JACS
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY
Communication
pubs.acs.org/JACS

α-Arylation of Saturated Azacycles and *N*-Methylamines via Palladium(II)-Catalyzed C(sp^3)−H Coupling

Jillian E. Spangler,[†] Yoshihisa Kobayashi,[‡] Pritha Verma,[†] Dong-Hui Wang,[†] and Jin-Quan Yu*[,†]

[†]Department of Chemistry, The Scripps Research Institute, 10550 North Torrey Pines Road, La Jolla, California 92037, United States
[‡]Medicinal Chemistry, Eisai Product Creation Systems, Eisai Co., Ltd., 5-1-3 Tokodai, Tsukuba-shi, Ibaraki 300-2635, Japan

Supporting Information

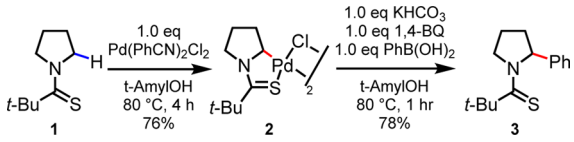
ABSTRACT: Pd(II)-catalyzed α-C(sp^3)−H arylation of pyrrolidines, piperidines, azepanes, and *N*-methylamines with arylboronic acids has been developed for the first time. This transformation is applicable to wide arrays of pyrrolidines and boronic acids, including heteroaromatic boronic acids. A diastereoselective one-pot heterodiarylation of pyrrolidines has also been achieved.

The prevalence of cyclic saturated amines in bioactive natural products and pharmaceutical compounds has led to significant interest in the functionalization of C(sp^3)−H bonds adjacent to nitrogen.[1] Important progress has been made in the direct arylation of cyclic amines through α-anion,[2] α-radical,[3−5] and α-cation[6] pathways. Extensive efforts at Merck led to the development of an elegant procedure for the enantioselective arylation of *N*-Boc-pyrrolidine via an asymmetric lithiation/Negishi coupling.[2d] In contrast, direct α-arylation through transition-metal-catalyzed C(sp^3)−H bond activation remains underdeveloped.[7−11] To date, all pioneering studies on metal-catalyzed arylation have employed low-valent Ru(0) catalysts, although the high reaction temperatures required for these transformations (120−150 °C) often lead to overarylation and poor stereocontrol. These methods also use heterocyclic directing groups that require multiple steps to remove.

In 2006, our group disclosed a method for the Pd-catalyzed C(sp^3)−H oxidation of *N*-methylcarbamates.[12] Our early efforts in this field, in conjunction with the high value of α-aryl cyclic amines, prompted us to develop a method for Pd-catalyzed α-C(sp^3)−H arylation of cyclic amines. Herein we report the discovery of a method for the direct Pd(II)-catalyzed α-C(sp^3)−H cross-coupling of pyrrolidines, piperidines, and azepanes with aryl- and heteroarylboronic acids, a rare example of the coupling of methylene C−H bonds with organometallic reagents. The excellent monoselectivity of this reaction also enables one-pot sequential diastereoselective diarylation.

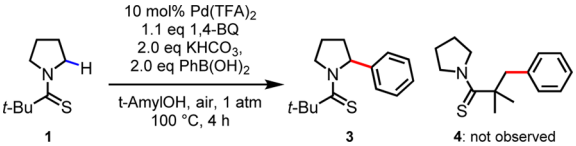
Although our initial efforts to achieve Pd-catalyzed α-C(sp^3)−H arylation with carbamate or heterocyclic directing groups were generally unsuccessful, we were inspired by a 1981 report of the cyclopalladation of *N*-alkylthioamides[13] to explore the α-C(sp^3)−H arylation of thioamides. We were pleased to find that palladacycle **2** can be formed as an air-stable yellow solid upon heating of thioamide **1** with stoichiometric $Pd(PhCN)_2Cl_2$ (Scheme 1). Moreover, **2** readily undergoes efficient cross-coupling with phenylboronic acids at 80 °C in *tert*-amyl alcohol in the presence of a mild base and stoichiometric 1,4-benzoquinone (1,4-BQ) to provide 2-phenylpyrrolidine **3** in 78% yield. This reaction can be conducted without exclusion of oxygen with no decrease in yield. Consistent with our early discovery of Pd(II)-catalyzed cross-coupling of C−H bonds with organotin reagents,[14] 1,4-BQ is essential as a promoter for reductive elimination, as no product formed without it.

Scheme 1. Stoichiometric Pyrrolidine α-Arylation



Upon further reaction development, we found that the formation of **2** and subsequent cross-coupling with phenylboronic acid can be rendered catalytic by treatment of **1** with 10 mol % $Pd(TFA)_2$ catalyst and 1,4-BQ (Table 1). We were pleased to find that the arylation is highly monoselective (>20:1 mono:diarylation). It is interesting to note that no functionaliza-

Table 1. Optimization of Amine α-Arylation



entry	deviation from standard conditions[a]	yield (%)[b]
1	none	82
2	10 mol % $PdCl_2(PhCN)_2$	63
3	10 mol % $PdCl_2$	57
4	10 mol % $Pd(OAc)_2$	7
5	10 mol % $Pd(OTf)_2$·MeCN	22
6	10 mol % (allyl)$PdCl_2$	37
7	no BQ	0
8	0.5 equiv of BQ	34
9	1.5 equiv of BQ	61
10	with 2.0 equiv of PhBPin	8
11	with 2.0 equiv of $PhBF_3K$	0

[a]Standard conditions: thioamide **1** (0.2 mmol, 1.0 equiv), arylboronic acid (0.4 mmol, 2.0 equiv), $Pd(TFA)_2$ (0.02 mmol, 0.1 equiv), 1,4-BQ (0.22 mmol, 1.1 equiv), $KHCO_3$ (0.4 mmol, 2.0 equiv), *t*-AmylOH (4.0 mL), 100 °C, 4 h. [b]Determined by ^1H NMR analysis of the crude products using mesitylene as the internal standard.

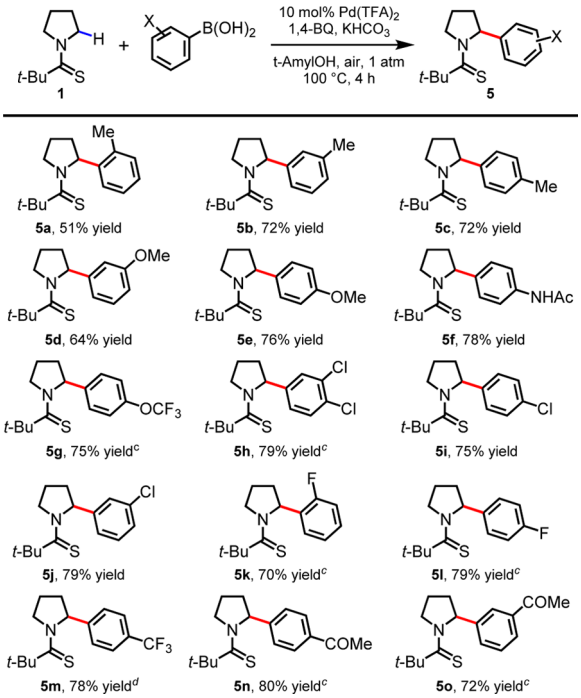
Received: July 6, 2015
Published: August 31, 2015

DOI: 10.1021/jacs.5b06740
J. Am. Chem. Soc. 2015, 137, 11876−11879

tion at the terminal methyl groups of the thioamide (**4**) was observed, despite significant precedent for the preferential activation of primary C−H bonds over secondary C−H bonds.[15] It is also surprising that our workhorse catalyst, $Pd(OAc)_2$, gave a negligible amount of product (entry 4). 1,4-BQ is also uniquely successful as the oxidant in this transformation because of facile oxidation of the thioamide with the other oxidants that we examined, including Ag(I) salts and peroxides; the resultant amide is an unreactive byproduct in this directed α-arylation.

With these optimized reaction conditions in hand, we next evaluated the arylboronic acid scope (Table 2). This C−H

Table 2. Pyrrolidine α-Arylation: Boronic Acid Scope[a,b]

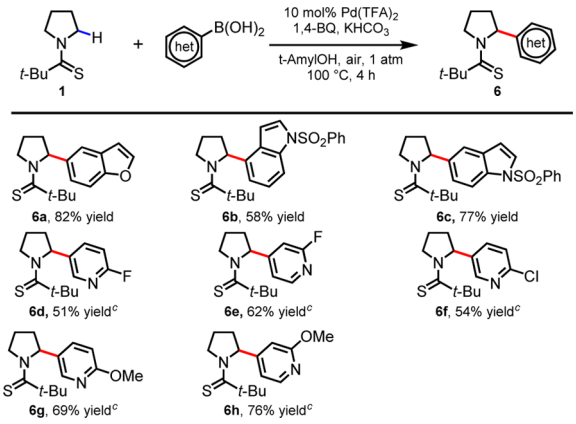


[a]Reaction conditions: thioamide **1** (0.2 mmol, 1.0 equiv), arylboronic acid (0.4 mmol, 2.0 equiv), $Pd(TFA)_2$ (0.02 mmol, 0.1 equiv), 1,4-BQ (0.22 mmol, 1.1 equiv), $KHCO_3$ (0.4 mmol, 2.0 equiv), *t*-AmylOH (4.0 mL), 100 °C, 4 h. [b]Yields after isolation by chromatography are shown. [c]1.2 equiv of 1,4-BQ. [d]1.4 equiv of 1,4-BQ.

arylation protocol is tolerant of a broad range of coupling partners, including both electron-rich (entries **5a**−**f**, 51−78% yield) and electron-poor (entries **5g**−**o**, 70−80% yield) boronic acids. However, the use of electron-rich boronic acids does lead to a slight increase in the formation of the corresponding diarylated product (4−8%). We were pleased to find that para-, meta-, and even sterically hindered ortho-substituted boronic acids (**5a** and **5k**, 51−70% yield) can all be effectively coupled. The reaction is tolerant of a range of functional groups, including ketones (**5n** and **5o**, 72−80% yield), amides (**5f**, 78% yield), ethers (**5e** and **5g**, 75−76% yield), and aryl halides (**5h**−**l**, 70−79% yield).

The relatively efficient coordination of the thioamide directing group with Pd(II) catalysts led us to speculate that this coupling reaction would be compatible with heteroarylboronic acids, which are generally challenging coupling partners in Pd-catalyzed $C(sp^3)$−H functionalization reactions because of their propensity to coordinate to the Pd catalyst. We were pleased to find that a broad range of heteroarylboronic acids react to provide α-heteroaryl pyrrolidines (Table 3). Electron-rich benzofuran- and indole-containing boronic acids are particularly good coupling

Table 3. Heteroarylboronic Acid Scope[a,b]



[a]Reaction conditions: thioamide **1** (0.2 mmol, 1.0 equiv), arylboronic acid (0.4 mmol, 2.0 equiv), $Pd(TFA)_2$ (0.02 mmol, 0.1 equiv), 1,4-BQ (0.22 mmol, 1.1 equiv), $KHCO_3$ (0.4 mmol, 2.0 equiv), *t*-AmylOH (4.0 mL), 100 °C, 4 h. [b]Yields after isolation by chromatography are shown. [c]3 equiv of 1,4-BQ.

partners, providing the corresponding pyrrolidine products in excellent yields (**6a**−**c**, 58−82% yield). A variety of substituted pyridinylboronic acids can be effectively coupled in good yields with complete monoselectivity (**6d**−**h**, 51−76% yield). However, the coupling of unsubstituted pyridinylboronic acids was not successful under the current conditions. Presumably, the pyridyl outcompetes the thioamide to coordinate with the Pd catalyst. Similar phenomena have been observed in asymmetric hydrogenation of 2-pyridyl cyclic imines.[16]

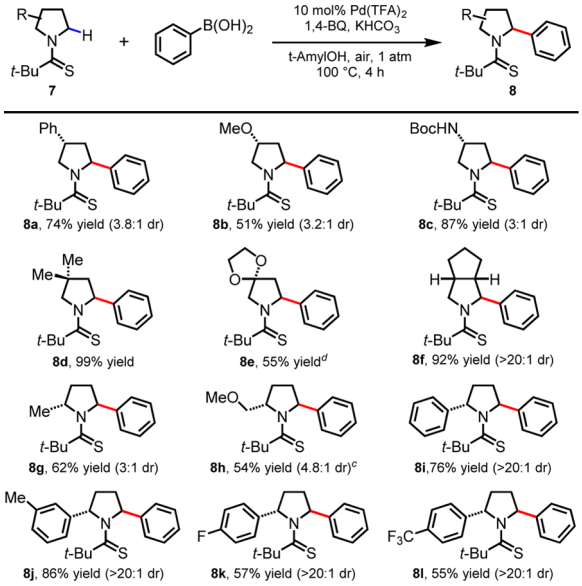
We next turned our attention to the pyrrolidine scope (Table 4). 3-Substituted (**8a**−**e**, 51−99% yield) and 2-substituted (**8g**−**l**, 54−86% yield) pyrrolidines couple efficiently in this transformation with moderate to high levels of diastereoselectivity. In all cases arylation occurs selectively at the less hindered α-methylene with preferential formation of the *trans* diastereoisomer.[17] An array of heteroatom-substituted pyrrolidines are tolerated (**8b**, **8c**, **8e**, and **8h**, 51−87% yield), and a bicyclo[3.3.0]pyrrolidine is also an effective substrate (**8f**, 92% yield). An array of 2,5-diaryl pyrrolidines can be synthesized using this protocol with extremely high levels of diastereoselectivity (**8i**−**l**, 55−86% yield, >20:1 dr). In accordance with our previous observation that electron-rich boronic acids lead to higher levels of diarylation, **8i** and **8j** (76−86% yield) showed higher reactivity than **8k** and **8l** (55−57% yield).

We subsequently found that this arylation can be extrapolated into a consecutive one-pot heterodiarylation to provide 2,5-diarylated pyrrolidines (Table 5). All of these reactions proceed with complete diastereoselectivity (>20:1 dr). Notably, this one-pot procedure does not require the addition of a second batch of Pd catalyst. We observed that the use of a more monoselective electron-deficient boronic acid in the first arylation step provides a higher yield of the heterodiarylated product with negligible formation of the undesired homodiarylated byproducts.

In examining the reactivity of other *N*,*N*-dialkylthioamides in our α-$C(sp^3)$−H arylation reaction (Table 6), we discovered that *N*-methylthioamides are also competent substrates in this transformation, affording the corresponding benzylthioamides in good yields (**11a**−**e**, 68−94% yield). The reaction of *N*-

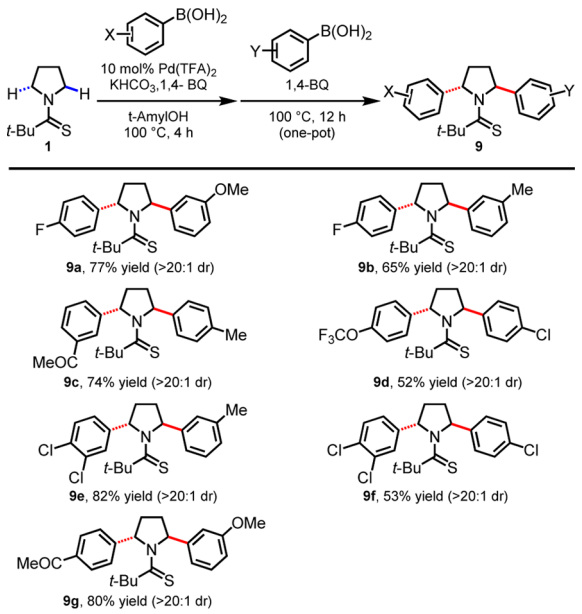
DOI: 10.1021/jacs.5b06740
J. Am. Chem. Soc. 2015, 137, 11876−11879

Table 4. Pyrrolidine Substrate Scope[a,b]



[a]Reaction conditions: thioamide **7** (0.2 mmol, 1.0 equiv), arylboronic acid (0.4 mmol, 2.0 equiv), $Pd(TFA)_2$ (0.02 mmol, 0.1 equiv), 1,4-BQ (0.4 mmol, 2.0 equiv), $KHCO_3$ (0.4 mmol, 2.0 equiv), *t*-AmylOH (4.0 mL), 100 °C, 4 h. [b]Yields after isolation by chromatography are shown. [c]0.15 equiv of $Pd(TFA)_2$ (0.03 mmol). [d]1.4 equiv of 1,4-BQ (0.28 mmol), 0.15 equiv of $Pd(TFA)_2$ (0.03 mmol).

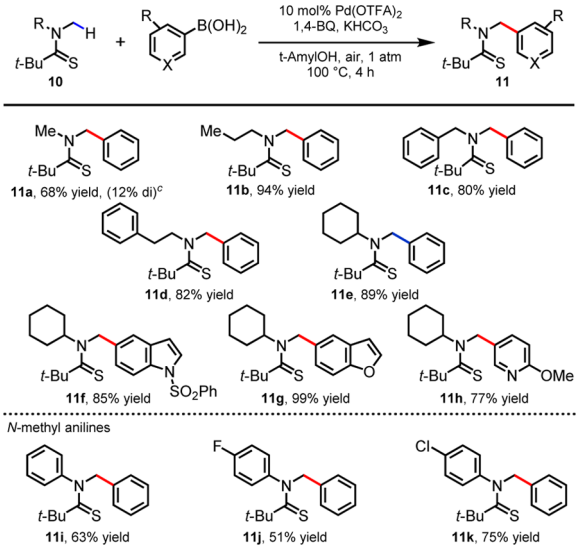
Table 5. One-Pot Heterodiarylation of Pyrrolidines[a,b]



[a]Reaction conditions: thioamide **1** (0.2 mmol, 1.0 equiv), arylboronic acid 1 (0.4 mmol, 2.0 equiv), $Pd(TFA)_2$ (0.02 mmol, 0.1 equiv), 1,4-BQ (0.28 mmol, 1.4 equiv), $KHCO_3$ (0.4 mmol, 2.0 equiv), *t*-AmylOH (4.0 mL), 100 °C, 4 h, then arylboronic acid 2 (0.4 mmol, 2.0 equiv), 1,4-BQ (0.4 mmol, 2.0 equiv), 12 h. [b]Yields after isolation by chromatography are shown; dr values were determined by ^1H NMR.

methylthioamides with both electron-rich and electron-deficient heteroarylboronic acids can also be achieved (**11f–h**, 77–99% yield). In all cases the reaction is completely regioselective; no methylene C(sp^3)–H arylation is observed. Surprisingly, *N*-methylanilines also undergo regioselective α-C(sp^3)–H arylation (**11i–k**, 51–75% yield) without reacting at the ortho positions of the aryl group.

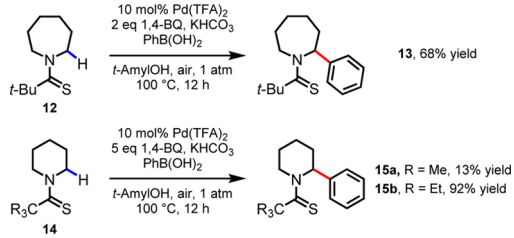
Table 6. Arylation of *N*-Methylamines[a,b]



[a]Reaction conditions: thioamide **10** (0.2 mmol, 1.0 equiv), arylboronic acid (0.4 mmol, 2.0 equiv), $Pd(TFA)_2$ (0.02 mmol, 0.1 equiv), 1,4-BQ (0.4 mmol, 2.0 equiv), $KHCO_3$ (0.4 mmol, 2.0 equiv), *t*-AmylOH (4.0 mL), 100 °C, 4 h. [b]Yields after isolation by chromatography are shown. [c]1.0 equiv of 1,4-BQ (0.2 mmol).

We also explored the application of our methodology to the arylation of larger azacycles. As shown in Scheme 2, azepane **12**

Scheme 2. Arylation of Larger Azacycles



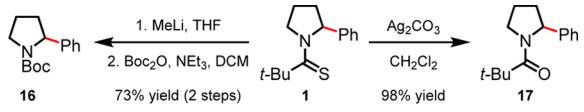
undergoes arylation in good yield under standard reaction conditions (**13**, 68% yield). In contrast, the arylation of piperidine **14a** proceeds in poor yield, even with addition of a large excess of 1,4-BQ (**15a**, 13% yield). Further studies demonstrated that while palladacycle formation from **14a** is facile, the reductive elimination is significantly slower than that from complex **2**. Thus, we hoped to optimize this transformation via the use of a more bulky thioamide directing group in order to promote reductive elimination.[18] We were pleased to find that the use of the bulky 2,2-diethylbutanoic acid directing group (**14b**) provides the corresponding product **15b** in excellent yield (92% yield) without the formation of any diarylated byproduct.

Finally, these arylated products can be readily deprotected by cleavage of the thioamide with methyllithium at 0 °C to give the corresponding amines in good yields after protection as the Boc-carbamates (e.g., **16**, 73% yield; Scheme 3).[19] Alternatively, thioamide **1** can be converted to amide **17** by oxidation with Ag(I) salts in nearly quantitative yield.

In conclusion, we have demonstrated the α-arylation of saturated azacycles and *N*-methylamines via Pd(II)-catalyzed C(sp^3)–H coupling with boronic acids. This method enables

DOI: 10.1021/jacs.5b06740
J. Am. Chem. Soc. 2015, 137, 11876–11879

Scheme 3. Thioamide Deprotection



highly monoselective arylation as well as sequential diastereoselective diarylation of pyrrolidines. The successful C−H coupling of pyrrolidines with arylboronic acids also demonstrates the first example of Pd-catalyzed cross-coupling of methylene C−H bonds with organometallic reagents.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.5b06740.

Crystallographic data for **9a** (CIF)
Experimental procedures and spectral data (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*yu200@scripps.edu

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank The Scripps Research Institute, EISAI Co., Ltd., and NIH NIGMS (2R01GM084019) for financial support and Dr. Richard Clark from Eisai for helpful discussions.

■ REFERENCES

(1) For reviews, see: (a) Campos, K. R. *Chem. Soc. Rev.* **2007**, *36*, 1069. (b) Mitchell, E. A.; Peschiulli, A.; Lefevre, N.; Meerpoel, L.; Maes, B. U. W. *Chem. - Eur. J.* **2012**, *18*, 10092.

(2) (a) Beak, P.; Kerrick, S. T.; Wu, S.; Chu, J. *J. Am. Chem. Soc.* **1994**, *116*, 3231. (b) Dieter, R. K.; Li, S. *Tetrahedron Lett.* **1995**, *36*, 3613. (c) Dieter, R. K.; Li, S. *J. Org. Chem.* **1997**, *62*, 7726. (d) Campos, K. R.; Klapars, A.; Waldman, J. H.; Dormer, P. G.; Chen, C.-Y. *J. Am. Chem. Soc.* **2006**, *128*, 3538. (e) Klapars, A.; Campos, K. R.; Waldman, J. H.; Zewge, D.; Dormer, P. G.; Chen, C.-Y. *J. Org. Chem.* **2008**, *73*, 4986. (f) Barker, G.; O'Brien, P.; Campos, K. R. *Org. Lett.* **2010**, *12*, 4176. (g) Barker, G.; McGrath, J. L.; Klapars, A.; Stead, D.; Zhou, G.; Campos, K. R.; O'Brien, P. *J. Org. Chem.* **2011**, *76*, 5936. (h) Seel, S.; Thaler, T.; Takatsu, K.; Zhang, C.; Zipse, H.; Straub, B. F.; Mayer, P.; Knochel, P. *J. Am. Chem. Soc.* **2011**, *133*, 4774. (i) Beng, T. K.; Gawley, R. E. *Org. Lett.* **2011**, *13*, 394. (j) Millet, A.; Larini, P.; Clot, E.; Baudoin, O. *Chem. Sci.* **2013**, *4*, 2241.

(3) (a) Murahashi, S.-I. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2443. (b) Li, Z.; Li, C. J. *J. Am. Chem. Soc.* **2004**, *126*, 11810. (c) Li, Z.; Li, C. J. *J. Am. Chem. Soc.* **2005**, *127*, 3672. (d) Catino, A. J.; Nichols, J. M.; Nettles, B. J.; Doyle, M. P. *J. Am. Chem. Soc.* **2006**, *128*, 5648. (e) Yoshikai, N.; Mieczkowski, A.; Matsumoto, A.; Ilies, L.; Nakamura, E. *J. Am. Chem. Soc.* **2010**, *132*, 5568. (f) Ratnikov, M. O.; Xu, X.; Doyle, M. P. *J. Am. Chem. Soc.* **2013**, *135*, 9475.

(4) For C−H coupling of tetrahydrofuran with arylboronic acids via radical abstraction, see: Liu, D.; Liu, C.; Li, H.; Lei, A. *Angew. Chem., Int. Ed.* **2013**, *52*, 4453.

(5) For α-arylation of amines via photoredox, see: (a) McNally, A.; Prier, C. K.; MacMillan, D. W. C. *Science* **2011**, *334*, 1114. (b) Singh, A.; Arora, A.; Weaver, J. E. *Org. Lett.* **2013**, *15*, 5390. (c) Prier, C. K.; MacMillan, D. W. C. *Chem. Sci.* **2014**, *5*, 4173. (d) Beatty, J. W.; Stephenson, C. R. J. *Acc. Chem. Res.* **2015**, *48*, 1474.

(6) (a) Baslé, O.; Li, C.-J. *Org. Lett.* **2008**, *10*, 3661. (b) Dai, C.; Meschini, F.; Narayanam, J. M. R.; Stephenson, C. R. J. *J. Org. Chem.* **2012**, *77*, 4425. (c) Girard, A. S.; Knauber, T.; Li, C.-J. *Angew. Chem., Int. Ed.* **2014**, *53*, 74.

(7) (a) Pastine, S. J.; Gribkov, D. V.; Sames, D. *J. Am. Chem. Soc.* **2006**, *128*, 14220. (b) Prokopcová, H.; Bergman, S. D.; Aelvoet, K.; Smout, V.; Herrebout, W.; Van der Veken, B.; Meerpoel, L.; Maes, B. U. W. *Chem. - Eur. J.* **2010**, *16*, 13063. (c) Peschiulli, A.; Smout, V.; Storr, T. E.; Mitchell, E. A.; Eliás, Z.; Herrebout, W.; Berthelot, D.; Meerpoel, L.; Maes, B. U. W. *Chem. - Eur. J.* **2013**, *19*, 10378. (d) Dastbaravardeh, N.; Schnürch, M.; Mihovilovic, M. D. *Org. Lett.* **2012**, *14*, 1930. (e) Schwarz, M. C.; Dastbaravardeh, N.; Kirchner, K.; Schnürch, M.; Mihovilovic, M. D. *Monatsh. Chem.* **2013**, *144*, 539. (f) Kumar, N. Y. P.; Jeyachandran, R.; Ackermann, L. *J. Org. Chem.* **2013**, *78*, 4145.

(8) For Ta-catalyzed hydroaminoalkylation, see: (a) Herzon, S. B.; Hartwig, J. F. *J. Am. Chem. Soc.* **2007**, *129*, 6690. (b) Herzon, S. B.; Hartwig, J. F. *J. Am. Chem. Soc.* **2008**, *130*, 14940. (c) Eisenberger, P.; Ayinla, R. O.; Lauzon, J. M. P.; Schafer, L. L. *Angew. Chem., Int. Ed.* **2009**, *48*, 8361. (d) Payne, P. R.; Garcia, P.; Eisenberger, P.; Yim, J. C.-H.; Schafer, L. L. *Org. Lett.* **2013**, *15*, 2182. (e) Garcia, P.; Lau, Y. Y.; Perry, M. R.; Schafer, L. L. *Angew. Chem., Int. Ed.* **2013**, *52*, 9144. (f) Chong, E.; Brandt, J. W.; Schafer, L. L. *J. Am. Chem. Soc.* **2014**, *136*, 10898.

(9) For Ru/Ir-catalyzed hydroaminoalkylation, see: (a) Jun, C.-H. *Chem. Commun.* **1998**, 1405. (b) Chatani, N.; Asaumi, T.; Yorimitsu, S.; Ikeda, T.; Kakiuchi, F.; Murai, S. *J. Am. Chem. Soc.* **2001**, *123*, 10935. (c) Pan, S.; Endo, K.; Shibata, T. *Org. Lett.* **2011**, *13*, 4692. (d) Bergman, S. D.; Storr, T. E.; Prokopcová, H.; Aelvoet, K.; Diels, G.; Meerpoel, L.; Maes, B. U. W. *Chem. - Eur. J.* **2012**, *18*, 10393. (e) Schmitt, D. C.; Lee, J.; Dechert-Schmitt, A.-M.; Yamaguchi, E.; Krische, M. J. *Chem. Commun.* **2013**, *49*, 6096. (f) Schinkel, M.; Wang, L.; Bielefeld, K.; Ackermann, L. *Org. Lett.* **2014**, *16*, 1876.

(10) For Ir-catalyzed alkenylation of amides, see: (a) Tsuchikama, D.; Kasagawa, M.; Endo, K.; Shibata, T. *Org. Lett.* **2009**, *11*, 1821. (b) Pan, S.; Matsuo, Y.; Endo, K.; Shibata, T. *Tetrahedron* **2012**, *68*, 9009.

(11) For Rh/Ir-catalyzed borylation of amines and amides, see: (a) Kawamorita, S.; Miyazaki, T.; Iwai, T.; Ohmiya, H.; Sawamura, M. *J. Am. Chem. Soc.* **2012**, *134*, 12924. (b) Li, Q.; Liskey, C. W.; Hartwig, J. F. *J. Am. Chem. Soc.* **2014**, *136*, 8755.

(12) Wang, D.-H.; Hao, X.-S.; Wu, D.-F.; Yu, J.-Q. *Org. Lett.* **2006**, *8*, 3387.

(13) (a) Tamaru, Y.; Kagotani, M.; Yoshida, Z. *Angew. Chem., Int. Ed. Engl.* **1981**, *20*, 980. (b) Dunina, V. V.; Golovan, E. B.; Kazakova, E. I.; Potapov, G. P.; Beletskaya, I. P. *Metalloorg. Khim.* **1991**, *4*, 1391. (c) Nojima, Y.; Nonoyama, M.; Nakajima, K. *Polyhedron* **1996**, *15*, 3795. (d) Dunina, V. V.; Gorunova, O. N.; Kuznetsova, E. D.; Turubanova, E. I.; Livantsov, M. V.; Grishin, Y. K.; Kuzmina, L. G.; Churakov, A. V. *Russ. Chem. Bull.* **2006**, *55*, 2193. For direct Pd insertion into α-C−H bonds of amines, see: (e) Lu, C. C.; Peters, J. C. *J. Am. Chem. Soc.* **2004**, *126*, 15818.

(14) Chen, X.; Li, J.-J.; Hao, X.-S.; Goodhue, C. E.; Yu, J.-Q. *J. Am. Chem. Soc.* **2006**, *128*, 78.

(15) For recent reviews of transition-metal-catalyzed C(sp^3)−H functionalization, see: (a) Daugulis, O.; Do, H.-Q.; Shabashov, D. *Acc. Chem. Res.* **2009**, *42*, 1074. (b) Jazzar, R.; Hitce, J.; Renaudat, A.; Sofack-Kreutzer, J.; Baudoin, O. *Chem. - Eur. J.* **2010**, *16*, 2654. (c) Lyons, T. W.; Sanford, M. S. *Chem. Rev.* **2010**, *110*, 1147. (d) Wasa, M.; Engle, K. M.; Yu, J.-Q. *Isr. J. Chem.* **2010**, *50*, 605. (e) Baudoin, O. *Chem. Soc. Rev.* **2011**, *40*, 4902.

(16) Guo, C.; Sun, D.-W.; Yang, S.; Mao, S.-J.; Xu, X.-H.; Zhu, S.-F.; Zhou, Q.-L. *J. Am. Chem. Soc.* **2015**, *137*, 90.

(17) The stereochemistry was confirmed by X-ray analysis of **9a** (see the Supporting Information). The structure was deposited with the Cambridge Crystallographic Data Center (CCDC-1408481).

(18) (a) Mann, G.; Shelby, Q.; Roy, A. H.; Hartwig, J. F. *Organometallics* **2003**, *22*, 2775. (b) Culkin, D. A.; Hartwig, J. F. *Organometallics* **2004**, *23*, 3398.

(19) (a) Lubosch, W.; Seebach, D. *Helv. Chim. Acta* **1980**, *63*, 102. (b) Hodgson, D. M.; Kloesges, J. *Angew. Chem., Int. Ed.* **2010**, *49*, 2900. (c) Hodgson, D. M.; Pearson, C. I.; Thompson, A. L. *J. Org. Chem.* **2013**, *78*, 1098.

DOI: 10.1021/jacs.5b06740
J. Am. Chem. Soc. 2015, 137, 11876−11879