

See discussions, stats, and author profiles for this publication at: <https://www.researchgate.net/publication/261254460>

ChemInform Abstract: Pd(II)–Catalyzed Intermolecular Arylation of Unactivated C(sp³)–H Bonds with Aryl Bromides Enabled by 8–Aminoquinoline Auxiliary.

ARTICLE in ORGANIC LETTERS · MARCH 2014

Impact Factor: 6.36 · DOI: 10.1021/ol500745t · Source: PubMed

CITATIONS

32

READS

22

6 AUTHORS, INCLUDING:



Chao wu

Xi'an Jiaotong University

29 PUBLICATIONS 355 CITATIONS

SEE PROFILE



Xiaoming Zeng

Xi'an Jiaotong University

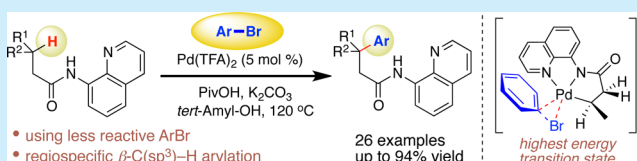
30 PUBLICATIONS 729 CITATIONS

SEE PROFILE

Pd(II)-Catalyzed Intermolecular Arylation of Unactivated C(sp³)-H Bonds with Aryl Bromides Enabled by 8-Aminoquinoline AuxiliaryYu Wei,^{†,§} Huarong Tang,^{‡,§} Xuefeng Cong,[†] Bin Rao,[†] Chao Wu,^{*,†} and Xiaoming Zeng^{*,†}[†]Center for Organic Chemistry and Materials Physics Center, Frontier Institute of Science and Technology, [‡]School of Materials Science and Engineering, Xi'an Jiaotong University, Xi'an, Shaanxi, 710054, P. R. China

S Supporting Information

ABSTRACT: An example of using readily available, less reactive aryl bromides as arylating reagents in the Pd(II)-catalyzed intermolecular arylation of unactivated C(sp³)-H bonds is described. This reaction was promoted by a crucial 8-aminoquinolinyl directing group and a K₂CO₃ base, enabling regioselective installation of an aryl scaffold at the β-position of carboxamides. A mechanistic study by DFT calculations reveals a C(sp³)-H activation-led pathway featuring the oxidative addition as the highest energy transition state.



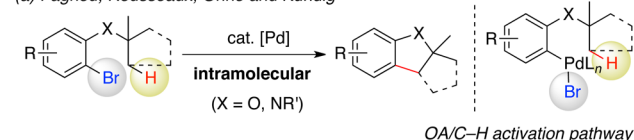
The direct functionalization of alkanes is fundamentally important to organic synthesis.¹ In particular, transition-metal-catalyzed intermolecular arylation of alkanes, which couples unactivated sp³-hybridized C-H bonds with aryl moieties, is recognized as one of the most powerful strategies to construct valuable arylated alkyl scaffolds.² Progress in the field has been achieved via chelation-assisted C(sp³)-H activation,^{3–5} typically relying on palladium catalysis reported by Daugulis,⁶ Yu,⁷ Chen,⁸ and others.⁹ Iron- and nickel-catalyzed versions were also developed by Nakamura and Chatani.¹⁰ However, such a useful strategy continues to pose significant challenges and these reactions are limited to relative activated aryl substrates such as iodoarenes,^{6,7c,d,8,9b–d,10b} prefunctionalized arylboronic reagents,^{7a,b,e} organozinc,^{10a} and hyperiodonium salts.^{9a} To develop a general procedure, there is a high demand to explore challenging transformations using unreactive aryl partners.

Aryl bromides are an important class of arylating reagents that are readily available, easy to handle, and cost-attractive. Although palladium-catalyzed intramolecular C(sp³)-H bond arylation with aryl bromides has been achieved (Scheme 1a),¹¹ methods using these electrophiles to convert unactivated C(sp³)-H bonds to C(sp³)-aryl bonds by an intermolecular coupling still remain to be disclosed. Herein, we report an intermolecular arylation that uses aryl bromides to enable regioselective coupling with unactivated C(sp³)-H bonds, by the assistance of a directing group and Pd(II) catalytic system (Scheme 1b).¹² In general, the use of less reactive aryl bromides could largely improve the practicality with broad applicability. It provides an alternative approach for the arylation of alkanes and enriches the limited types of C(sp³)-H bond activation.^{3–5}

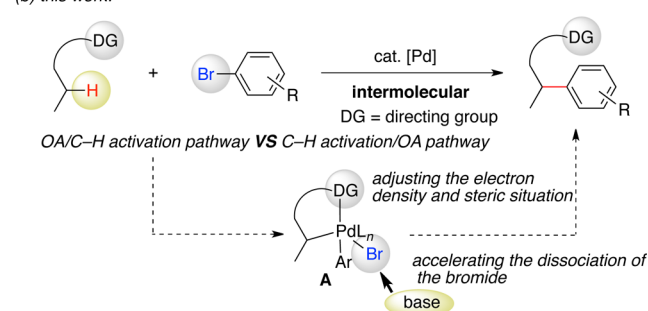
As compared with the known iodoarene-based arylation,^{6,7c,d,8,9b–d,10b} a considerable challenge for this new transformation is that aryl bromides are less facile for the oxidative addition (OA) to the formation of a high-valent Pd species such as Pd(IV). Apart from the inherent unreactive nature of aryl bromides, the electronic properties of Pd catalysts

Scheme 1. Palladium-Catalyzed Arylation of Unactivated C(sp³)-H Bonds with Aryl Bromides

(a) Fagnou, Rousseaux, Ohno and Kündig



(b) this work:



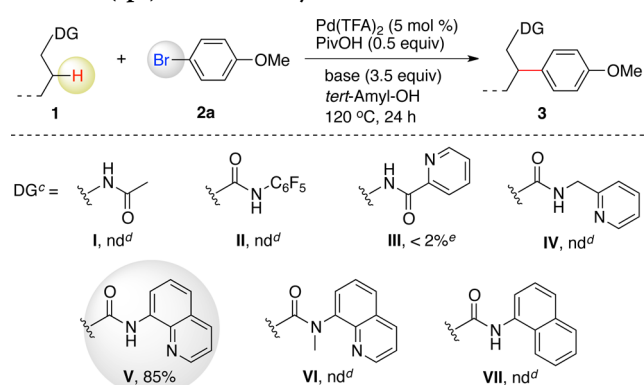
may have a prominent influence for insertion of the C(sp²)-Br bonds. We assumed that a suitable directing group on the substrates may not only assist the cleavage of C(sp³)-H bonds but also adjust the electron density and steric situation around the Pd center, allowing the OA to proceed smoothly, while an appropriate base can accelerate the dissociation of the bromide from Pd by replacement with the anion to deliver active catalytic species (Scheme 1b).

To test our hypothesis, at the outset the effect of directing groups was investigated by treatment of 4-bromoanisole with various directing-group-possessing alkanes (Table 1). In the presence of Pd(TFA)₂ as a catalyst, K₂CO₃ as a base, and pivalic acid as an additive, the C(sp³)-H bond arylation of

Received: March 11, 2014

Published: March 31, 2014

Table 1. Evaluation the Effect of Directing Groups and Bases for the C(sp³)–H Bond Arylation^{a,b}



entry ^f	DG	base	yield (3a)
1	V	K ₂ CO ₃	80%
2	V	KHCO ₃	79%
3	V	Na ₂ CO ₃	19%
4	V	K ₃ PO ₄	14%
5	V	KOAc	18%
6	V	KF	27%
7	V	CsF	36%
8	V	Cs ₂ CO ₃	nd ^c
9	V	NaO ^t Bu	nd ^c
10	V	AgOAc	nd ^c

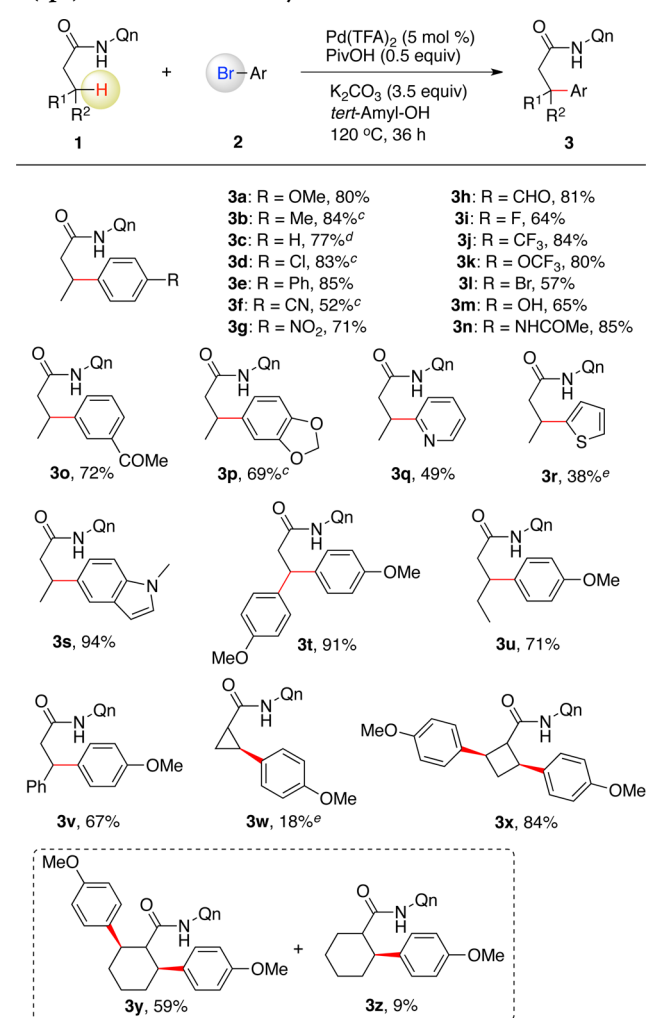
^aReaction conditions: **1** (0.1 mmol), **2a** (0.4 mmol), Pd(TFA)₂ (0.005 mmol), base (0.35 mmol), PivOH (0.05 mmol), *tert*-Amyl-OH (0.2 mL), 120 °C, 24 h. ^b¹H NMR yield using 1,1,2,2-tetrachloroethane as an internal standard. ^cK₂CO₃ was employed as the base. ^dNot detected. ^eGC yield. ^fPd(TFA)₂ (0.01 mmol) and *tert*-Amyl-OH (0.5 mL) were used in these entries.

monodentate amides (**I** and **II**) does not occur. *N,N*-Bidentate picolinamide (**III**) provides the β -selective arylation product in a trace amount of yield. Gratifyingly, the use of carboxamide bearing an 8-aminoquinolinyl moiety (**V**), a highly useful bidentate directing group discovery by Daugulis,^{6a,13} significantly improves the transformation, affording the β -arylated product **3a** in 85% NMR yield. This may be ascribed to the rigid and planar bidentate structural feature of 8-aminoquinolinyl, assisting the reaction to occur. In contrast, *N*-methyl-protected and *N*-naphthalenyl carboxamides (**VI** and **VII**) fail to give the arylation products.

The catalyst screening shows that Pd(TFA)₂ is superior to Pd(OAc)₂, PdCl₂, Pd(PPh₃)₂Cl₂, and Pd(dba)₂ in the reaction.¹⁴ Note that the base heavily influences the conversion. K₂CO₃ and KHCO₃ proved to be suitable bases in this case (Table 1). Other bases such as Na₂CO₃, K₃PO₄, KOAc, and CsF give lower performance. Whereas Cs₂CO₃, NaO^tBu, and AgOAc inhibited the reaction. These results indicate that a combination of potassium and carbonate is required to improve the transformation; it may accelerate the dissociative replacement of the bromide in the catalysis. Replacing pivalic acid with AcOH, TfOH, and CF₃CO₂H results in lower yields.¹⁴ A high concentration favors the conversion. Note that with the exception of a different Pd(II) catalyst, our optimized arylation conditions are analogous to those of the C(sp³)–H alkylation described by Daugulis, where the corresponding arylation products from aryl bromides were not obtained.^{6d}

The scope of the sp³ C–H bond arylation is illustrated in Scheme 2. Various electron-rich and -deficient aryl bromides

Scheme 2. Pd-Catalyzed Intermolecular Arylation of C(sp³)–H Bonds with Aryl Bromides^{a,b}



^aReaction conditions: **1** (0.3 mmol), **2** (1.2 mmol), Pd(TFA)₂ (0.015 mmol), K₂CO₃ (1.05 mmol), PivOH (0.15 mmol), *tert*-Amyl-OH (0.5 mL), 120 °C, 36 h. Qn = quinolin-8-yl. ^bIsolated yield. ^c24 h. ^d130 °C. ^e140 °C.

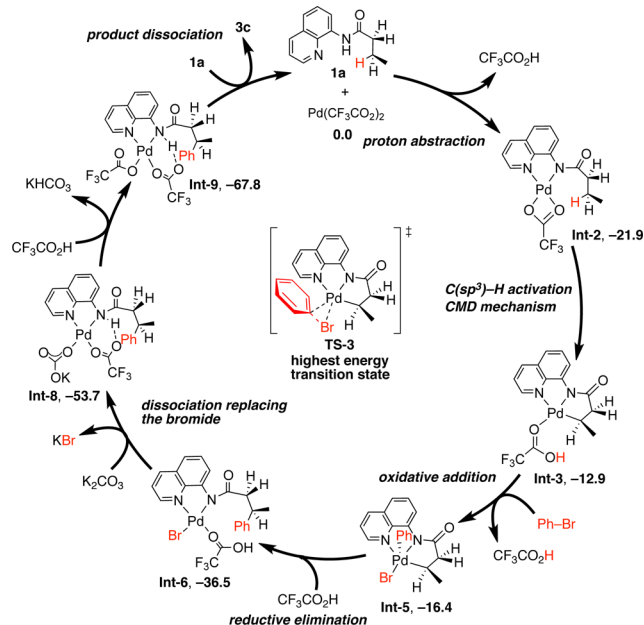
allow regiospecific coupling with unactivated C(sp³)–H bonds, giving β -arylated products (**3a–3o**) in good to excellent yields (52–85%). A broad range of functional groups such as fluoride, chloride, alkoxy, aldehyde, alkoxy carbonyl, hydroxyl, cyano, nitro, and amide are well tolerated. Interestingly, the use of 1,4-dibromobenzene provides an unexpected product **3l** in which one of the bromo substituents is retained, which provides an opportunity for postsynthetic functionalization. Synthetically valuable heteroaromatic scaffolds, including benzodioxolyl, pyridyl, thienyl, and indolyl, are successfully incorporated into the alkyl scaffolds of carboxamides (**3p–3s**).

Encouraged by these results, the variation of the alkyl substituents on the carboxamides was probed next. Interestingly, ethanecarboxamide generates diarylated product **3t** in excellent yield (91%). Replacing the ethyl substituent with *n*-butyl and phenylethyl groups results in monoarylation products **3u** and **3v**. We were pleased to find that cycloalkyl-bearing carboxamides are suitable substrates in the transformation. Compared with cyclopropanecarboxamide (**3w**), cyclobutyl-substituted carboxamide furnishes the β,β' -diarylated compound **3x** in good yield (84%). In contrast, the formation of

mixed mono- and diarylated products (**3y** and **3z**) in a 6.5:1 ratio was observed when using cyclohexanecarboxamide.

To reveal a feasible pathway between two distinct OA/C(sp³)–H activation sequences (Scheme 1b), density functional theory (DFT) was performed using the reaction of **1a** with bromobenzene as a model.¹⁴ The 8-aminoquinolinyl group on the substrate initially serves as an L- and X-type ligand to bind to Pd(II) by a proton abstraction, followed by the cleavage of the β -C(sp³)–H bond via a concerted metalation–deprotonation (CMD) mechanism (Scheme 3).

Scheme 3. Proposed Mechanism with DFT Study^a



^aThe values are given in kcal mol⁻¹.

It is worth noting that the following OA step was found to have the overall highest energy transition state TS-3 (Figure 1, path

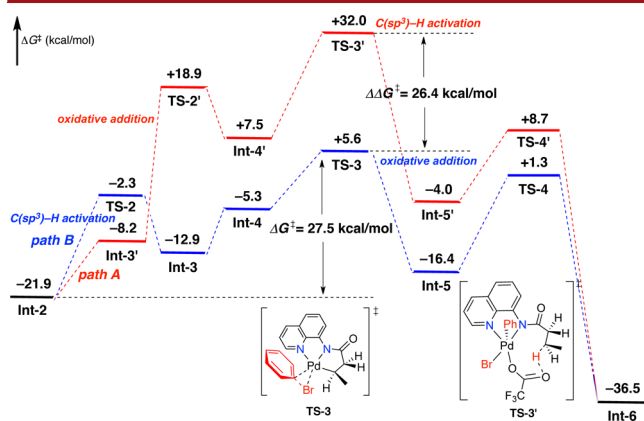
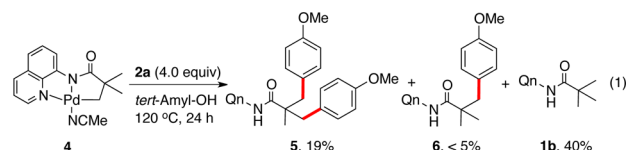


Figure 1. Free energy profiles for competing paths A and B.

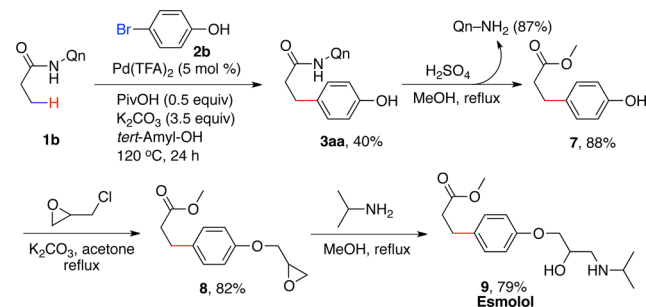
B), which implies a difficult OA process for insertion of aryl bromide into Pd(II). Then the C(sp³)–phenyl bond can be formed by a reductive elimination. The K₂CO₃ base facilitates the dissociative replacement of the bromide with the carbonate by an endothermic process, giving a carbonate-bound species Int-8, which liberates the arylation product **3c** by two consecutive ligand exchanges.

In contrast, the reaction by path A has the overall highest energy transition state TS-3' of 32.0 kcal/mol for the C(sp³)–H activation step, which is 26.4 kcal/mol higher than that of the related OA in path B (Figure 1).¹⁴ Such a bigger energy gap ($\Delta\Delta G^\ddagger = 26.4$ kcal/mol) suggests that the transformation through path B is energetically more feasible and is probably involved in the reaction. A controlling experiment by treatment of the bicyclic Pd(II) species **4** with aryl bromide also evidences the feasibility of this reaction pathway (eq 1).



To demonstrate its utility in synthesis, we explored the possibility of using this method for the concise synthesis of valuable derivatives. Owing to its good compatibility with the hydroxyl group, the arylation of ethanecarboxamide **1b** and 4-bromophenol allows easy production of the arylation product **3aa**, and then the 8-aminoquinolinyl on the auxiliary can be removed in H₂SO₄/MeOH (Scheme 4). The resulting methyl ester **7** can undergo the cross-coupling and ring-opening processes, giving rise to the cardioselective β -blocker drug molecule Esmolol **9**.¹⁵

Scheme 4. Synthesis of Drug Molecule Esmolol



In summary, we have developed an efficient intermolecular arylation of unactivated C(sp³)–H bonds with aryl bromides. The ability to use less reactive, cost-attractive aryl bromides is a particular feature of this protocol. Further benefits include complete β -site selectivity, a broad substrate scope, and high compatibility with various important functional groups. The use of an 8-aminoquinolinyl directing group and an appropriate K₂CO₃ base is crucial to achieve this reaction. With a mechanism unlike that of the intramolecular arylation of aryl bromides (Scheme 1a),^{11c} the present transformation may occur by an energetically feasible C(sp³)–H activation-led pathway, having the highest energy transition state for the OA step. Kinetic experiments to investigate the effect of substitutions are ongoing.

■ ASSOCIATED CONTENT

Supporting Information

Detailed optimization data; experimental procedures; characterization data of all new compounds; detailed optimized geometries and free energies. This material is available free of charge via the Internet at <http://pubs.acs.org>.

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: zengxiaoming@mail.xjtu.edu.cn.

*E-mail: chaowu@mail.xjtu.edu.cn.

Author Contributions

[§]Y.W. and H.T. contributed equally.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

Support for this work by the National Natural Science Foundation of China [Nos. 21202128 (X.Z.), 21203143 (C.W.)] and XJTU is gratefully acknowledged.

■ REFERENCES

- (1) (a) Jia, C.; Kitamura, T.; Fujiwara, Y. *Acc. Chem. Res.* **2001**, *34*, 633. (b) *Transition Metal-Catalyzed Functionalization of Alkanes*; Pérez, P. J., Ed.; Catalysis by Metal Complexes 38; Springer Science: Dordrecht, 2012.
- (2) (a) Ackermann, L. *Modern Arylation Methods*; Wiley-VCH: Weinheim, 2009. (b) Yu, J.-Q.; Shi, Z.-J. *Topics in Current Chemistry*; Springer: Heidelberg, 2010; Vol. 292. For selected reviews on arylation, see: (c) Bellina, F.; Rossi, R. *Chem. Rev.* **2010**, *110*, 1082. (d) Ackermann, L.; Vicente, R.; Kapdi, A. R. *Angew. Chem., Int. Ed.* **2009**, *48*, 9792. (e) Culkin, D. A.; Hartwig, J. F. *Acc. Chem. Res.* **2003**, *36*, 234.
- (3) For selected reviews on C(sp³)-H activation, see: (a) Godula, K.; Sames, D. *Science* **2006**, *312*, 67. (b) Daugulis, O.; Do, H.-Q.; Shabashov, D. *Acc. Chem. Res.* **2009**, *42*, 1074. (c) Chen, X.; Engle, K. M.; Wang, D.-H.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2009**, *48*, 5094. (d) Wasa, M.; Engle, K. M.; Yu, J.-Q. *Isr. J. Chem.* **2010**, *50*, 605. (e) Jazzar, R.; Hitce, J.; Renaudat, A.; Sofack-Kreutzer, J.; Baudoin, O. *Chem.—Eur. J.* **2010**, *16*, 2654. (f) Lyons, T. W.; Sanford, M. S. *Chem. Rev.* **2010**, *110*, 1147. (g) Li, H.; Li, B.-J.; Shi, Z.-J. *Catal. Sci. Technol.* **2011**, *1*, 191. (h) Li, B.-J.; Shi, Z.-S. *Chem. Soc. Rev.* **2012**, *41*, 5588. (i) Baudoin, O. *Chem. Soc. Rev.* **2011**, *40*, 4902.
- (4) Rouquet, G.; Chatani, N. *Angew. Chem., Int. Ed.* **2013**, *52*, 11726.
- (5) For selected recent examples on C(sp³)-H activation, see: (a) He, J.; Wasa, M.; Chan, K. S. L.; Yu, J.-Q. *J. Am. Chem. Soc.* **2013**, *135*, 3387. (b) Zhang, S.-Y.; Li, Q.; He, G.; Nack, W. A.; Chen, G. *J. Am. Chem. Soc.* **2013**, *135*, 12135. (c) Zhang, S.-Y.; He, G.; Nack, W. A.; Zhao, Y.; Li, Q.; Chen, G. *J. Am. Chem. Soc.* **2013**, *135*, 2124. (d) He, G.; Zhao, Y.; Zhang, S.; Lu, C.; Chen, G. *J. Am. Chem. Soc.* **2012**, *134*, 3. (e) Ano, Y.; Tobisu, M.; Chatani, N. *J. Am. Chem. Soc.* **2011**, *133*, 12984. (f) Chen, F.-J.; Zhao, S.; Hu, F.; Chen, K.; Zhang, Q.; Zhang, S.-Q.; Shi, B.-F. *Chem. Sci.* **2013**, *4*, 4187. (g) Chen, K.; Hu, F.; Zhang, S.-Q.; Shi, B.-F. *Chem. Sci.* **2013**, *4*, 3906. (h) Shang, Y.; Jie, X.; Zhou, J.; Hu, P.; Huang, S.; Su, W. *Angew. Chem., Int. Ed.* **2013**, *52*, 1299.
- (6) (a) Zaitsev, V. G.; Shabashov, D.; Daugulis, O. *J. Am. Chem. Soc.* **2005**, *127*, 13154. (b) Shabashov, D.; Daugulis, O. *Org. Lett.* **2005**, *7*, 3657. (c) Shabashov, D.; Daugulis, O. *J. Am. Chem. Soc.* **2010**, *132*, 3965. (d) Nadres, E. T.; Santos, G. I. F.; Shabashov, D.; Daugulis, O. *J. Org. Chem.* **2013**, *78*, 9689. (e) Tran, L. D.; Daugulis, O. *Angew. Chem., Int. Ed.* **2012**, *51*, 5188.
- (7) (a) Giri, R.; Maugel, N.; Li, J.-J.; Wang, D.-H.; Breazzano, S. P.; Saunders, L. B.; Yu, J.-Q. *J. Am. Chem. Soc.* **2007**, *129*, 3510. (b) Wang, D.-H.; Wasa, M.; Giri, R.; Yu, J.-Q. *J. Am. Chem. Soc.* **2008**, *130*, 7190. (c) Wasa, M.; Engle, K. M.; Yu, J.-Q. *J. Am. Chem. Soc.* **2009**, *131*, 9886. (d) Wasa, M.; Chan, K. S. L.; Zhang, X.-G.; He, J.; Miura, M.; Yu, J.-Q. *J. Am. Chem. Soc.* **2012**, *134*, 18570. (e) Chan, K. S. L.; Wasa, M.; Chu, L.; Laforteza, B. N.; Miura, M.; Yu, J.-Q. *Nat. Chem.* **2014**, *6*, 146.
- (8) (a) He, G.; Chen, G. *Angew. Chem., Int. Ed.* **2011**, *50*, 5192. (b) Nack, W. A.; He, G.; Zhang, S.-Y.; Lu, C.; Chen, G. *Org. Lett.* **2013**, *15*, 3440.
- (9) (a) Pan, F.; Shen, P.-X.; Zhang, L.-S.; Wang, X.; Shi, Z.-J. *Org. Lett.* **2013**, *15*, 4758. (b) Zhang, Q.; Chen, K.; Rao, W.-H.; Zhang, Y.; Chen, F.-J.; Shi, B.-F. *Angew. Chem., Int. Ed.* **2013**, *52*, 13588. (c) Reddy, B. V. S.; Reddy, L. R.; Corey, E. J. *Org. Lett.* **2006**, *8*, 3391. (d) Gutekunst, W. R.; Baran, P. S. *J. Am. Chem. Soc.* **2011**, *133*, 19076.
- (10) (a) Shang, R.; Ilies, L.; Matsumoto, A.; Nakamura, E. *J. Am. Chem. Soc.* **2013**, *135*, 6030. (b) Aihara, Y.; Chatani, N. *J. Am. Chem. Soc.* **2014**, *136*, 898.
- (11) (a) Nakanishi, M.; Katayev, D.; Besnard, C.; Kündig, E. P. *Angew. Chem., Int. Ed.* **2011**, *50*, 7438. (b) Lafrance, M.; Gorelsky, S. I.; Fagnou, K. *J. Am. Chem. Soc.* **2007**, *129*, 14570. (c) Rousseaux, S.; Gorelsky, S. I.; Chung, B. K. W.; Fagnou, K. *J. Am. Chem. Soc.* **2010**, *132*, 10692. (d) Watanabe, T.; Oishi, S.; Fujii, N.; Ohno, H. *Org. Lett.* **2008**, *10*, 1759.
- (12) The example of Ni-catalyzed arylation using aryl bromides was recently disclosed. See: Li, M.; Dong, J.; Huang, X.; Li, K.; Wu, Q.; Song, F.; You, J. *Chem. Commun.* **2014**, *50*, 3944.
- (13) For selected reviews on the use of 8-aminoquinolyl as directing groups in C-H activation reactions, see: Reference 4 and (a) Corbet, M.; De Campo, F. *Angew. Chem., Int. Ed.* **2013**, *52*, 9896. For selected recent examples, see: (b) Asako, S.; Ilies, L.; Nakamura, E. *J. Am. Chem. Soc.* **2013**, *135*, 17755. (c) Matsubara, T.; Asako, S.; Ilies, L.; Nakamura, E. *J. Am. Chem. Soc.* **2014**, *136*, 646. (d) Aihara, Y.; Chatani, N. *J. Am. Chem. Soc.* **2013**, *135*, 5308. (e) Aihara, Y.; Chatani, N. *Chem. Sci.* **2013**, *4*, 664. (f) Wu, X.; Zhao, Y.; Ge, H. *J. Am. Chem. Soc.* **2014**, *136*, 1789. (g) Tran, L. D.; Roane, J.; Daugulis, O. *Angew. Chem., Int. Ed.* **2013**, *52*, 6043. (h) Song, M. S. W.; Lackner, M. S. S.; Ackermann, L. *Angew. Chem., Int. Ed.* **2014**, *53*, 2477.
- (14) Please see Supporting Information for more details.
- (15) Zhang, C. A.; Erhardt, P. W. *Synth. Commun.* **2012**, *42*, 722 and references cited therein.