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Remote C–H Activation of Phenyl-Substituted Alkenes by BH_3·THF: Mechanism and Applications

Jesús A. Varela, Diego Peña, Bernd Goldfuss,[†] Kurt Polborn, and Paul Knochel*

Department Chemie, Ludwig-Maximilians-Universität, Butenandtstrasse 5-13 (Haus F), 81377 München, Germany

paul.knochel@cup.uni-muenchen.de

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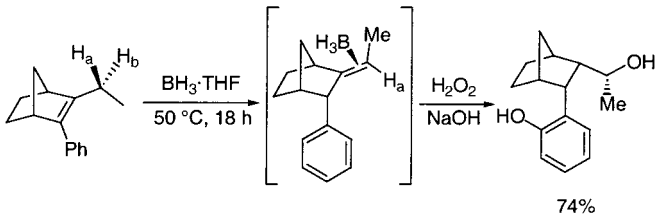
ABSTRACT



The hydroboration of tetrasubstituted alkenes and, in particular, bicyclic alkenes with BH_3·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 three centers has been controlled. A mechanistic study provides general rules for remote C–H activation and leads to new synthetic applications.

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, we have shown that allylic C−H bonds can be stereoselectively functionalized using a thermal rearrangement of tertiary organoboranes.[2−4] 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). We have also discovered that a remote C−H activation can be performed with tetrasubstituted alkenes bearing bulky substituents, such as **4**.[4] Its treatment with borane−THF (50 °C; 12 h) provides cyclic organoborane **5**, which after oxidative workup (NaOH, H_2O_2) provides the diol **6** in 80% yield (Scheme 1). Herein, we wish to

[†] Organisch-Chemisches Institut der Universität Heidelberg, Im Neuenheimer Feld 270, D-29120 Heidelberg, Germany.

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(2) Some remote C−H activations of organoboranes have been described: (a) Köster, R.; Larbig, W.; Rotermund, G. W. *Liebigs Ann*. **1965**, *682*, 21. (b) Köster, R.; Rotermund, G. *Angew. Chem*. **1960**, *72*, 563. (c) Köster, R.; Benedikt, G.; Fenzl, W.; Reinert, K. *Liebisgs Ann*. **1967**, *702*, 197.

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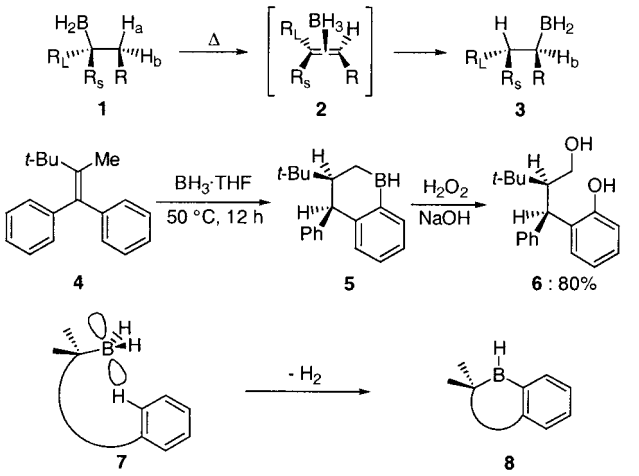
Scheme 1

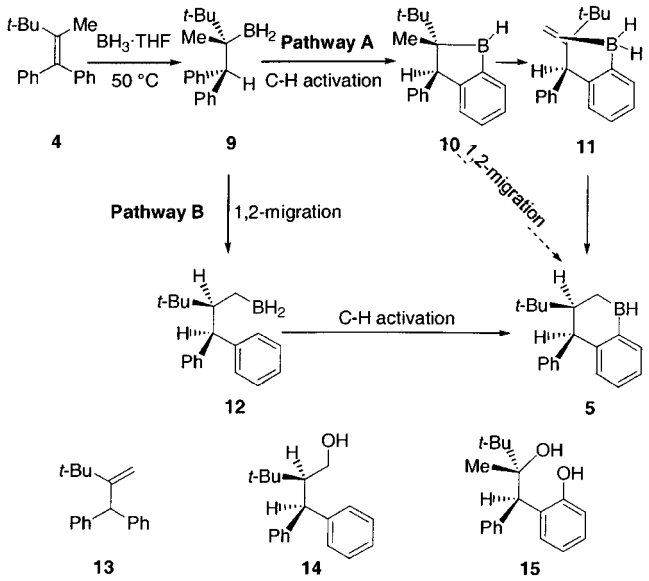


describe a mechanistic study of this rearrangement. The results of this study led us to design other systems of type **7**, which lead to products of type **8** via a C−H activation.

Remarkably, the conversion of the alkene **4** to the boracycle **5** produces an intermediate cyclic organoborane **5** bearing the two bulky substituents (Ph and t-Bu) in a *cis* arrangement. It should also be noted that this high diastereoselectivity implies that only one of the two diastereotopic aromatic rings of **4** undergoes C−H activation. To explain these results, we have envisioned two reaction pathways, **A** and **B**, leading to the cyclic organoborane **5**. In the first pathway, the initial hydroboration product **9**, which is obtained by the reaction of the tetrasubstituted alkene **4** with BH_3·THF, can undergo a C−H activation of a phenyl ring.[5,6] This would lead to the cyclic five-membered boracycle **10**. This heterocycle then undergoes a 1,2-migration,[7,8] leading via borane−olefin complex **11** to the observed product **5**. Interestingly, the coordination of boron to the olefin in **11** during 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, with the bulky *tert*-butyl and phenyl groups being in a *trans* relationship in **10**.

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 therefore performed a series of experiments which clearly prove the proposed pathway **A**. First, we prepared the isomeric alkene **13** and submitted it to the hydroboration conditions used for the conversion of **4** to **5** (BH_3·THF (3 equiv), 50 °C, 24 h). We observed after oxidative workup (H_2O_2, NaOH) the alcohol **14** only and none of the diol **6**; **14** 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 interrupted the hydroboration of **4** after

Scheme 2



1 h of reaction time. The oxidative workup of the reaction mixture provides two products, the final diol **6** (25% yield) and also the tertiary diol **15** (32% yield). Diol **15** is clearly the resulting oxidation product of the cyclic organoborane **10** postulated in pathway **A**. The relative stereochemistry of **6** and **15** was established by X-ray analysis (see Supporting Information). These results imply that the C−H activation reaction is especially efficient if a boracyclopentane is formed. We therefore prepared the trisubstituted alkene **16** and were pleased to find that the hydroboration of **16** with BH_3·THF and subsequent heating of **16** in THF at 50 °C for 24 h furnished, after oxidative workup, 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 °C.

To elucidate the origins of the diastereoselectivities in the intramolecular C−H activations of **9**, the four possible transition structures of the dehydrogenation processes (cf. Scheme 2: conversion of **9** to **10**, Scheme 4)[5] were optimized and analyzed by frequency computations using the MNDO

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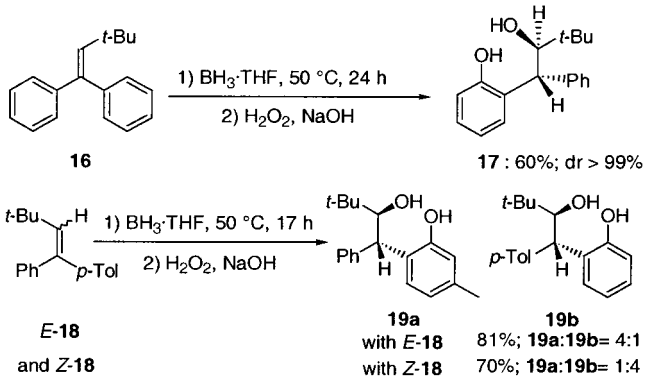
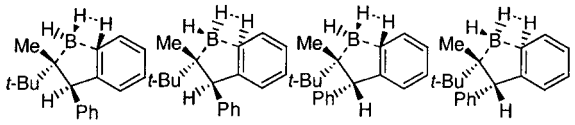
Scheme 3



method.[9,10] B3LYP/6-31G*[11] single-point computations using the IEF-PCM[12] solvation model and THF as solvent were employed to assess the relative energies of the transition structures.

Scheme 4



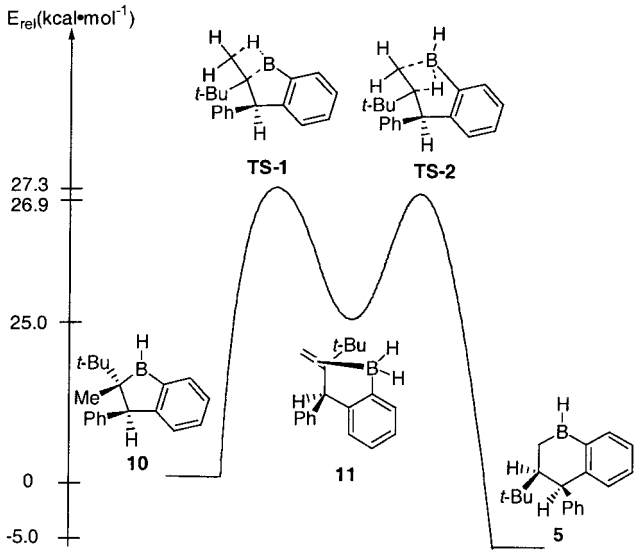
	9a-TS	9b-TS	9c-TS	9d-TS
[a]E_{tot} (a.u.):	-763.8553	-763.8512	-763.8463	-763.8499
E_{rel}(Kcal•mol^{-1}):	0.0	+2.6	+5.6	+3.4

[a] IEF-PCM (THF) B3LYP/6-31G*//MNDO

From these results, the most favorable transition structure is **9a-TS**, in which the two hydrogens that undergo elimination and the *tert*-butyl and the phenyl group are *trans*. This transition structure would afford the intermediate boracycle **10**, which does indeed lead to the observed product **15**.

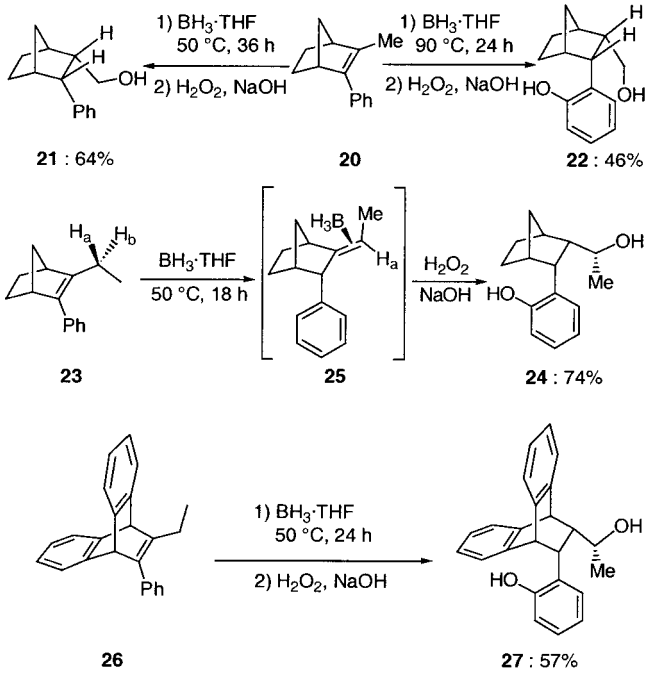
IEF-PCM (THF) B3LYP/6-31G*//MNDO computations were also performed on the 1,2-migration step (Scheme 5). They show that the dehydroboration and the rehydroboration steps have very similar activation energies (**TS-1** and **TS-2**) but the six-membered boracycle **5** is 5.0 kcal•mol^{-1} more favorable than the corresponding five-membered boracycle **10**.

Scheme 5



According to our study, the presence at least of one bulky substituent is required for mild remote C−H activation (steric compression activates the C−H bond). We therefore turned our attention to bicyclic systems. Thus, the [2.2.1] bicyclic alkene **20** reacts with BH_3•THF at 50 °C (36 h) and

Scheme 6



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(12) Polarized Continuum Model (PCM) and Integral Equation Formalism (IEF): (a) Miertus, S.; Scrocco, E.; Tomasi, J. *Chem. Phys.* **1981**, *55*, 117−129. (b) S. Miertus Tomasi, J. *Chem. Phys.* **1982**, *65*, 239−245. (c) Cossi, M.; Barone, V.; Cammi, R.; Tomasi, J. *Chem. Phys. Lett.* **1996**, *255*, 327−335. (d) Cances, E.; Mennucci, B.; Tomasi, J. *J. Chem. Phys.* **1997**, *107*, 3032−3041.

undergoes a selective boron migration leading, after oxidative workup, to the primary alcohol **21**. Further heating of the alkene **20** and BH_3·THF at 90 °C for 24 h leads to a C−H activation of the phenyl ring and gives, after oxidation with H_2O_2/NaOH, the diol **22** (Scheme 6).

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 this does not allow the preferential formation of a five-membered boracycle. Instead 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,[3,4] a faster 1,2-migration and furnishes only one diastereomeric diol (**24**) with a relative control of these adjacent chiral centers. The observed diastereoselectivity (confirmed by X-ray analysis) 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**. Other types of tetrasubstituted alkenes undergo the C−H activation reaction. Thus, the alkene **26** leads, under typical reaction conditions (BH_3·THF (3 equiv); 50 °C, 24 h), to the diol **27** as one diastereoisomer in 57% yield.

In conclusion, we have determined the mechanism of the diastereoselective activation of aryl-substituted alkenes. This allowed us to find several new systems that undergo 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 applications are currently underway in our laboratories.

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Supporting Information Available: Experimental procedures and spectroscopic data. This material is available free of charge via the Internet at http://pubs.acs.org.

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