

**Ultrastabilized Boranes: A Study into the  
Synthesis, Structure and Reactivities of  
Heterosubstituted Organoboranes**

By

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## DECLARATION

I, Cathryn Anne Slabber, hereby certify that this experimental work and the discussion thereof is a result of my own investigation in the School of Chemistry of the University of KwaZulu-Natal (Pietermaritzburg), under the supervision of Professor R.S. Robinson

This work was carried out by me, and has not already been accepted in substance for any degree and is not being submitted in candidature for any other degree.

Signed.....

C. A. Slabber

I hereby certify that this statement is correct.

Signed.....

Prof R. S. Robinson (Supervisor)

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# Ultrastabilized Boranes: A Study into the Synthesis, Structure and Reactivities of Heterosubstituted Organoboranes

## Abstract

Three heterosubstituted boranes were successfully synthesized from the corresponding amines and borane dimethyl sulfide (BH<sub>3</sub>-DMS) in high yields, and were noted to be significantly more stable than the analogous dioxo-compounds. *In situ* <sup>11</sup>B NMR spectroscopy indicated that the mechanism of the reaction to form these boranes contains two intermediates and supports a step-wise addition mechanism. <sup>15</sup>N NMR spectroscopic analysis of the boranes identified a downfield shift in the location of the nitrogen signal from the typical amine region towards the aromatic region, supporting the theory of electron back-donation from the nitrogen lone pair to the boron atom's vacant *p<sub>z</sub>*-orbital. The three boranes proved to be suitable hydroboration reagents under microwave-assisted conditions, with Wilkinson's catalyst and a rhodium(I) carbonyl hydride catalyst both showing catalytic ability, however yields were noted to be dependent on the borane, the olefin and the catalyst.

Twelve heterosubstituted boranes were successfully synthesized in high yields as products from condensation reactions between diamines and boronic acids both in solution and under microwave-assisted solvent-free conditions, which resulted in the reaction time being reduced from three hours to 15 minutes. <sup>15</sup>N NMR spectroscopic analysis of these compounds showed a similar downfield shift in the amine signal as was observed previously, lending support to the electron back-donation explanation for the stability of these compounds.

Crystals suitable for X-Ray diffraction analysis were grown for four 1,8-diaminonaphthalene-based boranes, and analysis of the data showed that the compounds are not planar as originally thought, rather there is a degree of torsion inherent in each of the structures, ranging from a slight (3-4%) to a substantial deviation (19-20%).

It was shown that heterosubstituted boranes can be used in Petasis reactions as the organoborane reagent in a number of cases, although the reaction conditions used were not optimized for these compounds. Microwave irradiation was also successfully employed in the Petasis reactions, which reduced the reaction time from 48 hours to 10 minutes.

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## List of Abbreviations

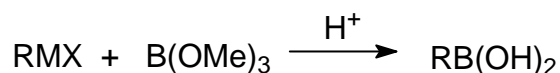
9-BBN	9-Borabicyclo[3.3.1]nonane
Ar <sub>2</sub> BOH	Generic diarylborinic acid
Ar <sub>3</sub> B	Generic triarylborane
ArB(OH) <sub>2</sub>	Generic arylboronic acid
BF <sub>3</sub>	Boron trifluoride
BF <sub>3</sub> ·OEt <sub>2</sub>	Boron trifluoride-diethyl etherate complex
BH <sub>3</sub>	Borane
BH <sub>3</sub> ·DAS	Borane-diisoamyl sulfide complex
BH <sub>3</sub> ·DMS	Borane-dimethyl sulfide complex
BH <sub>3</sub> ·FMS	Borane-fluorous dimethyl sulfide
BH <sub>3</sub> ·THF	Borane-tetrahydrofuran complex
BNCT	Boron Neutron Capture Therapy
BX <sub>3</sub>	Generic boron trihalide
Cat <sub>3</sub> B <sub>2</sub>	2,2'-[1,2-phenylenebis(oxy)]bis-1,3,2-benzodioxaborolane
DFT	Density Functional Theory
DMF	Dimethylformamide
DMS	Dimethyl sulfide
H <sub>2</sub> BCl·DMS	Monochloroborane-dimethyl sulfide complex
H <sub>2</sub> BThx	Thexylborane
HBAph	1,3,2-Benzoxazaborolane
HBCat	Catecholborane
HBCy <sub>2</sub>	Dicyclohexylborane
HBDan	Naphtho[1,8- <i>de</i> ][1,3,2]diazaborinine
HBIpc <sub>2</sub>	Diisopinocampheylborane
HBPda	1,3,2-Benzodiazaborolane
HBPIn	Pinacolborane

HBThia	1,3,2-Benzodithioborolane
HFIP	Hexafluoroisopropanol
HMBC	Heteronuclear Multiple Bond Correlation
HMQC	Heteronuclear Multiple Quantum Coherence
HOMO	Highest occupied molecular orbital
HSQC	Heteronuclear Single Quantum Coherence
INEPT	Insensitive Nuclei Enhanced by Polarization Transfer
IR	Infrared
LUMO	Lowest unoccupied molecular orbital
MCR	Multicomponent Reaction
NHC	<i>N</i> -heterocyclic carbene
NMR	Nuclear Magnetic Resonance
OTf	Trifluoromethanesulfonate, Triflate
Ph	Phenyl
R <sub>2</sub> BX	Generic dialkylborane halide
RBX <sub>2</sub>	Generic alkylborane dihalide
Salen	<i>N,N'</i> -Bis(salicylidene)
THF	Tetrahydrofuran
UV/Vis	Ultraviolet-visible (spectroscopy)

# 1. Organoboranes in Synthesis: A Review

## 1.1. Introduction

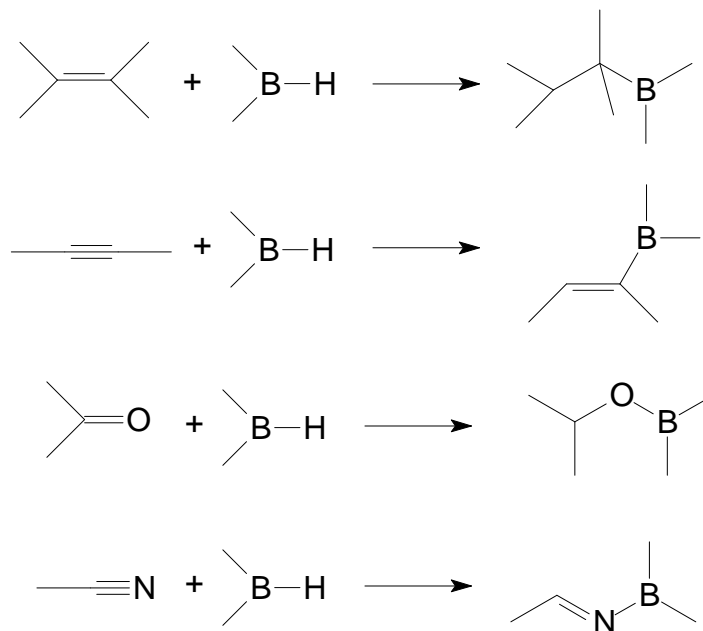
Organoboranes, those organic compounds containing a boron atom, are today a vital part of a number of important reactions, as well as having a wide range of industrial uses.<sup>1</sup> Prior to the 1950's, the majority of organoboranes were created by a Grignard-type reaction between an organometallic compound,<sup>2</sup> such as an organozinc,<sup>3</sup> organolithium or an organomagnesium<sup>4</sup> compound, and a boronate ester or halide (**Scheme 1**). Hydroboration reactions were not without drawbacks, as the reaction between diborane and alkenes was known to be sluggish.<sup>5</sup>



M = Mg, Li, Zn  
X = halide

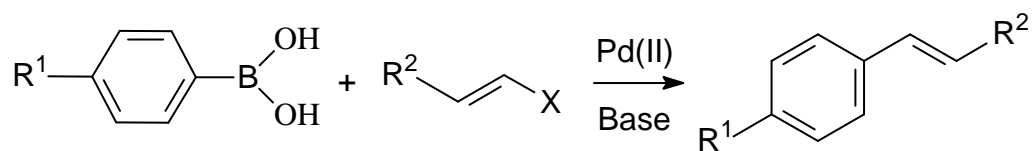
*Scheme 1.*

During the 1950's, Brown and Subba Rao introduced a hydroboration reaction into mainstream chemistry, which allowed for the formation of organoborane reagents under milder conditions than those previously used.<sup>6</sup> This monumental contribution, based on the observation of Brown that ethereal solutions greatly increased the rate of the reaction and lowered the required reaction temperatures,<sup>7</sup> opened the door to the widespread formation, and further use, of organoborane reagents. Organoborane reagents could thus be produced from not only alkenes and alkynes, but also from reagents containing carbonyl and cyano groups (**Scheme 2**).<sup>8</sup>



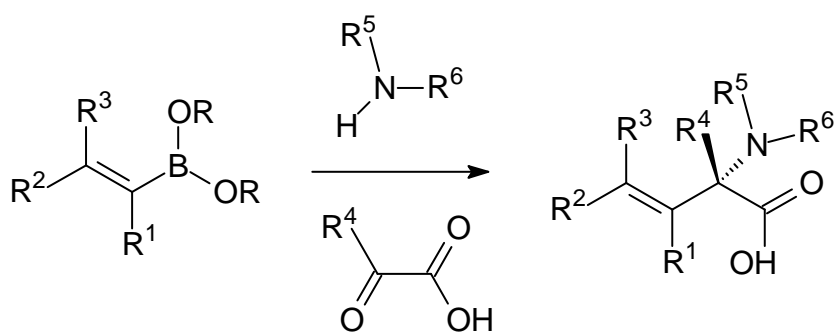
*Scheme 2.*

As the reactions used to create organoboranes became simpler, there was a rapid increase in the number and type of reactions which made use of these reagents. By far the single largest use of organoboranes is as reagents in the Suzuki reaction.<sup>9</sup> One of the many palladium-catalyzed reactions, the Suzuki reaction (**Scheme 3**), results in the formation of a carbon-carbon bond by reaction of an organoborane reagent and an aryl or vinyl halide. This reaction is used in the production of poly-olefins, substituted biphenyls, styrenes and a number of pharmaceutically important compounds.<sup>10</sup> Recently, the Suzuki reaction has been employed in the synthesis of organic photochromic compounds.<sup>11</sup> This may pave the way for development of these compounds in optoelectrical devices such as optical fibers, as processes used in the synthesis of these compounds have been beleaguered with expensive starting materials and low yields.



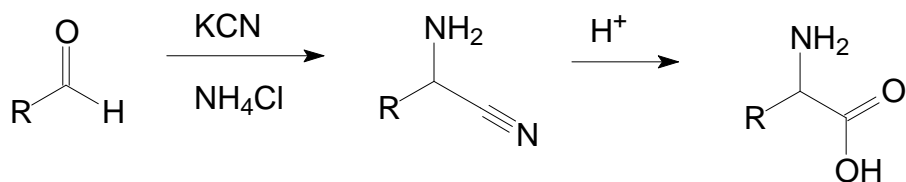
*Scheme 3.*

One of the newer reactions to utilize the unique properties of organoborane reagents is the Petasis reaction.<sup>12</sup> A variation on the Mannich reaction, this reaction between an aldehyde or  $\alpha$ -keto acid, an organoborane and an amine (**Scheme 4**) has been used in the synthesis of Uniflorine A, a possible antidiabetic agent.<sup>13</sup> What sets this reaction apart from the Mannich and other previous multistep reactions is that the side chain is derived from the organoborane reagent.<sup>14</sup> As such an incredibly large number of non-natural  $\alpha$ -amino acids can be easily synthesized, which could allow for the rapid discovery of compounds with pharmaceutical properties.<sup>1</sup>



*Scheme 4.*

In comparison to the Strecker amino acid synthesis<sup>15</sup> (**Scheme 5**), where an aldehyde or ketone and ammonium chloride are condensed using potassium cyanide to form an  $\alpha$ -aminonitrile which is subsequently hydrolyzed to yield the amino acid,<sup>16</sup> the Petasis reaction has a number of distinct advantages. The Petasis reaction does not require the use of the highly toxic potassium cyanide, and it is highly stereoselective, while the Strecker reaction results in the formation of racemic  $\alpha$ -aminonitriles, and thus racemic amino acids, unless asymmetric auxiliaries<sup>17</sup> or catalysts are used.<sup>18</sup>



*Scheme 5.*

The Petasis reaction can be used to synthesize  $\beta,\gamma$ unsaturated  $\alpha$ -amino acids,<sup>12a,19</sup> while the Strecker reaction yields unsubstituted amino acids from aldehydes if ammonium salts are used, and substituted amino acids if primary or secondary amines are used. Similarly,  $\alpha,\alpha$ -disubstituted amino acids can be formed using ketones in the place of the aldehydes.<sup>20</sup>

Organoboranes, especially arylboranes, have in the recent past been used successfully as catalysts in a number of organic synthesis reactions, many of which show regio-, stereo- or enantioselectivity.<sup>21</sup> The power of these reagents as catalysts is due to the inherent Lewis acidity of the arylboranes as a result of the vacant  $2p$ -orbital located on the boron atom. These arylboranes have numerous advantages over the traditional boron-containing Lewis acids such as  $\text{BF}_3$ , as the compounds are stable in air and water and at elevated temperatures, and reactions can be carried out across a large portion of the pH range. Triarylboranes containing electron-withdrawing groups, such as tris(pentafluorophenyl)borane **1** (**Figure 1**) have shown excellent catalytic activity in reactions such as the Mukaiyama aldol reaction (**Scheme 6**), the Sakurai-Hosomi allylation reaction (**Scheme 7**) and the Diels-Alder reaction of cyclopentadiene and 2-methyl-2-propanal (**Scheme 8**), while diaryborinic acids and arylboronic acids have also proven to be suitable models upon which to base chiral boron catalysts.<sup>22</sup>

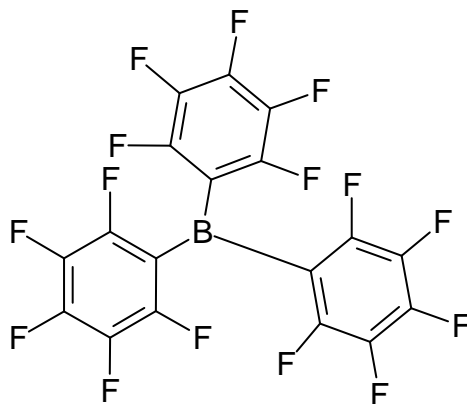
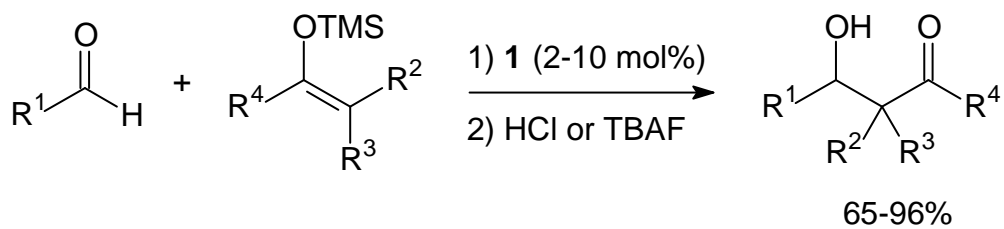
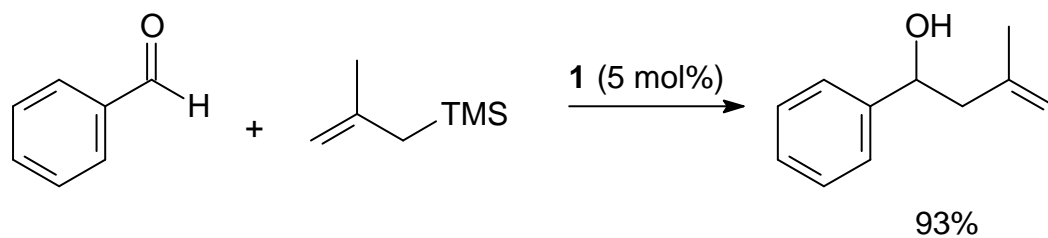


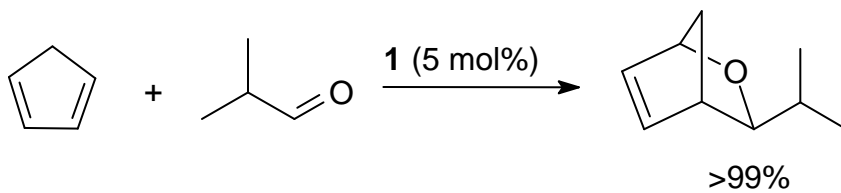
Figure 1.



Scheme 6.

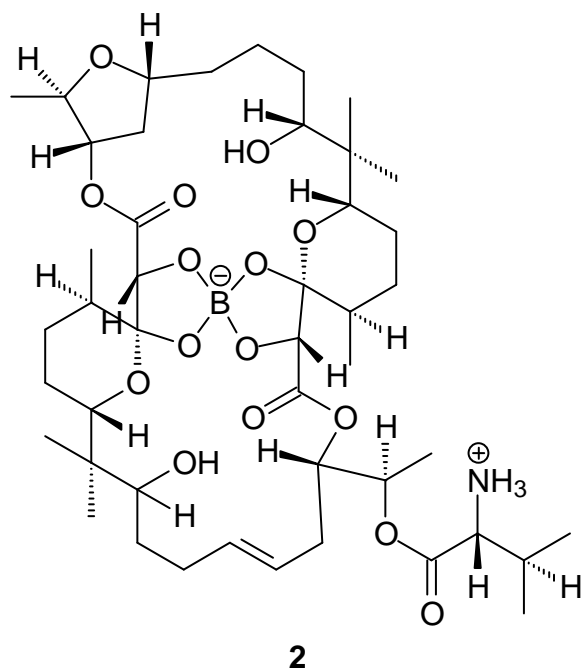


Scheme 7.



Scheme 8.

Organoboranes do not belong solely in the domain of the synthetic chemist – even though reactions where organoboranes are involved as reagents or catalysts make up the largest number of uses for organoboranes, there are a number of other, non-synthetic, uses for these compounds. Boromycin **2**, the first boron-containing antibiotic found in nature (**Figure 2**), was isolated from *Streptomyces antibioticus* in 1971.<sup>23</sup> It is effective against the majority of Gram-positive bacteria, but not against Gram-negative bacteria. The bacteriocidal activity of this polyether macrolide antibiotic is due to the boromycin negatively affecting the cytoplasmic membrane, which results in the loss of potassium ions from the cell. Recently, boromycin has been shown to have anti-HIV activity, as it was found to inhibit the replication of both a clinically isolated HIV-1 strain and the cultured strain *in vitro*.<sup>24</sup> Boromycin is thought to interfere with the later stages of HIV infection, and possibly the maturation step in the replication of the HI virus.



**2**  
*Figure 2.*

The biosynthesis of boromycin, as proposed by Chen, Chang and Floss,<sup>25</sup> is in contrast to the formation of other macrolide antibiotics. In these classical macrolides, methyl branches are formed by the incorporation of different chain extension units

such as propionate and methylmalonate by Coenzyme A.<sup>26</sup> Rather, each half of the carbon backbone of the boromycin macrolide is formed from seven acetate extension units, each of which are modified by C-methylation through the transfer of three methyl groups of methionine.<sup>27</sup> Also atypical is the basis of the starter unit – the three carbon atoms are derived from glycerol, and not from propionate, lactate or pyruvate as would be expected.<sup>25</sup>

The structurally-similar aplasmomycin **3**, isolated in 1976 from a strain of *S. griseus*, (**Figure 3**) is a novel ionophoric or lipid-soluble, macrolide antibiotic.<sup>28</sup> It is effective against Gram-positive bacteria, including mycobacteria and has shown *in vivo* activity against *Plasmodium berghei*. Essentially a symmetrical dimer built around the four-coordinate boron atom, aplasmomycin and boromycin have almost identical conformations and matching configurations at all but one asymmetric carbon, (labeled with \* in Figure 3) with the only other major difference between the two being the presence of a D-valine moiety in boromycin.

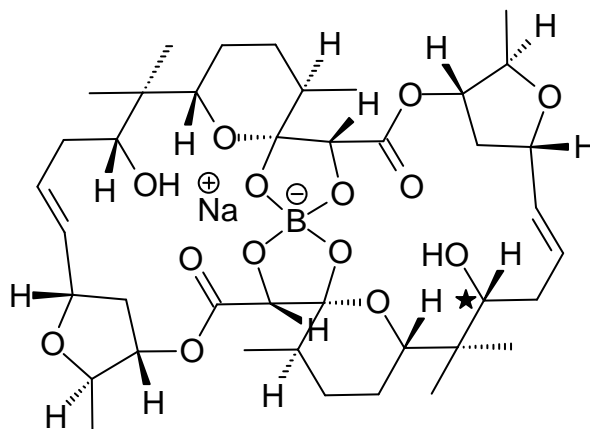
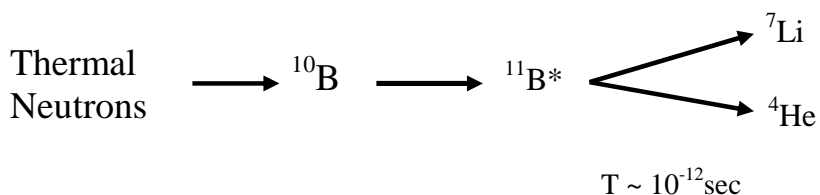


Figure 3.

The biosynthesis of aplasmomycin is very similar to the biosynthesis of boromycin, in that each half of the aplasmomycin skeleton is made up of a starter unit and seven acetate extension units, and the starter unit is again derived from glycerol.<sup>29</sup> Treatment of deboroaplasmomycin with boric acid resulted in the reformation of the complete aplasmomycin molecule, which indicates the likelihood

that the macrocyclic ring system is created first, and the insertion of the boron atom is one of the final steps.<sup>29</sup>

One of the most exciting and more controversial uses of organoborane compounds in a non-synthesis setting is in the field of Boron Neutron Capture Therapy (BNCT). An experimental cancer treatment, it involves the injection of an otherwise harmless substance containing boron-10 ( $^{10}\text{B}$ ) into the tumor, and the irradiation of that tumor with a relatively risk-free low energy or thermal neutron beam. The neutrons cause the  $^{10}\text{B}$  atom to absorb a neutron to become an excited boron-11 ( $^{11}\text{B}^*$ ) atom for a few milliseconds, before splitting into a lithium-7 ( $^7\text{Li}$ ) atom and a highly energetic helium-4 ( $^4\text{H}$ ) atom, also known as an  $\alpha$ -particle (Scheme 9). Both of these atoms cause severe cell damage by ionization of proteins and other cellular machinery, but the damage is restricted to a distance that is approximately the diameter of a cell. This treatment was initially controversial as treatment of cancer in patients required the on-site presence of large nuclear reactors, and so a number of research institutions and countries halted research into this type of treatment. Recent developments have provided a portable non-nuclear source of thermal neutrons, and it is possible and highly likely that large-scale research into this potentially lifesaving treatment will recommence in the future.



*Scheme 9.*

Although there are a number of elements that could potentially be used for BNCT-like therapy, there are several reasons why  $^{10}\text{B}$  is well suited to this use.<sup>30</sup> Firstly, the distance of damage caused by the products of the reaction is in the order of the diameter of a cell, which allows for incredibly precise targeting of a cancer cell without damaging surrounding, healthy tissues.  $^{10}\text{B}$  is also common, as

approximately 20% of all naturally-occurring boron is this non-radioactive isotope, making enrichment of boron-containing substances straightforward and uncomplicated, as well as non-lethal. The chemistry of boron is well known and understood, making the inclusion of a boron atom into a chemical structure simple and effective. A final benefit to using boron is that the particles produced during BNCT therapy kill both dividing and non-dividing cells, as opposed to the more traditional therapies which only kill actively dividing cells.<sup>31</sup>

To be effective as a treatment, the boron atoms must be taken up by the cells, and that is easier to do if the boron is attached to a compound which is naturally taken up in the body. If the  $^{10}\text{B}$  atom could be coupled to a molecule that is taken up preferentially by the tumor cells, more  $^{10}\text{B}$  would accumulate in the tumor cells, and the damage to these cells would be much greater than to the healthy cells with a lower  $^{10}\text{B}$  concentration. As of yet, no research has been published on which naturally-occurring compounds might be a suitable transport vehicle for  $^{10}\text{B}$  atoms, and as such the majority of compounds used in research are very large inorganic molecules (**Figure 4**), such as sodium tetraborate **4** and disodium undecahydromercapto-closo-dodecacarborate **5**.

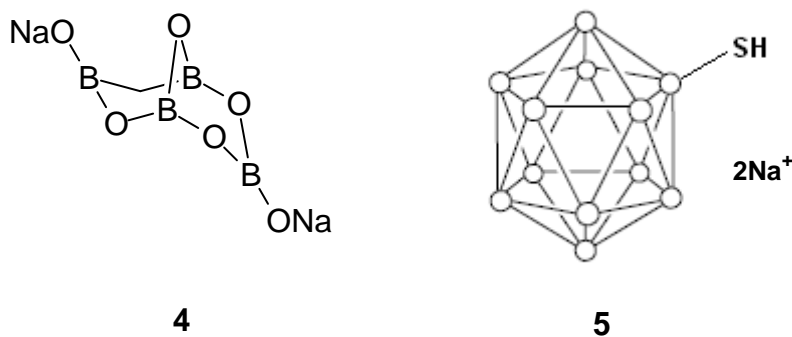


Figure 4.\*

\* Structure 5: Boron atoms symbolized with o

## 1.2. Review of Organoborane Chemistry

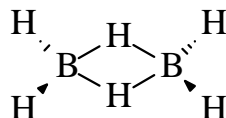
As tools for the formation of carbon-carbon bonds, organoborane reagents have been widely explored in organic synthesis reactions. These reagents have been widely used in hydroboration reactions, the Suzuki reaction, and more recently the Petasis reaction, and have also proved effective in allylboration reactions, copper(II)-catalyzed heteroatom couplings, and rhodium-catalyzed additions to carbonyl compounds.<sup>1</sup> They have also found gainful employment as catalysts in a number of reactions. Organoboranes are fascinating reagents as they are readily available with a wide variety of functional groups, non-toxic. More importantly there are a number of new generation organoboranes which are air and water stable.

### 1.2.1. Hydroboration reactions

The vast majority of the initial exploration into borane chemistry was carried out in H. C. Brown's laboratories.<sup>9</sup> Borane reagents have since become incredibly important for catalytic reactions and organic transformations of highly complex, highly functionalized molecules, and are used in the synthetic routes of a number of pharmaceutical products.<sup>32</sup>

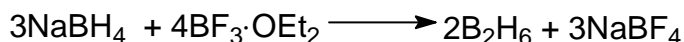
#### 1.2.1.1. Hydroboration reagents

The simplest of the hydroboration reagents, diborane **6** ( $B_2H_6$ ) (**Figure 5**) is a colourless gas that forms explosive mixtures when exposed to air, and often spontaneously ignites at room temperature in moist air. As such, diborane was often generated *in situ*, often by the addition of a solution of sodium borohydride in diglyme to a boron trifluoride ether solution, (**Scheme 10**) and the diborane gas produced was then passed into the solution of the compound to be hydroborated.<sup>6b</sup>



**6**

Figure 5.



Scheme 10.

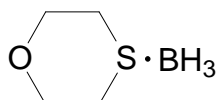
Although a highly reactive reagent by itself, reactions using diborane were known to require temperatures in the range of 25°C – 75°C.<sup>6a</sup> In a paper published in 1957, Brown and Subba Rao introduced the concept of carrying out hydroboration reactions in ethereal solutions at room temperature.<sup>6b</sup> Yields from reactions across a range of structurally-varied olefins were often in the range of 90-95%, and could be carried out in solutions of the olefins in tetrahydrofuran (THF), diglyme or diethyl ether. Trace amounts of ether carried over from the creation of diborane in ether solutions were shown to catalyze these reactions.<sup>6b</sup>

What was unknown at the time, although alluded to in 1939, was that the active boron reagent was borane, (BH<sub>3</sub>) termed “borine” by the authors.<sup>8a</sup> The reaction of the ethereal solvents with diborane results in the formation of weak, readily dissociated borane adducts, which are significantly more reactive than the diborane dimer. This led to the development of more stable complexes of BH<sub>3</sub> with a ligand (BH<sub>3</sub>·L). Many of the boron-containing compounds are able to act as Lewis acids due to the vacant 2*p*-orbital present on the electron-deficient boron atom, and as such, these adducts are often formed using ligands which are Lewis bases, such as THF or dimethyl sulfide (DMS). Of these borane adducts, there is a definite stability trend depending on the ligand used. The borane-tetrahydrofuran complex (BH<sub>3</sub>·THF) is the most stable of the ether complexes, but is the most reactive of the borane complexes that are commercially available.<sup>33</sup> Although the most stable of the ether complexes, it reacts rapidly at temperatures below 0°C, and reductive cleavage of

THF by the hydride ion (H<sup>-</sup>) occurs at room temperature, resulting in a loss of hydroboration ability. As a result of this, careful monitoring of the conditions was required in reactions where BH<sub>3</sub>·THF was used, in order to prevent the elevation of temperatures.

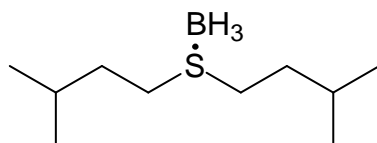
This problem was solved with the development of a borane-dimethyl sulfide complex (BH<sub>3</sub>·DMS). Initially reported in 1954<sup>34</sup> and studied in 1959 by Stone and co-workers,<sup>35</sup> BH<sub>3</sub>·DMS has many advantages over BH<sub>3</sub>·THF in that it is indefinitely stable under nitrogen when refrigerated and it is soluble in a wide range of aprotic solvents as it does not react with these solvents.<sup>36</sup> Commercially available solutions of BH<sub>3</sub>·DMS are much more concentrated than those of BH<sub>3</sub>·THF - for example, the molar concentration of BH<sub>3</sub>·DMS is approximately 2.2 M, while that of BH<sub>3</sub>·THF is 0.2 M.

One drawback to using BH<sub>3</sub>·DMS is the dimethyl sulfide itself. Volatile and highly flammable, this foul-smelling solvent is not miscible in water, and thus has its own set of safety and environmental problems. Borane-1,4-oxathiane **7** (**Figure 6**) was set forward by Brown and Mandal<sup>37</sup> as an alternative to the BH<sub>3</sub>·DMS, and although less volatile and more stable, as well as having a less noxious odour, this reagent is more expensive, and thus its use as a hydroboration reagent has been limited. Another alternative to BH<sub>3</sub>·DMS, borane-diisoamyl sulfide (BH<sub>3</sub>·DAS) **8** (**Figure 7**) was proposed by Zaidlewicz *et al.* in 2000.<sup>38</sup> Taking advantage of the pleasanter odour of diisoamyl sulfide as compared to dimethyl sulfide, these new hydroboration agents were more reactive towards 1-octene. However, BH<sub>3</sub>·DAS was found to be immiscible in water, which posed a problem when products were to be isolated.



**7**

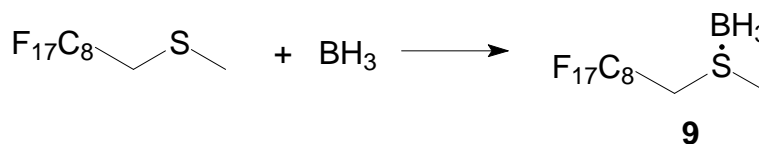
*Figure 6.*



**8**

Figure 7

One of the more recent additions to the multitude of sulfide borane carriers is fluoros dimethyl sulfide, which associates with  $\text{BH}_3$  to form borane-fluorous dimethyl sulfide ( $\text{BH}_3\cdot\text{FMS}$ ) **9**. Formed by the reaction of diborane with 2-(perfluorooctyl)ethyl methyl sulfide, (**Scheme 11**)  $\text{BH}_3\cdot\text{FMS}$  is odourless and the fluoros dimethyl sulfide can be recovered and recycled from solution.<sup>39</sup>



Scheme 11.

Boranes are also known to form complexes with amines, such as triethylamine and *N*-phenylmorpholine. These borane-amine complexes are more stable than  $\text{BH}_3\cdot\text{DMS}$ , but they exhibit lowered reactivity towards alkenes, and consequently, higher temperatures and longer reaction times are required during hydroboration reactions, which can lead to isomerization of the alkene.<sup>40</sup> As such, these borane-amine adducts have not been widely used in hydroboration reactions, but rather as reducing agents for other functional groups.

A wide range of mono- and dialkylboranes have been developed over the years in an attempt to overcome the limitations imposed on the usefulness of boranes in organic synthesis due to the predisposition of borane to form trialkylboranes from a wide range of alkenes. Although these trialkylboranes are synthetically useful in a number of reactions, they significantly reduce the yield of products if formation of the mono- or disubstituted boranes is needed.<sup>41</sup> Commonly used alkylated boranes

include 1,1,2-trimethylpropylborane or thexylborane **10**, dicyclohexylborane **11** and 9-borabicyclo[3.3.1]nonane **12** (9-BBN) (**Figure 8**).

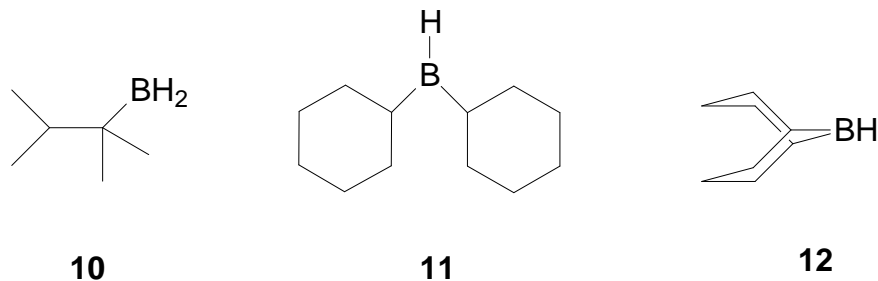
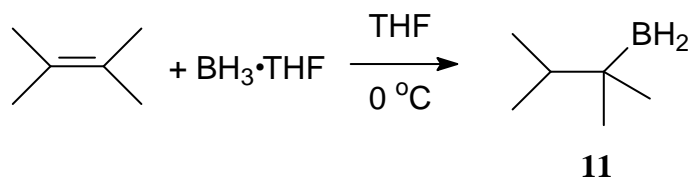
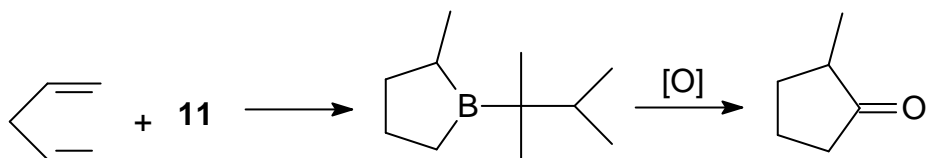


Figure 8.

Thexylborane (H<sub>2</sub>BThx) **10**, the product of the hydroboration of 2,3-dimethyl-2-butene with BH<sub>3</sub>·THF, (**Scheme 12**) exists as a monomer in THF solutions, due to the large steric interactions of the thexyl group.<sup>42</sup> The most readily available of the monoalkylated boranes, it is generally prepared and used without storage as it has been reported that the tertiary alkyl group isomerizes to a primary alkyl group on standing at room temperature.<sup>41</sup> H<sub>2</sub>BThx has proven invaluable in the formation of a dialkylborane from two different alkenes as well as in the cyclic hydroborations (**Scheme 13**) of dienes.<sup>43</sup>

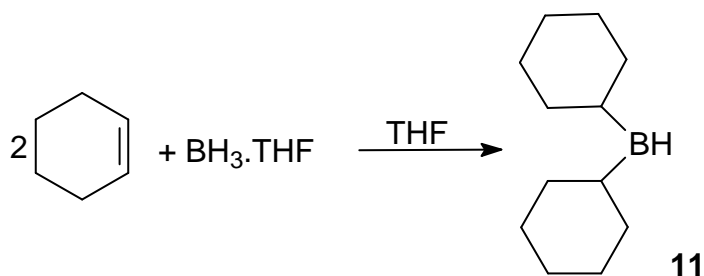


Scheme 12.

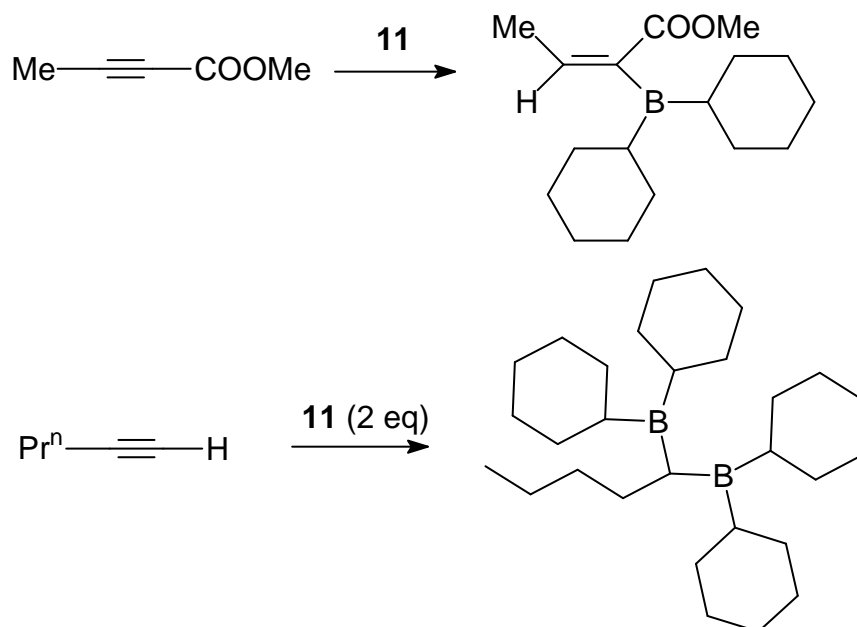


Scheme 13.

Dicyclohexylborane (HBCy<sub>2</sub>) **11** was first reported in the 1970's as the product from the controlled hydroboration of cyclohexene with BH<sub>3</sub>·THF<sup>44</sup> (**Scheme 14**). As this reagent is less sterically hindered than 9-BBN, it allows for a greater possibility of dihydroboration occurring if alkynes are used, and the hydroboration of terminal alkynes can be controlled to such a degree as to yield either vinylboranes or *gem*-dibora derivatives.<sup>45</sup> (**Scheme 15**)



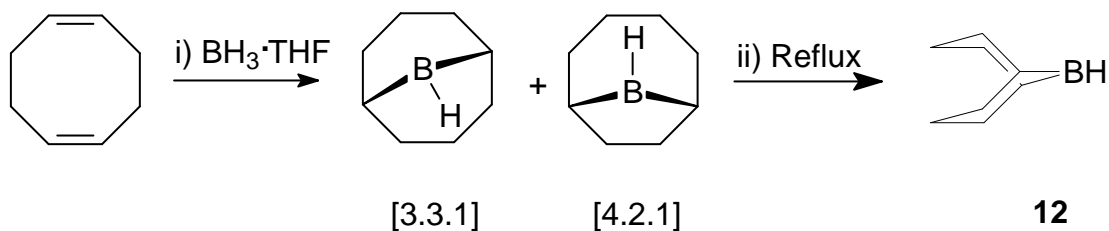
*Scheme 14.*



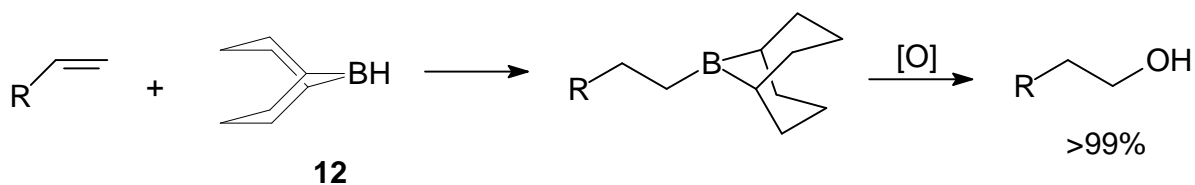
*Scheme 15.*

9-Borabicyclo[3.3.1]nonane (9-BBN) **12** is produced as one of two products from the controlled hydroboration of 1,5-cyclooctadiene with BH<sub>3</sub>·THF, (**Scheme 16**) with the other product, 9-borabicyclo[4.2.1]nonane, isomerized to the thermodynamically more stable [3.3.1] compound on the application of heat.<sup>41</sup> As a hydroboration

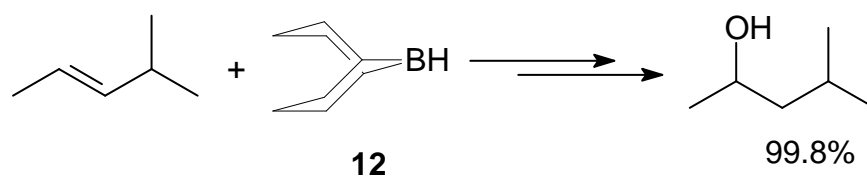
reagent, it demonstrates extraordinary regioselectivity, with the hydroboration of terminal olefins resulting in placement of the boron atom at the terminal position in 99% of cases, (**Scheme 17**) while the regioselectivity shown on the hydroboration of *cis*-4-methyl-2-pentene (**Scheme 18**) results in virtually exclusive selection of the second carbon.<sup>46</sup>



*Scheme 16.*



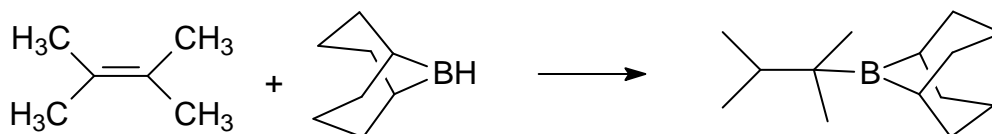
*Scheme 17.*



*Scheme 18.*

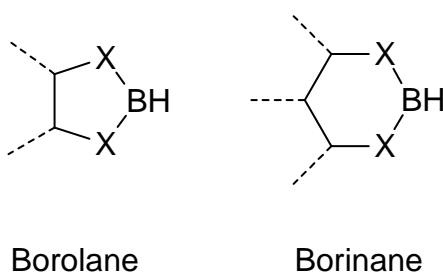
Although existing as a dimer in the solid state,<sup>47</sup> 9-BBN can exist as either a dimer or a monomer in solution, depending on whether the solvent is a coordinating solvent or not. In solvents such as carbon tetrachloride and cyclohexane, 9-BBN exists exclusively as a dimer, whilst an equilibrium is established between the 9-BBN dimer and a complexed solvent-9-BBN monomer in solvents such as THF and dimethyl sulfide. While not as reactive towards internal alkenes as some of the other boranes, its stability at elevated temperatures allows these reactions to be carried

out at 60-80°C.<sup>48</sup> 9-BBN is however able to hydroborate tetrasubstituted double bonds, something which is not possible with other boranes<sup>49</sup> (**Scheme 19**). Outside of hydroboration reactions, 9-BBN is used in the reduction of carbonyl groups of  $\alpha,\beta$ -unsaturated aldehydes and ketones to yield allylic alcohols with 100% selectivity,<sup>50</sup> and the 9-BBN-pyridine complex has been used in the selective reduction of aldehydes in the presence of ketones.<sup>51</sup>



*Scheme 19.*

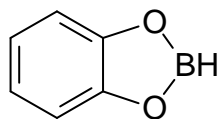
A class of borane compounds which has received a large amount of attention in the last few years are the heterosubstituted boranes. These boranes are defined by the presence of a heteroatom, such as oxygen, sulfur, nitrogen, or a halogen, which is directly bonded to the boron atom. As a result of the presence of the heteroatoms, all of these reagents show reduced reactivity as compared to  $\text{BH}_3$  as the Lewis acidity of the boron atom has been tempered.<sup>48</sup> Heterosubstituted boranes can further be divided into two families based on whether a five-membered ring or a six-membered ring is formed. Those compounds containing a five-membered ring are known as borolanes, while those with a six-membered ring are called borinanes. (**Figure 9**)



*Figure 9.*

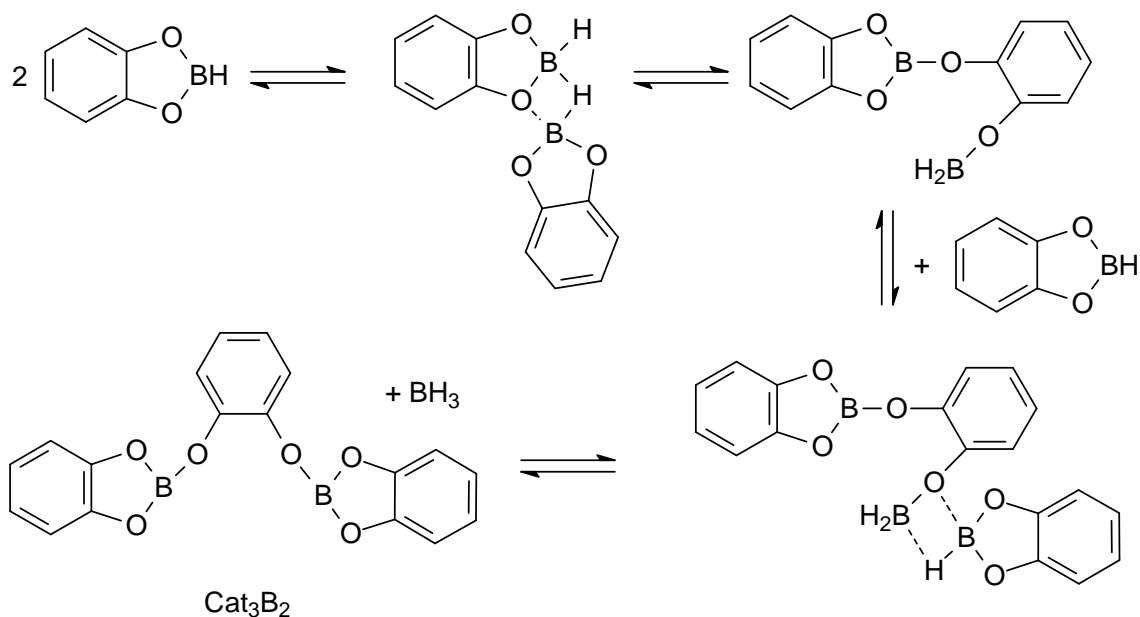
Of the heterosubstituted boranes, the largest number of reagents are dioxaboranes, which are formed by the reaction of glycols or diols with  $\text{BH}_3$ . These reagents are poorer hydroboration reagents than  $\text{BH}_3$ , as the oxygen atoms are able to back-donate electron density to the electrophilic boron atom, thereby reducing the reactivity of the borane.

One of the more widely used reagents in organic transformation reactions is benzo-1,3,2-dioxaborolane, or catecholborane (HBCat) **13**.<sup>52</sup> (Figure 10) Although a superior hydroboration reagent as compared to some of the alkoxy boranes, it has reduced reactivity when compared to  $\text{BH}_3$ , and it has been reported to undergo a disproportionation, or degradation, reaction, yielding 2,2'-[1,2-phenylenebis(oxy)]bis-1,3,2-benzodioxaborolane ( $\text{Cat}_3\text{B}_2$ ).<sup>53</sup> Rose and Shore proposed a mechanism for the formation of the disproportionation product of ethylene glycol-based boranes which can be extended to other dioxaboranes.<sup>54</sup> (Scheme 20) This mechanism involves the formation of a key four-centered transition state, which could then initiate a rearrangement resulting in the formation of the final disproportionation product and the release of  $\text{BH}_3$ .



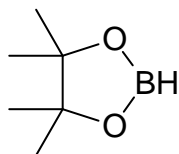
**13**

Figure 10.



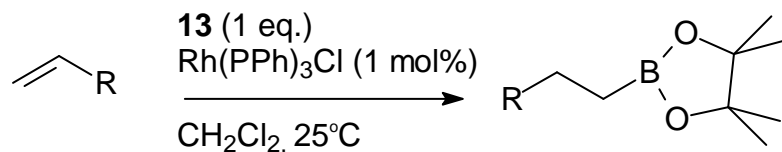
Scheme 20.

In the 1990's, a new dioxaborane reagent, 4,4,5,5-tetramethyl-1,3,2-dioxaborolane or pinacolborane (HBPin) **14**, (**Figure 11**) was introduced by Tucker and co-workers.<sup>52a</sup> Created by the reaction of pinacol with BH<sub>3</sub>, this reagent shows enhanced stereo- and regioselectivity as compared to HBCat, although disproportionation side-reactions remain a problem. Another problem encountered with the use of HBPin is that it is remarkably unreactive in comparison to some of the other hydroboration reagents, and initially the use of this reagent was limited until Srebnik and Pereira reported the catalytic ability of Rh(I) in the previously unsuccessful hydroboration of alkenes<sup>55</sup> (**Scheme 21**). Interestingly, the regioselectivity of the products obtained from the rhodium-catalyzed hydroboration of allylbenzene (**Scheme 22**) is reversed as compared to uncatalyzed reaction, and this was also observed in the hydroboration of 1-octene when rhodium trichloride was used as a catalyst.<sup>52a,56</sup>

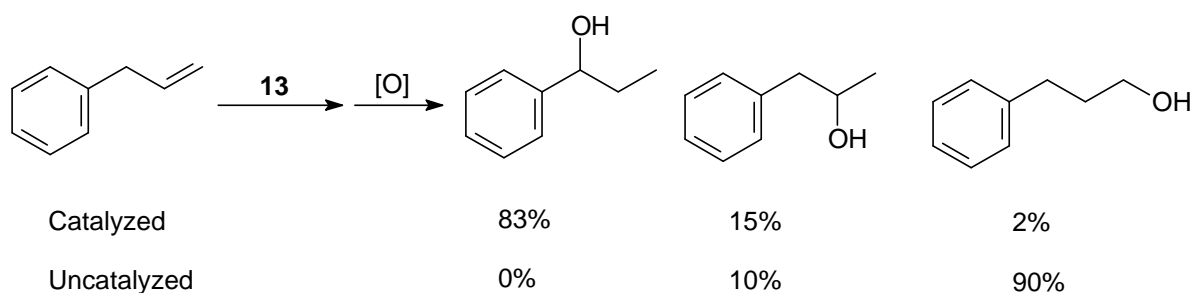


**14**

Figure 11.

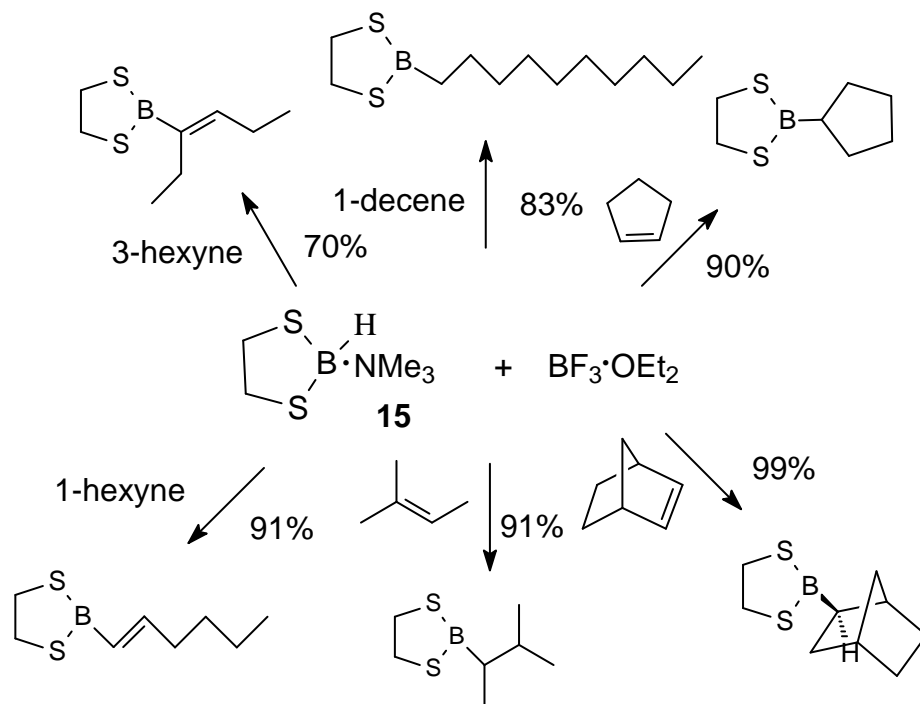


Scheme 21.



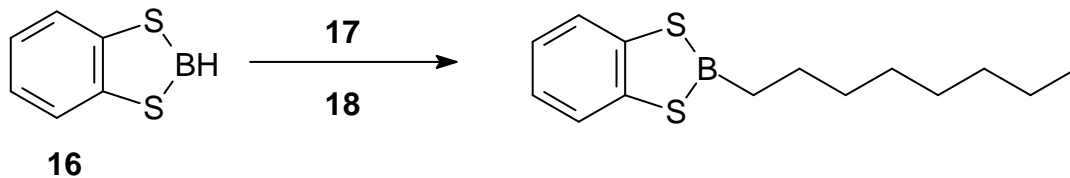
Scheme 22.

Although the formation of dithiaboranes is decades old, with the first being reported in the 1970's, very few of these boranes have been researched in depth. 1,3,2-dithiaborolane-trimethyl amine complex **14** has been shown to be a highly effective hydroboration reagent across a range of alkenes and alkynes, when treated with  $\text{BF}_3 \cdot \text{OEt}_2$  in boiling benzene<sup>57</sup> (**Scheme 23**).



Scheme 23.

Recently, 1,3,2-benzodithiaborolane (HBThia) **16** has been shown to be a suitable hydroboration reagent for 1-octene **17** and *trans*-4-octene in both uncatalysed reactions and in reactions catalyzed by Wilkinson's catalyst ( $\text{Rh}(\text{PPh}_3)_3\text{Cl}$ ) **18** (Scheme 24).<sup>58</sup> HBThia is a possible alternative to HBCat, especially in the rhodium-catalyzed reactions, as it is more stable than HBCat, and although a disproportionation product was formed in a manner similar to HBCat, it is to a much lesser degree. This is thought to be due to the ability of sulfur to back-donate electron density from the lone pair of electrons on the sulfur atom into the vacant  $p_z$ -orbital of the boron atom, (Figure 12) which impedes the formation of the key 4-centered intermediate as found in the disproportionation of HBCat, as shown in Scheme 20. This back-donation of electron density also results in the Lewis acidity, and thus the reactivity, of the borane reagent being lowered.<sup>59</sup>



Scheme 24.

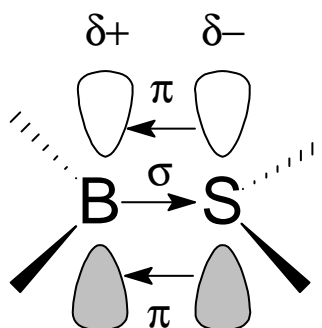
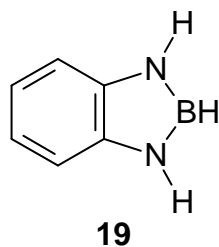
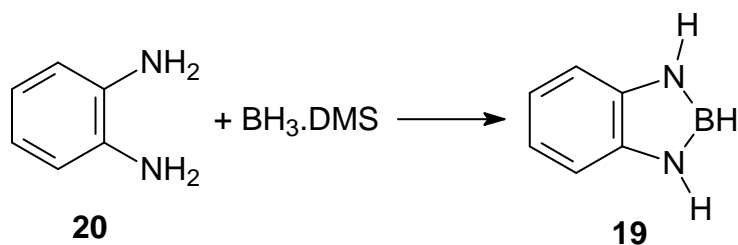


Figure 12.

In the same paper, Hadebe *et al.*,<sup>58</sup> reported the formation of a 1,3,2-benzodiazaborolane analogue (HBPda) **19** (**Figure 13**) to HBCat, from 1,2-phenylenediamine **20** and  $\text{BH}_3\text{-DMS}$  (**Scheme 25**). It was observed to be unreactive towards 1-octene unless Wilkinson's catalyst was employed in the reaction, and completely unreactive towards *trans*-4-octene. This observation was in accordance with other studies which noted a comparable lack of reactivity in borylation-type reactions.<sup>53</sup> This could again be ascribed to the back-donation of electron density from the lone pair of electrons on the nitrogen atom into the vacant  $p_z$ -orbital of the boron atom, and the further lack of reactivity between *trans*-4-octene and HBPda can be ascribed to enhanced steric demands of both HBPda and *trans*-4-octene. It was also observed that HBPda does not undergo the disproportionation reactions which plague the usefulness of HBCat, HBPin and HBThia. This is most likely due to the increased amount of back-donation of the electron density from the nitrogen atoms to the boron atom as compared to HBThia, resulting in reduced electron density on the nitrogen atoms. This prevents the dimerization seen in HBCat, HBPin and HBThia, and thus the formation of the disproportionation product.

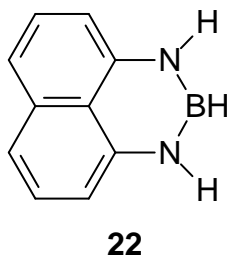


*Figure 13.*



*Scheme 25.*

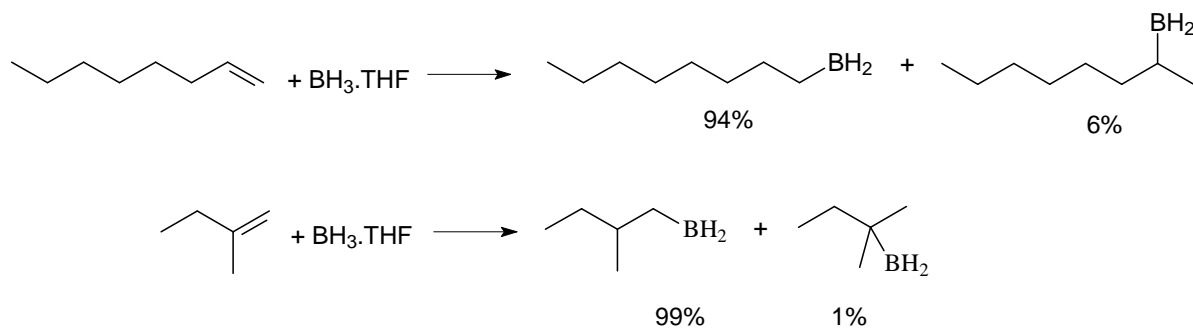
As research into new and novel organoboranes continued, a large number of compounds were tested as possible bases for organoboranes.<sup>60</sup> One of the compounds tested was 1,8-diaminonaphthalene **21**. The product of the reaction between **21** and boron trichloride was, after reduction with lithium aluminium hydride, shown to be naphtho[1,8-*de*][1,3,2]diazaborinine (HBDan) **22** (**Figure 14**). While this pseudo-aromatic heterocycle initially showed promise as a remarkably stable hydroboration reagent, it was unreactive towards a number of alkenes and after a number of years the research into these compounds was virtually abandoned.



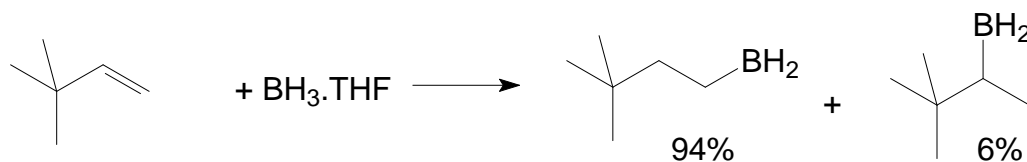
*Figure 14.*

### 1.2.1.2. Regioselectivity in Hydroboration Reactions

Hydroboration reactions are highly regioselective reactions, as the majority of products obtained show anti-Markovnikov addition of the boron to the least sterically-hindered carbon atom<sup>9</sup> (**Scheme 26**). This behaviour appears to be attributable to steric effects rather than electronic effects for simple 1-alkenes,<sup>61</sup> as the presence of alkyl groups at the 2-position of an alkene augments the attachment of the boron atom to the terminal carbon, an observation also seen with internal alkenes. The presence of a branched alkyl group at positions other than the terminal or adjacent carbon does not affect the product distribution (**Scheme 27**).



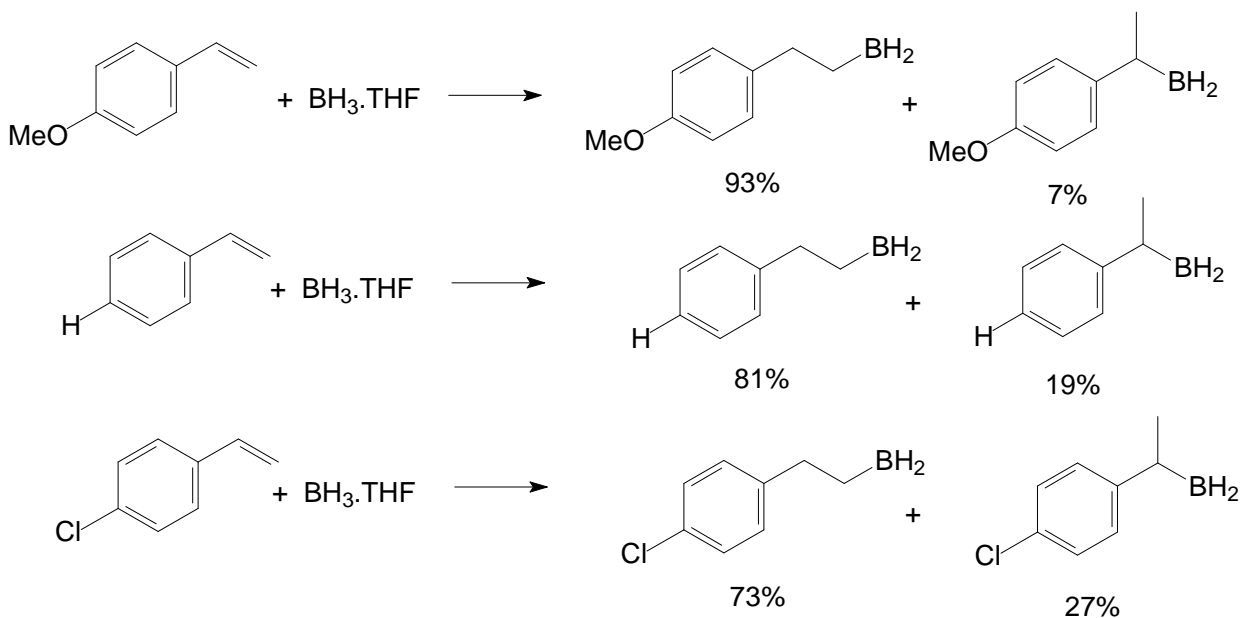
Scheme 26.



Scheme 27.

Electronic effects are, however, responsible for the increased formation of the Markovnikov product in aryl-substituted alkenes. The amount of Markovnikov product formed, where the boron is situated on the more sterically-hindered carbon, is highly dependant on any substituents present on the aryl rings (**Scheme 28**). Electron-donating groups, such as alkoxy groups, lead to decreased placement of the boron atom at the non-terminal position, while electron-withdrawing groups, such as halides, result in the increased formation of the Markovnikov product. This

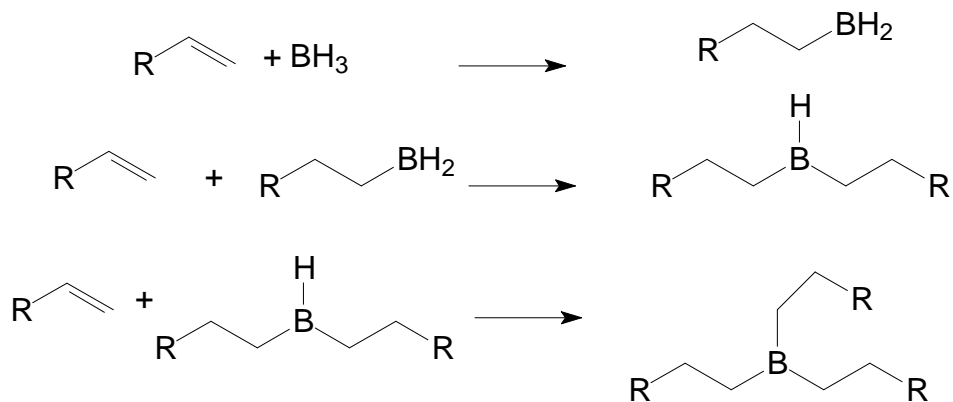
phenomenon can be explained in terms of the resonance effects produced by the various substituents.



Scheme 28.

### 1.2.1.3. The Hydroboration Reaction Mechanism

A hydroboration reaction, in its broadest sense, involves the addition of a boron-hydrogen bond across unsaturated carbon-carbon, carbon-oxygen or carbon-nitrogen bonds. Depending on a number of factors, such as the structure of the alkene as well as the structure of the hydroboration reagent used, it is possible to form, through a stepwise addition of alkyl groups, a trialkylborane (**Scheme 29**). Whilst appearing deceptively simple, the mechanism of this reaction has been the subject of much heated debate and discussion over the years.



Scheme 29.

When this reaction was initially published, the reaction mechanism was originally thought to involve the formation of a four-center transition state (**Figure 15**) between the double bond and the boron-hydrogen bond of the borane.<sup>62</sup> This was proposed as  $\text{BH}_3$  has a vacant  $2p$ -orbital perpendicular to the plane of the three boron-hydrogen bonds, (**Figure 16**) and thus would act as an electrophile.<sup>41</sup> Electrons from the alkene are donated into this vacant  $p$  orbital, through the more electronegative  $sp^2$  carbon, and the borane hydride donates electrons to the more electropositive  $sp^2$  carbon. This donation and acceptance of electrons results in the  $\pi$ -bond between the two carbon atoms, and the boron-hydrogen bond becoming weakened, with bonds being formed between the carbon and boron atoms, and between the carbon and hydrogen atoms.

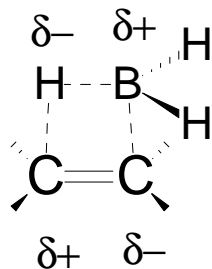


Figure 15.

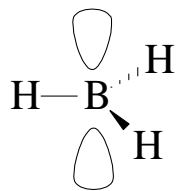
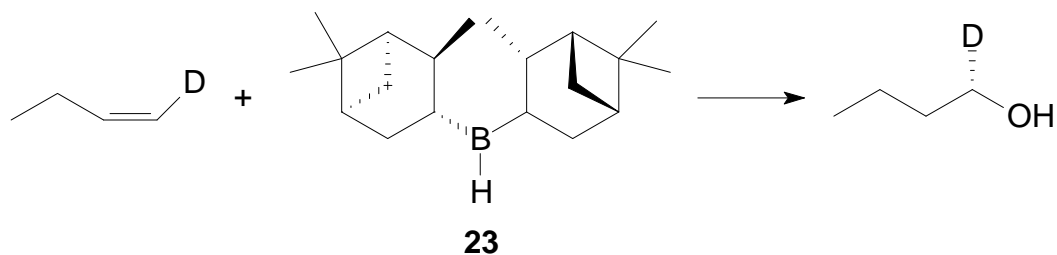


Figure 16.

This mechanism was supported by the fact that the majority of hydroboration reactions were *cis*-addition reactions, and Hückel calculations on substances such as propene showed that the terminal carbon atom possessed a higher electron density than the adjacent, non-terminal carbon, which explained the anti-Markovnikov regioselectivity of these reactions.<sup>63</sup> While this mechanism could account for the hydroboration of cycloalkenes and other simple alkenes,<sup>64</sup> it could not explain the formation of the deuterated product from the reaction of *cis*-1-butene-1*d* and diisopinocampheylborane (HBIPC<sub>2</sub>) **23**<sup>65</sup> (**Scheme 30**). Based on Brown's mechanism, the *S* configuration was expected, rather than the *R* configuration realized in this reaction. Streitwieser then proposed a three-center  $\pi$ -transition state (**Figure 17**), created due to attractive forces between the vacant *2p* orbital on the borane and the alkene electron cloud. This new triangular transition state was able to explain both the *cis* stereochemistry observed for the products of many hydroboration reagents, as well as explaining reactions that Brown's model could not.



Scheme 30.

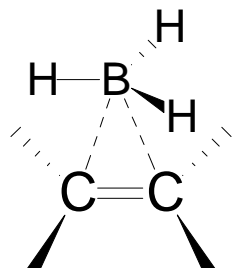
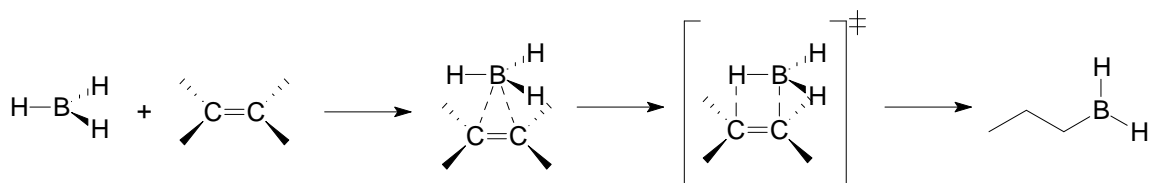


Figure 17.

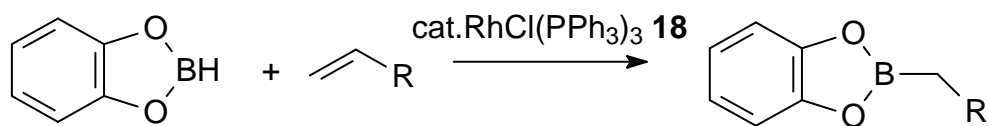
This three-center  $\pi$ -transition state was further supported by Jones, whose study into the symmetry considerations of the hydroboration reaction mechanism showed that the four-centered transition state proposed by Brown had significant symmetry barriers.<sup>66</sup> Gas-phase kinetic studies carried out by Fehlner in the 1970's also lent support to the three-center transition state mechanism.<sup>67</sup> Later, Lipscomb and co-workers<sup>64</sup> put forward a suggestion that both the 3-center and the 4-center transition states are present in the reaction mechanism<sup>68</sup> (**Scheme 31**). In this mechanism, the 3-center  $\pi$ -transition state is a pre-transition state intermediate, with the 4-center transition state being a description of the true transition state. A two-step process, reported by Nagase *et al.*<sup>69</sup> in 1980, provided the support needed for this mechanism. In this process, the 3-center  $\pi$ -complex is formed initially, without any energy barrier, followed by the creation of the product *via* the 4-center transition state.



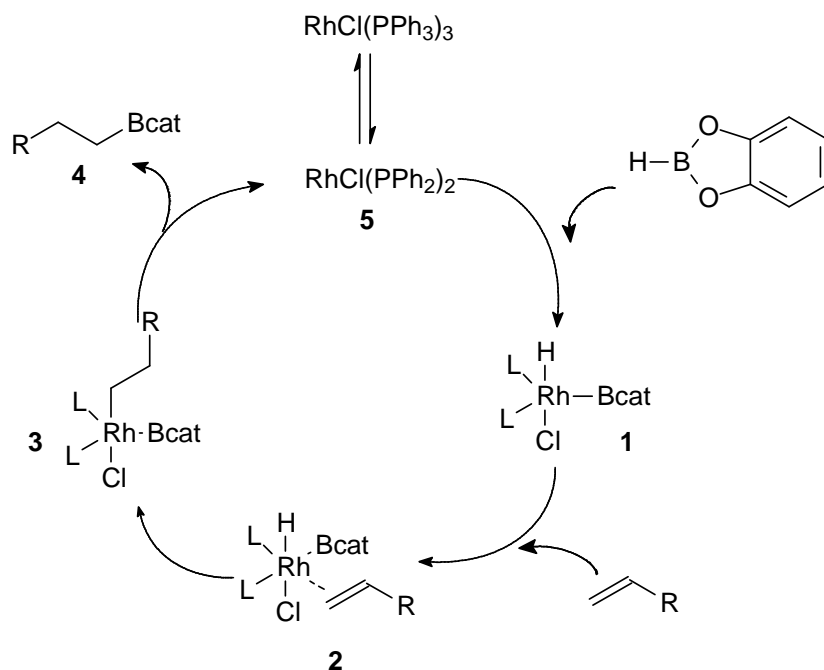
Scheme 31.

This reaction mechanism is currently the prevailing mechanism used to understand the misleadingly uncomplicated hydroboration reaction. However, there is still much ongoing debate and research being carried out with regards to this reaction.

The mechanism of the rhodium-catalyzed hydroboration of alkyls, catalyzed by Wilkinson's catalyst ( $\text{RhCl}(\text{PPh}_3)_3$ ) **18** (**Scheme 32**) is well understood, as a large amount of research has been carried out since the discovery that oxidative addition of HBCat to the metal center of **18** occurs readily.<sup>70</sup> This catalyst had previously been used in hydrosilation<sup>71</sup> and hydrogenation<sup>72</sup> reactions. The initial mechanism (**Scheme 33**) was proposed by Manning and Nöth in 1985.<sup>73</sup> The first step involves the addition of the B-H bond to the coordinatively unsaturated rhodium(I) center, resulting in a rhodium borane hydride species (**Scheme 33**, compound **1**). This complex then coordinates the alkyl compound across the multiple bond, and hydride migration from the rhodium center (**Scheme 33**, compound **3**) results in the formation of a single rhodium-carbon bond. Reductive elimination of the alkyl borane (**Scheme 33**, compound **4**) allows for the regeneration of the unsaturated catalyst (**Scheme 33**, compound **5**). In keeping with the anti-Markovnikov products obtained in uncatalyzed reactions, the products of this reaction are generally the anti-Markovnikov product, as the formation of these products ensures that the least sterically hindered approach is used.



*Scheme 32.*



Scheme 33.

#### 1.2.1.4. Scope and Limitations of the Hydroboration Reaction

The hydroboration reaction has progressed a long way since the initial revolutionary paper published by Brown and Subba Rao in 1956. There are hundreds of possible hydroboration agents, each with their own benefits and shortcomings, and innumerable numbers of alkenes, alkynes and other compounds that have proved to be suitable substrates for hydroboration reactions.<sup>32</sup> The scope of the hydroboration reaction thus is restricted only by the imagination of the chemist.

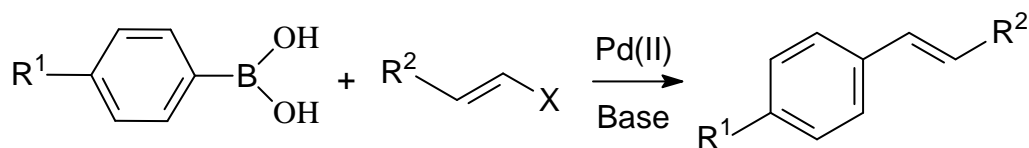
There are a number of more generalized drawbacks to hydroboration reactions. The hydroboration agents tend to be unstable to air, water and elevated temperatures, and consequently require more complicated handling and storage procedures than would be ideal. The newer hydroboration agents, such as HBThia and HBPda, are more stable than the older generation of reagents, but they are still sensitive to water and air.<sup>58</sup> Although these reagents are more stable, they are thus,

by definition, more unreactive when used in a reaction, and have need of expensive rhodium(I)-based catalysts in order to obtain the same yields as the older generation reagents.

Another “disadvantage” to the hydroboration reaction is in the anti-Markovnikov addition preferred by these reagents. Sterically hindered substrates, such as internal alkenes, are therefore more difficult to hydroborate, especially if bulky boranes are used. While the rhodium catalysts have also proved useful with these reagents, a further complication is introduced as the yield of the hydroborated product is also dependent on the size of the catalyst itself.

### 1.2.2. The Suzuki Reaction

If an investigation was carried out to evaluate the reason for carrying out a chemical reaction, those that result in the formation of a carbon-carbon bond will most likely make up the largest proportion.<sup>9</sup> As a result of the widespread need for the creation of this bond, between multitudes of differing varieties of substrates and yielding an even wider range of products, a huge number of reactions and methods exist, each one suited to a particular task. Of the reactions with the greatest industrial applications, the palladium-catalyzed reaction between an organoborane reagent and an aryl halide, a reaction known as the Suzuki reaction, (**Scheme 34**) is often preferentially used, as the Suzuki reaction does not make use of toxic reagents, and does not result in the formation of toxic byproducts.<sup>74</sup>



*Scheme 34.*

Industrially, the synthesis of a number of compounds involves the Suzuki reaction. Pharmaceutical products based on biaryls<sup>10a</sup> and oxazoles,<sup>10b</sup> such as clusiparalicone A **24**, hennoxazole A **25**, virginiamycin M<sub>2</sub> **26** and leucascandrolide A **27** (**Figure 18**), are examples of natural products where the Suzuki reaction could be successfully employed in vital carbon-carbon bond formation.

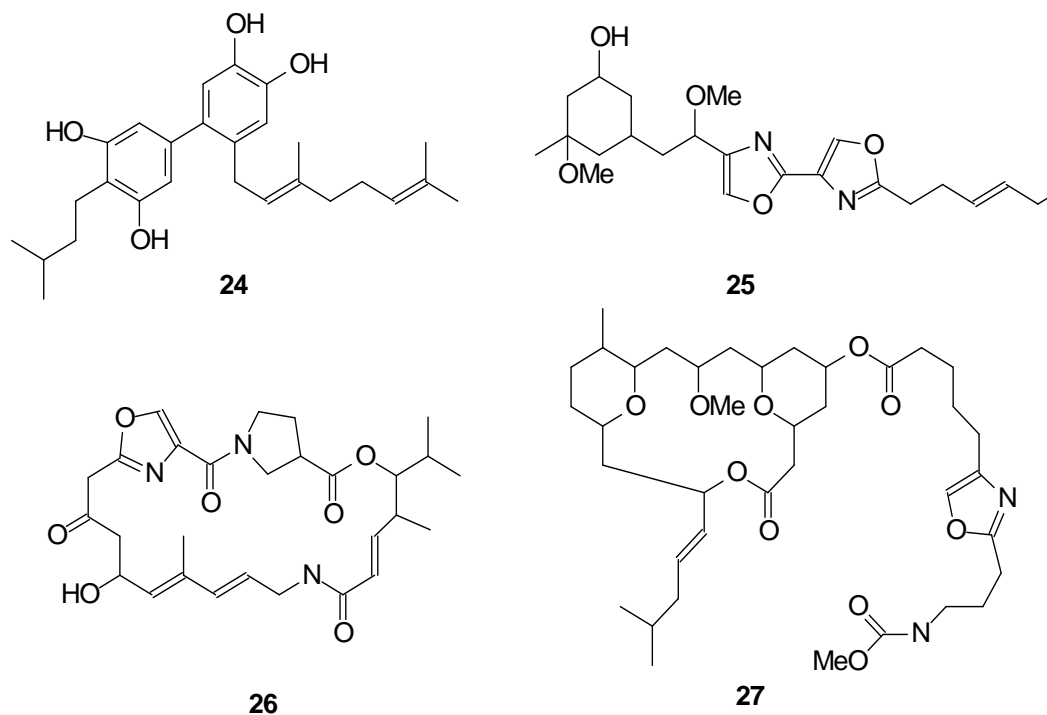
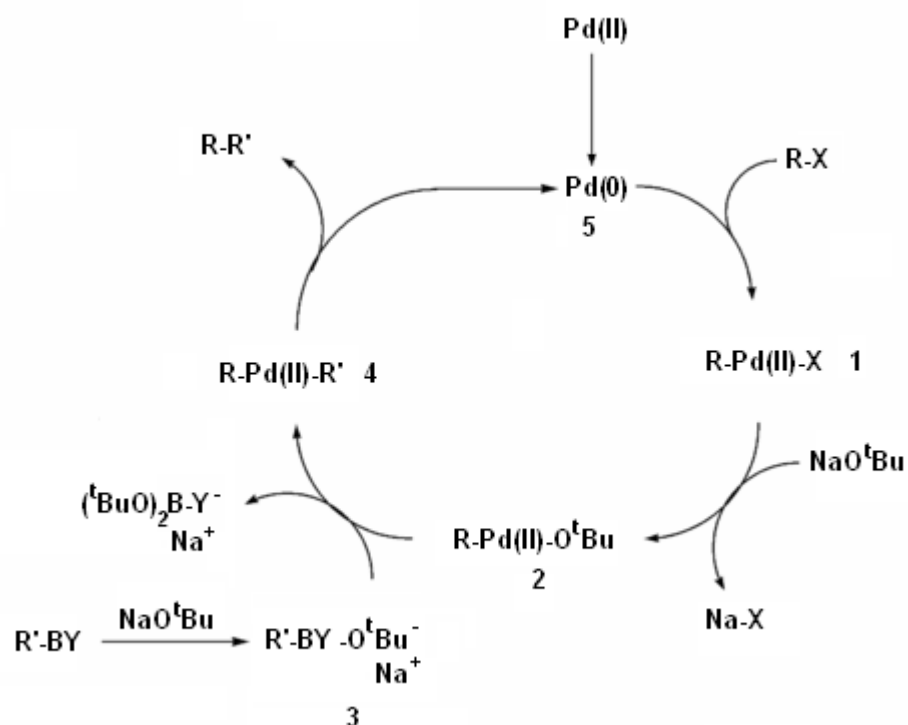


Figure 18.

### 1.2.2.1. Mechanism Of The Suzuki Reaction

The mechanism for the Suzuki reactions (**Scheme 35**) is very similar to the mechanisms of the other palladium-catalyzed reactions, such as the Heck reaction, the Negishi Reaction and the Stille Reaction. Oxidative addition of the palladium(0) metal center into the alkyl-halide bond results in a palladium(II) alkyl halide species **1**. The halide is then replaced by a base, resulting in a palladium(II) alkyl base species **2**. A transmetalation step allows for the exchange of the base from the palladium(II) species for the alkyl substituent present on an activated borane. Reductive elimination of the cross-coupled alkyl product from the dialkyl palladium(II) complex **4** allows the palladium(0) catalyst **5** to be regenerated.<sup>9,75</sup>



Scheme 35.

The reaction mechanism is such as to allow the oxidative addition to retain the stereochemistry of vinylic halides, and cause the inversion of the symmetry of products derived from benzylic and allylic halides. A *cis*-palladium complex is initially formed, before isomerization into the *trans*-configuration.<sup>76</sup> The reductive elimination was shown to retain the stereochemistry of the precursor species by the use of a deuterium-labelling study carried out by Ridgway and Woerpal.<sup>77</sup> A number of *cis*- and *trans*-dideuteroalkenes were coupled to  $\alpha$ -iodocyclohexanone *via* a Suzuki reaction, and subjected to  $^1\text{H}$  NMR spectroscopic analysis. The results obtained from the  $^1\text{H}$  NMR experiments showed different coupling constants for the products, which indicated that the protons of interest did not share the same conformation. The coupling constants were then used to show that the *cis*-dideuteroalkene yielded a *syn*-product, and the *trans*-dideuteroalkenes yielded an *anti*-product, each of which proves that the symmetry of the reagent is maintained in the final product.



For the most part, the most successful organohalides are aryl or vinyl halides, the majority of which are organobromides or organoiodides. Initial reactions using organochlorides and other unactivated organohalides were initially unsuccessful and therefore these were not used as often as the organobromides or organoiodides. The unreactivity of the organochlorides can be ascribed to a number of factors, one of which is the strength of the carbon-chlorine bond present in the molecule.<sup>80</sup> In terms of dissociation energies, carbon-chlorine bonds have a value of 95kcal/mol, whereas carbon-bromine bonds and carbon-iodine bonds are weaker, with dissociation energy values of 80 kcal/mol and 65 kcal/mol respectively.<sup>80</sup> This, along with the inherent electrophilic nature of the reagents, could prevent, or certainly reduce, the organochlorides from adding to the palladium(0) center during the rate-determining oxidative addition step, resulting in a slower reaction rate, or none at all. However, due to the organochlorides being a cheaper alternative, research continued in an attempt to realize the economical advantage possible should these reagents be used. Large, electron rich phosphine-based ligands have been successfully used,<sup>9,81</sup> and *N*-heterocyclic carbines (NHC's),<sup>82</sup> mixed phosphorous-oxygen donor ligands<sup>83</sup> and ferrocene-based phosphine ligands<sup>84</sup> have also shown promise as ligands in organochloride-containing Suzuki reactions.

### **1.2.2.3. Scope and Limitations of the Suzuki Reaction**

As the Suzuki reaction is a reaction that has found widespread use in both industrial and research settings, a large amount of information is available regarding the types of reagents, catalysts and conditions that can be successfully employed. While the reagents most commonly used in this reaction are generally aryl or vinyl in nature, it is possible to successfully incorporate alkyl reagents into these reactions, as both the organoborane reagent and the organohalide reagent in the same reaction.<sup>85</sup>

Non-phosphine-based ligands, such as NHC's,<sup>82</sup> 1,3-dicarbonyls<sup>86</sup> and *N*-phenylurea<sup>87</sup> have also been developed in the attempt to move away from the

environmentally-harmful phosphine ligands more often used, and in some cases ligand-free reactions have been reported. Palladium on carbon,<sup>88</sup> palladium acetate,<sup>83</sup> palladium-salen<sup>86</sup> (*N,N'*-bis(salicylidene)-palladium(II)) and palladium-quinoline<sup>89</sup> (Pd(quinoline-8-carboxylate)<sub>2</sub>) are prime examples of catalysts employed in these ligand-free reactions.

The list of conditions that can be used for a Suzuki reaction is almost as long as the list of reagents that can be used in the reaction. Reactions can be carried out in a range of solvents, such as THF, dimethylformamide (DMF) and even water,<sup>90</sup> or in a solvent-free system. Reactions can be carried out at temperatures ranging from -78°C to 140°C,<sup>91</sup> under inert atmospheres or in air,<sup>90</sup> and microwave irradiation can also be used to speed up the reaction.<sup>79,92</sup>

At present there are very few things which limit the use of the Suzuki reaction. The major shortcoming of the Suzuki reaction is the need for the expensive palladium catalysts, although this has been combated somewhat in the development of tethered palladium catalysts,<sup>91b,93</sup> which allows for easier removal of the catalyst from the reaction and thus more efficient recycling of the catalyst. As an alternative to palladium, nickel has been used in some Suzuki reactions to great effect, and also in a number of the other palladium-catalyzed reactions.<sup>42a,60</sup> The benefits to using nickel as a catalyst are cost, as always, and at present the use of a nickel catalyst is the only method able to couple unactivated secondary alkyl halides.<sup>61</sup> Use of a nickel catalyst can require a specific ligand or ligand system, and a 1,2 diamine, *trans-N,N'*-dimethyl-1,2-cyclohexanediamine,<sup>61</sup> has been shown to afford a method to couple the secondary alkyl electrophiles with alkyl boron starting materials at room temperature.

### 1.2.3. The Petasis Reaction

The drive to provide non-natural  $\alpha$ -amino acid derivatives as scaffolds and building blocks in drug discovery and combinatorial chemistry has seen a number of reactions and routes developed and discovered. The majority of these methods are intricate, multistep processes,<sup>18a,94</sup> and there existed a need for a simple multicomponent reaction (MCR) methodology which could be used to create a wide variety of these amino acid-based compounds, which could be further manipulated to other molecules as needed. Petasis and co-workers<sup>12a,19</sup> developed a three-component variation of the Mannich reaction, which allowed for the synthesis of  $\beta,\gamma$ -unsaturated  $\alpha$ -amino acids. (**Figure 19**) These types of unsaturated amino acids have been shown to be mechanism-based irreversible inhibitors of numerous pyridoxal phosphate dependent enzymes, including amino acid aminotransferases and decarboxylases.<sup>95</sup>

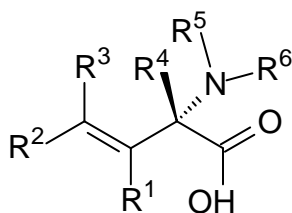
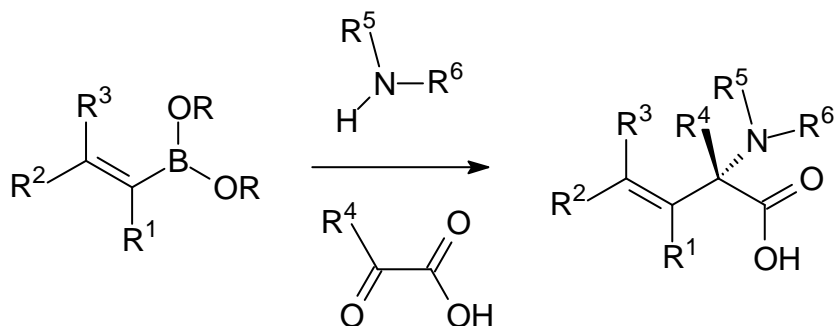


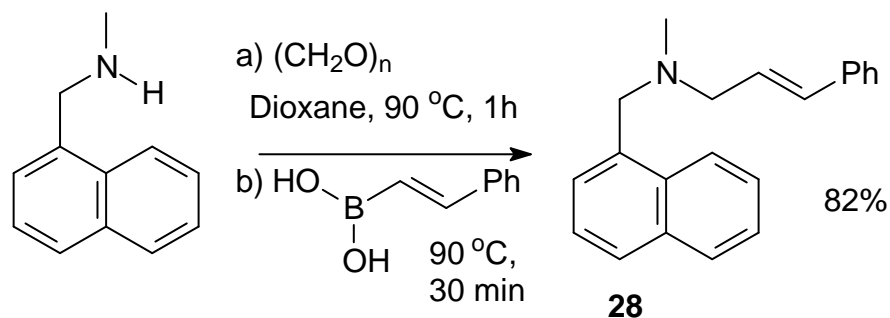
Figure 19.

The Petasis reaction, or the Borono-Mannich reaction, is essentially a condensation of an organoboronic acid or boronate with an amine and an R-keto acid or aldehyde. (**Scheme 37**) The novelty in the approach in the synthesis of these compounds as opposed to the pure Mannich reaction, is in the fact that the organoborane reagent provides the side chain.<sup>14</sup> The first reported reaction to make use of this methodology was the formation of naftifine **28**, a topical antifungal, in 82% yield from tertiary allylamines in dioxane at 90°C<sup>19</sup> (**Scheme 38**). One of the benefits to using the Petasis reaction is that it is a highly enantioselective reaction. This enantioselectivity has been increased with the use of chiral amines and organoborane reagents, resulting in enantioenriched  $\alpha$ -amino acids.<sup>12a,96</sup> Another

method that has shown the ability to increase the enantioselectivity of the Petasis reaction is in the use of chiral catalysts, such as biphenols,<sup>97</sup> diols<sup>97</sup> and binaphthols<sup>98</sup>



Scheme 37.

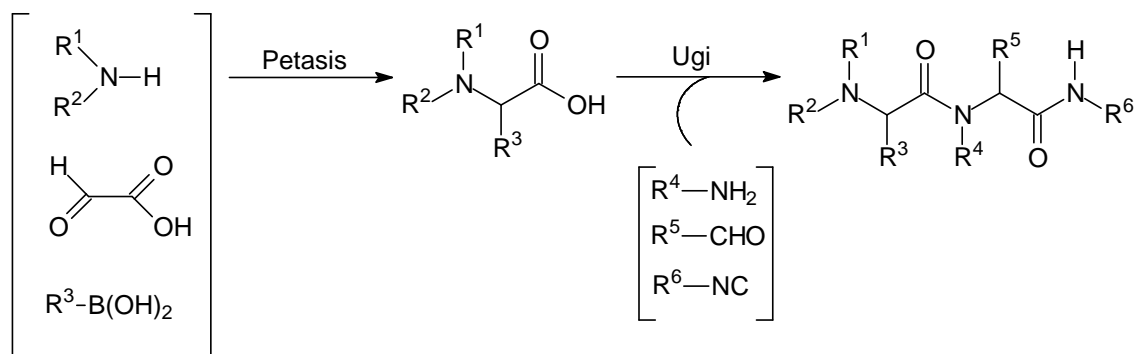


Scheme 38.

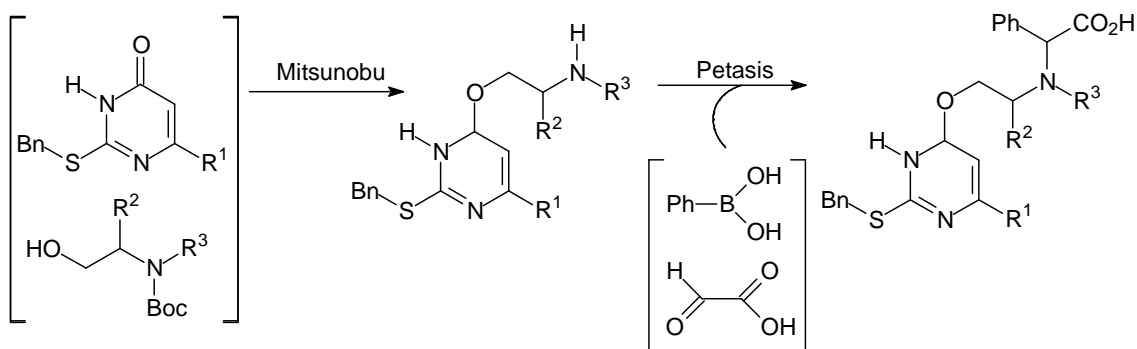
Subsequently, the Petasis reaction has been extended to include a wide variety of primary and secondary amines, aldehydes and organoborane reagents, as well as an assortment of solvents and reaction conditions, yielding a wide range of small organic molecules, such as functionalized  $\alpha$ -amino acids,  $\alpha$ -hydroxyl amines, alkylaminophenols, 2-hydroxyl morpholines, piperazinones<sup>99</sup> and 2*H*-chromenes.<sup>1,12a,100</sup> Microwave irradiation has also been successfully employed to dramatically shorten the otherwise lengthy reaction times.<sup>101</sup>

The Petasis reaction has also been successfully employed in a number of tandem or sequential reactions. When combined with reactions such as the Ugi reaction<sup>102</sup> (**Scheme 39**), or the Mitsunobu reaction<sup>103</sup> (**Scheme 40**), vast multi-dimensional libraries of compounds can be easily and rapidly created, allowing for

swift development of combinatorial libraries. Other reactions that have been successfully combined with the Petasis reaction include amine propargylation<sup>104</sup> and palladium-catalyzed reactions.<sup>105</sup>



Scheme 39.



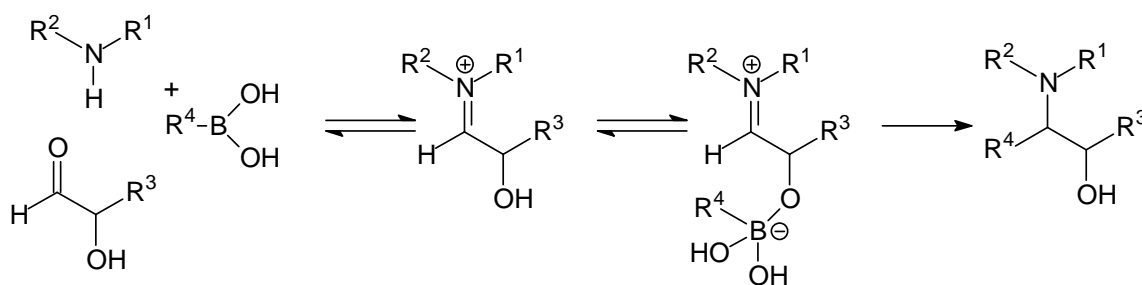
Scheme 40.

### 1.2.3.1. Mechanism of the Petasis Reaction

The Petasis reaction, being a fairly new reaction, is not as well understood as some of the other reactions, simply because it has not been around for a long period of time. As such, the mechanism of the Petasis has not been completely elucidated, and there are at present two competing schools of thought.

According to Petasis,<sup>19</sup> the reaction mechanism (**Scheme 41**) consists of the condensation of the aldehyde and the amine, resulting in the formation of an imine.

This imine bond then reacts with the boronic acid to give the final amine product. Whilst expected to be relatively inert towards the aldehyde, the reaction between the boronic acid and the imine is facilitated by the adjacent hydroxy group on the aldehyde *via* the formation of a tetrahedral, 4-coordinate boronate salt, which is able to transfer the boron substituents to the imine moiety.<sup>13</sup>

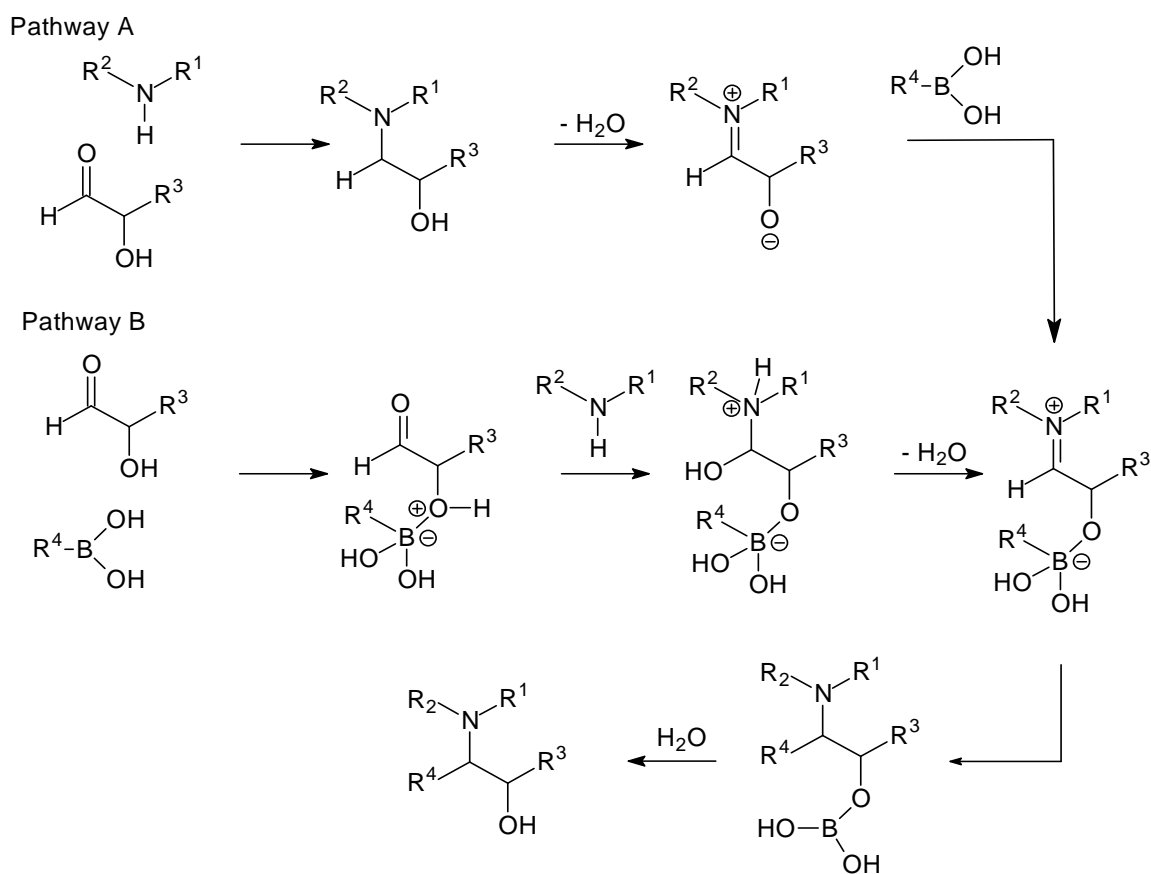


Scheme 41.

Although the majority of reports where the Petasis reaction has been used demonstrate the use of aldehydes containing groups such as hydroxyls or carboxyls, both of which can promote the formation of the quaternary boron salt, Petasis reported the successful use of paraformaldehyde, which lacks these types of substituents, as the aldehyde.<sup>19</sup>

A number of studies have been carried out to determine the accuracy of this mechanism, using a variety of different aldehydes. Using Density Functional Theory calculations (DFT), Gois *et al.*<sup>106</sup> carried out an investigation into the mechanism presented by Petasis, using glyoxylic acid as the aldehyde. The results obtained from this study were in accordance with the proposed mechanism. Further support for this mechanism was reported by Hansen and co-workers, who provided evidence for the formation of the quaternary boronate salt. They observed an upfield shift in the <sup>11</sup>B NMR chemical shift for the boronic acid after glyoxylic acid had been added to a solution of phenylboronic acid.<sup>107</sup> This shift is indicative of a tetracoordinated boronate species,<sup>108</sup> and was observed prior to the addition of the amine.

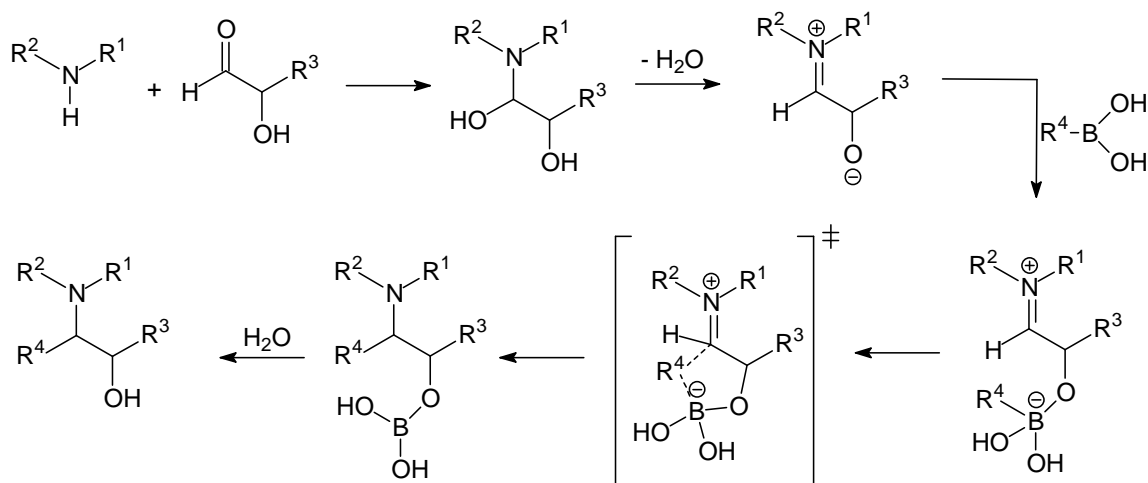
Two different pathways have been proposed for the reaction of  $\alpha$ -hydroxy aldehydes, but only recently have DFT calculations been carried out which support one of the pathways.<sup>109</sup> The first pathway, proposed by Petasis in 2001, contends that the formation of the boron salt occurs after the formation of the imine,<sup>110</sup> (**Scheme 42**, Pathway A) while Schlienger<sup>107</sup> and Voisin<sup>111</sup> propose that the imine formation is the second step, with the formation of the boron salt being the initial step. (**Scheme 42**, Pathway B)



*Scheme 42.*

When the energies for the transition states for both pathways were compared, it was observed that pathway A was the most reliable. It was also noted that the coordination of the boronic acid and the aldehyde can only be possible if a dehydration mechanism is used, without the creation of the tetravalent boronate species. While Petasis' mechanism was shown as the most favourable, it still

required a few small changes. Tao *et al.*<sup>109</sup> proposed a five-membered ring transition state for the conversion of a carbinolamine intermediate into possibly a zwitterion species, presented as an epoxide-type species from geometry optimization, via a dehydration reaction. (**Scheme 43**) Consequently, the mechanism for the entire reaction consists of nucleophilic addition of the amine to the aldehyde, forming a carbinolamine, followed by dehydration of the carbinolamine into an iminium intermediate. Coordination of the iminium species to the boronic acid generates the tetra-coordinated boronate intermediate, and the C-C bond forms as a result of the intramolecular transfer of the organo group. Finally, hydrolysis of this intermediate species results in the formation of the final products.



Scheme 43.

The high degree of stereocontrol observed by Petasis and Zavialov in their work with  $\alpha$ -hydroxy aldehydes is maintained in this reaction mechanism. While *anti*- $\beta$ -amino alcohols are exclusively formed from racemic  $\alpha$ -hydroxy aldehydes, single enantiomers are formed from enantiomerically pure starting materials.<sup>12b</sup> In the case of vinyl boronic acids, the diastereocontrol is due to the preferential selection of the reactive conformation of the quaternary boronate species, as this is where the 1,3-allylic strain is minimized.<sup>13,112</sup>

The generally accepted mechanism is also supported for reactions where salicylaldehyde is used. DFT calculations and experimental results were in concordance, however the aryl migration towards the electrophilic carbon was noted to be solvent-sensitive.<sup>106,113</sup> It was also found that a 4-methoxy substituent on the phenylboronic acid decreased the transition state energy barrier, which increased the migration ability of the aryl substituent.

A study of glyoxylic acid, salicylaldehyde and glycoaldehyde showed the following order of reactivity: glycoaldehyde > glyoxylic acid > salicylaldehyde.<sup>106</sup> The success of the reaction is, however, also dependant on the nature of the other two components, as well as the solvent choice. Bulky primary amines have proved to be satisfactory alternatives despite the higher reactivity observed with secondary amines, and vinyl boronic acids have been shown to be more reactive than their aryl analogues. As the boronic acid substituent appears to be the higher energy demanding step, the higher reactivity of the vinyl boronic acids is thus in all probability related to the higher migration ability of that moiety.

### **1.2.3.2. Scope and Limitations of the Petasis Reaction**

The Petasis reaction is an unusual paradox of a reaction. It is extremely adaptable, and a large number of compounds can be created. On the other hand, this reaction is a difficult one to optimize as a wide variety of solvents, reagents and conditions which can be altered. As such, the yields of the reactions are often dependant on the selection of reagents, solvents and conditions.

With regards to the various components, secondary amines more often than not result in higher yields as compared to primary amines, however bulky primary amines can also be used, with good yields resulting. Vinylic boronic acids tend to show the greatest reactivity in the Petasis reactions, and phenyl boronic acids can also be used. Of the aldehydes most commonly used, glycolaldehydes appear to be the most reactive, followed by glyoxylic acid and salicylaldehyde.

#### 1.2.4. Catalysis Reactions

Many of the boron-containing compounds currently available are able to act as mild Lewis acids due to the vacant  $2p$ -orbital present on the electron-deficient boron atom. The conventional boron Lewis acids ( $BX_3$ ,  $RBX_2$  and  $R_2BX$ , where  $X = F, Cl, Br$  or  $OTf$ ) are accepted as common tools in organic synthesis reactions. These reagents, more often than not, are used in stoichiometric ratios and are thus more of a co-reagent than a true catalyst, and under anhydrous conditions as these reagents decompose very easily in small volumes of water.<sup>21</sup> In order to combat the shortcomings of these highly reactive reagents, arylboron compounds containing electron-withdrawing groups have been shown to work as Lewis acids with comparable strength to the traditional boron Lewis acids, without a number of the intrinsic problems associated with these Lewis acids. Given this mild Lewis acidity, stability in water, acid and base solutions and at elevated temperatures, and the ability to easily exchange groups around nitrogen and oxygen atoms attached to the boron atom, triarylboranes, diarylboranes and arylboranes have been used as catalysts or temporary scaffolds in a variety of regio-, stereo- and enantioselective synthesis reactions. While the actual reaction mechanism depends on what reaction is to be carried out, the role of the catalytic organoboranes in each of the reactions is as a Lewis acid. There has been very little work published on the role of these catalysts in the various reactions, and it is possible that merely describing the organoboranes as working as Lewis acids may be incomplete or inaccurate.<sup>21</sup>

##### 1.2.4.1. Triarylboranes as Catalysts

Of the triarylboranes ( $Ar_3B$ ), tris(pentafluorophenyl)borane **1** has been observed to have comparable Lewis acidity to  $BF_3$ , but as there are no highly-reactive B-F bonds, it is stable in both air and pure oxygen, is water- and heat-tolerant, and is soluble in a number of organic solvents. Compound **1** functions in catalytic quantities in aerobic conditions, but greater yields can be realized if anhydrous conditions are employed.

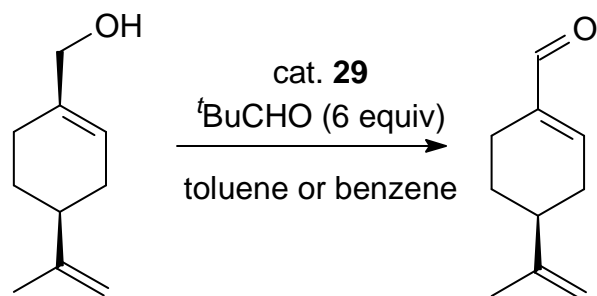
Compound **1** has been shown to catalyze aldol and allylation reactions of aldehydes with various silyl reagents, Diels-Alder reactions of cyclopentadiene with 2-methyl-2-propanal,<sup>22a</sup> as well as the aldol-type reactions of imines with ketene silyl acetals.<sup>22a,114</sup> This is due in part to the affinity of **1** to nitrogen-containing compounds, and the relatively low B-N bond energy and stability. The formation of *N*-unsubstituted  $\beta$ -lactams from the *in situ* treatment of *N,N'*-bis(trimethylsilyl) $\beta$ -amino acid esters with MeMgBr have also been successfully catalyzed by **1**.<sup>22a</sup>

For the Lewis acid or protic promoted rearrangement of epoxides to carbonyl compounds, BF<sub>3</sub>·OEt<sub>2</sub> is often the Lewis acid of choice.<sup>115</sup> However, it cannot be considered a catalyst, as it must often be added in equimolar (or slightly less than equimolar) amounts to counteract the consumption or alteration of BF<sub>3</sub>·OEt<sub>2</sub> during the reaction. As a catalyst in the rearrangement reactions of trisubstituted epoxides, Compound **1** has proved to be both highly efficient and highly selective, possibly due to the bulkiness of the three phenyl groups,<sup>116</sup> and has been shown to play a catalytic role in the regioselective hydrostannylation reaction of alkynes, allenes and alkenes with tributyltin hydride to yield almost exclusively the  $\beta$ -hydrostannylation products

#### 1.2.4.2. *Diarylborinic acids as Catalysts*

Diarylborinic acids, with the general form Ar<sub>2</sub>BOH, are strong Lewis acids, and as such, the dehydration of many  $\beta$ -hydroxy carbonyl products is favoured. In Mukaiyama aldol condensation reactions and the subsequent selective dehydration of the  $\beta$ -hydroxy carbonyl compounds formed, diarylborinic acids, especially those with electron-withdrawing groups such as bis(pentafluorophenyl)borinic acid **29** and bis(2,4,6-trifluoro-3,5-bis(trifluoromethyl)phenyl)borinic acid **30**, (**Figure 20**) have been used to good effect<sup>117</sup> (**Scheme 44**). Interestingly, the corresponding arylborinic acids show much lower catalytic activities, and it is also interesting to





Scheme 45.

### 1.2.4.3. Arylboronic acids as Catalysts

Yamamoto found that arylboronic acids ( $\text{ArB}(\text{OH})_2$ ) with electron-withdrawing groups, in particular 3,4,5-trifluorophenylboronic acid **31** (Figure 21), act as a catalyst for the amidation and esterification reactions of carboxylic acids,<sup>119</sup> and the amidation of ureas using an arylboronic acid catalyst has also been reported.<sup>120</sup>

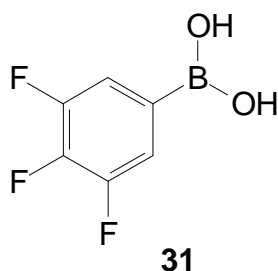
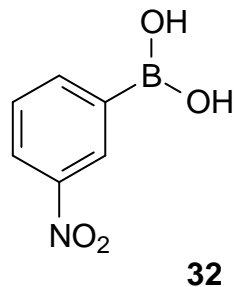


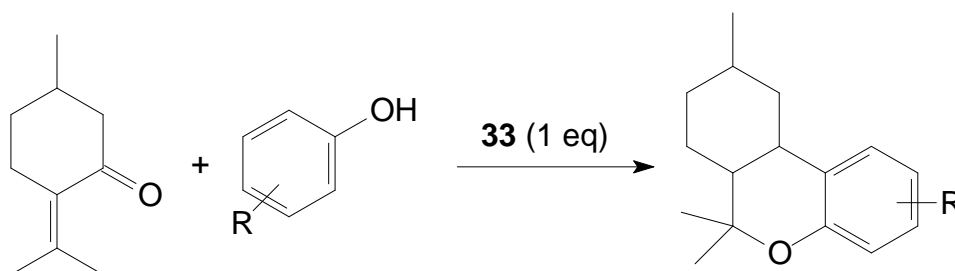
Figure 21.

**31** has also been shown to catalyse the formation of acyl azides from sodium azide and carboxylic acids in a one-pot reaction,<sup>121</sup> as well as the reduction of carboxylic acids to alcohols.<sup>122</sup> 3-Nitrobenzeneboronic acid **32** (Figure 22) has also proved to be a successful catalyst in some reactions, for example the transesterification reactions of  $\beta$ -keto esters.<sup>123</sup>



*Figure 22.*

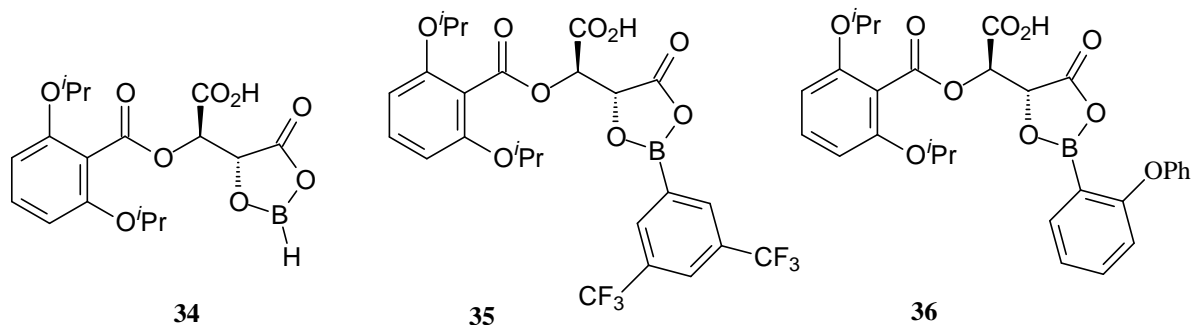
The *ortho*-specific  $\alpha$ -hydroxylation of phenols by aldehydes (**Scheme 46**) is known to be mediated by phenylboronic acid **33**,<sup>124</sup> where a cyclic boronate, formed by a [3,3] sigmatropic rearrangement, is thought to be the key intermediate. This process, with its mild conditions, has been successfully used in the synthesis of benzo-fused heterocycles, including *2H*-chromenes<sup>100a</sup> and tetrahydrocannabinoids.<sup>124b</sup>



*Scheme 46.*

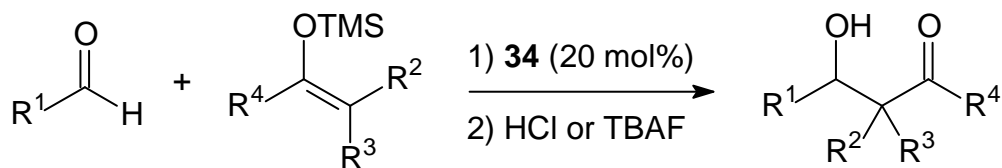
#### 1.2.4.4. Chiral Arylboron Catalysts

Enantioselective reactions are of great importance and interest as these reactions allow for the introduction of chiral centers and chiral functional groups into a molecule. A number of chiral (acyloxy)boranes, such as **34**, **35** and **36** (**Figure 23**) have shown promise in the catalysis of a number of enantio- and diastereoselective reactions such as the Mukaiyama aldol reaction, the Sakurai-Hosomi allylation and the asymmetric Diels-Alder reaction.

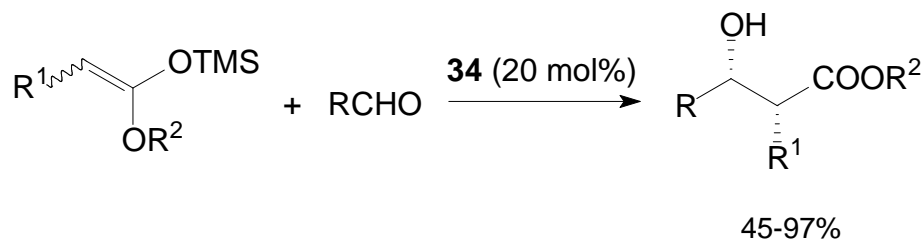


*Figure 23*

Chiral (acyloxy)borane **34** has proven to be an outstanding catalyst at 20 mol% for the Mukaiyama reaction (**Scheme 47**), and studies have shown that the aldol reaction is catalyzed without sacrificing the enantioselectivity of these reactions at catalyst loading levels of between 10 and 20 mol%, when **35** is used,<sup>125</sup> and the enantioselectivity of the reaction can be increased without a reduction in yield by using a catalyst loading of 20 mol% when **36** is used.<sup>126</sup> Aldol-type reactions of achiral aldehydes and ketene silyl acetals (**Scheme 48**) are also catalyzed by **34**, yielding *syn*- $\alpha$ -hydroxy esters regardless of the stereochemistry of the silyl ethers used.<sup>127</sup>

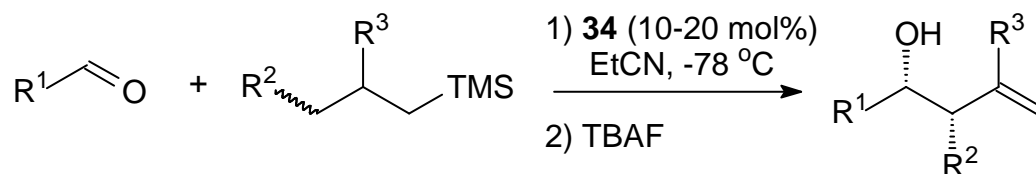


*Scheme 47*



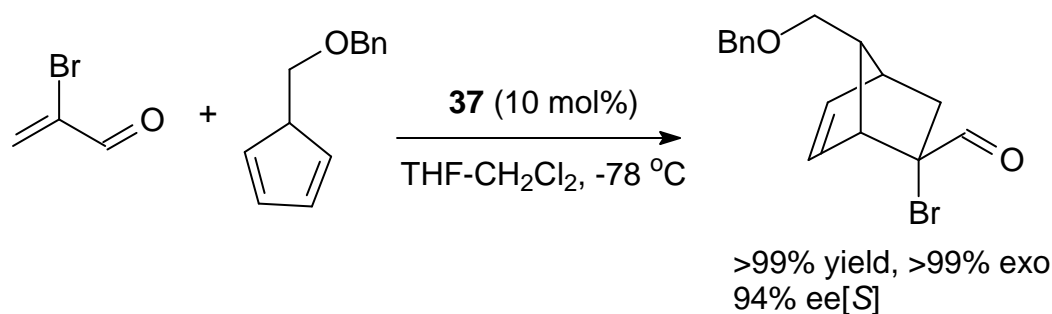
*Scheme 48*

Excellent enantiomeric excesses can be realized in the Sakurai-Hosomi reaction when **34** is used as a catalyst (**Scheme 49**), giving rise to homoallylic alcohols where the major isomer produced contains syn configuration, again regardless of the geometry of the starting materials.<sup>128</sup>

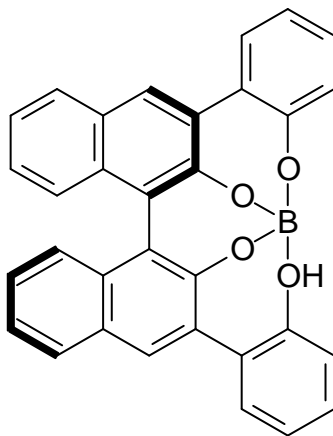


*Scheme 49*

The fact that most boranes are Lewis acids has allowed for their use as catalysts in Diels-Alder reactions to great success. High *exo* selectivity and enantioselectivity has been reported for cycloadditions of  $\alpha$ -substituted  $\alpha,\beta$ -enals (**Scheme 50**) with the Brønsted acid assisted chiral Lewis acid catalyst **37** (**Figure 24**), however, reactions of  $\alpha$ -unsubstituted  $\alpha,\beta$ -enals often result in low enantioselectivity.<sup>21</sup> The use of **38** (**Figure 25**) in a catalytic role rather than **37** affords high selectivity with both substituted and unsubstituted reagents. Diarylborinic acids have also shown enhanced catalytic ability in Diels-Alder reactions, and this has been ascribed to the enhanced Lewis acidity and steric bulk of these compounds.

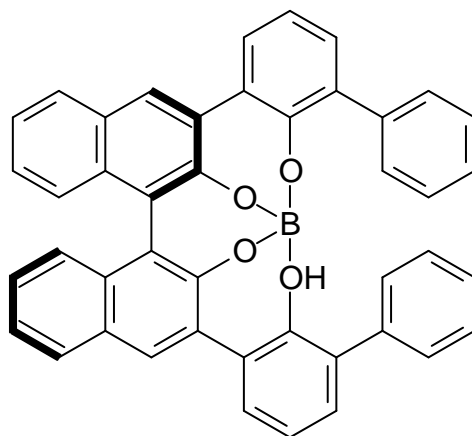


*Scheme 50*



37

Figure 24



38

Figure 25

### **1.3. Project Objectives**

As the range of reactions covers such a wide variety of reactions, it is necessary to select one or two avenues of research and to focus on the reactions contained therein. As such the focus of this research is two-fold: The first aim is to synthesize a number of heterosubstituted boranes, and the second is to use the newly synthesized compounds in a reaction as the organoborane reagent.

The heterosubstituted boranes will be synthesized by one of two routes. The first route of synthesis will be the formation of heterosubstituted boranes using a suitable diamine or oxoamine and  $\text{BH}_3\cdot\text{DMS}$ , followed by rhodium(I) catalyzed hydroboration of olefins. This will allow for the study of the stability of the heterosubstituted borohydrides and their reactivity with regards to a number of olefins, as well as the study of the catalytic ability of two rhodium(I) compounds, one of which is not known as a catalyst for hydroboration reactions.

The second will be the condensation of boronic acids with the diamines or oxoamines to yield the heterosubstituted boranes in a one-pot reaction, and to evaluate the application of microwave irradiation to the solvent-free synthesis of these compounds. This could provide a faster, "greener", more cost-effective route for the synthesis of these heterosubstituted boranes as neither a rhodium(I) catalyst nor a solvent is needed.

The final section of the project will deal with the use of the heterosubstituted borane compounds in the Petasis reaction, a multicomponent reaction between an aldehyde, an amine and an organoborane to yield amino acids. This investigation will answer the questions of whether these reagents can be used in the Petasis reaction, and what, if any, advantage is gained using these reagents over the more common boronic acids.

## **2. Results and Discussion: Preparation of Hydroboration Reagents and Rhodium-Catalyzed Hydroboration Reactions**

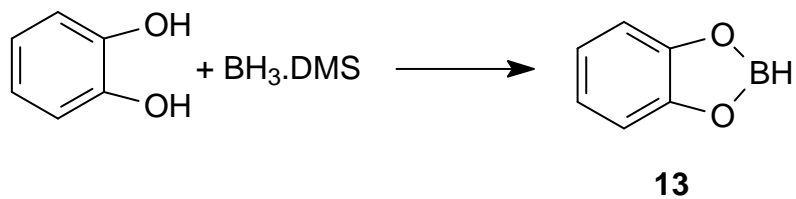
### **2.1. Study Objectives**

In this chapter, the synthesis of three heterosubstituted boranes will be studied using  $^{11}\text{B}$  NMR spectroscopic analysis, a technique which allows for the direct observation of the boron atom. The stability of these reagents regarding exposure to air and elevated temperatures will also be investigated, as will the reactivity of these reagents with regards to three olefins. The use of two rhodium(I) compounds as catalysts for hydroboration reactions will also be explored.

$^{15}\text{N}$  NMR spectroscopic analyses of the heterosubstituted boranes will be carried out in order to determine whether there is any evidence to support the current understanding of the nature and stability of these boranes, thought to be due to the back-donation of electron density of the nitrogen lone pairs into the vacant  $p_z$ -orbital present on the boron atom.

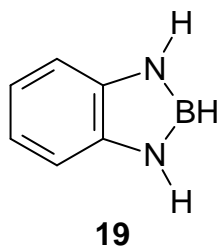
### **2.2. Preparation of Hydroboration Reagents**

While there are a large number of different alkylated hydroboration reagents, each with their own benefits and drawbacks, there are only a few methods used to create these reagents. The most widely used method is simply to react a borane-ligand complex, such as  $\text{BH}_3\cdot\text{DMS}$ , with a suitable alkyl or heterosubstituted reagent, such as catechol, (**Scheme 1**) to yield the alkylated reagent, in this case HBCat **13**.



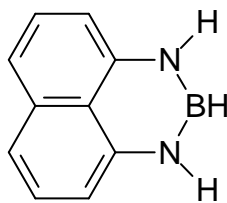
*Scheme 1.*

Whilst highly reactive, HBCat is also extremely unstable and prone to undergoing disproportionation reactions.<sup>54</sup> 1,3,2-benzodiazaborolane (HBPda) (**19**) (**Figure 1**) was first proposed as an alternative hydroboration reagent to HBCat in 2006.<sup>58</sup> Based on 1,2-phenylenediamine, HBPda showed enhanced stability towards disproportionation reactions, but this inherent stability resulted in reduced reactivity as a hydroboration reagent.



*Figure 1.*

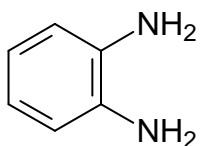
A borane reagent based on 1,8-diaminonaphthalene has not been widely used as a hydroboration reagent, even though the first synthesis of naphtho[1,8-*de*][1,3,2]diazaborinane (HBDan) **22** (**Figure 2**) was published in 1961, where it was named 8-bora-7,9-diazaro-*peri*-naphthene.<sup>60</sup> Synthesized from the reaction of 1,8-diaminonaphthalene and boron trichloride, followed by reduction by lithium aluminium hydride, it was able to be handled in air for short periods of time without significant oxidation, something which was almost unheard of for such reagents.



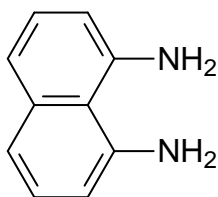
**22**

*Figure 2.*

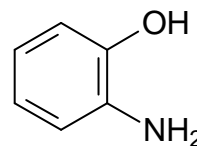
As very little work has been published on the formation and use of nitrogen substituted boranes as hydroboration reagents, 1,2-phenylenediamine **20**, 1,8-diaminonaphthalene **21** and 2-aminophenol **39** (**Figure 3**) were selected as scaffolds on which to base the hydroboration reagents.



**20**



**21**



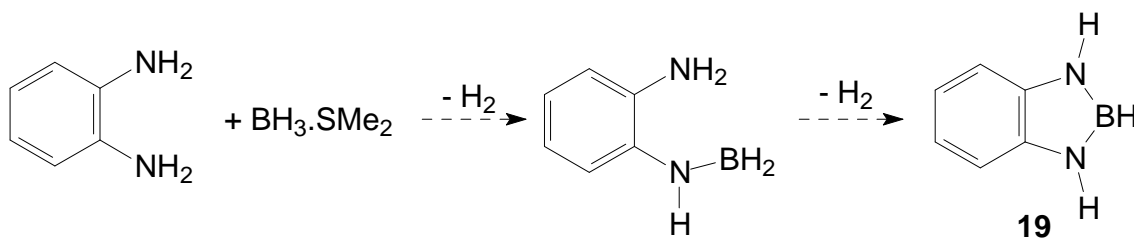
**39**

*Figure 3.*

The diamine compounds were selected over compounds that would yield more reactive hydroboration reagents, such as HBCat, HBPIn and HBThia,<sup>58</sup> in order to minimize the formation of the disproportionation products observed with these borolanes. HBPda is known to be more thermally stable than HBCat, HBPIn or HBThia, as it did not show the same propensity to undergo disproportionation reactions, and it was hoped that the naphthalene-based borinane would also not undergo this reaction, as the remarkable stability of this borinane has been reported.<sup>129</sup> Diamines are also better choices for the formation of hydroboration reagents than phosphorous-based compounds, as they are significantly more reactive than phosphorous-based boranes. For example,  $\text{BH}_3\cdot\text{PPh}_3$  is an indefinitely air stable solid. 2-Aminophenol was selected as it was hoped that by having a mixed N,O donor, the reactivity of the borane would be increased as compared to HBPda

and HBDan due to the oxygen donor atom, but less likely to undergo disproportionation reactions due to the presence of the nitrogen donor atom. Whether a borane based upon 2-aminophenol has similar stability concerns with regards to thermal decomposition and disproportionation as HBCat, HBPIn and HBThia is unknown, even though this compound was first synthesized in 1961.<sup>130</sup>

Mechanistically, very little is understood regarding the formation of these boranes. It is likely that the same step-wise addition of  $\text{BH}_3$  to the amine reagent is followed as is observed in the formation of other boranes. The reaction between  $\text{BH}_3$  and the amine would then yield a borane intermediate where a bond has been formed between the boron atom and one of the donor atoms, with the liberation of 1 mol of  $\text{H}_2$  gas. Addition of the boron atom to the second donor atom, effecting the closure of the ring would result in the liberation of a second mol of gaseous  $\text{H}_2$  (**Scheme 2**). Whether this is the case, or whether there is a more complex mechanism behind this reaction remains to be seen.



Scheme 2.

As previously stated, HBPda is unreactive as a hydroboration reagent towards 1-octene unless a rhodium-based catalyst is used, and even then it remains unreactive towards *trans*-4-octene. These observations have been attributed in part to the back-donation of electron density from the lone pair of electrons on the nitrogen atom into the vacant  $p_z$ -orbital of the boron atom (**Figure 4**) which transfers an added measure of stability to this reagent. In the case of the reaction between *trans*-4-octene and HBPda, there is an added element of steric hinderance as the addition of the alkene to the rhodium metal center is restricted. HBDan has not found wide application as a hydroboration reagent, most likely due to its stability. However,

it has recently found use as a protecting group for a number of  $\beta$ -styrylboronic acids when an iridium-based catalyst is used.<sup>131</sup> This iridium catalyst had previously been used to catalyze the hydroboration of olefins with HBCat and other hydroboration reagents.<sup>132</sup>

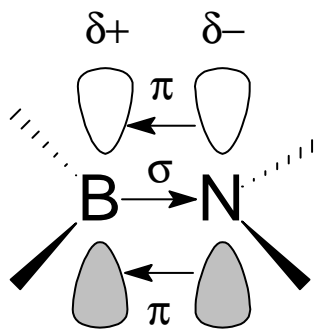
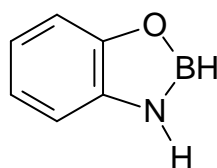


Figure 4.

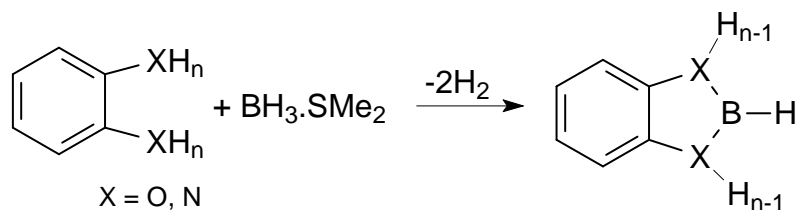
There has also been very little work published on the use of 2-aminophenol as a scaffold for a hydroboration agent, and as such 1,3,2-benzoxazaborolane **40** (HBaph) (**Figure 5**) is a relatively novel compound. Whether this reagent will have the desired combination of stability and reactivity cannot be predicted. If HBaph does react as desired, it could unlock the possibility of extensive use of heterosubstituted boranes in synthesis and industrial applications.



**40**

Figure 5

While a few methods exist for the formation of heterosubstituted boranes, one of the simplest methodologies is to react an amine compound with  $\text{BH}_3\cdot\text{DMS}$  in  $\text{CH}_2\text{Cl}_2$  (**Scheme 3**). As  $\text{BH}_3\cdot\text{DMS}$  is notoriously air- and moisture-sensitive, an inert atmosphere, such as argon or nitrogen, is required.



*Scheme 3.*

### 2.2.1. Synthesis of 1,3,2-Benzodiazaborolane (HBPda)

HBPda **19** was successfully synthesized from 1,2-phenylenediamine **20** and  $\text{BH}_3\text{-DMS}$  after five hours in refluxing  $\text{CH}_2\text{Cl}_2$  as a pale pink solution in virtually quantitative yields. The exclusive formation of HBPda was confirmed by the presence of a doublet at 24 ppm in the  $^{11}\text{B}$  NMR spectrum (**Figure 6**) of the reaction mixture corresponding to HBPda, and a quartet at -20 ppm corresponding to the borane starting material. The lack of other signals in the spectrum showed that no unwanted side reactions or disproportionation reactions had occurred. Proton-decoupled  $^{11}\text{B}$  NMR analysis of the reaction mixture caused the doublet to collapse into a singlet, proving that only one B-H species was present.

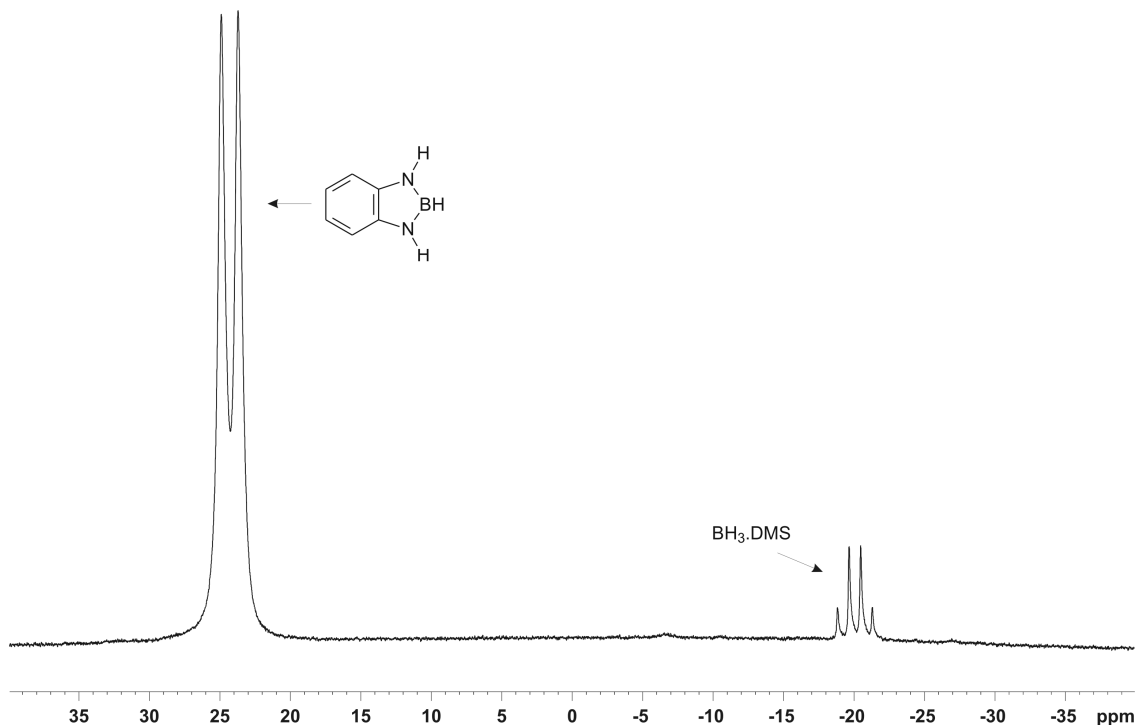


Figure 6.

### 2.2.1.1. Stability observations

In agreement with observations made by Hadebe,<sup>58</sup> HBPda was observed to be significantly more stable than HBCat with regards to temperature and exposure to air. The most obvious sign of enhanced stability is in the fact that the reaction to form HBPda must be carried out in refluxing  $\text{CH}_2\text{Cl}_2$ , whereas HBCat is synthesized at temperatures well below zero. Although HBThia is synthesized at room temperature, indicating increased stability as compared to HBCat, this reaction required 24 hours to effect complete conversion to the desired product.

A second indication of the enhanced stability of HBPda as compared to HBCat, HBPin and HBThia is the lack of observable amounts of the disproportionation product in the  $^{11}\text{B}$  NMR spectra as compared to that of HBCat, (**Figure 7**) This side reaction which beleaguered the use of these reagents in further reactions is thought to involve the formation of a four-centered transition state as a vital step in the mechanism proposed by Rose and Shore,<sup>54</sup> (**Scheme 4**) and it is likely that the

increased amount of electron back-donation between the nitrogen and boron atoms prevents the formation of an analogous transition state in HBPda.

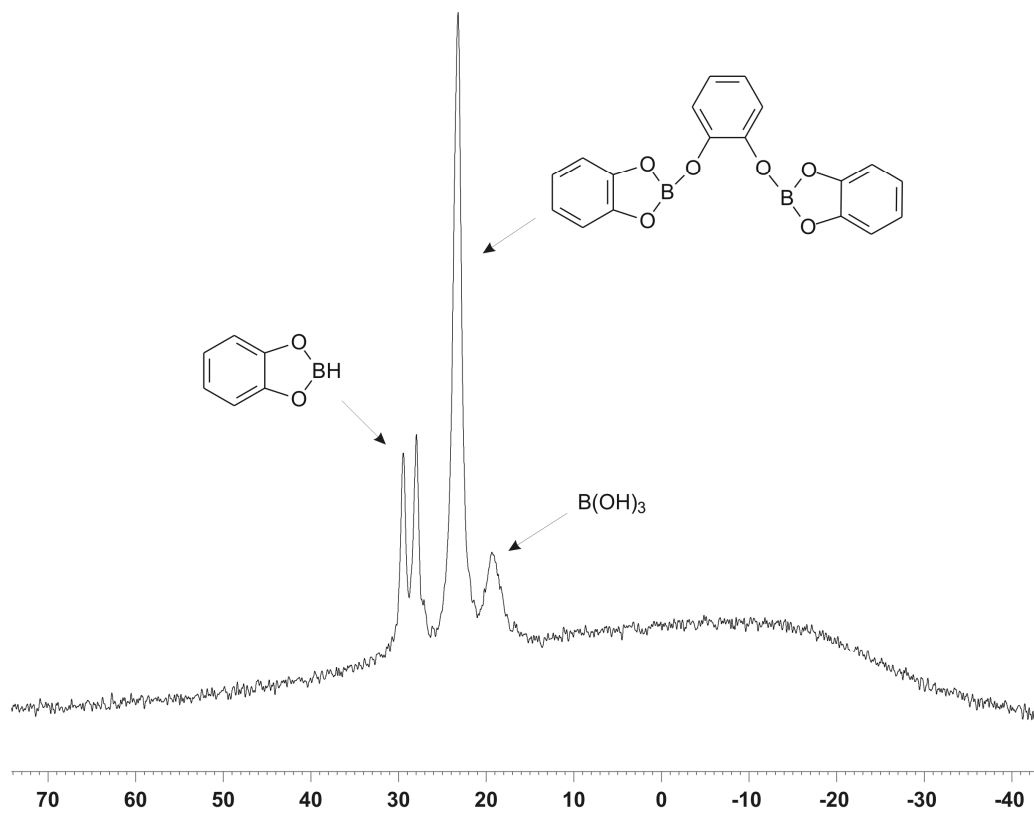
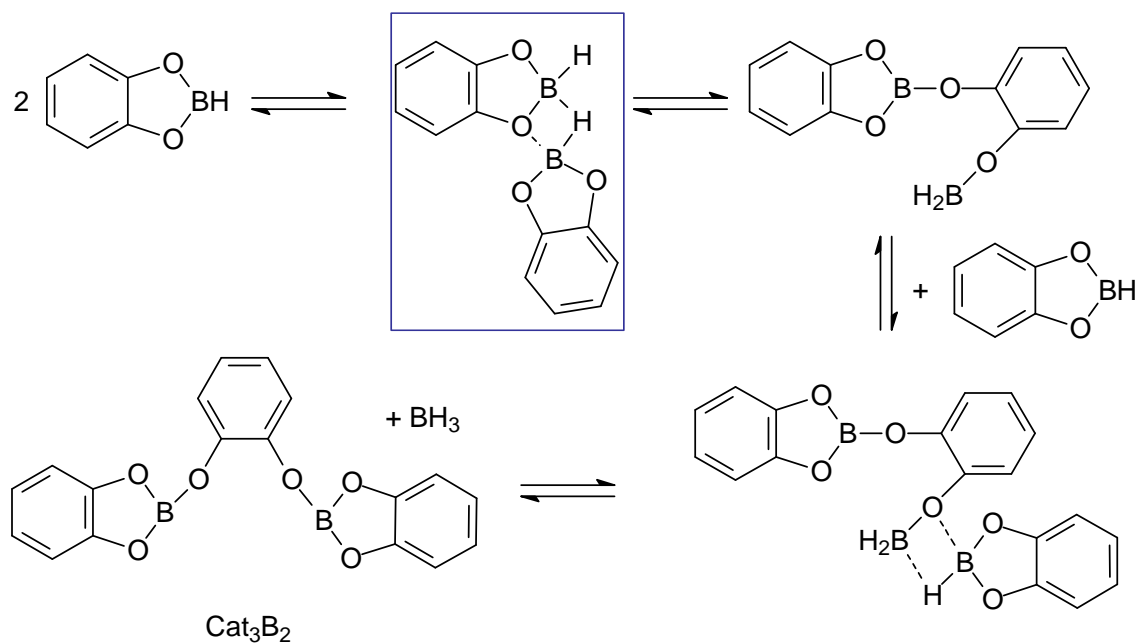


Figure 7.



*Scheme 4.*

HBPda was also observed to be stable under  $N_2$  at room temperature for upwards of six weeks, even in the presence of an alkene.  $^{11}B$  NMR analysis showed no indications of the presence of boric acid or the disproportionation product after seven weeks under these conditions. This is again in contrast to HBCat, which is stored below  $5\text{ }^\circ\text{C}$  in order to extend the lifespan of this reagent, and even then the formation of the disproportionation product cannot be avoided.

Exposure to air also did not negatively affect HBPda, as a sample which had been exposed to the atmosphere for a few hours did not show any oxidation of HBPda to boric acid in the  $^{11}B$  NMR spectrum. In addition, HBPda is not affected by the presence of pure oxygen, either in gaseous form or dissolved in a solvent. This was established as a reaction where a solution of Wilkinson's catalyst in  $CH_2Cl_2$  had been oxidized by bubbling pure oxygen through the solution prior to addition to HBPda did not show any significant changes in the  $^{11}B$  NMR spectrum which would indicate oxidation or any other degradation reactions.

### 2.2.1.2. $^{15}\text{N}$ NMR results

As standard procedure, complete NMR analyses were carried out on HBPda, including measurement of  $^{15}\text{N}$  chemical shifts *via* either  $^{15}\text{N}$ - $^1\text{H}$  HSQC or HMBC experiments (**Figure 8**). The first interesting observation was the location of the  $^{15}\text{N}$  chemical shift. This signal has been shifted downfield (**Figure 9**) into an area between the region typical of amines or other  $\text{sp}^3$ -hybridized nitrogen atoms, (0-90 ppm) and the region typical of pyridine-type compounds and other  $\text{sp}^2$ -hybridized nitrogen atoms<sup>133</sup> (from 220ppm). This is unexpected as it was previously assumed that the nitrogen atoms behave as typical amines, whereas this result appears to show that some multiple bond character exists between the nitrogen and boron atoms, lending support to the current theory that electron back-donation occurs between the nitrogen and boron atoms.

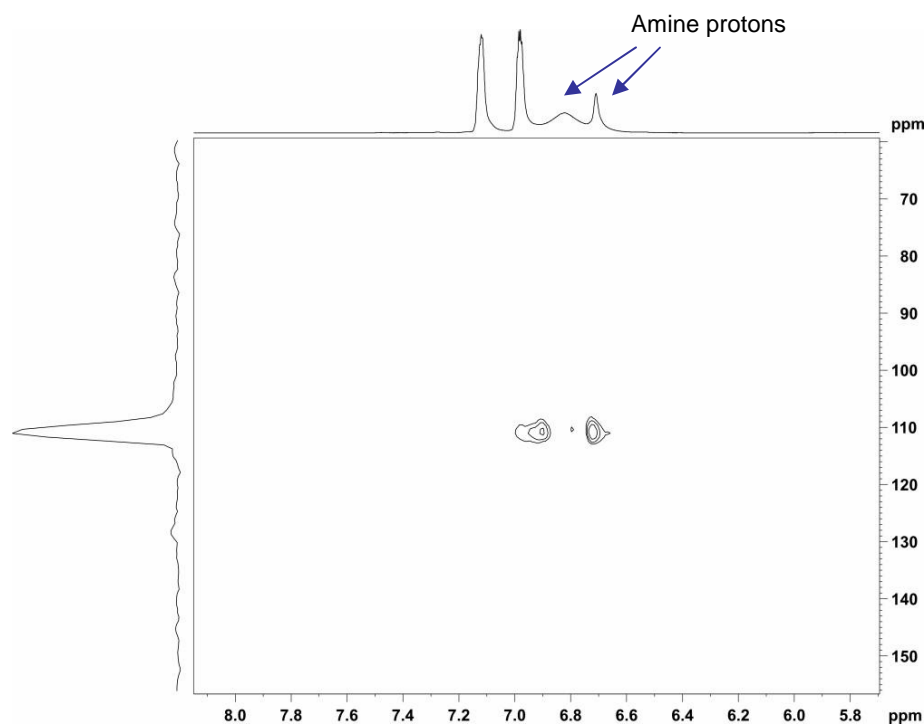


Figure 8

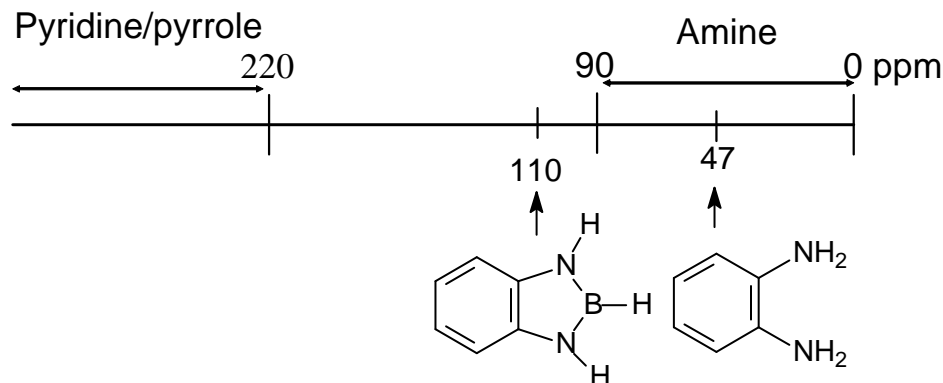
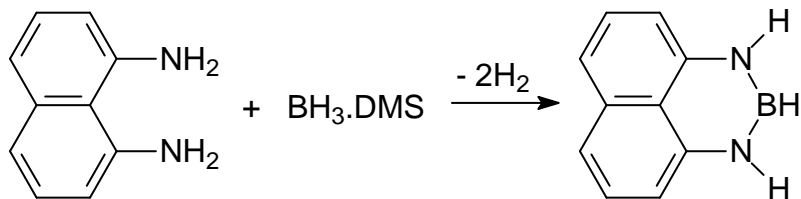


Figure 9. (Not to scale)

Another interesting observation is that the  $^{15}\text{N}$ - $^1\text{H}$  correlation studies appear to show the presence of two chemically non-equivalent protons, as evidenced by the two amine signals at 6.71 and 6.82 ppm in the  $^1\text{H}$  spectrum of the  $^{15}\text{N}$ - $^1\text{H}$  HSQC spectrum in Figure 3.9. This seems to indicate that the extent of electron back-donation is not spread evenly across the nitrogen-boron-nitrogen system; however, further investigation is needed to confirm this suspicion.

### 2.2.2. Synthesis of Naphtho[1,8-de][1,3,2]diazaborinane (HBDan)

The borinane naphtho[1,8-de][1,3,2]diazaborinane (HBDan) **22** was successfully synthesized in virtually quantitative yields, from the reaction of 1,8-diaminonaphthalene **21** and  $\text{BH}_3\cdot\text{DMS}$  (**Scheme 5**) after 5 hours in refluxing  $\text{CH}_2\text{Cl}_2$ , as a pale yellow solution. HBDan has previously been isolated as a pale pink solid which turns purple after extended exposure to the atmosphere,<sup>60</sup> however the isolation was reported to be complicated and unnecessary in this case as all further reactions were to be carried out in solution.



Scheme 5.

$^{11}\text{B}$  NMR analysis confirmed the exclusive formation of the borinane **22** (**Figure 10**) as only signals corresponding to the product (27 ppm) and the starting borane (-20 ppm) were observed. Proton decoupling of the  $^{11}\text{B}$  NMR spectrum again resulted in the collapse of the doublet into a singlet, indicating the presence of only one B-H species

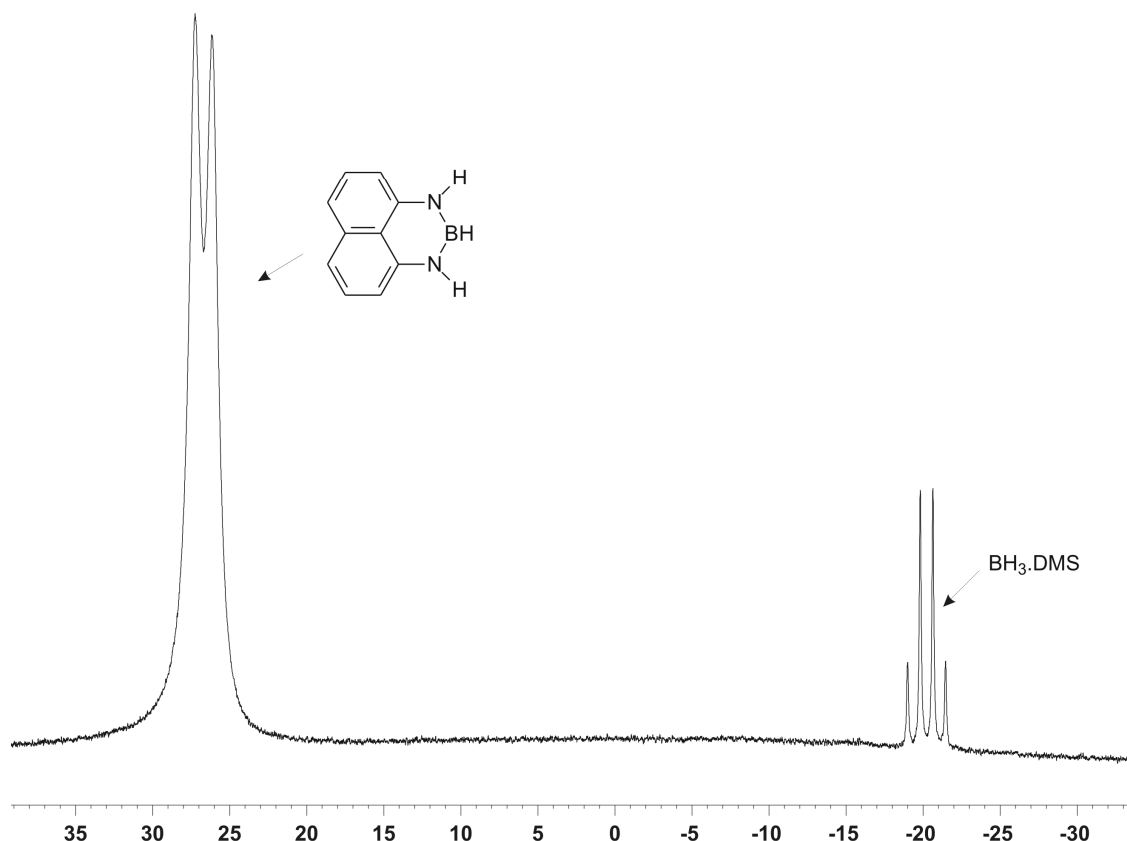


Figure 10.

### 2.2.2.1. Stability Observations

HBDan, as expected, was more stable than HBCat at elevated temperatures and over time. Elevated temperatures were required to effect complete formation of HBDan, as was also the case for HBPda, and no sign of disproportion was observed in any  $^{11}\text{B}$  NMR spectrum, even in the presence of alkenes.

HBDan did not appear as stable as HBPda, however, as formation of an as yet unidentified precipitate prevents the use of this reagent after storage for 4 weeks at room temperature under N<sub>2</sub>. This apparent loss of stability as compared to HBPda could be due to the formation of the six-membered borinane ring, as opposed to the five-membered borolane ring found in HBPda, however it is more likely that the stability of these reagents is not dependant simply on the structure of the boron heterocycle.

### 2.2.2.2. <sup>15</sup>N NMR Results

Similar NMR analyses were carried out on HBDan, including the <sup>15</sup>N-<sup>1</sup>H correlation studies (**Figure 11**) as carried out on HBPda. Again, the <sup>15</sup>N chemical shift has been shifted into the region between those of the sp<sup>3</sup>-hybridized nitrogen atoms (0-90 ppm) and the sp<sup>2</sup>-hybridized nitrogen atoms (from 220 ppm) (**Figure 12**).

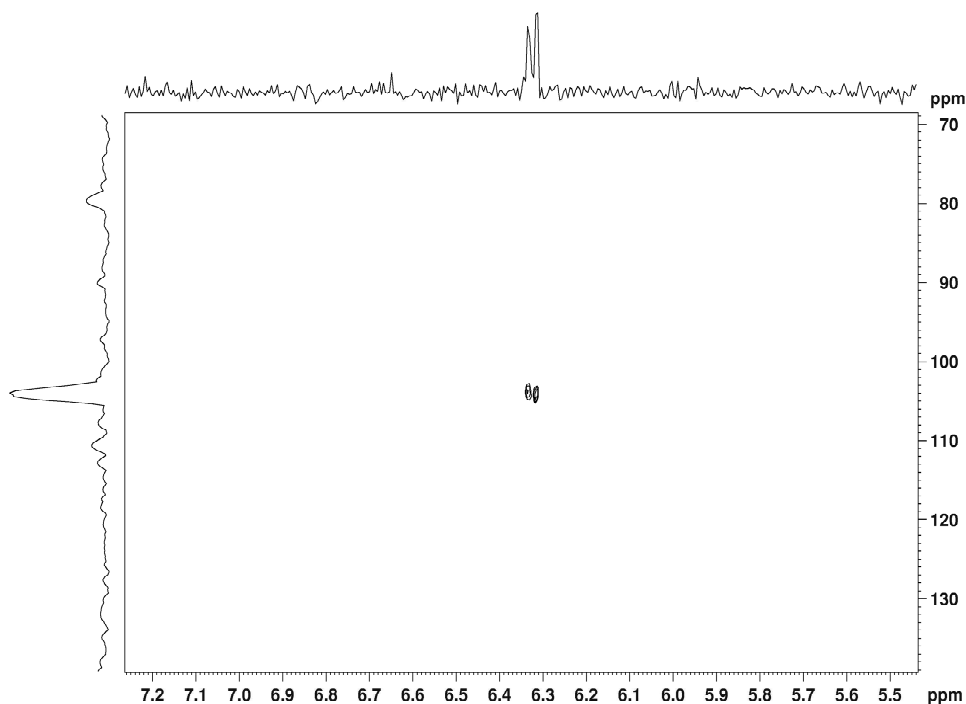


Figure 11.

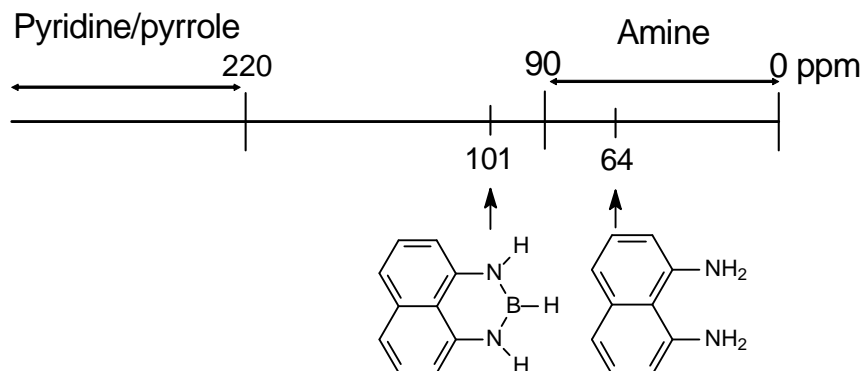


Figure 12. (Not to scale)

In contrast to the results obtained for HBPda,  $^{15}\text{N}$ - $^1\text{H}$  HSQC results show the presence of chemically equivalent amine protons. This may indicate that the electron back-donation between the nitrogen and boron atoms in HBDan occurs to a lesser extent than in HBPda, or that the electron density is spread across the molecule more evenly. As is the case for HBPda, further work is required to completely explain these results in depth.

### 2.2.2.3. $^{11}\text{B}$ NMR Results and Mechanistic Implications

During the course of a reaction to synthesize HBDan, samples were removed at regular intervals and subjected to *in situ*  $^{11}\text{B}$  NMR analysis in order to determine the extent of the reaction. What appeared to be at least two different intermediates in this reaction were observed (**Figure 12**).

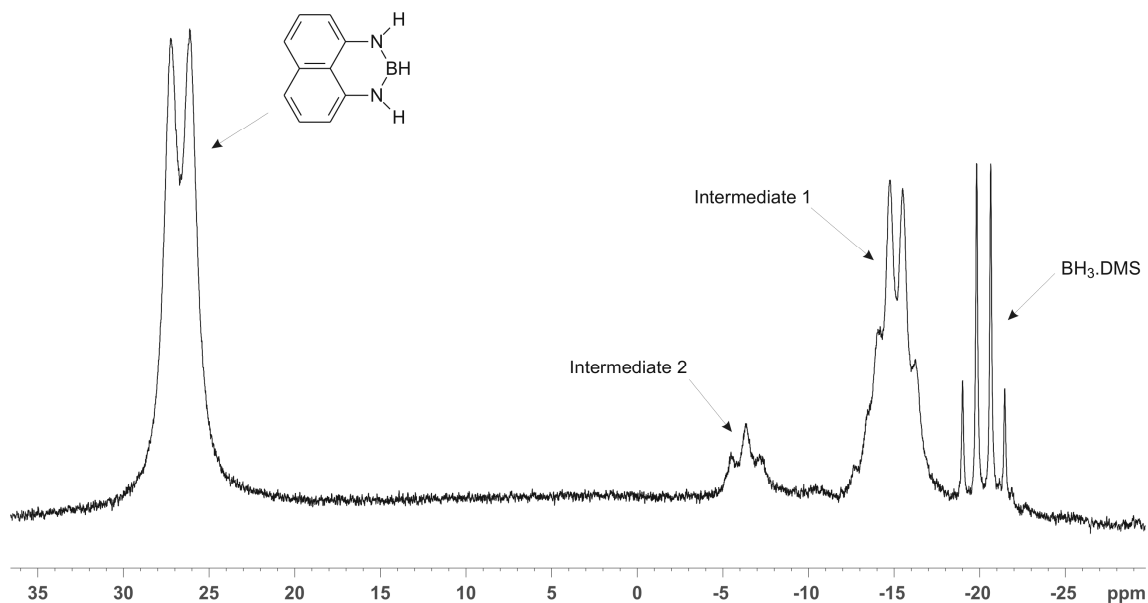
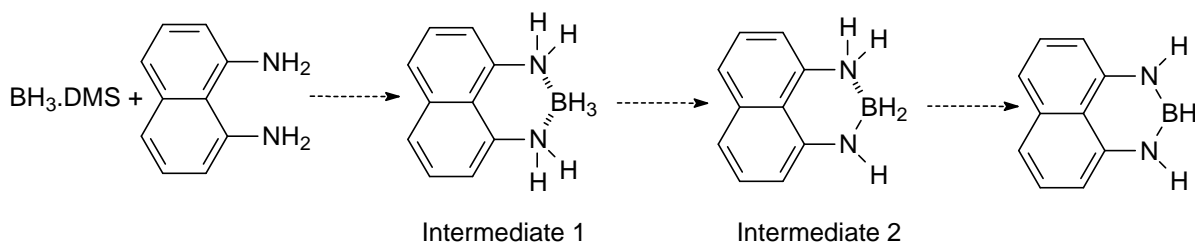


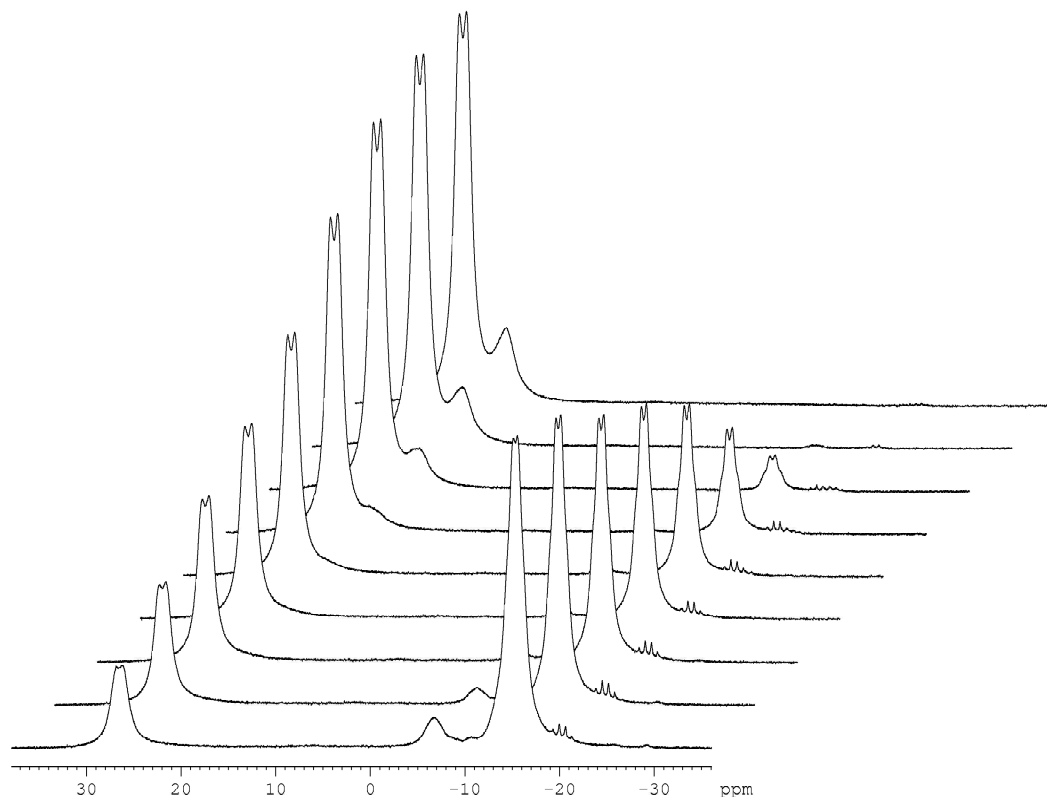
Figure 13.

These intermediates, a quartet at -15 ppm and a triplet at -6 ppm, could provide support for a stepwise addition mechanism (**Scheme 6**). The dissociation of the  $\text{BH}_3\text{-SMe}_2$  complex to yield a  $\text{BH}_3$ -amine complex prior to the dissociation of any boron-hydrogen bonds or the formation of any boron-nitrogen bonds would result in a quartet being observed in the  $^{11}\text{B}$  spectrum, as the boron atom is still directly connected to three protons. The emergence of the triplet at -6 ppm also appears to be proof of a two-hydrogen-one-nitrogen intermediate borane species. The loss of a second mol of  $\text{H}_2$  gas as the second boron-nitrogen bond is formed results in the formation of the final product, and the corresponding doublet is detected in the NMR spectrum.



Scheme 6.

These intermediates are stable for a number of hours in a sealed NMR tube, and this allowed the course of the reaction to be followed over 18 hours, and the results support the initial observations made (**Figure 14**). The progress of this reaction proceeded as expected, with the triplet and second quartet disappearing and the doublet increasing in size over time as the product is formed, which is in accordance with the mechanism proposed in Scheme 6. This reaction is dependant on the concentrations of both the borane and the amine, as reactions where these concentrations were varied resulted in slightly different results.



*Figure 14.*

There appears to be an element of solvent interaction in the formation of the second quartet, as reactions carried out in THF show similar intermediates; however the shifts of these intermediates are significantly different to those observed in  $\text{CH}_2\text{Cl}_2$ . This may be due to the  $\text{CH}_2\text{Cl}_2$  being a non-coordinating solvent, whereas THF is a coordinating solvent, as well as being a Lewis base. This solvent

interaction is not without precedent, as Xaba and Jaganyi<sup>134</sup> reported the retardation of the rate of reactions involving  $\text{H}_2\text{BCl}\cdot\text{DMS}$  when the solvent was switched from  $\text{CH}_2\text{Cl}_2$  to THF, due to the exchange of THF for DMS in solution, a phenomenon attributed to being dependant on both electronic and steric effects. It is likely that the instantaneous base exchange noted by Xaba and Jaganyi also occurs in this system, resulting in the observed shift of the signals in the  $^{11}\text{B}$  NMR spectrum.

These observations prompted attempts to follow the reaction using solution Infrared (IR) spectroscopy, as the formation of the first intermediate is complete in less than 5 minutes, and  $^{11}\text{B}$  NMR analysis could not be used to follow the reaction any more closely than had already been done. Unfortunately this proved a futile exercise as there was no observable change in the IR spectra that could be used to prove or disprove this mechanistic hypothesis. Previous work carried out by Caserio *et al.*<sup>60</sup> reported a band at  $2550\text{ cm}^{-1}$  which was ascribed to the boron-hydrogen bond, and if the reaction could be halted or slowed down far enough to allow for the identification of the intermediates, this region may provide new information. Potentially, a low temperature solution IR study could be used to investigate the proposed mechanism further.

Unfortunately no computational studies into the mechanism of this type of hydroboration reaction have been published which could be used to explain these observations, and the computational modeling required to support or disprove this theoretical mechanism are beyond the scope of this project. As such, these observations and the preliminary NMR work could provide the basis for an interesting investigation into this mechanism. Reaction information, such as the rate constants and activation energies, could be determined from the *in situ*  $^{11}\text{B}$  NMR experiments, as this technique has previously been used to great effect.<sup>134-135</sup>

### 2.2.3. Synthesis of 1,3,2-benzoxazaborolane (HBaph)

2-Aminophenol also proved to be a suitable foundation on which to base a borane reagent, as the reaction of 2-aminophenol and  $\text{BH}_3$  resulted in the almost quantitative formation of the desired 1,3,2-benzoxazaborolane **40** (HBaph) as a clear colourless liquid after stirring at room temperature for 72 hours. The formation of HBaph was confirmed by the formation of a doublet at 28 ppm in the  $^{11}\text{B}$  NMR spectrum (**Figure 15**), which collapsed into a singlet when a proton decoupled  $^{11}\text{B}$  NMR analysis was carried out, indicating the presence of only one B-H species.

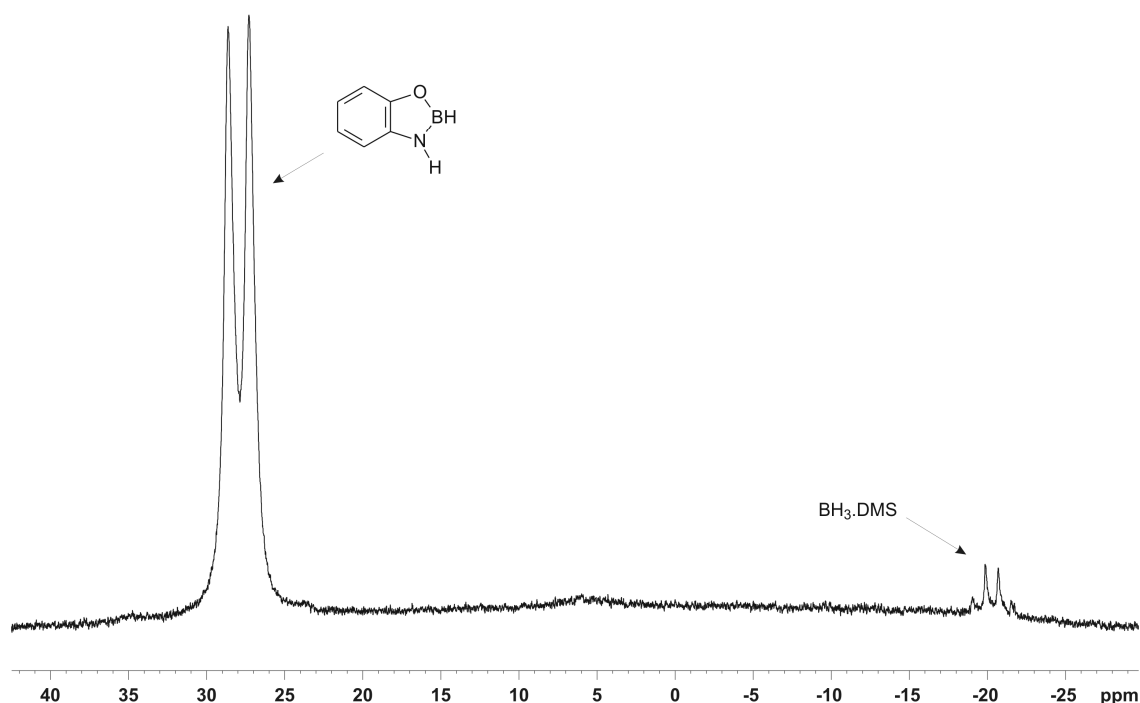


Figure 15.

#### 2.2.3.1. Stability observations

HBaph appears to be less stable than either HBPda or HBDan, as reactions where reflux conditions were employed in order to shorten the lengthy reaction times resulted in the increased appearance of a singlet in the  $^{11}\text{B}$  NMR spectrum at 23 ppm, along with those peaks corresponding to  $\text{BH}_3$  and HBaph (**Figure 16**). The

shift of this signal is consistent with those observed for the disproportionation products formed in the catechol-BH<sub>3</sub> reaction (22 ppm), and it is therefore possible that this new signal is due to the formation of a disproportionation-type product, either similar in structure to that observed for HBCat, or to the tri-boro cyclic product (**Figure 17**), described by Brotherton and Steinberg.<sup>130</sup> In contrast to HBCat, where large amounts of the disproportionation product are formed, even at low temperatures, there is a significantly smaller amount of this disproportionation product formed. This would suggest that the connection of one nitrogen atom to the boron atom reduces the tendency of the compound to undergo a disproportionation type reaction as is found for HBCat.

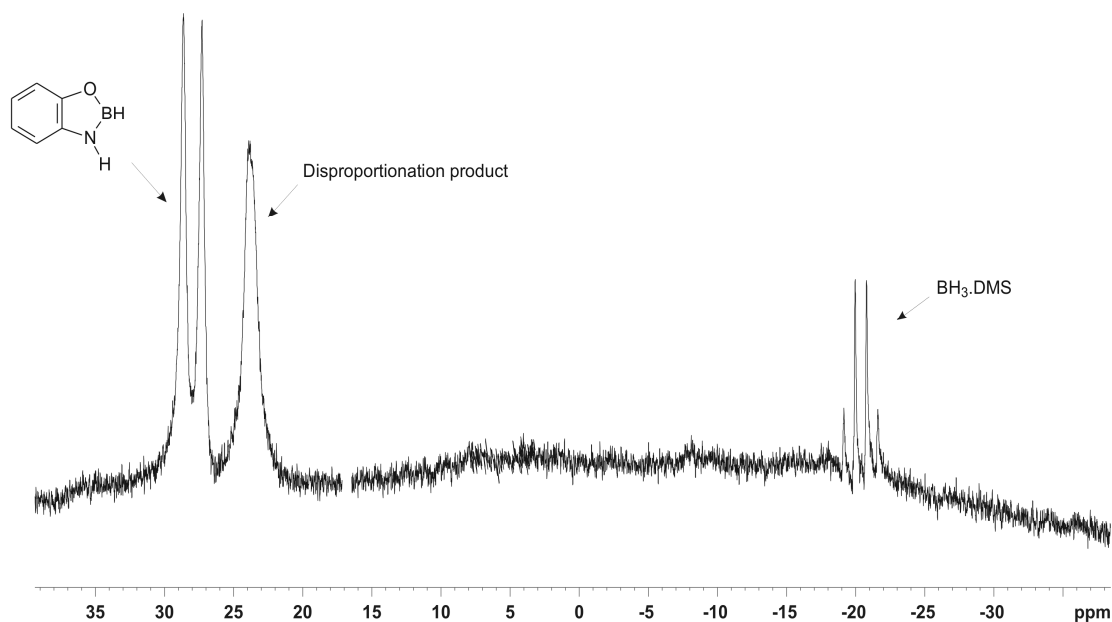


Figure 16.

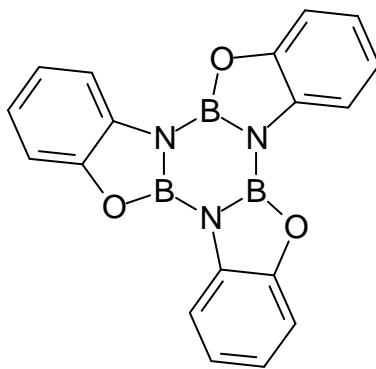


Figure 17.

HBaph does appear to be more stable than HBCat, as the synthesis of this compound can be carried out at room temperature without the formation of significant amounts of the disproportionation product, typically less than 5-10%. The drawback to this room temperature reaction is that the reaction requires 72 hours to go to completion.

### **2.2.3.2. <sup>15</sup>N NMR Observations**

As unusual results were obtained for the <sup>15</sup>N chemical shifts for HBPda and HBDan. HBaph was subjected to <sup>15</sup>N-<sup>1</sup>H correlation studies in an attempt to determine whether the downfield shift in the signal as compared to the starting material is also observed. Unfortunately, the <sup>15</sup>N-<sup>1</sup>H HSQC and HMBC experiments which had worked so well for HBPda and HBDan did not show the presence of any nitrogen signals at all. This could be due to the lowered concentration of the amine in the sample, as there is only one amine and one amine proton per molecule, whereas the diamine compounds contain two amines and two amine protons per molecule. As such, an INEPT (Insensitive Nuclei Enhanced by Polarization Transfer) experiment was run instead, as this was the next best choice for observing <sup>15</sup>N signals. The results of this experiment (**Figure 18**) show that the downfield shift has again occurred, with a signal observed at 111 ppm (**Figure 19**).

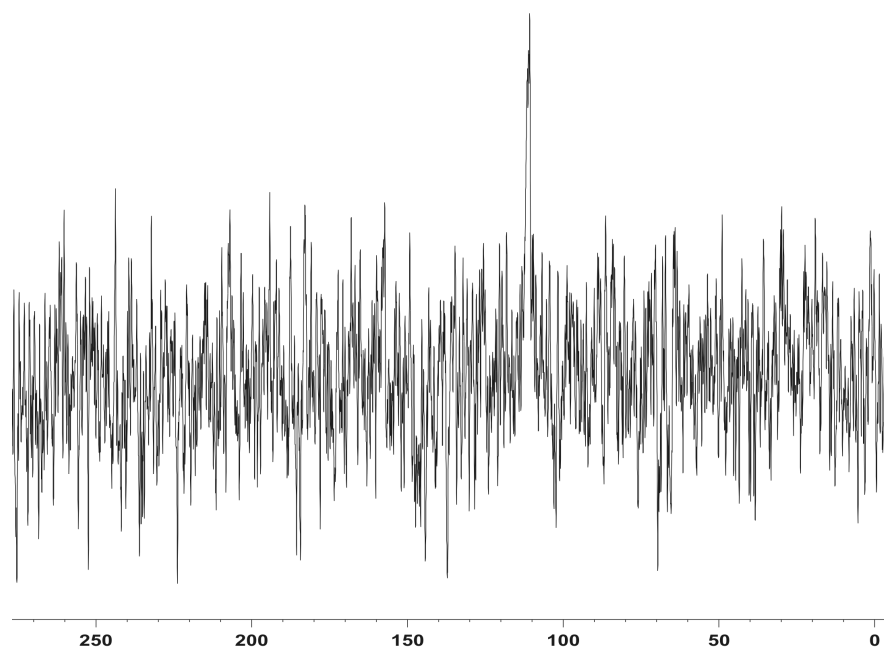


Figure 18

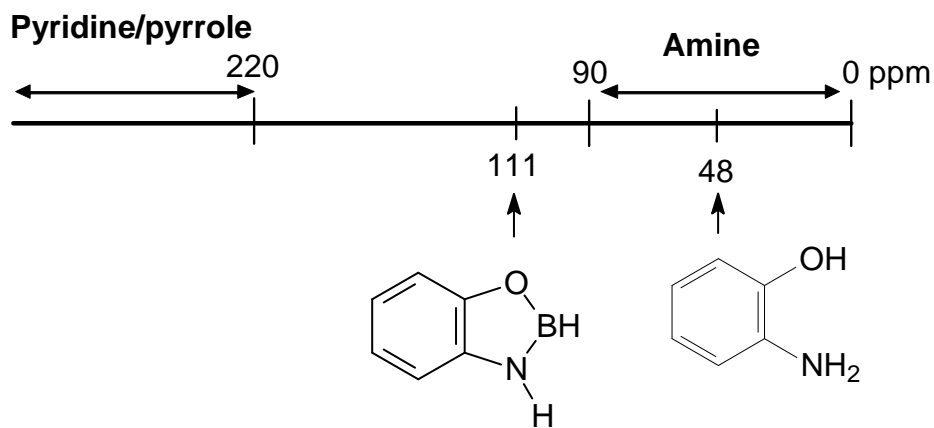
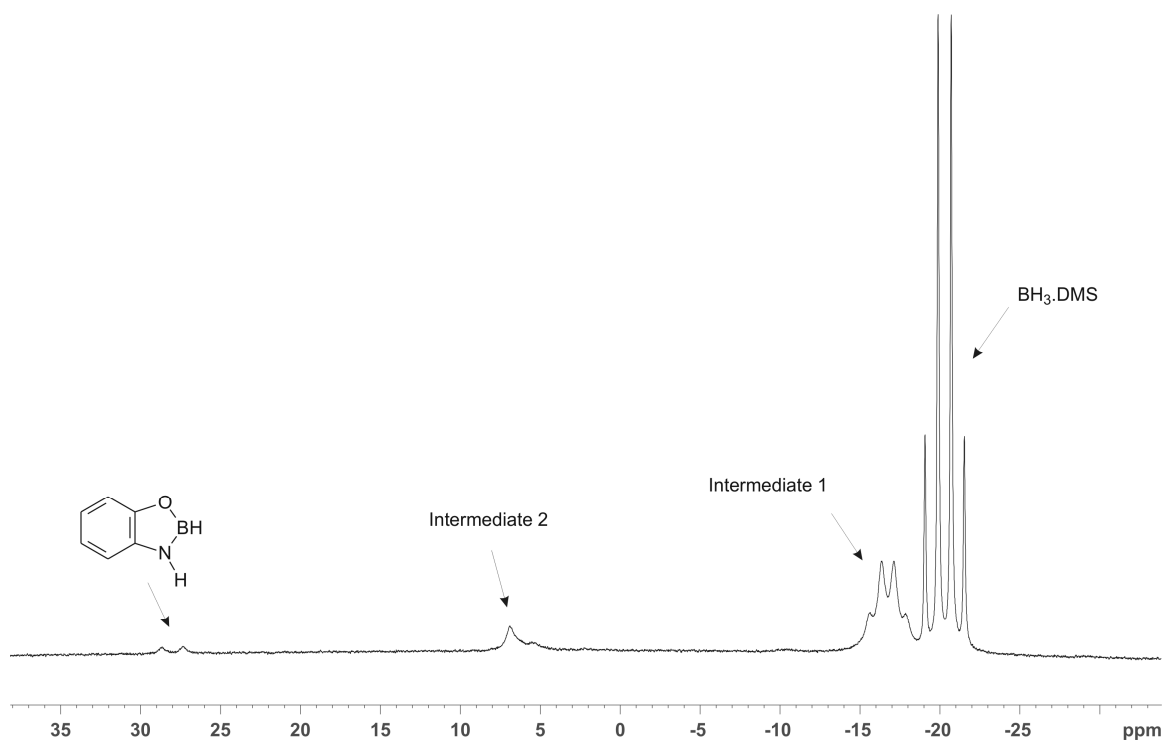


Figure 19.

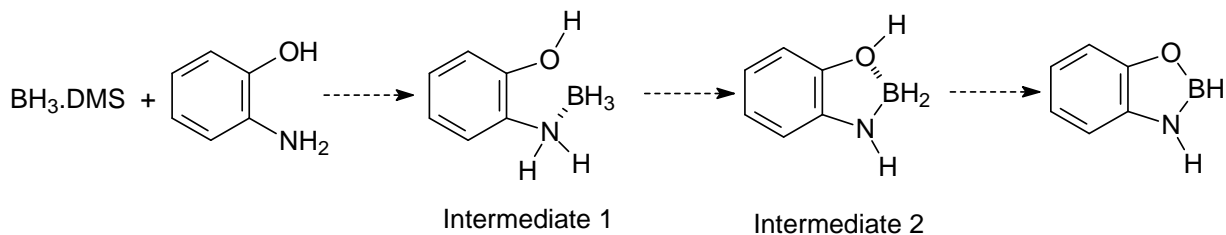
### 2.2.3.3. $^{11}\text{B}$ NMR Results and Mechanistic Implications

Due to the extended timescale of this reaction, the reaction solution was sampled in order to ascertain the extent of the reaction using  $^{11}\text{B}$  NMR spectroscopy. Interestingly, a number of the spectra showed similar features to those observed for

HBDan (**Figure 20**). Common to both HBDan and HBaph is the presence of a quartet at -17 ppm, and if the same hypothetical reaction mechanism applies to the formation of HBaph, then this signal is most likely due to the displacement of DMS by the nitrogen lone pairs, (**Scheme 7**) rather than the formation of an oxygen-boron bond. Although the triplet found at -10 ppm in the HBDan spectrum is not observed, a new signal is observed at 7 ppm, which may correspond to the second intermediate. The formation of the boron-nitrogen bond prior to the formation of a boron-oxygen bond is supported by the shifts of the second quartet and the new signal, as the vast majority of boron-oxygen bonds result in the appearance of a signal in the  $^{11}\text{B}$  NMR spectrum in the 0 to 20 ppm range. Literature offered no explanation as to why the boron-nitrogen bond would be formed before the formation of the boron-oxygen bond, and this remains an unsolved mystery



*Figure 20.*



*Scheme 7.*

These observations lend support to the step-wise mechanism proposed for HBDan, however, this does not provide conclusive proof, and further investigation and research is required.

### 2.3. Rhodium-Catalyzed Hydroboration Reactions

HBPda and HBDan are known to be unreactive towards alkyl reagents unless the reaction is catalyzed by a rhodium-based catalyst, or rarely an iridium-based catalyst.<sup>131b</sup> As such, no uncatalyzed reactions were carried out as this would have proven to be a waste of time and resources. The lack of reactivity of these compounds without the presence of an active catalyst was however confirmed as the result of other reactions where the catalysts were later shown to be destroyed, as no products were observed to have formed, even when the samples were allowed to stand for six weeks. It was hoped that HBaph would prove to be reactive enough to hydroborate alkyls without the need for a catalyst, however this was not the case, even after 48 hours at reflux.

In an effort to better understand the reactivities of HBPda, HBDan and HBaph, two rhodium(I) catalysts, namely Wilkinson's Catalyst ( $\text{Rh}(\text{PPh}_3)_3\text{Cl}$ ) **18** and tris(triphenylphosphine)rhodium(I) carbonyl hydride ( $\text{Rh}(\text{PPh}_3)_3(\text{CO})\text{H}$ ) **41** (**Figure 21**) were chosen for a study into the use of these compounds as hydroboration reagents. Wilkinson's catalyst is known to catalyze reactions between HBPda and 1-octene, amongst others, while the use of the rhodium carbonyl hydride catalyst in these hydroboration reactions has not been reported. As hydroboration reactions are known to be highly regioselective, with the almost exclusive formation

of the anti-Markovnikov product, it was hoped that the use of the rhodium carbonyl hydride catalyst would provide a means to access the alternate Markovnikov product. It was also hoped that this alternative catalyst would enable the hydroboration of internal alkenes, as these reactions have proven to be very low yielding when Wilkinson's catalyst is used.

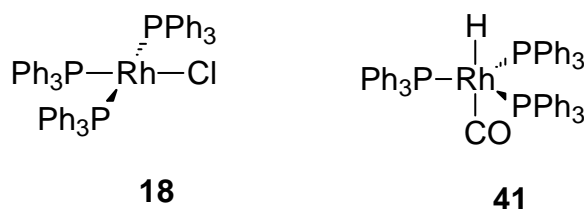


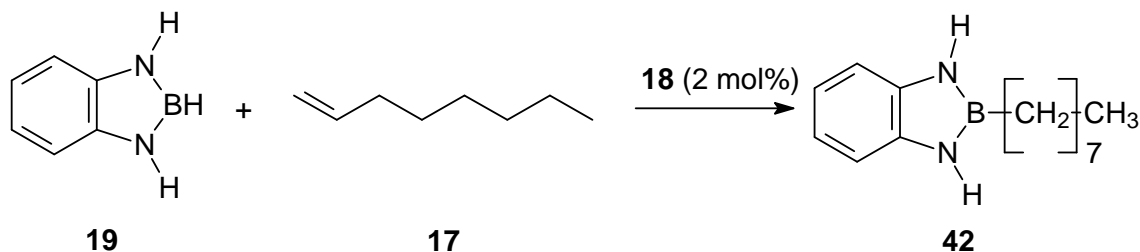
Figure 21.

Should **41** prove to have catalytic ability in hydroboration reactions, one of the drawbacks to more widespread use is the cost associated with this compound – it is approximately twice the price of the Wilkinson's catalyst, with 1g of **41** retailing at approximately R1600 per gram, whereas **18** retails at R811 per gram. A second drawback to the use of this catalyst is its air sensitivity.

### 2.3.1. Reactions Catalyzed by Wilkinson's Catalyst - $\text{RhCl}(\text{PPh}_3)_3$

In 2006, Hadebe published an article wherein Wilkinson's catalyst was shown to successfully catalyze the reaction between 1-octene **17** and HBPda **19** to yield 2-octyl-1,3,2-benzodiazaborolane **42** (**Scheme 8**), a reaction reported to have a yield of 70% when a catalyst loading of 2 mol%, based on a 10x excess of olefin, was employed. Attempts to emulate these yields under the conditions given in literature failed to give the yields noted, even when the reaction was allowed to continue at reflux for 48 hours. Hadebe<sup>136</sup> and others<sup>55</sup> had previously noted an enhancement in the catalytic activity of **18** after oxidation of the catalyst, accomplished either by treatment with hydrogen peroxide or by bubbling oxygen through a solution of the catalyst in a solvent such as  $\text{CH}_2\text{Cl}_2$ . A crystal structure of a dinuclear rhodium complex (Figure 22) obtained by Bennett and Donaldson from a concentrated,

oxygen-saturated solution of Wilkinson's catalyst is thought to correspond to the activated catalyst.<sup>137</sup>



Scheme 8.

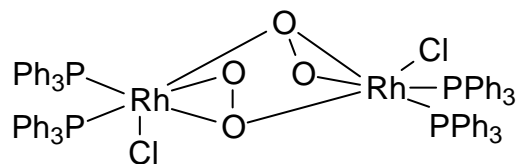


Figure 22.

Due to the initial lack of success with the unoxidized catalyst, the oxygen-treatment approach was attempted a number of times in reactions of HBPda with 1-octene. The results, disappointingly, contradicted these findings, as the reaction did not proceed at the rate reported in the literature. In an effort to understand the reasons for this failure, a <sup>31</sup>P-<sup>1</sup>H} NMR analysis was carried out on the oxidized catalyst in solution prior to addition to a reaction vessel containing HBPda and 1-octene. The results of this experiment (**Figure 23**) showed the presence of a large amount of triphenylphosphine-oxide [(Ph)<sub>3</sub>PO] in the solution, and very little evidence of coupling between the phosphorus atom and the rhodium center, as shown by the small doublet at 32 ppm. A <sup>31</sup>P-<sup>1</sup>H} NMR analysis of unoxidized **18** (**Figure 24**) conversely does not show the large triphenylphosphine-oxide peak, indicating that it is a result of the oxidation and decomposition of **18**. This result was consistent with other <sup>31</sup>P-<sup>1</sup>H} NMR analyses carried out on reaction samples containing the oxidized Wilkinson's catalyst.

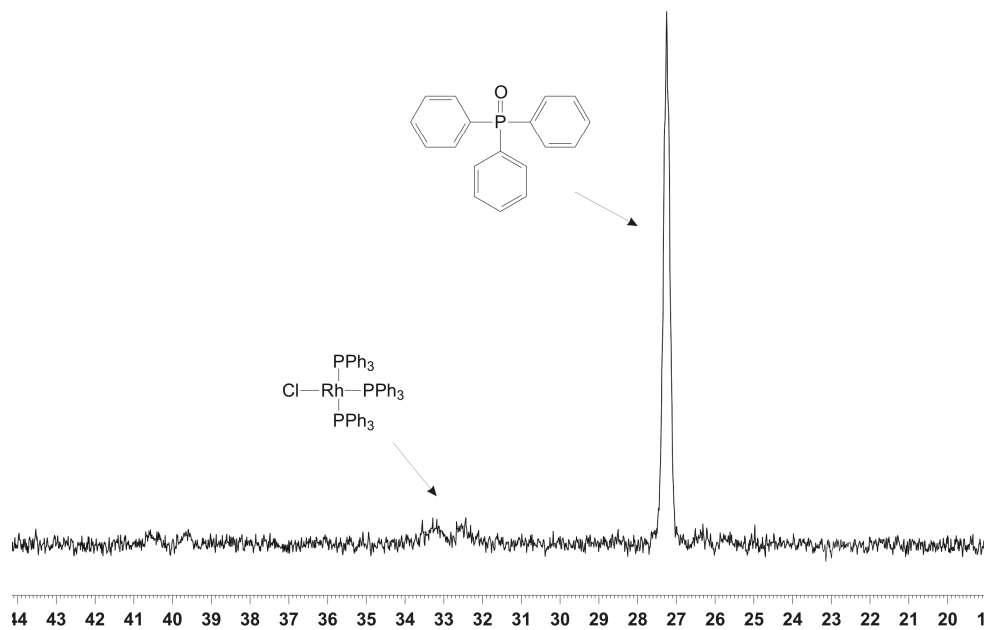


Figure 23.

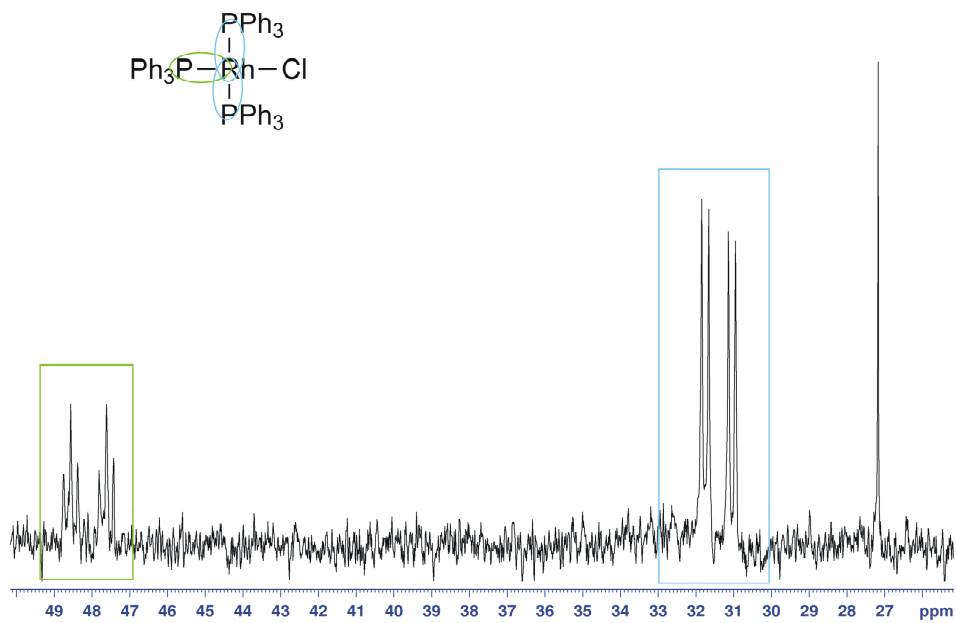
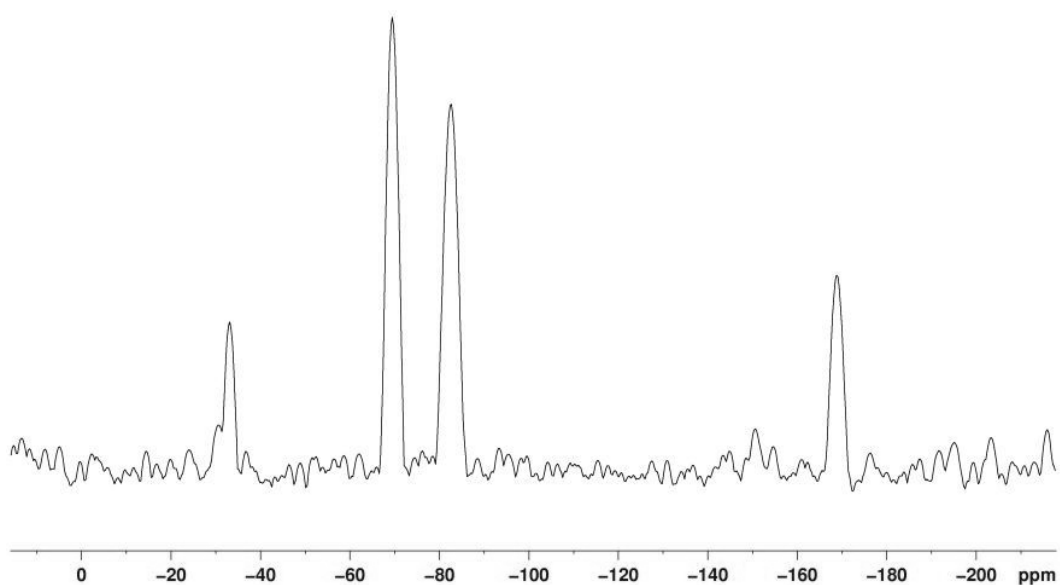


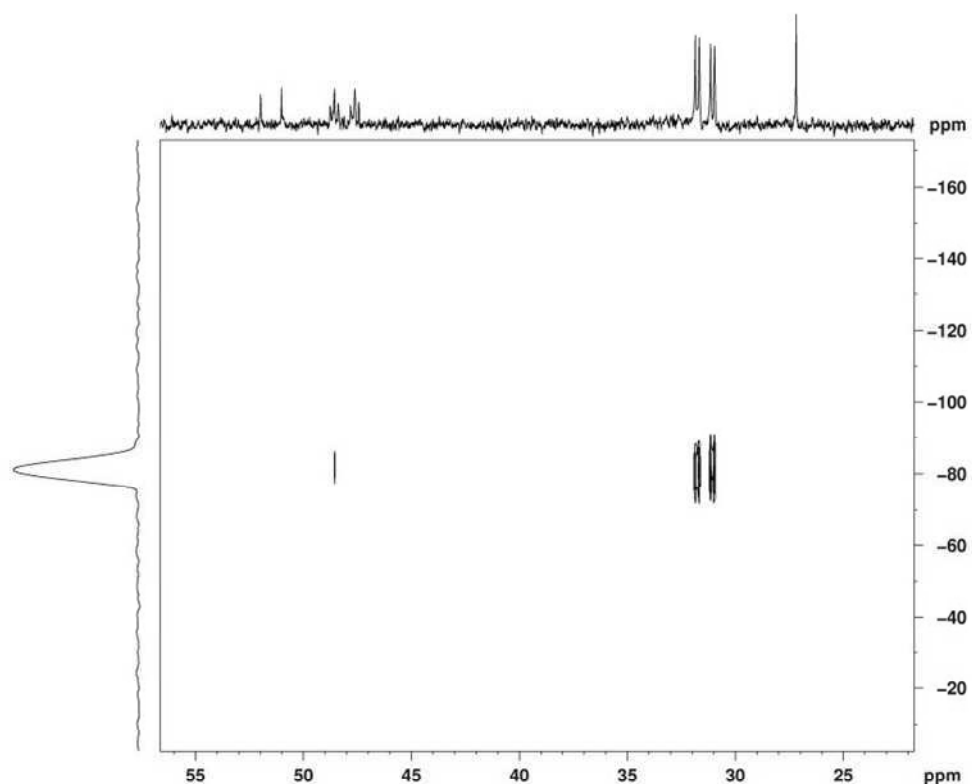
Figure 24.

Similar results are obtained when the rhodium-phosphorous bond is examined directly using a  $^{103}\text{Rh}$ - $^{31}\text{P}$  HMQC NMR analysis. The oxidized catalyst does not show

any coupling between the rhodium and the phosphorus, and further degradation of the rhodium results in the appearance of multiple rhodium species, (**Figure 25**) whereas the unoxidized catalyst shows coupling between the two atoms (**Figure 26**). This destruction of the catalyst may be the reason for the poor results obtained in this study, however as the same procedures were followed as laid out in literature, this does not account for the enhanced activity reported in those studies.

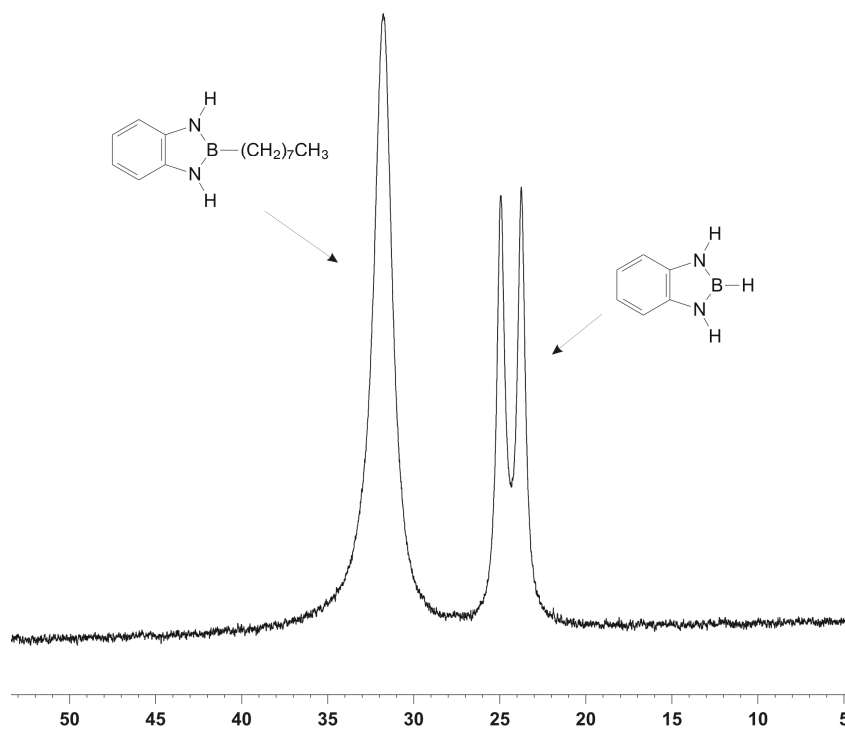


*Figure 25.*



*Figure 26.*

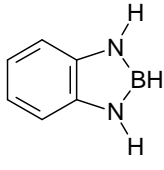
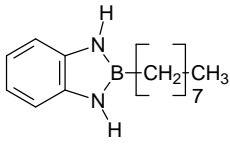
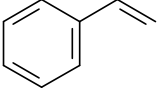
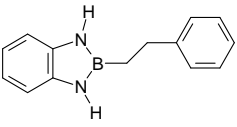
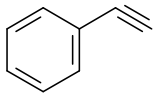
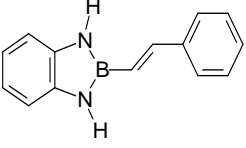
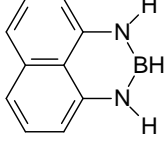
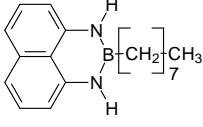
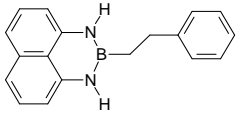
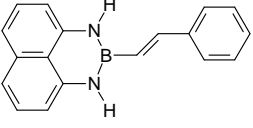
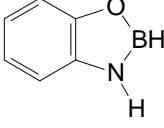
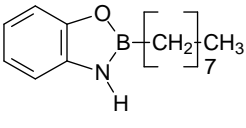
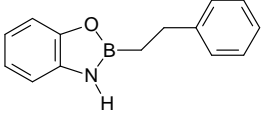
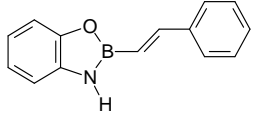
After the disappointing results obtained with both the oxidized and unoxidized catalysts, the experimental method was scrutinized for possible improvements. A search of the literature yielded a number of alternative methods that could be tested. When the catalyst loading was increased from 2 mol% to 10 mol%, the ratio of borane to alkyl was increased from a 1:1 ratio to 1:10, and microwave irradiation employed in place of reflux conditions, the test reaction of HBPda and 1-octene afforded **42** in a yield of 63% in 20 minutes at 100W (**Figure 27**).



*Figure 27.*

The conditions established for the PdaBH-octene reaction were then employed for the reactions of HBPda, HBDan and HBaph with one of three alkyl reagents, with the time of microwave irradiation extended to one hour (**Table 1**).

Table 1

Entry	Borane	Alkyl	Product	% Conversion (NMR Yield)
1	 <b>19</b>	<b>17</b>	 <b>42</b>	85
2	<b>19</b>	 <b>43</b>	 <b>44</b>	21
3	<b>19</b>	 <b>45</b>	 <b>46</b>	4
4	 <b>21</b>	<b>17</b>	 <b>47</b>	10
5	<b>21</b>	<b>43</b>	 <b>48</b>	4
6	<b>21</b>	<b>45</b>	 <b>49</b>	62
7	 <b>40</b>	<b>17</b>	 <b>50</b>	18 <sup>a</sup>
8	<b>40</b>	<b>43</b>	 <b>51</b>	32
9	<b>40</b>	<b>45</b>	 <b>52</b>	25 <sup>a</sup>

Reaction conditions: Borane in CH<sub>2</sub>Cl<sub>2</sub> (2.10 × 10<sup>-4</sup> mol, 1ml) olefin (2.10 × 10<sup>-3</sup> mol, 10 eq), RhCl(PPh<sub>3</sub>)<sub>3</sub> (2.10 × 10<sup>-5</sup> mol, 10 mol%), μW 150 °C, 100W, 60min. <sup>a</sup> Reaction time 30 minutes

The results obtained for these reactions range from very poor yields to yields in excess of 80%, as detected by  $^{11}\text{B}$  NMR analysis of the reaction mixture. This is in parallel with observations made by Evans *et al.* on the substrate-dependent nature of the rhodium-catalyzed hydroboration reaction.<sup>138</sup> Isolation of the products from the reaction mixture proved extremely problematic, despite a number of methods being attempted, as these compounds are unstable and do not survive the isolation process.

The yield obtained for the reaction of HBPda and 1-octene is in accordance with literature yields, however the lack of coupling between **43** and HBPda (**Table 1**, entry 2) is worrisome as this reaction is known to proceed well under thermal conditions, (80% after 60 hours) and it was assumed that this reaction should work under the microwave conditions employed. This reaction was repeated with styrene which had been freshly distilled in order to remove the stabilizing agent; however the yields did not improve. The reason for this lack of reactivity is still unknown, as investigations into the purity of all of the reagents and the catalyst did not put forward any possibly impure compounds. It is possible that this particular reaction is not suited to the microwave conditions employed, and that the addition of microwave irradiation results in the polymerization of the styrene.

Interestingly, the results obtained for the coupling reaction between HBDan and phenylacetylene (**Table 1**, entry 6) is significantly higher than the 5% yield reported by Iwate and Suginome in their report on the use of HBDan as a protecting group.<sup>131a</sup> This is most likely due to the differences in reaction methodology – Iwate and Suginome carried out reactions at room temperature, in contrast to the microwave reaction methodology carried out in this report.

As expected, HBaph proved more reactive than either HBPda or HBDan, but regrettably the major products in the reactions of HBaph with 1-octene, styrene and phenylacetylene were not the desired product. Rather, the disproportionation

product was produced rapidly in high yields, along with some of the desired product. **(Figure 28)** In the reactions to form compounds **50** and **52**, (**Table 1**, entries 7 and 9), the reaction was essentially complete after 30 minutes, with no starting material present in the  $^{11}\text{B}$  NMR spectra. Although the reaction to form **51** (**Table 1**, entry 8) was irradiated for the full hour, similar results are obtained – the reaction is low-yielding but complete, with no starting borane observed in the spectra. These results are disappointing, although not completely unsurprising, as the disproportionation reaction of HBCat is known to be catalyzed by triphenylphosphine as well as a number of metals<sup>139</sup> and this may also be the case for HBaph.

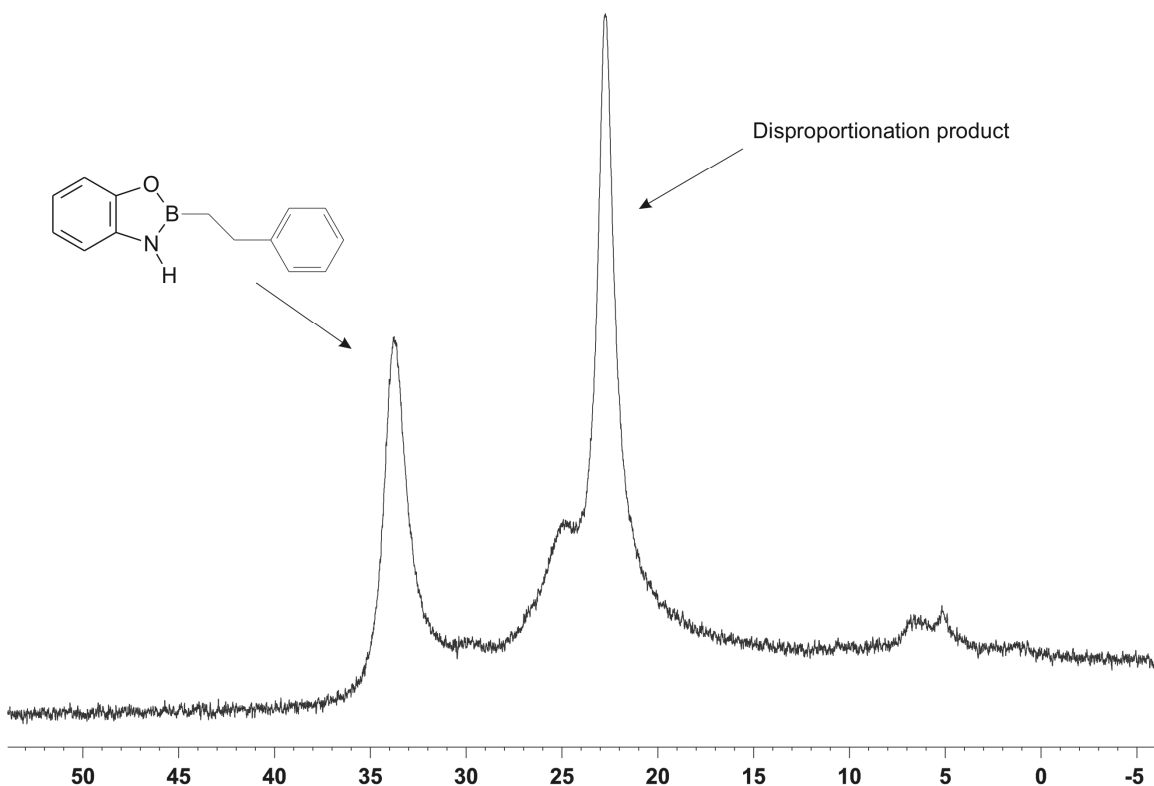


Figure 28

### **2.3.2. Reactions Catalyzed by Tris(triphenylphosphine)rhodium(I) Carbonyl Hydride - $\text{Rh}(\text{PPh}_3)_3(\text{CO})\text{H}$**

Tris(triphenylphosphine)rhodium(I) carbonyl hydride  $\text{Rh}(\text{PPh}_3)_3(\text{CO})\text{H}$  **41** is not a catalyst commonly used in hydroboration-type reactions; rather it is more frequently used as a catalyst in ring-opening isomerization reactions of methylenecyclopropanes to 1,3-dienes.<sup>140</sup> As the reactions where **18** was being used as the catalyst were proving to be initially unsuccessful, **41** was employed in order to determine whether it showed any catalytic activity in hydroboration reactions.

One disadvantage that arises when this catalyst is used is that the catalyst itself is intensely air-sensitive, and rapidly degrades on exposure to air. Thus the preparation of reactions is complicated somewhat by the need to maintain an oxygen-free environment when handling the catalyst, a precaution not necessarily required for dealing with Wilkinson's catalyst, as it is less air sensitive. However, as all reactions were carried out so as to exclude oxygen and moisture as much as possible, this did not pose a significant challenge.

The conditions established for the reactions catalyzed by Wilkinson's catalyst were employed for the reactions using the rhodium-hydride catalyst, and the results obtained again range from low to almost quantitative yields (**Table 2**).

Table 2.

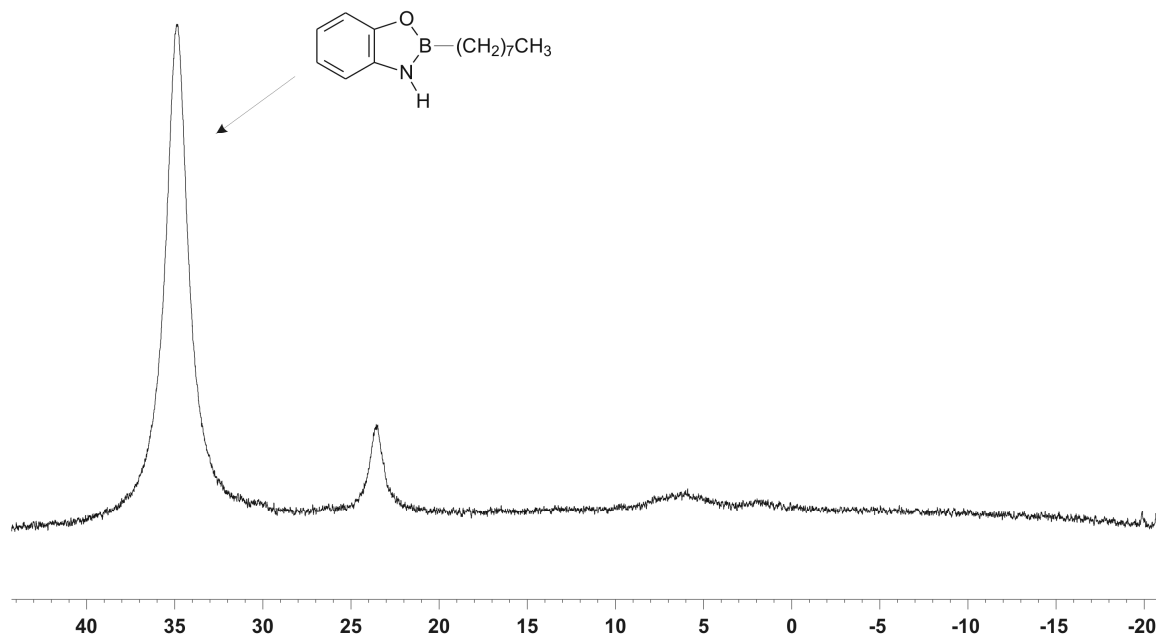
<b>Entry</b>	<b>Borane</b>	<b>Alkyl</b>	<b>Product</b>	<b>% Conversion</b>
1	<b>19</b>	<b>17</b>	<b>42</b>	89
2	<b>19</b>	<b>43</b>	<b>44</b>	20
3	<b>19</b>	<b>45</b>	<b>46</b>	64
4	<b>21</b>	<b>17</b>	<b>47</b>	92
5	<b>21</b>	<b>43</b>	<b>48</b>	34
6	<b>21</b>	<b>45</b>	<b>49</b>	75
7	<b>40</b>	<b>17</b>	<b>50</b>	81 <sup>a</sup>
8	<b>40</b>	<b>43</b>	<b>51</b>	91 <sup>a</sup>
9	<b>40</b>	<b>45</b>	<b>52</b>	80 <sup>a</sup>

Reaction conditions: borane in CH<sub>2</sub>Cl<sub>2</sub> (2.10 x10<sup>-4</sup> mol, 1ml) olefin (2.10 x10<sup>-3</sup> mol, 10 eq), Rh(PPh<sub>3</sub>)<sub>3</sub>(CO)H (2.10 x10<sup>-5</sup> mol, 10 mol%),  $\mu$ w 150 °C, 100W, 60min <sup>a</sup> No microwave irradiation

This catalyst afforded a number of interesting results when compared to the reactions catalyzed by **18**. The reaction between HBPda and 1-octene **17** resulted in almost identical yields (**Table 1**, entry 1 and **Table 2**, entry 1), as did the reaction between HBPda and styrene **43**, while the yield obtained from the reaction of HBDan and 1-octene increased from 10% (**Table 1**, entry 4) to an astounding 89% (**Table 2**, entry 4). The reaction between HBDan and phenylacetylene **45** is also increased with the use of **41**, from a modest 64% yield (**Table 1**, entry 6) to a good yield of 75% (**Table 2**, entry 6), and this is also the case for the reactions between HBDan and **43**, where the yields are increased from 4% to 34% (**Table 1**, entry 5 and **Table 2**, entry 5). This enhanced catalytic activity is not restricted to HBDan, as a similar trend is observed in the reaction between HBPda and **45** (**Table 1**, entry 3 and **Table 2**, entry 3), where the use of **18** resulted in a disappointing yield of 4%, while a moderate yield of 64% is obtained with the use of **41** as the catalyst.

The most astounding results were obtained for the reactions of HBaph and the three alkyl reagents (**Table 3**, entries 7, 8 and 9). The reactions of HBaph and **17**

(**Figure 29**) and **43** (**Figure 30**) resulted in the quantitative conversion to the product within 10 minutes, without the application of any microwave irradiation or heat, and the reaction of HBAph and **44** was 80% complete at the same stage, (**Figure 31**) also without the use of microwave irradiation. The only disproportionation product observed in these reactions was due to its presence in the HBAph solution prior to the addition of the alkyl reagents or the catalysts. This is completely opposite behaviour to the results obtained when Wilkinson's catalyst was used, where the disproportionation product was the major product formed.



*Figure 29*

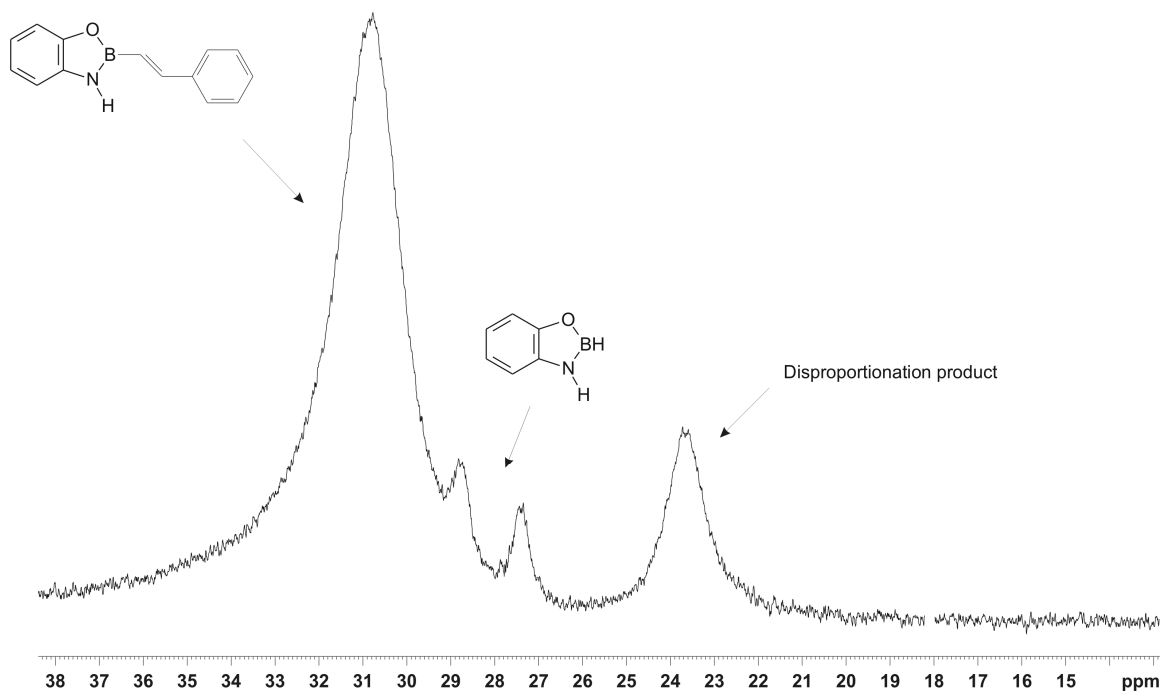


Figure 30

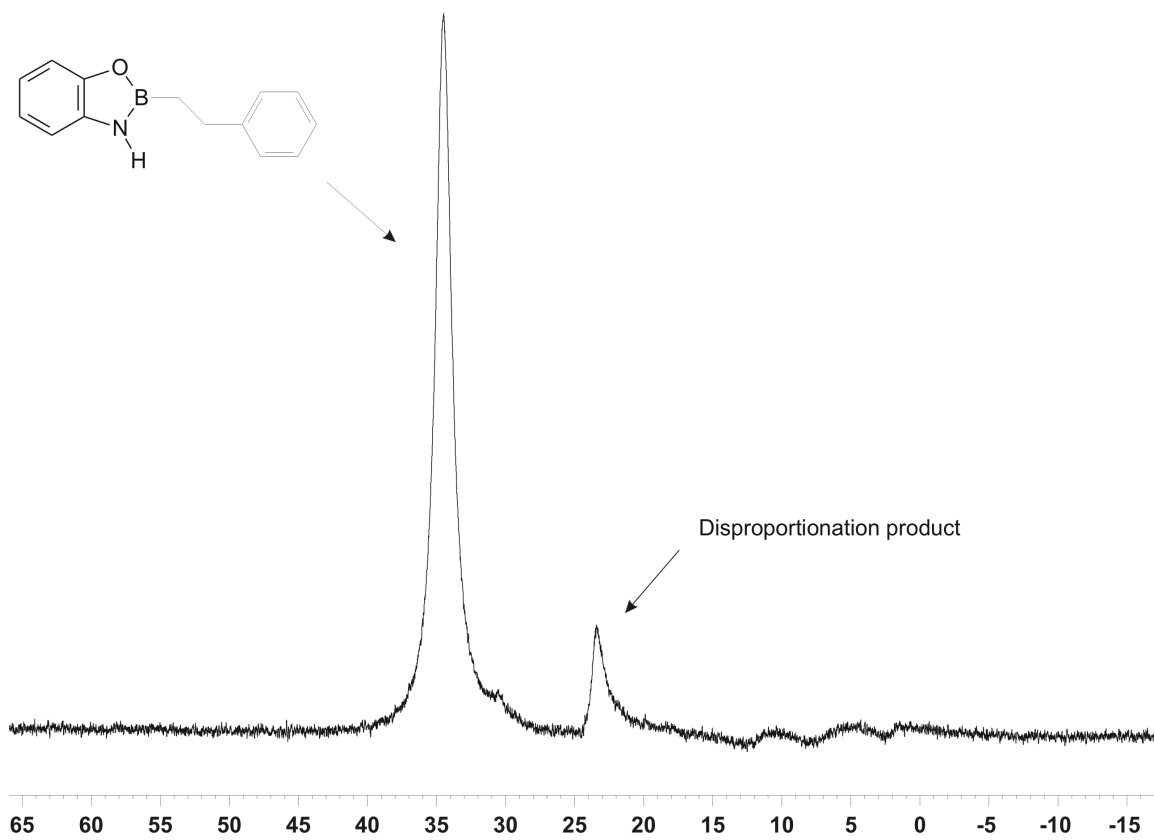


Figure 31

This variation in yields due to the use of **41** as oppose to **18** points to a mechanism that differs slightly to that proposed by Manning and Nöth for the hydroboration of alkenes using Wilkinson's catalyst.<sup>73</sup> The differences may simply be due to the different geometry around the rhodium atom, with the square planar Wilkinson's catalyst being slightly less reactive as compared to the trigonal bipyramidal rhodium hydride catalyst,<sup>140b</sup> an idea supported by Bennett and Donaldson, who reported that the activated catalyst contained trigonal bipyramidal geometry.<sup>137</sup> The reason for the altered reactivity may be more complex than simple geometry, as the presence of the hydride may play a role in the mechanism as one of the steps requires the insertion of a hydride to the multiple bond.

## **2.4. Conclusions**

In summary, three heterosubstituted boranes were successfully synthesized from the corresponding amines and  $\text{BH}_3\cdot\text{DMS}$  in high yields. These compounds were observed to be stable under  $\text{N}_2$  for a period of time, and two of the three boranes could be exposed to the atmosphere without serious degradation of the borane occurring.

$^{11}\text{B}$  NMR spectroscopy of the reaction mixtures indicated that the mechanism of the reaction to form these boranes contains two intermediates and supports a step-wise addition mechanism. *In situ*  $^{11}\text{B}$  NMR spectroscopy also confirmed that the reaction proceeds as expected based on the proposed mechanism with the intermediates disappearing over time with the corresponding formation of the product.

$^{15}\text{N}$  NMR spectroscopic analysis of the boranes identified a downfield shift in the location of the nitrogen signal from the starting material towards the aromatic region. This appears to support the current understanding of the enhanced stability of these boranes, which has been ascribed to the back-donation of electrons from the nitrogen lone pair to the boron atom's vacant  $p_z$ -orbital.

The three boranes proved to be suitable hydroboration reagents, with Wilkinson's catalyst and a rhodium carbonyl hydride catalyst both showing catalytic ability. However the yields of the reaction were observed to be dependant on the borane, the olefin and the catalyst used. Microwave irradiation was successfully engaged in the reactions; nonetheless the rhodium hydride-catalyzed reactions of the 2-aminophenol based borane and the olefins did not require microwave irradiation to effect almost quantitative yields of the desired product.

## **2.5. Recommendations for Future Work**

A number of questions have been raised during the course of these investigations, and in some cases the questions have not yet been answered.

The discovery of two intermediates in the formation of HBDan and HBaph has raised questions regarding the mechanism governing the otherwise apparently simple reaction. Low temperature Infrared studies could prove to be of use in determining other structural information regarding these intermediates, as this technique provides a significantly faster analysis of the reaction mixture than is possible with  $^{11}\text{B}$  NMR.

Once possible structures of the intermediates have been determined, computational modeling of the intermediates and the products could aid in the understanding of the mechanism of the reaction. Modeling may also provide information into the nature of the boron-nitrogen bond.

Answering the question of the mechanism for the formation of HBDan and other heterosubstituted boranes raises other questions, for example what are the kinetics of the reaction, what are the rate constants, and other activation parameters. A number of these questions could be answered by using *in situ*  $^{11}\text{B}$  NMR spectroscopic analysis to study the kinetics of the reaction, and the various parameters could be determined from the data collected.  $^{11}\text{B}$  NMR analysis is well

suited to these types of studies, as the atom of interest is probed directly, rather than deduction of data from adjacent atoms.

As the tris(triphenylphosphine)rhodium(I) carbonyl hydride catalyst shows a different reactivity from Wilkinson's catalyst as a catalyst for hydroboration reactions, a mechanistic study into the reasons for these differences is needed. As tris(triphenylphosphine)rhodium(I) carbonyl hydride is not typically used as a hydroboration catalyst, this is potentially a new application for this compound.

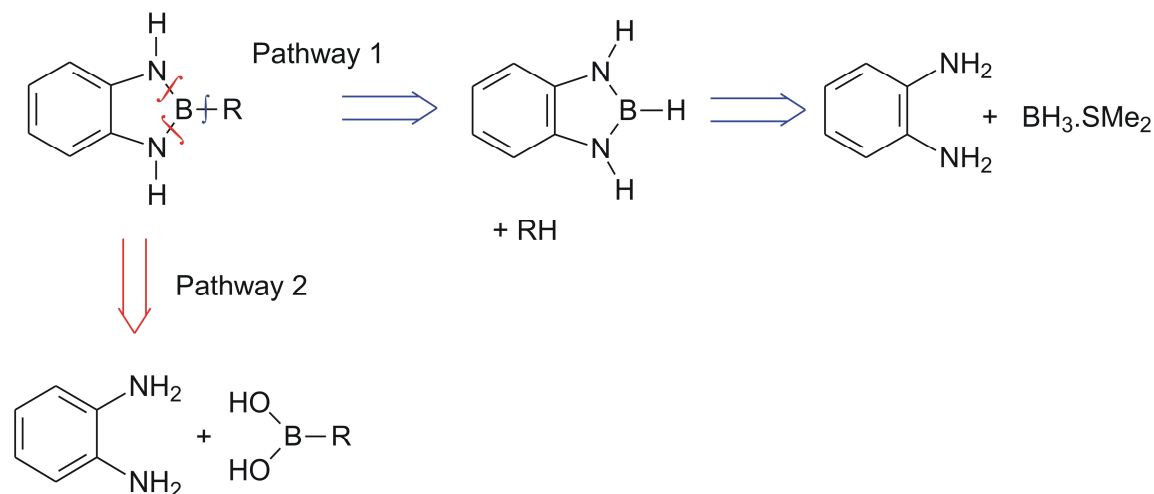
### ***3. Results and Discussion: Condensation Reactions of Diamines and Boronic Acids***

#### ***3.1. Study Objectives***

In this chapter the synthesis of heterosubstituted boranes by condensation reactions of diamines and boronic acids will be investigated as an alternative route to the synthesis reactions carried out in Chapter 2. The applicability of microwave-assisted solvent-free methodology to the synthesis of these compounds will be examined, as this could provide a faster, “greener” and more cost-effective synthetic route to these compounds, as well as removing the difficulties encountered with the air- and moisture-sensitive reagents used previously.

#### ***3.2. Condensation Reactions of 1,2-Phenylenediamine and Boronic Acids***

While the rhodium-catalyzed formation of heterosubstituted boranes is well known and widely used, the expense of the catalyst often reduces the desire of a chemist to use these types of reactions. A search of the literature yielded an alternative method of synthesis of these reagents, (**Scheme 1**) as opposed to the synthesis of the heterosubstituted boranes as described in Chapter 3. The first method (Pathway 1) involved the formation of the boron-heteroatom bond prior to the formation of the boron-carbon bond, while the second method (Pathway 2) relies on the formation of the boron-heteroatom bond after the synthesis of the boron-carbon bond. This cyclization reaction can be easily accomplished with simple 1,2-diamines or diols and boronic acids, with the liberation of 2 moles of H<sub>2</sub>O.



*Scheme 1*

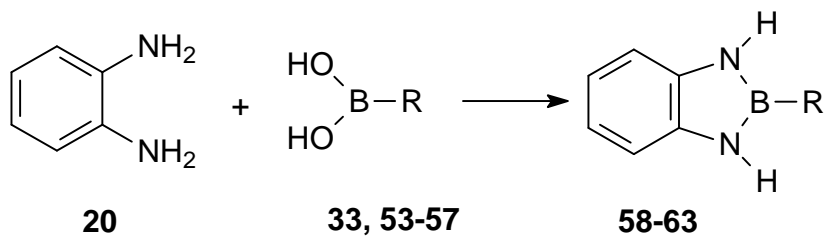
The major benefits to this second approach are that neither the starting materials nor the products are air-sensitive, and there is no longer a need for the rhodium catalyst. Another major benefit is that a large variety of boronic acids and a wide range of diamines or diols are available commercially, and the boronic acids can be synthesized in the laboratory as necessary. As such, there is an almost endless supply of possible organoborane reagents, and it is foreseeable that these reagents could be customized as needed with regard to reactivity and structure. While the use of heterosubstituted boranes as reagents in synthesis reactions is relatively limited at present, the synthesis of these reagents *via* a condensation reaction is more than half a century old. Sugihara and Bowman<sup>141</sup> and Pailer and Fenzl<sup>142</sup> reported the synthesis of both five- and six-membered heterocyclic organoboranes in the late 1950's and early 1960's from phenylboronic acid and a variety of diamines, diols and a few amino alcohols such as aminophenol, and even aminothiophenol was successfully used.

Many years later, the work carried out by these two research groups was used as the basis for the utilization of phenylboronic acid as a protecting group for a range of bi- or polyfunctional alcohols, amines, acids and thiols.<sup>129</sup> Phenylboronic acid was chosen as the protecting group as it is readily available, the protected products formed are generally crystalline, even with functionalized groups on the reagents

undergoing the protection, and the protecting group could be removed easily by heating in aqueous  $\text{NaHCO}_3$  for two hours.

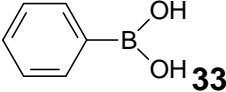
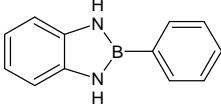
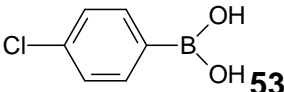
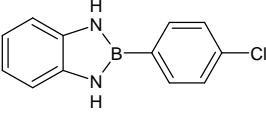
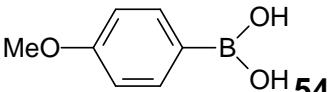
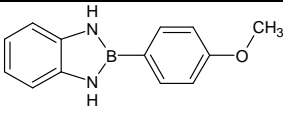
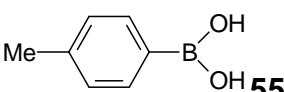
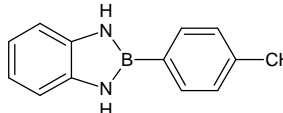
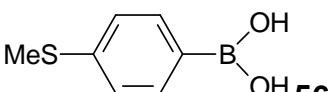
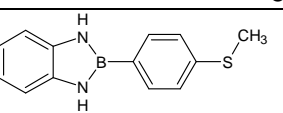
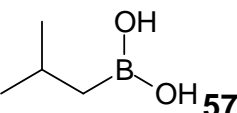
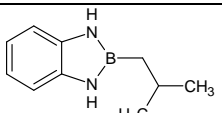
### 3.2.1. Reactions in Solution

The reaction of 1,2-phenylenediamine with a range of boronic acids (**Scheme 2**) containing electron-withdrawing and electron-donating substituents in toluene under Dean and Stark conditions proceeded with excellent yields in all cases, without the need for further purification (**Table 1**). The majority of the products (**53-62**) proved insoluble in cold toluene and simply precipitated out as the solution cooled. Compound **63** did not precipitate out of solution as observed with the other compounds; however removal of the solvent under reduced pressure resulted in a crystalline solid which yielded excellent NMR spectroscopic data for the crude solid (**Figure 1**), which did not show significant contamination with either of the starting materials.



*Scheme 2*

Table 1

Entry	Amine	Boronic Acid	Product	Isolated Yield <sup>a</sup>
1	20	 <b>33</b>	 <b>58</b>	95
2	20	 <b>53</b>	 <b>59</b>	97
3	20	 <b>54</b>	 <b>60</b>	94
4	20	 <b>55</b>	 <b>61</b>	89
5	20	 <b>56</b>	 <b>62</b>	95
6	20	 <b>57</b>	 <b>63</b>	90

<sup>a</sup> Reaction conditions: **20** (2 mmol), boronic acid (2 mmol) Toluene (50 ml), 110 °C, 3 hours.

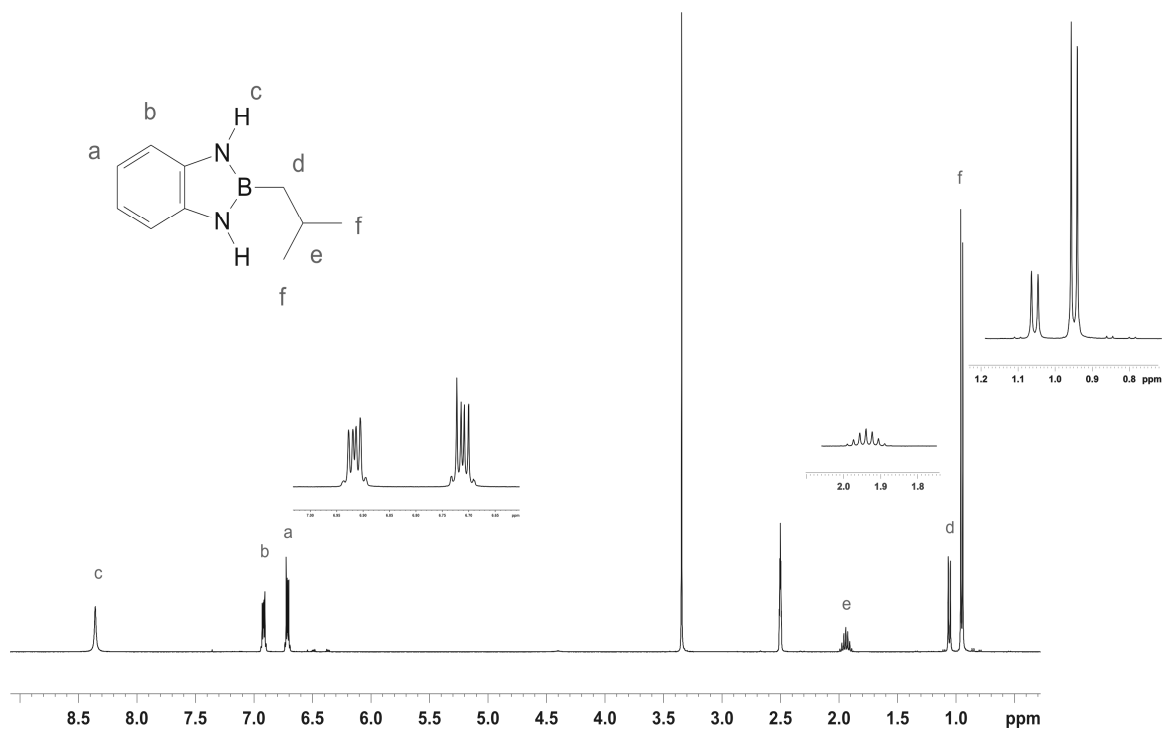


Figure 1

### 3.2.2. Microwave-assisted Solvent-free Reactions

Although the reaction of **20** and the boronic acids proceeded very well in solution, a solvent-free method was sought in an attempt to avoid the use of environmentally hazardous solvents.<sup>143</sup> Compound **53** had been successfully created in quantitative yields in both a ball mill and in a melt *in vacuo* in one hour,<sup>129</sup> and thus it was hoped that the application of microwave irradiation to the melt would shorten the reaction times needed for this reaction, and that this methodology would prove suitable for the other five boronic acids as well. Microwave irradiation has been widely used in recent times in an attempt to broaden the reach of “green” chemistry. As such, microwave irradiation has been employed in a wide variety of applications, from protection and deprotection reactions, condensation reactions and isomerization reactions, heterocyclic synthesis to treatment of industrial waste.<sup>144</sup>

Initial optimization reactions between **20** and **33** showed the reaction to be high on complete in 15 minutes at 150W and 150°C (87% conversion to **53**), and the yield

did not increase significantly when the reaction time was extended to 30 minutes. This methodology was then applied to all of the boronic acids, and very good to excellent yields were obtained. (Table 2)

Table 2

<b>Entry</b>	<b>Amine</b>	<b>Boronic Acid</b>	<b>Product</b>	<b>Isolated Yield</b>
<b>1</b>	<b>20</b>	<b>33</b>	<b>58</b>	87
<b>2</b>	<b>20</b>	<b>53</b>	<b>59</b>	92
<b>3</b>	<b>20</b>	<b>54</b>	<b>60</b>	88
<b>4</b>	<b>20</b>	<b>55</b>	<b>61</b>	82
<b>5</b>	<b>20</b>	<b>56</b>	<b>62</b>	87
<b>6</b>	<b>20</b>	<b>57</b>	<b>63</b>	70

Reaction conditions: **20** (0.4 mmol), boronic acid (0.4 mmol)  $\mu$ w 150 °C, 150 W, 15 min

The majority of the yields are comparable to those obtained for the reactions carried out in solution, with the only major difference appearing in the reaction between **20** and **57**. (Table 1, entry 6 and Table 2, entry 6) This is due to sublimation of **57** inside the microwave vessel, as this effectively prevented **57** from being incorporated into the reaction. These results clearly show that the use of microwave irradiation in a condensation reaction of **20** and the boronic acids is possible, and a significant reduction of the reaction time, from three hours to 15 minutes, can be realized. Perhaps most importantly, this method allows for the synthesis of the products without the need for an environmentally hazardous solvent.

### 3.2.3. $^{15}\text{N}$ NMR Results

Complete NMR spectroscopic analyses were carried out on compounds **58-63** including similar  $^{15}\text{N}$ - $^1\text{H}$  HMBC and HSQC analyses as carried out for HBPda, HBDan and HBaph. As was observed for these compounds, the  $^{15}\text{N}$  chemical shifts (**Table 3**) have been shifted downfield into the region between that for amines and pyridine-type compounds (**Figure 2**)

Table 3.

Product	$^{15}\text{N}$ NMR signal (ppm)
<b>58</b>	104
<b>59</b>	111
<b>60</b>	107
<b>61</b>	110
<b>62</b>	109
<b>63</b>	113

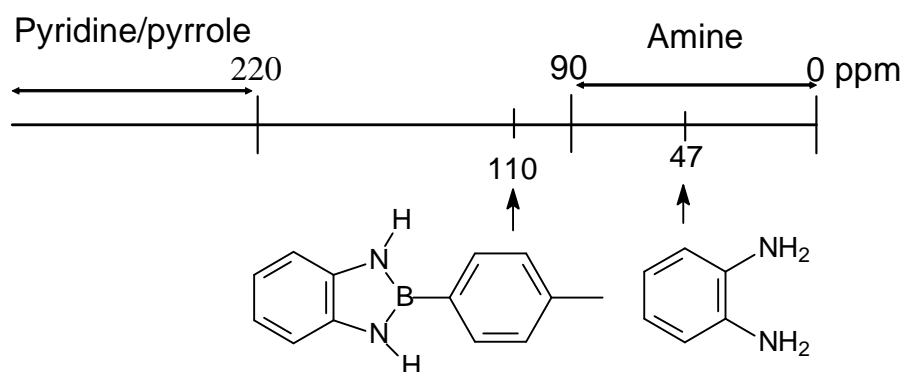


Figure 2. (Not to Scale)

While the chemical shifts appear very similar, it is interesting to note that the amine protons no longer appear to be chemically non-equivalent, as was observed in the  $^{15}\text{N}$ - $^1\text{H}$  NMR spectroscopic analysis of HBPda, as only one amine signal is noted in the  $^1\text{H}$  NMR spectra (**Figure 3**). This observation is in accordance with

crystal structures obtained by Weber *et al.* for structurally similar 1,3-diethyl-1,3,2-benzodiazaborolanes<sup>145</sup> (**Figure 4**), however a direct comparison between **58** and the compounds presented is made more difficult as the compounds published by Weber contain ethyl groups on the nitrogen atoms, whereas **58** does not. Whether these ethyl groups affect the electron distribution around the nitrogen-boron-nitrogen system is unclear, as DFT calculations carried out by Weber *et al.* on analogous methylated structures do not show any distortion of either the HOMO or the LUMO in these molecules.<sup>145</sup>

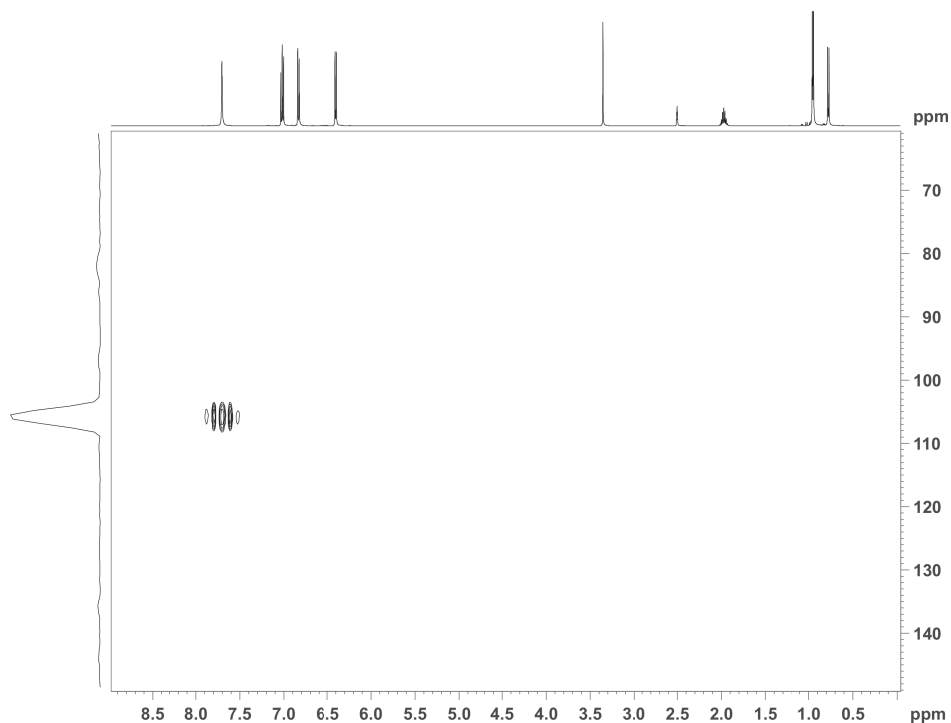


Figure 3

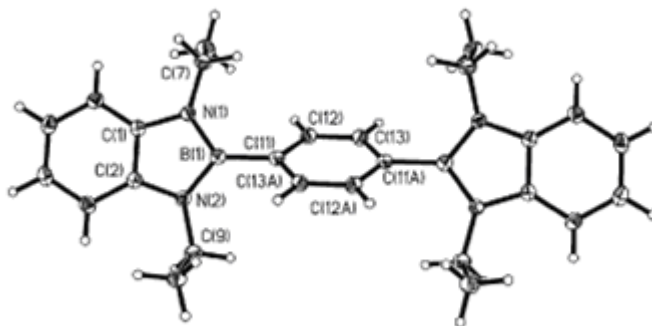
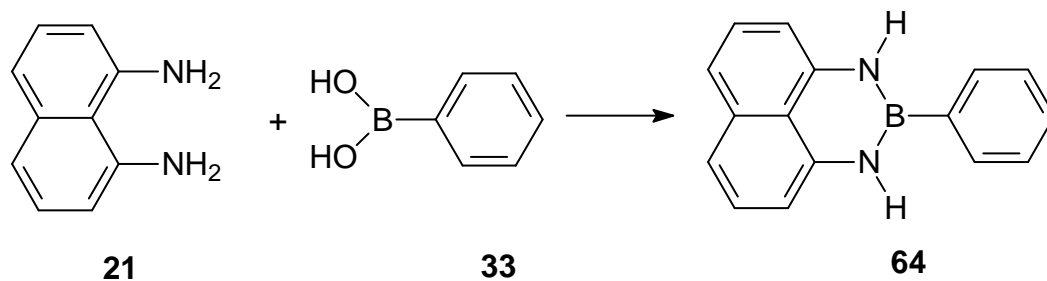


Figure 4

### 3.3. Condensation Reactions of 1,8-Diaminonaphthalene and Boronic Acids

One of the earliest reported syntheses for a 1,8-diaminonaphthalene-based borane is found in an article by Letsinger and Hamilton, published in 1958.<sup>146</sup> The identity of compound **64**, initially named 8-phenyl-8-bora-7,9-diazaro-*peri*-naphthene and synthesized by the reaction of 1,8-diaminonaphthalene **21** and phenylboronic acid **33** (**Scheme 3**), was called in to question by Caserio, Cavallo and Wagner, who reported a compound of the same name, which was the product of the reaction between 1,8-diaminonaphthalene and phenyldichloroborane in benzene solution.<sup>60</sup> The dispute arose due to an 18 °C difference in the reported melting points for the two supposedly identical compounds. However, as these reactions were carried out before the era of modern analytical techniques such as NMR and Mass Spectrometry, it is still unclear which of the two groups synthesized the correct compound, or whether the difference in the melting points reported was due to environmental differences or due to researcher error.

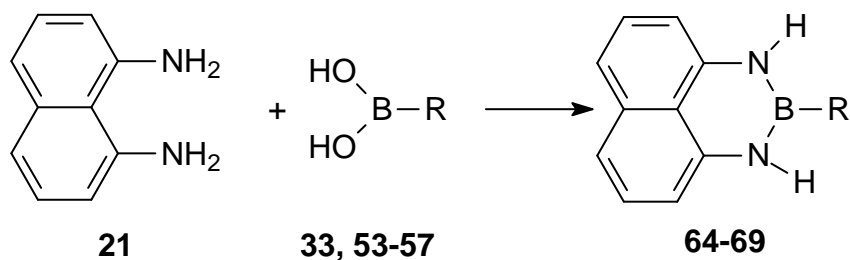


*Scheme 3.*

Protection of a number of diamines, including **21**, with **33** was attempted by Kaupp *et. al.* in 2003,<sup>129</sup> and while protection is possible, deprotection of the amines required the use of a strong acid or base. This is contrary to what is desired in a protection reaction, as the protecting group needs to be removed easily in order to make the reaction viable, and the harsh conditions required could alter the rest of the molecule in undesirable ways. The authors however did note the atypical stability of the protected naphthalene, and suggested that these compounds may be useful in electrophilic aromatic substitution reactions.

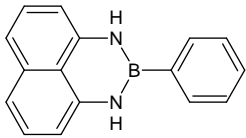
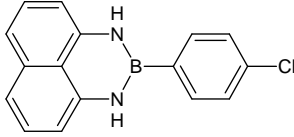
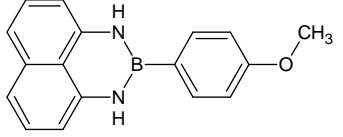
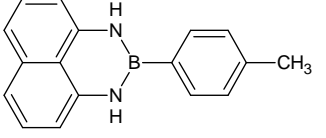
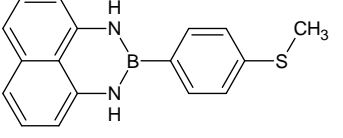
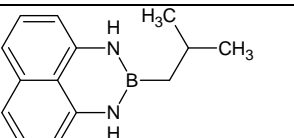
### 3.3.1. Reactions in Solution

Compounds **64-69** were successfully synthesized in very good yields from **21** and boronic acids **33** and **53-57** (**Scheme 4**) under the same conditions as used for the synthesis of compounds **58-63** (**Table 4**) These compounds did not show the same propensity to precipitate out of solution as readily as the phenylenediamine-based compounds, and therefore the solvent was removed under reduced pressure to yield dark purple solids in all cases. NMR analysis of these crude solids confirmed the formation of the desired product in high yields. Column chromatography on silica was used effectively to remove the impurity causing the discoloration, and clean samples of the products were obtained, unfortunately with a corresponding loss of the product.



*Scheme 4*

Table 4

Entry	Amine	Boronic Acid	Product	% Conversion <sup>a</sup>	Isolated Yield <sup>b</sup>
1	21	33	 <b>64</b>	85	77
2	21	53	 <b>65</b>	75	66
3	21	54	 <b>66</b>	80	73
4	21	55	 <b>67</b>	80	72
5	21	56	 <b>68</b>	76	65
6	21	57	 <b>69</b>	84	76

Reaction conditions: **21** (2 mmol), boronic acid (2 mmol) Toluene (50 ml), 110 °C, 3 hours. <sup>a</sup> % conversion determined by NMR analysis of the crude product. <sup>b</sup> Isolated yield after purification on silica, eluting with CH<sub>2</sub>Cl<sub>2</sub>

However, comparison of the NMR results obtained for the crude samples and the purified samples showed very little difference, as observed in the case of compound **65** (Figure 5), and it is possible that the discoloration is caused by a very small amount of a highly coloured impurity present in the amine (<5%). As such, the crude

product could logically be used in subsequent reactions without purification at this stage, with final purification occurring when the final product is isolated.

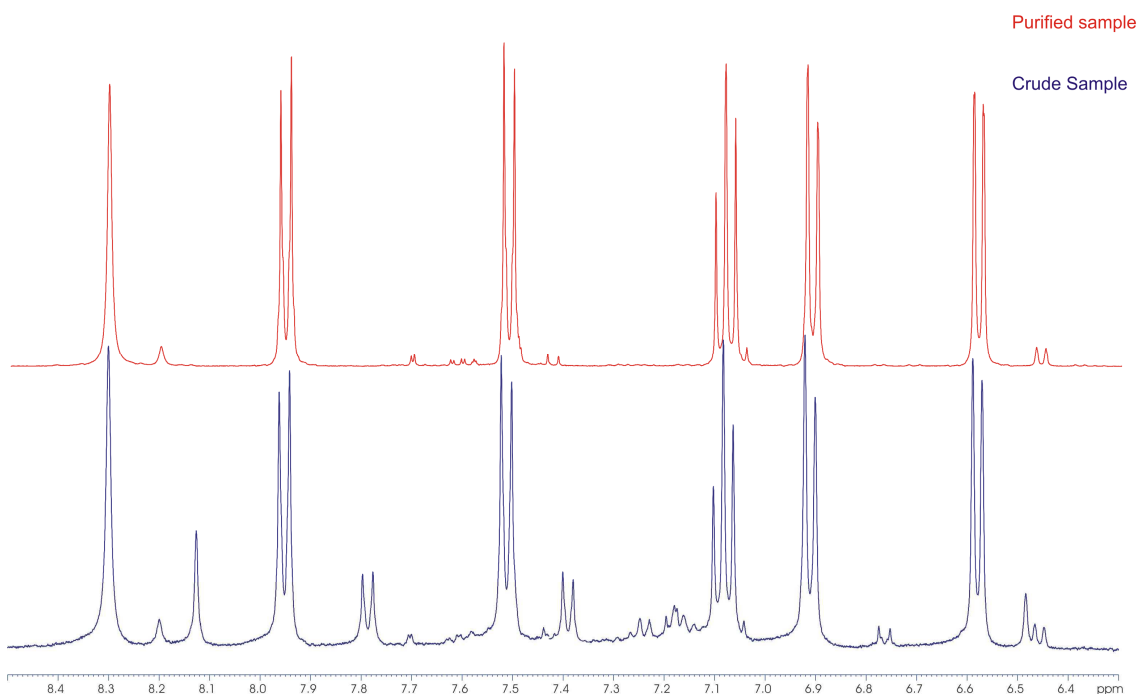


Figure 5

### 3.3.2. Microwave-assisted Solvent-free Reactions

As very good yields were obtained for the microwave assisted reactions of **20** and the various boronic acids, the same conditions were employed for the reactions of **21** with the boronic acids. As was the case for the reactions involving **20**, very good results were obtained in 15 minutes (**Table 5**). Again, NMR spectroscopic analysis was used to determine the percent conversion obtained in the reaction prior to chromatography of the compound on silica.

Table 5.

<b>Entry</b>	<b>Amine</b>	<b>Boronic Acid</b>	<b>Product</b>	<b>% Conversion<sup>a</sup></b>	<b>Isolated Yield<sup>b</sup></b>
<b>1</b>	<b>21</b>	<b>33</b>	<b>64</b>	90	82
<b>2</b>	<b>21</b>	<b>53</b>	<b>65</b>	88	78
<b>3</b>	<b>21</b>	<b>54</b>	<b>66</b>	95	88
<b>4</b>	<b>21</b>	<b>55</b>	<b>67</b>	76	68
<b>5</b>	<b>21</b>	<b>56</b>	<b>68</b>	80	71
<b>6</b>	<b>21</b>	<b>57</b>	<b>69</b>	75	69

Reaction conditions: **21** (0.4 mmol), boronic acid (0.4 mmol) 150 °C, 150 W, 15 min; <sup>a</sup> % conversion determined by NMR analysis of the crude product. <sup>b</sup> Isolated yield after purification on silica, eluting with CH<sub>2</sub>Cl<sub>2</sub>

Again these results show the applicability of microwave irradiation to the condensation reactions of **21** and the boronic acids. As was also the case for the reactions carried out in solution, the <sup>1</sup>H NMR spectra of the crude solids obtained shows a high degree of purity, with the dark purple colour due to some minor, highly coloured impurity.

### 3.3.3. <sup>15</sup>N NMR Results

Based on the <sup>15</sup>N NMR results obtained for HBDan and in light of the observations made for compounds **58-63**, compounds **64-69** were subjected to <sup>15</sup>N NMR spectroscopic analysis to determine the chemical shift of the nitrogen atoms. As seen with the other compounds, the <sup>15</sup>N chemical shift for all of the compounds had shifted significantly downfield, away from the typical amine region and towards the aromatic region (**Figure 6**). While these shifts are more alike (**Table 6**) than

those measured for compounds **58-63**, these results still point to some form of delocalization of electrons occurring from the nitrogen lone pair to the boron atom.

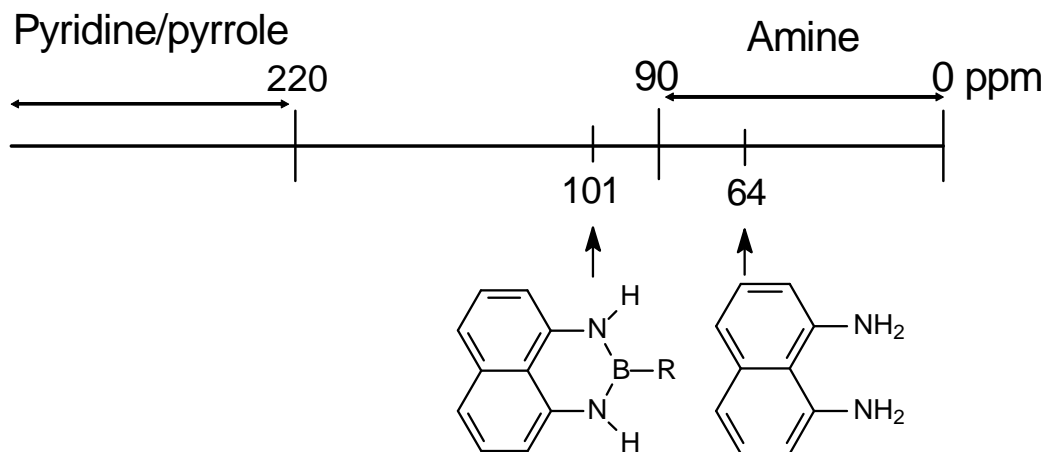


Figure 6.

Table 6.

<b>Product</b>	<b><math>^{15}\text{N}</math> NMR signal (ppm)</b>
<b>64</b>	101
<b>65</b>	101
<b>66</b>	101
<b>67</b>	101
<b>68</b>	100
<b>69</b>	106

As was observed in the  $^{15}\text{N}$  NMR spectroscopic analysis of HBDan and compounds **58-63**, the amine protons appear chemically identical for compounds **64-69**. What is interesting to note however, is the fact that the shifts recorded for compounds **64-69** appear to be more alike than those recorded for compounds **58-63**. Whether this indicates that the electron distribution along the nitrogen-boron-nitrogen ring system is less affected by the presence of electron-withdrawing or

electron-donating groups on the aryl ring in compounds **64-69** than **58-63** is unclear, and as very little structural information is available regarding naphthalene-based boranes, a search of the literature yielded no explanation for these observations.

#### **3.3.4. X-Ray Diffraction Analysis Results**

During the course of purification of compounds **64-69**, crystals were observed forming as the column chromatography solvent evaporated. This prompted an attempt to grow crystals suitable for X-ray diffraction analysis, as very little solid state structural information has been previously reported for any compound containing such a nitrogen-boron bond,<sup>145</sup> and even less on a diamidonaphthalene-based borane. Recrystallization of compounds **64-69** from CH<sub>2</sub>Cl<sub>2</sub> yielded crystalline material for all six compounds, but unfortunately two compounds, **66** and **69**, did not yield crystals that were of suitable quality for X-ray diffraction analysis.

The remaining four compounds were analyzed using X-ray diffraction spectroscopy, and good spectroscopic data was obtained for all (**Table 7**, selected data). Analysis of the data revealed a number of unexpected results. Only compound **65** was close to planarity (**Figure 7**), with a torsion angle of 3.3° and 4.3°, not all four as was expected. The other three compounds were distorted further, with a torsion angle of 5.6° and 6.0° measured for **64** (**Figure 8**), 19.5° and 20.0° for **67** (**Figure 9**) and the largest torsion angles of 19.8° and 20.3° observed for compound **68** (**Figure 10**). When the various bond angles are inspected, it is interesting to note that there does not appear to be a uniform bond length applicable to these compounds. The nitrogen-boron-nitrogen bond varies very little from the average bond angle of 115.5°, but this average is itself deviant from the bond angle of 109.5° expected for a six-membered cyclohexane-type structure. The bond angles are roughly halfway between the angles known for cyclohexane and for benzene (120°), and this could be due to the electron-backdonation of the nitrogen lone pairs, forming a pseudo-aromatic, or a partial aromatic type structure.

Table 7

	<b>64</b>	<b>65</b>	<b>67</b>	<b>68</b>
<b>Space Group</b>	P2 <sub>1</sub>	P2 <sub>1</sub>	P2 <sub>1</sub> /n	P2 <sub>1</sub> /c
<b>R-Factor (%)</b>	3.92	3.86	5.54	5.00
<b>B-N Bond Length (Å)</b>	N <sup>1</sup> -B <sup>6</sup> : 1.412(3) N <sup>5</sup> -B <sup>6</sup> : 1.417(3)	N <sup>1</sup> -B: 1.405(3) N <sup>5</sup> -B: 1.416(3)	N <sup>1</sup> -B <sup>6</sup> : 1.417(3) N <sup>5</sup> -B <sup>6</sup> : 1.414(2)	N <sup>1</sup> -B: 1.413(2) N <sup>5</sup> -B: 1.416(2)
<b>N-B-N Bond Angle (°)</b>	115.6(2)	115.6(2)	115.1(2)	115.8(1)
<b>C-N-B Bond Angle (°)</b>	C <sup>2</sup> -N <sup>1</sup> -B <sup>6</sup> : 123.8(2) C <sup>4</sup> -N <sup>5</sup> -B <sup>6</sup> : 123.9(2)	C <sup>5</sup> -N <sup>1</sup> -B: 123.6(2) C <sup>1</sup> -N <sup>2</sup> -B: 124.2(2)	C <sup>2</sup> -N <sup>1</sup> -B <sup>6</sup> : 124.3(2) C <sup>4</sup> -N <sup>5</sup> -B <sup>6</sup> : 124.0(2)	C <sup>1</sup> -N <sup>1</sup> -B: 123.6(2) C <sup>9</sup> -N <sup>2</sup> -B: 123.8(2)
<b>N-B-C Bond Angle (°)</b>	N <sup>1</sup> -B <sup>6</sup> -C <sup>7</sup> : 122.3(2) N <sup>5</sup> -B <sup>6</sup> -C <sup>7</sup> : 122.1(2)	N <sup>1</sup> -B-C <sup>10</sup> : 122.2(2) N <sup>2</sup> -B-C <sup>10</sup> : 122.2(2)	N <sup>1</sup> -B <sup>6</sup> -C <sup>7</sup> : 121.1(2) N <sup>5</sup> -B <sup>6</sup> -C <sup>7</sup> : 123.7(2)	N <sup>1</sup> -B-C <sup>11</sup> : 122.3(1) N <sup>2</sup> -B-C <sup>11</sup> : 121.9(1)
<b>N-B-C-C Torsion Angle (°)</b>	N <sup>1</sup> -B <sup>6</sup> -C <sup>7</sup> -C <sup>8</sup> : 6.0(3) N <sup>1</sup> -B <sup>6</sup> -C <sup>7</sup> -C <sup>12</sup> : -176.2(2) N <sup>5</sup> -B <sup>6</sup> -C <sup>7</sup> -C <sup>8</sup> : -172.2(2) N <sup>5</sup> -B <sup>6</sup> -C <sup>7</sup> -C <sup>12</sup> : 5.6(3)	N <sup>1</sup> -B-C <sup>10</sup> -C <sup>11</sup> : -4.3(4) N <sup>1</sup> -B-C <sup>10</sup> -C <sup>15</sup> : 174.3(2) N <sup>2</sup> -B-C <sup>10</sup> -C <sup>11</sup> : 178.0(2) N <sup>2</sup> -B-C <sup>10</sup> -C <sup>15</sup> : -3.3(4)	N <sup>1</sup> -B <sup>6</sup> -C <sup>7</sup> -C <sup>8</sup> : 19.5(3) N <sup>1</sup> -B <sup>6</sup> -C <sup>7</sup> -C <sup>13</sup> : -156.0(2) N <sup>5</sup> -B <sup>6</sup> -C <sup>7</sup> -C <sup>8</sup> : -164.5(2) N <sup>5</sup> -B <sup>6</sup> -C <sup>7</sup> -C <sup>13</sup> : 20.0(3)	N <sup>1</sup> -B-C <sup>11</sup> -C <sup>12</sup> : -159.8(2) N <sup>1</sup> -B-C <sup>11</sup> -C <sup>16</sup> : -20.3(2) N <sup>2</sup> -B-C <sup>11</sup> -C <sup>12</sup> : 19.8(2) N <sup>2</sup> -B-C <sup>7</sup> -C <sup>12</sup> : -160.0(2)

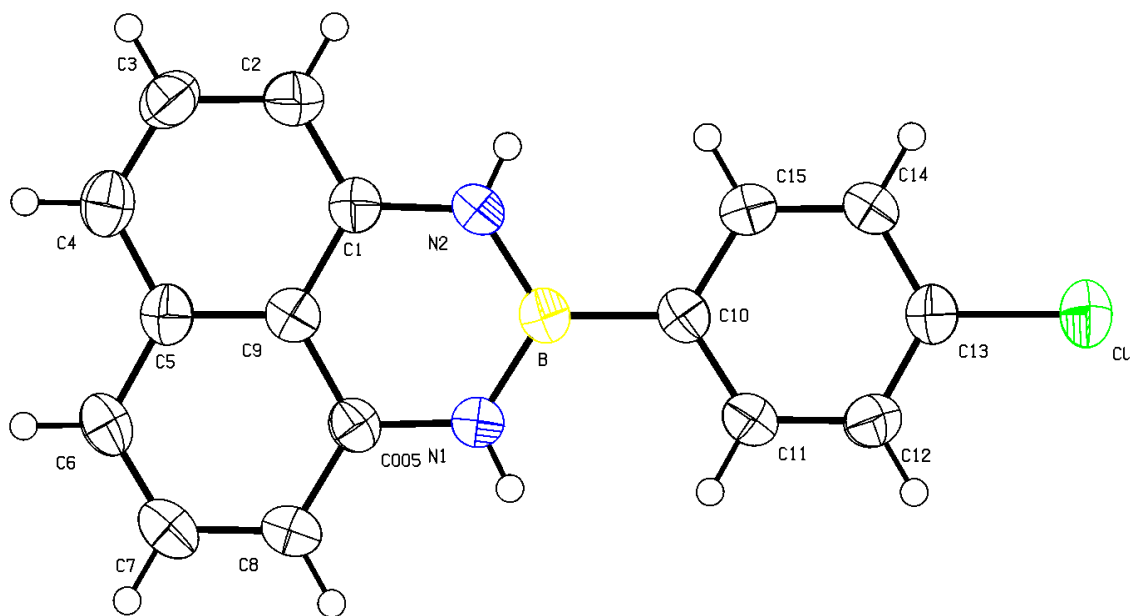


Figure 7

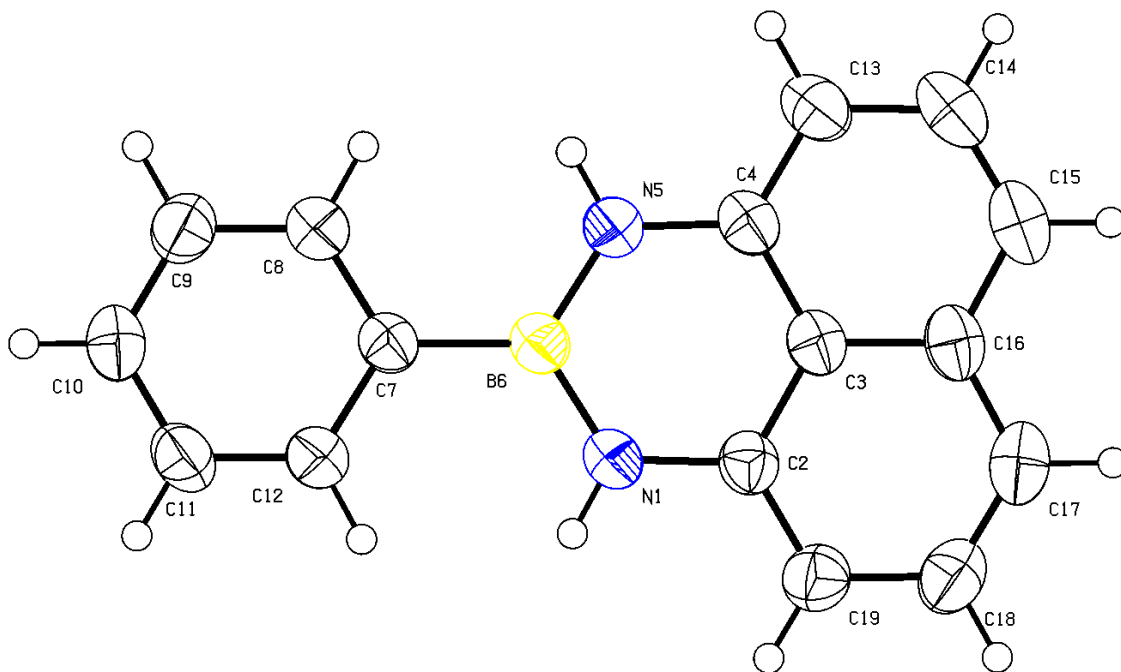


Figure 8

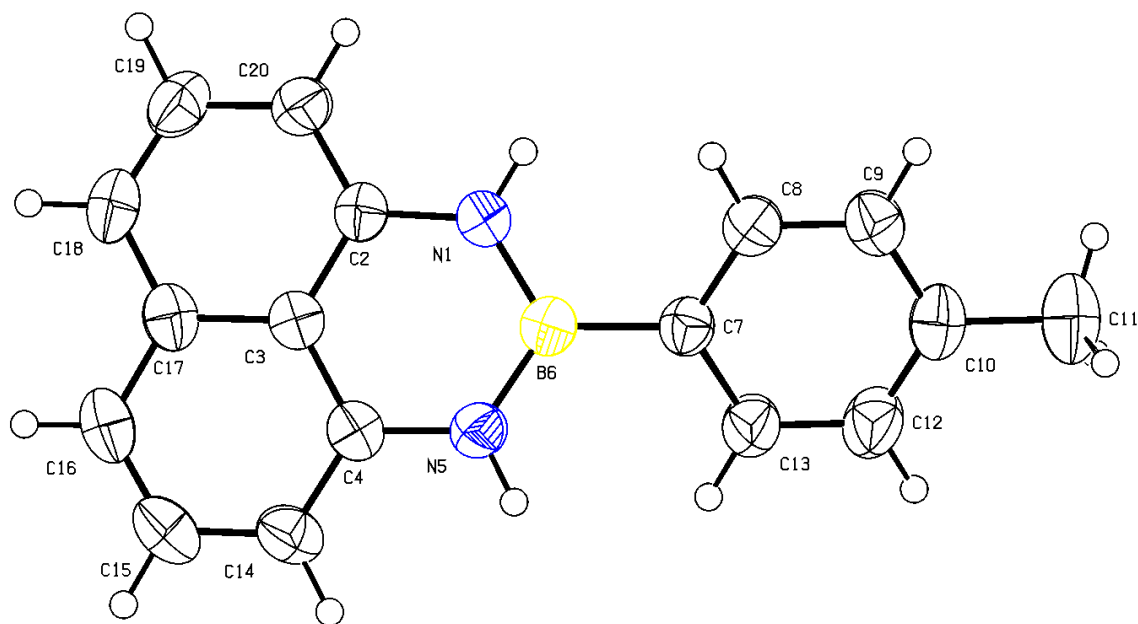


Figure 9

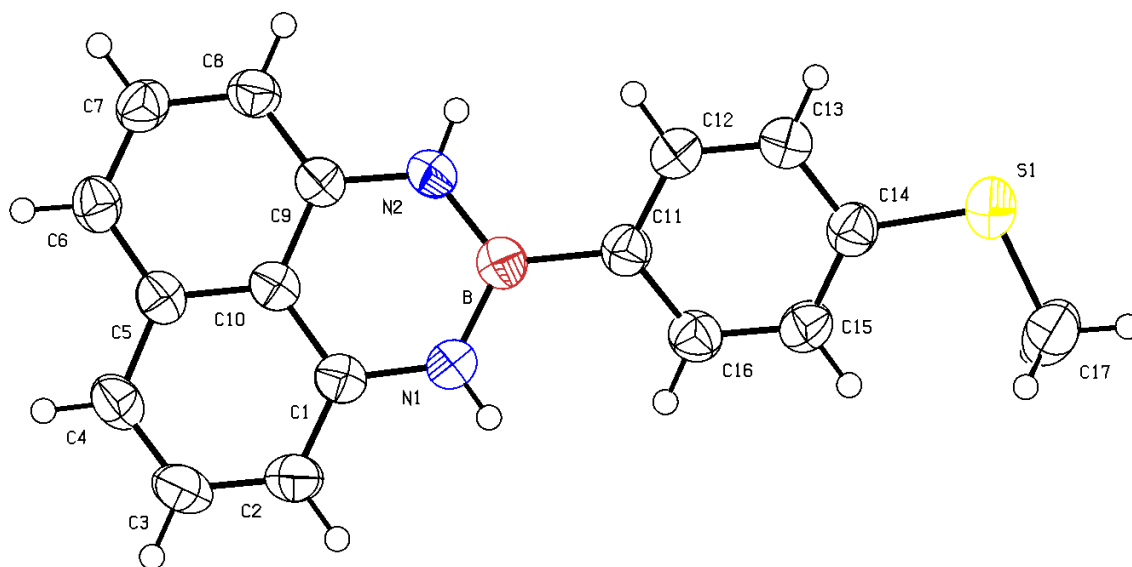


Figure 10

When these crystal structures are compared to the bis- and tri-benzodiazaborolanes put forward by Weber *et al.*,<sup>145</sup> the first difference seen is that the boron-nitrogen bonds in the naphthalene-based compounds are significantly shorter. This is most likely due to the inherent difference between the 5- and 6-membered heterocyclic rings. The second major difference is in the torsion angles present in the molecules. In the naphthalene compounds, the torsion angles range from 3.3° to 20.3° (average 12.4°), while in the phenylenediamine-based compounds the torsion angles range from 33.9° to 49.8° (average 46.2°).

### **3.4. Conclusion**

In conclusion, six phenylenediamine-based boranes and six diaminonaphthalene-based boranes were successfully synthesized in high yields. Microwave irradiation was successfully employed in the solvent-free synthesis of the compounds, and the reaction time was reduced from 3 hours to 15 minutes on application of microwave irradiation. The crude solids for the naphthalene-based compounds were determined by <sup>1</sup>H NMR spectroscopic analysis to be of sufficient purity as to remove the need for purification in all but the most stringent conditions.

<sup>15</sup>N NMR spectroscopic analysis of these twelve compounds showed a significant downfield shift in the position of the signal, away from the region of typical sp<sup>3</sup>-hybridized amines and toward the region typical of sp<sup>2</sup>-hybridized amines. These observations support the theory that electron back-donation from the nitrogen lone pair to the vacant p<sub>z</sub>-orbital on the boron atom.

Crystals suitable for X-Ray diffraction analysis were grown for four of the naphthalene-based boranes, and good spectroscopic data was obtained for all four samples. Analysis of the data showed that the compounds are not planar as originally thought, rather there is a degree of torsion inherent in each of the structures, ranging from a slight deviation (3-4%) to a substantial deviation (19-20%).

### **3.5. Recommendations for future work**

Again, a number of questions have been raised during the course of this study, questions mainly regarding the structure of the heterosubstituted boranes.

As very little structural data is available regarding heterosubstituted boranes, the growth of suitable crystals of the phenylenediamine-based boranes and the remaining two diaminonaphthalene-based boranes and subsequent X-ray diffraction analysis of these crystals would increase the amount of information available on these compounds. As similar compounds are known to have interesting photophysical properties, UV/Vis spectroscopic analysis of these compounds could be insightful into the possible future uses of these compounds. Structural information gleaned from the X-ray diffraction analyses and solid state NMR spectroscopic analysis could provide a measure of understanding the reasons for these properties, and also provide insight into the possible modification of these types of compounds into compounds suitable for use in optoelectronic and other optical devices.

Computational modeling of these compounds would also provide more insight into the nature of these compounds, as it could provide an explanation for the presence of what appear to be chemically non-equivalent amine protons on the phenylenediamine-based compounds, as well providing more understanding into the nature of the boron-nitrogen bonds in these compounds. X-ray diffraction analysis carried out at low temperature (100 K) may also allow for the determination of the placement of the electrons in these bonds, which would in turn explain the nitrogen-boron-nitrogen bond angles observed.

## **4. On the Use of Heterosubstituted Borolanes and Borinanes in the Petasis Reaction**

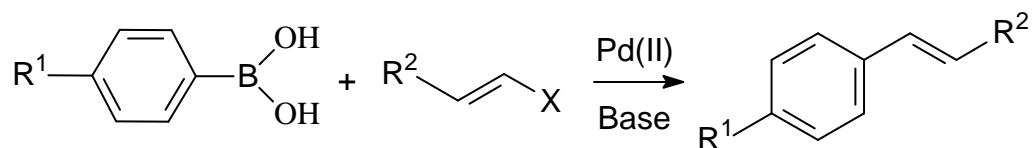
### **4.1. Study Objectives**

In this chapter, the heterosubstituted boranes synthesized in Chapter 3 will be studied as possible organoborane reagents in the Petasis reaction, a reaction where an aldehyde or  $\alpha$ -keto acid, an amine and an organoborane reagent is coupled to yield an amino acid. If the reactions using the heterosubstituted boranes result in high yields, the enantioselectivity of the reactions will be examined to determine whether there is any change in the enantioselective nature of the reaction.

The applicability of microwave irradiation to the Petasis reaction, both with boronic acids and the heterosubstituted boranes, will be studied in an attempt both to decrease the extended timescale of the reactions and to increase the yields of the reactions.

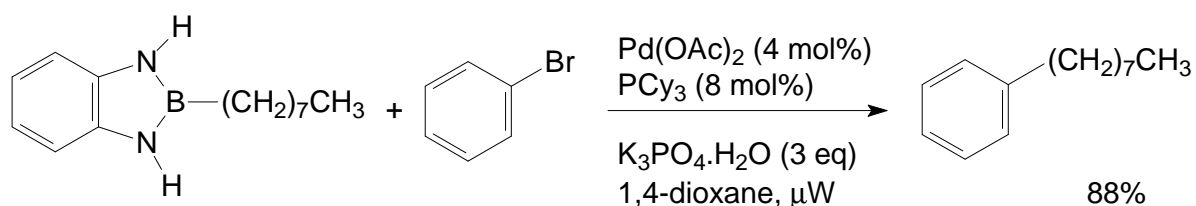
### **4.2. Petasis Reactions**

While doing research simply for the sake of the research itself is a brilliant idea, research cannot and should not be carried out without some form of an application for the results in mind. As such, a reaction was sought that would make use of the unique properties of these organoborane reagents. Previous work within the research group initially suggested the application of the organoboranes in the Suzuki reaction (**Scheme 1**). This palladium-catalyzed reaction results in the formation of a carbon-carbon bond between an aryl or vinyl halide and an organoborane reagent, and 2-octyl-1,3,2-benzodiazaborolane **42** has successfully been used in these reactions as the organoborane reagent.<sup>79</sup>

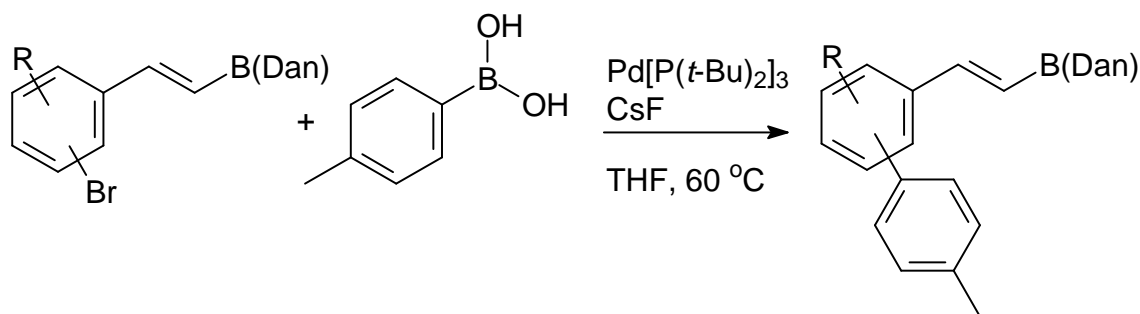


Scheme 1.

A search of the literature brought to light the fact that HBDan had previously been used as a protecting group for boronyl moiety<sup>131a</sup> (**Scheme 2**) and the protected compounds had subsequently been used in Suzuki reactions. These protected compounds underwent Suzuki coupling only at the unprotected boronic acid, and not at the diaminonaphthalene-protected boron atom (**Scheme 3**). While this result was desirable for the authors, that coupling at the protected boron atom did not take place did not bode well for the use of compounds **64-69** as Suzuki reagents, without major adjustment of the reaction conditions.

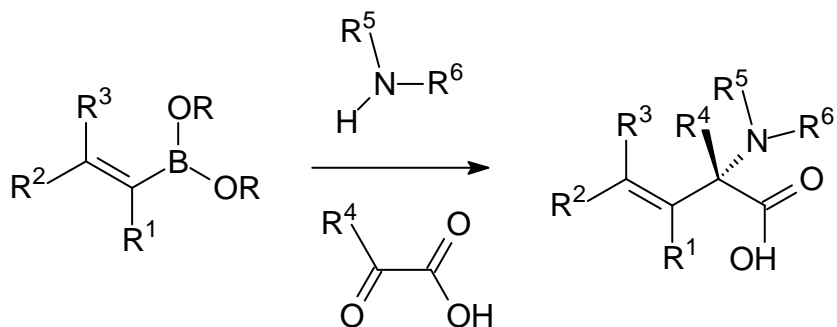


Scheme 2.



Scheme 3

Focus was then drawn to the Petasis reaction, a multicomponent reaction (MCR) in which an organoborane, an amine and an aldehyde or  $\alpha$ -keto acid are coupled to yield a substituted amino acid (**Scheme 4**).



Scheme 4.

An investigation into the possible use of the diaminoboranes as reagents in Petasis reactions was planned, using a variety of amines and aldehydes. It was hoped that these reagents would, in the first instance, prove to be successful reagents in the reaction, and secondly, if the reactions proved successful, that these reagents would impart an added degree of stereoselectivity to the reaction.

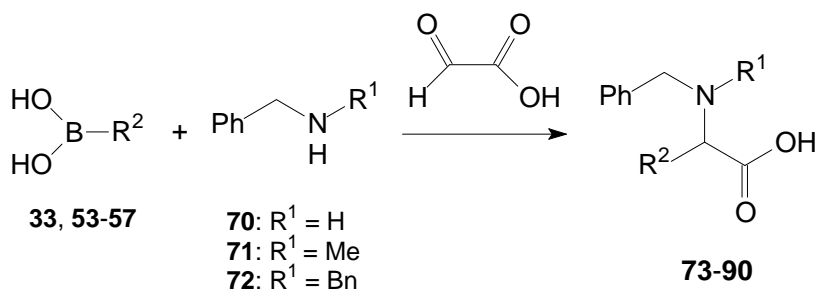
Currently there is an almost endless number of reaction methodologies that have been successfully employed in Petasis reactions. Ranging from the simple to the complex, each set of reagents, solvents and conditions is specifically suited to the unique needs of the particular reaction. Therefore, the simple method set forward by Petasis in 1997<sup>12a</sup> was selected as the method that would be followed for the reactions carried out during this project.

#### 4.2.1. Petasis Reactions with Glyoxylic Acid

As the majority of the reactions carried out in the literature make use of boronic acids and glyoxylic acid,<sup>1</sup> and despite the Petasis reaction being known to be a difficult one, reactions were carried out with both the boronic acids and compounds **58-63**, with a variety of amines and aldehydes. Initial test reactions with compounds **64-69** did not show any formation of the product under the conditions employed and as such these compounds were excluded from the study. This lack of reactivity of these compounds in the Petasis reaction is most likely due to the steric bulk of these reagents, as the larger naphthalene ring would retard the interaction of the boron

atom with the hydroxyl group of the aldehyde. A similar lack of reactivity was noted by Southwood *et al.*<sup>96d</sup> for dioxoboranes, where the larger organoborane reagents proved to be less reactive than the smaller reagents. The back-donation of electron density from the nitrogen lone pairs could also impede the reactivity of these naphthalene-based reagents, as this would decrease the electrophilicity of the boron atom, making the interaction with the hydroxyl group weaker.

The boronic acid reactions carried out during this investigation (**Scheme 5**) would provide a means of comparing the results obtained (**Table 1**) for the synthesis of the phenylglycine derivatives **73-90** with those which have been previously published, as well as providing a base for comparing the yields obtained with compounds **58-63**.



*Scheme 5*

Table 1.

Entry	Borane	Ph-CH <sub>2</sub> -NH <sub>2</sub> <b>70</b>		Ph-CH <sub>2</sub> -N(H)-CH <sub>3</sub> <b>71</b>		Ph-CH <sub>2</sub> -N(H)-CH <sub>2</sub> -Ph <b>72</b>	
		Cpd	Yield	Cpd	Yield	Cpd	Yield
1	<b>33</b>	<b>73</b>	24	<b>79</b>	82	<b>85</b>	90
2	<b>53</b>	<b>74</b>	17	<b>80</b>	nd	<b>86</b>	61
3	<b>54</b>	<b>75</b>	57	<b>81</b>	65	<b>87</b>	58
4	<b>55</b>	<b>76</b>	58	<b>82</b>	77	<b>88</b>	56
5	<b>56</b>	<b>77</b>	45	<b>83</b>	92	<b>89</b>	63
6	<b>57</b>	<b>78</b>	nd <sup>a</sup>	<b>84</b>	nd	<b>90</b>	nd

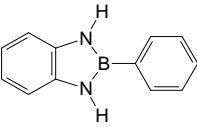
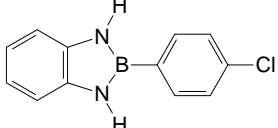
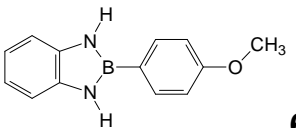
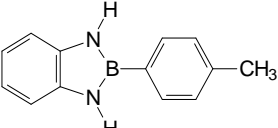
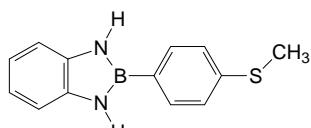
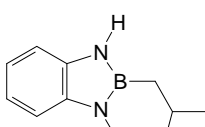
Reaction conditions: Borane ( $2 \times 10^{-3}$  mol), amine ( $2 \times 10^{-3}$  mol), glyoxylic acid ( $2 \times 10^{-3}$  mol), CH<sub>2</sub>Cl<sub>2</sub> (10ml), room temperature, 48hrs <sup>a</sup> nd = Not detected

The results obtained for the boronic acid reactions compare favourably to those reported in the literature. Unsurprisingly, boronic acid **57** did not yield any product in any of the three reactions, as the use of alkyl chains in the Petasis reaction is very rare and in the majority of cases very low yielding.<sup>1</sup> The most surprising result is that no product was detected for the reaction to yield compound **80**, as this reaction has been reported to have good yields, albeit with slightly different reaction conditions. The reason for this lack of reactivity may be due to the electron-withdrawing chlorine atom, however the reaction with amine **72** resulted in a moderate yield and therefore this is most likely not the full reason for the lack of reactivity noted.

What is most interesting to note is that in the majority of cases, the reactions where *N*-benzylmethylamine **71** is the amine, the yields are highest. This slight reduction in yield is also noted in literature<sup>1</sup> where the increased steric bulk of dibenzylamine **72** was thought to affect the yields of these reactions.<sup>1,96d,101</sup>

In order to determine whether compounds **58-63** are suitable reagents for Petasis reactions, these compounds were substituted for the boronic acids and the reactions were carried out under the same conditions as used previously (**Table 2**).

Table 2

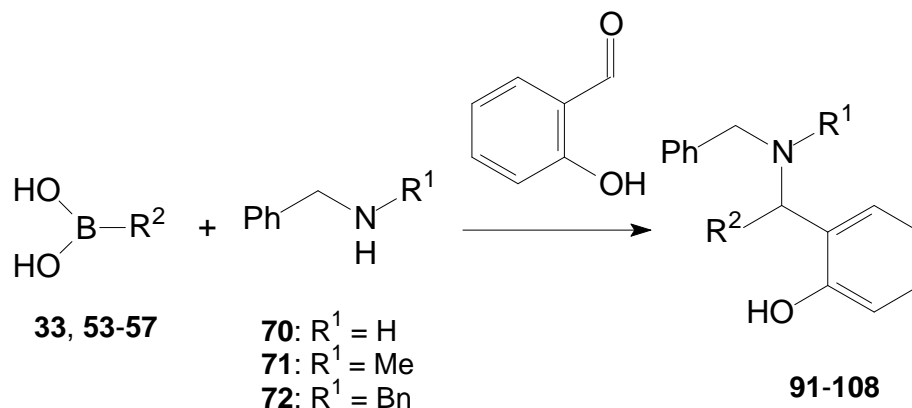
Entry	Borane	Ph-CH <sub>2</sub> -NH <sub>2</sub> <b>70</b>		Ph-CH <sub>2</sub> -N(CH <sub>3</sub> ) <sub>2</sub> <b>71</b>		Ph-CH <sub>2</sub> -N(CH <sub>2</sub> Ph) <sub>2</sub> <b>72</b>	
		Cpd	Yield	Cpd	Yield	Cpd	Yield
1	 <b>58</b>	<b>73</b>	nd <sup>a</sup>	<b>79</b>	nd	<b>85</b>	nd
2	 <b>59</b>	<b>74</b>	nd	<b>80</b>	nd	<b>86</b>	nd
3	 <b>60</b>	<b>75</b>	7	<b>81</b>	58	<b>87</b>	50
4	 <b>61</b>	<b>76</b>	nd	<b>82</b>	35	<b>88</b>	30
5	 <b>62</b>	<b>77</b>	nd	<b>83</b>	61	<b>89</b>	24
6	 <b>63</b>	<b>78</b>	nd	<b>84</b>	nd	<b>90</b>	nd

Reaction conditions: Borane ( $2 \times 10^{-3}$  mol), amine ( $2 \times 10^{-3}$  mol), glyoxylic acid ( $2 \times 10^{-3}$  mol), CH<sub>2</sub>Cl<sub>2</sub> (10ml), room temperature, 48hrs <sup>a</sup> nd = Not detected

When compared to the results obtained in Table 5.1, the results of these reactions are, at face value, very disappointing. There is a drastic reduction in yield on substitution of the boronic acids, however the reactions where compounds **60**, **61** and **62** were successfully employed appear to show the same pattern of yields as was observed for the boronic acids, where the less bulky secondary amine **71** showed higher yields than the bulkier secondary amine **72**. Nonetheless, as the Petasis reaction is known to require very specific conditions depending on the substrates used, the fact that even a small amount of the products were formed shows that these reagents are able to undergo Petasis reactions. The low yields observed most likely demonstrate the need for a different set of reaction conditions.

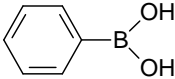
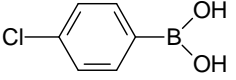
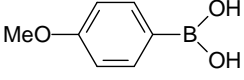
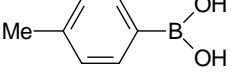
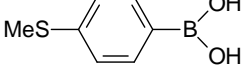
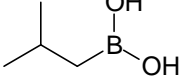
#### 4.2.2. Petasis Reactions with Salicylaldehyde

Another common aldehyde used in Petasis reactions is salicylaldehyde, and no study into this reaction could be considered complete without it. As such, salicylaldehyde was substituted for glyoxylic acid, (**Scheme 6**) and reactions were carried out using the same boronic acids and amines as previously used (**Table 3**). As salicylaldehyde is known to be less reactive than glyoxylic acid,<sup>106</sup> the yields for these reactions were expected to be reduced in comparison to the results obtained for glyoxylic acid.



Scheme 6

Table 3

Entry	Borane	Ph-CH <sub>2</sub> -NH <sub>2</sub> <b>70</b>		Ph-CH <sub>2</sub> -N(H)-CH <sub>3</sub> <b>71</b>		Ph-CH <sub>2</sub> -N(H)-CH <sub>2</sub> -Ph <b>72</b>	
		Cpd	Yield	Cpd	Yield	Cpd	Yield
<b>1</b>		<b>91</b>	nd <sup>a</sup>	<b>97</b>	40	<b>103</b>	12
<b>2</b>		<b>92</b>	nd	<b>98</b>	38	<b>104</b>	6
<b>3</b>		<b>93</b>	nd	<b>99</b>	42	<b>105</b>	2
<b>4</b>		<b>94</b>	nd	<b>100</b>	45	<b>106</b>	11
<b>5</b>		<b>95</b>	nd	<b>101</b>	37	<b>107</b>	15
<b>6</b>		<b>96</b>	nd	<b>102</b>	nd	<b>108</b>	nd

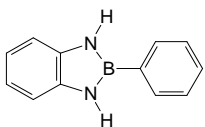
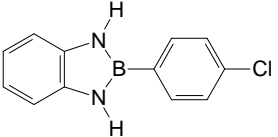
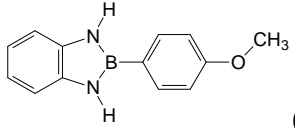
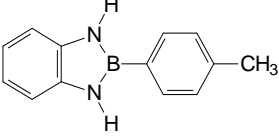
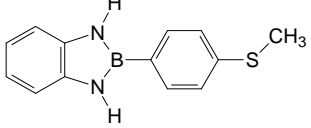
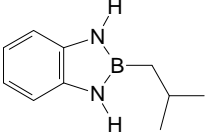
Reaction conditions: Borane ( $2 \times 10^{-3}$  mol) amine ( $2 \times 10^{-3}$  mol), salicylaldehyde ( $2 \times 10^{-3}$  mol), CH<sub>2</sub>Cl<sub>2</sub> (10ml), room temperature, 48hrs <sup>a</sup> nd = Not detected

On comparison of the yields obtained with salicylaldehyde the initial suspicions regarding the reactivity of salicylaldehyde were confirmed. No product was detected with the primary amine **70**, and the yields for the two secondary amines are significantly reduced. However, on comparison to literature yields reported for similar reactions, the yields obtained correspond reasonably well. As seen with glyoxylic acid and as expected, the use of boronic acid **57** again did not result in the formation of the desired products.

Despite the poor yields obtained with the boronic acids and salicylaldehyde reactions, compounds **58-63** were used in the Petasis reaction as the organoborane

reagent (**Table 4**) in the hope that these reagents would increase the yields of the reactions.

Table 4

Entry	Borane	Ph-CH <sub>2</sub> -NH <sub>2</sub> <b>70</b>		Ph-CH <sub>2</sub> -N(H)-CH <sub>3</sub> <b>71</b>		Ph-CH <sub>2</sub> -N(H)-CH <sub>2</sub> -Ph <b>72</b>	
		Cpd	Yield	Cpd	Yield	Cpd	Yield
1	 <b>58</b>	<b>91</b>	nd <sup>a</sup>	<b>97</b>	5	<b>103</b>	nd
2	 <b>59</b>	<b>92</b>	nd	<b>98</b>	nd	<b>104</b>	nd
3	 <b>60</b>	<b>93</b>	nd	<b>99</b>	11	<b>105</b>	nd
4	 <b>61</b>	<b>94</b>	nd	<b>100</b>	10	<b>106</b>	nd
5	 <b>62</b>	<b>95</b>	nd	<b>101</b>	14	<b>107</b>	nd
6	 <b>63</b>	<b>96</b>	nd	<b>102</b>	nd	<b>108</b>	nd

Reaction conditions: Borane ( $2 \times 10^{-3}$  mol) amine ( $2 \times 10^{-3}$  mol), salicylaldehyde ( $2 \times 10^{-3}$  mol), CH<sub>2</sub>Cl<sub>2</sub> (10ml), room temperature, 48hrs <sup>a</sup> nd = Not detected

As expected, the heterosubstituted boranes **58-63** gave poor yields for the few reactions where a product could be detected. Despite these poor results, the presence of any amount of product is a good sign as it means that the reaction does proceed, however the reactions are not optimized for these reagents. As with the

previous reactions, amine **71** resulted in the best yields obtained, which confirms the suspicion that the size of the amine also contributes to the overall reaction yield.

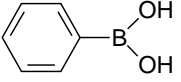
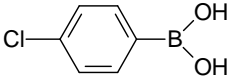
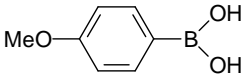
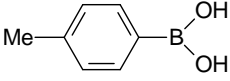
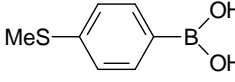
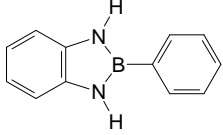
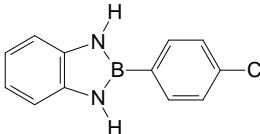
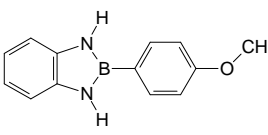
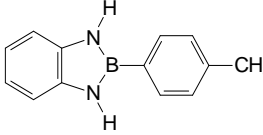
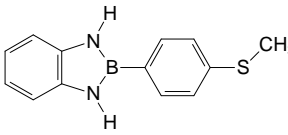
### ***4.3. Microwave-assisted Petasis Reactions***

Even though the conditions for the Petasis reaction are relatively mild, the one drawback to the use of this reaction in the formation of compound libraries is the reactions require reaction times of 48 hours. In an attempt to speed up the reaction, McLean, Tye and Whittaker<sup>101</sup> successfully employed microwave irradiation for a range of arylboronic acids, amines and aldehydes, and it was hoped that this would be true in these reactions. Based on the results obtained for the reactions carried out in solution, as well as other published results, it was decided not to include compounds **57** and **70** in the study.

#### ***4.3.1. Microwave-assisted Petasis Reactions with Glyoxylic Acid***

The microwave methodology used by McLean, Tye and Whittaker was adopted as the methodology to be followed, as this would provide a convenient comparison point of the yields obtained for these reactions (**Table 5**) to existing literature methods, as well as being very simple. As is the case with the previous Petasis reactions carried out without microwave irradiation, these reactions are highly customizable with regards to the microwave settings which can be used, as well as the suitability of the solvent to microwave irradiation.

Table 5

Entry	Borane	Ph-CH <sub>2</sub> -N(H)-CH <sub>3</sub>		Ph-CH <sub>2</sub> -N(H)-CH <sub>2</sub> -Ph	
		71	Yield	72	Yield
1	 <b>33</b>	<b>79</b>	63	<b>85</b>	50
2	 <b>53</b>	<b>80</b>	30	<b>86</b>	2
3	 <b>54</b>	<b>81</b>	46	<b>87</b>	31
4	 <b>55</b>	<b>82</b>	69	<b>88</b>	61
5	 <b>56</b>	<b>83</b>	54	<b>89</b>	38
6	 <b>58</b>	<b>79</b>	10	<b>85</b>	15
7	 <b>59</b>	<b>80</b>	nd <sup>a</sup>	<b>86</b>	nd
8	 <b>60</b>	<b>81</b>	38	<b>87</b>	21
9	 <b>61</b>	<b>82</b>	39	<b>88</b>	11
10	 <b>62</b>	<b>83</b>	48	<b>89</b>	6

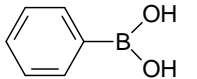
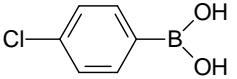
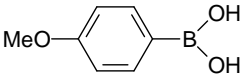
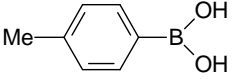
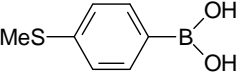
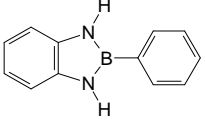
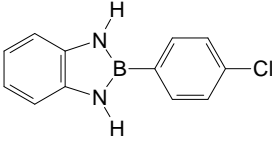
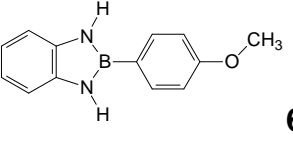
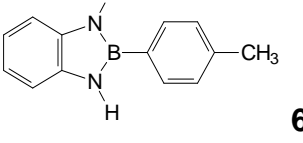
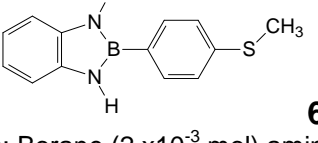
Reaction conditions: Borane ( $2 \times 10^{-3}$  mol) amine ( $2 \times 10^{-3}$  mol), glyoxylic acid ( $2 \times 10^{-3}$  mol), CH<sub>2</sub>Cl<sub>2</sub> (10ml), 120 °C, 300W, 10 minutes <sup>a</sup> nd = not detected

As anticipated based on the results of the previous reactions, the substitution of compounds **58-62** for the boronic acids resulted in a significant reduction in the yields of the reaction. However, these results show that microwave irradiation can be applied successfully to the Petasis reaction, and to these reaction conditions. The yields obtained for the reactions with the boronic acids are lower than those obtained without the microwave irradiation (**Table 1**), however it must be remembered that these reactions were carried out over a mere 10 minutes, and not the 48 hours as for the other reactions. It is possible that adjustment of the reaction conditions, including increasing the duration of microwave irradiation, will increase the yields of the reactions.

#### ***4.3.2. Microwave-assisted Petasis Reactions with Salicylaldehyde***

Again, in the search of completeness, microwave irradiation was applied to the Petasis reaction with salicylaldehyde (**Table 6**). Based on the yields obtained for the reactions carried out without microwave irradiation, it is expected that these reactions will be lower yielding than the corresponding glyoxylic acid reactions carried out previously.

Table 6

Entry	Borane	Ph-CH <sub>2</sub> -N(H)-CH <sub>3</sub>		Ph-CH <sub>2</sub> -N(H)-CH <sub>2</sub> -Ph	
		71	72	71	72
		Cpd	Yield	Cpd	Yield
1	 <b>33</b>	<b>97</b>	58	<b>103</b>	50
2	 <b>53</b>	<b>98</b>	45	<b>104</b>	nd <sup>a</sup>
3	 <b>54</b>	<b>99</b>	68	<b>105</b>	60
4	 <b>55</b>	<b>100</b>	71	<b>106</b>	62
5	 <b>56</b>	<b>101</b>	73	<b>107</b>	60
6	 <b>58</b>	<b>97</b>	8	<b>103</b>	26
7	 <b>59</b>	<b>98</b>	3	<b>104</b>	4
8	 <b>60</b>	<b>99</b>	15	<b>105</b>	22
9	 <b>61</b>	<b>100</b>	30	<b>106</b>	nd
10	 <b>62</b>	<b>101</b>	21	<b>107</b>	nd

Reaction conditions: Borane ( $2 \times 10^{-3}$  mol) amine ( $2 \times 10^{-3}$  mol), glyoxylic acid ( $2 \times 10^{-3}$  mol), CH<sub>2</sub>Cl<sub>2</sub> (10ml), 120 °C, 300W, 10 minutes. <sup>a</sup> nd = not detected

The yields obtained for these reactions did significantly decrease on the substitution of compounds **58-62**, as was observed for the previous reactions. What is interesting to note is that the application of microwave irradiation appears to increase the yields of the reactions of boronic acids as compared to the same reactions carried out over 48 hours. The reason for this phenomenon is still unknown, as a search of the literature did not provide any information that could explain the observed yields.

#### **4.4. Conclusions**

The results obtained clearly show that heterosubstituted boranes can be used in Petasis reactions as the organoborane reagent in a number of cases. Despite the reactions being low-yielding, that any product is formed is a sign that this reaction could be optimized by adjusting the reaction conditions. Alkylborane **63** did not react successfully, which could indicate that a measure of aromaticity on the borane reagent is needed to enable the reaction to proceed. Compounds **64-69** did not yield any products, most likely due to the large steric size of the compounds, which could reduce the rate of reaction. Primary amine **70**, although reactive in a number of cases, did not show the same reactivity as was observed for the secondary amines, a phenomenon which had been previously noted in the literature.

Microwave irradiation was also successfully employed in Petasis reactions, which reduced the reaction time from 48 hours to 10 minutes. In the case of reactions with the boronic acids and salicylaldehyde there was an increase in the yields obtained with the application of microwave irradiation, however an explanation for these observations is still needed.

#### ***4.5. Recommendations for Future Work***

Despite a number of the reactions being low-yielding, and a number not resulting in the formation of the desired product, the results obtained from this study have provided insight into the scope and limitations of the notoriously sensitive Petasis reaction. Heterosubstituted boranes can be successfully employed in Petasis reactions; however the conditions employed in this study are not optimal for these compounds. The solvent is known to be involved in the yields obtained, and changing the solvent to water, methanol or hexafluoroisopropanol (HFIP) may result in increased yields of these reactions. Increasing the temperature at which the reaction is carried out could also result in increased yields.

While the application of microwave irradiation resulted in the formation of the desired product in a number of cases, the reaction yields could possibly be optimized by increasing the duration of the microwave irradiation, changing the reaction temperature or by altering the power setting used.

## 5. Project Summary

The objectives set forward at the beginning of this project have, for the most part, been successfully carried out. Although some of the results obtained are not what was expected or desired, all of the results have broadened the amount of information that is known about the synthesis, the structure and the reactivity of heterosubstituted boranes.

In Chapter 2, three heterosubstituted boranes were successfully synthesized from the corresponding amines and  $\text{BH}_3\cdot\text{DMS}$  in high yields, and were noted to be significantly more stable with regards to both air exposure and temperature than the analogous oxo-compounds.  $^{11}\text{B}$  NMR spectroscopy of the reaction mixtures indicated that the mechanism of the reaction to form these boranes contains two intermediates and supports a step-wise addition mechanism, an observation confirmed by *in situ*  $^{11}\text{B}$  NMR spectroscopy.  $^{15}\text{N}$  NMR spectroscopic analysis of the three boranes identified a downfield shift in the location of the nitrogen signal from the typical  $\text{sp}^3$ -hybridized amines region towards the aromatic region, supporting the theory of the back-donation of electrons from the nitrogen lone pair to the boron atom's vacant  $p_z$ -orbital

The three boranes proved to be suitable hydroboration reagents under microwave-assisted conditions, with Wilkinson's catalyst and a rhodium(I) carbonyl hydride catalyst both showing catalytic ability, however yields were noted to be dependent on the borane, the olefin and the catalyst. The rhodium hydride-catalyzed reactions of the 2-aminophenol based borane and the olefins did not require microwave irradiation to effect almost quantitative yields of the desired product.

In Chapter 3, twelve heterosubstituted boranes were successfully synthesized in high yields both in solution and under microwave assisted solvent-free conditions. This resulted in the reaction time being reduced to 15 minutes, with yields comparable to the reactions carried out in solution over three hours.  $^{15}\text{N}$  NMR

spectroscopic analysis of these compounds showed a similar downfield shift in the amine signal as was observed for the compounds in Chapter 2, lending support to the electron back-donation explanation for the stability of these compounds.

Crystals suitable for X-Ray diffraction analysis were grown for four 1,8-diaminonaphthalene-based boranes, and good spectroscopic data was obtained for these samples. Analysis of the data showed that the compounds are not planar as originally thought, rather there is a degree of torsion inherent in each of the structures, ranging from a slight deviation (3-4%) to a substantial deviation (19-20%).

In Chapter 4, it was shown that heterosubstituted boranes can be used in Petasis reactions as the organoborane reagent in a number of cases, although the reaction conditions used were not optimized for these compounds. The lack of reactivity of a number of compounds points to steric hindrance being an issue in the mechanism of the reaction, as well as a possible need for electron density on the organoborane reagent. Microwave irradiation was also successfully employed in Petasis reactions, which reduced the reaction time from 48 hours to 10 minutes.

When all is considered, this project has successfully answered the questions set out at the beginning, and has provided a number of new questions which still need answering.

## 6. Experimental Section

### 6.1. Instrumentation and General Procedures

All glassware used in the synthesis of air- and moisture-sensitive compounds was thoroughly dried overnight in an oven heated at ca. 150 °C. The glassware was further flame-dried with a hot air gun under reduced pressure and cooled under a stream of dry nitrogen, which was passed through a mixture of silica gel and 0.4 nm molecular sieves prior to use. Glass syringes, cannulae and needles were oven-dried prior to use. The glassware was assembled, and all joints were wrapped with Teflon® tape and subsequently sealed with Parafilm “M”® to ensure a closed system.

Dry solvents were prepared using a Puresolv MD 7 purification system from Innovative Technologies, and were transferred using standard techniques for air- and moisture-sensitive compounds.

NMR spectra were recorded on either a Bruker Avance III 500 or Avance III 400 at the following frequencies: <sup>1</sup>H, 500/400 MHz; <sup>11</sup>B, 160/128 MHz; <sup>13</sup>C, 125/100 MHz; <sup>15</sup>N, 50 MHz. Unless otherwise specified, all NMR experiments were carried out at 30 °C. All chemical shifts are reported in units of ppm. All proton and carbon chemical shifts are quoted relative to the relevant solvent signals (DMSO-d<sub>6</sub>, <sup>1</sup>H, 2.50 ppm, <sup>13</sup>C, 39.5 ppm; CDCl<sub>3</sub>, <sup>1</sup>H, 7.26 ppm, <sup>13</sup>C, 77.0 ppm). All <sup>11</sup>B and <sup>15</sup>N chemical shifts are reported relative to BF<sub>3</sub>-etherate (0 ppm) and liquid ammonia (0 ppm), respectively. All coupling constants are reported in Hertz. <sup>11</sup>B NMR experiments were conducted in quartz tubes, which were all oven-dried, flushed with dry nitrogen and sealed with a rubber septum prior to injection of the sample or reagents.

Low resolution masses and mass fragmentation patterns were recorded on a Thermofinnegan TraceGC-PolarisQ coupled gas chromatograph-mass spectrometer

(ion trap) using electron impact ionization (70 eV). High resolution masses were determined with a Waters Acquity-LCT Premier coupled high performance liquid chromatograph-mass spectrometer (time-of-flight) using electrospray ionization in either positive or negative mode.

Merck aluminium sheets pre-coated with silica gel 60 F254 were used for thin layer chromatography. Column ("flash") chromatography was carried out using Merck silica gel 60 according to the method of Still, Kahn, and Mitra.<sup>147</sup>

Centrifugal (radial) chromatography was carried out on a Harrison Research chromatotron using plates coated with Merck silica gel 60 F254.

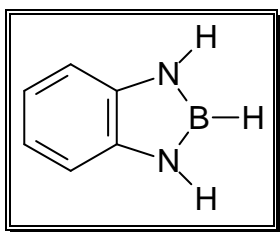
X-Ray diffraction data were collected on an Oxford Diffraction Xcalibur2 CCD 4-circle diffractometer equipped with an Oxford Instruments Cryojet. The data were collected at room temperature unless otherwise stated, with Mo K $\alpha$  ( $\lambda = 0.71073$  Å) radiation at a crystal-to-detector distance of 50 mm using omega scans at  $\theta = 29.389^\circ$ , with varying exposure times taken at 2.01 kW X-ray power with  $0.75^\circ$  frame widths. The data were reduced with the program CrysAlis RED<sup>148</sup> using outlier rejection, scan speed scaling, as well as standard Lorentz and polarization correction factors. Unless otherwise stated, direct methods (SHELXS-97, WinGX32)<sup>149</sup> were used to solve the structures. All non-H atoms were located in the E-map and refined anisotropically with SHELXL-97.<sup>150</sup> All hydrogen atoms in each of the structures resolved were included as idealized contributors in the least squares process with standard SHELXL-97<sup>150</sup> parameters, unless otherwise stated.

## 6.2. Preparation of Hydroboration Reagents and Rhodium-Catalyzed Hydroboration Reactions

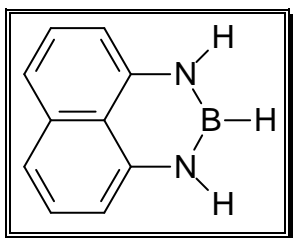
### 6.2.1. Preparation of Hydroboration Reagents

**General Procedures for the synthesis of compounds 19 and 22:** To a solution of amine in  $\text{CH}_2\text{Cl}_2$  ( $1.054 \times 10^{-2}$  mol in 50 ml,  $2.108 \times 10^{-1}$  M) under nitrogen was added  $\text{BH}_3 \cdot \text{SME}_2$  ( $1.054 \times 10^{-2}$  mol, 1 ml) dropwise *via* a syringe over 15 minutes at room temperature. The resulting solution was stirred and reflux was maintained until NMR results showed complete conversion to the product, approximately 5 hours.

**General Procedures for the synthesis of compound 40:** Same as for compounds 19 and 22, but solution stirred at room temperature for 72 hours.

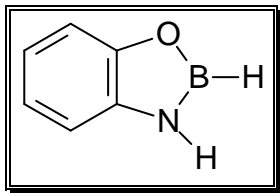


**1,3,2-benzodiazaborolane (HBPDa) 19:** Opaque pink solution, >95%.  $^1\text{H}$  NMR (500 MHz,  $\text{CH}_2\text{Cl}_2$ )  $\delta$  4.46 ppm (q,  $J = 101$  Hz) 6.71 ppm (s) 6.82 ppm (br. s) 6.95-7.12 ppm (m)  $^{11}\text{B}$  NMR (128 MHz,  $\text{CH}_2\text{Cl}_2$ )  $\delta$  26 ppm (d,  $J = 137$  Hz)  $^{13}\text{C}$  NMR (125 MHz,  $\text{CH}_2\text{Cl}_2$ )  $\delta$  111.1 ppm (d) 119.2 ppm (d) 135.6 ppm (s)  $^{15}\text{N}$  NMR (51 MHz,  $\text{CH}_2\text{Cl}_2$ )  $\delta$  110 ppm (s).



**Naphtho[1,8-*de*][1,3,2]diazaborinane (HBDan) 22:** Opaque brown solution, >95%.  $^1\text{H}$  NMR (400 MHz,  $\text{CH}_2\text{Cl}_2$ )  $\delta$  4.09 ppm (q,  $J = 134$  Hz) 5.49 ppm (br. s) 6.29-6.31 ppm (m) 6.98-7.09 ppm (m);  $^{11}\text{B}$  NMR (128 MHz,  $\text{CH}_2\text{Cl}_2$ )

$\delta$  26 ppm (d,  $J = 137$  Hz);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CH}_2\text{Cl}_2$ )  $\delta$  111.2 ppm (d) 117.2 ppm (s) 119.8 ppm (d) 126.2 ppm (d) 137.0 ppm (s) 144.5 ppm (s);  $^{15}\text{N}$  NMR (51 MHz,  $\text{CH}_2\text{Cl}_2$ )  $\delta$  104 ppm (s)



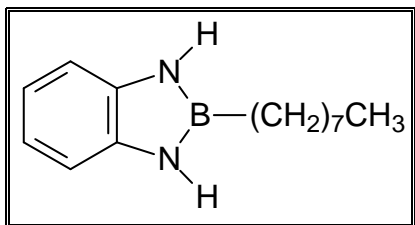
**1,3,2-benzoxazaborolane (HBAPh) 40:** Opaque white solution, 85%.  $^1\text{H}$  NMR (400 MHz,  $\text{CH}_2\text{Cl}_2$ )  $\delta$  6.35 ppm (t,  $J = 7.4$  Hz) 6.40 ppm (v. br. s) 6.42 ppm (t,  $J = 7.4$  Hz) 6.48 ppm (d,  $J = 7.4$  Hz) 6.62 ppm (d,  $J = 7.4$  Hz);  $^{11}\text{B}$  NMR (128 MHz,  $\text{CH}_2\text{Cl}_2$ )  $\delta$  28 ppm (d,  $J = 171$  Hz)  $^{13}\text{C}$  NMR (125 MHz,  $\text{CH}_2\text{Cl}_2$ )  $\delta$  110.8 ppm (d) 111.6 ppm (d) 119.6 ppm (d) 121.4 ppm (d) 134.3 ppm (s) 148.8 ppm (s)

**General Procedure for the Arrayed *in situ*  $^{11}\text{B}$  NMR Experiments:**  $\text{BH}_3 \cdot \text{SMe}_2$  was injected into a nitrogen-purged, septum capped quartz NMR tube, followed by a solution of 1,8-diaminonaphthalene in  $\text{CH}_2\text{Cl}_2$  (0.5ml). The tube was shaken briefly and transferred to the magnet. The delay between the mixing of reagents and the start of the first experiment was 40 seconds. Analysis was carried out for 18 hours or until the reaction was complete.

### 6.2.2. Rhodium-Catalyzed Hydroboration Reactions

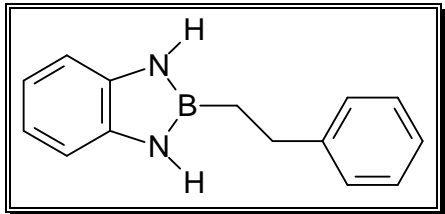
**General Procedures for the microwave-assisted rhodium-catalyzed hydroboration reactions of compounds 19, 22 and 40:** The olefin ( $2.10 \times 10^{-3}$  mol, 10 eq.) was added to a quartz NMR tube and the tube was capped with a septum and purged under a stream of dry  $\text{N}_2$ . The tube was then held under a stream of dry  $\text{N}_2$  and the septum removed. The catalyst ( $2.10 \times 10^{-5}$  mol, 10 mol%) was quickly added to the tube and the septum replaced. A solution of the borane in  $\text{CH}_2\text{Cl}_2$  (1.0 ml,  $2.10 \times 10^{-4}$  mol) was injected *via* a syringe and the tube shaken to mix. The tubes were subjected to  $^{11}\text{B}$  NMR analysis prior to insertion into the cavity of a CEM explorer synthetic microwave. The reaction was irradiated at  $150^\circ\text{C}$  for one hour

(100W), and the progress of the reaction was monitored by  $^{11}\text{B}$  NMR analysis of the reaction mixture.



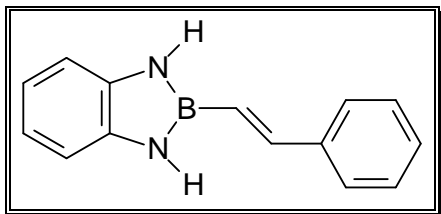
**2-Octyl-1,3,2-benzodiazaborolane 42:** Wilkinson's

catalyst, 85%, Rhodium carbonyl hydride catalyst, 89%.  $^1\text{H}$  NMR (500 MHz,  $\text{CH}_2\text{Cl}_2$ )  $\delta$  0.88 ppm (t,  $J = 13.8$  Hz) 1.27 ppm (br. s) 4.56 ppm (br. s) 7.44-7.49 ppm (m) 7.53-7.58 ppm (m) 7.63-7.69 ppm (m) 7.73-7.79 ppm (m)  $^{11}\text{B}$  NMR (128 MHz,  $\text{CH}_2\text{Cl}_2$ )  $\delta$  33 ppm (s)  $^{13}\text{C}$  NMR (125 MHz,  $\text{CH}_2\text{Cl}_2$ )  $\delta$  14.0 ppm (q) 22.6 ppm (t) 24.4 ppm (t) 29.2 ppm (t) 29.4 ppm (t) 31.9 ppm (t) 32.4 ppm (t) 128.5 ppm (d) 128.7 ppm (d) 132.0 ppm (d) 132.7 ppm (d,) 134.7 ppm (s); HRMS calcd for  $\text{C}_{14}\text{H}_{24}\text{BN}_2$ : 231.2033; found 231.2030.

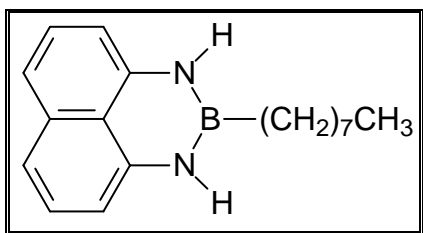


**2-(2-Phenylethyl)-1,3,2-benzodiazaborolane 45:**

Wilkinson's catalyst, 21%, Rhodium carbonyl hydride catalyst, 20%.  $^{11}\text{B}$  NMR (128 MHz,  $\text{CH}_2\text{Cl}_2$ )  $\delta$  32 ppm (s); HRMS calcd for  $\text{C}_{14}\text{H}_{15}\text{BN}_2$ : 221.9346; found 221.9348.

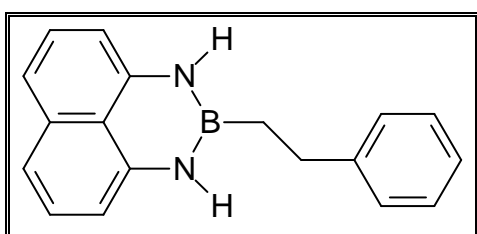


**2-(2-*trans*-Phenylvinyl)-1,3,2-benzodiazaborolane 46:** Wilkinson's catalyst, 4%, Rhodium carbonyl hydride catalyst, 64%.  $^{11}\text{B}$  NMR (128 MHz,  $\text{CH}_2\text{Cl}_2$ )  $\delta$  27 ppm (s); HRMS calcd for  $\text{C}_{14}\text{H}_{13}\text{BN}_2$ : 219.9189; found 219.9182.

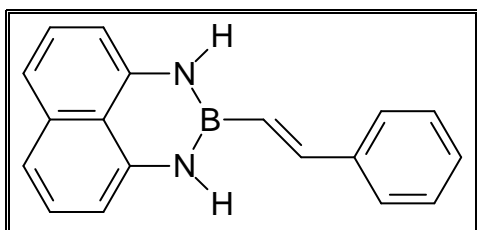


**2-Octyl-naphtho[1,8-de][1,3,2]diazaborinane 47:**

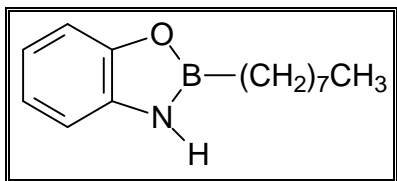
Wilkinson's catalyst, 10%, Rhodium carbonyl hydride catalyst, 92%.  $^{11}\text{B}$  NMR (128 MHz,  $\text{CH}_2\text{Cl}_2$ )  $\delta$  27 ppm (s); HRMS calcd for  $\text{C}_{18}\text{H}_{25}\text{BN}_2$ : 280.2111; found 280.2114.



**2-(2-Phenylethyl)-naphtho[1,8-de][1,3,2]diazaborinane 48:** Wilkinson's catalyst, 4%, Rhodium carbonyl hydride catalyst, 34%.  $^{11}\text{B}$  NMR (128 MHz,  $\text{CH}_2\text{Cl}_2$ )  $\delta$  27 ppm (s); HRMS calcd for  $\text{C}_{18}\text{H}_{17}\text{BN}_2$ : 272.1387; found 272.1384



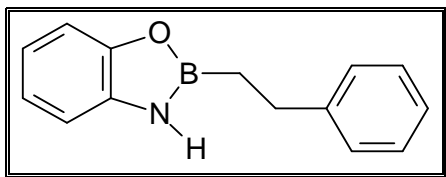
**2-(2-*trans*-Phenylvinyl)-naphtho[1,8-de][1,3,2]diazaborinane 49:** Wilkinson's catalyst, 62%, Rhodium carbonyl hydride catalyst, 75%.  $^{11}\text{B}$  NMR (128 MHz,  $\text{CH}_2\text{Cl}_2$ )  $\delta$  28 ppm (s); HRMS calcd for  $\text{C}_{18}\text{H}_{15}\text{BN}_2$ : 270.1231; found 270.1233.



**2-Octyl-1,3,2-benzoxazaborolane 50:**

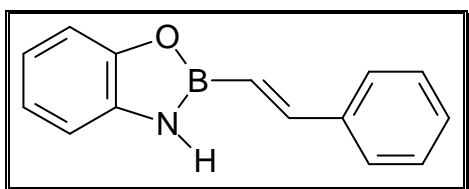
Wilkinson's catalyst, 18% (30 min microwave irradiation), Rhodium carbonyl hydride catalyst,

81%. (no microwave irradiation).  $^{11}\text{B}$  NMR (128 MHz,  $\text{CH}_2\text{Cl}_2$ )  $\delta$  34 ppm (s); HRMS calcd for  $\text{C}_{14}\text{H}_{22}\text{BNO}$ : 231.1695; found 231.1691.



**2-(2-Phenylethyl)-1,3,2-benzoxazaborolane 51:**

Wilkinson's catalyst, 32%. Rhodium carbonyl hydride catalyst, 89%. (no microwave irradiation)  $^{11}\text{B}$  NMR (128 MHz,  $\text{CH}_2\text{Cl}_2$ )  $\delta$  34 ppm (s); HRMS calcd for  $\text{C}_{14}\text{H}_{14}\text{BNO}$ : 223.1071; found 223.1068.



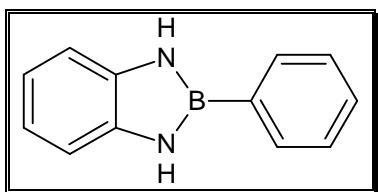
**2-(2-trans-Phenylvinyl)-1,3,2-benzoxazaborolane 52:** Wilkinson's catalyst, 25% (30 min microwave irradiation). Rhodium carbonyl hydride catalyst, 89%. (no microwave irradiation).  $^{11}\text{B}$  NMR (128 MHz,  $\text{CH}_2\text{Cl}_2$ )  $\delta$  31 ppm (s); HRMS calcd for  $\text{C}_{14}\text{H}_{12}\text{BNO}$ : 221.0951; found 221.0955.

### **6.3. Condensation Reactions of Diamines and Boronic Acids**

#### **6.3.1. Condensation Reactions of 1,2-Phenylenediamine and Boronic Acids**

**General Procedures for the synthesis of compounds 58-63: Method A** To a solution of **20** in toluene ( $4.11 \times 10^{-3}$  mol in 50 ml,  $8.20 \times 10^{-2}$  M) was added the boronic acid ( $4.11 \times 10^{-3}$  mol) in one portion. The round-bottomed flask was equipped with a Dean and Stark trap, and the solution was stirred and heated at  $110^\circ\text{C}$  for 3 hours. The precipitate was isolated by filtration and washed with toluene (15ml).

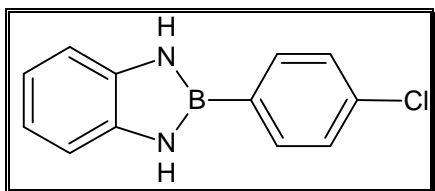
**Method B** The boronic acid ( $4.10 \times 10^{-4}$  mol) and **20** ( $4.10 \times 10^{-4}$  mol) were added to a microwave tube and sealed with a microwave septum. The tube was shaken to mix and subjected to microwave irradiation at 100°C for 15 minutes (150W) under a closed system.  $^1\text{H}$ ,  $^{11}\text{B}$  and  $^{13}\text{C}$  NMR spectra were used to confirm the product obtained by this method was identical to that obtained for Method A.



**2-Phenyl-1,3,2-benzodiazaborolane 58 - Method A**

Pale yellow solid, 95%.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  6.80-6.84 ppm (m) 7.04-7.07 ppm (m) 7.38-7.43 ppm (m) 7.88-7.91 ppm (m) 9.08 ppm (s);  $^{11}\text{B}$  NMR  $\delta$  29 ppm (s);  $^{13}\text{C}$  NMR  $\delta$  111.2 ppm (d) 119.4 ppm (d) 128.0 ppm (d) 129.7 ppm (d) 132.9 ppm (d) 136.3 (s);  $^{15}\text{N}$  NMR  $\delta$  104 ppm (s); GCMS  $m/z$  194.2  $[\text{M}+\text{H}]^+$  (100%); HRMS calcd for  $\text{C}_{12}\text{H}_{10}\text{BN}_2$ : 193.0937; found 193.0938.

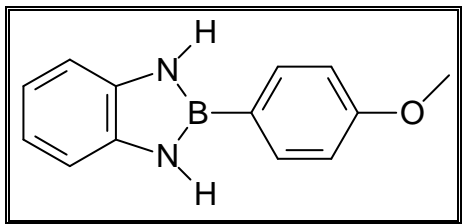
**Method B** Beige solid, 95%.



**2-(4-Chlorophenyl)-1,3,2-benzodiazaborolane 59 -**

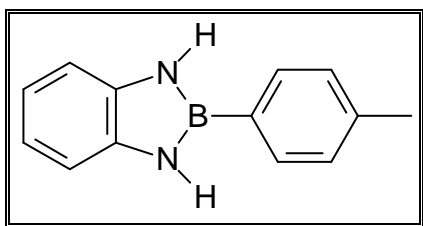
**Method A** White solid, 97%.  $^1\text{H}$  NMR  $\delta$  6.80-6.84 ppm (m) 7.03-7.07 ppm (m) 7.49 ppm (d,  $J=8.2$  Hz) 7.90 ppm (d,  $J=8.2$  Hz) 9.16 ppm (s);  $^{11}\text{B}$  NMR  $\delta$  28 ppm (s);  $^{13}\text{C}$  NMR  $\delta$  111.3 ppm (d) 118.9 ppm (d) 128.5 ppm (d) 134.7 ppm (s) 135.6 ppm (d) 137.5 ppm (s);  $^{15}\text{N}$  NMR  $\delta$  111 ppm (s); GCMS  $m/z$  228.1  $[\text{M}+\text{H}]^+$  (100%); HRMS calcd for  $\text{C}_{12}\text{H}_9\text{BN}_2\text{Cl}$ : 227.0547; found 227.0551.

**Method B** Off-white solid, 92%.



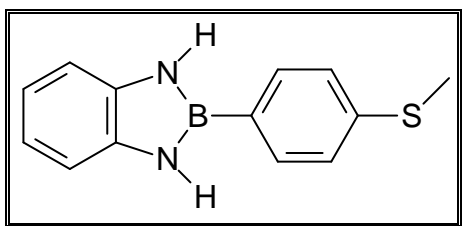
**2-(4-Methoxyphenyl)-1,3,2-benzodiazaborolane 60 - Method A** White crystalline solid, 94%.  $^1\text{H}$  NMR  $\delta$  3.81 (s) 6.76-6.80 ppm (m) 6.98 ppm (d,  $J=8.7$  Hz) 6.99-7.03 ppm (m) 7.82 ppm (d,  $J=8.6$  Hz) 8.94 ppm (s);  $^{11}\text{B}$  NMR  $\delta$  29 ppm (s);  $^{13}\text{C}$  NMR  $\delta$  55.4 (q) 111.0 ppm (d) 114.1 ppm (d) 118.9 ppm (d) 135.4 (d) 138.1 ppm (s) 160.7 ppm (s)  $^{15}\text{N}$  NMR  $\delta$  107 ppm (s); GCMS  $m/z$  224.2  $[\text{M}+\text{H}]^+$  (100%); HRMS calcd for  $\text{C}_{13}\text{H}_{12}\text{BN}_2\text{O}$ : 223.1043; found 223.1041.

**Method B** Off-white solid, 62%.



**2-(4-methylphenyl)-1,3,2-benzodiazaborolane 61 - Method A** White solid, 89%.  $^1\text{H}$  NMR  $\delta$  2.33 ppm (s) 6.77-6.81 ppm (m) 7.01-7.05 ppm (m) 7.23 ppm (d,  $J= 8.2$  Hz) 7.78 ppm (d,  $J= 7.9$  Hz) 9.01 ppm (s);  $^{11}\text{B}$  NMR  $\delta$  30 ppm (s);  $^{13}\text{C}$  NMR 21.6 ppm (q) 111.2 ppm (d) 118.6 ppm (d) 129.0 ppm (d) 133.9 ppm (d) 137.7 ppm (s) 139.1 ppm (s);  $^{15}\text{N}$  NMR  $\delta$  110 ppm (s); GCMS  $m/z$  208.2  $[\text{M}+\text{H}]^+$  (100%); HRMS calcd for  $\text{C}_{13}\text{H}_{12}\text{BN}_2$ : 207.1094; found 207.1098.

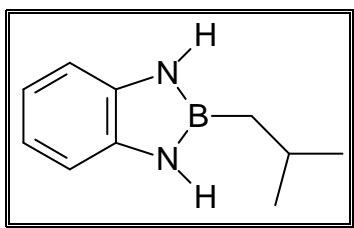
**Method B** Off-white solid, 78%.



**2-[4-(methylsulfanyl)phenyl]-1,3,2-benzodiazaborolane 62 - Method A** White crystalline solid, 95%.  $^1\text{H}$  NMR 3.30 ppm (s) 6.78-6.81 ppm (m) 7.00-7.05 ppm (m)

7.30 ppm (d,  $J = 8.3$  Hz) 7.82 ppm (d,  $J = 8.3$  Hz) 9.08 ppm (s);  $^{11}\text{B}$  NMR  $\delta$  28 ppm (s);  $^{13}\text{C}$  NMR 14.7 ppm (q) 111.1 ppm (d) 118.7 ppm (d) 125.6 ppm (d) 134.3 ppm (d) 137.7 ppm (s) 140.1 ppm (s);  $^{15}\text{N}$  NMR  $\delta$  109 ppm (s); GCMS  $m/z$  240.1  $[\text{M}+\text{H}]^+$  (100%) 225.1 (50%) HRMS calcd for  $\text{C}_{13}\text{H}_{12}\text{BN}_2\text{S}$ : 239.0814; found 239.0812.

**Method B** Pale beige solid, 87%.



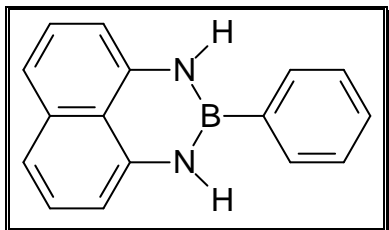
**2-(2-Methylpropyl)-1,3,2-benzodiazaborolane 63 - Method A** Beige solid, 90%.  $^1\text{H}$  NMR  $\delta$  0.96 ppm (d,  $J = 6.5$  Hz) 1.07 ppm (d,  $J = 7.1$  Hz), 1.91-1.99 ppm (m) 6.70-6.73 ppm (m) 6.91-6.94 ppm (m) 8.33 ppm (s);  $^{11}\text{B}$  NMR  $\delta$  32 ppm (s)  $^{13}\text{C}$  NMR  $\delta$  23.0 ppm (t) 25.9 ppm (q) 26.2 ppm (d) 110.6 ppm (d) 118.0 ppm (d) 137.4 ppm (s)  $^{15}\text{N}$  NMR  $\delta$  113 ppm (s); GCMS  $m/z$  174.1 (45%)  $[\text{M}+\text{H}]^+$  131.1 (30%) 118.1 (100%); 117.1 (26%)

**Method B** Beige solid, 70%

### 6.3.2. Condensation Reactions of 1,8-Diaminonaphthalene and Boronic Acids

**General Procedures for the synthesis of compounds 64-69: Method C** Same as for compounds **58-63**, but solvent removed in vacuo and the crude product purified by column chromatography on silica, eluting with  $\text{CH}_2\text{Cl}_2$ .

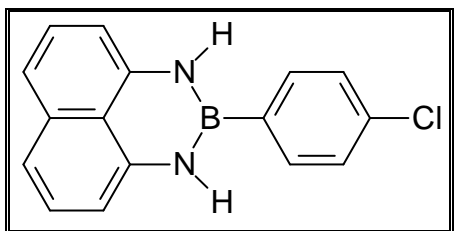
**Method D** Same as for compounds **58-63**, but crude product was purified by column chromatography on silica, eluting with  $\text{CH}_2\text{Cl}_2$ .  $^1\text{H}$ ,  $^{11}\text{B}$  and  $^{13}\text{C}$  NMR spectra in  $\text{DMSO}-d_6$  were used to confirm the product obtained by this method was identical to that obtained for Method C.



**2-Phenyl-naphtho[1,8-de][1,3,2]diazaborinane 64 -**

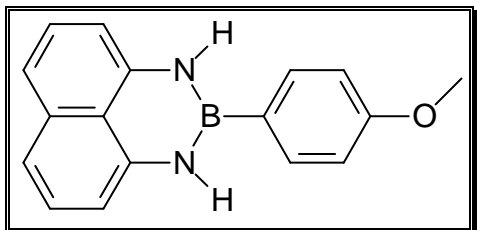
**Method C** Pale green crystalline solid, 77%.  $^1\text{H}$  NMR  $\delta$  6.60 ppm (dd,  $J=7.5$  Hz,  $J=0.75$  Hz) 6.91 ppm (dd,  $J=8.3$  Hz,  $J=0.72$  Hz) 7.09 ppm (dd,  $J=7.8$  Hz) 7.42-7.48 ppm (m) 7.92-7.94 ppm (m) 8.24 ppm (s)  $^{11}\text{B}$  NMR  $\delta$  30 ppm (s)  $^{13}\text{C}$  NMR  $\delta$  106.1 ppm (d) 116.7 ppm (d) 120.1 ppm (s) 128.1 ppm (d) 130.4 ppm (d) 133.1 ppm (d) 136.4 ppm (s) 142.8 ppm (s)  $^{15}\text{N}$  NMR  $\delta$  101 ppm (s); GCMS  $m/z$  244.2  $[\text{M}+\text{H}]^+$  (70%); HRMS calcd for  $\text{C}_{16}\text{H}_{12}\text{BN}_2$ : 243.1094; found 243.1092.

**Method D** Pale green crystalline solid, 79%.



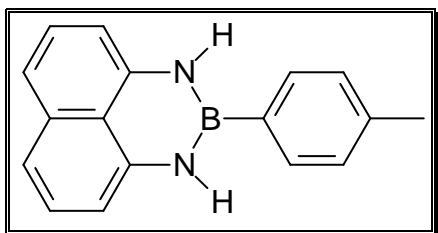
**2-(4-Chlorophenyl)-naphtho[1,8-de][1,3,2]diazaborinane 65 - Method C**, Brown crystalline solid, 66%.  $^1\text{H}$  NMR  $\delta$  6.58 ppm (dd,  $J=7.3$  Hz,  $J=0.85$  Hz) 6.91 ppm (dd,  $J=8.3$  Hz,  $J=0.84$  Hz) 7.08 ppm (dd,  $J=7.8$  Hz) 7.49-7.53 ppm (m) 7.94-7.97 ppm (m) 8.30 ppm (s)  $^{11}\text{B}$  NMR  $\delta$  29 ppm (s)  $^{13}\text{C}$  NMR  $\delta$  106.2 ppm (d) 116.8 ppm (d) 120.2 ppm (s) 128.1 ppm (d) 128.2 ppm (d) 135.0 ppm (d) 135.5 ppm (s) 136.4 ppm (s) 142.3 ppm (s)  $^{15}\text{N}$  NMR  $\delta$  101 ppm (s); GCMS  $m/z$  278.2  $[\text{M}+\text{H}]^+$  (90%); HRMS calcd for  $\text{C}_{16}\text{H}_{11}\text{BN}_2\text{Cl}$ : 277.0704; found 277.0701.

**Method D** Brown crystalline solid, 72%.



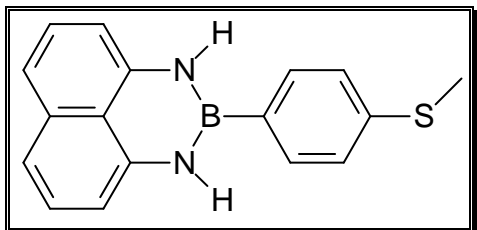
**2-(4-Methoxyphenyl)-naphtho[1,8-de][1,3,2]diazaborinane 66 - Method C** Grey crystalline solid 73%.  $^1\text{H}$  NMR  $\delta$  3.81 ppm (s) 6.58 ppm (dd,  $J= 7.4$  Hz,  $J= 0.95$  Hz) 6.88 ppm (dd,  $J= 8.2$  Hz,  $J= 0.76$  Hz) 7.00 ppm (d,  $J= 8.7$  Hz) 7.07 ppm (t  $J= 8.0$  Hz) 7.89 ppm (d,  $J= 8.7$  Hz,) 8.19 ppm (s)  $^{11}\text{B}$  NMR  $\delta$  29 ppm (s)  $^{13}\text{C}$  NMR  $\delta$  55.5 ppm (q) 105.9 ppm (d) 113.7 ppm (d) 116.5 ppm (d) 119.9 ppm (s) 128.1 ppm (d) 134.8 ppm (d) 136.4 ppm (s) 142.9 ppm (s) 161.5 ppm (s)  $^{15}\text{N}$  NMR  $\delta$  101 ppm (s); HRMS calcd for  $\text{C}_{17}\text{H}_{14}\text{BN}_2\text{O}$ : 273.1199; found 273.1201.

**Method D** Grey crystalline solid, 81%.



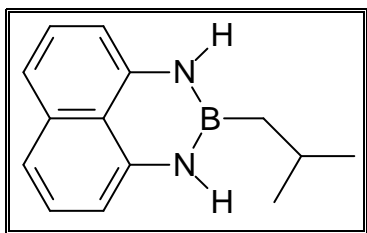
**2-(4-Methylphenyl)-naphtho[1,8-de][1,3,2]diazaborinane 67 - Method C** Pale green crystalline solid, 72%.  $^1\text{H}$  NMR  $\delta$  2.35 ppm (s) 6.58 ppm (dd,  $J= 7.4$  Hz,  $J= 0.85$  Hz) 6.89 ppm (dd,  $J= 8.2$  Hz,  $J= 0.90$  Hz) 7.09 ppm (dd,  $J= 7.8$  Hz) 7.25 ppm (dd,  $J= 8.0$  Hz,  $J= 0.60$  Hz) 7.82 ppm (d,  $J= 7.9$  Hz) 8.19 ppm (s)  $^{11}\text{B}$  NMR  $\delta$  29 ppm (s)  $^{13}\text{C}$  NMR  $\delta$  21.6 ppm (q) 106.0 ppm (d) 116.6 ppm (d) 120.0 ppm (s) 128.1 ppm (d) 128.7 ppm (d) 133.2 ppm (d) 136.4 ppm (s) 139.9 ppm (s) 142.9 ppm (s)  $^{15}\text{N}$  NMR  $\delta$  101 ppm (s); GCMS  $m/z$  258.2  $[\text{M}+\text{H}]^+$  (80%) 207.1 (100%) 166.2 (40%); HRMS calcd for  $\text{C}_{17}\text{H}_{14}\text{BN}_2$ : 257.1250; found 257.1248.

**Method D** Pale green crystalline solid, 57%.



**2-[4-(Methylsulfonyl)phenyl]-naphtho[1,8-de][1,3,2]diazaborinane 68 - Method C**, pale brown crystalline solid, 65%.  $^1\text{H}$  NMR  $\delta$  2.52 ppm (s) 6.58 ppm (dd,  $J= 7.4$  Hz,  $J= 0.85$  Hz) 6.89 ppm (dd,  $J= 8.1$  Hz,  $J= 0.82$  Hz) 7.07 ppm (m) 7.31 ppm (d,  $J= 8.4$  Hz) 7.87 ppm (d,  $J= 8.3$  Hz) 8.22 ppm (s)  $^{11}\text{B}$  NMR  $\delta$  29 ppm (s)  $^{13}\text{C}$  NMR  $\delta$  14.7 ppm (q) 106.1 ppm (d) 116.6 ppm (d) 120.1 ppm (s) 125.2 ppm (d) 128.1 ppm (d) 133.6 ppm (d) 136.4 ppm (s) 141.0 ppm (s) 142.8 ppm (s)  $^{15}\text{N}$  NMR  $\delta$  100 ppm (s); GCMS  $m/z$  267.1  $[\text{M}+\text{H}]^+$  (15%) 207.1 (100%) 191.1 (20%)

**Method D** Brown crystalline solid, 71%.



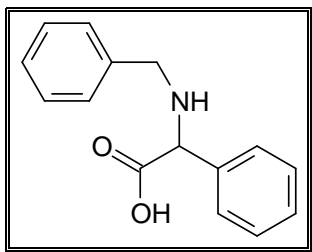
**2-(2-Methylpropyl)-naphtho[1,8-de][1,3,2]diazaborinane 69 - Method C**, Grey crystalline solid, 76%.  $^1\text{H}$  NMR  $\delta$  0.77 ppm (d,  $J= 7.4$  Hz) 0.95 ppm (d, 6.6 Hz) 1.9-2.0 ppm (m) 6.39 ppm (dd,  $J= 7.5$  Hz,  $J= 0.95$  Hz) 6.83 ppm (dd,  $J= 8.4$  Hz,  $J= 0.83$  Hz) 7.02 ppm (m) 7.70 ppm (s)  $^{11}\text{B}$  NMR  $\delta$  33 ppm (s)  $^{13}\text{C}$  NMR  $\delta$  24.8 ppm (d) 25.4 ppm (q) 25.8 ppm (t) 104.9 ppm (d) 115.6 ppm (d) 119.4 ppm (s) 127.5 ppm (d) 135.9 ppm (s) 142.4 ppm (s)  $^{15}\text{N}$  NMR 100 ppm (s); GCMS  $m/z$  244.2  $[\text{M}+\text{H}]^+$  (100%) 181.2 (40%) 168.2 (45%)

**Method D** Grey crystalline solid, 68%.

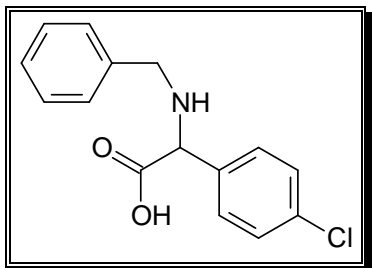
#### 6.4. On the Use of Heterosubstituted Borolanes and Borinanes in the Petasis Reactions

**General Procedure for the synthesis of compounds 73-108: Method A.** To a solution of aldehyde ( $2 \times 10^{-3}$  mol) in  $\text{CH}_2\text{Cl}_2$  (10ml) was added the borane ( $2 \times 10^{-3}$  mol) in one portion. The solution was stirred for 5 minutes and the amine ( $2 \times 10^{-3}$  mol) was added. The reaction was sealed and stirred at room temperature for 48 hours, after which the solution was filtered and the solvent allowed to evaporate over time. All yields determined by GC-MS analysis of the crude reaction mixture. Yields using compounds **58-63** given in brackets; nd = not detected.

**Method B:** To a solution of aldehyde ( $2 \times 10^{-3}$  mol) in  $\text{CH}_2\text{Cl}_2$  (10ml) in a microwave tube was added the borane ( $2 \times 10^{-3}$  mol) in one portion. The solution was stirred for 5 minutes and the amine ( $2 \times 10^{-3}$  mol) was added. The reaction was sealed with a microwave septum and irradiated for 10 minutes at  $120^\circ\text{C}$  (300W). The solution was filtered and the solvent allowed to evaporate over time. All yields determined by GC-MS analysis of the crude reaction mixture. Yields using compounds **58-63** given in brackets; nd = not detected.

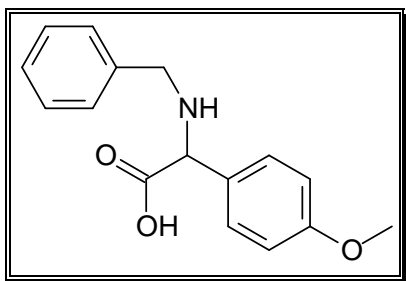


**(Benzylamino)(phenyl)acetic acid 73 – Method A:** White solid, 24% (nd).  $^1\text{H}$  NMR  $\delta$  3.75 ppm (d,  $J= 13.4$  Hz) 3.53 ppm (d,  $J= 13.4$  Hz) 3.62 ppm (d,  $J= 13.4$  Hz) 4.28 ppm (s) 7.23-7.28 ppm (m) 7.30-7.35 ppm (m) 7.39 ppm (t,  $J= 7.44$  Hz) 7.47 ppm (d,  $J= 7.44$  Hz);  $^{13}\text{C}$  NMR  $\delta$  57.8 ppm (d) 71.8 ppm (d) 127.1 ppm (d) 128.0 (d) 128.2 ppm (d) 128.4 ppm (d) 128.7 ppm (d) 172.1 ppm (s); HRMS calcd for  $\text{C}_{15}\text{H}_{16}\text{NO}_2$ : 242.1181; found 242.1182.



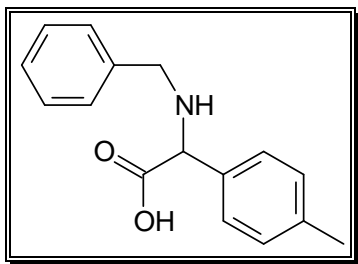
**(Benzylamino)(4-chlorophenyl)acetic acid 74 –**

**Method A:** White solid, 17% (nd).  $^1\text{H}$  NMR  $\delta$  3.96 ppm (s) 4.69 ppm (s) 7.23-7.28 ppm (m) 7.28-7.45 ppm (m)  $^{13}\text{C}$  NMR  $\delta$  51.4 ppm (s) 70.9 ppm (d) 127.4 ppm (d) 128.0 (d) 128.2 ppm (d) 128.6 ppm (d) 128.7 ppm (d) 129.4 ppm (d) 130.5 ppm (d) 135.0 ppm (s) 135.9 ppm (d) 171.9 ppm (s); HRMS calcd for  $\text{C}_{15}\text{H}_{15}\text{NO}_2\text{Cl}$ : 276.0791; found 276.073.



**(Benzylamino)(4-methoxyphenyl)acetic acid 75 –**

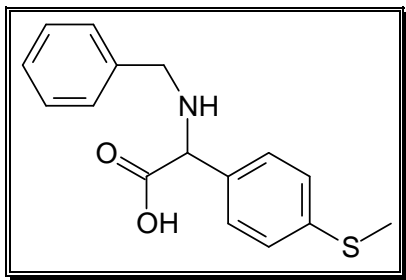
**Method A:** White solid, 57% (7%).  $^1\text{H}$  NMR  $\delta$  3.50 ppm (d,  $J= 13.3$  Hz) 3.61 ppm (d,  $J= 13.3$  Hz) 3.15 ppm (s) 4.20 ppm (s) 6.94 ppm (d,  $J= 8.84$  Hz) 7.23-7.28 ppm (m) 7.34 ppm (d,  $J= 4.40$  Hz) 7.38 ppm (d,  $J= 8.75$  Hz);  $^{13}\text{C}$  NMR  $\delta$  55.5 ppm (q) 58.2 ppm (t) 71.8 ppm (d) 114.3 ppm (d) 127.6 (d) 128.7 ppm (d) 129.0 ppm (s) 129.2 ppm (d) 130.4 ppm (d) 138.7 ppm (s) 159.5 ppm (s) 172.9 ppm (s); HRMS calcd for  $\text{C}_{16}\text{H}_{18}\text{NO}_3$ : 272.1287; found 272.1289.



**(Benzylamino)(4-methylphenyl)acetic acid 76 –**

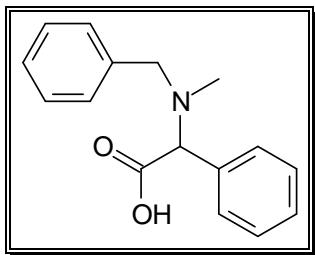
**Method A:** Pale yellow solid, 58% (nd).  $^1\text{H}$  NMR  $\delta$  2.29 ppm (s) 3.51 ppm (d,  $J= 13.5$  Hz) 3.61 ppm (d,  $J= 13.4$  Hz) 4.22 ppm (s) 7.19 ppm (d,  $J= 7.76$  Hz) 7.23-

7.28 ppm (m) 7.29-7.36 ppm (m);  $^{13}\text{C}$  NMR  $\delta$  20.7 ppm (q) 57.8 ppm (d) 71.5 ppm (d) 127.1 ppm (d) 128.0 (d) 128.2 ppm (d) 128.6 ppm (d) 128.7 ppm (d) 128.9 ppm (d) 133.6 ppm (s) 137.2 ppm (s) 138.2 ppm (s) 172.3 ppm (s) HRMS calcd for  $\text{C}_{16}\text{H}_{18}\text{NO}_2$ : 256.1338; found 256.1337.



**(Benzylamino)[4-(methylsulfonyl)phenyl]acetic**

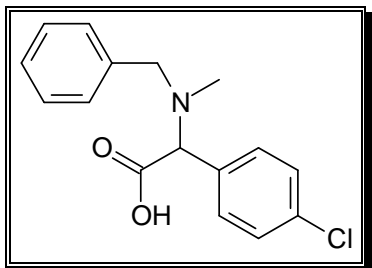
**acid 77 – Method A:** White solid, 45% (nd).  $^1\text{H}$  NMR  $\delta$  2.47 ppm (s) 3.49 ppm (d,  $J = 13.0$  Hz) 3.59 ppm (d,  $J = 13.0$  Hz) 4.21 ppm (s) 7.22-7.34 ppm (m) 7.39 ppm (d,  $J = 8.28$  Hz);  $^{13}\text{C}$  NMR  $\delta$  15.0 ppm (q) 58.3 ppm (t) 71.8 ppm (d) 126.2 ppm (d) 127.5 (d) 128.7 ppm (d) 129.1 ppm (d) 129.7 ppm (d) 133.9 ppm (s) 138.4 ppm (s) 138.9 ppm (s) 138.2 ppm (s) 172.7 ppm (s); HRMS calcd for  $\text{C}_{16}\text{H}_{18}\text{NO}_2\text{S}$ : 288.1058; found 288.1059.



**(Benzylmethylamino)(phenyl)acetic acid 79 – Method A:**

White solid, 82% (nd).  $^1\text{H}$  NMR  $\delta$  2.10 (s) 3.75 ppm (d,  $J = 13.4$  Hz) 3.53 ppm (d,  $J = 13.4$  Hz) 3.62 ppm (d,  $J = 13.4$  Hz) 4.28 ppm (s) 7.23-7.28 ppm (m) 7.30-7.35 ppm (m) 7.39 ppm (t,  $J = 7.44$  Hz) 7.47 ppm (d,  $J = 7.44$  Hz);  $^{13}\text{C}$  NMR  $\delta$  38.4 ppm (q) 57.8 ppm (d) 71.8 ppm (d) 127.1 ppm (d) 128.0 (d) 128.2 ppm (d) 128.4 ppm (d) 128.7 ppm (d) 172.1 ppm (s); HRMS calcd for  $\text{C}_{16}\text{H}_{18}\text{NO}_2$ : 256.1338; found 256.1339. (edit spectra)

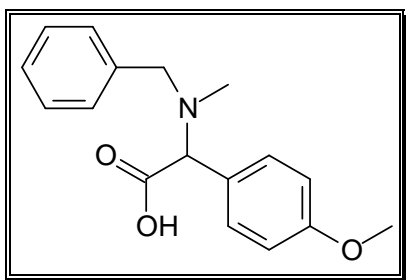
**Method B:** 63% (10%).



**(Benzylmethylamino)(4-chlorophenyl)acetic acid 80 –**

**Method A:** White solid, 84% (nd).  $^1\text{H}$  NMR  $\delta$  2.44 (s) 3.96 ppm (s) 4.69 ppm (s) 7.23-7.28 ppm (m) 7.28-7.45 ppm (m)  $^{13}\text{C}$  NMR  $\delta$  32.3 ppm (q) 51.4 ppm (s) 70.9 ppm (d) 127.4 ppm (d) 128.0 (d) 128.2 ppm (d) 128.6 ppm (d) 128.7 ppm (d) 129.4 ppm (d) 130.5 ppm (d) 135.0 ppm (s) 135.9 ppm (d) 171.9 ppm (s); HRMS calcd for  $\text{C}_{16}\text{H}_{17}\text{NO}_2\text{Cl}$ : 290.0948; found 290.0945.

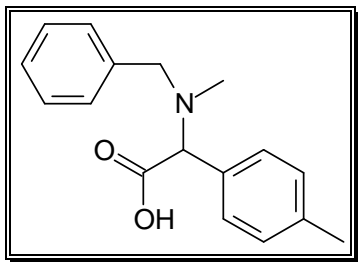
**Method B:** 30% (nd).



**(Benzylmethylamino)(4-methoxyphenyl)acetic acid**

**81 – Method A:** White solid, 65% (58%).  $^1\text{H}$  NMR  $\delta$  2.09 (s) 3.50 ppm (d,  $J=$  13.3 Hz) 3.61 ppm (d,  $J=$  13.3 Hz) 3.15 ppm (s) 4.20 ppm (s) 6.94 ppm (d,  $J=$  8.84 Hz) 7.23-7.28 ppm (m) 7.34 ppm (d,  $J=$  4.40 Hz) 7.38 ppm (d,  $J=$  8.75 Hz);  $^{13}\text{C}$  NMR  $\delta$  38.9 ppm (q) 55.5 ppm (d) 58.2 ppm (t) 71.8 ppm (d) 114.3 ppm (d) 127.6 (d) 128.7 ppm (d) 129.0 ppm (s) 129.2 ppm (d) 130.4 ppm (d) 138.7 ppm (s) 159.5 ppm (s) 172.9 ppm (s); HRMS calcd for  $\text{C}_{17}\text{H}_{20}\text{NO}_3$ : 286.1443; found 286.1441.

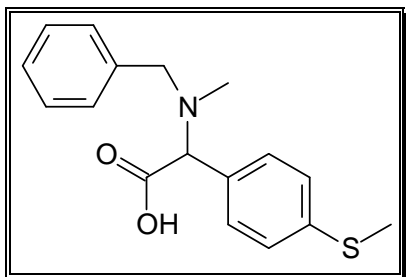
**Method B:** 46% (38%).



**(Benzylmethylamino)(4-methylphenyl)acetic acid 82 –**

**Method A:** White solid, 77% (35%).  $^1\text{H}$  NMR  $\delta$  2.09 (s) 2.29 ppm (s) 3.51 ppm (d,  $J=$  13.5 Hz) 3.61 ppm (d,  $J=$  13.4 Hz) 4.22 ppm (s) 7.19 ppm (d,  $J=$  7.76 Hz) 7.23-7.28 ppm (m) 7.29-7.36 ppm (m);  $^{13}\text{C}$  NMR  $\delta$  20.7 ppm (q) 38.4 ppm (q) 57.8 ppm (d) 71.5 ppm (d) 127.1 ppm (d) 128.0 (d) 128.2 ppm (d) 128.6 ppm (d) 128.7 ppm (d) 128.9 ppm (d) 133.6 ppm (s) 137.2 ppm (s) 138.2 ppm (s) 172.3 ppm (s); HRMS calcd for  $\text{C}_{17}\text{H}_{20}\text{NO}_2$ : 270.1494; found 270.1495.

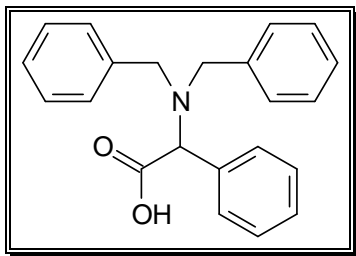
**Method B:** 69% (39%).



**(Benzylmethylamino)[4-(methylsulfanyl)phenyl]**

**acetic acid 83 – Method A:** White solid, 92% (61%).  $^1\text{H}$  NMR  $\delta$  2.09 (s) 2.47 ppm (s) 3.49 ppm (d,  $J=$  13.0 Hz) 3.59 ppm (d,  $J=$  13.0 Hz) 4.21 ppm (s) 7.22-7.34 ppm (m) 7.39 ppm (d,  $J=$  8.28 Hz);  $^{13}\text{C}$  NMR  $\delta$  15.0 ppm (q) 38.9 ppm (q) 58.3 ppm (t) 71.8 ppm (d) 126.2 ppm (d) 127.5 (d) 128.7 ppm (d) 129.1 ppm (d) 129.7 ppm (d) 133.9 ppm (s) 138.4 ppm (s) 138.9 ppm (s) 138.2 ppm (s) 172.7 ppm (s); HRMS calcd for  $\text{C}_{17}\text{H}_{20}\text{NO}_2\text{S}$ : 302.1215; found 302.1213.

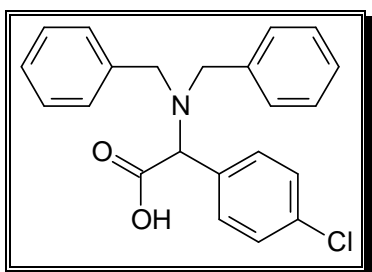
**Method B:** 54% (48%).



**(Dibenzylamino)(phenyl)acetic acid 85 – Method A:**

Pale yellow solid, 90% (nd).  $^1\text{H}$  NMR  $\delta$  3.61 (d,  $J= 14.1$  Hz) 3.75 ppm (d,  $J= 14.1$  Hz) 4.39 ppm (s) 7.21-7.26 ppm (m) 7.30-7.45 ppm (m);  $^{13}\text{C}$  NMR  $\delta$  54.2 ppm (t) 55.5 ppm (s) 65.9 ppm (d) 127.5 ppm (d) 128.2 (d) 128.7 ppm (d) 128.8 ppm (d) 129.0 ppm (d) 130.4 ppm (d) 137.2 ppm (s) 139.7 ppm (s) 173.2 ppm (s); HRMS calcd for  $\text{C}_{22}\text{H}_{21}\text{NO}_2\text{Na}$ : 354.1470; found 354.1467.

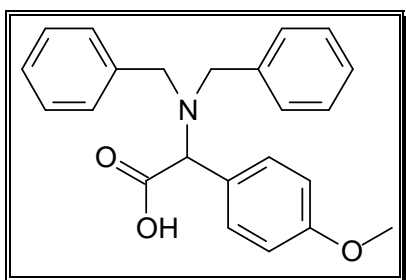
**Method B:** 50% (15%).



**(Dibenzylamino)(4-chlorophenyl)acetic acid 86 –**

**Method A:** Pale yellow solid, 74% (nd).  $^1\text{H}$  NMR  $\delta$  3.59 (d,  $J= 14.3$  Hz) 3.73 ppm (d,  $J= 14.3$  Hz) 4.37 ppm (s) 7.22-7.27 ppm (m) 7.20-7.65 ppm (m);  $^{13}\text{C}$  NMR  $\delta$  54.2 ppm (t) 55.4 ppm (t) 65.3 ppm (d) 127.5 ppm (d) 127.8 (d) 128.8 ppm (d) 128.9 ppm (d) 132.9 ppm (s) 136.4 ppm (d) 139.5 ppm (s) 172.8 ppm (s); HRMS calcd for  $\text{C}_{22}\text{H}_{21}\text{NO}_2\text{Cl}$ : 366.1261; found 366.1263.

**Method B:** 2% (nd)

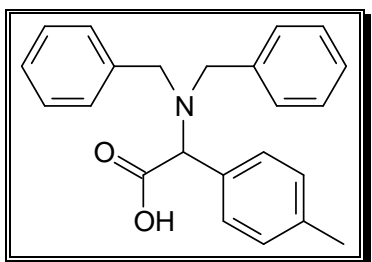


**(Dibenzylamino)(4-methoxyphenyl)acetic acid 87 –**

**Method A:** Pale yellow solid, 72% (50%).  $^1\text{H}$  NMR  $\delta$  3.66 (d,  $J= 14.6$  Hz) 3.72-

3.80 ppm (m) 4.37 ppm (br. s) 6.86-6.91 ppm (m) 6.94-6.98 ppm (m) 7.21-7.33 ppm (m);  $^{13}\text{C}$  NMR  $\delta$  54.2 ppm (t) 55.3 ppm (q) 55.4 ppm (t) 55.6 ppm (d) 113.4 ppm (d) 114.3 (d) 127.6 ppm (d) 128.8 ppm (d) 129.0 ppm (d) 130.4 ppm (d) 136.3 ppm (s) 159.3 ppm (s) 161.4 ppm (s); HRMS calcd for  $\text{C}_{23}\text{H}_{24}\text{NO}_3$ : 362.1756; found 362.1754.

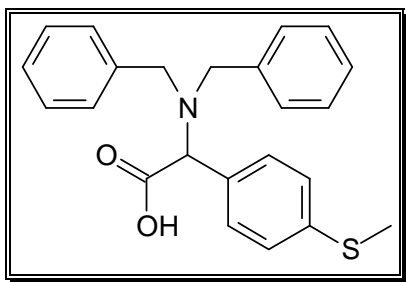
**Method B:** 31% (21%).



**(Dibenzylamino)(4-methylphenyl)acetic acid 88 –**

**Method A:** Pale yellow solid, 56% (30%).  $^1\text{H}$  NMR  $\delta$  2.28 ppm (s) 3.60 (d,  $J=$  14.3 Hz) 3.74 ppm (d,  $J=$  14.3 Hz) 4.35 ppm (s) 7.19-7.26 ppm (m) 7.30-7.34 ppm (m);  $^{13}\text{C}$  NMR  $\delta$  21.4 ppm (q) 54.0 ppm (t) 55.4 ppm (t) 65.6 ppm (d) 127.5 ppm (d) 127.7 ppm (d) 128.8 ppm (d) 129.0 ppm (d) 129.4 ppm (d) 134.1 ppm (s) 137.4 ppm (s) 139.8 ppm (s) 173.3 ppm (s) HRMS calcd for  $\text{C}_{23}\text{H}_{23}\text{NO}_2\text{Na}$ : 368.1626; found 368.1623.

**Method B:** 61% (11%).

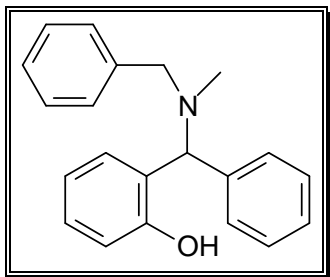


**(Dibenzylamino)[4-(methylsulfanyl)phenyl]acetic acid 89 –**

**Method A:** Pale yellow solid, 63% (24%).  $^1\text{H}$  NMR  $\delta$  2.43 ppm (s) 3.60 (d,  $J=$  14.1 Hz) 3.75 ppm (d,  $J=$  14.1 Hz) 4.34 ppm (s) 7.21-7.26 ppm (m) 7.27-7.35 ppm (m);  $^{13}\text{C}$  NMR  $\delta$  15.0 ppm (q) 54.0 ppm (t) 55.4 ppm (t) 65.6 ppm (d) 126.3 ppm (d) 127.5 ppm (d) 128.7 ppm (d) 128.8 ppm (d) 129.6 ppm (d) 133.7 ppm (d)

138.2 ppm (s) 139.7 ppm (s) 173.2 ppm (s); HRMS calcd for  $C_{23}H_{23}NO_2NaS$ : 400.1347; found 400.1346.

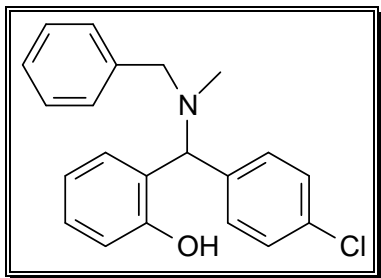
**Method B:** 38% (6%).



**2-[[Benzyl(methyl)amino](phenyl)methyl]phenol 97 –**

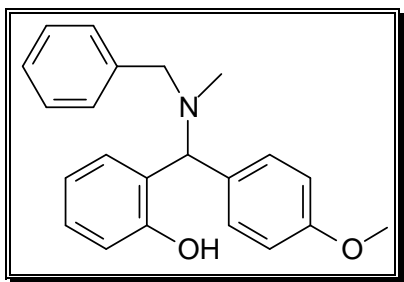
**Method A:** Pale yellow solid, 40% (5%).  $^1H$  NMR  $\delta$  1.99 ppm (s) 3.42 (d,  $J=13.3$  Hz) 3.51 ppm (d,  $J=13.3$  Hz) 4.88 ppm (s) 6.74-6.79 ppm (m) 6.99-7.05 ppm (m) 7.31-7.39 ppm (m) 7.52 ppm (d,  $J=7.3$  Hz);  $^{13}C$  NMR  $\delta$  32.8 ppm (q) 52.0 ppm (t) 59.3 ppm (t) 70.0 ppm (d) 116.3 ppm (d) 117.7 ppm (d) 119.6 ppm (d) 120.0 ppm (d) 122.8 ppm (s) 129.6 ppm (d) 133.7 ppm (d) 138.2 ppm (s) 139.7 ppm (s) 173.2 ppm (s); HRMS calcd for  $C_{21}H_{22}NO$ : 304.1701; found 304.1696.

**Method B:** 58% (8%)



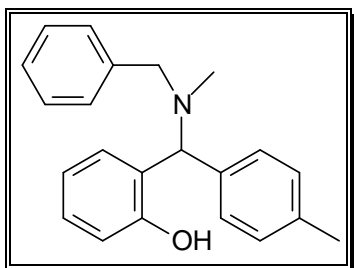
**2-[[Benzyl(methyl)amino](4-chlorophenyl)methyl]phenol 98 – Method A:** Pale yellow solid, 38% (nd).  $^1H$  NMR  $\delta$  1.99 ppm (s) 3.31 ppm (s) 3.42 (d,  $J=13.2$  Hz) 3.50 ppm (d,  $J=13.3$  Hz) 4.83 ppm (s) 6.73-6.78 ppm (m) 6.89 ppm (d,  $J=8.7$  Hz) 7.24-7.36 ppm (m) 7.42 ppm (d,  $J=7.3$  Hz);  $^{13}C$  NMR  $\delta$  32.8 ppm (q) 59.3 ppm (d) 70.0 ppm (t) 116.3 ppm (d) 117.7 ppm (d) 119.6 ppm (d) 120.0 ppm (d) 122.8 ppm (s) 129.6 ppm (d) 133.7 ppm (d) 138.2 ppm (s) 139.7 ppm (s) 173.2 ppm (s); HRMS calcd for  $C_{21}H_{21}NOCl$ : 338.1312; found 338.1318.

**Method B:** 45% (3%)



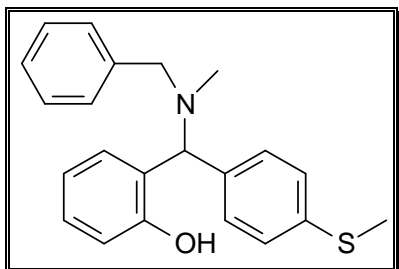
**2-[[Benzyl(methyl)amino](4-methoxyphenyl)methyl]phenol 99 – Method A:** Pale yellow solid, 42% (11%).  $^1\text{H}$  NMR  $\delta$  1.99 ppm (s) 2.24 ppm (s) 3.42 (d,  $J= 13.3$  Hz) 3.51 ppm (d,  $J= 13.3$  Hz) 4.84 ppm (s) 6.73-6.79 ppm (m) 7.12 ppm (d,  $J= 7.7$  Hz) 7.31-7.36 ppm (m) 7.39 ppm (d,  $J=7.8$  Hz) 10.78 ppm (s);  $^{13}\text{C}$  NMR  $\delta$  39.4 ppm (q) 55.3 ppm (t) 55.4 ppm (q) 59.2 ppm (t) 70.0 ppm (d) 114.3 ppm (d) 116.3 ppm (d) 119.5 ppm (d) 127.5 ppm (d) 128.1 ppm (d) 128.2 ppm (s) 128.6 ppm (d) 128.8 ppm (d) 129.1 ppm (s) 133.7 ppm (d) 139.0 ppm (s) 156.0 ppm (s) 158.8 ppm (s); HRMS calcd for  $\text{C}_{22}\text{H}_{24}\text{NO}_2$ : 334.1807; found 334.1805.

**Method B:** 68% (15%).



**2-[[Benzyl(methyl)amino](4-methylphenyl)methyl]phenol 100 – Method A:** Pale yellow solid, 45% (10%).  $^1\text{H}$  NMR  $\delta$  1.99 ppm (s) 3.42 (d,  $J= 13.3$  Hz) 3.51 ppm (d,  $J= 13.3$  Hz) 4.88 ppm (s) 6.74-6.79 ppm (m) 6.99-7.05 ppm (m) 7.31-7.39 ppm (m) 7.52 ppm (d,  $J=7.8.7$  Hz);  $^{13}\text{C}$  NMR  $\delta$  21.1 ppm (q) 39.8 ppm (q) 59.3 ppm (t) 70.2 ppm (d) 116.3 ppm (d) 119.5 ppm (d) 127.5 ppm (d) 128.1 ppm (d) 128.2 ppm (s) 128.5 ppm (d) 128.7 ppm (d) 128.8 ppm (d) 129.0 ppm (s) 134.7 ppm (d) 136.7 ppm (s) 136.8 ppm (d) 156.0 ppm (s) 158.8 ppm (s); HRMS calcd for  $\text{C}_{22}\text{H}_{24}\text{NO}$ : 318.1858; found 318.1856.

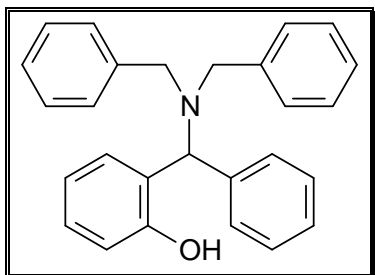
**Method B:** 71% (30%).



**2-[[Benzyl(methyl)amino][(4-methylsulfanyl)phenyl]methyl]phenol 101 –**

**Method A:** Pale yellow solid, 37% (14%).  $^1\text{H}$  NMR  $\delta$  1.99 ppm (s) 2.43 ppm (s) 3.59 ppm (s) 5.25 ppm (s) 6.74-6.79 ppm (m) 6.99-7.05 ppm (m) 7.31-7.39 ppm (m) 9.94 ppm (s);  $^{13}\text{C}$  NMR  $\delta$  15.0 ppm (q) 21.1 ppm (q) 53.6 ppm (t) 54.8 ppm (d) 58.8 ppm (t) 69.0 ppm (d) 115.8 ppm (d) 119.1 ppm (d) 127.5 ppm (d) 128.1 ppm (d) 128.2 ppm (s) 128.5 ppm (d) 128.7 ppm (d) 128.8 ppm (d) 129.0 ppm (s) 134.7 ppm (d) 136.7 ppm (s) 136.8 ppm (d) 155.3 ppm (s); HRMS calcd for  $\text{C}_{22}\text{H}_{24}\text{NOS}$ : 350.1579; found 350.1575.

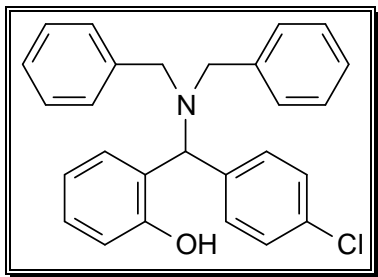
**Method B:** 73% (21%).



**2-[(Dibenzylamino)(phenyl)methyl]phenol 103 –**

**Method A:** Yellow solid, 12% (nd).  $^1\text{H}$  NMR  $\delta$  3.42 (d,  $J=13.3$  Hz) 3.51 ppm (d,  $J=13.3$  Hz) 4.88 ppm (s) 6.74-6.79 ppm (m) 6.99-7.05 ppm (m) 7.31-7.39 ppm (m) 7.52 ppm (d,  $J=7.3$  Hz);  $^{13}\text{C}$  NMR  $\delta$  52.0 ppm (t) 59.3 ppm (t) 70.0 ppm (d) 116.3 ppm (d) 117.7 ppm (d) 119.6 ppm (d) 120.0 ppm (d) 122.8 ppm (s) 129.6 ppm (d) 133.7 ppm (d) 138.2 ppm (s) 139.7 ppm (s) 173.2 ppm (s); HRMS calcd for  $\text{C}_{27}\text{H}_{26}\text{NO}$ : 380.2014; found 380.2011.

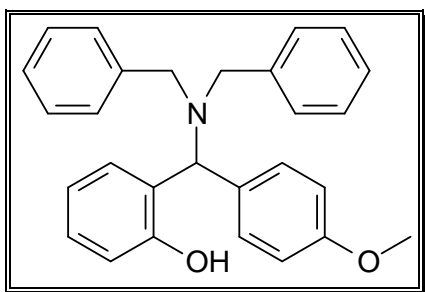
**Method B:** 50% (26%).



**2-[(Dibenzylamino)(4-chlorophenyl)methyl]phenol**

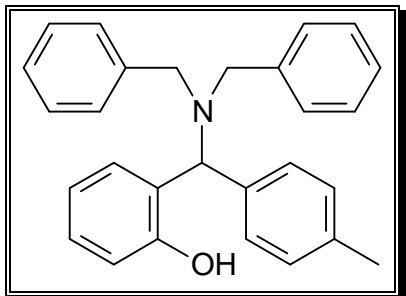
**104 – Method A:** Yellow solid, 6% (nd).  $^1\text{H}$  NMR  $\delta$  3.31 ppm (s) 3.42 (d,  $J=$  13.2 Hz) 3.50 ppm (d,  $J=$  13.3 Hz) 4.83 ppm (s) 6.73-6.78 ppm (m) 6.89 ppm (d,  $J=$  8.7 Hz) 7.24-7.36 ppm (m) 7.42 ppm (d,  $J=$ 7.3 Hz);  $^{13}\text{C}$  NMR  $\delta$  59.3 ppm (d) 70.0 ppm (t) 116.3 ppm (d) 117.7 ppm (d) 119.6 ppm (d) 120.0 ppm (d) 122.8 ppm (s) 129.6 ppm (d) 133.7 ppm (d) 138.2 ppm (s) 139.7 ppm (s) 173.2 ppm (s);; HRMS calcd for  $\text{C}_{27}\text{H}_{25}\text{NOCl}$ : 414.1625; found 414.1625.

**Method B:** nd (4%)



**2-[(Dibenzylamino)(4-methoxyphenyl)methyl]phenol 105 – Method A:** Yellow solid, 2% (nd).  $^1\text{H}$  NMR  $\delta$  2.24 ppm (s) 3.42 (d,  $J=$  13.3 Hz) 3.51 ppm (d,  $J=$  13.3 Hz) 4.84 ppm (s) 6.73-6.79 ppm (m) 7.12 ppm (d,  $J=$  7.7 Hz) 7.31-7.36 ppm (m) 7.39 ppm (d,  $J=$ 7.8 Hz) 10.78 ppm (s);  $^{13}\text{C}$  NMR  $\delta$  39.4 ppm (q) 55.3 ppm (t) 59.2 ppm (t) 70.0 ppm (d) 114.3 ppm (d) 116.3 ppm (d) 119.5 ppm (d) 127.5 ppm (d) 128.1 ppm (d) 128.2 ppm (s) 128.6 ppm (d) 128.8 ppm (d) 129.1 ppm (s) 133.7 ppm (d) 139.0 ppm (s) 156.0 ppm (s) 158.8 ppm (s); HRMS calcd for  $\text{C}_{28}\text{H}_{28}\text{NO}_2$ : 410.2120; found 410.2111.

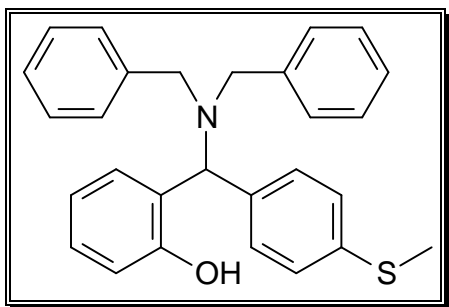
**Method B:** 60% (22%)



**2-[(Dibenzylamino)(4-methylphenyl)methyl]phenol**

**106 – Method A:** Yellow solid, 11% (nd).  $^1\text{H}$  NMR  $\delta$  2.24 ppm (s) 3.42 (d,  $J=$  13.3 Hz) 3.51 ppm (d,  $J=$  13.3 Hz) 4.84 ppm (s) 6.73-6.79 ppm (m) 7.12 ppm (d,  $J=$  7.7 Hz) 7.31-7.36 ppm (m) 7.39 ppm (d,  $J=$ 7.8 Hz) 10.78 ppm (s);  $^{13}\text{C}$  NMR  $\delta$  55.3 ppm (t) 55.4 ppm (q) 59.2 ppm (t) 70.0 ppm (d) 114.3 ppm (d) 116.3 ppm (d) 119.5 ppm (d) 127.5 ppm (d) 128.1 ppm (d) 128.2 ppm (s) 128.6 ppm (d) 128.8 ppm (d) 129.1 ppm (s) 133.7 ppm (d) 139.0 ppm (s) 156.0 ppm (s) 158.8 ppm (s); HRMS calcd for  $\text{C}_{28}\text{H}_{28}\text{NO}$ : 394.2171; found 394.2177.

**Method B:** 62% (nd)



**2-[(Dibenzylamino)[(4-methylsulfanyl)phenyl]methyl]phenol 107 – Method A:** Yellow solid, 15% (nd).  $^1\text{H}$  NMR  $\delta$  2.43 ppm (s) 3.42 (d,  $J=$  13.3 Hz) 3.51 ppm (d,  $J=$  13.3 Hz) 4.85 ppm (s) 6.74-6.79 ppm (m) 6.99-7.05 ppm (m) 7.31-7.39 ppm (m) 7.52 ppm (d,  $J=$ 7.8.7 Hz);  $^{13}\text{C}$  NMR  $\delta$  15.0 ppm (q) 53.6 ppm (t) 54.8 ppm (d) 58.8 ppm (t) 69.0 ppm (d) 115.8 ppm (d) 119.1 ppm (d) 127.5 ppm (d) 128.1 ppm (d) 128.2 ppm (s) 128.5 ppm (d) 128.7 ppm (d) 128.8 ppm (d) 129.0 ppm (s) 134.7 ppm (d) 136.7 ppm (s) 136.8 ppm (d) 155.3 ppm (s); HRMS calcd for  $\text{C}_{28}\text{H}_{26}\text{NOS}$ : 424.1735; found 424.1741.

**Method B:** 60% (nd)

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