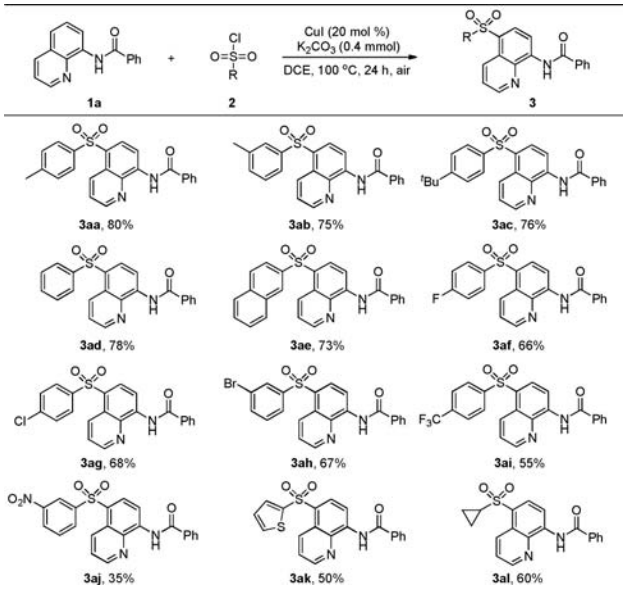
entry	catalyst	base	solvent	yield (%)[b]
1	CuCl	K_2CO_3	DCE	26
2	CuBr	K_2CO_3	DCE	22
3	CuI	K_2CO_3	DCE	80
4	CuSCN	K_2CO_3	DCE	45
5	$CuBF_4$	K_2CO_3	DCE	21
6	–	K_2CO_3	DCE	trace
7[c]	CuI	K_2CO_3	DCE	72
8	CuI	Na_2CO_3	DCE	22
9	CuI	Cs_2CO_3	DCE	70
10	CuI	^{t}BuOLi	DCE	51
11	CuI	–	DCE	trace
12	CuI	K_2CO_3	toluene	56
13	CuI	K_2CO_3	CH_3CN	24
14	CuI	K_2CO_3	dioxane	49
15	CuI	K_2CO_3	^{t}BuOH	32
16[d]	CuI	K_2CO_3	DCE	56

[a]Reaction conditions: **1a** (0.2 mmol), **2a** (0.4 mmol), copper catalyst (20 mol %), base (0.4 mmol), solvent (1 mL) at 100 °C under air for 24 h. [b]Isolated yield. [c]Copper catalyst (10 mol %). [d]At 90 °C.

catalyst-free conditions, and reducing the catalyst loading resulted in a decreased yield of the desired product (entries 6 and 7). Among the bases examined, including K_2CO_3, Na_2CO_3, Cs_2CO_3, and ^{t}BuOLi, K_2CO_3 was the best choice (entry 3 vs entries 8–10); other bases (e.g., K_3PO_4, $NaHCO_3$, $KHCO_3$, KF, and ^{t}BuOK) generated the desired product in even lower yields (see SI); no desired product was observed in the absence of the base (entry 11). The results show that K_2CO_3 play a central role, and the lower efficacy of other bases may be influenced by their basicity and solubility in the solvent.[11] Then, other solvents such as toluene, CH_3CN, dioxane, and ^{t}BuOH were also examined, and it was found that none of them could match the efficacy of DCE (entry 3 vs entries 12–15). Finally, the yield of **3aa** dropped to 56% when the oil bath temperature was altered from 100 to 90 °C (entry 16). The molecular structure of **3aa** was unambiguously confirmed by single crystal X-ray diffraction study.

With the optimized reaction conditions in hand, we explored the applicability of the present sulfonylation protocol and examined a series of sulfonyl chlorides (Scheme 2). The results demonstrate that arylsulfonyl chlorides bearing electron-donating, -neutral, or -withdrawing groups on the benzene ring are all well tolerated in this reaction, and the desired products can be obtained in moderate to good yields (**3aa**–**3aj**). Comparatively, substrates containing an electron-donating

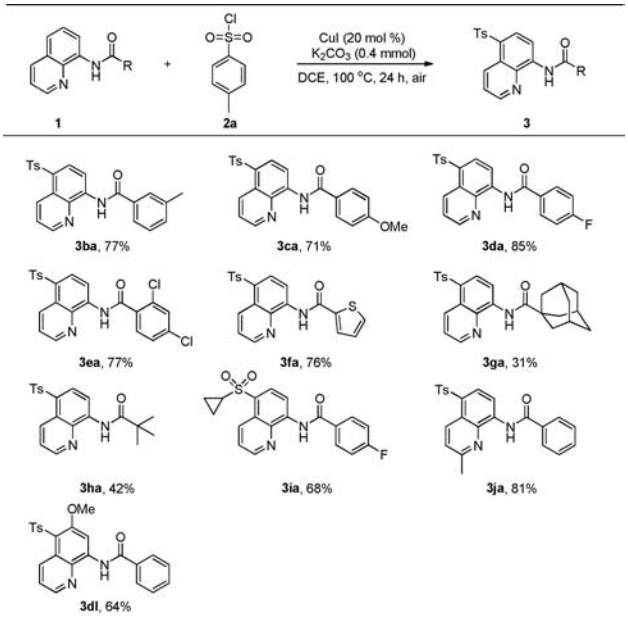
Scheme 2. Substrate Scope of Sulfonyl Chlorides



group could lead to the coupling products in slightly higher yields. For example, when arylsulfonyl chlorides possessed electron-donating groups (e.g., Me and ^{t}Bu), the target products were obtained in 80%, 75%, and 76% yields, respectively (**3aa**–**3ac**). Electron-neutral arylsulfonyl chlorides such as benzenesulfonyl chloride and naphthalenesulfonyl chloride could also afford the desired products in 78% and 73% yield, respectively (**3ad** and **3ae**). Substrates with electron-withdrawing groups (e.g., F, Cl, Br, CF_3, and NO_2) provided the corresponding products in a 35%–68% yield range (**3af**–**3aj**). To our delight, the heterocyclic sulfonyl chloride could also produce the desired products in a moderate yield (**3ak**). Note that the reaction could tolerate the aliphatic sulfonyl chloride, generating the product in 60% yield (**3al**).

Then, the scope of 8-aminoquinoline amides was explored under the standard reaction conditions (Scheme 3). The

Scheme 3. Substrate Scope of 8-Aminoquinoline Amides

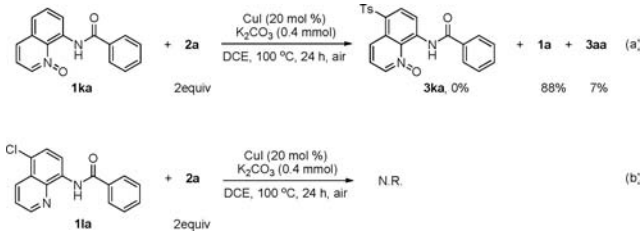


DOI: 10.1021/acs.orglett.5b03114
Org. Lett. 2015, 17, 6086–6089

electronic effect was not obvious on the benzene ring of benzamides, and the desired products were afforded in moderate to good yields (**3ba**−**3ea**). Remarkably, the heterocyclic amide could afford the sulfonylated product in good yield (**3fa**). However, aliphatic amides could generate the products in relatively lower yields (**3ga** and **3ha**). Moreover, cyclopropanesulfonyl chloride could also react with a fluoro-substituted 8-aminoquinoline derivative, affording the desired product in a moderate yield of 68% (**3dl**). In addition, the substrates bearing Me and MeO groups on the quinoline ring could afford the desired products in 81% and 64% yields, respectively (**3ia** and **3ja**). The slight decrease of the yield of **3ja** might be attributed to the influence of the steric hindrance of the 6-MeO group.

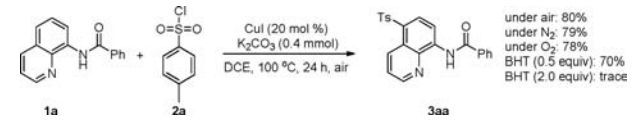
However, when the quinoline ring was changed into quinoline *N*-oxide, no desired product (**3ka**) was observed, but **1a** and **3aa** were obtained as byproducts in 88% and 7% yields, respectively (Scheme 4a). If the C5−H position was blocked by a Cl group (**1la**), the reaction did not occur at all, which was unlike the report of the Wei group (Scheme 4b).[8d]

Scheme 4. Two Examples of Other Type of Substituted Quinoline Ring



Further studies were performed to obtain insight into the mechanism (Scheme 5). Performing the reaction under a

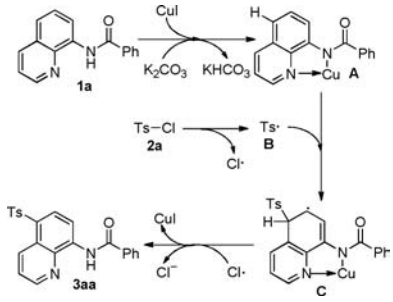
Scheme 5. Control Experiments



nitrogen or oxygen atmosphere instead of air resulted in similar yields of **3aa**, which showed that oxygen might have no effect on this sulfonylation and an oxidant might be not essential for this system. The addition of radical inhibitor 2,6-diisopropyl-4-methylphenol (BHT) resulted in inhibition of the reaction, indicating that the reaction might involve radical steps. Wei's mechanism which includes Cu(I) and Cu(III) species may be correct. However, our reaction system is different from Wei's. Our experiment results indicate our reaction system proceeds via the radical process, so a single electron transfer mechanism is proposed.

Though the detailed mechanism of this sulfonylation remains unclear, a tentative mechanism is proposed on the basis of the previous reports[8,12] and the above-mentioned results (Scheme 6). First, in the presence of a base, the coordination of **1a** with CuI affords the chelated intermediate **A**. On the other hand, the homolytic cleavage of **2a** releases a *p*-tolylsulfonyl radical **B** and a chloro radical via a single electron transfer process. Then, the addition of the radical **B** to the intermediate **A** occurs at the C5 position to form an intermediate radical **C**. Finally,

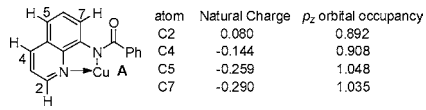
Scheme 6. Plausible Mechanism



decomposition of **C** provides the desired product **3aa**, along with the regeneration of the active copper(I) species to fulfill the catalytic cycle.

In order to demonstrate that the reaction occurs at the C5 position, we calculated the theoretical data of some carbon atoms (C2, C4, C5, C7) on the quinoline ring of the chelated intermediate **A** (Scheme 7). The natural charges of the C2, C4,

Scheme 7. Natural Charge Distribution and p_z Orbital Occupancy of the C2, C4, C5, and C7 Atoms in the Structure A



atom	Natural Charge	p_z orbital occupancy
C2	0.080	0.892
C4	-0.144	0.908
C5	-0.259	1.048
C7	-0.290	1.035

C5, and C7 atoms are predicted to be 0.080, −0.144, −0.259, and −0.290, respectively. However, the natural charges include contributions from all valence electrons. Considering that the direction of the p_z orbital is in accordance with the π orbital of the quinolone ring, the p_z orbital occupancy would be more effective to assess the reactivity of a specific atom. Among the four carbon atoms, C5 has the largest p_z orbital occupancies, implying that C5 may be the most likely electrophilic reactive site.[13]

In conclusion, we have developed a copper-catalyzed direct sulfonylation of 8-aminoquinoline amides with sulfonyl chlorides, providing a facile and convenient route to C5−H sulfonylated 8-aminoquinoline amides. This reaction features a mild catalytic system and good tolerance of substrates including aliphatic sulfonyl chlorides. Moreover, a different single electron transfer mechanism is outlined on the basis of our experimental results and theoretical data of some carbon atoms. Finally, we indicate that oxygen has no obvious effect on this reaction and isolation from air or oxygen is not necessary in this reaction.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b03114.

Experimental details, characterizations, and NMR spectra of all products (PDF)
X-ray data for **3aa** (CIF)

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: yangf@zzu.edu.cn.

DOI: 10.1021/acs.orglett.5b03114
Org. Lett. 2015, 17, 6086−6089

*E-mail: wyj@zzu.edu.cn.
*E-mail: yusheng.wu@tetranovglobal.com.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We are grateful to the National Natural Science Foundation of China (Nos. 21102134, 21172200) for financial support.

■ REFERENCES

(1) (a) Williams, T. M.; Ciccarone, T. M.; MacTough, S. C.; Rooney, C. S.; Balani, S. K.; Condra, J. H.; Emini, E. A.; Goldman, M. E.; Greenlee, W. J.; Kauffman, L. R.; O'Brien, J. A.; Sardana, V. V.; Schleif, W. A.; Theoharides, A. D.; Anderson, P. S. *J. Med. Chem.* **1993**, *36*, 1291. (b) Vedula, M. S.; Pulipaka, A. B.; Venna, C.; Chintakunta, V. K.; Jinnapally, S.; Kattuboina, V. A.; Vallakati, R. K.; Basetti, V.; Akella, V.; Rajgopal, S.; Reka, A. K.; Teepireddy, S. K.; Mamnoor, P. K.; Rajagopalan, R.; Bulusu, G.; Khandelwal, A.; Upreti, V. V.; Mamidi, S. R. *Eur. J. Med. Chem.* **2003**, *38*, 811. (c) Barbuceanu, S. F.; Almajan, G. L.; Saramet, I.; Draghici, C.; Tarcomnicu, A. I.; Bancescu, G. *Eur. J. Med. Chem.* **2009**, *44*, 4752.

(2) (a) Zhang, C. P.; Vicic, D. A. *J. Am. Chem. Soc.* **2012**, *134*, 183. (b) Reddick, J. J.; Cheng, J.; Roush, W. R. *Org. Lett.* **2003**, *5*, 1967. (c) Wang, G.; Mahesh, U.; Chen, G. Y. J.; Yao, S. Q. *Org. Lett.* **2003**, *5*, 737. (d) Meadows, D. C.; Sanchez, T.; Neamati, N.; North, T. W.; Gervay-Hague, J. *Bioorg. Med. Chem.* **2007**, *15*, 1127. (e) Frankel, B. A.; Bentley, M.; Kruger, R. G.; McCafferty, D. G. *J. Am. Chem. Soc.* **2004**, *126*, 3404. (f) Noshi, M. N.; El-awa, A.; Torres, E.; Fuchs, P. L. *J. Am. Chem. Soc.* **2007**, *129*, 11242. (g) Sulzer-Mossé, S.; Alexakis, A.; Mareda, J.; Bollot, G.; Bernardinelli, G.; Filinchuk, Y. *Chem. - Eur. J.* **2009**, *15*, 3204.

(3) (a) Simpkins, N. In *Sulfones in Organic Synthesis*; Baldwin, J. E., Magnus, P. D., Eds.; Pergamon Press: Oxford, 1993. (b) Block, E. *Reaction of Organosulfur Compounds*; Academic Press: New York, 1978. (c) Jensen, F. R.; Goldman, G. In *Friedel–Crafts and Related Reactions*; Olah, G., Ed.; Wiley-Interscience: New York, 1964; Vol. *III*, p 1319.

(4) For reviews on transition-metal-catalyzed C–H bond functionalization, see: (a) Burland, D. M.; Miller, R. D.; Walsh, C. A. *Chem. Rev.* **1994**, *94*, 31. (b) Kanis, D. R.; Ratner, M. A.; Marks, T. J. *Chem. Rev.* **1994**, *94*, 195. (c) Ishow, E.; Bellaïche, C.; Bouteiller, L.; Nakatani, K.; Delaire, J. A. *J. Am. Chem. Soc.* **2003**, *125*, 15744. (d) Sun, C. L.; Li, B. J.; Shi, Z. J. *Chem. Commun.* **2010**, *46*, 677. (e) Bellina, F.; Rossi, R. *Chem. Rev.* **2010**, *110*, 1082. (f) Song, G.; Wang, F.; Li, X. *Chem. Soc. Rev.* **2012**, *41*, 3651. (g) Papagiannouli, I.; Iliopoulos, K.; Gindre, D.; Sahraoui, B.; Krupka, O.; Smokal, V.; Kolendo, A.; Couris, S. *Chem. Phys. Lett.* **2012**, *554*, 107. (h) Gao, K.; Yoshikai, N. *Acc. Chem. Res.* **2014**, *47*, 1208. (i) Yang, L.; Huang, H. M. *Chem. Rev.* **2015**, *115*, 3468.

(5) For transition-metal-catalyzed C–C bond formation *via* C–H activation, see: (a) Kuhl, N.; Hopkinson, M. N.; WencelDelord, J.; Glorius, F. *Angew. Chem., Int. Ed.* **2012**, *51*, 10236. (b) Yeung, C. S.; Dong, V. M. *Chem. Rev.* **2011**, *111*, 1215. (c) Ackermann, L. *Chem. Rev.* **2011**, *111*, 1315. (d) Li, C. J. *Acc. Chem. Res.* **2009**, *42*, 335.

(6) For transition-metal-catalyzed C–heteroatom bond formation *via* C–H activation, see: (a) Tran, L. D.; Roane, J.; Daugulis, O. *Angew. Chem., Int. Ed.* **2013**, *52*, 6043. (b) Louillat, M. L.; Patureau, F. W. *Org. Lett.* **2013**, *15*, 164. (c) Pan, J.; Su, M.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2011**, *50*, 8647. (d) John, A.; Nicholas, K. M. *J. Org. Chem.* **2011**, *76*, 4158. (e) Shuai, Q.; Deng, G.; Chua, Z.; Bohle, D. S.; Li, C. J. *Adv. Synth. Catal.* **2010**, *352*, 632. (f) Mei, T. S.; Wang, X.; Yu, J. Q. *J. Am. Chem. Soc.* **2009**, *131*, 10806. (g) Li, J. J.; Mei, T. S.; Yu, J. Q. *Angew. Chem., Int. Ed.* **2008**, *47*, 6452. (h) Tsang, W. C. P.; Zheng, N.; Buchwald, S. L. *J. Am. Chem. Soc.* **2005**, *127*, 14560. (i) Matsubara, T.; Asako, S.; Ilies, L.; Nakamura, E. *J. Am. Chem. Soc.* **2014**, *136*, 646. (j) Wang, T.; Zhou, W.; Yin, H.; Ma, J. A.; Jiao, N. *Angew. Chem., Int. Ed.* **2012**, *51*, 10823. (k) Chen, L.; Shi, E.; Liu, Z.; Chen, S.; Wei, W.; Li, H.; Xu, K.; Wan, X. *Chem. - Eur. J.* **2011**, *17*, 4085. (l) Wang, X.; Lu, Y.; Dai, H. X.; Yu, J. Q. *J. Am. Chem. Soc.* **2010**, *132*, 12203. (m) Shen, C.; Zhang, P. F.; Sun, Q.; Bai, S. Q.; Hor, T. S. A.; Liu, X. G. *Chem. Soc. Rev.* **2015**, *44*, 291.

(7) (a) Zhao, X. D.; Dimitrijević, E.; Dong, V. M. *J. Am. Chem. Soc.* **2009**, *131*, 3466. (b) Ge, B. Y.; Wang, D. W.; Dong, W. F.; Ma, P. M.; Li, Y. L.; Ding, Y. Q. *Tetrahedron Lett.* **2014**, *55*, 5443. (c) Xu, Y. F.; Liu, P.; Li, S. L.; Sun, P. P. *J. Org. Chem.* **2015**, *80*, 1269. (d) Zhang, D.; Cui, X. L.; Zhang, Q. Q.; Wu, Y. J. *J. Org. Chem.* **2015**, *80*, 1517.

(8) (a) Wu, Z. Y.; Song, H. Y.; Cui, X. L.; Pi, C.; Du, W. W.; Wu, Y. J. *Org. Lett.* **2013**, *15*, 1270. (b) Liu, J. D.; Yu, L.; Zhuang, S. B.; Gui, Q. W.; Chen, X.; Wang, W. D.; Tan, Z. *Chem. Commun.* **2015**, *51*, 6418. (c) Rao, W. H.; Shi, B. F. *Org. Lett.* **2015**, *17*, 2784. (d) Liang, H. W.; Jiang, K.; Ding, W.; Yuan, Y.; Shuai, L.; Chen, Y. C.; Wei, Y. *Chem. Commun.* **2015**, *51*, 16928.

(9) Saidi, O.; Marafie, J.; Ledger, A. E. W.; Liu, P. M.; Mahon, M. F.; Kociok-Köhn, G.; Whittlesey, M. K.; Frost, C. G. *J. Am. Chem. Soc.* **2011**, *133*, 19298.

(10) (a) Xiao, F. H.; Chen, S. Q.; Chen, Y.; Huang, H. W.; Deng, G. J. *Chem. Commun.* **2015**, *51*, 652. (b) Sun, K.; Chen, X. L.; Li, X.; Qu, L. B.; Bi, W. Z.; Chen, X.; Ma, H. L.; Zhang, S. T.; Han, B. W.; Zhao, Y. F.; Li, C. J. *Chem. Commun.* **2015**, *51*, 12111.

(11) Ouyang, K. B.; Xi, Z. F. *Huaxue Xuebao* **2013**, *71*, 13.

(12) Suess, A. M.; Ertem, M. Z.; Cramer, C. J.; Stahl, S. S. *J. Am. Chem. Soc.* **2013**, *135*, 9797.

(13) Fu, R.; Lu, T.; Chen, F. W. *Acta Phys. -Chim. Sin.* **2014**, *30*, 628.

DOI: 10.1021/acs.orglett.5b03114
Org. Lett. 2015, 17, 6086–6089