Organic LETTERS
Letter
pubs.acs.org/OrgLett

Copper-Catalyzed Cross-Coupling Reaction of Allyl Boron Ester with 1°/2°/3°-Halogenated Alkanes

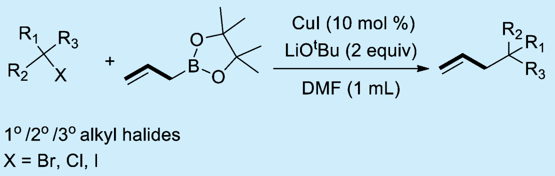
Guang-Zu Wang,[†] Jian Jiang,[†] Xiao-Song Bu,[†] Jian-Jun Dai,[†] Jun Xu,[‡] Yao Fu,*[,‡] and Hua-Jian Xu*[,†]

[†]School of Medical Engineering, School of Chemistry and Chemical Engineering, Hefei University of Technology, Hefei 230009, P. R. China

[‡]Department of Chemistry, University of Science and Technology of China, Hefei 230026, China

Ⓢ *Supporting Information*

ABSTRACT: The cross-coupling reaction of allyl boron ester with 1°/2°/3°-halogenated alkanes in the presence of copper has been developed for the first time, which provides a mild and efficient method for the construction of saturated C(sp^3)−C(sp^3) bonds. This protocol shows excellent compatibility with the nonactivated primary, secondary, and even tertiary halogenated alkanes under mild conditions.



Transition-metal-catalyzed cross-coupling reactions of organometallic reagents (e.g., Mg and Li) with halogenated alkanes provide an effective method for the construction of C−C bonds in organic synthesis.[1] For instance, the Pd- and Ni-catalyzed aryl−alkyl[2] and alkyl−alkyl[3] cross-coupling reactions have been widely developed. Recently, as an efficient and environmentally friendly catalytic species, the development of Cu-catalyzed cross-coupling reactions of halogenated alkanes with organometallic reagents have attracted great attention by chemists in the past decades.[4] In 2011, Liu et al. successfully achieved the Cu-catalyzed cross-coupling reactions between aryl boronate esters and primary alkyl electrophiles.[5] Lately, for the formation of C(sp^3)−C(sp^3) bonds, the cross-coupling reaction of halogenated alkanes with alkyl Grignard reagents under Cu catalysis has also been achieved.[6] However, the disadvantages of Grignard reagents are well-known, including moisture-sensitivity, manipulation difficulty, and decreased functional-group tolerance. Therefore, it remains a great challenge to develop more general and efficient Cu-catalyzed C(sp^3)−C(sp^3) cross-coupling reactions for constructing saturated C−C bonds.

Herein, we describe a mild and convenient method for the coupling reaction of allyl boron ester with primary, secondary, and even tertiary halogenated alkanes, thus providing a practical means for the construction of saturated C−C bonds. The advantages of this approach are as follows: (1) Compared with Grignard reagents, the organoboron reagents show better commercial availability and higher functional-group tolerance.[7] (2) This protocol shows excellent compatibility with the nonactivated primary, secondary, and even tertiary halogenated alkanes under mild conditions. It is worth noting that nucleophilic substitution reactions of unactivated secondary halogenated alkanes always suffer from E2 elimination and remain challenging.[8]

Our study began by examining the cross-coupling of (3-bromopropyl)benzene (**1a**) with allyl boron ester [allylB(pin)]. We initially used CuI as the catalyst, DMF as the solvent, and KO^{t}Bu as the base, attaining a relatively low yield of 15%. To improve the yield, bases were first optimized in our system. When replacing the KO^{t}Bu with less basic NaO^{t}Bu, LiO^{t}Bu, LiOMe, and K$_2$CO$_3$, we found that alkalinity had a significant effect on the yield and LiO^{t}Bu proving to be optimal giving a yield of 83% (Table 1, entries 1−5). Next, the influence of catalyst and solvent were investigated (Table 1, entries 6−12). We screened a variety of copper salts, including copper(I) and copper(II); however, they did not show better catalytic activity compared with CuI. Utilizing coordinating solvents such as THF, toluene, and DMA resulted in lower activity. To further optimize the reaction conditions, the influence of the ligand was investigated by use of three different ligands. Unfortunately, neither the phosphine ligands nor the nitrogen ones showed any positive effect (Table 1, entries 13−15). When we decreased the temperature from 60 to 40 °C and room tempreture, a drastically decreased yield was observed (Table 1, entries 16−17). When 5 mol % of catalyst was employed in the system, we found that only 72% yield was obtained (Table 1, entry 18). Meanwhile, the alkyl iodide was also acceptable coupling partners in this coupling reaction, but the alkyl chloride was not (Table 1, entries 19 and 20). When **1a** was treated under the conditions for the nonactivated alkanes, a lower yield of 65% was obtained (Table 1, entry 21). Finally, the necessity for catalyst and base was confirmed by the blank reaction, and we found that the reactions did not occur if they were omitted (Table 1, entries 22 and 23).

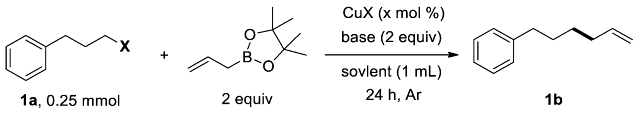
Having identified the optimum reaction conditions, we next set out to examine the scope and limitations of this reaction, and the results are summarized in Scheme 1. First, (3-bromopropyl)benzene (**1a**), (2-bromoethyl)benzene (**1b**), and (4-bromobutyl)benzene (**1c**) were employed to investigate the effect of chain length on the reaction. We found that all of them could participate in the reaction to give a good yield.

Received: June 2, 2015

© XXXX American Chemical Society

DOI: 10.1021/acs.orglett.5b01612
Org. Lett. XXXX, XXX, XXX−XXX

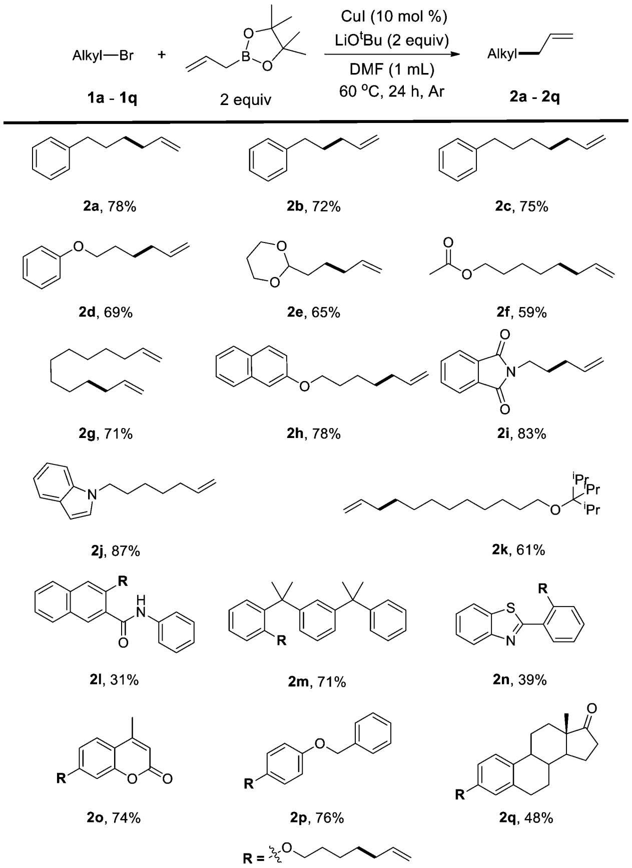
Table 1. Optimization of the Reaction Conditions[a]



entry	catalyst	base	solvent	T (°C)	yield[b] (%)
1	CuI	KO^{t}Bu	DMF	60	15
2	CuI	NaO^{t}Bu	DMF	60	30
3	CuI	LiO^{t}Bu	DMF	60	83
4	CuI	LiOMe	DMF	60	6
5	CuI	K_2CO_3	DMF	60	trace
6	CuCl	LiO^{t}Bu	DMF	60	60
7	CuO	LiO^{t}Bu	DMF	60	15
8	$CuBr_2$	LiO^{t}Bu	DMF	60	39
9	$Cu(acac)_2$	LiO^{t}Bu	DMF	60	28
10	CuI	LiO^{t}Bu	THF	60	3
11	CuI	LiO^{t}Bu	toluene	60	trace
12	CuI	LiO^{t}Bu	DMA	60	32
13[c]	CuI	LiO^{t}Bu	DMF	60	27
14[d]	CuI	LiO^{t}Bu	DMF	60	48
15[e]	CuI	LiO^{t}Bu	DMF	60	55
16	CuI	LiO^{t}Bu	DMF	40	68
17	CuI	LiO^{t}Bu	DMF	25	48
18[f]	CuI	LiO^{t}Bu	DMF	60	72
19[g]	CuI	LiO^{t}Bu	DMF	60	79
20[h]	CuI	LiO^{t}Bu	DMF	60	23
21[i]	CuI	LiO^{t}Bu	DMF	60	65
22		LiO^{t}Bu	DMF	60	trace
23	CuI		DMF	60	trace

[a] Reaction conditions: **1a** (0.25 mmol) (X = Br), catalyst (10 mol %), base (2 equiv), and solvent (1 mL) at 60 °C for 24 h under an Ar atmosphere. [b] GC yield using diphenyl as an internal standard. [c] With 20 mol % of Pph$_3$. [d] With 20 mol % of Pcy$_3$. [e] With 20 mol % of TMEDA. [f] 5 mol % of catalyst was employed. [g] X = I. [h] X = Cl. [i] Halogenated alkanes (0.25 mmol), allylB(pin) (2 equiv), CuI (10 mol %), TMEDA (20 mol %), LiO^{t}Bu (0.5 mmol), and DMF (1 mL) at 0 °C for 48 h under an Ar atmosphere. $Cu(acac)_2$ = cupric acetylacetonate, DMF = *N*,*N*-dimethylformamide, THF = tetrahydrofuran, Pcy$_3$ = tricyclohexylphosphine, TMEDA = tetramethylethylenediamin.

Scheme 1. Copper-Catalyzed Cross-Coupling Reaction of Allyl Boron Ester with Primary Halogenated Alkanes[a]



[a] Reaction conditions: halogenated alkanes (0.25 mmol), allylB(pin) (2 equiv), CuI (10 mol %), LiO^{t}Bu (0.5 mmol), and DMF(1 mL) at 60 °C for 24 h under an Ar atmosphere.

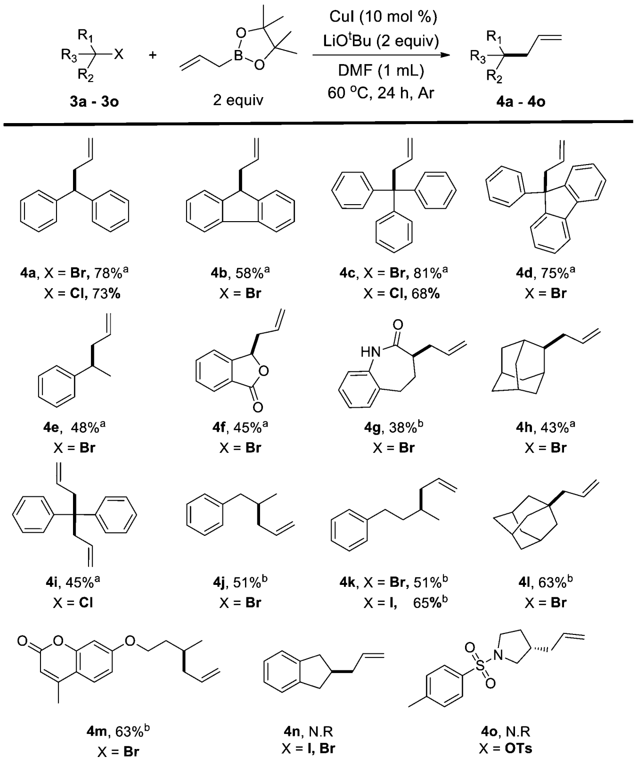
Furthermore, various substrates with synthetically important functional groups such as ether (**1d**, **1h**), ketal (**1e**), ester (**1f**), olefin (**1g**), amide (**1i**), and silyl ether (**1k**) were studied. Most of them were well tolerated with yields as desired except for the secondary amine with a lower yield of 31% (**1l**), which may be due to the effect of active hydrogen on the nitrogen atom. Finally, compounds with heteroatoms, which are typically the skeleton structures of drug molecules, were good substrates for this reaction system (**1j**,**m**−**q**).

Apart from the primary halogenated alkanes, secondary and even tertiary halogenated alkanes were also good substrates in our system (Scheme 2). Moreover, the alkyl bromide, alkyl chloride, and alkyl iodide all reacted well in our system. For the activited halogenated alkanes, such as halogen-substituted benzyl (**3a**−**e**), *ortho*-halogen-substituted ester (**3f**), *ortho*-halogen-substituted amide (**3g**), and halogen-substituted adamantane (**3h**), we could obtain the desired result under the optimal reaction conditions. For the dichlorodiphenylmethane (**3i**), the diallyl-substituted products were obtained with good yield. To further illustrate the importance of the copper−allylB(pin) system, we next investgated the compatibility of nonactivated alkanes. It should be noted that byproduct (such as olefin) produced via loss of hydrogen halide is formed more easily for the nonactivated alkanes in the reaction process.[9] Unfortunately, we can obtain only trace amounts of product under the standard conditions. However, by adding the catalytic amount of TMEDA and decreasing the temperature to 0 °C, we were surprised that the reaction could proceed smoothly in good yield (**3j**−**m**). Unfortunately, for substrate **3n**, we could not obtain the desired product; instead, a rearrangement product was obtained in good yield (see part 3 in the Supporting Information). For the chiral alkyl tosylate (**3o**), the reaction system is limited. In short, this work shows excellent compatibility with the nonactivated primary, secondary, and even tertiary halogenated alkanes under mild conditions.

Next, we attempted the reastion using the 3-substituted allylboronates. However, none of them led to the desired products. Moreover, we also used the allyl alkyl bromide, and the results are shown in the Supporting Information, part 3.

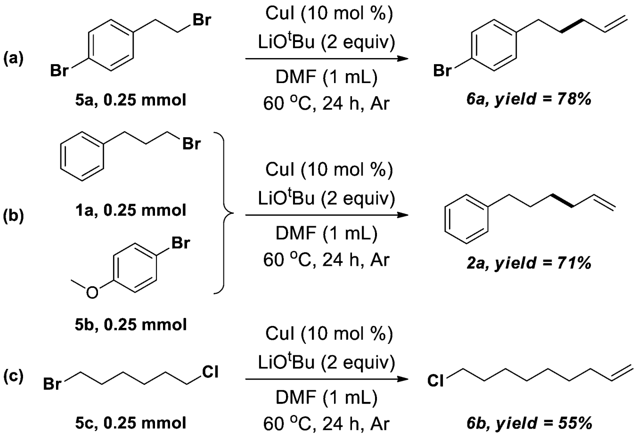
We chose **5a** as the representative to study the reactivity difference between alkyl and aryl halogen atoms. When **5a** was treated with allylB(pin), only the desired alkyl−alkyl cross-coupling product **6a** was obtained in high yield (Scheme 3 (a)), indicating a good chemoselectivity of this reaction. We allowed **1a** and **5b** to react under the same conditions, and as anticipated, only **2a** was formed (Scheme 3 (b)). Subsequently, the reactivity difference between alkyl bromine and chlorine

Scheme 2. Copper-Catalyzed Cross-Coupling Reaction of Allyl Boron Ester with Secondary and Tertiary Halogenated Alkanes[a]



[a]Reaction conditions: halogenated alkanes (0.25 mmol), allylB(pin) (2 equiv), CuI (10 mol %), LiO^{t}Bu (0.5 mmol), and DMF(1 mL) at 60 °C for 24 h under an Ar atmosphere. [b]Reaction conditions: halogenated alkanes (0.25 mmol), allylB(pin) (2 equiv), CuI (10 mol %), TMEDA (20 mol %), LiO^{t}Bu (0.5 mmol), and DMF (1 mL) at 0 °C for 48 h under an Ar atmosphere.

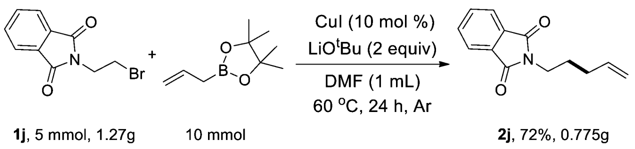
Scheme 3. Selectivity of the Cross-Coupling Reaction



atom was investigated by employing 6-chlorohexyl bromide (**5c**) as an example, and only the bromine-substituted product **6b** was obtained, demonstrating the reactivity order Br > Cl (Scheme 3 (c)) (for detailed results, see part 4 of the Supporting Information). When we reduced the amount of the allylBpin to 1 equiv, a drastically decreased yield was observed for **6a**, **2a**, and **6b**. However, we did not observe any products of the aryl-Br and alkyl-Cl.

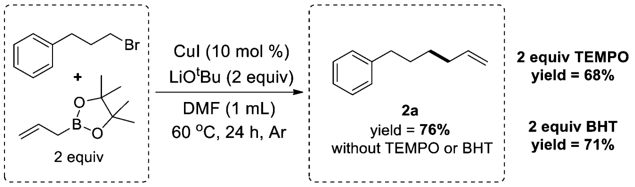
In a scale-up experiment (Scheme 4), **1j** was successfully executed on a larger scale (5 mmol) under the optimum conditions, attaining **2j** with a relatively high yield of 72%.

Scheme 4. Gram-Scale Experiment



Finally, to shed light on the mechanism of the new Cu-catalyzed $C(sp^3)-C(sp^3)$ cross-coupling reaction, TEMPO (2,2,6,6-tetramethylpiperidine-*N*-oxyl) and BHT (butylated hydroxytoluene) were employed as the radical scavengers as shown in Scheme 5. The results demonstrated lower yields (68% and 71% for the TEMPO and BHT, respectively) compared with those performed under standard conditions (76%), which ruled out the possibility of a radical mechanism.

Scheme 5. Investigation of the Mechanism



On the basis of the literature,[10,11] we proposed that the reaction may undergo a transmetalation between CuI and the allylB(pin) to form an allylcopper species intermediate. After that, the organocopper species would react with the halogenated alkanes to afford the final product. As for the mechanism, it may be very complex. By adding TEMPO and BHT, we ruled out the possibility of a radical mechanism of the primary alkanes. However, for the tertiary alkanes, it probably underwent a radical mechanism,[12,8a] and continuing research will be carried out in our laboratory in the future.

To summarize, an efficient and general method for the coupling reaction of allyl boron ester with primary, secondary, and even tertiary halogenated alkanes has been described for the construction of diverse $C(sp^3)-C(sp^3)$ bonds. The compatibility of nonactivated secondary and even tertiary alkyl halides expands the concept and scope of copper-catalyzed cross-coupling reactions in a fundamental sense. Additionally, this reaction showed good chemselectivity for the alkyl halogens compared with aryl ones.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Detailed experimental procedures and spectra data for all compounds. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b01612.

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: fuyao@ustc.edu.cn.
*E-mail: hjxu@hfut.edu.cn.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We gratefully acknowledge financial support from the National Natural Science Foundation of China (Nos. 21272050, 21472033, 21325208, 21361140372) and the Program for New Century Excellent Talents in University of the Chinese Ministry of Education (NCET-11-0627).

■ REFERENCES

(1) (a) Lipshutz, B. H.; Sengupta, S. *Org. React.* **1992**, *1*, 135. (b) Posner, G. H. *Org. React.* **1975**, *22*, 253. (c) Wakefield, B. J. *Organolithium Methods*; Academic Press: London, 1988; Chapter 8. (d) Wakefield, B. J. *Organomagnesium Methods in Organic Synthesis*; Academic Press: London, 1995; Chapter 8.

(2) (a) Zultanski, S. L.; Fu, G. C. *J. Am. Chem. Soc.* **2013**, *135*, 624. (b) Xiao, B.; Liu, Z.-J.; Liu, L.; Fu, Y. *J. Am. Chem. Soc.* **2013**, *135*, 616. (c) Jiao, L.; Herdtweck, E.; Bach, T. *J. Am. Chem. Soc.* **2012**, *134*, 14563. (d) Lyons, T. W.; Sanford, M. S. *Chem. Rev.* **2010**, *110*, 1147. (e) Shabashov, D.; Daugulis, O. *J. Am. Chem. Soc.* **2010**, *132*, 3965. (f) Vechorkin, O.; Proust, V.; Hu, X. *J. Am. Chem. Soc.* **2009**, *131*, 9756. (g) Chen, X.; Engle, K. M.; Wang, D.-H.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2009**, *48*, 5094. (h) Sebelius, S.; Olsson, V. J.; Wallner, O. A.; Szabó, K. J. *J. Am. Chem. Soc.* **2006**, *128*, 8150. (i) Yamamoto, Y.; Takada, S.; Miyaura, N. *Chem. Lett.* **2006**, *35*, 704. (j) Yamamoto, Y.; Takada, S.; Miyaura, N. *Chem. Lett.* **2006**, *35*, 1368. (k) Farmer, J. L.; Hunter, H. N.; Organ, M. G. *J. Am. Chem. Soc.* **2012**, *134*, 17470. (l) Yang, Y.; Buchwald, S. L. *J. Am. Chem. Soc.* **2013**, *135*, 10642. (m) Chausset-Boissarie, L.; Ghozati, K.; LaBine, E.; Chen, J. L. Y.; Aggarwal, V. K.; Crudden, C. M. *Chem. - Eur. J.* **2013**, *19*, 17698.

(3) (a) Jiang, X.; Sakthivel, S.; Kulbitski, K.; Nisnevich, G.; Gandelman, M. *J. Am. Chem. Soc.* **2014**, *136*, 9548. (b) Liang, Z.; Xue, W.; Lin, K.; Gong, H. *Org. Lett.* **2014**, *16*, 5620. (c) Yi, J.; Lu, X.; Sun, Y.-Y.; Xiao, B.; Liu, L. *Angew. Chem., Int. Ed.* **2013**, *52*, 12409. (d) McCann, L. C.; Hunter, H. N.; Clyburne, J. A. C.; Organ, M. G. *Angew. Chem., Int. Ed.* **2012**, *51*, 7024. (e) Lu, Z.; Fu, G. C. *Angew. Chem., Int. Ed.* **2010**, *49*, 6676. (f) Vechorkin, O.; Hu, X. *Angew. Chem., Int. Ed.* **2009**, *48*, 2937. (g) Csok, Z.; Vechorkin, O.; Harkins, S. B.; Scopelliti, R.; Hu, X. *J. Am. Chem. Soc.* **2008**, *130*, 8156. (h) Anderson, T. J.; Jones, G. D.; Vicic, D. A. *J. Am. Chem. Soc.* **2004**, *126*, 8100. (i) Terao, J.; Todo, H.; Watanabe, H.; Ikumi, A.; Kambe, N. *Angew. Chem., Int. Ed.* **2004**, *43*, 6180. (j) Zhou, J.; Fu, G. C. *J. Am. Chem. Soc.* **2003**, *125*, 12527. (k) Giovannini, R.; Stüdemann, T.; Dussin, G.; Knochel, P. *Angew. Chem., Int. Ed.* **1998**, *37*, 2387.

(4) (a) Guo, X.-X.; Gu, D.-W.; Wu, Z.-X.; Zhang, W.-B. *Chem. Rev.* **2015**, *115*, 1622. (b) Cahiez, G.; Gager, O.; Buendia, J. *Angew. Chem., Int. Ed.* **2010**, *49*, 1278. (c) Herber, C.; Breit, B. *Eur. J. Org. Chem.* **2007**, *2007*, 3512. (d) Beletskaya, I. P.; Cheprakov, A. V. *Coord. Chem. Rev.* **2004**, *248*, 2337. (e) Cahiez, G.; Chaboche, C.; Jézéquel, M. *Tetrahedron* **2000**, *56*, 2733. (f) Arai, M.; Nakamura, E.; Lipshutz, B. H. *J. Org. Chem.* **1991**, *56*, 5489. (g) Lipshutz, B. H. *Acc. Chem. Res.* **1997**, *30*, 277. (h) Burns, D. H.; Miller, J. D.; Chan, H. K.; Delaney, M. O. *J. Am. Chem. Soc.* **1997**, *119*, 2125.

(5) Yang, C.-T.; Fu, Y.; Zhang, Z.-Q.; Liu, Y.-C.; Liu, L. *Angew. Chem., Int. Ed.* **2011**, *50*, 3904.

(6) (a) Yang, C.-T.; Zhang, Z.-Q.; Liang, J.; Liu, J.-H.; Lu, X.-Y; Chen, H.-H.; Liu, L. *J. Am. Chem. Soc.* **2012**, *134*, 11124. (b) Ren, P.; Stern, L.-A.; Hu, X. *Angew. Chem., Int. Ed.* **2012**, *51*, 9110. (c) Shen, R.-W.; Iwasaki, T.; Terao, J.; Kambe, N. *Chem. Commun.* **2012**, *48*, 9313. (d) Sai, M.; Yorimitsu, H.; Oshima, K. *Bull. Chem. Soc. Jpn.* **2009**, *82*, 1194. (e) Terao, J.; Todo, H.; Begum, S. A.; Kuniyasu, H.; Kambe, N. *Angew. Chem., Int. Ed.* **2007**, *46*, 2086. (f) Kim, J. H.; Chung, Y. K. *Chem. Commun.* **2013**, *49*, 11101.

(7) (a) *Metal-Catalyzed Cross-Coupling Reactions*; de Meijere, A., Diederich, F., Eds.; Wiley-VCH: Weinheim, 2004. (b) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457. (c) Lloyd-Williams, P.; Giralt, E. *Chem. Soc. Rev.* **2001**, *30*, 145. (d) Kleeberg, C.; Dang, L.; Lin, Z.-Y.; Marder, T. B. *Angew. Chem., Int. Ed.* **2009**, *48*, 5350. (e) Darses, S.; Genet, J. P. *Chem. Rev.* **2008**, *108*, 288. (f) Zhao, H.; Dang, L.; Marder, T. B.; Lin, Z. *J. Am. Chem. Soc.* **2008**, *130*, 5586. (g) Sieber, D. J.; Liu, S.-B.; Morken, J. P. *J. Am. Chem. Soc.* **2007**, *129*, 2214. (h) Zhao, H.; Lin, Z.; Marder, T. B. *J. Am. Chem. Soc.* **2006**, *128*, 15637.

(8) (a) Tsuji, T.; Yorimitsu, H.; Oshima, K. *Angew. Chem., Int. Ed.* **2002**, *41*, 4137. (b) Ohmiya, H.; Yorimitsu, H.; Oshima, K. *Org. Lett.* **2006**, *8*, 3093.

(9) (a) Martin, R.; Fürstner, A. *Angew. Chem., Int. Ed.* **2004**, *43*, 3955. (b) Hatakeyama, T.; Okada, Y.; Yoshimoto, Y.; Nakamura, M. *Angew. Chem., Int. Ed.* **2011**, *50*, 10973. (c) Phapale, V. B.; Bunuel, E.; García-Iglesias, M.; Caŕdenas, D. J. *Angew. Chem., Int. Ed.* **2007**, *46*, 8790. (d) Ohmiya, H.; Tsuji, T.; Yorimitsu, H.; Oshima, K. *Chem. - Eur. J.* **2004**, *10*, 5640.

(10) Hornillos, V.; Pérez, M.; Fananas-Mastral, M.; Feringa, B. L. *J. Am. Chem. Soc.* **2013**, *135*, 2140.

(11) (a) Yoshikai, N.; Nakamura, E. *Chem. Rev.* **2012**, *112*, 2339. (b) Tseng, C. C.; Paisley, S. D.; Goering, H. L. *J. Org. Chem.* **1986**, *51*, 2884. (c) Takahashi, K.; Ishiyama, T.; Miyaura, N. *Chem. Lett.* **2000**, 982. (d) Yang, C.-T.; Fu, Y.; Zhang, Z.-Q.; Tajuddin, H.; Wu, C.-C.; Liang, J.; Liu, J.-H.; Fu, Y.; Czyzewska, M.; Steel, P. G.; Marder, T. B.; Liu, L. *Angew. Chem., Int. Ed.* **2012**, *51*, 528.

(12) (a) Ren, P.; Vechorkin, O.; von Allmen, K.; Scopelliti, R.; Hu, X. *J. Am. Chem. Soc.* **2011**, *133*, 7084. (b) Someya, H.; Ohmiya, H.; Yorimitsu, H.; Oshima, K. *Org. Lett.* **2008**, *10*, 969.

DOI: 10.1021/acs.orglett.5b01612
Org. Lett. XXXX, XXX, XXX−XXX