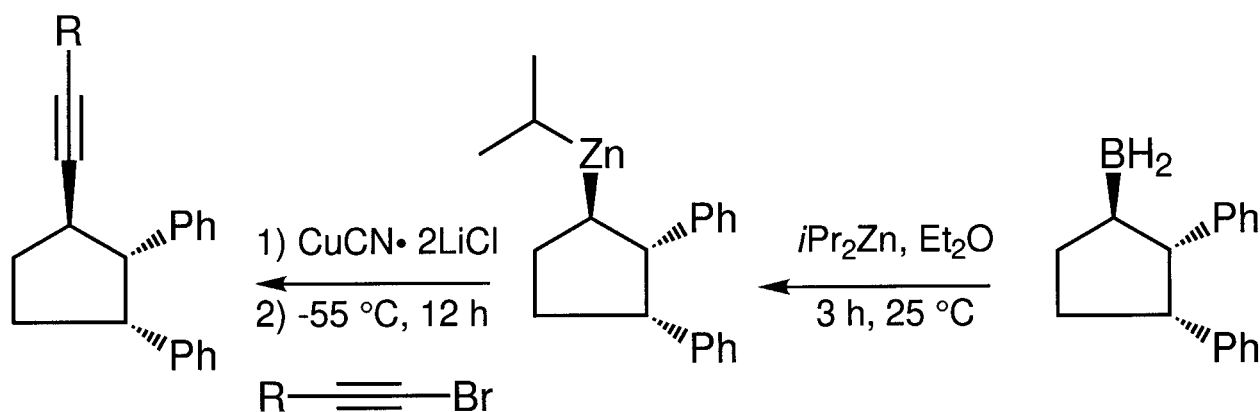


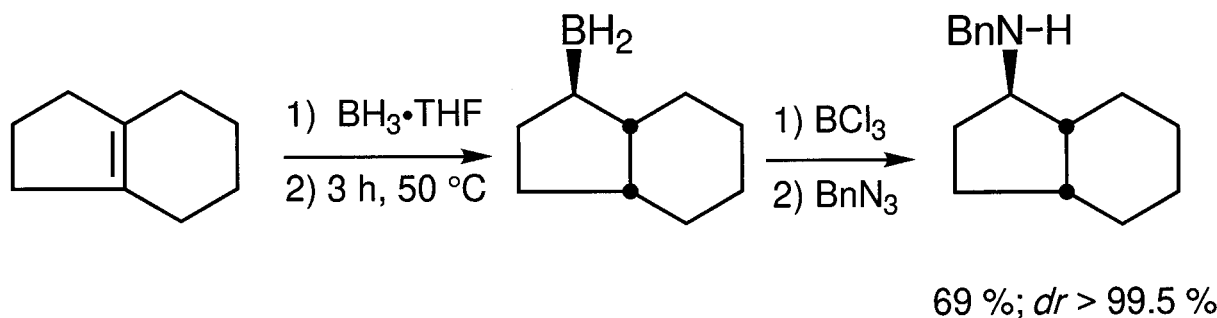
The hydroboration of tetrasubstituted cyclic alkenes produces tertiary organoboranes, which undergo a stereoselective rearrangement to furnish organoboranes bearing three adjacent stereocenters. These species can be converted into a variety of products.



1 diastereoisomer

With bicyclic systems, a preferential migration in the direction of the five-membered ring is observed.

Further details are given on the following pages.

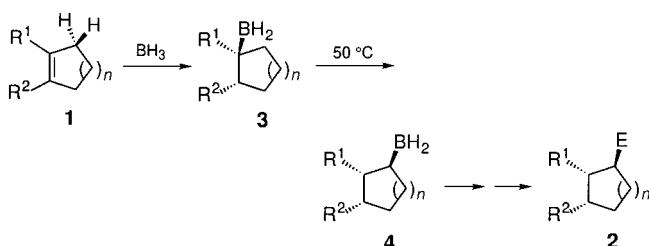


Stereoselective Allylic C–H Activation with Tertiary Alkylboranes: A New Method for Preparing Cycloalkyl Derivatives with Three Adjacent Stereocenters**

Frédéric Lhermitte and Paul Knochel*

Dedicated to Professor Gernot Boche
on the occasion of his 60th birthday

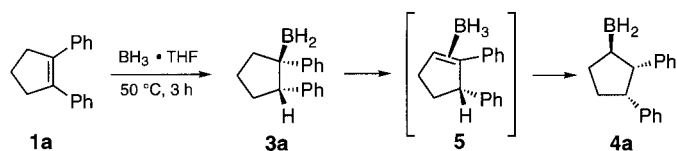
The functionalization of unreactive carbon–hydrogen bonds is an active field of investigation.^[1] Transition metal complexes have been used with great success for selectively activating C–H bonds,^[1, 2] and a few examples involving main group organometallic compounds have been described.^[3] Herein, we report a highly stereoselective C–H activation of an allylic position that allows the construction of three adjacent stereocarbon centers by making use of a rearrangement of a tertiary alkylborane. Whereas most organoboranes undergo rearrangements at elevated temperature,^[4] it was noticed by Rickborn and Wood^[5] and Field and Galagher^[6] that cyclic tetrasubstituted alkenes undergo such a dyotropic rearrangement^[7] under much milder conditions. We found that this approach allows a highly stereoselective conversion of various cyclic or acyclic tetrasubstituted alkenes of type **1** into polyfunctional products of type **2** in a one-pot reaction via the intermediate organoboranes **3** and **4** (Scheme 1).



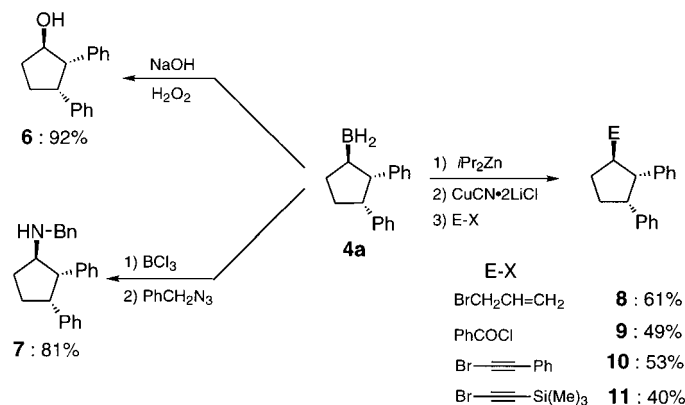
Scheme 1. Synthesis of **2** from **1** by hydroboration ($\rightarrow$ **3**) and migration ($\rightarrow$ **4**). $n = 1, 2$.

Thus, 1,2-diphenylcyclopentene (**1a**) was smoothly hydroborated with $\text{BH}_3 \cdot \text{THF}$ (THF, 50°C , 3 h) to provide the tertiary alkylborane **3a**, which undergoes a stereoselective *syn* migration leading to the less sterically hindered secondary organoborane **4a** (Scheme 2). The high stereochemical control is explained by assuming a dehydroboration of **3a** to form the alkene–borane complex **5**, which undergoes a second hydroboration. Here, there can be no dissociation from the alkene, as this would result in a decrease in stereoselectivity.^[5, 6]

The alkylborane **4a** was trapped with several electrophiles with retention of stereochemistry (Scheme 3). Thus, oxidation



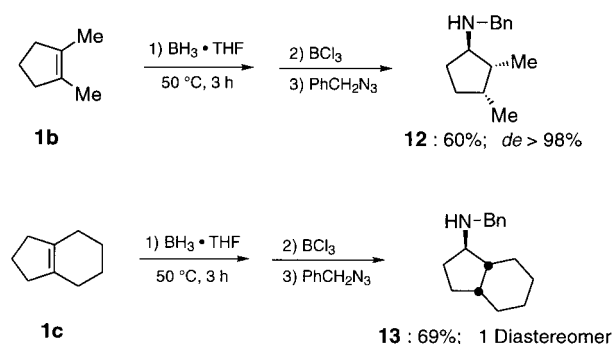
Scheme 2. Synthesis of **4a**.



Scheme 3. Synthesis of **6–11**.

of **4a** with 30% H_2O_2 affords the cyclopentanol **6** in 92% overall yield as a single stereoisomer. Treatment of **4a** with boron trichloride followed by benzyl azide^[8] (25°C , 1 h) provides the amine **7** as one stereoisomer in 81% overall yield. Transmetalation of **4a** to the corresponding organozinc compound^[9] by treatment with $i\text{Pr}_2\text{Zn}$ (2 equiv) and subsequent transformation to the zinc–copper reagent^[10] by addition of $\text{CuCN} \cdot 2\text{LiCl}$ furnishes—after reaction with electrophiles such as allyl bromide, benzoyl chloride, 2-phenylethynyl bromide, or 1-bromo-2-trimethylsilylacetylene—the expected products **8–11** with diastereomeric excesses of greater than 97% and in 40–61% overall yield.

Extension of this rearrangement to other tetrasubstituted alkenes has been examined (Scheme 4). Both 1,2-dimethylcyclopentene (**1b**) and the bicyclic alkene **1c** undergo the



Scheme 4. Synthesis of **12** and **13**.

stereoselective rearrangement. Amination of **1b** and **1c** ($1. \text{BH}_3 \cdot \text{THF}$, 50°C , 3 h; $2. \text{BCl}_3$, 25°C , 3 h; $3. \text{PhCH}_2\text{N}_3$, 25°C , 1 h)^[8] led to the desired stereoisomers **12** and **13** in 60–69% overall yield.^[11]

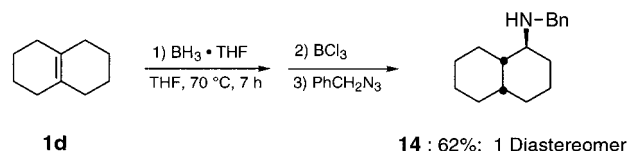
Interestingly, in the case of **1c** the migration takes place almost exclusively in the direction of the five-membered ring.

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This may be due to the proper alignment of the adjacent C–H bond with the C–B bond in the five-membered ring facilitating the dehydroboration. In a six-membered ring, there would be an angle of about 60° between the C–H and C–B bonds; this alignment would require a higher energy of activation.

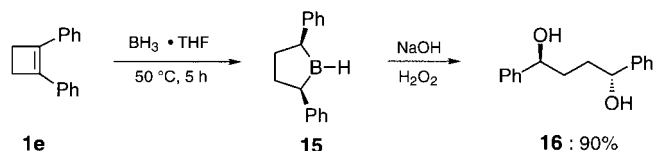
With bicyclo[4.4.0]dec-1(6)-ene (**1d**) the hydroboration must be carried out, as expected, at 70 °C in refluxing THF (Scheme 5). In this case also, a highly stereoselective migration takes place despite the elevated temperature. After



Scheme 5. Synthesis of **14**.

amination (1. $\text{BH}_3 \cdot \text{THF}$, 70 °C, 7 h; 2. BCl_3 , 25 °C, 3 h; 3. PhCH_2N_3 , 25 °C, 1 h)^[8] the bicyclic amine **14** was obtained in 62 % yield as a single stereoisomer.

A novel stereoselective borane rearrangement was found upon use of 1,2-diphenylcyclobut-1-ene (**1e**; Scheme 6). After initial hydroboration, cleavage of the cyclobutene ring



Scheme 6. Synthesis of **16**.

occurred to provide the intermediate boracyclopentane **15**. After oxidation with H_2O_2 the *meso*-diol **16** was isolated in 90 % yield as a pure diastereoisomer.

In summary, we have shown that the migration of tertiary boranes constitutes a novel stereoselective method for preparing cyclic and bicyclic rings. The reaction corresponds formally to an stereoselective activation of allylic C–H bonds.

Experiment Section

Typical procedure for the amination: Preparation of (1*R**,2*R**,3*R**)-*N*-benzyl-2,3-dimethylcyclopentylamine (**12**): A $\text{BH}_3 \cdot \text{THF}$ solution (3 mL, 1.5 equiv, 3 mmol, 1.0 M) was slowly added to 1,2-dimethylcyclopentene (**1b**; 192 mg, 2 mmol) in THF (10 mL) at 25 °C. After 10 min the resulting solution was heated at 50 °C for 3 h. The solvent and excess of borane were removed under vacuum, and the residue was diluted with CH_2Cl_2 (10 mL), treated at 0 °C with a solution of BCl_3 (8 mL, 4 equiv, 8 mmol, 1.0 M) in CH_2Cl_2 , and stirred for 3 h at 25 °C. After removal of the solvent and excess of BCl_3 under vacuum, the residue was diluted with CH_2Cl_2 (10 mL) and treated at 0 °C with a solution of benzyl azide (2.4 mL, 1.2 equiv, 1.0 M) in CH_2Cl_2 . After 1 h at 25 °C the reaction was quenched with aq NaOH (10 mL, 3.0 M), extracted with ether, and dried (MgSO_4). The crude residue was purified as the hydrochloride by addition of a solution of dry HCl in ether. Analytically pure **12**·HCl was obtained after filtration (287 mg, 1.2 mmol, 60 % yield).

Typical procedure for the allylation: Preparation of (1*S**,2*S**,3*S**)-1-allyl-2,3-diphenylcyclopentane (**8**): A $\text{BH}_3 \cdot \text{THF}$ solution (3 mL, 1.5 equiv, 3 mmol, 1.0 M) was slowly added to 1,2-diphenylcyclopentene (**1a**; 440 mg, 2 mmol) in THF (10 mL) at 25 °C. After 10 min the resulting

solution was heated at 50 °C for 3 h. The solvent and excess borane were removed under vacuum, and the residue was treated with a solution of $i\text{Pr}_2\text{Zn}$ (0.8 mL, 2 equiv, 4 mmol, 5.0 M) in ether at 25 °C for 4 h. After removal of the solvent and excess of $i\text{Pr}_2\text{Zn}$ under vacuum, the residue was diluted with THF (10 mL). The black precipitate of zinc was removed by filtration, and the filtrate was slowly treated at –90 °C with a solution of $\text{CuCN} \cdot 2\text{LiCl}$ in THF (0.4 mL, 0.2 equiv, 1.0 M) and after 15 min with allyl bromide (6 mL, 3 equiv, 6 mmol, 1.0 M) in THF. The reaction was allowed to warm up to 25 °C and was quenched after 1 h with aq HCl (10 mL, 3.0 M) and extracted with ether. The crude product obtained after evaporation of the solvent was purified by chromatography (pentane) to provide analytically pure **8** (320 mg, 1.2 mmol, 61 % yield).

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- [11] The hydroboration of **1b** provides, after oxidation with 30 % H_2O_2 , the expected alcohol (80 %) accompanied by the epimer at the hydroxyl position (1–2 %) as well as tertiary alcohol (18 %) that did not undergo migration. However, by the amination procedure, only the product resulting from the major isomer could be detected. The boron–zinc exchange of **4b** obtained by the hydroboration of **1b** provides, after copper-catalyzed allylation, two epimeric allylated products in the ratio 92:8 and in 51 % yield upon isolation. This shows that in this case the secondary cyclopentylzinc intermediate is less configurationally stable.^[9]