KJE-3900

MASTER'S THESIS IN CHEMISTRY

The Preparation of N-Methyliminodiacetic Acid Protected Alkynyl Boronates

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Contents

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Any errors or omissions in this thesis are the sole responsibility of the author. If there is anything in it that is useful or good:

SDG

Summary

The purpose of this work is to document the attempted syntheses of N-methyliminoacetic acid (MIDA) -protected alkynyl boronates according to procedures and methodologies that have been successfully employed in the syntheses of MIDA-protected alkyl, alkenyl, aryl and heteroaryl boronates. The rationale for the development of this class of MIDA-protected boronates is presented, both in terms of some of the more synthetically useful boronic acid reactions, which would demonstrate the desirability of the inclusion of the boronic functionality in the molecule, and in terms of the alkynyl functionality and its synthetic utility. This was done to show the potential synthetic utility and versatility of these MIDA-protected boronates.

The synthetic approaches to these desirable compounds are presented. The results of each of these synthetic approaches are examined, and potential shortcomings and errors in each approach are identified.

New synthetic approaches and potential experiments are identified that may be successful in the goal of successful syntheses of these potentially valuable synthetic building blocks.

Keywords: alkynyl boronates, N-methyliminodiacetic acid, protecting group, Suzuki coupling, Pauson-Khand reaction, trifluoroborate salts, boron electrophilicity, stability, building blocks

1

Introduction

1.1 General

The synthesis of organic compounds has been, is, and will likely continue to be, the single greatest impetus in the advancement of organic chemistry. These compounds can be natural products, modified natural products, or completely new and novel compounds. The field of organic synthesis has expanded since Kolb's synthesis of acetic acid in 1845[1]. The total synthesis of organic compounds, both natural and unnatural products, and the chemical modification of existing compounds, will continue to be a driving force in organic chemistry well into the 21st century. To support this burgeoning research, many reactions have been developed and modified. There have been new reagents developed, and variations on reactions and reaction conditions have been investigated. The results of these areas of investigation have been reported in the primary and review literature, in basic and advanced textbooks[2-5], and monographs[6-10], including many compilations of name reactions[11-13], which are supplemented by works on protecting groups[14-16].

Among the many name reactions that are currently in use, some of the most useful involve the formation of new carbon-carbon bonds, thereby leading to greater molecular size and complexity. One of the most useful carbon-carbon bond forming reactions is the Suzuki (or Suzuki-Miyuara) cross-coupling reaction[1, 8, 17-19]. This involves the reaction of an organoboronic acid with an organohalide with a Pd^0 catalyst, under basic conditions. It has many advantages over other related carbon-carbon bond forming reactions, such as the Stille reaction[11-13, 20, 21]. The comparatively low toxicity of organoboron compounds, coupled with the ease of removal of boron side products, make the Suzuki coupling a powerful tool in organic synthesis. There are some serious drawbacks, however. The boronic acid group can be very sensitive to a variety of reaction conditions[22-29], which can limit its use in certain multistep reactions. There have been various protecting groups developed for the boronic acid functionality. They include simple esters, 1,2 and 1,3 diol esters[15, 21], pinacol esters[24, 25], diethanolamine esters[24, 25] and others[27-

[30]. All of these methods have failed to produce a boronate ester that is well attenuated against a wide range of reaction conditions, yet is also easy and convenient to deprotect when necessary.

Recently, there has been considerable interest and research in the use of N-methyliminodiacetic acid (MIDA) (Figure 1.1) as a protecting group for the boronic acid function. MIDA boronates possess a wide variety of properties that make their use in multistep reactions extremely attractive[24]. They are free flowing, monomeric crystals, which are stable under prolonged storage, under air, on the benchtop. They are stable to silica gel, and are therefore easily purified by chromatography. They are soluble in a range of polar and nonpolar solvents, and can withstand extremely harsh reaction conditions, including chromic acid oxidation. Yet they are easily hydrolyzed under mild basic conditions to yield the corresponding boronic acid.

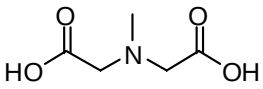


Figure 1.1 N-Methyliminodiacetic Acid

An initial study by Mancilla[31], involving iminodiacetic acid and MIDA-protected phenyl boronates, has continued into ongoing activities in several research groups. One of the leading research groups in this area has been that of Burke[24, 32-39]. All of the reported research in this area has focused on the use of MIDA to protect alkyl, alkenyl, aryl and heteroaryl boronic acids. There has been little reported data on the preparation and use of MIDA-protected alkynyl boronates.

1.2 Objective and Approach

A protected alkynyl boronate could be of potential value in cycloaddition reactions, such as the Diels-Alder and Pauson-Khand reactions. The objective of this research project has been to attempt to develop and prepare a series of MIDA-protected alkynyl boronates (Figure 1.2), analogous to the currently accessible MIDA-protected alkyl, alkenyl, aryl and heteroaryl boronates.

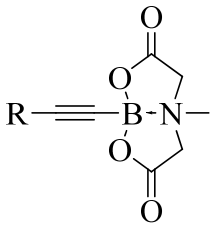


Figure 1.2 MIDA-Protected Alkynyl Boronate

There are currently several methods for the preparation of MIDA-protected alkyl, alkenyl, aryl and heteroaryl boronates. These were adapted to attempt to prepare MIDA-protected alkynyl boronates. Additionally, two novel methods were developed, based upon related procedures for other protecting groups (Figure 1.3).

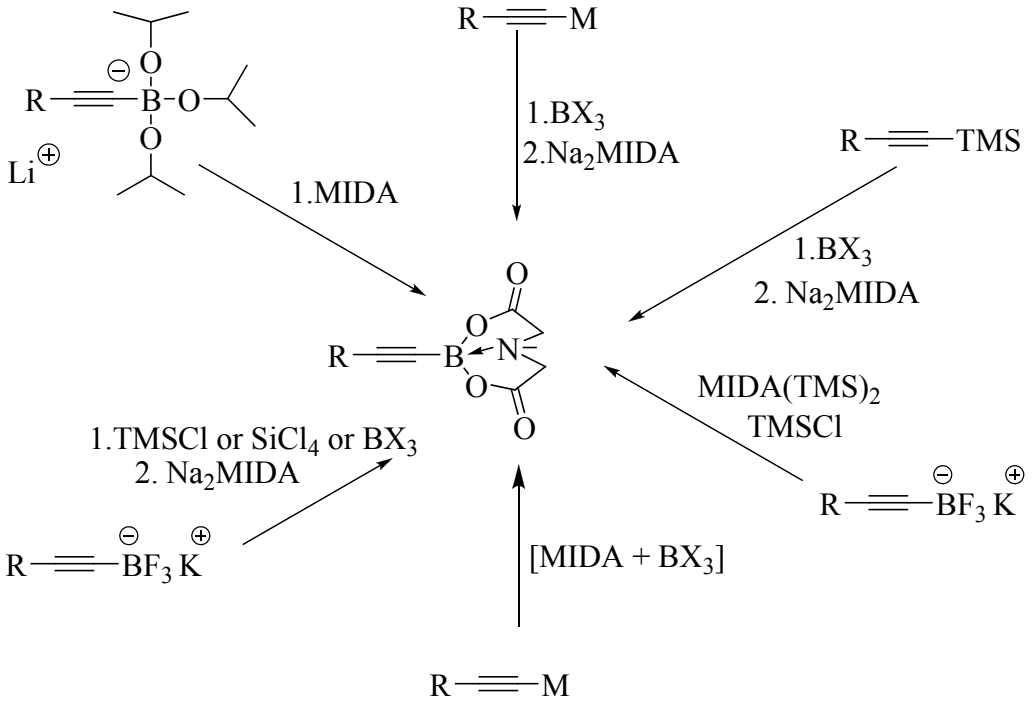


Figure 1.3 Routes to MIDA-Protected Alkynyl Boronates

The approaches that were selected for this project were:

- Reaction of the alkyne Grignard or lithiate with triisopropylborate, then with MIDA
- Reaction of a trimethylsilyl (TMS) -protected alkyne with boron halides, then with the sodium salt of MIDA (Na_2MIDA)
- Reaction of the alkyne Grignard or lithiate with boron halides, then with Na_2MIDA
- Reaction of Na_2MIDA with boron halides, then with the alkyne Grignard
- Activation of trifluoroboronate salts, then reaction with Na_2MIDA, or with TMS-protected MIDA

These approaches will be discussed in greater detail in subsequent sections.

2

Background Information

2.1 The Role of Alkynes and Boronic Acid Derivatives in Organic Synthesis

Organic synthesis can be considered the fundamental driving force for all of organic chemistry. The search for ways to replicate naturally occurring products, related analogs of these compounds, and the search for new and completely distinctive molecules has provided the impetus for the development of new reactions, the optimization of reaction conditions, and the development of theories to explain and predict the course of organic reactions, leading to the synthesis of new and modified compounds. A visit to the organic chemistry section of any reasonably equipped university library will reveal a plethora of books devoted to the subject of organic synthesis. There are the general books[4-6, 40, 41] on the subject, usually focused on the strategies of synthesis, and the tactics developed to accommodate the strategies developed. There are also volumes compiling the various name reactions[11-13] and others detailing practical considerations involved in the effective conduct of organic synthetic transformations[9, 10, 42-45]. This is not to be considered an exhaustive listing of books, but rather as an illustrative example of the importance that the synthesis of both well characterized and novel compounds has in organic chemistry. In addition, there are literally hundreds of journals with some degree of focus in organic synthesis, with thousands of articles being published annually.

There are, generally speaking, two approaches to take in organic synthesis[4, 40]. One may begin with the target molecule, and begin to "disconnect" it (retrosynthetic analysis)[4, 41] to "synthons" which may in turn be correlated to available reagents; or one may begin with existing compounds and functional groups ("building blocks"), and begin to synthesize more complex, or more versatile compounds from them. In either case, the syntheses can be conducted by a linear approach (Figure 2.1), by a convergent approach (Figure 2.2) or by combinations of the two. The use of building blocks facilitates the development of a synthetic strategy involving greater use of convergent syntheses rather than a simple, straight-line linear synthesis. Convergent syntheses

allow for greater flexibility in synthesis modifications, and have higher yields than linear syntheses. This project has focused on the development of robust building blocks incorporating a protected boronic acid derivative, in order to allow for simpler, yet more flexible, convergent synthetic strategies.

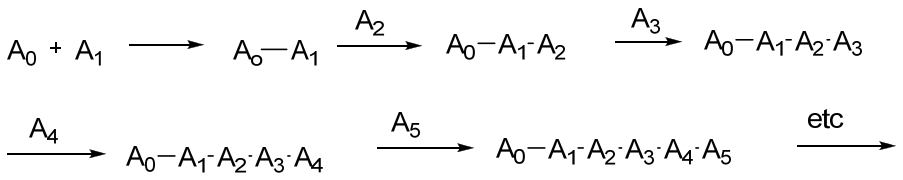


Figure 2.1 Linear Approach to Synthesis

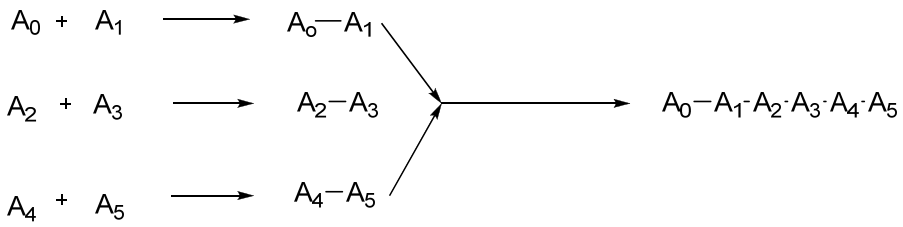


Figure 2.2 Convergent Approach to Synthesis

The goal of this research project was to develop an effective protecting group for a boronic acid derivative that also contained an adjacent alkyne functionality, that the diverse chemistries of both functional groups could be utilized in the same building block compound. The formation of a boronic functionality in an alkyne containing molecule, the protection of that boronic group, subsequent reactions of the alkynyl functionality, followed by deprotection and reactions of the boronic function, would allow for greater flexibility in synthesizing complex molecules.

Some of the interesting reactions of the alkynyl and boronate functionalities in creating complexity in organic compounds are briefly examined below, in order to demonstrate some of the potential advantages of protected alkynyl boronates.

2.2 Some Interesting Reactions of the Boronic Acid Functional Group

2.2.1 General

The purpose of this section is not to provide an exhaustive compilation of the reactions, and reactivity, of organoboron compounds. Its purpose is to illustrate some of the reactions that have made organoboron chemistry such a fertile area of research in organic synthesis. The reader who is interested in a more comprehensive study of organoboron chemistry is directed to numerous monographs[7, 8, 11, 13, 17-22, 46-49] and review articles[1, 24, 26, 30, 50-52], among many others, for further details on the scope and viability of organoboron chemistry.

2.2.2 The Suzuki Reaction

The Suzuki reaction, or as it is often referred to, the Suzuki-Miyaura reaction (Figure 2.3) is one of the most useful reactions in organic synthesis[50]. It is a Pd^0 catalyzed cross-coupling reaction between an organoboronate and an organohalide under basic conditions. The basis of the reaction is transmetallation from boron to palladium.

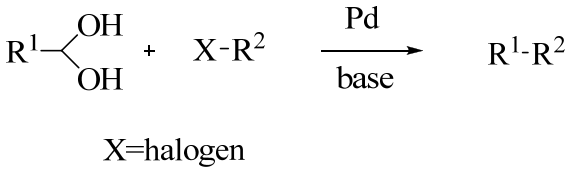


Figure 2.3 The Suzuki-Miyaura Coupling Reaction

The organohalide can be alkenyl, aryl or heteroaryl, and the boron reagent can be alkyl, alkenyl, aryl or heteroaryl.

The mechanism of the Suzuki-Miyaura reaction is generally held to be similar to other Pd^0 catalyzed cross-coupling reactions[21]. The initial step is oxidative addition of the Pd^0 catalyst to

the organohalide, followed by transmetallation with boron, and finally reductive elimination of the product. A representative reaction cycle is provided (Figure 2.4).

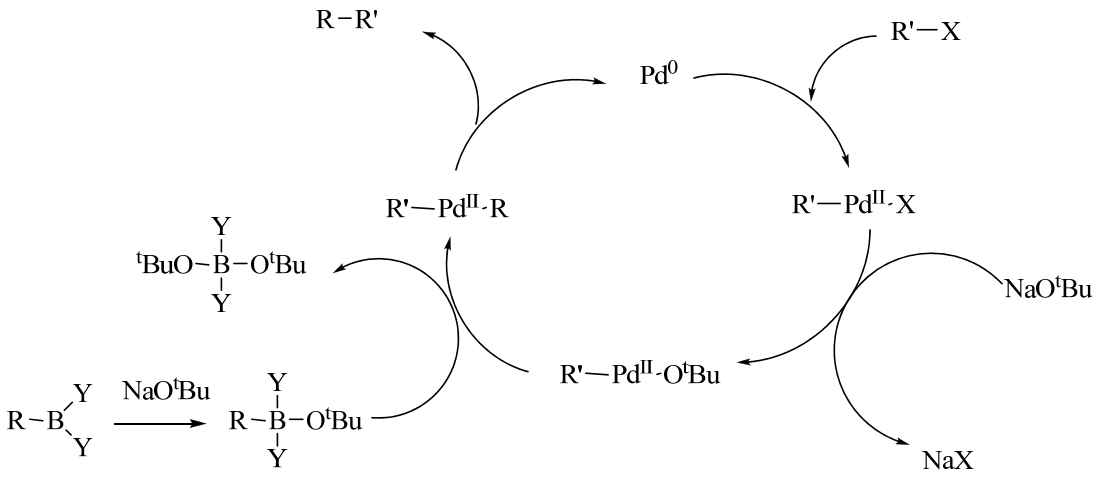


Figure 2.4 General Mechanism of the Suzuki-Miyaura Reaction

The Suzuki reaction has several advantages over other cross-coupling reactions such as the Kumada coupling (Grignard reagents), the Negishi coupling (organozinc reagents), the Hiyama coupling (organosilicon reagents), and the Stille coupling (organotin reagents)[21]. The organoboron reagents can be synthesized by a variety of methods, including mild or *in situ* conditions. The organoboron reagents, by comparison to other organometallic compounds, are of fairly low toxicity, and the boron containing by products are easily removed from the product by aqueous extraction. The Suzuki reaction does have some limitations, though. The reaction does require either base or fluoride to occur, which may not be compatible with some substrates. The use of anhydrous conditions can often mitigate this problem. The reagents also can be difficult to purify, and are polar compounds, which can react with many common reagents, which limits their use in many multistep syntheses. The deactivation of the organoboron reagent via various protecting groups has been the focus of considerable efforts by many research groups, as will be discussed below.

The Suzuki reaction is a powerful tool for creating new carbon-carbon bonds in multistep reactions. The relative ease of reactivity of the organoboron reagent with other reactants, however, often requires that the organoboron functionality be introduced immediately prior to the Suzuki coupling step. The development of a range of effective protecting groups for the organoboron reagent will greatly widen the scope of this reaction in multistep organic syntheses.

2.2.3 Other Reactions of Organoboronates

There are many other reactions of organoboron compounds that have utility in organic synthesis. Two of these reactions are summarized, in order to further elaborate on the advantages of organoboron compounds, and to demonstrate the need for effective protecting groups for these versatile reagents.

Chan-Lam Coupling The Chan-Lam coupling[11] is the reaction between an alkyl, alkenyl or aryl boronic acid and an N-H or O-H functionality, catalyzed by Cu^{II}, resulting in a new C-N or C-O bond. The reaction appears to proceed by transmetallation between boron and copper.

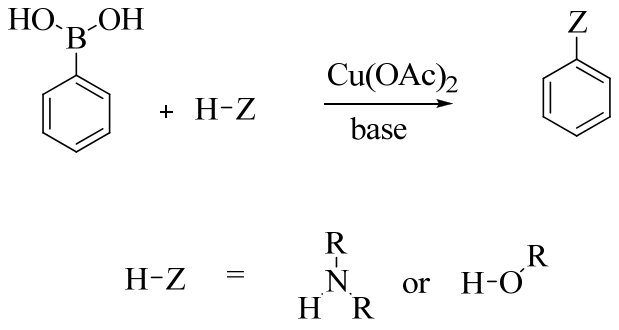


Figure 2.5 The Chan-Lam Coupling Reaction

Liebeskind-Srogl Coupling The Liebeskind-Srogl coupling[11] is the Cu^{I} catalyzed reaction between an organoboronic acid and a thioester to produce a ketone.

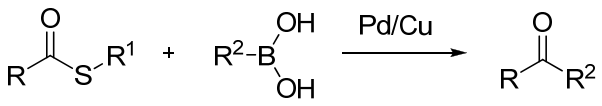


Figure 2.6 The Liebeskind-Srogl Coupling Reaction

2.3 Some Interesting Reactions of the Alkyne Functional Group

2.3.1 General

As was the case with the organoboronate chemistry discussed above, the purpose of this section is not to provide an exhaustive review of the chemistry and reactivity of alkynes. Such a review would be well beyond the scope of this paper. Its purpose is to illustrate some of the reactions that make alkyne chemistry a valuable tool in organic synthesis. Specifically, this section will briefly examine four cycloaddition reactions that are of known utility in creating complex molecules. As in the case of the organoboronates discussed above, the reader who is interested in other alkyne reactions, or these reactions in greater detail, is directed to a number of basic and advanced textbooks[2, 3, 5], monographs[53-55], and review articles[56-59], among many others, for further information.

2.3.2 The Diels-Alder Reaction

The Diels-Alder reaction is undoubtedly the best known of all pericyclic reactions[3, 54, 60]. It is classified as a thermally allowed [4+2] cycloaddition between a diene and a dienophile. It is, therefore, an excellent reaction pathway for the formation of six-membered ring systems. Alkynes can readily function as dienophiles, particularly if there are electron withdrawing groups attached to the triple bond, resulting in cyclohexadiene structures (Figure 2.7).

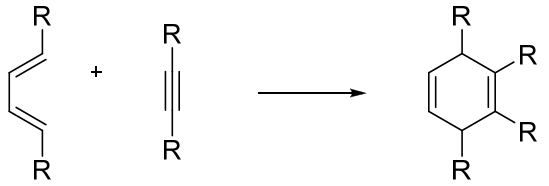


Figure 2.7 The Diels-Alder Reaction

An alkynyl boronate would produce a boryl 1,3 cyclohexadiene system. These types of compounds are currently unknown[61]. Protected alkynyl boronates could enable these compounds to be synthesized.

2.3.3 The Pauson-Khand Reaction

The Pauson-Khand reaction is another extensively researched reaction[55, 57, 59, 62-68]. The Pauson-Khand reaction is a pathway to cyclopentenones. Like the Diels-Alder reaction and cyclotrimerization reactions, it is a powerful tool for increasing molecular complexity[68]. The cyclopentenone ring structure is present in a variety of natural products and drug targets, including prostaglandins. Other biologically active compounds also contain cyclopentenone structures, due to the versatility of the α,β-unsaturated carbonyl functionality[59].

Cyclopentenones can therefore be utilized in natural product and drug syntheses, and the inclusion of a boronic functionality, capable of participating in Suzuki couplings or other reactions, would create potential building blocks for increasing complexity for natural product and medicinal chemistry.

The Pauson-Khand is formally a [2+2+1] cycloaddition reaction involving an alkyne, an alkene, and carbon monoxide (CO) (Figure 2.8). It can be either intermolecular or intramolecular, and entails the formation of three new bonds, and one or two new cyclic structures (in the intermolecular and intramolecular versions, respectively). The initial studies involved reactions with stoichiometric quantities of dicobalt octacarbonyl, to provide for the complexation of the alkyne with Co, and for providing the CO necessary for the reaction. More recent studies have developed the use of other transition metal catalysts, such as Zr, Ni, Fe, Ti, W, and Mo

derivatives for the stoichiometric reaction, and Co, Ti, Ru, Ir and Rh complexes for the catalytic version of this reaction[56, 68].

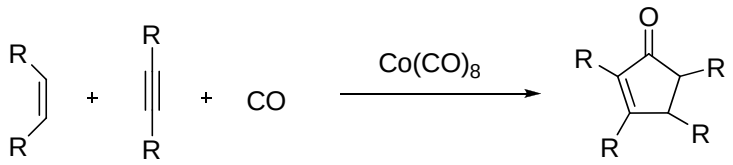


Figure 2.8 The Pauson-Khand Reaction

2.3.4 The Azide-Alkyne Huisgen Cycloaddition

The Azide-Alkyne Huisgen Cycloaddition is a 1,3 cycloaddition reaction between an azide and a terminal or internal alkyne to produce a 1,2,3-triazole (Figure 2.9)**.** 1,2,3-triazoles are used as building blocks for more complex chemical compounds such as pharmaceuticals[69]. The copper-catalyzed azide-alkyne Huisgen cycloaddition is a valuable tool in "click chemistry", a chemical philosophy proposed by Sharpless[70] which describes an approach tailored to prepare compounds quickly and reliably by joining smaller units together. This approach mimics nature, which also produces compounds by joining together smaller modular units.

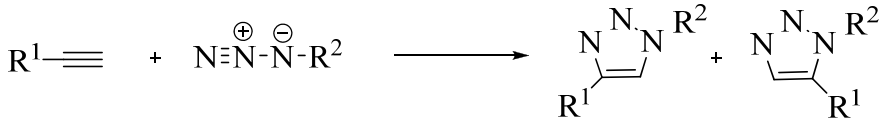


Figure 2.9 The Azide-Alkyne Huisgen Reaction

2.3.5 Alkyne Cyclotrimerization

An alkyne cyclotrimerization reaction is a [2+2+2] cycloaddition reaction in which three alkyne molecules combine to form a six-membered aromatic compound[20, 71]. The reaction is not completely a pericyclic one. It has not been observed to occur without the use of metal catalysis; and the metal catalyst assembles the ring stepwise via intermediates. The cyclization of acetylene to benzene was first reported by Berthelot in 1866. The reaction required very high temperatures and was not very selective, producing a complex mixture of products. Interest in this area remained minimal until the 1940s, when Reppe discovered that nickel could catalyze the formation of substituted benzenes from acetylenic compounds. Subsequent research has developed additional catalytic systems, with many different transition metals, with improved selectivity and utility. A suitably protected boronic functionality, attached to one or more of the individual acetylenic components of such reactions, could form the basis for increasing molecular complexity and diversity in natural product and pharmaceutical chemical research[72].

The proposed reaction mechanism for these cyclotrimerizations involves the coordination of two alkynes, followed by the formation of a metallacyclopentadiene. This metallacyclopentadiene can either insert another alkyne and undergo a reductive elimination to form the arene, or it may react as the diene in a [4+2] cycloaddition, and then eliminate the metal species to form the arene. Either pathway will yield the same product. A representative reaction cycle, using a cobalt catalyst, is provided (Figure 2.10).

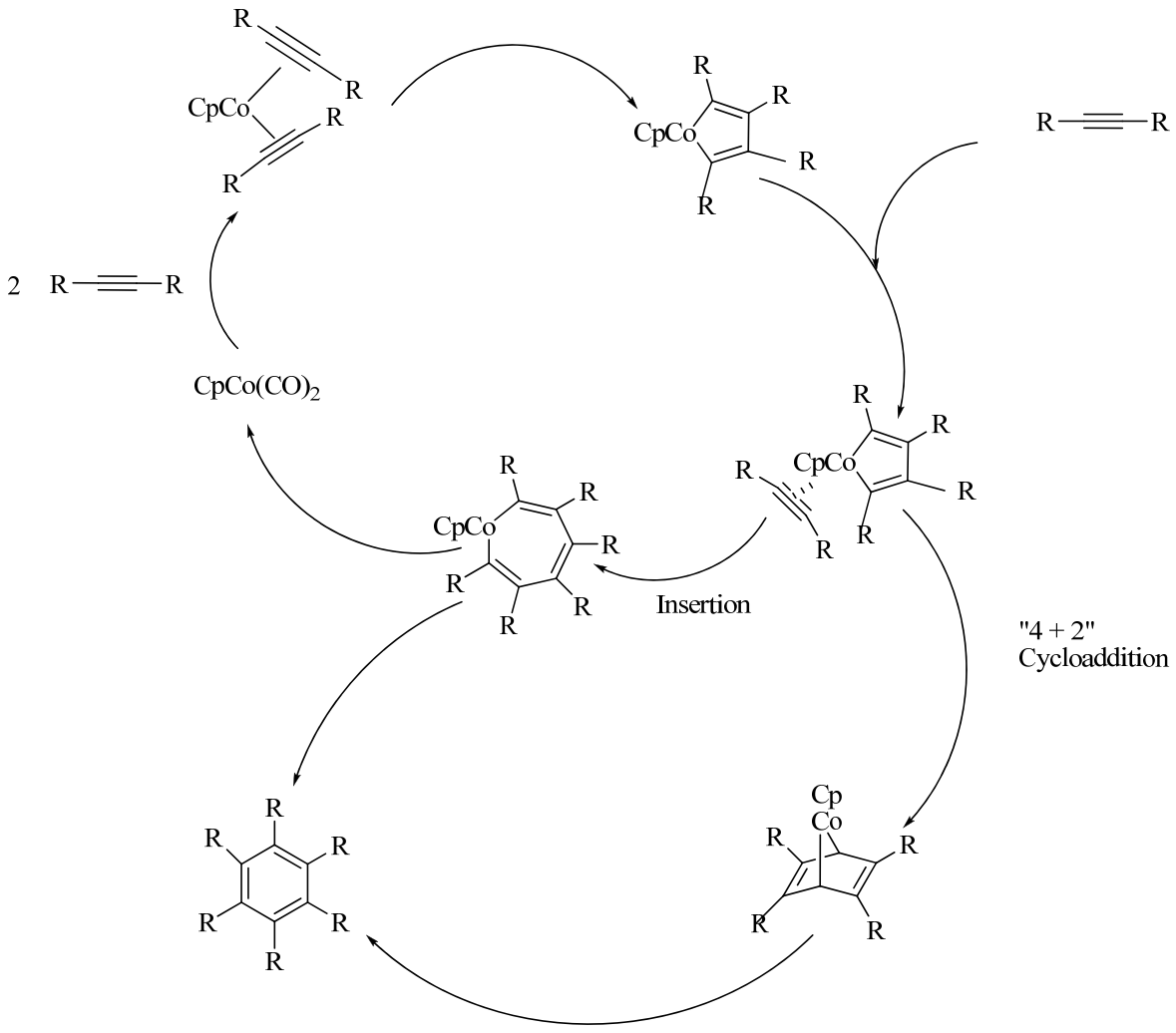


Figure 2.10 Proposed Reaction Cycle for Alkyne Cyclotrimerization

2.4 Protection of the Boronic Acid Functional Group

2.4.1 General

The preceding sections attempted to illustrate some of the interesting reactions, and some potential applications, of both the boronic and the alkyne functional groups. In the course of any synthesis, whether involving these functional groups, or others, it is often necessary to shield one or more functional groups from the conditions of a given reaction step, and then reactivating these functional groups as required for subsequent reactions. These incompatibilities of functional groups with various reaction conditions have plagued the synthetic chemist almost for

the entire history of organic chemistry. Protecting groups have been developed for many functional groups, and have been compiled in various excellent monographs on the subject[14-16, 73]. There are certain desired characteristics for an effective protecting group[14]:

1. The protecting group should be easily and efficiently introduced.
2. It should be cheap or readily available.
3. It should be easy to characterize and avoid complications such as the creation of new stereogenic centers.
4. It should be stable to chromatography.
5. It should be stable to the widest possible range of reaction conditions.
6. It should be removed selectively and efficiently under highly specific conditions.
7. The by-products of the deprotection should be easily separated from the substrate.

There are, of course, disadvantages to the use of protecting groups. Each protecting group implies two additional steps in an overall reaction scheme—protection and deprotection. This will inevitably lead to a reduction in overall yield, and a sometimes significant increase in costs due to materials and researcher time. However, the use of protecting groups is often unavoidable in the pursuit of novel and complex molecules. Careful selection and utilization of the various protecting groups available for each specific functional group, and for each set of reaction conditions, coupled with careful synthesis analysis and planning, will mitigate the negative impacts of functional group protection and deprotection, and will permit the most efficient synthetic pathways to desired target molecules.

Protecting groups, with their varied methods of introduction and removal, have been developed for most common functional groups, and compiled in a number of excellent monographs[14-16, 73]. These common functional groups include hydroxyl, diols, phenol, thiol, carbonyl, carboxyl, amino, phosphate, alkene, diene and alkyne groups. In only one of these monographs[15], are any protection techniques discussed that are specifically for the boronic acid group. These techniques are limited to the use of simple unhindered, and stereochemically hindered diols. There are,

however, other types of protecting groups that have demonstrated potential for use in boronic acid functional group protection.

In the protection of boronic acids, it is necessary to consider both the reactivity of the B-O bond, and, because of the valence deficiency of boron, the effects of a low-energy unoccupied p-orbital (Figure 2.11).

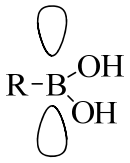


Figure 2.11 The Vacant p-orbital of a Boronic Acid

2.4.2 Simple Diols

Boronic acids readily form esters from simple alcohols such as methanol or 2-propanol. Such esters are available commercially, but are very prone to hydrolysis, and must be handled under strict anhydrous and anaerobic conditions. In a similar manner, boronic acids can form esters with simple 1,2 and 1,3 diols (Figure 2.12). These esters are more stable, and are more easily formed due to the favorable equilibrium[23].

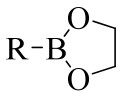


Figure 2.12 1,2 Diol-Protected Boronic Acid

As with the simple esters, such diol esters, while easily formed, are also very susceptible to hydrolysis[15]. This limits their utility in many reactions.

2.4.3 Pinacol Esters

Cyclic esters are more stable protecting groups for the boronic acid functionality. In particular, pinacol esters (Figure 2.13) are very stable, and are the most commonly encountered commercially available boronate esters[25]. They are readily formed, and help attenuate the boronic acid reactivity by a partial overlap of the nonbonding electron pairs on the oxygen atoms with the vacant orbital on the boron atom[24] (Figure 2.14). However, they are not as easy to remove, often requiring relatively harsh conditions.

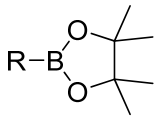


Figure 2.13 Pinacol Boronate Ester

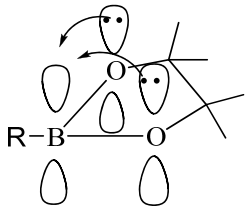


Figure 2.14 Orbital Overlap in Pinacol-Boronate Protection

Sterically hindered pinacol derivatives have been successful employed in stereoselective syntheses[27, 28].

2.4.4 Diethanolamines

The use of diethanolamines can result in even more stable boronate esters (Figure 2.15), due to the overlap of the nonbonding electron pair on the basic nitrogen with the empty orbital on boron (Figure 2.16).

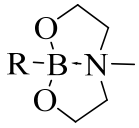


Figure 2.15 Diethanolamine Boronate Ester

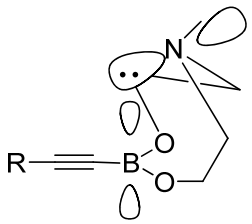


Figure 2.16 Orbital Overlap in Diethanolamine-Boronate Protection

Such esters can be readily removed by treatment with aqueous acid or ammonium chloride[25]. Hence this would be a useful protecting group in nonacidic reaction conditions. However, for reactions such as the Suzuki-Miyaura coupling, which require basic conditions; this would entail liberating the free boronic acid and then transferring it to the basic reaction conditions, a step that would subject the liberated boronic acid to degradation and other undesired side reactions. Additionally, these esters are not stable to silica gel[24].

2.4.5 N-Methyliminodiacetic Acid

There has, in recent years, been a tremendous amount of research in the area of boronic acid protection by use of the N-methyliminodiacetic acid ligand (MIDA)[24, 32, 35, 39] (Figure 2.17). Much of this research has been conducted by Burke's group at the University of Illinois. In fact, a recent monograph of name reactions[74] has a section entitled "Burke's boronates" describing this class of compounds (Figure 2.18). The research project for this thesis was to expand upon these efforts. The use of this ligand to prepare protected boronic acid derivatives of terminal alkynes will be discussed in greater detail in the Results and Discussion section of this thesis. Some general information is provided here.

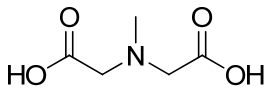


Figure 2.17 N-Methyliminodiacetic Acid (MIDA)

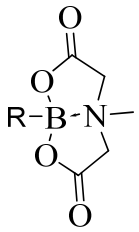


Figure 2.18 MIDA-Protected Boronate

MIDA-protected boronates are, in general, easy to prepare, and are very stable compounds, with an almost unlimited shelf life. They are highly crystalline, free-flowing solids, which are compatible with silica gel chromatography, allowing for isolation and purification by column chromatography, and reaction monitoring by thin layer chromatography (TLC). They are also stable under a wide variety of reaction conditions, including chromic acid oxidations.

The boronic acid can be liberated under very mild conditions using aqueous bases such as NaOH or even $NaHCO_3$. MIDA-protected boronates have been used in a wide range of iterative Suzuki coupling schemes, leading to complex total syntheses of natural products and pharmaceutical agents[24].

In a manner similar to the diethanolamines, MIDA-protected boronates attenuate the reactivity of the low-energy empty orbital on boron with an effective overlap of the nonbonding electron pair of the nitrogen with the vacant orbital of the boron.

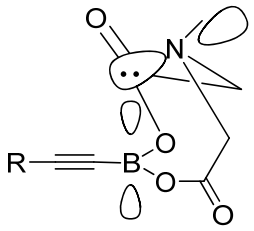


Figure 2.19 Orbital Overlap in MIDA-Protected Boronates

Many of these compounds are commercially available. Sigma-Aldrich currently lists, in its on-line catalog, 71 different MIDA-protected boronate building block compounds. They encompass a range of boronic acid derivatives; alkyl (9), alkenyl (9), alkynyl (2), aryl (34) and heteroaryl

(17). They currently are among the premier protecting groups for the boronic acid functional group, particularly when being using in iterative cross-coupling reactions[24]. Their stability could also be of great utility in other multistep reaction schemes.

2.4.6 Trifluoroborate Salt

Boron has a high affinity for fluoride, and a trifluoroborate salt (Figure 2.20) can be formed by treatment of the boronic acid with KHF_2 [25, 75, 76]. These compounds are crystalline and very stable toward air and water, owing to the tetrahedral stabilization of the boron atom[77]. These trifluoroborate salts have been used directly in reactions as protected boronate equivalents[78, 79], or as intermediates in the formation of other protected boronates, such as those using the MIDA ligand.

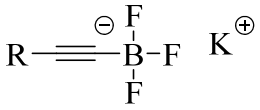


Figure 2.20 A Potassium Trifluoroborate Salt

3

Results and Discussion

"For it is easy in experimentation to be deceived, and to think one has seen and discovered what we desire to see and discover."

Luigi Galvani

3.1 General

Boronic acids are extremely valuable building blocks in organic synthesis[22]. There has been considerable interest recently in the development of robust N-methyliminodiacetic acid (MIDA) -protected boronic acids[24, 32-39]. MIDA boronates have many advantages in extending the utility of boronic acid chemistry. They can be prepared, analyzed, and purified easily. They are monomeric, free-flowing crystalline solids that are stable to long-term storage under air. They are stable to a wide range of laboratory reaction conditions, yet can be readily hydrolyzed, when desired, under mild basic conditions[24], making them ideal additions to the synthetic chemist's arsenal of reagents.

The above paragraph is very true for most boronic acid derivatives. A considerable amount of research has been done in the areas of MIDA-protected alkyl, alkenyl, aryl and heteroaryl boronates[24, 32-39]. Many of these compounds are now commercially available, and the number continues to grow.

The same cannot be said of alkynyl boronates. There are no published procedures and methodologies for the preparation of MIDA-protected alkynyl boronates. Currently, there are two MIDA-protected alkynyl boronates commercially available, and they are of the two simplest

alkynes, ethyne and propyne. No established procedures could be determined for their preparation.

The objective of this project was to attempt to replicate the great success of utilizing the MIDA group in the protection of alkyl, alkenyl, aryl and heteroaryl boronates, and extend it to the preparation of alkynes, bearing alkyl and aryl substituents as well as hydrogen. These MIDA-protected alkynyl boronates were to be made available for other reactions involving the alkynyl functional group; specifically cycloaddition reactions such as the Pauson-Khand reaction.

Several different approaches (Figure 3.1) were examined and tested, in order to determine if the MIDA-protecting group could be successfully applied to an alkynyl boronate, and to determine also the most effective and efficient methods to accomplish this transformation. These approaches were presented in the Introduction section of this thesis, and will be examined in more detail in subsequent paragraphs.

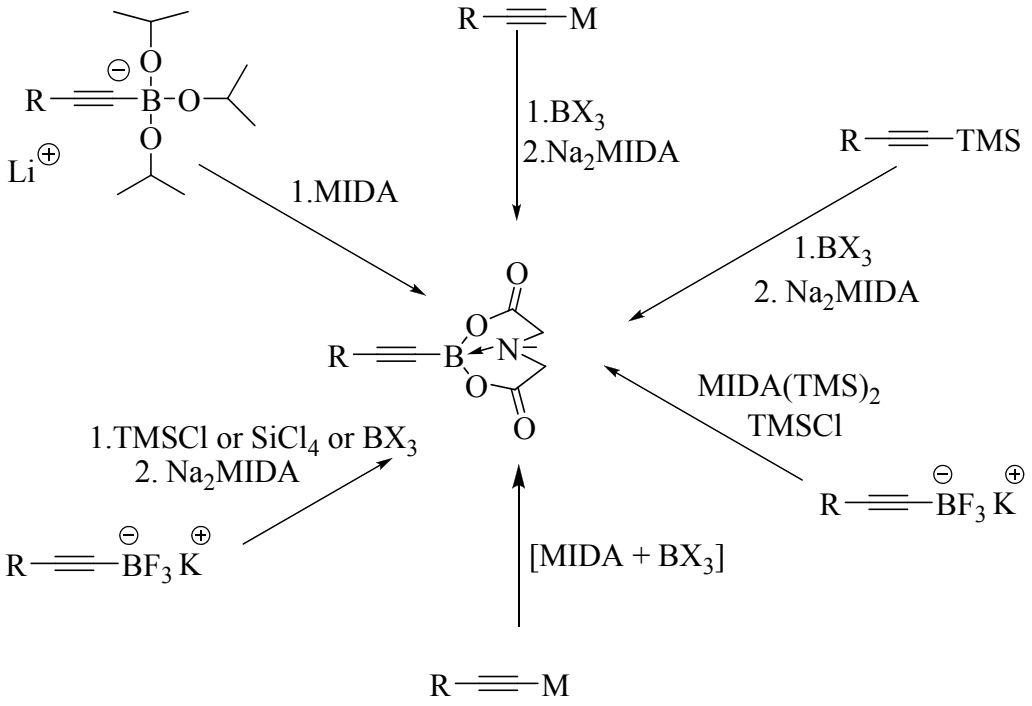


Figure 3.1 Approaches to MIDA-Protected Alkynyl Boronates

Unfortunately, the methods and conditions that have been tested, to date, have not been able to successfully duplicate the MIDA protection of alkyne boronates that was reported for alkyl, alkenyl, aryl and heteroaryl boronates[24, 32-39]. A MIDA-protected aryl boronate was successfully prepared, in accordance with the reported procedures, but no isolatable amounts of MIDA-protected alkynyl boronates were produced by any of the synthetic approaches tested. Potential reasons for the inability to produce isolatable MIDA-protected alkynyl boronates will be examined, in both the general terms of alkyne and boron reactivities, and in each specific approach. For each approach, the reactions will be examined, possible causes for the failure will be developed, and additional experiments that might remedy the difficulties, or provide greater insights in the problems associated with the preparation of MIDA-protected alkynyl boronates, will be suggested.

3.2 The Alkynyl Boron Bond

MIDA-protected alkyl, alkenyl, aryl and heteroaryl boronates have been well developed[24, 32-39]. MIDA-protected alkynyl boronates have not yet been investigated to the same degree. There are profound differences between alkenes, aromatic compounds, and definitely alkanes, and alkynes. The triple bond of an alkyne is not merely a simple increase over the double bond of an alkene[2, 3]. An alkyne is in a state of sp hybridization, as opposed to the sp^3 hybridization of an alkane, or the sp^2 hybridization of an alkene. The greater s character of the alkyne triple bond increases its electronegativity[80], resulting in the triple bond being shorter, and the electrons more tightly held. This can readily be seen in the relative acidity of the alkynyl hydrogen, as opposed to the alkyl, aryl and alkenyl hydrogens. The approximate pKa of the terminal alkynyl hydrogen is approximately 25[2], while the corresponding pKa's of alkyl hydrogens are 48–50, the pKa's of alkenyl hydrogens c. 44, and the pKa's of phenyl hydrogens c. 43[2]. As a result, alkynyl hydrogens can be easily abstracted by common laboratory reagents, such as butyl lithium or sodium amide, while the hydrogens of the other classes are extremely difficult to remove. The terminal C-H bond is shorter in alkynes than in alkanes and alkenes. Increasing s-contribution to the hybridization level is a cause of this. This shortening is directly proportional to the amount of s-character, so the change from ethane (33% s-character) to ethyne (50% s-character) is about twice the change of going from ethane (25% s-character) to ethane (33% s-character)[80]. The boron-carbon would be similarly shortened. This may contribute to the alkynyl boronates,

particularly when still linked to a metal fragment, being vulnerable to many electrophiles at the position β to the boron atom[81].

Boron is a Group 13 element and assumes a trigonal sp^2 configuration, with a low-energy empty orbital. Boron is electron deficient and seeks to fill its empty orbital, thus making it a powerful electrophile.

3.3 Stabilization of the Boronate Group

The electrophilicity of the boronic acid functional group can be attenuated by the use of various protecting groups. These protecting groups usually involve the formation of an ester linkage. The boron oxygen bond is extremely strong, being in the order of 808 kJ/mole[82]. Additionally, the overlap from the lone electron pairs on the oxygen can help attenuate the electrophilicity of the boron (Figure 3.2).

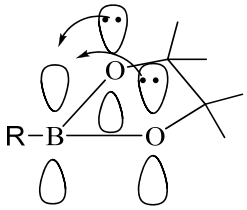


Figure 3.2 Electrophilicity Attenuation by Pinacol Ester

If the protecting group possesses an amino function, as is the case with diethanolamine (Figure 3.3) and MIDA (Figure 3.4), the attenuation of the boron electrophilicity can be even more dramatic. The greater overlap of the electron lone pair on the nitrogen with the empty boron orbital can be closer and less strained, thereby decreasing the boron electrophilicity, which is what was desired in the protecting group.

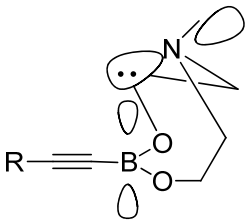


Figure 3.3 Orbital Overlap in Diethanolamine

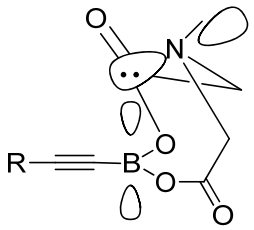


Figure 3.4 Orbital Overlap in MIDA

This decrease in the electrophilicity of the boron might be a contributing factor to an increased weakening of the carbon-boron bond, and increase the reactivity of the alkyne, rendering it more difficult to form the MIDA ester, or allowing for competing reactions that might destroy the MIDA-protected alkynyl boronate if formed (Figure 3.5).

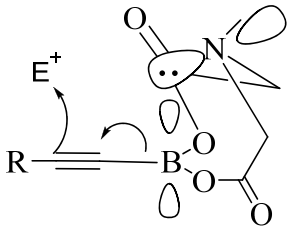


Figure 3.5 Weakening of Boron-Carbon Bond

3.4 Preparation of Starting Materials and Related Reactions

MIDA was prepared from iminodiacetic acid, formalin and formic acid according to the Organic Syntheses procedure of Ballmer[37, 39]. The reaction produced MIDA in an efficient manner, allowing for large quantities of this compound to be synthesized in the laboratory. The starting materials are inexpensive, and no special equipment is necessary. While MIDA is commercially available, this procedure allows for independence from the supplier, and an increased confidence in the products to be used in the subsequent reactions. Generating sufficient quantities of MIDA in the laboratory also allows for the rapid conversion of MIDA to other MIDA derivatives, in usable quantities, without undue concern for the depletion of the stock.

Na_2MIDA was prepared from the reaction of MIDA with NaOH, according to the procedure of Uno[37]. Excess NaOH is removed by refluxing with methanol, and the resultant white solid is dried by lyophilization with MeCN. A free-flowing white powder was obtained, which was used in subsequent reactions.

It was necessary to prepare a TMS-protected form of MIDA for testing in various reactions. There were no published procedures for the preparation of TMS-protected MIDA (Figure 3.6). Silyl esters of carboxylic acids are seldom used due to their sensitivity to mild acid or base conditions[14]. Therefore, different methods of protecting labile hydrogens and β-lactams with TMS were adapted: the method of Hergott[83] employing trimethylchlorosilane (TMSCl), and the methods of Bruynes[84] and Fritz[85], which used 1,1,1,3,3,3-hexamethyldisilazane (HMDS) with a saccharin catalyst.

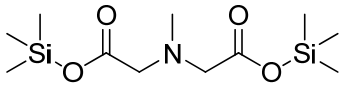


Figure 3.6 TMS-Protected MIDA

The procedure of Hergott [43] did not introduce the desired TMS functionality. TMSCl was reacted with both MIDA and Na_2MIDA with the same result. However the procedure developed from those of Bruynes[84] and Fritz[85] yielded the desired TMS-protected MIDA in a reproducible manner. The procedure that was used involved the reaction of MIDA with 1,1,1,3,3,3-hexamethyldisilazane (HMDS) in the presence of saccharin as a catalyst (Figure 3.7).

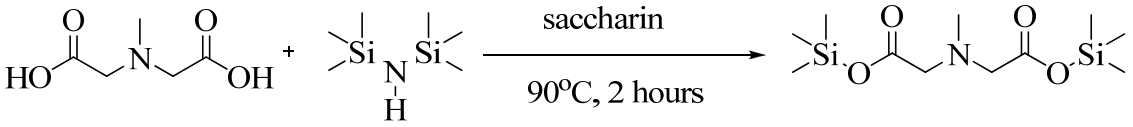


Figure 3.7 Preparation of TMS-Protected MIDA

After removal of residual solvent, the product was purified by vacuum distillation (138–140°C, 2.9 X 10^{-1} mbar) to yield a clear white viscous liquid (12.45 g, 85%). The product is extremely sensitive to atmospheric moisture, and was handled and stored under argon.

Extensive research has been done in the area of MIDA-protected alkenyl, alkyl, aryl and heteroaryl boronates[24, 32-39]. It was desired to replicate one of these preparations, in order to confirm the validity of the procedures and techniques employed in this project. Therefore, MIDA-protected phenyl boronate was prepared by a variation on the method of Ballmer[39] by reacting phenylboronic acid with MIDA in DMSO and toluene (Figure 3.8).

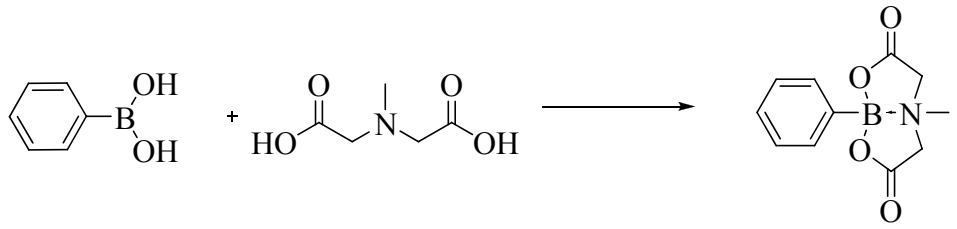
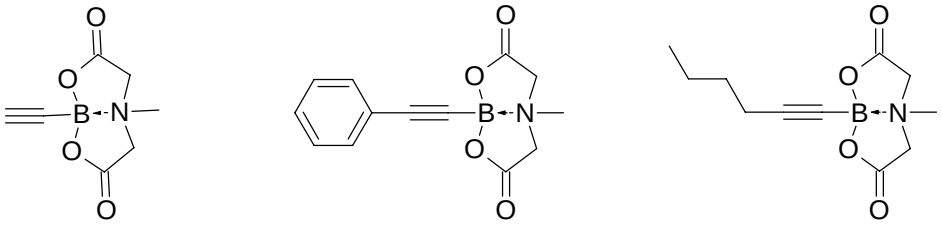


Figure 3.8 Preparation of MIDA-Protected Phenyl Boronate

MIDA was reacted directly with benzeneboronic acid, with toluene added to form an azeotrope with the liberated H_2O. The reaction was heated for 6 hours, with replenishment of toluene, and the product isolated by precipitation with Et_2O. Amber crystals were obtained (0.1061 g, 46%). This experiment demonstrated the ease of formation of MIDA-protected aryl boronates, and provided a reference to the desired preparation of MIDA-protected alkynyl boronates.

3.5 Target Molecules and Approaches

Three different types of MIDA-protected terminal alkynyl boronates were selected as targets. They were ethynyl (**1**), phenyl ethynyl (**2**), and hex-1-ynyl (**3**) (Figure 3.9). These compounds were selected in order to have some diversity in the carbon chain attached to the alkyne.



1 **2** **3**

Figure 3.9 Target Molecules for the MIDA Protection Study

Ethynylboronic acid MIDA ester (**1**) is commercially available and represents the simplest possible alkyne. Because of its availability as a reference, most of the syntheses conducted for this project were directed toward this compound. The total number of experiments for each target molecule is displayed in Table 3.1.

Table 3.1 Total Target Molecule Experiments

Target Molecule	**1**	**2**	**3**
Number of Experiments	29	17	3

The approaches that were selected for this project were:

- Reaction of the alkyne Grignard or lithiate with borate esters, then with MIDA
- Reaction of a trimethylsilyl (TMS) -protected alkyne with boron halides, then with the sodium salt of MIDA (Na_2MIDA)
- Reaction of the alkyne Grignard or lithiate with boron halides, then with Na_2MIDA
- Reaction of Na_2MIDA with boron halides, then with the alkyne Grignard
- Activation of trifluoroboronate salts, then reaction either with Na_2MIDA or with TMS-protected MIDA

Each of these sets of reactions will now be discussed in turn.

3.6 Syntheses of MIDA-Protected Boronates via Reactions of Organometallic Compounds with Borate Esters, then with MIDA

3.6.1 Results

This series of experiments was intended to prepare MIDA-protected alkynyl boronates by transesterification of simple alkynyl boronate esters with MIDA. The syntheses were based on the research of Burke's laboratory[24, 32-39], with related research and procedures of Pietruszka[86] , Mancilla[31], Brown[23, 87-89] and Matteson[90, 91]. The number of experiments for each target molecule is given in Table 3.2. Variations were made in solvents, reaction temperatures, borate esters, and reaction times. Additionally, MIDA-protected methyl and isopropyl borates were prepared, in order to examine and validate earlier procedures, and to determine any reaction similarities and difficulties.

Table 3.2 Transesterification Experiments

Target Molecule	**1**	**2**	**3**
Number of Experiments	9	4	1

The purpose of this series of experiments was to try to prepare MIDA-protected alkynyl boronates in a manner similar to that which had been so successful with alkyl, alkenyl, aryl and heteroaryl boronates[24, 32-39]. Additional experiments were conducted to evaluate earlier research, where the intermediate simple boronate esters were reacted with acid prior to isolation[23, 87-91]. Two types of acid, anhydrous HCl in ether, and BF_3 etherate were used. Variations were made in solvents, to determine the necessity of using DMSO as a solvent for MIDA, and toluene as an azeotrope former.

This series of experiments provided some interesting insights into the formation of the target boronates. Traces of what could be interpreted as the target boronate were detected in three of the experiments, and isopropyl MIDA borate was detected in two others.

The first set of experiments attempted to replicate the procedures of Gillis[33-35]. The basic reaction (Figure 3.10) was between either an ethynyl Grignard reagent or lithiated acetylene with either triisopropyl borate or trimethyl borate. The intermediate simple boronate ester was not

isolated, but was reacted with MIDA to effect a transesterification to a MIDA-protected boronate ester.

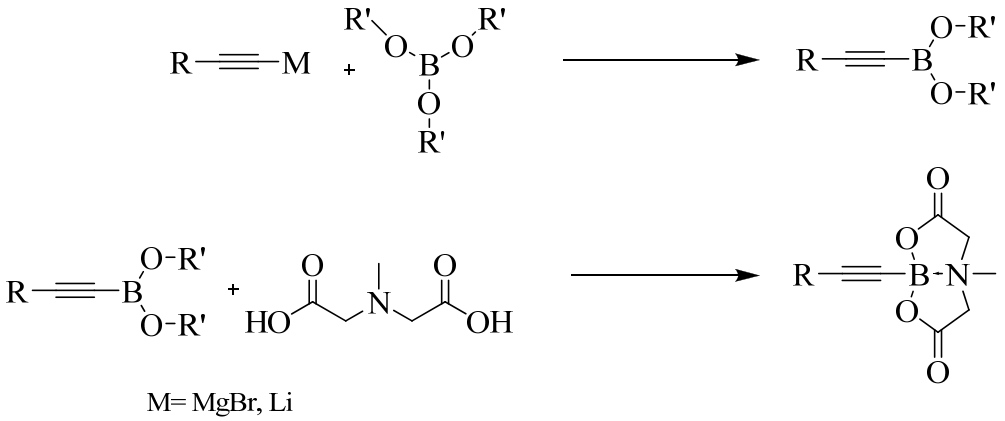


Figure 3.10 Basic Transesterification Reaction

The first two experiments were to compare the effects of temperature and time upon the initial simple ester formation. Both experiments were conducted using **1** as the target molecule. The first experiment reacted triisopropyl borate with the ethynyl Grignard reagent at -78°C for 30 minutes. The second experiment reacted triisopropyl borate with the ethynyl Grignard reagent at -78°C for 15 minutes, followed by a reaction time of 1 hour at RT. A much darker product was noted in this second procedure. Upon removal of excess solvent, the simple esters were transferred, dropwise to a second flask containing MIDA in DMSO at 90°C, and distilled under vacuum. Toluene was added to the flask in the second experiment. Distillation was continued for 2 hours, with replacement of toluene in the second experiment. The crude products were put on a flash column (Et_2O: MeCN, 5:1). Poor separation was noted in both cases. The product from the first reaction (at -78°C only) indicated some of the desired product was present, along with other compounds. The second reaction, with the additional reaction time of 1 hour at RT, failed to indicate the presence of any product.

These results were consistent with Brown[89], who reported that the addition of lithium acetylides to borate esters was a reversible process, with low temperatures favoring the product. Additionally, Brown[87] also reported that attempts to transesterify isopropyl boronate esters resulted in an almost instantaneous cleavage of the alkynyl boron bond

and the regeneration of the alkyne. The lability of the boron sp carbon bond, and the extreme sensitivity to temperature and reaction conditions were also noted.

A similar set of experiments were conducted using **2** as the target molecule. In the first experiment phenyl acetylene and triisopropyl borate were mixed together at -78°C, and then reacted with BuLi at -78°C for 20 minutes, followed by 20 minutes at RT, while in the second experiment phenyl acetylene was reacted with BuLi at -78°C for 90 minutes, then at RT for 20 minutes, followed by addition to triisopropyl borate at -78°C and stirring at -78°C for 20 minutes. The simple esters were transferred to a second flask containing MIDA, DMSO and toluene. Distillation under atmospheric pressure was continued for 2 hours, with replacement of toluene. No product was detected in either reaction mixture.

These results were again consistent with Brown[87, 89]. The formation of the simple ester is favored at lower temperatures. The same difficulties in transesterification would also apply. It was also reported[87] that a phenylethynyl isopropyl boronate ester exhibited a tendency to polymerize upon heating. This may be a contributing factor to all reactions involving a phenyl, or any aryl, substituted alkyne. The problem was reported to be controlled by the addition of a free radical inhibitor.

In one of these experiments, phenyl acetylene and triisopropyl borate were mixed prior to formation of the acetylide by BuLi. In this experiment, the BuLi could act both as a base, abstracting the hydrogen from the alkyne and forming the acetylide anion, or it could act as a nucleophile, and attack the borate directly.

A similar experiment was conducted using **3** as the target molecule. Hex-1-yne and triisopropyl borate were mixed together at -78°C, and then reacted with BuLi at -78 °C for 30 minutes, followed by 30 minutes at RT. The simple ester was transferred to a second flask containing MIDA, DMSO and toluene. Distillation under atmospheric pressure was continued for 3 hours, with replacement of toluene. No product was detected in the reaction mixture.

These results were once again consistent with Brown[87, 89]. Allowing the simple esterification reaction to occur at a higher temperature will drive the equilibrium back

toward the reactants. The difficulties in transesterification will have to be addressed for all of these reactions.

In this experiment, the alkyne and triisopropyl borate were again mixed prior to formation of the acetylide by BuLi. As before, the BuLi could act either as a base, or as a nucleophile.

Brown[23, 87-89] and Matteson[90, 91] both reported the necessity to acidify the simple esterification reaction to form the ester cleanly. The later procedures[24, 32-39] omit this step. A set of experiments was developed to determine the necessity and value of acidification in these syntheses. The first group of experiments was a set of two experiments, using **1** as the target molecule, using anhydrous HCl in Et_2O as the acidifying agent. The first experiment reacted triisopropyl borate with the ethynyl Grignard reagent at -78°C for 30 minutes. Anhydrous HCl in Et_2O was added at -78°C. The resultant clear yellow solution was transferred to a second flask containing MIDA, DMSO and toluene, stirred at RT for 1 hour, and azeotropically distilled for 2 hours, with replenishment of toluene. TLC and NMR (DMSO) indicated the possible presence of 1, along with other compounds. The second experiment reacted triisopropyl borate with the ethynyl Grignard reagent at -78°C for 30 minutes, followed by a reaction time of 90 minutes at RT. Anhydrous HCl in Et_2O was added at RT. The resultant brown solution was transferred to a second flask containing MIDA, DMSO and toluene, stirred at RT for 1 hour, and azeotropically distilled for 2 hours, with replenishment of toluene. TLC indicated that no desired product was present in the reaction mixture. The reaction was repeated for target molecule **2**. Phenyl acetylene and triisopropyl borate were mixed together at -78°C, and then reacted with BuLi at -78°C for 90 minutes, followed by 90 minutes at RT. The reaction was cooled to -78°C and anhydrous HCl in Et_2O was added. The white suspension was transferred to a second flask containing MIDA, DMSO and toluene, stirred at RT for 30 minutes, and azeotropically distilled for 45 minutes, with replenishment of toluene. Upon solvent removal a viscous liquid remained. NMR (DMSO) indicated the possible presence of 2, along with other compounds. The second group of experiments used BF_3 etherate as the acidifying agent in the synthesis of **1**. Three experiments were conducted, all with BF_3 etherate added at -78°C. One experiment stirred the mixture at 0°C for 1 hour, prior to addition to Na_2MIDA. The other two experiments went from

low temperature to Na_2MIDA in MeCN and MIDA in DMSO respectively. No product was detected in any reaction mixture.

> The results are consistent with those reported by Brown[23, 87-89]. Acidification was reported necessary to achieve the simple ester cleanly, and the acidification should take place at low temperatures, which would favor the formation of the boronate ester over the reactants. Matteson[90, 91] also reports the necessity of acidification, also at low temperatures.

The last set of experiments was based on the recent procedure of Dick[38], which addresses the instability of 2-pyridyl boronic acids, and the utilization of MIDA protection for these compounds. MIDA protection was achieved in the same manner as in other compound types reported by Burke's group[24, 32-39], through the intermediates of isopropyl esters. Dick reported low yields at 55°C, with degradation products due to protodeborylation of the labile 2-pyridyl boron bond. It was surmised that the degradation reactions were occurring before MIDA complexation could occur, and that raising the internal reaction to 115°C would dramatically increase the overall yield. This seemed to be a good analogy to the problems being experienced with the alkynyl boronates. A set of two experiments were planned, one each for target molecules **1** and **2**. The procedure of Dick[38] was replicated. The ethynyl Grignard reagent, or the phenyl acetylene and BuLi, was reacted with triisopropyl borate at -78°C for 1 hour, then at RT for 3 hours. The resultant mixtures were transferred by cannula to a stirred mixture of MIDA in DMSO at 115°C. Care was taken to add the mixtures slowly to the MIDA, to keep the temperature around 115°C. However, rapid evaporation of the reaction solvents often lowered the temperature to around 90°C. The ethynyl **1** was worked up by Et_2O precipitation followed by flash chromatography. The phenyl **2** was worked up directly by flash chromatography. In both cases, NMR (MeCN) indicated the presence, among other compounds, of a compound with similar shifts and couplings to the desired products. Mass spectrometry confirmed that presence of the isopropyl MIDA boronate (Figure 3.11).

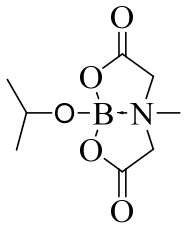


Figure 3.11 Isopropyl MIDA Borate

These results were also consistent with Brown[87], as well the difficulties reported by Dick[38]. The labile sp carbon boron bond tends to favor the formation of the simple isopropyl MIDA boronates, with the concurrent liberation of the alkyne.

These results also demonstrate the competing reactions that are occurring. As Brown[87, 89] reported, the formation of the simple ester is favored at lower temperatures. Acidification was necessary to obtain the simple ester cleanly, and this acidification should take place also at low temperatures. The simple ester does not transesterify to the desired compound. The initial reaction between either the ethynyl Grignard reagent or the lithium acetylide would yield an ionic addition compound (Figure 3.12).

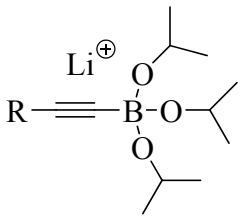


Figure 3.12 Lithium Boronate Salt

If this compound were acidified it would yield the alkynyl isopropyl boronate, which would not transesterify with a diol, and presumably with MIDA. If it were introduced into a DMSO solution of MIDA at 115°C, the equilibrium would favor the reverse reaction to regenerate the reactants. Once again, a MIDA-protected alkynyl boronate would not be formed. The overall reactions are presented (Figure 3.13).

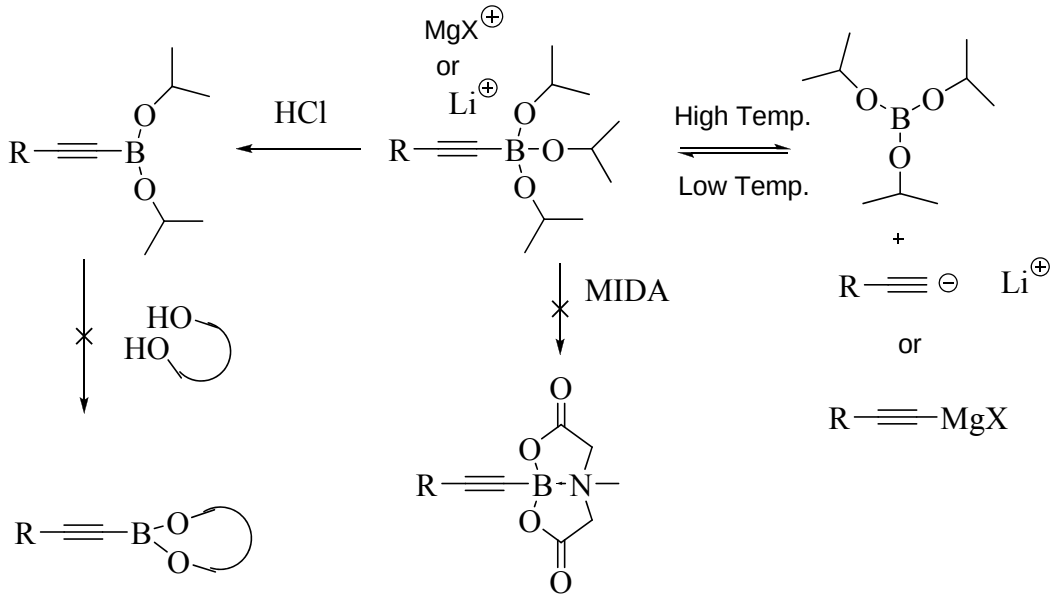


Figure 3.13 Reaction Summary

Under the reaction conditions reported by Dick[38], the high temperature of the MIDA solution in DMSO would regenerate the original starting materials, which could then react with the MIDA and form the MIDA isopropyl borate (Figure 3.14).

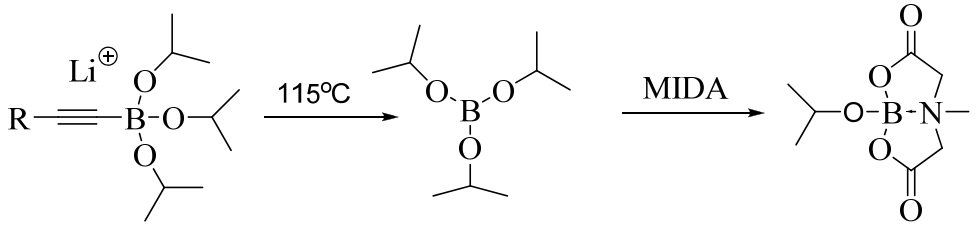


Figure 3.14 Formation of MIDA Isopropyl Borate

A series of experiment were conducted to test the transesterifcation of the simple boronate esters of trimethyl borate and triisopropyl borate with MIDA. Methyl borate was reacted with both MIDA and Na_2MIDA without any detectable MIDA boronate being formed. Heating triisopropyl borate with MIDA, with toluene led to a mixture of compounds, which NMR (CD_3OD) indicated might contain the desired isopropyl MIDA boronate.

Again, this is consistent with Brown[87]. There is a problem in transesterification of the simple boronate esters to the more complex MIDA boronates. The method of Dick[38] may be the most effective in overcoming these difficulties.

3.6.2 Possible Interferences with Desired Products

As has been discussed above, these results are all consistent with Brown[87, 89]. The addition of lithium acetylides to borate esters is a reversible process, with low temperatures favoring the product. The attempted transesterification of isopropyl boronates results in an almost instantaneous cleavage of the alkynyl boron bond and the regeneration of the alkyne. As Dick[38] reported for the 2-pyridyl boron bond, the boron sp carbon bond is also very labile, and is extremely sensitive to temperature and reaction conditions[22].

3.6.3 Proposed Experiments

A systematic plan to overcome the difficulties associated with the transesterification route to MIDA-protected boronates would include several steps:

The thermal stability of the commercially available alkynyl MIDA boronates should be evaluated to determine if the procedure of Dick[38] might be a viable approach.

If the reactivity and lability of the alkynyl boron bond is a probable cause for the failure of these transesterification reactions, the alkyne function, after formation of the simple ester, should be protected by a suitable agent, such as dicobalt octacarbonyl[20, 73]. This should lower the reactivity of the triple bond to a degree that the transesterification reaction can occur in the same way as with alkyl, alkenyl, aryl and heteroaryl boronates. It would be necessary to examine the various transition metal options for the protection of alkynes to determine the conditions necessary for deprotection, and evaluate their compatibility with the MIDA protecting group.

The preparation of the simple boronate esters should be conducted at -78°C, and the reaction quenched with anhydrous HCl at that temperature.

The simple boronates should be isolated, per the procedures of Brown[23, 87-89], and well characterized prior to reactions with MIDA.

3.7 Syntheses of MIDA-Protected Boronates via Reactions of TMS-Protected Alkynes with Boron Halides, then with Na_2MIDA

3.7.1 Results

This set of experiments was intended to prepare MIDA-protected alkynyl boronates by reaction of TMS-protected alkynes with boron halides, followed by reaction with Na_2MIDA. The syntheses were based on the procedures of Uno[37] Singleton[92] and Soundararajan[93].

Variations were made in the boron halides, reaction temperatures and reaction times. The number of experiments for each target molecule is given in Table 3.3.

Table 3.3 Reactions of TMS-Protected Alkynes

Target Molecule	**1**	**2**	**3**
Number of Experiments	4	2	0

A pair of experiments was developed to examine the effect of reacting BBr_3 with the TMS-protected alkyne, followed by reaction with Na_2MIDA (Figure 3.15). The experiments were conducted using **1** as the target molecule. In the first experiment, TMS-protected acetylene was added dropwise to a stirred solution of BBr_3 in DCM at 0°C and stirred for 2 hours at 0°C. The resultant dark brown liquid was transferred to a suspension of Na_2MIDA in MeCN and stirred at 0°C for 1 hour. The second experiment repeated this procedure with the exception that the TMS-protected acetylene and BBr_3 were stirred for 30 minutes at 0°C, followed by 2 hours at RT. Neither procedure yielded any of the desired product. A light brown precipitate formed which decomposed upon exposure to air.

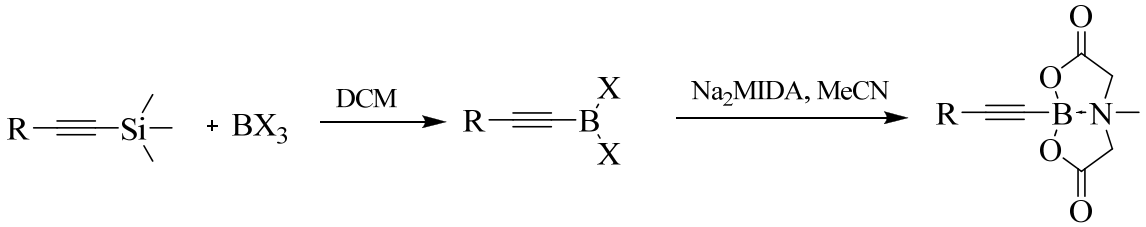


Figure 3.15 MIDA-Protected Boronate Esters via TMS-Protected Alkynes

The next pair of experiments used BCl_3 in place of BBr_3. In the first of these experiments, TMS-protected acetylene was added dropwise to a stirred solution of BCl_3 in DCM at 0°C and stirred for 20 minutes at 0°C, followed by 2 hours at RT. The resultant dark brown liquid was

transferred to a suspension of Na_2MIDA in MeCN at 0°C and stirred at RT for 2 hours. The second experiment repeated this procedure with the exception that the TMS-protected acetylene and BCl_3 were stirred for 20 minutes at -78°C, then at 0°C for 1 hour, followed by 90 minutes at RT. As before, neither procedure yielded any of the desired product.

The third pair of experiments replicated these experiments, using **2** as the target molecule. TMS-protected phenyl acetylene was added dropwise to a stirred solution of BCl_3 in DCM at 0°C and stirred for 30 minutes at 0°C, followed by 2 hours at RT. The dark brown suspension was transferred to a suspension of Na_2MIDA in MeCN at 0°C and stirred at RT for 1 hour. The second experiment repeated this procedure with the exception that all solvents were freshly distilled. Neither experiment yielded any of the desired product.

3.7.2 Possible Interferences with Desired Products

There are several potential explanations for the failure of these reactions to produce the desired target molecules. The TMS-protected alkyne was added, dropwise, to the boron halide, therefore over-alkynylation of the boron[81] is unlikely. However, alkynyl boronates are still vulnerable to many electrophiles, such as boron halides, at the position β to the boron atom.

Dihaloboranes are also extremely sensitive to air and moisture[22]. Therefore, any contamination by air or water, whether in the solvents, the Na_2MIDA, or in the reaction assembly or during mass transfer, could destroy the dihaloborane, and prevent the formation of the MIDA-protected boronate.

3.7.3 Proposed Experiments

A set of experiments to examine the difficulties associated with the preparation of MIDA-protected boronates via the syntheses of dihaloboranes and their subsequent reaction with Na_2MIDA could include the following:

The experiments could be repeated under strict anhydrous conditions, employing Schlenk glassware only, an argon atmosphere, and rigorous drying of all solvents and reagents.

As the vulnerability of the sp carbon in the position β to the boron atom of the alkynyl boron bond to electrophiles may be a factor, the triple bond of the TMS-protected alkyne could be protected by a suitable agent, such as dicobalt octacarbonyl[20, 73]. This should

lower the reactivity of the triple bond to a degree that electrophiles will not be able to react with it.

A TMS-protected alkyne could be reacted with the preformed MIDA borohalides discussed in Section 3.9. This would eliminate the need to form a dihaloborane prior to MIDA complexation.

3.8 Syntheses of MIDA-Protected Boronates via Reactions of Organometallic Compounds with Boron Halides, then with Na_2MIDA

3.8.1 Results

This series of experiments was intended to prepare MIDA-protected alkynyl boronates by reaction of the ethynyl Grignard reagent or the lithium acetylide with boron halides, followed by addition to Na_2MIDA. The syntheses were based on the procedures of Kabalka[94, 95] and Uno[37]. Variations were made in solvents, boron halides, reaction temperatures, and reaction times. The number of experiments for each target molecule is given in Table 3.4.

Table 3.4 Reactions of Organometallics with Boron Halides

Target Molecule	**1**	**2**	**3**
Number of Experiments	3	6	0

A set of three experiments were developed to examine the effect of reacting BF_3 etherate with the ethynyl Grignard reagent followed by reaction with Na_2MIDA (Figure 3.16). The experiments were conducted using **1** as the target molecule. The first experiment reacted Na_2MIDA and the ethynyl Grignard reagent with BF_3 etherate at RT for 60 hours. The second experiment reacted Na_2MIDA and the ethynyl Grignard reagent with BF_3 etherate at 0°C for 16 hours. The third experiment reacted the Grignard with BF_3 etherate at -78°C, then transferred the resultant difluoroborane to Na_2MIDA at 0°C and stirred for 16 hours. No desired product was detected in any of these experiments.

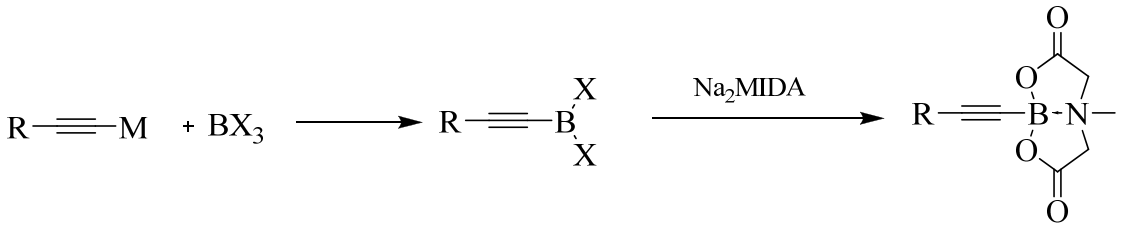


Figure 3.16 Protected Boronates via Alkynylation of Boron Halides

A similar set of three experiments were conducted using **2** as the target molecule. In the first experiment phenyl acetylene and BuLi were reacted at -78°C for 30 minutes, followed by dropwise addition of BF_3 etherate at -78°C for 30 minutes followed by 1 hour at RT, then addition to Na_2MIDA in MeCN at 0°C for 1 hour, followed by RT for 16 hours. In the second experiment phenyl acetylene and BuLi were reacted at -78°C for 30 minutes, followed by addition to Na_2MIDA in MeCN at 0°C for 16 hours. In the third experiment phenyl acetylene and BuLi were reacted at -78°C for 30 minutes, followed dropwise addition of BF_3 etherate at -78°C for 30 minutes, then addition to Na_2MIDA in MeCN at 0°C for 1 hour, followed by RT for 16 hours. None of these procedures produced any detectable level of the desired product.

A final set of three experiments were conducted using **2** as the target molecule, and substituting BCl_3 for BF_3 etherate. In the first experiment phenyl acetylene and BuLi were reacted at -78°C for 30 minutes, followed by dropwise addition of BCl_3 at -78°C for 30 minutes followed by 1 hour at RT, then addition to Na_2MIDA in MeCN at RT for 16 hours. In the second experiment phenyl acetylene and BuLi were reacted at -78°C for 30 minutes, followed by dropwise addition of BCl_3 at -40°C for 1 hour, then addition to Na_2MIDA in MeCN at 0°C 1 hour, followed by RT for 16 hours. In the third experiment was an exact repeat of the second, only with freshly distilled solvents, and azeotropically dried Na_2MIDA. These experiments also did not yield any detectable levels of the desired product.

3.8.2 Possible Interferences with Desired Products

As there were in the experiments using TMS-protected alkynes, there are several potential explanations for the failure of these reactions to produce the desired target molecules. The boron halides were either added in one portion, or dropwise, to the ethynyl Grignard reagent or lithium

acetylide, therefore over-alkynylation of the boron[81] is quite possible. The alkynyl borohalides, if formed, are also vulnerable to electrophilic attack at the position β to the boron atom.

As in the case of the TMS-protected alkynes above, dihaloboranes are extremely sensitive to air and moisture[22]. Therefore, any contamination by air or water, whether in the solvents, the Na_2MIDA, or in the reaction assembly or during mass transfer, could destroy the dihaloborane, and prevent the formation of the MIDA-protected boronate.

3.8.3 Proposed Experiments

A set of experiments similar to that proposed for the further investigation of the reactions of TMS-protected alkynes as a route to MIDA-protected boronates could include the following:

The experiments could be repeated under strict anhydrous conditions, employing Schlenk glassware only, an argon atmosphere, and rigorous drying of all solvents and reagents.

The experiments could be conducted using the dropwise of the ethynyl Grignard reagent or lithium acetylide to the cold, vigorously stirred solution of the boron halides. This would minimize the effect of over-alkynylization.

As the vulnerability of the sp carbon in the position β to the boron atom of the alkynyl boron bond to electrophiles may be a factor, the triple bond of the ethynyl Grignard reagent or lithium acetylide could be protected by a suitable agent, such as dicobalt octacarbonyl[20, 73]. This should lower the reactivity of the triple bond to a degree that electrophiles will not be able to react with it.

3.9 Syntheses of MIDA-Protected Boronates via Reactions of Na_2MIDA with Boron Halides, then Reactions with Organometallic Compounds

3.9.1 Results

The reaction of Na_2MIDA with boron halides, then with a Grignard reagent (Figure 3.17) did not have any direct literature references. It was designed to establish whether or not MIDA connected to a boron monohalide could be synthesized, and whether it could react with the Grignard reagents. Variations were made in reaction temperatures, reaction times, and boron halide.

A set of experiments was developed to examine the effect of preforming a MIDA borohalide, by reacting Na_2MIDA with boron halides, which could then be further reacted with the ethynyl Grignard reagent to form the MIDA-protected boronate. The number of experiments for each target molecule is given in Table 3.5.

Table 3.5 Reactions of Na_2MIDA with Boron Halides

Target Molecule	**1**	**2**	**3**
Number of Experiments	3	0	0

Three experiments were conducted to determine the feasibility of this approach. In the first experiment, BBr_3 was added dropwise to Na_2MIDA in dry MeCN and stirred at -78°C for 15 minutes, to yield a bright yellow suspension. The ethynyl Grignard reagent was added dropwise and stirred at -78°C for 30 minutes, followed by 30 minutes at RT. The second experiment reacted the BBr_3 with the Na_2MIDA at 0°C for 30 minutes, followed by RT for 16 hours. The Grignard reagent was added at 0°C and stirred at RT for 2 hours. The third experiment was a repeat of the second one, with the substitution of BCl_3 for BBr_3. None of these experiments yielded the desired target compound.

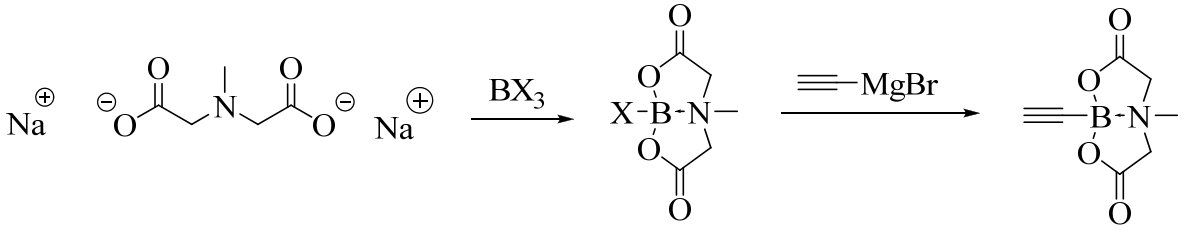


Figure 3.17 Reactions of Na_2MIDA with Boron Halides & Grignard

While the successful preparation of a MIDA-protected borohalide has not yet been reported, a related procedure reported by Aldridge[96] has produced a similar compound by reacting BF_3 etherate with TMS-protected N-methyldiethanolamine.

3.9.2 Possible Interferences with Desired Products

The product of the reaction between the Na_2MIDA and the boron halides was not isolated, but was rather reacted *in situ* with the ethynyl Grignard reagent. The desired intermediate may not be formed at all, or may be mixed with many side products.

The reaction of the Na_2MIDA with the boron halide would probably change the acidic nature of the boron atom. Boron halides are, indeed, hard acids, but reaction with Na_2MIDA with its attendant ligand exchange, might change the boron into a soft acid[97], or at least as softer one. The ethynyl Grignard reagent, and lithium acetylides also, are hard bases. Hard bases react best with hard acids, and soft acids react best with soft bases. The change in ligand might adversely affect this particular acid-base reaction. Transmetallation is usually a solution to such a problem.

3.9.3 Proposed Experiments

A set of experiments to evaluate the effectiveness of preforming a MIDA borohalides as a route to MIDA-protected boronates could include the following:

The intermediate borohalide compounds could be isolated and characterized. This would establish whether this initial reaction occurs at all, and if so, whether it gives a good yield and is easily purified.

The procedures described by Aldridge[96] with TMS-protected N-methyldiethanolamine could be evaluated as a viable method for producing MIDA analogs.

The ethynyl Grignard reagent or lithium acetylide could be transmetallated to a “softer” metal, such as Cu[97]. This might allow for a better acid-base reaction between the alkyne and the preformed MIDA borohalide.

A TMS-protected alkyne, such as those discussed in Section 3.7, could be reacted with the preformed MIDA borohalides. This would eliminate the need to form a dihaloborane prior to MIDA complexation.

3.10 Syntheses of MIDA-Protected Boronates via Activation of the Trifluoroborate Salts, then Reaction with Na_2MIDA

3.10.1 Results

This series of experiments was intended to prepare MIDA-protected alkynyl boronates by reaction of the potassium trifluoroborate salt, activated by TMSCl, BF_3 etherate, or BCl_3 with Na_2MIDA. These experiments were based on the procedures of Kim[98] and Bardin[99]. Variations were made in boron or silicon halides, reaction temperatures, and reaction times. The number of experiments for each target molecule is given in Table 3.6.

Table 3.6 Activation of Trifluoroborate Salts

Target Molecule	**1**	**2**	**3**
Number of Experiments	5	3	0

A set of five experiments were developed to examine the effect of activating a trifluoroborate salt with Lewis acids, creating a dihaloborane, followed by reaction with Na_2MIDA (Figure 3.18). These experiments were conducted using **1** as the target molecule. The first experiment reacted Na_2MIDA, potassium ethynyltrifluoroborate and TMSCl at RT for 60 hours. The second experiment reacted potassium ethynyltrifluoroborate and TMSCl at -78°C for 2 hours, followed by reaction with Na_2MIDA at 0°C for 16 hours. The third experiment repeated the second, with the substitution of $SiCl_4$ for TMSCl. The fourth experiment reacted potassium ethynyltrifluoroborate and BF3 etherate at -78°C for 30 minutes, then reacted with Na_2MIDA at 0°C for 1 hour, followed by 1 hour at RT. The fifth experiment reacted Na_2MIDA with potassium ethynyltrifluoroborate at RT for 16 hours. There were no detectable levels of the desired product found in any of these experiments.

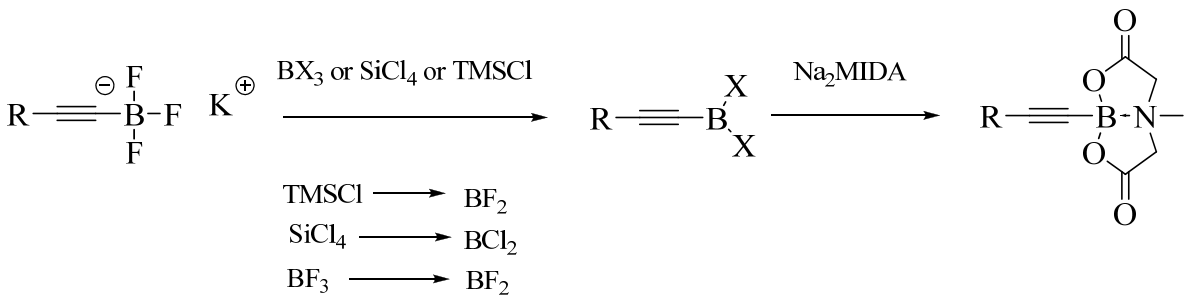


Figure 3.18 MIDA-Protected Boronates via Activation of Trifluoroborate Salts

A similar set of three experiments were conducted using **2** as the target molecule. In the first experiment potassium phenylethynyltrifluoroborate and BF_3 etherate were reacted at -78°C for 30 minutes, followed -40°C for 1 hour, then addition to Na_2MIDA at -40°C for 1 hour, followed by RT for 16 hours. The second experiment repeated the first, with the difference that the trifluoroborate salt and BF_3 etherate were reacted at -78°C for 45 minutes, followed by 1 hour at RT. The third experiment repeated the second, with the substitution of BCl_3 for BF_3 etherate. As in the case of the ethynyl salt, no detectable levels of the desired product were found in any of these experiments.

3.10.2 Possible Interferences with Desired Products

As in the case with TMS-protected alkynes and organometallic reagents reacting with boron halides discussed above, the reaction of Lewis acids with the trifluoroborate salt will generate dihaloboranes, which are extremely sensitive to air and moisture[22]. Therefore, any contamination by air or water, whether in the solvents, the Na_2MIDA, the trifluoroborate salt itself, or in the reaction assembly or during mass transfer, could destroy the dihaloborane, and prevent the formation of the MIDA-protected boronate.

3.10.3 Proposed Experiments

A set of experiments similar to that proposed for the further investigation of the reactions of trifluoroborate salt activated by boron halides as a route to MIDA-protected boronates could include the following:

The experiments could be repeated under strict anhydrous conditions, employing Schlenk glassware only, an argon atmosphere, and rigorous drying of all solvents and reagents.

As the vulnerability of the sp carbon in the position β to the boron atom of the alkynyl boron bond to electrophiles may be a factor, the triple bond of the trifluoroborate salt could be protected by a suitable agent, such as dicobalt octacarbonyl[20, 73]. This should lower the reactivity of the triple bond to a degree that electrophiles will not be able to react with it.

3.11 Syntheses of MIDA-Protected Boronates via Reactions of the Activated Trifluoroborate Salts with TMS-Protected MIDA

3.11.1 Results

The preparations of MIDA-protected boronates by reaction of the potassium trifluoroborate salt, activated by TMSCl, with TMS-protected MIDA were based on the procedures of Yamamoto[76]. Variations were made in silylating agent, solvents, reaction times, and in isolation of the TMS-protected MIDA.

This series of experiments was intended to prepare MIDA-protected alkynyl boronates by reaction of the potassium trifluoroborate salt, activated by TMSCl with TMS-protected MIDA. The purpose was to be able to compare the reactions of the TMS-protected MIDA against the reactions of Na_2MIDA with activated trifluoroborate salts. The number of experiments for each target molecule is given in Table 3.7.

Table 3.7 Reactions with TMS-Protected MIDA

Target Molecule	**1**	**2**	**3**
Number of Experiments	4	3	2

The first set of four experiments was developed to examine the effect of reacting the trifluoroborate salt with the TMS-protected MIDA (Figure 3.19) produced by reaction of either TMSCl or HMDS with Na_2MIDA. The experiments were conducted using **1** as the target molecule. In these experiments, the TMS-protected MIDA was not isolated, purified or characterized. In the first experiment, TMS-protected MIDA prepared from TMSCl was reacted directly with potassium ethynyltrifluoroborate, with activation of the later by TMSCl, at RT for

16 hours. The second experiment repeated this procedure with the exception that the temperature was held at 58°C for 16 hours. The third experiment reacted potassium ethynyltrifluoroborate, activated by TMSCl, with TMS-protected MIDA, obtained from the reaction of Na_2MIDA with HMDS, at RT for 3 hours, using DME as a solvent. The fourth experiment repeated the third, with the substitution of DCM for DME as the solvent, and a reaction time of 60 hours at RT. The desired product was not produced in any of these experiments.

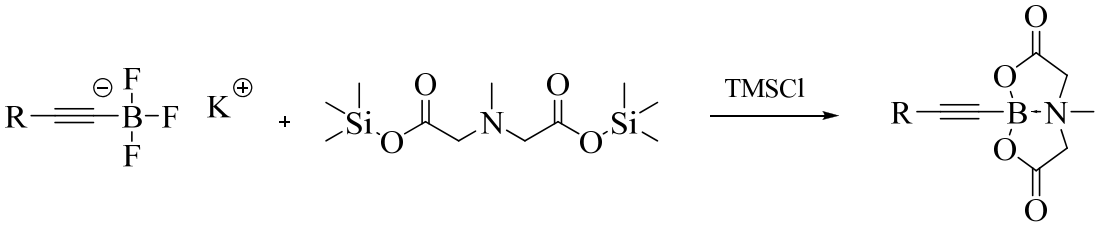


Figure 3.19 Reactions of Trifluoroborate Salts with TMS-Protected MIDA

These experiments were the preliminary investigations into using TMS-protected MIDA in the same manner that Yamamoto[76] had utilized TMS-protected diols. The TMS-protected MIDA, like all TMS-protected acids, is very unstable[14], and required very careful handling during preparation, isolation, purification and characterization. These experiments either did not produce the desired TMS-protected MIDA, or it decomposed prior to further reactions.

A similar set of three experiments were conducted using **2** as the target molecule. In each experiment potassium phenylethynyltrifluoroborate, activated by TMSCl, was reacted with TMS-protected MIDA, obtained from the reaction of Na_2MIDA with HMDS, at RT for 60 hours. The only variation was the choice of solvent for each reaction: acetone, DCM, and MeCN. As before, none of the desired product was detected.

This set of experiments was repeated for target molecule **3**. Potassium hexynyltrifluoroborate activated by TMSCl, was reacted with TMS-protected MIDA, obtained from the reaction of Na_2MIDA with HMDS, at RT for 60 hours. The only variation was the choice of solvent for each reaction: DCM or MeCN.

3.11.2 Possible Interferences with Desired Products

As has been noted for all experiments involving dihaloborane compounds, the presence of water and air cannot be tolerated[22]. Therefore, any contamination by air or water will destroy the dihaloborane, and prevent the formation of the MIDA-protected boronate. Additionally, the TMS-protected MIDA is extremely sensitive to moisture, decomposing within seconds upon exposure to the atmosphere.

3.11.3 Proposed Experiments

A set of experiments to determine the effectiveness of using TMS-protected MIDA as a route to MIDA-protected boronates could include the following:

The experiments could be repeated under strict anhydrous conditions, employing Schlenk glassware only, an argon atmosphere, and rigorous drying of all solvents and reagents.

The reactions of the TMS-protected MIDA with trifluoroborate salts activated by other Lewis acids could be investigated, using the same stringent anhydrous conditions.

The reactions could be repeated with TMS-protected diols, as reported by Yamamoto[76], to determine whether the reactions are feasible, and what conditions favor the reactions.

4

Conclusions

The syntheses of alkynyl boronic acid derivatives protected by the N-methyliminodiacetic acid (MIDA) group were attempted. The objective was to duplicate the demonstrated success of MIDA protection for alkyl, alkenyl, aryl and heteroaryl, and to ascertain if this versatile protecting group for the boronic acid functional group could be applied to the protection of boronic acids containing an alkynyl functionality directed attached to the boron atom. The synthetic utility of such MIDA-protected alkynyl boronates could then be evaluated in further investigations into traditional alkyne reactions, including cycloaddition reactions such as the Pauson-Khand and Diels-Alder reactions.

Several approaches were examined for theses syntheses. They basically revolved on the principles of transesterification from simple alkynyl boronates, and the generation, by various means, of highly reactive dihaloboranes, and subsequent reaction with MIDA, or with a MIDA derivative.

The alkynyl group demonstrated its particular reactivity and uniqueness. It was not possible to synthesize a MIDA-protected alkynyl boronate by any of the methods attempted. The reactions either did not proceed as anticipated, or the products decomposed readily to starting materials or intractable tars.

Despite the inability to produce the desired alkynyl MIDA-protected boronate, these experiments, and attendant literature research has led to some interesting observations. The alkynyl group can have major effects on reactions performed on a molecule. The sp nature of the triple bond so alters its reactivity that reactions commonly conducted on alkyl, alkenyl, aryl and heteroaryl boronic acids and their derivatives can lead to unexpected side reactions and decomposition.

There are still many variations on these experiments that could be of synthetic worth. In these alkynes, the reactivity of the alkynyl group, as well as the boronic acid function, will need to be attenuated. There are well-established methods of protecting the alkynyl functionality by transition metal complexes that radically alter the alkynyl reactivity. The use of alkynyl protecting groups may allow for the preparation of MIDA-protected boronates will the same relative ease as has been demonstrated with the MIDA-protected alkyl, alkenyl, aryl and heteroaryl boronates. Synthetic pathways that eliminate the necessity of preparing and handling the highly reactive alkynyl dihaloboranes are also worthy of investigation.

5

Experimental

5.1 General

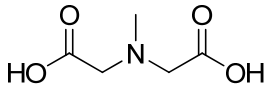
Materials. Commercial reagents were purchased from Sigma-Aldrich, Fluka, Aesar, and Merck, and used as received unless otherwise noted. Boron trifluoride diethyl etherate was redistilled prior to use[45]. Solvents were purchased from Sigma-Aldrich, Fluka, and Fisher Scientific, or taken from the departmental solvent dispensing unit, and used either as received, or further purified or dried as noted in the specific procedure[43, 45, 100]. Tetrahydrofuran (THF) was distilled from sodium/benzophenone. Potassium trifluoroboronate salts of ethyne, phenylethyne, and 1-hexyne were prepared by Dr. Annette Bayer, and used as received.

General Experimental Procedures. Unless otherwise noted, all reactions were conducted in oven-dried glassware under nitrogen. Standard reaction procedures, including air-sensitive reaction and transfer techniques, were employed[7, 42-44, 101-104]. Reaction products were monitored by thin layer chromatography (TLC) using Merck silica gel 60 F254 plates. Compounds were visualized by UV exposure, iodine, basic $KMnO_4$, and molybdophosphoric acid. Flash column chromatography was performed using established methods[44, 105] on a 1 cm diameter column, unless otherwise noted.

Structural Analysis. ^{1}H and ^{13}C NMR spectra were recorded on a Varian 400 MHz spectrometer, unless otherwise noted. Chemical shifts (δ) are reported in parts per million (ppm) downfield from tetramethylsilane. NMR data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, quint = quintet, sext = sextet, sept = septet, m = multiplet, br = broad, app = apparent), and integration. ChemDraw NMR prediction software was used to predict approximate chemical shifts and multiplicities. Mass spectra were obtained from a Thermo Scientific LTQ Orbitrap XL spectrometer. Mass spectra acquisition and analysis were performed by Jostein Johansen.

5.2 Synthesis of Starting Materials

N-Methyliminodiacetic Acid (MIDA). The Organic Syntheses procedure of Ballmer and Gillis[39] was followed. A 250 ml 3-neck round-bottom flask was fitted with a reflux condenser, a pressure-equalizing addition funnel and a thermometer. All joints were protected with Teflon sleeves. The flask was charged with 25.15 g (190 mmol) of iminodiacetic acid and 21.8 ml formalin (37%, 290 mmol). A milky suspension was noted. The mixture was magnetically stirred and refluxed for 30 minutes. Formic acid (15 ml, 380 mmol) was added dropwise over a period of 15 minutes. Effervescence was noted during addition. The clear yellow reaction mixture was refluxed for 30 minutes, and then cooled to RT. The cooled reaction mixture was transferred to a 1000 ml Erlenmeyer flask equipped with a magnetic stirring bar, and the reaction flask was rinsed with 2 X 6.25 ml distilled water. Absolute ethanol (187.5 ml) was slowly added dropwise, with the formation of a voluminous white precipitate. The precipitate was collected, washed with 50 ml of ethanol, and dried under vacuum suction for 10 minutes. The solid material was transferred to a 100 ml round-bottom flask, and lyophilized under vacuum overnight with liquid nitrogen. A free-flowing white powder was obtained (21.69 g, 78%).



NMR correlated with predicted and reported values.

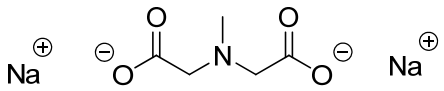
^{1}H NMR (600 MHz, CD_3OD) δ: 2.85 (s, 3 H), 3.83 (s, 4 H)

^{13}C NMR (CD_3OD) δ: 42, 57, 172

MS—148

Sodium Salt of N-Methyliminodiacetic Acid (Na_2MIDA). The procedure of Uno[37], was followed. A 250 ml round-bottom flask, equipped with a magnetic stir bar, was charged with 14.72 g (100 mmol) of N-methyliminodiacetic acid, prepared above, 12.04 g (300 mmol) of

NaOH, and 30 ml of distilled water. The mixture was stirred for 30 minutes at RT. The resultant clear yellow liquid was concentrated to dryness on the rotary evaporator, and then placed on the vacuum line for 30 minutes. Dry methanol (50 ml) was added and the mixture refluxed for 30 minutes. The reaction mixture was filtered and the solids returned to the flask. The addition of dry methanol (50 ml) and refluxing for 30 minutes was repeated twice. The reaction mixture was filtered, and the solids washed with 3 X 20 ml portions of dry methanol, followed by suction drying. The dry solids were transferred to a tared flask. Acetonitrile (5 ml) was added to facilitate transfer and assist in drying. Solvent was removed on the rotary evaporator, and the flask was lyophilized overnight on the vacuum line with liquid nitrogen. A free-flowing white powder was obtained (10.34 g, 52%).



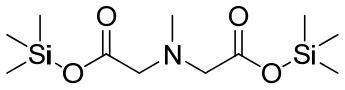
NMR correlated with predicted and reported values.

^{1}H NMR (600 MHz, CD_3OD) δ: 2.23 (s, 3 H), 2.94 (s, 4 H)

Trimethylsilyl Derivative of N-Methyliminodiacetic Acid via Trimethylsilyl Chloride. A 50 ml Schlenk flask was equipped with a magnetic stir bar and a reflux condenser. The upper joint was sealed with a rubber septum pierced by a 19-gauge needle to relieve pressure and allow for by-product venting. The entire apparatus was cooled under nitrogen and flushed three times with vacuum and nitrogen. N-methyliminodiacetic acid (0.1536 g, 1.04 mmol) was added rapidly. Dichloromethane, freshly distilled from CaH_2, and stored under nitrogen (5 ml) was added. The reaction vessel was purged under a rapid flow of nitrogen. Trimethylsilyl chloride (TMSCl) (0.33 ml, 2.4 mmol) was injected quickly into the stirred suspension. The reaction mixture was stirred at RT for 1 hour. An additional 10 ml of distilled dichloromethane was added and the reaction mixture was heated to reflux. Refluxing was maintained for 60 hours. Solvent was removed on the rotary evaporator, followed by high vacuum. ^{1}H NMR (400 MHz, $CDCl_3$) indicated that the desired product was not present in the sample.

The process was repeated using Na_2MIDA instead of MIDA. The results were the same as above.

Trimethylsilyl Derivative of N-Methyliminodiacetic Acid via Hexamethyl Disilazane HMDS). A 250 ml Schlenk flask was equipped with a magnetic stir bar and a reflux condenser. The upper joint was sealed with a rubber septum pierced by a 19-gauge needle to relieve pressure and allow for by-product venting. The entire apparatus was cooled under nitrogen and flushed three times with vacuum and nitrogen. The flask was charged with N-methyliminodiacetic acid (7.35 g, 50 mmol), and a catalytic amount of saccharin (0.99 g.) followed by 30 ml of anhydrous dimethoxyethane. HMDS (40 ml, 200 mmol), was injected through the septum. The reaction mixture was heated to 90˚C. pH indicator paper, moistened with H_2O and held near needle outlet, indicated the strongly basic gaseous by-product NH_3. After 30 minutes at 90˚C, the white suspension changed to a clear yellow liquid. The reaction was maintained at reflux at 90˚C for 2 hours, and then cooled to RT. The reflux condenser was quickly replaced with a short path distillation head. High vacuum was applied, and residual HMDS and dimethoxyethane were distilled off. The receiving flask was changed, vacuum and heating were reapplied, and the fraction boiling at 138–140˚C at $2.9X10^{-1}$ mbar was collected. The product was a clear white, viscous liquid (12.45 g, 86%). The product decomposes rapidly in the presence of atmospheric water and oxygen, reverting back to MIDA. The product was stored under argon, and handled using standard air-sensitive techniques. NMR samples were prepared under an inert atmosphere using $CDCl_3$ that had been dried over $CaCl_2$ for 24 hours.

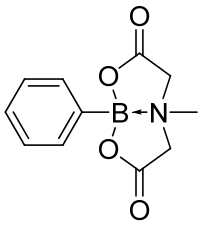


NMR correlated with predicted values.

^{1}H NMR (400 MHz, CD_3Cl) δ: 0.01 (s, 6 H), 2.30 (s, 3 H), 3.30 (s, 4 H)
^{13}C NMR (CD_3Cl) δ: 0, 42, 58, 172

Synthesis of MIDA-protected phenyl boronate. The Organic Syntheses procedure of Ballmer and Gillis[39] for 4-bromophenylboronic MIDA ester was followed. A 100 ml round-bottom

flask, equipped with a magnetic stir bar, was charged with 0.1209 g (0.99 mmol) of benzeneboronic acid, and 0.1518 g (1.03 mmol) of N-methyliminodiacetic acid. DMSO (dried over molecular sieves) (0.5 ml), and dry toluene (9.5 ml) were added. A soxhlet extractor (30 ml capacity) was attached and 80% filled with molecular sieves. Dry toluene was added to the return level, and a reflux condenser attached. The reaction was heated to reflux, and maintained overnight. The soxhlet extractor and reflux condenser were removed, and a short-path distillation head was attached. The reaction mixture was heated at 90°C for 6 hours, with replacement of toluene to facilitate reaction completion. A white solid began to form. Solvent was removed on the rotary evaporator (bath temperature 40°C). The resultant amber liquid was taken up in 3 ml of acetone (dried over molecular sieves) and 15 ml anhydrous diethyl ether was added. The reaction mixture was placed in the refrigerator overnight. The supernatant liquid was decanted and the crystals washed in diethyl ether and dried on the vacuum line. Amber crystals were obtained (0.1061 g, 46%).



NMR correlated with predicted values.

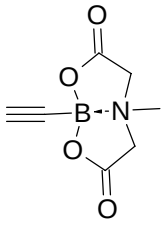
^{1}H NMR (400 MHz, CD_3Cl) δ: 2.56 (s, 3 H), 3.77 (d, 2 H), 3.90 (d, 2 H), 7.30 (s, 2 H), 7.40 (s, 2 H), 7.50 (s, 1 H)

MS—256

5.3 Syntheses of MIDA-Protected Boronates via Reactions of Organometallic Compounds with Borate Esters

5.3.1 Preparation of Ethynylboronate MIDA Ester (1)

5.3.1.1 By reaction of a Grignard reagent with triisopropyl borate followed by addition to MIDA in DMSO, distilling at reduced pressure. A 50 ml round-bottom flask was charged with ethynyl magnesium bromide (0.5 M in THF, 5 ml, 2.5 mmol) and cooled in an acetone-cardice bath. Triisopropyl borate (4.5 ml. 2.75 mmol) was injected via syringe. The mixture was allowed to stir at -78°C for 30 minutes, then allowed to come to RT. Dimethyl sulfoxide (DMSO) dried over molecular sieves (4 ml) was added. The reaction flask was placed on the rotary evaporator to remove THF. MIDA (0.8579 g, 5.84 mmol) was dissolved in 5 ml dry DMSO in a separate flask which was fitted with a short-path distillation head, with a rubber septum in place of a thermometer, and set up for vacuum distillation. The mixture was heated until DMSO began to distill (bath temperature 90°C). The boronate solution was taken up in a syringe, and injected, through the rubber septum, into the distilling DMSO. The reaction flask was washed with 2 X 5 ml portions of dry DMSO, which was added to the reaction flask. The reaction was maintained at 90°C for 90 minutes, with careful distillation of DMSO. Reaction mixture was a very viscous amber liquid, which was insoluble in acetone, but yielded a white suspension in acetonitrile (MeCN). The mixture was filtered and the yellow solution concentrated. A TLC analysis was run (silica plate, Et_2O:MeCN, 5:1; rf—0.33). Flash-column chromatography was run (10 cm column height, silica gel, eluent—Et_2O:MeCN, 5:1). No effective separation was noted. The fractions were collected and concentrated. NMR in DMSO was conducted and indicated the possible presence of the target compound, along with other compounds.



1

NMR correlated with predicted and reference (commercially available product) values.

^{1}H NMR (400 MHz, DMSO) δ: 2.03 (s, 1 H), 2.69 (s, 3 H), 3.87 (d, 2 H), 4.10 (d, 2 H)

^{13}C NMR (DMSO) δ: 0, 41, 42, 58, 117, 166, 168

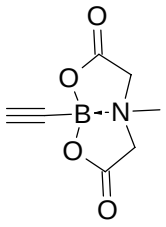
MS—212, 219, 233, 377, 378, 379

5.3.1.2 By reaction of Grignard reagent with triisopropyl borate, at -78°C and RT, followed by addition to MIDA in DMSO, distilling at reduced pressure. The procedure of 5.3.1.1, above, was repeated, with the modification of conducting the reaction between the Grignard reagent and the triisopropyl borate at -78°C for 15 minutes, followed by a reaction time of 1 hour at RT. A much darker-colored product was noted. Toluene was added to the reaction mixture in addition to DMSO to form an azeotrope with the expected isopropanol. NMR (DMSO) indicated that the desired target was not present.

5.3.1.3 By reaction of Grignard reagent with trimethyl borate, at -78°C and -20°C, followed by addition to MIDA and azeotropic distillation with toluene. A 25 ml, 2-neck, round-bottom flask was equipped with a short-path distillation head and septum, and charged with trimethyl borate (0.18 ml, 1.5 mmol), followed by 2 ml of dry toluene. The flask was cooled in an acetone-cardice bath for 15 minutes. Ethynyl magnesium bromide (0.5 M in THF, 2.5 ml, 1.25 mmol) was injected dropwise via syringe. The reaction mixture was stirred for 1 hour at -78°C, and then placed in a methanol-ice bath for a further reaction time of 1 hour at -20°C. The reaction mixture was allowed to warm to RT, and MIDA (0.39 g, 2.65 mmol) was added to the resultant light brown suspension. DMSO (0.5 ml) and toluene (5 ml) were added. The reaction was heated, under N_2, to distill off toluene/azeotrope, with periodic replacement of toluene, for 2 hours. Two distinct phases were noted: a clear liquid, and a murky dark brown solid. Residual solvent was removed on the rotary evaporator, and the resultant solids taken up in acetone. Diethyl ether was added to produce white crystals. The crystals were collected, washed with cold Et_2O, and dried. NMR analysis (DMSO) revealed no trace of the desired target molecule.

5.3.1.4 By reaction of Grignard reagent with triisopropyl borate, then anhydrous HCl in Et_2O at -78°C, followed by addition to MIDA in DMSO and azeotropic distillation with toluene. A 25 ml round-bottom flask was equipped with a septum and charged with 4 ml of dry THF. The flask was cooled in an acetone-cardice bath, and triisopropyl borate (0.23 ml, 1.0 mmol) was injected and the solution cooled at -78°C for 30 minutes. Ethynyl magnesium

bromide (0.5 M in THF, 2.25 ml, 1.1 mmol) was injected via syringe in 0.1 ml increments over a period of 5 minutes. The reaction was stirred at -78°C for 30 minutes. Anhydrous HCl in Et_2O (2 M, 0.6 ml, 1.2 mmol) was injected. A clear yellow solution resulted. Stirring was continued at -78°C for an additional 20 minutes, and the flask was then allowed to warm to RT. A second 25 ml round-bottom flask was fitted with a short path distillation head and charged with MIDA (0.1825 g, 1.24 mmol), anhydrous DMSO (0.5 ml) and dry toluene (4 ml). The boronate reaction mixture was transferred via cannula to the stirred MIDA solution; the reaction flask was washed with 5 ml of dry THF, and transferred. The mixture was stirred at RT for 30 minutes, and then heated to distillation of the toluene/azeotrope for 2 hours, with periodic replenishment of toluene. Residual solvent was removed on the rotary evaporator. The resultant reddish yellow solid was taken up in refluxing acetone and filtered hot. This process was repeated three times. The combined filtrates were concentrated to yield a dark amber viscous liquid (0.09650 g). A TLC analysis was run, using the commercially available target molecule (Sigma-Aldrich) (silica plate, Et_2O:MeCN, 5:1). Two parallel spots were detected at rf—0.91. NMR (DMSO) also indicated the possible presence of the target molecule, along with additional compounds.



1

NMR correlated with predicted and reference (commercially available product) values.

^{1}H NMR (400 MHz, MeCN) δ: 2.7 (s, 1 H), 3.5 (s, 3 H), 3.9 (d, 2 H), 4.1 (d, 2 H)

^{13}C NMR (MeCN) δ: 0, 14, 24, 25, 26, 41, 42, 45, 62, 118, 167, 168

MS—157, 183, 256

5.3.1.5 By reaction of Grignard reagent with triisopropyl borate in dichloromethane (DCM) at -78°C and RT, then anhydrous HCl in Et_2O at RT, followed by addition to MIDA in DMSO and azeotropic distillation with toluene. The procedure of 5.3.1.4, above, was repeated with the exception of using DCM, freshly distilled from CaH_2, in place of dry THF, allowing the Grignard and the triisopropyl borate to react at RT for 90 minutes after 30 minutes at -78°C, and reaction with the anhydrous HCl in Et_2O at RT for 15 minutes. The resultant yellowish brown liquid was added to MIDA as above. After removal of the solvent, a small amount of a tarry dark brown material was obtained. A TLC analysis was run, using, as a reference, the commercially available target molecule (Sigma-Aldrich) (silica plate, Et_2O: pentane, 95:5). No product was detected. (rf of commercial product—0.29)

5.3.1.6 By reaction of Grignard reagent with triisopropyl borate, then BF_3 etherate at -78°C and 0°C, followed by addition to Na_2MIDA in DMSO and THF. A 25 ml round-bottom flask was equipped with a septum and charged with triisopropyl borate (0.35 ml, 1.5 mmol). The flask was cooled in an acetone-cardice bath for 30 minutes, and ethynyl magnesium bromide (0.5 M in THF, 3.0 ml, 1.5 mmol) was injected dropwise via syringe. The reaction mixture was stirred at -78°C for 1 hour. BF_3 etherate (0.33 ml, 2.6 mmol) was injected. The flask was transferred to an ice-water bath and stirred for 1 hour. The mixture was transferred via cannula to a second flask containing Na_2MIDA (0.3653 g, 2.0 mmol), DMSO (0.3 ml), and dry THF (3 ml). The reaction flask was rinsed with 5 ml of dry THF. The flask was stirred at 0°C overnight. Solvent was removed on the rotary evaporator, and the solids taken up in 10 ml of acetone. The resultant suspension was filtered through a thin pad of Celite and concentrated. A dark tarry mass was observed. TLC did not indicate the presence of desired product. The NMR was unavailable, but mass spectral analysis did not detect the desired target molecule.

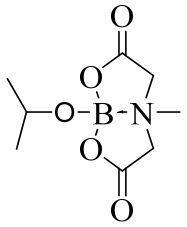
5.3.1.7 By reaction of Grignard reagent with triisopropyl borate at -78°C and RT, then BF_3:Et_2O at -78°C, followed by addition to MIDA in toluene only. A 25 ml round-bottom flask was equipped with a septum and charged with triisopropyl borate (0.23 ml, 1.0 mmol). The flask was cooled in an acetone-cardice bath for 15 minutes, and ethynyl magnesium bromide (0.5 M in THF, 2.0 ml, 1.0 mmol) was injected dropwise via syringe. The reaction mixture was stirred at -78°C for 1 hour, then allowed to come to RT and stirred for 4 hours. The flask was cooled in the acetone-cardice bath for 15 minutes, and BF_3:Et_2O (0.30 ml, 2.5 mmol) was

injected in one portion and stirred at -78°C for 15 minutes. The contents were transferred, via cannula, to a second flask charged with MIDA (0.1528 g, 1.04 mmol) and 5 ml toluene, at -78°C. The reaction flask was rinsed with 2 X 5 ml portions of dry THF. The resultant suspension was stirred at -78°C overnight. The septum was replaced with a short-path distillation head, and toluene/azeotrope was distilled, with replacement of toluene, for 4 hours. The reaction mixture was a dark brown liquid. Solvent was removed on the rotary evaporator, and 20 ml of acetone were added. An immediate fuming was noted. The mixture was filtered, washed with acetone, and the resultant dark brown liquid was concentrated. Diethyl ether was added. No precipitation was noted, and no product could be isolated.

5.3.1.8 By reaction of Grignard reagent with triisopropyl borate at -78°C and RT, then BF_3:Et_2O at -78°C, followed by addition to Na_2MIDA in MeCN. The procedure of 5.3.1.7, above, was repeated, with the exception that Na_2MIDA was used in place of MIDA, MeCN was used instead of toluene, the addition to the Na_2MIDA was stirred at 0°C overnight, and there was no distillation step. After concentration on the rotary evaporator, the solids were taken up in refluxing acetone, filtered hot, and cooled before addition of Et_2O. The resultant white crystals were dried (0.1818 g). However NMR spectra run in both MeCN and DMSO indicated no trace of the desired target molecule.

5.3.1.9 By reaction of Grignard reagent with triisopropyl borate at -78°C and RT, followed by addition to MIDA in DMSO at 115°C. A 25 ml Schlenk flask was equipped with a septum and charged with triisopropyl borate (1.15 ml, 5.0 mmol) and dry THF (8 ml). The flask was cooled in an acetone-cardice bath for 15 minutes, and ethynyl magnesium bromide (0.5 M in THF, 10.0 ml, 5.0 mmol) was injected dropwise via syringe. The reaction mixture was stirred at -78°C for 1 hour, then allowed to come to RT and stirred for 3 hours. The contents were transferred dropwise, via cannula, to a second 50 ml 2-neck flask, equipped with a thermometer and a short-path distillation head, and charged with MIDA (1.753 g, 8.0 mmol) and anhydrous DMSO (6 ml) at 115°C. The rate of addition was about one drop per second to keep the reaction temperature from dropping below 105°C. The reaction flask was rinsed with 2 X 5 ml portions of dry THF. The resultant suspension was stirred at 115°C for 1 hour. The temperature was lowered to 75°C, and DMSO was distilled off under vacuum (6.6×10^{-1} mbar). The reaction mixture was a dark brown liquid. The viscous liquid was taken up in hot MeCN (20 ml), filtered, the filtrate

transferred to another flask, cooled, and DCM (60 ml) and Et_2O (250 ml) were added. A white precipitate formed. The flask was cooled in the refrigerator overnight. Residual DMSO prevented the formation of collectible crystals. NMR (MeCN) indicated the possible presence of the desired product. The ether was decanted, and the solids taken up in hot MeCN, and adsorbed onto Celite (10.6 g). MeCN was removed on the rotary evaporator to yield a coarse, free-flowing powder. The Celite was further dried on the high vacuum line overnight to remove as much DMSO as possible. A small amount of the crude material was retained for a series of TLC experiments, using the commercially available material as a reference. The optimal eluent was determined to be EtOAc:MeCN, 10:1. A flash column (5 X 10 cm) was run. Fractions 4–6 indicated the possibility of a trace amount of a compound which correlated to the rf value of 0.45 for the commercially available product. NMR (MeCN) did not reveal the presence of a detectable amount of the desired compound. However, there was some indication that there might be some MIDA isopropyl borate, among other compounds.



^{1}H NMR (400 MHz, DMSO) δ: 3.1 (s), 4.0 (m), 4.2 (m), 4.4 (m)

MS—175, 190, 212, 286

5.3.2 Preparation of Phenylethynylboronate MIDA Ester (2)

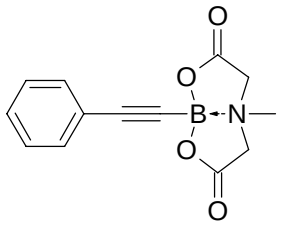
5.3.2.1 By formation of lithium acetylide, then reaction with triisopropyl borate at -78°C and RT, followed by addition to MIDA and azeotropic distillation with toluene. A 25 ml, 2-neck, round-bottom flask was equipped with a short-path distillation head and septum, and charged with phenylacetylene (0.24 ml, 3.8 mmol), triisopropyl borate (1.10 ml, 4.6 mmol) and 4.5 ml of dry THF. The flask was cooled in an acetone-cardice bath for 20 minutes. Butyl lithium (BuLi), (1.6 M in hexanes, 3.1 ml, 4.9 mmol) was injected dropwise. A clear yellow liquid was observed. The reaction was stirred at -78°C for 20 minutes. The flask was allowed to warm to RT, an additional 3.5 ml of dry THF was added, and the mixture was stirred for 20 minutes. A white suspension formed. MIDA (0.84 g, 5.7 mmol) was added, followed by toluene (5 ml). The

flask was then heated to distill off the toluene/azeotrope for 2 hours, with periodic replenishment of toluene. Residual solvent was then removed on the rotary evaporator. The yellow solids were taken up in acetone and filtered. The filtrate was concentrated to yield a clear liquid. NMR (DMSO) indicated no trace of the desired target molecule.

5.3.2.2 By formation of lithium acetylide, then reaction with triisopropyl borate at -78°C and RT, followed by addition to MIDA in DMSO and azeotropic distillation with toluene. A 25 ml, 2-neck, round-bottom flask was equipped with a short-path distillation head and septum and charged with phenylacetylene (0.21 ml, 1.9 mmol), followed by 2.5 ml of dry THF. The flask was cooled in an acetone-cardice bath for 20 minutes. BuLi (1.6 M in hexanes, 1.5 ml, 2.4 mmol) was injected dropwise. A clear yellow liquid was observed. The reaction was stirred at -78°C for 90 minutes. The flask was allowed to warm to RT and stirred for 20 minutes. A white suspension formed. The flask was cooled to -78°C, triisopropyl borate (0.53 ml, 2.3 mmol) was injected, and the mixture stirred at -78°C for 20 minutes. The flask was warmed to RT, and MIDA (0.42 g, 2.85 mmol) was added, followed by DMSO (0.8 ml) and toluene (2.5 ml). The flask was then heated to distill off the toluene/azeotrope for 2 hours, with periodic replenishment of toluene. Residual solvent was then removed on the rotary evaporator. The solids were taken up in acetone and filtered. The filtrate was concentrated to yield a dark yellow viscous liquid. NMR (DMSO) indicated no trace of the desired target molecule.

5.3.2.3 By formation of lithium acetylide, then reaction with triisopropyl borate, then anhydrous HCl in Et_2O at -78°C, followed by addition to MIDA in DMSO and azeotropic distillation with toluene. A 25 ml round-bottom flask was equipped with a septum and charged with phenylacetylene (0.11 ml, 1.0 mmol), triisopropyl borate (0.23 ml, 1.0 mmol), and DCM (freshly distilled from CaH_2, 3 ml). The solution cooled at -78°C for 15 minutes. BuLi (1.6 M in hexanes, 0.70 ml, 1.1 mmol) was injected dropwise. The reaction was stirred at -78°C for 90 minutes. The flask was allowed to warm to RT and stirred for 90 minutes. Anhydrous HCl in Et_2O (2 M, 0.8 ml, 1.6 mmol) was injected. A white suspension formed. A second 25 ml round-bottom flask was fitted with a short-path distillation head and charged with MIDA (0.2249 g, 1.53 mmol), anhydrous DMSO (3 ml) and dry toluene (2 ml). The boronate reaction mixture was transferred via cannula to the stirred MIDA solution. The reaction flask was washed with 3 ml of dry DCM, and transferred. The mixture was stirred at RT for 30 minutes, and then heated to

distillation of the toluene/azeotrope for 45 minutes, with periodic replenishment of toluene. Residual solvent was removed on the rotary evaporator. A viscous amber liquid was obtained. NMR (DMSO) indicated the possible presence of the target molecule, along with additional compounds.



2

NMR corresponded with predicted values.

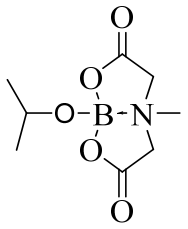
^{1}H NMR (400 MHz, DMSO) δ: 2.95 (s, 1 H), 3.62 (s, 3 H), 3.95 (d, 2 H), 4.32 (d, 2 H)

^{13}C NMR (DMSO) δ: 46, 48, 59, 62, 130, 132, 168

MS—166, 198, 223, 268, 319, 325

5.3.2.4 By formation of lithium acetylide, then reaction with triisopropyl borate at -78°C and RT, followed by addition to MIDA in DMSO at 115°C. A 25 ml Schlenk flask was equipped with a septum and charged with triisopropyl borate (1.2 ml, 5.0 mmol), phenylacetylene (0.55 ml, 5 mmol) and dry THF (8 ml). The flask was cooled in an acetone-cardice bath for 15 minutes, and BuLi (1.6 M in hexanes, 3.1 ml, 5.0 mmol) was injected dropwise via syringe. The reaction mixture was stirred at -78°C for 1 hour, then allowed to come to RT and stirred for 3.5 hours. The contents were transferred dropwise, via syringe, to a second 50 ml 2-neck flask, equipped with a thermometer and a short-path distillation head, and charged with MIDA (1.11025 g, 7.5 mmol) and anhydrous DMSO (6 ml) at 115°C. The rate of addition was about one drop per second to keep the reaction temperature from dropping below 105°C. The reaction flask was rinsed with 2 X 5 ml portions of dry THF. The resultant suspension was stirred at 115°C for 15 minutes. The temperature was lowered to 75°C, and DMSO was distilled off under vacuum (1.5 X 10^{-1} mbar). The reaction mixture was a light brown liquid. The viscous

liquid was taken up in MeCN (20 ml), and adsorbed onto Celite (2.0 g). MeCN was removed on the rotary evaporator to yield a coarse, free-flowing powder. The Celite was further dried on the high vacuum line overnight to remove as much DMSO as possible. A flash column (3 X 10cm, eluent EtOAc initial 30 ml, then EtOAc:MeCN, 10:1) was run. Fractions 8–12 indicated the possibility of a compound which could roughly correlate to the rf value of 0.45 for the commercially available ethynyl compound. NMR (MeCN) did not reveal the presence of the desired compound. However, there was some indication that there might be some MIDA isopropyl borate, among other compounds.



^{1}H NMR (400 MHz, MeCN) δ: 1.2 (d), 2.8 (d), 3.9 (d), 4.1 (d)

^{13}C NMR (DMSO) δ: 0, 13, 24, 26, 27, 41, 44, 62, 65, 118, 158

MS—238, 289

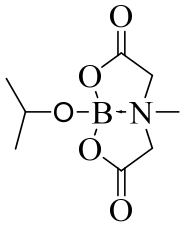
5.3.3 Preparation of 1-Hexynylboronate MIDA Ester (3)

5.3.3.1 By formation of lithium acetylide, then reaction with triisopropyl borate at -78°C and RT, followed by addition to MIDA and azeotropic distillation with toluene. A 25 ml, 2-neck, round-bottom flask was equipped with a short-path distillation head and septum, and charged with 1-hexyne (0.43 ml, 3.8 mmol), triisopropyl borate (1.06 ml, 4.6 mmol) and 5 ml of dry THF. The flask was cooled in an acetone-cardice bath for 30 minutes. BuLi (1.6 M in hexanes, 3.2 ml, 5.1 mmol) was injected dropwise. The reaction was stirred at -78°C for 30 minutes. The flask was allowed to warm to RT and stirring continued for 30 minutes. MIDA (0.83 g, 5.7 mmol) was added, followed by toluene (5 ml). The flask was then heated to distill off the toluene/azeotrope for 3 hours, with periodic replenishment of toluene. Residual solvent was then removed on the rotary evaporator. The orange solids were taken up in acetone and

filtered. The filtrate was concentrated to yield a clear yellow liquid. NMR (DMSO) indicated no trace of the desired target molecule.

5.3.4 Preparation of Simple Boronate Esters

5.3.4.1 By reaction of MIDA with triisopropyl borate and azeotropic distillation with toluene. A 25 ml, 2-neck, round-bottom flask was equipped with a short-path distillation head and septum, and charged with triisopropyl borate (0.53 ml, 2.3 mmol), MIDA (0.32 g, 2.25 mmol), isopropanol (5 ml), and dry toluene (5 ml). The reaction was heated, with periodic replacement of toluene, for 2.5 hours. Residual solvent was removed on the rotary evaporator, to yield a light brown oil (0.0743) g. NMR analysis (CD_3OD) indicated the presence of the desired product, along with impurities.



^1H NMR (400 MHz, CD_3OD) δ: 1.04 (6 H), 3.92 (d, 2 H), 4.13 (d, 2 H)

5.3.4.2 By reaction of MIDA with trimethyl borate, without DMSO, and azeotropic distillation with toluene. A 25 ml, 2-neck, round-bottom flask was equipped with a short-path distillation head and septum, and charged with trimethyl borate (0.12 ml, 1.0 mmol), MIDA (0.1521 g, 1.1 mmol), dry THF (6 ml), and dry toluene (5 ml). The reaction was heated, with periodic replacement of toluene, for 4 hours. Residual solvent was removed on the rotary evaporator, and the resultant solids dried on the vacuum line. NMR analysis (CD_3OD) revealed only unreacted starting material.

5.3.4.3 By reaction of Na_2MIDA with trimethyl borate and azeotropic distillation with toluene. A 25 ml, 2-neck, round-bottom flask was equipped with a short-path distillation head and septum, and charged with trimethyl borate (0.12 ml, 1.0 mmol), Na_2MIDA (0.2161 g, 1.1 mmol), dry MeCN (5 ml), and dry toluene (5 ml). The reaction was heated, with periodic replacement of toluene, for 2 hours. Residual solvent was removed on the rotary evaporator to yield a dark tar. NMR analysis (CD_3OD) revealed no trace of the desired target molecule.

5.4 Syntheses of MIDA-Protected Boronates via Reactions of TMS-Protected Alkynes with Boron Halides

5.4.1 Preparation of Ethynylboronate MIDA Ester (1)

5.4.1.1 By reaction of trimethylsilyl acetylene with boron tribromide followed by addition to Na_2MIDA. A 25 ml round-bottom flask was equipped with a septum and charged with boron tribromide (0.28 ml, 3 mmol) and 5 ml degassed DCM. The flask was cooled in an ice-water bath, and trimethysilylacetylene (0.43 ml, 3 mmol) was added dropwise. The mixture was stirred at 0°C for 2 hours. The color of the solution darkened from an initial light yellow to a very dark brown. The product was taken up by syringe and transferred to a 25 ml round-bottom flask charged with Na_2MIDA (0.60 g, 3 mmol) and MeCN (5 ml). The temperature was kept below 5°C during the addition. The mixture was stirred at RT for 1 hour. The suspension was filtered through a thin pad of Celite, concentrated on the rotary evaporator, and Et_2O was added to the clear amber filtrate. A light brown precipitate formed, which decomposed on the filter. NMR spectra run on the filtrate in both acetone and DMSO indicated no trace of the desired target molecule.

5.4.1.2 By reaction of trimethylsilyl acetylene with boron tribromide at 0°C and RT, followed by addition to Na_2MIDA. The procedure of 5.4.1.1, above, was repeated with the following modification: After addition of the trimethylsilylacetylene to the boron tribromide in DCM, the reactants were stirred for 30 minutes at 0°C, and then for 2 hours at RT. The rest of the procedure was unchanged. A dark brown precipitate formed after Et_2O addition. NMR spectra run in both MeCN and $CDCl_3$ indicated no trace of the desired target molecule.

5.4.1.3 By reaction of trimethylsilyl acetylene with boron trichloride at 0°C and RT, followed by addition to Na_2MIDA. A 25 ml round-bottom flask was equipped with a septum and charged with boron trichloride (1 M in DCM, 1.0 ml, 1.0 mmol) and 5 ml of DCM freshly distilled from CaH_2. The flask was cooled in an ice-water bath for 20 minutes, and trimethysilyl acetylene (0.16 ml, 1.1 mmol) was added dropwise. The reactants were stirred at 0°C for 20 minutes, and then at RT for 2 hours. A clear dark brown liquid resulted. A second 25 ml round-bottom flask was charged with Na_2MIDA (azeotropically dried with toluene, 0.2013 g, 1 mmol)

and MeCN (dried over CaH_2 and freshly distilled from CaH_2, 5 ml). The resultant slurry was stirred in an ice-water bath for 2 hours. The boron adduct was transferred by cannula to the Na_2MIDA suspension and stirred at RT for 2 hours. The reaction mixture was filtered, and the solids washed with acetone. Excess solvent was removed on the rotary evaporator and Et_2O added. The resultant white precipitate was collected and dried (0.4790 g). However, NMR (acetone) indicated no trace of the desired target molecule.

5.4.1.4 By reaction of trimethylsilyl acetylene with boron trichloride at -78°C, 0°C and RT, followed by addition to Na_2MIDA. The procedure of 5.4.1.3, above, was repeated except for the initial reaction between the trimethylsilylacetylene and the BCl_3 being done at -78°C. A 25 ml round-bottom flask was equipped with a septum and charged with boron trichloride (1 m in DCM, 1.0 ml, 1.0 mmol) and 3 ml of DCM freshly distilled from CaH_2. The flask was cooled in an acetone-cardice bath for 10 minutes, and trimethysilylacetylene (0.16 ml, 1.1 mmol) was added dropwise. The reactants were stirred at -78°C for 20 minutes, at 0°C for 1 hour, and then at RT for 90 minutes. The flask was returned to the ice-water bath for 30 minutes. A second 25 ml round-bottom flask was charged with Na_2MIDA (azeotropically dried with toluene, 0.1972 g, 1 mmol) and MeCN (dried over CaH_2 and freshly distilled from CaH_2, 5 ml). The resultant slurry was stirred in an acetone-cardice bath for 30 minutes. The boron adduct was transferred by cannula to the Na_2MIDA suspension and stirred at -78°C for 20 minutes, then at 0°C for 40 minutes, and finally at RT overnight. The reaction mixture was filtered, and the solids washed with acetone. Excess solvent was removed on the rotary evaporator and Et_2O added. The white precipitate was separated by decanting, washing with Et_2O, and drying (0.0826 g). However, NMR (acetone) did not indicate the presence of the target molecule.

5.4.2 Preparation of Phenylethynylboronate MIDA Ester (2)

5.4.2.1 By reaction of 1-phenyl-2-(trimethylsilyl) acetylene with boron trichloride at 0°C and RT, followed by addition to Na_2MIDA. A 25 ml round-bottom flask was equipped with a septum and charged with boron trichloride (1 M in DCM, 1.0 ml, 1.0 mmol) and DCM (5 ml). The flask was cooled in an ice-water bath for 30 minutes, and 1-phenyl-2-(trimethylsilyl) acetylene (0.21 ml, 1.1 mmol) was added dropwise. The reactants were stirred at 0°C for 30 minutes, and then at RT for 2 hours. A clear dark brown suspension resulted. A second 25 ml round-bottom flask was charged with Na_2MIDA (azeotropically dried with toluene, 0.2005 g, 1

mmol) and MeCN (5 ml). The resultant slurry was stirred in an ice-water bath for 1 hour. The boron adduct was transferred by cannula to the Na_2MIDA suspension and stirred at 0°C for 15 minutes, then at RT for 1 hour. The reaction mixture was concentrated on the rotary evaporator, and the solids taken up in acetone. Et_2O was added, causing the formation of a few small crystals. NMR (MeCN) indicated no trace of the desired target molecule.

5.4.2.2 By reaction of 1-phenyl-2-(trimethylsilyl) acetylene with boron trichloride at 0°C and RT, followed by addition to Na_2MIDA, using ultra-dry solvents. The procedure of 5.4.2.1, above, was repeated except for the use of solvents freshly distilled from CaH_2. No apparent change was noted in the color of the reaction mixture until the precipitation with Et_2O. A white precipitate was collected, washed in Et_2O, and dried (0.1137 g). However, NMR (MeCN) indicated no trace of the desired target molecule.

5.5 Syntheses of MIDA-Protected Boronates via Reactions of Organometallic Compounds with Boron Halides

5.5.1 Preparation of Ethynylboronate MIDA Ester (1)

5.5.1.1 By reaction of Grignard reagent with BF_3 etherate at RT, in the presence of Na_2MIDA in THF. A 25 ml round-bottom flask was equipped with a septum and charged with Na_2MIDA (0.39 g, 2 mmol), ethynylmagnesium bromide (0.5 M in THF, 3.2 ml, 1.6 mmol), BF_3 etherate (0.35 ml, 2.8 mmol) and dry THF (3 ml). The reaction mixture was stirred at RT for 60 hours. Solvent was removed on the rotary evaporator, and the solids taken up in acetone. The resultant slurry was filtered, and the solids washed with acetone. The combined filtrates were concentrated to yield a white solid (0.1251 g). The mass spectral analysis indicated that the expected product was possible; however, NMR (MeCN) indicated no trace of the desired target molecule.

5.5.1.2 By reaction of Grignard reagent with BF_3 etherate at 0°C, in the presence of Na_2MIDA in THF. The procedure of 5.5.1.1, above, was repeated except that the temperature was maintained at 0°C for 16 hours. The mass spectral analysis indicated that the expected product was not present.

5.5.1.3 By reaction of Grignard reagent with BF_3 etherate at -78°C, followed by the addition of Na_2MIDA in MeCN at 0°C. The procedure of 5.5.1.2, above, was repeated except that the Grignard reagent was added dropwise to the BF_3 etherate at -78°C, then added to the Na_2MIDA in MeCN at 0°C. As in 5.5.1.1, above, the mass spectral analysis indicated that the expected product was possible; however, NMR (MeCN) indicated no trace of the desired target molecule.

5.5.2 Preparation of Phenylethynylboronate MIDA Ester (2)

5.5.2.1 By formation of lithium acetylide, then reaction with BF_3 etherate at -78°C and RT, followed by the addition of Na_2MIDA in MeCN at 0°C and RT. A 25 ml round-bottom flask was equipped with a septum and charged with phenylacetylene (1.1 ml, 1.0 mmol), dry MeCN (2 ml) and cooled in an acetone-cardice bath for 30 minutes. BuLi (1.0 M in hexanes, 1.2 ml, 1.2 mmol) was added dropwise. The reaction mixture became bright yellow in color. Stirring was continued at -78°C for 30 minutes. BF_3 etherate (0.25 ml, 1.5 mmol) was added dropwise, and the reaction stirred for at -78°C for 30 minutes. The cooling bath was removed, and the reaction was stirred at RT for 1 hour. The color darkened to a reddish brown. The reaction mixture was transferred via cannula to a second flask containing Na_2MIDA (0.2763 g, 1.5 mmol), DCM (1 ml) and MeCN (1 ml) at 0°C, and stirred for 1 hour at 0°C, then overnight at RT. Solvent was removed on the rotary evaporator, and the solids taken up in warm acetone. The slurry was filtered, washed with warm acetone, and the filtrate was reduced to c. 1 ml. After cooling to 0°C, diethyl ether (2 ml) was added and the flask immersed in an ice-water bath. A voluminous white precipitate formed (0.0852 g). However, NMR (MeCN) indicated no trace of the desired target molecule.

5.5.2.2 By formation of lithium acetylide, then reaction with boron trifluoride etherate at -78°C, followed by the addition of Na_2MIDA in MeCN at 0°C. The procedure of 5.5.2.1, above, was repeated, with the exceptions that the reactions were conducted at lower temperatures throughout. The phenylacetylene was reacted with BuLi at -78°C for 45 minutes, and then with the BF_3 etherate at the same temperature for 2 hours. The reaction mixture was added to a stirred mixture of Na_2MIDA in MeCN and stirred at 0°C overnight. Product workup was as before. After addition of diethyl ether, no recoverable product was precipitated.

5.5.2.3 By formation of lithium acetylide, then reaction with boron trifluoride etherate in DCM at -78°C and -40°C, followed by the addition of Na_2MIDA in DCM at 0°C and RT. The procedure of 5.5.2.1, above, was repeated, with the exceptions that the reactions were conducted in DCM for all reactions, and at -78°C and for 20 minutes for the reaction of phenyl acetylene with BuLi, at -78°C and 1 hour, and at -40°C for 2 hours for the BF_3 etherate addition, and at 0°C and 1 hour, and at RT overnight for the reaction with Na_2MIDA. As in 5.5.2.1, above, a voluminous white precipitate formed (0.1537 g). However, NMR ($CDCl_3$) indicated no trace of the desired target molecule.

5.5.2.4 By formation of lithium acetylide, then reaction with boron trichloride at -0°C, followed by the addition of Na_2MIDA in DCM at RT. A 25 ml round-bottom flask was equipped with a septum and charged with phenylacetylene (5.5 ml, 5.0 mmol), dry DCM (2 ml) and cooled in an ice-water bath for 30 minutes. BuLi (1.0 M in hexanes, 5.5 ml, 5.5 mmol) was added dropwise, followed by DCM (4 ml) to facilitate stirring of the yellow slurry. Stirring was continued at -78°C for 30 minutes. BCl_3 (1 M in hexanes, 5.5 ml, 5.5 mmol) was added dropwise, and the reaction stirred for at RT for 1 hour. A dark brown suspension formed, which was transferred to a stirred solution of Na_2MIDA (1.1904 g, 6.0 mmol) in DCM (15 ml) and stirred overnight at RT. Workup yielded a few tan crystals in a dark brown filtrate. NMR (MeCN) indicated no trace of the desired target molecule.

5.5.2.5 By formation of lithium acetylide, then reaction with boron trichloride in DCM at -78°C and -40°C, followed by the addition of Na_2MIDA in DCM at 0°C and RT. The procedure of 5.5.2.4, above, was repeated, with the exceptions that the reactions were conducted at -78°C, and for 30 minutes at -40°C for the reaction of phenylacetylene with BuLi, and for 1 hour at 0°C for the BCl_3 addition, and at RT overnight for the reaction with Na_2MIDA in DCM and MeCN. As in 5.5.2.4, above, a few small colloidal crystals were obtained. NMR (MeCN) indicated no trace of the desired target molecule.

5.5.2.6 By formation of lithium acetylide, then reaction with boron trichloride in DCM at -78°C and -40°C, followed by the addition of Na_2MIDA in DCM at 0°C and RT, using freshly purified and redistilled solvents, and azeotropically dried Na_2MIDA. The procedure of 5.5.2.4, above, was repeated, with the exceptions that DCM and MeCN were freshly purified and redistilled[45], and the Na_2MIDA was azeotropically dried by heating under vacuum with dry

toluene. Et_2O workup yielded very fine white crystals (0.631 g). However, NMR (MeCN) indicated no trace of the desired target molecule.

5.6 Syntheses of MIDA-Protected Boronates via Reactions of Na_2MIDA with Boron Halides, Then Reactions with Organometallic Compounds.

5.6.1 Preparation of Ethynylboronate MIDA Ester (1)

5.6.1.1 By reaction of Na_2MIDA with BBr_3, then with the Grignard reagent at -78°C. A 50 ml Schlenk flask was equipped with a septum and charged with Na_2MIDA (0.2111 g, 1.1 mmol), dry MeCN (25 ml) and cooled in an acetone-cardice bath for 10 minutes. BBr_3 (0.10 ml, 1.0 mmol) was injected slowly, and the reaction stirred for 15 minutes. A bright yellow suspension formed. Ethynylmagnesium bromide (0.5 M in THF, 2.0 ml, 1.0 mmol) was injected dropwise. The resultant orange suspension was stirred at -78°C for 30 minutes and at RT for 30 minutes. The reaction mixture was filtered, the solids washed with MeCN, and solvent removed on the rotary evaporator. The resultant solid material was taken up in acetone (5 ml), and precipitated with Et_2O. A voluminous white precipitate formed, which upon drying, yielded a small quantity of a brown, pungent oil. NMR (CD_3OD) indicated no trace of the desired target molecule.

5.6.1.2 By reaction of Na_2MIDA with BBr_3, then with the Grignard reagent at 0°C and RT. The procedure of 5.6.1.1, above, was repeated, with the exceptions that the reactions were conducted at higher temperatures throughout. The reaction of Na_2MIDA with BBr_3 was run at 0°C for 30 minutes and at RT overnight. The addition of ethynylmagnesium bromide was run at 0°C for 30 minutes and at RT for 2 hours. Flash column chromatography was run (11.5 cm column height, silica gel, eluent—EtOAc:pentane, 95:5). The fractions were collected and concentrated. NMR (CD_3OD) indicated no trace of the desired target molecule in any fraction.

5.6.1.3 By reaction of Na_2MIDA with BCl_3, then with the Grignard reagent at 0°C and RT. The procedure of 5.6.1.2, above, was repeated, with the exceptions that BCl_3 was used instead of BBr_3. The results were as above. NMR (CD_3OD) indicated no trace of the desired target molecule in any fraction.

5.7 Syntheses of MIDA-Protected Boronates via Activation of the Trifluoroborate Salts, then Reaction with Na_2MIDA.

5.7.1 Preparation of Ethynylboronate MIDA Ester (1)

5.7.1.1 By activation of the trifluoroborate salt with trimethylsilyl chloride (TMSCl) at RT. A 10 ml round-bottom flask was equipped with a septum and charged with Na_2MIDA (0.2635 g, 1.3 mmol), potassium ethynyltrifluoroborate (0.0597 g, 0.5 mmol) and MeCN (3 ml). TMSCl (0.13 ml, 1.0 mmol) was injected. The reaction mixture was stirred at RT under N_2 for 60 hours. Solvent was removed on the rotary evaporator, and the solids taken up in acetone. The resultant slurry was filtered, and the solids washed with acetone. The combined filtrates were concentrated to yield a small amount of white solids. NMR (MeCN) indicated no trace of the desired target molecule.

5.7.1.2 By activation of the trifluoroborate salt with TMSCl at -78°C. The procedure of 5.7.1.1, above, was repeated, with the exceptions that the reaction between the trifluoroborate salt and TMSCl was run at -78°C, with stirring for 2 hours, followed by reaction with the Na_2MIDA at 0°C for 60 hours. The results were as above. NMR (MeCN) indicated no trace of the desired target molecule.

5.7.1.3 By activation of the trifluoroborate salt with tetrachlorosilane at RT. The procedure of 5.7.1.1, above, was repeated, with the substitution of tetrachlorosilane for TMSCl. A dark brown viscous tar was produced. NMR (MeCN) indicated no trace of the desired target molecule.

5.7.1.4 By activation of the trifluoroborate salt with BF_3 etherate at -78°C, followed by the addition of Na_2MIDA in MeCN at 0°C and RT. A 25 ml round-bottom flask was equipped with a septum and charged with potassium ethynyltrifluoroborate (0.1316 g, 1.0 mmol), dry THF (3 ml), and stirred at -78°C for 1 hour. BF_3 etherate (0.35 ml, 2.7 mmol) was injected, and the mixture stirred at -78°C for 30 minutes. The reaction mixture was transferred via cannula to a stirred solution of Na_2MIDA in MeCN (3 ml) at 0°C. The reaction was stirred at 0°C for 1 hour and at RT for 60 hours. The solvents were removed on the rotary evaporator, the solids taken up in acetone, filtered and precipitated with Et_2O. White crystals were obtained (0.2734 g). The

mass spectral analysis indicated that the expected product was possible; however, NMR (MeCN) indicated no trace of the desired target molecule.

5.7.1.5 By direct reaction of the trifluoroborate salt with Na_2MIDA at 0°C and RT. A 25 ml Schlenk flask was equipped with a septum and charged with (potassium ethynyltrifluoroborate (0.1374 g, 1.0 mmol), MeCN (3 ml), and stirred at RT for 30 minutes. The flask was transferred to an ice-water bath, and stirring continued for 30 minutes. The solution was transferred via cannula to a stirred solution of Na_2MIDA in MeCN (5 ml) at 0°C. The reaction was stirred at 0°C for 1 hour and at RT for overnight. The solvents were removed on the rotary evaporator, the solids taken up in acetone, filtered and precipitated with Et_2O. White crystals were obtained. However, NMR (MeCN) indicated no trace of the desired product.

5.7.2 Preparation of Phenylethynylboronate MIDA Ester (2)

5.7.2.1 By activation of the trifluoroborate salt with BF_3 etherate at -78°C and 0°C, followed by the addition of Na_2MIDA in MeCN at 0°C and RT. A 25 ml round-bottom flask was equipped with a septum and charged with potassium phenylethynyltrifluoroborate (0.1142 g, 0.5 mmol), DCM (5 ml) and stirred at RT for 15 minutes, and at -78°C for 1 hour. BF_3 etherate (0.2 ml, 1.0 mmol) was added dropwise, and the reaction stirred at -78°C for 30 minutes and then at -40°C for 1 hour. The reaction mixture was transferred via cannula to a second flask containing Na_2MIDA (0.3128 g, 1.0 mmol) in MeCN (5 ml) at -40°C, and stirred for 1 hour, then overnight at RT. Solvent was removed on the rotary evaporator, and the solids taken up in acetone. The slurry was filtered, washed with warm acetone, and the filtrate was reduced to c. 1 ml. After cooling to 0°C, diethyl ether (2 ml) was added and the flask immersed in an ice-water bath. A white precipitate formed (0.1176 g). However, NMR (acetone) indicated no trace of the desired target molecule.

5.7.2.2 By activation of the trifluoroborate salt with BF_3 etherate at -78°C and RT, followed by the addition of Na_2MIDA in MeCN at 0°C and RT. The procedure of 5.7.2.1, above, was repeated, with the exceptions that the reaction between potassium phenylethynyltrifluoroborate and BF_3 etherate was conducted at -78°C for 45 minutes, and at RT for 1 hour. Results were as above. NMR (acetone) indicated no trace of the desired target molecule.

5.7.2.3 By activation of the trifluoroborate salt with BCl_3 at -78°C and -40°C, followed by the addition of Na_2MIDA in DCM at 0°C and RT. The procedure of 5.7.2.1, above, was repeated, with the exceptions that BCl_3 was used in place of BF_3 etherate and was conducted at -78°C for 30 minutes, and at -40°C for 2 hours. Results were as above. NMR (MeCN) indicated no trace of the desired target molecule.

5.8 Syntheses of MIDA-Protected Boronates via Reaction with TMS-Protected MIDA.

5.8.1 Preparation of Ethynylboronate MIDA Ester (1)

5.8.1.1 By reaction of the trifluoroborate salt with TMS-protected MIDA formed with TMSCl at RT. A 25 ml Schlenk flask was equipped with a septum and charged with TMS-protected MIDA (prepared by reaction of MIDA with TMSCl, 0.65 ml, 2.0 mmol), potassium ethynyltrifluoroborate (0.1339 g, 1.0 mmol) and acetone (dried over molecular sieves, 5 ml). TMSCl (0.65 ml, 2.1 mmol) was injected. The reaction mixture was stirred at RT under N_2 for 16 hours. Solvent was removed on the rotary evaporator, and the solids taken up in acetone. The resultant slurry was filtered, and the solids washed with acetone. The filtrates were concentrated to yield a white solid. NMR (acetone) indicated no trace of the desired target molecule.

5.8.1.2 By reaction of the trifluoroborate salt with TMS-Protected MIDA formed with TMSCl at RT, with an excess of TMSCl. A 50 ml Schlenk flask was equipped with a reflux condenser and charged with Na_2MIDA (0.1979 g, 1.0 mmol), MeCN (redistilled from CaH_2, 3 ml) and dichloroethane (DCE) (redistilled from CaH_2, 4 ml). TMSCl (1.1 ml, 2.0 mmol) was injected. The reaction mixture was stirred at 58°C for 16 hours, and allowed to cool to RT. The TMS-protected MIDA was transferred via syringe to a stirred solution of potassium ethynyltrifluoroborate (0.1321 g, 1.0 mmol) in acetone (dried over molecular sieves, 3 ml) and dry DCE (1 ml). The reaction was stirred at RT for 2 hours. TMSCl (0.60 ml, 1.0 mmol) was added. The reaction was stirred at RT overnight. The reaction mixture was filtered and washed with acetone. Solvent was removed on the rotary evaporator to yield a white solid. NMR (acetone) indicated no trace of the desired target molecule.

5.8.1.3 By reaction of the trifluoroborate salt in Dimethoxymethane (DME) with TMS-Protected MIDA formed with HMDS. A 25 ml Schlenk flask was equipped with a septum and

charged with potassium ethynyltrifluoroborate (0.1322 g, 1.0 mmol), and DME (redistilled from CaH_2, 3 ml) and stirred at 50°C for 30 minutes, then cooled to RT. TMSCl (0.05 ml) was injected to eliminate any residual water. The TMS-protected MIDA (0.30 ml, 1.0 mmol) was injected by syringe, followed by TMSCl (0.30 ml, 2.0 mmol). The reaction was stirred at RT for 3 hours. Solvent was removed on the rotary evaporator, the solids taken up in acetone, and precipitated with Et_2O, to yield a white solid (0.1608 g). NMR (MeCN) indicated no trace of the desired target molecule.

5.8.1.4 By reaction of the trifluoroborate salt in DCM with TMS-Protected MIDA formed with HMDS. A 50 ml Schlenk flask was equipped with a septum and charged with potassium ethynyltrifluoroborate (0.1327 g, 1.0 mmol), DCM (redistilled from CaH_2, 5 ml) and stirred at RT for 10 minutes. The TMS-protected MIDA (0.50 ml, 1.8 mmol) was injected by syringe, followed by TMSCl (0.60 ml, 4.0 mmol). The reaction was stirred at RT for 60 hours. The product was taken up in a small amount of silica gel, and flash column chromatography was run (8.5 cm column height, silica gel, eluent—EtOAc:pentane, 95:5). Ten 10 ml fractions were collected. TLC indicated a possible correlation with the commercial available product in fractions 2 and 3 (rf—0.20). Fractions 1–3 were combined and the solvent was removed on the rotary evaporator to yield a white solid (0.1128 g). However, NMR (MeCN) indicated no trace of the desired target molecule. Fractions 4–10 were also combined and concentrated to yield a trace amount of solid. Again, NMR (MeCN) indicated no trace of the desired target molecule.

5.8.2 Preparation of Phenylethynylboronate MIDA Ester (2)

5.8.2.1 By reaction of the trifluoroborate salt in acetone with TMS-protected MIDA formed with HMDS. A 50 ml Schlenk flask was equipped with a septum and charged with potassium phenylethynyltrifluoroborate (0.2143 g, 1.1 mmol), and acetone (dried over molecular sieves, 5 ml). The TMS-protected MIDA (0.50 ml, 1.8 mmol) was injected by syringe, followed by TMSCl (0.60 ml, 4.0 mmol). The reaction was stirred at RT for 60 hours. The product was taken up in a small amount of silica gel, and flash column chromatography was run (10 cm column height, silica gel, eluent—EtOAc:pentane, 95:5). Ten 10 ml fractions were collected. TLC indicated possible product in fractions 2 and 3. Fractions 1–3 were combined and the solvent was removed on the rotary evaporator to yield a white solid (0.0288 g). However, NMR (acetone) indicated no trace of the desired target molecule.

5.8.2.2 By reaction of the trifluoroborate salt in DCM with TMS-protected MIDA formed with HMDS. The procedure of 5.8.2.1, above, was repeated, with the substitution of DCM (distilled from CaH_2) for acetone. NMR (MeCN) indicated no trace of the desired target molecule.

5.8.3 Preparation of 1-Hexynylboronate MIDA Ester (3)

5.8.3.1 By reaction of the trifluoroborate salt in DCM with TMS-protected MIDA formed with HMDS. A 50 ml Schlenk flask was equipped with a septum and charged with potassium hex-1-nyltrifluoroborate (0.1831 g, 0.95 mmol), DCM (redistilled from CaH_2, 5 ml) and stirred at RT for 10 minutes. The TMS-protected MIDA (0.50 ml, 1.8 mmol) was injected by syringe, followed by TMSCl (0.60 ml, 4.0 mmol). The reaction was stirred at RT for 60 hours. The product was taken up in a small amount of silica gel, and flash column chromatography was run (8.5 cm column height, silica gel, eluent—EtOAc:pentane, 95:5). Ten 10 ml fractions were collected. However, NMR (MeCN) indicated no trace of the desired target molecule in any fraction.

5.8.3.2 By reaction of the trifluoroborate salt in MeCN with TMS-protected MIDA formed with HMDS. The procedure of 5.8.3.1, above, was repeated, with the substitution of MeCN (distilled from CaH_2) for DCM. Workup was by precipitation with Et_2O. NMR (MeCN) indicated no trace of the desired target molecule.

6

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Appendices

Appendix A. Abbreviations

BuLi	butyl lithium
DCE	dichloroethane
DCM	dichloromethane
DME	dimethoxyethane
DMSO	dimethyl sulfoxide
Et2O	diethyl ether
EtOAc	ethyl acetate
HMDS	1,1,1,3,3,3-hexamethyldisilazane
IR	infrared
MeCN	acetonitrile
MIDA	N-methyliminodiacetic acid
MS	mass spectrometry
Na2MIDA	N-methyliminodiacetic acid, sodium salt
NMR	nuclear magnetic resonance
pKa	-log acidity constant
rf	retention factor
RT	room temperature
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	trimethylsilyl
TMSCl	trimethylsilyl chloride
X	halogen

Appendix B. NMR Spectra

Figure B.1 ^{1}H NMR Spectrum of N-methyliminodiacetic acid (MIDA) in CD_3OD

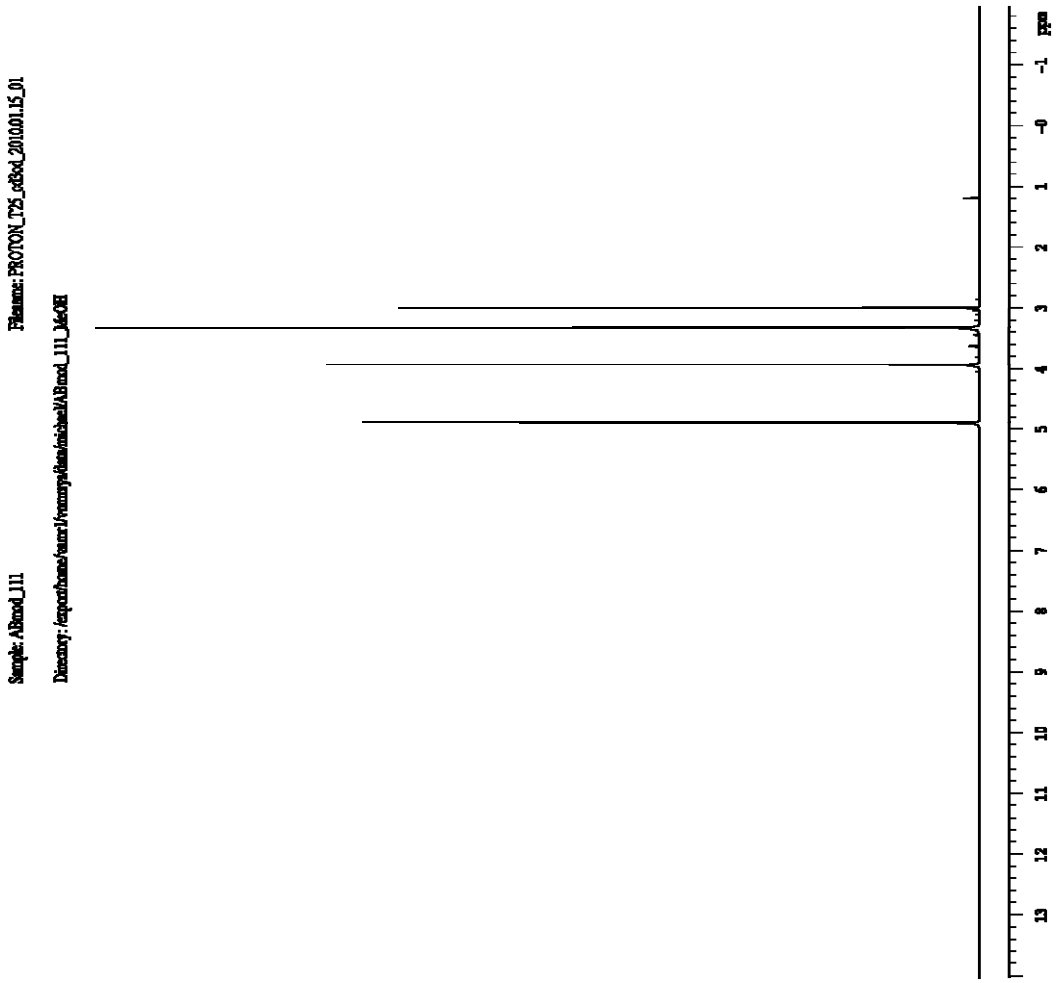


Figure B.2 ^{1}H NMR Spectrum of MIDA in D_2O

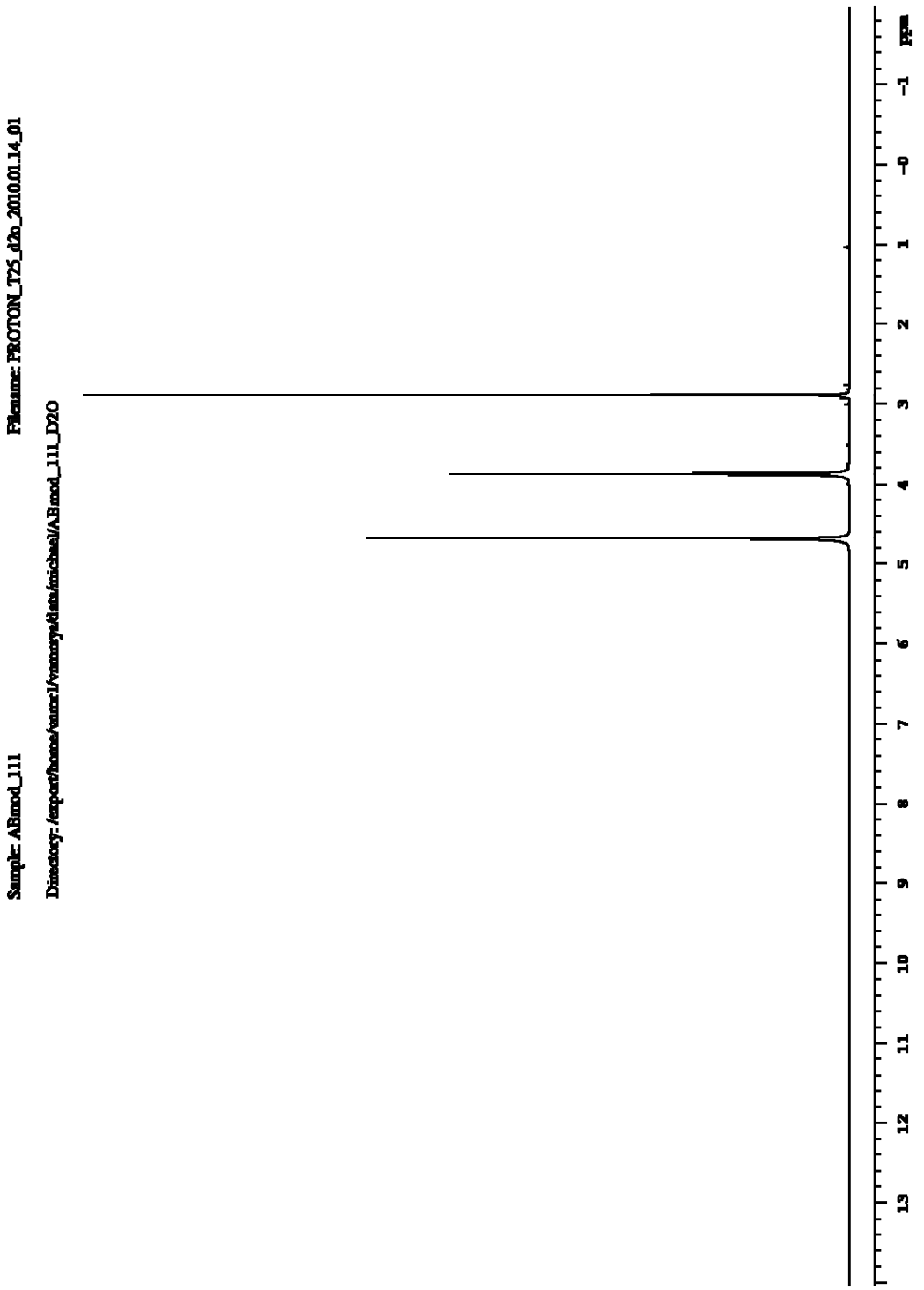


Figure B.3 ^{13}C NMR Spectrum of MIDA in DMSO

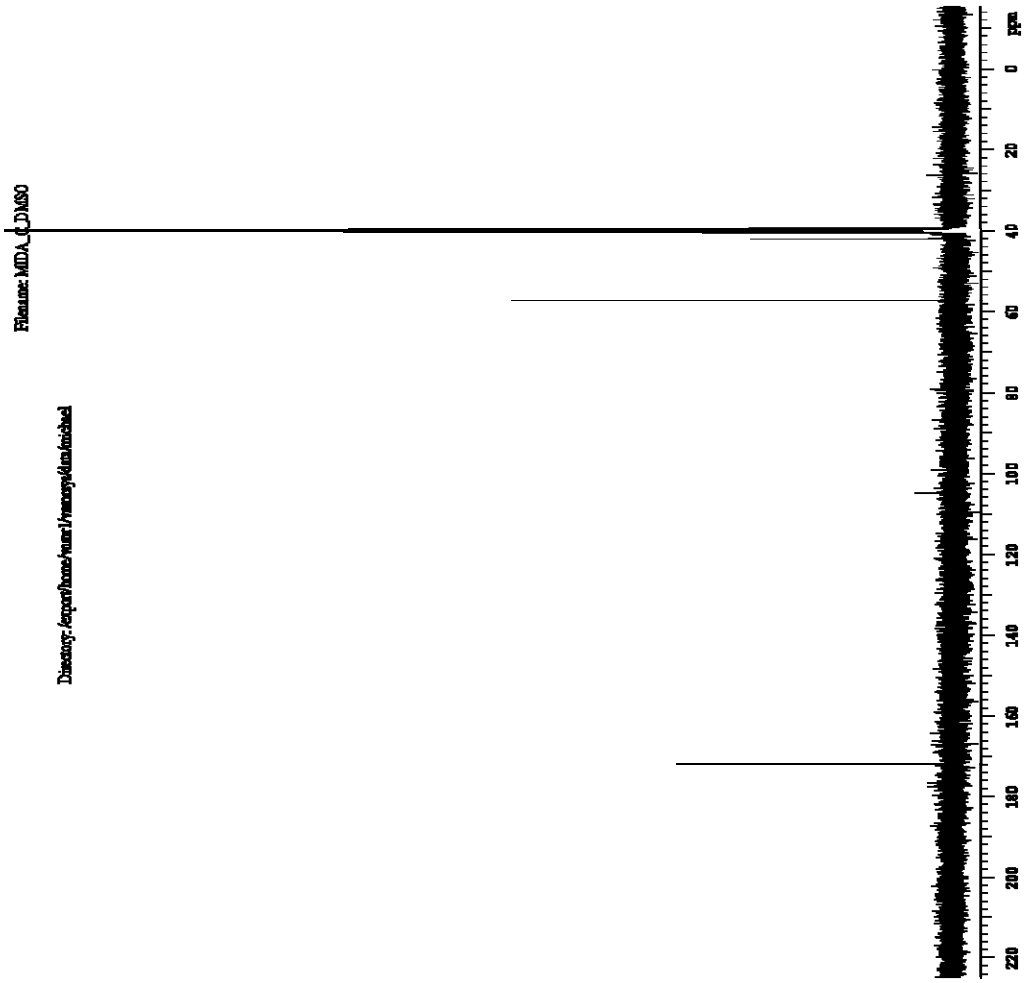


Figure B.4 ^{1}H NMR Spectrum of Na_2MIDA in CD_3OD

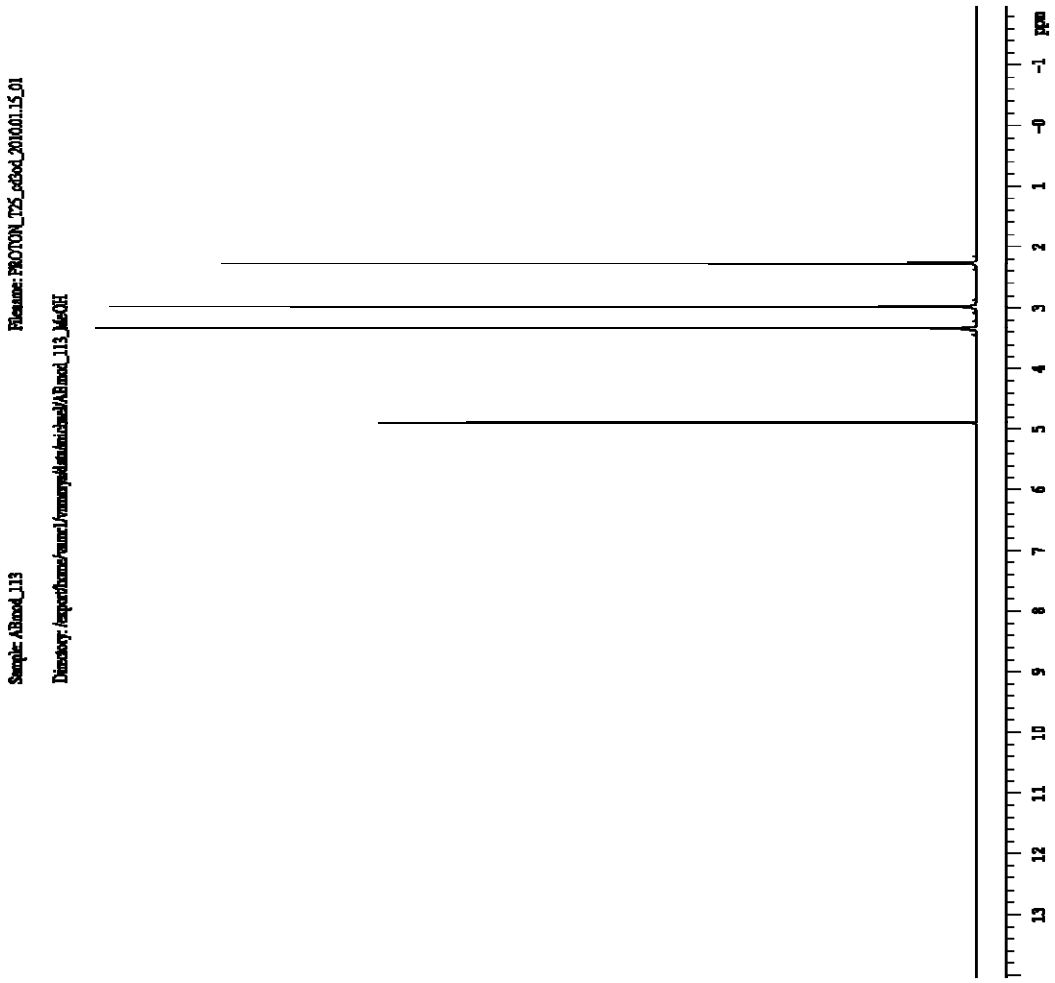


Figure B.5 ^{1}H NMR Spectrum of TMS-Protected MIDA in CD_3Cl

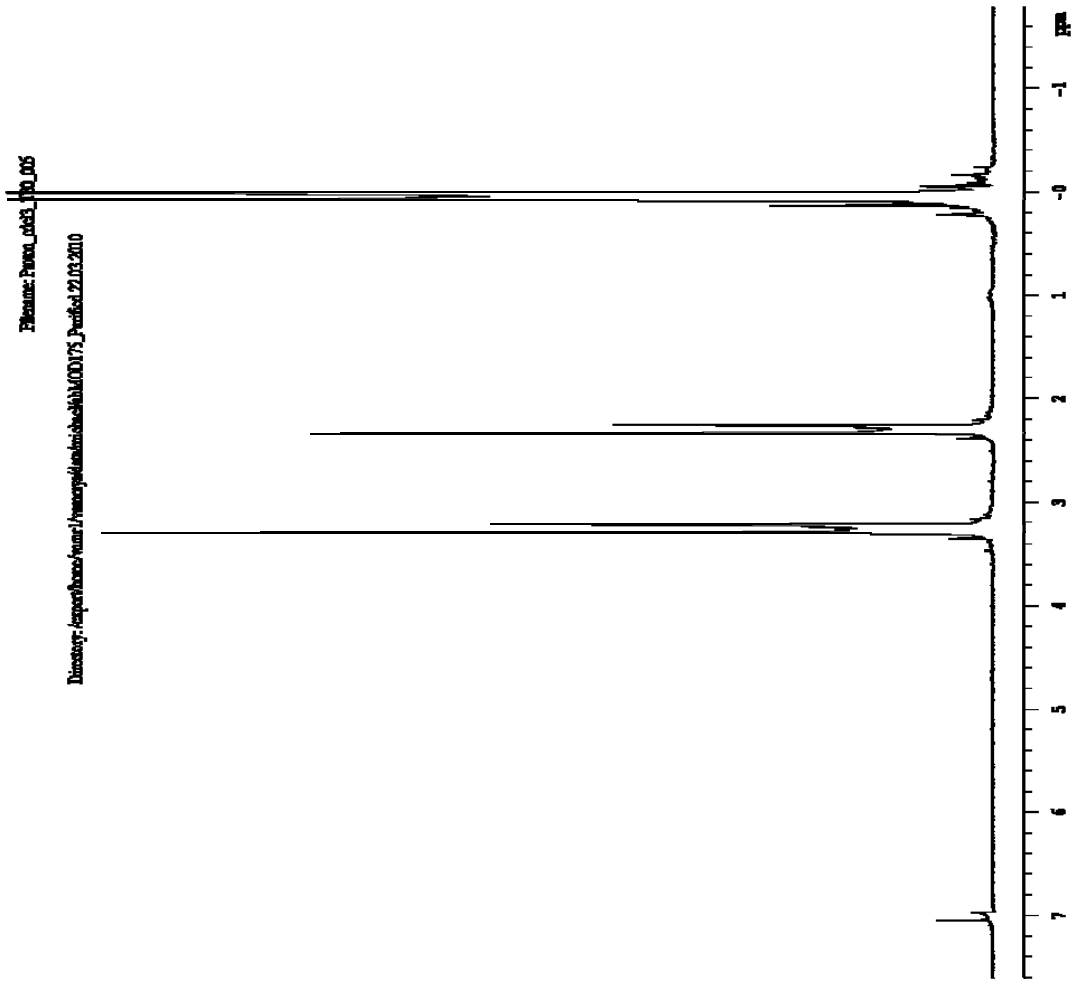


Figure B.6 ^{13}C NMR Spectrum of TMS-Protected MIDA in CD_3Cl

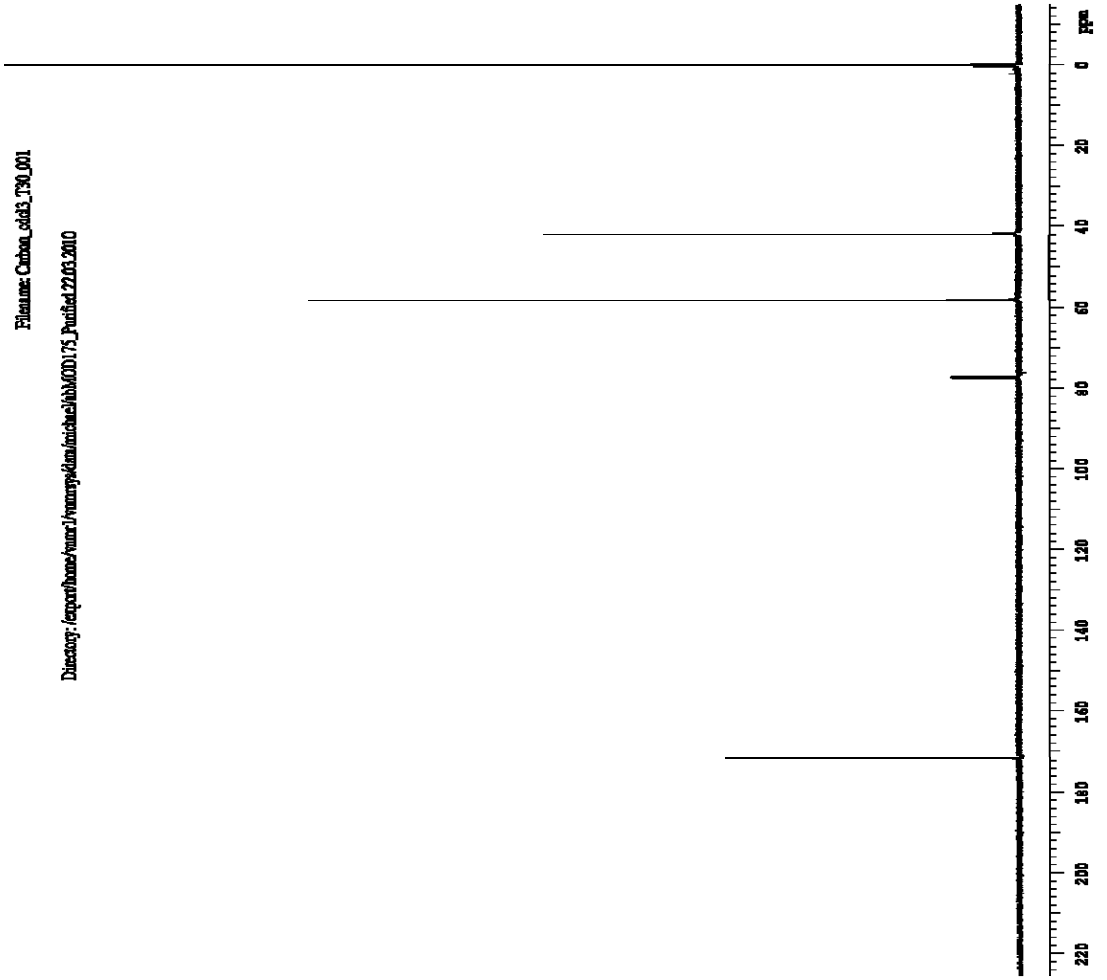


Figure B.7 ^{1}H NMR Spectrum of MIDA-Protected Phenyl Boronate in CD_3Cl

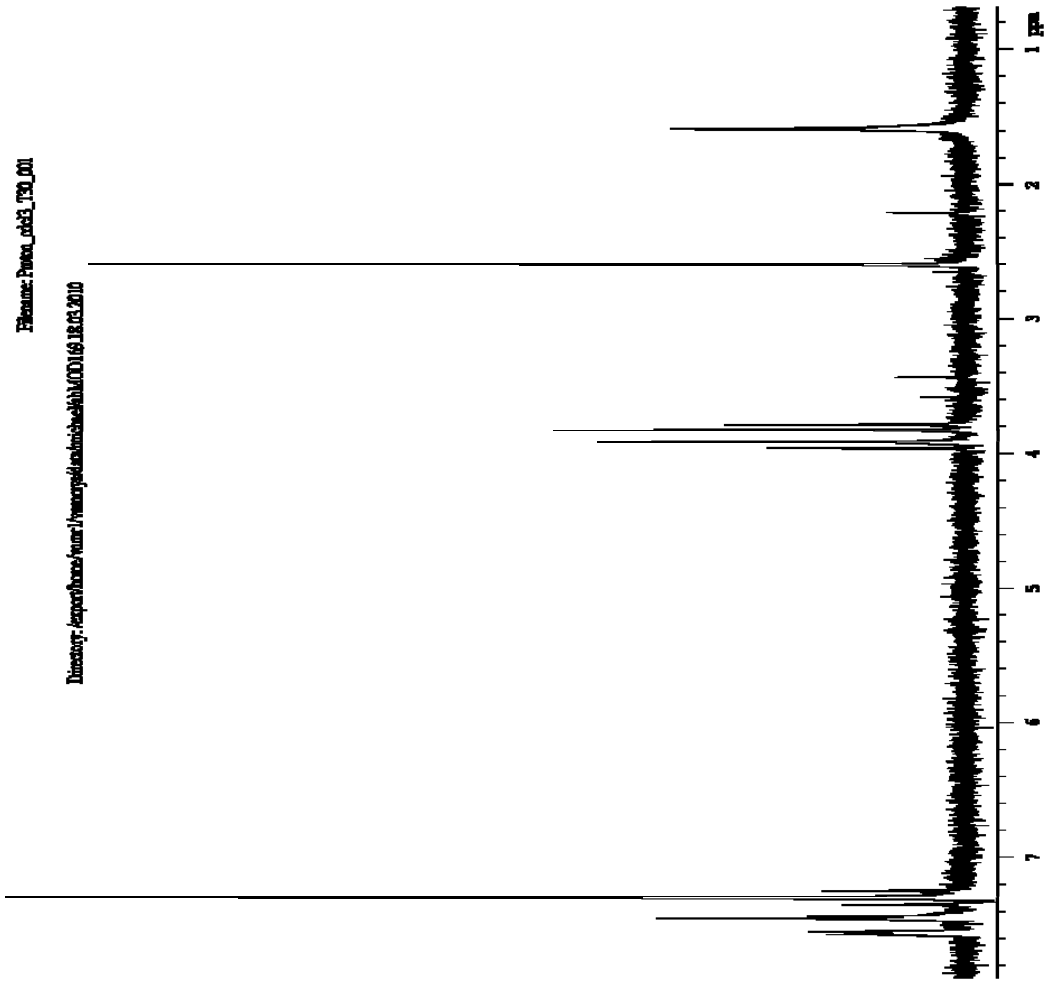


Figure B.8 ^{13}C NMR Spectrum of MIDA-Protected Phenyl Boronate in CD_3Cl

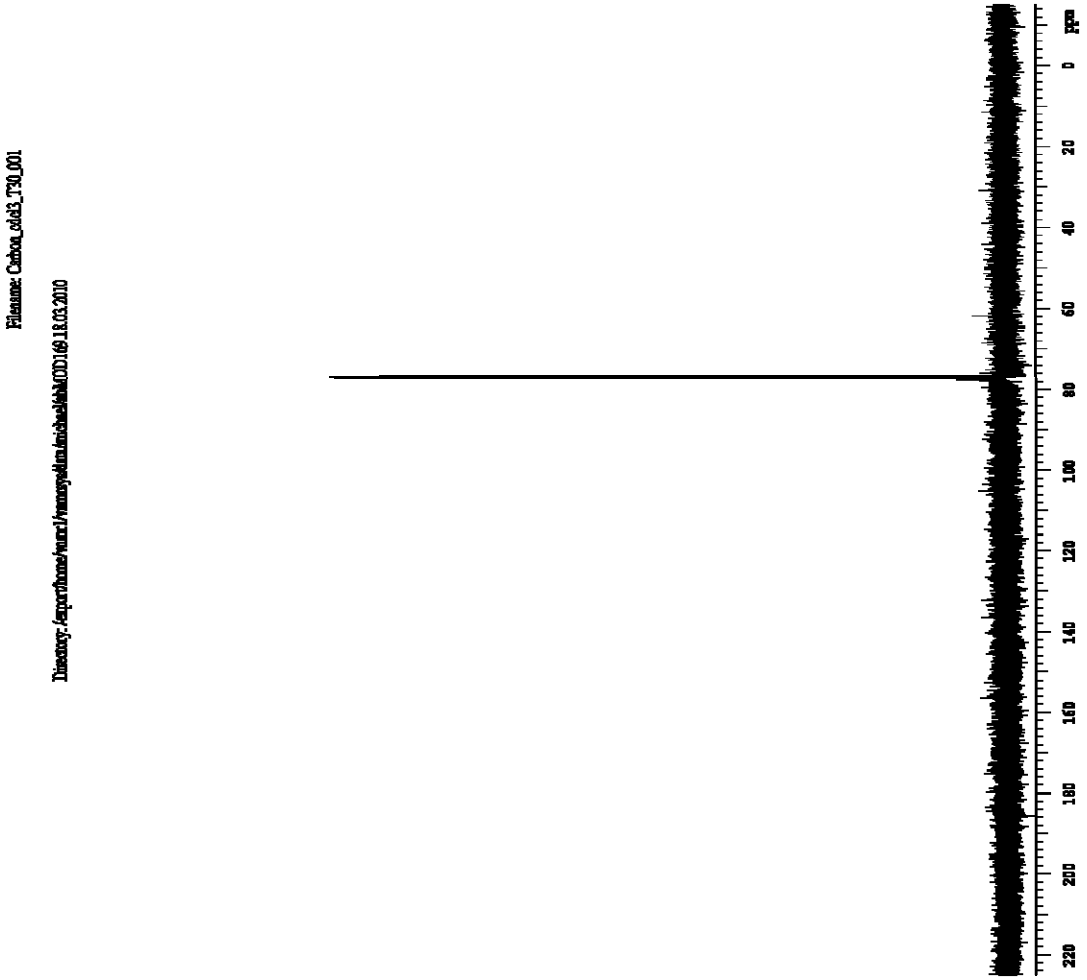


Figure B.9 ^{1}H NMR Spectrum of Possible MIDA-Protected Ethynyl Boronate in DMSO

Fraction 1

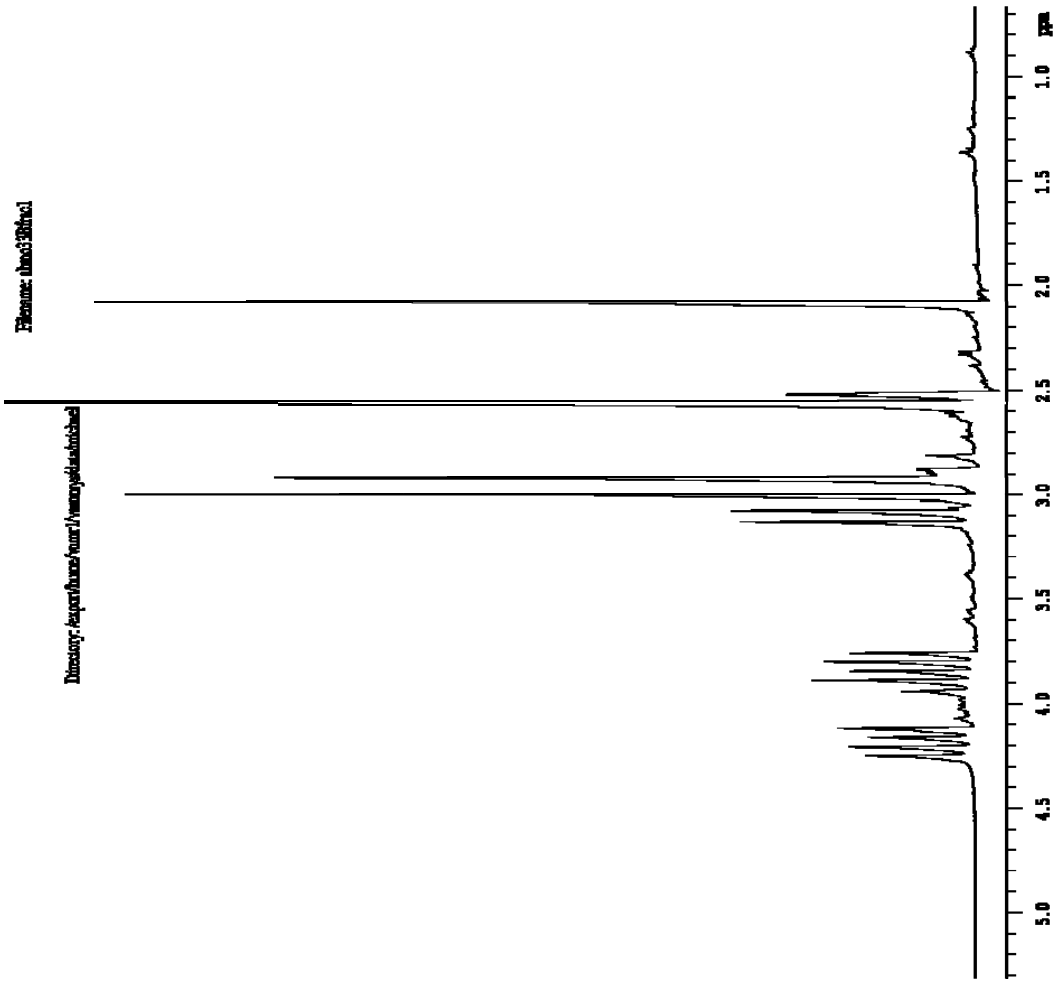


Figure B.10 ^{13}C NMR Spectrum of Possible MIDA-Protected Ethynyl Boronate in DMSO

Fraction 1

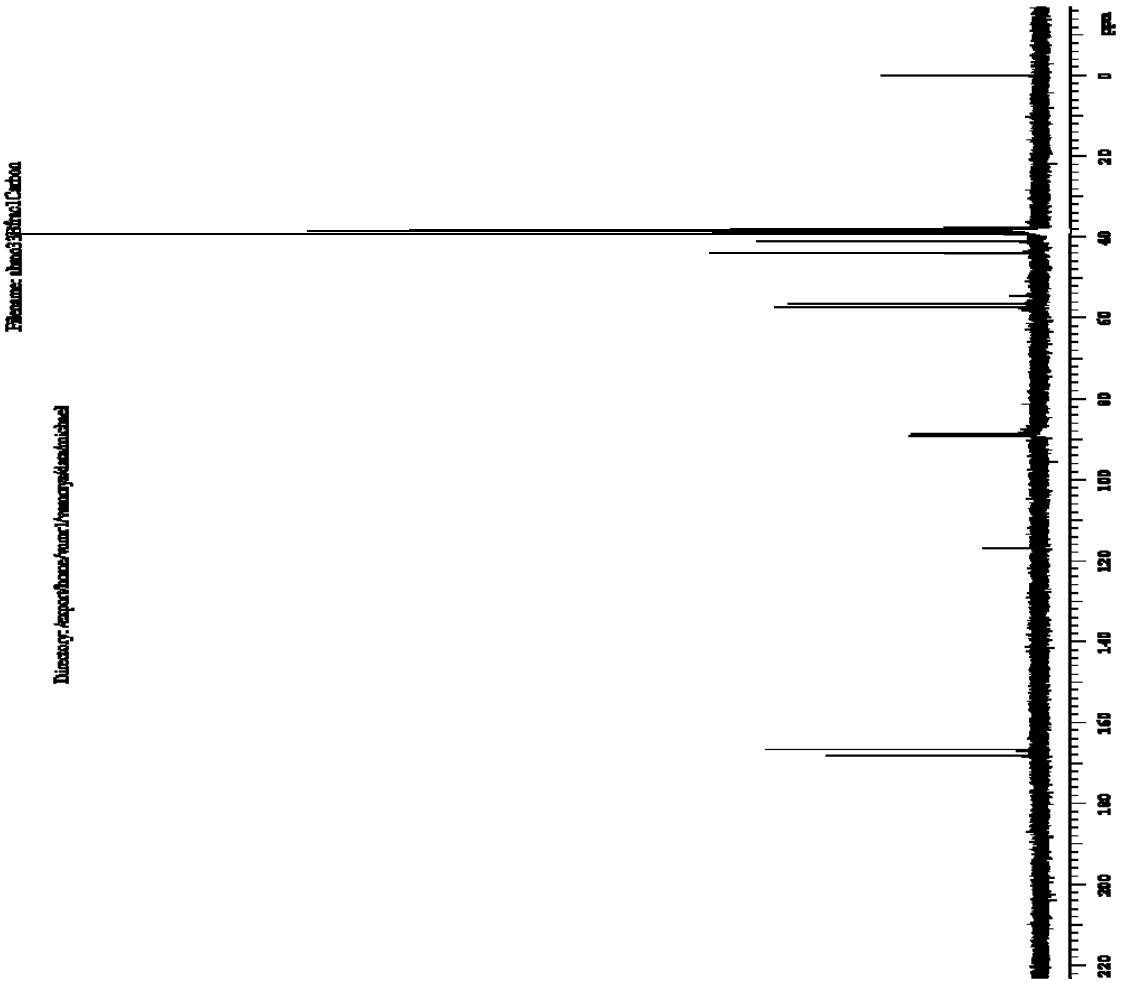


Figure B.11 ^{1}H NMR Spectrum of Possible MIDA-Protected Ethynyl Boronate in DMSO

Column Purge

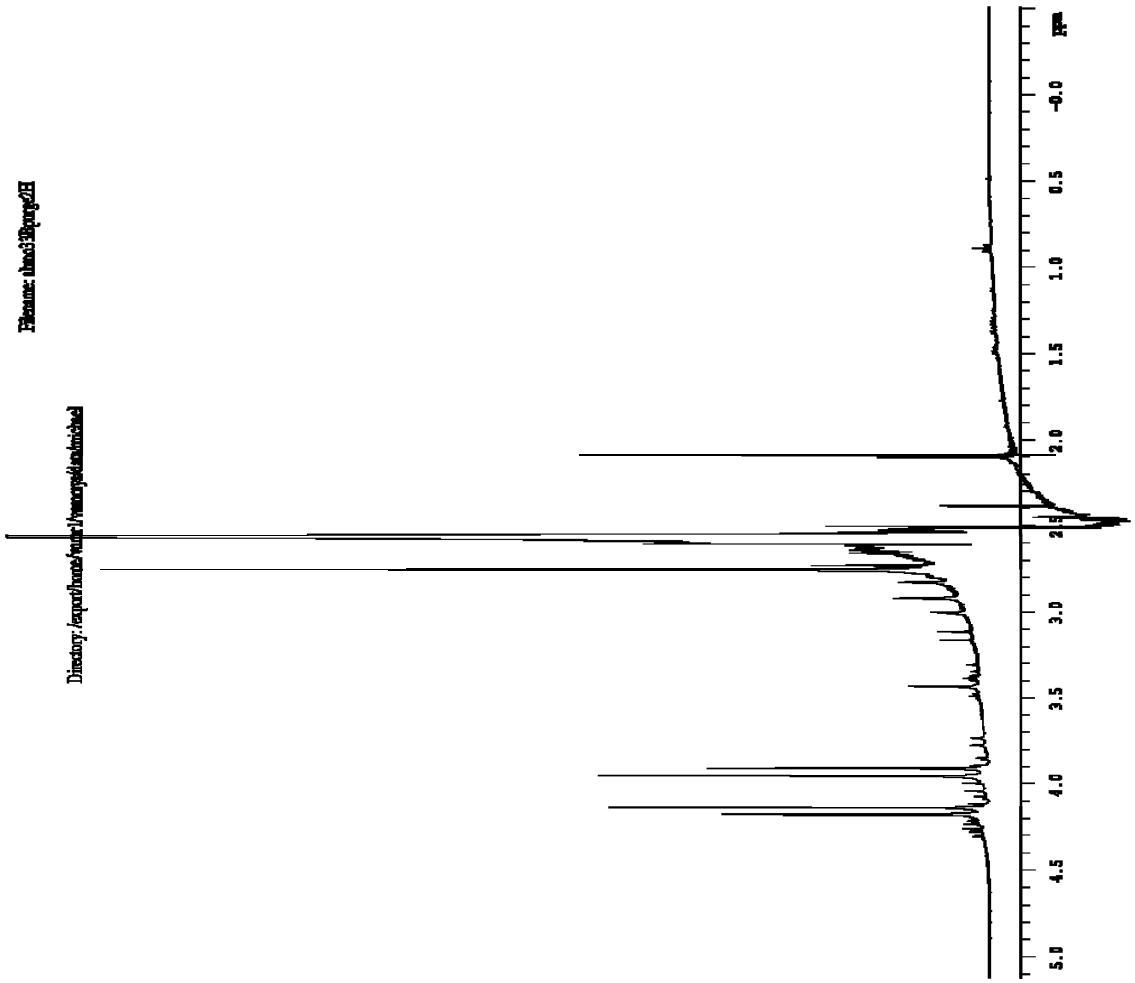


Figure B.12 ^{13}C NMR Spectrum of Possible MIDA-Protected Ethynyl Boronate in DMSO

Column Purge

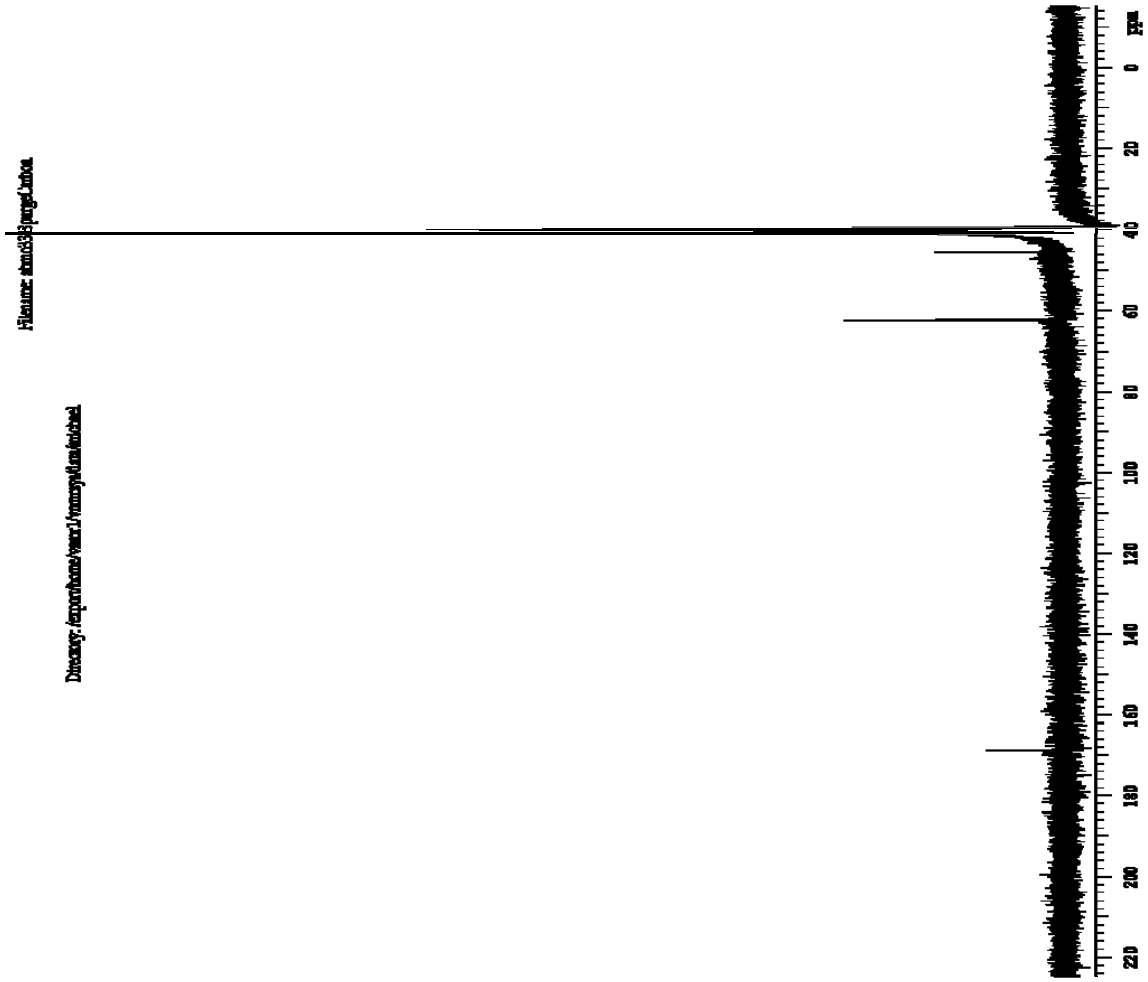


Figure B.13 ^{1}H NMR Spectrum of Possible MIDA-Protected Ethynyl Boronate in MeCN

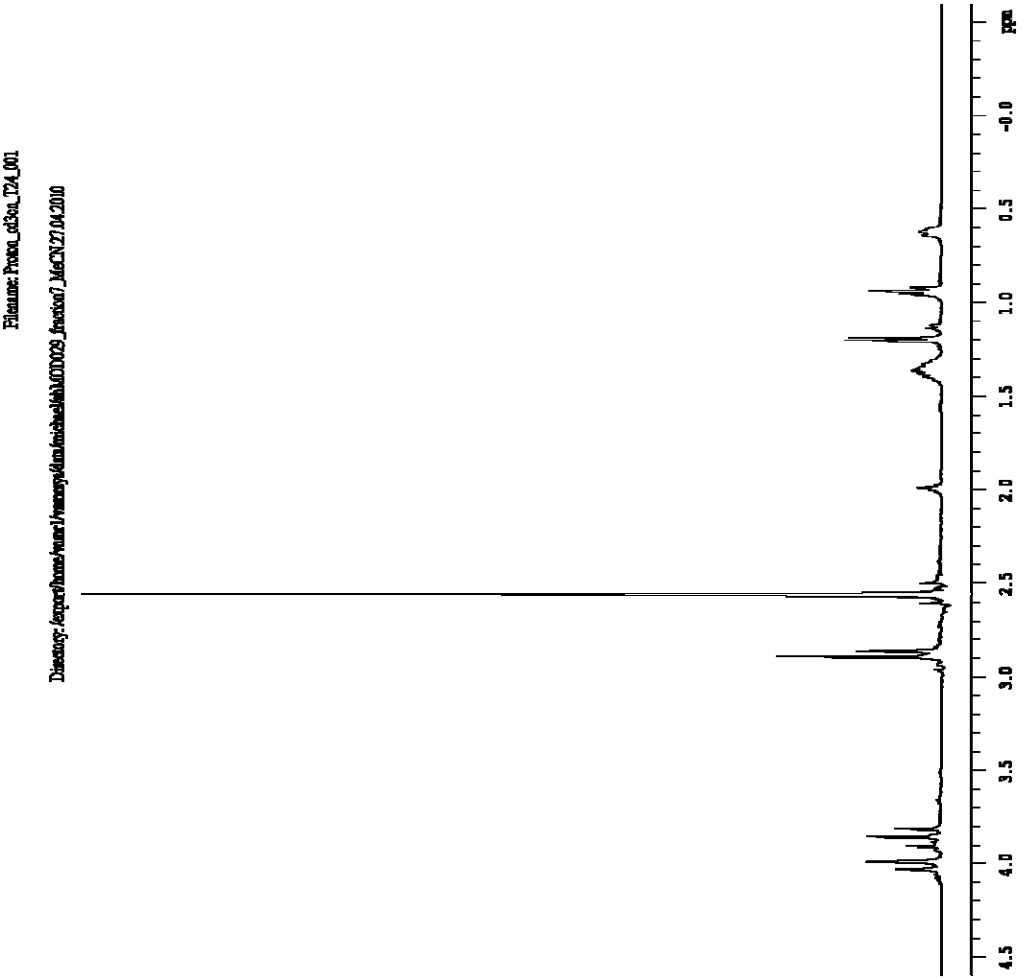


Figure B.14 ^{13}C NMR Spectrum of Possible MIDA-Protected Ethynyl Boronate in MeCN

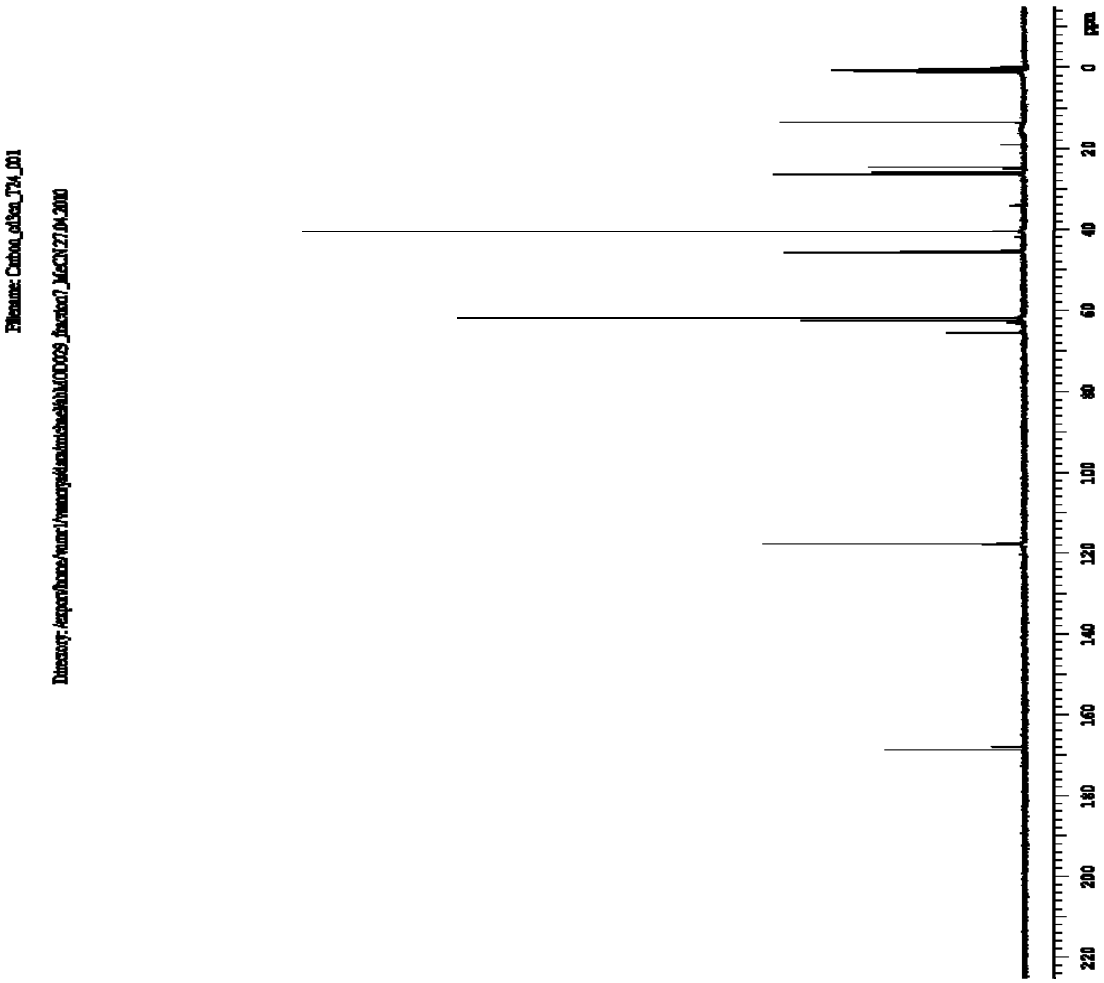


Figure B.15 ^{1}H NMR Spectrum of Possible MIDA-Protected Ethynyl Boronate in DMSO

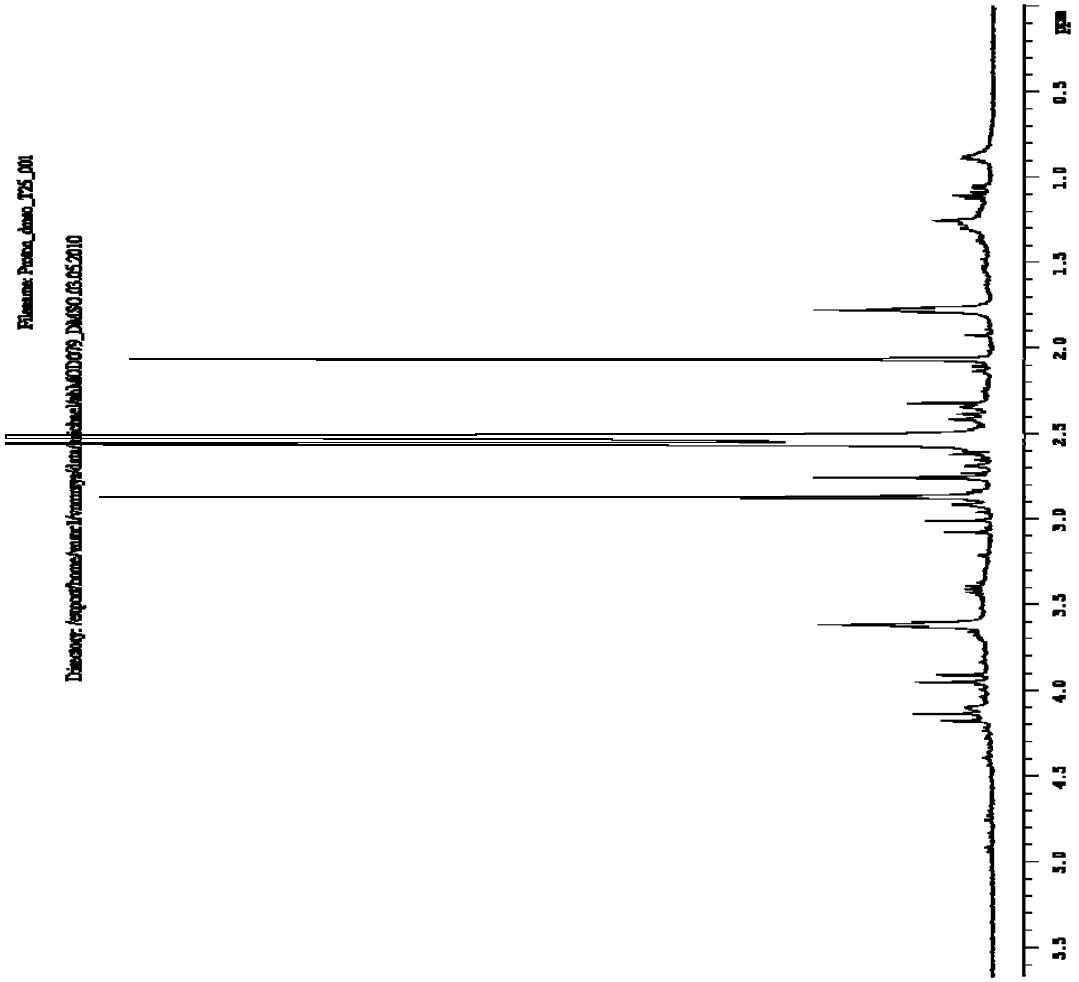


Figure B.16 ^{13}C NMR Spectrum of Possible MIDA-Protected Ethynyl Boronate in DMSO

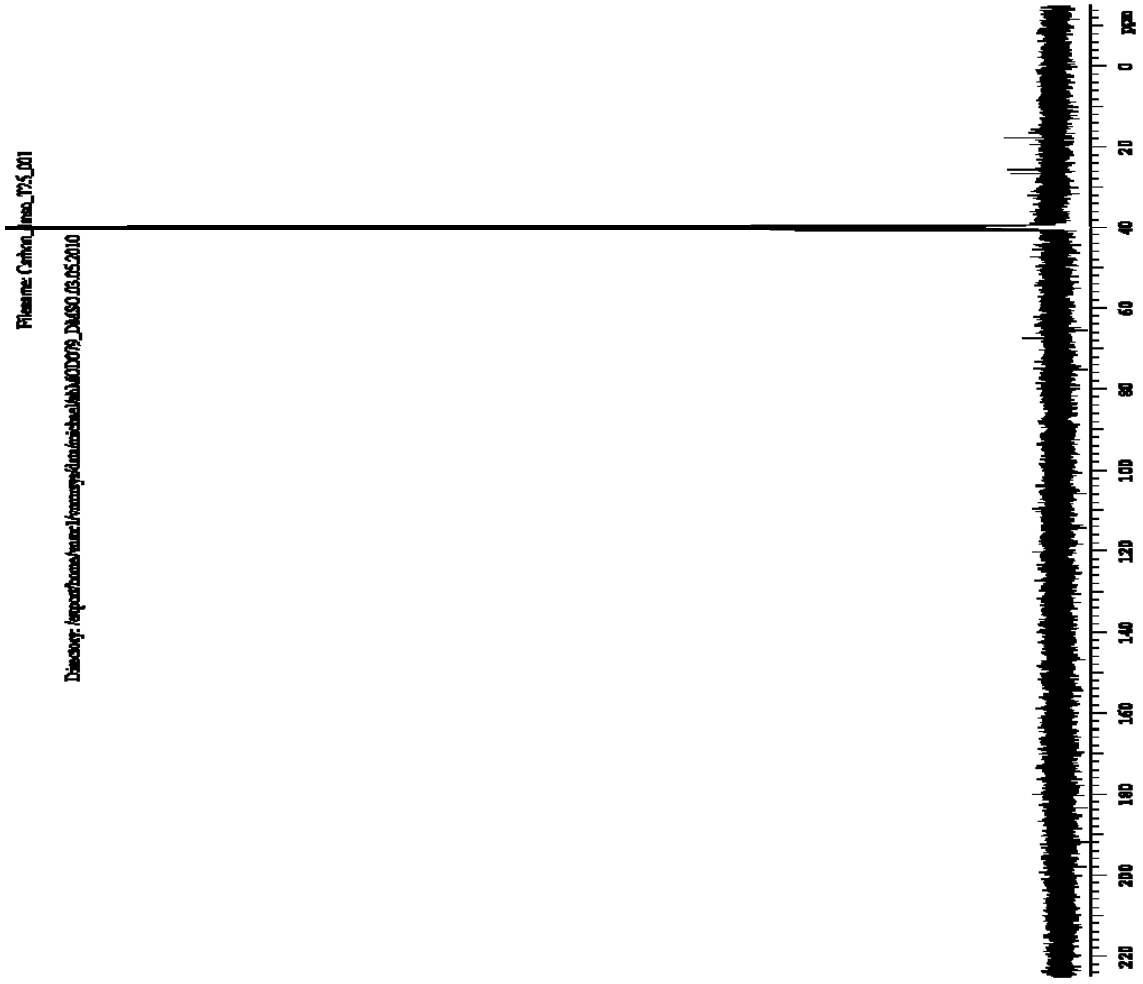


Figure B.17 ^{1}H NMR Spectrum of Possible MIDA-Protected Phenyl Ethynyl Boronate in DMSO

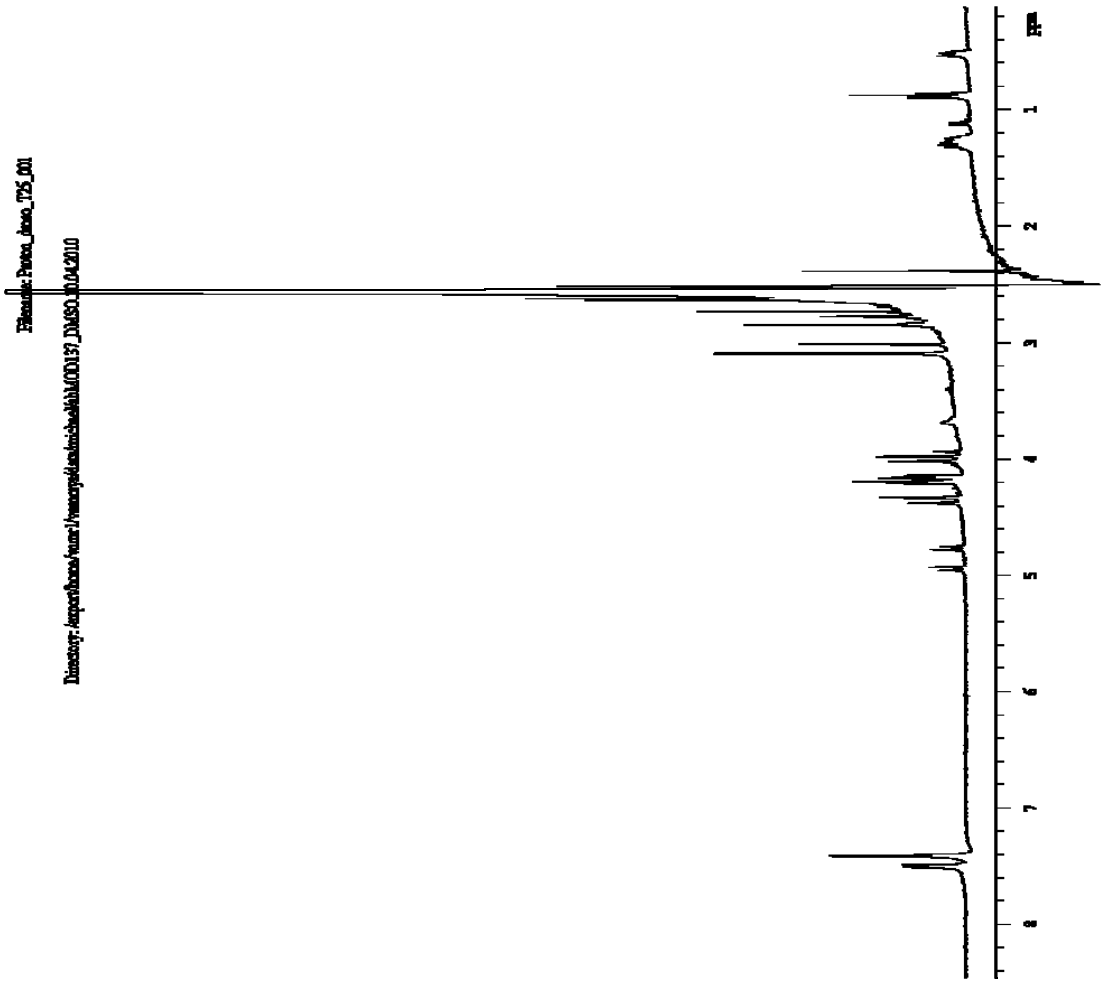


Figure B.18 ^{13}C NMR Spectrum of Possible MIDA-Protected Phenyl Ethynyl Boronate in DMSO

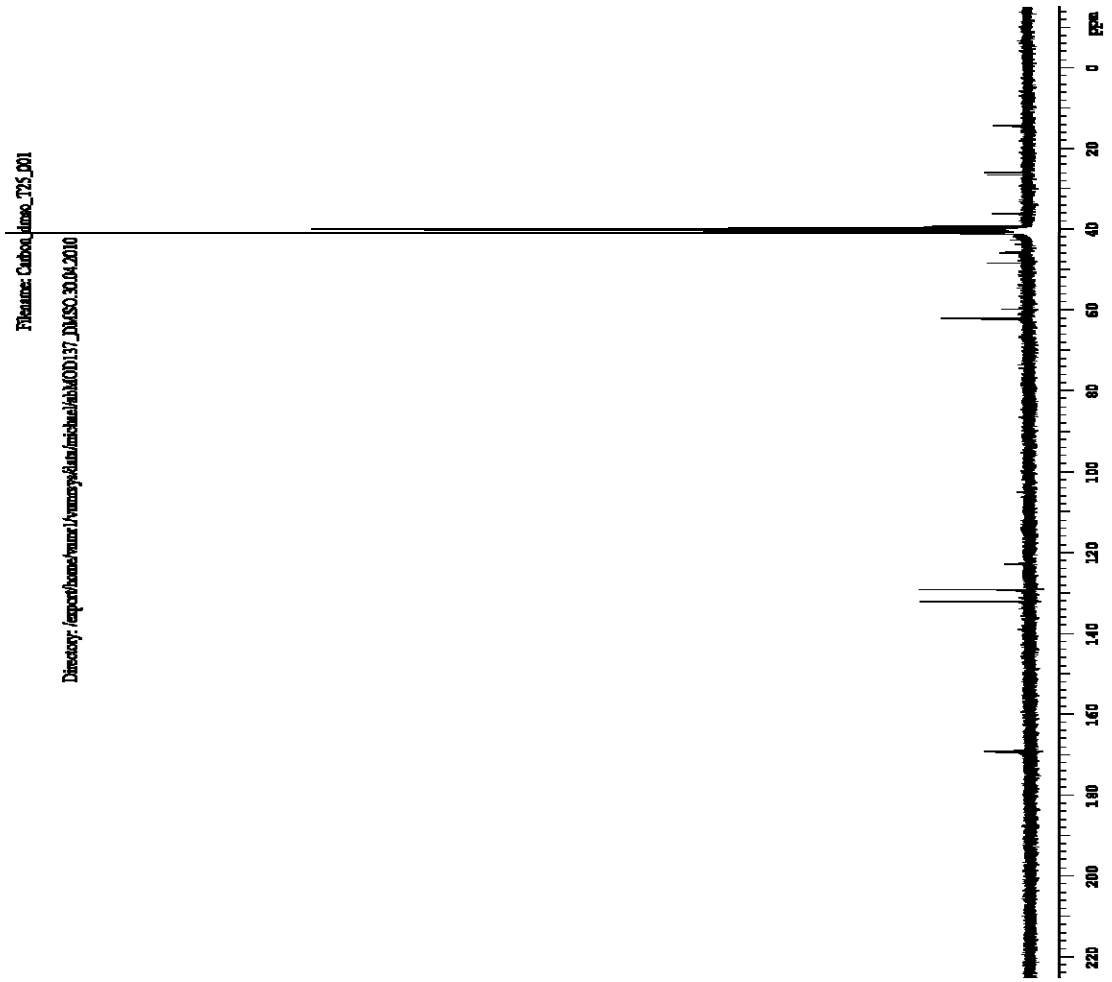


Figure B.19 ^{1}H NMR Spectrum of Possible MIDA-Protected Isopropyl Borate in MeCN

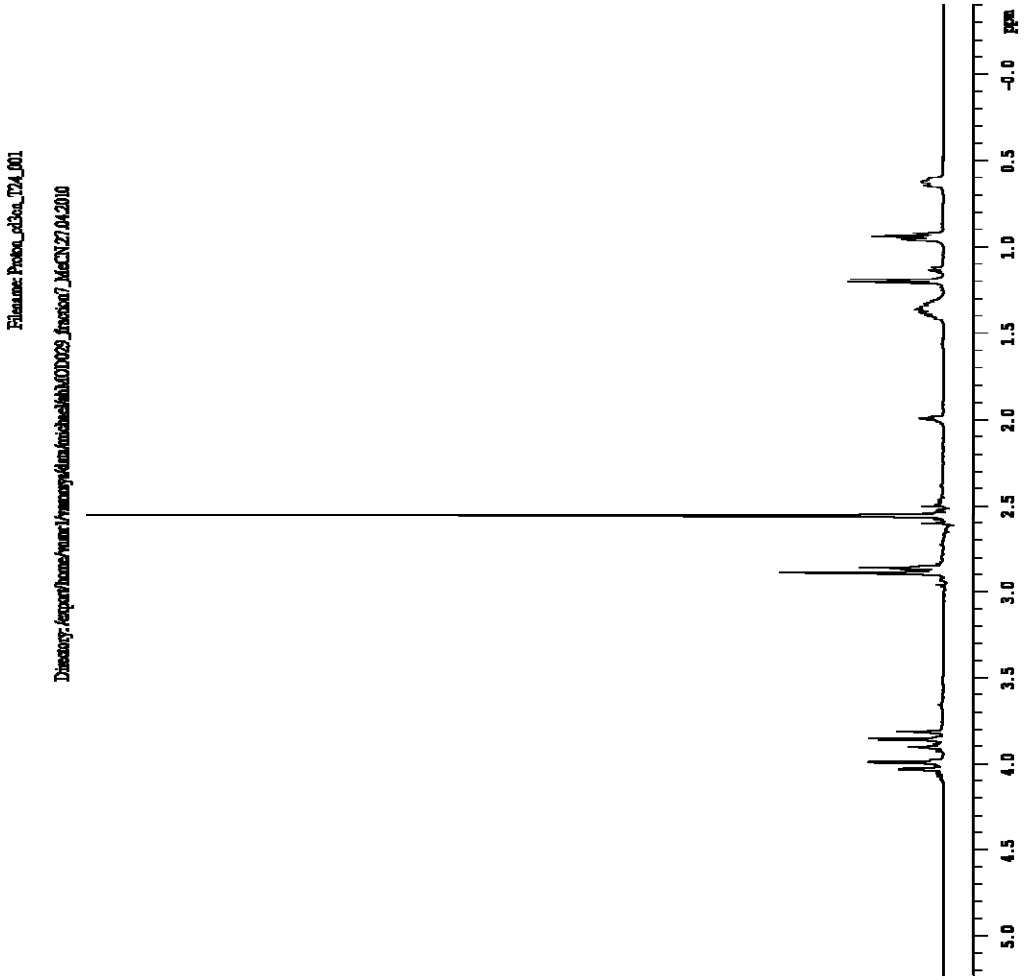


Figure B.20 ^{13}C NMR Spectrum of Possible MIDA-Protected Isopropyl Borate in MeCN

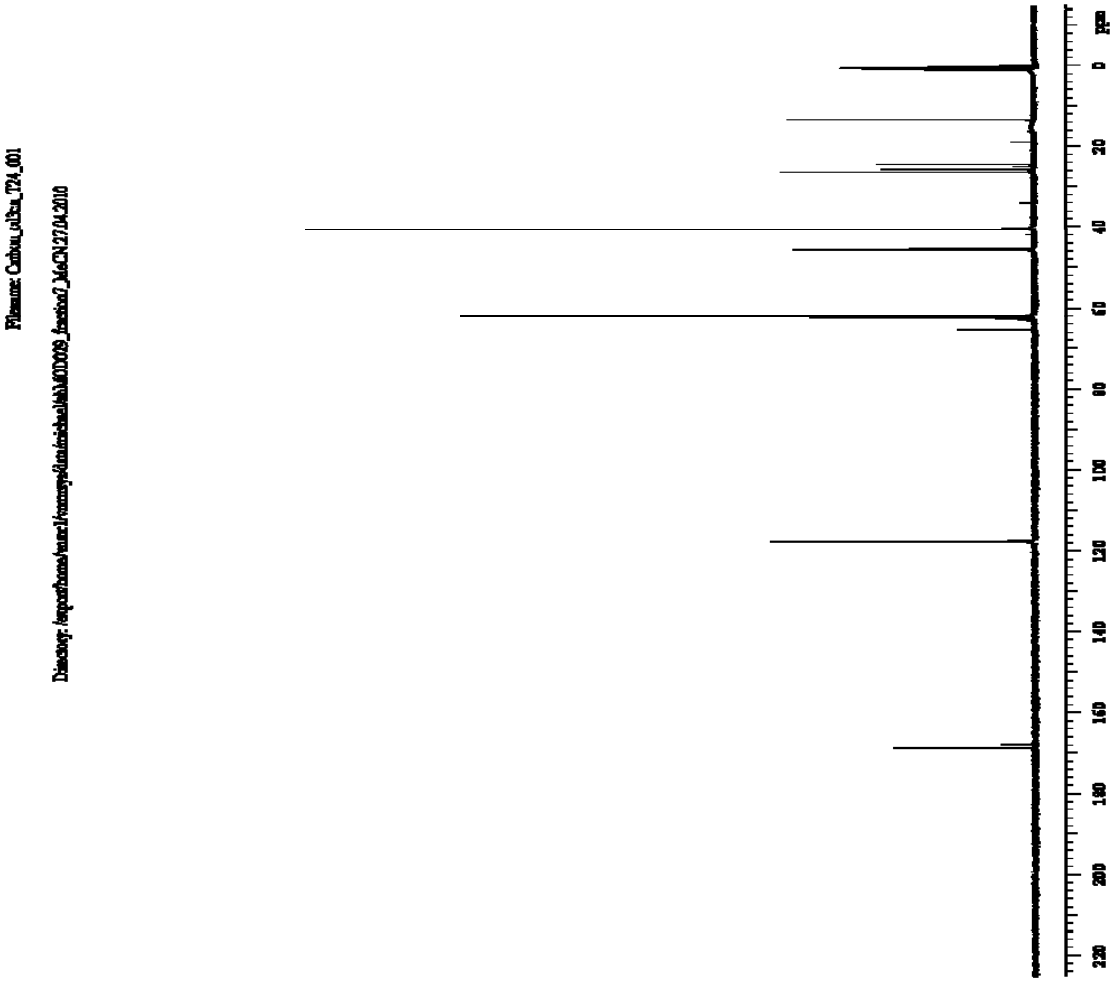


Figure B.21 ^{1}H NMR Spectrum of Possible MIDA-Protected Isopropyl Borate in MeCN

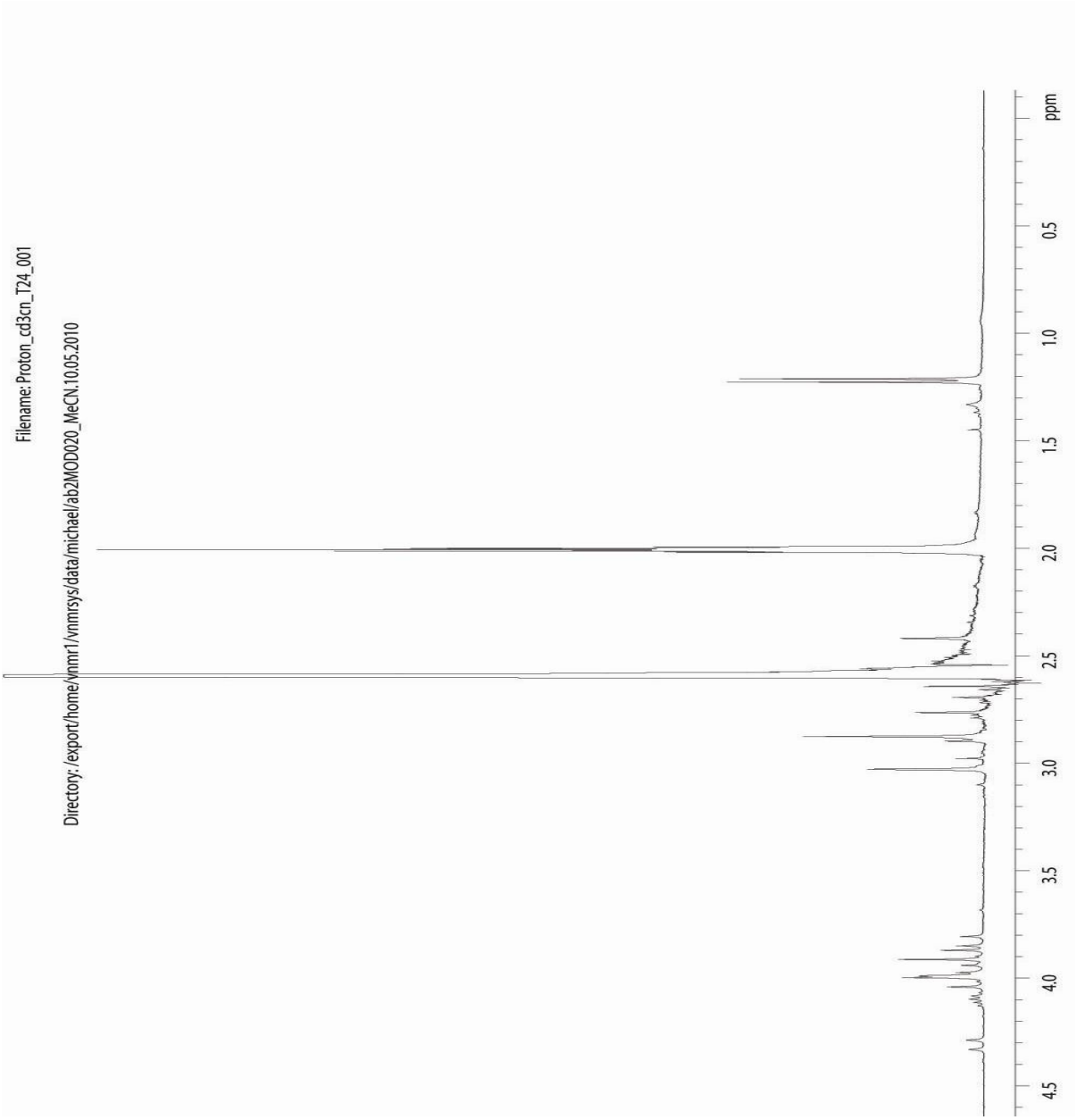


Figure B.22 ^{13}C NMR Spectrum of Possible MIDA-Protected Isopropyl Borate in MeCN

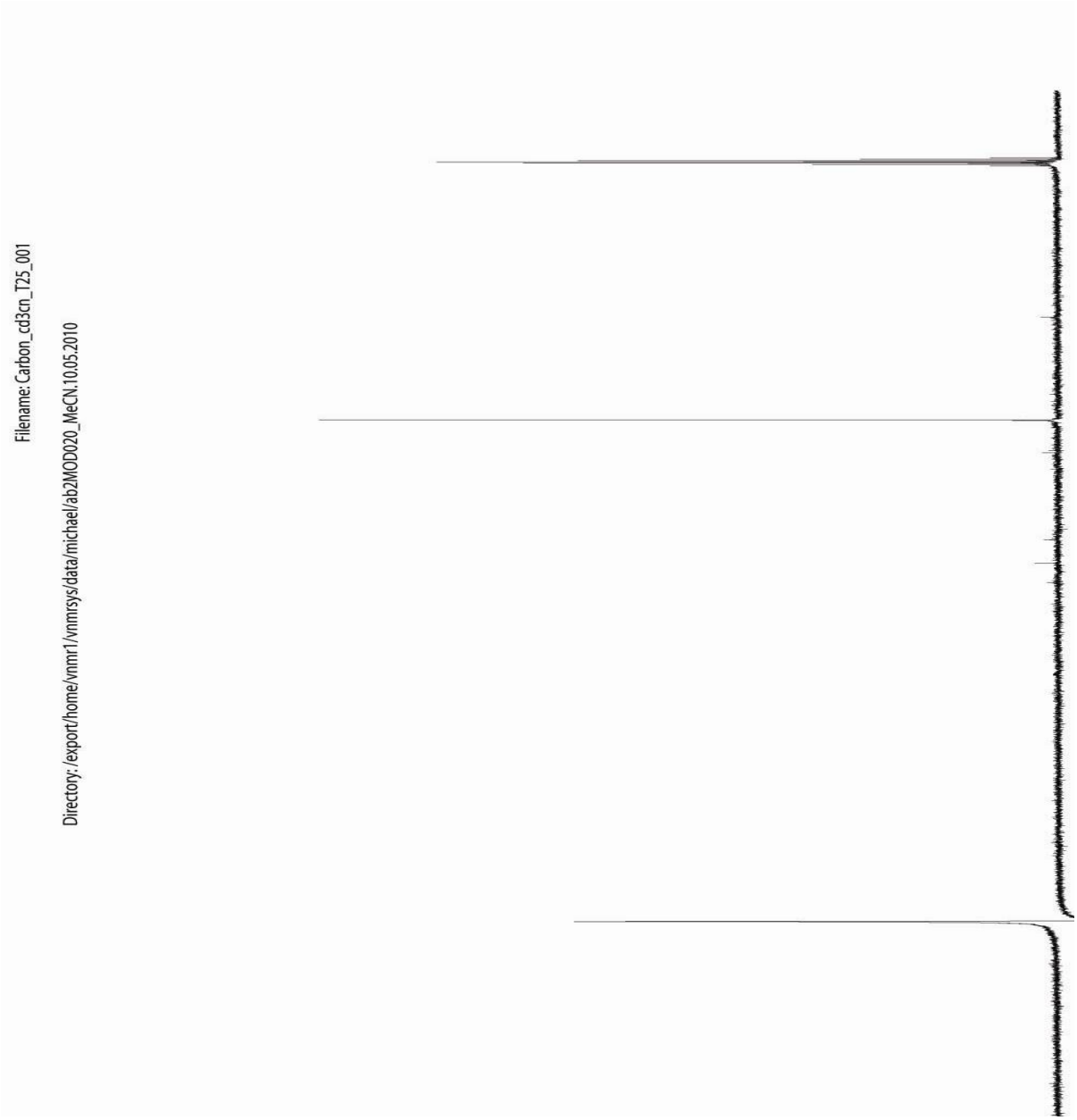


Figure B.23 ^{1}H NMR Spectrum of Possible MIDA-Protected Isopropyl Borate in MeCN

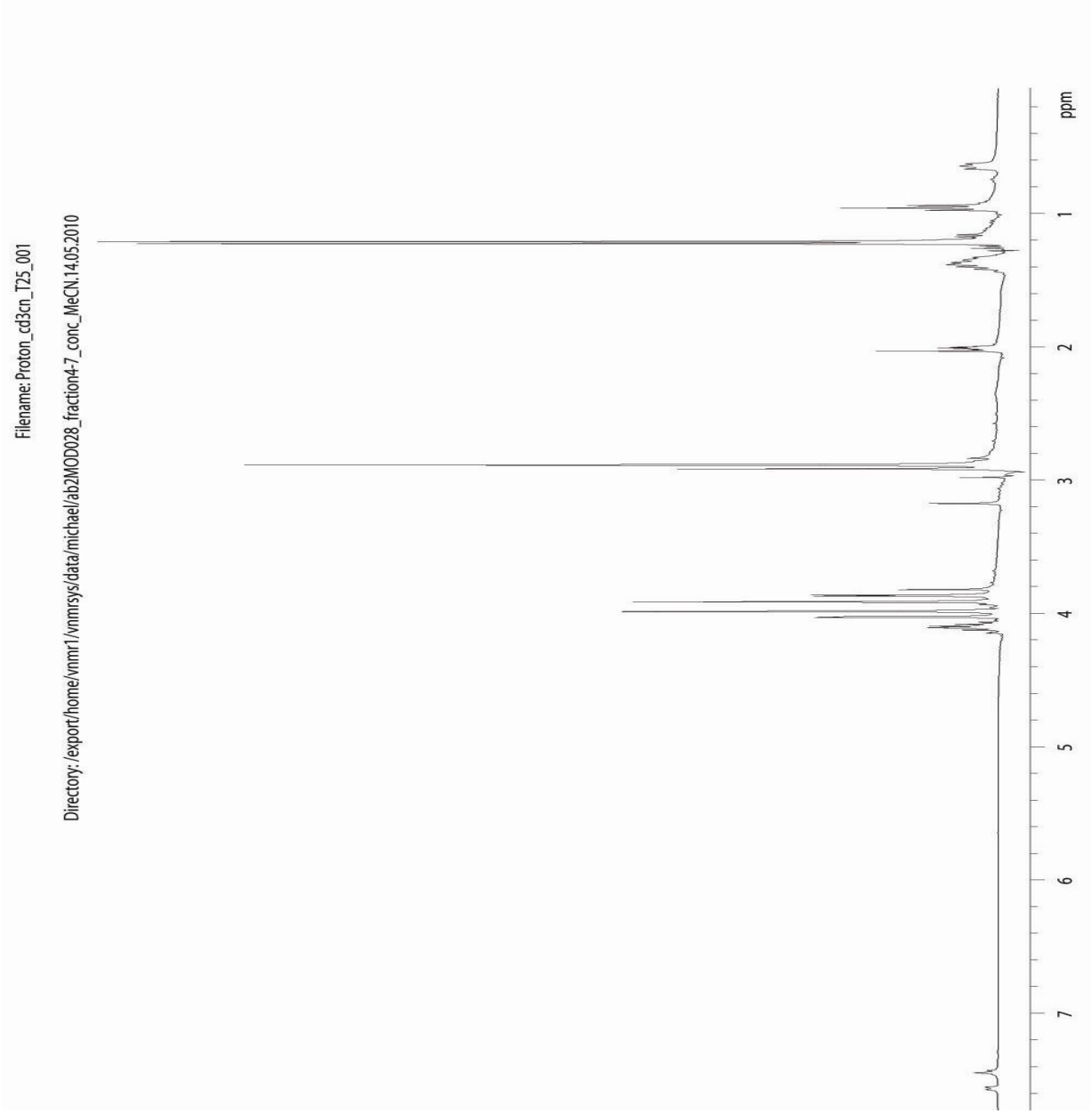


Figure B.24 ^{13}C NMR Spectrum of Possible MIDA-Protected Isopropyl Borate in MeCN

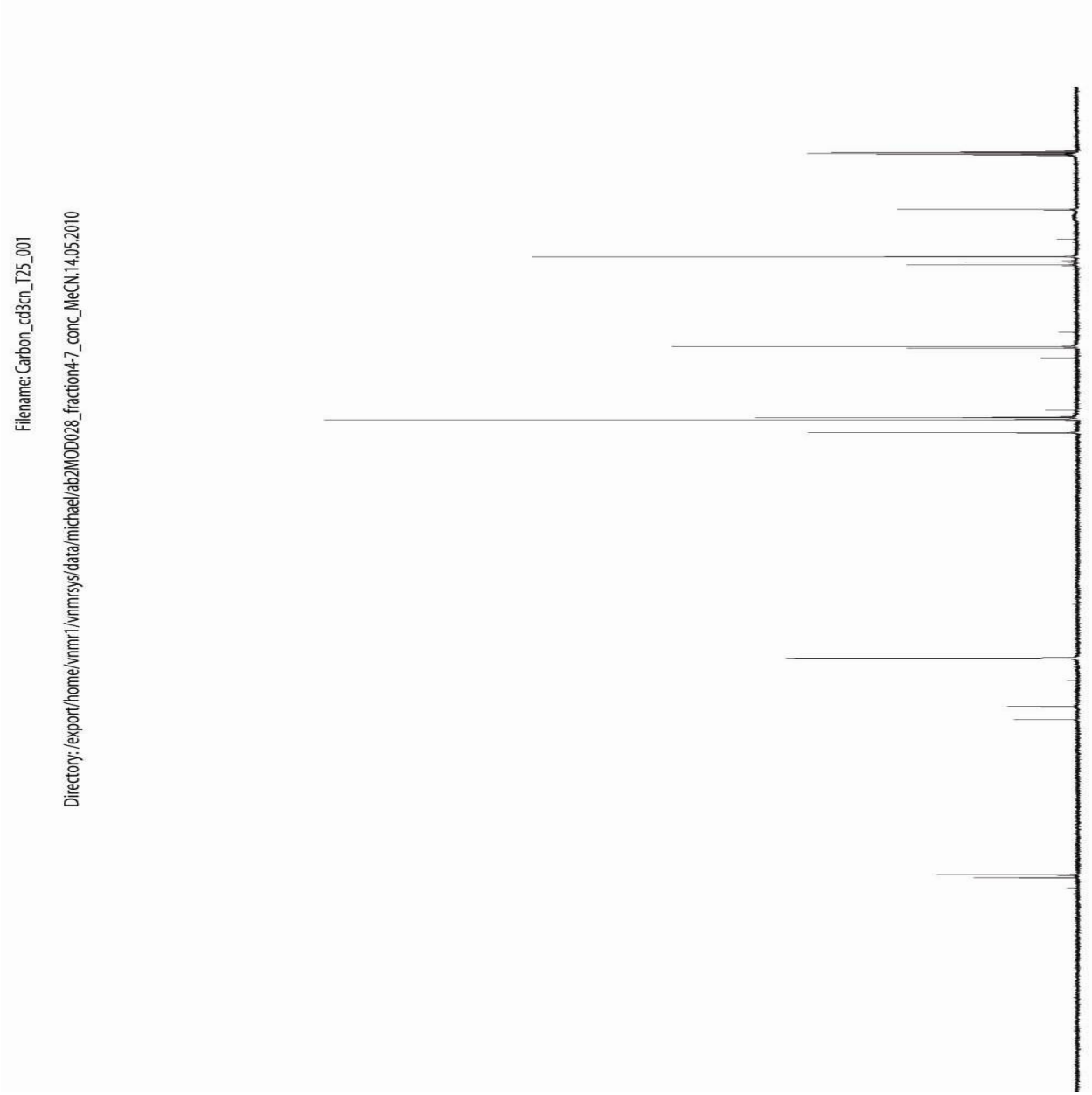


Figure B.25 ^{1}H NMR Spectrum of Possible MIDA-Protected Isopropyl Borate in MeCN

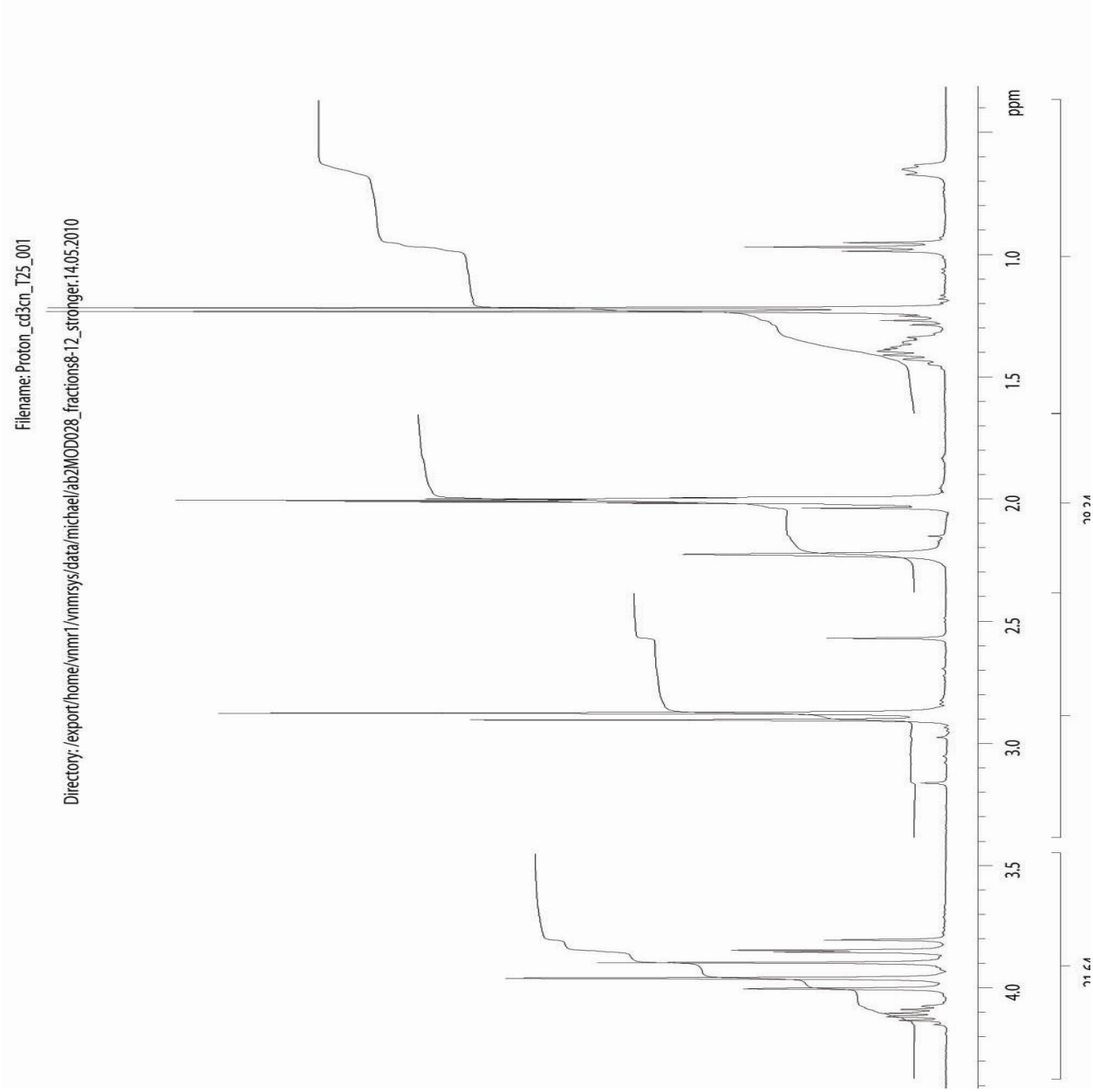


Figure B.26 ^{1}H NMR Spectrum of Possible MIDA-Protected Isopropyl Borate in MeCN

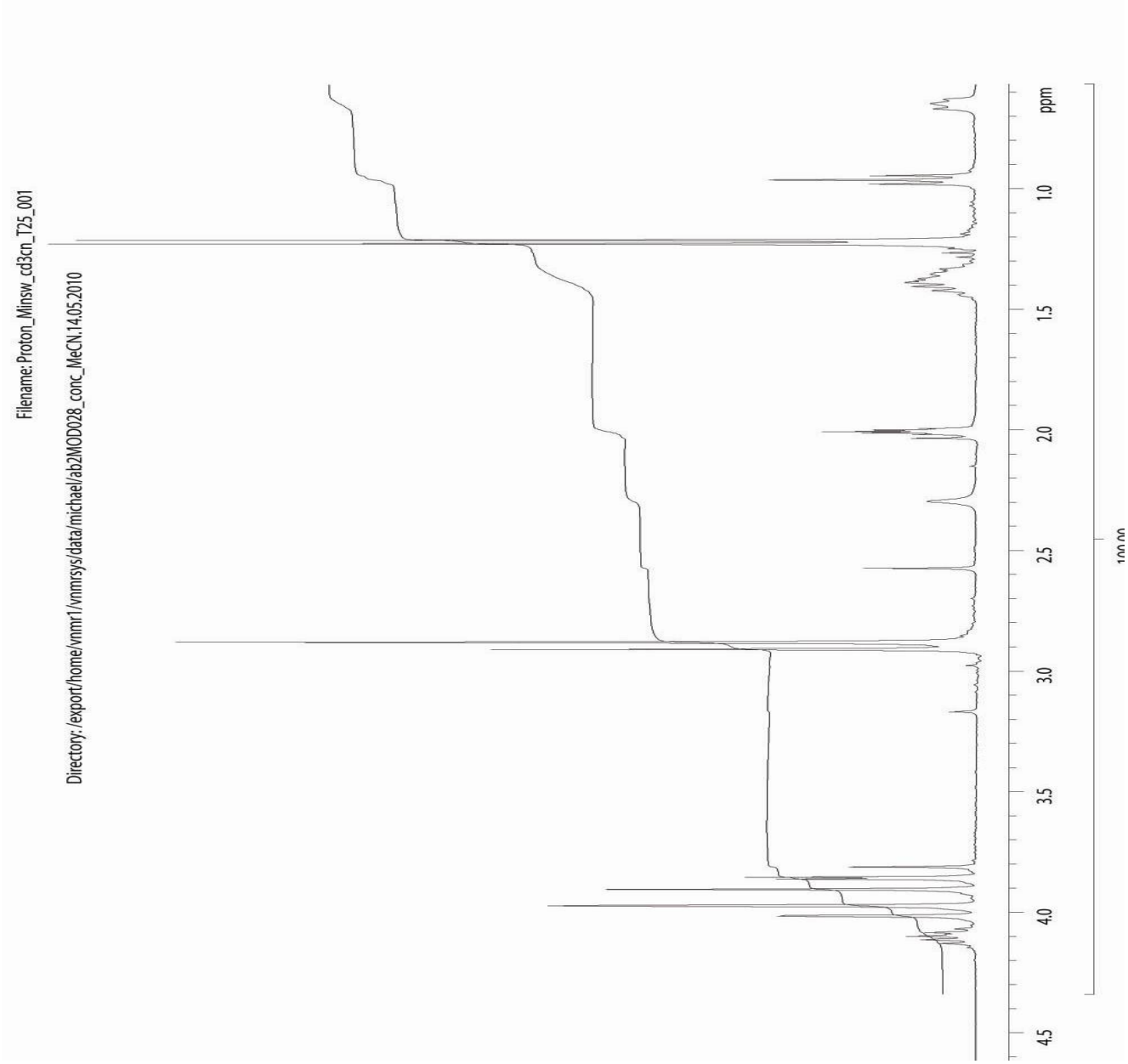


Figure B.27 ^{1}H NMR Spectrum of Possible MIDA-Protected Isopropyl Borate in MeCN

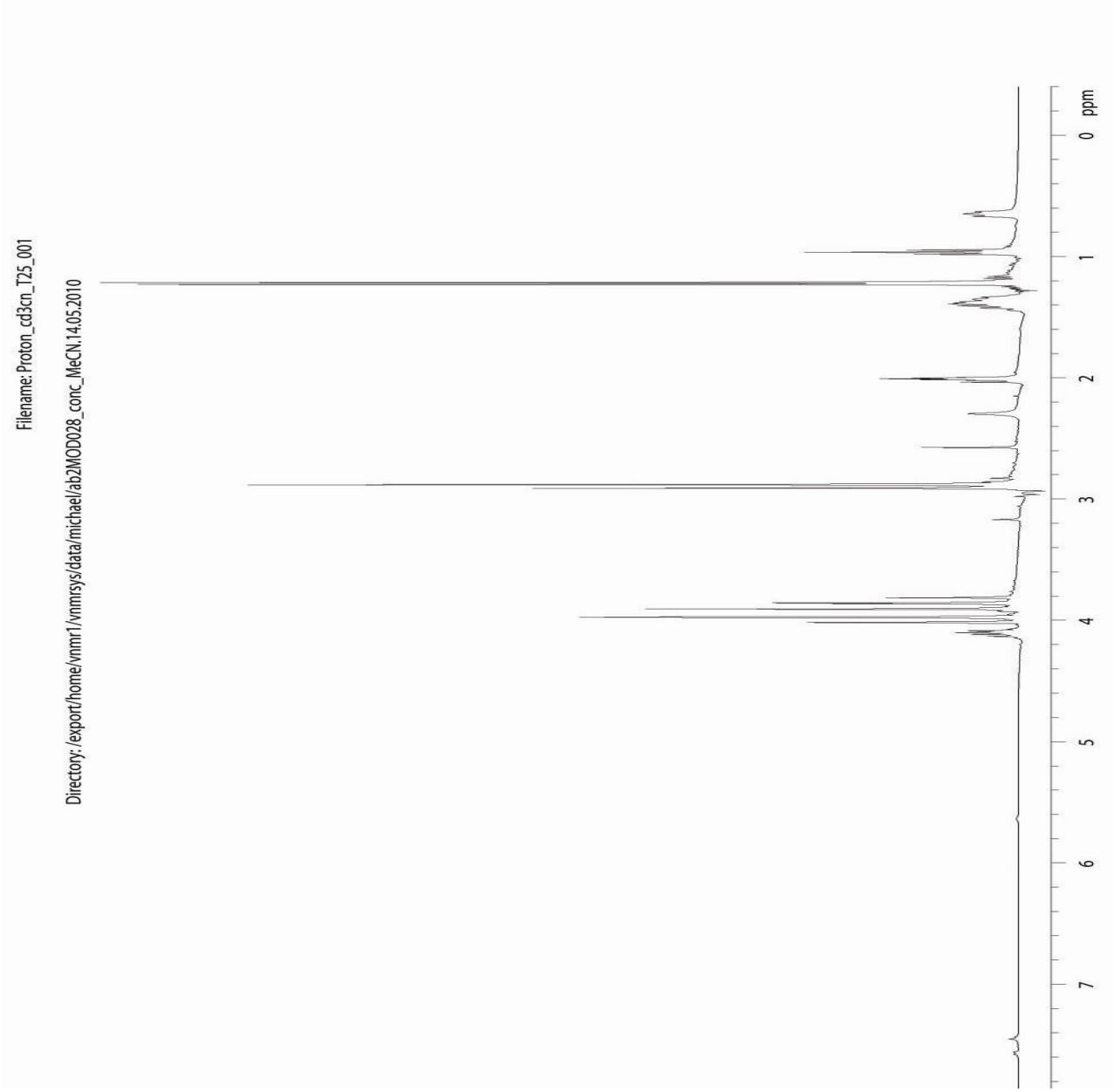


Figure B.28 ^{1}H NMR Spectrum of Possible MIDA-Protected Isopropyl Borate in MeCN

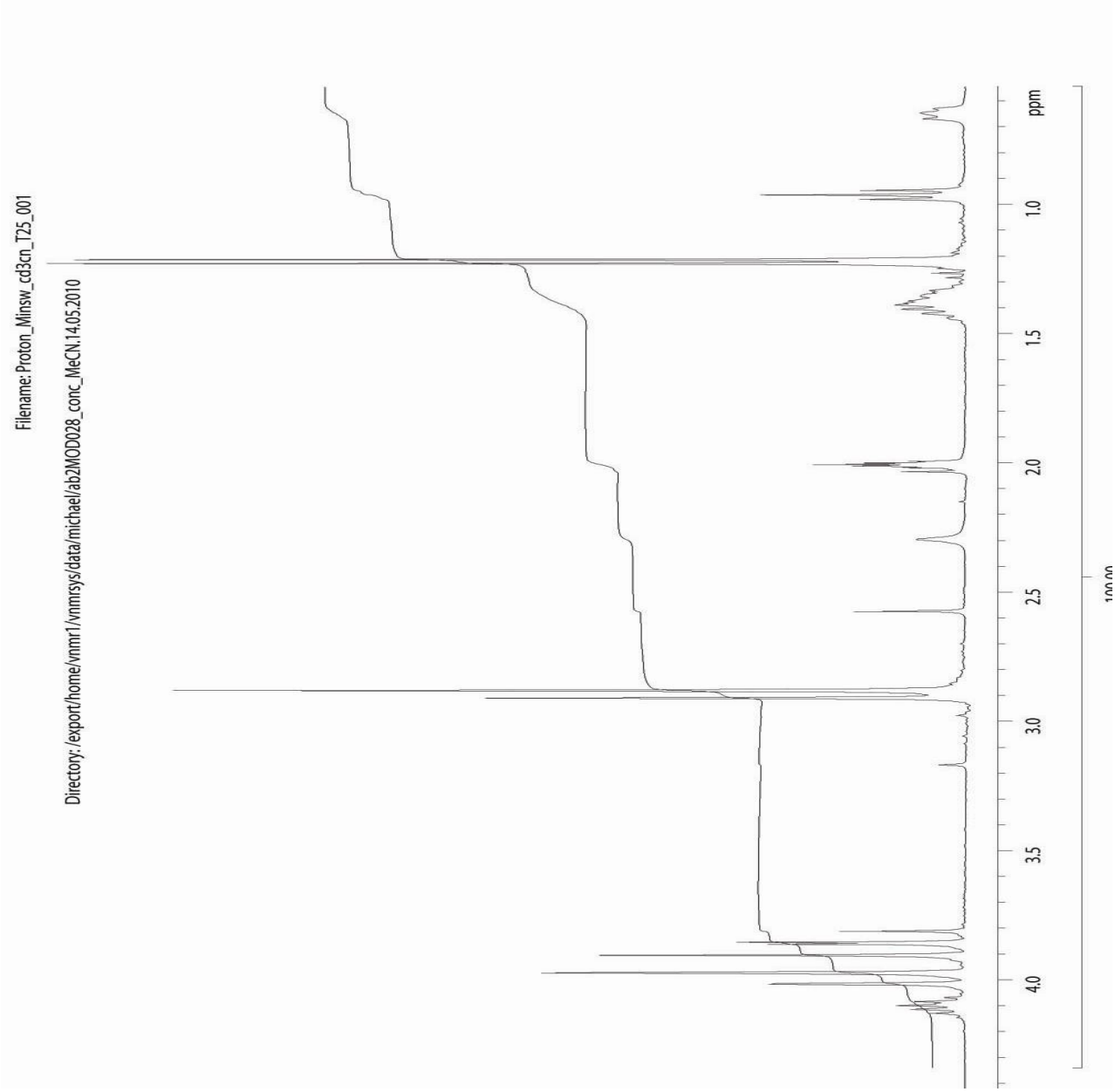
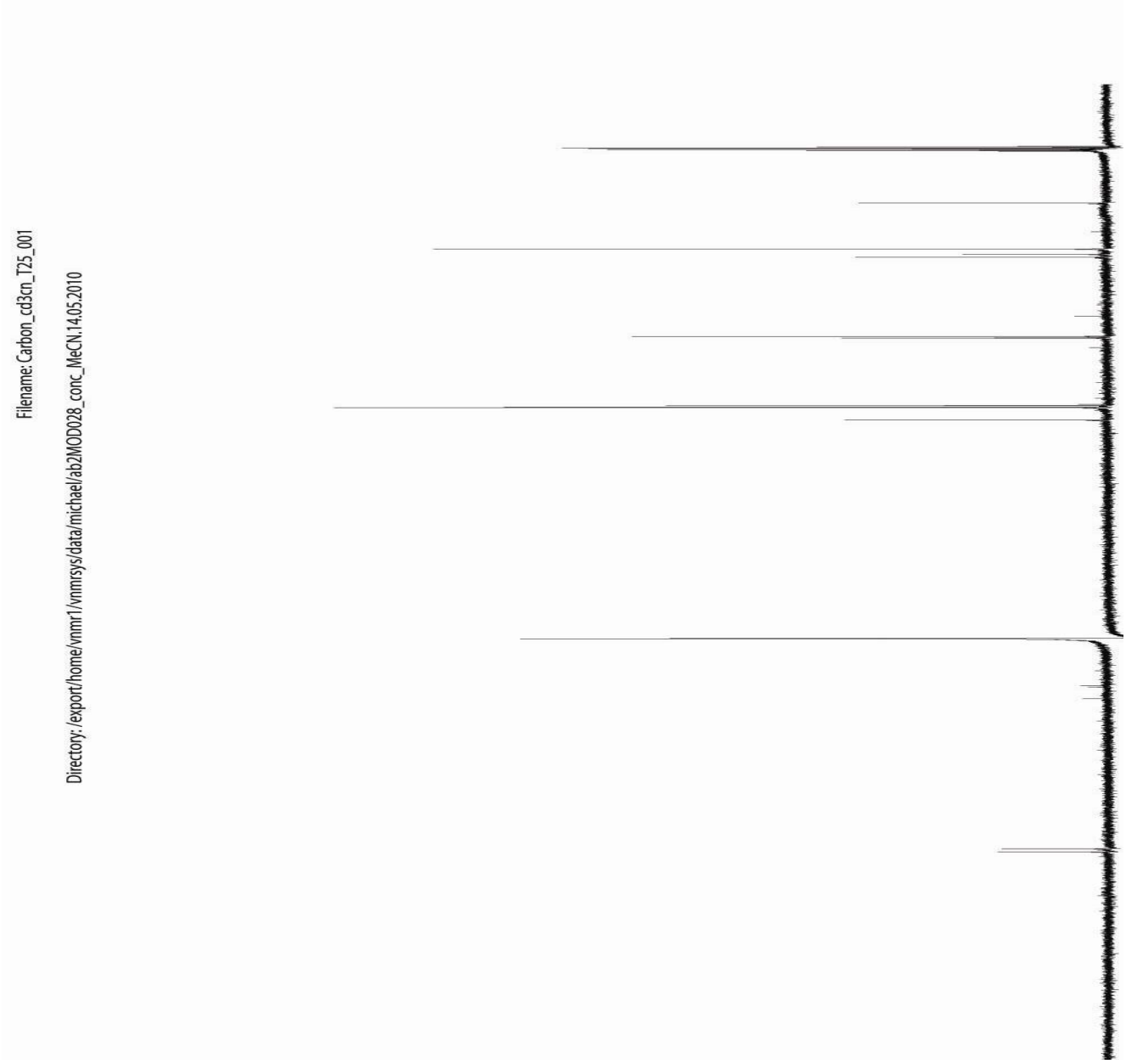


Figure B.29 ^{13}C NMR Spectrum of Possible MIDA-Protected Isopropyl Borate in MeCN



Appendix C. Mass Spectra

Figure C.1 Mass spectrum of N-methyliminodiacetic acid (MIDA)

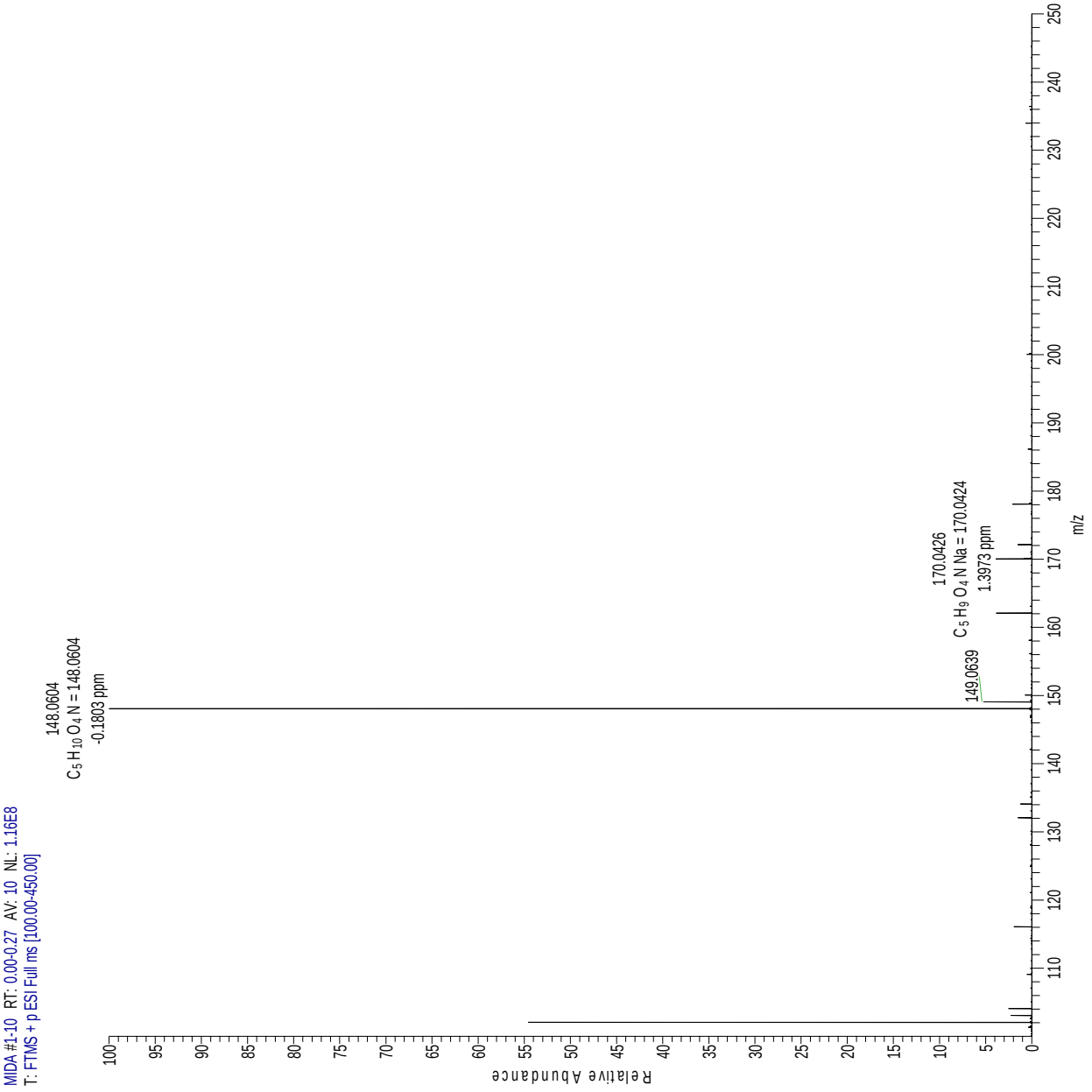


Figure C.2 Mass spectrum of MIDA-protected phenyl boronate

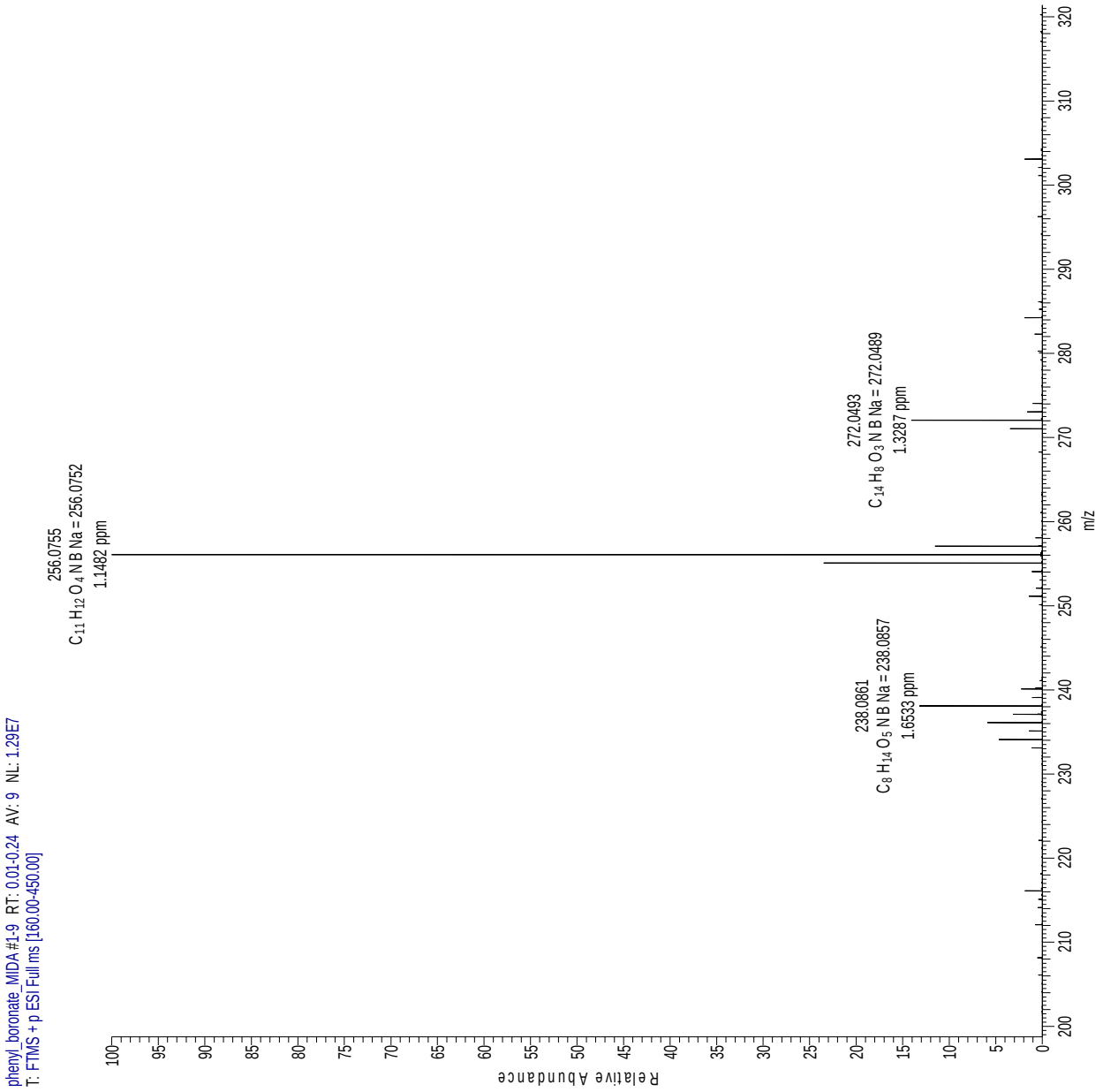


Figure C.3 Mass spectrum of possible MIDA ethynyl boronate-exp33

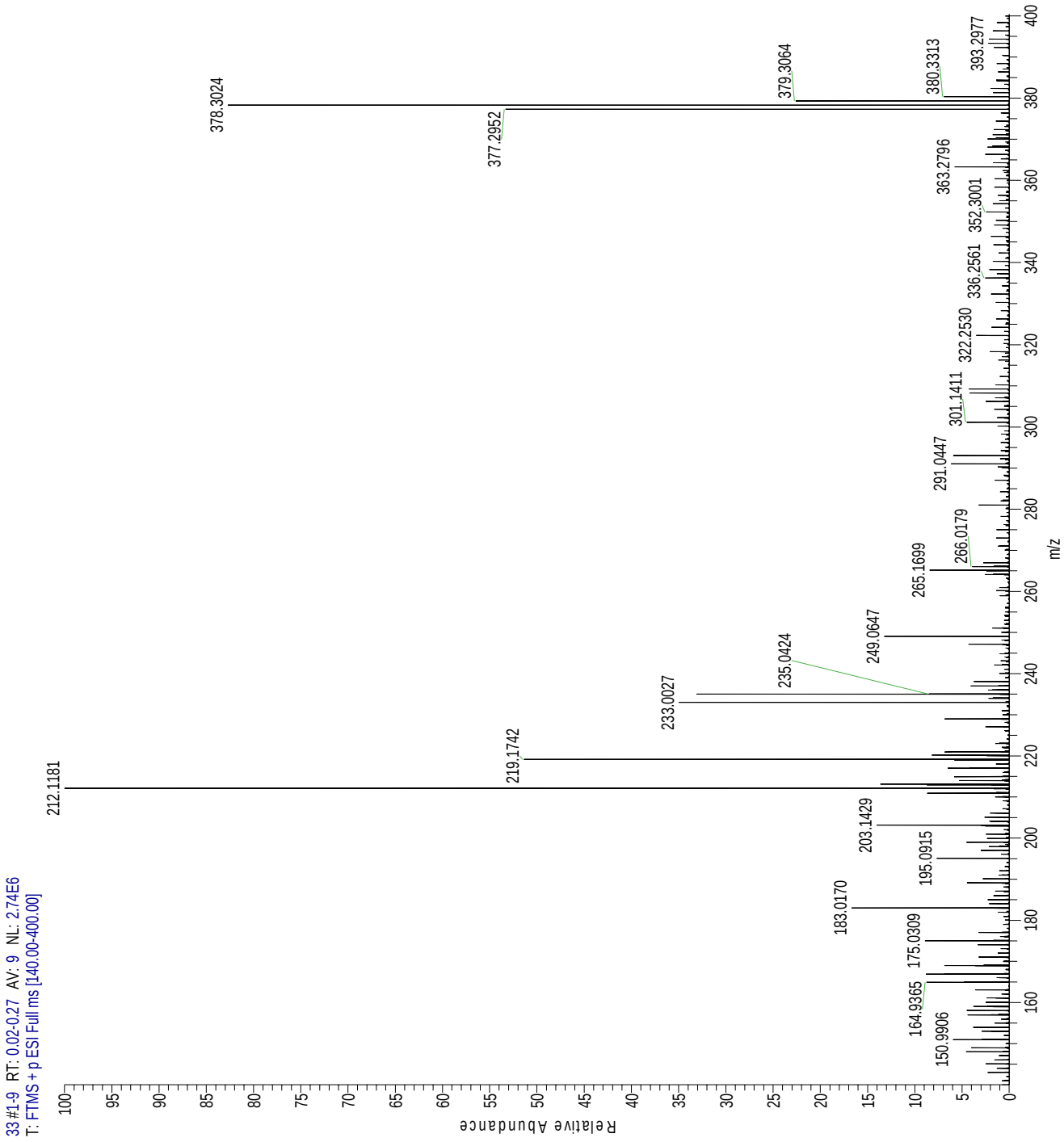


Figure C.4 Mass spectrum of possible MIDA ethynyl boronate-exp79

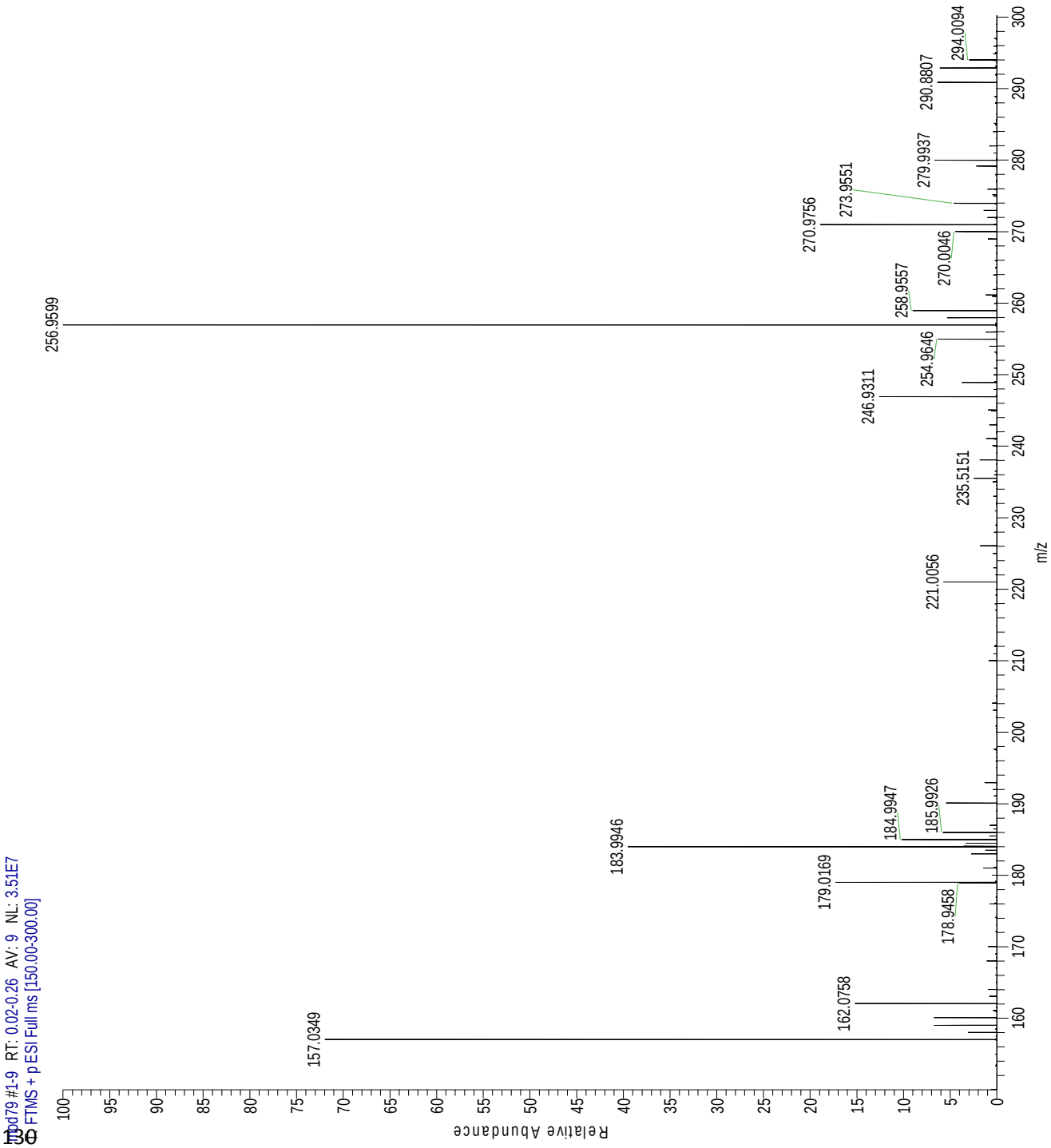


Figure C.5 Mass spectrum of possible MIDA phenylethynyl boronate-exp137

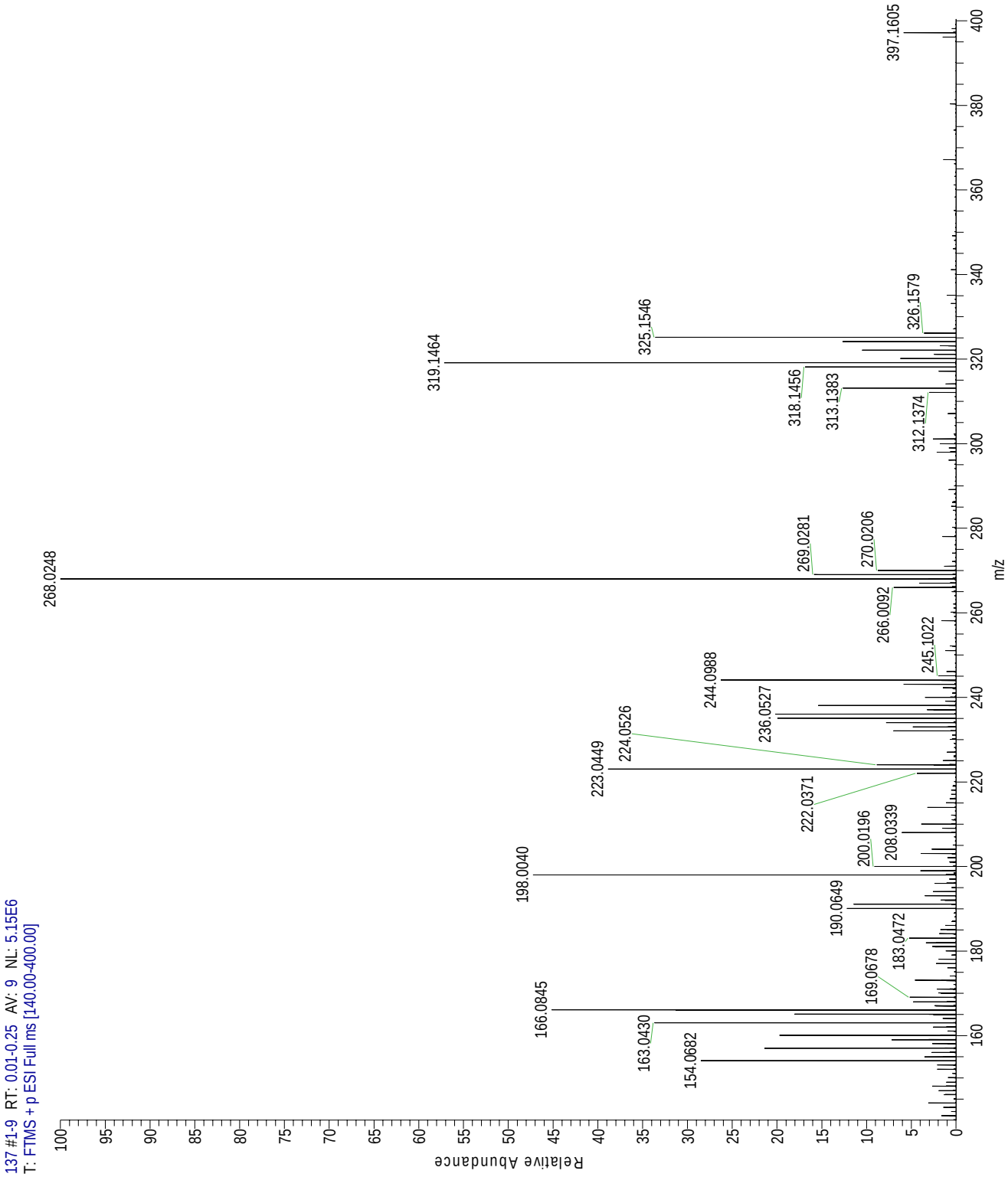


Figure C.6 Mass spectrum of experiment abMOD 020 fractions 7-11

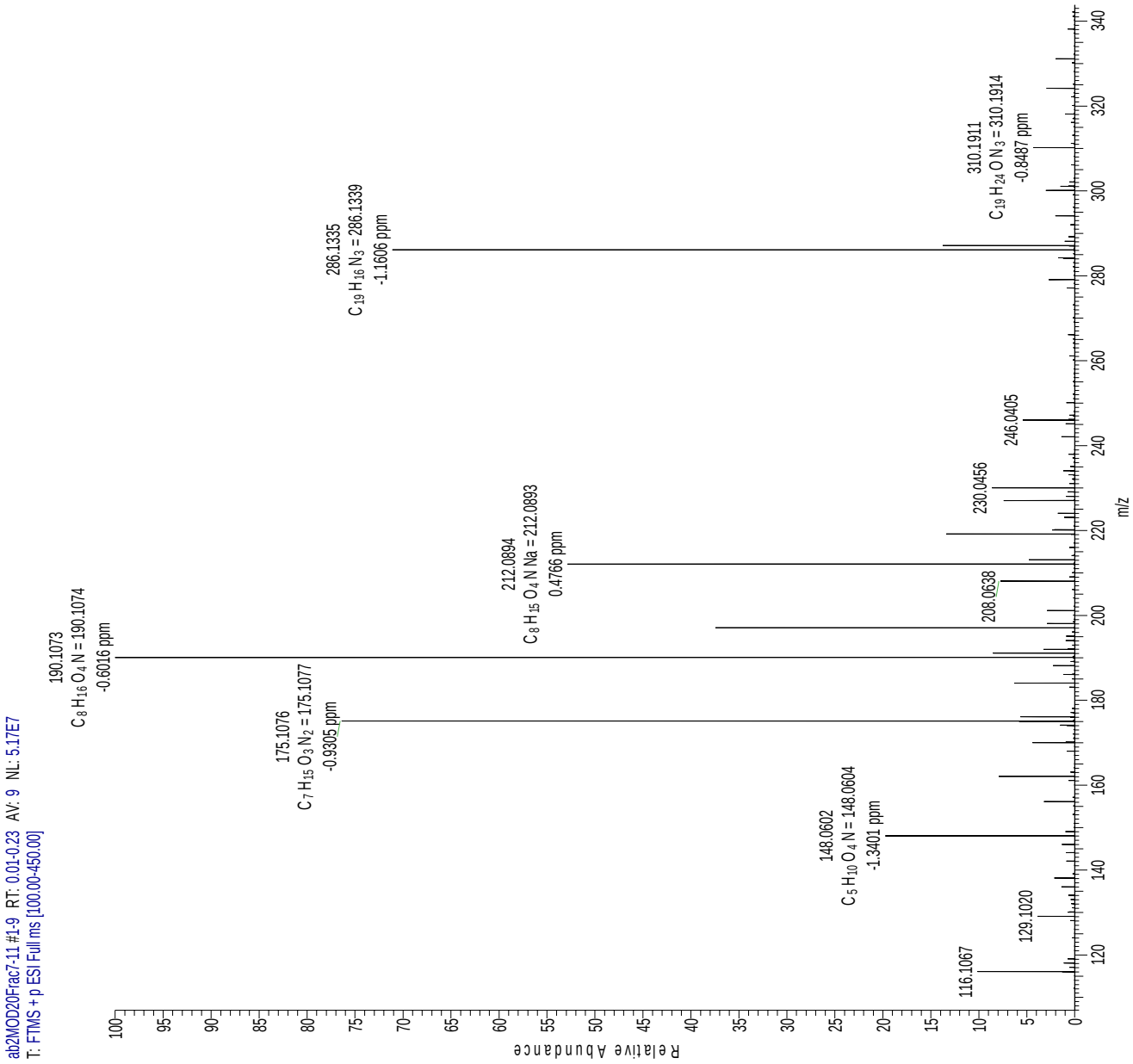


Figure C.7 Mass spectrum of experiment abMOD 020 fractions 12-16

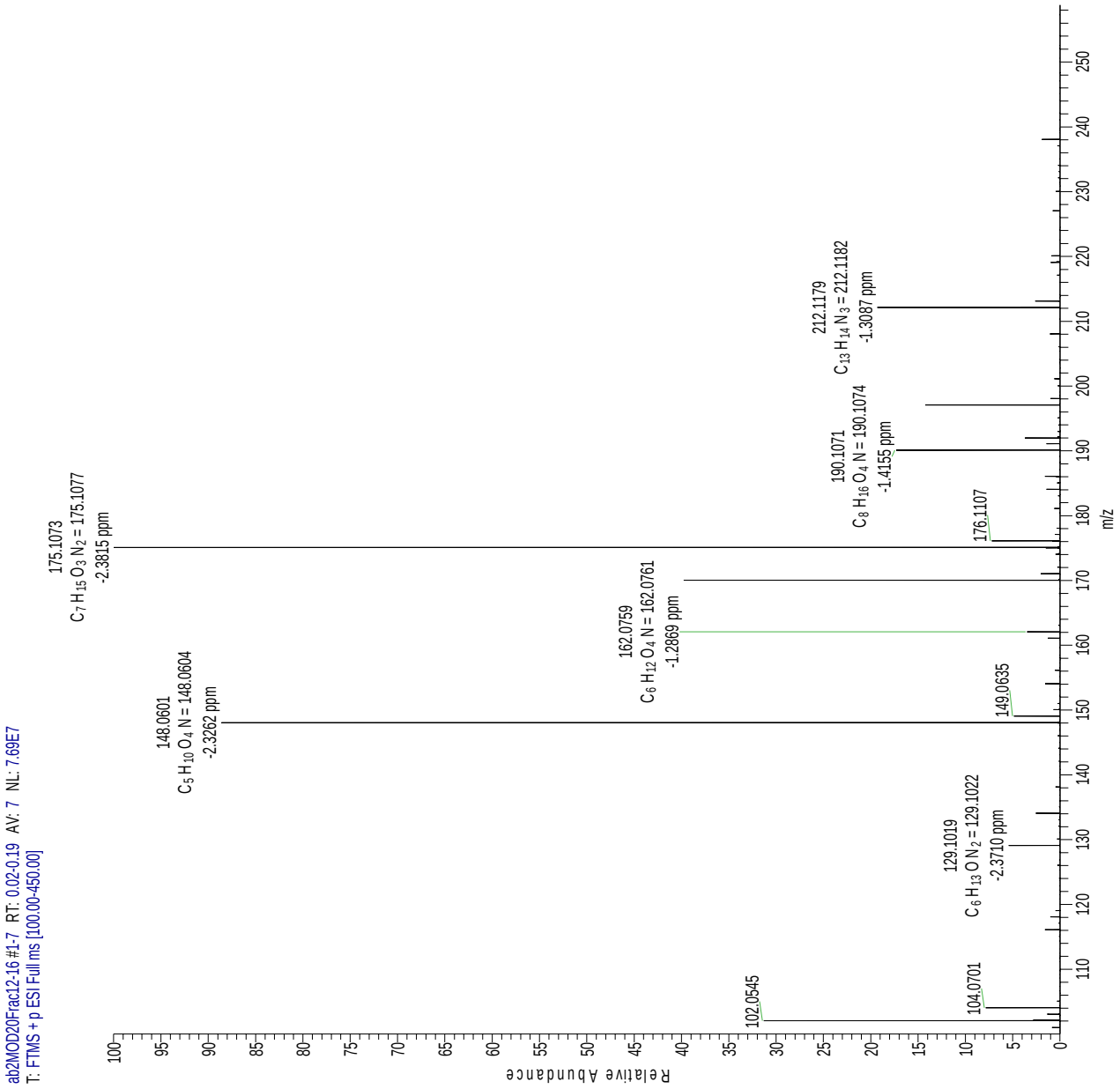


Figure C.8 Mass spectrum of experiment abMOD 028 fractions 4-7

Evidence of MIDA-protected isopropyl boronate

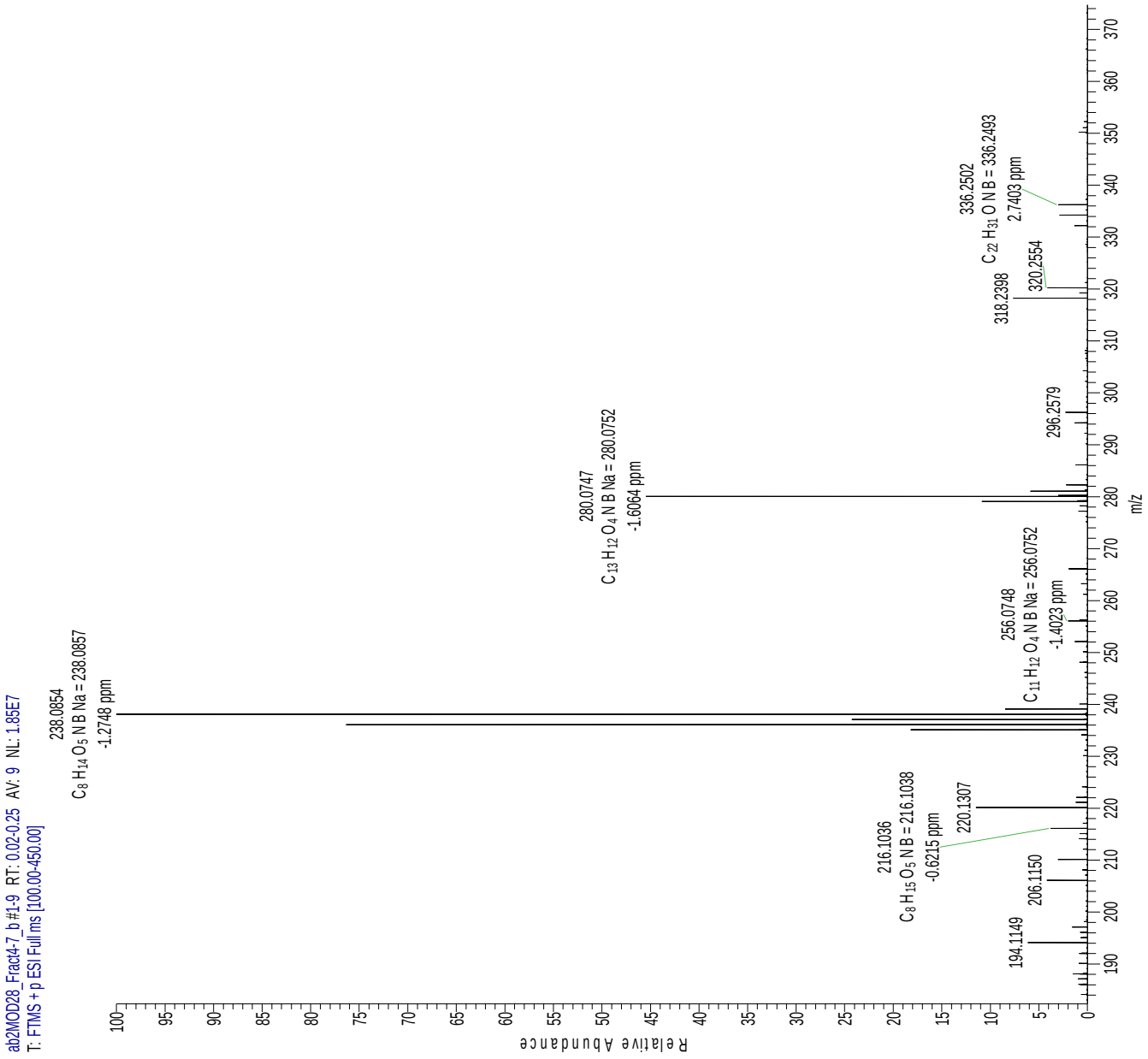


Figure C.9 Mass spectrum of experiment abMOD 028 fractions 8-12

Evidence of MIDA-protected isopropyl boronate

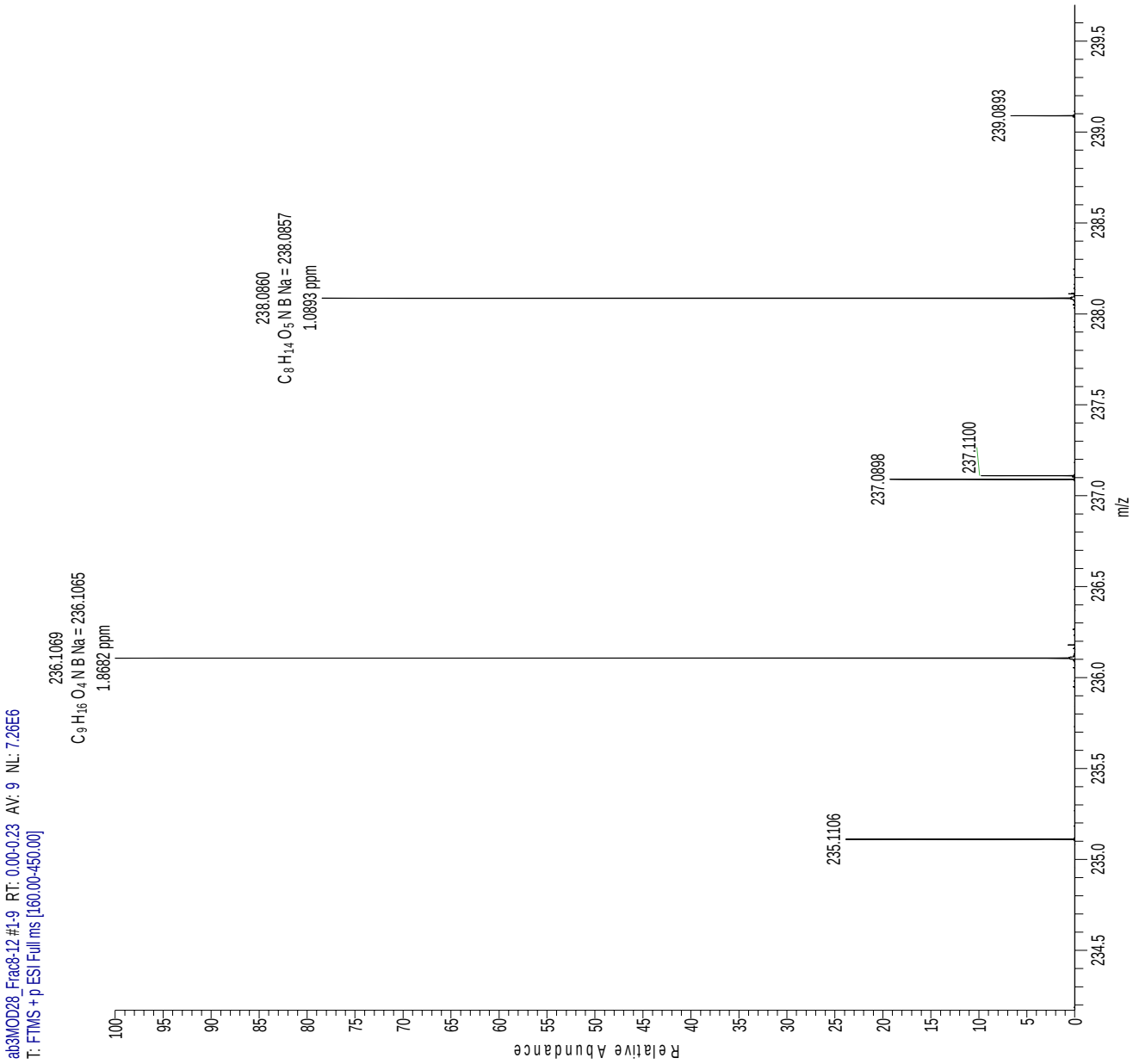
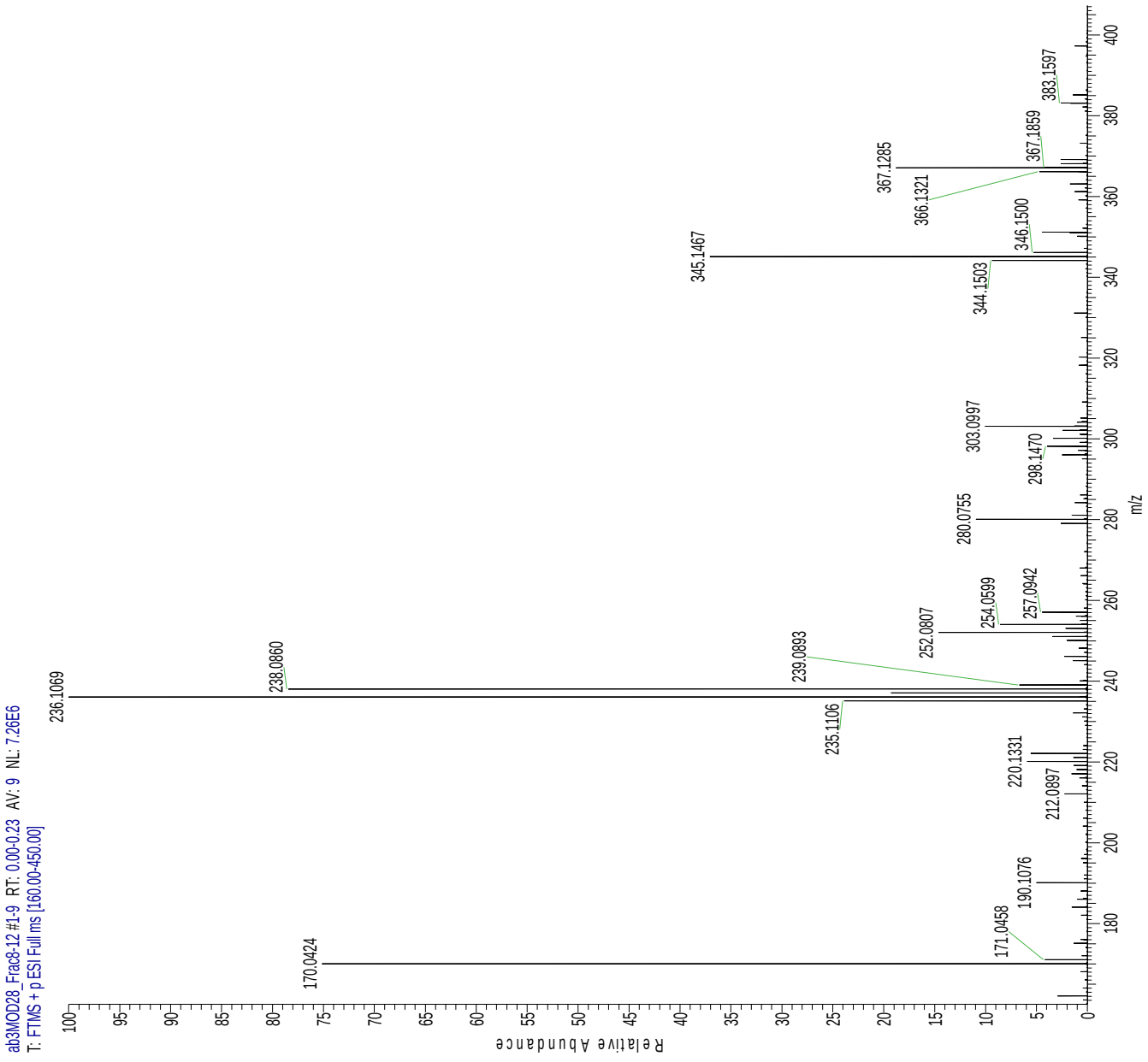


Figure C.10 Mass spectrum of experiment abMOD 028 fractions 8-12

Evidence of MIDA-protected isopropyl boronate



Appendix D. IR Spectra

Figure D.1 IR Spectrum of N-methyliminodiacetic acid (MIDA)

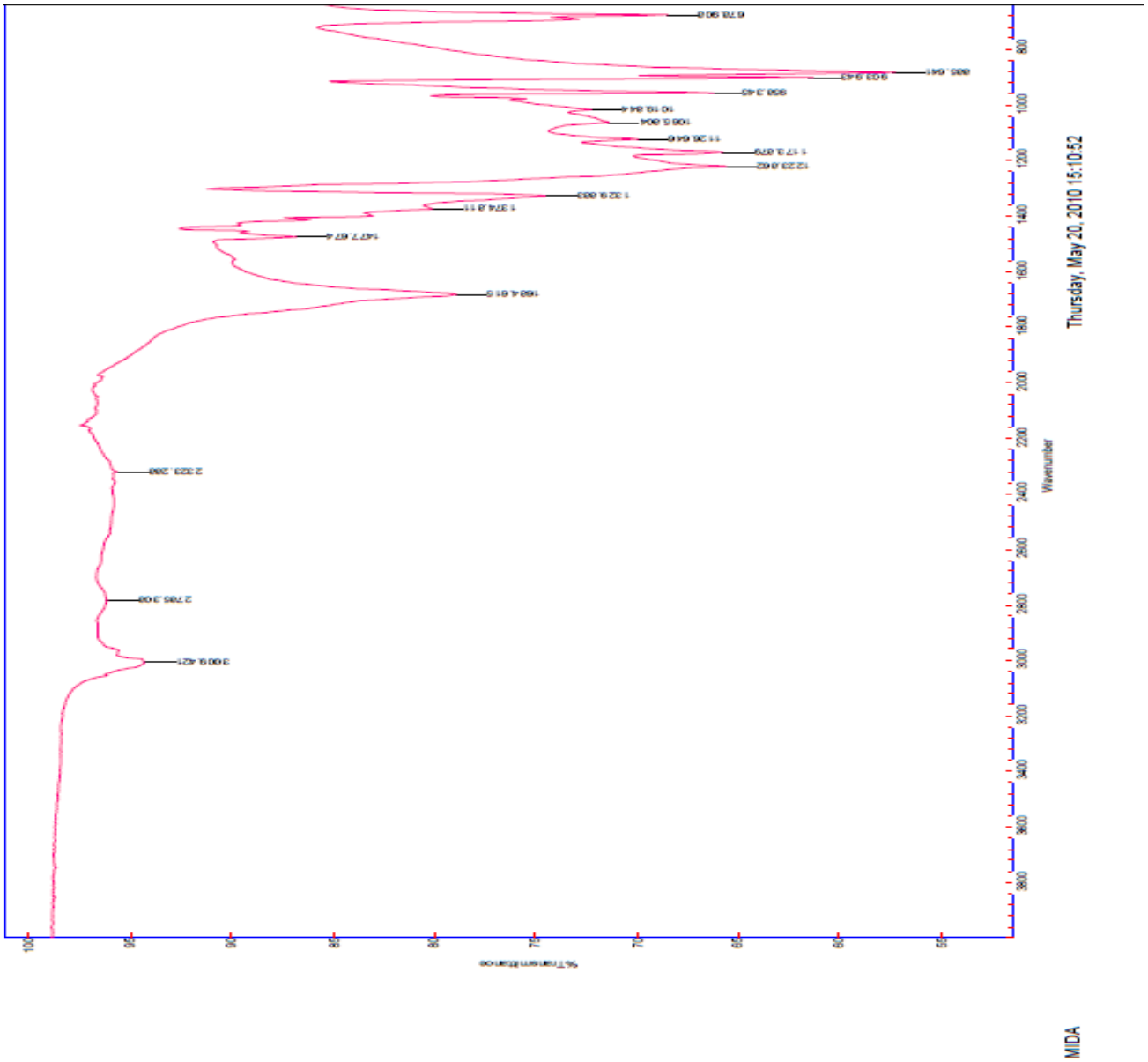


Figure D.2 IR Spectrum of TMS-Protected MIDA

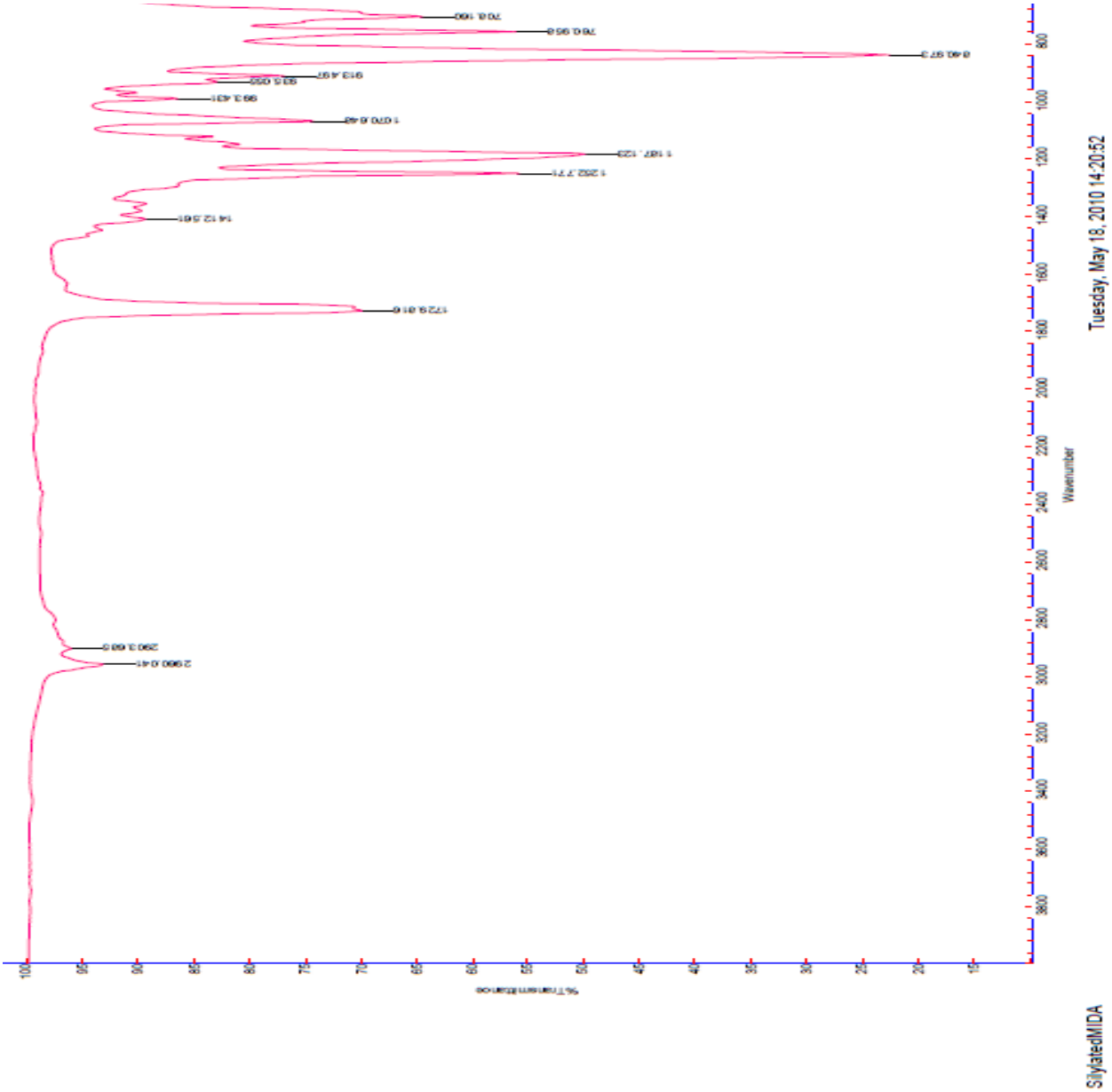


Figure D.3 IR Spectrum of MIDA-protected phenyl boronate

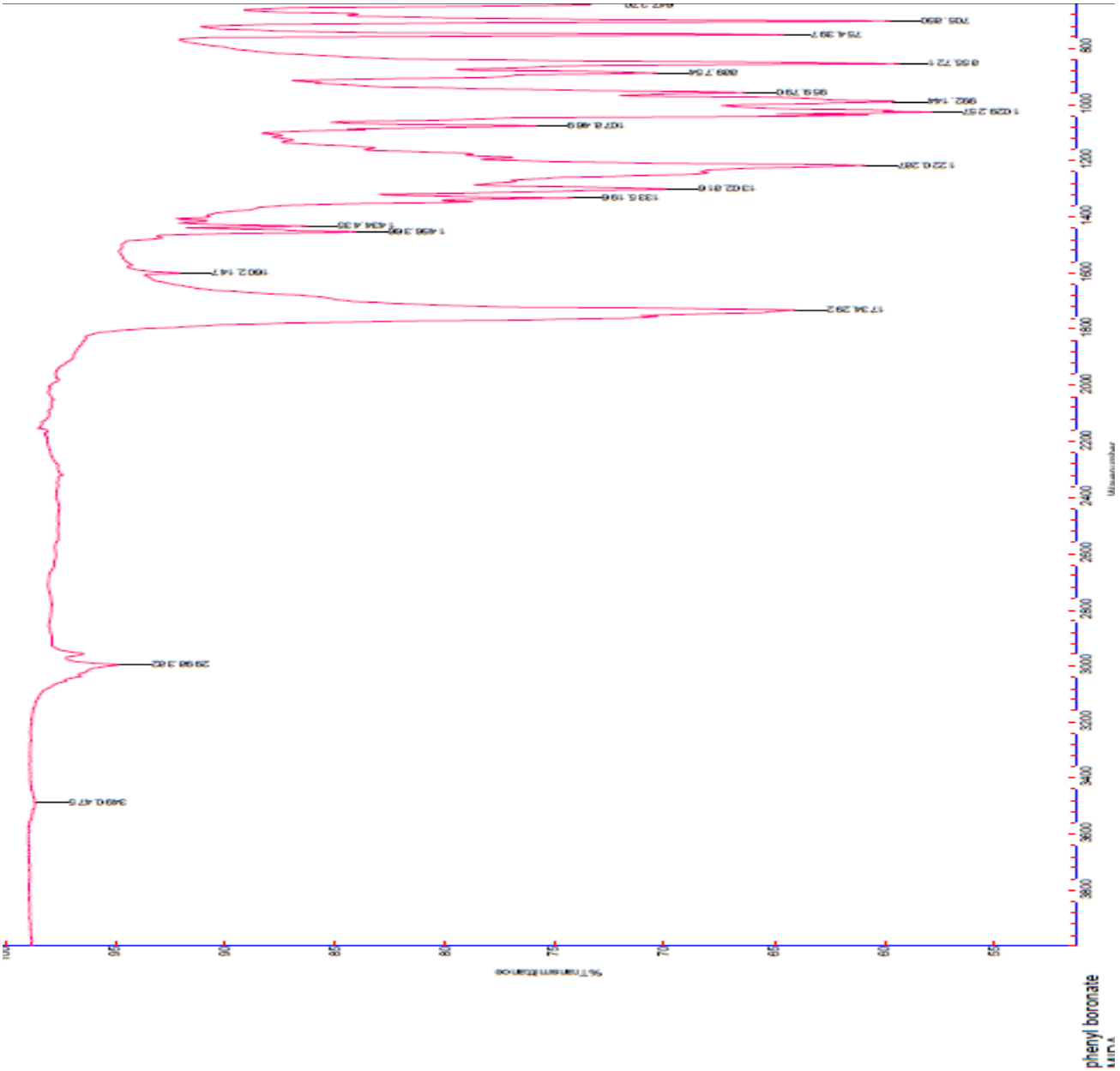


Figure D.4 IR Spectrum of experiment abMOD 020 fractions 7-11

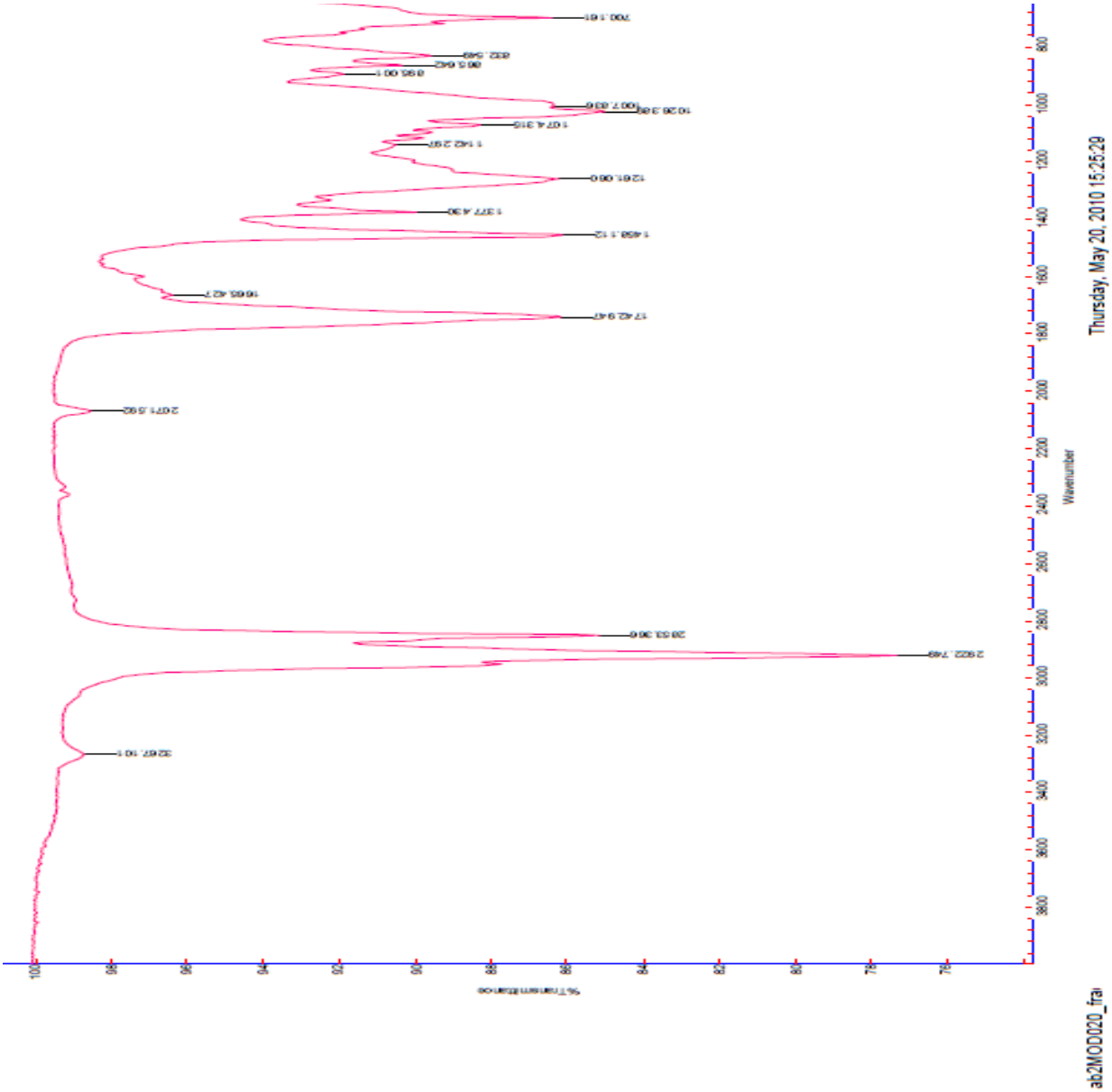


Figure D.5 IR Spectrum of experiment abMOD 028 fractions 4-7

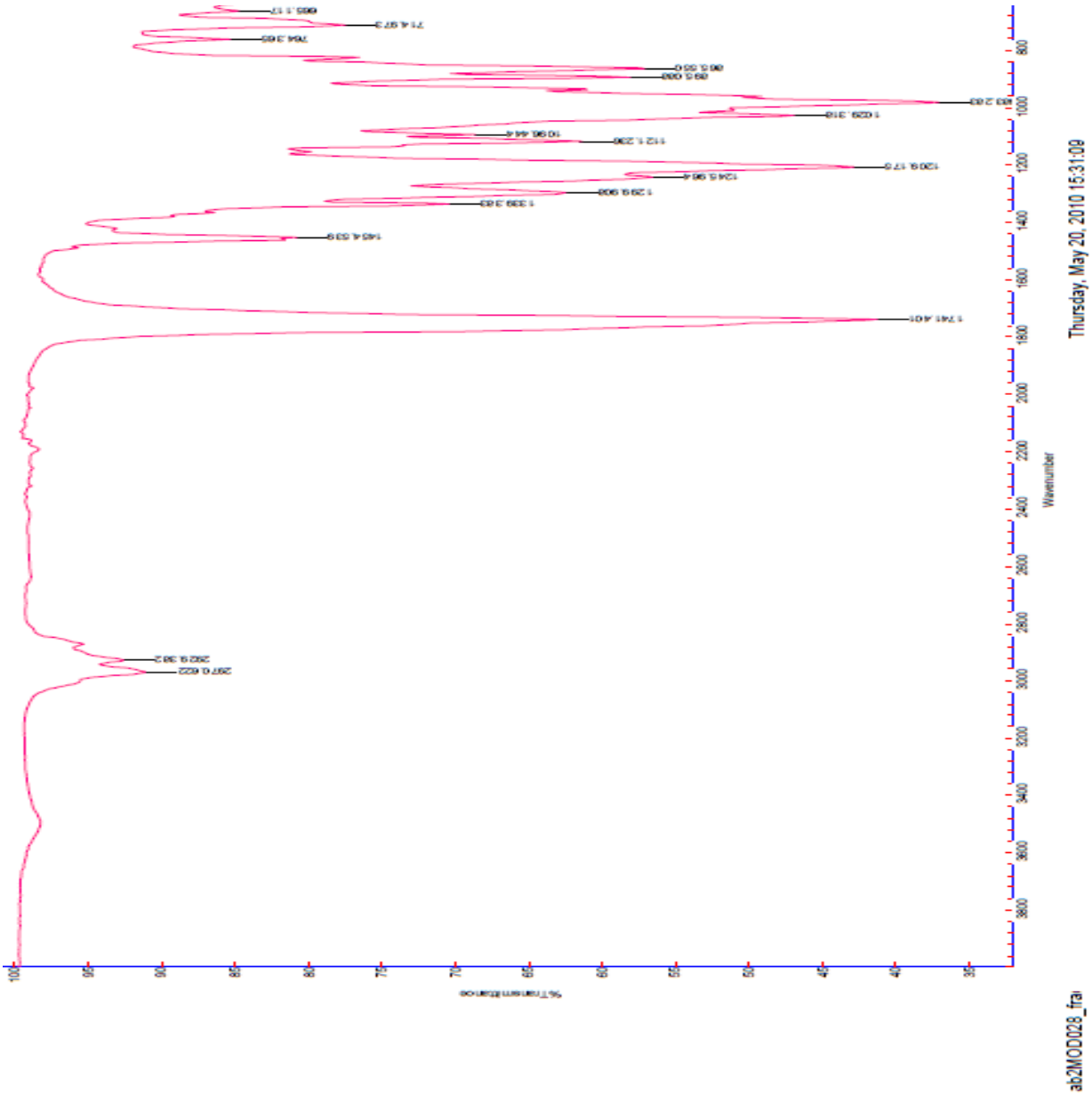
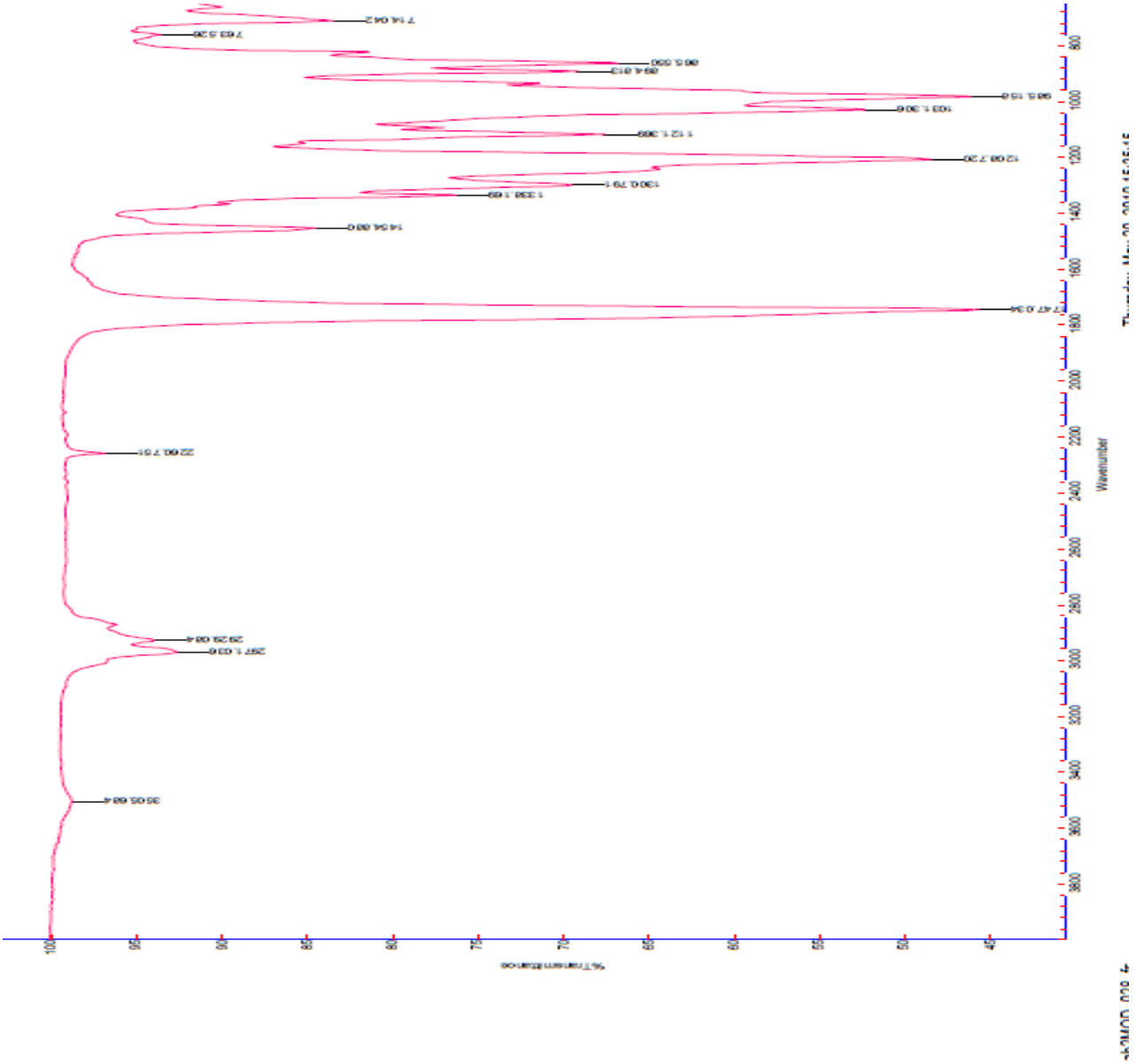


Figure D.6 IR Spectrum of experiment abMOD 028 fractions 8-12



A work such as this is actually never complete.

One must declare it to be complete when one has done all that is possible given the time and circumstances.

Johann Wolfgang von Goethe "Italian Journey" (1787)