C–C Bond Formation

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Intramolecular Cyclopropanation of 1,4-Dienes through Hydroboration–Homologation: Easy Access to Bicyclo[3.1.0]hexanes

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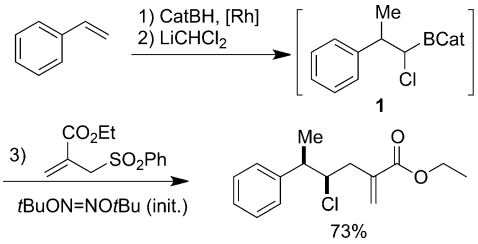
Abstract: *An intramolecular cyclopropanation reaction involving B-(1-chloroalkyl)catecholborane intermediates generated from 1,4-dienes through hydroboration with catecholborane and Matteson homologation was developed. This sequential procedure leading to bicyclo[3.1.0]hexanes involves the formation of three new sigma C–C bonds at the same carbon atom. A mechanistic study supports the involvement of carbocationic intermediates.*

Bicyclo[3.1.0]hexanes are present in a variety of natural and non-natural products with attractive biological activities.[1–4] They are also interesting synthetic intermediates and are often involved in ring-opening reactions owing to the ring strain contained in such bicyclic structures.[5–8] The same ring strain makes their synthesis difficult and challenging. As a consequence, synthetic chemists are eager to develop methods for the construction of molecules containing the bicyclo[3.1.0]hexane framework.[9–11] Their preparation often requires the intermediacy of highly reactive species such as carbenes and metallocarbenes, as exemplified by the well-established transition-metal-catalyzed intramolecular cyclopropanation of unsaturated α-diazocarbonyl compounds.[12–14] Other methods involving metalation of unsaturated terminal epoxides[15,16] and aziridines,[17] intramolecular Simmons–Smith cyclopropanation,[18] and sulfur ylide chemistry[19,20] have also been reported. 1-Haloalkylboronates are potential precursors of carbenes and carbenoids but have not been used for intramolecular cyclopropanation except for a palladium-catalyzed intermolecular cyclopropanation of norbornene with halomethylboronates.[21] Herein, we disclose an uncatalyzed and spontaneous intramolecular cyclopropanation process involving *B*-(1-chloroalkyl)catecholborane intermediates that are easily available through selective hydroboration of dienes and their subsequent Matteson homologation.

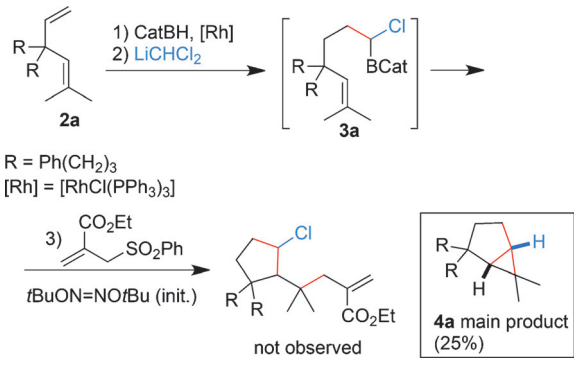
Recently, we have examined the Matteson homologation of *B*-alkylcatecholboranes with lithiated dichloromethane. An efficient procedure for the preparation of *B*-(1-chloroalkyl)catecholboranes such as **1** was developed.[22] These organoboranes were used in as a source of 1-chloroalkyl radicals in various processes, including allylation reactions involving allylsulfones (Scheme 1). The homologation–intermolecular radical addition sequence is applicable to a wide range of substrates.



Scheme 1. Intermolecular addition of 1-chloroalkyl radicals to alkenes. init. = initiator.

In order to extend this chemistry to radical cyclization, the 1,4-diene **2a** was prepared and subjected to the optimized reaction conditions developed for the intermolecular radical addition.[22] None of the expected chlorocyclopentane was observed, but one main product, identified as the bicyclo-[3.1.0]hexane **4a**, was obtained in modest 25% yield (Scheme 2). This product is already formed during the homologation sequence and all attempts to isolate the intermediate *B*-(1-chloroalkenyl)catecholborane **3a** failed. To the best of our knowledge, such an intramolecular cyclopropanation process has never been reported.

Based on these preliminary results, optimization of the cyclopropanation process was investigated. Selective hydroboration of the diene **2a** proved to be difficult to control. Both the uncatalyzed[23] and *N*,*N*-dimethylacetamide-catalyzed[24] reactions involve transient formation of BH_3 and therefore led to bis-hydroboration of the diene. The best results were obtained by catalysis with Wilkinson's catalyst [$RhCl(PPh_3)_3$].[25–27] However, this process is complicated by several



Scheme 2. Attempted cyclization of a 1-chloroalkenyl radical and discovery of the intramolecular cyclopropanation.

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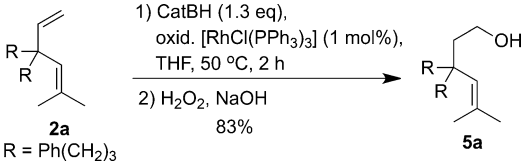
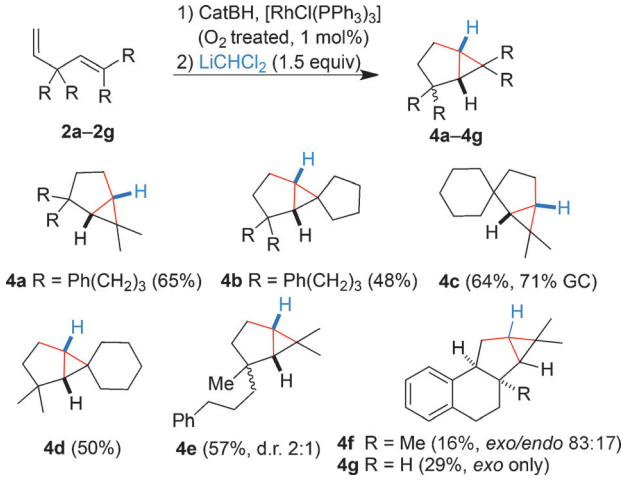
side reactions such as alkene isomerization and hydrogenation, as well as bishydroboration by BH_3 generated by Rh-mediated catecholborane degradation.[28] The quality of the $[RhCl(PPh_3)_3]$ has a pronounced effect on the result. Hydroboration of the 1,4-diene **2a** with catecholborane catalyzed by fresh $[RhCl(PPh_3)_3]$ leads, after oxidative workup, to significant amounts of aldehyde from an intermediate vinylboronate ester or *gem*-bisborylated product. By using the partially oxidized Wilkinson's catalyst described by Evans and coworkers,[29–32] hydroboration of **2a** with catecholborane followed by oxidation gave the desired primary alcohol **5a** in 83% yield (Scheme 3). Similar results for the hydroboration of a silylated allylic alcohol were reported by Burgess and coworkers.[26]



Scheme 3. Hydroboration of **2a** with CatBH in a reaction catalyzed by partially oxidized $[RhCl(PPh_3)_3]$.

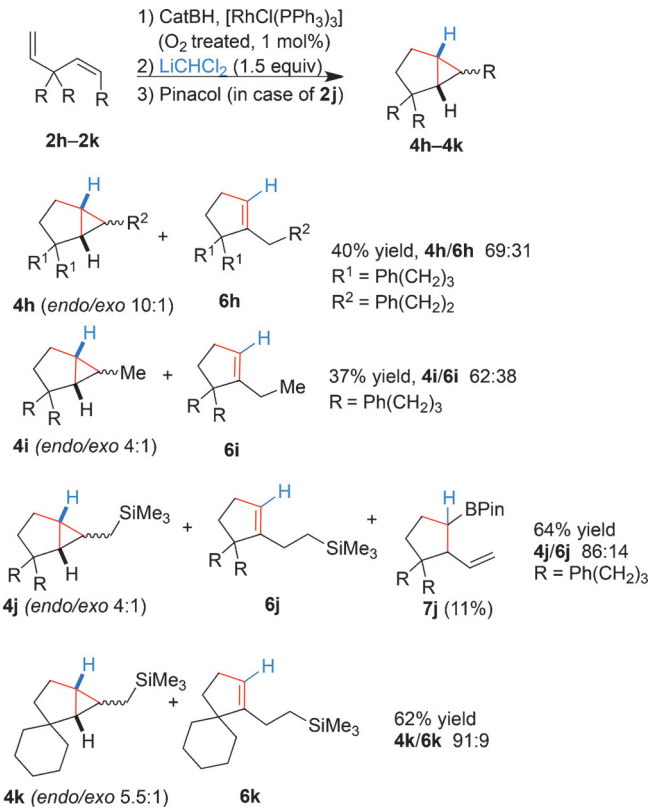
With the optimized hydroboration conditions in hand, the homologation–cyclopropanation sequence starting from **2a** was reexamined (Scheme 4). The use of a small excess (1.5 equivalents) of the in situ prepared dichloromethyllithium gave the best results. The concentration of the substrate had an influence on the reaction yield and best results were obtained at 0.1M (0.2M: 50% GC yield, 0.1M: 67% GC yield). Under these optimized conditions, **4a** was isolated in 65% yield, thus demonstrating the efficiency of this unusual transformation. In order to examine the scope of the cyclopropanation reaction, a variety of 1,4-dienes were prepared and examined under the optimized conditions. 1,4-Dienes **2b**–**2e**, which are disubstituted at the terminal position, undergo regioselective hydroboration and homologation to furnish the corresponding bicyclo[3.1.0]hexanes



Scheme 4. Synthesis of fused cyclopropanes **4a**–**4g**.

4b–**4e** in 48–65% yield (Scheme 4). As expected for such a substitution pattern, the $[RhCl(PPh_3)_3]$-catalyzed hydroboration occurs regioselectively at the unsubstituted terminal position.[27] Dienes **2f** and **2g**, prepared from α-tetralone, afforded the tetracyclic products **4f** and **4g** in 15% and 29% yield.[33] In these two examples, the rhodium-catalyzed hydroboration of the exocyclic 1,1-disubstituted alkenes proved to be slow and incomplete, likely owing to steric hindrance.

1,4-Dienes monosubstitued at one of the terminal positions (**2h**,**2i**) gave lower yields as a result of the moderate regioselectivity of the hydroboration step, as well as the formation of cyclopentene byproducts **6h** and **6i** (Scheme 5).

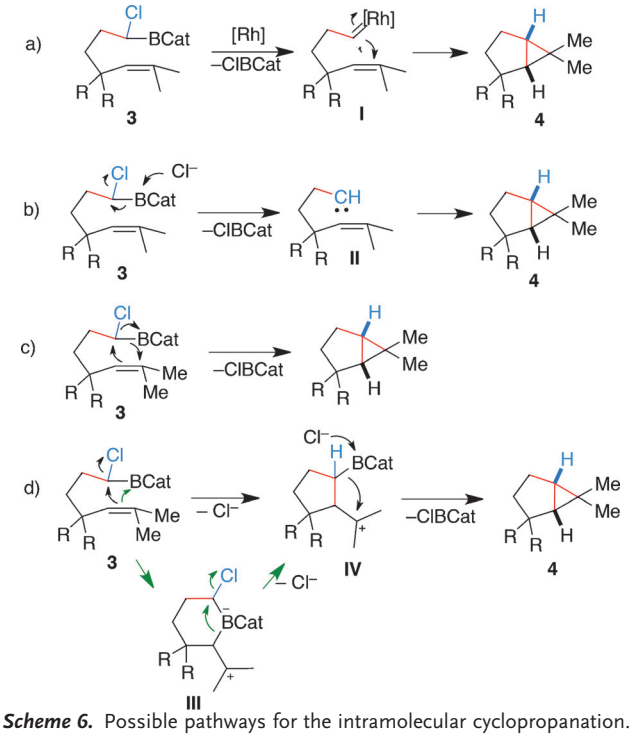


Scheme 5. Intramolecular cyclopropanation of 1,4-dienes monosubstitued at one of the terminal position.

With substrates **2j** and **2k**, which contain a bulky trimethylsilyl substituent, the hydroboration was more selective and the yields increased to 64% for **4j** and 62% yield for **4k**. Formation of the alkenes **6j** and **6k** is also observed, albeit in much lower proportions. In the case of **2j**, a second byproduct, the boronate **7j**, was isolated in 11% yield after treatment of the crude product with pinacol.[34] The structure and relative *endo* configuration of the major diastereomer of **4j** was determined by single-crystal X-ray crystallography (see the Supporting Information).[35] By analogy, the relative configuration of the major isomer of the other three examples (**4h**, **4i** and **4k**) was tentatively assigned as *endo*. This assignment is also supported by the ^{1}H-NMR spectra, which show coupling constants involving the cyclopropane hydrogen atom at C(6) that are larger for the major *endo* isomers (*endo*-

4h, 8.6 Hz, *cis* coupling constant) than for the minor isomer (*exo*-**4h**, 3.1 Hz, *trans* coupling constant).[36]

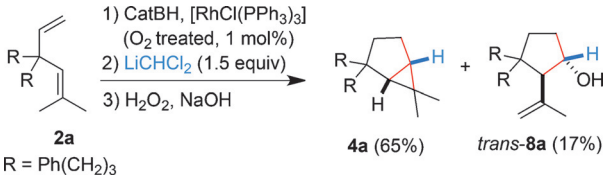
The mechanism of this intramolecular cyclopropanation reaction is puzzling. First of all, compound **3** could not be observed but rearranges spontaneously under our reaction conditions to the cyclopropane **4** (Scheme 6). This is in strong contrast to simple α-chloroboranes such as **1** (Scheme 1),



Scheme 6. Possible pathways for the intramolecular cyclopropanation.

which are stable and easily observed by ^{1}H- and ^{11}B-NMR.[22] Several possible mechanisms were envisaged. First, a rhodium-catalyzed cyclopropanation via a metallocarbene of type **I** (Scheme 6a) was ruled out by running the reaction without any catalyst. Hydroboration of **2a** under neat conditions followed by the standard procedure with chloromethyllithium afforded the bicyclic compound **4a** in 19% yield. The lower yield relative to the reaction involving a rhodium catalyst is due to lower efficiency of the hydroboration under these conditions. A mechanism involving the formation of the free carbene **II** was considered next (Scheme 6b). This could not be unambiguously ruled out, however, no side product resulting from typical carbene chemistry, such as a C–H insertion product, could be detected. Moreover, 1-chloroalkylcatecholborane derivatives such as **1** are stable and do not react with alkenes, even reactive alkenes such as norbornene. Third, a fully concerted mechanism necessitating the presence of a suitably placed double bond was envisaged (Scheme 6c). In this mechanism, the electron-rich double bond attacks the 1-chloroalkylborane with a concerted migration of the chloride anion to the boron atom and attack of the nucleophilic C–B bond on the terminal position of the double bond. Finally, an analogous stepwise mechanism can also be envisaged (Scheme 6d). This mechanism involves the formation of a carbocationic intermediate **IV**, which leads to the three-membered ring.[37–40] The formation of **IV** may take place through direct nucleophilic substitution of the chloride by the olefin or through initial reaction at the boron center to form intermediate **III**, followed by a 1,2-migration of the ate complex (green arrows). This mechanism has the great advantage of taking into account the side products that are observed (see below). A related cationic mechanism has been proposed by Brown and co-workers to rationalize alkene formation upon thermal treatment of α-chloroboronic esters.[41–43]

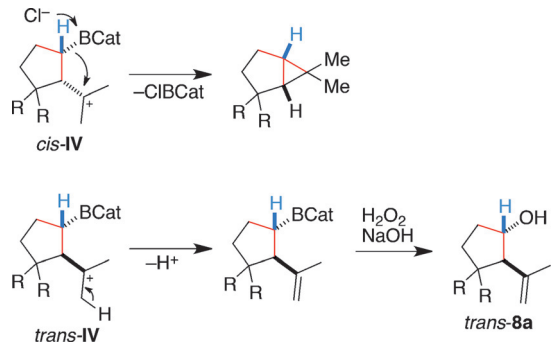
In order to gain some insight into the reaction mechanism, **2a** was subjected again to our optimized reaction conditions, followed by an oxidative workup with H_2O_2/NaOH, in order to isolate stable compounds derived from potential *B*-alkylcatecholboranes byproducts (Scheme 7). Interestingly, besides **4a**, the alcohol *trans*-**8a** was isolated as a byproduct. The dinitrobenzoate was prepared and its relative *trans* configuration could be assessed by single-crystal X-ray structure analysis (see the Supporting Information).[44] The corresponding *cis* isomer of alcohol **8a** could not be detected in the reaction mixture.



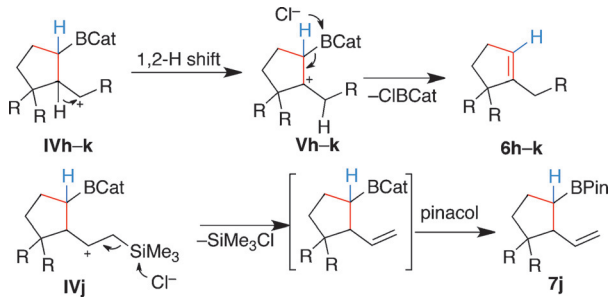
Scheme 7. Reaction of **2a** followed by oxidative workup.

This observation supports the pathway shown in Scheme 6d. The cationic intermediate **IV** is presumably formed as a *cis*/*trans* mixture and only *cis*-**IV** can afford the bicyclo[3.1.0]hexane **4a** (Scheme 8). The *trans* stereoisomer of **IV** cannot undergo the final cyclization step. Loss of a proton affords a boronic ester intermediate that gives the alcohol *trans*-**8a** after oxidative workup.

The mechanism involving a carbocation intermediate of type **IV** can also explain the formation of the byproducts **6h**–**6k**. In this case, a fast 1,2-hydride shift leading to the tertiary carbocation **V** takes place, followed by a rapid β-fragmentation of ClBCat to give compounds of type **6** (Scheme 9).



Scheme 8. Possible reaction pathway leading to *trans*-**8a**.



Scheme 9. Proposed mechanism for the formation of byproducts **6h–k** and **7j**.

Interestingly, with the trimethylsilyl diene **2j**, the desilylation product **7j** is also observed in 11% yield (see Scheme 5). This can be explained by a fast elimination of the silyl group from **IVj** that competes with the 1,2-hydride shift.

In conclusion, we have developed an intramolecular cyclopropanation reaction involving *B*-(1-chloroalkyl)catecholborane intermediates generated from 1,4-dienes through hydroboration with catecholborane and Matteson homologation. This cascade procedure involves the formation of three new sigma C–C bonds at the same carbon atom and it can be applied to the synthesis of various bicyclo[3.1.0]hexanes with moderate to good yields. In addition, on the basis of a mechanistic study, we propose that the reactions go through unexpected carbocationic intermediates. Extension of this chemistry to other ring sizes is currently under investigation and will be reported in due course.

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Keywords: boronic esters · chlorides · cyclopropanation · homologation · hydroboration

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[33] The relative configuration of the major isomer of **4f** was attributed based on ^{1}H-NMR NOE experiments. The relative configuration of the minor diastereomer has not been established.
[34] According to ^{1}H- and ^{13}C-NMR spectra, the byproduct **7j** exists as a single diastereomer, the relative configuration of which was not established.
[35] CCDC 1439558 contains the supplementary crystallographic data for compound **4j**. These data can be obtained free of

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