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C-C Borylation

Mild Ring-Opening 1,3-Hydroborations of Non-Activated Cyclopropanes

Di Wang, Xiao-Song Xue, Kendall N. Houk*, and Zhuangzhi Shi*

Abstract: The Brown hydroboration reaction, first reported in 1957, is the addition of B-H across an olefin in an anti-Markovnikov fashion. Here, we solved a long standing problem on mild 1,3hydroborations of non-activated cyclopropanes. A three-component system including cyclopropanes, boron halides and hydrosilanes has been developed for borylative ring-opening of cyclopropanes following anti-Markovnikov's rule under mild reaction conditions. Density functional theory (M06-2X) calculations show that the preferred pathway involves a cationic boron intermediate that is quenched by hydride transfer from the silane.

Cyclopropanes are a fundamentally important class of compounds not only because such small rings are found in many biologically active compounds but also because a broad range of pharmaceutical and agrochemical agents are synthesized from cyclopropanes, as they can serve as useful synthetic building blocks.^[1] The inherent ring strain present in small rings is frequently used for ring-opening reactions, many of which are not readily accessible by other conventional methods.^[2] Most of the existing cyclopropane ringopening approaches have relied on the specific functional group assistance, including 1) polarizing one of the C-C bonds through the attachment of an activated donor-acceptor cyclopropane,^[3] and 2) the attachment of directing groups that favour oxidative addition by a transition metal to form metallacyclobutane intermediates (Figure 1a).^[4] Although non-activated cyclopropanes are the most common three-membered ring systems found in nature, methods for the selective ring-opening of them remain scarce.^[5] Some elegant research works have recent demonstrated that they could undergo 1,3-addition of B(C₆F₅)₃/⁷Bu₃P,^[6] 1,3-aminofluorination,^[7] 1,3difluorination,^[8] 1,3-deoxygenation^[9] and elimination^[10] reactions. Nevertheless, the development of new systems for efficient opening/functionalization of these compounds under mild and environmentally friendly conditions is still in high demand.

Alkylboronic esters play important roles in a variety of fields ranging from material science to drug discovery and organic synthesis.^[11] The well-known Brown hydroboration of olefins is a classic transformation to synthesize them.^[12] Hydroboration with HBR₂ (R = H, alkyl et al.) typically occurs in an anti-Markovnikov manner. It proceeds via a four-membered concerted transition state: the hydrogen and the boron atoms added on the same face of the double bond (Figure 1b).^[13] However, such a pathway for the hydroboration of cyclopropanes is very sluggish.^[14] High reaction temperatures and poor functional group compatibility make this transformation less practical. Because boron halides were known to electrophilic borylation with arenes, heteroarenes,^[15] alkynes^[16]

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a) General Strategies for Ring Opening of Cyclopropanes:





Figure 1. Ring-opening reactions of cyclopropanes

BBra + PhSil

and alkenes,^[17] we envisioned that the alkene-like π -donating properties of non-activated cyclopropanes could take place the similar electrophilic ring-opening and borylation. Herein, we describe the discovery of a mild three-component system for the ring-opening 1,3-hydroboration of non-activated cyclopropanes as well as the simplest cyclopropane gas under a balloon pressure, using BBr₃ as a boron source and PhSiH₃ as an external hydride source (Figure 1c). Through mechanistic experiments and density functional theory (DFT) calculations, we identified a stepwise pathway for this transformation, which allows high reactivity at room temperature.

We began our investigation by monitoring the reactivity of 2-(1methylcyclopropyl)naphthalene (1a) in the presence of boron Lewis acids (Table 1). The reaction was found to be facile with 1.2 equivalents of BBr3 as a boron source in the presence of PhSiH3 as a hydride source. In DCM at room temperature for 1 hour, 4,4,5,5tetramethyl-2-(3-(naphthalen-2-yl)butyl)-1,3,2-dioxaborolane (2a) is formed in 92% GC yield after pinacol protection. PhSiH₃ is crucial for high conversion (entry 2). Inorganic reducing agents such as NaBH₄ and LiAlH₄ and other hydrosilanes such as Et₃SiH and Ph2MeSiH were also effective and afforded boronate 2a in 48-63% yields as the only ring-opened product (entries 3-6). The addition of BCl₃ also gave desired product 2a in 80% yield (entry 7), but BF₃ did not work in this reaction (entry 8). Further exploration showed that the common reagents applied in Brown hydroborations (BH3'THF and HBBr2'Me2S) were completely ineffective in our reaction, suggesting 2a is formed by a different pathway (entries 9 and 10).

With the optimal conditions in hand, we examined the scope of this 1,3-hydroboration reaction (Table 2). Substrates containing spiro cyclopropanes with an indane or tetralin scaffold (2b-c) were all rapidly ring-opened, and the corresponding pinacol boronate esters were isolated in excellent yields. Halogen substituents (F, Cl, Br and I) work well under the reaction conditions (2d-h), highlighting the potential of this process in combination with further conventional cross-coupling transformations. While the Odemethylation process with BBr3 is well documented, substrate 1i bearing a methoxy group is compatible with this process, affording

desired product **2i** in 55% yield. The reaction of 1,1diphenylcyclopropane (**1j**) in our system afforded desired **Table 1.** Reaction Optimization^[a]



Entry	Variation from the "standard conditions"	Yield of 2a (%) ^[b]
1	none	92 (81) ^[c]
2	without PhSiH ₃	trace
3	NaBH ₄ instead of PhSiH ₃	48
4	LiAlH ₄ instead of PhSiH ₃	55
5	Et ₃ SiH instead of PhSiH ₃	52
6	Ph ₂ MeSiH instead of PhSiH ₃	63
7	BCl ₃ instead of BBr ₃	80
8	BF ₃ ·Et ₂ O instead of BBr ₃	0
9	BH ₃ ·THF instead of BBr ₃ + PhSiH ₃	0
10	HBBr ₂ ·Me ₂ S instead of BBr ₃ + PhSiH ₃	0

[a] Conditions: All reactions were run at a 0.20-mmol scale in 1.0 mL of DCM at room temperature for 1 hour, and then pinacol (0.6 mmol) in Et₃N was added, and the mixture was stirred for another 1 hour. [b] GC yield. [c] Isolated yield.

product 2i in 92% yield. Boronates 2k and 2l were obtained in good yields from 1,1-arylalkylcyclopropanes after the ring-opening reactions. 1,1-Dialkylcyclopropanes 1m-o could also be subjected to our reaction conditions and desired products 2m-o were obtained in good yields after the ring-opening/hydroboration reaction. Notably, this reaction is not limited to cyclopropanes with a quaternary carbon centre. Monosubstituted cyclopropanes 1p-v bearing aryl, benzyl and alkyl groups worked well in this protocol and gave corresponding products 2p-v with good yields and excellent regioselectivity. Among these substrates, those containing Br (2s), OPh (2t), SPh (2u) and carbazole (2v) functionalities were well tolerated. Ring-opening and borylation of fused 1,2-disubstituted cyclopropane 1w occurred most favourably at the secondary methylene position, and ring expansion products were not observed. Trans-1,2-alkylarylcyclopropane 1x was regioselectively converted into 2x in 60% yield. However, cis-1,2-diphenylcyclopropane (1y) was transformed into product 2y by cleavage of the most sterically hindered σ bond. This mild hydroboration procedure can also be utilized in late-stage functionalization of complexed biologically active molecules. The investigation was started with the preparation of cyclopropane 1z from estrone. Then, 1z was subjected to this developed method to produce 2z in 56% isolated yields with good diastereoselectivity.

The activation of small molecules has been an increasingly popular area of research over recent years.[18] C-H borylation of small molecules such as methane,^[19] ethane^[19a] and cyclopropanes^[20] recently. However, have been developed C-C bond cleavage/borylation of small molecules remains a maior challenge.^[21] Having established optimal reaction conditions, we found that the 1,3-hydroboration of cyclopropane gas (3) under the pressure generated by a balloon could produce "PrBpin (4) in 71% yield (Scheme 1).

Compared to traditional Brown hydroborations of olefins, the value of a 1,3-hydroboration of cyclopropanes is highlighted by the fact that the corresponding product contains an additional methylene substituent. As shown in Scheme 2, dehydroabietic acid (5) with a carboxylic acid group readily produce olefin 6 and cyclopropane 7 in good yields. Not surprisingly, ring-opening of compound 7 on a gram-scale results in boronate 8 with excellent yield. As noted at the outset, the boronate group is an extremely versatile intermediate in

organic synthesis because it can be converted into other important compounds by reactions such as Brown oxidation (9a), amination **Table 2.** Substrate Scope^[a]



[a] Reaction Conditions: 1 (0.50 mmol), BBr₃ (0.60 mmol), PhSiH₃ (0.60 mmol) in DCM (2.5 mL) at room temperature, 1 hour; then add pinacol (1.5 mmol) in Et₃N was added, and the reaction was stirred for an additional 1 hour. [b] Using 1 (0.55 mmol), BBr₃ (0.50 mmol). [c] Using 1 (0.50 mmol), BBr₃ (1.10 mmol). [d] Determined by crude ¹H NMR.

(9b), arylation (9c), heteroarylation (9d), and vinylation (9e) reactions (For details, see supporting information).



Scheme 1. 1,3-Hydroboration of Cyclopropane.

Several experiments were conducted to provide insight into the potential mechanism of this transformation (Scheme 3). When the reaction of 1a is conducted with PhSiD₃ under standard reaction conditions, the D label is nearly fully incorporated into 2a (84% yield, 98% D). This observation confirmed that the hydrosilane is

the sole source of the hydrogen atom in the product (Scheme 3a). We further employed (R, R)-**1x** under the standard reaction



Scheme 2. Derivatization of 1,3-Hydroboration Products.

conditions, and desired product (*R*)-2x was formed in 62% yield with 58% ee. As the reaction temperature was gradually reduced, the enantioselectivity of the product increased to 93% (Scheme 3b). To further explore this process, PhSiD₃ was added to the above reaction, and the hydrogen on the chiral carbon was deuterated. Moreover, the ratio of deuteration is consistent with the racemization product. These results suggest that *in situ*-formed benzylic carbon cations should be intermediates in these reactions and that 1,2-H migration is likely to occur during the C–C cleavage process (Scheme 3c).



Scheme 3. Mechanistic Experiments.

To better understand the mechanism of the 1,3-hydroboration of cyclopropanes, DFT calculations were performed on the model reaction of cyclopropylbenzene and BBr₃.^[22] As shown in Figure 2, the C-C cleavage of cyclopropylbenzene promoted by BBr3 to give benzylic cation IN1 via TS1 requires a barrier of 19.8 kcal/mol. The benzylic carbon abstracts a hydride from PhSiH₃ through TS2 with a barrier of 9.1 kcal/mol relative to IN1. Such a barrier would allow the benzylic carbon to undergo 1,2-H migration, which has a barrier of only 6.3 kcal/mol. This is in line with the experimental observation of the racemized hydroboration product in the hydroboration of chiral cyclopropane 1x. Based on the computed energy profile of the overall reaction pathway, the C-C cleavage is the rate-determining step, with an overall activation free energy of 19.8 kcal mol⁻¹. This is consistent with the relatively mild conditions required for the reaction. Notably, the calculated activation free energy for the hydroboration of cyclopropylbenzene by BH₃ via a concerted process is as high as 28.7 kcal/mol (TS1').^[12]

CPCM(CH₂Cl₂)-M06-2X/6-311++G(d,p)//CPCM(CH₂Cl₂)-B3LYP/6-31G(d) Δ G: kcal mol⁻¹



Figure 2. DFT-Computed Potential Energy Profile for the Model Reaction Between Cyclopropylbenzene and BBr₃ (standard state, 1 mol L⁻¹).

In conclusion, we have discovered a direct, catalyst-free method for the 1,3-hydroboration of non-activated cyclopropanes under mild reaction conditions. With the developed system in hand, the first conversion of cyclopropane to *n*-propyl boronic esters has been achieved. The reaction proceeds via a stepwise pathway through energetically favourable transition states instead of a concerted fourmembered transition state. As a practical method, the reaction cleanly and regioselectively produces widely used alkyl boronic esters in good to excellent yields. Due to these advantages, this reaction should be of high synthetic value.

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Keywords: metal-free $\cdot hydroboration$ $\cdot cyclopropanes$ $\cdot DFT$ $\cdot C\text{-}C$ activation

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Mild Ring-Opening 1,3-Hydroborations of Non-Activated Cyclopropanes



CarBon A mild three-component system was developed for the preparation of alkylboronic esters *via* ring-opening 1,3-hydroborations of non-activated cyclopropanes. This method has good functional group compatibility and can serve as a powerful synthetic tool for late-stage borylative ring-opening of cyclopropanes in complex compounds.