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Formal Nucleophilic Boryl Substitution of Organic Halides with Silylborane/Alkoxy Base System

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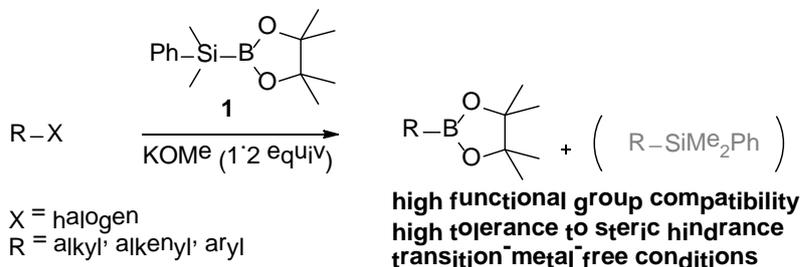
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Abstract: Boryl substitution of organohalides with a silylborane and alkoxy bases is described. This reaction can be applied to various functionalized aryl halides. Alkyl and alkenyl halides, and even sterically congested aryl bromides also provided the corresponding borylated products in high yields. Mechanistic studies indicated that neither trace transition-metal impurities nor aryl radical species involved in this reaction. (57 words)

Introduction: Aryl boronate esters are regarded as essential building blocks due to their broad applicability to various C–X (X = C, N, O) bond-forming reactions and ease of handling [1–3]. Reactions of a carbon nucleophile such as an Grignard or lithium reagent with trialkylboronate esters are common methods for the preparation of organoboronates [1,3–6]. However, these reactions generally lack functional group compatibility because of the strong basicity and nucleophilicity of the organometallic reagents. Over the past two decades, transition-metal-catalyzed boryl substitution of aryl halides and C–H borylation with high functional group tolerance have been developed as complementary methods to the conventional procedures [7–15]. However, the high process cost of the catalysts and transition-metal impurities in the products often make them unsuitable for pharmaceutical production purpose [16]. To overcome this, several transition-metal-free borylation reactions such as the Sandmeyer-type borylations [17,18] and electrophilic arene C–H borylations [19–24] have been developed recently, but there are still limitations in terms of both the substrate scope and regioselectivity. Recently, we reported K(O-*t*-Bu)-catalyzed silaboration of aromatic alkenes [25]. During our studies on the silaboration and borylation reactions [26–30], we found that PhMe₂Si–B(pin) (**1**) showed unexpected reactivity in the presence of an alkoxy base: the formal nucleophilic boryl substitution of aryl, alkenyl, and alkyl halides (Scheme 1). This boryl substitution reaction is counterintuitive, because silyl substitution should be anticipated on the basis of the general reactivity of silylboranes. Kawachi, Tamao, and co-workers [31–36] have reported that reacting a silylborane with a stoichiometric amount of strong base such as RLi, MeMgBr, or K(O-*t*-Bu) affords the silyl nucleophilic species. Hoveyda and co-workers [37] reported that a chiral N-heterocyclic carbene can also activate silylboranes, enabling catalytic enantioselective silylation of α,β -unsaturated compounds. These examples indicate that silylboranes react with a base or nucleophilic catalyst to generate the silyl nucleophile rather than the boryl nucleophile [38–40]. Generation of nucleophilic boryl species by base activation of diboron was recently reported from

the laboratories of Hoveyda [41,42] and Fernández [43–45]. However, there have been no reports for silylborane showing a boryl nucleophile.



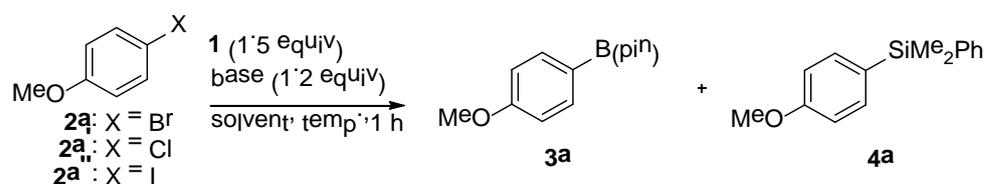
Scheme 1. Boryl Substitution in the Silylborane/Alkoxy Base System

Herein, we report a novel, transition-metal-free boryl substitution of aryl, alkenyl, and alkyl halides with silylborane **1** and alkoxy bases. The reaction provides the boryl substitution products in high yields with high borylation/silylation (B/Si) ratios. A part of the results described in this manuscript was already reported in our previous paper [46].

Results and Discussion: We started to explore the reactions of *p*-bromoanisole **2a** with silylborane **1** under various conditions (Table 1) [47,48]. The reaction of **2a** (1.0 equiv) with **1** (1.5 equiv) and KOMe (1.2 equiv) in the 1,2-dimethoxyethane (DME) as the solvent at 30 °C afforded the boryl substitution product in a high yield and with an excellent borylation/silylation ratio (total 92% yield, B/Si = 95:5, borylation product **3a**: 87% GC yield, 77% isolated, entry 1). No reaction occurred without the base (entry 2). This reaction proceeded rapidly; requiring only 15 min to reach completion while comparable transition-metal-catalyzed borylations [8,9,11,12], which are conventional methods for production of functionalized aryl boronates, require several hours at 80–100 °C under standard conditions. Etheral solvents are suitable for this boryl substitution (entries 1 and 3–7). The use of THF afforded similar results to those for DME (85% yield, B/Si = 94:6, entry 3), while toluene or CH₂Cl₂ gave the product in lower yields (entries 4 and 5, respectively). When *N,N*-dimethylformamide (DMF) or MeOH was used as a solvent, silylborane **1** was consumed completely, but no desired product was obtained (entries 6 and 7). Next, the effects of reaction temperature were investigated (entries 8 and 9). The reaction at a higher temperature of 50 °C afforded similar results to those at 30 °C (87% yield, B/Si = 95:5, entry 8), whereas the reaction at 0 °C resulted in lower B/Si selectivity as compared to the reactions at 30 and 50 °C (83% yield, B/Si = 86:14, entry 9). The reaction was performed at high concentration and gave only slightly inferior results (in 1/10 amount of the solvent, 87% yield, 92:8, entry 10). Bases other than KOMe proved to be inferior (entries 11–17). LiOMe gave no product and NaOMe resulted in a lower B/Si ratio (entries 11 and 12, respectively). Using K(O-*t*-Bu) resulted in a significant decrease in the product yield and B/Si selectivity (66%, B/Si = 73:27, entry 13). No reaction occurred with weaker inorganic

bases (entries 14–16). The reaction with a strong organic base (DBU, 1,8-diazabicyclo[5.4.0]-7-undecene) also gave no desired product (entry 17). We next investigated the effects of the halogen group. *p*-Chloroanisole **2a'** gave the product **3a** in lower yield, while *p*-iodoanisole **2a''** provided the product with a yield and B/Si ratio comparable to those for **2a** (entries 18 and 19).

Table 1. Optimization of Reaction Conditions for the Boryl Substitution of Aryl Halides with PhMe₂Si–B(pin)/Alkoxy Bases



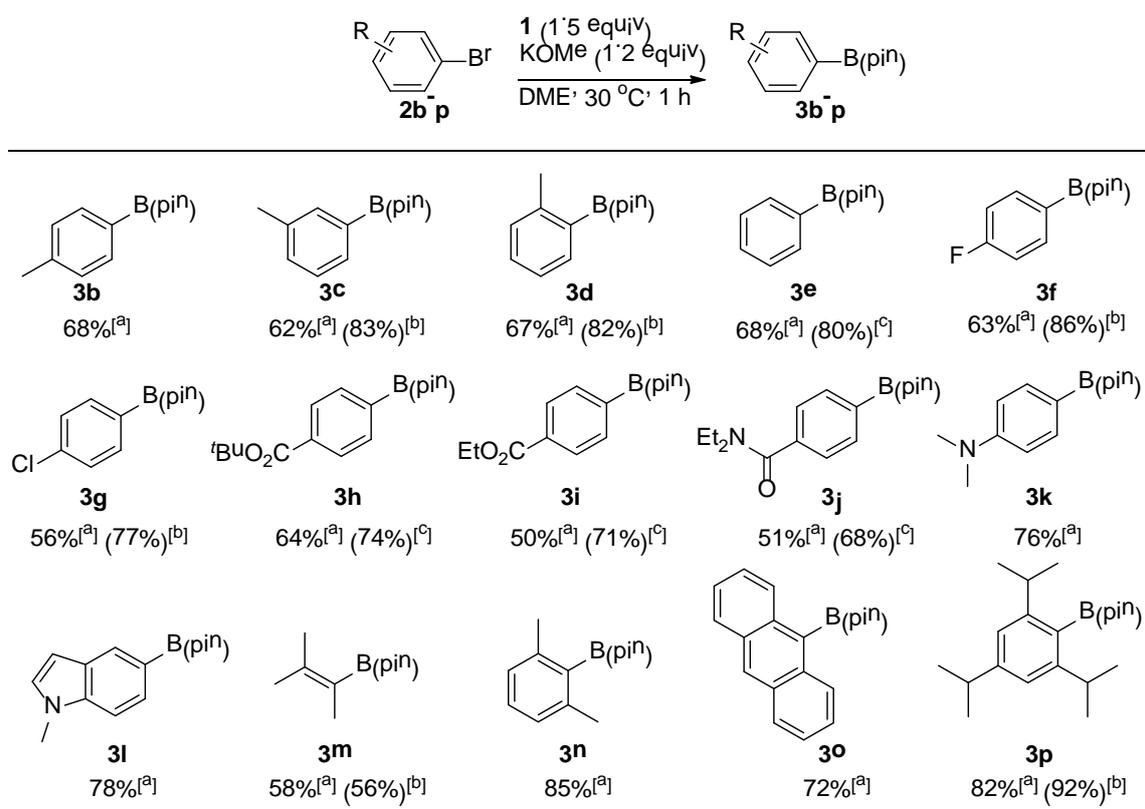
Entry	X	Solvent	Base	Temp. (°C)	Yield (%) ^[a]	B/Si
1	Br	DME	KOMe	30	92 (77) ^[b]	95:5
2	Br	DME	none	30	0	
3	Br	THF	KOMe	30	85	94:6
4	Br	toluene	KOMe	30	20	95:5
5	Br	CH ₂ Cl ₂	KOMe	30	10	50:50
6	Br	DMF	KOMe	30	0	
7	Br	MeOH	KOMe	30	0	
8	Br	DME	KOMe	50	87	95:5
9	Br	DME	KOMe	0	83	86:14
10 ^[c]	Br	DME	KOMe	30	87	92:8
11	Br	DME	LiOMe	30	0	
12	Br	DME	NaOMe	30	81	80:20
13	Br	DME	K(O ⁻ t-Bu)	30	66	73:27
14	Br	DME	KOAc	30	0	
15	Br	DME	K ₂ CO ₃	30	0	
16	Br	DME	KF	30	0	
17	Br	DME	DBU	30	0	
18	Cl	DME	KOMe	30	27	85:15
19	I	DME	KOMe	30	81	96:4

[^a] GC yield; [^b] Isolated yield; [^c] The reaction was performed in 1/10 amount of the solvent

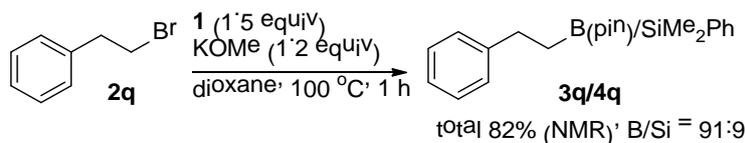
With the optimized conditions in hand, the substrate scope of this reaction was examined with a variety of aryl bromides (Table 2). Aryl bromides with a neutral or electron-donating substituent underwent the reaction in high yields (**3b–3e**). The substitution position of the methyl

group in **2b–2d** had no significant effect on the yields. Reactions of electron-deficient substrates (**2f** and **2g**) also provided the borylated products (**3f** and **3g**) in good yields, respectively. In addition, other electron-deficient substrates bearing an ester group (**2h** and **2i**) were also tolerated and no transesterified byproduct was detected. Reactions with nitrogen-containing aryl bromides **2j–2l** gave the desired products in high yields (**3j–3l**, 68–78% yield). Boryl substitution of the alkenyl bromide **2m** also proceeded in 58% yield without any silaborated byproduct. Surprisingly, the sterically hindered 1-bromo-2,6-dimethylbenzene **2n** and 9-bromo-anthracene **2o** afforded the borylated products in high yields (**3n** and **3o**, 85 and 72% yield, respectively). In addition, the sterically more congested 1-bromo-2,4,6-triisopropylbenzene **2p** also reacted to provide the borylation product **3p** in excellent yield (92% yield). It is noteworthy that boryl substitution of substrate **2p** has been reported as a difficult transformation even using diboron and transition-metal catalysts [9, 12, 49]. This boryl substitution reaction was also successfully applied to the reaction of alkyl bromide **2q** in dioxane at 100 °C to give the corresponding product **3q** in good yield with high B/Si selectivity (Scheme 2, total 82% yield, B/Si = 91:9).

Table 2. Substrate Scope of Boryl Substitution with PhMe₂Si–B(pin)/KOMe System

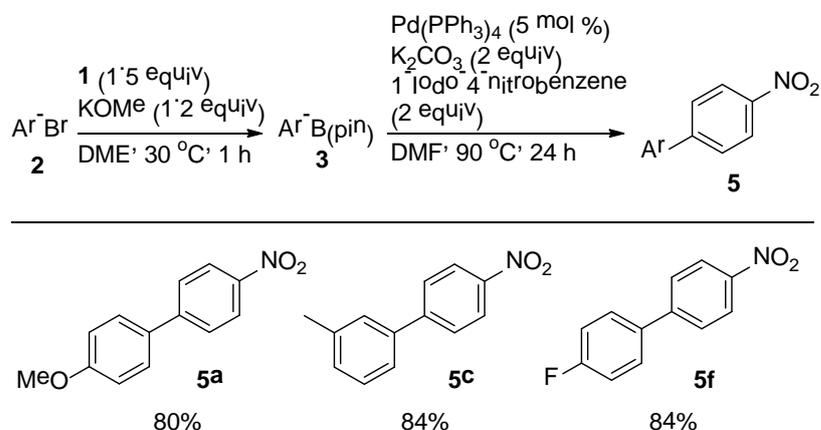


[^a] Isolated yield; [^b] NMR yield; [^c] GC yield

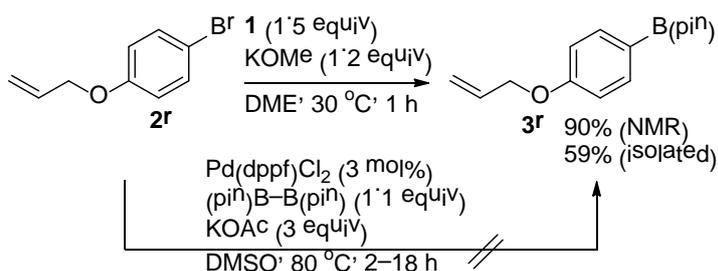


Scheme 2. Boryl Substitution Reaction with Alkyl Halide **2q**

We next examined sequential boryl substitution/Suzuki–Miyaura coupling procedures to show the practical utility of our reaction. Conventional Suzuki–Miyaura coupling conditions could be used after workup of the borylation without chromatographic purification of the arylboronate intermediates and afforded the corresponding cross coupling products in high yields (80–84% yields, Scheme 3). The utility of this boryl substitution reaction was further demonstrated by the reaction of the aryl halide **2r** having an allyloxy group, which is a functional group sensitive to the palladium-catalyzed borylation (Scheme 4). Generally, palladium (0) species react with any allyloxy group to generate π -allyl palladium species, which lead to the decomposition of the allyloxy group. In fact, the reaction of aryl halide **2r** under typical palladium-catalyzed borylation conditions [50] resulted in the decomposition of the substrate, whereas our boryl substitution method afforded the desired product **3r** in 90% yield.

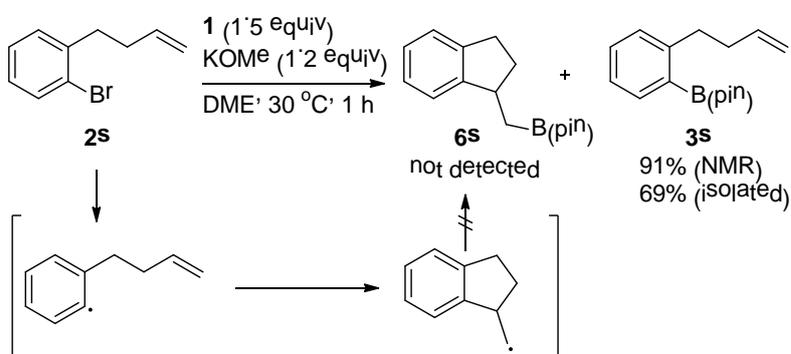


Scheme 3. Sequential Boryl Substitution and Suzuki–Miyaura Coupling^[a]

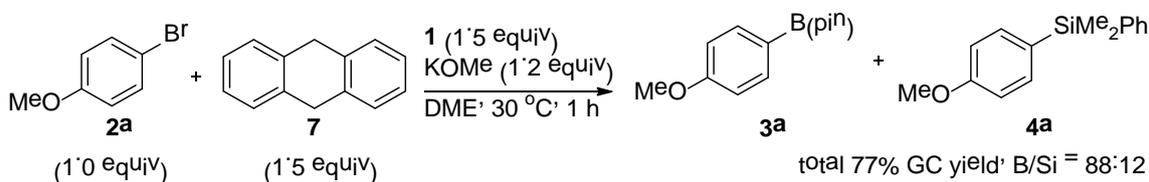


Scheme 4. Chemoselective Boryl Substitution of 4-Allyloxyphenyl Bromide **2r**

As for the reaction mechanism, we first investigated the possibility of aryl radical mediated mechanism. To probe this, the reaction of *o*-(3-butenyl)bromobenzene **2s** was conducted (Scheme 5). The corresponding aryl radical 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 [51]. The reaction of **2s** under the standard conditions afforded the acyclic borylated product **3s** in 91% yield, and no cyclic borylated product **6s** was detected. In addition, reaction of 4-bromoanisole **2a** in the presence of 1,9-dihydroanthracene **7**, which is a known radical scavenger, was carried out to find that no significant retardation in the reaction rate was observed (Scheme 6).



Scheme 5. Mechanistic Investigations into Aryl Radical Mediated Mechanism

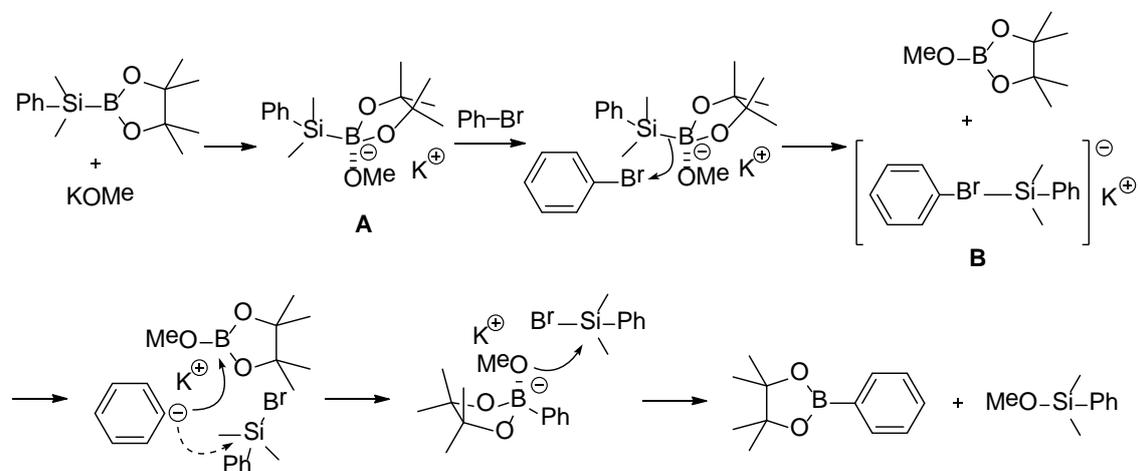


Scheme 6. Mechanistic Investigations with Radical Scavenger **7**

We next assumed that there was contamination by transition-metal impurities in the metal alkoxide reagents [52,53]. However, significant amounts of any transition-metal (Ni, Pd, Pt, Rh, Ru,

Au, Ag and Co) were not detected on the basis of the ICP-AES analysis [54]. In addition, the borylation reactions were repeated in the presence of transition-metal salts (5–10 mol %), but showed no acceleration in the reaction [46]. Control experiments with virgin reagents and new labwares conducted by another research group showed almost the same results (boryl substitution of **2a** under the same reaction conditions in Table 1, entry 3. 82% total GC yield; B/Si = 95:5). These results indicate that the boryl substitution reaction involves neither a transition-metal- nor aryl radical mediated mechanism.

From these results, we propose a possible reaction mechanism as shown in Scheme 7, which includes neither transition-metal nor radical mechanism. In this proposed mechanism, potassium methoxide first coordinates the boron atom of the silylborane **1** to give the silylborane/alkoxy base complex **A**, whose existence was suggested by the ^{11}B NMR experiment [25]. On the basis of the studies on the reactions of silyllithium species and organohalides reported by Strohmann and co-workers [55,56], the aryl anion species seems to be produced subsequently through the formation of the ate complex **B**, which is generated via nucleophilic attack of the silyl group to the Br atom of the aryl bromide [57–61]. Next, the aryl anion attacks the boron electrophile preferentially rather than silyl bromide to give the corresponding aryl pinacol borate, followed by the reaction of methoxide with the in situ generated silyl bromide. We observed the generation of dimethylmethoxyphenylsilane in this reaction, which is consistent with the proposed mechanism.



Scheme 7. Proposed Mechanism

Conclusion: We have achieved the first transition-metal-free boryl substitution of alkyl, alkenyl, and aryl halides with the silylborane **1** and alkoxy bases. This reaction tolerated a variety of functional groups including esters which are fragile in the presence of strong nucleophiles or basic reagents. This reaction is highly reactive; the borylation of unhindered substrates finished within 30 min. For more challenging, sterically-hindered aryl bromides, the reaction was completed within one hour at room temperature to give the corresponding borylated products in high yields. As for the reaction mechanism, the results of the preliminary investigations discounted catalysis due to transition-metal

contamination and aryl radical mediated process.

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solution was stirred for 3 h at 0 °C. After that, the mixture was added to the H₂O (100 mL), then extracted with Et₂O (50 mL). The organic layer was washed with water (50 mL x 2). The combined organic layer was then dried over MgSO₄, followed by evaporation. The crude product was purified by boric acid-impregnated silica-gel chromatography [48] to give borylated product **3a** (77% yield) as a colorless oil (Table 1, entry 1).

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