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Diborative Reduction of Alkynes to 1,2-Diboryl-1,2-Dimetalloalkanes: Its Application for the Synthesis of Diverse 1,2-Bis(boronate)s

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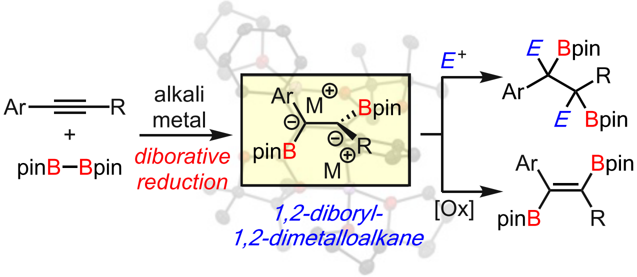
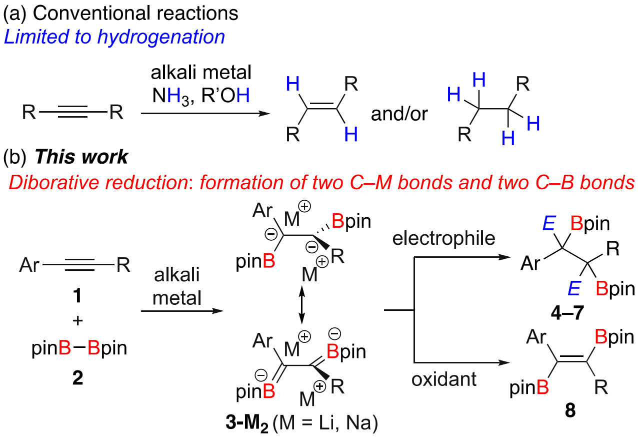
Supporting Information

ABSTRACT: Reduction of alkynes with alkali metals in the presence of B_2pin_2 results in diboration of alkynes. Distinct from conventional dissolving metal hydrogenations, two carbon−boron bonds and also two carbon−alkali metal bonds can be constructed in one operation to form 1,2-diboryl-1,2-dimetalloalkanes. The 1,2-diboryl-1,2-dimetalloalkanes generated are readily convertible to a wide range of vicinal bis(boronate)s. In particular, oxidation of the 1,2-dianionic species provides (*E*)-1,2-diborylalkenes, unique *anti*-selective diboration of alkynes being thus executed.



Reduction of C−C triple bonds by means of alkali metals is one of the most fundamental transformations in organic synthesis, as represented by dissolving metal reduction of alkynes to give *trans*-alkenes (Scheme 1a).[1,2] Naturally, such reduction always results in the formation of new C−H bonds by in situ protonation. Introduction of other atoms or groups besides hydrogens onto alkynes under strongly reducing conditions has been far less investigated. To realize such reductive functionalizations, the vinylic radical anion intermediates should be rapidly trapped by aprotic electrophiles. Otherwise, undesirable protonation or oligomerization[3] of the labile intermediates would occur. However, electrophiles are hardly compatible with strongly reducing conditions and normally undergo reductive decomposition. Therefore, reductive functionalizations of alkynes have been limited to useful yet specific intramolecular reactions.[4]

Scheme 1. Reductive Functionalization of Alkynes with Alkali Metals



We recently became interested in developing new transformations based on the strong reducing ability of alkali metals.[5] During the course of our investigation, we accidentally found that diborative reduction of alkynes **1** occurred in the presence of bis(pinacolato)diboron (**2**, B_2pin_2) and alkali metal to afford 1,2-diboryl-1,2-dimetalloalkanes **3-M**$_2$ (Scheme 1b).

Alkoxy-substituted B_2pin_2 is resistant to reduction by alkali metals.[6] On the other hand, because of the vacant p orbitals of the boron atoms, B_2pin_2 can rapidly react with the vinylic anionic species to suppress the undesired protonation or oligomerization. Moreover, the vacant p orbitals of the boron atoms installed render the 1,2-dianionic species **3-M**$_2$ sufficiently stable by delocalizing the negative charge. These features allowed us to accomplish an unusual reductive transformation of alkynes: the simultaneous formation of two carbon−boron bonds and two carbon−alkali metal bonds in one operation.

1,2-Dianionic species **3-M**$_2$ were converted to diverse 1,2-diborylalkanes **4**−**7** via electrophilic trapping. Oxidation of 1,2-dianionic **3-M**$_2$ with 2,3-dibromobutane furnished the corresponding 1,2-diborylalkenes **8**. Of note, the reaction preferentially afforded *E* isomers that are otherwise difficult to synthesize. This diborative reduction/oxidation sequence represents a rare example of *anti*-selective diboration of

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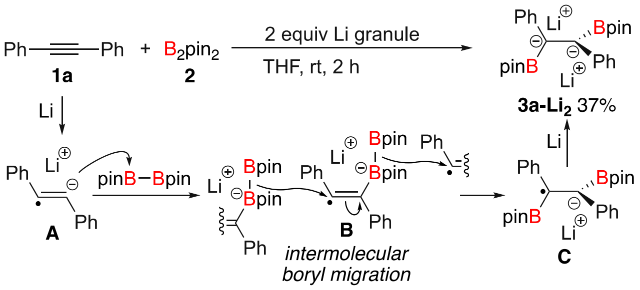
alkynes. Moreover, successive transformations of the two boryl groups installed clearly demonstrate the synthetic utility of bis(boronate)s **4**−**8**.[7,8]

First, we tried to identify the structure of **3a-Li$_2$** generated from diphenylacetylene (**1a**), diboron **2** and Li metal. Equimolar amounts of **1a** and **2** were treated with 2 equiv of Li granules in THF at room temperature (Scheme 2). The desired **3a-Li$_2$** gradually precipitated as yellow solids and was obtained in 37% yield as a THF adduct. Recrystallization of **3a-Li$_2$** from THF afforded yellow crystals of **3a-Li$_2$(thf)$_3$**, in which one Li$^+$ is coordinated by one THF molecule and the other Li$^+$ is associated with two THF molecules.

Scheme 2. Synthesis of 3a-Li$_2$ and a Possible Mechanism



The structure of **3a-Li$_2$(thf)$_3$** was unambiguously determined by single-crystal X-ray diffraction analysis, as shown in Figure 1.[9,10] The unit cell of the crystal consists of two independent molecules **Y** and **Z** having similar structural parameters. The C2−C3 bonds (1.529(2) and 1.526(2) Å) are significantly elongated compared with general C≡C triple bonds and are regarded as single bonds. Conversely, the C2−B1 (1.482(2) and 1.478(2) Å) and C3−B2 (1.478(2) and 1.482(2) Å) bonds are considerably shorter than C−B single bonds (1.58−1.62 Å)[11] and rather close to C═B double bonds (1.42−1.45 Å).[11] The double-bond character of these C−B bonds is also suggested by natural bond orbital (NBO) analysis.[12−14] Delocalization of the negative charge to the p orbitals of the boron atoms would make the C−B bonds short. Lithium cations Li1 and Li2 interact with C1 and C4, respectively (C1−Li1, 2.326(3) and 2.342(4); C4−Li2, 2.659(3) and 2.644(3)), which indicates slight delocalization of the negative charge to the benzene rings. The summations of the angles around C2 (359.7° and 358.5°, C1−C2−C3, C1−C2−B1, and B1−C2−C3) and C3 (358.1° and 357.4°, C2−C3−C4, C2−C3−B4, and B2−C3−C4) are close to 360°, which supports the sp^2-hybridized character of C2 and C3.[15] In the crystalline state, the two planes defined by C1−C2−B1 and C4−C3−B2 are found to be nearly orthogonal, as confirmed by the torsion angles of 86.5(2)° and 82.5(2)° (B1−C2−C3−B2).

A possible reaction mechanism for the generation of **3a-Li$_2$** is depicted in Scheme 2. First, one-electron reduction of alkyne **1a** would generate radical anion **A**, which would rapidly react with **2** to form borate species **B**. Subsequently, the terminal boryl group would migrate to the *β*-carbon to generate radical anion **C**. Mechanistic investigations[16] suggest that this boryl migration would proceed intermolecularly: the terminal boryl group would engage in nucleophilic attack onto the less crowded radical-centered *β*-carbon of **B**. Finally, **3a-Li$_2$** would be generated via one-electron reduction of **C**.[17]

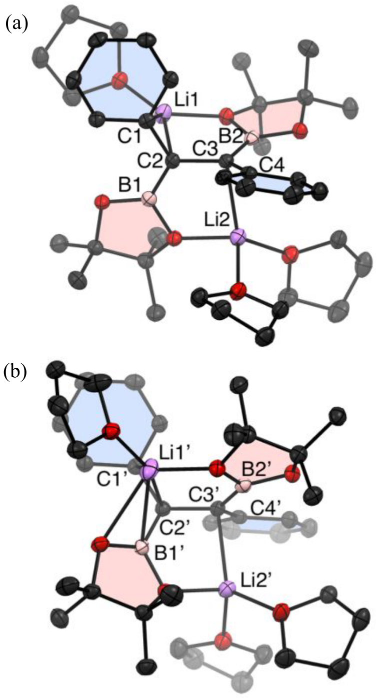


Figure 1. Structures of two independent molecules (a) **Y** and (b) **Z** of **3a-Li$_2$(thf)$_3$**. Thermal ellipsoids are drawn at 50% probability. All of the hydrogen atoms and the cocrystallized molecules of THF have been omitted for clarity. Selected bond distances (Å), angles (deg), and torsion angles (deg) for **Y**: C1−C2 1.454(2), C2−C3 1.529(2), C3−C4 1.454(2), C2−B1 1.482(2), C3−B2 1.478(2), C1−Li1 2.326(3), C2−Li1 2.187(3), C3−Li2 2.281(3), C4−Li2 2.659(3), C1−C2−C3 119.0(1), C1−C2−B1 122.9(1), B1−C2−C3 117.8(1), C2−C3−C4 119.1(1), C2−C3−B4 116.8(1), B2−C3−C4 122.2(1), C1−C2−C3−C4 77.3(2), B1−C2−C3−B2 86.5(2). Structural data for **Z**: C1′−C2′ 1.451(2), C2′−C3′ 1.526(2), C3′−C4′ 1.449(2), C2′−B1′ 1.478(2), C3′−B2′ 1.482(2), C1′−Li1′ 2.342(4), C2′−Li1′ 2.212(4), C3′−Li2′ 2.288(3), C4′−Li2′ 2.644(3), C1′−C2′−C3′ 118.7(1), C1′−C2′−B1′ 123.0(1), B1′−C2′−C3′ 116.8(1), C2′−C3′−C4′ 119.7(1), C2′−C3′−B4′ 114.0(1), B2′−C3′−C4′ 123.7(1), C1′−C2′−C3′−C4′ 78.4(2), B1′−C2′−C3′−B2′ 82.5(2).

To establish this reductive process to be useful in organic synthesis, we then optimized the reaction conditions for the formation of 1,2-diboryl-1,2-dimetalloalkane **3a-M$_2$**. A mixture of alkyne **1a** and B$_2$pin$_2$ was treated with 2 equiv of alkali metal in THF at 0 °C for 0.5 h before the addition of *i*PrOH to form 1,2-diborylalkane **4a** (Table 1; see Tables S1−S3 for more details). When Li granules were used, the yield of **4a** was only 12% (entry 1). Slow electron transfer attributed to the small surface area of granular Li would be problematic. Although the use of Li powder gave better results, the yield was not satisfactory (entry 2). To accelerate the electron transfer, we focused on Na dispersion having a large surface area (average particle size < 10 *μ*m) as an electron donor.[18] To our delight, the yield of **4a** was dramatically improved to 88% (entry 3). However, the diastereomeric ratio (d.r.) was lower than that observed in the reaction with Li powder (entry 2). Considering that Li cation would have a positive effect on the d.r., we conducted the reaction with Na dispersion in the presence of 2 equiv of LiI. Although the selectivity was low when the protonation was conducted at 0 °C, a 69% yield of **4a** was obtained with high d.r. (90:10) upon addition of *i*PrOH at −78 °C (entries 4 and 5). In the absence of LiI, the d.r. decreased to 60:40 even after protonation at −78 °C (entry 6).

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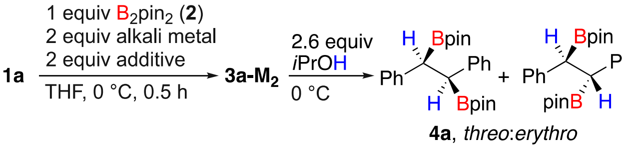
Table 1. Optimization Study



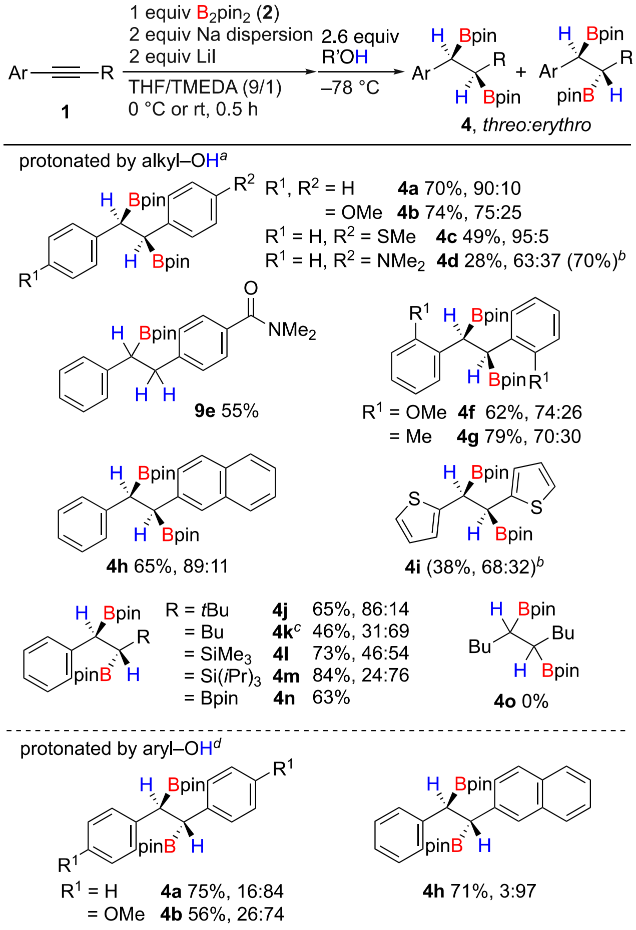
entry	alkali metal	additive	NMR yield (%)	d.r.
1	Li granules	none	12	65:35
2	Li powder	none	37	82:18
3	Na dispersion	none	88	64:36
4	Na dispersion	LiI	69	63:37
5[a]	Na dispersion	LiI	69	90:10
6[a]	Na dispersion	none	75	60:40
7[a,b]	Na dispersion	LiI	82	90:10

[a] *i*PrOH was added at −78 °C. [b] 9/1 v/v THF/TMEDA.

Eventually, **4a** was obtained in 82% yield with high d.r. by using a THF/TMEDA (9/1 v/v) cosolvent system (entry 7).

With the optimal conditions in hand, we explored the reaction scope with respect to alkynes **1** using proper aliphatic alcohols (MeOH, *i*PrOH, or $C_6H_{13}OH$; see the Supporting Information for details) for the protonation (Scheme 3). Diarylacetylenes **1b−d** possessing electron-donating groups at the *para* positions successfully underwent the reaction to afford **4b−d** with moderate to high diastereoselectivity. Because of the instability of **4d** on silica gel, the isolated yield of **4d** was decreased to 28%. When dimethylaminocarbonyl-substituted alkyne **1e** was used, monoborylation product **9e** was obtained as a single product. After the formation of 1,2-diborylalkane **4e**, deborylative protonation would proceed to afford **9e** because of the resonance effect of the aminocarbonyl group. The present diboration accommodates sterically hindered *ortho*-substituted diarylacetylenes **1f** and **1g** to furnish 1,2-diborylalkanes **4f** and **4g**, respectively. 2-Naphthyl-substituted acetylene **1h** took part in the reaction to furnish **4h** with good diastereoselectivity. The reaction of bis(2-thienyl)acetylene (**1i**) afforded product **4i** in 38% yield with 38% recovery of **1i**. Not only diarylacetylenes but also alkyl aryl acetylenes **1j** and **1k** could be involved in the reaction. *tert*-Butylacetylene **1j** afforded the *threo* isomer of **4j** as the major product. Interestingly, replacement of the *tert*-butyl group with a butyl group reversed the stereoselectivity: the reaction of 1-phenyl-1-hexyne (**1k**) mainly furnished *erythro*-**4k** with moderate diastereoselectivity. Silyl substituents on the acetylenic carbons of **1l** and **1m** endured the reaction; the corresponding diboration products **4l** and **4m** were obtained in good yields. The bulkier silyl group led to better *erythro* selectivity. Boron-substituted alkyne **1n** successfully underwent the reaction to afford 1,1,2-triborylalkane **4n** in 63% yield. Alkynes **1** should have at least one aromatic ring on their acetylenic carbons; 5-decyne (**1o**) was recovered after the reaction because electron transfer from Na dispersion would not proceed.

Scheme 3. Scope with Respect to Alkynes



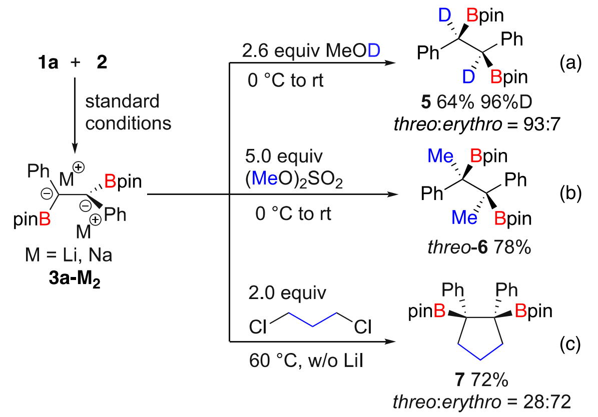
[a] alkyl−OH: MeOH, *i*PrOH, or $C_6H_{13}OH$. [b] Determined by ^1H NMR analysis. [c] Isolated as the 1,2-diol after oxidation with H_2O_2. [d] aryl−OH: 4-methoxyphenol or 2-*tert*-butyl-4-methoxyphenol.

Surprisingly, changing the proton source from aliphatic alcohols to more acidic phenols led to reversal of the diastereoselectivity (Scheme 3, bottom). When the reactions of diarylacetylenes **1a**, **1b**, and **1h** were terminated with phenols, the *erythro* isomers of **4a**, **4b**, and **4h** were obtained as the major products.

Twofold protonation of 1,2-dianion **3** would successively proceed to afford **4**, and the diastereoselectivity of **4** would be determined in the second protonation step. After the first protonation, the conjugate base of the proton source can coordinate to the alkali metal or boron, which might affect the diastereoselectivity of the second protonation. Indeed, the stereoselectivity is roughly correlated to the acidity of the proton source (see Table S3).

To demonstrate the versatility of 1,2-dianionic species **3**, we performed the reactions with several electrophiles for the synthesis of a suite of bis(boronate)s (Scheme 4). Deuteration of **3a-M$_2$** with MeOD proceeded (Scheme 4a), and the major isomer, *threo*-**5**, was isolated in 64% yield (93:7 d.r.; 96% deuterium incorporation) by column chromatography on silica gel. When dimethyl sulfate was used, **3a-M$_2$** underwent dimethylation to provide **6** (Scheme 4b). The *threo* isomer (confirmed by X-ray crystallographic analysis; see Figure S3)[9] was obtained as the dominant product and isolated as the single isomer in 78% yield.[19] Treatment of **3a-M$_2$** with 1,3-dichloropropane furnished the corresponding 1,2-diborylcyclopentane **7**, but the yield was only 26%. It is known that 1,2-disodiostilbene reacts with alkyl chlorides to provide alkylation products in higher yields than 1,2-dilithiostilbene.[19b−d] Indeed, the yield of **7** improved to 72% in the absence of LiI (conditions in Table 1, entry 6). In contrast to the dimethylation, the cycloalkylation preferentially afforded the *erythro* isomer (Scheme 4c).[20] The reaction with 1,3-dichloropropane first generates a 3-chloropropylated anionic

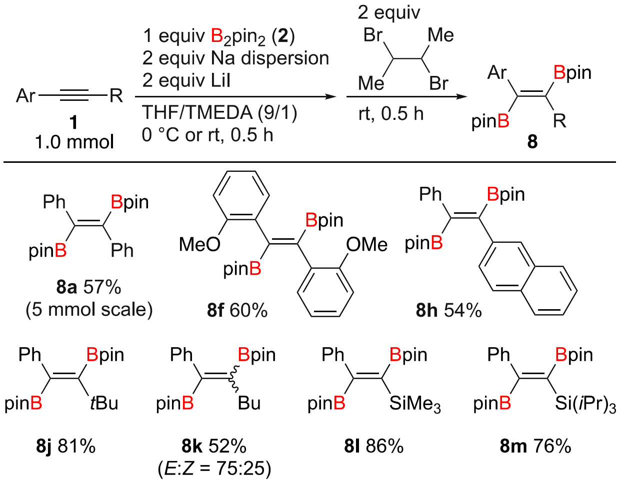
Scheme 4. Deuteration and Alkylations of 3a-M$_2$



intermediate, in which the two boronate moieties can interact with each other through a sodium cation. The interaction would fix the conformation of the intermediate to control the final intramolecular alkylation, affording *ethryro*-**7**.

Next, we expected the synthesis of 1,2-diborylalkenes **8** via oxidation of 1,2-diboryl-1,2-dimetalloalkanes **3-M$_2$** by means of a proper oxidizing reagent. After optimization of oxidants, treatment of **3a-M$_2$** with 2,3-dibromobutane was found to give the corresponding 1,2-diborylstilbene **8a** in 82% NMR yield. To our surprise, the *E* isomer was obtained as the major product and isolated in 57% yield by column chromatography on silica gel (Scheme 5). In general, 1,2-diborations of alkynes proceed in a *syn* manner, and *anti*-selective diborations to afford (*E*)-1,2-diborylalkenes are quite limited:[21] the applicable substrates are restricted to propargyl alcohols,[21a] alkynoates,[21b] and alkynamides,[8b] or the use of a special diborane(4) reagent, pinB−B(mesityl)$_2$, is necessary.[21c] The present *anti*-selective diboration based on the diborative reduction/oxidation sequence is a unique and versatile method for the synthesis of (*E*)-1,2-diborylalkenes.

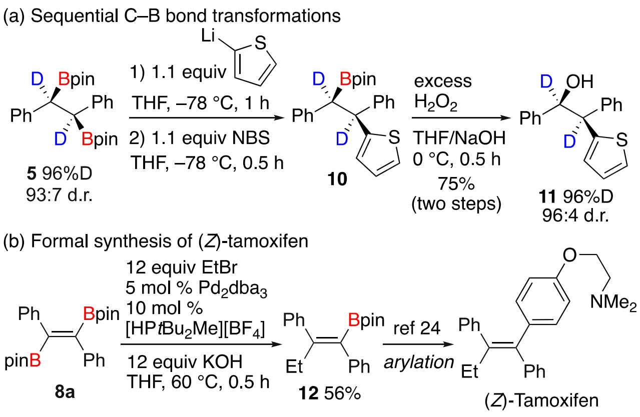
Scheme 5. *anti*-Diboration of Alkynes 1 via the Diborative Reduction/Oxidation Sequence



Diarylacetylenes **1f** and **1h** also underwent the *anti*-diboration to afford **8f** and **8h** in moderate yields (Scheme 5). *tert*-Butyl-substituted alkyne **1j** was converted to (*E*)-**8j** selectively, while the reaction of 1-phenyl-1-hexyne (**1k**) furnished **8k** with moderate stereoselectivity (*E*:*Z* = 75:25). These results indicate that the stereoselectivity would be determined by the steric repulsion between the original substituents on the alkyne. Indeed, the use of trialkylsilyl-substituted **1l** and **1m** stereoselectively afforded (*E*)-diborylalkenes **8l** and **8m**, respectively. Notably, the *anti*-selective diboration was applicable to gram-scale synthesis: 1.2 g of **8a** (57% yield) was obtained from 5 mmol of **1a**.

To validate the synthetic utility of the diborative reduction, we undertook transformations of two of the bis(boronate) products. According to the stereoretentive arylation of alkylboronates with aryllithiums reported by Aggarwal,[22] successive treatment of **5** with 1.1 equiv of 2-thienyllithium and NBS provided the desired product **10** with one of the two boron moieties being intact (Scheme 6a). Subsequent oxidation of the C−B bond with H$_2$O$_2$ furnished deuterated triarylethanol **11** in 75% yield over two steps. We also attempted a formal synthesis of (*Z*)-tamoxifen, an antiestrogenic anticancer drug, using (*E*)-1,2-diborylalkene **8a**. By the use of catalytic amounts of Pd$_2$dba$_3$ (dba = dibenzylideneacetone) and [HP*t*Bu$_2$Me][BF$_4$],[23] ethylation of **8a** with bromoethane was found to proceed satisfactorily, after a brief optimization, at a reaction temperature as high as 60 °C and in a short reaction time (0.5 h). The desired monoethylation product **12** was obtained in 56% yield as a promising precursor of (*Z*)-tamoxifen (Scheme 6b).[24,25]

Scheme 6. Derivatizations of Bis(boronate)s



In summary, we have developed a diborative reduction of alkynes by means of B$_2$pin$_2$ and alkali metals. This diborative reduction is distinct from conventional dissolving metal hydrogenations in versatility and extensibility. A key intermediate, 1,2-diboryl-1,2-dilithioethane **3a-Li$_2$**, was successfully isolated and unambiguously characterized by single-crystal X-ray diffraction analysis. 1,2-Dimetalloalkanes **3-M$_2$** were prepared in a synthetically useful way and converted to a wide range of valuable bis(boronate)s such as 1,2-diborylalkanes **4**−**7** and (*E*)-1,2-diborylalkenes **8** that are difficult to obtain with existing methods.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b01622.

Experimental procedures, X-ray crystallographic analysis, computational studies, and spectral data (PDF)

Cartesian coordinates of the optimized structure of **3a-Li$_2$(thf)$_3$** (XYZ)

Accession Codes

CCDC 1908190, 1910932, 1911287, and 1911966−1911968 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by e-mailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, U.K.; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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(9) For XRD analyses, see the Supporting Information (CCDC 1908190, 1910932, 1911287, and 1911966−1911968).

(10) **3a-Li$_2$(thf)$_3$** ($C_{38}H_{58}B_2Li_2O_7\cdot C_4H_8O$) (CCDC 1910932): FW = 734.44, λ = 0.71073 Å, T = −170 °C, triclinic, $P\bar{1}$ (No. 2), a = 11.0497(2) Å, b = 18.6017(3) Å, c = 20.7064(3) Å, α = 88.627(1)°, β = 80.275(1)°, γ = 84.140(1)°, V = 4172.88(12) Å^3, Z = 4, D_{calc} = 1.169 g cm^{-3}, μ = 0.077 mm^{-1}, $2\theta_{max}$ = 52.0°, measd./unique reflns. = 64930/16352 (R_{int} = 0.0512), 989 parameters, GOF = 1.025, R_1 = 0.0506/0.0649 [$I > 2\sigma(I)$/all data], wR_2 = 0.1305/0.1418 [$I > 2\sigma(I)$/all data], largest diff. peak and hole 0.647 and − 0.433 e Å^{-3}.

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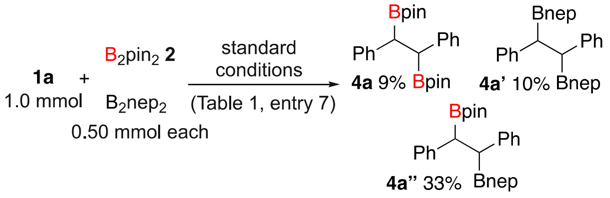
(13) The structural features of **3a-Li$_2$(thf)$_3$** could be reproduced by theoretical structure optimizations at the B3PW91-D3(BJ)/6-311G(2d,p) level of theory. The details of the theoretical calculations are shown in the Supporting Information.

(14) On the basis of NBO calculations, two NBOs were found between B1−C2 and also between B2−C3. B1−C2: (1) σ bond (1.953 e), B1(32%, sp$^{1.29}$)−C2(68%, sp$^{1.74}$); (2) π bond (1.724 e), B1(22%, sp$^{99.99}$)−C2(78%, sp$^{99.99}$). B2−C3: (1) σ bond (1.951 e),

B2(32%, sp$^{1.30}$)−C3(68%, sp$^{1.75}$); (2) π bond (1.737 e), B2(21%, sp$^{99.99}$)−C3(79%, sp$^{99.99}$).

(15) The sp^2-hybridized characters of C2 and C3 are suggested by the NBO calculations: C1−C2, C1(51%, sp$^{1.83}$)−C2(49%, sp$^{2.06}$); C2−C3, C2(50%, sp$^{2.24}$)−C3(50%, sp$^{2.28}$); C3−C4, C3(49%, sp$^{2.02}$)−C4(51%, sp$^{1.84}$).

(16) When the reaction of **1a** (1.0 mmol) was conducted in the presence of 0.50 mmol of B_2pin_2 (**2**) and bis(neopentylglycolato) diboron (B_2nep_2), boron-scrambled product **4a″** was obtained (eq 1). In addition, because **2** was recovered after treatment with Na dispersion in the absence of **1a**, reduction of **2** to boryl anion species would be excluded. These results suggest that the boryl migration in Scheme 2 would proceed intermolecularly.



(1)

(17) Other possible mechanisms are shown in Scheme S1.

(18) Na dispersion is a highly reactive yet easy-to-handle reducing agent, and its application to organic synthesis has attracted increasing attention. For recent examples, see: (a) An, J.; Work, D. N.; Kenyon, C.; Procter, D. J. Evaluating a Sodium Dispersion Reagent for the Bouveault−Blanc Reduction of Esters. *J. Org. Chem.* **2014**, *79*, 6743−6747. (b) Han, M.; Ma, X.; Yao, S.; Ding, Y.; Yan, Z.; Adijiang, A.; Wu, Y.; Li, H.; Zhang, Y.; Lei, P.; Ling, Y.; An, J. Development of a Modified Bouveault−Blanc Reduction for the Selective Synthesis of *α,α*-Dideuterio Alcohols. *J. Org. Chem.* **2017**, *82*, 1285−1290. (c) Han, M.; Ding, Y.; Yan, Y.; Li, H.; Luo, S.; Adijiang, A.; Ling, Y.; An, J. Transition-Metal-Free, Selective Reductive Deuteration of Terminal Alkynes with Sodium Dispersions and EtOD-d_1. *Org. Lett.* **2018**, *20*, 3010−3013. (d) Lei, P.; Ding, Y.; Zhang, X.; Adijiang, A.; Li, H.; Ling, Y.; An, J. A Practical and Chemoselective Ammonia-Free Birch Reduction. *Org. Lett.* **2018**, *20*, 3439−3442. (e) Zhang, B.; Li, H.; Ding, Y.; Yan, Y.; An, J. Reduction and Reductive Deuteration of Tertiary Amides Mediated by Sodium Dispersions with Distinct Proton Donor-Dependent Chemoselectivity. *J. Org. Chem.* **2018**, *83*, 6006−6014. (f) Ding, Y.; Luo, S.; Adijiang, A.; Zhao, H.; An, J. Reductive Deuteration of Nitriles: The Synthesis of *α,α*-Dideuterio Amines by Sodium-Mediated Electron Transfer Reactions. *J. Org. Chem.* **2018**, *83*, 12269−12274. (g) Asako, S.; Nakajima, H.; Takai, K. Organosodium Compounds for Catalytic Cross-Coupling. *Nat. Catal.* **2019**, *2*, 297−303.

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(20) The stereochemistry of *threo*-**7** obtained as the minor product was determined by X-ray crystallographic analysis (see Figure S4).[9]

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(25) The use of excess amounts of bromoethane and KOH was crucial because bromoethane was consumed by KOH at 60 °C.