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Silaborative Carbocyclizations of 1,7-Enynes. Diastereoselective Preparation of Chromane Derivatives

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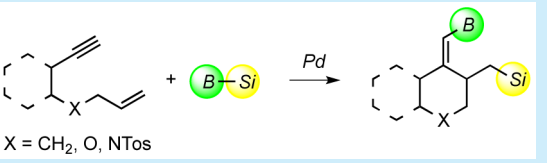
Supporting Information

ABSTRACT: Palladium(0)-catalyzed carbocyclization of 1,7-enynes mediated by (chlorodimethylsilyl)pinacolborane proceeds with 1,8-addition of the silicon and boron functions to give functionalized cyclohexane derivatives with boron attached to the exocyclic olefin. A variety of chromane dervatives are accessible by this method. In contrast to the analogous reactions with 1,6-enynes, the configuration of the newly formed stereogenic center is controlled by a stereogenic center present in the substrate.



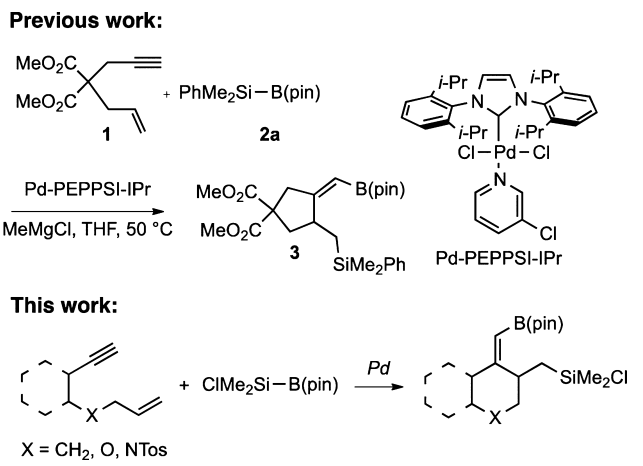
Cyclizations of 1,6-enynes catalyzed by a variety of metal complexes have been extensively studied, and numerous synthetically versatile methods for the construction of substituted five-membered carbocycles and heterocycles have emerged from these studies.[1] In contrast, examples of cycloisomerizations or other types of alkene−alkyne couplings of 1,7-enynes to provide six-membered rings are more rare, and the cyclized products are often obtained in moderate yields.[2]

Bismetallative cyclizations employing interelement compounds,[3] which contain a bond between two main group elements, lead to cyclic products containing two reactive functional groups.[4] Further functional group transformations of the primarily obtained products generate large structural diversity, thereby making bisfunctionalization−cyclizations synthetically powerful processes. Whereas such methods have been explored for 1,6-enynes, using Si−Sn, B−Sn, and B−Si interelement compounds,[5] borastannylative carbocyclization of 1-ethenyl-2-(2-propyn-1-yloxy)benzene is the single example of a bisfunctionalization−cyclization generating a six-membered carbocycle.[6] Instead of the desired cyclic compounds, products from 1,2-addition of the interelement compound to the triple bond[7] are commonly obtained.[6]

Cárdenas and co-workers have also reported cyclizations of 1,7-enynes[8] and dienynes[9] with concomitant introduction of a single reactive group. Boron−boron compounds were used in these reactions, but as a result of the mode of activation, the reactions led to incorporation of only one boron function; with most substrates the product with boron at the terminal alkene carbon atom of the starting enyne was obtained as the sole isomer. A monofunctionalized cyclohexane derivative was also obtained by rhodium-catalyzed silylative cyclization of 4,4-bis(carbomethoxy)oct-7-en-1-yne, using $PhMe_2SiH$, which gave a low yield (34%) of a product from initial addition of Pd−Si to the alkyne and, thus, with the silyl function at the olefinic bond of the product.[10]

Silaborative cyclizations[11] are particularly attractive since the resulting products are nontoxic and possess functions with orthogonal reactivities, which can be transformed in a variety of ways.[12] Our previous work included cyclization of 1,6-enyne **1** using (dimethylphenylsilyl)pinacolborane (**2a**)[13] to give **3** (Scheme 1).[14] Dichloro-*N*,*N*-bis[2,6-(diisopropyl)phenyl]-imidazolium (3-chloropyridine) palladium, Pd-PEPPSI-IPr,[15] served as an efficient catalyst for the process, which provided the products in excellent yields with control of regiochemistry as well as olefinic bond configuration, the latter being a consequence of the mechanism of the reaction.

Scheme 1. Silaborative Cyclizations



The present work describes the extension of this method to 1,7-enynes. For these studies, (chlorodimethylsilyl)-pinacolborane **2b**,[16] which exhibits higher reactivity than **2a**[17] and which results in products disposed for further transformations,[18] was used (Scheme 2). Reaction of **4** with compound **2b** in the presence of Pd-PEPPSI-IPr did not, however, yield the desired cyclic compound but resulted in 1,2-

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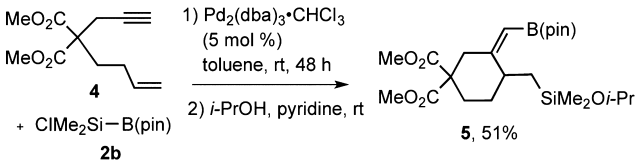
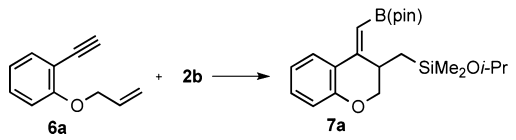
Scheme 2. Silaborative Cyclization of 1,7-Enyne



addition to the triple bond, evidently as a result of reductive elimination being more rapid than insertion of the alkene into the Pd−C bond. In contrast, use of $Pd_2(dba)_3$·$CHCl_3$ gave compound **5**, the product from 1,8-silaboration, as a single diastereomer in a moderate yield of 51%.

Silaborative cyclization of 1-ethynyl-2-(2-propen-1-yloxy)-benzene (**6a**) provided chromane derivative **7a**, also as a single diastereomer. The effect of variation of the reaction conditions was studied using this substrate (Table 1). Best results were

Table 1. Optimization of Reaction Conditions[a]



entry	catalyst	Si−B	solvent	temp (°C)	yield (%)
1	Pd-PEPPSI-IPr[b]	**2b**	THF	20	73
2	Pd-PEPPSI-IPr[b]	**2b**	THF	50	76
3	$Pd_2(dba)_3$·$CHCl_3$	**2b**	toluene	20	65
4	$Pd_2(dba)_3$·$CHCl_3$/Cy_3P	**2b**	toluene	50	58
5	$Pd_2(dba)_3$·$CHCl_3$/Ph_3P	**2b**	toluene	50	56
6	(η^3-C_3H_5)Pd-(Ph_3P)Cl	**2b**	toluene	20	60
7	Pd-PEPPSI-IPr[b]	**2a**	THF	50	–
8	$Pd_2(dba)_3$·$CHCl_3$	**2a**	toluene	50	–

[a]Reaction time 48 h, 5 mol % catalyst, ligand/metal 1.2:1, **6a**/**2b** 1.2:1. 2-Propanol and pyridine were added prior to workup. [b]MeMgCl used for reduction of Pd(II).

obtained from reactions catalyzed by Pd-PEPPSI-IPr in THF (entries 1−2); at 50 °C, 76% of cyclized product was isolated. With this substrate, reaction in the presence of $Pd_2(dba)_3$·$CHCl_3$ resulted in a lower yield (entry 3). Catalysts prepared from $Pd_2(dba)_3$·$CHCl_3$ and a phosphine ligand or (η^3-C_3H_5)Pd(PPh_3)Cl also gave inferior results (entries 4−6). Even at 50 °C, no cyclized product was obtained from attempted addition of the less reactive silylborane **2a** (entries 7 and 8).

Since chromanes and chromenes[19] display useful biological properties, it was of interest to examine whether substrates functionalized in the aromatic ring underwent the cyclization and at the same time study the influence of substituents on the reactivity. The reactions proceeded smoothly using substrates with both electron-donating and electron-withdrawing substituents to give products **7b−g**; no major impact of the electronic properties on the reactivity was observed (Figure 1).

By use of the same procedure, the *N*-tosyl analogue of **6a**, **8**, afforded hydroquinoline derivative **9** in good yield, and cyclization of enyne **10** produced an isomeric chromane, **11**,[20] employing catalytic $Pd_2(dba)_3$·$CHCl_3$ (Scheme 3).

Attempted cyclizations of 1,7-enynes **12−14** under the conditions specified in Table 1, entry 2, did not result in the desired product; from **13** and **14** the compounds from 1,2-addition to the triple bond were instead obtained as the single

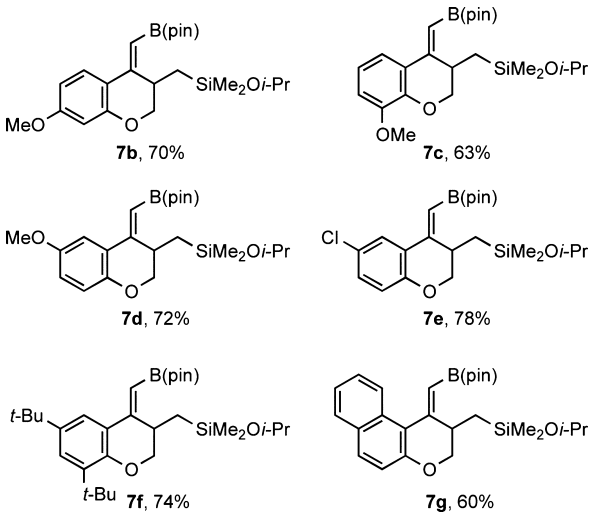
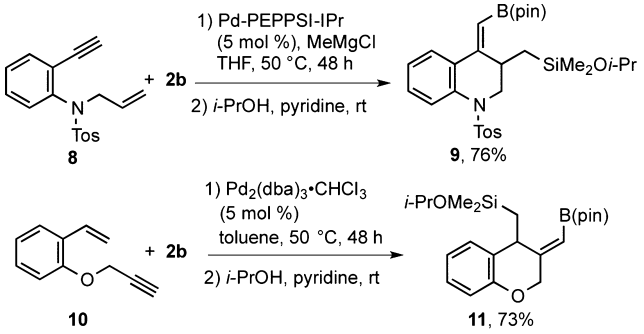
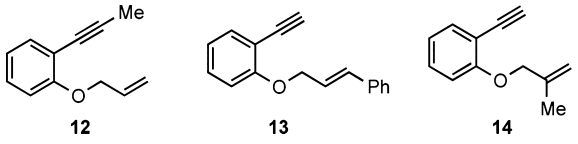


Figure 1. Synthesis of chromane derivatives.

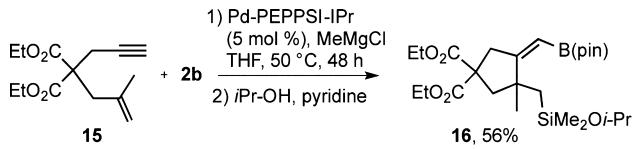
Scheme 3. Preparation of Tetrahydroquinoline and Chromene



products, and from attempted reaction of **12** only starting material was recovered. In analogy to **13**, 1,6-enynes with terminal olefinic substiuents were unreactive, affording low yields of products.[14] In contrast, 1,6-enyne **15** gave a cyclopentane derivative with an all-carbon quaternary center (**16**) in the presence of Pd-PEPPSI-IPr (Scheme 4).



Scheme 4. Cyclization of Substituted 1,6-Enyne



Only a few diastereoselective[2a,c,k,p] or enantioselective[1d,2a,j] cyclizations of 1,7-enynes to cyclohexane derivatives have been reported. We were pleased to observe that the relative configuration of the newly formed center could be controlled by substituents at sp^3-centers of the 1,7-enyne. Thus, cyclization of *rac*-**17** gave a 5:1 diastereomeric mixture of **18** (Scheme 5). Chiral 1,6-enynes reacted with lower selectivity.

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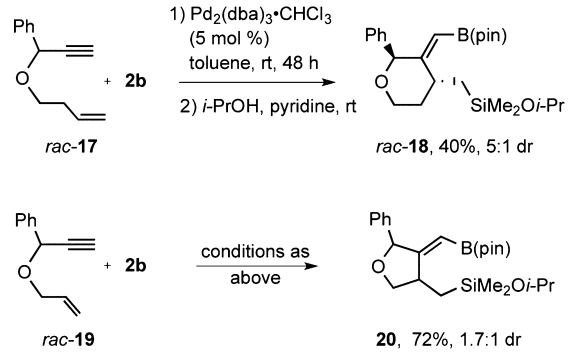
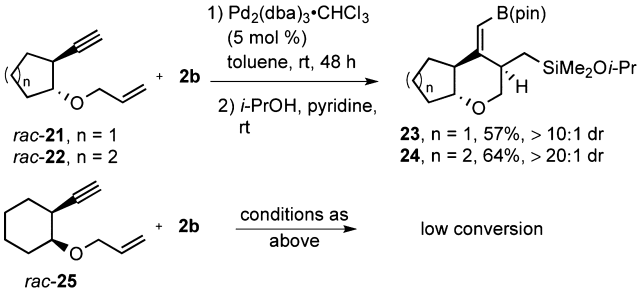
Thus, under the same conditions, *rac*-**19** gave cyclopentane derivative **20** as a 1.7:1 mixture of diastereomers.

Scheme 5. Cyclization of Chiral 1,7- and 1,6-Enynes



The trans-disubstituted enynes (*R**,*S**)-**21** and (*R**,*S**)-**22**, with both substituents in an equatorial position, reacted with high diastereoselectivity to give bicyclic compounds **23** and **24**, respectively, whereas cis isomer (*R**,*R**)-**25**, in which the alkyne substituent according to ^{1}H NMR occupies an axial position, gave a low yield of product when subjected to the same reaction, most likely since addition to the axial alkyne bond is sterically unfavored (Scheme 6).

Scheme 6. Diastereoselective Preparation of Bicyclic Compounds



The relative configurations of **18**, **23**, and **24** were determined by ^{1}H NMR spectroscopy. In **18**, NOE interactions between H_{6a} and H_2 as well as between H_{6a} and the methylene protons adjacent to silicon showed that the substituents are trans oriented with the silicon substituent occupying an axial position as also verified by the coupling constants (Figure 2). In contrast, the corresponding substituents in **23** and **24** were found to be cis, as shown by a NOE interaction between H_a and H_b.

The reaction is assumed to follow a mechanism analogous to that of similar processes, consisting of oxidative addition of the silylborane to Pd(0) followed by addition of PdSi and B to the alkyne and stereochemistry-determining insertion of the alkene into the carbon−palladium bond and final reductive elimination (Scheme 7).

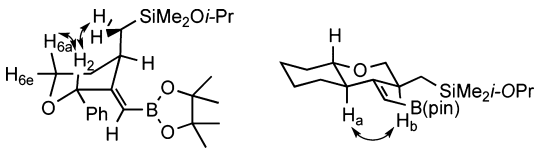
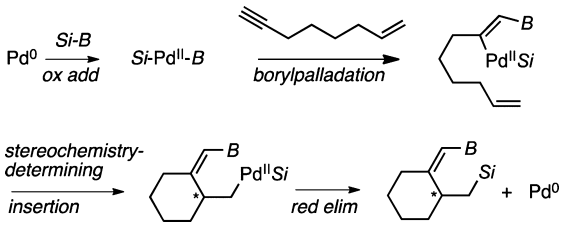


Figure 2. NOE interactions in **18** (left) and **24** (right).

Scheme 7. Mechanism for Silaborative Cyclization



The stereochemistry of products **23** and **24** can be rationalized by assuming a six-membered chair formed transition state (A, Figure 3). Assuming that the phenyl group in **17** is forced into an axial position (B, Figure 3), as a result of steric interaction with the olefinic bond when placed in equatorial position (C, Figure 3), the observed stereochemistry of the product can be explained.

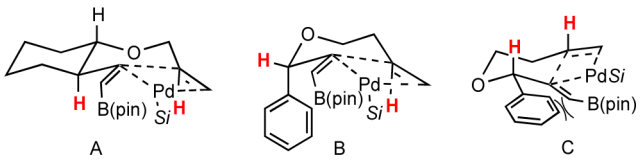


Figure 3. Proposed transition states for stereochemistry-determining migratory insertion.

In conclusion, we have developed an atom economic cyclization of 1,7-enynes, which provides cyclohexane derivatives containing reactive boron and silicon functional groups. With proper reaction conditions, products from 1,2-addition to the alkyne can usually be avoided. Cyclization of chiral substrates proceeds with high diastereoselectivity.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b03479.

Experimental procedures, characterization data, and copies of ^{1}H and ^{13}C NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) Reviews on metal-catalyzed cyclizations of 1,*n*-enynes: (a) Michelet, V.; Toullec, P. Y.; Genet, J.-P. *Angew. Chem., Int. Ed.* **2008**, *47*, 4268−4315. (b) Lee, S. I.; Chatani, N. *Chem. Commun.* **2009**, 371−384. (c) Watson, I. D. G.; Toste, F. D. *Chem. Sci.* **2012**, *3*,

DOI: 10.1021/acs.orglett.5b03479
Org. Lett. XXXX, XXX, XXX−XXX

2899−2919. (d) Marinetti, A.; Jullien, H.; Voituriez, A. *Chem. Soc. Rev.* **2012**, *41*, 4884−4908.
(2) (a) Trost, B. M.; Czeskis, B. A. *Tetrahedron Lett.* **1994**, *35*, 211−214. (b) Chatani, N.; Morimoto, T.; Muto, T.; Murai, S. *J. Am. Chem. Soc.* **1994**, *116*, 6049−6050. (c) Trost, B. M.; Li, Y. *J. Am. Chem. Soc.* **1996**, *118*, 6625−6633. (d) Trost, B. M.; Toste, F. D. *J. Am. Chem. Soc.* **2000**, *122*, 714−715. (e) Fernández-Rivas, C.; Méndez, M.; Echavarren, A. M. *J. Am. Chem. Soc.* **2000**, *122*, 1221−1222. (f) Fernández-Rivas, C.; Méndez, M.; Nieto-Oberhuber, C.; Echavarren, A. M. *J. Org. Chem.* **2002**, *67*, 5197−5201. (g) Krafft, M. E.; Boñaga, L. V. R.; Wright, J. A.; Hirosawa, C. *J. Org. Chem.* **2002**, *67*, 1233−1246. (h) Chatani, N.; Inoue, H.; Kotsuma, T.; Murai, S. *J. Am. Chem. Soc.* **2002**, *124*, 10294−10295. (i) Harada, K.; Tonoi, Y.; Kato, H.; Fukuyama, Y. *Tetrahedron Lett.* **2002**, *43*, 3829−3832. (j) Hatano, M.; Mikami, K. *J. Am. Chem. Soc.* **2003**, *125*, 4704−4705. (k) Trost, B. M.; Dong, L.; Schroeder, G. M. *J. Am. Chem. Soc.* **2005**, *127*, 10259−10268. (l) Bajracharya, G. B.; Nakamura, I.; Yamamoto, Y. *J. Org. Chem.* **2005**, *70*, 892−897. (m) Miyanohana, Y.; Chatani, N. *Org. Lett.* **2006**, *8*, 2155−2158. (n) Ota, K.; Lee, S. I.; Tang, J.-M.; Takachi, M.; Nakai, H.; Morimoto, T.; Sakurai, H.; Kataoka, K.; Chatani, N. *J. Am. Chem. Soc.* **2009**, *131*, 15203−15211. (o) Huang, C.; Kothandaraman, P.; Koh, B. Q.; Chan, P. W. H. *Org. Biomol. Chem.* **2012**, *10*, 9067−9078. (p) Rao, W.; Sally; Koh, M. J.; Chan, P. W. H. *J. Org. Chem.* **2013**, *78*, 3183−3195. (q) Mailyan, A. K.; Krylov, I. M.; Bruneau, C.; Dixneuf, P. H.; Osipov, S. N. *Eur. J. Org. Chem.* **2013**, *2013*, 5353−5363. (r) Kaminsky, L.; Clark, D. A. *Org. Lett.* **2014**, *16*, 5450−5453. (s) Yamashita, K.; Fujii, Y.; Yoshioka, S.; Aoyama, H.; Tsujino, H.; Uno, T.; Fujioka, H.; Arisawa, M. *Chem. - Eur. J.* **2015**, *21*, 17491−17494.
(3) (a) Beletskaya, I.; Moberg, C. *Chem. Rev.* **1999**, *99*, 3435−3461. (b) Suginome, M.; Ito, Y. *Chem. Rev.* **2000**, *100*, 3221−3256. (c) Beletskaya, I.; Moberg, C. *Chem. Rev.* **2006**, *106*, 2320−2354.
(4) Cho, H. Y.; Morken, J. P. *Chem. Soc. Rev.* **2014**, *43*, 4368−4380.
(5) (a) Onozawa, S.-y.; Hatanaka, Y.; Tanaka, M. *Chem. Commun.* **1997**, 1229−1230. (b) Onozawa, S.-y.; Hatanaka, Y.; Choi, N.; Tanaka, M. *Organometallics* **1997**, *16*, 5389−5391. (c) Mori, M.; Hirose, T.; Wakamatsu, H.; Imakuni, N.; Sato, Y. *Organometallics* **2001**, *20*, 1907−1909. (d) Sato, Y.; Imakuni, N.; Mori, M. *Adv. Synth. Catal.* **2003**, *345*, 488−491. (e) Sato, Y.; Imakuni, N.; Hirose, T.; Wakamatsu, H.; Mori, M. *J. Organomet. Chem.* **2003**, *687*, 392−402.
(6) Singidi, R. R.; Kutney, A. M.; Gallucci, J. C.; RajanBabu, T. V. *J. Am. Chem. Soc.* **2010**, *132*, 13078−13087.
(7) Apte, S.; Radetich, B.; Shin, S.; RajanBabu, T. V. *Org. Lett.* **2004**, *6*, 4053−4056.
(8) Pardo-Rodríguez, V.; Buñuel, E.; Collado-Sanz, D.; Cárdenas, D. J. *Chem. Commun.* **2012**, *48*, 10517−10519.
(9) López-Durán, R.; Martos-Redruejo, A.; Buñuel, E.; Pardo-Rodríguez, V.; Cárdenas, D. J. *Chem. Commun.* **2013**, *49*, 10691−10693.
(10) Ojima, I.; Vu, A. T.; Lee, S.-Y.; McCullagh, J. V.; Moralee, A. C.; Fujiwara, M.; Hoang, T. H. *J. Am. Chem. Soc.* **2002**, *124*, 9164−9174.
(11) (a) Ohmura, T.; Suginome, M. *Bull. Chem. Soc. Jpn.* **2009**, *82*, 29−49. (b) Oestreich, M.; Hartmann, E.; Mewald, M. *Chem. Rev.* **2013**, *113*, 402−441.
(12) (a) Si: Denmark, S. E.; Regens, C. S. *Acc. Chem. Res.* **2008**, *41*, 1486−1499. (b) Chang, W.-T. T.; Smith, R. C.; Regens, C. S.; Bailey, A. D.; Werner, N. S.; Denmark, S. E. *Org. React.* **2011**, *75*, 213−745. (c) B: Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457−2483.
(13) Tanaka and co-workers published one previous example using a different silylborane and obtained the product with inferior yield.
(14) (a) Gerdin, M.; Nadakudity, S. K.; Worch, C.; Moberg, C. *Adv. Synth. Catal.* **2010**, *352*, 2559−2570. See also: (b) Ohmura, T.; Oshima, K.; Taniguchi, H.; Suginome, M. *J. Am. Chem. Soc.* **2010**, *132*, 12194−12196.
(15) Organ, M. G.; Abdel-Hadi, M.; Avola, S.; Hadei, N.; Nasielski, J.; O'Brien, C. J.; Valente, C. *Chem. - Eur. J.* **2007**, *13*, 150−157.
(16) Ohmura, T.; Masuda, K.; Furukawa, H.; Suginome, M. *Organometallics* **2007**, *26*, 1291−1294.
(17) Ohmura, T.; Masuda, K.; Suginome, M. *J. Am. Chem. Soc.* **2008**, *130*, 1526−1527.
(18) Zhou, H.; Moberg, C. *J. Am. Chem. Soc.* **2012**, *134*, 15992−15999.
(19) Majumdar, N.; Paul, N. D.; Mandal, S.; de Bruin, B.; Wulff, W. D. *ACS Catal.* **2015**, *5*, 2329−2366.
(20) This compound gave an analogous product by borastannylative cyclization; see ref 6.

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Org. Lett. XXXX, XXX, XXX−XXX