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Anomalous Reactivity of Silylborane: Transition-Metal-Free Boryl Substitution of Aryl, Alkenyl, and Alkyl Halides with Silylborane/Alkoxy Base Systems

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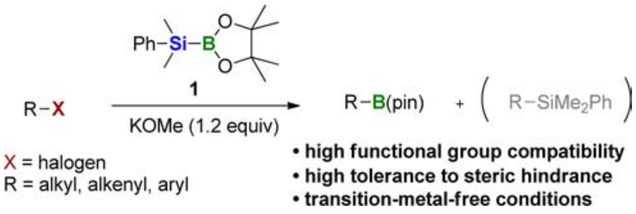
Supporting Information

ABSTRACT: An unexpected borylation of organic halides with a silyborane in the presence of an alkoxy base has been observed. This formal nucleophilic boryl substitution can be applied to a broad range of substrates with high functional group compatibility. Even sterically hindered aryl bromides afforded the corresponding boryl compounds in high yields. Preliminary mechanistic studies indicated that this boryl substitution is promoted by neither transition-metal contamination nor a radical-mediated process.

Arylboronates are recognized as essential synthetic building blocks because of their wide applicability to C−X (X = C, N, O) bond-forming reactions and ease of handling.[1] Reacting a carbon nucleophile such as an aryl Grignard or aryllithium reagent with a trialkylboronate is a common synthetic method for arylboronates.[1b,d,2] However, these reactions generally have low functional group compatibility because of the strong basicity and nucleophilicity of the reagents. Over the past two decades, transition-metal-catalyzed boryl substitution of aryl halides and arene C−H borylation with high functional group tolerance have been developed as complementary synthetic methods.[3] However, the high process cost and heavy-metal impurities in the products often make them unsuitable for pharmaceutical production.[4] To overcome this, several transition-metal-free borylation reactions such as the Sandmeyer-type borylation[5] and electrophilic arene C−H borylations[6] have been developed recently, but there are still limitations in terms of both the substrate scope and regioselectivity. Recently, we reported base-mediated silaboration of aromatic alkenes.[7,8] While studying the silaboration reaction, we found that the silylborane $PhMe_2Si-B(pin)$ (**1**) showed unexpected reactivity in combination with an alkoxy base: the formal nucleophilic borylation of aryl, alkenyl, and alkyl halides (Scheme 1).

This boryl substitution reaction is counterintuitive, as silyl substitution should be anticipated on the basis of the general reactivity of silylboranes. Kawachi, Tamao, and co-workers have reported that reacting a silylborane with a stoichiometric amount of strong base such as RLi, MeMgBr, or KO^tBu affords the silyl nucleophilic species.[9,10] Hoveyda and co-workers reported that a chiral N-heterocyclic carbene (NHC) can also activate silylboranes, enabling catalytic enantioselective silylation of α,β-unsaturated compounds.[11] These examples suggest that silylborane compounds generate the silyl nucleophile rather than the boryl nucleophile when a base or nucleophilic catalyst is used.[12,13] Herein we describe a novel, transition-metal-free boryl substitution of aryl, alkenyl, and alkyl halides with silylborane/base reagents. The reaction affords the desired borylation products in high yields with high borylation/silylation ratios.

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



First, we explored the reactions of *p*-bromoanisole (**2a**) with silylborane **1** under a variety of conditions (Table 1). No reaction occurred without a promoter (entry 1). Using KOMe in the reaction of **1** with **2a** afforded the counterintuitive boryl substitution product in high yield with an excellent borylation/silylation ratio (borylation product **3a**, 87% GC yield; isolated **3a**, 77%; total, 92% GC yield; B/Si = 95:5; entry 2). This reaction proceeded very rapidly, requiring only 15 min to reach completion at 30 °C, while comparable transition-metal-catalyzed borylations require several hours at 80−100 °C.[3b,c,e,f] Ethereal solvents are suitable for this boryl substitution (entries 2−7). The use of tetrahydrofuran (THF) afforded results similar to those for 1,2-dimethoxyethane (DME) (85% yield, B/Si = 94:6; entry 3), while both toluene and CH_2Cl_2 provided the product in lower yields (entries 4 and 5, respectively). When *N*,*N*-dimethylformamide (DMF) or MeOH was used, silylborane **1** was consumed completely, but no desired product was detected (entries 6 and 7). Next, the effects of reaction temperature were examined (entries 8 and 9). The reaction at a higher temperature of 50 °C gave results similar to those at 30 °C (87% yield, B/Si = 95:5; entry 8), whereas lowering the reaction temperature to 0 °C resulted in unfavorable B/Si selectivity in comparison with the reactions at 30 and 50 °C (83% yield, B/Si = 86:14; entry 9). The reaction performed at high concentration gave only

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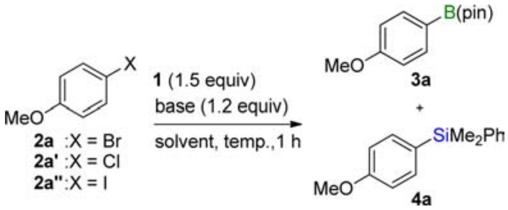
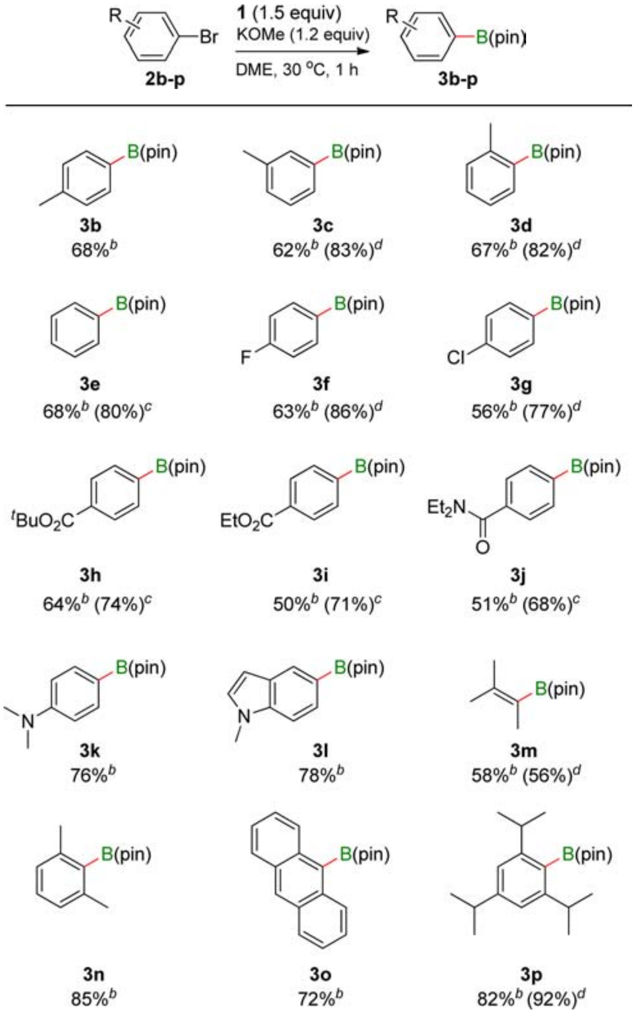
Table 1. Optimization of the Reaction Conditions for Boryl Substitution of Aryl Halides with PhMe$_2$Si−B(pin)/Base[a]



entry	X	solvent	base	temp. (°C)	yield (%)[b]	B/Si[c]
1	Br	DME	none	30	0	
2[d]	Br	DME	KOMe	30	92 (77)	95:5
3	Br	THF	KOMe	30	85	94:6
4	Br	toluene	KOMe	30	20	95:5
5	Br	CH_2Cl_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[e]	Br	DME	KOMe	30	87	92:8
11	Br	DME	LiOMe	30	0	
12	Br	DME	NaOMe	30	81	80:20
13	Br	DME	KO^{t}Bu	30	66	73:27
14	Br	DME	KOAc	30	0	
15	Br	DME	K_2CO_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] Reaction conditions: A mixture of **1** (0.75 mmol) and a base (0.6 mmol) in a solvent (5 mL) was stirred for 10 min at 30 °C, after which aryl halide **2** (0.5 mmol) was added. The resultant mixture was stirred for 1 h. [b] Total GC yield of **3a** and **4a**. [c] Ratio of borylated product to silylated product. [d] The isolated yield of **3a** is shown in parentheses. [e] The reaction was conducted under high-concentration conditions (0.5 mL of DME solvent).

Table 2. Substrate Scope of Boryl Substitution of Aryl Bromides Using the PhMe$_2$Si−B(pin)/KOMe System[a]

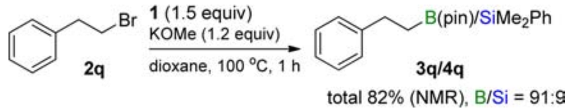


[a] Reaction conditions: A mixture of silylborane **1** (0.75 mmol) and KOMe (0.6 mmol) in DME (5 mL) was stirred for 10 min at 30 °C, after which aryl halide **2** (0.5 mmol). was added. The resultant mixture was stirred for 1 h at 30 °C. [b] Isolated yield. [c] GC yield. [d] NMR yield.

slightly inferior results (87% yield, B/Si = 92:8; entry 10). Bases other than KOMe proved to be inferior (entries 11−17). LiOMe provided no product (entry 11), and NaOMe resulted in a lower B/Si ratio (entry 12). Using KO^{t}Bu resulted in a significant decrease in the product yield and B/Si ratio (66%, B/Si = 73:27; entry 13). No reaction occurred with weaker bases such as KOAc, K_2CO_3, and KF (entries 14−16). The reaction with a strong organic base, 1,8-diazabicyclo[5.4.0]-undec-7-ene (DBU), also resulted in no reaction (entry 17). Finally, we investigated the effects of the halogen group. *p*-Chloroanisole (**2a′**) gave the product **3a** in lower yield, while *p*-iodoanisole (**2a″**) afforded the product with a yield and B/Si ratio comparable to those for **2a** (entries 18 and 19).

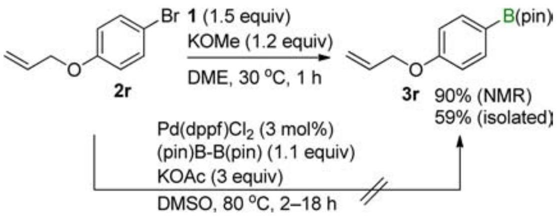
With the optimized conditions in hand, we examined the scope of the boryl substitution with various aryl bromides (Table 2). Neutral or electron-rich aryl bromides (**2b−e**) underwent the reaction to give **3b−e** in high yields. The substitution position of the methyl group in **2b−d** had no significant effect on the yield. Reactions with electron-deficient substrates **2f** and **2g** also gave the desired products (**3f** and **3g**, respectively) in good yields. Additionally, electron-deficient substrates containing an ester group (**2h** and **2i**) were also tolerated in this reaction, and no transesterified byproduct was detected. Reactions with nitrogen-containing aryl bromides **2j−l** afforded the desired borylation products **3j−l** in high yields (68−78%). Boryl substitution of alkenyl bromide **2m** also proceeded in 58% yield without any silaborated byproduct. Furthermore, sterically congested 1-bromo-2,6-dimethylbenzene (**2n**) and 9-bromoanthracene (**2o**) gave the corresponding borylated products **3n** and **3o** in high yields (85 and 72%, respectively). In addition, sterically demanding 1-bromo-2,4,6-triisopropylbenzene (**2p**) also reacted to give the borylation product **3p** in excellent yield (92% yield). It is noteworthy that boryl substitution of **2p** has been reported to be difficult even using diboron and transition-metal catalysts.[14] This boryl substitution system was also successfully applied to the reaction of alkyl bromide **2q** to give the corresponding product **3q** in good yield with high B/Si selectivity (**3q**, 75%; total, 82%; B/Si = 91:9; Scheme 2).

Scheme 2. Boryl Substitution Reaction with Alkyl Halide 2q

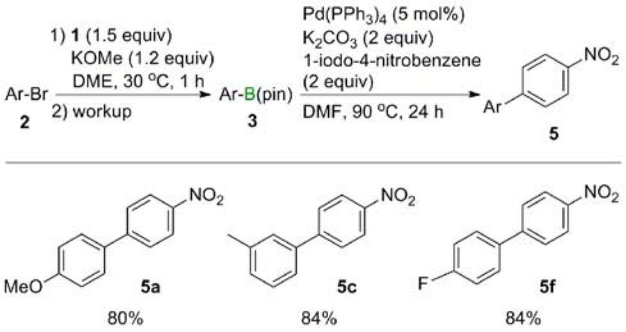


The usefulness of this boryl substitution reaction was further confirmed by the reaction of aryl halide **2r** containing an allyloxy group, which is sensitive to the palladium-catalyzed reaction (Scheme 3). Generally, Pd(0) species react with any allyloxy group to generate π-allylpalladium species, leading to the removal of the allyloxy group. In fact, the reaction of **2r** under typical palladium-catalyzed borylation conditions[15] resulted in the decomposition of the substrate, whereas our boryl substitution method gave the desired product **3r** in 90% yield. We also examined a sequential boryl substitution/Suzuki−Miyaura coupling procedure to demonstrate the practical utility of our reaction. Conventional Suzuki−Miyaura coupling conditions could be applied after workup of the borylation without chromatographic purification of the arylboronate intermediates and gave the corresponding cross-coupling products in high yields. (Scheme 4).

Scheme 3. Chemoselective Boryl Substitution of 4-Allyloxyphenyl Bromide (2r)



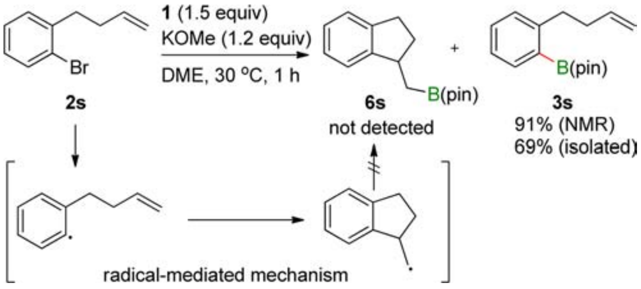
Scheme 4. Sequential Boryl Substitution and Suzuki−Miyaura Coupling[a]



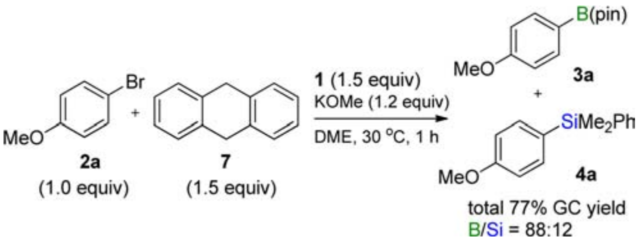
[a]Isolated yields are shown.

Finally, to investigate the reaction mechanism, we first assumed that there was some contamination by transition-metal impurities in the base. However, no significant amount of any transition metal (Ni, Pd, Pt, Rh, Au, Ag, Ir, Ru, or Co) was detected in the KOMe reagent.[16] In addition, repeating the borylation reaction in the presence of a transition-metal (Ni, Pd, Cu, Pt, Rh, Ag, Ir, Ru, Fe, or Co) salt showed no acceleration in the reaction (see the Supporting Information). Control experiments with virgin reagents and new labware conducted by another research group showed almost the same results (**3a** in THF: 82% total GC yield; B/Si = 95:5). We next explored the possibility of a radical-mediated mechanism by performing the reaction on *o*-(3-butenyl)bromobenzene (**2s**) (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.[17] 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, the reaction of 4-bromoanisole **2a** in the presence of 1,9-dihydroanthracene (**7**), a known radical scavenger, was conducted. No significant retardation in the reaction rate was observed (Scheme 6).

Scheme 5. Mechanistic Investigations of an Aryl-Radical-Mediated Mechanism



Scheme 6. Mechanistic Investigations with Radical Scavenger 7



These results indicate that the boryl substitution reaction involves neither a transition-metal- nor radical-mediated mechanism. As a possible alternative mechanism, we speculate that the reaction could be triggered by nucleophilic attack of the silyl nucleophile on the bromo group of the substrate followed by C−B bond formation (see the Supporting Information).[18] Further mechanistic studies will be required in order to verify this counterintuitive reactivity.

In summary, we have demonstrated the first transition-metal-free boryl substitution of aryl, alkenyl, and alkyl halides using silylborane **1** and an alkoxy base. This reaction tolerates a variety of functional groups, including esters, which are fragile in the presence of strong nucleophiles and basic reagents. This reaction is fast, as the borylation of unhindered substrates finished within 30 min. For more challenging, sterically hindered aryl bromides, the reaction reached completion within 1 h at room temperature, giving the corresponding boronates in high yields. As for the reaction mechanism, the results of the preliminary investigations discounted catalysis due to transition-metal contamination and any radical-mediated process. We are now trying to apply this borylation reaction to the synthesis of various organoboron compounds bearing a variety of substituents on the boron atom, including a diarylboryl moiety. Further investigations of the mechanism and synthetic applications of this reaction are also in progress.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental procedures, characterization of all new compounds, and the data assessing the effect of adding a transition-metal salt on the boryl substation reaction. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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