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A Mechanistic Alternative for the Intramolecular Hydroboration of Homoallylic Amine and Phosphine Borane Complexes

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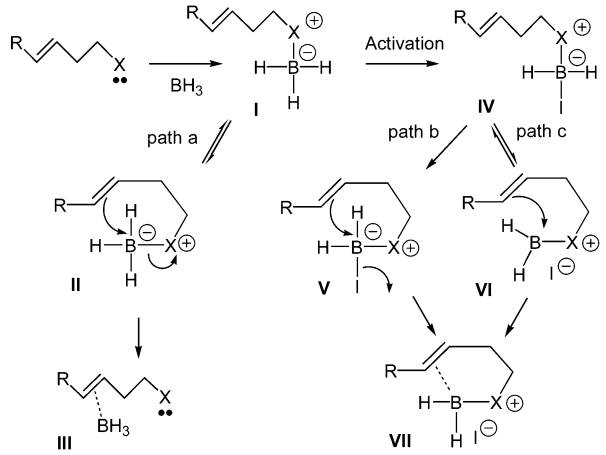
There have been many attempts to demonstrate intramolecular, heteroatom-directed hydroboration, dating back more than 30 years.[1−3] Although circumstantial evidence consistent with an internal mechanism has been reported in some cases,[1b] there are very few convincing examples. The most definitive examples involve transition-metal-catalyzed internal hydroborations of allylic and homoallylic substrates with potentially coordinating functional groups.[2] Panek et al. have reported another system where intramolecular hydroboration is supported by substantial evidence,[3] but questions remain regarding the mechanistic details.

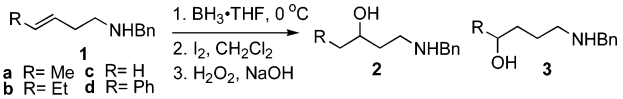
Under metal-free conditions, intramolecular hydroboration might occur upon heating a borane Lewis acid−Lewis base complex **I** (Scheme 1, path a). For complex **I** to undergo internal hydroboration, the alkene must displace the heteroatom leaving group to give an olefin complex **III**. With X = oxygen, this mechanism would involve the same bonding interactions that are proposed for the intermolecular hydroboration using borane etherates, as indicated by theoretical considerations.[4] However, the process represented by transition state **II** would amount to a nucleophilic substitution reaction involving an endocyclic B−X bond as the formal leaving group. There are no established precedents for such reactions involving five- or six-center transition states, a consequence of unfavorable geometry for the necessary orbital interactions.[5] Therefore, reactions of isolable complexes **I** (X = N, P) require heating to dissociate the complex[6] and take place by intermolecular hydroboration via the free borane.[6f]

Scheme 1



We have considered mechanistic alternatives for internal hydroboration that circumvent the problem of endocyclic leaving group displacement (Scheme 1, paths b and c). Activating an amine borane complex (X = nitrogen) with iodine should generate an intermediate **IV** that contains a reactive B−I bond.[7] If the halogen remains connected, a tethered olefin could undergo intramolecular hydroboration by an S_N2-like displacement of the exocyclic iodide leaving group as shown by transition state **V**. Should initial heterolysis of the B−I bond be necessary (path c), the resulting trivalent borenium ion **VI** is expected to be a highly electrophlic hydroborating reagent that operates in an S_N1-like mode. The key result of either mechanism is the formation of an olefin-borane π complex **VII** that is configured for internal hydroboration via a transition state having ion pair character.

Table 1. Iodine-Promoted Hydroboration of Acyclic Homoallylic Amines



entry[a]	substrate	yield (%)	products	ratio[b]
1	**1a**	83	**2a**/**3a**	11:1
2	**1b**	82	**2b**/**3b**	10:1
3	**1c**	90	**2c**/**3c**	1:3
4	**1d**	82	**2d**/**3d**	2:1
5[c]	**1a**	78	**2a**/**3a**	10:1

[a] Activation with 50 mol % iodine unless noted. [b] NMR assay. [c] Activation using 10 mol % iodine, 1 h at room temperature in $CDCl_3$.

To test the feasibility of this proposal, we opted to use readily accessible homoallylic amine boranes. These complexes should be easily activated by iodine according to literature precedents for saturated analogues.[7] Hydroboration would then occur by an intramolecular pathway via a fused bicyclic or a bridged bicyclic transition state, either of which is stereoelectronically feasible.[8]

Substrates **1a** and **1b** were complexed with 1.0 equiv of BH_3·THF. Treatment of each complex with 50 mol % of iodine resulted in rapid hydrogen evolution, presumably due to formation of an iodoborane complex.[7] After 30 min at room temperature, followed by oxidation, major products **2a** and **2b** were obtained (Table 1, entries 1 and 2, 10−11:1 ratio). A control experiment using **1a** and excess borane at room temperature gave a 2.4:1 ratio of **2a**:**3a**. Therefore, the regioselectivity of Table 1, entry 1, clearly indicates an intramolecular pathway. A more demanding test for internal direction utilized an amine containing a terminal double bond (Table 1, entry 3). The results show that steric bias favoring C−B bonding at the less hindered position is dominant in this case. Amine **1d** also displays lower regioselectivity (2:1), a finding that is consistent with previous reports for the intermolecular hydroboration of styrenes as compared to simple alkenes.[9,10]

The cyclic amine borane **4** undergoes facile iodine-promoted hydroboration and was a useful substrate to verify that product stereochemistry is consistent with a four-center hydroboration pathway (Scheme 2). The amino alcohol **5**, obtained after hydroboration and oxidation, is expected to display a trans relationship between H_a and H_b, resulting from syn delivery of boron and hydride to the olefin. NMR analysis was possible after benzoylation to give **6**, and J = 9.5 Hz between H_a and H_b confirmed the expected trans stereochemistry.

We considered the possibility that a catalytic amount of iodine might be sufficient to promote hydroboration of homoallylic amine

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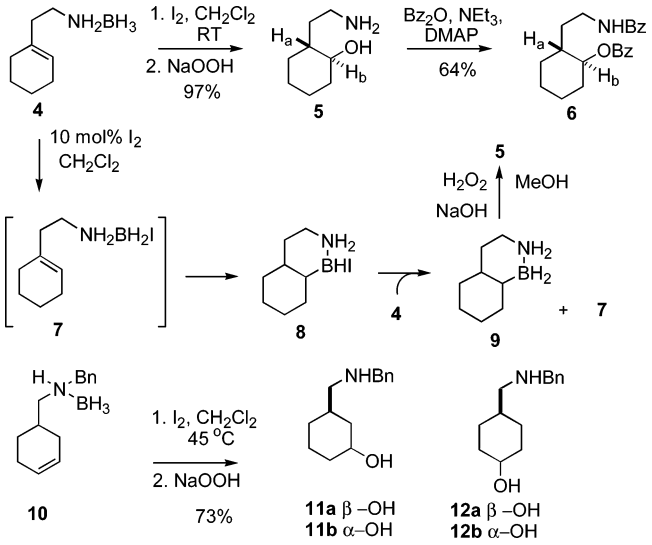
Scheme 2



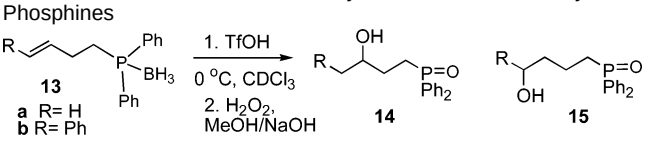
borane complexes (Scheme 2). This option was explored using cyclic substrate **4**. Treatment with 10 mol % of I_2 at room temperature resulted in complete consumption of olefin in less than 2 h, and the stable amine borane **9** (46%) was isolated after chromatography. Alternatively, addition of 10% I_2 followed by oxidation provided the expected amino alcohol **5** in 87% yield. While the details and efficiency of the catalytic cycle have yet to be explored, the results show that iodoborane **7** (20 mol %, formed in situ from 10 mol % I_2) induces the conversion of at least 4 additional equiv of **4** to the cyclic isomer **9**. Transfer of iodine from the intermediate **8** to **4** is indicated by these observations. An equally facile catalytic reaction occurred with **1a** to give amino alcohol products **2a** and **3a** (Table 1, entry 5). The intramolecular process constitutes a new mechanism for catalytic hydroboration from amine boranes.

Iodine-induced hydroboration starting from the cyclohexenyl derivative **10** provides strong evidence for the intramolecular pathway. Following oxidation, amino alcohols **11a**, **12a**, and (tentatively) **12b** were formed in a ratio of 10:3:1. The minor component could not be purified, but the tentative assignment is based on ^{1}H NMR comparisons with the mixture of all four isomers (1.2:1.2:1:1 **11a**:**11b**:**12a**:**12b**) obtained by reaction of **10** with excess BH_3•THF. Clearly, **11a** and **12a** are formed by intramolecular hydroboration. If the minor product is indeed **12b**, then its formation may be due to competing intermolecular hydroboration by an unknown pathway.

The possibility of intramolecular hydroboration starting from analogous phosphine boranes[6e,f] was also tested. Initial attempts to activate **13a** with iodine resulted in hydroboration as expected, but the NMR spectrum revealed the formation of unknown byproducts. An alternative method of activation proved more effective. Thus, **13a** or **13b** was treated with 1.1 equiv of triflic acid, resulting in vigorous hydrogen evolution at ice bath temperatures. Warming to room temperature and the usual oxidative workup resulted in the oxidation of phosphorus as well as boron. This gave a mixture of isomeric hydroxyalkylphosphine oxides **14** (major) and **15** (Table 2), while a control experiment from **13a** (excess borane, room temperature) afforded a typical 88:12 ratio in favor of **15a**. The triflic acid activation was also tested with the amine borane **1a** and was found to give results identical to those of Table 1, entry 1 (83% yield, 11:1 ratio of **2a**:**3a**).

Differences in regioselectivity are apparent by comparison of Table 2 data with the analogous amine borane reactions (Table 1; entries 3, 4). If one assumes that internal hydroboration occurs via an alkene complex **VII** (X = PPh_2) and involves the usual four-center transition state, then the phosphine boranes react with a preference for fused, bicyclic transition states (five-center delivery of boron to the nearest alkene carbon). In the nitrogen series, bridged, bicyclic transition states (six-center delivery of boron to the remote alkene carbon) are also significant, and this pathway becomes dominant for the terminal alkene **1c** (Table 1, entry 3). Tentatively, the contrast with the phosphine boranes is attributed to longer phosphorus versus nitrogen bonds, but leaving group differences (triflate vs iodide) may also play a role.

Table 2. TfOH-Promoted Internal Hydroboration of Homoallylic Phosphines



entry[a]	substrate	yield (%)[b]	products	ratio
1	**13a**	87	**14a/15a**	3:1
2	**13b**	88	**14b/15b**	93:7

In summary, the first examples of intramolecular hydroboration starting from homoallylic amine or phosphine boranes are reported. The process involves activation via incorporation of a leaving group at boron, leading to a new mechanistic pathway for internal hydroboration. Pending further study, we suggest an ion pair π-complex **VII** as the key species responsible for internal hydroboration.[11]

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

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(11) Preliminary studies suggest that intermolecular hydroboration with stable borane complexes is also possible using analogous activation methods. This work will be described elsewhere.

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