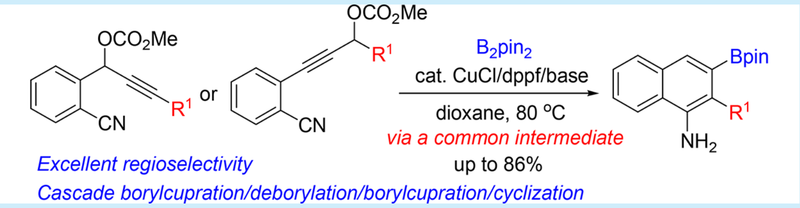
Organic LETTERS
Cite This: *Org. Lett.* XXXX, XXX, XXX−XXX
Letter
pubs.acs.org/OrgLett

Copper-Catalyzed Borylative Cyclization of *o*-(Cyano)phenyl Propargyl Carbonates: Synthesis of Functionalized 1-Naphthylamines

Meijun Xiong,[†] Hui Hu,[†] Xiaoping Hu, and Yuanhong Liu*

State Key Laboratory of Organometallic Chemistry, Center for Excellence in Molecular Synthesis, Shanghai Institute of Organic Chemistry, University of Chinese Academy of Sciences, Chinese Academy of Sciences, 345 Lingling Lu, Shanghai 200032, People's Republic of China

Supporting Information



ABSTRACT: Copper-catalyzed borylative cyclization of *o*-(cyano)phenyl propargyl carbonates leads to a highly efficient and regioselective synthesis of 3-boryl-1-naphthylamines. A cascade sequence involving the formation of allenyl boronates via borylcupration, deborylation, borylcupration, and cyclization is proposed for this reaction. The resulting products have been applied for the synthesis of a variety of functionalized 1-naphthylamines via oxidation or metal-catalyzed coupling reactions.

1-Naphthylamines are important structural motifs found in a variety of biologically active substances and natural products.[1] They are also widely used as useful building blocks in synthetic chemistry and the dyestuffs industry.[2] Especially, 1-naphthylamines bearing functionalities on the amino-substituted aryl rings have been shown to display unique biological activities (Figure 1).[3] However, efficient routes for the synthesis of functionalized 1-naphthylamines are quite limited, which include reduction of nitroarenes or azides,[4a,b] metal catalyzed C−N coupling,[4c] Semmler−Wolff reactions,[4d] benzannulations,[4e−h] etc.[4] Most of these procedures suffer from harsh reaction conditions, limited substrate availability, or low functional group tolerance. Therefore, the development of an efficient and regioselective protocol to 1-naphthylamines is highly desirable.

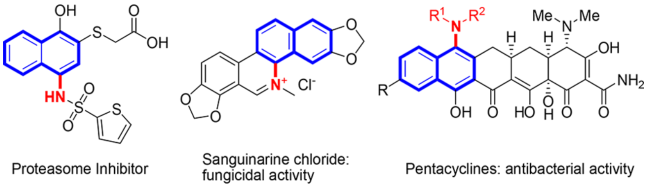
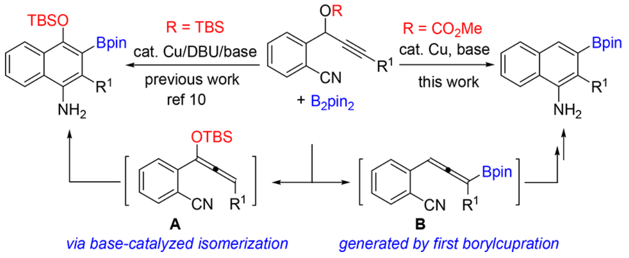


Figure 1. Representative bioactive compounds bearing 1-aminonaphthalene structure.

In recent years, copper-catalyzed borylation of unsaturated π-systems such as alkynes, allenes, and alkenes have emerged as one of the most efficient methods for the synthesis of organoboron derivatives.[5] In these transformations, the copper-boryl species adds in a *syn*-fashion across the carbon−carbon multiple bonds to give β-borylorganocopper species, which could be trapped by a variety of electrophiles such as proton, tin electrophiles, organohalides, carbonyl compounds, allyl phosphates, etc. Incorporation of the borylcupration step into a cascade sequence with concomitant C−C bond-forming cyclization would be highly attractive for the rapid construction of architecturally complex structures from easily available starting materials. Although many intermolecular borylative three-component coupling reactions have been reported,[5] copper-catalyzed borylative cyclizations have rarely been exploited. In this regard, borylation has been developed, followed by aldol,[6] alkylation,[7] carboxylation,[8] and conjugate addition[9] by the research groups of Lam, Ito, Hou, and Lin et al. Recently, we have reported a copper(I)-catalyzed borylcupration/cyclization of *o*-(cyano)phenyl propargyl ethers that produce 4-OTBS-3-boryl-1-naphthylamines (Scheme 1).[10]

Scheme 1. Copper-Catalyzed Borylative Cyclization of Propargyl Derivatives



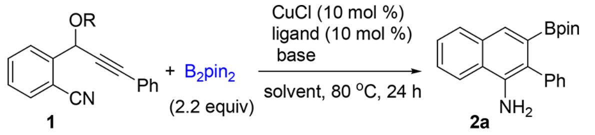
Received: May 9, 2018

DOI: 10.1021/acs.orglett.8b01457

These reactions proceed via regioselective addition of the borylcopper species to an allene intermediate **A** generated in situ through base-catalyzed propargyl-allenyl isomerization followed by nucleophilic attack to the nitrile moiety. During our study on the chemistry of propargyl derivatives, we found that when a carbonate was employed, instead of the TBS ether, 3-boryl-1-naphthylamines were formed under the optimized reaction conditions. It was realized that double borylcuprations might take place and the allenyl boronate intermediate **B** was possibly formed through the first borylcupration. To our knowledge, for the metal-catalyzed synthesis of allenyl boronates, only Cu(I)-[11] or Pd/Cu[12]-catalyzed transformation of propargyl carbonates, and the Cu-catalyzed direct borylation of propargyl alcohols,[13] to allenyl boronates has been reported. However, these reactions were restricted to the propargyl substrates bearing an alkyl group on either end of the alkyne terminus and/or the propargylic position.[14] Furthermore, the cascade reaction involving the allene generation by these methods has not been established. The unique reaction mode, high regioselectivity, and the use of an economic copper catalyst in our newly discovered reactions prompted us to further study this transformation. Herein, we present an efficient method to borylated 1-naphthylamines based on borylcupration reactions. In addition, derivatizations of the products by amination, oxidation, and Suzuki–Miyaura coupling reactions were also performed to demonstrate the synthetic utility of this reaction.

Initially, the copper-catalyzed cyclization of propargyl carbonate **1a** bearing a phenyl group at the alkyne terminus with B_2pin_2 was performed under a variety of reaction conditions (Table 1). After investigation of the reaction parameters such as copper salts, ligand, base, and solvent, we found that the appropriate choice of base is crucial for the success of the reaction. For example, when CsF, KO^{t}Bu, or K_2CO_3 was added to the reaction mixture, the desired 3-boryl-1-naphthylamine **2a** either was obtained in low yields (8–23%) or resulted in a complex reaction mixture (Table 1, entries 1–3). Possibly, substrate decomposition occurred during the reaction process in these cases. To our delight, boronate **2a** was obtained in 44% and 62% yields with Cs_2CO_3 or KOH as the base additive (Table 1, entries 4–5). The best yield of **2a** was achieved using $NaHCO_3$ as the base (Table 1, entry 6). The formation of the single product **2a** also indicated that highly regioselective borylcupration was involved in the reaction. Decreasing the amount of $NaHCO_3$ to 2.0 equiv delivered **2a** in a lower yield of 51% (Table 1, entry 7). Without a base, **2a** was not observed, indicating the important role of the base (Table 1, entry 8). A control experiment indicated that no decomposition took place by stirring the mixture of carbonate **1a** with $NaHCO_3$ in dioxane at 80 °C for 24 h. The effects of the ligands on the reaction course were also examined. Among various monophosphine ligands, PPh_3 gave the best result (Table 1, entries 9–11). Dppp and 1,10-phen ligands also promoted this cyclization reaction, furnishing **2a** in 62% and 53% yields, respectively (Table 1, entries 12 and 14). However, Xantphos showed low efficiency for this reaction (Table 1, entry 13). Without a ligand, only 33% of **2a** was obtained (Table 1, entry 15). It was noted that the desired product could not be formed in the absence of a copper catalyst. A good yield of **2a** was also observed when toluene was used as the solvent (Table 1, entry 16). Benzyl carbonate **3a** could be used instead of the methyl carbonate (Table 1, entry 19). However, employing propargyl acetate (**3b**) or benzoate (**3c**) led to **2a** in low yields (Table 1, entries 20–21). The use of the TBS ether **3d** or nonprotected **3e** was ineffective for this reaction (Table 1, entries 22–23).

Table 1. Optimization Studies for the Formation of 2a

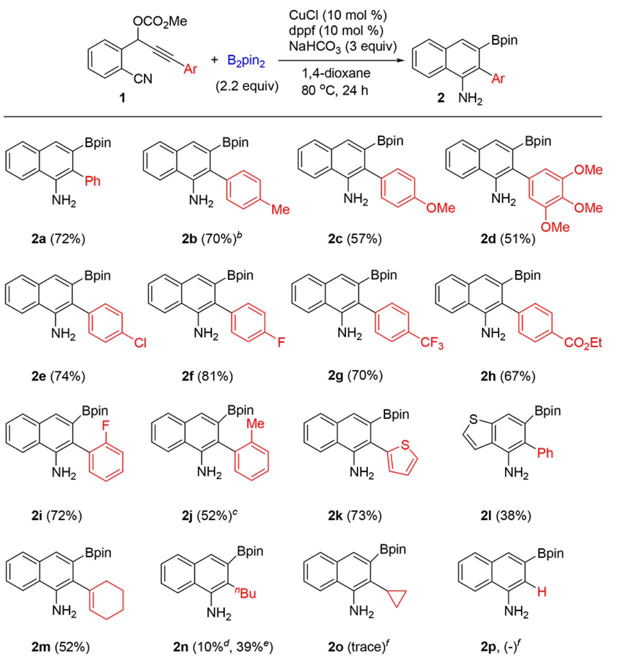


entry	R	ligand	base (equiv)	solvent	yield (%)[a]
1	CO_2Me (**1a**)	dppf	CsF (3)	1,4-dioxane	8
2	CO_2Me (**1a**)	dppf	KO^{t}Bu (3)	1,4-dioxane	-[b]
3	CO_2Me (**1a**)	dppf	K_2CO_3 (3)	1,4-dioxane	23
4	CO_2Me (**1a**)	dppf	Cs_2CO_3 (3)	1,4-dioxane	44
5	CO_2Me (**1a**)	dppf	KOH (3)	1,4-dioxane	62
6	CO_2Me (**1a**)	dppf	$NaHCO_3$ (3)	1,4-dioxane	72
7	CO_2Me (**1a**)	dppf	$NaHCO_3$ (2)	1,4-dioxane	51
8	CO_2Me (**1a**)	dppf	-	1,4-dioxane	0 (99)
9	CO_2Me (**1a**)	PPh_3	$NaHCO_3$ (3)	1,4-dioxane	68
10	CO_2Me (**1a**)	$PMePh_2$	$NaHCO_3$ (3)	1,4-dioxane	55
11	CO_2Me (**1a**)	P*n*-Bu_3	$NaHCO_3$ (3)	1,4-dioxane	43
12	CO_2Me (**1a**)	dppp	$NaHCO_3$ (3)	1,4-dioxane	62
13	CO_2Me (**1a**)	Xantphos	$NaHCO_3$ (3)	1,4-dioxane	31
14	CO_2Me (**1a**)	1,10-phen	$NaHCO_3$ (3)	1,4-dioxane	53
15	CO_2Me (**1a**)	-	$NaHCO_3$ (3)	1,4-dioxane	33 (37)
16	CO_2Me (**1a**)	dppf	$NaHCO_3$ (3)	toluene	71
17	CO_2Me (**1a**)	dppf	$NaHCO_3$ (3)	THF	43
18	CO_2Me (**1a**)	dppf	$NaHCO_3$ (3)	CH_3CN	trace
19	CO_2Bn (**3a**)	dppf	$NaHCO_3$ (3)	1,4-dioxane	68
20	Ac (**3b**)	dppf	$NaHCO_3$ (3)	1,4-dioxane	31 (43)
21	Bz (**3c**)	dppf	$NaHCO_3$ (3)	1,4-dioxane	28 (40)
22	TBS (**3d**)	dppf	$NaHCO_3$ (3)	1,4-dioxane	0
23	H (**3e**)	dppf	$NaHCO_3$ (3)	1,4-dioxane	3

[a] Isolated yields. The yields of the recovered **1a** are shown in parentheses. [b] Complicated mixture.

With the optimized reaction conditions in hand (Table 1, entry 6), the scope of the *o*-(cyano)phenyl propargyl carbonates **1** was evaluated (Scheme 2). A wide variety of aryl-substituted alkynes exhibited tolerance for this reaction. It was found that the aromatic rings at the alkyne terminus bearing electron-donating or -withdrawing groups were all compatible under the standard reaction conditions. For example, a *p*-Me-substituted aryl alkyne afforded **2b** in 70% yield. However, *p*-OMe or 3,4,5-tri(OMe)-substituted alkynes transformed to the corresponding products **2c** and **2d** in lower yields (51–57%). The use of *p*-Cl, *p*-F, *p*-CF_3, *p*-CO_2Et, and *o*-F-substituted aryl alkynes afforded **2e**–**2i**[15] in good yields of 67–81%. With a phenyl ring bearing a Me group at the *ortho*-position, the desired product **2j** was formed in a moderate yield, indicating that the reactivity of the propargyl substrates could be influenced by their steric hindrance. Heteroaryl alkynes such as the 2-thienyl-substituted one could also be incorporated successfully into the cascade sequence, giving **2k** in 73% yield. The substrate bearing a thienyl nitrile framework afforded **2l** in 38% yield. The use of an alkenyl-substituted alkyne afforded **2m** in moderate yield (52%). However, when an alkyl-substituted alkyne such as *n*-butyl-substituted **1n** was used, only 10% of the desired product **2n** was observed, and **1n** was recovered in 27% yield under the standard reaction conditions. Increasing the reaction temperature to 130 °C improved the yield of **2n** to 39%. The use of cyclopropyl-substituted alkyne or terminal alkyne resulted in a complex

Scheme 2. Scope of *o*-(Cyano)phenyl Propargyl Carbonates[a]

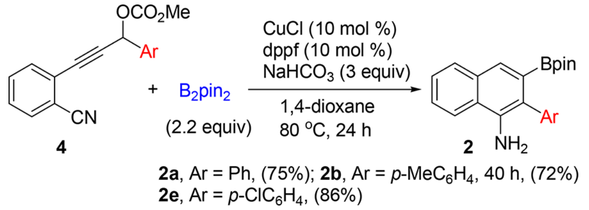


[a]Isolated yields. [b]42 h. [c]40 h. [d]Substrate **1n** was recovered in 27% yield. [e]130 °C, 10 h. [f]Complex mixture was observed.

reaction mixture (**2o** and **2p**), and the starting material was mostly (**2o**) or completely (**2p**) consumed.

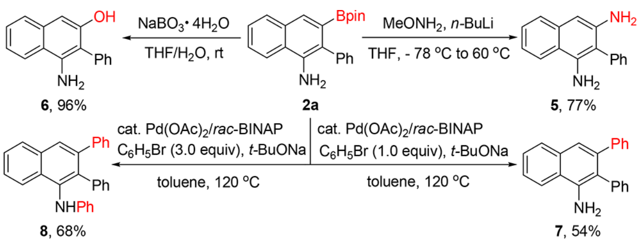
Encouraged by the above results, we next investigated the reactivity of propargyl carbonates **4** bearing an *ortho*-cyanophenyl group at the alkyne terminus (Scheme 3). To our surprise, the same products of 3-boryl-1-naphthylamine **2** were formed under the standard reaction conditions. The yields of the products were comparable to that obtained in the catalytic cyclization of *o*-(cyano)phenyl propargyl carbonates **1**. The results indicate that a common intermediate should be involved in the cyclization reactions of substrates **1** and **4**.

Scheme 3. Copper-Catalyzed Borylative Cyclization of Propargyl Carbonates 4



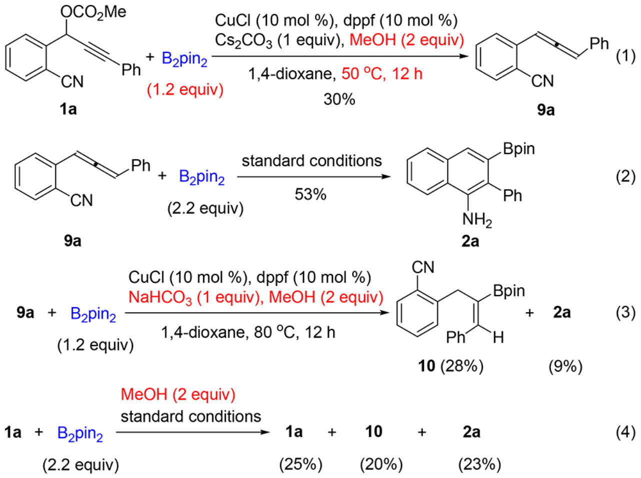
The boronated 1-naphthylamines obtained through the present method could serve as versatile substrates for accessing various functionalized 1-naphthylamines. For example, in the presence of $MeONH_2$ and *n*-BuLi,[16] boronate **2a** was converted to naphthalene-1,3-diamine **5** in 77% yield (Scheme 4). Oxidation of **2a** with $NaBO_3{\cdot}4H_2O$ proceeded efficiently to give **6** in 96% yield. Suzuki coupling reaction of **2a** with 1.0 equiv or 3.0 equiv bromobenzene afforded the corresponding phenylated products **7** and **8** via C−C or C−C/C−N coupling reactions in 54% and 68% yields, respectively.

Scheme 4. Transformations of the Cyclized Product 2a



To understand the reaction mechanism, various control experiments were carried out. To probe the possible reaction intermediates, hydroborylation of carbonate **1a** in the presence of 2.0 equiv MeOH was carried out. It was found that when the reaction was performed at 50 °C in the presence of 1.0 equiv of Cs_2CO_3, allene **9a** was formed in 30% yield (Scheme 5, eq 1).

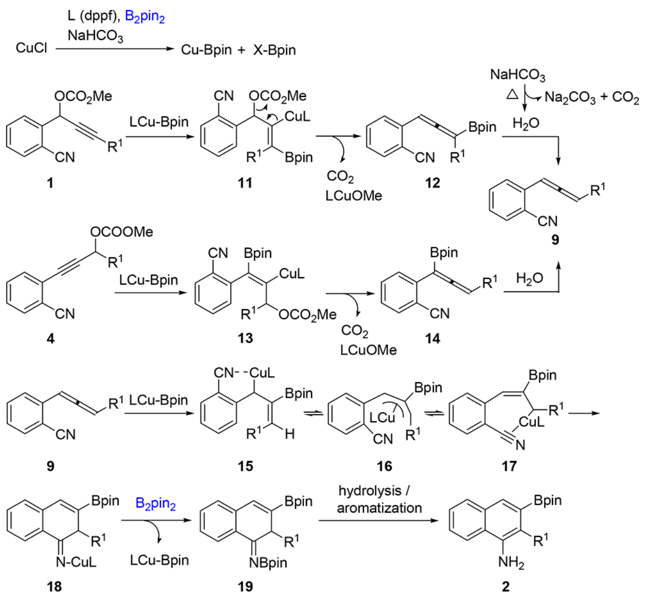
Scheme 5. Control Experiments



The desired allenyl boronate was not observed, possibly due to its low stability. This allenyl boronate may easily undergo protodeborylation in the presence of a proton source.[12,17] Reaction of allene **9a** with B_2pin_2 under the standard reaction conditions afforded the desired **2a** in 53% yield (Scheme 5, eq 2), implying that the allene serves as a reaction intermediate in copper-catalyzed cascade reactions. When the reactions of **9a** or **1a** with B_2pin_2 were carried out in the presence of 2.0 equiv MeOH under the standard reaction conditions, alkene **10** was observed (Scheme 5, eqs 3−4). The results indicate that an allyl copper intermediate was involved in the reaction process. The geometric configuration of **10** was confirmed by X-ray crystallographic analysis.[15]

Based on the above-mentioned results, a possible reaction mechanism for this reaction is presented in Scheme 6. In the initial step, a LCu-Bpin intermediate was generated by the reaction of CuCl with the ligand and B_2pin_2 assisted by a base. Regioselective 1,2-*cis*-addition of the Cu−B species to the alkyne moiety takes place to give an alkenylcopper(I) intermediate **11**. Elimination followed by decomposition provides LCu-OMe species and CO_2 with concomitant formation of the allenyl boronate **12**. Protodeborylation of **12** by H_2O, possibly produced from the thermal decomposition of $NaHCO_3$ or from that contaminated in the reaction mixture, delivers allene intermediate **9**. Similarly, borylcupration of the propargyl carbonate **4** affords the same intermediate **9**. Next, the Cu−B species adds to the allene from the less encumbered face of the allene to form an (*E*)-allylcopper **15** according to the results of the control experiment (Scheme 5, eqs 3−4), or

Scheme 6. Possible Reaction Mechanism



allylcopper **17** (the stereochemistry was not known), and both of these intermediates might be stabilized by the cyano group. (*E*)-Allylcopper **15** might isomerize to allylcopper **17** through a π-allylcopper intermediate **16** derived from $\eta^1-\eta^3$ interconversion.[18] Nucleophilic attack of the allylcopper moiety in **17** to the cyano group, followed by transmetalation, gives an iminoboron intermediate **19** and regenerates the copper catalyst. Hydrolysis and aromatization of **19** deliver the final product **2**. The challenging issue in borylcupration of allenes lies in the regioselectivity. Copper-catalyzed borylation of allenes has been studied by various groups such as Tsuji, Ma, and Hoveyda,[19] However, the high regioselectivity leading to allyl copper species was observed mainly with terminal allenes. The results shown in the borylation of intermediate **9** indicates that π-allyl copper species could also be selectively formed from internal 1,3-diaryl-substituted allenes.

In summary, we have developed a copper-catalyzed borylative cyclization of *o*-(cyano)phenyl propargyl carbonates, which provides a highly substituted 3-boryl-1-naphthylamines with excellent regioselectivity and wide functional group compatibility. The resulting products have been applied for the synthesis of functionalized 1-naphthylamines via oxidation or coupling reactions. The reaction likely proceeds through the generation of allenyl boronates via copper-catalyzed borylation of propargyl carbonates, followed by cascade deborylation/borylcupration and cyclization reactions. Further applications of this cascade reaction to the synthesis of diverse complex molecules are currently underway.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b01457.

Experimental details, spectroscopic characterization of all new compounds (PDF)

Accession Codes

CCDC 1841186 and 1841193 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: yhliu@sioc.ac.cn.

ORCID

Yuanhong Liu: 0000-0003-1153-5695

Author Contributions

[†]M.-J.X. and H.H. contributed equally.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank the National Key Research and Development Program (2016YFA0202900), the Science and Technology Commission of Shanghai Municipality (18XD1405000), the Strategic Priority Research Program of the Chinese Academy of Sciences (Grant No. XDB20000000), and Shanghai Institute of Organic Chemistry (sioczz201807) for financial support.

■ REFERENCES

(1) (a) Cui, H.; Kamal, Z.; Ai, T.; Xu, Y.; More, S. S.; Wilson, D. J.; Chen, L. *J. Med. Chem.* **2014**, *57*, 8340. (b) Naumiec, G. R.; Jenko, K. J.; Zoghbi, S. S.; Innis, R. B.; Cai, L.; Pike, V. W. *J. Med. Chem.* **2015**, *58*, 9722.

(2) (a) Matsumoto, K.; Dougomori, K.; Tachikawa, S.; Ishii, T.; Shindo, M. *Org. Lett.* **2014**, *16*, 4754. (b) Seth, K.; Roy, S. R.; Kumar, A.; Chakraborti, A. K. *Catal. Sci. Technol.* **2016**, *6*, 2892.

(3) (a) Ge, Y.; Kazi, A.; Marsilio, F.; Luo, Y.; Jain, S.; Brooks, W.; Daniel, K. G.; Guida, W. C.; Sebti, S. M.; Lawrence, H. R. *J. Med. Chem.* **2012**, *55*, 1978. (b) Lv, P.; Chen, Y.; Shi, T.; Wu, X.; Li, Q. X.; Hua, R. *Pestic. Biochem. Physiol.* **2017**, DOI: 10.1016/j.pestbp.2017.06.009. (c) Sun, C.; Hunt, D. K.; Clark, R. B.; Lofland, D.; O'Brien, W. J.; Plamondon, L.; Xiao, X.-Y. *J. Med. Chem.* **2011**, *54*, 3704.

(4) (a) Yadav, V.; Gupta, S.; Kumar, R.; Singh, G.; Lagarkha, R. *Synth. Commun.* **2012**, *42*, 213. (b) Rolla, F. *J. Org. Chem.* **1982**, *47*, 4327. (c) Shen, Q.; Hartwig, J. F. *J. Am. Chem. Soc.* **2006**, *128*, 10028. (d) Hong, W. P.; Iosub, A. V.; Stahl, S. S. *J. Am. Chem. Soc.* **2013**, *135*, 13664. (e) Sagar, P.; Fröhlich, R.; Würthwein, E.-U. *Angew. Chem., Int. Ed.* **2004**, *43*, 5694. (f) Gao, P.; Liu, J.; Wei, Y. *Org. Lett.* **2013**, *15*, 2872. (g) Reddy, R. S.; Prasad, P. K.; Ahuja, B. B.; Sudalai, A. *J. Org. Chem.* **2013**, *78*, 5045. (h) Zhao, S.-C.; Shu, X.-Z.; Ji, K.-G.; Zhou, A.-X.; He, T.; Liu, X.-Y.; Liang, Y.-M. *J. Org. Chem.* **2011**, *76*, 1941.

(5) For recent reviews, see: (a) Semba, K.; Fujihara, T.; Terao, J.; Tsuji, Y. *Tetrahedron* **2015**, *71*, 2183. (b) Neeve, E. C.; Geier, S. J.; Mkhalid, I. A. I.; Westcott, S. A.; Marder, T. B. *Chem. Rev.* **2016**, *116*, 9091. (c) Yoshida, H. *ACS Catal.* **2016**, *6*, 1799.

(6) (a) Burns, A. R.; González, J. S.; Lam, H. W. *Angew. Chem., Int. Ed.* **2012**, *51*, 10827. (b) Welle, A.; Cirriez, V.; Riant, O. *Tetrahedron* **2012**, *68*, 3435. (c) Zhao, Y. S.; Tang, X. Q.; Tao, J.-C.; Tian, P.; Lin, G.-Q. *Org. Biomol. Chem.* **2016**, *14*, 4400.

(7) (a) Kubota, K.; Iwamoto, H.; Yamamoto, E.; Ito, H. *Org. Lett.* **2015**, *17*, 620. (b) Ito, H.; Kosaka, Y.; Nonoyama, K.; Sasaki, Y.; Sawamura, M. *Angew. Chem., Int. Ed.* **2008**, *47*, 7424. (c) Kubota, K.; Yamamoto, E.; Ito, H. *J. Am. Chem. Soc.* **2013**, *135*, 2635. (d) Ito, H.; Toyoda, T.; Sawamura, M. *J. Am. Chem. Soc.* **2010**, *132*, 5990. (e) Zhong, C.; Kunii, S.; Kosaka, Y.; Sawamura, M.; Ito, H. *J. Am. Chem. Soc.* **2010**, *132*, 11440.

(8) Zhang, L.; Cheng, J.; Carry, B.; Hou, Z. *J. Am. Chem. Soc.* **2012**, *134*, 14314.

(9) Liu, P.; Fukui, Y.; Tian, P.; He, Z.-T.; Sun, C.-Y.; Wu, N.-Y.; Lin, G.-T. *J. Am. Chem. Soc.* **2013**, *135*, 11700.
(10) Xiong, M.; Xie, X.; Liu, Y. *Org. Lett.* **2017**, *19*, 3398.
(11) Ito, H.; Sasaki, Y.; Sawamura, M. *J. Am. Chem. Soc.* **2008**, *130*, 15774.
(12) Zhao, T. S. N.; Yang, Y.; Lessing, T.; Szabó, K. J. *J. Am. Chem. Soc.* **2014**, *136*, 7563.
(13) Mao, L.; Szabó, K. J.; Marder, T. B. *Org. Lett.* **2017**, *19*, 1204.
(14) A Pd/Ag-catalyzed borylation of terminal alkynes has been reported (three examples); see ref 12.
(15) For X-ray crystallography of compounds **2h** and **10**, see the Supporting Information.
(16) Mlynarski, S. N.; Karns, A. S.; Morken, J. P. *J. Am. Chem. Soc.* **2012**, *134*, 16449.
(17) Nave, S.; Sonawane, R. P.; Elford, T. G.; Aggarwal, V. K. *J. Am. Chem. Soc.* **2010**, *132*, 17096.
(18) Russo, V.; Herron, J. R.; Ball, Z. T. *Org. Lett.* **2010**, *12*, 220.
(19) (a) Meng, F.; Jung, B.; Haeffner, F.; Hoveyda, A. H. *Org. Lett.* **2013**, *15*, 1414. (b) Semba, K.; Shinomiya, M.; Fujihara, T.; Terao, J.; Tsuji, Y. *Chem. - Eur. J.* **2013**, *19*, 7125. (c) Yuan, W.; Song, L.; Ma, S. *Angew. Chem., Int. Ed.* **2016**, *55*, 3140.

DOI: 10.1021/acs.orglett.8b01457