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JOURNAL OF THE AMERICAN CHEMICAL SOCIETY

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Asymmetric Synthesis of Borylalkanes via Copper-Catalyzed Enantioselective Hydroallylation

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Supporting Information

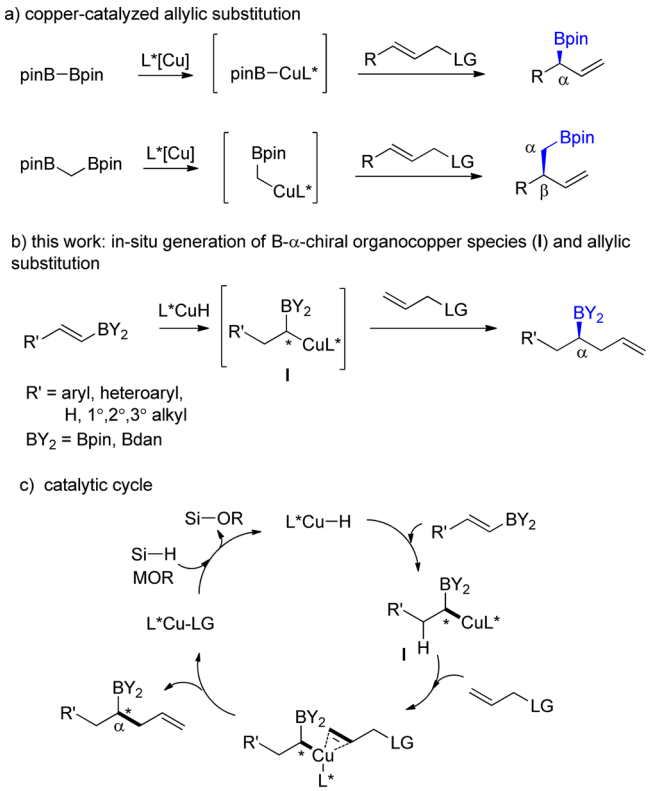
ABSTRACT: An efficient synthetic method for preparing enantioenriched secondary borylalkanes has been achieved through a copper-catalyzed regio- and enantioselective hydroallylation of alkenyl boronates and boramides employing hydrosilanes and allylic phosphates. In the presence of a copper catalyst with a chiral Walphos ligand, a range of alkenylboron compounds with an aryl, heteroaryl, or alkyl substituent produced secondary homoallylic alkylboron compounds in good yields and with high enantioselectivities up to 99% ee. The utility of the resulting alkylboronates was demonstrated in an efficient synthesis of (*S*)-massoialactone.

As organoboranes are valuable reagents in organic synthesis due to their versatility in functionalization, the demand for stereochemically well-defined organoboronates is increasing.[1] While useful methods to prepare enantioenriched organoboron compounds have been developed, such as metal-catalyzed borylation[2] and stoichiometric lithiation−borylation,[3] the search for novel and more powerful asymmetric synthetic methods continues. In general, the creation of simple alkylboron compounds with high enantiocontrol presents a greater challenge than the production of boron compounds with a biasing or directing substituent.[4]

Transition-metal-catalyzed C−C bond formation through allylic substitution is one of the powerful methods to construct molecules.[5] Among allylation methods, copper-catalyzed allylic substitution, or addition of an organometallic nucleophile to an electrophile with an allylic leaving group, has proven to be widely applicable and versatile in synthesis.[6,7] A typical approach to the synthesis of organoboron compounds by copper-catalyzed allylic substitution is installation of the C−B bond using a diboron as the nucleophile to yield α-chiral allylboron compounds.[8] Recently, the use of 1,1-diborylalkanes as the organometallic component to yield organoboron products by S_N2'-selective substitution was reported by the Cho, Hoveyda, and Xiao group, respectively.[9] However, regio- and enantioselective substitution[9b,c] was only reported with 1,1-diborylmethane, which afforded β-chiral (from B), primary organoboron compounds. All of these methods discard one B moiety from the diboron starting material for activation and depend on the use of stereochemically well-defined prochiral allylic electrophiles to create stereogenic centers during the addition (Scheme 1, (a)).

On the other hand, we have previously described the formation of both racemic and enantioenriched boron(B)-α-chiral organocopper species in our investigations of copper-catalyzed hydroboration of alkenylboron compounds and alkynes.[10] While a variety of B-α-chiral organocopper species can in principle be easily prepared with atom economy, the use of such organocopper species has rarely been reported except for a couple of asymmetric reactions with heteroatom-based electrophiles.[10a,11] We envisioned that the efficient addition of secondary B-α-chiral organocopper species (**I**), generated in situ by hydrocupration, to an allylic electrophile[12] would establish a protocol to furnish chiral alkylboron compounds (Scheme 1b and c). Allylic substitution by chiral benzyl organocopper species was recently reported by the Buchwald group.[12] However, hindered chiral boryl-organocopper species such as **I** have not been used yet in a tandem allylation reaction.

Scheme 1. Organoboron Synthesis via Copper-Catalyzed Allylic Substitution



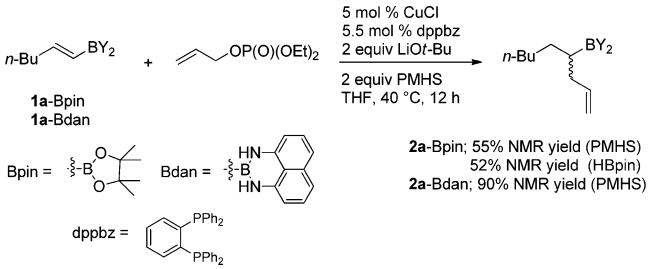
Received: October 27, 2016
Published: November 3, 2016

DOI: 10.1021/jacs.6b11229
J. Am. Chem. Soc. 2016, 138, 15146−15149

Herein we report a highly enantioselective synthesis of alkyl organoboron compounds starting from easily preparable alkenylboron compounds, by an efficient addition of B-α-chiral organocopper species to allyl phosphates. The keys to the successful transformation are (1) highly regio- and enantioselective hydrocupration to borylalkenes and (2) subsequent asymmetric C−C bond formation with high efficiency.

We initiated our investigation by examining reactions of 1-borylhexene (**1a**) with hydride reagents and allylic electrophiles under various reaction conditions using copper and racemic ligands. Poly(methylhydrosiloxane) (PMHS) was more efficient than hydroboranes as the hydride source, and diethyl allyl phosphate was most suitable as the allylic electrophile (see Supporting Information for details; Table S1).[13] As shown in Scheme 2, the desired alkylboron (**2a**) was obtained with good conversion.

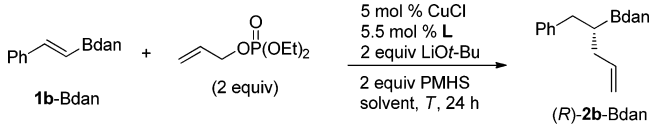
Scheme 2. Tandem Hydrocupration and Allylation



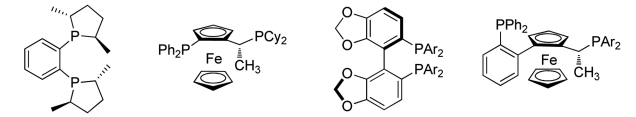
Based on the racemic results, we surveyed suitable chiral ligands with the model substrate **1b**-Bdan (Table 1). **L1**, **L2**, and **L3** ligands, which had been representative ligands in the previous copper-catalyzed asymmetric hydroboration of internal alkenes,[10a,14] resulted in either poor enantioselectivity or low reactivity in the allylic substitution (entries 1−3), indicating that the C−C bond formation step also affects the overall reactivity and enantioselectivity. In particular, the bulky **L3** ligand displayed very low reactivity despite good enantioselectivity (entry 3). With a change to the Segphos (**L4**) ligand with less bulky phenyl groups on the phosphine, a dramatic increase in product yield with the same 92% ee[15] was observed (entries 4 and 5). In comparison with **L4**, the Walphos (**L5**) ligand displayed slightly decreased reactivity under the screening conditions, but higher enantioselectivity (entry 6). The conversion could be enhanced by increasing the reaction temperature to 60 °C (entry 7) or switching the solvent to other ethereal solvents (entries 8 and 9). Finally, the use of diethyl ether as the solvent furnished the desired product in both high isolated yield and excellent enantioselectivity (99% ee), suggesting that **L5** was the optimal ligand for **1b**-Bdan among the screened ligands.

To examine the scope of alkenylboron substrates in the hydroallylation, we prepared a variety of alkenyl pinacol boronates (**1**-Bpin) and 1,8-diaminonaphthalene boramides (**1**-Bdan) with an aryl, heteroaryl, or alkyl substituent (Table 2).[10c,16] First, **1a**-Bpin and **1b**-Bpin substrates were tested using the catalytic combination of CuCl/**L4** in THF or CuCl/**L5** in diethyl ether to assess their reactivity and enantioselectivity. The conditions using the Walphos (**L5**) ligand yielded the corresponding products, **2a**-Bpin and **2b**-Bpin, with higher enantioselectivity than the conditions using **L4**. Moreover, the reaction of **1a**-Bdan with an alkyl-substituent furnished the desired product (**2a**-Bdan) with excellent ee (99% ee). The

Table 1. Optimization of Reaction Conditions



entry	chiral ligand (**L**)	solvent	T (°C)	% conv[a] (% yield)[b]	ee[c] (%)
1	**L1**	THF	40	80 (50)	8 (*S*)
2	**L2**	THF	40	83 (33)	28 (*S*)
3	**L3**	THF	40	11 (-)	92 (*S*)
4	**L4**	THF	40	65 (55)	92 (*S*)
5[d]	**L4**	THF	40	100 (70)	92 (*S*)
6[d]	**L5**	THF	40	87 (67)	98 (*R*)
7[d]	**L5**	THF	60	100 (78)	96 (*R*)
8[d]	**L5**	MTBE[e]	40	100 (81)	93 (*R*)
9[d]	**L5**	Et_2O	40	100 (84)	99 (*R*)



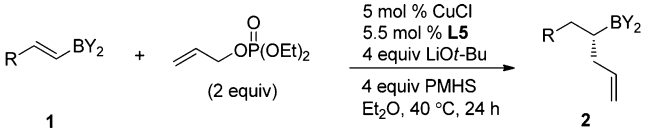
[a]Determined by NMR with an internal standard. [b]Isolated yield. [c]% ee determined by HPLC analysis. [d]4 equiv of LiO*t*-Bu and PMHS were used. [e]MTBE = *tert*-butyl methyl ether.

CuCl/**L5** catalytic system was found to be broadly applicable to alkyl- or aryl-substituted, alkenyl pinacol boronates and Bdan-substrates, in order to produce the desired chiral secondary alkylboron compounds with high enantioselectivity. The examples in Table 2 suggest that highly enantioenriched alkylboron products (**2a**) with no steric bias could easily be prepared by our current protocol. Halogen-containing (**2c** and **2d**), electron-donating (**2e** and **2f**), and ortho-substituted (**2f**) aryl-substituted alkenylborons were feasible substrates for the reaction, leading to the desired products. Of note, the **2d**-Ban product included a bromo functional group with a masked boron group, which could be used for metal-catalyzed coupling reactions.[17] Heteroaryl-substituted alkenylboron compounds were similarly suitable for the reaction (**2g** and **2h**), but an aryl-substituted alkenyl boron substrate containing the strongly electron-withdrawing CF_3 group yielded the desired product (**2i**) along with the regioisomeric product (**2i′**) in a 2:1 ratio, which resulted from a less regioselective hydrocupration. Secondary alkyl substituents and a propargyl moiety did not significantly affect the reactivity of the reaction, furnishing the desired product **2j** and **2k** with good enantioselectivities. However, the bulky *tert*-butyl substituted substrate reacted slowly with incomplete conversion and moderately decreased ee (**2l**). Finally, hydroallylation of the terminal vinyl pinacol boronate proceeded smoothly to yield the product (**2m**) with high enantioselectivity.

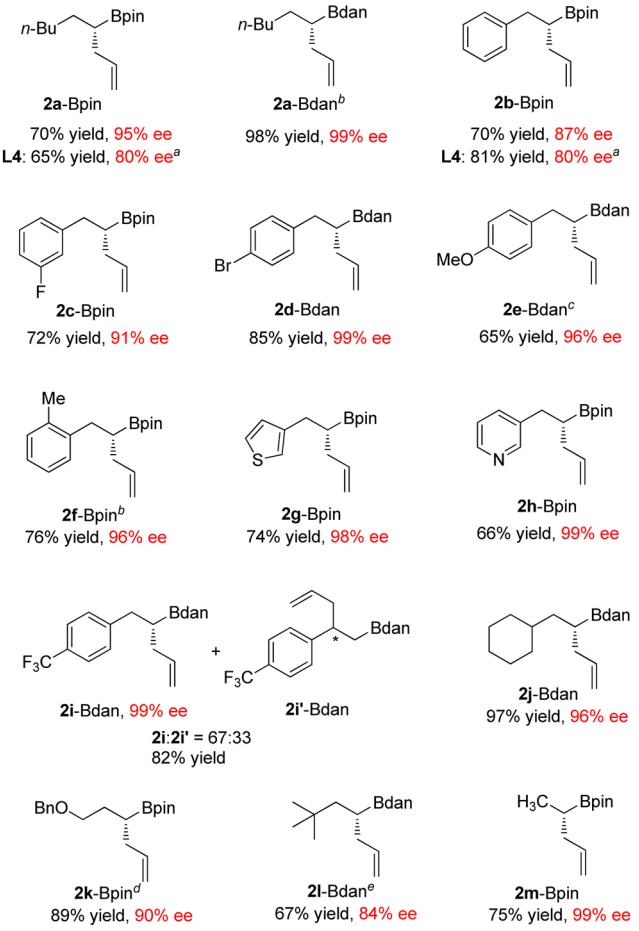
In a further survey of substrates, we noted limitations of the current copper-Walphos catalyst in the hydroallylation of alkenylboron compounds with different steric demands (Figure 1).[18] *cis*-**1b**-Bdan (**A**) was reactive to afford **2b**-Bdan in good

DOI: 10.1021/jacs.6b11229
J. Am. Chem. Soc. 2016, 138, 15146−15149

Table 2. Copper-Catalyzed Enantioselective Hydroallylation of 1



1 2



[a]The opposite enantiomer of **2** was obtained with **L4**. [b]Reaction time was 12 h. [c]The reaction was carried out at 60 °C in THF for 36 h due to the low solubility of **1e**-Bdan in diethyl ether. [d]Conducted in THF. [e]73% conversion was observed in 36 h.

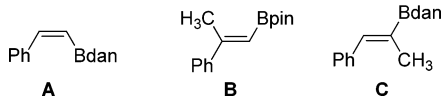
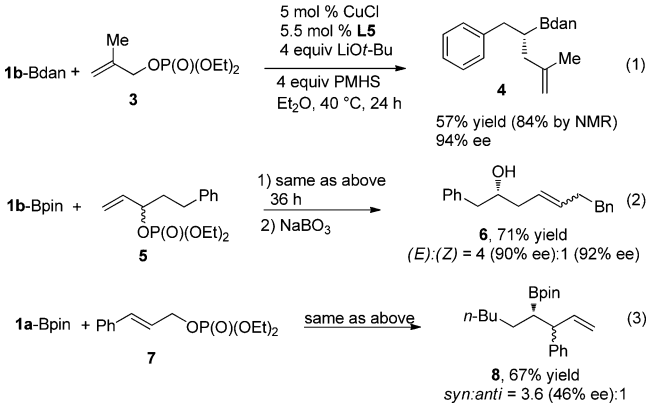


Figure 1. Inefficient or unreactive substrates with Cu-**L5** catalyst.

yield, but in a disappointing 4% ee; in contrast to results from the (*E*)-isomer; this was attributed to poor enantioselectivity in the hydrocupration step. A *β*-disubstituted alkenyl boron substrate (**B**) was not reactive with the starting material remaining intact. Moreover, an attempt to use a trisubstituted alkenylboron, **C**, for the synthesis of chiral tertiary organoboron compounds was not successful and resulted in no product formation under our catalytic conditions. The enantioselective catalysis of cis compounds and trisubstituted alkenylboron substrates needs further improvement, and efforts are ongoing.

Next, we briefly investigated the scope of the allyl phosphate in the hydroallylation of **1** (Scheme 3). For this, 2-

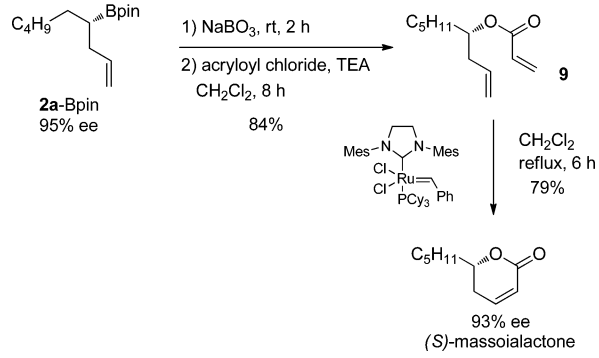
Scheme 3. Scope of Allylic Phosphates



methylallylphosphate (**3**) and a secondary allyl phosphate (**5**) were employed as the coupling partners under the optimized conditions using **L5** as the ligand (reactions 1 and 2). Both allylic substrates reacted smoothly to give the corresponding coupled products with good enantioselectivity. The allylic moiety of **3** was efficiently incorporated into the product, and the use of **5** showed a preferable *E*-selectivity. An internal allylic phosphate (**7**) was reactive as well,[19] but the reaction resulted in a diastereomeric mixture of products with low enantioselectivity (Scheme 3, reaction 3).[20]

To demonstrate the utility of the enantioenriched organoboron products obtained by our protocol, an efficient synthesis of the unnatural isomer, (*S*)-massoialactone,[21] was carried out (Scheme 4). Oxidation of **2a**-Bpin, acryloylation, and ring-closing metathesis[22] yielded the desired product in good overall yield.

Scheme 4. Enantioselective Synthesis of (*S*)-Massoialactone



In summary, we developed a copper-catalyzed method for the synthesis of highly enantioenriched alkylboron compounds via tandem hydrocupration and allylation. The Walphos (**L5**)-copper catalyst was found to be suitable for the allylation of B-*α*-chiral organocopper species generated from a wide range of internal and terminal alkenylboron compounds including pinacol boronates and 1,8-diaminonaphthylboramides, with various alkyl, aryl, and heteroaryl substituents. This protocol provides an easy access to chiral secondary homoallylic alkylboron compounds with high enantioselectivity. Efforts to expand the use of B-*α*-chiral organocopper species in catalytic bond formations are currently underway.

DOI: 10.1021/jacs.6b11229
J. Am. Chem. Soc. 2016, 138, 15146−15149

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.6b11229.

Experimental procedures, characterization of products, and NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This research was supported by National Research Foundation of Korea (NRF) grants (NRF-2016R1A2B4011719 and NRF-2016R1A4A1011451), funded by the Korea government (MEST).

■ REFERENCES

(1) (a) *Contemporary Boron Chemistry*; Davidson, M. G., Hughes, A. K., Marder, T. B., Wade, K., Eds.; Royal Society of Chemistry: Cambridge, 2000. (b) *Organoboranes for Syntheses*; ACS Symposium Series 783; Ramachandran, P. V., Brown, H. C., Eds.; American Chemical Society: Washington, DC, 2001. (c) *Boronic Acids: Preparation and Applications in Organic Synthesis, Medicine and Materials*, 2nd ed.; Hall, D. G., Ed.; Wiley-VCH: Weinheim, 2011.

(2) For reviews, see: (a) Carroll, A.-M.; O'Sullivan, T. P.; Guiry, P. J. *Adv. Synth. Catal.* **2005**, *347*, 609−631. (b) Beletskaya, I.; Moberg, C. *Chem. Rev.* **2006**, *106*, 2320−2354. (c) Burks, H. E.; Morken, J. P. *Chem. Commun.* **2007**, 4717−4725. (d) Ohmura, T.; Suginome, M. *Bull. Chem. Soc. Jpn.* **2009**, *82*, 29−49. (e) Lee, S.; Yun, J. *Top. Organomet. Chem.* **2015**, *49*, 73−92.

(3) (a) Stymiest, J. L.; Bagutski, V.; French, R. M.; Aggarwal, V. K. *Nature* **2008**, *456*, 778−782. (b) Bagutski, V.; French, R. M.; Aggarwal, V. K. *Angew. Chem., Int. Ed.* **2010**, *49*, 5142−5145.

(4) (a) Morgan, J. B.; Miller, S. P.; Morken, J. P. *J. Am. Chem. Soc.* **2003**, *125*, 8702−8703. (b) Lee, Y.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2009**, *131*, 3160−3161. (c) Noh, D.; Chea, H.; Ju, J.; Yun, J. *Angew. Chem., Int. Ed.* **2009**, *48*, 6062−6064. (d) Xi, Y.; Hartwig, J. F. *J. Am. Chem. Soc.* **2016**, *138*, 6703−6706.

(5) For reviews, see: (a) Bruneau, C.; Renaud, J.-L.; Demerseman, B. *Pure Appl. Chem.* **2008**, *80*, 861−871. (b) Trost, B. M.; Crawley, M. L. *Top. Organomet. Chem.* **2011**, *38*, 321−340. (c) Butt, N. A.; Zhang, W. *Chem. Soc. Rev.* **2015**, *44*, 7929−7967. (d) Cherney, A. H.; Kadunce, N. T.; Reisman, S. E. *Chem. Rev.* **2015**, *115*, 9587−9652. (e) Koschker, P.; Breit, B. *Acc. Chem. Res.* **2016**, *49*, 1524−1536.

(6) For reviews, see: (a) Alexakis, A.; Bäckvall, J. E.; Krause, N.; Pàmies, O.; Diéguez, M. *Chem. Rev.* **2008**, *108*, 2796−2823. (b) Geurts, K.; Fletcher, S. P.; van Zijl, A. W.; Minnaard, A. J.; Feringa, B. L. *Pure Appl. Chem.* **2008**, *80*, 1025−1037. (c) Langlois, J.-B.; Alexakis, A. *Top. Organomet. Chem.* **2011**, *38*, 235−268. (d) Shintani, R. *Synthesis* **2016**, *48*, 1087−1100.

(7) For Cu-catalyzed allylic substitution using organoboron nucleophiles: (a) Ohmiya, H.; Yokobori, U.; Makida, Y.; Sawamura, M. *J. Am. Chem. Soc.* **2010**, *132*, 2895−2897. (b) Shintani, R.; Takatsu, K.; Takeda, M.; Hayashi, T. *Angew. Chem., Int. Ed.* **2011**, *50*, 8656−8659. (c) Jung, B.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2012**, *134*, 1490−1493. (d) Nagao, K.; Yokobori, U.; Makida, Y.; Ohmiya, H.; Sawamura, M. *J. Am. Chem. Soc.* **2012**, *134*, 8982−8987. (e) Hojoh, K.; Shido, Y.; Ohmiya, H.; Sawamura, M. *Angew. Chem., Int. Ed.* **2014**, *53*, 4954−4958. (f) Shi, Y.; Jung, B.; Torker, S.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2015**, *137*, 8948−8964.

(8) (a) Ito, H.; Ito, S.; Sasaki, Y.; Matsuura, K.; Sawamura, M. *J. Am. Chem. Soc.* **2007**, *129*, 14856−14857. (b) Guzman-Martinez, A.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2010**, *132*, 10634−10637. (c) Park, J. K.; Lackey, H. H.; Ondrusek, B. A.; McQuade, D. T. *J. Am. Chem. Soc.* **2011**, *133*, 2410−2413. (d) Yamamoto, E.; Takenouchi, Y.; Ozaki, T.; Miya, T.; Ito, H. *J. Am. Chem. Soc.* **2014**, *136*, 16515−16521.

(9) (a) Kim, J.; Park, S.; Park, J.; Cho, S. H. *Angew. Chem., Int. Ed.* **2016**, *55*, 1498−1501. (b) Shi, Y.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2016**, *55*, 3455−3458. (c) Zhang, Z.-Q.; Zhang, B.; Lu, X.; Liu, J.-H.; Lu, X.-Y.; Xiao, B.; Fu, Y. *Org. Lett.* **2016**, *18*, 952−955.

(10) (a) Feng, X.; Jeon, H.; Yun, J. *Angew. Chem., Int. Ed.* **2013**, *52*, 3989−3992. (b) Lee, S.; Li, D.; Yun, J. *Chem. - Asian J.* **2014**, *9*, 2440−2443. (c) Jang, W. J.; Lee, W. L.; Moon, J. H.; Lee, J. Y.; Yun, J. *Org. Lett.* **2016**, *18*, 1390−1393.

(11) Nishikawa, D.; Hirano, K.; Miura, M. *J. Am. Chem. Soc.* **2015**, *137*, 15620−15623. Addition of chiral Cu-alkylboronates generated from 1,1-diborylethane to aldehyde: (b) Joannou, M. V.; Moyer, B. S.; Meek, S. J. *J. Am. Chem. Soc.* **2015**, *137*, 6176−6179.

(12) Wang, Y.-M.; Buchwald, S. L. *J. Am. Chem. Soc.* **2016**, *138*, 5024−5027.

(13) When screened coupling conditions were not effective, hydrosilylation or direct allylation of **1** seemed to slightly drop in yield. Degradation of the product was not observed under catalytic conditions.

(14) Noh, D.; Yoon, S. K.; Won, J.; Lee, J. Y.; Yun, J. *Chem. - Asian J.* **2011**, *6*, 1967−1969.

(15) The absolute configuration of **2b**-Bdan was determined by comparing optical rotation data of the corresponding hydroxyl compound with literature value. (a) Kumar, A. N.; Bhatt, S.; Chattopadhyay, S. *Tetrahedron: Asymmetry* **2009**, *20*, 205−209. (b) Jain, P.; Antilla, J. C. *J. Am. Chem. Soc.* **2010**, *132*, 11884−11886.

(16) (a) Brown, H. C.; Gupta, S. K. *J. Am. Chem. Soc.* **1972**, *94*, 4370−4371. (b) Lee, J.-E.; Kwon, J.; Yun, J. *Chem. Commun.* **2008**, 733−734.

(17) (a) Noguchi, H.; Hojo, K.; Suginome, M. *J. Am. Chem. Soc.* **2007**, *129*, 758−759. (b) Noguchi, H.; Shioda, T.; Chou, C.-M.; Suginome, M. *Org. Lett.* **2008**, *10*, 377−380.

(18) See the Supporting Information (Scheme S1) for details.

(19) For more screening results with allylic phosphates, see the Supporting Information (Scheme S2).

(20) The diastereomeric ratio was determined by ^{1}H NMR analysis and the major diastereomer was determined to be syn with the corresponding hydroxy compound after oxidation of **8**. Tan, K.-T.; Chng, S.-S.; Cheng, H.-S.; Loh, T.-P. *J. Am. Chem. Soc.* **2003**, *125*, 2958−2963.

(21) (a) Cavill, G. W. K.; Clark, D. V.; Whitefield, F. B. *Aust. J. Chem.* **1968**, *21*, 2819−2823. (b) Pais, G. C. G.; Fernandes, R. A.; Kumar, P. *Tetrahedron* **1999**, *55*, 13445−13450. (c) Fournier, L.; Kocienski, P.; Pons, J.-M. *Tetrahedron* **2004**, *60*, 1659−1663.

(22) (a) Chatterjee, A. K.; Morgan, J. P.; Scholl, M.; Grubbs, R. H. *J. Am. Chem. Soc.* **2000**, *122*, 3783−3784. (b) Banwell, M. G.; Coster, M. J.; Karunaratne, O. P.; Smith, J. A. *J. Chem. Soc. Perkin Trans. 1* **2002**, 1622−162.

DOI: 10.1021/jacs.6b11229
J. Am. Chem. Soc. 2016, 138, 15146−15149