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Graphical Abstract

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Metal-free halogenation of arylboronate with *N*-halosuccinimide

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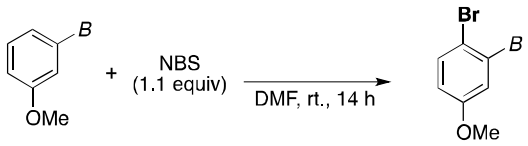
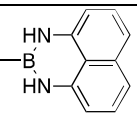
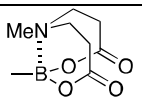
ABSTRACT

Efficient bromination and chlorination of aryl pinacol boronates was accomplished without the addition of metal reagent. The reaction proceeded efficiently with electron-rich arylboronates or heteroarylboronates in DMF or acetonitrile, to afford mono-, di-, or trihalogenated aryl pinacol boronates.

Functionalization of aryl boronic acids and esters has attracted great interest because the products are widely applicable to the synthesis of complex organic molecules.[1,2] Halogenated arylboronates, especially, are useful building blocks for the synthesis of arene-based pharmaceutical compounds through multiple Suzuki-Miyaura cross-coupling reactions.[3,4,5] Although the borylation of haloarenes was developed for the synthesis of haloarylboronates,[3,4] the reverse method, the halogenation of arylboronates, is less developed.[5,6] Difficulties in the halogenation of arylboronates result from the high reactivity of the C-B bond toward electrophiles, which results in *ipso*-substitution. Olah *et al*. reported the reaction of arylboronic acids with *N*-halosuccinimide (NBS) to afford haloarenes;[7] Szumigala *et al*. reported a similar reaction with *N*,*N*'-dibromo-5,5-dimethylhidantoin (DBH).[8] For this reason, studies on the halogenation of arylboronic acids or boronates have been rarely reported. In 1962, Kuivila reported the bromination of 3-anisylboronic acid with bromine in acetic acid.[5a] Recently, silver-mediated halogenation of arylboronic acids and gold-catalyzed halogenation of arylboronates were reported by Hall[5b] and Wang,[5c] respectively. These reactions were effective methods for the preparation of halogenated arylboronates. However, they required metal reagents to afford the desired products. The present report describes the development of a convenient and effective method for the synthesis of halogenated arylboronates without the addition of a metal reagent.

Table 1. Screening of boronic esters for bromination reactions



Entry	Borane	Result
1	—B(OH)$_2$	no reaction
2		no reaction
3		complex mixture
4	—BF$_3$K	complex mixture
5	—B(pin)	69%

First, the bromination of 3-anisylboronic acid derivatives with NBS as a bromonium cation source in DMF was examined (Table 1).[9] Unfortunately, boronic acid did not undergo bromination successfully (Table 1, entry 1). The DAN(1,8-

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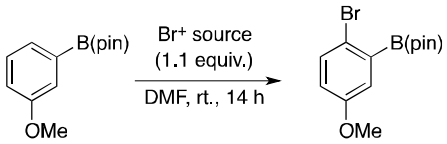
diaminonaphthalene)-protected boronic acid[10] also was recovered after reaction (Table 1, entry 2). Use of MIDA (*N*-methyliminodiacetic acid) boronate[11] (Table 1, entry 3) or trifluoroborate[12,13] (Table 1, entry 4) resulted in decomposition to afford a complex mixture of products. However, use of pinacol boronate produced pinacol 2-bromo-5-methoxyphenylboronate (**1**) in 69% yield (Table 1, entry 5).

Next, bromonium cation sources were investigated. DBH (Table 2, entry 2) and *N*-bromophthalimide (NBP) (Table 2, entry 3) acted as bromonium cation sources to afford **1**, albeit in lower yield.

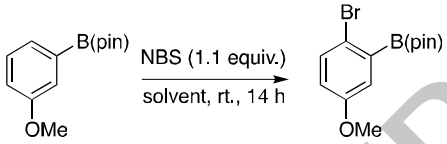
Table 2. Screening of brominum cation sources for bromination reactions.



Entry	Br^+	NMR yield (%)
1	NBS	81
2	DBH[a]	52
3	NBP	40

[a] 0.55 equiv.

Table 3. Screening of solvents for bromination reactions

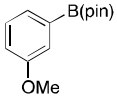
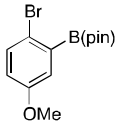
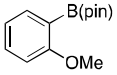
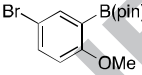
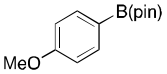
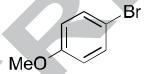
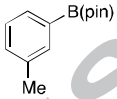
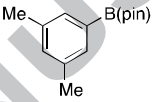
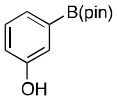
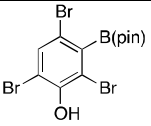
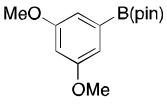
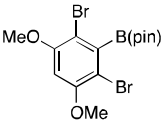
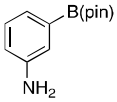
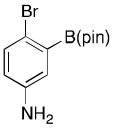
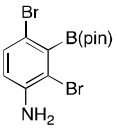
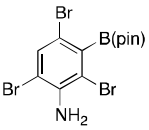
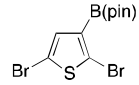
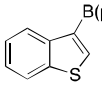
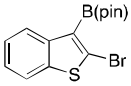


Entry	Solvent	NMR yield (%)
1	DMF	81 (69)[c]
2	CH_2Cl_2	19
3	hexane	no reaction
4	THF	38
5	EtOH	5
6	NMP	9
7	CH_3CN	80
8[a]	DMF	82
9[b]	DMF	93 (87)[c]

[a] NBS (1.5 equiv.) [b] NBS (2.2 equiv.)
[c] Isolated yield in parentheses

The effect of the solvent was important in promotion of the reaction (Table 3). Reaction in dichloromethane, which is a common solvent for electrophilic bromination of aromatic compounds, resulted in lower reactivity to give the product in 19% yield (Table 3, entry 2). The reaction performed in hexane did not proceed, and only pinacol 3-anisylboronate was recovered (Table 3, entry 3). In other solvents, such as THF, ethanol, and NMP (*N*-methylpyrrolidone), lower reactivity was observed (Table 3, entry 4-6). Reaction in acetonitrile was successful and afforded **1** in high yield (Table 3, entry 7). Addition of excess NBS improved the yield of **1** to 87% (Table 3, entry 9).

Table 4. Bromination of pinacol arylboronates[a]

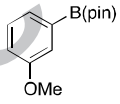
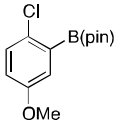
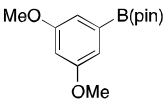
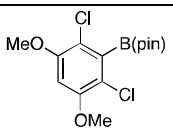
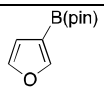
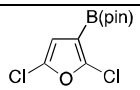
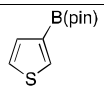
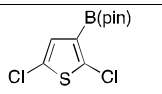
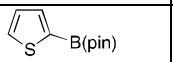
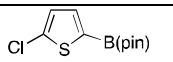
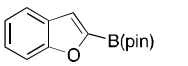
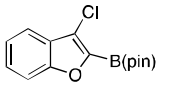
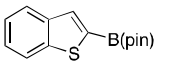
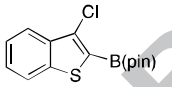
Entry	ArB(pin)	Product	Yield (%)
1[b]			87
2			39
3			(95)
4		-	0
5		-	0
6[c]			75
7[b]			90
8			50
9[b]			56
10[c]			91
11			13
12[b]			65
13[b]			38

[a] Reactions were performed using pinacol aryl borate (50 mg) and NBS (1.1 equiv) in DMF (1 mL) at rt for 14 h. [b] NBS (2.2 equiv.) [c] NBS (3.3 equiv.)

Substrate scope was then investigated (Table 4). Reaction of pinacol 2-anisylboronate succeeded to give pinacol 2-methoxy-5-bromophenylboronate in 39% yield (Table 4, entry 2). Reaction of pinacol 4-anisylboronate resulted in *ipso*-substitution to afford 4-bromoanisole (Table 4, entry 3). Arylboronates containing a slightly electron-rich substituent, such as pinacol 3-tolylboronate and pinacol 3,5-dimethylphenylboronate, failed to undergo a similar bromination (Table 4, entry 4-5). In contrast, bromination was successful with more electron-rich arylboronates to afford the corresponding products (Table 4, entry 6-13). Bromination of pinacol 3-hydroxyphenyl boronate gave the mixture of mono-, di-, and tribrominated compounds. Treatment of 3.3 equiv. of NBS afforded pinacol 2,4,6-tribromo-3-hydroxyphenylboronate in 75% yield (Table 4, entry 6). Reaction of pinacol 3,5-dimethoxyphenylboronate with 1.1 equiv. of NBS also could not be controlled and afforded a mixture of mono- and dibrominated products. Using 2.2 equiv. of NBS alleviated this problem, giving pinacol 2.6-dibromo-3-hydroxyphenylboronate and pinacol 2,6-dibromo-3,5-dimethoxypnehylboronate as the sole product in 90% yield (Table 4, entry 7). For pinacol 3-aminophenylboronate, the bromination reaction could be controlled by adjusting the NBS amount: 1.1 equiv. of NBS gave the monobrominated product in 50% yield (Table 4, entry 8), 2.2 equiv. of NBS produced the dibrominated product in 56% yield (Table 4, entry 9), and 3.3 equiv. of NBS produced the tribrominated product in 91% yield (Table 4, entry 10). Bromination of pinacol heteroarylboronates also could be accomplished through reaction with NBS to afford mono- or dibrominated compounds (Table 4, entry 11-13). Reaction of pinacol 3-thiophenylboronate with 1 equiv. of NBS resulted in a mixture of 2-brominated and 5-brominated products. Reaction with 2 equiv. of NBS gave pinacol 2,5-dibromo-3-thiopheneylboronate as the sole product.

Chlorination of aryl pinacol boronate was performed by treatment of NCS (*N*-chlorosuccinimide) in DMF. Chlorination was successful when using aryl pinacol boronates with highly electron-donating substituents or heteroaryl pinacol boronates. Some reactions were performed at elevated temperatures because the reactivity of NCS was slightly lower than that of NBS (Table 5, entry 2-3 and 5-7).

Table 5. Chlorination of aryl pinacol boronates[a]

Entry	ArB(pin)	Product	Yield
1			82
2[a,c]			87
3[b,c]			48
4[b]			66
5[c]			40
6[d]			39
7[d]			70

[a] Reactions were performed using pinacol arylborate (50 mg) and NCS (1.1 equiv) in DMF (1 mL) at rt for 14 h. [b] NBS (2.2 equiv.) [c] Reaction was performed at 100°C. [d] Reaction was performed at 130°C.

Iodination also was examined by reaction of NIS with 3-anisyl pinacol boronate. However, *ipso*-substitution occurred to give iodoanisole as the sole product.[6]

In conclusion, a general method for bromination and chlorination of pinacol arylboronates was developed. Although the substrates applicable to this reaction were limited, reactions proceeded without the need for a metal reagent, providing halogenated arylboronates that are difficult to synthesize by other methods.

Acknowledgments

The authors declare no competing financial interest.

References and notes

1. Hall, D. G. *Boronic Acids*; Wiley-VCH: Weinheim, 2005.
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14. **General Procedure**: To a solution of 3-anisyl pinacol borane (50 mg, 0.21 mmol) in DMF (1 mL) was added *N*-bromosuccinimide (82 mg, 0.46 mmol). After stirring at room temperature for 14 h, resultant solution was treated with 10% $Na_2S_2O_3$ aq. (10 ml) and was extracted with Et_2O (10 ml x 3). The combined organic phase was washed with H_2O (10 ml x 2) and brine (10 ml x 1) and dried over $MgSO_4$. After removal of solvent under reduced pressure, the residue was chromatographed on silica gel with Hexane to afford 2-bromo-5-methoxyphenyl pinacol borate (57.3 mg, 87% yield) as colorless oil