SYNTHESIS AND BIOLOGICAL EVALUATION OF FUNCTIONALIZED BENZOXABOROLES AS POTENTIAL ANTIMICROBIAL AGENTS

A THESIS
SUBMITTED TO THE FACULTY OF THE GRADUATE SCHOOL
OF THE UNIVERSITY OF MINNESOTA
BY

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IN PARTIAL FULFILLMENT OF THE REQUIREMENTS
FOR THE DEGREE OF
MASTER OF SCIENCE

Prof. Paul Kiprof, Adviser

October 2012

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Acknowledgements

I would like to thank my adviser Dr. Paul Kiprof for his never-ending wisdom and insight that aided me in completing this project. I would also like to thank Dr. Venkatram R. Mereddy and the members of his lab for their guidance and assistance with helping me to develop a deeper understanding of organic chemistry. Thank you to Dr. Paul Siders for being a member of my committee and taking the time to review my thesis. Finally, I would like to thank the UMD Chemistry Department for giving me an opportunity to further expand my understanding of chemistry and science.

ABSTRACT

Boronic acids are extremely valuable compounds that have applications in medicinal, and materials chemistry, and also as cross-coupling agents in synthetic chemistry. Boronic acids often function as inhibitors for various enzymes due to their unique electronic and physicochemical properties. *B*-hydroxy-1,2-oxaborolanes (benzoboroxoles) are a class of cyclic boronic acid derivatives and are highly important organic synthons because of their structural stability and their ability to undergo important C-C bond forming reactions such as Suzuki cross coupling. Several of these cyclic boronic acids are found to possess excellent pharmacological properties as antifungal, antimalarial and anti-inflammatory agents. However, the existing literature methodologies for the synthesis of highly functionalized benzoboroxoles are difficult and often are not suitable for large scale synthesis.

We have been working on the development of novel synthetic methodologies for the synthesis of functionalized benzoxaboroles as potential therapeutic agents. Previously, we have synthesized several benzoxaboroles employing Baylis-Hillman, Barbier allylation, and Passerini reaction protocols. In continuation of our interest on the development of structurally diverse benzoboroxoles, we synthesized several novel derivatives starting from 2-formylphenylboronic acid utilizing aldol reaction as the key step. Our studies in this area including the synthesis and structural characterization data will be presented.

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INTRODUCTION

I. Selected Highlights of Boron Chemistry

Boron is a Group 13 element which has unique characteristics in contrast to its fellow group elements and other metalloid counterparts. Boron has much higher ionization energy than the other Group 13 elements. [1] For example, it requires a minimum of 800 kJ/mole to convert B → B^{1+} compared to 578 kJ/mole for Al → Al^{1+} and 579 kJ/mole for Ga → Ga^{1+}. [2, 3, 4] The difference in ionization energy contributes to the observation that the other Group 13 elements are markedly more metallic than the boron element and more willing to lose an electron with less energy input. Boron's chemistry is therefore not governed by the fact that it forms ions easily. [1]

Boron does share some characteristics of its metalloid, diagonal neighbor silicon, e.g., both elements are semiconducting in their pure form and are found naturally as oxygen containing minerals. [1] In addition, silicon has a similar ionization energy of 782 kJ/mole for Si → Si^{1+}. [5] The differences between the two elements lie in their chemical bonding tendencies. Silicon hydrides form hydrocarbon-like chain structures, while boron tends to take shape as polyhedral cluster structures (Figure 1).

Like carbon, boron can form stable covalently bonded molecular frames by bonding to itself but also with 3 center, 2 electron with hydrogen bonding configuration that forms clusters as opposed to chains. It can also form rings with electron-donor atoms such as N, P, O, and S. Due to the easy promotion of the s^2p valence shell ground state to a hybridized sp^2 state having 3 singly occupied valence orbitals, trivalent boron (BX_3), has a trigonal planar arrangement as a neutral monoboron species. A stable tetrahedral BX_4^{1-}

anion is formed when a Lewis base (for example $:X^-$) is added and boron, though sp^3 hybridized and *tetracoordinate*, remains *trivalent*. The electron deficiency inherent in boron (3 valence electrons) compared to carbon (4 valence electrons) is compensated by boron forming dative bonds in which boron is the electron pair acceptor (Lewis acid), π-bonds with 2nd row elements such as in BF_3, and multi-centered bonds with hydrogen in which three or more atoms are linked by a single electron pair. This enables boron to cluster readily and other elements combine with it to form stable polyhedral molecules, called heteroboranes. [1]

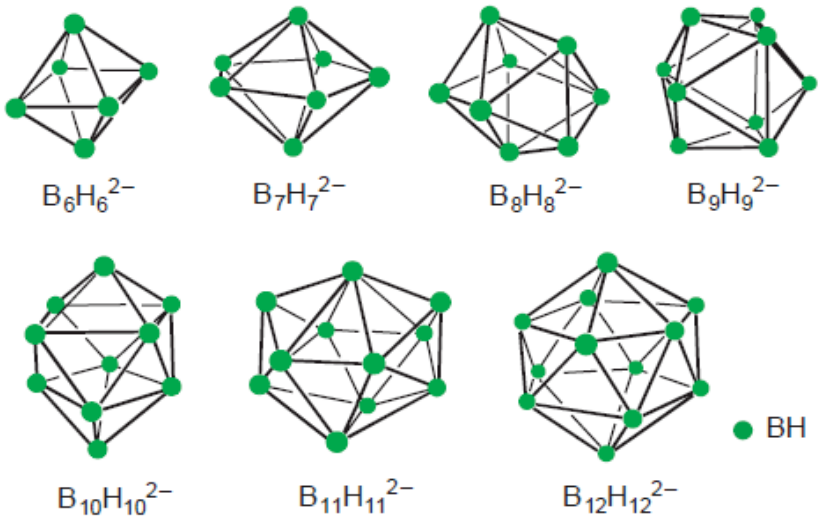


Figure 1. Structures of $B_nH_n^{2-}$ dianions. [6]

Because boron can covalently bond to itself, it is the only other element like carbon that can build molecules of unlimited size. Boron clusters demonstrate a wide variety of stable structures and because of their unusual construction have opened up new ways of thinking that depart from the old methods of understanding chemical reactivity and

bonding. [6]

Some highlights of boron chemistry include Negishi cross-coupling applied to B-Br bonds in small closo-ferracarboranes as a means of effecting controlled substitution at boron, with subsequent linkage to form a polymetallacarborane system (Figure 2). [7]

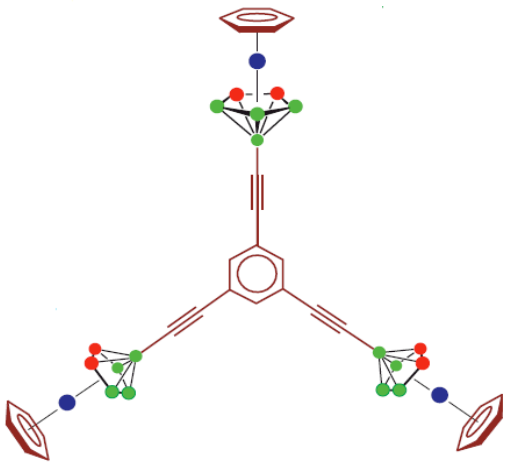


Figure 2. Molecular structure of $[(C_6H_6)Fe(Et_2C_2B_4H_3\text{-}7C\#C]_3C_6H_3$. [7]

In 1994, thermolysis of *arachno*-4-SB_8H_{12} generated a eighteen-vertex dithiaborane (*anti*)-[9,9′-$S_2B_{16}H_{16}$] by a simple cluster fusion previously unrealized for heteroborane species (Figure 3). [8]

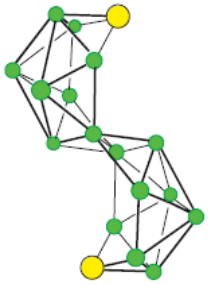


Figure 3. Molecular structure of $S_2B_{16}H_{16}$. [8]

Just within this year, 2012, it was demonstrated by Braunschweig *et al.* at the University of Würzburg, that an ambient-temperature, stable, boron-boron triple bond was formed making boron one of the few elements on the periodic table, along with nitrogen and carbon (and to some extent oxygen), to form homoatomic triple bonds. They performed a reduction of a bis(N-heterocyclic carbene)-stabilized tetrabromodiborane with sodium naphthalenide, yielding isolable diboryne compounds. Further characterization confirmed that the compound had a halide-free linear system containing a boron-boron triple bond (Figure 4). [9]

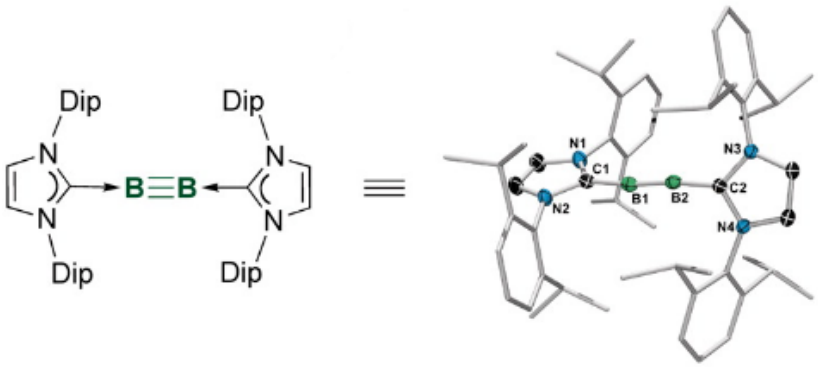


Figure 4. Molecular and crystallographic structure of B-B triple bonding. [9]

As shown in the few examples above, boron's bonding versatility and molecular stability of its resulting compounds make it an important contributor to opening new doors in research for medicinal, technological, materials and other applications.

II. Boron in Medicine

In 1935, it was shown that when the nuclei of the ^{10}B isotope collided with slow neutrons it produced helium-4 nuclei (α particles). [10] A year later, a physician named G. L. Locher discovered that if the reaction was performed in tissue, the particles would destroy the immediate cell but not the closest neighboring cells. [11] Thus, leading to the pursuit of attempting to selectively integrate ^{10}B into inoperable cancerous tumor cells using irradiated, low-energy neutrons. This process became known as boron neutron capture theory (BNCT). During Locher's time, the only boron compounds available contained only one boron atom and had high toxicity and low solubility so it was not until the discovery of the $B_nH_n^{2-}$ polyhedral borane anions and their carborane equivalents in the early 1960's that BNCT was able to demand important consideration in nuclear medicine. [12]

Not only is $B_{12}H_{12}^{2-}$ the largest member of the family of $B_nH_n^{2-}$ stable boron anions (Figure 1) it has very high water solubility and its dicesium salt can survive temperatures of over 800 ^oC with no decomposition making it one of the most stable molecules ever. [6] $B_{12}H_{12}^{2-}$ has a very low toxicity in humans and its source of stability lies in its highly delocalized bonding in the boron structure with 26 electrons occupying 13 bonding molecular orbitals on the polyhedral surface. [14] In 1964, by taking advantage of the stability, solubility and high boron content of the $B_{12}H_{12}^{2-}$ polyboron cluster, a Japanese physician, H.D. Hatanaka, used a mercapto-substituted derivate, $B_{12}H_{11}SH^{2-}$ on mice and rabbits with the goal to treat human brain tumor patients using

BNCT. He found that the nucleophilic sulfhydryl group was able to be affixed to tumor tissue and serum proteins. [13]

Since the 1960's and in more recent times, the exploration of carborane- and borane-substituted BNCT agents has expanded greatly. Areas under study include polyamines, glucosides, carbohydrates, nucleosides, and immunoconjugates, and liposomes. Another approach is to attach boron clusters to tumor antibodies targeted to specific cell types. Those under study are glycosides and porphyrins attached to several carborane cages, like the tetracarboranyl porphyrin (Figure 5). [16, 17]

BNCT has been undergoing clinical trials in the United States and in other countries and to date, trials approved by the U.S. Food and Drug Administration have been limited to patients afflicted with the deadly brain tumor glioblastoma multiforme (GBM). These trials just use three boron compounds: phenylboronic acids, 4-dihydroxyborylphenylalanine; a mercaptosubstituted derivative of $B_{12}H_{12}^{2-}$, $Na_2(B_{12}H_{11}SH)$; and the salt $Na_2(B_{10}H_{10})$. [15]

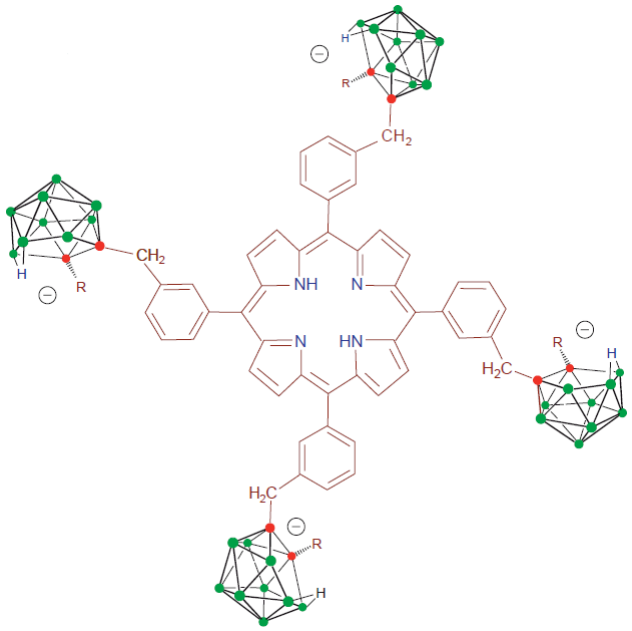


Figure 5. Porphyrin with four attached *nido*-C_2B_9 cage substituents. [17]

In the study of boronic acids, benozoboroxoles play an important role, especially since the discovery of the Suzuki-Miyaura coupling reaction. Benzoboroxoles are cyclic hemiesters of phenylboronic acids have been used in a wide variety of applications in the field of medicine and pharmacology. Benzoboroxoles exhibit high stability due to their five-membered ring structure (Figure 6). [18]

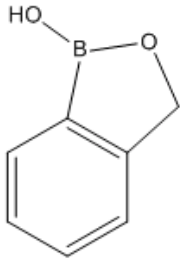


Figure 6. Molecular structure of basic benzoboroxole. [18]

They have become a very important group of organic compounds and benzoboroxole and their derivatives have been used as potential treatments for fungal infections and African sleeping sickness (African trypanosomiasis). [18, 19] A fluoro-substituted benzoboroxole, AN2690, was identified for clinical trials for onychomycosis topical treatment, a toe and fingernail infection. The history and synthesis of benzoboroxoles will be discussed later in this section.

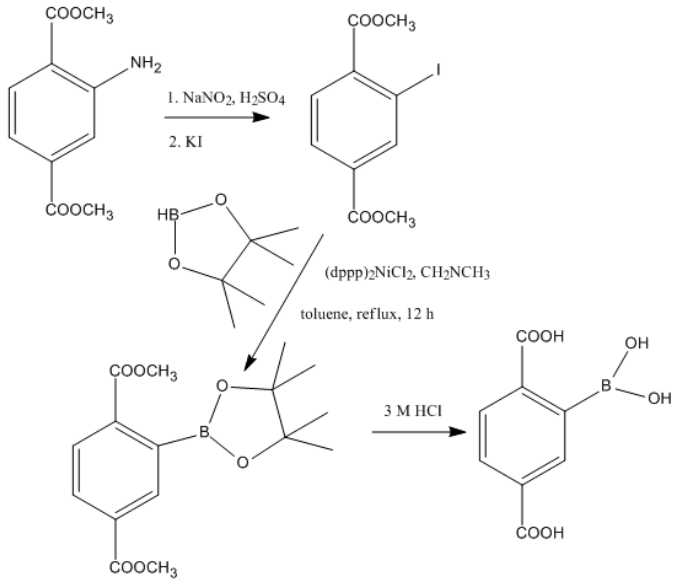
III. Boron in Materials

Another interesting and expanding application of boron is in fire retardant compounds related to benzoboroxoles are based on the work of V. Benin in 2011 at the University of Dayton. He proposed the synthesis of boron functionalized reactive molecules which could co-polymerize with thermosettype polymers such as epoxy and polyurethane. [26] A nonreactive flame retardant molecule/polymer which is blended into the polymer can be used in an application when a polymeric material requires a flame retardant. A reactive flame retardant molecule can also be used because it can bond directly to the polymer during polymerization or by side-chain/grafting reactions. [27, 28]

The use of reactive flame retardants had become more desirable because they do not leach out over time into the environment like other flame retardant additives that are not covalently bound to the polymer. [29] Another goal is to develop condensed phase (char forming) reactive flame retardants. This is so more of the polymer fuel can be converted into low-flammability carbon char instead of the polymer mass being pyrolyzed as high heat release decomposition products. [30]

Research beginning in the year 2000, demonstrated that boron showed some interesting condensed phase activity when available in a boronic acid or boroxine structure. [31] Using the previous studies as a starting point and the understanding of the capabilities of boron in flame retardancy, Benin and his group used catalytic processes to add boron based groups to aromatic compounds such as terephthalates and phenols to form compounds that could act as reactive flame retardants. [26]

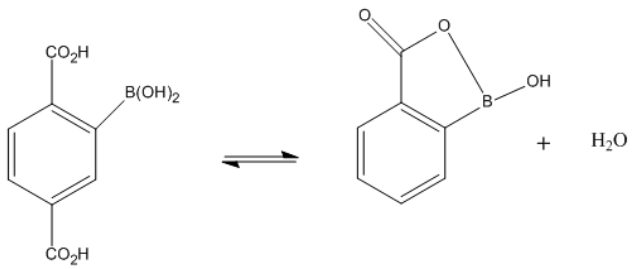
Scheme 1 shows the synthesis of boronoterephthalic acid. The first compound, iodoterephthalate, was subjected to a transition metal-catalyzed coupling reaction to introduce boronic ester functionality. The cyclic boronic ester was prepared using $(dppp)_2NiCl_2$ as a catalyst, triethylamine as a base, with the pinacol boronate being hydrolyzed in acidic conditions to yield a boronoterephthalic acid. [26]



Scheme 1. Schematic of monoboronic ester/acid. [26]

The boronic esters and acids were then tested for heat release/char formation potential with a pyrolysis combustion flow calorimeter (PCFC) and compared to the charring and lowered heat release potential of terephthalic acid, dimethyl terephthalate, and hydroquinone, which served as non-flame retardant standards. They concluded that the boronic acid groups that were capable of crosslinking and condensed phase char formation yielded the greatest reduction in heat release. More research is being done to further justify the use of boron in flame retardant materials, and the work is promising. [26]

Benin *et al.* propose that the compounds have an open-ring structure but our work with oxidized benzoboroxoles suggests a closed ring structure (Scheme 2).

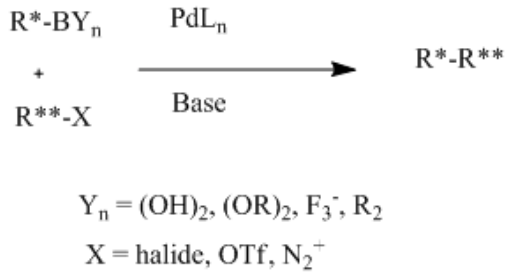


Scheme 2. Schematic of the equilibrium closed-ring benzoboroxole.

IV. Suzuki Coupling Reaction

The Suzuki Coupling reaction (Scheme 3) is considered an integral part of countless synthetic routes used to build complex organic chemicals. It is a palladium-catalyzed cross coupling between organoboronic acid and halides. The scope of the reaction is not restricted to aryls, but includes alkyls, alkenyls and alkynyls. Potassium trifluoroborates and organoboranes or boronate esters may be used in place of boronic

acids. Due to the stability, ease of preparation and low toxicity of the boronic acid compounds, there is currently widespread interest in applications of Suzuki Coupling, with new developments being reported constantly. A variety of organoboranes may be used to cause the transfer of the organic coupling partner to the reactive palladium center via *transmetallation*. [21, 22]



Scheme 3. Schematic for Suzuki coupling reaction. [22]

The reactants are readily available, nontoxic, air-and water stable, and the reactions can be performed under mild conditions and are agreeable to a variety of reaction conditions. In addition, the inorganic boron byproducts can be easily removed after completion of the reaction. The coupling progresses with high regio- and stereoselectivity, and is minimally affected by steric hindrance. It does not affect most functional groups in the molecule, so it can be used in a one-pot synthesis. [21, 22]

V. History of Synthesis of Benzoboroxole

In 1957, H.R. Snyder and his colleagues performed the synthesis of *o*-bromomethylbenzeneboronic acids by the direct bromination of the tolueneboronic acids.

They postulated because of the numerous useful transformations to which benzyl halides and aromatic aldehydes could be submitted, it appeared probable that the substituted benzeneboronic acids carrying bromo-methyl and aldehyde functions attached to the ring would be important intermediates for the synthesis of a variety of boron-containing aromatic compounds. [24] Their work was based on a previous publication in the same year (1957) by K. Torssell who accomplished the synthesis of the compounds by introducing bromine into the methyl groups of the tolueneboronic acids. [23] Both Torssell and Snyder's group used the Ziegler bromination, but Snyder's group refined the reaction by extracting the *o*-bromomethylbenzeneboronic acid into aqueous 15% potassium hydroxide which stood at room temperature for one hour before acidification. The resulting product was the same that was obtained by Torssell, a cyclic ester given the name boronophthalide (Figure 6). Snyder noted that the boronic acid derivative proved to be remarkably stable by resisting the action of dehydrating agents, being recovered unchanged after reflux with thionyl chloride, and being resistant to hydrolytic cleavage of the boronic function by acids or bases. [24] In 1959, Snyder and W.J. Lennarz published the first preparations of derivatives of boronphthalide, to include the findings that the boronphthalide could be nitrated without deboronation or oxidation of the methylene group. [25] This particular nitration will be discussed further in the Results and Discussion section of this paper.

In 1983, H.C. Brown and his group simplified the procedure that was previously developed for the preparation of boronic esters with primary and secondary alcohols, glycols, and tertiary alcohols. The older method used an azeotrope distillation of a

ternary mixture for the esterification of boronic acids. The more convenient method used by Brown *et al*. was that the equilibrium may be displaced in favor of an ester by carrying out the reaction in pentane with which the water component separated and the ester could be extracted from the organic layer. [32]

16 years later, in 1999, V. Zhdankin and his group formally characterized the benzoboroxole (Figure 6) structure through an X-ray crystal structure that also demonstrated that the benzoboroxole crystallized as a dimer due to the hydrogen bonding involving the OH groups (Figure 7). In addition, they simplified the synthesizing method by reacting *o*-bromobenzyl alcohol with butyllithium and the intermediate was reacted with trisopropylborate in ether at -78^{o}C with 86% yield. [33]

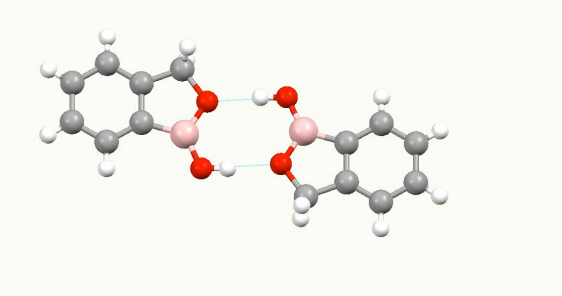
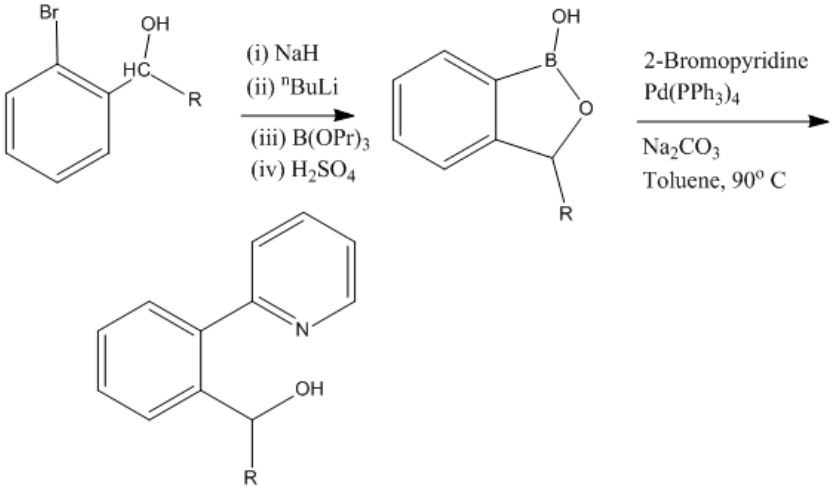


Figure 7. X-ray crystal structure of dimerized benzoboroxole. [33]

Prior to 2007, the established synthesis methods of benzoboroxoles were limited. The methods were often not practical for large scale and comparable synthesis. In 2007, Mereddy *et al.* at the University of Minnesota-Duluth developed a more convenient single pot transformation procedure by using *o*-bromobenzyl alcohols. The *o*-bromobenzyl alcohol was reacted with trimethyl borate and NaH was used for the initial

deprotonation of the hydroxyl group. n-BuLi was then used to cause debromination and the dianion generated was treated with triisopropylborate to produce the intermediate boronate. Acidic hydrolysis of the boronate ester with 10% sulfuric acid and purification resulted in the benzoboroxole (Scheme 4). They used the product for a variety of cross-coupling reactions using Suzuki-Miyaura conditions. Mereddy *et al.* group succeeded in producing multigram quantities with a highly scalable protocol that allowed for a more cost effective approach. [34]

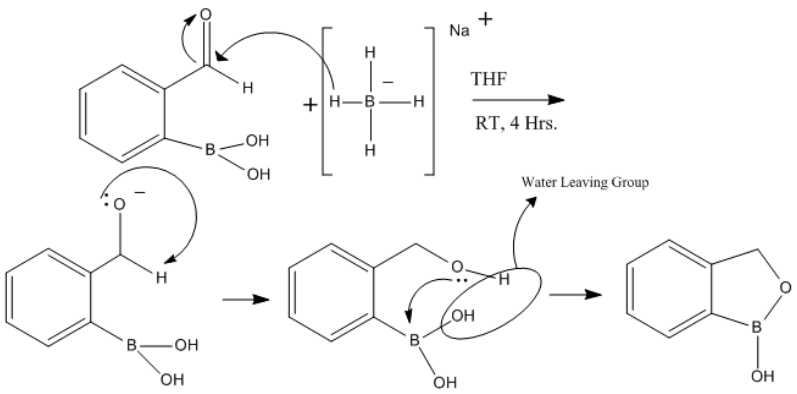


Scheme 4. Schematic of preparation and Suzuki cross-coupling of benzoboroxole. [34]

RESULTS AND DISCUSSION

I. Reduction of 2-Formyl Boronaldehyde with Sodium Borohydride

To study and optimize nitration of benzoboroxole large amounts were needed. To this end, a newer synthesis was employed which was recently developed in the Mereddy group instead of the NaH/BuLi reaction of bromobenzyl alcohols discussed earlier.



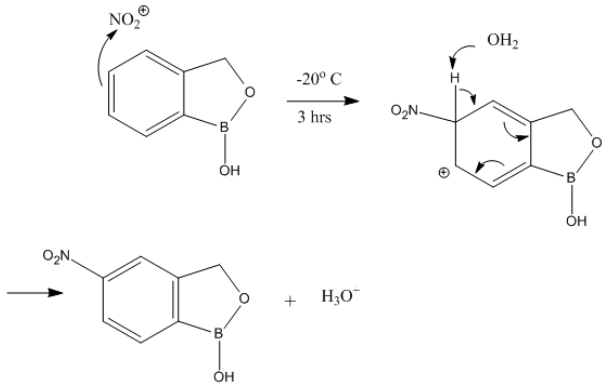
Scheme 5. Mechanism of sodium borohydride reduction of 2-formyl boronaldehyde.

Sodium borohydride is a salt that is made up of a sodium cation (Na^+) and a borohydride anion (BH_4^-) and is selective in the reduction of aldehydes producing primary alcohols. Due to boron's low electronegativity compared to carbon and hydrogen atoms having a similar electronegative status as carbon, the B-H bond is polarized giving the H atom a more negative charge and boron a more positive charge with the B-H bond serving as a source of hydride ion ($:H^-$). [37] As the mechanism in Scheme 5 shows, this allows the nucleophilic hydride ion to attack the carbonyl carbon which is followed by the protonation of the carbonyl oxygen. The more electronegative

oxygen will then attack the less electronegative boron, forming a ring, followed by the evacuation of a H_2O leaving group producing the benzoboroxole.

The ^1H NMR spectrum had an integration of 7 with the four aromatic hydrogen peaks located in the aromatic region of the spectrum starting at 7.33 ppm and ending at 7.75 ppm respectively. The methylene group hydrogen atoms had a peak at 4.99 and the alcohol hydrogen peak was positioned at 9.18 ppm. The ^{13}C NMR spectrum had 6 spectral lines accounting for all carbons with the exception of C-B-OH which would predictably have no signal or there may be two signals together. Both the ^1H NMR and ^{13}C NMR compared to reference NMRs verified the benzoboroxole structure.

II. Electrophilic Substitution (Nitration) of Benzoboroxole with 16 M Nitric Acid



Scheme 6. Mechanism of nitration of benzoboroxole with 16 M fuming nitric acid. NO_2^+ is produced from the dehydration of HNO_3^-.

A phenyl ring, like a simple benzene ring, has clouds of π electrons above and below its sigma bond framework and although the π electrons are in a stable aromatic system, they are available to attack a strong electrophile (E^+) to give a carbocation. A

sigma complex (arenium ion) is formed with a sp^3-hybrid carbon atom that interrupts the ring of *p* orbitals producing a non-aromatic system but results in a resonance-stablized carbocation. The loss of aromaticity contributes to the endothermic nature of the first step and the sigma complex regains aromaticity by the loss of the proton on the tetrahedral carbon atom, leading to the substitution product. [37]

Nitration of the aromatic ring is typically done by reacting the compound with a mixture of nitric acid and sulfuric acid with sulfuric acid acting as a catalyst and reacting with the nitric acid to form the strong electrophile, the nitronium ion (NO_2^+), which is the active reagent in aromatic nitration. [37] This method was initially performed to nitrate the benzoboroxole but the reaction length was timely and the yield was small, approximately 34%. Lennarz and Snyder (1959) performed the nitration using 16 M fuming nitric acid (90% HNO_3) at a temperature of -40^o C with an 84% yield. [25] Because nitric acid has both acidic and basic properties, under these conditions it is able to undergo an autoprotolysis reaction and form its own nitronium ions (Scheme 7). In autoprotolysis, a proton is transferred between two identical molecules, one of which acts as a Brønsted acid, releasing a proton which is accepted by the other molecule acting as a Brønsted base. [37] Due to this phenomenon and the high concentration of nitric acid the absence of sulfuric acid from the reaction is possible. Lennarz and Snyder's procedure was performed with minor adjustments in favor of the sulfuric acid mixture (Scheme 6).

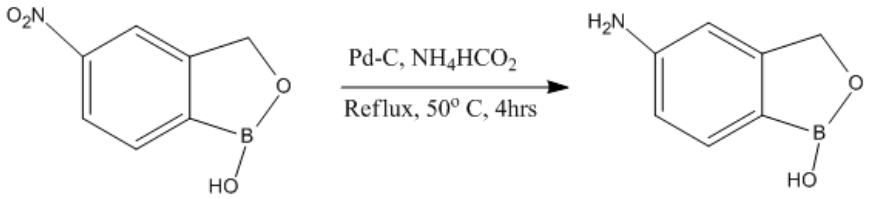
$$2HNO_3 \rightleftharpoons NO_2^+ + NO_3^- + H_2O$$

Scheme 7. Autoprotolysis of nitric acid. [37]

The nitro group is found in para position to the boron atom. [37] The mechanism in Scheme 6 shows the nitronium ion reacting with the aromatic ring in the meta position forming a intermediate sigma complex then losing a proton to form 5-nitroboronophthalide as reported in the literature.

To verify the structure of 5-nitroboronophthalide, a ^1H NMR was performed showing a singlet at 9.61 ppm for the B-OH, a aromatic region further up-field than the benzoboroxole aromatic region (7.76 – 8.60 ppm) due to the nitro group's deshielding resulting from its strong electronegativity. At 8.60 ppm, the peak was a singlet and the two other aromatic peaks down-field were both doublets. This is significant not only to verify the structure, but to verify in the upcoming reaction that the nitro group was reduced to an amine. The CH_2 group was present with a singlet at 5.18.

III. Reduction of 5-Nitroboronophthalide to 5-Aminoboronphthalide



Scheme 8. Reduction reaction of 5-nitroboronphthalide to 5-aminoboronphthalide.

Aromatic nitro groups are easily reduced to primary amino groups by using a catalytic hydrogenation and acidic reduction by an active metal (Scheme 8). A common reason for performing this reduction is to make substituted anilines. This type of reduction was developed by the dye industry which uses aniline derivatives for azo

coupling reactions to make aniline dyes, but now has become a staple, base reaction in boron chemistry applications as well. [37] For instance, in a recent study, substituted amino groups have shown in vitro growth inhibition IC_{50} values as low as 0.02 μg/mL and in vivo efficacy in acute murine infection models against *Tryapnosoma brucei* (African sleeping sickness). [19]

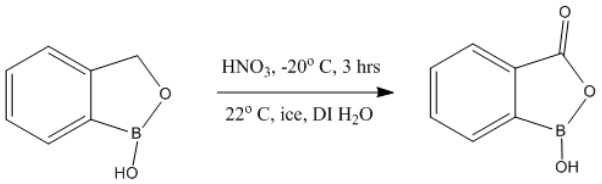
This particular reaction was very sensitive to conditions and temperatures above 50^{o} C for more than 4 hours could lead to decomposition of the compound. In addition, attempts to purify the compound via column chromatography or recrystallization were unsuccessful, so gentler procedures during the work-up process are needed to maintain the integrity of the compound.

An interesting result of the reduction of NO_2 to NH_2 as it pertains to the benzoboroxole is that the 5-aminoboronphthalide shows photoluminescence of yellow while excited in the ultraviolet region. Fluorescent boron compound synthesis is a growing field of study in technology and medicine and molecules like the 5-aminoboronphthalide and its derivatives have much potential for practical use.

To verify the structure of 5-aminonitroboronophthalide, a ^{1}H NMR was performed and 6 peaks were evident. The B-OH singlet was located at 8.87 ppm and the aromatic peaks were positioned more up-field than the nitro NMR due to the higher shielding and lower electronegativity of the NH_2 group. The aromatic singlet that represented the adjacent hydrogen to the nitro group in the nitration reaction ^{1}H NMR that was downfield from the other two aromatic doublets (8.60 ppm) shifted up-field between the aromatic doublets at 6.90 ppm which is characteristic of a successful

reduction. The NH_2 singlet peak presented at 5.01 ppm and the CH_2 peak at 4.81 ppm respectively.

IV. Oxidation of Benzoboroxole



Scheme 9. Oxidation of benzoboroxole.

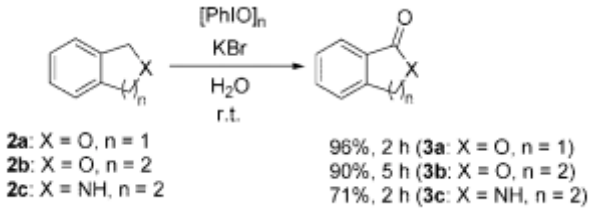
No literature was found that showed that the oxidation of the CH_2 group on the benzoboroxole forming the product in Scheme 9. Benin *et al.* reported oxidation of methyls to carboxylic acids in the presence of boronic acids but no closed ring structure with benzoboroxole was used. The oxidized product was synthesized by running the nitration temperature reaction at higher temperature, adjusting it from -20° C to 22° C after the 3 hour nitration reaction time had elapsed and before ice and water were added in the nitration reaction (Scheme 6). In this reaction, it would appear that the nitration and the oxidation were competing with one another with a benzylic oxidation being the victor.

One feasible explanation of why the oxidation took place in lieu of the nitration is because the benzoboroxole in this particular reaction has an activated benzyl group. The allylic position adjacent to C=C in a benzene ring often shows enhanced reactivity due to

the proximity of the adjacent π system. This type of arrangement is called a benzyl group, consisting of a benzene ring and a methylene (-CH_2-) group. The π system of a benzene ring can stabilize an adjacent carbocation by donating electron density through induction. The benzylic cations are readily formed as intermediates during chemical reactions due to their stability and susceptible to oxidation. These reactions are typically done with $Cr_2O_7^{2-}$ or MnO_4^- in H_2SO_4 and higher temperature. [37]

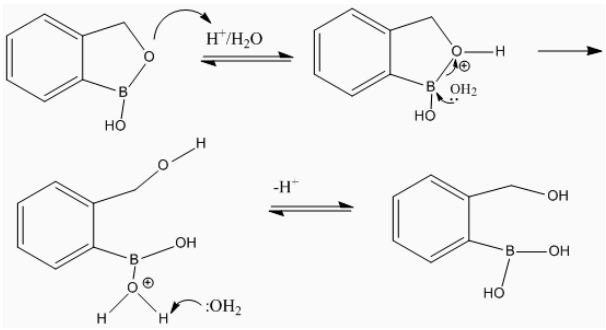
It was demonstrated by Bahulayan *et al.* in 2002 that when using bentonite clay as a catalyst with dilute HNO_3 that they were able to perform a benzylic oxidation under reflux conditions when the benzyl groups were present. Using the same conditions (sans reflux) they were able to perform nitrations when there were no benzyl groups present. [40] Furthermore, in cases of hypervalent iodine, a group in Osaka, Japan (2008) produced a benzylic C-H oxidation in compounds with activating groups such as other aromatic substituents by reacting $[PhIO]_n$ and KBr in water at room temperature. Their goal was to establish a more chemically green process by developing oxidation methods that can be done in aqueous conditions as opposed to older methods that are more toxic to the environment. They were able to produce good yields as a result of the selective oxidation at the benzyl positions adjacent to the heteroatoms (Scheme 10). They also noted that organoiodine (III) compounds were not very reactive in water and the reactions with $[PHIO]_n$ in the absence of KBr did not result in the formation of the oxidation products and applying the reaction using other compounds with no activated benzyl groups obtained very low yields (less than 20%). [39] Both literature examples thus verify

further that activated benzyl groups can influence whether a nitration or oxidation will take precedence.



Scheme 10. Benzylic oxidation of aromatic compounds having activated benzyl groups. [39]

Our assessment of the reaction mechanism involves the hydrolysis and ring-opening of the benzoboroxole to produce a free benzyl alcohol which then can be oxidized. [37] Similarly, the benzoboroxole ring structure could have been opened due to acid-catalyzation by water and would have resulted in an activated benzyl diol susceptible to oxidation (Scheme 11).



Scheme 11. Mechanism for acid-catalyzed opening of the benzoboroxole ring.

Considering that the benzoboroxole in this reaction has an activating group for both the nitration and a group susceptible to oxidation, another factor, temperature, could have been a factor in producing the product. It is not clear of the importance of a

temperature adjustment as to whether or not an oxidation or nitration results. In 1958, P.M. Kochergin *et al.* published a paper reporting that *p*-nitrobenzaldehyde was obtained through nitration of benzylalcohol at -5 to 5° C and the conversion of *p*-nitrobenzyl nitrate to *p*-nitrobenzaldehyde was carried out at 10-15° C. [41] Nitrates form with alcohols and can oxidize alcohols. In addition, nitrogen dioxide is produced, another strong oxidizing agent (Scheme 11). [37]

$$4HNO_3 \rightarrow 2H_2O + 4NO_2 + O_2$$

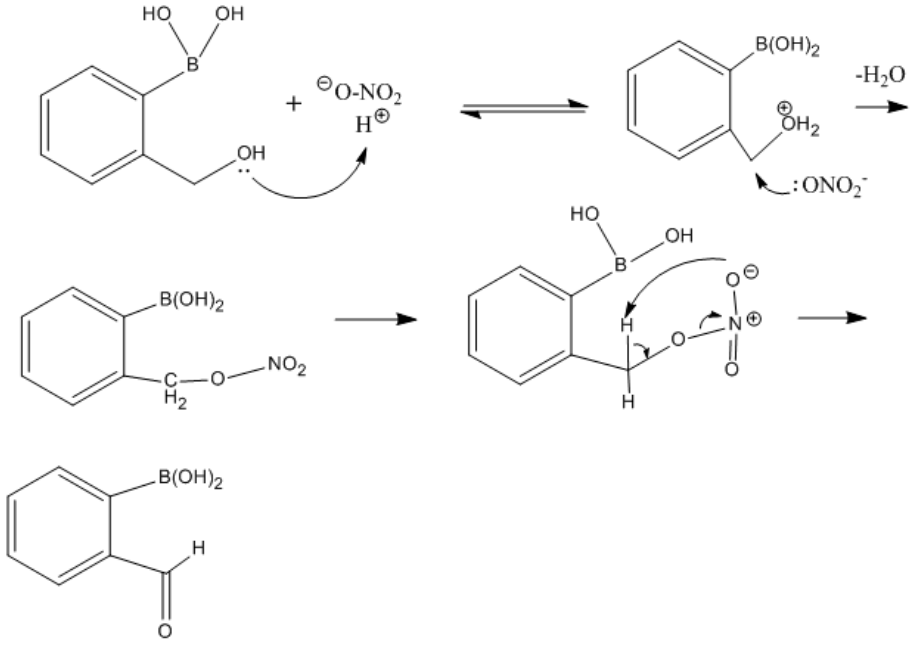
Scheme 12. Decomposition of nitric acid forming nitrogen dioxide and dioxygen. [37]

It is interesting to note that when the nitrogen dioxide is dissolved in the acid it colors the solution and compound yellow, which was the color that was present during the nitration reaction maintained at -40^{o} C throughout. At the higher temperature (-20^{o} C), and when exposed to air, the reaction mixture turned a reddish-brown and gave off reddish-brown vapors of NO_2, which is exactly what was reported by the literature. [37]

Obtaining the activation energies (E_a) and entropy (ΔS) values of both reactions would be useful tools to help compare the propensity of each product to form, but could not be obtained due to time restraints.

Assuming that the benzoboroxole was hydrolyzed by H_2O giving a primary alcohol (Scheme 12) and the increase in heat caused a decomposition of the HNO_3, the nitrate ion could then initiate an oxidation reaction resulting in the elimination of the nitrate ester. This would initially produce an aldehyde and reduce the nitrogen from +5

to +3 and oxidize the carbon from -1 to +1. This constitutes the oxidation of the alcohol to the aldehyde.



Scheme 13. Mechanism for the oxidation of benzyl alcohol.

The oxidation with nitric acid is similar to the use of the chromic acid reagent and potassium permanganate to oxidize primary alcohols. Since these oxidizing agents are strong enough to oxidize primary alcohols they can also oxidize aldehydes. Aldehydes are typically difficult to produce under these conditions and the reactions generally oxidize all the way to a carboxylic acid as shown in Scheme 13. [37]

Another strategy for oxidation, assuming nitration did not take place and knowing the activated benzyl group is present, is that the benzoboroxole ring remained intact. The influence of the higher temperature sped up the oxidation while the nitration, which requires cooler temperatures, was comparatively much slower and was not able to form.

Without the benefit of further studies, this strategy is merely hypothetical but should be considered in any future research.

A third option for the oxidation of the benzoboroxole takes into account that hydrolysis was not required and nitration had taken place. A feasible mechanism is that with a single electron-transfer, the replacement of the nitro group by hydrogen could have occurred due to the presence of NO_2 radicals produced by the reaction conditions. In 1978, Kornblum *et al.* discussed how it was not until 1954 that the first useful synthesis of tertiary nitroparaffins was described. Since that time, a number of other reactions which also gave pure aliphatic and alicyclic tertiary nitro compounds have been found. These reactions are also capable of providing tertiary nitro compounds in which other functional groups are present. Given past research, Kornblum reported a new reaction which was the replacement of a nitro group by hydrogen using electron-transfer reactions of aliphatic nitro compounds based on the work of Boyle and Bunnett. [42, 43] The reaction mechanism for this electron-transfer reaction is complex and the method would need more study for further consideration.

To verify the structure of *oxo*-benzoboroxole, a ^1H NMR was recorded. The aromatic peaks were doublets at 8.71, 8.60, 8.38 and 8.24 ppm respectively. The peaks were located slightly further downfield than the peaks of the nitrated benzoboroxole due to the deshielding effect of the carbonyl. The OH singlet peak was located at 7.51 ppm. There were no further peaks. The CH_2 peak that was present in the nitrated benzoboroxole, was clearly missing in the oxidized compound indicating that the oxidation had occurred.

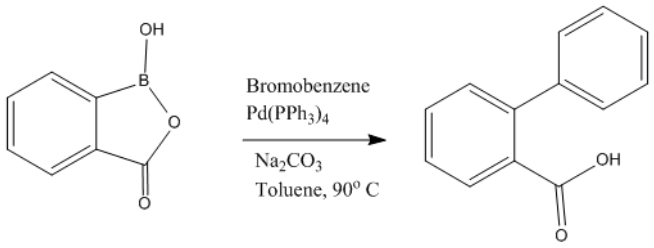
The ^{13}C NMR showed significant peaks at 167.43, 161.36, 149.30, 137.64, 131.53, 129.83 and 120.39 ppm. The highest peaks belong to the ester carbon (167.43 ppm) and the carbon closest to the boron (161.36 ppm). The aromatic peaks range from 149.30 to 120.39 ppm which is typical of aromatic peaks with the deshielding influence of the oxidation.

The GC/MS demonstrated a molecular ion peak (M^+) and a parent peak of 149 m/z with a retention time of 22.80 minutes. The molecular weight of the oxo-benzoboroxole is calculated to be 148 m/z, so the GC/MS further verified the structure. It is interesting to note that a dimer peak was also present at 279 m/z (149 (x2) minus H_2O). Zhdankin *et al.* as noted earlier, were able to form dimers with boron compounds thus further demonstrating the strong bonding to oxygen characteristic of the benzoboroxole molecule.

The IR spectrum had two significant functional group peaks at 3220.36 and 1718.26 cm^{-1}. The broad peak at 3220.36 cm^{-1} indicated the OH group which is typical of this type of functional group. The α, β-unsaturated ester has a functional group range of 1730 to 1715 cm^{-1}. The strong peak at 1718.26 cm^{-1} is within this range and verifies the existence of an ester indicating the predicted closed-ring form of the molecule.

An ^{11}B NMR was performed and a strong, sharp peak at 18.93 ppm was on the spectrum as the oxo-benzoboroxole. The standard BF_3 peak was at 0 ppm and a very small peak at about 32 ppm was evident that the benzoboroxole starting material was still present in small amounts.

V. Suzuki Coupling Reaction of Oxo-Benzoboroxole



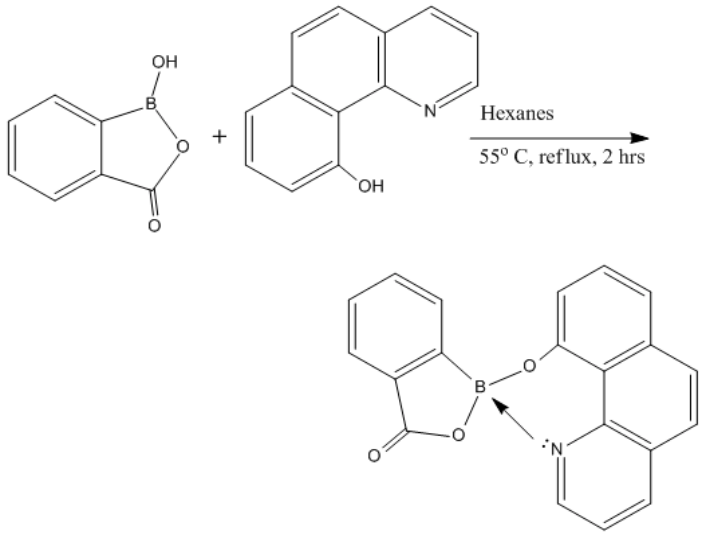
Scheme 14. Schematic of Suzuki coupling reaction of oxo-benzoboroxole.

As discussed earlier, the Suzuki coupling reaction (Scheme 14) is a palladium-catalyzed cross coupling between organoboronic acid and halides. Bromobenzene was reacted with oxo-benzoboroxole using the same experimental conditions as reported by Mereddy *et al*. [34] The reaction was accomplished as an exercise to demonstrate the previously observed capabilities of the benzoboroxole compounds to be used in Suzuki coupling reactions.

The ^{1}H NMR spectrum showed two complicated aromatic regions. The first region ranged from 8.07 to 7.97 ppm and the second region ranged from 7.65 to 7.55 ppm. In addition, a singlet was found at 2.09.

VI. Reaction of Oxo-Benzoboroxole with 10-Hydroxybenzo[h]quinoline

10-Hydroxybenzo[h]quinoline is a Lewis base and chelating agent. When reacted with oxo-benzoboroxole, because it has both oxygen and nitrogen, it can form an ester and nitrogen adduct (Scheme 15). This reaction was performed multiple times. This was the third attempt at reacting oxo-benzoboroxole with a hydroxyl quinoline derivative.



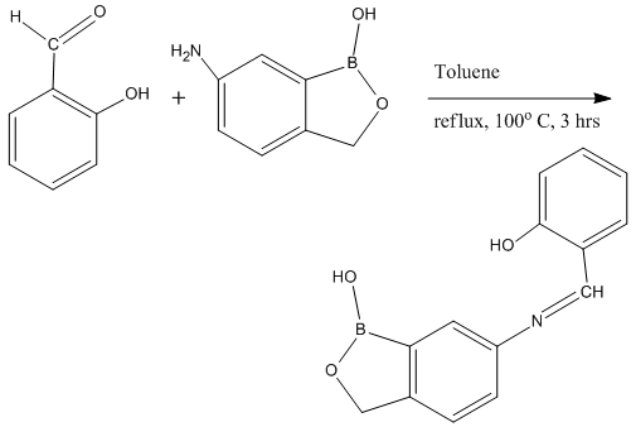
Scheme 15. Reaction of 10-hydroxybenzo[h]quinoline with oxo-benzoboroxole.

The reaction product was tested using GC/MS. The spectrum had three significant retention times. The GC/MS results are inconclusive at this point and may hint that a small amount of product was formed.

^{1}H NMR results showed a complex aromatic region and other impurity peaks upfield and the ^{13}C spectrum had 12 carbon peaks ranging from 113.83 ppm to 159.16 ppm. Both spectra were inconclusive and could not be used to verify the predicted structure. Due to time constraints further reaction refinement and analysis could not be accomplished.

VII. Schiff Base Reaction of Salicylaldehyde and 5-Aminoboronphthalide

Schiff bases are important intermediates for the synthesis of various bioactive compounds and are typically formed by the condensation of a primary amine and aldehyde or ketone (Scheme 16). They have been reported to demonstrate a variety of biological activities including antibacterial, antifungal, and anti-cancer activities. [44]



Scheme 16. Schiff base reaction of salicylaldehyde and 5-aminoboronphthalide.

This reaction was attempted, but failed to produce successful results. Typically, the boron forms an adduct accepting the electron pair from the nitrogen changing the coordination from trigonal planar to tetrahedral. The lack of success in completing this reaction could potentially come from the proximity of the groups on both reactants which prevented the coordination of the boron to the nitrogen. In addition, upon work-up of the reaction, 5-aminoboronphthalide appears to be sensitive to changing conditions causing decomposition. The product that resulted from this reaction fluoresced yellow when under UV-Vis lighting could have been due to the fluorescent nature of the benzoboroxole. Further consideration and refinement is necessary to complete a Schiff base reaction with this type of primary amine.

EXPERIMENTAL

I. Materials

2-Formylphenylboronic acid was purchased from AK Scientific, Inc. All other reactants were of reagent grade, purchased from Acros Organics, Alfa Aesar and Sigma Aldrich, and used without further purification. All solvents were used without further drying or purification and were of ACS grade purchased from Fisher Scientific.

II. Instruments

(i) Nuclear Magnetic Spectroscopy (NMR)

NMR spectra were produced using the Varian INOVA 500 MHz spectrophotometer. The instrument was maintained at 25^{o} C operating at 500 MHz for ^{1}H NMR, 160 MHz for ^{11}B NMR, and 126 MHz for ^{13}C NMR. Tetramethylsilane (TMS) was used at the internal standard for calibration. The deuterated solvent used for each respective spectrum is referenced to the appropriate literature peak shift. [35] Experimental spectra are contained in the appendix.

(ii) Mass Spectroscopy

Mass spectra were obtained with a Thermo Advantage Max® ion-trap instrument operating in the atmospheric pressure ionization mode (APCI-MS). Flow injections were performed with acetonitrile. The source temperature was 350 °C and the ion-transfer capillary was 170 °C.

Experimental spectra are contained in the appendix.

(iv) Infrared Spectroscopy

A KBr pellet was formed and IR was run on Perkin-Elmer FT-IR BX with routine mid-IR capabilities (4000 cm-1 to 400 cm-1) at standard room temperature for the detector.

Experimental spectra are contained in the appendix.

III. Experimental Procedure

(i) Preparation of Benzoboroxole

The synthesis of benzoboroxole was modified from the reported synthesis.[34] A sodium borohydride reduction was accomplished by reacting 2-formylphenyl boronaldehyde (3.00g, 20mmol) with sodium borohydride (0.757 g, 20mmol) in 40 ml of tetrahydrofuran and an ice bath for four hours. The resulting product was worked up by incrementally adding a total of 20 mL saturated ammonium chloride. The organic layer was separated from the aqueous layer by washing with ethyl acetate and a separatory funnel four times and poured into a flask with a molecular sieve. The ethyl acetate was then evaporated using a roto-vap apparatus and the product was placed in a desiccator to remove any excess moisture. The product was a white solid and the yield was 95%. The resulting thin layer chromatography (TLC) plate and NMR spectrum (^{1}H: 500 MHz) was consistent with reference spectrum and verified structure and purity.

^{1}H NMR (DMSO): δ (ppm) = 9.18 (s), 7.75 - 7.73 (d), 7.49 – 7.46 (t), 7.42 – 7.41 (d), 7.36 – 7.34 (t), 4.99 (s).

^{13}C NMR (DMSO): δ (ppm) = 161.32, 147.89, 126.33, 126.16, 123.77, 70.78.

(ii) Preparation of 5-Nitroboronophthalide

The synthesis of 5-nitroboronophthalide was performed consistent with the reported synthesis. [25] The benzoboroxole (1.92 g, 16.0 mmol) was added to 11.6 mL of fuming Nitric Acid (16M) maintained at a temperature of -40^{o} C. The addition was done portionwise and completed in about 20 minutes. The mixture was stirred at constant temperature of approximately -40^{o} C for 3 hours. Ice and water were added to the cold mixture (maintained at -40^{o} C) which then was stored in the refrigerator overnight. The pale, yellow, solid product was filtered out using vacuum filtration and water. The yield produced was approximately 46%. NMR spectrum (^{1}H: 500 MHz) verified compound's structure by being consistent with reference spectrum.

^{1}H NMR (DMSO): δ (ppm) = 9.61 (s), 8.60 (s), 8.38 (d), 7.76 (d), 5.18 (s).

(iii) Preparation of 5-Aminoboronphthalide

The synthesis of 5-aminoboronphthalide was modified from the reported synthesis. [38] 5-nitroboronphthalide (1.68 g, 9.38 mmol) was reacted with ammonium formate (2.36 g, 37.52 mmol) with Pd-C as a catalyst in 40 ml of THF. The reaction was refluxed and held at a constant temperature of 50^{o} C for 4 hours. The catalyst was filtered off using a methanol wash and the fluorescent yellow filtrate was collected. The solvents were evaporated off via a roto-vap

apparatus and a yellow/tan solid remained as the product. The yield was about 66% and the NMR spectrum (^{1}H: 500 MHz) verified compound's structure by being consistent with reference spectrum.

^{1}H NMR (DMSO): δ (ppm) = 8.87 (s), 7.01 (d), 6.90 (s), 6.73 (d), 5.01 (s), 4.81 (s).

(iv) Preparation of Oxidized Benzoboroxole.

The synthesis of oxidized benzoboroxole was a novel synthesis. The benzoboroxole (11.6 g, 98.3 mmol) was added to 70 mL of fuming Nitric Acid (16M) maintained at a temperature of -20^o C. The addition was done portion-wise and completed in about 20 minutes. The mixture was stirred at constant temperature of approximately -20^o C for 3 hours. The surrounding temperature was then allowed to warm to room temperature (22^o C) and ice and water were added to the reaction. The dark yellow mixture turned reddish-brown and reddish-brown gas was emitted. The mixture was immediately covered and placed in the freezer overnight. The compound crystallized into a bright, yellow solid and the remaining solution was the same yellow color. The solid was washed in a filter with deionized H_2O and dried leaving a yellow solid compound with a 52% yield. NMR spectrum (^{1}H, ^{13}C, ^{11}B: 500 MHz), GC/MS and IR are consistent with the compound's structure.

^{1}H NMR (DMSO): δ (ppm) = 8.71 (d), 8.60 (d), 8.38 (d), 8.24 (d), 7.51(s).

^{13}C NMR (DMSO): δ (ppm) = 167.43, 161.36, 149.30, 137.74, 131.53, 129.83, 120.39.

GC/MS (DMSO): Retention Time: 22.80 minutes, M^+/Parent Peak: 149 m/z, M^+ Peak (Dimer): 279 m/z.

IR (cm^{-1}): 3220.68, 1718.26, 1521.66, 1351.20, 1299.48, 1193.53, 1072.81, 784.56, 735.71.

^{11}B (ppm): 18.93, 0.00 (standard).

(v) Preparation of Suzuki Coupling of Oxo-Benzoboroxole

The Suzuki coupling reaction was performed consistent with the reported synthesis. [34] Bromobenzene (0.4 ml, 1 mmol) was reacted with oxo-benzoboroxole (0.074 g, 0.5 mmol) in 3.0 ml of toluene, 0.2 g of Na_2CO_3, 40 mg of $Pd(PPh_3)_4$ within an argon gas environment for 4 hours at 90^o C. The organic layer was separated from the aqueous layer by washing with water and ethyl ether using a separatory funnel four times and poured into a flask with a molecular sieve. The ethyl ether was then evaporated using a roto-vap apparatus and the product was placed in a desiccator to remove any excess moisture. The product was a brown solid and the yield was 65%. The resulting NMR spectrum (^{1}H: 500 MHz) and GC/MS was consistent with the predicted product.

^{1}H NMR (DMSO): δ (ppm) = 8.07 – 7.97 (complex aromatic region), 7.64 – 7.56 (complex aromatic region), 2.09 (s).

(vi) Preparation of 10-Hydroxybenzo[h]quinoline with Oxo-Benzoboroxole

The oxo-benzoboroxole (.535 g, 3.61 mmol) and 10-hydroxybenzo[h]quinoline (.710 g, 3.61 mmol) were added to 30 mL dry (molecular sieve) hexanes. The reaction was refluxed and maintained at a temperature of 55^{o} C for 2 hours. The reaction was cooled slowly at room temperature and then place in the freezer for 30 minutes. Dark orange needle-like crystals formed and fluoresced orange under UV-Vis lighting. The solvent was poured off leaving a 75% yield. NMR spectrum (^{1}H, ^{13}C: 500 MHz) and GC/MS were inconclusive.

(vii) Preparation of Schiff Base Reaction of Salicylaldehyde and 5-Aminoboronphthalide

The 5-aminoboronphthalide (1.33 g, 9.00 mmol) and salicylaldehyde (.752 ml, 9.00 mmol) were added to 30 mL toluene. The reaction was refluxed and then maintained at a temperature of 100^{o} C for 3 hours. The dark orange product settled at the bottom of the flask and fluoresced orange under UV-Vis lighting. The solvent was removed in vacuo leaving an orange solid compound with a 70% yield. An unsuccessful attempt was tried to recrystallize the product using acetone. Clean NMR spectrum (^{1}H, ^{13}C: 500 MHz) and GC/MS were not able to be obtained. Due to the sensitive decomposition nature of the 5-aminoboronphthalide, refinement of reaction conditions and experimental handling is recommended for further analysis.

CONCLUSION

The synthesis of benzoboroxoles with various reactants was performed and these compounds were characterized to further the study of boron compounds in medicine, technology and other groundbreaking applications. Results of the reactions varied.

The synthesis of benzoboroxole was successful with a reduction of 2-formylphenyl boronic acid using sodium borohydride. It is a straightforward, one-pot reaction that produces high yields and mass production potential perfected by Mereddy *et al.* No further improvements are suggested.

The nitration of benzoboroxole was successful and is more efficient and simple using 16 M fuming nitric acid as opposed to the nitric acid/sulfuric acid combination. This reaction works well with good yields as long as the temperature is well controlled and the addition of benzoboroxole contains little or no impurity.

The reduction of 5-nitroboronophthalide to 5-aminoboronphthalide was successful and special care should be taken in experimental condition deviations. The amino compound is sensitive to decomposition via thermal and work-up and purification techniques. This compound gives entrance to a new class of compounds. Derivates of amino-boron compounds have shown to be very important in medicinal studies.

The novel synthesis of oxo-benzoboroxole was successful by changing the temperature conditions slightly from the nitration reaction. Other novel studies

that use related compounds with open-ring structures have been identified and further research should be attempted with oxo-benzoboroxole. In addition, the chemical and reactive differences should be analyzed between benzoboroxole and oxo-benzoboroxole for a deeper understanding of the potential of both compounds.

A Suzuki coupling reaction was accomplished using oxo-benzoboroxole with inconclusive results. In addition, the 10-hydroxybenzo[h]quinoline reaction was also unsuccessful. Both reactions were attempted several times using various conditions. These reaction types were previously performed successfully using benzoboroxole. Oxo-benzoboroxole reactions may need further refinement and analysis to successfully perform these known reactions along with the detailed comparison of chemical properties with benzoboroxole.

The Schiff base reaction with 5-aminoboronphthalide and salicylaldehyde was not successful and resulted in inconclusive results. This could be due to the lack of boron forming an adduct with nitrogen because the bonding proximity of both elements on the compounds were not ideal.

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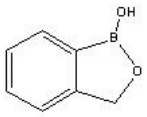
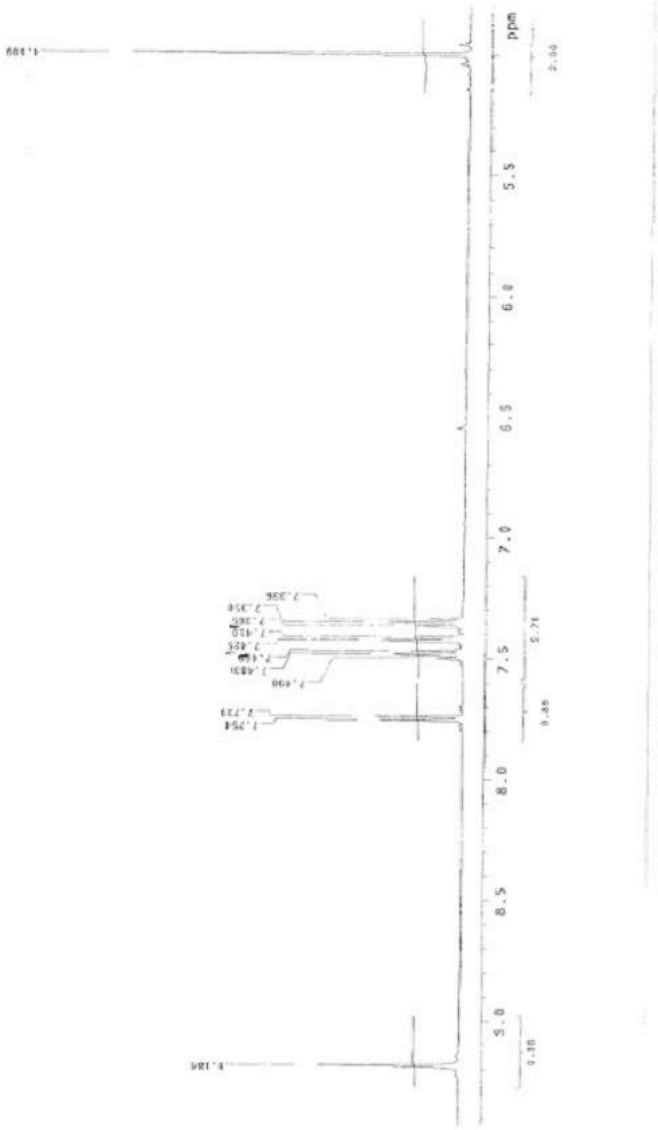
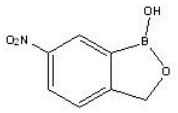
APPENDIX I

^{1}H NMR SPECTRA

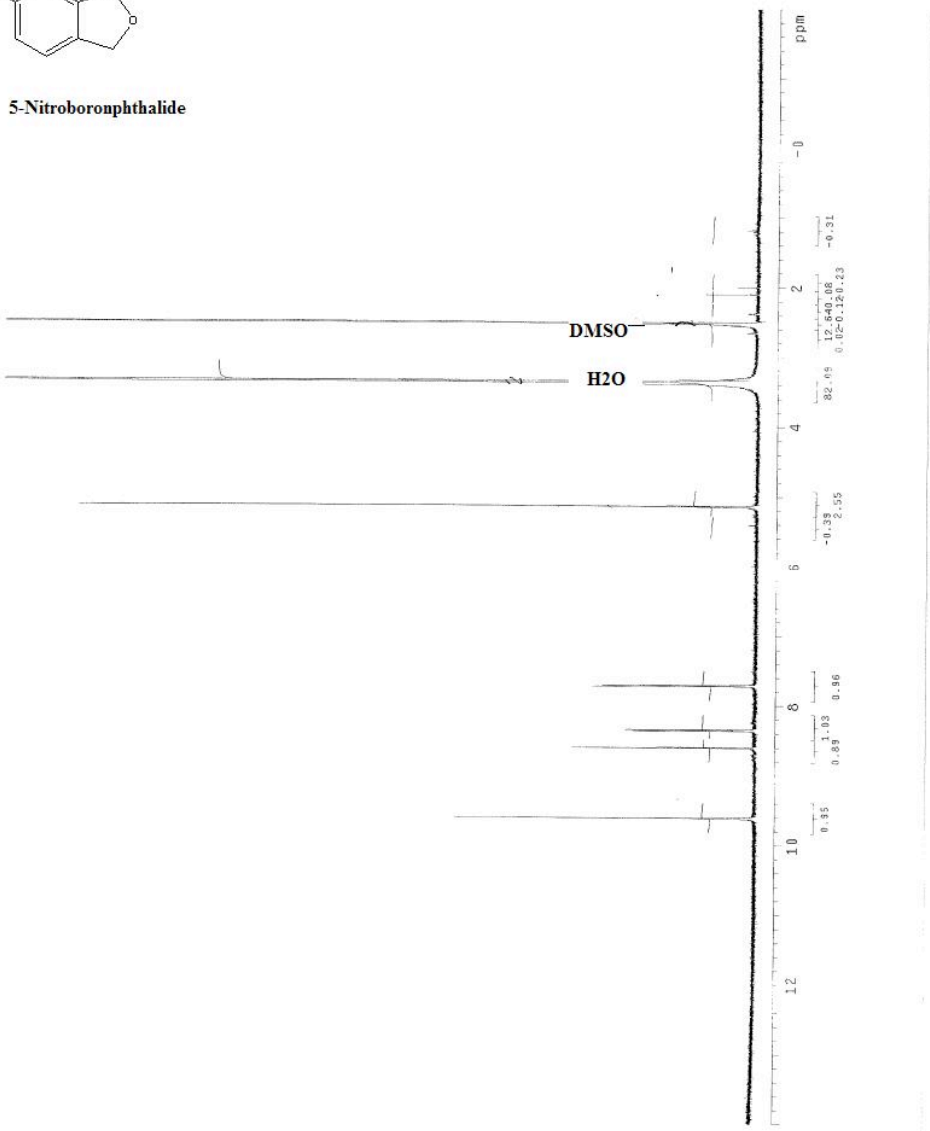


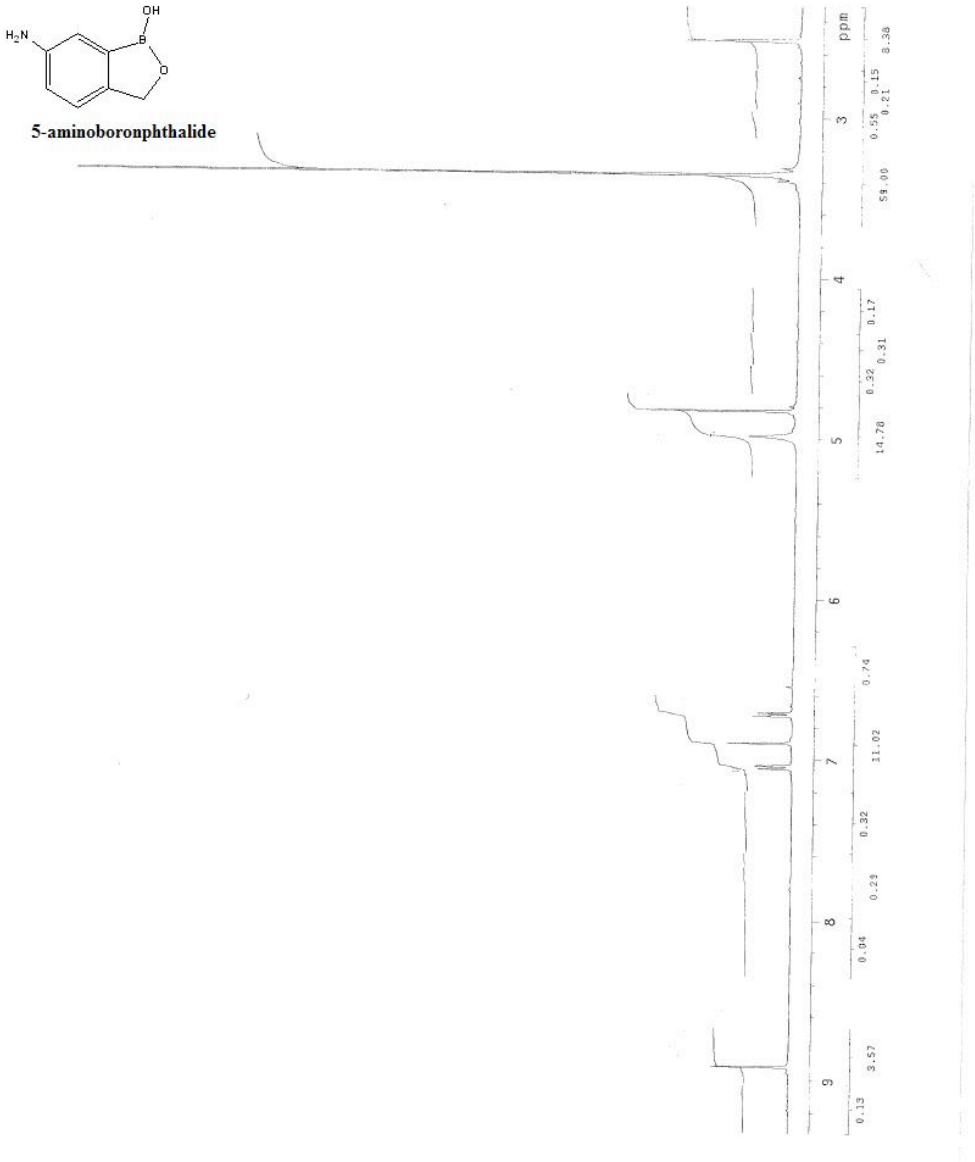
Benzoboroxle





5-Nitroboronphthalide

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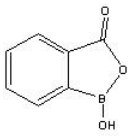
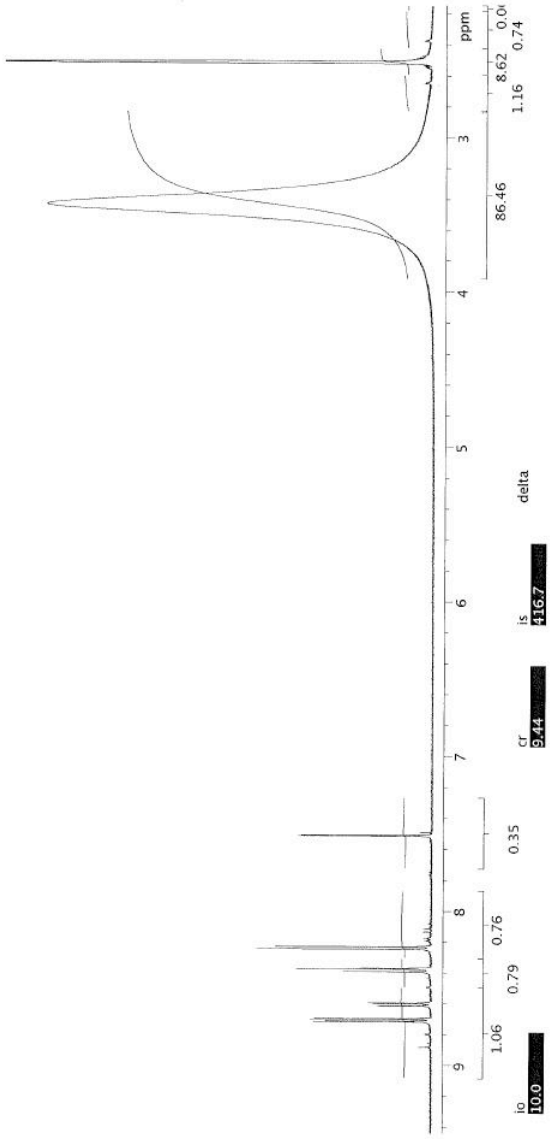
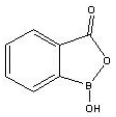
B
O
5-aminoboronphthalide
ppm

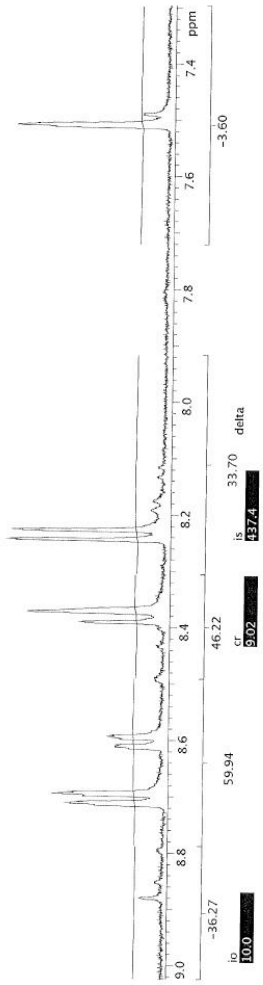


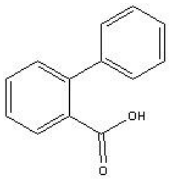
Oxo-Benzoboroxle



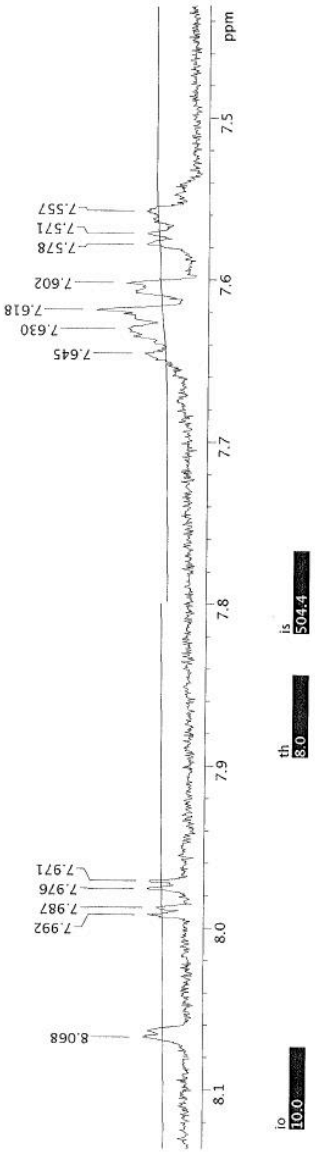


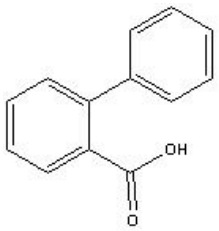
Aromatic Region of Oxo-Benzoboroxle



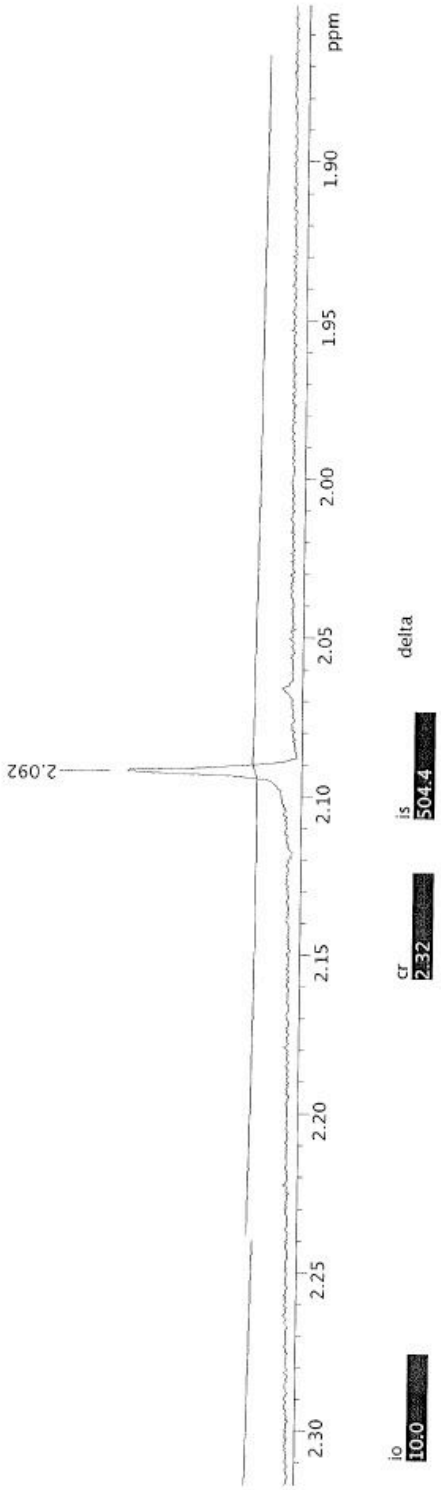


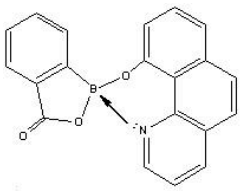
Suzuki Coupling of Oxo-Benzoboroxle





Suzuki Coupling of Oxo-Benzoboroxle





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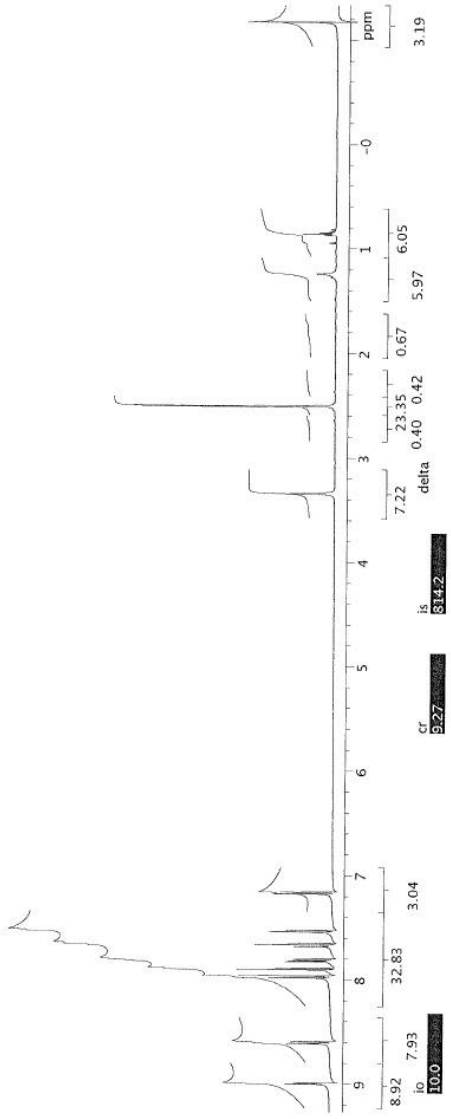

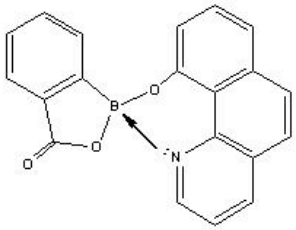

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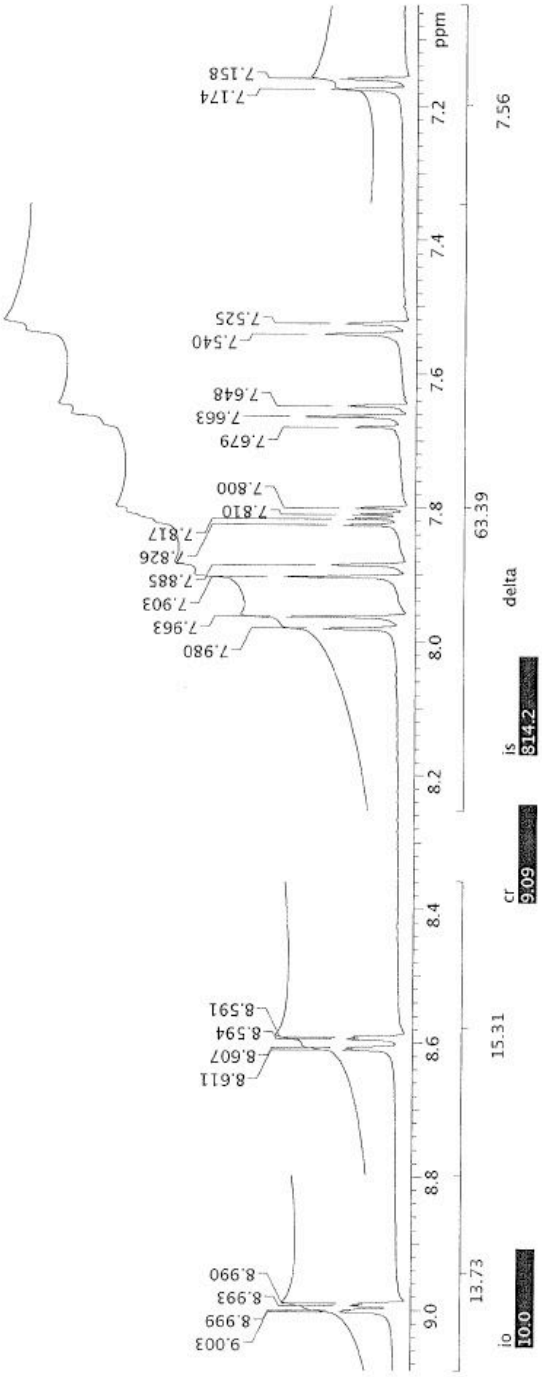
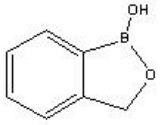
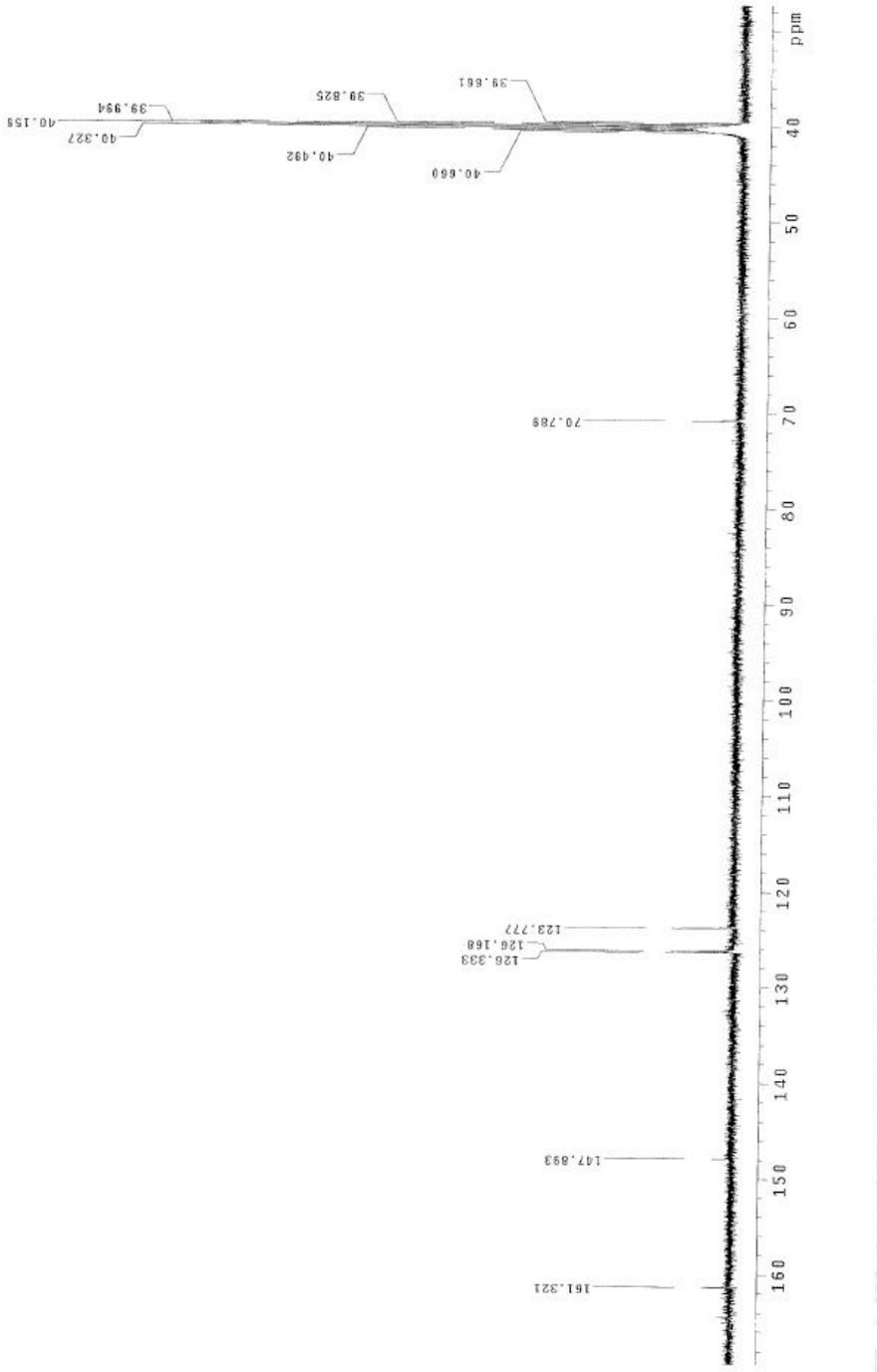


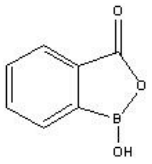
APPENDIX II

^{13}C NMR SPECTRA

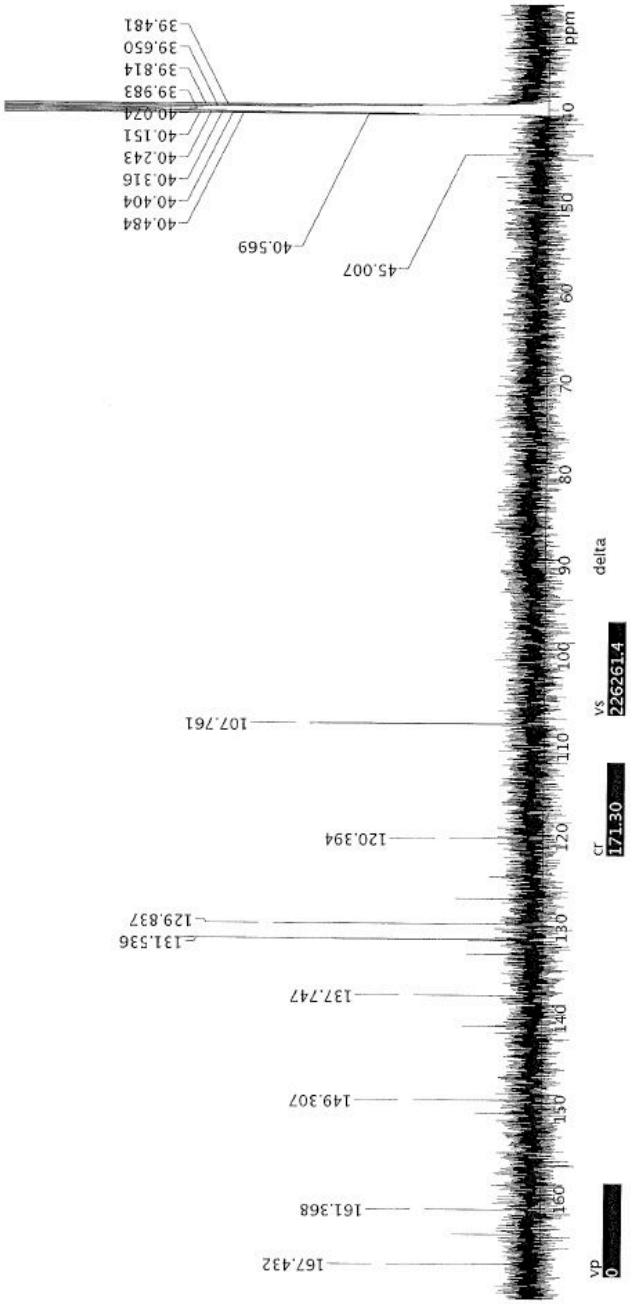


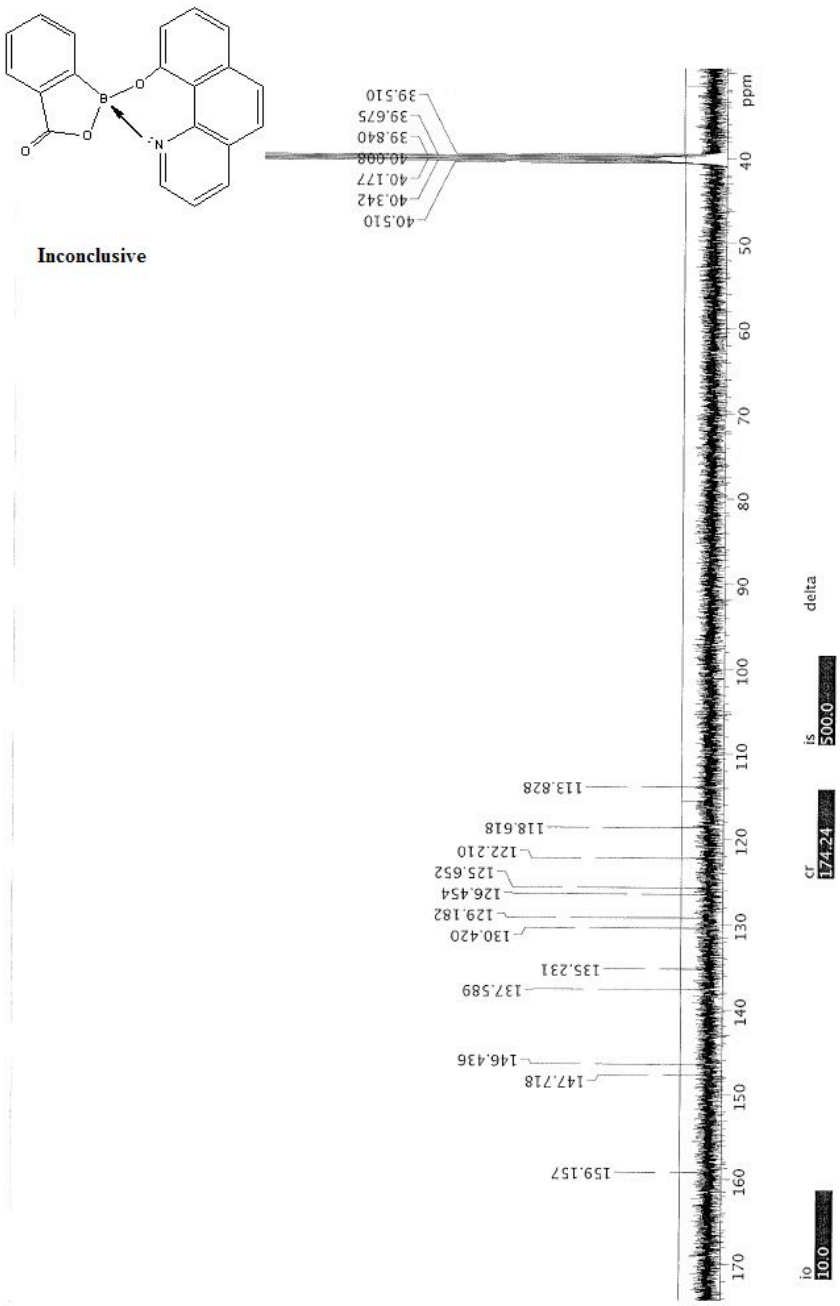
Benzoboroxle





Oxo-Benzoboroxle

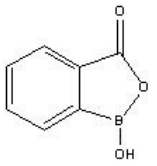




Inconclusive

APPENDIX III

GC/MS SPECTRA



Oxo-Benzoboroxle

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Instrument : GC/MS Ins
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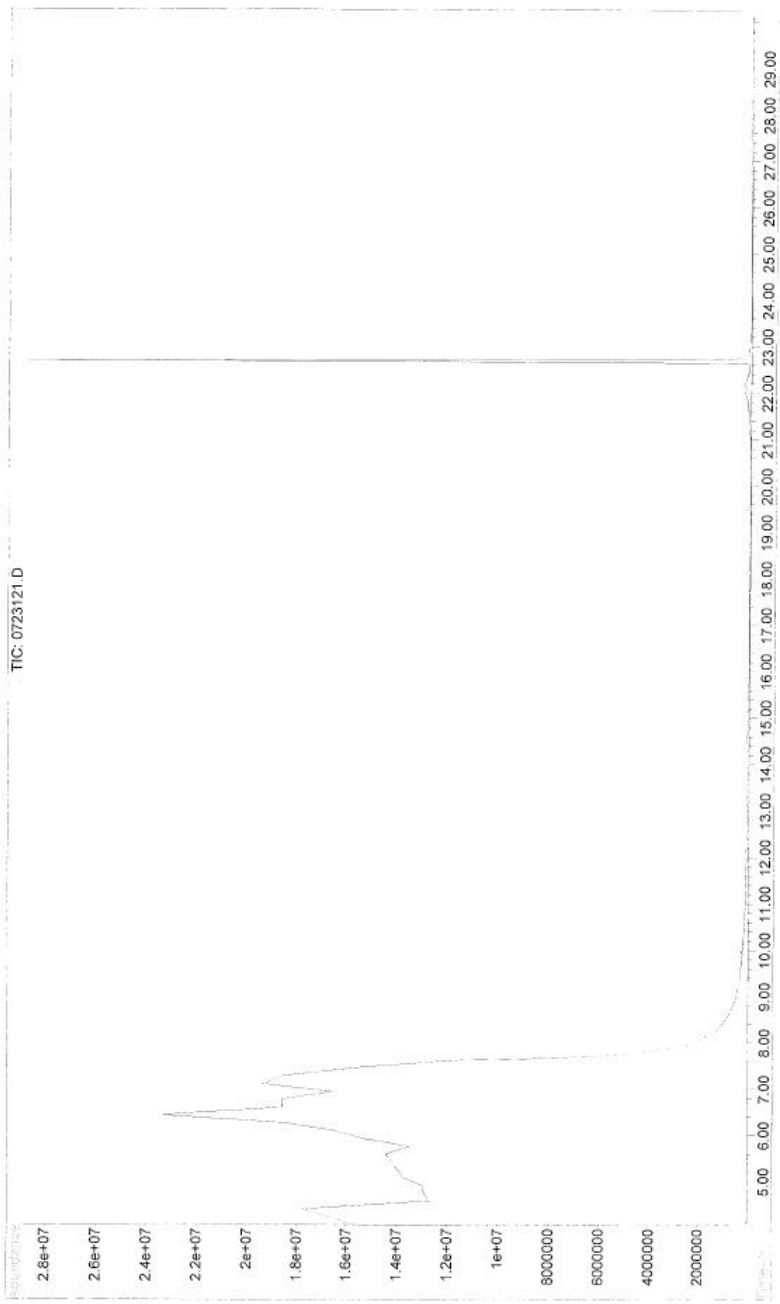

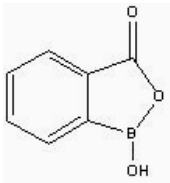

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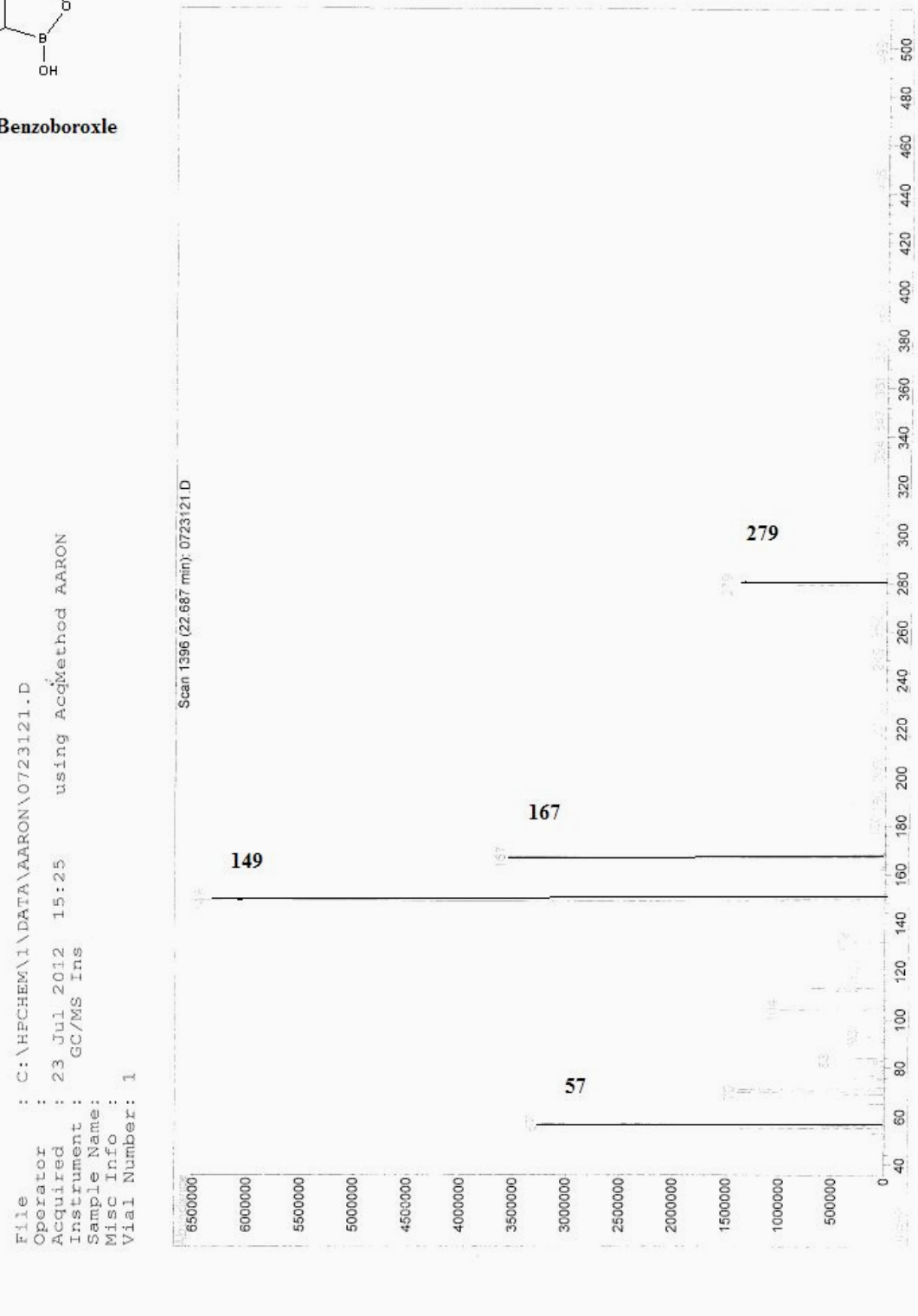
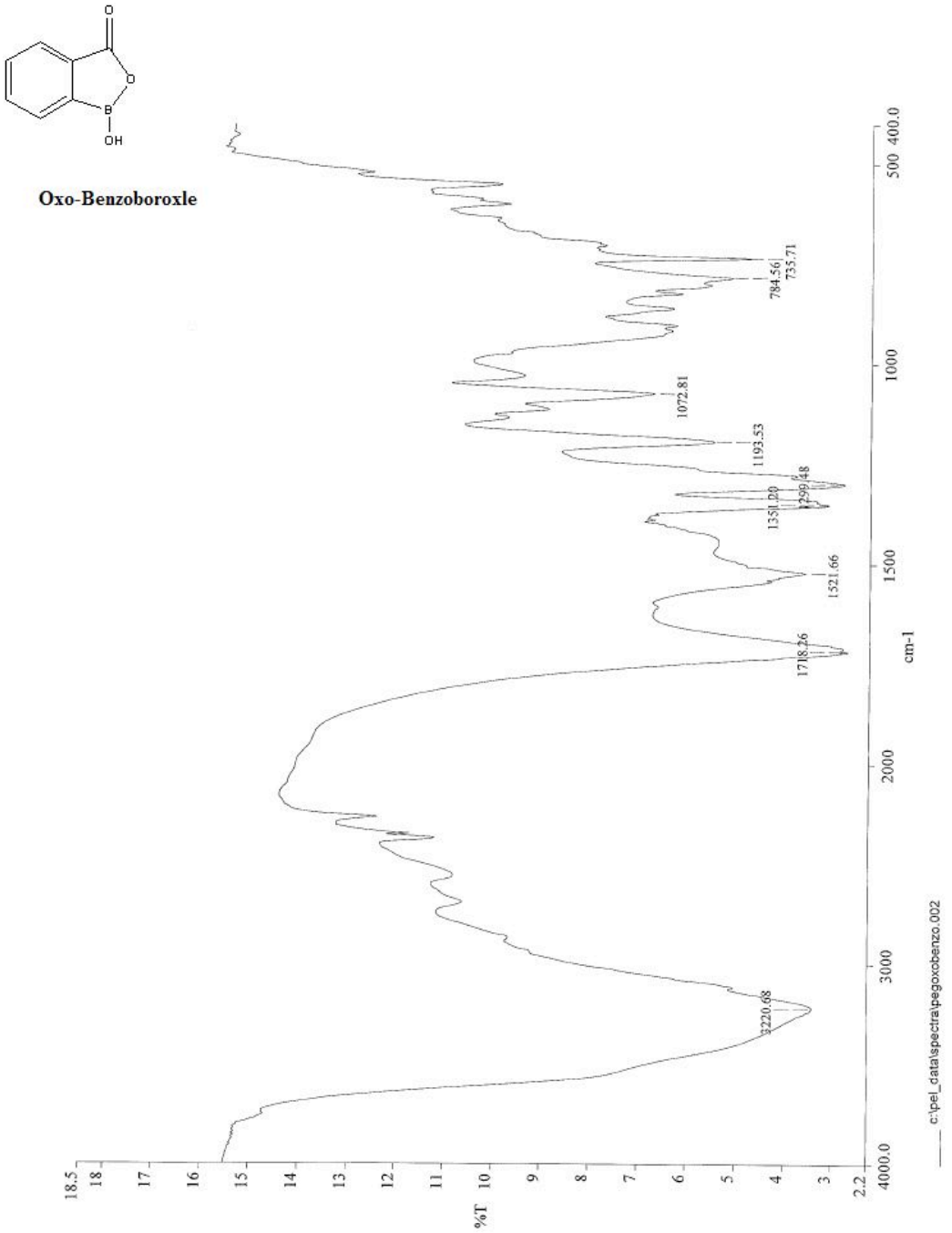


APPENDIX IV

IR SPECTRA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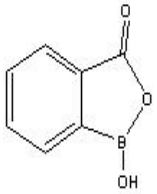
APPENDIX V

^{11}B NMR SPECTRA



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