THE SYNTHESIS AND APPLICATION OF HETEROATOM BOROLANES CONTAINING NITROGEN, OXYGEN AND SULFUR.

Dissertation submitted to the University of KwaZulu-Natal for the Degree in Master of Science (Chemistry)

By

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DISSERTATION DECLARATION

The experimental work described in this dissertation was carried out in the School of Chemistry and Physics, University of Kwa-Zulu Natal, Pietermaritzburg Campus, under the supervision of Prof R. S. Robinson.

These studies represent original work by the author and have not otherwise been submitted by the candidate for any other degree.

Signed……..

Khethukuthula Nozipho Hadebe

(Candidate)

Signed……..

Prof Ross S. Robinson

(Supervisor)

This Dissertation is dedicated

To the late Ms. Zamahlubi C. L. Hadebe

Even if you are gone, I will cherish your memory forever and hold your teachings in my heart and mind.

Love you still.

07/10/2010

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Okundlula konke ngindlulisa udumo nokubonga kuSimakade uSomandla ngokuba engiyikho kungenxa yakhe. Nakuzo izinyenye zakhithi ngithi ngiyabonga kini MaHlubi, boBhungane, Makhulukhulu, nina boMthimkhulu, ninaMangelengele, ningigcine njalo.

ABSTRACT

There is a constant need for robust and highly reactive hydroborating reagents which will be able to yield stable organoborane compounds upon their hydroboration with olefins. These stable organoborane compounds can be used as a starting material in a number of cross-coupling reactions. The objectives of this project were to synthesize heterocyclic borolanes (with mixed donor atoms) and to evaluate the stability and reactivity of such borolanes towards the hydroboration reaction. The second part of the objective was to evaluate the application of arylbenzo-1,3,2-diazaborolane compounds as potential arylating reagent in the copper(II)acetate catalyzed *N*-arylation of imidazole using the Chan-Lam coupling reaction.

Three heterocyclic borolanes were successfully synthesized from the reaction of borane-dimethyl sulfide complex with the corresponding chelating group in yield ranging from 45-96 %. These borolane showed good stability towards atmospheric oxidation and disproportionation due to elevated temperatures. A density functional calculation conducted on these borolanes showed that there was an decrease in the gap energy in the order of benzo-1,3,2-dioxaborolane > benzo-1,3,2-oxothiaborolane > benzo-1,3,2-thiazaborolane > benzo-1,3,2-dithiaborolane > benzo-1,3,2-diazaborolane. The use of benzo-1,3,2-thiazaborolane as a hydroborating reagent showed that this compound was prone to disproportionation.

The condensation reaction of boronic acid with 1,2-diaminophenyl, 1,2-dihydroxybenzene and *o*-aminophenyl mercaptan, resulted in the synthesis of eleven arylbenzo-1,3,2-boronate esters in yields between 66-99 %. The investigation on the use of arylbenzo-1,3,2-diazaboronate ester as *N*-arylating reagents in the Chan-Lam coupling showed that these compounds were unsuitable arylating reagents and that the boronic acid proved to be better arylating reagent.

CONTENTS

LIST OF ABBREVIATIONS

Å	Angstroms
$B(OH)_3$	Boric acid
B_2H_6	Diborane
BF_3	Boron triflouride
BH_3	Borane
B–O	Boron–Oxygen bond
CH_2Cl_2	Dichloromethane
COD	1,5-Cyclooctadiene
$Cu(OAc)_2$	Cupric acetate
d	Doublet
D& S	Dean and Stark apparatus
DFT	Density Functional Theory
DPPE	1,2-Bis(diphenylphosphino)ethane
Et_2O	Diethyl Ether
h.	Hours
HBoxothia	Benzo-1,3,2-oxothiaborolane
HBPin	Pinacolborane
HBthiaza	Benzo-1,3,2-thiazaborolane
J	Coupling constant
m	Multiplet
M	mol/dm^3
MW	Microwave

M–B	Metal–Boron bond
n-Bu	*n*-Butyl
NMR	Nuclear Magnetic Resonance
PPh_3	Triphenyl phosphine
$RhCl(PPh_3)_3$	Wilkinson's catalyst
RT	Room temperature
s	Singlet
SMe_2	Dimethyl sulfide
t	Triplet
THF	Tetrahydrofuran
TMEDA	Tetramethylethylene diamine

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CHAPTER 1

1.1. Introduction

1.1.1. Boron

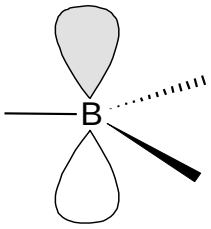


Figure 1: Structure of boron in the trigonal planar geometry, showing the p_z-orbital.

Boron is a metalloid, a group 13 element, with a formal oxidation state of +3 and has a vacant p_z-orbital perpendicular to the molecular plane (**Figure 1**). The vacant p_z-orbital makes boron naturally electron deficient and causes this element adopt a trigonal planar geometry. The boron element was first discovered and isolated as boric acid in 1808 by two groups of scientists, the Humphry Davy's group and the Joseph-Louis Gay-Lussac and Louis-Jacques Thénard group, working independently.[1] The formation of boron in nature occurs as a by-product of the direct impact of cosmic rays of the interstellar carbon and oxygen nuclei; during a process known as cosmic ray spallation. As this process is not efficient for the formation of boron, boron has a low abundance on the earth's crust.[2]

In nature, boron is isolated as borax: white crystals that have a high solubility in water. In the 1800's borax was found in remote salt lakes in the mountains of Tibet, as well as in the western parts of the United States of America. Beatty[3] reports that pure boron can be obtained from borax using several methods; however, the main method being used is that which involves three reactions steps. The initial reaction involves the conversion of pure borax into boron carbide; this reaction is followed by the reaction of the boron carbide with chlorine gas to generate boron trichloride. Lastly, pure boron is evolved by mixing

boron trichloride with hydrogen gas, resulting in the pure boron element and hydrochloric acid as a byproduct. [3]

There are two allotropes of boron, the crystalline form which is a hard, diamagnetic shiny black solid and the amorphous form which is a brown powder. The crystalline form has four polymorphs, α, β, γ and T.[4] Boron compounds have found wide and significant applications in pharmaceutical, cosmetic, pesticide and industrial chemistry.[5] The most well-known important uses of boron compounds are in the making of fiberglass, heat resistant borosilicate glass and in cleaning products.[3,4] In pharmaceuticals, boron derivatives are used in boron neutron capture therapy for cancer treatment.[6] There are also reports about the use of boron compounds for the treatment of candidiasis, but this method is still under evaluation.[5,7,8]

Boron is able to form three covalent bonds using its outermost electrons, and as a result of the vacant p_z-orbital it can be involved in π-back donations.[4] In the next sub-sections attention will be directed to boron compounds containing halides, as well as hydrogen.

1.1.1.1. Boron Trihalides

Boron is able to react with a number of halogens to yield the corresponding boron trihalides. Since the halogens have a filled p_z-orbital they are able to back donate their electrons to the empty p_z–orbital of the boron atom (**Figure 2**). The degree of back donation is, among other factors, dependent on the size of the halogen, i.e. the bigger the size of the halogen the lower the degree of back donation. The degree of back-donation has been shown to affect the Lewis acidity of the boron trihalide. BF_3 is a relatively weak Lewis acid as fluorine is smaller in size and is able to effectively back donate, creating a partial multi π-bond character for the B–F bond. As you move down in group seven of the periodic table, the relative π-back donation decreases in the sequence F> Cl> Br> I, this makes the strength of the Lewis acid increase.[1,4]

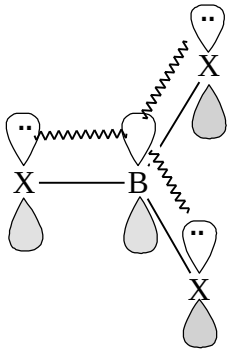


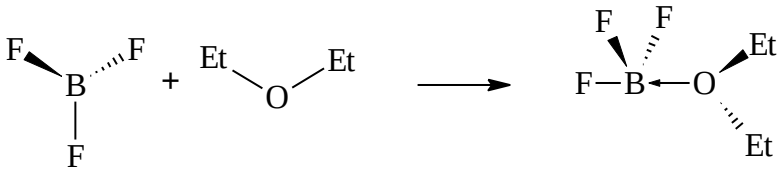
Figure 2: <u>Illustration of the π-back donation between the p_z –orbital of boron and the halides</u>.

The synthesis of boron halide can be achieved using a number of methods. **Equation** 1 shows the method that was employed for the synthesis of boron trifluoride. Boron trifluoride is used in the hydroboration reaction and has an application in organic synthesis as a Lewis acid.

$$6\ KBF_4 + B_2O_3 + 6\ H_2SO_4 \longrightarrow 8\ BF_3 + KHSO_4 + 3\ H_2O$$

Equation 1

As boron trihalides are strongly Lewis acidic, they can easily react with Lewis bases to form adducts, which are more stable.[4] The reaction of BF_3 with diethyl ether affords the stable $O(Et)_2{:}BF_3$ adduct (**Scheme 1**)[4]



Scheme 1

All of the boron halides are volatile, and are prone to hydrolysis in the presence of water to form boric acid [$B(OH)_3$].The boron trihalides discussed above (BF_3, BCl_3, BBr_3 and BI_3) are all useful reagents in organic synthesis, as they are able to undergo many reactions including the cleavage of alkenes, alkynes, amines, ethers and thiols; due to

their high reactivity.[9] They have an important role in the hydroboration reaction as they are used as starting materials in the synthesis of mono and dihalogenated boranes. Boron trihalides have also found applications as catalysts in the hydroboration reactions.[10,11]

1.1.1.2. Boron Hydrides

Boron is able to form hydrides and the simplest being the borane (BH_3) with a sp^2 hybridized boron central atom. Borane exits in a gaseous form and usually as the dimerized form diborane (B_2H_6). The boron center is sp^3 hybridized in diborane; this dimerized compound has what is known as 'banana' bonds, where the bonds between the B–H–B are sharing two electrons between the three atom centers (**Figure 3**). The terminal B–H bonds are the 'normal' two center, two electrons covalent bond.[12,13]

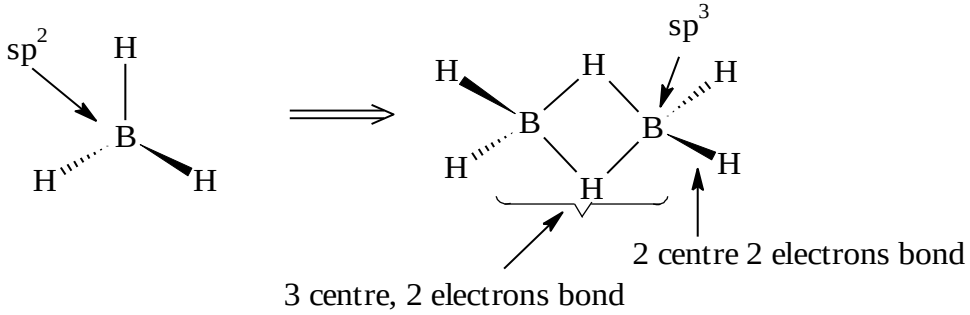
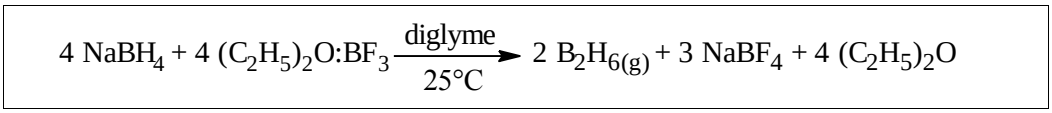


Figure 3: <u>Illustration of borane and the diborane dimer, with the hybridization on the boron atom in each boron hydride</u>.

The synthesis of diborane during the initial discovery and usage was difficult to achieve, however, in the early literature there were two methods that were reported for the synthesis of diborane. The first method, according to Brown, was that reported by Stock which involved the preparation and hydrolysis of magnesium boride followed by the thermal decomposition of the boron hydride obtained.[10] The second method, reported by Schlesinger and Burg, involves the reduction of boron chloride by hydrogen in an electric discharge at low pressure.[14] Over the years a number of methods have been developed and reported for the synthesis of diborane, but the method that is mostly preferred[15] is the treatment of sodium borohydride with boron trifluoride-ethyl etherate in diglyme

(**Equation 2**).[16] Kanth and Brown have reported that replacing the boron fluoride-ethyl etherate with boron trifluoride-diglyme adduct improves the generation of diborane.[15]



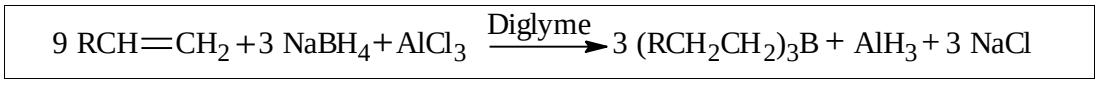
$$4\ NaBH_4 + 4\ (C_2H_5)_2O{:}BF_3 \xrightarrow[25°C]{\text{diglyme}} 2\ B_2H_{6(g)} + 3\ NaBF_4 + 4\ (C_2H_5)_2O$$

Equation 2

Similar to the boron trihalides, boron hydrides have an incomparable role in organic synthesis with the most noteworthy being that of the hydrides used in Brown's hydroboration reaction; which provides organic intermediates.[16]

1.1.2. Hydroboration

The discovery of hydroboration is attributed to Herbert C. Brown, who made this discovery in the 1950's[17] as a result of serendipity. The discovery of hydroboration occurred when Brown and co-workers made an observation during the reduction of ethyl oleate using sodium borohydride with aluminum chloride as a catalyst, in diglyme. During the course of the reduction experiment, Brown and co-workers observed that 2.37 equivalents of hydride were being consumed per mole of ester, instead of 2.00 equivalents of the hydride that they had observed earlier when reducing ethyl stearate.[18] After much investigation, they deduced that the sodium borohydride was reacting with the olefin (**Equation 3**).[19]



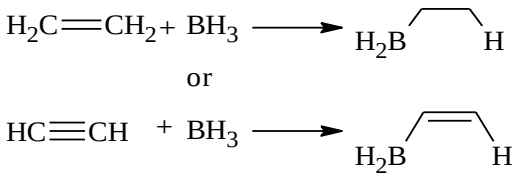
$$9\ RCH{=}CH_2 + 3\ NaBH_4 + AlCl_3 \xrightarrow{\text{Diglyme}} 3\ (RCH_2CH_2)_3B + AlH_3 + 3\ NaCl$$

Equation 3

It was this observation that gave rise to one of the most important organic synthesis methodology available today, which is the hydroboration reaction.[20]

1.1.2.1. Scope and Stoichiometry

Brown describes hydroboration as the addition of a boron-hydrogen bond over a double or triple bond of an olefin, to generate an organoborane compound (**Scheme 2**).[10,19,21]



Scheme 2

The addition of the boron-hydrogen bond is not limited to an alkene and/or alkyne bonds but it can be added to other multiple bonds, including–C=O, –C≡N and –N=N (**Figure 4**), however, these reactions are referred to as reduction reactions.

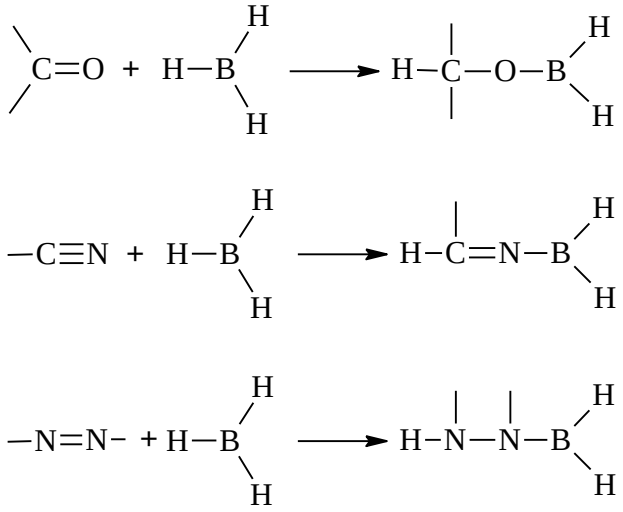
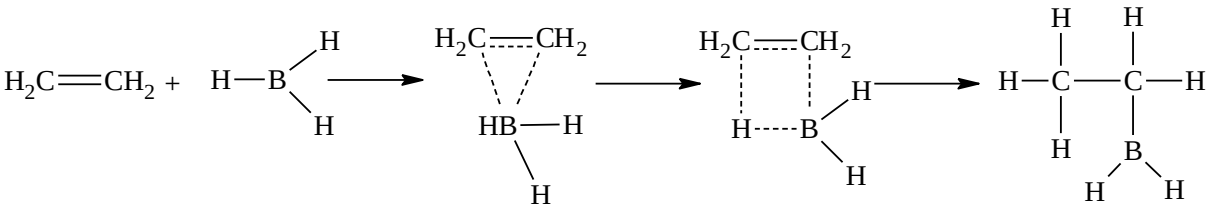


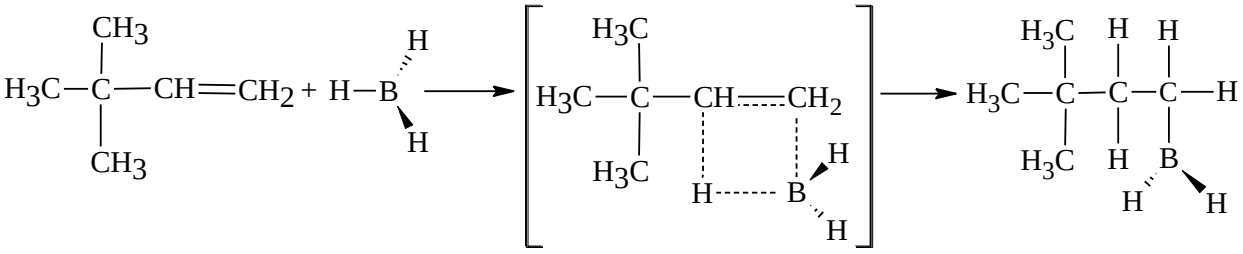
Figure 4: <u>Addition of the boron-hydrogen bond into multi-bond compounds.</u>

The hydroboration reaction involves a four-membered transition state addition, with a *cis*-addition of the boron and hydrogen over the double bond (**Scheme 3**).



Scheme 3

The boron-hydrogen bond is presumed to be polarized ($B^{\delta+}$–$H^{\delta-}$) and the hydrogen possesses some hydridic character; this results in the addition of the B–H occurring *via* an anti-Markovnikov addition (**Scheme 4**).[10,22]



Scheme 4

The preference for the anti-Markovnikov addition is not affected by the degree of branching on the alkyl group. However, when an alkyl group is replaced by an aryl group (e.g. styrene) the distribution of the boron atom between the terminal and internal carbons changes dramatically (**Figure 5**).[10]

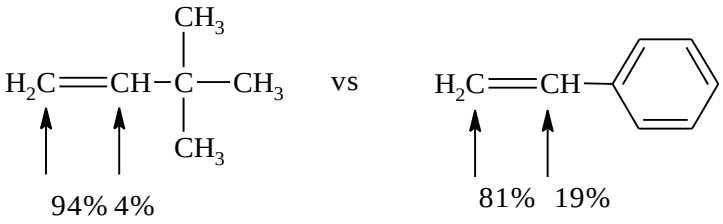


Figure 5: <u>Distribution of the boron atom between the internal and terminal carbons</u>.

Brown and Sharp further reported that the substitution of the styrene on the *para*-position alters the distribution of the boron addition over the double bond. They stated that the

attachment of electron-donating groups promoted the addition of the boron atom at the terminal position; whereas the electron-withdrawing groups promoted the addition of the boron atom at the internal position.[23]

From the literature reports, it states that boron has a preference for the less hindered carbon when the unsaturated bond is attached to an alkyl group; furthermore there are steric considerations associated with the hydroboration reaction of such olefins. Brown and Subba Rao[24] reported that the hydroboration addition is a rapid and quantitative reaction at room temperature, for the addition of simple alkenes to borane, resulting in trialkylborane forming (**Figure 6**).[24]

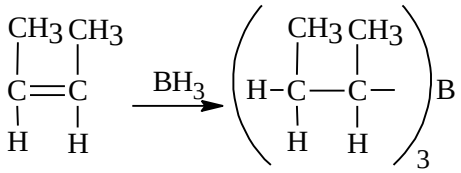


Figure 6: <u>Reaction of an unhindered alkene with borane</u>.

The same cannot be said when borane reacts with a trisubstituted alkene. Brown and co-workers observed that the trialkylborane was not being formed, but rather afforded a dialkylborane (**Figure 7**).

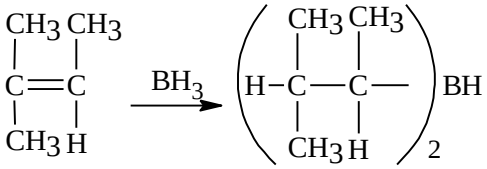


Figure 7: <u>Reaction of a trisubstituted alkene with borane</u>.

They further reported that the reaction of a tetrasubstituted alkene with borane results in the formation of monoalkylboranes (**Figure 8**).

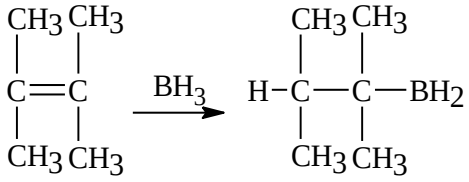


Figure 8: Reaction of a tetrasubstituted alkene with borane.

They stated that even for both the mono- and dialkylborane, it is possible to react further to a trialkylborane however, the reaction is quite slow.[19] This lead Brown and Subba Rao to conclude that the hydroboration reaction is susceptible to steric factors and that if a double or triple bond is deeply embedded within large groups, the hydroboration rate will be slower than that of an unhindered bond.[24]

1.1.3. Hydroborating Reagents

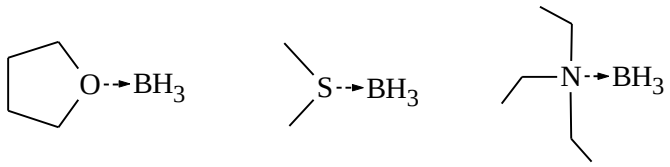
Six decades since the first report on the hydroboration reaction, a number of hydroborating reagents have been discovered and used for the reaction. The initial reagent used was diborane, this reagent was coupled with a Lewis base to form a borane adduct, which presented more stability than the diborane. However, the need for stereoselectivity resulted in the development of mono- and dialkylboranes as hydroborating reagents. New studies were constantly underway to improve the hydroboration reaction conditions, with that saw the development of new hydroborating reagents. The introduction of heterocyclic borolanes, by Shore and Rose,[25] saw the need to manipulate the boron heterocyclic chemistry and develop more robust hydroborating reagents. In this section, more attention will be paid towards the synthesis, stability and hydroborating ability of some of the hydroborating reagents reported to date.

1.1.3.1. Borane Adducts

Diborane was used as the first hydroborating reagent and reacted sluggishly with olefins; however, in the presence of a weak Lewis base, at room temperature, it underwent a rapid reaction to form a monomeric borane adduct. These adducts serve as better hydroborating

reagents than the diborane, and demonstrate enhanced stability.[22] A wide variety of borane adducts are available for the hydroboration reaction whose stability and reactivity remarkably depends on the Lewis base attached to the boron atom.

The preparation of all the borane complexes is essentially the same involving the generation of the diborane gas,[15] which is followed by the absorption of the gas by the appropriate solvent.[20,22]



1 **2** **3**

Figure 9: <u>Borane Adducts of tetrahydrofuran, dimethyl sulfide and triethylamine; in the order of increasing stability.</u>

Borane tetrahydrofuran (**Figure 9-1**): A useful reagent which tolerates many functional groups during the hydroboration reaction; however, this reagent is limited to the use of tetrahydrofuran as the reaction solvent.[22,26]

Borane dimethylsulfide (**Figure 9-2**): Reports state that this reagent is the most used hydroborating agent, as it is indefinitely stable and allows for a range of reaction solvents to be used; however, it's drawback is that it has an malodorous odor due to the dimethyl sulfide.[26,27]

Borane triethylamine (**Figure 9-3**): This reagent has found application in the cyclic hydroboration of trienes as the liberation of borane is slow; however, such reactions requires an elevated temperatures.[26,28]

The stability of borane adducts increases in the order O> S> N, as a result of the back donation from the O, S or N to the boron's p_z-orbital.[28,29]

1.1.3.2. Boron Halides Lewis Base Adducts

In literature, there is evidence which indicates that the use of boron halides as hydroborating reagents is dominated by four boron halide derivatives; namely the mono- and di-chloroborane and mono- and di-bromoborane.[30] The boron halide derivatives can be prepared under various reaction conditions, which include the reaction of lithium borohydride with boron trichloride at 0°C in the presence of ethyl ether (EE) to yield the di-chloroborane derivative (**Scheme 5-1**);[31,32]however, the most convenient synthesis is achieved through the redistribution reaction between borane-dimethyl sulfide with the corresponding boron trihalide (**Scheme 5-2**).[30]

$$LiBH_4 + 3\ BCl_3 \xrightarrow[\text{Ethyl ether}]{0°C} 4\ HBCl_2.EE + LiCl_{(S)} \qquad \textbf{(1)}$$

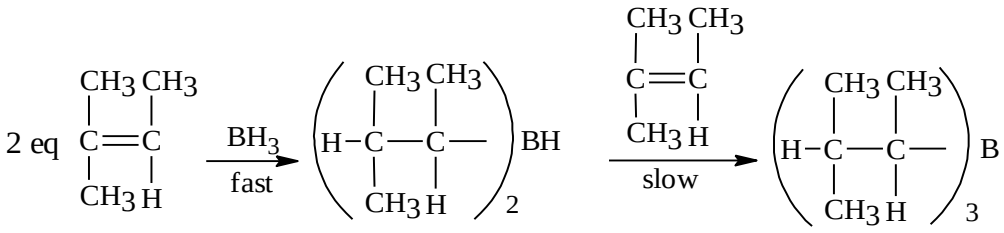
$$H_3B.SMe_2 + 2\ SMe_2 + 2\ BBr_3 \xrightarrow[12\ \text{hours}]{40°C} 3\ HBBr_2.SMe_2 \qquad \textbf{(2)}$$

Scheme 5

The boron halides derivatives differ from each other in terms of their stability as well as hydroborating ability. Tribromoborane is a stronger Lewis acid than trichloroborane, therefore BBr_3 derivatives are expected to be less reactive that those of BCl_3. This indicates the relative reactivity of trihaloborane derivatives; the monohaloborane is more reactive than dihaloborane; as dihaloborane is a stronger Lewis acid. Brown and Ravindran concluded that the order of the relative reactivity of the boron halide derivatives towards olefins increases in the order monochloro- > monobromo-> dichloro- > dibromoborane.[30,33] They further stated that solvent effects should be taken into consideration during the hydroboration reaction of haloborane derivatives, as some solvents coordinate to the borane. The reaction of dichloroborane diethyl etherate with an olefin requires the presence of boron trichloride, which captures the diethyl etherate, thereby allowing dichloroborane to react.[34]

1.1.3.3. Alkylboranes

The reaction of a slightly hindered olefin with borane gives rise to a mono- or dialkylborane species due to steric interferences. Brown and Zweifel reported that the reaction of borane with 2-methyl-2-butene occurs rapidly to produce bis-3-methyl-2-butylborane (disiamylborane).[35] Any further reaction that occurs between the dialkylborane adds 2-methyl-2-butene at a relatively slow rate (**Scheme 6**).



Scheme 6

Based on the above reaction (**Scheme 6**), Brown and Zweifel suggested that the formed dialkylborane might possess an enhanced selectivity than that of borane.[35] In a comparative study they confirmed that indeed the dialkylborane was a selective hydroborating reagent. Brown and Zweifel observed the placement of the boron atom in the less hindered terminal carbon when disiamylborane was allowed to react with different alkenes. **Figure 10** illustrates the percentage of the placement of disiamylborane on 1-hexene, styrene and an ally chloride. [36,37]

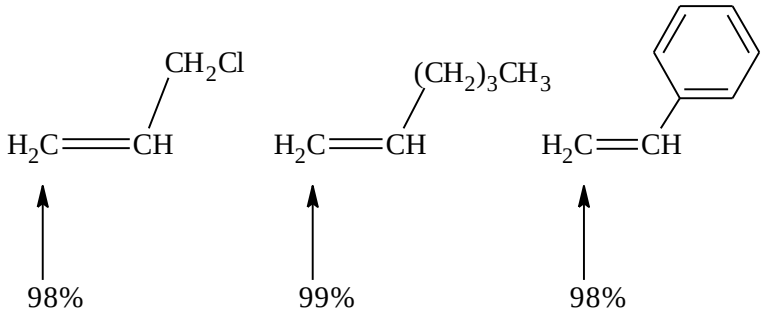
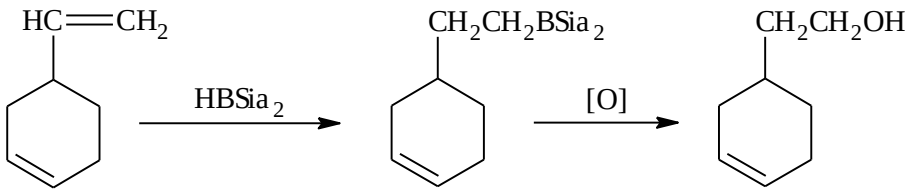


Figure 10: <u>The percentage of the placement of disiamylborane on 1-hexene; styrene and an allychloride.</u>

The discovery of these alkyl substituted boranes allowed for the selective hydroboration of a particular double bond in a structure that has more than one unsaturated carbon-carbon bond using diisopinocampheylborane ($HBSia_2$) (**Scheme 7**).[21,37]



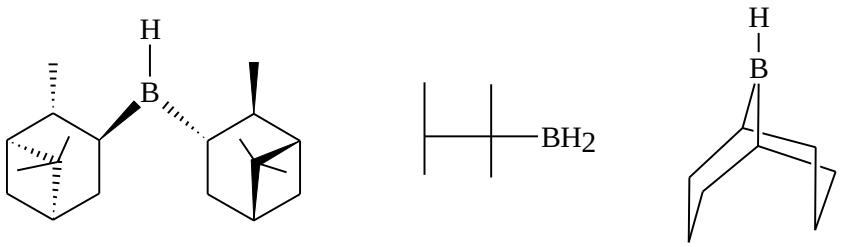
Scheme 7

It has been reported that due to their selectivity, alkyl substituted boranes have become important hydroborating reagents in comparison to borane as it had not demonstrated such selectivity towards olefins.[38] Due to their versatility, a wide range of alkyl substituted boranes have been reported. These include:

- Diisopinocampheylborane (**Figure** 11-**1**): This alkyl substituted boranes derivative is used in asymmetric synthesis with certain olefins.[39,40]

- Thexylborane (**Figure** 11-**2**): This derivative has found exceptional application in the cyclic hydroboration of dienes and the terminal alkynes.[41,42]

- 9-borabicyclo [3.3.1] nonane (**Figure** 11-**3**): This reagent has a remarkable thermal and air stability. Reports state that it also possesses a higher regioselectivity than the other alkyl substituted boranes in its hydroboration reaction with terminal olefins; however, the rate of reaction is very slow with olefins.[21,43]

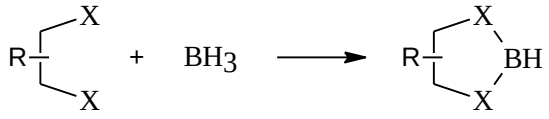


1 **2** **3**

Figure 11: <u>Alkylborane derivatives hydroborating reagents.</u>

1.1.3.4. Heterosubstituted Cyclic Boranes

During the early 1960's Rose and Shore reported that they had synthesized 1,3,2-dioxaborolane from the reaction of diborane and ethylene glycol at 196°C.[25]It was this initial report that lead to the discovery and use of heterosubstituted cycle boranes as hydroborating reagents. The main characteristic of heterosubstituted cycle borane is that upon the reaction of borane with a di-heteroatom compound a ring forms with both the heteroatoms directly bonded to the boron atom (**Scheme 8**). Heterosubstituted cycle boranes can be divided into two clusters according to the size of ring, i.e. 5-membered cyclic rings are known as borolanes whilst the 6-membered cyclic rings are known as borinanes.[44]

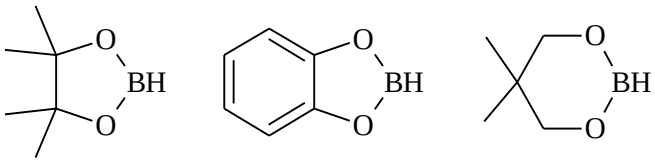


Where X = S, O or N

Scheme 8

There are many heterosubstituted cyclic boranes reported in the literature, but the most prominent are the oxygenated derivatives of cyclic borane (**Figure 12**). As a result of the π-back donation of electrons from the oxygen atom to the empty p_z-orbital of the boron atom, all the dioxaborane derivatives are less reactive compared to BH_3 and

dialkyborane,[22,45] however, the main setback with some of the simple oxygen derivatives boranes is their susceptibility to disproportionation.[44,46]



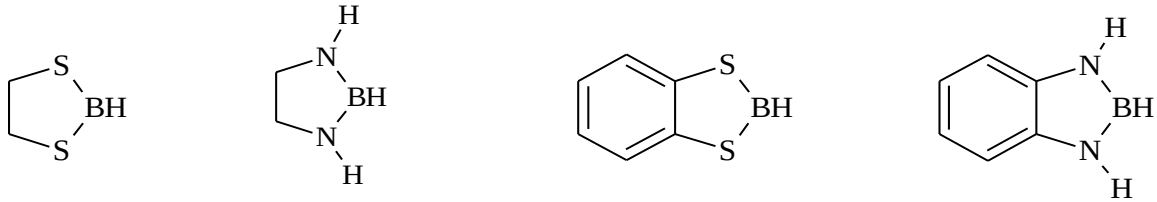
pinacolborane catecholborane HBneop

Figure 12: Oxygen substituted borane derivatives.[47-50]

Zaidlewicz reported that pinacolborane and catecholborane have an extensive use in the catalytic hydroboration of olefins.[22]

- Catecholborane: Can hydroborate alkene and alkynes at elevated temperature. Has a higher reactivity towards alkynes, therefore can allow for the selective hydroboration of the triple bond in the presence of a double bond.
- Pinacolborane: Has been reported to efficiently reduce ketones[51] and can undergo hydroboration with internal olefins in the presence of a catalyst to yield the isomerized terminal pinacolborolane compounds.[52,53]

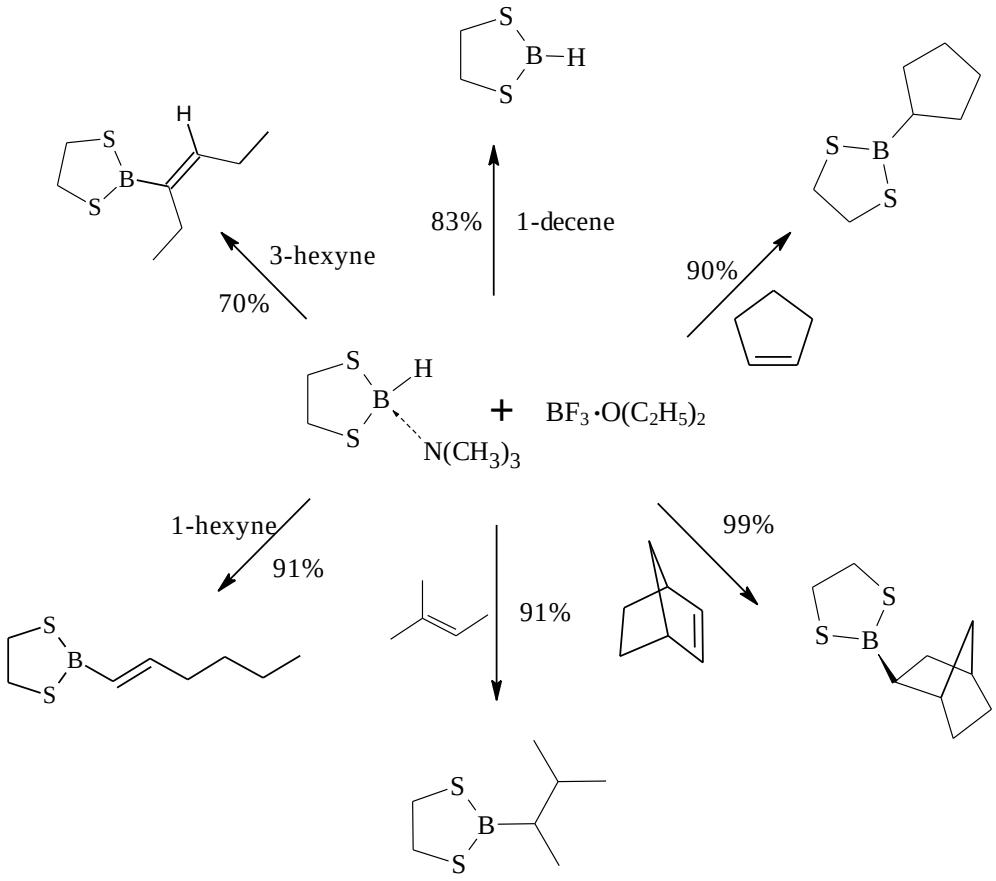
As stated above, there are reports in the literature that indicate that the preparation and utilization of heterosubstituted cyclic boranes is not only limited to the use of oxygenated masking agents, but sulfur and nitrogen are also being used (**Figure 13**).[54,55]



1,3,2-dithiaborolane 1,3,2-diazaborolane benzo-1,3,2-dithiaborolane benzo-1,3,2-diazaborolan

Figure 13: Sulfur and nitrogen substituted borane derivatives.

The first report on the use of dithiaborolanes as hydroborating reagents was made by Thaisrivongs and Wuest, when they reported that 1,3,2-dithiaborolane was able to efficiently convert a representative groups of alkenes and alkynes (**Scheme 9**).[55]



Scheme 9

Almost three decades later, Hadebe *et al.* reported the synthesis of sulfur and nitrogen derivative analogues of catecholborane (**Figure 14**). They reported that these derivatives presented better stability than the oxygen companion, were less prone to disproportionation, and that the sulfur derivative was more reactive than the *N*-analogue towards the hydroboration of 1-octene (**Figure 14**).

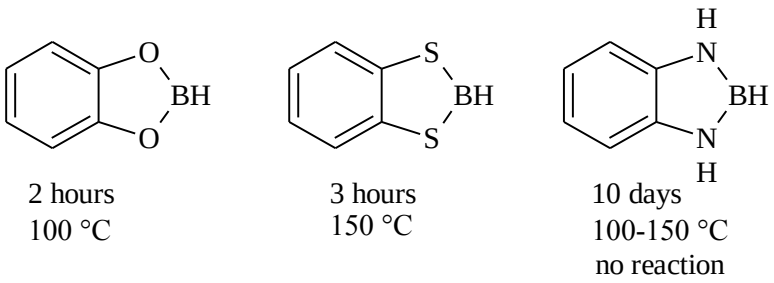
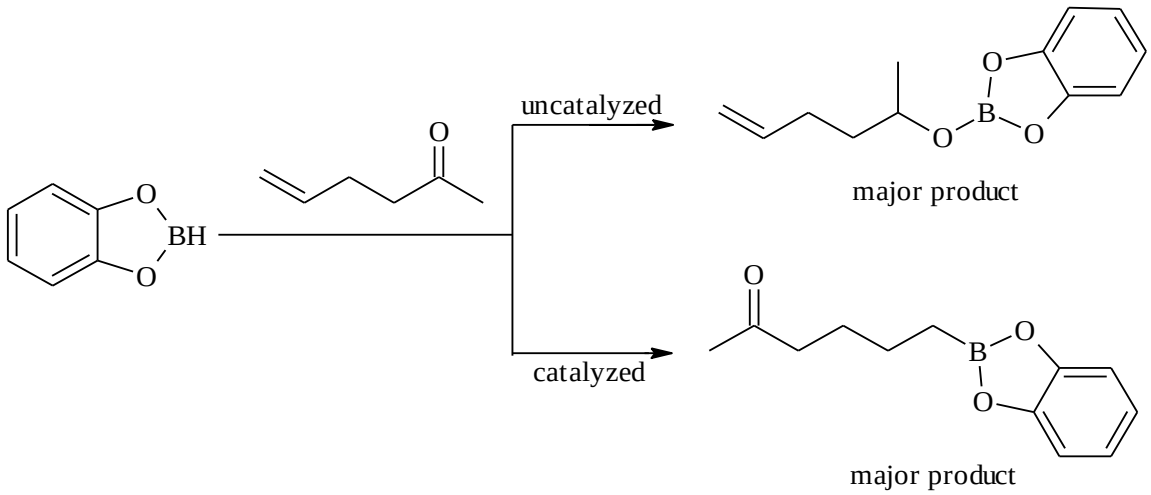


Figure 14: <u>The observed trend for the hydroboration of 1-octene with catecholborane and its S and N-analogues</u>.

The above trend observed by Hadebe *et al*. could be attributed to the fact that nitrogen atoms are able to back donate more electrons to the vacant p_z-orbital of the boron atom better than to the corresponding sulfur atoms. [54]

1.1.4. Transition Metals in Hydroboration

The use of transition metal complexes to catalyze the hydroboration of alkenes has attracted much attention in organic chemistry. This interest in this reaction is because product of this reaction offers similar or opposite regio-, chemo-, and/or stereoselectivity to those generated by the uncatalyzed hydroboration reaction. The start of transition metal catalyzed reactions was due to a report by Kono and Ito in 1975, which demonstrated that the Wilkinson's catalyst is able to undergo oxidative addition.[56] These findings by Kono and Ito were further explored by Männing and Nöth, who ten years later reported that rhodium complexes catalyzed the hydrogenation and hydroboration of alkenes at room temperature. Männing and Nöth informed that transition metals complexes can be chemoselective to multifunctional groups **(Scheme 10)**.[57]



Scheme 10

Since the first report by Männing and Nöth, a number of transition metal complexes have been reported in literature that catalyze the hydroboration of alkenes and alkynes with the various hydroborating reagents discussed above. These catalysts include the complexes of rhodium,[58,59] iridium,[59,60] palladium,[24,39] platinum,[20,36] ruthenium,[40] titanium,[41,42] zirconium,[38,43] and nickel[22,37] (**Figure 15**).

$[Rh(PPh_3)Cl]$ $[Cp_2Ti(CO)_2]$ $[Ni(dppe)Cl_2]$ $[Ru(PPh_3)_4Cl_2]$

$[Rh(CO)(PPh_3)Cl]_2$ $[HZrCp_2Cl]$ $[Pd(PPh_3)_4]$ $[Ir(COD)(PChx_3)py]PF_6$

Figure 15: <u>Selected transition metal catalyst complexes used in catalytic hydroboration</u>.

The reaction mechanism of the catalyzed hydroboration depends on the catalyst and other factors, and is different from the uncatalyzed reaction. Catalytic hydroboration reactions are carried out in common solvents including dichloromethane, tetrahydrofuran, etc.

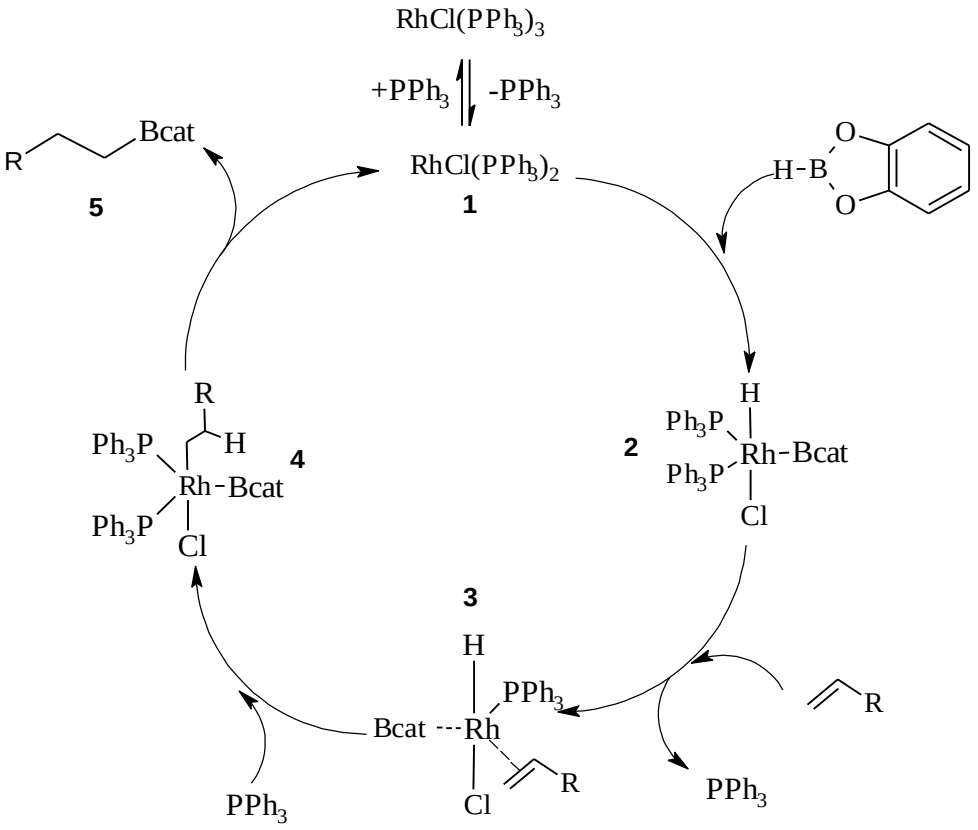
1.1.4.1. Rhodium Catalyzed Hydroboration

Rhodium is one of the rarest elements found on the earth's crust and was one of the first elements used for homogeneous catalysis; consequently there is extensive literature on

this subject. The ease of oxidative addition to the four-coordinate square planar rhodium(I) to give the octahedral coordinate rhodium(III) species has attributed to the popularity of rhodium catalysts.[61]

As stated above Männig and Nöth were the first to report the first examples of rhodium-catalyzed hydroboration of olefins. These authors discovered that, under the influence of tris(triphenylphosphine)chlororhodium (I) (Wilkinson's catalyst), the hydroboration of certain alkenes by catecholborane can be accomplished at room temperature, instead of the elevated temperature (100°C) required for the uncatalyzed hydroboration. They also observed that the catalyzed hydroboration showed noticeably different chemoselectivity and regioselectivity (**Scheme** 10).[57]

The mechanism of the rhodium complex catalyzed hydroboration reactions has been extensively studied; Männig and Nöth proposed the catalytic mechanism based on the hydroboration of an alkene with catecholborane (**Scheme 11**), suggesting a dissociative mechanistic pathway. The pathway was further supported by Evans and co-workers after conducting deuterium labeling experiments. [58]



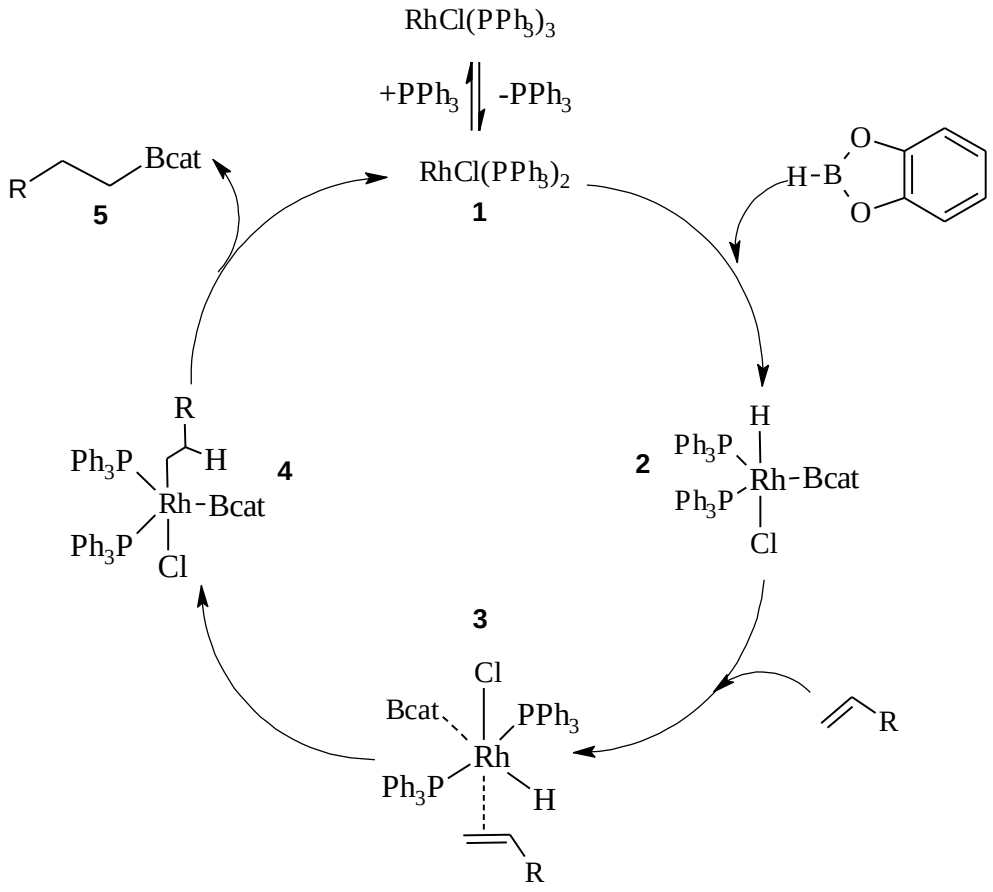
Scheme 11

The dissociative mechanism proposed for the hydroboration of an olefin with a Wilkinson's catalyst entails the loss of a phosphine ligand to provide the transient species, $RhCl(PPh_3)_2$ with a vacant coordination site. The transient species enters the catalytic cycle and is successively followed by (refer to **Scheme 11**):

- The oxidative addition of the catecholborane (B–H bond) to the metal center (**1→2**)to form the rhodium boryl species.
- An olefin coordination into the metal center results in the displacement of a second phosphine ligand to form a penta-coordinated rhodium intermediate complex (**2→3**).
- Thereafter there is the subsequent insertion of the olefin into the Rh–H or Rh–B bond in conjunction with the phosphine ligand binding to the metal center (**3→4**).

- And finally the reductive elimination of the borolane product (**5**) completes the catalytic cycle by regenerating the transient species (**4→1**).

Baker and co-workers[62] rejected the mechanism suggested by Männing and Nöth, and they proposed an alternative dissociative mechanism for the hydroboration. The mechanistic pathway that they proposed was relatively similar to that of the associative mechanistic pathway but had a subtle difference (**Scheme 12**). [62]



Scheme 12

The first and second steps of the associative pathway are similar to that of the dissociative pathway, but the difference arises when the olefin has to coordinate to the rhodium centre, as seen in **Scheme 12-3**.The coordination of the olefin occurs without the loss of the phosphine ligand from the metal center, this generates a hexa-coordinate

intermediate. This step is followed by the reductive elimination that yields the borolane ester compound, similar to the dissociative pathway.[62]

There have been numerous reports about the investigation of both the dissociative and associative mechanistic pathways, and the results obtained conflict each other and support the pathways. The DFT study conducted by Ziegler and co-workers on the comparison of both the pathways is the most convincing study and it concluded that both pathways are feasible.[63] In their study, Ziegler and co-workers were in agreement with the work proposed by Burgess and co-workers; that thermodynamically the associative pathway is favoured. However, they go on to state that the dissociative pathway is possible with bulky electron-withdrawing phosphine ligands. [63]

1.1.4.1.1. Reaction Conditions

Ligand Effects: Pereira and Srebnik[53] described the use of pinacolborane to hydroborate phenylacetylenein the presence of Wilkinson's catalyst gives two regio-isomers in the ratio of 48:52, in favor of the Markovnikov addition product. They further stated that when one of the phosphine ligands in the rhodium center is substituted by a carbon monoxide ligand, there is a drastic change in the regioselectivity of the catalyst towards phenylacetylene. This changes the ratio to 98:2 with an increased preference for the anti-Markovnikov addition product. A number of reports in the literature show that fine tuning of the ligand substituted on the rhodium metal center can have an effect on the regioselectivity of the hydroboration reaction, and the products formed.[53,57,63,64]

Substrate Effects: Fu and co-workers reported that the rate of the catalyzed hydroboration reaction is extremely sensitive to the olefin substitution pattern. They demonstrated using two rhodium-catalyst complexes that remarkably there is a quantitative hydroboration of terminal alkenes by catecholborane within minutes at room temperature. However, 1,1-disubstituted olefins took hours, 1,2-disubstituted olefins took even longer and trisubstituted were quite unreactive. They noted that the sensitivity of the catalyzed reaction to steric effects provides an opportunity for selective hydroboration of the less hindered of two olefins within a substrate.

Lata and Crudden[65] have reported the effects of adding a Lewis acid to the catalyzed hydroboration reaction. They have illustrated that the addition of Lewis acids such as *tris*-pentafluoroboron as co-catalysts have an intense effect on the Rh-catalyzed hydroboration of olefins with HBPin. For instance aliphatic olefins do not react at all in non-coordinating solvents, but upon adding 2 % $B(C_6F_5)_3$, the reaction goes to completion within minutes. Likewise, the reaction of aromatic olefins with HBPin occurs slowly, with no selectively in the absence of $B(C_6F_5)_3$, but is accelerated and more selective upon the addition of $B(C_6F_5)_3$. Mechanistic studies suggest that the Lewis acid needs to be present throughout the course of the reaction as it appears that the Lewis acid, along with THF, is involved in the heterolytic cleavage of the B–H bond of HBPin.[65]

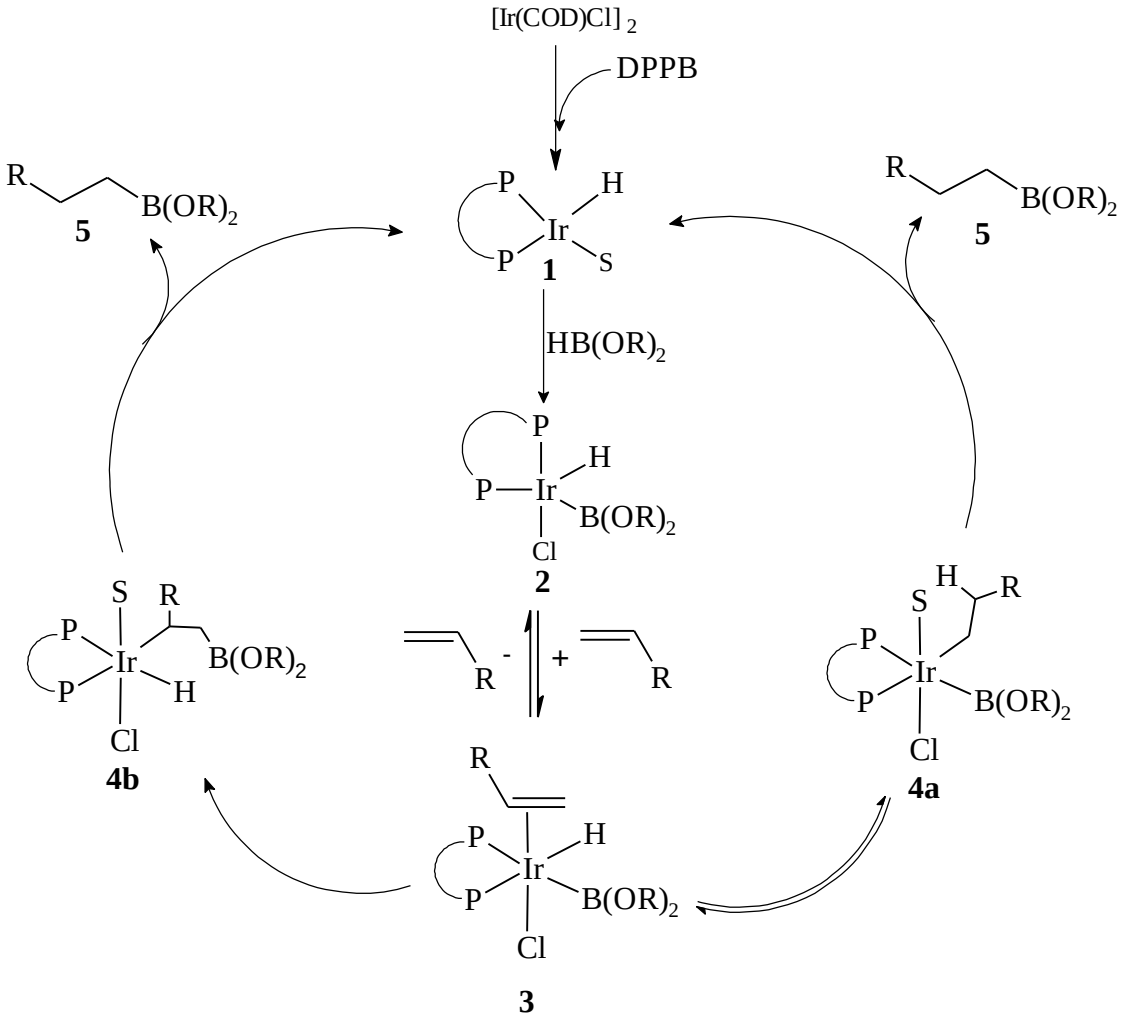
1.1.4.2. Iridium Catalyzed Hydroboration

Iridium is a group 9, d-block element found directly below rhodium and can form compounds with oxidation states from –3 to +6. Unlike rhodium, there are few applications of iridium catalysis and the most widely used iridium complex is Vaska's complex (*trans*-$[IrCl(CO)(PPh_3)_2]$.[66]It has been reported that iridium(I) can easily undergo oxidative addition to form the stable iridium(III) complex; however, the reductive elimination of Ir(III) to Ir(I) is a rather difficult and slow process. The difficult nature of the reductive elimination is a result of the strong Ir–ligand bond strength and the interaction between the positive charge on the metal with the π-bonding ligands.[67]

The application of iridium based catalysis is a new area in the hydroboration reaction, but these catalysts have shown some selectivity for terminal products, compared to their rhodium counterparts. One on the early reports of Ir(I) catalyzed hydroboration was reported by Evans and co-workers, when they described the hydroboration of 1-decene with catecholborane in the presence of the Crabtree catalyst ($[Ir(COD)(PCy_3)(py)]PF_6$), which has been used in the homogenous catalysis.[59]

A number of efforts have been made to elucidate the mechanistic pathway of the iridium catalyzed hydroboration. Hartwig[68] conducted calometric and computational studies and proposed a mechanism. This was supported by the empirical study on the behavior of

iridium catalyst conducted by Vaska and DiLudio,[69]and recently, deuterium labeling study conducted by Crudden.[60]



Scheme 13

Scheme 13 illustrates the proposed mechanism which is similar in many aspects to that of the rhodium catalyzed hydroboration It also involves the formation of the active Ir catalytic species by cracking the iridium chloro-bridged dimer with DPPB and displacing COD in $[Ir(COD)Cl]_2$. This Ir (I) species then enters the catalytic cycle and is subsequently followed by:

- The oxidative addition of the dialkoxyborane to give a penta-coordinated iridium complex (**2**). The isolation and characterization of these penta-coordinated intermediates has been reported for reactions with catecholborane.[70]

- The alkene coordinates associatively to the metal to afford the intermediate (**3**)a hexa-coordinated metal center.

- After the coordination of the catalyst the next step can proceed via two pathways, both of which lead to product (**5**) a linear boronate ester.

    - The first pathway is an iridium boryl manifold (**3 – 4a – 1**). This route involves the insertion of the alkene into an Ir–B bond **4a**, which is Hartwig and co-workers showed to be thermodynamically favored.[68] If R– is a benzyl group, there is a beneficial stability that arises from π-benzyl complex (**Figure 16**). [60]

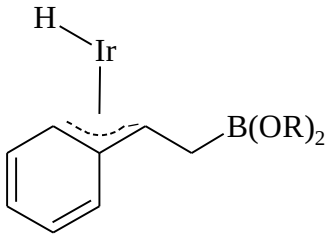


Figure 16: π–benzyl complex observed by Crudden and co-workers for the hydroboration of styrene.

    - The alternative route is the iridium hydride manifold (**3 – 4b – 5**). The first step of this pathway is insertion of the alkene into the Ir–H bond and is reversible based on the deuterium studies by Crudden and co-workers.[60] Though there is no π-benzyl complex intermediate formed by this pathway it is still able to undergo the final step of the catalytic cycle.

The final step is the reductive elimination for both **4a** and **4b**which generates the linear organoboronate ester product and regenerates the active catalyst site.

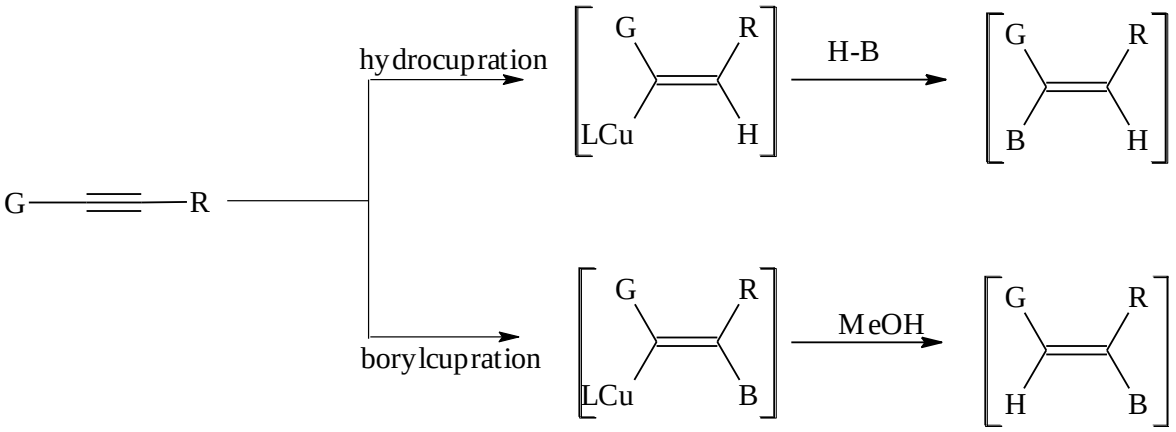
1.1.4.2.1. Reaction Conditions

Ligand Effect: A number of iridium complexes have been investigated for their ability to catalyze the hydroboration reaction. Some of the complexes studied include $[Ir(COD)(PCy_3)(py)]PF_6$, *trans*-$IrCl(CO)(PPh_3)_2$, $IrCl(COE)(PMe_3)_3$ and $[Ir(COD)Cl]_2$, with catecholborane.[59] All of the catalysts examined were able to form a stable iridium boryl compound, and some of these compounds were ineffective catalyst precursors or needed a long time to achieve hydroboration.[59] Literature also shows that complexes not containing CO ligands are able to catalyze the reaction. Recently, Miyaura and co-workers reported the use of $[Ir(COD)Cl]_2$ with diphosphines to give high yields with addition of boron at the terminal position, and Vogels and co-workers have reported similar results while using $[CpIrCl_2]_2$as the catalyst. [50,71]

Solvent Effects: Ethereal solvents such as DME, THF are documented as the solvent of choice in hydroboration reactions due to catalyst solubility. Toluene is routinely used as a solvent under conditions that promote the formation of vinylborane.[60,72]

1.1.4.3. Copper Catalyzed Hydroboration

The use of copper(I) as a catalyst for the hydroboration of alkenes has emerged recently, and reports indicate that these catalysts possess an excellent region- and enantioselectivity. One of the reasons that make copper(I) catalysts even more favorable than the other catalysts used to mediate hydroboration is the fact that copper catalysts are cost effective, more reactive and insensitive to air and moisture. The use of copper(I) in the hydroboration reactions is affected by the ligand that is coordinated to the copper(I) metal center. The variation of the chelating ligand on the metal center allows for different regioselectivity and stereoselectivity in the hydroboration reaction. The hydroboration of alkenes or alkynes using copper(I) can be achieved by hydrocupration and borylcupration[73] (**Scheme 14**)which leads to stereoselectivity and enantioselectivity. The two methods, which are thehydrocupration and borylcupration for the hydroboration of olefins using copper-catalyst, will be discussed in detail below.



Scheme 14

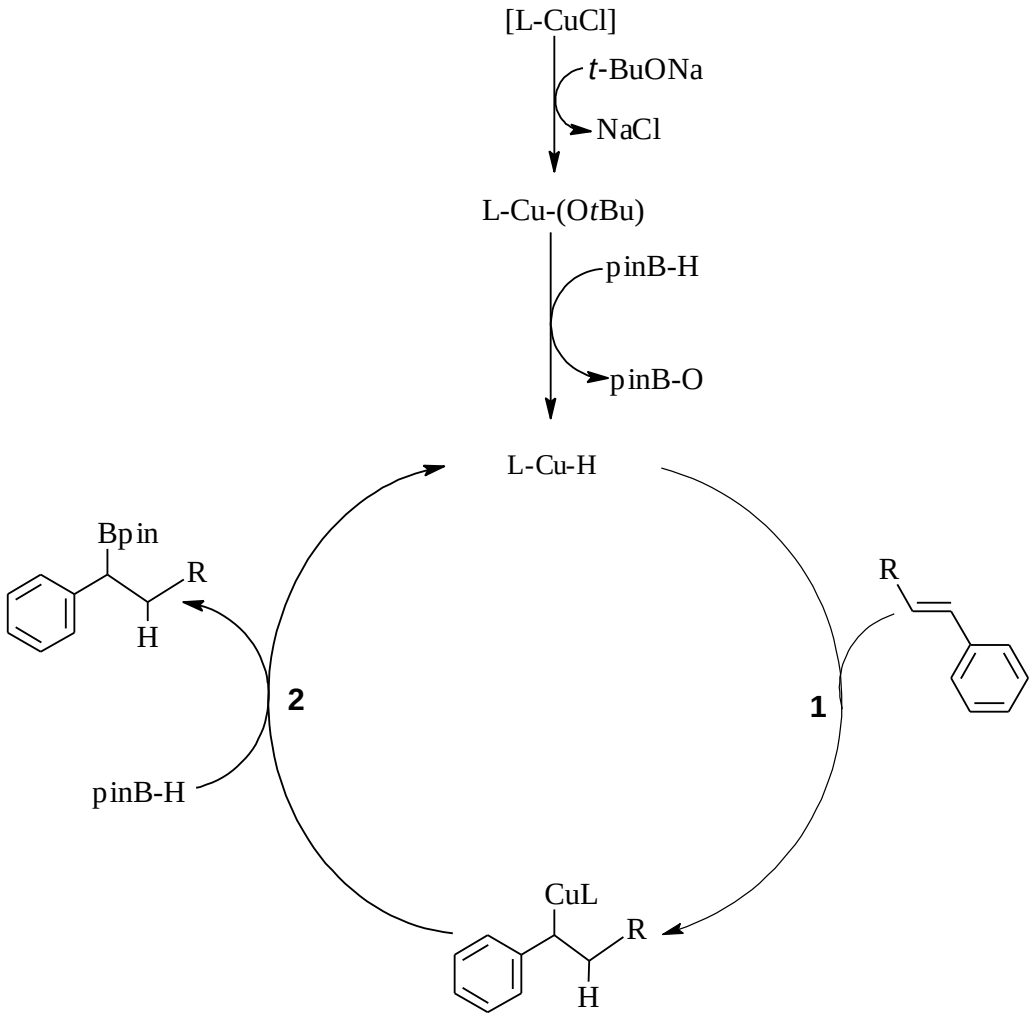
1.1.4.3.1. Hydrocupration

Hydrocupration refers to the addition of a monoboron hydroborating reagent, into the unsaturated carbon-carbon bond. For hydrocupration and borylcupration, initially LCuO-t-Bu has to be generated from LCuCl and NaOtBu. From the above reaction the active catalysis reagent (copper hydride for the hydrocupration) is generated, thereafter the catalytic cycle starts. The cycle process is achieved using two steps:

(1) The regioselective addition of the Cu–H to the alkene.

(2) The transmetallation of the Cu with the monoboron hydroborating reagent. [74]

The following is the proposed mechanism for the hydroboration of styrene with pinacolborane (**Scheme 15**).[74]



Scheme 15

The first step involves the regioselective addition of the styrene into the Cu–H bond. Selectively, the copper gets bound to the electron rich α-carbon and the hydride binds to the electron-deficient *β*-carbon (**Figure 17**). [74]

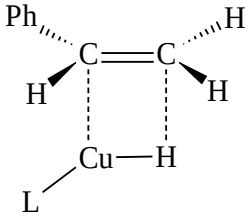


Figure 17: <u>Transition state of the Cu–H addition of styrene</u>.

Using density functional theory; Yun and co-workers observed that there is an increase in the bond length of L–Cu, Cu–H and C=C; while the bond angle between L-Cu-H decreases. This addition step is exothermic, and the rate determining step of the reaction.[75]

The second step involves the transmetallation of the Cu–C bond with pinacolborane(**Figure 18**).For the addition of the Cu-H across the double bond of styrene, Yun and co-workers calculated that the will be a bond elongation from 1.550Å to 1.634Å and L–Cu–H angle decreases by 21-24°.[75] Hydrocupration has a high stereoselectivity and regioselectivity, therefore leading to α-hydroboration (i.e. adds according to the Markovnikov's rule).[25]

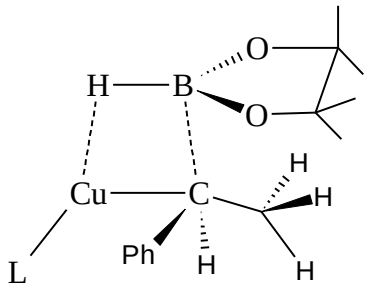
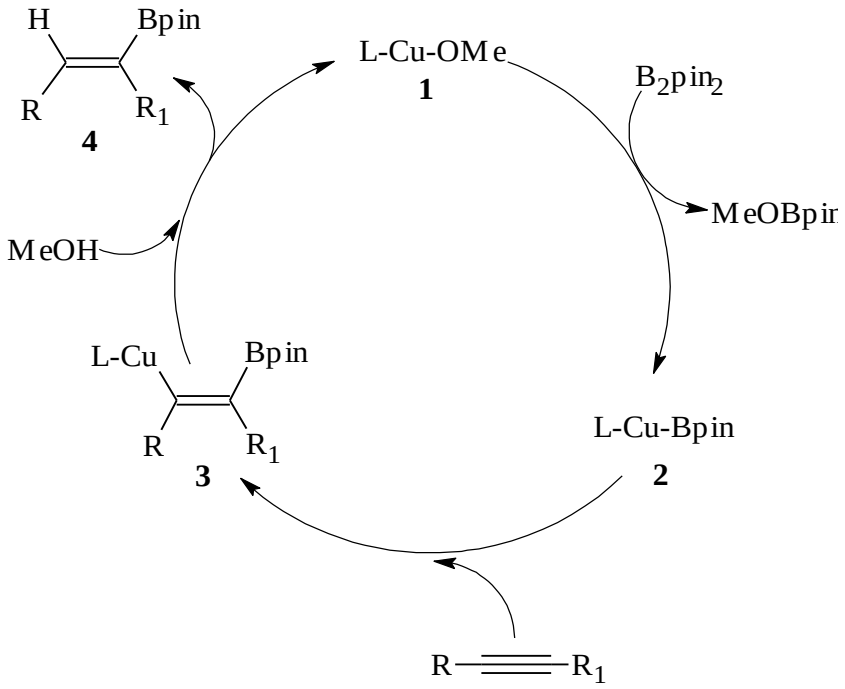


Figure 18: <u>Transition state postulated for the Cu-C transmetallation with HBpin.</u>

Yun and co-workers have reported that the coordination of a phosphate bidentate ligand to the copper metal center results in copper having a better catalytic activity towards the hydroboration (hydrocupration) of styrene than when coordinated to a monodentate phosphate ligand.[74,75] They articulatedthis is a result of a more positive electron density on the copper center when coordinated to a bidentate ligand, as it has a better electron donor capacity when compared to the monodentate ligand; the electron density is in turn available to be transferred to styrene. There are also steric effects associated with the copper(I), bidentate ligands, as they make the reaction complex more unstable, resulting in the decrease of the activation barriers. They also state that the presence of an electron withdrawing group on the *para*-position in styrene results in a higher conversion rate.[75]

1.1.4.3.2. Borylcupration

Borylcupration refers to a copper(I) catalyzed addition of a diboron hydroboration reagent to unsaturated carbon-carbon double or triple bonds. This reaction can afford a monoboryl-alkene/alkyne or a diborylalkane/alkyne. The reaction of diboron reagents with alkyne will be discussed below and a closer attention will be paid to the manner in which the borylcupration differs from the hydrocupration; and the implication of this on regioselectivity (**Scheme 16**).[73]



Scheme 16

The above cycle initiallyinvolves the generation of [LCuBpin] (**2**) which is achieved by the reaction of [LCuOMe] with bis(pinacolato)diboron. This step is subsequently followed by the *syn*-addition of the alkyne into the newly generated copper-boryl bond, resulting in the formation of the intermediate (**3**). The addition of the alkyne to the copper-boryl bond is similar to the addition of alkynes to the hydrocupration, as they both have the copper bound to the α-carbon. The difference is that instead of the hydride adding to the*β*-carbon, the boryl is adding. At this stage there is a distinct reversal of the

regioselectivity. The final step involves the protonation of the intermediate (**3**)with methanol, providing the product (**4**) which is the *β*-product and the regeneration of (**1**), for the catalytic cycle.

The use of *N*-heterocyclic carbene ligands,[76] 1,3-dimethyl-imidazoline ligand and its derivative complexes[77] on the copper metal center have been reported to be the ideal ligands for the borylcupration of both alkenes and alkynes.[78,79] Hoveyda and co-workers have reported that by altering the electronic effects of a ligand on the copper center during borylcupration, one can selectively choose a site (on the α and/or *β*-carbon), for the addition of the boryl species. [76]

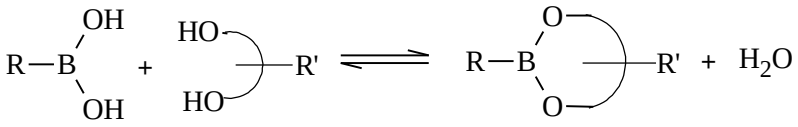
The main reason that both the hydrocupration and borylcupration are able to conserve the regioselectivity is due to the initial steps for both reactions, in hydrocupration the generation of [LCuH] and in borylcupration the generation of [LCuBpin]. When looking at the rhodium and iridium it can be noted that the initial step involves the oxidative addition of the B–H bond on the metal center giving H–M–B. This means that there are two catalytic species (H–M and M–B) that can enter the cycle, whereas with copper that is not the case.

1.1.5. Boronic Esters

1.1.5.1. Preparation of Boronic Esters

Boronic esters are obtained by an esterification type reaction between boronic acids and dialcohol derivatives or diols. This reaction results in the hydroxyl group of the boronic acid being replaced by the alkoxy group (**Scheme 17**). This is a relatively simple reaction, with the overall system being at equilibrium, faster the reaction being faster with diols. The reaction solvent is vital for this reaction as the borolane can easily precipitate out of the solvent thereby favoring the forward reaction. A number of methods can be used to hinder the backward hydrolysis reaction; including the use of a dehydrating reagent and/or the use of the Dean and Stark apparatus. These methods will

allow for the complete conversion of the boronic acid into an ester. The conversion results in an ester which is less polar as the hydrogen bond donor capacity (through the hydroxyl group) of the boronic acid is lost.[80]



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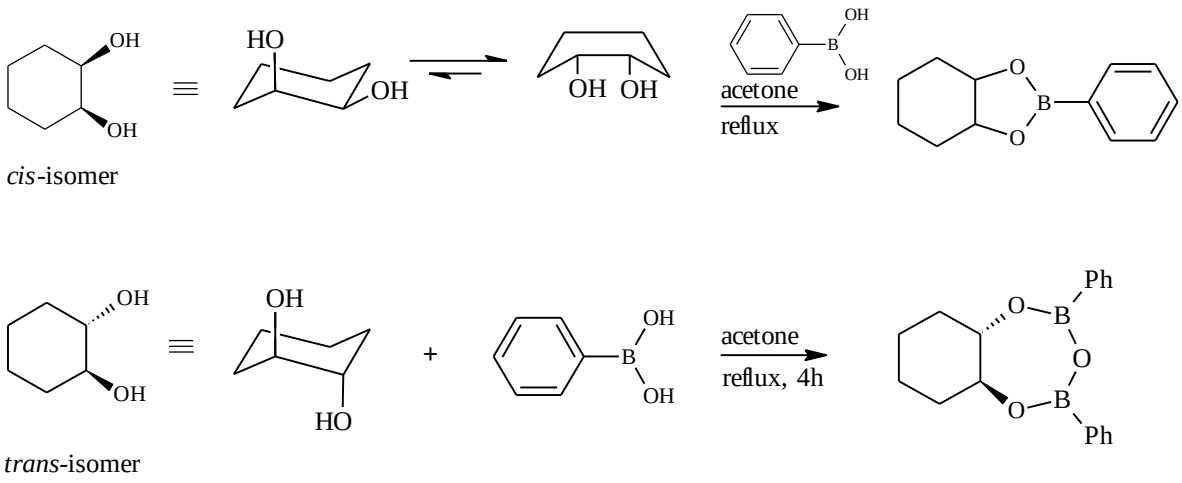
Scheme 17

The geometry of the hydroxyl group is critical for the "esterification" reaction with cyclic-1,2-diols. Bowman and Sugihara[81] observed the ease of forming phenylboronic ester using*cis*-1,2-cyclopentanediol and *cis*-1,2-cyclohexanediol, when compared to using their *trans*-derivatives under anhydrous conditions. These observations were attributed to the small amount of energy required to make the C–O bond in the *cis*-isomer co-planar (as they are essentially co-planar) whereas the *trans*-isomer requires more energy to force the two *trans*-groups into a co-planar position (as they are distinctly not). **Scheme 18**shows the chair conformation of both *cis*- and *trans*-1,2-cyclohexanediol; this shows just how far apart the hydroxyl group are in the *trans*-isomer compared to the *cis*-isomer.[81] The *cis* and *trans*-esterification with cyclic diols has been further investigated by Ahn and Chan using dynamic combinational chemistry. This method selects the most thermodynamically stable product in an equilibrating mixture and has shown that the *cis*-isomer is favorable for the above mentioned reaction.[82,83]



Scheme 18

A number of boronic esters have been reported in literature (**Figure 19**) as stated earlier they are relatively stable, however, the stability of the boronate esters varies as a result of the bidentate ligand attached. Roy and Brown[84] investigated a number of diols with different structure in order to determine which forms a more thermodynamically stable boronate ester, by investigating the rate of trans-esterification. They found that the rigid pre-organized diols resulted in the most stable esters (**7**). They further reported that the 6-membered boronate (**3**) has the geometrically optimal overlap of the boron orbital with oxygen lone pairs making it more stable than the 5-membered ring (**5**)owing to the B–O conjugation stabilizing effects.[84,85] Compounds **9** and **10** represent a tetrahedral boronic ester derived from diethanolamine. These have an internal coordination between the lone pair of the nitrogen and the vacant boron p_z -orbital. As a result of this internal coordination, these derivatives are stabilized against the hydrolysis reaction and atmospheric oxidation.[85]

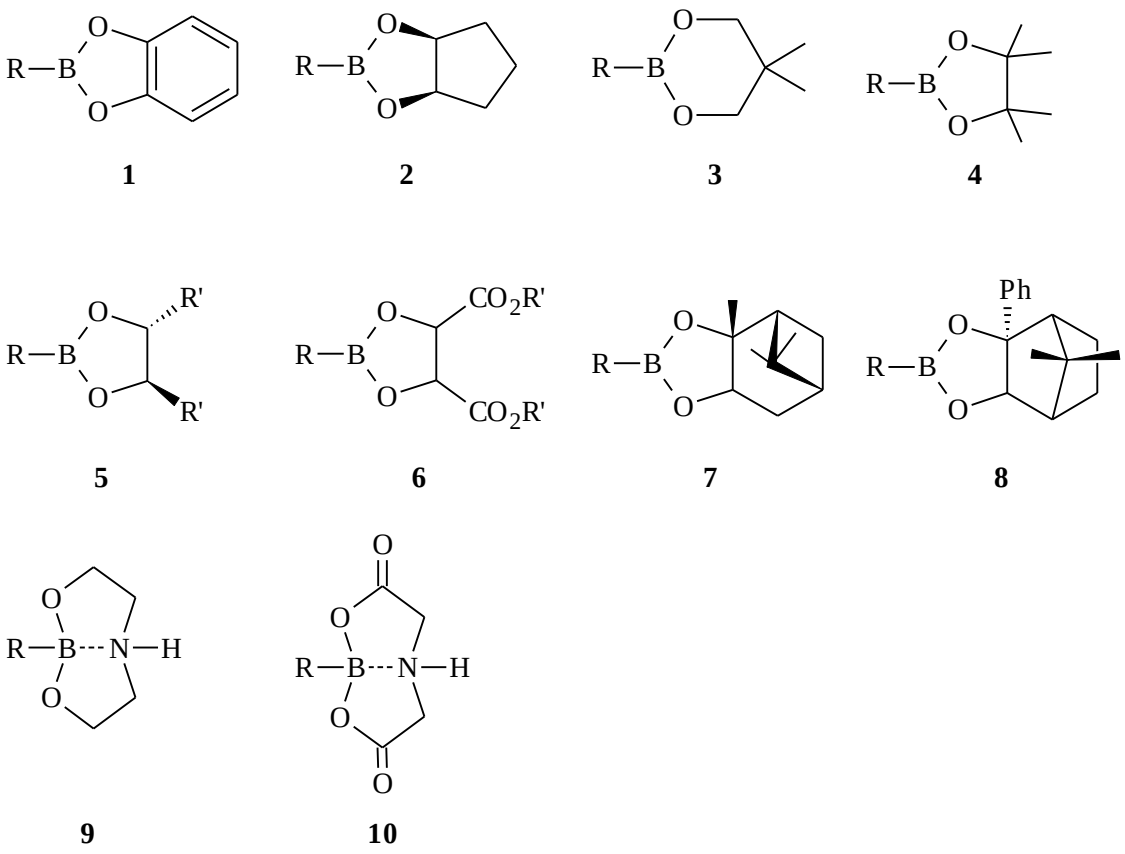


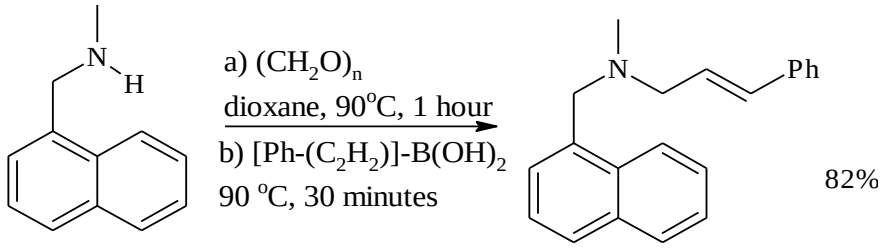
Figure 19: Commonly known and studied boronic esters.[80]

1.1.6. Organoboranes in Organic Synthesis

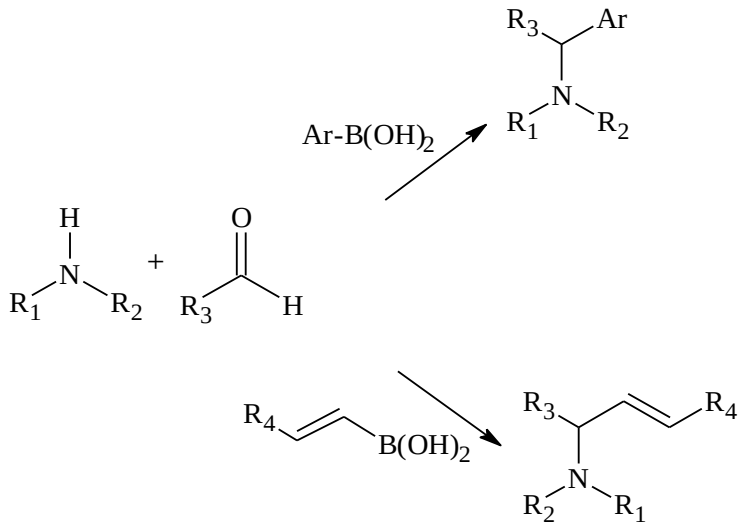
Organoborane reagents have found a wide spread application in organic synthesis as a suitable tool for the formation of new C–C, C–O and C–N bonds. The main reasons for their popularity are because they are easily available, are stable towards air and water; have a low toxicity and are tolerant to many functional groups. Organoborane compounds have been applied to Suzuki-Miyaura cross-coupling; there are other reactions such as the multi-component Petasis-Boron Mannich reaction, the copper-catalyzed Chan-Lam coupling, allyboration and rhodium catalyzed addition of carbonyl compounds to alkenes. The most well-known application of organoborane compounds is in the Suzuki-Miyaura cross-coupling, to be discussed below.

1.1.6.1. Petasis Reaction

The Petasis reaction was first reported by Petasis and co-workers in 1993, when they discovered this variation of the Mannich reaction as a practical approach to the synthesis of a geometrically pure antifungal reagent, *naftifine* (**Scheme 19**).[86] *Naftifine* is the active compound in the Naftin gel® and is a representative of the structural class of antimycotics, the allylamine derivative and has been reported to have good activity against a wide range of pathogenic fungi.[87] The Petasis reaction involves the amidation and esterification of a carboxylic acid catalyzed by a boronic acid (**Scheme 20**).[88]



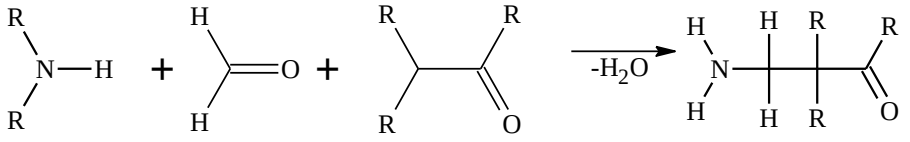
Scheme 19



Scheme 20

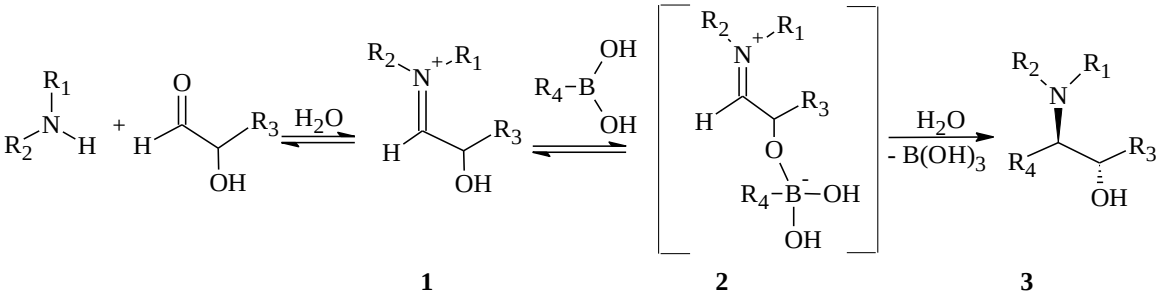
The Petasis reaction is also known as the Petasis-Borono Mannich reaction as it involves a somewhat similar chemistry to the Mannich reaction (**Scheme 21**). Petasis reported that this reaction, as a type II multi-component reaction, is one of the best tools available for

the preparation of a large library of compounds; which upon the simple modification of a substituent can lead to a new and diverse set of molecules. The Petasis reaction is highly enantioselective and this makes it a preferred synthetic methodology.[89]



Scheme 21

The precise mechanism for the Petasis reaction is not fully understood; however, Petasis initially reported that the mechanism (**Scheme 22**) involved the condensation of an aldehyde with a primary or secondary amine to form an imine or an iminium (**1**). This newly formed imine reacts with the boronic acid through the intermediate (**2**) to afford the secondary or tertiary amine (**3**).[86] As boronic acids are relatively inert towards an aldehyde functional group, the presence of the adjacent hydroxyl group facilitates this reaction. It activates the boronic acid through the formation of a tetrahedron boronate salt, which is able to transfer the boron substituent to the imine or iminium moiety.[90]



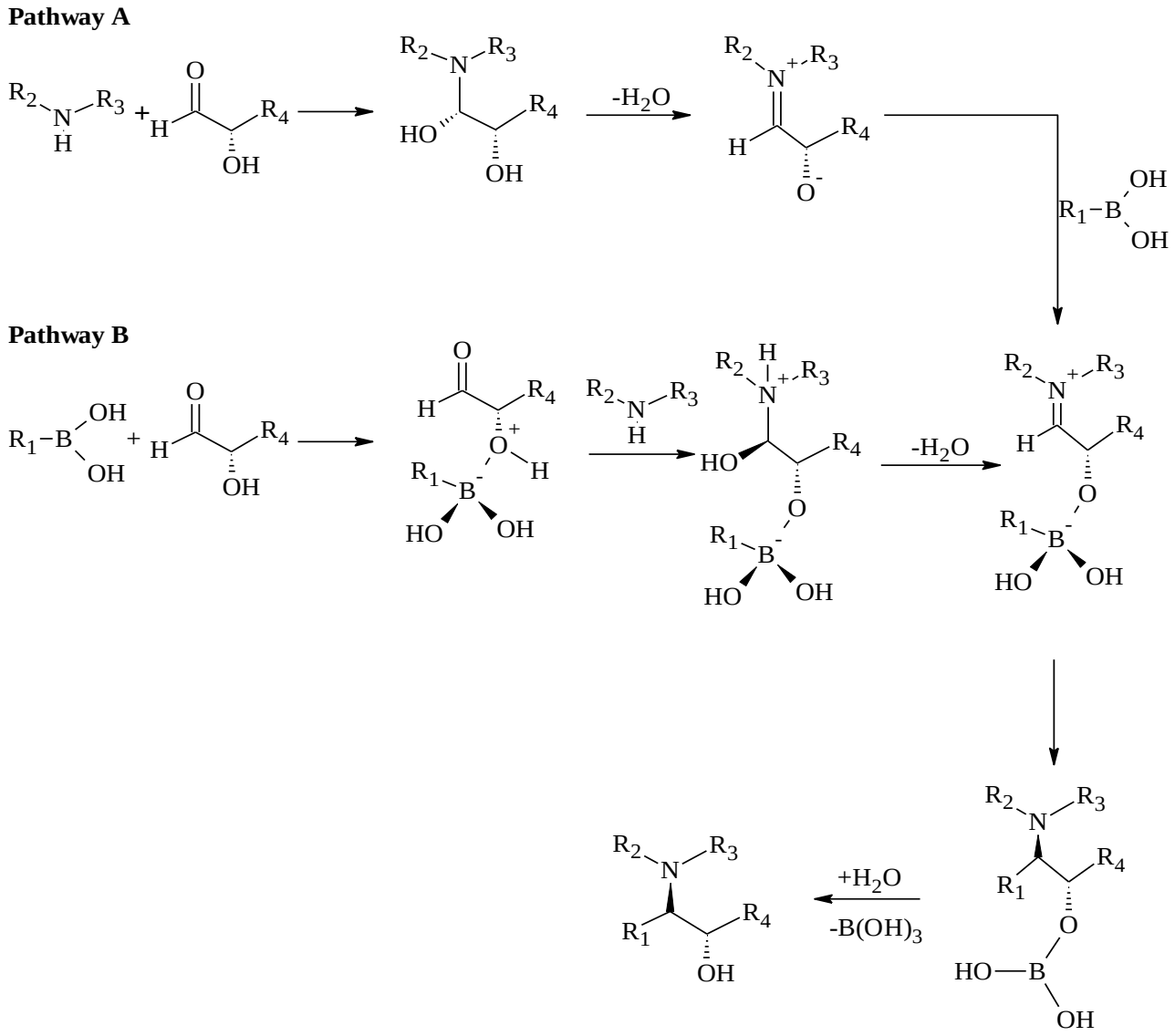
1 **2** **3**

Scheme 22

In literature, most reports illustrate the use of an aldehyde containing hydroxyl or carboxyl groups which promote the formation of the tetrahedron boronate salt. Petasis has reported the successful use of paraformaldehyde, which does not contain such groups.[86]

As there are several mechanisms that are proposed in the literature for the Petasis reaction, numerous studies have been equally presented in the literature to determine the accuracy of these mechanisms with the focus being on the use of different aldehydes.[91-93] Gois and co-workers[94] have reported the use of Density Functional Theory (DFT) calculations to explore and validate the mechanism that was presented by Petasis (**Scheme 22**)using glyoxylic acid as the aldehyde. The results that they obtained in this study were in accordance with the mechanism by Petasis and further support for this mechanism had previously been presented by Hansen and co-workers.[91] Hansen and co-workers had observed that there was an^{11}B-NMR upfield chemical shift of the boron species upon the addition of glyoxylic acid, before the amine was added; which was an indication of the formation of the quaternary boronate salt.

There are two mechanistic pathways that have been proposed for the α-hydroxyl aldehyde reaction; however, it is only recently that DFT calculations which support one of the pathways have been reported. Pathway A, which was proposed by Petasis, suggests the boronate salt forms after the formation of the imine (**Scheme 23**-Pathway A)[93] and pathway B, which was proposed by Schlienger[91] and Voisin[95], suggests that the formation of the boronate salt precedes the formation of the imine (**Scheme 23**-Pathway B).

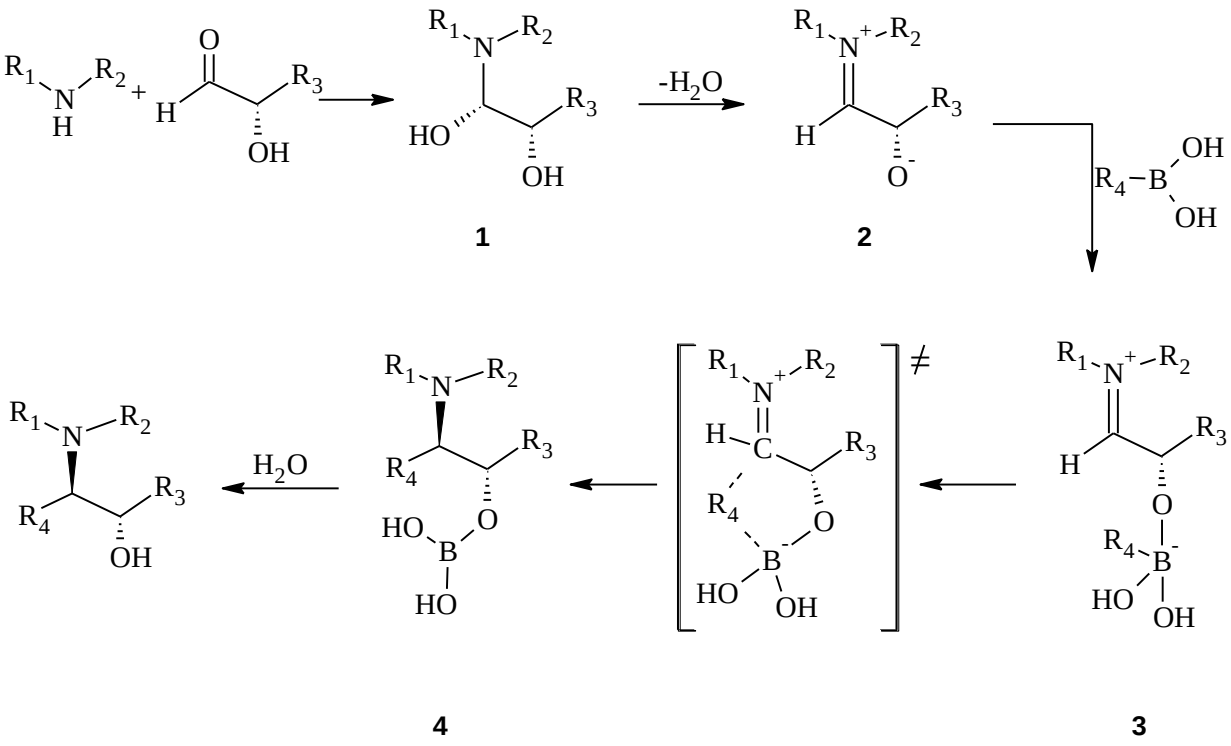


Scheme 23

Upon the comparison of the calculated transition state energies, pathway A was deduced to be the most reliable pathway for the Petasis reaction. The deduction was further supported by the early observation of the inertness of boronic acid towards aldehyde groups.[90]

Though the Petasis mechanism was highly favorable, it had minor shortfalls which Tao and co-workers corrected through their proposal of a transition state that is a five-membered ring. This transition state allowed for the conversion of a carbinolamine

intermediate (**Scheme 24-1**) into a possible zwitterion species (**Scheme 24-2**) via dehydration. This zwitterion species was presented as an epoxide species from geometry optimization (**Scheme 24)**.[92]



Scheme 24

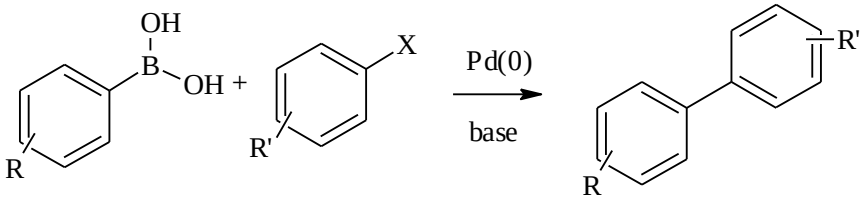
The coordination of the boronic acid to the imine, results in the formation of the boronate salt (**Scheme 24-3**) and an intramolecular transfer of the organo group through the transition state forms intermediate **Scheme 24-4**; which upon hydrolysis affords the desired amine. The stereochemistry is maintained throughout the course of the reaction as Petasis and co-workers had observed with their work involving α-hydroxyl aldehydes.[92]

The above mechanism has also been accepted for the reaction with salicylaldehyde, as experimental results and DFT calculations were consistent with those of the α-hydroxyl aldehyde. Other reports; however, state that the migration of the aryl towards the electrophilic carbon appears to be solvent sensitive and *para*-substituents on a phenylboronic acid decrease the transition state energy barrier; which increases the migration of the aryl group.[94,96,97]

In the study conducted with three different aldehydes, it was reported that the reactivity of aldehydes towards the Petasis reaction is as follows: glycolaldehyde> glyoxylic acid> salicylaldehyde. Particularly, the nature of the other two components (amine and boronic acid) affects the overall success of the reaction. With regards to amines, secondary amines demonstrate a high reactivity towards the reaction, but bulky amines are reported to be a good choice as well. Vinyl boronic acid is reported to be more reactive than its aryl counterpart, this can be attributed to its higher migration ability.[98] There are reports in the literature about the use of water as a solvent for the Petasis reaction and this condition still preserves the selectivity; however, elevated temperatures are required.[94] McLean and co-workers have reported the use of microwave irradiation to decrease the overall reaction time, with no effect on the yield.[99]

1.1.6.2. Suzuki Reaction

Reactions that result in the formation of new carbon-carbon bonds are very important in organic chemistry as they allow for the synthesis of complex molecules from simple precursors. The palladium catalyzed Suzuki-Miyaura cross–coupling, under basic conditions, has become one of the most powerful and important reactions in organic chemistry for the formation of new carbon-carbon bond.[80] In 1976, Suzuki and co-workers reported the smooth cross-coupling between vinyl boron derivatives with vinyl halides in the presence of a catalytic amount of palladium(0), under basic conditions (**Scheme 25**). Since then, the scope of this reaction has expanded beyond vinyl boron derivatives to other kinds of organoborane compounds which can readily undergo a reaction with organic electrophiles.[80]

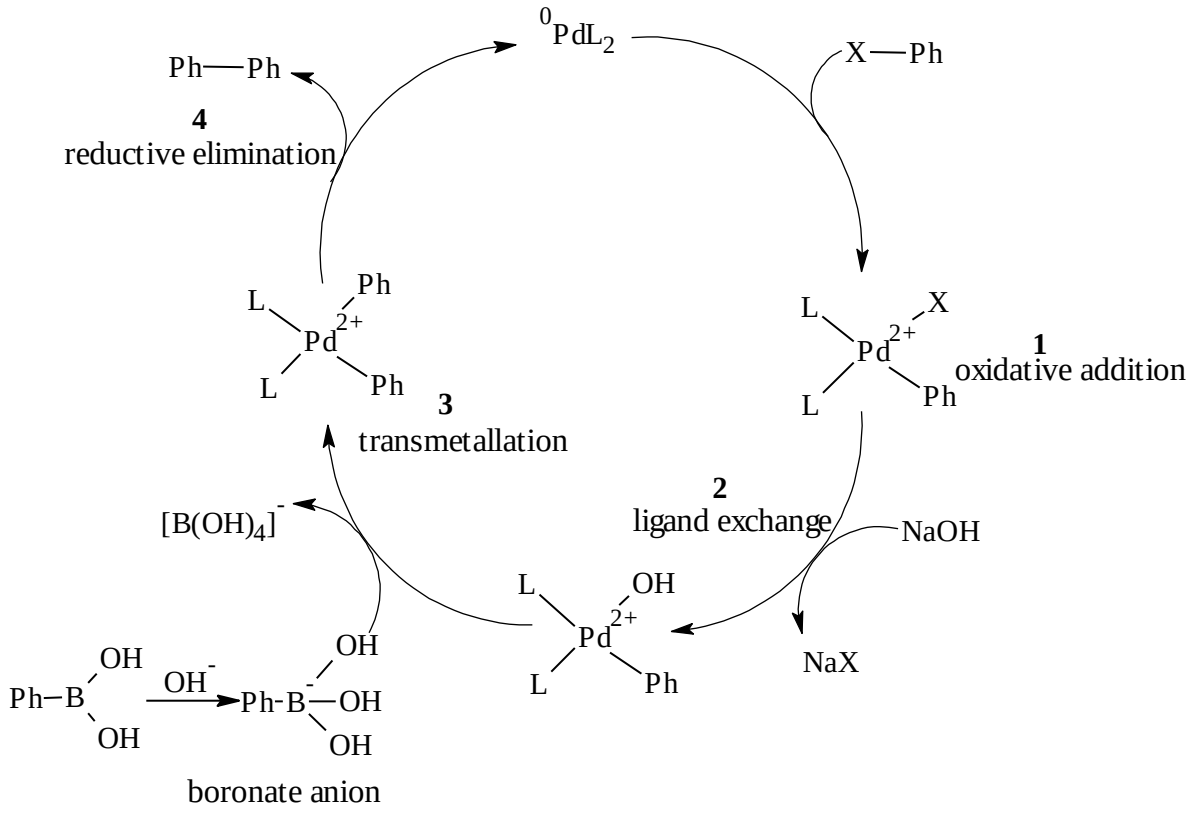


Scheme 25

The Suzuki-Miyaura coupling has a catalytic cycle which involves the following steps (**Scheme 26**):

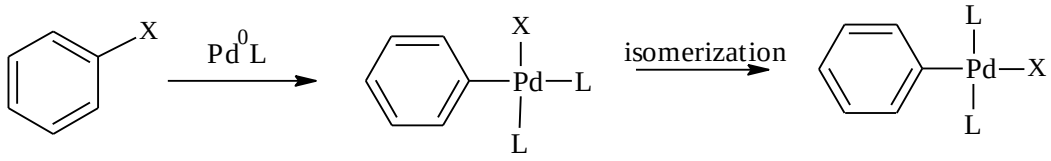
- Oxidative addition
- Transmetallation
- Lastly the reductive elimination.

The cyclic steps involved in the Suzuki-Miyaura reaction are consistent with the general catalytic cycle for the cross-coupling reaction of organometallics.[100] The oxidative addition and reductive elimination steps for the Suzuki-Miyaura cross-coupling are well studied and understood as they are fundamentally common processes for all cross-coupling reactions; the same can't be said about the transmetallation step.[100]



Scheme 26

The oxidative addition of alky-, allyl-, 1-alkenyl-, 1-alkynl- and benzyl-halide to palladium(0) complex affords the formations of the stable *trans*-σ-palladium(II) complex. Casado and Espinet reported that the oxidative addition initially forms a *cis*–complex, which rapidly isomerizes to the *trans*-isomer (**Scheme 27**).[101] The configuration of the product formed is retained for alkenyl halides, whereas there is an inversion of the configuration for allyl- and benzylhalides. Alkyl halides possessing *β*-hydrogens are not favorable because of the competing *β*-hydride elimination process. However, Netherton and co-workers have reported the first method for achieving Suzuki-Miyaura cross-coupling of alkyl bromides that contained *β*-hydrogens.[102]



cis *trans*

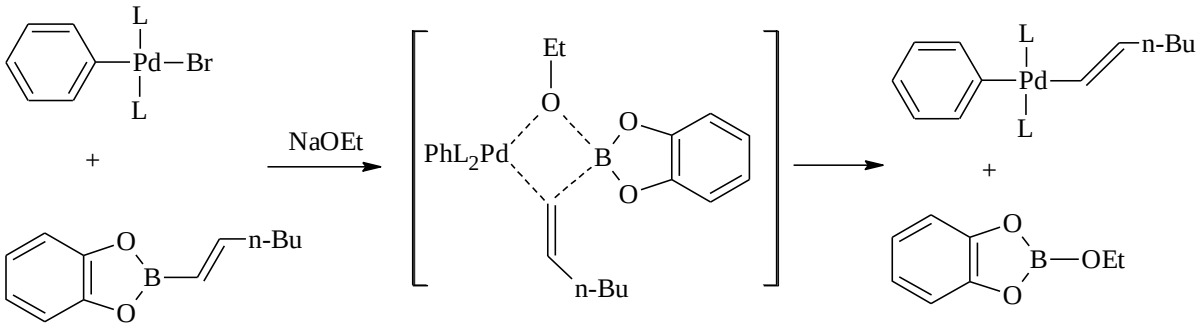
Scheme 27

The oxidative addition step is reported to be the rate determining step in the catalytic cycle. A study of the relative reactivity of the alkyl and aryl halides towards the palladium complex found that alkyl and aryl halides bearing electron-withdrawing groups were more reactive than those bearing electron donating groups. The reactivity decreases in the order I> OTf> Br>> Cl.[100]

A report by Farina and co-worker indicates that the ligands coordinating to the palladium metal center have an important role in improving the oxidative reaction; as the formation of a coordinated unsaturated palladium complex is achieved with ease on a catalyst coordinated with less than four phosphine ligands.[103]

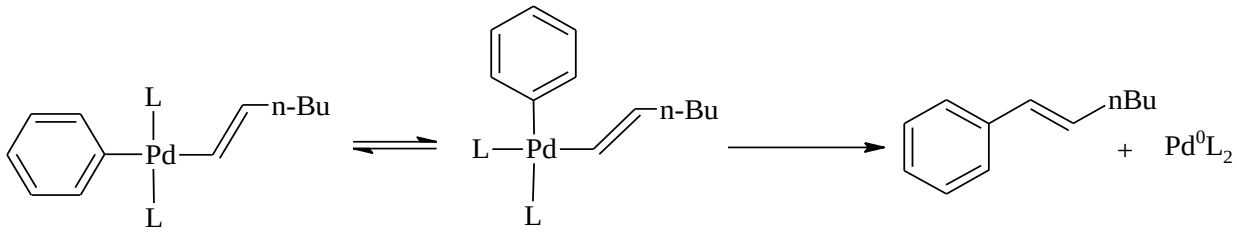
The second step is the transmetallation step of the boryl-alkyl bond into the palladium hydroxyl complex. In the literature there are reports that state that organoboranes are relatively inert towards the palladium complex and they have to be quaternized using a second base equivalent to form the borolane species, which in turn make the organic group a better nucleophile.[104] The increased nucleophilicity of the organo-group allows

for it to be transmetalated into the palladium complex to form the R–Pd–R′ complex through a four-centered hydroxo-μ_2-bridged transition state (**Scheme 28**).[105]



Scheme 28

The final step is the reductive elimination, which involves the isomerization of the *trans*-complex into the *cis*-isomer, thereby allowing for the elimination of the newly formed product and the regeneration of the palladium(0) complex (**Scheme 29**). There are reports which suggest that there is participation by the π-orbitals of the aryl group during the new C–C bond formation. This accounts for the reactivity order: observed, diaryl-> (alkyl)aryl-> dipropyl- > diethyl-> dimethylpalladium, in the reductive elimination of palladium(II) complexes.



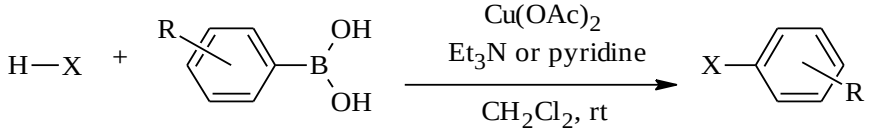
Scheme 29

Due to its favorability as an important synthetic approach towards C–C bond formation, a large amount of research has been diverted towards the development and improvement of this method. Specifically, much attention has been paid towards the development of new

and more reactive organoboranes coupling partners and the use of microwave irradiation to improve the overall cross coupling.[106]

1.1.6.3. Chan-Lam Reaction

The use of organoborane compounds in the formation of carbon-carbon bonds is well studied and understood; the Suzuki-Miyaura cross-coupling. This method has proved to be very important in organic synthesis for such bonds (**section1.1.6.2**), as there is a diverse set of organoborane compounds readily available commercially and it is a robust methodology. [80]The formation of a carbon-heteroatom bond (where the heteroatom is N, O or S) is not fully researched. More so, the use of organoboranes for the formation of heteroatom-carbon bonds has not equally been explored. In 1998, Chan and co-workers reported a method that allowed for the formation of aryl amine and aryl ether compounds, by arylating nitrogen-hydrogen and oxygen-hydrogen bonds. This method involved the use of phenylboronic acid in the presence of cupric acetate and a tertiary amine at room temperature, under ambient atmosphere. This method presented arylboronic acid as an efficient arylating reagent (**Scheme 30**), whilst employing mild conditions.[107]



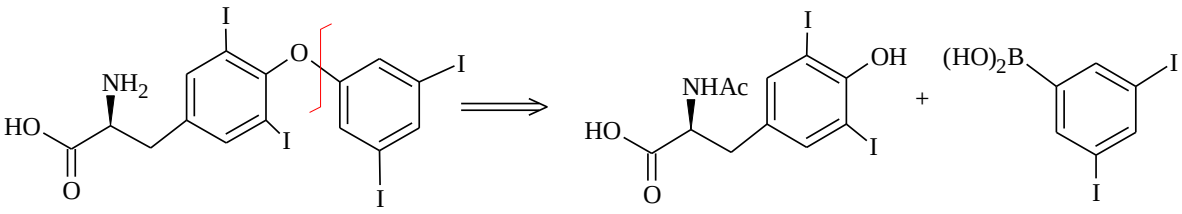
Where X= N, O

Scheme 30

Compounds containing a carbon-nitrogen or carbon-oxygen bond have an important role in biological systems and are widely used in the pharmaceutical industry as starting materials for the preparation of more complex and biologically active compounds. [108]Few methods have been reported in the literature that allow for the formation of these bonds, yet most of these methods are harsh and require elevated temperatures., An example would be the Ullmann reaction; Buchwald and Hartwig's palladium-catalyzed C(aryl)–N cross-coupling.[109] The copper(II)-promoted N–H and O–H arylation using boronic acid has a chemistry similar to that of bismuth arylation, with the boronic acid having an

advantage of being more aryl economical and giving consistent results with functionalized groups.[107,109]

The use of the Chan-Lam coupling in the synthesis of biological compounds was reported by Evans and co-workers when they demonstrated the possible synthesis of thyroxine (**Scheme 31-1**) using boronic acid (**Scheme 31**) .[110]



1 **2** **3**

Scheme 31

1.1.6.3.1. Reaction Conditions

The original protocol that Chan and co-workers employed for phenol arylation involved stirring the phenol with an aryl boronic acid (2 to 3 equiv.), anhydrous copper(II) acetate (1 to 2 equiv.) and triethylamine (2 to 3 equiv.) in dichloromethane at room temperature for 1-2 days. These conditions were sufficient to allow for boronic acid arylation to take place, but they were not optimal for this methodology. Evans and co-workers went on to find the optimal conditions for this reaction. During their investigation they screened a range of copper salts to find a superior copper source. After completing the study, they reported that:

- $Cu(OPiv)_2$, $Cu(NO_3)_2$, $Cu(acac)_2$ and Cu(TFA) all promoted the arylation reaction, but with yields inferior to those obtained with $Cu(OAc)_2$.
- $CuSO_4$, $CuCl_2$ and $Cu(ClO_4)_2$ failed to catalyze the reaction.
- $Cu(OTFA)_2$ resulted in the formation of a significant amount of biaryl, so $Cu(OAc)_2$remained the best copper source.[110]

In 2000, Collman and Zhong reported the use of $[Cu(OH)TMEDA]_2Cl_2$ as a catalyst for *N*-arylation reaction, under an oxygen atmosphere in the absence of a base. The shortfall of this catalyst is that it is only limited to the *N*-arylation of imidazoles derivatives.[111] Quanch and Batey reported that they achieved *N*-arylation with the hydrated complex of $Cu(OAc)_2$ at 40°C under an oxygen atmosphere and in the absence of a base, on a range of N-substrates.[112] The ability of $Cu(OAc)_2.H_2O$ to catalyze the *N*-arylation was further supported by Kantam and co-workers when they observed that after four hours *N*-arylation of imidazole with phenylboronic acid was achieved.

Evans and co-workers also reported in their work on the arylation of 4-*tert*-butylphenol with phenylboronic acid, that the exposure of the reaction mixture to oxygen was advantageous; they further stated that running the reaction in a dry and pure oxygen atmosphere has no significance over conducting it in an ambient atmosphere (Table 1).[110] Evans's findings were supported by Lam when he reported that the addition of a mild oxidizing reagent would be more efficient for the conversion of Cu(II) than molecular oxygen.[113]

Table 1: The reaction yields observed for the arylation reaction under different atmospheric conditions

Entry	Atmosphere	Yield (%)
1	Argon	34
2	Oxygen	71
3	Air	71

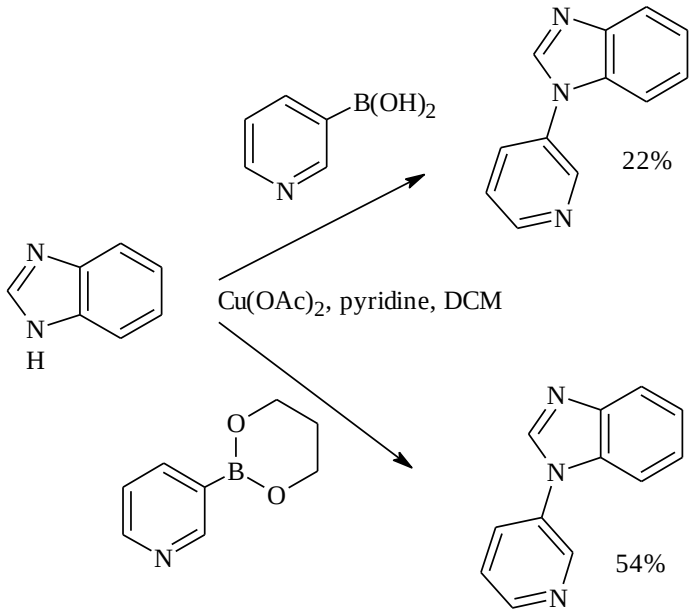
Evans and co-workers also postulated that the diminished yields obtained were a direct result of the competitive arylation of water, forming phenol and diphenyl ether. The postulation by Evans and co-workers was supported by Lam and co-workers, after they conducted a study using labeled O_2 and H_2O, in the absence of an OH substrate. They

observed that there was no incorporation of ^{18}O in the isolated phenol when they used $^{18}O_2$, but there was an incorporation when H_2O^{18} was used.[114] Evans and co-workers reported that the addition of powdered 4Å molecular sieves suppressed this side reaction.[110]

Chan reports that the use of triethylamine or pyridine as promoters are noteworthy, but they do not demonstrate a distinct substrate-based trend as they had observed with triarylbismuth.[107,109] The dependence of the arylation yield on the equivalent amine base, was reported by Evans, noting that five equivalents were required for an optimal yield.[110]

A study by Combs and co-workers using *N*-arylation of morphine as a prototype, found that dichloromethane and 1,4-dioxane were the optimum solvents,[115] while Evans and co-workers found that dichloromethane is the optimum solvent for the *O*-arylation reaction; but the reaction tolerated a range of solvents, with acetonitrile and toluene affording satisfactory yields.[110] Kantam and co-workers have reported the use of ionic liquid (bmim/BF_4) systems as solvents as they showed a drastic effect on the yields obtained for *N*-arylation.

Chan and co-workers, in an effort to identify the controlling factors of the arylating reagents, reported the use of phenylboronic acid derivative as arylating reagents in the *N*- and *O*-arylation. After investigating the effects of these derivatives on cross-coupling with three substrates, they reported that ancillary oxo-ligand on the boron had a drastic influence on the cross-coupling reactions. They stated that boronic esters are more efficient arylating reagents than phenylboronic acids, with the exception being the catechol derivative (**Scheme 32**).[116] The use as arylating reagents is not limited to arylboronic acid or its derivatives, but alkenyl[117] and alkynylboronic acid[118], as well as borate salts. [112]



Scheme 32

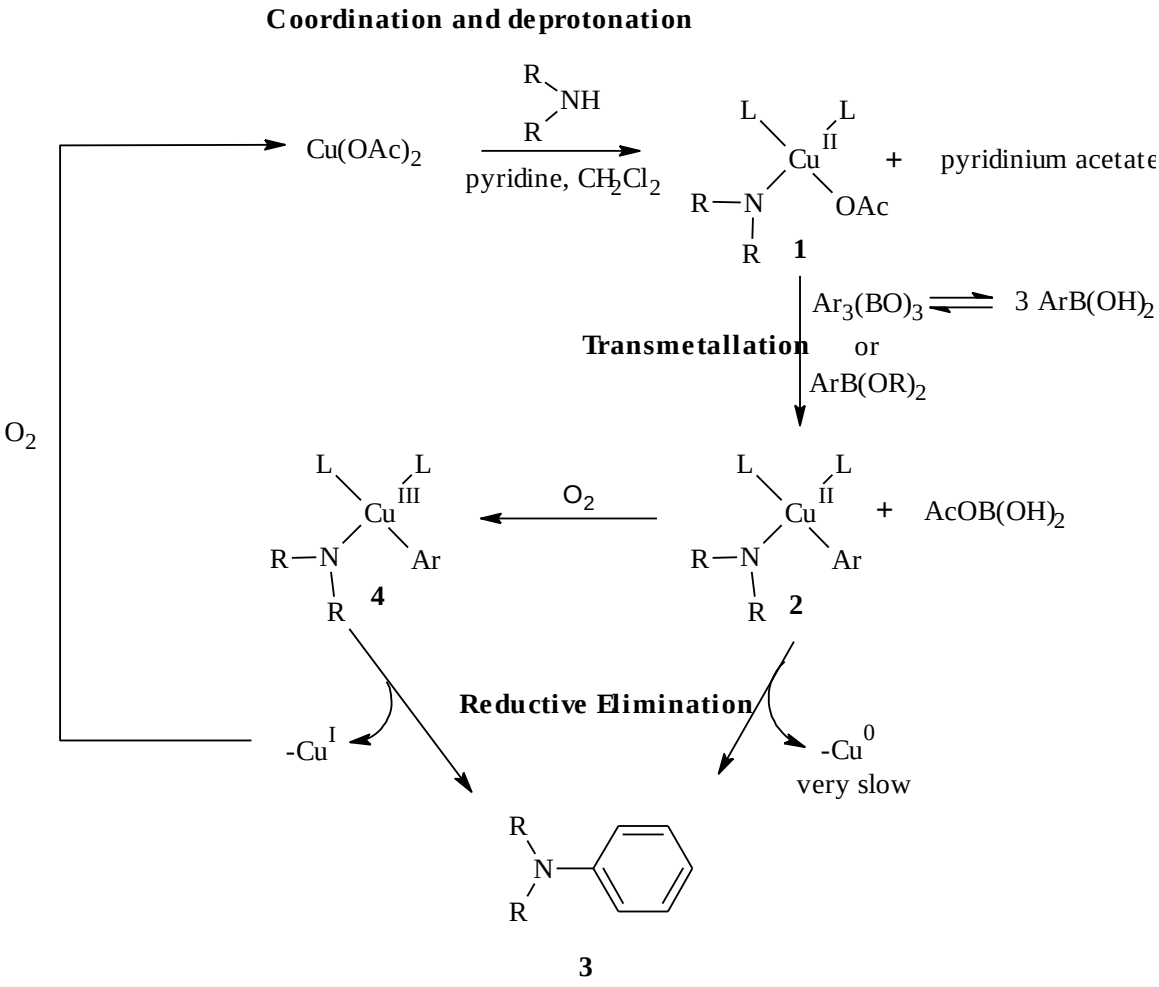
In a review by Qiao and Lam[119], the diversity of the coupling substrate for the Chan-Lam cross-coupling is well documented. They report that the cross-coupling can be employed in the synthesis of C–N, C–O, C–S, C–Se, C–Te, C–Cl, C–Br, and C–I containing compounds.

1.1.6.3.2. Mechanistic Considerations

The precise mechanism for the arylation using organoborane compounds is not fully understood; however, as stated earlier, the N- and *O*-arylation reactions have chemistry similar to that of triarylbismuth. Lam and co-workers[113] hypothesized that the first step of the reaction mechanism involves a rapid coordination or ligand exchange and the dissolution of copper(II)acetate by the *N*-heterocycle, to form complex **1** (**Scheme 33**). The postulation arose after they observed a colorless solution due to the completely insoluble nature of cupric acetate in dichloromethane; upon the addition of the heterocycle there was an instant deep blue color change, indicating the formation of **1**.

The second step involves the transmetallation of the arylboronic acid with **1**, to yield the imidazole-aryl-copper(II) complex **2**, which can undergo reductive elimination using one of the two pathways. The first pathway is similar to Buchwald-Hartwig's palladium

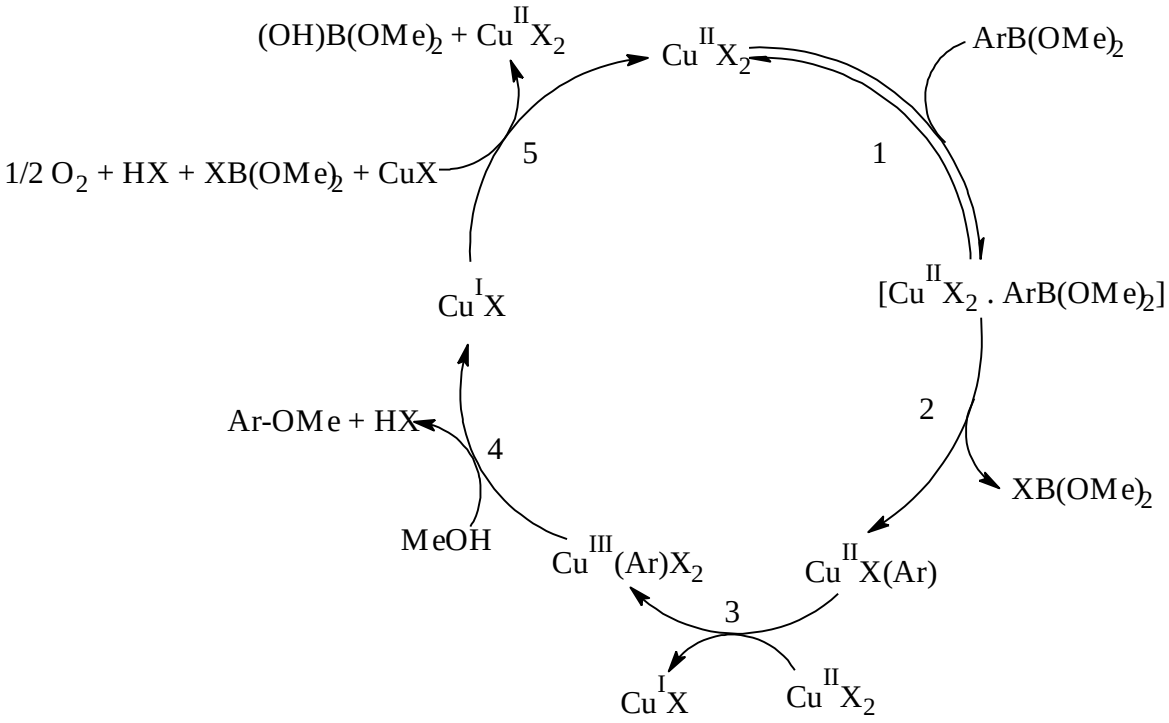
chemistry, which requires elevated temperatures, this pathway reduces the Cu(II) into Cu(0), and it is very slow. The second pathway involves the oxidation of Cu(II) to Cu(III) (**2** to **4**) by oxygen, this higher oxidation state of copper can reductively eliminate the desired product and a copper(I) complex. The copper(I) complex can be oxidized by oxygen to copper(II) and re-enter the catalytic cycle. Reports suggest that the reactive copper(III) intermediates are known and have been postulated for the Ullmann reaction. Kinetics and EPR studies indicate that the second pathway is the most favorable mechanism for reductive elimination.[113]



Scheme 33

For *O*-arylation, King and co-workers reported the mechanism utilized is an 'oxidase'-style mechanism **(Scheme 34**). This mechanism consists of four steps, transmetallation,

disproportionation, reductive elimination and aerobic oxidation.[120] This mechanism is similar to that of *N*-arylation, with the distinct difference being that the N–H bond adds to the copper(II) center before the transmetallation with the boron compound during *N*-arylation, whereas for *O*-arylation the introduction of the O–H bond happens after the transmetallation process.



Scheme 34

Even though the Chan-Lam cross-coupling was first reported in 1998, it has greatly advanced as a carbon-heteroatom cross-coupling methodology. There are ongoing developments towards this cross-coupling; these include the expansion of the scope of substrates and boron reagents, the fine tuning of the reaction solvents and additives, as well as the development of new solution and solid-phase catalytic systems.[115,119,121,122] Reports in the literature further state that in addition to the diversity and robustness of this reaction, the low cost of the copper catalyst employed is what sets Chan-Lam coupling aside from the other heteroatom-carbon cross-coupling methods.[119]

1.2. Research done within the Robinson group

A range of research output has been conducted within the Robinson group which involves:

- The synthesis of nitrogen and sulfur based heterocyclic hydroborating reagents (**Figure 20**) in an attempt to find more robust and reactive hydroborating reagents.[54]

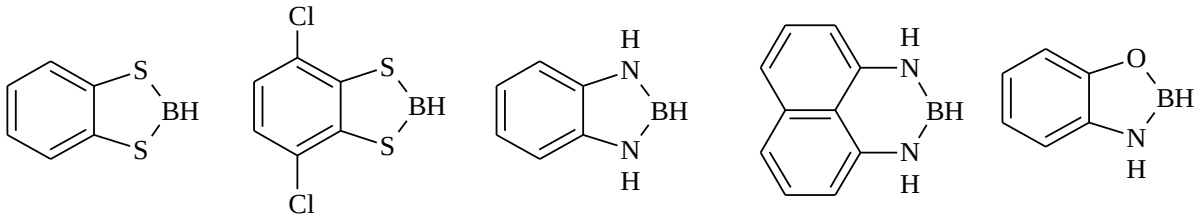
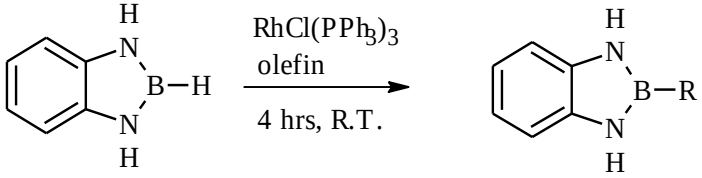


Figure 20: <u>Borolane compounds that have been synthesized by the Robinson group</u>.

- The subsequent hydroboration reaction of these hydroborating reagents (synthesized above) with a wide range of olefins using a rhodium based catalyst(**Scheme 35**) and direct hydroboration.[54]



Scheme 35

- There has been work focusing on the condensation reaction of boronic acid with diamines and oxoamines using microwave irradiation (**Figure 21**) for a more green chemistry approach to the synthesis of borolane esters.

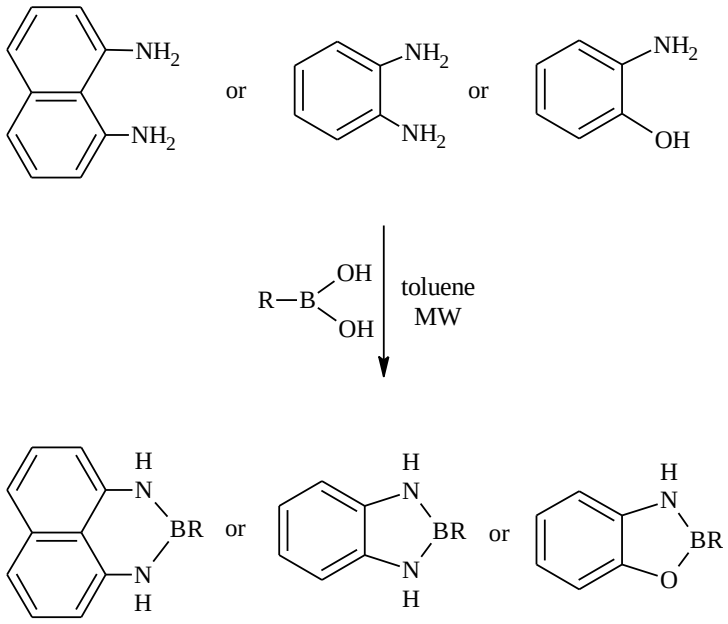
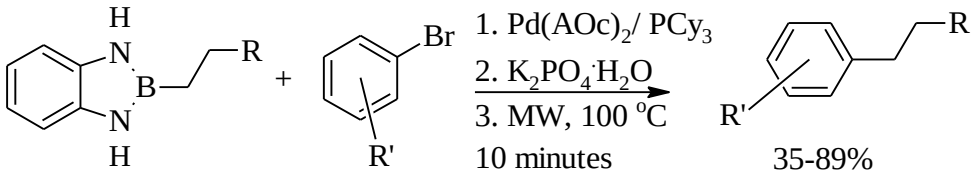


Figure 21: <u>Microwave mediated conversion of boronic acid to borolane.</u>

- The application of the *N*-heterosubstituted alkyl-boranes as coupling partners in the Suzuki cross-coupling and the Petasis Borono-Mannich reactions (**Scheme 36**) has been researched.[106]



Scheme 36

1.3. Project Objectives

The application of hetero-substituted cyclic hydroborating reagents has been limited to the use of either N or S or O, as a sole donor atom to form the boron hydride (**Figure 20** above).Minimal research has been reported on the use of two different donor atoms to form the boron hydride.

- The first objective of this research output was to synthesize boron hydrides with two different donor atoms, (**Figure 22**). The stability of these borolanes was evaluated by exposure to high temperature and the atmosphere, furthermore a density functional calculation was conducted to compare the gap energy of these new borolanes with that of shown in **Figure 20**.

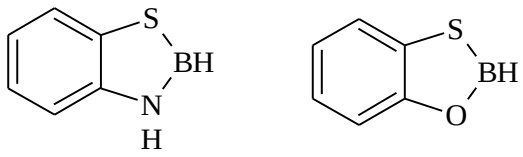
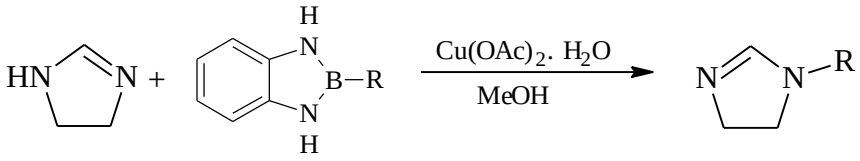


Figure 22: <u>Borolane compounds with two different donor atoms attached to boron.</u>

- The next objective was to examine the reactivity of benzo-1,3,2-thiazaborolane towards the hydroboration of 1-octene using two catalyst systems that have been reported to catalyze the hydroboration.

- As the use of a catalyst in the hydroborating reaction can prove to be expensive, the use of a condensation reaction as a method to synthesize various heterosubstituted borolanes was attempted by condensing various boronic acids with different chelating groups.

- Lastly the application of aryl-1,3,2-diazaborolane as potential arylating reagents for the Chan-Lam cross-coupling reaction was evaluated (**Scheme 37**)



Scheme 37

CHAPTER 2

2.1. Results and Discussion: Preparation of the Hydroborating Reagents

2.1.1. Study Objectives

In this chapter, the focus will be on the synthesis of three heterosubstituted cyclic borolane. The newly formed borolanes will be studied using the ^{11}B NMR spectroscopic analysis method. The^{11}B NMR spectroscopy has been used for structural elucidation of compounds bearing a boron atom, as it allows for the direct observation of the boron atom.The chemical shift of the boron atom observed in the ^{11}B NMR spectrum depends on a range of factors such as the nature of the groups attached on the boron atom, its charge, and the coordination number. A boron atom attached to an electron rich substituent will have a high field shift due to the electron cloud shielding it, whereas, that bonded to an electron poor substituent will have a low field shift as it is unshielded.[123]

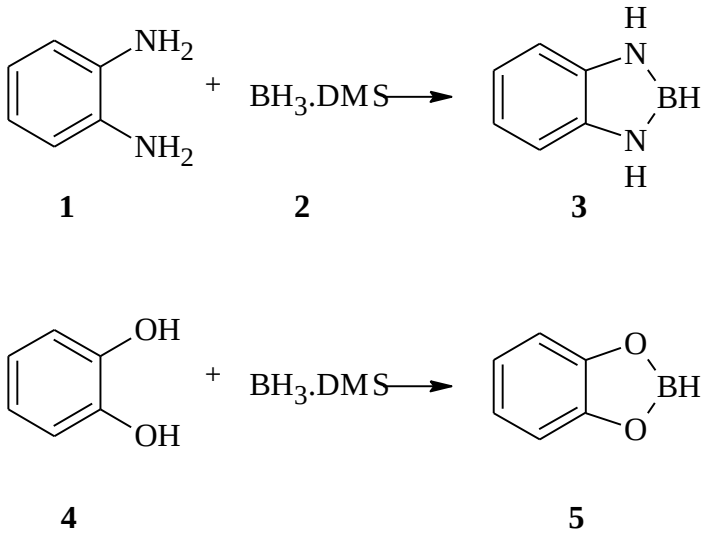
Infrared spectroscopy analysis will also be conducted on the synthesized borolane to identify the bonds formed, so as validate the formation of the borolane. The stability of the borolanes will be investigated, by exposing the reagents to elevated temperature and atmospheric air.

A density functional theory calculation was conducted, with the intention of finding out the availability of the heterocyclic borolane reagents for the hydroboration reaction.

Lastly, the reactivity of benzo-1,3,2-thiazaborolane towards the hydroboration reactions will be investigated for the hydroboration of 1-octene using two catalyst namely the Wilkinson’s catalyst and .

2.1.2. Preparation of Hydroborating Reagents

A wide range of hydroborating reagents have been reported in the literature as discussed in **section 1.1.3**. (Chapter 1), each reagent has its own benefit and shortcomings. However, the preparation methods described in the literature all essentially involve the reaction (**Scheme 38**)of a borane complex **2** with the suitable alkyl or heterosubstituted reagent **1** or **4**, to yield the desired hydroboration reagent (catecholborane,**38-5** or 1,3,2-benzodiazaborolane, **38-3**).[47,54]



Scheme 38

Catecholborane (HBCat) has been excessively used as a hydroborating reagent in the hydroboration reaction due to its high reactivity towards olefins. This reagent however, is prone to undergo disproportionation reaction thereby decreasing the yields of the hydroboration reaction (**Figure 23**). [13,54]

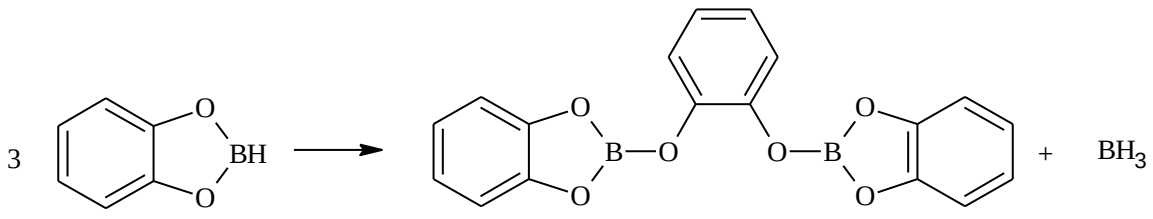


Figure 23: <u>Disproportionation reaction of catecholborane</u>

Due to the disproportionation reported with oxygen containing heterocyclic boranes such as pinacolborane and catecholborane the need for more robust hydroborating reagents was identified.[108] In the section to follow an investigation was conducted on the use of a ligand with two different donor atoms to form a heterosubstituted cyclic borolane.

In **section 1.1.2.2.1.**, it was described that the stability of borane is dependent on the kind of Lewis base forming a dative bond with borane. Numerous reports have shown that there is a swift oxidation of compounds that have been synthesized using borane-tetrahydrofuran complex, even when handled with enormous care under a dry nitrogen atmosphere.[22] On some occasions, the borane cleaves the furan ring and the complex becomes oxidized prior to any reaction. Due to the difficulties reported, the more stable borane-dimethyl sulfide will be used as a borane source for all the reaction in the synthesis of the heterocyclic borolanes.[124,125]

2.1.2.1. Preparation of Benzo-1,3,2-diazaborolane

The preparation of diaza-heterocyclic borolanes was first reported by Caserio Jr. and co-workers[126] in 1961, when they synthesized a compound named 8-bora-7,9-diazaro-peri-naphthene. They showed that the reaction of 1,8-diaminonaphthalene and boron trichloride, followed by the reduction with lithium aluminum hydride yielded a heterocyclic compound which could be handled in air for a short period without significant oxidation occurring.[126] Subsequently four decades after the initial report by Caserio and co-workers, Hadebe and Robinson reported the synthesis of benzo-1,3,2-diazaboronate by applying a method similar to that of the synthesis of catecholborane.[47,48,54]

Recently, Davis and co-workers[127] reported that benzo-1,3,2-diazaborolane can be synthesized by the reaction of the borazine with *o*-phenylenediamine at 60 ºC for 72 hours in tetrahydrofuran(**Figure 24**). This reaction involves essentially the extraction of the B-H bond of the borazine, but this reaction methodology has harsher conditions than those described by Hadebe and Robinson.[54,127]

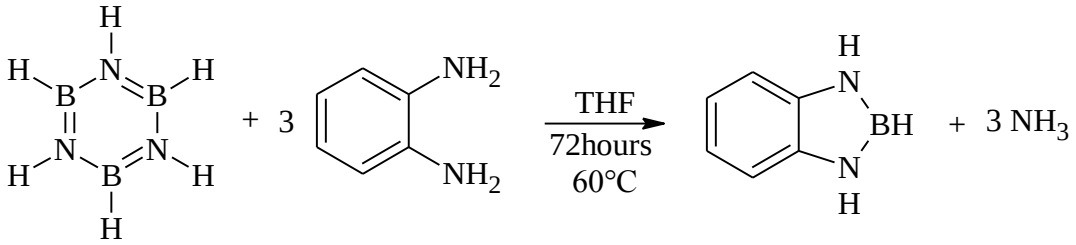
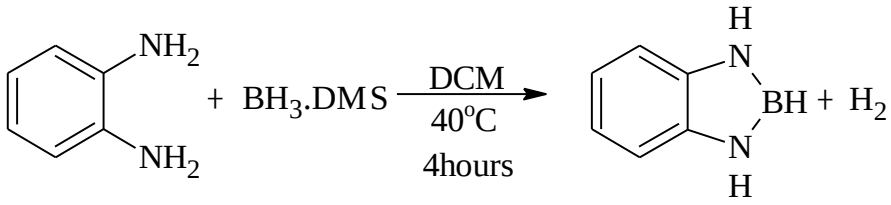


Figure 24:<u>Formation of 1,3,2-benzodiazaborolane from the reaction of borazine and *o*-phenylenediamine</u>

Using the synthetic methodology reported by Hadebe and Robinson, benzo-1,3,2-diazaborolane (HBPda) was successfully synthesized by the reaction of *o*-phenylenediamine with borane-dimethyl sulfide complex in a 1:1 mole ratio under reflux in dry dichloromethane(**Scheme 39**), to afford a light pink liquid of benzo-l,3,2-diazaborolane in an good yield of 96 %, which is in agreement with the yield obtained by Hadebe and Robinson of 95 %.



Scheme 39

The ^{11}B nucleus has a spin of 3/2; therefore, the interaction of a single ^{11}B nucleus with a single ^{1}H nucleus in a magnetic field, results in the ^{1}H nucleus to "see" four different fields, M = 3/2, 1/2, -1/2, -3/2.[128] Due to this the ^{1}H NMR spectrum of B–H coupling will be a quartet and all the four peaks will have equal intensity. The ^{1}H nucleus has a spin of 1/2; hence, from the view of the ^{11}B nucleus it will see two different fields, M= 1/2, -1/2. This results in the^{11}B nucleus being in either of the two fields, with the first one being where the ^{1}H spin is parallel to the external field, and the second one is where it is antiparallel to the external field. Consequently, the ^{11}B NMR absorption for B–H will be asymmetrical doublet.[123]

The[11]B NMR spectroscopic data analysis of the solution obtained showed a spectrum with two peaks, a doublet at 24.1 ppm which is consistent with the chemical shift reported by Davis and co-workers of 23.9 ppm for the formation of benzo-1,3,2-diazaborolane and a quartet at -18.0 ppm corresponding to the starting material borane-dimethyl sulfide complex (**Figure 25**).[127]

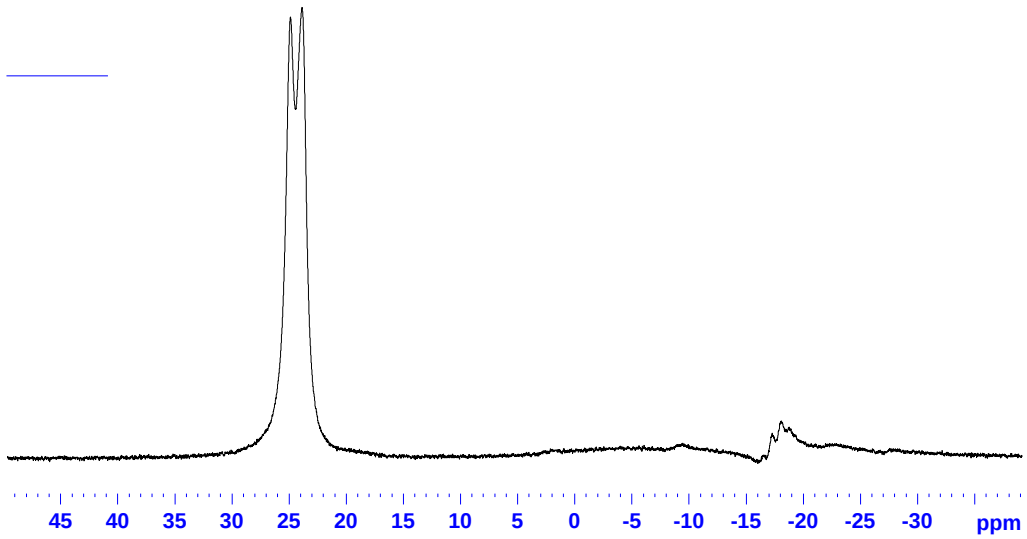


Figure 25: [11]B NMR spectroscopic analysis spectrum observed forbenzo-1,2,3-diazaborolane with BH_3·DMS

To determine the stability of the synthesized borolane two samples of benzo-l,3,2-diazaborolane were analyzed; the first sample was allowed to reflux in toluene at 100ºC for a three days whilst the second sample was exposed to air for two hours. An [11]BNMR analysis was conducted and examination of the spectroscopic data showed that the doublet at 24.1 ppm was still prevalent in both the samples and there were no new peaks observed; this was an indication that HBPda was stable towards disproportionation at elevated temperature and atmospheric oxidation. These observations are in agreement with those made by Hadebe [129] and Slabber[130] which presented HBPda as a more robustness heterocyclic borolane in comparison to HBCat and HBPin. The stability demonstrated by HBPda can be the direct effect of the strong π-back donation of electrons to the empty p_z-orbital of the boron atom from the lone pair on the nitrogen

atom**(Figure 26)**.[131]In a study by Denk on the B–X bond (where X is nitrogen) back donation and dipole moment, it was shown that there was a shift of π-electrons from nitrogen to the boron atom which is due to the high electronegativity of nitrogen.[131]

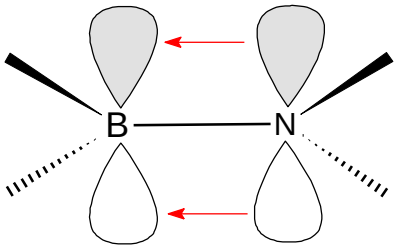


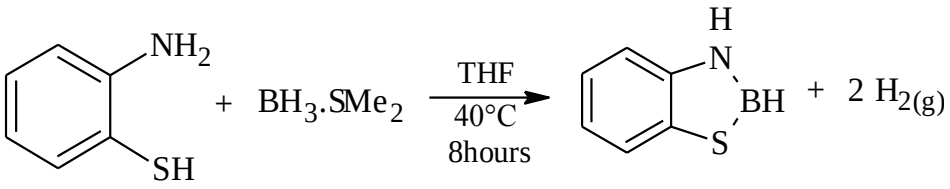
Figure 26: π-interaction between the empty boron p_z-orbital and the lone pair on nitrogen

2.1.2.2. Preparation of Benzo-1,3,2-thiazaborolane

While benzo-1,3,2-diazaborolane appears to be more stable than catecholborane, the stabilizing effect of the nitrogen atom also make the boron atom labile towards the hydroboration reaction.[54] Literature shows that the use of benzo-1,3,2-diazaborolane is limited to metal catalyzed hydroboration, this comes after the hydroborating reagent failed to undergo direct hydroboration with 1-octene after ten days at 100-150 °C whilst catecholborane can result in a 94 % conversion to the desired organoborane within four hours.[48] The formation of the sulfur derivative of catecholborane,benzo-1,3,2-dithiaborolane(HBThia) has been described in the literature, this compound appears to a better hydroborating reagent than benzo-1,3,2-diazaborolane as it is able to undergo direct hydroboration with 1-octene.[54,129]The disadvantage of HBThia is that the starting material 1,2-benzenedithiol is odoriferous, which makes the synthesis and use of this hydroborating reagent unfavourable.

After evaluating the pros and cons ofbenzo-1,3,2-dithiaborolane and benzo-1,3,2-diazaborolane, it was decided that by substituting one of the nitrogen atoms with a sulfur atom in HBPda, should result in a less labile hydroborating reagent whilst the presence of one thiol–group should minimize the odor associated with 1,2-benzenedithiol. The synthesis of the heterocyclic compound benzo-1,3,2-thiazaborolane(HBThiaza) was

easily achieved from the reaction of an equimolar amount of 2-aminothiophenol and borane-dimethyl sulfide complex in tetrahydrofuran at 40 °C, under a dry nitrogen atmosphere (**Scheme 40**).



Scheme 40

The ^{11}B-NMR spectroscopic data observed for the reaction mixture after an hour of stirring indicated the presence of a number of peaks (**Figure 27**), five peaks were observed in the ^{11}B NMR spectrum, these were are a singlet at 20.0 ppm which is the boric acid peak, a quartet at –19.6 ppm which corresponds to the starting material, borane-dimethylsulfide, a triplet at –7.93 ppm, a doublet at 27.5 ppm and second doublet at 37.5 ppm. The peaks at –7.93 ppm and at 27.5 ppm are an indication that there is a possibility that the formation of benzo-1,3,2-thiazaborolane involves two transition state, whereas the doublet peak found at 37.5 ppm was assigned to be the peak corresponding to benzo-1,3,2-thiazaborolane.

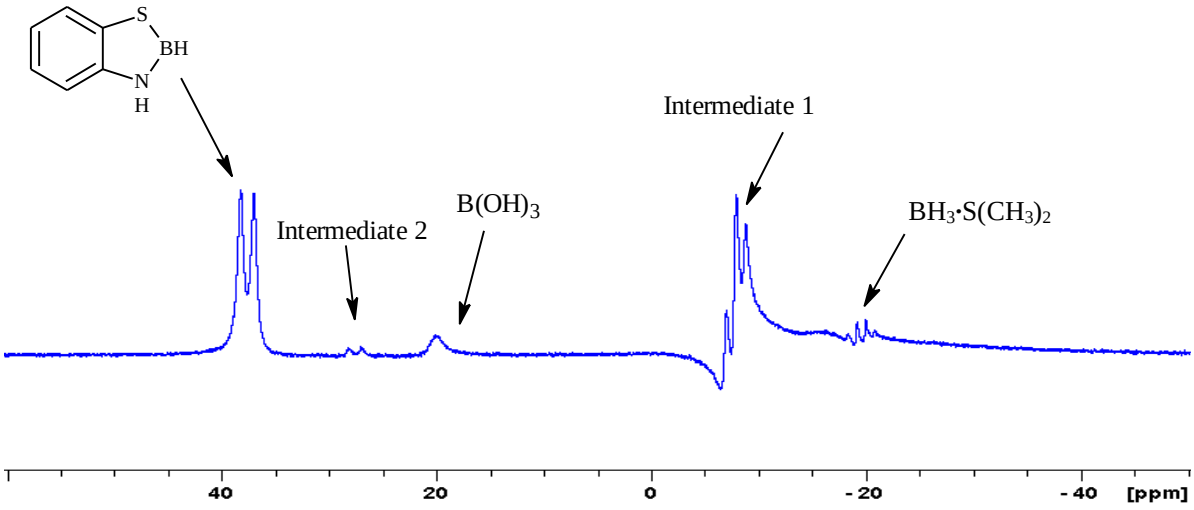
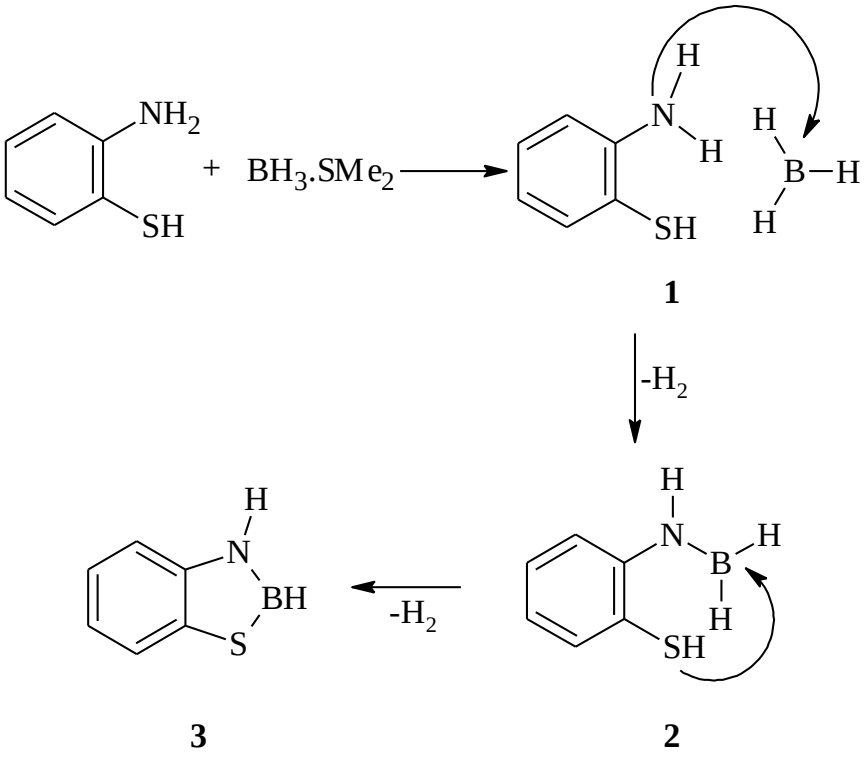


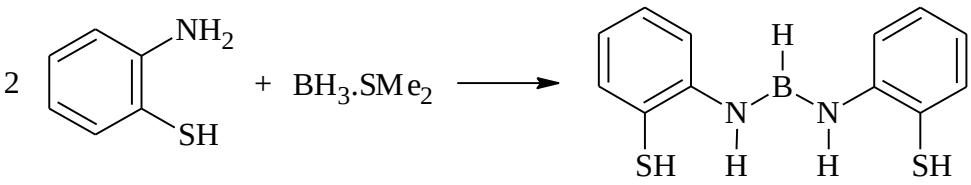
Figure 27:[11]B-NMR spectrum for the synthesis of benzo-1,3,2-thiazaborolane after one hour of stirring.

By interpreting the ^{11}B NMR spectroscopic data the mechanism illustrated by **Scheme 41** can be postulated; with the first step of the mechanism being the nucleophilic attack of the nitrogen atom on the boron atom (**Scheme 41-1**), resulting in the formation of an intermediate with a sp^2 hybridized boron species bonded to the nitrogen and two hydrogen atom. The presence of two hydrides on thesp^2 hybridized boron intermediate should result in a triplet to be observed when an^{11}B NMR spectroscopic analysis is conducted, as can be seen in **Figure 27** that a triplet peak is observed at –7.93 ppm. The assumption that the peak at –7.93 ppm is due to a resonance of boron bonded to nitrogen atom rather than the sulfur group is in accordance with the chemical shift of boron reported by Hermanek on the work involving the use of NMR in the elucidation of structures of boranes and its derivatives.[132] The second step will be the attack of the boron atom by the sulphur which will result in the formation of the heterocyclic HBThiaza compound (**Scheme 41-2&3**) resulting in the doublet peak observed at 37.5 ppm, with a $J_{B\text{-}H}$=171.5 Hz coupling, which is consistent with a B-H coupling constant



Scheme 41

The intermediate labelled as intermediate 2 with a chemical shift of 27.5 ppm in **Figure 27** is proposed to be due to the boron atom being bonded to two aminothiophenol group using the nitrogen atoms (**Scheme 42**). This bond appears to be a weak bond, which can be the result of steric strains as upon continued stirring of the reaction for further seven hours results in intermediate 2 disappearing.



Scheme 42

After 8 hours of stirring, a ^{11}B-NMR spectroscopic data analysis (**Figure 28**) showed a clean spectrum with a doublet peak at 37.5 ppm ($J_{B\text{-}H}$ 171.5 Hz) indicating a total conversion of aminothiophenol to milky yellow solution of benzo-1,3,2-thiazaborolane and the boric acid. The chemical shift observed for HBThiaza is an indication that this

compound has a mixture of both nitrogen and sulfur, as nitrogen borane compound resonate between 20-30 ppm and those of sulfur have a shift in the 50-60 ppm.

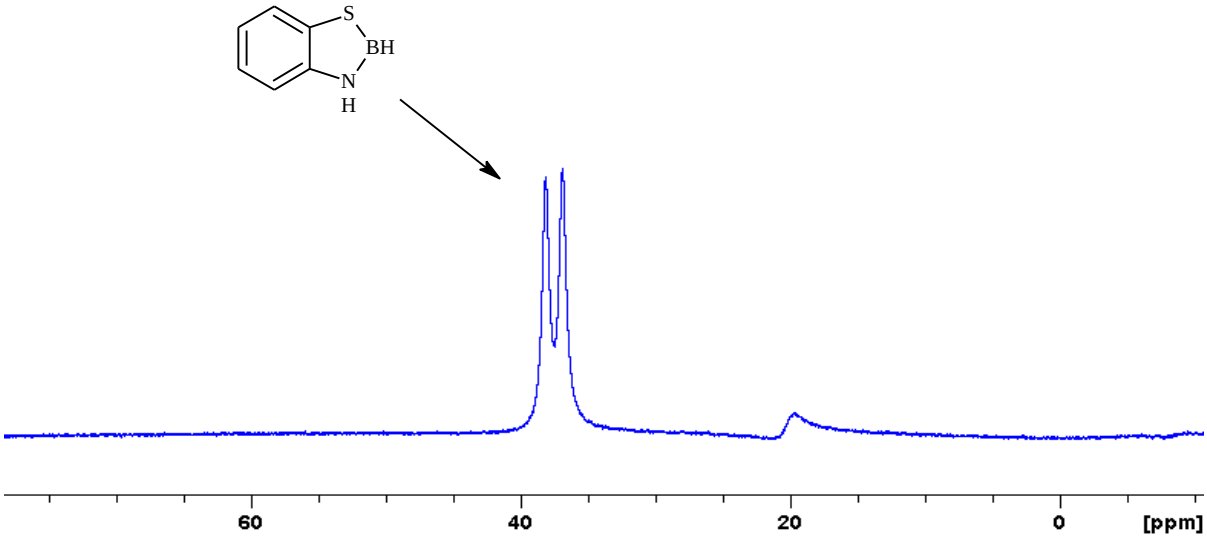


Figure 28: ^{11}B-NMR spectrum for the synthesis of benzo-1,3,2-thiazaborolane after 8 hours stirring.

Mass spectrometry (MS) is a spectroscopic method that involves the ionization of a chemical compound to generate a charged molecule or molecule fragments and the measurement of the mass-to-charge ratio which is recorded in a spectrum.[133] The MS spectrum obtained for HBThiaza is shown in **Figure** 29 and has an intense base peak has an *m/z* ratio of 134.0240 with a 100 % abundance which corresponds with the calculated mass for $[M^+]$= 134.9945 where M^+ is C_6H_6BNS

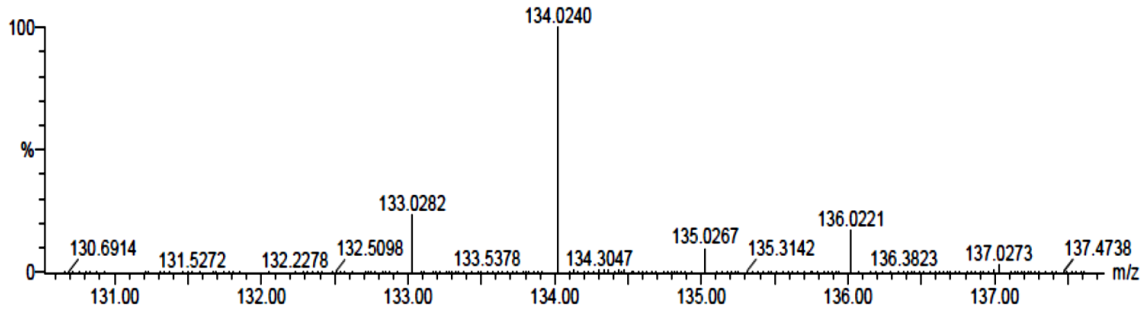


Figure 29:<u>MS spectrum obtained for benzo-1,3,2-thiazaborolane*m/z* 134.0240, calc.(M^+) 134.9945</u>

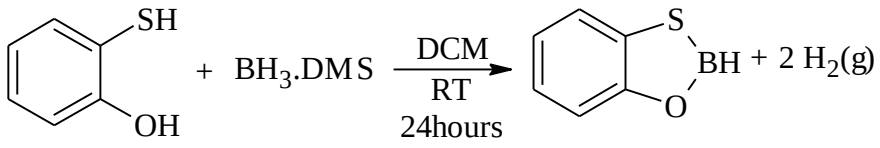
The vibrational spectrum of a molecule is considered to be a unique physical property and is characteristic to that molecule only. The formation of an infrared spectrum is the result of the absorption of electromagnetic radiation at frequencies that corresponds with the vibration of a specific set of chemical bonds from within the molecule.[134] The infrared spectrum of the product displayed absorption bands at 1183 cm^{-1}, 1446 cm^{-1} and 2405 cm^{-1} which can be linked to the stretching vibrations of B–H, B–N and S–B respectively. The stretching vibrations observed for HBThiaza are similar to those that have been reported by Davidson[135] and Aubrey and co-workers. [136]

Benzo-1,3,2-thiazaborolane exhibited a good stability as it did not disproportionate after being stored for five days at room temperature under an atmosphere of nitrogen gas. This stability demonstrated by benzo-1,3,2-thiazaborolane exceeds that of catecholborane which requires to be stored at a temperature below 0 ºC at all times. In an effort to determine the robustness of HBThiaza, two freshly prepared samples of compound were exposed to one of the two conditions; allowed to stand in open air for 2 hours at room temperature or refluxed in toluene for 48 hours under a nitrogen atmosphere. The ^{11}B NMR spectroscopic data analysis of the samples showed that the HBThiaza was stable, at a doublet peak at 37.5 ppm was the dominant peak. These observations are not surprising as nitrogen and sulfur are good donor atom and should be able to bring about some form of stability to HBThiaza.

2.1.2.3. Preparation of Benzo-1,3,2-oxothiaborolane

The synthesis of benzo-1,3,2-oxothiaborolane (HBOxo) was attempted after the successful synthesis of the mixed donor atom above (benzo-1,3,2-thiazaborolane). HBOxo was synthesized with the notion that a catecholborane derivative that has one of the oxygen atoms substituted by a sulfur atom will result in a compound which will not be prone to disproportionation as observed with catecholborane whilst having a better reactivity than the benzo-1,3,2-dithioborolane. The aromatic ring in 2-mercaptophenol has an electron cloud conjugated around the ring, this electron cloud can be donated to the sulfur and oxygen atom and these electrons can be transferred to the boron atom thereby stabilizing benzo-1,3,2-oxothiaborolane against disproportionation. Since there is one sulfur substituent, the degree of π-back donation will not be too pronounced to result in the great reduction of the electrophilic characteristic of the boron atom.

The synthesis of catecholborane requires low temperature (0 °C) and that of benzo-1,3,2-dithiaborolane requires 25 °C, the synthesis of HBOxo was successfully achieved by the reaction of borane-dimethyl sulfide complex with an equimolar amount of 2-mercaptophenol. The reaction mixture was warmed from 0 °C to room temperature over 24 hours (**Scheme 43**) whilst maintaining an atmosphere of nitrogen gas.



Scheme 43

The reaction was found to be slow and mild with no observable effervescence at room temperature.[11]B-NMR spectroscopic data analysis revealed a doublet at 43.9 ppm which was tentatively assigned as the product peak due to the observed coupling constant J_{B-H} of 179.8 Hz which relates to the coupling between the boron and hydrogen atoms, there is also the presence of the starting material peak at –20.7 ppm and a weak singlet peak at 34.1 ppm can be attributed to an oxygen trisubstituted boron compound(**Figure 30**).

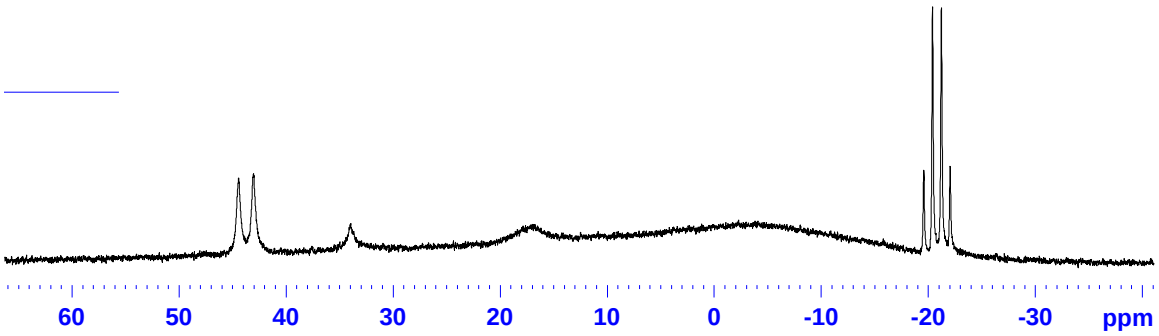
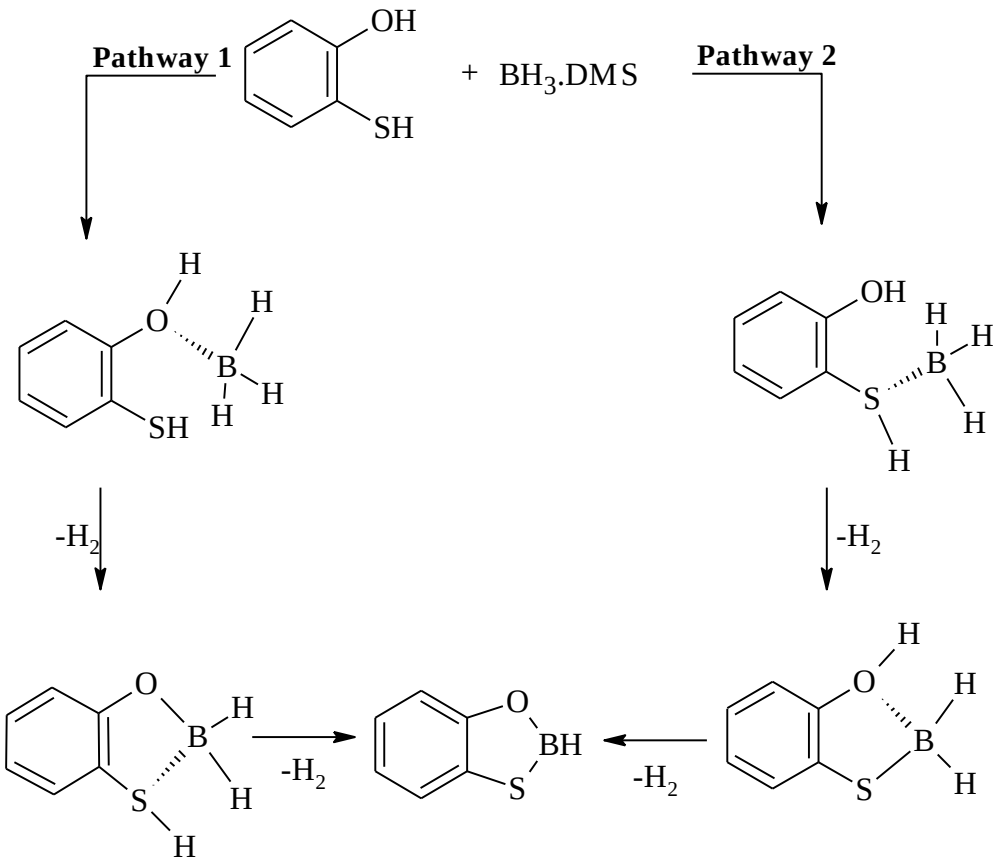


Figure 30: ^{11}B NMR spectrum of benzo-1,3,2-oxothiaborolane after an hour of stirring

After allowing the reaction to continue stirring for seven more hours, an ^{11}B NMR spectroscopic data revealed the presence of a doublet peak at 43.9 ppm and a small singlet peak at 17.8 ppm corresponding to boric acid. Once again the chemical shift observed for benzo-1,3,2-oxothiaborolane does not have a shift characteristic to the oxygen borane compound (25-35 ppm) nor does it have that typical of the sulfur borane derivative (50-60 ppm).

The ^{11}B-NMR spectroscopic data obtained after an hour of stirring the reaction did not provide any viable reflection on the mechanism of the formation of benzo-1,3,2-oxothiaborolane. **Scheme 44** represents a proposed mechanism with two possible pathways; the first pathway involves the attack of boron by the oxygen, which upon the elimination of hydrogen gas will yield intermediate **Scheme** 44-**1**, the sulfur will then attack the boron thereby leading to a closure in the ring which will form HBOxo. The second pathway depicts the sulfur group attacking the boron atom first to form an intermediate **Scheme** 44-**2** when the hydrogen gas is evolved. The oxygen atom then attacks this intermediate to form benzo-1,3,2-oxothiaborolane.



Scheme 44

This first pathway is rather unfavorable when considering that the reaction medium is an aprotic solvent, so there should be no reversal of the nucleophilicity of the hydroxyl-group, therefore this lead to the postulation of the second pathway. The second pathway is more favorable and likely, as in an aprotic medium the thiol-group is a better nucleophile that the hydroxyl-group, therefore sulfur should be the first to attack the electrophilic boron center. [137]

HBOxo appeared to be stable towards oxidation and disproportionation after samples were allowed to stand in open air for an hour at room temperature or refluxed in toluene for 48 hours under a nitrogen atmosphere. These observations indicate that there is some stabilizing effect brought about by the presence of sulfur on the boron atom as literature shows that any exposure of catecholborane to atmosphere resulted in instant disproportionation.[44]

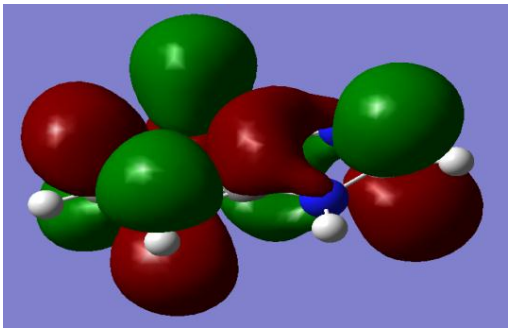
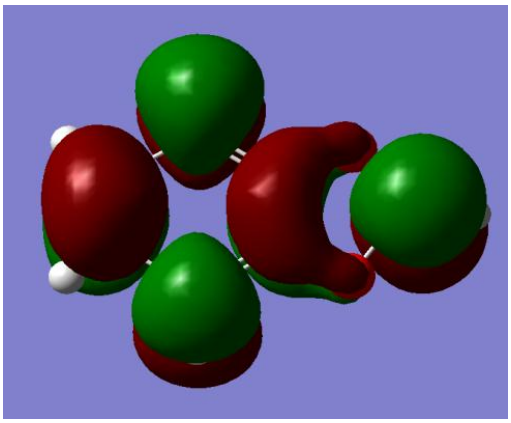
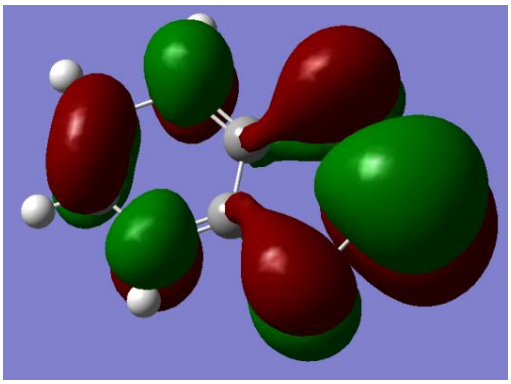
2.1.3. DFT calculation on the hydroborating reagents

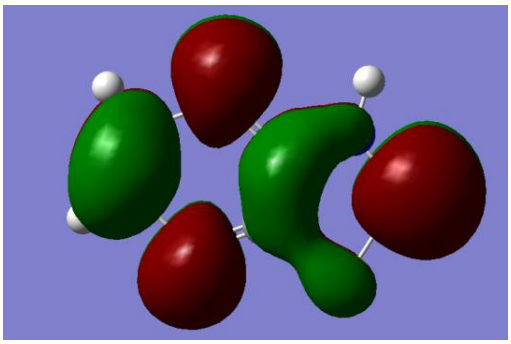
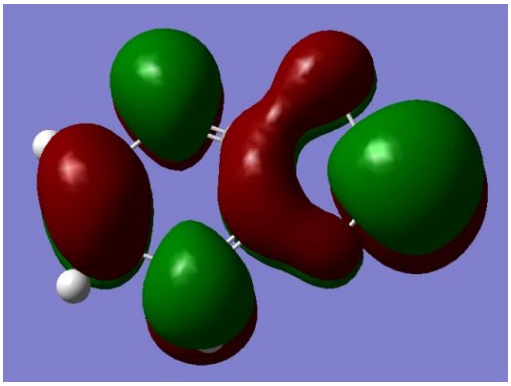
In chapter 1, **section 1.1.3**. it was discussed how the change in the groups bonded to the boron atom changes the behaviour of a hydroborating reagent towards hydroboration. This occurs as a result of the electron cloud that such groups donate to the p_z orbital of the boron atom; in the preceding section, the synthesis of three heterosubstituted borolanes was discussed. In this section a brief attention was focused on computational studies to evaluate the stability and availability to react of the synthesized mixed donor atoms borolanes (HBThiaza and HBOxo), compared to benzo-1,3,2-diazaborolane (HBPda); benzo-1,3,2-dioxaborolane (HBCat) and benzo-1,3,2-dithiaborolane (HBThia). This is not a full study of all the factors involved in the stability of such borolanes but it will be used to determine whether it is feasible to explore the hydroboration reaction of these mixed donor atom borolanes.

The computational calculations in this study were computed using the Gaussian 09W. The use of the Gaussian software has had a wide application in a range of chemical areas since its invention almost four decades ago. A density functional theory with B3LYP method with the 3-21G+ basis set level of theory was employed for all calculations

In this section computational studies were conducted for five cyclic borolanes namely: benzo-1,3,2-diazaborolane; benzo-1,3,2-dioxaborolane; benzo-1,3,2-dithiaborolane; benzo-1,3,2-thiazaborolane and benzo-1,3,2-oxothiaborolane. This computational study was done in an effort to shed some light on the stability of these hydroborating reagents and to find out how stability of the borolane containing mixed donor atoms compares to that which does not. The study was not used to predict the reactivity of these five hydroborating reagents towards the hydroborating reaction.

Table 2: LUMO diagrams and the HOMO-LUMO energy gap calculated for the heterocyclic borolanes.

Borolane	LUMO Diagram	ΔE (kJ/mol) HOMO-LUMO
Benzo-1,3,2-diazaborolane (HBPdiaza)		-539.5
Benzo-1,3,2-dioxaborolane (HBCat)		-594.6
Benzo-1,3,2-dithiaborolane		-553.1

Benzo-1,3,2-thiazaborolane (HBthiaza)		-559.3
Benzo-1,3,2-oxothiaborolane (HBoxothia)		-572.7

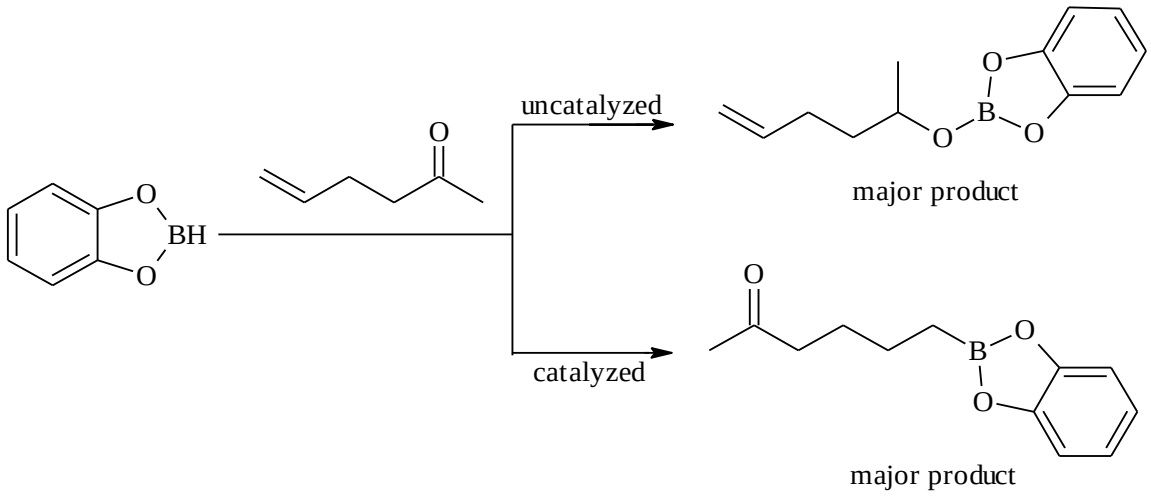
As it can be seen in Table 2, the evaluation of the HOMO-LUMO gap energies obtained, shows that catecholborane has the largest gap than all the other benzo-1,3,2-borolanecompounds. The energy gap decreases in the following order HBCat > HBOxo > HBThiaza > HBThia > HBPda. These observations reveal that the HOMO and LUMO orbitals with the p_z symmetry are distant for HBCat; hence, the amount of π-back bonding is reduced, this compound will be unstable and most likely to disproportionate. However, when looking at the energy gap for the two novel borolanes (HBThiaza and HBOxo) the energy gap is much lower than that of benzo-1,3,2-dioxaborolaneindicating that they are much more stable. The gap energy for HBThiaza is smaller than that of HBOxo, indicating that the π-back donation is more pronounced in HBThiaza than in HBOxo. These novel borolanes however, are less stable than benzo-1,3,2-dithiaborolane and benzo-1,3,2-dioxaborolane, as these have a smaller gap energy.

The computational work conducted above demonstrated that the mixed donor atom borolanes show better stability than catecholborane, with this in mind the quest to find

out the reactivity of one of the mixed donor atom borolanes. Further computational studies needs to be conducted to evaluate energy required for the hydroboration reaction and the disproportionation reaction for the above borolanes. In the next section two of the five borolanes will be allowed to undergo hydroboration with 1-octene in the presence of the Wilkinson's catalyst or [chloro(1,5-cyclooctadiene)iridium(I)].

2.1.4. Metal Catalyzed Hydroboration

In **section 1.1.2.3**. (Chapter 1) the use of transition metal in the hydroboration reaction was exploredas the products synthesized from this reaction provide for a similar or opposite regio-, chemo-, and/orstereoselectivity to those generated by the uncatalyzed hydroboration reaction. The pioneers of the metal catalyzed hydroboration reaction were Kono and Ito who in 1975 revealed that the Wilkinson's catalyst is able to undergo oxidative addition.[56] These findings by Kono and Ito were subsequently explored by Männing and Nöth, who a decade later reported that rhodium complexes can catalyze the hydrogenation and hydroboration of alkenes at room temperature. Männing and Nöth indicated that transition metals complexes can be chemoselective to multifunctional groups, as shown in **Scheme 45** the catalyzed reaction adds catecholborane over the alkene double whereas with the uncatalyzed it is added over the carbonyl group.[57]

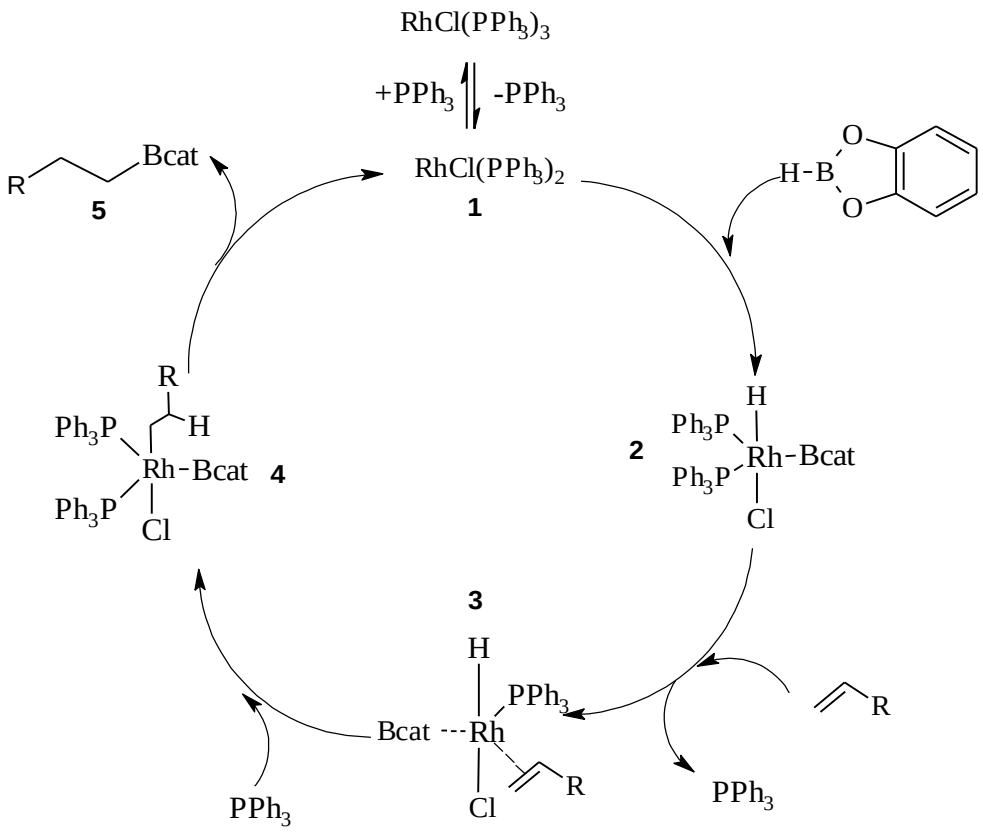


Scheme 45

With the successful synthesis of HBThiaza which demonstrated good stability, the quest to better understand its reactivity towards hydroboration was undertaken using two catalyst systems, namely the Wilkinson's catalyst ([$RhCl(PPh_3)_3$])and [chloro(1,5-cyclooctadiene)iridium(I)] ([$IrCl(cod)]_2$). Both these catalyst have been reported to catalyze the hydroboration reaction with a range of hydroborating reagents to yield terminal organoborane compounds in good yields. [60,108,138]

2.1.4.1. [$RhCl(PPh_3)_3$] Catalyzed Hydroboration

The application of rhodium in catalysis has been discussed in **section 1.1.2.3.1.** (Chapter 1), this element was one of the first metals to be used in homogenous catalysis subsequently it is well studied. The ease of the oxidative addition to the four-coordinate square planar rhodium(I) to give the octahedral coordinate rhodium(III) species has attributed to the popularity of rhodium catalyst.[61] The mechanism of the rhodium catalyzed hydroboration reactions has been extensively studied; Männig and Nöth proposed the catalytic mechanism for the hydroboration based on the reaction of an alkene with catecholborane (**Scheme 46**). They proposed a dissociative mechanistic pathway as the mechanism that resulted in the addition of catecholborane to the double bond of the alkene. This pathway was supported by Evans and co-workers after conducting deuterium labeling experiments.[58] However, Baker and co-workers[62] rejected the dissociative mechanism suggested by Manning and Noth, and proposed an associative mechanism for the hydroboration. The mechanistic pathway that they offered was reasonably similar to that of the dissociative pathway with a minor difference. [62]



Scheme 46

The dissociative mechanism proposed for the hydroboration of an olefin in the presence of a Wilkinson's catalyst entails the loss of a phosphine ligand to provide the transient species $RhCl(PPh_3)_2$ with a vacant coordination site. The transient species enters the catalytic cycle and is successively followed by (**Scheme** 46):

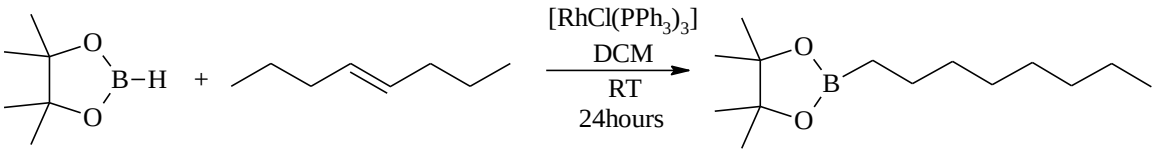
- The oxidative addition of the catecholborane (B–H bond) to the metal center to form the rhodium boryl species**.**
- The coordination of the olefin into the metal center results in the displacement of a second phosphine ligand to form a penta-coordinated rhodium intermediate complex.
- Thereafter there is the subsequent insertion of the olefin into the Rh–H or Rh–B bond in conjunction with the phosphine ligand binding to the metal center.

- And finally the reductive elimination of the borolane product completes the catalytic cycle by regenerating the transient species.

For the associative pathway, the first and second steps are the same as those of the dissociative pathway with the difference arising with the olefin coordination to the rhodium center. The coordination of the olefin to the metal center transpires without a loss of the phosphine ligand from the metal center, this generates a hexa-coordinate intermediate. This step is followed by the reductive elimination that yields the boronate ester compound similar to the dissociative pathway.[62]

2.1.4.1.1. Hydroboration of trans-4-octene with pinacolborane

The ability of the Wilkinson's catalyst to hydroborate trans-4-octene was first explored using pinacolborane. The catalyst displayed a good catalytic activity when trans-4-octene (1 mmol) was reacted with pinacolborane (1 mmol) in the presence of $[RhCl(PPh_3)_3]$(2.0 mol%), at room temperature after stirring for 24 hours (**Scheme 47**). This reaction resulted in the generation of octyl-pinacolboronate ester in a 98 % yield which corresponds well with that reported by Pereira and Srebnik[53] of 92 %.



Scheme 47

Analysis of the reaction after for hours of stirring using the ^{11}B NMR spectroscopic data revealed the presence of four resonance peaks which were assigned as shown in **Figure 31.** After 24 hours of stirring the ^{11}B NMR spectroscopic data showed the presence of one major peak at 33.9 ppm and a minor peak corresponding to the disproportionation product at 22.1 ppm.

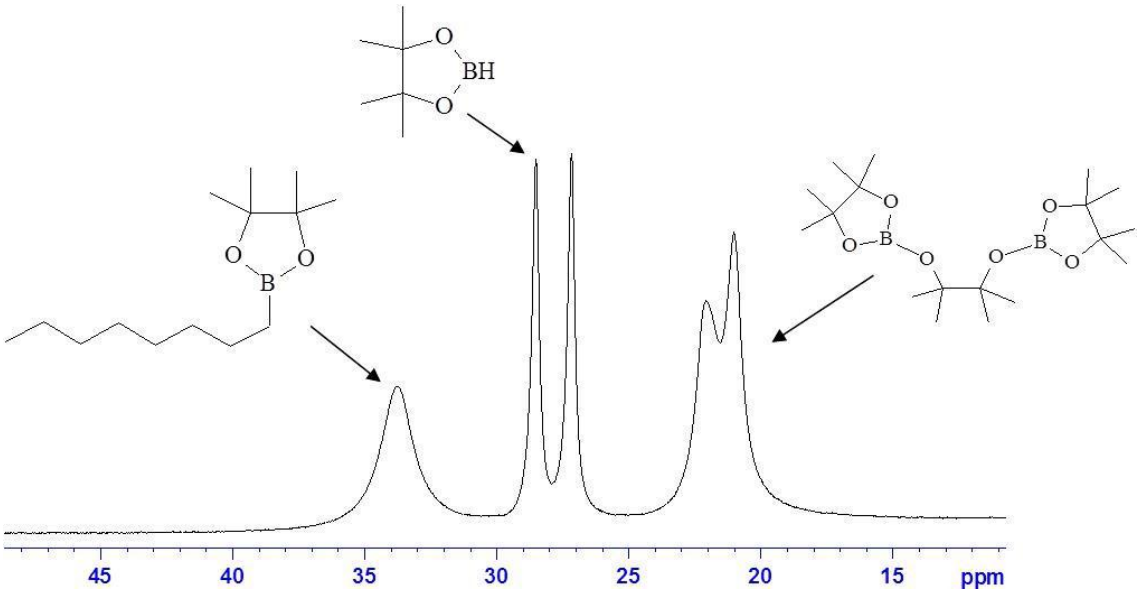
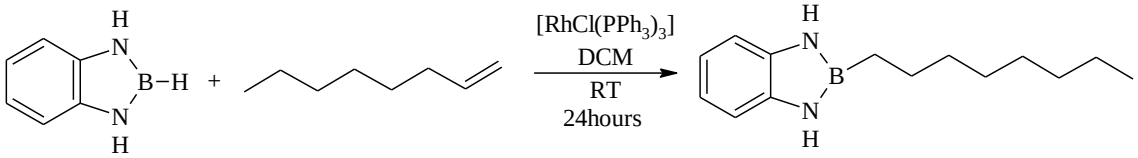


Figure 31: ^{11}B NMR fragments obtained for the [RhCl(PPh$_3$)$_3$] catalyzed hydroboration reaction with pinacolborane.

The ^{1}H NMR spectroscopic data indicated that the product formed above was 1-octyl-pinacolboronate ester, this is once again consistent with the observation made by Pereira and Srebnik[53] that the hydroboration of trans-4-octene with pinacolborane using the Wilkinson's catalyst exclusively afford the terminal boronate ester product. [53]

2.1.4.1.2. Hydroboration of 1-octene with benzo-1,3,2-diazaborolane



Scheme 48

The application of the Wilkinson's catalyst in the catalytic addition of benzo-1,3,2-diazaborolane over the double bond in 1-octene was first reported by Hadebe and Robinson. In this report Hadebe and Robinson showed the successful synthesis of octylbenzo-1,3,2-diazaboranate ester in a 70 % yield by the reaction of HBPda with 1-

octene using $RhCl(PPh_3)_3$(20 mol%).[54] Efforts to match the 70 % yield reported by Hadebe were unsuccessful when the ratio of 1-octene to HBPda was 1:1, as the ^{11}B NMR spectroscopic data showed a 10 % conversion to the desired (**Figure 32**), after allowing the reaction to proceed for 24 hours at room temperature (**Scheme 48**).

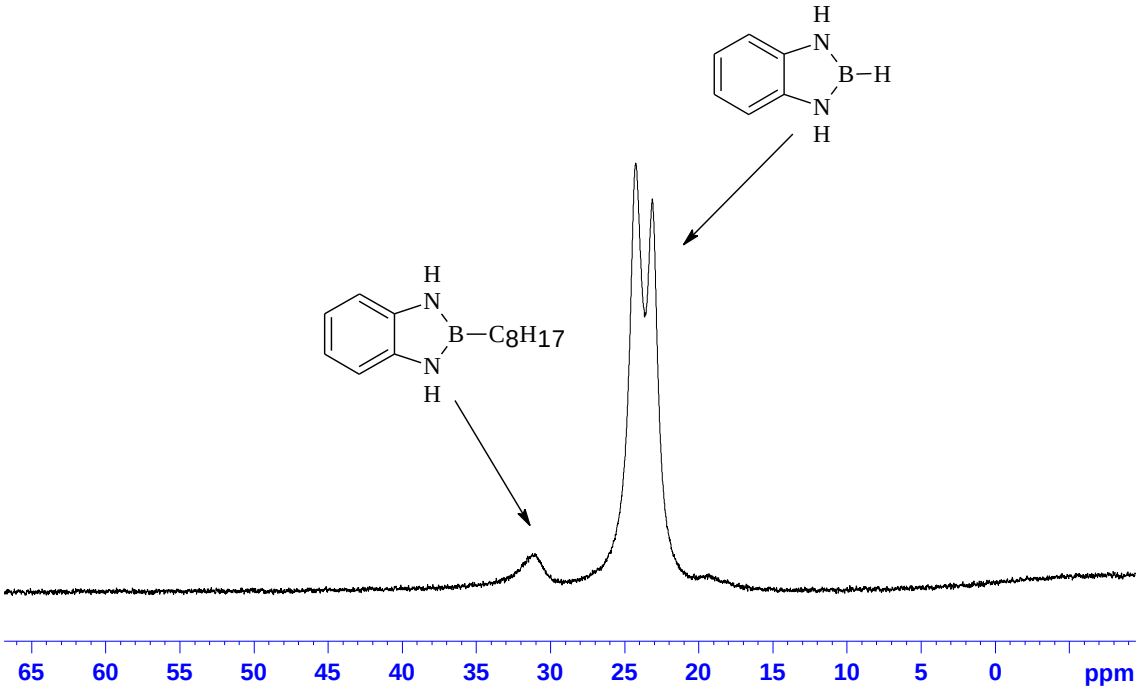


Figure 32: ^{11}B NMR spectroscopic data observed for the[$RhCl(PPh_3)_3$] catalyzed hydroboration of 1-octene (1:1 ratio).

Increasing the temperature to 50 °C and stirring the reaction for a further 24 hours didn't have any effect on the reaction yield, whilst increasing the olefin: HBPda ratio to 1:7 resulted in the total conversion of HBPda to octylbenzo-1,3,2-diazaborolane, with some traces of boric acid observed (**Figure 33**). These results indicate the dependence of the above reaction on the amount of the olefin used in the reaction, which is consistent with the report by Evans and co-workers[58] on the substrate dependence of rhodium catalyzed hydroboration.

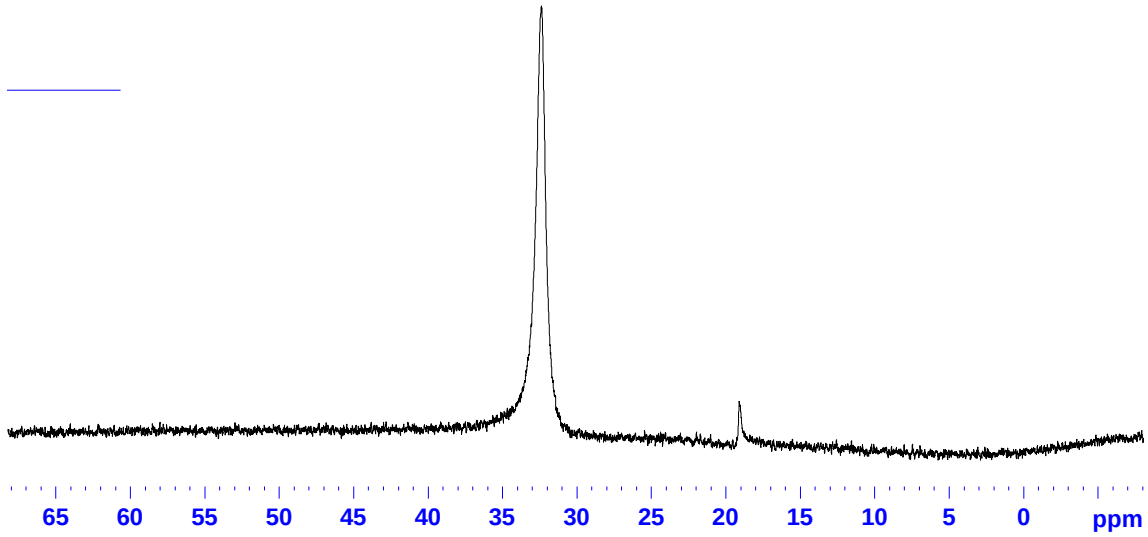
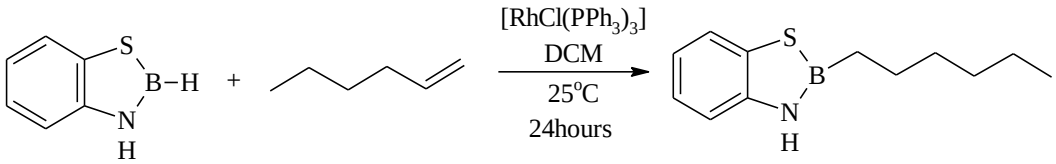


Figure 33:^{11}B NMR spectroscopic data observed for the[RhCl(PPh$_3$)$_3$] catalyzed hydroboration of 1-octene by HBPda (1:7 ratio).

2.1.4.1.3. Hydroboration of 1-octene with benzo-1,3,2-thiazaborolane

The Wilkinson's catalyst demonstrated excellent activity towards hydroboration using pinacolborane and HBPda. Using the reaction conditions that were employed with pinacolborane and HBPda, HBThiaza was reacted with 1-octene in the presence of Wilkinson's catalyst for 24 hours at 25 °C (**Scheme** 49).



Scheme 49

The^{11}B-NMR spectroscopic data analysis conducted after 14 hours revealed the formation of a new trisubstituted boron species, highfield of HBThiaza; this was an indication that the newly formed boron species was an electron rich compound (**Figure 34**).

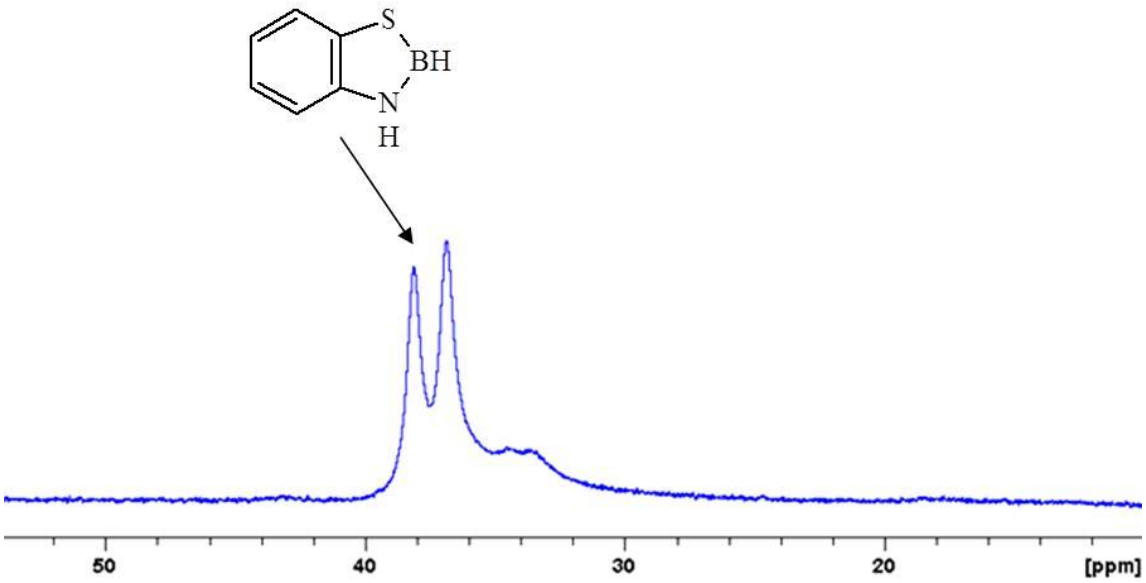


Figure 34: ^{11}B NMR spectroscopic data analysis observed for the [RhCl(PPh$_3$)$_3$] catalyzed hydroboration of 1-octene with benzo-1,3,2-thiazaborolane after 14 hours.

After 36 hours, the starting material had completely disappeared and the ^{11}B NMR spectroscopic data showed that a singlet peak at 31.8 ppm, indicating the disappearance of the B-H bond from HBThiaza.

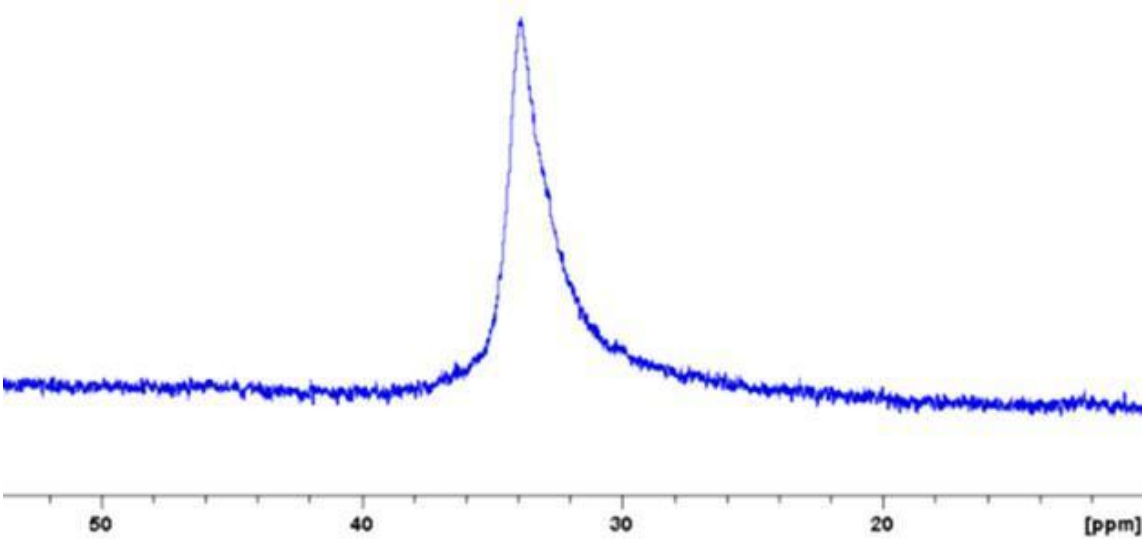


Figure 35: ^{11}B NMR spectrum of [RhCl(PPh$_3$)$_3$] catalyzed hydroboration with benzo-1,3,2-thiazaborolane after 36 hours

Braunschweig and Colling[139] reported on their review work with transition metal complexes of boron that the addition of boron to the metal centre results in a low field shift of boryl-metal on the ^{11}B NMR compared to the starting material borane.[139] The claims by Braunschweig and Colling are supported by the report Bell and co-workers[140] as they observed a low field shift on the ^{11}B NMR to 32 ppm for the boryl(hydrido) complex (Rh(H)Cl(BzBpin)(PPh$_3$)$_2$)compared to the 27 ppm observed for 4,4,5,5-tetraphenyl-1,3,2-dioxaborolane (BzBpin).[140] As literature suggested that the high field shield observed in **Figure 35** was not due to the oxidative addition of HBThiaza to the rhodium metal center, infrared spectroscopy analysis was conducted which revealed the absence of the absorption band at 2405 cm^{-1} which corresponds to the B-S bond. The resonance peak was then assumed to be due to the disproportionation of HBThiaza

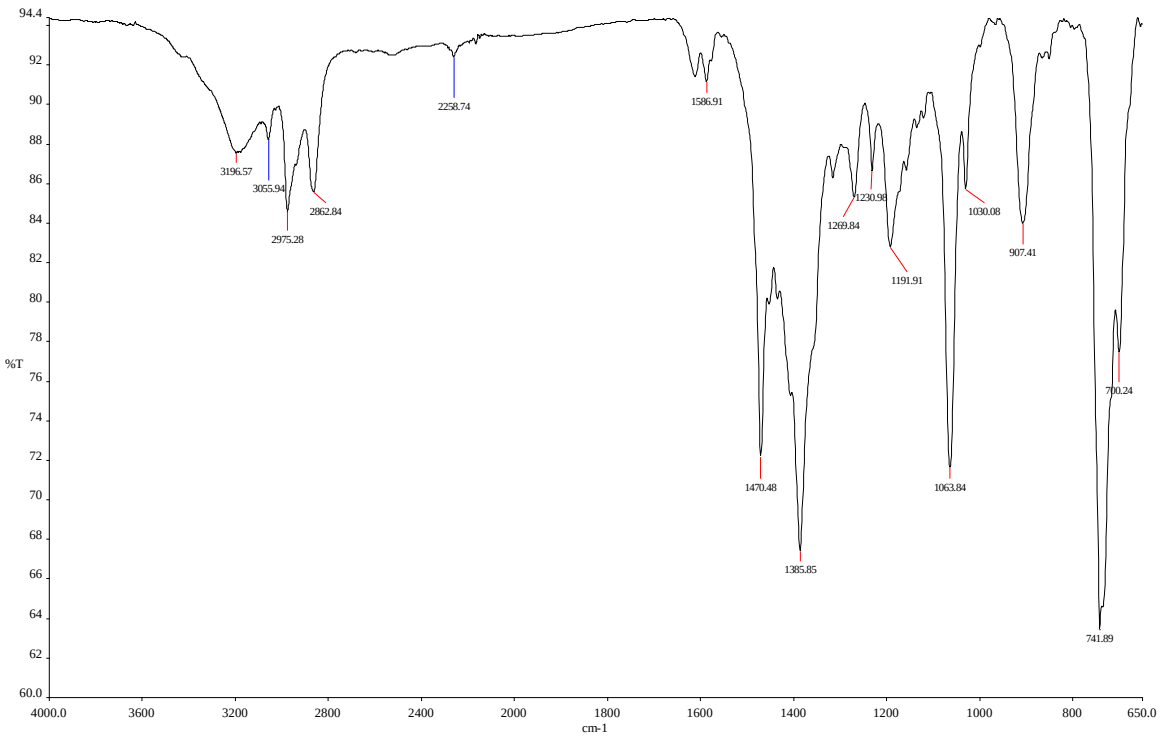


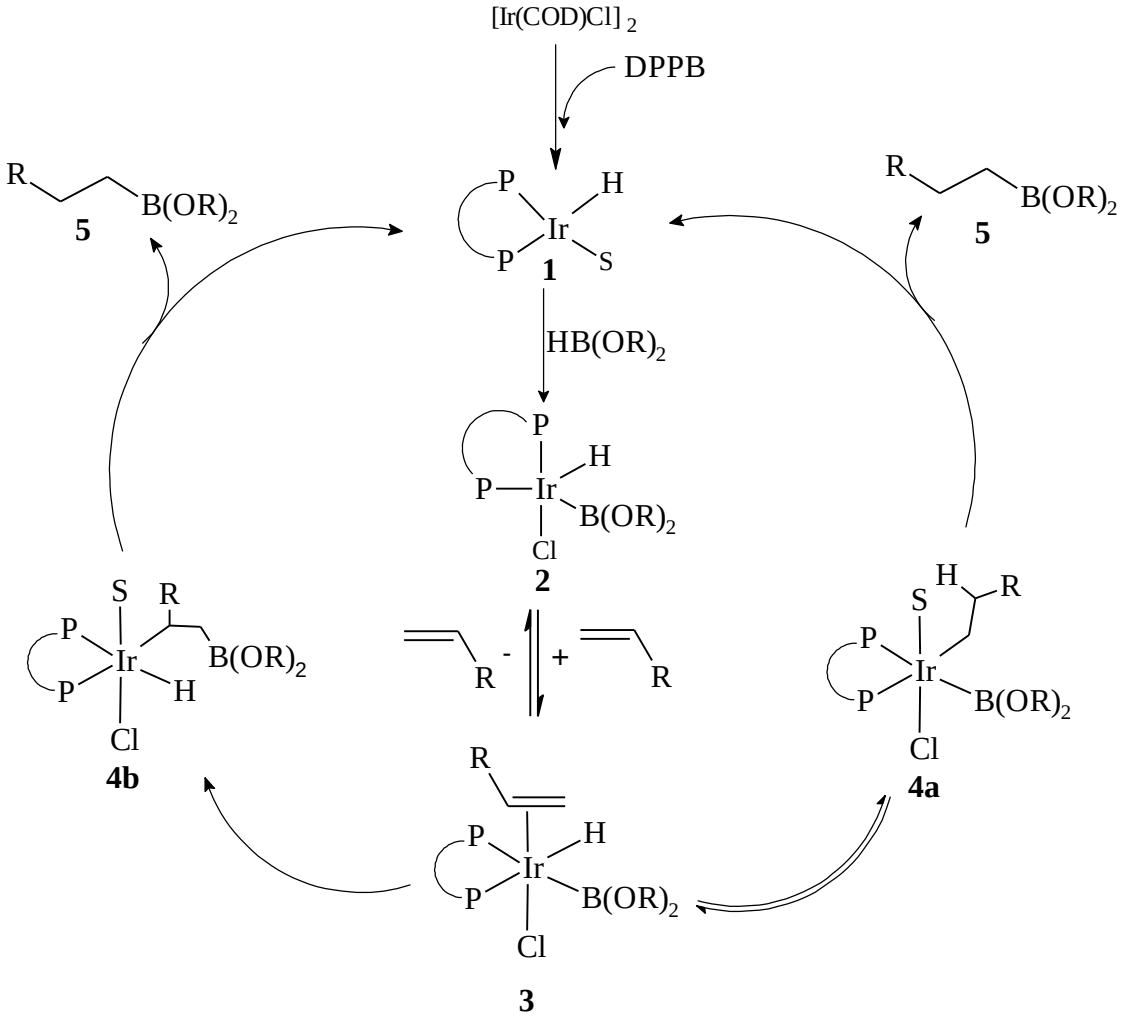
Figure 36: IR spectrum observed for the [RhCl(PPh$_3$)$_3$]catalyzed hydroboration of 1-octene

2.1.4.2. [IrCl(cod)]$_2$ Catalyzed Hydroboration

The application of iridium in metal catalysis is not as popular as that of rhodium, with Vaska's complex (*trans*-[IrCl(CO)(PPh$_3$)$_2$]) being the most widely used iridium complex.[66] The literature reveal the ease at which iridium(I) undergoes oxidative addition to form the stable iridium(III) complex; however, the reductive elimination of Ir(III) back to Ir(I) has been said to be difficult and slow process. The difficulty of the reductive elimination is due to the strong Ir–ligand bond strength and the interaction between the positive charge on the metal with the π–bonding ligands.[67]

The initial work on the use of iridium complex as a catalyst for hydroboration was reported by Evans and co-workers, when they described the hydroboration of 1-decene with catecholborane in the presence of the Crabtree catalyst complex ([Ir(COD)(PCy$_3$)(py)]PF$_6$).The Crabtree catalyst has been previously used in

homogenous catalysis.[59] Since the use of iridium in catalyzed hydroboration is still a new venture, the mechanistic pathway is not fully understood. There is a number of research studies being conducted towards the understanding of the mechanism. Hartwig[68] has conducted calometric and computational studies and proposed a mechanism for the iridium catalyzed hydroboration. The mechanism proposed by Hartwig was supported by the empirical study on the behavior of iridium catalyst conducted by Vaska and DiLudio[69] and recently a deuterium labeling studies conducted by Crudden.[60]



Scheme 50

Scheme 50demonstrates the proposed mechanism which is related in many aspects to that of the rhodium catalyzed hydroboration, as it also includes the formation of the active iridium catalytic species by cracking the iridium chloro-bridged dimer with 1,4-bis(diphenylphosphino)butane(DPPB) and displacing COD when $[Ir(COD)Cl]_2$. This iridium(I) species enters the catalytic cycle and is followed by the next steps (assuming a reaction between a dialkoxyborane and 1-alkene):

- The oxidative addition of the dialkoxyborane to yield a penta-coordinated iridium complex **2**. There are report on the isolation and characterization of these penta-coordinated intermediates for reactions with catecholborane.[70]

- The associative coordination of the 1-alkene to the metal to afford intermediate **3** a hexa-coordinated metal center.

- After the coordination of the catalyst the next step can proceed via two pathways, both of which lead to product **5** a linear boronate ester.

    - The first pathway is an iridium boryl manifold (**3–4a–1**). This route involves the insertion of the alkene into an Ir–B bond 4a, which Hartwig and co-workers showed to be thermodynamically favored.[68] If R– is a benzyl group, there is a beneficial stability that arises from π-benzyl complex.[60]

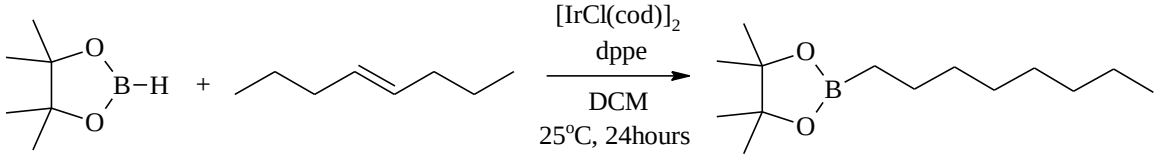
    - The alternative route is the iridium hydride manifold (**3–4b–5**). The first step of this pathway is insertion of the alkene into the Ir–H bond and is reversible based on the deuterium studies by Crudden and co-workers.[60] Though there is no π-benzyl complex intermediate formed by this pathway it is still able to undergo the final step of the catalytic cycle. .

- The final step is the reductive elimination for both 4a and 4b which generates the linear organoboronate ester product and regenerates the active catalyst site.

2.1.4.2.1. Hydroboration of 1-octene with pinacolborane

The application of iridium(I) catalyst is a relatively new addition in the hydroboration reaction. To find the ideal reaction conditions for such a reaction, pinacolborane and 1-octene were allowed to react using the conditions stipulated below. The reaction conditions employed are similar to those reported by Yamamoto and co-workers,[71] as the addition of a phosphine ligand was described to increase the overall yields of the reaction.

The $[IrCl(cod)]_2$catalyst displayed a good catalytic activity when trans-4-octene was reacted with pinacolborane in the presence of $[IrCl(cod)]_2$(1.5mol%) and dppb, at room temperature after stirring for 24 hours (**Scheme 51**). Purification on radial chromatography with dichloromethane afforded octyl-pinacolboronate ester in a 82 % yield which agrees favourable with that of Yamamoto and co-workers.[71]



Scheme 51

The^{11}B NMR and ^{1}H NMR spectroscopic methods were used to validate the synthesized compound. The^{11}B NMR spectrum showed a singlet peak at 34.2ppm and ^{1}H NMR spectroscopic data revealed the presence of five resonance peaks at δ_H 0.76 ppm (2H, t); 0.87 ppm (3H, t); 1.23 ppm (12H, s);1.25 ppm (10H, s) and 1.33-1.45 ppm (2H, m) assignable to 14; 15; 5,5´,7 &7´; 9,10,11,12&13; 8 respectively. These assignments are consistent with those assigned by Yamamoto and co-workers.

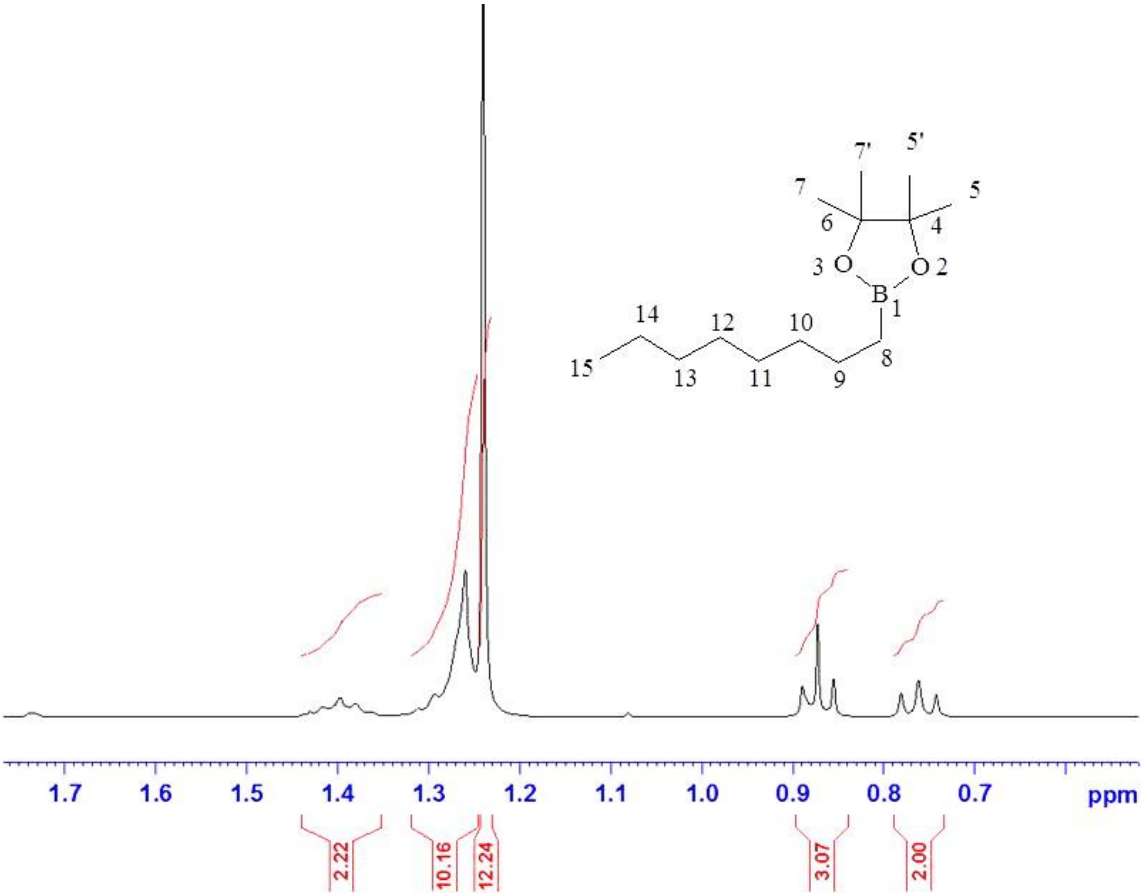
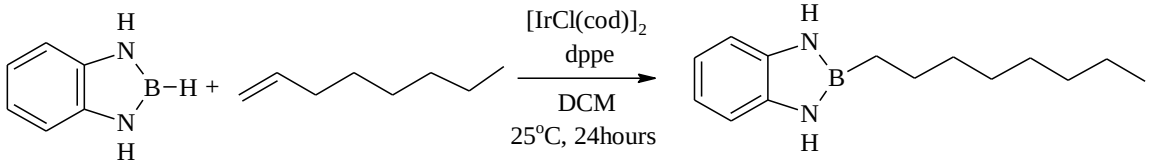


Figure 37: ^{1}H NMR spectrum obtained forthe $[IrCl(cod)]_2$ catalyzed hydroborationof *trans*-4-octene with pinacolborane

With the such a successful reaction, the next attempt on the use of $[IrCl(cod)]_2$ as a hydroboration catalyst was explored with benzo-1,3,2-diazaborolane.

2.1.4.2.1. Hydroboration of 1-octene with benzo-1,3,2-diazaborolane



Scheme 52

The catalytic addition of benzo-1,3,2-diazaborolane to 1-octene was investigated using $[IrCl(cod)]_2$; as mentioned earlier, this addition has thus far been reported to be catalyzed by Wilkinson's catalyst.[129] Using the conditions employed for the pinacolborane addition above, HBPda was successfully added 1-octene in a 72 % isolated yield (**Scheme** 52).

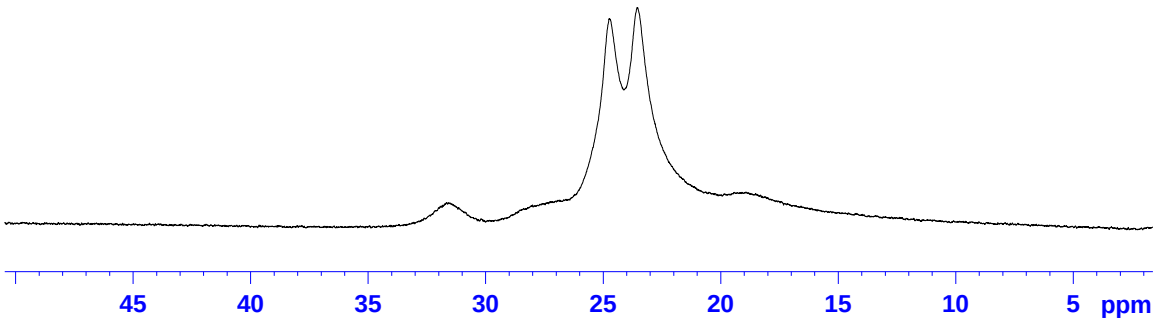
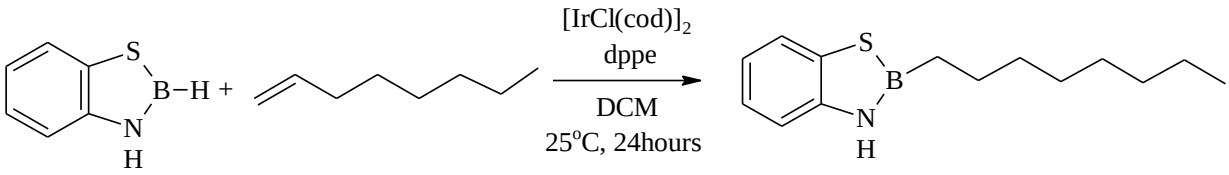


Figure 38: ^{11}B NMR spectrum of $[IrCl(cod)]_2$ catalyzed hydroboration with benzo-1,3,2-diazaborolane after 24 hours.

After allowing the reaction to stir for 24 hours, the ^{11}B NMR spectroscopic data showed a singlet peak at 31.6 ppm, which is consistent with the chemical shift reported by Hadebe and co-workers, and that observed above using $[RhCl(PPh_3)_3]$catalyst complex (**Figure 32**). The results show that $[IrCl(cod)]_2$can successfully catalyse the addition of a relatively labile borane reagent resulting in yields similar to those obtained using Wilkinson's. Furthermore, this successful addition provides an alternative metal catalyst complex for such a reaction.

2.1.4.2.2. Hydroboration of 1-octene with benzo-1,3,2-thiazaborolane



Scheme 53

The $[IrCl(cod)]_2$ catalyst complex showed it is able to successfully catalyze the hydroboration addition of pinacolborane and HBPda to an olefin. Using the reaction conditions that were employed with pinacolborane and HBPda, HBThiaza was reacted with 1-octene in the presence of $[IrCl(cod)]_2$ catalyst complex for 24 hours at 25 °C (**Scheme 53**).

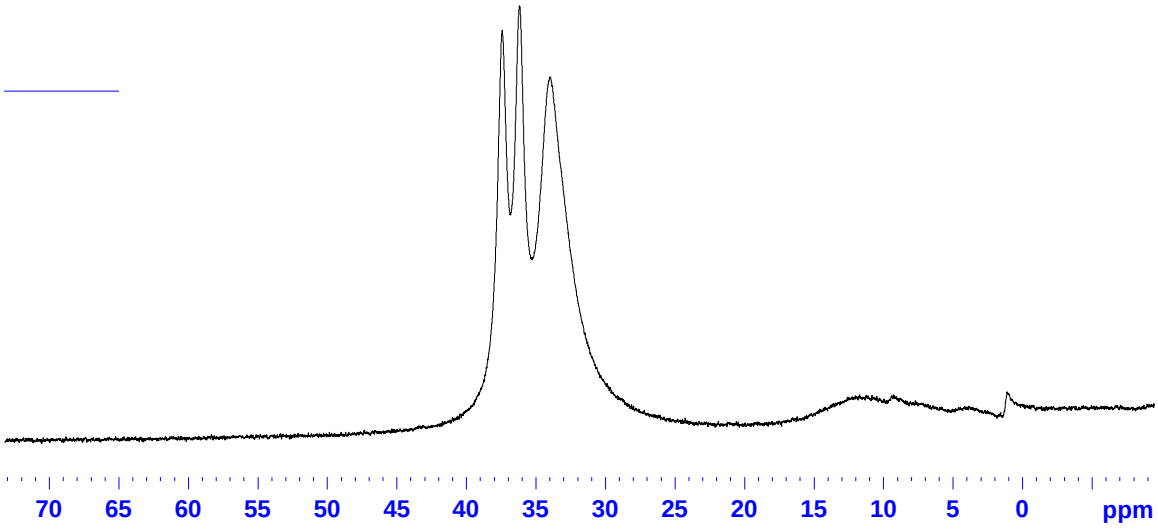


Figure 39: ^{11}B NMR spectroscopic data analysis observed for the$[IrCl(cod)]_2$ catalyzed hydroboration of 1-octene with benzo-1,3,2-thiazaborolane after 14 hours.

Similarly to the reaction catalyzed by the Wilkinson's, the^{11}B-NMR spectroscopic data analysis conducted after 14 hours revealed the formation of a new trisubstituted boron species at 33.0 ppm. This species was high field compared to HBThiaza; this was an indication that the newly formed boron species was an electron rich compound, which was identified earlier to be a disproportionation product (**Figure 39**).

2.2. Conclusion

Three heterocyclic borolanes were successfully synthesized from the reaction of borane-dimethyl sulfide complex and the corresponding chelating group in yield ranging from 45-96 %. These borolane showed good stability towards atmospheric oxidation and disproportionation due to elevated temperatures.

The ^{11}B NMR spectroscopic data of the mixed donor atom heterocyclic borolane (HBThiaza and HBOxo) showed that there were intermediate that were formed during the synthesis of these compounds. For HBThiaza, it was postulated that the nitrogen attacks the borane first followed by the sulfur atom attack on the boron atom. For the formation of HBOxo, the sulfur was postulated to be the first to attack the borane followed by the sulfur attack, leading to the ring closure.

DFT computation studies showed that HBThiaza and HBOxo presented better stability than benzo-1,3,2-dioxaborolane as they had a smaller HOMO-LUMO energy gap.

$[RhCl(PPh_3)_3]$and $[IrCl(cod)]_2$catalyzed hydroboration with pinacolborane and benzo-1,3,2-diazaborolane gave excellent yields in the range of 72-98 %. The successful application of $[IrCl(cod)]_2$complex in the hydroboration reaction using with benzo-1,3,2-diazaborolane increases the metal catalyst complexes that can be used such reaction. The catalyzed hydroboration of 1-octene with HBThiaza was unsuccessful as this reaction resulted in the disproportionation of the borolane.

2.3. Recommendations for Future Work

The mechanism of the formation of the mixed atom heterocyclic borolane was partially based on the ^{11}B NMR spectroscopic data obtained; a computational modeling study focusing on the mechanism of formation should be conducted. The modeling studies can also account for the disproportionation observed in the catalyzed reaction with HBThiaza.

The reactivity of HBOxo towards the hydroboration reaction was not investigated, this work can be done as this borolane might give better results than those obtained with HBThiaza.

The $[IrCl(cod)]_2$catalyst complex showed good reactivity towards the hydroboration reaction of HBPda with 1-octene. A range of olefin substrate can be evaluated to determine whether this catalyst can be used as an alternative to the Wilkinson's catalyst which has thus far failed to catalyze internal olefins with HBPda.

In the following chapter, an alternative route will be used for the synthesis of organoborane compounds and the application of arylbenzo-1,3,2-diazaboronate esters will be investigated as possible arylating reagents for the Chan-Lam coupling reaction.

CHAPTER 3

3.1. Results and Discussion: Synthesis of Boronate Esters using a Condensation Reaction

3.1.1. Study Objectives

There are two parts in this chapter; the first part will discuss the synthesis of a range of heterosubstituted boronate esters by replacing the hydroxyl group of the boronic acid with a suitable chelating ligand using the condensation reaction. The condensation reaction methodology provides an alternative route for the synthesis of boronate esters over the expensive metal catalyzed reaction of alkenes with moisture and air sensitive hydroborating reagents (**Figure 40**).

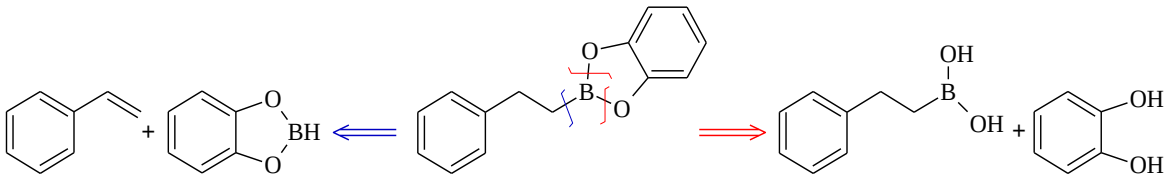


Figure 40: Retrosynthesisof an arylboronate ester.

The second part of this chapter will be on the investigation of arylbenzo-1,3,2-diazaboronate ester compounds that were synthesized in the first part as possible arylating reagents for the Chan-Lam reaction.

3.1.2. Boronic Acids: A Preview

Boronic acid compounds have acquired their popularity due to their application as coupling partners in a wide range of coupling reactions; these reactions include Suzuki-Miyaura, Petasis, Chan-Lam coupling reaction (**Section 1.1.6**).[86,100,107] The first synthesis of boronic acids was described by Falkland; when he noted that the reaction of diethyl zinc with triethylborate afforded an air-sensitive intermediate which upon its oxidation by the atmosphere yielded triethylboronic acid.[108] Since then there are numerous methods that have been described in the literature for the preparation of boronic acid,[108] but the classical route for the synthesis of aryl and 1-alkyboronic acid uses a Grignard or lithium reagent with trialkyborate (**Figure 41**).

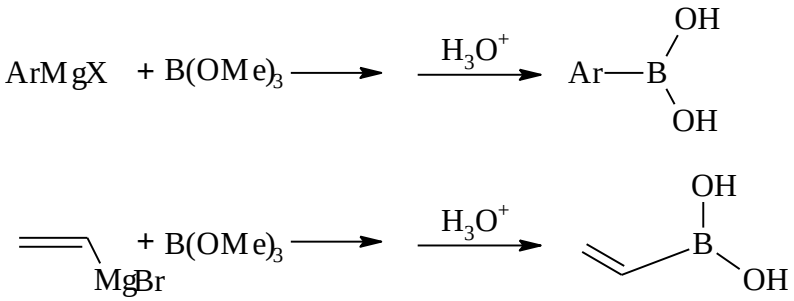
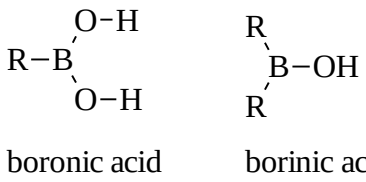


Figure 41: <u>The classical route used for the synthesis of aryl- and 1-alkenylboronic acids.</u>

However, with this route there are side reactions that have been reported including bisalkylation which gives rise to the corresponding borinic acid (**Figure 42**) and the formation of trialkylboranes has also been observed.[108]



boronic acid borinic acid

Figure 42: <u>Structure of boronic acid and borinic acid</u>

To avoid the side reactions mentioned, Miyaura stipulated that instead of using the Grignard reagents, lithium compounds can be reacted with the sterically hindered borates (such as triisopropylborate) followed by acidification using hydrochloric acid.[100] The bulky triisopropylborane will hinder the attack of the boron atom by the second R-group there by preventing bis-alkylation (**Figure 43**).

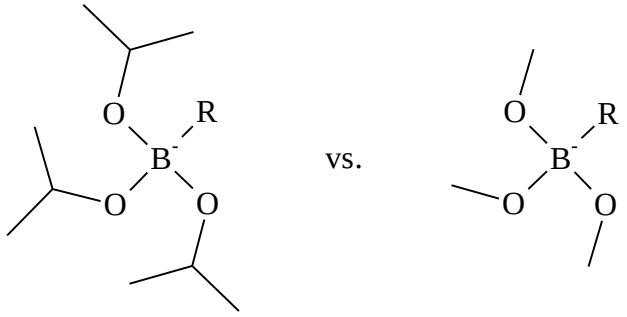
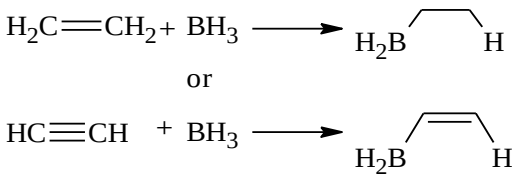


Figure 43:<u>Illustration of the steric hindrance brought about by the isopropyl-group over the boron atom compared to that of the methyl-group</u>.

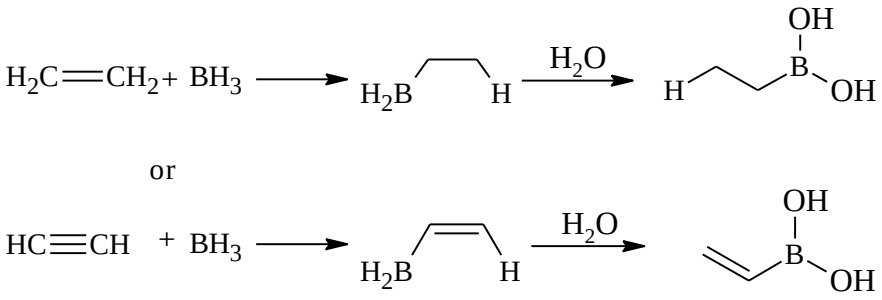
The alternative method for the synthesis of boronic acid is the hydroboration of alkenes with a hydroborating reagent, which proceeds virtually quantitatively viaa *cis*, anti-Markovnikov addition onto double bonds.[108] Brown describes hydroboration as the addition of a boron-hydrogen bond over a double or triple bond of an olefin, to generate an organoborane compound (**Scheme 54**).[19]



Scheme 54

The hydroboration of alkenes or alkynes which can be achieved using a number of hydroborating reagents including catecholborane, BBr_3 or $HBCl_2$.[9] Some of the hydroborating reagents are unable to achieve hydroboration or require long reaction time, due to this a number of transition metal catalysts can be employed to afford the organoborane compounds, however, route this proves to be a rather expensive.[61,108,141]

The hydrolysis of the organoborane compounds formed during the hydroboration reaction yields organoboronic acids (**Scheme 55**).



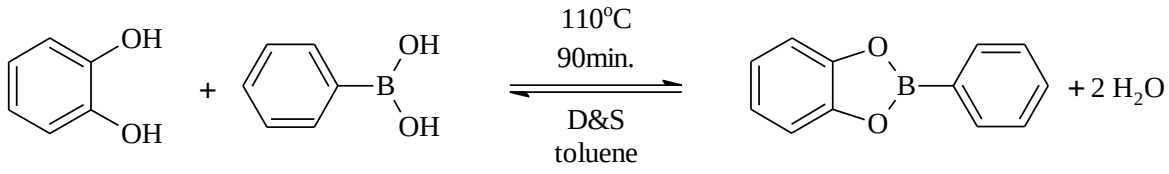
Scheme 55

3.1.3. Condensation Reactions of Boronic Acids and 2-hydroxyphenyl

The synthesis of boronic esters from boronic acids and diols has been reported in the literature, with the first being that which was documented by Kuivila and co-workers when they described the preparation of boronic esters of phenylboronic acids by reacting it with sugar such as mannitol and sorbitol in warm water.[142] Sugihara and Bowman[81] and Pailer and Fenzl[143] in the late 1950's and early 1960's respectively, reported the successful synthesis of five– and six–membered heterocyclic organoboranes from the condensation reaction of phenylboronic acid and a range of diamines, diols and a few amino alcohols.[81,143]

The work done by these groups discussed above pioneered the use of boronic acids as protecting groups for an array of bi– and polyfunctional alcohols, amines, acids and thiols.[144] The use of boronic acid as protecting groups has seen phenylboronic acid being the favorite reagent due to its ability to form generally crystalline products even with functionalized groups, the ease of removing it by heating the protected compound in aqueous sodium bicarbonate and lastly, phenylboronic acid is easily available.[144]

3.1.3.1. Synthesis of 2-phenylbenzo-1,3,2-dioxaboronate ester



Scheme 56

2-phenylbenzo-1,3,2-dioxaboronateester was successfully synthesized by reacting phenylboronic acid with catechol under reflux in dry toluene using a Dean and Stark apparatus for 1.5 hours (**Scheme 56**). The toluene was removed and the solution concentrated *in vacuo*, the crystals that had formed were collected by filtration and washed with cold methanol to afford 90 % yield which is in good correspondence with the yield reported by Rambo and Lavigne.[145]

The collected crystals yielded a ^{1}H NMR spectrum displaying 5 resonance peaks at δ_H 7.15, m; δ_H 7.34, m; δ_H 7.52, t; δ_H 7.60, t, and δ_H 8.12, d assignable to a, b, d, e and c, respectively (refer to **Figure 44**). The formation of the desired product was indicated by the disappearance of the singlet at 7.99 ppm corresponding to the hydroxyl protons which was observed in the ^{1}H NMR spectrum for phenylboronic acid (**Figure 45**). The ^{1}H NMR spectrum of 2-phenylbenzo-1,3,2-dioxaboronate ester didn't show any contamination from either of the starting material used, furthermore the integral ratio is in agreement with the number of protons that are expected for the desired product.

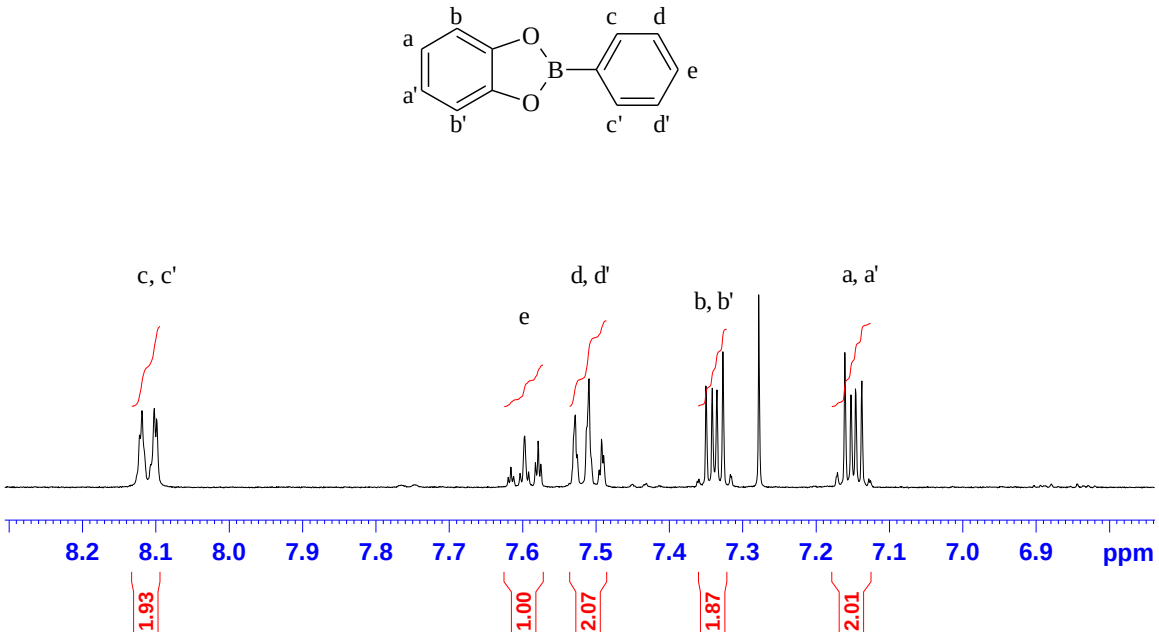


Figure 44: [1]H-NMR spectrum of 2-phenylbenzo-1,3,2-dioxaboronate ester in $CDCl_3$-d.

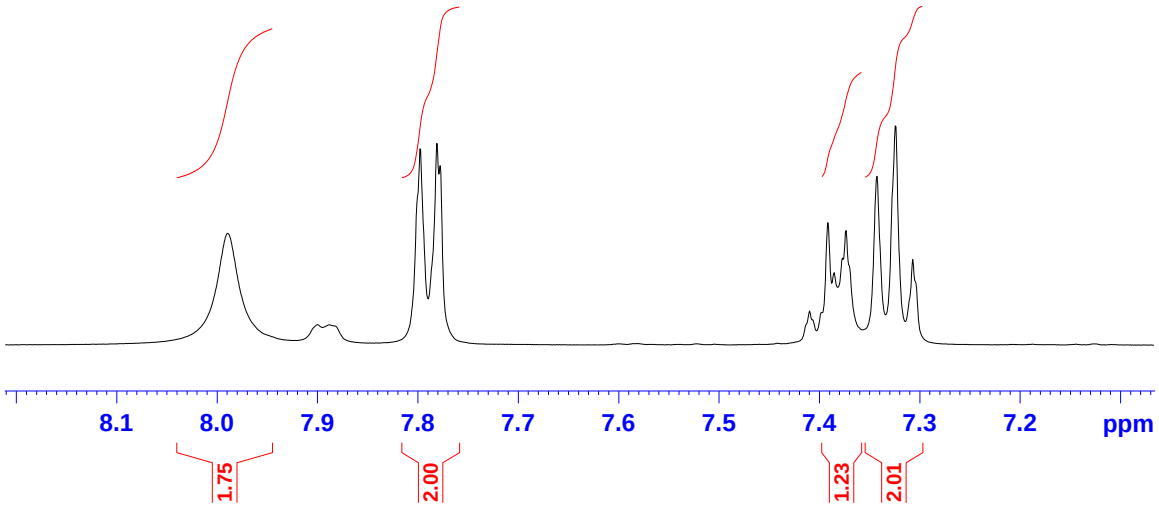


Figure 45: [1]H NMR spectrum obtained for phenylboronic acid in DMSO-d_6.

Rambo and Lavigne[145] reported that the aromatic protons ortho to the mono-ester borolane (on the boron side) are shifted downfield (approximately ~ 8.0 ppm; $\Delta\delta$ ~ 0.3 ppm). There is an extended conjugation through the planar ester and/or through geometric constraints enforced on the boron thereby increasing the Lewis acidity of the

boron. Observing the ^{1}H NMR spectrum for phenybenzo-1,3,2-boronate ester, it can be seen that there has been a shift downfield from 7.76 ppm observed for phenylboronic acid (**Figure 45**) to 8.12 ppm (**Figure 44**).[145]

The ^{11}B-NMR spectroscopic data shows two singlets at 32.4 ppm and 29.2 ppm corresponding to phenylbenzo-1,3,2-dioxaboronate ester and phenylboronic acid respectively, indicative of a boron atom bound to three groups for both compounds (**Figure 46**), the esterified boron atom has shifted downfield due to the increased Lewis acidity on the boron atom.

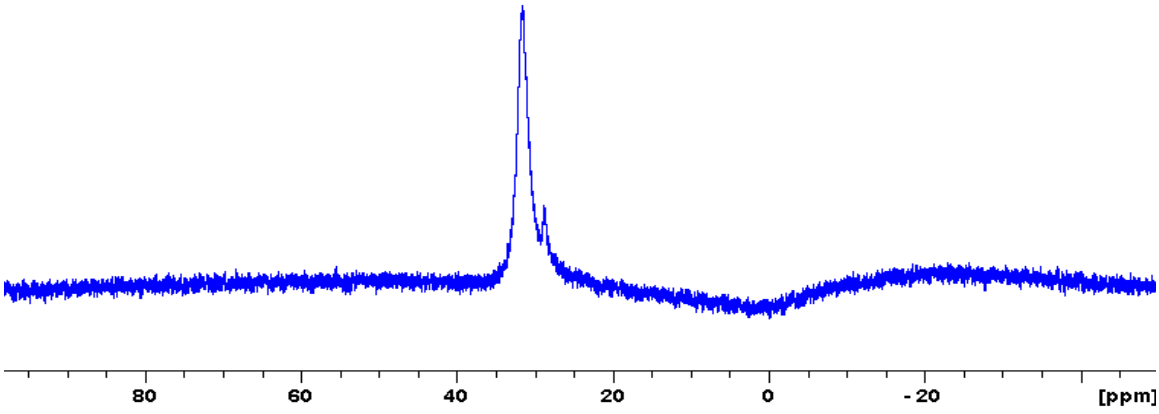
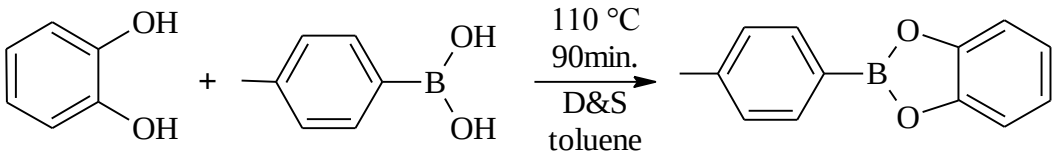


Figure 46: ^{11}B NMR spectrum of 2-phenylbenzo-1,3,2-dioxaboronate ester in toluene.

3.1.3.2. Synthesis of 2-(4-methyl)phenylbenzo-1,3,2-dioxaboronate ester



Scheme 57

Using the procedure for the synthesis of 2-phenylbenzo-1,3,2-dioxaboronate ester, 2-(4-methyl)phenylbenzo-1,3,2-dioxaboronate ester was successfully synthesized by the reaction of (4-methyl)-phenylboronic acid with catechol under reflux in dry toluene using Dean and Stark apparatus for 1.5 hours (**Scheme 57**). The toluene was removed and the solution concentrated *in vacuo*, the crystals that had formed were collected by filtration and washed with cold methanol to afford a 91 % yield. The ^{11}B NMR spectrum revealed a downfield shift of the boron atom to 31.5 ppm from 28.6 ppm (**Figure 47**).

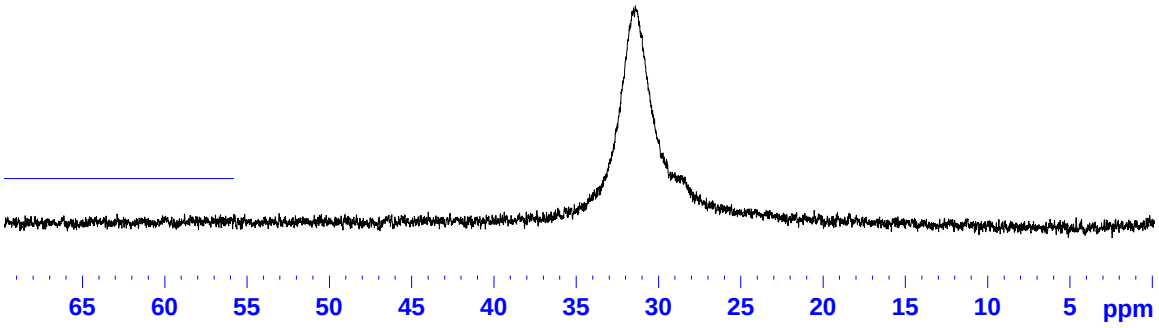


Figure 47: ^{11}B NMR spectrum obtained for 2-(methyl)phenylbenzo-1,3,2-dioxaboronate ester in toluene

Upon conducting the infrared analysis of the crystals obtained from the reaction the infrared spectrum showed the absence of the broad absorption band in the 3300-3200 cm^{-1}range corresponding to O–H stretching frequency as can be seen in **Figure 48**, this is indicative that neither of the hydroxyl groups present in both starting material are present

in this compound and the peaks at 1350 cm^{-1} and 1330 cm^{-1} have been reported to be those associated with the B–O bond.[145]

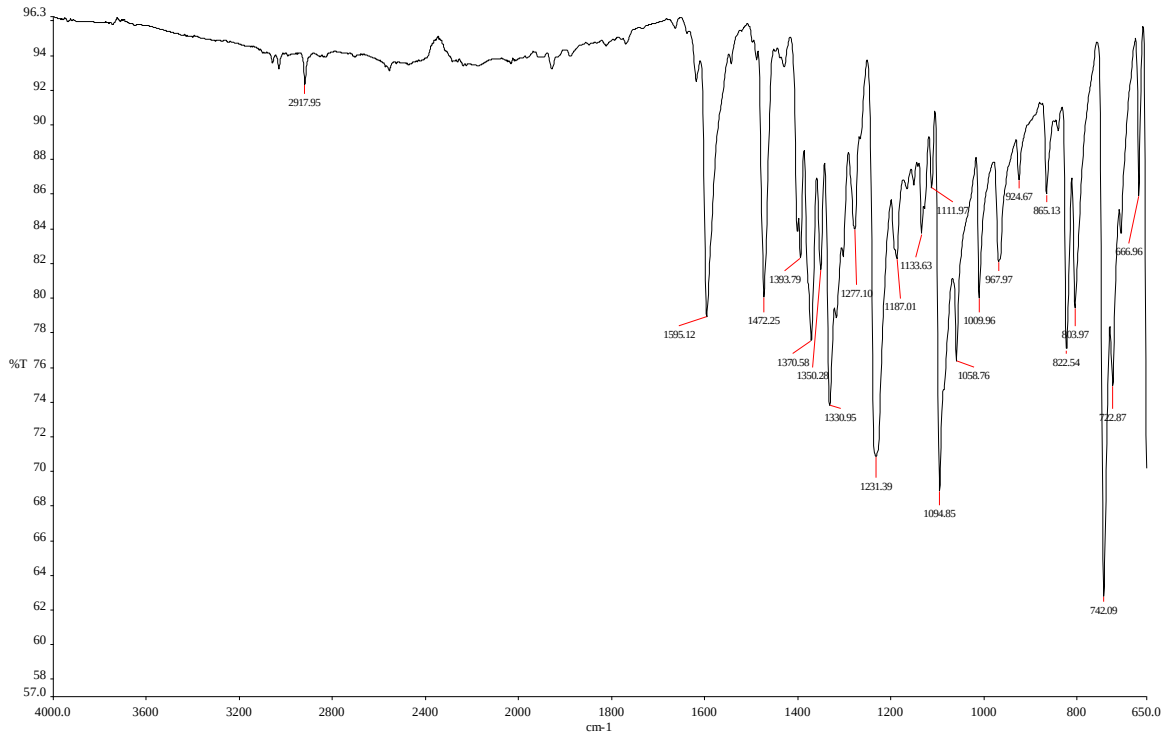


Figure 48: <u>Infrared spectrum of 2-(4-methyl)phenylbenzo-1,3,2-dioxaboronate ester.</u>

The resulting compound gave a ^{1}H NMR spectrum displaying 4 resonance signals at δ_H 2.45, s; δ_H 7.16, m; δ_H 7.34, m and δ_H 8.01, d assignable to e, a, (b& d) and c (**Figure 49**). The integral ratio is in agreement with the number of protons that are expected for the desired product and the LRMS showed a molecular ion peak (*m/z*) of 241.0635, corresponding to the calculated molar mass of $[M^+ MeO^-]$ where M^+ is $C_{13}H_{11}BO_2$.

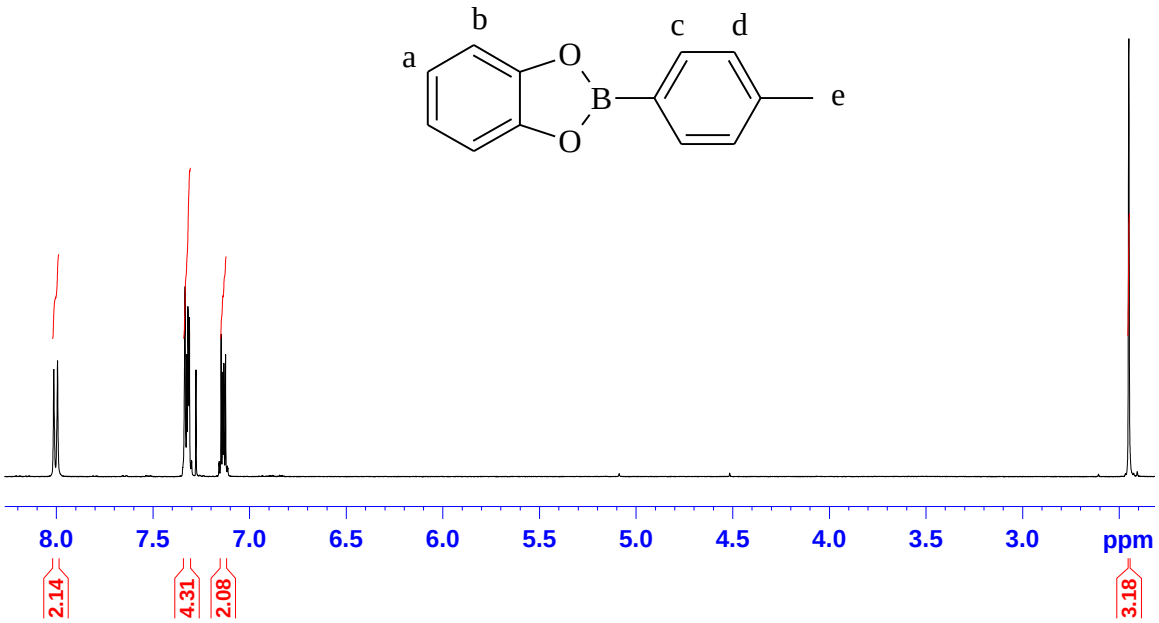
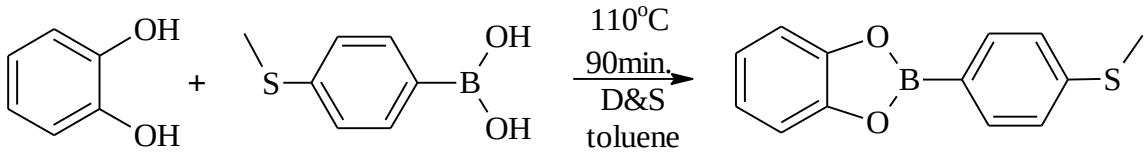


Figure 49: ^{1}H NMR spectrum of 2-(4-methyl)phenylbenzo-1,3,2-dioxaboronate ester in $CDCl_3$.

3.1.3.3. Synthesis of 2-(4-methylthio)phenylbenzo-1,3,2-dioxaboronate ester



Scheme 58

The 2-(4-methylthio)phenylbenzo-1,3,2-diazaboronate ester was successfully synthesised in 95 % isolated yield from the cyclo-condensation of catechol and 4-(methylthio)phenylboronic acid (**Scheme 58**). The ^{11}B NMR spectroscopic data of this compound revealed a singlet at 31.3 ppm (**Figure 50**). Analysis with the ^{1}H NMR showed an upshift of the ortho-protons to 7.97-8.02 ppm (**Figure 51**) from 7.65-7.69 ppm

initially observed for 4-(methylthio)phenylboronic acid, this is consistent with the observations reported by Rambo and Lavigne.[145]

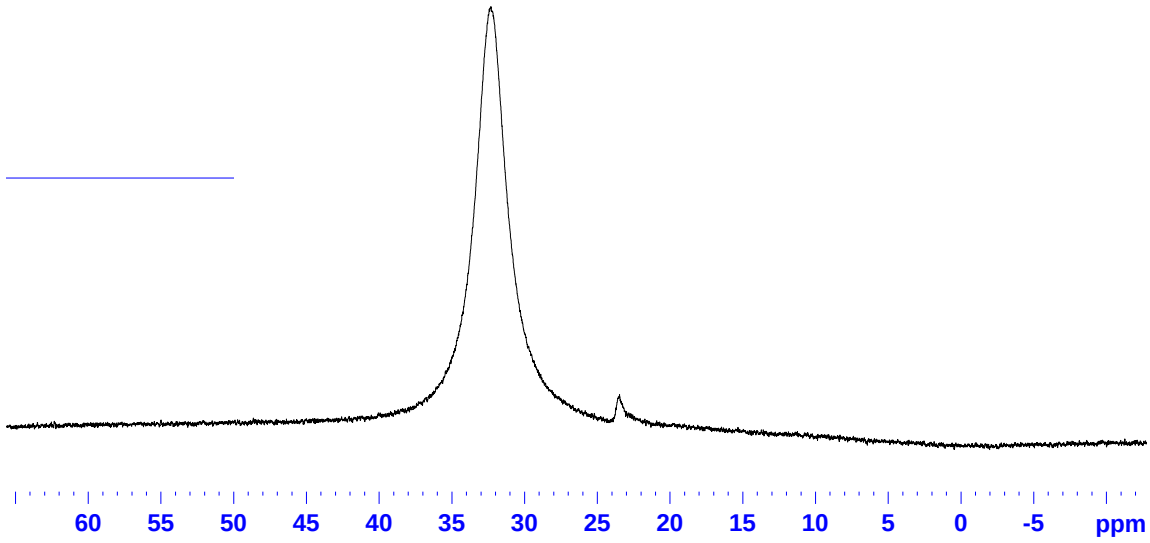


Figure 50: ^{11}B NMR observed for2-(4-methylthio) phenylbenzo-1,3,2-diazaboronate ester in toluene

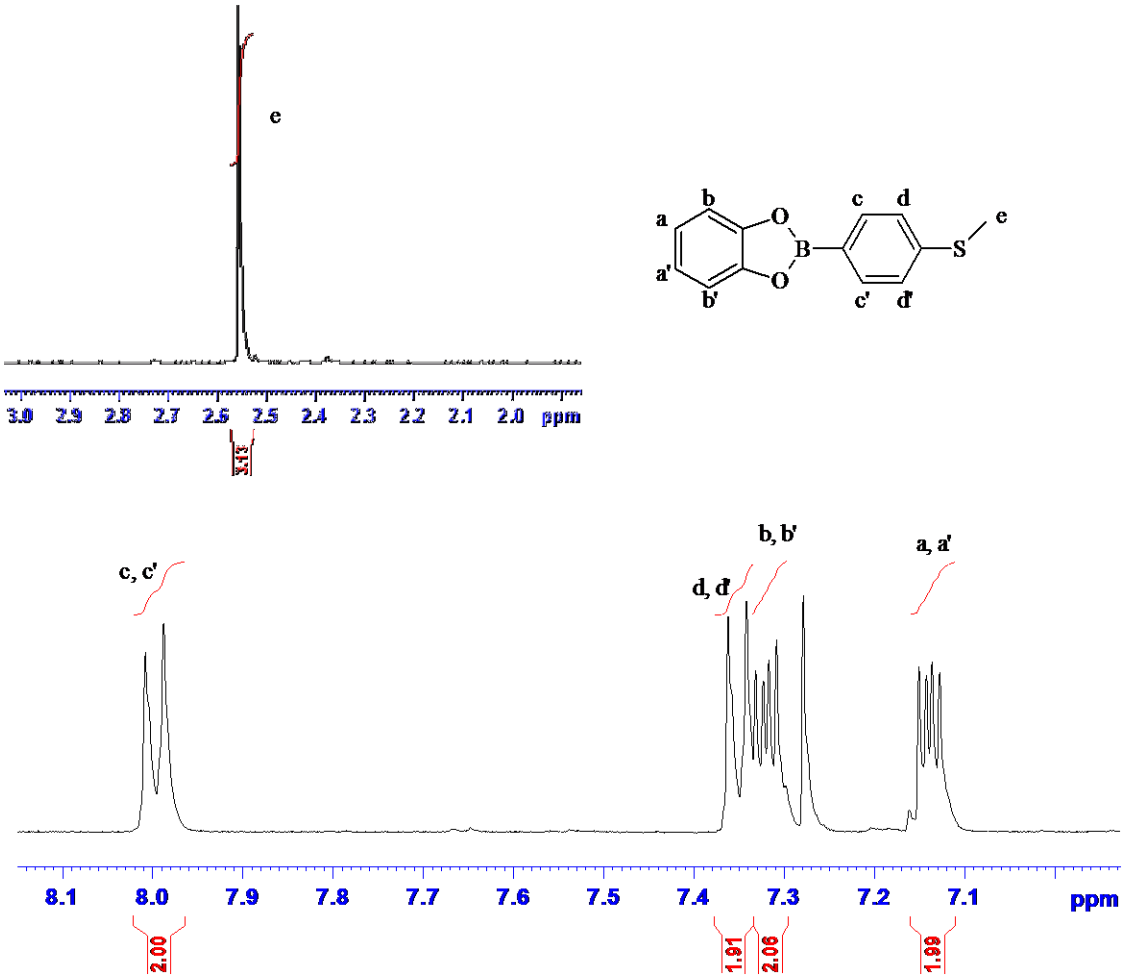


Figure 51: ^{1}H NMR observed for2-(4-methylthio) phenylbenzo-1,3,2-diazaboronate ester in $CDCl_3$

The LRMS revealed a clean M/S spectrum showing a significant molecular peak with an *m/z* ratio of 273.0476 corresponding to the calculated mass for $[M^{+}MeO^{-}]$ of 273.1351 g/mol, where $M^{+} = C_{13}H_{11}BO_2S$ (**Figure 52**) and a second peak with *m/z* ratio 259.0334.

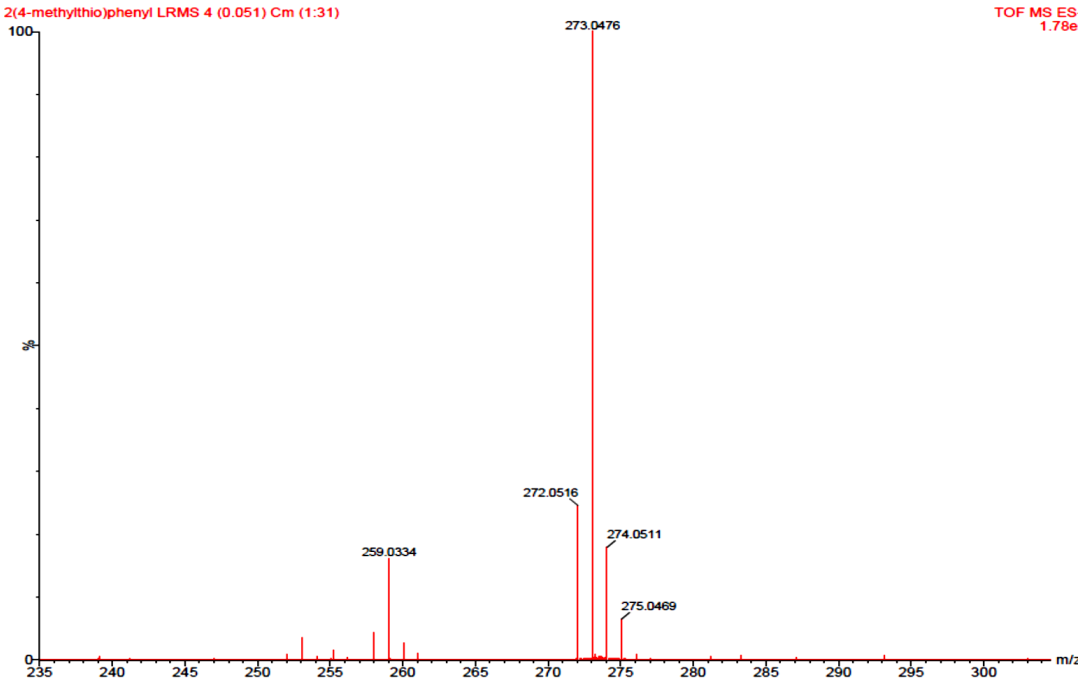
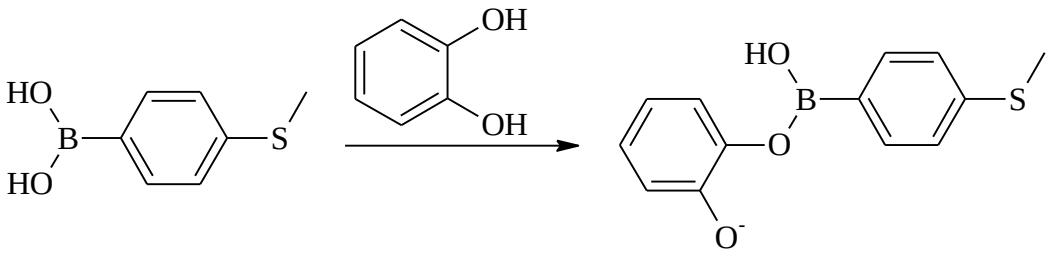


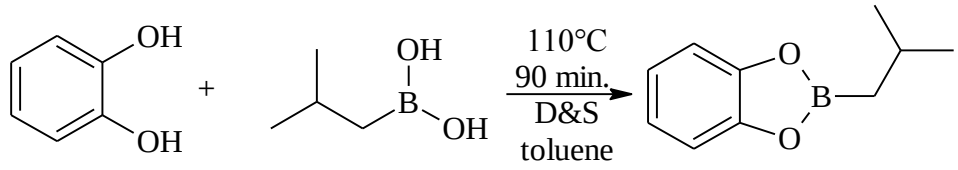
Figure 52: <u>MS spectrum obtained for 2-(4-methylthio) phenylbenzo-1,3,2-diazaboronate ester *m/z* 273.0476 in MeOH.</u>

The peak observed with *m/z* ratio 259.0334 in **Figure 52** corresponds to a molecular formula $C_{13}H_{13}BO_3S$ which is a compound that formed as a result of the incomplete condensation of the boronic acid (**Scheme 59**), this assignment is supported by the presence of a singlet peak at 24.1 ppm in the ^{11}B NMR spectroscopic data (**Figure 50**).



Scheme 59

3.1.3.4. Synthesis of 2-(2-methyl)propylbenzo-1,3,2-dioxaboronate ester



Scheme 60

The preparation of compound 2-(2-methyl)propylbenzo-1,3,2-dioxaboronate ester was successfully achieved from the condensation of 2-methylpropylboronic acid with catechol (**Scheme 60**)**.** The desired product was obtained in 70 % yield as a dark brown solid. Analysis of the ^{1}H NMR spectrum showed that the integral ratios of the protons is equivalent to the number of protons expected for the predicted structure, furthermore there has been a upshift of the protons attached to the carbon atom labelled C (**Figure 53**) similar to that reported by Rambo and Lavigne[145] for the ortho-protons of benzyl group attached to the boron-atom.

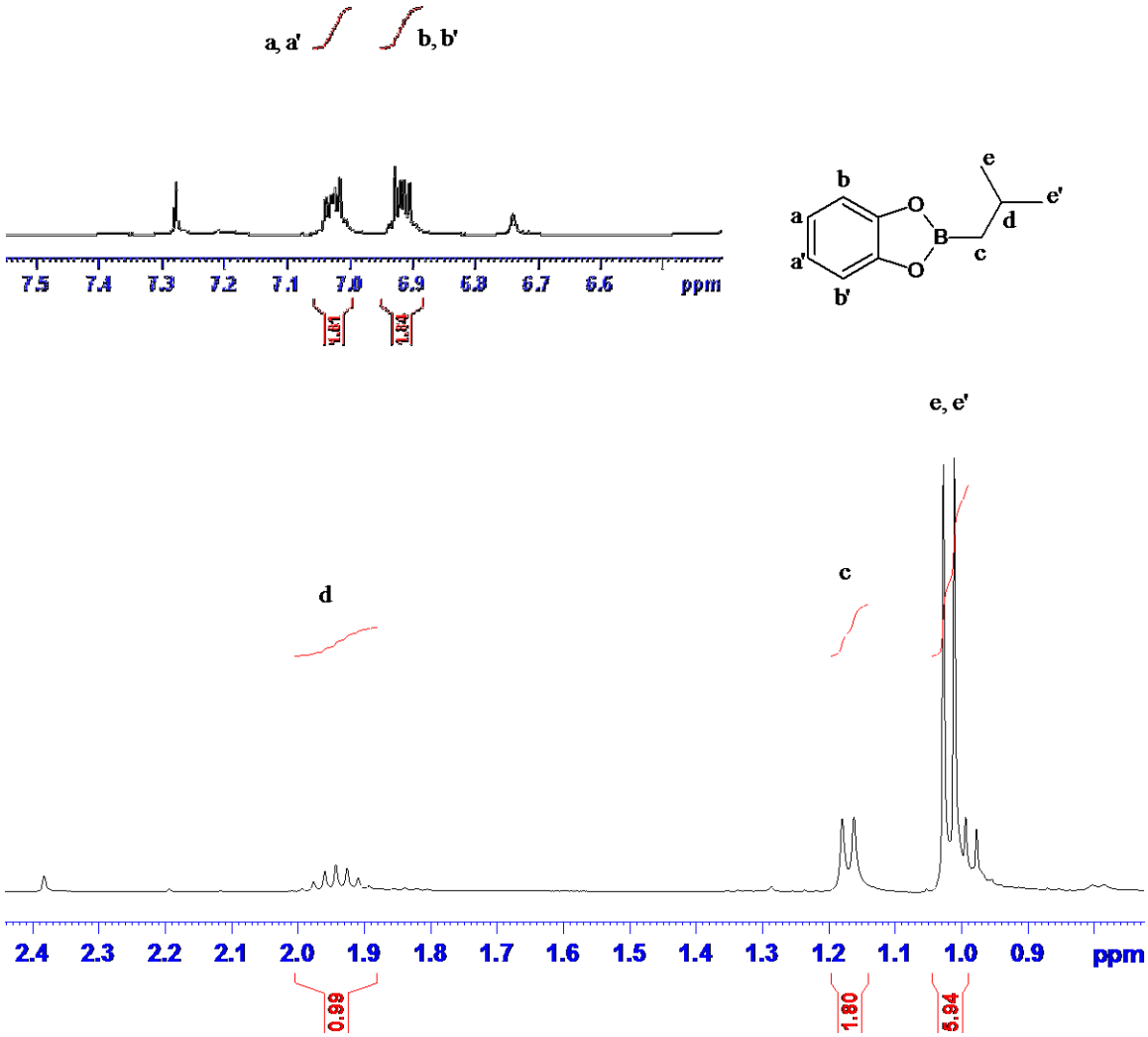


Figure 53: ^{1}H NMR spectrum observed for 2-(2-methyl)propylbenzo-1,3,2-dioxaboronate ester in $CDCl_3$.

^{13}C NMR and ^{11}B NMR spectroscopic data of this product also confirmed successful synthesis of the title compound. The ^{13}C NMR showed 5 peaks (25.2 ppm; 26.4 ppm; 110.5 ppm; 119.1 ppm and 136.4 ppm), there is an absence of the 6th peak is due to the rapid quadrupolar relaxation associated with ^{11}B–^{13}C coupling which results in the broadening of the *ipso*-carbon causing the signal to be often lost in the baseline noise(**Figure 54**).[108] The ^{11}B NMR spectroscopic data revealed an upfield shift of the boron atom to 35.4 ppm as a result of the increased Lewis acidity of the boronate ester.[108]

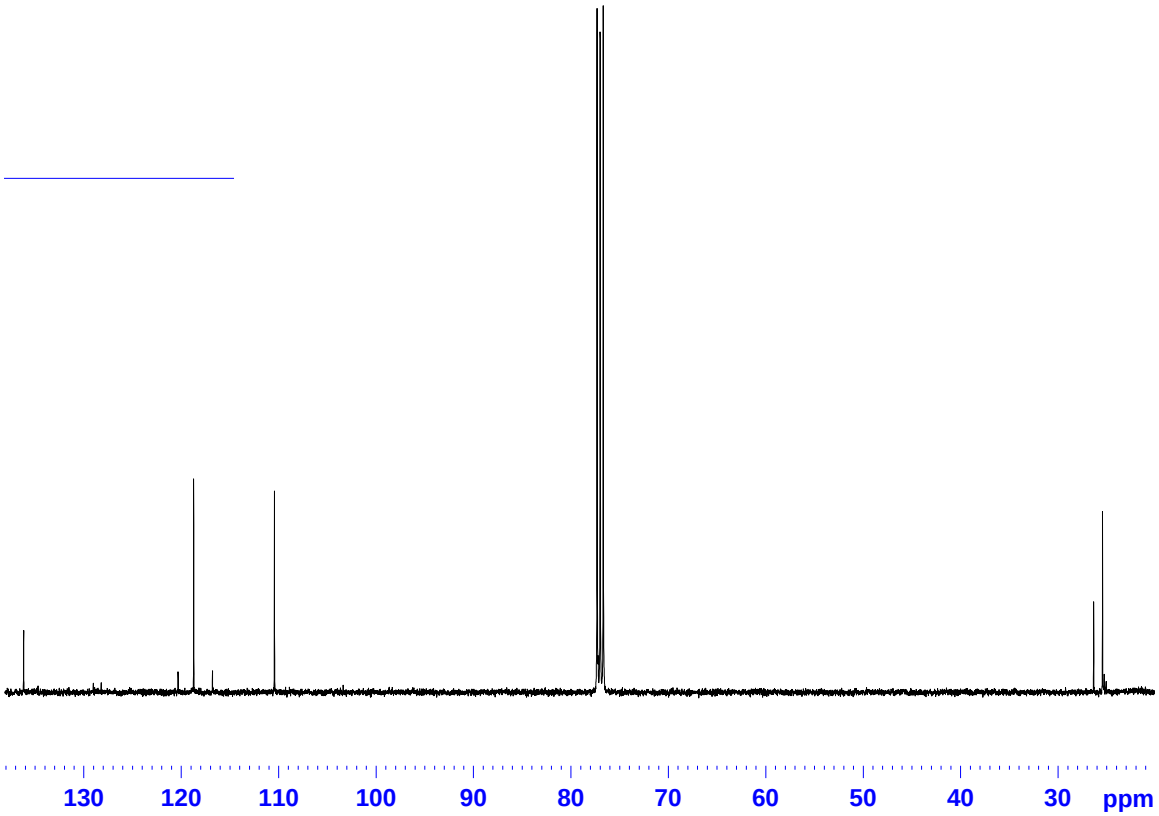


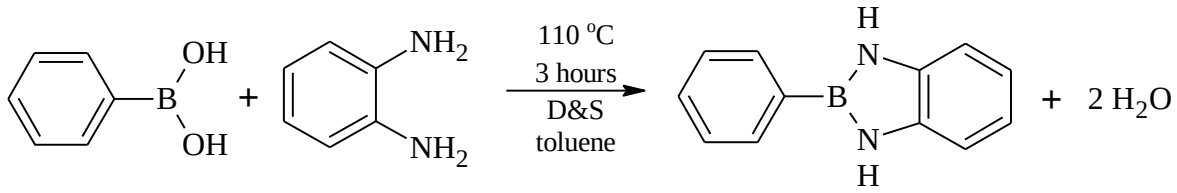
Figure 54: ^{13}C NMR spectrum observed for 2-(2-methyl)propylbenzo-1,3,2-dioxaboronate ester in $CDCl_3$.

3.1.4. Condensation Reactions of Boronic Acids and 1,2-phenylenediamine

As stated earlier the condensation reaction provides a cheap alternative route to the synthesis of organoborane compounds. The Rh(I) and Ir(I) catalyzed hydroboration discussed in chapter two required more than 24 hours reaction time to yield any product, furthermore these catalyst are expensive. Using the highly stable boronic acid and *o*-phenylenediamine, diazaborolane esters can be easily synthesized in a shorter time, in this section attention will be focused on the synthesis of such compounds.

3.1.4.1. Synthesis of 2-phenylbenzo-1,3,2-diazaboronate ester

Phenylboronic acid and *o*-phenylenediamine in equimolar quantity were refluxed in dry toluene using a Dean and Stark apparatus for 3 hours as illustrated in **Scheme 61** to yield 2-phenylbenzo-1,3,2-diazaboronate ester. The toluene was evaporated and the mixture was concentrated and purified by column chromatography to afford 2-phenylbenzo-1,3,2-diazaboronate in 99 % yield which is higher than the yield of 91 % reported by Soloway and Nyilas.[146]



Scheme 61

^{11}B NMR spectroscopic data analysis is very useful for the evaluation of the hybridization around the boron atom, the ^{11}B NMR spectrum of 2-phenylbenzo-1,3,2-diazaboronate showed a single peak at 28.4 ppm indicating the presence of a sp^2 boron in solution (**Figure 55**), this is in agreement with the ^{11}B NMR resonance reported by Solomon and Nyilas.[146]

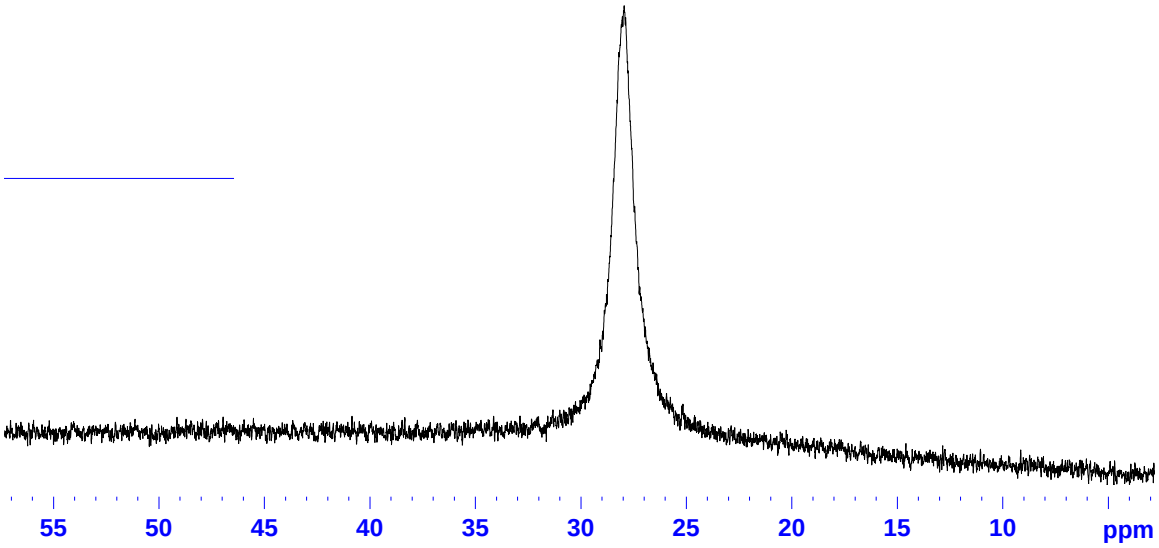


Figure 55: ^{11}B NMR spectrum observed for 2-phenylbenzo-1,3,2-diazaboronate ester

The collected crystals yielded a ^{1}H NMR spectrum displaying 5 resonance peak at δ_H 6.89, m; δ_H 7.14, m; δ_H 7.42, m; δ_H 7.94, m, and δ_H 9.09, s assignable to a,a´; b,b´; e,e´,f; d,d´ and c,c´ respectively (**Figure 56**). The integral ratio is in agreement with the number of protons that are expected for the desired product.

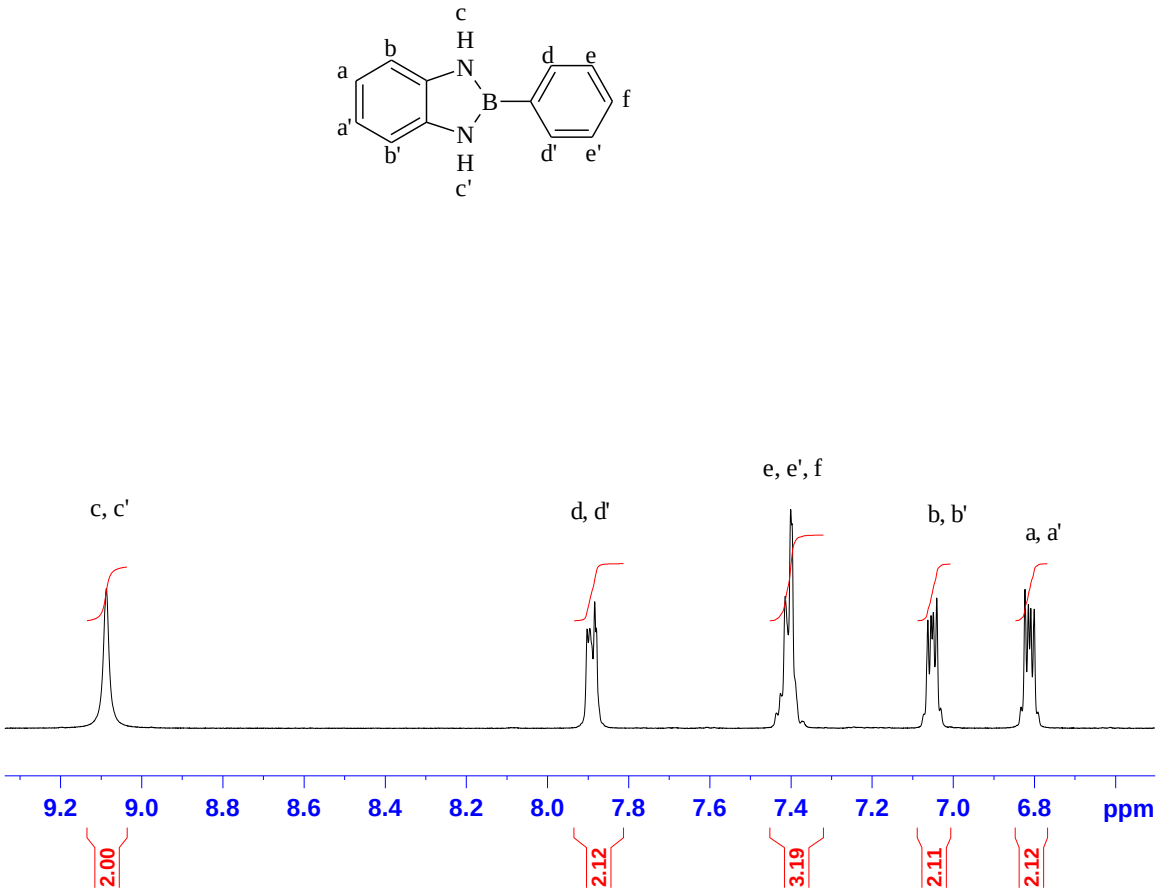


Figure 56: ^{1}H NMR spectrum of 2-phenylbenzo-1,3,2-diazaboronate ester in DMSO-d_6.

Figure 57 shows the ^{13}C NMR, there are only six peaks observed at 112 ppm, 119 ppm, 128 ppm, 130 ppm, 134 ppm, 138 ppm, corresponding to six of the seven carbons that should be observed. This has been reported to be due to therapid quadrupolar relaxation associated with ^{11}B–^{13}C coupling results in a broadened signal for the *ipso*-carbon, and therefore this signal is most often lost in baseline noise and not observed in the ^{13}C spectrum for the carbon atom that is directly bound to the boron atom are not always found,[108] as discussed earlier.

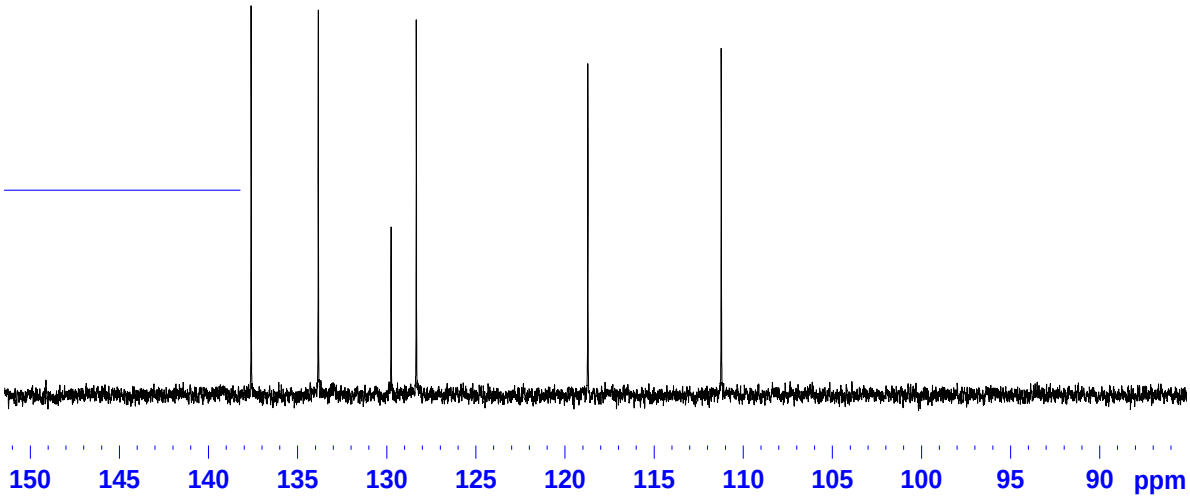
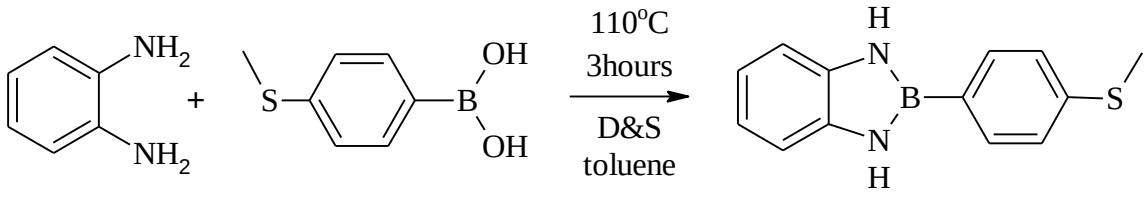


Figure 57: ^{13}C NMR observed for 2-phenylbenzo-1,3,2-diazaboronate ester in DMSO-d$_6$.

3.1.4.2. Synthesis of 2-(4-methylthio)phenylbenzo-1,3,2-diazaboronate ester



Scheme 62

The reaction of 4-(methylthio)-phenylboronic acid with *o*-phenylenediamine afforded 2-(4-methylthio) phenylbenzo-1,3,2-diazaboronate ester, which didn't require further purification, with an isolated yield of 98 % as an off-white crystalline product. To confirm the structure of this compound ^{1}H NMR spectroscopic analysis was conducted, the spectrum revealed the compound to be pure and the integral ratio corresponded to the number of protons expected for 2-(4-methylthio) phenylbenzo-1,3,2-diazaboronate ester as it is shown in **Figure 58**.

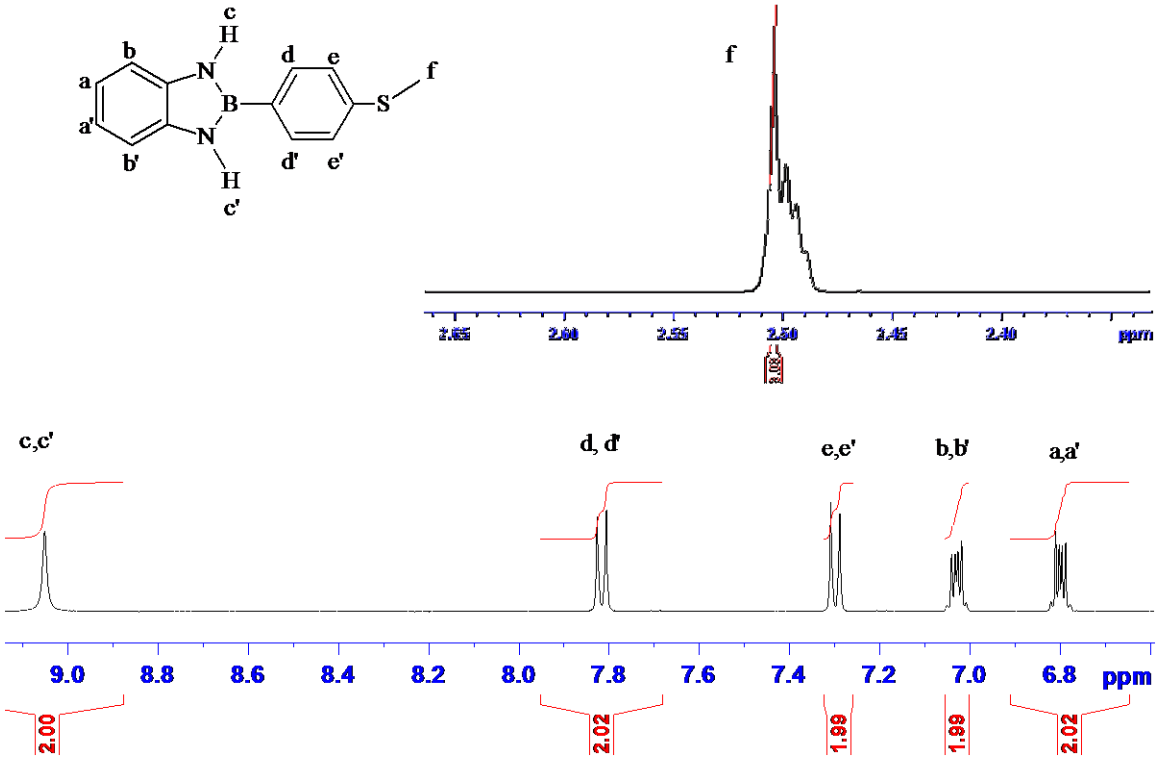
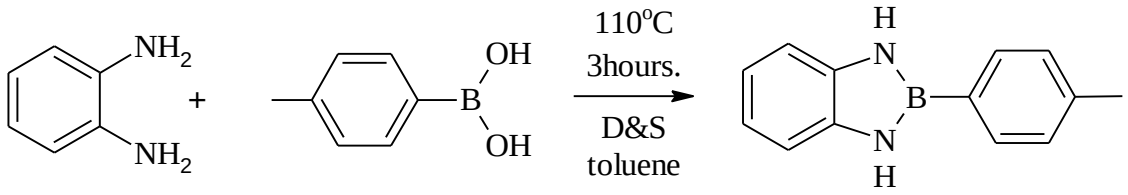


Figure 58: ^{1}H NMR spectrum of 2-(4-methylthio)phenylbenzo-1,3,2-diazaboronate ester in DMSO-d_6.

The ^{11}B NMR revealed a singlet at 28.8 ppm which is consisted with that reported by Slabber of 28.0 ppm when the spectra was resolved using $CDCl_3$, the slight upfield shift has been reported by Rambo and Lavigne to be due to the change in solvent.[145]

3.1.4.3. Synthesis of 2-(4-methyl)phenylbenzo-1,3,2-diazaboronate ester



Scheme 63

The compound was successfully synthesised in 90 % isolated yield from the condensation of *o*-phenylenediamine and 4-methylphenylboronic acid (**Scheme 63**). The ^{1}H NMR, ^{13}C NMR and ^{11}B NMR showed spectrums that are consistent with those reported in the literature[130] and are consistent with the proposed structure. Figure 59 shows a ^{1}H NMR spectrum with six resonance peaks at δ_H 2.33, s; δ_H 6.76-6.82, m; δ_H 7.02-7.07, m; δ_H 7.22, d; δ_H 7.78, d; and δ_H 9.01,s which are assignable to f; a,a´; b,b´; e,e´; d,d´ and c,c´ respectively.

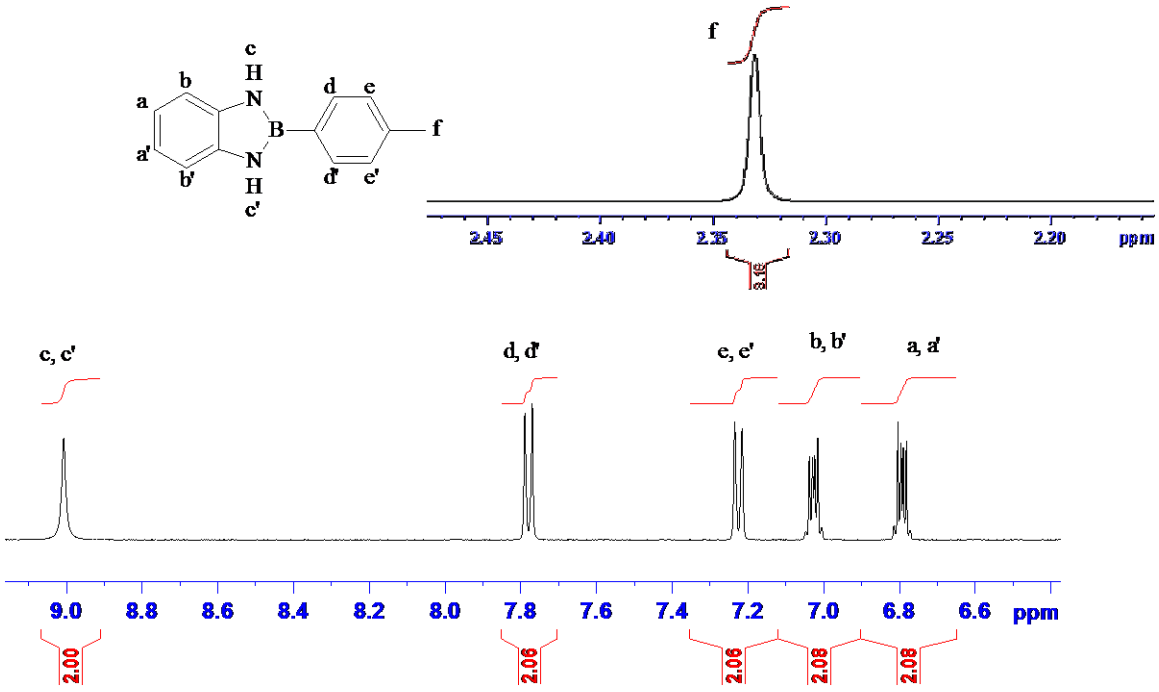
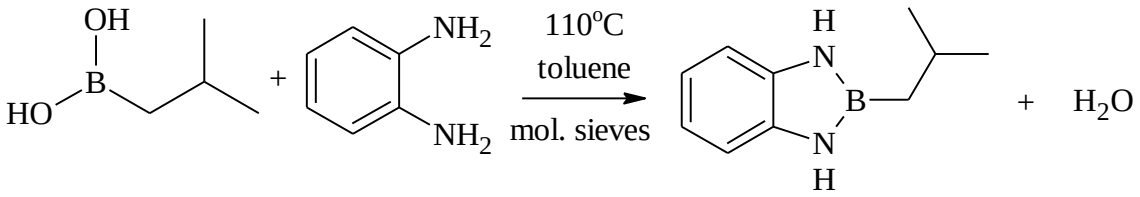


Figure 59: ^{1}H NMR observed for 2-(4-methyl) phenylbenzo-1,3,2-diazaboronate ester in DMSO-d6

3.1.4.4. Synthesis of 2-(2-methyl)propylbenzo-1,3,2-diazaboronate ester



Scheme 64

The reaction of 2-methylpropylboronic acid and *o*-phenylenediamine resulted in 2-(2-methylpropyl)benzo-1,3,2-diazaboronate to be successfully synthesized in a 80 % yield by refluxing equimolar amounts of the starting material in dry toluene charged with activated molecular sieves as shown in **Scheme 64**. Upon the removal of the molecular

sieves and the evaporation of toluene, the resulting beige solid yielded an ^{11}B NMR spectrum with a singlet peaks at 29.5 ppm (**Figure 60**) this downfield shift of the boron atom is expected when boron is bonded to a nitrogen atom as there is an increased back-donation from nitrogen to the boron (**Figure 61**).[54,146]

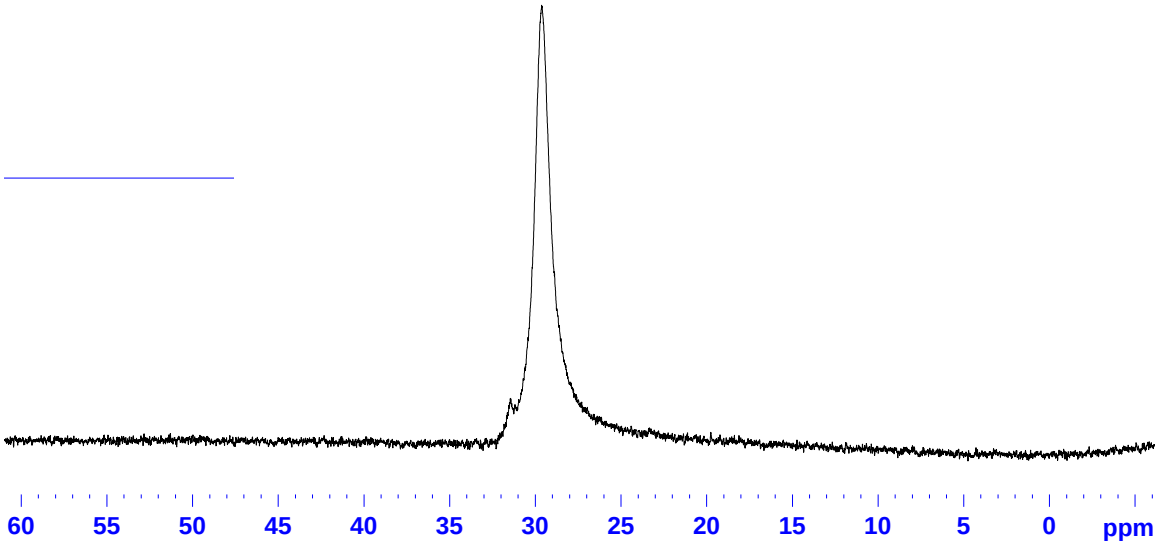


Figure 60: ^{11}B NMR observed for 2-(2-methyl)propylbenzo-1,3,2-diazaboronate ester

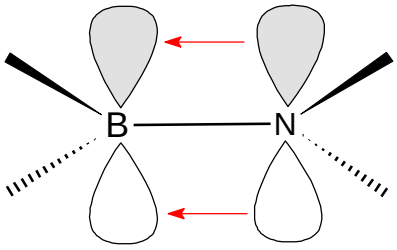
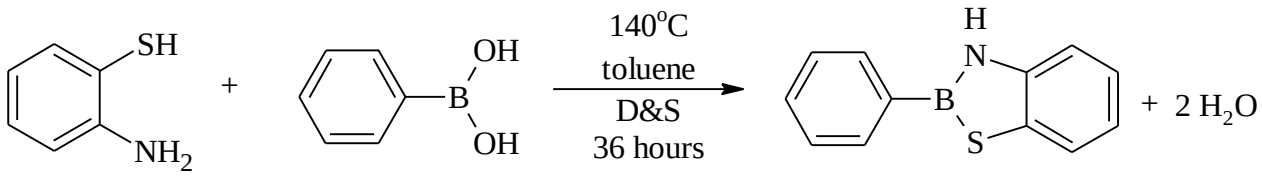


Figure 61: π-interaction between the empty boron p_z-orbital and the lone pair on nitrogen

3.1.5. Condensation Reactions of Boronic Acids and 2-aminophenylmercaptan

3.1.5.1. Synthesis of 2-phenylbenzo-1,3,2-thiazaboronate ester



Scheme 65

Phenylboronic acid was successfully converted into 2-phenylbenzo-1,3,2-thiazaboronate ester by allowing it to reflux in the presence of aminothiophenol in dry toluene, in a round bottom flask connected with the Dean and Stark apparatus, for 36 hours at 140 ˚C (**Scheme 65**). After 36 hours ^{11}B-NMR spectroscopic data analysis revealed two singlet peaks at 44.4 ppm (corresponding to the desired product) and 28.8 ppm being that of the starting product indicating 90 % conversion[1] (**Figure 62**).

[1]Based on ^{11}B-NMR spectrum

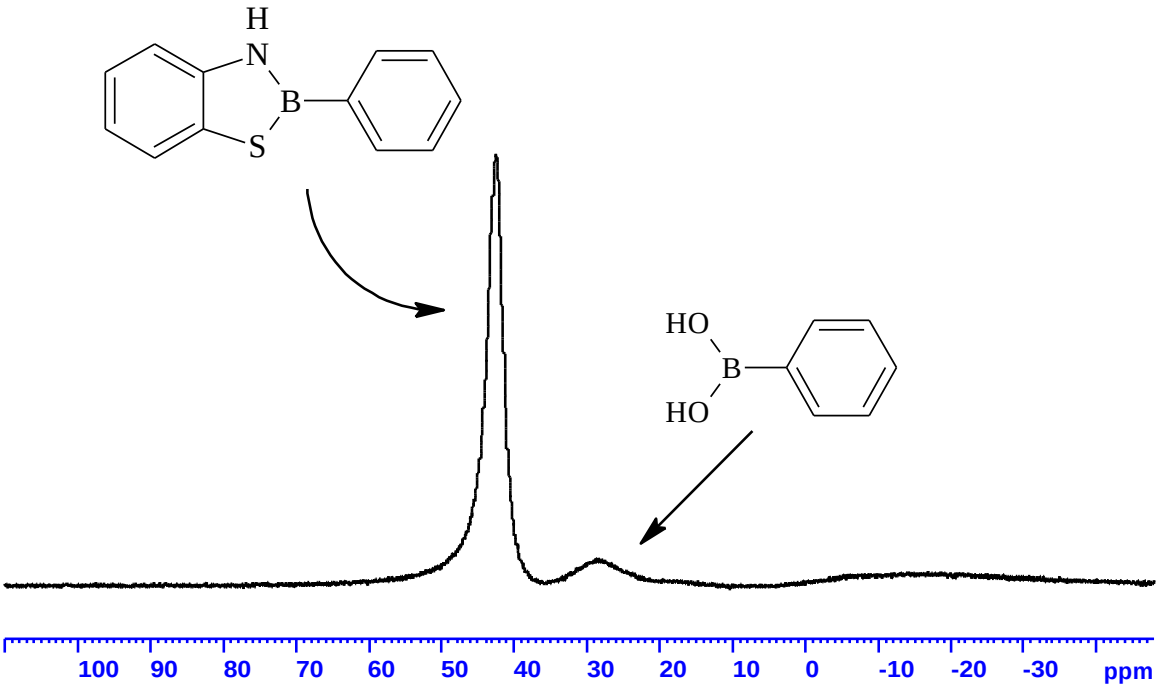
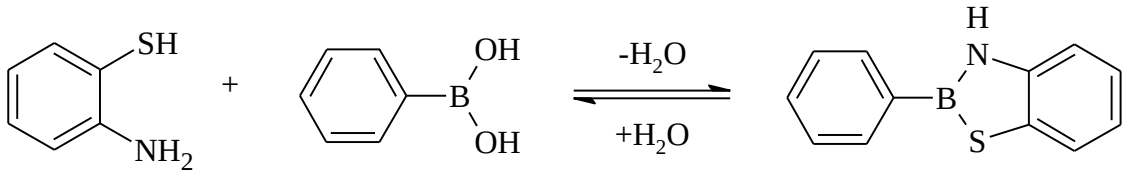


Figure 62: ^{11}B NMR spectrum observed for 2-phenylbenzo-1,3,2-thiazaboronate ester after 12 hrs refluxing in toluene.

The ^{11}B NMR spectrum observed does not give any clue about any possible mechanism of formation, as it does not have any peaks that cannot be accounted for. However, looking at the *p*Ka values of RNH_2 and RSH; RSH is a stronger acid than RNH_2; therefore, the nitrogen is the better nucleophile which will be first to attack the boron atom, then the sulfur.[137]



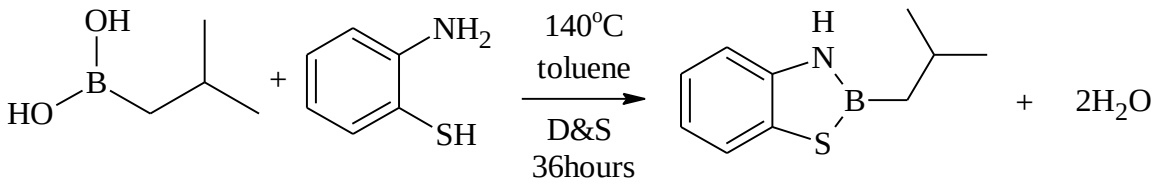
Scheme 66

Upon the removal of the solvent the ^{11}B NMR spectroscopic data shows a high field shift of the boron compound, indicating the product reverses back to the starting material. This is an indication that the reaction was in equilibrium and that the conditions that favored

the forward reaction (**Scheme 66**) have been removed. A noteworthy explanation that can maybe account for the ^{11}B NMR observation is that there are stabilizing effects that toluene has on the newly formed compound. The removal of toluene, causes them to be diminished, there by exposing the boron atom to nucleophilic attack by H_2O, these observations are consistent with those made by Toyata and Oki.[147]

The observed stability of the compound is unexpected when considering the electronic factors that should be present in this compound, as contains nitrogen and sulfur substituents. These substituents are known to be better nucleophiles than oxygen and they both have a lone pair of electrons that should be able to donate electrons to the vacant p_z-orbital on boron through intra-molecular back-donation thereby stabilizing the boron atom from nucleophilic attack. The aromatic ring acts as a pool of electrons; which should allow for better back–donation to occur into empty p_z –orbital, thereby stabilizing the compound against oxidation.

3.1.5.2. Synthesis of 2-(2-methyl)propylbenzo-1,3,2-thiazaboronate ester



Scheme 67

Using the same method stipulated in 3.1.5.1, 2-methylpropylboronic was converted into 2-(2-methylpropyl)-benzo-1,3,2-thiazaboronate by allowing to reflux in the presence of aminothiophenol in dry toluene, in a round bottom flask connected with the Dean and Stark apparatus, for 36 hours at 140 ˚C (**Scheme 67**). After 12 hours ^{11}B-NMR analysis revealed two singlet peaks at 45.3 ppm (corresponding to the desired product) and 32.3

ppm being that of the starting product indicating 66 % conversion, and after 36 hours there was still no change in the conversion percentage.

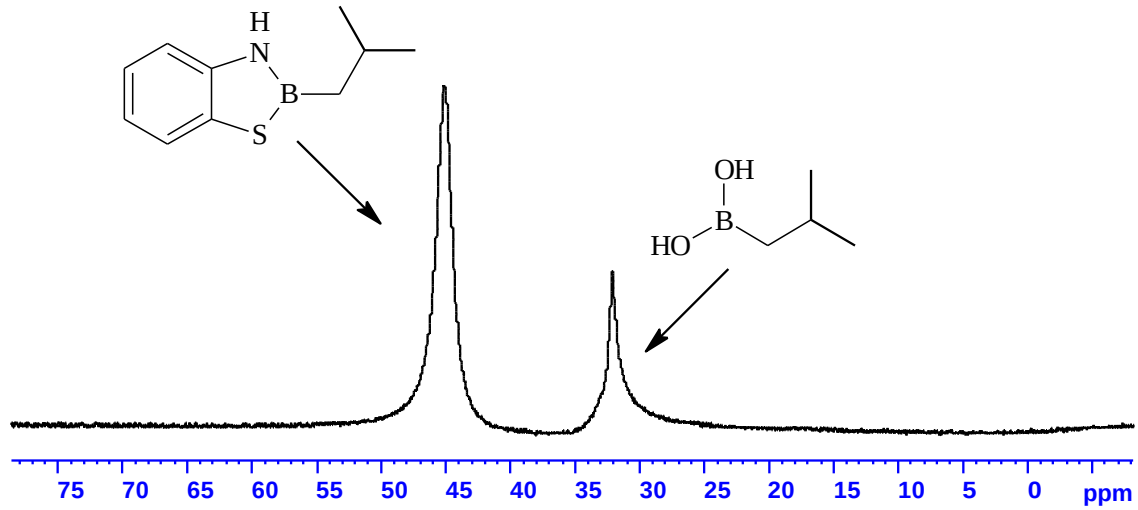


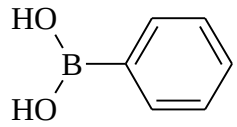
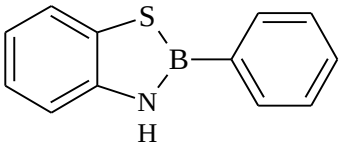
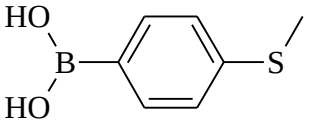
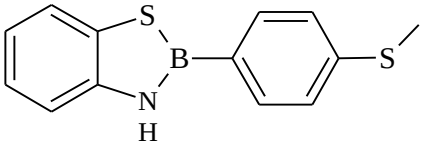
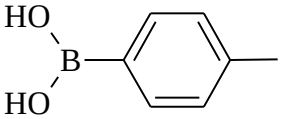
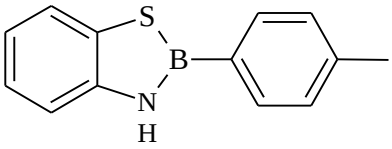
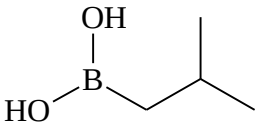
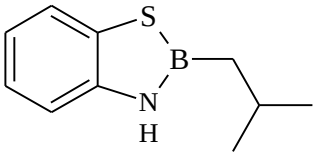
Figure 63: ^{11}B NMR spectrum observed for 2-(2-methyl)propylbenzo-1,3,2-thiazaboronate ester.

As observed with the arylbenzo-1,3,2-thiazaboronate esters, the removal of the solvent favors the reverse reaction as well, indicating that the solvent effects affects both aryl and alkylboronate esters.

Table 3 represents a summary of the R–benzo-1,3,2-thiazaboronate that were synthesized using the condensation reaction but were not isolated and analyzed due to the reverse reaction being favored upon solvent removal.

Table 3: Benzo-1,3,2-thiazaboronate ester compounds synthesized from the condensation reaction R-boronic acid and of 2-aminophenylmercaptan

Entry	Boronic acid	Product	Chemical	Yield

			Shift (ppm)	(%)[2]
1			44.4	90
2			42.2	86
3			42.4	70
4			45.3	66

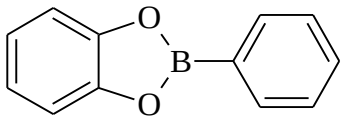
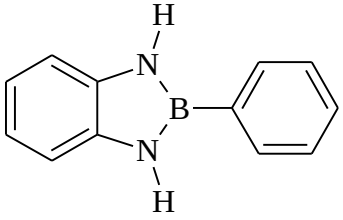
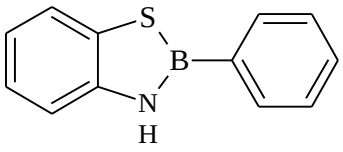
3.1.6. Summary of Condensation Reactions

The shift of the boron atom in ^{11}B NMR has been reported to be highly dependent on the charge density on the boron atom, the charge on the boron atom is sequentially influenced by the π–donor strength of the attached adjacent groups.[123] There are reports stating that the greater the π–donor ability of the atoms bonded directly to the boron atom the greater will be the π–bonding between boron and the surrounding atoms, this results in a higher electron density on the boron atom, thereby shifting the ^{11}B NMR resonance up field.[148]

[2]Based on ^{11}B NMR conversion of R-boronic acid to corresponding boronic ester

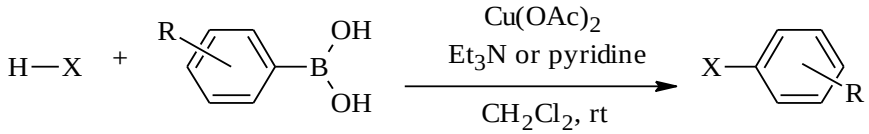
Table 4 shows the ^{11}B chemical shift of the phenylboronic acid derivatives synthesized in this chapter; as mentioned above these shift are an indication of the electron density in each boron atom brought about by the atoms attached to boron. The nitrogen based (phenylbenzo-1,3,2-diazaboronate ester) boronate ester are found more up field followed by the oxygen derivative then the nitrogen and sulphur derivative. Looking at these results only it can be noted that the diazaboronate ester derivatives have the most shielded boron atom, which is the result of the high π-back donation between the N–B bond.[149] It can also be observed that the ^{11}B chemical shift of the phenybenzo-1,3,2-thiazaboronate ester is found slightly up field than the ^{11}B chemical shift of the dithiaborolane derivatives that were reported by Hadebe and this is an indication of the slight shielding brought about by the nitrogen atom in this compound through the π-back donation mentioned above.[54]

Table 4: ^{11}B chemical shift of various phenylboronate esters synthesized from the condensation of phenylboronic acid and various chelating ligands

Ester	Chemical Shift (ppm)
	32.8
	28.4
	44.4

3.1.7. *N*-arylation of imidazole via the Chan-Lam reaction.

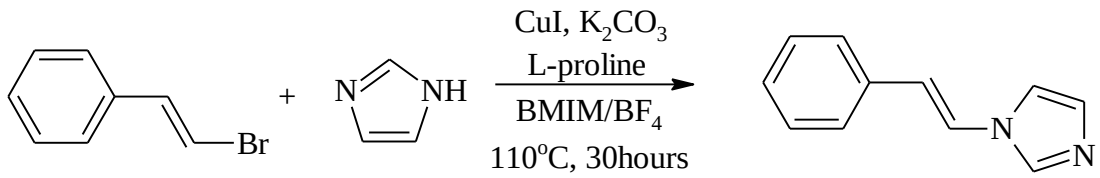
As detailed in section 1.1.5.3.1, the Chan-Lam coupling reaction was first documented by Chan and co-workers, when they reported a new synthetic route for the formation of new C–N and C–O bonds. This method involved the arylation of the X–H bond (where X is oxygen or nitrogen) by the aryl-group of the arylboronic acid in the presence of a copper(II) catalyst (**Scheme 68**). This method presented organoboranes compounds as efficient arylating reagent. [107]



Where X= N, O

Scheme 68

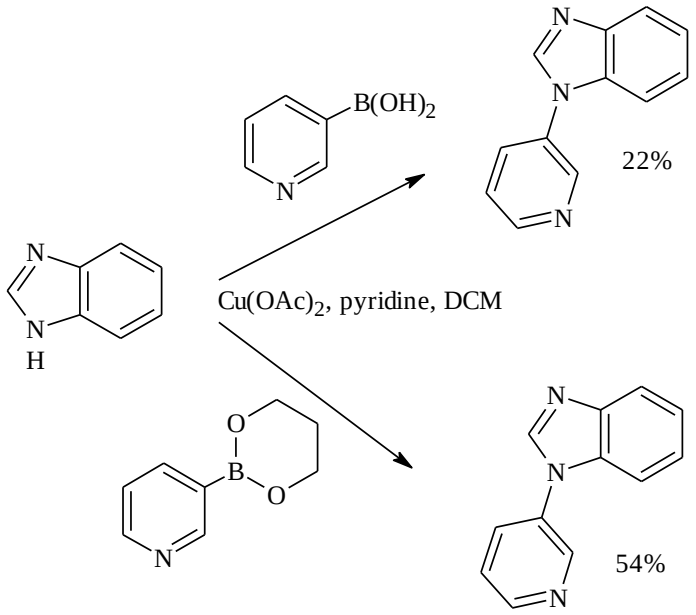
Compounds containing a carbon-nitrogen or carbon-oxygen bond have an important role in the biological systems and are widely used in the pharmaceutical industry as starting material for the preparation of more complex and biologically active compounds.[115] There are few methods that have been reported in the literature that allow for the formation of such bonds; however, these methods have been reported to be harsh and require elevated temperatures. An example of such a method is the Ullmann reaction, Buchwald and Hartwig's palladium-catalyzedC(aryl)–N cross-coupling.[109] A typical Ullmann reaction involves the coupling of an arylhalide with an excess of copper at 200 °C, and the generated active copper species undergoes an oxidative addition with a second equivalent of the arylhalide to afford a biaryl compound. The modification of the Ullmann reaction allows for the synthesis of ethers and amines is known as the Ullmann condensation, which also still requires temperatures above 100 °C and long reaction time (**Scheme 69**).[150] The copper(II) promoted N–H and O–H arylation using boronic acids is similar to the bismuth arylation chemistry but employs milder conditions.[109]



Scheme 69

Since the report by Chan and co-workers, there have been numerous reports regarding the optimization of the reaction condition. Evans and co-workers have reported that anhydrous copper(II)acetate is by far the best catalyst for the Chan-Lam coupling when using triethylamine or pyridine as promoters at room temperature.[110] Quanch and co-workers have reported that at 40 °C, the hydrous copper(II)acetate catalyzes the reaction without the need for a promoters such pyridine and triethylamine.[112]

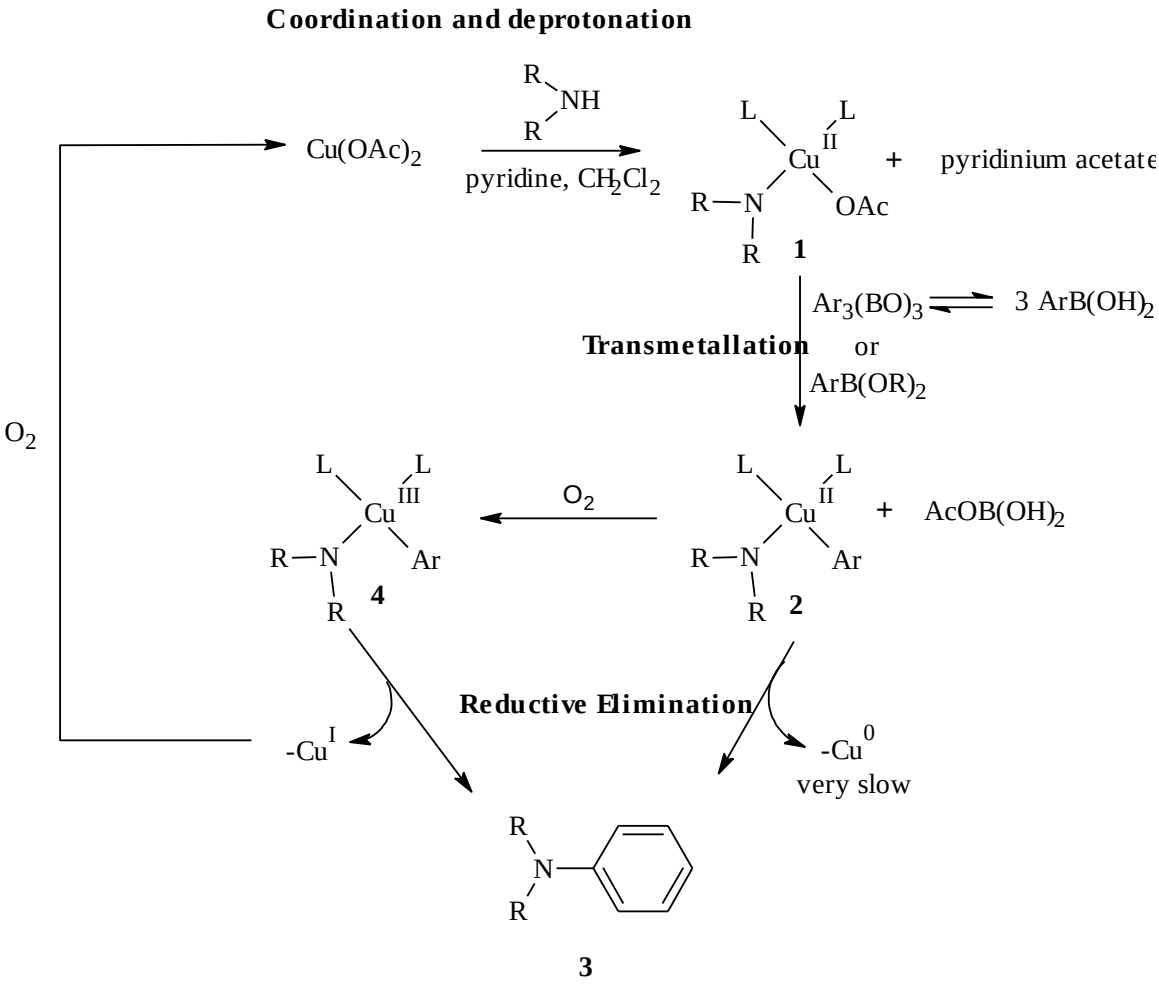
Chan and co-workers have in an effort to identify the controlling factors of the arylating reagents reported on the use of phenylboronic acid derivatives as arylating reagents for the *N*– and *O*–arylation. Subsequently, they reported that ancillary oxo-ligand on the boron has a drastic influence on the cross-coupling reactions and that boronic esters are more efficient arylating reagents than phenylboronic acids.[116]Lam and co-workers explored the cross-coupling reaction between 3-pyridylboronic acid with benzimidazole and obtained a 22 % yield. However, changing the boron reagent to the corresponding propylene glycol boronic ester resulted in a higher yield of 54 % (Scheme 70).[116]



Scheme 70

A study by Combs and co-workers using *N*-arylation of morphine as a prototype, found that dichloromethane and 1,4-dioxane were the optimum solvents[115] while Evans and co-workers found that dichloromethane is the optimum solvent for the *O*-arylation reaction, but the reaction tolerated a range of solvents, with acetonitrile and toluene affording moderate yields.[110] Kantam and co-workers have reported the use of ionic liquids (bmim/BF_4) systems as solvents as they show a drastic effect on the yields obtained for *N*-arylation.

The mechanism of the Chan-Lam coupling has been proposed by Lam and co-workers to be similar to that of the triarylbismuth arylation. They stated that the first step involves the rapid coordination or ligand exchange and the dissolution of copper(II)acetate by the *N*-heterocycle (**Scheme 71-complex 1**). The second step involves the trans-metallation of the arylboronic acid complex **1** to form complex **2** which can form the *N*-aryl compound by undergoing one of the two pathways available.[113]



Scheme 71

Even though the Chan-Lam cross-coupling reaction was first reported in 1998, it has greatly advanced as a carbon-heteroatom cross-coupling methodology. There are ongoing developments on this cross-coupling reaction; which include the expansion of the scope of substrates and boron reagents, the fine tuning of the reaction solvents and additives, as well as, the development of new solution and solid-phase catalytic systems.[115,119,121,122] Reports further state that in addition to the diversity and robustness of this reaction, the low cost of the copper catalyst used sets the Chan-Lam coupling reaction aside of the other heteroatom-carbon cross-coupling.[119]

In the section to follow an investigation into the use of arylbenzo-1,3,2-diazaboronate ester as possible arylating reagents for the Chan-Lam coupling reaction with imidazole

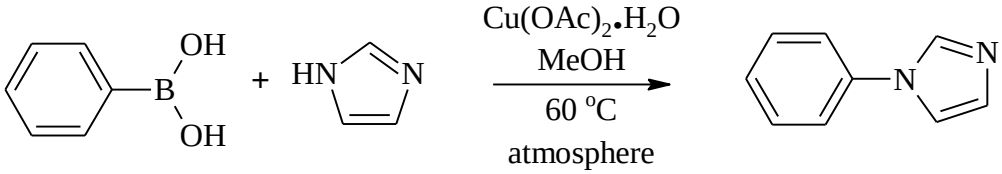
will be reported. The exploration of the arylbenzo-1,3,2-diazaboronateester as possible arylating reagents for the Chan-Lam reaction stems from the report by Lam and co-workers on the use of dioxa-boronic acid derivatives as arylating reagents, which proved to have a drastic effect on the yield.[116]

3.1.7.1. Synthesis of *N*-aryl imidazole compounds

There are a large number of drugs containing the *N*-arylimidazolyl group that have been reported in the literature and these drugs are said to have a range of important biological activities, these include the cyclic AMP phosphodiesterase and thromboxane synthase inhibitors, the cardiotonic and antiglaucoma agents, and AMPA receptors antagonists. As a result of such drugs, there is a constant need for the development of efficient synthetic procedures to form *N*-arylimidazole units.[151-153]

There are a number of reaction methodologies that have been reported for the *N*-arylation reaction using the Chan-Lam reaction, which use a variety of solvents, copper source and temperature. For this investigation of arylbenzo-diazaboronate as arylating compounds the synthetic method reported by Kantam and co-workers will be adapted. Kantam and co-workers presented a method that does not require the presence of any promoter, whilst allowing for the conversion to the product in a few hours, moreover the reaction doesn't need pure oxygen but it is stirred in air.[154]

3.1.7.1.1. Synthesis of *N*-phenylimidazole



Scheme 72

N–phenylimidazole was successfully synthesized by adding $Cu(OAc)_2.H_2O$ (10 mol %) to methanol in a round-bottom flask, the mixture was charged with imidazole and

phenylboronic acid successively and allowed to reflux at 60 °C for 5 hours in air (**Scheme 72**), to form the named compound in a 85 % yield. The obtained yield is in good agreement with the yield obtained by Kantam and co-workers[154] (90 %) and exceeds that obtained by Collman and Zhong[111] in their *N*-arylation of imidazole using $[Cu(OH)•TMEDA]_2Cl_2$ as a copper source.

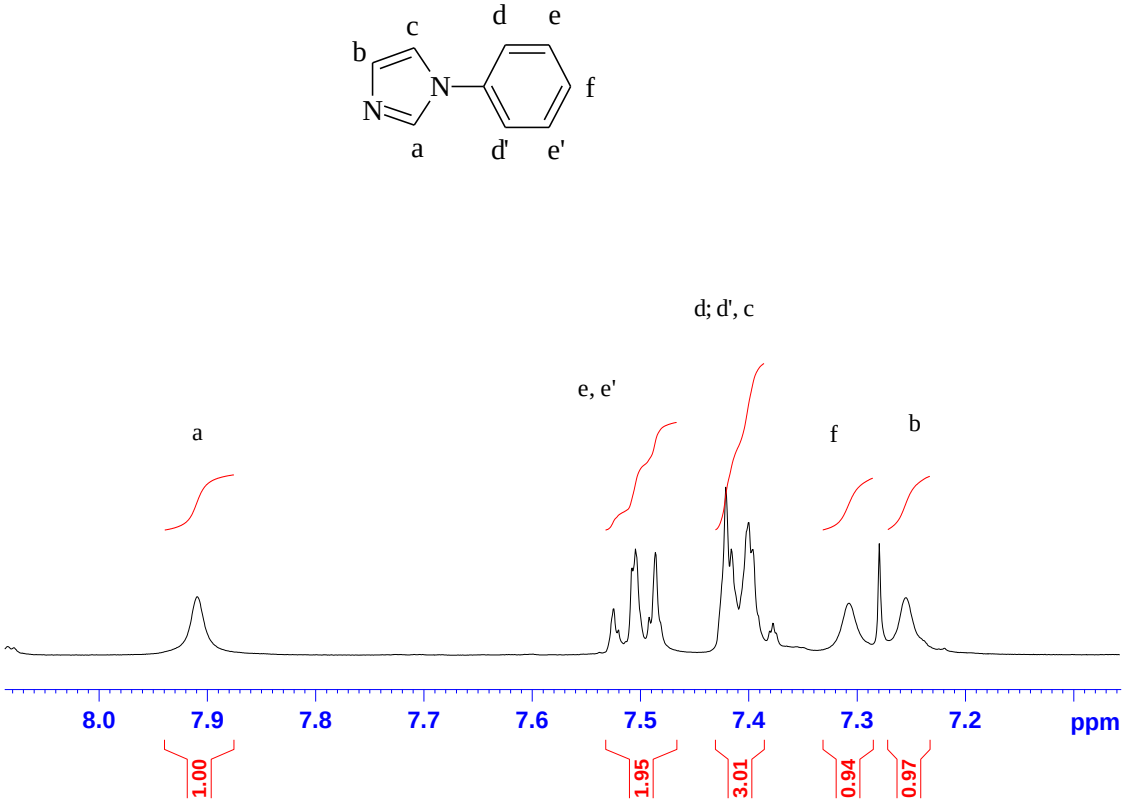
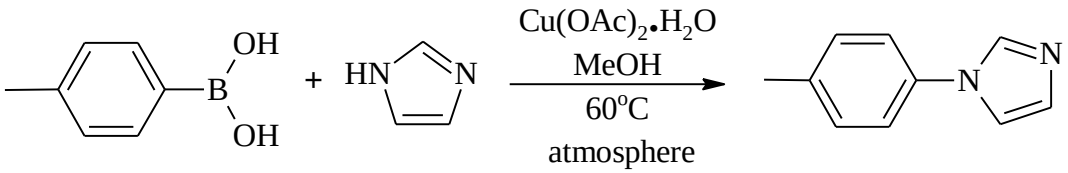


Figure 64: ^{1}H NMR spectrum observed for *N*-phenylimidazole in $CDCl_3$.

Purification by column on silica gel with ethly acetate and *n*-hexane (1:1) as eluent resulted in a milky white oil, which generated a spectrum with five resonance when the ^{1}H NMR spectroscopic analysis was conducted.^{1}H NMR (400 MHz, $CDCl_3$), δ_H, ppm: 7.25 (2H, s,); 7.31 (1H, s,); 7.39–7.43 (3H, d, J=8.34Hz); 7.48-7.53 (2H, t); 7.90 (1H, s) assignable to b, f, (d, d', c) (e, e') and a, respectively (**Figure 64**). The integral ratio is in agreement with the number of protons that are expected for the desired product, and ^{1}H NMR spectroscopic data obtained is in accordance with that reported by Collman and Zhong.[111]

3.1.7.1.2. Synthesis of *N*-(4-methyl)-phenylimidazole

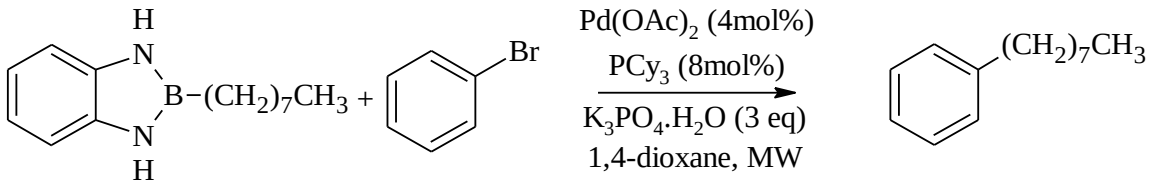


Scheme 73

The above compound was synthesized by the reaction of (4-methyl)-phenylboronic acid and imidazole applying the reaction conditions illustrated in **Scheme 73**in a 76 % yield, which is lower than that reported by Kantam and co-workers[154] and Collman and Zhong[111] After purification on silica gel with ethyl acetate and *n*-hexane as eluent, there was only one spot observed in the TLC plate and analysis of the ^{11}B NMR spectroscopic data showed the absent of any boron peak, indicating the absence of (4-methyl)-phenylboronic acid. ^{1}H NMR spectroscopic data revealed five resonance peaks at δ_H (400 MHz, $CDCl_3$): 2.42 (s, 3H); 7.21 (d, 1H); 7.29 (s, 4H); 7.93 (s, 1H) and 7.98 (d, 1H). The observed spectroscopic data and yield is consistent with that reported by Kantam and co-workers.[154]

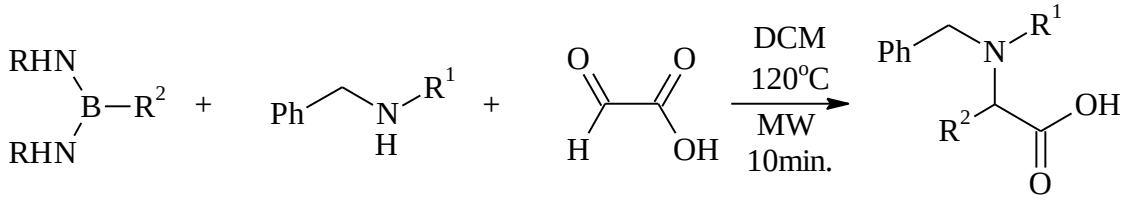
3.1.7.1.3. Coupling reaction with arylbenzo-1,3,2-diazaboronate esters

The application of arylbenzo-1,3,2-diazaboronate esters as cross-coupling reagents has been explored for two cross-coupling reactions within the Robinson group. Sithebe and co-workers reported that2-alkenyl and 2-alkyl-benzo-1,3,2-diazaboronates provides a new alternative as a coupling partners for the Suzuki-Miyaura cross-coupling reaction with good yields. They demonstrated that benzo-1,3,2-diazaborolane derivatives are able to undergo the cross-coupling reaction with a wide variety of arylhalides using the inexpensive palladium(II)acetate (**Scheme 74**), thereby making the use of such compounds favourable.[106]



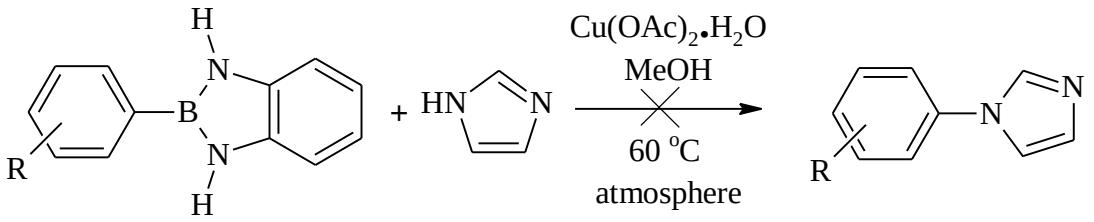
Scheme 74

An investigation into the use of arylbenzo-1,3,2-diazaboronate ester as a coupling partner in the Petasis multi-component reaction has been reported by Slabber.[130] From the investigation the author demonstrated that the coupling of an arylbenzo-1,3,2-diazaborolane compound, with an amine and an aldehyde or α-keto acid resulted in the formation of substituted amino acids in low yields.(**Scheme 75**)[130]



Scheme 75

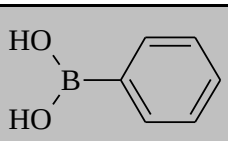
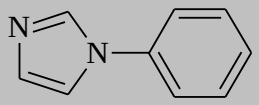
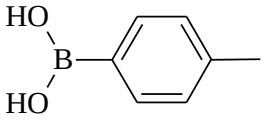
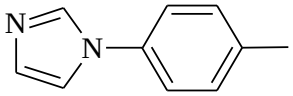
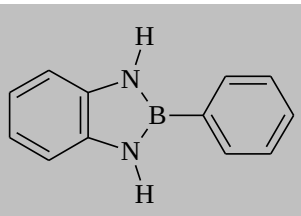
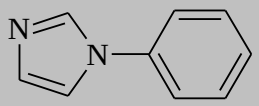
Chan and co-workers reported that the use of organoborane compounds with ancillary oxo-ligand on the boron atom had a strong effect of the Chan-Lam cross-coupling reaction, with the exception being the catechol-derivative which appears to be readily hydrolyzed to the boronic acid derivative.[116] Hadebe and co-workers reported that the nitrogen derivatives of catecholboronate ester appeared to be robustness against oxidation; therefore, these nitrogen-derivatives will be investigated as arylating reagents.[54] By using the synthetic method applied for the synthesis of the phenylimidazole compounds above, an investigation into the use of arylbenzo-1,3,2-diazaboronate ester was conducted (**Scheme 76**).

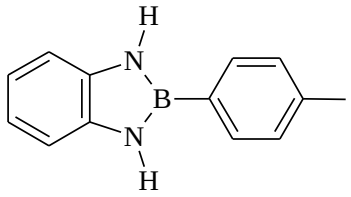
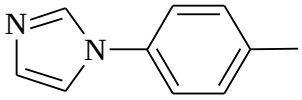
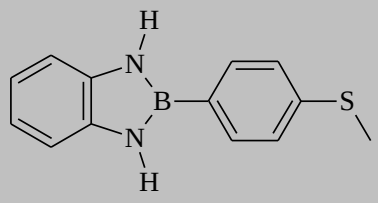
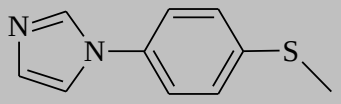


Scheme 76

It can be seen above, thatthe conditions illustrated in **Scheme 76** allowed for the successful *N*-arylation of imidazole to *N*-phenylimidazole when an arylboronic acid was used (**Table 5** entry 1&2). The reaction of phenylbenzo-1,3,2-diazaboronateester with imidazole was allowed to stir for 24 hours at 60 °C and analysis with the thin layer chromatography showed no product formation (**Table 5**-entry 3) but the presence of the spot corresponding to the phenylbenzo-1,3,2-diazaboronate ester. Likewise a similar observation was made with the other arybenzo-1,3,2-boronate esters (entry 4&5).

Table 5:*N*-aryl imidazole attempted to be synthesis of using arylbenzo-1,3,2-diazaboronate ester

Entry	Organoborane compound	Product	Yield (%)
1			85
2			62
3			None

4			None
5			None

The reaction failed to form the desired compound after its temperature was increased to 80 °C and allowed to stir for 24 hours. The use an anhydrous copper(II)acetate catalyst did not have any effect on the reaction; likewise there was no observed change in the reactivity when activated molecular sieves were added to the reaction flask. The reaction solvent was changed to dichloromethane, which was the solvent used by Chan and co-workers in their work with boronic acid derivatives, but this also proved to be unfruitful.[116] Due to time a wide range of reaction conditions (including the application of microwave irradiation which has proven to be a rather important method in the use of benzo-1,3,2-diazaboronate ester compounds as coupling partners) were not explored which could have resulted in a positive result. [106,119,130]

The failing of the reaction can be due to a number of factors such as steric hindrance on the boron atom or the decreased Lewis acidity on the boron atom may result in decreased reactivity, making it labile towards the reaction.

3.2. Conclusion

The condensation reaction of boronic acid with 1,2-diaminophenyl, 1,2-dihydroxybenzene and *o*-aminophenyl mercaptan, resulted in a range of arylbenzo-1,3,2-

boronate esters that were successfully synthesis in good yields between 66-99 %. The boronate esters synthesized by the condensation of boronic acid and *o*-aminophenyl mercaptan were unstable upon the removal of toluene, and were only characterized using ^{11}B NMR spectroscopy. The boron atom showed a great dependence on the adjacent groups attached to it which affected the ^{11}B NMR chemical shift with the most deshielded boron found down field and the most shielded found up field.

The investigation on the use of arylbenzo-1,3,2-diazaboronateester as *N*-arylating reagents in the Chan-Lam coupling showed that these compounds were unsuitable. This could be the direct effect of the steric hindrance around the boron atom and the labile nature of the boron as a result of the π-back donation between the boron p_z-orbital and the lone pair on the nitrogen atom.

3.3. Recommendations for future work

The study has proven to be successful with respect to the first objective with the exception being the condensation reaction with *o*-aminophenyl mercaptan. In an effort to eliminate the dependence of the arylbenzo-1,3,2-thiazaboronate ester on the solvent, a dry reaction can be investigated as well as the application of microwave irradiation.

Whilst the application of arylbenzo-1,3,2-diazaboronate ester as arylating reagent in solution for this investigation did not yield any results, literature suggests that the application of microwave irradiation can have an impact on the product yield for a number of reactions. The use of microwave radiation and the fine tuning of ligands on the metal center were not explored in the reported investigation due to time, this can be used as a starting point for future research.

CHAPTER 4

4.1. Experimental

4.1.1. Chemicals, General Procedure and Instrumentation

All the starting materials used in the reactions were obtained from commercial sources and were used without further purifications. The reactions were performed in anhydrous solvents which were prepared using the Puresolv MD 7 purification system from Innovative Technologies.

The glassware, cannulas and metal needles were dried in an oven at *ca.* 100 °C overnight before use. Due to the sensitive nature of the reactions when exposed to air and moisture, the glassware was further flame dried with a hot air gun for *ca.* 10 min under a reduced pressure and allowed to cool under a stream of nitrogen gas, which had passed through a mixture of silica gel and 0.4 nm molecular prior. The glassware was assembled, and all the joints were wrapped and sealed with Teflon® tape and Parafilm "M"® respectively. Reactions requiring high temperature were heated using a silicon oil bath and a heat stirrer to the desired temperatures. Merck silica gel 60 F254 pre-coated on an aluminium sheet and Merck silica gel 60 were used for the thin layer chromatography and column chromatography respectively.

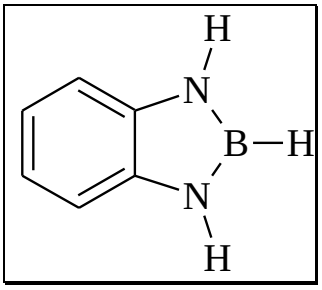
^{1}H NMR (400 MHz), ^{13}C NMR (100 MHz) and ^{11}B NMR (128 MHz) were recorded on a Varian Bruker Avance III 400 (9.4 T) spectrometer in a normal glass NMR tubes. All the NMR spectra were recorded as solution in specified deuterated solvents and are reported in parts per million (ppm) downfield from TMS peak at 0 ppm. The ^{11}B NMR spectra were referenced to BF_3-OEt_2 (External, neat, with capillary tube of acetone–d6 for the deuterium lock).High-resolution mass spectra were recorded using a Waters Acquity LCT premier(TOF) ultra-performance liquid chromatography-mass spectrometry and the low resolution(Electron Impact) mass spectra were recorded using ThermoFinnigan trace

GC, coupled with a Polaris Q mass spectrometer. The infrared spectrums were recorded using ID Fourier Transform Infrared instrument, the samples were placed on a diamond top and compressed with infrared pressure steel.

The computational calculation conducted in this study was computed using Gaussian 09 software package which is the newest series in the Gaussian series of electronic structural programs and all processing done using the Gaussview program.

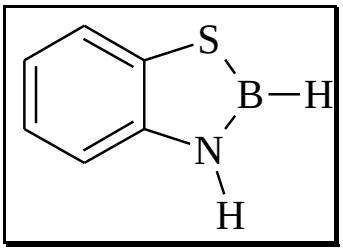
4.1.2. Preparation of Hydroborating Reagents

4.1.2.1. Preparation of Benzo-1,3,2-diazaborolane



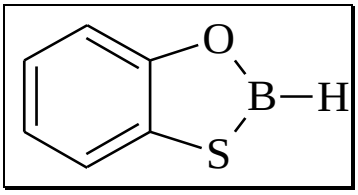
1,2-diaminebenzene (1.00 mmol, 108 mg) was dissolved in dry tetrahydrofuran (20 ml) in a flame dried round-bottomed flask, under a nitrogen gas atmosphere. Upon the complete dissolution of the brown solid 1,2-diaminobenzene, borane-dimethyl sulfide complex (1 M, 1.0 ml, 1 mmol) was introduced drop wise, using a syringe through a rubber septum into the reaction flask. The resulting mixture was allowed to reflux for four hours, whilst maintaining the nitrogen atmosphere. Benzo-1,3,2-diazaborolane was obtained as a light pink solution (96 %) δ_B (128 MHz; BF_3 OEt_2) = 24.1 ppm (d, $J_{B–H}$ = 156 Hz)

4.1.2.2. Preparation of Benzo-1,3,2-thiazaborolane



1,2-aminothiophenol (2 mmol, 250 mg) was dissolved in dry tetrahydrofuran (20 ml)in a flame dried round-bottomed flask, under an atmosphere of nitrogen gas. The resulting solution was allowed to stir for 10 minutes at 40 °C; there after borane-dimethyl sulfide complex (1 M, 2.0 ml, 2 mmol) was added drop wise, through the rubber septum into the reaction flask. The resulting mixture was allowed to stir for eight hours, whilst maintaining the nitrogen gas atmosphere and temperature at 40 °C. Benzo-1,3,2-thiazaborolane was obtained as a milky yellow solution (95 %) δ_B (128 MHz; BF_3 OEt_2) = 37.5 ppm (d, J_{B-H} =171.5 Hz). *m/z* 134.0240 (calc. 134.9925)

4.1.2.3. Preparation of Benzo-1,3,2-oxothiaborolane



2-Thiophenol (2.00 mmol, 252 mg) was dissolved in dry dichloromethane (20 ml) in a flame dried round-bottomed flask, under a nitrogen gas atmosphere. After 5 minutes of stirring at room temperature, borane-dimethyl sulfide complex (1 M, 2.0 ml, 2 mmol) was introduced drop wise, using a syringe through the septum into the reaction flask. The resulting mixture was allowed to stir at room temperature (25 °C) for 12 hours, whilst maintaining the nitrogen atmosphere. Benzo-1,3,2-oxothiaborolane was obtained as a clear solution (45 %) δ_B (128 MHz; BF_3 OEt_2) = 43.6 ppm (d, J_{B-H} = 179.8 Hz)

4.1.3. Hydroboration Reaction

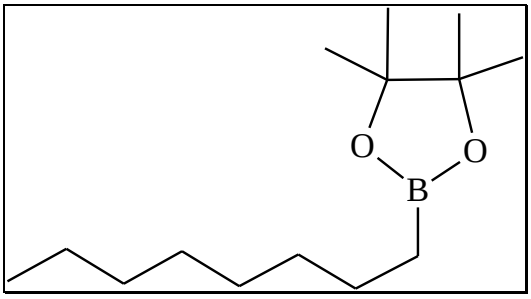
4.1.3.1. Iridium Catalyzed Hydroboration.

General Procedure B

Around-bottom flask containing a solution of $[Ir(cod)Cl]_2$(0.102 mmol, 72 mg) and DPPE (0.210 mmol, 82 mg) dissolved in dichloromethane (5 ml), is flushed with nitrogen gas and fitted with a rubber septum. To this solution the hydroborating reagent (1 mmol) was added using a dried syringe, followed by the addition of 1-octene (1.0 mmol, 0.16 ml). The reaction flask was allowed to stir for 36 hours at room temperature.

After 36 hours the reaction was quenched with methanol (1 ml) and water (3 ml), the product was extracted using ether (3×5 ml) and dried using $MgSO_4$. Chromatography on silica gel or radial chromatography with dichloromethane gave the pure product.

- **Octyl-4,4,5,5-tetramethyl-[1,3,2]-dioxaborolane**



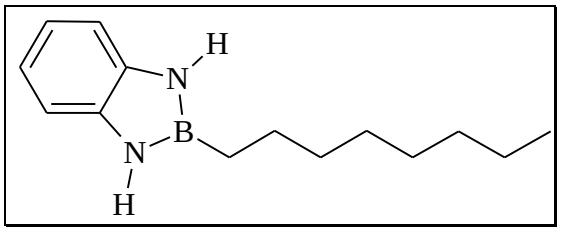
The named compound was successfully synthesized by the reaction of pinacolborane and *trans*-4-octene using general procedure B in an 83 % yield.

^{1}H NMR (400 MHz, $CDCl_3$): δ_H 0.74 (2H, t); 0.86 (3H, t); 1.22 (12H, s); 1.26 (10H, s) and 1.34-1.46 (2H, m).

^{13}C NMR (100 MHz, $CDCl_3$): δ_C 13.9; 22.7; 23.8; 29.3; 29.2; 31.7; 32.3 and 82.7.

^{11}B NMR (128 MHz, $CDCl_3$): δ_B 34.2 ppm

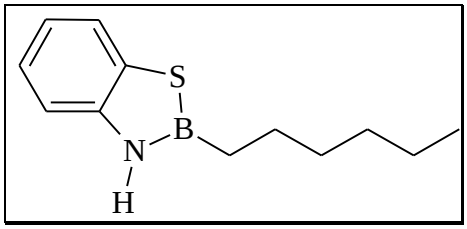
- **Octylbenzo-1,3,2-diazaboronate ester**



The named compound was successfully synthesized by the reaction of benzo-1,3,2-diazaborolane and 1-octene using general procedure B in a 83 % yield.

^{11}B NMR (128 MHz, $CDCl_3$): δ_B 31.6 ppm

- **Octylbenzo-1,3,2-thiazaboronate ester**



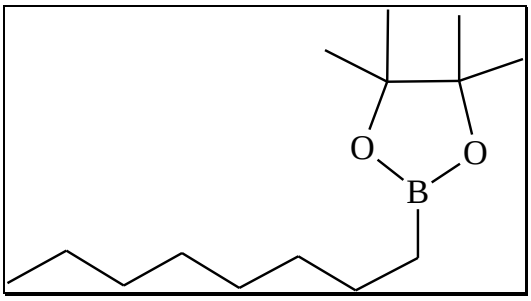
The synthesis of the named compound was unsuccessful with a disproportionation peak observed at 33 ppm.

4.1.3.2. Rhodium Catalyzed Hydroboration

General Procedure C

The hydroborating agent was injected into an oven dried, nitrogen purged round-bottom flask. A solution with 1-octene (0.25 mmol, 0.40 ml) and Wilkinson's catalyst (0.05 mmol, 46.2 mg) in dry dichloromethane was added to the reaction flask using a cannula. The content of the round bottom flask was allowed to stir for 24 hours at 25 °C or as indicated.

- **Octyl-4,4,5,5-tetramethyl-[1,3,2]-dioxaborolane**



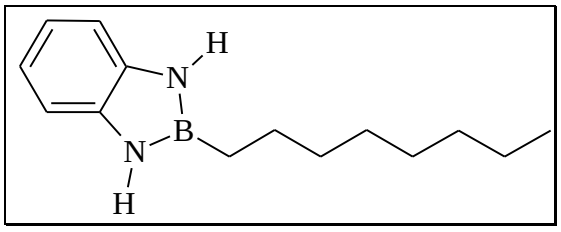
The title compound was synthesized using general procedure C by reacting 1-octene with pinacolborane, which formed orange oil in a 98 % yield.

^{1}H NMR (400 MHz, $CDCl_3$): δ_H (ppm) 0.76 (2H, t); 0.87 (3H, t); 1.23 (12H, s); 1.25 (10H, s) and 1.33-1.45 (2H, m).

^{13}C NMR (100 MHz, $CDCl_3$): $\delta_{C\ (}$ppm) 14.0; 22.6; 23.9; 29.2; 29.3; 31.8; 32.4 and 82.7.

^{11}B NMR (128 MHz, $CDCl_3$): δ_B 33.9 ppm

- **Octylbenzo-1,3,2-diazaboronate ester**

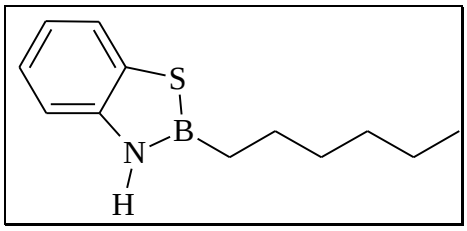


The named compound was successfully synthesized by the reaction of pinacolborane and 1-octene using general procedure C in an 83 % yield.

^{1}H NMR (400 MHz, $CDCl_3$): δ_H (ppm) 0.78 (2H, t); 0.91 (3H, t); 1.30 (12H, s); 6.60-6.65 (2H, m, H-5) and 6.70-6.75 (2H, m).

^{11}B NMR (128 MHz, $CDCl_3$): δ_B 31.5ppm (B-1)

- **Octylbenzo-1,3,2-thiazaboronate ester**



The synthesis of the above compound was unsuccessful.

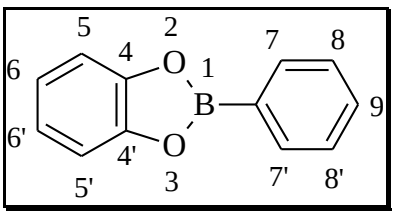
4.1.4. Condensation Reactions of Boronic Acids

4.1.4.1. Condensation reactions with 2-hydroxyphenyl

General procedure D

To a solution of catechol in dry toluene (5 mmol in 50 ml, 0.1 M), 5×10^{-3} mol of boronic acid is added. The round bottom flask is then connected with the Dean and Stark apparatus, the reaction was allowed to proceed for 1.5 hours at 110 °C. After 2 hours, toluene was evaporated to 10 ml by removing the Dean and Stark apparatus. The crystalline product was collected by filtration, and washed with 2×15 ml cold methanol.

- **2-Phenyl-1,3,2-benzodioxaboronate ester**



The above mentioned compound was synthesized by the reaction of phenylboronic acid with 1,2-dihydroxybenzene using the general procedure D.

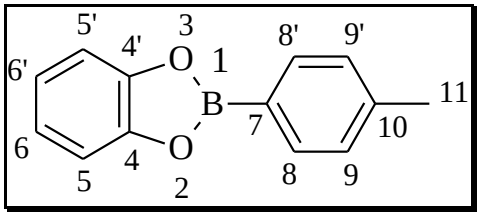
^{1}H NMR (400 MHz, $CDCl_3$): δ_H (ppm) 7.15 (2H, m, H-6,6´); 7.34 (2H, m, H-5, 5´); 7.52 (2H, t, H-8, 8´); 7.60 (1H, t, H-9) and 8.12 (2H, d, *J*= 7.56Hz, H-7, 7´).

^{13}C NMR (100 MHz, $CDCl_3$): δ_C (ppm) 112 (C-5,5´); 123 (C-6, 6´); 128 (C-8,8´); 132 (C-9); 135 (C-7,7´) and 148 (C-4, 4´)

^{11}B NMR (128 MHz, $CDCl_3$): δ_B32.4 ppm (B-1)

LRMS *m/z* found 227.0723, calc. for$[C_{13}H_{12}BO_3\ MeO]^+$ =227.0435

- **<u>2-(4-tolyphenyl)-1,3,2-benzodioxaboronate ester</u>**



The reaction of (4-methyl)-phenylboronic acid with 1,2-dihydroxybenzene using the general procedure D yielded the title compound.

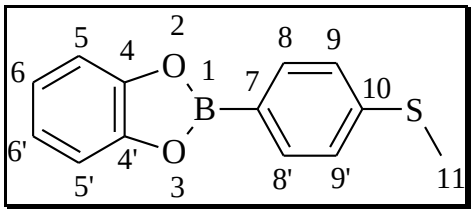
^{1}H NMR (400 MHz, $CDCl_3$): δ_H (ppm) 2.45 (3H, s, H-11); 7.11-7.15 (2H, m, H-6, 6´); 7.31-7.35 (4H, m, H-5, 5´, 9, 9´) and 8.01 (2H, d, *J*= 7.96Hz, H-8, 8´).

^{13}C NMR (100 MHz, $CDCl_3$): δ_C (ppm) 22 (C-11); 113 (C-5,5´); 122 (C-6, 6´); 129 (C-9,9´); 135 (C-8,8´); 143 (C-10) and 148 (C-4, 4´)

^{11}B NMR (128 MHz, $CDCl_3$): δ_B 31.5 ppm (B-1)

LRMS *m/z* found 241.0835, calc. for $[C_{14}H_{14}BO_3\ MeO]^+$ = 241.0701

- **2-[4-(methylthio)]-phenylbenzo-1,3,2-dioxaboronate ester**



2-[4-(methylthio)]-phenylbenzo-1,3,2-dioxaboronate ester was synthesized by reacting equimolar amounts of4-(methylthio)-phenylboronic acid and 1,2-dihydroxybenzene using the general procedure D.

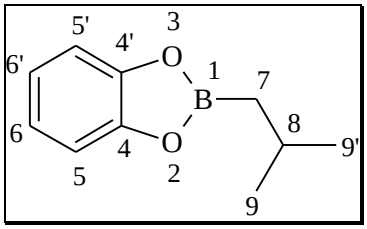
^{1}H NMR (400 MHz, $CDCl_3$): δ_H (ppm) 2.55 (3H, s, H-11); 7.11-7.15 (2H, m, H-6, 6´); 7.30-7.33 (2H, m, H-5,5´); 7.33-7.38 (2H, d,*J*= 8.08Hz, H-9) and 7.97-8.02 (2H, d, *J*= 7.94Hz, H-7, 7´).

^{13}C NMR (100 MHz, $CDCl_3$): δ_C (ppm) 15 (C-11); 112 (C-5, 5´); 123 (C-6,6´); 126 (C-9,9´); 135 (C-9, 9´); 144 (C-10) and 149 (C-4, 4´)

^{11}B NMR (128 MHz, $CDCl_3$): δ_B 31.6 ppm (B-1)

LRMS *m/z* found 273.0476, calc. for $[C_{14}H_{14}BO_3S\ MeO]^+$ = 273.1351

- **2-(2-methyl)propylbenzo-1,3,2-dioxaboronate ester**



Using the general procedure D, the above compound was synthesized by the reaction of 2-(methyl)-propylboronic acid with 1,2-dihydroxybenzene.

^{1}H NMR (400 MHz, $CDCl_3$): δ_H (ppm) 1.02 (6H, d, *J*=6.67 Hz, H-9, 9´); 1.16 (2H, d, *J*=7.06 Hz, H-7); 1.91-2.00 (1H, m, H-8); 6.88-6.94 (2H, m, H-6, 6´) and 7.01 (2H, d, H-5, 5´).

^{13}C NMR (100 MHz, $CDCl_3$): δ_C (ppm) 26 (C-9,9´); 27 (C-8); 111 (C-5, 5´); 119 (C-6,6´);and 136 (C-4, 4´)

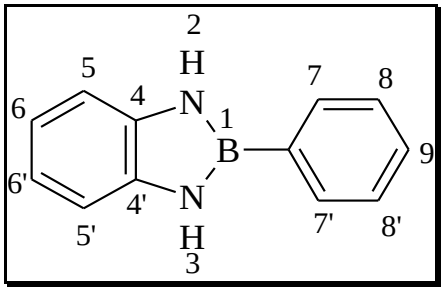
^{11}B NMR (128 MHz, $CDCl_3$): δ_B 31.5 ppm (B-1)

4.1.4.2. Condensation Reaction with 1,2-phenylenediamine

General procedure E

To a solution of *o*-phenylenediaminein dry toluene (5×10^{-3} mol in 50 ml, 0.1 M), 5×10^{-3} mol of R–boronic acid was added. The round bottom flask was then connected with the Dean and Stark apparatus, and the reaction mixture is allowed to stir for 3 hours at 140 ˚C. At the end of the 3 hours, the toluene was removed*in vacuo* and the remaining crystals collected by filtration.

- **<u>2-phenylbenzo-1,3,2-diazaboronate ester</u>**



Using the general procedure E, 2-phenylbenzo-1,3,2-diazaboronate ester was synthesized by the condensation of phenylboronic acid with *o*-phenylenediamine.

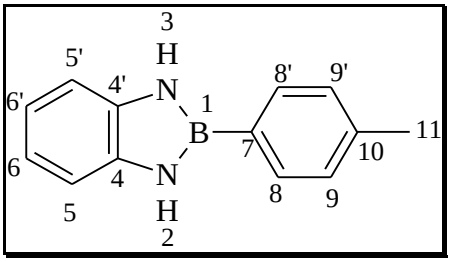
^{1}H NMR (400 MHz, $CDCl_3$): δ_H (ppm) 6.78-6.84 (2H, m, H-6, 6´); 7.01-7.09 (2H, m, H-5, 5´); 7.38-7.44 (3H, d, *J*=6.70Hz, H-8, 8´,9); 7.91 (2H, d, *J*=7.40Hz, H-7, 7´) and 9.09 (2H, s, H-2, 3).

^{13}C NMR (100 MHz, $CDCl_3$): δ_C (ppm) 111 (C-5,5´); 119 (C-6, 6´); 128 (C-8,8´); 129 (C-9); 134 (C-7,7´) and 137 (C-4, 4´)

^{11}B NMR (128 MHz, $CDCl_3$): δ_B 30.1 ppm (B-1)

LRMS *m/z* found 194.8953, calc. for $[C_{12}H_{11}BN_2]^+$ = 194.04014

- **<u>2-(4-tolyphenyl)benzo-1,3,2-diazaboronate ester</u>**



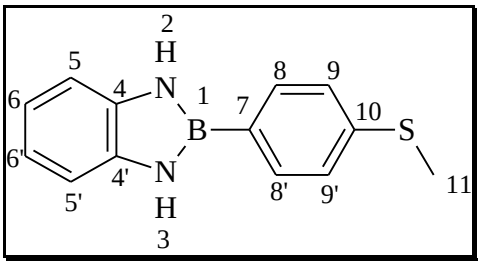
The reaction of (4-methyl)-phenylboronic acid with *o*-phenylenediamine using the general procedure D yielded the title compound.

^{1}H NMR (400 MHz,DMSO-d_6): δ_H (ppm)2.33 (3H, s, H-11); 6.77-6.83 (2H, m, H-6, 6´); 7.01-7.05 (2H, m, H-5, 5´); 7.22 (2H, d, *J*=7.77 Hz, H 9, 9´); 7.76-7.80 (2H, d, *J*=7.85 Hz, H-8, 8´) and 9.01 (2H, s, H-2, 3).

^{13}C NMR (100 MHz, DMSO-d_6): δ_C (ppm) 22 (C-11); 111 (C-5,5´); 119 (C-6, 6´); 129 (C-9,9´); 134 (C-8,8´); 138 (C-10) and 139 (C-4, 4´)

^{11}B NMR (128 MHz, DMSO-d_6): δ_B 29.1 ppm (B-1)

- **2-[4-(methylthio)]phenylbenzo-1,3,2-diazaboronate ester**



^{1}H NMR (400 MHz, DMSO-d_6): δ_H (ppm) 2.51 (3H, s, H-11); 6.78-6.82 (2H, m, H-6, 6´); 7.01-7.05 (2H, m, H-5, 5´); 7.30 (2H, d, *J*= 8.19 Hz, H-9, 9´); 7.81 (2H, d, *J*= 8.16 Hz, H-8, 8´) and 9.05 (2H, s, H-2, 3).

^{13}C NMR (100 MHz, DMSO-d_6): δ_C (ppm) 22 (C-11); 111 (C-5, 5´); 119 (C-6,6´); 129 (C-9,9´); 134 (C-9, 9´); 138 (C-10) and 139 (C-4, 4´)

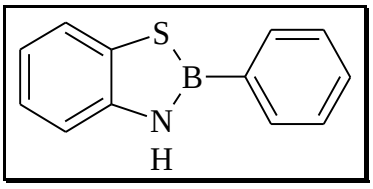
^{11}B NMR (128 MHz, DMSO-d_6): δ_B 28.8 ppm (B-1)

4.1.4.3. Condensation reaction with 2-aminophenylmercaptan

General procedure F

To a solution of aminothiophenol in dry toluene (5×10^{-3} mol in 50 ml, 0.1M), 5×10^{-3} mol of boronic acid is added. The round bottom flask is then connected with the Dean and Stark apparatus, and the reaction mixture was allowed to stir for 36 hours at 140 ˚C. The ^{11}B-NMR was used to monitor the course of the reaction every 30 minutes. After the specified time has elapsed, toluene was removed *in vacuo*.

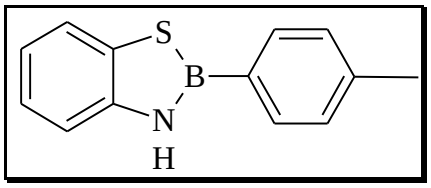
- **2-phenylbenzo-1,3,2-thiazaboronate ester**



Phenylboronic acid was successfully converted into 2-phenylbenzo-1,3,2-thiazaboronate ester by allowing it to reflux in the presence of aminothiophenol using the general procedure F in a 90 % conversion yield.

^{11}B NMR (128 MHz, MeOD): δ_B 44.4 ppm, (SBN)

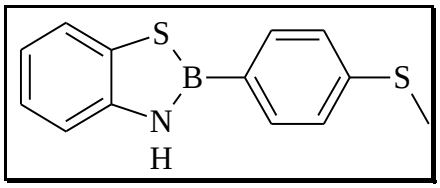
- **2-(4-tolyphenyl)benzo-1,3,2-thiazaboronate ester**



The reaction of (4-methyl)-phenylboronic acid with aminothiophenol using the general procedure F resulted in the formation of the title compound, 2-(4-tolyphenyl)benzo-1,3,2-thiazaboronate ester in a 70 % conversion yield. [3]

^{11}B NMR (128 MHz, MeOD): δ_B 42.2 ppm (SBN)

- **2-[4-(methylthio)]phenylbenzo-1,3,2-thiazaboronate ester**

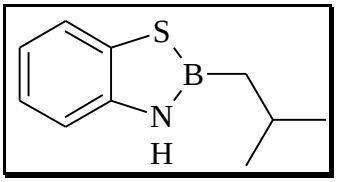


[3]Based on ^{11}B NMR spectroscopic data

2-[4-(methylthio)]phenylbenzo-1,3,2-thiazaboronate ester was synthesized by the reaction of phenylboronic acid with aminothiophenol using the general procedure F in a 86 % yield.

^{11}B NMR (128 MHz, MeOD): δ_B 42.4 ppm (SBN)

- **2-(2-methyl)propylbenzo-1,3,2-thiazaboronate ester**



Using the general procedure F, 2-methylpropylboronic allowed to reflux in toluene in the presence of aminothiophenol to yield 2-(2-methyl)propylbenzo-1,3,2-thiazaboronate ester in a 66 % conversion yield.

^{11}B NMR (128 MHz, MeOD): δ_B 45.3 ppm (SBN)

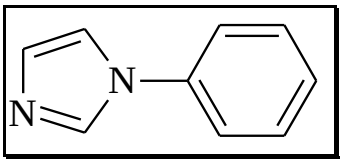
4.1.4.4. Chan-Lam coupling reactions

General Synthesis G

$Cu(OAc)_2.H_2O$ (10 mol % 0.020 g) was added to methanol (5 ml) in a 25 ml round-bottom flask, to the mixture imidazole and arylboron compound (1 mmol) were successively (1 mmol, 0.0681 g) and allowed to reflux at 60 °C for 5 hours in air.

After 5 hours, the product was extracted with diethyl ether: *n*–hexane (1:1), 3×10 ml and dried with anhydrous magnesium sulfate. The solvent was removed under vacuum to approximately 3 ml to afford the *N*-arylated product

- ***N*-phenylimidazole**

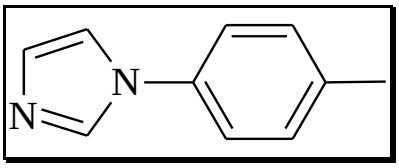


N-phenylimidazole was successfully synthesized using the general procedure G, as a milky white oil in an 85 % yield.

^{1}H NMR (400 MHz, $CDCl_3$): δ_H, ppm: 7.25 (2H, s,), 7.31 (1H, s,), 7.40 (3H, d, *J*=8.34 Hz), 7.48-7.53 (2H, t, *J*=7.80 Hz), 7.90 (1H, s)

^{13}C NMR (100 MHz, $CDCl_3$): δ_C, ppm: 121.6, 127.6, 130.1, 133.7, 137.4

- ***N*–(4-methylphenyl)imidazole**



N–phenylimidazole was successfully synthesized by adding $Cu(OAc)_2.H_2O$ (10 mol % 0.020 g) to methanol (5 ml) in a 25 ml round-bottom flask, the mixture was then charged with imidazole (1 mmol, 0.0681 g) and tolyboronic acid (1 mmol) successively, as a milky white oil (60 %)

^{1}H NMR (400 MHz, $CDCl_3$), δ_H, ppm: 2.43 (3H, s,), 7.21 (1H, d, *J*=7.13Hz), 7.29 (4H, s,), 7.93 (1H, s), 7.95-7.99 (1H, d, *J*=7.57Hz).

^{13}C NMR (100 MHz, $CDCl_3$), δ_C, ppm: 20.9, 118.7, 121.6, 128.2, 130.1, 133.8, 135.1, 138.2

CHAPTER 5

5.1. References

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