Organic LETTERS

Letter

Cite This: Org. Lett. XXXX, XXX, XXX−XXX

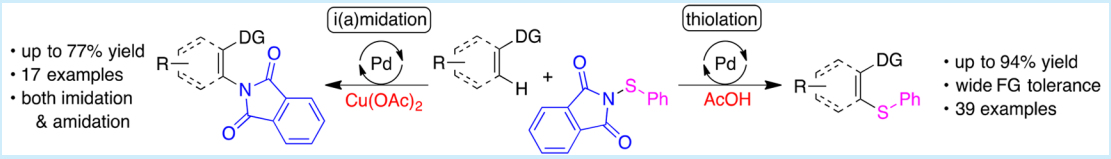
pubs.acs.org/OrgLett

Lewis Acid/Brønsted Acid Controlled Pd(II)-Catalyzed Chemodivergent Functionalization of C(sp^2)−H Bonds with *N*-(Arylthio)i(a)mides

Manthena Chaitanya and Pazhamalai Anbarasan*

Department of Chemistry, Indian Institute of Technology Madras, Chennai-600036, India

Supporting Information



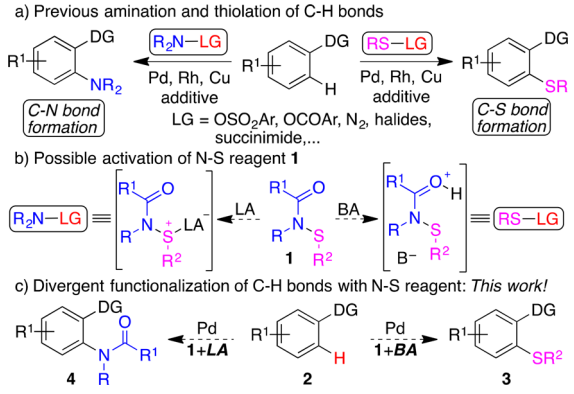
ABSTRACT: An efficient and chemodivergent palladium-catalyzed thiolation (C−S) and imidation (C−N) of directing group-assisted C−H bonds have been accomplished employing *N*-(arylthio)imides in combination with either Brønsted acid or Lewis acid, respectively. Notable features of the developed methodologies include excellent diversity, high functional group tolerance, wide substrate scope, and use of a single N−S reagent. Importantly, the developed hypothesis was also successfully extended to the amidation of C−H bonds. A plausible mechanistic pathway was proposed based on the preliminary mechanistic study.

Selectivity is a fundamental challenge in organic synthesis, and it has been the prime focus to achieve the maximum synthetic efficiency in various synthetic sequences. Among these, chemoselective transformations have provided a significant advantage to simplify the synthetic strategies for complex molecules, due to the efficiency to target a specific site in a polyfunctionalized target.[1] In this context, transition-metal-catalyzed direct functionalization of an abundant C−H bonds has seen exponential growth in recent decades,[2] where high regioselectivity for *ortho* C−H bonds was achieved with a directing group. However, chemoselectivity in the C−H bond functionalization has been scarcely studied.

Particularly, transition-metal-catalyzed C−S and C−N bond formations via functionalization of C−H bonds have gained significant attention.[3] For instance, direct functionalization of C−H bonds to C−S bonds include metal-free[4] and transition-metal-catalyzed[5] thiolation employing various electrophilic sulfenylating reagents such as diaryldisulfide, *N*-(arylthio)-succinimide, etc. On the other hand, the transition-metal-catalyzed amination of C−H bonds was developed under either oxidative conditions with amines[6] or the directed C−H amination employing electrophilic nitrogen sources having a weak N−X bond,[7] such as chloramines, hydroxyl amines, and azides, under redox neutral conditions (Scheme 1a). However, no unified approach for the construction of either a C−S or C−N bond from a C−H bond employing a single electrophilic reagent has been demonstrated in the literature. Herein, we disclose a unified approach for palladium-catalyzed thiolation and i(a)midation of a C−H bond employing *N*-(arylthio)i(a)-mide as a suitable reagent in the presence of either a Brønsted acid (BA) or Lewis acid (LA), respectively.

The literature strategies for the functionalization of C−H bonds to C−S and C−N bonds utilize an electrophilic reagent

Scheme 1. Metal-Catalyzed Functionalization of C−H Bond to C−N and C−S Bonds



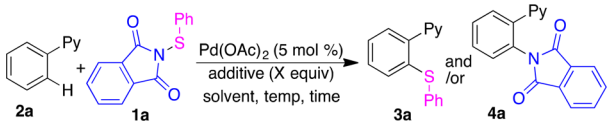
in which the sulfur and nitrogen are attached to a good leaving group (LG).[6,7] We envisioned *N*-(arylthio)i(a)mides (N−S reagent) in combination with either a BA or LA as a suitable reagent for the divergent functionalization of C−H bonds to either C−S or C−N bonds. It was anticipated that a BA and LA would coordinate with the amide oxygen and sulfur of **1**, respectively, and as a consequence either the i(a)mide or arylthio moiety could selectively act as a good leaving group to drive the chemodivergent functionalization (Scheme 1b). Successful development of these reactions would provide ready access to either C−S or C−N bonds from a single reagent, *viz* *N*-(arylthio)i(a)mides in the metal-catalyzed C−H bond functionalization (Scheme 1c).

Received: April 23, 2018

DOI: 10.1021/acs.orglett.8b01281
Org. Lett. XXXX, XXX, XXX−XXX

Based on the hypothesis, palladium-catalyzed and BA-mediated thiolation of C−H bond was investigated employing 2-phenylpyridine **2a** as a model substrate. The initial reaction of 2-phenylpyridine **2a** and 2 equiv of *N*-(phenylthio)phthalimide **1a** in the presence of 5 mol % of $Pd(OAc)_2$ and 20 equiv of acetic acid in toluene at 100 °C did not afford the expected thiolation product **3a** (Table 1, entry 1). Gratifyingly, switching

Table 1. Optimization of Palladium-Catalyzed Divergent Functionalization of C−H Bond with N−S Reagent[a]



entry	additive (*X* equiv)	solvent	temp (°C)	time (h)	yield (%)[b] 3a	4a
1	AcOH (20)	toluene	100	18	–	–
2	–	AcOH	100	18	53	–
3	–	AcOH	80	18	5	–
4	–	AcOH	120	18	63	–
5[c]	–	AcOH	120	18	74	–
6[d]	AcOH (20)	toluene	100	18	80	–
7	CuI (0.5)	toluene	120	36	–	20
8	AgOAc (0.5)	toluene	120	36	–	–
9	CuBr (0.5)	toluene	120	36	–	53
10	$Cu(OAc)_2·H_2O$ (0.5)	toluene	120	36	–	77

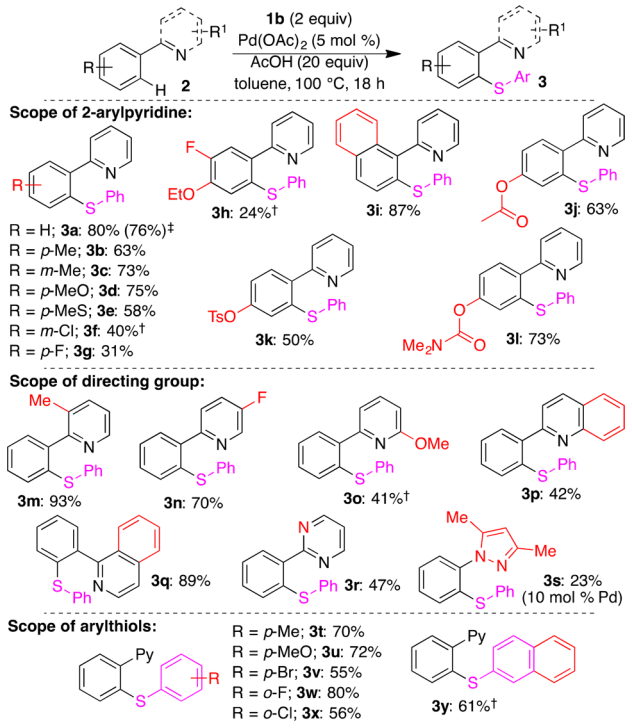
[a]Reaction conditions: **2a** (0.2 mmol, 1 equiv), **1** (0.4 mmol, 2 equiv), $Pd(OAc)_2$, additive, toluene (1 mL), temp, time. Py = 2-Pyridinyl. [b]All are isolated yields. [c]10 mol % of $Pd(OAc)_2$. [d]*N*-(Phenylthio)-succinimide **1b** was used instead of **1a**.

to acetic acid as a solvent afforded **3a** in 53% yield, where the complete decomposition of **1a** was observed (Table 1, entry 2). This successfully demonstrates the significance of acetic acid in C−S bond formation and the unique activation of **1a**.

Subsequently, decreasing the temperature led to only 5% of **3a**, but increasing the temperature to 120 °C gave the product **3a** in 63% yield (Table 1, entries 3 and 4). Changing the loading of $Pd(OAc)_2$ to 10 mol % gave the product **3a** in 74% yield at 120 °C (Table 1, entry 5). Interestingly, a similar result was observed using *N*-(phenylthio)succinimide **1b** as the reagent in toluene at 100 °C with 20 equiv of AcOH (Table 1, entry 6). Successively, Pd-catalyzed and LA-mediated imidation of C−H bond was studied. The reaction of **2a** with **1a** provided the product **4a** in 20% yield in the presence of 5 mol % of $Pd(OAc)_2$ and 0.5 equiv of CuI in toluene at 120 °C, and importantly, no thiolation product was observed (Table 1, entry 7). Next, to improve the yield of imidation, various copper and silver based Lewis acids were examined, and the best yield (77%) was achieved with 0.5 equiv of $Cu(OAc)_2·H_2O$ (Table 1, entries 7−10; see Supporting Information (SI)).

After identifying the optimal conditions for the divergent functionalization of the C−H bond either to C−S or C−N bonds by simple switching of a BA or LA, the scope and generality of the palladium-catalyzed thiolation was envisaged. Initially, the effect of various groups on the arene moiety was investigated with **1b**, since it gave comparable reactivity and yield under mild conditions (Scheme 2). Electron-neutral and -donating groups on the arene gave the corresponding thiolated products **3b−3e** in good yields. Similarly, formation of halogen-containing arylthiolated products **3f−3h** were achieved in

Scheme 2. Palladium-Catalyzed Arylthiolation of Arenes[a]



[a]All are isolated yields. †Yield based on ^1H NMR. ‡1 mmol scale reaction.

moderate to good yields. It is important to note that various functional groups such as OAc, OTs, and carbamate on the arene moiety were well tolerated and gave products **3j−3l** in 63%, 50%, and 73% yields, respectively.

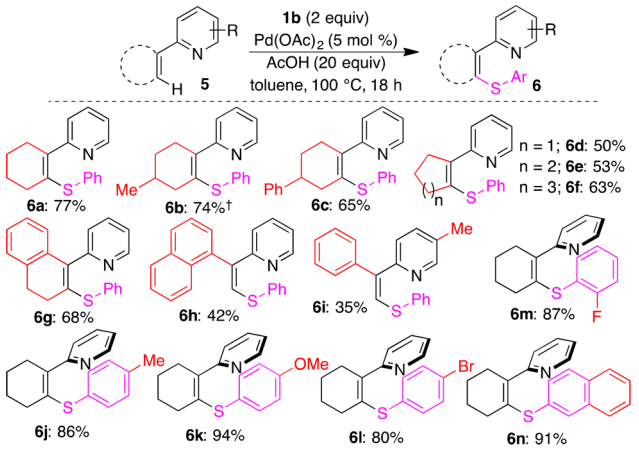
Similarly, various substituents such as methyl, methoxy, and fluoro on the pyridine-directing group were also well tolerated and gave the thiolated products **3m−3o** in good yields. In addition, other directing groups such as quinoline, isoquinoline, pyrimidine, and pyrazole were also proven to be good directing groups in the C−H bond thiolation. Next, the effect of various substituents on the arylthio moeity of **1b** under the optimized conditions was examined (Scheme 2). Thiolating reagents derived from methyl, methoxy, and halogenated thiophenol, as well as 2-naphthylthiol furnished the corresponding products **3t−3x** in good yields.

Subsequently, the methodology was extended to the thiolation of the C(sp^2)−H bond of alkenes. To our delight, reaction of 2-(cyclohexen-1-yl)pyridine **5a** with **1b** under the optimized conditions afforded the thiolated product **6a** in 77% yield, and it is worth noting that this is the first report on the thiolation of alkenes (Scheme 3). Subsequently, various substituted cyclohexenylpyridine and cycloalkenylpyridines were examined, which afforded products **6b−6g** in good yields. 1,1-Disubstituted alkenes also showed compatibility to furnish products **6h−6i** in moderate yields. Furthermore, the reaction of **5a** with various thiolating reagents gave products **6j−6n** in excellent yields.

After the successful demonstration of Pd-catalyzed and BA-mediated thiolation of C−H bonds, the scope and generality of the Pd/Cu cocatalyzed imidation of arenes were investigated (Scheme 4). Simple alkyl, electron-donating, and halogen-containing arenes gave imidated products **4a−4h** in ∼70% yield. Importantly, enolizable ketone, carbonate, and carba-

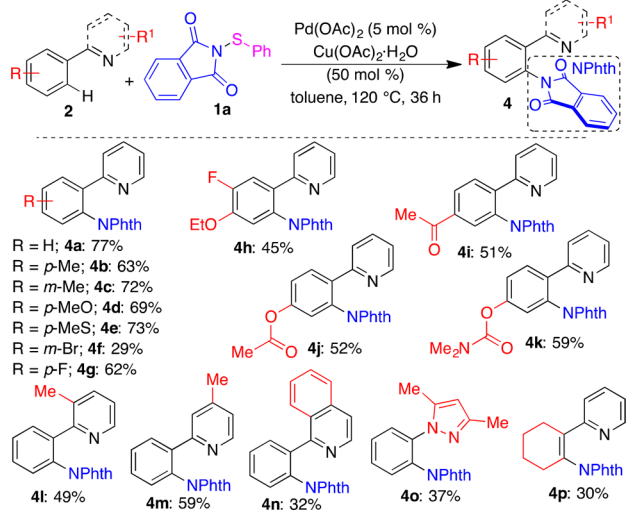
DOI: 10.1021/acs.orglett.8b01281
Org. Lett. XXXX, XXX, XXX−XXX

Scheme 3. Palladium-Catalyzed Arylthiolation of Alkenes[a]



[a]All are isolated yields. †Yield based on ^{1}H NMR.

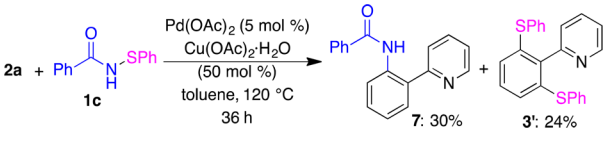
Scheme 4. Pd/Cu Cocatalyzed Imidation of C−H Bond



mates were well tolerated under the optimized conditions and afforded products **4i**−**4k** in good yields. Substituted pyridines, isoquinoline, and pyrazole-directed imidation gave products **4l**−**4o** in good yields. Notably, the optimized conditions are also suitable for the synthesis of imidated alkene **4p** *via* imidation of the C−H bond of alkene.

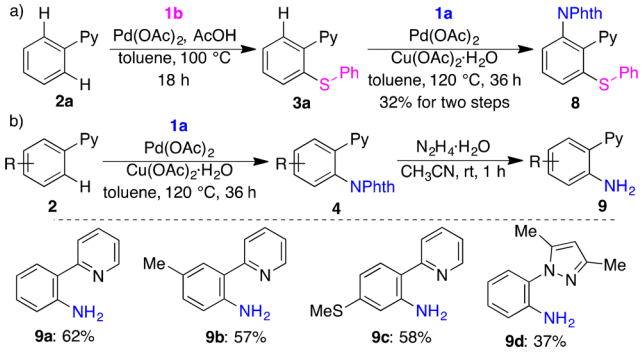
Next, the extension of the developed methodology for the amidation of the C−H bond was envisaged. Among the various reagents examined, the reaction of *N*-(phenylthio)benzamide **1c** (2 equiv) with 2-phenylpyridine **2a** (1 equiv) under the optimized conditions afforded the amidated product **7** in 30% yield, along with the formation of dithiolated product **3′** in 24% yield (Scheme 5). This reaction indicated that the hypothesis could be extended to the amidation of the C−H bond.

Scheme 5. Pd/Cu Cocatalyzed Amidation of C−H Bond



Next, the utility of the developed transformation was demonstrated through orthogonal functionalization and indirect amination of the C−H bond. Thus, synthesis of the orthogonally functionalized product **8** was accomplished via the Pd-catalyzed and AcOH-mediated thiolation of the C−H bond of **2a** to **3a**, followed by the Pd/Cu cocatalyzed imidation in 32% yield for two steps (Scheme 6a). Furthermore, the imide

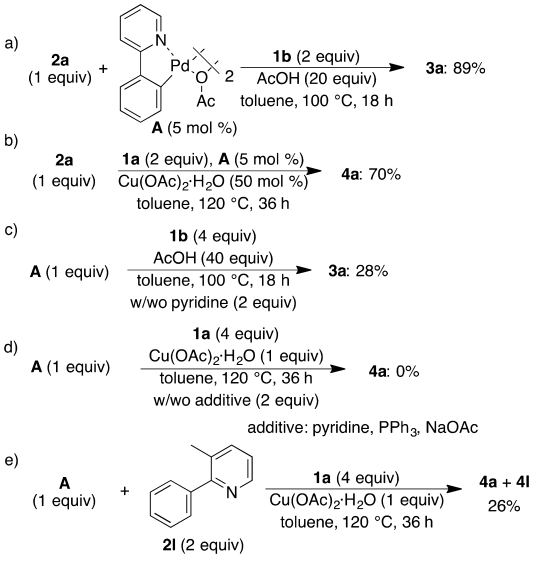
Scheme 6. Synthetic Utility



in **4a**, **4c**, **4e**, and **4o** was transformed to the amine by reaction with hydrazine hydrate in up to 62% overall yield, demonstrating a two-step approach to amination of C−H bonds (Scheme 6b).

To gain insight into the reaction mechanism, a series of control experiments, as well as variable temperature FTIR and NMR studies, were performed (Scheme 7). Treatment of **2a**

Scheme 7. Mechanistic Investigation



and **1b** in the presence of 5 mol % of palladacycle **A** as the catalyst, synthesized from **2a** and $Pd(OAc)_2$ and 20 equiv of AcOH, furnished the product **3a** in 89% yield. Similarly, formation of the imidation product **4a** was also observed in 70% yield from **2a** under the optimized conditions with 5 mol % of palladacycle **A**.

On the other hand, a stoichiometric reaction of palladacycle **A** with 4 equiv of **1b** and 40 equiv of AcOH afforded the product **3a** in 28% yield. Surprisingly, no reaction was observed with palladacycle **A** under the imidation conditions with 4 equiv of **1a**. Expecting that the dimeric palladacycle **A** may be relatively

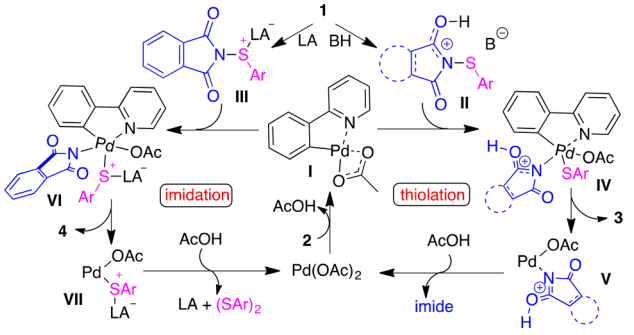
DOI: 10.1021/acs.orglett.8b01281
Org. Lett. XXXX, XXX, XXX−XXX

stable under the reaction conditions, as well as to release the product from the catalyst, the addition of an equimolar amount of additives such as pyridine, PPh_3, and NaOAc was examined. However, significant improvement was not observed in either the thiolation or imidation reactions. Interestingly, addition of **2l** under the imidation conditions with **A** gave a mixture of imidated products **4a** and **4l** in 26% yield. These results suggest that (i) dimeric palladacycle **A** may be the resting state of the catalyst, (ii) the active monomeric catalyst may be generated from **A**, and (iii) a bulky nucleophile such as 2-arylpyridine is essential to release the product from a palladium complex.

Next, variable temperature FTIR and NMR studies of **1b** with acetic acid and **1a** with $Cu(OAc)_2$ were studied to understand their mode of interaction. Interestingly, a significant shift in C═O stretching frequency from 1731 to 1717 cm^{-1} was observed in the FTIR with acetic acid and the same was absent with $Cu(OAc)_2$ (see SI). It was supported by the downfield shift of the carbonyl carbon (175.2 ppm to 175.7 ppm) in the ^{13}C NMR with AcOH. In the ^{1}H NMR, no significant change in the aromatic signal was observed with AcOH. On the other hand, a downfield shift of aromatic protons (6.74−6.93 ppm to 6.83−7.01 ppm) was observed with $Cu(OAc)_2$. In addition, a downfield shift in the sulfur attached quaternary carbon of phenyl was also observed in the ^{13}C NMR. These observations suggest that the AcOH protonates the imide oxygen and $Cu(OAc)_2$ coordinates with the sulfur.

Based on the preliminary studies mentioned above and earlier reports on the thiolation and imidation of C−H bonds,[3b] a plausible mechanism was proposed for the developed transformations (Scheme 8). The reaction starts with the

Scheme 8. Plausible Mechanism



formation of palladacycle **I** from the Pd-catalyst and **2** via C−H bond functionalization. Next, oxidative addition of AcOH activated N−S reagent **II**, as shown by VT-FTIR and NMR studies, onto **I** would afford **IV**, which on C−S reductive elimination would furnish the thiolated product **3**. Similarly, reaction of **I** with $Cu(OAc)_2$ activated N−S reagent **III** would give **VI**, which on subsequent C−N reductive elimination would afford the imidated product **4**. Alternatively, the direct electrophilic thiolation or imidation[8] of **I** with **II** or **III** would also give the expected products **3**/**4**. Regeneration of catalyst from **V** and **VII** on reaction with AcOH would complete the catalytic cycle.

In conclusion, we have successfully developed chemodivergent Pd-catalyzed functionalization of an aryl C−H bond with *N*-(arylthio)imides employing either a BA or LA as promoter for the construction of C−S and C−N bonds, respectively. The present methodology is operationally simple, tolerates various functional groups, and utilizes a single reagent to allow the synthesis of arylthiolated and imidated products in good yields. In addition, the developed methodology was successfully extended to the amidation of an aryl C−H bond. Notably, utility of the developed methodology was demonstrated through the orthogonal functionalization and a two-step amination of C−H bonds. Furthermore, a possible mode of activation of *N*-(arylthio)imides with a BA/LA and a plausible mechanism was also proposed based on the preliminary mechanistic investigation.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b01281.

Experimental details, characterization data, ^{1}H and ^{13}C NMR spectra of isolated compounds (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: anbarasansp@iitm.ac.in.

ORCID

Pazhamalai Anbarasan: 0000-0001-6049-5023

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank the Indian Institute of Technology Madras (Project No. CHY/16-17/840/RFIR/ANBA) for financial support. M.C. thanks CSIR, New Delhi for a fellowship.

■ REFERENCES

(1) (a) Trost, B. M.; Dong, G. *Nature* **2008**, *456*, 485. (b) Young, I. S.; Baran, P. S. *Nat. Chem.* **2009**, *1*, 193. (c) Afagh, N. A.; Yudin, A. K. *Angew. Chem., Int. Ed.* **2010**, *49*, 262−310.

(2) (a) Yamaguchi, J.; Yamaguchi, A. D.; Itami, K. *Angew. Chem., Int. Ed.* **2012**, *51*, 8960−9009. (b) Bergman, R. G. *Nature* **2007**, *446*, 391−393.

(3) (a) Zhu, X.; Chiba, S. *Chem. Soc. Rev.* **2016**, *45*, 4504−4523. (b) Lyons, T. W.; Sanford, M. S. *Chem. Rev.* **2010**, *110*, 1147−1169. (c) Cho, S. H.; Kim, J. Y.; Kwak, J.; Chang, S. *Chem. Soc. Rev.* **2011**, *40*, 5068−5083.

(4) (a) Prasad, C. D.; Balkrishna, S. J.; Kumar, A.; Bhakuni, B. S.; Shrimali, K.; Biswas, S.; Kumar, S. *J. Org. Chem.* **2013**, *78*, 1434−1443. (b) Parumala, S. K. R.; Peddinti, R. K. *Green Chem.* **2015**, *17*, 4068−4072. (c) Yang, D.; Yan, K.; Wei, W.; Zhao, J.; Zhang, M.; Sheng, X.; Li, G.; Lu, S.; Wang, H. *J. Org. Chem.* **2015**, *80*, 6083−6092. (d) Tian, H.; Yang, H.; Zhu, C.; Fu, H. *Adv. Synth. Catal.* **2015**, *357*, 481−488. (e) Hostier, T.; Ferey, V.; Ricci, G.; Gomez Pardo, D.; Cossy, J. *Org. Lett.* **2015**, *17*, 3898−3901.

(5) (a) Zhang, S.; Qian, P.; Zhang, M.; Hu, M.; Cheng, J. *J. Org. Chem.* **2010**, *75*, 6732−6735. (b) Zhang, M.; Zhang, S.; Pan, C.; Chen, F. *Synth. Commun.* **2012**, *42*, 2844−2853. (c) Anbarasan, P.; Neumann, H.; Beller, M. *Chem. Commun.* **2011**, *47*, 3233−3235. (d) Saravanan, P.; Anbarasan, P. *Org. Lett.* **2014**, *16*, 848−851. (e) Tian, H.; Zhu, C.; Yang, H.; Fu, H. *Chem. Commun.* **2014**, *50*, 8875−8877. (f) Chu, L.; Yue, X.; Qing, F.-L. *Org. Lett.* **2010**, *12*, 1644−1647. (g) Zhang, X.-S.; Li, G.; Zhang, X.-G.; Zhang, X.-H. *Tetrahedron* **2015**, *71*, 5458−5464.

(6) (a) Kim, H.; Chang, S. *ACS Catal.* **2016**, *6*, 2341−2351. (b) Tsang, W. C. P.; Zheng, N.; Buchwald, S. L. *J. Am. Chem. Soc.* **2005**, *127*, 14560−14561. (c) Wasa, M.; Yu, J.-Q. *J. Am. Chem. Soc.* **2008**, *130*, 14058−14059. (d) Mei, T.-S.; Wang, X.; Yu, J.-Q. *J. Am.*

DOI: 10.1021/acs.orglett.8b01281
Org. Lett. XXXX, XXX, XXX−XXX

Chem. Soc. **2009**, *131*, 10806−10807. (e) Neumann, J. J.; Rakshit, S.; Dröge, T.; Glorius, F. *Angew. Chem., Int. Ed.* **2009**, *48*, 6892−6895. (f) Shrestha, R.; Mukherjee, P.; Tan, Y.; Litman, Z. C.; Hartwig, J. F. *J. Am. Chem. Soc.* **2013**, *135*, 8480−8483. (g) Brasche, G.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2008**, *47*, 1932−1934. (h) Monguchi, D.; Fujiwara, T.; Furukawa, H.; Mori, A. *Org. Lett.* **2009**, *11*, 1607−1610. (i) Wang, Q.; Schreiber, S. L. *Org. Lett.* **2009**, *11*, 5178−5180. (j) Cho, S. H.; Yoon, J.; Chang, S. *J. Am. Chem. Soc.* **2011**, *133*, 5996−6005. (k) John, A.; Nicholas, K. M. *J. Org. Chem.* **2011**, *76*, 4158−4162. (l) Xu, H.; Qiao, X.; Yang, S.; Shen, Z. *J. Org. Chem.* **2014**, *79*, 4414−4422.

(7) (a) Tan, Y.; Hartwig, J. F. *J. Am. Chem. Soc.* **2010**, *132*, 3676−3677. (b) Ng, K.-H.; Chan, A. S. C.; Yu, W.-Y. *J. Am. Chem. Soc.* **2010**, *132*, 12862−12864. (c) Liu, X.-Y.; Gao, P.; Shen, Y.-W.; Liang, Y.-M. *Org. Lett.* **2011**, *13*, 4196−4199. (d) Ng, K.-H.; Ng, F.-N.; Yu, W.-Y. *Chem. Commun.* **2012**, *48*, 11680−11682. (e) Kawano, T.; Hirano, K.; Satoh, T.; Miura, M. *J. Am. Chem. Soc.* **2010**, *132*, 6900−6901. (f) Ng, K.-H.; Zhou, Z.; Yu, W.-Y. *Chem. Commun.* **2013**, *49*, 7031−7033. (g) Ryu, J.; Shin, K.; Park, S. H.; Kim, J. Y.; Chang, S. *Angew. Chem., Int. Ed.* **2012**, *51*, 9904−9908. (h) Kim, J. Y.; Park, S. H.; Ryu, J.; Cho, S. H.; Kim, S. H.; Chang, S. *J. Am. Chem. Soc.* **2012**, *134*, 9110−9113. (i) Yu, D.-G.; Suri, M.; Glorius, F. *J. Am. Chem. Soc.* **2013**, *135*, 8802−8805. (j) Tang, R.-J.; Luo, C.-P.; Yang, L.; Li, C.-J. *Adv. Synth. Catal.* **2013**, *355*, 869−873. (k) Grohmann, C.; Wang, H.; Glorius, F. *Org. Lett.* **2013**, *15*, 3014−3017. (l) Yu, S.; Wan, B.; Li, X. *Org. Lett.* **2013**, *15*, 3706−3709. (m) Raghuvanshi, K.; Zell, D.; Rauch, K.; Ackermann, L. *ACS Catal.* **2016**, *6*, 3172−3175.

(8) (a) Yoo, E. J.; Ma, S.; Mei, T.-S.; Chan, K. S. L.; Yu, J.-Q. *J. Am. Chem. Soc.* **2011**, *133*, 7652−7655. (b) Grohmann, C.; Wang, H.; Glorius, F. *Org. Lett.* **2012**, *14*, 656−659.

DOI: 10.1021/acs.orglett.8b01281
Org. Lett. XXXX, XXX, XXX−XXX