

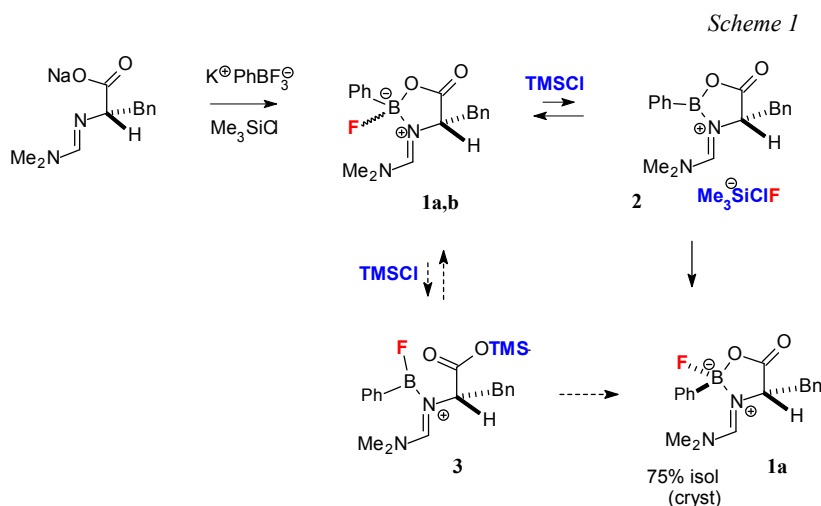
ELECTROPHILIC CATIONIC BORANES

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On this occasion of the 7th Walden Symposium in Riga, I would like to tell you the story of our involvement with cationic electrophilic borane intermediates. My lecture will begin with a brief history of our work and will then make an even briefer connection with the history of tricoordinate cationic boron structures. Toward the end of my talk, we will see some of the most recent studies featuring the chemistry of these potent electrophiles.

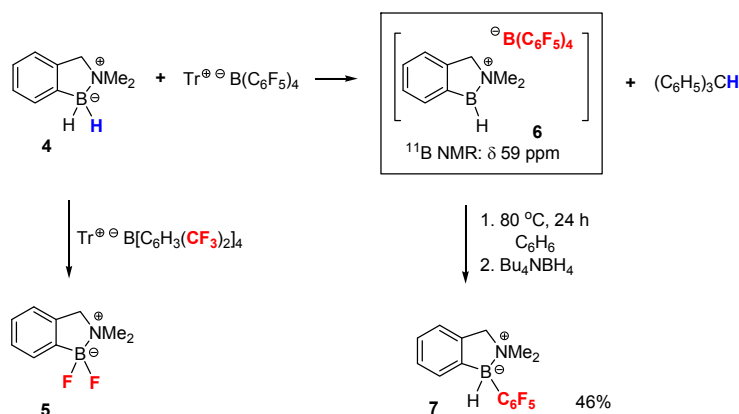
More than twenty years ago, we had become interested in the phenomenon of crystallization-induced asymmetric transformation as a way to control boron configuration [1–3]. The key example is shown in Scheme 1 and involves the TMSCl-induced conversion of a diastereomer mixture **1a,b** in solution to a crystalline solid with a very high diastereomer ratio favoring the indicated diastereomer **1a** (75% overall from starting amidine). We could show that the diastereomers **1a** and **1b** equilibrate in solution, and that the more stable crystalline diastereomer **1b** is strongly favoured in the solid state. Although the crystallization process is a fascinating phenomenon, for purposes of today's lecture, I would like to draw your attention to the proposed mechanism of diastereomer interconversion via compounds **2** or **3**. These intermediates contain tricoordinate boron and have a formal positive charge, so compounds **2** or **3** would be borenium salts according to the Nöth terminology [4]. We favour the pathway via **2**, assuming that the fluorophilic role of silicon will prevail, but the alternative pathway via the compound **3** is also reasonable and has not been ruled out. This was our first encounter with borenium salts, and stimulated the studies that I would like to summarize today. By coincidence,



this study also stimulated our development of potassium aryltrifluoroborate salts as stable sources of boronic acid derivatives [2]. The trifluoroborate salts have become important in more recent investigations of palladium-catalyzed coupling applications by Molander *et. al.*

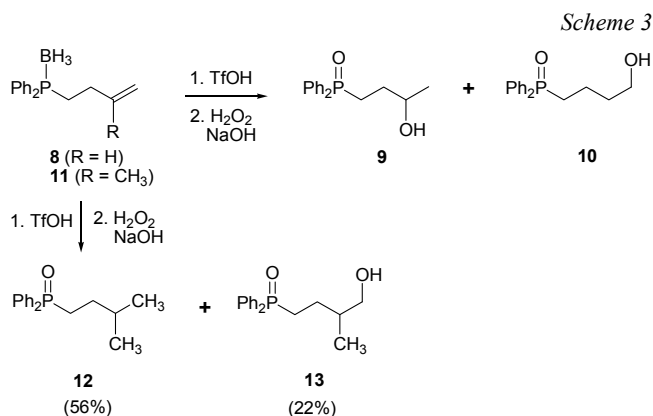
During our attempts to understand the importance of delocalization as a stabilizing factor for borenium cations **2** or **3**, we attempted to generate a less stabilized cation by hydride abstraction from the cyclic amine borane **4** using trityl tetrakis[*bis*-trifluoromethylphenyl]borate (Scheme 2) [5]. The rather shocking outcome of this experiment was the recovery of difluoroborane complex **5**, but no sign of borenium salt. Evidently, the expected cationic boron intermediate was sufficiently electrophilic to abstract fluoride from the CF₃ groups. Eventually, we did manage to detect the borenium cation **6** in solution by using the more stable tetrakis[pentafluorophenyl]borate anion in the hydride abstraction step by trityl cation, but cation **6** proved to be exceptionally reactive and could only be detected under scrupulously anhydrous conditions [6]. When the compound **6** was warmed in benzene, another surprising event was observed, namely the decomposition to a pentafluorophenylborane complex **7**. Of course, this is another indication of exceptional electrophilicity, and it is also one of the first examples of intermolecular aromatic borylation.

Scheme 2

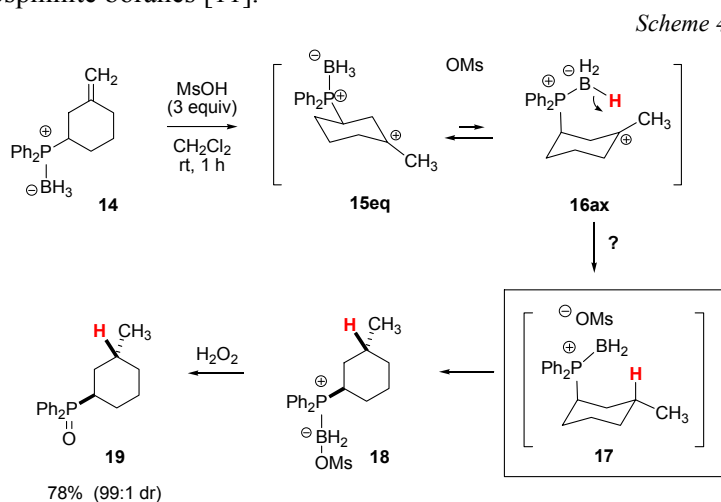


Over the following years, we investigated a variety of cyclic and acyclic amine boranes to learn whether the activated tricoordinate boron intermediates and equivalent species would be capable of typical B–H chemistry such as hydroboration of alkenes. Briefly summarized, we did see hydroboration events [7], and encountered the interesting intramolecular directing effects by nitrogen and by oxygen [8–10]. I won't dwell on those studies today, but will mention our investigation of unsaturated phosphine boranes. This was the first case where we were able to define conditions for intramolecular hydroboration using triflic acid activation from the compound **8** to the hydroboration products **9** and **10** after standard oxidative workup (Scheme 3), presumably resulting from the intermediate formation of a $\text{RPh}_2\text{P}\cdot\text{BH}_2\text{OTf}$ complex. We do not know the mechanism of hydroboration in this case. One possibility is that $\text{RPh}_2\text{P}\cdot\text{BH}_2\text{OTf}$ acts as a source of tricoordinate boron by $\text{S}_{\text{N}}1$ heterolysis of the B–O bond, but internal nucleophilic attack at boron atom by the alkene to displace TfO may present a lower activation barrier. In that case, the mechanism would resemble an $\text{S}_{\text{N}}2$ -like nucleophilic attack from the back-side of the TfO

bond at boron atom. In any event, the hydroboration process was not the only available reaction pathway. We also observed a competing ionic hydrogenation pathway in the case of the more highly substituted alkene **11**, resulting in the hydrogenated compound **12** as well as the hydroborated compound **13**. Presumably, the ionic hydrogenation involves the competing protonation of the double bond followed by the internal hydride transfer to give the compound **12**.

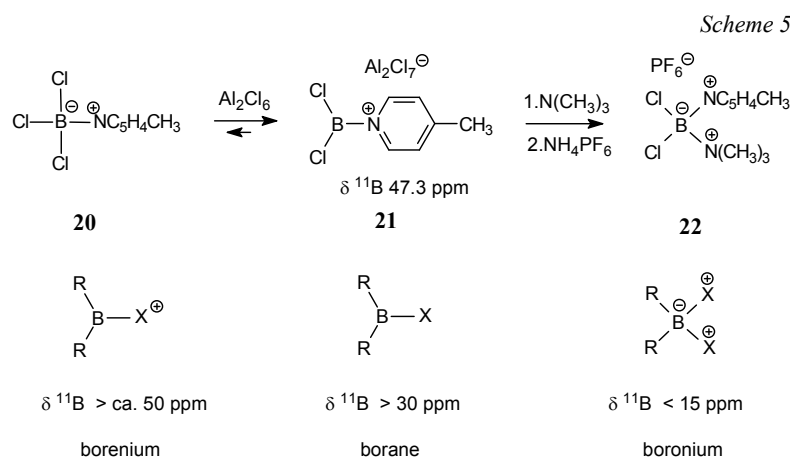


The conversion from the compound **11** to **12** implicates an intramolecular hydride transfer that should occur with predictable stereochemistry in suitable environment. This possibility was explored in the phosphine borane series as shown in Scheme 4 [11]. Here, the 3-cyclohexylidenediphenylphosphine borane **14** was treated with methanesulfonic acid resulting in a mixture of carbocation conformers **15eq** and **16ax**. The latter is capable of internal hydride transfer, an event that presumably generates the borenium intermediate **17**. If this is correct, then conversion to the mesyloxyborane complex **18** occurs rapidly and oxidative workup affords the compound **19** with excellent diastereocontrol. Several analogous ionic hydrogenations were also observed starting from phosphinite boranes [11].



Among the above examples from our work, we have seen one case where a borenium salt is observable (structure **6**, Scheme 2), and other examples where the tricoordinate borenium intermediates are implied by the reactivity considera-

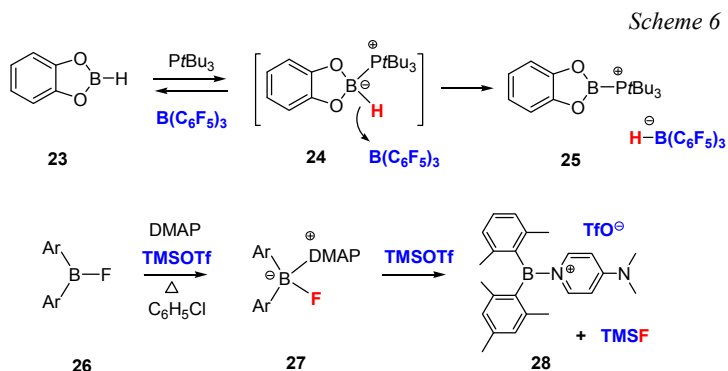
tions, but are not observed due to the formation of more stable tetracoordinate boron species (**2** vs. **1**; **17** vs. **18**). This difference is clearly related to the nature of the anion. Thus, the minimally interactive $\text{B}(\text{C}_6\text{F}_5)_4^-$ anion is capable of resisting bond-forming events as the counterion for the borenium cation **6**, but MsO^- or TfO^- ions prefer to form covalent bonds and afford tetracoordinate boron adducts. These and similar observations piqued our curiosity and interest, and so did some reports in the older literature. It seems that borenium cations had been regarded as viable species during the 1950's, to the extent that an ionic (tricoordinate boron) structure $\text{Me}_3\text{N}\cdot\text{BCl}_2^+ \text{Cl}^-$ had been seriously contemplated [12] for what we now know to be the simple Lewis base–Lewis acid adduct $\text{Me}_3\text{N}\cdot\text{BCl}_3$. However, such structural uncertainties were resolved with the advent of ^{11}B NMR spectroscopy, and by the late 1960's it had become increasingly clear that tricoordinate borenium salt structures are likely only in systems that contain stabilizing *n*-donor substituents (usually N, less often O) at boron atom, or in certain other cases where the negatively charged counterion is exceptionally stable and non-interactive [4]. The first well-defined borenium example lacking N or O *n*-donors was the aluminate salt **21**, observed in the solution upon treatment of the boron trichloride complex **20** with aluminium chloride, and characterized by the ^{11}B NMR chemical shift (47.3 ppm) as containing tricoordinate boron by comparison with characteristic values for tricoordinate vs. tetracoordinate boron (Scheme 5) [13]. Structure **21** was further supported by its facile reaction with nucleophiles, as in the conversion to boronium salt **22** (tetracoordinate boron) upon treatment with trimethylamine.



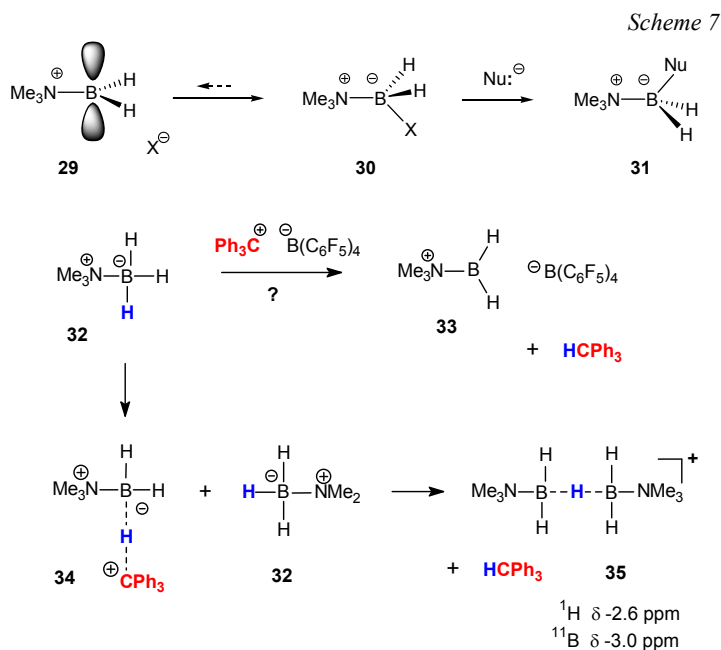
Structure **21** is somewhat stabilized by the pyridinium π -system, and perhaps also by the chloride unshared electron pairs. Its survival in solution indicates that the chloride ion binds more strongly to aluminium atom than to boron atom, but the covalent adduct **20** is more stable than the corresponding dissociated borenium chloride salt. Thus, conversion of the compound **20** to the borenium species requires assistance by a strong "chlorophile".

Over the subsequent years, a number of other more or less stabilized borenium salts have been generated by abstraction of one of the boron substituents in a Lewis base–borane complex (Scheme 6). Two examples from the literature are shown in Scheme 6. In the first example, catechol borane **23**, is converted

into phosphine complex **24** in the presence of $\text{B}(\text{C}_6\text{F}_5)_3$ as the hydridophile, resulting in the formation of borenium salt **25** [14]. Stabilization by the unshared electron pairs at oxygen is one reason why the compound **25** is favoured in this hydride transfer equilibrium. In the second case, fluoride is abstracted from the DMAP complex **27**, generated from diarylboron fluoride **26**. Trimethylsilyl triflate functions as a fluorophile in this example and affords the isolable borenium salt **28** [15]. Tricoordinate boron is favoured by the steric bulk of the hindered aryl groups, as well as by π -delocalization.



From the precedents of Schemes 5 and 6, it is clear that tricoordinate boron cations are possible if n -donor or π -donor groups are attached to boron atom. It therefore seemed logical to ask whether any stabilizing group is really essential. After all, monomeric *tert*-hexyl 2,3-dimethyl-2-butyl borane is a perfectly well-behaved example of tricoordinate boron due to the steric protection provided by the bulky, quaternary carbon substituent. One can easily imagine a nitrogen analogue **29** that has a quaternary nitrogen atom connected to boron atom in similar steric environment (Scheme 7).



Of course, the quaternary nitrogen atom in the compound **29** has a net positive charge, and the trimethylammonium subunit is certainly more electronegative than *tert*-hexyl group. The electron-withdrawing effect would increase the electrophilicity of the compound **29** compared to *tert*-hexyl borane, and the literature suggests that the effect would be large enough to strongly favour the covalent amine borane complex **30** over the borenium salt **29** [4], but the question is by how much? A related question can be asked about the remarkably facile nucleophilic displacement reactions of the compound **30** (X = iodide) to afford products **31**. If these are S_N1 reactions that take place via equilibrium formation of the borenium ion **29**, then there is no mystery, but the literature suggests that such conversions proceed by the S_N2 mechanism [16, 17]. These and similar considerations stimulated attempts in our laboratory to generate the compound **29** under conditions where it might be observable.

We already knew that amine boranes react readily with trityl cation to form triphenylmethane, and the compound **32** was no exception as triphenylmethane was easily detected by NMR assay when TrB(C₆F₅)₄ was added at room temperature or below. However, no sign of a tricoordinate boron signal corresponding to the compound **33** was ever detected by ¹¹B NMR spectroscopy. Instead, we observed a dominant new signal at δ -3.0 ppm, the characteristic region for tetracoordinate boron, along with a B-H signal at -2.6 ppm in the ¹H spectrum. The unusual hydride-bridged structure **35**, connected by a 3-center 2-electron bond (3c2e), was initially assigned from the NMR data as well as other evidence [18], and was recently confirmed by the X-ray crystallography (Fig. 1) [19]. One of the more informative bits of evidence initially supporting this and related structures was that 50 mol.% of TrB(C₆F₅)₄ is sufficient to consume all of the starting compound **32**, and no further hydride abstraction is detected if more of TrB(C₆F₅)₄ is added.

The above experiment did not answer the question of whether hydride abstraction produced the borenium intermediate **33**, although it certainly made clear that if this intermediate **33** was formed, then it was rapidly captured by unreacted amine borane **32** to afford the hydride-bridged structure **35**. We saw no evidence that formally excludes this simple interpretation, but we also found no evidence to exclude an alternative possibility that is illustrated in Scheme 6, proceeding from the compound **32** via the 3c2e structure **34**, formed by interaction of trityl cation as the acceptor and B-H bond of the compound **32** as the donor. The partially bonded hydride and trityl subunits in the compound **34** constitute the unusual, but very good leaving group HCPPh₃, and the B-H bond of the compound **32** is a good nucleophile. Therefore, an S_N2-like displacement of triphenylmethane by nucleophilic attack of the compound **32** can be proposed as a route to the compound **35** that does not require the formation of the borenium intermediate **33**. This is the route that we currently favour for the facile room temperature process, but a role for the compound **33** is not ruled out.

Prior to Scheme 7, we have tried to show the formal charge notation familiar to organic chemists to represent the boron complexes, neutral as well as cationic. However, a formal negative charge at tetravalent boron clouds the issue for nucleophilic displacement from the compound **30** to **31** (What?! An anionic nucleophile attacks an anionic boron?). This is because the reactivity of the compound **30** depends mostly on the energy of the σ* orbital corresponding to the B-X bond and on the leaving group ability of the substituent X. Further-

more, the formal charge does not reflect the charge distribution (most of the negative charge resides near the boron ligands). Matters become progressively worse in the case of the 3c2e structures **34** and **35**. It would be fair to say that the formal charge convention becomes an impediment to understanding the nature of these structures, and approaches the nonsensical for the hydride-bridged cation **35**. For that reason, only the net charge is shown for the compound **35**, and a similar practice will be followed for some of the other unusual structures to be encountered later on.

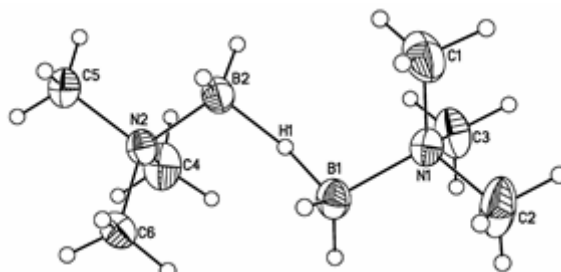
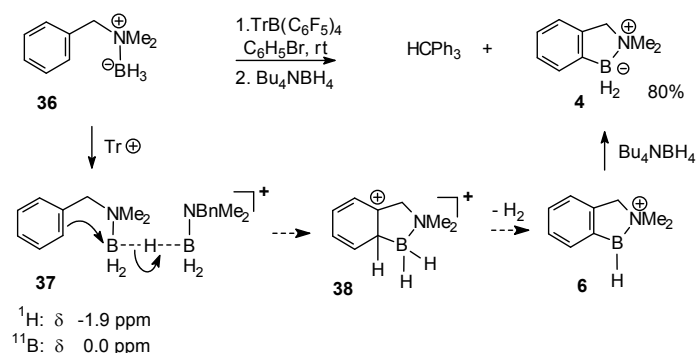


Fig. 1. Crystal structure of the compound **35** ($\text{B}(\text{C}_6\text{F}_5)_4^-$ omitted for clarity).

During our initial study of other cases of hydride abstraction from Lewis base–borane complexes, we found that hydride bridged dimers related to the compound **35** react readily with weak nucleophiles [18]. This observation suggested that intramolecular nucleophilic attack by aromatic π -bonds acting as the nucleophiles might result in a Friedel–Crafts type process that would amount to an electrophilic aromatic borylation (Scheme 8). Initial results were quite promising and internal borylation to give the compound **4** was indeed observed when benzylamine borane **36** was treated with $\text{TrB}(\text{C}_6\text{F}_5)_4$ at room temperature, followed by reductive quenching with Bu_4NBH_4 [6]. However, careful control of stoichiometry revealed that the observed intermediate hydride bridged structure **37** is not electrophilic enough to cyclize at room temperature. It proved necessary to treat the cation **37** with additional $\text{TrB}(\text{C}_6\text{F}_5)_4$, at which point the stoichiometric borylation proceeded efficiently. For simplicity, the cyclization mechanism is illustrated as an electrophilic substitution to form a carbocationic intermediate **38**, but an alternative C–H insertion pathway is equally plausible based on available evidence. We have not been able so far to establish the role of added $\text{TrB}(\text{C}_6\text{F}_5)_4$ in the cyclization. One possible interpretation is that the trityl cation somehow promotes conversion of the cation **37** into a reactive borenium cation as the key intermediate that undergoes cyclization, but alternative explanations are conceivable and the issue remains open.

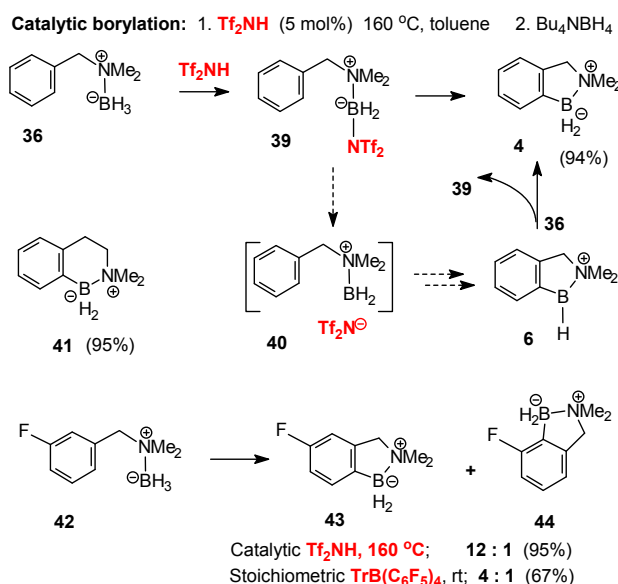
Another aspect of the stoichiometric cyclization process deserves mention. When the reaction was monitored by NMR spectroscopy, it was possible to show that the initial cyclization product prior to reductive quenching is the marginally stable borenium cation **6**, the same cation that we had generated earlier by hydride abstraction from the compound **4** (Scheme 2). Computations suggest that the conversion from the compound **38** to **4** is a 4-center process resulting in the evolution of hydrogen, rather than the classical Friedel–Crafts "end-game" of proton removal from the compound **38** leading directly to the formation of the compound **4**.

Scheme 8



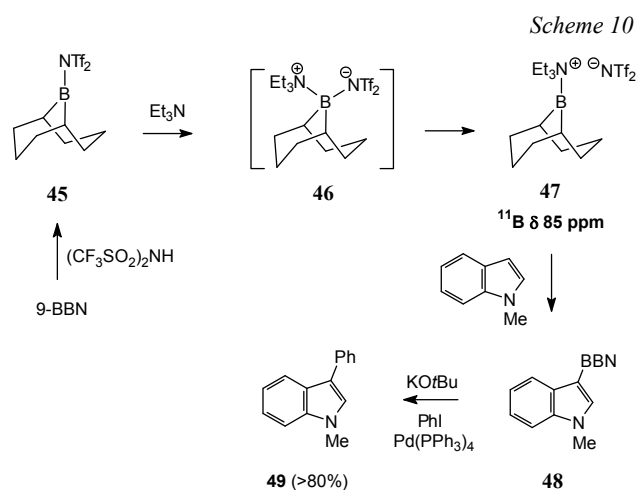
The stoichiometric nitrogen-directed internal borylation shown in Scheme 8 is reasonably general and works with other tethered aromatic amine boranes. However, the stoichiometric use of $\text{TrB}(\text{C}_6\text{F}_5)_4$ is not ideal from a cost perspective, so we have investigated catalytic versions of this process. The most promising method found so far uses 5% of the strong acid Trf_2NH as the activating agent and works best at temperatures above 120°C (Scheme 9). For convenience, we chose to operate at 160°C as a way to avoid having to periodically assay the highly moisture-sensitive system, and to ensure complete conversion. When the compound **36** was reacted under the catalytic conditions, the result was a highly efficient, clean conversion into the internal borylation product **4** (94%). Quenching was done as usual, but in this case it was not essential because the tentative catalytic cycle shown in Scheme 8 ensures that most of the intermediate borenium ion **6** is quenched by the starting amine borane **36** to regenerate the activated intermediate **39** as well as to form the product **4**. Intermediate **39** can be observed at lower temperatures and is clearly a precatalyst for the borylation. However, the suggested catalytic cycle via the borenium bistriflimidate **40** should be regarded as one of several possibilities that have not yet been evaluated fully.

Scheme 9



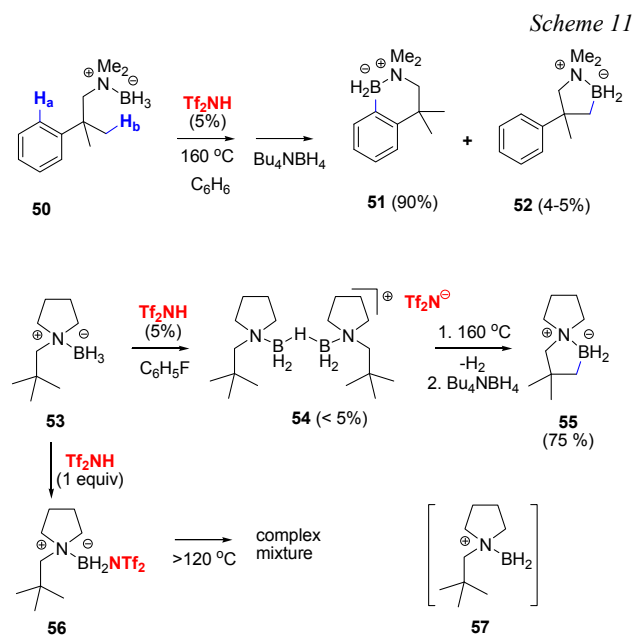
The catalytic procedure works surprisingly well, considering the high temperature, and tends to be much cleaner than the stoichiometric borylation. Thus, the catalytic internal borylation of *N,N*-dimethyl(phenethyl)amine borane produced the compound **41** in 95% yield, and the same reaction from the compound **42** gave a 12 : 1 mixture of regioisomers **43** and **44**, also in 95% yield. The corresponding stoichiometric activation affords 4:1 ratio of the compounds **43** and **44** in 67% yield, indicating differences in the product-determining steps for the catalytic vs. stoichiometric procedures. The better efficiency under the catalytic conditions probably reflects the greater stability of the bistriflimidate anion, and perhaps, the absence of the stoichiometric by-product triphenylmethane.

We have also seen cases of intermolecular borylation using borenium reagents. Scheme 10 illustrates the application of a hindered, 9-BBN-derived borenium salt **47** for this purpose [20]. Generation of the compound **47** begins with treatment of the 9-BBN-NTf₂ reagent **45** with triethylamine. The triethylamine complex **46** is probably formed as an intermediate, but it does not survive due to steric hindrance involving the 9-BBN core and is spontaneously converted into the borenium salt **47** according to the characteristic ¹¹B NMR signal at δ 85 ppm for tricoordinate boron. This interesting structure is the first (and so far, only) borenium ion to be detected under condensed phase conditions that lacks any stabilizing *n*-donor or *π*-donor substituents. In the presence of electron-rich aromatic substrates, the borenium salt **47** reacts to afford the borylation products, as illustrated for *N*-methylindole. The resulting borylated indole **48** is very sensitive to protodeboronation, but can be intercepted under Suzuki coupling conditions to give the arylated product **49**.



Our study of the nitrogen-directed aromatic borylation suggested that a C–H insertion mechanism is a plausible alternative to the classical Friedel–Crafts mechanism. To explore some of the implications, we examined an interesting substrate **50** that is capable of aliphatic as well as aromatic borylation (Scheme 11) [19]. Under the catalytic conditions with Tf₂NH at 160 °C, the compound **50** gave 90% yield of the aromatic borylation product **51**, but it also gave a small amount of the regioisomeric insertion product **52** resulting from insertion into an aliphatic C–H bond. This is a high-yielding reaction for hindered aliphatic amine boranes, and was studied in some depth in the case of the

compound **53**. The first event was the expected activation step, and a small amount of the hydride-bridged intermediate **54** was detected in halogenated solvents at room temperature. Upon heating to 160 °C, the borylation proceeded on a timescale of hours to give the compound **55** (75 % isolated after borohydride quench to convert activated species to amine boranes). On the other hand, when the compound **53** was treated with a full equivalent of Tf₂NH at room temperature, the expected conversion into the activated derivative **56** was observed. Heating the compound **56** gave a complex mixture of products suggesting decomposition, but only a small amount of borylation. This sobering observation raises questions about the identity of the key intermediate responsible for the C–H insertion step. Judging from the catalytic experiment, some species equivalent to the borenium salt **57** must be generated already at room temperature to explain the initial conversion to hydride-bridged compound **54**, and our experience with the compound **46** (Scheme 10) indicates that heterolysis of B–NTf₂ bond to generate the compound **57** is a reasonable prospect upon heating of the compound **56**. Nevertheless, the borylation proceeds much better from the compound **54** than from **56**. These observations hint that the key intermediate responsible for borylation is derived from the compound **54** in some way other than by simple dissociation to the borenium salt **57**, but we do not yet have enough information to make a specific proposal, nor can we rule out a role for **57**.



This brings us to the end of my story regarding electrophilic boron intermediates. We have much more to do to understand the nature of the reactive intermediates responsible for the aliphatic C–H borylations, and work continues to find a way to lower the reaction temperature for the catalytic process. On the other hand, the catalytic procedure provides access to unusual amine boranes that are not available via simple hydroboration of unsaturated amines, and has interesting potential for the preparation of borylated aromatic substrates. We have a better sense regarding the role of borenium salts as intermediates in several other applications, such as the ionic hydrogenation chemistry, our earlier

study of related heteroelement-directed hydroborations, and our first encounter with borenium salts in the context of crystallization-induced asymmetric transformation.

In closing, I would like to thank Prof. P. Trapencieris for initiating and organizing this conference for more than a decade, and to congratulate him as the co-recipient of this year's Walden Medal. I would also like to extend my congratulations to Prof. R. Valters as co-recipient of this honour, and to thank him for his important contributions during our efforts to coordinate activities involving the American Chemical Society, Riga Technical University, and the Fundamental Academic Library in Riga during the 1990's. Finally, I would like to express my appreciation and respect to Prof. J. Stradiņš for his many efforts on behalf of science, history, and national awareness in Latvia. It was his 1984 letter that started my scientific contacts with Riga, and his writings that made me aware of Walden's Latvian origins. It was no accident that my interests turned increasingly to stereochemistry in the subsequent years, and eventually, to the resulting pursuit of organoboron chemistry that you have heard about today.

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