Organic LETTERS

Letter

pubs.acs.org/OrgLett

# Palladium-Catalyzed 6-Endo Selective Alkyl-Heck Reactions: Access to 5-Phenyl-1,2,3,6-tetrahydropyridine Derivatives

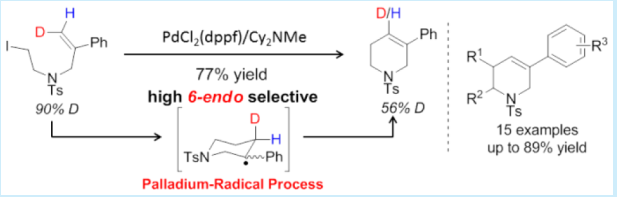
Xu Dong,[†] Ying Han,[†] Fachao Yan,[†] Qing Liu,*[,†] Ping Wang,[†] Kexun Chen,[†] Yueyun Li,[†] Zengdian Zhao,[†] Yunhui Dong,[†] and Hui Liu*[,†,‡]

[†]School of Chemical Engineering, Shandong University of Technology, 266 West Xincun Road, Zibo 255049, P. R. China

[‡]College of Materials Science and Engineering, Hunan University, Changsha, Hunan 410082, China

Supporting Information

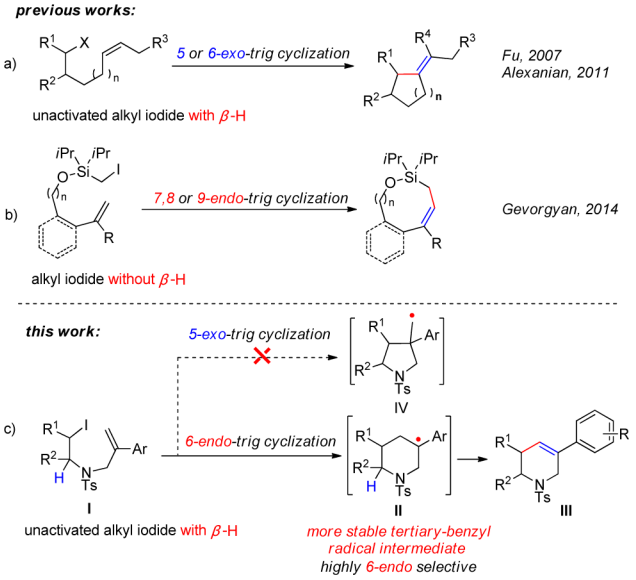
**ABSTRACT:** A new type of palladium-catalyzed 6-*endo*-selective alkyl-Heck reaction of unactivated alkyl iodides has been described. This strategy provides efficient access to a variety of 5-phenyl-1,2,3,6-tetrahydropyridine derivatives, which are important structural motifs for bioactive molecules. This process displays a broad substrate scope with excellent 6-*endo* selectivity. Mechanistic investigations reveal that this alkyl-Heck reaction performs via a hybrid palladium-radical process.




The palladium-catalyzed Mizoroki−Heck reaction is a fundamental synthetic tool throughout organic chemistry and related disciplines, achieving the direct cross-coupling of alkenes with halides or sulfonates to valuable molecules.[1] The significant contribution of the Heck reaction to synthetic chemistry led to R. Heck, A. Suzuki (Suzuki Coupling) and E. Negishi (Negishi Coupling) being awarded the 2010 Nobel Prize in chemistry.[2] Compared with the Heck reaction of $Csp^2$ halides, the analogues reaction with $Csp^3$ halides, in particular, unactivated substrates bearing $\beta$-hydride, has been less investigated.[3] The harsh conditions for the oxidative addition of $Csp^3$ halides to low-valent transition metals and premature $\beta$-hydride elimination of putative alkylmetal are significant challenges for chemists.[4]

Despite the difficulties in alkyl-Heck-type transformation, some elegant strategies have emerged recently. In 2007, Fu and co-workers developed the first palladium-catalyzed intramolecular Heck reactions of unactivated, $\beta$-hydrogen-containing alkyl halides (Br, Cl) via 5-*exo*-trig cyclization (Scheme 1a).[5] NHC (*N*-heterocyclic carbene) ligands were considered to promote migratory insertion over the competitive $\beta$-hydride elimination, in which an $S_N2$ oxidative addition mechanism was proposed but not a radical process. In 2011, the Alexanian group described 5-*exo*-trig and 6-*exo*-trig types of intramolecular alkyl-Heck reactions, and a hybrid palladium-radical mechanism was demonstrated to explain the suppression of $\beta$-hydride elimination (Scheme 1a).[6] Both protocols underwent conventional *exo* selective cyclization (Scheme 1a). However, an ***endo***-trig Heck reaction is quite rare;[7] to date, there is only one example of an ***endo***-selective alkyl-Heck reaction reported by the Gevorgyan group in 2014.[8] The 7,8,9-*endo*-selective alkyl-Heck reactions were described, which were suggested to occur via a hybrid palladium-radical process (Scheme 1b). Two crucial factors promote the transformations: (a) the use of the silyl tether favor *endo*-selective cyclization without substrate bias; (b) no competitive $\beta$-hydride elimination issue exists. However, to the best of our knowledge, there are no reports on the 6-*endo*-trig-selective alkyl-Heck reaction, which inspires us to investigate this untouched chemistry. Herein, we report a highly 6-***endo***-selective alkyl-Heck reaction with unactivated alkyl iodides bearing a $\beta$-hydride, delivering 5-phenyl-1,2,3,6-tetrahydropyridine structural motifs efficiently (Scheme 1c). The 5-*exo*-trig cyclization is not detected.

**Scheme 1. Palladium-Catalyzed Intramolecular Alkyl-Heck-Type Reactions**




**Received:** June 20, 2016



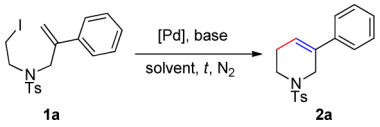

DOI: 10.1021/acs.orglett.6b01787
Org. Lett. XXXX, XXX, XXX−XXX

Our laboratory has been interested in developing palladium-promoted radical reactions with unactivated alkyl iodides bearing a $\beta$-hydride.[9] We are aware that 5-*exo* cyclization is a much more tendentious route than the 6-*endo* style, while 6-*endo* forms a relatively stable secondary or tertiary radical intermediate.[10] To reconsider the radical mechanism, we hypothesize that if the stability of radical intermediate generated from the radical addition to the double bond is increased, the reaction might be impelled to proceed as a 6-*endo* cyclization. As designed in Scheme 1c, substrate **I** is supposed to generate a fairly stable tertiary-benzyl radical intermediate **II** via 6-***endo***-trig cyclization (VS 5-*exo*), followed by $\beta$-hydride elimination to furnish 5-phenyl-1,2,3,6-tetrahydropyridine derivates **III**. Notably, this transformation might provide a distinct strategy to convert facile synthesized substrates into various 5-phenyl-1,2,3,6-tetrahydropyridine derivatives, a structural motif that has been widely found in natural products and pharmaceutical compounds, such as the P75NTR receptor inhibitor, Fms-like tyrosine kinase 3 inhibitor, C-KIT inhibitor, Chemokine receptor $CXCR_3$ inhibitor, and (+)-Ipalbidine (for details see Supporting Information).[11]

To test the hypothesis, our efforts commenced with the investigation of unactivated iodide **1a** (Table 1). Substrate **1a** was subjected to the conditions comprised of 10 mol % $PdCl_2$(dppf) and 2.0 equiv of $K_2CO_3$ at 130 °C in toluene under $N_2$. However, no reaction was detected (entry 1). The same result was obtained from $Cs_2CO_3$ (entry 2). Gratifyingly, when $Et_3N$ was used as a base, the desired 6-membered tetrahydropyridine derivate **2a** was obtained in 48% yield (entry 3). Following these promising results, we continued with further exploration of organic bases. To our delight, when *N*-cyclohexyl-*N*-methylcyclohexanamine instead of $Et_3N$ was used as the base, the yield was increased dramatically to 79% (entry 5). By screening the reaction temperature, we found that decreasing the reaction temperature to 110 °C could give **2a** in 80% yield; however, the yield decreased suddenly to a 26% yield together with high recovery of the starting material at 80 °C, indicating the temperature was crucial to this transformation (entries 6 and 7). Employment of different catalysts/ligands, such as $Pd(OAc)_2$/dppf, $Pd(OAc)_2/PPh_3$, $Pd(PPh_3)_4$, and $PdCl_2(PPh_3)_2$, did not give positive results (entries 8−11), except the combination of $Pd(PPh_3)_4$ and dppf afforded a 73% yield (entry 12). Furthermore, the screening of solvent showed that toluene was also the better choice (entries 13−16). On the basis of these results, the optimal conditions were determined to include $PdCl_2$(dppf) combined with $Cy_2NMe$ in toluene at 110 °C (entry 6).

With the optimized conditions in hand, we next aimed to explore the substrate scope of this transformation. Excellent functional group compatibility was obtained among the aryl rings (Scheme 2). The substrates with strong electron-donating groups, such as alkoxy at the ortho and meta positions, resulted in formation of the corresponding products smoothly. Interestingly, the *ortho*-OEt group led to a decrease in yield; however, the disubstituted substrate could furnish the desired tetrahydropyridine derivates **2d** in excellent yield. Furthermore, the substrate possessing the strong electron-withdrawing substituent CN efficiently produced 6-*endo* product **2e**. Remarkably, the reaction showed great tolerance to the halides; in particularly, bromo could survive very well under these conditions,[12] which was potentially transformed to more valuable molecules via cross-coupling (**2h** and **2i**).

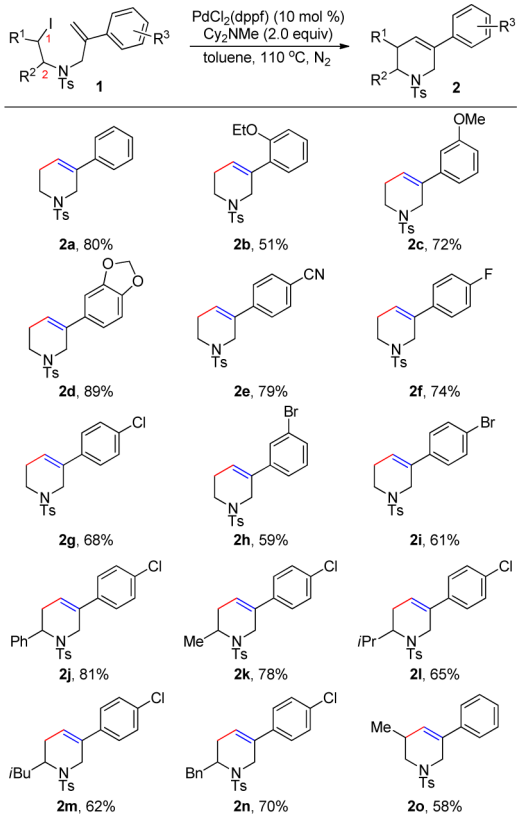
**Table 1. Alkyl-Heck Reaction of an Unactivated Alkyl Iodides: Influence of Reaction Parameters**[a]




| entry | catalyst | base | solvent | $t$ (°C) | yield[b] (%) |
|---|---|---|---|---|---|
| 1 | $PdCl_2$(dppf) | $K_2CO_3$ | toluene | 130 | NR |
| 2 | $PdCl_2$(dppf) | $Cs_2CO_3$ | toluene | 130 | NR |
| 3 | $PdCl_2$(dppf) | $Et_3N$ | toluene | 130 | 48 |
| 4 | $PdCl_2$(dppf) | DIPEA | toluene | 130 | 33 |
| 5 | $PdCl_2$(dppf) | $Cy_2NMe$ | toluene | 130 | 79 |
| 6 | $PdCl_2$(dppf) | $Cy_2NMe$ | toluene | 110 | 80 |
| 7 | $PdCl_2$(dppf) | $Cy_2NMe$ | toluene | 80 | 26[c] |
| 8 | $Pd(OAc)_2$/dppf[d] | $Cy_2NMe$ | toluene | 110 | ND |
| 9 | $Pd(OAc)_2/PPh_3$[e] | $Cy_2NMe$ | toluene | 110 | ND |
| 10 | $Pd(PPh_3)_4$ | $Cy_2NMe$ | toluene | 110 | 20 |
| 11 | $PdCl_2(PPh_3)_2$ | $Cy_2NMe$ | toluene | 110 | 24 |
| 12 | $Pd(PPh_3)_4$/dppf[d] | $Cy_2NMe$ | toluene | 110 | 73 |
| 13 | $PdCl_2$(dppf) | $Cy_2NMe$ | $PhCF_3$ | 110 | 39 |
| 14 | $PdCl_2$(dppf) | $Cy_2NMe$ | xylene | 110 | 53 |
| 15 | $PdCl_2$(dppf) | $Cy_2NMe$ | dioxane | 110 | 45 |
| 16 | $PdCl_2$(dppf) | $Cy_2NMe$ | PhCl | 110 | ND |

[a]Reaction conditions: **1a** (0.2 mmol), [Pd] (0.02 mmol), base (0.4 mmol), solvent (2.0 mL). [b]Isolated yields. [c]The starting material was recovered in 71% yield. [d]30 mol % dppf was used. [e]25 mol % $PPh_3$ was used.

**Scheme 2. Scope of 6-Endo Heck-Type Cyclyzation**[a,b]




[a]Reaction Conditions: **1** (0.2 mmol), $PdCl_2$(dppf) (0.02 mmol), $Cy_2NMe$ (0.4 mmol), toluene (2.0 mL). [b]Isolated yields.

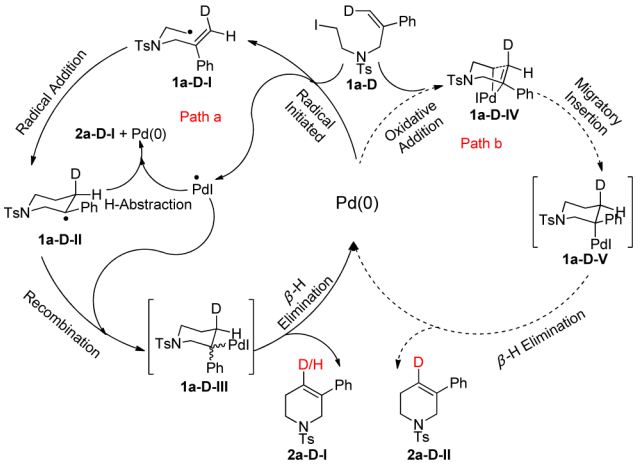


DOI: 10.1021/acs.orglett.6b01787
Org. Lett. XXXX, XXX, XXX−XXX

To further explore the substrate scope of this strategy, the substitutions at alkyl tether were investigated. Introduction of different groups, such as Ph, Me, *i*Pr, *i*Bu, and Bn at the C2-position of the alkyl tether, resulted in good to excellent yields (Scheme 2, **2j**−**2n**). In addition, the secondary alkyl iodide also performed successfully, affording the *endo* cyclized product **2o** in 58% yield (Scheme 2, **2o**).

To gain a better understanding of this transformation, we are eager to explore the reaction mechanism. As demonstrated in Scheme 1c, alkyl iodide is supposed to generate a radical intermediate easily in the presence of Pd(0), discussed by Cook,[10e−g] Alexanian,[13] Gevorgyan,[8] Zhou,[14] Ryu,[15] Tong,[16] Jiang,[17] and so on.[18] These prior works led us to propose a hybrid palladium-radical mechanism as shown in path a (Scheme 3). Taking the deuterated substrate **1a-D** as an

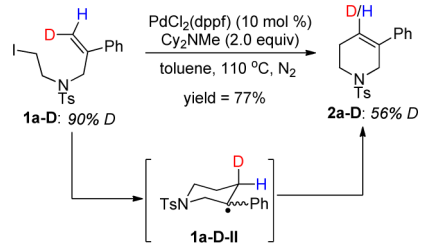
**Scheme 3. Proposed Reaction Mechanism for 6-Endo Alkyl-Heck Reaction**




example, alkyl radical **1a-D-I** will be generated under the standard conditions, which subsequently affords a fairly stable tertiary-benzyl radical **1a-D-II** via 6-***endo*** cyclization. Next, recombination of **1a-D-II** with ·PdI produces racemic alkylpalladium intermediate **1a-D-III**, which undergoes *β-hydride* or *β-deuterium* elimination delivering products **2a-D-I** with both H and D. Alternatively, hydrogen abstraction from **1a-D-II** by ·PdI could also be responsible for **2a-D-I**. In addition, the classical Heck-type mechanism path b is also an alternative choice for this reaction (Scheme 3). Followed by oxidative addition of **1a-D**, stereospecifically intramolecular insertion of olefin to the C−Pd bond via transition state **1a-D-IV** gives intermediate **1a-D-V** with a well-defined stereochemistry. Finally, *syn* selective *β-hydride* elimination should perform to yield **2a-D-II**, where deuterium is reserved fully.

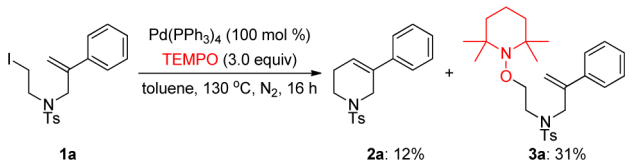
Basing on the hypothesis of deuterium scrambling, the deuterated substrate **1a-D** (90% D) with (*E*)-configuration terminal olefin was synthesized, which was then subjected to the optimized conditions (Scheme 4). To our delight, the deuterated product **2a-D** was isolated in 77% yield with deuterium erosion to 56%. Apparently, the observation of deuterium erosion supported the formation of radical intermediate **1a-D-II** which might undergo configuration scrambling naturally. This process was responsible for the deuterium erosion of the product, demonstrating the 6-***endo***-alkyl-Heck reaction was more likely to undergo a hybrid palladium-radical process.

**Scheme 4. Deuterium Scrambling Investigation**




In order to obtain direct evidence for the formation of carbon-centered radicals in the current reaction, we performed this cyclization in the presence of TEMPO (2,2,6,6-tetramethylpiperidine 1-oxyl) (Scheme 5). After screening several

**Scheme 5. TEMPO Testing Experiment**[a,b,c]




[a]Reaction conditions: **1a** (0.2 mmol), toluene (2.0 mL), 130 °C. $N_2$, 16 h. [b]Isolated yields. [c]No **1a** was recovered.

conditions (for details see SI), we were pleased to isolate **3a** in 31% yield by using 100 mol % $Pd(PPh_3)_4$, accompanying 12% cyclization product **2a**. This evidence strongly proved the generation of a carbon-centered radical intermediate. So the radical mechanism, path a in Scheme 3, was preliminarily established.

In summary, we have developed a highly 6-***endo***-selective alkyl-Heck reaction catalyzed by palladium. This strategy is applicable to the synthesis of valuable 5-phenyl-1,2,3,6-tetrahydropyridine scaffolds and tolerates a variety of alkyl iodides. A hybrid palladium-radical process is strongly supported by the results of a TEMPO testing experiment and deuterium scrambling investigation. The stable tertiary-benzyl radical intermediate is crucial for the highly 6-***endo*** selectivity. Further applications are in progress in our laboratory.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b01787.

Experimental procedures and compound characterization data (PDF)

## ■ AUTHOR INFORMATION

### Corresponding Authors

*E-mail: qingliu0315@163.com.
*E-mail: huiliu1030@sdut.edu.cn.

### Notes

The authors declare no competing financial interest.

## ■ ACKNOWLEDGMENTS

Financial support was provided by NSFC (21302057 and 21405095), the Young Talents Joint Fund of Shandong Province (ZR2015JL005), and Special Funding for Postdoc-



DOI: 10.1021/acs.orglett.6b01787
Org. Lett. XXXX, XXX, XXX−XXX

toral Innovation Project of Shandong Province (201501002). We are grateful to the support from Zibo Positive Additive Co., Ltd.

## REFERENCES

(1) For review of the Heck reaction, see: (a) Bräse, S.; de Meijere, A. In *Metal-Catalyzed Cross-Coupling Reactions*; de Meijere, A., Diederich, F., Eds.; Wiley-VCH: New York, 2004; Chapter 5. (b) *The Mizoroki-Heck Reaction*: Oestreich, M., Ed.; John Wiley & Sons: West Sussex, U.K., 2009.

(2) (a) Schoenberg, A.; Bartoletti, I.; Heck, R. F. *J. Org. Chem.* **1974**, *39*, 3318. (b) Schoenberg, A.; Heck, R. F. *J. Org. Chem.* **1974**, *39*, 3327. (c) Schoenberg, A.; Heck, R. F. *J. Am. Chem. Soc.* **1974**, *96*, 7761. (d) Wu, X.-F.; Anbarasan, P.; Neumann, H.; Beller, M. *Angew. Chem., Int. Ed.* **2010**, *49*, 9047. (e) Negishi, E. *Angew. Chem., Int. Ed.* **2011**, *50*, 6738. (f) Suzuki, A. *Angew. Chem., Int. Ed.* **2011**, *50*, 6722.

(3) For examples of palladium-catalyzed Heck reactions of activated alkyl halides that *lack* $\beta$ hydrogens, see: (a) Benzylic electrophiles: Heck, R. F.; Nolley, J. P., Jr. *J. Org. Chem.* **1972**, *37*, 2320. (b) Wu, G.-Z.; Lamaty, F.; Negishi, E.-I. *J. Org. Chem.* **1989**, *54*, 2507. (c) Yi, P.; Zhuangyu, Z.; Hongwen, H. *Synth. Commun.* **1992**, *22*, 2019. (d) Yi, P.; Zhuangyu, Z.; Hongwen, H. *Synthesis* **1995**, *1995*, 245. (e) Kumar, P. *Org. Prep. Proced. Int.* **1997**, *29*, 477. (f) Wang, L.; Pan, Y.; Jiang, X.; Hu, H. *Tetrahedron Lett.* **2000**, *41*, 725. (g) Higuchi, K.; Sawada, K.; Nambu, H.; Shogaki, T.; Kita, Y. *Org. Lett.* **2003**, *5*, 3703. (h) Narahashi, H.; Yamamoto, A.; Shimizu, I. *Chem. Lett.* **2004**, *33*, 348. $\alpha$-Halocarbonyls: (i) Mori, M.; Oda, I.; Ban, Y. *Tetrahedron Lett.* **1982**, *23*, 5315. (j) Glorius, F. *Tetrahedron Lett.* **2003**, *44*, 5751. For leading references to related reactions of allylic electrophiles, see: (k) Oppolzer, W. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 38. For examples of palladium-catalyzed Heck reactions of an unactivated alkyl halide that is not prone to $\beta$-hydride elimination (1-bromoadamantane), see: (l) Bräse, S.; Waegell, B.; de Meijere, A. *Synthesis* **1998**, *1998*, 148.

(4) (a) Collman, J. P. *Acc. Chem. Res.* **1975**, *8*, 342. (b) Pearson, R. G.; Figdore, P. E. *J. Am. Chem. Soc.* **1980**, *102*, 1541. For reviews on catalytic carbon−carbon bond-forming reactions employing unactivated alkyl halides as substrates, see: (c) Ozawa, F.; Ito, T.; Yamamoto, A. *J. Am. Chem. Soc.* **1980**, *102*, 6457. (d) Luh, T.-Y.; Leung, M.-K.; Wong, K.-T. *Chem. Rev.* **2000**, *100*, 3187. (e) Frisch, A. C.; Beller, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 674. (f) Hartwig, J. *Organotransition Metal Chemistry: From Bonding to Catalysis*; University Science Books: Sausalito, CA, 2009; Chapter 10, p 398. (g) Sumino, S.; Ui, T.; Hamada, Y.; Fukuyama, T.; Ryu, I. *Org. Lett.* **2015**, *17*, 4952.

(5) Firmansjah, L.; Fu, G. C. *J. Am. Chem. Soc.* **2007**, *129*, 11340.

(6) Bloome, K. S.; McMahen, R. L.; Alexanian, E. J. *J. Am. Chem. Soc.* **2011**, *133*, 20146.

(7) (a) Hegedus, L. S.; Sestrick, M. R.; Michaelson, E. T.; Harrington, P. J. *J. Org. Chem.* **1989**, *54*, 4141. (b) Owczarczyk, Z.; Lamaty, F.; Vawter, E. J.; Negishi, E. *J. Am. Chem. Soc.* **1992**, *114*, 10091. (c) Rigby, J. H.; Hughes, R. C.; Heeg, M. J. *J. Am. Chem. Soc.* **1995**, *117*, 7834. (d) Dankwardt, J. W.; Flippin, L. A. *J. Org. Chem.* **1995**, *60*, 2312. (e) Iimura, S.; Overman, L. E.; Paulini, R.; Zakarian, A. *J. Am. Chem. Soc.* **2006**, *128*, 13095. (f) Klein, J. E. M. N.; Muller-Bunz, H.; Ortin, Y.; Evans, P. *Tetrahedron Lett.* **2008**, *49*, 7187. (g) Kim, S. H.; Lee, S.; Lee, H. S.; Kim, J. N. *Tetrahedron Lett.* **2010**, *51*, 6305. (h) Kotoku, N.; Sumii, Y.; Kobayashi, M. *Org. Lett.* **2011**, *13*, 3514. (i) Gao, P.; Cook, S. P. *Org. Lett.* **2012**, *14*, 3340.

(8) Parasram, M.; Iaroshenko, V. O.; Gevorgyan, V. *J. Am. Chem. Soc.* **2014**, *136*, 17926.

(9) Liu, Q.; Dong, X.; Li, J.; Xiao, J.; Dong, Y.; Liu, H. *ACS Catal.* **2015**, *5*, 6111.

(10) (a) Ishiyama, T.; Murata, M.; Suzuki, A.; Miyaura, N. *J. Chem. Soc., Chem. Commun.* **1995**, 295. (b) Stadtmuller, H.; Vaupel, A.; Tucker, C. E.; Stüdemann, T.; Knochel, P. *Chem. - Eur. J.* **1996**, *2*, 1204. (c) Ryu, I.; Kreimerman, S.; Araki, F.; Nishitani, S.; Oderaotoshi, Y.; Minakata, S.; Komatsu, M. *J. Am. Chem. Soc.* **2002**, *124*, 3812. (d) Liu, H.; Qiao, Z.; Jiang, X. *Org. Biomol. Chem.* **2012**, *10*, 7274. (e) Monks, B. M.; Cook, S. P. *J. Am. Chem. Soc.* **2012**, *134*, 15297. (f) Monks, B. M.; Cook, S. P. *Angew. Chem., Int. Ed.* **2013**, *52*, 14214. (g) Fruchey, E. R.; Monks, B. M.; Patterson, A. M.; Cook, S. P. *Org. Lett.* **2013**, *15*, 4362. (h) Wang, J.-Y.; Su, Y.-M.; Yin, F.; Bao, Y.; Zhang, X.; Xu, Y.-M.; Wang, X.-S. *Chem. Commun.* **2014**, *50*, 4108. (i) Liu, Q.; Chen, C.; Tong, X. *Tetrahedron Lett.* **2015**, *56*, 4483. (j) Wang, H.; Guo, L.-N.; Duan, X.-H. *J. Org. Chem.* **2016**, *81*, 860. (k) Reference 5. (l) Reference 6.

(11) (a) Wikström, H.; Sanchez, D.; Lindberg, P.; Hacksell, U.; Arvidsson, L. E.; Johnsson, A. M.; Thorberg, S. O.; Nilsson, J. L. G.; Svensson, K. *J. Med. Chem.* **1984**, *27*, 1030. (b) Amat, M.; Cantó, M.; Llor, N.; Escolano, C.; Molins, E.; Espinosa, E.; Bosch, J. *J. Org. Chem.* **2002**, *67*, 5343. (c) Macchia, M.; Cervetto, L.; Demontis, G. C.; Longoni, B.; Minutolo, F.; Orlandini, E.; Ortore, G.; Papi, C.; Sbrana, A.; Macchia, B. *J. Med. Chem.* **2003**, *46*, 161. (d) Chang, M.-Y.; Hsu, R.-T.; Chen, H.-P.; Lin, P.-J. *Heterocycles* **2006**, *68*, 1173. (e) Verendel, J. J.; Zhou, T.; Li, J.a-Q.; Paptchikhine, A.; Lebedev, O.; Andersson, P. G. *J. Am. Chem. Soc.* **2010**, *132*, 8880.

(12) Sumino, S.; Ryu, I. *Org. Lett.* **2016**, *18*, 52.

(13) (a) Bloome, K. S.; Alexanian, E. J. *J. Am. Chem. Soc.* **2010**, *132*, 12823. (b) McMahon, C. M.; Alexanian, E. J. *Angew. Chem., Int. Ed.* **2014**, *53*, 5974. (c) Venning, A. R. O.; Bohan, P. T.; Alexanian, E. J. *J. Am. Chem. Soc.* **2015**, *137*, 3731. (d) Reference 6.

(14) (a) Zou, Y.; Zhou, J. *Chem. Commun.* **2014**, *50*, 3725. (b) Wu, X.; See, J. W. T.; Xu, K.; Hirao, H.; Roger, J.; Hierso, J.-C.; Zhou, J. *Angew. Chem., Int. Ed.* **2014**, *53*, 13573.

(15) (a) Ryu, I. *Chem. Soc. Rev.* **2001**, *30*, 16. (b) Fusano, A.; Fukuyama, T.; Nishitani, S.; Inouye, T.; Ryu, I. *Org. Lett.* **2010**, *12*, 2410. (c) Fusano, A.; Sumino, S.; Fukuyama, T.; Ryu, I. *Org. Lett.* **2011**, *13*, 2114. (d) Fusano, A.; Sumino, S.; Nishitani, S.; Inouye, T.; Morimoto, K.; Fukuyama, T.; Ryu, I. *Chem. - Eur. J.* **2012**, *18*, 9415. (e) Sumino, S.; Ui, T.; Ryu, I. *Org. Lett.* **2013**, *15*, 3142. (f) Sumino, S.; Fusano, A.; Fukuyama, T.; Ryu, I. *Acc. Chem. Res.* **2014**, *47*, 1563.

(16) (a) Chen, C.; Hu, J.; Su, J.; Tong, X. *Tetrahedron Lett.* **2014**, *55*, 3229. (b) Chen, C.; Hou, L.; Cheng, M.; Su, J.; Tong, X. *Angew. Chem., Int. Ed.* **2015**, *54*, 3092. For a recent review of Pd(0) catalyzed C−X bond formation, see: (c) Liu, H.; Li, C.; Qiu, D.; Tong, X. *J. Am. Chem. Soc.* **2011**, *133*, 6187. (d) Chen, C.; Tong, X. *Org. Chem. Front.* **2014**, *1*, 439. (e) Reference 10i.

(17) (a) Liu, H.; Wei, J.; Qiao, Z.; Fu, Y.; Jiang, X. *Chem. - Eur. J.* **2014**, *20*, 8308. (b) Reference 10d.

(18) For a survey of the mechanisms of oxidative addition of palladium(0) to alkyl halides, see: (a) Stille, J. K.; Lau, K. S. Y. *Acc. Chem. Res.* **1977**, *10*, 434. (b) Reference 9 and the references therein.



DOI: 10.1021/acs.orglett.6b01787
*Org. Lett.* XXXX, XXX, XXX−XXX