PROPOSED SYNTHETIC APPROACH OF QUATERNARY CARBON VIA BORON MEDIATED TRANSFER

FINAL REPORT

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by

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ADT	2- azido -4,6- dimethoxy -1,3,5- triazine
DI	Deionized
DCM	Dichloromethane
DMF	Dimethylformamide
eq	equivalent
NMR	nuclear magnetic resonance
TBAF	Tetra-n-butylammonium flouride
TLC	Thin-layer chromatography

1. Introduction

One of the most desirable syntheses to organic chemists today is forming a carbon-carbon bond.[1] In the last 30 years, the ability to synthesize carbon-carbon bonds in synthetic organic chemistry has improved, which showed a vast improvement in natural product synthesis.[2] With the help of various chiral auxiliaries, reagents, and catalysts available nowadays, the formation of even tertiary stereocenters is made more accessible than before. However, forming quaternary carbons, which are carbons with 4 bonds to other carbons, is still a big hurdle, making their syntheses more challenging. This predicament means that most ways to show new or more manageable pathways toward quaternary carbon synthesis are valuable and desirable to chemists. [3] That is the reason why this project wants to find a way to synthesize carbons with a quaternary stereocenter in an accessible way that can be reproduced easily, by using the functionality of a alpha carbon on a carbonyl group with the formation of an boron enolate intermediate followed by an addition of an electrophile to result in a quaternary carbon.

1.1 Quaternary Carbons and their typical syntheses

The importance of the carbon-carbon bond does not only show up in synthetic organic chemistry. It is also valuable for other chemical branches, such as the pharmaceutical industry. Carbon has a characteristic called catenation, which means it can form long bonds with itself, and carbon bonds are strong and stable, making carbon-based molecules stable. This characteristic also explains why big molecules of life are formed on a carbon-based structure; for example, the DNA in the human body is carbon-bond-based. Quaternary carbons can be found in critical medical compounds like morphine or cortisone, both essential in the pharmaceutical industry[4]. Figures **1** and **2** depict the structures of morphine and cortisone. The quaternary carbons are highlighted to show their importance in the structure. So, making their synthesis more available is a big help for the pharmaceutical industry,

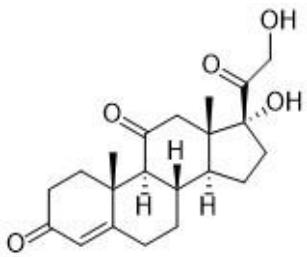

Figure 1: Structure of cortisone

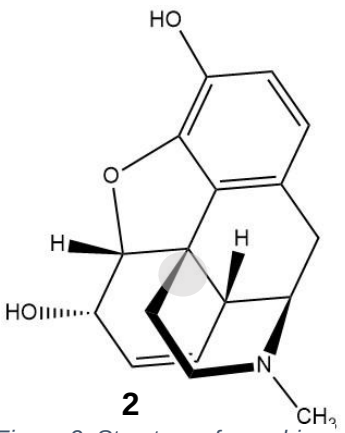

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Figure 2: Structure of morphine

and it will help people who need this specific pain medication because it makes it available more efficiently, which could also mean a deduction in price.

Bordwell and Clemens proposed one way of synthesizing quaternary carbons in 1982. They investigated the synthesis of quaternary carbons, particularly interested in synthesizing quaternary aldehydes through permanganate oxidation of nitro compounds. According to their research, a tertiary nitro group reacts the easiest in an electron-transfer substitution, and with this knowledge, they were able to produce quaternary carbon-carbon bonds from tertiary nitro compounds. For their synthetic approach, the first step was to convert nitromethane into its salt. This part was done by using an excess amount of sodium hydride. However, this only worked when used with DMSO as the solvent; the nitromethane did not show the same reaction when they used DMF. Bordwell and Clemens explained this by saying that a catalytic amount of dimsyl sodium was formed, which only happens when the reaction is done with DMSO, not when reacting with DMF. These results meant a limit on which groups could be used for the tertiary nitro group. They went with a CH2NO2 group that was included in the molecule. In their first tries at the synthesis, they worked with the Nef reaction, but the results were unsatisfactory, so they changed their approach to potassium permanganate. Bordwell and Clemens modified a procedure for the usage of potassium permanganate to suit their synthesis, and with this approach, they got good results and were working towards a new way of synthesizing quaternary compounds.[5]

1.2 Diazo compounds

A diazo compound was chosen as a starting material. A diazo group is a group of two bonded nitrogens at the terminal position in a compound. This group can be depicted in literature in two ways, which can be seen in Figure 3. The negative charge is either at the carbon bonded to the diazo group or at one of the nitrogens in the group, while the positive charge is on the other nitrogen in the group. The structure of the diazo group either shows two double bonds, one between the bonded carbon and nitrogen and the other between the two nitrogen atoms, or the structure shows a triple bond between the nitrogens of the diazo group.

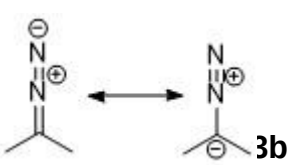


Figure 3: Structure of diazo group depiction

Diazo compounds are useful building blocks in organic synthesis since they can be the precursor to carbenes for example.[6] A carbene is a molecule which has a neutral charge but has a valence of two and two unshared valence electrons. The compound is in theory charged but neutral[7].

Diazo groups can also be found in compounds with antimicrobial and antitumor characteristics. If the diazo compound is stabilized, it shows excellent compatibility with living systems and shows potential for use in the field of chemical biology[8]. An example of a useful natural compound in which a diazo group occurs would be the group of kanamycin, which is a group of antibiotics derived from a culture broth of

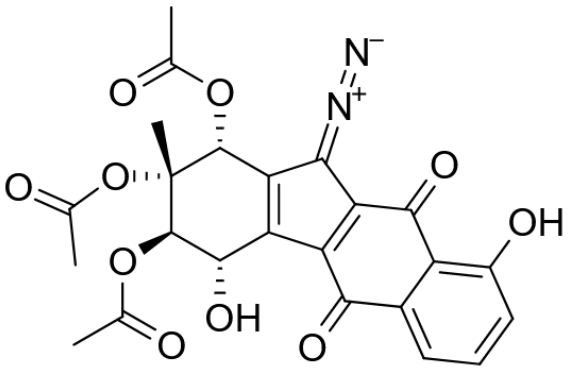


Figure 4: Structure of Kinamycin a

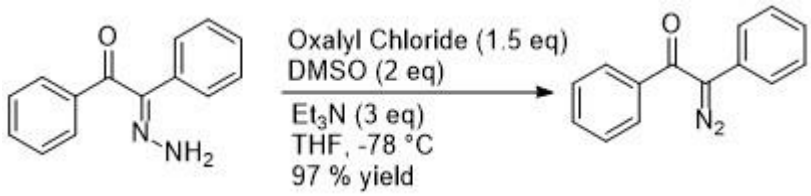
streptomyces murayamaensis sp. nov. Hata et Ohtani by Omura in 1970. This compound was thought to have a cyanamide group instead of a diazo group, but it was later found out that it was, in fact, a diazo moiety[9]. Another group that has naturally diazo groups in its structure is the group of lomaivicitins. They are analogs from 9- diazafluorene and show strong characteristics in terms of anticancer functionality through their ability to split DNA. The anticancer ability of some lomaivicitins is 100 times more potent than that of kinamycins. There are also natural amino acids, which include a diazo group, the most notable being azaserine, which is remarkably similar to glutamine [10].

Diazo groups, in contrast to their very popular relative in chemical biology, the azido group, are smaller and have a broader range in reactivity. Von Pechmann discovered the simplest form of a diazo group in 1894, and this compound is called diazomethane. Like most diazo alkanes, diazomethane is highly toxic and can react with an explosion if handled without care.

1.3 Diazo compound syntheses

The synthesis of a diazo compound can be achieved in multiple ways. With the use of a transfer agent onto an active methylene or methine compounds or through the synthesis of hydrazones by dehydrogenation[6].

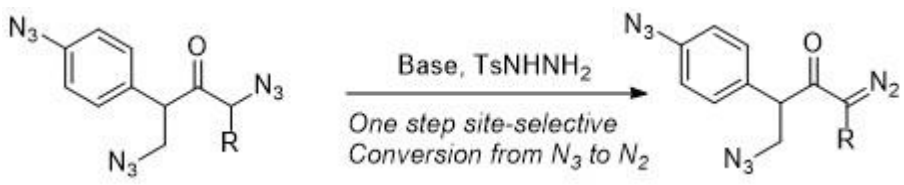
An example of a diazo preparation through dehydrogenation of hydrazones was done by Javed and Brewer. In their synthesis "activated" DMSO was used to dehydrogenate the hydrazone compound, instead of the more common but also more toxic heavy-metal salts, like mercury (II) oxide or lead (IV) acetate. With their alternative of using DMSO the risk of a problematic and potentially hazardous purification as well as isolation process can be reduced. For their approach the isolation of the diazo compound can be easily achieved by a simple filtration of the reaction. They added benzil monohydrazone **5** in CH_2Cl_2 with 2.1 eq of triethylamine



Scheme 1: Dehydrogenation of benzil monohydrazone to 2 - diazo- 1, 2 - diphenylethanone

to a solution cooled down to – 78 °C of chlorodimethylsulfonium. After the workup for this reaction which was an extraction they resulted in 2- diazo -1,2- diphenylethanone **6** with a very high yield of over 90 percent. This yield was determined by a gas evolution measurement. Another way Javed and Brewer supported the high yield claim was to subject the products of the reaction to an esterification with excess benzoic acid which led to good yields for benzoate esters. [11].

A different way of preparation of a diazo compound was published in 2018. In this

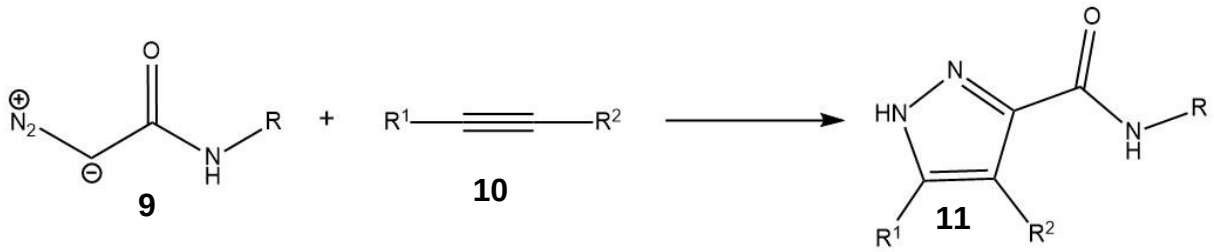


Scheme 2: selective conversion of azido group to diazo compound:

paper it is reported that with β eliminiation in basic conditions the decomposition of sulfonyl hydrazones can be promoted and produce a diazo group in a one step synthesis. They selected DMSO as the solvent, because of its polarity and aproic character, the formation of sulfonyl hydrazones before any degradation or

polymerization happens. DMSO was also selected because it would work at a temperature where the unstable imino carbonyl intermediates would not decompose. In their first try they used DBU which only yielded in a trace amount oof the desired diazo product. When using alkoxides the yield jumped to 56 %. Through more trials which included using weaker bases in the second step they concluded that using pyrrolidine gave the best yield with 84 %. TBAF was used with pyrrolidine in combination specifically for amidines since without the TBAF the amines and inorganic bases took a longer time to react as well as not reacting without heating. While testing the same reaction with ketones the previously successful combination of TBAF and pyrrolidine only yielded low percentages and did not show the same success as with amidines. The research paper did not include less reactive groups on the alpha carbon such as aryl or other unreactive alkyl groups. [12]

One of the most common reactions a diazo group is utilized in is the 1,3 dipolar addition. One example was shown by Gold, Aronoff, and Raines in 2016. They



Scheme 3: Pyrazole product after 1,3 dipolar cycloaddition with diazacetamide

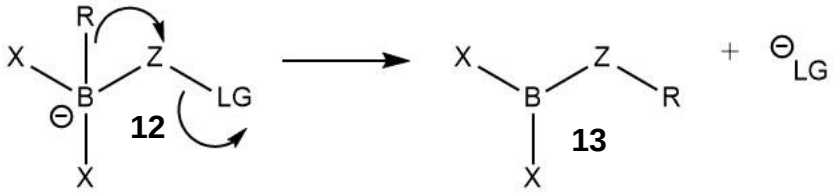
reacted diazo acetamide with an alkyne which formed a pyrazole product. In their research they found out that, cycloadditions of diazo compounds have a character that gives them an advantage which is that their decreased distortion energy and increased interaction energy. This is mostly because of the high nucleophilic character of the diazo group, the nucleophilic character also makes the 1,3 cycloaddition with diazo group react faster than with for example an azido group.. Gold, Aronoff and Raines believe that to achieve a high and selective reactivity with 1,3 dipolar additions it is important for both reaction partners to have a proper pairing of electrons. [13].

1.4 Use of boron in organic chemistry

Boron is usually used in the familiar reactions of hydroborations[14] and Suzuki coupling[15]. While the Suzuki coupling does result in a carbon carbon bond, it does so by using an organometallic catalyst[15] and the boron is not directly involved in forming

said bond. For this project, the methods looked at were those where the boron acts as a mediator to form the carbon carbon bond.

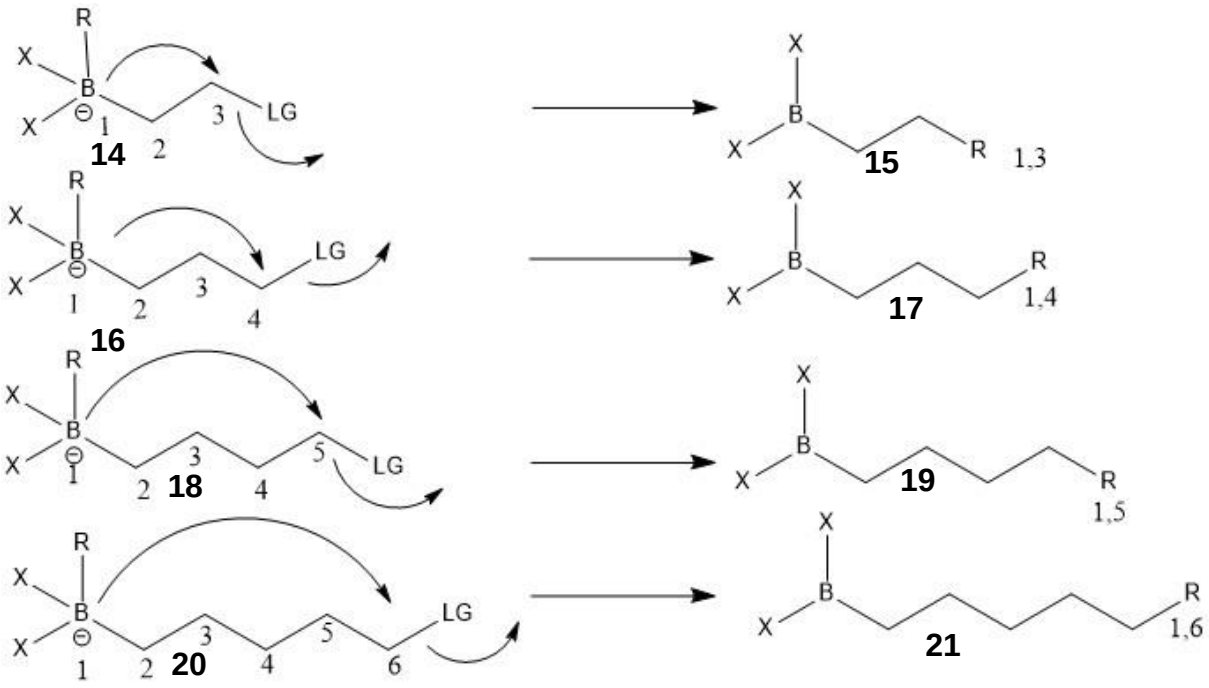
The use of boron as a mediator to form a new carbon-carbon bond have been investigated for over 40 years. The transfer happens when a electronegative boron center transfers an appendage that contains a carbon to an electrophilic new atom.



Scheme 4: Typical depiction of a 1,2 boron mediated transfer

The ways that boron is used as a mediator to move a nucleophilic group to an electrophilic carbon center can be classified by counting the number of steps it has to move starting from the boron ending at the carbon center that the boron appendage gets transferred to. [16].

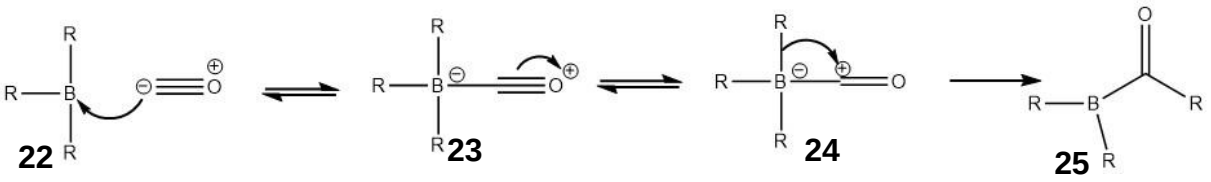
In the scheme above R is the moved boron appendage from **12** that contains a carbon, LG is the leaving group, Z is the electrophilic new atom and X is any not included group. In this scheme the boron atom would be labeled one, the Z atom would be labelled as 2 making it a boron mediated 1,2 transfer. These transfers can be classified from 1,2 boron mediated transfer all the way through 1,6 boron



Scheme 5: Examples of different types of boron mediated transfers

mediated transfers with 1,2 being the most common among them[16] and the one of interest for this specific project.

An early example of a 1,2-boron mediated transfer was a carbonylation of trialkyl boranes done by Hillman[17]



Scheme 6: Hillmans carbonylation of trialkylboranes

A trialkyl borane **22** reacts with carbon monoxide and forms **23**. This molecule **23** is in equilibrium with the boronate complex **24**. Because this boronate complex **24** is formed the carbon becomes positively charged and one of the R groups is nucleophilic, which are both properties necessary in order to achieve a migration of the boron appendage. Since both characteristics are now present the R group migrates to the positively charged carbon and the final borane product **25** is formed. Hillmans study was about forming trialkylboranes in which he uses three 1,2 boron mediated transfers in a row the one showed in scheme 6 being the first one of the three reacted in water and ethanol. The second migration yields an epoxide intermediat and in the third reaction this intermediate trimerizes after the carbon-oxygen bond is cleaved and the final product is a boronic anhydride[17]. Hillmans approach ad usage of three consecutive 1,2 boron mediated transfers suggest that the usage of boron as transfer agent is efficient and it shows that the formation of a new carbon carbon bond via boron mediated transfer is an energetically favored method.

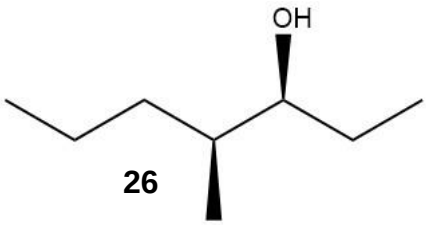
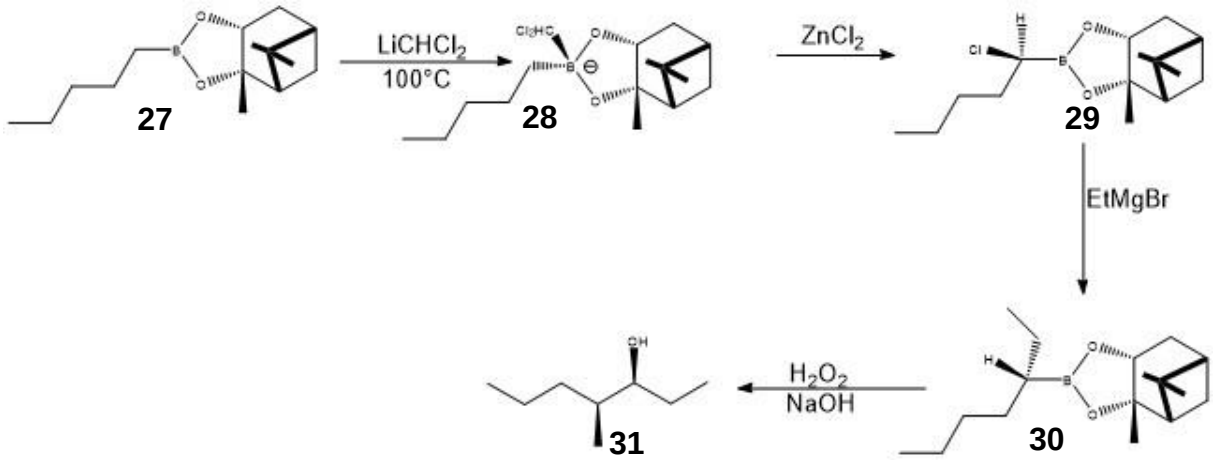


Figure 5: (3S, 4S)-4-methyl -3- heptanol

Another use of the 1,2-boron mediated transfer can be seen in the work of Matteson, where he used the method to synthesize different insect pheromones, like (3S, 4S)–4 methyl -3– heptanol.

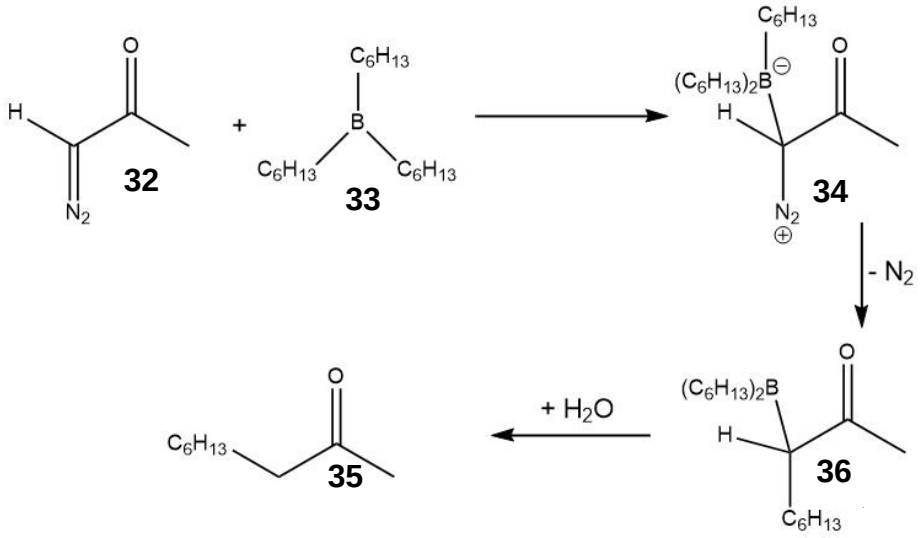
He achieved this by using a chiral boronic ester in a boronic ester homologation. In



Scheme 7: Chiral synthesis of (3S, 4S) -4- methyl -3- heptanol

the first step of the chital secondary alcohol (dichloromethyl)lithium was added to the chiral boronic ester **27** . This formed **28** a borate complex. After that through the addition of zinc chloride one of the boron appendages migrated to give the desired intermediate **29**, with the stereoselectivity that was wanted at carbon number three . After the addition of a Grignard and a workup with peroxide and sodium hydroxide, which removed the boronic acid, the desired chiral alcohol **31** was obtained with the wanted stereoselectivity Without the addition of the zinc chloride the diastereoselectivity as well as the yield would not have been as high as with the addition.[18]

Hooz and Linke showed progress in the research on 1,2 Boron mediated transfers as well, but they were focusing primarily on diazo acetone and trihexylborane.[19]



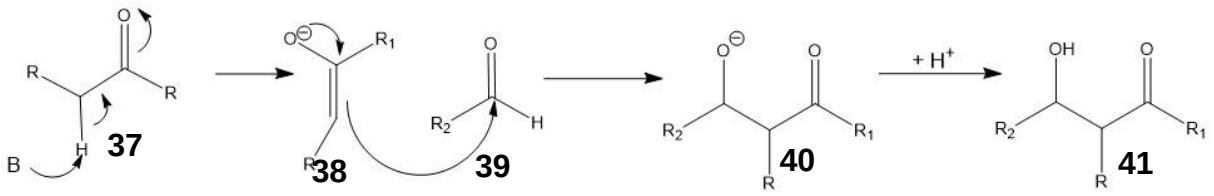
Scheme 8: Reaction of diazo acetone with trihexylboranes

Diazo acetone **32** was added to a 0 °C cold solution of trihexylborane **33** over the course of 20 minutes forming **34** a Lewis-acid base complex. The transfer of the boron appendage happened rapidly; this was monitored by the evolution of nitrogen gas formation. After the R group transfer occurred, an aqueous workup was done to remove the boron as boronic acid and **35** an acetone alkyl derivative was formed. Hooz work further utilizes ethyl diazoacetate as a starting material and it includes terminal alkene groups as the R groups on the boron which adds to the stability as well as the functionality of products. [19]

1.5 Enolates

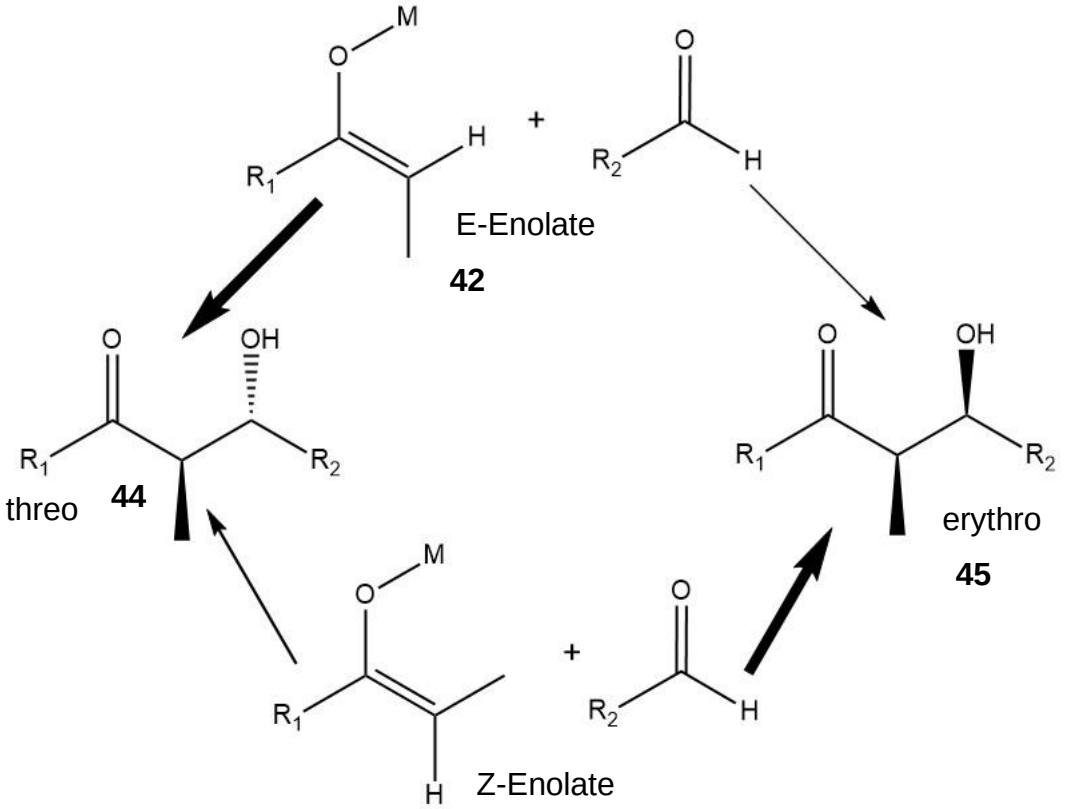
Enolates are intermediates that are particularly useful because of their nucleophilic character at the alpha carbon of the carbonyl[20]. This nucleophilic characteristic can also be found in boron enolates making them easy to exploit for 1,2 boron mediated transfers. The general formation of an enolate can be done by deprotonating a carbonyl compound. The negative charge on the enolate can be stabilized by transferring it to the corresponding oxygen. It can also be stabilized by coordinating with a cation depending on the solvent and base that were used.[20] The stereochemistry of enolates is heavily influence by the conditions of the reactions it is formed in, depending on temperature, solvent and base the enolate is either in Z form which gives it the alpha carbon substituent cis to the anionic oxyen. The E enolate has its alpha carbon substituent trans to the anionic oxygen.

One very commonly known reaction with enolates as the intermediate, where the outcome is a carbon carbon bond is the Aldol condensation, which is a fundamental reaction in organic synthesis.[21]



Scheme 9: General depiction of a aldol condensation mechanism

In the first step a base is used to break the C-H bond at the alpha carbon, which results in **38** an enolate ion. The electron density shifts to carbon which gives it a



Scheme 10: Product of an aldol condensation with metal enolates

nucleophilic character. Since the carbon now has a nucleophilic character, it can react with the electrophilic aldehyde **39** and forms a new carbon carbon bond while the carbonyl is reduced. The last step is a protonation on the negatively charged oxygen to give the final product of a secondary alcohol.

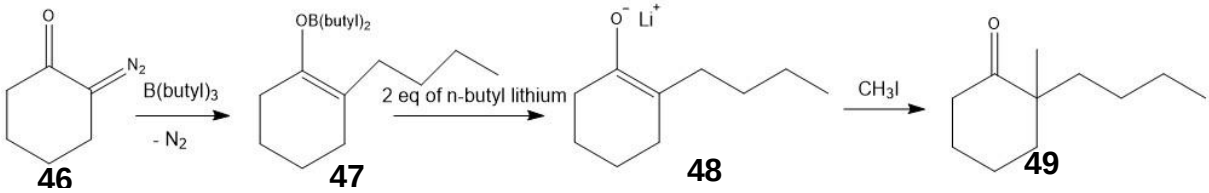
Some methods use metal cations for the stabilization of the oxygen anion. Their mechanism is extremely similar to the methods described before. Evans et. al. focused the research on aldol condensation with different metal enolates, specifically boron enolates, and the effect that the R group and the chelating agent had on the formation of the product. Evans describes the way E as well as Z metal enolates react.

The arrows in bold show the more favored product depending on the starting stereochemistry of the enolate. The other way of forming the product is no as favored due to R_1 R_2 axial interactions. The hypothesis that the product formation is faored based on the influence of the R_1 group was proven correct when R_1 was a substituent that was sterically more demanding and more bulky in size[22]. In his work

Evans writes that if the length of the M-O bond and the length of the M-L were decreased the interaction between sterics of axial L and axial R^2 would increase. His results also undermine the efficiency of using boron as a chelating agent.[21] His results are also consistent with the results that boron enolate provide the most stereoselectivity when used in aldol condensation.[23] The findings described in the chapter above support the use of boranes used in this project.

1.6 Combination of Enolates and new carbon-carbon bonds

The successful combination of enolates and the formation of new carbon carbon bonds through the addition of an electrophile have been documented in literature

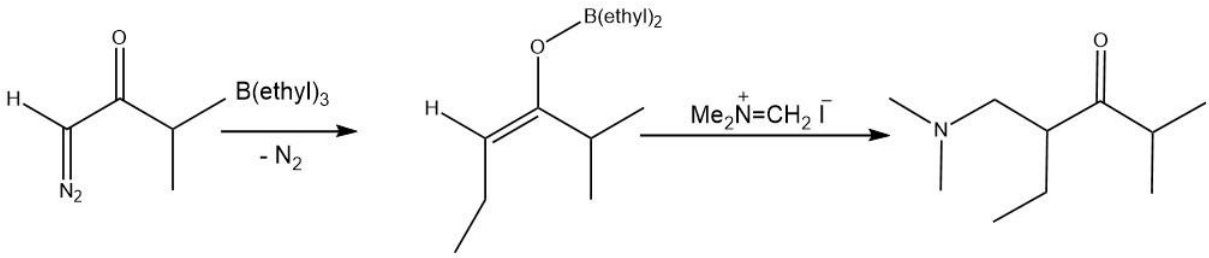


Scheme 11: synthesis of dialkylated ketones through a boron enolate and a lithium enolate intermediate

before. Pasto did one example where in his published work he focuses on preparing dialkylated ketones from diazo ketones, which is the combination of a 1,2 boron mediated transfer and haloalkanes in general[24].

At first the diazo cyclohexanone **46** is reacted with the tri-n-butyl boron to form **47** the boron enolate via aa Hooz type boron mediated 1,2 transfer. Then two equivalents of n-butyl lithium are added, and the lithium enolate **48** is formed, after the boron enolate is cleaved. Only if two equivalent are added can this happen, with only one equivalent the boron forms a reversible tributylborane and lithium enolate After an addition of methyl iodide, the final product **49** the dialkylated ketone is formed through methylation[24]. The difference of this mechanism to the one in this project is that the boron enolate is not the desired intermediate.

Another reaction that includes enolates and their nucleophilic character as well as an electrophile, was done by using a reaction of boron enolates with the Mannich



Scheme 12: reaction with Mannich reagent and an enolate intermediate

reagent.[25]

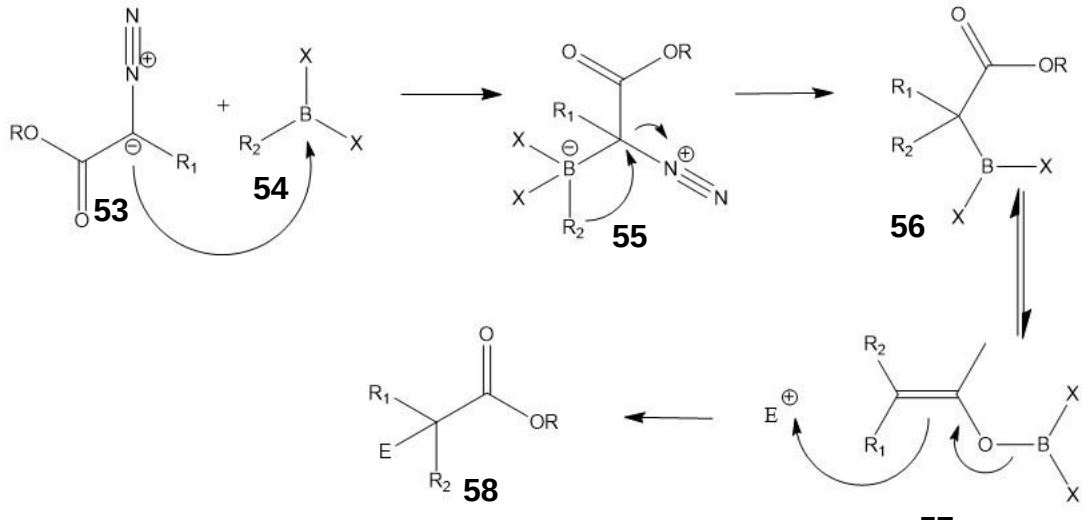
The triethyl borane was added to the diazo compound **50** and the enolate **51** was formed, the diazo part became nitrogen gas. The Mannich reagent (dimethyl-(methylene) ammonium iodide) in DMSO was added to the solution which was in THF and the final product **52** the amino ketone was formed. For this reaction the usage of DMSO was necessary since the yield without it was about 10 % but with the addition of DMSO that yield rose to between 80 and 100 %[25]

1.7 Project specific background

This project is based on the work previously done by a student in the Persichini group Mark Dobish, in his paper he used methyl 2-diazo- 3 phenyl propanoate as a diazo starting material to try and form a new carbon carbon bond with a quaternary stereocenter[20]. The difference to this project is, even though there were tests done with the same Alpha diazo ester, a different method of synthesizing a different alpha diazo compound as a starting material was also researched and used in the experimentation.

2. Objectives

The Objective of this research is to find a way to utilize boron enolates and their nucleophilic characteristic to synthesize a new way of forming a new carbon-carbon bond where the target carbon results in a quaternary stereocenter. In the work done before by other authors the result of an electrophilic addition to an enolate group has mostly been a carbon with a tertiary stereocenter. For the starting material, a



Scheme 13: proposed mechanism for the reaction in this project

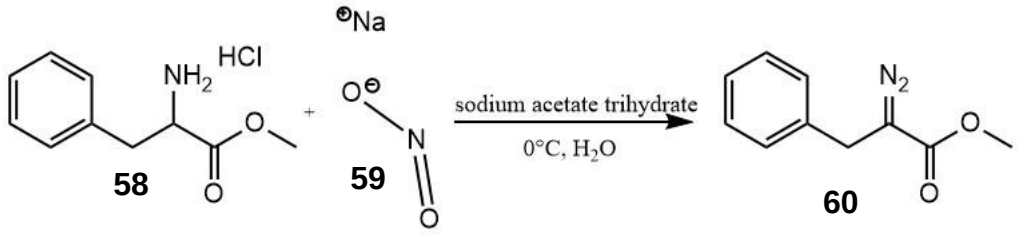
compound was chosen with the hopes of yielding a quaternary carbon due to the functional group being at the alpha carbon of the carbonyl. The starting material is going to be synthesized in a way that is quick and efficient. The chosen starting material a diazo compound will be reacted with trialkyl boranes and the formed enolate will be reacted with electrophiles to hopefully result in a quaternary carbon.

The negative charge at the diazo group carbon at the starting material **53** attacks the boron center at the trialkyl borane **54**. It forms a boronate complex **55** where one Boron appendage migrates to the carbon that is newly bonded to the boron, because the boron is negatively charged. Then the bond between the diazo groupand the carbon gets cut and nitrogen gas is formed. A keto – enol tautomerism occurs and the enolate intermediate is formed. The nucleophilic enolate **57** is reacted with an electrophile to give a quaternary carbon as the product.

3. Results and Discussion

The first step was to find a suitable starting material for the reaction. The chosen starting material for this project was an alpha diazo compound, this was chosen based on functionality as well as the fact that when the diazo group bond to the carbon gets cut the nitrogen gas that evolves is completely harmless and does not need to be separated from the product in an extra step during the workup.

Two different ways of synthesizing the starting material were investigated and tried. The first method was adapted by Mark Dobish from LaForge[20,26] and it uses the amine of the carbonyl on the alpha carbon.



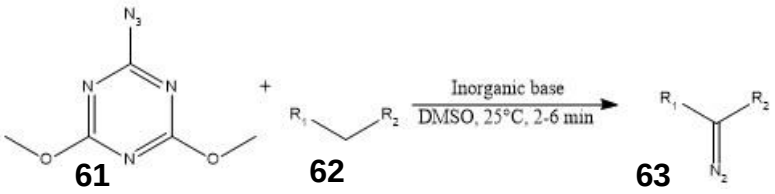
Scheme 14: reaction of first tested method by LaForge adapted by Dobish

Sodium acetate trihydrate was added to a solution of L-phenylalanine methyl ester hydrochloride in DI water at 0 °C. After the sodium nitrite was dissolved in deionised water it was added to the flask. Diethyl ether was added and the solution turned yellow slowly. After the flask was left to stir overnight it was doused with 2M sulfuric acid. The organic layer was separated from the aqueous layer ,was washed and

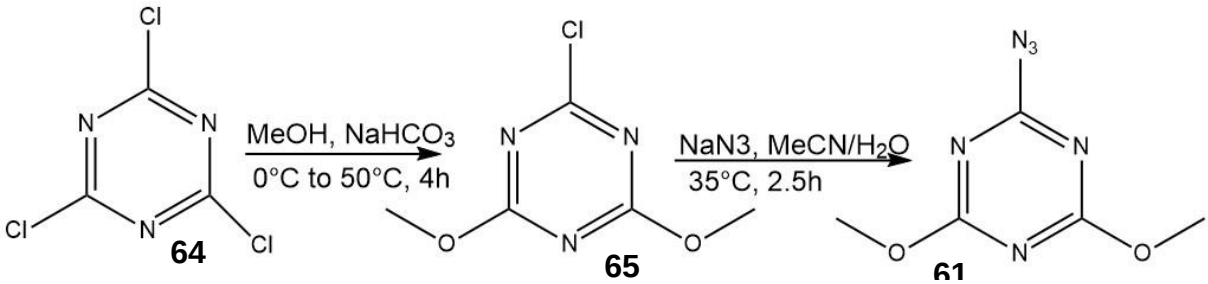
dried over anhydrous magnesium sulfate multiple times. To further purify the alpha Diazo ester a column chromatography was done to yield the ester at 25%. This was expected since the literature values were very low as well. A lot of the product was lost during the workup and some decomposed at the bottom of the column. The result of this experiment was analyzed by NMR, which showed even after the column, that a lot of impurities were still in the NMR spectrum. Even after more tries of purification of the alpha diazo ester, the impurities were impossible to get rid of. In the TLC no impurities were seen they only showed up once the NMR spectrum was taken.

The experiment conducted for the synthesis of the first alpha diazo ester, Methyl 2-diazo -3- phenylpropanoate, was repeated 3 times with different scales in mmol. The first time with 3 mmol and 1 eq, the TLC for this try of the experimentation still showed some rest of the starting product so another eq of sodium nitrite and sodium acetate trihydrate was added to give a proper result with no starting material showing up in the TLC. The next runs were done two times with 5 mmol both using 2 eq. The measurement for these different tries can be found in the tables 1-3.

Since the first method proved to be not very cost and time effective and because the impurities that were seen in the NMR spectrum were not efficiently separated from the diazo ester compound, different methods of synthesizing an alpha diazo ester were researched. The method that was decided upon was based on the use of a Diazo transfer agent called 2-azido-4,6-dimethoxy-1,3,5-triazine (ADT) created by Shibo Xie, Ziqiang Yan and others in 2018[8]. This compound utilizes an active methylene group on a compound to transfer a diazo group. An active methylene group is a carbon that is between two electron withdrawing groups.



Scheme 16: General diazo transfer with ADT as the transfer agent



Scheme 15: synthesis of ADT

The transfer agents more commonly used are sulfonyl azides which can be dangerous in preparation or 2-azide- 1,3 -dimethylimidazolinium (ADM) where the preparation can be expensive, and the starting materials can be moisture sensitive as well as dangerous while handling. In general, the problem of separating the rest of the transfer agent after the transfer has occurred is also an issue that has to be thought of, because most sulfonamide derivatives are less convenient to separate from the synthesized diazo compound[6]. ADT is a stable solid at room temperature and its starting materials have a low cost as well as easy to get.[8]

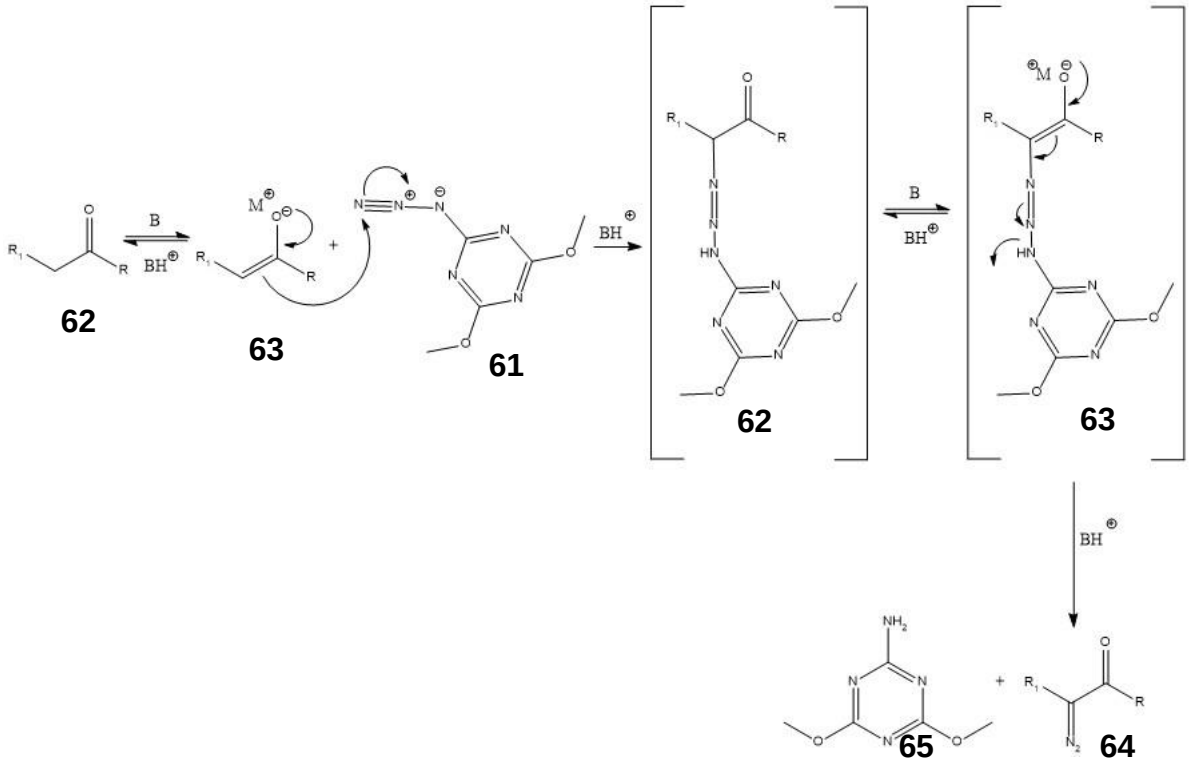
At first ADT had to be prepared to synthesize the Alpha diazo compound. For this cyanuric chloride, $NaHCO_3$ and MeOH were combined and stirred at 0°C for 30 minutes. The reaction was brought back to room temperature for 1.5 hours and was then heated to 50°C for an additional 2 hours. The solution was washed with DCM and DI water dried and concentrated. This step was not done in our lab we purchased the intermediate **65** and started the reaction from this step in the synthesis. The intermediate 2-chloro – 4,6- dimethoxy- 1,3,5- triazine **65** and acetonitrile were combined in a flask and stirred. A solution of sodium azide in deioinised water was added and the reaction was left to stir for 2.5 hours at 35 °C. The organic layer was extracted and washed with DCM and deionised water. After it was dried and concentrated it yielded the product ADT **61** as a white crystal with 80 %. The NMR that was done was, after this step did not show any impurities at all after just a concentration of the mixture was done and so there was no necessity to use any further purification steps to try and purify the product ADT further. This

makes the synthesis of ADT very quick to be done which is already an improvement to the method that was tried before.

For the Diazo transfer itself the compound with the active methylene group, which was in the case of our project, Ethyl acetoacetate, $NaHCO_3$ and DMSO were combined. After the ADT was added the solution stirred for 2 minutes at room temperature. The solution was washed with DCM and DI water and dried. A TLC was done to monitor the reaction, after the TLC in (hexane: ethyl acetate, 5:1) the TLC plate was dipped in I_2 in silica and then dipped into a vanillin solution. The TLC plate showed a very clear separation of the polar byproduct which did not move from the baseline and the alpha diazo compound which had a retention factor around 0.6. After this a silica plug was used to purify the compound which gave a yield of 74% in a pale-yellow liquid. The NMR of the crude product before the silica plug showed very clearly that there was the polar byproduct together with the wanted diazo ester. But after letting the mixture flow through just 5 cm of silica in hexane: ethyl acetate, 5:1 relation there was no sign of any byproducts or impurities in the ^1H NMR that was taken afterwards. The second method of synthesizing the starting material by using the diazo transfer agent ADT was taking a shorter amount of time then the first method that was used as well as giving a higher yield for the starting diazo ester. Even though the second method used one more step in the procedure to result in the diazo ester, because the ADT[8] had to be synthesized first, it was still faster than using the first method from LaForge[26].

The experiment for the synthesis of this compound was repeated multiple times as there was more of the diazo ester material needed to progress further in the experiments. The first time the experiment was done on a 1 mmol scale to assess the result. After a positive outcome, the experiment was scaled up to 3 mmol where more of the wanted alpha diazo ester could be obtained. The specific measurements for the different scales of this experiment can be found in the experimental section at the tables 9 and 10[31].

In general, the mechanism for this can be explained as follows. The added base removes a proton from the active methylene group which yields an enolate compound **63**. The nucleophilic character of the enolate makes an attack on the ADT

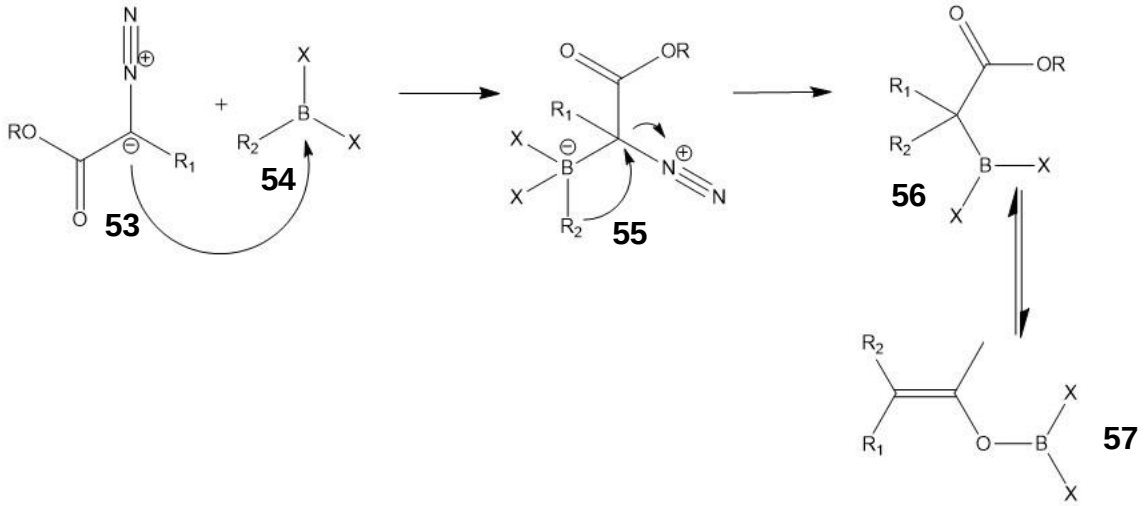


Scheme 17: mechanism f diazo transfer with ADT

possible, which occurs, after this a proton transfer happens and leaves two intermediates in equilibrium. A cleavage in the nitrogen nitrogen bond at intermediate **63** results in the end product the diazo compound **64** and a polar side product **65** which can be easily separated by a column chromatography.

This method proved to be a lot more time efficient, since it only took one day instead of at least three which is why only a few tests were done with the first method by LaForge[26] While working with the second method the only explored pathway was with ethyl acetoacetate as a compound with an active methylene group. This was done to test the method without looking at the stereochemistry of the compound.

The next step was to synthesize the boron enolate. This was done by reacting the diazo starting materials with a trialkylborane.



Scheme 18: proposed mechanism of trialkylborane reacting with alpha diazo ester compound

The negative charge at the carbon of the diazo group attacks the boron center and forms a bond. Since the boron is now negatively charged, one of the boron appendages moves in a 1,2-boron mediated transfer to the carbon next to the boron and the diazo group leaves in the form of the very stable nitrogen gas. The next step is a keto-enol tautomerism where the boron enolate **57** is formed. A keto-enol tautomerism is a chemical equilibrium between a keto form of a molecule and its enol form.

This part was done with the diazo compound made from the first method by LaForge adapted by Dobish[20,26], repeated with the diazo compound made by the diazo transfer with ADT[8], as well as with a store-bought diazo ester, Ethyl diazoacetate.

The Diazo compound was put in a flask under nitrogen and triethylborane was added the reaction stirred for 24 hours and was monitored by TLC and NMR.

If the proposed mechanism was correct the peaks in the Boron NMR should be in a Region of 50 ppm which would show the presence of a boron with one heteroatom and two carbon substituents, which means the enolate was formed. Another peak expected was at 80 ppm which would show a boron with no heteroatom and three carbon substituents, this would mean that the compound did not react with the trialkylborane at all, since this would show the starting material was still present. With the bought Ethyl diazo acetate, the Boron NMR showed a peak at 20 and a small one at 0. ppm. The peak at 20 ppm would mean that the boron has three heteroatoms and no carbon substituents. This meant that with this Diazo compound a reaction occurred, just not the one predicted. A different explanation for the unexpected peak

could be that the Lewis acidity of the borane could be influenced by lone electron pairs in the reaction.

The bought diazo ester ethyl diazoacetate was also reacted with tributylborane to see if a difference in the trialkylborane would have influence on the NMR spectrum. After combing both liquids in a flask that was put under nitrogen the solution was left to stir overnight. The next day workup was done. The solution was concentrated in vacuum and analyzed via NMR again. The Boron NMR for this reaction showed two peaks one at 30 ppm and one at 20 ppm. The peak at 30 ppm would mean that the boron had two heteroatoms and on carbon substitute. The same NMR tube was measured at 50 °C to see if a different result would show up, but the there was no significant difference in the Boron NMR after heating of the NMR tube.

The Diazo compound made by the first method was also used in a reaction with Triethylborane, to not waste any experiment that was done before and have different data points of different alpha diazo esters reacting with triethylborane to see if the groups on the whole carbon molecule would make a difference in stability and other characteristics of the enolate formed. The NMR for this showed two peaks one at 30 ppm and one at 20 ppm.

And finally, the Diazo compound synthesized by Diazo transfer via ADT showed a Boron spectrum which was not able to be analyzed. Because of this a look at the proton NMR was taken and it had peaks that assumably mean that there are three different compounds in the product based on the three singlets at 2.61, 2.48 and 2.33 ppm. This shows three different methyl groups next to the oxygen. The separation of these compounds will be the next step that are to be done in order to progress in the chemistry and move forward. After these compounds are separated a better view of a Boron NMR can be done.

Even though the Boron NMR did not show the expected result a trial with adding an electrophile to the reacted Trialkylborane and the diazo ester was done with the product of the bought alpha Diazo ester the Ethyl diazo acetate.

A small amount of D_2O was added to an NMR tube of the reaction and the tube was shook and a new Boron NMR was taken after 2 hours as well as after 24 to see if a reaction took place, and if there was a difference in time.

When adding the D_2O to the NMR tube with reaction of Ethyl diazoacetate and Triethylborane, the NMR showed a new peak at 30 ppm which means a change definitely occurred and the D_2O reacted with the compound. There was still a peak at 20 ppm this could mean, that not all of the boron enolate reacted, more experiments are to be done with this information to find out the reason for this behavior. This peak change was only visible after waiting 24 hours, the NMR taken before did show any different result to the NMR taken before the addition of D_2O.

When the D_2O was added to the NMR tube with Ethyl diazoacetate and tributylborane the peak at 20 ppm was gone completely and only the peak at 30 ppm was still there. Here too the NMR was taken after different waiting periods. Again, one after 2 hours and after 24 hours. There was no significant change yet after 2 hours, the change was only visible after waiting for 24 hours, the next day.

4. Conclusion

This paper describes the work over a duration over 5 months. Even though the desired product, a quaternary carbon was not achieved successfully big steps in the direction of the proposed reaction mechanism were taken. The enolate intermediate was not recovered successfully, but a reaction that can be explord further in the future took place. The shift in the boron NMR after the addition of the electrophile also hints at different reactions that took place instead of the enolate electrophile reaction. The method for synthesizing a diazo ester was done successfully through a new approach with the diazo transfer agent ADT. The data gathered from this research will be valuable towards a future successful method of synthesizing a quaternary carbon via a boron mediated transfer. For a future research on this topic we would propose an appropriate active methylene group with a tertiary stereocenter to start, the proposed mechanism can then be explored further in this direction. As well as the further investigation of the boron enolate formation after the reaction of trialkylboranes with the diazo ester. Choosing an appropriate group on the alpha diazo ester to further stabilize the compound might bring an improvement as well.

5. Experimental

All results were analyzed by ^{1}H NMR, ^{13}HC NMR and ^{11}B NMR with a JOEL JNM-ECP400 FT-NMR as solutions in deuterated solvents. The chemical shifts are described in parts per million. (ppm) Any water used in the experiment is assumed to

be deionized water. Every column chromatography was done with EMD silica gel 60. The composition of the solvent is written on a volume/ volume basis (v/v).

Synthesis of Methyl 2- diazo -3- phenylpropanoate: In a clean 100 ml round bottom flask L-phenylalanine methyl ester hydrochloride (1.076 g; 5 mmol; 1 eq) was dissolved in 15 ml of DI water and cooled to 0 °C. The sodium acetate trihydrate (1.3608 g; 10 mmol; 2 eq) was added to the flask. Then sodium nitrite (0.6899 g,10 mmol; 2 eq) was dissolved in 5 ml of DI water and eventually added to the round bottom flask as well. The solution was stirred for 12 hours and monitored by TLC (hexane: ethyl acetate; 1: 1). The next day 1 ml of 2 M sulfuric acid was added, and the solution was stirred overnight again to make sure the reaction was complete. After completion of the reaction 5 ml of diethyl ether was added.

The organic layer was separated and washed with 20 ml 10% sodium bicarbonate. To the aqueous layer, another 5 ml of ether was added, and the ether layer was separated and washed with 10 % sodium bicarbonate again. The ether layers were combined and dried over anhydrous magnesium sulfate. Then the layers were filtered, concentrated and purified via column chromatography (hexane: ethyl acetate; 2:1) to give a yellow oil (0.2435 g; 25%). ^{1}H NMR (400 MHz; $CDCl_3$): δ 7.29 (m, 5H), 3.77 (s, 3H), 3.12 (s, 1H)

Table 1: Measurements for Preparation of Methyl 2- diazo -3- phenylpropanoate 3 mmol 1 eq

Name of compound	mass [g]	Mmol	eq
L-phenylalanine methyl ester hydrochloride	0.647	3	1
Sodium nitrite	0.207	3	1
Sodium acetate trihydrate	0.408	3	1

Table 2: Measurements for Preparation of Methyl 2- diazo -3- phenylpropanoate 3 mmol 2 eq

Name of compound	mass [g]	Mmol	eq
L-phenylalanine methyl ester hydrochloride	0.647	3	1
Sodium nitrite	0.414	6	2
Sodium acetate trihydrate	0.816	6	2

Table 3: Measurements for Preparation of Methyl 2- diazo -3- phenylpropanoate 5 mmol 2 eq

Name of compound	mass [g]	Mmol	eq
L-phenylalanine methyl ester hydrochloride	1.076.	5	1
Sodium nitrite	0.6899	10	2
Sodium acetate trihydrate	1.3608	10	2

Reaction of ethyl diazoacetate with triethylborane: The ethyl diazoacetate (15 % in toluene; 2.28 ml; 3 mmol; 1 eq) was added in a clean 15 ml round bottom flask equipped with a stirring bar. The flask was put under nitrogen. The Triethylborane (1 M; 3 ml; 3 mmol; 1 eq) was added to the flask. The solution was left to stir overnight. The next day the flask was concentrated down and analyzed by NMR to yield a yellow liquid (0.3761 g; 70%). ^{11}B NMR (126.4 MHz; $CDCl_3$): δ 17.3, 1.4

A small part of this experiment was put in an NMR tube and analyzed after adding 2 drops of D_2O were added. ^{11}B NMR (126.4 MHz; $CDCl_3$): δ 32.2, 17. 3. After this to the same tube 2 drops of 3M HCl were added and analyzed. The NMR result showed no change to when the deuterium oxide was added.

Table 4:Measurements for reaction of ethyl diazoacetate with triethylborane 1 mmol 1 eq

Name of compound	Volume [ml]	Mmol	eq
Ethyl diazoacetate	0.76	1	1
Triethylborane	1	1	1

Table 5: Measurements for reaction of ethyl diazoacetate with triethylborane 3 mmol 1 eq

Name of compound	Volume [ml]	Mmol	eq
Ethyl diazoacetate	2.28.	3	1
Triethylborane	3	3	1

Reaction of Methyl 2- diazo -3- phenylpropanoate with triethylborane: The Methyl 2- diazo -3- phenylpropanoate (0.0709g; 0.37 mmol; 1 eq) in hexane was added to a clean 10 ml round bottom flask equipped with a stirring bar. The flask was put under nitrogen. The triethylborane (1 M in hexane, 0.37 ml; 0.37 mmol; 1 eq) was added to the flask. The solution was left to stir overnight. The next day the flask was concentrated down and analyzed by NMR. ^{11}B NMR (126.4 MHz; $CDCl_3$): δ 31.8, 19.6

Synthesis of ADT: A clean 15 ml round bottom flask was charged with 2- chloro -4,6- dimethoxy -1,3,5- triazine (0.528 g; 3 mmol; 1 eq) and 3 ml of acetonitrile. A stirring bar was introduced to the flask. The sodium azide (0.195 g; 3 mmol; 1 eq) was dissolved in DI water and added to the flask. The solution was heated to 35°C and stirred for 2.5 hours. The mixture was concentrated down in a vacuum, then extracted, and washed with DCM and DI water two times. The organic layers were combined and dried with magnesium sulfate, filtered, and concentrated on the rotavapor to yield a white solid (0.4581 g; 83%). The result was analyzed by NMR. ^{1}H NMR (400 MHz; $CDCl_3$): δ 4.03 (s, 6H). ^{13}C NMR (100 MHz; $CDCl_3$): δ 173.3, 172.3, 55.7

Table 6:Measurements for the synthesis of ADT 1 mmol 1 eq

Name of compound	mass [g]	Volume [ml]	Mmol	eq
2- chloro -4,6- dimethoxy -1,3,5- triazine	0.176	/	1	1
acetonitrile	/	1	/	1
Sodium azide	0.065	/	1	1

Table 7:Measurements for the synthesis of ADT 3 mmol 1 eq

Name of compound	mass [g]	Volume [ml]	Mmol	eq
2- chloro -4,6- dimethoxy -1,3,5- triazine	0.528.	/	3	1
acetonitrile	/	3	/	1
Sodium azide	0.195	/	3	1

Table 8: Measurements for the synthesis of ADT 6 mmol 1 eq

Name of compound	mass [g]	Volume [ml]	Mmol	eq
2- chloro -4,6- dimethoxy -1,3,5- triazine	1.053.	/	6	1
acetonitrile	/	6	/	1
Sodium azide	0.390	/	6	1

Preparation of o: In a clean 25 ml round bottom flask ethyl acetoacetate (0.39 ml; 3 mmol; 1 eq) was combined with $NaHCO_3$ (0.012601 g; 1.5 mmol; 0.5 eq) and 12 ml of DMSO. The ADT (0.54642 g; 3 mmol; 1 eq) was added. The mixture was left to stir for 2 minutes at 25 °C and monitored by TLC. The reaction was extracted with Ethyl acetate and DI water two times. The organic layers were combined, dried with

magnesium sulfate, and concentrated in vacuum. The product was purified with a silica plug (hexane: ethyl acetate; 5:1) and resulted in a pale-yellow liquid. (0.343 g; 75 %). The result was analyzed by NMR. ^{1}H NMR (400 MHz; $CDCl_3$): δ 4.27 (q, 2H), 2.45 (s, 3H), 1.30 (t, 3H) ^{13}C NMR (100 MHz; $CDCl_3$): δ 190.34, 161.51, 61.53, 28.34, 14.42

Table 9: Measurements for the preparation of ethyl -2- diazo -3- oxobutanoate 1 mmol 1, 0.5 eq

Name of compound	mass [g]	Volume [ml]	Mmol	eq
Ethyl acetoacetate	/.	0.128	1	1
2- azido -4,6- dimethoxy -1,3,5- triazine	0.182	/	1	1
Sodium bicarbonate	0.042	/	0.5	0.5

Table 10:Measurements for the preparation of ethyl -2- diazo -3- oxobutanoate 3 mmol 1, 0.5 eq

Name of compound	mass [g]	Volume [ml]	Mmol	eq
Ethyl acetoacetate	/	0.39	3	1
2- azido -4,6- dimethoxy -1,3,5- triazine	0.546	/	3	1
Sodium bicarbonate	0.126	/	1.5	0.5

Reaction of ethyl -2- diazo -3- oxobutanoate with triethylborane: A 10 ml flask, which was equipped with a stirring bar, was charged with ethyl -2- diazo -3- oxobutanoate (0.07807 g; 0.5 mmol; 1 eq). The flask was put under nitrogen. The triethylborane (2 M, 0.25 ml; 0.5 mmol. 1 eq) was added and the flask was left to stir overnight. The product (0.0948 g, 80%) was concentrated down and analyzed by NMR. ^{1}H NMR (400 MHz; $CDCl_3$): δ 4.45 (q, 1H), 4,30 (q, 3H), 4.05 (d, 1H), 3.61 (d, 1H), **2.61 (s, 2H), 2.48 (s, 4H), 2.33 (s, 2H)**, 1.43 (t, 2H), 1.32 (dt, 6H), 0.73 (m, 3H), 0.47 (q, 2H)

Reaction of ethyl diazoacetate with tributylborane: In a clean 10 ml round bottom flask ethyl diazoacetate (0.76 ml; 1 mmol; 1 eq) was added. A magnetic stirring bar was added. The flask was put under nitrogen and tributylborane (1 M, 1 ml; 1 mmol; 1eq) was added. The reaction was left to stir overnight. The next day the mixture was concentrated in a vacuum and analyzed by NMR at two different temperatures (room temperature and 50 °C), but there was no difference to see. ^{11}B NMR (126.4 MHz; $CDCl_3$): δ 29.8, 18.6

A small part of the product was put into a NMR tube and 2 drops of D_2O were added. The result was analyzed by NMR. ^{11}B NMR (126.4 MHz; $CDCl_3$): δ 29.8

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7. Appendix

I: Methyl 2- diazo -3- phenylpropanoate

II: Ethyl diazoacetate plus triethylborane ; Ethyl diazoacetate plus triethylborane plus D_2O

III: Methyl 2- diazo -3- phenylpropanoate plus triethylborane

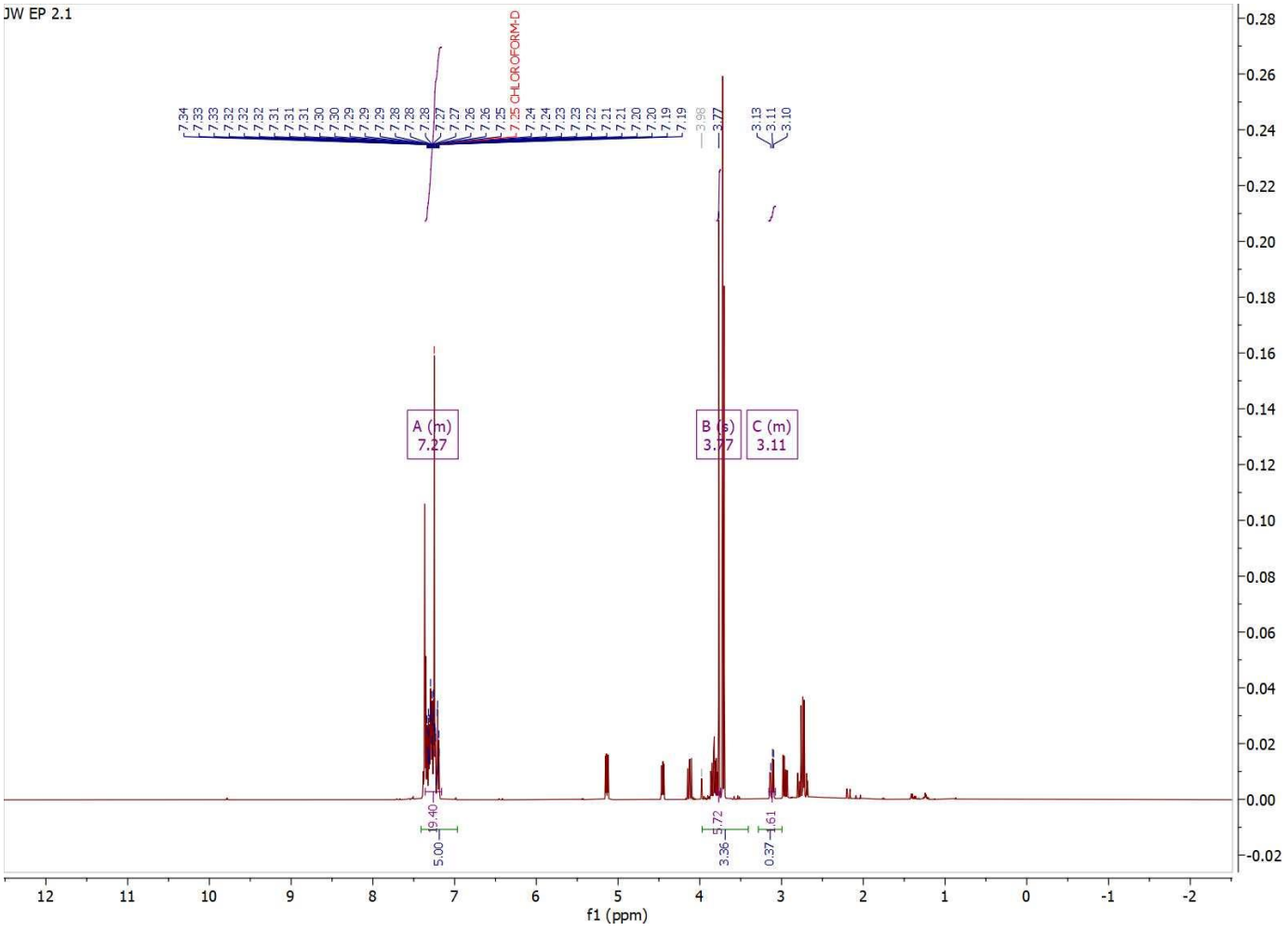
IV: ADT

V: ethyl -2- diazo -3- oxobutanoate

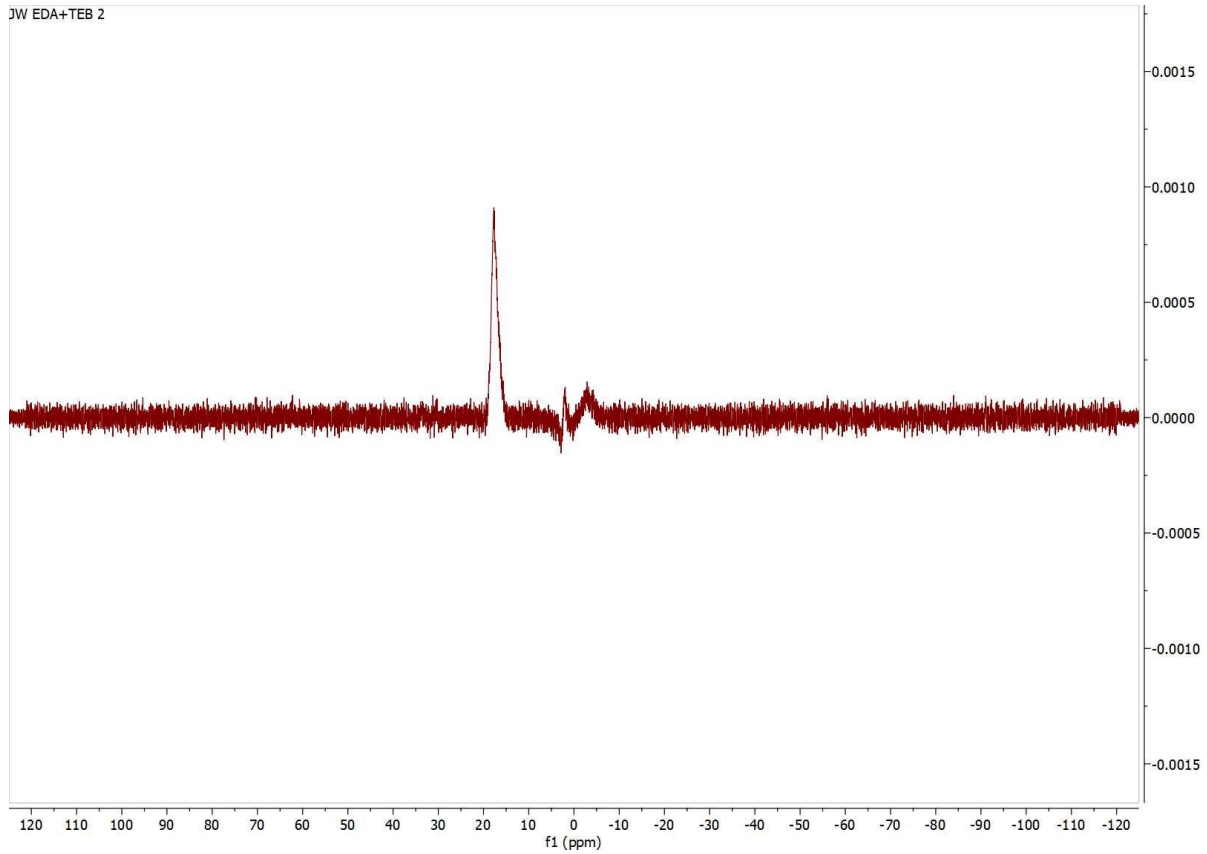
VI: ethyl -2- diazo -3- oxobutanoate plus triethylborane

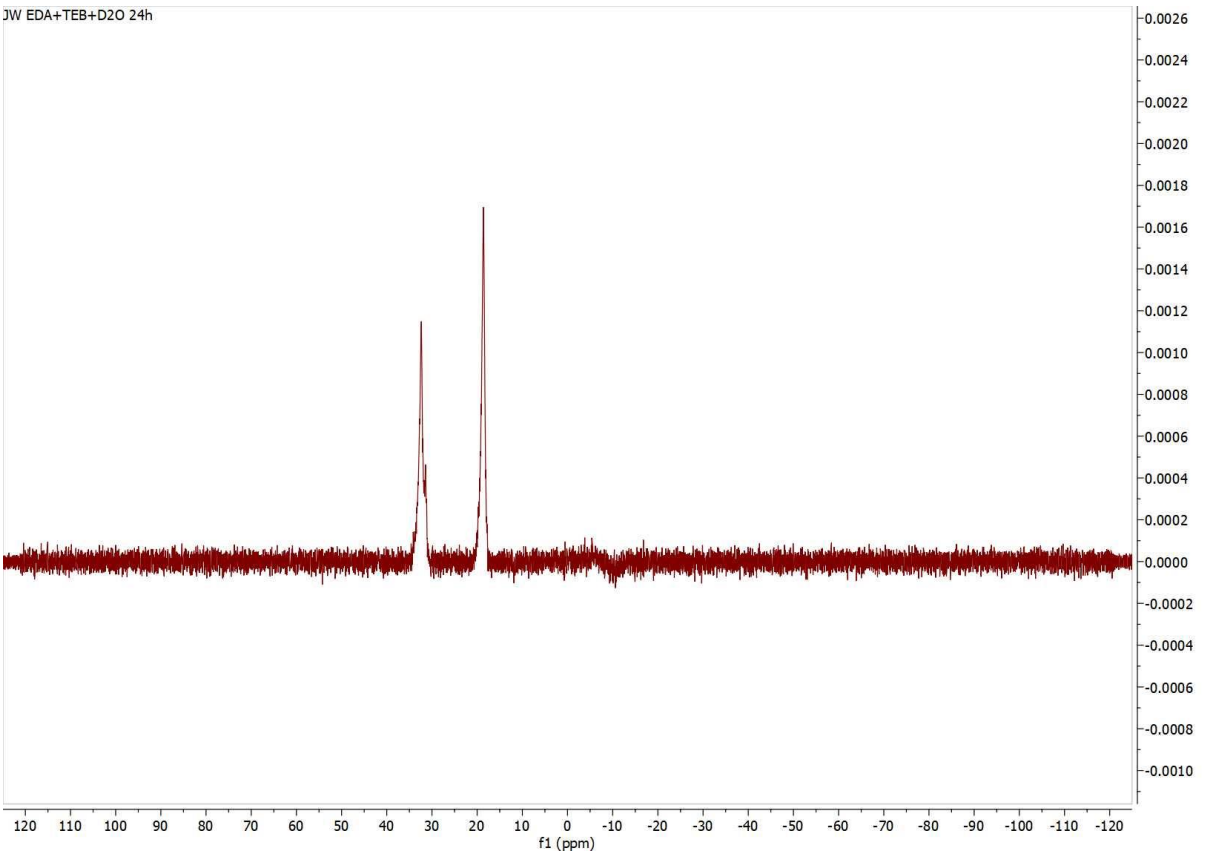
VII: Ethyl diazo aetate plus tributylborane

I)

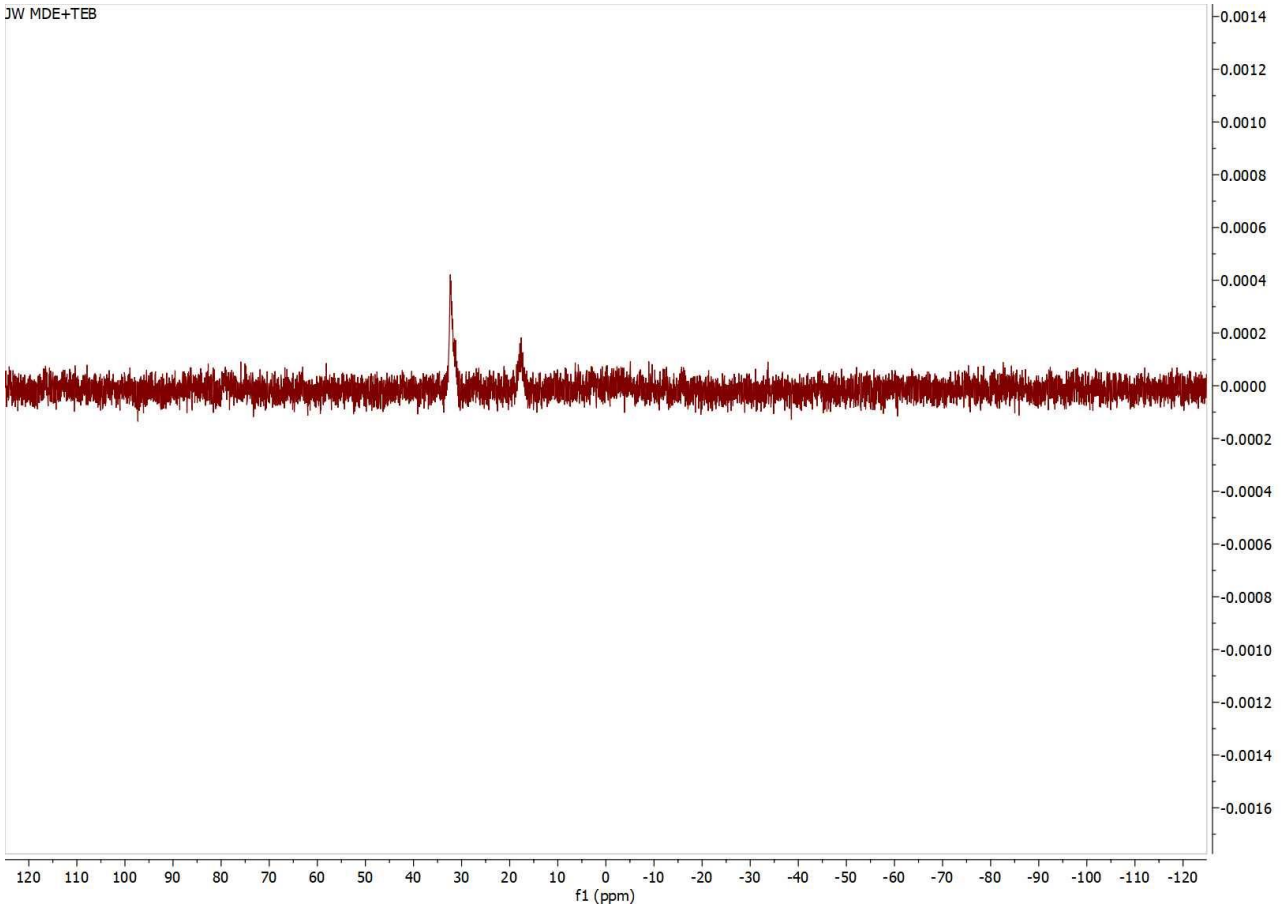


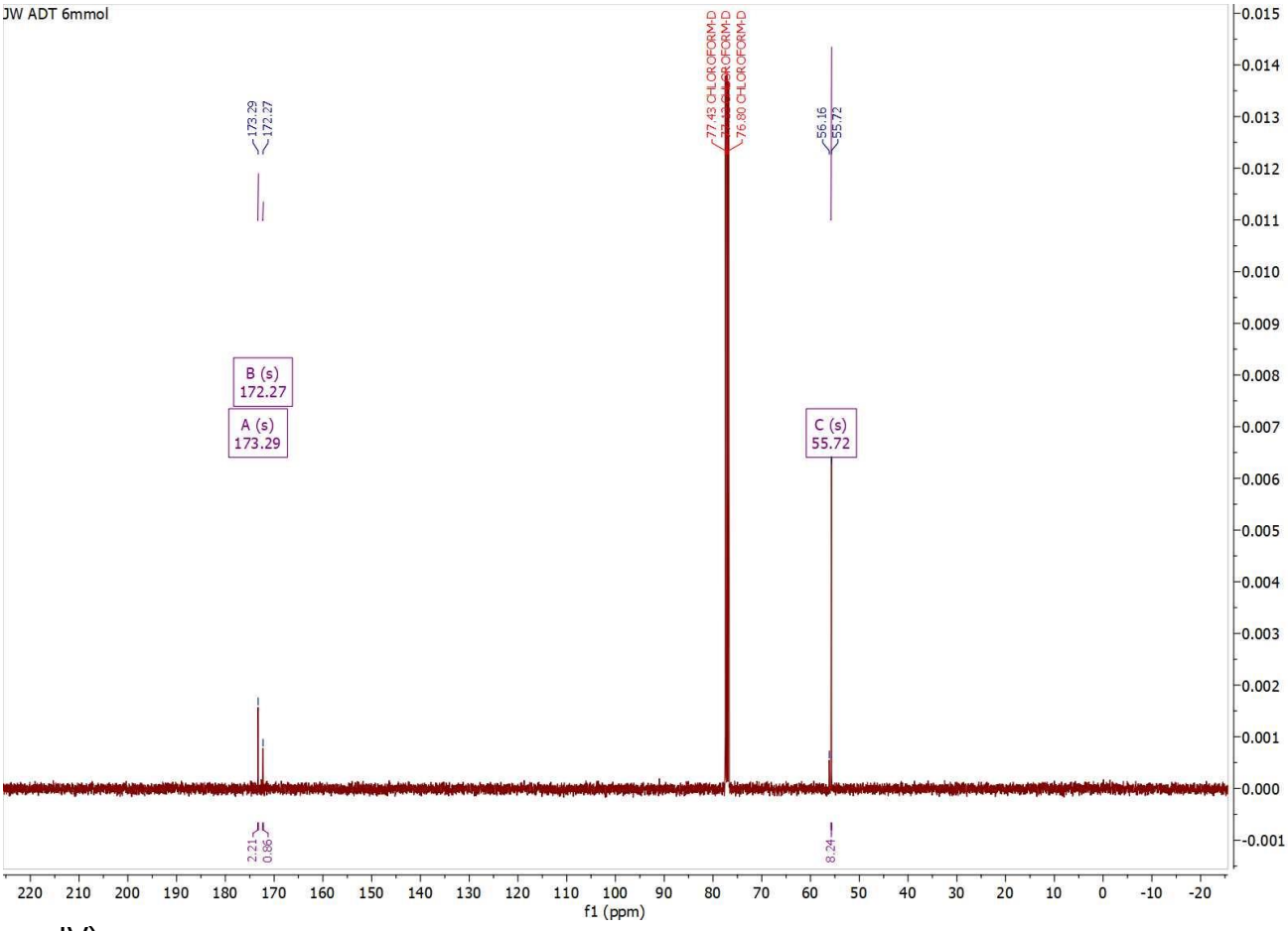
II)


JW EDA+TEB 2
0.0015
0.0010
0.0005
0.0000
-0.0005
-0.0010
-0.0015
120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120
f1 (ppm)

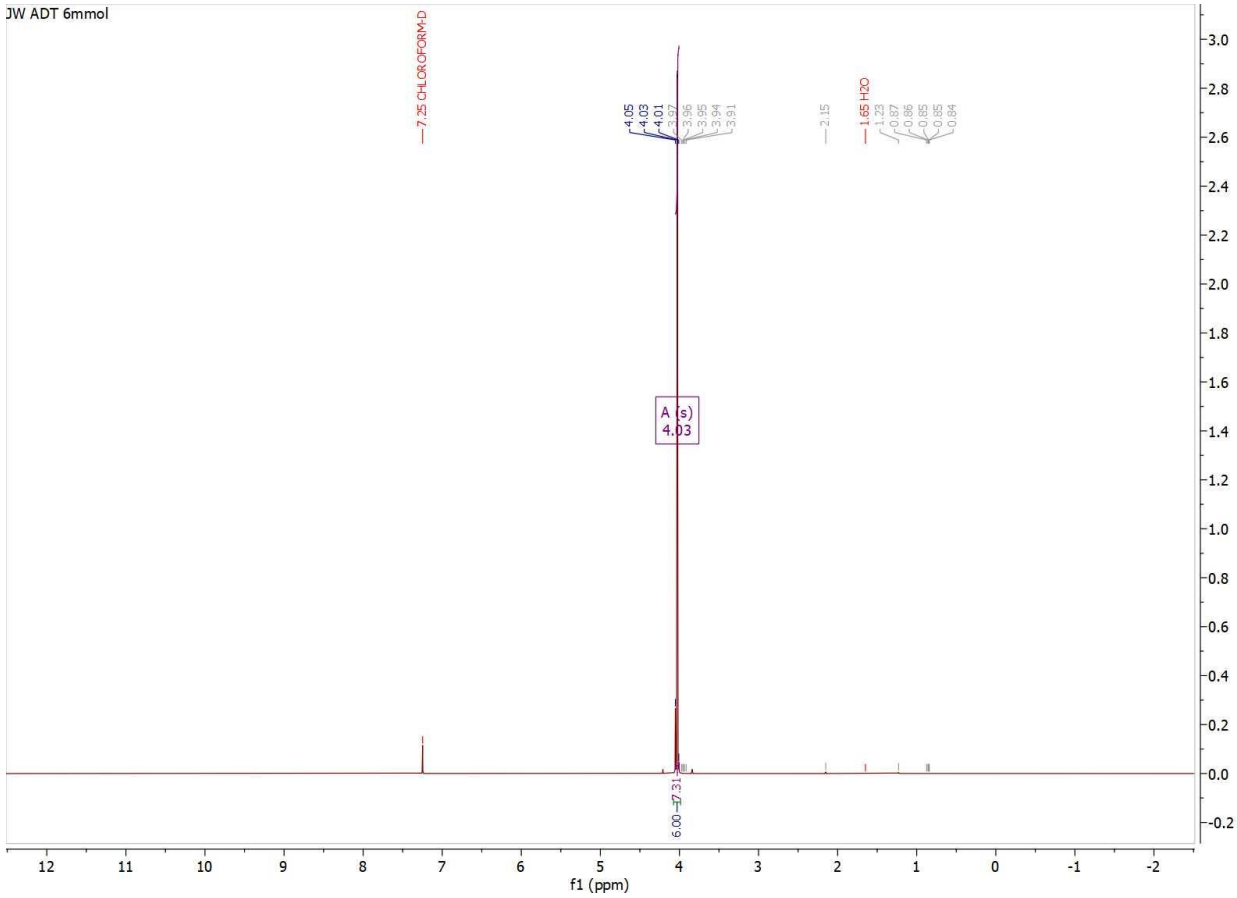

JW EDA+TEB+D2O 24h
0.0026
0.0024
0.0022
0.0020
0.0018
0.0016
0.0014
0.0012
0.0010
0.0008
0.0006
0.0004
0.0002
0.0000
-0.0002
-0.0004
-0.0006
-0.0008
-0.0010
120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120
f1 (ppm)

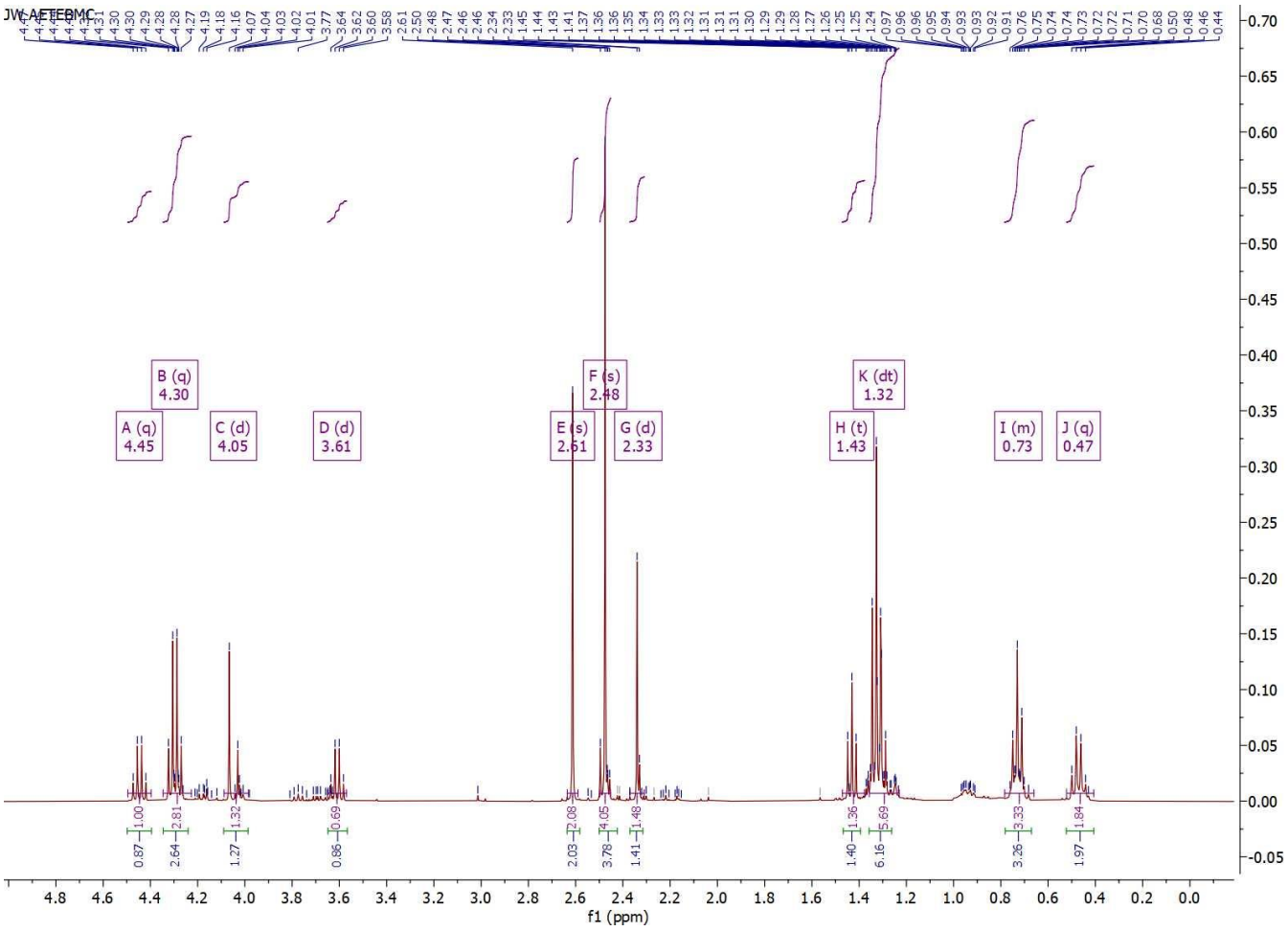
III)


JW MDE+TEB
f1 (ppm)

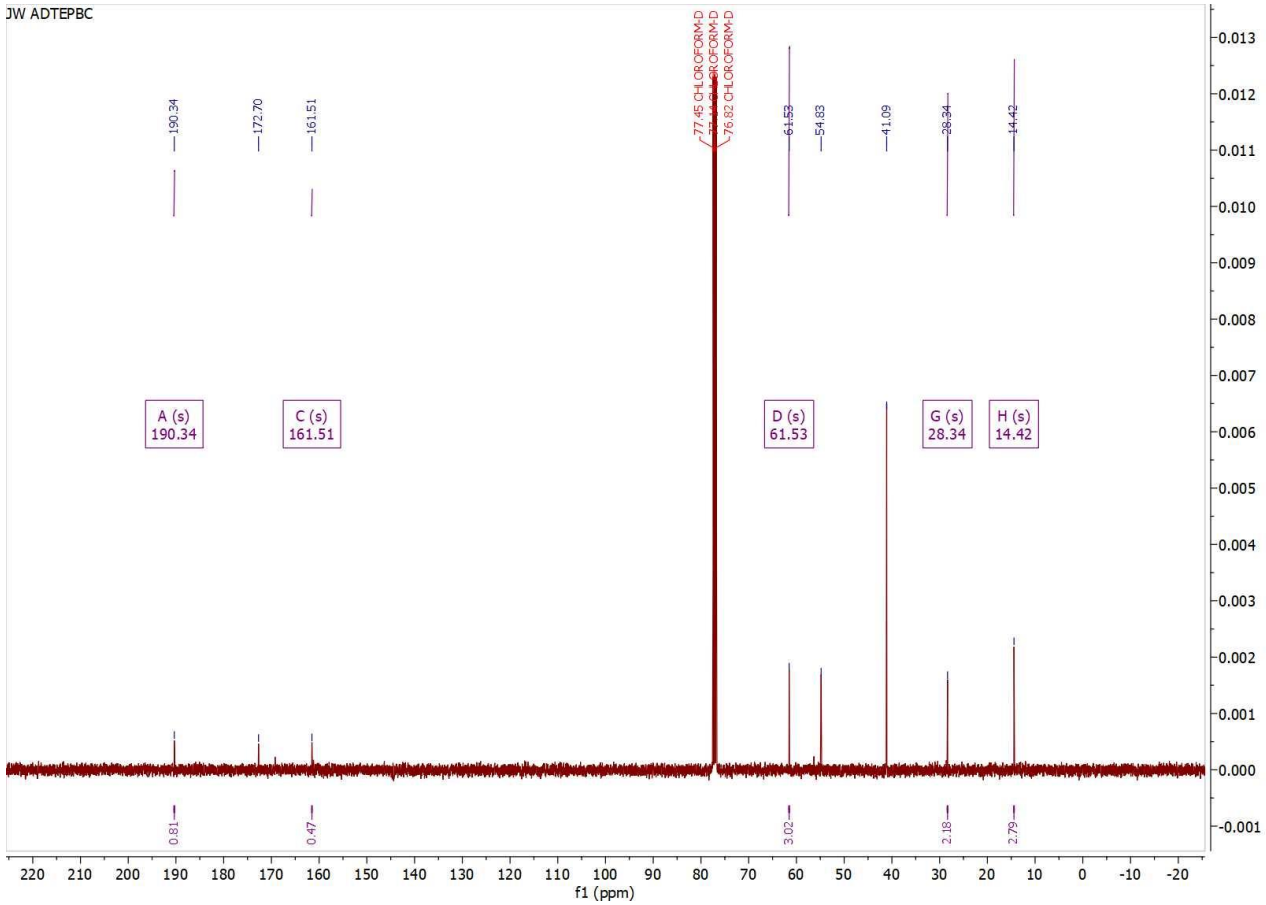

JW ADT 6mmol
173.29
172.27
77.43 CHLOROFORM-D
76.80 CHLOROFORM-D
56.16
55.72
B (s)
172.27
A (s)
173.29
C (s)
55.72
2.21
0.86
8.24
f1 (ppm)

IV)

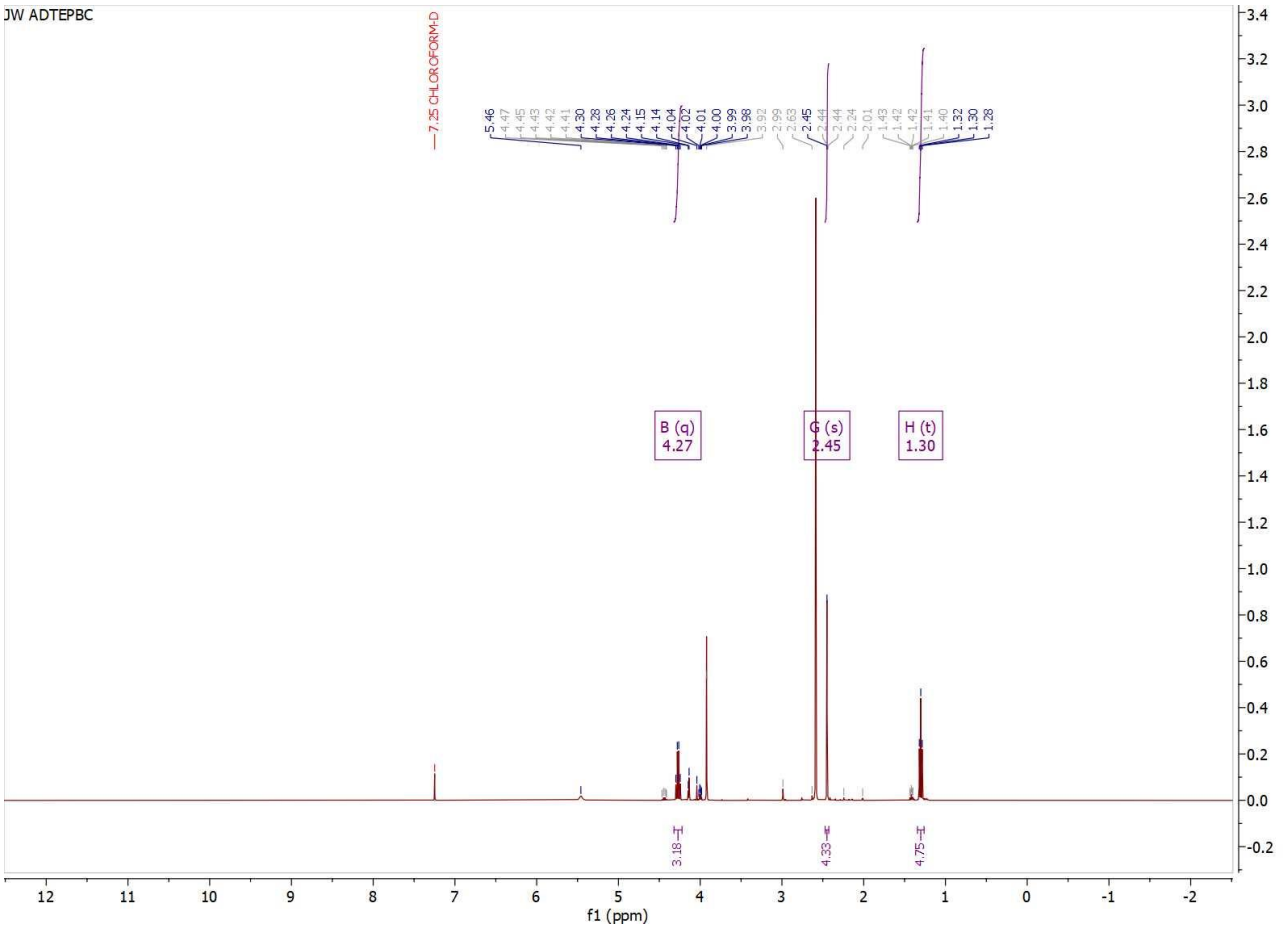

JW ADT 6mmol
7.25 CHLOROFORM-D
4.05
4.03
4.01
3.97
3.96
3.95
3.94
3.91
2.15
1.65 H2O
1.29
0.87
0.86
0.85
0.84
A (s)
4.03
6.00
7.31
f1 (ppm)

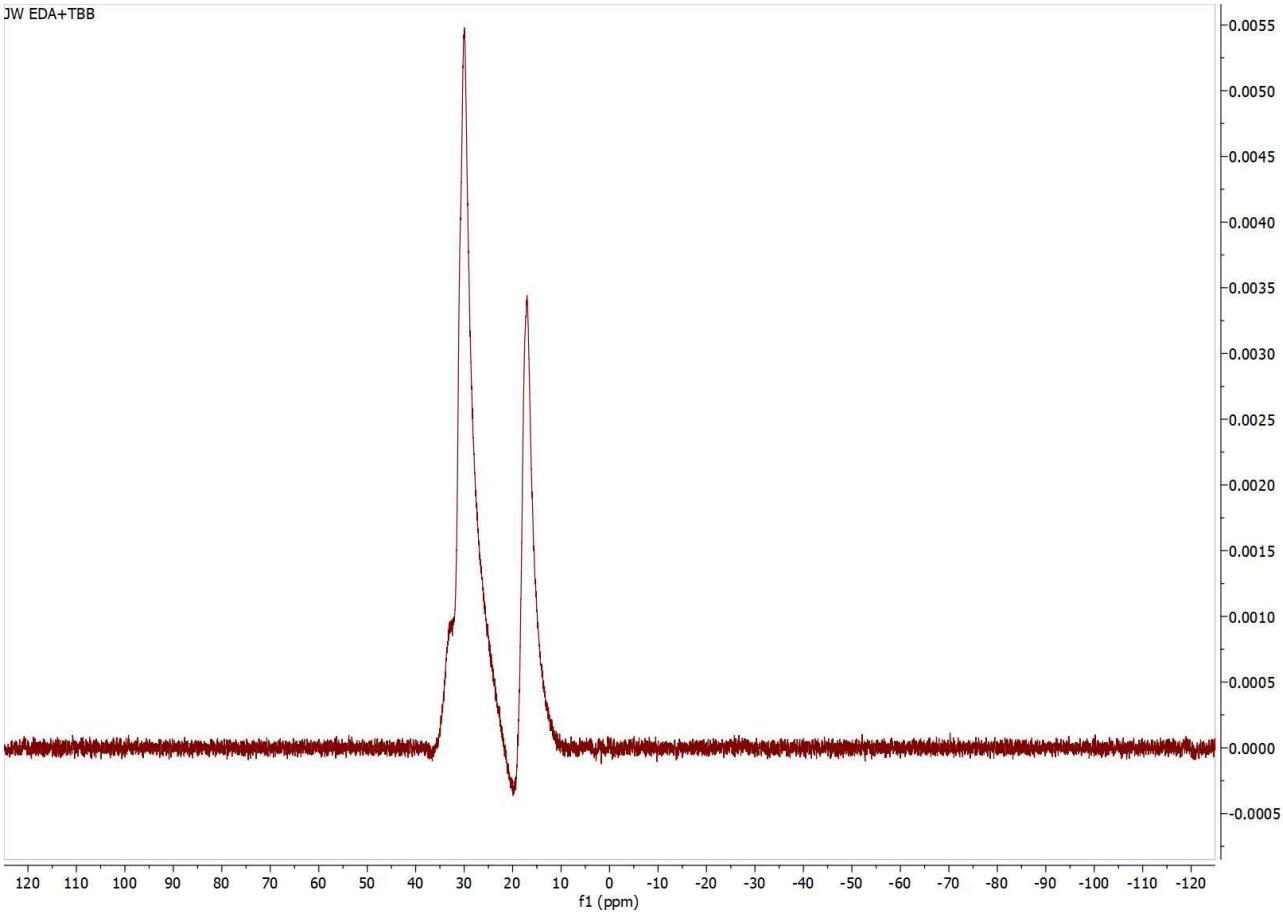

JW AETEBMC
B (q)
4.30
A (q)
4.45
C (d)
4.05
D (d)
3.61
F (s)
2.48
E (s)
2.61
G (d)
2.33
K (dt)
1.32
H (t)
1.43
I (m)
0.73
J (q)
0.47
1.00
2.81
1.32
0.69
2.08
4.05
1.48
1.36
5.69
3.33
1.84
0.87
2.64
1.27
0.86
2.03
3.78
1.41
1.40
6.16
3.26
1.97
f1 (ppm)

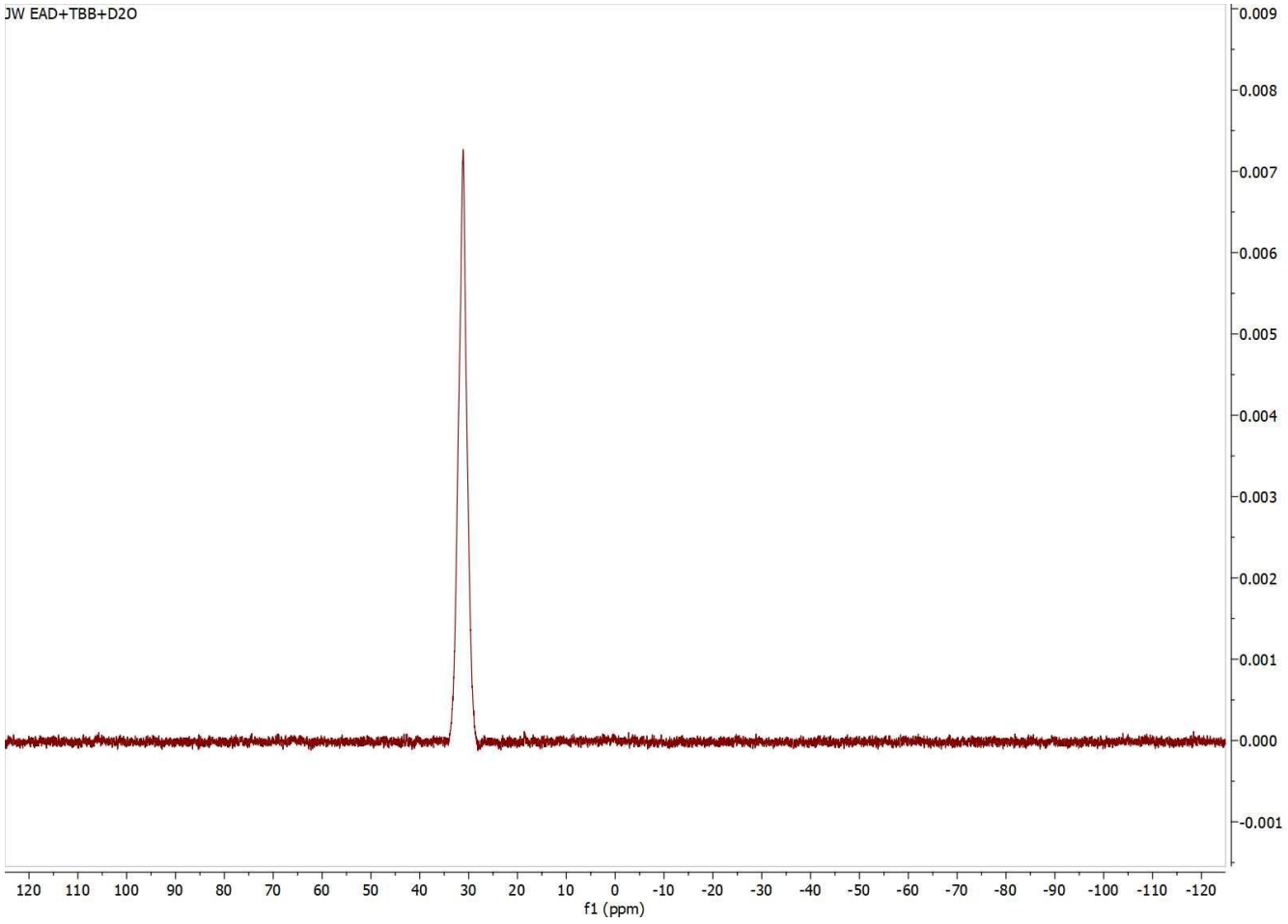
V)


JW ADTEPBC
190.34
172.70
161.51
77.45 CHLOROFORM-D
77.13 CHLOROFORM-D
76.82 CHLOROFORM-D
61.53
54.83
41.09
28.34
14.42
A (s)
190.34
C (s)
161.51
D (s)
61.53
G (s)
28.34
H (s)
14.42
0.81
0.47
3.02
2.18
2.79
f1 (ppm)

VI)


JW ADTEPBC
7.25 CHLOROFORM-D
B (q)
4.27
G (s)
2.45
H (t)
1.30
3.18
4.33
4.75
f1 (ppm)


JW EDA+TBB
0.0055
0.0050
0.0045
0.0040
0.0035
0.0030
0.0025
0.0020
0.0015
0.0010
0.0005
0.0000
-0.0005
120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120
f1 (ppm)


JW EAD+TBB+D2O
0.009
0.008
0.007
0.006
0.005
0.004
0.003
0.002
0.001
0.000
-0.001
120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120
f1 (ppm)

VII)