JACS
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY
Communication
pubs.acs.org/JACS

Borylation of Propargylic Substrates by Bimetallic Catalysis. Synthesis of Allenyl, Propargylic, and Butadienyl Bpin Derivatives

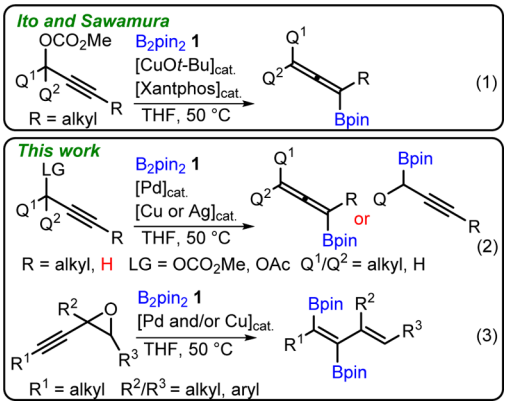
Tony S. N. Zhao, Yuzhu Yang, Timo Lessing, and Kálmán J. Szabó*

Department of Organic Chemistry, Arrhenius Laboratory, Stockholm University, SE-10691 Stockholm, Sweden

Supporting Information

ABSTRACT: Bimetallic Pd/Cu and Pd/Ag catalytic systems were used for borylation of propargylic alcohol derivatives. The substrate scope includes even terminal alkynes. The reactions proceed stererospecifically with formal S_N2' pathways to give allenyl boronates. Opening of propargyl epoxides leads to 1,2-diborylated butadienes probably via en allenylboronate intermediate.

Allenyl and propargyl boronates are very useful reagents in organic synthesis for the preparation of stereo- and regiodefined allenes and propagylic compounds via C−C bond formation.[1] Yet, access to these reagents is severely limited by the relatively few synthetic methods available.[1i−l,2] In the past decade a number of very useful transition-metal-catalyzed procedures have been reported for the synthesis of the structurally related allyl boronates,[3] which fostered increased activity in the field of carbonyl allylboration. However, particularly few methods have been reported for the transition-metal-catalyzed transformation of propargylic substrates to allenyl and propargyl boronate derivatives.[2a] As far as we know, the only catalytic transformation was reported by Ito and Sawamura[2a] using B_2pin_2 (**1**) as a boronate source with propargylic carbonates in the presence of the CuO*t*-Bu catalyst (eq 1). This procedure has been one of the most important

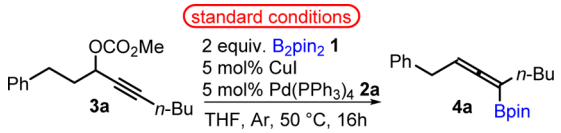


synthetic approaches to a large variety of allenyl boronates.[1f,g,2b] This procedure (eq 1) usually requires use of freshly sublimated CuO*t*-Bu to give high yields. In addition, terminal alkynes could not be used as substrates, probably because of the easy deprotonation by the CuO*t*-Bu catalyst.

Considering the increasing demand for these useful reagents,[1f−h,n,o] there is a need for further development of new catalytic procedures. Thus, we have decided to develop a mild neutral approach for the synthesis of allenyl-Bpin derivatives, which is based on Pd-catalysis (eq 2). To our surprise using solely Pd as a catalyst proved to be inefficient for the transformation of propargylic alcohol derivatives under the reaction conditions that were optimal for the borylation of the analogous allyl alcohol derivatives.[3a−d] Instead of borylation only rearrangement and elimination reactions occurred usually independently from the presence or absence of B_2pin_2 (**1**).

We have found that propargyl carbonates or other derivatives of propargyl alcohol can be borylated with high yields, if a bimetallic Pd/Cu catalyst system is employed (eq 2). The optimized conditions involved a propargylic carbonate substrate (such as **3a**), B_2pin_2 (**1**) as the boronate source, and the use of both $Pd(PPh_3)_4$ and CuI in catalytic amounts without any addition of base (Table 1). Phosphonate as a leaving group can

Table 1. Variation of the Reaction Conditions



entry	deviation from the standard conditions	yield (%)
1	no change	92
2	$-OPO(OEt)_2$ as LG instead of $-OCO_2Me$	74
3	−OH or −OAc as LG instead of $-OCO_2Me$	<5
4	without $Pd(PPh_3)_4$ or without CuI	<5
5	$Pd_2(dba)_3$ **2b**/30 mol % PPh_3 instead of $Pd(PPh_3)_4$	89
6	under air	18
7	$CuCl_2$ or CuCN instead of CuI	40−70
8	Ag_2O instead of CuI	38

be used instead of carbonate (entry 2). When we used a propargylic alcohol or acetate (entry 3) substrate under our standard conditions, formation of **4a** was not observed. We got the same result, when the acetate substrate was reacted together with NaOMe, which was slowly added to the reaction mixture. The desired product **4a** did not form, when either $Pd(PPh_3)_4$ or CuI was omitted (entry 4).

When $Pd(PPh_3)_4$ was replaced with $Pd_2(dba)_3/PPh_3$ catalyst, the yield was almost identical (entry 5). Interestingly, by applying this catalyst system with toluene as solvent, **4a** was formed, even if CuI was omitted. However, in this case a

Received: March 19, 2014
Published: May 13, 2014

   dx.doi.org/10.1021/ja502792s | J. Am. Chem. Soc. 2014, 136, 7563−7566

significant amount of byproducts were formed and the yield dropped to 39%.

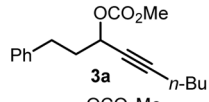
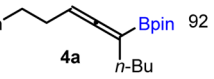
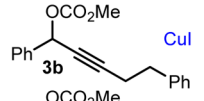
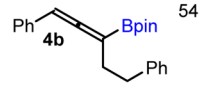
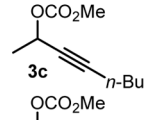
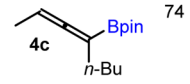
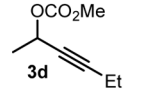
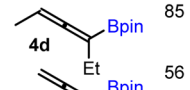
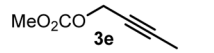
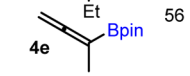
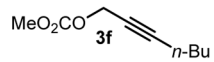
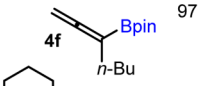
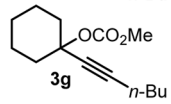
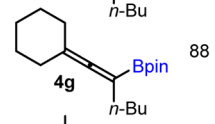
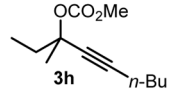
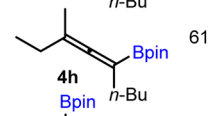
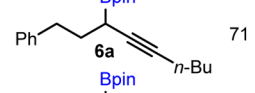
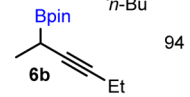
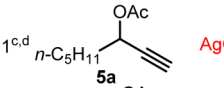
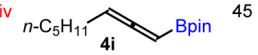
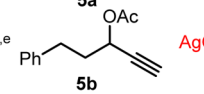
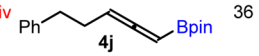
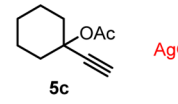
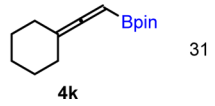
The yield was strongly reduced, when the reaction was not conducted under inert conditions (entry 6). Other Cu-salts, such as $CuCl_2$ or CuCN, could also be used albeit with a lower yield of **4a** (entry 7). The reaction could also be conducted using Ag_2O as a cocatalyst (entry 8). However, when CuI was replaced by Ag_2O, large amounts of byproducts were formed and, thus, the yield dropped substantially. Crudden and co-workers[4] reported that Ag_2O can be employed in Suzuki–Miyaura[5] type couplings to accelerate the transmetalation of the organoboronate substrate. It can apparently be used as a cocatalyst for the activation of B_2pin_2, as well. This observation helped us to solve the problems related to borylation of terminal propagylic substrates (see below).

The synthetic scope of the borylation for internal propargylic substrates is broad (Table 2, entries 1–8). The yields are usually high, when aliphatic moieties are attached to the alkyne, such as for the borylation of **3a**, **3c–d**, **3f–h**. In the case of phenyl substitution (**3b**) the yield was lower due to the lower reactivity of the substrate (entry 2). Terminal Bpin allenes, such as **4e–f** can also be efficiently prepared. The fair isolated yield for **4e** is due to the volatility of the product. Interestingly, when **3a** and **3d** reacted in the presence of CuCl instead of CuI the isomeric propargylic products **6a** and **6b** were formed (cf. entries 1, 9 and entries 4, 10). In this reaction, a formal S_N2 type displacement of the carbonate occurred. However, formation of products **6a–b** was not observed, when CuCl was replaced with other chloride salts, such as KCl (in the presence of CuI). Unfortunately, the effect of CuCl was not general and we could not change the allenyl vs propargyl selectivity for the rest of the reactions.

Synthesis of monosubstituted allenyl boronates (such as **4i–k**) is particularly challenging. Using transition-metal-catalyzed borylation methods, monosubstituted allenyl boronates are expected to form by transformation of terminal alkynes (such as **5a–c**). We have found a single multistep synthesis of such a species in the literature by Roush and co-workers.[1g] A transition-metal-catalyzed procedure using a propargylic substrate and B_2pin_2 is not available at all. By the procedure described in the seminal paper of Ito and Sawamura[2a] (eq 1) only traces of these type of monosubstituted allenyl boronates are formed. A possible reason is that the precursors of such allenyl-Bpin compounds are terminal alkynes, such as **5a–c**, which readily undergo Glaser homocoupling[6] particularly under basic conditions. Therefore, a Cu-catalyst (or cocatalyst) cannot be used in these borylation reactions. The Glaser coupling of propargyl acetates is more difficult[6] than that for propargyl carbonates; therefore, we employed **5a–c** as substrates. We have found that Cu can be replaced by Ag as the cocatalyst in the borylation process. Although Ag_2O (Table 1, entry 8) is effective, the best results could be achieved by AgOAc and AgOPiv (entries 11–13). In these reactions, $Pd_2(dba)_3$ **2b** with PPh_3 gave better results for **5a–b** (entries 11–12) than $Pd(PPh_3)_4$ as a catalyst and we changed the solvent to toluene. The relatively low yields (31–45%) are due to the instability of allenyl-Bpin derivatives **4i–k**. These compounds easily undergo protodeborylation under the reaction and purification.

Inspired by our previously published results for Pd-catalyzed silylation and stannylation of propargylic substrates to obtain functionalized allenyl silanes and stannanes,[7] we considered propargyl epoxide substrates **7a–e** as well (eq 3, Table 3).

Table 2. Synthesis of Allenyl and Propargylic Boronates[a]

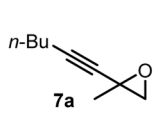
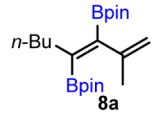
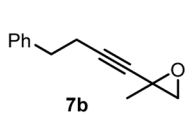
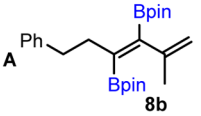
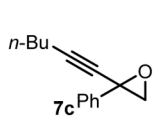
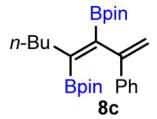
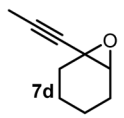
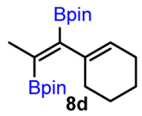
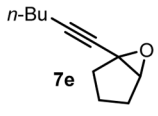
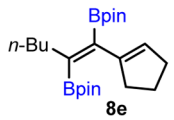
entry	substrate	co-catalyst	product	yield (%)[b]
1		CuI		92
2		CuI		54
3		CuI		74
4		CuI		85
5		CuI		56
6		CuI		97
7		CuI		88
8		CuI		61
9	**3a**	CuCl		71
10	**3d**	CuCl		94
11[c,d]		AgOPiv		45
12[c,e]		AgOPiv		36
13[f]		AgOAc		31

[a]General procedure: **3** (0.30 mmol), **2a** (0.015 mmol), cocatalyst (0.015 mmol), **1** (0.60 mmol) was stirred in THF (1.2 mL) at 50 °C for 16 h. [b]Isolated yields. [c]Reaction conditions: **5** (0.3 mmol), **2b** (0.015 mmol), cocatalyst (0.03 mmol), **1** (0.60 mmol), PPh_3 (0.06 mmol), in toluene (0.3 mL). [d]At 40 °C for 12 h. [e]At 45 °C for 8 h. [f]Reaction conditions: **5** (0.3 mmol), **2a** (0.03 mmol), cocatalyst (0.03 mmol), **1** (0.60 mmol), in toluene (0.6 mL) at 35 °C for 16 h.

Using the same conditions (method A) as those for the borylation of propargylic carbonates, diborylated butadienes (**8a–e**) were obtained. The intermediate product of the reaction is probably the expected allenyl-Bpin species. Since this intermediate product has an allyl alcohol character a subsequent borylation step may occur[3i] to give a diborylated butadienyl derivative (**8a–e**) as the final product (see eq 5 and a brief discussion in the mechanistic part). The reaction of the propargyl epoxides was faster than that for the allenyl carbonates, and thus the temperature could be reduced from 50 °C to room temperature. The reaction proceeds with high selectivity providing mainly (entries 1,3) or exclusively (entries 7,9) one stereoisomer. The reaction with method A occurred with a low yield for **7c** and **7e**. It was found that by using the $CuCl/PCy_3$ catalyst and substoichiometric amounts of KO*t*-Bu

dx.doi.org/10.1021/ja502792s | J. Am. Chem. Soc. 2014, 136, 7563–7566

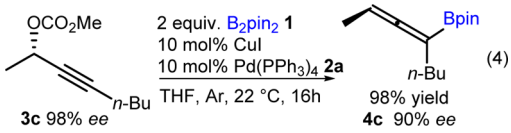
Table 3. Synthesis of Borylated Butadienes by Transformation of Propargylic Epoxides

entry	substrate	method[a]	product	yield (%)[b]	E/Z[c]
1	 **7a**	**A**	 **8a**	59	8:1
2	**7a**	**B**	**8a**	94	12:1
3	 **7b**	**A**	 **8b**	42	4:1
4	**7b**	**B**	**8b**	83	10:1
5	 **7c**	**A**	 **8c**	<5	n.d.
6	**7c**	**B**	**8c**	62	8:1
7	 **7d**	**A**[d]	 **8d**	70	>95:1
8	**7d**	**B**	**8d**	97	>95:1
9	 **7e**	**A**[d]	 **8e**	19	>95:1
10	**7e**	**B**	**8e**	91	>95:1

[a]General procedure; **Method A**: 7 (0.30 mmol), **1** (0.90 mmol), **2a** (0.03 mmol), CuI (0.03 mmol), in THF (1.2 mL) stirred at 22 °C for 16 h under Ar. **Method B**: 7 (0.30 mmol), **1** (0.90 mmol), CuCl (0.03 mmol), KO*t*-Bu (0.09 mmol), PCy_3 (0.09 mmol) in THF (1.2 mL) stirred at 22 °C for 16 h under Ar. [b]Isolated yields. [c]*E*/*Z* isomer ratios determined from crude ^{1}H NMR. [d]Reactions were performed in MeOH (1.2 mL) at 50 °C.

(method B) the yields can be substantially improved (cf. entries 5,6 and entries 9,10). The rest of the epoxide opening reactions also gave better yields with method B than with method A.

We have briefly studied the stereochemistry of the reaction. It was found that the displacement of the carbonate leaving group of **3** proceeds with a very high level of chirality transfer (eq 4). When compound **3c**[8] was reacted with B_2pin_2 using



$Pd(PPh_3)_4$ and CuI catalysts at room temperature, chiral allenyl-Bpin **4c** was obtained. The stereochemical outcome of this reaction and the procedure by Ito and Sawamura (eq 1)[2a] are identical.

A plausible mechanism for the reaction is given in Figure 1. The first step of the process is oxidative displacement of the carbonate group of **3** with an S_N2' mechanism (eq 4) to give **9**. The oxidative addition probably requires precoordination of the substrate to Pd. This precoordination may be hindered by bulky substituents. For example steric interaction between palladium and the phenyl substituent in **3b** may be unfavorable for the π-coordination. This may explain the low reactivity of

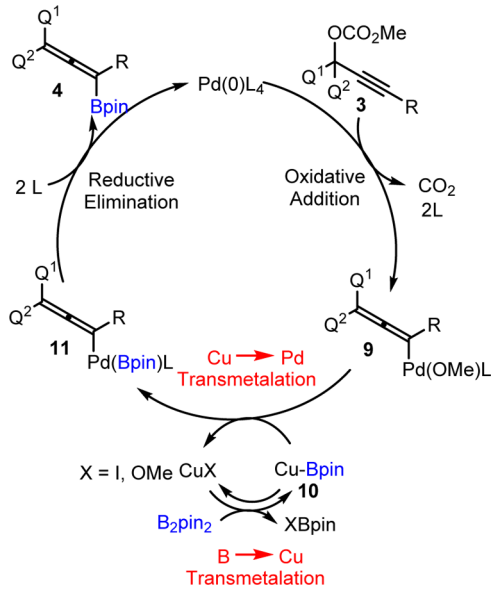


Figure 1. Plausible mechanism for the borylation.

3b and the relatively poor yield for the formation of **4b** (Table 2, entry 2).

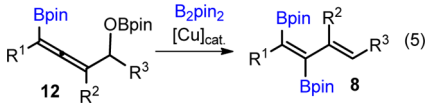
Complex **9** is supposed to undergo transmetalation with Cu-Bpin complex **10**. Formation of **10** occurs by transmetalation of the CuI catalyst with B_2pin_2. Such type of transmetalation reactions were first described by Sadighi[9] and co-workers, and similar reactions have been suggested as the key step for many Cu-catalyzed borylation reactions.[2a,3g,10] This B_2pin_2 → Cu-Bpin transmetalation is probably favored in the presence of KO*t*-Bu, as the driving force of the process is formation of stable *t*-BuO-Bpin. However, under neutral conditions using CuI as catalyst the reaction is slower and probably reversible. Therefore, the subsequent Cu-Bpin → Pd-Bpin transmetalation should proceed with close proximity to quickly consume Cu-Bpin complex **10**. Thus, Cu serves as a transmetalation cocatalyst in the process. The iodide and the methoxy counterions can be exchanged between Cu, Pd, and Bpin. When small amounts of CuOMe are formed the efficiency of the Cu cocatalyst to facilitate the transmetalation is substantially improved.

The reductive elimination of Bpin in complex **11** is probably fast[11] to give product **4**. When CuCl is used as a cocatalyst instead of CuI the carbonate of **3** is displaced by a formal S_N2 mechanism instead of an S_N2' pathway, and therefore propargyl boronate is formed instead of the allenyl product (Table 2, entries 9, 10). A similar change of allenyl vs propargyl selectivity was reported for the Pd-catalyzed stannylation of propargylic substrates.[7] The S_N2-type of displacement of the carbonate was not observed in the Cu-catalyzed borylation of propargyl carbonates (eq 1).[2a] The exact reason for the S_N2-type stereochemistry using CuCl (instead of CuI) is still unclear. Kurosawa and co-workers[12] studied the structure and isomerization possibilities of η^1 and η^3 propargyl and allenyl palladium complexes. These authors found that halide ligands (iodide, bromide, and chloride) have a strong effect on the equilibrium of the different forms. It was concluded that chloride ligands in particular strongly stabilize the η^1-propargyl palladium complexes. Exploration of the mechanistic relevance of these observations on the propargyl vs allenyl boronate

dx.doi.org/10.1021/ja502792s | J. Am. Chem. Soc. 2014, 136, 7563−7566

selectivity of the above process is the subject of ongoing studies in our laboratory.

As mentioned above the epoxide opening reactions (Table 3) probably give the expected allenyl boronates **12** with an allyl-OBpin moiety. This allyl-OBpin species undergoes a second Cu-catalyzed borylation with an S_N2'-type mechanism to give the corresponding butadiene product **8** (eq 5).



In summary, we have shown that allenyl boronate derivatives can be obtained from propargyl alcohol derivatives using a bimetallic Pd/Cu catalyst system without strong bases. The mild neutral conditions allow even borylation of terminal alkynes using a Pd/Ag bimetallic system. Under a Pd/CuCl system a propargyl-Bpin product could be obtained instead of the allenyl boronate derivatives. We have also succeeded in preparing 1,2-diborylated butadiene derivatives by opening of propargyl epoxides. The borylation of propargylic carbonates with a Pd/Cu bimetallic system proceeds stereospecifically via an S_N2' mechanism. We propose that the Cu cocatalyst assists in the activation of B_2pin_2 and facilitates the transmetalation step. We hope that these studies contribute to the broader application of allenyl and propargyl boronates in advanced synthesis and natural product chemistry.[1b−d,f,g,l,n]

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Detailed experimental procedures and compound characterization data are given. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

kalman@organ.su.se.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

The authors thank the financial support of the Swedish Research Council (VR) and the Knut och Alice Wallenbergs Foundation. Y.Y. thanks the Olle Engkvist Foundation for a postdoctoral fellowship.

■ REFERENCES

(1) (a) Hall, D. G. *Boronic Acids*; Wiley: Weinheim, 2011. (b) Marshall, J. A. *J. Org. Chem.* **2007**, *72*, 8153. (c) Yu, S.; Ma, S. *Chem. Commun.* **2011**, *47*, 5384. (d) Ding, C.-H.; Hou, X.-L. *Chem. Rev.* **2011**, *111*, 1914. (e) Cid, J.; Gulyas, H.; Carbo, J. J.; Fernandez, E. *Chem. Soc. Rev.* **2012**, *41*, 3558. (f) Chen, M.; Roush, W. R. *J. Am. Chem. Soc.* **2012**, *134*, 10947. (g) Tsai, A. S.; Chen, M.; Roush, W. R. *Org. Lett.* **2013**, *15*, 1568. (h) Barnett, D. S.; Schaus, S. E. *Org. Lett.* **2011**, *13*, 4020. (i) Ikeda, N.; Arai, I.; Yamamoto, H. *J. Am. Chem. Soc.* **1986**, *108*, 483. (j) Corey, E. J.; Yu, C. M.; Lee, D. H. *J. Am. Chem. Soc.* **1990**, *112*, 878. (k) Brown, H. C.; Khire, U. R.; Racherla, U. S. *Tetrahedron Lett.* **1993**, *34*, 15. (l) Canales, E.; Gonzalez, A. Z.; Soderquist, J. A. *Angew. Chem., Int. Ed.* **2007**, *46*, 397. (m) Matsumoto, Y.; Naito, M.; Uozumi, Y.; Hayashi, T. *Chem. Commun.* **1993**, 1468. (n) Jain, P.; Wang, H.; Houk, K. N.; Antilla, J. C. *Angew. Chem., Int. Ed.* **2012**, *51*, 1391. (o) Partridge, B. M.; Chausset-Boissarie, L.; Burns, M.; Pulis, A. P.; Aggarwal, V. K. *Angew. Chem., Int. Ed.* **2012**, *51*, 11795.

(2) (a) Ito, H.; Sasaki, Y.; Sawamura, M. *J. Am. Chem. Soc.* **2008**, *130*, 15774. (b) Sasaki, Y.; Sawamura, M.; Ito, H. *Chem. Lett.* **2011**, *40*, 1044.

(3) (a) Ishiyama, T.; Ahiko, T.-A.; Miyaura, N. *Tetrahedron Lett.* **1996**, *37*, 6889. (b) Raducan, M.; Alam, R.; Szabó, K. J. *Angew. Chem., Int. Ed.* **2012**, *51*, 13050. (c) Selander, N.; Kipke, A.; Sebelius, S.; Szabó, K. J. *J. Am. Chem. Soc.* **2007**, *129*, 13723. (d) Olsson, V. J.; Sebelius, S.; Selander, N.; Szabó, K. J. *J. Am. Chem. Soc.* **2006**, *128*, 4588. (e) Ito, H.; Kawakami, C.; Sawamura, M. *J. Am. Chem. Soc.* **2005**, *127*, 16034. (f) Ito, H.; Ito, S.; Sasaki, Y.; Matsuura, K.; Sawamura, M. *J. Am. Chem. Soc.* **2007**, *129*, 14856. (g) Ito, H.; Miya, T.; Sawamura, M. *Tetrahedron* **2012**, *68*, 3423. (h) Ding, J. Y.; Hall, D. G. *Angew. Chem., Int. Ed.* **2013**, *52*, 8069. (i) Semba, K.; Fujihara, T.; Terao, J.; Tsuji, Y. *Angew. Chem., Int. Ed.* **2013**, *52*, 12400. (j) Zhang, P.; Roundtree, I. A.; Morken, J. P. *Org. Lett.* **2012**, *14*, 1416. (k) Kiesewetter, E. T.; O'Brien, R. V.; Yu, E. C.; Meek, S. J.; Schrock, R. R.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2013**, *135*, 6026.

(4) (a) Imao, D.; Glasspoole, B. W.; Laberge, V. S.; Crudden, C. M. *J. Am. Chem. Soc.* **2009**, *131*, 5024. (b) Glasspoole, B. W.; Ghozati, K.; Moir, J. W.; Crudden, C. M. *Chem. Commun.* **2012**, *48*, 1230.

(5) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457.

(6) Fairlamb, I. J. S.; Bauerlein, P. S.; Marrison, L. R.; Dickinson, J. M. *Chem. Commun.* **2003**, *0*, 632.

(7) (a) Kjellgren, J.; Sundén, H.; Szabó, K. J. *J. Am. Chem. Soc.* **2004**, *126*, 474. (b) Kjellgren, J.; Sundén, H.; Szabó, K. J. *J. Am. Chem. Soc.* **2005**, *127*, 1787.

(8) Matsumura, K.; Hashiguchi, S.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1997**, *119*, 8738.

(9) Laitar, D. S.; Müller, P.; Sadighi, J. P. *J. Am. Chem. Soc.* **2005**, *127*, 17196.

(10) (a) Zhao, H.; Dang, L.; Marder, T. B.; Lin, Z. *J. Am. Chem. Soc.* **2008**, *130*, 5586. (b) Dang, L.; Zhao, H.; Lin, Z.; Marder, T. B. *Organometallics* **2007**, *27*, 4443. (c) Dang, L.; Zhao, H.; Lin, Z.; Marder, T. B. *Organometallics* **2007**, *26*, 2824. (d) Kleeberg, C.; Dang, L.; Lin, Z.; Marder, T. B. *Angew. Chem., Int. Ed.* **2009**, *48*, 5350. (e) Ito, H.; Okura, T.; Matsuura, K.; Sawamura, M. *Angew. Chem., Int. Ed.* **2010**, *49*, 560.

(11) Larsson, J. M.; Szabó, K. J. *J. Am. Chem. Soc.* **2013**, *135*, 443.

(12) Tsutsumi, K.; Ogoshi, S.; Nishiguchi, S.; Kurosawa, H. *J. Am. Chem. Soc.* **1998**, *120*, 1938.