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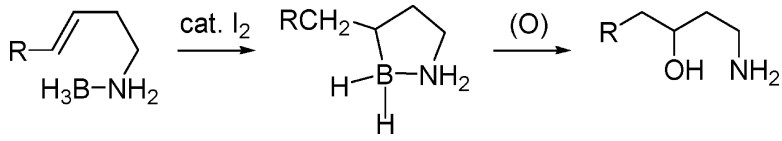

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Amine-Directed Hydroboration: Scope and Limitations

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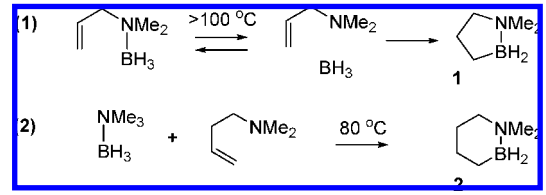
Abstract: Iodine activation induces intramolecular hydroboration of homoallylic and bis-homoallylic amine boranes with good to excellent control of regiochemistry compared to control experiments using excess THF•BH_3. Deuterium labeling and other evidence confirm that the iodine-induced hydroboration reaction of homoallylic amine boranes occurs via an intramolecular mechanism equivalent to the classical 4-center process and without competing retro-hydroboration. Longer carbon chain tethers result in lower regioselectivity, whereas the shorter tether in allylic amines results in a switch to dominant intermolecular hydroboration. Regioselectivity in THF•BH_3 control experiments is higher for the allylic amine boranes compared to the iodine activation experiments, whereas the reverse is true for homoallylic amine borane activation.

Introduction

Unsaturated amine borane complexes have been known for many years to be isolable molecules that easily survive exposure to the air at room temperature.[1] This stability can be attributed to the strength of the bond between nitrogen and boron in the Lewis acid−Lewis base complex and is consistent with prior reports that demonstrate conversion of alkenylamine boranes into isomeric hydroboration products upon heating (eq 1).[1b] Like other simple hydroborations,[2] this process likely involves reversible dissociation to borane and the free Lewis base ligand (i.e., the amine), followed by a conventional intermolecular hydroboration and subsequent internal N−B bond formation to afford the cyclic borane complex **1**. In related studies, thermally induced borane transfer has been demonstrated from a saturated amine borane to an unsaturated amine, as shown in eq 1 using trimethylamine borane as the source of borane.[1c] Formation of **2** requires cleavage of the N−B bond at some stage prior to hydroboration and is most easily understood if this occurs by a simple dissociative event. Also consistent is the well-known dissociation of amine boranes at similar temperatures in the absence of alkenes.[3]



We could find no cases in the prior literature to suggest that unsaturated amine boranes are capable of hydroboration by an intramolecular mechanism that might occur below the temperature for N−B dissociation. Similar conclusions have been reached for the comparably stable unsaturated phosphines boranes.[4] These issues are relevant to the prospects for heteroatom-directed intramolecular hydroboration,[5] a problem in hydroboration chemistry that was recognized long ago.[6] Prior to our work, the only well-defined examples of heteroatom direction via bonding interactions involving Lewis basic electron pairs are in the transition metal catalyzed hydroborations.[7] These reactions are believed to take place via an O−M bonding interaction, and not an O−B interaction.

As part of a program designed to develop new methods for heteroatom-directed hydroboration, we have initiated a study of amine borane activation. A preliminary account of this work has appeared,[8] as well as a report describing the analogous activation of phosphine boranes.[9] We now describe the activation of unsaturated amine boranes in detail.

According to the classical dissociative mechanism, hydroboration (HB) requires a trivalent borane to access the 4-center transition state. However, initial formation of an olefin borane π-complex via S_N2-like alkene bonding at the backside of the

(1) (a) Dewar, M. J. S.; Gleicher, G. J.; Robinson, B. P. *J. Am. Chem. Soc.* **1964**, *86*, 5698. (b) Dewar, M. J. S.; Rona, P. *J. Am. Chem. Soc.* **1967**, *89*, 6294. (c) Polívka, Z.; Ferles, M. *Collect. Czech. Chem. Commun.* **1969**, *34*, 3009. (d) Polívka, Z.; Kubelka, V.; Holubová, N.; Ferles, M. *Collect. Czech. Chem. Commun.* **1970**, *35*, 1131. (e) Wille, H.; Goubeau, J. *Chem. Ber.* **1972**, *105*, 2156. (f) Baboulene, M.; Torregrosa, J.-L.; Speziale, V.; Lattes, A. *Bull. Chim. Soc. Fr.* **1980**, II-565. (g) Midland, M, M.; Kazubski, A. *J. Org. Chem.* **1992**, *57*, 2953.

(2) Brown, H. C.; Chandrasekharan, J. *J. Am. Chem. Soc.* **1984**, *106*, 1863.

(3) (a) Brown, H. C.; Bartholomay, H., Jr; Taylor, M. D. *J. Am. Chem. Soc.* **1944**, *66*, 435. (b) Haaland, A. *Angew. Chem, Int. Ed. Engl.* **1989**, *28*, 992. (c) Brown, H. C.; Kanth, J. V. B.; Dalvi, P. V.; Zaidlewicz, M. *J. Org. Chem.* **2000**, *65*, 4655.

(4) (a) Schmidbaur, H.; Sigl, M.; Schier, A. *J. Organomet. Chem.* **1997**, *529*, 323. (b) Gaumont, A.-C.-C.; Bourumeau, K.; Denis, J.-M.; Guenot, P *J. Organomet. Chem.* **1994**, *484*, 9.

(5) Hoveyda, A. H.; Evans, D. A.; Fu, G. C. *Chem. Rev.* **1993**, *93*, 1307.

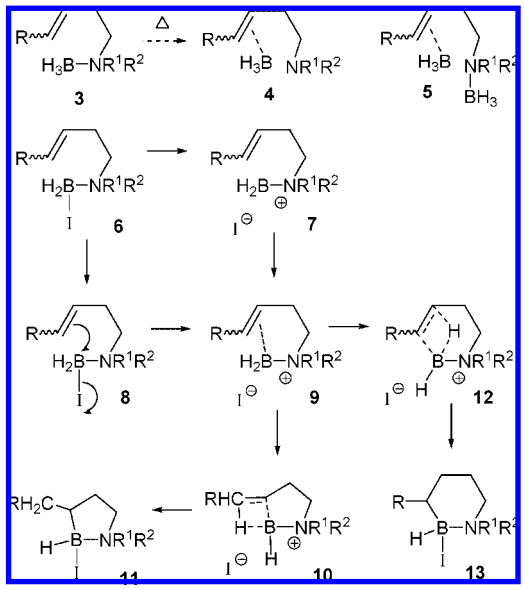
(6) Schulte-Elte, K. H.; Ohloff, G. *Helv. Chim. Acta* **1967**, *50*, 153.

(7) (a) Evans, D. A.; Fu, G. C.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1988**, *110*, 6917. (b) Evans, D. A.; Fu, G. C. *J. Am. Chem. Soc.* **1991**, *113*, 4042. (c) Evans, D. A.; Muci, A. R.; Stürmer, R. *J. Org. Chem.* **1993**, *58*, 5307.

(8) Scheideman, M.; Shapland, P.; Vedejs, E. *J. Am. Chem. Soc.* **2003**, *125*, 10502.

(9) Shapland, P.; Vedejs, E. *J. Org. Chem.* **2004**, *69*, 4094.

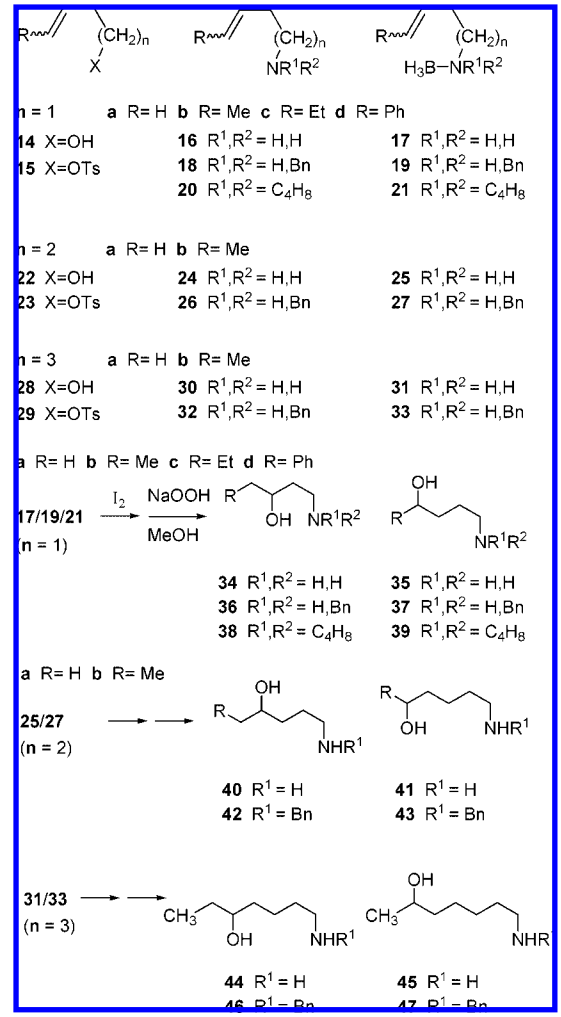
Scheme 1



amine borane N−B bond might also be considered, by analogy to the mechanism suggested for borane etherate hydroborations based on computational studies.[10] If such a pathway were to operate for unsaturated amine boranes **3**, then a slow reaction would be expected for two reasons. First, the inherent stability of the N−B bond works against any mechanism that requires N−B bond cleavage, including an S_N2-like pathway. Second, and more important, the orbital requirements for internal nucleophilic attack are not satisfied in the case of **3** or related homoallylic and bis-homoallylic amine boranes because the potential nitrogen leaving group bond would be endocyclic with respect to the hypothetical cyclic transition state.[11] This means that there should be no rate advantage for HB via an internal S_N2-like displacement process involving the C=C subunit of an unsaturated amine borane acting in the role of the nucleophile, as long as the amine nitrogen acts as the leaving group. The above analysis implies that **3** would have to react via a dissociative pathway, presumably via π-complexes such as **4** or **5**. These intermediates may well undergo further reaction with a preference for one of the two regioisomeric 4-center transition states due to electronic factors associated with the amine or amine borane subunits, but such effects are poorly understood and their role is difficult to anticipate. The goal of the present study was to determine whether a more predictable version of regiocontrolled hydroboration is feasible via amine borane intermediates where the N−B bond remains intact.

We began with the premise that an internal hydroboration may be possible starting from a stable amine borane of general structure **3** if a good exocyclic leaving group is introduced at boron, as in the iodoborane complex **6** (Scheme 1). We could imagine a dissociative S_N1-like mechanism via an ion pair **7**, or an S_N2-like internal nucleophilic substitution process via the bonding interactions shown for **8**. In either event, the initial result would be the formation of a tethered olefin π-complex ion pair **9**. Bond reorganization via the fused bicyclic 4-center transition state **10** with subsequent ion pair recombination would then afford **11**. Competition by a bridged bicyclic transition state **12** to give the regioisomeric product **13** is also conceivable, but this was expected to be the minor pathway.

Scheme 2



Results and Discussion

To test the above premise, a series of homoallylic amines were prepared, usually from the alcohols **14** by aminolysis of the tosylates **15** (Scheme 2). Amines **16**, **18**, and **20** were then easily converted into the isolable amine boranes **17**, **19**, and **21** by treatment with THF•BH_3. Similar conventional methods were used to prepare homologous alkenylamine boranes **25**, **27**, and **31**, **33**.

After a preliminary survey of common electrophiles, we quickly settled on iodine as the activating agent. Iodination of amine boranes is fast, easy to do, and has a long history.[12] According to the stoichiometry, molecular iodine is fully utilized in conversion of **3** to **6**. Apparently, the initially formed byproduct HI reacts with **3** to generate a second equivalent of the iodoborane complex **6**, together with hydrogen gas. When the iodine activation method was applied to homoallylic amine

(10) (a) Clark, T.; Wilhelm, D.; Schleyer, P. V. R. *J. Chem. Soc., Chem. Commun.* **1983**, 606. For relevant mechanistic studies, see: (b) Pasto, D.; Lepeska, B.; Cheng, T.-C. *J. Am. Chem. Soc.* **1972**, *94*, 6083. (c) Pasto, D. J.; Lepeska, B.; Balasubramaniyan, V. *J. Am. Chem. Soc.* **1972**, *94*, 6090.

(11) Beak, P. *Acc. Chem. Res.* **1992**, *25*, 215.

(12) (a) Ryschkewitsch, G. E.; Garrett, J. M. *J. Am. Chem. Soc.* **1967**, *89*, 4240. (b) Nainan, K. C.; Ryschkewitsch, G. E. *J. Am. Chem. Soc.* **1969**, *91*, 330. For generation of diiodoborane amine complexes and applications for selective hydroboration, see: (c) Reddy, C. K.; Periasamy, M. *Tetrahedron* **1992**, *48*, 8329.

Table 1

entry[a]	amine borane	yield from amine	R^1, R^2	R	*n*	products	ratio[b]	yield
1	**17a**	77%	H, H	H	1	**34a:35a**	1:1	69%[c]
2	*E*−**17b**	79%	H, Me	Me	1	**34b:35b**	43:1	85%[c]
3	*E*−**17b**[d]	79%	H, Me	Me	1	**34b:35b**	38:1[d]	83%[c]
4	**19a**	>90%	H, Bn	H	1	**36a:37b**	1:3	90%
5	*E*−**19b**	>90%	H, Bn	Me	1	**36b:37b**	13:1	83%
6	*E*−**19b**	76%	H, Bn	Me	1	**36b:37b**	18:1[e]	79%
7	*E*−**19b**	>90%	H. Bn	Me	1	**36b:37b**	10:1[f]	79%
8	*Z*−**19b**	>90%	H. Bn	Me	1	**36b:37b**	>20:1	87%
9	*E*−**19c**	>90%	H, Bn	Et	1	**36c:37c**	10:1	82%
10	*E*−**19d**	>90%	H, Bn	Ph	1	**36d:37d**	2:1	82%
11	*E*-**19d(D_3)**	73%	H, Bn	Ph	1	**36d(D_1):37d(D_1)**	3:1	NA
12	Z-**21c**	77%	$(CH_2)_4$	Et	1	**38c:39c**	>30:1	92%
13	**25a**	41%	H,H	H	2	**40a:41a**	1:1.5	35%
14	*E*-**25b**	55%	H,H	Me	2	**40b:41b**	4:1	84%
15	*Z*-**25b**	71%	H,H	Me	2	**40b:41b**	14:1	92%
16	**27a**	63%	H,Bn	H	2	**42a:43a**	1:3	71%
17	*E*−**27b**	92%	H,Bn	Me	2	**42b:43b**	4:1	76%
18	*Z*−**27b**	83%	H,Bn	Me	2	**42b:43b**	39:1	80%
19	*E*−**31b**	63%	H,H	Me	3	**44:45**	2:1	95%
20	Z-**31b**	54%	H,H	Me	3	**44:45**	2:1	91%
21	Z−**33b**	83%	H,Bn	Me	3	**46:47**	1.5:1	63%

[a] Conditions, 50 mol% I_2/DCM, rt; yields refer to aminoalcohols isolated by chromatography as a mixture of regioisomers after workup with NaOOH. [b] NMR assay. [c] Reaction quenched after 30 min. [d] Catalytic activation with 10 mol% I_2. [e] Recrystallized substrate. [f] Activation using TfOH.

boranes, HB occurred at room temperature on a time scale of hours according to product assay after standard oxidative workup with alkaline hydrogen peroxide. However, initial attempts to characterize the presumed intermediates **6** or the initial products **11** and **13** using NMR methods were not informative. Numerous signals were observed in the crude ^{1}H NMR spectrum prior to oxidative workup, as would be expected from the presence of diastereomers involving stereogenic boron as well as regioisomers, but the sheer complexity of the spectrum suggested the presence of additional unknown species. Thus, structures **6**, **11**, and **13** were tentatively drawn based on stoichiometry and product assay after oxidative workup.

As shown in Table 1, activation with 50 mol% I_2 in CH_2Cl_2 converts a broad range of unsaturated amines into amino alcohols. Good to excellent regiocontrol was observed in the representative case of *E*-**19b** (entry 5; 13:1 **36b**:**37b**) as well as a number of other examples (entries 2, 6, 8, 12, 15, 18), leaving little doubt that an internally directed HB had been achieved. Somewhat improved 18:1 selectivity for **36b**:**37b** was obtained in the iodine experiments when *E*-**19b** was recrystallized prior to activation (entry 6), but the 13:1 ratio using *E*-**19b** partially purified by simple plug filtration over silica gel (entry 5) has been retained in Table 1 to allow better comparisons with other entries where the amine borane substrate could not be crystallized.

To test for competition by an intermolecular hydroboration pathway, the iodine activation of crystallized *E*-**19b** was conducted at two different concentrations. However, the ratio of regioisomeric aminoalcohols obtained with 0.1 or 1.0 M solutions of the purified substrate was identical (18:1 **36b**:**37b**), suggesting an intramolecular pathway. Additional evidence was provided by a control experiment where *E*-**19b** was treated with excess borane in THF (2 equiv). This gave a much lower ratio of **36b**:**37b** (2.4:1) as expected for conventional intermolecular HB. Finally, *E*-**19b** was activated in the usual way, but in the presence of added β-methylstyrene (2 equiv) as a potential trap for dissociated borane species or other species capable of intermolecular HB. After oxidative workup, this experiment gave conversion of *E*-**19b** to **36b**:**37b** as usual, along with recovered β-methylstyrene. Only traces of the alcohol products derived from β-methylstyrene were detected (<10%). Thus, the internal hydroboration was not suppressed by the external alkene.

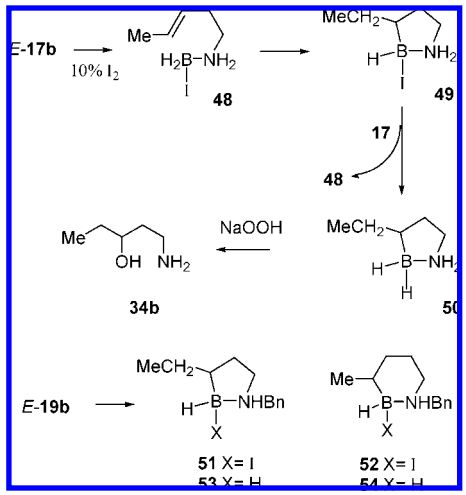
Activation with triflic acid as the electrophile[9] was briefly compared with the iodine method using *E*-**19b** as the substrate (entry 7). Internal HB occurred on a similar time scale, but regiocontrol was lower (10:1 **36b**:**37b**). In view of the inconvenience of handling triflic acid compared to iodine, the procedure was not pursued further.

Higher regioselectivity was observed for the iodine-induced internal HB of *Z*-alkenes compared to the *E*-isomers (compare entries 8 vs 5, 15 vs 14, or 18 vs 17). Thus, with Z-**19b** as the substrate, the standard activation; oxidation procedure gave a single product **36b** by NMR assay (entry 8). To establish detection limits, authentic1,4-amino alcohol **37b** was prepared independently.[13] According to a calibration study, **37b** would have been detected at the 5% level, indicating >20:1 **36b**:**37b** selectivity for the iodine-induced hydroboration of Z-**19b**. The role of olefin geometry was more pronounced for the bishomoallylic amine boranes, especially for the *N*-benzyl derivatives (entries 18 vs 17). However, the relatively modest selectivities for some, but not all of the *E*-alkenylamine boranes indicate that the directing effect arises from a combination of factors. In this light, it was no surprise to find that the directing effect is not sufficient to overwhelm other factors that contribute to HB regioselectivity. For example, terminal alkenes reacted with low selectivity (entries 1, 4, 13, 16), as did a phenyl-substituted substrate (entry 10). In the latter example, the result can be understood by comparing the product ratio with that expected from the standard (intermolecular) HB selectivity for β-methyl-styrene, 86:14 in favor of the benzylic alcohol after oxidative workup.[14] For the amine-directed HB reaction (entry 11), the benzylic alcohol is the *minor* product (1:3 ratio).

Attempts to extend the amine-directed hydroboration to tertiary amine derivatives encountered complications. The alkenyl pyrrolidine borane Z-**21c** was relatively well behaved,

(13) Crich, J.; Picione, R. *Org. Lett.* **2003**, *5*, 781.
(14) (a) Brown, H. C.; Sharp, R. L. *J. Am. Chem. Soc.* **1966**, *88*, 5851. (b) Brown, H. C.; Zweifel, G. *J. Am. Chem. Soc.* **1960**, *1960*, 4708.

Scheme 3



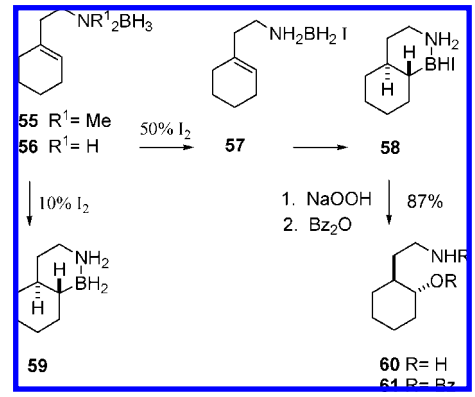
and conversion of the alkene occurred within 5 h at rt, although the amino alcohol **38c** was not recovered cleanly due to competing formation of the *N*-oxide during oxidative workup. In contrast, the dibenzylated analog of amine borane *E*-**19b** (R^1, R^2 = Bn) gave low conversion under the standard conditions, and unreacted amine was recovered together with the regioisomeric amino alcohols (1.0:3.5:1.5 ratio).

Deuterium labeling experiments were utilized to probe the amine-directed hydroborations in greater detail. Labeled *E*-**19d**(D_3) was prepared by the addition of the parent amine to THF•BD_3 (generated *in situ* from $NaBD_4$ + iodine).[15] An equivalent of *E*-**19b** was then added to *E*-**19d**(D_3) and the mixture was activated with iodine as usual. After oxidative workup, the resulting amino alcohol products were analyzed for the presence of deuterium. Within limits of detection by $ESMS^{(+)}$ and ^1H NMR, neither **36b** nor **37b** contained deuterium that might be traced to intermolecular crossover or disproportionation events involving *E*-**19d**(D_3). Furthermore, ^1H NMR integration revealed the presence of **36d**(D_1) and **37d**(D_1), the expected products of intramolecular deuteroboration. The control experiment using *E*-**19d**(D_3) as the only substrate in the iodine activation gave identical spectral data for the signals assigned to **36d**(D_1) and **37d**(D_1). These results rule out a significant (>5%) role for retro-hydroboration and deuteroboration pathways that would be expected to produce **36d**(D_2) and **37d**(D_2) by H/D scrambling. Therefore, the reaction of *E*-**19d**(D_3) with iodine involves a kinetically controlled, intramolecular hydroboration.

An experiment was carried out with substrate *E*-**17b** to learn whether a catalytic amount of iodine would be sufficient for conversion of the amine borane (Table 1, entry 3) to hydroboration products (Scheme 3). Treatment with 10 mol% iodine resulted in a somewhat slower conversion of the substrate compared to the experiment using 50 mol% iodine (2 h vs 0.3 h at rt), but oxidative workup gave the amino alcohol **34b** as the dominant product with nearly the same yield and excellent selectivity (Table 1, entry 4 vs entry 3). This observation indicates that the initially formed hydroboration product **49** can react with the substrate *E*-**17b** by reversible hydride-iodide exchange, a process that would regenerate the activated **48** as well as the cyclic amine borane **50**. The experiment was

(15) Narayanan, C.; Periasamy, M. *J. Organomet. Chem.* **1987**, *323*, 145.

Scheme 4



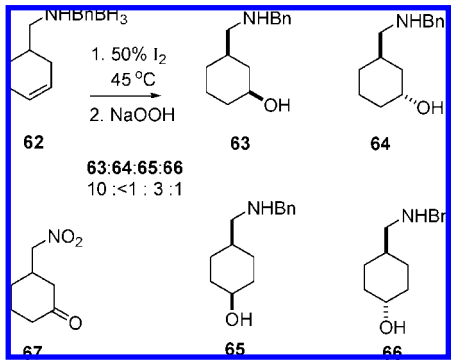
therefore repeated without oxidative workup, and formation of **50** was confirmed by isolation after chromatography (41% yield).

The catalytic iodine procedure was also performed with *E*-**19b**. Initial attempts to oxidize the reaction mixture from hydroboration led to variable product recovery and a 7:1 ratio of amino alcohols **36b** and **37b**. The problem was traced to lower reactivity in the oxidative cleavage step for the presumed cyclic amine borane intermediates **53** and **54**, structures that are relatively stable compared to the precursor iodoboranes **51** and **52** that accumulate under conditions of stoichiometric activation. Improved reactivity in the oxidative cleavage was achieved by the addition of 40 mol% of iodine to the product mixture obtained from catalytic hydroboration to force the conversion of **53** and **54** back to **51** and **52**. This gave a 10:1 ratio of amino alcohol products *E*-**36b**:*E*-**37b** (79% yield). Of course, reactivation by adding iodine negates any practical advantage for catalytic activation in the hydroboration step for this case. No further attempt was made to characterize the mixture of regioisomers and epimers **53** and **54** or to identify the factors responsible for the diminished 10:1 regioselectivity compared to the stoichiometric activation method.

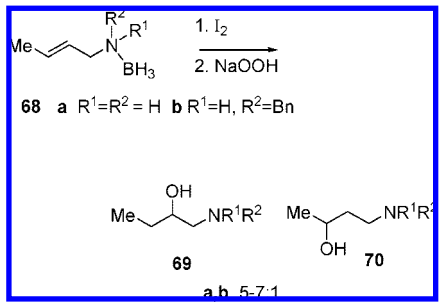
Iodine activation was explored in substrates **55** and **56**, structures where complications due to regioisomer or epimer formation were not expected (Scheme 4). Stoichiometric activation of **55** gave no hydroboration products at rt, consistent with the pattern of slower reactions for the tertiary amine boranes as noted earlier. However, the analogous primary amine borane **56** behaved normally using either 50 mol% or 10 mol% iodine at rt. In the stoichiometric reaction, oxidative workup afforded the amino alcohol **60**, but purification was easier after benzoylation to give the bis-benzoyl derivative **61**. The latter structure provided an opportunity to determine whether the stereochemistry corresponds to the typical *syn* delivery of boron and hydride to the olefin via a 4-center hydroboration pathway. This was confirmed by the diaxial *trans* relationship for H_a and H_b in **61**, assigned from the vicinal coupling constant (J = 9.5 Hz).

The catalytic activation method using 10 mol% iodine at rt also worked well with **56**. Complete consumption of olefin required less than two hours and cyclic amine borane **59** was isolated from the mixture in 46% yield after chromatography. Under these reaction conditions, propagation of the catalytic cycle likely occurs by reversible transfer of iodine from **58** to **56** to regenerate the activated iodoborane complex **57**. The catalytic hydroboration could also be initiated by the addition of 10 mol% of $Et_3N\cdot BH_2I$ to **56**, as expected according to the proposed catalytic cycle via reversible H/I exchange. The cyclic

Scheme 5



Scheme 6



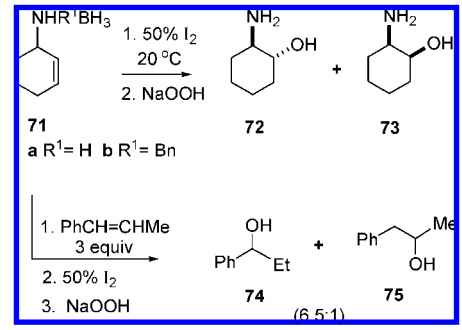
amine borane **59** could be oxidized with NaOOH to the amino alcohol **60** in 87% yield without further activation, provided that the oxidation was allowed to proceed for >8 h at rt. The stereochemistry of **60** obtained using the catalytic iodine method was confirmed by conversion to **61**.

As an additional probe of the stereochemical consequences of internal hydroboration, the bis-homoallylic amine borane **62** (obtained as a mixture of inseparable *N*-epimers) was subjected to the iodine activation conditions at rt (Scheme 5). Hydroboration was sluggish compared to the substrates of Table 1 (24 h for complete alkene consumption), but warming to 45 °C gave conversion within 4−5 h. Oxidation with NaOOH then afforded 1,3- and 1,4-amino alcohols **63** and **65** as major products in a 10:3 ratio. The *syn* stereochemistry obtained for each of these compounds is consistent with an internal mechanism. None of the 1,3-*trans* isomer **64** was found and only a small amount of **66** was detected, presumably resulting from some form of intermolecular hydroboration due to the higher temperature. The major product **63** was identified by comparison with the mixture of isomers **63** + **64** obtained by LAH reduction from ketone **67**.[16] In contrast to the iodine-promoted reaction, intermolecular hydroboration of **62** using excess THF•BH_3 gave a nearly equal mixture of all four possible isomers **63**−**66** by NMR assay.

Having shown that homoallylic and bis-homoallylic amine boranes undergo intramolecular hydroboration upon treatment with iodine, we turned to the allylic amine analogues to learn whether an amine-directed HB pathway would be possible with the shorter tether (Scheme 6). The expected amino alcohol products did form in some examples using iodine activation and oxidative workup, but reproducibility was poor. This was surprising because the iodine activation of homoallylic amine boranes had consistently afforded HB products even though minimal precautions were taken to exclude air or moisture. By

(16) White, D. A.; Baizer, M. M. *J. Chem. Soc., Perkin Trans. 1* **1973**, 2230.

Scheme 7

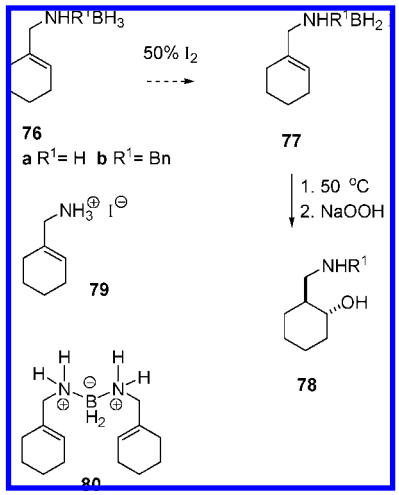


comparison, the allylic amine borane activations required carefully optimized inert atmosphere conditions to achieve substantial conversion. Despite these precautions, iodine activation of crotylamine borane **68a** rarely gave better than 50% yield of amino alcohols **69a** and **70a** (5−7:1 ratio), and some experiments gave no amino alcohol products at all. Furthermore, several tries with the secondary *N*-benzylcrotylamine borane **68b** afforded no hydroboration products upon treatment with 50 mol% of iodine at rt. Heating the reaction mixture at 45 °C did give partial conversion on a time scale of hours (6:1 ratio of **69b**:**70b** along with ca. 20% recovered *N*-benzylcrotylamine), but iodine activation of the tertiary substrate **68** ($R^1 = R^2 =$ Bn) gave no hydroboration regardless of temperature. Routine control experiments using excess THF•BH_3 also gave unexpected results. Thus, treatment of **68a** or **68b** with excess THF•BH_3 followed by NaOOH gave improved ratios of **69**:**70** after 2 h at 0 °C (**a**, 9:1; **b**, 10−13:1) compared to the iodine activation experiments.

Further tests were conducted using the cyclic allylic amine boranes **71a**,**b** to determine whether the stereochemistry of HB products would correspond to an internal hydroboration pathway (Scheme 7). However, **71a** gave 1,2-*trans* amino alcohol **72a** as the major product (≥3:1 **72**:**73**; iodine activation at rt over 4−5 h, followed by oxidative workup) while **71b** gave no amino alcohols at room temperature. Formation of the *trans* isomer **72** suggests competition by an intermolecular mechanism, so the experiment was repeated in the presence of 1 equiv of β-methylstyrene in an attempt to shut down intermolecular pathways. This experiment should favor **73**, the presumed product of the nitrogen-directed intramolecular pathway, but the major amino alcohol was the same *trans*-isomer **72** (2:1 **72**:**73**) although the product ratio was lower. Alcohols **74** and **75** were also obtained from this experiment, providing clear evidence for competing intermolecular HB. When iodine activation of **71a** was performed in the presence of 3 equiv of β-methylstyrene, alcohols **74** and **75** were the exclusive products (6.5:1 ratio). This ratio is similar to the result from reaction of β-methylstyrene with THF•BH_3 (**74**:**75** = 5.7:1). The above experiments show that intermolecular HB pathways are not only accessible, but potentially dominant in the reaction of **71a** under the conditions of iodine activation, in contrast to the behavior of homoallylic amine boranes.

Similar reactivity trends were found in a comparison of amine boranes **76a** and **76b**, although conversion to hydroboration products was slower (Scheme 8). HB did occur if the resulting mixture was heated at 45−50 °C (2 h), resulting in the amino alcohol **78a** (74%) after oxidative workup along with ca. 10% of cyclohexenylmethylamine. On the other hand, the corresponding sequence starting with **76b** gave at most 10% of **78b**,

Scheme 8



and ca. 90% of the material was recovered as the unreacted *N*-benzylcyclohexenylmethylamine.

In an attempt to understand the puzzling reactivity and reproducibility trends, the crude product after iodine activation of **76a** was examined at rt using ^{1}H NMR spectroscopy. The olefinic signal of the starting complex **76a** (δ ca. 5.65 ppm) was replaced by two new signals at δ ca. 5.85 ppm and 6.0 ppm together with several minor maxima. The major signal at 6.0 ppm, along with a broad absorption at δ ca. 7.5−7.8 ppm and a broad singlet at 3.6 ppm, were identified by comparison with the corresponding signals of cyclohexenylmethylammonium iodide **79**. Evidence regarding the new signal at δ 5.85 ppm is less conclusive, but this absorption was enhanced by addition of free cyclohexenylmethylamine to freshly activated **76a**, presumably containing **77a**. This suggests a boronium salt structure **80** as the species responsible for the δ 5.85 ppm signal, but **80** could not be isolated to confirm this assignment. Furthermore, the presence of **77a** after iodine addition could not be established due to the complexity of the ^{11}B NMR spectrum.

The most important observation from the above study is that formation of the ammonium salt **79** is a major pathway resulting from iodine activation of **76a**. We do not have detailed evidence regarding how **79** is formed, although the HI generated in the first stage of iodine activation would have to be the principal suspect. Direct protonation of the N−B bond via a three-center two-electron interaction is one possibility, and another is dissociation of the amine-BH_2I complex followed by protonation at nitrogen. In either case, the results would indicate a weaker N−B bond for the allylic amine boranes compared to the homoallylic or bis-homoallylic amine complexes. This is consistent with the electron-withdrawing inductive effect of the olefinic sp^2 carbon, a factor that is responsible for the lower pK_a (by ca. 1 pK_a unit) of ammonium salts derived from allylic amines compared to their saturated amine analogues.[17] The same inductive effect should lower the stability of allylic amine boranes, and could be the reason why allylic amine nitrogen becomes partially protonated during iodine activation. In any case, *N*-protonation requires that one or more trivalent boron species (presumably, BH_3 or BH_2I) would have to be released as the N−B bond is cleaved. This would explain why the allylic amine borane reactions are highly sensitive to experimental variables, why the products are mostly those expected from an intermolecular hydroboration, and why some of our experiments with the allylic amines gave no hydroboration products even though the reactions were conducted under nitrogen. Dichloromethane is not an ideal solvent for hydroborations because the borane-solvent complex is labile, at least compared to THF•BH_3, and is easily destroyed by contaminants.

Given the insights obtained from the study of **76a**, we reexamined the reactions of the crotylamine borane **68a**. Immediately upon addition of iodine (ca. 5 mol%) to **68a**, a broad singlet appeared at δ 7.35 ppm that shifted to δ 7.55 ppm as more iodine (50 mol% total) was added. Over the same time scale, the broad signal due to the complexed NH_2 protons shifted from ca. δ 3.65 to 4.45 ppm. New olefinic signals also appeared, and basic oxidative workup returned unreacted crotylamine, as would be expected assuming that crotylammonium iodide is formed during activation. If sufficient care was taken to maintain inert conditions, the amino alcohols **69a** and **70a** were also recovered after oxidative workup (69% yield). However, we could not extract meaningful structural evidence regarding the hydroboration products prior to oxidative workup from the complex ^{1}H or ^{11}B NMR spectra.

In response to reviewer comments, one more series of NMR experiments was initiated in an attempt to obtain more evidence regarding the activated borane intermediates using simple model amine boranes as well as the well-behaved, primary homoallylic amine-derived borane *E*-**17b**. The latter substrate affords the best overall combination of regioselectivity (43:1) and product yield (>80%) in amine-directed HB, and has the simplest structure. Nevertheless, the ^{1}H NMR spectrum after activation using 50 mol% iodine (0 °C to rt, 40 min) could not be interpreted beyond noting a broad signal at δ 7.45 ppm (ca. 0.1−0.15 H) suggesting minor formation of ammonium salts, as well as six maxima between δ 3.1 to 3.6 ppm with extensive splitting and overlap in the expected CH_2NH region. Minor broad signals were also present, along with complex, overlapping upfield signals. The ^{11}B NMR spectrum showed several maxima between δ 6 and δ −25 ppm. In striking contrast, when the same substrate *E*-**17b** was treated with 5 mol% iodine (catalytic conditions), the ^{11}B NMR spectrum was relatively clean and consisted of the signals for unreacted *E*-**17b** together with the cyclized product amine borane **50**. Evidently, the NMR complexity using 50 mol% iodine is due at least in part to the formation of N−B−I species, but control experiments with simple models (see below) suggest that the presence of N−H bonds in the substrate *E*-**17b** is the main problem. As already reported in the early literature, amine boranes lacking N−H bonds react cleanly with iodine. For example, treatment of the tertiary amine borane Me_3NBH_3 with iodine affords the iodoborane complex Me_3NBH_2I as a single species.[18a] We also observe a single well-resolved NMR signal with the expected triplet coupling (δ ^{11}B = −9.3 ppm, t, J = 131 Hz). On the other hand, reaction of the known primary amine borane *n*$BuNH_2BH_3$[18b] with 50 mol% iodine in chloroform produces multiple ^{11}B maxima. Minor signals observed at δ 18.1 ppm (diborane by chemical shift comparisons)[19] and δ −23 ppm (N−BH_2X, br t, J_{BH} = ca. 135 Hz) were relatively sharp, but accounted for less than 4% of total signal intensity. Two major peaks (δ −7 and −17 ppm) were also observed, but these resonances were broad and featureless, and could not be assigned with certainty, although the chemical shifts are near the range

(17) Brown, H. C.; McDaniel, D. H.; Hafliger, O. *Determination of Organic Structures by Physical Methods*; Academic Press: New York, 1955; Vol. 1, p 567.

reported for dimeric hydrogen bridged amine boranes (δ 4 to −11 ppm) that might be formed via elimination of HI from nBuNH$_2$BH$_2$I, followed by 2 + 2 combination of the transient monomer [nBuNHBH$_2$].[20]

Although definitive structural evidence was not obtained despite considerable effort, the NMR studies do show that complexity is inherent in the iodine activation of amine boranes that contain N−H bonds, such as the primary amine borane *E*-**17b**. Despite this complexity, the amine-directed hydroborations proceed with good to excellent regioselectivity and conversion in a number of cases. Because multiple species are present in solutions containing the iodine-activated intermediates, the isolation of internal hydroboration products in good yields supports the notion that the unidentified activated intermediates are formed reversibly. According to this interpretation, the byproducts of iodine activation undergo interconversion with iodoborane complexes such as **6**, and internal HB eventually drives the equilibrium to cyclic amine boranes.

Summary

Homoallylic or bis-homoallylic amine borane activation using molecular iodine occurs via an intramolecular mechanism to favor the products expected from a bicyclic hydroboration transition state. The process satisfies the requirements for a simple intramolecular mechanism, including tests based on regiocontrol, stereochemistry, and deuterium labeling. Added external alkene does not compete effectively for the reactive hydroborating agent, although there is minor release of active hydroborating species capable of intermolecular HB in some cases, as evidenced by the formation of the *trans*-amino alcohol **66** (ca. 7% relative yield) starting from **62**. In general, the amine-directed reaction is not very sensitive to the presence of traces of air or moisture, and requires only minimal precautions as long as there is sufficient reactivity for internal HB at room temperature. Finally, formation of the expected cyclic amine borane products has been confirmed by isolation from experiments conducted under mild catalytic conditions using 5 mol% iodine.

In contrast, the allylic amine borane activation experiments do not satisfy any of the tests for an intramolecular reaction. Although we cannot exclude minor competition by an intramolecular mechanism in some of the allylic substrates, there is no compelling reason to propose that the relatively strained internal hydroboration transition states are feasible in the allylic series. To the contrary, there is evidence suggesting substantial cleavage of the N−B bond already at room temperature.

In another contrast between the homoallylic and allylic amine boranes, the latter undergo regioselective *intermolecular* hydroboration using the standard THF•BH$_3$ procedure to form primarily the 1,2-amino alcohols[21] after oxidative workup, while the homoallylic substrates react nonselectively. Iodine activation dramatically improves regioselectivity with the homoallylic and bis-homoallylic amine boranes, but actually lowers selectivity for the allylic analogues compared to the excess THF•BH$_3$ control experiments. Several early reports describing the intermolecular hydroborations of allylic amine substrates with THF•BH$_3$ have encountered similar regioselectivity,[22,23] but we have found no prior reports of directed (i.e., intramolecular) hydroborations via intermediates having an intact N−B bond throughout the sequence. The possibility that certain amine boranes may be capable of *intermolecular* hydroboration with N−B bonding in the transition state has been raised, based on experiments using chiral amine boranes.[24] Mechanistically, this proposal constitutes a plausible extension of the idea that some hydrobo-

(18) (a) Denniston, M. L.; Chiusano, M.; Brown, J.; Martin, D. R. *J. Inorg. Nucl. Chem.* **1976**, *38*, 379. The reported chemical shift is "27.2 ppm upfield from trimethyl borate" in benzene; our chemical shift value is referenced to boron trifluoride etherate in deuterochloroform. (b) Yamamoto, Y.; Miyamoto, K.; Nakatani, Y.; Yamamoto, T.; Miyaura, N. *J. Organomet. Chem.* **2006**, 4909.

(19) A value of δ 17.6 ppm is reported for diborane in chloroform by Kanth, J. V. B.; Brown, H. C. *Tetrahedron Lett.* **2000**, *41*, 9361.

(20) (a) Beachley, O. T.; Washburn, B. *Inorg. Chem.* **1976**, *15*, 725. (b) Boddeker, K. W.; Shore, S. G.; Bunting, R. K. *J. Am. Chem. Soc.* **1966**, *88*, 4396.

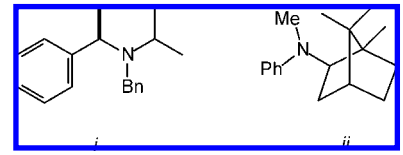
(21) (a) Preferred formation of 2-aminoalcohol derivatives has also been observed using *N*-protected allylic amine substrates that contain electron withdrawing substituents at nitrogen: Fujita, Y.; Irreverre, F.; Witkop, B. *J. Am. Chem. Soc.* **1964**, *86*, 1844. (b) Burgess, K.; Ohlmeyer, M. J. *J. Org. Chem.* **1991**, *56*, 1027. (c) Sibi, M. P.; Li, B. *Tetrahedron Lett.* **1992**, *33*, 4115. (d) Hodgson, D. M.; Thompson, A. J.; Wadman, S.; Keats, C. J. *Tetrahedron* **1999**, *55*, 10815.

(22) (a) Lyle, R. E.; Carle, K. R.; Ellefson, C. R.; Spicer, C. K. *J. Org. Chem.* **1970**, *35*, 802. (b) Caron-Sigaut, C.; Le Men-Olivier, L.; Hugel, G.; Levy, J.; Le Men, J. *Tetrahedron* **1979**, *35*, 957. (c) Mirand, C.; Massiot, G.; Le Men-Olivier, L.; Levy, J. *Tetrahedron Lett.* **1982**, *23*, 1257.

(23) (a) Nemia, M. M. B.; Lee, J.; Joullié, M. M. *Synth. Commun.* **1983**, *13*, 1117. (b) Torregrosa, J. J.; Baboulene, M.; Speziale, V.; Lattes, M. *Tetrahedron* **1983**, *39*, 3101. (c) Torregrosa, J. L.; Baboulene, M.; Speziale, V.; Lattes, A. *C. R. Acad. Sci. Paris II* **1983**, *297*, 297. (d) Brown, H. C.; Vara Prasad, J. V. N.; Gupta, A. K. *J. Org. Chem.* **1986**, *51*, 4296. (e) Brown, H. C.; Vara Prasad, J. V. N. *Heterocycles* **1987**, *25*, 641.

(24) (a) Naryana, C.; Periasamy, M. *J. Chem. Soc., Chem. Commun.* **1987**, 1857. (b) Andres, C.; Delgado, M.; Pedrosa, R. *Anal. Quim.* **1993**, *89*, 629.

(25) (a) Reference 24a describes several reactions of alkenes in the presence of chiral tertiary *N*-phenylamines. By far the highest enantioselectivities were reported with 2,3-dihydrofuran (0.7 g scale, benzene solution) in the presence of a 1:1 ratio of *in situ* generated amine boranes *i* (11.6 ± 2.3% ee for 3-hydroxytetrahydrofuran) or *ii* (19.2 ±2.4% ee for 3-hydroxytetrahydrofuran) using a workup consisting of standard base/peroxide oxidative cleavage followed by distillation from the crude product mixture,



i *ii*

chromatography, redistillation, and ee assay based on optical rotation. In two attempts to repeat the reaction using *i* (0.107 and 0.056 g scale), we opted not to perform the distillations due to the smaller quantities. The usual uncertainties involving optical rotation were another consideration. Starting with *i* (found α_D +19.2, c 3.2, CHCl$_3$; reported α_D +17.29, c 3.92, CHCl$_3$), the hydroboration and oxidative cleavage were done following ref 24a, but gave a titrated amine borane concentration of 0.17 M (reported data correspond to 0.25 M amine borane). The weights and volumes were adjusted for the smaller scale, but purification of 3-hydroxytetrahydrofuran was performed by flash chromatography (37% yield). This was followed by conversion to the Mosher ester to allow NMR assay by ^{19}F NMR spectroscopy (found dr = 1.02:1.00). According to this procedure, the alcohol product is racemic within experimental uncertainty. We briefly considered repeating the analogous reaction with *ii*, but were unable to find the citation describing the method of synthesis. Using an alternative method, the amine precursor of *ii* was obtained according to NMR comparisons. This study was discontinued when the amine did not match the optical rotation (found α_D −8.4, c 5.87, EtOH; reported α_D −22, c 6, EtOH) in ref 24a. (b) In principle, asymmetric induction could be due to the S$_N$2-like displacement of amine by alkene as proposed in ref 24, or to non-covalent interactions involving the chiral amine in the transition state. Except for the experiments using *i* or *ii* with 2,3-dihydrofuran in ref 24a, the other examples described in ref 24a, b report ee values in the range of 1−5% ee based on optical rotation.

rations may involve an S_N2-like mechanism,[10] but other explanations for low ee merit consideration. Our work has not addressed intermolecular reactions beyond attempts to repeat one of the chiral amine examples[24a] on small scale.[25] Our studies as described above establish that activation of the isolable homoallylic amine borane complexes follows an intramolecular mechanism, and that related reactions can be exploited for the regiocontrolled synthesis of 3-aminoalcohols.

Acknowledgment. This work was supported by the National Institutes of Health (GM067146). We dedicate this paper to Prof. E. J. Corey on the occasion of his 80th birthday.

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

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