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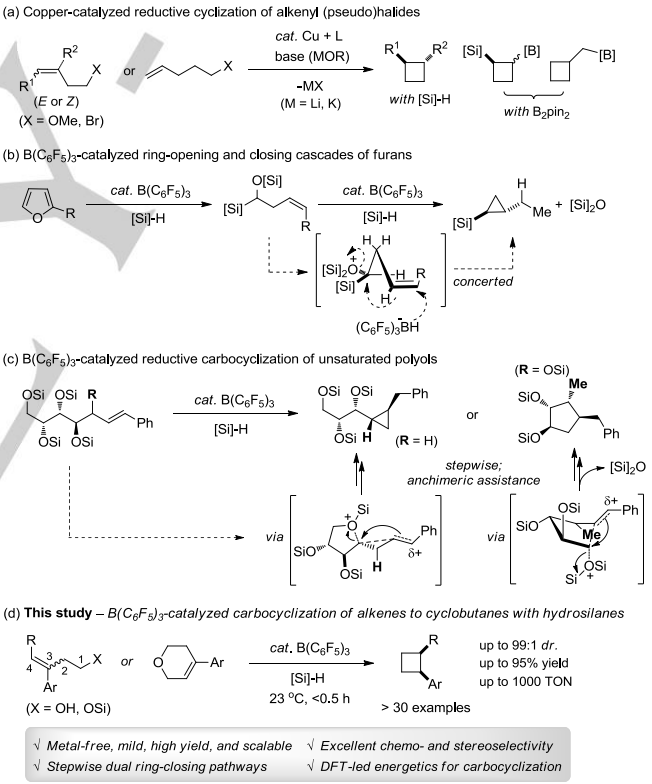
Reductive Carbocyclization of Homoallylic Alcohols to *syn*-Cyclobutanes via Boron-Catalyzed Dual Ring-Closing Pathway

Chinmoy Kumar Hazra, Jinhoon Jeong, Hyunjoong Kim, Mu-Hyun Baik,* Sehoon Park,* and Sukbok Chang*

Abstract: *Organoborane-catalyzed reductive carbocyclization of homoallylic alcohols has been developed by using hydrosilanes as a reducing reagent to provide a range of 1,2-disubstituted arylcyclobutanes. It proceeds in a cis-selective manner with high efficiency under mild conditions. Mechanistic studies including deuterium scrambling and Hammett studies, and DFT calculations allowed to propose a dual ring-closing pathway.*

Four-membered carbocycles such as cyclobutanes and cyclobutenes are valuable intermediates in organic synthesis as they can undergo a wide range of ring-opening, -contraction, or -expansion reactions.[1] They give access to many scaffolds found in biologically active molecules that are difficult to be prepared by other means in drug design.[2] Conventional catalytic methods for the synthesis of such four-membered carbocycles can be largely divided in two types: (i) intra- or intermolecular [2+2] cycloadditions[3,4] and (ii) ring-expansion of cyclopropylcarbinyl precursors by a Wagner-Meerwein shift.[5,6] A powerful alternative to the conventional approaches has been developed independently by Ito and Buchwald, where alkene substrates bearing (pseudo)halides undergo reductive cyclization *via* copper catalysis. This reaction was proposed to involve a ring closure on organocuprate intermediates formed *in situ*, accompanied by the release of a (pseudo)halide salt (Scheme 1a).[7]

Recently, we reported a $B(C_6F_5)_3$-catalyzed cascade conversion of furans providing silicon-functionalized compounds, in which a homoallylic intermediate was assumed to undergo a *concerted* S_N2'-type ring-closing process to furnish cyclopropanes with exclusive *trans*-selectivity (Scheme 1b).[8] Gagné found that $B(C_6F_5)_3$ promotes a reductive cyclization of silyl-protected unsaturated polyols to give cyclopropanes and cyclopentanes depending on substituents adjacent to an alkenyl moiety (Scheme 1c).[9] Unlike in our previous work,[8] Gagné suggested a *stepwise* pathway involving an intramolecular attack of a neighbouring alkenyl group at the activated C–O bond of silaoxonium ion taking advantage of an *anchimeric assistance*[10] to generate a benzylic cation with C–C bond formation. Inspired by these results, we envisioned that homoallylic alcohols bearing an aryl substituent at the C-3 position may undergo a carbocyclization with the anchimeric assistance by an adjacent alkenyl group to give cyclobutanes under a $B(C_6F_5)_3$/silane catalytic system. Reported herein is the first boron-catalyzed reductive cyclobutanation of homoallylic alcohols with hydrosilanes (Scheme 1d). The present catalysis produces a range of 1,2-disubstituted (hetero)arylcyclobutanes with remarkably high efficiency and excellent *cis*-selectivity. Experimental and computational experiments strongly support a *stepwise,* dual ring-closing pathway.



Scheme 1. a–c) Reductive catalytic approaches towards the synthesis of carbocycles. d) $B(C_6F_5)_3$-catalyzed reductive cyclobutanation (this work).

At the outset of this study, we chose one representative homoallylic *O*-silyl ether (Scheme 1d, R = Me; X = $OSiEt_3$) and optimized reaction conditions (see the S.I.). It underwent a condensative cyclization when 1.5 equiv of $EtMe_2SiH$ was used in the presence of 2.0 mol % of $B(C_6F_5)_3$ in dichloromethane to afford 1,2-disubstituted cyclobutane quantitatively in 0.5 h at 23 °C. The stereochemistry of the product was determined to be *syn* by 2D NMR experiments, and its diastereomeric ratio (*dr.*) was calculated by ^1H NMR of the crude reaction mixture (*dr.* >95:5).

[*] Dr. C. K. Hazra, J. Jeong, H. Kim, Prof. Dr. M-H. Baik, Dr. S. Park, Prof. Dr. S. Chang
Center for Catalytic Hydrocarbon Functionalizations
Institute for Basic Science (IBS),
Daejeon 305-701 (South Korea)
and
Department of Chemistry
Korea Advanced Institute of Science & Technology (KAIST)
Daejeon 305-701 (South Korea)
E-mail: mbaik2805@kaist.ac.kr
sehoonp@kaist.ac.kr
sbchang@kaist.ac.kr

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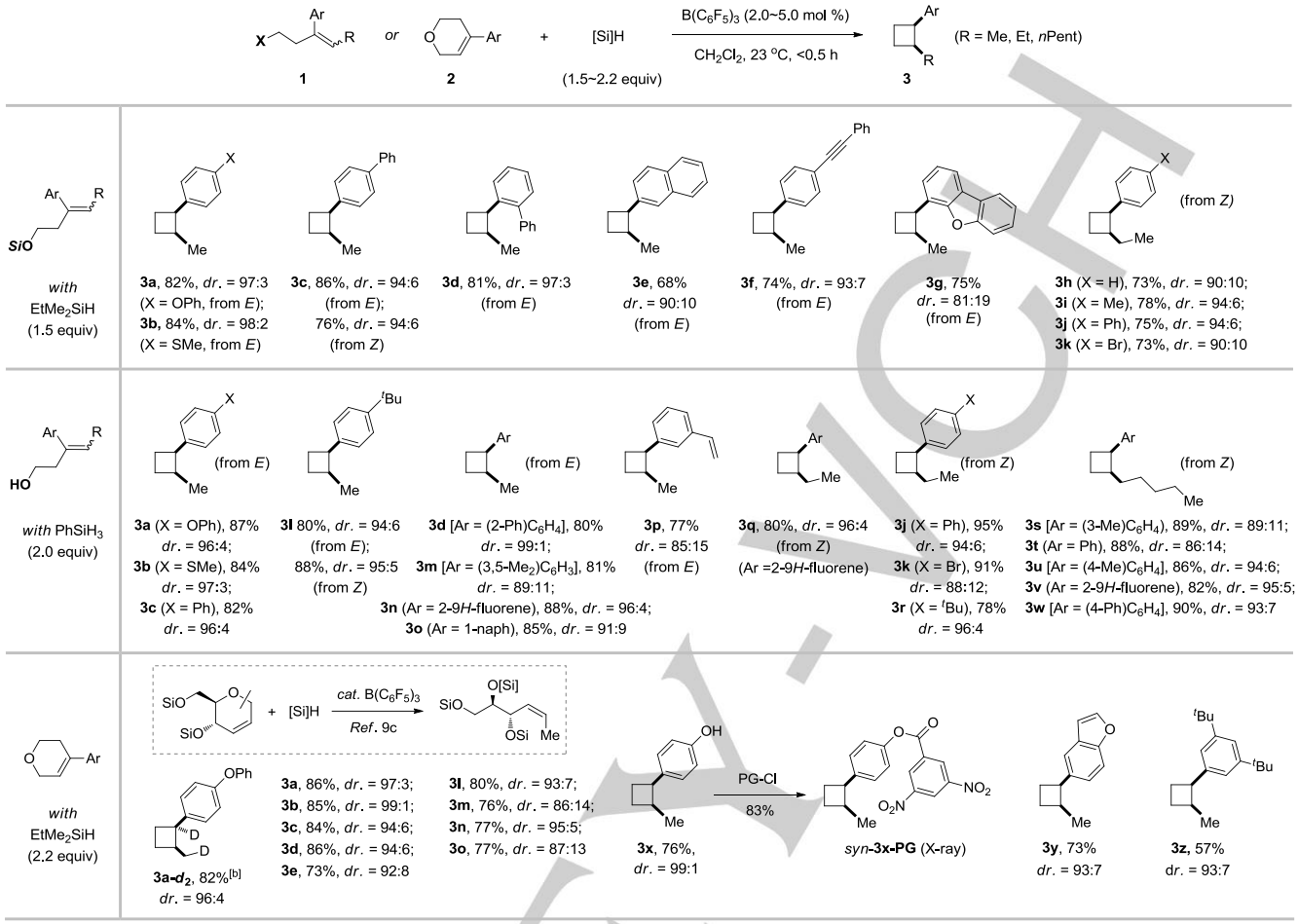
***Table 1*:** Substrate scope in the ring-closing of silyl-protected and parent homoallylic alcohols.[a]



[a] $B(C_6F_5)_3$ (2.0~5.0 mol %), substrate (0.2 mmol), $EtMe_2SiH$ or $PhSiH_3$ (1.5~2.2 equiv) in CH_2Cl_2 at 23 °C for 0.5 h: Isolated products yields are presented. Diastereomeric ratio (*dr.*) was determined by ^1H NMR analysis of the crude reaction mixture. ***Si*** = $SiMe_3$, $SiEt_3$, or $SiMe_2{}^tBu$. [b] 2.2 equiv of $PhMe_2SiD$ was used instead of $EtMe_2SiH$.

With the optimized conditions in hand [2.0 mol % $B(C_6F_5)_3$, 1.5 equiv of $EtMe_2SiH$, CH_2Cl_2, 23 °C], we investigated substrate scope in the cyclobutanation of silyl-protected homoallylic alcohols (Table 1, top). In general, the reaction was highly facile to be completed within 0.5 h and diastereoselectivity was excellent in most cases. Functional groups such as phenoxy or thioether, which were known to be labile under the reductive conditions,[11] were compatible (**3a** and **3b**, respectively). Significantly, the olefinic geometry (*E* or *Z*) of substrates was not a stereochemistry-determining factor as demonstrated in the formation of *syn*-cyclobutane **3c**. Analogous substrates bearing biphenyl or naphthyl groups were also reactive and selective for this cyclizative transformation (**3d** and **3e**, respectively). A substrate bearing an alkynyl moiety was also smoothly cyclized leading to *syn*-**3f**. However, an *O*-silyl homoallyl ether having a dibenzofuranyl group underwent the desired cyclization in decreased diastereoselectivity (**3g**). As in the case of **3c**, when a series of (*Z*)-*O*-silyl homoallyl ethers of a 3-hexenyl skeleton (R = Et) were subjected to the standard conditions, the corresponding 1,2-arylethylcyclobutanes were formed with *syn*-stereochemistry (**3h**–**3k**).[12]

Next, we were curious as to whether *unprotected* homoallylic alcohols could be viable for the reductive cyclobutanation. This route was envisioned to be synthetically more convenient since the above *O*-silyl homoallyl ethers were prepared from the parent alcohols. Pleasingly, the cyclization of homoallylic alcohols occurred under slightly modified conditions (Table 1, middle: 5.0 mol % $B(C_6F_5)_3$, 2 equiv of $PhSiH_3$).[13] A series of homoallylic alcohols having aryl groups were reactive to be converted to the corresponding cyclobutanes in high *syn*-selectivity (**3a**–**3d** and **3l**–**3o**). Notably, a vinyl substituent at the phenyl moiety remained intact although the diaseteroselectivity was slightly decreased (**3p**). Replacing an olefinic substituent from methyl (R = CH_3) to ethyl (R = CH_2CH_3) and pentyl (R = $(CH_2)_4CH_3$) did not deteriorate the reaction efficiency and diastereoselectivity (**3j**–**3k** and **3q**–**3w**).

Gagné *et. al*. showed that 3,6-dihydro-2*H*-pyrans undergo selective *allylic C–O bond cleavage* to generate silyl-protected homoallylic alcohols via $B(C_6F_5)_3$ catalysis (Table 1, bottom-dotted box).[9c] Inspired by this report, we envisaged to test C-4 aryl-substituted dihydropyrans as substrates for the cyclobutanation. Indeed, a series of 4-aryl-dihydro-2*H*-pyrans were smoothly transformed to *syn*-cyclobutanes under the similar conditions (Table 1, bottom: 2.0 mol % $B(C_6F_5)_3$, 2.2 equiv of $EtMe_2SiH$). As in the reaction of *O*-silyl homoallyl ethers, the cyclobutanation of pyran substrates bearing electronic and/or steric variations showed good to excellent reactivity and *syn*-selectivity. The reaction of a pyran substrate with a deuterated hydrosilane afforded **3a**-d_2 with excellent *syn*-diastereoselectivity, demonstrating the selective ring-opening

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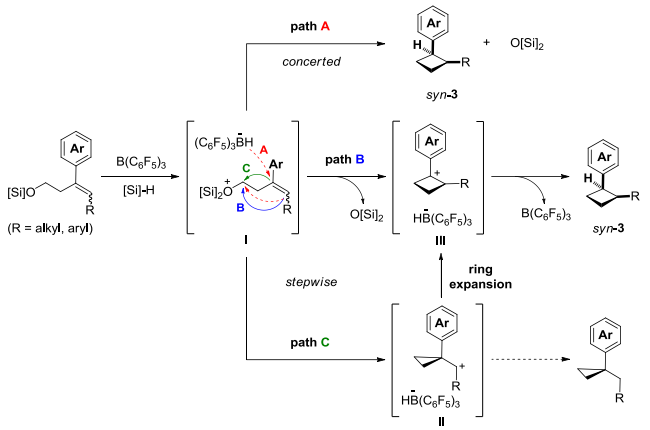
and closing cascade of the pyran substrates. It is noteworthy that the reaction of a 2*H*-pyran possessing a benzofuranyl group cleanly gave the desired product **3y** in good yield.

Based on the present selectivity and precedent reports,[8,9] three cyclization pathways can be proposed (Scheme 2): (i) S_N2'-type *concerted* mechanism (path A), (ii) *stepwise* cyclobutanation (path B), and (iii) *stepwise* ring-closing and ring-expansion cascade (path C). All three possible pathways are assumed to be initiated by the formation of a silaoxonium ion complexed with borohydride (**I**).[14]

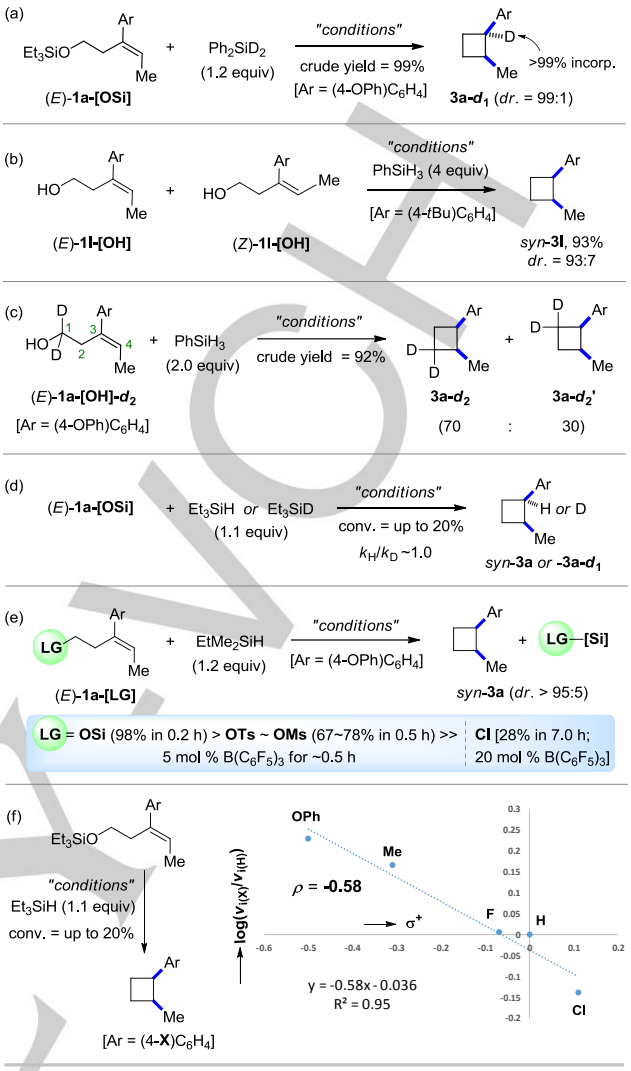


Scheme 2. Possible reaction pathways for cyclobutanation.

To validate the mechanistic details in the present cyclization, we carried out a series of experimental mechanistic studies. A reaction of (*E*)-**1a-[OSi]** with Ph_2SiD_2 (1.2 equiv) in the presence of $B(C_6F_5)_3$ catayst proceeded to afford *syn*-**3a-*d*$_1$** with a complete deuterium incorporation (Scheme 3a). The $B(C_6F_5)_3$-catalyzed reaction of 1:1 mixture of *E*/*Z* isomeric **1l-[OH]** with $PhSiH_3$ furnished a single product **3l** in 93% yield with 93:7 of *dr.* (Scheme 3b). This result may support the stepwise pathways B or C, where a cyclobutyl benzylic carbocation **III** (Scheme 2) will be generated as a common intermediate irrespective of the olefinic geometry in homoallylic alcohol substrates.[15]

We designed a reaction of a bis-deuterated homoallylic alcohols at the C-1 position (**1a-[OH]-*d*$_2$**) to see the involvement of path B and/or path C (Scheme 3c). In path C, a 1:1 mixture of cyclobutane products incorporating bis-deuteriums at the C-3 and C-4 position (**3a-*d*$_2$**/**3a-*d*$_2$'**) is predicted while a single labeled product **3a-*d*$_2$** only will be obtained if it follows path B since a direct formation of a cyclobutyl carbocation **III** from the presupposed silaoxonium ion **I** will be assumed. Intruigingly, the reaction of **1a-[OH]-*d*$_2$** afforded a ~ 7:3 mixture of **3a-*d*$_2$** and **3a-*d*$_2$'** in 92% crude yield, suggesting that path B and C are operative in a bifurcation manner for the ring-closing process.[16]

To identify the rate-determining step (*RDS*), kinetic isotope effect (KIE) was measured to be 1.0 in cyclization reactions of **1a-[OSi]** with Et_3SiH and its deuterium analogue (Scheme 3d). Again, this result may suggest that a S_N2'-type nucleophilic attack of $(C_6F_5)_3BH^-$ at the C-3 position of a silaoxonium ion **I** is less likely.[17] When substrates possessing different types of leaving groups at the C-1 position were allowed to react, the cyclizative reaction efficiency was observed to decrease in this order: LG = $OSiEt_3$ > OTs ~ OMs >> Cl (Scheme 3e). Together with KIE data, this result corroborates that the RDS step would be a condensative intramolecular cyclization to form a carbocation intermediate.



Scheme 3. Experimental mechanistic studies. "*conditions*": $B(C_6F_5)_3$ (2~10 mol %) in CH_2Cl_2 at 23 °C.

Electronic effects on the cyclization rate were subsequently investigated (Scheme 3f). Plot of $v_{i(X)}/v_{i(H)}$ against the σ^+ Hammett constants provided ρ value of –0.58 (R^2 = 0.95), indicating that substrates having more electron-rich aryl groups lead to increased reaction rates.[18] This small ρ value can be taken to indicate an early transition state,[19] where no strong resonance interaction occurs,[20] while there is a small positive charge polarization at the C-3 position in the RDS.

Scheme 4 visualizes the mechanism of cyclobutane formation starting from the silaoxonium ion intermediate **A** that we obtained from extensive explorations of the mechanism using density functional calculations. For the forward reaction, the intermediate **A** first traverses the transition state **A-TS-B** which is 16.0 kcal/mol higher in energy than **A**. From **A-TS-B**, the reaction affords the cyclopropane **B** which is energetically downhill by –5.9 kcal/mol. However, with the given energy landscape, there is a very shallow minimum for **B**, which is presumed to lead some portion of activated molecules at the transition state to directly proceed to the intermediate **C** *not via* **B**.[21]

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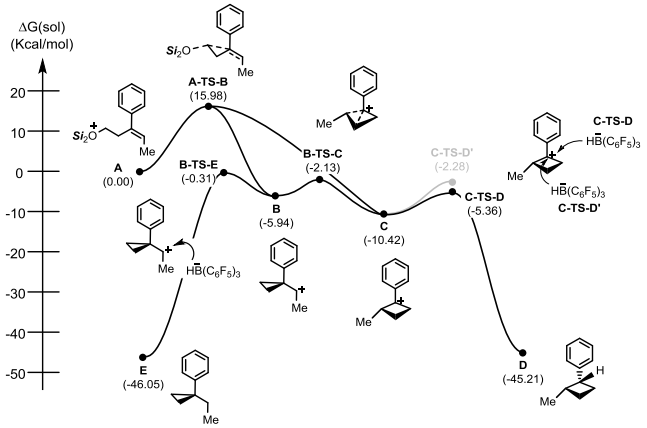
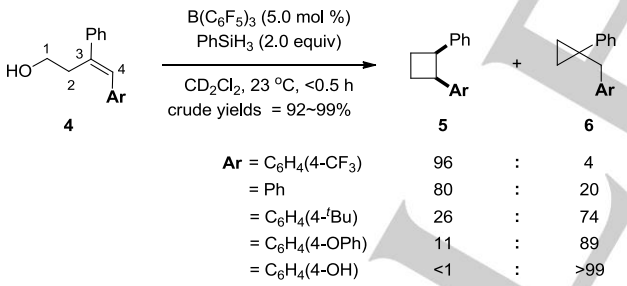


Scheme 4. DFT-derived energetics of the $B(C_6F_5)_3$-mediated carbocyclization of (*E*)-3-phenylpent-3-en-1-ol with Et_3SiH (All structures were optimized at the M06/6-31G** level of theory).

Starting from intermediate **B**, the reaction may proceed through either intermolecular hydridation to form a cyclopropane product **E** or intramolecular ring-expansion to generate a cyclobutane intermediate **C**. The barriers for both possibilities are too low at 5.6 and 3.8 kcal/mol, respectively, to infer any significant difference in the rate of these steps. Instead, it is more meaningful that the hydridation to proceed to the left hand side in Scheme 4 is an intermolecular process, whereas the ring-expansion to the right hand side is an entropically beneficial intramolecular event. Therefore, **C** at –10.4 kcal/mol should be formed exclusively. The intermediate **C** may then be attacked by a borohydride to give the product **D**, traversing another low barrier of 5.4 kcal/mol. The hydridation from the top side is estimated to be preferred by ~3 kcal/mol over the bottom side attack to give the *syn*-selective product **D**.



Scheme 5. Electronic effects of the C-4 aryl substituents on product distribution.

An additional mechanistic assumption was that if the reaction pathway involves a ring-expansion process (path C),[22,23] we may see a product distribution between cyclopropanes and cyclobutanes and that the ratio will be susceptible to the electronic variation of substrates. Indeed, when electronically variable diaryl-3-butenols (**4**) were subjected to the standard conditions, reductive carbocyclization smoothly proceeded to afford a mixture of cyclobutanes and cyclopropanes in varied ratios (Scheme 5). Significantly, substrates bearing electron-rich C4-aryl groups were cyclized leading to cyclopropanes mainly. These data further support the conclusion that (*i*) path C is operative, and (*ii*) hydride transfer to the electron-rich cyclopropylcarbinyl cation is facile. Additionally, our computed mechanistic model explains the electronic effect of aryl groups (see the S.I.).

In summary, we have developed a borane-catalyzed carbocyclization of homoallylic alcohols and dihydro-2*H*-pyrans to produce *syn*-1,2-disubstituted cyclobutanes in high yields and with excellent selectivity. Mechanistic studies indicate that stepwise dual ring-closing pathways are operative, while the condensative intramoelcular cyclization is turnover limiting. Tuning the electronic nature of C4-aryl groups of homoallyl substrates can alter the reaction path to lead to cyclopropanes.

Acknowledgements

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Conflict of interest

The authors declare no conflict of interest.

Keywords: Carbocyclization • Cyclobutanes • Homoallylic alcohols •Anchimeric assistance • Stepwise dual pathways

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[12] A gram-scale reaction of (*E*)**-1a-[OSi]** with $EtMe_2SiH$ (1.1 equiv) in the presence of $B(C_6F_5)_3$ (0.1 mol %) produced **3a** in 83% isolated yield (1.38 g) with >95% of *syn*-selectivity within 0.5 h at 23 °C (see the S.I.).

[13] The use of $PhSiH_3$ as as reductant instead of $EtMe_2SiH$ in the cyclobutanation of free homoallylic alcohols led to slightly better yields and *syn*-selectivity (see the S.I.).

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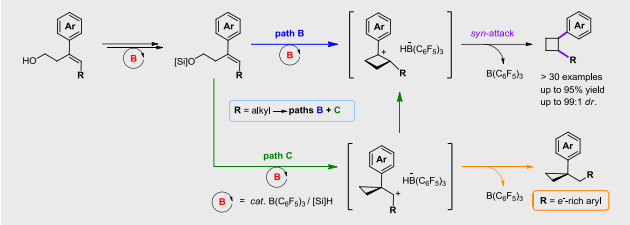

Transition-metal free, organoborane-catalyzed reductive cyclobutanation of homoallylic alcohols and their *O*-silyl ethers has been developed giving rise to 1,2-disubstituted arylcyclobutanes with high efficiency and excellent *cis*-selectivity. Experimental and computational mechanistic studies led us to propose stepwise dual ring-closing pathways driven by carbocation rearrangements.

Chinmoy Kumar Hazra, Jinhoon Jeong, Hyunjoong Kim, Mu-Hyun Baik, Sehoon Park,* and Sukbok Chang**

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Reductive Carbocyclization of Homoallylic Alcohols to syn-Cyclobutanes via Boron-Catalyzed Dual Ring-Closing Pathway

[*] Dr. C. K. Hazra, J. Jeong, H. Kim, Prof. Dr. M.-H. Baik, Dr. Prof. Dr. S. Chang
Center for Catalytic Hydrocarbon Functionalizations
Institute for Basic Science (IBS),
Daejeon 305-701 (South Korea)