

Chemoselective Coupling of 1,1-Bis[(pinacolato)boryl]alkanes for the Transition-Metal-Free Borylation of Aryl and Vinyl Halides: A Combined Experimental and Theoretical Investigation

Yeosan Lee,^{†,‡} Seung-yeol Baek,^{‡,§,||} Jinyoung Park,[†] Seoung-Tae Kim,^{§,||} Samat Tussupbayev,^{§,||} Jeongho Kim,[†] Mu-Hyun Baik,^{*,§,||} and Seung Hwan Cho^{*,†,||}

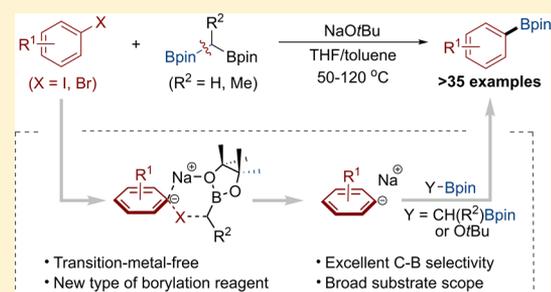
[†]Department of Chemistry and Division of Advanced Nuclear Engineering, Pohang University of Science and Technology (POSTECH), Pohang, 37673, Republic of Korea

[§]Department of Chemistry, Korea Advanced Institute of Science and Technology (KAIST), Daejeon, 34141, Republic of Korea

^{||}Center for Catalytic Hydrocarbon Functionalizations, Institute for Basic Science (IBS), Daejeon, 34141, Republic of Korea

Supporting Information

ABSTRACT: A new transition-metal-free borylation of aryl and vinyl halides using 1,1-bis[(pinacolato)boryl]alkanes as boron sources is described. In this transformation one of the boron groups from 1,1-bis[(pinacolato)boryl]alkanes is selectively transferred to aryl and vinyl halides in the presence of sodium *tert*-butoxide as the only activator to form organoboronate esters. Under the developed borylation conditions, a broad range of organohalides are borylated with excellent chemoselectivity and functional group compatibility, thus offering a rare example of a transition-metal-free borylation protocol. Experimental and theoretical studies have been performed to elucidate the reaction mechanism, revealing the unusual formation of Lewis acid/base adduct between organohalides and α -borylcarbanion, generated in situ from the reaction of 1,1-bis[(pinacolato)boryl]alkanes with an alkoxide base, to facilitate the borylation reactions.



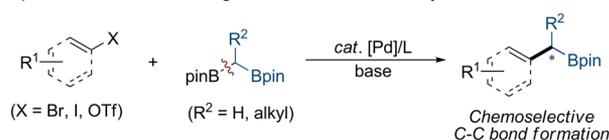
- Transition-metal-free
- Excellent C-B selectivity
- New type of borylation reagent
- Broad substrate scope

INTRODUCTION

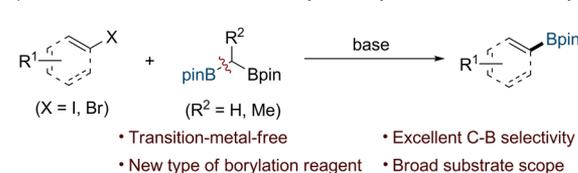
1,1-Bisborylalkanes have recently emerged as a new class of coupling reagents in organic synthesis.^{1,2} Prompted by the seminal report by Endo and Shibata on the palladium-catalyzed chemoselective cross-coupling of aryl halides with 1,1-bis[(pinacolato)boryl]alkanes,² several considerable efforts were made for the utilization of 1,1-bis[(pinacolato)boryl]alkanes in a variety of chemo- and enantioselective transformations.^{3–6} For example, Morken^{3a,b} and Hall^{3c} independently developed an elegant palladium/chiral phosphine system for the enantioselective coupling of aryl^{3a,c} and vinyl^{3b} halides with 1,1-bis[(pinacolato)boryl]alkanes to afford chiral secondary alkylboronate esters. Wang and co-workers reported that vinyl bromides and 1,1-dibromoalkenes could react with 1,1-bis[(pinacolato)boryl]alkanes in the presence of a palladium catalyst, providing 1,4-dienes and allenes.^{3d} Fu and Xiao described that aryl triflates could work as facile electrophiles in chemoselective cross-couplings with 1,1-bis[(pinacolato)boryl]alkanes.^{3e} While these studies illustrate the unique reactivity and selectivity of 1,1-bis[(pinacolato)boryl]alkanes in the coupling with aryl (pseudo)halides, they typically involve the formation of a C–C bond (Scheme 1a). The formation of a C–B bond with aryl and vinyl halides employing 1,1-bis[(pinacolato)boryl]alkanes as a boron source has thus far been elusive.

Scheme 1. Chemoselective Coupling of Aryl and Vinyl (Pseudo)halides with 1,1-Bis[(pinacolato)boryl]alkanes

a) C–C bond formation of organohalides with 1,1-bisborylalkanes



b) **This work:** C–B bond formation of aryl and vinyl halides with 1,1-bisborylalkanes



Organoboronate esters are highly versatile building blocks in organic synthesis, and methods for their preparation continue to inspire organic chemists.⁷ Consequently, extensive efforts have been made to develop efficient strategies for the installation of boron-containing groups into organic molecules. While such compounds are typically prepared by the reaction of

Received: November 14, 2016

Published: December 14, 2016

Table 1. Evaluation of Reaction Conditions for the Borylation of Aryl Iodides with 1,1-Bis[(pinacolato)boryl]alkanes^a

entry	R ¹	R ²	base	solvent	temp (°C)	yield ^b (%)
1	OMe	H	LiOtBu	toluene	120	6
2	OMe	H	NaOtBu	toluene	120	70
3	OMe	H	KOtBu	toluene	120	<1
4	OMe	H	LiOMe	toluene	120	<1
5	OMe	H	NaOMe	toluene	120	50
6	OMe	H	KOMe	toluene	120	<1
7	OMe	H	KF	toluene	120	<1
8	OMe	H	NaOtBu	THF	120	71
9	OMe	H	NaOtBu	1,4-dioxane	120	70
10 ^c	OMe	H	NaOtBu	toluene/THF	120	91 (85) ^d
11 ^c	OMe	H	NaOtBu	toluene/THF	100	80
12 ^c	OMe	H	NaOtBu	toluene/THF	80	5
13 ^c	OMe	Me	NaOtBu	toluene/THF	120	75
14 ^c	OMe	H	NaOtBu	toluene/THF	120	<1
15 ^c	F	H	NaOtBu	toluene/THF	120	90
16 ^c	F	H	NaOtBu	toluene/THF	80	90 (73) ^d

^aReaction conditions: **A1** or **A2** (0.2 mmol), **B1** or **B2** (2.0 equiv), base (2.0 equiv), and solvent (2.0 mL) at indicated temperature for 6 h. ^bGC yield of **C1** or **C2** using dodecane as an internal standard. ^cA 1:1 mixture of toluene/THF was used as the solvent. ^dYield in parentheses indicates the isolated yield.

organometallic nucleophiles, such as Grignard or organolithium reagents, with boron electrophiles,⁷ recent efforts have focused on the catalytic borylation of aryl (pseudo)halides⁸ or simple arenes.⁹ Electrophilic borylations are also well documented.¹⁰ Despite these splendid advances, transition-metal-free borylation is in high demand because of its low cost and convenience, and several examples have been reported using diboron compounds such as B₂pin₂ or B₂(OH)₄.¹¹ Therefore, finding new reagents for the borylation of aryl and vinyl halides remains an important challenge. In particular, reagents that enable new synthetic methodologies with increased selectivity and efficiency in the construction of target boron compounds are highly sought after.

In this context, Ito previously showed that silylborane reagents may be used to achieve similar transformations,^{12a,b} and a mechanism based on DFT calculations was proposed.^{12c}

Herein, we report the transition-metal-free borylation of aryl and vinyl halides using commercially available bis[(pinacolato)boryl]methane as a new class of boron transfer reagents (Scheme 1b).¹³ Our protocol significantly enriches the growing class of useful reactions of 1,1-bis[(pinacolato)boryl]alkanes, representing the first example for the formation of C–B bond of aryl halides using 1,1-bis[(pinacolato)boryl]alkanes. Mechanistically, these new reactions constitute an interesting platform for discovering how the general Lewis acid/base characteristics of aryl halides and 1,1-bis[(pinacolato)boryl]alkanes can be exploited to carry out a demanding reaction in a controlled and specific manner.

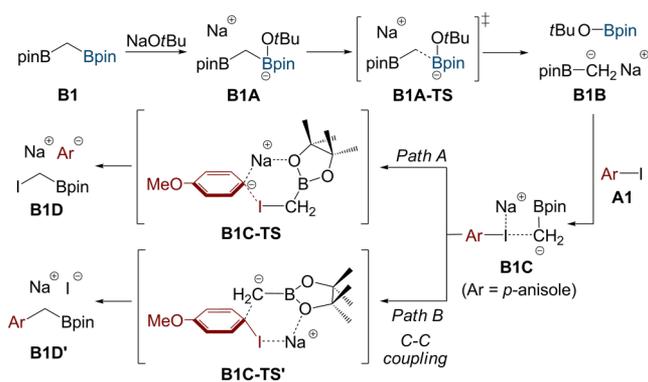
RESULTS AND DISCUSSION

Reaction Development. In line with our recent efforts utilizing 1,1-bis[(pinacolato)boryl]alkanes in organic synthesis,⁶ we hypothesized initially that 1,1-bis[(pinacolato)boryl]alkanes may be suitable reagents for the transfer of boron to aryl and

vinyl halides with unusual chemoselectivity. Interestingly, the reaction of 4-iodoanisole (**A1**) with bis[(pinacolato)boryl]methane (**B1**) in the presence of LiOtBu in toluene at 120 °C proceeded to form 4-methoxyphenyl boronate ester **C1** in 6% yield (Table 1, entry 1), as determined by gas chromatography (GC) analysis. Using NaOtBu as a base (entry 2) significantly increased the yield of **C1** to 70%, whereas other alkoxide and fluoride bases (entries 3–7) gave decreased yields compared with that achieved with NaOtBu. Solvent screening (entries 8–10) revealed that an equal mixture of toluene/THF provided the highest yield (entry 10). Lowering the reaction temperature resulted in a decrease in the yield (entries 11 and 12). The treatment of 1,1-bis[(pinacolato)boryl]ethane (R² = Me) instead of **B1** also afforded the borylated product **C1** (entry 13) in slightly lower yield of 75%, suggesting that substituted 1,1-diboryl compound could also be used as a boron source in the current process. No conversion was observed in the absence of a base (entry 15). Notably, the borylation of 4-fluoro-1-iodobenzene (**A2**) as a substrate afforded the desired borylated product **C2** in good yield even at 80 °C with nearly equal efficiency to the reaction performed at 120 °C (entries 16 and 17), suggesting that the reaction is influenced by the electronic properties of aryl iodides we conducted. It is interesting to note that the borylated products **C1** and **C2** were formed as the only reaction products and no alkylation products, **D1** or **D2**, were detected under optimized conditions.

Theoretical Studies. Scheme 2 summarizes the initial phase of our proposed mechanism, and Figure 1 shows the DFT calculated reaction free energy profile using 4-iodoanisole (**A1**) and bis[(pinacolato)boryl]methane (**B1**) as the borylating agent. The reaction starts with the activation of **B1** furnished by the *tert*-butoxide anion attacking one of the boryl moieties in a nucleophilic fashion. The reactant complex **B1A** at a relative free energy of –1.7 kcal/mol undergoes B–C bond

Scheme 2. First Part of the Mechanism for the Borylation of 4-Iodoanisole



cleavage to form the sodium α -borylcarbanion **B1B**, liberating the *tert*-butoxyboronate ester. This process is 12.3 kcal/mol uphill traversing the transition state **B1A-TS** associated with a barrier of 17.5 kcal/mol. Therefore, the initialization step is energetically reasonable and it should be rapid under normal reaction conditions. To push the reaction forward, **B1B** may react with aryl iodide to afford a weakly bound Lewis acid/base adduct **B1C**, which was located at 13.6 kcal/mol. The adduct **B1C** shows a linear C–I–C arrangement, as illustrated in Figure 2. Formally, the borylcarbanion acts as a Lewis base to bind to the iodide, which serves as the complementary Lewis acid. This binding motif is reminiscent of what is known as an “ate-complex” of iodine.¹⁵ In a typical ate-complex, such as lithium bis(pentafluorophenyl) iodinate,^{15d} the C–I–C fragment is symmetric and C–I bonds are relatively short (~ 2.3 Å). **B1C** is notably different, because the iodine atom is flanked by two very different functional groups: namely, a para methoxy-aryl and an α -borylcarbanion fragment. The α -borylcarbanion is

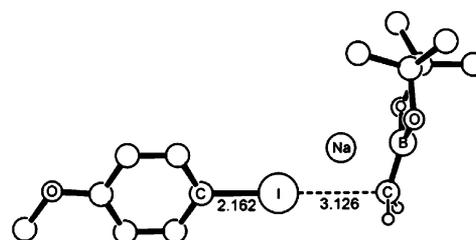
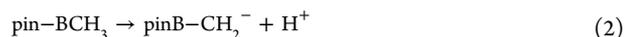
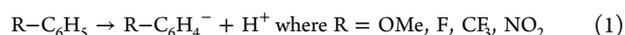


Figure 2. DFT-optimized geometry of **B1C** with selected distances in Å. Nonessential hydrogen atoms were omitted for clarity.

a much weaker base than the methoxy-aryl carbanion, as the electron-withdrawing boryl fragment stabilizes the anionic charge. To compare the strengths of the basicities and to establish a gauge, we evaluated the gas-phase free energies of the proton abstraction reactions 1 and 2.



As summarized in Table 2, our calculations show that the methoxy-aryl carbanion is indeed the strongest Brønsted base with the deprotonation of its conjugate acid requiring 396.8 kcal/mol. As anticipated, the α -borylcarbanion is a much weaker base and the deprotonation of borylmethane is nearly 19 kcal/mol easier at 378.4 kcal/mol in gas phase.¹⁷ Interestingly, this deprotonation energy is much smaller than that of an aryl carrying highly electron-withdrawing groups like –F or –CF₃, for which we calculated deprotonation energies of 392.4 and 385.9 kcal/mol. As a result of these notable difference in the electron-donating nature of the two carbanions, the intermediate **B1C** is not a classical ate-complex

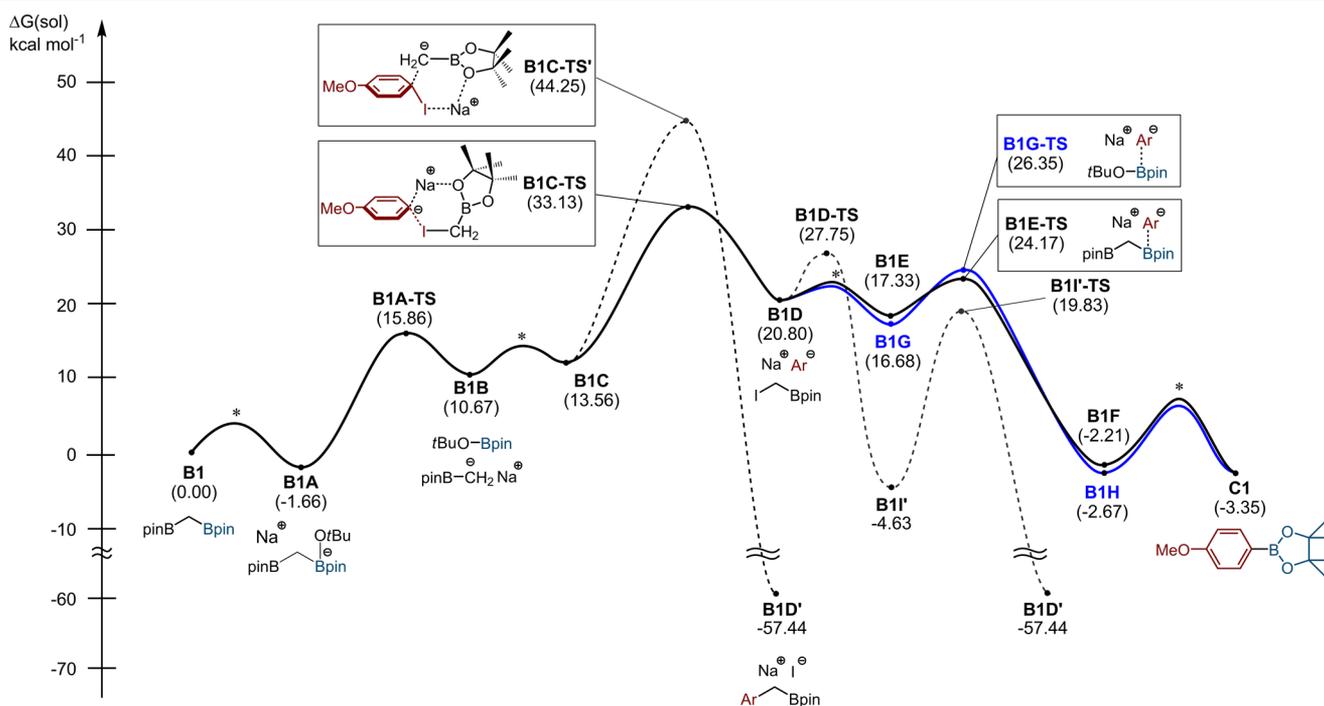


Figure 1. Energy profile for the transition-metal-free borylation of 4-iodoanisole (**A1**) with bis[(pinacolato)boryl]methane (**B1**). Transition states marked by * were not explicitly located.

Table 2. Gas- and Aqueous-Phase Free Energies of the Deprotonation **Reaction 1** and **2** in kcal/mol

	$\Delta_r G$ (gas)	$\Delta_r G$ (water) ^a
MeO–C ₆ H ₅	396.8	70.9
F–C ₆ H ₅	392.4	68.4
F ₃ C–C ₆ H ₅	385.9	67.3
pinB–CH ₃	378.4	53.9

^aAbsolute aqueous solvation free energy of the proton was taken equal to -265.9 kcal/mol.¹⁶

and displays significantly different C–I bonds. One of the C–I distances is close to the sum of covalent radii (2.162 Å), while the other is significantly longer, 3.126 Å, and the negative charge is additionally stabilized by the sodium cation, as illustrated in **Figure 2**. If the sodium cation is removed, these bonds become 2.289 and 2.622 Å, respectively.

The nucleophilic substitution at iodine in path A proceeds via the transition state **B1C-TS**, which was located at 33.1 kcal/mol, to form the iodomethyl boronate ester **B1D**. The C–I–C fragment is again not symmetric in **B1C-TS** with the newly forming C–I bond being 2.312 Å long, as shown in **Figure 3**,

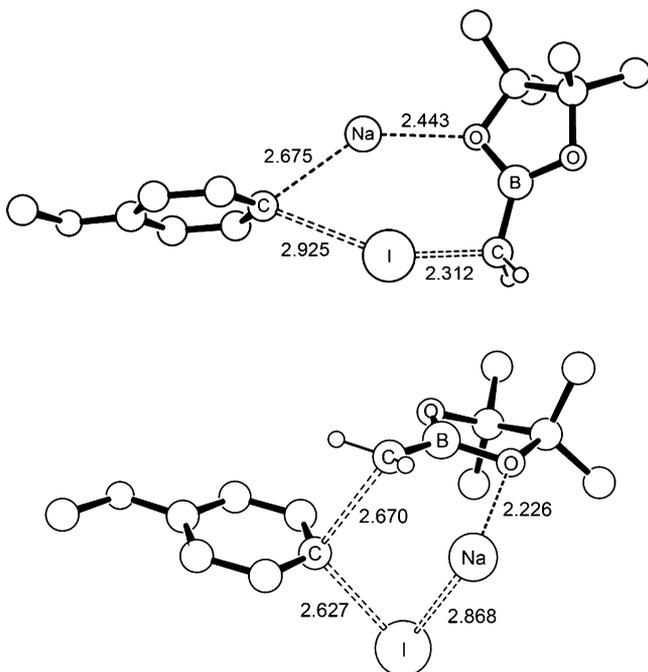
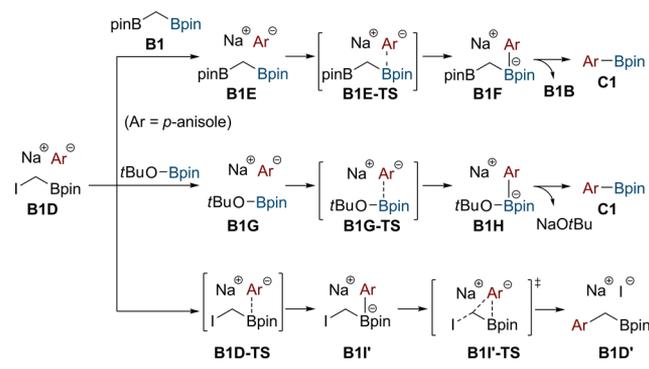


Figure 3. DFT-optimized geometries of **B1C-TS** and **B1C-TS'** with selected distances in Å. Nonessential hydrogen atoms were omitted for clarity.

and the rupturing bond being at 2.925 Å. The sodium has moved and bridges the aryl-anion and the Bpin moiety. In path B, the electrophilic attack of the carbanion by the Ar-group must traverse **B1C-TS'** to give **B1D'**. Our calculations suggest that the C–C coupling product **B1D'** is 78.2 kcal/mol lower in energy than **B1D**, i.e., the formation of **B1D'** is thermodynamically much more preferable. But the resting state **B1A** must overcome a barrier of 45.9 kcal/mol to form **B1D'**, whereas only 34.7 kcal/mol is required to reach **B1D**. Hence, in spite of the great stability of **B1D'** its formation is kinetically impossible and forming the thermodynamically less favorable Lewis acid/base pair **B1D** is the only reaction viable, as illustrated in solid black lines in **Figure 1**.

The NaAr moiety formed transiently in intermediate **B1D** is highly reactive and will readily engage an equivalent of bis[(pinacolato)boryl]methane **B1** or *tert*-butoxyboronate ester, both present in large excess quantities in solution, as illustrated in **Scheme 3**. The anionic Ar[−] fragment can attack

Scheme 3. Second Part of the Mechanism for the Borylation of 4-Iodoanisole



the Lewis acidic boron in **B1** or *t*BuO–Bpin via **B1E-TS** and **B1G-TS**, respectively, to give the Ar–borate species **B1F** or **B1H**. Both reaction steps have very low barriers, which is not surprising for a reaction where Ar[−], a strong and hard Lewis base, attacks strong and hard Lewis acids. Whereas our calculations indicate that the formation of monoborate species **B1F** is slightly preferred kinetically, the computed energy differences are too small to be physically meaningful. Finally, both **B1F** and **B1H** may release Na[H₂C–Bpin] or NaOtBu, respectively, to yield the borylation product **C1**.¹⁸

In one possible side reaction C–C coupling may occur after **B1D** is formed as a result of the reaction between ICH₂Bpin and NaAr. Here, the aryl-anion may attack the boron atom of ICH₂Bpin directly to give intermediate **B1I'**, which is 25.4 kcal/mol lower in energy than **B1D**. The following C–C coupling to generate **B1D'** proceeds via **B1I'-TS** at a relative free energy of 19.8 kcal/mol, thus giving a barrier of 24.5 kcal/mol. This barrier is much higher than that for the formation of the monoborate species **B1F** and **B1H**, but is reasonable for the given reaction conditions. Therefore, the reaction pathway affording the undesired product **B1D'** has the potential to become one of the unproductive side reactions. But at any given time during the course of the reaction, the concentration of free ICH₂Bpin is negligible compared to the overwhelming abundance of both **B1** and *t*BuO–Bpin. Thus, the only way this side reaction can occur is within the product complex **B1D** caught in a solvent cage. Experimentally, there is no evidence for this reaction taking place, in good agreement with our interpretation of the calculated reaction energy profiles. This is a remarkable finding, given the exceptionally great thermodynamic driving force, mentioned above.

A more detailed analysis of the relative energies reveals that the higher barrier for the C–C coupling step associated with **B1C-TS'**, a nucleophilic aromatic substitution, is due to a strong electrostatic repulsion between the π -cloud of aryl moiety, the anionic methylene-carbanion, and the anionic iodide leaving group. At 2.627 Å, the C–I bond is not yet fully broken, and at 2.670 Å, the C–C bond is not yet formed in the transition state **B1C-TS'** (**Figure 3**). The electron-donating nature of the methoxy group in the para position compounds the electrostatic penalty. Our calculations show that the energy

of B1C-TS' can be significantly lowered by ~ 6 and ~ 10 kcal/mol if the methoxy group in the para position is replaced by electron-withdrawing $-F$ or $-CF_3$ groups, respectively (see Supporting Information). Therefore, the kinetic challenge associated with path B, which is ultimately responsible for the chemoselectivity described above, stems from the fact that the transition state is early and the aryl fragment is too electron-rich to provide a viable reaction partner for the incoming carbanion. This mechanistic insight and the magnitude of change in the transition state energy as a function of the electron density of the aryl-iodide is a potentially powerful handle for controlling the reaction. A more detailed study of how to control the reaction mechanism by functionalizing the aryl-iodide moiety is in progress in our laboratories and will be reported elsewhere in due course.

Experimental Mechanistic Studies. To challenge and possibly find support for the computed reaction mechanism, several experiments were conducted. First, we used inductively coupled plasma atomic emission spectroscopy (ICP-AES)¹⁴ to ensure that there are no trace amounts of transition-metal contaminants in NaOtBu, which may possibly be responsible for the reactivity. We confirmed that no transition metal impurities could be detected. Moreover, no acceleration of the reaction rate was observed when catalytic amounts of several transition metals were deliberately employed in the reaction, thus ruling out the possibility of a transition-metal-mediated mechanism (Figure 4).¹⁹

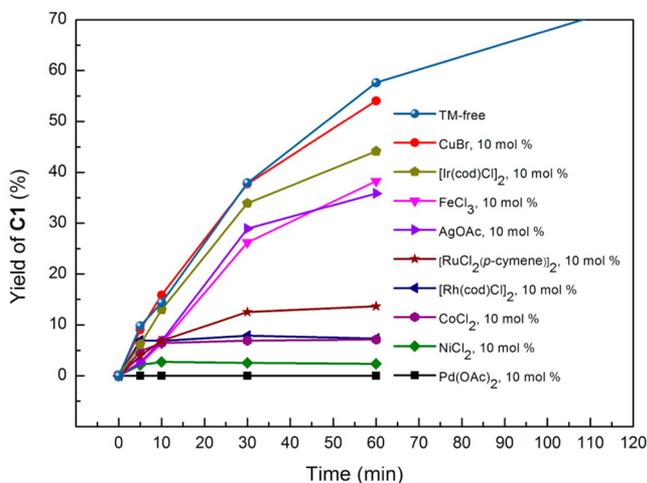
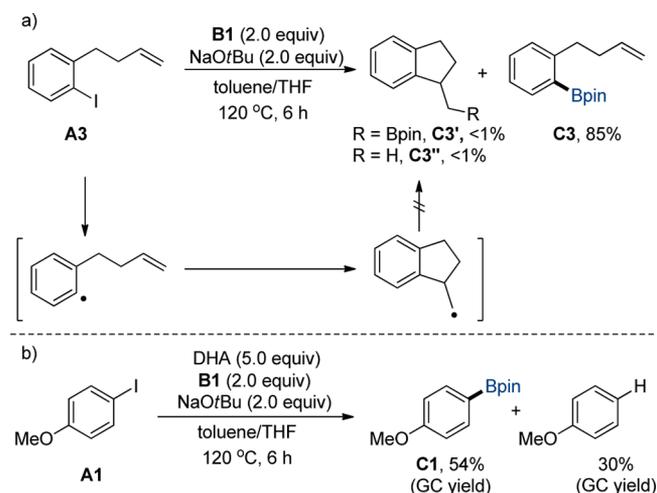


Figure 4. Comparison of initial rates in the presence of various transition-metal catalysts.

Given the propensity of aryl iodides to undergo homolytic bond cleavage leading to radical species,²⁰ we sought to exclude such alternative mechanism. Unfortunately, density functional theory is notoriously unreliable for modeling radical pathways and, thus, we did not attempt to calculate the radical pathway. Instead, we chose to test for such a possibility experimentally. When an aryl iodide containing a pendant olefin (**A3**) was subjected to the standard reaction conditions, the arylboronate ester **C3** was formed in 85% isolated yield; however, formation of the cyclized product **C3'** or **C3''** was not detected by crude ¹H NMR and GC-MS analysis (Scheme 4a).²¹ In addition, when the reaction of **A1** with **B1** was performed in the presence of 5.0 equiv of the radical scavenger 9,10-dihydroanthracene (DHA), the product **C1** was formed in

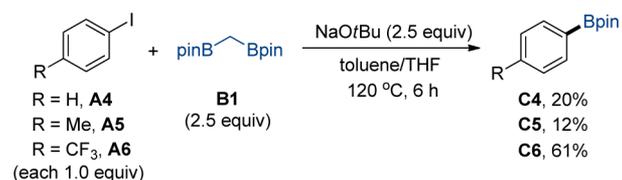
Scheme 4. Probe for an Aryl Radical Mechanism



slightly lower yield along with detectable amounts of anisole (Scheme 4b). To understand how the anisole was formed under the reaction conditions, we performed a control experiment by subjecting 9,10-dihydroanthracene to in situ generated sodium aryl anion. It was found that the corresponding arene was formed in nearly quantitative yield,¹⁴ implying that benzylic C–H bonds of 9,10-dihydroanthracene are deprotonated by the aryl anion species to yield anisole.²² Because a recent radical-mediated borylation reaction has shown that the reaction was completely inhibited in the presence of an excess amount of 9,10-dihydroanthracene, we could eliminate a reaction pathway involving aryl radical intermediates with a fair level of certainty.²³

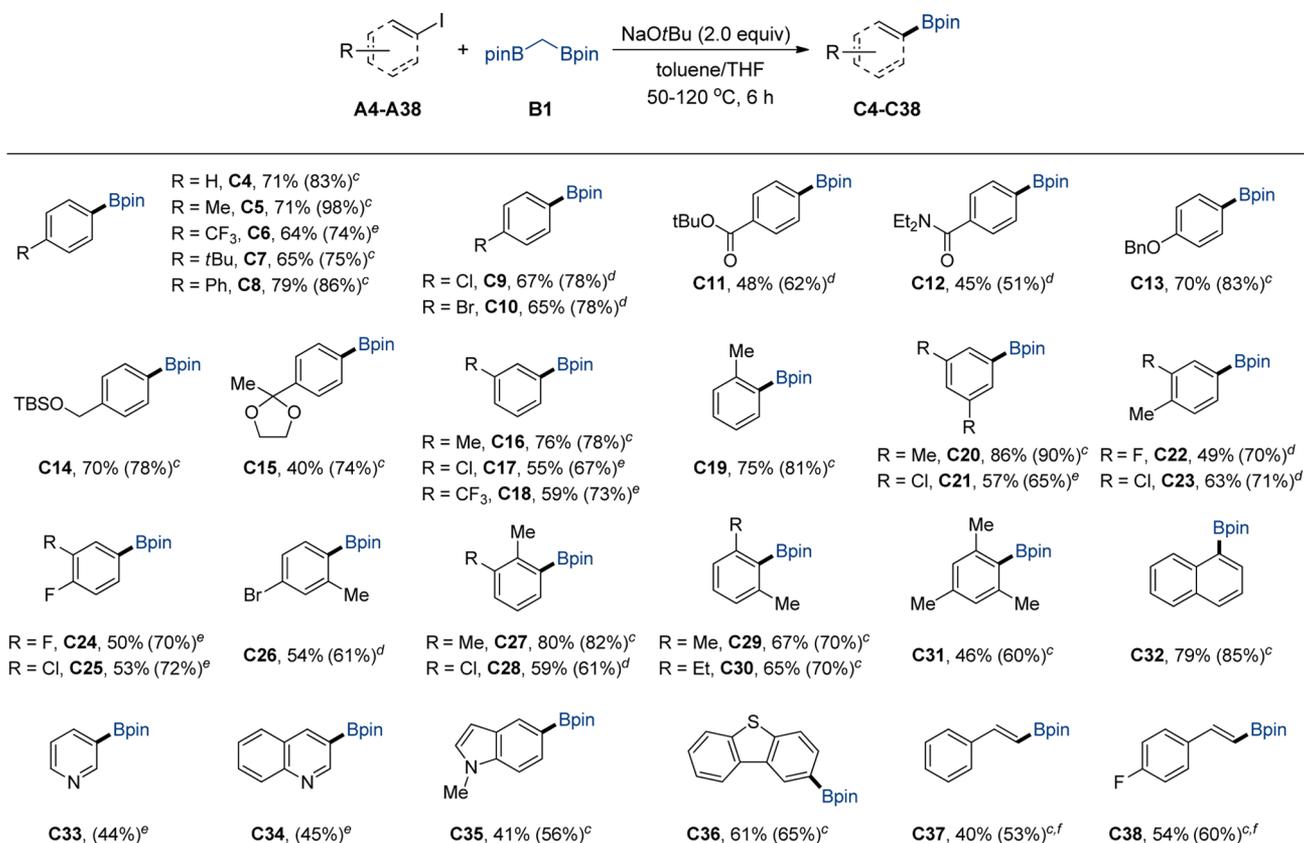
A key component of our proposed mechanism is the involvement of the aryl anion in reaction path A, as discussed above. In search of experimental support for this notion, we performed competition experiments using **B1** and electronically different para-substituted aryl iodides, as outlined in Scheme 5.

Scheme 5. Intermolecular Competition Experiment



When an equimolar mixture of **A4/A5/A6** (0.2 mmol each) was heated at 120 °C in toluene/THF in the presence of 2.5 equiv each of **B1** (0.5 mmol) and NaOtBu (0.5 mmol) in a single vessel, the electron-deficient aryl iodide (**A6**) underwent borylation more rapidly than the electronically neutral (**A4**) and electron-rich (**A5**) aryl iodides. Whereas this observation does not prove that the aryl anion is really involved, it is very consistent with the calculated reaction pathway discussed above and supports our proposal that an aryl anion species is involved as a key intermediate in our borylation protocol.

Scope of Borylation of Aryl Iodides. On the basis of this mechanistic understanding, the substrate scope of our borylation reaction was investigated, as enumerated in Table 3. Because the mechanism suggests that the borylation reaction should be highly dependent on the electronic nature of aryl iodides, as it is directly involved in the rate-determining step,

Table 3. Borylation of (Hetero)aryl and Vinyl Iodides with Bis[(pinacolato)boryl]methane^{a,b}

^aReaction conditions: **A** (0.2 mmol), **B1** (2.0 equiv), NaOtBu (2.0 equiv), and toluene/THF (2.0 mL, 1:1) at indicated temperature for 6 h. ^bYield of isolated product is given. ¹H NMR yield using dibromomethane as an internal standard is shown in parentheses. ^cRuns at 120 °C. ^dRuns at 80 °C. ^eRuns at 50 °C. ^f1,4-Dioxane was used as a solvent instead of toluene/THF.

and we were able to qualitatively confirm this dependence in our experiments, we explored the scope by fine-tuning the reaction temperature while varying the nature of the aryl iodides. The borylation of aryl iodides containing electronically neutral (**C4**) and donating (**C5**, **C7–C8**) substituents at the para position provided the desired products in good yields at 120 °C. Interestingly, aryl iodides bearing a CF₃ (**C6** and **C18**) group borylated readily even at 50 °C. Furthermore, 1-chloro- and 1-bromo-4-iodobenzene were successfully reacted with **B1** at 80 °C, conveniently leaving the chloro and bromo groups intact (**C9** and **C10**) for further elaboration. Substrates containing ester (**C11**) and amide (**C12**) reacted in good to moderate yields at 80 °C. Protected alcohol (**C13** and **C14**) and masked ketone (**C15**) groups are also tolerated. The presence of substituents at the meta (**C16–C18**) and ortho (**C19**) positions of the aryl rings has little impact upon reaction efficiency. Moreover, aryl iodides containing two additional substituents were suitable for the borylation and provided the corresponding boronate esters (**C20–C28**) in good to excellent yields. The protocol developed here could also be applied to sterically demanding substrates, which were exceedingly difficult to access by previously known catalytic borylation protocols.⁸ The reaction of 1,3-dimethyl-(**C29**), 1-ethyl-3-methyl-(**C30**), and 1,3,5-trimethyl-(**C31**) substituted aryl iodides afforded the corresponding borylated products in good yields. Notably, substrates having at least one halide group in the aryl ring underwent borylation at temperatures ranging from 50 to 80 °C, whereas alkyl-substituted aryl iodides required high temperature (120 °C) to afford satisfactory

product yields. 1-Iodonaphthalene was also found to be an effective substrate for the borylation reaction forming the borylated products **C32** in good to moderate yields. We were pleased to observe that heteroaryl iodides could also be utilized as efficient substrates under the present borylation conditions. Electron deficient heteroaryl iodides such as 3-iodopyridine and 3-iodoquinoline reacted with **B1** at 50 °C to provide the desired products **C33** and **C34** in moderate yields. Moreover, 8-iodo-*N*-methylindole and 3-iododibenzothiophene were also viable substrates, and products **C35** and **C36** were obtained in satisfactory yields at elevated temperature (120 °C). Finally, we were able to apply the developed borylation protocol to *trans*-vinyl iodides when 1,4-dioxane was used as the solvent to obtain a single stereoisomer of the borylated products **C37** and **C38** in moderate yields.

Substituent Effects and Scope of Borylation of Aryl Bromides. The theoretical studies described above shed light on why electron deficient aryl iodides facilitated the borylation reaction under mild conditions. In order to rationalize these electronic effects, the complete free energy pathway profiles for three representative aryl iodides (**A1**, **A2**, and **A6**) were calculated and are summarized in Figure 5.¹⁴ The change of substituent does not affect the mechanism significantly: the conversion of **B1A** to **B1D** via the transition state **B1C-TS** is still the rate-limiting step. The free energy barrier for the formation of **B1C-TS** from **A1** was 34.8 kcal/mol since the formation of **A2-B1C-TS** from **A2** and **A6-B1C-TS** from **A6** was found to be lower in energy than **B1C-TS** by 1.6 and 2.9 kcal/mol, respectively. This findings are in excellent agreement

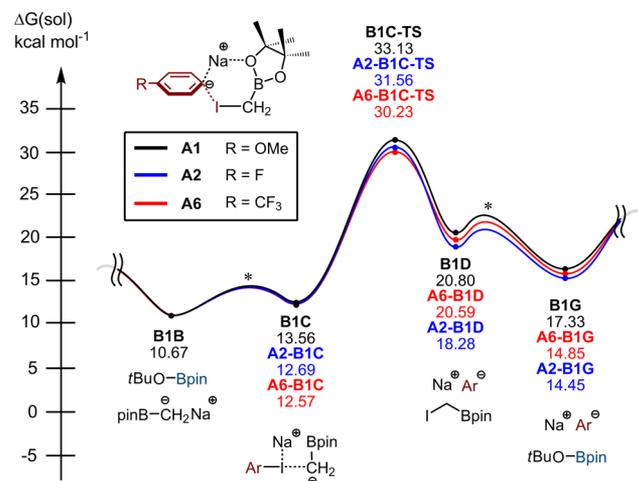


Figure 5. Comparison of free energy varying electronic nature of aryl iodides. Transition states marked by * were not explicitly located.

with the experimental results (Tables 1 and 2) that aryl iodides bearing electron-withdrawing substituents underwent the borylation under relatively mild conditions. To test whether this borylation process occurs with aryl bromides in a similar fashion, we performed DFT calculations using 1-bromo-4-(trifluoromethyl)benzene (**E1**) as a model substrate (Figure 6). These calculations suggest that **E1-B1C-TS** located at 32.9 kcal/mol is the highest energy transition state, implying that this reaction may be feasible at high temperatures.¹⁴

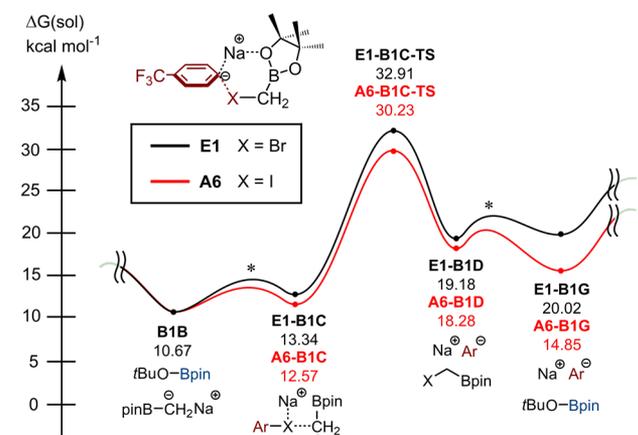


Figure 6. Comparison of free energy for the borylation of 1-iodo-4-(trifluoromethyl)benzene (**A6**) and 1-bromo-4-(trifluoromethyl)benzene (**E1**) with **B1**. Transition states marked by * were not explicitly located.

With this result in mind, we reinvestigated the reaction parameters for the borylation using 1-bromo-4-(trifluoromethyl)benzene **E1** and **B1** as model substrates, which were initially not found to be viable substrates. After extensive reoptimization,¹⁴ we found that **E1** undergoes borylation in the presence of an excess amount of **B1** (3.0 equiv) and THF as the solvent at elevated temperature (120 °C) with prolonged reaction time (12 h) to afford the corresponding borylated product **C6** in 37% ¹H NMR yield (Table 4). Further investigation showed that 1,1-bis[(pinacolato)boryl]ethane (**B2**) was a more effective borylation reagent than **B1** to form **C6** (55%), which may be attributed to making the carbon that undergoes C–Br formation more electron-rich. By using

Table 4. Borylation of Aryl Bromides with 1,1-Bis[(pinacolato)boryl]alkanes^{a,b}

R^1 -C ₆ H ₄ -Br + pinB-C(R ²)-Bpin E1-E6 R ² = H, B1 R ² = Me, B2		$\xrightarrow[\text{THF, 120 }^\circ\text{C, 12 h}]{\text{NaOtBu (2.0 equiv)}}$	R^1 -C ₆ H ₄ -Bpin C
	C6 , 37% (B1) 55% (B2)		C9 , 26% (B1) 50% (B2)
	C23 , 34% (B1) 50% (B2)		C18 , 38% (B1) 51% (B2)
	C1 , 5% (B1) 15% (B2)		C4 , 6% (B1) 17% (B2)

^aReaction conditions: aryl bromide (**E**, 0.2 mmol), **B1** or **B2** (3.0 equiv), NaOtBu (2.0 equiv), and THF (2.0 mL) at 120 °C for 12 h. ^b¹H NMR yield using dibromomethane as an internal standard is given.

these modified reaction conditions, the reactions of aryl bromides bearing electron-withdrawing substituents such as 1-bromo-4-chlorobenzene (**E2**), 1-bromo-3-(trifluoromethyl)benzene (**E3**), and 4-bromo-2-chloro-1-methylbenzene (**E4**) with **B1** or **B2** afforded the products **C9**, **C18**, and **C23** in low to moderate yields. It should be noted that **B2** gives higher yields when reacting with aryl bromides. As anticipated, electronically rich (**E5**) and neutral (**E6**) aryl bromides exhibited low reactivity (**C1** and **C4**).

CONCLUSION

In summary, we developed a transition-metal-free borylation of aryl and vinyl halides employing 1,1-bis[(pinacolato)boryl]alkanes as the boron source. This operationally simple reaction proceeds chemoselectively, thus transferring one boron group from 1,1-bis[(pinacolato)boryl]alkanes to aryl or vinyl halides to form diverse organoboronate esters with high functional group tolerance. Combining theoretical and experimental studies, we were able to understand how aryl halides and α -borylcarbanion, generated in situ by combination of 1,1-bis[(pinacolato)boryl]alkanes and NaOtBu, are able to generate sodium aryl anion species, which can subsequently undergo C–B bond formation reactions. This work constitutes the first example for the formation of C–B bond of aryl halides using 1,1-bis[(pinacolato)boryl]alkanes as boron source with integrated theoretical and experimental studies. We believe that the present transition-metal-free borylation protocol will provide a powerful tool for the preparation of synthetically useful organoboron compounds with uncommon chemoselective coupling of 1,1-bis[(pinacolato)boryl]alkanes.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.6b11757.

Experimental procedures, characterization of compounds (¹H and ¹³C NMR spectra), kinetic profiles, Cartesian coordinates of DFT-optimized structures, benchmark calculations, and computational details (PDF)

AUTHOR INFORMATION

Corresponding Authors

*seunghwan@postech.ac.kr

*mbaik2805@kaist.ac.kr

ORCID

Seoung-Tae Kim: 0000-0003-4067-9567

Samat Tussupbayev: 0000-0003-3470-1510

Seung Hwan Cho: 0000-0001-5803-4922

Author Contributions

*Y.L. and S.-Y.B. contributed equally to this work.

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

This research was supported by the Basic Science Research Program through the National Research Foundation of Korea (NRF) funded by the Ministry of Science, ICT & Future Planning (NRF-2015R1C1A1A02036326). M.-H.B. acknowledges support from the Institute for Basic Science (IBS-R10-D1) in Korea. J.P. thanks the National Research Foundation of Korea (NRF) for the global Ph.D. fellowship (NRF-2016H1A2A1908616).

REFERENCES

- (1) (a) Lee, J. C. H.; McDonald, R.; Hall, D. G. *Nat. Chem.* **2011**, *3*, 894. (b) Feng, X.; Jeon, H.; Yun, J. *Angew. Chem., Int. Ed.* **2013**, *52*, 3989. (c) Lee, J. C. H.; Sun, H.-Y.; Hall, D. G. *J. Org. Chem.* **2015**, *80*, 7134.
- (2) (a) Endo, K.; Ohkubo, T.; Hirokami, M.; Shibata, T. *J. Am. Chem. Soc.* **2010**, *132*, 11033. (b) Endo, K.; Ohkubo, T.; Shibata, T. *Org. Lett.* **2011**, *13*, 3368. (c) Endo, K.; Ohkubo, T.; Ishioka, T.; Shibata, T. *J. Org. Chem.* **2012**, *77*, 4826. (d) Endo, K.; Ishioka, T.; Shibata, T. *Synlett* **2014**, *25*, 2184.
- (3) For transition-metal-catalyzed C–C bond forming reactions of 1,1-bis[(pinacolato)boryl]alkanes with organohalides, see: (a) Sun, C.; Potter, B.; Morken, J. P. *J. Am. Chem. Soc.* **2014**, *136*, 6534. (b) Potter, B.; Szymaniak, A. A.; Edelstein, E. K.; Morken, J. P. *J. Am. Chem. Soc.* **2014**, *136*, 17918. (c) Sun, H.-Y.; Kubota, K.; Hall, D. G. *Chem. - Eur. J.* **2015**, *21*, 19186. (d) Li, H.; Zhang, Z.; Shangguan, X.; Huang, S.; Chen, J.; Zhang, Y.; Wang, J. *Angew. Chem., Int. Ed.* **2014**, *53*, 11921. (e) Cui, L.-C.; Zhang, Z.-Q.; Lu, X.; Xiao, B.; Fu, Y. *RSC Adv.* **2016**, *6*, 51932.
- (4) For transition-metal-catalyzed C–C bond forming reactions of 1,1-bis[(pinacolato)boryl]alkanes with other electrophiles, see: (a) Zhang, Z.-Q.; Yang, C.-T.; Liang, L.-J.; Xiao, B.; Lu, X.; Liu, J.-H.; Sun, Y.-Y.; Marder, T. B.; Fu, Y. *Org. Lett.* **2014**, *16*, 6342. (b) Joannou, M. V.; Moyer, B. S.; Meek, S. J. *J. Am. Chem. Soc.* **2015**, *137*, 6176. (c) Joannou, M. V.; Moyer, B. S.; Goldfogel, M. J.; Meek, S. *J. Am. Chem. Soc.* **2015**, *137*, 14141. (d) Xu, S.; Shangguan, X.; Li, H.; Zhang, Y.; Wang, J. *J. Org. Chem.* **2015**, *80*, 7779. (e) Shi, Y.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2016**, *55*, 3455. (f) Zhang, Z.-Q.; Zhang, B.; Lu, X.; Liu, J.-H.; Lu, X.-Y.; Xiao, B.; Fu, Y. *Org. Lett.* **2016**, *18*, 952. (g) Zhan, M.; Li, R.-Z.; Mou, Z.-D.; Cao, C.-G.; Liu, J.; Chen, Y.-W.; Niu, D. *ACS Catal.* **2016**, *6*, 3381. (h) Ebrahim-Alkhalil, A.; Zhang, Z.-Q.; Gong, T.-J.; Su, W.; Lu, X.-Y.; Xiao, B.; Fu, Y. *Chem. Commun.* **2016**, *52*, 4891.
- (5) For transition-metal-free C–C bond forming reactions of 1,1-bis[(pinacolato)boryl]alkanes, see: (a) Hong, K.; Liu, X.; Morken, J. P. *J. Am. Chem. Soc.* **2014**, *136*, 10581. (b) Coombs, J. R.; Zhang, L.; Morken, J. P. *J. Am. Chem. Soc.* **2014**, *136*, 16140.
- (6) (a) Kim, J.; Park, S.; Park, J.; Cho, S. H. *Angew. Chem., Int. Ed.* **2016**, *55*, 1498. (b) Park, J.; Lee, Y.; Kim, J.; Cho, S. H. *Org. Lett.* **2016**, *18*, 1210. (c) Jo, W.; Kim, J.; Choi, S.; Cho, S. H. *Angew. Chem., Int. Ed.* **2016**, *55*, 9690. (d) Kim, J.; Cho, S. H. *Synlett* **2016**, *27*, 2525.

(7) (a) Hall, D. G. *Boronic Acids*; Wiley-VCH: Weinheim, Germany, 2005. (b) Suzuki, A.; Brown, H. C. *Organic Synthesis via Boranes*; Aldrich: Milwaukee, WI, 2003. (c) Brown, H. C.; Cole, T. E. *Organometallics* **1983**, *2*, 1316.

(8) For selected examples of transition-metal-catalyzed borylation of organo(pseudo)halides: (a) Ishiyama, T.; Miyaura, N. *Chem. Rec.* **2004**, *3*, 271. (b) Miyaura, N. *Bull. Chem. Soc. Jpn.* **2008**, *81*, 1535. (c) Chow, W. K.; Yuen, O. Y.; Choy, P. Y.; So, C. M.; Lau, C. P.; Wong, W. T.; Kwong, F. Y. *RSC Adv.* **2013**, *3*, 12518. (d) Kleeberg, C.; Dang, L.; Lin, Z.; Marder, T. B. *Angew. Chem., Int. Ed.* **2009**, *48*, 5350. (e) Molander, G. A.; Trice, S. L. J.; Dreher, S. D. *J. Am. Chem. Soc.* **2010**, *132*, 17701. (f) Yamamoto, T.; Morita, T.; Takagi, J.; Yamakawa, T. *Org. Lett.* **2011**, *13*, 5766. (g) Nagashima, Y.; Takita, R.; Yoshida, K.; Hirano, K.; Uchiyama, M. *J. Am. Chem. Soc.* **2013**, *135*, 18730. (h) Bose, S. K.; Marder, T. B. *Org. Lett.* **2014**, *16*, 4562. (i) Liu, X.-W.; Echavarren, J.; Zarate, C.; Martin, R. *J. Am. Chem. Soc.* **2015**, *137*, 12470. (j) Niwa, T.; Ochiai, H.; Watanabe, Y.; Hosoya, T. *J. Am. Chem. Soc.* **2015**, *137*, 14313. (k) Zarate, C.; Manzano, R.; Martin, R. *J. Am. Chem. Soc.* **2015**, *137*, 6754. (l) Tobisu, M.; Kinuta, H.; Kita, Y.; Rémond, E.; Chatani, N. *J. Am. Chem. Soc.* **2012**, *134*, 115. (m) Tobisu, M.; Nakamura, K.; Chatani, N. *J. Am. Chem. Soc.* **2014**, *136*, 5587.

(9) For selected examples of C–H borylations: (a) Mkhalid, I. A. I.; Barnard, J. H.; Marder, T. B.; Murphy, J. M.; Hartwig, J. F. *Chem. Rev.* **2010**, *110*, 890. (b) Hartwig, J. F. *Acc. Chem. Res.* **2012**, *45*, 864. (c) Ros, A.; Fernández, R.; Lassaletta, J. M. *Chem. Soc. Rev.* **2014**, *43*, 3229. (d) Cho, J.-Y.; Tse, M. K.; Holmes, D.; Maleczka, R. E., Jr.; Smith, M. R., III. *Science* **2002**, *295*, 305. (e) Dombay, T.; Wernicke, C. G.; Jiang, S.; Grellier, M.; Vendier, L.; Bontemps, S.; Sortais, J.-B.; Sabo-Etienne, S.; Darcel, C. *J. Am. Chem. Soc.* **2015**, *137*, 4062. (f) Furukawa, T.; Tobisu, M.; Chatani, N. *J. Am. Chem. Soc.* **2015**, *137*, 12211. (g) Kuninobu, Y.; Ida, H.; Nishi, M.; Kanai, M. *Nat. Chem.* **2015**, *7*, 712. (h) Légaré, M.-A.; Courtemanche, M.-A.; Rochette, É.; Fontaine, F.-G. *Science* **2015**, *349*, 513. (i) Smith, K. T.; Berritt, S.; González-Moreiras, M.; Ahn, S.; Smith, M. R., III; Baik, M.-H.; Mindiola, D. J. *Science* **2016**, *351*, 1424.

(10) For selected examples of electrophilic borylations: (a) De Vries, T. S.; Prokofjevs, A.; Vedejs, E. *Chem. Rev.* **2012**, *112*, 4246. (b) Ingleson, M. J. *Synlett* **2012**, *23*, 1411. (c) Ingleson, M. J. *Top. Organomet. Chem.* **2015**, *49*, 39. (d) Stahl, T.; Mütther, K.; Ohki, Y.; Tatsumi, K.; Oestreich, M. *J. Am. Chem. Soc.* **2013**, *135*, 10978.

(11) For examples of transition-metal-free borylations: (a) Mo, F.; Jiang, Y.; Qiu, D.; Zhang, Y.; Wang, J. *Angew. Chem., Int. Ed.* **2010**, *49*, 1846. (b) Zhu, C.; Yamane, M. *Org. Lett.* **2012**, *14*, 4560. (c) Qiu, D.; Jin, L.; Zheng, Z.; Meng, H.; Mo, F.; Wang, X.; Zhang, Y.; Wang, J. *J. Org. Chem.* **2013**, *78*, 1923. (d) Zhang, J.; Wu, H.-H.; Zhang, J. *Eur. J. Org. Chem.* **2013**, *2013*, 6263. (e) Yu, J.; Zhang, L.; Yan, G. *Adv. Synth. Catal.* **2012**, *354*, 2625. (f) Erb, W.; Hellal, A.; Albin, M.; Rouden, J.; Blanchet, J. *Chem. - Eur. J.* **2014**, *20*, 6608. (g) Miralles, N.; Romero, R. M.; Fernández, E.; Muñoz, K. *Chem. Commun.* **2015**, *51*, 14068. (h) Mfuh, A. M.; Doyle, J. D.; Chhetri, B.; Arman, H. D.; Larionov, O. V. *J. Am. Chem. Soc.* **2016**, *138*, 2985. (i) Chen, K.; Zhang, S.; He, P.; Li, P. *Chem. Sci.* **2016**, *7*, 3676. (j) Chen, K.; Cheung, M. S.; Lin, Z.; Li, P. *Org. Chem. Front.* **2016**, *3*, 875.

(12) (a) Yamamoto, E.; Izumi, K.; Horita, Y.; Ito, H. *J. Am. Chem. Soc.* **2012**, *134*, 19997. (b) Yamamoto, E.; Ukigai, S.; Ito, H. *Chem. Sci.* **2015**, *6*, 2943. (c) Uematsu, R.; Yamamoto, E.; Maeda, S.; Ito, H.; Taketsugu, T. *J. Am. Chem. Soc.* **2015**, *137*, 4090.

(13) The bis[(pinacolato)boryl]methane is commercially available from Aldrich (catalog number 794287) and TCI (catalog number B4103).

(14) See the [Supporting Information](#) for details.

(15) (a) Winkler, H. J. S.; Winkler, H. J. *J. Am. Chem. Soc.* **1966**, *88*, 964. (b) Winkler, H. J. S.; Winkler, H. J. *J. Am. Chem. Soc.* **1966**, *88*, 969. (c) Rogers, H. R.; Houk, J. J. *J. Am. Chem. Soc.* **1982**, *104*, 522. (d) Farnham, W. B.; Calabrese, J. C. *J. Am. Chem. Soc.* **1986**, *108*, 2449. (e) Harada, T.; Katsuhira, T.; Oku, A. *J. Org. Chem.* **1992**, *57*, 5805. (f) Beak, P.; Allen, D. J. *J. Am. Chem. Soc.* **1992**, *114*, 3420. (g) Ando, K. *J. Org. Chem.* **2006**, *71*, 1837. (h) Cheung, M. S.; Marder, T. B.; Lin, Z. *Organometallics* **2011**, *30*, 3018.

(16) (a) Tissandier, M. D.; Cowen, K. A.; Feng, W. Y.; Gundlach, E.; Cohen, M. J.; Earhart, A. D.; Coe, J. V. *J. Phys. Chem. A* **1998**, *102*, 7787. (b) Camaioni, D. M.; Schwerdtfeger, C. A. *J. Phys. Chem. A* **2005**, *109*, 10795.

(17) Note that we use gas-phase free energies to obtain a direct and most immediate measure of the intrinsic deprotonation energy. These are not to be confused with solution phase deprotonation energies. The solvation energy of a proton is ~ 260 kcal/mol in water, and the solvation energies of the carbanions will be ~ 50 – 100 kcal/mol. Thus, the solution phase free energy of deprotonation will be much smaller in absolute number. Here, we are interested in assessing the electronic energy, as it will be the most direct measure for how the anionic fragments will behave as binding partners.

(18) During the course of the reaction, we detected $(\text{CH}_2\text{Bpin})_2$ and $t\text{BuOCH}_2\text{Bpin}$, which are presumably formed by the reaction between (iodomethyl)boronate ester (ICH_2Bpin) and α -borylcarbanion (**B1B**) or alkoxide anion, by GC–MS.

(19) The alkylated product **D1** was solely obtained in the presence of $\text{Pd}(\text{OAc})_2$ as a catalyst. For related works, see refs 2 and 3.

(20) For selected examples of aryl radical generation from aryl iodides in the presence of alkoxide base: (a) Shirakawa, E.; Itoh, K.; Higashino, T.; Hayashi, T. *J. Am. Chem. Soc.* **2010**, *132*, 15537. (b) Qiu, Y.; Liu, Y.; Yang, K.; Hong, W.; Li, Z.; Wang, Z.; Yao, Z.; Jiang, S. *Org. Lett.* **2011**, *13*, 3556. (c) Wei, W.; Dong, X.; Nie, S.; Chen, Y.; Zhang, X.; Yan, M. *Org. Lett.* **2013**, *15*, 6018. (d) Chen, Y.; Zhang, X.; Yuan, H.; Wei, W.; Yan, M. *Chem. Commun.* **2013**, *49*, 10974. (e) Drapeau, M. P.; Fabre, I.; Grimaud, L.; Ciofini, I.; Ollevier, T.; Taillefer, M. *Angew. Chem., Int. Ed.* **2015**, *54*, 10587. (f) Barham, J. P.; Coulthard, G.; Emery, K. J.; Doni, E.; Cumine, F.; Nocera, G.; John, M. P.; Berlouis, L. E. A.; McGuire, T.; Tuttle, T.; Murphy, J. A. *J. Am. Chem. Soc.* **2016**, *138*, 7402.

(21) Annunziata, A.; Galli, C.; Marinelli, M.; Pau, T. *Eur. J. Org. Chem.* **2001**, *2001*, 1323.

(22) We carried out the borylation reaction of 4-iodoanisole (**A1**) with **B1** in the presence of 1.0 equiv of *tert*-butanol as a proton source. As anticipated, detectable amounts of anisole (19%), presumably captured by *tert*-butanol, were formed along with the desired borylated product (20%) in 60% conversion of **A1**. This result provides supportive evidence that aryl anion is likely involved as a reactive species in the reaction. For details, see the [Supporting Information](#).

(23) Bose, S. K.; Fucke, K.; Liu, L.; Steel, P. G.; Marder, T. B. *Angew. Chem., Int. Ed.* **2014**, *53*, 1799.