Organic LETTERS

Letter

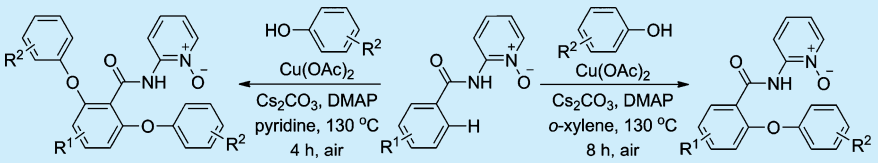
pubs.acs.org/OrgLett

Copper-Mediated Direct Aryloxylation of Benzamides Assisted by an *N,O*-Bidentate Directing Group

Xin-Qi Hao,[†] Li-Juan Chen,[†] Baozeng Ren,[‡] Liu-Yan Li,[†] Xin-Yan Yang,[†] Jun-Fang Gong,[†] Jun-Long Niu,*[,†] and Mao-Ping Song*[,†]

[†]The College of Chemistry and Molecular Engineering, Henan Key Laboratory of Chemical Biology and Organic Chemistry and [‡]School of Chemical Engineering and Energy, Zhengzhou University, Zhengzhou 450001, People's Republic of China

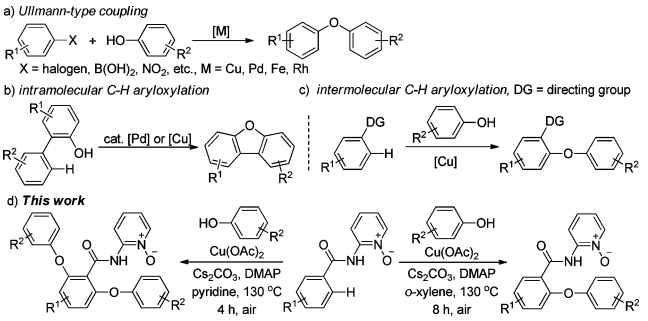
Supporting Information



ABSTRACT: Copper-mediated selective mono- or diaryloxylation of benzamides has been achieved by using 2-aminopyridine 1-oxide as a new and removable *N,O*-bidentate directing group. The reaction system shows a broad substrate scope and provides a straightforward way for the synthesis of mono- and diaryloxylated benzoic acids.

Biaryl ethers represent an important structural motif because of their broad application in natural products, pharmaceuticals, functional materials and other synthetics.[1] Consequently, many methods have been developed for the formation of these molecules.[2] Typically, the biaryl ether linkages are constructed *via* the metal-assisted Ullmann-type[3] couplings of prefunctionalized arene building blocks such as aryl halides, arylboronic acids or nitrobenzenes with phenols reported mainly by the Buchwald and the Hartwig groups (Scheme 1 a).[4] From a synthetic perspective, direct C−H aryloxylation of arenes with phenols would be an attractive and ideal alternative to the aforementioned couplings. Despite the boom of C−H bond activation and functionalization,[5] such a reaction involving the coupling of phenol hydroxyls with C−H bonds has so far remained elusive compared with the C−H bond alkoxylation and hydroxylation.[6,7] The reason is due to the poor nucleophilicity of the phenoxide resistant to C−O reductive elimination from the metal center[4d] and the sensitivity of phenols to the oxidants such as PhI(OAc).[8] Recently, successful intramolecular aryloxylation of arenes with Pd or Cu catalysts was achieved by Liu,[9a] Yoshikai,[9b] and Zhu[9c] (Scheme 1 b). Nevertheless, the intermolecular aryloxylation of arenes possessing directing groups, which was pioneered by Yu and co-workers,[10] has been less explored (Scheme 1 c).[11] Thus, the search for new variants to accomplish intermolecular C−H bond aryloxylation is still expected to extend the scope of the synthetic application.

Scheme 1. C−O Bond Formation Routes to Biaryl Ethers



On the other hand, chelating-assisted transformation is now one of the viable methods for activating specific C−H bond through a cyclometalation reaction.[12] Among them, functional groups containing neutral or anionic heteroatoms such as nitrogen, oxygen, and sulfur have been widely used as monodentate directing groups. Additionally, a double-coordination strategy employing a bidentate directing group to promote the activation of C−H bonds via the formation of a pincer-type metallacycle has been developed. Since the pioneering work of Daugulis and co-workers[13] on the use of picolinamide or 8-aminoquinoline as an *N,N*-bidentate directing group, important advances in palladium-catalyzed arylation, alkylation, carbonylation, alkoxylation, and intramolecular amination of C−H bonds have been made.[14,15] Very recently, notable catalyst improvements based on the relatively cheaper metal catalysts such as iron, nickel, and ruthenium and novel synthetic applications were reported by the groups of Nakamura[16] and Chatani.[17] Furthermore, Daugulis and Miura developed copper-catalyzed and copper-mediated direct C−C and C−X (X = S, F, N) cross-coupling reactions using this auxiliary strategy.[18] Inspired by these successes and the capability of a terdentate pincer ligand to undergo facile C−H bond activation and subsequent cyclometalation,[19] we focused our efforts on developing a new bidentate directing

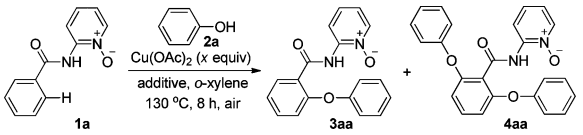
Received: December 20, 2013

   dx.doi.org/10.1021/ol500166d | *Org. Lett.* XXXX, XXX, XXX−XXX

group to promote C(sp^2)−H activation and functionalization (Scheme 1, d).

Herein, we report the 2-aminopyridine 1-oxide group, easily synthesized from 2-aminopyridine, as an *N,O*-bidentate directing group for copper-mediated mono- and diaryloxylation of benzoic acid derivatives. The model reaction of 2-benzamidopyridine 1-oxide (**1a**) and phenol (**2a**) was used to optimize the reaction conditions (see the Supporting Information for more extensive screening results). The reaction was found to proceed more efficiently in nonpolar solvents than in polar ones, and *o*-xylene was found to be the best solvent. The reaction proceeds most efficiently under an air atmosphere. The screening on different copper salts showed that **3aa** could be isolated in 37% yield by using $Cu(OAc)_2$ in *o*-xylene after 8 h (Table 1, entry 1). Introduction of 4-dimethylaminopyridine

Table 1. Optimization of Reaction Conditions[a,b]



entry	$Cu(OAc)_2$ (equiv)	Cs_2CO_3 (equiv)	DMAP (equiv)	**3aa** (%)	**4aa** (%)
1	1	0	0	37	0
2	1	0	0.5	42	0
3	1	1	0	45	0
4	1	1	0.5	71	27
5	0.5	1	0.5	51	12
6		1	0.5	0	0
7	2	1	0.5	63	9
8[c]	1.5	1.5	0.75	11	55
9[c,d]	2	1.5	1.5	0	76

[a]Amide (0.2 mmol), phenol (0.6 mmol), solvent (1 mL). [b]Isolated yields. [c]Pyridine solvent. [d]Reaction time is 4 h. DMAP = 4-dimethylamiopryidine.

(DMAP) or Cs_2CO_3 resulted in higher yields (entries 2 and 3). Addition of both Cs_2CO_3 and DMAP to the reaction system was found to be crucial for this transformation, producing monophenoxylated product **3aa** and diaryloxylated product **4aa** in a 2.6:1 ratio and 98% combined yield (entry 4). Decreasing the amount of $Cu(OAc)_2$ to 0.5 equiv led to lower efficiency (entry 5), and the reaction did not work when $Cu(OAc)_2$ was removed (entry 6). Next, we aimed at achieving symmetrical bisfunctionalization of **1a** via a double C−H aryloxylation reaction (entries 7−9). Surprisingly, simply increasing the amount of $Cu(OAc)_2$ gave reduced efficiency (entries 7 and 8). To our delight, switching the solvent from *o*-xylene to pyridine and increasing the ratio of Cs_2CO_3/DMAP to 1:1 significantly improved the selectivity for the diphenoxylated product **4aa**, and a 76% yield was obtained with excellent mono/di selectivity after a shorter reaction time (entry 9). Structures of **3aa** and **4aa** were confirmed by X-ray crystallography (Supporting Information). It is noteworthy that the copper salt is less expensive and environmentally friendly, and this protocol is conducted under convenient operating conditions despite the requirement for stoichiometric or greater quantities of $Cu(OAc)_2$.

Studies on directing groups (Figure 1) showed that the 2-aminopyridine 1-oxide motif appeared to be uniquely effective for the reaction under identical conditions (Table 1, entry 4). The absence of any reaction in the case of other structurally

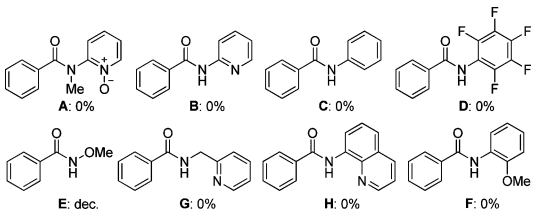
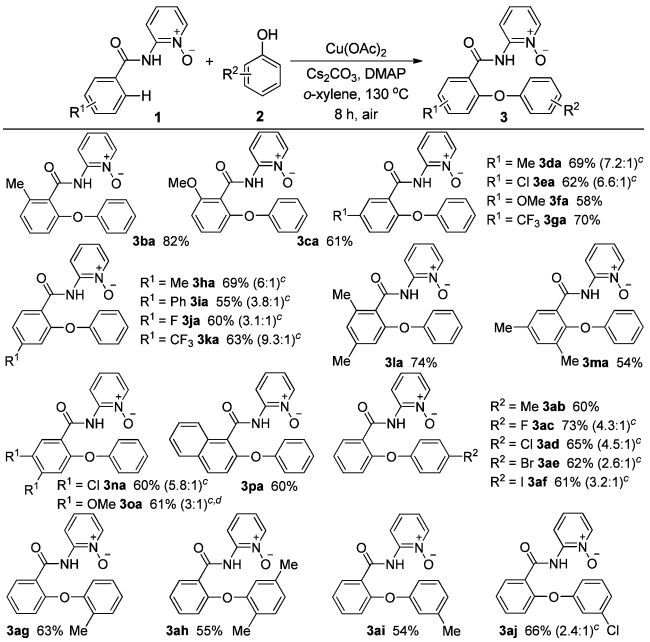


Figure 1. Directing groups for aryloxylation of C−H bonds.

similar but monodentate directing groups (**A**−**E**) highlighted the key role of the *N,O*-bidentate coordinating group. In addition, other *N,N*- or *N,O*-bidentate directing groups such as 2-pyridinylmethylamine (**G**) and 2-methoxyaniline (**F**) could not promote this reaction either. Notably, 8-aminoquinoline (**H**) was found to be inefficient under the current reaction conditions.

The scope of the reaction with respect to monoaryloxylation of benzamide substrates was subsequently examined under the optimized conditions A (Scheme 2). Evaluation of substituted

Scheme 2. C−H Monoaryloxylation of Benzoic Acid Derivatives[a,b]



[a]Conditions A: same reaction conditions as Table 1, entry 4. [b]Yields correspond to the monoaryloxylated products. The ratio of mono/di is in parentheses and determined by ^{1}H NMR analysis of the crude reaction mixture; mono- and diaryloxylated products were readily separated by silica gel column chromatography. See the Supporting Information for details. Pyridine solvent.

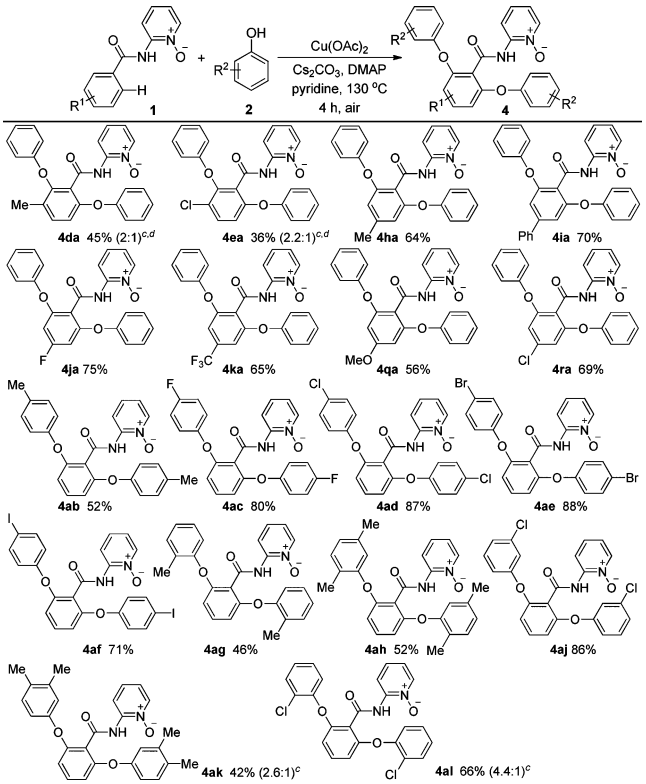
amides established that the reaction is compatible with electronically and sterically diverse substituents at the *ortho*, *meta*, and *para* positions of the phenyl ring including trifluoromethyl, methoxy, fluoro, and chloro functional groups. For *ortho*-substituted substrates **1b**,**c**, single monoaryloxylation products were isolated in yields of 82% and 61%. When non-*ortho*-substituted benzoic acid derivatives **1d**−**k** were used, the reaction afforded both mono- and diaryloxylated species with the former as main products; reactions of *meta*-substituted amides **1d**−**g** revealed high regioselectivity in favor of activation of the sterically less hindered C−H bonds. Moreover,

dx.doi.org/10.1021/ol500166d | Org. Lett. XXXX, XXX, XXX−XXX

disubstituted substrates **1l–o** bearing methyl, methoxy, or chloro groups provided the corresponding product in moderate to good yield (**3la–oa**). The naphthyl substrate could be successfully employed in 60% yield with single selectivity (**3pa**). Different substituted phenols were also investigated, and the reaction provided the desired product regardless of electronic and steric properties of substituents (**3ab–aj**). Notably, the fluoro, chloro, bromo, and even iodo moieties on amides or phenols were all well tolerated under these reaction conditions, providing a complementary platform for further transformation through cross-coupling reactions.

The diaryloxylation of various amides with phenols was next tested, and representative results are illustrated in Scheme 3.

Scheme 3. C–H Diaryloxylation of Benzoic Acid Derivatives[a,b]

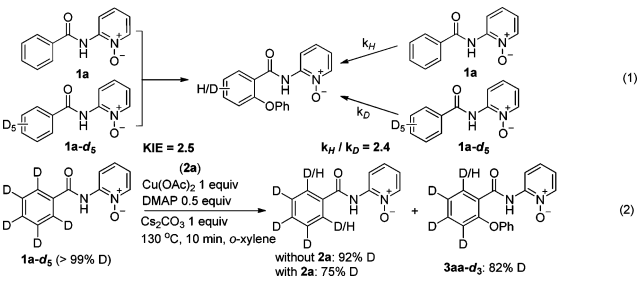


[a]Conditions B: same reaction conditions as Table 1, entry 9. [b]Yields correspond to the diaryloxylated products. The ratio of di/mono is in parentheses and determined by ^{1}H NMR analysis of the crude reaction mixture; mono- and diaryloxylated products were readily separated by silica gel column chromatography. Please see Supporting Information for details. The mono-C6-substituted product.

Similar to monoaryloxylation, amides with a broad substitution pattern and of different electronic nature were tolerated. Lower yields and regioselectivities were observed for *meta*-substituted amides **1a** and **1c**, likely due to steric effects. Nonetheless, the diaryloxylated products **4da** and **4ea** could still be isolated in reasonable yields (45% and 36%, respectively). Not unexpectedly, good results were obtained with *para*-substituted substrates; in all cases examined, double *o*-C–H bonds were activated (**4ha–ra**), and no monoaryloxylated products were observed. This reactivity was also observed in various phenols bearing electron-donating and -withdrawing groups, affording the single biaryloxylated products with good yield (**4ab–aj,al**). Importantly, this protocol was highly compatible with not only fluoro, chloro, and bromo but also the more challenging iodide to afford the highly valuable halo-substituted benamides. Additionally, multisubstituted products could also be obtained in moderate yield, and the reaction of sterically hindered phenols was slightly disfavored (**4ah,ak**). These reactions are particularly notable as the preparation of such 2,6-diphenoxybenzoic acid derivatives appears to be difficult through the cross-coupling reaction of benzene halides and phenols.[20]

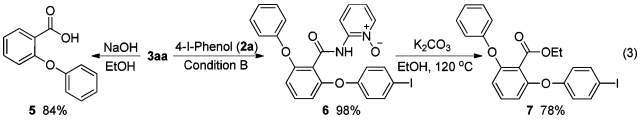
Further studies were performed to obtain insight into the mechanism (Scheme 4). The presence of 2,2,6,6-tetramethylpi-

Scheme 4. Deuteration and Isotope Effect Experiments



peridine-*N*-oxyl (TEMPO, 1 equiv) as a radical scavenger had a negligible effect on the reaction outcome under conditions A (65% yield of **3aa**), which ruled out the possibility of a radical mechanism proposed by Yu. Next, a deuteration experiment was conducted for 10 min under otherwise standard reaction conditions A (Scheme 4). Treatment of a 1:1 mixture of **1a** and **1a**-d_5 provided a kinetic isotopic effect (KIE) of 2.5, thus indicating that the C–H activation process came into play. Moreover, a similar KIE was obtained from the comparison of the initial rates of **1a** and the aryl-d_5 substrate **1a**-d_5 (k_H/k_D = 2.4, Scheme 4, eq 1), suggesting that the C–H bond cleavage was involved in the rate-determining step (Scheme 4, eq 1). In addition, the H/D exchange reaction of **1a**-d_5 was performed in both the absence and presence of **2a**, and a significant loss of deuterium content was found in the presence of **2a** (Scheme 4, eq 2). These observations suggest that the cleavage of C–H bond is reversible, and in the absence of **2a**, an equilibrium between substrate + copper and the *ortho*-metalated species might be in operation for the initial stage of the reaction. On the basis of the above results and Stahl's work on Cu(II)-mediated oxidation of aryl C–H bonds,[21] it seems reasonable to speculate that the reaction proceeds via a CNO-pincer Cu(III) intermediate, although the mechanism of the reaction is unclear at present.

Finally, we showed that the 2-aminopyridine 1-oxide motif can be efficiently removed from the monophenoxylated product **3aa** in a one-step procedure (eq 3). In addition, **3aa**



could be obtained on a 2 mmol scale in 68% yield, which revealed a bench-scale preparation. Coupling of **3aa** with 4-iodophenol provided the bis-diaryl ether **6** in 98% yield. The 2-aminopyridine 1-oxide auxiliary can also be removed by ethanolysis affording the corresponding ethyl ester **7** in 78% yield. This result illustrates an alternative method to prepare nonsymmetrical diaryloxylated benzoic acids.

dx.doi.org/10.1021/ol500166d | Org. Lett. XXXX, XXX, XXX–XXX

In conclusion, we have demonstrated that the readily available 2-aminopyridine 1-oxide can be used as an efficient *N*,*O*-bidentate directing group for the direct copper-mediated aryloxylation of arenes. The use of this new directing group enabled selective mono- or diaryloxylation of benzamide substrates, showing a further beneficial aspect of the bidentate auxiliary. This protocol presents a series of advantages, such as a broad substrate scope, cheaply available reagents, and convenient operating conditions, thus providing a straightforward way for the synthesis of *o*-aryloxylated benzoic acids. Further exploration of the synthetic utilities of this structurally new bidentate motif and in-depth mechanistic study are currently in progress.

■ ASSOCIATED CONTENT

Supporting Information

Experiment details and full spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: niujunlong@zzu.edu.cn.
*E-mail: mpsong@zzu.edu.cn.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We are grateful to the National Natural Science Foundation of China (Nos. 21072177 and 21272217) for financial support of this work.

■ REFERENCES

(1) (a) Evano, G.; Blanchard, N.; Toumi, M. *Chem. Rev.* **2008**, *108*, 3054. (b) Takeuchi, D.; Asano, I.; Osakada, K. *J. Org. Chem.* **2006**, *71*, 8614. (c) Wang, C.; Piel, I.; Glorius, F. *J. Am. Chem. Soc.* **2009**, *131*, 4194. (d) Maetani, S.; Fukuyama, T.; Ryu, I. *Org. Lett.* **2013**, *15*, 2754. (e) Campeau, L.-C.; Parisien, M.; Jean, A.; Fagnou, K. *J. Am. Chem. Soc.* **2006**, *128*, 581. (f) Zhang, H.; Shi, R.; Gan, P.; Liu, C.; Ding, A.; Wang, Q.; Lei, A. *Angew. Chem., Int. Ed.* **2012**, *51*, 5204.

(2) For recent reviews, see: (a) Ley, S. V.; Thomas, A. W. *Angew. Chem., Int. Ed.* **2003**, *42*, 5400. (b) Beletskaya, I. P.; Cheprakov, A. V. *Coord. Chem. Rev.* **2004**, 2337. (c) Ma, D.; Cai, Q. *Acc. Chem. Res.* **2008**, *41*, 1450. (d) Monnier, F.; Taillefer, M. *Angew. Chem., Int. Ed.* **2009**, *48*, 6954.

(3) Ullmann, F. *Ber. Dtsch. Chem. Ges.* **1904**, *37*, 853.

(4) For selected references, see: (a) Marcoux, J.-F.; Doye, S.; Buchwald, S. L. *J. Am. Chem. Soc.* **1997**, *119*, 10539. (b) Mann, G.; Hartwig, J. F. *Tetrahedron Lett.* **1997**, *46*, 8005. (c) Mann, G.; Incarvito, C.; Rheingold, A. L.; Hartwig, J. F. *J. Am. Chem. Soc.* **1999**, *121*, 3224. (d) Aranyos, A.; Old, D. W.; Kiyomori, A.; Wolfe, J. P.; Sadighi, J. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 4369. (e) Bistri, O.; Correa, A.; Bolm, C. *Angew. Chem., Int. Ed.* **2008**, *47*, 586. (f) Kim, H. J.; Kim, M.; Chang, S. *Org. Lett.* **2011**, *13*, 2368. (g) Zheng, X.; Ding, J.; Chen, J.; Gao, W.; Liu, M.; Wu, H. *Org. Lett.* **2011**, *13*, 1726.

(5) For some recent reviews of C−H functionalization, see: Chen, X.; Engle, K. M.; Wang, D.-H.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2009**, *48*, 5094. See the Supporting Information for complete citations.

(6) Enthaler, S.; Company, A. *Chem. Soc. Rev.* **2011**, *40*, 4912.

(7) For selected references, see: (a) Liu, W.; Ackermann, L. *Org. Lett.* **2013**, *15*, 3484. (b) Yan, Y.; Feng, P.; Zheng, Q.-Z.; Liang, Y.-F.; Lu, J.-F.; Cui, Y.; Jiao, N. *Angew. Chem., Int. Ed.* **2013**, *52*, 5827. (c) Shan, G.; Yang, X.; Ma, L.; Rao, Y. *Angew. Chem., Int. Ed.* **2012**, *51*, 13070. (d) Gulevich, A. V.; Melkonyan, F. S.; Sarkar, D.; Gevorgyan, V. *J. Am. Chem. Soc.* **2012**, *134*, 5528. (e) Bhadra, S.; Matheis, C.; Katayev, D.; Gooßen, L. J. *Angew. Chem., Int. Ed.* **2013**, *52*, 1. (f) Desai, L. V.; Stowers, K. J.; Sanford, M. S. *J. Am. Chem. Soc.* **2008**, *130*, 13285. (g) Wang, G.-W.; Yuan, T.-T. *J. Org. Chem.* **2010**, *75*, 476.

(8) Kuram, M. R.; Bhanuchandra, M.; Sahoo, A. K. *Angew. Chem., Int. Ed.* **2013**, *52*, 4607.

(9) (a) Xiao, B.; Gong, T.-J.; Liu, Z.-J.; Liu, J.-H.; Luo, D.-F.; Xu, J.; Liu, L. *J. Am. Chem. Soc.* **2011**, *133*, 9250. (b) Wei, Y.; Yoshikai, N. *Org. Lett.* **2011**, *13*, 5504. (c) Zhao, J.; Wang, Y.; He, Y.; Liu, L.; Zhu, Q. *Org. Lett.* **2012**, *14*, 1078.

(10) Chen, X.; Hao, X.-S.; Goodhue, C. E.; Yu, J.-Q. *J. Am. Chem. Soc.* **2006**, *128*, 6790.

(11) While this manuscript was in preparation, Daugulis and co-workers reported the copper-catalyzed etherification of *meta*- or/and *para*-substituted arenes with picolinamide or 8-aminoquinoline directing groups: Roane, J.; Daugulis, O. *Org. Lett.* **2013**, *15*, 5842.

(12) For selected reviews involving removable or transformable directing groups, see: (a) Colby, D. A.; Bergman, R. G.; Ellman, J. A. *Chem. Rev.* **2010**, *110*, 624. (b) Rousseau, G.; Breit, B. *Angew. Chem., Int. Ed.* **2011**, *50*, 2450. (c) Lyons, T. W.; Sanford, M. S. *Chem. Rev.* **2010**, *110*, 1147. (d) Neufeldt, S. R.; Sanford, M. S. *Acc. Chem. Res.* **2012**, *45*, 936. (e) Song, G.; Wang, F.; Li, X. *Chem. Soc. Rev.* **2012**, *41*, 3651. (f) Arockiam, P. B.; Bruneau, C.; Dixneuf, P. H. *Chem. Rev.* **2012**, *112*, 5879. (g) Kozhushkov, S. I.; Ackermann, L. *Chem. Sci.* **2013**, *4*, 886.

(13) Zaitsev, V. G.; Shabashov, D.; Daugulis, O. *J. Am. Chem. Soc.* **2005**, *127*, 13154.

(14) For a recent review on direct C−H functionalization through the aid of a bidentate directing group, see: Rouquet, G.; Chatani, N. *Angew. Chem., Int. Ed.* **2013**, *52*, 11726.

(15) For representative examples of palladium catalysis, see: (a) Reddy, B. V. S.; Reddy, L. R.; Corey, E. J. *Org. Lett.* **2006**, *8*, 3391. (b) Giri, R.; Maugel, N.; Foxman, B. M.; Yu, J.-Q. *Organometallics* **2008**, *27*, 1667. (c) Gou, F.-R.; Wang, X.-C.; Huo, P.-F.; Bi, H.-P.; Guan, Z.-H.; Liang, Y.-M. *Org. Lett.* **2009**, *11*, 5726. (d) Shabashov, D.; Daugulis, O. *J. Am. Chem. Soc.* **2010**, *132*, 3965. (e) Feng, Y.; Wang, Y.; Landgraf, B.; Liu, S.; Chen, G. *Org. Lett.* **2010**, *12*, 3414. See the Supporting Information for complete citations.

(16) Shang, R.; Ilies, L.; Matsumoto, A.; Nakamura, E. *J. Am. Chem. Soc.* **2013**, *135*, 6030.

(17) (a) Aihara, Y.; Chatani, N. *J. Am. Chem. Soc.* **2013**, *135*, 5308. (b) Shiota, H.; Ano, Y.; Aihara, Y.; Fukumoto, Y.; Chatani, N. *J. Am. Chem. Soc.* **2011**, *133*, 14952. (c) Inoue, S.; Shiota, H.; Fukumoto, Y.; Chatani, N. *J. Am. Chem. Soc.* **2009**, *131*, 6898. (d) Aihara, Y.; Chatani, N. *Chem. Sci.* **2013**, *4*, 664. (e) Rouqueta, G.; Chatani, N. *Chem. Sci.* **2013**, *4*, 2201.

(18) (a) Truong, T.; Klimovica, K.; Daugulis, O. *J. Am. Chem. Soc.* **2013**, *135*, 9342. (b) Tran, L. D.; Roane, J.; Daugulis, O. *Angew. Chem., Int. Ed.* **2013**, *52*, 6043. (c) Tran, L. D.; Popov, I.; Daugulis, O. *J. Am. Chem. Soc.* **2012**, *134*, 18237. (d) Nishino, M.; Hirano, K.; Satoh, T.; Miura, M. *Angew. Chem., Int. Ed.* **2013**, *52*, 4457.

(19) Our group has recently been working on the new pincer metal catalysts via the direct metal-induced C_{aryl}−H bond activation. For a brief review, see: (a) Niu, J.-L.; Hao, X.-Q.; Gong, J.-F.; Song, M.-P. *Dalton Trans.* **2011**, *40*, 5135. For recent publications, see: (b) Hao, X.-Q.; Xu, Y.-X.; Yang, M.-J.; Wang, L.; Niu, J.-L.; Gong, J.-F.; Song, M.-P. *Organometallics* **2012**, *31*, 835. (c) Wang, T.; Hao, X.-Q.; Huang, J.-J.; Niu, J.-L.; Gong, J.-F.; Song, M.-P. *J. Org. Chem.* **2013**, *78*, 8712. (d) Wang, T.; Niu, J.-L.; Liu, S.-L.; Huang, J.-J.; Gong, J.-F.; Song, M.-P. *Adv. Synth. Catal.* **2013**, *355*, 927.

(20) Kalinin, A. V.; Bower, J. F.; Riebel, P.; Snieckus, V. *J. Org. Chem.* **1999**, *64*, 2986.

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