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Mechanistic Variations in Ionic Hydrogenation of Unsaturated Phosphine and Amine Boranes

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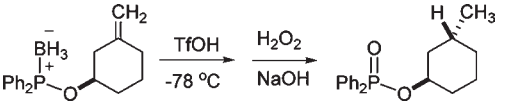
ABSTRACT

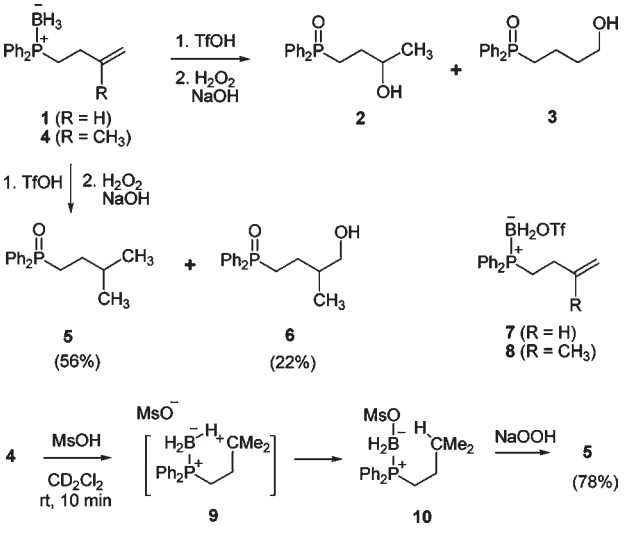


Internal hydride transfer occurs when tethered carbocations are generated from unsaturated phosphine or phosphinite boranes. 3-Methylenecyclohexyl-derived boranes 12 or 18 react with MsOH to give ionic hydrogenation products with high *syn*-selectivity. With unsaturated amine boranes, initial hydrogen evolution gives BH_2(OMs) complexes, but IH occurs using excess MsOH in a slower second stage. A diastereoselective reaction occurs from 26b using camphorsulfonic acid (first stage) and MsOH (second stage), affording 33 (68% ee) after hydrolysis.

An earlier publication from our laboratory reported that internal hydroboration occurs when the butenylphosphine borane **1** is activated with TfOH (1.1 equiv), resulting in alcohols **2** and **3** (3:1 ratio) after standard oxidative workup (Scheme 1).[1] However, the same procedure applied to the methyl-substituted analogue **4** affords **5** as the major product (56%) due to competing ionic hydrogenation (IH).[2] The expected alcohol **6** is a minor product in this case (22%). Evidently, formation of the intermediate **7** as required for internal hydroboration is faster starting from **1**, while protonation of the disubstituted alkene **4** is faster compared to the formation of **8**. The result is a modest advantage for the IH pathway.[1]

We have revisited the activation of **4** to gain mechanistic insight and to learn whether modified conditions would favor the ionic hydrogenation pathway with Lewis base borane complexes. Weaker acids were examined in an attempt to minimize hydrogen evolution and hydroboration, but **4** was unreactive with CF_3CO_2H after 1 h at rt. The more acidic methanesulfonic acid (MsOH) did initiate the ionic hydrogenation, although the reaction was slow using stoichiometric MsOH. On the other hand, with 3 equiv of acid the alkene was consumed within 10 min at rt according to a ^{1}H NMR assay. A major intermediate was detected prior to oxidative workup, tentatively assigned structure **10** from the downfield shift of the B–*H* signal

Scheme 1. Ionic Hydrogenation of Phosphine **1**



(2H, centered at δ 3.3 ppm, compared to δ 1.0 ppm for the B–*H* signal of **4**) and a singlet integrating for 3H at δ 2.84 ppm (H_3C–SO_3B). A minor phosphonium salt

(1) Shapland, P.; Vedejs, E. *J. Org. Chem.* **2004**, *69*, 4094.
(2) Kursanov, D. N.; Parnes, Z. N.; Loim, N. M. *Synthesis* **1974**, 633.

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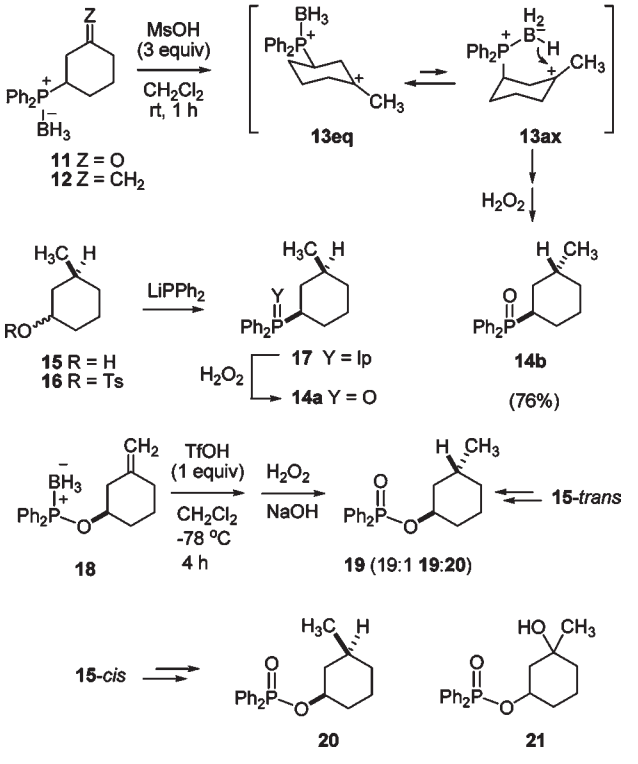
byproduct corresponding to P−B bond protonolysis was also indicated by the presence of a small doublet of triplets at δ 7.8 ppm ($^1J_{PH}$ = 508 Hz, $^3J_{HH}$ = 6.2 Hz) in the ^{1}H NMR spectrum. Oxidative workup of the reaction mixture gave **5** in an improved 78% yield along with 12% of **6**. However, these results do not require that alkene hydrogenation necessarily involves an intramolecular hydride transfer as implied from **9** to **10**.

A cylic phosphine borane environment was designed to confirm that IH occurs via intramolecular hydride transfer. Thus, phosphine borane **12** was prepared by Wittig methylenation of the known cyclohexanone **11**.[3] Subjecting **12** to the MsOH activation conditions (0.1 M in **12**) followed by oxidative workup resulted in isolation of **14b** as the sole reduction product; no trace of **14a** was observed by ^{1}H NMR assay (>99:1 dr). This remarkable stereoselectivity did not erode until the concentration of **12** was increased from ca. 0.1 to 1.0 M. The latter experiment gave a 7:1 ratio of **14b**:**14a**, suggesting minor competition by an intermolecular hydride transfer to the intermediate cation **13eq**. However, the major product was the same isomer **14b**, corresponding to an internal hydride transfer via the less stable cation conformer **13ax**.

To confirm the assigned stereochemistry, the minor diastereomer **14a** was prepared independently from the

Scheme 2. Directed Intramolecular Ionic Hydrogenation



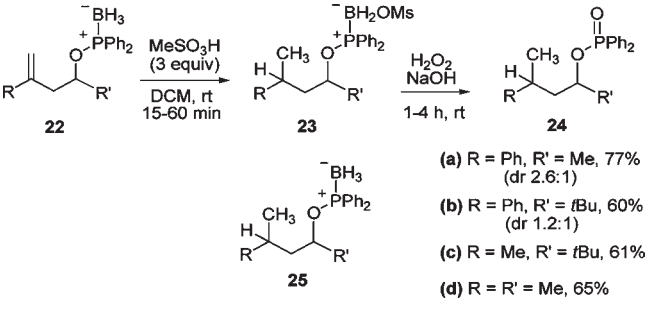
reaction of $LiPPh_2$ with a 2.6:1 *cis*/*trans* mixture of tosylates **16** (from the commercial mixture of alcohols **15**-*cis* and **15**-*trans*). Isomer **15**-*trans* reacted faster in the S_N2 displacement with inversion to give **17**, and **14a** was obtained as a single diastereomer after oxidation.

Intramolecular hydride transfer was also observed in a related phosphinite borane **18**, available from 3-methylene cyclohexanol via conversion to the phosphinite with $ClPPh_2/NEt_3$ and subsequent treatment with THF•BH_3. The reaction of **18** with MsOH followed by oxidative workup gave **19** as the major diastereomer (**19**:**20**, 5:1 at rt; 19:1 at −10 °C), but several inseparable byproducts including **21** (according to ^{1}H NMR and mass *m*/*z* data) were also formed. The major product **19** could not be purified unless activation was performed with TfOH (1 equiv) at −78 °C. This variation gave the same 19:1 ratio of **19**:**20**, but fewer byproducts were formed and **19** could be purified in 43% yield after repeated chromatography. The minor isomer **20** could not be isolated, but the structure was established by independent synthesis of both **19** and **20** from **15**-*trans* and **15**-*cis*, respectively.

The phosphinite example of Scheme 2 suggested other applications for oxygen-directed, diastereoselective ionic hydrogenation. Accordingly, several acyclic phosphinite boranes **22** were studied (Scheme 3) and good conversion to saturated products **23** was generally observed using the standard MsOH activation procedures, as evidenced by the formation of **24** after oxidative workup. However, diastereoselectivity was modest at best and could not be significantly improved at lower temperatures or (in the case of **24b**) at 10-fold greater dilution to minimize intermolecular hydride transfer. Furthermore, the initial products included not only the "activated" and easily cleaved mesyloxyborane complexes **23** expected from internal hydride transfer but also the analogous borane complexes **25**. In contrast to **23**, the borane adducts **25** are stable, isolable, and quite resistant to oxidative cleavage using the conventional $NaOH/H_2O_2$ recipe. The origins of **25** were not probed experimentally, but disproportionation by hydride/mesylate exchange would explain the outcome. Minor products of competing hydroboration were also detected in some cases.

Having demonstrated a simple one-stage activation pathway for internal IH in the phosphorus examples, we

Scheme 3. Acyclic Phosphinite Boranes

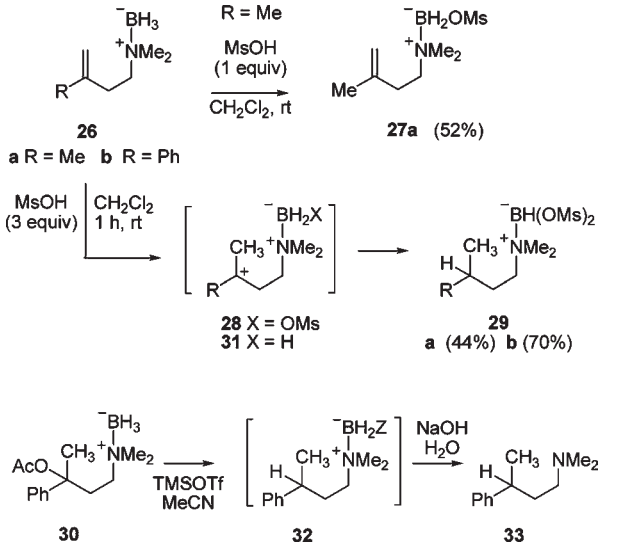


turned to the investigation of unsaturated amine boranes. Although IH was eventually observed, it became clear that

(3) Imamoto, T.; Oshiki, T.; Onozawa, T.; Kusumoto, T.; Sato, K. *J. Am. Chem. Soc.* **1990**, *112*, 5244.

the amine boranes follow a more complex pathway upon MsOH activation. In contrast to phosphine borane **4**, the amine borane **26a** reacted with stoichiometric MsOH to release hydrogen *without* undergoing IH.[4] An organic product was also formed, identified as the unsaturated mesyloxyborane complex **27a** from NMR and MS data (52% recovered after flash chromatography, partial decomposition). Further reaction of **27a** with excess MsOH or treatment of **26a** with 3 equiv of MsOH was necessary to effect ionic hydrogenation of the alkene, affording an isolable bis-mesyloxyborane complex **29a** (44%). This is the product expected from internal hydride transfer at the stage of carbocation **28**, assisted (or followed) by bonding of the mesyloxy anion at boron. Similar treatment of **26b** with 3 equiv of MsOH gave **29b** (70%).[5] The higher yield probably reflects easier protonation of the styrene **27b** compared to **27a** due to greater stabilization of the cationic intermediate **28b**. Evidently, the electron-withdrawing *B*-mesyloxy group of **27** formed in the first stage of MsOH activation attenuates hydridic reactivity and allows competing protonation of the alkene with subsequent IH via **28** in the second stage.

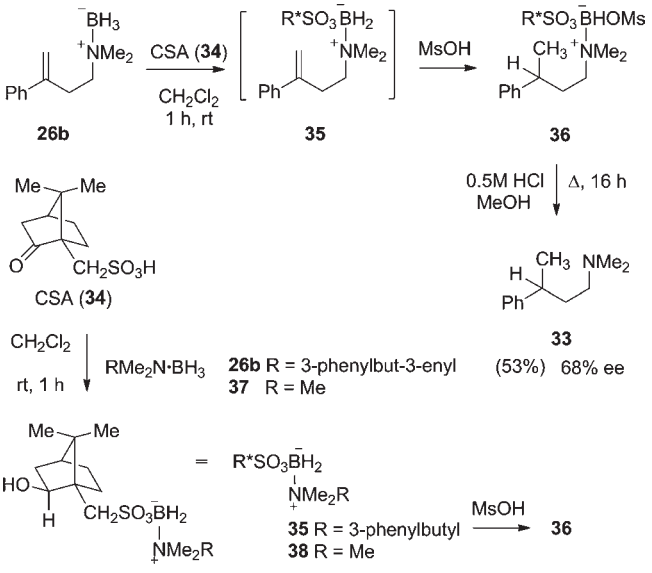
Scheme 4. Ionic Hydrogenation of Amine Boranes



In view of the unproductive evolution of hydrogen starting from **26** and MsOH, an alternative approach for generation of the key carbocationic intermediate was evaluated starting from the tertiary acetate **30**. Treatment of **30** with boron trifluoride etherate in dichloromethane resulted in conversion to saturated products within 1 h at rt, and workup with aqueous NaOH afforded the free amine **33** (83%). In contrast to the MsOH activation procedure from **26b**, the intermediate complex resulting from IH did not survive the aqueous workup. This is consistent with a single stage IH pathway via carbocation **31**, followed by hydride transfer to give the hydrolytically labile **32** (Z = OTf or OAc). No evidence for the formation of a stable $(TfO)_2BH$ complex analogous to the bis-mesyloxy complex **29b** was found using the Lewis acid activation method. These observations are consistent with a one-stage activation mechanism from **30**, but NMR spectroscopy assay prior to NaOH workup indicated a more complex situation, implicating unknown disproportionation events as well as the one-stage IH process.[6,7]

According to the two-stage IH mechanism of Scheme 4 for amine borane activation, it should be possible to use a different sulfonic acid in each stage. This feature has interesting consequences using a chiral acid such as camphorsulfonic acid (CSA) in the first stage because the expected nonracemic intermediate **35** (Scheme 5) may function as a chiral hydride donor in a second stage initiated by subsequent addition of excess MsOH. To test this premise, **26b** was treated with (+)-CSA (1 equiv) followed by MsOH (2 equiv). Ionic hydrogenation did take place according to ^{1}H NMR assay (ca. 75% conversion of the alkene). However, the initial products could not be separated and proved difficult to identify or assay, presumably because several diastereomers of **36** are possible given the presence of stereogenic boron as well as carbon. To simplify the assay, the mixture of products was cleaved using HCl in refluxing MeOH to afford the chiral amine **33**. Determination of 68% ee for **33** by HPLC on a chiral support confirmed that the intramolecular hydride transfer step had occurred with surprisingly high (84:16) diastereofacial selectivity.

Scheme 5. Ionic Hydrogenation of **18b** Using CSA/MsOH



Although the above result supported initial incorporation of a chiral CSA subunit by bonding at boron as

(4) $Et_3N\cdot BH_3$ reacts with CF_3CO_2H at rt in DCM to give H_2, with >50% conversion in 45 min, and is more hydridic than $Bu_3P\cdot BH_3$ (<2% conversion under the same conditions). For systematic comparisons, see: Funke, M.-A.; Mayr, H. *Chem.—Eur. J.* **1997**, *3*, 1214.

(5) Complex **21b** survives treatment with $LiAlH_4$, Bu_4NF, and methanolic KHF_2 at rt (16 h). Cleavage to the parent amine occurs in refluxing MeOH/HCl (43% after 16 h) or by reaction with 8 equiv of DMAP in refluxing MeOH or with neat pyrrolidine at reflux.

suggested for **35**, some of the observations were not consistent with the expected mechanism. The vigorous hydrogen evolution that was seen upon addition of MsOH to simple amine boranes was not observed in the first stage (CSA addition to **26b**) or in the second stage (MsOH addition). Furthermore, the structure of **36** (R^*SO_3 = camphorsulfonyloxy) presumed by analogy to the mechanism of Scheme 4 could not be reconciled with the presence of a proton signal at δ 4.11 ppm, a ^{13}C signal at δ 76.4 ppm, and the absence of a carbonyl stretch in the IR spectrum in the crude product. However, the NMR spectrum did support the presence of a modified camphor subunit as well as the methanesulfonyloxy fragment, and could be understood assuming initial reduction of the camphor carbonyl group to the corresponding hydroxyl, a conclusion that was also supported by an O−H stretch at 3496 cm^{-1} in the IR spectrum. Overall, this evidence supports modified structures for **35** and **36** with R^*SO_3 = *dihydro*-camphorsulfonyloxy. However, the product mixture of diastereomers and residual unsaturated amine boranes could not be separated. Fortunately, convincing indirect support for structure **36** was obtained from the related reaction of CSA with trimethylamine borane (**37**). In this case, the resulting trimethylamine complex **38** was characterized by X-ray crystallography, and NMR comparisons with crude **36** revealed the expected similarities for characteristic chemical shifts.

In view of the corrected structure of **36** and the absence of substantial hydrogen evolution in either the CSA or MsOH steps, a distinct amine borane activation mechanism is involved using CSA. In the first stage, one hydride of the substrate **26b** reduces the carbonyl group of CSA (**34**) to afford **35** (R^*SO_3 = *dihydro*-camphorsulfonyloxy), a process that is probably assisted by intramolecular carbonyl protonation by the sulfonic acid. In the second stage, MsOH protonates the alkene, followed by internal hydride migration to convert **35** into **36**. This modification of the two-stage pathway resembles the simpler mechanism using excess MsOH in that both mechanisms lead from **26a** to a stable bis-sulfonyloxyborane complex. However, the initial hydride abstraction steps are different and involve different electrophiles in the first stage.

To summarize, internal IH via a one-stage mechanism has been demonstrated for unsaturated phosphine or phosphinite boranes. The decisive event involves carbocation generation by protonation of the double bond with MsOH, followed by rapid internal hydride transfer. For analogous unsaturated amine boranes, a two-stage pathway for IH is favored using sulfonic acids for activation because hydrogen evolution is faster than in the phosphorus series. The resulting unsaturated amine-$MsOBH_2$ complex participates in a relatively slow second stage IH via carbocation generation and hydride transfer.

A different activation pathway for the first stage is favored using CSA (**34**) in place of MsOH. Instead of initiating hydrogen evolution, CSA abstracts hydride via internal acid-catalyzed carbonyl reduction. Addition of MsOH then triggers IH in the second stage to afford saturated products. An alternative one-stage internal IH is also possible with amine boranes via Lewis acid induced carbocation generation from tertiary acetoxyalkylamine boranes. Lewis acid activation affords the free amine product after basic workup because the initially formed **28** is easily hydrolyzed, in contrast to MsOH activation where the corresponding products are the hydrolytically robust $(MsO)_2BH$ complexes **29**.

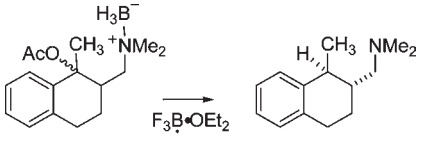
We could find a single prior study where internal hydride transfer from an amine borane has been proposed (acid-induced reduction of indoles by a tethered amine borane).[8] Judging from the simple aqueous workup, this reaction involves a one-stage activation pathway, probably because the increased basicity of the indole double bond favors direct protonation over hydrogen evolution. Internal ionic hydrogenation has also been encountered in a study involving tethered alkoxysilane substrates where the presence of a single SiH bond ensures the one-stage IH mechanism.[9] Further studies are warranted to explore applications of the diverse mechanistic pathways for ionic hydrogenation.

Acknowledgment. This work was supported by the National Institute of General Medicine (GM067146). The authors also thank Dr. J. W. Kampf for solving the crystal structure of **25** and Dr. V. Cwynar for the NOESY study (Dept. of Chemistry, University of Michigan).

Supporting Information Available. Experimental procedures and characterization data (PDF). Crystal data for **25** (CIF). This material is available free of charge via the Internet at at http://pubs.acs.org.

(6) For prior reports of one stage IH with amine boranes, see: Berger, J. G. *Synthesis* **1974**, 508. Maryanoff, B. E.; McComsey, D. F. M. *J. Org. Chem.* **1978**, *43*, 2733.

(7) Lewis acid catalyzed IH was also observed from *i* to *ii* (82%, 2.4:1 dr (major product shown, based on NOESY data), and similar results were observed using TMSOTf (MeCN solution). MsOH-induced IH from the exocyclic alkene corresponding to *i* gave a complex mixture including unsaturated products formed by a competing olefin migration.



i *ii*

(8) Berger, J. G.; Teller, S. R.; Adams, C. D.; Guggenberger, L. J. *Tetrahedron Lett.* **1975**, 1807.

(9) McCombie, S. W.; Ortiz, C.; Cox, B.; Ganguly, A. K. *Synlett.* **1993**, 541. These authors described the internal ionic hydrogenation process using the abbreviation IIH.