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Jillian R. Sanzone, Chunhua Tony Hu, and Keith A. Woerpel J. Am. Chem. Soc., Just Accepted Manuscript • Publication Date (Web): 01 Jun 2017 Downloaded from http://pubs.acs.org on June 2, 2017

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Uncatalyzed Carboboration of Seven-Membered-Ring *trans*-Alkenes: Formation of Air-Stable Trialkylboranes

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Supporting Information Placeholder

ABSTRACT: Seven-membered-ring *trans*-alkenes undergo rapid, uncatalyzed carboboration reactions to form trialkylboranes as single diastereomers. In contrast with other trialkylboranes, which can ignite in the presence of oxygen, these trialkylboranes are stable in air. Hindered trialkylboranes can undergo reverse hydroboration reactions to form allylic silanes or can be oxidized to afford highly substituted triols. This reaction sequence permits the construction of compounds with up to five consecutive stereocenters. Control experiments and computational studies support a concerted mechanism for the migratory insertion of the alkene into the carbon–boron bond, similar to the mechanism for hydroboration.

The reactions of organoboranes are powerful transformations in synthetic organic chemistry.¹ For example, the hydroboration of alkenes, the stereospecific and often stereoselective addition of a boron-hydrogen bond across a carbon-carbon double bond, is a commonly used transformation for adding the elements of water to unsaturated substrates.² The addition of boron–oxygen,³ boron-nitrogen,⁴ and boron-carbon⁵ bonds across the carbon-carbon triple bond of alkynes have also been reported, and recently catalyst-free 1.2-carboborations of diarylchloroboranes and diarylborinium ions with alkynes was observed.⁶ The corresponding reaction of boron-carbon bonds with alkenes is considerably more difficult. Metal-catalyzed variants of this reaction have been reported,⁷ but little progress has been made in developing a metal-free carboboration using simple trialkylboranes.⁸

Here, we report that the uncatalyzed *syn*-addition of trialkylboranes to seven-membered-ring *trans*-alkenes occurs at room temperature in high yields and with high diastereoselectivity. The resulting hindered boranes are air-stable, unlike most trialkylboranes, which are pyrophoric.⁹ Analysis of single-crystal X-ray crystallographic studies gives insight into the unique stability of these compounds. Mechanistic studies indicate that the carboboration reaction occurs through a concerted, four-

membered ring transition state similar to the widely used hydroboration reaction. The resulting boranes can be oxidized with retention of configuration to form triols with five consecutive stereocenters.

Initial experiments indicated that an alkene can react with a trialkylborane provided the alkene is sufficiently strained. *trans*-Alkene 1, which can be prepared from 1,3-pentadiene, a silylene source, and benzaldehyde,¹⁰ reacted with triethylborane in the absence of any catalyst to form borane 2 in 92% isolated yield in under two hours (eq 1). A single stereoisomer of a new product was formed, with three new ethyl resonances present in the ¹H NMR spectrum. The structure was tentatively assigned as 2.



Several properties of **2** contrasted with the properties associated with trialkylboranes. Compound **2** was found to be stable to column chromatography and air, compared to most trialkylboranes, which react explosively with oxygen.⁹ Attempts to make Lewis acid-base complexes with ammonia, triethylamine, and trime-thylphosphine, or to form borates with cesium fluoride and sodium azide, were also unsuccessful. The ¹¹B NMR chemical shift of δ 32.1 ppm for borane **2** was dramatically different from chemical shifts of other trialkylboranes (δ 80–90 ppm).¹¹ The large upfield shift is more consistent with a Lewis acid-base complex where a heteroatom coordinates to a trialkylborane.¹²

The unusual properties of borane 2 led us to conduct additional experiments to confirm the structure. When a solution of trialkylborane 2 in C₆D₆ was heated to 80 °C in a sealed tube with *n*-butylamine, *cis*-alkene 3 and aminoborane 4 were formed in 95% and 85% yields, respectively, as determined by ¹H NMR spectroscopic analysis (Scheme 1). Hydrogen gas was also observed (δ 4.43 ppm). Formation of aminoborane 4 and hydro-

Scheme 1. Dehydroboration of Trialkylborane 2



The reaction of compound **2** with an alkene further confirmed the structure (Scheme 1). Heating borane **2** in the presence of allylbenzene **5** yielded trialkylborane **6** (74%) and *cis*-alkene **3** (96%). This alkylborane had a ¹¹B NMR chemical shift of δ 85.9 ppm, which is consistent with product **6** having a diethylboryl functional group. ^{11, 14} The results shown in Scheme 1 would not be consistent if new carbon–boron and carbon–carbon bonds were not formed during the original carboboration reaction (eq 1).



Figure 1. Molecular structure of trialkylborane **2** (ellipsoids set at 50% probability). The hydrogen atoms, except those on C1–C5, have been removed for clarity.

Eventually, crystals suitable for X-ray diffraction studies were obtained to confirm the structure and give insight into the unusual stability of **2**. The stereochemical configuration of this product is consistent with *syn*addition of the carbon-boron bond across the carboncarbon double bond, as observed for hydroboration. The stability of trialkylborane **2** towards oxygen and Lewis bases is likely a result of steric protection, a characteristic that allows isolation of unstable and reactive compounds.¹⁵ The methyl and ethyl substituents on C2 and C4, respectively, block access to the empty orbital on the boron atom. These groups also prevent free rotation around the C3–B1 bond, forcing trialkylborane **2** to adopt the conformer shown in the X-ray crystal structure (Figure 1).

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Hyperconjugation of adjacent bonds also contribute to the stability of trialkylborane 2. The bond angles of the methylene carbons attached to the boron atom are closer to sp^2 hybridization (C16-C15-B1 = 119.08 (13)° and $C18-C17-B1 = 120.62 (15)^{\circ}$) than sp³ hybridization. The B1-C15 and B1-C17 bond lengths (1.570 (2) Å and 1.574 (2) Å) are shorter than the B1–C3 bond length (1.6042 (18) Å) and shorter than typical carbon-boron bond lengths (1.60 Å).¹⁶ The large bond angles and short bond lengths are likely the result of the filled orbitals of the methylene groups on C15 and C17 donating electron density into the empty orbital on the boron atom, further adding to the stability of trialkylborane 2^{17} . The donation of electron density from the α -C-H bonds due to the locked conformation of borane 2, and donation of other nearby bonds, likely account for the unusual ¹¹B NMR chemical shift.¹⁸

Table 1. Substrate Scope of Carboboration



^aIsolated yields based on *trans*-alkene. ^bUnpurified yield: the carbon–boron bond was oxidized to obtain a yield over two steps (see Supporting Information).

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58 59 60 The *syn*-carboboration is general for a number of *trans*-alkenes (Table 1). Aryl, alkenyl, and alkyl groups were tolerated under the reaction conditions. In all cases, addition was completely stereoselective and regioselective. If two alkene functional groups were present, carboboration only occurred on the strained double bond (i.e., **10** and **13**). Trialkylboranes containing five consecutive stereocenters (**16**) can be synthesized with complete control of diastereoselectivity in each step. Additionally, triethylborane or tri-*n*-butylborane can be used as the borane source. Preliminary results show that any unpurified trialkylborane derived from the hydroboration of an alkene will be tolerated, as illustrated by the formation of borane **18**.¹⁹

The 1,2-carboboration of alkenes is sensitive to steric effects and strain. Alkenes with tertiary allylic carbon atoms did not react with triethylborane. Trisubstituted *trans*-alkenes were also too hindered to react with triethylborane. Sterically demanding trialkylboranes could not be used: no reaction was observed between 1 and tri*sec*-butylborane. A strained *trans*-cyclooctene²⁰ reacted only slowly with triethylborane, indicating the extent to which strain is important for reactivity.²¹

Given that the uncatalyzed migratory insertion of an alkene into the carbon-boron bond is unprecedented, efforts were made to provide insight into the reaction mechanism. Three mechanisms for the carboboration reaction were considered. One possible mechanism has a four-centered transition state resembling the mechanism of the hydroboration of alkenes (Figure 2, I). Alternatively, stepwise pathways involving a radical (Figure 2, II) or a zwitterion (Figure 2, III) are possible.

$$\begin{bmatrix} t - Bu \\ -Si \\ -O \\ R^{*} \\ -BR_{2} \\ R^{*} \\ -D \\ R^{*} \\ R^{$$

Figure 2. Possible transition state and intermediates of carboboration reaction.

Several experiments provide evidence against a mechanism involving radicals. A radical mechanism would likely include intermediate II, a free radical that would react rapidly with other radicals. In the presence of a radical trap (TEMPO),²² the reaction proceeded smoothly, and no additional products were observed. Furthermore, crossover experiments provide evidence against a mechanism where the boron atom and alkyl group are separated (intermediate II). Carboboration of *trans*-alkene 1 in the presence of a mixture of triethylborane and tri-*n*-butylborane afforded only products where all three alkyl groups were identical (2 and 7).²¹ Additionally, stabilization of a β -silyl radical is small (1 kcal/mol).²³ As a result, both γ - and β -silyl radicals should form as intermediates, leading to a mixture of

regioisomeric products. Furthermore, such a radical would not be configurationally stable, so products could be formed as mixtures of stereoisomers. Only a single stereoisomer was observed in the reactions of trialkylboranes and *trans*-alkenes, however. These results are more consistent with a concerted mechanism.²⁴

A stepwise pathway involving a zwitterionic intermediate is also possible (Figure 2, III),²⁵ but several factors are inconsistent with this mechanism. Formation of βsilyl carbocations similar to III have resulted in nucleophilic attack of the ring oxygen on the carbocation and rearrangement to form five-membered ring products.²⁶ No such rearrangement products were observed in the carboboration reactions. A stepwise mechanism should also allow trisubstituted alkenes to undergo carboboration because these *trans*-alkenes react rapidly with hindered electrophiles in a stepwise fashion.^{20b} Trisubstituted alkenes were unreactive with triethylborane, however. Additionally, a zwitterionic, stepwise mechanism implies that nucleophilicity of the alkene is an important factor for carboboration to occur. When nucleophilic enamines, which should be more nucleophilic than a strained allylic silane,^{20b, 27} were subjected to the carboboration reaction, no reaction was observed. This observation is inconsistent with a stepwise mechanism involving zwitterionic intermediates. Taken together, these data are more consistent with a concerted mechanism similar to the mechanism for hydroboration.

Computational studies also support a concerted mechanism. Model structures of the starting materials and possible transition states were investigated using density functional methods (M06-2X/6-311+G(2d,p)).² A low-energy four-membered transition state²⁸ involving concerted addition of a carbon-boron bond to the carbon-carbon double bond (i.e., syn-carboboration) was found for addition to a trans-oxasilacycloheptene related to 1 (about 3 kcal/mol). In contrast, for an unstrained alkene (ethylene), the syn-carboboration transition state was over 20 kcal/mol higher in energy than the starting materials. The computational results were also consistent with the regioselectivity observed: the transition state leading to the observed isomer was 5 kcal/mol lower in energy than the transition state with the other regiochemistry. Efforts to identify intermediates along a stepwise pathway led only to high-energy structures.

The carbon–boron bond and carbon–silicon bonds can be oxidized to yield synthetically useful products. Oxidation of the carbon–boron bond in trialkylborane **2**, followed by base-mediated rearrangement, formed oxasilacyclopentane **19** in 66% yield over two steps.²⁹ Oxidation of the carbon–silicon bond, using conditions optimized for hindered silyloxy groups,³⁰ yielded triol **20**. Previously reported routes to synthesize a product with a similar substitution pattern were longer, with some steps proceeding with low diastereoselectivity.³¹ Scheme 2. Oxidation of Carbon–Boron and Carbon– Silicon Bonds



In conclusion, the *syn*-carboboration of alkenes, although not generally observed during *syn*-hydroboration, is an equally viable reaction. The resulting trialkylboranes were formed as single diastereomers, and up to five consecutive stereocenters can be formed in a few synthetic steps. The product's carbon–boron and carbon–silicon bonds can be oxidized to form synthetically useful triols.

ASSOCIATED CONTENT

The Supporting Information is available free of charge ontheACSPublicationswebsite.

Experimental procedures, stereochemical proofs, X-ray data, and full characterization (PDF) X-ray crystallographic data for 2 (CIF) X-ray crystallographic data for ent-10 (CIF)

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Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

This research was supported by the National Science Foundation (CHE-1362709). J.R.S. was supported by a Margaret Strauss Kramer Fellowship from the NYU Department of Chemistry. K.A.W. thanks the Global Research Initiatives, NYU and NYU Florence, for a fellowship. NMR spectra were acquired with the TCI cryoprobe and Bruker Advance 400 were supported by the National Institutes of Health (OD016343) and the National Science Foundation (CHE-01162222), respectively. We thank Dr. Chin Lin for his assistance with NMR spectroscopy and mass spectrometry. C.H. thanks the support from the Materials Research Science and Engineering Center (MRSEC) program of the National Science Foundation (NSF) under Award Numbers DMR-0820341 and DMR-1420073.

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