UNIVERSITY OF TROMSØ UIT

FACULTY OF SCIENCE AND TECHNOLOGY
DEPARTMENT OF CHEMISTRY

# Synthesis of β-substituted β-aminoboronates

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# SYNTHESIS OF β-SUBSTITUTED β-AMINOBORONATES

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# ABSTRACT

In relation to previous work done at the University of Tromsø concerning the synthesis of amino acid analogues of boron, a new approach for the synthesis β-substituted β-aminoboronates has been developed.

Several strategies were pursued in order to synthesize the β-substituted β-aminoboronates during the course of the study. These include among others the attempted coupling of a boronate and enolate with a subsequent reduction and the preparation of a Grignard reagent from an α-bromoketal followed by attempted coupling to a boronate and then reduction.

One strategy in particular appertaining to the non-stereospecific synthesis of β-substituted β-aminoboronates seemed promising:

A commercial boronic ester was converted to dichloromethyl boronate by treatment with (dichloromethyl)lithium and then esterification following work-up. A nucleophilic substitution of chlorine using an organometallic reagent led to the α-chloroalkyl boronate. Displacement of the remaining chlorine using an azide led to the α-azidoalkyl boronate, which was subsequently converted to the β-azido-α-chloroalkyl boronate after homologation. Selective reduction of the chlorine succeeded by a reduction of the azide led to the β-substituted β-aminoboronate.

The last two steps of the strategy involves the conversion of the β-aminoboronate to the β-aminoboronic acid followed by esterification using an enantiomerically pure carbohydrate.

Due to time constraints these steps were never completed for the target molecules, but exploratory experiments seem to suggest they can be synthesized by oxidation to the boronic acid using sodium periodate with a consecutive esterification using azeotropic distillation of water to drive the reaction.

At the University of Tromsø it was discovered that for certain benzylic halides ultrasound quite unexpectedly led to dimerization. The scope and limitations of this discovery was explored during the early parts of this study and the findings published.

# LIST OF ABBREVIATIONS

| | |
|---|---|
| $^{1}$H-NMR | Proton nuclear magnetic resonance |
| $^{13}$C-NMR | Carbon nuclear magnetic resonance |
| gCOSY | Gradient-selected correlated spectroscopy |
| GC | Gas chromatography |
| MS | Mass spectrometry |
| HRMS | High resolution mass spectrometry |
| IR | Infrared (spectroscopy) |
| MW | Microwave |
| TLC | Thin layer chromatography |
| α | Alpha |
| β | Beta |
| γ | Gamma |
| δ | Delta, also used to signify chemical shift values in nuclear magnetic resonance spectroscopy |
| EI | Electron ionization |
| CI | Chemical ionization |
| ppm | Parts per million |
| $cm^{-1}$ | Reciprocal centimeters |
| Me | Methyl |
| i-Pr | Iso-propyl |
| Ph | Phenyl |

| | |
|---|---|
| Bn | Benzyl |
| Ar | Argon |
| THF | Tetrahydrofuran |
| DCM | Dichloromethane |
| BuLi | n-butyllithium |
| LDA | Lithium diisopropyl amide |
| HMDS | Hexamethyldisilazane |
| TMSCl | Chlorotrimethylsilane |
| BHT | Butylated hydroxytoluene |

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# 1. INTRODUCTION

## 1.1. Amino acids, peptides and proteins[1]

Amino acids are small molecules consisting of an amine ($-NH_2$) group and a carboxylic group (-COOH). Amino acids are the building blocks of the peptides and proteins and are therefore crucial for the biological function of the human body. The amino acids are called α-, β-, γ- or δ-amino acids depending on which carbon relative to the carboxylic group the amino group is attached (Figure 1).

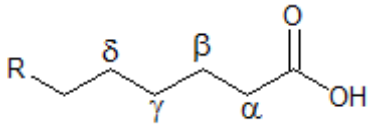



**Figure 1 –** Greek lettering determines which carbon the amino group is attached to relative to the carboxylic group.

There are only 20 naturally occurring amino acids. Humans can synthesize 10 of these, but the remaining 10 must be a part of the daily intake in order for human protein synthesis to be possible. Amino acids are not only used for protein synthesis in the human body but also as neurotransmitters and for transport of fatty acids among others.[2-3] Of the 20 naturally occurring amino acids, all of them are α-amino acids (Figure 2).

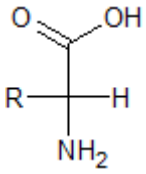



**Figure 2 –** An α-amino acid. The amino group is bonded to the α-carbon.

The amino acids differ depending on which R-group is attached. For all the naturally occurring amino acids except Glycine (R = H), the α-carbon will denote a stereogenic center and thus there will be two possible enantiomers (Figure 3).

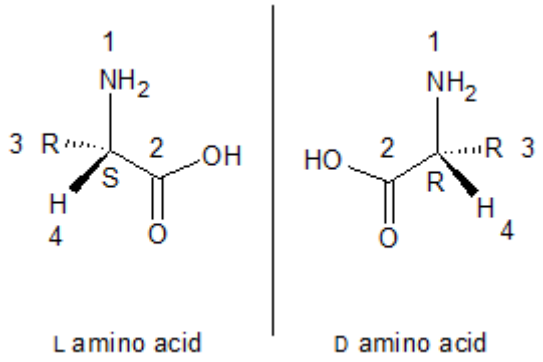



**Figure 3 –** Enantiomers of an amino acid.

Only one of these enantiomers commonly exists in nature, the L-amino acids or natural amino acids. The D-amino acids are rarely found in nature and are often referred to as unnatural amino acids for this reason. For the naturally occurring α-amino acids the stereogenic center will always have the S-configuration, with the only exception being cysteine (R = $CH_2SH$). This is because the sulfur sidechain will get a higher priority than carboxyl-group and thus make the stereogenic center R and not S.

Amino acids function as both acids and bases because of the basic amine-group (-$NH_2$) and the acidic carboxyl-group (-COOH). This in turn makes it possible for the amino acid to exist in several different forms depending on the pH of the solution in which it is dissolved.

At around neutral pH (~7) the amino acid will exist in a zwitterionic form because of a proton transfer occurring from the carboxyl-group to the amine-group, resulting in a positive charge on the amine-group and a negative charge on the carboxyl-group giving an overall neutral molecule. At acidic pH (≤2) the amino acid will be protonated at the carboxyl-group giving it an overall positive charge. At basic pH (≥10) the amino acid will be deprotonated at the carboxyl- and the amine-group giving it an overall negative charge (Figure 4). Amino acids with additional carboxyl-groups in their side-chain are often referred to as acidic amino acids, while those with additional amine-groups are considered basic amino acids. Most others are considered neutral amino acids.

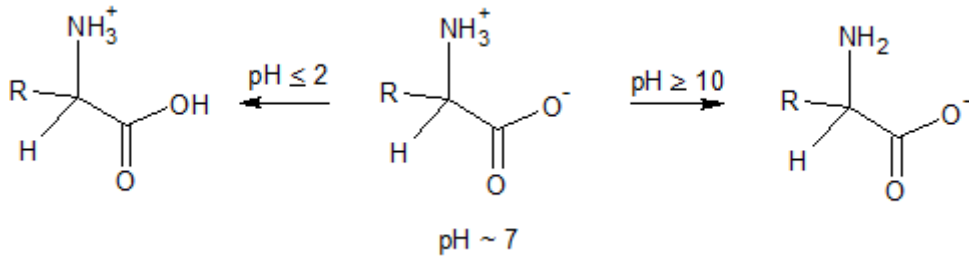



**Figure 4 –** The different forms of an amino acid.

Amino acids can form peptides and proteins by peptide-bonds. These are amide bonds between the amine-group and the carboxyl-group on another amino acid (Figure 5).

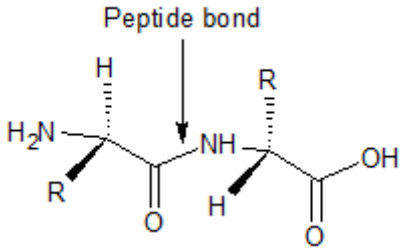



**Figure 5 –** Two amino acids having formed a dipeptide.

When two different amino acids combine they can theoretically form two different dipeptides based on which of the amino acids' amine-groups react with which carboxyl-group (Figure 6). The two different dipeptides will be constitutional isomers of one another since they have the same molecular formula but the connectivity of the atoms will be different.

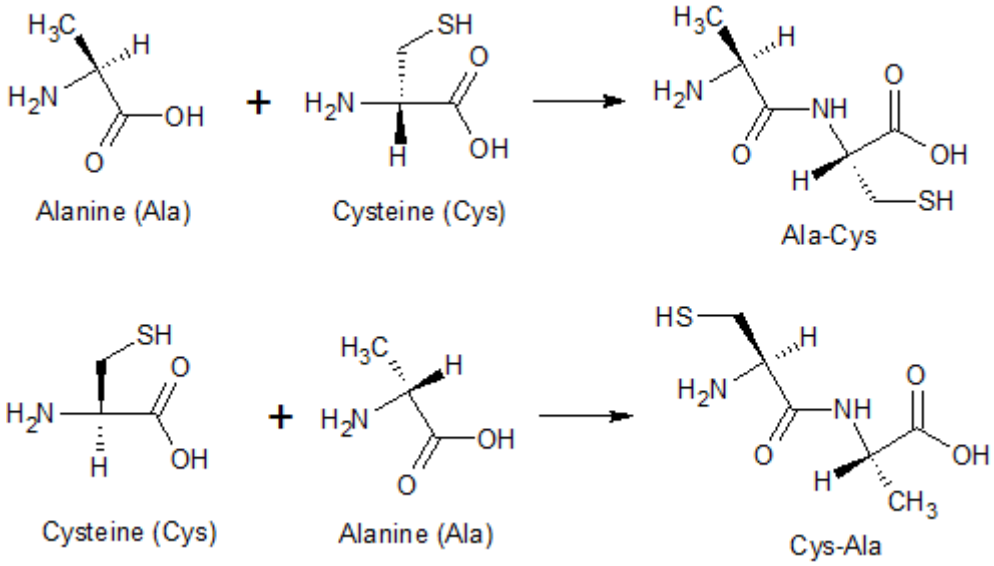



**Figure 6 –** Different dipeptides forming from Alanine and Cysteine.

When many amino acids combine by peptide bonds in long linear chains they are referred to as polypeptides. Chains with more than 40 amino acids are generally referred to as proteins and can contain one or more polypeptides.

The geometry of the peptide bond is planar with all the six atoms involved in the bond (carbonyl-group, amine-group and α-carbons to these groups) lying in the same plane. All bond angles are 120° and the carbonyl- and amine-group are situated 180° from one another.

The planarity can be explained by the carbonyl-group, which is $sp^2$-hybridized. In addition the lone pair of nitrogen can be delocalized, providing the amine-group with a partial double bond character (Figure 7).

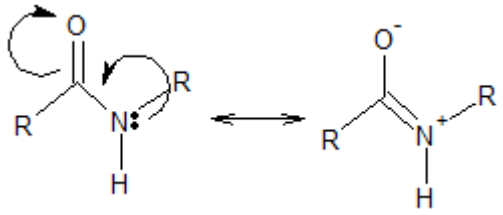



**Figure 7 –** Peptide-bond resonance structures.

This partial double bond character on the amine-group restrains the rotation about the carbon-nitrogen bond, effectively only allowing two different conformations. Either the R-groups can be oriented trans or cis to one another, that is a dihedral angle of either 180° or 0° respectively (Figure 8). The trans conformation is typically more stable since the R-groups are situated away from each other.

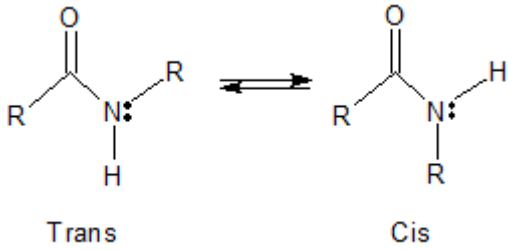



**Figure 8 –** The allowed conformations of the peptide bond.

Today many different amino acids are known, classified as either α-, β-, γ- or δ-amino acids with a wide spread in properties based on their polarity, basicity, acidity and structure of the side-chain (aliphatic, aromatic, unsaturated, heterocyclic, cyclopropane, cyclobutane, halogen-containing, sulfur-containing, selenium-containing and phosphorous-containing).[4]

### 1.1.1. β-amino acids and antimicrobial peptides[5]

β-amino acids occur rarely in nature as their free amino acids or as substructures of peptides and alkaloids (basic molecules containing nitrogen derived from plants or animals).[6] They have been discovered both in marine and terrestrial environments in prokaryotic (bacteria) and eukaryotic organisms.

The most commonly encountered β-amino acid is β-alanine, which unlike α-alanine, has the amine-group on the β-carbon relative to the carboxyl-group. Also since β-alanine has two protons attached to the β-carbon it lacks the stereogenic center that α-alanine possesses (Figure 9).

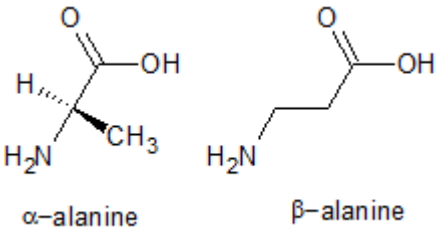



**Figure 9** – α-alanine and β-alanine.

β-alanine is found in plants, fungi, animals and bacteria, which is not surprising since it is a precursor to pantothenic acid (vitamin $B_5$) which is necessary for primary metabolism in all kingdoms of life. β-alanine has also been shown to have an effect on the level of carnosine in the human body, making athletes less fatigued and overall increase the effectiveness of their muscles.[7]

β-amino acids can, like their α-counterparts, form β-peptides by peptide-bonds. Several natural alkaloids and peptides consisting of β-amino acids are potent antibacterial, antifungal and/or cytotoxic compounds and are therefore of great interest in the search for new antibiotics.

Peptides that display antimicrobial activity are often referred to as antimicrobial peptides and antimicrobial peptides based on β-amino acids have been shown to have a good effect at mimicking host-defense peptides with minimal protease (enzymatic hydrolysis).[8-9]

The development of antimicrobial peptides has long been an important objective at the University of Tromsø.[10-13]

More recently the synthesis of antimicrobial peptides based on α-substituted β-aminoboronic-acids and esters have resulted in potential new antitubercular drugs.[14-15]

In addition the synthesis of a library of α-aminoboron containing peptidomimetics have led to several compounds which exhibited either antimicrobial, antifungal or kinase (enzymes that transfers phosphate-groups to various substrates) inhibition or promotion.[16]

## 1.2. Boron, boronic acids and its derivatives – structure and properties[17-18]

Borax has been known for several thousand years. Elemental boron was however not discovered until 1808 when the British chemist Sir H. Davy and the French chemists L.-J. Gay. Lussac and L.-J. Thénard, made the discovery independently of each other. It proved quite hard to produce a clean sample of the element, and thus the first chemist credited with preparing 99.8 % clean boron was the American chemist E. Weintraub.[19]

Boron is a metalloid, although not metallic in its elemental form. Boron occupies the first period in the third main group of the periodic table of elements. It is in many ways similar to carbon, which neighbors boron in the first period of the fourth main group of the periodic table. Examples of the nomenclature and structure of some common classes of boronic compounds has been illustrated in figure 10.

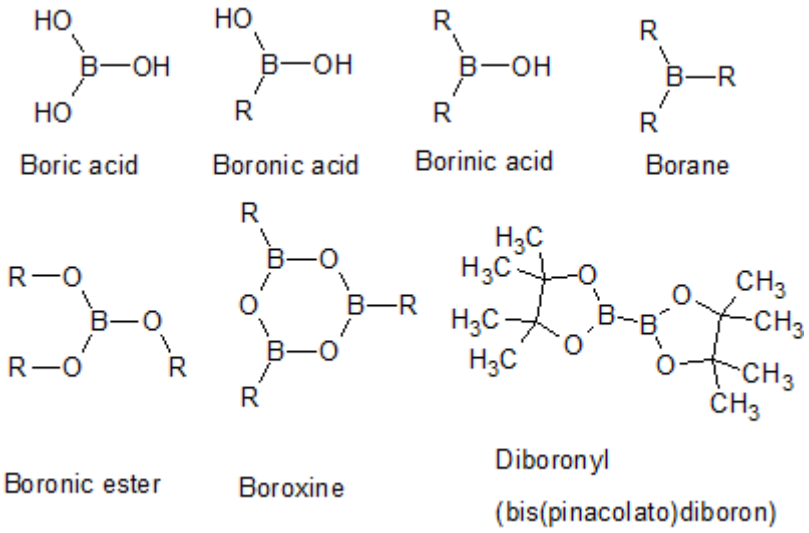



**Figure 10 –** Nomenclature and structure of some common classes of boron compounds.

The size of the boron atom is slightly bigger than that of carbon, but not so much that attached groups cannot interact. This is important if a chiral center is to be made, as a chiral auxiliary attached to boron can direct the chirality of said center. This is utilized in the Matteson homologation procedure which will be described in more detail later.[20] The boron atom can

also easily be oxidized or replaced with other electrophiles while retaining the stereochemistry.

Boron is more electropositive than carbon and organic boron compounds behave much like traditional main-group organometallic compounds. The oxidation state of boron is most commonly +3, but it can also form unstable compounds with oxidation states less than +3 (e.g. B2F2 and BF).[21-22]

Boron in its +3 oxidation state retains a trigonal planar configuration where all bond angles are 120$^{o}$ and the boron is sp$^{2}$ hybridized. The tri-coordinated organic boron compound is isoelectronic with a positively charged carbocation (Figure 11).

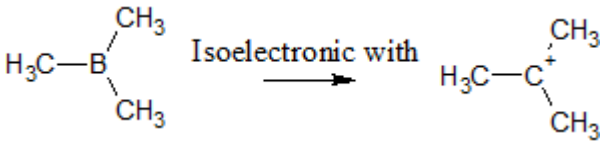



**Figure 11 –** Tri-coordinated boron isoelectronic with carbocation.

The trigonal planar geometry of the tri-coordinated organic boron compounds is due to the fact that boron has a vacant p-orbital. This p-orbital can be used to coordinate a nucleophile or other basic species, which in turn will make the boron sp$^{3}$ hybridized, negatively charged and tetrahedral with bond angles of 109$^{o}$. The tetra-coordinated organic boron compound is isoelectronic with a neutral tetra-coordinated carbon (Figure 12). A boronic acid is in equilibrium with its trigonal planar and tetrahedral geometry (Figure 13).

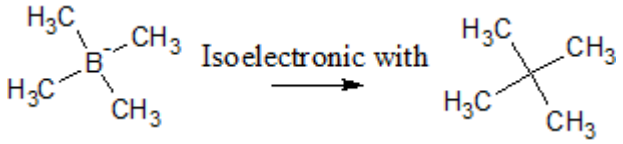



**Figure 12** – Tetra-coordinated boron isoelectronic with neutral tetra-coordinated carbon.

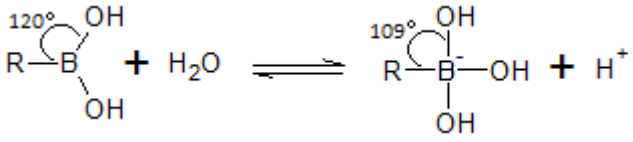



**Figure 13 –** Boronic acid in equilibrium between its trigonal planar and tetrahedral geometry.

Another interesting class of boronic acid derivatives are boroxines (Figure 14). Boroxines are cyclotrimeric anhydrides of boronic acids, which they also exist in equilibrium with. The boroxine ring itself is virtually flat, is isoelectronic with benzene and also possess an aromatic

character due to the vacant p-orbitals. Boroxines can easily be made by dehydrating boronic acids, e.g. by azeotropic distillation of water or dehydrating agents.

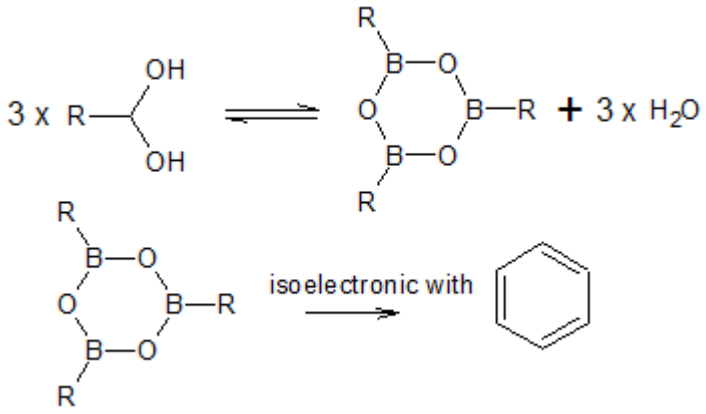



**Figure 14 –** Boroxine isoelectronic with benzene.

The carbon-boron bond lengths and the strength of the carbon-boron bonds are very similar to those of carbon-carbon bonds. The average bond energy of the carbon-boron bond is 322.9 kJ/mol$^{-1}$ compared to an average of 357.5 kJ/mol$^{-1}$ for carbon-carbon bonds. The difference in bond energy for boron-oxygen and carbon-oxygen bonds is substantial, with average bond energies of 519.2 kJ/mol$^{-1}$ and 383.5 kJ/mol$^{-1}$ for boron-oxygen- and carbon-oxygen bonds respectively. The boron-oxygen bond strength is in a large part due to conjugation between the lone pairs on oxygen and the vacant p-orbital on boron. This conjugation confers partial double bond character to the boron-oxygen bond. The only bond stronger than the boron-oxygen bond is the boron-fluorine bond with an average bond strength of 644.6 kJ/mol$^{-1}$. Even though boron is quite easily oxidized it turns out that oxidative cleavage of boron-carbon bonds under atmospheric conditions (water and oxygen) is a kinetically slow process and as such, most boronic acids are quite stable under an oxygen atmosphere or in water solutions over a wide pH range.

Ligand exchange on boronic acids is usually restricted to boron-carbon or boron-oxygen ligands both for reasons of enantioselective synthesis and thermodynamic reasons. Substitution of the boron-carbon ligands of boronic acids are often very slow processes and substitutions of the boron-oxygen ligands are thermodynamically unfavored. In general water or alcohols will readily displace most boron-halogen or boron-nitrogen ligands. The ligands most competitive to boron-oxygen ligands are nitrogen-ligands, which will displace most boron-halide ligands. There has been little interest in research on boron-sulfur ligands so far, so the data regarding these are limited. They are however thought of being about equal to

most boron-halide ligands. Mixed ligands also exist, with one example being dimethoxyboron chloride. Despite being thermodynamically unfavored there exist a few methods of converting boronic- esters and acids to their corresponding haloboranes (Figure 15).

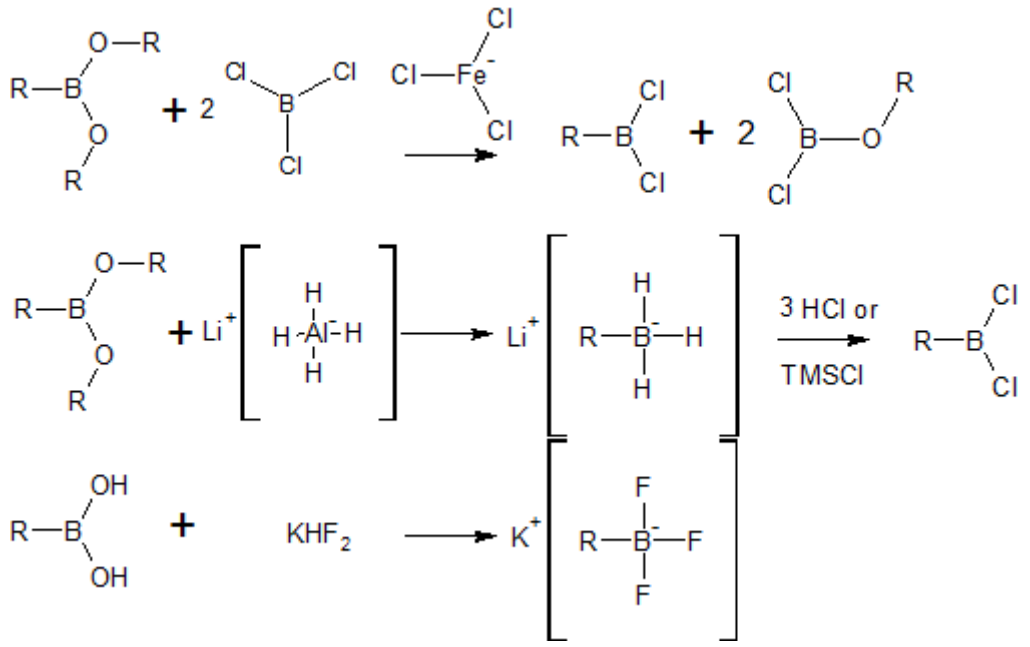



**Figure 15** – Conversion of boronic- esters and acids to haloboranes,

There are several other synthetic important reactions involving boronic acids with perhaps the most well-known being the Suzuki-Miyaura cross-coupling reaction (Figure 16).[23]

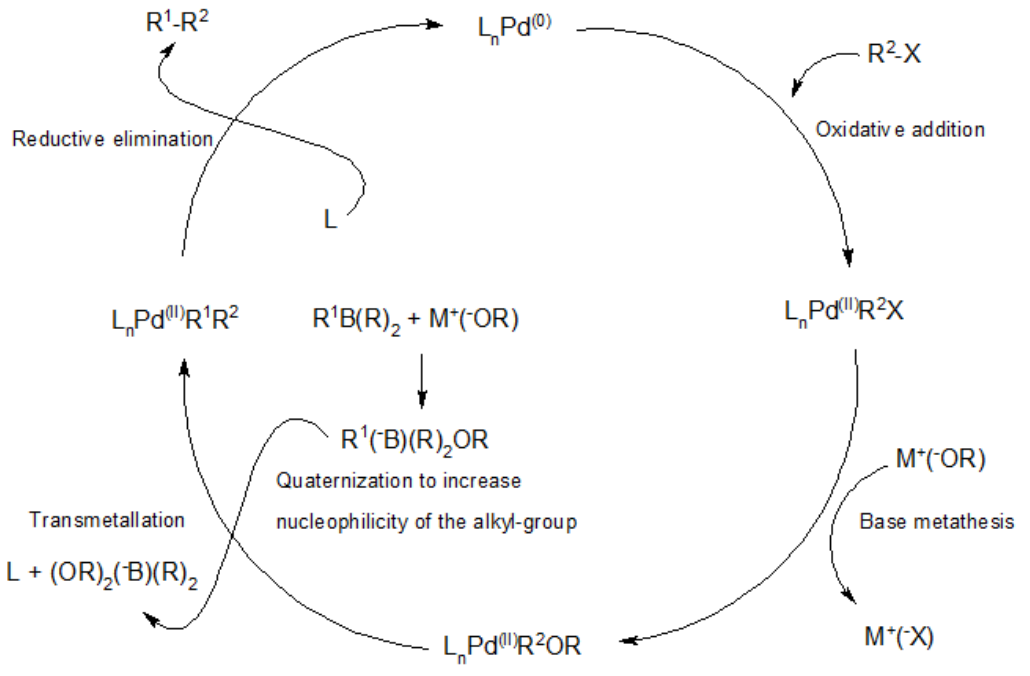



**Figure 16** – The Suzuki-Miyaura cross-coupling.

The vacant p-orbital makes boron function and react as a Lewis acid. This can be explained when one looks at the ionization equilibrium of boronic acids illustrated in figure 17.

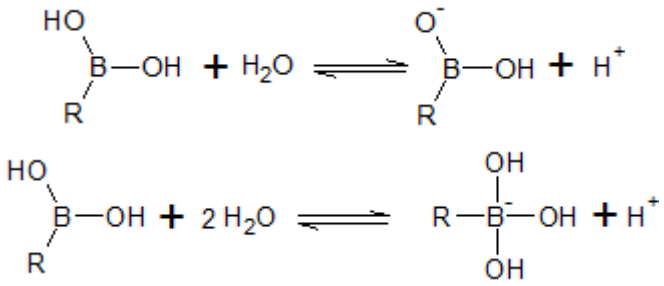


**Figure 17 –** Ionization equilibrium of boronic acids in water.

The vacant p-orbital makes it possible for the boronic acid to ionize the water and thus form hydroxonium ions by indirect proton transfer. This means that the more electron-deficient or electrophilic the boron-atom is, the more acidic the boronic acid will be, as the boron-atom can better stabilize the resulting negative charge. The most acidic boronic acids are those with the more electron-withdrawing groups, and in general aryl groups are more acidic than alkyl groups. $pK_a$'s for boronic acids are usually in the range of 9-11, but for certain electron-poor boronic acids the $pK_a$ can be lower.

Diphenylboronic acid has a reported $pK_a$ of 6.2, while one of the most acidic boronic acids known is 3-pyridinylboronic acid with a $pK_a$ of only 4 (Figure 18).

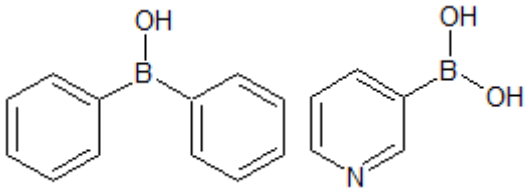


**Figure 18 –** Diphenylboronic acid and 3-pyridinylboronic acid.

Boronic acids with sterically hindered groups on the other hand, will be less acidic than their counterparts since they might hinder the boronic acid from attaining the required tetrahedral geometry.

The toxicity of boronic acids is considered low and as such should be suitable for medicinal purposes. This is evidenced by recent drug design where the boronic acid moiety plays an integral part in anticancer, antibacterial and antiviral drugs in addition to being utilized as glucose sensors for diabetes.[24-25]

### 1.2.1. β-aminoboronic acids and esters

β-aminoboronic acids are, as the name implies, the analogues of β-amino acids (Figure 19).

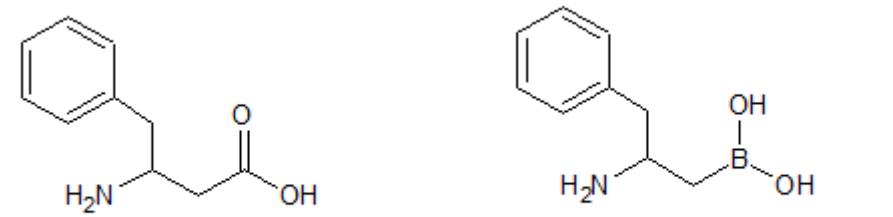



**Figure 19** – Structural comparison of a β-amino acid and a β-aminoboronic acid.

These molecules can be synthesized from simple starting materials and coupled with regular amino acids to form β-peptides and β-polypeptides (Figure 20).

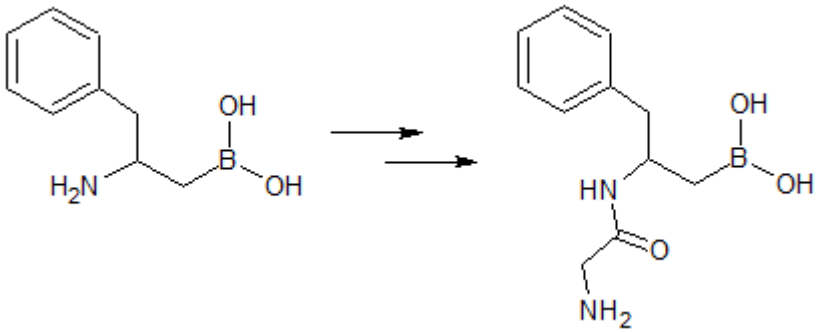
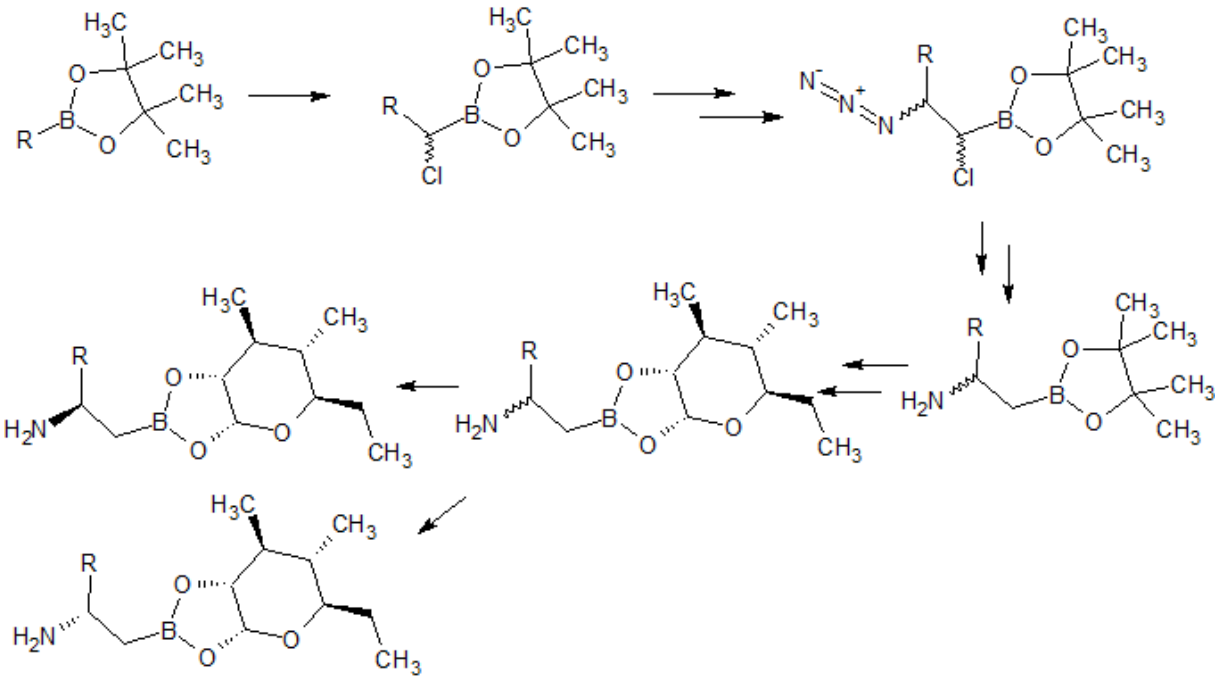



**Figure 20** – Coupling of a β-aminoboronic acid to glycine.

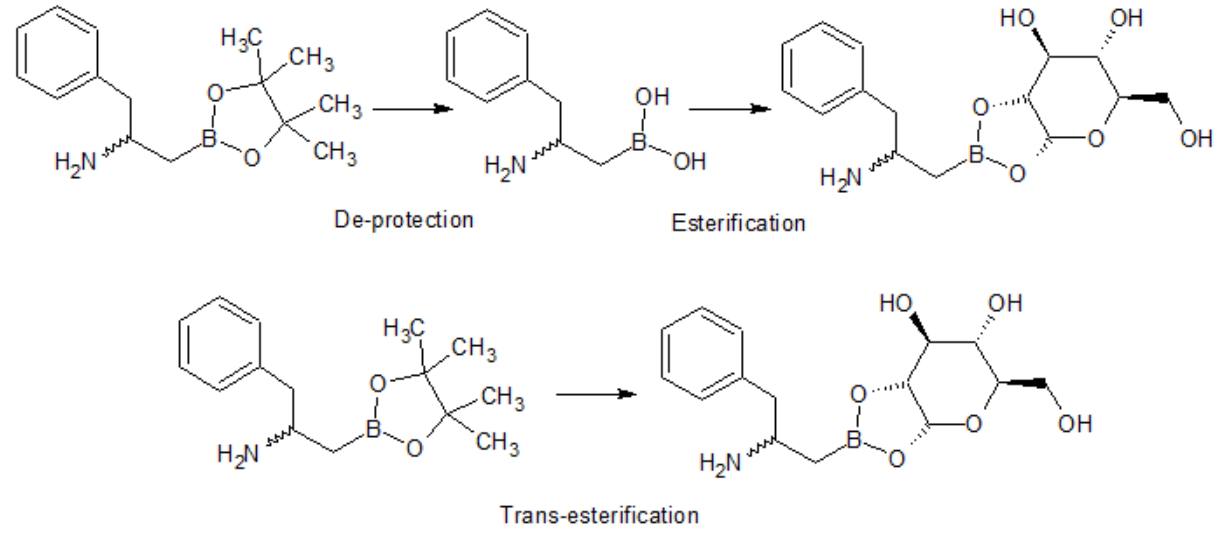
With recent work at the University of Tromsø turning up a selection of α-substituted β-aminoboronic- acids and esters showing promising activity against tuberculosis it was of interest to investigate this further. The previous work showed no clear trend as to whether the β-aminoboronic- acids or esters had the most activity against tuberculosis, but it seemed as if the bulkier substituents gave the better activity. It was theorized whether or not this increased activity could be as a result of the size of the substituents or due to the extra lipophilicity resulting from these bigger substituents.[14]

In light of these studies it would therefore be of interest to synthesize selected β-aminoboronates with a variety of different sized substituents (Me, i-Pr, Ph, Bn) in the β-position. The boronic acid moiety would initially be protected as its pinacol-ester, as pinacol is quite resistant towards hydrolysis. In the final step the boronic ester moiety would be trans-esterified, or de-protected and esterified again, using a set of commercially available enantiomerically pure carbohydrates (in particular α-D-glucose) to increase water solubility

and potentially increase activity (Scheme 1 and 2). If a compound exhibited antimicrobial activity its diastereomers would, if possible, be resolved, or it would be synthesized as its pure enantiomer using enantiomerically pure carbohydrates as chiral directors from the start.



**Scheme 1** – Scheme for the synthesis of β-substituted β-aminoboronates.




**Scheme 2** – Schemes for the removal of the protecting group and insertion of the carbohydrate into the molecule.

From the proposed reaction pathway it became clear that two main reactions in this synthesis would be the Matteson homologation reaction and the Grignard reaction which each will be described in detail in the preceding chapters.[20, 26]

### 1.2.2. Esterification of the boronic acid moiety[18]

In order to avoid unwanted side-reactions the boronic acid should initially be protected as its boronic ester. This is done by esterifying the boronic acid moiety using a diol or an alcohol. Common alcohols for this transformation are methanol and 2-propanol while common diols are ethylene glycol, 1,3-propandiol, 2,2-dimethyl-1,3-propanediol, 2-methyl-2,4-pentanediol, pinacol, pinanediol and cathecol among others (Figure 21).

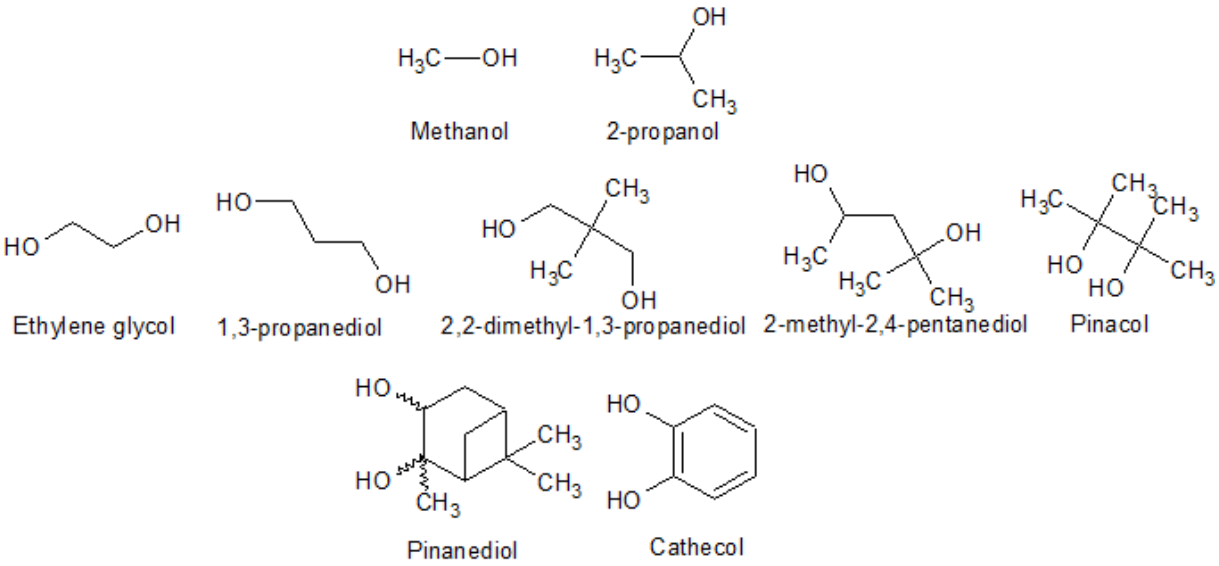



**Figure 21** – Common alcohols and diols used for the protection of boronic acids.

The process of the esterification is an equilibrium that can be driven forward if the product of the reaction is insoluble in the reaction solvent or by removal of water.[27] Water can be removed by azeotropic distillation (Dean-Stark), with the use of dehydrating agents such as magnesium sulfate, sodium sulfate or molecular sieves.

The same process can be employed for the esterification of the boronic acid moiety with carbohydrates, but as mentioned earlier regioselectivity could potentially be a problem with many OH-groups.

## 1.3. Carbohydrates[28]

A carbohydrate is a general term for polyhydroxy aldehydes and ketones or compounds that can be hydrolyzed to such. The simplest carbohydrates are monosaccharides, which have three to seven carbons in a straight chain with either a carbonyl-group at the terminal carbon or at the β-carbon relative to the terminus. They are dubbed aldoses or ketoses depending on whether this carbonyl-group is an aldehyde or ketone respectively (attached to terminal

carbon or the β-carbon relative to the terminus). The remaining carbons in the chain usually have hydroxyl-groups attached (Figure 22).

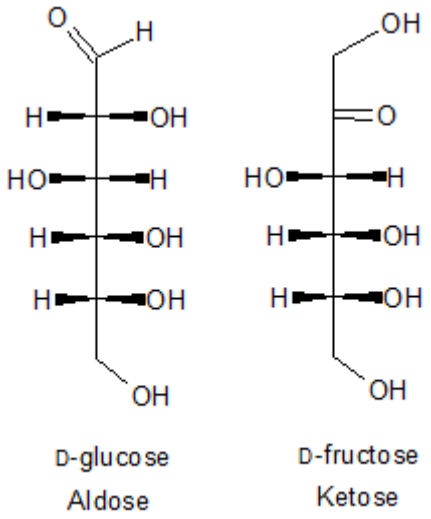



**Figure 22** – Examples of an aldose and a ketose.

The names of the monosaccharides change both depending on the number of carbons in the chain and whether it's an aldose or ketose, e.g. aldopentose or ketoheptose.

All carbohydrates contain one or more stereogenic centers. The aldohexoses contain four stereogenic centers which gives a total of $2^4 = 16$ stereoisomers. Other examples include aldopentoses with $2^3 = 8$ stereogenic centers and ketopentoses with $2^2 = 4$ stereogenic centers, aldotrioses with only 2 stereogenic centers and ketotrioses without stereogenic centers at all.

All naturally occurring monosaccharides have the D-configuration. It's the stereogenic center farthest away from the carbonyl-group that determines the configuration of a monosaccharide. If this stereogenic center has the OH-group pointing to the right in a Fischer projection, it is denoted as a D-monosaccharide (Figure 23).

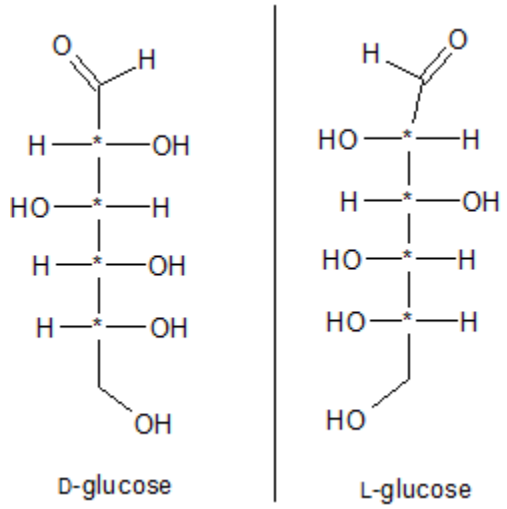



**Figure 23** – Fischer projection of the two enantiomers of glucose.

Monosaccharides with five or more carbons rarely exist in their acyclic form and most often undergo intramolecular cyclizations to form hemiacetals or hemiketals depending on whether it's an aldose or ketose reacting. Aldopentoses can react at either carbon 4 or 5 and cyclize to either a furanose or a pyranose ring. Studies show that the six-membered ring is the predominant structure in solution for D-ribose.[29] It seems likely that also ketohexoses can form both furanose- and pyranose rings by reaction at either carbon 5 or 6 (Figure 24).

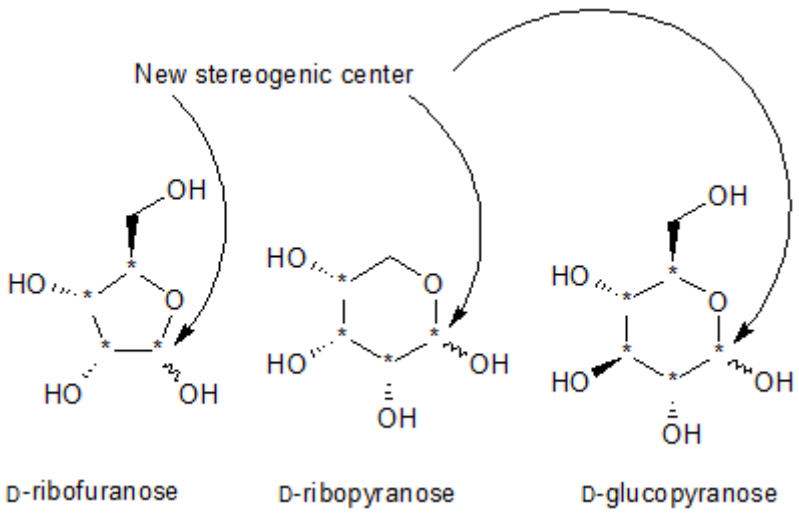



**Figure 24** – Ring cyclizations of monosaccharides.

The cyclization will create a new stereogenic center at the carbonyl-carbon, often referred to as the anomeric carbon, which is the hemiacetal or hemiketal carbon of the ring. Depending on the position of the OH-group in the new stereogenic center relative to the $CH_2OH$-group, it is either denoted as an α- or β cyclic monosaccharide. If the OH-group is down and trans to

the $CH_2OH$-group it is α, while it's β if the OH-group is up and cis to the $CH_2OH$-group (Figure 25).

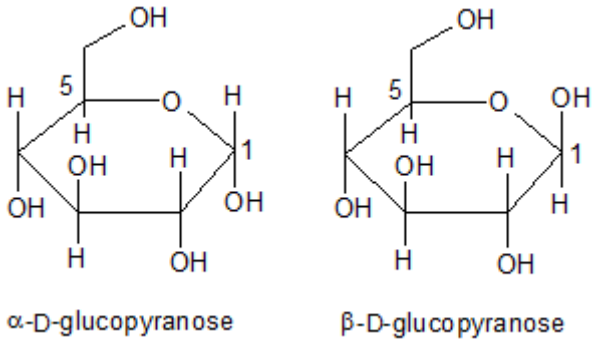



**Figure 25** – α- and β cyclic monosaccharide.

Saccharides can be classified as monosaccharides, disaccharides or polysaccharides (3 or more monosaccharides linked together) depending on how many structural monosaccharide units are linked together through glycosidic links. Glycosidic links can be viewed as acetals. The glycosidic link will be formed from the anomeric carbon of one monosaccharide and any OH-group on another monosaccharide. For six-membered rings, the carbon atoms are marked from 1 to 6 beginning with the anomeric carbon. The ring that does not contain the glycosidic link is marked from 1 prime to 6 prime. Most commonly disaccharides will form between the anomeric carbon and the 4 prime OH-group. The structure of the mono-, di- or polysaccharide will depend on the orientation of the OH-group on the anomeric carbon - α or β (Figure 26).

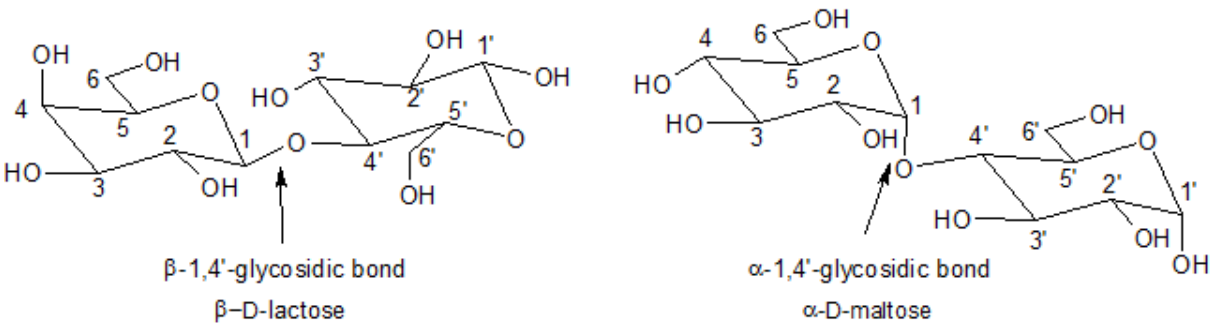



**Figure 26** – α- and β glycosidic linkages in disaccharides.

There exists a plethora of biologically important polysaccharides. Cellulose is a polysaccharide found in almost all plant walls and wood. It consists of repeating units of glucose bonded together by β-1,4-glycosidic bonds.

Starch, which is the main carbohydrate found in roots and plants and an important food source for both humans and animals, consists of an unbranched and a branched molecule called amylose and amylopectin respectively. Amylose has glucose molecules linked together by α-1,4'-glycosidic bonds while amylopectin has glucose molecules linked together by both α-1,4'-glycosidic bonds and α-1,6'-glycosidic bonds (Figure 27).

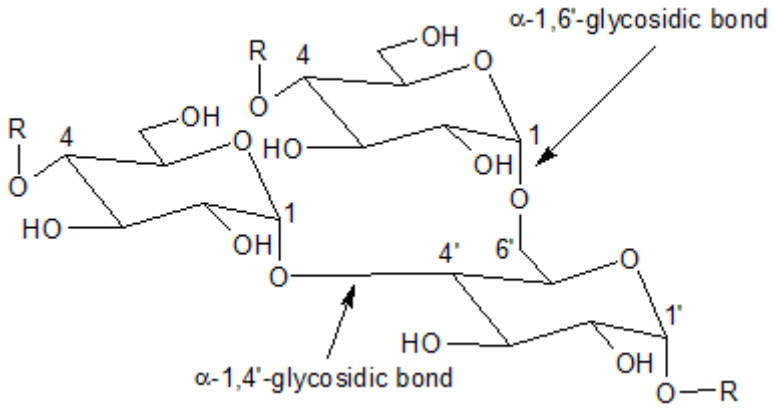



**Figure 27** – A branched polysaccharide.

Glycogen, the major source of energy for both humans and animals, is stored in the body as a polymer of glucose consisting of α-1,4'-glycosidic bonds and α-1,6'-glycosidic bonds, similar to amylopectin.

Finally some of the most biologically important polysaccharides are N-glycosides, formed in the reaction of monosaccharides and amines under mildly acidic conditions (Figure 28). Examples of such important N-glycosides include D-ribose and 2-deoxy-D-ribose which are the building blocks of RNA and DNA (Figure 29).

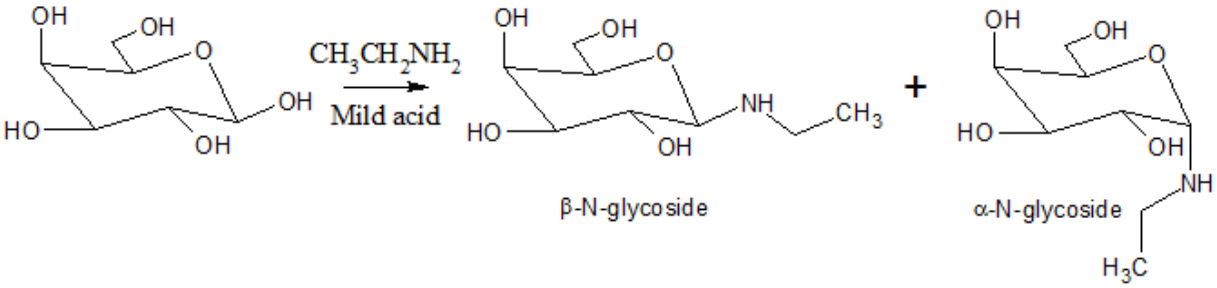



**Figure 28** – Formation of α- and β-N-glycoside from β-D-glucopyranose.

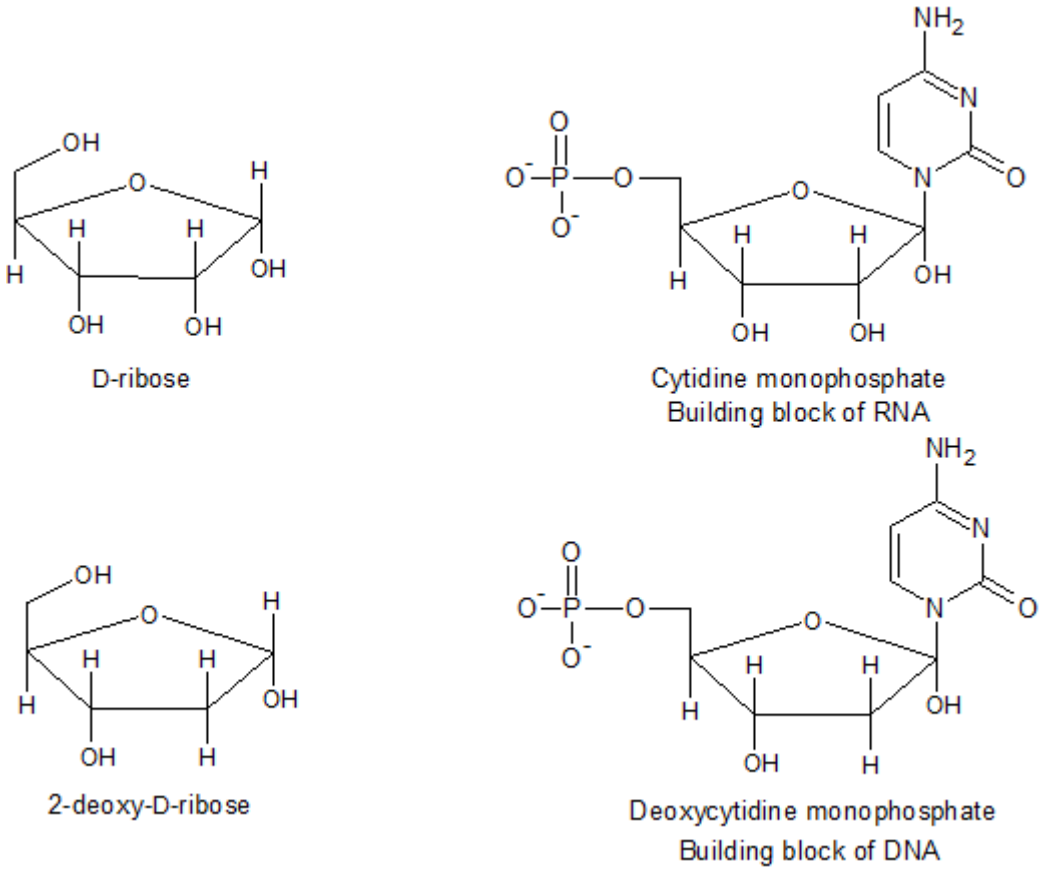



**Figure 29** – N-glycoside building blocks for RNA and DNA.

## 1.4. Chemical reactions and methods of special importance in this study

### 1.4.1. The Grignard reaction[26, 30]

Victor Grignard reported as early as the year 1900 that the reaction of an alkyl halide with magnesium metal in diethyl ether produced a solution of an organomagnesium compound that reacted with aldehydes and ketones to give secondary and tertiary alcohols (Figure 30). Compounds consisting of a carbon bonded to a metal are usually called organometallic reagents.

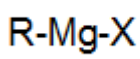



**Figure 30** – The general structure of a Grignard reagent.

The most common organometallic reagents are those of magnesium, lithium or copper but others, such as Sn, Si, Ti, Al and Hg also exist. These reagents are versatile tools for creating carbon-carbon bonds because of the metal being more electropositive than the carbon, thereby lending electron density to the carbon increasing its nucleophilicity. The more electropositive the metal being used is, the more polar the carbon-metal bond becomes and the more reactive the organometallic reagent becomes. Judging by this it is obvious that the most reactive organometallic reagents are those of lithium and magnesium.

Grignard reagents will readily react with oxygen and water and as such, the reaction is carried out under an atmosphere of argon or nitrogen and using anhydrous solvents.

Grignard reagents can be prepared by the reaction of an alkyl-, aryl-, benzyl-, vinyl- or allyl chlorine, bromine or iodine with magnesium in anhydrous ethereal solvents such as diethyl ether or tetrahydrofuran or in certain aprotic, nucleophilic solvents such as tertiary amines (Figure 31).

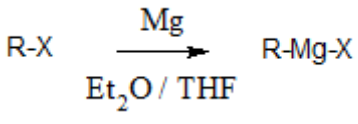



**Figure 31** – The formation of a Grignard reagent.

The choices of solvent for the Grignard reaction is crucial as the oxygen on the ethereal solvents will complex with the magnesium and help stabilize the reagent (Figure 32).

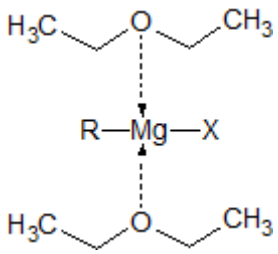



**Figure 32** – Diethyl ether stabilizing a Grignard reagent.

There exists an equilibrium in solutions of alkyl- and aryl Grignard reagents, called the Schlenk-equillibrium (Figure 33).[31-32]

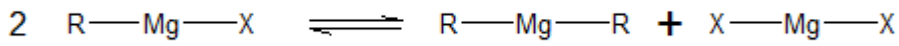



**Figure 33** –The Schlenk-equillibrium.

The addition of 1,4-dioxane to a Grignard reagent will push this equilibrium to the right-hand side and make dihalide magnesium salts to precipitate from the solution, effectively forming dialkyl- or diaryl magnesium compounds. The dialkyl or diaryl magnesium reagents are superior alkylating agents compared to normal Grignard reagents in that higher yields and cleaner reactions are generally observed.

Usually the creation of a Grignard reagent starts quite slow, most often due to magnesium oxide on the surface of the magnesium or moisture. As more and more of the magnesium-surface becomes exposed the reaction can quickly become extremely exothermic, and as such, great care must be taken in slowly adding the alkyl halide to the solution at such a rate that the solution keeps a steady reflux.

In certain cases, probably depending on the substrate and/or the magnesium, the reaction can be very slow. In cases such as these it can help to add a few crystals of iodine or 1,2-dibromoethane in order to help expose more of the magnesium-surface. Alternatively Rieke-magnesium, which is finely powdered activated magnesium resulting from the reduction of magnesium chloride with an alkali-metal such as K, Na or Li, can be used.[33]

Heating the solution or applying ultrasound can also help start the reaction. At the University of Tromsø it was discovered that for certain benzylic halides ultrasound quite unexpectedly led to dimerization. The scope and limitations of this discovery was explored and the findings described in full in the results and discussions-chapter.[34] The use of ultrasound in chemistry, dubbed sonochemistry, will be explained in the next chapter.

Grignard reagents can react as nucleophiles with a wide variety of electrophiles, including carbonyl compounds, acid derivatives such as α-halo carbonyls or esters, nitriles and carbon dioxide among others (Figure 34).

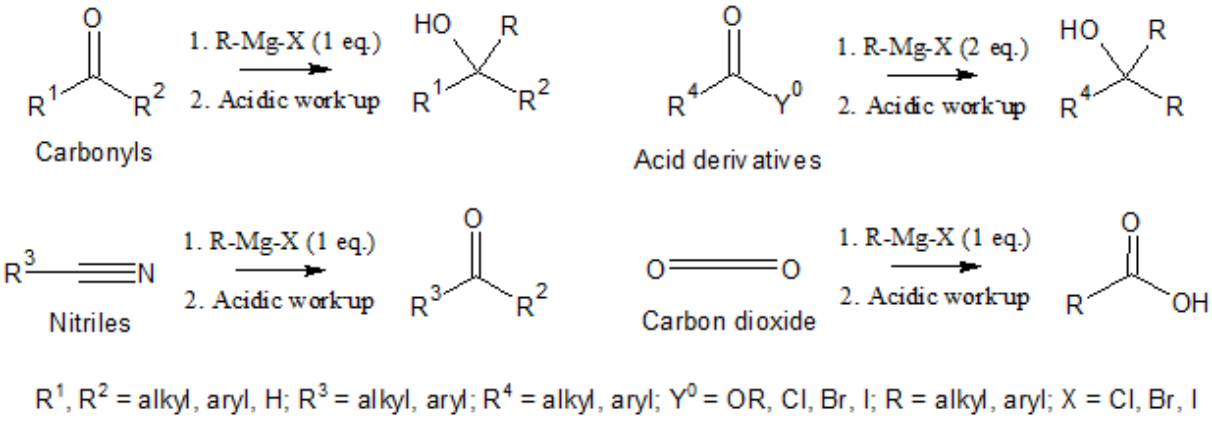



**Figure 34** – General reactions with Grignard reagents.

When Grignard reagents react with carbonyl compounds it is believed that the reaction follows a concerted- or a radical pathway (Figure 35).

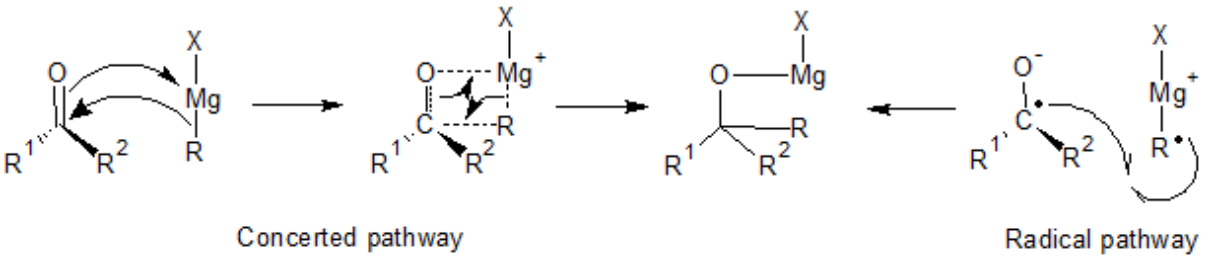



**Figure 35** – The proposed mechanisms for the reactions of Grignard reagents with carbonyl compounds.

Grignard reagents can also act as a base which is illustrated with magnesium bromodiphenylmethane reacting with water in figure 36. This is also a good way to see why strict anhydrous conditions are so important in the formation of Grignard reagents.

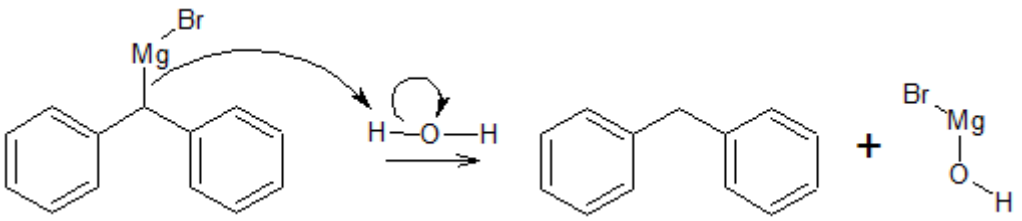


**Figure 36** – Magnesium bromodiphenylmethane reacting with water.

More obscure reactions can occur when certain Grignard reagents are reacted with hindered ketones. In these cases enolization of the ketone becomes the major reaction pathway.[35]

### 1.4.2. Sonochemistry[36]

Sound can be seen as waves of compression and expansion passing through gases, liquids or solids. Human hearing is capable of detecting such waves when they are in the range of the frequencies our ears can detect, which is from a few Hertz to around 16 kHZ. These frequencies have similarities to electromagnetic radiation in some ways, but show quite big differences in other areas. Sound can for instance not travel through the vacuum of space like electromagnetic radiation because it is dependent on matter to compress and expand through.

Ultrasound is high-pitched sound with frequencies higher than what we can detect with our ears. Ultrasound has many applications, both of medical and more practical nature. It can be used to monitor unborn fetuses, for breaking up kidney stones accumulated in the kidney or for treatment of cartilage tissue injuries. On the more practical side it is used for cleaning jewelry, emulsifying cosmetics and foods, wielding plastics, cutting alloys; it can even be found in certain dog whistles and burglar alarms.

The chemical aspects of ultrasound, sonochemistry, began in 1894 when Sir John I. Thornycroft and Sydney W. Barnaby discovered that the propellers of experimental high-speed torpedo boats produced large cavitational bubbles that gave rise to severe vibrations on the vessel. It was later discovered that the vibrations were due to enormous turbulence, heat and pressure produced when cavitational bubbles imploded on the surface of the propeller. This discovery was largely a forgotten chapter until the 1980s when inexpensive and stable laboratory-scale ultrasonic devices were becoming more prevalent.

Sonochemistry is largely separated in three areas – homogenous sonochemistry of liquids, heterogenous sonochemistry of liquid-liquid or liquid-solid systems and sonocatalysis, which can be seen as an overlap of the first two.

When a solution is being ultrasonically irradiated, the sound waves will not directly interact with the molecules of the solution. This is quite obvious when looking at the wavelengths of ultrasound, usually in the range of 10 cm (0.1 meters) to $10^{-3}$ cm (0.00001 meters), which is gigantic compared to atomic dimensions (femtometres – $10^{-15}$ meters).

The ultrasonic irradiation will instead lead to the formation of small cavitational bubbles in the reaction liquid, as the expansion of the ultrasonic sound waves pull the molecules away

from each other. The cavitations will grow as they absorb energy from the ultrasonic sound wave. At a certain point they will have grown to a size where they can no longer efficiently absorb energy from the ultrasonic sound waves and they will implode. The implosion leads to enormous amounts of localized heat and pressure with temperatures in excess of 5000 $^{o}$C, pressures in excess of 1000 atmospheres and heating/cooling rates in excess of $10^{10}$ K/s. It is these extreme conditions that create the environment necessary for sonochemical reactions.

The ultrasound is usually created by applying an AC-current (alternating current) to a piezoelectric ceramic causing it to vibrate (Figure 37). A piezoelectric material has the ability to accumulate an electrical charge and in most cases this material is PZT - lead zirconate titanate.

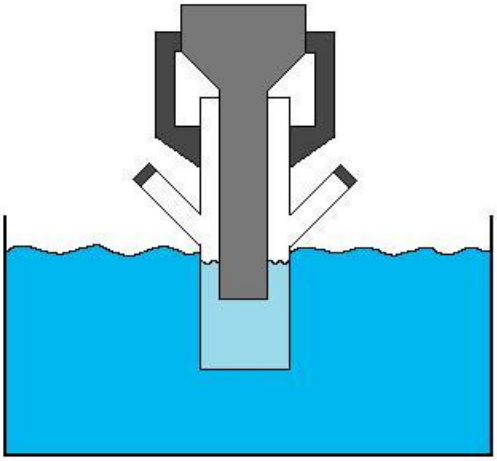


**Figure 37** – Piezoelectrically vibrating titanium rod immersed in a reaction liquid.

Homogenous sonochemistry of aqueous solutions have been studied quite extensively and most often results in the release of hydrogen-gas ($H_2$) and hydrogen-peroxide ($H_2O_2$), with more high-energy products in the form of superoxide ($HO_2$), atomic hydrogen (H), hydroxyl (-OH) and even solvated electrons ($e^-$). Sonolysis of water produces both strong oxidants and reductants. Homogenous sonochemistry of organic liquids have not been studied much, but reports seem to indicate the formation of free radicals in almost all organic media, while pyrolysis products also seem to emerge when sonochemistry is applied to simple hydrocarbons (gases and alkenes).

Heterogenous sonochemistry of liquid-solid systems is an important technique in chemistry today, especially in organometallic reactions where ultrasound can increase the reaction rate substantially. The cavitational bubbles created by the ultrasonic irradiation will implode near

the surface of the metal, causing it to break up and reveal highly reactive surfaces. In addition heterogenous sonochemistry has been applied successfully, and increased the reaction rates of oxidations, substitutions and the formation of metal-complexes.

Other applications of heterogenous sonochemistry include intercalation, which is the process of absorbing inorganic or organic compounds between atomic sheets of certain solids (molybdenum sulfite or graphite in particular). This can change the optical, electronic and catalytic properties of the intercalated materials.

Ultrasound reportedly also can be used in the creation of amorphous metals which are metals that lack any kind of crystal structure. This is usually extremely hard as the metal would have to be molten and then cooled down by approximately $10^6$ K/s to prevent the crystal structure from forming.

Catalysis is of great importance both in industry and smaller scale laboratories. It can be divided in homogenous catalysis, which is a molecular or ionic catalyst dissolved in a liquid, or heterogenous catalysis, which is a solid state catalyst with liquid or gas reactants. Usually it can be a big problem to activate and keep the catalysts activated, and there is also a problem with the cost of some of the catalysts as many of them are based on rare earth metals. Sonocatalysis is an area of sonochemistry that involves the use and activation of less reactive and less expensive materials for use in such processes, and as such, holds great promise for the future of ultrasound in both industry and smaller-scale laboratory work.

### 1.4.3. The Matteson homologation reaction

The Matteson homologation is the name of a reaction discovered in 1980 by Donald S. Matteson as a convenient way of synthesizing pure α-chloroalkyl boronates using a boronic ester with a chiral auxillary (Figure 38).[20] The term homologation is generally used on reactions where the substrate is transformed into the next or previous member of the homologous series.

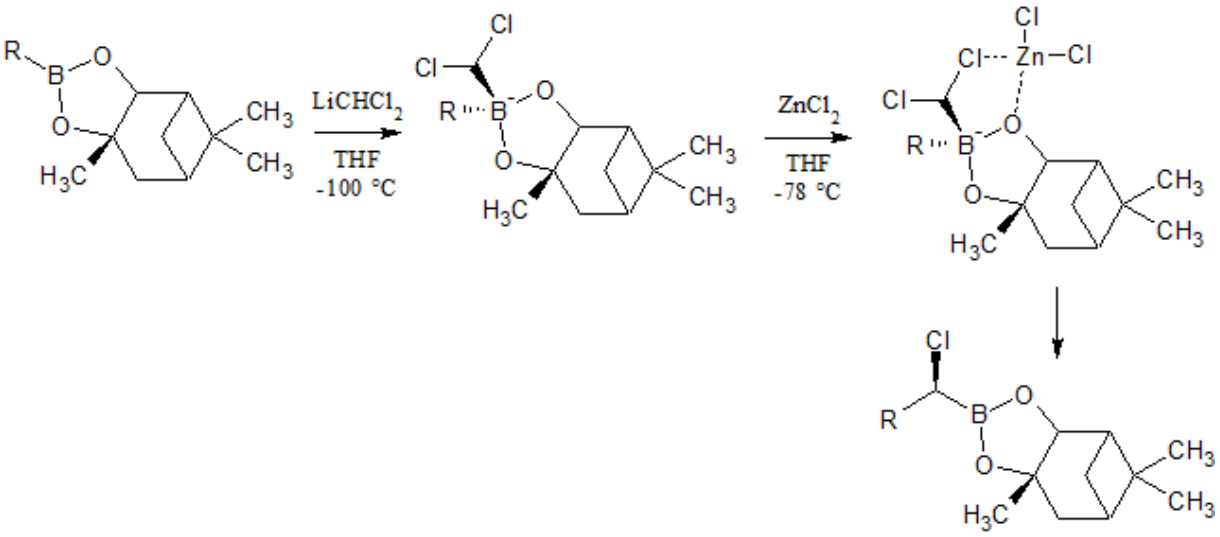



**Figure 38** – The proposed mechanism for the Matteson homologation. In this case the chiral auxiliary being used is (+)-pinanediol.

The Matteson reaction is performed by first preparing (dichloromethyl)lithium by the very careful drop-wise addition of n-butyllithium to a solution of dichloromethane in tetrahydrofuran at -100 $^{o}$C. The (dichloromethyl)lithium solution is then reacted with a boronic ester containing a chiral auxiliary in a similar careful fashion. The anionic intermediate that forms from this reaction will rearrange to an α-chloroalkyl boronate by a 1,2-migration of the R-group with high stereoselectivity when anhydrous zinc chloride is added. Achiral boronic esters can also be used if the stereochemistry is of no concern.

Another route leading to α-chloroalkyl boronates is to first synthesize a dichloromethyl boronate by treating a boronate with (dichloromethyl)lithium. The resulting dichloromethyl boronate is then reacted with a Grignard- or organolithium reagent. However with this method the enantiomeric purity will be low (Figure 39).[37-39]

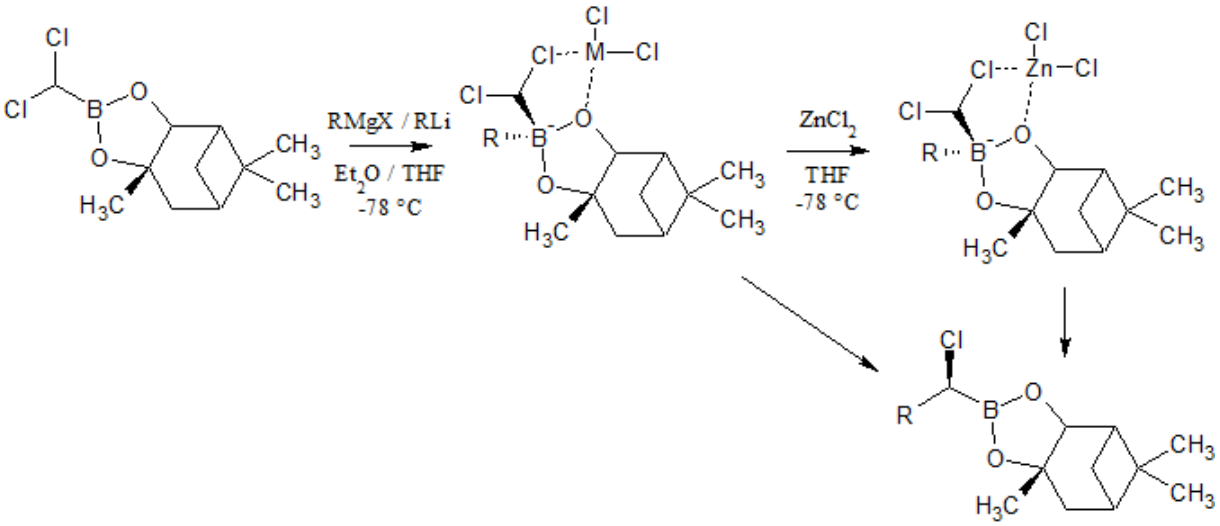



**Figure 39** – Preparation of an α-chloroalkyl boronate using a dichloromethyl boronate. In this case the chiral auxiliary being used is (+)-pinanediol

The use of zinc chloride in the Matteson homologation is of great importance. Zinc chloride provides stereoselectivity and is responsible for the re-arrangement of the intermediate boron-complex. The chelation between zinc, oxygen and chlorine is the driving force in the migration of the R-group and departure of the chlorine. More importantly is the fact that zinc chloride hinders epimerization of the product.[40-41] Epimerization is racemization of the product due to chlorine exchange at the stereogenic center which inverts the stereochemistry. Zinc chloride hinders epimerization of the product by capturing chloride ions generated in the reaction as $LiZnCl_3$ or $Li_2ZnCl_4$.

A wide range of nucleophiles will undergo 1,2-rearrangements similar to Grignard reagents and organolithiums, including esters ($^-$OR), sulfides ($^-$SR), amines ($^-NR_2$), azides ($^-$N3) and cyanomethides ($^-$CH2CN).

The stereoselectivity and versatility of this reaction makes it an important tool in chemistry and in particular in the synthesis of the compounds in this study – β-substituted β-aminoboronates.

# 2. AIMS OF THE THESIS

Recent work at the University of Tromsø had discovered new α-substituted α- and β-aminoboron containing peptidomimetics that showed antimicrobial, antifungal and antitubercular activity, in addition to kinase inhibition and promotion.

As an extension of the previous work being done at the University of Tromsø it was therefore of interest to synthesize new β-substituted β-aminoboronates and benchmark these against the recently published compounds.

In relation to the results from the previous work it was decided to use a small set of structurally different substituents for the β-position (Me, i-Pr, Ph, Bn), in addition to esterifying the boronic acid moiety using a set of commercially available enantiomerically pure carbohydrates (in particular α-D-glucose) to increase water solubility and potentially increase activity.

If a compound exhibited antimicrobial activity its diastereomers would, if possible, be resolved, or it would be synthesized as its pure enantiomer using enantiomerically pure carbohydrates as chiral directors.

Time constraints made it obvious that benchmarking against the recently published compounds would be out of the question and thus the following two aims were set:

To develop a general protocol for the synthesis of β-substituted β-aminoboronates either by:

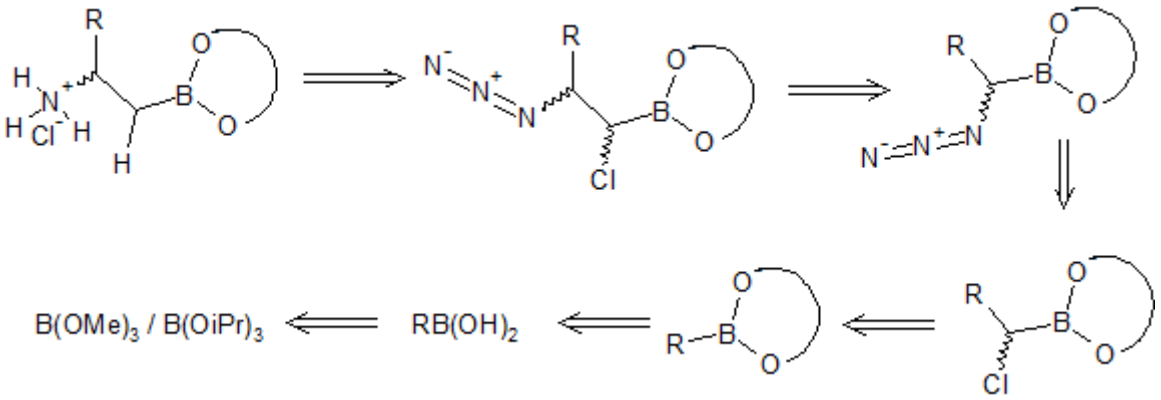
- Non-stereospecific synthesis as racemates followed by coupling to enantiomerically pure carbohydrates and then resolution of the diastereomers.
- Stereospecific synthesis using enantiomerically pure carbohydrates as chiral directors from the start.

# 3. RESULTS AND DISCUSSION

## 3.1. Strategies used in the synthesis of β-substituted β-aminoboronates

Three different strategies for the synthesis of β-substituted β-aminoboronates were attempted during the course of this study.

One of these strategies, henceforth referred to as "Strategy 1", is illustrated in Scheme 3.

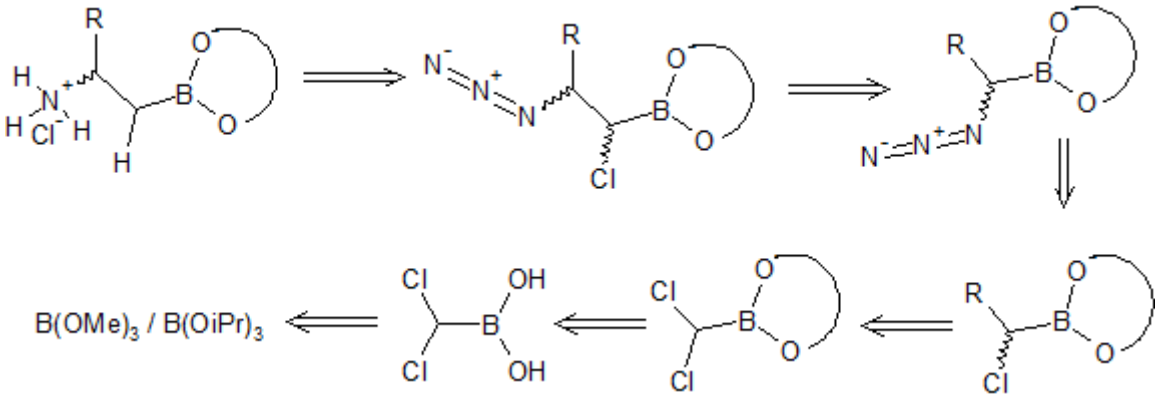



**Scheme 3** – Retrosynthetic analysis of the synthesis of β-substituted β-aminoboronates by Strategy 1.

A boronic ester such as trimethylborate or triisopropylborate is reacted with a Grignard-reagent leading to the boronic acid upon quenching. The boronic acid is then esterified using a diol leading to a boronic ester. The boronic ester is then homologated to an α-chloroalkyl boronate using the Matteson homologation procedure. The chlorine is displaced in a nucleophilic substitution reaction by azide and the product is once again homologated leading to a β-azido-α-chloroalkyl boronate. A reduction of the chlorine- and azide-group leads to the β-substituted β-aminoboronate, which for instance can be isolated as its amine hydrochloric salt to avoid re-arrangement of the amine-group to boron.

This strategy utilizes a double Matteson homologation and would provide high stereochemical control when applied to chiral boronates, but the Matteson homologation reaction however, is a very difficult reaction requiring careful monitoring and adjustment of reaction conditions such as temperature, stirring rate, addition rate of both reagents and substrates and even the way the reagents and substrates are administered. The conversion from starting material to product of these reactions is seldom complete and as such, a mixture of starting material and product can apply.

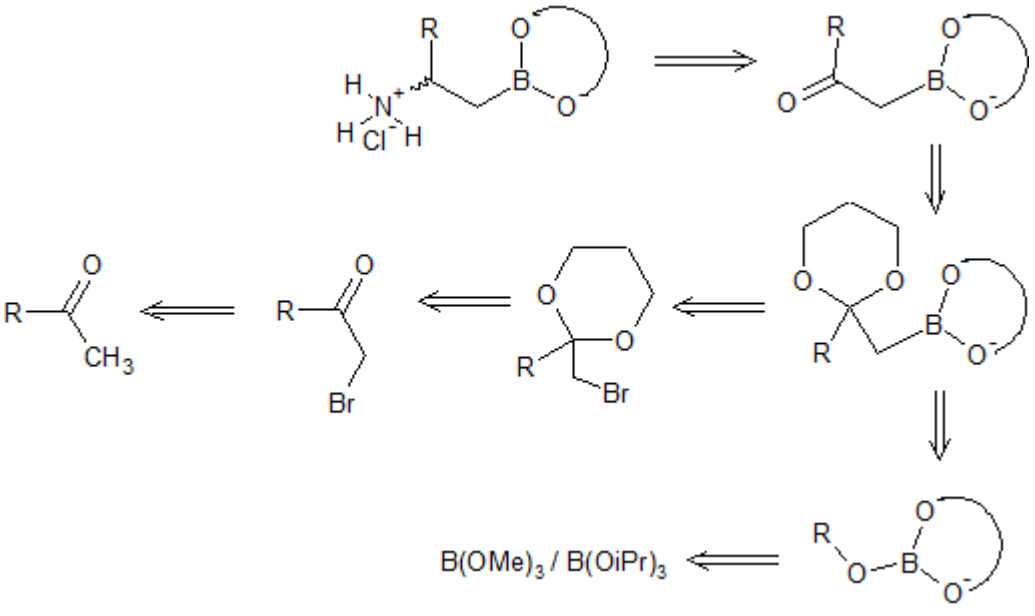
Another strategy, henceforth referred to as "Strategy 2", is illustrated in Scheme 4.




**Scheme 4** – Retrosynthetic analysis of the synthesis of β-substituted β-aminoboronates by Strategy 2.

This strategy avoids one homologation step by utilizing a different boronic ester for the homologation. The boronic ester is synthesized by reacting trimethylborate or triisopropylborate with (dichloromethyl)lithium, which again is prepared by reacting dichloromethane and n-butyllithium. The resulting dichloromethyl boronic acid is esterified to the dichloromethyl boronic ester. The rest of the strategy is identical to the previous one. This strategy is not suitable for synthesizing enantiomerically pure products as the stereochemical control of the substrate is expected to be low.[42]

The third and final strategy, henceforth referred to as "Strategy 3", is illustrated in Scheme 5.




**Scheme 5** – Retrosynthetic analysis of the synthesis of β-substituted β-aminoboronates by Strategy 3.

This strategy had not been described before and it was therefore of great interest to see if it would work, especially considering the ease of synthesis and low cost compared to the other

two strategies. The disadvantage of this strategy however, would be the loss of stereochemical control during the synthesis. The basic idea behind the strategy is as follows:

A cheap, commercially available ketone (with the same R-group as the expected β-substituted product) is turned into its α-bromoketone via the enol under acidic conditions. The α-bromoketone is then protected as its ketal and converted to a Grignard reagent. The Grignard reagent is then coupled with a boronic ester, prepared by trans-esterifying trimethylborate or triisopropylborate with a diol. With a diol like pinacol or pinandiol, hydrolysis should be possible selectively on the ketal functional group, leaving the diol intact. A reductive amination in the end, for instance the Leuckart-reaction (reductive amination using ammonium formate, formamide or formic acid and formamide), would give the expected β-substituted β-aminoboronate which again could be isolated as its amine hydrochloric salt.

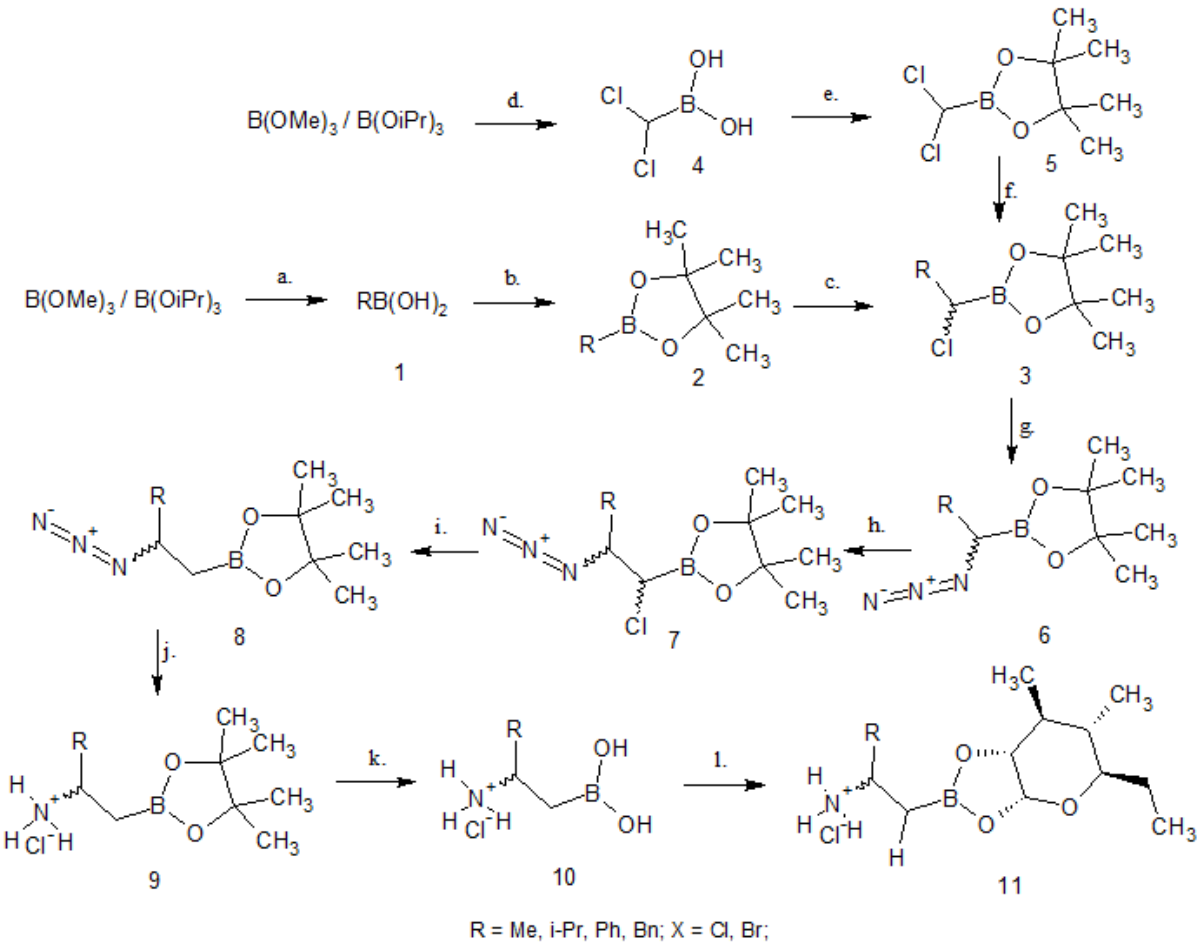
All three strategies described were pursued to some extent, and several exploratory experiments were also performed in attempts to find better reaction conditions or improve yields.

In addition the first semester of this study was used to explore the scope and limitations of the previously mentioned ultrasound promoted dimerization of benzylic halides.

The syntheses and results are described in the following chapters.

## 3.2. Synthesis of β-substituted β-aminoboronates by Strategies 1 and 2

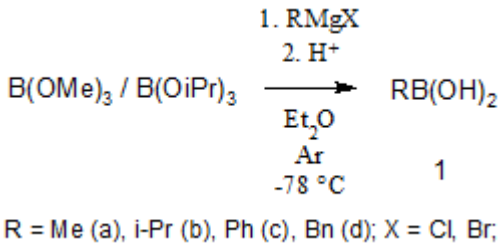
The chosen pathway for the synthesis of β-substituted β-aminoboronates is illustrated in Scheme 6. It involves both strategies 1 and 2 described in the previous chapter.




**Scheme 6** – The chosen pathway for synthesizing β-substituted β-aminoboronates by strategies 1 and 2.

### 3.2.1. Synthesis of boronic acids

Trimethylborate or triisopropylborate was converted to boronic acids **1a-1d** according to Scheme 7.




**Scheme 7** – Scheme for synthesizing boronic acids.

The procedure used is straight forward.[43] The borate starting material was dissolved in diethyl ether and the corresponding Grignard reagent added drop-wise at -78 $^{o}$C to the solution during stirring and strict anhydrous conditions. The solution was stirred overnight and then quenched, and the aqueous phase extracted using diethyl ether. The organic phase was washed with distilled water and the boronic acid extracted from the organic phase using an aqueous basic solution. The resulting solution was acidified, saturated and extracted with diethyl ether to give the boronic acid after drying and evaporation of solvents.

In total there were 16 syntheses of compounds **1a-1d** as summarized in Table 1.

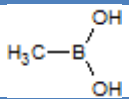
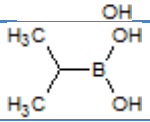
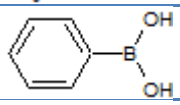
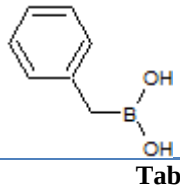
| Structure | Compound | Yield % |
|---|---|---|
|  | **1a** | 0 |
|  | **1b** | 46-58 |
|  | **1c** | 74 |
|  | **1d** | 71 |

**Table 1** – Isolated yields from the synthesis of compounds **1a-1d**.

For the larger substituents, such as benzyl and phenyl, the procedure works well. With smaller substituents, resulting in lower molecular weight boronic acids, the procedure does not yield the same results. Boronic acids with low molecular weight become very water soluble and

therefore difficult to isolate and is the probable cause for the low yields seen in the synthesis of compound **1a**.[44]

It was assumed that the aqueous workup could be the culprit of the poor results and it was changed accordingly. The washing of the organic phase with distilled water in the first step of the work-up was skipped. After acidifying the aqueous solution it was saturated with sodium chloride, diethyl ether was added and the solution was left to stir over the night in an attempt to extract the methylboronic acid into the organic phase. Despite this new work-up routine no product was ever isolated in any of the reactions.

After five failed attempts at synthesizing compound **1a** reacting both trimethyl- and triisopropyl borate with methylmagnesium bromide and methyl lithium, alternative methods were investigated in an attempt to synthesize compound **1a** as its boronate.[45-47]

A method involving the reaction of triisopropyl borate and methyl lithium, followed by anhydrous acidic quench was attempted, but still no product could be detected (Figure 41). As a consequence of this it was decided to attempt to introduce the methyl-group at the next step instead, using a boroxine or a different boronic ester than trimethyl- or triisopropyl borate.

At the time no plausible explanations could be given for the poor result, but in retrospect an explanation could perhaps be that the product had evaporated during the concentration on the rotary evaporator. At atmospheric pressure (760 torr), diisopropyl methylboronate has a boiling point of 105-107 ºC. The rotary evaporator used in the lab can easily reach pressures as low as 20-30 torr, which would equate to a boiling point of 5-16 ºC for diisopropyl methylboronate.

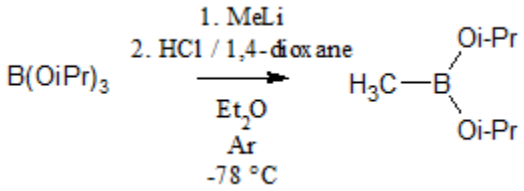



**Figure 41** – Synthesis of diisopropyl methylboronate.

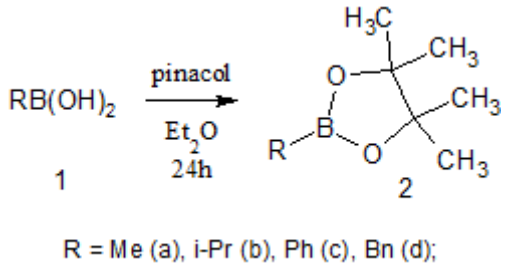
NMR data of boronic acids can be notoriously hard to interpret due to the tendency of boronic acids to form boroxines, and in some cases dimers. GC-MS and MS analysis can be used for identification in these cases or when the boronic acid has otherwise been chemically derivatized.

This is evident with compound **1d** which shows two extra peaks at 5.11 – 4.99 and 4.35 – 4.30 ppm in the $^{1}$H-NMR spectrum (Appendix 5). These peaks are most likely a result of boroxine formation.

Later derivatization of the same compound with 1,3-propanediol shows that it indeed was the correct boronic acid (Appendix 7-8).

### 3.2.2. Synthesis of boronates

The boronic acids were converted to boronates **2a-2d** according to Scheme 8.




**Scheme 8** – Scheme for synthesizing boronates.

The boronic acids were esterified by stirring them together with pinacol in diethyl ether overnight. The solvents were evaporated, the residual compound dissolved in pentane and filtered through silica to yield the boronate after concentration in vacuo.

The reaction is an equilibrium reaction which can be shifted in the direction of product formation by removing excess water produced in the reaction using a dehydrating agent. However the reaction also proceeds very well despite using any dehydrating agents and possible reasons for this could be the stability of the five-membered ring in the product compared to the stability of the starting material and/or the increase in entropy resulting from the formation of three molecules on the product side (2 molecules of water is produced in the reaction) compared to the two on the starting material side.

During the course of the study magnesium sulfate, sodium sulfate and 4Å molecular sieves were tested as dehydrating agents for these reactions. In most cases the yields were actually quite a bit lower when dehydrating agents were used, most likely as a result of absorbance of product or starting material on the dehydrating agent (in the case of magnesium- and sodium sulfate) because a too large excess was used.

Since compound **1a,** methylboronic acid, had not been successfully synthesized in the previous step it was necessary to prepare it at this stage. The strategy was to synthesize a

boronate that would give a product that was less water soluble after methylation than methylboronic acid was.

A couple of boronates were synthesized for this purpose, namely 2-methoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**2e**) and 2-isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**2f**). These compounds were synthesized by refluxing an excess of the appropriate boronic ester together with pinacol in hexane. By using an excess of the boronic ester compared to pinacol, the work-up would only consist of evaporating the solvent and the boronic ester starting material on the rotary evaporator in order to obtain pure product (Figure 42).

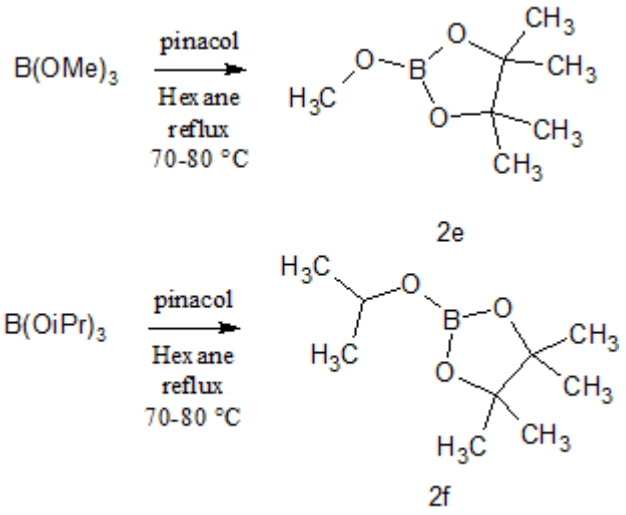



**Figure 42** – Synthesis of boronates used in the synthesis of compound **2a**.

Compound **2f** was selected as a candidate for the experiment and two experiments were run, one using methyl magnesium bromide and the other using methyl lithium (Figure 43).

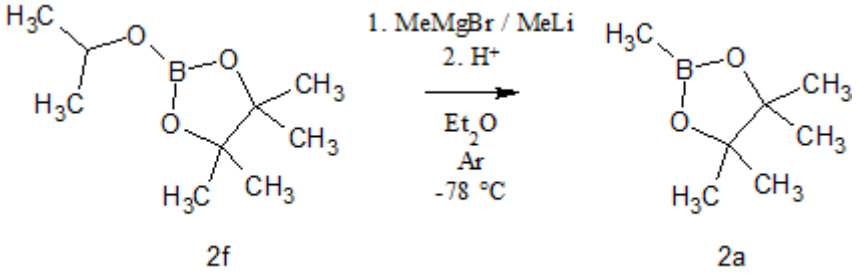



**Figure 43** – Synthesis of compound **2a**.

Analysis by NMR seemed to indicate the presence of mostly starting material, however when analyzed by GC-MS it was observed that some product had formed in the reaction. Using

methyl lithium as the methylating agent resulted in the formation of more product than when using methyl magnesium bromide.

In the end compound **2a** had to be synthesized by reacting store-bought trimethylboroxine with pinacol in diethyl ether following the same procedure as with the other boronic acids (Figure 44).

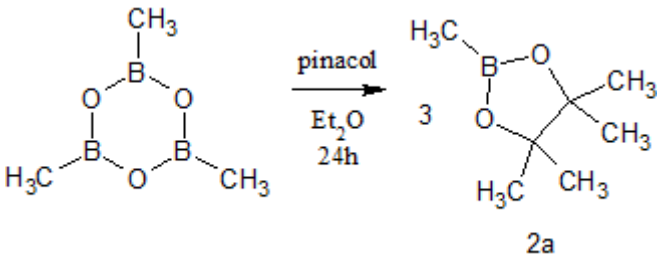



**Figure 44** – Synthesis of compound **2a** using trimethylboroxine.

$^{13}$C-NMR analysis of compound **2b** showed an extra peak in the pinacol methyl carbon area (~24 ppm) indicating a possible by-product (Appendix 13).

Analysis of compound **2b** by GC-MS confirmed a by-product with a molecular mass of 186 g/mol compared to that of the product which is 170 g/mol. Two syntheses were run in order to try and identify the by-product.

Preparation of compound **1b** was achieved with both starting materials – trimethyl borate and triisopropyl borate. After esterification with pinacol to compound **2b**, a GC-MS analysis was run on each sample. The compound prepared from trimethyl borate contained mostly the expected product, but also some of the by-product (Appendix 14-16). The compound prepared from triisopropyl borate however showed the exact opposite (Appendix 17-19). The main component of the sample was in fact the by-product, while the expected product was the minor component (Figure 45). This seemed quite strange seeing as the only thing that separated the starting materials were the ester-groups on the boron.

The leaving groups from these reactions would be methanol and iso-propanol from trimethyl borate and triisopropyl borate respectively. Judging from the mass spectra of the two components it seemed as if the difference could in fact be due to either an isopropyl-group or an isopropoxy-group attached to the boron. By comparing the mass spectra of the by-product with that of compound **2f** (Appendix 29) it was revealed that the by-product was, surprisingly

enough, compound **2f**. The oxidation of boron-carbon bonds are, as already mentioned in the introduction, very slow processes.

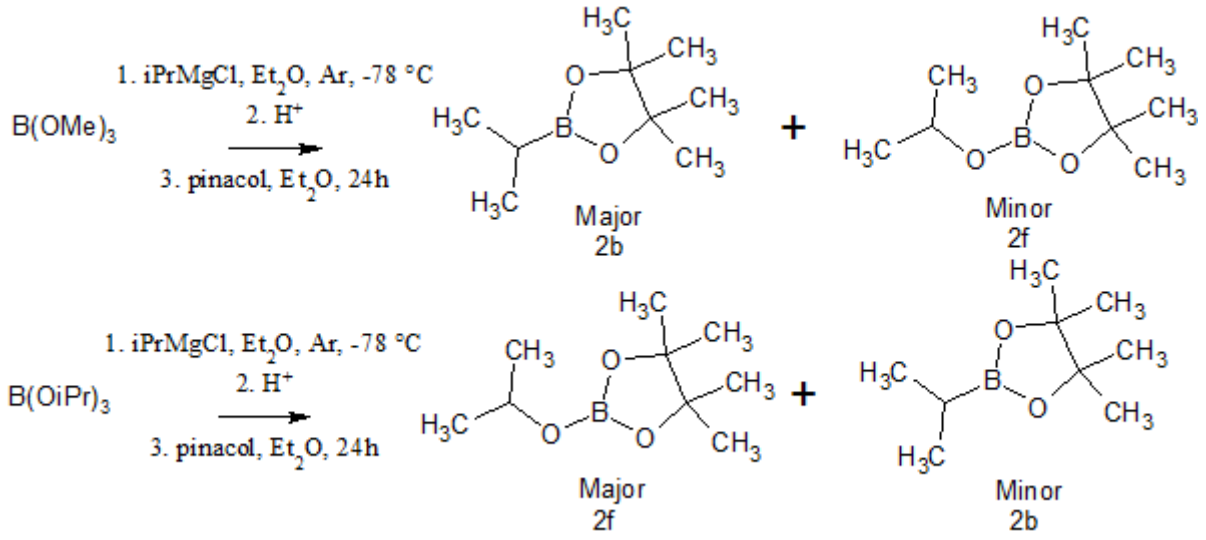



**Figure 45** – Syntheses of compound **2b** leading to compound **2f** as a byproduct in differing amounts.

It seems likely that the isopropoxy-group is more stable than the isopropyl-group as the reaction of triisopropyl borate and isopropylmagnesium chloride leads to almost exclusively compound **2f**, possibly indicating an exchange of the isopropyl-group with the isopropanol being produced in the reaction. The only logical way to explain this in the reaction of trimethyl borate and isopropylmagnesium chloride would be if the Grignard-reagent had been exposed to oxygen; perhaps during the reaction, leading to isopropanol in the solution.

For these compounds a total of 11 syntheses were run with the results summarized in Table 2. As can be seen from the table, compounds **2b** and **2d** show a big variation in yields. This is due to two outliers in the experimental data where an excessive use of dehydrating agent was utilized, resulting in low yields most probably due to absorption of starting material and product on the dehydrating agent.

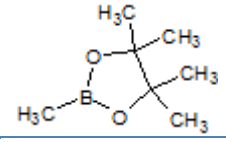
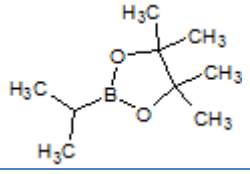
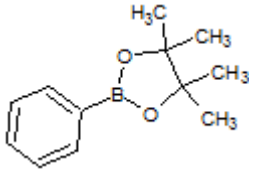
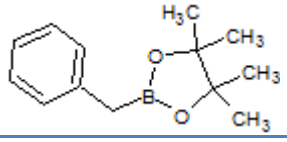
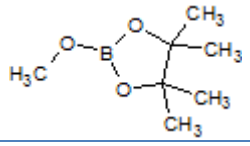
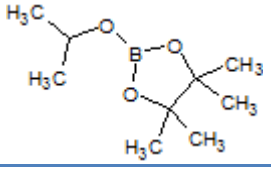
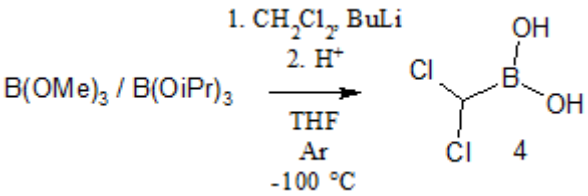
| Structure | Compound | Yield % |
|---|---|---|
|  | **2a** | 87 |
|  | **2b** | 37-95 |
|  | **2c** | 75 |
|  | **2d** | 29-82 |
|  | **2e** | 78 |
|  | **2f** | 85 |

**Table 2** – Isolated yields from the synthesis of compounds **2a**-**2f**.

### 3.2.3. Synthesis of dichloromethyl boronic acids

Trimethylborate or triisopropylborate was converted to dichloromethyl boronic acid **4** according to Scheme 9.




**Scheme 9** - Scheme for synthesizing dichloromethyl boronic acids.

The dichloromethyl boronic acids were obtained by reacting (dichloromethyl)lithium with trimethyl borate under strict anhydrous conditions. The (dichloromethyl)lithium was prepared by the drop-wise addition of n-butyllithium to a stirred solution of dichloromethane in tetrahydrofuran at -100 °C. The boronic ester was then added in a similar drop-wise fashion to the suspension of (dichloromethyl)lithium and the solution allowed to reach -78 °C. The solution was quenched at -41 °C and the aqueous and organic layers separated. The aqueous layer was extracted with diethyl ether and the combined organic phases washed with a saturated solution of aqueous ammonium chloride. Drying and concentration in vacuo gave the dichloromethyl boronic acid.

Due to a few initial mishaps following the original procedure it was slightly altered.[38] The addition of the borate starting material was changed to a drop-wise addition instead of adding everything at once, which promptly turned the solution black. Changing the cooling bath from the ethanol/liquid nitrogen-bath to dry ice/acetone was done for convenience as it is easier to maintain the temperature for longer periods of time using the latter. Also there would be no need to keep the temperature at -100 °C after the (dichloromethyl)lithium had reacted. The quenching of the solution was performed at -41 °C instead of doing it at -100 °C. At lower temperatures the solution turned very dark and the aqueous phase froze. The final change to the procedure was to wash the crude dichloromethyl boronic acid with a saturated solution of aqueous ammonium chloride in order to remove lithium salts formed in the reaction.

The NMR spectra of compound **4** are hard to interpret due to several extra peaks; most likely as a result of boroxine formation (Appendix 47-48). However the peak at 5.27 ppm in the $^{1}$H-NMR spectrum is believed to be the dichloromethyl proton.

In total 6 syntheses of compound **4** were done as summarized in Table 3.

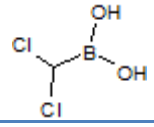
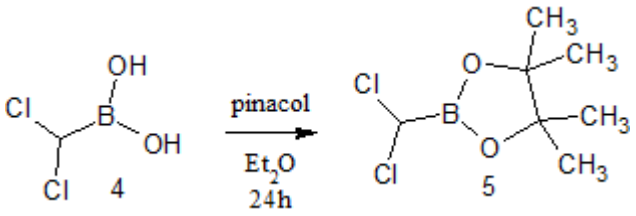
| Structure | Compound | Yield % |
|---|---|---|
|  | **4** | 25-136 |

**Table 3** – Isolated yields from the synthesis of compound **4**.

Following the original procedure led to the lowest yield. The solution got very dark, almost black, with subsequently poor yield. The outlier in the opposite end of the scale is most certainly due to the crude containing some solvent still when it was weighed. Most commonly the yields would be in the 60 percent range.

### 3.2.4. Synthesis of dichloromethyl boronates

The boronic acids were converted to dichloromethyl boronates **5** according to Scheme 10.




**Scheme 10** - Scheme for synthesizing dichloromethyl boronates.

The esterification of the dichloromethyl boronic acids were achieved in the same manner as previously described for boronic acids. The dichloromethyl boronic acids were stirred together with pinacol in diethyl ether overnight. The solvents were evaporated, the residual compound dissolved in pentane and filtered through silica to yield the dichloromethyl boronate after concentration in vacuo.

The yields for this reaction were not very impressive and as a result, reactions were run using dehydrating agents such as 4Å molecular sieves, magnesium- or sodium sulfate. The results were approximately the same when using dehydrating agents as when not using them.

In total 6 syntheses of compound **5** were done as summarized in Table 4.

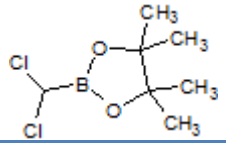
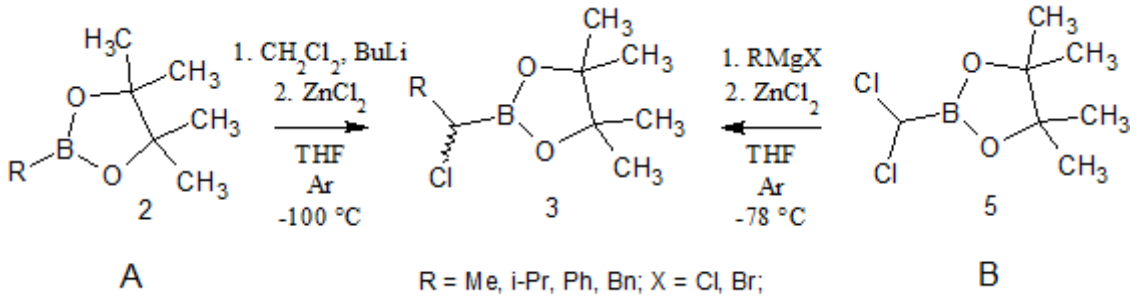
| Structure | Compound | Yield % |
|---|---|---|
|  | **5** | 31-56 |

**Table 4** - Isolated yields from the synthesis of compound **5**.

### 3.2.5. Synthesis of α-chloroalkyl boronates

The boronates were converted to α-chloroalkyl boronates **3** according to Schemes 11A and 11B.




**Scheme 11A/B** - Schemes for synthesizing α-chloroalkyl boronates.

For the conversion of compound **2** to **3** the following procedure was used.[48]

Dichloromethyl(lithium) was prepared by the drop-wise addition of n-butyllithium to a stirred solution of dichloromethane in tetrahydrofuran at -100 $^{o}$C during strict anhydrous conditions. The boronate was then added in a similar fashion to the suspension of (dichloromethyl)lithium and the resulting solution allowed to reach -78 $^{o}$C. Anhydrous zinc chloride was added drop-wise and the solution left to stir overnight. The solution was diluted with diethyl ether, washed with saturated aqueous ammonium chloride, separated and concentrated on the rotary evaporator. The residual oil was diluted with pentane and washed once more with saturated aqueous ammonium chloride before the organic layer was separated, dried and concentrated in vacuo to give the α-chloroalkyl boronate.

For the conversion of compound **5** to **3** the following procedure was used.[49]

Dichloromethyl boronate was dissolved in diethyl ether and the corresponding Grignard reagent added drop-wise at -78 $^{o}$C during stirring and strict anhydrous conditions. Anhydrous zinc chloride was added drop-wise and the solution left to stir overnight. The solution was then diluted with diethyl ether, washed with saturated aqueous ammonium chloride, separated and concentrated in vacuo. The residual oil was dissolved in pentane, washed again with saturated aqueous ammonium chloride and then dried and concentrated on the rotary evaporator to give the α-chloroalkyl boronate.

Both procedures lead to the same product, typically with a higher overall yield following the first procedure, but with a higher purity in the latter case. The first procedure, which is a

typical Matteson homologation, is a very challenging procedure which always resulted in some remaining starting material and thus additional purification steps. In addition the pinacol protecting group used for the boronic acid moiety is achiral, so the benefit of using the first procedure was void.

Preparation of α-chloroalkyl boronates was straightforward using the latter procedure and also eliminated the previous problem with the methyl substituent and the by-product in the preparation of compound **2b**. Only compound **2d** was homologated using the first procedure before the other procedure became the method of choice for synthesizing compound **3a-3d**.

GC-MS analysis of compound **3c** (Appendix 40) showed unreacted starting material and biphenyl present in the sample complicating analysis by NMR (Appendix 38-39). The peak at 4.48 ppm in the $^{1}$H-NMR spectrum is believed to be the α-proton to boron. The integral should be 1H, but is smaller due to the by-products being part of the total integral. The peak at 5.35 ppm in the $^{1}$H-NMR spectrum and the peak at 85.78 ppm in the $^{13}$C-NMR spectrum belongs to compound **5**. Very rarely can the α-carbons of boron be seen. This could however be the case with the peak at 115.26 ppm in the $^{13}$C-NMR spectrum. The presence of biphenyl makes interpreting the aromatic carbons a challenge, but judging by the intensity of the peaks it seems as if the peaks belonging to biphenyl could be located at 128.51 ppm, 127.22 and 126.38. The quaternary carbons cannot be seen for either compound **3c** or biphenyl due to noise.

In total 14 syntheses of compounds **3a**-**3d** were done as summarized in Table 5.

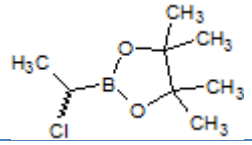
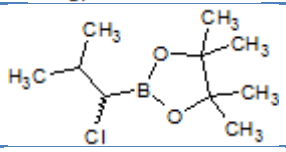
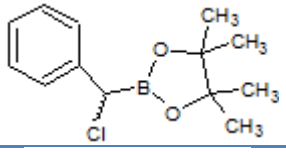
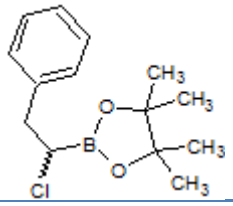
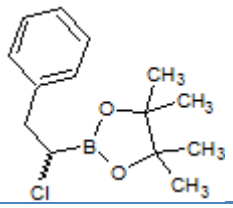
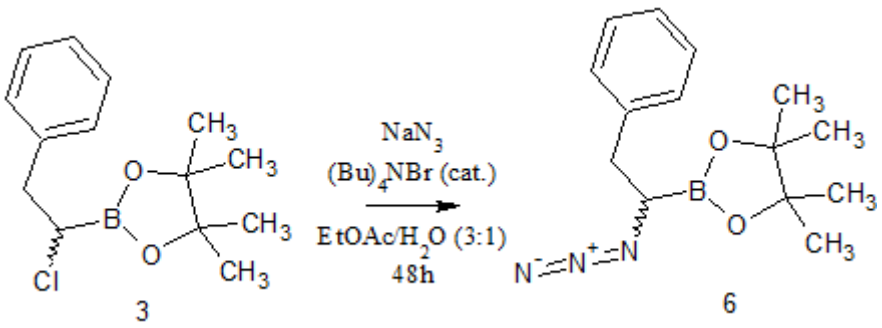
| Structure | Compound | Yield % |
|---|---|---|
|  | **3a** | 48 |
|  | **3b** | 33 |
|  | **3c** | 44 |
|  | **3d** | 50-90 |
|  | **3d** (prepared from **2d**) | 26-79 |

**Table 5** – Isolated yields from the synthesis of compounds **3a-3d**.

Due to time constraints it was decided to focus on one of the compounds for the remainder of the synthesis. The compound chosen was compound **3d**, in forthcoming steps referred to without the letter.

### 3.2.6. Synthesis of α-azidoalkyl boronates

The α-chloroalkyl boronates were converted to α-azidoalkyl boronates **6** according to Scheme 12.




**Scheme 12** - Scheme for synthesizing α-azidoalkyl boronates.

The procedure used for the conversion of the α-chloroalkyl boronate to the α-azidoalkyl boronate is described below.[48]

Sodium azide and tetrabutylammonium bromide was dissolved in a solution of ethyl acetate and water and stirred. The α-chloroalkyl boronate was added drop-wise to the solution and the resulting solution left to stir for 48 hours. The organic phase was separated and the aqueous phase extracted with ethyl acetate. The combined organic phases were concentrated on the rotary evaporator, diluted with pentane, washed with saturated aqueous ammonium chloride, dried and concentrated in vacuo to give the α-azidoalkyl boronate.

In the original procedure the solution was stirred for 24 hours after the addition of the α-chloroalkyl boronate. In a few cases this led to only partial conversion so it was decided to extend the stirring period to 48 hours to ensure a complete conversion.

One of the reasons for the slower conversion rate could be that the solvent was changed from dichloromethane to ethyl acetate for safety reasons. Azides can displace chlorine from dichloromethane producing highly explosive substances such as diazidomethane.

In total compound **6** was synthesized 6 times as summarized in Table 6.

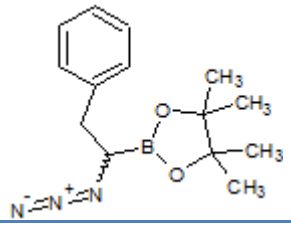
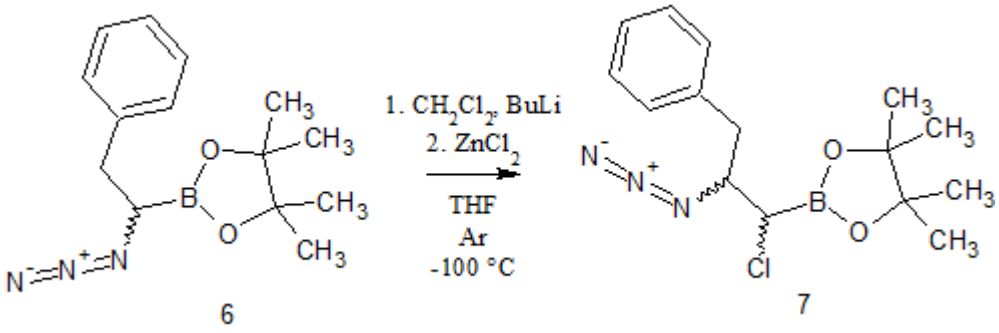
| Structure | Compound | Yield % |
|---|---|---|
|  | **6** | 54-81 |

**Table 6** - Isolated yields from the synthesis of compound **6**.

### 3.2.7. Synthesis of β-azido-α-chloroalkyl boronates

The α-azidoalkyl boronates were converted to β-azido-α-chloroalkyl boronates **7** according to Scheme 13.




**Scheme 13** - Scheme for synthesizing β-azido-α-chloroalkyl boronates.

The procedure is the same as the one used in previous steps to homologate boronic esters.[48]

Dichloromethyl(lithium) was prepared by the drop-wise addition of n-butyllithium to a stirred solution of dichloromethane in tetrahydrofuran at -100 $^{o}$C during strict anhydrous conditions. The α-azidoalkyl boronate was then added in a similar fashion to the suspension of (dichloromethyl)lithium and the solution allowed to reach -78 $^{o}$C. Anhydrous zinc chloride was added drop-wise and the solution left to stir overnight. The solution was diluted with diethyl ether, washed with saturated aqueous ammonium chloride, separated and concentrated on the rotary evaporator. The residual oil was diluted with pentane and washed once more with saturated aqueous ammonium chloride before the organic layer was separated, dried and concentrated in vacuo to give the β-azido-α-chloroalkyl boronate.

As with the first homologation step the conversion from starting material to product was never complete, but results steadily improved as the reaction was repeated and the experience increased.

The $^{13}$C-NMR spectrum showed some splitting of the peaks in addition to a small amount of unhomologated starting material (Appendix 57).

The reaction was repeated a total of 6 times with the results summarized in Table 7.

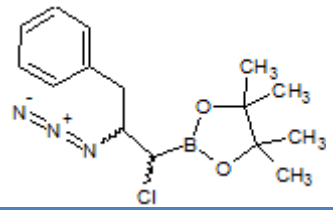
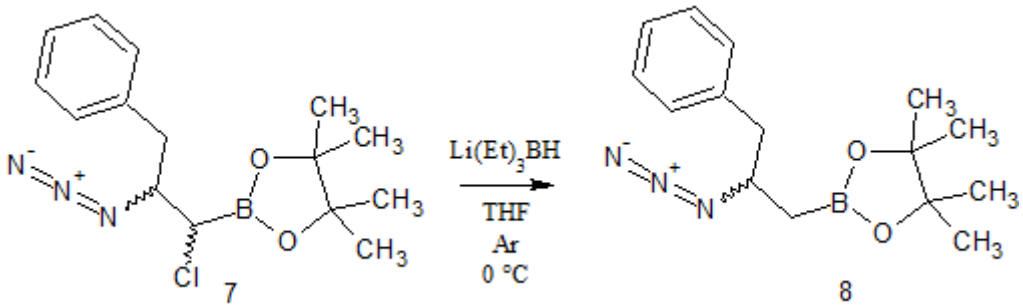
| Structure | Compound | Yield % |
|---|---|---|
|  | **7** | 52-61 |

**Table 7** - Isolated yields from the synthesis of compound **7**.

### 3.2.8. Synthesis of β-azidoalkyl boronates

The β-azido-α-chloroalkyl boronates were converted to β-azidoalkyl boronates **8** according to Scheme 14.




**Scheme 14** - Scheme for synthesizing β-azidoalkyl boronates.

The procedure followed in order to reduce the β-azido-α-chloroalkyl boronate to its β-azidoalkyl boronate is described below.

The β-azido-α-chloroalkyl boronate was dissolved in tetrahydrofuran and lithium triethylborohydride added drop-wise during stirring at 0 °C under anhydrous conditions. The solution was stirred for 3 hours and then diluted with diethyl ether, washed with saturated aqueous ammonium chloride, dried and concentrated on the rotary evaporator to give the β-azidoalkyl boronate.

Initially this reaction was carried out according to previous syntheses done on similar compounds at the university - the reaction was performed at -78 °C and left to warm up overnight while stirring.[50] The yields were average and often there was still unreacted starting material present after the reaction. It was speculated that the reason could be that the azide was also reduced at elevated temperatures. It was therefore decided to run a series of experiments in an attempt to find better experimental conditions for the reaction.

A series of four experiments were run at four different temperatures. In each case after the addition of the lithium triethylborohydride the solution was kept at its chosen reaction temperature for 3 hours before being worked up. $^{1}$H-NMR analysis showed a new peak emerging in the pinacol area at 1.27 ppm (Appendix 62-64) corresponding to compound **8**.

The results are illustrated in Table 8.

| Temperature $^{o}$C | Conversion % | Yield % |
|---|---|---|
| -78 (dry ice/acetone) | 0 | 0 |
| -41 (dry ice/acetonitrile) | 20 | 30 |
| -18 (dry ice/benzyl alcohol) | 58 | 70 |
| 0 (ice) | 100 | 77 |

**Table 8** – Experiments run to possibly determine better reaction conditions in the synthesis of compound **8**.

From these results it seems likely that the temperature should be somewhere between -18 $^{o}$C and 0 $^{o}$C for the reaction to proceed well. The highest yields were obtained using reaction temperatures of 0 $^{o}$C, so the procedure was changed to reflect this new information.

This seems reasonable when compared to other studies where similar reactions has been run at -30 $^{o}$C and at room temperature (25 $^{o}$C).[51-52]

The next step in the synthesis consists of reducing the azide to the amine. It would perhaps seem like a better and more efficient strategy to reduce both the azide and the chlorine at once, but that could lead to an unwanted by-product. If the azide-group is reduced to the amine before the chlorine is reduced, the amine could potentially do a nucleophilic substitution of the chlorine or re-arrange to the boron-atom (Figure 46).

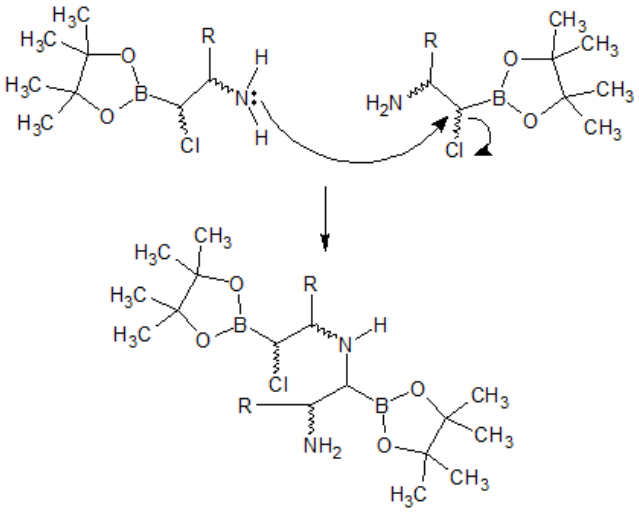


**Figure 46** – A potential by-product formed if the azide is reduced before the chlorine.

With the plethora of available reducing agents the choice of using lithium triethylborohydride for this reaction is not arbitrary. Experiments using lithium aluminum hydride has been shown to yield mixtures of the expected product, borane and lithium borane salts as a result of over-reduction.[52] The work-up of lithium aluminum hydride requires careful quenching in order to avoid "caking" of lithium salts and product. The work-up of lithium triethylborohydride is very easy compared, as can be seen from the procedure.

The Staudinger reaction (Figure 47), which is the reduction of azides using triphenylphosphine, has also been tested in previous work done at the university, resulting in a re-arrangement of the amine from the β-carbon to the boron-atom itself.[53-54]

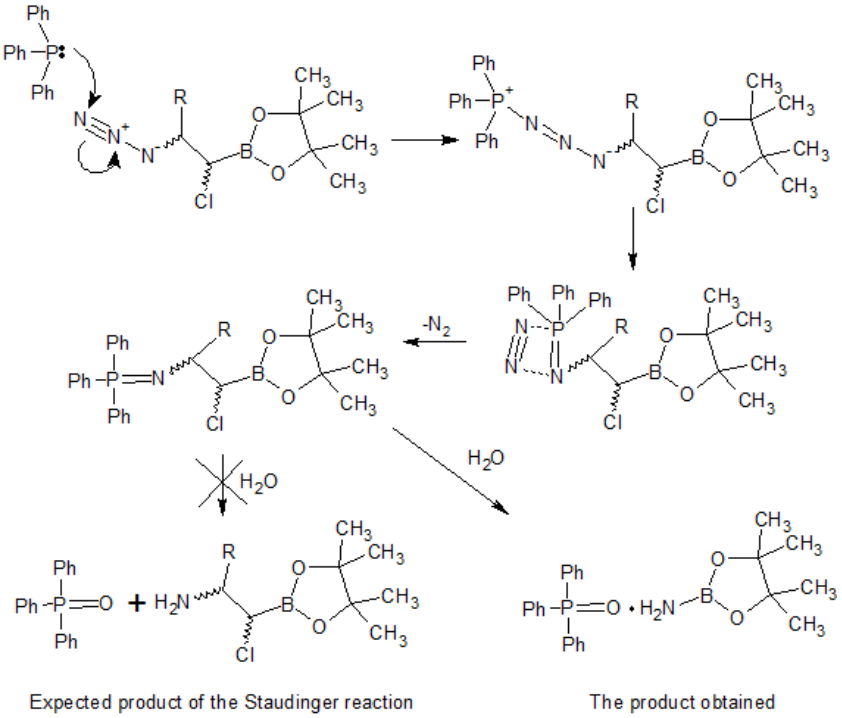



**Figure 47** – The mechanism of the Staudinger reaction and results when applied to β-azidoalkyl boronates.

There were 4 syntheses of compound **8**, excluding the three experiments that did not give a full conversion when exploring reaction conditions. The results have been summarized in Table 9.

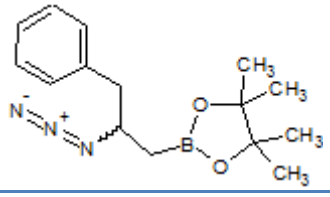
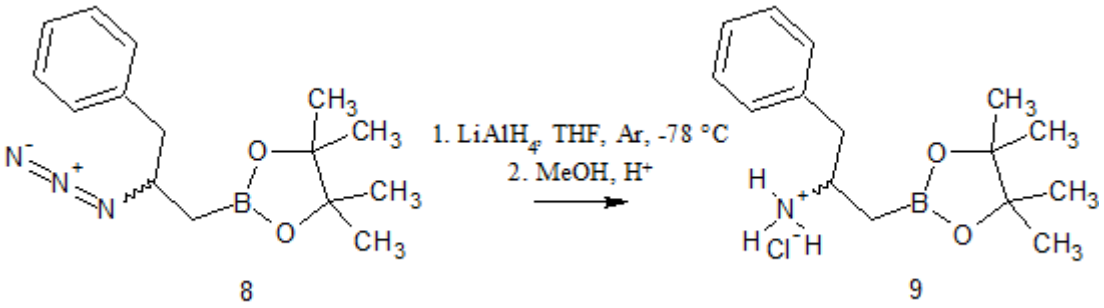
| Structure | Compound | Yield % |
|---|---|---|
|  | **8** | 67-78 |

**Table 9** - Isolated yields from the synthesis of compound **8**.

### 3.2.9. Synthesis of β-aminoboronates

The β-azidoalkyl boronates were converted to β-aminoboronates **9** according to Scheme 15.




**Scheme 15** - Scheme for synthesizing β-aminoboronates.

The procedure for synthesizing compound **9** is described below.[55]

The β-azidoalkyl boronate was dissolved in tetrahydrofuran and lithium aluminum hydride added drop-wise at -78 ºC during stirring and strict anhydrous conditions. After the addition was completed the solution was left to stir overnight. The solution was diluted with diethyl ether and equal volumes of water, 15 % aqueous sodium hydroxide and water were added very slowly drop-wise to the solution in that order. The solution was vacuum-filtered using a large volume of diethyl ether and the resulting ethereal solution washed with saturated aqueous ammonium chloride, dried and concentrated in vacuo. The residual oil was dissolved in pentane and an excess of hydrochloric acid in methanol was added slowly at 0 ºC and the solution left to stir overnight. The solvents were evaporated and the residual oil washed in boiling pentane to give what judging by analytical data (Appendix 65-67) appeared to be a mixture of the expected amine salt and the amine.

Analysis by infrared spectroscopy (Appendix 68) showed that the typical azide absorption peak at around 2100 reciprocal centimeters ($cm^{-1}$) was gone, which excluded that any starting material could be left. The IR also showed absorptions very typical of primary amines, such as the scissoring stretch at around 1600 $cm^{-1}$ and out-of-plane wagging at 700-750 $cm^{-1}$. What looked to be the C-N stretch also appeared at around 1150 $cm^{-1}$. The symmetric and asymmetric N-H stretches were not present in the spectrum, but this could be due to the presence of the primary amine salt. Primary amine salts have broad N-H stretches, which in this case could be the reason why only this stretch was seen and not the symmetric and asymmetric stretches one would expect of a primary amine.

Analyis by HRMS detected a mass of 262.1975 corresponding well with the exact mass of the protonated aminoboronate which is 262.1978. A different work-up method should be employed in order to separate the compounds; perhaps as simple as just washing the compound with ice-cold ether. Another solution could be to treat the mixture of amine and amine salt with hydrochloric acid in methanol again to convert more of the amine to its amine salt. It seems likely that using a bigger excess of hydrochloric acid in methanol and/or a prolonged reaction time when performing this reaction could potentially eliminate the problem.

Due to time constraints, in particular the writing of this thesis, it was decided to put the synthesis following these strategies on a hiatus and focus on the last two steps of the strategy using cheap, store-bought starting materials.

The synthesis of compound **9** was performed three times with the results indicated in Table 10.

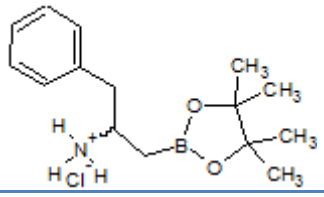
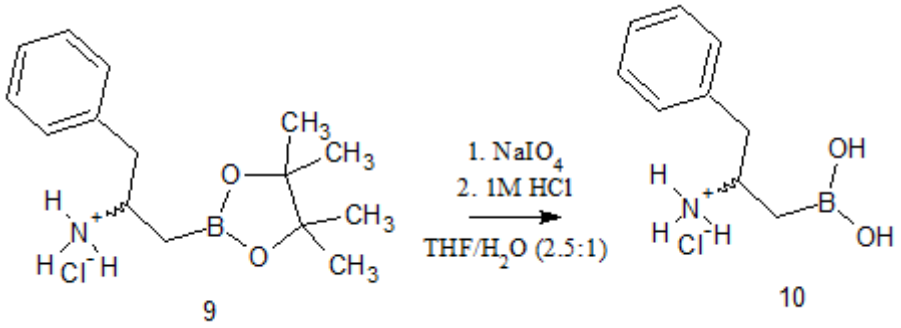
| Structure | Compound | Yield % |
|---|---|---|
|  | **9** | 18-35 |

**Table 10** - Isolated yields from the synthesis of compound **9**.

The yields for these reactions were not impressive and it is likely that over-reduction of the boronic ester moiety to borane and lithium borane salts, as mentioned in the last chapter, could have occurred. The aluminum salts being formed in the reaction could also quite possibly have trapped some of the product. The yields can also be expected to be lower as analysis seemed to indicate the presence of both the aminoboronate and the amine salt.

### 3.2.10. Synthesis of β-aminoboronic acids

The plan for converting the β-aminoboronates to β-aminoboronic acids **10** is illustrated in Scheme 16.




**Scheme 16** - Scheme for synthesizing β-aminoboronic acids.

The initial idea was to convert compound **9** directly to compound **11** through a trans-esterification using α-D-glucose.

The first few attempts were carried out using trimethyl- and triisopropyl borate in diethyl ether or tetrahydrofuran together with α-D-glucose, but the expected product could not be detected by HRMS analysis (Figure 48).

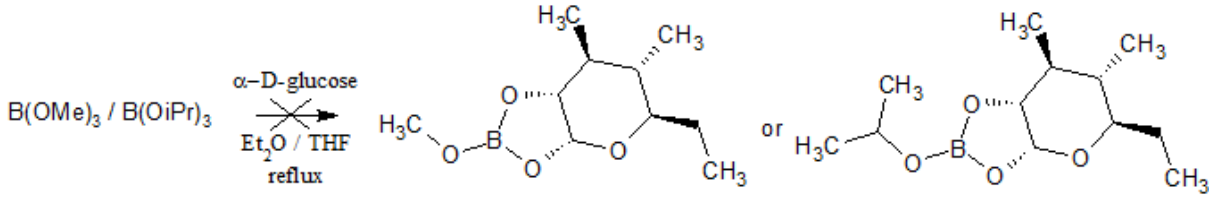



**Figure 48** – Trans-esterification experiments using α-D-glucose.

Refluxing compound **2c** together with α-D-glucose in tetrahydrofuran for 48 hours resulted in miniscule amounts of product (Figure 49).

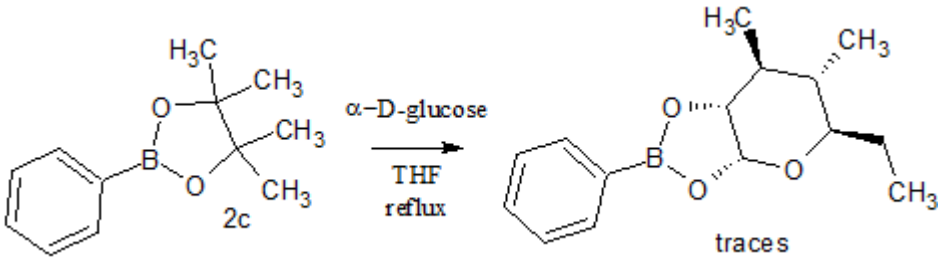



**Figure 49** – Attempted trans-esterification experiment using compound **2c**.

From these experiments it seemed like the idea of trans-esterifying compound **9** to compound **11** would be quite hard to achieve, so it was decided to try esterification using boronic acids instead.

Two experiments were run where phenylboronic acid (compound **1c**) was refluxed together with α-D-glucose in tetrahydrofuran or methanol. HRMS analysis found a mass of 321.1122 corresponding to the product and sodium + methanol adduct (methanol used as solvent for HRMS) with an exact mass being 321.1121. The crude yields from these reactions were 27 % and 32 % respectively, far better than the results obtained by the attempted trans-esterification.

From this point on the idea of using trans-esterification were forfeit and a method for removing the hydrolysis-resistant pinacol-group became the new goal.

Compound **2c** was attempted hydrolyzed a couple of times using increasingly acidic conditions but as expected, not much of the hydrolyzed product could be detected afterwards.

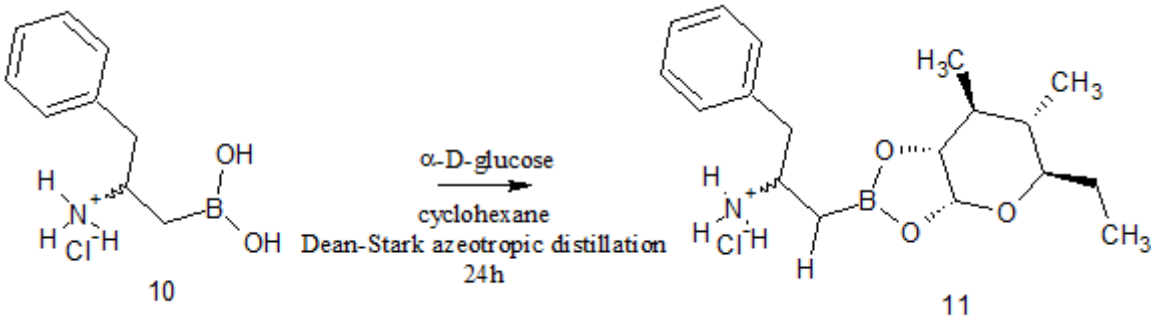
An article detailing the oxidative cleavage of aryl pinacol boronates using sodium periodate seemed like the solution to the problem.[56]

Compound **2c** was dissolved in a 2.5:1 solution of tetrahydrofuran and water and placed in a round-bottomed flask. Sodium periodate was added to the flask and the solution set to stir for 15 minutes before 1 M hydrochloric acid was added to the reaction mixture. The solution was allowed to stir for 4 hours before it was extracted with ethyl acetate. The organic layers were then combined, washed with water and brine, and dried over magnesium sulfate. The solution was filtered and concentrated on the rotary evaporator to give the expected phenylboronic acid in an 85 % yield (Appendix 69).

From these findings and the published article, it seems reasonable to believe that this procedure can be used equally well with compound **9**.

### 3.2.11. Synthesis of β-aminoboronates of α-D-glucose

The plan for converting the β-aminoboronic acids to β-aminoboronates **11** is illustrated in Scheme 17.




**Scheme 17** - Scheme for synthesizing β-aminoboronates of α-D-glucose.

Judging by the previous results obtained by refluxing boronic acids and α-D-glucose in tetrahydrofuran and methanol, it was decided to use a Dean-Stark apparatus to azeotropically distill off the water produced in the reaction, and thus hopefully increase the conversion percentage. Benzene is a common solvent employed in the azeotropic distillation of water but since it is a carcinogenic, it was substituted for toluene.

An experiment was run where a Dean-Stark apparatus was connected to a round-bottomed flask and a condenser. The flask was charged with phenylboronic acid (compound **1c**) and α-D-glucose dissolved in toluene. The flask was then lowered into a silicon oil bath placed on top of a hot-plate magnetic stirrer. The fractionating column of the Dean-Stark apparatus was covered in aluminum foil to decrease heat-loss during distillation. The solution was set to stir and the silicon oil was heated up to the point where the toluene started to reflux. Unfortunately at this temperature (111 $^{o}$C) the α-D-glucose melted and turned black inside the flask.

The solvent had to be substituted for one with similar azeotropic properties, but with a lower boiling point than toluene. The only Dean-Stark traps that were available were ones made for azeotropically distilling lower-density solvents than water, so the solvent would also have to be of less density than water. For this reason it was decided to use cyclohexane which is very similar to benzene in properties, but without the carcinogenicity.

The same experimental setup as described earlier was used and the reaction ran using cyclohexane as the solvent. The solution was refluxed overnight and it was then concentrated

on the rotary evaporator, dissolved in chloroform and washed with distilled water. The organic phase was separated, dried over magnesium sulfate, filtered and concentrated on the rotary evaporator again to yield hair-thin, white, fluffy crystals.

NMR analysis was performed on the crystals showing what could be the expected product and something else, possibly remnants of α-D-glucose. HRMS analysis confirmed that the crystals contained a product with the correct mass (mass: 321.1122 sodium and methanol adducts) in addition to α-D-glucose.

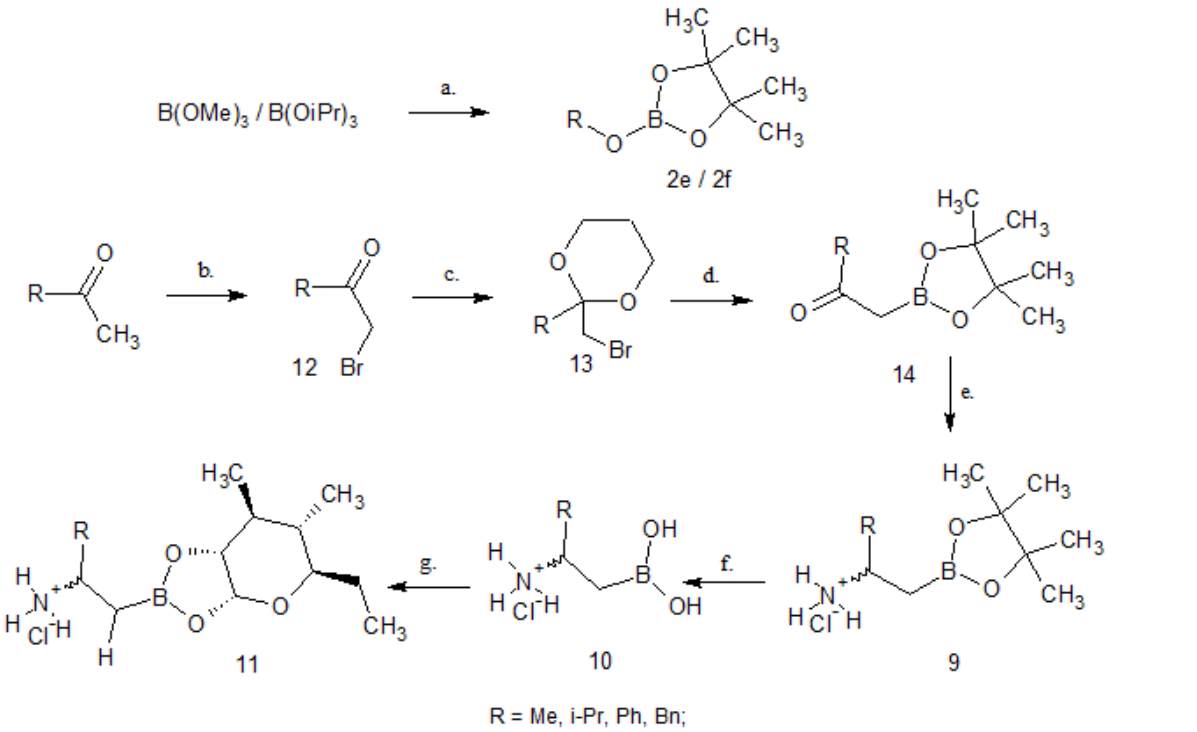
It is likely that the chloroform was polar enough to dissolve some of the glucose during the first wash and as such, a less polar solvent should have been used for this. The crystals were then dissolved in dichloromethane and washed once more with distilled water. The organic phase was separated, dried over magnesium sulfate, filtered and concentrated on the rotary evaporator to yield the same hair-like crystals as before.

HRMS analysis now only showed the mass of the expected product which indicated that the glucose had been removed during the wash. NMR analysis (Appendix 70-72) still showed what appeared to be more than one compound and it was hypothesized that it could be that the hydroxyl-groups of α-D-glucose had attached in different ways to the boronic acid, resulting in different constitutional isomers.

At the time of this writing this is as far as the synthesis following these strategies has come. The next obvious step would be to purify the crystals and the simplest method would perhaps be a recrystallization in order to separate the product and potential isomers of the product.

## 3.3. Synthesis of β-substituted β-aminoboronates by Strategy 3

The chosen pathway for the synthesis of β-substituted β-aminoboronates by strategy 3 is illustrated in Scheme 18.




**Scheme 18** - The chosen pathway for synthesizing β-substituted β-aminoboronates by strategy 3.

The syntheses of compounds **2e** and **2f** have already been described in one of the previous chapters and are in short achieved by refluxing an excess of the appropriate boronic ester together with pinacol in hexane. Evaporation of the solvent and the excess boronic ester starting material on the rotary evaporator provides the expected product (Figure 50).

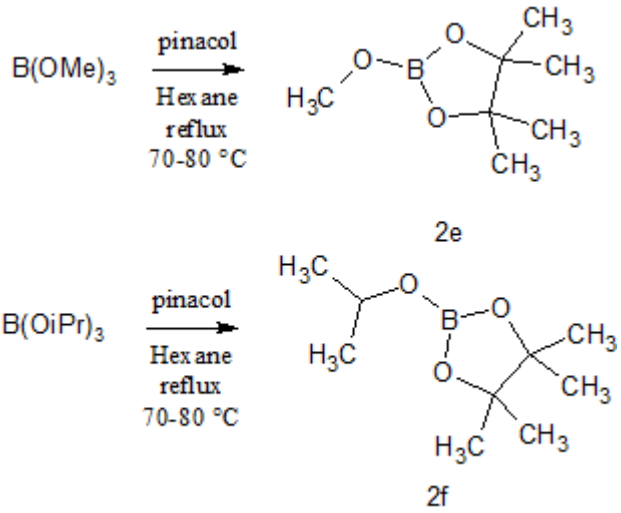



**Figure 50** – Syntheses of compounds **2e** and **2f**.

### 3.3.1. Exploratory experiments using lithium enolates, enamines and silyl enol ethers

The first few syntheses were accomplished in order to investigate the reactivity of some boronic esters towards different enolates. If an enolate would react with a boronic ester it would simplify the strategy even more. It was decided to prepare the lithium enolate of acetophenone and attempt to react it with one of the commercially available boronic esters.

The lithium enolate of acetophenone was prepared by dissolving it in freshly distilled tetrahydrofuran and placing it in a three-necked round-bottomed flask. The flask was cooled -78 $^{o}$C using a dry ice/acetone-bath, an inert atmosphere was maintained and the solution stirred. Lithium bis(trimethylsilyl)amide was slowly added drop-wise to the solution and the solution left to stir for 15 minutes after the addition was completed. Another three-necked flask was prepared containing trimethyl borate. The flask was cooled to -78 $^{o}$C and an inert atmosphere maintained. The lithium enolate of acetophenone was then added slowly, drop-wise to the stirred solution of trimethyl borate and the flask left to stir overnight. It was then diluted with diethyl ether, quenched with 10 % citric acid and the organic phase separated. The organic phase was then dried over magnesium sulfate, filtered and concentrated on the rotary evaporator. A GC-MS analysis (Appendix 73-76) was performed on the crude showing acetophenone, the aldol product of acetophenone and a strange by-product in the form of tris(trimethylsilyl)borate. There was very little hexamethyldisilazane, the by-product of the enolization, detected in the sample (Figure 51).

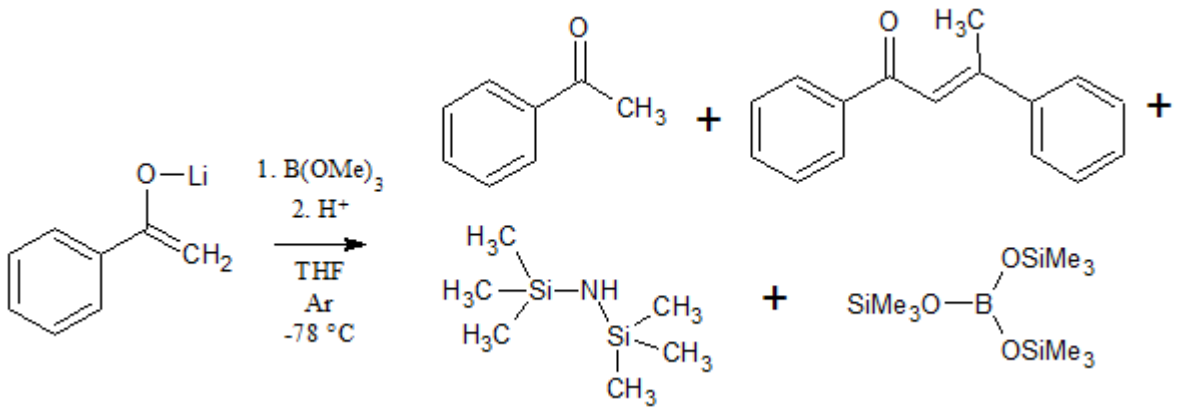



**Figure 51** – Products obtained from reacting the lithium enolate of acetophenone with trimethyl borate.

The formation of tris(trimethylsilyl)borate was interesting because of its industrial use in micro- and optoelectronics, as a neutron adsorbent and as a catalyst in certain polymerization processes.[57] The synthesis of tris(trimethylsilyl)borate usually requires heat and some of the methods used for its preparation are heating hexamethyldisiloxane and boric anhydride at 350 $^{o}$C in an autoclave, heating hexamethyldisilthiane and boric acid at 120 $^{o}$C or heating boric acid and trimethytacetoxysilane at 110 $^{o}$C.

A couple of follow-up experiments were attempted where trimethyl borate was added directly to a stirred solution of lithium bis(trimethylsilyl)amide at -78 $^{o}$C and at 25 $^{o}$C in an effort to see if this would result in tris(trimethylsilyl)borate being formed. A GC-MS analysis run on the crude showed that this was not the case.

Another experiment was run following the first procedure, but where trimethyl borate was added to the stirred solution of lithium enolate and not the other way around as originally done. GC-MS analysis showed only acetophenone and the aldol product. At this point it was decided to abandon the efforts of synthesizing tris(trimethylsilyl)borate and focus on attempted coupling using other enolates.

The focus was shifted to enamines, more specifically 1-morpholinocyclohexene. An experiment was carried out where trimethyl borate was dissolved in freshly distilled tetrahydrofuran and placed in a three-necked round-bottomed flask. While maintaining an inert atmosphere, 1-morpholinocyclohexene was added slowly drop-wise to the stirred solution. The solution was stirred overnight and then quenched with 10 % citric acid. The organic phase was separated, dried over magnesium sulfate, filtered and concentrated on the rotary evaporator. GC-MS analysis confirmed that only the hydrolyzed enamine, cyclohexanone, was present in the sample (Figure 52).

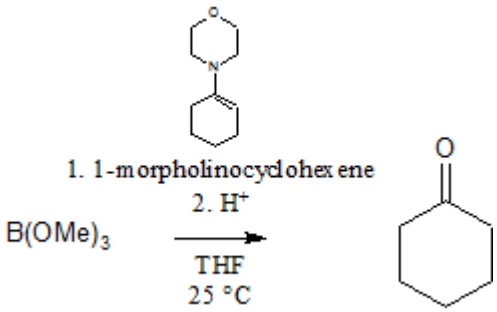



**Figure 52** - Product obtained from reacting 1-morpholinocyclohexene with trimethyl borate.

The final exploratory experiment was to react a silyl enol ether of acetophenone with trimethyl borate.

The silyl enol ether was prepared by cooling a three-necked round-bottomed flask to -78 $^{o}$C and charging it with lithium diisopropyl amide, while maintaining an inert atmosphere. Acetophenone was dissolved in freshly distilled tetrahydrofuran and added drop-wise to the solution during continuous stirring. After the addition was completed the solution was stirred for another 45 minutes before chlorotrimethylsilane was added drop-wise and the solution left to stir overnight. The solution was diluted with pentane, filtered and concentrated on the rotary evaporator. It was then diluted with pentane once more, filtered and concentrated on the rotary evaporator to give the pure silyl enol ether in a 90 % yield (Figure 53).

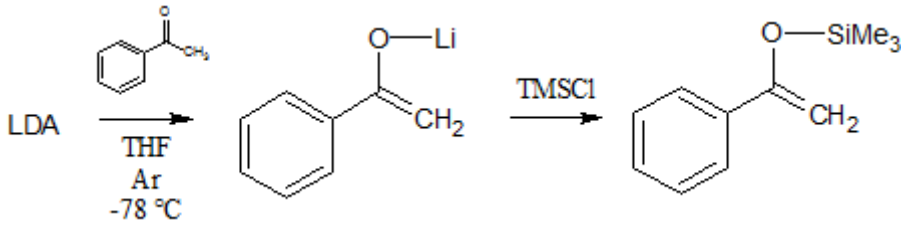



**Figure 53** – Synthesis of 1-phenyl-1-(trimethylsilyloxy)ethylene.

The silyl enol ether was then attempted reacted with trimethyl borate. Trimethyl borate was dissolved in freshly distilled tetrahydrofuran and placed in a round-bottomed flask. The flask was cooled to -78 $^{o}$C using a dry ice/acetone-bath and an inert atmosphere was maintained. The silyl enol ether was then added drop-wise to the solution during continuous stirring. The solution was allowed to stir overnight and the crude was then analyzed by GC-MS which determined that no reaction had taken place; only silyl enol ether and some decomposition product (ethylbenzene) could be detected.

It was conjectured whether some heat had to be applied for the reaction to occur and it was decided to try some microwave-assisted experiments. A stoichiometric amount of the silyl enol ether and trimethyl borate were placed in sealed vessels and irradiated with microwaves for 10 minutes each. At 120 ºC using no solvent the silyl enol ether started to slightly decompose to ethylbenzene (Appendix 77) and at 150 ºC using methanol as the solvent the silyl enol ether decomposed completely to ethylbenzene and acetophenone (Appendix 78).

The results are summarized in Table 11.

| Temperature ºC | Solvent | Result |
|---|---|---|
| 50 | None | Unchanged |
| 80 | None | Unchanged |
| 120 | None | Silyl enol ether slightly decomposed |
| 120 | Methanol | Unchanged |
| 150 | Methanol | Silyl enol ether completely decomposed |

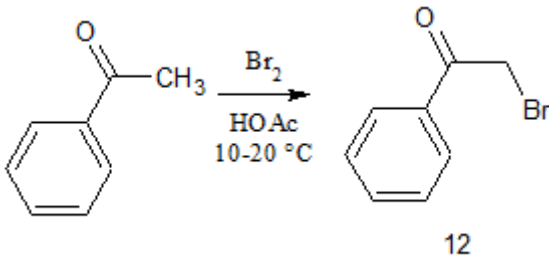
**Table 11** – Results of microwave-assisted experiments of 1-phenyl-1-(trimethylsilyloxy)ethylene and trimethyl borate.

Another experiment was run where the silyl enol ether and trimethyl borate was dissolved in freshly distilled tetrahydrofuran and placed in a three-necked flask. The flask was connected to a condenser and an inert atmosphere was maintained. The solution was sonicated for 2 hours while continuously cooling the ultrasonic bath using ice. A GC-MS analysis was run on the crude showing that no reaction had taken place.

As a result of this the synthetic effort was shifted towards strategy 3 with the first step being the synthesis of an α-bromoketone.

### 3.3.2. Synthesis of α-bromoketones

The ketones were converted to α-bromoketones **12** according to Scheme 19. For this strategy only acetophenone, the phenylsubstituted ketone was used




**Scheme 19** – Scheme for synthesizing α-bromoketones.

The procedure followed is described below.[58]

Acetophenone was dissolved in glacial acetic acid kept at a temperature of 10 ºC to 20 ºC while bromine was added drop-wise. The solution was transferred to another flask and cooled on ice to make the crystalline product precipitate from the solution. The crystals were vacuum-filtered several times using ice-cold water until the color of the crystals were off-white/beige. Oven-drying until the next day gave the α-bromoketones.

GC-MS analysis (Appendix 81) showed mostly the correct product but also a small amount of di-brominated product as could be expected.

The silyl enol ether prepared in the exploratory experiments was also converted to compound **12** by dissolving it in anhydrous dichloromethane and placing it in a three-necked round-bottomed flask. The flask was connected to a dropping funnel and an inert atmosphere maintained. The flask was submerged in an ice bath and the solution set to stir. Bromine was added to the dropping funnel and slowly added to the solution. After the addition was completed the solution was set to stir for 15 minutes before being slowly quenched with sodium sulfite. It was then separated, washed with distilled water, dried over magnesium sulfate, filtered and concentrated on the rotary evaporator. The yield of the isolated compound was 80 % and contained the expected product, di-brominated product and some decomposed starting material (Appendix 82).

The synthesis of compound **12** was performed twice with the results summarized in Table 12.

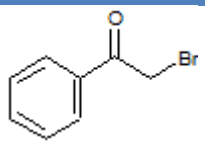
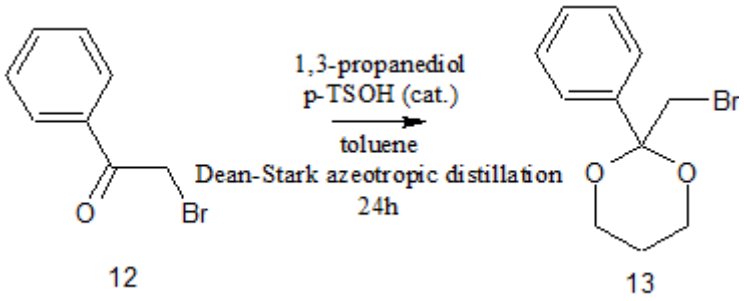
| Structure | Compound | Yield % |
|---|---|---|
|  | **12** | 80 |

**Table 12** - Isolated yields from the synthesis of compound **12**.

### 3.3.3. Synthesis of bromoketals

The α-bromoketones were converted to bromoketals **13** according to Scheme 20.




**Scheme 20** - Scheme for synthesizing bromoketals.

The procedure followed is described below.[59]

A solution containing α-bromoketone, 1-3-propanediol, para-toluenesulfonic acid and toluene was azeotropically distilled for 24 hours using a Dean-Stark apparatus. The solution was then washed with 5 % sodium carbonate, dried and concentrated in vacuo to give the bromoketal.

The synthesis of compound **13** has been summarized in Table 13.

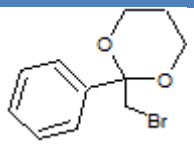
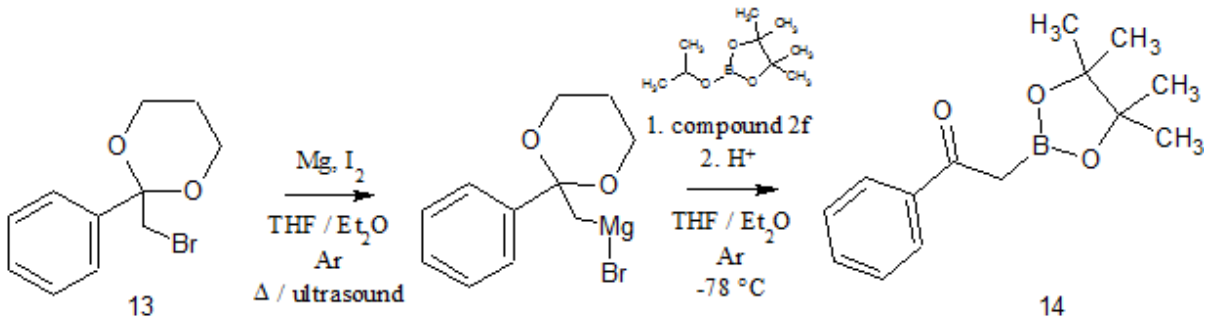
| Structure | Compound | Yield % |
|---|---|---|
|  | **13** | 85 |

**Table 13** - Isolated yields from the synthesis of compound **13**.

### 3.3.4. Synthesis of β-ketoboronates and some final thoughts on this strategy

The bromoketals were attempted converted to β-ketoboronates **14** according to Scheme 21.




**Scheme 21** - Scheme for synthesizing β-ketoboronates.

Creating the organometallic reagent from compound **13** proved harder than anticipated. Initial attempts were performed using typical conditions employed in the creation of Grignard reagents.

Finely churned magnesium turnings were placed in a three-necked round bottom flask together with a few crystals of iodine and anhydrous diethyl ether. A condenser was attached and an inert atmosphere maintained in the flask. A few drops of bromoketal were added to the stirred solution without any noticeable effect. More bromoketal was added and the solution heated for a few while, but still to no avail. After adding around half of the bromoketal in this manner it was decided to reflux the solution for a bit. The rest of the bromoketal was added and the solution refluxed for an hour but still most, if not all, of the magnesium turnings remained. It was decided to abandon the experiment and repeat it using ultrasound instead.

A small-scale test experiment was run with the same experimental setup as previously, where the only difference was the flask being immersed in an ultrasonic bath. The flask was charged with magnesium, a few crystals of iodine, bromoketal and anhydrous diethyl ether and sonicated for a few hours. During the sonication the solution was kept at 0 $^{o}$C by the continuous addition of ice. Another three-necked flask was prepared containing trimethyl borate dissolved in diethyl ether. The flask was cooled to -78 $^{o}$C using a dry ice/acetone-bath, an inert atmosphere maintained and the solution set to stir. The prepared Grignard reagent was then added drop-wise to the stirred solution. After the addition of the Grignard reagent was completed the solution was allowed to stir overnight. The solution was then quenched at 0 $^{o}$C using anhydrous 4M hydrochloric acid in 1,4-dioxane. After stirring the solution for 15 minutes it was filtered and concentrated on the rotary evaporator. It was then diluted with pentane, filtered and concentrated on the rotary evaporator again.

A GC-MS analysis run on the crude compound showed that no reaction had taken place; only unreacted- and hydrolyzed starting material were isolated. This indicated that the Grignard reagent had not formed during the sonication (Figure 54).

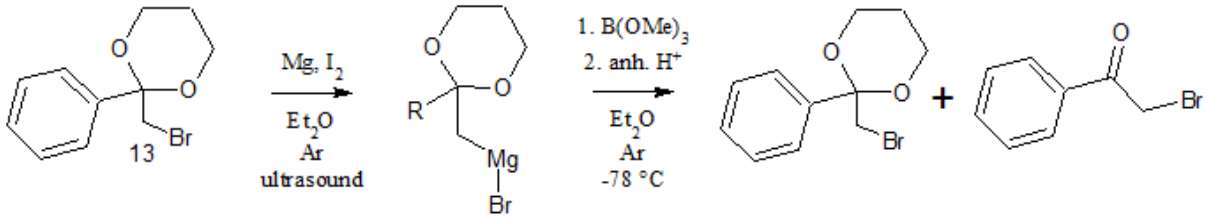



**Figure 54** – Products isolated from a test experiment using ultrasound.

When investigating the scope and limitations of the previously mentioned ultrasound promoted dimerization of benzylic halides it was in one case discovered that changing the solvent led to better yields and in another case led to no reaction taking place (more on this in the next chapter). Therefore it was decided to repeat the ultrasonic reaction using tetrahydrofuran as the solvent instead of diethyl ether.

The solution of magnesium, iodine, bromoketal and tetrahydrofuran was sonicated for a few hours and added drop-wise at -78 $^{o}$C to a solution of compound **2f** dissolved in tetrahydrofuran. The solution was stirred overnight, diethyl ether added and the solution quenched using 10 % sulfuric acid at 0 $^{o}$C. The organic phase was separated, the aqueous phase extracted with diethyl ether and the combined organic phases dried over magnesium sulfate. The solution was then filtered and concentrated on the rotary evaporator.

A GC-MS analysis run (Appendix 87) on the crude showed acetophenone, hydrolyzed starting material and a homo-coupled product indicating that some Grignard reagent indeed had formed, but had not reacted with the boronate (Figure 55).

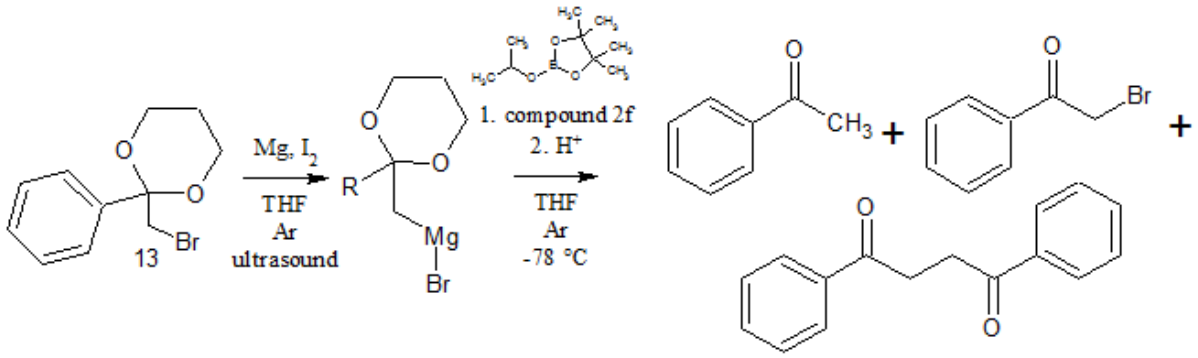



**Figure 55** - Products isolated from an attempted synthesis of compound **14**.

For reasons unknown tetrahydrofuran provided better results than diethyl ether for this reaction. One could speculate that maybe it is because tetrahydrofuran somehow can coordinate better to magnesium in the presence of the ketal functional group or just simply due to its higher boiling point.

Unfortunately there was no time left at this stage in order to further explore this. As some Grignard reagent did form it is possible that compound **14** could be synthesized using this strategy. A couple of ideas for future attempts could be to reflux the reaction mixture after the addition of the Grignard reagent was completed, or perhaps by ultrasonically creating the Grignard reagent in the presence of the boronate.

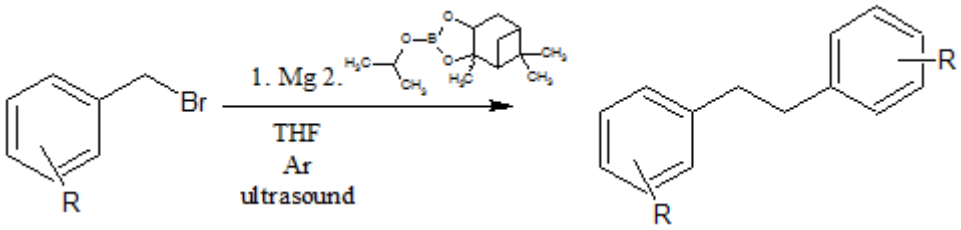
Another alternative could be to prepare the Grignard reagent using Rieke magnesium formed from the reduction of magnesium chloride and an alkali-metal, as previously mentioned.

However if the reaction at some stage would work it is plausible that the ketal, once hydrolyzed to its ketone, could re-arrange directly to the boron-atom leading to another product.

If compound **14** could be synthesized without re-arranging, the next step in the strategy would be to reduce the ketone to an amine using the Leuckart-reaction.[60] An optimized procedure for this reductive amination involves refluxing a solution of the ketone, formamide and water for 6 hours followed by acidic quenching and work-up.[61] The remaining steps in the synthesis of the β-substituted β-boronates following this strategy would then be the same as in the previous strategies.

## 3.4. Ultrasound promoted dimerization of benzylic halides

In one of the previously mentioned studies done at the University of Tromsø it was discovered that benzylic halides unexpectedly dimerized when irradiated with ultrasound.[62] The discovery was made as a result of an attempt to make benzylboronates using lab-prepared benzylic Grignard reagents (Scheme 22).




**Scheme 22** – Ultrasound led to a coupling product instead of the expected benzyl boronate.

This was interesting as traditionally the couplings of benzylic halides are accomplished using transition metal catalysts. Many different catalysts have been successfully employed for this type of coupling including nickel, cobalt, iron, palladium, zinc and copper.[63-67]

Other methods used for creating biaryl compounds include among other the oxidative cross-coupling of arenes using single electron transfer (SET) induced reactions, radical reactions induced by photolysis of benzylic halides using manganese catalysts or electrochemical coupling in lithium perchlorate using magnesium electrodes.[68-70]

Compared to many of the methods described above the ultrasound induced coupling seemed like a cheaper and more straightforward procedure. The reaction seemed to be limited to primary and secondary benzylic halides as neither tertiary benzylic halides nor aliphatic or aromatic halides reacted.

It was of interest to determine the scope and limitations of the reaction by investigating the effect different substituents on the aromatic moiety would have on the reaction. The first semester of this study was therefore devoted to this investigation.

A set of compounds were selected as candidates for the investigation. The compounds could be roughly divided into three classes; benzylic compounds with electron-withdrawing substituents, benzylic compounds with electron-donating substituents and benzylic compounds without substituents. The different compounds have been illustrated in Figure 56.

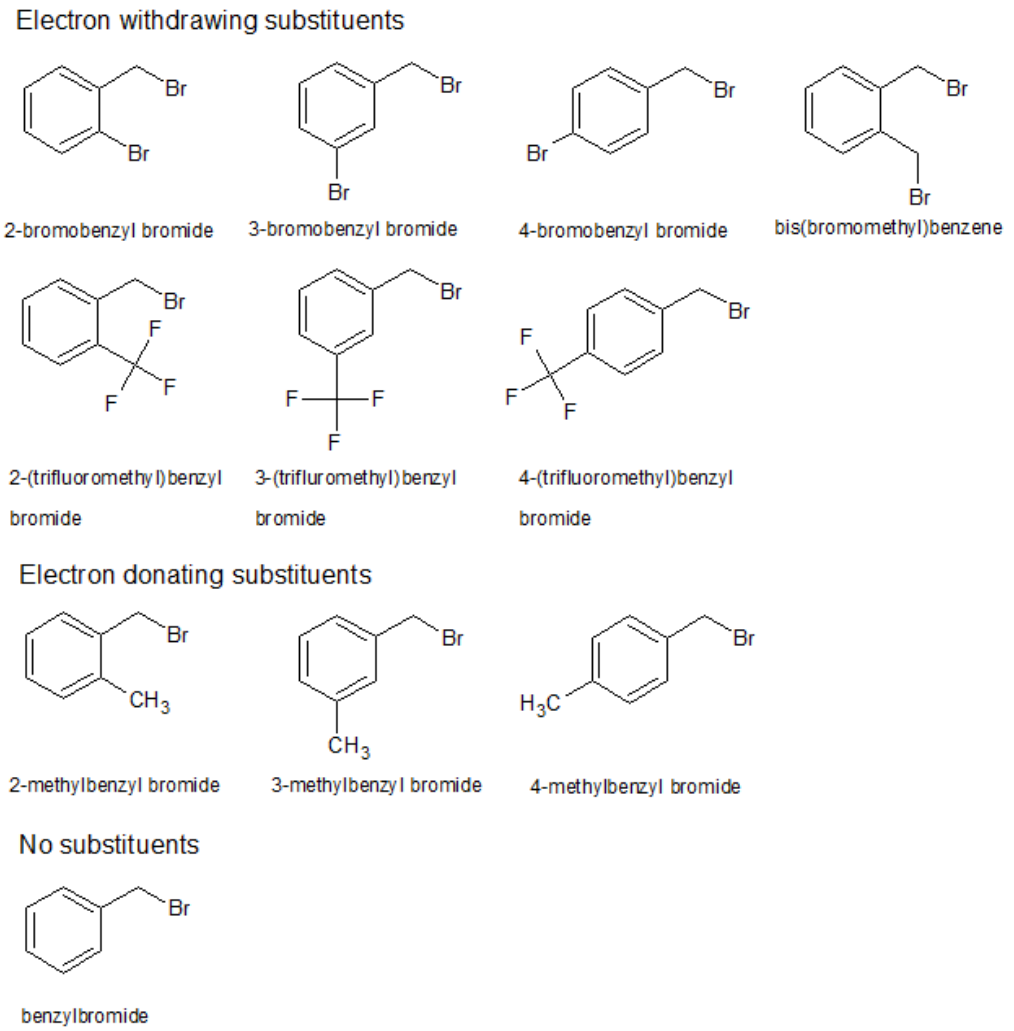
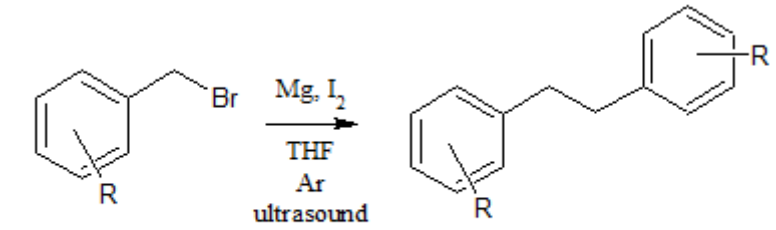



**Figure 56** – The candidate compounds chosen for investigating the scope and limitations of the ultrasound promoted dimerization of benzylic halides.

These compounds were attempted dimerized according to Scheme 23.




**Scheme 23** - Scheme for synthesizing compounds **15-25**.

A flask was charged with magnesium turnings, tetrahydrofuran and a few crystals of iodine. The flask was irradiated with ultrasound while benzyl halide was added drop-wise to the solution during strict anhydrous conditions. After the addition had been completed the reaction mixture was sonicated for 3 hours while keeping the temperature in the ultrasonic bath low using ice. The solution was quenched and the organic phase separated. The aqueous phase was extracted with diethyl ether and the combined organic phases dried and concentrated on the rotary evaporator. Column chromatography was then performed on silica using pentane to eluate the impurities and 5 % ethyl acetate in pentane to eluate the product.

The results from the syntheses have been summarized in Table 14.

| Compound | Substituent | Yield % |
|---|---|---|
| **15** | -Br (Ortho) | 13[a] |
| **16** | -Br (Meta) | 19[a] |
| **17** | -Br (Para) | 12[a] |
| **18** | -$CH_2Br$ (Ortho) | 20 |
| **19** | -$CF_3$ (Ortho) | 0 |
| **20** | -$CF_3$ (Meta) | 28 |
| **21** | -$CF_3$ (Para) | 4[a] |
| **22** | -$CH_3$ (Ortho) | 61 |
| **23** | -$CH_3$ (Meta) | 31 |
| **24** | -$CH_3$ (Para) | 48 |
| **25** | - | 23 |

**Table 14** – Isolated yields from the syntheses of compound **15-25**.

From these results it can be seen that the expected product was isolated in all cases except in the synthesis of compound **19**. It was speculated that this perhaps could be caused by steric

[a] Purified with preparative TLC using 10 % dichloromethane in pentane

hindrance resulting from the trifluoromethyl-group being in the ortho position next to the benzylic group.

It was decided to see whether or not changing the solvent would have any effect on the outcome in the synthesis of compound **19** so another reaction was run in anhydrous diethyl ether instead of tetrahydrofuran. The results however showed the same; no reaction had taken place.

There were several other similar exploratory experiments performed. Changing the solvent from tetrahydrofuran to diethyl ether in the synthesis of compounds **21** and **23** resulted in no reaction taking place in the first case and a better yield in the latter.

All the syntheses were performed using a small excess of magnesium so it was decided to run some exploratory experiments in order to see whether using stoichiometric amounts or an excess of magnesium would make any difference. Compound **17** was synthesized three times using varying amount of magnesium, but the results from these syntheses did not show any significant difference. The results are summarized in Table 15.

| Equivalents of magnesium used | Ratio product to starting material |
|---|---|
| 0.5 | 60:40 |
| 0.6 | 80:20 |
| 0.7 | 75:25 |

**Table 15** – Effects of varying the amount of magnesium used in the synthesis of compound **17**.

The synthesis of compound **18** resulted in several compounds which were isolated and analyzed by NMR, but a positive identification proved very hard as the spectra were messy with lots of overlapping peaks. It was hypothesized whether the isolated compounds perhaps could be polymers as the starting material had two bromines that potentially could react. One of the isolated compounds (Appendix 94) however did seem to indicate the expected product or another possible product – benzocyclobutane (Figure 57).

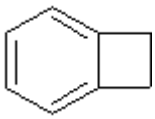


**Figure 57** – Benzocyclobutane.

$^{13}$C-NMR analysis (Appendix 95) showed four distinct peaks appearing to be in much better accordance with theoretical data for compound **18** than for benzocyclobutane. Unfortunately

at the time of this synthesis GC-MS was not available, so the compound was never positively identified as either compound **18** or benzocyclobutane. In retrospect this could potentially have been done using NMR if the compound had been radically halogenated prior to analysis.

It was discovered that no x-ray data had been published on compound **20** so when a successful crystallization was achieved using pentane, it was decided to submit one of the crystals for an x-ray diffraction study (Figure 58). Unfortunately the data obtained from the diffraction study did not meet the requirements for publishing. The x-ray data can be found in the experimental section.

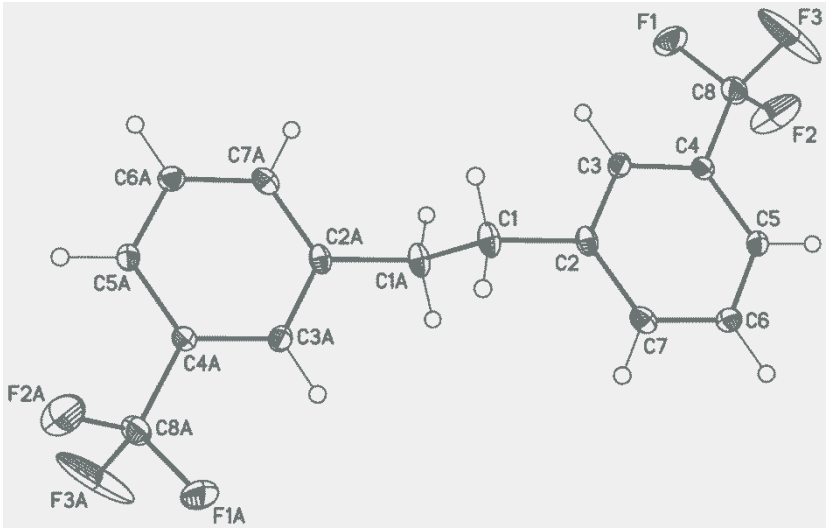



**Figure 58** – The x-ray structure of compound **20**.

Investigating the scope and limitations of the ultrasound promoted dimerization of benzylic halides it seems as if though both steric and electronic factors influence the reactivity. Previous experiments run using tertiary benzylic halides showed that they did not react at all and neither did compound **19**, with the bulky ortho-substituted trifluoromethyl-group. Strongly electron-withdrawing substituents attached to the aromatic moiety gave worse yields than aromatic moieties substituted with electron-donating groups, which make sense. There is no clear pattern to be seen in relation to the position of the group on the aromatic moiety.

The full published article regarding this investigation can be found under the heading "Article" in the Appendices section.

# 4. CONCLUSION

As a continuation of the work done at the University of Tromsø in relation to the synthesis of amino acid analogues of boron, a new approach for the synthesis of β-substituted β-aminoboronates has been developed.

The approach involves the non-stereospecific synthesis of β-substituted β-aminoboronates followed by oxidation to the boronic acid and subsequent esterification using an enantiomerically pure carbohydrate.

The oxidation to the boronic acid and following esterification were never done for the target molecules due to time constraints, but exploratory experiments seem to indicate they can be done.

It was discovered that for certain benzylic halides ultrasound quite unexpectedly led to dimerization. The scope and limitations of this discovery was explored and the findings published.

# 5. EXPERIMENTAL

All reagents used were purchased from Sigma-Aldrich Co. LLC and used as received. Tetrahydrofuran was distilled from sodium benzophenone ketyl. Reactions requiring anhydrous conditions were performed under an argon atmosphere in glassware that had been oven-dried for 6 to 24 hours at 120 ºC prior to use.

NMR spectra were recorded on a Varian Mercury 400 Plus (400 MHz / 101 MHz). Chemical shift values (δ) are given in parts per million (ppm) and multiplicity with the corresponding letter(s) (singlet = s, doublet = d, triplet = t,…, multiplet = m). For all recorded NMR spectra the residual signal of $CDCl_3$ was used as the internal standard set to 7.26 ppm and 77.2 ppm for $^{1}H$ and $^{13}C$ respectively. $^{1}H$-NMR peaks showing an extra signal at 1.56 ppm is due to water in the deuterated chloroform used as solvent. Signals from the carbons α to boron cannot be detected using $^{13}C$-NMR. Some of the $^{13}C$-NMR spectra has noise in the form of pulses in a repeating pattern due to interference from a nearby, yet to be found, radio transmitter. Spectra were processed using MestreNova v.8.01 and the coupling constants calculated in MestreNova using chemical shift values with 3 decimals.

IR spectra were recorded on a Varian 7000e FT-IR spectrometer.

GC-MS spectra were recorded on a Thermo Scientific ITQ 1100 + Trace GC Ultra. For samples dissolved in tetrahydrofuran the antioxidant butylated hydroxytoluene will show a signal in the interval of 5.95-6.00 minutes. Strong samples sometimes showed ions with higher molecular weight than the molecular ion due to chemical pseudo-ionization. All samples were analyzed using electron ionization. In many cases the molecular ion is so weak that only the $^{11}B$-isotope can be seen in the spectra.

MS spectra were recorded on a Thermo electron LTQ Orbitrap XL + Electrospray ion source (ION-MAX). Samples were dissolved in 0.1 % formic acid in methanol and injected by syringe at a flow rate of 5 µL/min. The molecular ion of compounds containing either a boronic acid moiety or an azide group could not be detected.

Preparative TLC performed on Silica gel $F_{254}$ 2mm from Merck.

**General procedure for preparing boronic acids 1b-1d:**

Trimethyl borate (100 mmol) was dissolved in anhydrous diethyl ether (50 mL) and placed in a three-necked round-bottomed flask. An argon atmosphere was maintained in the flask and the flask cooled to -78 $^{o}$C using a dry ice/acetone-bath. The flask was placed on a magnetic stirrer and the contents set to stir while the Grignard-reagent (105 mmol) was added drop-wise to the solution. After the addition was complete the solution was allowed to reach room-temperature (25 $^{o}$C) while stirring overnight. It was then quenched with 10 % aqueous sulfuric acid (20 mL) and the ether-layer separated. The aqueous layer was extracted with diethyl ether (3 x 50 mL) and the combined organic phases washed with distilled water (50 mL) and then extracted with aqueous 2 M potassium hydroxide (3 x 50 mL). The combined aqueous extracts were acidified to pH 2 using 20 % aqueous sulfuric acid and the solution was then saturated with sodium chloride. Diethyl ether was added (50 mL), the organic phase separated and the aqueous phase extracted with more diethyl ether (2 x 50 mL). The combined organic phases were dried over magnesium sulfate, filtered and then concentrated on the rotary evaporator to give the expected boronic acid.

**Preparation of iso-propyl boronic acid 1b:**

From trimethyl borate (10 g, 96 mmol), iso-propyl magnesium chloride 2 M (50.5 mL, 101 mmol), diethyl ether (50 mL): 4.9 g (58 %); white solid.

$^{1}$H-NMR (400 MHz, $CDCl_3$): δ 4.15 (s, 1H), 1.01 (dd, *J* = 6.9, 2.9 Hz, 6H).

$^{13}$C-NMR (101 MHz, $CDCl_3$): δ 17.38, 18.16.

The spectra can be found in Appendix 1-2.

**Preparation of phenyl boronic acid 1c:**

From trimethyl borate (10 g, 96 mmol), phenyl magnesium chloride 2 M (50.5 mL, 101 mmol), diethyl ether (50 mL): 8.65 g (74 %); white solid.

$^{1}$H-NMR (400 MHz, $CDCl_3$): δ 8.30 - 8.21 (m, 2H), 7.65 – 7.57 (m, 1H), 7.57 – 7.48 (m, 2H).

$^{13}$C-NMR (101 MHz, $CDCl_3$): δ 135.64, 132.69, 127.98.

The spectra can be found in Appendix 3-4.

**Preparation of benzyl boronic acid 1d:**

From trimethyl borate (5 g, 48 mmol), benzyl magnesium chloride 2 M (26.5 mL, 53 mmol), diethyl ether (50 mL): 8.65 g (71 %); white solid.

$^{1}$H-NMR (400 MHz, $CDCl_3$): δ 7.41 – 7.09 (m, 5H), 2.38 (s, 2H).

$^{13}$C-NMR (101 MHz, $CDCl_3$): δ 136.32, 129.00, 128.61, 125.43.

The spectra can be found in Appendix 5-6.

**Preparation of 2,4,4,5,5-pentamethyl-1,3,2-dioxaborolane 2a:**

Trimethyl boroxine (1 g, 8 mmol) and pinacol (3.01 g, 25 mmol) was dissolved in anhydrous diethyl ether (25 mL) and placed in a round-bottomed flask. The flask was fitted with a rubber septum and a syringe containing a small plug of glass wool with a layer of calcium chloride on top. The flask was then placed on a magnetic stirrer and stirred overnight. The solution was concentrated on the rotary evaporator, diluted with pentane (50 mL) and filtered through a small layer of silica. After concentrating the solution on the rotary evaporator again the expected 2,4,4,5,5-pentamethyl-1,3,2-dioxaborolane was obtained: 0.97 g (87 %); colorless liquid.

$^{1}$H-NMR (400 MHz, $CDCl_3$): δ 1.23 (s, 12H), 0.23 (s, 3H).

$^{13}$C-NMR (101 MHz, $CDCl_3$): δ 82.98, 24.80.

GC-MS: 1.95 min, $M^+$ = 143.

The spectra can be found in Appendix 9-11.

**General procedure for preparing boronates 2b-2d:**

Boronic acid (100 mmol) and pinacol (110 mmol) was dissolved in anhydrous diethyl ether (50 mL) and placed in a round-bottomed flask. The flask was fitted with a rubber septum and a syringe containing a small plug of glass wool with a layer of calcium chloride on top was inserted in the septum. The flask was then placed on a magnetic stirrer and stirred overnight. The solution was concentrated on the rotary evaporator, diluted with pentane (50 mL) and filtered through a small layer of silica. After concentrating the solution on the rotary evaporator again the expected boronate was obtained.

**Preparation of 2-isopropyl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane 2b:**

From isopropyl boronic acid (2.11 g, 24 mmol), pinacol (3.12 g, 26 mmol), diethyl ether (50 mL): 3.87 g (95 %); colorless liquid.

$^{1}$H-NMR (400 MHz, $CDCl_3$): δ 1.23 (s, 12H), 0.97 (d, *J* = 6.4 Hz, 5H).

$^{13}$C-NMR (101 MHz, $CDCl_3$): δ 82.77, 24.83, 24.68, 17.94.

GC-MS: 2.65 min, $M^+$ = 171.

The spectra can be found in Appendix 12-16.

**Preparation of 2-phenyl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane 2c:**

From phenyl boronic acid (8.65 g, 71 mmol), pinacol (9.23 g, 78 mmol), diethyl ether (50 mL): 10.81 g (75 %); white crystals.

$^{1}$H-NMR (400 MHz, $CDCl_3$): δ 7.85 (m, 2H), 7.51 – 7.45 (m, 1H), 7.42 – 7.36 (m, 2H), 1.38 (s, 12H).

$^{13}$C-NMR (101 MHz, $CDCl_3$): δ 134.74, 131.24, 127.69, 83.76, 24.87.

The spectra can be found in Appendix 20-21.

**Preparation of 2-benzyl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane 2d:**

From phenyl boronic acid (8.91 g, 65 mmol), pinacol (8.51 g, 72 mmol), diethyl ether (50 mL): 11.69 g (75 %); colorless liquid.

$^{1}$H-NMR (400 MHz, $CDCl_3$): δ 7.38 – 7.09 (m, 5H), 2.30 (s, 2H), 1.23 (s, 12H).

$^{13}$C-NMR (101 MHz, $CDCl_3$): δ 138, 128.96, 128.24, 124.80, 83.40, 24.71.

One peak mistakenly not marked in the $^{13}$C-NMR spectra (Appendix 23). The peak in question is the one at 138 ppm, the quaternary aromatic carbon.

The spectra can be found in Appendix 22-23.

**Preparation of 2-methoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane 2e:**

Trimethyl borate (10 g, 96 mmol) and pinacol (5.68 g, 48 mmol) was dissolved in hexane (200 mL) and placed in a round-bottomed flask. The flask was connected to a condenser and lowered into a silicon oil bath placed on top of a hot-plate magnetic stirrer. The top of the condenser was attached to a drying tube containing calcium chloride. The solution was refluxed for an hour before being concentrated on the rotary evaporator to give the expected 2-methoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane: 5.96 g (78 %); colorless liquid.

$^{1}$H-NMR (400 MHz, $CDCl_3$): δ 3.59 (s, 3H), 1.25 (s, 12H).

$^{13}$C-NMR (101 MHz, $CDCl_3$): δ 82.74, 52.60, 24.59.

GC-MS: 2.66 min, $M^+$ = 159.

The spectra can be found in Appendix 24-26.

**Preparation of 2-isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane 2f:**

Triisopropyl borate (10 g, 53 mmol) and pinacol (3.14 g, 26 mmol) was dissolved in hexane (200 mL) and placed in a round-bottomed flask. The flask was connected to a condenser and lowered into a silicon oil bath placed on top of a hot-plate magnetic stirrer. The top of the condenser was attached to a drying tube containing calcium chloride. The solution was refluxed for an hour before being concentrated on the rotary evaporator to give the expected 2-isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane: 4.13 g (85 %); colorless liquid.

$^{1}$H-NMR (400 MHz, $CDCl_3$): δ 4.32 (h, $J$ = 11.1, 6.8, 5.6 Hz, 1H), 1.24 (s, 12H), 1.19 (d, $J$ = 6.1 Hz, 6H).

$^{13}$C-NMR (101 MHz, $CDCl_3$): δ 82.41, 67.30, 24.55, 24.30.

GC-MS: 3.21 min, $M^+$ = 185.

The spectra can be found in Appendix 27-29.

**Preparation of dichloromethyl boronic acid 4:**

A solution of tetrahydrofuran (100 mL), distilled from sodium benzophenone ketyl, was placed in a three-necked round-bottomed flask containing dichloromethane (12.26 g, 140 mmol). An argon atmosphere was maintained and the flask cooled to -100 $^{o}$C using an ethanol/liquid nitrogen-bath. The flask was placed on a magnetic stirrer and the contents of the flask was vigorously stirred as n-butyllithium 2.7 M (35.65 mL, 96 mmol) was added drop-wise, very slowly by the wall of the flask, making sure it was chilled properly before reaching the solution. The suspension of (dichloromethyl)lithium was stirred for 30 minutes, maintaining the temperature, before trimethyl borate (10 g, 96 mmol) was added drop-wise to the solution. After the addition was completed the bath was changed to a dry ice/acetone-bath maintaining -78 $^{o}$C and then stirred for another hour. The solution was allowed to reach -41 $^{o}$C by exchanging the cooling bath for a dry ice/acetonitrile-bath and then subsequently quenched with 5 N hydrochloric acid (30 mL).The solution was stirred for 10 minutes, the organic layer separated and the aqueous layer extracted with diethyl ether (3 x 50 mL). The combined organic phases were washed with a saturated aqueous solution of ammonium chloride (3 x 50 mL), dried over magnesium sulfate, filtered and concentrated on the rotary evaporator to give dichloromethyl boronic acid: 11.45 g (93 %); golden liquid.

$^{1}$H-NMR (400 MHz, $CDCl_3$): δ 7.88 (s, 2H), 5.27 (s, 1H), 3.82 (m, 5H), 3.64 (s, 0.28H), 1.90 (m, 5H).

$^{13}$C-NMR (101 MHz, $CDCl_3$): δ 68.19, 25.46.

The spectra can be found in Appendix 47-48.

**Preparation of 2-dichloromethyl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane 5:**

Dichloromethyl boronic acid (8 g, 62 mmol) and pinacol (7.71 g, 65 mmol) was dissolved in anhydrous diethyl ether (100 mL) and placed in a round-bottomed flask. The flask was fitted with a rubber septum and a syringe containing a small plug of glass wool with a layer of calcium chloride on top was inserted in the septum. The flask was then placed on a magnetic stirrer and stirred overnight. The solution was concentrated on the rotary evaporator, diluted with pentane (50 mL) and filtered through a small layer of silica. After concentrating the solution on the rotary evaporator again the expected 2-dichloromethyl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane was obtained: 5.7 g (56 %); colorless liquid.

$^{1}$H-NMR (400 MHz, $CDCl_3$): δ 5.34 (s, 1H), 1.33 (s, 12H).

$^{13}$C-NMR (101 MHz, $CDCl_3$): δ 85.77, 24.42.

GC-MS: 4.13 mins, $M^+$ = 210.

The spectra can be found in Appendix 49-52.

**General procedure for preparing α-chloroalkyl boronates 3a-3d:**

A three-necked round-bottomed flask was charged with the dichloromethyl boronate (50 mmol) dissolved in tetrahydrofuran (50 mL) distilled from sodium benzophenone ketyl. The flask was cooled to -78 $^{o}$C using a dry ice/acetone-bath and an inert atmosphere was maintained in the flask. The flask was placed on a magnetic stirrer and the Grignard reagent (10.5 mmol) added drop-wise to the stirred solution. After the addition was completed the solution was left to stir for an hour. Anhydrous zinc chloride in diethyl ether 1 M (200 mmol) was added drop-wise to the solution and the solution left to stir overnight. The solution was then diluted with diethyl ether (100 mL), washed with saturated aqueous ammonium chloride (3 x 50 mL), separated and concentrated. The residual oil was dissolved in pentane (50 mL), washed once more with saturated aqueous ammonium chloride (50 mL) before being separated and dried over magnesium sulfate. Filtering the solution and concentration on the rotary evaporator gave the expected α-chloroalkyl boronate.

**Preparation of 2-(1-chloroethyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane 3a:**

From 2-dichloromethyl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (2.83 g, 13.4 mmol), methyl magnesium chloride 3 M (4.7 mL, 14 mmol), tetrahydrofuran (25 mL), zinc chloride 1 M (53.6 mL, 53 mmol): 1.23 g (48.2 %); colorless liquid.

$^{1}$H-NMR (400 MHz, $CDCl_3$): δ 3.50 (q, *J* = 7.6 Hz, 1H), 1.53 (d, *J* = 7.6 Hz, 3H), 1.28 (s, 12H).

$^{13}$C-NMR (101 MHz, $CDCl_3$): δ 84.39, 24.55, 20.34.

GC-MS: 3.60 mins, $M^+$ = 191.

The spectra can be found in Appendix 30-33.

**Preparation of 2-(1-chloro-2-methylpropyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane 3b:**

From 2-dichloromethyl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (2.80 g, 13.2 mmol), isopropyl magnesium chloride 2 M (7 mL, 14 mmol), tetrahydrofuran (25 mL), zinc chloride 1 M (53.6 mL, 53 mmol): 0.96 g (33.3 %); colorless liquid.

$^{1}$H-NMR (400 MHz, $CDCl_3$): δ 3.24 (d, *J* = 6.9 Hz, 1H), 2.10 (h, *J* = 6.7 Hz, 1H), 1.28 (s, 12H), 1.02 (dd, *J* = 11.4, 6.7 Hz, 6H).

$^{13}$C-NMR (101 MHz, $CDCl_3$): δ 84.26, 31.91, 24.58, 20.41, 19.91.

GC-MS: 4.54 min, $M^+$ = 218.

The spectra can be found in Appendix 34-37.

**Preparation of 2-[chloro(phenyl)methyl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane 3c:**

From 2-dichloromethyl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (1.7 g, 8 mmol), phenyl magnesium chloride 2 M (4.23 mL, 8.4 mmol), tetrahydrofuran (20 mL), zinc chloride 1 M (32.2 mL, 32 mmol): 0.89 g (44 %); yellow-tinted liquid.

$^{1}$H-NMR (400 MHz, $CDCl_3$): δ 7.68 – 6.82 (m, 5H), 4.48 (s, 0.27H), 1.45 – 1.08 (m, 12H).

$^{13}$C-NMR (101 MHz, $CDCl_3$): δ 128.72, 128.62, 127.76, 126.38, 115.26, 84.78, 24.51.

GC-MS: 6.54 mins, $M^+$ = 252.

The spectra can be found in Appendix 38-43.

**Preparation of 2-(1-chloro-2-phenylethyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane 3d:**

From 2-dichloromethyl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (4.26 g, 20 mmol), benzyl magnesium chloride 2 M (10.6 mL, 21 mmol), tetrahydrofuran (30 mL), zinc chloride 1 M (80.8 mL, 81 mmol): 4.78 g (90 %); yellow-tinted liquid.

**From 2d**: A solution of tetrahydrofuran (15 mL), distilled from sodium benzophenone ketyl, was placed in a three-necked round-bottomed flask containing dichloromethane (0.77 g, 9 mmol). An argon atmosphere was maintained and the flask cooled to -100 $^{o}$C using an ethanol/liquid nitrogen-bath. The flask was placed on a magnetic stirrer and the contents of the flask vigorously stirred as n-butyllithium 2.7 M (2 mL, 5.5 mmol) was added drop-wise, very slowly by the wall of the flask, making sure it was chilled properly before reaching the

solution. The suspension of (dichloromethyl)lithium was stirred for 30 minutes, maintaining the temperature, before 2-benzyl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (1 g, 4.5 mmol) was added drop-wise to the solution. After the addition was completed the bath was changed to a dry ice/acetone-bath maintaining -78 $^{o}$C and then stirred for another hour. Anhydrous zinc chloride in diethyl ether 1 M (6.9 mL, 6.8 mmol) was added drop-wise to the solution and it was then left to stir overnight. The solution was then diluted with diethyl ether (50 mL), washed with saturated aqueous ammonium chloride (3 x 20 mL), separated and concentrated on the rotary evaporator. The residual oil was diluted with pentane (50 mL) and washed once more with saturated aqueous ammonium chloride (20 mL). The organic phase was then separated and dried over magnesium sulfate. Filtering the solution and concentration on the rotary evaporator gave the expected 2-(1-chloro-2-phenylethyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane: 0.95 g (79 %); colorless oil.

$^{1}$H-NMR (400 MHz, $CDCl_3$): δ 7.38 – 7.16 (m, 1H), 3.59 (t, *J* = 8.2 Hz, 1H), 3.21 – 3.05 (m, 2H), 1.22 (d, *J* = 7.2 Hz, 12H).

$^{13}$C-NMR (101 MHz, $CDCl_3$): δ 138.34, 129.20, 128.31, 126.72, 84.43, 40.23, 24.54, 24.49.

GC-MS: 6.92 mins, $M^+$ = 266.

The spectra can be found in Appendix 44-46.

**Preparation of 2-(1-azido-2-phenylethyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane 6:**

A round-bottomed flask was charged with sodium azide (22.83 g, 350 mmol) and tetrabutylammonium bromide (0.56 g, 1.7 mmol) and the contents dissolved in a 3:1 ratio of ethyl acetate and water (200 mL). The flask was placed on a magnetic stirrer and the solution stirred vigorously as 2-(1-chloro-2-phenylethyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (9.36 g, 35 mmol) was added slowly drop-wise to the solution. After the addition was completed the solution was allowed to stir for 48 hours. The aqueous- and organic phases were separated and the aqueous phase extracted with ethyl acetate (3 x 50 mL). The combined organic phases were concentrated on the rotary evaporator, diluted with pentane (50 mL), washed with saturated aqueous ammonium chloride (3 x 50 mL) and then dried over magnesium sulfate. The solution was filtered and concentrated on the rotary evaporator again yielding 2-(1-azido-2-phenylethyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane: 7.8 g (81 %); yellow tinted oil.

$^{1}$H-NMR (400 MHz, $CDCl_3$): δ 7.32 – 7.16 (m, 5H), 3.35 (dd, *J* = 8.7, 5.8 Hz, 1H), 3.05 - 2.88 (m, 2H), 1.24 (s, 12H).

$^{13}$C-NMR (101 MHz, $CDCl_3$): δ 138.60, 129.13, 128.41, 126.64, 84.53, 36.65, 24.73.

IR ($cm^{-1}$): 2979.84, 2930.39, 2090.11, 1726.69, 1603.87, 1454.36, 1372.68, 1343.98, 1252.42, 1212.60, 1139.08, 1077.54, 1030.89, 988.07, 848.65, 749.60, 697.88, 669.50.

The spectra can be found in Appendix 53-55.

**Preparation of 2-(2-azido-1-chloro-3-phenylpropyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane 7:**

A solution of tetrahydrofuran (50 mL), distilled from sodium benzophenone ketyl, was placed in a three-necked round-bottomed flask containing dichloromethane (2.03 g, 24 mmol). An argon atmosphere was maintained and the flask cooled to -100 $^{o}$C using an ethanol/liquid nitrogen-bath. The flask was placed on a magnetic stirrer and the contents of the flask vigorously stirred as n-butyllithium 2.7 M (5.32 mL, 14 mmol) was added drop-wise, very slowly by the wall of the flask, making sure it was chilled properly before reaching the solution. The suspension of (dichloromethyl)lithium was stirred for 30 minutes, maintaining the temperature, before 2-(1-azido-2-phenylethyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (3.27 g, 12 mmol) was added drop-wise to the solution. After the addition was completed the bath was changed to a dry ice/acetone-bath maintaining -78 $^{o}$C and then stirred for another hour. Anhydrous zinc chloride in diethyl ether 1 M (18 mL, 18 mmol) was added drop-wise to the solution and it was then left to stir overnight. The solution was then diluted with diethyl ether (50 mL), washed with saturated aqueous ammonium chloride (3 x 50 mL), separated and concentrated on the rotary evaporator. The residual oil was diluted with pentane (50 mL) and washed once more with saturated aqueous ammonium chloride (50 mL). The organic phase was then separated and dried over magnesium sulfate. Filtering the solution and concentration on the rotary evaporator gave the expected 2-(2-azido-1-chloro-3-phenylpropyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane: 2.33g (61 %); yellow oil.

$^{1}$H-NMR (400 MHz, $CDCl_3$): δ 7.36 – 7.10 (m, 5H), 3.92 – 3.67 (m, 1H), 3.38 (dd, *J* = 16.4, 5.9 Hz, 1H), 3.12 – 3.04 (m, 1H), 2.94 – 2.79 (m, 1H), 1.27 (d, *J* = 2.9 Hz, 12H).

$^{13}$C-NMR (101 MHz, $CDCl_3$): δ. 136.78, 129.43, 128.72, 128.29, 85.08, 66.64, 65.42, 38.37, 38.05, 24.60, 24.55.

gCOSY: Appendix 58.

The spectra can be found in Appendix 56-58.

**Preparation of 2-(2-azido-3-phenylpropyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane 8:**

2-(2-azido-1-chloro-3-phenylpropyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (1.86 g, 5.7 mmol) was dissolved in tetrahydrofuran (20 mL), distilled from sodium benzophenone ketyl, and placed in a three-necked round-bottomed flask. An argon atmosphere was maintained and the flask cooled to 0 $^{o}$C using an ice bath. The flask was put on a magnetic stirrer and the contents stirred as triethylborohydride (7.5 mL, 7.5 mmol) was added slowly drop-wise to the solution. After the addition was completed the solution was stirred for 3 hours at 0 $^{o}$C. The solution was diluted with diethyl ether (50 mL), washed with aqueous saturated aqueous ammonium chloride (3 x 20 mL), dried over magnesium sulfate, filtered and concentrated on the rotary evaporator to give 2-(2-azido-3-phenylpropyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane: 1.27 g (77 %); golden oil.

$^{1}$H-NMR (400 MHz, $CDCl_3$): δ 7.38 – 7.14 (m, 5H), 3.88 – 3.83 (m, 1H), 2.95 – 2.80 (m, 2H), 1.28 (d, *J* = 3.4 Hz, 12H), 1.19 – 1.17 (m, 2H).

$^{13}$C-NMR (101 MHz, $CDCl_3$): δ 138.08, 129.43, 128.43, 126.63, 83.59, 61.27, 42.99, 24.82, 24.80.

gCOSY: Appendix 61.

HRMS found: 310.1704 (Na adduct), exact mass: 310.1702 (Na adduct).

The spectra can be found in Appendix 59-61.

**Preparation of 1-phenyl-3-(tetramethyl-1,3,2-dioxaborolan-2-yl)propan-2-ammonium hydrochloride 9:**

2-(2-azido-3-phenylpropyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (1.1 g, 3.8 mmol) was dissolved in tetrahydrofuran (15 mL), distilled from sodium benzophenone ketyl, and placed in a three necked round-bottomed flask. The flask was put on a magnetic stirrer and the contents stirred as lithium aluminum hydride (2.3 mL, 4.6 mmol) was added slowly drop-wise to the solution. After the addition was completed the solution was left to stir overnight. The solution was diluted with diethyl ether (50 mL) then water was added slowly drop-wise (2 mL) followed by 15 % aqueous sodium hydroxide (2 mL) and water again (2 mL). The

solution was left to stir for an hour before it was vacuum-filtered using a large volume of diethyl ether (150 mL) to wash the filter-cake thoroughly. The filter-cake was crushed continuously during the wash. The ethereal solution was then washed with saturated aqueous ammonium chloride (3 x 20 mL), dried over magnesium sulfate, filtered and concentrated on the rotary evaporator. The residual oil was dissolved in pentane (25 mL) and an excess of hydrochloric acid in methanol 1.25 M (5 mL, 6.25 mmol) was slowly added at 0 $^{o}$C to the solution. The solution was then left to stir overnight. The solvents were removed under vacuum and the residual oil washed with boiling pentane. The solvents were decanted and the residue concentrated on the rotary evaporator to give what appeared to be a mixture of 1-phenyl-3-(tetramethyl-1,3,2-dioxaborolan-2-yl)propan-2-amine and 1-phenyl-3-(tetramethyl-1,3,2-dioxaborolan-2-yl)propan-2-ammonium hydrochloride: 0.39 g (35 %); dark brown oil.

$^{1}$H-NMR (400 MHz, $CDCl_3$): δ 7.36 – 7.11 (m, 12.75H), 3.66 – 3.63 (m, 1H), 2.93 (m, 1H), 2.63 – 2.59 (m, 1H), 1.76 – 1.66 (m, 2H), 1.44 – 1.36 (1H), 1.24 – 1.19 (m, 12H), 0.85 – 0.81 (m, 2H).

$^{13}$C-NMR (101 MHz, $CDCl_3$): δ 136.04, 129.62, 128.83, 128.52, 128.14, 127.15, 125.53, 84.17, 82.92, 51.40, 40.64, 38.57, 37.92, 37.84, 35.89, 26.09, 24.93, 24.82, 24.25, 22.10.

IR ($cm^{-1}$): 3374.85, 3061.75, 3027.10, 2976.35, 2930.90, 2862.75, 1805.63, 1502.54, 1495.75, 1454.02, 1405.70, 1378.53, 1324.71, 1270.17, 1217.72, 1142.27, 1109.90, 1090.07, 1000.26, 966.69, 950.86, 884.39, 846.10, 749.68, 697.99, 656.60.

gCOSY: Appendix 67.

HRMS found: 262.1975, exact mass: 262.1978.

The spectra can be found in Appendix 65-68.

**Preparation of phenacyl bromide 12:**

A three-necked round-bottomed flask with an attached dropping funnel was loaded with acetophenone (11.72 g, 97 mmol) dissolved in glacial acetic acid (25 mL). The flask was placed on a magnetic stirrer submerged in a water bath maintaining a temperature between 10 $^{o}$C and 20 $^{o}$C. Bromine (5 mL, 97 mmol) was placed in the dropping funnel and then slowly added drop-wise to the vigorously stirred solution. After the addition was completed the solution was transferred to an Erlenmeyer-flask and cooled in an ice-water bath to ensure that the crystalline product precipitated from the solution. The crude product was washed several

times with distilled ice-cold water (150 mL) using a Büchner-funnel attached to a vacuum pump. When the crystals had changed color to an off-white/beige color they were oven-dried until the next day giving the expected phenacyl bromide: 15.44 g (80 %); off-white crystals.

$^{1}$H-NMR (400 MHz, $CDCl_3$): δ 8.10 – 7.16 (m, 5H), 4.60 (d, *J* = 1.8 Hz, 2H).

$^{13}$C-NMR (101 MHz, $CDCl_3$): δ 191.25, 133.94, 129.69, 128.92, 128.85, 30.08.

GC-MS: 5.26 min, $M^+$ (199) cannot be seen.

The spectra can be found in Appendix 79-81.

**Preparation of 2-(bromomethyl)-2-phenyl-1,3-dioxane 13:**

A round-bottomed flask was charged with phenacyl bromide (10 g, 50 mmol), 1-3-propanediol (4.2 g, 55 mmol), para-toluenesulfonic acid (0.1 g, 0.5 mmol), toluene (200 mL) and a magnet. The flask was placed on a hot-plate magnetic stirrer and lowered into a silicon oil bath. A Dean-Stark apparatus was fitted with a condenser and attached to the flask. The fractionating column of the Dean-Stark apparatus was covered in aluminum foil to decrease heat-loss during distillation. The solution was set to stir and the silicon oil was heated up to the point where the toluene started to reflux. The solution was left refluxing overnight and was then washed with 5 % sodium carbonate (50 mL) and dried over magnesium sulfate. The solvent was removed under vacuum giving the 2-(bromomethyl)-2-phenyl-1,3-dioxane: 11.03 g (85 %); dark brown oil.

$^{1}$H-NMR (400 MHz, $CDCl_3$): δ 7.64 – 7.14 (m, 5H), 3.97 (ddt, *J* = 10.6, 5.0, 1.6 Hz, 2H), 3.82 (tdd, *J* = 11.9, 2.7, 1.5, 2H), 3.43 (s, 2H), 2.19 (qt, 12.7, 5.0 Hz, 1H), 1.26 (d, 10.3 Hz, 1H).

$^{13}$C-NMR (101 MHz, $CDCl_3$): δ 136.95, 128.84, 128.78, 127.91, 125.27, 98.84, 61.68, 41.08, 25.04.

GC-MS: 6.75 min, $M^+$ (257) cannot be seen.

gCOSY: Appendix 85.

The spectra can be found in Appendix 83-86.

**General procedure for preparing compounds 15-25:**

A three-necked flask was connected to a condenser and placed in an ultrasonic bath. The flask was charged with magnesium turnings (60 mmol), three crystals of iodine and tetrahydrofuran (50 mL) distilled from sodium benzophenone ketyl. An argon atmosphere was maintained in the flask and the contents irradiated during the drop-wise addition of benzyl halide (100 mmol). After the addition had been completed the reaction mixture was sonicated for 3 hours while continuously adding ice to the ultrasonic bath to keep the temperature low. The solution was then quenched with 5 % hydrochloric acid (30 mL) and the aqueous and organic phases separated. The aqueous phase was extracted with diethyl ether (3 x 20 mL) and the combined organic phases dried over magnesium sulfate, filtered and concentrated on the rotary evaporator. Column chromatography was performed on silica using pentane to eluate the impurities and 5 % ethyl acetate in pentane to eluate the product.

**Preparation of 1,2-bis-(2-bromophenyl)ethane 15:**

From 2-bromobenzyl bromide (1.03 g, 4.1 mmol), magnesium (0.06 g, 2.4 mmol), tetrahydrofuran (30 mL): 0.09 g (13 %); pink crystalline solid.

$^{1}$H-NMR (400 MHz, $CDCl_3$): δ 7.56 (dd, *J* = 8.2, 1.3 Hz, 2H), 7.28 – 7.16 (m, 4H), 7.12 – 7.03 (m, 2H), 3.06 (s, 4H).

$^{13}$C-NMR (101 MHz, $CDCl_3$): δ 140.56, 132.79, 130.62, 127.81, 127.43, 124.47, 36.44.

The spectra can be found in Appendix 88-89.

**Preparation of 1,2-bis-(3-bromophenyl)ethane 16:**

From 3-bromobenzyl bromide (1 g, 4 mmol), magnesium (0.06 g, 2.4 mmol), tetrahydrofuran (30 mL): 0.13 g (19 %); white solid.

$^{1}$H-NMR (400 MHz, $CDCl_3$): δ 7.37 – 7.31 (m, 4H), 7.16 (td, *J* = 7.5, 1.2 Hz, 2H), 7.08 (dt, *J* = 7.8, 1.4 Hz, 2H), 2.88 (s, 4H).

$^{13}$C-NMR (101 MHz, $CDCl_3$): δ 143.47, 131.15, 129.97, 129.26, 127.13, 122.47, 37.25.

The spectra can be found in Appendix 90-91.

**Preparation of 1,2-bis-(4-bromophenyl)ethane 17:**

From 4-bromobenzyl bromide (1.01 g, 4 mmol), magnesium (0.06 g, 2.4 mmol), tetrahydrofuran (30 mL): 0.08 g (12 %); light grey solid containing crystals.

$^{1}$H-NMR (400 MHz, $CDCl_3$): δ 7.40 – 7.38 (m, 4H), 7.01 – 6.99 (m, 4H), 2.85 (s, 4H).

$^{13}$C-NMR (101 MHz, $CDCl_3$): δ 140.07, 131.39, 130.24, 119.80, 37.02.

The spectra can be found in Appendix 92-93.

**Preparation of 5,6,11,12-tetrahydrodibenzo[a,e][8]annulene 18:**

From bis(bromomethyl)benzene (2 g, 7.6 mmol), magnesium (0.22 g, 9 mmol), tetrahydrofuran (30 mL): 0.16 g (20 %); yellow solid.

$^{1}$H-NMR (400 MHz, $CDCl_3$): δ 7.09 – 6.88 (m, 8H), 2.80 – 2.59 (m, 8H).

$^{13}$C-NMR (101 MHz, $CDCl_3$): δ 139.40, 129.14, 126.30, 34.14.

The spectra can be found in Appendix 94-95.

**Preparation of 1,2-bis-(3-trifluoromethylphenyl)ethane 20:**

From 3-(trifluoromethyl)benzyl bromide (1.01 g, 4.2 mmol), magnesium (0.06 g, 2.5 mmol), tetrahydrofuran (30 mL): 0.19 g (28 %); colorless/pink hued crystals.

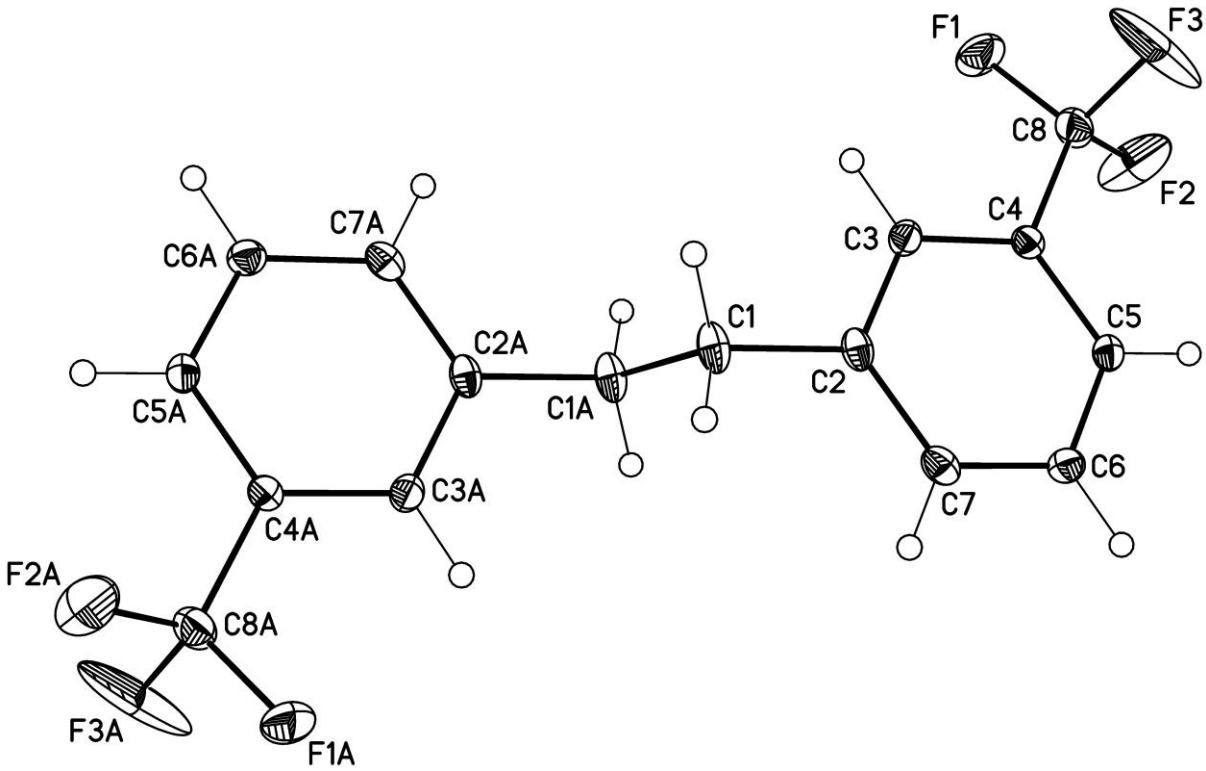
$^{1}$H-NMR (400 MHz, $CDCl_3$): δ 7.47 (d, $J$ = 8.5 Hz, 2H), 7.43 – 7.36 (m, 4H), 7.31 (d, $J$ = 8.2 Hz, 2H), 3.00 (s, 4H).

$^{13}$C-NMR (101 MHz, $CDCl_3$): δ 141.76, 131.87, 128.82, 125.18, 125.15, 123.07, 123.03, 37.39.

The spectra can be found in Appendix 96-97.

X-ray crystal data: Empirical formula C16 H12 F6, Formula weight 318.26, Temperature 100(2) K, Wavelength 0.71073 Å, Crystal system Monoclinic, Space group $P2_1/c$, Unit cell dimensions a = 7.7356(3) Å, α = 90°, b = 13.4193(6) Å, β = 110.5250(10)°, c = 7.2025(3) Å, γ = 90°, Volume 700.20(5) $Å^3$, Z 2, Density (calculated) 1.509 $Mg/m^3$, Absorption coefficient 0.143 $mm^{-1}$, F(000) 324, Crystal size 0.20 x 0.15 x 0.15 $mm^3$, Theta range for data collection 2.81 to 30.00°, Index ranges -10<=h<=10, -18<=k<=18, -10<=l<=10, Reflections collected

8957, Independent reflections 2037 [R(int) = 0.0211], Completeness to theta = 30.00° 100.0 %, Absorption correction Semi-empirical from equivalents, Max. and min. transmission 0.979 and 0.972, Refinement method Full-matrix least-squares on $F^2$, Data / restraints / parameters 2037 / 0 / 100, Goodness-of-fit on $F^2$ 1.001, Final R indices [for 1774 rflns with $I>2\sigma(I)$] R1 = 0.0501, wR2 = 0.1249 R indices (all data) R1 = 0.0571, wR2 = 0.1298, Largest diff. peak and hole 0.523 and -0.518 e.$Å^{-3}$.




**Preparation of 1,2-bis-(4-trifluoromethylphenyl)ethane 21:**

From 4-(trifluoromethyl)benzyl bromide (0.69 g, 2.9 mmol), magnesium (0.04 g, 1.6 mmol), tetrahydrofuran (30 mL): 0.02 g (4 %); white crystalline solid.

$^1$H-NMR (400 MHz, $CDCl_3$): δ 7.54 (d, *J* = 7.9 Hz, 4H), 7.26 (d, *J* = 8.0 Hz, 4H), 3.00 (s, 4H).

$^{13}$C-NMR (101 MHz, $CDCl_3$): δ 144.98, 128.74, 125.32, 125.36, 122.90, 37.21.

The spectra can be found in Appendix 98-99.

**Preparation of 1,2-bis-(2-methylphenyl)ethane 22:**

From 2-methylbenzyl bromide (1 g, 5.4 mmol), magnesium (0.08 g, 3.2 mmol), tetrahydrofuran (30 mL): 0.34 g (61 %); green crystalline solid.

$^{1}$H-NMR (400 MHz, $CDCl_3$): δ 7.39 – 7.32 (m, 8H), 3.08 (s, 4H), 2.53 (s, 6H).

$^{13}$C-NMR (101 MHz, $CDCl_3$): δ 140.33, 136.05, 130.40, 129.07, 126.31, 126.26, 34.37, 19.48.

The spectra can be found in Appendix 100-101.

**Preparation of 1,2-bis-(3-methylphenyl)ethane 23:**

From 3-methylbenzyl bromide (1.01 g, 5.4 mmol), magnesium (0.08 g, 3.2 mmol), tetrahydrofuran (30 mL): 0.18 g (31 %); colorless liquid.

$^{1}$H-NMR (400 MHz, $CDCl_3$): δ 7.40 – 7.25 (m, 2H), 7.24 – 7.21 (m, 6H), 3.09 (s, 4H), 2.55 (s, 6H).

$^{13}$C-NMR (101 MHz, $CDCl_3$): δ 142.09, 138.01, 129.44, 128.45, 126.84, 125.62, 38.23, 21.61.

The spectra can be found in Appendix 102-103.

**Preparation of 1,2-bis-(4-methylphenyl)ethane 24:**

From 4-methylbenzyl bromide (1 g, 5.4 mmol), magnesium (0.08 g, 3.2 mmol), tetrahydrofuran (30 mL): 0.27 g (48 %); green solid.

$^{1}$H-NMR (400 MHz, $CDCl_3$): δ 7.22 – 7.16 (m, 8H), 2.98 (s, 4H), 2.43 (s, 6H).

$^{13}$C-NMR (101 MHz, $CDCl_3$): δ 138.95, 135.34, 129.09, 128.39, 37.74, 21.12.

The spectra can be found in Appendix 104-105.

**Preparation of bibenzyl 25:**

From benzyl bromide (1 g, 5.8 mmol), magnesium (0.08 g, 3.5 mmol), tetrahydrofuran (30 mL): 0.12 g (23 %); white crystalline solid.

$^{1}$H-NMR (400 MHz, $CDCl_3$): δ 7.31 – 7.24 (m, 4H), 7.20 – 7.18 (m, 4H), 2.93 (s, 4H).

$^{13}$C-NMR (101 MHz, $CDCl_3$): δ 141.85, 128.53, 128.41, 126.00, 38.03.

The spectra can be found in Appendix 106-107.

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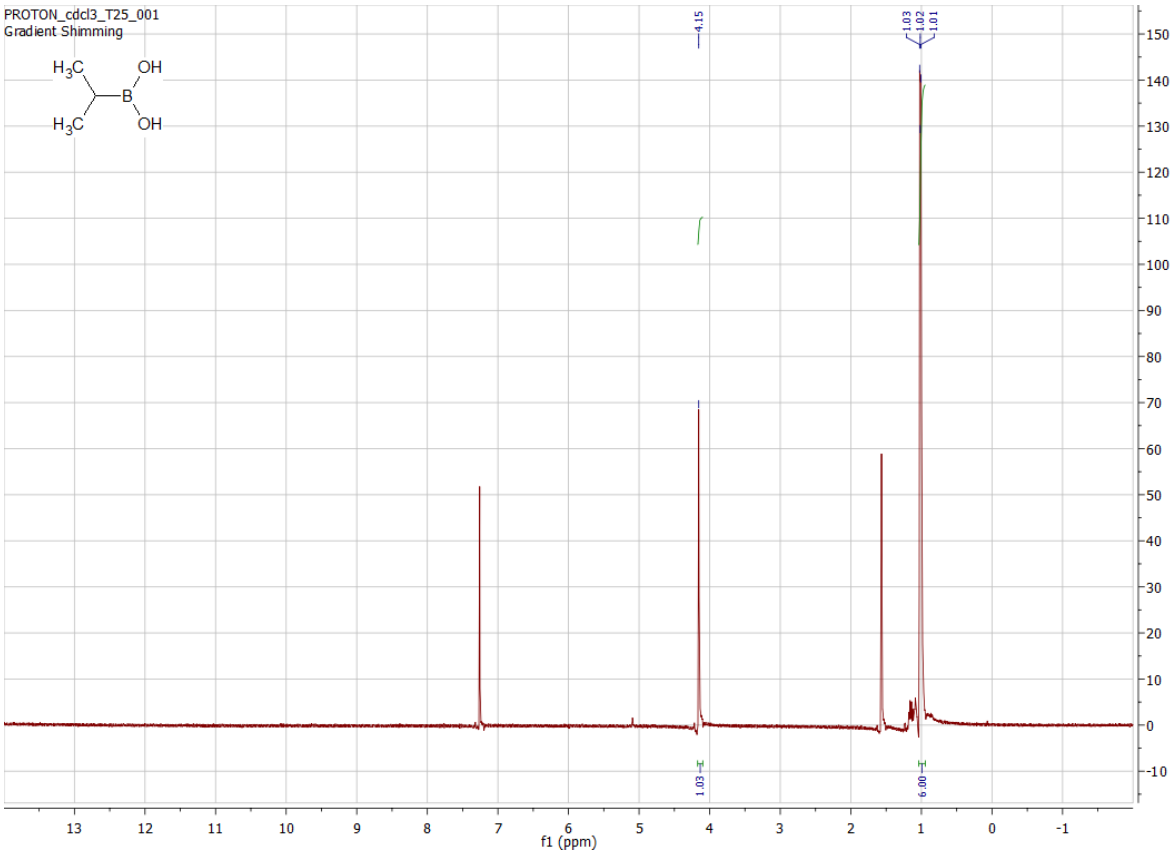
# APPENDICES

## Appendix 1

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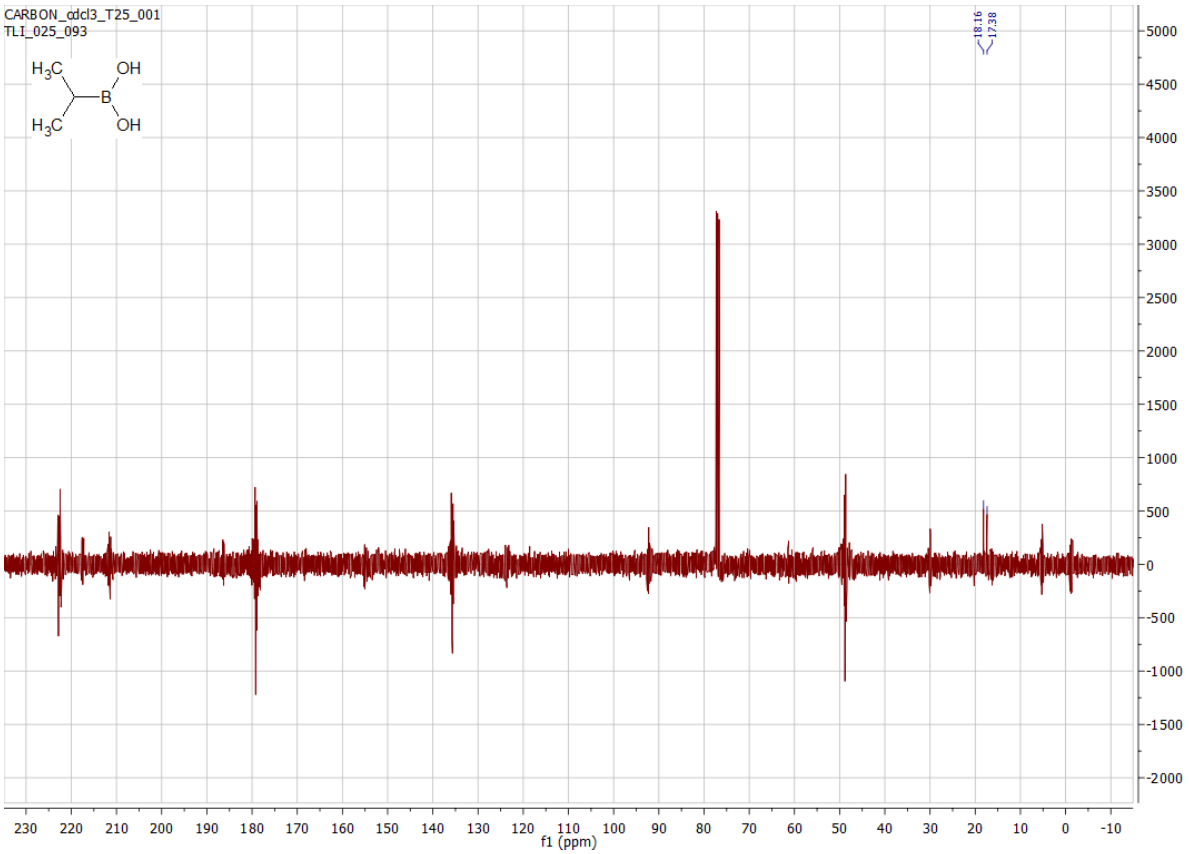

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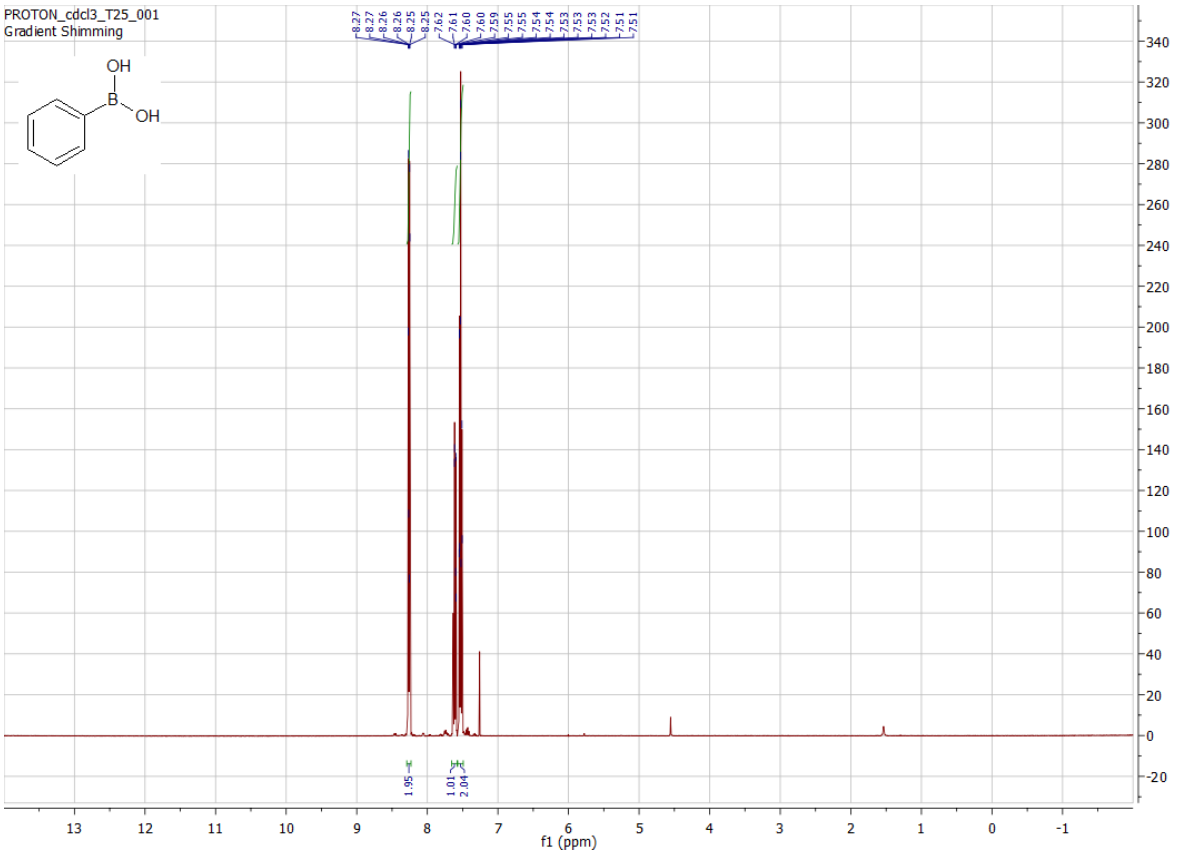


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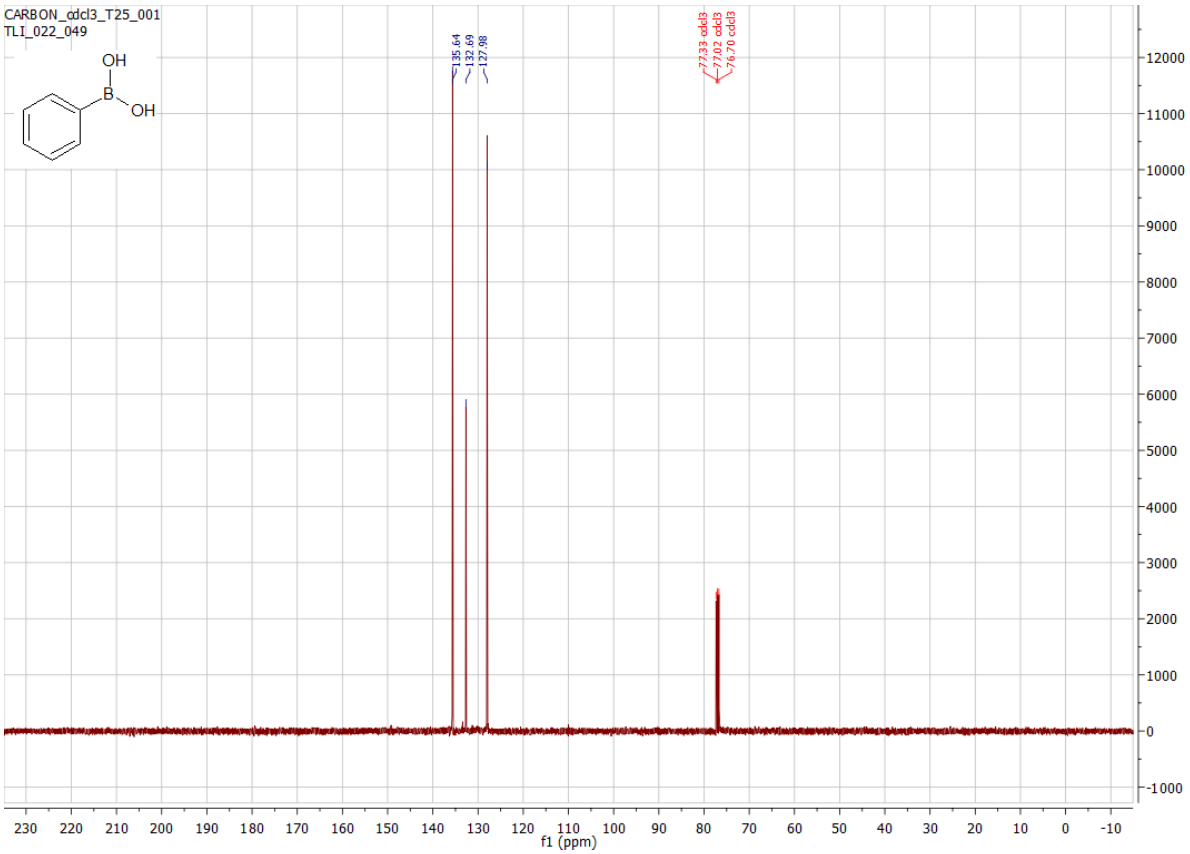

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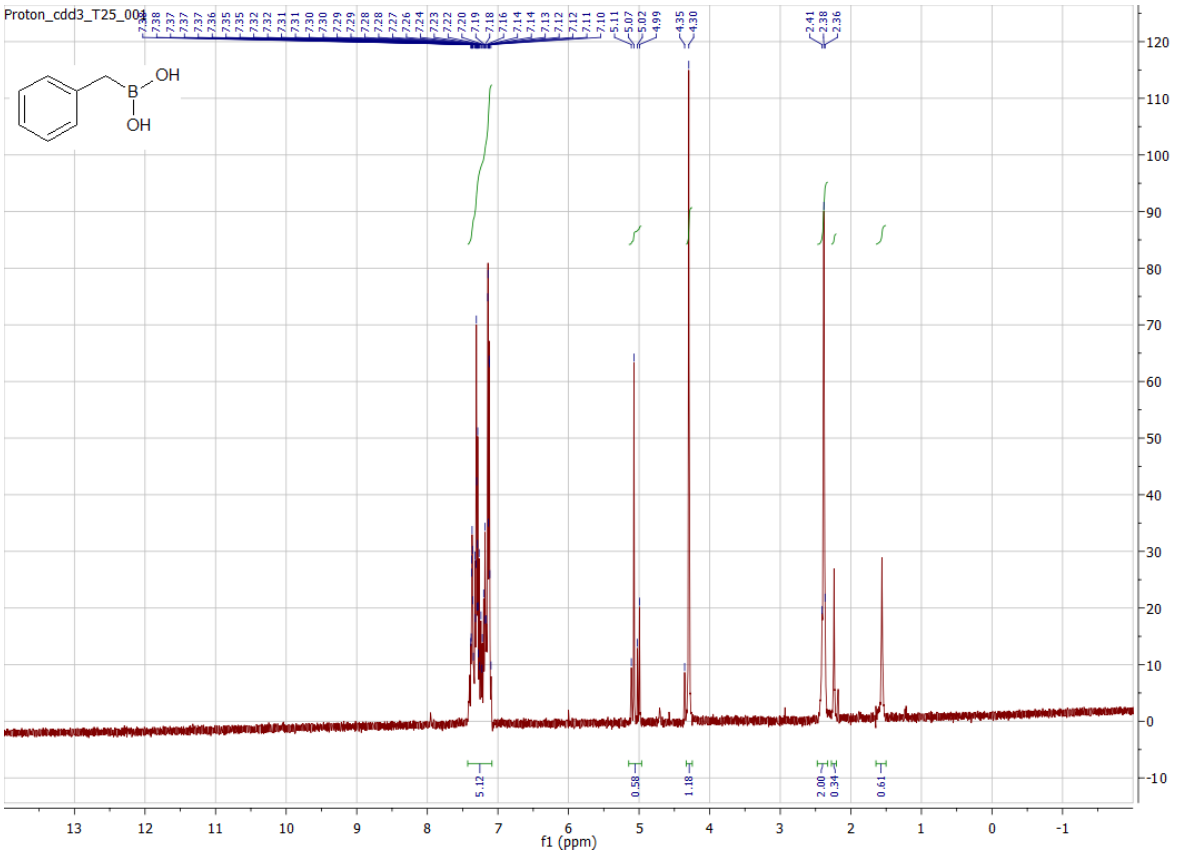


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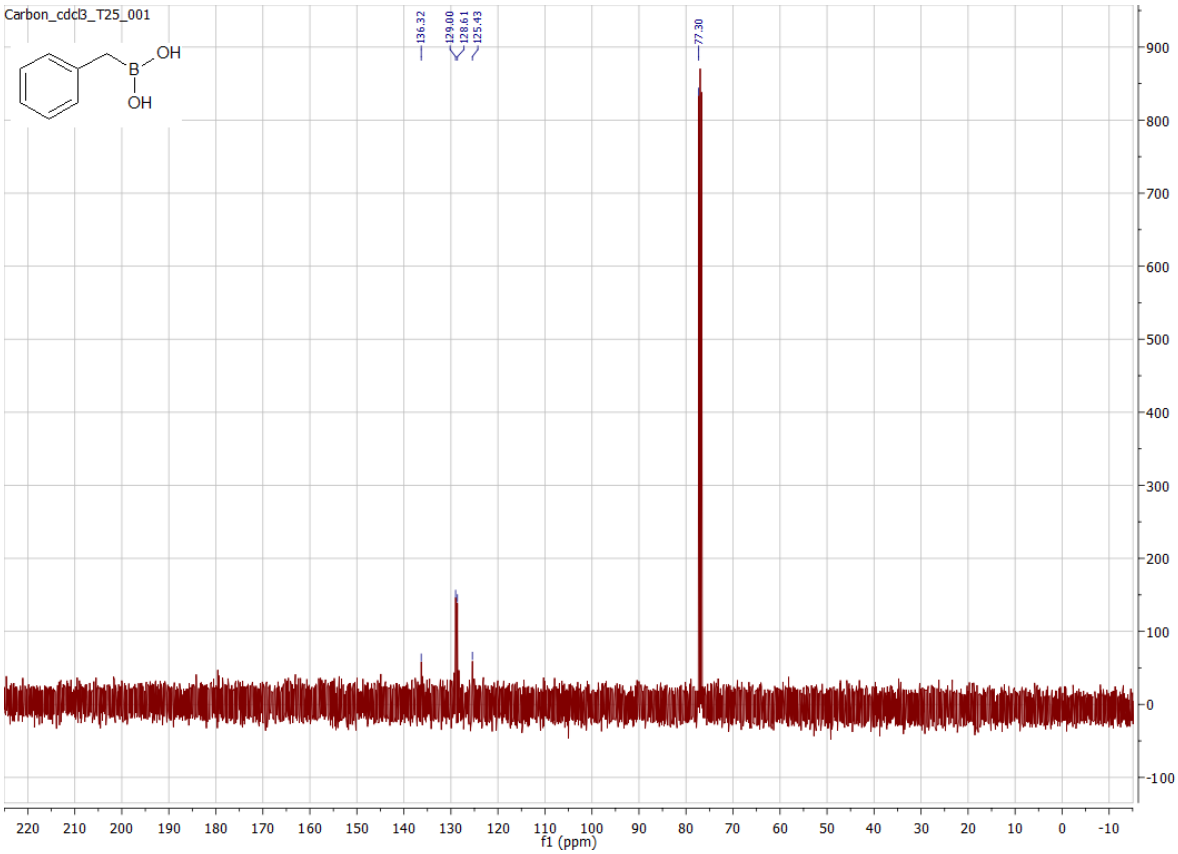

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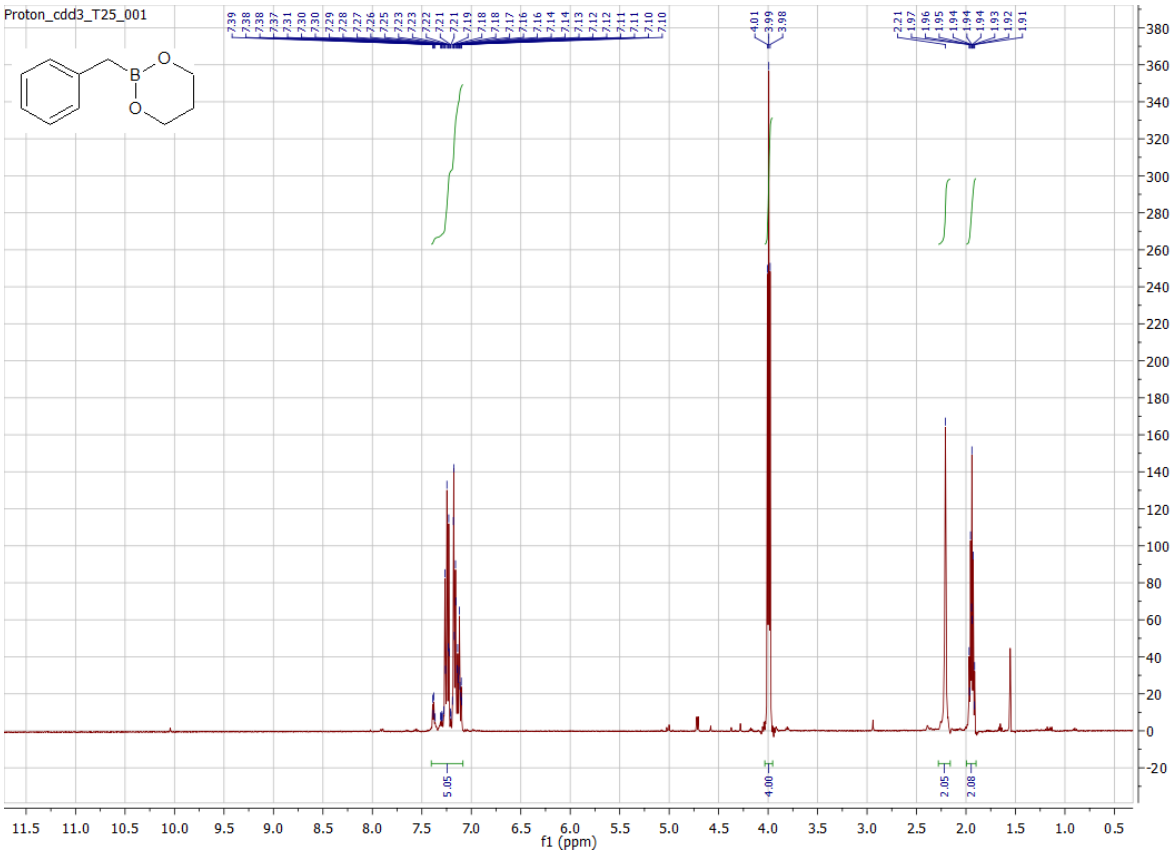


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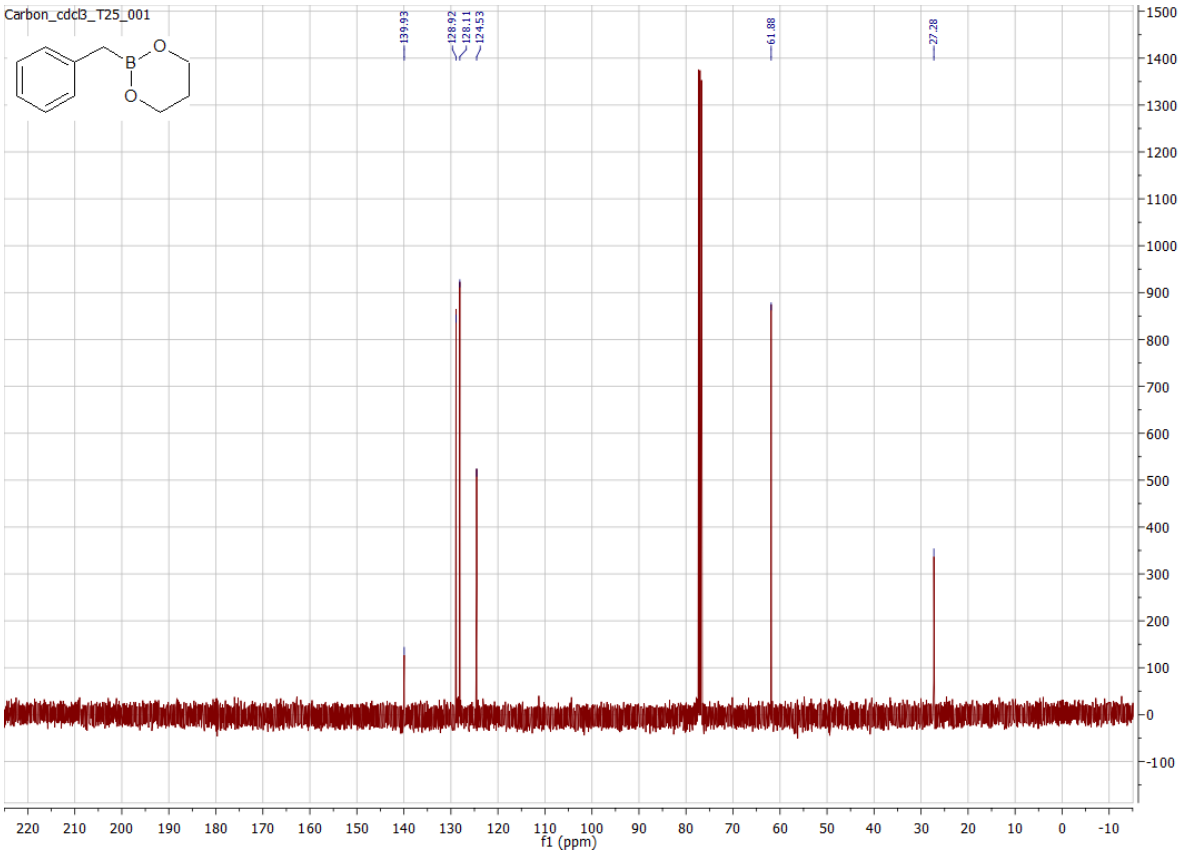

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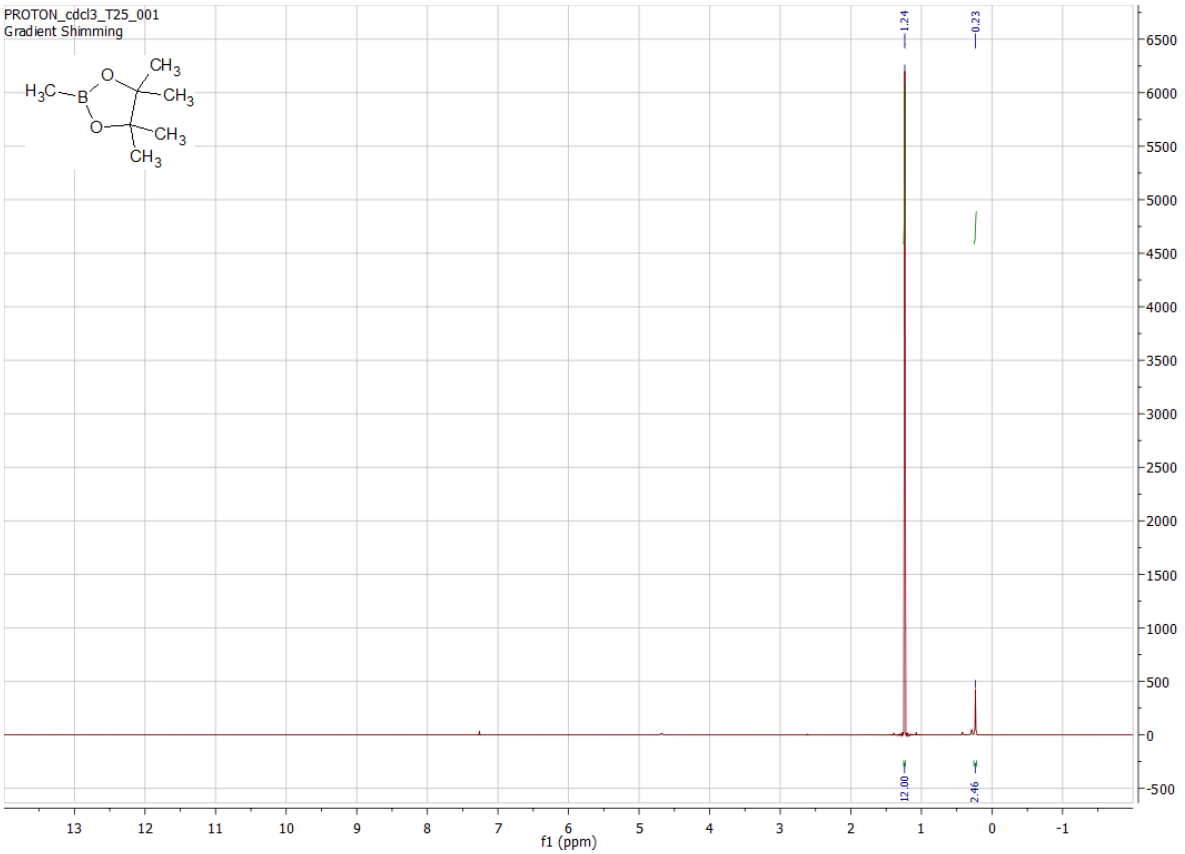


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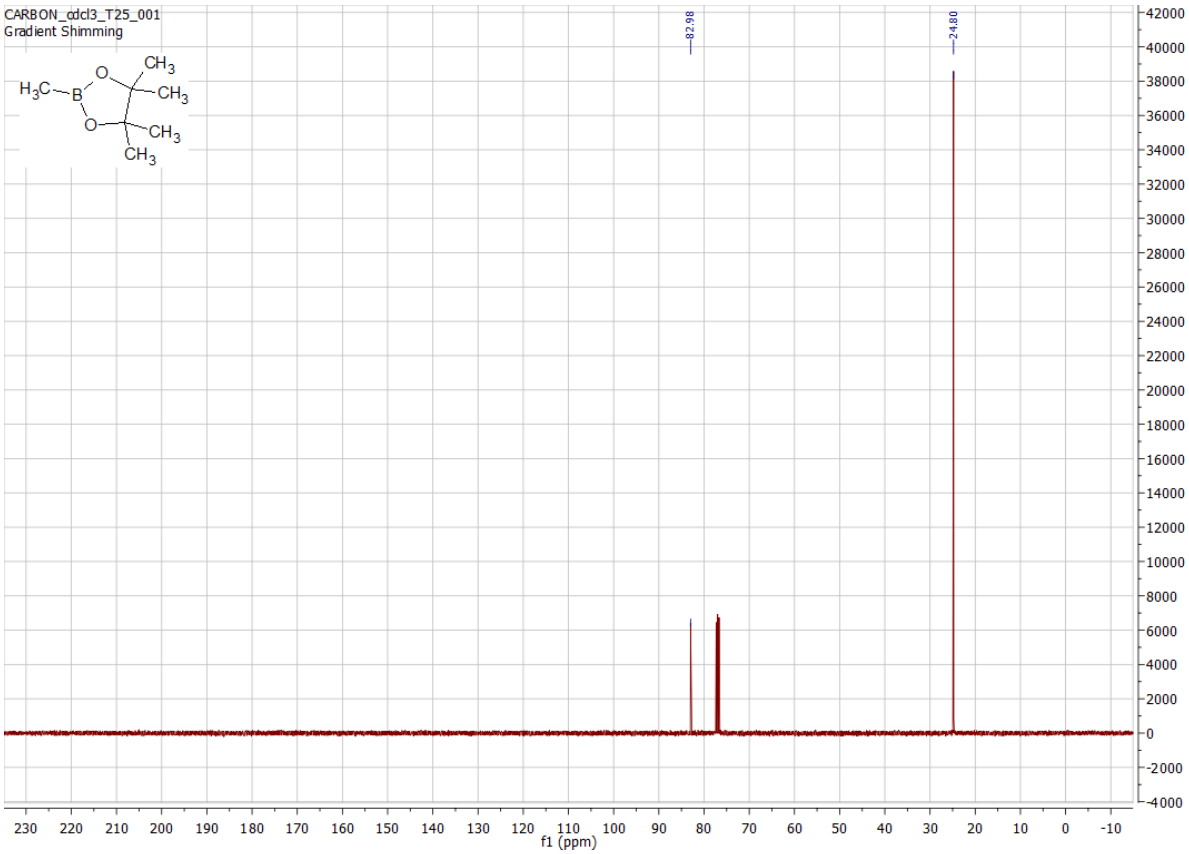

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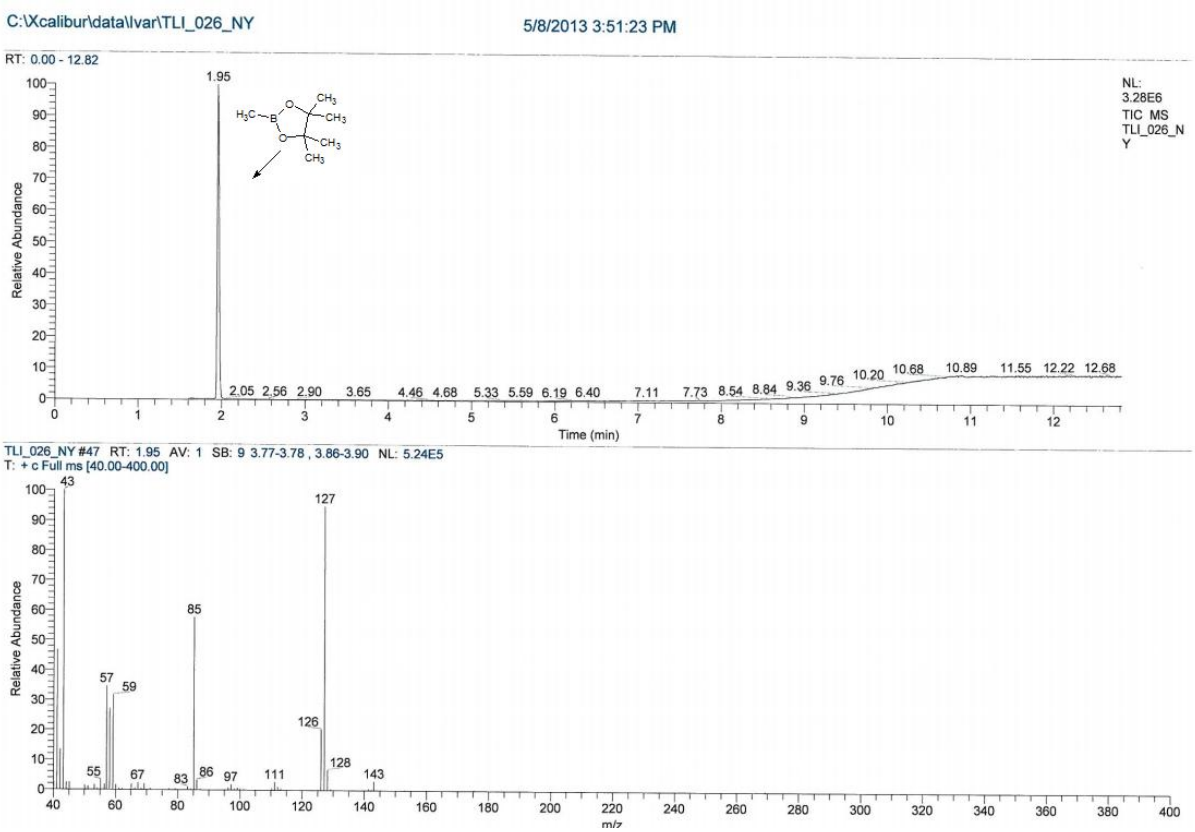


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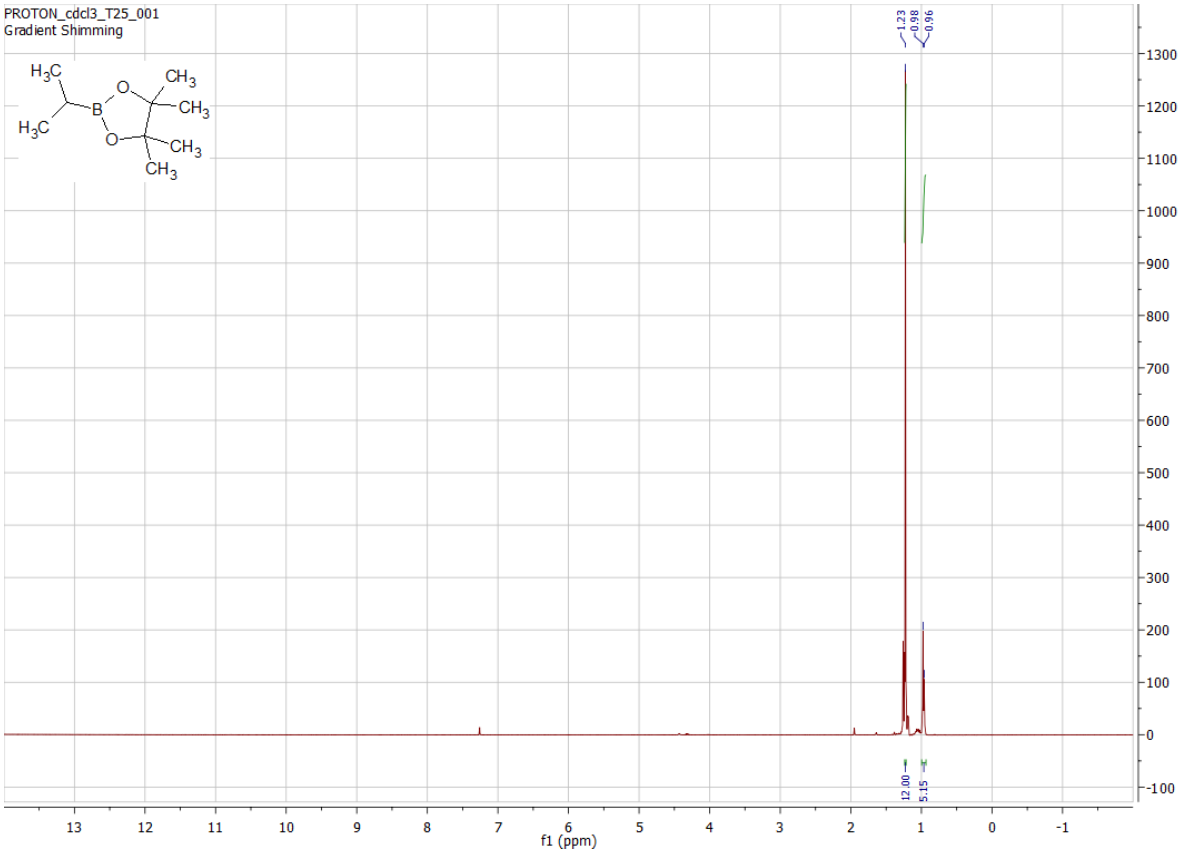

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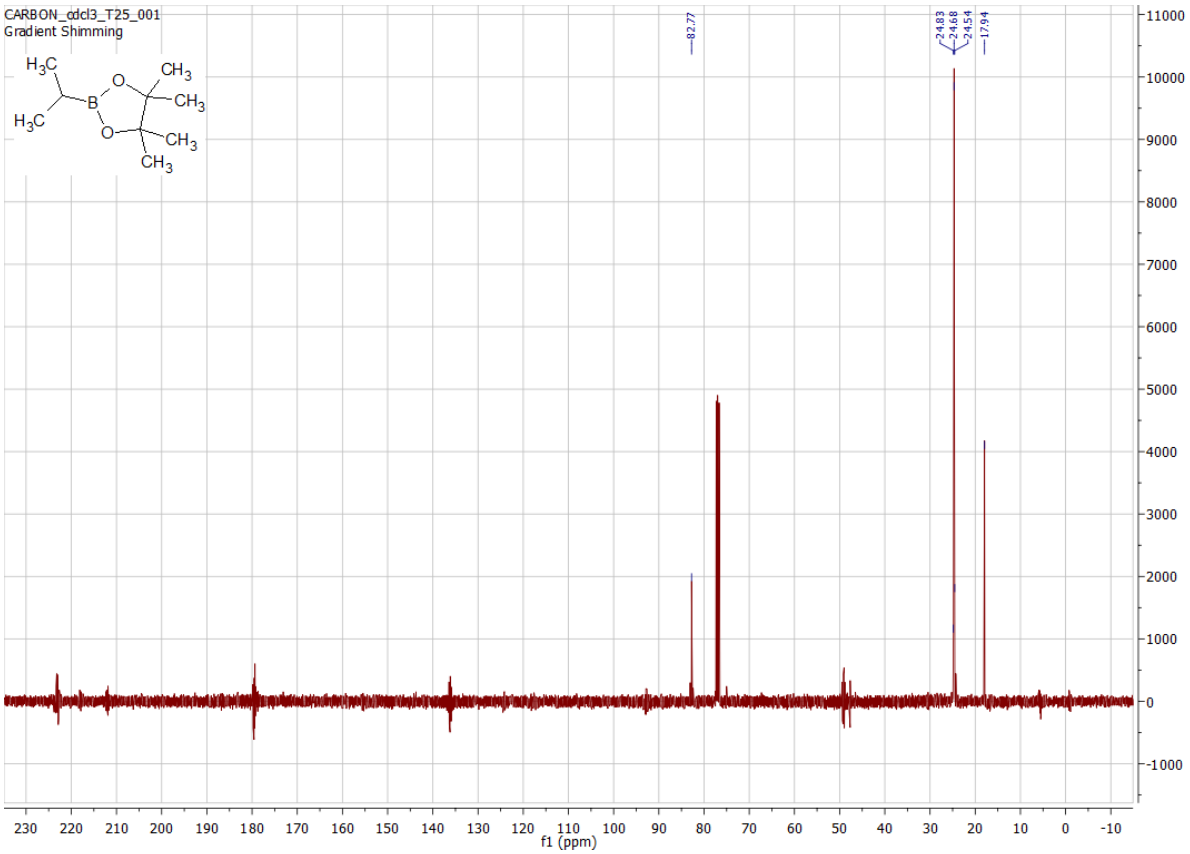


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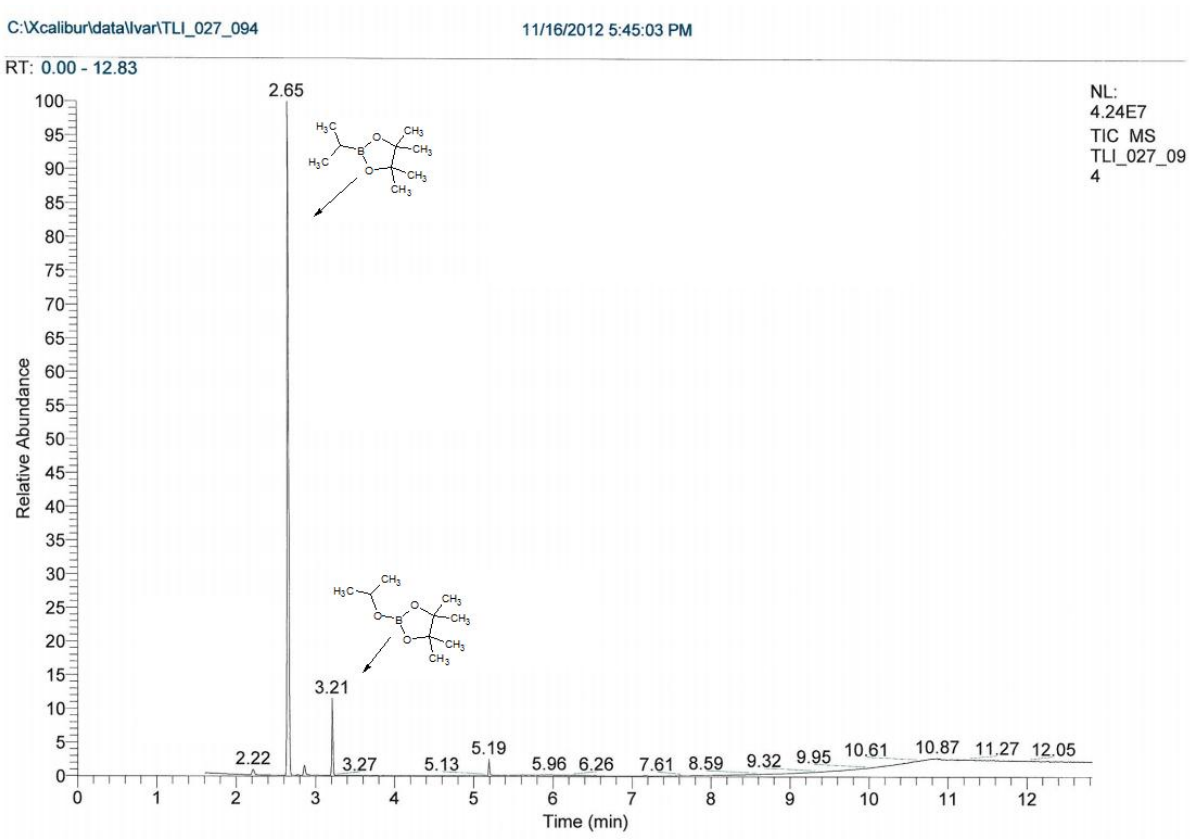

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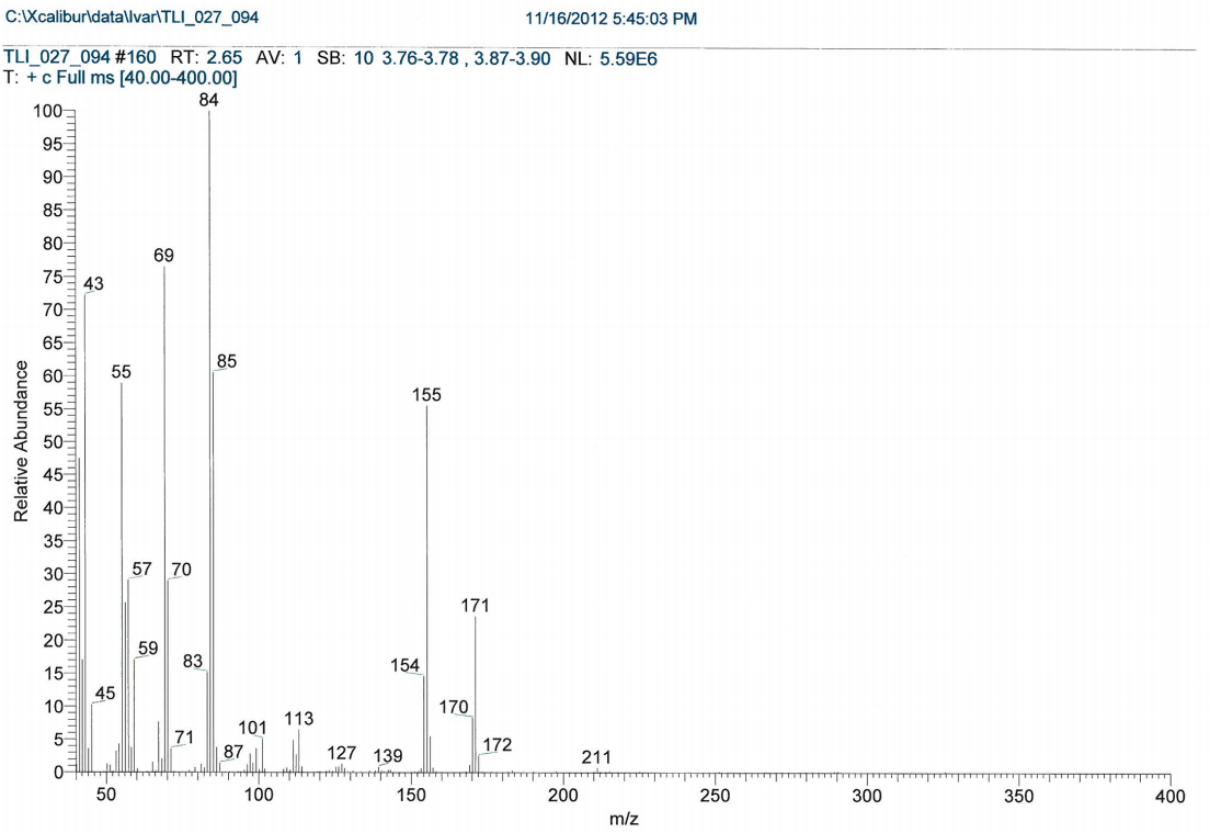


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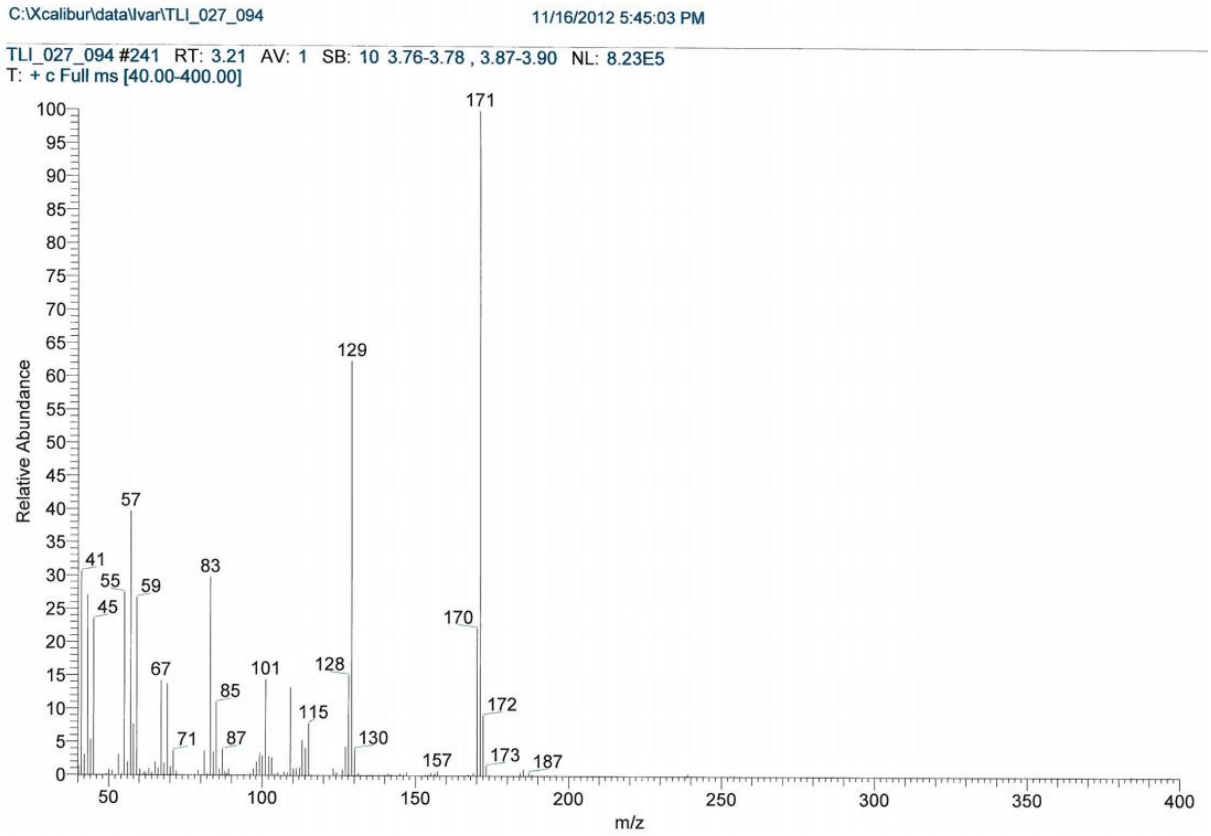

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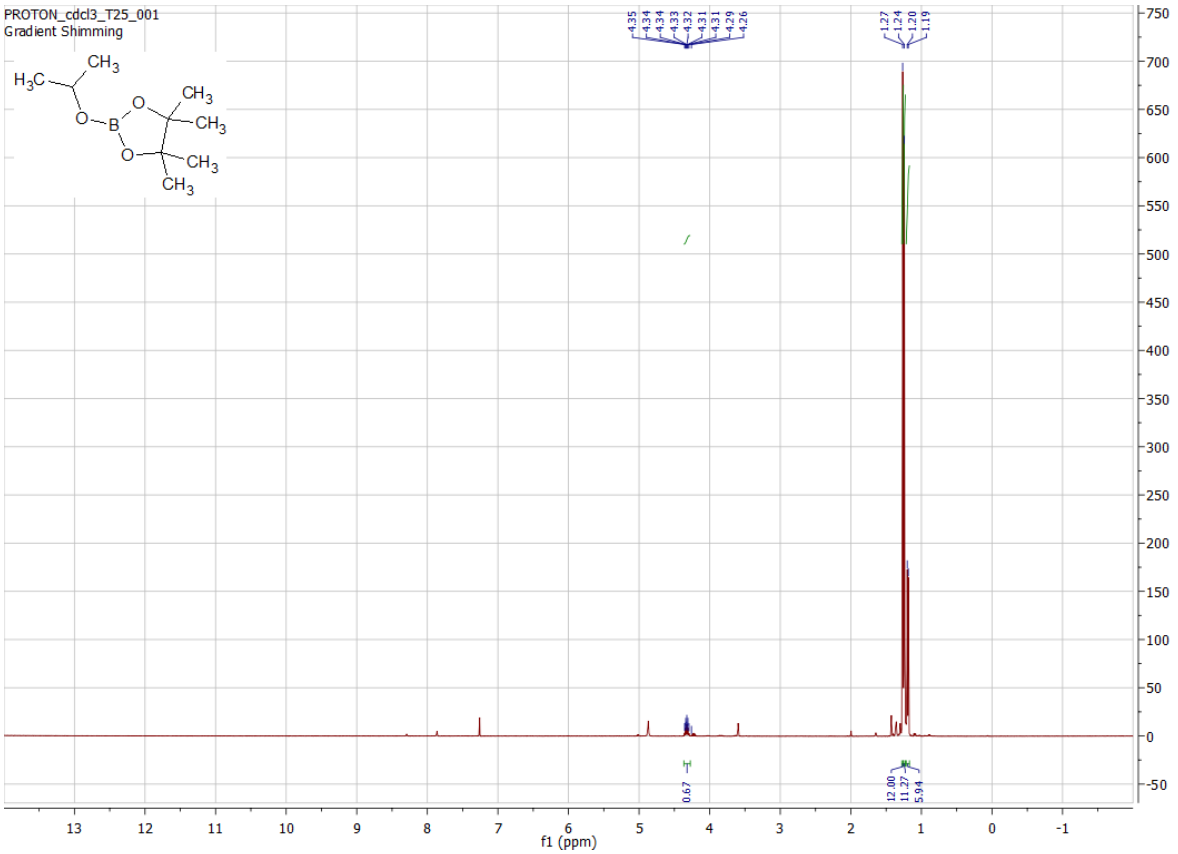


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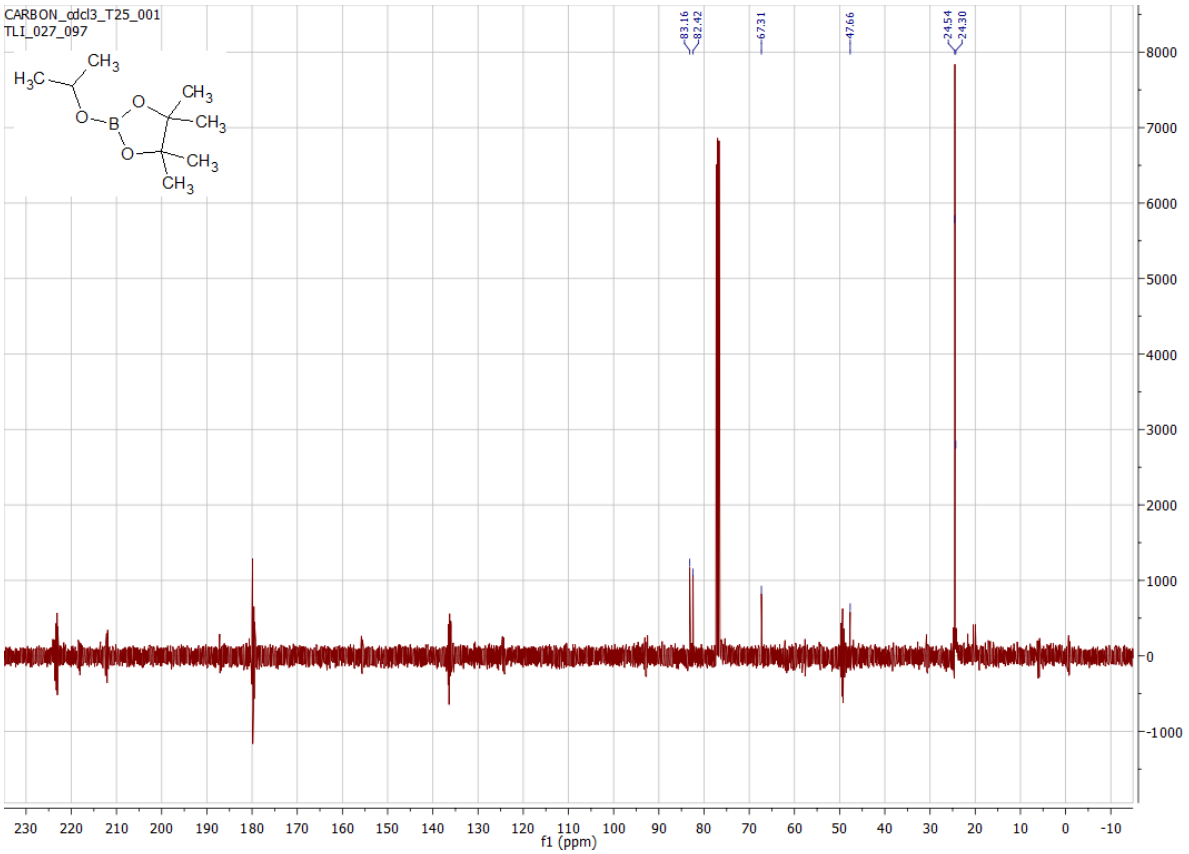

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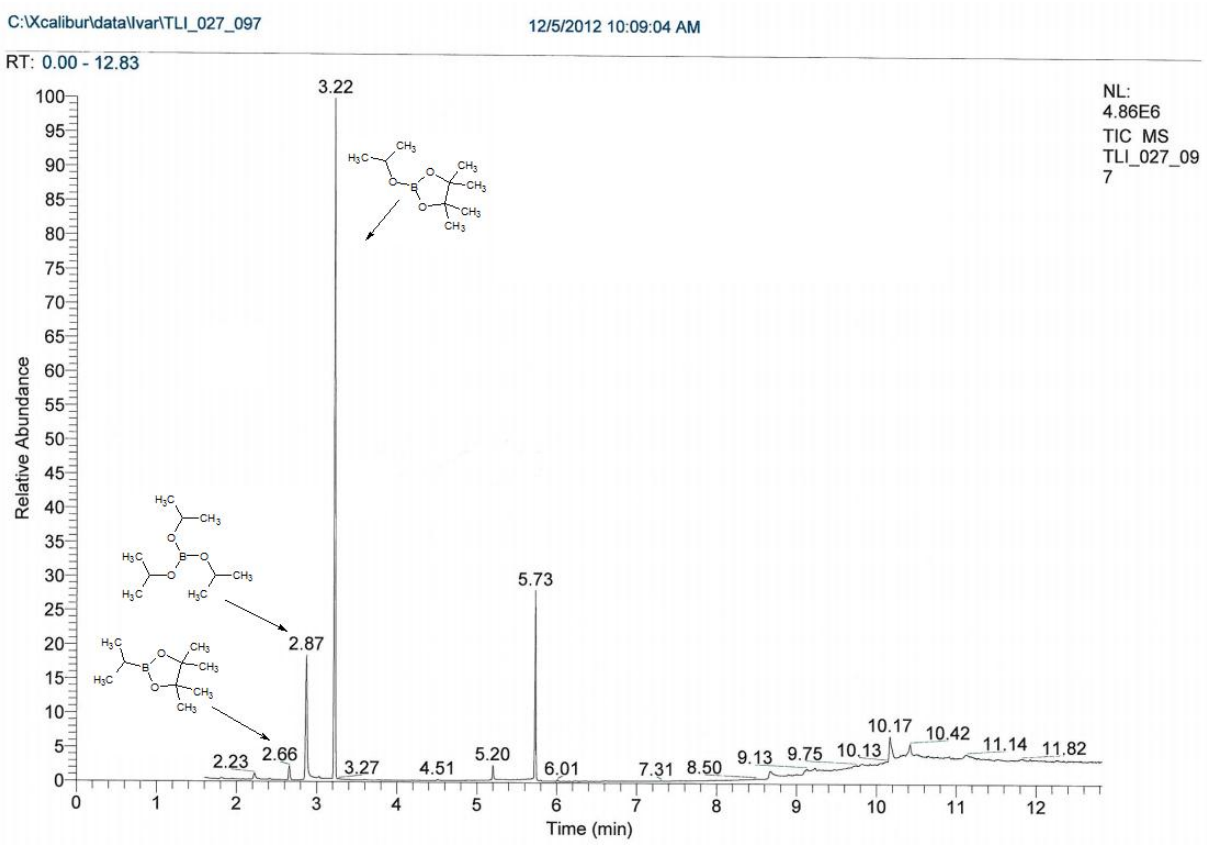


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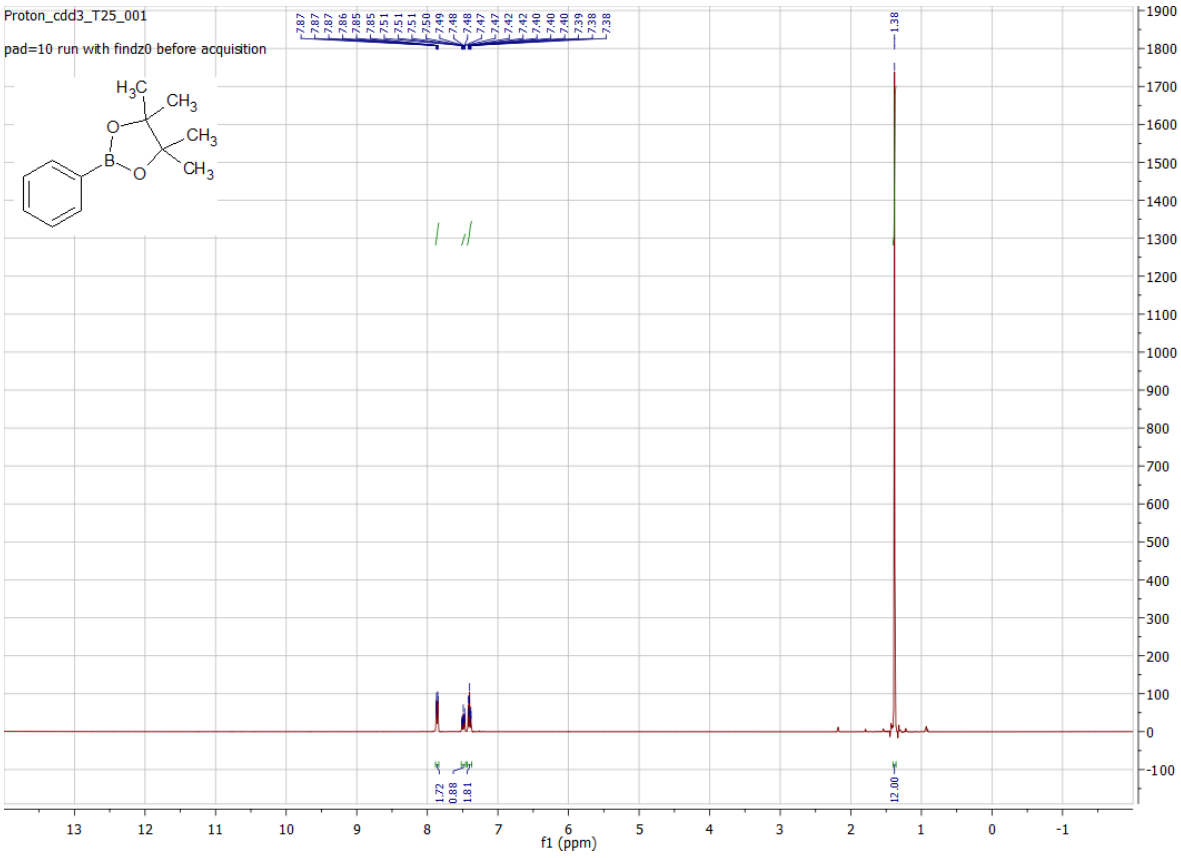
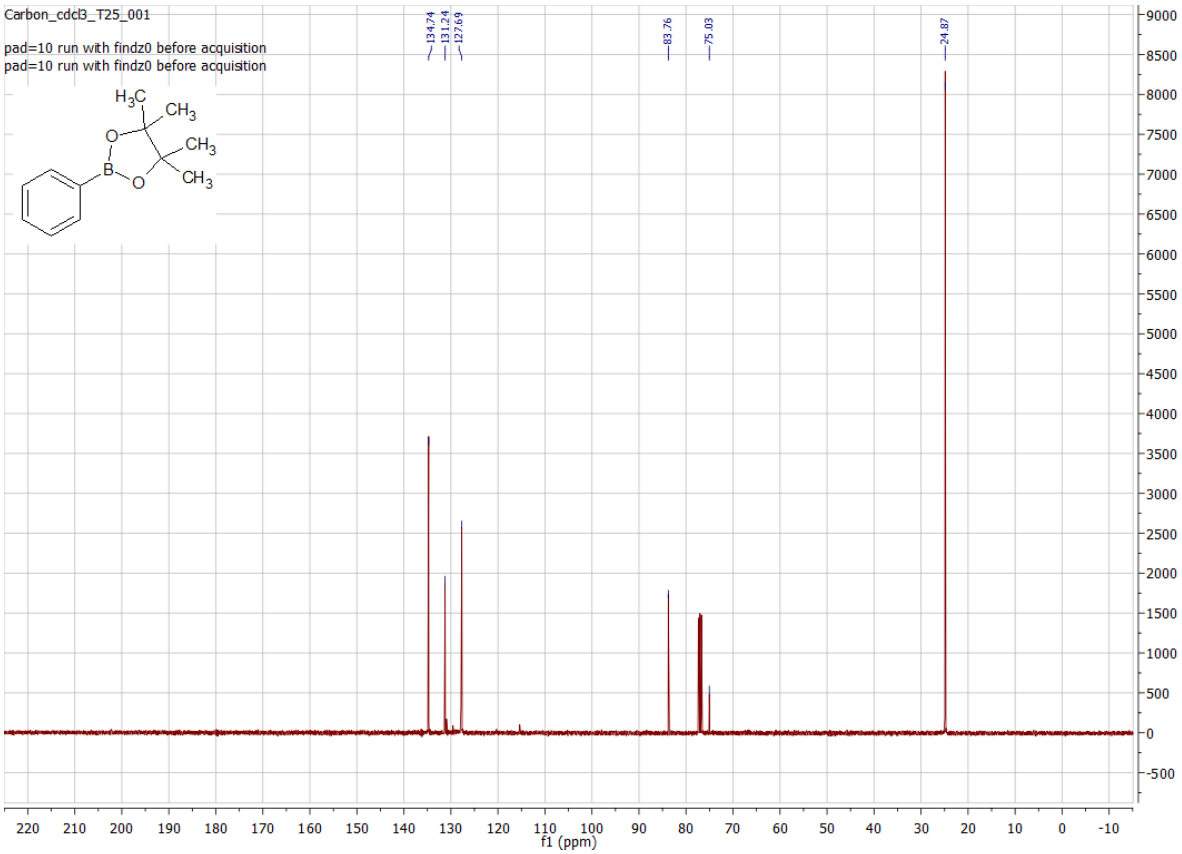


## Appendix 21

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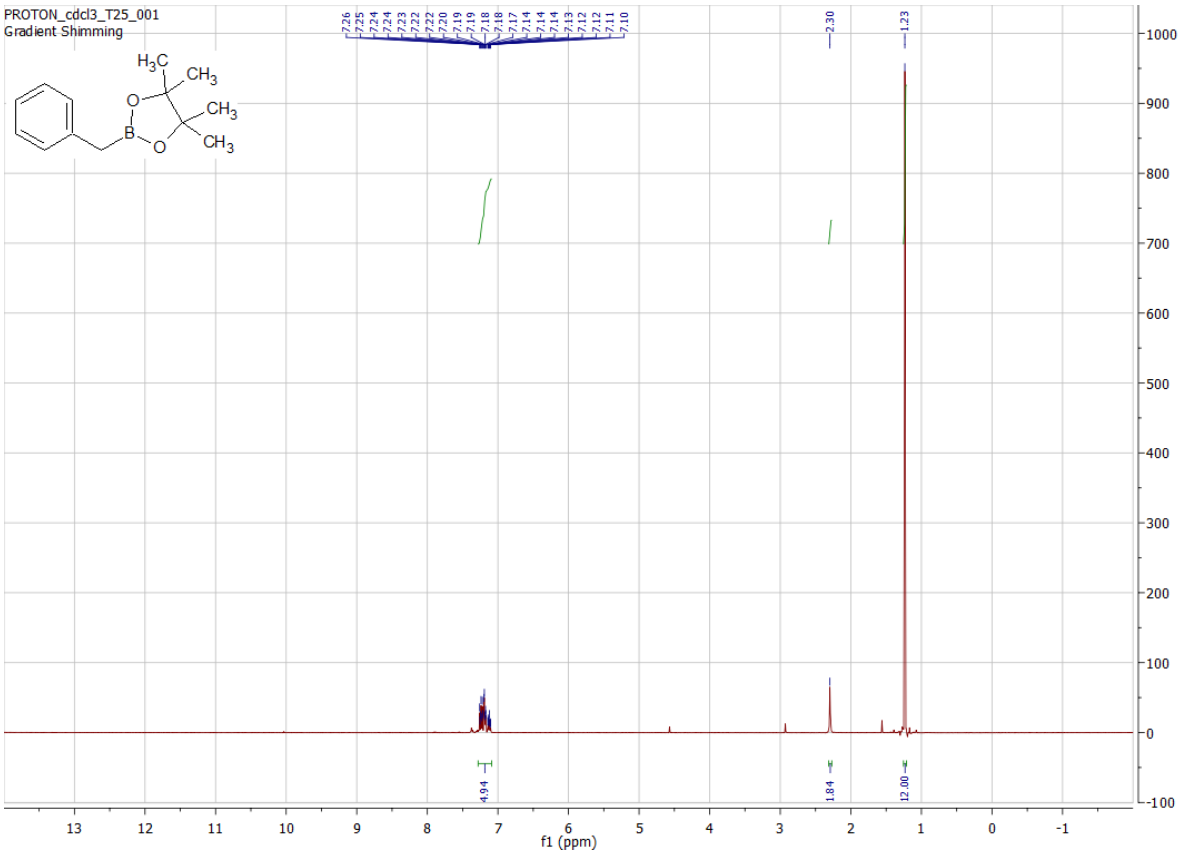

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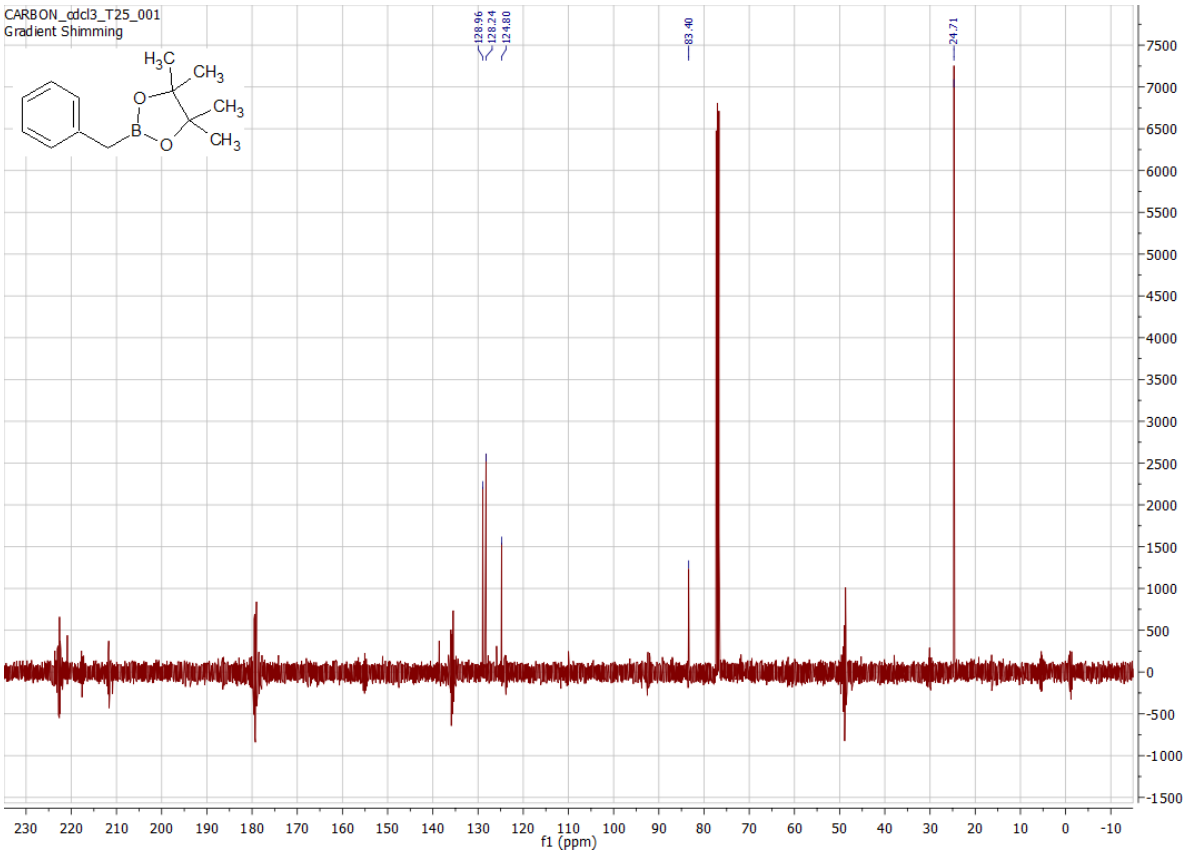


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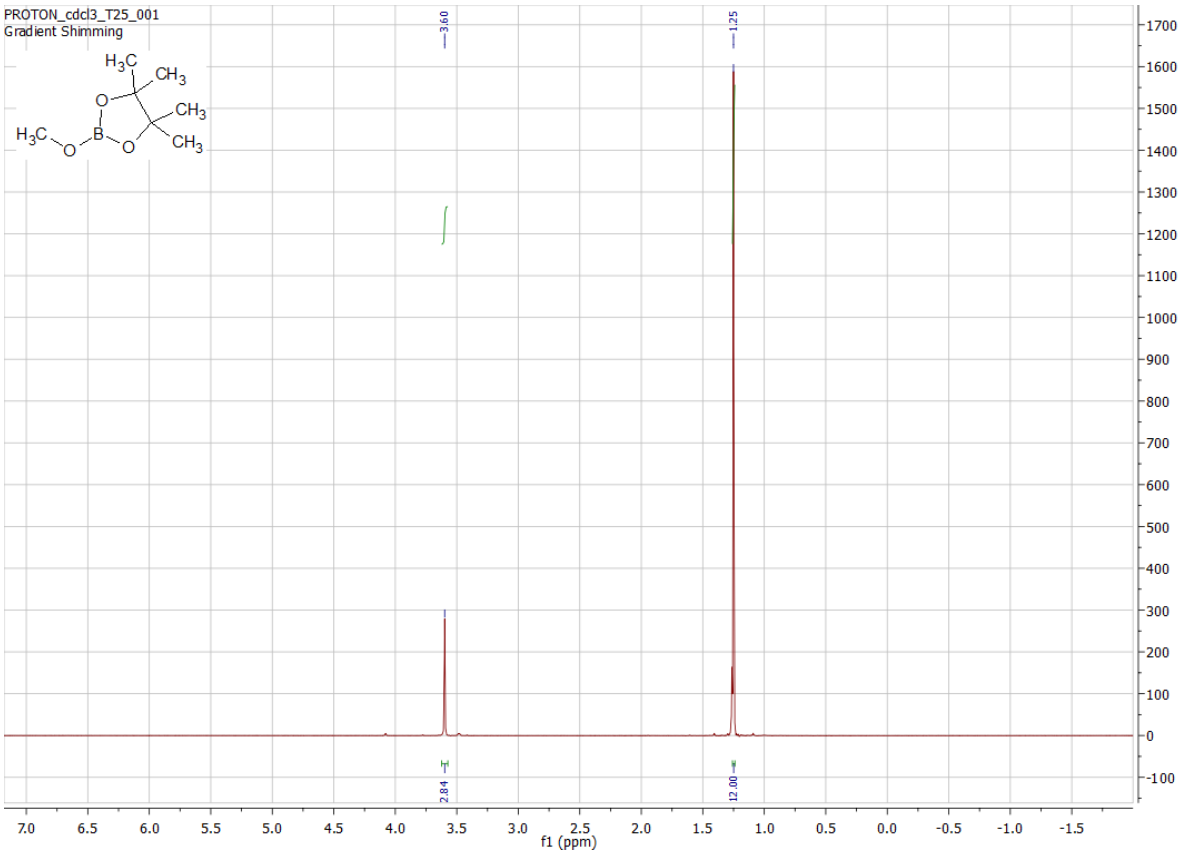

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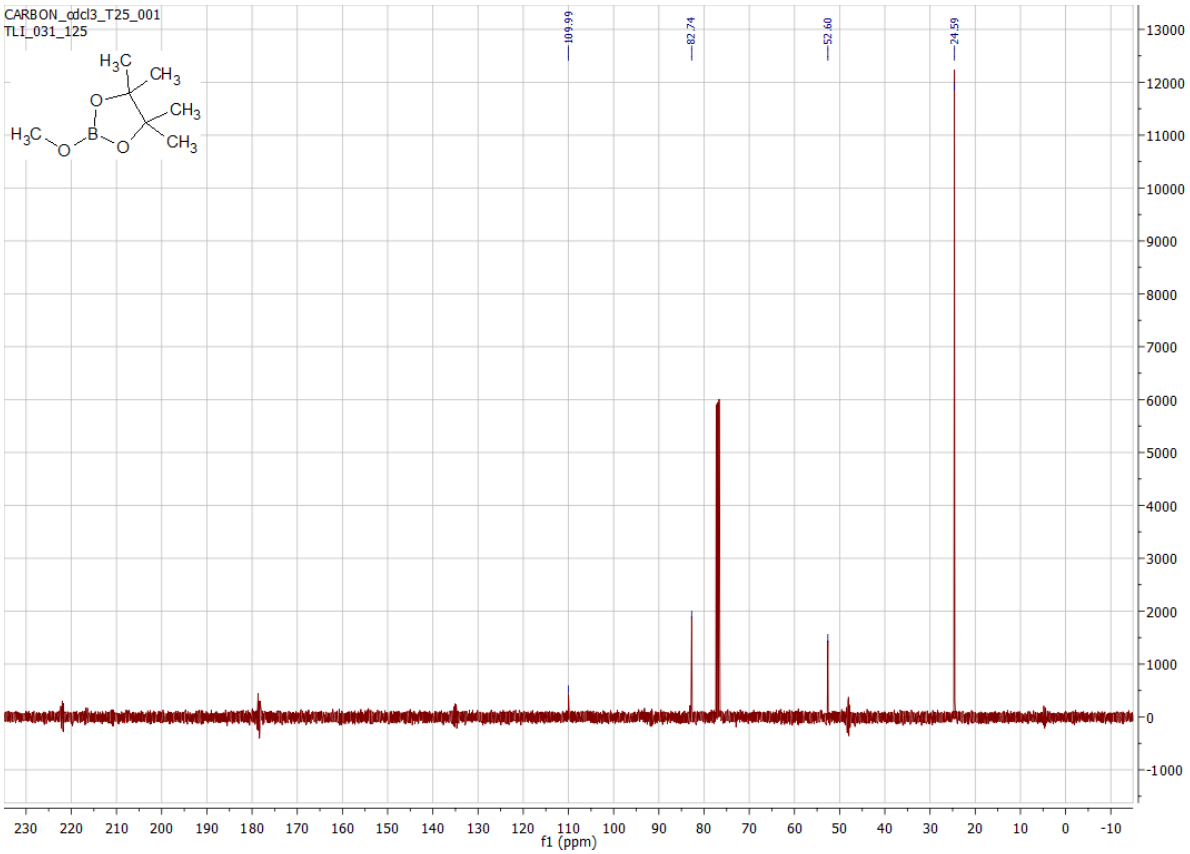


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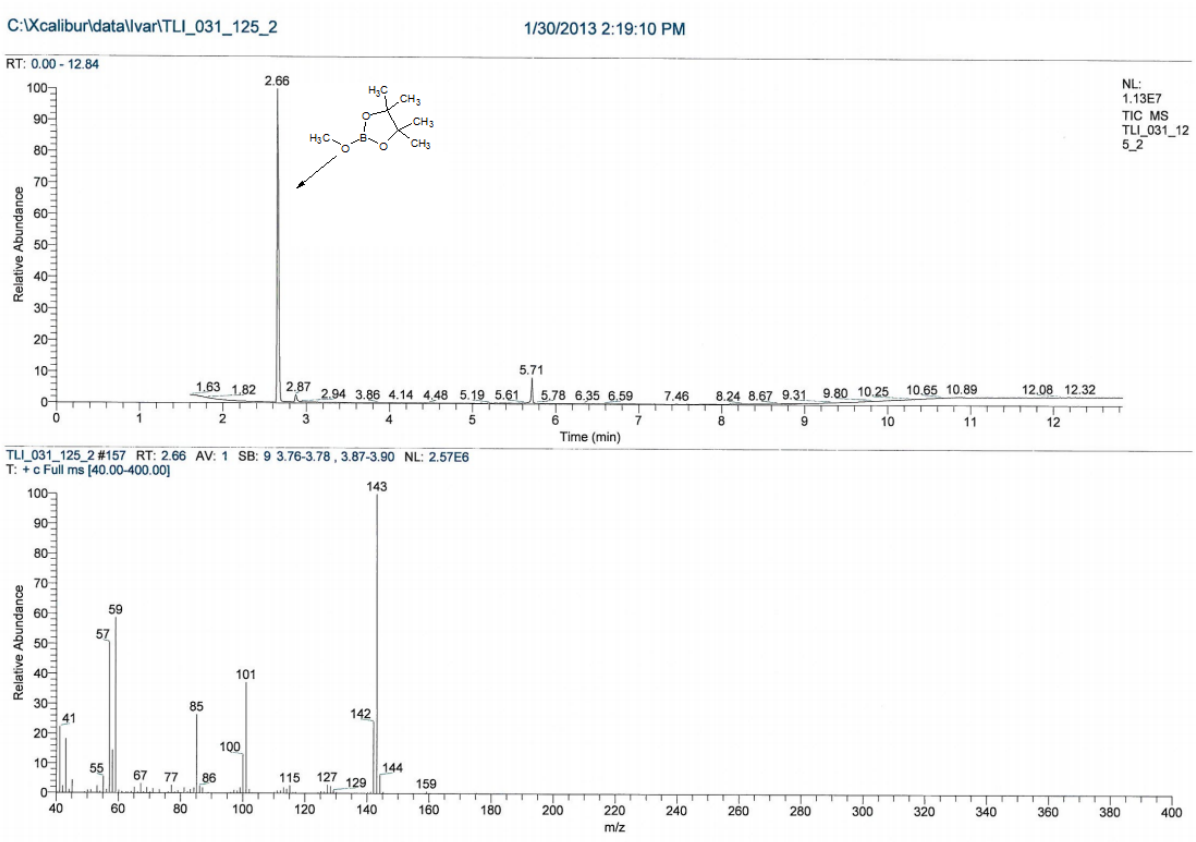

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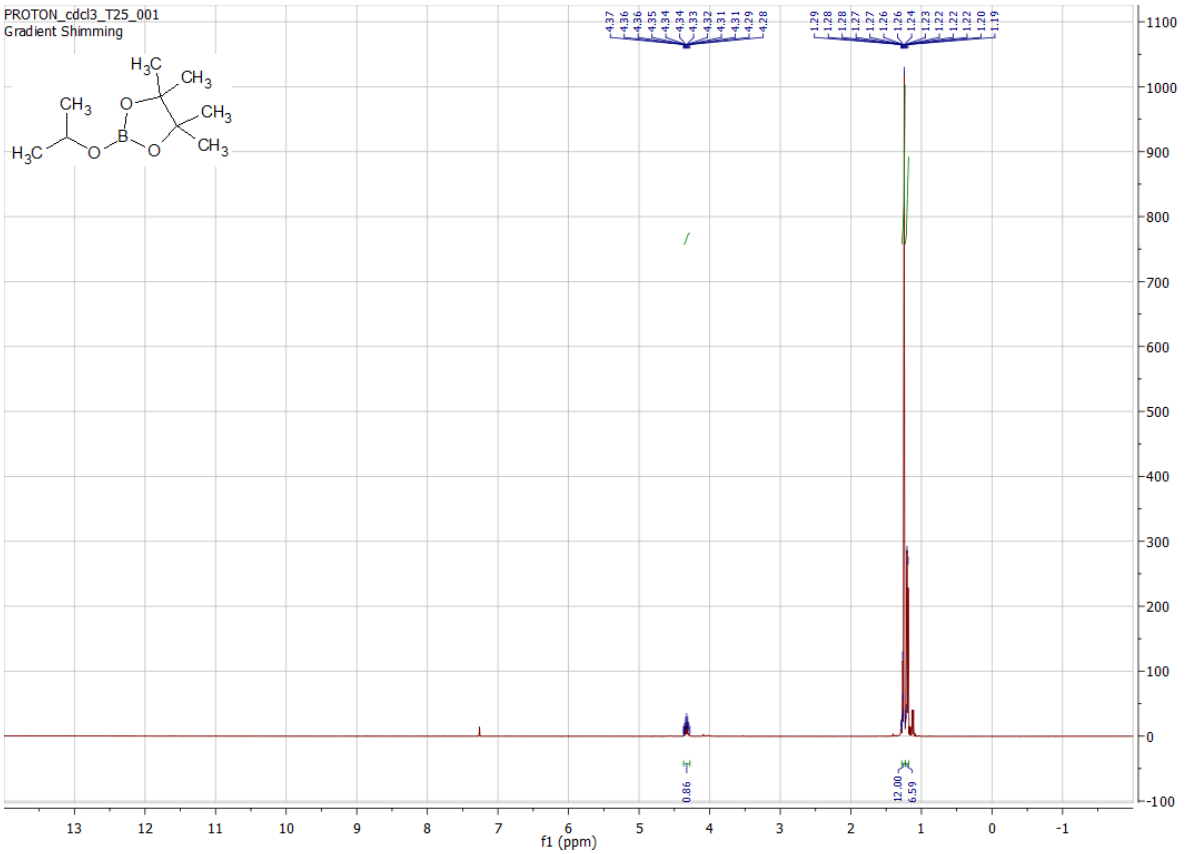


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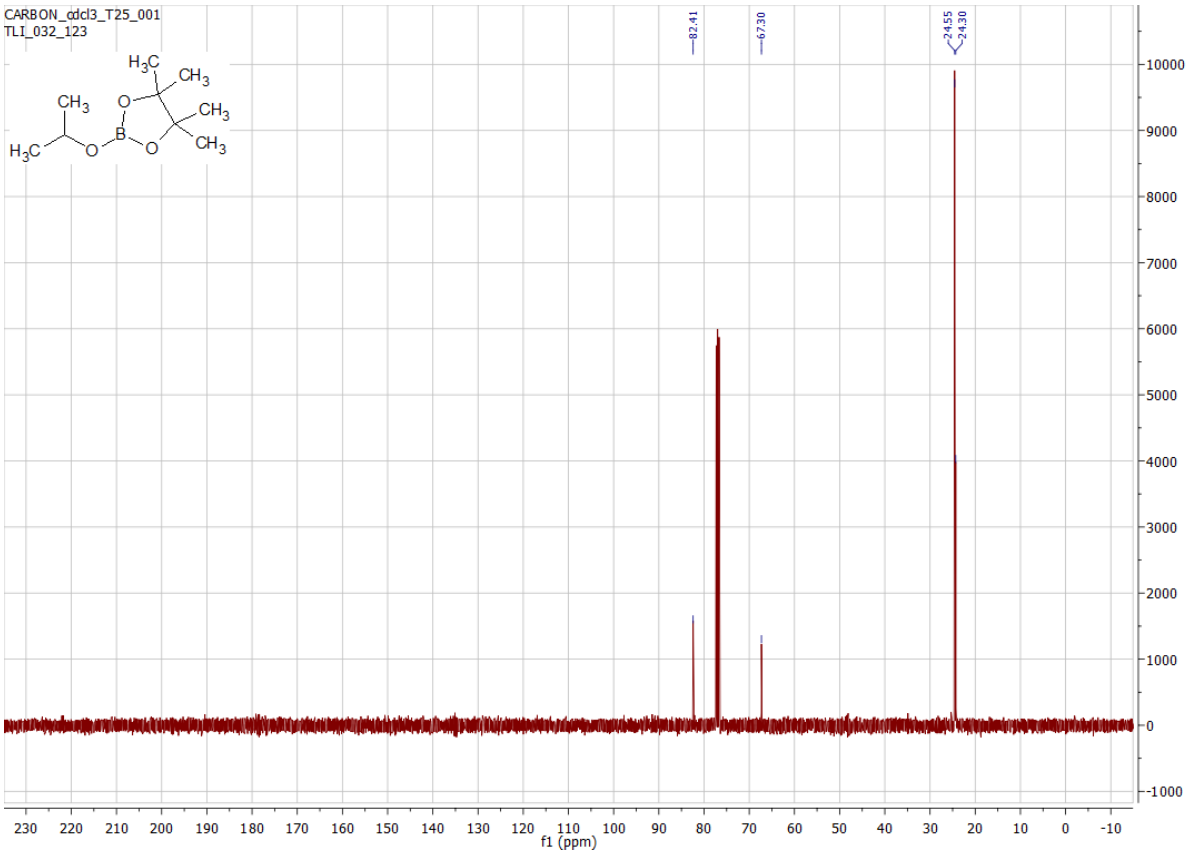

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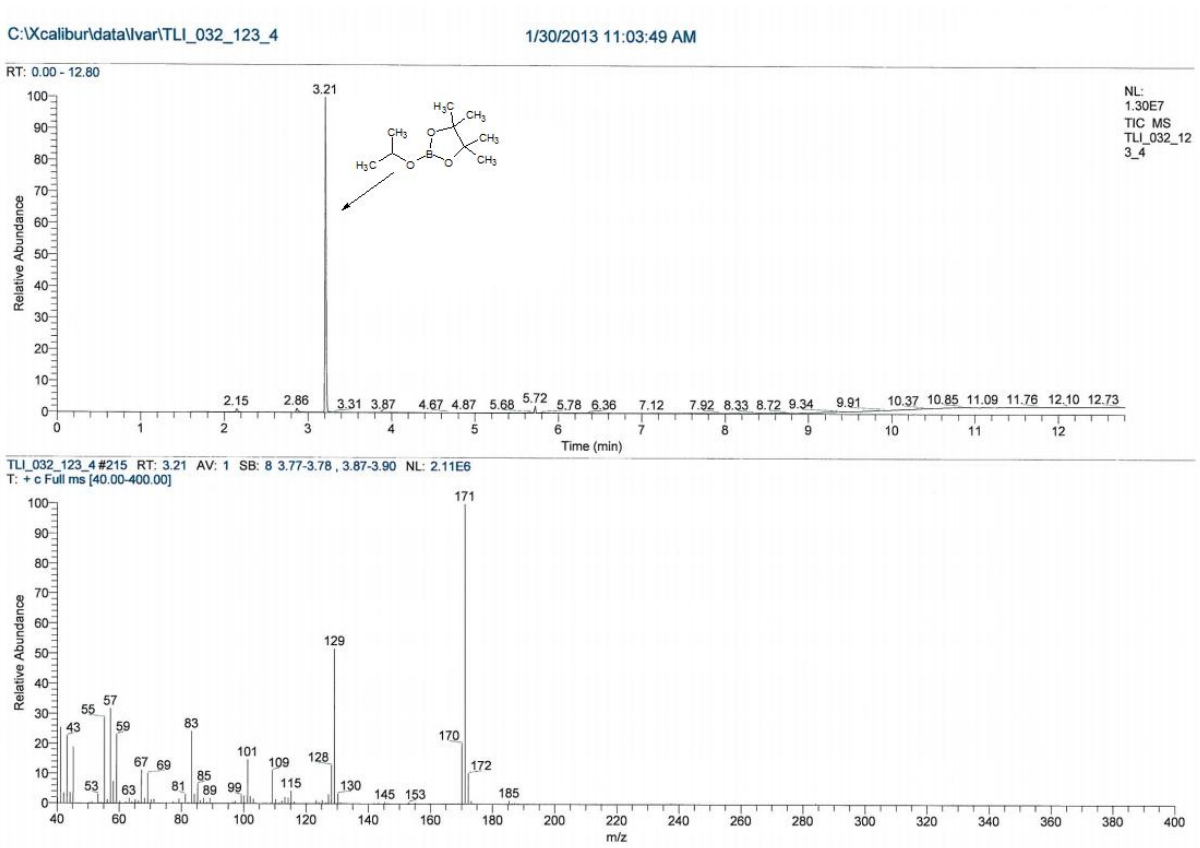


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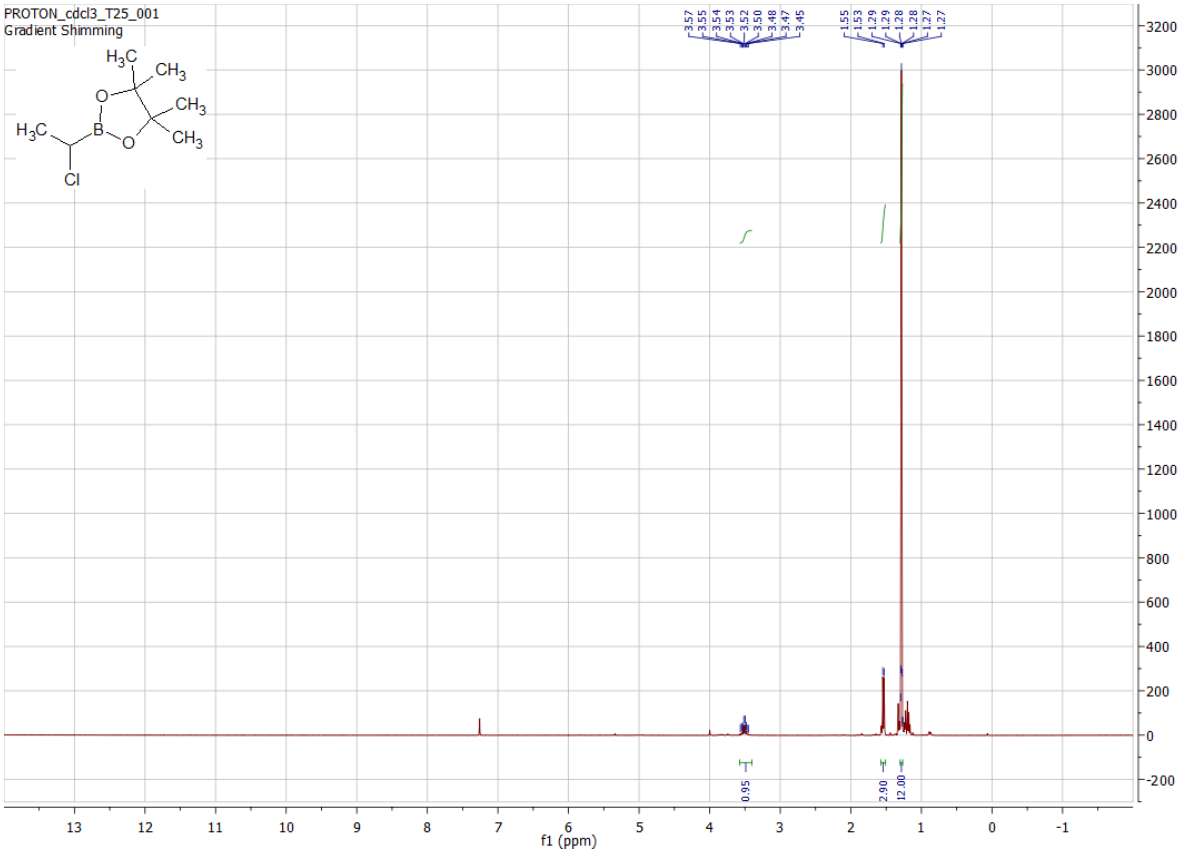

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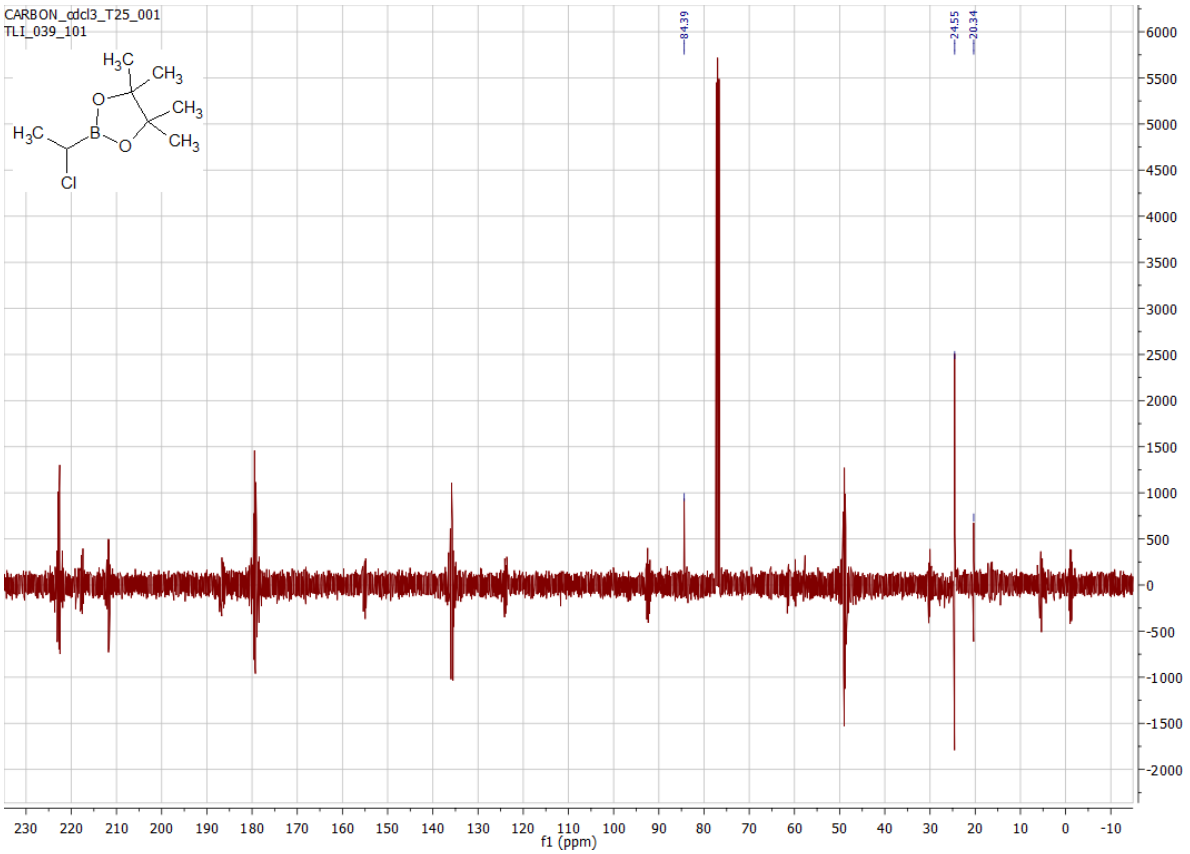


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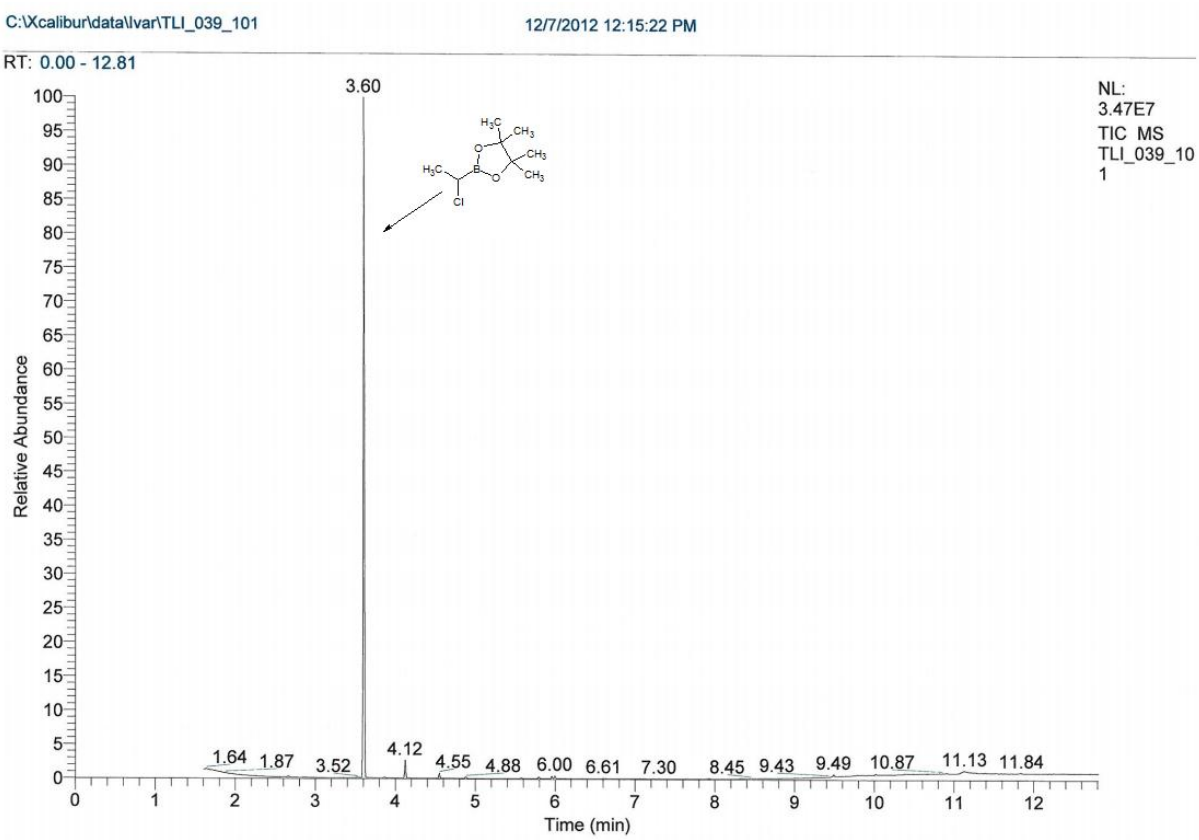

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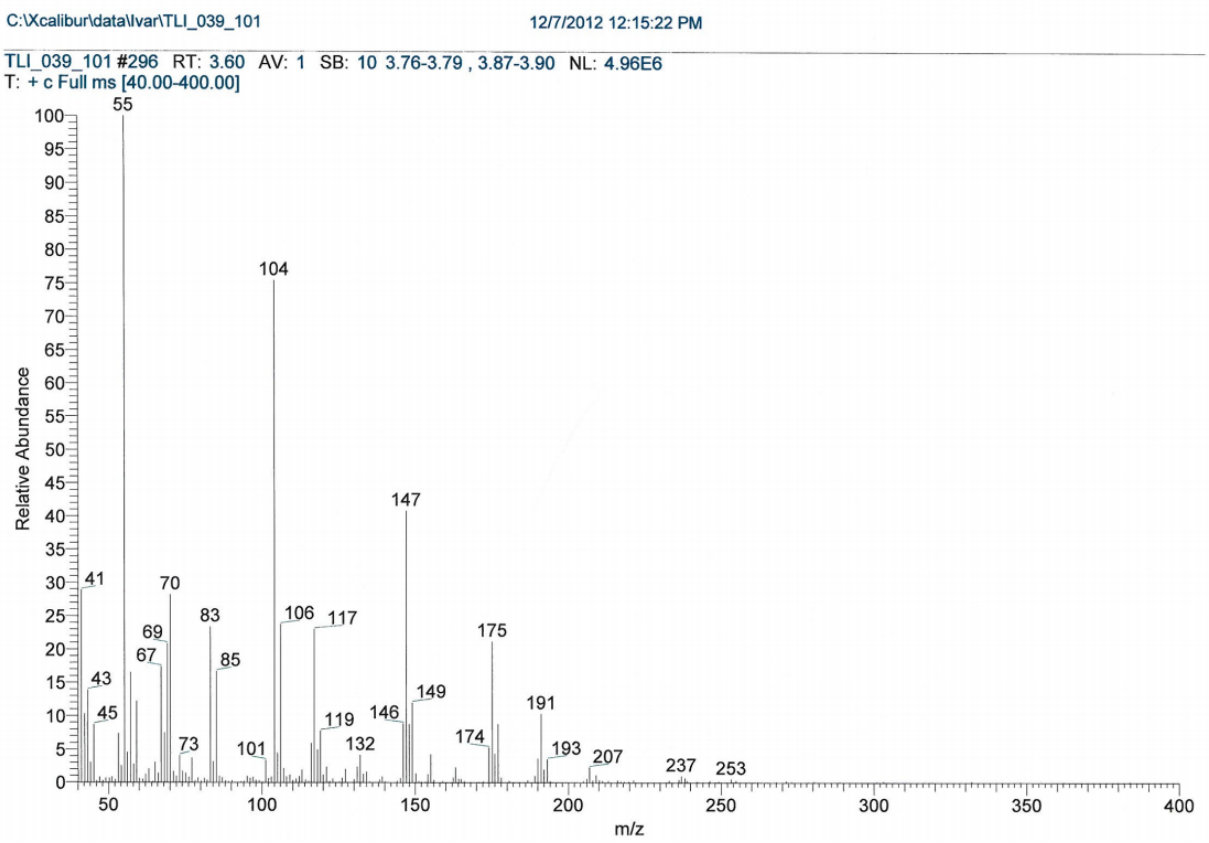


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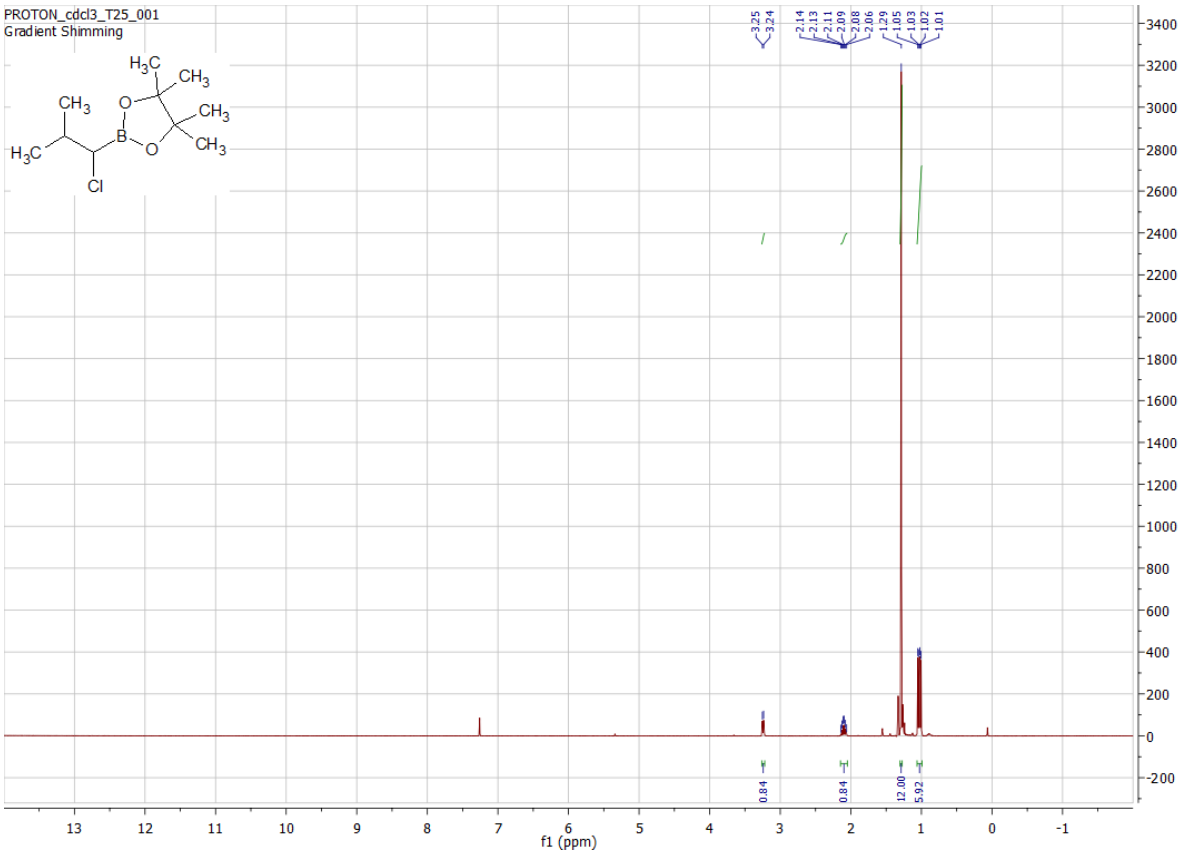

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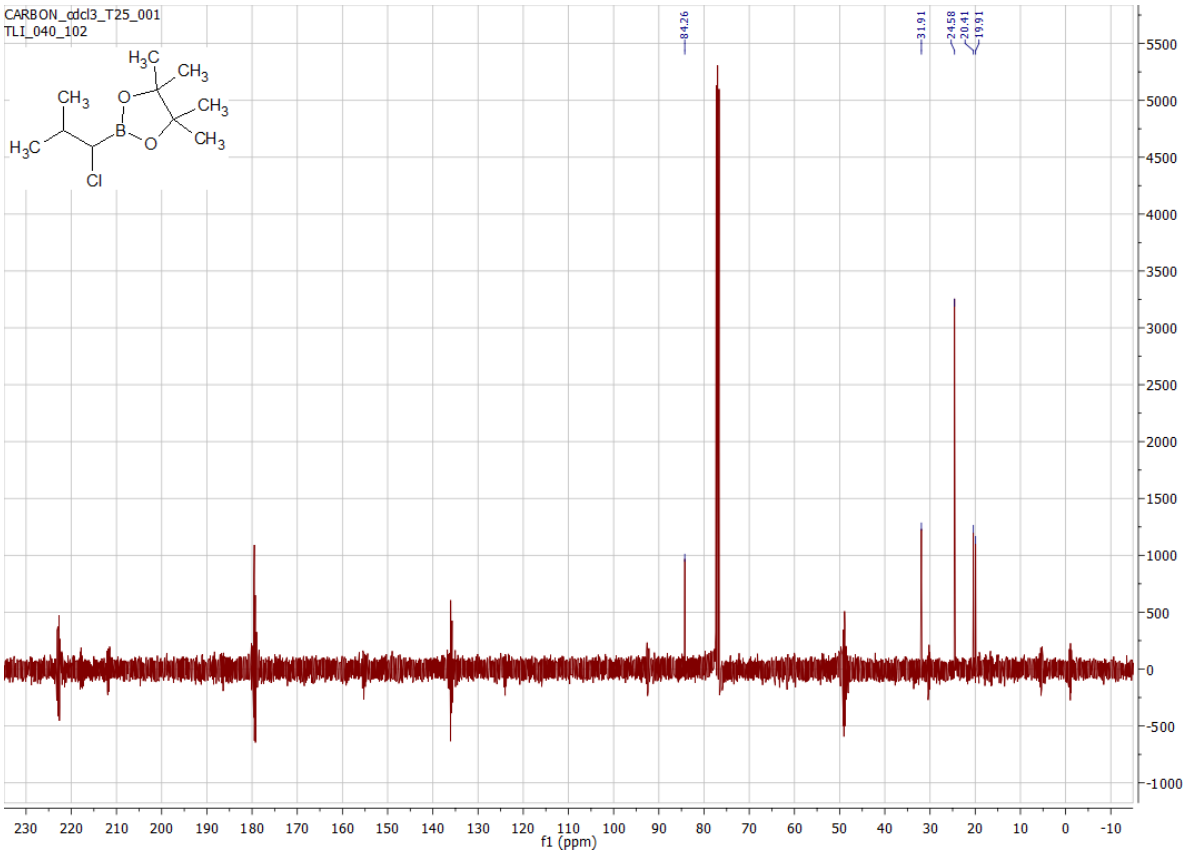


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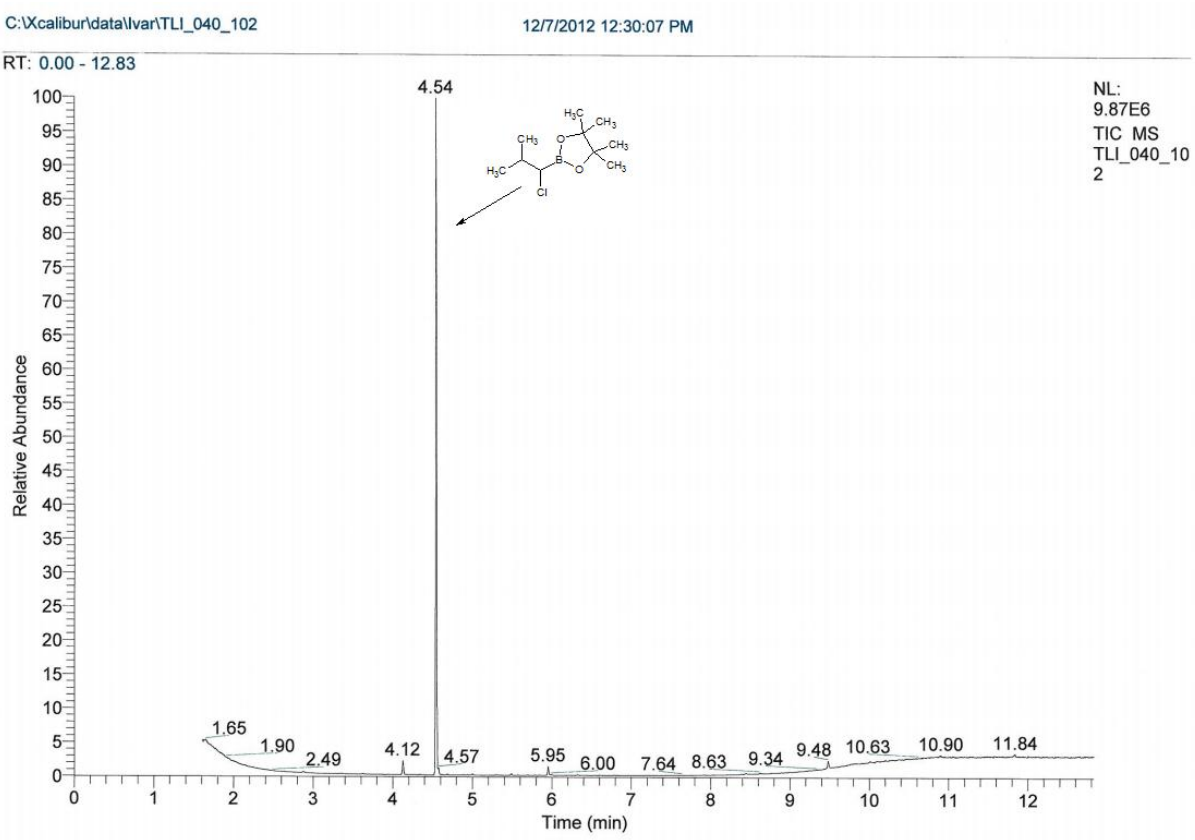

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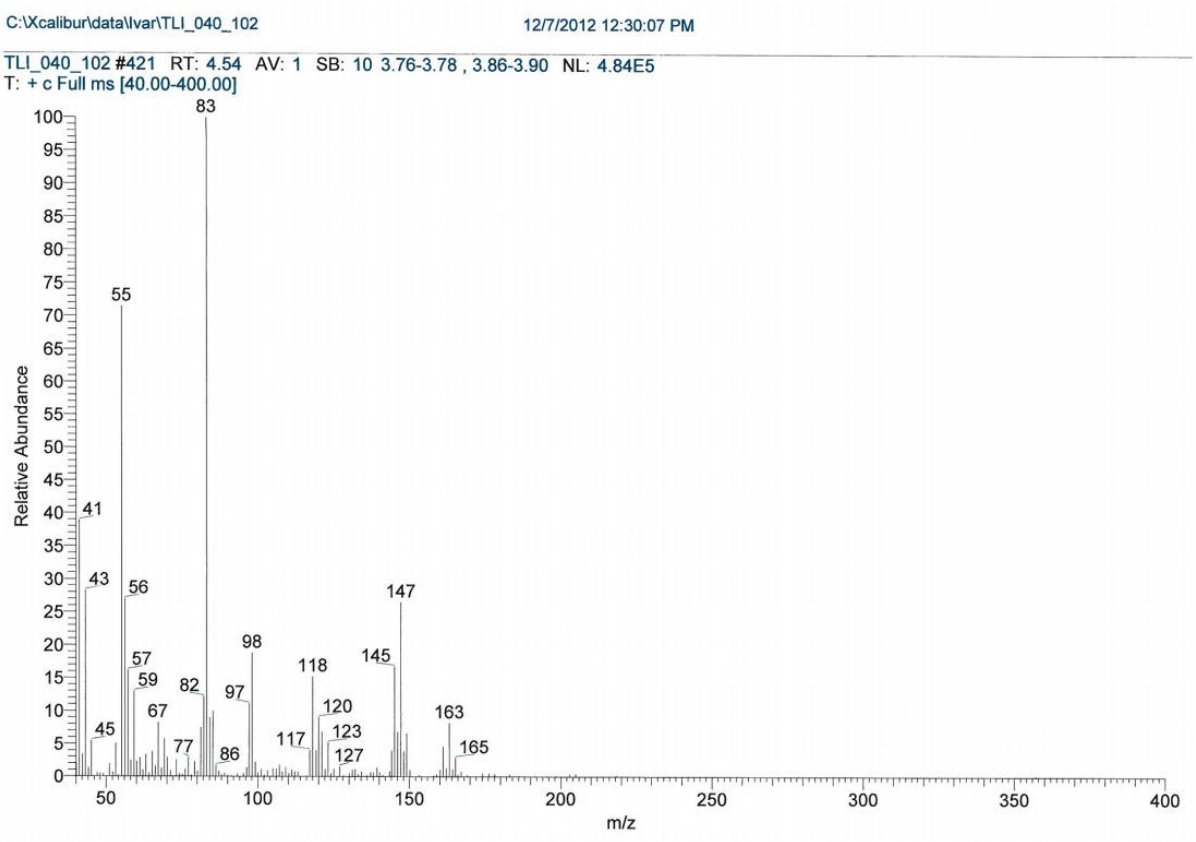


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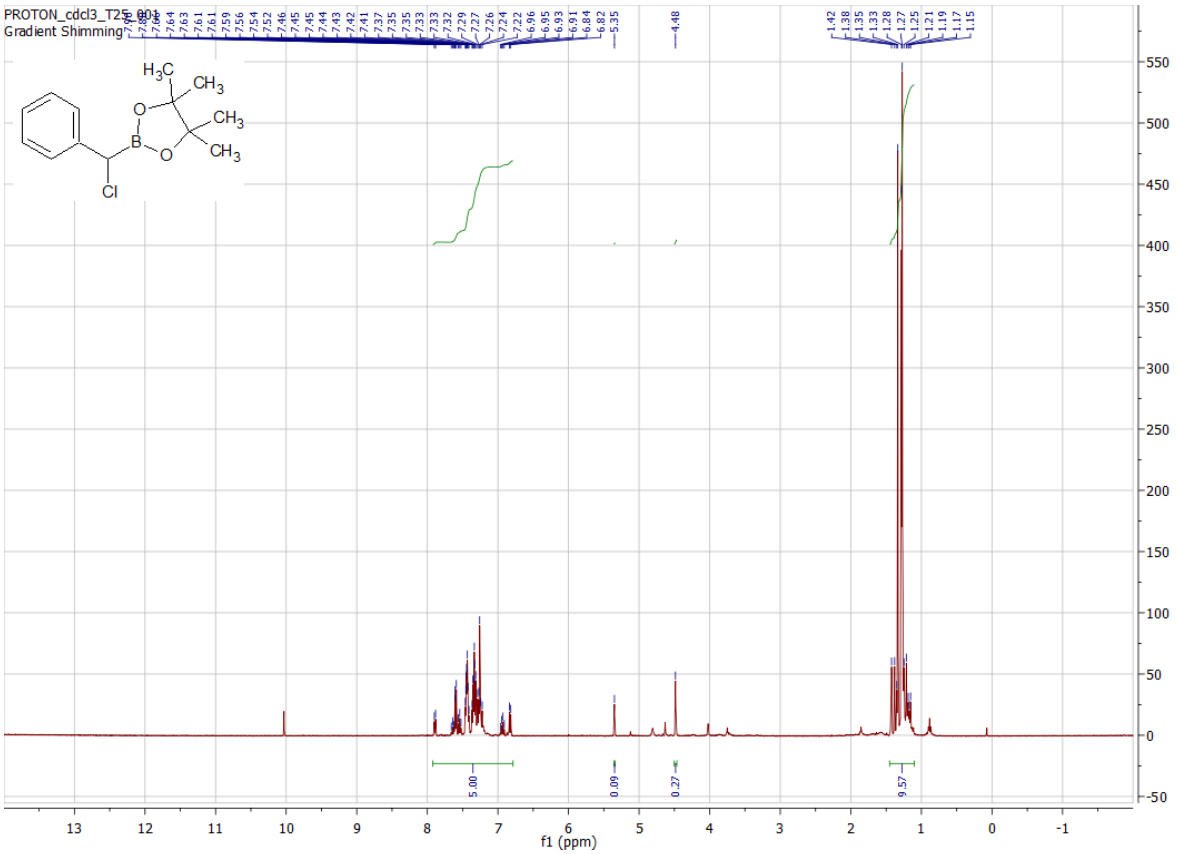

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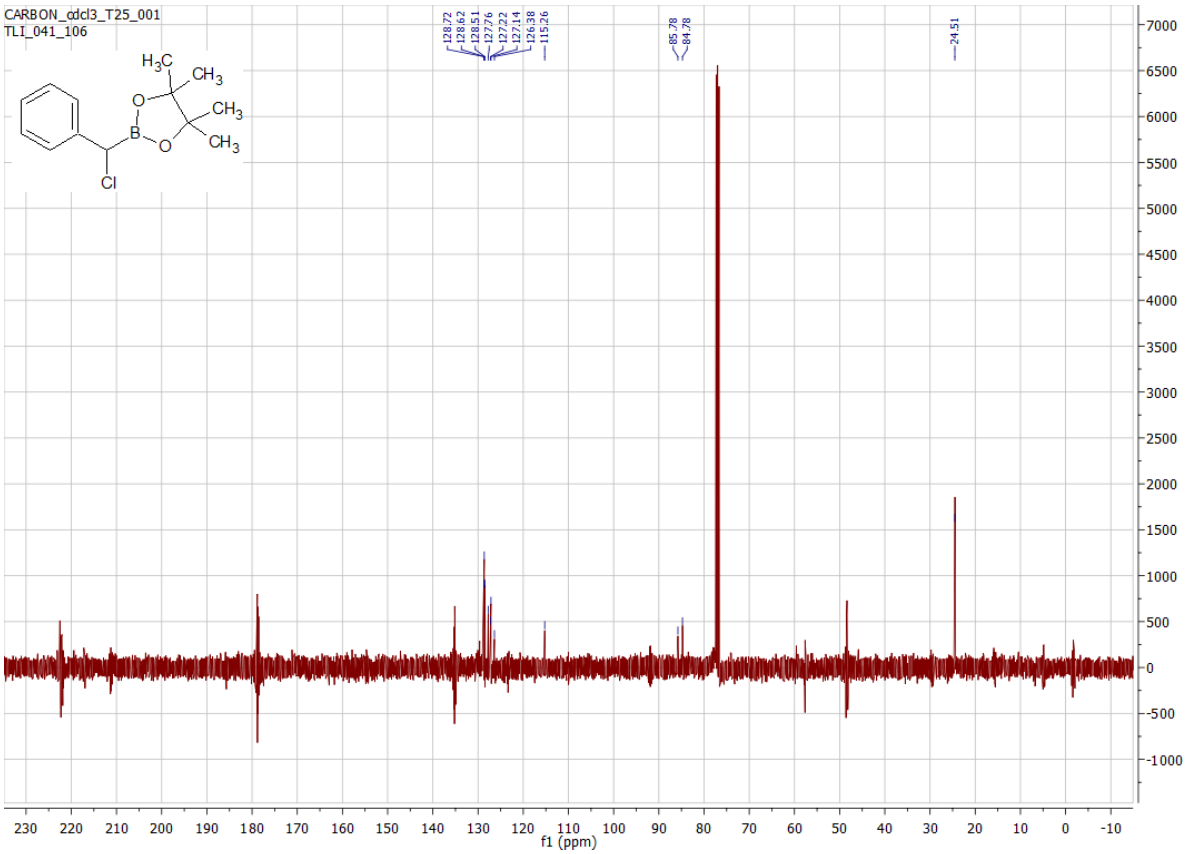


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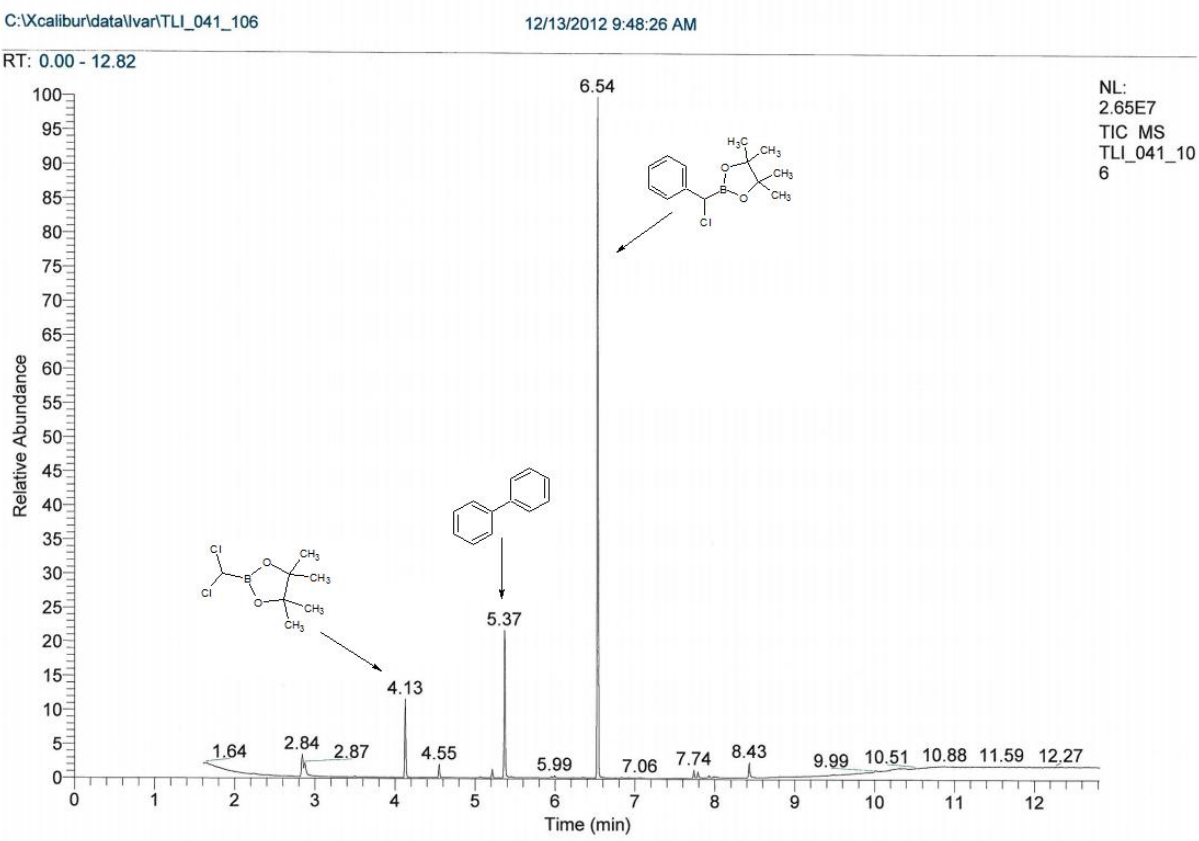

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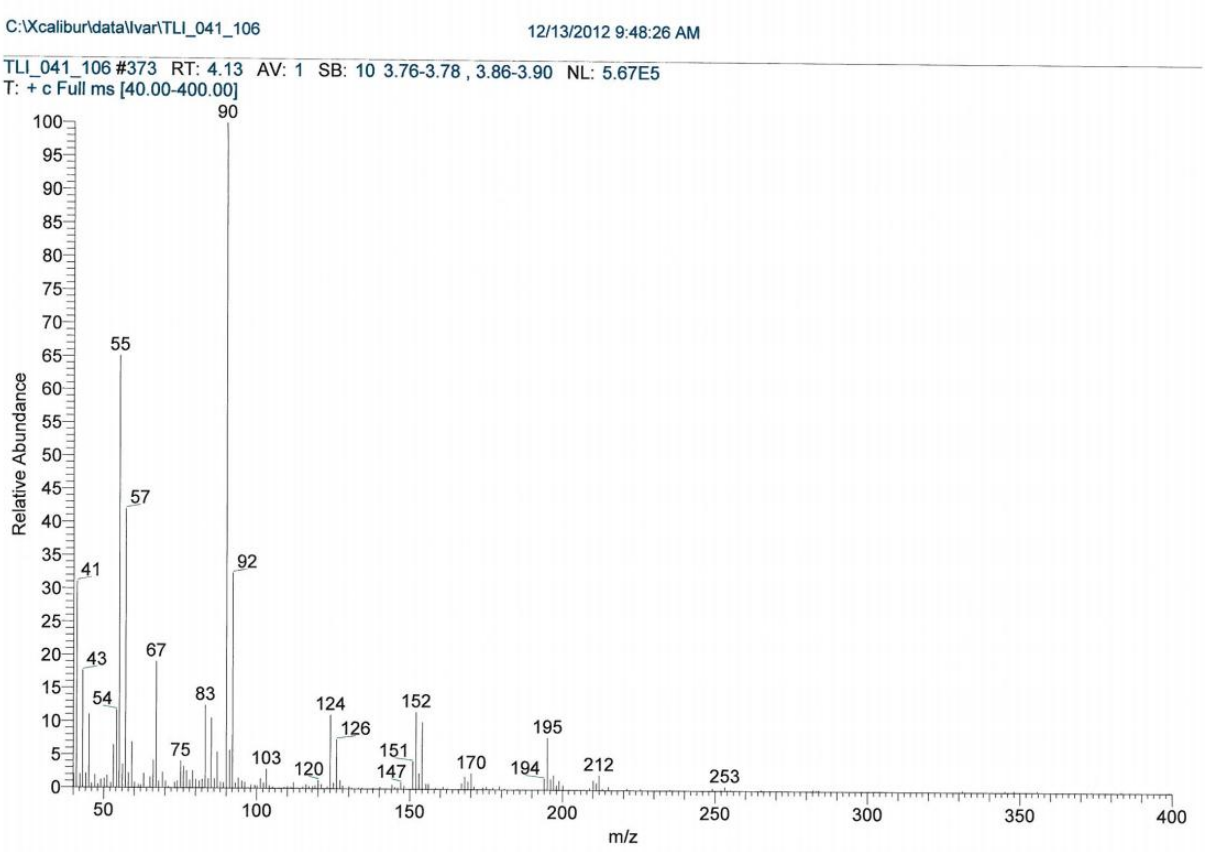


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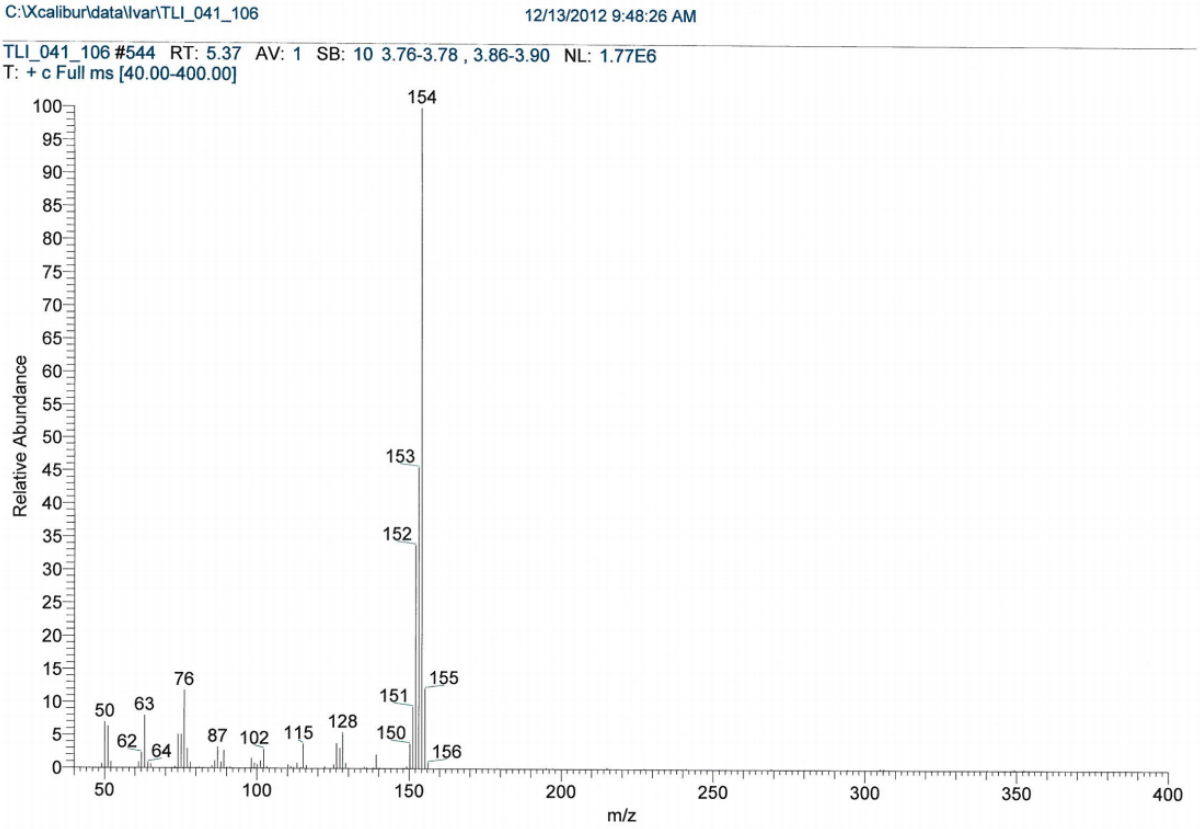

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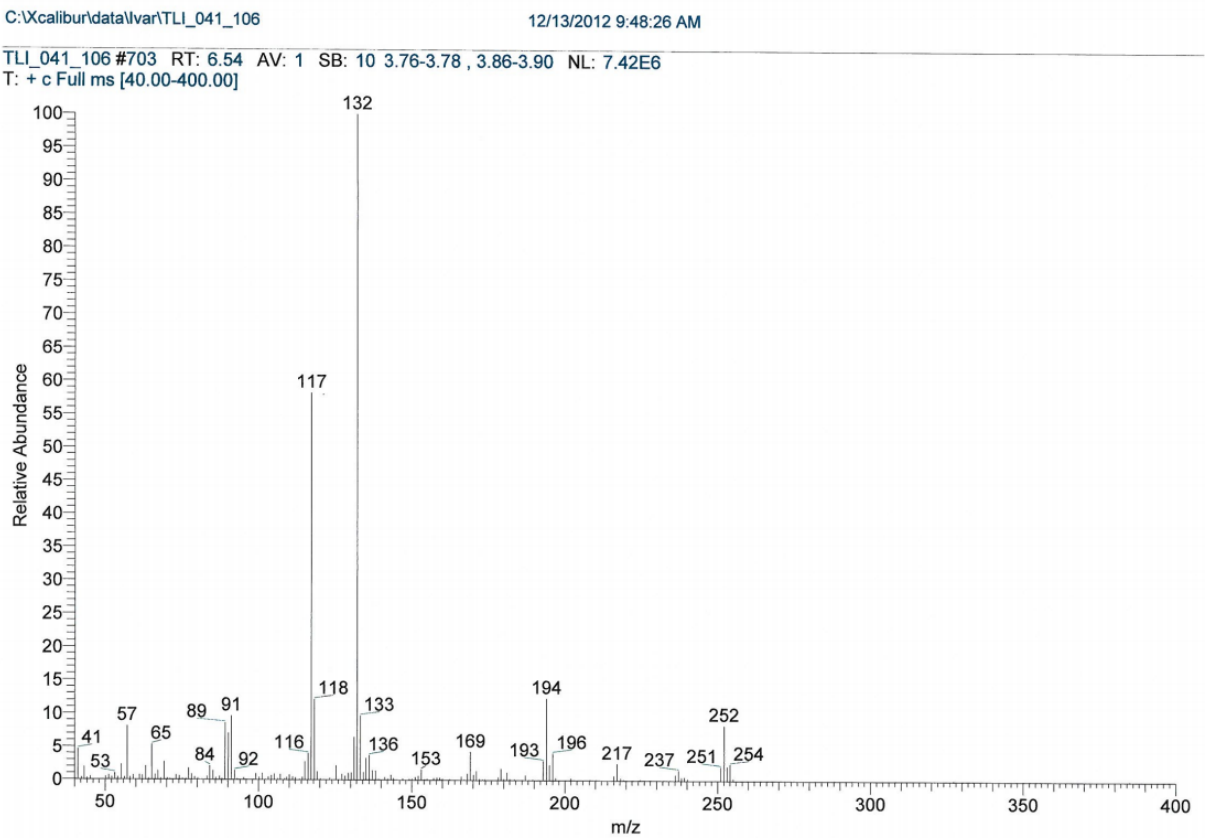


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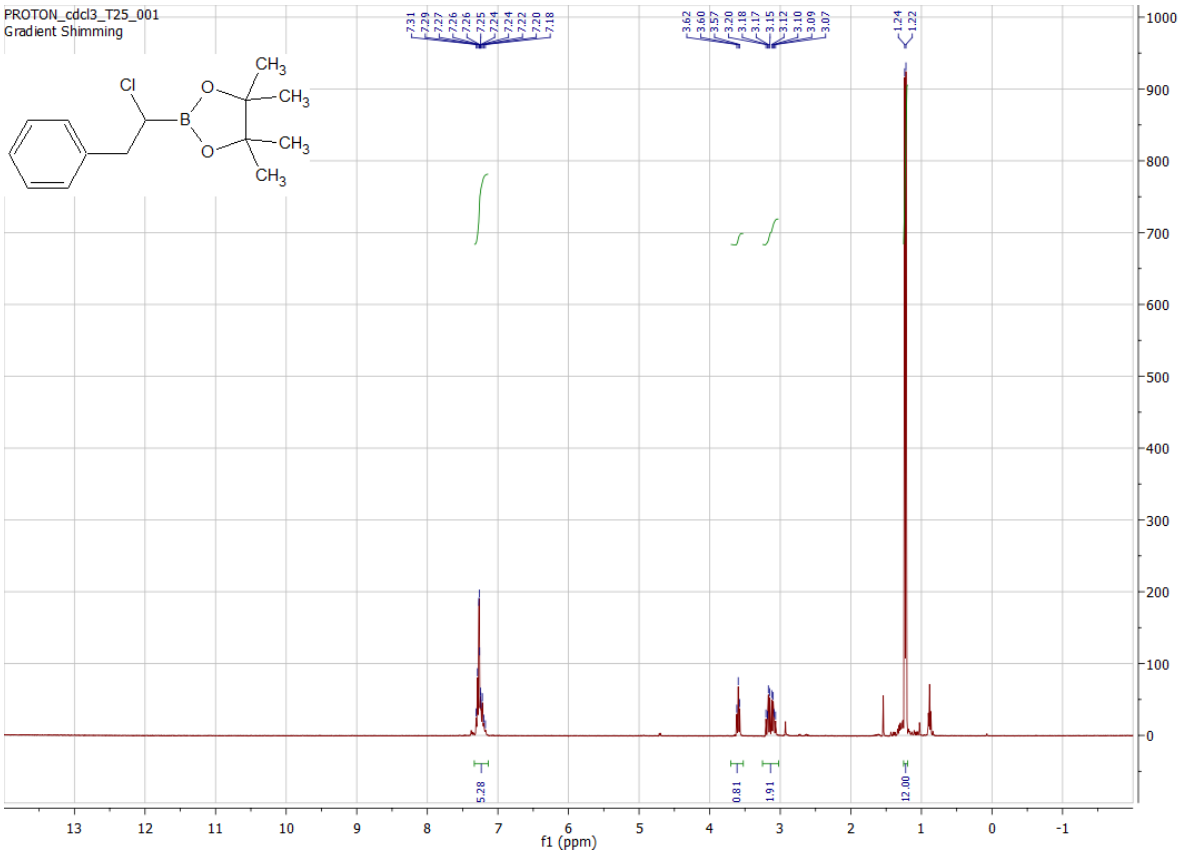

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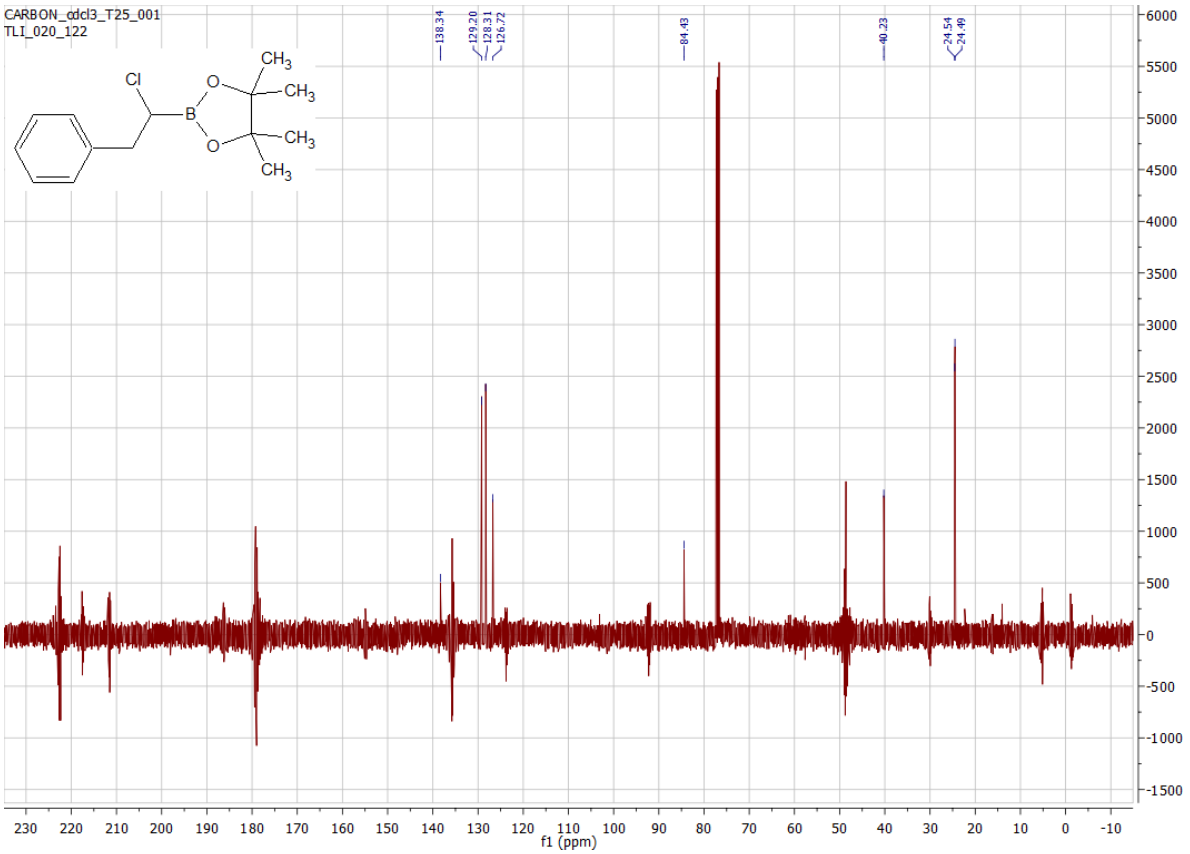


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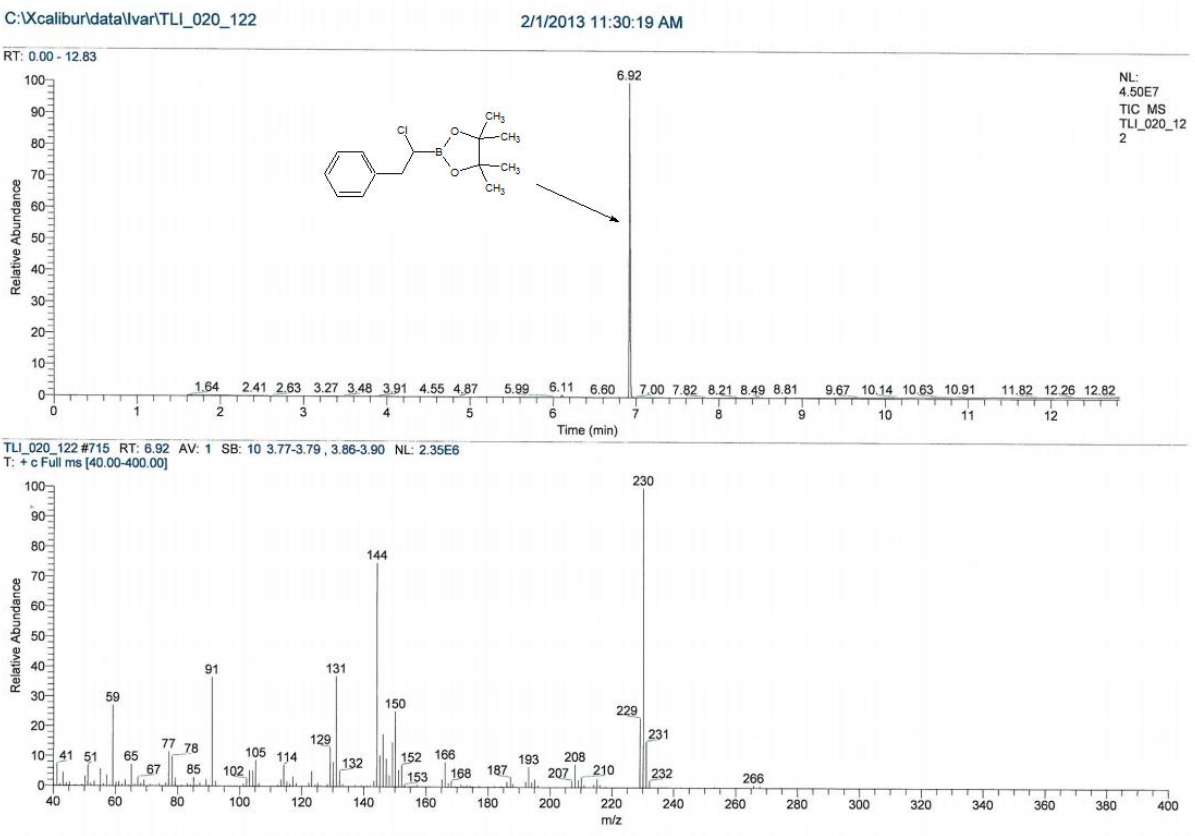

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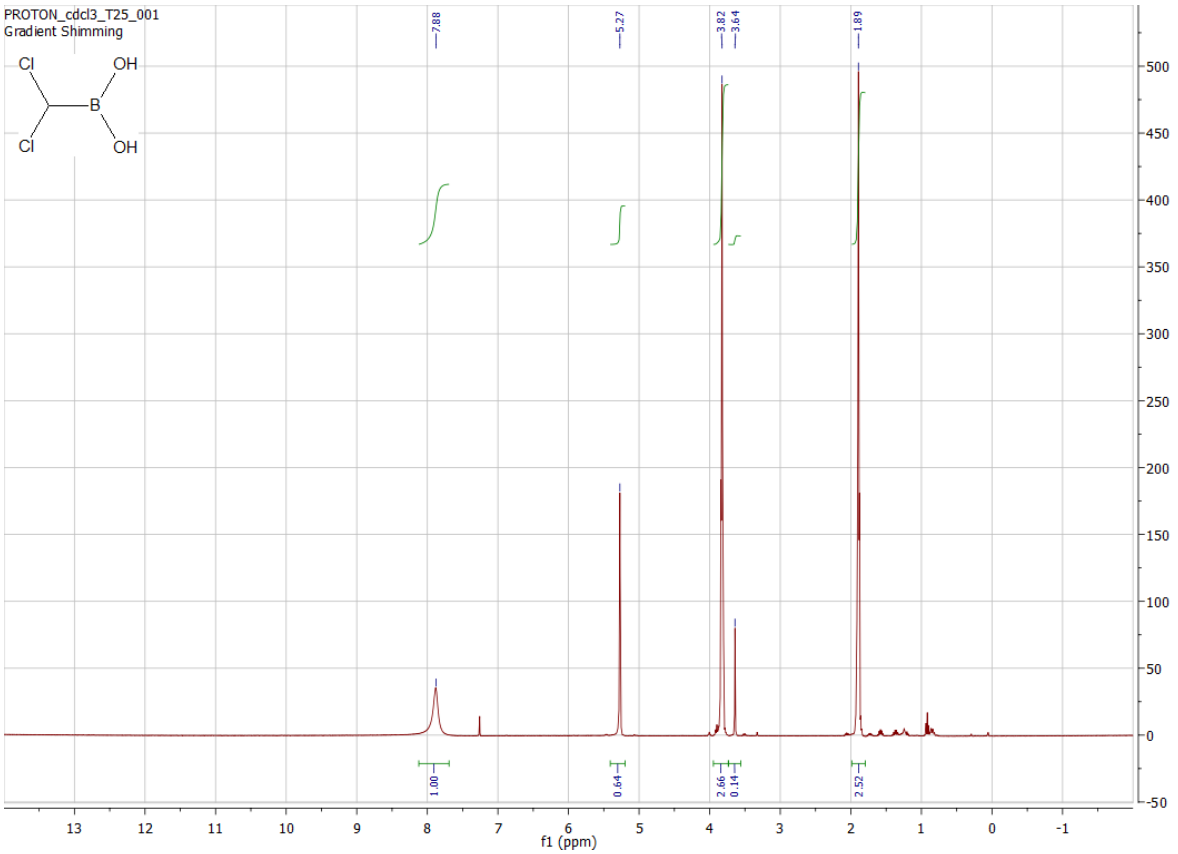


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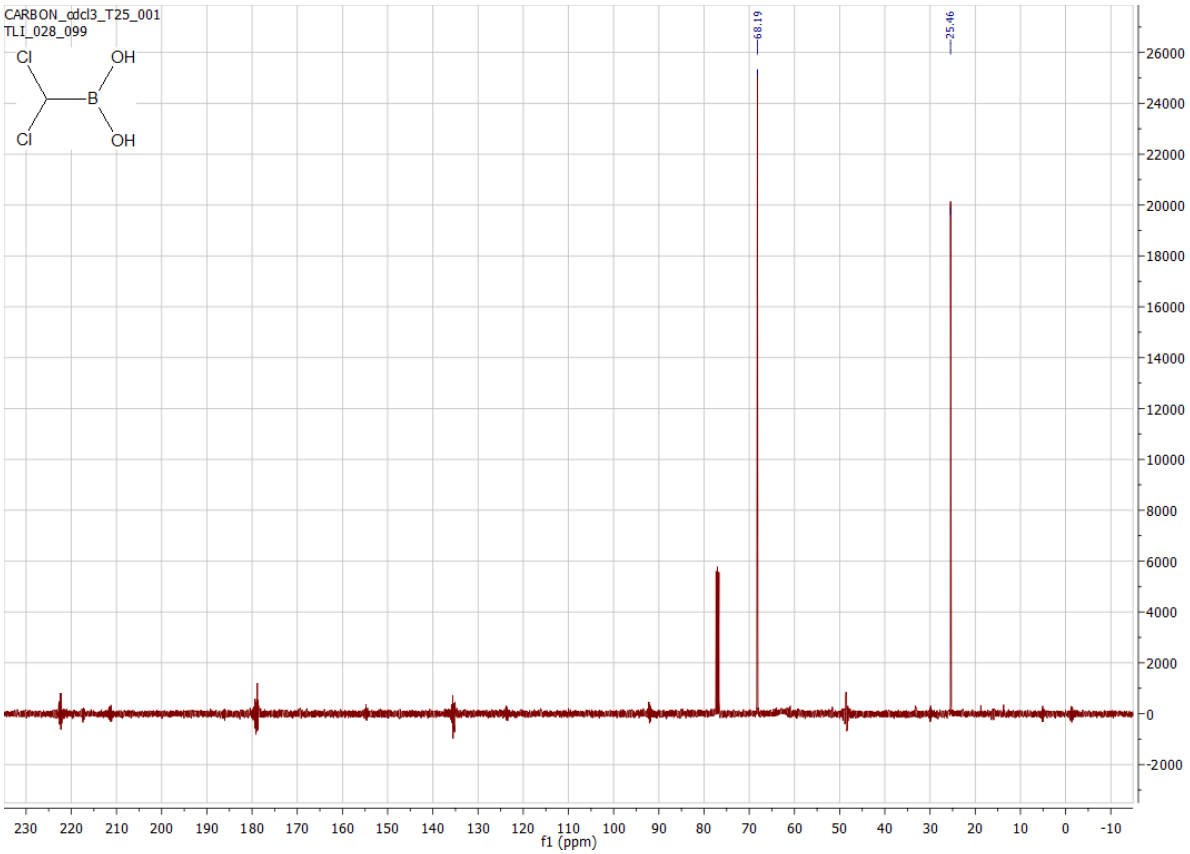

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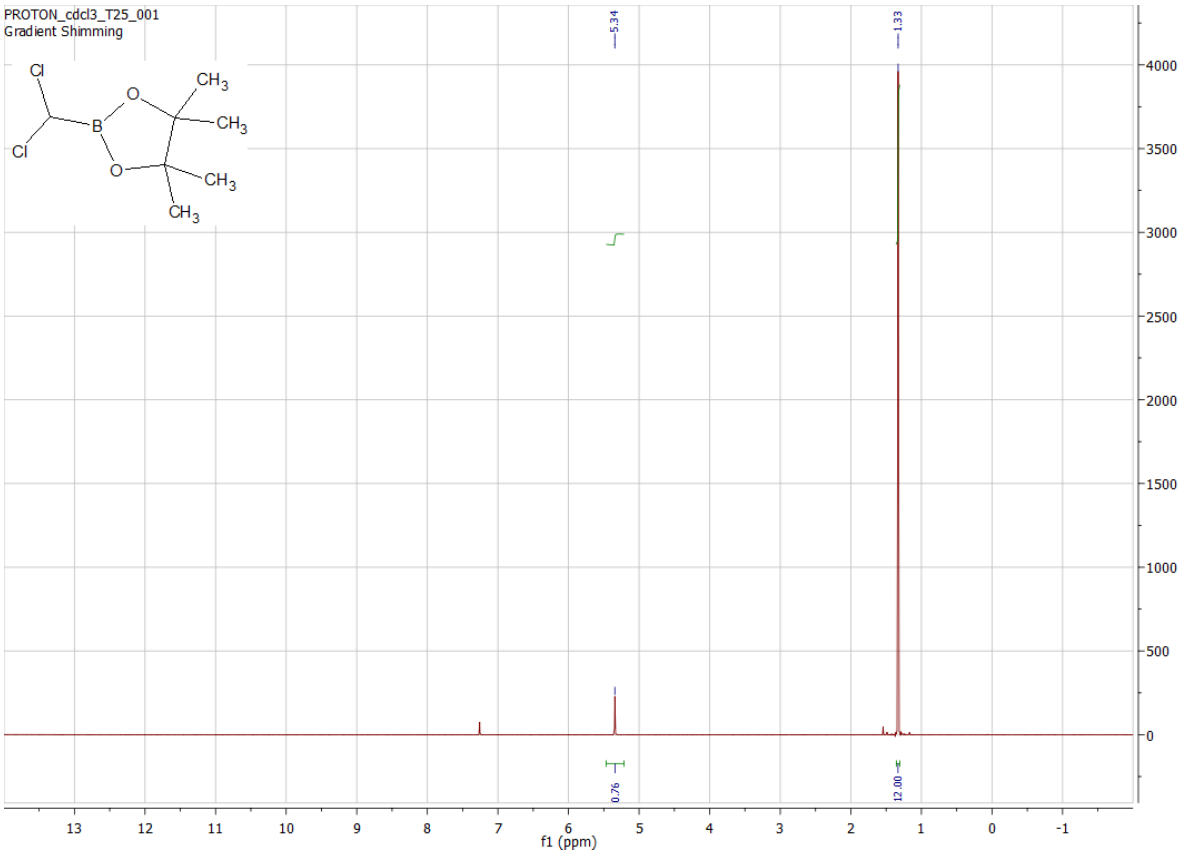


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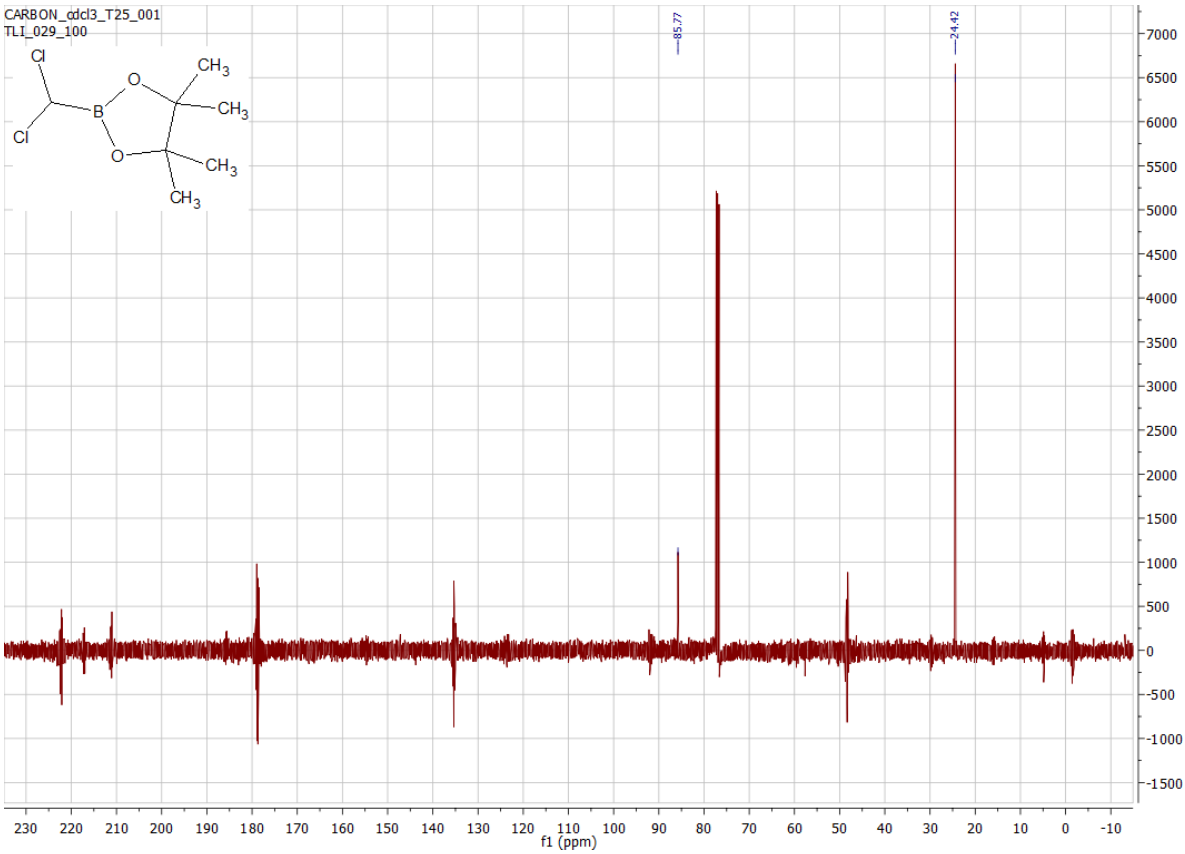

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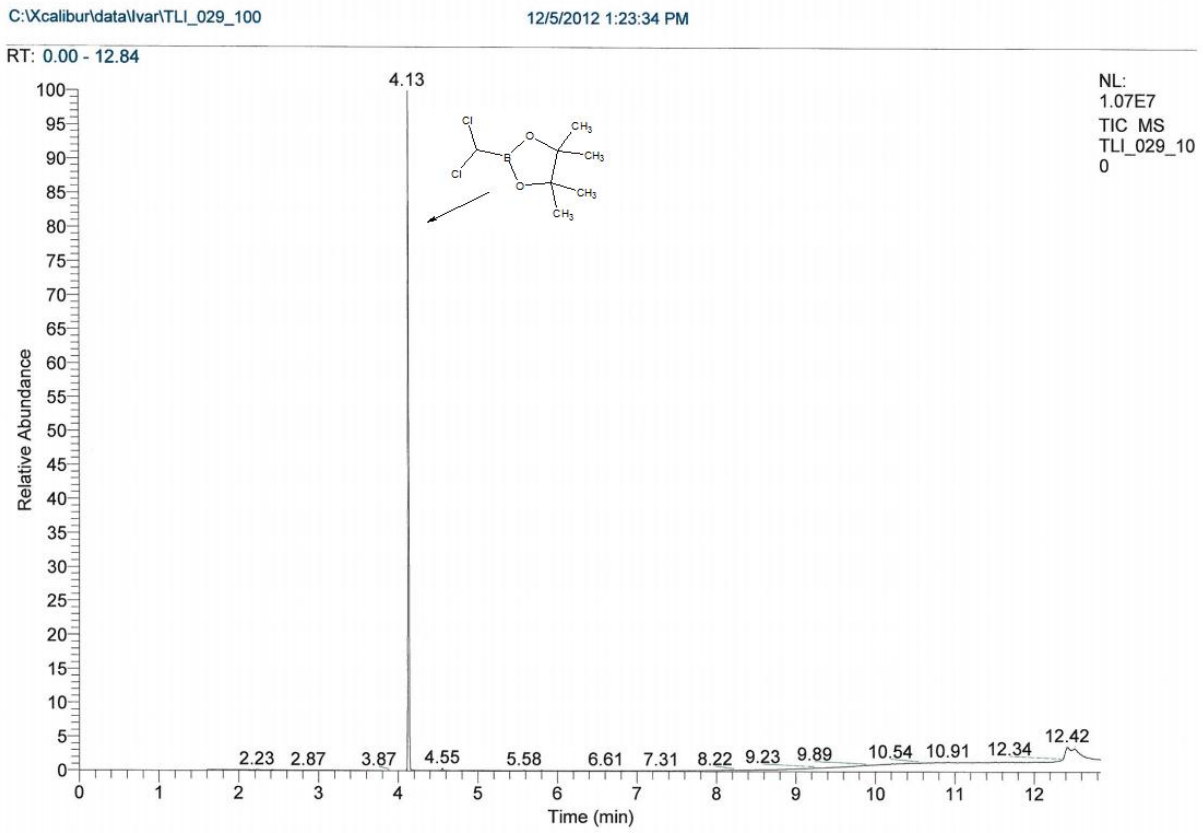


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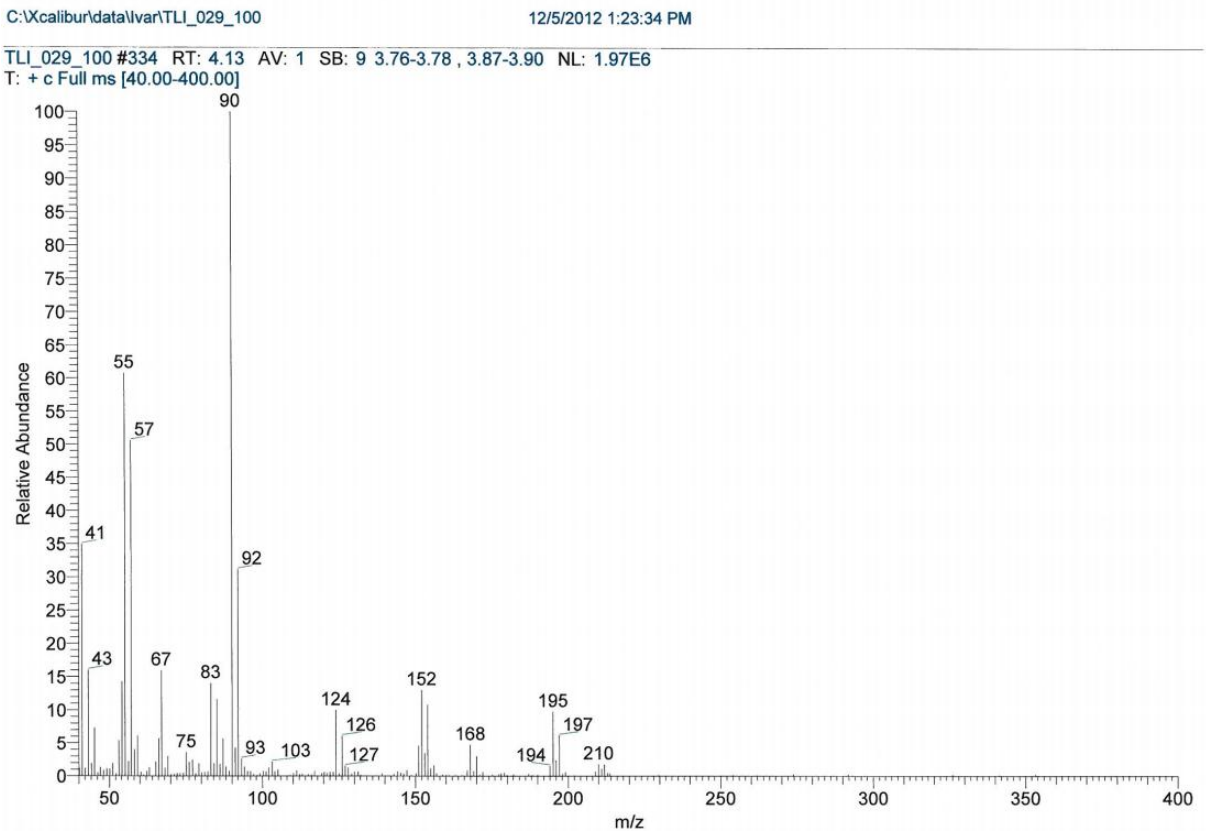

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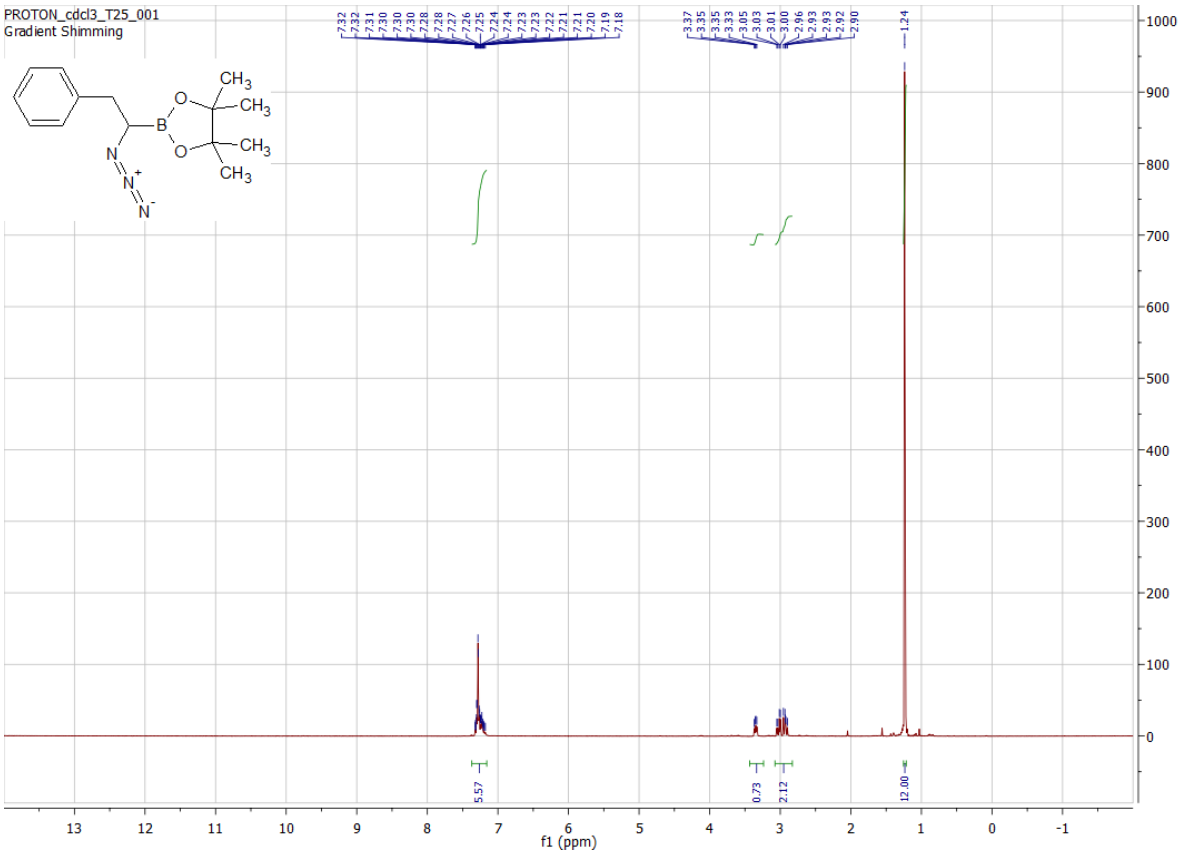


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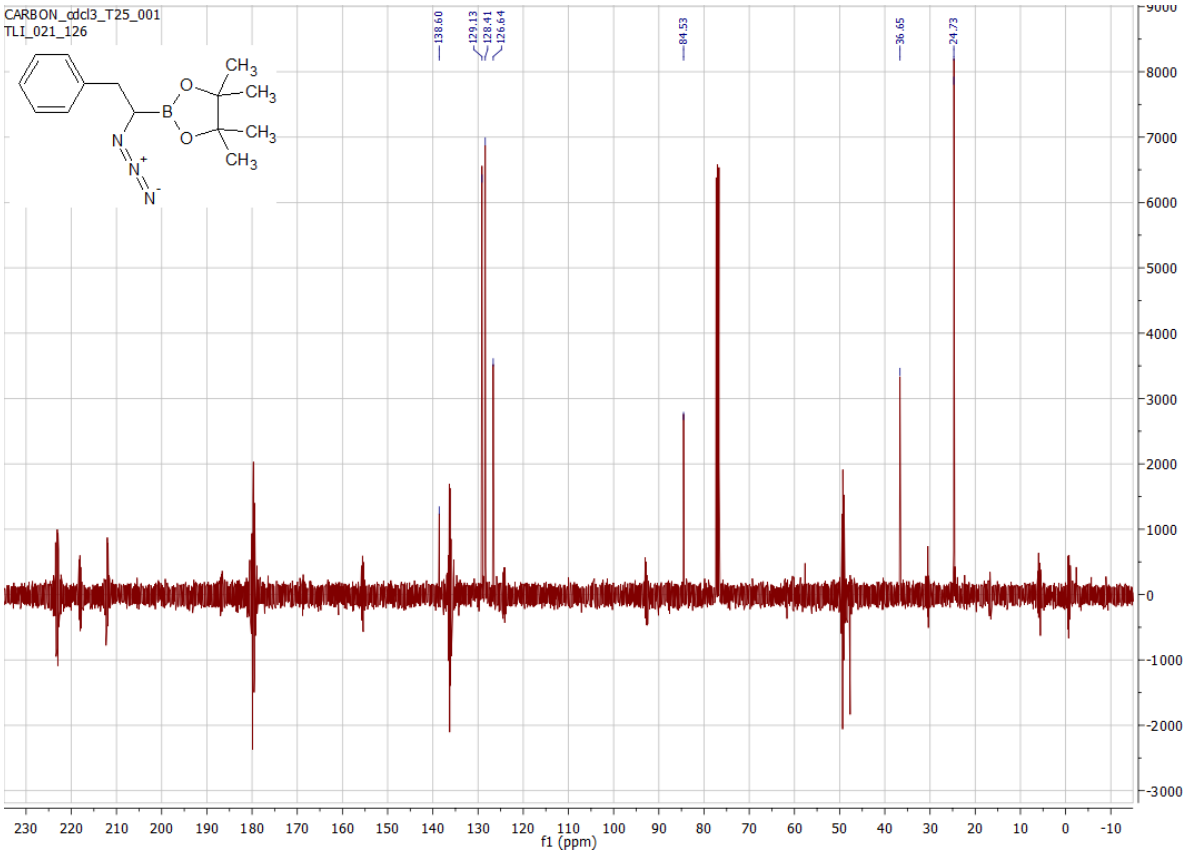
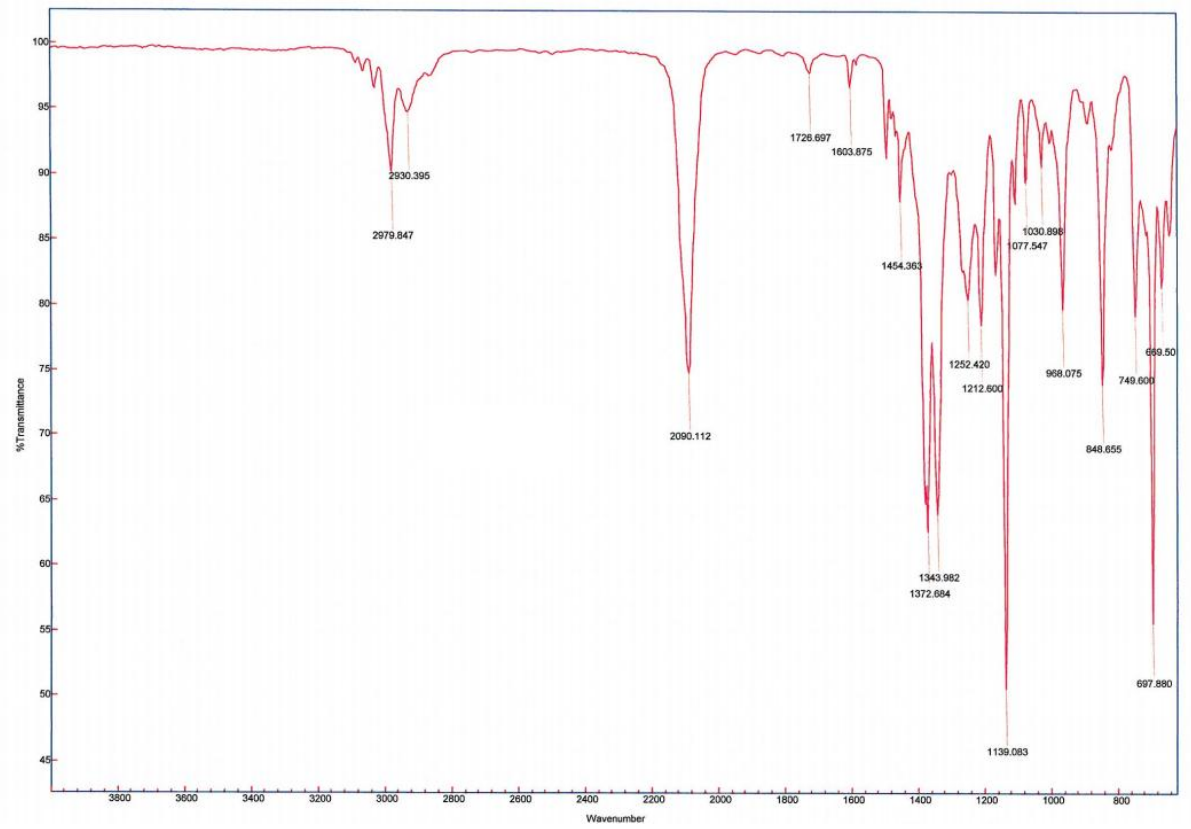


## Appendix 55

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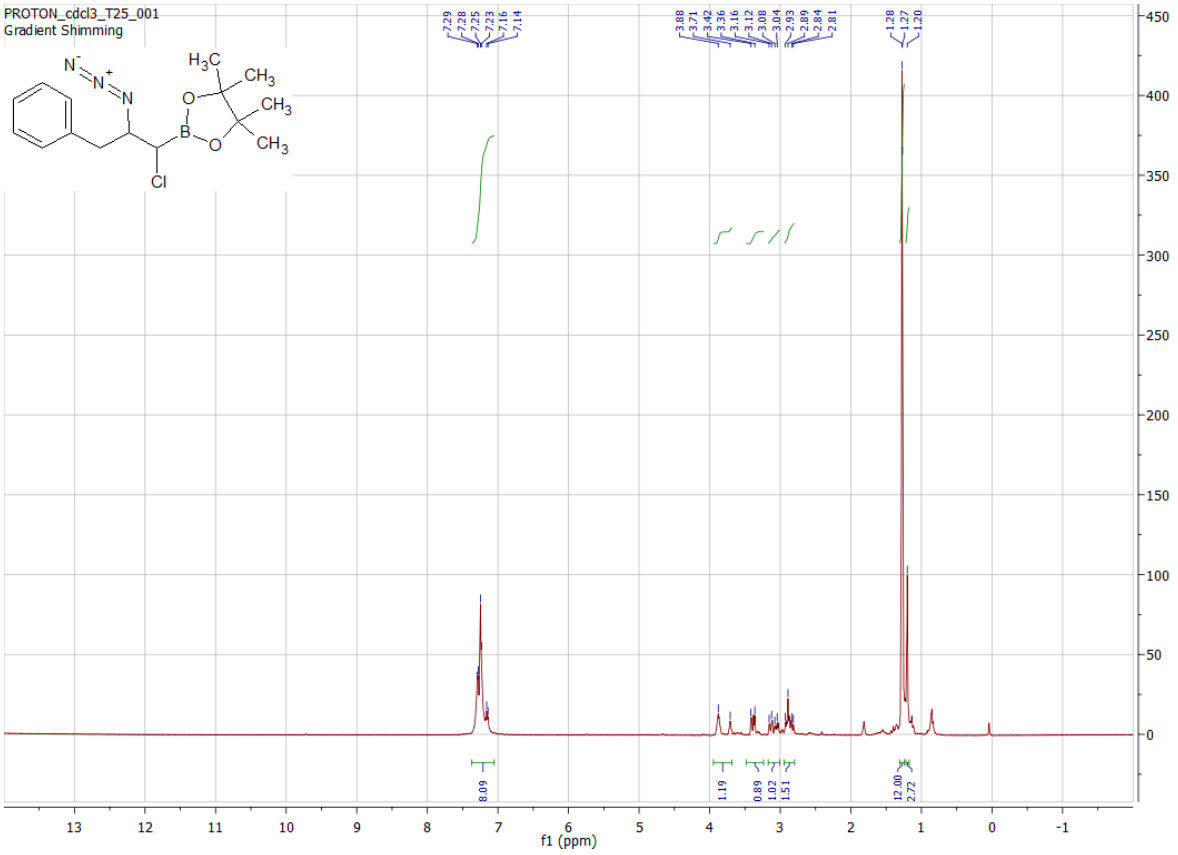
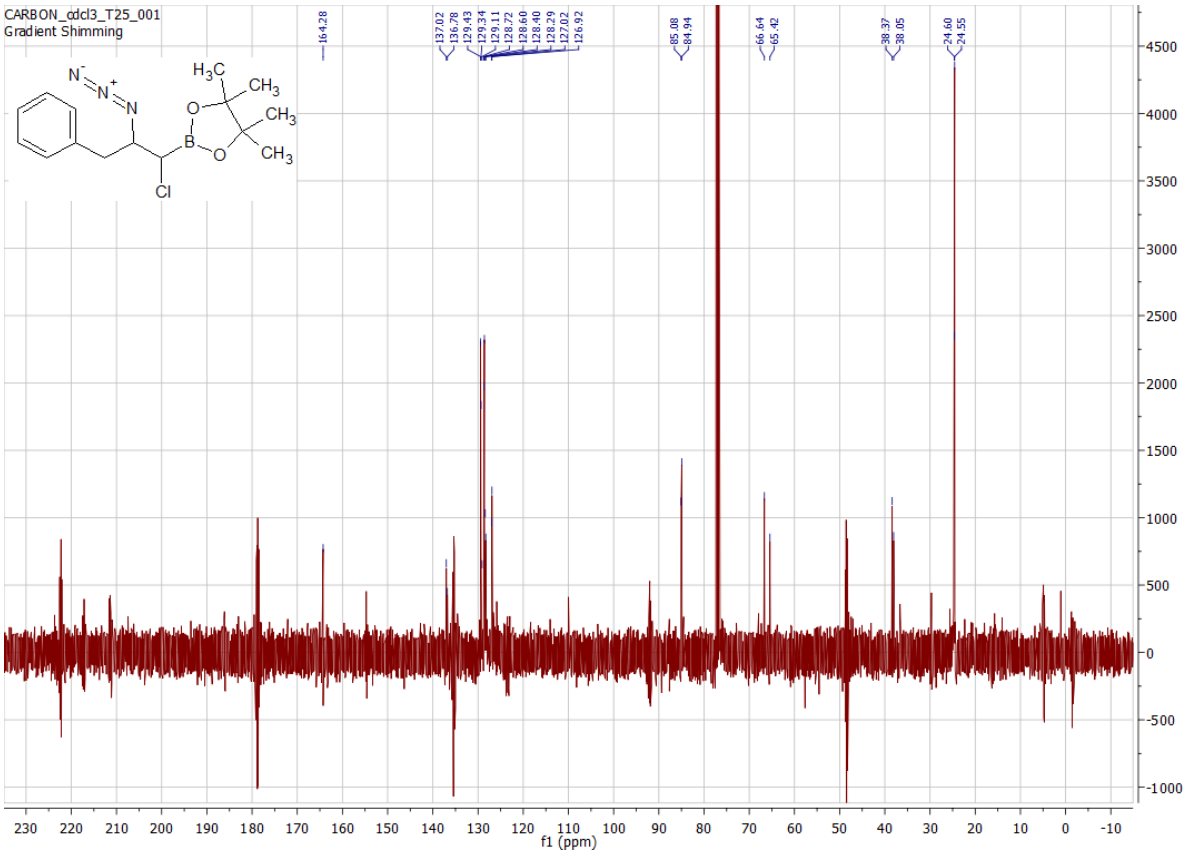
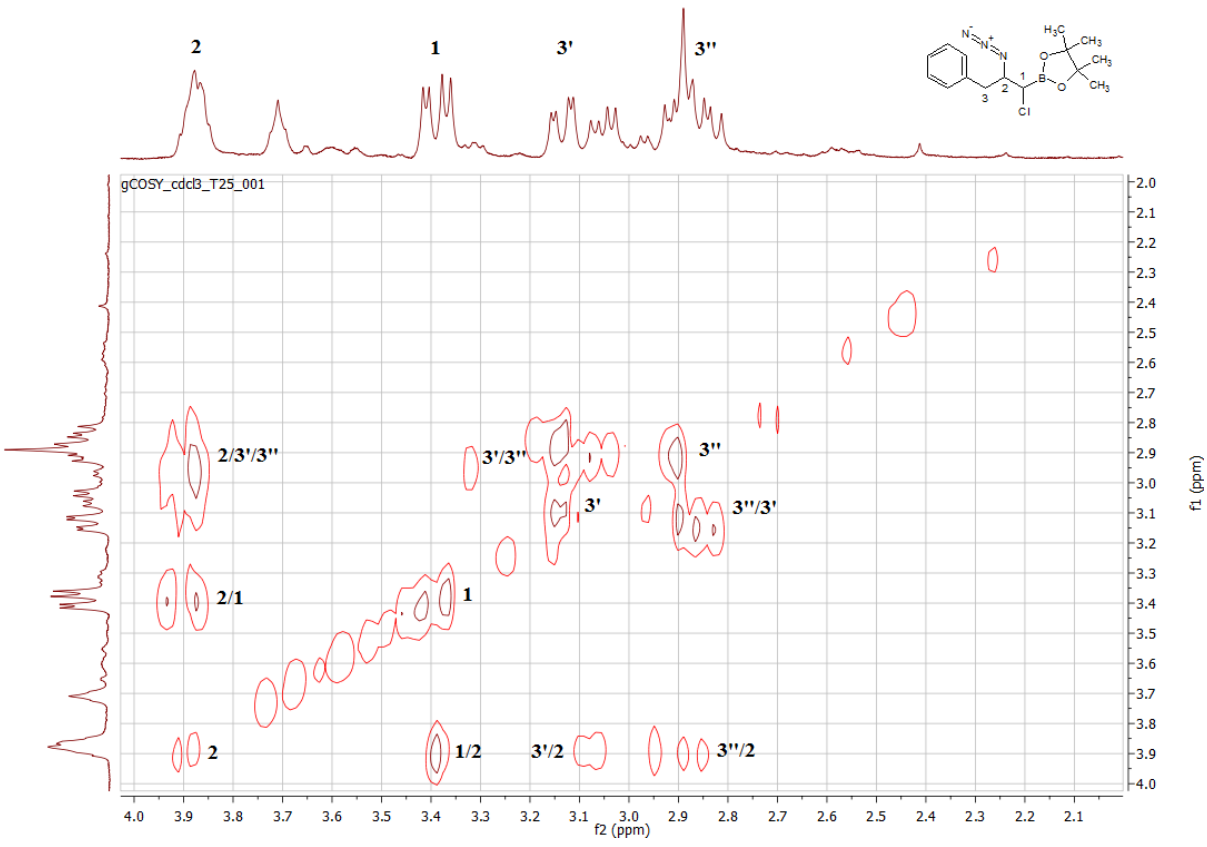


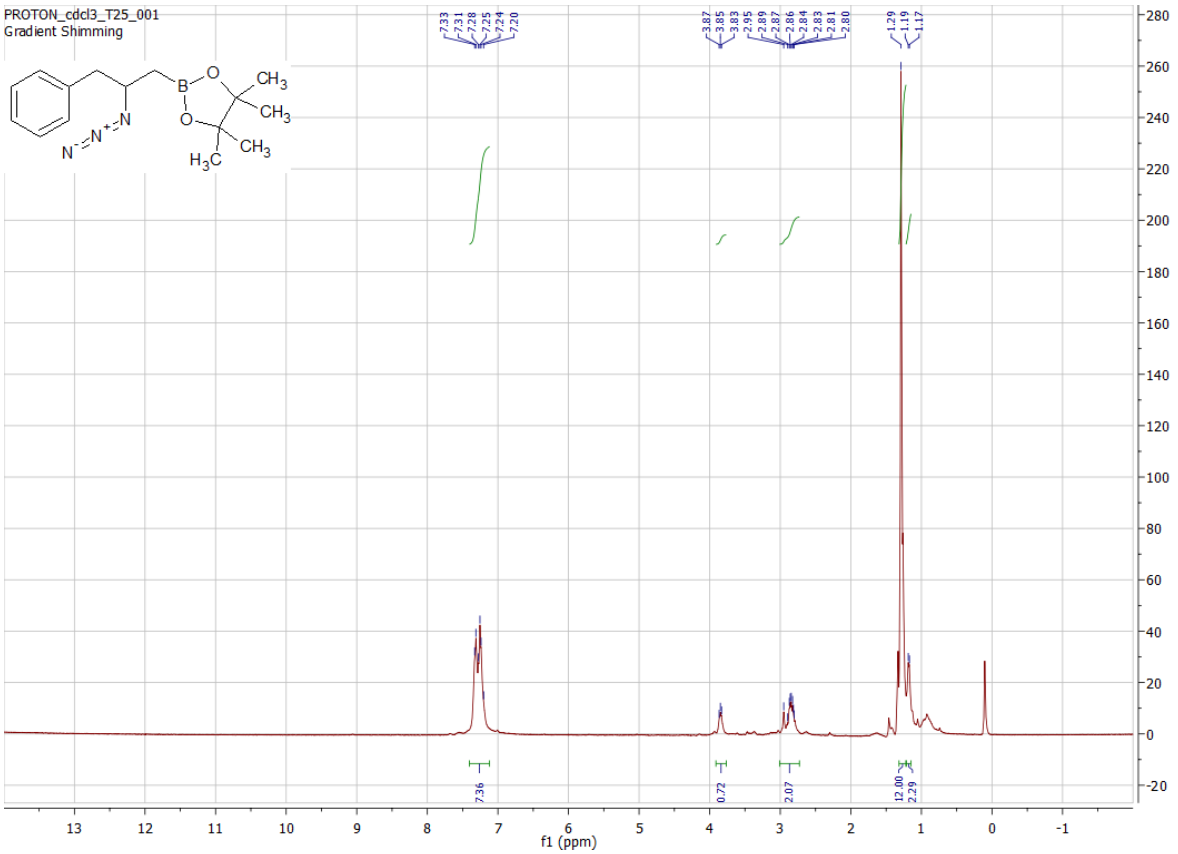
## Appendix 57




## Appendix 58



## Appendix 59

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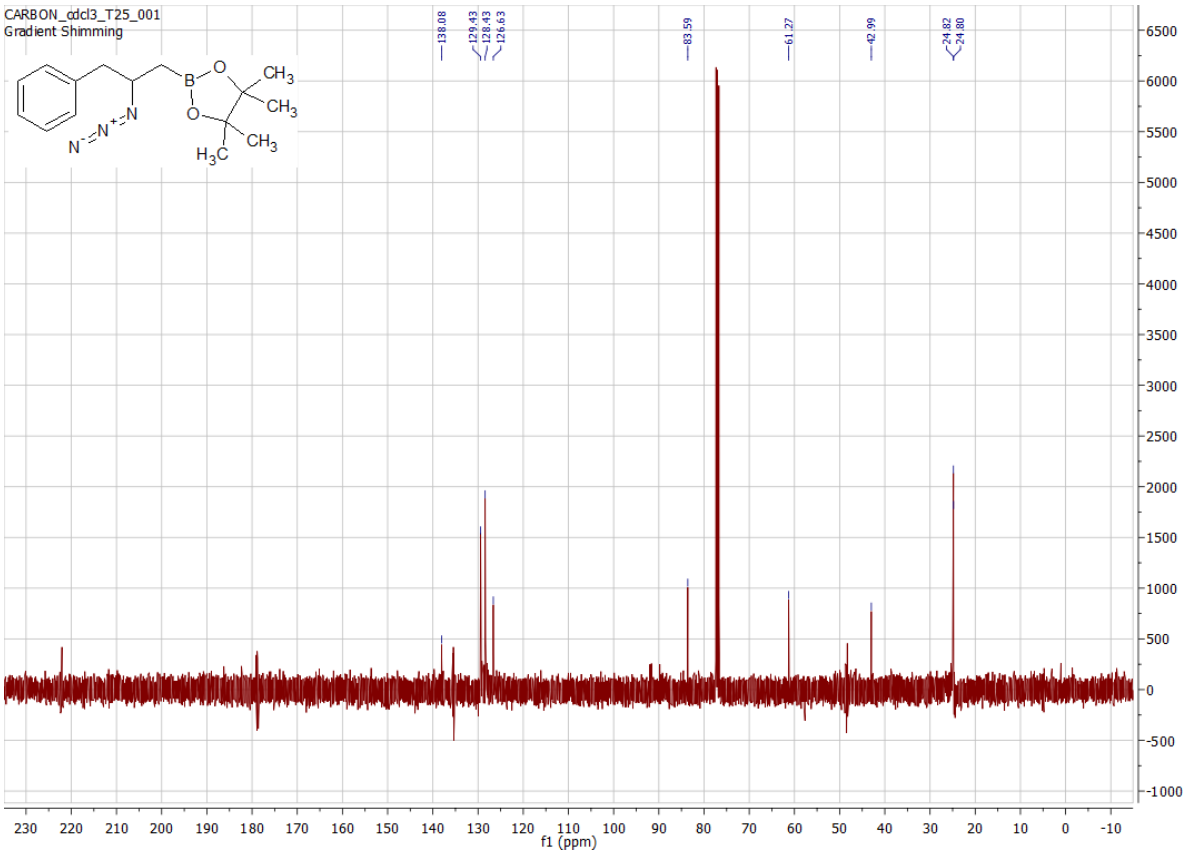
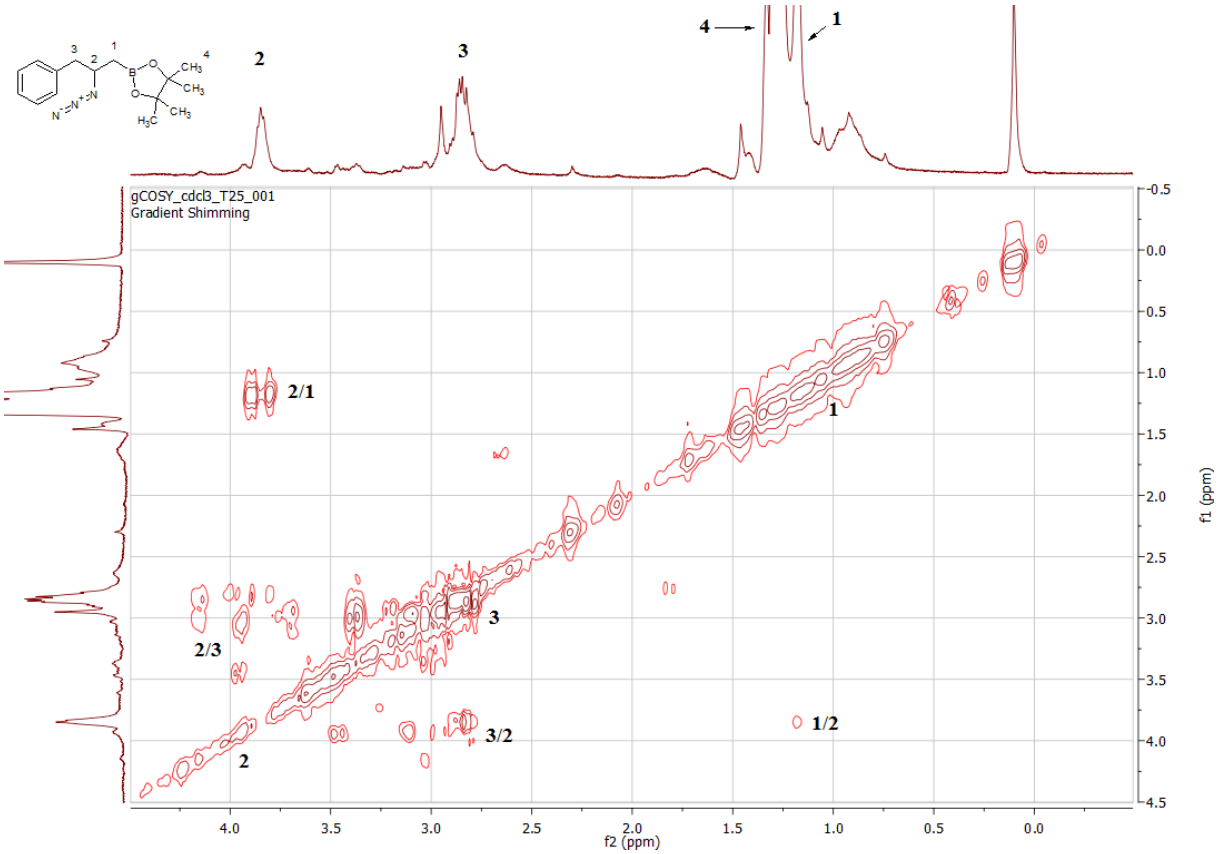
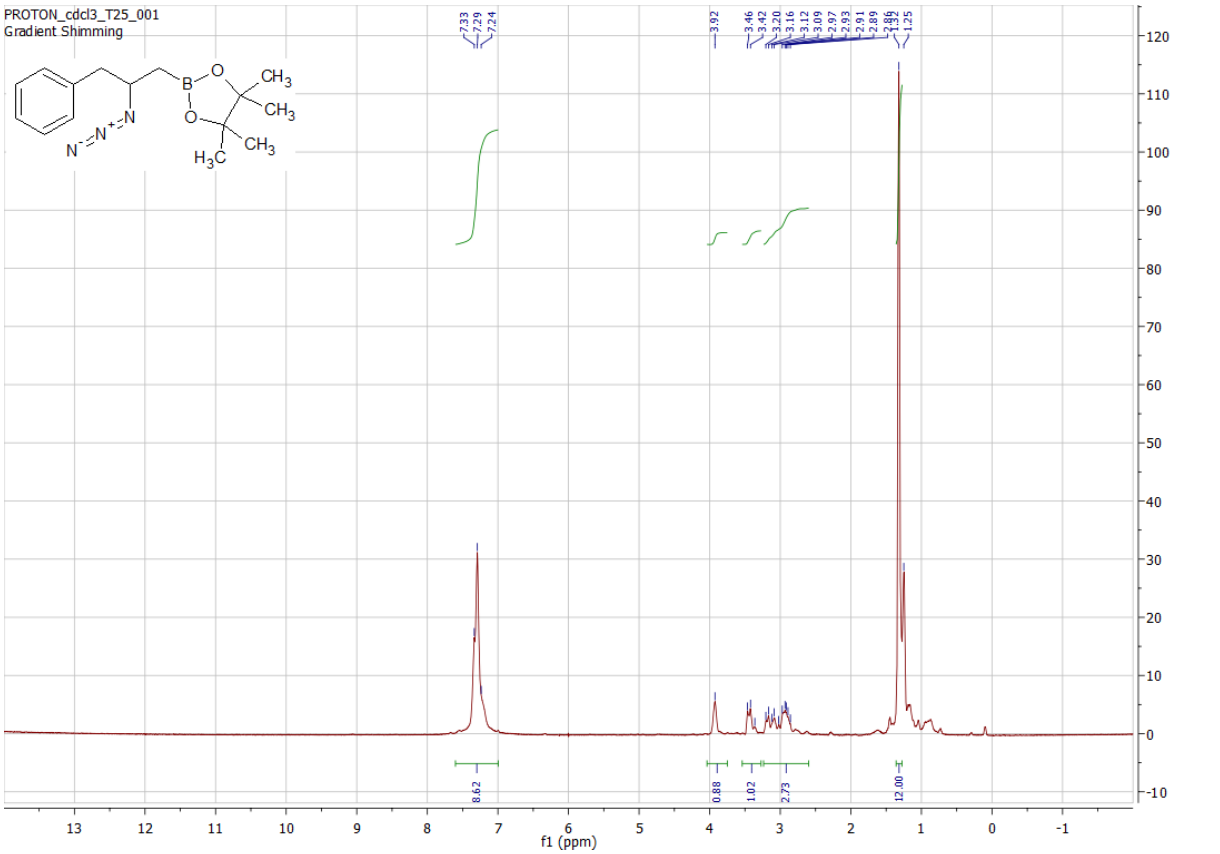


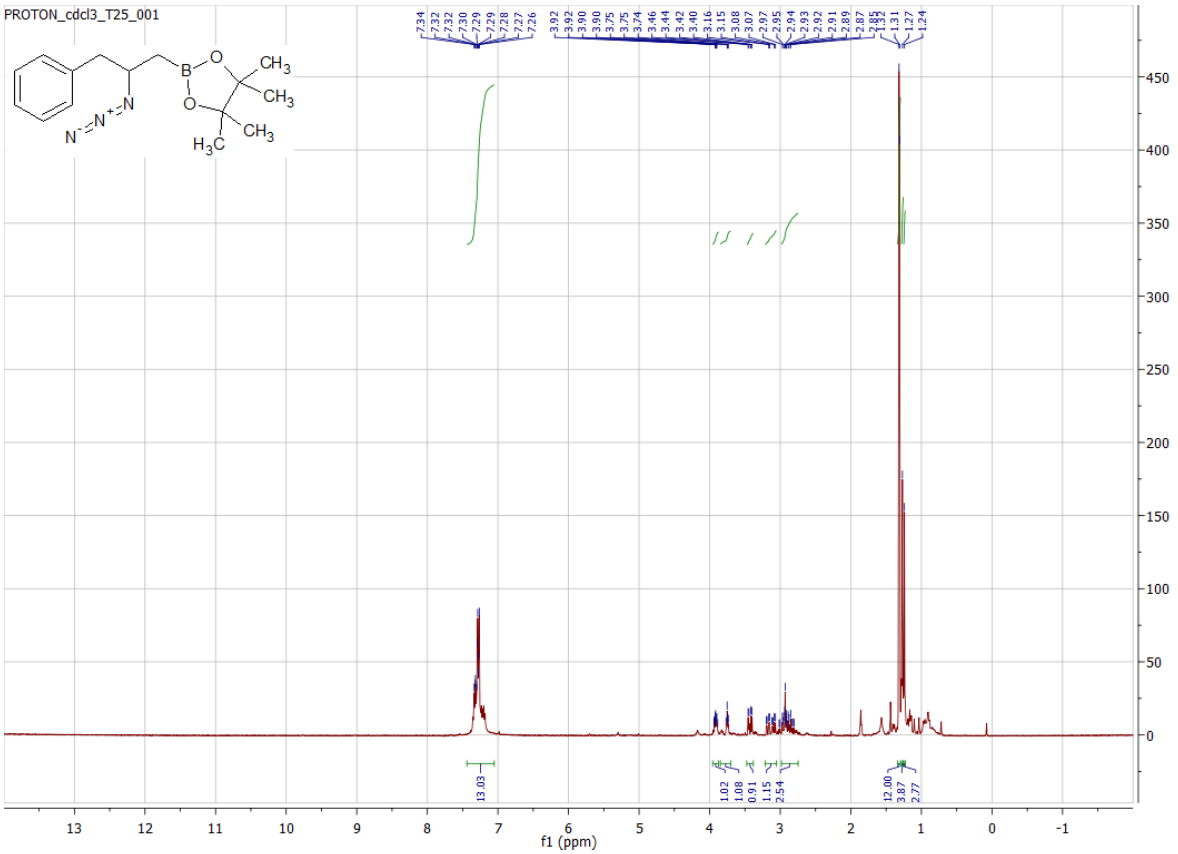
## Appendix 61




## Appendix 62



## Appendix 63

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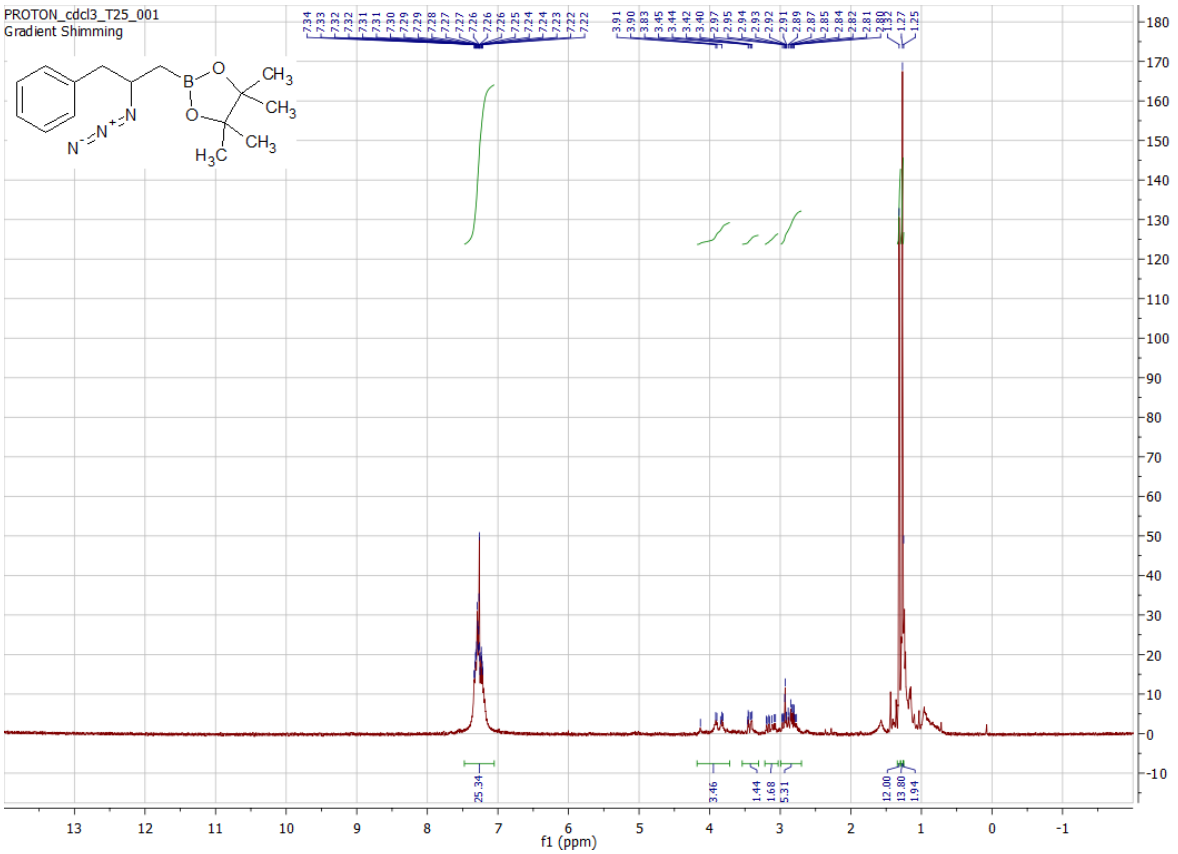
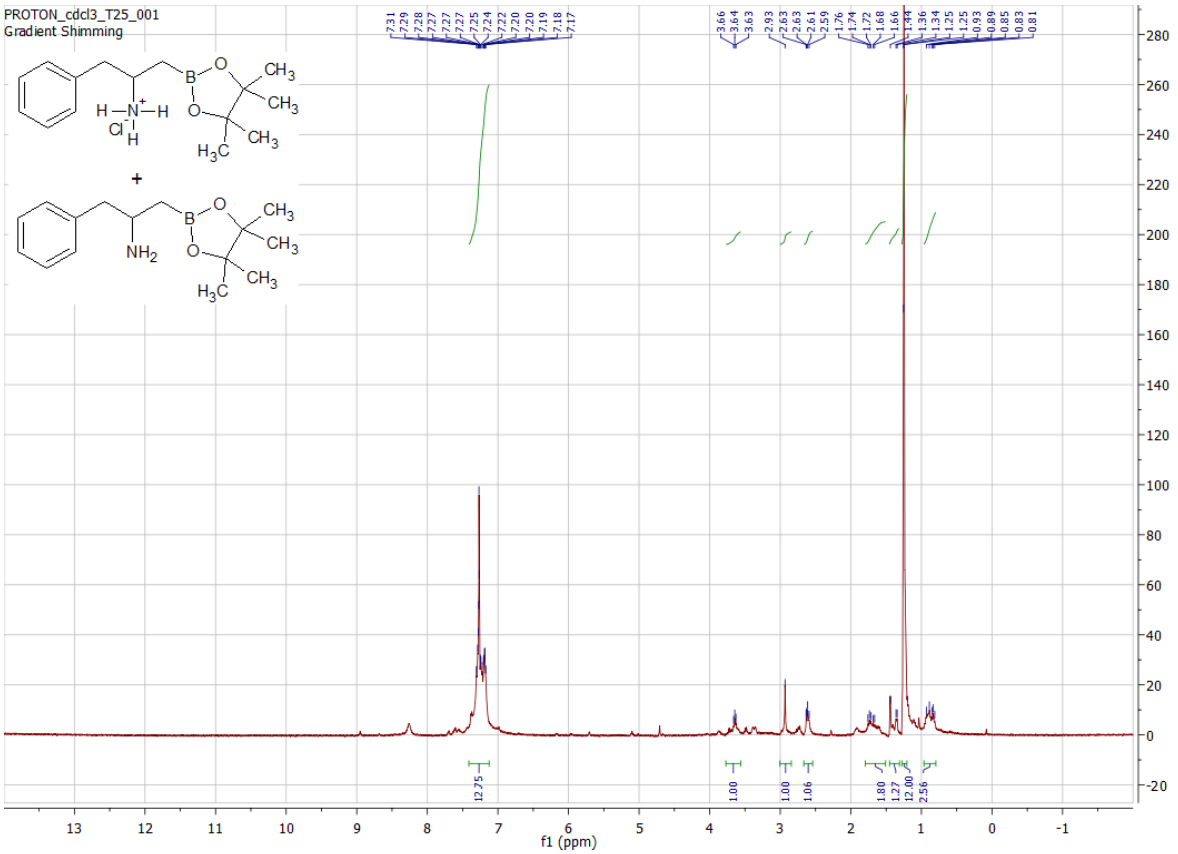


## Appendix 65

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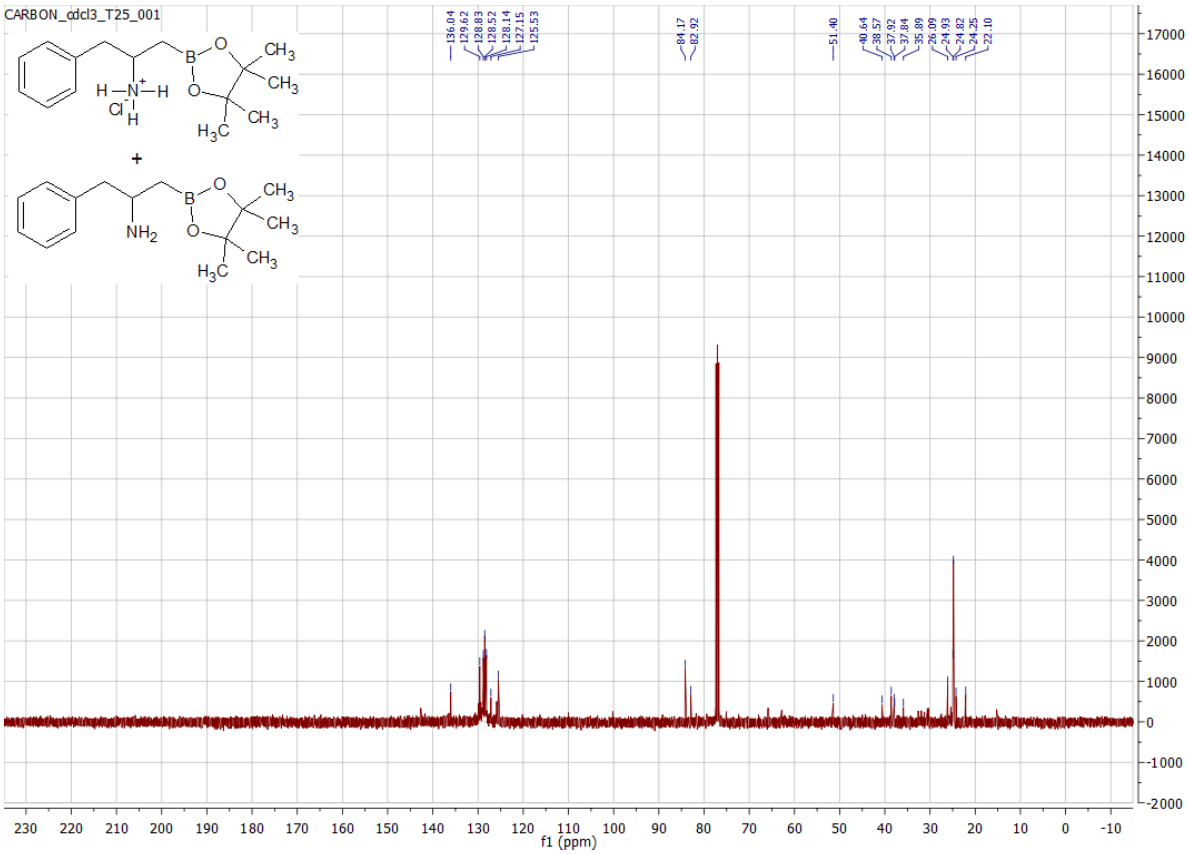
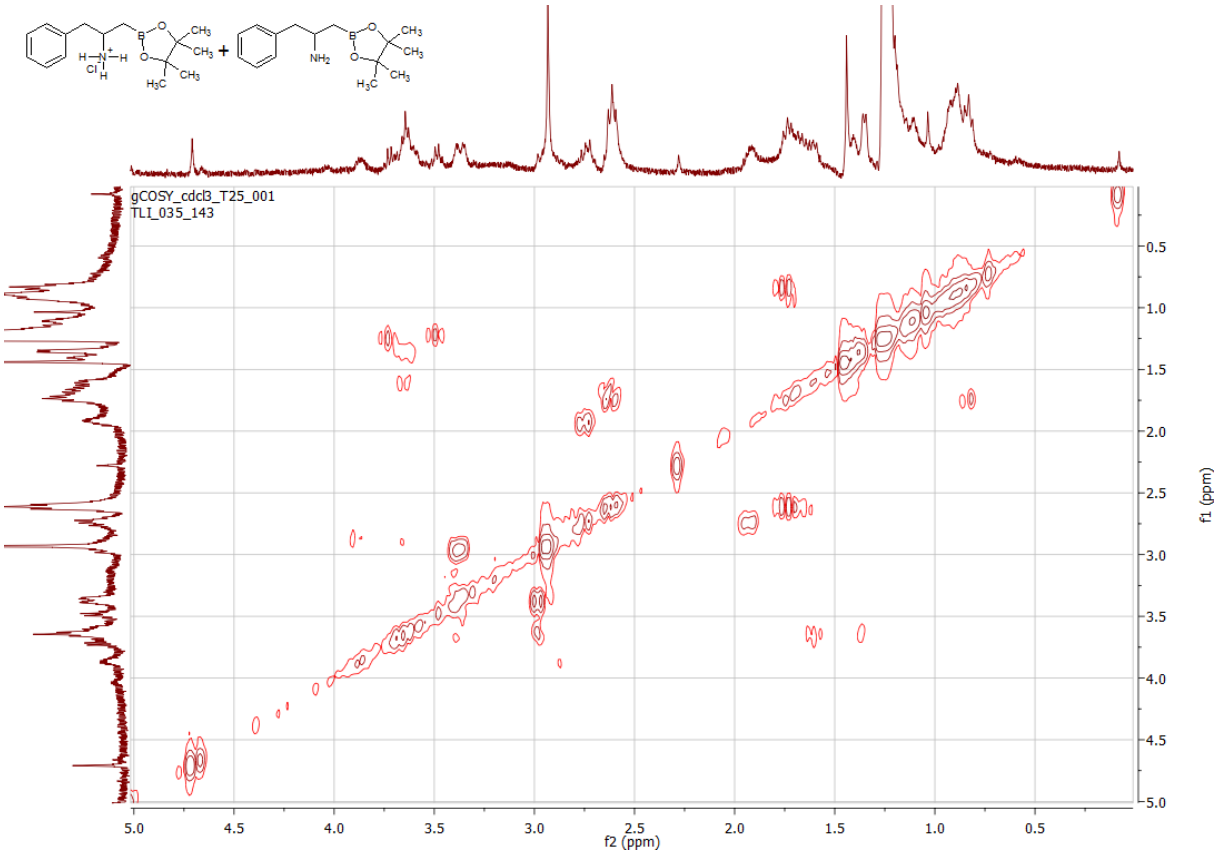
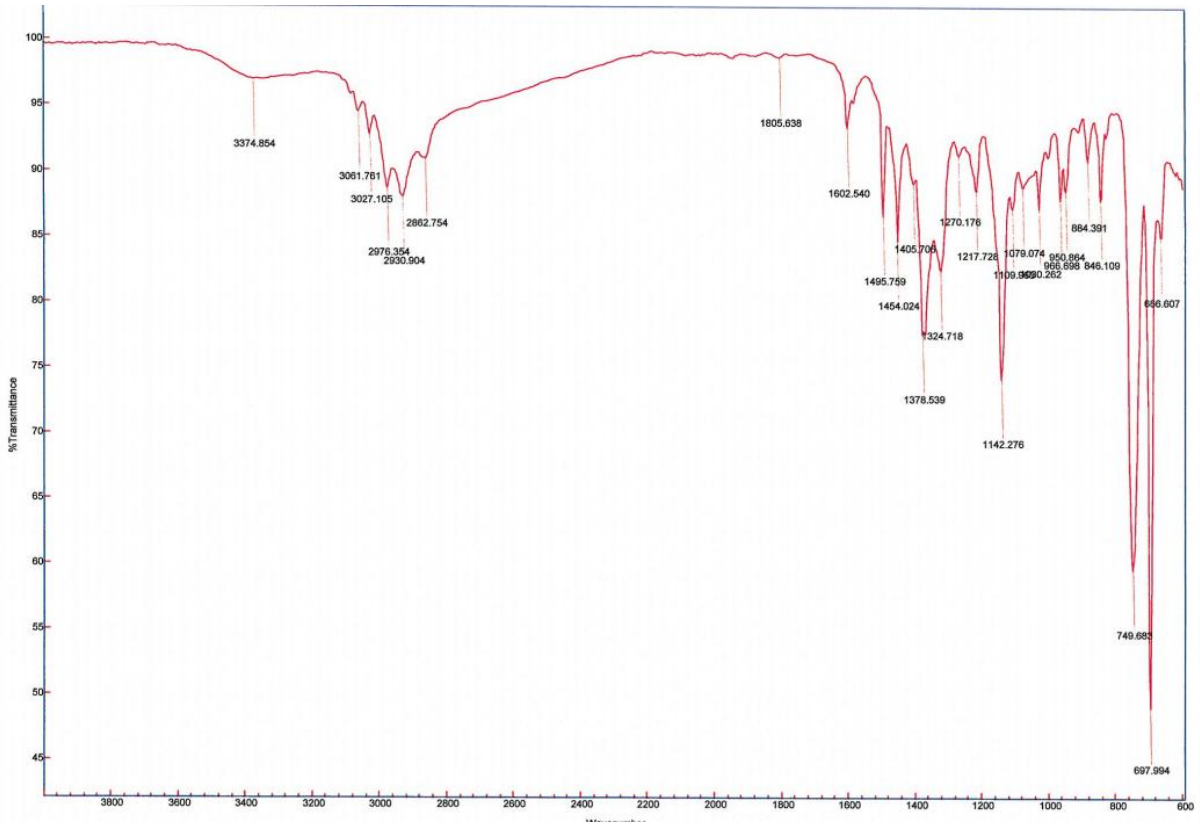


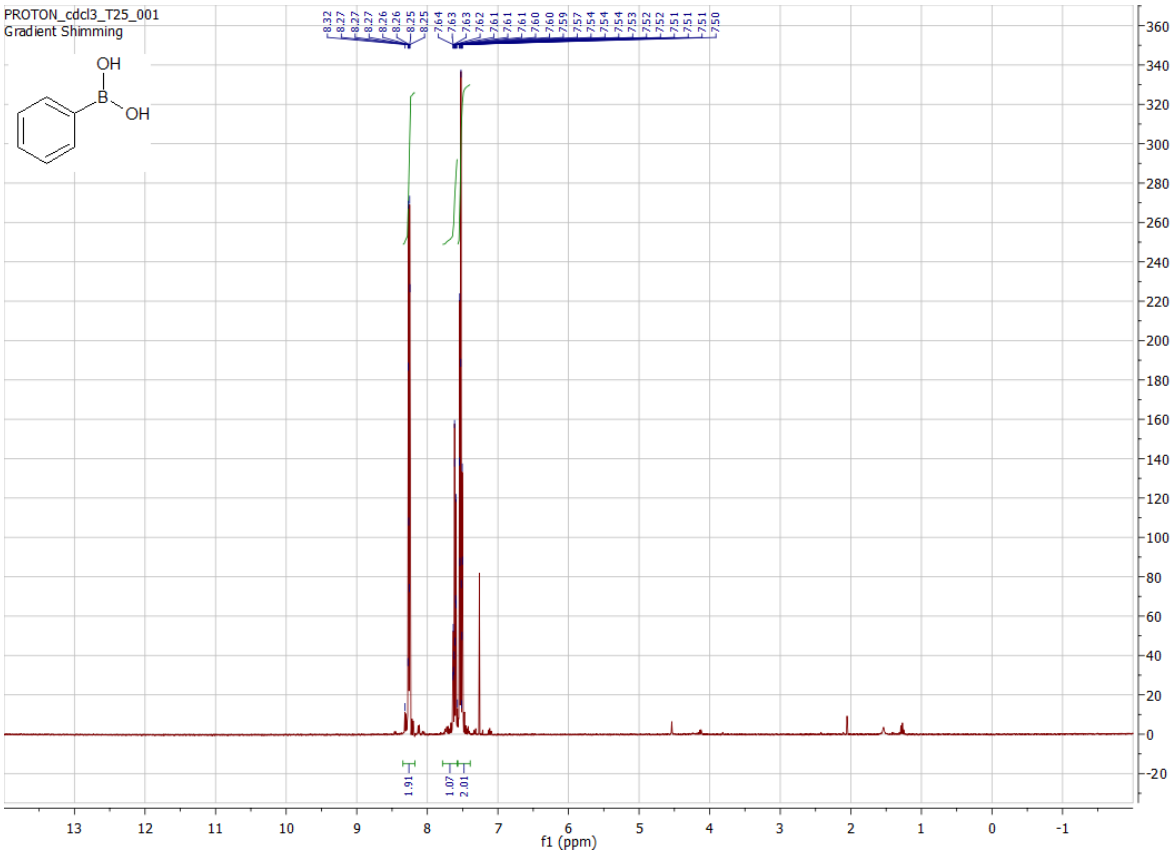
## Appendix 67



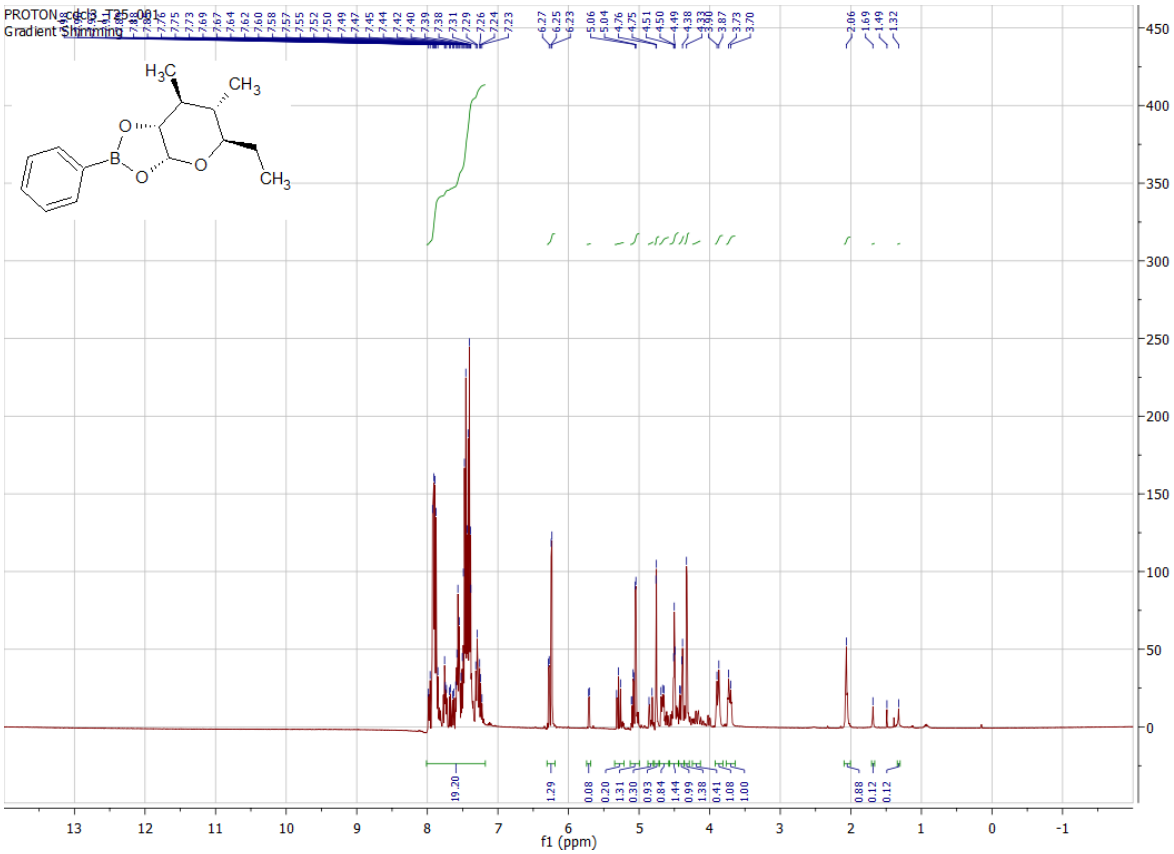

## Appendix 68



## Appendix 69




## Appendix 70



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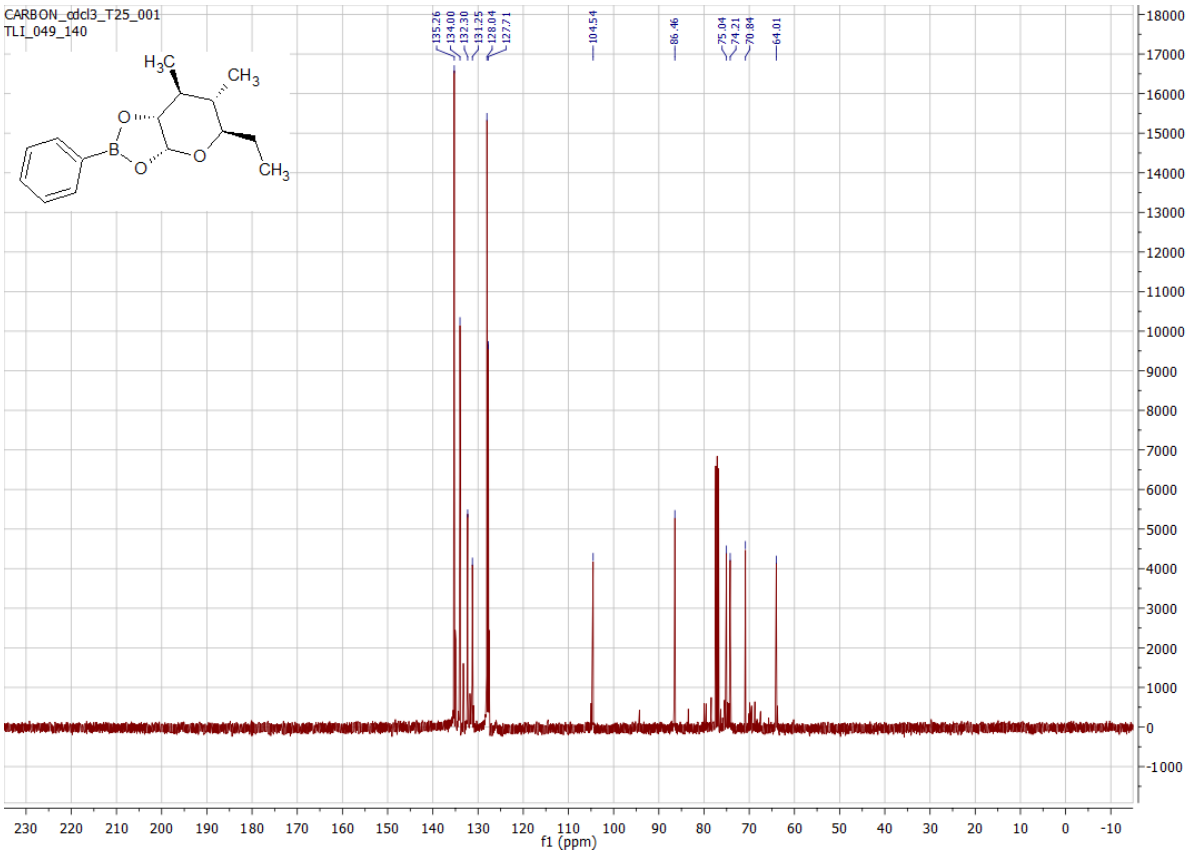
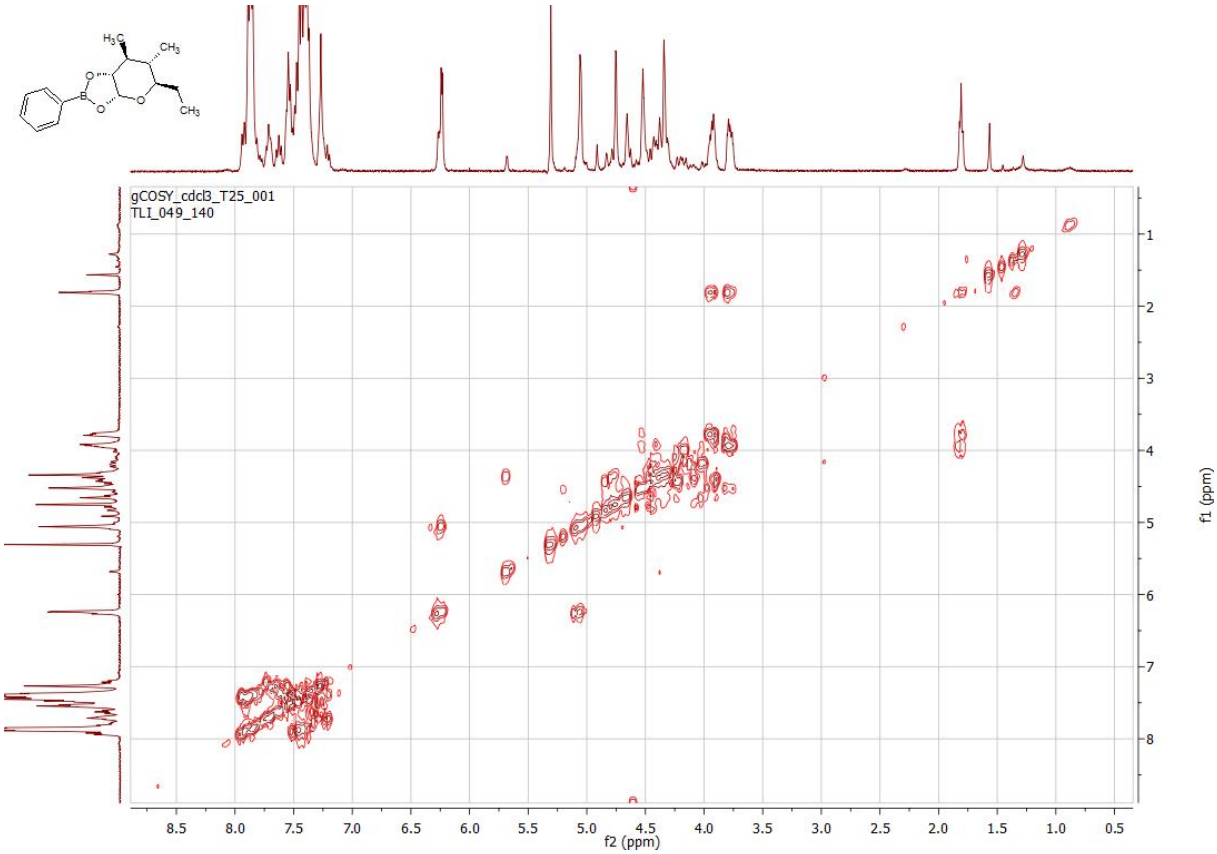
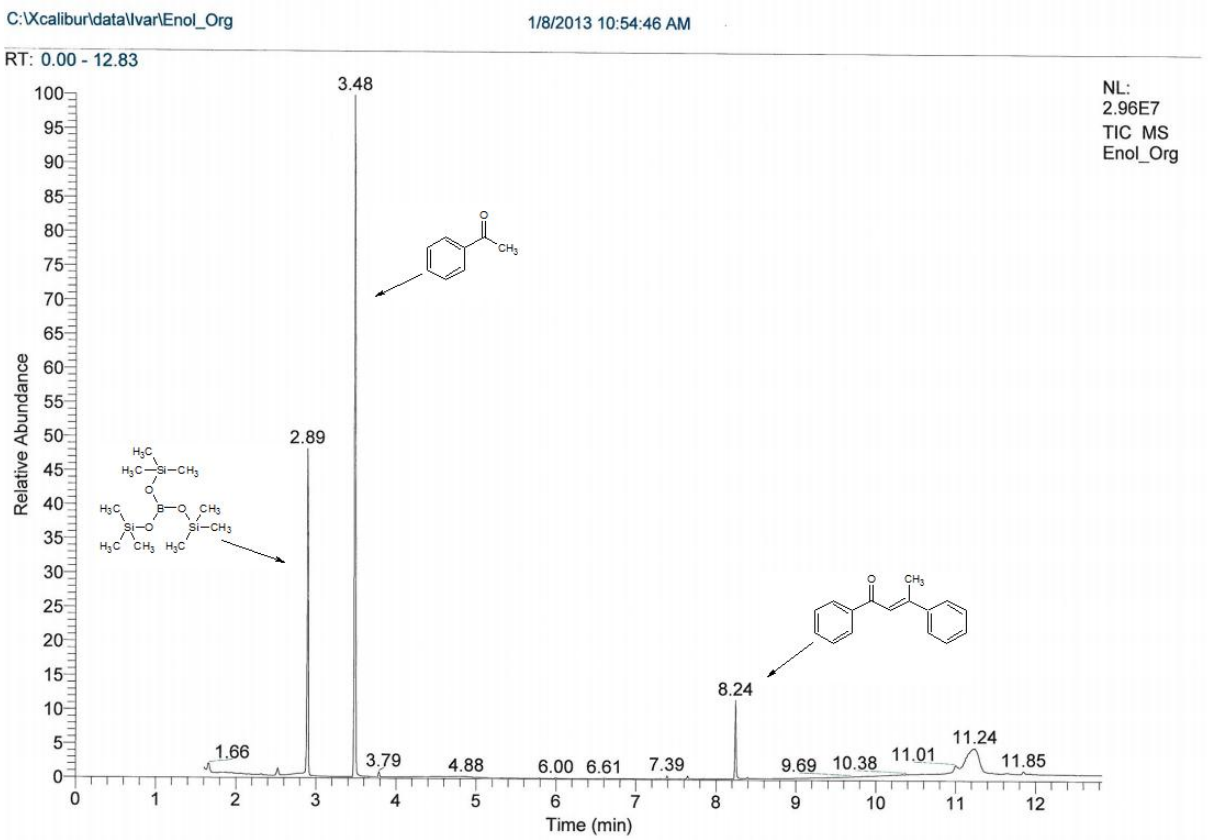


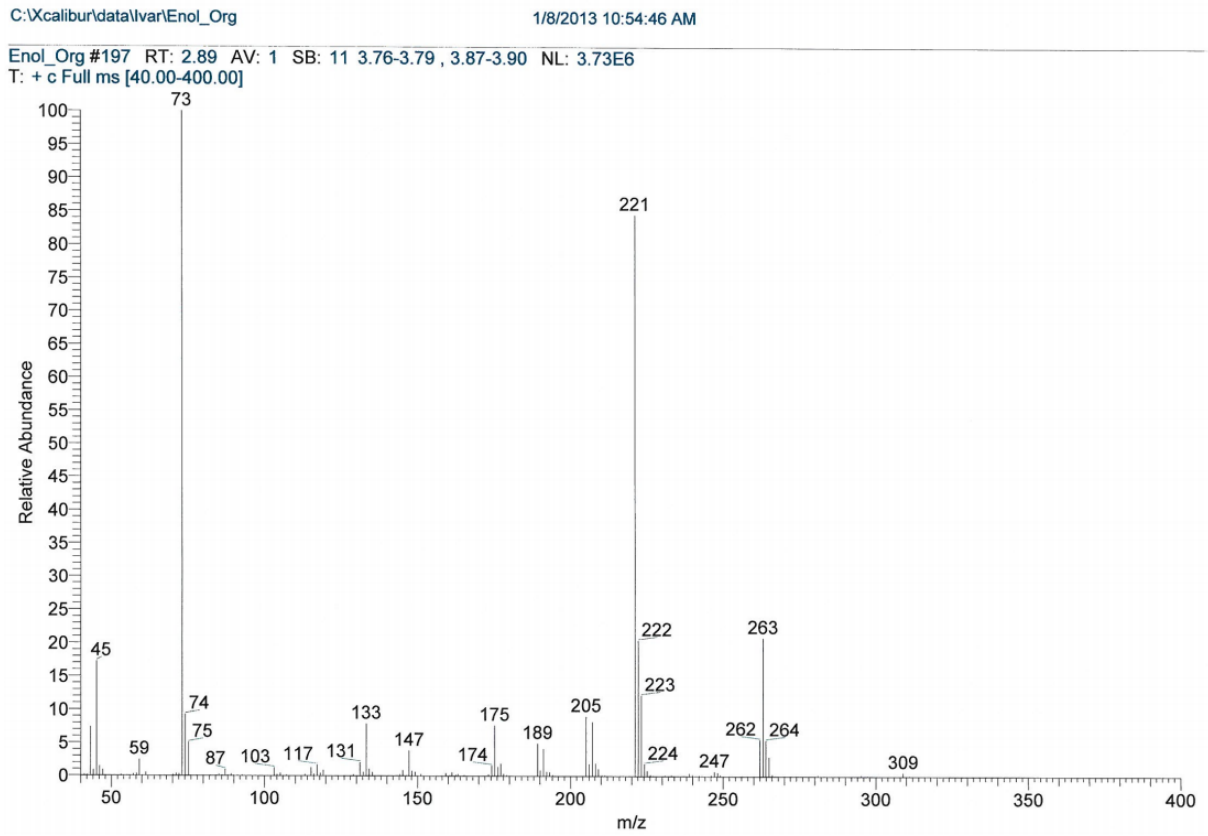

## Appendix 72



## Appendix 73




## Appendix 74



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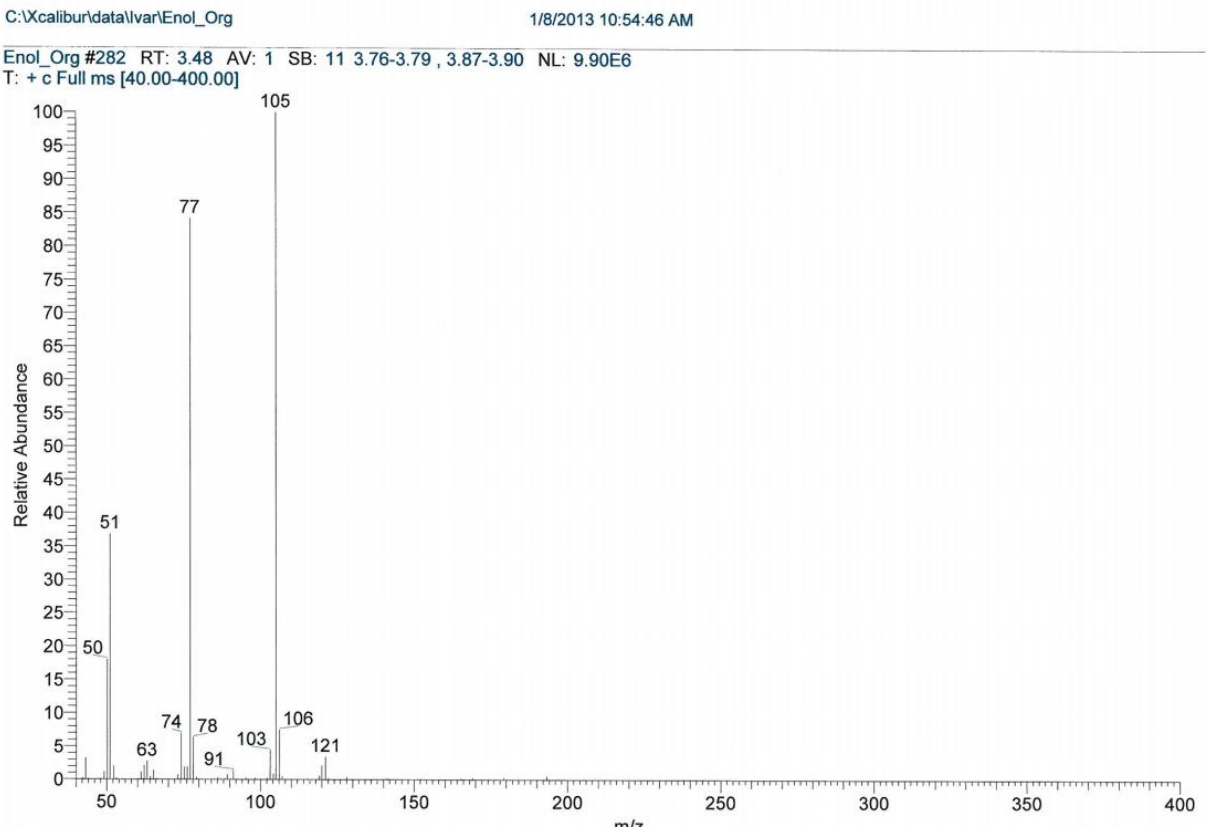


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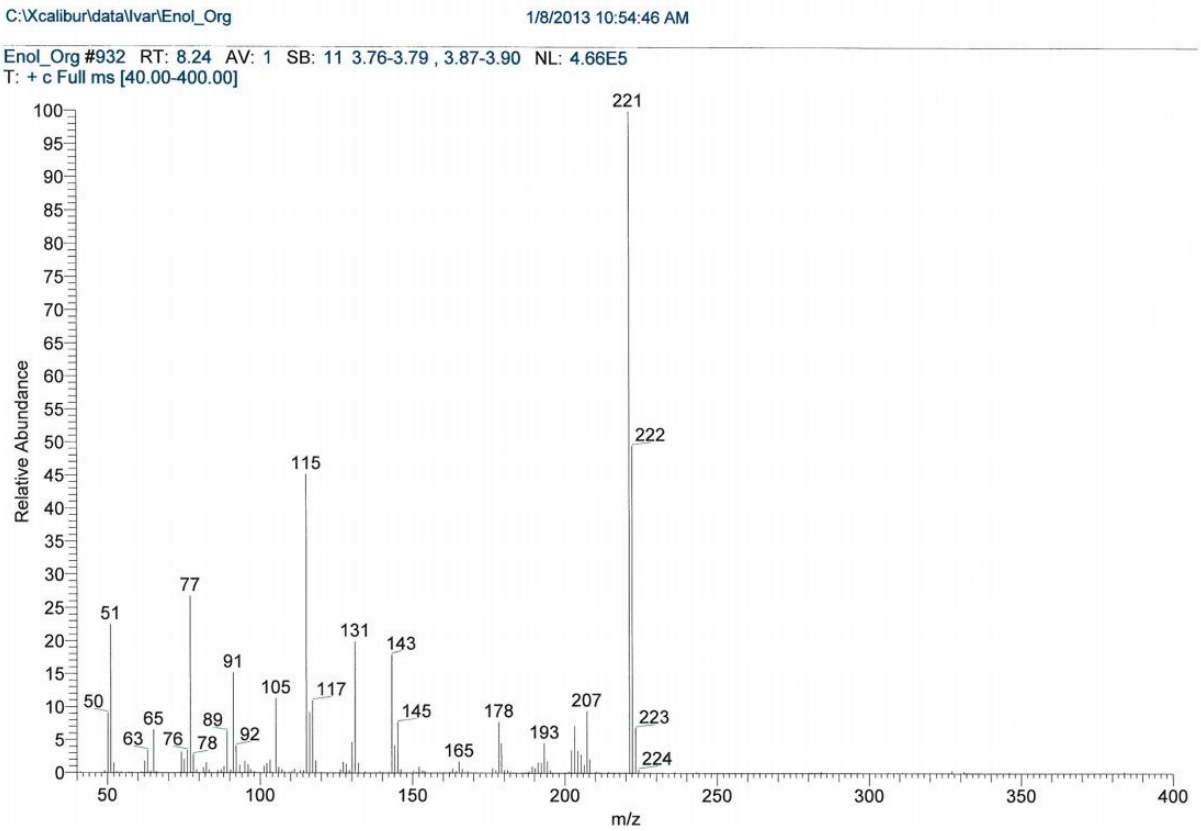
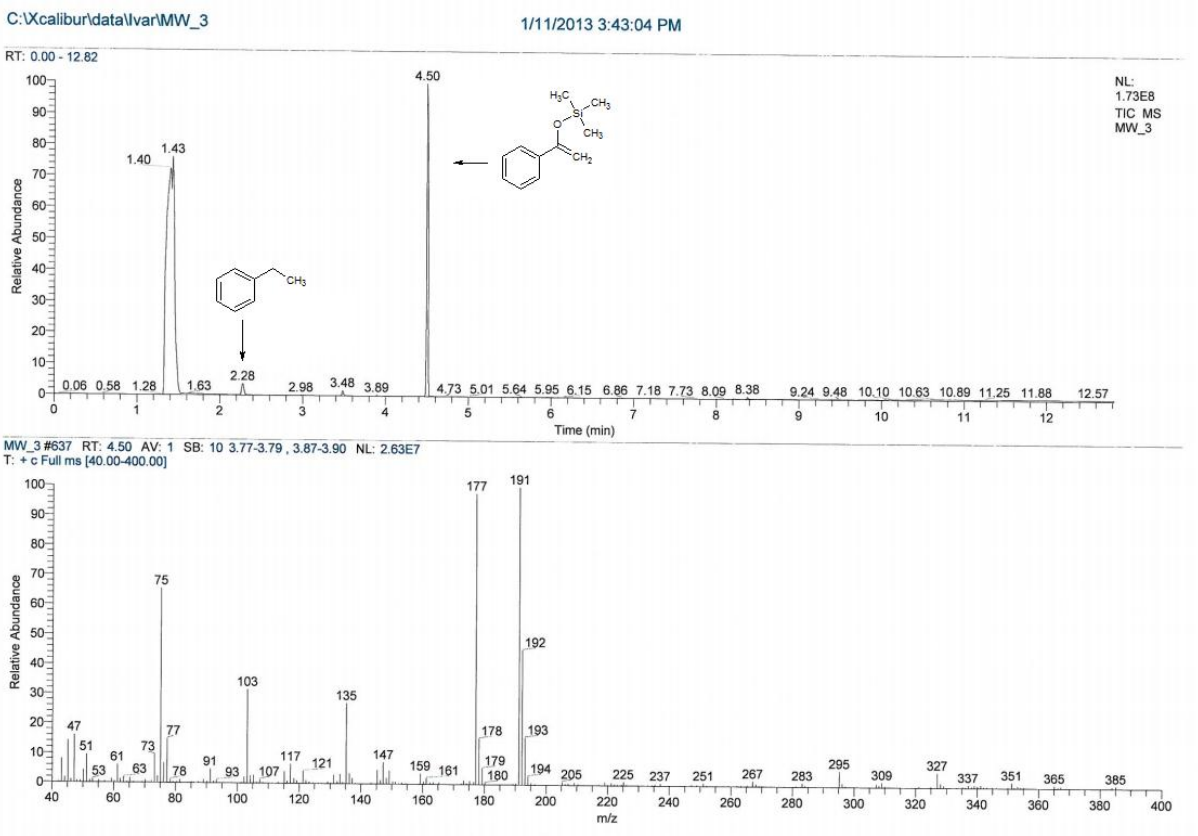
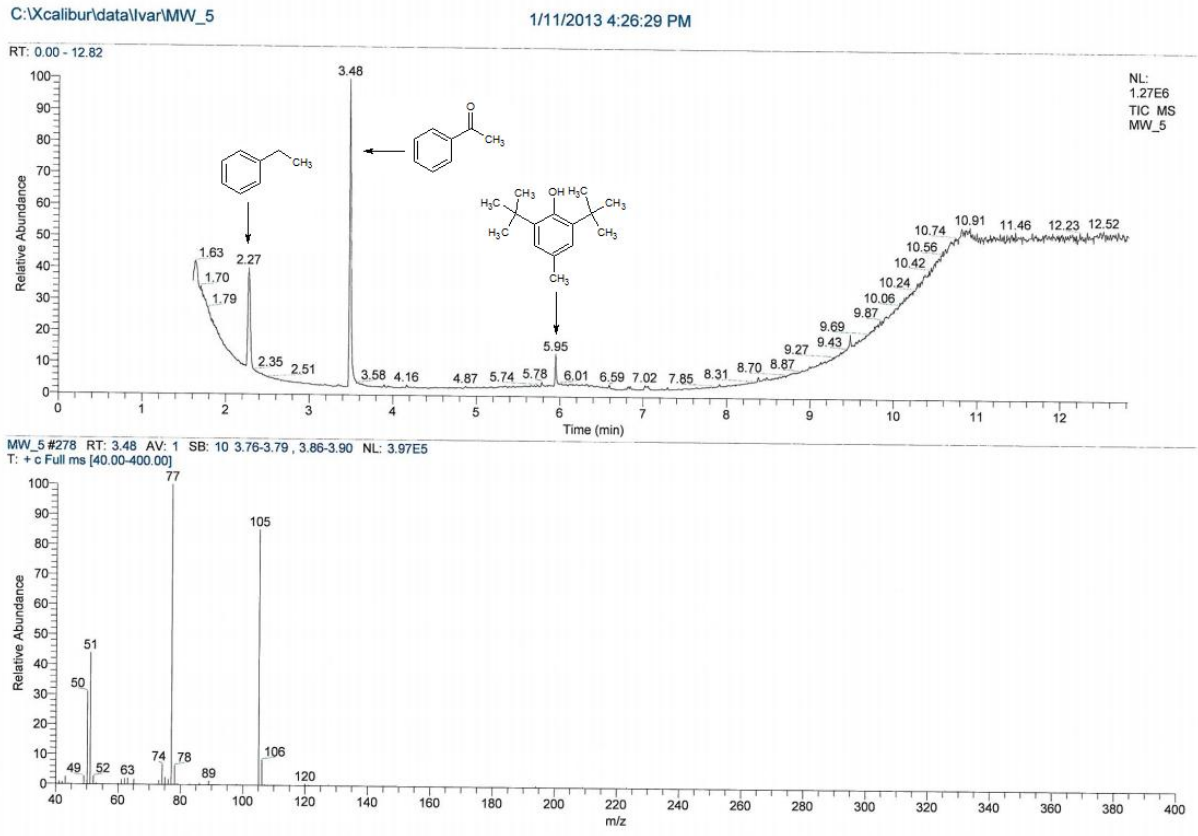


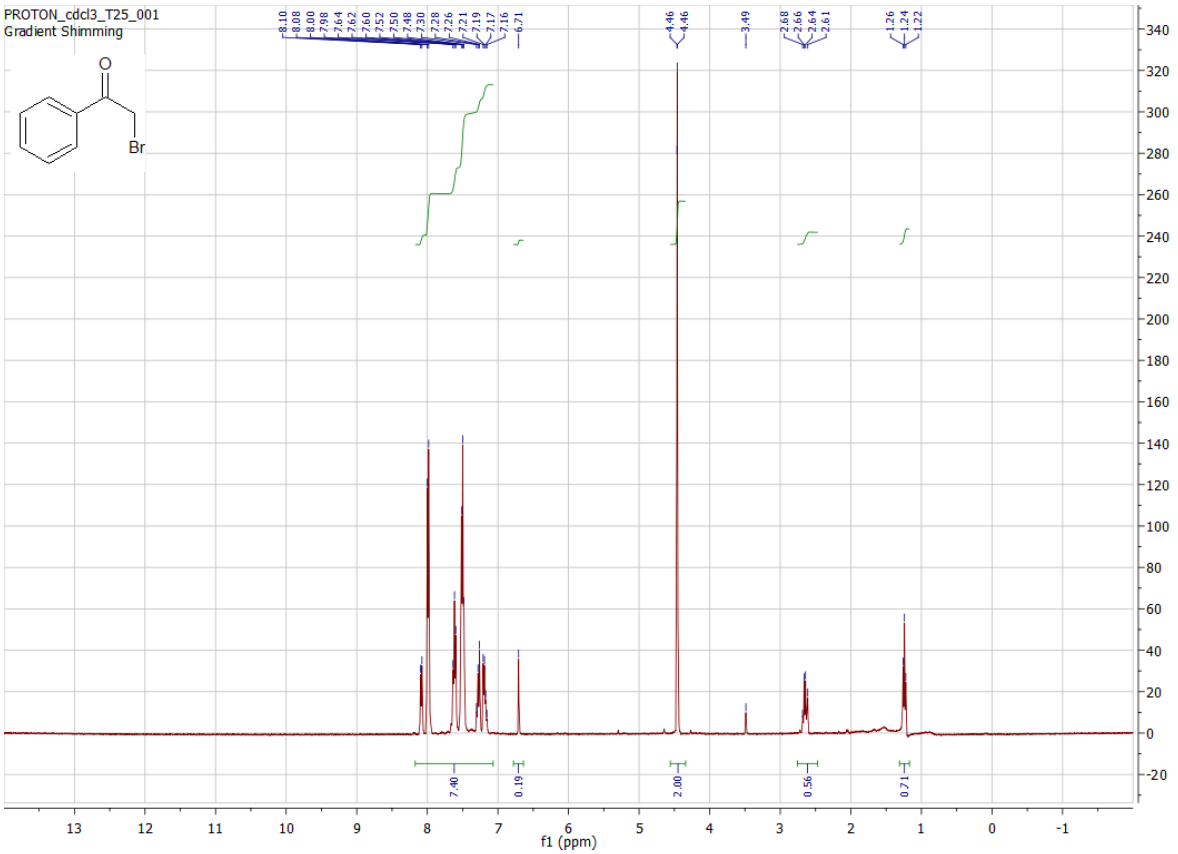
## Appendix 77




## Appendix 78



## Appendix 79

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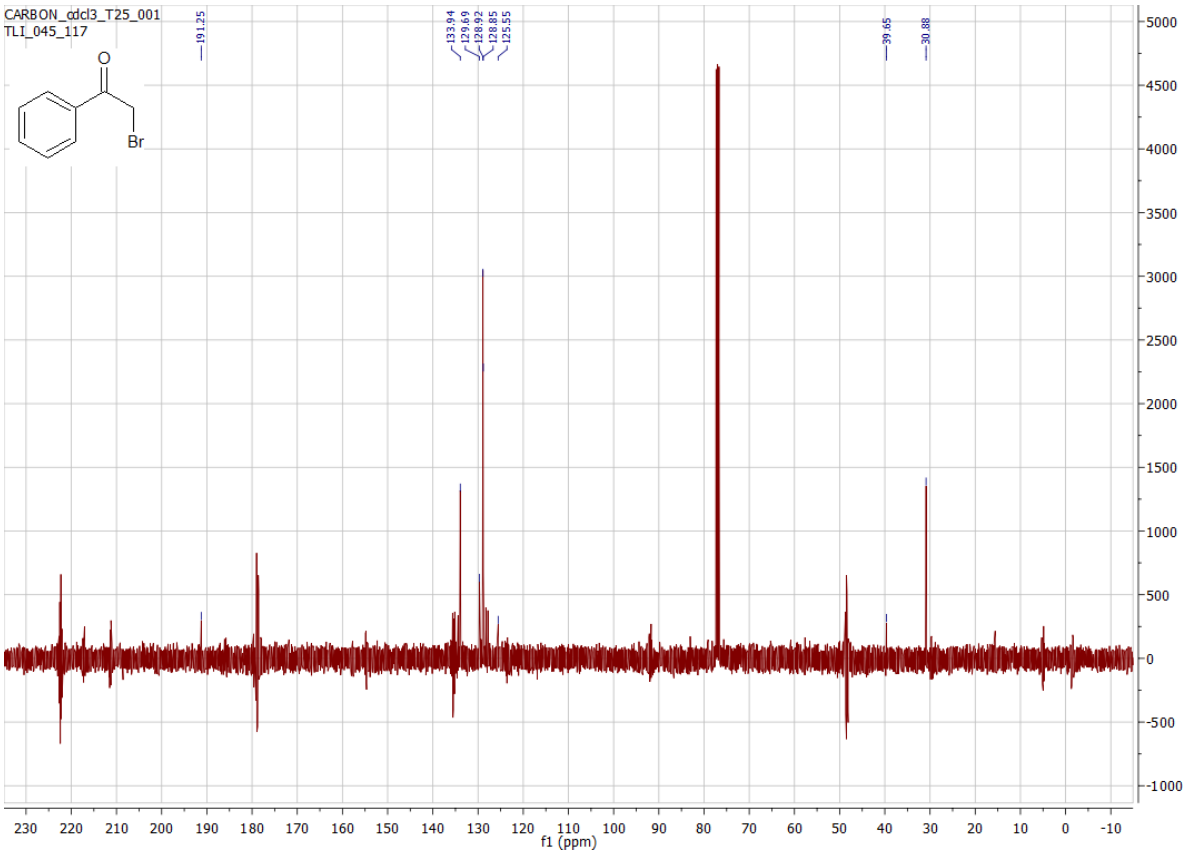

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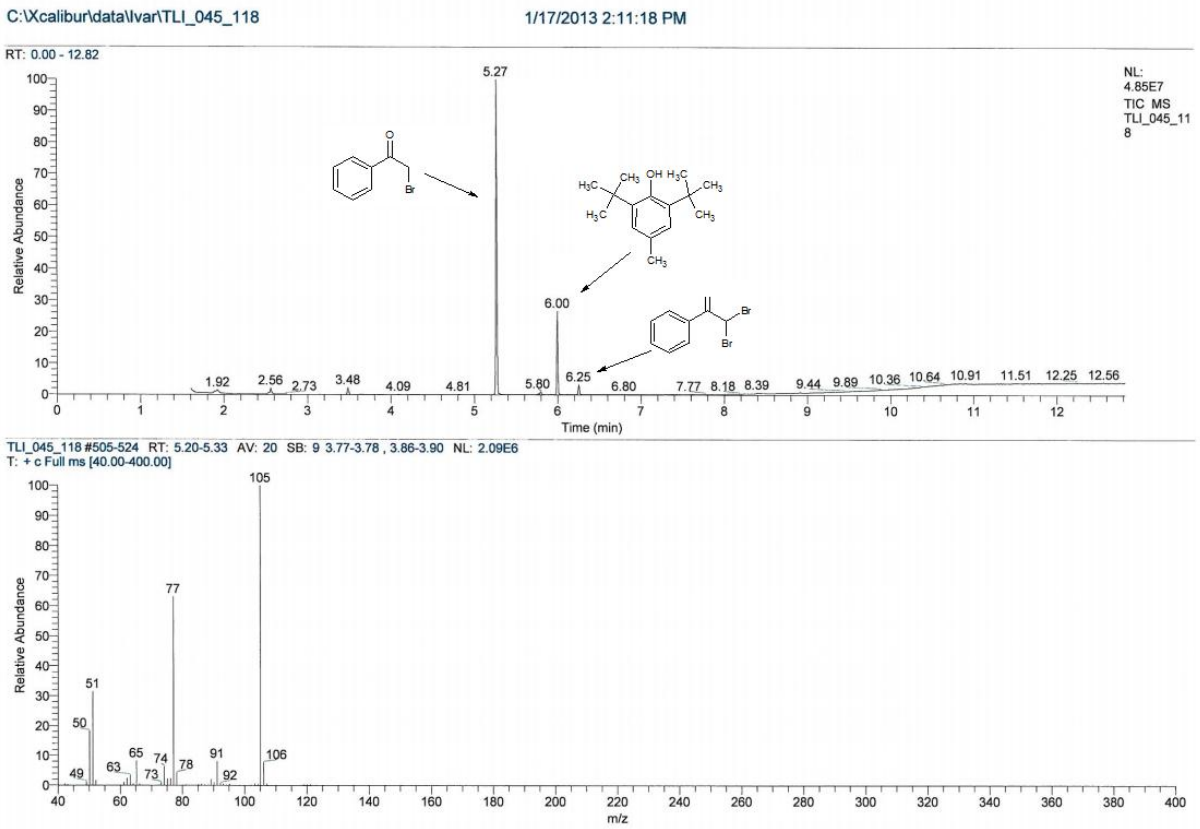


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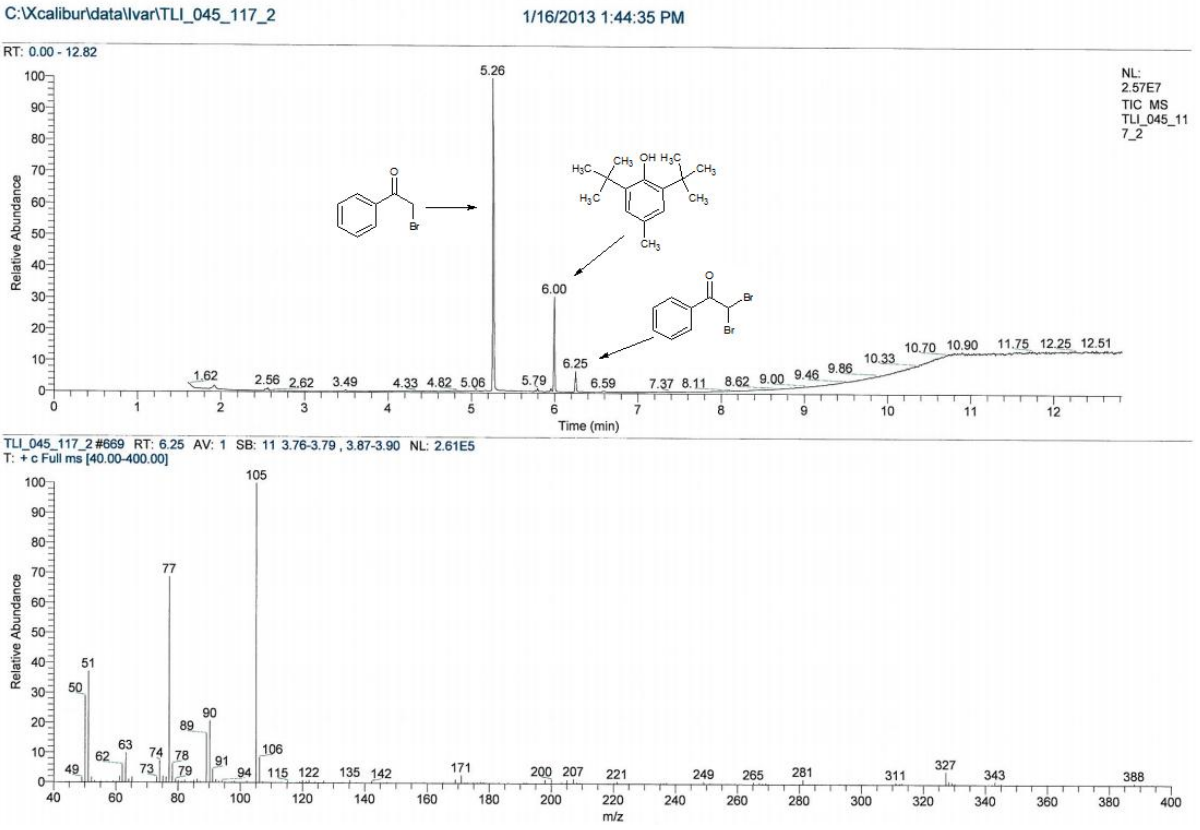

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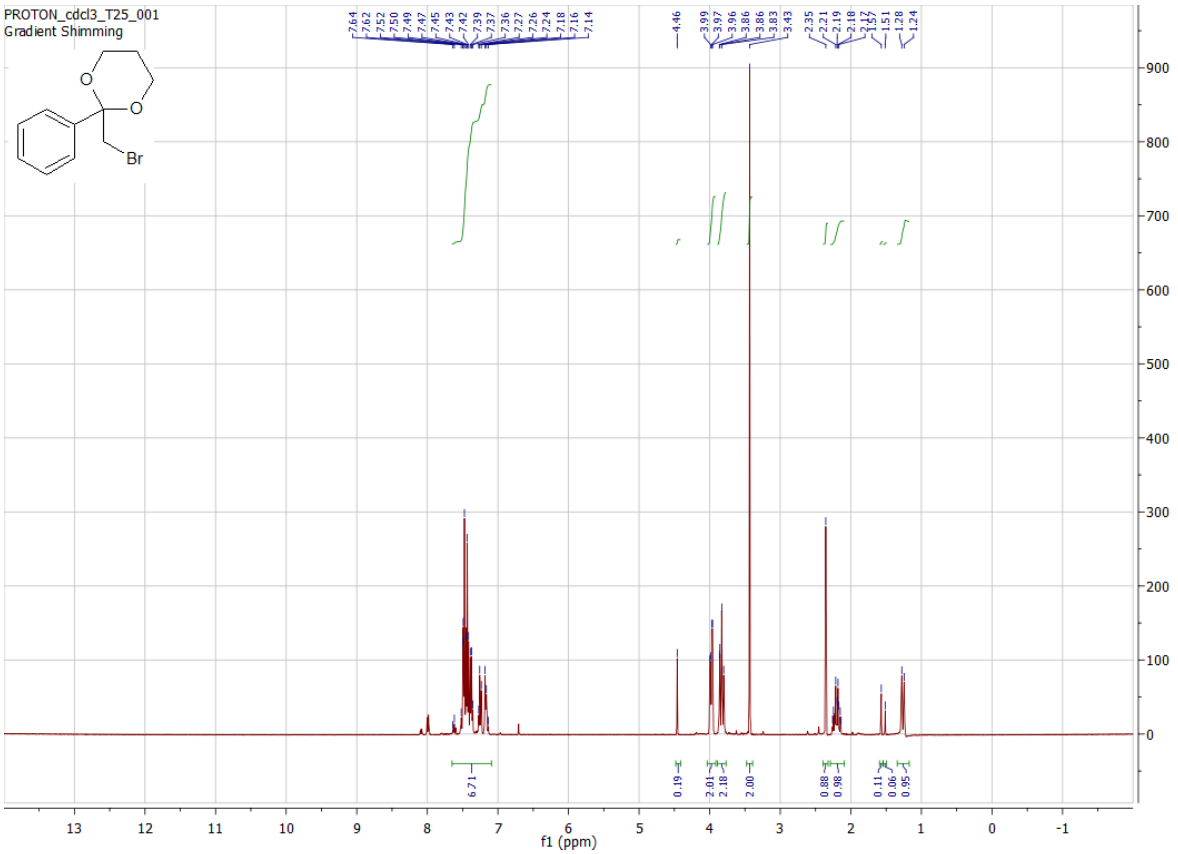


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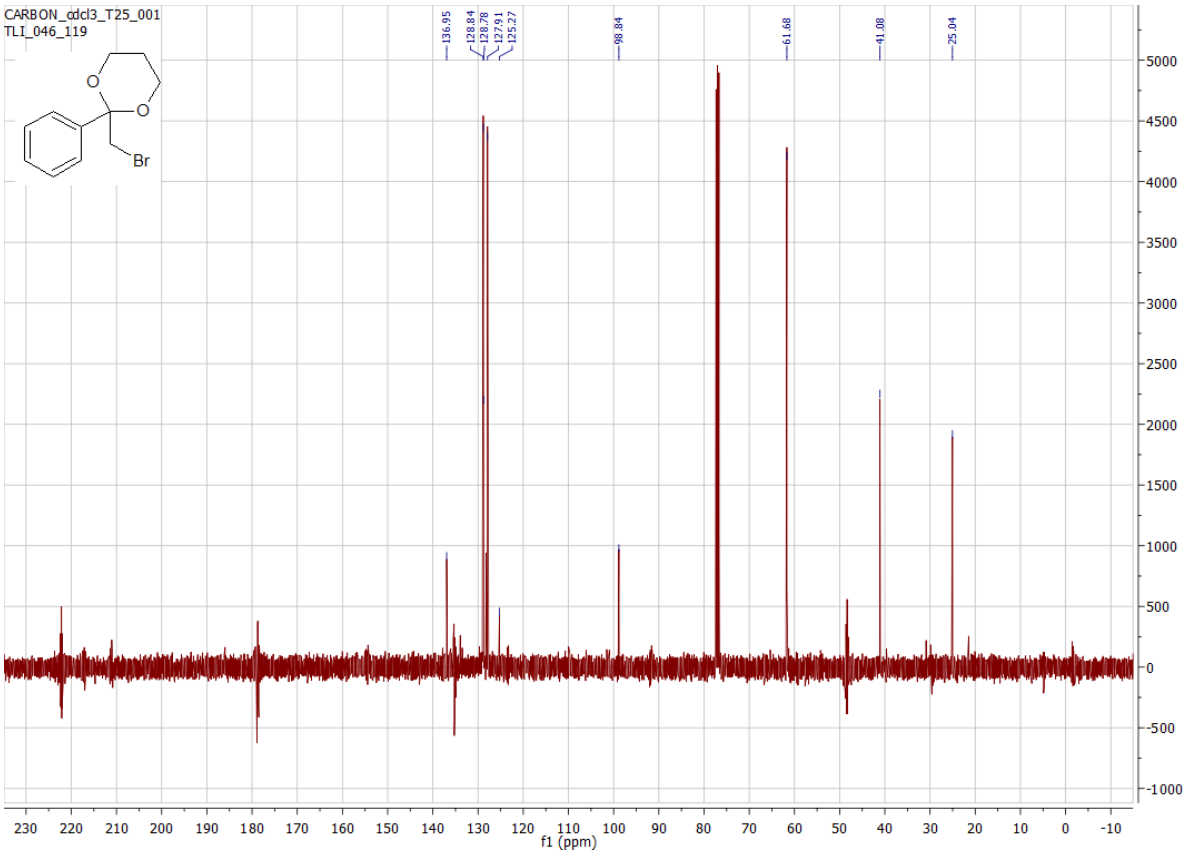

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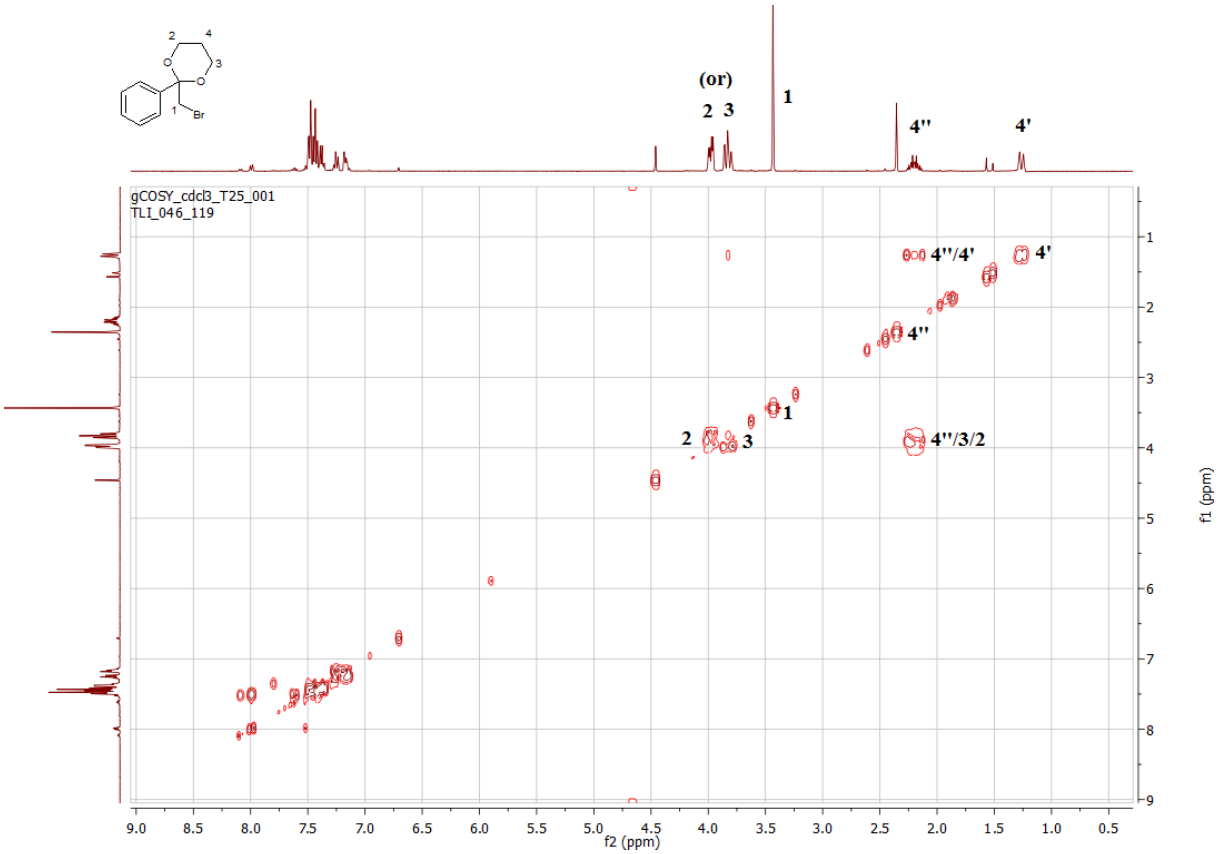


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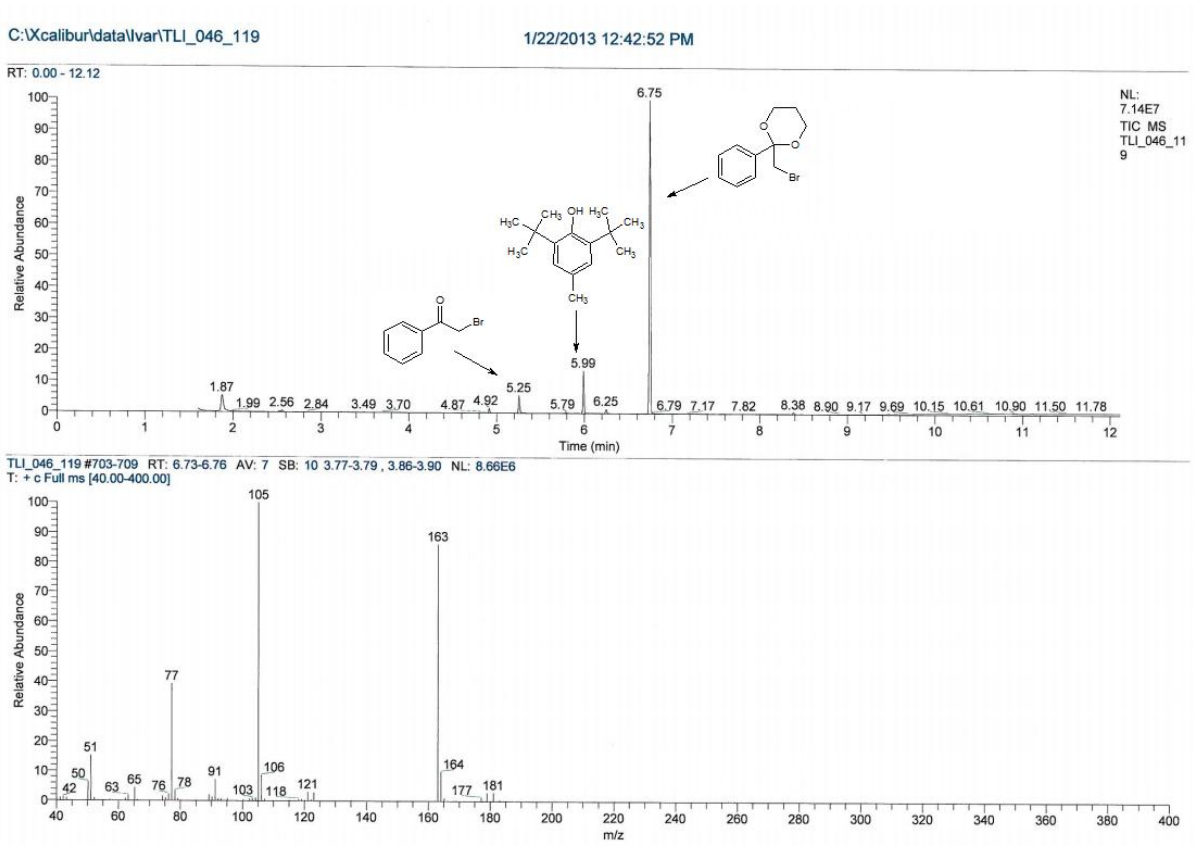

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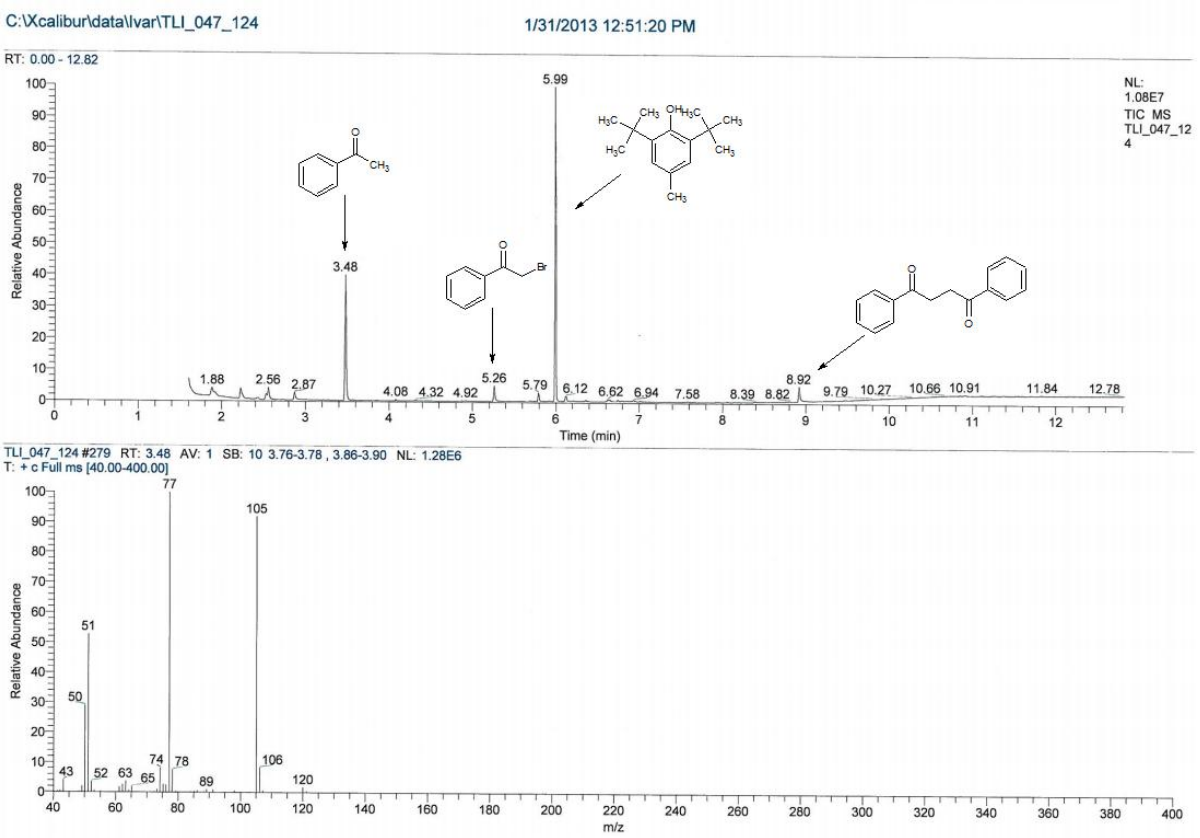


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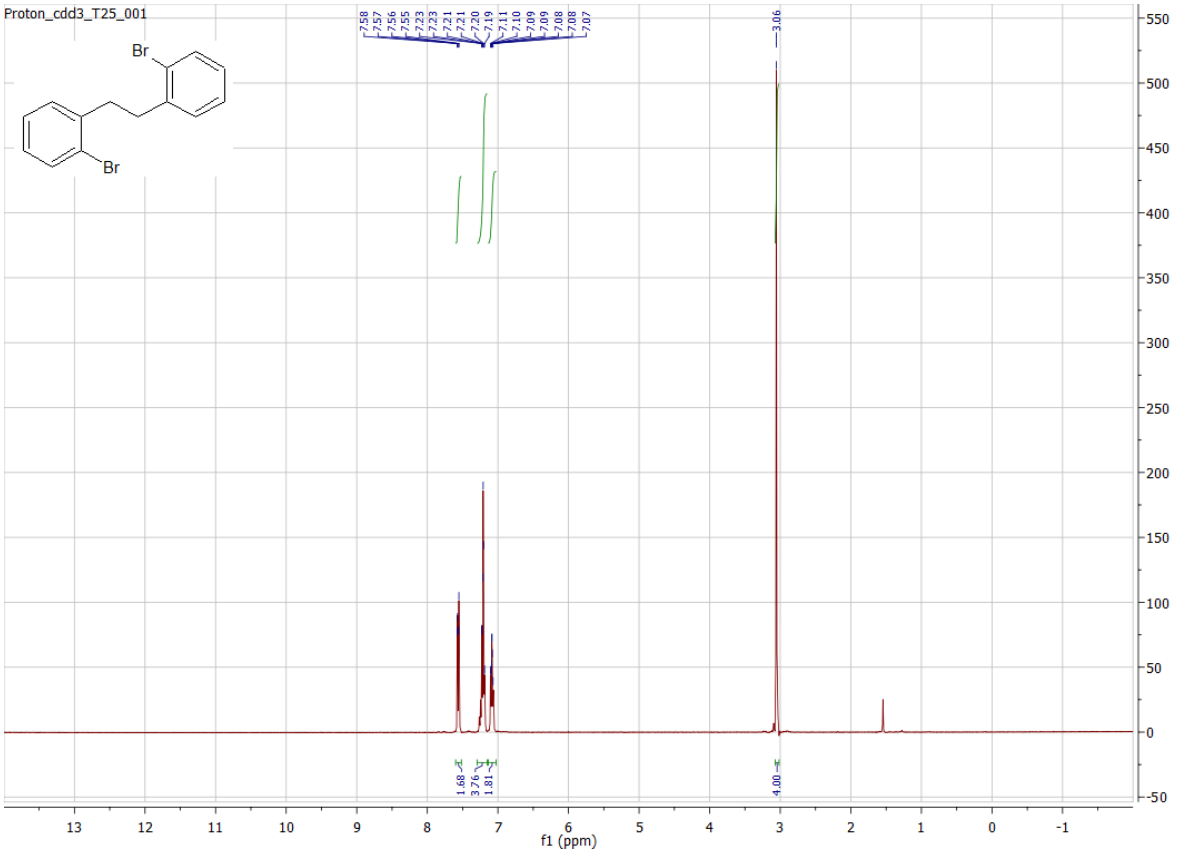

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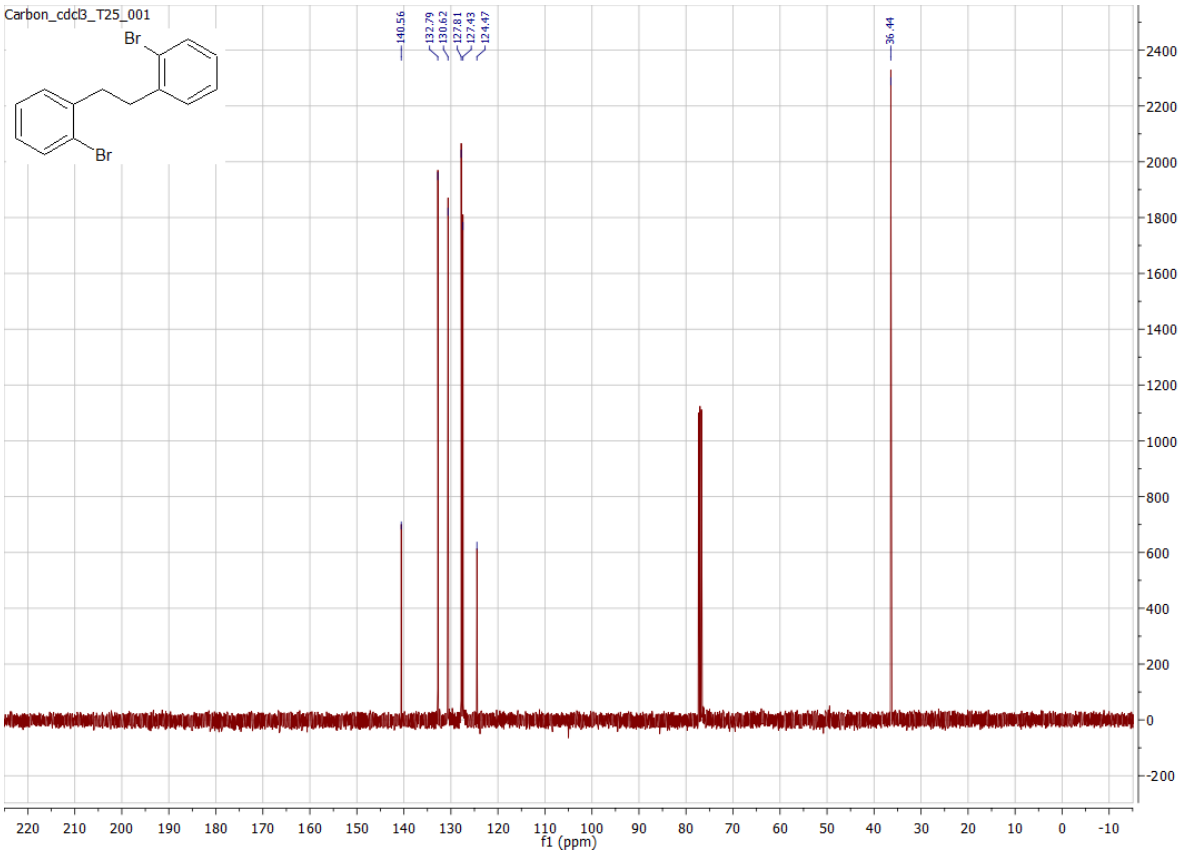


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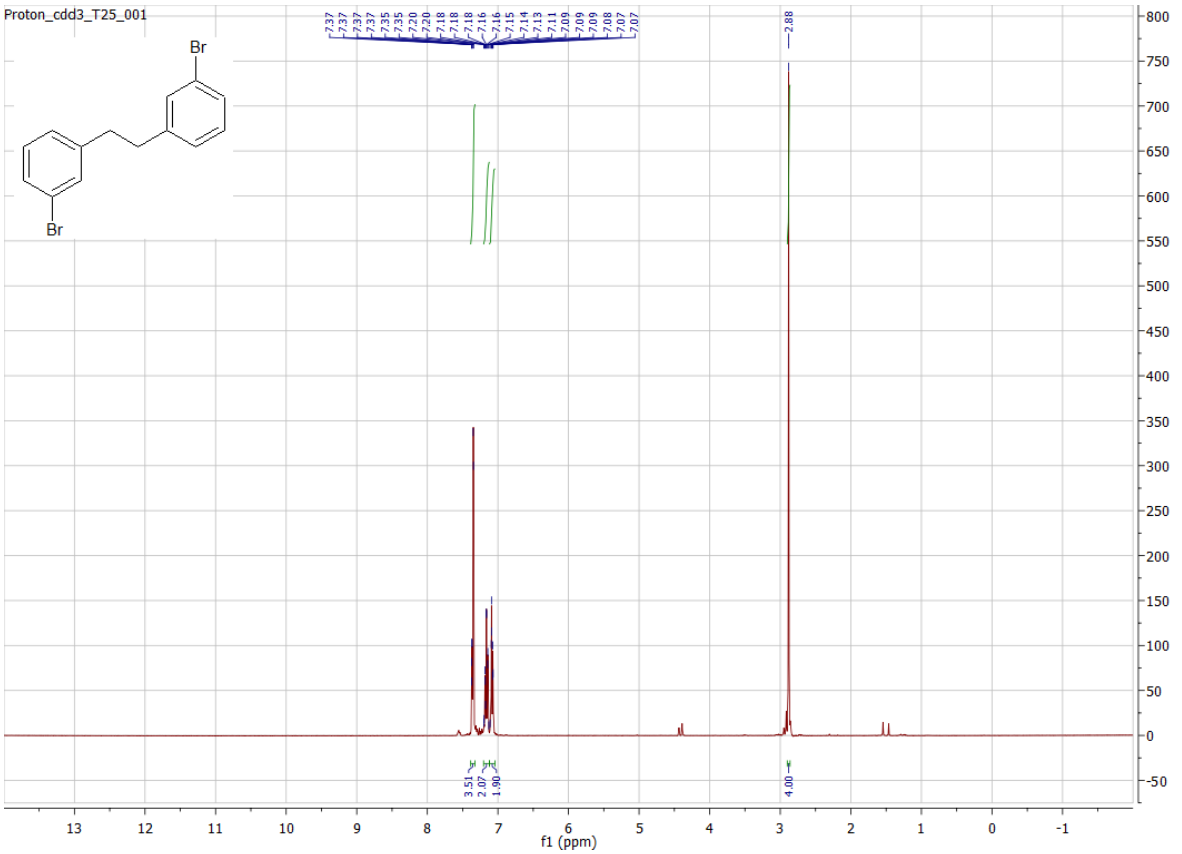

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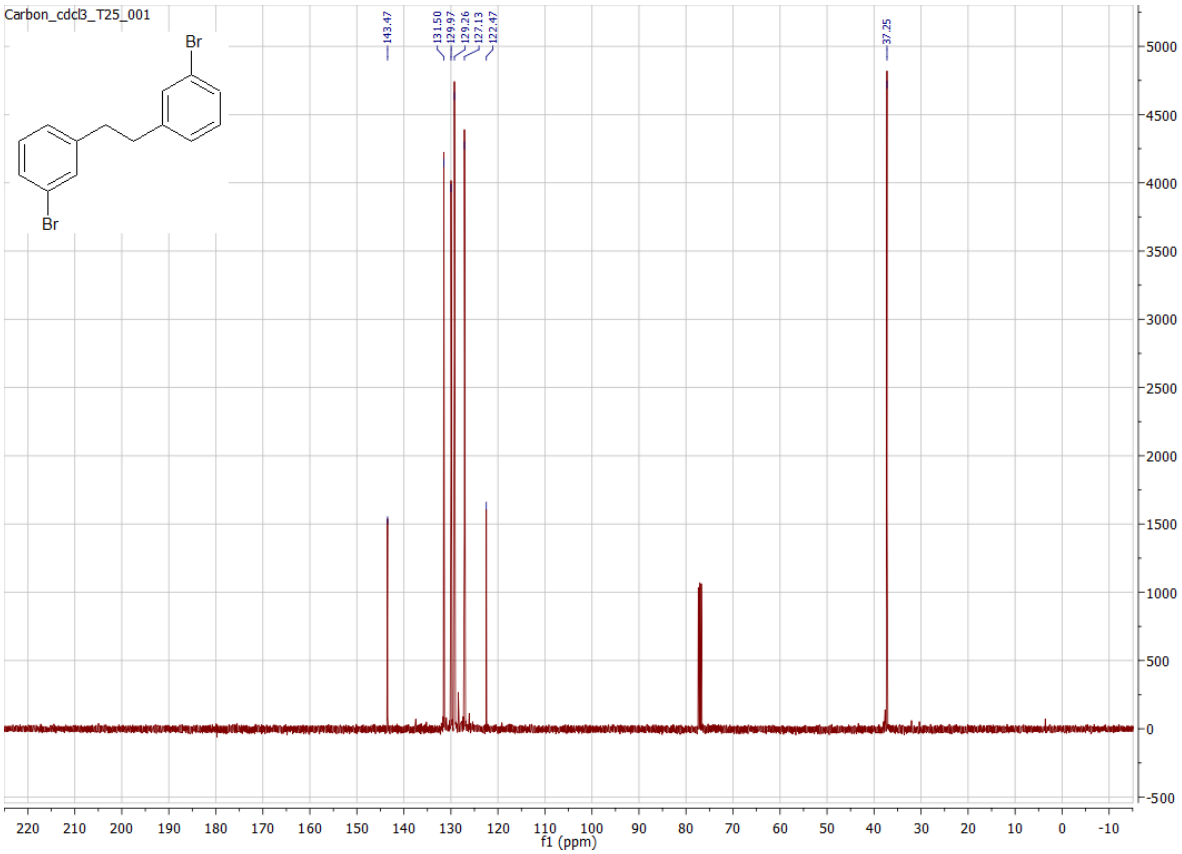


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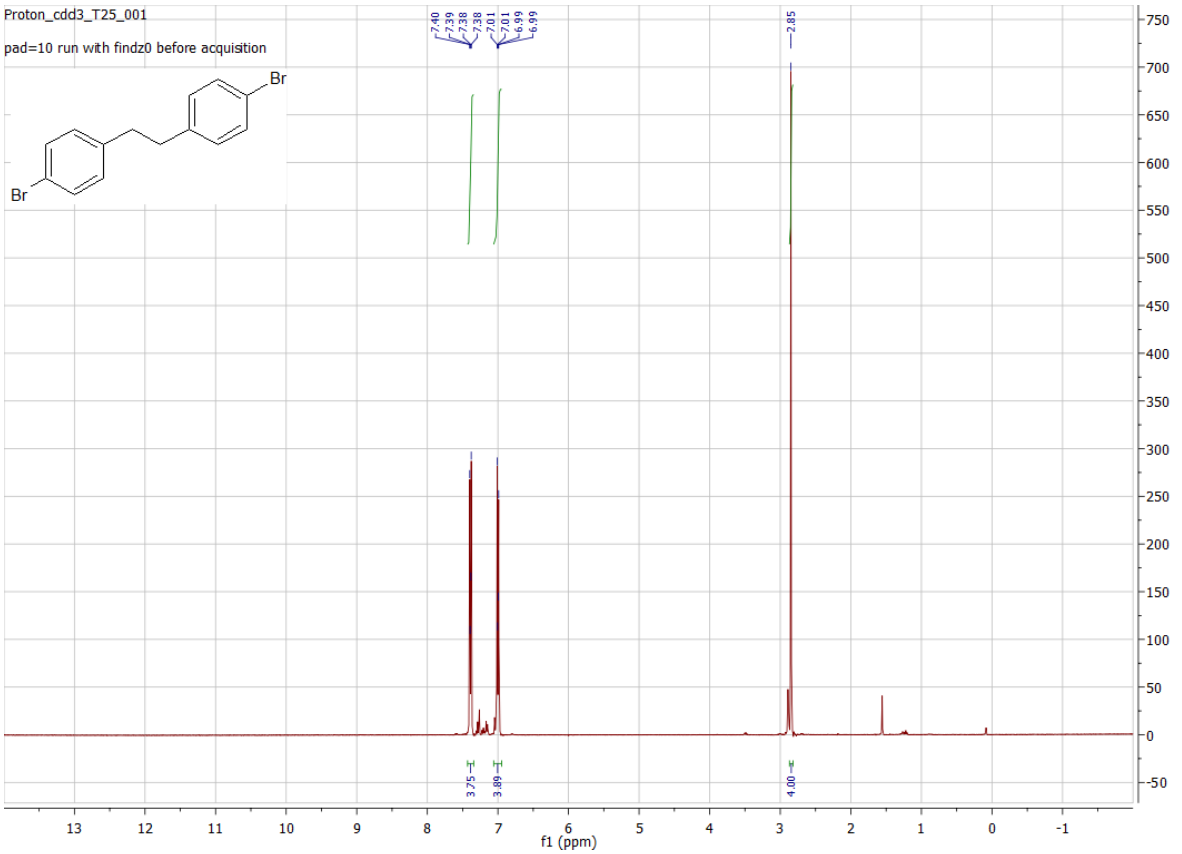

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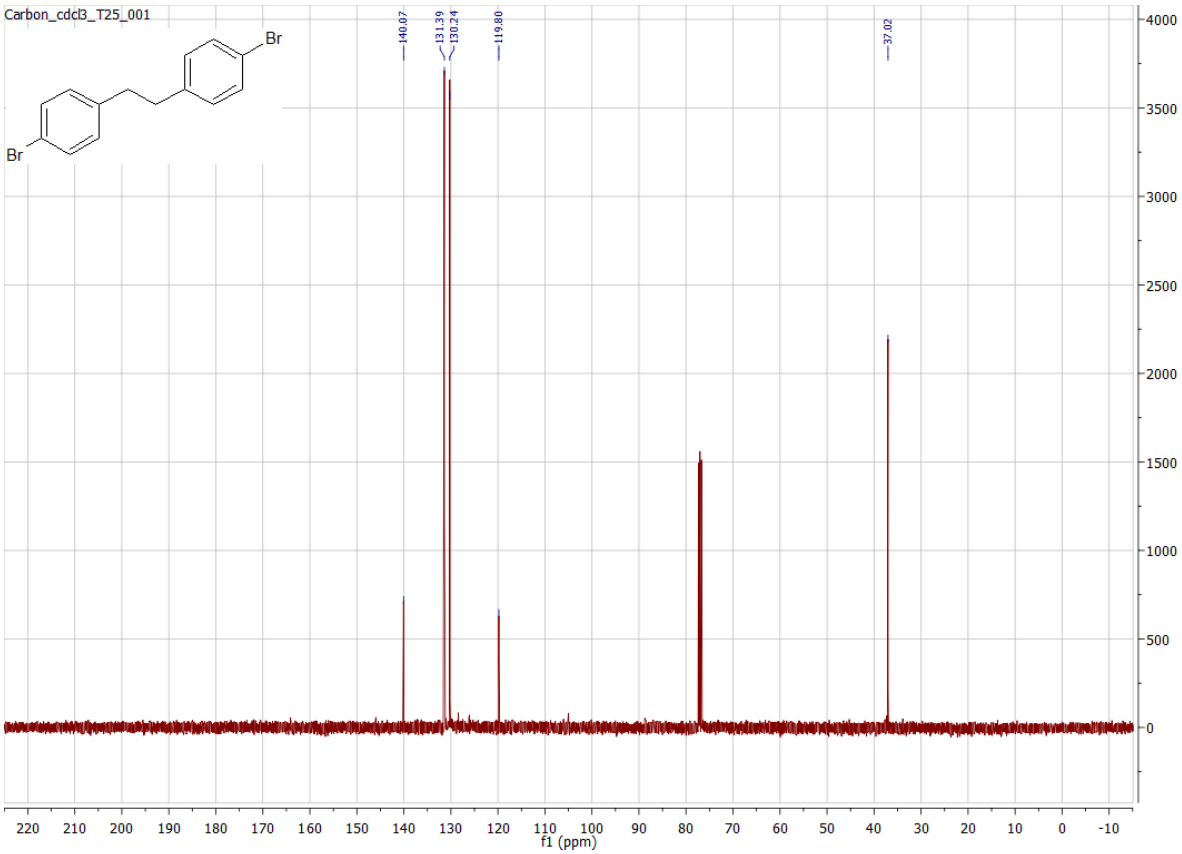


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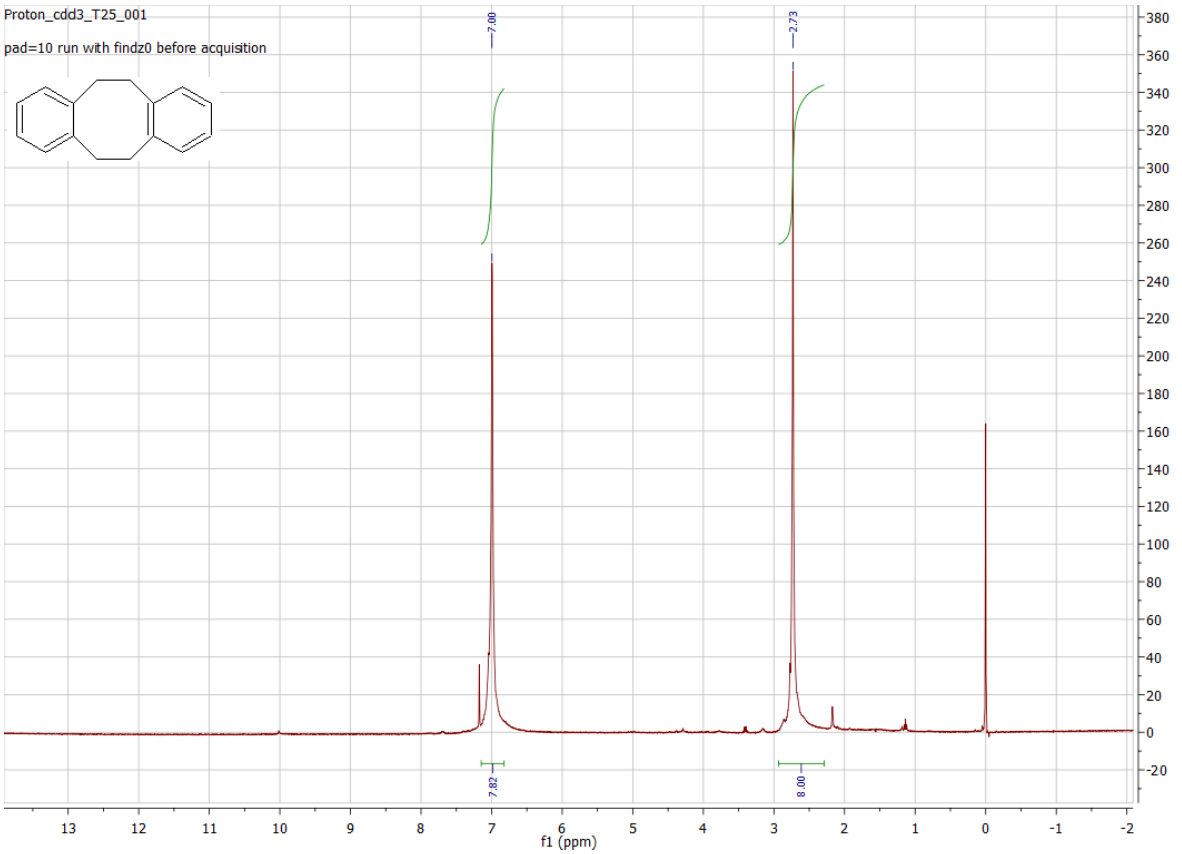

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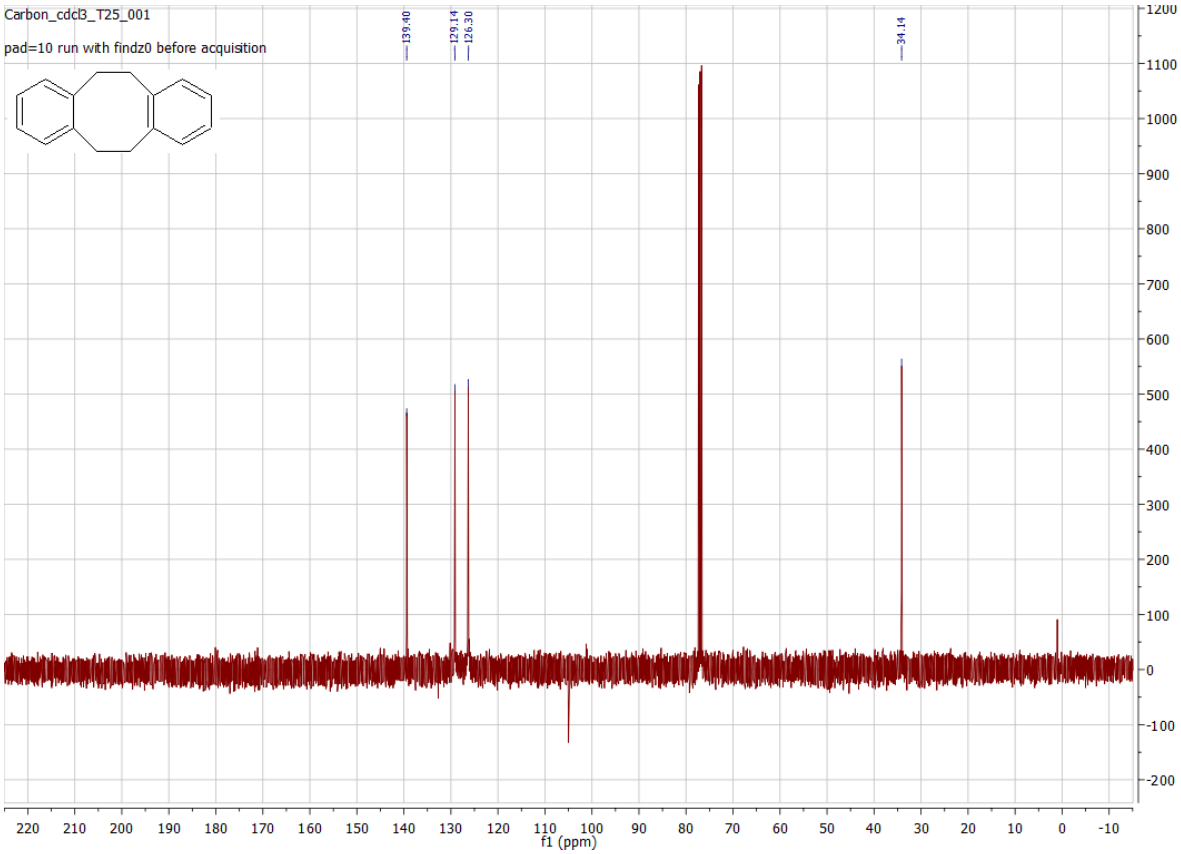


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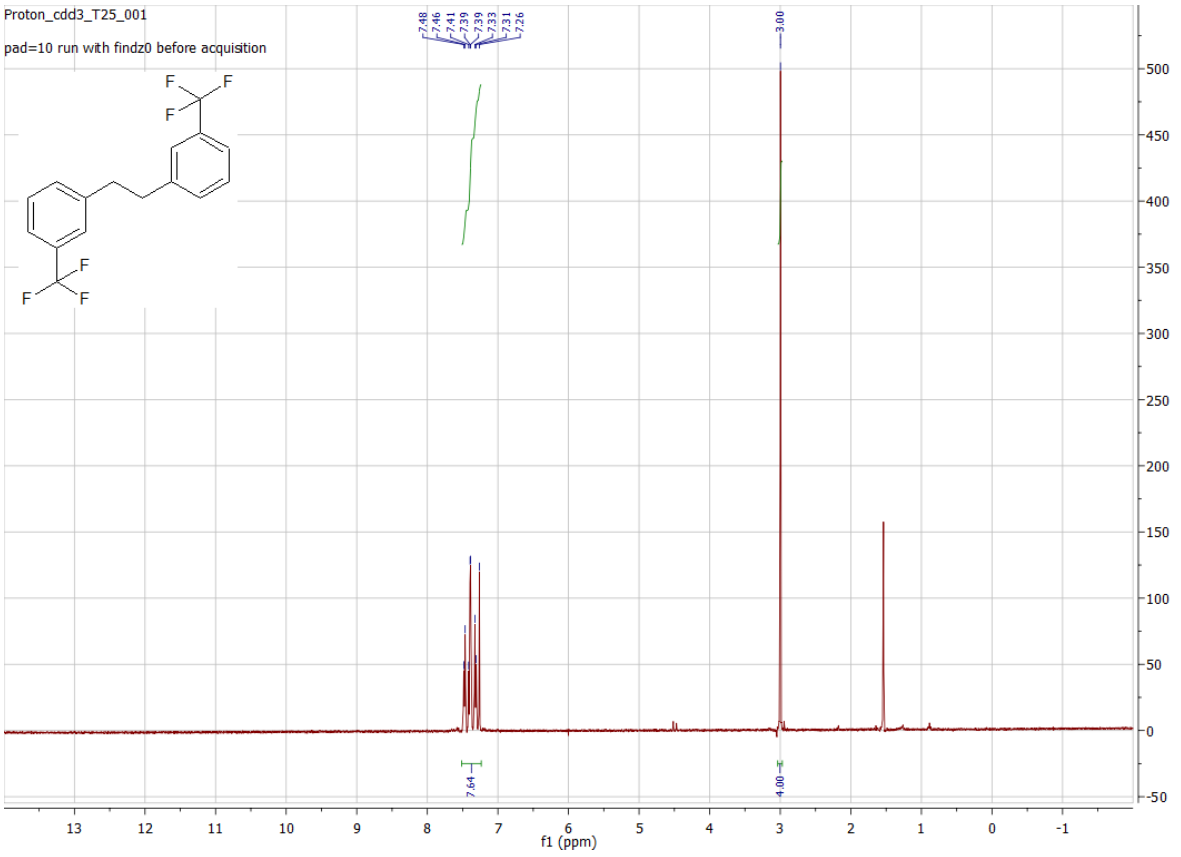

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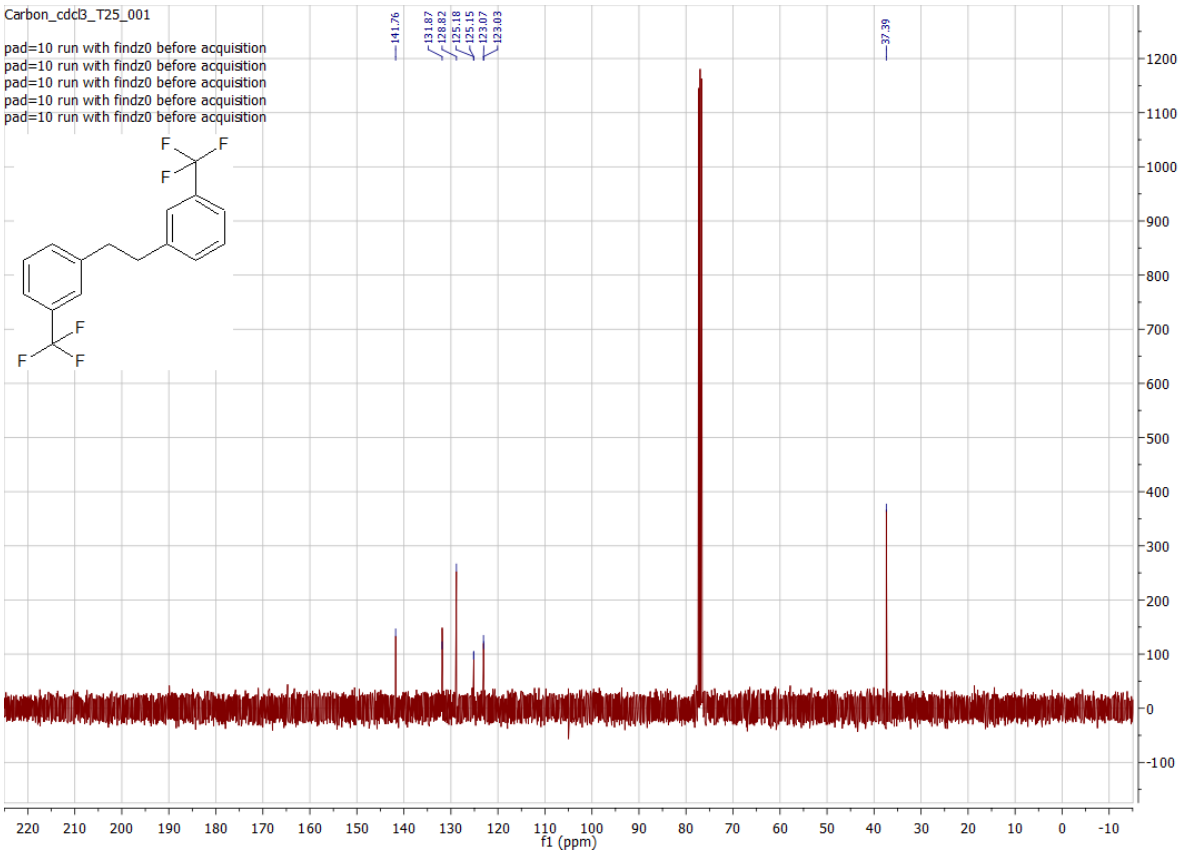


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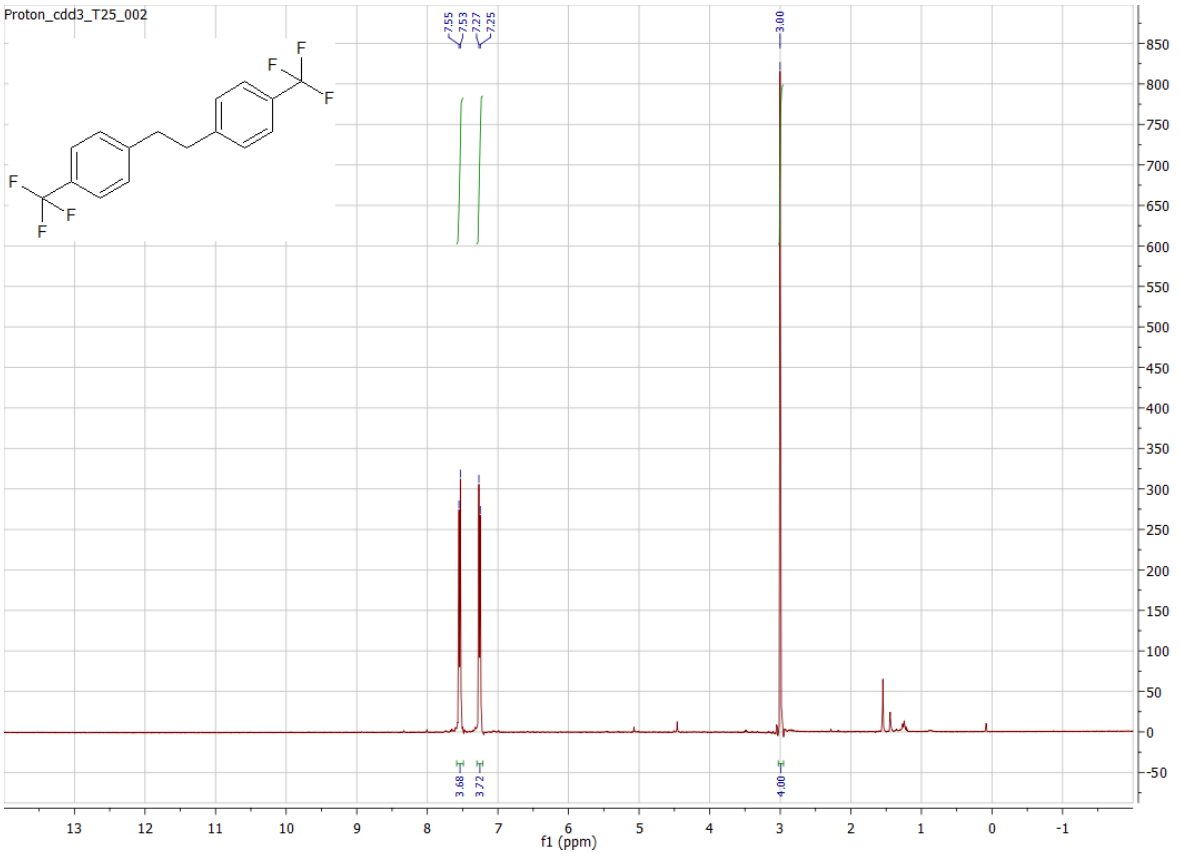

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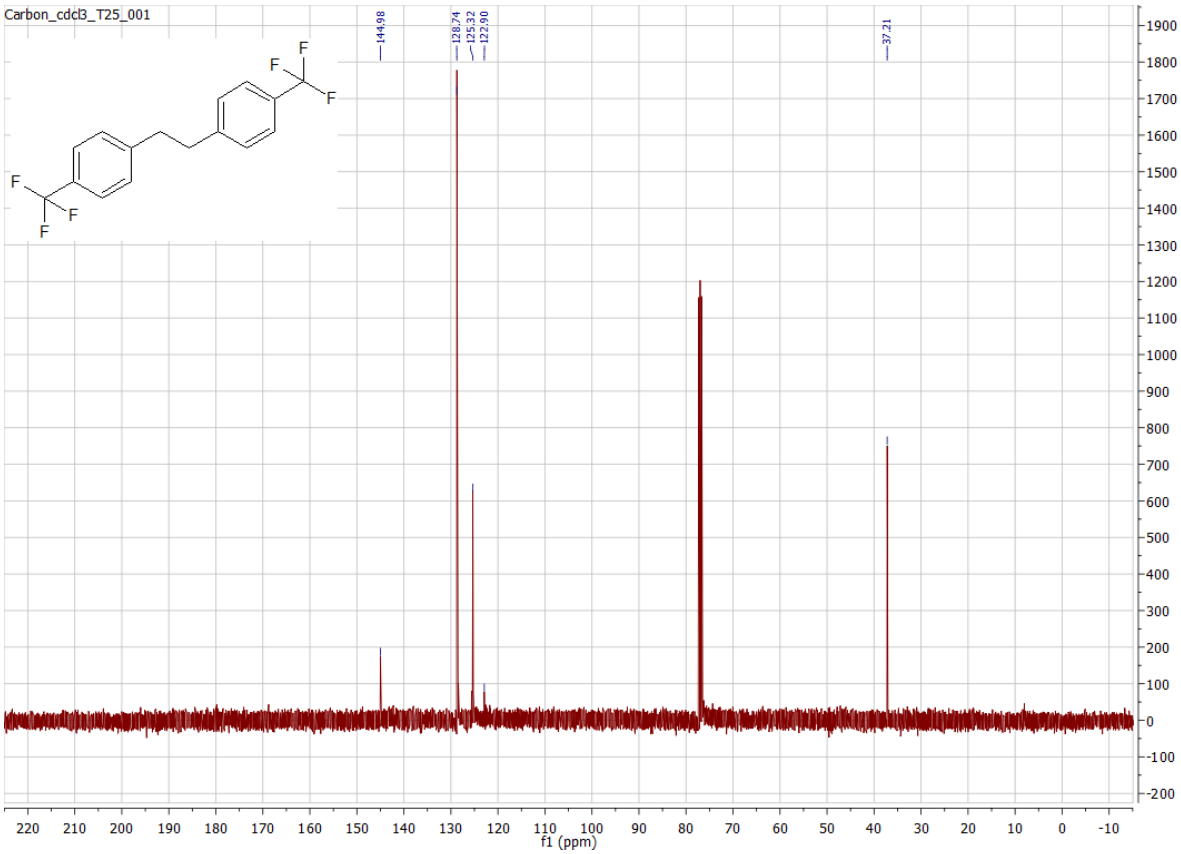


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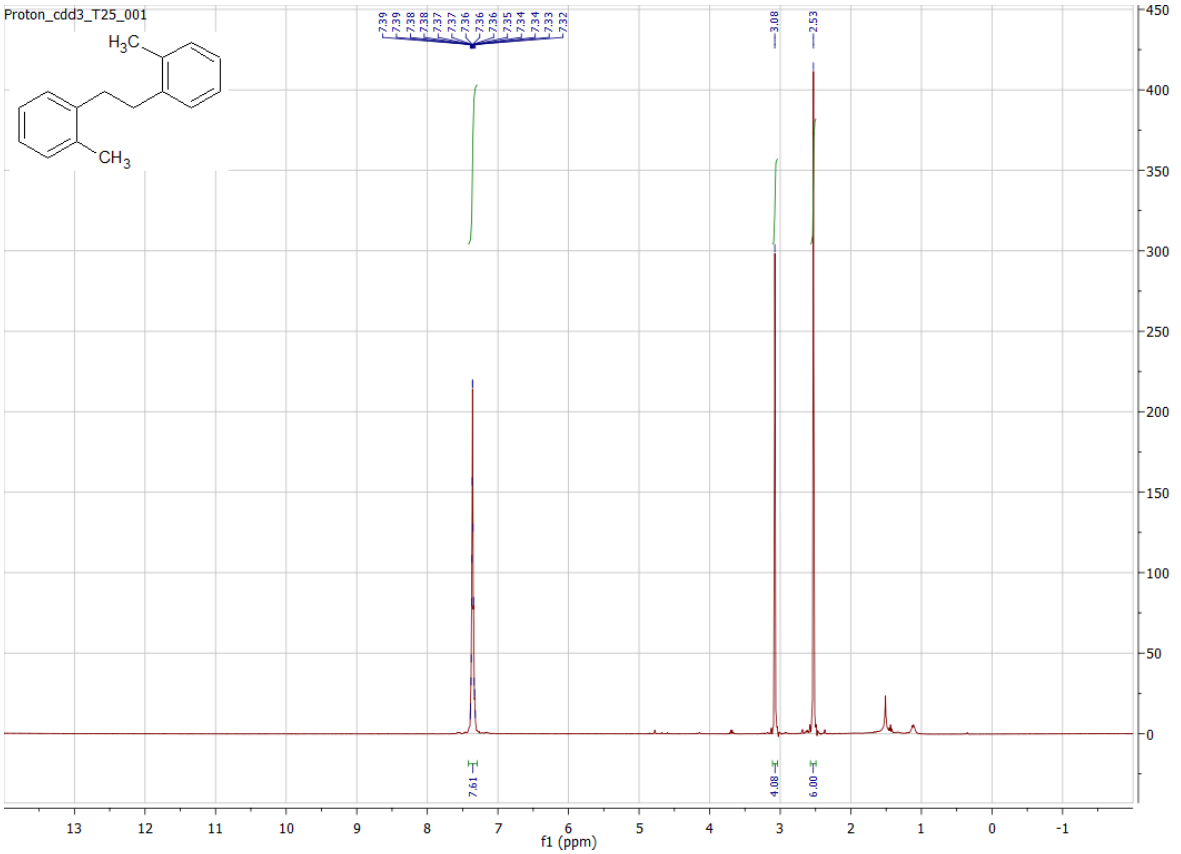

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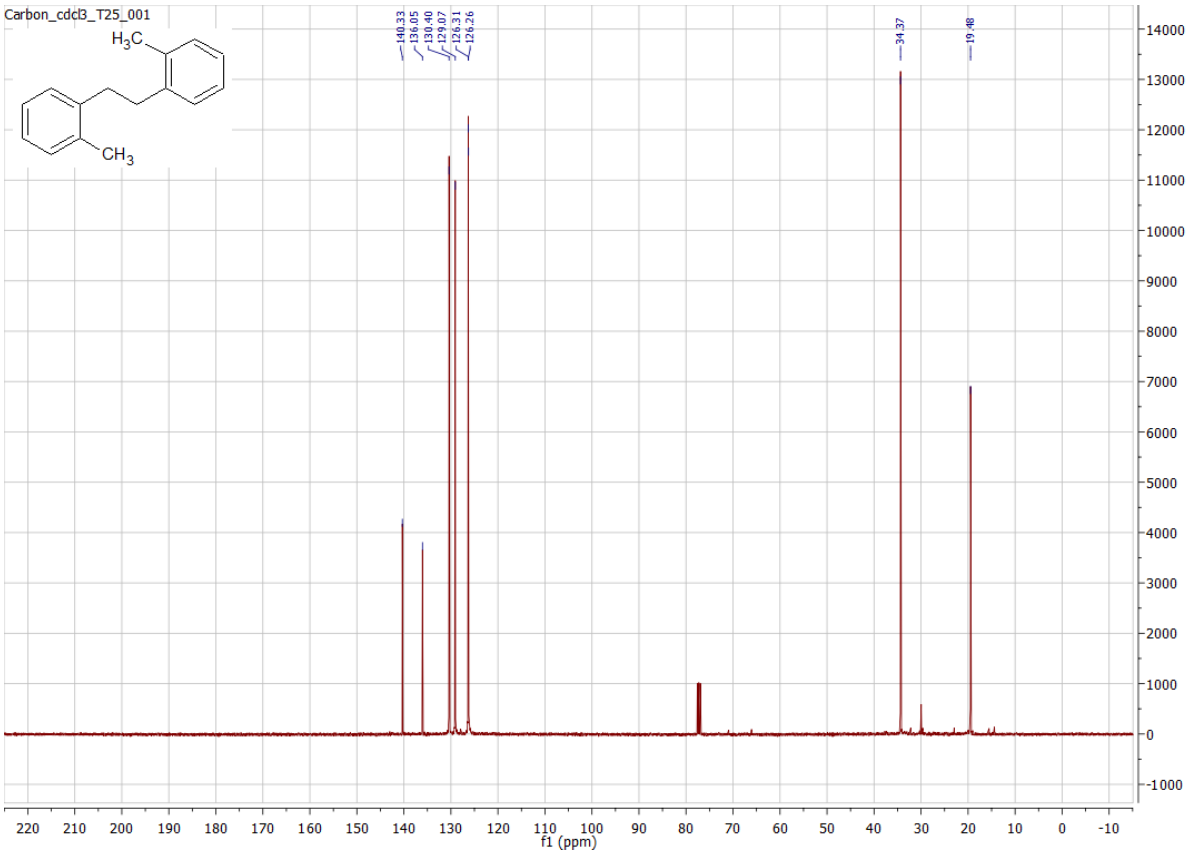


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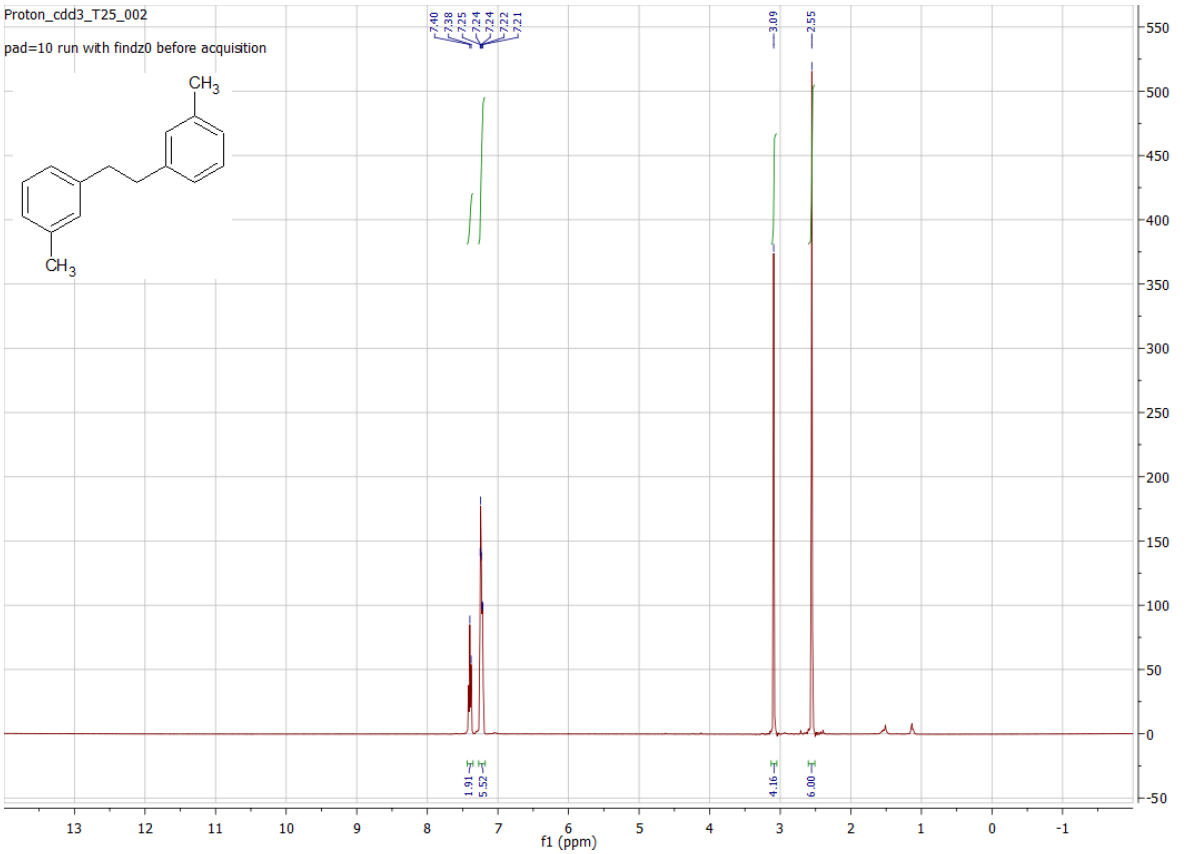

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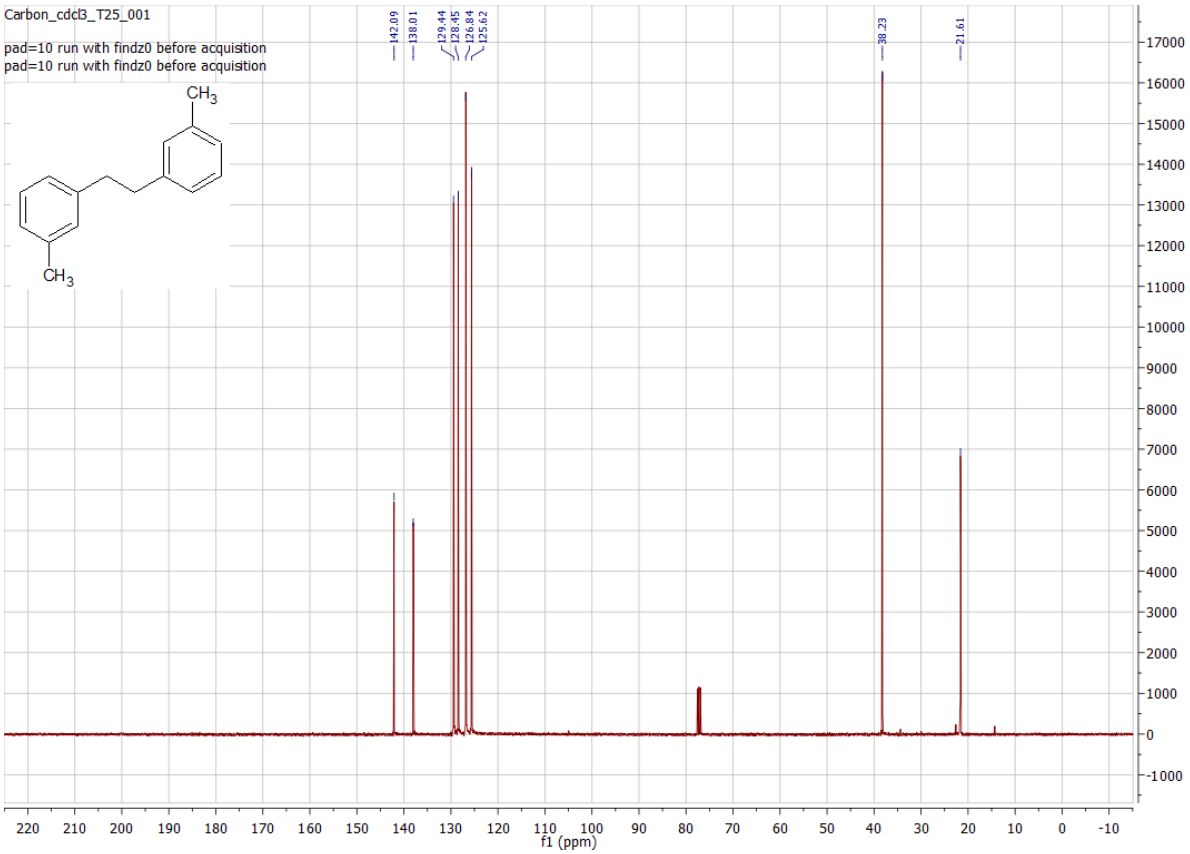


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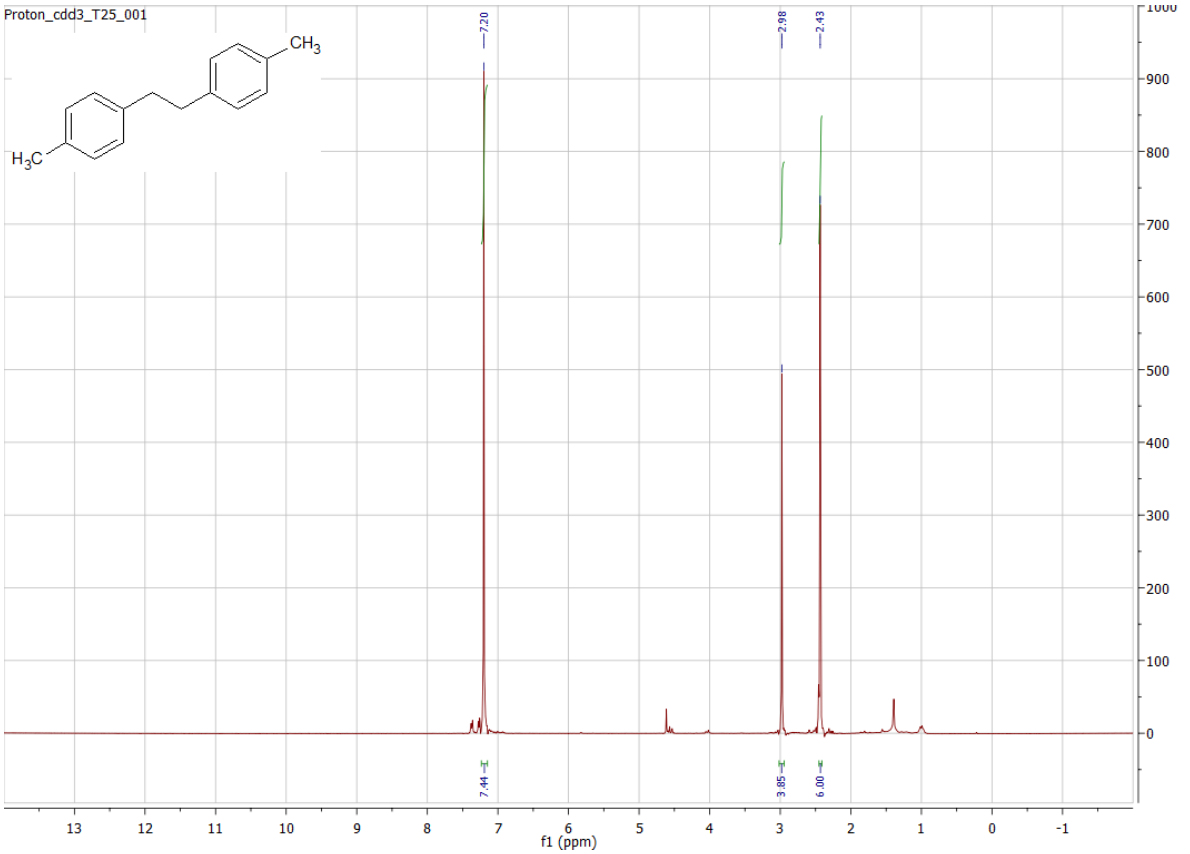

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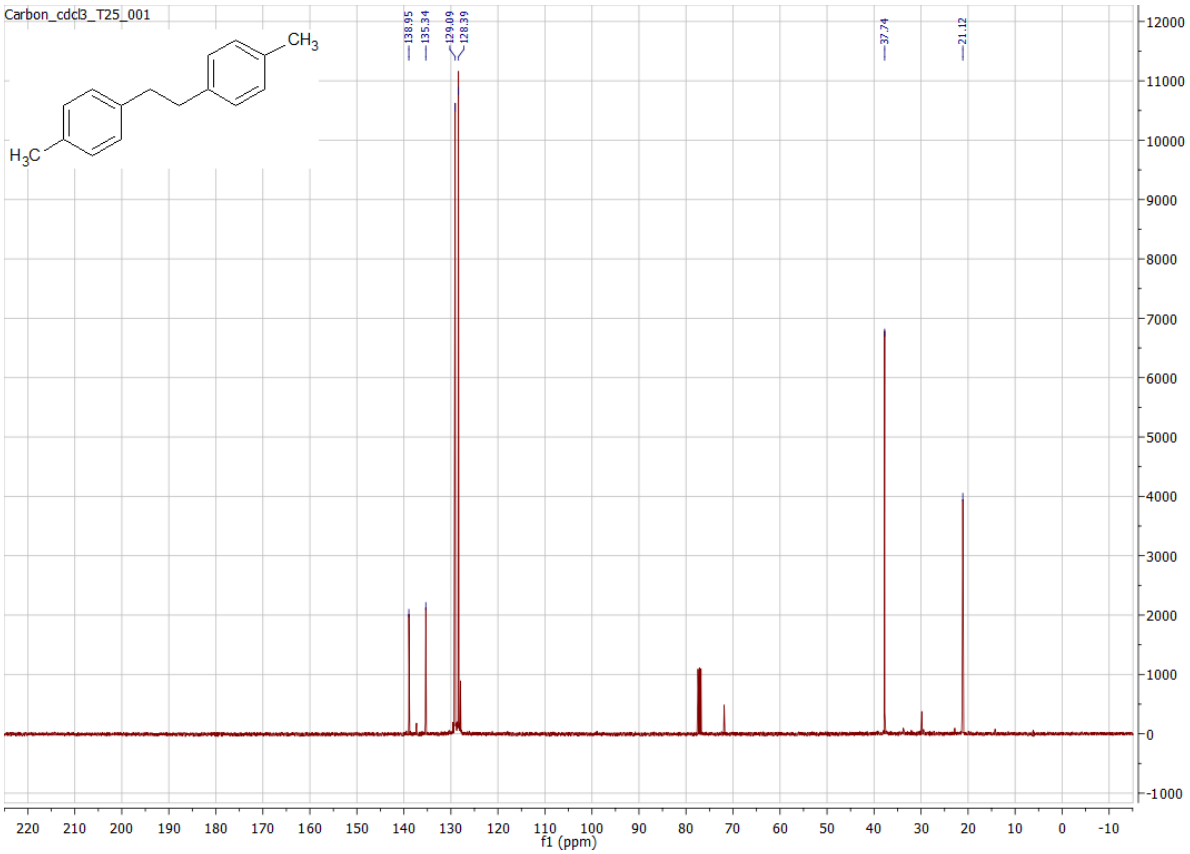


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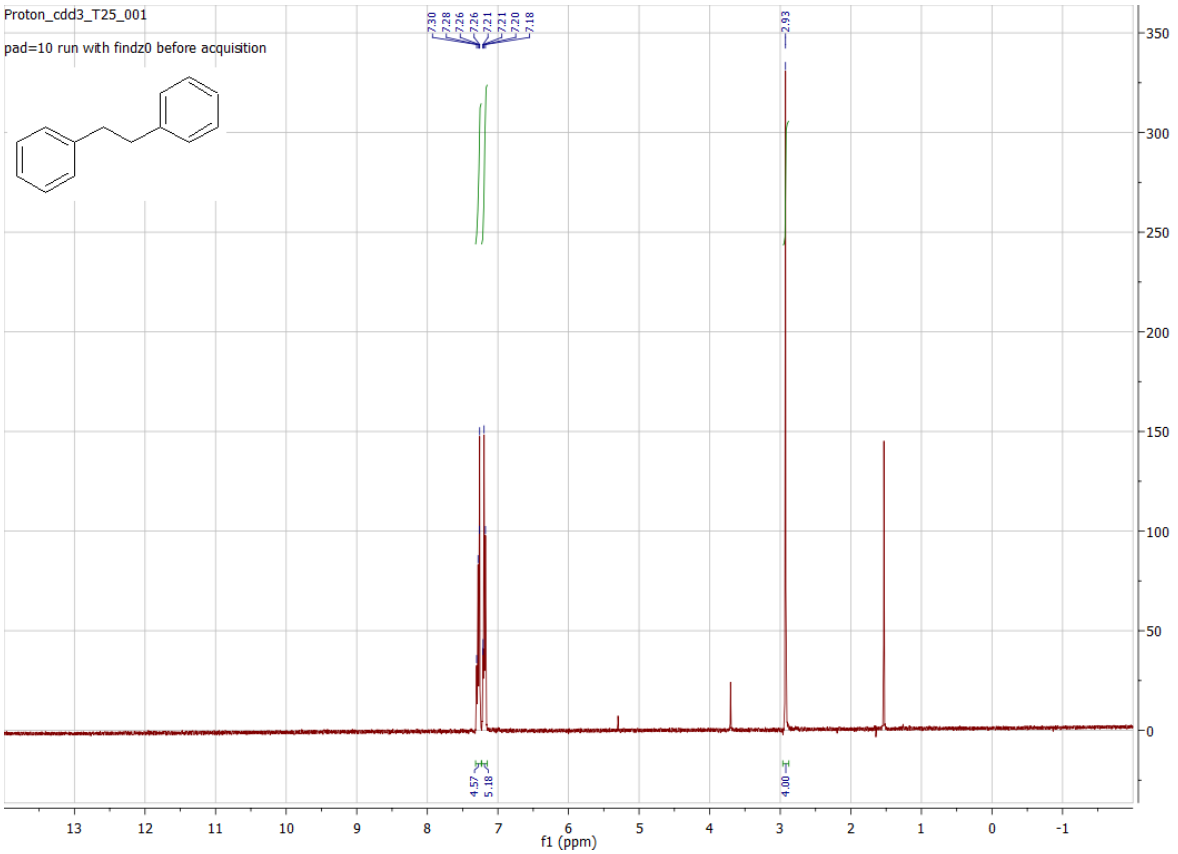

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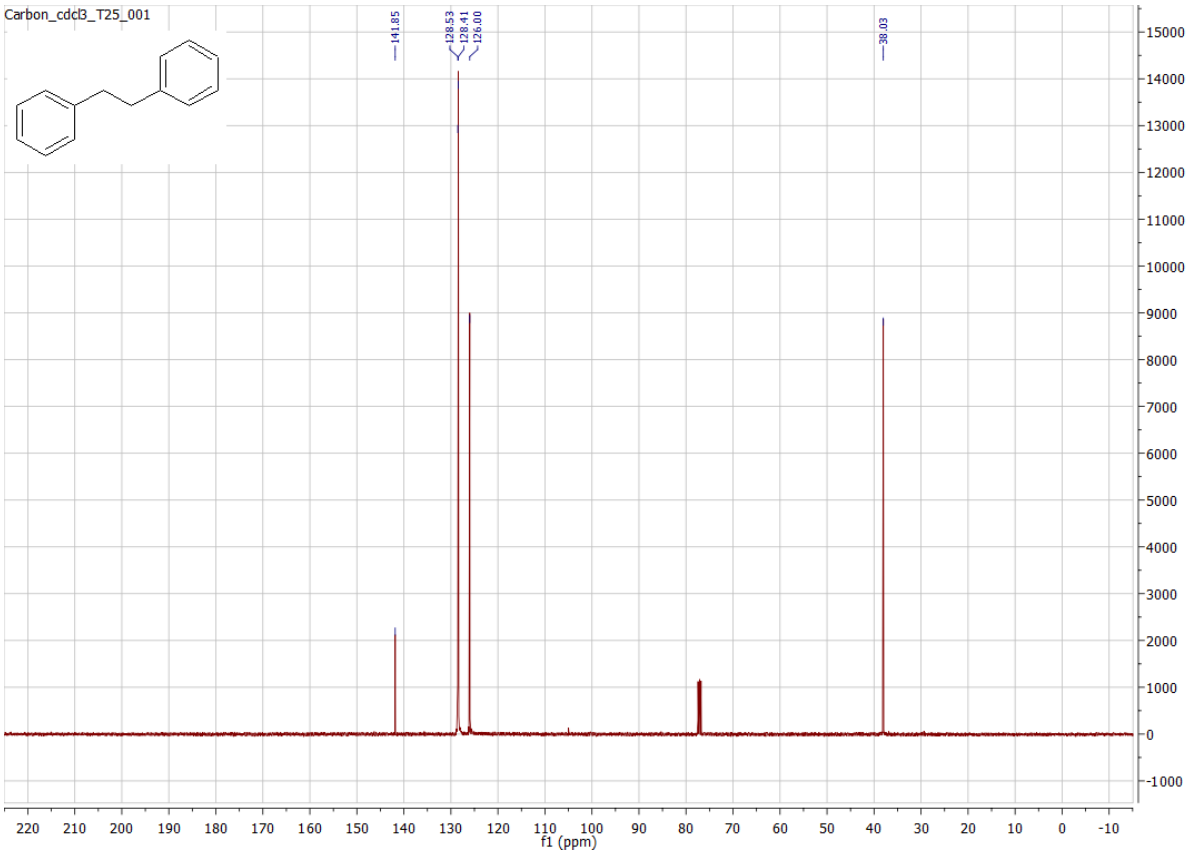

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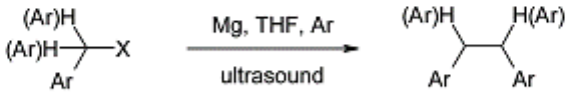
# ULTRASOUND-PROMOTED DIMERIZATION OF BENZYLIC HALIDES

**Olga V. Gozhina, Ivar K. Thomassen, and Tore Lejon**
*Department of Chemistry, University of Tromsø, Tromsø, Norway*

## GRAPHICAL ABSTRACT




X = Br, Cl

14 examples

**Abstract** *Simple and straightforward coupling of benzylic compounds was achieved by sonicating benzylic halides in the presence of magnesium.*

**Keywords** Benzylic halide; coupling; Grignard; ultrasound

## INTRODUCTION

Carbon–carbon-bond forming reactions are important tools in organic synthesis and there are a number of methods available, ranging from simple substitution reactions to more elaborate catalytic ones. In general, it is more complicated with more substituted reacting centers.

When coupling benzylic compounds, methods used include transition-metal-catalyzed coupling of halides[1,2] and oxidative additions.[3] Other methods include single-electron transfer (SET) in the reaction of lithium thiolates with trityl halides, which has been studied in detail.[4] SET is also involved in the chemoselective reductions of vicinal dihalides with magnesium in methanol.[5] However, most couplings of benzylic halides are reductive couplings using organometallic compounds as catalysts. Examples include the dimerization in the presence of vitamin B12 and Ti(III) citrate,[6] electrochemical coupling in lithium perchlorate solution using magnesium electrodes,[7] zinc in aqueous media,[8] ruthenium carbonyls,[9,10] and iron(II) oxalate.[11]

It was therefore surprising when it was discovered that attempted substitution on boronates[12] in some cases led to homocoupling of the halide, if the formation of

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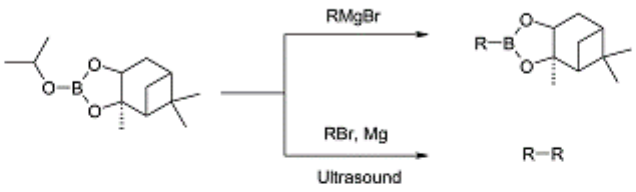



**Scheme 1.** Reaction of Grignard reagent with boronates.

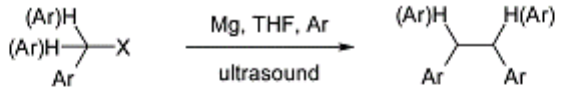
Grignard reagent was performed with ultrasound in a one-pot procedure. This was never observed when utilizing preformed Grignard reagent (Scheme 1).



## RESULTS AND DISCUSSION

The most surprising fact about the coupling reaction was that it was faster than the addition to the boronate, and the scope and limitations of the reaction was therefore investigated. It was soon clear that the reaction did not proceed with alkyl halides or aromatic halides. On the other hand, it worked well with both primary and secondary benzylic bromides, while tertiary benzylic bromides were unreactive (Table 1).

**Table 1.** Coupling of benzylic halides under sonication




| Starting material | Yield (%) |
|---|---|
| 1-α-Bromomethyl-naphtalene | 40 |
| 9-Bromofluorene | 91 |
| Bromo-diphenylmethane | 75 |
| α-Bromotoluene | 23 |
| 4-Bromo-α-bromotoluene | 12[a] |
| 4-Methyl-α-bromotoluene | 48 |
| 2-Methyl-α-bromotoluene | 61 |
| 2-Bromo-α-bromotoluene | 13[a] |
| 3-Bromo-α-bromotoluene | 19[a] |
| 3-Methyl-α-bromotoluene | 31 |
| 3-Trifluoromethyl-α-bromotoluene | 28 |
| 4-Trifluoromethyl-α-bromotoluene | 4[a] |
| 2-Trifluoromethyl-α-bromotoluene | No reaction |
| Triphenylmethylbromide | No reaction |
| 1-α-Chloromethyl naphthalene and 9-Bromofluorene | 82[b] |

[a]Isolated by preparative TLC.
[b]All three possible products formed.

However, isolated yields were often disadvantaged by the fact that the coupled product was difficult to separate from the by-product produced from the protonation of non-coupled Grignard reagent. An experiment was performed with α-chloromethyl naphthalene and 9-bromofluorene to evaluate the importance of the halide. In this case all three possible compounds were formed, which indicates that the structure of the starting material is more important than which halide is employed. Reactivity seems to be influenced by both steric and electronic factors as yields were less when the aromatic moiety was substituted with strongly electron-withdrawing groups, and triphenyl methylbromide did not react at all. Prolonged reaction time did not result in greater yields for any of the substrates.

## EXPERIMENTAL

In a typical experiment, a three-necked flask equipped with an argon inlet, a condenser, and a dropping funnel was charged with magnesium turnings (60 mmol) and 1 or 2 crystals of iodine. A small amount of tetrahydrofuran (THF) was added to cover the magnesium, and a solution of halide (100 mmol) in THF (50 mL) was added dropwise. The reaction was performed in an ultrasound bath, keeping the temperature of the mixture below 30 °C by the occasional addition of ice. After the addition was complete, the reaction mixture was sonicated for 3 h before it was quenched with 5% aqueous hydrochloric acid (50 mL). After separation, the water phase was extracted with diethyl ether (3 × 20 mL). The organic phases were then combined and dried over anhydrous magnesium sulfate, and the solvent was removed under reduced pressure. Column chromatography was performed on silica using pentane to elute any impurities and 5% ethyl acetate in pentane was used to elute the product. All spectroscopic data were in accordance with earlier published data.[13–19]



## ACKNOWLEDGMENT

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