Ring-opening 1,3-arylboration of arylcyclopropanes mediated by BCl₃†

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Herein, we report a ring-opening 1,3-arylboration of aryl cyclopropanes using BCl₃ in the presence of arene nucleophiles. Formal 1,3-oxo arylation and 1,3-amino arylation of the arylcyclopropane via one-pot derivatization of the installed boron group were also achieved.

Cyclopropane derivatives are versatile building blocks in organic synthesis used frequently. Transformations utilizing their ring strain and unique reactivity have been actively studied. Among them, the ring-opening reaction is one of the important transformations that provide synthetically useful 1,3-functionalized molecules. The cyclopropane ring-opening strategy mainly utilizes donor–acceptor cyclopropanes due to their high reactivity. The transition metal-mediated process is also used for cyclopropanes bearing a chelating group that can coordinate to transition metals. On the other hand, the ring-opening 1,3-functionalization reaction of simply substituted cyclopropanes, such as aryl-substituted cyclopropane, has not been studied so much. Recently, ring-opening of cyclopropane by phosphine/borane frustrated Lewis pairs, 1,3-amino-fluorination by N–F reagents, 1,3-oxylfluorination and 1,3-difluorination by fluoriiodine reagents, 1,3-dioxgenation by hypervalent iodine reagent, oxo-amination by photoredox catalysis, and 1,3-hydroisilylation by silylum-ion have been successfully reported. However, the development of new ring-opening 1,3-functionalization reactions of simply substituted cyclopropanes is still significant due to the limited variety of functional groups that can be introduced.

Recently, the methods using boron halides as a borane source has been actively studied and applied to metal-free electrophilic borylation reaction with arenes, heteroarenes, alkynes, and alkenes. In this context, Shi and Houk have successfully developed a ring-opening 1,3-hydroboration of cyclopropanes using BBr₃ in the presence of PhSiH₃ (Scheme 1a). On the other hand, ring-opening 1,3-hydroarylation of monosubstituted cyclopropanes, including simply substituted cyclopropanes, was developed by Rowley and Moran. This reaction has been accomplished using catalytic TiOH in 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP) (Scheme 1b). Both methods are useful, but one functional group introduced is limited to a hydrogen atom. Inspired by these works, we sought to develop a new 1,3-functionalization of cyclopropanes. Herein, we report a ring-opening 1,3-arylboration of aryl cyclopropanes using BCl₃ in the presence of arene nucleophiles (Scheme 1c).

We began our study on the ring-opening 1,3-arylboration of cyclopropanes using cyclopropylbenzene (1a) and toluene (10 equiv.) as a model reaction (Table 1). The use of BCl₃ in CH₂Cl₂ at room temperature was not effective, and allylbenzene was mainly obtained (entry 1). Allylbenzene is considered to be produced through a formation of benzyl cation via C–C bond cleavage by BCl₃, a formation of homobenzyl cation by 1,2-hydride migration, and subsequent dissociation of the boron group. On the other hand, when the reaction was carried out at −30 °C, the formation of allylbenzene was suppressed, and the desired 1,3-arylborated product 2a was isolated in 11% yield via in situ formations of the pinacol boronate ester by treatment with pinacol and triethylamine (entry 2). Encouraged by these results, we further investigated different borane reagents for the reaction. When BBr₃ was used, 2a was not produced. Instead,
allylbenzene was formed even at low temperature (entry 3). The use of B-bromocatecholborane or BF$_3$·OEt$_2$ was also not effective (entries 4 and 5). From these results, BCl$_3$ was found to be an optimal reagent. Then, we investigated the reaction time and reaction temperature in detail. It was found that extending the reaction time to 48 hours improves the yield to 45% (entry 6). On the other hand, further studies on the reaction temperature did not improve the yield (entries 7 and 8). Finally, it was found that the amount of BCl$_3$ used is essential for improving the efficiency of the reaction (entry 9 and 10), and when 5 equivalent of BCl$_3$ was used, compound 2a was obtained in 81% yield. Regarding the amount of nucleophile, the yield was decreased when the amount of toluene was reduced to 5 equivalent (entry 11). Therefore, the optimal reaction conditions found for the 1,3-arylboration of arylcyclopropane involved treatment with BCl$_3$ (5 equiv.) in CH$_2$Cl$_2$ in the presence of toluene (10 equiv.).

With optimized conditions in hand, we investigated the substrate scope of this transformation (Table 2). p-tBu cyclopropylbenzene and 2-cyclopropylbenzene gave 2b and 2c in moderate to excellent yields. In contrast, p-PhO cyclopropylbenzene gave only a 16% yield, showing that the oxygen atom in the substrate could not be preferable for the reaction, probably due to the high affinity of oxygen atom toward BCl$_3$. On the other hand, bromo or chloro substituted aryl cyclopropanes worked well (2e, 2f). We also studied the scope of nucleophiles with 1a. The reactions using benzene were first examined, but it was found that benzene gave a complex mixture (not shown in table). It is probably because the nucleophilicity of cyclopropylbenzene was relatively higher than that of benzene. Therefore, we focused on a series of alkyl-substituted benzenes. p-Xylene, mesitylene, p-Et benzene, p-tBu benzene, and biphenyl provided the corresponding products 2g–2k in good yield. The reaction with 1,2,3,4-tetrahydro-1H-naphthalene also proceeded to give 2l regioselectively.

![Scheme 2](image.png)

Scheme 2: Formal 1,3-oxy arylation and 1,3-amino arylation. Conditions for 4: 1a (0.20 mmol), BCl$_3$ (1.0 mmol), CH$_2$Cl$_2$ (1.2 mL), 30 °C, 48 h then 2 M NaOH/30% H$_2$O$_2$ (1.5 mL, 1:1 v/v), 0 °C, 3 h; conditions for 5: 1a (0.20 mmol), BCl$_3$ (1.0 mmol), toluene (2.0 mmol), CH$_2$Cl$_2$ (1.2 mL), 30 °C, 48 h, then evaporation, PhCH$_2$N$_3$ (0.4 mmol), CH$_2$Cl$_2$ (1.5 mL), rt, 2 h.

### Table 1: Study of reaction conditions

| Entry | Reagent (equiv.) | Temp. (°C) | Time (h) | Yield (%) |
|-------|-----------------|------------|----------|-----------|
| 1$^b$ | BCl$_3$ (1.1)   | rt         | 2        | Trace     |
| 2     | BCl$_3$ (1.1)   | −30        | 5        | 11        |
| 3     | BBr$_3$ (1.1)   | −30        | 10       | N.D.$^c$  |
| 4$^b$ | $B$-Bromocatecholborane (1.1) | −30 | 10 | N.R.$^d$ |
| 5$^b$ | BF$_3$·OEt$_2$ (1.1) | −30 | 10 | N.R.$^d$ |
| 6     | BCl$_3$ (1.1)   | −30        | 48       | 45        |
| 7     | BCl$_3$ (1.1)   | −20        | 48       | 31        |
| 8     | BCl$_3$ (1.1)   | −40        | 48       | Trace     |
| 9     | BCl$_3$ (3.0)   | −30        | 48       | 66        |
| 10    | BCl$_3$ (5.0)   | −30        | 48       | 81        |
| 11$^c$| BCl$_3$ (5.0)   | −30        | 48       | 62        |

$^a$ p : o = 20 : 1. $^b$ Pinacol and NEt$_3$ were not treated. $^c$ Not detected. $^d$ No reaction. $^e$ Toluene (5 equiv.).

### Table 2: Scope of aryl cyclopropanes

| Entry | Reagent (equiv.) | Temp. (°C) | Time (h) | Yield (%) |
|-------|-----------------|------------|----------|-----------|
| 1     | BCl$_3$ (5.0)   | −30        | 48       | 81        |
| 2     | BCl$_3$ (1.1)   | −30        | 10       | 45        |
| 3     | BCl$_3$ (1.1)   | −40        | 48       | Trace     |
| 4     | BCl$_3$ (1.1)   | −30        | 48       | 66        |
| 5     | BCl$_3$ (5.0)   | −30        | 48       | 62        |

$^a$ Ratio of p : o. $^b$ Ratio of β : α.

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yield.\textsuperscript{14} It should be noted that 3,3-diaryl-propylamine is a structural motif found in some pharmaceuticals such as fen-dilline.\textsuperscript{13} These one-pot transformations can be considered as a formal 1,3-oxo arylation or 1,3-amino arylation of the arylcyclopropane, which has not been reported so far.

A possible reaction mechanism was depicted in Scheme 3. Given the reported paper,\textsuperscript{11} this ring-opening 1,3-arylboration is suggested to proceed in a stepwise manner. That is, the treatment of BCl\textsubscript{3} to aryl cyclopropane could generate a zwitterionic intermediate i. The following nucleophilic addition of an arene to benzylic cation could give intermediate ii, which is transformed to pinacol borate by the reaction with pinacol and triethylamine.

In summary, we have developed a method for the 1,3-arylboration of arylcyclopropanes to provide 3,3-diaryl-propyl boronic esters for the first time. It was found that BCl\textsubscript{3} was optimal as the boron source in the presence of arene nucleophiles. The formal 1,3-oxo arylation and 1,3-amino arylation of the arylcyclopropane via one-pot derivatization of the installed boron group were also achieved. A full account of these studies will be reported in due course.

**Conflicts of interest**

There are no conflicts to declare.

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