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Trans-Diborylation of Alkynes: *Pseudo*-Intramolecular Strategy Utilizing a Propargylic Alcohol Unit

Yuki Nagashima,[†] Keiichi Hirano,*[,†] Ryo Takita,[‡] and Masanobu Uchiyama*[,†,‡]

[†]Graduate School of Pharmaceutical Sciences, The University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-0033, Japan

[‡]Advanced Elements Chemistry Research Team, RIKEN Center for Sustainable Resource Science, and Elements Chemistry Laboratory, RIKEN, 2-1 Hirosawa, Wako-shi, Saitama 351-0198, Japan

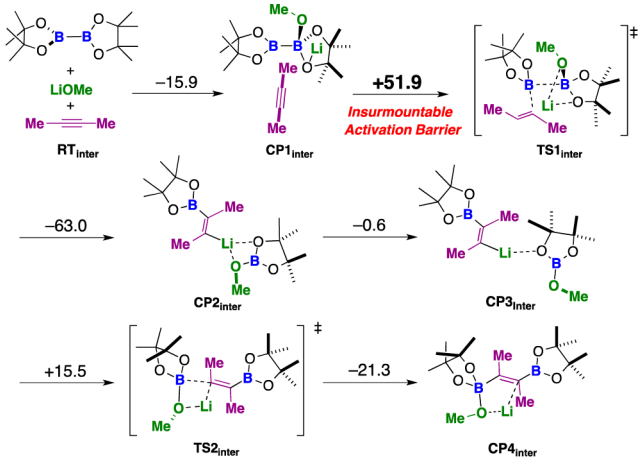
Supporting Information

ABSTRACT: We present the first *trans*-selective diborylation reaction of alkynes. By means of theoretical calculation-assisted reaction analysis, we designed a *pseudo*-intramolecular reaction of diboron, propargyl alcohol, and a base to facilitate B−B bond activation and C−B bond formation with high efficiency. This approach provides synthetically versatile and densely functionalized 4-borylated 1,2-oxaborol-2(5*H*)-oles (vinyldiboronates) in a straightforward manner. Detailed computational analysis showed that the directing alkoxide functionality markedly lowers the activation energy of B−C bond formation.

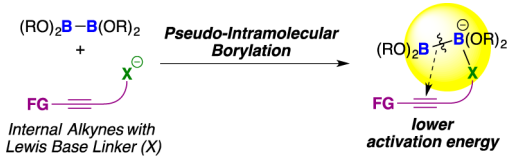
Vinylboronates are widely used in organic synthesis as building blocks for regio-/stereoselective construction of multisubstituted olefins. They are readily storable and easy to handle, and their C−B bonds can be easily transformed into C−C and C−heteroatom bonds by means of various synthetic methods, as represented by the Suzuki−Miyaura cross-coupling reaction.[1,2] Hydroborations,[3] haloborations[4] and diborylations[5] of alkynes are excellent methods for synthesis of vinylboronates or vinyldiboronates. However, in all cases, the reactions are triggered by interaction between a vacant orbital of a transition metal (or boron atom) and a π-orbital of acetylene, and therefore *cis*-addition is predominant. Finding a means to obtain *trans*-selectivity in borylation reactions remains an important challenge. We anticipated that *trans*-addition should be accomplished by addition of a boryl anion equivalent to acetylene.[6−8] To examine the feasibility of this idea, we performed a model calculation using butyne, bis(pinacolato)-diboron, and LiOMe (Scheme 1). The results indicated that *trans*-borylation would proceed selectively (**CP2**$_{inter}$) through an anionic mechanism with 11.1 kcal/mol exothermicity, but it would be necessary to overcome a very high activation energy (+51.9 kcal/mol). In order to achieve this, we adopted a *pseudo*-intramolecular reaction strategy,[9] which enabled us to achieve regioselective *trans*-diborylation of alkynes for the first time. We show that this reaction provides versatile access to *trans*-vinyldiboronates and oxaboroloples (Scheme 2).

All initial attempts at intermolecular reaction using various acetylenes and bis(pinacolato)diboron (**2a**) under various conditions were unsuccessful, as expected from the computational results. Thus, we focused on installing a heteroatom(s) on the acetylene skeleton to coordinate/activate diboron in order to lower the activation energy. After extensive

Scheme 1. DFT Calculation on Intermolecular Diborylation of 2-Butyne at the B3LYP/6-31+G* Level (ΔG in kcal/mol)



Scheme 2. Our Strategy (Working Hypothesis)



experimentation, we found that the combination of propargyl alkoxide, prepared from propargylic alcohol (**1a**) and base, and **2a** promoted the C−C triple bond without any catalyst (Table 1). Unexpectedly, the present *trans*-diborylation gave an oxaborole ring as a partial structure of the product. The reaction temperature and countercation of the base played crucial roles in determining the yield of this diborylation. The reaction progress was sluggish at room temperature, and only a trace amount of the desired product **3a** was obtained (entry 1). A higher yield of product **3a** was obtained at 50 °C, and the yield was further increased to 77% at 75 °C (entries 2 and 3). Use of MeLi gave **3a** in comparable yield to that obtained with ^{n}BuLi (entry 3 vs 4), whereas MeMgBr and NaH each gave only a small amount of **3a** (entries 5 and 6), indicating that the lithium cation most efficiently promotes the borylation. To our

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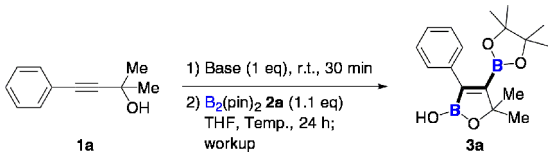
Table 1. Optimization of Reaction Conditions



1a 3a

entry	base	temp (°C)	yield (%)[a]
1	^{n}BuLi	rt	trace
2	^{n}BuLi	50	66
3	^{n}BuLi	75	77
4	MeLi	75	72
5	MeMgBr	75	trace
6	NaH	75	27

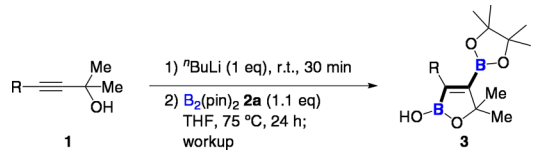
[a]Determined by ^{1}H NMR analysis.

knowledge, this is the first example of diborylation of alkynes giving the *trans*-product as the major product,[5j,k] though *trans-hydro*boration of alkynes,[3h,10,11] Pd-catalyzed *trans-sila*boration of terminal alkynes,[12] and classical *trans-carbometalation* of propargyl alcohols[6a,b] have been reported.

Next, we examined the scope and limitations of the *trans*-diborylation of propargylic alcohols (Table 2). The electronic effect at acetylene carbons showed little influence on the regioselectivity/reactivity and various phenyl propargylic alcohols with an electron-donating group (*o*/*p*-MeO and NH_2) as well as an electron-withdrawing group (Cl, CF_3, ester, and CN) on the phenyl ring were efficiently converted to the corresponding vinyldiboronates in high yields without formation of detectable amounts of isomers (entries 1−8). In addition, base/nucleophile-sensitive moieties such as ester and CN groups were compatible with the reaction conditions (entries 6 and 7). The acidic proton of aniline derivative **1h** was not deleterious to the reaction, and **3h** was obtained in 85% yield. Other aromatic rings and heterocycles such as pyridine, thiophene, and naphthalene rings caused no problem (entries 9−11). This reaction is not limited to aryl-substituted alkynes. Primary (entries 12 and 13) and secondary aliphatic substituents (entry 13) afforded the product in high yield. On the other hand, a tertiary alkyl group significantly slowed down the reaction, probably due to steric hindrance (entry 15). Distal multiple bonds were untouched in the cases of the conjugate enyne **1p** and diyne **1q** affording products **3p** and **3q** chemoselectively in good yields (entries 16 and 17). However, an acetylenic C−Br bond did not survive under these conditions (entry 18). We confirmed that this reaction could be conducted on a gram scale: pure **3a** was obtained in 87% yield (1.37 g) just by triturating the crude solid in cold hexane after workup.

This reaction also shows a wide scope for propargylic substituents and diborons (Table 3). A cyclic tertiary alcohol (**1s**) and secondary alcohols (**1t**, **1u**, **1v**, **1w**, and **1x**) were converted to the desired products (entries 1−6). In particular, chemoselective diborylation of the triple bond of **1u** was achieved even in the presence of the double bond, presumably because a transition-metal-free ionic reaction is involved (entry 5). The desired product was not formed with 3-phenyl-2-propyn-1-ol, where R^2 and R^3 are hydrogen, indicating the importance of the Thorpe−Ingold effect for this transformation. Bis(neopentylglycolato)diboron (**2b**) gave the corresponding vinylboronate **3y** in modest yield (entry 7). The unsymmetrical diboron **2c**[5g] underwent diborylation in a

Table 2. Scope and Limitations of *trans*-Diborylation of Propargylic Alcohols



1 3

Entry	Product	Yield (%)[a]	Entry	Product	Yield (%)[a]
1	**3a**	77 (89) 87[b]	10	**3j**	96
2	**3b**	94	11	**3k**	92
3	**3c**	88	12	**3l**	56 (79)
4	**3d**	97	13	**3m**	89
5	**3e**	73	14	**3n**	84
6[c]	**3f**	61	15	**3o**	35
7[c]	**3g**	74	16	**3p**	62
8	**3h**	85	17[c]	**3q**	72
9	**3i**	66[d]	18[c]	**3r**	n.d.

[a]Isolated yield. Yield in 1,4-dioxane as a solvent in parentheses. [b]5 mmol scale. [c]MeLi was used instead of ^{n}BuLi as a base. [d]Determined by ^{1}H NMR analysis.

stereo-/chemoselective manner (entry 8). Homopropargylic alcohols were not reactive under these reaction conditions.

We have demonstrated that the *trans*-diborylated products can be obtained from terminal acetylenes via sequential reactions in one pot (Scheme 3). Starting with acetone and 4-methoxyphenylacetylene, the *trans*-diborylated product **3b** was obtained in comparable yield to that of the two-pot procedure (*vide supra*). This method provides operationally more facile access to vinyldiboronates.

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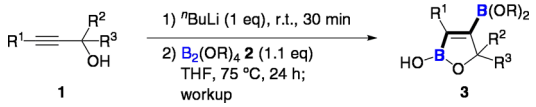
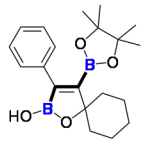
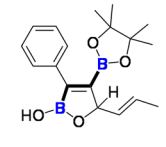
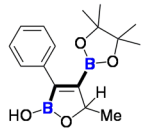
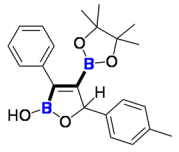
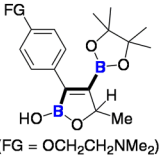
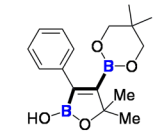
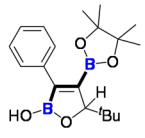
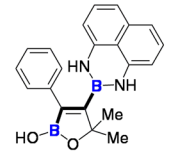
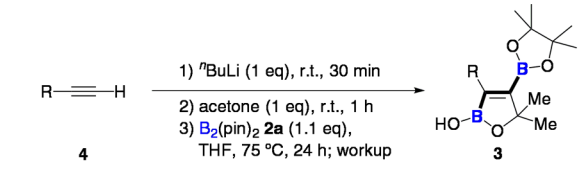
Table 3. Substrate Scope of Propargylic Alcohols and Diborons[a]

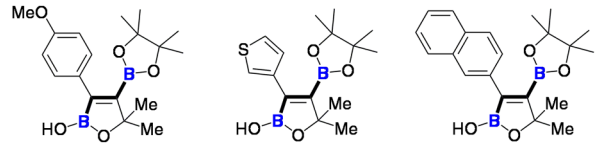


Entry	Product		Yield (%)[b]	Entry	Product		Yield (%)[b]
1		**3s**	88	5		**3w**	80
2		**3t**	93	6		**3x**	27
3	 (FG = $OCH_2CH_2NMe_2$)	**3u**	75	7		**3y**	49
4		**3v**	75	8		**3z**	82

[a] $B_2(OR)_4$ = bis(pinacolato)diboron (**2a**) (entries 1−6), bis(neopentylglycolato)diboron **2b** (entry 7), and unsymmetrical diboron (pin)B−B(dan) **2c**[5g] (entry 8) were used as diborons **2**. [b] Isolated yield.

Scheme 3. One-Pot *Trans*-Diborylation from Terminal Alkynes

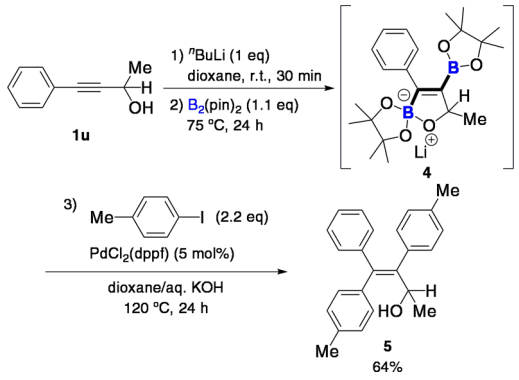




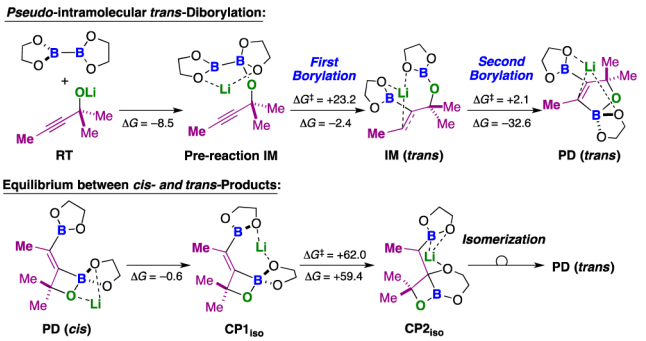
We also succeeded in the synthesis of a tetrasubstituted olefin via sequential diborylation/Suzuki−Miyaura cross-coupling processes in one pot (Scheme 4). The putative borate intermediate **4** generated by diborylation of **1u** was directly subjected to the coupling reaction with 4-iodotoluene without workup to give the desired olefin **5** in 64% yield. This result demonstrates the potential applicability of this methodology for regio-controlled synthesis of densely functionalized alkenes, such as tamoxifen derivatives.

Finally, DFT calculation was performed in order to shed light on the mechanism of this unprecedented *trans*-diborylation reaction. The calculated potential energy profiles are summarized in Scheme 5. Initial complexation of diboron and lithium propargyl alkoxide releases a small amount of energy

Scheme 4. Sequential *Trans*-Diborylation/Suzuki−Miyaura Cross-Coupling Processes in One Pot



Scheme 5. DFT Calculation on *Trans*-Diborylation of Lithium 2-Methylpent-3-yn-2-olate at the B3LYP/6-31+G* Level (ΔG in kcal/mol)



(−8.5 kcal/mol), and then borylation via B−B bond activation occurs with a significantly lowered activation energy (+23.2 kcal/mol) compared with the intermolecular case (Scheme 1). The second borylation contributes to a large energy gain (−32.6 kcal/mol), and the thermodynamically stable *trans*-product is formed. Aqueous workup hydrolyzes the borate part of **PD** (***trans***) to form the oxaborolole moiety. A possible equilibrium/pathway between the *cis*- and *trans*-diborylated products via rotation of the C−C bond was computed to require an extremely high activation energy (+62.0 kcal/mol) and is unlikely to occur under the present reaction conditions.[13]

In summary, we have developed an unprecedented *trans*-diborylation of alkynes by designing a *pseudo*-intramolecular reaction, such that the activation barrier of addition of boryl anion to the triple bond was significantly lowered. This methodology opens up facile access to synthetically versatile unsymmetrical vinyldiboronates with high functional group compatibility. The method provides a simple and direct route for the synthesis of regio-controlled tetrasubstituted olefins from various functionalized terminal alkyne precursors. In addition, the oxaborole skeleton and its analogues have recently been recognized as key structural platforms and potent pharmacophores in materials and pharmaceutical sciences.[14] Further work to expand the scope of the reaction and to study applications of the products, multiply substituted olefins/oxaboroloples, for the synthesis of biologically active and functional molecules is in progress.

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■ ASSOCIATED CONTENT

Supporting Information

Experimental details and NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Authors

k1hirano@mol.f.u-tokyo.ac.jp
uchiyama@mol.f.u-tokyo.ac.jp

Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) Carbon−heteroatom bond formation: (a) Shade, R. E.; Hyde, A. M.; Olsen, J.-C.; Merlic, C. A. *J. Am. Chem. Soc.* **2010**, *132*, 1202−1203. (b) Liu, S.; Liebeskind, L. S. *J. Am. Chem. Soc.* **2008**, *130*, 6918−6919. (c) Lam, P. Y. S.; Vincent, G.; Bonne, D.; Clark, C. G. *Tetrahedron Lett.* **2003**, *44*, 4927−4931. Carbon−carbon bond formation: For a review including 1,4-addition of vinyl boronates to enones, see: (d) Hayashi, T.; Yamasaki, K. *Chem. Rev.* **2003**, *103*, 2829−2844. For a seminal publication of the Petasis reaction, see: (e) Petasis, N. A.; Akritopoulou, I. *Tetrahedron Lett.* **1993**, *34*, 583−586.

(2) For comprehensive reviews on Suzuki−Miyaura cross-coupling reaction, see: (a) Suzuki, A. *Angew. Chem., Int. Ed.* **2011**, *50*, 6722−6737. (b) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457−2483 and references cited therein.

(3) Reviews on *cis*-hydroborations of alkynes using boranes: (a) Brown, H. C.; Campbell, J. B., Jr. *Aldrichmica Acta* **1981**, *14*, 3−11. (b) Beletskaya, I.; Pelter, A. *Tetrahedron* **1997**, *53*, 4957−5026. For pioneering work on stoichiometric Cu-mediated *cis*-hydroborations of terminal alkynes using diboron **2a**, see: (c) Takahashi, K.; Ishiyama, T.; Miyaura, N. *Chem. Lett.* **2000**, *29*, 982−983. (d) Takahashi, K.; Ishiyama, T.; Miyaura, N. *J. Organomet. Chem.* **2001**, *625*, 47−53. For Cu-catalyzed hydroboration of alkynes using diboron **2a**: (e) Lee, J.-E.; Kwon, J.; Yun, J. *Chem. Commun.* **2008**, 733−734. (f) Jang, H.; Zhugralin, A. R.; Lee, Y.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2011**, *133*, 7859−7871. (g) Sasaki, Y.; Horita, Y.; Zhong, C.; Sawamura, M.; Ito, H. *Angew. Chem., Int. Ed.* **2011**, *50*, 2778−2782. (h) Kim, H. R.; Yun, J. *Chem. Commun.* **2011**, *47*, 2943−2945. (i) Semba, K.; Fujihara, T.; Terao, J.; Tsuji, Y. *Chem.—Eur. J.* **2012**, *18*, 4179−4184. (j) Moure, A. L.; Arrayás, R. G.; Cárdenas, D. J.; Alonso, I.; Carretero, J. C. *J. Am. Chem. Soc.* **2012**, *134*, 7219−7222. (k) Park, J. K.; Ondrusek, B. A.; McQuade, D. T. *Org. Lett.* **2012**, *14*, 4790−4793. Switching from *cis*- to *trans*-selectivity of hydroalumination of alkynes has been reported, see: (l) Eisch, J. J.; Foxton, M. W. *J. Org. Chem.* **1971**, *36*, 3520−3526.

(4) For examples of highly *cis*-selective bromoboration of propyne and its mechanistic rationale, see: (a) Wang, C.; Tobrman, T.; Xu, Z.; Negishi, E.-I. *Org. Lett.* **2009**, *11*, 4092−4095. (b) Wang, C.; Uchiyama, M. *Eur. J. Org. Chem.* **2012**, 6548−6544.

(5) For a recent review on diborylation reactions: (a) Takaya, J.; Iwasawa, N. *ACS Catal.* **2012**, *2*, 1993−2006. Selected publications of Pt- or Cu-catalyzed *cis*-diborylations of alkynes: **Pt**: (b) Ishiyama, T.; Matsuda, N.; Miyaura, N.; Suzuki, A. *J. Am. Chem. Soc.* **1993**, *115*, 11018−11019. (c) Ishiyama, T.; Matsuda, N.; Murata, M.; Ozawa, F.; Suzuki, A.; Miyaura, N. *Organometallics* **1996**, *15*, 713−720. (d) Lesley, G.; Nguyen, P.; Taylor, N. J.; Marder, T. B.; Scott, A. J.; Clegg, W.; Norman, N. C. *Organometallics* **1996**, *15*, 5137−5154. (e) Thomas, R. L.; Souza, F. E. S.; Marder, T. B. *J. Chem. Soc., Dalton Trans.* **2001**, 1650−1656. (f) Marder, T. B.; Norman, N. C. *Top. Catal.* **1998**, 63−73. Suginome reported regioselective diborylation by Ir-catalysis in addition to Pt-catalysis. (g) Iwadate, N.; Suginome, M. *J. Am. Chem. Soc.* **2010**, *132*, 2548−2549. **Cu**: (h) Lillo, V.; Fructos, M. R.; Ramírez, J.; Braga, A. A. C.; Maseras, F.; Díaz-Requejo, M. M.; Pérez, P. J.; Fernández, E. *Chem.—Eur. J.* **2007**, *13*, 2614−2621. (i) Yoshida, H.; Kawashima, S.; Takemoto, Y.; Okada, K.; Ohshita, J.; Takaki, K. *Angew. Chem., Int. Ed.* **2012**, *51*, 235−238. For a recent nanoporous Au catalyzed reaction, see: (j) Chen, Q.; Zhao, J.; Ishikawa, Y.; Asao, N.; Yamamoto, Y.; Jin, T. *Org. Lett.* **2013**, *15*, 5766−5769. Lin, Marder, and Norman reported Co-catalyzed *cis*-diborylation of an alkyne, while a small amount of *trans*-product was obtained. (k) Adams, C. J.; Baber, R. A.; Batsanov, A. S.; Bramham, G.; Charmant, J. P. H.; Haddow, M. F.; Howard, J. A. K.; Lam, W. H.; Lin, Z.; Marder, T. B.; Norman, N. C.; Orpen, A. G. *Dalton Trans.* **2006**, 1370−1373.

(6) For an early review of carbometalations of alkynes, see: (a) Normant, J. F.; Alexakis, A. *Synthesis* **1981**, 841−870. As a representative example of carbometalation of propargylic alcohols, see: (b) Tessier, P. E.; Penwell, A. J.; Souza, F. E. S.; Fallis, A. G. *Org. Lett.* **2003**, *5*, 2989−2992. For a recent publication on *trans*-selective carbolithiation of alkyne, see: (c) Fressigné, C.; Girard, A.-L.; Durandetti, M.; Maddaluno, J. *Angew. Chem., Int. Ed.* **2008**, *47*, 891−893.

(7) Our group recently reported the generation and application of a boryl anion-equivalent, borylzincate, for borylzincation of a benzyne/terminal alkyne. Nagashima, Y.; Takita, R.; Yoshida, K.; Hirano, K.; Uchiyama, M. *J. Am. Chem. Soc.* **2013**, *135*, 18730−18733.

(8) For inspiring work on addition of Lewis base activated diborons to nonactivated olefins, see: Bonet, A.; Pubill-Ulldemolins, C.; Bo, C.; Gulyás, H.; Fernández, E. *Angew. Chem., Int. Ed.* **2011**, *50*, 7158−7161.

(9) Yamamoto, Y.; Ishii, J.-I.; Nishiyama, H.; Itoh, K. *J. Am. Chem. Soc.* **2005**, *127*, 9625.

(10) For formal *trans*-hydroboration: **Rh**/**Ir**: (a) Ohmura, T.; Yamamoto, Y.; Miyaura, N. *J. Am. Chem. Soc.* **2000**, *122*, 4990−4991. **Ru**: (b) Gunanathan, C.; Hölscher, M.; Pan, F.; Leitner, W. *J. Am. Chem. Soc.* **2012**, *134*, 14349−14352.

(11) Sundararaju, B.; Fürstner, A. *Angew. Chem., Int. Ed.* **2013**, *52*, 14050−14054.

(12) Ohmura, T.; Oshima, K.; Suginome, M. *Chem. Commun.* **2008**, 1416−1418.

(13) For details, see Supporting Information.

(14) Comprehensive reviews on boron-containing therapeutics, see: (a) Smoum, R.; Rubinstein, A.; Dembitsky, V. M.; Srebnik, M. *Chem. Rev.* **2012**, *112*, 4156−4220. (b) Baker, S. J.; Ding, C. Z.; Akama, T.; Zhang, Y.-K.; Hernandez, V.; Xia, Y. *Future Med. Chem.* **2009**, *1*, 1275−1288.