## LETTERS 2001 Vol. 3, No. 15 2395–2398

ORGANIC

## Remote C–H Activation of Phenyl-Substituted Alkenes by BH<sub>3</sub>·THF: Mechanism and Applications

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Received June 1, 2001

## ABSTRACT



The hydroboration of tetrasubstituted alkenes and, in particular, bicyclic alkenes with  $BH_3 \cdot THF$  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.<sup>1</sup> Recently, we have shown that allylic C–H bonds can be stereoselectively functionalized using a thermal rearrangement of tertiary

10.1021/ol016215a CCC: \$20.00 © 2001 American Chemical Society Published on Web 07/06/2001

organoboranes.<sup>2–4</sup> 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<sub>a</sub> (over H<sub>b</sub>) has been observed. The migration of H<sub>a</sub> leads to the most stable borane–olefin complex (R and R<sub>s</sub> 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**.<sup>4</sup> Its treatment with borane–THF (50 °C; 12 h) provides cyclic organoborane **5**, which after oxidative workup (NaOH, H<sub>2</sub>O<sub>2</sub>) provides the diol **6** in 80% yield (Scheme 1). Herein, we wish to

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<sup>(1) (</sup>a) Janowicz, A. H.; Bergman, R. G. J. Am. Chem. Soc. 1982, 104, 352. (b) Ryabov, A. D. Chem. Rev. 1990, 90, 403. (c) Adam, W.; Nestler, B. Angew. Chem. Int. Ed. Engl. 1993, 32, 733. (d) Murai, S.; Kaikiuchi, F.; Sekiine, S.; Tanaka, Y.; Kamatani, A.; Sonoda, M.; Chatani, N. Nature 1993, 366, 529. (e) Arndtsen, B. A.; Bergman, R. G. Science 1995, 270, 1970. (f) Crabtree, R. H. Chem. Rev. 1995, 95, 987. (g) Rispens, M. T.; Zardervan, C.; Feringa, B. L. Tetrahedron: Asymmetry 1995, 6, 661. (h) Sonoda, M.; Kakiuchi, F.; Chatani, N.; Murai, S. J. Organomet. Chem. 1995, 504, 151. (i) Trost, B. M.; Iwi, K.; Davies, I. W. J. Am. Chem. Soc. 1995, 117, 5371. (j) Williams, N. A.; Uchimaru, Y.; Tanaka, M. J. Chem. Soc., Chem. Commun. 1995, 1129. (k) Alaimo, P. J.; Arndtsen, B. A.; Bergman, R. G. J. Am. Chem. Soc. 1997, 119, 5269. (1) Grigg, R.; Savic, V. Tetrahedron Lett. **1997**, 38, 5737. (m) Luecke, H. F.; Bergman, R. G. J. Am. Chem. Soc. **1997**, 119, 11538. (n) Miyaluji, A.; Katsuki, T. Tetrahedron 1998, 54, 19339. (o) Johnson, J. A.; Sames, D. J. Am. Chem. Soc. 2000, 122, 6321. (p) Davies, H. M. L.; Antoulinakis, E. G. J. Organomet. Chem. 2001, 617, 47. (q) Davies, H. M. L.; Ren, P. J. Am. Chem. Soc. 2001, 123, 2070. (r) Dycker, G. Angew. Chem. Int. Ed. 1999, 28. 1698.

<sup>(2)</sup> 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.

<sup>(3) (</sup>a) Lhermitte, F.; Knochel, P. *Angew. Chem., Int. Ed.* **1998**, *37*, 2460.
(b) Bromm, L. O.; Laaziri, H.; Lhermitte, F.; Harms, K.; Knochel, P. *J. Am. Chem. Soc.* **2000**, *122*, 10218.

<sup>(4)</sup> Laaziri, H.; Bromm, L. O.; Lhermitte, F.; Gschwind, R. M.; Knochel, P. J. Am. Chem. Soc. **1999**, *121*, 6940.



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<sub>3</sub>•THF, can undergo a C-H activation of a phenyl ring.<sup>5,6</sup> This would lead to the cyclic five-membered boracycle 10. This heterocycle then undergoes a 1,2-migration,<sup>7,8</sup> 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

(6) Köster, W.; Siebert, W. Methoden der Organischen Chemie (Houben-Weyl), 4th ed.; Thieme: Stuttgart, 1952, 1982; Vol. 13, Part 3a, pp 1–908.

(7) For mechanistic studies on 1,2-boron migrations, see: (a) Wood, S.
E.; Rickborn, B. J. Org. Chem. 1983, 48, 555. (b) Field, L. D.; Galagher,
S. P. Tetrahedron Lett. 1985, 26, 6125.

(*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<sub>3</sub>·THF (3 equiv), 50 °C, 24 h). We observed after oxidative workup (H<sub>2</sub>O<sub>2</sub>, 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



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<sub>3</sub>•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)<sup>5</sup> were optimized and analyzed by frequency computations using the MNDO

<sup>(5)</sup> For a theoretical study of the direct borane-hydrocarbon dehydrogenation, see: Goldfuss, B.; Knochel, P.; Bromm, L. O.; Knapp, K. Angew. Chem., Int. Ed. 2000, 39, 4136.

<sup>(8) (</sup>a) Brown, H. C.; Zweifel, G. J. Am. Chem. Soc. **1966**, 88, 1433. (b) Brown, H. C.; Bhatt, M. V. J. Am. Chem. Soc. **1966**, 88, 1440.



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



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).

(10) Gaussian 98, Revision A.5. Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Zakrzewski, V. G.; Montgomery, J. A., Jr.; Stratmann, R. E.; Burant, J. C.; Dapprich, S.; Millam, J. M.; Daniels, A. D.; Kudin, K. N.; Strain, M. C.; Farkas, O.; Tomasi, J.; Barone, V.; Cossi, M.; Cammi, R.; Mennucci, B.; Pomelli, C.; Adamo, C.; Clifford, S.; Ochterski, J.; Petersson, G. A.; Ayala, P. Y.; Cui, Q.; Morokuma, K.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Cioslowski, J.; Ortiz, J. V.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Gonzalez, C.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Andres, J. L.; Gonzalez, C.; Head-Gordon, M.; Replogle, E. S.; Pople, J. A. Gaussian, Inc. Pittsburgh, PA, 1998.

(11) (a) Becke, A. D. J. Chem. Phys. **1993**, 98, 5648-5652. (b) Lee, C.; Yang, W.; Parr, R. G. Phys. Rev. B **1988**, 37, 785-789.

(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. 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<sup>-1</sup> more favorable than the corresponding five-membered boracycle **10**.



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<sub>3</sub>·THF at 50 °C (36 h) and



<sup>(9) (</sup>a) Dewar, M. J. S.; Thiel, W. J. Am. Chem. Soc. 1997, 99, 4907.
(b) Dewar, M. J. S.; McKee, M. L. J. Am. Chem. Soc. 1977, 99, 5231.

undergoes a selective boron migration leading, after oxidative workup, to the primary alcohol **21**. Further heating of the alkene **20** and BH<sub>3</sub>·THF at 90 °C for 24 h leads to a C–H activation of the phenyl ring and gives, after oxidation with H<sub>2</sub>O<sub>2</sub>/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,<sup>3,4</sup> 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<sub>b</sub> 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 (BH3•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.

Acknowledgment. We thank the DFG (SFB 260, Leibniz-Programm). J.A.V. thanks the Alexander-von-Humboldt Stiftung and the European Community (Marie Curie Fellowship of the program "Improving Human Research Potential and the Socio-economic Knowledge Base" contract number HPMFCT-2000-00451) for both fellowships. We thank Chemetall GmbH (Frankfurt) and Degussa-Hüls AG (Hanau) for generous gifts of chemicals.

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

OL016215A