Organic LETTERS

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Palladium-Catalyzed Sequential Nucleophilic Addition/Oxidative Annulation of Bromoalkynes with Benzoic Acids To Construct Functionalized Isocoumarins

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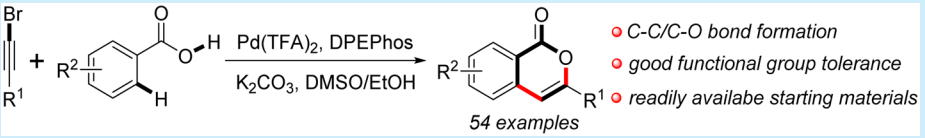
Supporting Information

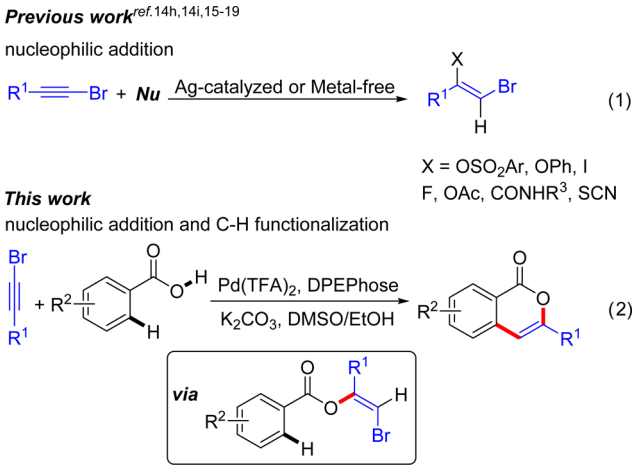


ABSTRACT: An efficient and robust protocol for the preparation of 3-substituted isocoumarins via palladium-catalyzed nucleophilic addition/oxidative annulation of bromoalkynes with benzoic acids has been developed. Remarkably, preliminary mechanistic studies indicated that the transformation might proceed via a stereo- and regioselective nucleophilic addition and C−H functionalization procedure.

Isocoumarins, especially 3-substituted isocoumarins, are an important scaffold of various natural products.[1,2] They not only show a broad range of biological and pharmaceutical activities, such as antitumor,[3] anti-inflammatory,[4] antibacterial,[5] antifungal,[6] antidiabetic,[7] immunomodulatory, and anti-HIV,[8] but also serve as useful and significant precursors for the synthesis of isocarbostyrils, isoquinolines, and isochromenes.[9] Due to the substantial applicability of isocoumarins, remarkable efforts have been devoted to develop efficient strategies for the synthesis of this scaffold.[10] For instance, Matsubara and co-workers reported a novel procedure for the synthesis of highly functionalized isocoumarins via Ni-induced decarboxylation of anhydrides with alkynes.[11] Subsequently, Ackermann and Warratz reported that isocoumarins were synthesized by ruthenium-catalyzed annulations of benzoic acids with alkynes.[12] However, most of the reported methods are only applicable to the synthesis of 3,4-disubstituted isocoumarins. Hence, it is highly desirable to further develop a novel and efficient strategy for the construction of 3-substituted isocoumarins.

During the past decades, haloalkynes have become powerful and highly versatile building blocks in organic chemistry, which exhibit abundant and tunable reactivities particularly in the presence of transition metal catalysts.[13] Therefore, remarkable efforts have been devoted to the synthesis of a valuable scaffold from haloalkynes.[14] Previously, we have reported a series of nucleophilic addition of fluoride,[15] iodide,[16] acetate,[17] isocyanide[18] and sulfide[19] to haloalkynes, providing the trisubstituted alkenes in excellent yields with exclusive *Z*-type configuration (Scheme 1, eq 1). In continuation of our interest in the field of haloalkyne chemistry, herein, we disclose an efficient strategy for the synthesis of 3-substituted isocoumarins via Pd-catalyzed nucleophilic addition/oxidative annulation of bromoalkynes with benzoic acids (Scheme 1 eq 2).

Scheme 1. Previous Work and This Work

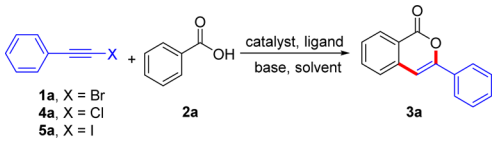


(Bromoethynyl)benzene **1a** and benzoic acid **2a** were used as the model substrate for the studies. A series of Pd catalysts were initially screened with 15 mol % of ligand and 2.0 equiv of K_2CO_3 in 2 mL of solvent (DMSO/EtOH = 2:1) at 120 °C for 20 h. As shown in Table 1, the reaction outcome was highly dependent on the Pd(0) generated *in situ* (Table 1, entries 1−4), and the best result was obtained with $Pd(TFA)_2$. Furthermore, various phosphine ligands were screened. Notably, DPEPhos (bis[2-(diphenylphosphino)phenyl] ether) increased the yield of **3a** from 49% to 83% (Table 1, entries 5−7). Control experiments revealed that both the palladium catalyst and phosphine ligand were critical for this trans-

Received: June 23, 2017

DOI: 10.1021/acs.orglett.7b01919
Org. Lett. XXXX, XXX, XXX−XXX

Table 1. Optimization of Reaction Conditions[a]



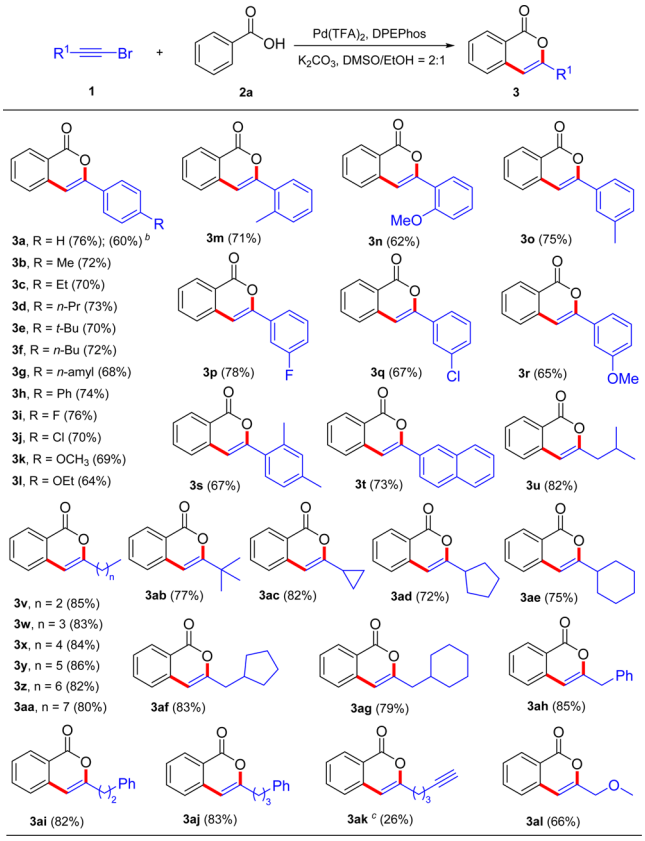
entry	catalyst	ligand	temp (°C)	base	yield[b] (%)
1	$Pd(PPh_3)_4$	PPh_3	120	K_2CO_3	9
2	$PdCl_2$	PPh_3	120	K_2CO_3	37
3	$Pd(OAc)_2$	PPh_3	120	K_2CO_3	41
4	$Pd(TFA)_2$	PPh_3	120	K_2CO_3	49
5	$Pd(TFA)_2$	XantPhos	120	K_2CO_3	65
6	**$Pd(TFA)_2$**	**DPEPhos**	**120**	**K_2CO_3**	**83 (76)**
7	$Pd(TFA)_2$	dppf	120	K_2CO_3	52
8	$Pd(TFA)_2$	–	120	K_2CO_3	n.d.
9	–	DPEPhos	120	K_2CO_3	n.d.
10	$Pd(TFA)_2$	DPEPhos	120	Cs_2CO_3	trace
11	$Pd(TFA)_2$	DPEPhos	120	MeONa	trace
12	$Pd(TFA)_2$	DPEPhos	120	Na_2CO_3	69
13	$Pd(TFA)_2$	DPEPhos	120	–	n.d.
14	$Pd(TFA)_2$	DPEPhos	110	K_2CO_3	76
15	$Pd(TFA)_2$	DPEPhoe	130	K_2CO_3	82
16[c]	$Pd(TFA)_2$	DPEPhos	120	K_2CO_3	57
17[d]	$Pd(TFA)_2$	DPEPhos	120	K_2CO_3	59 (54)
18[e]	$Pd(TFA)_2$	DPEPhos	120	K_2CO_3	46 (41)

[a]A mixture of **1a** (0.2 mmol), **2a** (0.1 mmol), base (0.2 mmol), catalyst (10 mol %), ligand (15 mol %), and DMSO/EtOH = 2:1 (2 mL) was sealed in a 25 mL Schlenk tube at 120 °C for 20 h under N_2. [b]GC yield based on **2a** using dodecane as internal standard. The number in the parentheses is isolated yield. n.d. = not detected. [c]6 mol % of catalyst was used. [d]**4a** was used for product **3a**. [e]**5a** was used for product **3a**.

formation (Table 1, entries 8–9). Subsequently, a variety of different inorganic bases were examined, and the best result was obtained in the presence of potassium carbonate (Table 1, entries 10–12). No product was obtained in the absence of the base (Table 1, entry 13). Additionally, a lower or higher reaction temperature reduced the yields slightly (Table 1, entries 14–15). Unfortunately, product **3a** was detected in 57% yield when the reaction was performed with a lower dosage (6 mol %) of $Pd(TFA)_2$ (Table 1, entry 16). With (chloroethynyl)benzene **4a** or (iodoethynyl)benzene **5a** as the substrate, the desired product **3a** was also obtained in reasonable yield (Table 1, entries 17–18). It is noteworthy to mention that the reaction was rather sensitive to solvent and DMSO/EtOH = 2:1 was found to be much better than other solvents (see Supporting Information for details).

With the optimal conditions established, the generality of the new protocol was subsequently investigated (Scheme 2). Gratifyingly, a variety of aryl bromoalkynes with different substituent groups on the phenyl ring underwent annulation with benzoic acid to furnish the desired products **3a–3t** in moderate to excellent yields. Generally, both electron-donating and -withdrawing groups at the phenyl ring were compatible with the catalytic system. Substituents at the *para*-, *ortho*-, or *meta*-position did not influence the yields dramatically (**3a–3r**). Additionally, 2-(bromoethynyl)-1,3-dimethylbenzene worked well under the standard reaction conditions, converting to the corresponding isocoumarin **3s** in 67% yield. Notably, 2-(bromoethynyl)naphthalene was also suitable for this catalytic system and transferred to the desired product **3t** in 73% yield.

Scheme 2. Synthesis of Isocoumarin Derivatives from a Range of Bromoalkynes and Benzoic Acid[a]



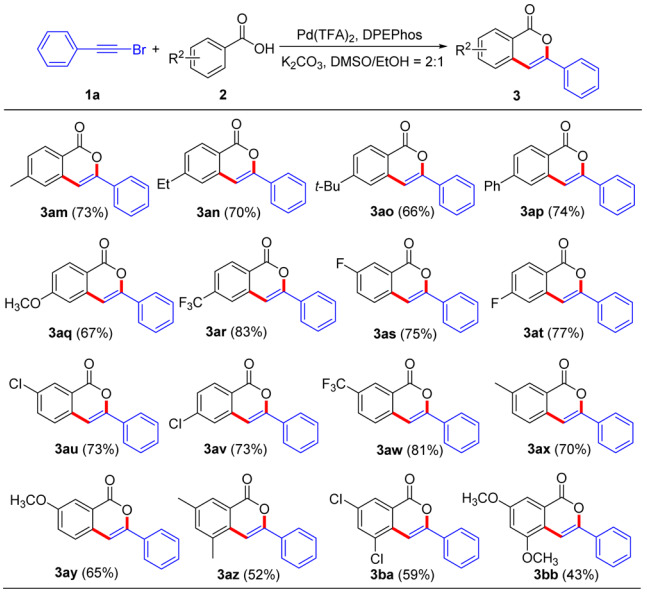
[a]A mixture of **1** (0.2 mmol), **2a** (0.1 mmol), K_2CO_3 (0.2 mmol), $Pd(TFA)_2$ (10 mol %), DPEPhos (15 mol %), and DMSO/EtOH = 2:1 (2 mL) was sealed in a 25 mL Schlenk tube at 120 °C for 20 h under N_2. Yields refer to isolated yield. [b]1 mmol scale. [c]3 equiv of **1ak** were used.

Furthermore, the reaction also proceeded smoothly with aliphatic bromoalkynes, which gave the corresponding isocoumarins in moderate to good yields (**3u–3al**). Remarkably, double bromoalkyne was found to yield **3ak** in an inferior isolated yield, albeit 3 equiv of double bromoalkynes were introduced incrementally. It is worth noting that the alkyl alkynes derived bromoalkynes that contained the valuable methoxy group could be converted to the nucleophilic addition/oxidative annulation product in 66% yield as well (**3al**). Finally, a scale-up reaction of (bromoethynyl)benzene **1a** and benzoic acid **2a** was tested; delightfully, this transformation could be achieved on 1 mmol scale and proceeded smoothly to give desired product **3a** with an acceptable decrease in yield (60%).

To further define the scope of our protocol, we then evaluated the compatibility of various benzoic acids in this transformation (Scheme 3). Under the optimized reaction conditions, various benzoic acid derivatives with *p*-Me, *p*-Et, *p*-*t*-Bu, *p*-Ph, *p*-OMe, and *p*-CF_3 substituents were explored, delivering the corresponding isocoumarins **3am–3ar** in 65–83% yields. Furthermore, fluorine and chloride groups were tolerated, providing the opportunity for further synthetic applications via classic cross-coupling reactions (**3as–3av**). Significantly, various *meta*-substituted benzoic acids, such as $-CF_3$, $-CH_3$, and $-OCH_3$ substitutions, were transformed to the desired products in moderate yields (**3aw–3ay**) with an

DOI: 10.1021/acs.orglett.7b01919
Org. Lett. XXXX, XXX, XXX–XXX

Scheme 3. Synthesis of Isocoumarin Derivatives from a Range of Benzoic Acids and (Bromoethynyl)benzene[a]



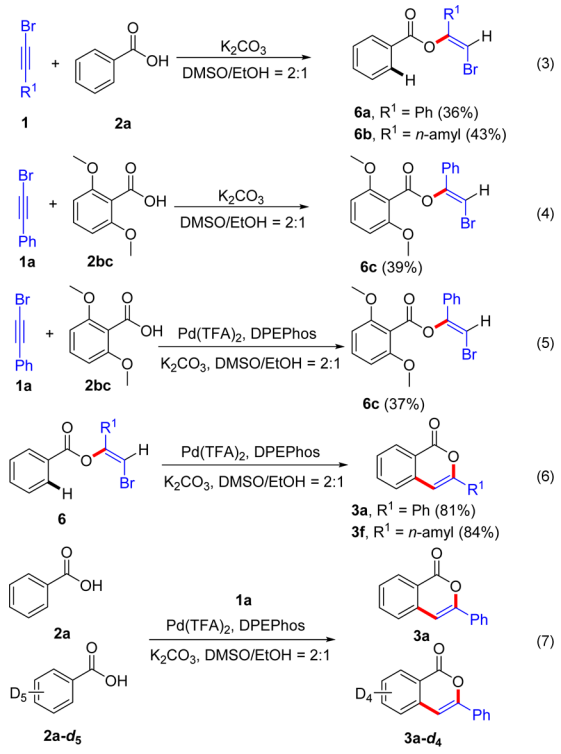
[a]A mixture of **1a** (0.2 mmol), **2** (0.1 mmol), K_2CO_3 (0.2 mmol), $Pd(TFA)_2$ (10 mol %), DPEPhos (15 mol %), and DMSO/EtOH = 2:1 (2 mL) was sealed in a 25 mL Schlenk tube at 120 °C for 20 h under N_2. Yields refer to isolated yield.

exclusive regioisomer. To our delight, when using the disubstituted arenecarboxylic acids as the substrates, the corresponding products could be isolated in 43−59% yields (**3az**−**3bb**).

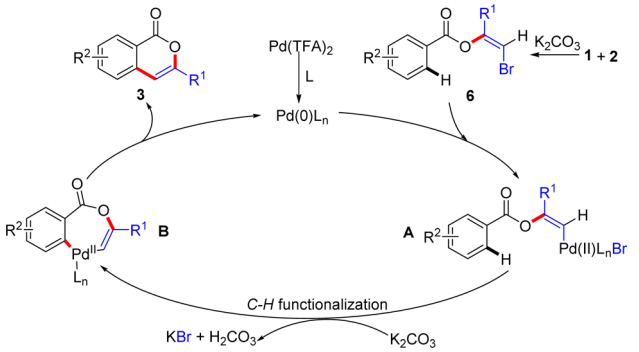
To further clarify the possible mechanism, a series of mechanistic experiments were performed as shown in Scheme 4. When **2a** and bromoalkynes (**1**) were treated in solvent (DMSO/EtOH = 2:1) using K_2CO_3 (2 equiv) as base, low yields of the corresponding nucleophilic addition products, (*Z*)-2-bromovinyl benzoates (**6a** and **6b**), were obtained (Scheme 4, eq 3). Similarly, the reaction of 2,6-dimethoxybenzoic acid and (bromoethynyl)benzene resulted in the formation of product **6c** in 39% yield (Scheme 4, eq 4). However, when the $Pd(TFA)_2$ and DPEPhos were used, the isolated yield of **6c** decreased from 39% to 37% (Scheme 4, eq 5), implying that the $Pd(TFA)_2$ might be uninvolved in the nucleophilic addition process. Pleasingly, when (*Z*)-2-bromovinyl benzoates were subjected to the standard reaction conditions, the desired products **3a** and **3f** were produced in 81% and 84% yields, respectively (Scheme 4, eq 6). Therefore, we presumed that the consumption of (*Z*)-2-bromovinyl benzoate **A** in the catalytic cycle increased its generation significantly. Finally, the transformation exhibited an intermolecular kinetic isotope effect both in a competitive experiment (k_H/k_D = 4.0) and in parallel reactions (k_H/k_D = 4.5) (Scheme 4, eq 7), which indicated that the C−H bond cleavage process should be the turnover-limiting step in the catalytic cycle.

In light of the above observations and previous reports,[14i,20] a plausible mechanism for this Pd-catalyzed *ortho*-C(sp^2)−H functionalization for the synthesis of isocoumarin derivatives is presented in Scheme 5. Initially, *cis*-nucleophilic addition of benzoic acids **2** to bromoalkynes **1** gave the intermediate **6**, which would undergo oxidative addition to Pd(0) species to generate intermediate **A**. Next, *ortho*-C(sp^2)−H activation results in the formation of seven-membered palladacyclic

Scheme 4. Control Experiments



Scheme 5. Proposed Mechanism



intermediate **B**. Finally, the reductive elimination of **B** affords the coupling product **3** and regenerates the active Pd(0) species for the next catalytic cycle.

In summary, we have established the Pd-catalyzed nucleophilic addition/oxidative annulation of bromoalkynes with benzoic acids, which provides an efficient strategy to construct 3-substituted isocoumarins. In addition, the *cis*-nucleophilic addition and C−H functionalization were regarded as the key procedures for this reaction. Remarkably, commercially available benzoic acids without preactivation and a one-pot procedure make this strategy attractive and practical. Further studies will be focused on the synthetic applications of this method, and the results will be reported in due course.

DOI: 10.1021/acs.orglett.7b01919
Org. Lett. XXXX, XXX, XXX−XXX

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b01919.

Experimental procedures, condition screening table, characterization data, and copies of NMR spectra for all products (PDF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

The authors thank the National Key Research and Development Program of China (2016YFA0602900), the National Natural Science Foundation of China (21490572 and 21420102003), and Pearl River S&T Nova Program of Guangzhou (201610010160).

■ REFERENCES

(1) (a) Barry, R. D. *Chem. Rev.* **1964**, *64*, 229. (b) Hill, R. A. In *Progress in the Chemistry of Organic Natural Products*; Springer Verlag: Wien, 1986; Vol. *49*, pp 1−78.

(2) (a) Wang, Q.; Matsuda, H.; Matsuhira, K.; Nakamura, S.; Yuan, D.; Yoshikawa, M. *Biol. Pharm. Bull.* **2007**, *30*, 388. (b) Yoshikawa, M.; Harada, E.; Naitoh, Y.; Inoue, K.; Matsuda, H.; Shimoda, H.; Yamahara, J.; Murakami, N. *Chem. Pharm. Bull.* **1994**, *42*, 2225. (c) Sudarshan, K.; Manna, M. K.; Aidhen, I. S. *Eur. J. Org. Chem.* **2015**, *2015*, 1797. (d) Chen, W.-Z.; Fan, L.-L.; Xiao, H.-T.; Xiao, W.; Wang, J.-T. *Chin. Chem. Lett.* **2014**, *25*, 749.

(3) Riveiro, M. E.; Moglioni, A.; Vazquez, R.; Gomez, N.; Facorro, G.; Piehl, L.; De Celis, E. R.; Shayo, C.; Davio, C. *Bioorg. Med. Chem.* **2008**, *16*, 2665.

(4) Furuta, T.; Fukuyama, Y.; Asakawa, Y. *Phytochemistry* **1986**, *25*, 517.

(5) Hussain, M.; Hussain, M. T.; Rama, N. H.; Hameed, S.; Malik, A.; Khan, K. M. *Nat. Prod. Res.* **2003**, *17*, 207.

(6) Kalinova, B.; Kindl, J.; Jiros, P.; Zacek, P.; Vasickova, S.; Budesinsky, M.; Valterova, I. *J. Nat. Prod.* **2009**, *72*, 8.

(7) Zhang, H.; Matsuda, H.; Kumahara, A.; Ito, Y.; Nakamura, S.; Yoshikawa, M. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 4972.

(8) Shikishima, Y.; Takaishi, Y.; Honda, G.; Ito, M.; Takeda, Y.; Kodzhimatov, O. K.; Ashurmetov, O.; Lee, K. H. *Chem. Pharm. Bull.* **2001**, *49*, 877.

(9) (a) Pal, S.; Chatare, V.; Pal, M. *Curr. Org. Chem.* **2011**, *15*, 782. (b) Devon, T. K.; Scott, A. I. *Handbook of Naturally Occurring Compounds*; Academic Press: New York, 1975; Vol. *1*, p 249. (c) Elderfield, R. C. *Heterocyclic Compounds*; Wiley: New York, 1951; Vol. *2*. (d) Li, W.; Wiesenfeldt, M. P.; Glorius, F. *J. Am. Chem. Soc.* **2017**, *139*, 2585. (e) Conda-Sheridan, M.; Park, E.-J.; Beck, D. E.; Reddy, P. V. N.; Nguyen, T. X.; Hu, B. J.; Chen, L.; White, J. J.; van Breemen, R. B.; Pezzuto, J. M.; Cushman, M. *J. Med. Chem.* **2013**, *56*, 2581. (f) Dasaradhan, C.; Kumar, Y. S.; Khan, F.-R. N.; Jeong, E. D.; Chung, E. H. *Tetrahedron Lett.* **2015**, *56*, 187. (g) Hathwar, V. R.; Manivel, P.; Khan, F. N.; Row, T. N. G. *CrystEngComm* **2009**, *11*, 284.

(10) (a) Ackermann, L.; Pospech, J.; Graczyk, K.; Rauch, K. *Org. Lett.* **2012**, *14*, 930. (b) Frasco, D. A.; Lilly, C. P.; Boyle, P. D.; Ison, E. A. *ACS Catal.* **2013**, *3*, 2421. (c) Kumar, M. R.; Irudayanathan, F. M.; Moon, J. H.; Lee, S. *Adv. Synth. Catal.* **2013**, *355*, 3221. (d) Li, X.; Liu, K.; Zou, G.; Liu, P. *Adv. Synth. Catal.* **2014**, *356*, 1496. (e) Prakash, R.; Shekarrao, K.; Gogoi, S.; Boruah, R. C. *Chem. Commun.* **2015**, *51*, 9972. (f) Tan, H.; Li, H.; Wang, J.; Wang, L. *Chem. - Eur. J.* **2015**, *21*, 1904. (g) Hara, Y.; Onodera, S.; Kochi, T.; Kakiuchi, F. *Org. Lett.* **2015**, *17*, 4850. (h) Kudo, E.; Shibata, Y.; Yamazaki, M.; Masutomi, K.; Miyauchi, Y.; Fukui, M.; Sugiyama, H.; Uekusa, H.; Satoh, T.; Miura, M.; Tanaka, K. *Chem. - Eur. J.* **2016**, *22*, 14190. (i) Nandi, D.; Ghosh, D.; Chen, S.-J.; Kuo, B.-C.; Wang, N. M.; Lee, H. M. *J. Org. Chem.* **2013**, *78*, 3445. (j) Yang, C.; He, X.; Zhang, L.; Han, G.; Zuo, Y.; Shang, Y. *J. Org. Chem.* **2017**, *82*, 2081.

(11) Kajita, Y.; Kurahashi, T.; Matsubara, S. *J. Am. Chem. Soc.* **2008**, *130*, 17226.

(12) Warratz, S.; Kornhaaβ, C.; Cajaraville, A.; Niepötter, B.; Stalke, D.; Ackermann, L. *Angew. Chem., Int. Ed.* **2015**, *54*, 5513.

(13) (a) Wu, W.; Jiang, H. *Acc. Chem. Res.* **2014**, *47*, 2483. (b) Jiang, H.; Zhu, C.; Wu, W. *Haloalkyne Chemistry*; Springer: Heidelberg, 2016; pp 1−77. (c) Trofimov, A.; Chernyak, N.; Gevorgyan, V. *J. Am. Chem. Soc.* **2008**, *130*, 13538. (d) Yoo, W.-J.; Allen, A.; Villeneuve, K.; Tam, W. *Org. Lett.* **2005**, *7*, 5853. (e) Hein, J. E.; Tripp, J. C.; Krasnova, L. B.; Sharpless, K. B.; Fokin, V. V. *Angew. Chem.* **2009**, *121*, 8162. (f) Crossley, J. A.; Browne, D. L. *J. Org. Chem.* **2010**, *75*, 5414. (g) Xie, L.; Wu, Y.; Yi, W.; Zhu, L.; Xiang, J.; He, W. *J. Org. Chem.* **2013**, *78*, 9190.

(14) (a) Rasolofonjatovo, E.; Theeramunkong, S.; Bouriaud, A.; Kolodych, S.; Chaumontet, M.; Taran, F. *Org. Lett.* **2013**, *15*, 4698−4701. (b) Ye, Q.; Cheng, T.; Zhao, Y.; Zhao, J.; Jin, R.; Liu, G. *ChemCatChem* **2015**, *7*, 1801. (c) Zhu, G.; Chen, D.; Wang, Y.; Zheng, R. *Chem. Commun.* **2012**, *48*, 5796. (d) Sauermann, N.; Gonzalez, M. J.; Ackermann, L. *Org. Lett.* **2015**, *17*, 5316. (e) Tan, H.; Li, H.; Ji, W.; Wang, L. *Angew. Chem., Int. Ed.* **2015**, *54*, 8374. (f) Huang, H.-Y.; Cheng, L.; Liu, J.-J.; Wang, D.; Liu, L.; Li, C.-J. *J. Org. Chem.* **2017**, *82*, 2656. (g) Ji, F.; Li, X.; Wu, W.; Jiang, H. *J. Org. Chem.* **2014**, *79*, 11246. (h) Zeng, X.; Liu, S.; Shi, Z.; Xu, B. *Org. Lett.* **2016**, *18*, 4770. (i) Wang, S.; Li, P.; Yu, L.; Wang, L. *Org. Lett.* **2011**, *13*, 5968.

(15) Li, Y.; Liu, X.; Ma, D.; Liu, B.; Jiang, H. *Adv. Synth. Catal.* **2012**, *354*, 2683.

(16) Chen, Z.; Jiang, H.; Li, Y.; Qi, C. *Chem. Commun.* **2010**, *46*, 8049.

(17) Chen, Z.; Li, J.; Jiang, H.; Zhu, S.; Li, Y.; Qi, C. *Org. Lett.* **2010**, *12*, 3262.

(18) Li, Y.; Zhao, J.; Chen, H.; Liu, B.; Jiang, H. *Chem. Commun.* **2012**, *48*, 3545.

(19) Jiang, G.; Zhu, C.; Li, J.; Wu, W.; Jiang, H. *Adv. Synth. Catal.* **2017**, *359*, 1208.

(20) (a) Tan, Y.; Hartwig, J. F. *J. Am. Chem. Soc.* **2010**, *132*, 3676. (b) Shi, Z.-J.; Zhang, C.; Li, S.; Pan, D.; Ding, S.; Cui, Y.; Jiao, N. *Angew. Chem.* **2009**, *121*, 4642. (c) González-Liste, P. J.; Francos, J.; García-Garrido, S. E.; Cadierno, V. *J. Org. Chem.* **2017**, *82*, 1507.

DOI: 10.1021/acs.orglett.7b01919
Org. Lett. XXXX, XXX, XXX−XXX