

MECHANISM AND APPLICATIONS OF THE REMOTE C-H ACTIVATION OF PHENYL SUBSTITUTED ALKENES BY $\text{BH}_3\cdot\text{THF}$

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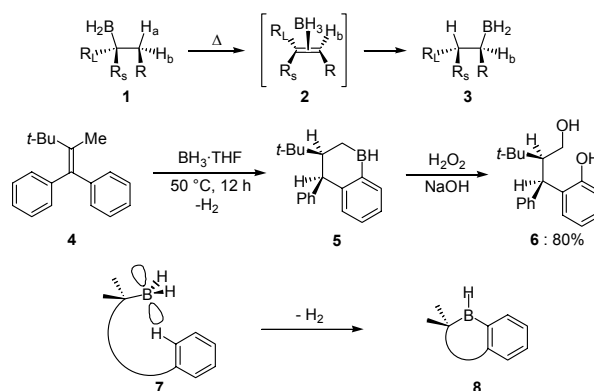
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Abstract

The aim of this work is the study of a method for the activation of unactivated C-H bonds under mild conditions. We use for this purpose the known hydroboration with BH_3 of double bonds strategically situated. This will allow the boron to be placed in a position close to the unactivated C-H bond. Thus, the hydroboration of tetrasubstituted alkenes and, in particular, bicyclic alkenes with $\text{BH}_3\cdot\text{THF}$ at 50 °C provides, via a highly stereoselective 1,2-rearrangement and a remote C-H activation, a diol in which the relative stereochemistry of up to three centers has been controlled.

1 INTRODUCTION

The activation of C-H bonds is an important synthetic target since it opens new possibilities for functionalizing unactivated C-H bonds. Most of these C-H activations have been performed using transition metal mediated reactions or transition metal catalyzed reactions [1]. Recently, it has been shown that allylic C-H bonds can be stereoselectively functionalized using a thermal rearrangement of tertiary organoboranes [2,3]. This reaction has been applied to both open chain and cyclic systems allowing the diastereoselective preparation of a variety of compounds. Thus, the thermal rearrangement of a tertiary organoborane of type **1** furnishes, with high selectivity via a tentative borane-olefin complex **2**, the more stable secondary organoborane **3**. A highly preferential migration of the hydrogen atom H_a (over H_b) has been observed. The migration of H_a leads to the most stable borane-olefin complex (R and R_s are in *cis* arrangement; Scheme 1). It was also disclosed that a remote C-H activation can be performed with tetrasubstituted alkenes bearing bulky substituents, such as **4** [3]. Its treatment with borane-THF (50 °C; 12 h) provides a cyclic organoborane **5**, which after oxidative work-up (NaOH , H_2O_2) provides the diol **6** in 80 % yield (Scheme 1). Herein, we wish to describe a mechanistic study of this rearrangement and application of this C-H activation to other systems of type **7**, which lead to products of type **8**.

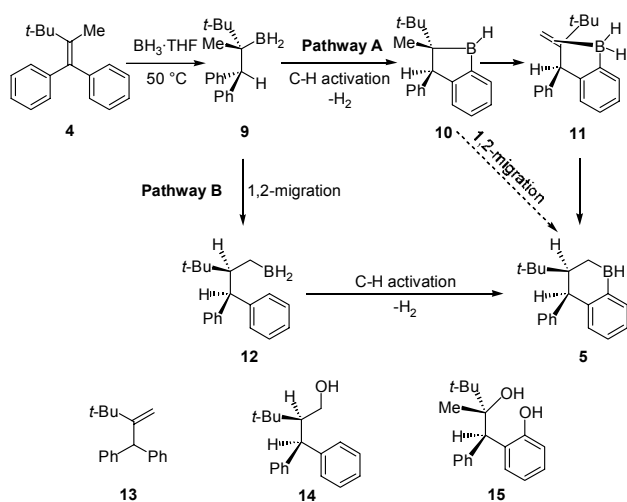


Scheme 1. Stereoselective thermic migration and remote C-H activation of tertiary organoboranes.

2 RESULTS

Remarkably, the conversion of the alkene **4** to the boracycle **5** occurs in such a way that the two bulky substituents (Ph and *t*-Bu) are *cis* to each other. It should also be noted that this high diastereoselectivity implies that only one of the two diastereotopic aromatic rings of **4** undergoes the C-H activation. In order to explain these results, we have envisioned two reaction pathways **A** and **B** leading to the cyclic organoborane **5** (Scheme 2). In the first pathway, the initial hydroboration product **9** which is obtained by the reaction of the tetrasubstituted alkene **4** with $\text{BH}_3\cdot\text{THF}$, can undergo a C-H activation of a phenyl ring [4,5]. This would lead to the cyclic five-membered boracycle **10**. This heterocycle then undergoes a 1,2-migration [6,7] leading via borane-olefin complex **11** to the observed product **5**. Interestingly, the coordination of boron to the olefin in **11** during all the migration process implies a *cis*-relationship between the *t*-Bu and Ph-substituent. The diastereoselective C-H-activation of the aromatic C-H bond of **9** leading to **10** can be readily explained by steric considerations; the bulky *tert*-butyl and phenyl groups being in a *trans*-relationship in **10**.

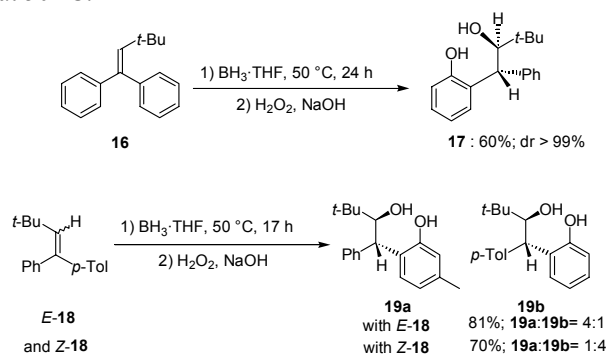
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Scheme 2. Mechanism of the C-H insertion, 1,2-migration of the tertiary borane **9**.

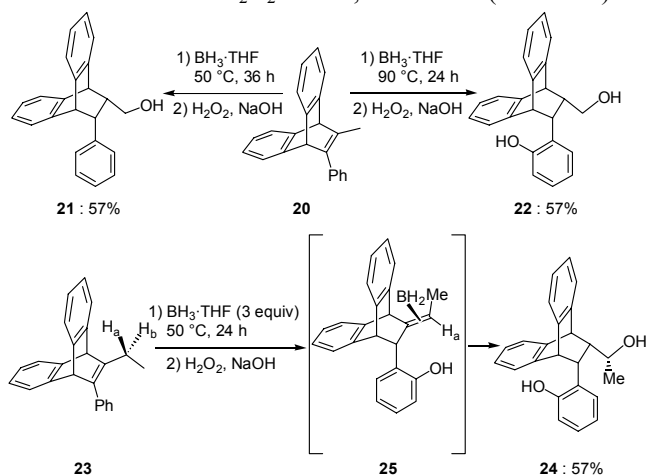
An alternative pathway (Pathway **B**) is also possible. In this case, the 1,2-migration leading to the primary organoborane **12** proceeds first and is followed by a C-H activation of the aromatic ring, leading to the boracycle **5**. Although the 1,2-migration process of **9** to **12** should readily occur under the reaction conditions, the observed diastereoselectivity of the C-H rearrangement is difficult to explain (*cis*-arrangement of the substituents in **5**). We have therefore performed a series of experiments, which clearly prove the proposed pathway **A**. Firstly, we have prepared the isomeric alkene **13** and have submitted it to the hydroboration conditions used for the conversion of **4** to **5** ($\text{BH}_3\cdot\text{THF}$ (3 equiv), $50\text{ }^\circ\text{C}$, 12 h). We have observed after oxidative work-up (H_2O_2 , NaOH) none of the diol **6**, but only the alcohol **14**, which was isolated in 63 % yield showing that the intermediate organoborane **12** is not an intermediate of the C-H activation process (Scheme 2). Furthermore, we have interrupted the hydroboration of **4** after one hour reaction time. The oxidative work-up of the reaction mixture provides two products, the final diol **6** (25 % yield), but also the tertiary diol **15** (32 % yield). This diol **15** is clearly the resulting oxidation product of the cyclic organoborane **10** postulated in the pathway **A**. The relative stereochemistry of **6** and **15** was established by X-ray analysis. These results imply that the C-H activation reaction is especially efficient if a boracyclopentane is formed. We have therefore prepared the trisubstituted alkene **16** and were pleased to find that the hydroboration of **16** with $\text{BH}_3\cdot\text{THF}$ and subsequent heating of **16** in THF at $50\text{ }^\circ\text{C}$ for 24 h furnished, after oxidative work-up, the diastereomerically pure diol **17** in 60 % yield (Scheme 3). We also prepared the *E*- and *Z*-tolyl substituted olefins *E*-**18** and *Z*-**18** and found as expected in the case of *E*-**18**, a selective activation of the tolyl ring (**19a**:**19b** = 4:1), whereas with the *Z*-isomer (*Z*-**18**), a selective activation of the phenyl ring was observed (**19a**:**19b** = 1:4). The formation of 20% of the

other C-H product can be explained as the alkenes *E*-**18** and *Z*-**18** slowly isomerize under the reaction conditions at $50\text{ }^\circ\text{C}$.



Scheme 3. Rearrangement of the hydroboration of trisubstituted olefins.

In order to extend the scope of this remote C-H activation, we have examined the hydroboration of some related tetrasubstituted olefins. Thus, the [2.2.2] bicyclic alkene **20** reacts with $\text{BH}_3\cdot\text{THF}$ at $50\text{ }^\circ\text{C}$ (36 h) and undergoes a selective boron migration leading, after oxidative work-up, to the primary alcohol **21**. Further heating of the alkene **20** and $\text{BH}_3\cdot\text{THF}$ at $90\text{ }^\circ\text{C}$ for 24 h leads to a C-H activation of the phenyl ring and gives, after oxidation with $\text{H}_2\text{O}_2/\text{NaOH}$, the diol **22** (Scheme 4).



Scheme 4. Stereoselective 1,2-migration and remote C-H activation of bicyclic tetrasubstituted olefins.

With this system, the C-H activation is not possible in the initial hydroboration product (*trans* arrangement of the boron and the phenyl ring) and a boron-migration occurs before the C-H activation (opposite reaction sequence as described in Scheme 2). The corresponding ethyl substituted alkene **23** undergoes, as observed in previous cases [2,3], a faster 1,2-migration and furnishes only one diastereomeric diol (**24**) with a relative control of these adjacent chiral centers. The observed diastereoselectivity is readily explained by the model depicted in Scheme 1. Thus, only the diastereotopic

hydrogen H_b undergoes the dehydroboration step leading to the less sterically hindered olefin **25**.

3 CONCLUSION

We have determined the mechanism of the diastereoselective activation of aryl substituted alkenes and found several new systems undergoing this stereoselective C-H activation. We have shown that this new reaction sequence allows the diastereoselective synthesis of up to three contiguous chiral centers. Further extensions and application are currently underway in our laboratories.

4 ACKNOWLEDGMENTS

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5 TYPICAL PROCEDURE FOR THE C-H REMOTE ACTIVATION

The preparation of 1-(2-hydroxyphenyl)-3,3-dimethyl-1-phenyl-2-butanol (**17**) is representative for the reactions of remote C-H activation.

A solution of BH₃·THF (9 mL, 9 mmol, 3 equiv) was added to a solution of 3,3-dimethyl-1,1-diphenyl-1-butene (**16**) (0.71 g, 3 mmol) in THF (25 mL) at room temperature under argon atmosphere. After stirring at 50 °C for 24 h the resulting mixture was quenched by addition of 2M NaOH (12 mL) and 30% H₂O₂ (12 mL). The resulting mixture was stirred at room temperature for 30 min and was then extracted with diethyl ether (10 mL). The combined organic layers were dried over MgSO₄, filtered and concentrated under reduced pressure. Column chromatography of the residue on silica flash (elution with pentane/diethyl ether 7/3) afforded the product **17** as a white solid (478 mg, 60% yield).

All the compounds were characterised by ¹H-NMR, ¹³C-NMR, mass spectroscopy, high-resolution mass spectroscopy and infrared.

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