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Ring-opening 1,3-arylboration of arylcyclopropanes mediated by BCl_3 †

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Herein, we report a ring-opening 1,3-arylboration of aryl cyclopropanes using BCl_3 in the presence of arene nucleophiles. Formal 1,3-oxy arylation and 1,3-amino arylation of the arylcyclopropane *via* one-pot derivatization of the installed boron group were also achieved.

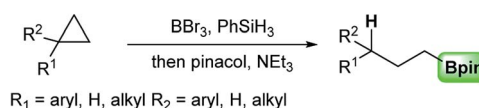
Cyclopropane derivatives are versatile building blocks in organic synthesis used frequently. Transformations utilizing their ring strain and unique reactivity have been actively studied.^{1–3} Among them, the ring-opening reaction is one of the important transformations that provide synthetically useful 1,3-functionalized molecules. The cyclopropane ring-opening strategy mainly utilizes donor–acceptor cyclopropanes due to their high reactivity.² The transition metal-mediated process is also used for cyclopropanes bearing a chelating group that can coordinate to transition metals.³ On the other hand, the ring-opening 1,3-functionalization reaction of simply substituted cyclopropane, such as aryl-substituted cyclopropane, has not been studied so much. Recently, ring-opening of cyclopropane by phosphine/borane frustrated Lewis pairs,⁴ 1,3-amino-fluorination by N–F reagents,⁵ 1,3-oxyfluorination and 1,3-difluorination by fluoriodine reagents,⁶ 1,3-dioxygenation by hypervalent iodine reagent,⁷ oxo-amination by photoredox catalysis,⁸ and 1,3-hydrosilylation by silylium-ion⁹ 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.¹⁰ In this context, Shi and Houk have successfully developed a ring-opening 1,3-hydroboration of cyclopropanes using BBr_3 in the presence of PhSiH_3 (Scheme 1a).¹¹ 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 TfOH in 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP) (Scheme 1b).¹² Both methods are useful, but one functional group introduced is

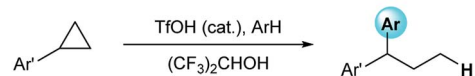
limited to a hydrogen atom. Inspired by these works, we sought to develop a new 1,3-functionalization of cyclopropanes. Herein, we report a ring-opening 1,3-arylboration of aryl cyclopropanes using BCl_3 in the presence of arene nucleophiles (Scheme 1c).

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 BCl_3 in CH_2Cl_2 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 BCl_3 , a formation of homobenzyl cation by 1,2-hydride migration, and subsequent dissociation of the boron group.¹³ On the other hand, when the reaction was carried out at $-30\text{ }^\circ\text{C}$, the formation of allylbenzene was suppressed, and the desired 1,3-arylboration product **2a** was isolated in 11% yield *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 BBr_3 was used, **2a** was not produced. Instead,

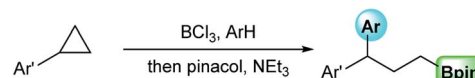
a. 1,3-hydroboration (Shi and Houk et al., 2018)



b. 1,3-hydroarylation (Rowley and Moran et al., 2018)



c. 1,3-arylboration (This work)



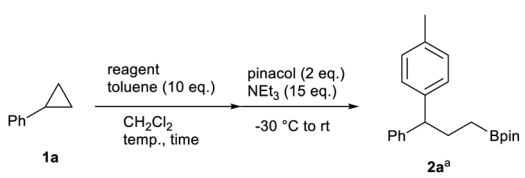
Scheme 1 1,3-Functionalization reactions of arylcyclopropanes.

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Table 1 Study of reaction conditions



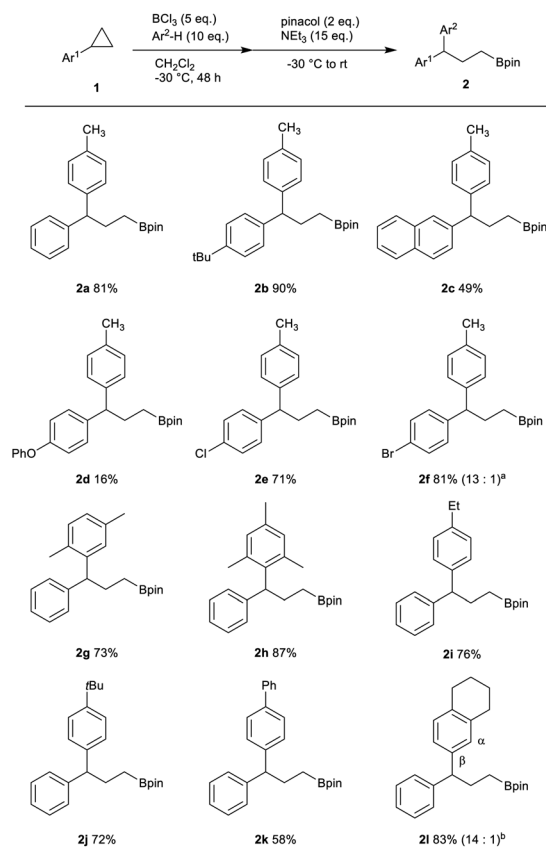
Entry	Reagent (equiv.)	Temp. (°C)	Time (h)	Yield (%)
1 ^b	BCl ₃ (1.1)	rt	2	Trace
2	BCl ₃ (1.1)	-30	5	11
3	BBr ₃ (1.1)	-30	10	N.D. ^c
4 ^b	<i>B</i> -Bromocatecholborane (1.1)	-30	10	N.R. ^d
5 ^b	BF ₃ ·OEt ₂ (1.1)	-30	10	N.R. ^d
6	BCl ₃ (1.1)	-30	48	45
7	BCl ₃ (1.1)	-20	48	31
8	BCl ₃ (1.1)	-40	48	Trace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

^a *p* : *o* = >20 : 1. ^b Pinacol and NEt₃ were not treated. ^c Not detected. ^d No reaction. ^e Toluene (5 equiv.).

allylbenzene was formed even at low temperature (entry 3). The use of *B*-bromocatecholborane or BF₃·OEt₂ was also not effective (entries 4 and 5). From these results, BCl₃ 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 BCl₃ used is essential for improving the efficiency of the reaction (entry 9 and 10), and when five equivalent of BCl₃ 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 BCl₃ (5 equiv.) in CH₂Cl₂ in the presence of toluene (10 equiv.).

With optimized conditions in hand, we investigated the substrate scope of this transformation (Table 2). *p*-*t*Bu cyclopropylbenzene and 2-cyclopropylnaphthalene 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 BCl₃. 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*-

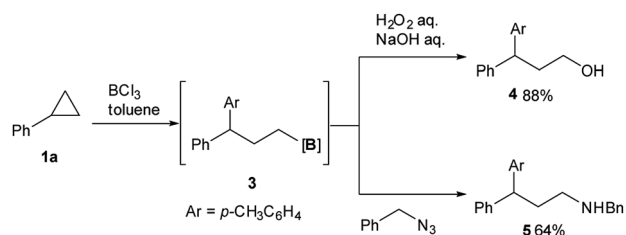
Table 2 Scope of aryl cyclopropanes



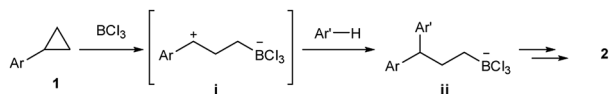
^a Ratio of *p* : *o*. ^b Ratio of β : α .

*t*Bu benzene, and biphenyl provided the corresponding products **2g**–**2k** in good yield. The reaction with 1,2,3,4-tetrahydronaphthalene also proceeded to give **2l** regioselectively.

One-pot derivatization using the installed boron group was also studied in addition to converting it into pinacol boronic esters for isolation. As shown in Scheme 2, oxidative workup of the C–B bond using hydrogen peroxide under basic conditions readily furnished alcohol **4** in excellent yield from **1a**. Also, the treatment of **3** with benzyl azide gave secondary amine **5** in 64%



Scheme 2 Formal 1,3-oxy arylation and 1,3-amino arylation. Conditions for **4**: **1a** (0.20 mmol), BCl₃ (1.0 mmol), toluene (2.0 mmol), CH₂Cl₂ (1.2 mL), -30 °C, 48 h then 2 M NaOH/30% H₂O₂ (1.5 mL, 1 : 1 v/v), 0 °C, 3 h; conditions for **5**: **1a** (0.20 mmol), BCl₃ (1.0 mmol), toluene (2.0 mmol), CH₂Cl₂ (1.2 mL), -30 °C, 48 h, then evaporation, PhCH₂N₃ (0.4 mmol), CH₂Cl₂ (1.5 mL), rt, 2 h.



Scheme 3 Proposed nucleophilic ring-opening of arylcyclopropanes.

yield.¹⁴ It should be noted that 3,3-diaryl-propylamine is a structural motif found in some pharmaceuticals such as fendilline.¹⁵ These one-pot transformations can be considered as a formal 1,3-oxy 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,¹¹ this ring-opening 1,3-arylboration is suggested to proceed in a stepwise manner. That is, the treatment of BCl_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_3 was optimal as the boron source in the presence of arene nucleophiles. The formal 1,3-oxy 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.

Acknowledgements

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References

- For reviews, see: (a) H. N. C. Wong, M. Y. Hon, C. W. Tse and Y. C. Yip, *Chem. Rev.*, 1989, **89**, 165–198; (b) O. G. Kulinkovich, *Chem. Rev.*, 2003, **103**, 2597–2632.
- For reviews, see: (a) H.-U. Reissig and R. Zimmer, *Chem. Rev.*, 2003, **103**, 1151–1196; (b) M. A. Cavitt, L. H. Phun and S. France, *Chem. Soc. Rev.*, 2014, **43**, 804–818; (c) T. F. Schneider, J. Kaschel and D. B. Werz, *Angew. Chem., Int. Ed.*, 2014, **53**, 5504–5523; (d) H. K. Grover, M. R. Emmett and M. A. Kerr, *Org. Biomol. Chem.*, 2015, **13**, 655–671; (e) S. J. Gharpure and L. N. Nanda, *Tetrahedron Lett.*, 2017, **58**, 711–720; (f) P. Singh, R. K. Varshnaya, R. Dey and P. Banerjee, *Adv. Synth. Catal.*, 2020, **362**, 1447–1484.
- For reviews, see: (a) M. H. Shaw and J. F. Bower, *Chem. Commun.*, 2016, **52**, 10817–10829; (b) L. Souillart and N. Cramer, *Chem. Rev.*, 2015, **115**, 9410–9464; (c) M. Rubin, M. Rubina and V. Gevorgyan, *Chem. Rev.*, 2007, **107**, 3117–3179.
- J. G. M. Morton, M. A. Dureen and D. W. Stephan, *Chem. Commun.*, 2010, **46**, 8947–8949.
- C. R. Pitts, B. Ling, J. A. Snyder, A. E. Bragg and T. Lectka, *J. Am. Chem. Soc.*, 2016, **138**, 6598–6609.
- (a) N. O. Ilchenko, M. Hedberg and K. J. Szabó, *Chem. Sci.*, 2017, **8**, 1056–1061; (b) S. M. Banik, K. M. Mennie and E. N. Jacobsen, *J. Am. Chem. Soc.*, 2017, **139**, 9152–9155.
- M. H. Gieuw, Z. Ke and Y.-Y. Yeung, *Angew. Chem., Int. Ed.*, 2018, **57**, 3782–3786.
- L. Ge, D.-X. Wang, R. Xing, D. Ma, P. J. Walsh and C. Feng, *Nat. Commun.*, 2019, **10**, 4367.
- A. Roy, V. Bonetti, G. Wang, Q. Wu, H. F. T. Klare and M. Oestreich, *Org. Lett.*, 2020, **22**, 1213–1216.
- For reviews see: (a) M. J. Ingleson, *Synlett*, 2012, **23**, 1411–1415; (b) A. Issaian, K. N. Tu and S. A. Blum, *Acc. Chem. Res.*, 2017, **50**, 2598–2609; (c) Y. Li and X.-F. Wu, *Angew. Chem., Int. Ed.*, 2020, **59**, 1770–1774 and references therein. Also, see: (d) A. J. Warner, J. R. Lawson, V. Fasano and M. J. Ingleson, *Angew. Chem., Int. Ed.*, 2015, **54**, 11245–11249; (e) A. J. Warner, A. Churn, J. S. McGough and M. J. Ingleson, *Angew. Chem., Int. Ed.*, 2017, **56**, 354–358; (f) Y. Wei, D. Liu, X. Qing and L. Xu, *Asian J. Org. Chem.*, 2017, **6**, 1575–1578; (g) C.-H. Yang, Y.-S. Zhang, W.-W. Fan, G.-Q. Liu and Y.-M. Li, *Angew. Chem., Int. Ed.*, 2015, **54**, 12636–12639.
- D. Wang, X.-S. Xue, K. N. Houk and Z. Shi, *Angew. Chem., Int. Ed.*, 2018, **57**, 16861–16865.
- E. Richmond, J. Yi, V. D. Vuković, F. Sajadi, C. N. Rowley and J. Moran, *Chem. Sci.*, 2018, **9**, 6411–6416.
- Z.-Y. Zhang, Z.-Y. Liu, R.-T. Guo, Y.-Q. Zhao, X. Li and X.-C. Wang, *Angew. Chem., Int. Ed.*, 2017, **56**, 4028–4032.
- H. C. Brown, A. M. Salunkhe and B. Singaram, *J. Org. Chem.*, 1991, **56**, 1170–1175.
- D. I. B. Kerr, J. Ong, N. M. Puspawati and R. H. Prager, *Eur. J. Pharmacol.*, 2002, **451**, 69–77.