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Transition-Metal-Free Boryl Substitution Using Silylboranes and Alkoxy bases

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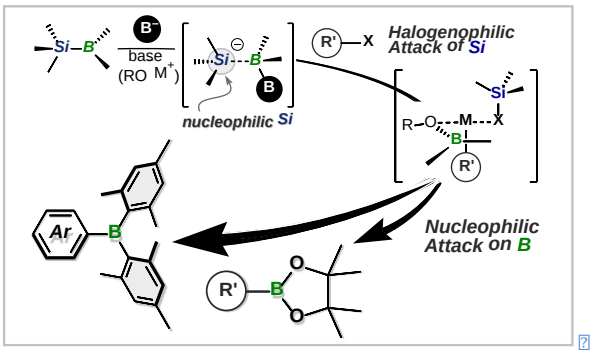

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Abstract: Silylboranes can be used as a borylation reagent for organohalides in the presence of alkoxy bases without transition metal catalysts. $PhMe_2Si$–B(pin) reacted with a variety of aryl, alkenyl, and alkyl halides including sterically hindered ones to provide the corresponding organoboronates in good yields with high borylation/silylation ratios, showing good functional group compatibility. Halogenophilic attack of a silyl nucleophile on organohalides and following nucleophilic attack on boron electrophile have been identified as crucial based on the results of extensive theoretical and experimental studies. This borylation reaction was further applied to the first direct dimesityl boryl ($BMes_2$) substitution of aryl halides using Ph_2MeSi–$BMes_2$ and Na(O-*t*-Bu), affording Aryldimesitylboranes, which are regarded as an important class of compounds for organic materials.

Key words silylborane, boryl substitution, borylation, aryldimesitylborane, halogenophilic attack, transition-metal-free, AFIR

1. Introduction

Organoboron compounds have become an indispensable reagent in modern organic chemistry as they can be converted into a wide variety of functional groups.[2] In addition, their modulable reactivity and good stability toward air and moisture play important roles to achieve the transformations and increase their utility. Reactions of boron electorophiles with organolithium reagents or Grignard reagents are a common method for the preparation of organoboron compounds.[2b,c,3] However, these methods generally have low functional group compatibility and are limited by the availability of the organometallic reagents. In recent years, a number of functional-group-tolerant transition-metal-catalyzed borylation reactions have been developed as the complementary methods.[4,5] However, there exist a strong need for developing transition-metal-free synthetic methods that can reduce the transition metal impurities in the products for pharmaceutical application as well as the high process cost .accompanied with the use of expensive transition-metal catalysts[6,7]

In order to solve the issue, several transition-metal-free borylation methods have been developed, including borylation reactions involved with Lewis-base activation of a B–B bond,[8] electrophilic[9] or radical-mediated[10] borylation. Despite these recent advances, these reactions still have issues in terms of their reactivity, regioselectivity and functional group compatibility. Among these transition-metal-free borylation reactions, boryl substitution reaction of organohalides is a reliable method to access the desired organoboron compounds. One of the major challenges is the compatibility of the reaction system with sterically-hindered and/or functionalized substrates.

Recently, we have developed formal nucleophilic boryl substitution reactions of organohalides with silylborane reagents and alkoxy bases, which are involved with Lewis base activation of the Si–B bond (Figure 1a).[11] This reaction was counterintuitive in that the reaction of silylborane with Lewis-base is supposed to generate a silyl nucleophile (Figure 1b), as seen in the reactions related to Lewis-base activation of Si–B bonds.[12] For example, Kawachi, Tamao and co-workers reported that reactions of a silylborane with a stoichiometric amount of strong base such as organolithium reagent, Grignard reagent, or

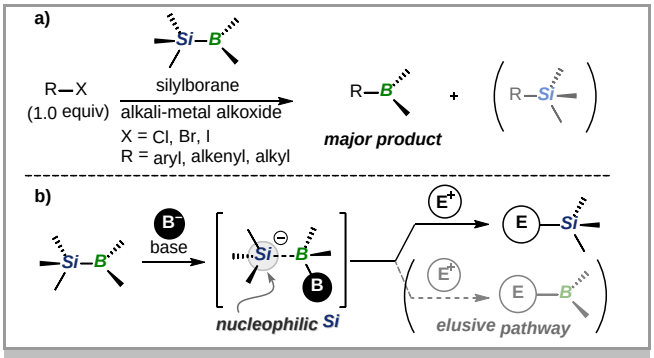
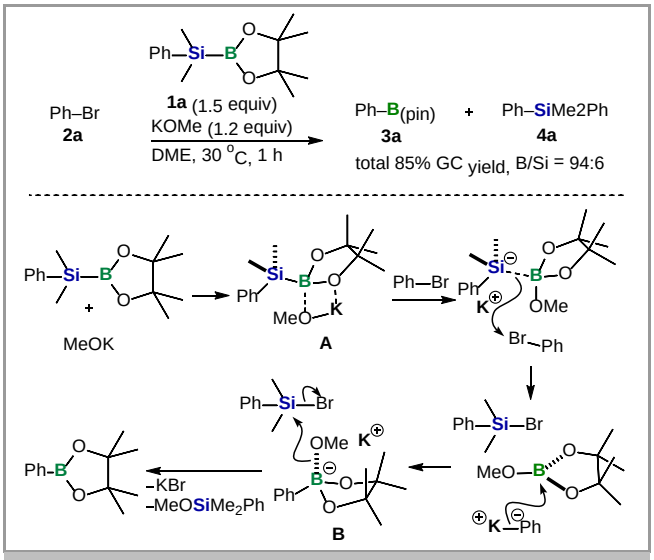


Figure 1 Boryl substitution with silylborane and alkoxy base

K(O-*t*-Bu) provides the corresponding silyl nucleophiles, which can react with a variety of electrophiles.[12a,f] Hoveyda and co-workers reported chiral N-heterocyclic carbene (NHC)-catalyzed enantioselective 1,4-silyl addition of α,β-unsaturated carbonyl compounds with silylborane in the presence of stoichiometric amount of base.[12b,i] These reactions indicate that silylboranes react with a base or nucleophilic catalyst to generate the silyl nucleophile rather than the boryl nucleophile,[8,13] and there had been no reports for silylborane showing a boryl nucleophile.

Our boryl substitution reactions are considered to follow a representative mechanism depicted in Scheme 1, based on experimental observations[11] and DFT studies using artificial force induced reaction (AFIR) method,[11c] which involves the formation of a carbanion species via a metal–halogen exchange.[14,15] The silyl substitution of phenyl halides with a silyllithium reagent was reported by Strohmann and co-workers.[16] Taking their proposed mechanism and our results into account, $PhMe_2Si–B(pin)$ (**1a**) and potassium methoxide initially form silylborane/KOMe complex **A**. Subsequent nucleophilic attack of the silyl moiety of complex **A** on the bromine atom of phenyl bromide **2a** leads to the formation of phenyl anion species. Then, the carbon nucleophile attacks on the boron electrophile rather than $PhMe_2SiBr$ to give the corresponding organoborate salt $[PhB(pin)OMe]^-K^+$ (**B**), which gives phenylboronate ester **3a** through the reaction of $[PhB(pin)OMe]^-K^+$ with the *in situ* generated $PhMe_2SiBr$. Ph_2Me_2Si (**4a**), silyl methyl ether and potassium bromide were formed as byproducts. This account highlights our recent research on the transition-metal-free boryl substitution reactions using silylborane reagents containing B(pin)[11a-c] or dimesitylboryl ($BMes_2$) group,[11d] and alkoxy bases, focusing on the scope, mechanism and limitations.

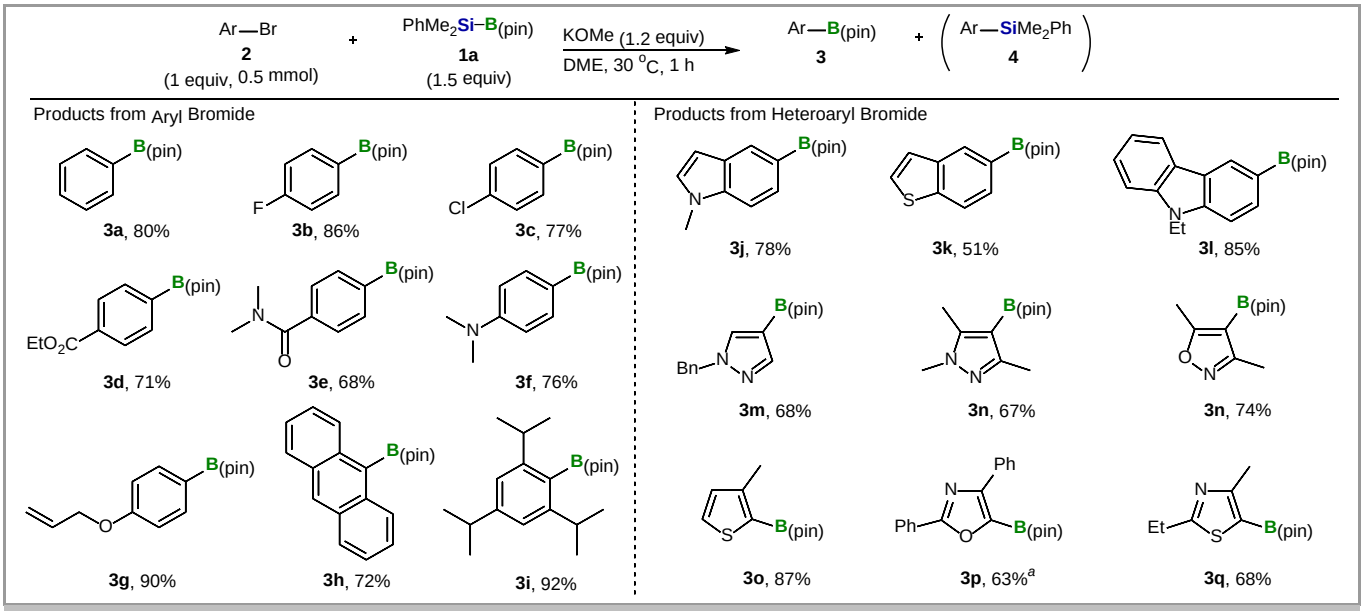


Scheme 1 Reaction mechanism of boryl substitution of PhBr with $PhMe_2Si–B(pin)$ in the presence of KOMe base

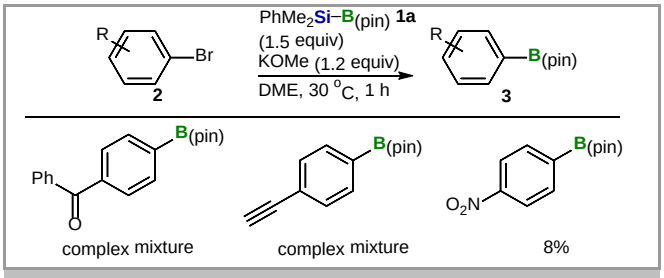
2. Boryl Sustitution Reaction of Organohalides with $PhMe_2Si–B(pin)$/Alkoxy Base

Silylborane has been used as a versatile reagents for the synthesis of organoboron and –silicon compounds.[12g,17] During the course of our study on developing reactions using silylborane reagents.[12d] We found that boryl substitution reaction with aryl halides with $PhMe_2Si–B(pin)$ **1a** in the presence of alkoxy bases.[11a-c] Screening of the reaction conditions identified the optimum conditions using silylborane **1a** (1.5 equiv), KOMe (1.2 equiv) in 1,2-dimethoxyethane (DME) at 30 °C for 1 h (Scheme 2). The use of the less bulky alkoxy base and ethereal solvent is important to ensure the good yield and Borylation/Silylation (B/Si) selectivity. The selected examples of substrates for this boryl substitution reaction of aryl halides are shown in Scheme 2. Electron-deficient or rich aryl bromides are tolerant under the reaction conditions (Scheme 2, left). The reaction of *p*-allyloxybromobenzene (**2g**) gave the borylated product in good yield. It should be noted that allyloxy group in aryl bromide **2g** is easily removed under the typical Pd(0)-catalyzed borylation conditions due to the formation of π-allyl Pd species.[11a] No transesterification was observed when the substrate having ethyl ester group was used. In addition, sterically-hindered 2,4,6-triisopropyl bromobenzene substrate **2i** also underwent the reaction providing the corresponding aryl boronic acid ester in high yield. It is noteworthy that transition-metal-catalyzed borylation of **2i** has been reported to be difficult without an exquisite ligand system.[4a,e] This method was also successfully applied to the synthesis of heteroaryl boron compounds (Scheme 2, right). Boryl substitution of heteroaryl bromide including indole, benzothiophene, carbazole, pyrazole, thiophene, oxazole, thioxazole derivatives underwent to give the corresponding organoboron compounds in good yields.[11b] On exploring the substrate scope with aryl and heteroaryl bromides, three limitations emerged. First, this borylation conditions could not accommodate substrates having electrophilic or protic functional groups. For example, aryl bromide containing nitro, ketone or terminal alkyne functional group resulted in very low yield or complex mixtures although several carbonyl groups such as ethyl esters and dialkyl amides were tolerant under the conditions (Scheme 3). This would be attributable to the side reactions of the functional groups with *in situ* generated silyl nucleophile. The other issues are contamination of silyl substituted product and decomposition of the borylated products in the purification process. For example, borylated products from 3-bromopyridine or 3-bromoquinoline using this method could not be isolated in

acceptable yields although ^{1}H NMR analysis of the crude reaction mixtures indicated the formation of borylated products in 68 and 58 % yields, respectively.

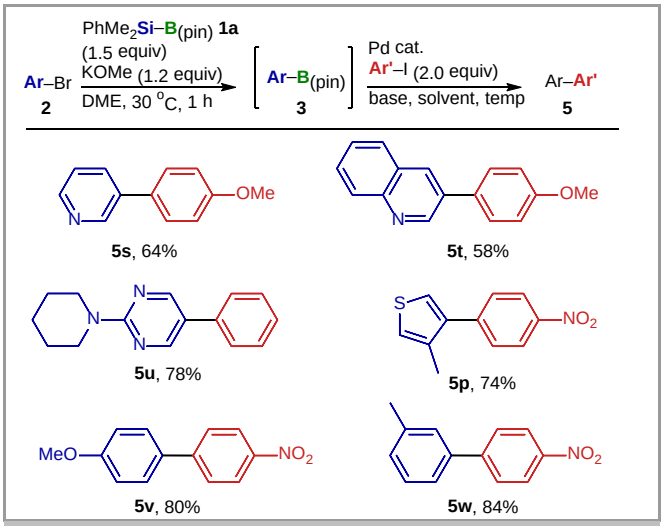


Scheme 2 Boryl substitution of aryl- and heteroaryl bromides with $PhMe_2Si$–B(pin) and alkoxy base: a) 3 equiv of **1a** and 2.4 equiv of KOMe were used.

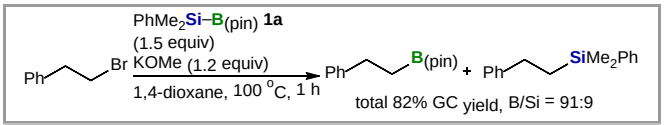


Scheme 3 Unsuccessful aryl bromide substrates

To utilize these unpurified borylated products, sequential boryl substitution/Suzuki-Miyaura coupling was developed (Scheme 4). This one-pot borylation/cross coupling sequence provided a facile access to the corresponding coupling products in good to high yields (58–84%). The present boryl substitution reaction is also applicable to the synthesis of alkyl boronates although the reaction condition requires higher reaction temperature than those for the synthesis of aryl boronate [equation 1, silylborane **1a** (1.5 equiv), KOMe (1.2 equiv) in 1,4-dioxane at 100 °C for 1 h].



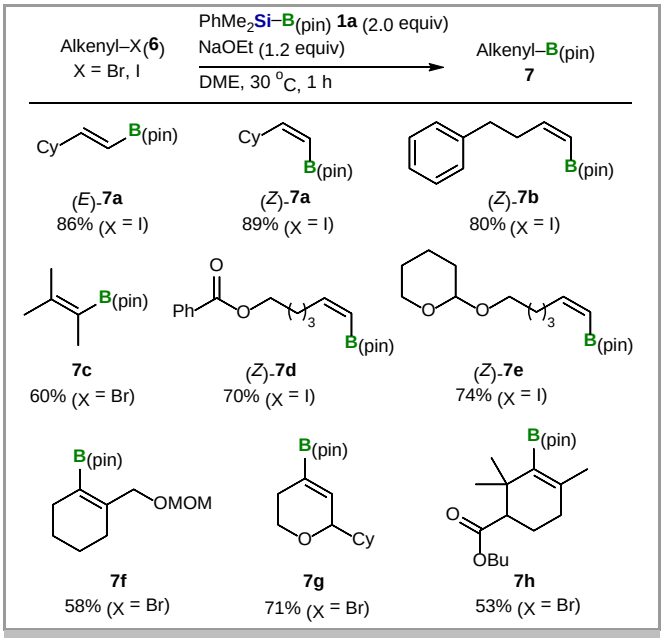
Scheme 4 Sequential boryl substitution/Suzuki-Miyaura coupling



Equation 1 Boryl substitution of phenethyl bromide using $PhMe_2Si$–B(pin) and KOMe

With regard to the synthesis of alkenyl boronates, the non-catalytic hydroboration of alkynes is a common and straightforward method to access (*E*)-alkenyl borates.[18] In contrast, the preparation of (*Z*)-alkenyl boronates requires an indirect trans-hydroboration using alkynyl bromides.[19] With this in mind, optimization of reaction conditions for boryl substitution of (*Z*)-alkenyl iodide was investigated, which lead to the optimum reaction conditions using $PhMe_2Si$–B(pin) (2 equiv) and NaOEt (1.5 equiv) in DME solvent at 30 °C (Scheme 5). The use of NaOEt is of importance to obtain the desired (*Z*)-

alkenyl boronate in high yield with high B/Si and *Z*/*E* ratios. With this conditions in hand, substrate scope was explored with a variety of (*Z*)- or (*E*)-alkenyl iodides and bromide (Scheme 5). This reaction conditions tolerated sterically hindered (*E*)- or (*Z*)-alkenyl iodides and (*Z*)-alkenyl iodides having benzoyl or acetal functional group. Tetrasubstituted alkenyl bromides are also viable substrates. It is worthy of note that a sterically hindered substrate containing butyl ester group underwent the reaction to afford the borylated product in good yield (53%).



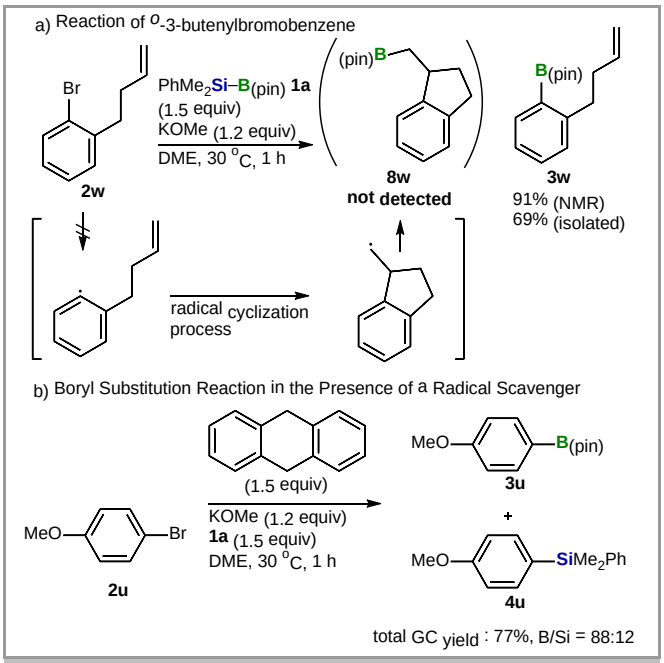
Scheme 5 Boryl substitution of alkenyl halides with $PhMe_2Si$–B(pin) and alkoxy base

3. Mechanistic investigations

We were intrigued to pursue the mechanism of the present borylation reaction. We assumed that the boryl substitution could undergo through one of four possible processes: (1) trace-transition-metal catalysis, (2) a radical-mediated mechanism, (3) a radical-anion-mediated mechanism or (4) a carbanion-mediated mechanism. It is worthy of note that a mechanism including a dearomatization process seems unlikely based on the results of the reaction of sterically-hindered aryl halides **2i**, which proceeded rapidly and afforded the borylated product in high yield, and the related mechanistic studies of silyl substitution of aryl halides.[16]

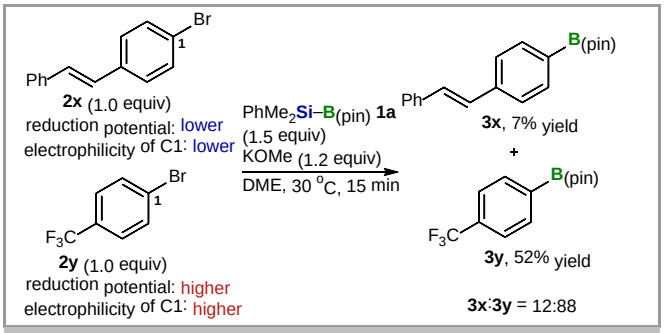
We first suspected that trace transition-metal impurities in the reaction mixture might catalyze the boryl substitution reaction.[20] However, ICP-AES analysis of KOMe base for the presence of various transition-metals (Ni, Pd, Pt, Rh, Au, Ag, Ir, Ru and Co) revealed that the concentrations of trace-transition metals were lower than those of the detection limits. In addition, the boryl substitution reaction was repeated in the presence of catalytic amount of transition-metal salts, which resulted in no acceleration in the yield or selectivity. Furthermore, control experiments with virgin reagents and labwares performed by another research group showed almost the same results. These results indicated no involvement of trace-transition-metal catalysis in this system.[11a]

Next, several experiments were carried out to investigate the possibility of a radical-mediated mechanism (Scheme 6).[11a,b] For this aim, boryl substitution reaction of *o*-(3-butenyl)bromobenzene (**2w**) was conducted. The corresponding aryl radical species has been reported to undergo 5-exo-trig cyclization with a rate constant of 10^8 s^{-1} to form 1-methylindane after hydrogen atom abstraction.[21] The reaction underwent to provide the corresponding acyclic borylated product in high yield, which did not indicate that radical intermediates are involved (Scheme 6a). In addition, the boryl substitution reaction of *p*-bromoanisole (**2u**) was performed in the presence of 9,10-dihydroanthracene as a radical scavenger, affording the corresponding borylated and silylated products in good yield and selectivity (total 77% yield, B/Si = 88:12, Scheme 6b). Furthermore, the reactions of (*Z*)- or (*E*)-alkenyl iodides underwent the borylation in completely stereoretentive manner (Scheme 5). This result also discounted the radical-mediated mechanism since generation of the corresponding vinyl radical species would lead to the *E*/*Z* isomerization of the intermediate, which would subsequently lead to a lower *E*/*Z* ratio of the products.[22]



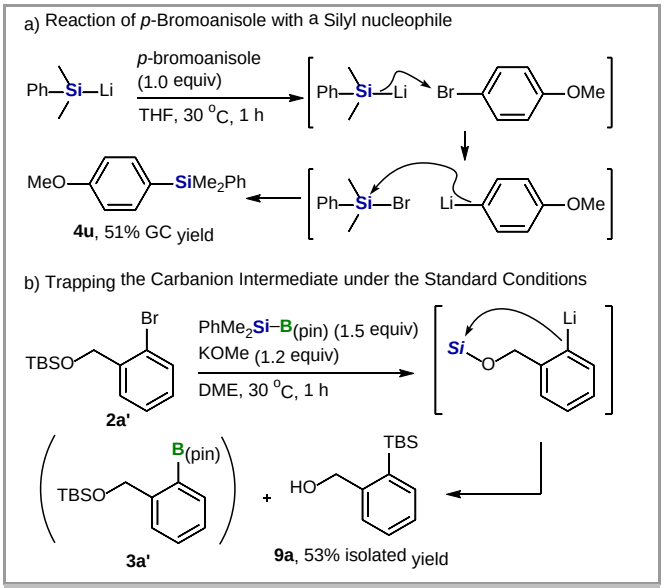
Scheme 6 Mechanistic investigations of an radical mediated mechanism

We then explored the possibility of a radical-anion-mediated mechanism by conducting a competition reaction with two different aryl bromides (Scheme 7).[11b] (*E*)-*p*-Bromostilbene (**2x**) has a lower reduction potential than 4-bromo(trifuoromethyl)benzene (**2y**), which easily reduced by electron donor to produce radical anion species, and the carbon atom bound to the bromine in **2x** is more electrophilic than that in **2y**.[23] The competition reaction with these substrates afforded the borylated products **3x** and **3y** in a ratio of 12:88. This observation indicates that the electron transfer process to **2x** probably less contributed whole reactivity: the involvement of a radical-anion-mediated mechanism is unlikely.



Scheme 7 Reaction of substrates having different reduction potential and electrophilicity

Next, the possibility of a carbanion-mediated mechanism was investigated.[11b,c] The halogenophilic attack process by the silyl nucleophile would be the key reaction in the carbanion-mediated mechanism. It is important to note that this process has not yet been studied in great detail.[14,15] With these considerations in mind, silyl substitution of *p*-bromoanisole **2u** with (dimethylphenylsilyl)lithium, which is a common silyllithium reagent, was examined (Scheme 8a). The reaction underwent to afford the silyl-substituted product **4u** in 51% yield. This reaction most probably involved an initial halogenophilic attack by the silyl nucleophile on the bromine atom, followed by reaction of the resultant silyl bromide with the aryllithium species to provide the silyl substitution product **4u**. Further experiment for trapping a carbanion intermediate observed intramolecular retro-Brook rearrangement product **9a'**, and no boryl substituted product **3a'** was detected (Scheme 8b). These observations provide evidences in support of the formation of the carbanion intermediate under the standard reaction conditions for the present boryl substitution reaction.



Scheme 8 Mechanistic investigation of an carbanion-mediated mechanism

4. DFT Mechanistic Studies Using Artificial Force Induced Reaction (AFIR) Method

DFT theoretical studies using artificial force induced reaction (AFIR) method were performed to understand the mechanistic details of the present boryl substitution. The AFIR method is an fully automated reaction path search method, developed by Maeda and Morokuma,[24] which explores association pathways between multiple reactant molecules, and identify approximate local minima (LM) and transition states (TS). In AFIR, the sum of the potential energy function of the reacting system and a force term are used as a model function. The force term eliminates potential barriers along a reaction coordinate, which enables rapid identification of the LMs and TSs by minimization of this function. The approximate stationary points can be reoptimized to locate the true LMs and TSs. DFT studies with AFIR method enable the identification of working reaction pathways, including unexpected ones, from the many different possibilities without estimating any of the TS structures.

From a number of the reaction mechanisms including unexpected ones, DFT mechanistic studies with AFIR method reached the carbanion-mediated mechanism, which is the most plausible mechanism among the four possible reaction mechanisms mentioned above.[11c] In addition, the DFT studies have also discounted the radical or radical-anion-mediated mechanism being involved in the boryl substitution reaction based on the results of CIS- and TDDFT-based electronic excitation energy calculations. Furthermore, the theoretical study revealed the origin of the good functional group compatibility and high reactivity toward sterically hindered aryl halide substrates of the present boryl substitution reaction with silylborane and alkoxy bases. In the case of the boryl substitution of phenyl bromide substrate, the results of the calculations unveiled that the activation free energy of the halogenophilic attack of *in situ* generated silyl nucleophile on phenyl bromide is significantly low ($\Delta\Delta G^{\ddagger}$ = 0.2 kcal/mol) while Si–B bond cleavage process in the $PhMe_2Si$–B(pin)/KOMe ate complex has an energy barrier of 18.4 kcal/mol, which is the substantial rate determining step (RDS) (Figure 2a). In addition, activation barriers of the following borylation or silylation process are 1.0 and 2.6 kcal/mol, respectively (Figure 3). The significantly low energy barriers of the halogenophillic attack and the following nucleophilic boryl/silyl substitution process indicate that these processes are significantly rapid enough to show good functional compatibility even when an ester group exists.

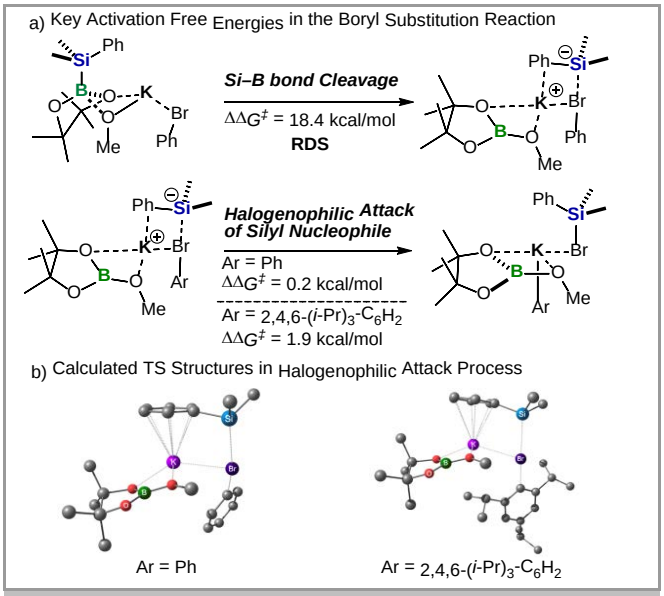


Figure 2 Activation free energies for Si–B bond cleavage and halogenophilic attack of silyl nucleophile on phenyl bromide: Gibbs free energy values (303.15 K, 1.0 atm) based on M06-L/6-311+G(2d,p) calculations are shown.

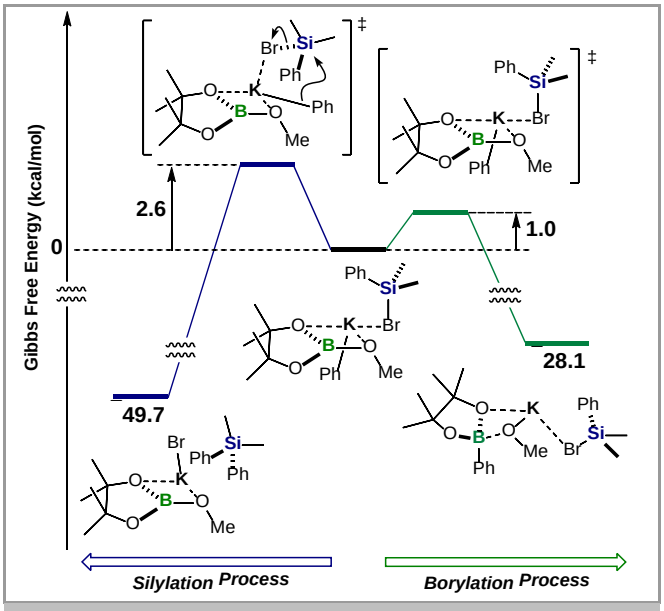
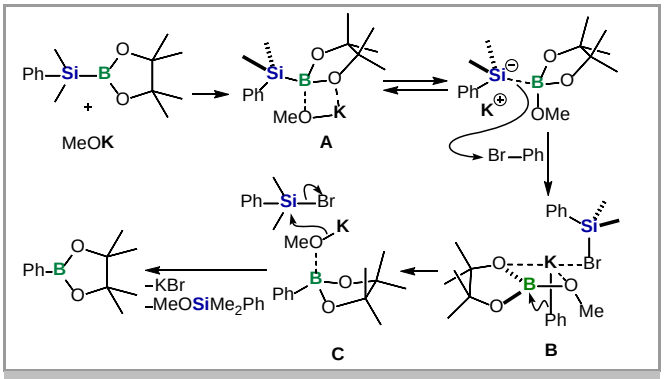


Figure 3 Free energy diagram for borylation or silylation process: Gibbs free energy values (303.15 K, 1.0 atm) based on M06-L/6-311+G(2d,p) calculations are shown.

In addition, calculated activation energy in the halogenophilic attack on sterically hindered 2,4,6-triisopropylbromobenzene (**2i**) was found to be reasonably low ($\Delta\Delta G^{\ddagger}$ = 1.9 kcal/mol, Figure 2b). This result is in good agreement with the high reactivity of sterically hindered substrates in the present boryl substitution reaction conditions. The TS structures indicate that the steric hindrance of the *ortho*-isopropyl groups in **2i** would be too far from the reactive σ*(C–Br) orbital to have a noticeable effect on the reactivity, whereas Pd catalysts directly interact with a C–Br bond in the aryl bromides in Miyaura borylation, causing this classical borylation sensitive to the steric hindrance. The overall reaction pathway is shown in Scheme 9. Initially, the silylborane/KOMe ate complex **A** is formed, followed by Si–B bond cleavage process, which is a reversible reaction. Then, the nucleophilic attack of the silyl nucleophile affords the phenyl potassium complex **B**, and nucleophilic attack of phenyl potassium species on the boron or silicon electrophiles occurs, which determines the B/Si selectivity. After that, resulting boron ate complex **C** reacts with the silyl bromide, providing the desired phenyl boronate.



Scheme 9 Reaction mechanism of boryl substitution of phenyl bromide with $PhMe_2Si$–B(pin) and KOMe base

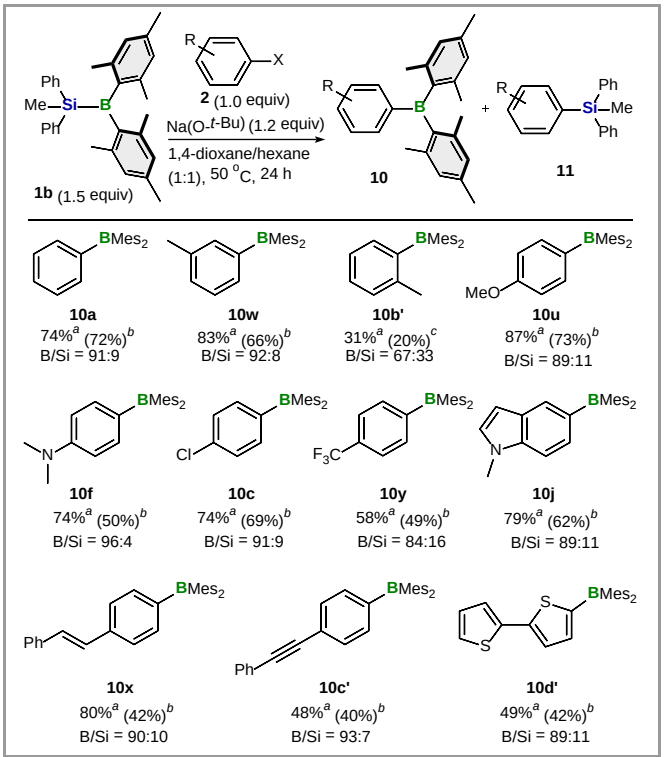
5. Dimesityl Boryl Sustitution of Aryl Halides with Ph_2MeSi-$BMes_2$/Na(O-*t*-Bu)

This borylation reaction was further applied to the direct synthesis of aryldimesitylboranes,[11d] which have attracted much attention as organic materials for electronic and optoelectronic devices.[25] Boron-containing π-conjugated systems show intriguing optical properties, which are attributable to the p-π* conjugation between the vacant p orbital of the three-coordinate boron center and the π* orbital of the attached carbon π-conjugated moieties. Among these compounds, dimesityl boryl ($BMes_2$) group has been frequently used because of its high π-acceptor property and high stability toward air and moisture.

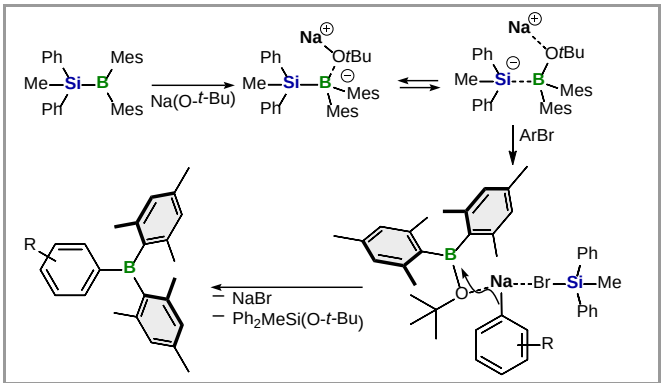
The dimesityl borylation of aryl halides were conducted under the optimized reaction conditions using Ph_2MeSi–$BMes_2$ (**1b**) (1.5 equiv) and Na(O-*t*-Bu) (1.2 equiv) in dioxane/hexane (1:1) solvent at 50 °C. This reaction requires the use of sterically hindered Na(O-*t*-Bu) base to efficiently promote the desired boryl substitution reaction while using small alkoxy bases such as KOMe or NaOMe were important for the synthesis of organoboronates using $PhMe_2Si$–B(pin) **1a** and alkoxy bases. In addition, dioxane solvent is also significant to assure the high yield and B/Si ratio. Selected examples of the viable substrates are shown in Scheme 10. Electronic change on the aryl ring in the substrates did not show siginificant impact on the yield and B/Si selectivity. A reaction of 2-methyl-bromobenzene substrate **2b'** showed low yield and low B/Si selectivity (31%, B/Si = 67:33). Aryl bromide bearing conjugated alkene or alkyne functional group or heteroaryl bromides (**2j**, **2x**, **2c'**, **2d'**) also underwent the reaction to afford the corresponding dimesityl borylation products in moderate to good yields and with good to high B/Si ratios.

A possible reaction mechanism for the dimesitylboryl substitution is presented in Scheme 11. At the outset of the reaction, Ph_2MeSi–$BMes_2$ and Na(O-*t*-Bu) form the corresponding ate complex. Following halogenophilic attack of nucleophilic Ph_2MeSi group on the bromine atom in the aryl bromide substrate provides the aryl anion intermediate.

Subsequent nucleophilic attack of the aryl anion species to $Mes_2B(O\text{-}t\text{-}Bu)$ affords aryldimesitylborane **10**. This follows the mechanism for boryl substitution with $PhMe_2Si$–B(pin) and an alkoxy base[11c], while the optimized conditions for dimesityl borylation are slightly different from those for B(pin) substitution [$PhMe_2Si$–B(pin) (1.5 equiv) and KOMe (1.2 equiv) in DME at 30 °C]. An important difference is that the dimesityl borylation needs the bulky sodium *tert*-butoxide base to assure high B:Si ratio while the use of a small methoxide base is crucial for high B/Si ratio for the pinacol boryl substitution. The strong Lewis acidity of dimesitylboryl group would be attributable to its distinct reactivity and B/Si selectivity, which are different from those in the borylation with $PhMe_2Si$–B(pin) and KOMe base..



Scheme 10 Dimesityl boryl substitution of aryl halides with Ph_2MeSi–$BMes_2$ and Na(O-*t*-Bu): a) Isolated yield, b) ^{1}H NMR yield.



Scheme 11 Plausible reaction mechanism of dimesityl boryl substitution of aryl halides

6. Conclusion

In this Account, we have described an overview of the recent our research on boryl substitution of organohalides with silylboranes and alkoxy bases. This system offers a novel access route to the aryl, heteroaryl, alkenyl and alkyl boronates from the corresponding organohalide substrates including sterically hindered ones without transition metal catalysts. In addition, the first direct dimesityl boryl substitution of aryl halides was also developed. These reactions undergo via halogenophilic attack of siliyl nuceophiles and following nucleophilic attack of the resultant carbanion species on in situ generated boron electrophiles. The results of the experimental and theoretical investigation are consistent with the reaction mechanism. Key challenges lie in the further expansion of the chemistry that can be achieved using the intriguing reactivity of silicon nucleophiles and improvement of functional group compatibility by modifying functional group on the boron and silicon atoms in silylborane reagents in combination with the optimization of reaction conditions.

Acknowledgment

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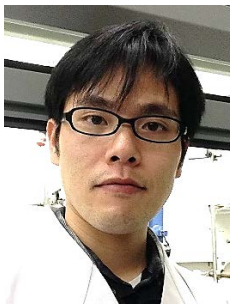

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Professor Hajime Ito was born in Osaka, Japan, in 1968. He completed the Ph.D. degree in 1996 under the direction of late Professor Yoshihiko Ito at Kyoto University. He then worked as an Assistant Professor at Tsukuba University in corroborating with Professor Akira Hosomi, and moved to Institute for Molecular Science. He also joined Professor Kim D. Janda's research group at the Scripps Research Institute as a research associate in 2001. In 2002 he was appointed as an Associate Professor at Hokkaido University, working with Professor Masaya Sawamura. He was promoted to a full Professor at the same university in 2010. His research interests include development of new synthetic reactions for organic synthesis as well as new organometallic functional materials.

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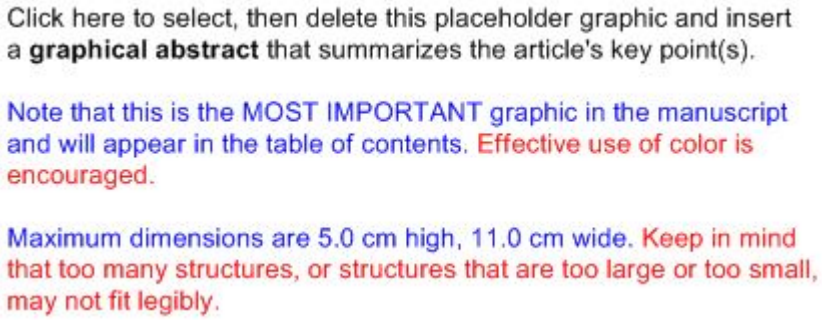

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