UNIVERSITY OF CALIFORNIA
SANTA CRUZ

SYNTHESIS OF BORONIC ACIDS AND ESTERS FROM PINACOLBORANE AND AMINOBORANE UNDER AMBIENT MAGNESIUM-, IODINE-, AND ZINC-MEDIATED CONDITIONS

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Christopher Lee William Murphy

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The Dissertation of Christopher L. W. Murphy is approved:

_____
Professor Bakthan Singaram, Advisor

_____
Professor Rebecca Braslau, Chair

_____
Professor Scott Lokey

_____
Tyrus Miller
Vice Provost and Dean of Graduate Studies

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Abstract

SYNTHESIS OF BORONIC ACIDS AND ESTERS FROM PINACOLBORANE AND AMINOBORANE UNDER AMBIENT MAGNESIUM-, IODINE-, AND ZINC-MEDIATED CONDITIONS

Christopher L.W. Murphy

Grignard reagents react with one equivalent of 4,4,5,5-tetramethyl-1,3,2-dioxaborolane (pinacolborane, HBpin) at ambient temperatures in tetrahydrofuran (THF) to afford the corresponding pinacol boronate esters. Initially formed trialkoxy alkyl borohydride intermediate quickly eliminates hydridomagnesium bromide (HMgBr) and affords the product boronate ester in very good yields. Hydridomagnesium bromide, in turn, disproportionates to a 1:1 mixture of magnesium hydride (MgH_2) and magnesium bromide ($MgBr_2$) on addition of pentane to the reaction mixture. This reaction can also be carried out under Barbier conditions where the neat HBpin is added to the flask prior to the in situ formation of Grignard reagent from the corresponding organic halide and magnesium metal. Pinacolboronate ester synthesis under Barbier conditions does not give Wurtz coupling side products from reactive halides, such as benzylic and allylic halides. Both di- and trihaloaryl species as well as dihalo heteroaryl species can also be used to produce the corresponding arylboronate esters under Barbier conditions with HBpin. The reaction between HBpin and various Grignard reagents is an efficient, mild, and general method for the synthesis of pinacolboronate esters.

Di*iso*propylaminoborane (BH_2-N(iPr)$_2$) is prepared by reacting lithium di*iso*propylaminoborohydride (*i*Pr-LAB) with trimethylsilyl chloride (TMSCl). Aliphatic, aromatic, and heteroaromatic (diisopropylamino)boranes are readily synthesized at ambient temperature (0 °C) in 1 hour by the reaction of Grignard reagents with BH_2-N(iPr)$_2$. Two contending reaction pathways have tentatively been identified. In one pathway, HMgBr acts as the leaving group from the initially formed bromomagnesium organo(di*iso*propylamino)borohydride, affording the product organodi*iso*propylaminoborane (RBH-N(iPr)$_2$). The increased sterics and the diminished Lewis acidity of RBH-N(iPr)$_2$ prevents it from further reacting with Grignard reagents. In the second pathway, the product may be formed by a hydride transfer from bromomagnesium organo(di*iso*propylamino)borohydride to the starting material BH_2-N(iPr)$_2$. It was found that only 1.2 equivalents of BH_2-N(iPr)$_2$ was required for greater than 95% conversion to the organo(di*iso*propylamino)borane. Simple acid hydrolysis of the product organo(di*iso*propylamino)borane leads to the corresponding boronic acid in good to excellent yield.

Functionalized arylzinc halides can be prepared by the direct insertion of zinc to functionalized arylzinc halides (ArZnX) mediated by lithium chloride (LiCl) in THF under refluxing conditions. LiCl is hypothesized to increase reactivity of the Zn surface through solvation of surface-bound ArZnX species, exposing a larger surface area of reactive Zn metal. The corresponding ArZnX species is capable of forming arylpinacolboronate esters from HBpin in low yields. HBpin is incompatible with LiCl in THF, as the Li^+ ion is suspected to strongly coordinate to the oxygen atoms of

Bpin and weaken the B-O bonds. Functionalized arylzinc iodides can also be prepared under catalytic conditions using cobalt bromide ($CoBr_2$) and Zn dust activated by TMSCl and 1,2-dibromoethane in acetonitrile. Subsequent reaction with HBpin is capable of forming the corresponding boronate ester in low yields. The complication with using HBpin is the coordination and side reactions that occur between HBpin and acetonitrile. The use of other solvents, such as THF, is not compatible with $CoBr_2$. The reaction also leads to reduction of the ArZnX as well as homocoupling to form Ar-Ar species. While producing lower yields of boronate esters, this presents a proof of concept for the possible use of other boron sources with these systems.

Iodine also reacts with pinacolborane at ambient reaction conditions in THF to form the iodoalkoxy borate species (4-iodobutoxy)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (IboxBpin). One equivalent of iodine and HBpin react to form IBpin, which then interacts with 4-, 5-, or 6-membered cyclic ethers by cleavage of one ether bond to form the corresponding iodoalkoxy pinacolborate. Treatment with aryl Grignard reagent reacts with one of iodoalkoxy pinacolborate in THF to form the corresponding aryl pinacolboronate ester while reforming and liberating THF as a leaving group.

CHAPTER 1

Review of Boronic Acid and Ester Synthesis and their Applications in Organic Chemistry

1.1 Introduction

1.1.1 Boron and Boranes

Boron is a metalloid found next to carbon on the periodic table, leading to some valuable similarities but also striking differences between boron and other common organic elements such as carbon, nitrogen, and oxygen. Pure boron is extremely difficult to prepare and is more commonly found in nature as BO_3 complexes in minerals. In terms of synthetic boron, boranes are compounds possessing a trivalent boron atom with three covalent bonds to hydrogen and/or carbon and a vacant p-orbital. This leads to an sp^2-hybridized boron atom with the substituents in a trigonal planar geometry. The simplest of boranes is trihydridoborane (BH_3), referred to as borane, but is unstable in its monomeric form due to the empty p-orbital and lack of a full octet. Borane instead forms the dimer diborane (B_2H_6) via a 3-center-2-electron bond where the two boron atoms share two electrons via the hydrogen atoms (Figure 1.1).[1,2] Borane monomers can be found in solution with coordinating organic solvents stabilizing the vacant orbital; tetrahydrofuran (BH_3:THF) and methyl sulfide (BMS) are two common combinations.

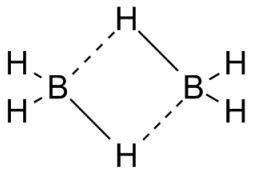


Figure 1.1 Structure of diborane (B_2H_6)

1.1.2 Boronic Acids and Esters

Derivatives of boranes containing carbon and oxygen fall under different classes of compounds, determined by the oxidation state of boron (Figure 1.2). A borinic acid is a boron atom bonded to a single hydroxyl group and two carbon atoms (RR'BOH). Boronic acids are further oxidized from borinic acids, with a single B-C bond replaced with a second B-OH bond ($RB(OH)_2$). The fully oxygenated derivative, boric acid, is the only naturally occurring form of boron and contains three hydroxyl substituents ($B(OH)_3$). In nature, borate (BO_3) species form minerals, similar to SiO_4 silicate minerals, with sodium, calcium, and magnesium.[3–5] All three classes of boron-hydroxyl molecules can be converted to their corresponding esters by replacing all OH groups with alkoxy (OR) groups to form borinate, boronate, or borate esters. Cyclic boronate esters are also possible, where the two oxygen atoms are tethered to each other via a single R group.

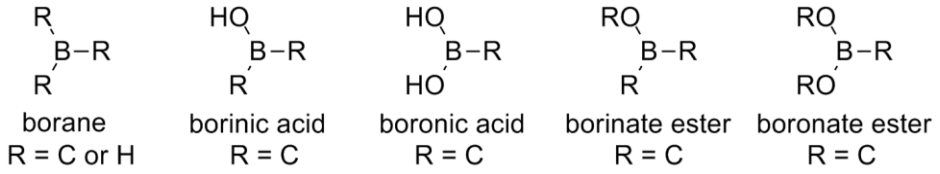


Figure 1.2 Nomenclature of various boron compounds

The nomenclature for cyclic boronate esters follows the Hantzch-Widman system for naming small heterocycles, where the prefix for boron is "boro." The five-membered cyclic boronic esters are called dioxaborolanes. For example, the pinacol ester of phenylboronic acid is 2-phenyl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane. Six-membered cyclic boronic esters are called dioxaborinanes.[6] Some examples of cyclic boronates are shown below (Figure 1.3).

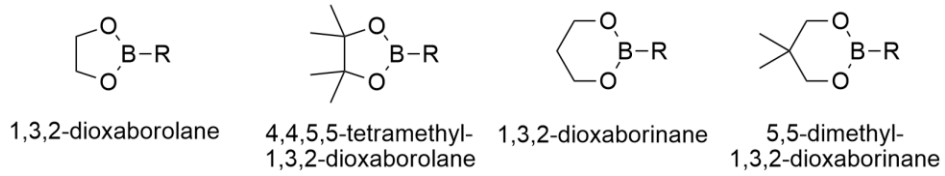
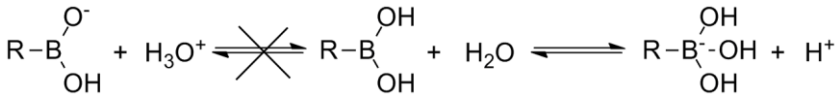


Figure 1.3 Examples of cyclic boronate esters

1.1.3 Structural, Electronic, and Acidic Properties

Boron has an electron configuration of $1s^2 2s^2 2p^1$ and most commonly the oxidation state III. In tricoordinateboronic acids and esters, the sp^2-hybridized boron atom possesses six valence electrons and a vacant p-orbital. The three substituents, one carbon and two oxygens, are orthogonal to the open orbital and give the molecule a trigonal planar geometry.[7] This imparts the boron atom with Lewis acidic

properties and it can readily react with Lewis bases to produce stable, octet-filled tetracoordinate species. They do not, however, act as Brønsted acids as the two hydroxyl hydrogens are only weakly acidic (Scheme 1.1). Instead, the acidity of boronic acids is measured by the indirect release of an acidic proton by a water molecule; this occurs after the water coordinates as a Lewis base to the boron.



Scheme 1.1 Ionization of boronic acids in water

For example, when phenylboronic acid is added to water, one equivalent of H_2O acts as a Lewis base and coordinates with the boron orbital, producing an anionic tetrahedral adduct $Ph(HO)_2B\text{-}OH_2$. This newly coordinated $–OH_2^+$moiety releases a proton to the solution, leaving an anionic boronate species with the negative charge dispersed among the three hydroxyl substituents ($Ph\text{-}B(OH)_3^-$).

The relative acidity of a boronic acid is directly proportional to its Lewis acidity, as dictated by the electronegativity of the bonded carbon substituent. The acidities of various boronic acids have been well documented (Table 1.1).For example, phenylboronic acid ($PhB(OH)_2$; pK_a 8.8) is comparable to phenol in acid strength, while fully oxygenated boric acid is less acidic ($B(OH)_3$; pK_a 9.2) as the additional oxygen further reduces the Lewis acidity of boron.[8]

For substituted arylboronic acids ($ArB(OH)_2$), an electron-donating aryl group decreases the acidity relative to phenylboronic acid. For example, the electron-

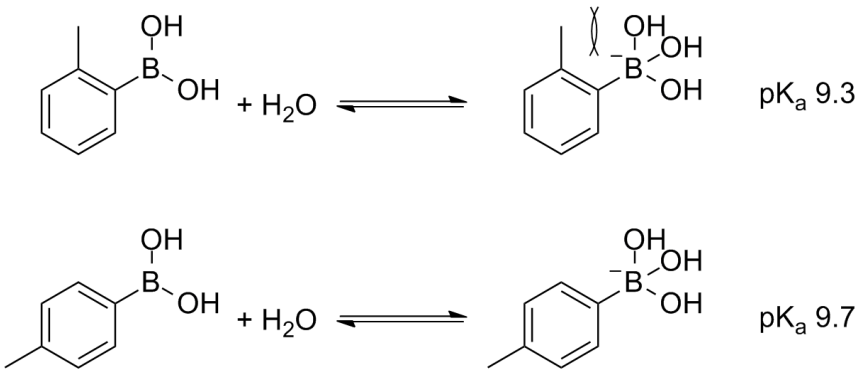
donating 4-methoxyphenylboronic acid is slightly less acidic (pK_a 9.3).[9] By comparison, the moderately electron-withdrawing 4-carboxyphenyl has a pK_a of 8.4.[10] The highly electron-withdrawing 4-nitrophenyl is significantly more acidic, with a pK_a of 7.1.[9]

Table 1.1 Ionization constants (pK_a) for a selection of boronic acids[8–12]

Boronic acid	pK_a
Methylboronic acid	10.4
Phenylboronic acid	8.9
3,5-Dichlorophenylboronic acid	7.4
3-Methoxyphenylboronic acid	9.3
4-Methoxyphenylboronic acid	8.4
2-Nitrophenylboronic acid	7.1
4-Nitrophenylboronic acid	8.6
2-Methylphenylboronic acid	9.0
3-Methylphenylboronic acid	9.3
4-Methylphenylboronic acid	9.1

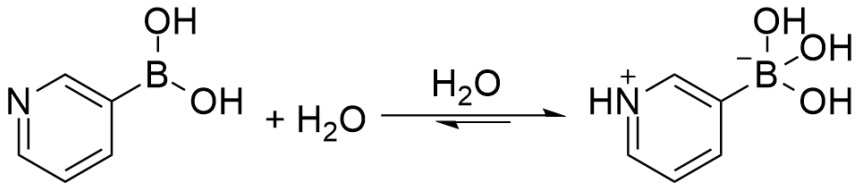
In tandem with Lewis acidity and electronic effects, steric interactions can also affect the pK_a. In molecules with bulky substituents, reduced acidity is seen when formation of the tetrahedral anion is hindered (Scheme 1.2). As expected, the slightly electron-donating tolyl group results in 4-tolylboronic acid having a pK_a of 9.3. When the methyl group is moved to the *ortho* position, as in 2-tolylboronic acid, the pK_a increases to 9.7. A combination of electronic and steric effects can be seen with 2- and 4-nitrophenylboronic acids.[13] While both compounds possess the highly electron-poor nitro group, their pK_a difference is drastic (9.2 vs. 7.1 respectively). Not only does the *ortho*-substituent resist formation of a tetrahedral adduct, an

oxygen of the nitro group is suspected to be capable of intramolecular coordination to the open boron orbital, directly competing with the coordination of a water.



Scheme 1.2 Steric effects on tetracoordinate anion formation and pK_a

Intramolecular effects work both ways, as 3-pyridylboronic acid is one of the most acidic boronic acids (pK_a 4.0): the coordinating water molecule releases an acidic proton while the basic pyridyl nitrogen readily accepts a proton to form a stable zwitterionic species (Scheme 1.3).[14]

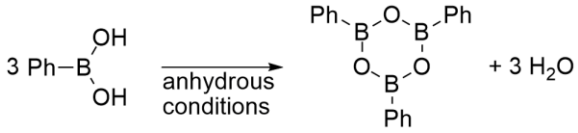


Scheme 1.3 Formation of the zwitterionic pyridinium boronic acid

The interaction between the vacant boron p-orbital and bonded oxygen lone pairs result in a much stronger B-O bond, an important factor in stabilizing the unfilled octet. A typical boronic acid B-O bond length ranges from 1.31-1.35 Å,[15]

while in the boronic ester the B-O bond slightly elongates to a range of 1.35-1.38 Å.[16] The B-O bond energy (519 kJ/mol) is considerably larger than its ethereal C-O counterpart (384 kJ/mol). Because the strength of the B-O bond depends heavily on the conjugation between lone pairs and the open p-orbital, any changes to the structure can have drastic effects on bond properties. The hydroxyl groups are also important for intermolecular bonding and interactions. Similar to their carboxylic acid cousins, boronic acids can form dimers in solution via hydrogen bonding, as confirmed by X-ray crystallography.[7] These dimeric pairs can further coordinate and stack to form supramolecular complexes.

Beyond simple hydrogen bonds, boronic acids are capable of more complex interactions. Under anhydrous conditions, typically through either azeotropic removal of water or drying over H_2SO_4 or P_2O_5, three boronic acid molecules spontaneously form a six-membered planar ring bonded via alternating B-O bonds (Scheme 1.4).[17] These compounds, due to the oxygen lone pairs and empty boron orbitals, are partially aromatic and isoelectric with benzene.

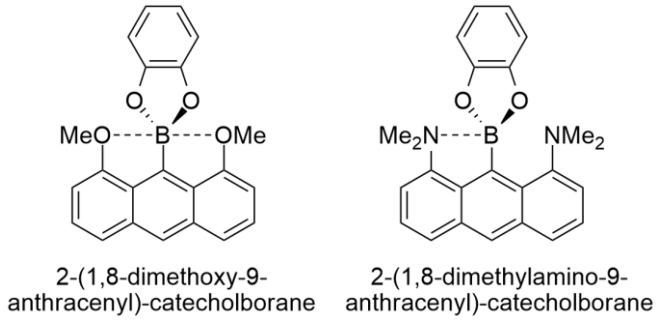


Scheme 1.4 Formation of triphenylboroxine

For supramolecular phenylboronic acid complexes, the central B-O motif of one boroxine stacks between two phenyl substituents of two boroxine atoms, allowing

the aromatic π-systems to coordinate to the vacant boron orbitals above and below.[18] Due to the rigid structure and fixed rotation of the planar six-membered B-O ring, boroxines are more reactive than individual boronic acid molecules as the back-bonding from the oxygen lone pairs is reduced. As a result, the boron becomes more Lewis acidic and encourages reaction or degradation, with boronic acids are typically stored wet rather than under anhydrous conditions. Sterics are another factor in boroxine formation, as *ortho*-substituted arylboronic acids resist formation of the six-membered ring.[19]

Unique intramolecular interactions are also possible for boronic esters, again enabled by stabilization of the unfilled octet via the vacant orbital (Figure 1.4). In both 2-(1,8-dimethoxy-9-anthracenyl)-catecholborane[20] and 2-(1,8-dimethylamino-9-anthracenyl)-catecholborane,[21] an intramolecular coordinate bond forms between the adjacent heteroatom lone pairs and the boron orbital. These interactions induce lengthening of the B-O ester bonds. In the dimethylamino derivative, the dative B-N bond is 1.67 Å and only occurs with one of the two amino nitrogens, while the dimethoxy derivative exhibits uniquely hypervalent properties from boron coordinating with both anthracyl oxygens.



2-(1,8-dimethoxy-9-anthracenyl)-catecholborane

2-(1,8-dimethylamino-9-anthracenyl)-catecholborane

Figure 1.4 Examples of boronate hyperconjugation

By comparison, the length of the B-C bond is dependent on the substituent, but ranges approximately between 1.55-1.59 Å in boronic acids and esters, which is longer than typical C-C bonds.[22] The B-C bond has a bond energy of 358 kJ/mol, larger than a C-C bond energy of 323 kJ/mol. The atom electronegativities in boronate esters are more complex, as the carbon atom is slightly more electronegative than the boron atom by approximately 0.5 Pauling units. This is heavily influenced by the vacant p-orbital and lack of a full octet being offset by two neighboring oxygen atoms acting as electron-donators. The boronate group thus provides a weak electron donating effect on the carbon substituent, visible in the ^{13}C NMR.[23] When the carbon is replaced by a hydrogen, such as in pinacolborane or catecholborane, a similar donating effect leads to hydrogen having a larger electronegativity and exhibiting hydride-like properties.

In aryl and alkenylboronate esters, moderate conjugation between boron and carbon occurs, which is heavily dependent on the Lewis acidity of the boron center.[24] In NMR studies of deshielding effects on alkenylboronate esters, a significant

downfield shift for the peak corresponding to the β carbon in the alkene is observed. This suggests a partial resonance structure between the α carbon and boron is formed, drawing electron density away from the β carbon. This hypothesis is supported by a minimal change in the peak corresponding to the α carbon and a shortening of the B-C bond length. This same effect is not seen in arylboronate esters where the aryl group is restricted from rotating and the aryl carbon is locked orthogonal to the boron atom p orbital due to either steric or dative interactions. Instead, the B-C bond is longer, as neighboring heteroatoms coordinate with the open orbital and prevent overlap with the π system. It should be noted that despite clear evidence for the electron-withdrawing properties of the boronate group, alkenylboronate esters do not show the same reactivity towards Michael donors that α,β-unsaturated carbonyl compounds do.[25]

1.1.4 Analysis of Boronic Acids and Esters

Several techniques are utilized in analysis of boron-containing species most commonly ^{11}B NMR spectroscopy. Boron has two naturally occurring isotopes, ^{10}B and ^{11}B, with ^{11}B being an excellent NMR active isotope (I = 3/2) with an abundance of 80%. The ^{11}B NMR shifts are typically reported in parts per million (ppm) relative to the external standard BF_3:Et_2O at 0 ppm.[26] The locations of the shifts are key in identifying the atomic substituents around boron. For example, boric derivatives (BO_3 species) typically come in the δ +17-23 ppm range. When replacing one oxygen with nitrogen (NBO_2 species), the peak shifts downfield to δ +24-28.

Replacing the nitrogen with carbon to form a boronate species (CBO_2 species) shifts the peak further downfield to approximately δ +30-35. Borinic compounds (C_2BO species) appear closer to the δ +50-60 ppm range. Finally, triorganoboranes (C_3B species) move well into the δ >+80 ppm range. It is important to note that the absence of any lone pair donating heteroatoms in trialkylboranes allows for coordination of an external ligand, sometimes creating drastic upfield shifts. For example, neat trimethylborane appears where expected at δ +86. Similarly, tributylborane in THF appears at δ +85. In contrast, once the Lewis base trimethylamine is added to trimethylborane in THF, the shift moves to δ -14. Intramolecular coordination is also possible, as seen in the trioxaazaboratricycloalkanes, where the tertiary amine lone pair coordinates back to the vacant p-orbital, shifting from the typical borate peak of δ +18 down to δ +1.[27] Shifts like this, in the zero to negative ppm range, are indicative of tetrahedral "ate" complexes, whether it is from an intramolecular dative interaction or simply a tetracoordinate boron with four bonds. Just as valuable is the coupling that occurs from ^{11}B-^{1}H bonds as measured in Hz, with the following typical splitting patterns: B-H doublet 120-190 Hz, BH_2 110-130 Hz, BH_3 90-110 Hz, and BH_4 70-80 Hz.[28]

1.2 Synthesis of Boronic Acids and Esters

Research of boronic acids and esters have two main areas of focus; (1) how to synthesize or introduce them into molecules and (2) how to utilize these functional groups once installed. Virtually ignored after their initial isolation in 1860,[29] interest

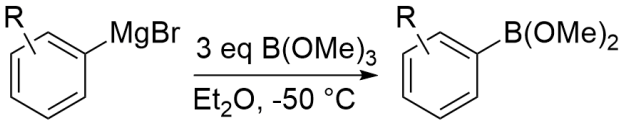
in boronic acids has seen exponential growth since the carbon-carbon cross-coupling reported by Suzuki and Miyaura in 1979.[30] Today, the number of papers focusing on boronic acids and esters average well into the hundreds every year, while before 1995 there had not been more than 300 papers total written on the subject. The awarding of the Nobel Prize in Chemistry to Akira Suzuki, with Ei-ichi Negishi and Richard Heck in 2010, further underlined the significance of these functional groups in the development of chemistry.

While boronic acids and esters are components in a growing number of valuable applications, these uses are completely irrelevant if the molecules cannot be efficiently synthesized. New processes for preparing boronic acids and esters under mild, efficient, and inexpensive methods is a growing area of research, highlighting the importance of these intermediates. With the vacant orbital on boron and similar electronegativities of boron and carbon in a B-C bond, authors have cited carbon nucleophiles or Lewis basic carbon synthons in general as potential routes towards designing new synthetic methods.

1.2.1 Early Synthetic Methods of Boronic Acids and Esters

Because of the Lewis acidic properties of boron, boronic acids are typically synthesized via organometallic intermediates. In 1931, Johnson optimized the synthesis of boronic acids from methylborate and Grignard reagents (Scheme 1.5).[31] The value in this method is its versatility; the success of the reaction is mainly dependent on the preparation of the Grignard reagent from aryl, alkenyl, and alkyl

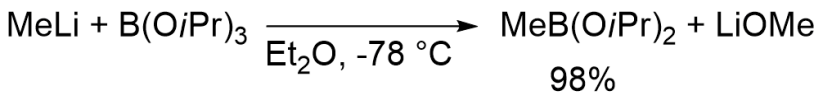
halides. An earlier iteration of this reaction from 1909 was the addition of methylborate to phenylmagnesium bromide.[32] In this reaction, diphenylborinic acid was the major product, with the desired phenylboronic acid forming in very low yield. The optimization later performed by Johnson sought to counteract the higher reactivity of the Grignard reagent by adding a solution of Grignard to a solution of methylborate dropwise at -12 °C, which greatly improved the yield of phenylboronic acid. Lowering the temperature below -50 °C gave increased yields.



Scheme 1.5 General synthesis of boronic esters via Grignard and methylborate

In 1983, Brown and Cole published an improved method for boronic acid synthesis.[33] Instead of Grignard reagents, various organolithium reagents were used, as well as a range of alkoxyboranes in an attempt to control the number of additions to boron. They first studied the steric effects of the alkoxyboranes and their tendency to undergo over-alkylation even at -78 °C. Beginning with trimethoxyborane and methyllithium, little conversion was seen, with the starting material recovered in 75% yield. What little reaction did proceed underwent full alkylation to trimethylborane. Increasing the carbon count by just one in trimethoxyborane, provided a significant difference with only 17% unreacted starting material remaining while the desired boronic ester was produced in 65% yield. Some over-alkylation did occur, with 10%

borinic ester and 7% triethylborane formed. Triisopropoxyborane provided a tremendous improvement, with a 98% yield of boronic ester (Scheme 1.6).

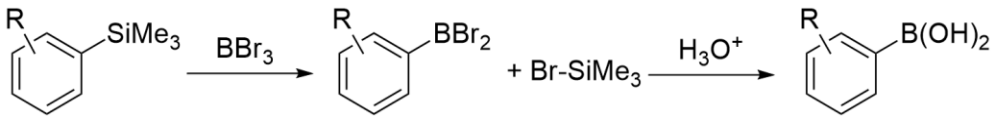


Scheme 1.6 Reaction of triisopropoxyborane with methyllithium

Interestingly, once established that triisopropoxyborane was the optimal borate substrate, adjusting the size of the organolithium nucleophile made little difference. Methyllithium, *n*-butyllithium, *sec*-butyllithium, and phenyllithium all provided the corresponding boronic ester in yields above 96% with isopropoxyborane, demonstrating the importance of the trialkoxyboranes used over the organometallic reagent. It was emphasized by the authors that the additions must occur slowly. This procedure has since been expanded to cover aryl, alkenyl, alkynyl, alkyl, and (α-haloalkyl)boronic esters.

While effective for simple systems with no functionality, these older methods utilizing organolithium or organomagnesium reagents require very specific conditions for optimal yields. The high reactivity of the organometallic intermediates prevents the existence of electrophilic functional groups or acidic protons, while requiring inert anhydrous conditions at cryogenic temperatures. All of these factors limit the scope of the reactions, particularly in large scale or industrial settings.

Another early method for synthesizing arylboronic acids specifically involved the transmetalation of aryl stannanes and silanes (Scheme 1.7).[34] Originally, diarylmercury and boron trichloride were used, however this method was extremely unpopular due to the high toxicity of organomercury reagents. In 1986, Haubold was able to adapt this system to trialkylarylsilanes and stannanes by choosing a hard boron species, boron tribromide.[35] The resulting arylboron dibromide species was then converted to the arylboronic acid via a simple aqueous workup. Haubold rationalized the thermodynamic advantage of this transformation by citing the higher stability of the B-C and M-Br bonds in the products over the starting B-Br and M-C bonds.



Scheme 1.7 Synthesis of boronic acids via transmetalation of arylsilanes

1.2.2 Miyaura Borylation

As boronic acids and esters saw more popularity in the literature, new methods emerged addressing many of the previously mentioned drawbacks. A significant improvement in the synthesis of these compounds was reported in 1995 when Miyaura and co-workers successfully synthesized arylpinacolboronates via palladium-catalyzed cross-coupling of aryl bromides, iodides, and triflates. The diboronyl ester bis(pinacolato)diboron (B_2pin_2) is used frequently in these transformations(Figure 1.5).[36]

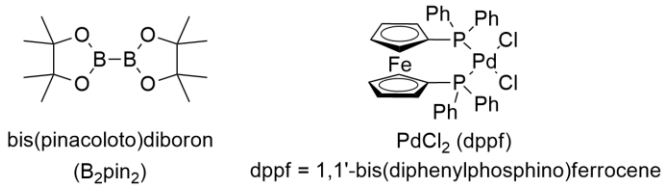
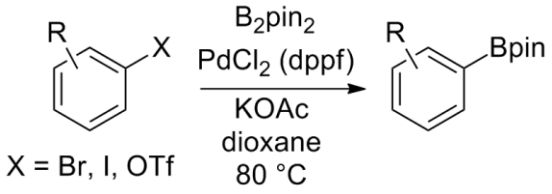


Figure 1.5 Structures of B_2pin_2 and $PdCl_2$ (dppf)

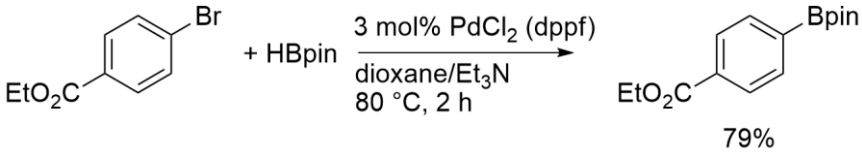
Previous methods utilized organolithium or Grignard reagents that required strict anhydrous conditions, showed low functional group compatibility, and were successfully only at cryogenic temperatures. For the coupling reaction, Miyaura utilized $PdCl_2$ complexed with dppf (1,1'-bis(diphenylphosphino)ferrocene, Figure 1.5) and the mild base potassium acetate (KOAc) in a polar aprotic solvent heated to 80 °C (Scheme 1.8). This improved system tolerates functionalities such as ketones, esters, nitriles, benzophenones, and benzaldehydes. The reaction is typically complete in less than 24 hours and is also compatible with a wide variety of haloaryl substrates, such as sterically hindered or electron-rich aryl halides. Aryl triflates are also acceptable substrates, which are easily generated from phenols.



Scheme 1.8 General procedure for the Miyaura borylation

Beyond this, studies have been carried out to expand the number of compatible boron sources. A major drawback in the original system was the high

cost of the diboronyl reagent, which shows poor atom economy as only one Bpin moiety is incorporated from B_2pin_2. Murata later performed the same cross-coupling reaction using instead the less expensive pinacolborane (HBpin), drastically improving the atom economy and affordability of the reaction (Scheme 1.9).[37] Improved yields were obtained when the alkoxide base was replaced with trimethylamine. The reaction was further optimized by replacing the solvent with dioxane. Similar to the B_2pin_2 system, the presence of functional groups did not interfere with the reaction. Some examples of successful reactions included ester, ketone, and nitrile functionalities.

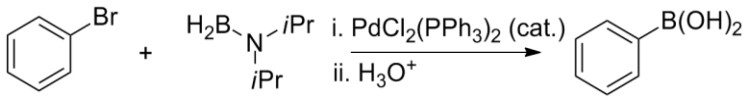


Scheme 1.9 Murata borylation of ethyl *p*-iodobenzoate

1.2.3 Synthesis of Boronic Acids via Aminoboranes

Recently, aminoboranes have seen success as a boron source for synthesizing boronic acids. Aminoboranes have several drawbacks that prevent their widespread use in organic synthesis. Originating from studies of hydroboration reactions, aminoboranes are often unreactive as hydroborating agents. Also, they easily form dimers or larger oligomers, reducing their reactivity and making purification difficult. Complexation can be mitigated by using branched dialkylaminoboranes, with diisopropylaminoborane commonly used, as these compounds resist the formation of

sterically congested dimers. In 2003, Vaultier and co-workers successfully used H_2B-$N(iPr)_2$ in the Pd-catalyzed borylation of aryl halides (Scheme 1.10).[38]



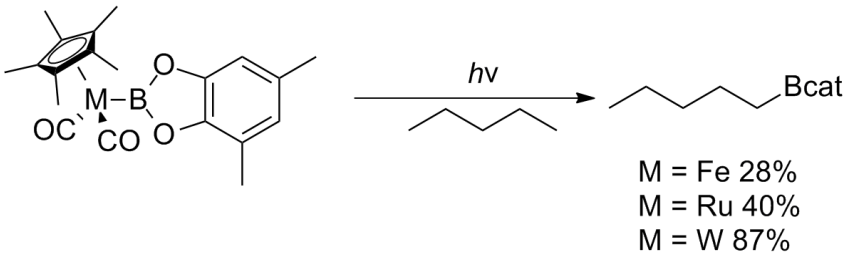
Scheme 1.10 Synthesis of phenylboronic acid from bromobenzene and $BH_2N(iPr)_2$ via palladium-catalyzed coupling

Similar to the system developed by Murata, Et_3N and dioxane were utilized as the base and solvent, respectively. The resulting organo(dialkylamino)boranes were synthesized in high yields and are easily hydrolyzed further to the corresponding boronic acids. By comparison, when the bulky 2,2,6,6-tetramethylpiperidinoborane was substituted by H_2B-$N(iPr)_2$, a significant drop in yield was observed.

1.2.4 C-H Activation

Beyond Pd-catalyzed borylation, other methods exist for synthesizing boronic acids and esters involving transition metal catalysts. One valuable route was the selective alkane borylation via C-H activation reported by Hartwig in 1997 (Scheme 1.11).[39] This stoichiometric process involved a transition metal complexed to an electrophilic main group element covalently bound to the metal. The complex was then photochemically reacted with alkanes to exclusively produce terminal alkylcatecholboronate esters. Hartwig initially tested metal complexes of both $Cp^*Fe(CO)_2Bcat$ and $Cp^*Ru(CO)_2Bcat$ with pentane, producing the esters in 28% and 40% yields respectively, while use of a $Cp^*W(CO)_2Bcat$ complex proved more

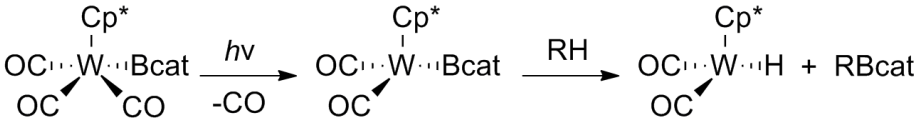
successful, providing an 85% yield. All three complexes showed high selectivity for borylation of alkanes at the primary position, with much smaller yields on secondary positions or primary positions near tertiary branch points.



Scheme 1.11 Selective functionalization of alkanes by transition-metal boryl complexes

Mechanistic analysis indicates that ligand dissociation is first induced photochemically followed by thermal reaction of the resulting intermediate with alkanes (Scheme 1.12). Several observations support the irreversible, photochemically induced dissociation of CO to initiate the reaction: (1) increased pressure of CO did not inhibit the reaction of $Cp^*W(CO)_3$with HBcat; (2) photolysis of $Cp^*W(CO)_3$ under 1 atm of ^{13}CO in pentane resulted in no incorporation of ^{13}CO into the starting material; (3) photolysis of $Cp^*W(CO)_3$ in the presence of PMe_3 resulted in the formation of $Cp^*W(CO)_2(PMe_3)$Bcat along with 1-pentylboronate ester. Considering that several ligand substitution reactions occur by photochemical extrusion of CO, the resulting intermediate is most likely $Cp^*W(CO)_2$Bcat. Subsequent alkane functionalization was driven by formation of a B-C bond, which is 10-15 kcal/mol stronger than the preceding C-H bond, through endothermic oxidative

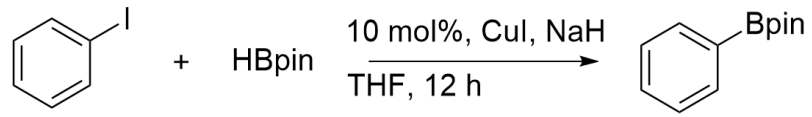
addition of the alkane C-H bond followed by exothermic reductive elimination of the boronate ester.



Scheme 1.12 Synthesis of 1-pentylboronate esters through photochemical ligand dissociation and thermal reaction of the $Cp^*W(CO)_3Bcat$ complex

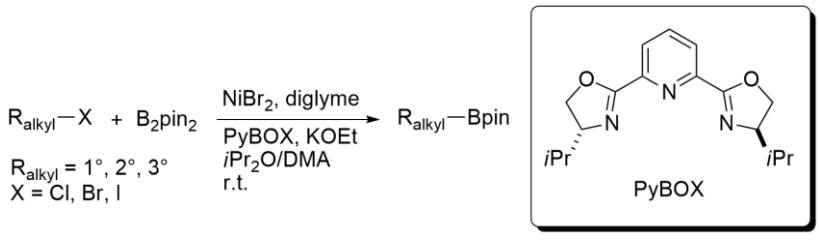
1.2.5 Synthesis of Boronic Acids and Esters Through Transition Metals

Less expensive transition metals have also been used successfully in the formation of boronic acids and esters (Scheme 1.13). Copper(I) iodide, in combination with L-proline, has previously been demonstrated by Ma to be a powerful catalyst for the coupling of aryl halides with some nucleophiles such as azides.[40] In examining the mechanism of this process, the authors noted similarities to the Miyaura borylation reaction, and suspected HBpin could be used as an alternative boron source. Initially, conditions that mimicked the Miyaura borylation (triethylamine base and refluxing dioxane) were unsuccessful. A stronger base, such as NaH, proved more successful and better yields were obtained at room temperature rather than higher temperatures. While the CuI catalyst is significantly less expensive than any Pd catalyst, only aryl iodides are compatible; aryl bromides do not provide any coupling product.



Scheme 1.13 Catalytic coupling of aryliodides with pinacolborane

Nickel has also been successful in the borylation of unactivated tertiary, secondary, and primary alkyl halides. In 2012, the Fu lab reported a catalyst formed in situ from nickel(II) bromide and diglyme with a tridentate PyBOX ligand accomplished Miyaura-type borylations with B_2pin_2 (Scheme 1.14).[41] Typically Suzuki processes are successful with bidentate ligands while tridentate ligands are optimal for Negishi reactions: the Ni- or Pd-catalyzed coupling of organozinc reagents with halides.[42] This system by Fu provides several advantages over the traditional Pd-based system such as regioselectivity, good functional group compatibility, and successful incorporation of unactivated tertiary electrophiles as coupling partners, an observation not seen previously in Ni-based borylation processes.



Scheme 1.14 Nickel-catalyzed coupling of alkyl electrophiles with B_2pin_2

With this new discovery, a series of competition experiments were performed to compare the reactivity of tertiary, secondary, and primary unactivated alkyl

bromides in Ni-catalyzed C-B bond formation. To Fu's surprise, tertiary bromides produced the highest yields of borylation product. This was in striking contrast to the competition study of a nickel/PyBOX-catalyzed C-C bond forming process, which showed a significant preference for primary halides over secondary halides. Tertiary halides were unreactive.

1.3 Applications of Boronic Acids and Esters

Boronic acid derivatives have become a crucial synthetic component in organic chemistry, drawing significant attention over the past three decades. This stems from the utility of boronic acid derivatives in two main areas of synthesis: the efficient formation of C-C bonds and stereocontrol in the asymmetric synthesis of some C-C bonds. One of the most well-known uses of boronic acids is the Suzuki-Miyaura cross-coupling reaction extensively studied in the 1980's.[43] This work, highlighting the utility of these compounds in C-C bond forming processes, marked the beginning of an exponential growth in research and development of boronic acids and esters as essential tools in organic synthesis.

1.3.1 Suzuki Coupling

The first major publication in this area came in a 1979 issue of *Tetrahedron Letters*.[30] In the article, Akira Suzuki and Norio Miyaura reported the successful cross-coupling of aryl halides with alkenyl boranes or catecholborates via a Pd(0)-catalyst and a strong base in high yields. An even more impactful article published two years later in 1981[43] highlighted a similar system in which biaryl species are

synthesized by coupling phenylboronic acids with aryl halides (Figure 1.6). Since its publication, the Suzuki coupling reaction has been heavily studied and optimized as well as drawing considerable focus to the synthesis of boronic acid derivatives. Many variations of (sp^3)C-B, (sp^2)C-B, and (sp)C-B containing substrates have been reported as compatible coupling partners. The impact of this system is best highlighted by the Nobel Prize in Chemistry awarded to Suzuki in 2010, shared with Richard Heck and Ei-ichi Negishi for coupling reactions. The Suzuki reaction is considered one of the most utilized reactions in pharmaceutical synthesis of carbon-carbon bonds.

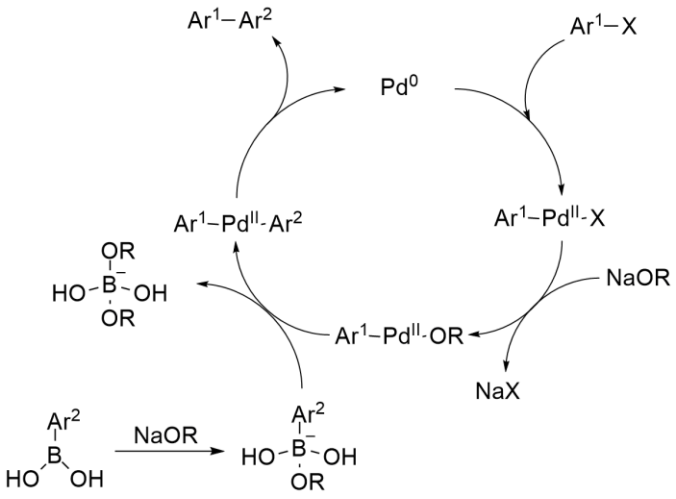


Figure 1.6 Mechanism of the Suzuki coupling reaction

The mechanism of the Suzuki coupling has been extensively studied and a general mechanism has been universally accepted. The catalytic cycle begins with a Pd(0)L_2 species which undergoes oxidative addition with the aryl halide substrate, producing an Ar-Pd(II)L_2-X intermediate. The two most common palladium sources

are $Pd(PPh_3)_4$ and $Pd_2(dba)_3$. $Pd(PPh_3)_4$ possesses two additional PPh_3 ligands that can inhibit the reaction. $Pd(PPh_3)_4$ is also highly sensitive to oxygen; it must be handled under inert atmosphere to avoid oxidation to Pd^{II}. $Pd(P^tBu_3)_2$ has recently found success as one reactive alternative, as the extremely large phosphine ligands provide active Pd(0) and only exist as bis-ligated Pd species, even with excess ligand present.[44]

The ligands employed have a significant impact on the reaction. Typically, strong sigma-donating ligands increase the electron density at the Pd core, increasing the reactivity of the rate-determining oxidative addition step. Trialkylphosphines and triarylphosphines are the most commonly used ligands. Recently, some phosphine ligands have been replaced by *N*-heterocyclic carbenes which impart high catalytic activity and stability while being air sensitive.[45] The starting aryl halide also affects the speed of the reaction as aryl iodides, bromides, and triflatesare compatible while aryl chlorides are not. This is attributed to the strong C-Cl bond resisting the oxidative addition of the Pd(0). Recently, a number of catalyst/ligand combinations have found success in reacting with aryl chlorides via Suzuki coupling.[46] Beyond aryl halides, vinyl halides retain stereochemistry during oxidative addition[47] while allyl and benzyl halides undergo inversion of stereochemistry.[48]

The organopalladium(II) species initially forms a cis-palladium complex, which isomerizes to the trans-palladium complex in the key reaction sequence.[49] While the exact role of the base is unknown, it is suspected a ligand exchange occurs

between the trans-organopalladium(II) intermediate and the base to produce a more reactive organopalladium(II)alkoxide or hydroxide, releasing the halide anion.[50–53] The Suzuki coupling reaction will not proceed in the absence of a base. Next, a transmetallation step occurs where the organopalladium(II) exchanges the newly acquired alkoxide with the aryl group of an organoboron substrate. Another suspected role of the added base is to activate the organoboron species and encourage the release of the aryl group during transmetallation. This step is driven by the formation of a tetracoordinate boronate anion, which is more electrophilic than a free boronic acid. The design of the arylboronic acid derivative is important, as a common side reaction is protolytic deboronation from ortho-substituted or electron-poor aryl boronates. Finally, a reductive elimination step regenerates the Pd(0) catalyst and eliminates the product with retention of stereochemistry. First, the trans-organopalladium(II) species rearranges back to a cis-organopalladium(II) species to align the two coupling partners.[54,55] Again, the ligand choice can affect the rate of elimination of the product, as bulky phosphine ligands force the partners closer together at an angle known as the Tolman angle.[56–58] The released $Pd(0)L_2$ catalyst is then free to reenter the catalytic cycle, beginning with another oxidative addition.

Today, a wide scope of boron reagents have been used successfully (Figure 1.7) such as organofluoroborates, alkylboranes, cyclic boronates, and even boronamides. The most commonly used organoborane moieties are 9-borabicyclo[3.3.1]nonae, disiamylborane, and dicyclohexylborane.

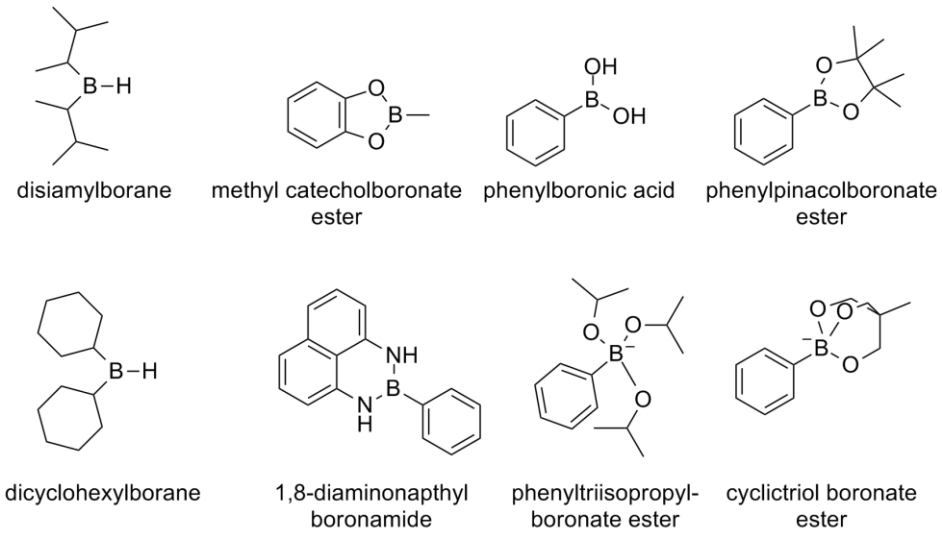


Figure 1.7 Some examples of commonly used boron reagents in Suzuki coupling

For boronic esters, the most commonly used organic moieties are pinacol, neopentyl-, and catecholboronate esters. Some advantages over their organoborane counterparts include stability, reactivity, relative cost, and simple preparation. In particular, the two oxygen atoms present in boronate esters possess lone pairs that can point into the empty p-orbital of the neighboring boron. This interaction reduces the Lewis-acidity of boronate esters compared to organoboranes. Boronate esters also have the advantage of being stable to silica gel in column chromatography, an efficient purification and isolation method incompatible with boronic acids.

In examining a number of boronate esters, observations can be made about requirements or restrictions for reagents to be successful cross-coupling partners (Figure 1.8). First, with cycloalkyl diols, such as 1,2-cyclohexanediol or 1,2-cyclopentanediol, *cis* stereochemistry is required for the reaction; *trans* diols do not

react.[59] On the same note, six membered cyclic boronate esters tend to be more stable and more reactive than their five membered ring counterparts. This is attributed to increased overlap between the oxygen lone pairs and the empty p-orbital of boron. Boronate esters that contain aryl-O bonds, as in catecholborane, show decreased reactivity, attributed to reduced lone pair donation to boron from competing resonance with the aryl π-conjugation.

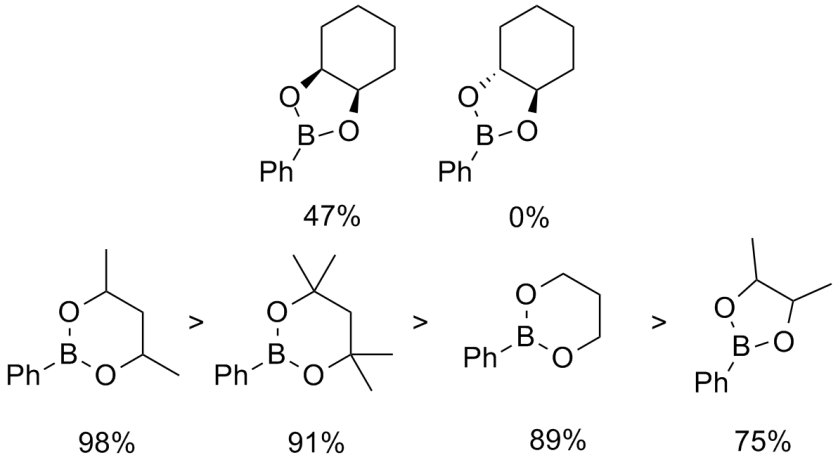
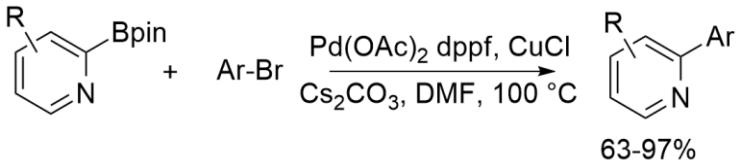


Figure 1.8 Percent transesterification from the glycol boronic ester

An example of the stability of boronic esters is the coupling of 2-pyridyl moieties with aryl bromides in the presence of copper salts (Scheme 1.15).[60] Typically, the cross-coupling of 2-pyridyl boronic acids is unsuccessful under general Suzuki coupling conditions. The transmetalation from boron to palladium of the electron-deficient 2-heterocyclic boronates is slow relative to protodeboronation. The authors suggest the copper salt is necessary to initiate a pre-transmetalation step to ultimately transfer the heteroarylboronic ester to the palladium catalyst, reducing the

amount of protodeboronation. While the reaction proceeds through a basic Suzuki coupling cycle, the direct transmetalation from heterocyclic boronates to palladium is slow. Addition of copper allows for an alternative intermediate transmetalation process to first form a 2-pyridyl copper species, followed by a second transmetalation to a palladium complex and completion of the Suzuki catalytic cycle.



Scheme 1.15 Coupling of unstable 2-pyridyl boronates via a copper-facilitated Suzuki coupling

By comparison, boronic acids have decreased solubility in organic solvents compared to neutral aqueous solutions. As previously noted, in anhydrous conditions boronic acids typically release three water molecules and form a boroxine moiety, a structure isoelectronic to benzene. Boroxines also show stability in part to the partial π-conjugation and aromatic character. As a result, the stoichiometry in a reaction can sometimes be ambiguous, leading to the use of excess boron reagent for complete conversion.

To date, there is still substantial disagreement and debate as to the mechanistic role of the base with boronic acids in the Suzuki coupling transmetalation. Computational studies suggest the base reacts with the boronic acid to form the boronate species, a process calculated to be practically barrier-less in terms of

energy.[50–52] However, studies performed in 2011 suggest a different oxo-palladium pathway exists as the kinetically favored pathway.[61–63] Studies performed by Amatore and Jutand set out four possible interactions during the transmetalation step: (a) the base plays no role, (b) the base initially reacts with the boronic acid, (c) the base reacts initially with the palladium catalyst, or (d) the base reacts with both boronic acid and palladium (Figure 1.9). After performing several reactions and analyzing kinetic data, the authors suggest that only the reaction between the neutral boronic acid and the hydroxy-palladium species occurs at a significant rate. Interestingly, this hydroxy-palladium species was formed from the halide complex, an observation in opposition to the computational studies performed earlier that suggest this process has a high energy barrier. In another example, the presence of a large excess of bromide ions, which forces the reaction equilibrium away from the hydroxy-palladium complex, significantly slowed the reaction rate between the boronate species and the halide complex, suggesting the formation of the trihydroxyboronate is unfavorable in the coupling process as it sequesters the boronic acid.

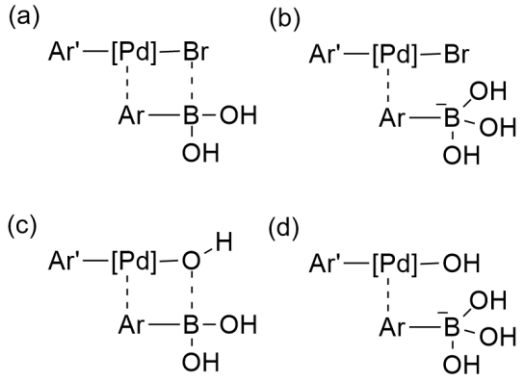
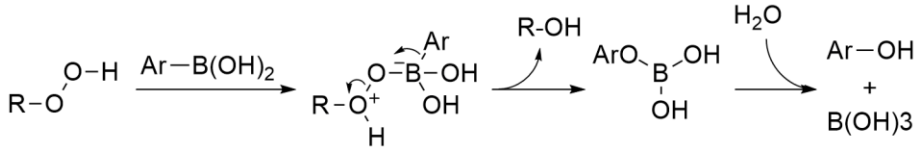


Figure 1.9 Four possible transmetallation scenarios: (a) no base, (b) boronate, (c) hydroxy-palladium, (d) hydroxy-palladium and boronate

In comparison to boronic esters, boronic acids are susceptible to various unwanted side reactions during Suzuki coupling such as protodeboronation, oxidation, and palladium-catalyzed homocoupling.[64] Ethereal solvents exposed to oxygen can easily form peroxides that interfere with the boronic acid reagents in Suzuki coupling. For example, in the coupling with arylboronic acids a 1,2-migration of the aromatic ring to the electrophilic oxygen of the peroxide can form undesired phenols (Scheme 1.16).[65]



Scheme 1.16 1,2-Migration of the aryl group to the electrophilic oxygen of peroxide

Oxygen can also cause unwanted homocoupling to occur, typically arising from incomplete degassing or leaking of air into the system through poorly fitted

joints (Figure 1.10).[66] This side process was investigated through electrochemical techniques and a catalytic cycle was proposed by Amatore and Jutand. The initial Pd(0) reacts with O_2 to form a Pd(II)peroxo complex. One oxygen of the peroxo species then coordinates with one aryl boronic acid equivalent, followed by a transfer of the aryl group to the Pd(II) center, and subsequent release of a perboric acid upon hydrolysis. Perboric acid then reacts with a second equivalent of aryl boronic acid to produce phenol, destroying two equivalents of aryl boronic acid overall. Finally, a third boronic acid transfers an aryl group to the Ar-Pd^{II} and reductively eliminates a homocoupled Ar-Ar product.

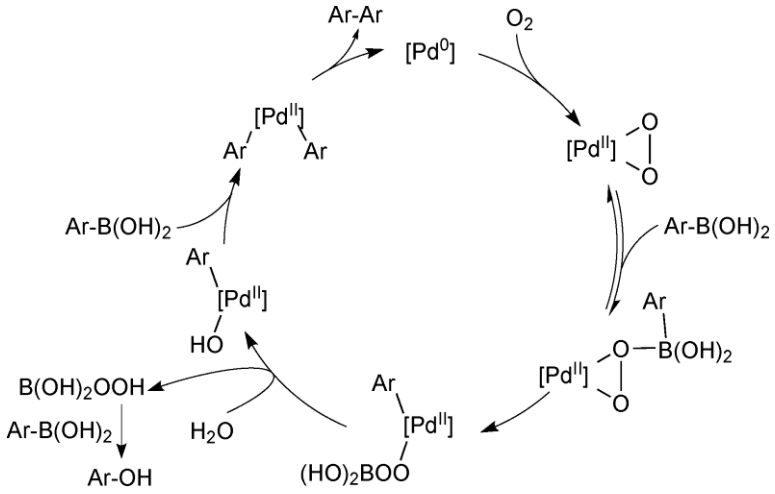
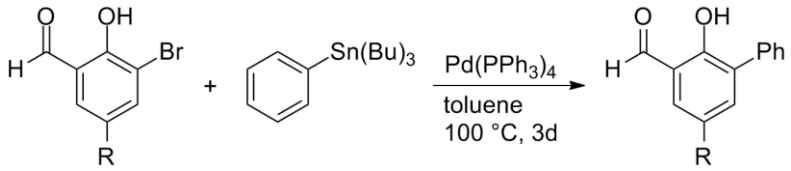


Figure 1.10 Oxidative homocoupling of arylboronic acids

Suzuki coupling, with its milder conditions and hospitable temperatures, is often investigated as an alternative to other reactions with conditions too harsh for sensitive substrates. To illustrate this, Nguyen and co-workers sought to develop an efficient synthesis of 3-aryl-substituted salen ligands, as their steric properties can

control asymmetric reactions.[67] For example, transition metal cyclopropanation catalysts utilizing salen ligands tend to afford the *trans* isomer.[68] It has been show that the sterics of the salen ligand, however, can lead to a reversed *cis* selectivity, such as installing a bulky aryl group at the 3-position of the salen ligand in Ru(salen)-catalyzed olefin cyclopropanation.[69] The synthesis of these 3-substituted salen rings can be difficult, especially when an alkyl substituent is present at the 5-position. Bulky 5-position alkyl groups, such as *tert*-butyl, are integral for high selectivity. Nguyen's goal was to develop a general synthesis for 3-aryl-5-*tert*-butyl aldehydes.

The group cited earlier work by Chan and co-workers where 3-(2-pyridal)-5-*tert*-butylsalicylaldehyde was synthesized via Stille coupling.[70] Nguyen was somewhat successful in using 3-bromo-5-*tert*-butylsalicylaldehyde and 3,5-dibromosalicylaldehyde with $PhSnBu_3$, giving the desired coupled products in 67% and 48% yields respectively (Scheme 1.17).



Scheme 1.17 Preparation of 3-aryl-substituted salicylaldehydes via Suzuki coupling

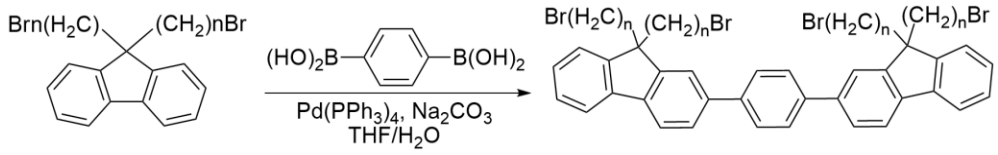
However, the harsh conditions of the Stille process (72 h at 100 °C) led Nguyen to study an alternative, namely a Suzuki coupling route. Immediately, the use of nontoxic and easily handled organoboronic acids over toxic organostannanes was a major improvement. Unfortunately, the optimal conditions for Suzuki coupling

varies widely depending on the steric and electronic properties of the substrates. To rapidly optimize the reaction for their particular conditions, the authors performed 12 reactions on 0.5 mM scales in vials placed in a heating block. These samples were then be easily analyzed via gas chromatography or ^{1}H NMR. After analyzing 17 different entries with reaction times of 16 or 40 h, this screening method significantly reduced the required time to optimize their reaction conditions. The authors reported several optimized conditions that gave 100% yields of a variety of functionalized 3-arylsalicylaldehydes with either catalytic $Pd(PPh_3)_4$ or $Pd(dppf)Cl_2$ in 3:1 DME/H_2O. While successful and highly efficient with sterically hindered substituents, some very bulky substituents proved unsuccessful.

Another growing area of research is the development of biological and chemical sensors. In particular, water-soluble conjugated polymers are valuable in the highly sensitive diagnosis of pathogenic microorganisms and detection of disease-related biomarkers.[71] However, solubility issues in aqueous environments arise from the overall low- to non-polar properties of the polymer back bone.[72] To mitigate this, the polymer is decorated with charged groups to facilitate the dissolution of the polymer.

Bazan and coworkers sought to synthesize and characterize 1,4-bis(9',9'-bis(6"-(*N*,*N*,*N*-trimethylammonium)-hexyl)-2'-fluorenyl)benzene and 1,4-bis(7'-(9",9"-bis(6'"-(*N*,*N*,*N*-trimethylammonium)hexyl)-2"-fluore-nyl)-9',9'-bis(6"-(*N*,*N*,*N*-trimethylammonium)hexyl)-2'-fluore-nyl)benzene octaiodide to

examine the chain dependence on optical processes in cationic water soluble conjugated polymers (Scheme 1.18).[73] In the synthesis of these molecules, the authors need to first synthesize the 1,4-bis(9',9'-bis(6"-(*N*,*N*-dimethylamino)hexyl)-2'-fluorenyl)-benzene building block. They were successful by first producing the charged moiety 2-bromo-9,9-bis(6'-(*N*,*N*-dimethylamino)hexyl)fluorene in three steps. Then, two equivalents were coupled to a central 1,4-phenyldiboronic acid linker via a Suzuki coupling with $Pd(dppf)Cl_2$ and K_2CO_3 in aqueous THF.

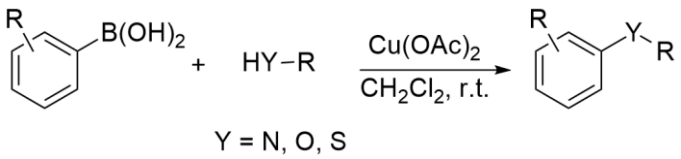


Scheme 1.18 General scheme for the synthesis of conjugated oligomers

1.3.2 Chan-Lam Coupling

Perhaps less distinguished, but just as powerful as Suzuki coupling, is the ability to couple aryl carbons with other heteroatoms such as nitrogen, oxygen, or sulfur (Scheme 1.19).[74] In particular, the area of crop protection and pharmaceutical research utilizes this methodology with aryl ethers, anilines, and aryl thioethers.[75] While examples of these transformations do exist in the literature, the methods employed often involve harsh conditions such as high temperatures, strong bases, and expensive catalysts. Recently, work developed by Chan and Lam highlighted the ability of copper(II) salts to couple oxygen and nitrogen functionalities with aryl boronic acids.[74] A major advantage this method demonstrated over previous

examples was the mild conditions required: the reaction was performed at room temperature without inert atmosphere in short reaction times.



Scheme 1.19 General conditions for the coupling of boronic acids with N-H, O-H, or S-H containing compounds

In the late 1980's, Derek Barton reported the arylation of aliphatic and aromatic amines from arylbismuth reagents and metallic copper or copper(II) salts.[76] This methodology was used to synthesize anilines through basic amine and indole arylation, but led to difficulties with less reactive N-H compounds. Reaction conditions were not ideal, even in the successful reactions, utilizing strong bases and high temperatures over long reaction times. This methodology was later improved, noting that the addition of an amine promoter (typically triethylamine or pyridine) increased yields and widened the range of compatible substrates.[77] As boronic acids saw increasing development and focus from their role in Suzuki coupling, Dominic Chan sought to replace arylbismuth with arylboronic acids as coupling partners with copper(II) salts. This new methodology proved successful in several C-O and C-N cross-coupling reactions utilizing alkenylboronic acids, siloxanes, and stannanes as well as the *N*-arylation of heterocyclic systems. This methodology was also developed into a catalytic process.[74,78,79] More recently, Chan-Lam coupling has

become a staple methodology with numerous labs worldwide optimizing and expanding the scope of the reaction.

Organocuprate reagents tend to form complex structures in solution, making experimental mechanistic studies challenging. The exact mechanism of the Chan-Lam cross-coupling reaction is currently being investigated, however a general mechanism has been proposed (Figure 1.11).[80] The arylboronic acid initially undergoes transmetalation with the bis-μ-hydroxy Cu(II) complex to form boric acid and an $L_2ArCu(II)OAc$ intermediate. This species coordinates with the phenol or aniline coupling partner, followed by oxidation of the Cu(II) to Cu(III) by O_2. A reductive elimination of the coupled product yields $L_2Cu(I)OAc$ which, in the presence of O_2 and H_2O, can be reconverted into bis-μ-hydroxy Cu(II) complex.

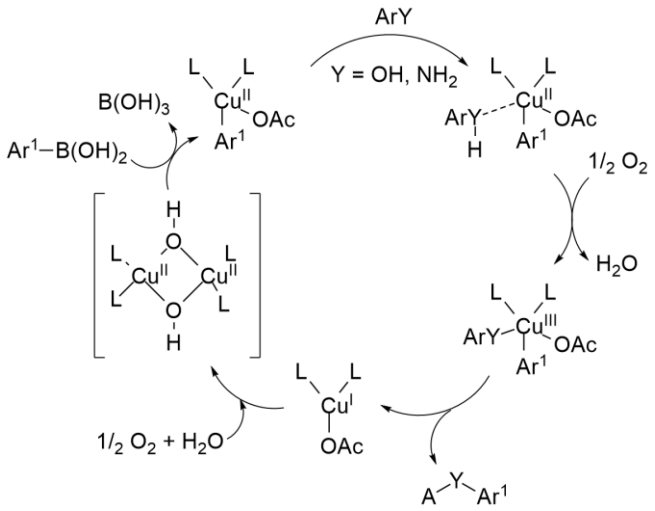
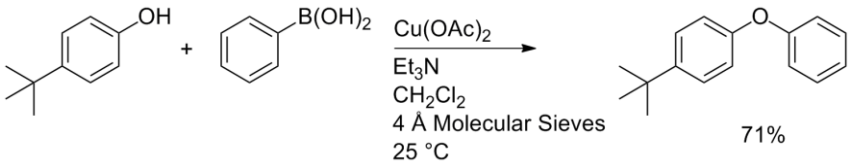


Figure 1.11 Proposed mechanism for Chan-Lam coupling of boronic acids with anilines or phenols

One of the first protocols used for the arylation of phenols reacted an excess of arylboronic acid with anhydrous copper(II) acetate.[74] The reaction was run in CH_2Cl_2 with the addition of Et_3N at room temperature for up to 48 hours. A wide range of non-participating functionalities were successfully used such as amines, anilines, amides, ureas, sulfonamides, and carbamates. In all of these cases, the ratio of boronic acid to copper(II) salt to tertiary amine additive was 2:1:2 and none were completed before 24 hours. The choice of tertiary amine played a major role in the final yield of coupled product; there seemed to be no appreciable trend with the substrate and amine used to maximize the yield. The use of electron-rich aryl boronic acids provided increased yields compared to unsubstituted boronic acids.

The strength of this protocol was highlighted by Evans, published in the same issue as Chan's first report, in the synthesis of the thyroxine which possessed a macrocyclic diaryl ether moiety common in vancomycin antibiotics.[78] Earlier methods to synthesize these moieties, such as the Ullman ether synthesis,[81] require high temperatures and strongly basic conditions that often degraded other functionalities present. To find optimal reaction conditions, Evans and co-workers utilized 4-*tert*-butylphenol and phenylboronic acid as a test system in CH_2Cl_2 (Scheme 1.20).

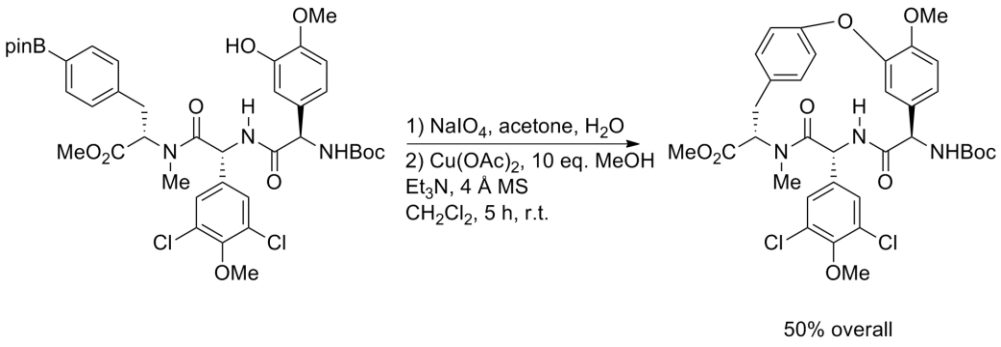


Scheme 1.20 Arylation of 4-*tert*-butylphenol with phenylboronic acid

Consistent with Chan's observations,[82] $Cu(OAc)_2$ was the most efficient copper(II) salt for arylation. Analysis of the unpurified reactions showed two unwanted side reactions for phenylboronic acid: homocoupling to produce diphenyl ether and formation of phenol. The authors attributed this to arylation of water, but as both were produced even under strict anhydrous conditions, it was suspected that formation of triphenylboroxine was generating water.[83] Addition of molecular sieves to sequester any generated water, and thus enhance formation of boroxine, significantly reduced any diphenyl ether or phenol formation and improve product yields. To confirm this suspicion, the reaction was also performed using 0.33 equivalents of triphenylboroxine, giving similar yields. Yields were further increased by adding a large excess of base (with 5 equivalents optimal) and exposure to atmospheric conditions (inert atmosphere significantly reduced yields).

Intramolecular C-O coupling has also been widely used in the synthesis of biologically active molecules. Snapper and Hoveyda utilized this methodology in the synthesis of the anti-HIV compound chloropeptin I, a natural product possessing a biologically active biaryl ether moiety (Scheme 1.21).[84] Interestingly, Hoveyda masked the boronic acid as the pinacol ester until the C-O coupling step and then

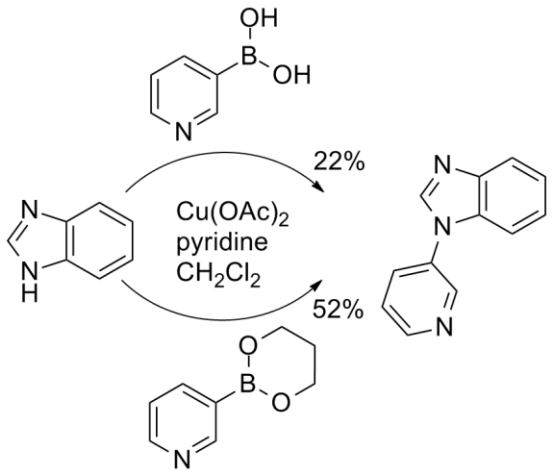
liberated the boronic acid via addition of $NaIO_4$. $Cu(OAc)_2$ proved the most optimal copper(II) salt. Unique to this reaction, however, was the requirement of 10 equivalents of methanol. The authors postulate the role of methanol could be increasing the solubility of the copper salt or possibly converting the free boronic acid into the dimethyl boronic ester. While both are possible according to the authors, the formation of dimethyl boronic ester correlates with an earlier observation by Chan in his investigation of boronic acids and esters as borylating agents.[79]



Scheme 1.21 Synthesis of chloropeptin I

In 2003, Chan performed an analysis of the controlling factors and efficiency of different boronic acids and esters in the C-N and C-O bond cross-coupling reaction (Scheme 1.22).[82] Phenylboronic acid was used as the baseline metric for several reasons: ease of formation of anhydrous boroxine, ease of esterification with various alcohols, and relative poor results in both N- and O-cross coupling reactions. For coupling partners, 3,5-di-*tert*-butylphenol, 4-phenylpiperidine, and 1-ethyl-2-benzimidazolinone were used to demonstrate alcohol, amine, and amide functionalities respectively. In almost every case, the ester derivatives performed

better than free phenylboronic acid. Phenylcatecholboronate ester showed poor yields, most likely resulting from rapid hydrolyzation back to the free boronic acid. Phenylpinacolborane also showed lower yields, as the methyl groups created significant steric congestion at the boron center. Conversely, triphenylboroxine provided the highest yields. The ease of phenylboronic acid to covert to the boroxine derivative in CH_2Cl_2 led the authors to speculate the active arylating agent in past publications was most likely the anhydrous boroxine moiety and not free boronic acid. Several early publications report increased yields with the addition of molecular sieves, again suggesting the formation of the boroxine greatly enhances reactivity.



Scheme 1.22 Copper promoted C-N cross-coupling with boronic acids and esters

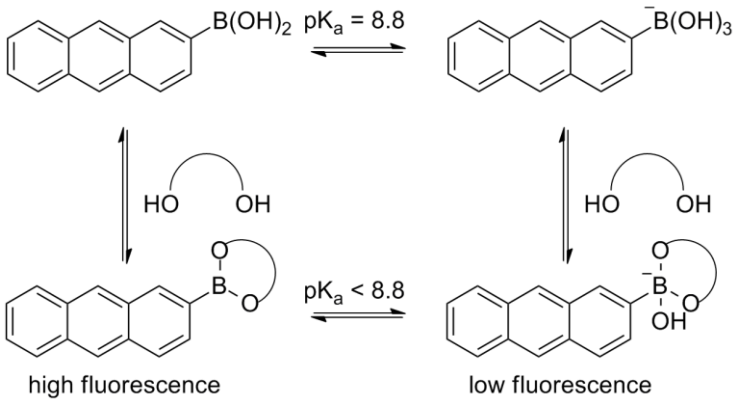
1.3.3 Boronic Acids as Saccharide Sensors

Beyond organic synthesis, boronic acids have also been used extensively in different systems such as saccharide sensors. Saccharides are critical compounds in the healthy lifecycle of all organisms through their numerous roles such as building

blocks, signaling and recognition components, and metabolic energy sources.[85] In particular, dysfunctions involving D-glucose transportation pathways have been attributed to numerous diseases such as renal glycosuria,[86] cystic fibrosis,[87] diabetes,[88] and cancer,[89] among others. Several industrial processes also utilize sugar detection, such as fermentation of food or alcohol and testing for enantiomeric purity of synthetic compounds.

The most common method of saccharide analysis involves enzymatic systems. However, these systems are often unstable to harsh conditions and require strict conditions for long term storage. Synthetic methods involving hydrogen bonding systems have also been applied, but these can give poor results, especially when detecting dilute neutral analytes.[90] Recently, boronic acids have risen to the forefront as efficient saccharide sensors due to their reversible covalent interactions with saccharides over weaker attractive forces.[91] Their interaction energy barrier is also high enough to allow only single molecule recognition. Typically, boronic acids interact with 1,2- or 1,3-diols to form five- or six-membered boronic esters in a covalent bond forming process. However, use of reducing saccharides can prove difficult in formation of the cyclic ester, as these sugars can isomerize between pyranose and furanose forms. In the simple case of phenylboronic acid, the order of selectivity (exhibited by most monoboronic acids) is D-fructose, followed by D-galactose, then D-glucose.[92]

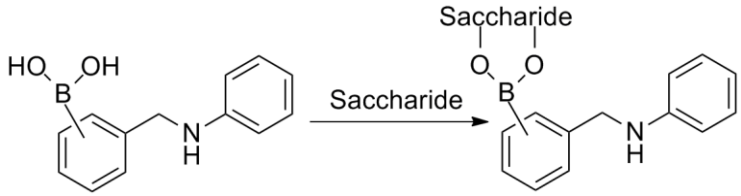
Fluorescent boronic acid sensors are extremely popular due to the inherent sensitivity of fluorescent readings. The amount of sensor required averages at 10^{-6} M, which significantly offsets the expensive cost of their synthesis. Fluorescent systems can also provide continuous sensors when paired with fiber optics systems.[93] One of the first sensors was designed around an internal charge transfer mechanism by Czarnik via a 2- and 9-anthrylboronic acid, where a saccharide would bind with the neutral boronic acid to produce a negatively charged boronate with a lower fluorescence than its neutral counterpart (Scheme 1.23).[94,95] Changing the fluorophore, as in 5-indolylboronic acid, shows an even stronger reduction in fluorescence, as the indolyl fluorophore is quenched when binding with oligosaccharides. The increased stability with the saccharide oligomer can be attributed to interactions with the N-H of the indole moiety.



Scheme 1.23 Equilibria of anthrylboronic acid in the presence of a polyol

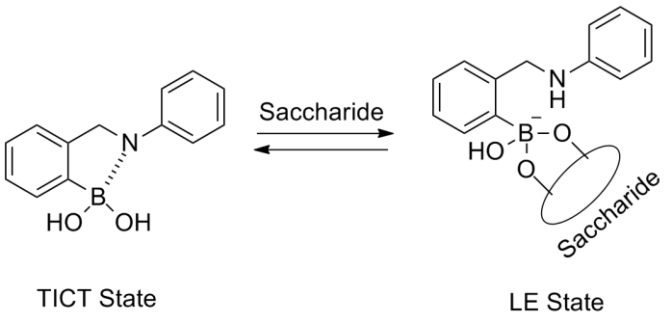
James has prepared a monoboronic acid fluorescent sensor capable of producing large shifts in emission wavelengths with saccharide binding (Scheme

1.24).[96] This sensor shows dual fluorescent properties via both a locally excited state and twisted internal charge transfer mechanism of the aniline fluorophore.



Scheme 1.24 Monoboronic acid fluorescent sensors

For example, when unbound in an aqueous solution at pH 8.2 and excited at 274 nm, an emission maxima is produced at 404 nm, partly due to the intramolecular interaction between boron and nitrogen, a twisted internal charge transfer (TICT) state. When the boronic acid covalently binds to a saccharide, this emission shifts to 362 nm and the B-N interaction is broken with the formation of the boronate, a locally excited state. An interesting observation is made when the *ortho*-boronic acid moiety is changed to a *meta*- or *para*-substitution pattern where intramolecular B-N binding is no longer possible. Excitation at 274 nm showed no TICT-related emission; instead, both show emission at 350 nm when excited at 240 and 244 nm respectively. The fluorescence enhancement from all three compounds when bound to D-fructose is 15-, 18-, and 25-fold from the fluorescence recovery of the aniline fluorophore. Despite this information, anilines are typically not used due to their poor properties as fluorophores, but this work presented a foundation for developing improved internal charge transfer systems.



Scheme 1.25 Locally excited (LE) and twisted internal charge transfers (TICT) states

The most popular fluorescent systems for atomic and molecular detection instead utilize photoinduced electron transfer (PET) mechanisms.[97–99] These sensors typically possess two components: a fluorophore and a receptor connected via a short linker. When bound to the analyte, the oxidation/reduction potential of the receptor can change the fluorescence by affecting the PET mechanism. One of the first examples of this, again prepared by James, possessed an anthracenyl group and *ortho*-arylboronic acid linked via a tertiary amine (Figure 1.12).[100,101] This amine linker encourages saccharide binding to the neighboring boronic acid under neutral pH while also controlling the fluorescence intensity via its lone pair. The strength of the Lewis acid-base interaction between the nitrogen and boron upon saccharide binding directly influences the fluorescence of this system and is crucial for success as a sensor. Weaker B-N interactions result in competition from the solvent and no signal is produced. This interaction cannot be too strong, as the saccharide would be unable to bind at all and no appreciable difference in signal could be detected.

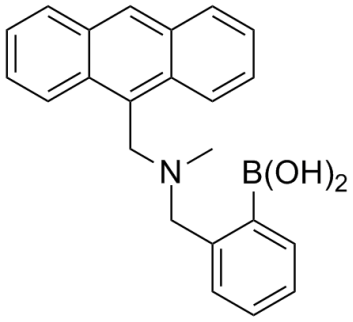


Figure 1.12 Monoboronic acid photoinduced electron transfer (PET) fluorescent sensor

1.4 Conclusion

In summary, boronic acids and esters have evolved into cornerstones of organic synthesis. With the initial discovery by Suzuki and Miyaura of the cross-coupling of boronic acids and aryl halides via a Pd-catalyst, the number of publications referencing boronic acids and/or esters has exponentially grown. The Suzuki coupling is often considered the most used synthetic method in pharmaceutical chemistry today. The initial discovery also spawned numerous analogous coupling reactions involving other metal centers such as copper, nickel, and iron, to name a few. Boronic acids and esters also possess many synthetically valuable properties such as low toxicity, stability under atmospheric conditions, unique NMR properties, low costs, and easy purification; all properties conducive to successful large scale reactions and industrial applications.

Boronic acids have also garnered attention in other applications through their selective binding with 1,2- or 1,3-diols. This interaction has been exploited in the

derivatization or protection of alcohols, but has seen more focus in the trapping and sensing of saccharides. Because of the unique structures each biologically active saccharide possesses boronic acid based sensors to be selective for different saccharides. Current systems use either enzymatic systems, which are too sensitive for harsh conditions, or hydrogen bonding-based systems, which offer low sensitivity due to the weak attraction of a hydrogen bond. In comparison, boronic acid based systems allow for the design of specific sensors for individual saccharides with sensitive and accurate results.

1.5 Thesis Outline

The second chapter of this thesis presents the synthesis of boronic acids and esters via Grignard chemistry. First, a selection of aryl(diisopropylamino)boranes are prepared from the reaction of aryl Grignard reagents with diisopropylamino borane, which are then hydrolyzed to the boronic acid under mild conditions. A similar system directly yields haloarylboronic esters from the corresponding aryl Grignard reagents, formed under Barbier conditions, reacting with pinacolborane.

The third chapter examines the reaction between pinacolborane and aryl halides in various zinc-based systems. First, a study was performed examining the effect of lithium chloride on the generation of organozinc reagents and their reactions with pinacolborane. A similar study followed, examining the efficacy of a zinc-cobalt catalytic system in the synthesis of arylboronic esters.

The fourth chapter examines the unique interaction between pinacolborane and iodine in both ether and hydrocarbon solvents. In the presence of I_2, pinacolborane is converted to iodopinacolborane, which is then capable of cleaving the C-O bond of various cyclic ethers. This produces a new borate species, iodobutylpinacolborate, which is utilized as a borylating agent with Grignard reagents that releases re-cyclized ether rather than producing hydrides generated in similar systems.

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CHAPTER 2

Reaction of Preformed Grignard Reagents and Grignards Prepared under Barbier Conditions with Pinacolborane and Aminoborane. Synthesis of Alkyl, Aryl, and Heteroaryl Boronic Acids and Esters

2.1 Introduction

Since the late 1970's, the number of applications utilizing boronic acids and esters as synthetic intermediates has increased exponentially and continues to grow at such a rate. Boronic acids and their derivatives have been utilized as integral components in many high profile and widely used processes including Suzuki coupling,[102] Chan-Lam coupling,[74] and the Petasis reaction.[103] Boronic esters have also been used as directors[20] while chiral boronic esters can undergo carbon insertion.[104] Boronate esters have also been used as catalytic enantioselective reducing agents highlighted by Corey, Bakshi, and Shibata through the CBS catalyst (Figure 2.1).[105] The list of examples including boronates and boronic acids as critical components is extensive while the methods for synthesizing these intermediates remain limited. This growing field requires new, mild, and efficient methods to synthesize boronic acids and esters that tolerate sensitive functionalities.

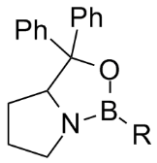


Figure 2.1 The Corey-Bakshi-Shibata (CBS) Catalyst

2.2 Preparation of Boronic Acids and Esters from Alkoxyboranes

The importance of boronic acids and esters cannot be understated; they are a critical synthetic intermediate in many reactions including the Suzuki-coupling, which was awarded the Nobel Prize and is considered one of the most widely used reactions in drug development.[106] Boronic acids have recently emerged as efficient sensors for saccharides in a time where metabolic diseases including diabetes and diseases linked to gut permeation are at an all-time high.[107] In order to access a wide range of diverse boronic acids and esters, new and efficient methods for their preparation are needed. In particular, the history of their synthesis has revolved around the reaction of an organometallic nucleophile with a trialkoxyborane species.[31] More recently with the development of cross-coupling methods, including the Miyaura borylation,[108] dialkoxyboranes and diboron species have also become boron sources of interest.

2.2.1 Bis(pinacolato)diboron vs. Pinacolborane as a Boron Source

The reagent 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi-(1,3,2-dioxaborolane), also known as bis(pinacolato)diboron (B_2pin_2, Figure 2.2), became a popular borylating agent after publication of the Miyaura borylation reaction.[109] The boronate esters derived from this reaction allow for mild work-up procedures and are stable both to silica gel chromatography and air. The pinacol ester moiety in particular is difficult to hydrolyze and preserves the boronic functionality due to its poor Lewis acidity and overall low reactivity. However, a major downside to this reagent is its poor atom

economy relative to the reagent cost. Currently priced at approximately $11 per mmol, the mechanism involves a Lewis base coordinating to one pinacolborane moiety, weakening the B-B bond, and liberating the other pinacolborane component to be installed via a C-B bond forming reaction. The former Lewis base-pinacolborane molecule is considered sequestered and lost, leading to a 50% loss in terms of atom economy and a loss of $5.50 per mmol worth of reagent.

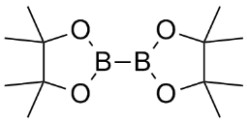


Figure 2.2 Bis(pinacolato)diboron (B_2pin_2)

As an alternative, 4,4,5,5-tetramethyl-1,3,2-dioxaborolane (HBpin, Figure 2.3) has seen success as a boron reagent in many reactions including hydroboration,[110] metal-catalyzed hydroboration,[111] generation of boron enolates,[112] Suzuki coupling,[113] Miyaura borylation,[48] and dehydrogenative borylation.[114] Similar to B_2pin_2, HBpin produces pinacolboronate esters stable to air and column chromatography conditions making isolation simple. However, unlike B_2pin_2, only a hydrogen atom is not incorporated into the product, giving nearly 100% atom economy. At approximately $2.60 per mmol, this is a significantly more efficient reagent for boronate ester synthesis.

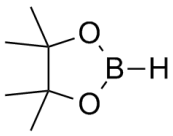
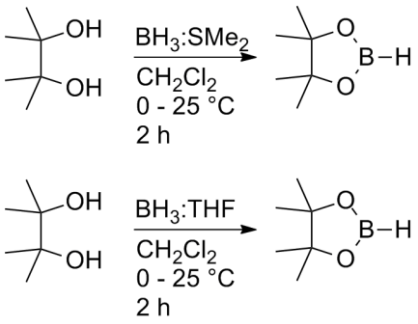


Figure 2.3 Pinacolborane (HBpin)

2.2.2 Preparation of Pinacolborane

Pinacolborane is typically synthesized from the addition of borane, such as BH_3:THF or BH_3:SMe_2, to a solution of pinacol in dichloromethane (Scheme 2.1).[110] The reaction is complete after 1 hour at 0 °C, followed by another 1 hour stirring at 25 °C, during which the vigorous release of H_2 gas is observed. While unnecessary, purification or collection of the pinacolborane can be achieved via simple vacuum distillation (43 °C, 50 mmHg).

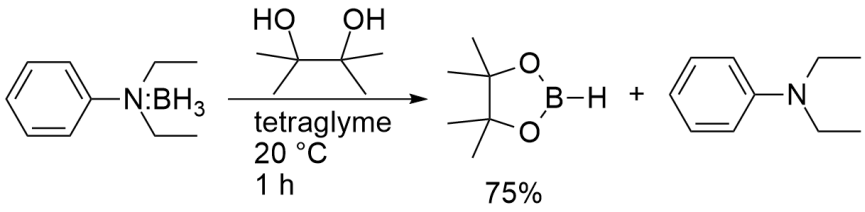


Scheme 2.1 Preparation of HBpin from BMS or BH_3:THF

More recently, Miyaura has published a method for the preparation of HBpin from amine-boranes, namely diethylaniline-borane.[115] In THF solutions absent of stabilizers, BH_3 is subjected to conditions that facilitate degradation via the ring opening of THF to produce tributoxyborane. Solutions of BH_3:THF are both highly

volatile and flammable and must be stored at low concentrations. Similar issues arise from the BH_3:SMe_2 complex, where the high volatility and high flammability can cause complications, paired with the release of the extremely unpleasant odor of dimethyl sulfide. While compatible for small scale reactions, these complications reduce the instances of these chemicals utilized on a large or industrial scale preparation. Fortunately, the analogous amine-borane complex does not exhibit the same drawbacks: amine-borane complexes have lower flammability, lower vapor pressure, and are inherently more stable at ambient temperatures.

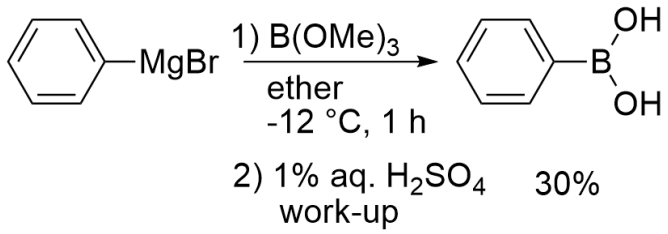
Miyaura demonstrated the successful conversion of various amine-borane complexes to pinacolborane through the 1:1 addition of pinacol to amine in tetraglyme at 20 °C after 1 hour of stirring. Interestingly, *N*,*N*-diethylaniline-borane complex was most promising, with 100% conversion and respectable isolated yields reported (Scheme 2.2). For small amine complexes such as NH_3 or *N*,*N*-dimethylaniline, the reaction was very slow and produced a significant amount of B_2pin_3. In contrast sterically hindered amines, such as *N*,*N*-diisopropylaniline, did not react at all. Miyaura went on to demonstrate this method could be used in the one-pot, two-step synthesis of unsymmetrical biaryls in high yields via an aromatic C-H borylation of arenes; the products were easily isolated via extraction with benzene. The yields were comparable or higher in relation to similar reactions that utilized B_2pin_2 as the boron source.



Scheme 2.2 Preparation of HBpin from diethylaniline borane complex

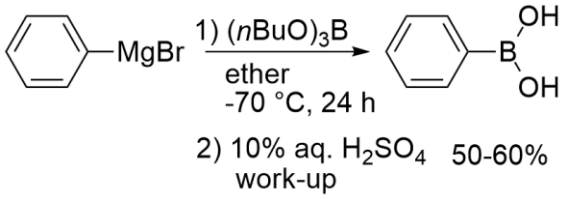
2.2.3 Synthesis of Boronic Acids and Esters from Organometallics and Alkoxyboranes

One of the original methods for synthesizing boronic acids emerged in 1909 and is still considered one of the simplest and least expensive despite its limited compatibility.[32] Originally investigated as possible route to antiseptics, early methods of arylboronic acid synthesis involved adding phenylmagnesium bromide to methylborate in ether at -15 °C. Many reproductions of this methodology provided poor yields, even when boron trifluoride was tested as an alternative boron source. In 1931, Johnson utilized this methodology to synthesize nitrophenylboronic acid derivatives, again citing antibacterial properties that showed no toxicity towards complex organisms.[31] As a note, the authors looked to synthesize phenylboronic acid followed by a subsequent nitration to produce the derivatives (Scheme 2.3). Despite earlier procedures yielding poor results, Johnson observed that a change in the order of addition significantly improved their yields of phenylboronic acid produced, but Johnson noted they were unable to obtain the yields of 50 and 86% previously claimed by Khotinsky and Melamed.



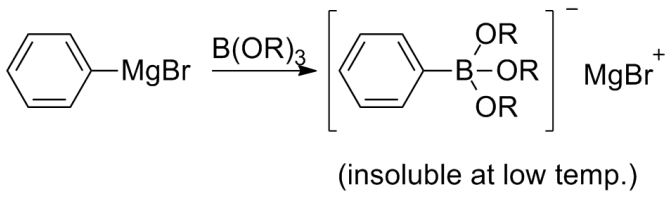
Scheme 2.3 Johnson's preparation of $PhB(OH)_2$ via PhMgBr and $B(OMe)_3$

Johnson continued his investigation the following year in hopes of expanding the method to other substituted phenylboronic acids, mainly phenols.[116] However, as the Grignard-based methods are incompatible in the presence of a hydroxyl group, the authors looked to produce the boronic acids containing other compatible functionalities and later convert them to hydroxyl groups. Some functionalized boronic acids were used in addition to phenylboronic acid, including *p*-tolyl-, *p*-anisyl-, and *p*-bromophenylboronic acid, all synthesized from the corresponding organomagnesium bromides added to a solution of *n*-butylborate in ether. In changing from methylborate to *n*-butylborate, the reaction temperature could be reduced from -15 °C to as low as -60 °C, and the yields were tremendously increased (Scheme 2.4).



Scheme 2.4 Johnson's preparation of $PhB(OH)_2$ via PhMgBr and $(n\text{BuO})_3\text{B}$

Under non-cryogenic conditions, a significant amount of diphenylborinic ester resulted from over-addition of a second Grignard reagent to the boronic ester intermediate. A third displacement can also occur to yield triphenylborane. While cryogenic temperatures tempers the reactivity of the organometallic reagent, the colder temperatures can also encourage precipitation of the first intermediate in the form of magnesium trialkoxyphenylborate, protecting it from further addition (Scheme 2.5). The arylboronic acid is easily recovered from an aqueous work-up that also hydrolyzes the ester substituents. This methodology has also been used with organolithium nucleophiles with similar success.



Scheme 2.5 Formation of the insoluble magnesium trialkoxyphenylborate

Washburn continued Johnson's work with a much more detailed study of the mechanism for phenylboronic acid formation via Grignards and methylborate in 1959.[117] Interestingly, Washburn summarized several procedures and observations published before 1959 only to highlight a field rife with contradictions and failed attempts to reproduce previously published results, prompting his investigation of a more commercially sound process for arylboronic acid formation. First, Washburn briefly revisited the procedure by Krause and Nitsche[118] where phenylmagnesium bromide was added to boron trifluoride, however the major product in this reaction

was diphenylborinic acid with no boronic acid present. Noting this result as well as the difficulty in handling trihaloboranes, BF_3 was replaced by methylborate as the boron source.

Several different aspects of the reaction were investigated, beginning with the rate of addition. Until this point, the Grignard reagent was typically added relatively slowly, but three runs at 0 °C with slow addition yielded an average of only 46.8%. Adjusting the addition speed, nine similar reactions were run with the Grignard reagent added rapidly instead of a slow rate of addition, increasing the average yield to 53.3%. Next, the effect of concentration was examined, with a clear decrease in the yield as the concentration of methylborate was increased (Figure 2.4). An extensive analysis was also performed on the effects from the reaction temperature. In general, reactions run below -60 °C gave the highest yields regardless of the rate of Grignard addition to methylborate, with an average yield of 85%. At higher temperatures close to 0 °C, fast addition gave better yields than slow addition; however both were significantly lower in comparison to reactions ran under cryogenic temperatures. Room temperature reactions produced significant borinic acid over the desired boronic acid, while very little borinic acid forms below 0 °C, and only trace amounts at -60 °C. The fast addition at -60 °C procedure was repeated with *p*-chlorobromobenzene and 1-bromonapthalene with similar satisfactory yields obtained for the corresponding boronic acids.

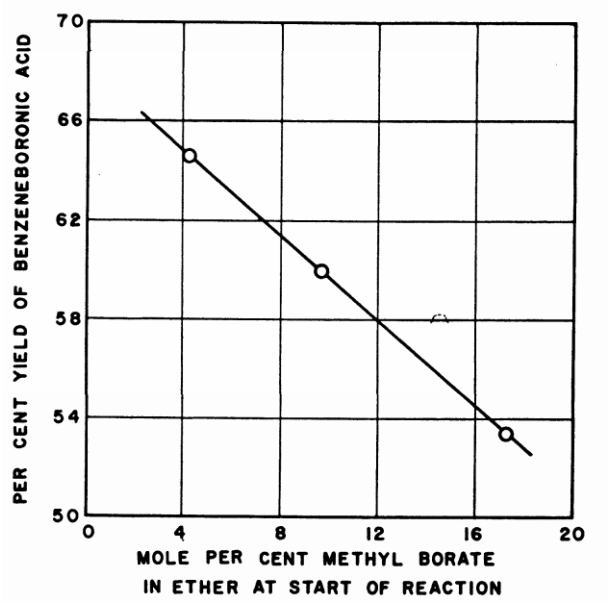
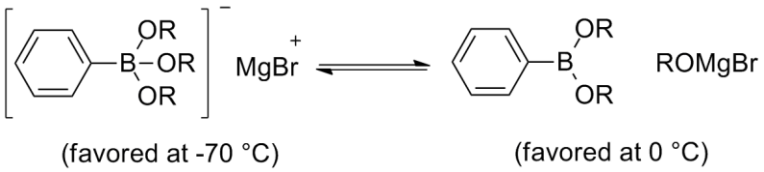


Figure 2.4 Washburn's analysis of initial methylborate concentration in the reaction with Grignards[117]

An equilibrium involving a tetracoordinate boronate anion is a key aspect of the reaction mechanism (Scheme 2.6). The fast reaction between phenylmagnesium bromide and methylborate stems from the reaction being highly exothermic, highlighted by the difference in yields between fast and slow addition procedures. The significant production of diphenylborinate ester at 0 °C also hints toward a possible controlling effect. A critical observation was that the formation of borinate occurred when the reaction was performed at 0 °C rather than running the reaction at -60 °C followed by warming to 0 °C for work-up. In both cases, the tetracoordinate "ate" complex is formed, however the complex remains stable under cryogenic temperatures while the reaction proceeds.



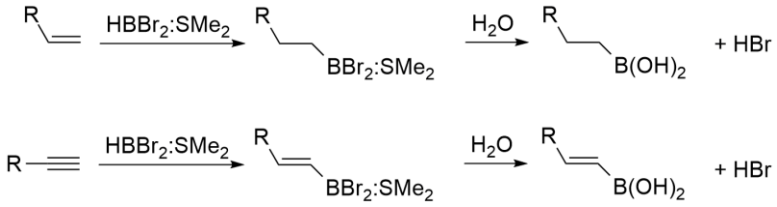
Scheme 2.6 Thermal decomposition of the tetracoordinate borate species

Near 0 °C, the "ate" complex undergoes thermal decomposition to the boronate ester, which in turn can react with another equivalent of Grignard to form the borinate "ate" complex. This side reaction is the favored reaction, as the diphenyl-substituted boron species is relatively more Lewis acidic than the monophenyl-substituted boron species, as fewer oxygen lone pairs are present to feed electron density into the open boron orbital.

Washburn also linked this observation with Johnson's reversal of the order of addition to further support this hypothesis. In the original method, methylborate was added to the Grignard reagent, resulting in an overwhelming ratio of Grignard to methylborate, driving the equilibrium towards formation of borinate ester. By reversing the order of addition, the concentration of Grignard is low relative to the amount of methylborate present, allowing for more controlled reaction.

This process optimized by Johnson and Washburn was the standard method for boronic acid and ester synthesis until the development of hydroboration by Brown offered an alternative. In 1983, Brown reported a method for the synthesis of alkyl- and alkenylboronic acids and esters via hydroboration (Scheme 2.7).[119] At the time, boronic acids had become extremely popular as synthetic intermediates as well as

protecting groups in carbohydrate chemistry due to their unique binding with 1,2- and 1,3-diols. First, the alkyl or alkenyl moiety was installed by the hydroboration of alkenes and alkynes with dibromoborane-dimethyl sulfide. From there, the alkyl- or alkenyldibromoborane-dimethyl sulfide was quickly converted in high yields to the boronic acids with the addition of water. During work-up, HBr formed from the hydrolyzation of the dibromoborane remains in the aqueous layer and does not add to the double bond in alkenylboronic acids.



Scheme 2.7 Hydroboration of alkenes and alkynes and subsequent hydrolyzation of the dibromoboranes

For esterification of boronic acids, Brown noted that esterification with simple alcohols typically involved the reflux of the acid with an excess of alcohol. By using a solvent such as benzene or toluene, the water produced from the esterification process could be removed via an azeotropic distillation. Other methods that remove water have also been demonstrated. Brown speculated that simply shaking the boronic acid and two equivalents of alcohol in pentane would be an efficient alternative. While boronate esters and simple alcohols are soluble in pentanes, the boronic acid and water are not, driving the equilibrium towards esterification. Despite the small complication of incomplete esterification from some alcohol

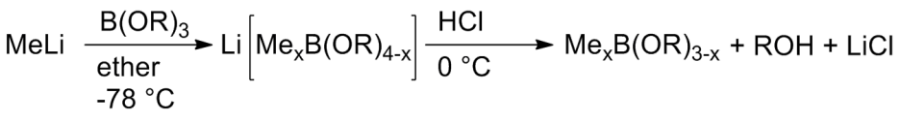
remaining dissolved in the aqueous layer, addition of excess alcohol yielded near quantitative conversion to the boronate ester.

Alkyl- and alkenyldichloroborane-dimethyl sulfide complexes reacted with simple alcohols to directly afford the boronate esters. When mixed with methanol, the alkyl- and alkenyldichloroborane-dimethyl sulfide complex produced quantitative yield of the methyl ester. Repeating this with the $RBBr_2$:Me_2S proved more difficult, as isolation of the methyl ester was complicated by the formation of Me_2S:HBr, which, in turn, hydrolyzed the methyl ester and gave mostly boronic acid on isolation. The original design involved one equivalent of the $RBBr_2$ reacting with two equivalents of alcohol. The first HBr produced would then complex with Me_2S while the second HBr equivalent would simply dissolve in the reaction mixture. However, with methanol and *tert*-butyl alcohol, HBr lead to a side reaction between methanol and Me_2S to produce a trimethylsulfonium bromide salt and water, leading to hydrolyzation of the ester and a decrease in boronate ester yield. This reaction with methanol was very fast, however ethanol and 2-propanol did not show the same complication, presumably due to the much slower formation of the corresponding sulfonium salt, allowing the faster esterification reaction to predominate.

In the same issue of *Organometallics*, Brown and Cole reported the first general preparation of boronate esters from organolithium reagents.[33] The addition of Grignard reagents to trialkoxyboranes often give lower yields for smaller alkyl groups and require extra steps for hydrolysis and esterification. In the case of alkyllithium

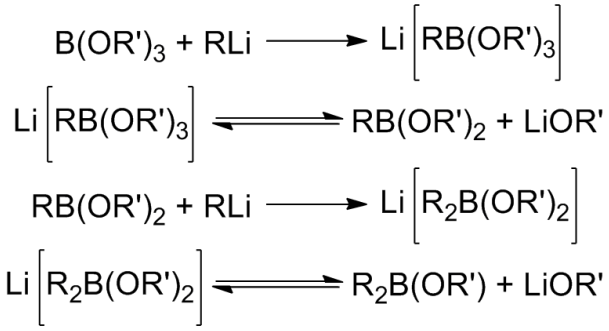
reagents, their high reactivity often results in over-addition to form borinic acids and esters.

Methyllithium was reacted with various borane sources at -78 °C, each producing a mixture of different "ate" complexes (Scheme 2.8). These complexes were then treated with anhydrous HCl to liberate the corresponding trimethylborane, dimethylborinate, methylboronate, and trialkoxyborane, whose yields were estimated via ^{11}B NMR. The results indicated the choice of trisubstituted borane was critical in favoring the monoalkylation. Trihaloboranes all produced low yields of both boronic and borinic esters while most of the starting material remained unreacted. Trimethoxyborane was tested both as the monomeric borane as well as the anhydrous trimethoxyboroxine, but both showed little to no reaction. What little did proceed only produced trimethylborane. The addition of just one carbon, triethylborane, showed a marked improvement, with a 65% yield of methylboronic ester and relatively low yields of both borinic ester and trimethylborane. Some starting material was also recovered. Triisopropoxyborane proved to be most optimal, with 98% yield of boronic ester obtained with only trace borinic ester and starting material recovered.



Scheme 2.8 Production of methylalkoxyborane adducts from methyllithium

Brown noted the key rests in the equilibrium favoring the monoalkyltrialkoxyborate complex, protecting the boron from further alkylation until liberated by a subsequent controlled protonation once the reaction is complete (Scheme 2.9). Smaller alkoxylithium salts, such as methoxy- or ethoxylithium, are less soluble in ether. Thus precipitation favors the formation of the boronic ester and disfavors the protected monoalkyltrialkoxyborate, driving the overall reaction towards overalkylation. In contrast, the highly soluble isopropoxylithium salt produced from the first alkylation helps to drive the equilibrium towards the "ate" complex and preserve the monoalkyltrialkoxyborate while not driving the reaction equilibrium further towards alkylation.



Scheme 2.9 Over-addition of methyllithium to form boronate and borinate esters

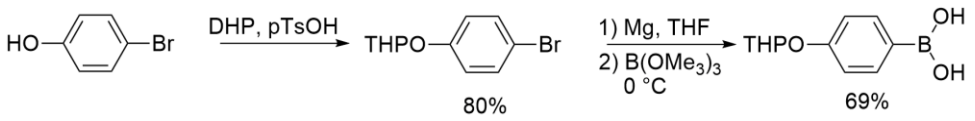
Various tributoxyboranes were tested, with tributoxy-, tri*iso*butoxy, and tri-*sec*-butoxyborane all giving high yields similar to tri*iso*propoxyborane. Conversly, tri-*tert*-butoxyborane predominantly gave starting material and a low yield of fully alkylated trimethylborane, despite the relatively high solubility of lithium *tert*-butoxide. In that reaction, the sterically congested borane was fairly unreactive and

any methyltri-*tert*-butoxyborate complex that did form readily liberated a *tert*-butoxy group, significantly relieving steric stress. The methyldi-*tert*-butylboronate ester, more reactive than the starting material, continued to alkylate, driven by the repeated production of a less sterically hindered product.

As recently as the 2000's, this process has been used on an industrial scale. Scientists at AstraZeneca looked to efficiently synthesize kilogram quantities of *p*-hydroxyphenylboronic acid with the goal of utilizing it as a source of slow phenol release under mild conditions.[120] For the hydroxyl protecting group, THP provided slow release in the presence of tosic acid in methanol with a pH of 2. Previously, the THP-protected *p*-phenoxyboronic acid had been synthesized from the transmetalation of 2-(4-bromophenoxy)-(2*H*)-tetrahydropyran with *tert*-butyllithium at -90 °C. This method is undesirable on an industrial scale, however, as the *tert*-butyllithium is extremely dangerous to handle. Since the THP ether functionality is compatible with Grignard reagents, Cladingboel looked to Johnson's procedure from the 1930's as a safer, improved alternative that can be run at 0 °C without *tert*-butyllithium as opposed to the -90 °C with *tert*-butyllithium.

Starting with 1 kg of the 2-(4-bromophenoxy)-(2*H*)-tetrahydropyran, Mg and I_2 were added to produce the corresponding Grignard reagent, followed by the addition of triisopropoxy borate. Instead of the desired boronate ester, a significant amount of UV active dimer side-product was produced. The authors believe the dimer did not result from a Wurtz-type coupling; ultimately they decided to not

investigate it further. Instead, the boron source was changed to methylborate, which is more common in the literature. In conjunction with adjusting the work-up to avoid boroxine formation under anhydrous conditions, the THP-protected arylboronic acid was isolated in high yield.



Scheme 2.10 Kilogram synthesis of 4-(2-(2*H*)-tetrahydropyranyloxy)phenylboronic acid

While Grignards have been the subject of many publications involving boronic acid and ester synthesis, these reports contain copious amounts of complications, unsuccessful modifications, and formation of multiple over-alkylation products. The most successful remedy for preventing over-addition has been use of a large excesses of borane source, however even this is sometimes ineffective. Mixed trialkoxyboranes have been reported as alternative boron sources with some success in the reaction with Grignard nucleophiles, such as isopropoxypinacolborane.

2.2.4 Synthesis of Boronic Acids and Esters from Grignards and Pinacolborane

This work sought to explore the reaction of Grignard reagents with boron sources containing a B-H bond rather than trialkoxyboranes. Pinacolborane offered several advantages, as it could produce directly the corresponding pinacolboronate

ester. Compared to boronic acids, the pinacol ester provides more oxidative and hydrolytic stability, due in part to the steric protection the four methyl groups provide to the boron center, and back bonding of both oxygen lone pairs into the vacant p orbital (Figure 2.5). The free boronic acid can be liberated by removal of the ester, to be used as a coupling partner in the Suzuki coupling. Analogous reactions have been reported, such as the addition of triorganosilyllithium reagents as well as alkynyllithium nucleophiles to HBpin.

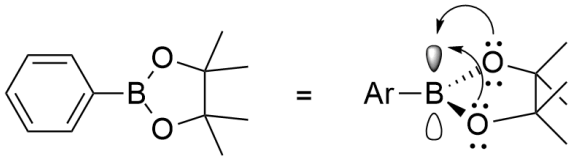
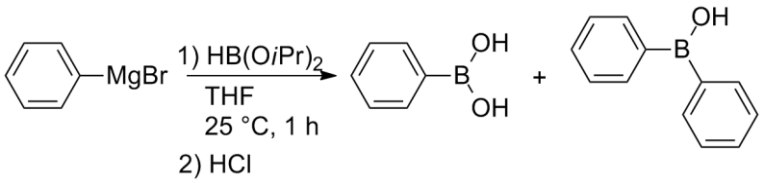


Figure 2.5 Partial molecular orbital view of pinacolborane

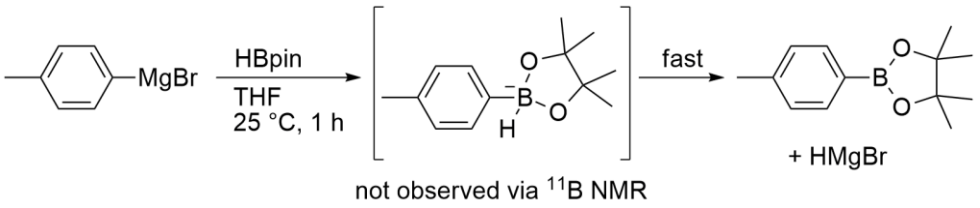
To begin the investigation of Grignards addition to dialkoxyboranes, *p*-tolylmagnesium bromide (*p*-tolylMgBr) was added to di*iso*propoxyborane at 25 °C and monitored via ^{11}B NMR (Scheme 2.11).[121] Unfortunately this provided a mixture of products, as seen with similar alkoxyborane systems, resulting from multiple additions of Grignard reagents to the boron source. However, similar results were not seen when HBpin was utilized as the boron source; the reaction of HBpin with *p*-tolylMgBr provided only monoaddition product. A similar investigation with phenyllithium was unsuccessful, giving a mixture of over-addition products. It was speculated the stronger Lewis acid/Lewis base interaction between Li^+ and the oxygen of the pinacol group weakened the B-O bond, allowing multiple additions to occur.



Scheme 2.11 Reaction of aryl Grignard with diisopropoxyborane

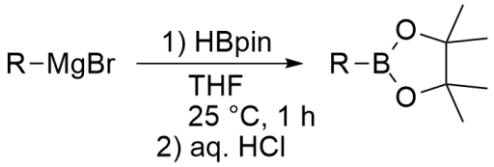
Only monoaddition product was obtained in the reaction of *p*-tolylMgBr with HBpin. Further examination showed that the use of freshly prepared Grignard reagent and pure HBpin was critical. A study using ^{11}B NMR was performed to monitor the stability of HBpin in various solvents. While a number of solvents showed degradation of HBpin over a few days, neat HBpin was stable at room temperature for at least 7 months.

It was speculated that upon addition of *p*-tolylMgBr to HBpin, the dialkoxyarylborohydride "ate" complex persists in solution until an aqueous work-up quenches the hydride and liberates the arylboronate ester (Scheme 2.12). However, after 1 hour of stirring of *p*-tolylMgBr with HBpin in THF at 25 °C, ^{11}B NMR analysis showed the absence of any dialkoxyarylborohydride complex in solution. Instead, only the arylboronate ester singlet was present (δ +32), indicating the immediate disproportionation of the "ate" complex. An extensive study on the formation of the liberated hydridomagnesium bromide (HMgBr) was performed by Singaram and Clary, confirming the propensity for the "ate" complex to immediately disproportionate to the metal hydride complex and boronate ester. They studied the reactivity and stability of both HMgBr and hydridomagnesium chloride (HMgCl).



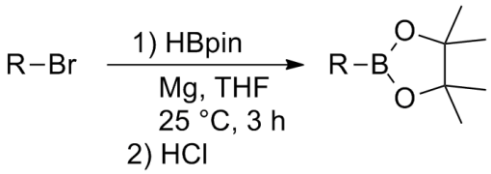
Scheme 2.12 Reaction of *p*-tolylmagnesium bromide with HBpin

With a representative example in hand demonstrating the success of this reaction, a series of alkyl- and arylpinacolboronate esters were formed from commercially available Grignard reagents (Scheme 2.13). To a rapidly stirred solution of HBpin in THF at 25 °C, Grignard reagents were added dropwise. The reaction was left to stir for 1 hour; ^{11}B NMR showed the complete disappearance of the doublet corresponding to HBpin (δ +28, J = 174 Hz) and appearance of a singlet corresponding to the boronate ester (~ δ +30). The reaction was then quenched by the addition of dilute HCl (1 M) and allowed to stir for 15 minutes before extraction with diethyl ether provided the boronate ester product. While 1 hour was required for arylmagnesium bromide nucleophiles, the alkylmagnesium bromides only required 30 minutes of reaction time for completion. While simple, the use of Grignard reagents significantly limits the number of compatible functional groups.



Scheme 2.13 General reaction of pre-formed Grignard reagents with HBpin

A similar process was believed possible via the in situ generation of Grignard reagents. The Barbier reaction is historically used with organometallic nucleophiles adding to carbonyl groups. The key distinction is the in situ generation of the organometallic reagent in the presence of the electrophile; no reaction takes place between the precursor alkyl halide and carbonyl electrophile. In contrast, the Grignard reaction is typically characterized as a two-pot method where the Grignard nucleophile is prepared separately before transfer to the electrophile. Postulating the addition of Grignard reagents to HBpin could be performed under Barbier conditions, a solution was prepared containing magnesium turning, HBpin, and organohalide in a 1.2:1:1 stoichiometric ratio. As expected, the reaction proceeded smoothly at 25 °C over 3 hours (Scheme 2.14). The slow disappearance of the solid Mg was a visual indicator of the reaction proceeding. Repeating the procedure without Mg turnings showed no reaction between HBpin and the aryl halide via ^{11}B NMR. Similar to the pre-formed Grignard reagents, these reactions under Barbier conditions were quenched with the addition of 1 M HCl and allowed to stir before liquid-liquid extraction with diethyl ether.

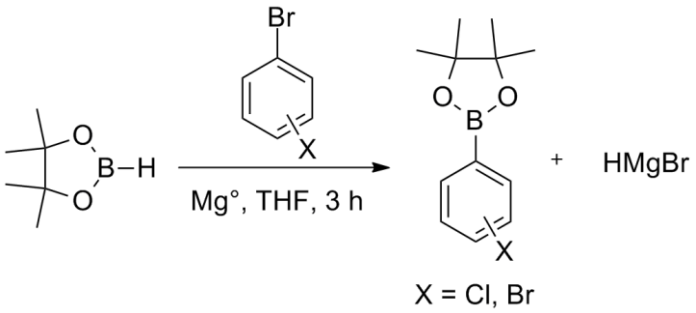


Scheme 2.14 General reaction of Grignard reagents with HBpin under Barbier conditions

2.2.5 Results in the Synthesis of Boronic Esters Utilizing Haloaryl Grignard Reagents Formed Under Barbier Conditions

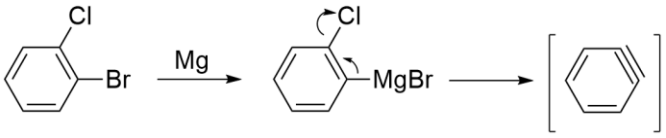
While the initial demonstration of this methodology was successful, the resulting alkyl and arylboronate esters produced were of limited use beyond a single application. For example a Suzuki coupling reaction would simply replace the boronate ester with an unreactive C-C bond. Singaram sought to demonstrate this procedure could be successfully used to synthesize mono- or dichloroarylpinacolboronate esters as a route towards multiple useful synthetic intermediates. While arylbromides and iodides are commonly used in the preparation of Grignard reagents, chlorides are often more difficult to convert, allowing the selective formation of chloroarylmagnesium bromide reagents and subsequent reaction with HBpin.

Similar to the previous methodology, *p*-bromochlorobenzene was added to a solution of HBpin in THF and magnesium turnings (Scheme 2.15). After 3 hours of stirring at 25 °C, no Mg was visible in the reaction mixture and a ^{11}B NMR analysis showed the complete disappearance of the doublet corresponding to HBpin (δ +28, J = 174 Hz). Instead, only the singlet representing the chloroarylboronate ester was visible (δ +31), indicating that only monoaddition was occurring.



Scheme 2.15 General reaction of haloaryl Grignard reagents with HBpin under Barbier conditions

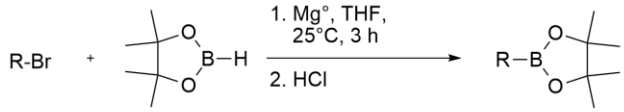
Expanding this same process to *o*-bromochlorobenzene was unsuccessful. Despite the rapid consumption of Mg, both TLC and ^{1}H NMR analysis showed a mixture of several products. Instances exist in the literature of similar complications in the preparation of Grignard reagents from *o*-dihalobenzenes.[122] In those cases, the insertion of Mg into the C-Br bond is immediately followed by elimination of the neighboring halide to form benzyne. It was suspected a similar interaction was occurring in this reaction, leading to a mixture of products upon acidic work-up.

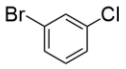
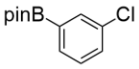
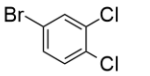
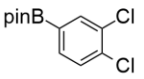
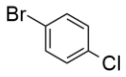
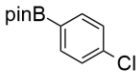
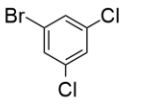
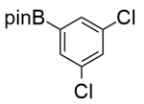
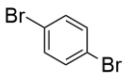
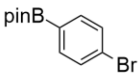
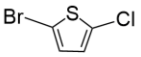
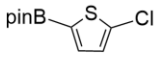
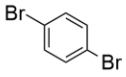
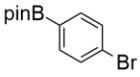
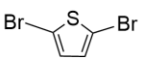
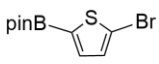
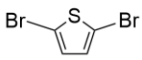
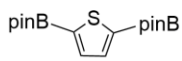


Scheme 2.16 Spontaneous formation of benzyne from 1,2-dihaloaryl compounds upon formation of Grignard

While a selection of substituted bromochloro- and bromodichlorobenzenes were successful, complications arose when the dihalothiophenes were used (Table 2.1).

Table 2.1 Synthesis of halo- and dihaloarylboronate esters under Barbier conditions[a]

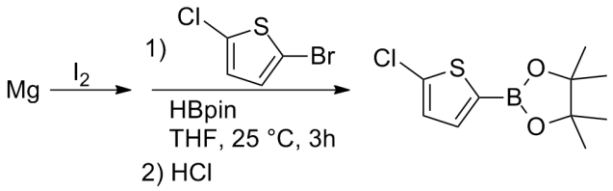


Haloaryl-Br	Product	yield [%]	Haloaryl-Br	Product	yield [%]
		73			81
		72			94
		89[b]			57[c]
		93			76[b,c]
					91[c]

[a]Reaction Conditions: HBpin (2.0 mmol), anhydrous THF (8 mL), Mg turnings (2.0 mmol), haloaryl substrate (2.0 mmol), argon, 25 °C, 1 h. [b]An excess of haloaryl substrate (3 eq) was used. [c]I_2 was added to the reaction vessel containing only Mg turnings and heated with a vent to activate the Mg and remove excess iodine.

Attempts to use this methodology for two heterocyclic substrates, 2-bromo-5-chlorothiophene and 2,5-dibromothiophene, were unsuccessful. The formation of the thiophene Grignard did not proceed after 24 h of stirring as evidenced by the Mg turnings still being present. To try to improve the reactivity, evaporated iodine was used to activate the magnesium turnings before addition of the remaining reagents.

This method has been widely used in cases where Mg insertion into C-X bonds is sluggish. The I_2 is believed to react with the Mg metal where the unreactive MgO film is thin or missing, producing MgI^+ that becomes solvated, and exposing fresh Mg surface for further Grignard formation.



Scheme 2.17 Preparation of thiophene Grignard reagents via I_2 activation of Mg

With this modification to the procedure, the thiophene substrates readily reacted with the activated Mg turnings to form the Grignard reagent and, subsequently, with HBpin. To note, in the cases containing two Br groups where mono-addition was desired, it required a three-fold excess of the haloaryl substrate due to the tendency for the haloaryl pinacolboronate products to form another Grignard reagent and react with HBpin a second time.

2.3 Preparation of Boronic Acids from Aminoboranes

Aminoboranes have been previously studied in material sciences as a route to boron nitride-based ceramics[123] as well as promising materials in the growing field of hydrogen storage.[124] They have also seen use as reducing agents[125] and synthetic intermediates.[126] Because of their propensity for polymerization, aminoboranes have also been investigated as monomer units for the construction of inorganic

polymers.[127] This readiness for dimer- and oligomerization, however, often leads to reduced reactivity and limited synthetic usefulness, leaving them ignored in the realm of synthetic organic chemistry.

2.3.1 Properties of Aminoboranes

Compounds containing a boron-nitrogen interaction possess unique properties not seen with boron-carbon or boron-oxygen species. B-N compounds contain a dative bond between the lone pair of the nitrogen and the open orbital of the boron and are referred to as amine-boranes ($R_2NH{:}BH_3$). Some examples include ammonia-trifluoroborane, $H_3N{:}BF_3$, and trimethylamine-borane, $Me_3N{:}BH_3$. This Lewis acid/Lewis base interaction causes the boron atom to display sp^3-like hybridization and a tetrahedral geometry. Analogous boron species with a labile Lewis base include borane-tetrahydrofuran (BH_3:THF) with a dative B-O bond and borane-dimethylsulfide ($BH_3{:}SMe_2$), with a B-S dative bond. In contrast, aminoboranes possess a formal sigma bond between boron and nitrogen with the nitrogen retaining a lone pair and boron possessing an open *p*-orbital (Figure 2.6).

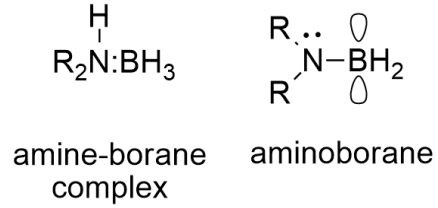


Figure 2.6 General structures for amine-borane and aminoborane

This interaction leads to unique properties for aminoboranes. Because of the neighboring lone pair/open orbital, it is suggested that aminoboranes exhibit pseudo double bond characteristics and an sp^2 hybridization with restricted rotation around the B-N double bond (Figure 2.7). To confirm this, a ^1H NMR study was performed to examine the restricted rotation of a non-symmetric aminoborane, in this case (methylphenylamino)dimethylborane.[128] The NMR analysis showed that both methyl groups of the boron existed in different magnetic environments relative to the methyl and phenyl substituents of the amino group.

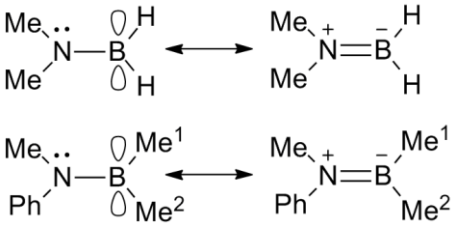


Figure 2.7 Double bond characteristics of aminoboranes

A detrimental result of the lone pair/open orbital structure of aminoboranes is their propensity to coordinate with one another and form complexes. For example, dihydridoaminoborane is relatively unreactive, stemming from the fact that it exists as a dimeric structure with intermolecular B-N bonding between two monomers (Figure 2.8).[129]

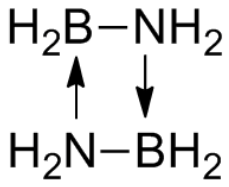


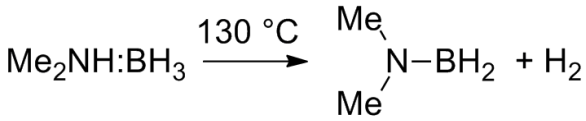
Figure 2.8 Dimerization of small aminoboranes

These coordinated species are easily identified by ^{11}B NMR spectroscopy. When in their monomeric forms, aminoboranes appear as a triplet at approximately δ +36 ppm with a splitting of 127 Hz. However, when coordinated with nitrogen in the dimeric form, the boron triplet shifts upfield to approximately δ +11 ppm, following the trend of tetracoordinate boron atoms. The splitting also tightens to 111 Hz. By integrating the peaks, a rough estimate of monomer to dimer ratio can be obtained.

This phenomenon is also seen with short chained dialkylaminoboranes, with dimethylaminoborane existing entirely in its dimeric form. Both diethyl- and di-*n*-propylaminoborane also exist as mixtures of monomers and dimers in ratios 40:60 and 20:80 respectively. Interestingly, di*iso*propylaminoborane purely exists in monomeric form, demonstrating that steric hindrance from the amino group can prevent the intermolecular coordination with a separate boron atom. This steric environment around the nitrogen is the key factor in determining the ratio of monomer to dimer. With larger carbon substituents that display somewhat restricted rotations, such as the nitrogen containing rings of pyrrolidino- or morpholinoborane,the steric bulk is not sufficient to prevent coordination and these tend to exists purely in dimeric form.

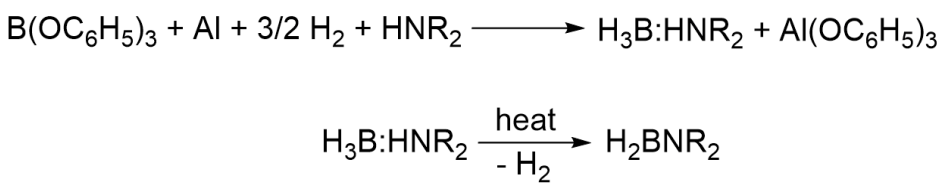
2.3.2 Synthesis of Aminoboranes

One method for preparing aminoboranes, R_2NBH_2, is the thermally-induced elimination of H_2 from an amine-borane complex, $R_2NH{:}BH_3$(Scheme 2.18).[130] The amine-borane complex can be formed by reacting diborane with the corresponding secondary amine. This same method can be used with monoalkylamine-boranes to liberate two equivalents of H_2 and form the corresponding borazine. Another commonly used method for preparing aminoboranes involves the reaction of a metal borohydride, such as $NaBH_4$, with a dialkylammonium chloride salt.



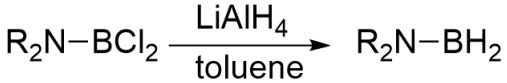
Scheme 2.18 Thermal decomposition of amine-borane to aminoborane

More recently, systems involving aluminum hydride reductions have been used as inexpensive and efficient alternatives to preparing aminoboranes (Scheme 2.19).[131] Ashby reported that aluminum and hydrogen reduced phenylborate in the presence of tertiary amines to give the corresponding amine-borane in quantitative yields. The strength in this method was the high solubility of the amine-boranes in contrast to the insoluble aluminum phenoxide byproduct, making isolation as simple as filtration. Again, the aminoborane was then obtained after thermal decomposition of the collected amine-borane.



Scheme 2.19 Preparation of amine-borane from aluminum and hydrogen

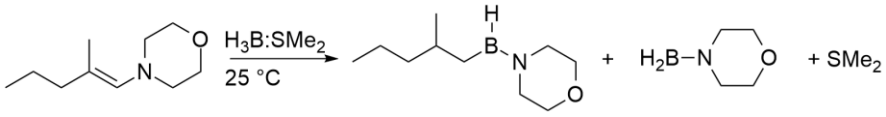
Similarly, dialkylaminoboranes can be prepared from aminodihaloboranes via reduction by lithium aluminum hydride ($LiAlH_4$) (Scheme 2.20).[132] The aminodihaloborane is prepared by stirring BCl_3 with the corresponding amine. Unfortunately, the success of this method is highly dependent on the steric bulk of the amino substituents. When the substituents of the aminodihaloborane are small, as in (dimethylamino)dihaloborane, a mixture of different products is formed alongside the desired monomeric aminoborane. When bulkier substituents are used, as in (diisopropylamino)dihaloborane, the aminoboranes monomer is produced in high yields with excellent conversion.



Scheme 2.20 General synthesis of an aminoborane from reduction of an aminodihaloborane

During their exploration into the hydroboration of *β,β*-disubstituted enamines with BH_3:SMe_2, Singaram reported the production of a morpholinoborane byproduct (Scheme 2.21). Efforts were focused on preparation of several different aminoboranes and a new method for their synthesis was reported. First, an amine-

borane complex was treated with either *n*-butyl- or methyllithium to afford the corresponding lithium aminoborohydride (LAB) reagent in quantitative yields. Then, methyl iodide was added at 0 °C to quench the borohydride and produce methane, leaving behind in solution only the aminoborane and LiI. This method has been since optimized, with TMSCl utilized as an alternative quencher to avoid the vigorous expulsion of methane gas.

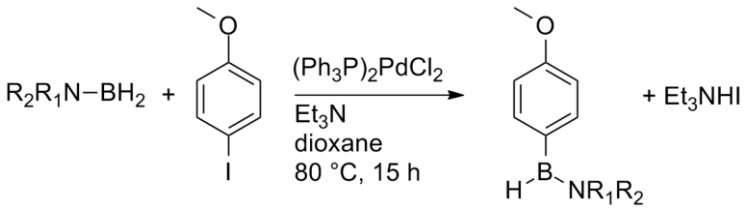


Scheme 2.21 Hydroboration of a *β,β*-disubstituted enamine with $H_3B{:}SMe_2$

Unfortunately, aminoborane dimers have been shown to be unreactive as hydroborating agents and inert in reduction processes. While this severely limits the use of aminoboranes due to their propensity for dimerization, diisopropylaminoborane (H_2B-N(*i*Pr)$_2$) has stood out as a particularly popular reagent in the study of aminoborane chemistry. In 2003, Vaultier reported the first use of monomeric dialkylaminoboranes as a boron source in the Pd catalyzed borylation of aryl halides, with H_2B-N(*i*Pr)$_2$ providing excellent results.[38]

The potential for dialkylaminoboranes to react in a Pd-catalyzed coupling reaction was examined. Various substituted aminoboranes were stirred with *p*-iodoanisole at 80 °C for 15 hours in the presence of a catalytic amount of $(Ph_3P)_2PdCl_2$ (Scheme 2.22). For the base, as required with Pd-catalyzed borylation reactions, Et_3N was used. As expected, the resulting yield of aryl(dialkylamino)-

monohydridoborane was entirely dependent on the steric bulk of the amino substituent in the originating aminoborane. With H_2B-N(iPr)$_2$, the yield of borylation product was nearly quantitative, while the more crowded di(2,2,6,6-tetramethylpiperidino)borane produced only 51% of the borylated product.

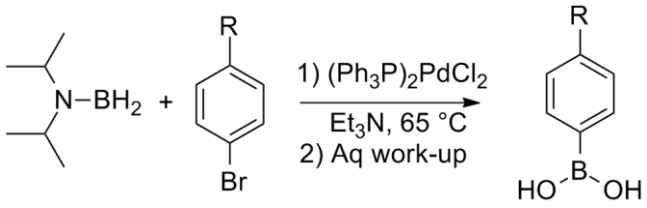


Scheme 2.22 General methodology of the Vaultier borylation

It has been shown previously that the aryldi*iso*propylaminoborane produced from this borylation method can be converted simply to the corresponding boronic acid through an aqueous quench.[133] On treatment with water, ^{11}B NMR analysis of the products shows only the presence of an arylboronic acid singlet (δ +30) and an amine-borane complex quartet (δ -20). Any peaks correlating to arylaminoboranes are absent. The two products are then easily separated via simple extraction. The aryldi*iso*propylaminoboranes can be directly converted to the arylboronic ester upon treatment with an alcohol or diol.

Singaram applied his method of in situ aminoborane preparation from the corresponding LAB reagent to Vaultier's borylation method in the aim of synthesizing boronic acids, rather than producing the aminoborane reactants through thermal decomposition (Scheme 2.23).[39] Singaram was indeed successful in

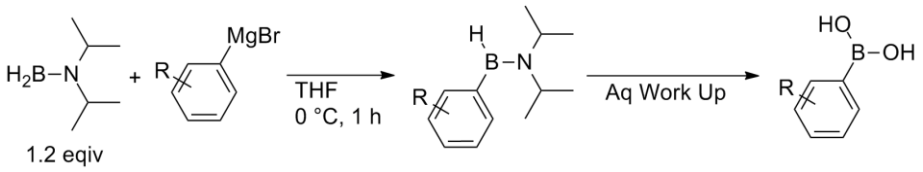
producing the aryl(dialkylamino)-monohydridoborane from in situ generated aminoboranes. These products were not isolated, but instead were treated to an aqueous work-up procedure to convert the aryl(dialkylamino)-monohydridoboranes to arylboronic acids in good yields.



Scheme 2.23 Singaram modification to the Vaultier borylation for the synthesis of boronic acids

2.3.3 Synthesis of Boronic Acids from Aminoboranes and Grignards Formed Under Barbier Conditions

As previously mentioned with pinacolborane, there have been no studies addressing the reaction of various organometallic reagents directly with aminoboranes, namely $H_2B\text{-}N(i\text{Pr})_2$. While it has been shown that aryldi*iso*propylaminoborane can be easily converted to either arylboronic acid or ester depending on the work-up conditions, arylaminoboranes have only been synthesized via Pd-catalyzed Vaultier borylation. After success in treating Grignards with HBpin, Singaram sought to apply this same methodology to a different boron source, $H_2B\text{-}N(i\text{Pr})_2$, to obtain arylboronic acids directly (Scheme 2.24).



Scheme 2.24 Preparation of boronic acids via Grignard reagents and aminoboranes

Several different organometallic reagents were studied as compatible nucleophiles with H_2B-N(*i*Pr)$_2$. First, H_2B-N(*i*Pr)$_2$ was prepared from the reaction of lithium di*iso*propylaminoborohydride and TMSCl at 25 °C. This reaction was quantitative; ^{11}B NMR (δ +35, t, J = 125 Hz) showed the product only in monomeric form. Upon addition of phenylzinc bromide to H_2B-N(*i*Pr)$_2$, no reaction was observed. Organolithium reagents were then explored, with *n*BuLi stirred with H_2B-N(*i*Pr)$_2$ at both 0 and -78 °C. In both cases, the ^{11}B NMR indicated numerous products had formed, stemming from the strong alkyllithium nucleophile undergoing multiple additions. Even at -78 °C, multiple additions occurred.

Grignard reagents were the investigated as they are slightly less reactive than alkyllithiums while significantly more reactive than organozinc reagents. The addition of one equivalent of *p*-tolylmagnesium bromide with H_2B-N(*i*Pr)$_2$ at 0 °C in THF was monitored via ^{11}B NMR. After 30 minutes, H_2B-N(*i*Pr)$_2$ was no longer visible while three new species had formed: the monoaddition product tolyl(di*iso*propylamino)borane (δ +35, d, J = 111 Hz), a small amount of bromomagnesium tolyl(di*iso*propylamino)borohydride (δ -12, t, J = 78 Hz), and bromomagnesium aminoborohydride (BrMgH_3BN(*i*Pr)$_2$, δ -22, q, J = 88 Hz).

The mechanism for this reaction pathway is postulated to be similar to that seen in the case of Grignard and HBpin (Figure 2.9). Initially, the tolyl Grignard reagent undergoes nucleophilic addition to $H_2B\text{-}N(i\text{Pr})_2$ to form a negatively charged "ate" complex. Then, the "ate" complex can proceed through one of two possible pathways of disproportionation. Either the hydride can be transferred to the magnesium bromide counter ion to produce HMgBr or a hydride can be transferred to a second equivalent of $H_2B\text{-}N(i\text{Pr})_2$ to give $MgH_3B\text{-}N(i\text{Pr})_2$. As the reaction only requires 1.2 equivalents of $H_2B\text{-}N(i\text{Pr})_2$ for yields greater than 95%, the second pathway requiring 2 equivalents of $H_2B\text{-}N(i\text{Pr})_2$ is discounted as the sole pathway. While no final conclusion was ever reached on the exact mechanistic pathway, it is hypothesized that instead these pathways proceed somewhat in tandem with one another.

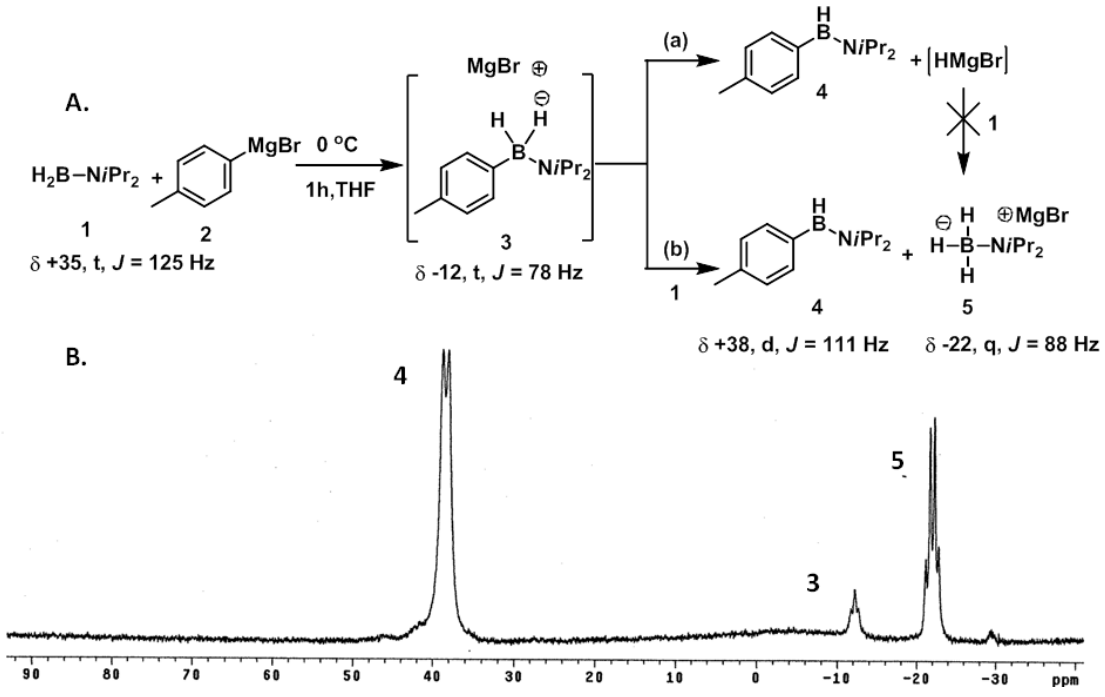


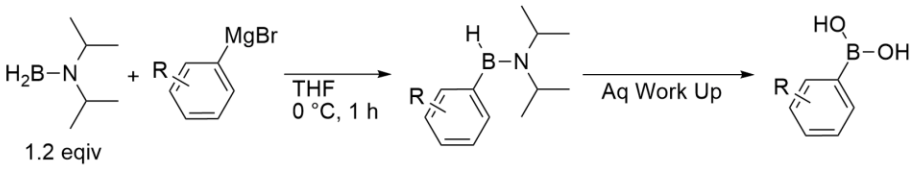
Figure 2.9 A. Proposed reaction pathways; B. ^{11}B NMR spectrum of reaction mixture. Reaction conditions: *p*-tolylmagnesiuim bromide (1 M/THF, 2.0 mmol) added to H_2B-N(*i*Pr)$_2$ (1 M, 2.0 mmol) under argon at 0 °C, 30 min

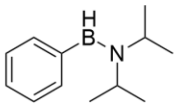
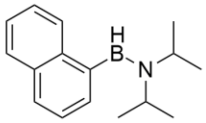
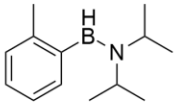
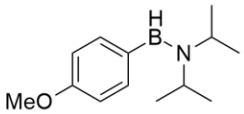
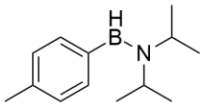
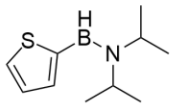
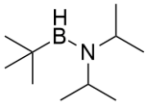
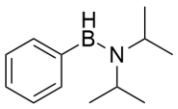
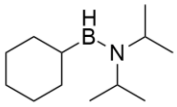
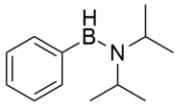
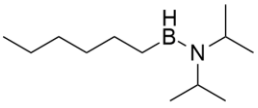
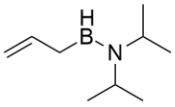
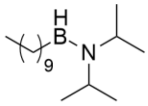
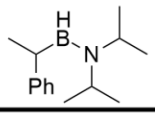
Singaram previously showed that aryl(di*iso*propylamino)boranes can be converted to either boronic acid (with acidic work-up) or boronic ester (with addition of an alcohol or diol). In this case, an ^{11}B NMR analysis of the products after a short HCl work-up is consistent with previous observations: the aryl(diisopropylamino)borane and aminoborohydride species is replaced by a singlet (δ +30) corresponding to the desired arylboronic acid and a smaller quartet (δ -20, *J* =

98 Hz) for the di*iso*propylamine-borane complex. A simple ether extraction is then sufficient for isolating the boronic acid.

With confirmation in hand that Grignards successfully react with $H_2B\text{-}N(i\text{Pr})_2$ and the corresponding organo(diisopropylamino)borane species can be converted into the boronic acid, Singaram sought to utilize this methodology to synthesize a range of boronic acids from pre-formed commercially available Grignard reagents as well as Grignards formed from aryl bromides under Barbier conditions (Table 2.2). Pre-formed Grignard reagents were added dropwise to $H_2B\text{-}N(i\text{Pr})_2$ and stirred at 0 °C for 1 hour. In one instance, a ^{11}B NMR analysis of the reaction with phenylmagnesium bromide at -45 °C showed full conversion after only 30 minutes of reaction time. The same reaction with Grignard reacted at -78 °C, however, was unsuccessful due to the solution freezing and preventing stirring, possibly due to a precipitate seizing the stir bar.

Table 2.2 Synthesis of boronic acids using pre-formed Grignard reagents[a] and under Barbier conditions[b]



Substrate	yield[c] (%)	Substrate	yield[c] (%)
	95		79[b]
	88		67[b]
	95		74[b]
	94		90[d,e]
	97		95[e,f]
	78		< 50[b,g]
	95		< 50[b,g]

[a]Reagents and conditions: BH_2-N(iPr)$_2$ (1 M, 2.4 mmol), Grignard reagent (1 M, 2.0 mmol), Ar, 0 °C, 1 h; [b]Barbier conditions: Mg° (2.0 mmol), BH_2-N(iPr)$_2$ (1 M/THF, 2.4 mmol), anhydrous THF (4.0 mL), organohalide (2.0 mmol), argon, 65 °C, 2-3 h; [c]Isolated yield of boronic acid after aqueous workup; [d]reaction temp. -45 °C; [e]crude yield [f]reaction temp.-78 °C; [g]Conversion based on ^{11}B NMR.

For the reaction under Barbier-type conditions, a selection of aryl bromides was added to a 1 M solution of H_2B-N(iPr)$_2$ in THF. Magnesium turnings were also added to the solution before being refluxed at 65 °C. The progress of the reaction was indicated by the gradual disappearance of Mg turnings. After 3 hours, a ^{11}B NMR indicated all of the starting material had been converted. The reaction mixture was then cooled before being quenched with 3 M HCl to liberate the arylboronic acid, which was collected via ether extraction. While successful for a number of aryl halides bearing various functional groups, both α-bromostyrene and 9-bromoanthracene were incompatible with the Barbier-type conditions. Interestingly, allyl and benzyl halides under Barbier conditions reacted quite rapidly in comparison to other aryl bromides. Upon analysis by ^{11}B NMR, however, it was clear that the increased rate of Mg consumption was related to homocoupling and reduction of the reactive allyl and benzyl bromides as indicated by the presence of a 1:1 mixture corresponding to B-allyl(diisopropylamino)borane and unreacted H_2B-N(iPr)$_2$.

The success of the reaction under Barbier conditions provides a much simpler route to the same products as the pre-formed Grignard reagents. For one, handling pyrophoric Grignard reagents in a flammable solvent can be avoided entirely, as often the aryl halides are solids at room temperature and air stable. In addition, the reaction is more convenient in that all reagents can be added from the beginning, avoiding the need for stepwise addition of reagents.

2.4 Conclusion

In conclusion, Grignard reagents have been shown as mild, efficient, and inexpensive routes towards the synthesis of boronic acids and esters in new methodologies when paired with previously unused boron sources. Historically, boronic acids and esters have been obtained via the reaction of organometallic nucleophiles, such as Grignards or organolithiums, with trialkoxyboranes. While useful, these methodologies tend to give a mixture of products from over-addition of the nucleophile. Several modifications have been reported to reduce this occurrence, however none have proved completely successful in the preparation of monoaddition boronic acids and esters.

Now, commercially available Grignard reagents added to a solution of HBpin in THF at 25 °C provides high yields of only the monoaddition boronate ester product with high atom economy. The work-up and isolation is simple, requiring only a short stir in dilute HCl before extraction via diethyl ether to provide the desired boronate esters. This same methodology has also been demonstrated successful in systems under Barbier conditions, allowing for simple one-pot routes towards boronate esters. The stability of the pinacolboronate ester prevents the over-addition of reactive Grignard reagents even at 25 °C with short reaction times of 1 to 3 hours.

The formation of boronic acids has also been demonstrated, with Grignard reagents formed from the corresponding alkyl and aryl halides under Barbier conditions. By introducing $H_2B\text{-}N(i\text{Pr})_2$ as the boron source, the addition of the

Grignard reagent produces an aryl(diisopropylamino)borane, which is cleanly converted to the arylboronic acid after acidic quench and extraction with diethyl ether. These new methods reported herein offer alternative routes to both boronic acids and esters in quantitative amounts while utilizing inexpensive reagents, ambient conditions, and flexibility without the need for a large excess of borane reagents, avoiding over-addition.

2.5 Experimental

General Methods. All reactions were performed in oven-dried, argon-cooled glassware. The HBpin was used as received from Aldrich and stored under Ar in a refrigerator held at 15 °C. All halide-containing substrates were used as received from Aldrich. Magnesium metal was used as received from Aldrich. Iodine was used as received from Aldrich. All air- and moisture-sensitive compounds were introduced via syringes or cannula through a rubber septum. HBpin was added via syringe, with the dispensed amount measured by mass difference of the syringe before and after addition. Tetrahydrofuran (THF) was freshly obtained by a solvent purification system (Pure Solv MD, Innovative Technology Inc.). NMR spectra were recorded in $CDCl_3$. Chemical shifts are reported relative to TMS (δ 0) for ^{1}H NMR (500 MHz) and is referenced to the $CDCl_3$ resonance (δ 77) for ^{13}C NMR (125 MHz) spectra. Data is reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, br =broad, m = multiplet, app = apparent), coupling constant, and integration. Boron NMR samples were recorded at 160.4 MHz and are

reported relative to the external standard $BF_3 \cdot Et_2O$ (δ 0). High-resolution mass spectra were obtained by electrospray ionization experiments.

General Procedure for the Preparation of B-Haloaryl Pinacolboronic Esters under Barbier-Type Conditions. The following procedure is representative. A 25 mL round-bottom flask equipped with a magnetic stir bar was charged with Mg turnings (0.048 g, 2.0 mmol) and fitted with a rubber septum. The flask was cooled to 25 °C and was purged with Ar. Anhydrous THF (4 mL) was added to the flask, followed by the addition of neat pinacolborane (0.29 mL, 2.0 mmol). The neat halide substrate (2.0 mmol) was then added dropwise over 5 min with constant stirring at 25 °C. The reaction was complete after 3 h, as evidenced by the disappearance of pinacolborane starting material (δ +27.7, d, J = 173.9 Hz) and the appearance of a singlet at +30.6 ppm via ^{11}B NMR. The reaction mixture was then cooled to 0 °C and acidified with 1 M HCl (3 mL) (*Caution! Hydrogen evolution*). After 10 min of stirring the reaction mixture was warmed to 25 °C and stirred for an additional 30 min. The reaction mixture was then transferred to a separatory funnel and extracted with diethyl ether (3 x 15 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and dried in vacuo, (25 °C, 1 Torr) to afford the corresponding pinacolboronate ester as an oil.

For solid substrates, the substrate was first added to an oven-dried, Ar charged sealed vial and dissolved in THF (1 mL). The resulting halide-THF solution was transferred dropwise to the flask containing Mg and HBpin via syringe.

For the dihalothiophene substrates, the Mg was activated prior to the introduction of THF by first adding I_2 crystals and warming until the I_2 sublimed and allowing the excess I_2 to vent out of the flask.

2-(3-Chlorophenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane Colorless oil; 73% yield (0.598 g). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.79 (s, 1H), 7.69 (d, *J* = 7 Hz, 1H),7.44 (d, *J* = 8 Hz, 1H), 7.32 (t, *J* = 7.5, 1H), 1.35 (s, 12H). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ 134.6, 132.7, 131.3, 129.2, 84.2, 24.8. ^{11}B NMR (160.4 MHz, $CDCl_3$): δ +31 (s).

2-(4-Chlorophenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane Colorless oil; 72% yield (0.373 g). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.76 (d, *J* = 8.5 Hz, 2H), 7.36 (d, *J* = 8.5 Hz, 2H), 1.35 (s, 12H). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ 137.5, 136.1, 128.1, 127.9, 83.9, 24.8. ^{11}B NMR (160.4 MHz, $CDCl_3$): δ +31 (s).

2-(4-Bromophenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane White solid; 89% yield (0.505 g). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.69 (d, *J* = 8 Hz, 2H), 7.53 (d, *J* = 8 Hz, 2H), 1.35 (s, 12H). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ 136.3, 133.2, 131.0, 126.3, 84.0, 24.9. ^{11}B NMR (160.4 MHz, $CDCl_3$): δ +32 (s).

1,4-Bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzene White solid; 93% yield (0.612 g). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.82 (s, 4H), 1.36 (s, 24H). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ 133.9, 83.9, 24.9. ^{11}B NMR (160.4 MHz, $CDCl_3$): δ +32 (s).

2-(3,4-Dichlorophenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane Yellow oil; 81% (0.442g). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.87 (s, 1H), 7.61 (d, *J* = 8 Hz, 1H), 7.45 (d, *J* = 8 Hz, 1H), 1.35 (s, 12H). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ 136.6, 135.5, 133.8, 132.3, 130.0, 84.4, 24.8, ^{11}B NMR (160.4 MHz, $CDCl_3$): δ +32 (s).

2-(3,5-Dichlorophenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane Yellow oil; 94% (0.513g). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.66 (d, *J* = 2 Hz, 2H), 7.44 (t, *J* = 2.5 Hz, 1H), 1.35 (s, 12H). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ 134.7, 135.5, 132.7, 132.4, 131.0, 84.5, 24.8, ^{11}B NMR (160.4 MHz, $CDCl_3$): δ +31 (s).

2-(5-Chloro-2-thienyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane Yellow oil; 57% (0.279g). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.41 (d, *J* = 4 Hz, 1H), 6.98 (d, *J* = 4 Hz, 1H), 1.34 (s, 12H). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ 136.8, 127.6, 84.3, 24.7. ^{11}B NMR (160.4 MHz, $CDCl_3$): δ +30 (s).

2-(5-Bromo-2-thienyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane Yellow oil; 76% (0.439g). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.38 (d, *J* = 3.5 Hz, 1H), 7.12 (d, *J* = 3.5 Hz, 1H), 1.34 (s, 12H). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ 137.6, 131.3, 84.3, 24.7. ^{11}B NMR (160.4 MHz, $CDCl_3$): δ +29 (s).

2,5-Bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)thiophene Yellow oil; 91% (0.612g). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.67 (s, 2H), 1.35 (s, 24H). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ 137.7, 84.1, 24.8. ^{11}B NMR (160.4 MHz, $CDCl_3$): δ +30 (s).

Synthesis of Diisopropylaminoborane from LAB and TMS-Cl. Diisopropylamine (3.51 mL, 25 mmol) was mixed with anhydrous THF (20.8 mL) in a 100-mL round-bottom flask. The solution was cooled to 0 °C (ice bath) and boranedimethylsulfide (2.5 mL, 10M solution in THF, 25 mmol) was added dropwise over 3 min via syringe. After stirring for 1 h at 0 °C *n*-butyl lithium (10 mL, 2.5 M solution in toluene, 25 mmol) was added dropwise over 5 min via syringe. After 1 hour of stirring at 0 °C a 0.5 mL aliquot was analyzed via ^{11}B NMR, which showed the solution to be lithium diisopropylaminoborohydride (δ -23.8, q, J = 84 Hz). The solution was then allowed to warm to 25 °C and subsequently trimethylsilyl chloride (3.20 mL, 25 mmol) was added dropwise over 5 min via syringe while stirring at room temp. After 1 h of stirring at room temperature a 0.5 mL aliquot was taken and analyzed via ^{11}B NMR, which showed the solution to be monomeric diisopropylaminoborane (δ +35.1, t, J = 125 Hz).

General Procedure for the Preparation of Arylboronic Acids Under Barbier-type Conditions. The following procedure for the preparation of 1-napthylboronic acid is representative. A 25-mL round-bottom flask equipped with a condenser and magnetic stir bar was charged with magnesium turnings (0.058 g, 2.4 mmol) and was activated by addition of iodine crystals and warming until iodine sublimed. The flask was cooled to 25 °C and was purged with argon. H_2B-N(iPr)$_2$ (2.4 mL, 2.4 mmol) was added to the flask and brought to reflux. 1-Bromonapthalene (1.33 mL, 2.0 mmol) was then added dropwise over five minutes with constant stirring at 65°C. The reaction was complete after 4 h as evidenced by the

disappearance of BH_2-N(*i*Pr)$_2$ starting material (δ +35, t, *J* = 125 Hz), and the appearance of a doublet at (δ 38, d, *J*=112 Hz) with the corresponding bromomagnesium aminoborohydride signal ($MgBr^{+}$-BH_3-N*i*Pr$_2$, δ -28, q, *J* = 88 Hz). The reaction was then cooled to 25 °C and acidified with 3M HCl (3mL) (CAUTION: *hydrogen evolution*). After 10 min of stirring the reaction mixture was warmed to 65 °C and stirred for an additional 15 min. The reaction mixture was then transferred to a separatory funnel and extracted with diethyl ether (3 x 15 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo* (25 °C, 1 Torr) to afford 1-napthylboronic acid as a white solid.

Phenylboronic acid White powder; 95% (0.234 g). ^{1}H NMR (500 MHz, $CDCl_3$): δ7.52 (t, *J* = 6 Hz, 2H), 7.61 (t, *J* = 7 Hz, 1H), 8.26 (d, *J* = 5.5 Hz, 2H)**;** ^{13}C NMR (125.7 MHz, $CDCl_3$): δ 128.0, 132.7, 135.7; ^{11}B NMR (160.4 MHz, $CDCl_3$): δ +30.7.

***o*-Tolylboronic acid** White powder; 88% (0.226 g). ^{1}H NMR (500 MHz, $CDCl_3$): δ2.82, 7.27 (m, 2H), 7.459 (dt, *J* = 1.5, 7 Hz, 1H), 8.22 (dd, *J* = 7 Hz, 1H); ^{13}C NMR (125.7 MHz, $CDCl_3$): δ 23.1, 125.3, 130.7, 132.3, 137.4, 146.4; ^{11}B NMR (160.4 MHz, $CDCl_3$): δ +31.9.

***p*-Tolylboronic acid** White powder; 95% (0.345 g). ^{1}H NMR (500 MHz, $CDCl_3$): *δ* 2.44 (s, 3H), 7.32 (d, *J* = 7.5 Hz, 1H), 8.13 (d, *J* = 7.5 Hz, 1H); ^{13}C NMR (125.7 MHz, $CDCl_3$): δ 21.9, 128.9, 133.7, 135.9, 143.1; ^{11}B NMR (160.4 MHz, $CDCl_3$): δ +30.4.

***t*-Butylboronic acid** White powder; 94% (0.481 g). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ 27.8; ^{11}B NMR (160.4 MHz, $CDCl_3$): δ +32.7.

Cyclohexylboronic acid White powder; 97% (0.497 g). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ 27.3, 27.5, 28.3; ^{11}B NMR (160.4 MHz, $CDCl_3$): δ +33.5.

***n*-Hexylboronic acid** White powder; 95% (0.404 g). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ 14.7, 23.4, 24.2, 25.0, 32.5, 32.8; ^{11}B NMR (160.4 MHz, $CDCl_3$): δ +34.4.

***n*-Decylboronic acid** White powder; 95% (0.888 g). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ 14.1, 22.7, 23.4, 24.4, 29.4, 29.5, 29.7, 31.9, 32.4; ^{11}B NMR (160.4 MHz, $CDCl_3$): δ +33.9.

1-Napthylboronic acid White powder; 79% (0.253 g). ^{1}H NMR (500 MHz, DMSO-d_6): δ3.44 (brs, 1H), 7.50 (m, 3H), 7.78 (d, *J* = 5 Hz, 1H), 7.91 (t, *J* = 9.5 Hz, 2H), 8.36 (brs, OH), 8.42 (dd, *J* = 8 Hz, 1 Hz, 1H),**;** ^{13}C NMR (125.7 MHz, DMSO-d_6): δ 128.2, 128.8, 129.1, 132.0, 132.9, 135.7; ^{11}B NMR (160.4 MHz, DMSO-d_6): δ +30.2.

4-Methoxyphenylboronic acid White powder; 67% (0.196 g). ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.89 (s, 3H), 7.03 (d, *J* = 8.5 Hz, 2H),8.17 (d, *J* = 8.5 Hz, 2H)**;** ^{13}C NMR (125.7 MHz, $CDCl_3$): δ 55.3, 113.7, 137.7, 163.4; ^{11}B NMR (160.4 MHz, $CDCl_3$): δ +29.1.

2-Thiopheneboronic acid White powder; 74% (0.221g). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.33 (dd, *J* = 3.5, 4.5 Hz, 1H), 7.83 (d, *J* = 4.5 Hz, 1H),8.06 (d, *J* = 4 Hz, 1H)**;** ^{13}C NMR (125.7 MHz, $CDCl_3$): δ 128.9, 135.1, 139.8; ^{11}B NMR (160.4 MHz, $CDCl_3$): δ +27.0.

Allylboronic acid ^{11}B NMR (160.4 MHz, $CDCl_3$): δ +42.1 (d, *J* = 147 Hz), +36.6 (t, *J* = 129 Hz).

1-Boronic acid ethylbenzene ^{11}B NMR (160.4 MHz, $CDCl_3$): δ +42.1 (d, *J* = 147 Hz, 1H), +36.6 (t, *J* = 123 Hz, 2H).

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CHAPTER 3

Synthesis of Pinacolboronates from Pinacolborane via Organozinc Reagents in Lithium Chloride- and Cobalt Bromide-Mediated Systems

3.1 Introduction

Modern synthesis of complex organic compounds commonly incorporates the reaction of a functionalized carbon electrophile with a carbon nucleophile. Many of these carbon nucleophiles are organometallic reagents, prepared from the corresponding carbon halide, possessing highly reactive carbon-metal bonds. While powerful, these transformations present complications in multi-functional targets, as the strong reactivity of the C-M bond can lead to unwanted reactions between other sensitive functional groups and the carbon nucleophile.

Recently, organozinc compounds have risen to prominence, partly due to their success in metal catalyzed cross-coupling reactions and nucleophilic addition reactions. Organozinc compounds tend to be less reactive than their analogous organomagnesium or organolithium counterparts, a property that led to organozinc reagents losing popularity in the early 20th century.[134] Recently, this reduced reactivity has been instead exploited to provide greater functional group tolerance compared to Grignard or lithium reagents, forcing organic chemists to revise previous opinions.

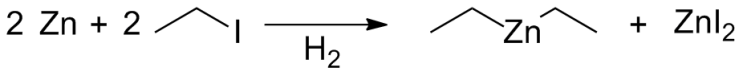
With the earlier success of Grignard reagents reacting with HBpin, one major drawback to that methodology was the lack of functional group tolerance. It was hypothesized that analogous organozinc reagents could undergo similar nucleophilic attack on borane electrophiles while providing the functional group tolerance needed to synthesize more complex and diverse targets. The following chapter describes

efforts to efficiently afford functionalized organozinc reagents and their reactions with borane sources.

3.2 Organozinc Reagents in Organic Synthesis

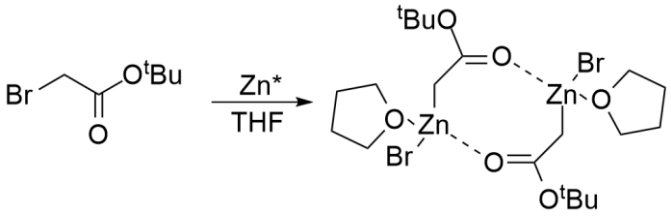
3.2.1 Initial Discovery and the Reformatsky Reaction

Before the discovery of the more reactive organomagnesium compounds in 1900, less reactive organozinc reagents were popular for the formation of carbon-carbon bonds. Both diorganozincs (R_2Zn) and organozinc halides (RZnX) are two of the first main-group organometallic reagents prepared. The first preparation was performed by Frankland in 1849 by heating ethyl iodide with zinc under a protective H_2 atmosphere to yield the highly pyrophoric diethyl zinc (Et_2Zn) (Scheme 3.1).[135,136] His discoveries were followed by extensive studies of the carbon-carbon bond forming capabilities of organozinc reagents with various electrophiles including acid chlorides,[137] aldehydes,[138] ketones,[139] and esters.[140] Despite numerous successful methodologies involving organozinc reagents and carbon electrophiles, they were replaced by the more reactive organomagnesium reagents discovered by Grignard and became unpopular reagents for C-C bond formation.[141]



Scheme 3.1 Preparation of diethylzinc under H_2 atmosphere

One reaction involving organozinc reagents that has remained popular was the synthesis of β-hydroxyesters from α-haloesters and metallic zinc developed by Reformatsky.[142] The Reformatsky reaction has been recognized as one of the most useful methodologies for C-C bond formation. More recently, both diastereoselective processes utilizing chiral auxiliaries[143] as well as enantioselective reactions directed by chiral ligands have been developed.[144] Reformatsky enolates are easily prepared *in situ* by the reaction of an α-halocarbonyl compound with an activated metal (Scheme 3.2). Most commonly Zn is used however examples including Sm,[145] Ti,[146] Cd,[147] In,[148] Rh,[149] and Ni[150] have been reported. More importantly, the location of the halogen substituent dictates where the metal insertion occurs and allows for regioselective enolate formation. As with most organozinc reagents, Reformatsky reagents are less reactive nucleophiles than analogous organolithium or organomagnesium reagents.



Scheme 3.2 Formation of the Reformatsky reagent

The Reformatsky reaction begins with the oxidative addition of Zn into the C-X bond of the α-haloester. The resulting *C*-zinc enolate, also referred to as the Reformatsky enolate, then coordinates to a second enolate molecule to form a dimer. These dimers undergo a rearrangement, both forming the *O*-zinc enolates. These *O*-

zinc enolates coordinate with the electrophile in a Zimmerman-Traxler transition state, such as an aldehyde or ketone, and a rearrangement results in C-C bond formation followed by acidic work-up to liberate the final β-hydroxyester.

The Reformatsky reaction is analogous to the aldol reaction with several advantages including a larger scope of compatible carbonyl electrophiles, more success in intramolecular reactions, and the enolate can be formed under neutral conditions; no acid or base is required to generate the enolate or activate the electrophile, respectively. In the reaction of the O-Zn enolate and a carbonyl electrophile, the two species coordinate to form a six-membered transition state similar to the transition state observed in aldol reactions (Figure 3.1). While demonstrating several advantages over the aldol reaction, it does possess some drawbacks, including difficulty in scaling up procedures and low diastereoselectivites.

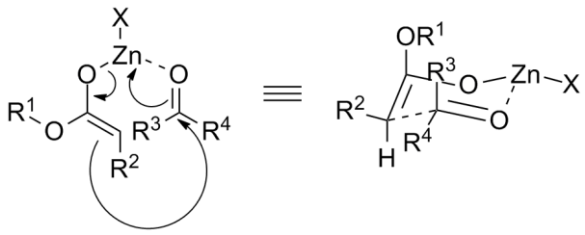
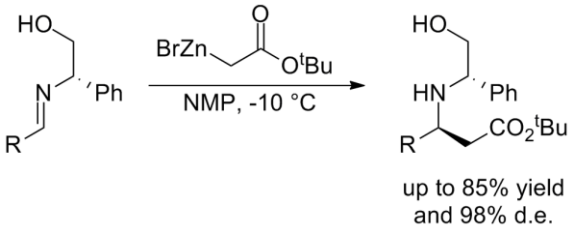


Figure 3.1 Six-membered Zimmerman-Traxler transition state of the Reformatsky reaction

In recent literature, zinc-mediated Reformatsky reactions are commonly used in the synthesis of β-aminoesters. These compounds are useful as intermediates in the

preparation of biologically active molecules. In the synthesis of xemilofiban, a platelet aggregation inhibitor, a Reformatsky-type reaction between an α-bromoester derivative and a chiral imine, derived from (*S*)-phenylglycinol, was successfully scaled up to 700 g (Scheme 3.3).[143]The resulting Reformatsky adduct was obtained in yields up to 85% and 98 % d.e. To prepare the zinc enolate ($BrZnCH_2CO_2tBu$), *t*-butyl bromoacetate was added slowly to activated Zn in refluxing THF. The authors note the solid organozinc reagent can be filtrated and stored at -20 °C for up to 6 months before use.



Scheme 3.3 General asymmetric synthesis of β-amino ester intermediates in the preparation of xemilofiban

3.2.2 Preparation of Organozinc by Direct Insertion

Several methods exist for the preparation of organozinc reagents. Analogous to the formation of Grignard reagents, organozinc reagents can be prepared by direct insertion of zinc into carbon-halogen bonds (Table 3.1).[151,152] Under mild conditions, the insertion of Zn to primary (50 °C) and secondary iodides (25 °C) in THF is rapid. For slow or difficult insertions, the reactivity can be increased by first activating Zn with 4-5 mol% 1,2-dibromoethane and 1 mol% chlorotrimethylsilane (TMSCl) before

addition of the halide substrate.[153,154] For example, the insertion of Zn activated by dibromoethane/TMSCl into butyl iodide is complete in under 3 h at 40 °C. Similarly, the insertion into 2-iodobutane is complete in under 1 hour at room temperature.[154] A wide range of functional groups tolerate this methodology, with only hydroxyl, nitro, or azide functionalities inhibit the formation of the organozinc reagent.[155–163]

Table 3.1 Reaction conditions for the preparation of organozinc halides from the corresponding organic halides and zinc (added as 2.5-3.0 M solution in THF)[154]

organic halide	T (°C)	t (h)
n-BuI	45-50	3-4
c-HexI	25-30	2
$NC(CH_2)_2I$	20	2
$(EtO)_2(O)P(CH_2)_2Br$	30	10
$pinBCH_2I$	20	0.1
$PhSCH_2Cl$	25	1
benzyl bromide	0-5	2
allyl bromide	10	4-5

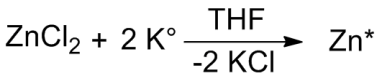
Allylic and benzylic iodides are significantly more reactive, with the reactions occurring as low as 5 °C. Allylic and benzylic bromides and chlorides can also facilitate the insertion of Zn; primary and secondary bromides and chlorides are unreactive towards Zn insertion.[152,155,156] Reactivity can be further enhanced by introducing a polar functional group in either the α- or β-position to the halide in an alkyl chain. For example, the insertion of Zn into butyl iodide in THF requires temperatures above 40 °C. In comparison, when a cyano group is present at the β-position relative to iodide, the insertion is successful at only 25 °C.[164–166]

Interestingly, the introduction of acetonitrile to a solution of 2-iodobutane in THF does not increase the rate of reaction, indicating the enhanced rate does not stem from simple increased solubility of the Zn reagent or activation of the Zn surface. The length of the chain between the polar functional group and iodide also shows a marked difference in reactivity, as the reactivity of secondary iodides with a δ-cyano group shows no appreciable increase in rate in comparison with 2-iodobutane.

Knochel has postulated that the position of the polar group is crucial for enhancing the rate of insertion by accepting an electron from the zinc surface, similar to observations noted by Walborsky in the formation of Grignard reagents.[167] Once the electron has been transferred to the polar group, a second transfer occurs where the electron moves into the σ* orbital of the C-X bond. These successive transfers of an electron occurs between close energy levels, thus increasing the rate of reaction, when compared to the direct electron transfer from the zinc surface to the σ* orbital of the C-X bond. For azide or nitro functionality, where the insertion of Zn does not proceed, the transfer of the electron between Zn and either the NO_2 or N_3 moieties is reversible and does not facilitate further transfer to the σ* orbital of the C-X bond.

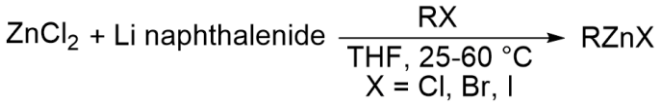
When required, activated Zn can be prepared by the reduction of anhydrous Zn salts.[151] Early versions of this methodology involved stirring potassium metal in a cooled solution of $ZnCl_2$in THF as the reaction is exothermic (Scheme 3.4). This activated Zn, called Rieke zinc, has been used in the rapid and efficient formation of Reformatsky reagents. For example, the controlled addition of ethyl 2-bromoacetate

to Rieke Zn in ether was successful at -5 °C while the corresponding chloroester was successful as low as 10 °C. The subsequent addition to cyclohexanone afforded the β-hydroxyester in near quantitative yields and no side reactions.[168]



Scheme 3.4 Preparation of activated Rieke zinc from Zn and K

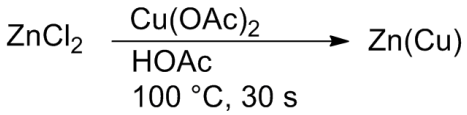
Rieke zinc also provided the first examples of the successful insertion into alkyl and aryl bromides, a process previously successful only with aryl iodides.[169] This success followed a new method for the formation of activated Zn, which produced a species more reactive than Zn prepared by reduction with potassium. Instead, activated Zn was prepared from treatment of $ZnCl_2$ with lithium napthalenide as the reducing agent (Scheme 3.5).[170] It was also discovered that the reduction could be carried out using catalytic quantities of naphthalene.[171] This new methodology provided access to previously difficult to form or unobtainable organozinc bromide and iodide reagents with tolerance for nitrile, ester, ketone, and chloride functionalities.



Scheme 3.5 Preparation of activated Rieke zinc from Zn and Li·naphthalenide

These forms of activated Zn have also seen success in tandem with the use of copper as a Zn-Cu alloy. The Zn-Cu couple is another activated form of Zn metal, with Zn comprising more than 90% of the total alloy, however the exact chemical structure of the alloy has not been defined. While the presence of copper does not appear to cause any additional influence to the reaction beyond simply activating the Zn surface, the ease of preparation, handling, and storage of the Zn-Cu amalgam is greater than that of activated Zn by Rieke's method or TMSCl and 1,2-dibromoethane.

The most commonly used and simple method for preparing Zn-Cu couple is LeGoff's protocol (Scheme 3.6). Zinc dust is added to a rapidly stirred solution of copper(II) acetate in hot acetic acid. After only 30 seconds, the stirring is stopped to allow the solid to settle before decantation. The solid is then rinsed once with acetic acid and three times with ether. The Zn-Cu couple is sensitive to moist air and can be stored under nitrogen for long storage times. Particularly active batches of Zn-Cu couple are also oxygen-sensitive and produce H_2 when in contact with strong acids.



Scheme 3.6 LeGoff's preparation of Zn-Cu couple

The Zn-Cu couple was first introduced by Simmons and Smith in 1959 in their investigation of alkene cyclopropanation. Zn-Cu couple was successful in reducing diiodomethane to produce iodomethylzinc iodide, which is in equilibrium

with both bis(iodomethyl)zinc and zinc iodide.[172] The organozinc carbenoid then reacts with an alkene to form a cyclopropane ring. This reaction is stereospecific, with a methylene intermediate reacting in a concerted fashion with the alkene. While the cyclopropanation typically occurs at the less hindered face, hydroxyl substituents can coordinate to the Zn and induces cyclopropanation *cis* to the hydroxyl group (Figure 3.2).[173]

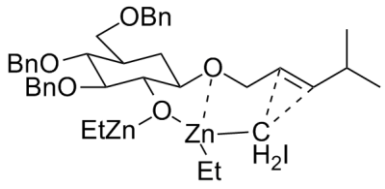
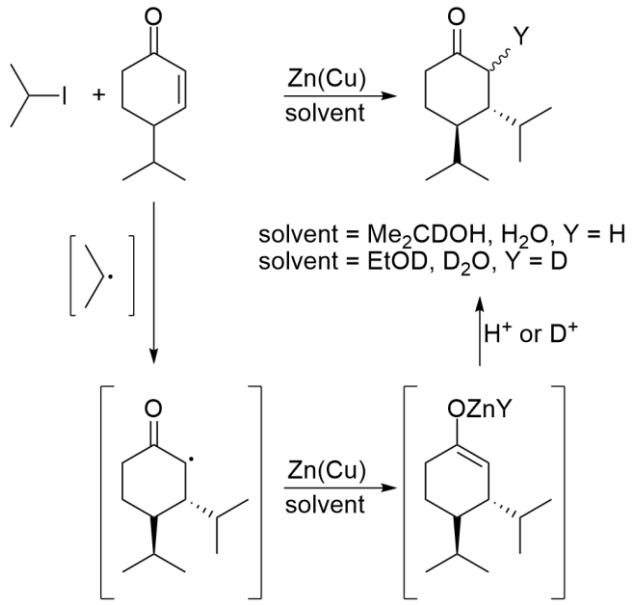


Figure 3.2 Simmons-Smith reaction directed by O-Zn coordination

Another carbon-carbon bond forming reaction involving Zn-Cu couple is the conjugate additions of alkyl iodides to Michael acceptors (Scheme 3.7).[174] Alkyl iodides can be added to alkenes possessing an electron-withdrawing group in the presence of Zn-Cu couple under sonication conditions. Perhaps more intriguing, the reaction was successfully performed in an aqueous solvent, allowing for very mild conditions while displaying compatibility with many reactive functional groups. It was proposed that the reaction mechanism proceeds through a radical intermediate formed from the reduction of alkyl iodide with the Zn-Cu couple, followed by formation of a Zn-stabilized enolate after addition of the alkyl radical. Both water and copper are required for the reaction to proceed, and a proton from water becomes

incorporated in the final product. When the reaction is performed in D_2O, a deuterium atom is incorporated.[175]



Scheme 3.7 Conjugate radical addition of isopropyl group to α-enone under sonochemical conditions

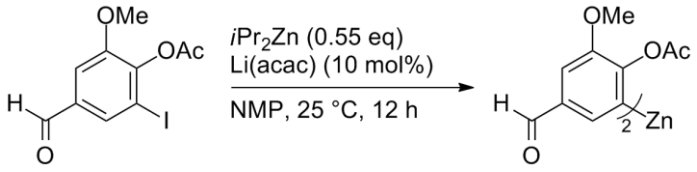
3.3 Preparation of Organozinc Reagents

3.3.1 Lithium Chloride

Organozinc reagents are interesting compounds in the important field of C-C bond forming reactions due to their mild reactivity, high chemo- and stereoselectivity, and high functional group tolerance. While valuable, these reagents tend to be difficult to prepare through direct insertion of Zn metal into carbon-halogen bonds. The most common method involves highly reactive Rieke-zinc, but this process involves dangerous conditions and the activity of the Rieke metals decreases with

time. The development of a practical procedure for Zn insertion with commercially available Zn dust is a highly desirable and ongoing area of focus.

One method for the preparation of polyfunctionalized organometallic reagents is the halogen-metal exchange reaction. The iodine-zinc exchange reaction allows for access to functionalized diaryl zinc compounds from the corresponding aryl iodides.[176] Early in its development, the halogen-zinc exchange reaction was only successful in preparation of primary and secondary dialkyl zinc compounds while failing with aryl iodides.[177] However, a catalytic Zn/I exchange reaction developed by Knochel was enhanced with the addition of 10 mol% Li(acac) to an aryl iodide and *i*Pr_2Zn (Scheme 3.8).[176]

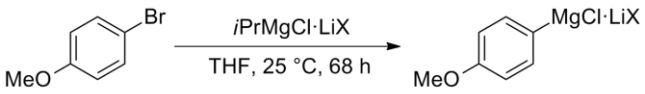


Scheme 3.8 Formation of functionalized diarylzinc via iodine-zinc exchange

A similar enhancement from the addition of Li was reported in the investigation of Br/Mg exchange.[178] Knochel noted that while Br/Li exchange is fast and occurs at low temperatures, the corresponding Br/Mg exchange is considerably slower. This forces the exchange to be performed at higher reaction temperatures that are incompatible with many functional groups. Several lithium salts were tested as additives in the exchange with *i*PrMgCl and the unreactive, electron-rich 4-bromoanisole (Table 3.2). In the absence of a lithium additive, an 18% conversion

was achieved after 68 hours of stirring at room temperature. Similar poor conversions (38-40% conversion) were seen with the addition of $LiBF_4$, LiBr, LiI, and $LiClO_4$. In contrast, LiCl led to a drastic improvement with a conversion of 70%. While quantities larger than one equivalent did not improve the conversion, smaller amounts led to lower conversions. The conversion was improved to 84% when a concentrated solution of *i*PrMgCl·LiCl (2.22 M) was prepared.

Table 3.2 Effect of the addition of lithium salts on the formation of 4-methoxyphenylmagnesium chloride[178]



LiX additive	Equiv.	Conv. (%)
-	-	18
$LiBF_4$	1.0	5
LiBr	1.0	40
LiI	1.0	38
$LiClO_4$	1.0	38
LiCl	1.0	70
LiCl	0.25	22
LiCl	0.5	43
LiCl	1.5	73
LiCl	2.0	74

With this information, Knochel sought to improve the synthesis of polyfunctionalized Zn reagents via LiCl addition. Previously, when iodobenzene was treated with commercially available Zn powder activated by 1,2-dibromoethane (5 mol%) and TMSCl (1 mol%), only a 5% conversion was achieved after 24 hours under reflux. An addition of 1.5 equivalents of LiCl saw this reaction reach quantitative conversion to form phenylzinc iodide after only 7 hours under reflux.

The presence of an *ortho* or *para* electron-withdrawing group increased the rate of insertion and allowed for the formation of the corresponding arylzinc iodides at room temperature. In the formation of *ortho*-trifluoromethylphenyl iodide, the presence of LiCl provided quantitative conversion at room temperature over 24 hours while the absence of LiCl required refluxing conditions to produce only 70% conversion. A similar effect was observed with ethyl 4-iodobenzoate, with a < 5% conversion achieved when LiCl was absent under refluxing conditions. At room temperature, the presence of LiCl provides quantitative conversion.

The exact role of the LiCl additive is unknown; several hypotheses have been presented. Knochel suggested that the LiCl rapidly removes the organozinc reagent from the metal surface by generating a highly soluble RZnX·LiCl complex (Figure 3.3). This allows for rapid subsequent reaction with an R-X molecule with the exposed Zn surface and prevents competitive deactivation of the active metal sites. Not only does LiCl increase the rate of RZnX formation, improved results in the subsequent transmetalation have also been demonstrated.[179] This is most likely also due to the improved solubility of the RZnX·LiCl and dissolution of the organozinc aggregates.

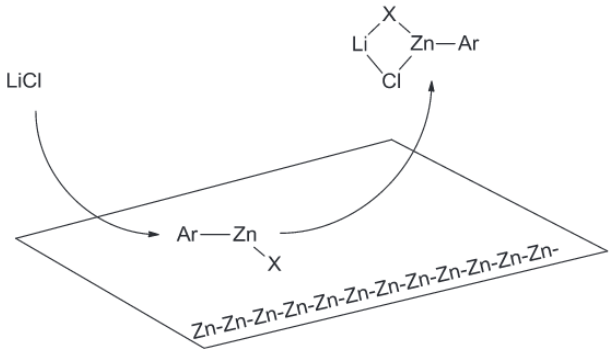


Figure 3.3 Formation and solvation of the RZnX·LiCl complex[178]

While these beneficial effects have been reported, their molecular mode of action is unknown. Koszinowski reported a study of THF solutions of the products formed in the LiCl-mediated Zn insertion reactions into various organic halides by anion-mode electrospray ionization mass spectrometry (ESI-MS).[180] In all cases, the reactions with RX (where X = Br, I) yielded mononuclear organozincate anions including $ZnRX_2^-$ and $ZnRXCl^-$. The reaction with benzyl chlorides instead produced polynuclear complexes such as $Zn_2Bn_2Cl_3^-$ and $Zn_3Bn_3Cl_4^-$. The controlling factor in the equilibria directing the stoichiometry and aggregation state of these complexes appears to be the halide ions. While these anion complexes are undoubtedly produced, the reaction mechanism for their formation is still unclear.

$$LiCl + RZnX \xrightarrow[THF]{} Li^+ ZnRClX^- \rightleftharpoons Li^+ + ZnRClX^-$$

Scheme 3.9 Reaction and subsequent dissociation between LiCl and RZnX

To more completely understand the role of LiCl, Blum reported fluorescence microscopy experiments with sensitivity as high as single-molecules (Figure 3.4).[181] Five mechanistic possibilities were considered initially with an alkyl iodide the substrate: (1) LiCl cleans impurities from the Zn surface before coordination of RI; (2) LiCl solubilizes surface RZnI, producing solution-phase reagent and exposing reactive Zn surface; (3) LiCl binding raises the Zn HOMO; (4) coordination of Li^+ lowers the LUMO of iodide; or (5) simultaneous LUMO lowering/HOMO raising with the amphoteric LiCl.

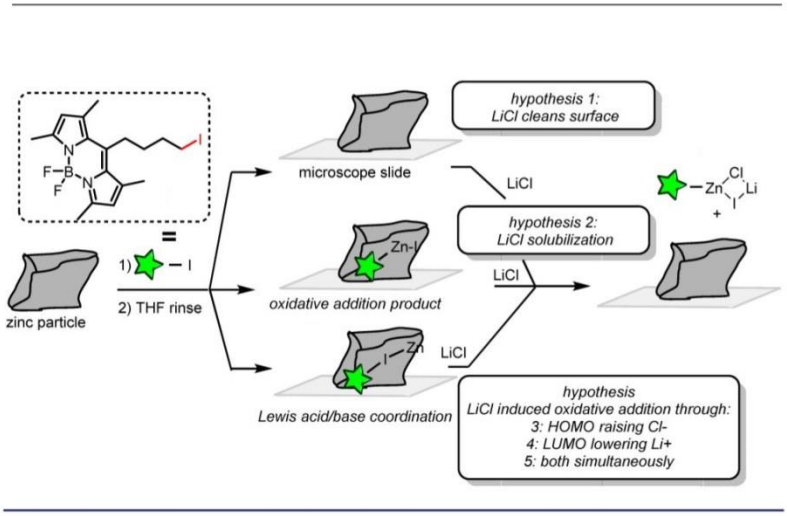


Figure 3.4 Possible functions of LiCl in the formation of organozinc reactions proposed by Blum[181]

Hypothesis 1 was initially dismissed as an initial reaction was observed between the Zn surface and the alkyl iodide in the absence of LiCl. When an aryl iodide was used instead of an alkyl iodide, no surface intermediate was generated, results inconsistent with hypotheses 3-5 and the effect LiCl would have on the

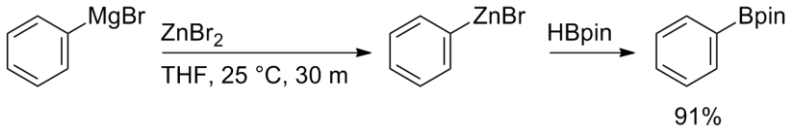
HOMO/LUMO interactions. Hypotheses 3 and 4 were further ruled out, as both lithium and chloride ions were required to transform the surface species; the absence of either ion was detrimental to reactivity. In support of hypothesis 2, not all locations on the Zn surface were equally active while addition of LiCl removed the organic material from the highly reactive locations, exposing a larger surface area of reactive Zn underneath.

3.3.1.1 Results

This work sought to adapt work published by Krasovskiy and Knochel exploring the effect of lithium salts accelerating the rate of Br/Mg exchange as a possible route towards organozinc nucleophile formation. If successful, functionalized organozinc reagents could be used as an alternative to restrictive Grignard reagents in the reaction with HBpin to provide boronic acids and esters. Knochel's group was successful in the preparation of functionalized organozinc reagents by the insertion of Zn in the presence of LiCl in THF. This system had several potential advantages in that (1) the introduction of LiCl reduced the amount of Zn required, (2) the system was run in THF which has been demonstrated as compatible with HBpin, and (3) Knochel reported no side products were produced. Lithium chloride salt does have the disadvantage of being extremely hygroscopic, as HBpin is sensitive to moisture.

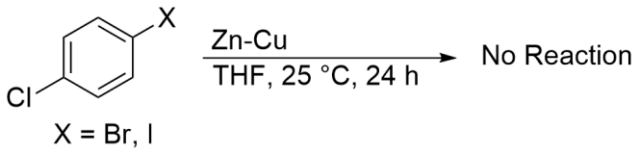
Several reactions were initially performed to examine the formation of organozinc reagents and their reaction with HBpin. In order to confirm the reaction

between organozinc reagents and HBpin would occur, phenylzinc bromide was prepared by the addition of phenylmagnesium bromide to previously dried $ZnBr_2$ in THF at room temperature (Scheme 3.10). After stirring for 30 min and observing the formation of $MgBr_2$ precipitate, HBpin was added. The resulting phenylpinacolboronate ester was cleanly formed in 91% yield. While this route did not provide any advantage over the previously reported method with Grignards, it did indicate that a reaction between organozinc halides and HBpin was possible.



Scheme 3.10 Formation of phenylzinc bromide via transmetalation followed by addition of HBpin

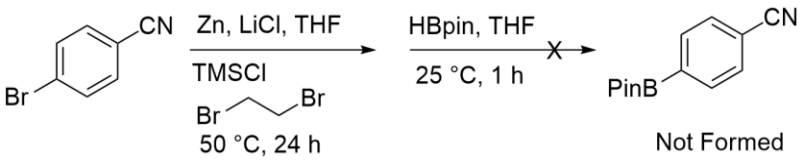
Zinc-copper couple was then used to prepare organozinc halides via direct insertion (Scheme 3.11). However, attempts to form the corresponding arylzinc reagents from both 4-bromochlorobenzene and 4-chloroiodobenzene with Zn-Cu were unsuccessful. Similarly, direct insertion via a 3-fold excess of unactivated Zn to 4-bromochlorobenzene and 4-chloroiodobenzene formed only trace yields of the corresponding arylzinc reagent.



Scheme 3.11 Formation of phenylzinc bromide via transmetalation followed by addition of HBpin

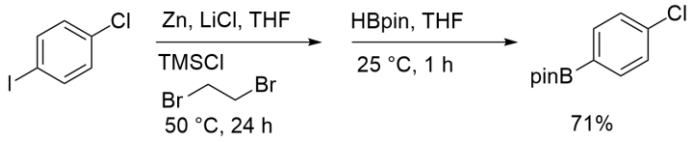
Noting Knochel's significant improvement with the addition of LiCl in the direct insertion of Zn, an attempt to cleanly form arylzinc halide in the presence of LiCl was investigated. Due to the hygroscopic nature of LiCl, all reactions began with a 30 minutes drying of Zn and LiCl under vacuum by directly heating the flask with a heat gun. After 30 minutes had elapsed, the vacuum was removed and Ar was introduced to the flask as it cooled to room temperature.

An attempt to form the corresponding arylzinc bromide from Zn, LiCl, and 4-bromobenzonitrile was unsuccessful (Scheme 3.12). Initially, 1.5 equivalents of Zn and 1 equivalent of LiCl were dried and THF was added. Zn was then activated by addition of TMSCl (1 mol%) and 1,2-dibromoethane (5 mol%) and allowed to stir. Unfortunately, after 3 hours a TLC indicated the insertion of Zn to the C-Br bond was not proceeding. After 24 hours of stirring at room temperature, similar results were observed. Regardless, HBpin was added dropwise to the solution. Interestingly, a small amount of HBpin degradation products were visible in the ^{11}B NMR (δ +22 and δ +4), similar to observations made by Clary in the reaction of aryllithiums with HBpin and Aggarwal's investigation of HBpin degradation products.



Scheme 3.12 Attempted formation of phenylzinc bromide via transmetalation followed by addition of HBpin

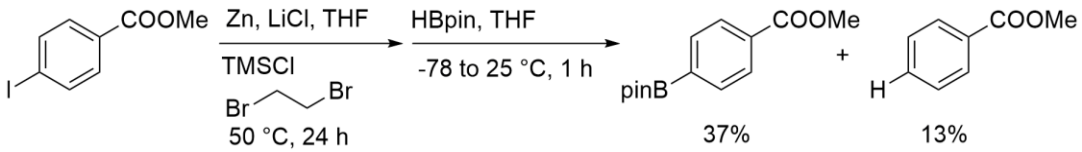
The same conditions were used to attempt the formation of the corresponding arylzinc iodide from unfunctionalized 4-chloroiodobenzoate (Scheme 3.13). Unlike the reaction with benzonitrile, TLC indicated that after 3 hours the formation of the arylzinc iodide was proceeding but was incomplete. After 24 hours, a trace amount of 4-chloroiodobenzoate was still visible via TLC and the reaction was cooled to room temperature before HBpin was added to the solution. After 1 hour, the ^{11}B NMR showed a 71% yield of 4-chlorophenylboronate ester had formed, but various degradation products were also present.



Scheme 3.13 LiCl-mediated formation of arylzinc iodide followed by addition of HBpin

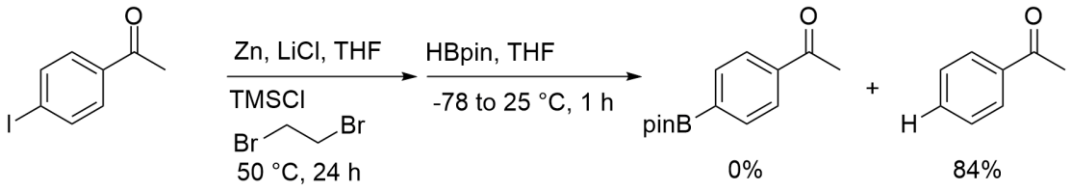
Returning to functionalized aryl iodides, methyl 4-iodobenzoate was added to a solution containing dried LiCl and Zn activated by TMSCl (1 mol%) and 1,2-dibromoethane (5 mol%). After stirring at 50 °C for 24 hours, the reaction was

cooled to -78 °C in an attempt to increase the stability of HBpin in the presence of LiCl. HBpin was added dropwise; while the ^{11}B NMR indicated the functionalized boronate ester was present, approximately 50% of the HBpin remained unreacted and several degradation species were visible. An acidic work-up of the reaction mixture and isolation via extraction indicated that reduction of the arylzinc iodide had also occurred to form 13% methyl benzoate in addition to the desired benzoate boronic ester in 37% yield.



Scheme 3.14 LiCl-mediated formation of arylzinc iodide followed by addition of HBpin under cryogenic conditions

A similar reaction between 4-iodoacetophenone and Zn in the presence of LiCl was performed (Scheme 3.15). After stirring at 50 °C for 24 hours, the reaction was cooled to -78 °C and HBpin was added dropwise. The reaction was warmed to room temperature while stirring for 1 hour. An ^{11}B NMR showed HBpin had been fully degraded; no desired ArBpin species was visible. Interestingly, an aqueous work-up of the reaction mixture and isolation of the organic products via extraction gave only acetophenone. It was hypothesized that while the arylzinc nucleophile had formed, the reaction with HBpin was slower than the degradation of HBpin, leading to quenching of the arylzinc iodide upon acidic work-up.



Scheme 3.15 LiCl-mediated formation of arylzinc iodide followed by addition of HBpin under cryogenic conditions

It was suspected that the order of addition could have been a factor in the degradation of HBpin with LiCl present. In the general reaction of Grignard and organolithium reagents with trimethoxyborane, it has been reported that addition of the boron source to a concentrated solution of reactive organometallic reagent was detrimental. Instead, when the organometallic reagent was added to a solution of trimethoxyborane in ether, yields were significantly increased. Analogous observations were made by Clary who noted that addition of pre-formed Grignard reagents to HBpin above -78 °C resulted in over-addition and formation of BO_3 side products. Similar issues were not observed in the reaction of Grignard reagents with HBpin at room temperature under Barbier conditions.

The reaction between methyl 4-iodobenzoate and Zn in the presence of LiCl was performed under Barbier conditions. First, the solid reagents were dried under vacuum at 120 °C for 30 minutes. After flushing with Ar and allowing the flask to cool to room temperature, THF and 4-iodobenzoate were added followed by HBpin. The reaction was then initiated by the addition of the 1,2-dibromoethane and TMSCl

activators. The reaction was stirred at 50 °C overnight. An ^{11}B NMR showed HBpin had been fully degraded; however no desired ArBpin species was visible.

Singaram and Clary previously observed incompatibility between HBpin and lithium reagents, namely aryllithium nucleophiles.[121] In the reaction of HBpin with halides under ambient Grignard and Barbier conditions, Clary briefly explored the compatibility of aryllithium reagents as an alternative. The reaction of phenyllithium with HBpin furnished a mixture of multiple addition and degradation products, even at -78 °C. It was hypothesized that the oxygens of the pinacol moiety strongly coordinate with the lithium cation, greatly reducing the strength of the B-O bond and allowed unwanted side reactions to occur.

A set of control experiments were performed to probe the interaction between HBpin and LiCl in THF. Aggarwal has previously examined the different oxidized products of HBpin and their respective NMR shifts (Figure 3.5).[182] Typically, O_4B^- species (such as pinBpin and $(HO)_2$Bpin) tend to show peaks between δ +8 and +4 in the ^{11}B NMR. This is consistent with observations made in the Zn/LiCl reactions where HBpin has been converted to a BO_3 side product, the major degradation peak at δ +22. This is sometimes accompanied by small peaks at both δ +7 and/or δ +4.

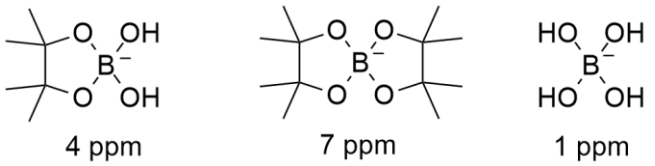
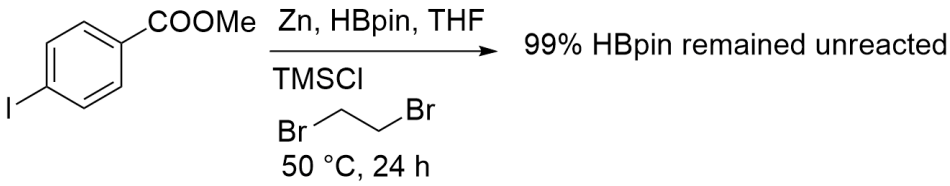


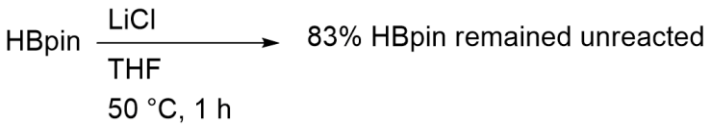
Figure 3.5 Formation of some Bpin degradation species in THF as observed by Aggarwal[182]

First, methyl 4-iodobenzoate and HBpin were stirred at 50 °C in THF overnight with Zn, TMSCl, and 1,2-dibromoethane; LiCl was omitted (Scheme 3.16). An ^{11}B NMR showed 99% of unreacted HBpin still present with a small peak (1%) at δ +22 indicative of a BO_3 species.



Scheme 3.16 Attempted formation of arylzinc iodide in the absence of LiCl

Then, to a 1 M solution of LiCl in THF, 1 equivalent of HBpin was added (Scheme 3.17). Immediately the mixture began to bubble and was left to stir for 1 hour. An ^{11}B NMR showed only 83% unreacted HBpin still present while 17% of an OBpin species was observed at 22 ppm.



Scheme 3.17 Interaction of HBpin and LiCl under refluxing conditions

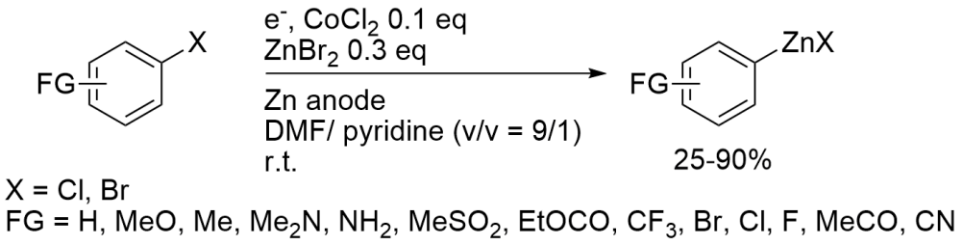
From these results, it can be inferred that organozinc reagents are capable of reacting with HBpin. The debilitating drawback of this methodology comes in the formation of organozinc reagents. Currently, one the most efficient methods of preparing organozinc reagents requires stoichiometric amounts of LiCl to be present. However, HBpin is extremely incompatible with any system containing LiCl. With a different method that could form the organozinc reagents reliably in higher yields, HBpin could be a compatible boron substrate in the synthesis of functionalized boronate esters from functionalized organozinc reagents.

3.3.2 Cobalt Bromide

Over the past three decades, transition metal-catalyzed cross-coupling reactions have opened new pathways for carbon-carbon bond formation, particularly in reactions involving $C(sp^2)$ centers where S_N2 substitution is impossible. While expensive and toxic metals are typically used as cross-coupling catalysts, including Pd and Ni, recently cobalt salts have emerged as simple, effective, and green alternatives.[183]

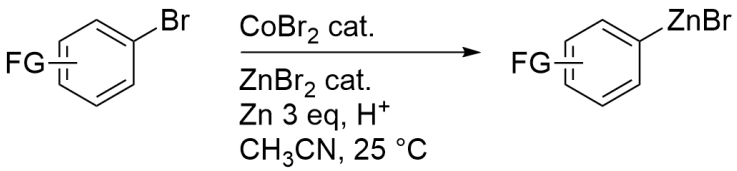
Cobalt was first used in the reduction of aryl chlorides or bromides in an electrochemical cell fitted with a sacrificial zinc anode in the presence of cobalt halide (Scheme 3.18).[184] In the presence of $ZnBr_2$, a cobalt-pyridine complex in DMF was suitable for efficient conversion of various functionalized aryl bromides or chlorides to the corresponding arylzinc halide intermediates. While the anodic process is straightforward with the reduction of Zn metal, the cathodic process is

more complex, involving the transitory electrogenerated Co(I)-pyridine species. Organic electrochemical reaction set-ups, however, are often considered exotic and difficult to properly control in comparison to conventional organic reactions.



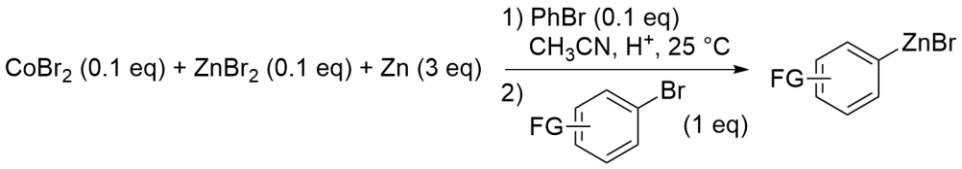
Scheme 3.18 Electrochemical formation of functionalized arylzinc halides using a sacrificial Zn anode

With the importance of arylzinc species in chemical synthesis, a new method was developed emerging from the hypothesis that a purely chemical reaction could be extended from the initial electrochemical process (Scheme 3.19).[185] In order to be successful, a chemical reducing agent would be necessary to replace an electric current for the preparation of arylzinc compounds catalyzed by cobalt. The aryl bromides could be activated by low-valence cobalt obtained from the chemical reduction of cobalt halide.



Scheme 3.19 Chemical formation of functionalized organozinc bromides from catalytic $CoBr_2$ and Zn

Perichon demonstrated the successful preparation of arylzinc bromides from the reaction of aryl bromides with commercially available zinc dust in the presence of a catalytic amount of both $CoBr_2$ (10 mol%) and $ZnBr_2$ (10 mol%) in acetonitrile (Scheme 3.20). The reaction was initiated by addition of trace trifluoroacetic acid (TFA) and was complete after 30 minutes at room temperature. In the beginning of the reaction, the functionalized aryl bromide was reduced to ArH; a sacrificial amount (10 mol%) of bromobenzene was added to circumvent need for an excess of functionalized aryl bromide.

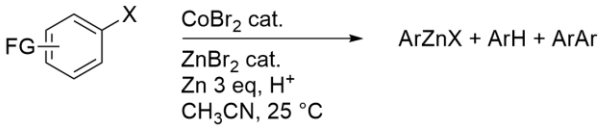


Scheme 3.20 Conditions for the catalytic formation of functionalized arylzinc bromide via Zn, $CoBr_2$, and $ZnBr_2$

While using 2 or 3 equivalents of Zn dust has no effect on the conversion to ArZnBr, using a greater than two-fold excess does greatly enhance the rate of the reaction. Activation by acetic acid rather than TFA also showed no appreciable difference in the rate or yield of conversion. Interestingly, $ZnBr_2$ was not necessary for the formation of the arylzinc bromide, but the absence of $ZnBr_2$ greatly increased the rate of dimerization side product that was formed. Only a small amount (10 mol%) of dried $ZnBr_2$ is capable of reducing the yield of ArAr dimer (Table 3.3). Previously in an electrochemical study, $ZnBr_2$ was suspected of stabilizing the Co(I)

species.[186] While successful in acetonitrile, the reaction produced no organozinc halide in either THF or dimethylacetamide (DMA).

Table 3.3 Distribution of arylzinc halide, reduction, and homocoupled products from various functionalized aryl halides[187]



FG	X	% ArZnX	% ArH	% ArAr	% conv.
H	Cl	0	0	0	0
H	Br	77	8	15	100
p-CH_3O	Br	86	8	6	100
m-CH_3O	Br	70	7	23	100
o-CH_3O	Br	93	7	0	100
p-CH_3O	I	88	8	3	100
p-CH_3	Br	71	9	20	100
p-NH_2	Br	40	52	0	100
p-$N(Me)_2$	Br	65	16	19	100
p-OH	Br	6	94	0	100
p-OCOMe	Br	80	13	7	100

The reaction is hypothesized to be initiated by the reduction of $CoBr_2$ by previously activated Zn dust (Scheme 3.21). The resulting $Co^{I}Br$ species then undergoes oxidative addition with the functionalized aryl halide to provide the trivalent cobalt complex $ArCo^{III}Br_2$. From there, $ArCo^{III}Br_2$ is reduced to $ArCo^{II}Br$ by excess Zn dust. The final step in the cycle is the transmetalation reaction between $ArCo^{II}Br$ and $ZnBr_2$ formed previously in the cycle, leading to the arylzinc species and regenerating the divalent cobalt.

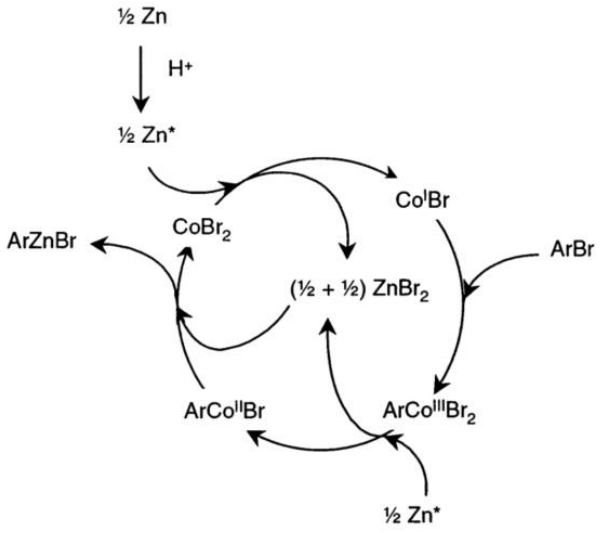


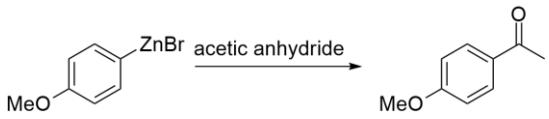
Figure 3.6 Proposed mechanism for the formation of arylzinc bromide from $CoBr_2$

Later work by Perichon sought to further examine key aspects of the mechanism, mainly if the cobalt catalyst played any role in subsequent reactions with electrophiles.[187] Perichon questioned if the reactive cobalt species acts as a cobalt(I)/cobalt(III) couple, analogous to nickel or palladium species, or instead as cobalt(II) with the reactive nucleophilic species being an organocobalt(II) reagent. This latter hypothesis stems from the observation that the transmetalation step in the formation of organozinc is reversible. While a definitive answer to the second question has not been reported, a comparison study was performed to test the role of cobalt in the subsequent reaction.

The reaction between acetic anhydride and 4-bromoanisole was performed, where the corresponding organozinc reagent could be formed through transmetalation of the organomagnesium species (Table 3.4). Comparable two-step reactions with the

organozinc species produced through either transmetalation or the $CoBr_2$/Zn method mentioned previously. In comparing the results, an enhanced reactivity was demonstrated in the $CoBr_2$ system. To contrast this, the reaction between the organozinc species prepared by transmetalation and acetic anhydride was slow. When 5% $CoBr_2$ is added to this transmetalated organozinc reagent, the coupling reaction with acetic anhydride occurs at an improved rate, indicating a dramatic effect on the reaction between the organozinc nucleophile and the electrophile.

Table 3.4 Comparison study to investigate the role of $CoBr_2$ in the coupling of acetic anhydride[187]

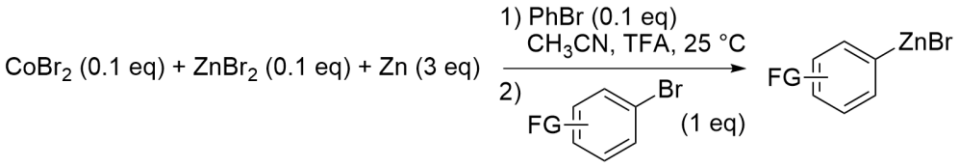


preparation method of ArZnBr	addition of $CoBr_2$	reaction time	yield (%)
cobalt catalyst in CH_3CN	no	23 h	76
transmetalation in THF	no	20 h	28
transmetalation in THF	yes, 5% vs ArBr	30 m	90

3.3.2.1 Results

This work in cobalt began with Gosmini and Perichon's adaptation to their electrochemical process. This new method is completely chemical, excluding the need for any electrochemistry and utilizing the activation of aryl bromides by low-valence cobalt species. This cobalt species arises from the reduction of cobalt (II) by zinc dust in acetonitrile.

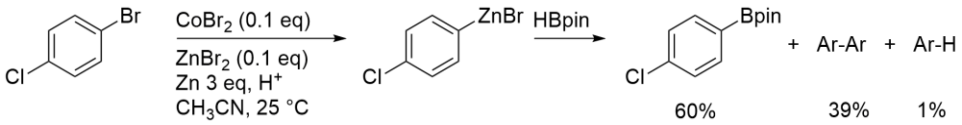
Zn, $ZnBr_2$, and $CoBr_2$ were added to acetonitrile in a 3:0.1:0.1 ratio before the addition of a catalytic amount of trifluoroacetic acid to activate the Zn dust (Perichon report that while increasing the amount of Zn dust enhances the rate of reaction, it does not affect the yields). To this, a catalytic amount of sacrificial bromobenzene was added, as ArH is formed at the beginning of the reaction. After 30 mins of stirring to complete that initial side reaction, 4-bromochlorobenzene was added to form the corresponding 4-chlorophenylzinc bromide. Initially, the solution possessed a blue/green color, corresponding to Co(II), which became pink presumably as the reaction began and Co(I) formed.



Scheme 3.21 Preparation of functionalized arylzinc bromides

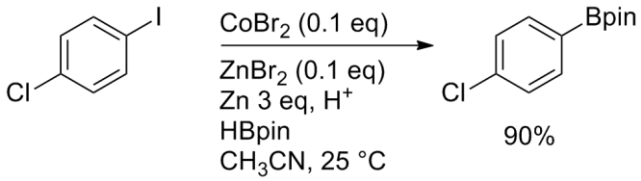
While Perichon subsequently coupled arylzinc halide compounds with aryl iodides and Pd, this research focused on testing the reactivity with boron species in a system analogous to the work with nucleophilic arylmagnesium halides adding to HBpin. To the prepared 4-chlorophenylzinc bromide, HBpin was added and the reaction stirred at room temperature overnight. The results were promising, as a small amount of aryl boronate ester was visible by ^{11}B NMR. However, this reaction also presented numerous drawbacks. The ^{11}B NMR showed multiple boron species were present, including the product and a peak at δ +27, indicating possible reaction

between HBpin and acetonitrile. The ^{1}H NMR also showed a mixture of products correlating to unreacted starting material, reduction of the aryl bromide, and homodimerization.



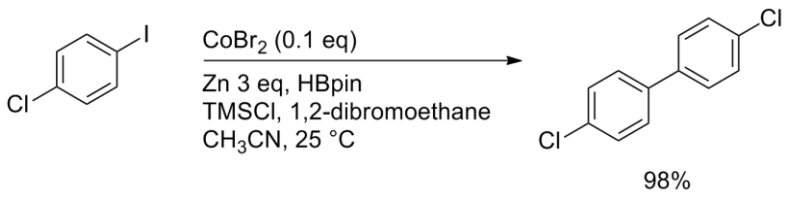
Scheme 3.22 Distribution of products from the formation of 4-chlorophenylzinc bromide and subsequent reaction with HBpin (relative yields calculated from ^{1}H NMR)

The reaction with Zn/$CoBr_2$ was also performed under Barbier conditions. After drying the solid reagents, both 4-chloroiodobenzene and the activating TMSCl/1,2-dibromoethane were added. Finally, HBpin was added and the solution was left to stir overnight at room temperature. The ^{11}B NMR indicated a similar mixture of products had been produced, however a much larger yield of the desired boronate ester was observed.



Scheme 3.23 Preparation of 4-chlorophenylpinacolboronate ester under Barbier conditions with catalytic $CoBr_2$

It was hypothesized that the presence of some reagents were unnecessary. The reaction was repeated with the omission of $ZnBr_2$ (Scheme 3.24). It was hypothesized that the reduction by-product, chlorobenzene, resulted from the presence of a strong acid. In order to diminish the amount of reduction product, the activation conditions were adjusted by replacing TFA with TMSCl/1,2-dibromoethane and, therefore, bromobenzene would not be required. While the reaction did proceed, a significant amount of the homodimer 4,4'-dichlorobiphenyl was produced. These results agreed with observations by Perichon that $ZnBr_2$ stabilizes Co(I) and reduces the amount of homodimerization. Another unexpected result was the aggregation of a magnetic solid on the poles of the stirbar; no other reports suggested formation of a magnetic solid. $ZnBr_2$ was confirmed as crucial for diminishing the homodimerization side reaction, it was suspected that interaction between acetonitrile and HBpin was detrimental for the reaction between the arylzinc bromide and HBpin.



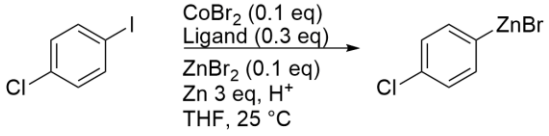
Scheme 3.24 Reaction of $CoBr_2$ and Zn in the absence of $ZnBr_2$

To prevent this, the reaction was performed in THF rather than acetonitrile. Both Zn and $CoBr_2$ were suspended in THF and allowed to stir, followed by addition of the activating agents. While $CoBr_2$ in acetonitrile produces a deep blue/green

colored solution, a solution in THF is a strong pink color. Within 30 minutes of the addition of all the reagents, the initial pink color had completely disappeared, leaving a colorless THF solution. Additionally, a large amount of grey magnetic solid formed and collected at the poles of the stir bar. The precipitate was hypothesized to be a Zn-Co alloy, as Co is paramagnetic. A powder X-ray diffraction was performed on the isolated solid, however the results were inconclusive. While both Co and $CoBr_2$ species were visible, several unknown peaks were present.

The acetonitrile solvent was suspected to also act as a ligand for stabilizing the cobalt complex. To test this hypothesis, several compounds were tested for their ability to stabilize Co in THF (Table 3.5). To four separate solutions of $CoBr_2$ in THF, 0.3 equivalents of pyridine, TMEDA, triethylamine, and acetonitrile were added and stirred at room temperature. In all four cases, the pink solution decolorized after 1 hour and produced a magnetic precipitate. Similar results were seen in a 1:1 mixture of THF/acetonitrile.

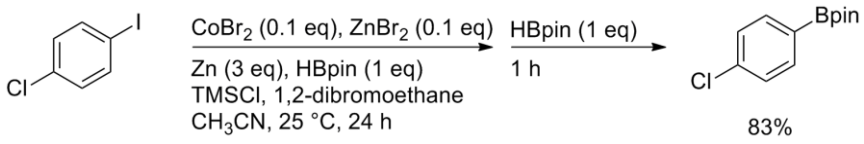
Table 3.5 Preparation of arylzinc bromide using various ligands in THF



Ligand	Starting Material Recovered?
pyridine	yes
TMEDA	yes
triethylamine	yes
acetonitrile	yes
acetonitrile[a]	yes

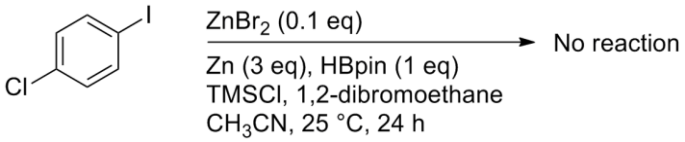
[a]Reaction run in 1:1 mixture of THF:acetonitrile

With acetonitrile identified as a requirement for the stability of Co, the lower yield of desired arylboronate ester was believed to result from the reaction of HBpin with the acetonitrile solvent. However, increasing the amount of HBpin did not significantly increase the yield of arylboronate ester. A reaction was performed under Barbier conditions with 1 equivalent of HBpin present. After stirring for 24 hours, 1 additional equivalent of HBpin was added and left to stir for 1 hour (Scheme 3.25). However, a before and after comparison of the spectra of reaction mixtures by ^{11}B NMR gave no change in the product ratios.



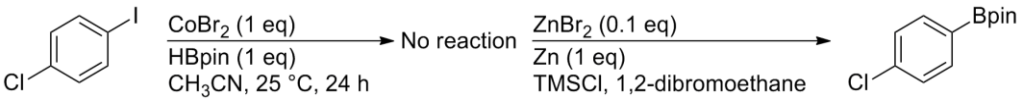
Scheme 3.25 Reaction of arylzinc iodide and an excess of HBpin introduced in separate additions

Several experiments were then performed to examine the requirements of the reaction. First, a Barbier reaction was performed omitting the $CoBr_2$ entirely. As expected, both the TLC and ^{11}B NMR of the reaction mixture indicated the reaction did not proceed (Scheme 3.26).



Scheme 3.26 Lack of reaction with Zn and $ZnBr_2$ in the formation of arylzinc iodide

A similar reaction was performed with Zn omitted and 1 equivalent of $CoBr_2$ added (Scheme 3.27). As expected, both TLC and ^{11}B NMR spectrum of the reaction mixture indicated the reaction did not proceed. After 24 hours of stirring and confirmation that the reaction had not progressed, 0.5 equivalents of Zn dust was added and both TLC and ^{11}B NMR suggested the reaction had begun. After an addition 0.5 equivalents of Zn, the reaction left to stir and was completed after 3 hours as indicated by both TLC and ^{11}B NMR.

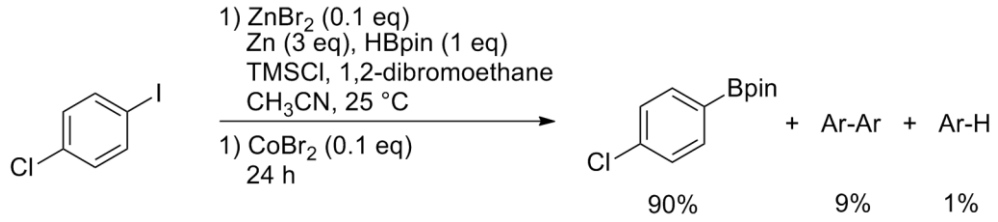


Scheme 3.27 Confirmation of the requirement for Zn in the preparation of arylzinc halides

Interestingly, a solution of Zn and $CoBr_2$ in acetonitrile retained the deep blue/green color even after the addition of the TMSCl/1,2-dibromoethane activating agents. This seems to indicate the presence of the aryl halide is necessary to begin the reaction. As expected, subsequent addition 4-chloroiodobenzene does initialize the reaction and results in a change of color.

Finally, the optimal results were obtained when the order of addition was changed. Previously, the solid reagents (Zn, $ZnBr_2$, and $CoBr_2$) were dried before addition of THF. To this, the activating agents and aryl iodide substrate were added followed by HBpin as the final addition. While the arylboronate ester was the major product, both the reduction and homodimerization products were also produced.

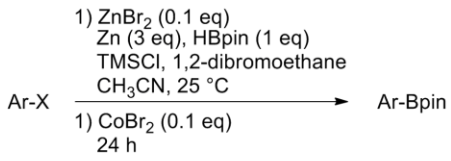
However, holding $CoBr_2$ as the final addition under Barbier conditions greatly diminished the amount of side products produced. It was hypothesized that when $CoBr_2$ was early in the order of addition, initial formation of the organozinc halide proceeded with the slow formation of homodimer; HBpin was added last and thus the electrophile was not present. When $CoBr_2$ was added after the HBpin electrophile, any organozinc reagent that formed underwent fast addition to the HBpin, a preferable route over formation of the homodimer.

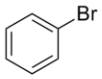
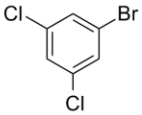
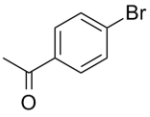
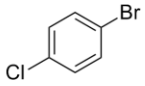
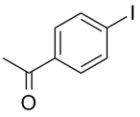
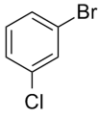
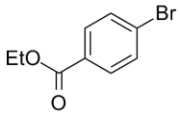
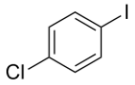
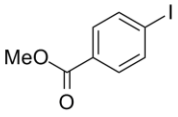
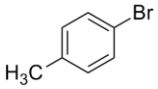
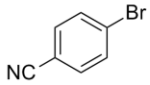
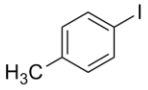
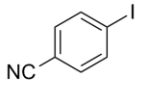
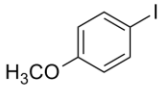


Scheme 3.28 Optimized procedure for the formation of arylzinc halide and subsequent reaction with HBpin under Barbier conditions (relative yields calculated from ^1H NMR)

With this optimal procedure, a range of reactions using unfunctionalized and functionalized aryl halides was performed (Table 3.6). In many cases, although the functionalized arylzinc reagents gave poor yields of the corresponding boronate esters, this methodology provides proof of concept that direct formation via arylzinc reagents is possible. The difficulty in the process stems from the use of HBpin as a boron source to afford pinacolboronate esters directly. Other boron sources may provide greater yields of boronate esters with fewer side reactions.

Table 3.6 Synthesis of unfunctionalized and functionalized arylpinacolboronates esters from arylzinc halides with catalytic $CoBr_2$; [a]yields calculated by ^1H NMR



Aryl Substrate	yield[a] (%)	Aryl Substrate	yield[a] (%)
	90		61
	79		0
	60		30
	70		28
	90		37
	0		0
	14		11
	81		

3.4 Conclusion

In summary, an extensive study was performed into the viability of using organozinc reagents in the formation of boronate esters. While more difficult to

produce than Grignard reagents, organozinc reagents possess the advantage of extensive functional group tolerance. Two of the most common methods currently in the literature for the preparation of organozinc reagents allow for safe, green, controlled preparations compared to previous methods. While demonstrating only limited success, several substrates do result in formation of the corresponding arylboronate esters.

Addition of stoichiometric amounts of LiCl reduces aggregation by forming soluble anionic complexes that abstract the reactive organozinc nucleophiles from the Zn surface. This has the added effect of exposing more reactive Zn underneath and driving the reaction forward. While the Zn/LiCl system was mostly unsuccessful with HBpin, some arylboronate ester did form from the reaction with dihalo substrates.

The use of catalytic $CoBr_2$ has enjoyed increased popularity, mainly due to the elimination of more toxic and expensive transition metals required for the formation of organozinc species. HBpin was successfully converted to the corresponding boronate ester from both dihalide as well as some functionalized aryl iodide species. Both systems demonstrate successful proof of concept for the direct synthesis of functionalized boronate esters. Future investigations will focus on utilizing new boron sources.

3.5 Experimental

General Methods. All reactions were performed in oven-dried, argon-cooled glassware. The HBpin was used as received from Aldrich and stored under Ar in a refrigerator held at 15 °C. All halide-containing substrates were used as received from Aldrich. Magnesium metal was used as received from Aldrich. Iodine was used as received from Aldrich. Zinc metal was used as received from Aldrich. All air- and moisture-sensitive compounds were introduced via syringes or cannula through a rubber septum. HBpin was added via syringe, with the dispensed amount measured by mass difference of the syringe before and after addition. Tetrahydrofuran (THF) was freshly obtained by a solvent purification system (Pure Solv MD, Innovative Technology Inc.). Acetonitrile was distilled over CaH_2. NMR spectra were recorded in $CDCl_3$. Chemical shifts are reported relative to TMS (δ 0) for ^1H NMR (500 MHz) and is referenced to the $CDCl_3$ resonance (δ 77) for ^{13}C NMR (125 MHz) spectra. Data is reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, br =broad, m = multiplet, app = apparent), coupling constant, and integration. Boron NMR samples were recorded at 160.4 MHz and are reported relative to the external standard $BF_3{\cdot}Et_2O$ (δ 0). High-resolution mass spectra were obtained by electrospray ionization experiments.

Preparation of Arylzinc Bromide from Magnesium Transmetalation. A 25 mL round-bottom flask equipped with a magnetic stir bar and fitted with a rubber septum was cooled to 25 °C and was purged with Ar. Anhydrous $ZnBr_2$ (0.675 g, 3.0

mmol) was added and the flask was re-purged with Ar. Anhydrous THF (12 mL) was added to the flask, followed by the addition of phenylmagnesium bromide (1 M, 3.0 mmol) dropwise over 5 min with constant stirring at 50 °C. After 30 min of stirring, a precipitate formed. HBpin (0.44 mL, 3.0 mmol) was then added and allowed to stir for an addition 30 min. The reaction was quenched with 1 M HCl (3 mL). The reaction mixture was then transferred to a separatory funnel and extracted with diethyl ether (3 x 15 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and dried in vacuo, (25 °C, 1 Torr) to afford phenylpinacolboronate ester in 91% yield.

Preparation of Arylzinc Halide from Zn-Cu Couple. A 25 mL round-bottom flask equipped with a magnetic stir bar and fitted with a rubber septum was cooled to 25 °C and was purged with Ar. Zn-Cu couple (0.546 g, 8.35 mmol) was added and the flask was re-purged with Ar. Anhydrous THF (12 mL) was added to the flask, followed by the addition of 4-chloroiodobenzene (1.02 g, 5.0 mmol) and HBpin (0.73 mL, 5.0 mmol). The reaction was refluxed overnight. After 24 hours, the reaction was cooled to room temperature and the reaction mixture was decanted. The solution was then quenched with 1 M HCl (3 mL). The reaction mixture was then transferred to a separatory funnel and extracted with diethyl ether (3 x 15 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and dried in vacuo, (25 °C, 1 Torr) to recover the 4-chloroiodobenzene starting material.

Preparation of Arylzinc Halide from Zn Insertion. A 25 mL round-bottom flask equipped with a magnetic stir bar and fitted with a rubber septum was cooled to 25 °C and was purged with Ar. Zn (0.392 g, 3.0 mmol) was added and the flask was re-purged with Ar. Anhydrous THF (12 mL) was added to the flask, followed by the addition of 4-chloroiodobenzene (0.872 g, 4.0 mmol) and HBpin (0.58 mL, 4.0 mmol). The reaction was refluxed overnight. After 24 hours, the reaction was cooled to room temperature and the reaction mixture was decanted. The solution was then quenched with 1 M HCl (3 mL). The reaction mixture was then transferred to a separatory funnel and extracted with diethyl ether (3 x 15 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and dried in vacuo, (25 °C, 1 Torr).

Preparation of Arylzinc Halide from Zn and LiCl. A 25 mL round-bottom flask equipped with a magnetic stir bar and fitted with a rubber septum was cooled to 25 °C and was purged with Ar. Zn (0.490 g, 7.5 mmol) and LiCl (0.211 g, 5.0 mmol) were added and the flask was re-purged with Ar. While venting, the flask was heated directly with a heat gun to a temperature of at least 120 °C for 30 min. The heat gun was then removed and the flask was purged with Ar as it cooled to room temperature. Anhydrous THF (12 mL) was added to the flask, followed by the addition of TMSCl (1 mol%) and 1,2-dibromoethane (5 mol%). Finally, 4-bromobenzonitrile (0.910 g, 5.0 mmol) was added and the reaction was refluxed overnight. After 24 hours, the reaction was cooled to room temperature and HBpin (0.73 mL, 5.0 mmol) was added. After 1 hour the reaction mixture was decanted. The solution was then quenched

with 1 M HCl (3 mL). The reaction mixture was then transferred to a separatory funnel and extracted with diethyl ether (3 x 15 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and dried in vacuo, (25 °C, 1 Torr).

Preparation of Arylzinc Halide from Zn and LiCl under Barbier Conditions. A 25 mL round-bottom flask equipped with a magnetic stir bar and fitted with a rubber septum was cooled to 25 °C and was purged with Ar. Zn (0.490, 7.5 mmol) and LiCl (0.211 g, 5.0 mmol) were added and the flask was re-purged with Ar. While venting, the flask was heated directly with a heat gun to a temperature of at least 120 °C for 30 min. The heat gun was then removed and the flask was purged with Ar as it cooled to room temperature. Anhydrous THF (12 mL) was added to the flask, followed by the addition of TMSCl (1 mol%) and 1,2-dibromoethane (5 mol%). Finally, 4-bromobenzonitrile (0.910 g, 5.0 mmol) and HBpin (0.73 mL, 5.0 mmol) were added. The reaction was refluxed overnight. After 24 hours, the reaction was cooled to room temperature and the reaction mixture was decanted. The solution was then quenched with 1 M HCl (3 mL). The reaction mixture was then transferred to a separatory funnel and extracted with diethyl ether (3 x 15 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and dried in vacuo, (25 °C, 1 Torr) to recover the 4-chloroiodobenzene starting material.

Preparation of Arylzinc Bromide from $CoBr_2$. A 25 mL round-bottom flask equipped with a magnetic stir bar and fitted with a rubber septum was cooled to 25 °C and was purged with Ar. Zn (0.392, 6 mmol), $CoBr_2$ (0.131g, 0.6 mmol), and

$ZnBr_2$ (0.135 g, 0.6 mmol) were added and the flask was re-purged with Ar. While venting, the flask was heated directly with a heat gun to a temperature of at least 120 °C for 30 min. The heat gun was then removed and the flask was purged with Ar as it cooled to room temperature. Anhydrous acetonitrile (12 mL) was added to the flask, followed by the addition of TMSCl (1 mol%) and 1,2-dibromoethane (5 mol%). Finally, aryl halide (5.0 mmol) and was added. The reaction was stirred at 50 °C overnight. After 24 hours, the reaction was cooled to room temperature and HBpin (0.58 mL, 4 mmol) was added dropwise. The reaction was stirred for 1 h. The reaction mixture was then decanted. The solution was then quenched with 1 M HCl (3 mL). The reaction mixture was then transferred to a separatory funnel and extracted with diethyl ether (3 x 15 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and dried in vacuo, (25 °C, 1 Torr) to provide the corresponding boronate ester.

Preparation of Arylzinc Bromide from $CoBr_2$ under Barbier Conditions. A 25 mL round-bottom flask equipped with a magnetic stir bar and fitted with a rubber septum was cooled to 25 °C and was purged with Ar. Zn (0.392 g, 6 mmol), $CoBr_2$ (0.131 g, 0.6 mmol), and $ZnBr_2$ (0.135 g, 0.6 mmol) were added and the flask was re-purged with Ar. While venting, the flask was heated directly with a heat gun to a temperature of at least 120 °C for 30 min. The heat gun was then removed and the flask was purged with Ar as it cooled to room temperature. Anhydrous acetonitrile (12 mL) was added to the flask, followed by the addition of TMSCl (1 mol%) and 1,2-dibromoethane (5 mol%). Finally, aryl halide (5.0 mmol) and HBpin (0.58 mL, 4

mmol) were added dropwise. The reaction was stirred at 50 °C overnight. After 24 hours, the reaction was cooled to room temperature and then decanted. The solution was then quenched with 1 M HCl (3 mL). The reaction mixture was then transferred to a separatory funnel and extracted with diethyl ether (3 x 15 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and dried in vacuo, (25 °C, 1 Torr) to provide the corresponding boronate ester.

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CHAPTER 4

Synthesis of Haloalkoxypinacolborates via Cyclic Ether Cleavage and the Synthesis of Pinacolboronate Esters Utilizing THF as a Leaving Group

4.1 Introduction

Since their initial discovery, boronic acids and esters have been prepared through treatment of trialkoxyboranes with a carbon nucleophile such as Grignard or organolithium reagents.[14,31,33,116,133] Despite the frequent use of these reagents, decades of publications have highlighted numerous drawbacks of this traditional. For example, obtaining high yields from the treatment of alkylborates with Grignard reagents requires that the Grignard be added to an ethereal solution of alkylborate; the reversed order of addition significantly lowers yields. Cryogenic conditions are also imperative to temper the high reactivity of the Grignard reagent and prevent over-addition. For alkyllithium reagents, the size of the borane trialkyl groups also greatly affects the yield; triisopropoxyborane must be used to ensure high yields.

In the investigation of alternative boron sources for both pre-formed Grignard reagents as well as Grignards formed under Barbier conditions, HBpin has emerged as a serviceable alternative. In the reaction with Grignard reagents, HBpin allows for only one nucleophilic addition; over-addition with HBpin does not occur. Work-up and isolation of the products are mild and efficient while directly affording the ester.

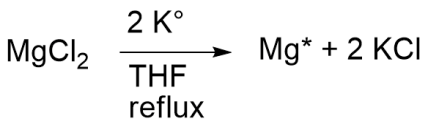
Despite these advantages over trialkoxyboranes, the use of HBpin does possess drawbacks. Pinacolborane as a reagent is air sensitive and demands careful handling. Previous studies by Singaram highlighted the limited stability of HBpin in various solvents.[121] In that same report, an extensive study was performed on the

formation and reaction of both HMgCl and HMgBr byproducts; HMgBr can further degrade to produce the reactive MgH_2.

In the investigation of the reaction between Grignard reagents and HBpin, it was discovered that I_2 reacts with HBpin to form IBpin, a reagent capable of cleaving the C-O bonds of various cyclic ethers.[188] For THF in particular, the butoxy moiety becomes incorporated between Bpin and iodine to form 4-iodobutylpinacolborate. The chapter herein outlines the C-O bond cleavage of IBpin and the viability of 4-iodobutylpinacolborate as an alternative boron source for the preparation of boronate esters from Grignards.

4.2 Activation of Magnesium for the Formation of Grignard Reagents

Numerous methods for the activation of Mg for sluggish organometallic reactions have been reported including activation by Rieke's method (Scheme 4.1),[189–191] evaporative sublimation,[192] addition of a catalytic amount of small haloalkyl compounds,[193]or treatment with aluminum hydrides.[194] Success has also been reported from the sonication of Mg turnings in ethereal solution.[195]

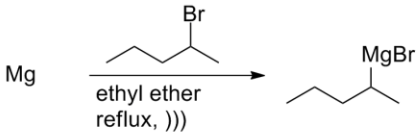


Scheme 4.1 Preparation of Rieke magnesium

The formation of Grignard reagents is severely inhibited by the presence of any water or alcohol molecules adsorbed to the Mg surface.[195] It has been proposed

that the sonication process shortens the induction period by dispersing any surface-bound oxygen species from the Mg. Two reactions were run side by side, monitoring the reaction of Mg turnings and 2-bromopentane at 50 °C with and without sonication in anhydrous diethyl ether (measured at 0.01% H_2O and 0.01% EtOH). In the absence of sonication, the induction period was 6 – 7 minutes, while the reaction under sonication was reported to have an induction period of < 0.17 minutes.

Table 4.1 Induction periods and yields for reaction of magnesium and 2-bromopentane in ethyl ether with varying water/alcohol content[195]



Ethyl Ether	Treatment[a]	Induction Period[b] (min)	Yield (%)
Anhydrous[c]	T	6-7	67
Anhydrous[c]	S	< 0.17	65
Reagent[d]	T	120-180[e]	54
Reagent[d]	S	3-4	53
Half saturated[f]	T	60-180[e]	58
Half saturated[f]	S	6-8	54

[a]T = thermal, S = sonochemical. [b]Results are an average of three independent determinations. [c]Contains 0.01% H2O, 0.01% EtOH. [d]Contains 0.5% H2O, 2% EtOH. [e]Reactions initiated only upon mechanical crushing of the magnesium at the time indicated. [f]Prepared by adding excess water to anhydrous ethyl ether, separating layers, and diluting the resulting wet ether with equal parts anhydrous ethyl ether.

Some reports in the literature suggest the vigorous stirring of dry Mg turnings in inert atmosphere is a sufficient alternative to chemical activation.[196] Formation of the Grignard reagent from the reaction of Mg powder and *p*-(dimethylamino)bromobenzene often fails when the Mg powder has not been activated by some method.[197] Even with activation, many activation methods have given unsatisfactory yields, leading to the analogous aryllithium reagents as an alternative. Mendel reported that simple activation of Mg by vigorous stirring under nitrogen atmosphere overnight was successful in producing higher yields of the *p*-(dimethylamino)phenylmagnesium bromide. The intense mechanical stirring caused milling of the Mg turnings to produce smaller fragments, which was then stored under inert atmosphere to prevent oxidation.

The most simple and common method of Mg activation has been treatment of solid Mg with sublimed I_2 followed by removal of the excess I_2 vapors (Figure 4.1).[198] Relatively simple, safe, and inexpensive, this process has seen use in both micro scale reactions as well as large scale quantities. The one drawback to using I_2 is recent classification of I_2 as a controlled substance. First, solid Mg and I_2 crystals are both added to an assembled, drying-tube capped reaction apparatus. Then, this semi-closed system is typically dried of adsorbed water through heating with a Bunsen burner. During this process, the I_2 is sublimed and coats the Mg surface. I_2 then reacts with Mg in locations where the unreactive MgO coating is either thin or absent, exposing a larger surface area of reactive Mg underneath.

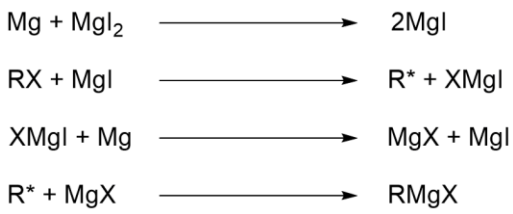


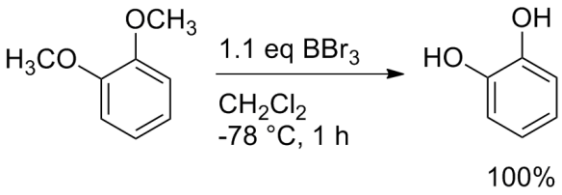
Figure 4.1 Proposed mechanism for the activation of magnesium with iodine

A variation to this method was developed by Gilman.[199] Magnesium turnings are added to benzene under a nitrogen atmosphere, followed by I_2. Then, dropwise addition of diethyl ether initiates the reaction. The mixture is stirred until the color disappears, signifying the complete reaction of the I_2. The solvents are then removed and the solid is dried via distillation, at which point the activated magnesium can be stored. To reactivate for use in a reaction, the solid is reheated until the I_2 color appears.

During the investigation of Grignard reagents and HBpin, complications arose in the formation of some heterocyclic Grignard reagents with untreated Mg. While the activation of Mg by iodine was later successful, in one reaction an excess of iodine remained present during the subsequent reaction between HBpin and the heterocyclic Grignard. This excess iodine led to a unique C-O bond cleavage reaction between iodine, Bpin, and the THF solvent.

4.3 Cleavage of Carbon-Oxygen Bonds with Boron Reagents

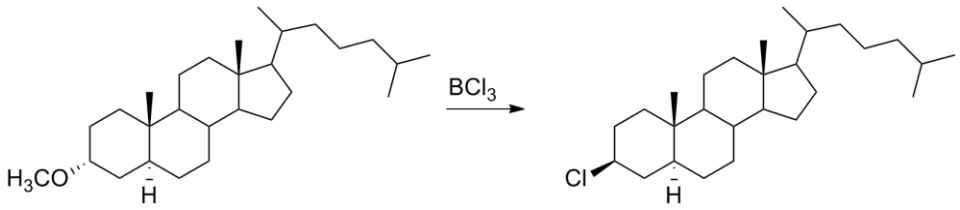
The reaction between various boron reagents and carbon-oxygen bonds has been reported.[200,201] For example, boron tribromide etherate (BBr_3:OEt_2) has been shown to selectively cleave aryl methyl ethers under mild conditions (Scheme 4.2).[202] Unfortunately, trihaloboranes tend to react with other sensitive functional groups due to the high Lewis acidity and tridentate nature of these compounds. Other reagents have been designed and tested to selectively cleave the carbon-oxygen bond by replacing the trihaloboranes with monohaloboranes containing two alkyl,[203] alkoxy,[204,205] thioalkyl,[206,207] or nitrogen-containing substituents[208] replacing the removed halides.



Scheme 4.2 *O*-Demethylation of catechol ether by boron tribromide

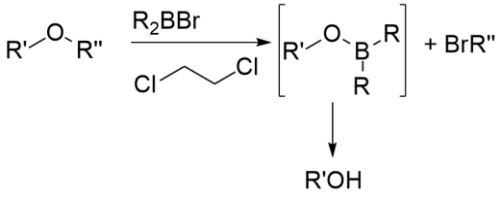
The investigations into these reagents originated from a need for ether-based protecting groups of alcohols by Yoakim.[203,209] Early on, the liberation of a parent alcohol from its methyl ether was achieved through treatment with organosilicon reagents,[19] thiol-Lewis acid reagents,[200] or boron halides. For example, BCl_3 was used to deprotect β-dihydrocholesterol 3-methyl ether but was unsuccessful, instead converting the steroid to 3-β-chlorocholestane (Scheme 4.3).[210] A similar conversion was seen with 2-methyltetrahydrofuran, which was treated with BBr_3 only to induce

non-regiocontrolled ring opening.[211] This competition between S_N1 versus S_N2 mechanisms are a common problem linked to the trihaloboranes.



Scheme 4.3 Conversion of β-dihydrocholesterol 3-methyl ether with BCl_3

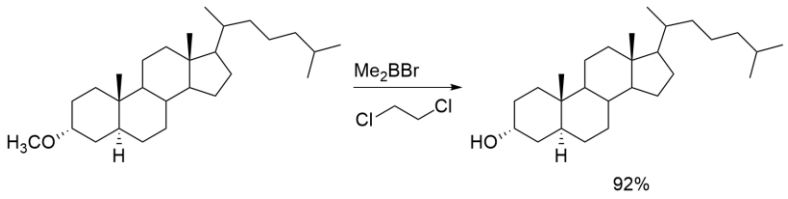
Despite these negative results, attempts were made to develop a modified monofunctional boron-halogen reagent that could selectively break the carbon-oxygen bond by exploiting the strong oxygenophilic character of boron. It was hypothesized that dialkylboron bromide reagents would be more controlled, as the steric and electronic effects of the two alkyl groups on boron could be changed to tune the reactivity of the B-Br bond and drive the reactivity towards either an S_N1 or $S_N2$mechanism as desired (Scheme 4.4).[209]



Scheme 4.4 Steric direction of ether cleavage by dialkylbromoborane

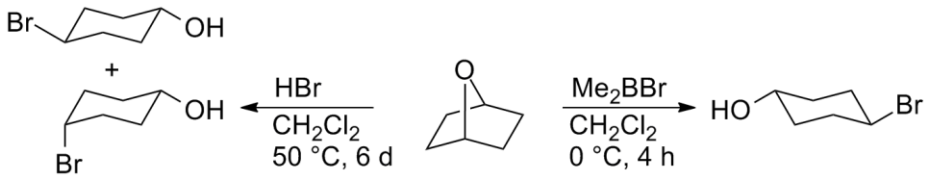
In fact, when β-dihydrocholesterol 3-methyl ether was treated with Me_2BBr in 1,2-dichloroethane at room temperature, β-dihydrocholesterol was recovered in high yields with only a trace amount of the substitution product formed (Scheme 4.5).

This proved successful with primary, secondary, and aryl alcohols while tertiary alcohols predominantly gave unwanted substitution product. The cleavage of cyclic ethers to give the corresponding bromoalcohols also smoothly occurred, an important example given the difficulty of organosilanes and thiol-Lewis acids to perform this transformation.



Scheme 4.5 Successful deprotection of β-dihydrocholesterol 3-methyl ether with Me_2BBr

Yoakim later reported a studyon the regiocontrolled opening of cyclic ethers, prompted by the observation that Me_2BBr typically cleaved C-O bonds in an S_N2 fashion. For example, the conversion of 2-methyltetrahydrofuran with Me_2BBrpredominantly yields 5-bromo-2-pentanol.[203] A range of different cyclic ethers were successfully cleaved to give the corresponding bromoalcohols in good yields. An interesting result was seen with the ring opening of the bicyclic ether 7-oxabicyclo[2.2.1]heptane via Me_2BBr, which gave only the *trans*-4-bromocyclohexanol after only 4 hours at 0 °C (Scheme 4.6). In contrast, the same ring opening performed with HBr afforded a mixture of both *cis*-and *trans*-products after 6 days at 50 °C.



Scheme 4.6 Cleavage of 7-oxabicyclo[2.2.1]heptane with both Me_2BBr and HBr

Brown continued investigating the realm of R_2BBr species, noting the formation of halohydrins predominantly proceeds through an S_N2 mechanism.[212] This should allow for the asymmetric C-O bond cleavage to proceed with a high degree of enantiotopic differentiation. This was during a time where the Brown lab was heavily invested in the field of asymmetric synthesis involving the reactions of boron-based chiral Lewis acids. *B*-Halodiisopinocampheylboranes (Ipc_2BX) were investigated, with both enantiomers being readily available from either (+)- or (-)-α-pinene (Figure 4.2).

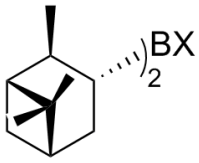
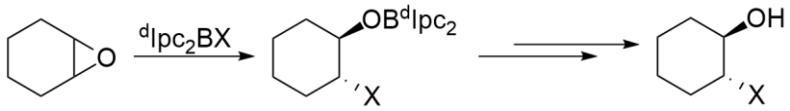


Figure 4.2 Structure of *B*-halodiisopinocampheylborane (Ipc_2BX) where X = Cl, Br, I

First, the interactions between $^{d}Ipc_2BX$ species and cyclohexene oxide were studied (Scheme 4.7). The $^{d}Ipc_2BX$ was derived from (+)-α-pinene and the effects of temperature, solvent, and molarity were all examined. As expected, an inverse correlation between the temperature and % ee was observed. At 0 °C, the reaction was complete in less than 5 minutes with poor induction. In order to produce good

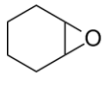
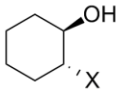
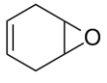
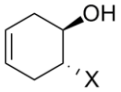
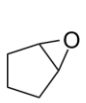
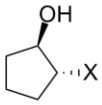
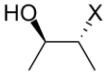
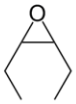
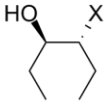
enantioselectivity, the reactions of $^{d}Ipc_2BCl$, $^{d}Ipc_2BBr$, and $^{d}Ipc_2BI$ required temperatures of -78 °C, -100 °C, and -100 °C respectively. Due to the inferior results for the reaction with cyclohexene oxide, $^{d}Ipc_2BCl$ was not studied further while $^{d}Ipc_2BBr$ and $^{d}Ipc_2BI$ became the focus.



Scheme 4.7 Reaction between cyclohexene oxide and $^{d}Ipc_2BX$ followed by reduction of the subsequent halohydrin

For both cyclohexene oxide and 1,4-cyclohexadiene monoepoxide, both $^{d}Ipc_2BBr$ and $^{d}Ipc_2BI$ gave high initial yields with excellent % ee (Table 4.2). A simple recrystallization in pentane could improve the % ee to nearly 100%. Reducing the ring size to cyclopentene oxide gave both reduced % ee and product yield. Similar results were seen when acyclic epoxides were employed.

Table 4.2 Optically active 1,2-halohydrins from *meso*-epoxides and $^{d}Ipc_2BX$[212]

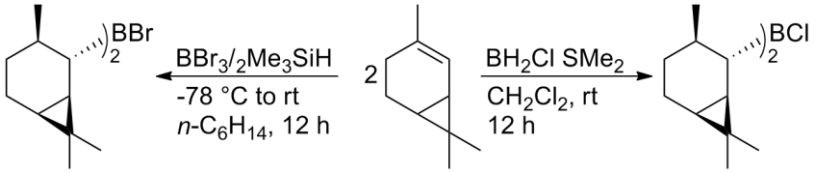
Epoxide	1,2-Halohydrin	X	Yield (%)	1*R*, 2*R* ee (%)
		Br	82	99
		I	89	100
		Br	72	63
		I	75	100
		I	63	52
		Br	69	61
		I	67	78
		Br	71	50
		I	75	69

In addition to the high optical induction from this reaction, the bond cleavage occurred in the same absolute fashion in all cases, with both $^{d}Ipc_2BBr$ and $^{d}Ipc_2BI$, yielding the (1*R*,2*R*)-halohydrins. These results were consistent with an anti C-O cleavage occurring with inversion at the S carbon of the *meso*-epoxide. To confirm this, a subsequent closing of the acyclic chiral non-racemic halohydrins was performed and afforded the starting *meso*-epoxide, an impossible result if the forward reaction occurred in a *syn* fashion. The direction of chirality in this transformation may be due to the conformations of the two isopinocamphyl rings, similar to the results seen with isopinocamphyl reagents in asymmetric hydroboration.[213]

One method of synthesizing complex optically active molecules involves starting from *meso*-compounds. In particular, vicinal halohydrins have be utilized as

intermediates for the synthesis of some halogenated natural products.[214,215] The desymmetrization of either *meso*- or racemic-epoxides has been achieved with a range of nucleophiles such as phenols, thiols, and amines. While halides have also been utilized as nucleophiles in the enantioselective cleavage of epoxides, only a small number of publications reported the synthesis of highly enantiomerically-enriched chlorohydrins. Only $^{d}Ipc_2BCl$ and $^{d}Ipc_2BBr$ provided moderate enantioselectivities in cleavage of *meso*-epoxides.

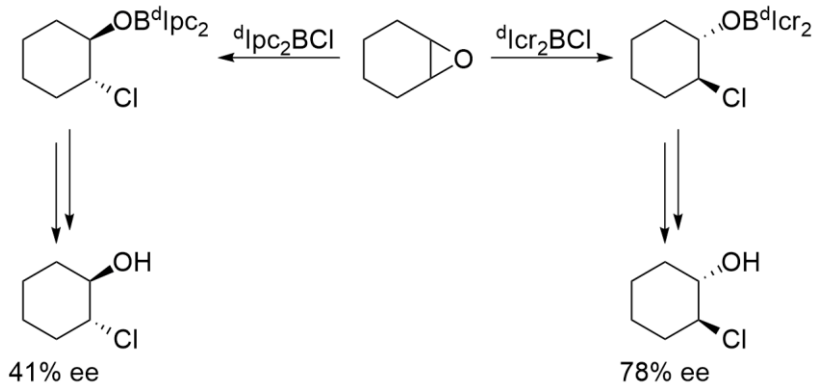
In 2006, Roy reported that hydroboration of commercially available (+)-2-carene with $BH_2Cl{\cdot}SMe_2$ produced *B*-chlorobis(2-isocaranyl)borane (2-$^{d}Icr_2BCl$), an alternative to Brown's $^{d}Ipc_2BCl$ (Scheme 4.8).[204] Roy also successfully synthesized *B*-bromobis(2-isocaranyl)borane (2-$^{d}Icr_2BBr$) from Matteson's BBr_3/Me_3SiH procedure. Both 2-$^{d}Icr_2BCl$ and 2-$^{d}Icr_2BBr$ showed marked improvement in the enantioselective cleavage of *meso*-epoxides over the $^{d}Ipc_2BX$ reagents.



Scheme 4.8 Preparation of 2-$^{d}Icr_2BCl$ and 2-$^{d}Icr_2BBr$

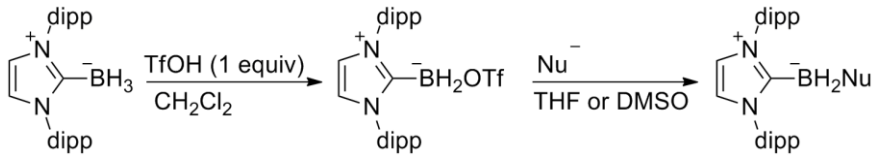
The cleavage of *meso*-cyclohexene oxide with 2-$^{d}Icr_2BCl$ provided an enantiomeric excess of 78% while $^{d}Ipc_2BCl$ only achieved an enantiomeric excess of 41% (Scheme 4.9). An 18-19% improvement was achieved in the case of *meso-cis*-2,3-butene oxide cleaved by 2-$^{d}Icr_2BCl$ in comparison to $^{d}Ipc_2BCl$. Similar results

were observed in the enantioselective ring opening with $^{d}Ipc_2BBr$. Previously, $^{d}Ipc_2BBr$ yielded respectable enantiomeric excesses with *meso*-cyclopentene oxide (57%) and *meso-cis*-2,3-butene oxide (61%). Revisiting this methodology with 2-$^{d}Icr_2BBr$ also showed improved enantiomeric excesses (67% and 78%, respectively).



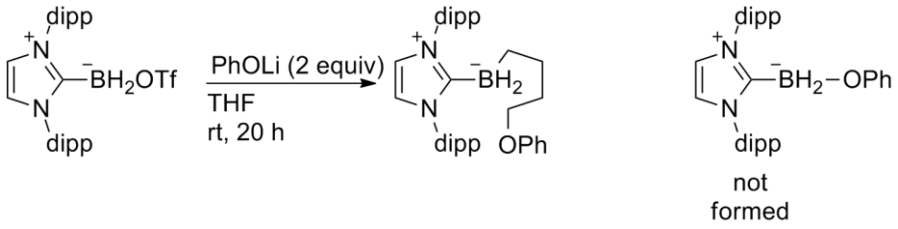
Scheme 4.9 Asymmetric ring opening of cyclohexene oxide with $^{d}Ipc_2BCl$ and $^{d}Icr_2BCl$

N-Heterocyclic carbene-boranes have emerged as reagents for free radical chemistry[216–218] and polymer synthesis.[219–221] Recently, Curran reported that NHC-BH_2X species, where X is a leaving group (OTf, Br, I), are easily prepared by the reactions of NHC-boranes with acids or nucleophiles (Scheme 4.10).[222]



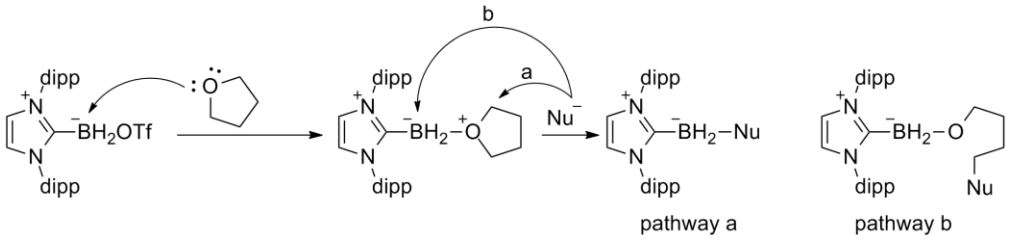
Scheme 4.10 Nucleophilic substitutions on NHC-boranes

The resulting intermediate complexes can be used as boron electrophiles. In one experiment, the expected product from the reaction of 1,3-bis(2,6-diisopropylphenyl)imidazole-2-ylidene (dipp-Imd) borane with lithium phenoxide (PhOLi) was dipp-Imd-BH_2OPh (Scheme 4.11). Despite the reaction completing after 20 hours at room temperature in THF, the resulting complex was the unexpected dipp-Imd-$BH_2O(CH_2)_4OPh$.



Scheme 4.11 Substitution of dipp-Imd borane with lithium phenoxide in THF

The reaction had incorporated one molecule from the THF solvent in between the electrophile borane and nucleophilic alkoxide. Instead of directly reacting with the phenoxide, the dipp-Imd-BH_2 acted as a Lewis base and complexed with a THF molecule. This interaction increased the electrophilicity of the cyclic ether C-O bond, followed by nucleophilic attack by phenoxide to cleave open the ring and tether the THF moiety between the phenoxide and borane.



Scheme 4.12 NHC-borane coordination with THF and two possible nucleophilic attack pathways

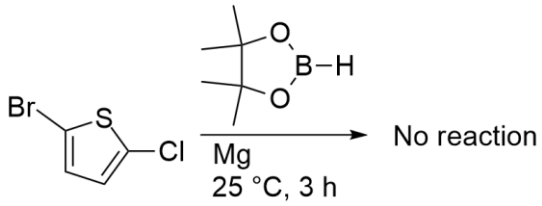
Several reactions were performed to study the mechanism. An overnight reflux of only dipp-Imd-BH_2 in THF yielded no ring-opened product. In a similar investigation, the reaction of dipp-Imd-BH_2OTf with 2,6-dimethylphenoxide (ArOK) in THF mainly produced ring-opening product with only trace of the substituted dipp-Imd-BH_2OAr. Conversly, the ring-opening mechanism could be bypassed by performing the reaction in toluene in the presence of a crown ether to increase the solubility of the alkoxide nucleophile.

4.4 Results

4.4.1 Reactions of Halides and Pinacolborane

When preparing Grignard reagents under Barbier conditions for the synthesis of pinacolboronate esters, formation of the 5-halo-2-thienylmagnesium bromides was unsuccessful (Scheme 4.13). To a solution of 2-bromo-5-chlorothiophene in THF, both HBpin and Mg turnings were added and the mixture was left to stir overnight at 25 °C. The presence of unreacted Mg prompted a ^{11}B NMR analysis of the reaction mixture, with the doublet corresponding to unreacted HBpin present (δ +28, J = 174

Hz) and no other boron species observed in solution. Work-up and isolation of the solution gave the recovered thiophene starting material. Typically, this same methodology with substituted bromochlorobenzenes was successful in forming the Grignard reagents and subsequent reaction with HBpin in only 3 hours.

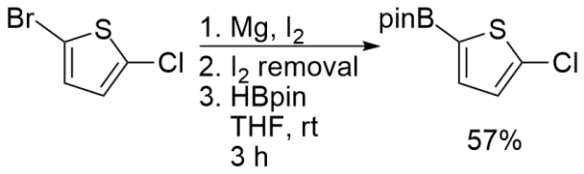


Scheme 4.13 Unsuccessful formation of thienyl Grignard under Barbier conditions

First, the quality of the Mg turnings was doubted, suspecting a significant amount of unreactive magnesium oxide coating was present. The first attempt to improve reactivity involved the treatment of the Mg turnings with 1 M HCl for 1 minute, followed by filtration. Then, the turnings were immediately rinsed with reagent acetone to remove residual water and acid before being transferred to a flask and stored under inert atmosphere until use. These turnings also proved unsuccessful in forming the thienylmagnesium bromide nucleophile.

Previous reports showed success when vigorous stirring could be used to mill dry Mg powder in inert atmosphere, therefore increasing the surface area of pure Mg. This methodology was attempted with the HCl-treated Mg turnings, however no reaction took place with the dihalothiophenes and the milled Mg.

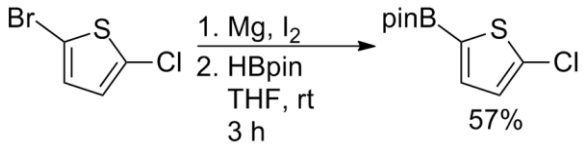
A simple and common method of Mg activation is treatment of solid Mg with sublimed I_2 followed by removal of the excess I_2 vapors (Scheme 4.14). First, a small crystal of iodine was added to an argon flushed flask containing Mg turnings. The flask was sealed and directly heated with a heat gun to sublimate the iodine. Once fully sublimated, the excess iodine vapors were removed by venting and THF was added to the solution, followed by HBpin and the 5-bromo-2-chlorothiophene substrate. The reaction proceeded as expected under Barbier conditions, completing in 3 hours to yield the 5-chloro-2-thienylpinacolboronate ester.



Scheme 4.14 Formation of thienylmagnesium bromide under Barbier conditions and synthesis of 5-chloro-2-thienylpinacolboronate ester

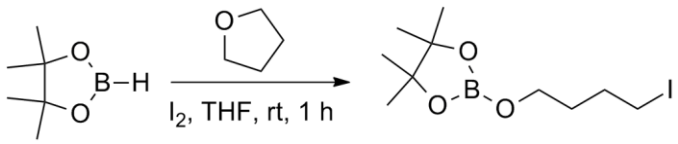
In one instance, I_2 was added to the reaction flask to activate the Mg towards reaction with the 2-chloro-5-bromothiophene substrate (Scheme 4.15). However, the excess I_2 was not removed via evaporation before the THF solvent was added and instead the excess $I_2$was dissolved in the reaction mixture to give a dark yellow-brown solution. It was hypothesized that the excess I_2 could be detrimental to the reaction, as previous literature reportedI_2 can react with B-H containing organoborane compounds. Despite this oversight of not evaporating the excess I_2, the remaining reagents were added (HBpin followed by the 2-chloro-5-bromothiophene substrate) to

the yellow-brown solution. The reaction mixture decolorized to a clear colorless solution after 3 hours and the desired boronate ester was produced. This result was unusual; it was predicted the I_2 would instantaneously inactivate HBpin and prevent addition of the Grignard reagent to form the boronate ester. Instead, the reaction seemed to yield the originally expected product.



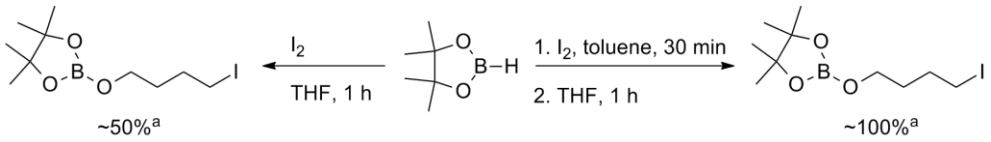
Scheme 4.15 Formation of thienylmagnesium bromide under Barbier conditions and synthesis of 5-chloro-2-thienylpinacolboronate ester

In order to understand this unexpected reaction, an examination of the reaction of I_2 and HBpin was performed. Tetrahydrofuran was added to a known amount of I_2 to produce a dark yellow solution, followed by the slow addition of one equivalent of HBpin. The yellow solution slowly clarified and after twenty minutes the isolated product was determined to be 4-iodobutylpinacolborate (IboxBpin) by ^{1}H, ^{13}C, and ^{11}B NMR spectroscopy.



Scheme 4.16 Formation of 4-iodobutylpinacolborate

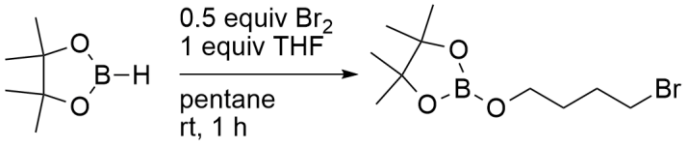
Interestingly, Brown's synthesis of $^{d}Ipc_2BX$ only required stirring 0.5 eq of I_2 with $^{d}Ipc_2BH$ in pentane. In contrast, our reaction using 0.5 eq I_2 in THF with HBpin stopped at 50% completion with unreacted HBpin still present in the ^{11}B NMR. An attempt was made to synthesize IBpin by mirroring Brown's reaction conditions, combining HBpin with 0.5 eq I_2 in pentane rather than THF. The IBpin species could not be characterized by ^{11}B NMR spectroscopy, most likely due to poor solubility of IBpin in pentane. However, repeating the same reaction in toluene also proved successful and the quantitative formation of IBpin was verified by ^{11}B NMR spectroscopy (Scheme 4.17).



Scheme 4.17 Formation of 4-iodobutylpinacolborate in both nonpolar and ether solvents; [a]yields calculated by ^{11}B NMR

It was hypothesized the bromide homolog BrBpin could be synthesized under similar conditions from Br_2. Pinacolborane was slowly introduced dropwise to a solution of Br_2 in pentane over 1 minute. Once the final drops of HBpin were added to the solution, the clarifying of the deep red color occurred almost instantly. A ^{11}B NMR confirmed the complete disappearance of HBpin. Presumably, the increased solubility of liquid Br_2 in pentane greatly increased the rate of reaction with HBpin. In contrast, the reduced solubility of I_2 in nonpolar solvents slowed the reaction rate with HBpin.

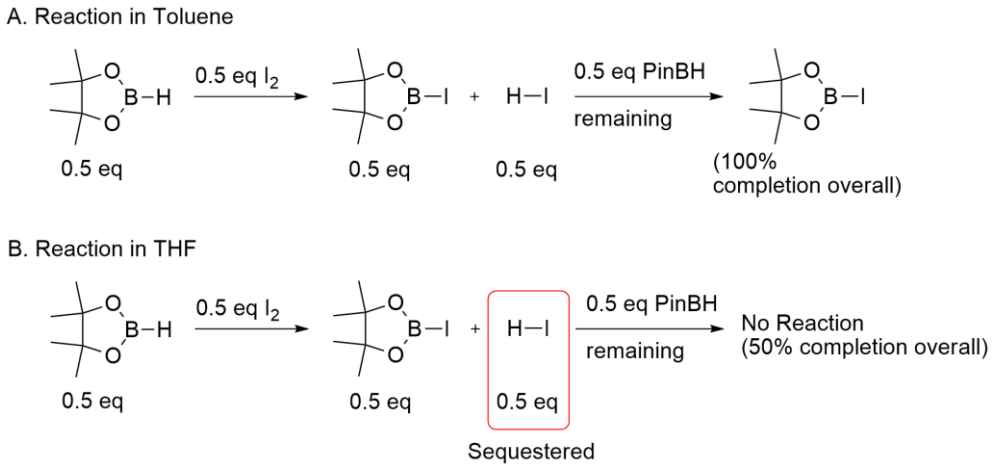
Similar results were observed in the preparation of 4-bromobutylpinacol borane in comparison to 4-iodobutylpinacolborate (Scheme 4.18). To a pentane solution containing 0.5 eq of Br_2 and 1 eq of THF, HBpin was added dropwise. As expected, the solution immediately clarified after the final drops of HBpin were added, indicating the disappearance of Br_2. The reaction was left to stir for 1 hour to ensure complete cleavage of THF to form the 4-bromobutylpinacol borate. Isolation via evaporation of the solvent provided yields of 4-bromobutylpinacol borate comparable to 4-iodobutylpinacolborate prepared with the analogous methodology. Despite the increased rate of reaction, the difficulty of handling Br_2 paired with the minimal difference in yields prompted 4-iodobutylpinacolborate to be the reagent of focus.



Scheme 4.18 Formation of BrBpin and subsequent cleavage of THF

The mechanistic pathway of the reaction between HBpin and I_2 was hypothesized (Scheme 4.19). The initial reaction between 0.5 eq I_2 and half of the HBpin produced IBpin and HI. In toluene or pentane, the HI is then available to react with the remaining half of the HBpin to produce IBpin and H_2. However, when this same reaction is carried out in THF, the 0.5 eq HI can undergo a side reaction, possibly creating 4-iodobutanol, and preventing HI from reacting with the remaining HBpin. This would require a full equivalent of I_2 to fully consume HBpin in the

presence of an ether solvent such as THF. These observations strongly correlated with observations made by Curran in the ring-opening reaction of NHC-boranes with THF.

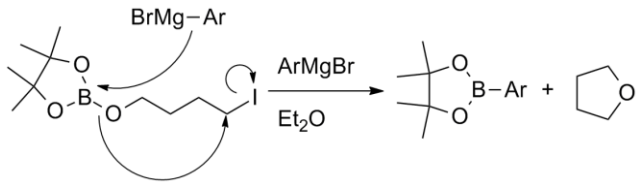


Scheme 4.19 Formation of IBpin in both toluene (A) and THF (B)

4.4.2 Reactions of Iodobutylpinacolborate with Grignard Reagents

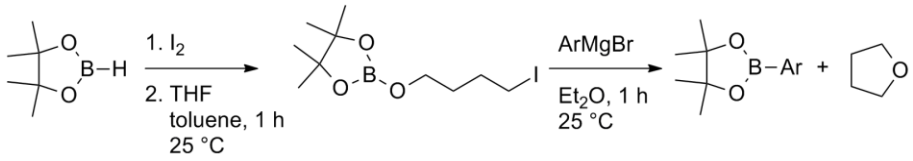
Because of the earlier successful synthesis of arylboronate esters from thienylmagnesium bromide and presumably 4-iodobutylpinacolborate, it was suspected that in-situ generated Grignard reagents were capable of reacting with the 4-iodobutylpinacolborate species in a similar manner Grignards reacting with HBpin. The variation between these reactions of Grignard reagents with 4-iodobutylpinacolborate and HBpin is the liberated leaving group once the Grignard nucleophile attacks (Scheme 4.20). With HBpin, hydride is liberated from the intermediate borate complex to form HMgBr and ArBpin. Subsequently, HMgBr readily dissociates to MgH_2 and $MgBr_2$ in solution. In this new reaction, 4-

iodobutoxide is released from the intermediate borate complex as a leaving group. This highly reactive haloalkoxide then undergoes intramolecular cyclization to re-form THF and afford ArBpin under neutral non-reducing conditions.



Scheme 4.20 Possible mechanism for the reaction of Grignard with 4-iodobutylpinacolborate

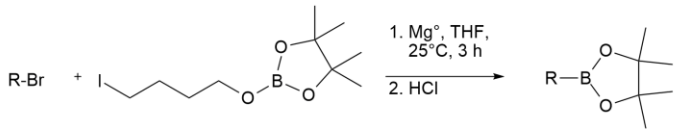
To probe the reaction, IBpin was separately synthesized in toluene under our general conditions, followed by dropwise addition of 1 equivalent of THF to produce 4-iodobutylpinacolborate (Scheme 4.21). The solvent was removed via evaporation and the product was checked by NMR spectrum for purity. Then, the 4-iodobutylpinacolborate was added to a solution of anhydrous diethyl ether, followed by dropwise addition of 3-tolylmagnesium bromide in Et_2O at -78 °C. The reaction was stirred and allowed to warm to room temperature, producing $MgBr_2$ as a white precipitate. A ^1H NMR spectrum of the isolated precipitate in D_2O showed the presence of THF, stemming from the release and subsequent cyclization of iodobutoxide. Singaram and Clary have previously reported that $MgBr_2$ readily coordinates to 4 equivalents of THF, confirmed by X-ray crystallography.

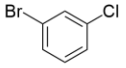
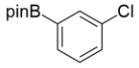
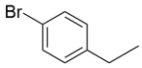
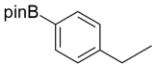
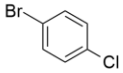
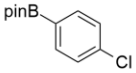
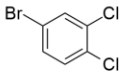
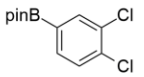
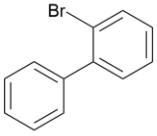
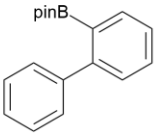
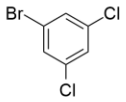
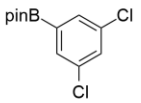
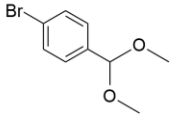
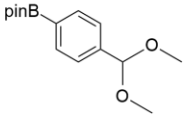


Scheme 4.21 Reaction of Grignard with 4-iodobutylpinacolborate to liberate the arylboronate ester and THF

After removal of the precipitate and subsequent aqueous work-up, the corresponding 3-tolyl pinacolboronate ester was confirmed as the product. With this information in hand, this system was tested with substrates that proved successful with previous work involving HBpin and Grignards formed under Barbier conditions (Table 4.3). In contrast to the reaction of HBpin, which results in release of MgH_2, this reaction provides a new method of synthesizing arylpinacolboronate esters from borates utilizing THF as a leaving group.

Table 4.3 Synthesis of arylboronate esters from IboxBpin; [a]reaction conditions: IboxBpin (2.0 mmol), anhydrous THF (8 mL), Mg turnings (2.0 mmol), haloaryl substrate (2.0 mmol), argon, 25 °C, 1 h. [b]1 M NH_4Cl (3 mL) was used instead of 1 M HCl during work-up.



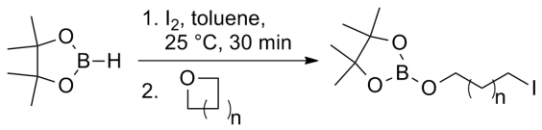
Haloaryl-Br	Product	Yield (%)	Haloaryl-Br	Product	Yield (%)
		79			85
		71			83
		85			88
					70[b]

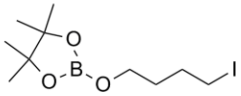
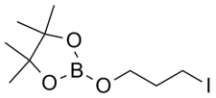
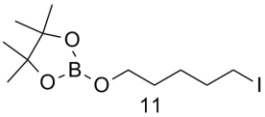
4.4.3 Cyclic Ether Cleavage by *B*-Halopinacolboranes

A study was performed on the cleavage of simple cyclic ethers using this new system, suspecting that different sized cyclic ethers could be employed to tune the electrophilicity of the boron center (Table 4.4). A very notable difference in the reaction rates with ethers of different ring sizes was observed. The initial reactions used THF, which only required 1 h of stirring in the presence of IBpin to form the

corresponding 4-iodobutylpinacolborate. When the ring size was increased to six atoms, by adding tetrahydropyran (THP) to IBpin instead of THF, the reaction required at least 24 h to go to completion. Conversely 1,3-trimethylene oxide (oxetane), a four membered cyclic ether, reacted almost instantaneously.

Table 4.4 Cleavage of various cyclic ethers by IBpin



Ether	Product	Yield (%)	Reaction time
	 9	97	1 h
	 10	83	< 1 min
	 11	89	24 h

The resulting chain length also had a profound impact on the stability of the iodoalkylborate products. Whereas 4-iodobutylpinacolborate degrades when the solvent is completely removed and left open to air, it also degrades within several hours in various solvents as evidenced by the dark yellow color that develops. The product of the reaction between IBpin and THP, 5-iodopentylpinacol borate, is relatively more stable, but still degrades in air and in polar solvents. In contrast 3-

iodopropylpinacolborate, which is produced from IBpin and trimethylene oxide, is much more stable even in the absence of solvent.

The relative stabilities of these three iodoalkoxypinacolborate derivatives can be rationalized by the propensity for recyclization of the liberated haloalkoxy moiety. While Baldwin's rules suggest that these cyclizations are possible, as 3- to 7-*exo-tet* cyclizations are favorable, the rate of formation for the 4-membered ring oxetane at room temperature is slow. Previous reports of oxetane synthesis via an intramolecular oxide displacement suggest refluxing temperatures are required. In contrast, the spontaneous formation of the 5-membered THF or 6-membered THP at room temperature is kinetically favorable.

4.5 Conclusion

In summary, a mild, efficient, and inexpensive method for synthesizing haloaryl pinacolboronate esters under Barbier conditions in good to excellent yields has been developed. Through the course of this work, a novel boron electrophile, IboxBpin, synthesized via the ring opening of cyclic ethers by IBpin has been discovered. This IBpin species can then react with different sized cyclic ethers to provide the corresponding iodoalkoxypinacol borates. IboxBpin in particular can also react with aryl Grignard reagents to produce the corresponding aryl pinacolboronate esters while liberating THF as a leaving group. This is an improvement, as previous work with HBpin leads to the release of hydride in the form of HMgBr which could

prove problematic for sensitive functionalities, where our current work liberates neutral THF and avoids potential compatibility issues.

4.6 Experimental

General Methods. All reactions were performed in oven-dried, argon-cooled glassware. The HBpin was used as received from Aldrich and stored under Ar in a refrigerator held at 15 °C. All halide-containing substrates were used as received from Aldrich. Magnesium metal was used as received from Aldrich. Iodine was used as received from Aldrich. All air- and moisture-sensitive compounds were introduced via syringes or cannula through a rubber septum. HBpin was added via syringe, with the dispensed amount measured by mass difference of the syringe before and after addition. Tetrahydrofuran (THF) was freshly obtained by a solvent purification system (Pure Solv MD, Innovative Technology Inc.). NMR spectra were recorded in $CDCl_3$. Chemical shifts are reported relative to TMS (δ 0) for ^1H NMR (500 MHz) and is referenced to the $CDCl_3$ resonance (δ 77) for ^{13}C NMR (125 MHz) spectra. Data is reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, br =broad, m = multiplet, app = apparent), coupling constant, and integration. Boron NMR samples were recorded at 160.4 MHz and are reported relative to the external standard $BF_3 \cdot Et_2O$ (δ 0). High-resolution mass spectra were obtained by electrospray ionization experiments.

General Procedure for the Preparation of IboxBpin in THF. A 25 mL round-bottom flask equipped with a magnetic stir bar and fitted with a rubber septum

was cooled to 25 °C and was purged with Ar. I_2 (0.508 g, 2.0 mmol) was added and the flask was re-purged with Ar. Anhydrous THF (8 mL) was added to the flask, followed by the addition of neat pinacolborane (0.29 mL, 2.0 mmol) dropwise over 5 min with constant stirring at 25 °C to provide a dark yellow solution. The reaction was complete after 1 h, as evidenced by changing the solution to colorless. Brine (3 mL) was then added. The reaction mixture was then transferred to a separatory funnel and extracted with diethyl ether (3 x 15 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and dried in vacuo, (25 °C, 1 Torr) to afford IboxBpin as a clear oil.

General Procedure for the Preparation of IodoalkoxyBpin in Toluene. The following procedure is representative. A 25 mL round-bottom flask equipped with a magnetic stir bar, fitted with a rubber septum and the flask was cooled to 25 °C and was purged with Ar. I_2 (0.254 g, 1.0 mmol) was added and the flask was re-purged with Ar. Dry toluene (8 mL) was added to the flask, producing a dark pink solution, followed by the addition of neat pinacolborane (0.29 mL, 2.0 mmol) dropwise over 5 min with constant stirring at 25 °C. A yellow fume evolved but was allowed to settle and dissolve. The formation of IBpin was complete after 30 min, as evidenced by the disappearance of pinacolborane starting material (δ +27.7, d, J = 173.9 Hz) and the appearance of a singlet at +21.6 ppm via ^{11}B NMR. The cyclic ether substrate (2.0 mmol) was then added dropwise and the reaction was allowed to stir. The reaction was complete after 1 h, as evidenced by changing the solution to colorless. Brine (3 mL) was then added to the reaction flask. The reaction mixture

was then transferred to a separatory funnel and extracted with diethyl ether (3 x 15 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and dried in vacuo, (25 °C, 1 Torr) to afford IodoalkoxyBpin.

2-(3-Iodopropoxy)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane Clear oil; 83% yield (0.518 g). ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.93 (t, *J* = 5.5 Hz, 2H), 3.29 (t, *J* = 6.5 Hz, 2H), 2.09 (m, 2H), 1.27 (s, 12H).^{13}C NMR (125.7 MHz, $CDCl_3$): δ83.0, 64.4, 35.0, 24.6, 2.5. ^{11}B NMR (160.4 MHz, $CDCl_3$): δ +23 (s). HRMS (ESI): *m/z* calcd for $C_9H_{18}BIO_3$ 311.04, found 311.10.

2-(4-Iodobutoxy)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane Clear oil; 97% yield (0.632 g). ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.88 (t, *J* = 6.2 Hz, 2H), 3.20 (t, *J* = 7.0 Hz, 2H), 1.90 (m, 2H), 1.67 (m, 2H), 1.22 (s, 12H).^{13}C NMR (125.7 MHz, $CDCl_3$): δ81.5, 62.3, 30.9, 28.5, 23.3, 5.3. ^{11}B NMR (160.4 MHz, $CDCl_3$): δ +22 (s). HRMS (ESI): *m/z* calcd for $C_{10}H_{20}BIO_3$ 325.06, found 325.06.

2-(5-Iodopentoxy)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane Clear oil; 89% yield (0.605 g). ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.87 (t, *J* = 6.5 Hz, 2H), 3.20 (t, *J* = 7.5 Hz, 2H), 1.87 (m, 2H), 1.61 (m, 2H), 1.49 (m, 2H), 1.26 (s, 12H).^{13}C NMR (125.7 MHz, $CDCl_3$): δ81.5, 62.3, 32.0, 29.1, 25.4, 23.3 5.5. ^{11}B NMR (160.4 MHz, $CDCl_3$): δ +23 (s). HRMS (ESI): *m/z* calcd for $C_{11}H_{22}BIO_3$ 339.07, found 339.10.

General Procedure for the Preparation of Pinacolboronate Esters from IboxBpin. The following procedure is representative. A 25 mL round-bottom flask equipped with a magnetic stir bar and fitted with a rubber septum was cooled to 25 °C

and purged with Ar. IboxBpin (0.651 g, 2.0 mmol) was added to the flask, followed by the addition of anhydrous THF (8 mL). The corresponding Grignard reagent (2.0 mmol) was then introduced dropwise over 5 min with constant stirring at 25 °C. The reaction was complete after 1 h, as evidenced by the disappearance of IboxBpin (δ +21.6) via ^{11}B NMR. 1 M HCl (3 mL) was then added to the reaction flask and left to stir for 5 min. The reaction mixture was then transferred to a separatory funnel and extracted with diethyl ether (3 x 15 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and dried in vacuo, (25 °C, 1 Torr) to afford the corresponding pinacolboronate ester.

2-(3-Chlorophenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane Colorless oil; 73% yield (0.598 g). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.79 (s, 1H), 7.69 (d, *J* = 7 Hz, 1H),7.44 (d, *J* = 8 Hz, 1H), 7.31 (t,*J* = 7.5, 1H), 1.36 (s, 12H). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ 134.6, 132.7, 131.3, 129.2, 84.2, 24.8.^{11}B NMR (160.4 MHz, $CDCl_3$): δ +31 (s).

2-(4-Chlorophenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane Colorless oil; 72% yield (0.373 g). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.76 (d,*J* = 8.5,2H), 7.63 (d, *J* = 8.5 Hz, 2H), 1.35 (s, 12H).^{13}C NMR (125.7 MHz, $CDCl_3$): δ 137.5, 136.1, 128.1, 127.9, 83.9, 24.8.^{11}B NMR (160.4 MHz, $CDCl_3$): δ +31 (s).

2-(2-Biphenyl-2-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane Colorless oil; 85% yield (0.476 g). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.80 (d, *J* = 7.5 Hz, 1H), 7.44 (m, 8H), 1.27 (s, 12H).^{13}C NMR (125.7 MHz, $CDCl_3$): δ 147.6, 143.3, 134.5, 130.1,

129.2, 129.0, 127.8, 126.8, 126.3, 83.7, 24.6.^{11}B NMR (160.4 MHz, $CDCl_3$): δ +33 (s).

2-(4-Ethylphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane Colorless oil; 85% yield (0.394 g). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.75 (d,*J* = 8 Hz,2H),7.23 (d,*J* = 8 Hz,2H), 2.69 (q,*J* = 7.5 Hz,2H), 1.34 (s, 12H),1.25 (t,*J* = 8 Hz,3H). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ 147.7, 134.9, 127.3, 83.6, 29.1, 24.9, 15.5.^{11}B NMR (160.4 MHz, $CDCl_3$): δ +33 (s).

2-(3,4-Dichlorophenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane Yellow oil; 83% (0.453g).^{1}H NMR (500 MHz, $CDCl_3$): δ 7.87 (s, 1H), 7.61 (d, *J* = 8 Hz, 1H), 7.45 (d, *J* = 8 Hz, 1H),1.35 (s, 12H). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ 136.6, 135.5, 133.8, 132.3, 130.0, 84.4, 24.8, ^{11}B NMR (160.4 MHz, $CDCl_3$): δ +32 (s).

2-(3,5-Dichlorophenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane Yellow oil; 88% (0.480g).^{1}H NMR (500 MHz, $CDCl_3$): δ 7.66 (d, *J* = 2 Hz, 2H), 7.45 (t, *J* = 2.5 Hz,1H), 1.35 (s, 12H). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ 134.7, 135.5, 132.7, 132.4, 131.0, 84.5, 24.8, ^{11}B NMR (160.4 MHz, $CDCl_3$): δ +31 (s).

2-(4-(Dimethoxymethyl)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane

Colorless oil; 70% yield (0.389 g). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.79 (d, *J* = 8 Hz, 2H), 7.42 (d, *J* = 8 Hz, 2H), 5.36 (s, 1H), 3.25 (s, 6H), 1.30 (s, 12H).^{13}C NMR (125.7 MHz, $CDCl_3$): δ 140.9, 134.7, 126.1, 102.9, 84.0, 52.6, 24.9.^{11}B NMR (160.4 MHz, $CDCl_3$): δ +30 (s).

Confirmation of THF Release from IboxBpin Reacting with Grignard Reagents. A 25 mL round-bottom flask equipped with a magnetic stir bar and fitted with a rubber septum was cooled to 25 °C and purged with Ar. IboxBpin (0.651g, 2.0 mmol) was added to the flask, followed by the addition of anhydrous THF (8 mL).Grignard reagent (2.0 mmol) was then introduced dropwise over 5 min with constant stirring at 25 °C. The reaction was complete after 1 h, as evidenced by the disappearance of IboxBpin (δ +21.6) via ^{11}B NMR with a precipitate forming. The precipitate was allowed to settle, the supernatant decanted off, and then taken up in $CDCl_3$ for ^{1}H and ^{13}C NMR analysis, with THF and toluene clearly visible.

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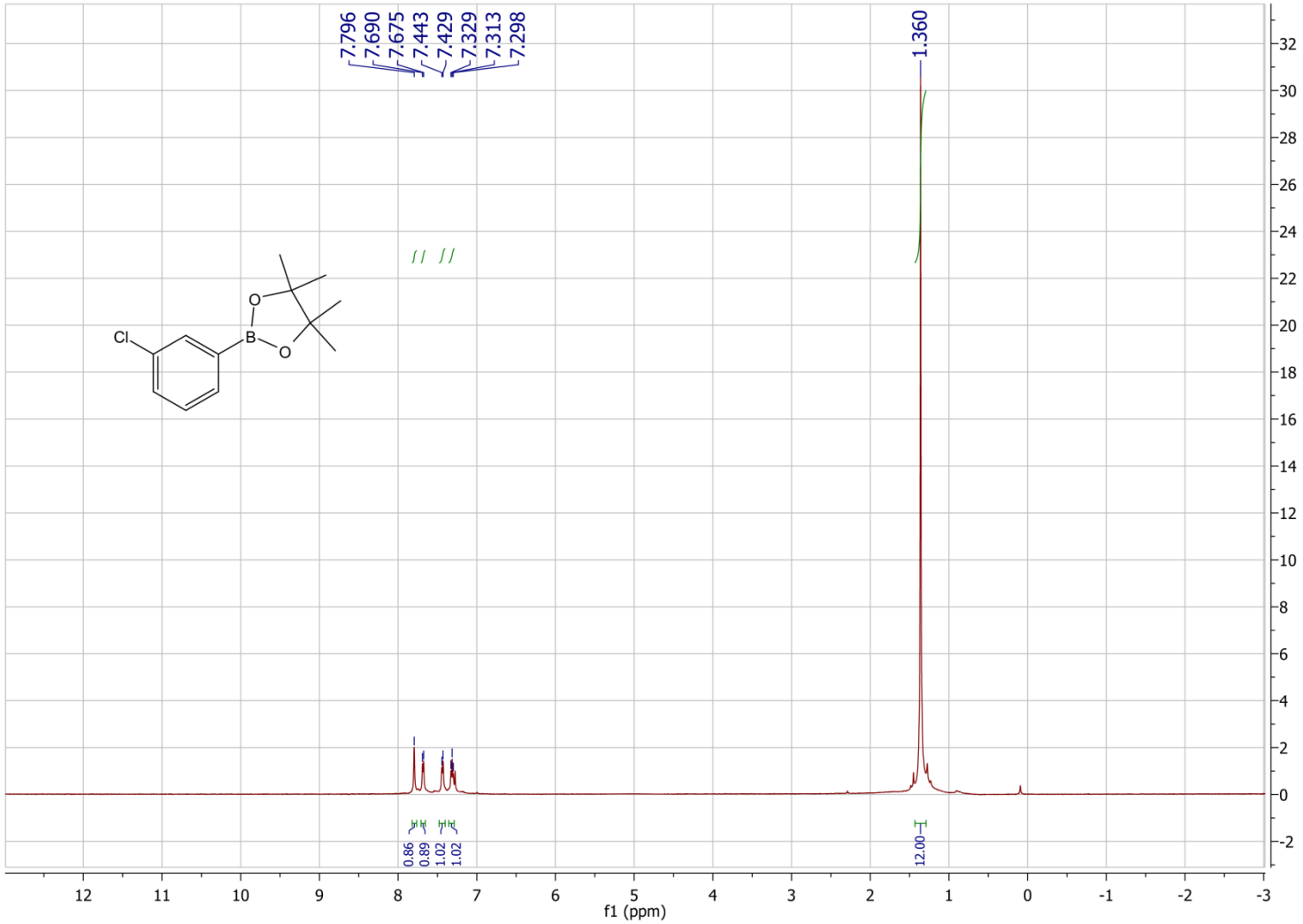
Appendix A

CHAPTER 2. ^{1}H, ^{11}B, and ^{13}C NMR Spectra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7.690
7.675
7.443
7.429
7.329
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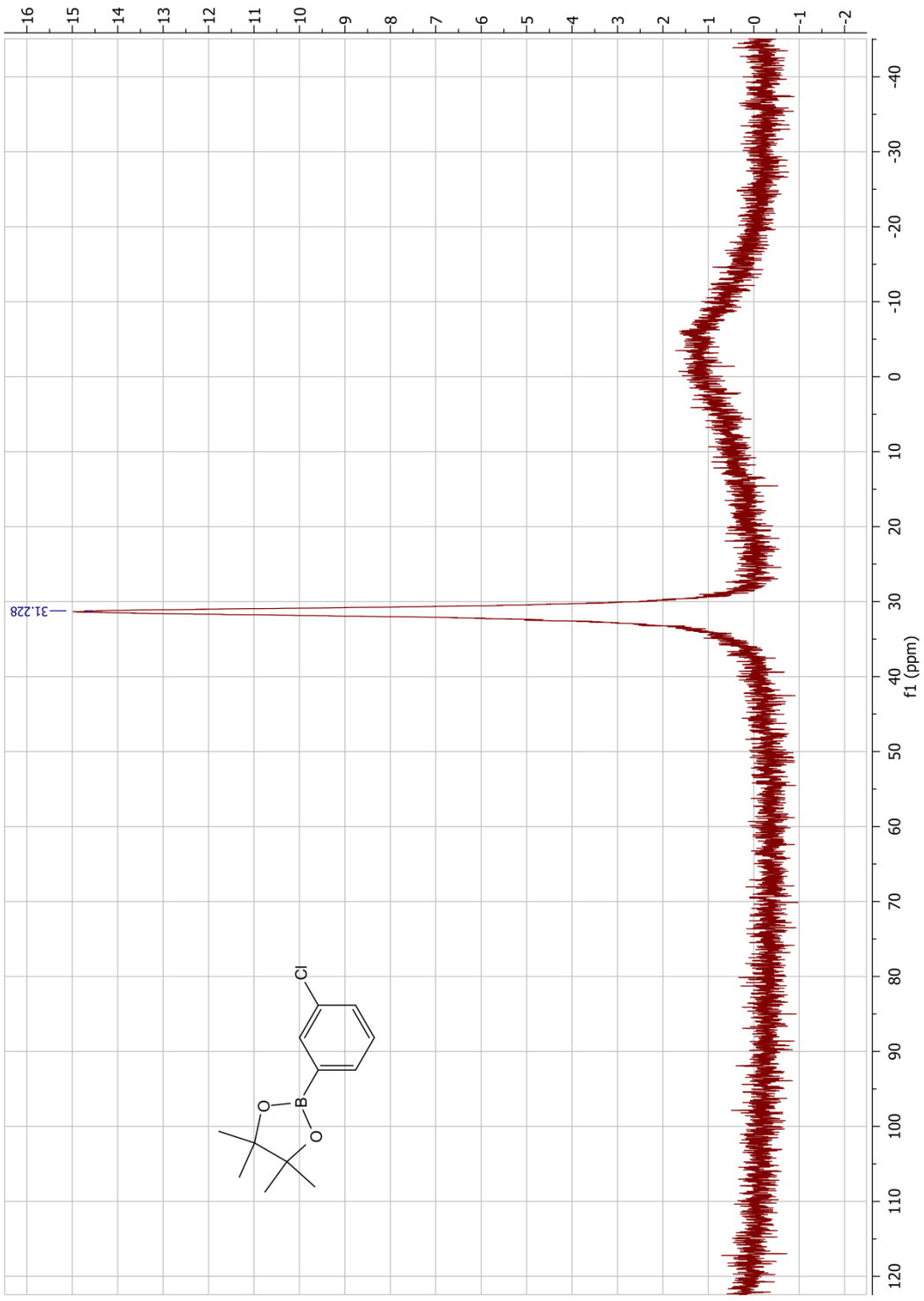
0.89
1.02
1.02
12.00
f1 (ppm)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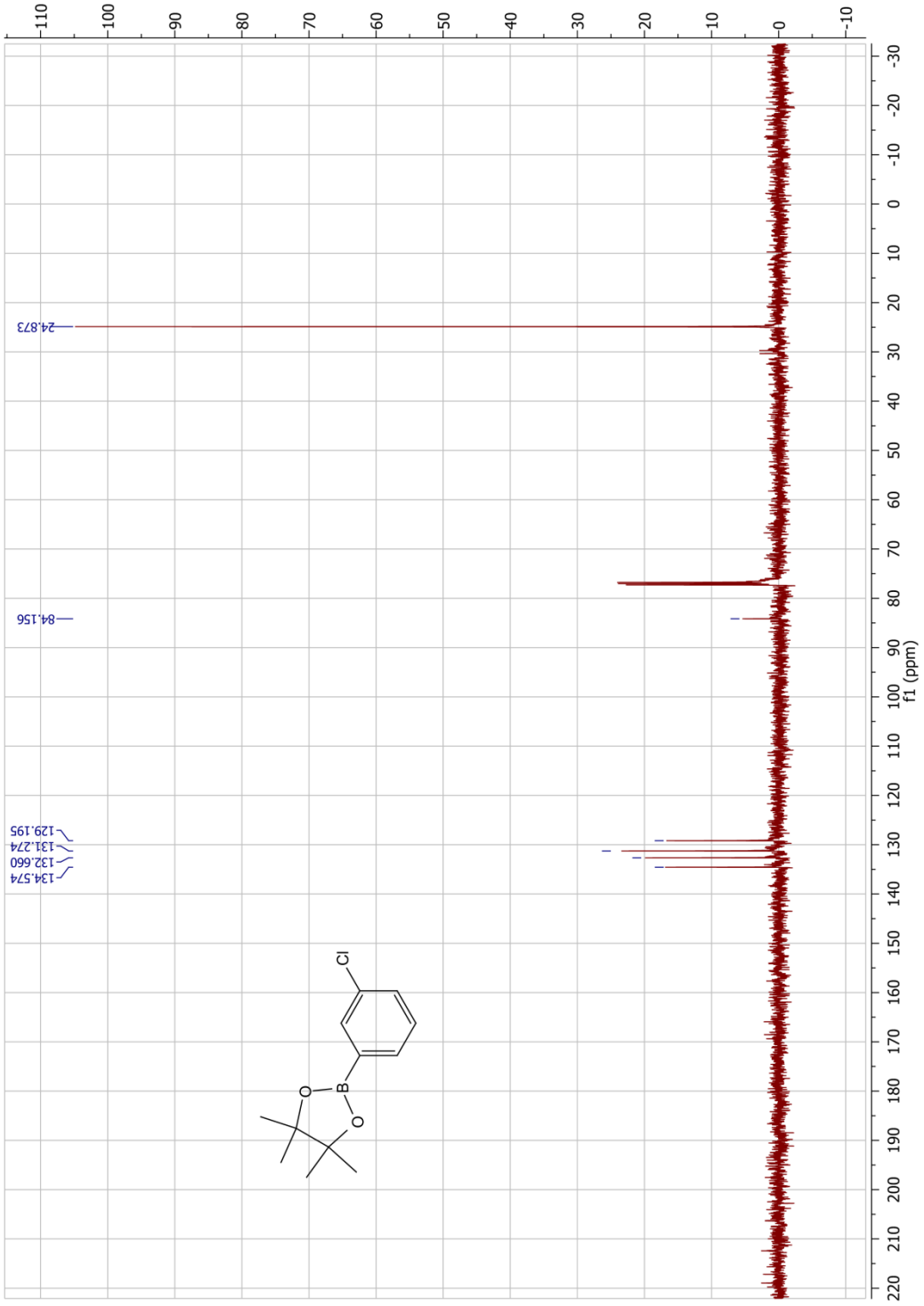
O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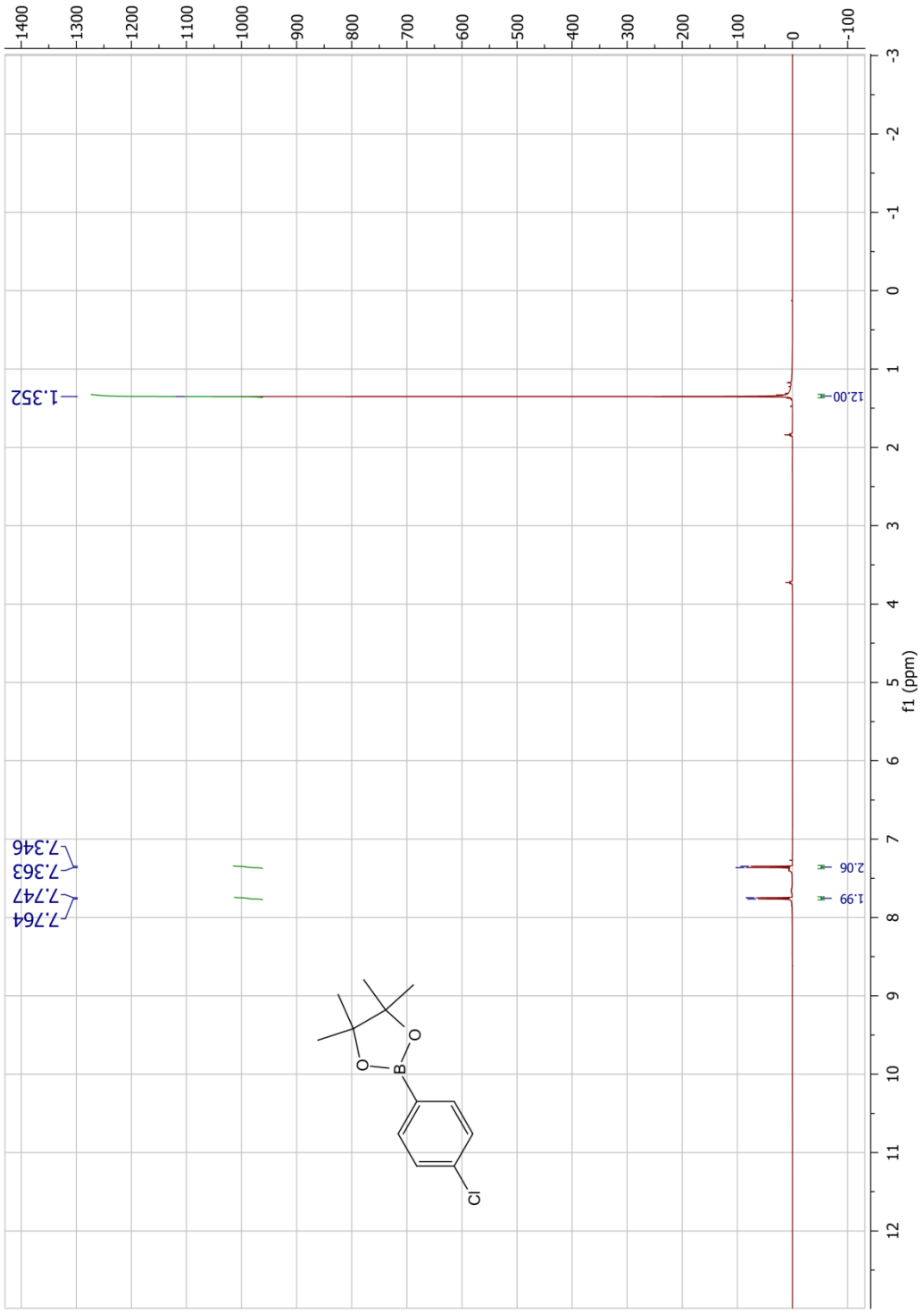
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1.99
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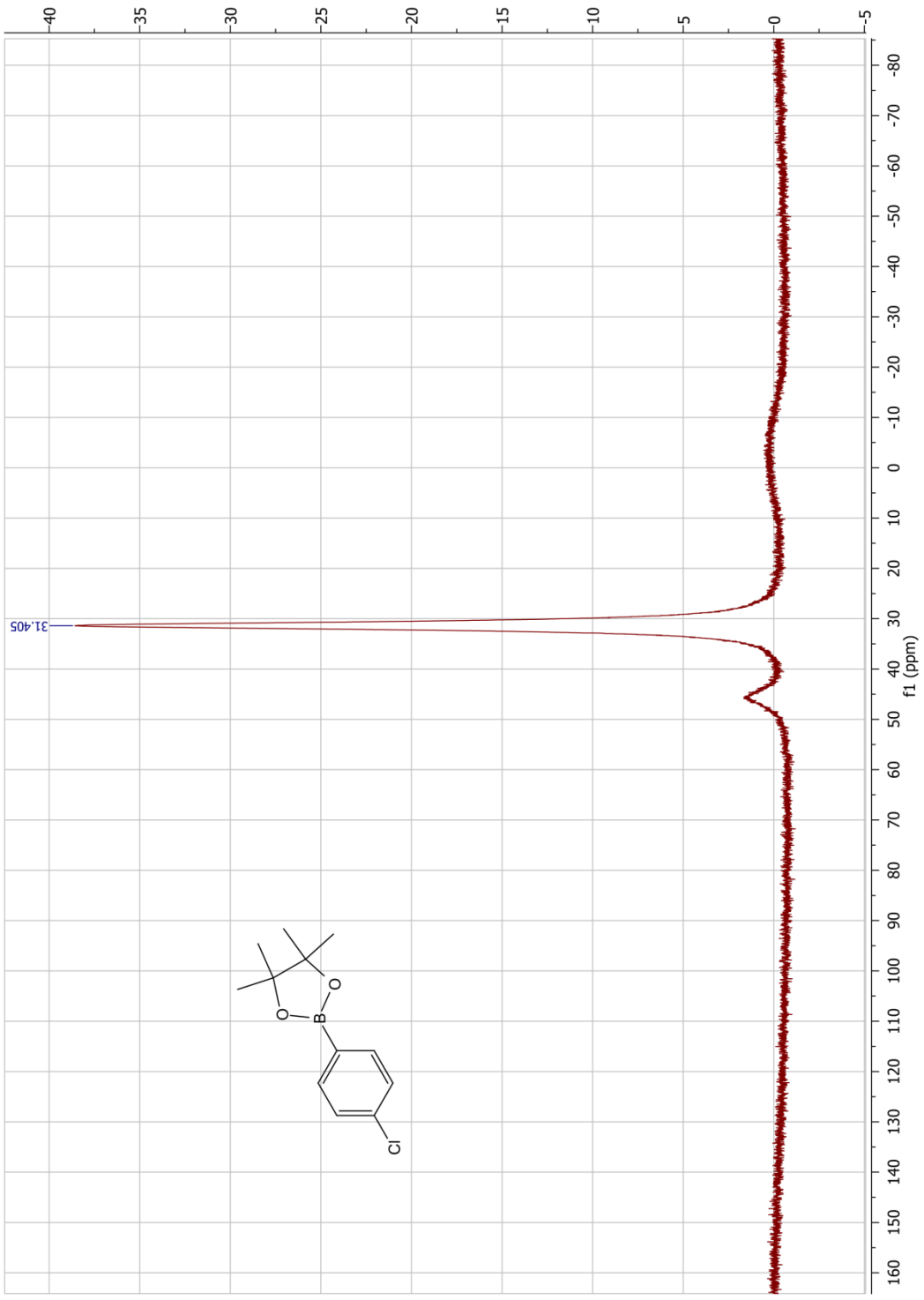
O
Cl
f1 (ppm)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O
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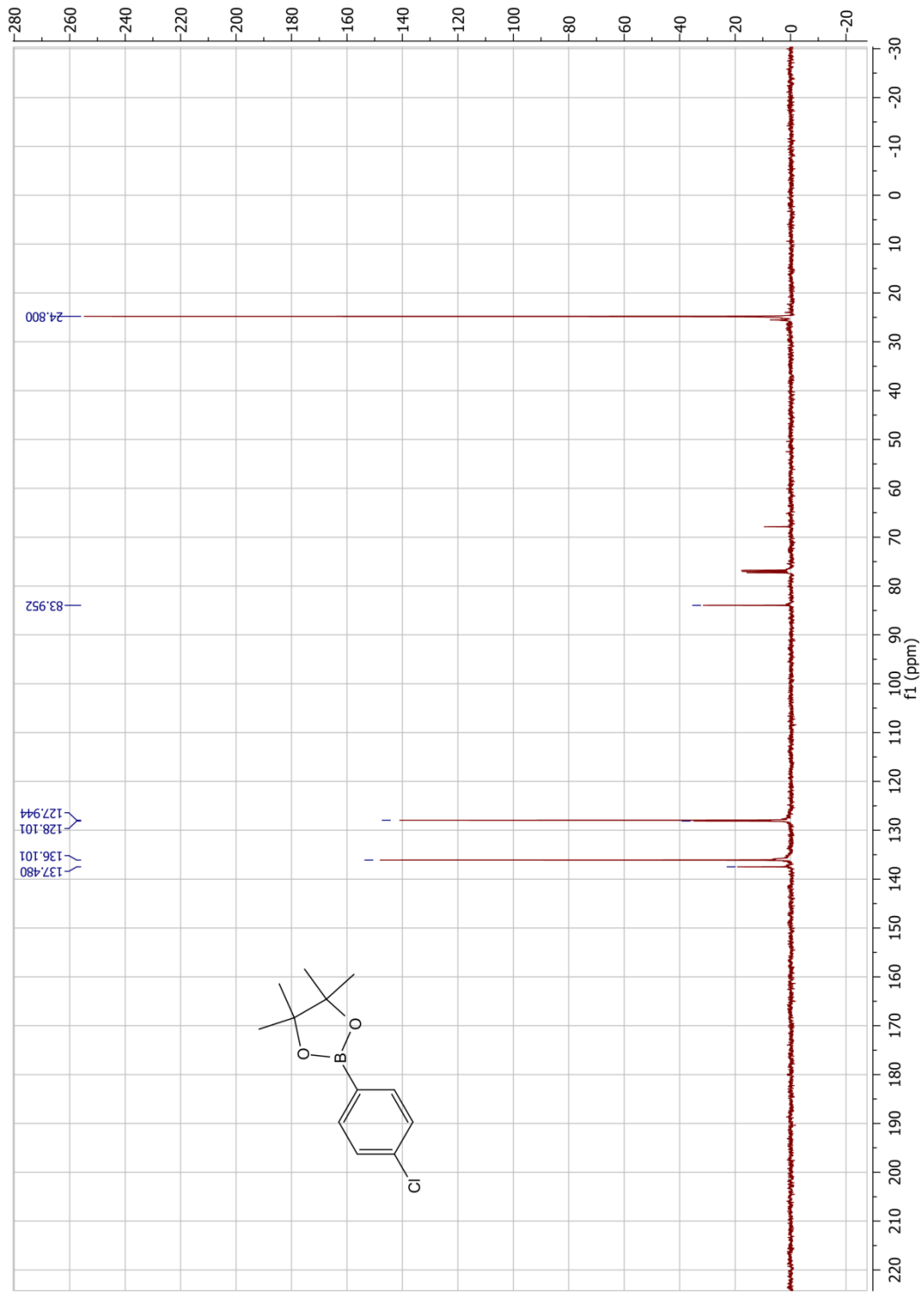
Cl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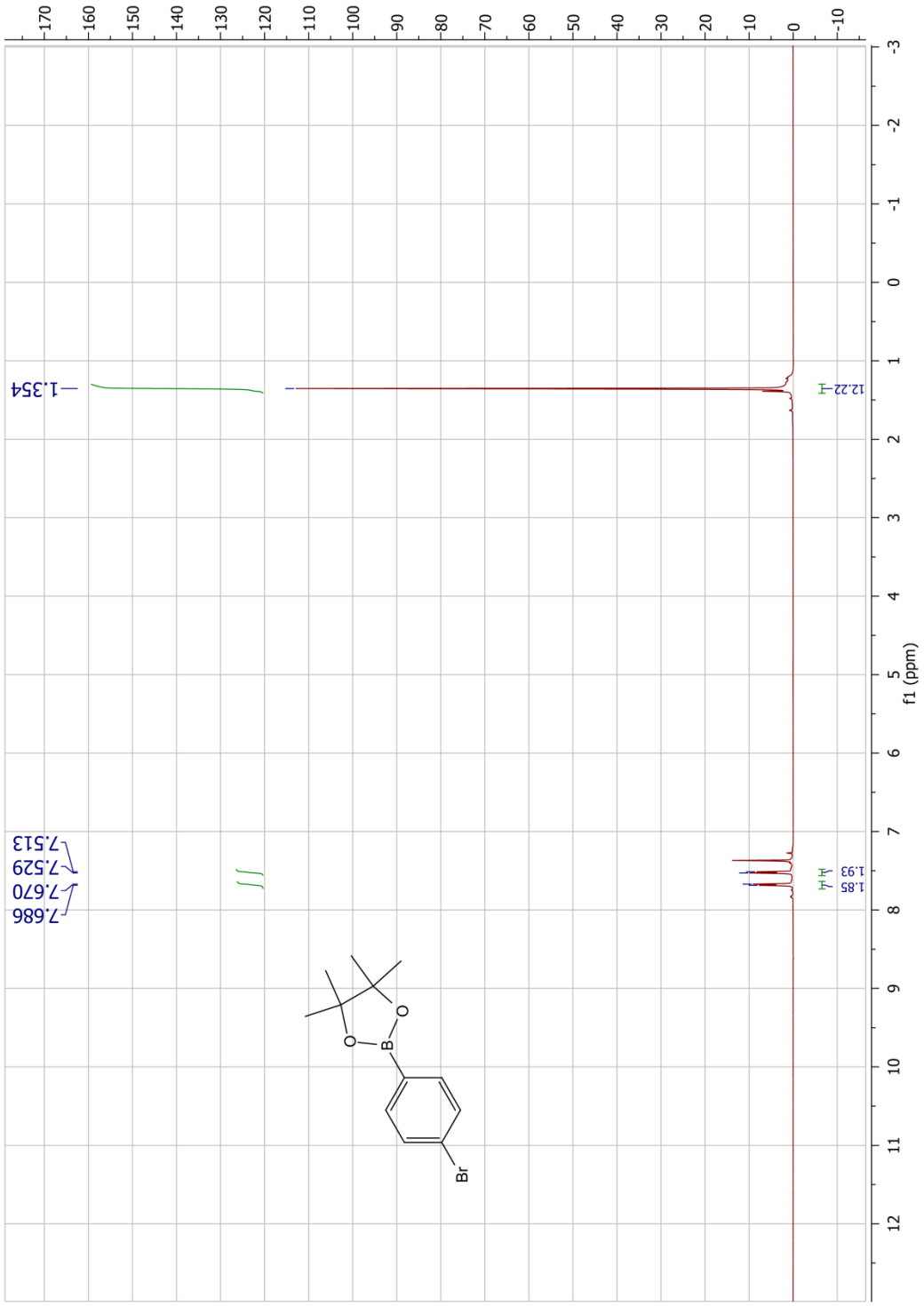
O
B
Cl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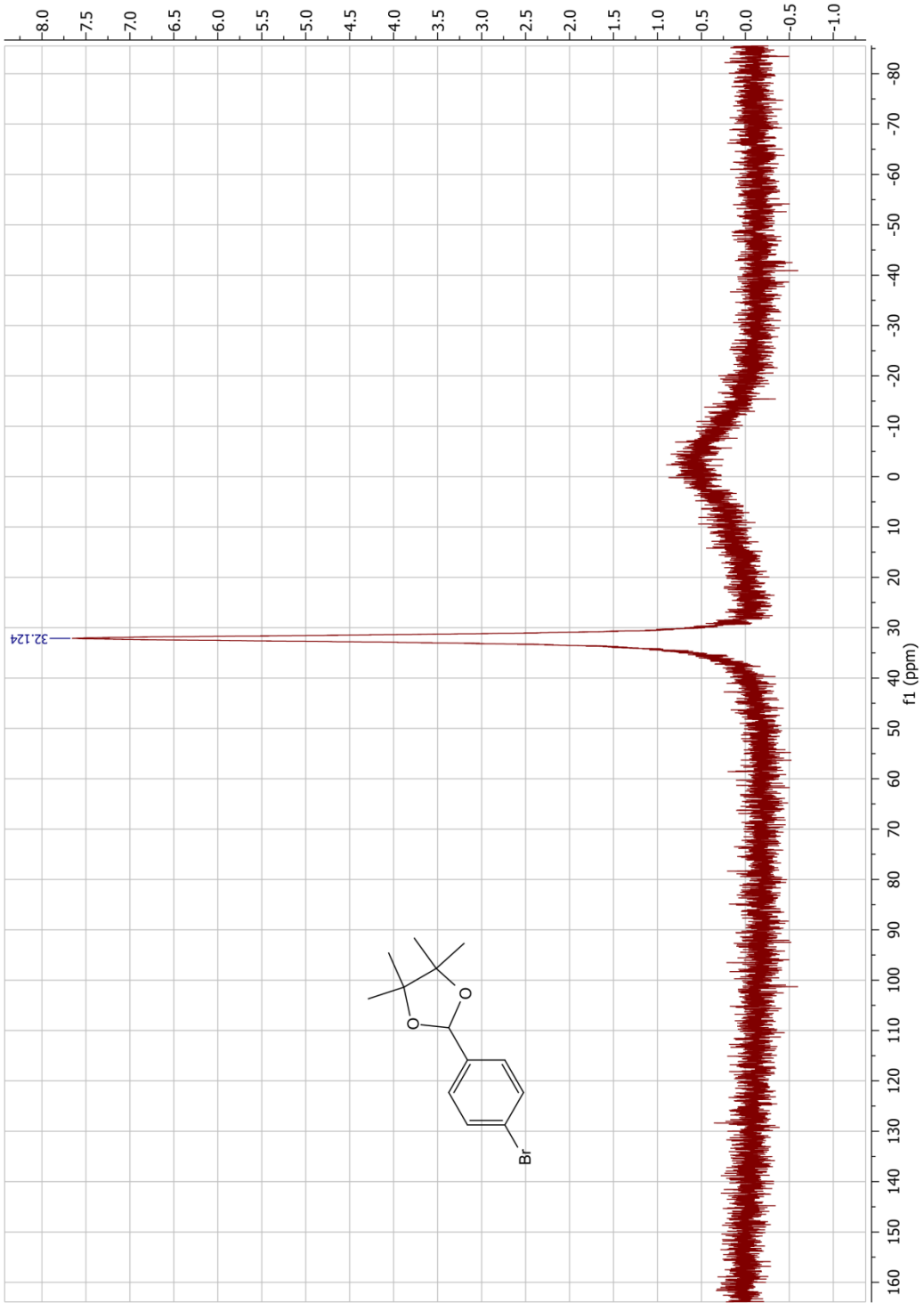
7.529
7.513
1.354
12.22
4.4
1.93
1.85
B
O
O
Br
f1 (ppm)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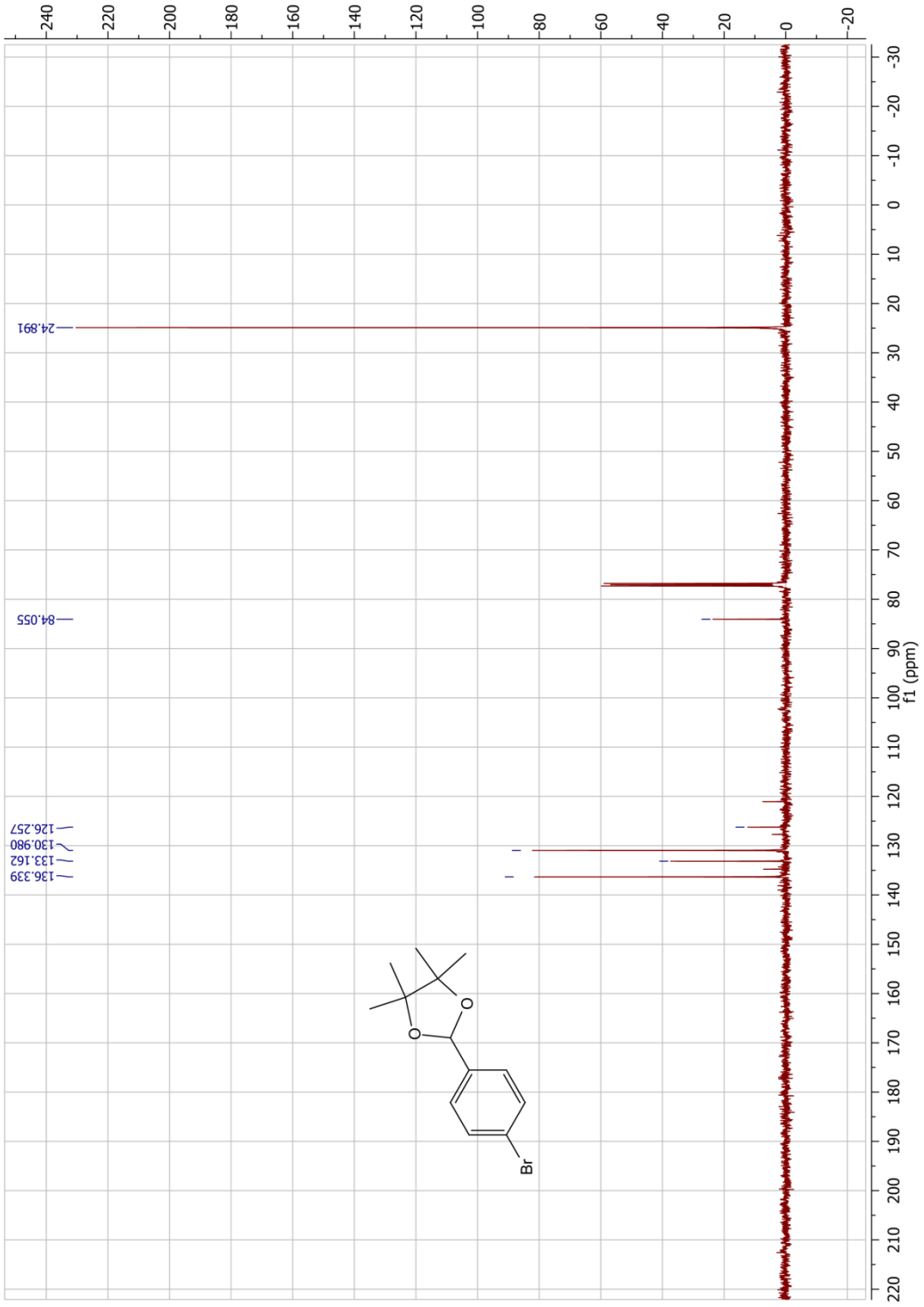
Br
O
O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O
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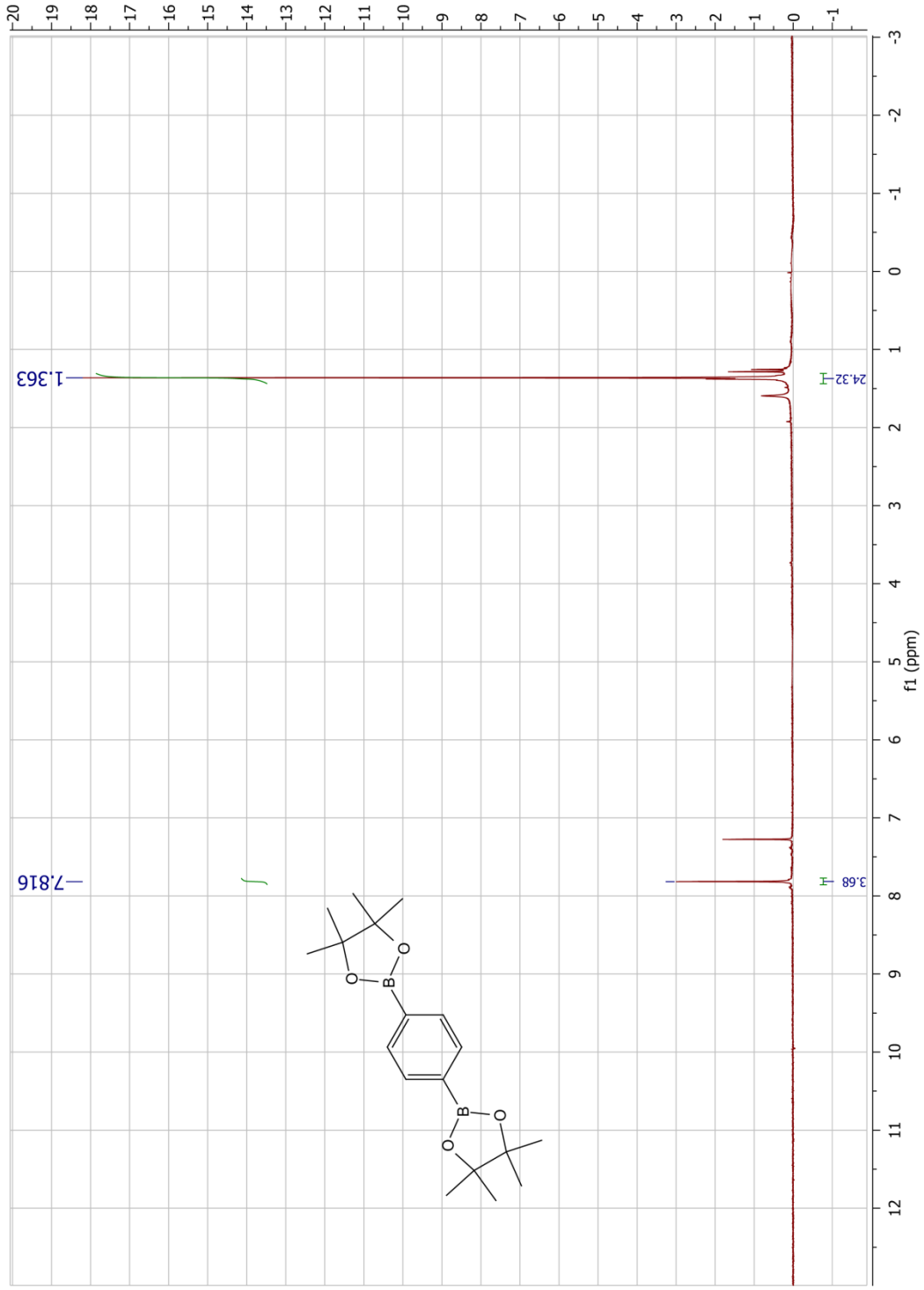
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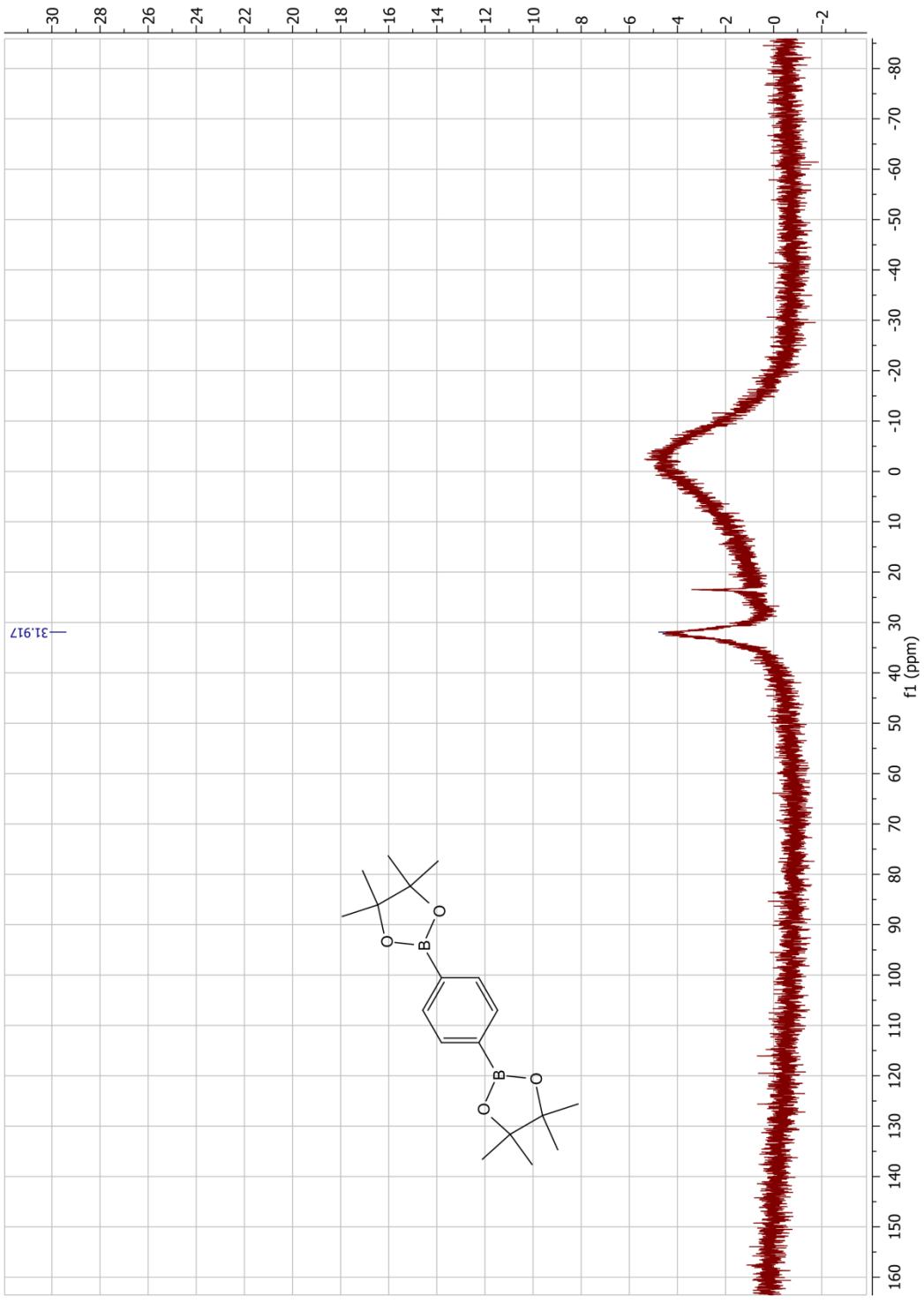
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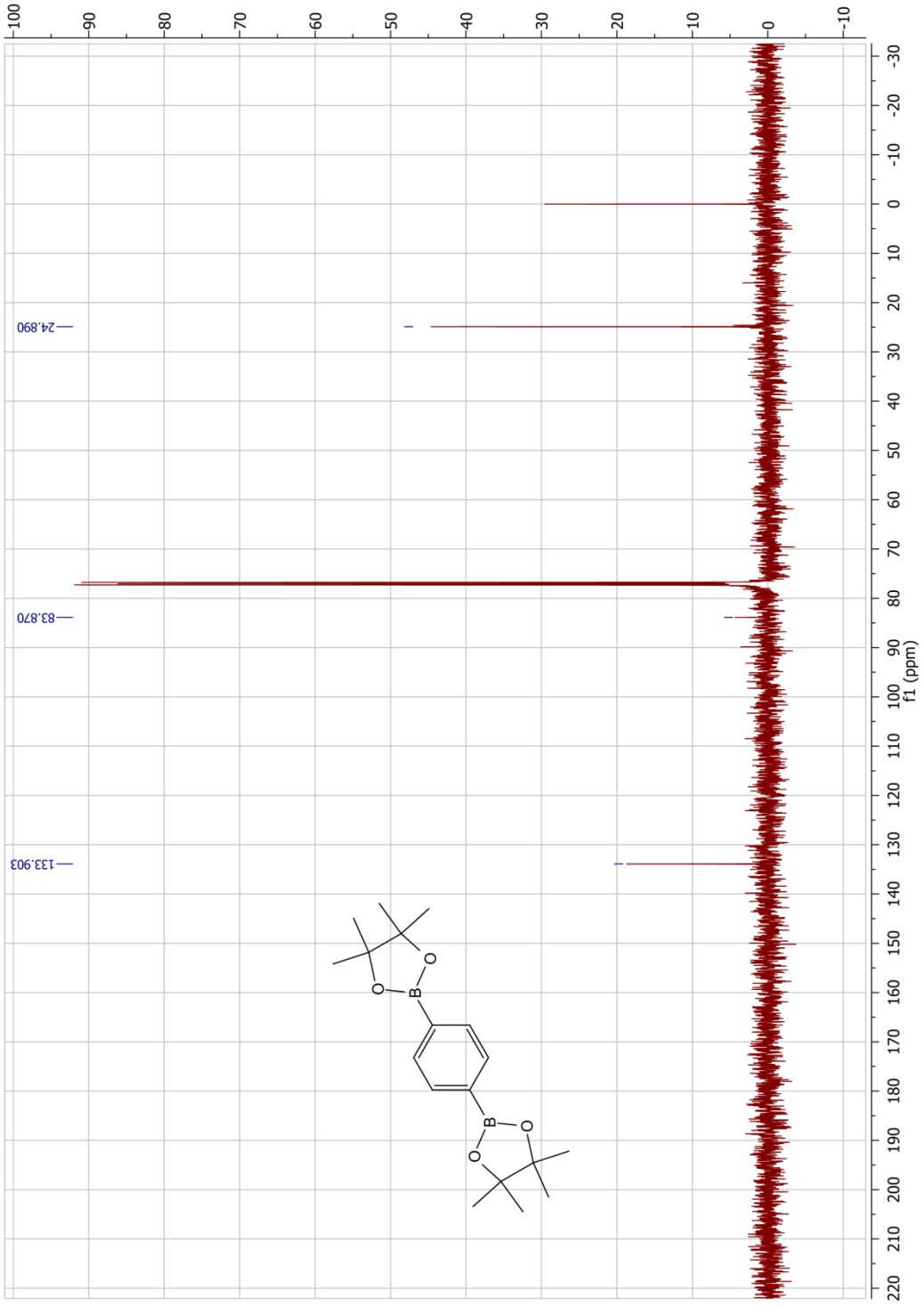
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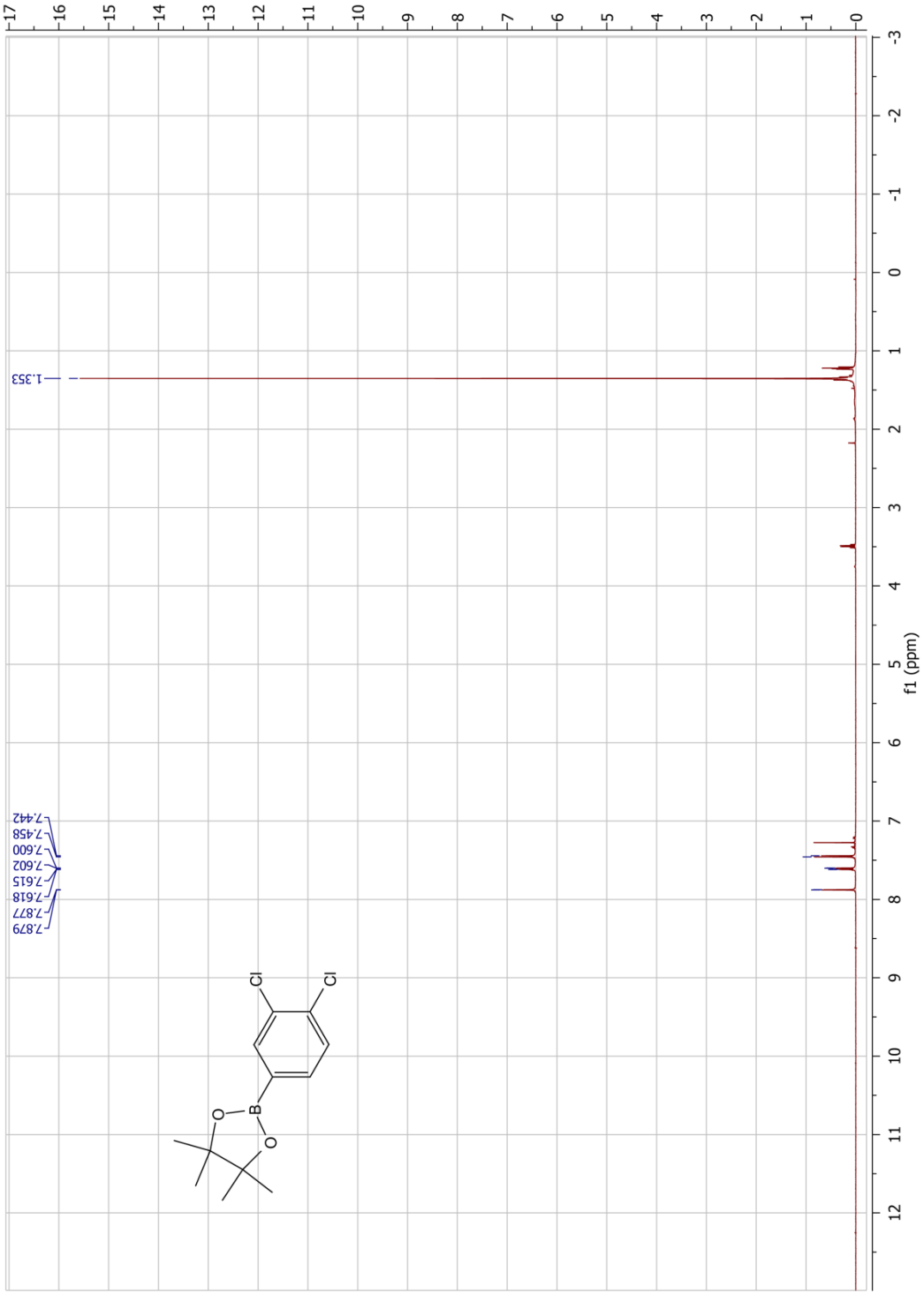
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Cl
Cl
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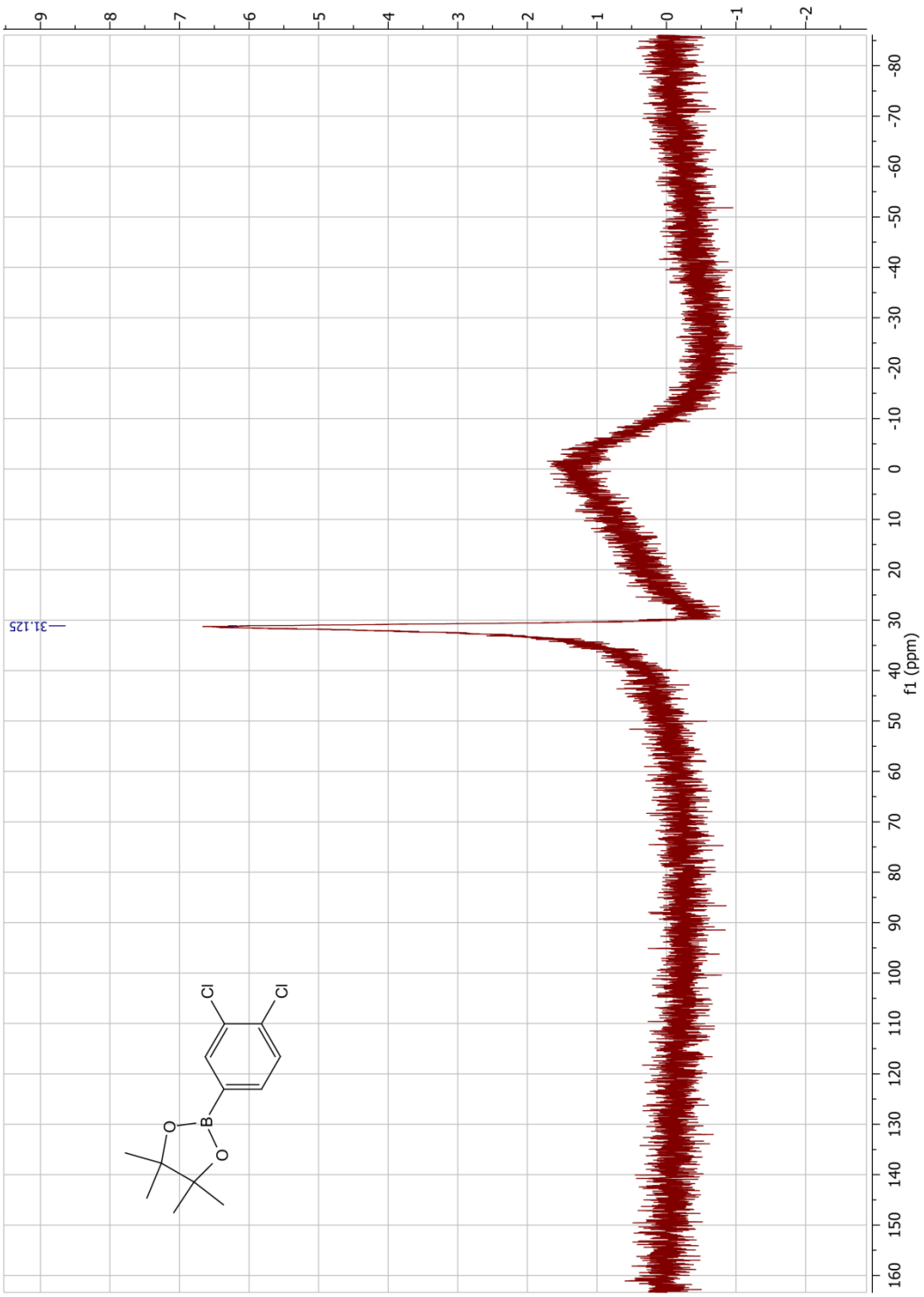
B
O
f1 (ppm)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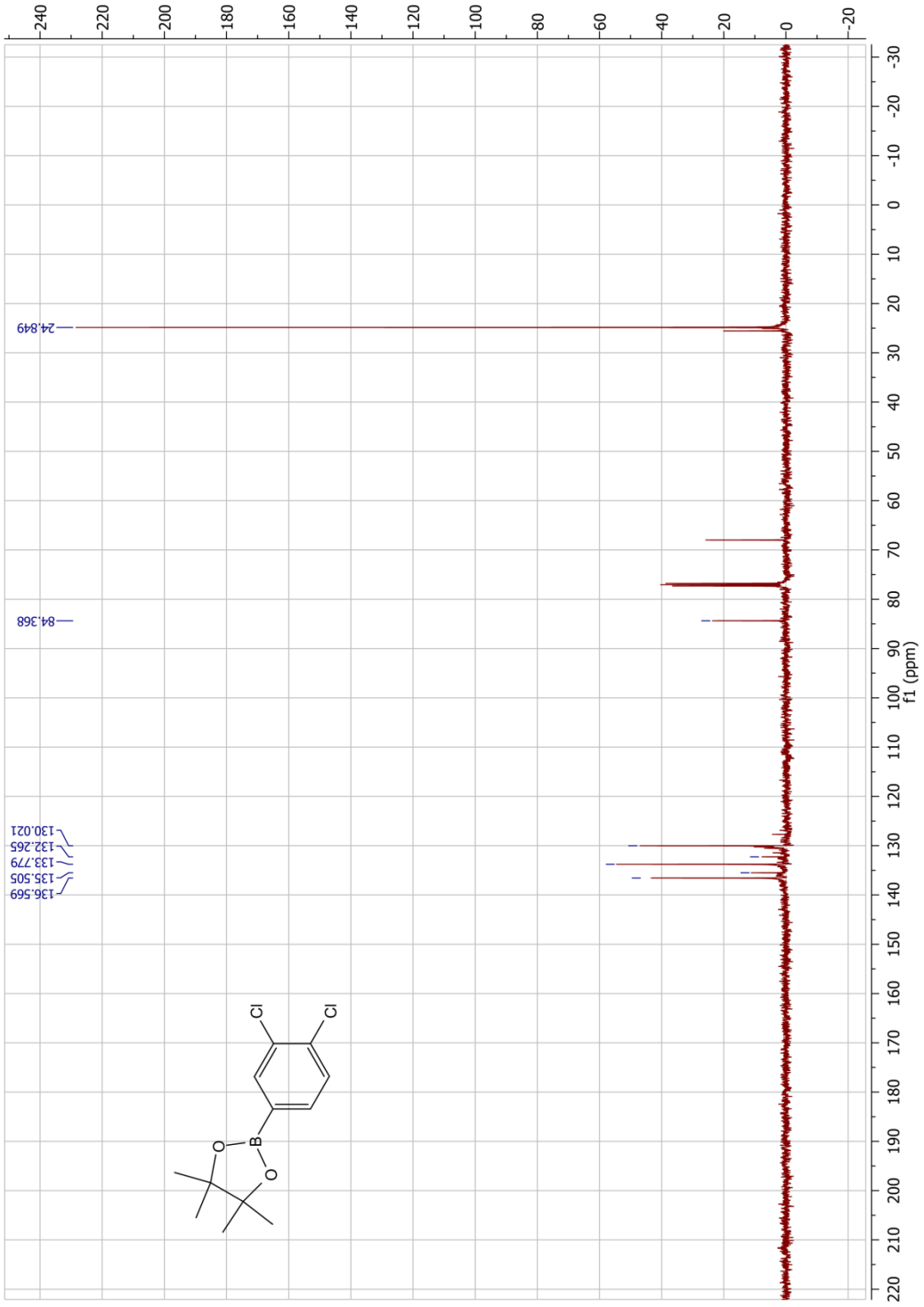
O
O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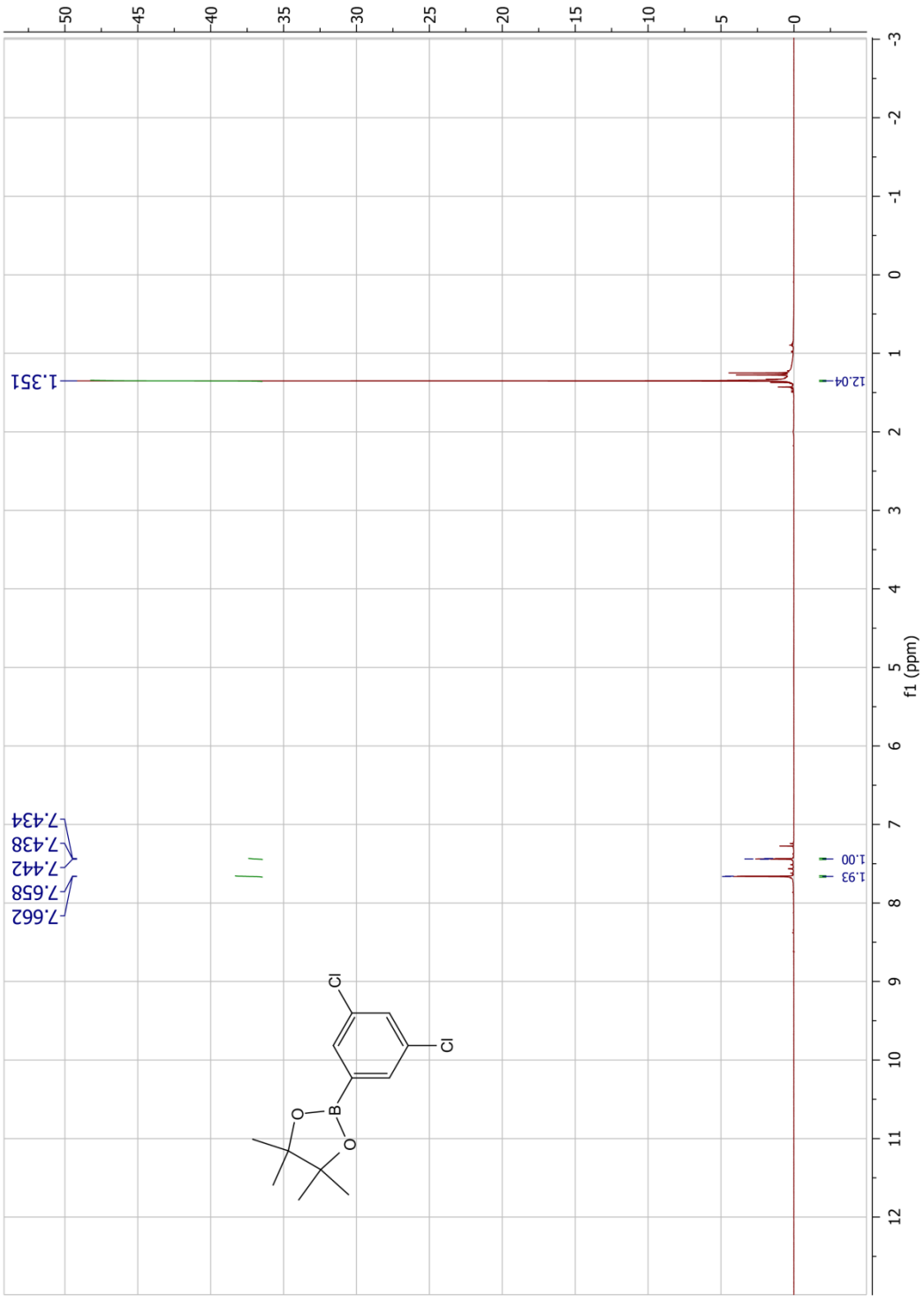
Cl
Cl
B
O
O
f1 (ppm)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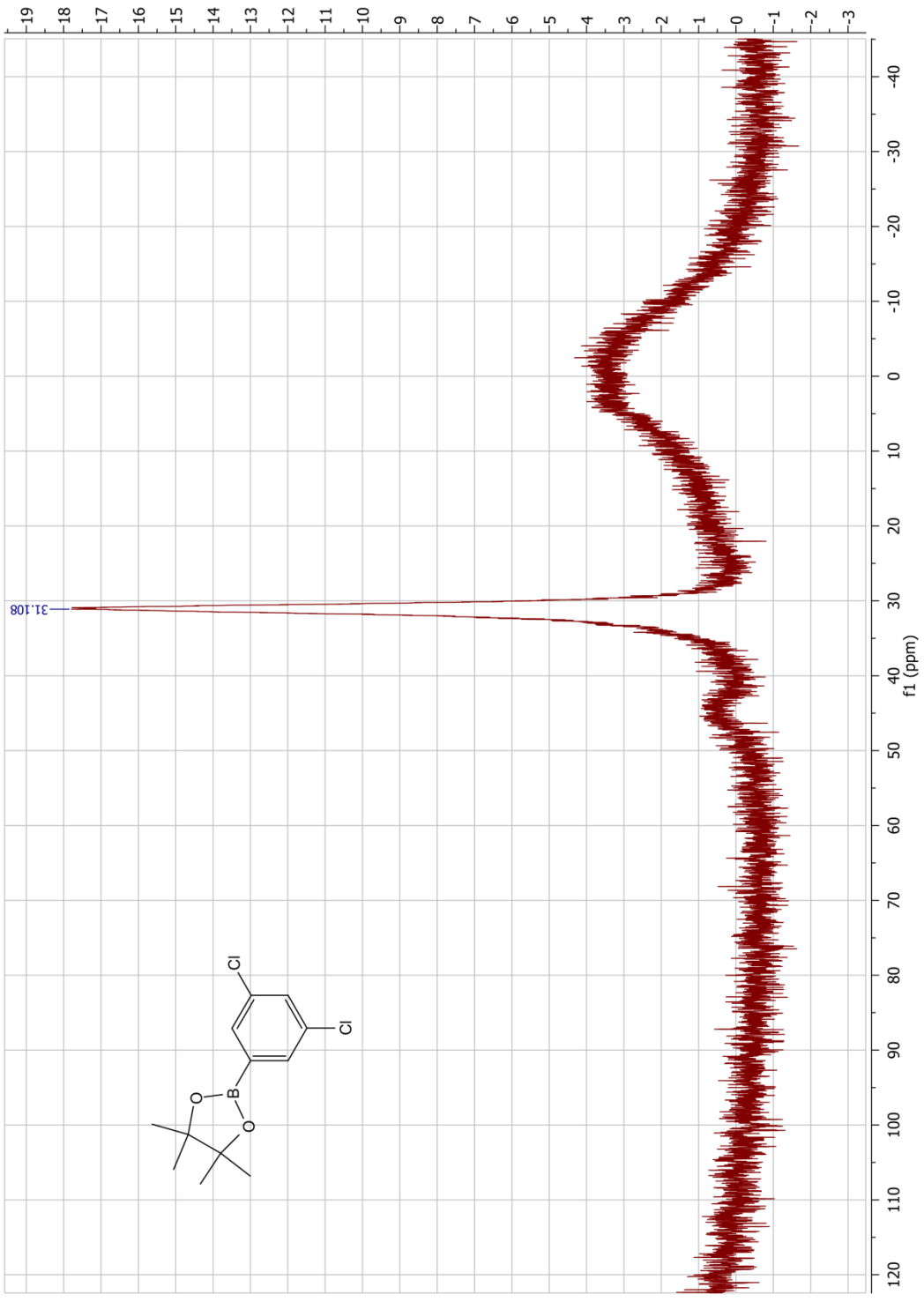
1.00
Cl
Cl
O
B
O
f1 (ppm)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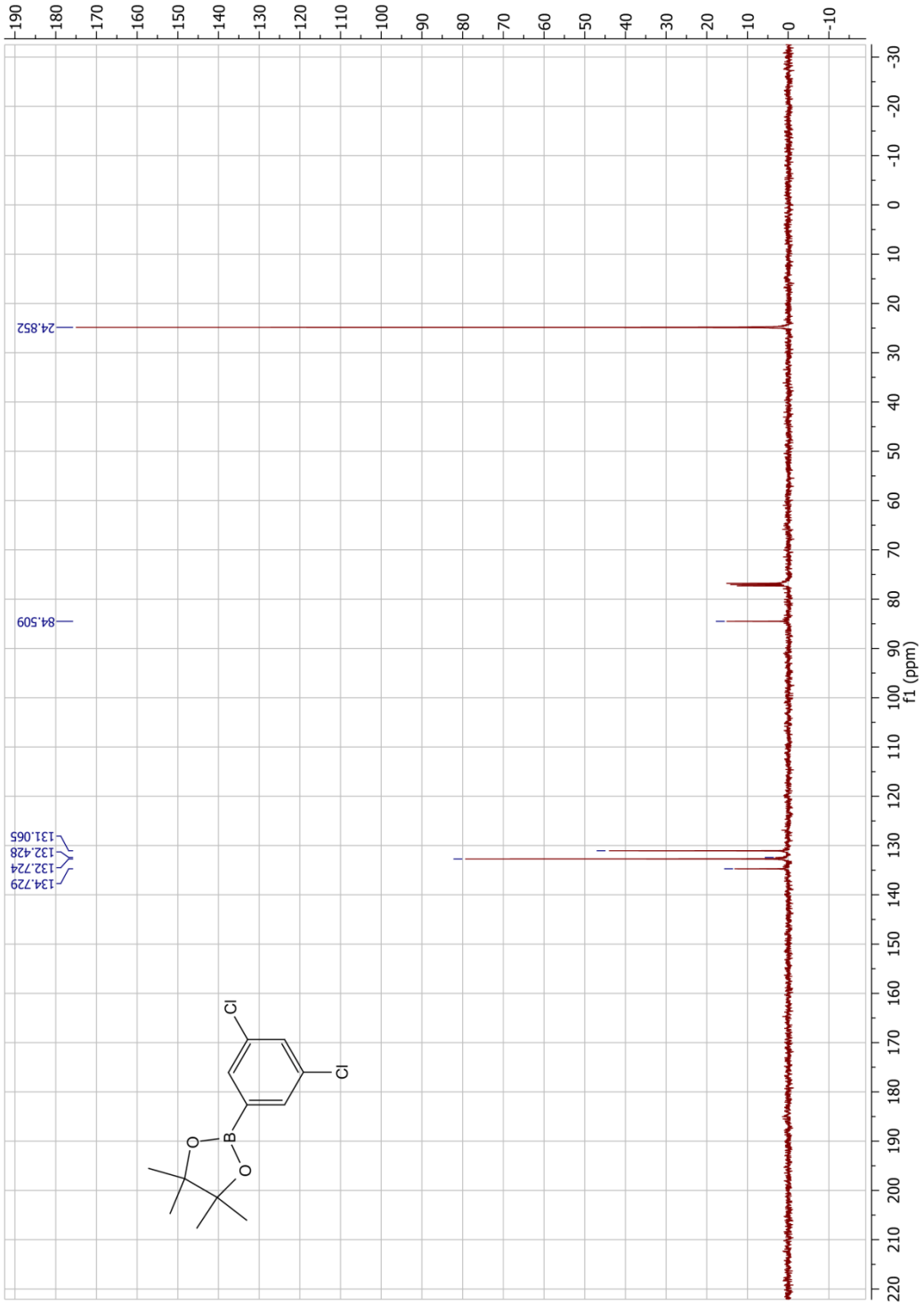
Cl
O
B
O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O
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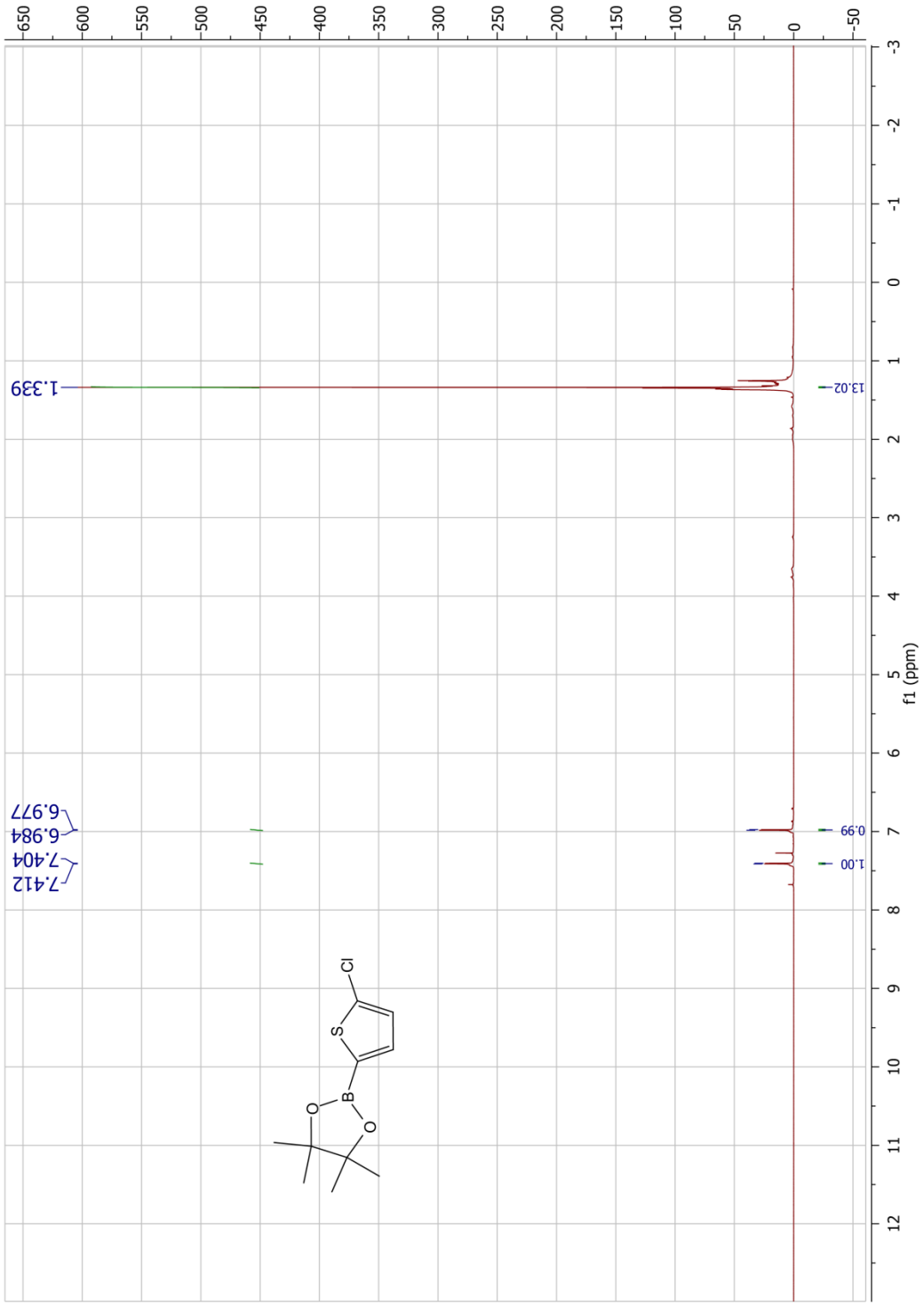
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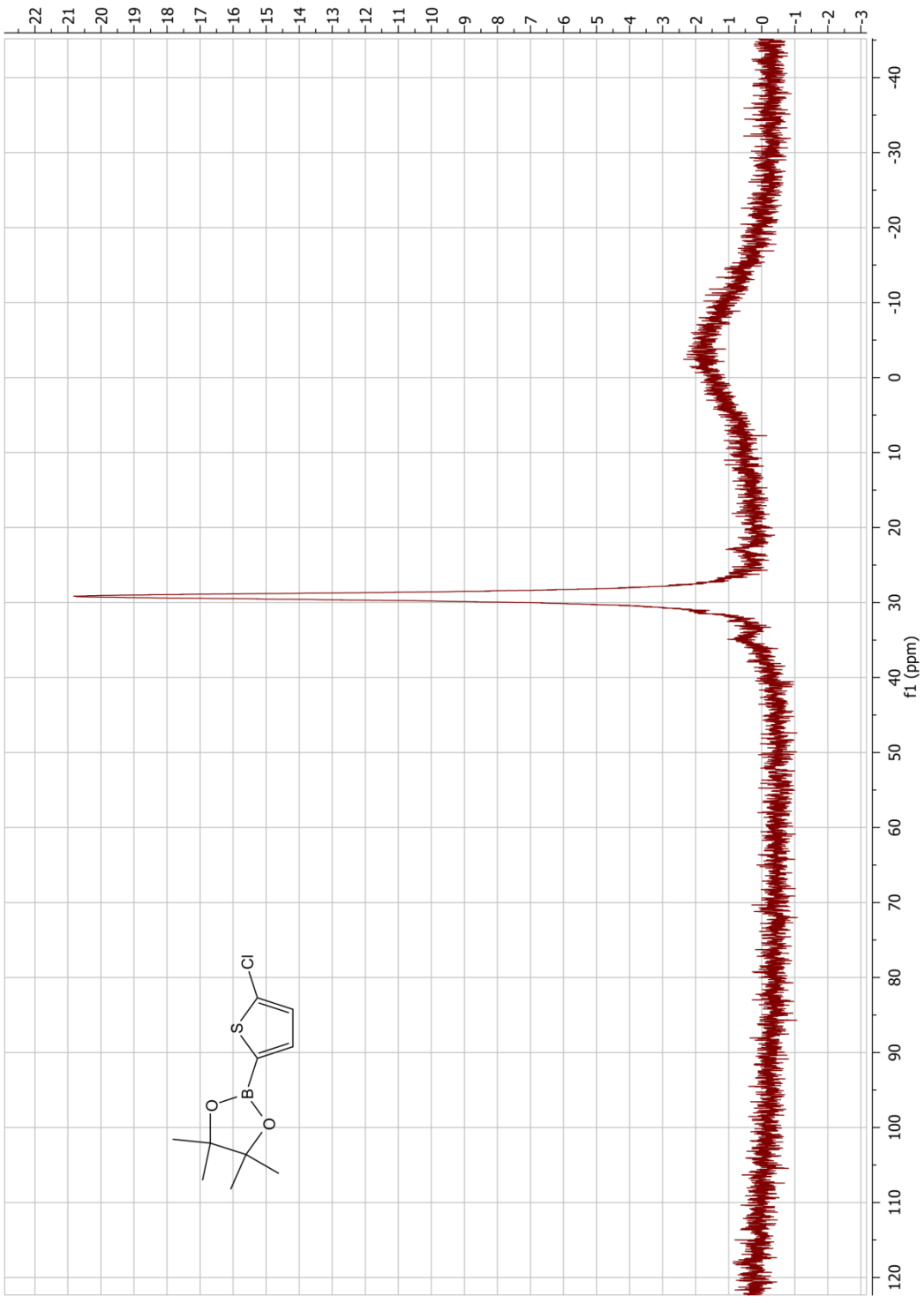
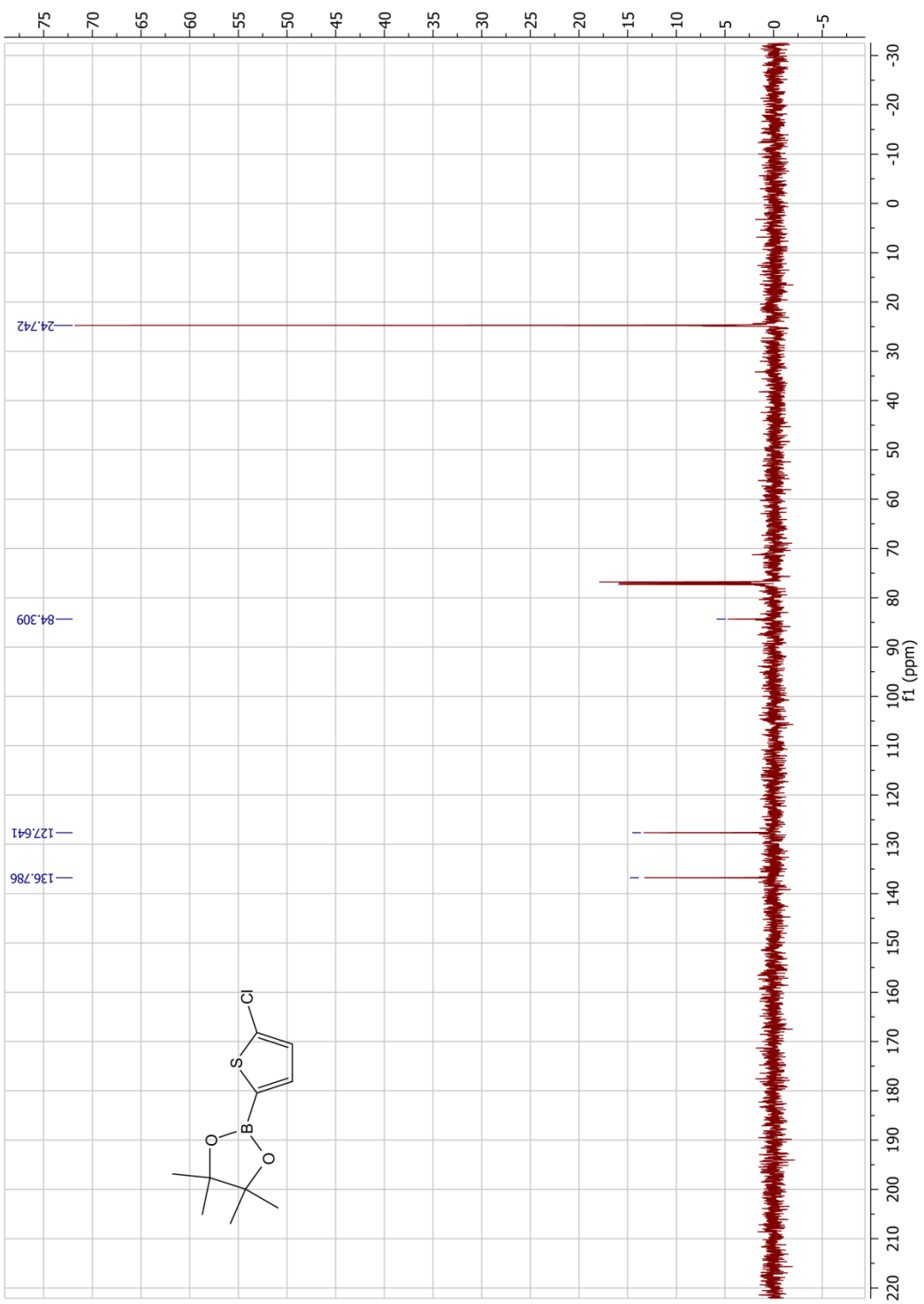
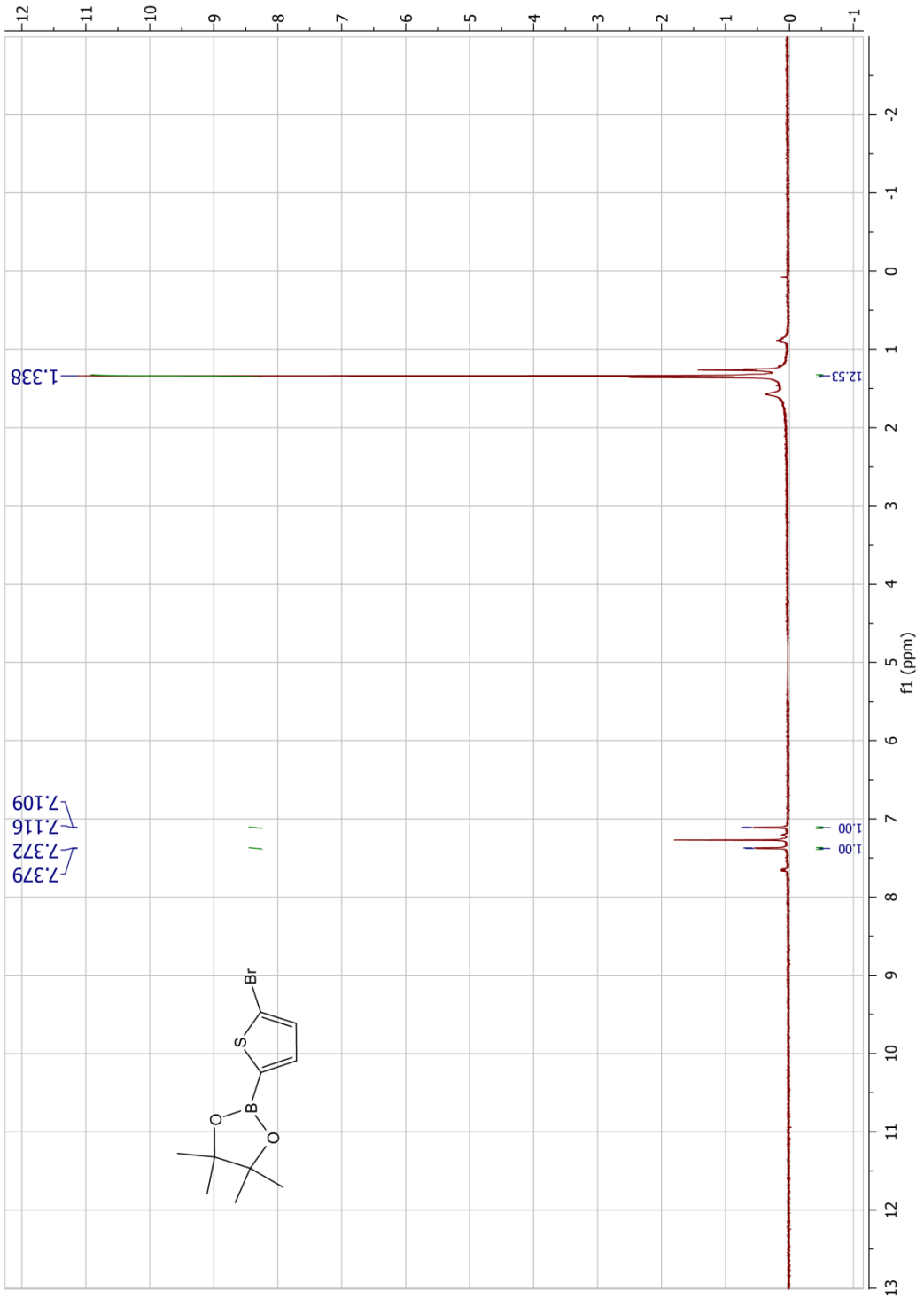
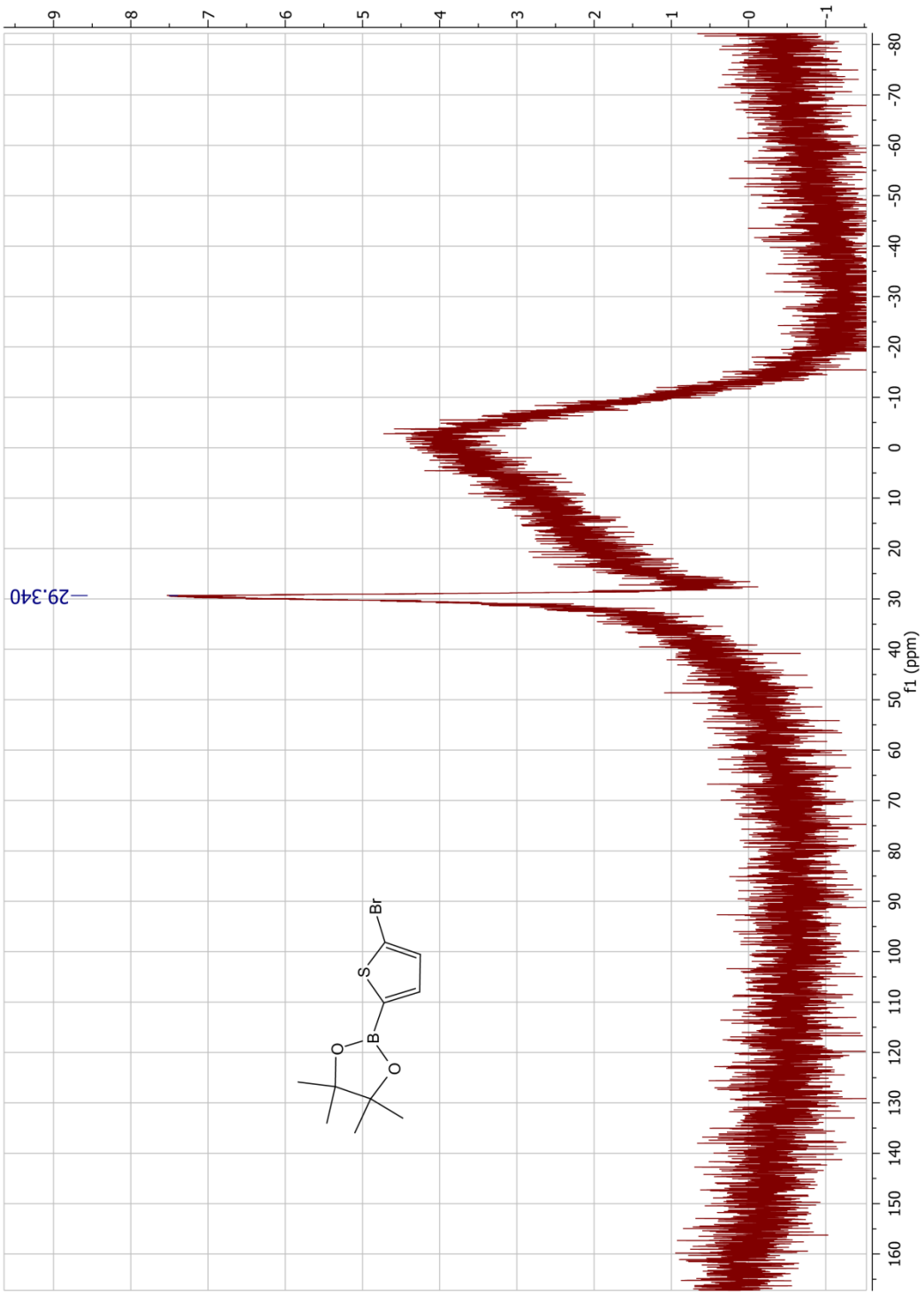
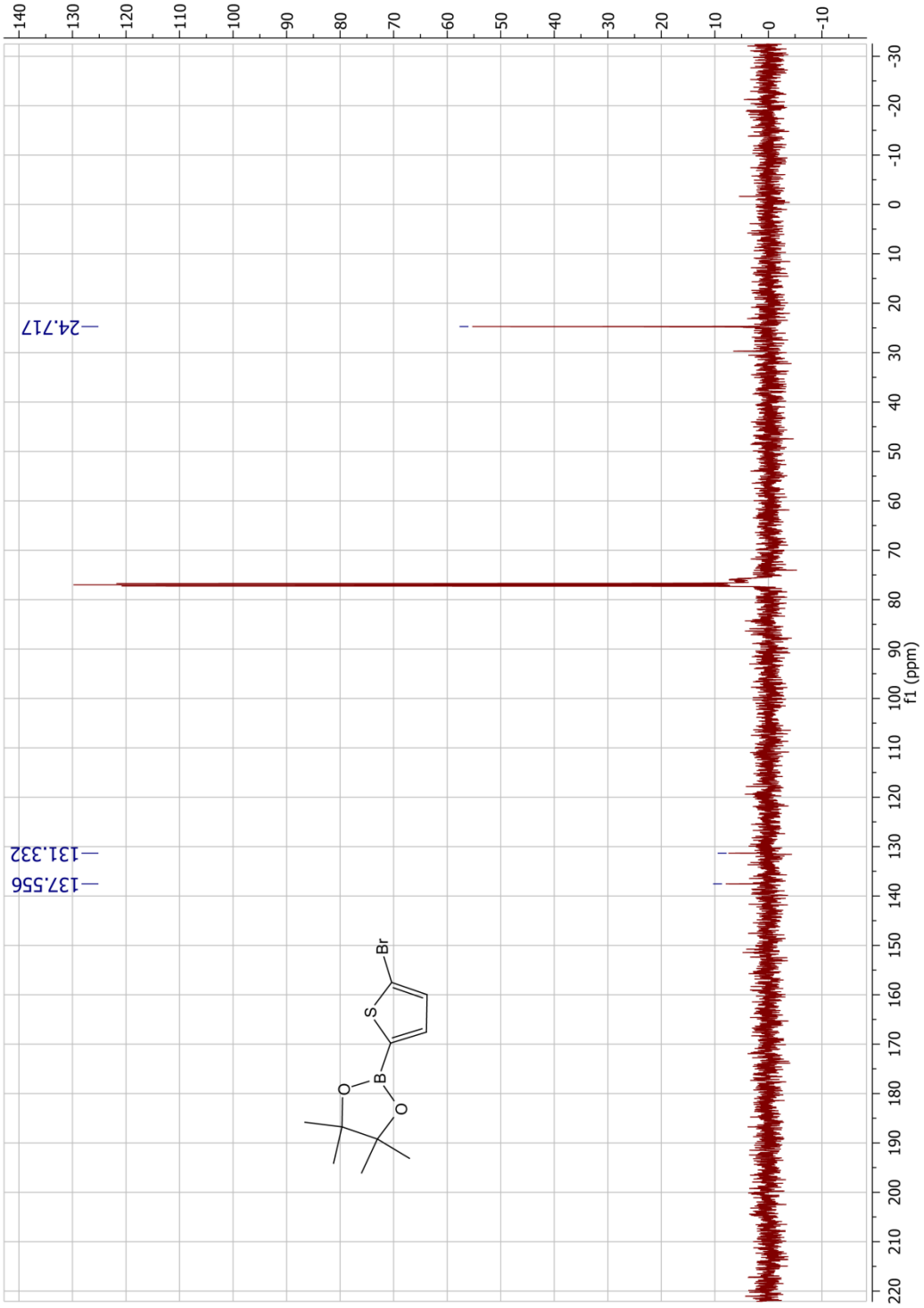
0.99
1.00
f1 (ppm)
Cl
S
B
O
O

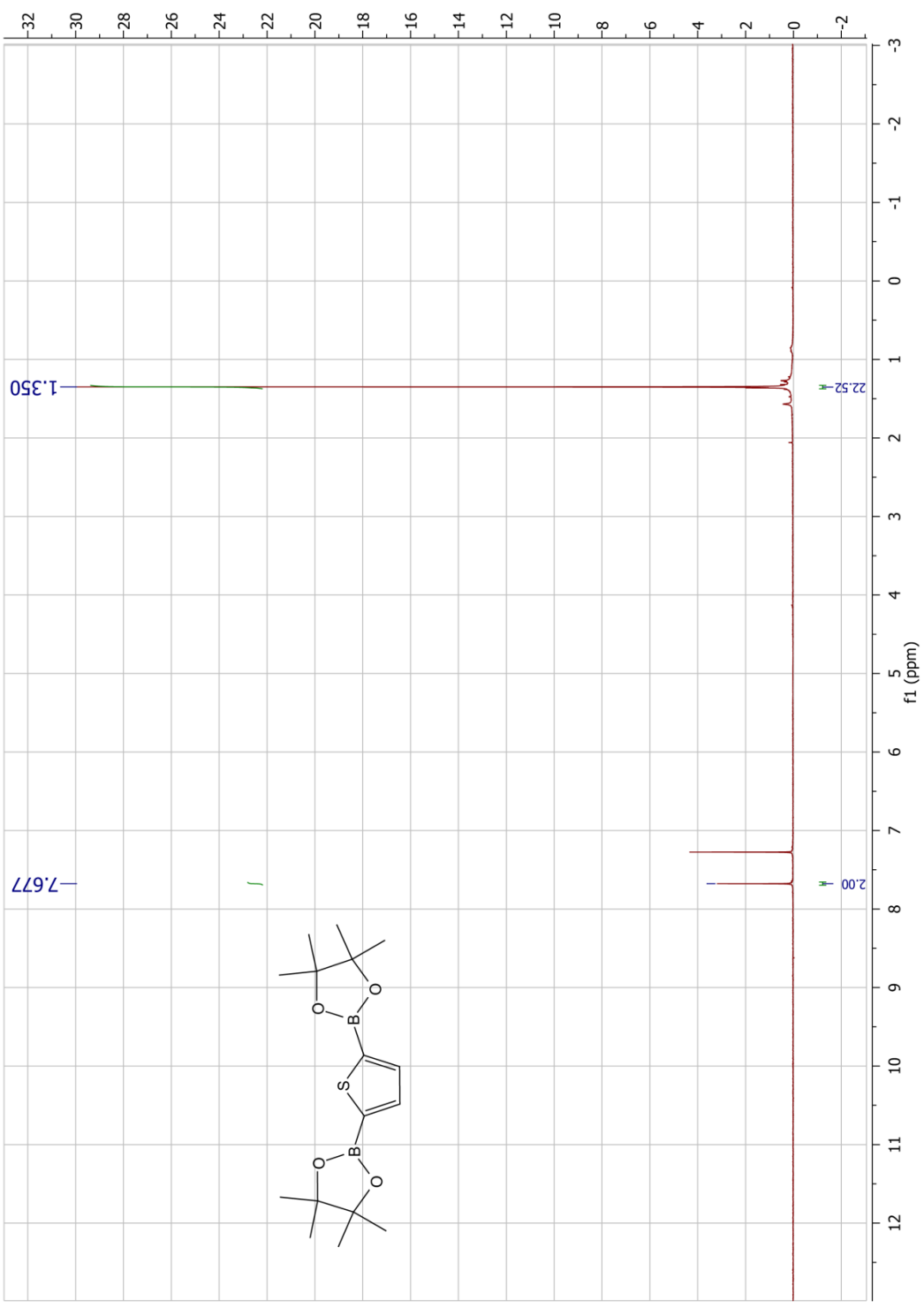

f1 (ppm)
Cl
S
B
O
O

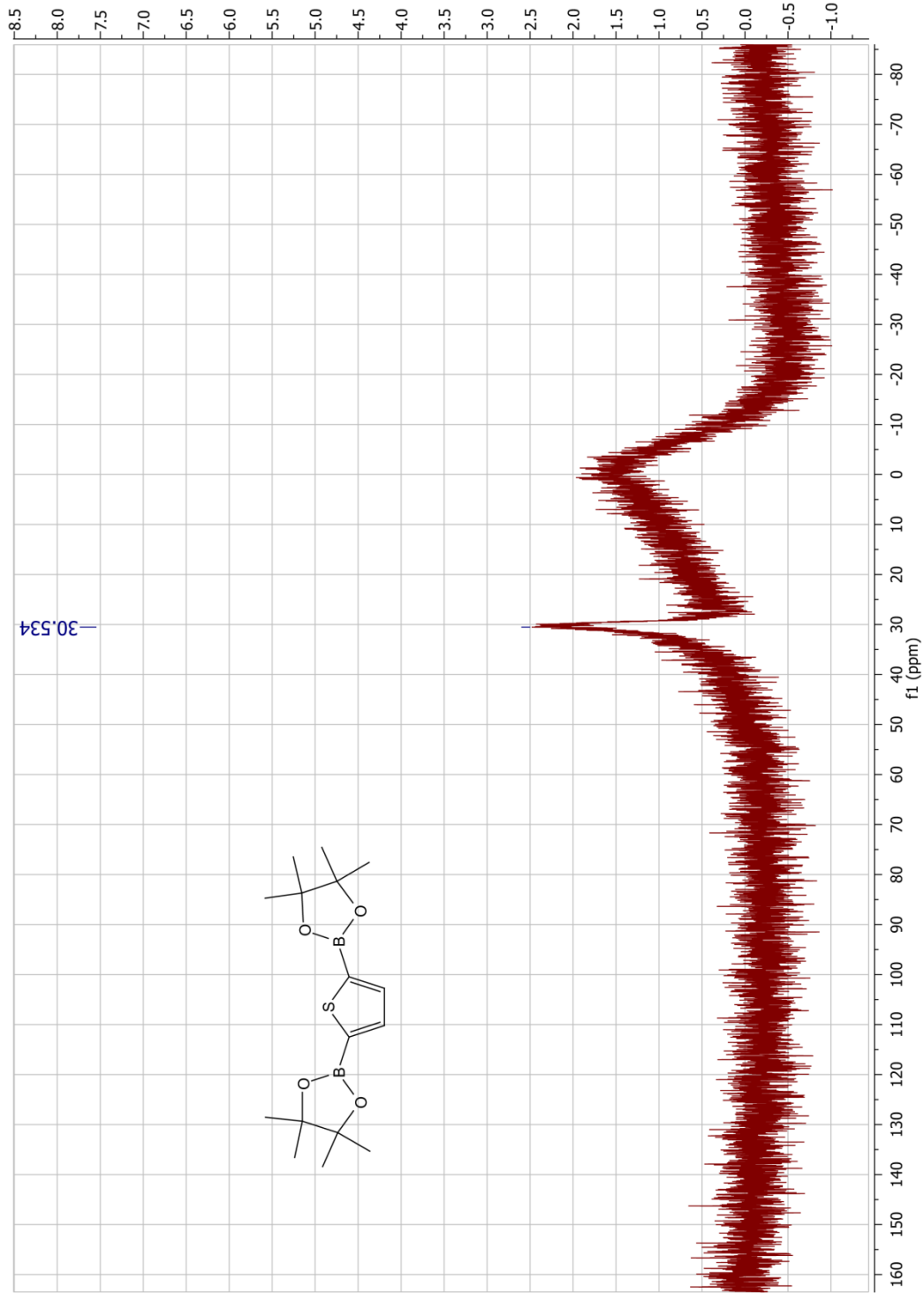

24.742
84.309
127.641
136.786
f1 (ppm)

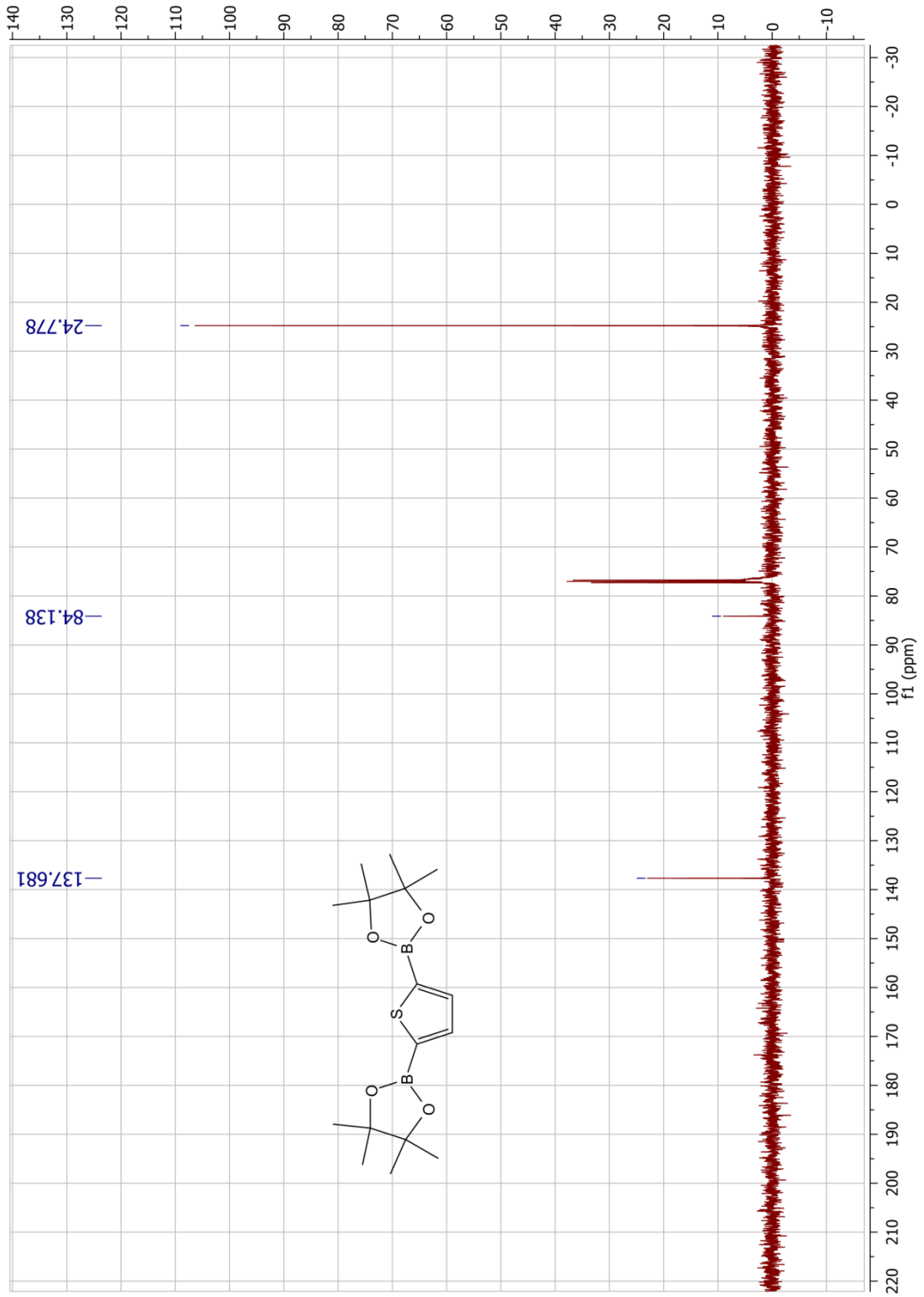

1.338
7.379
7.372
7.116
7.109
12.53
1.00
1.00
f1 (ppm)
Br
S
B
O
O

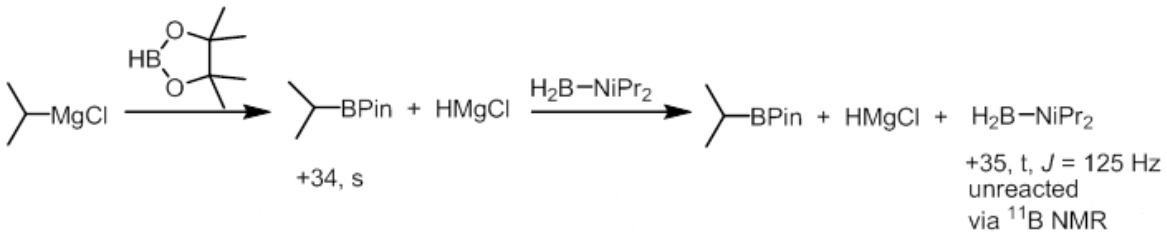

29.340
f1 (ppm)
Br
S
B
O
O

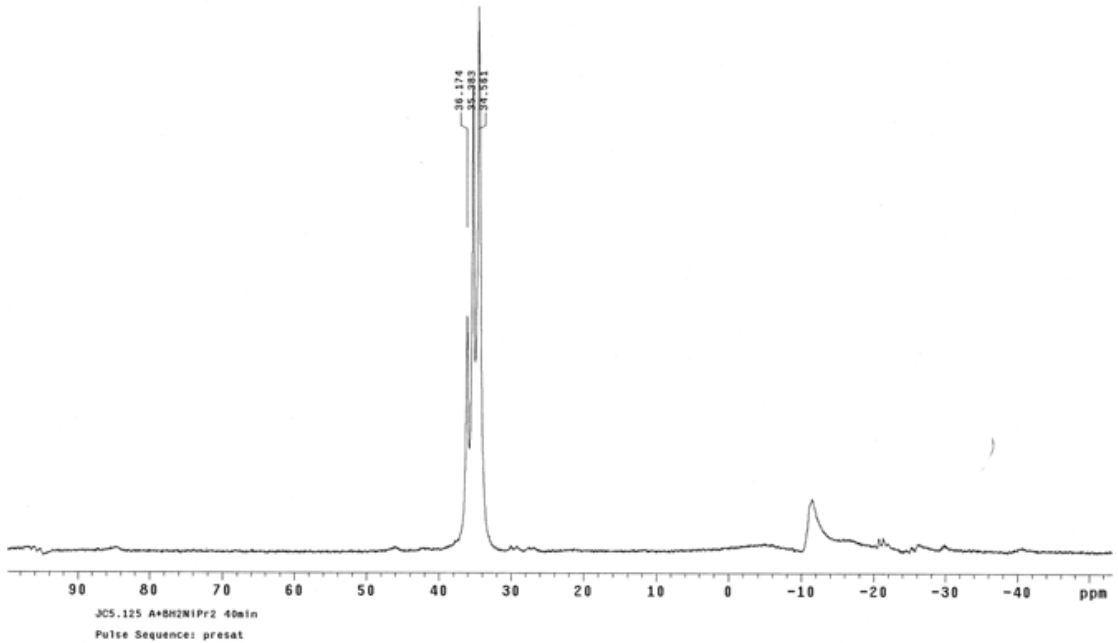

24.717
131.332
137.556
Br
S
B
O
O
f1 (ppm)

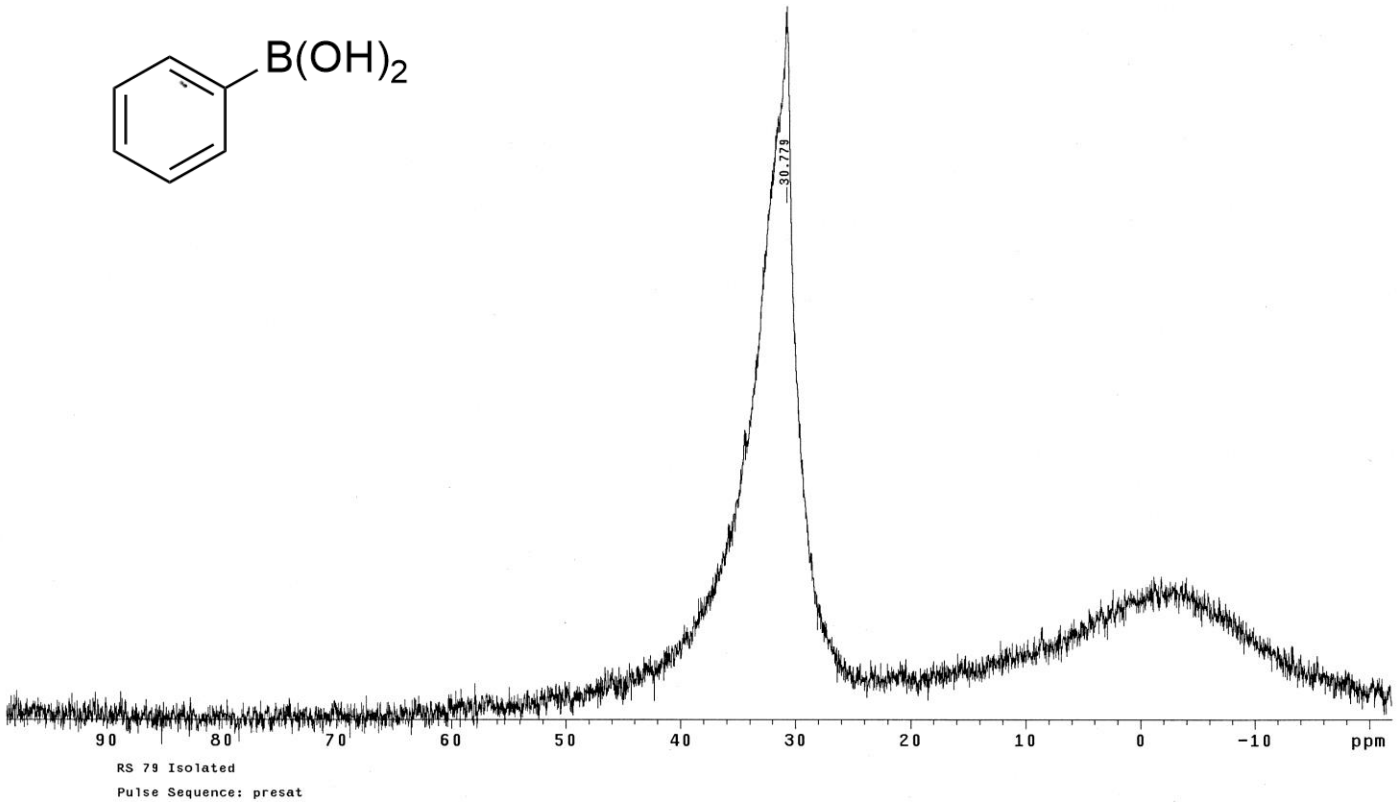

1.350
7.677
22.52
2.00
f1 (ppm)

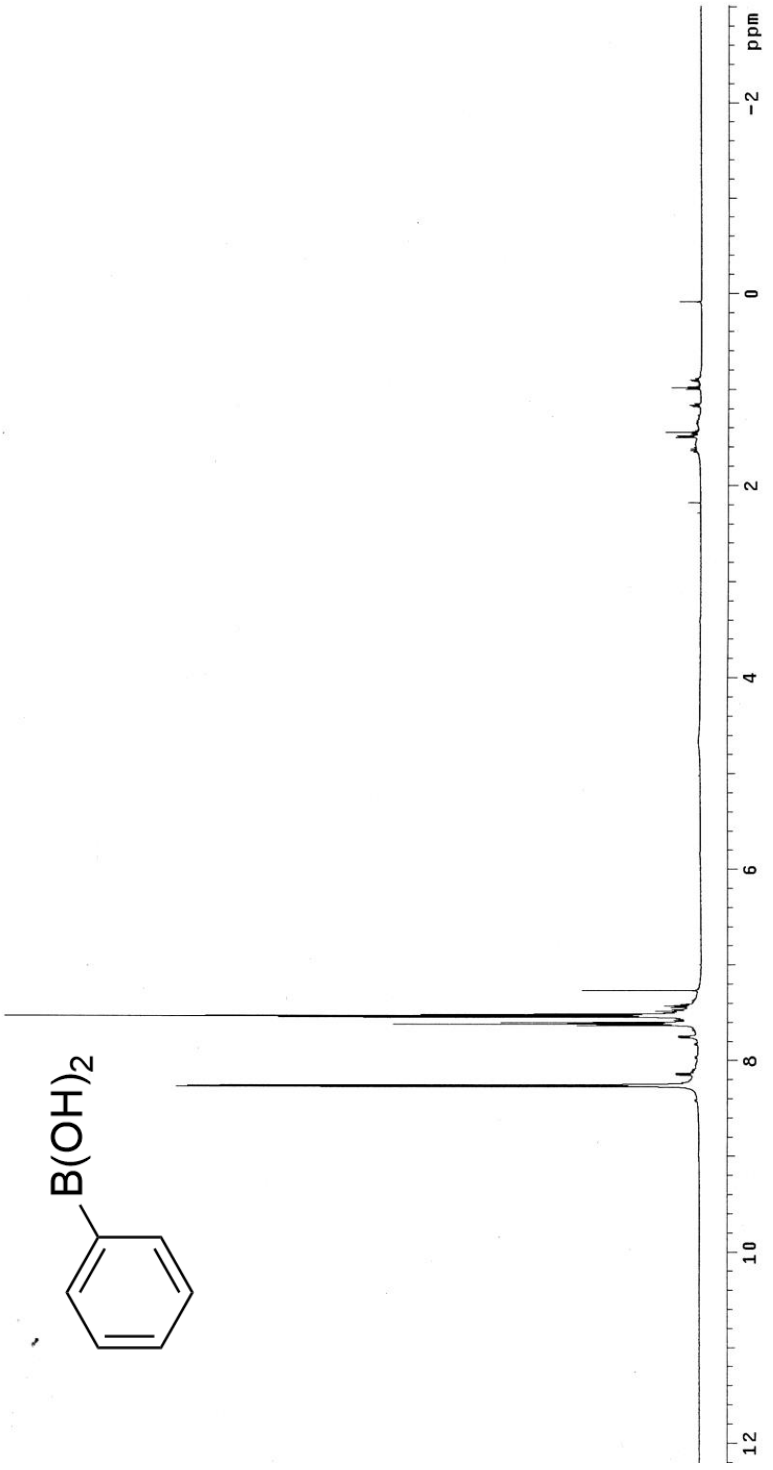

30.534
f1 (ppm)

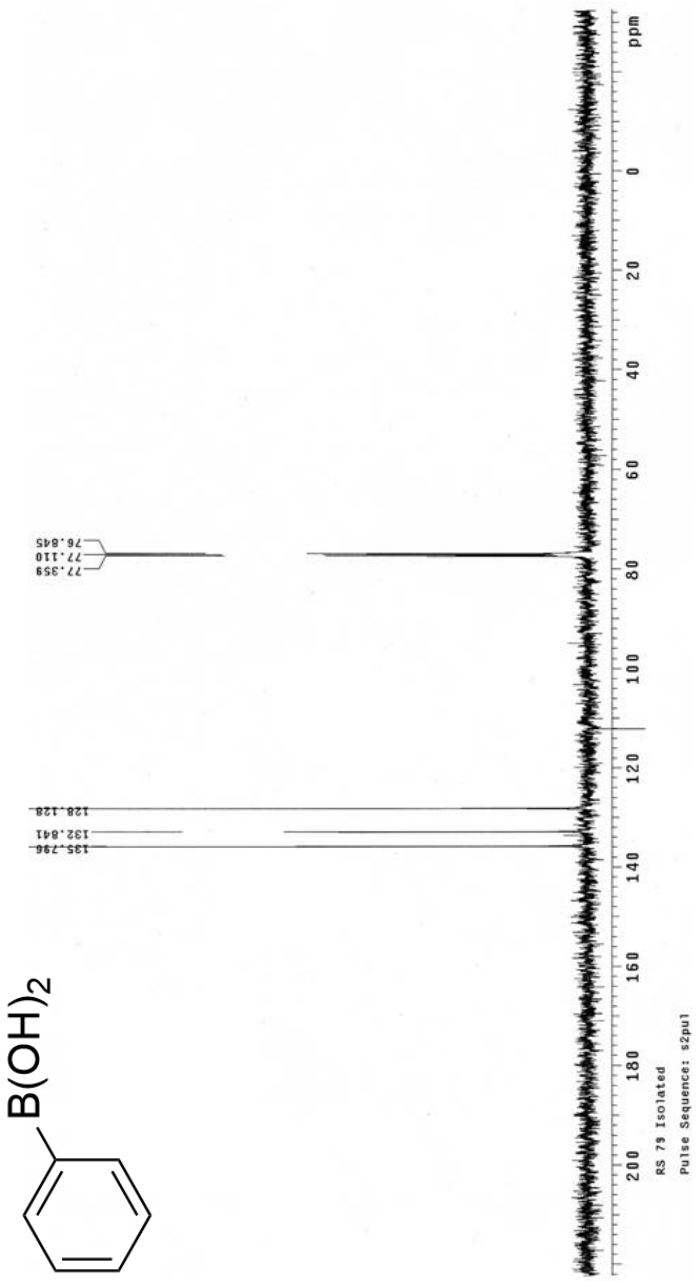

137.681
84.138
24.778
f1 (ppm)

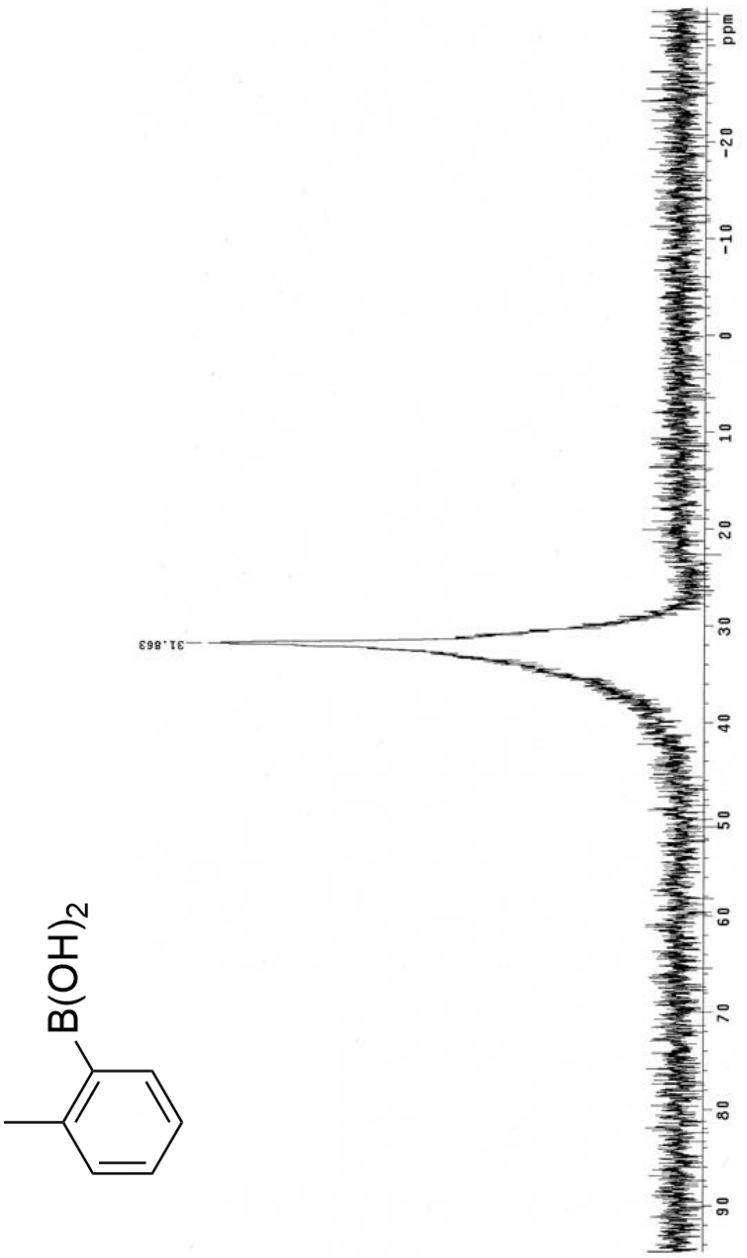

MgCl
HB
O
O
BPin + HMgCl
+34, s
H2B–NiPr2
BPin + HMgCl + H2B–NiPr2
+35, t, J = 125 Hz
unreacted
via 11B NMR

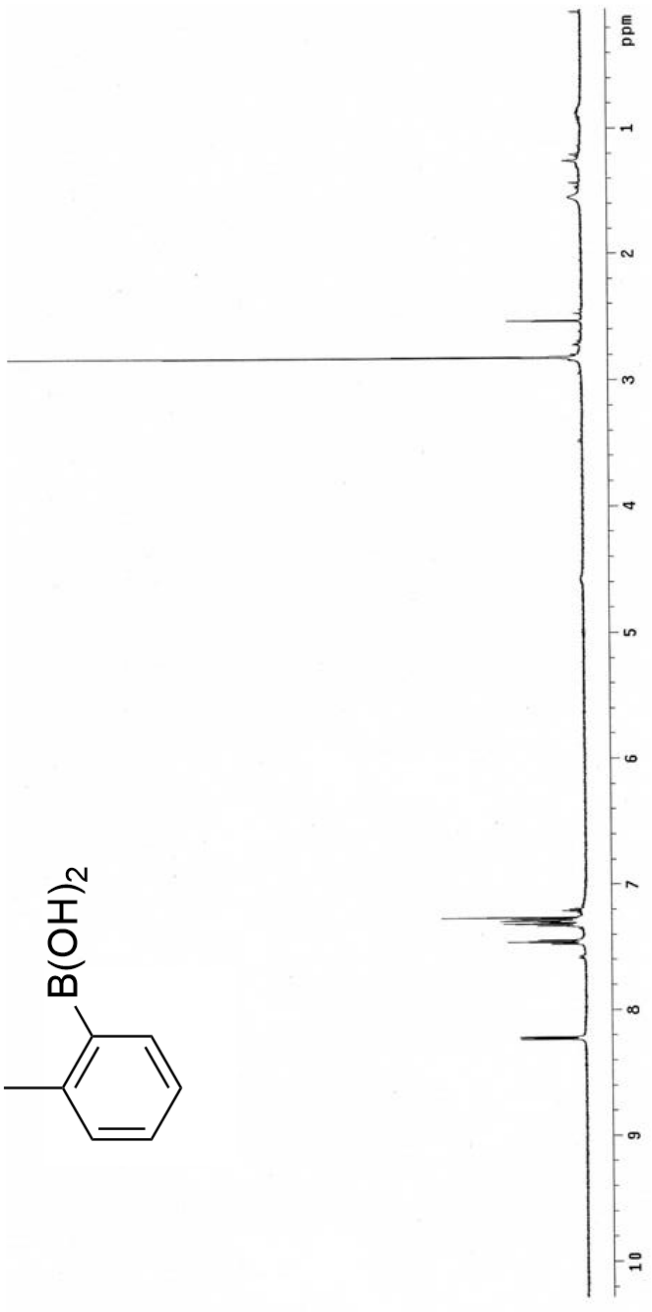

36.174
35.383
34.591
90
80
70
60
50
40
30
20
10
0
-10
-20
-30
-40
ppm
JC5.125 A+BH2NiPr2 40min
Pulse Sequence: presat

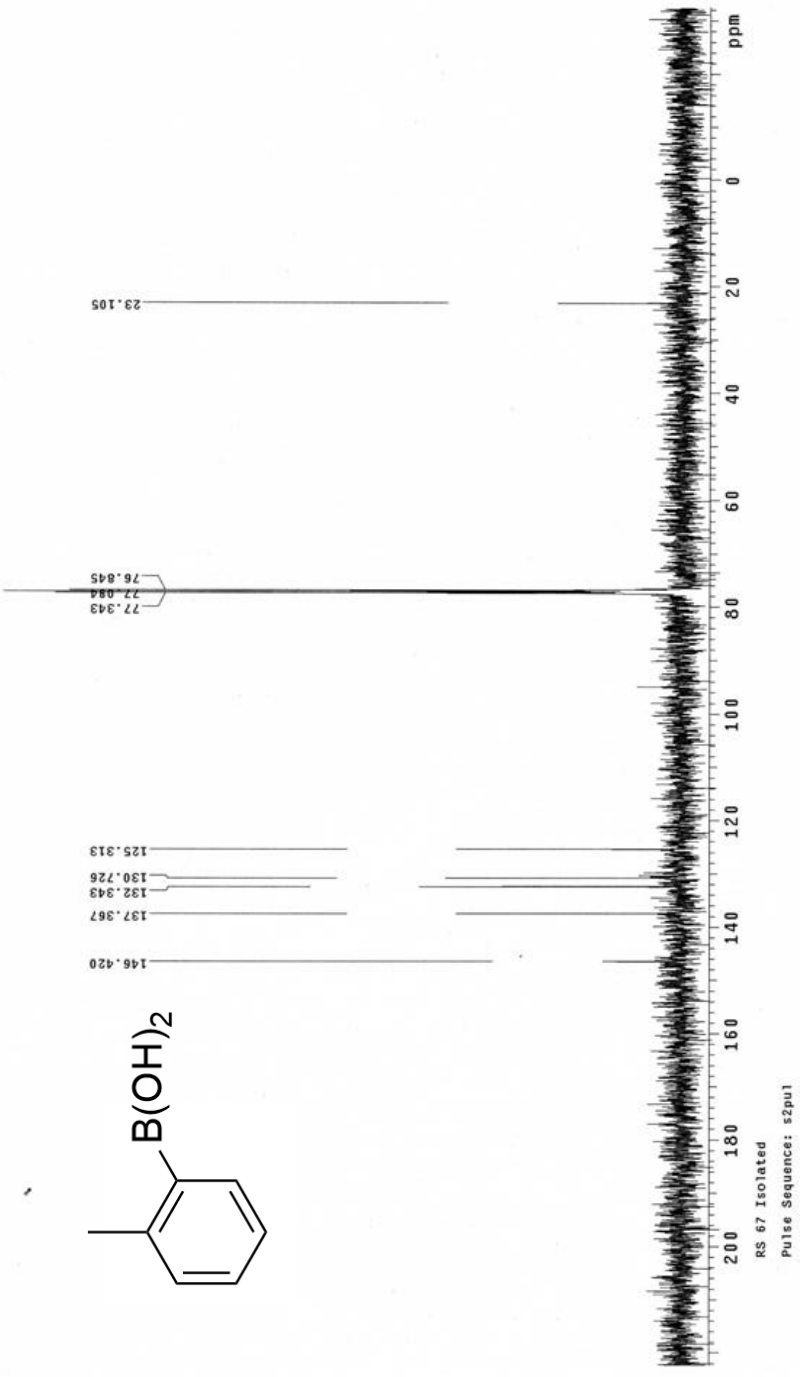

B(OH)2
30.779
90
80
70
60
50
40
30
20
10
0
-10
ppm
RS 79 Isolated
Pulse Sequence: presat


B(OH)2
12
10
8
6
4
2
0
−2
ppm

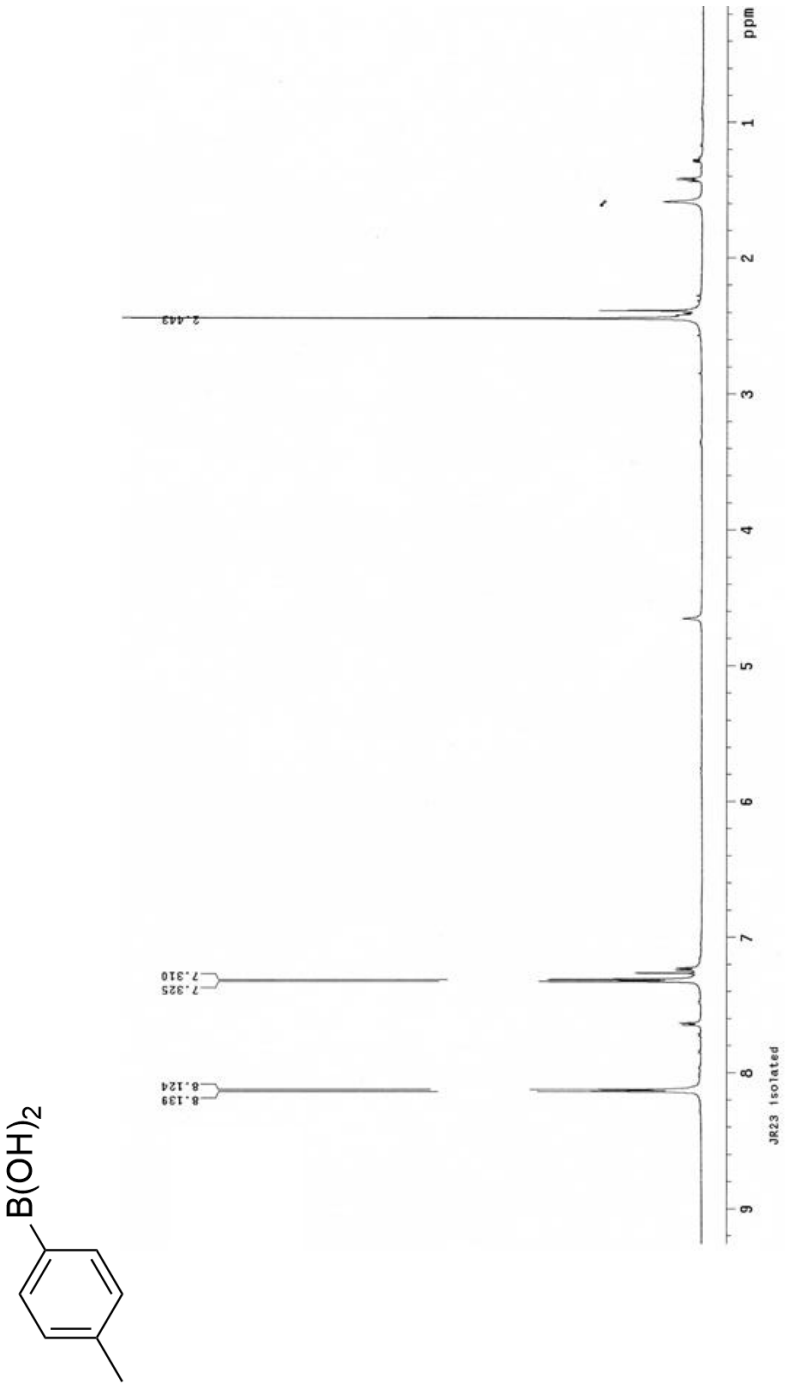

B(OH)2
135.796
132.841
128.128
77.359
77.110
76.845
ppm
RS 79 Isolated
Pulse Sequence: s2pul

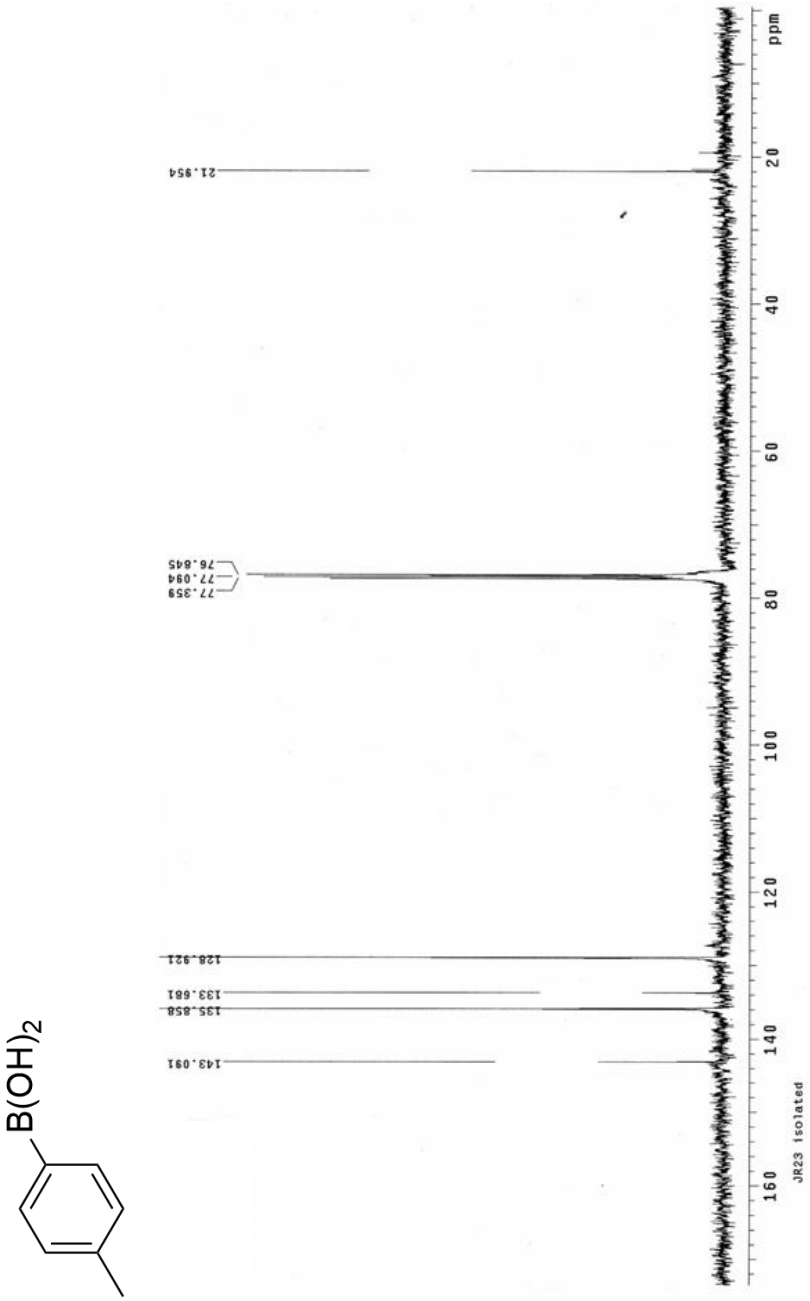

B(OH)2
31.863
ppm
90
80
70
60
50
40
30
20
10
0
-10
-20

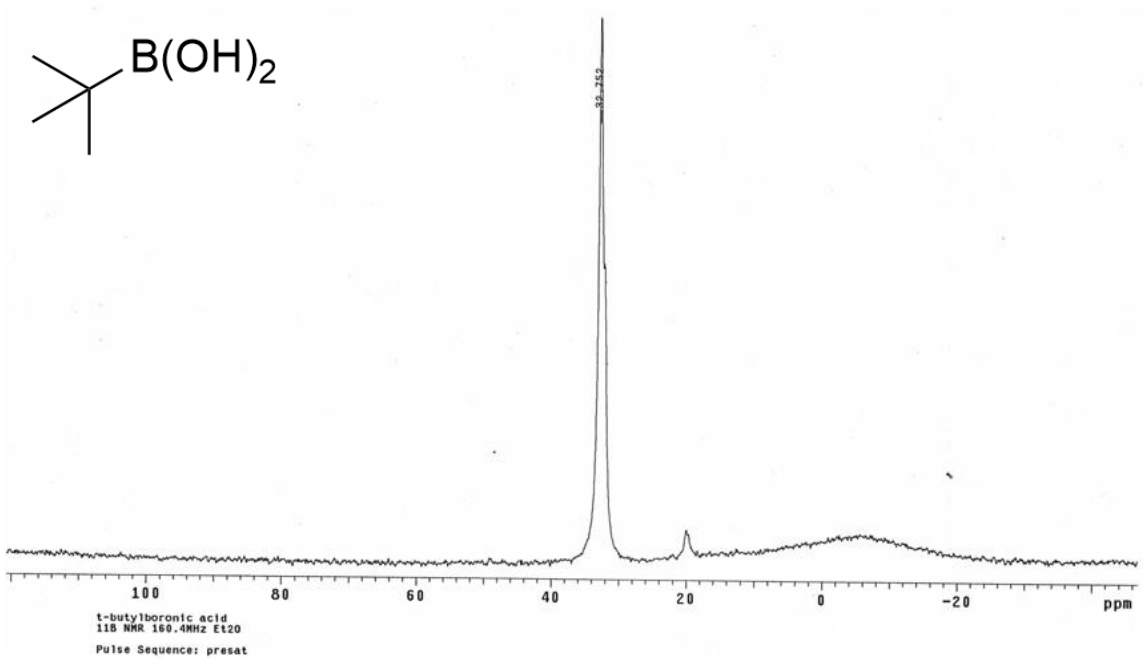

B(OH)2
ppm
1
2
3
4
5
6
7
8
9
10


B(OH)2
146.420
137.367
132.343
130.726
125.313
77.343
77.084
76.845
23.105
ppm
RS 67 Isolated
Pulse Sequence: s2pul

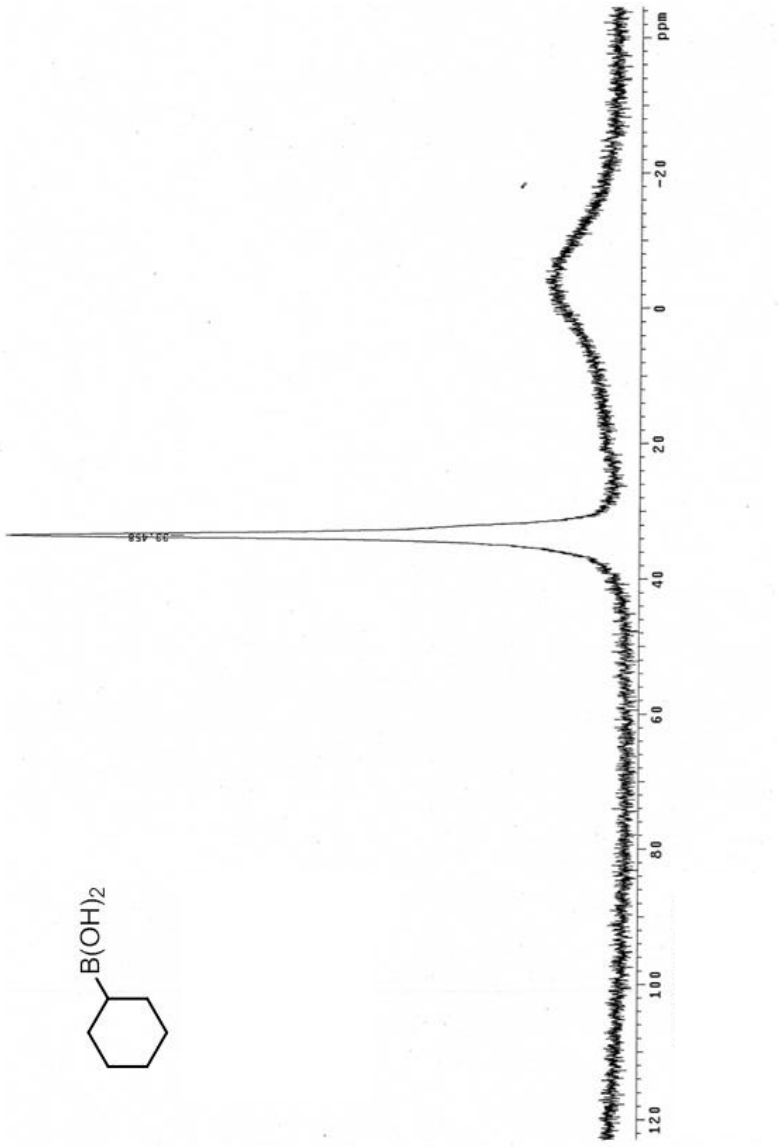
B(OH)2
30.432
ppm
JR23 isolated

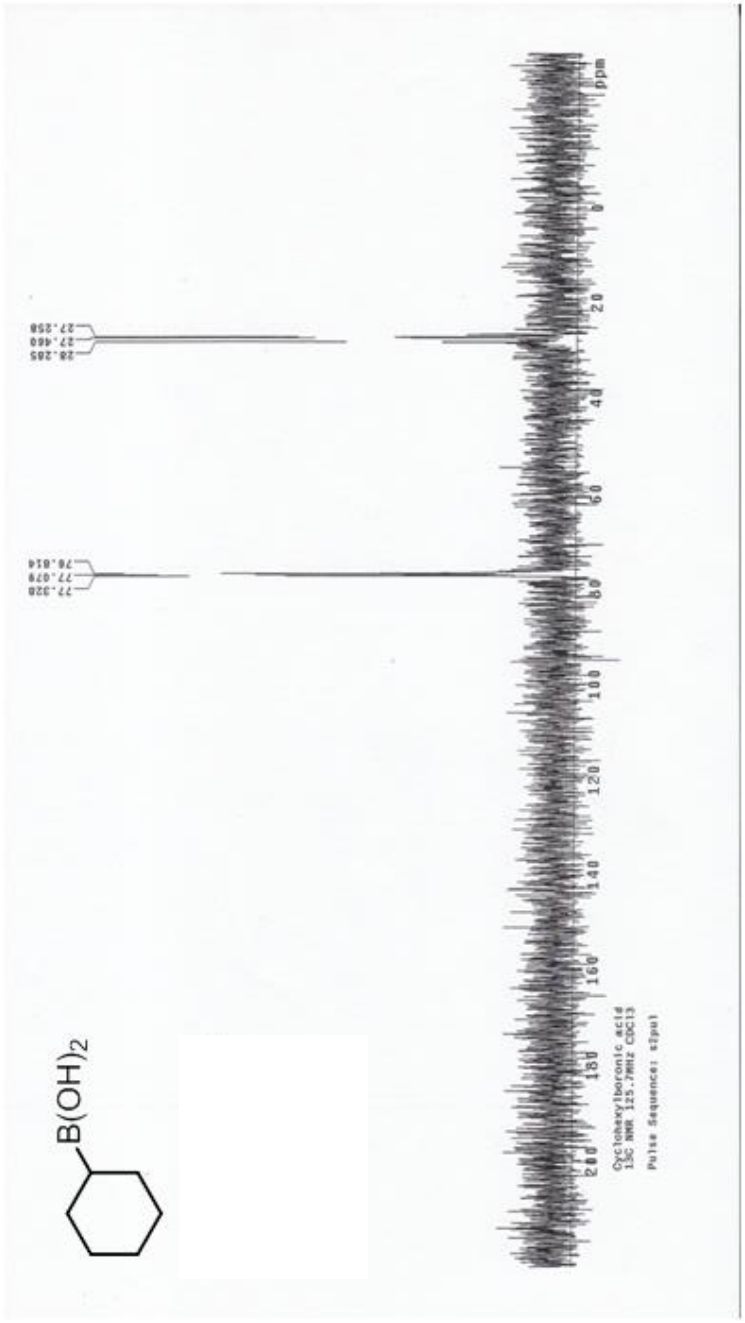

B(OH)2
8.139
8.124
7.325
7.310
2.443
9
8
7
6
5
4
3
2
1
ppm
JR23 isolated

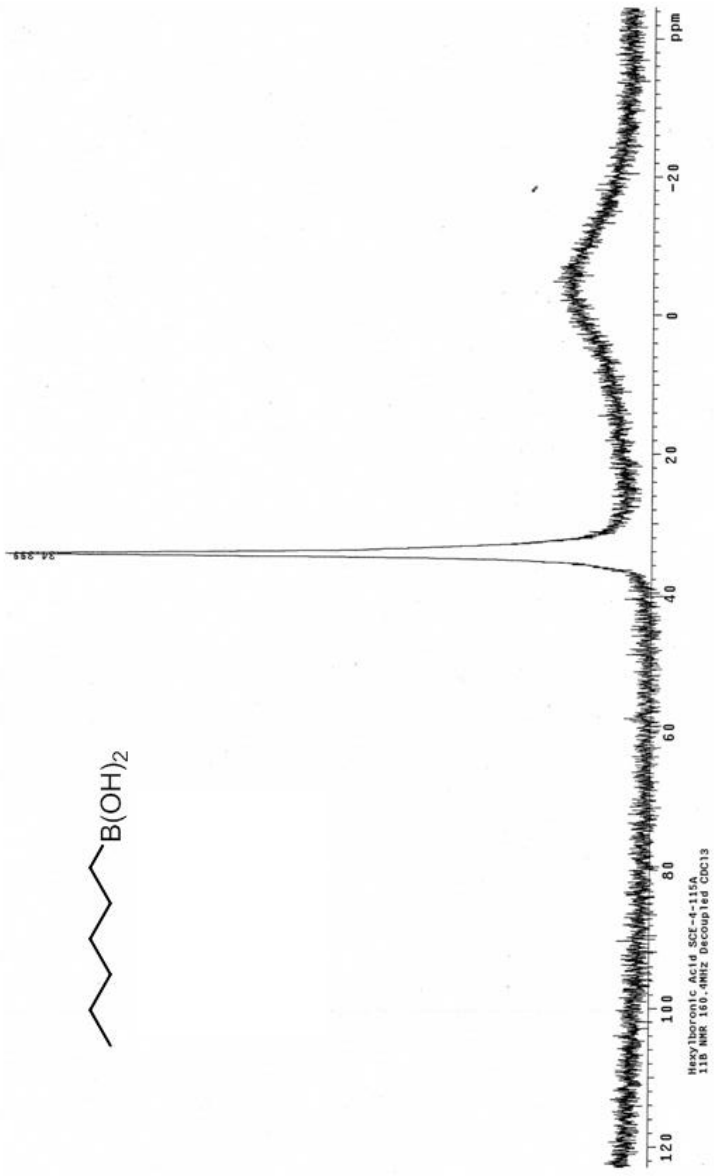

B(OH)2
21.954
77.359
77.094
76.845
128.921
133.681
135.858
143.091
ppm
20
40
60
80
100
120
140
160
JR23 isolated

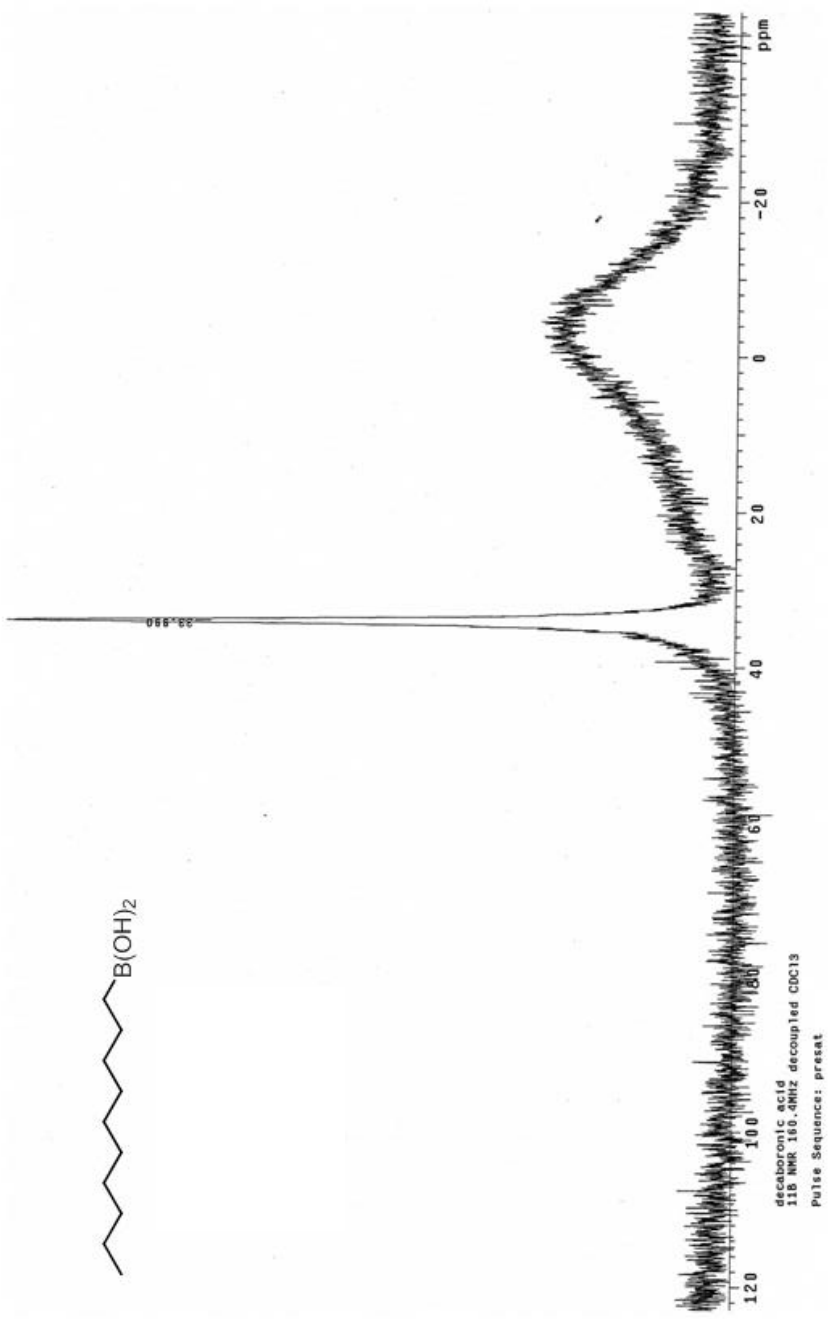

B(OH)2
32.252
100
80
60
40
20
0
-20
ppm
t-butylboronic acid
11B NMR 160.4MHz Et2O
Pulse Sequence: presat

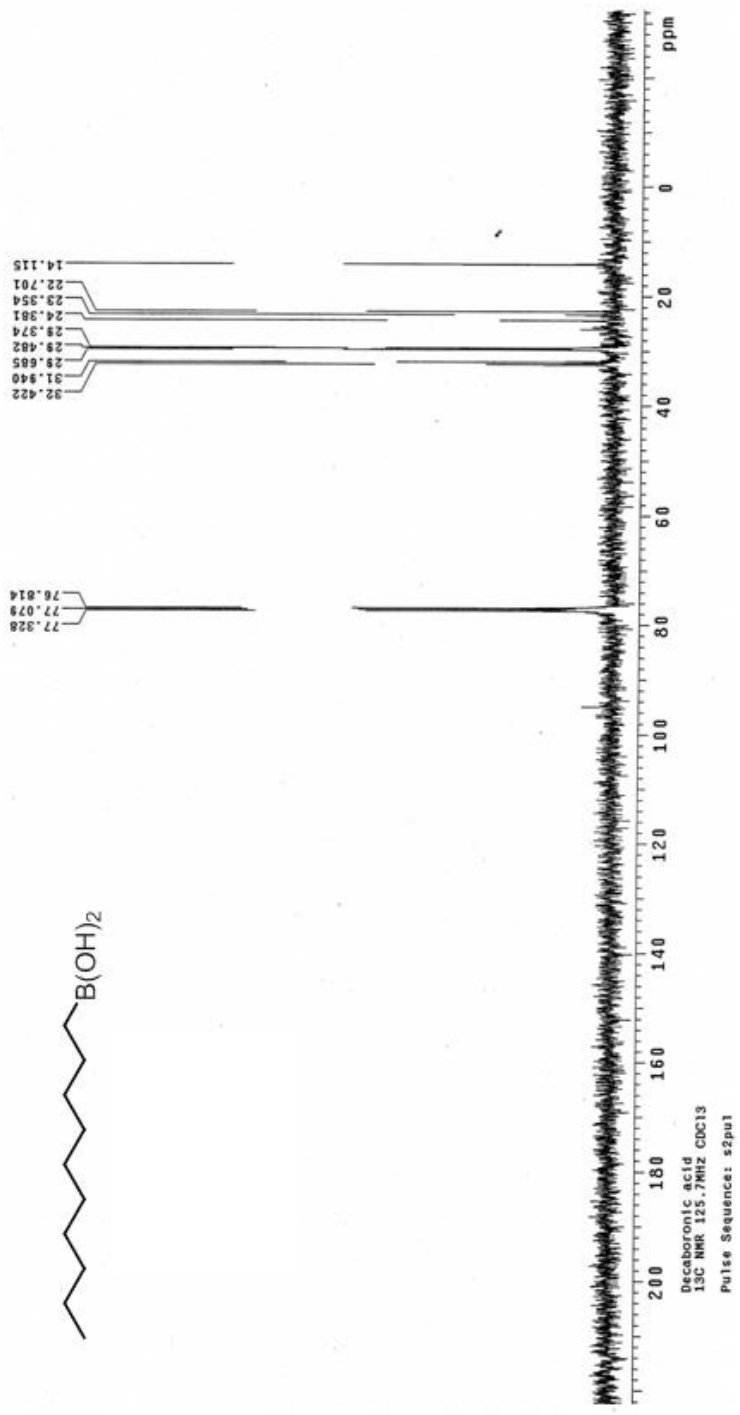
B(OH)2
27.762
39.168
39.339
39.510
39.681
39.836
200
180
160
140
120
100
80
60
40
20
0
-20
ppm
t-butylboronic acid
13C NMR 125.7MHz DMSO
Pulse Sequence: s2pul

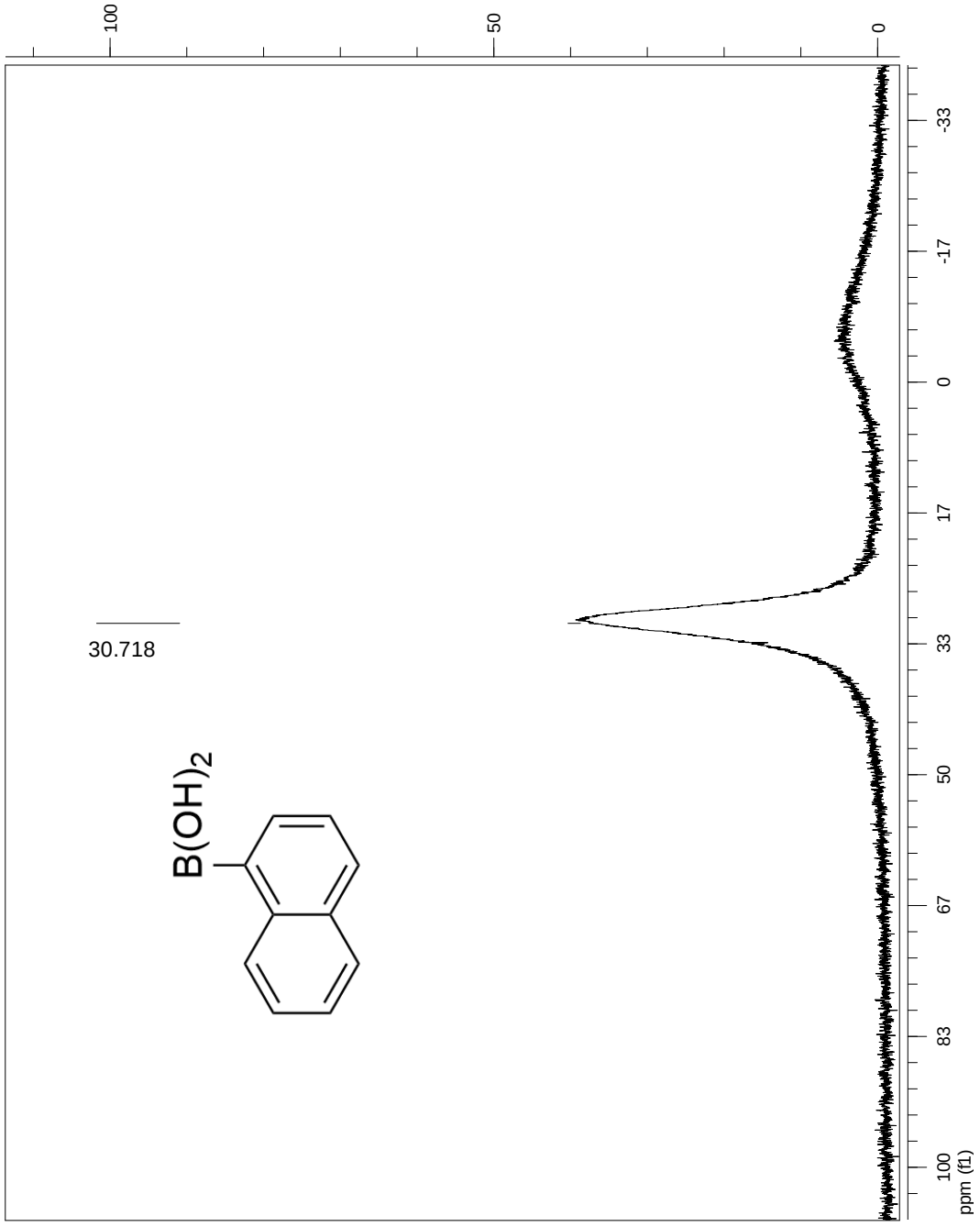

B(OH)2
30.458
ppm
120
100
80
60
40
20
0
-20

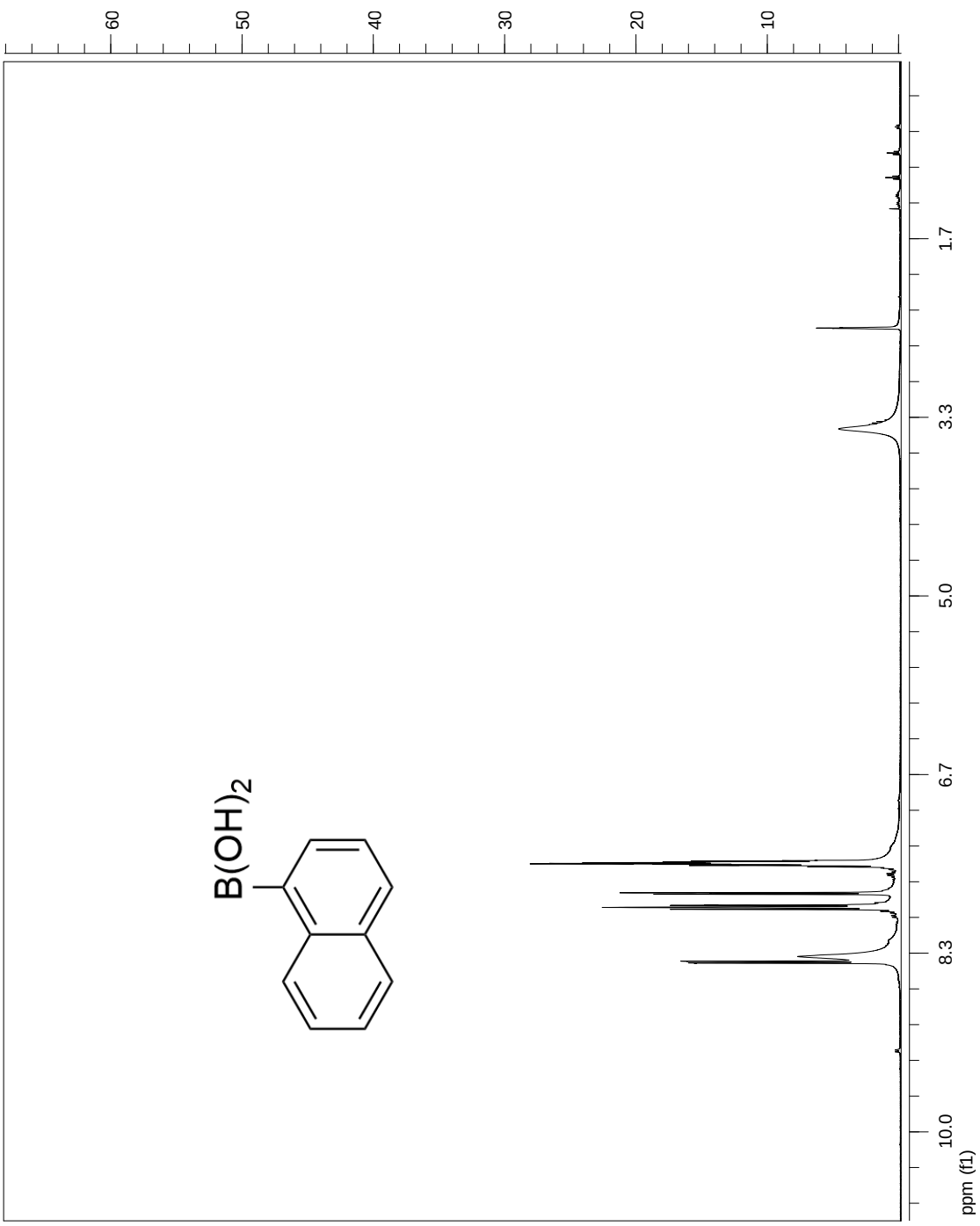

B(OH)2
Cyclohexylboronic acid
13C NMR 125.7MHz CDCl3
Pulse Sequence: s2pul
ppm
0
20
40
60
80
100
120
140
160
180
200
28.285
27.460
27.258
77.328
77.079
76.814

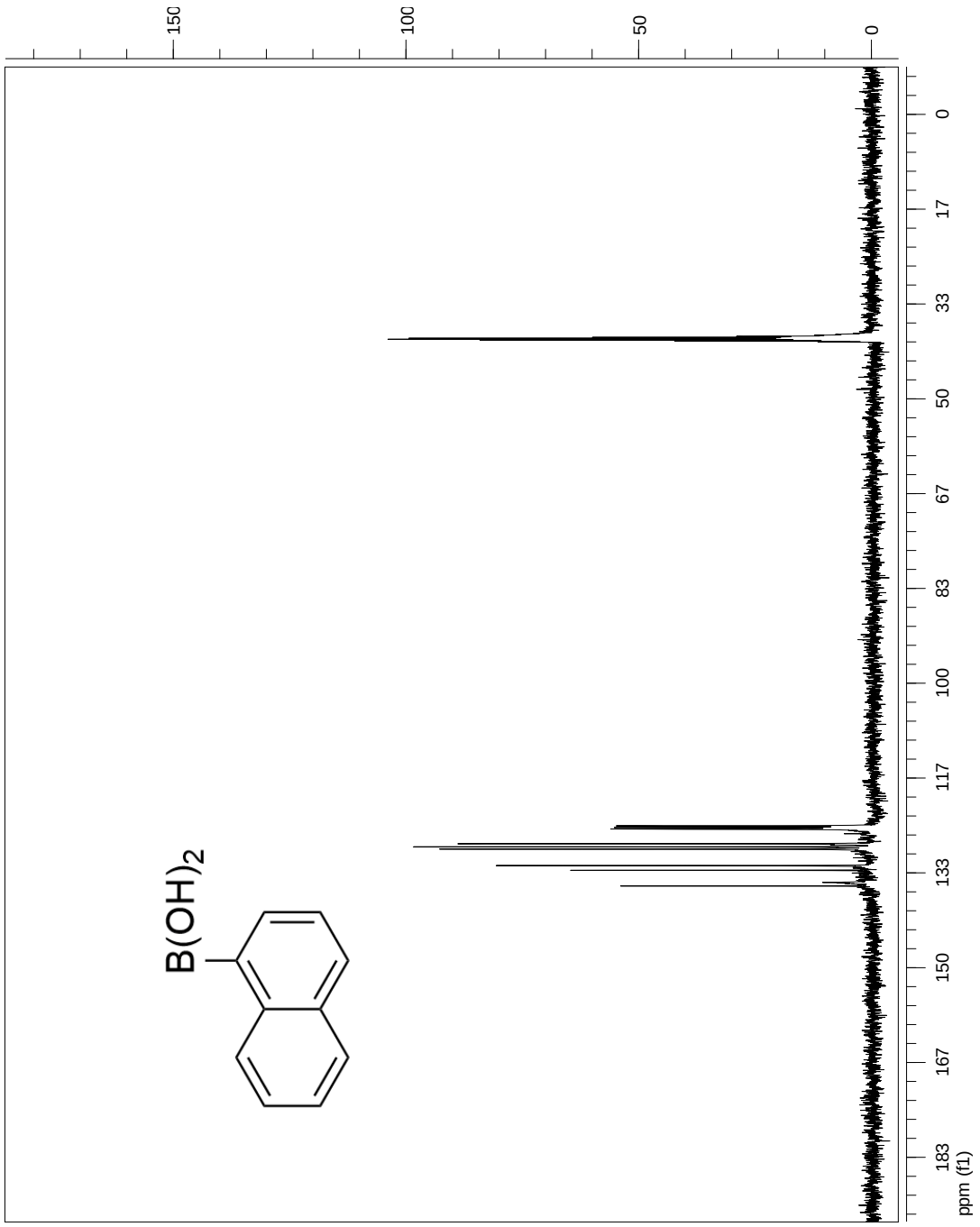

B(OH)2
34.085
120
100
80
60
40
20
0
-20
ppm
Hexylboronic Acid SCE-4-115A
11B NMR 160.4MHz Decoupled CDCl3

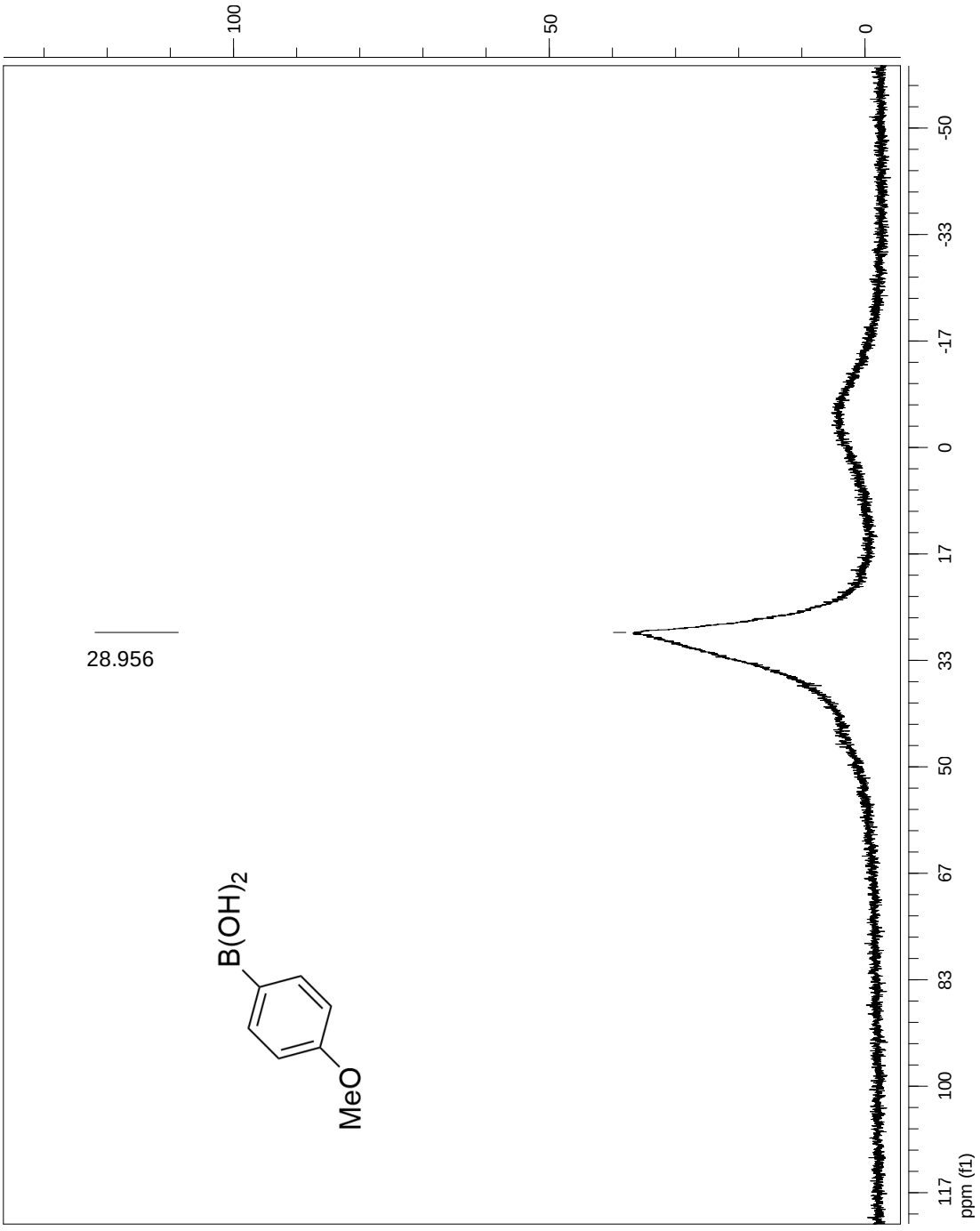

B(OH)2
33.850
ppm
120
100
80
60
40
20
0
-20
decaboronic acid
11B NMR 160.4MHz decoupled CDCl3
Pulse Sequence: presat

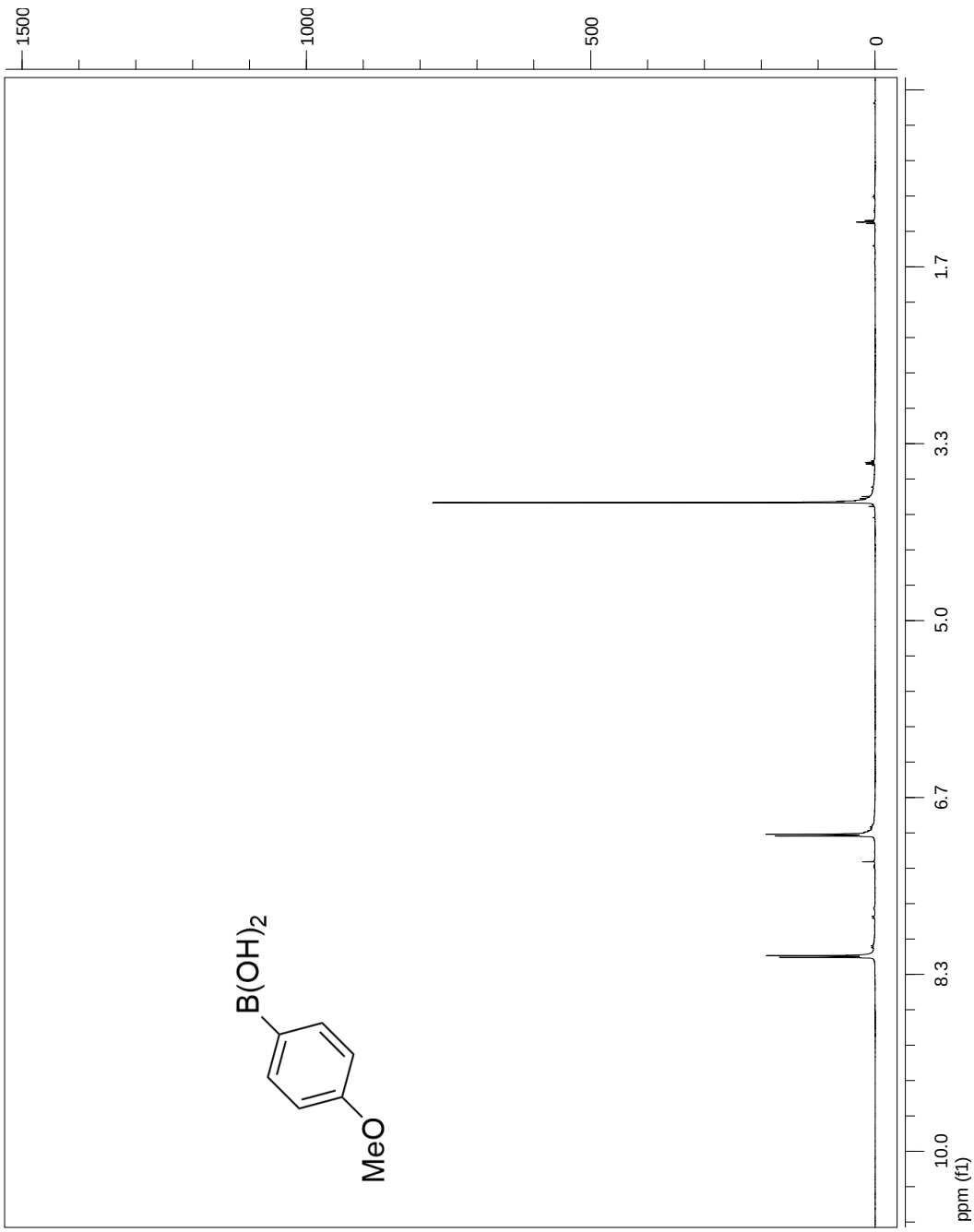

B(OH)2
14.115
22.701
23.354
24.381
29.374
29.482
29.685
31.940
32.422
77.328
77.079
76.814
ppm
0
20
40
60
80
100
120
140
160
180
200
Decaboronic acid
13C NMR 125.7MHz CDCl3
Pulse Sequence: s2pul

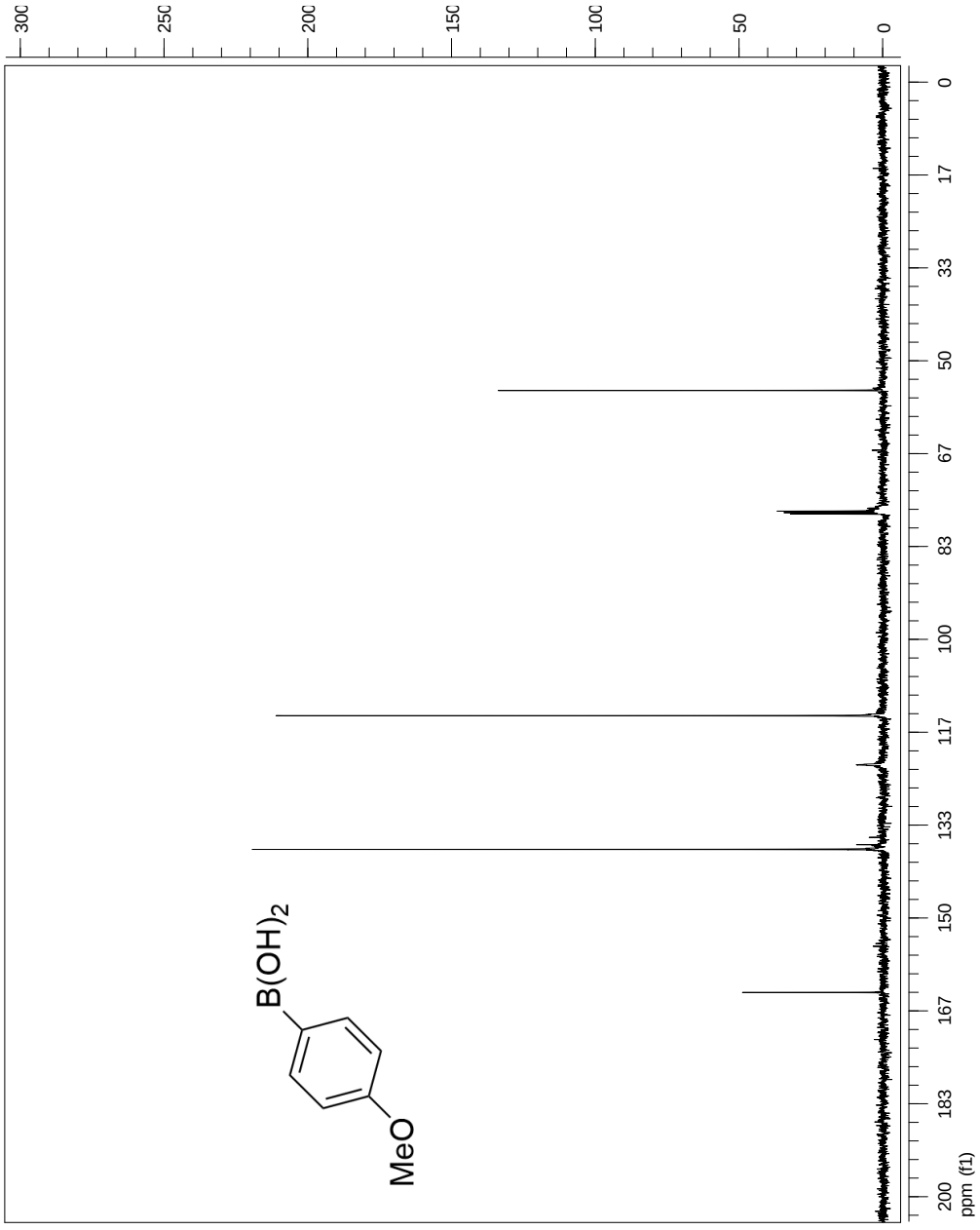

100
50
0
30.718
B(OH)2
100
83
67
50
33
17
0
-17
-33
ppm (f1)

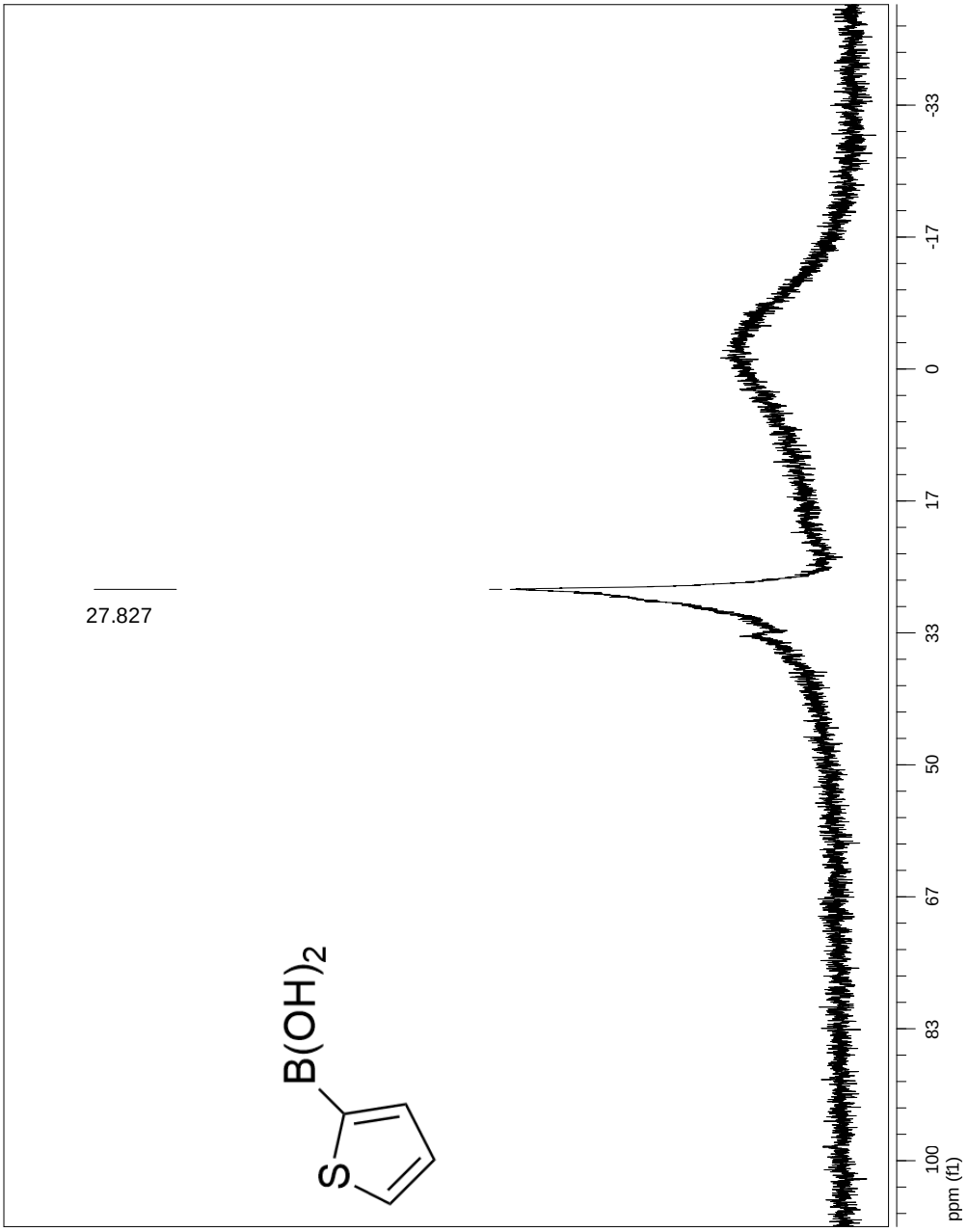

60
50
40
30
20
10
B(OH)2
10.0
8.3
6.7
5.0
3.3
1.7
ppm (f1)

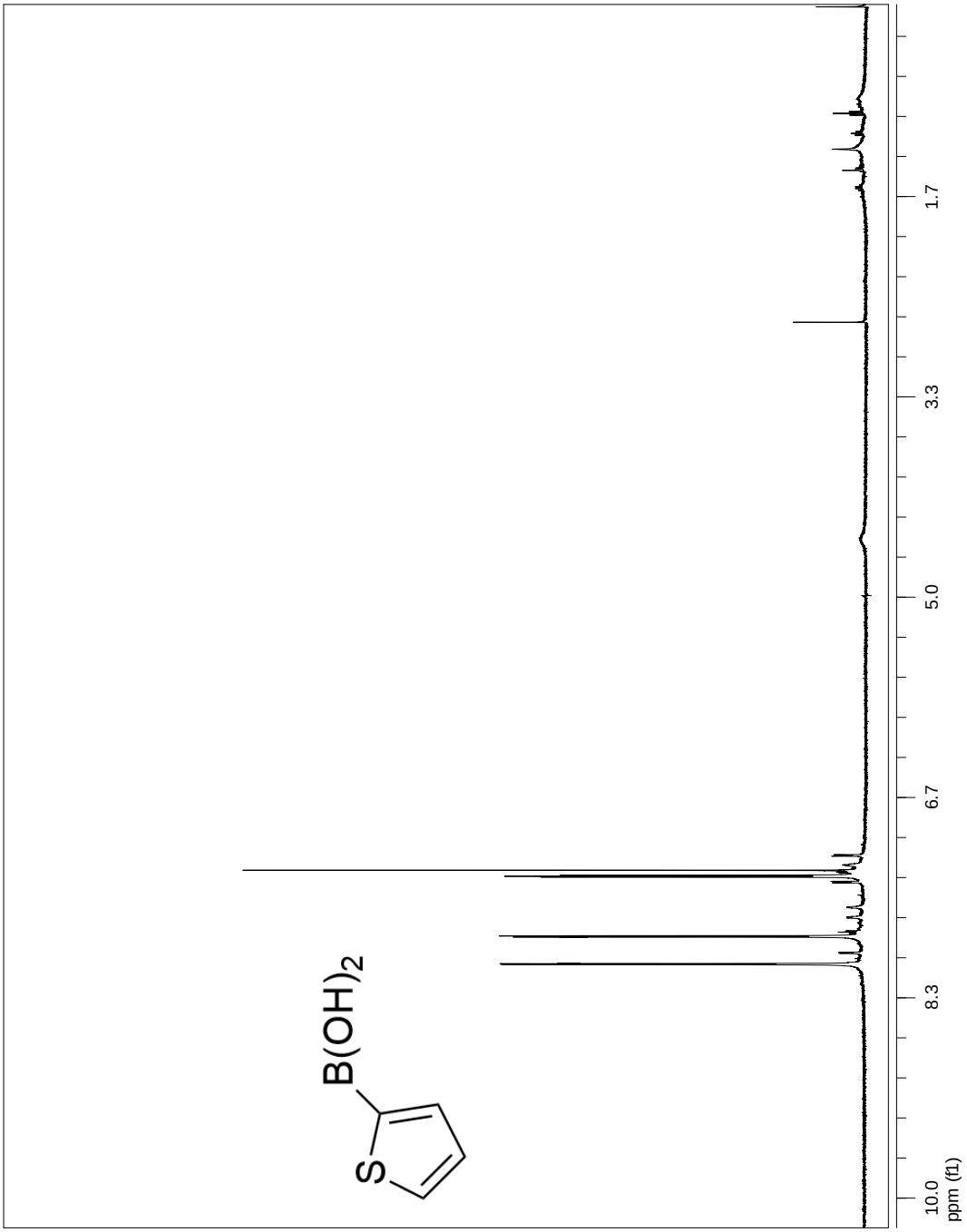

150
100
50
0
B(OH)2
0
17
33
50
67
83
100
117
133
150
167
183
ppm (f1)

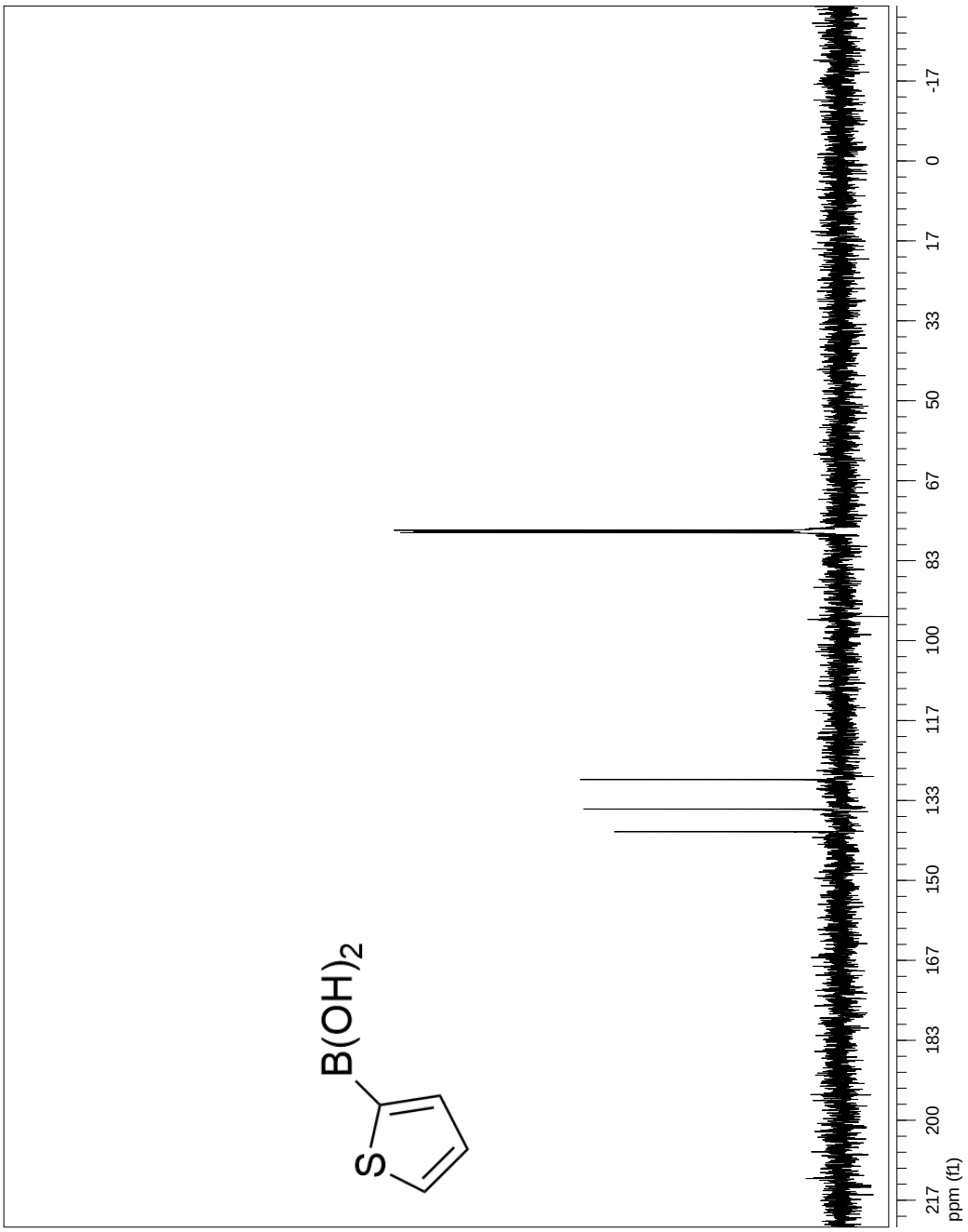

100
50
0
28.956
B(OH)2
MeO
117
100
83
67
50
33
17
0
-17
-33
-50
ppm (f1)

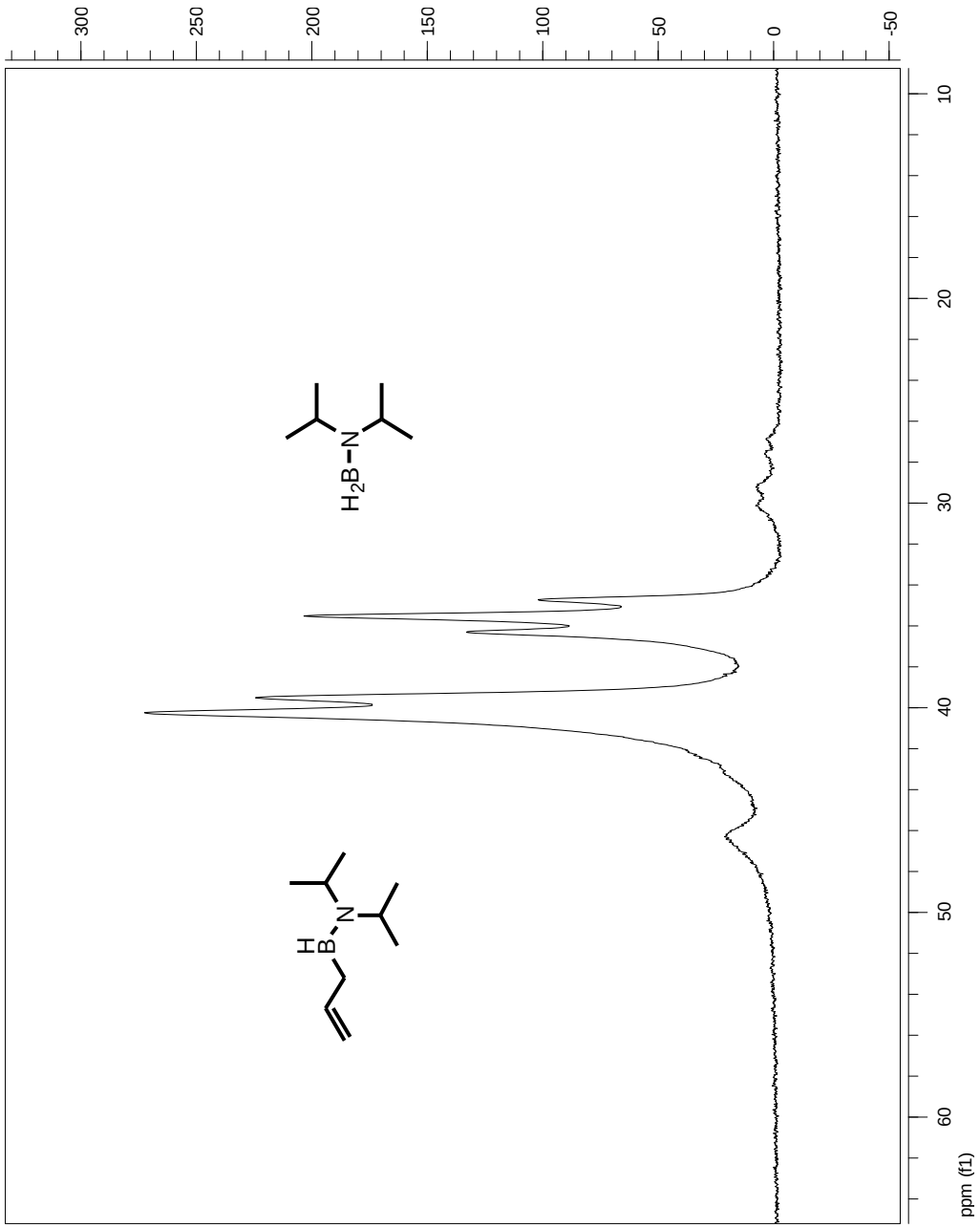

1500
1000
500
0
10.0
8.3
6.7
5.0
3.3
1.7
ppm (f1)
B(OH)2
MeO

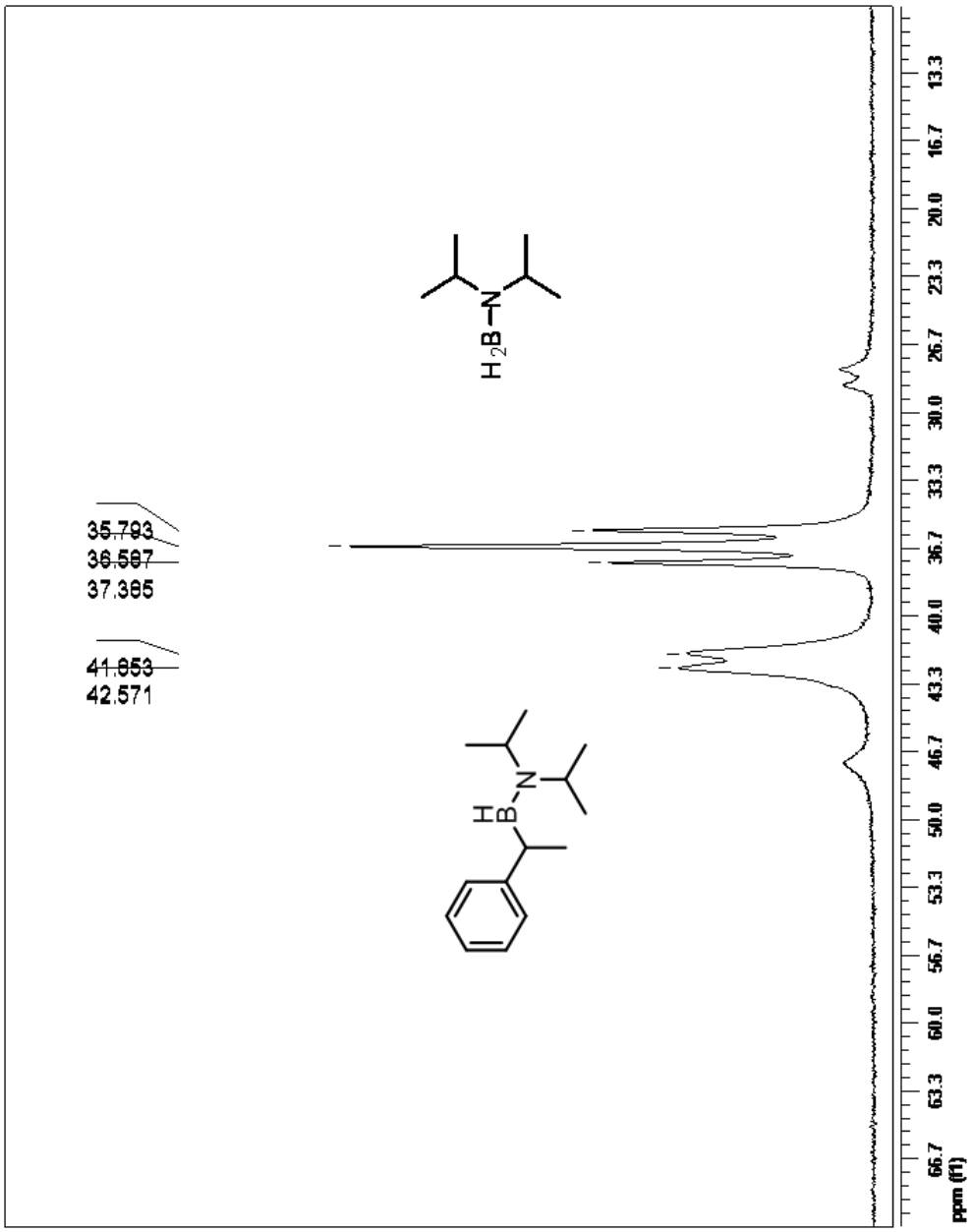

B(OH)2
MeO
300
250
200
150
100
50
0
0
17
33
50
67
83
100
117
133
150
167
183
200
ppm (f1)


27.827
B(OH)2
S
100
83
67
50
33
17
0
-17
-33
ppm (f1)


B(OH)2
S
10.0
8.3
6.7
5.0
3.3
1.7
ppm (f1)

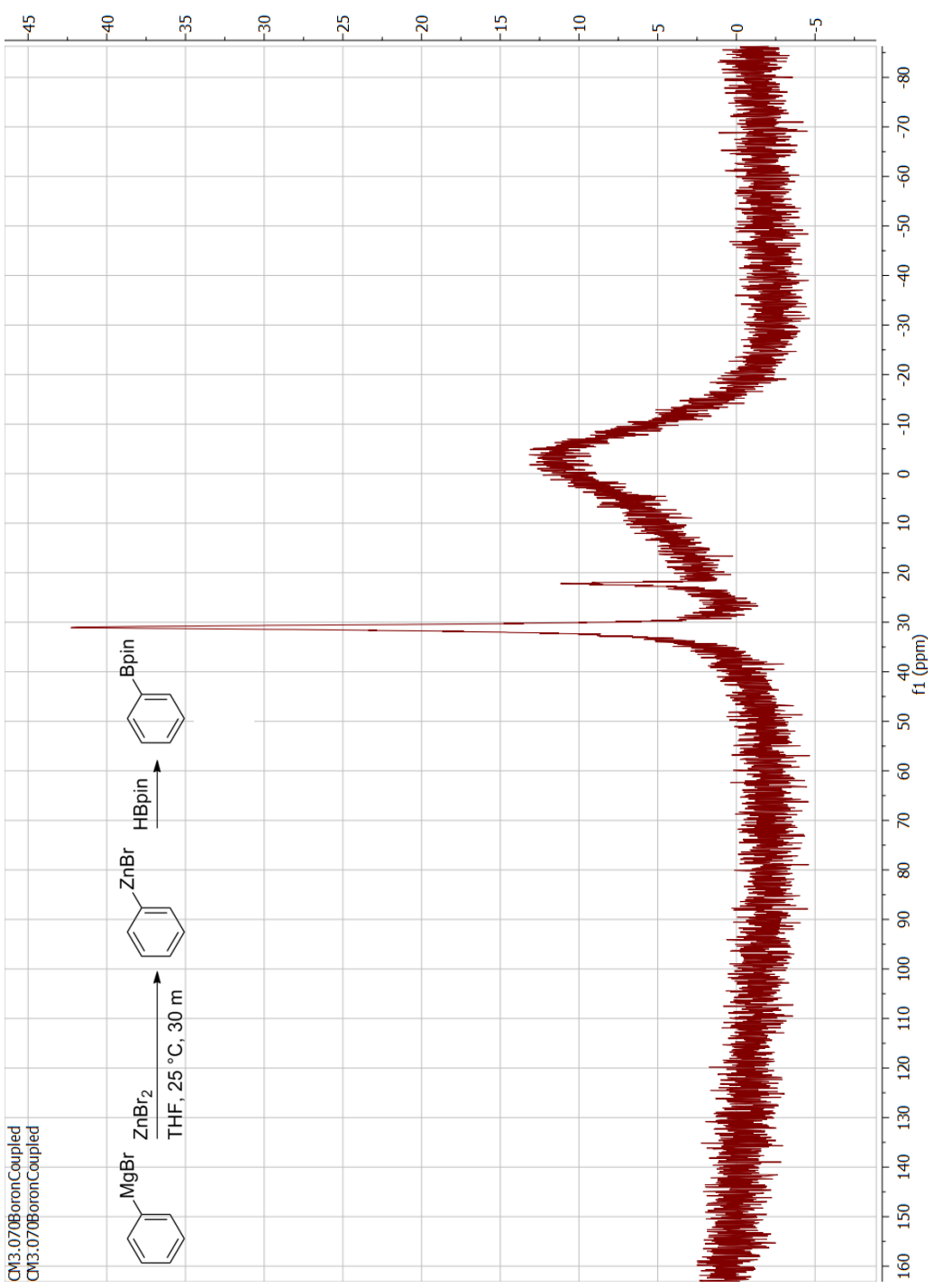

B(OH)2
S
217
200
183
167
150
133
117
100
83
67
50
33
17
0
-17
ppm (f1)

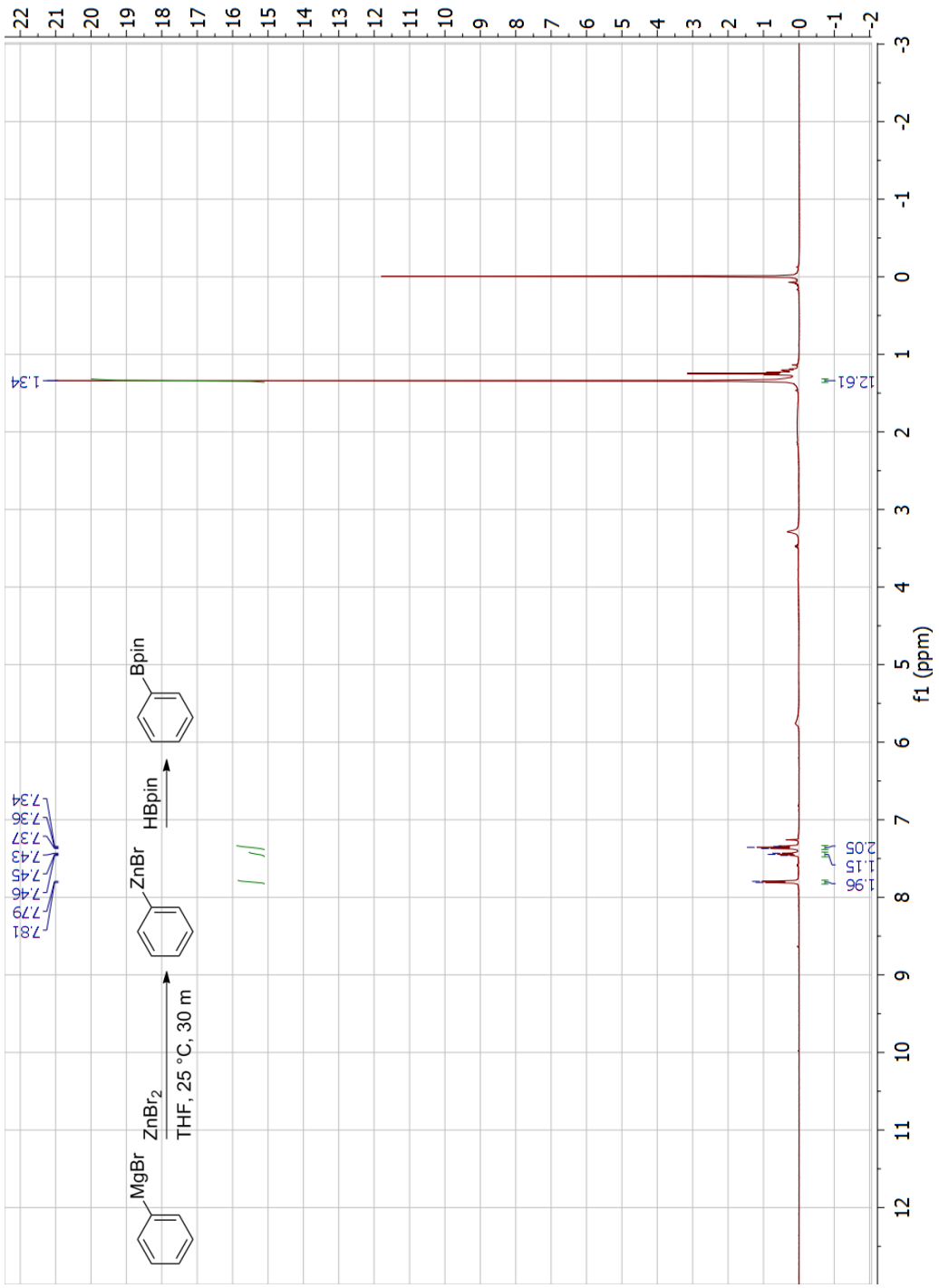

300
250
200
150
100
50
0
-50
10
20
30
40
50
60
ppm (f1)
H2B–N
H
B
N

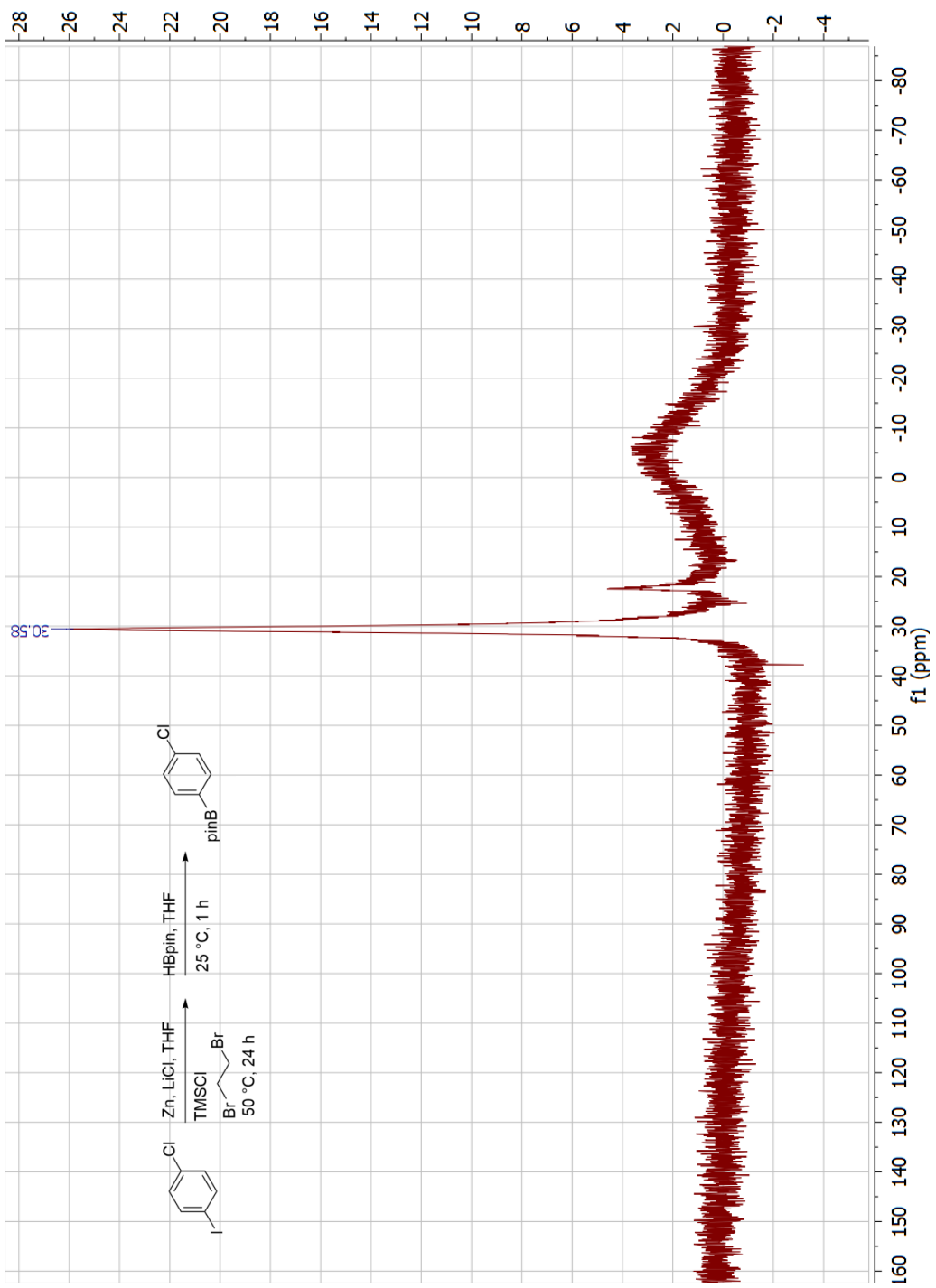

35.793
36.587
37.385
41.853
42.571
H2B
N
H
B
N
66.7
63.3
60.0
56.7
53.3
50.0
46.7
43.3
40.0
36.7
33.3
30.0
26.7
23.3
20.0
16.7
13.3
ppm (f1)

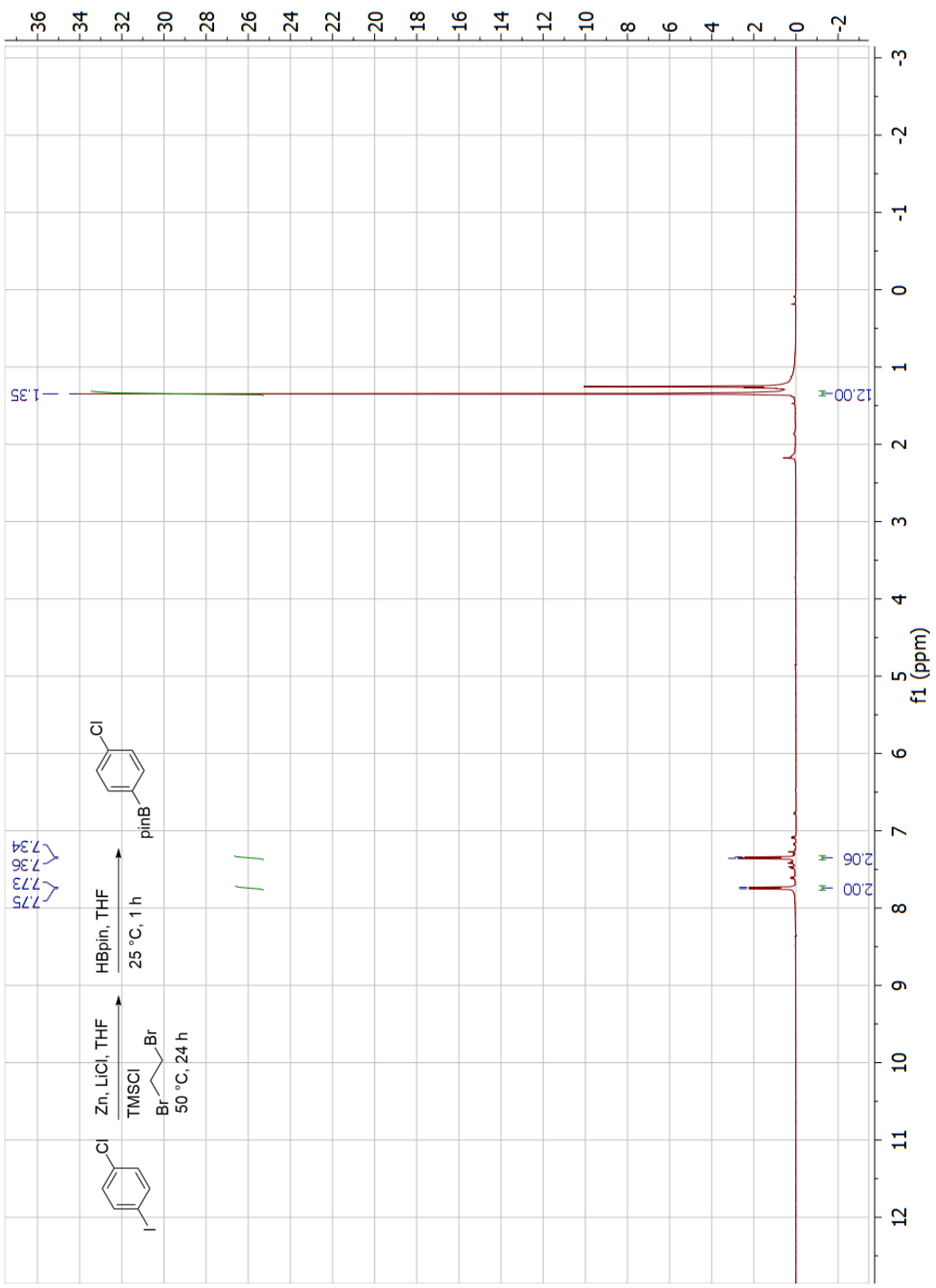
Appendix B

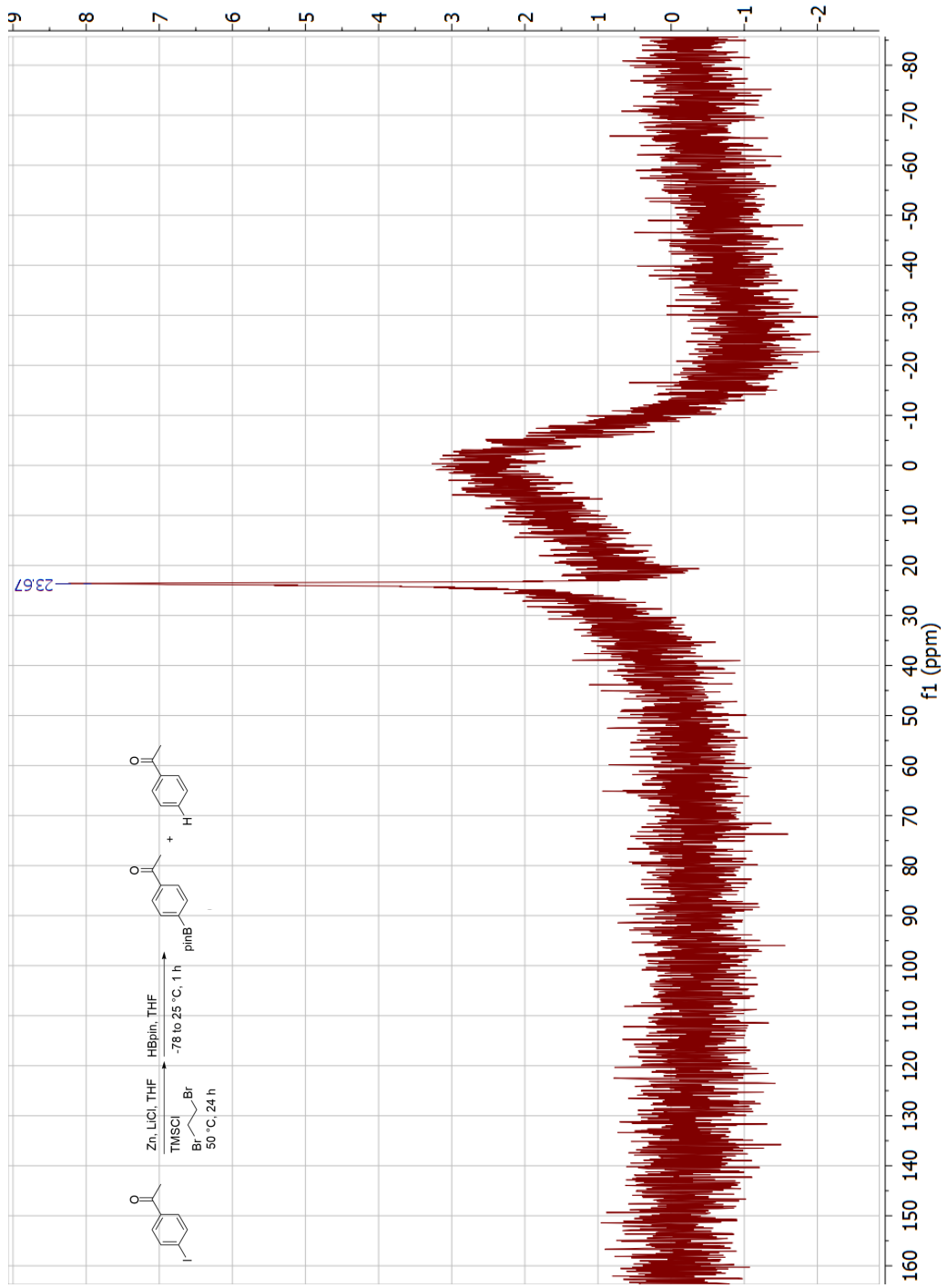
CHAPTER 3. ^{1}H, ^{11}B, and ^{13}C NMR Spectra

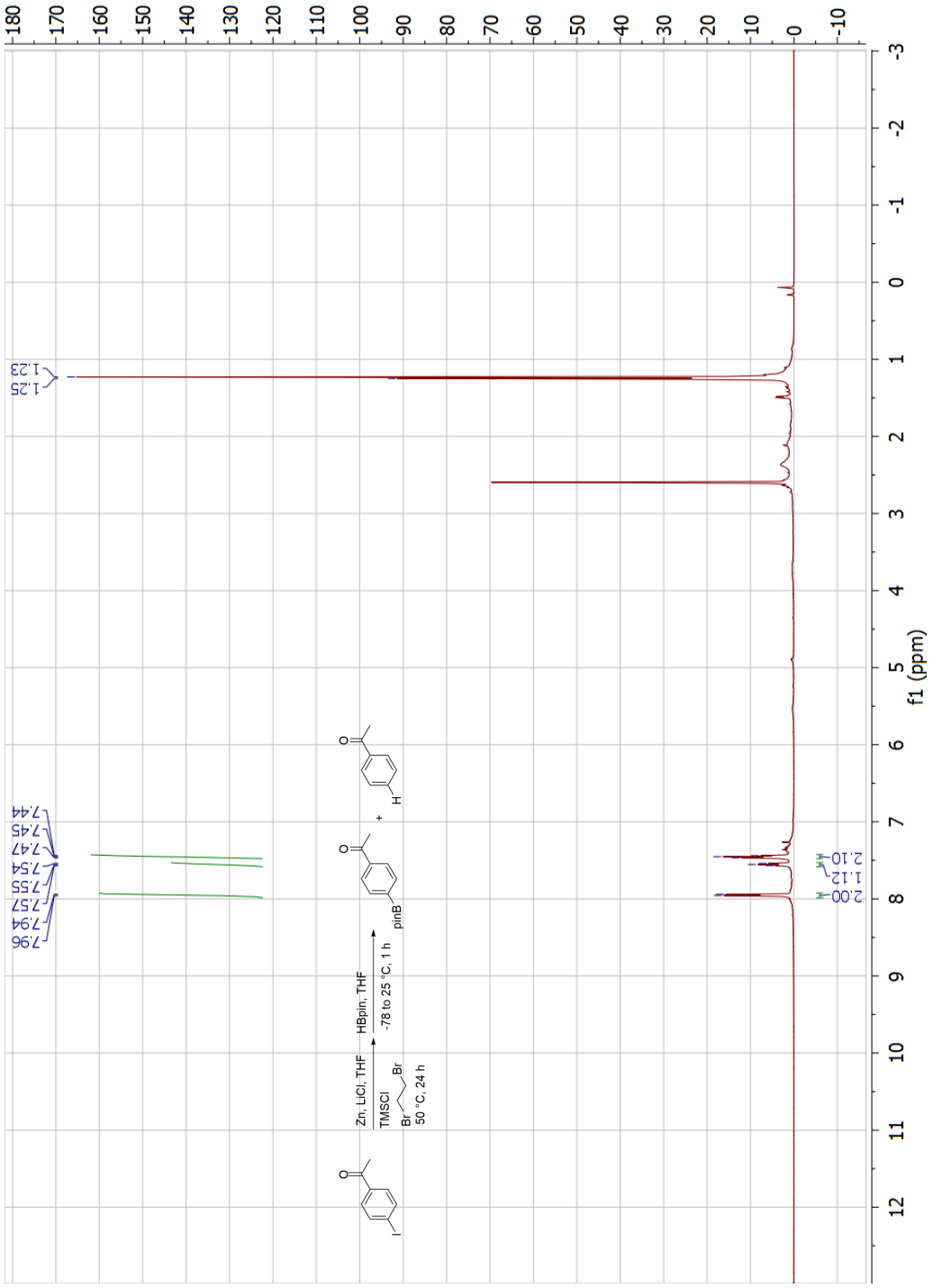

CM3.070BoronCoupled
CM3.070BoronCoupled
MgBr
ZnBr2
THF, 25 °C, 30 m
ZnBr
HBpin
Bpin
f1 (ppm)

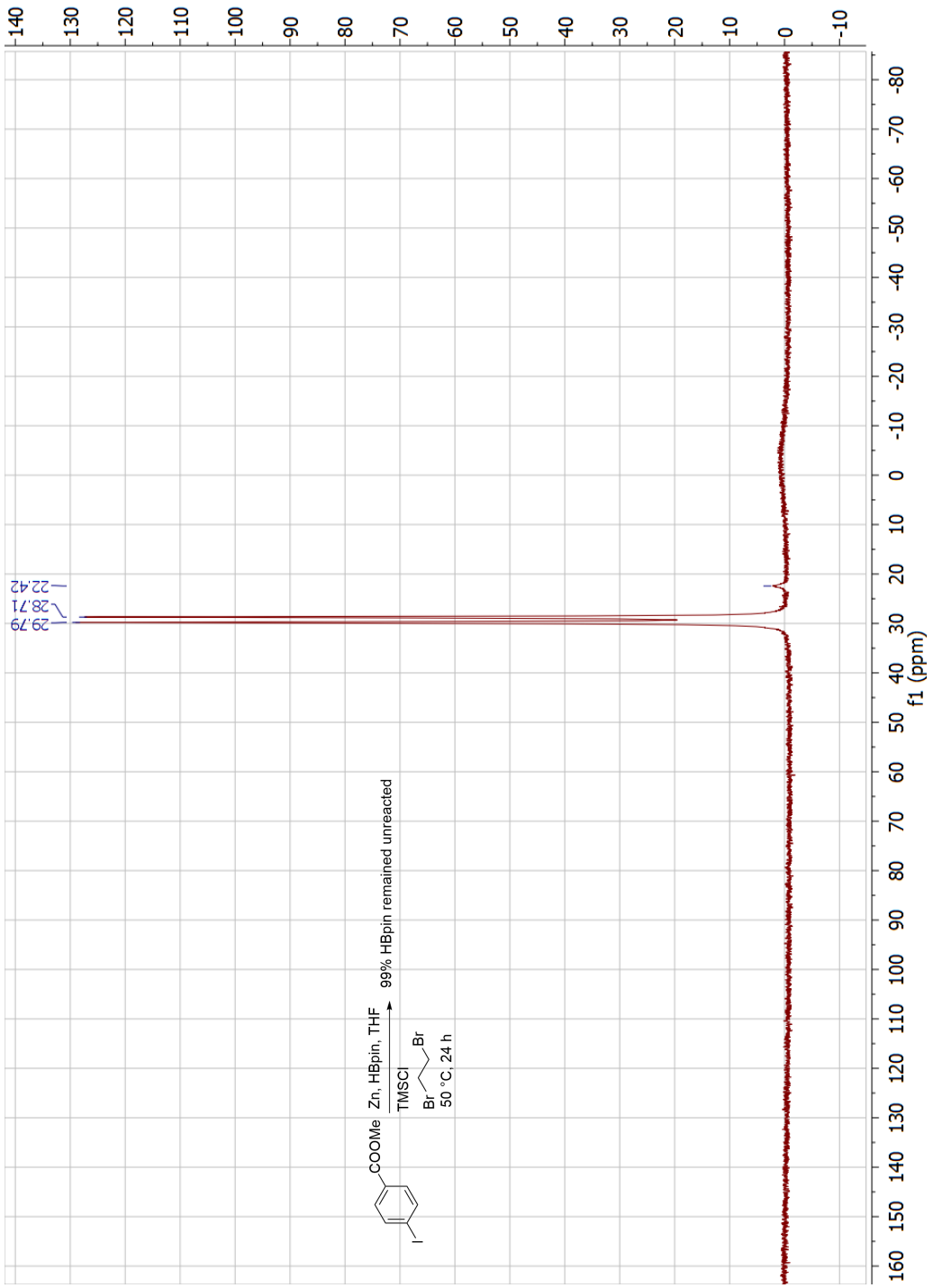

MgBr
ZnBr2
THF, 25 °C, 30 m
ZnBr
HBpin
Bpin
7.81
7.79
7.46
7.45
7.43
7.37
7.36
7.34
1.34
12.61
1.96
1.15
2.05
f1 (ppm)

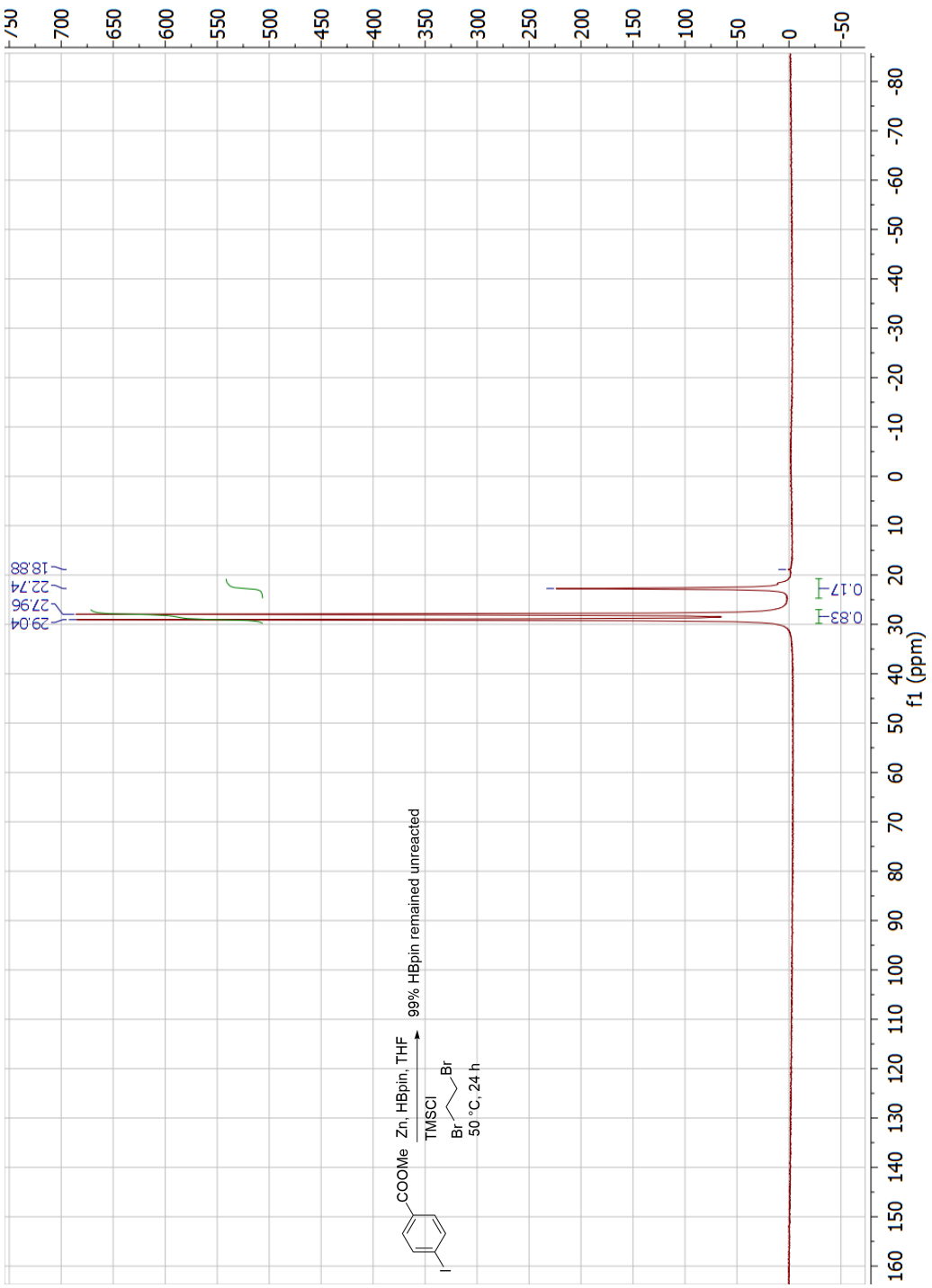

30.58
f1 (ppm)
Cl
I
Zn, LiCl, THF
TMSCl
Br
Br
50 °C, 24 h
HBpin, THF
25 °C, 1 h
Cl
pinB

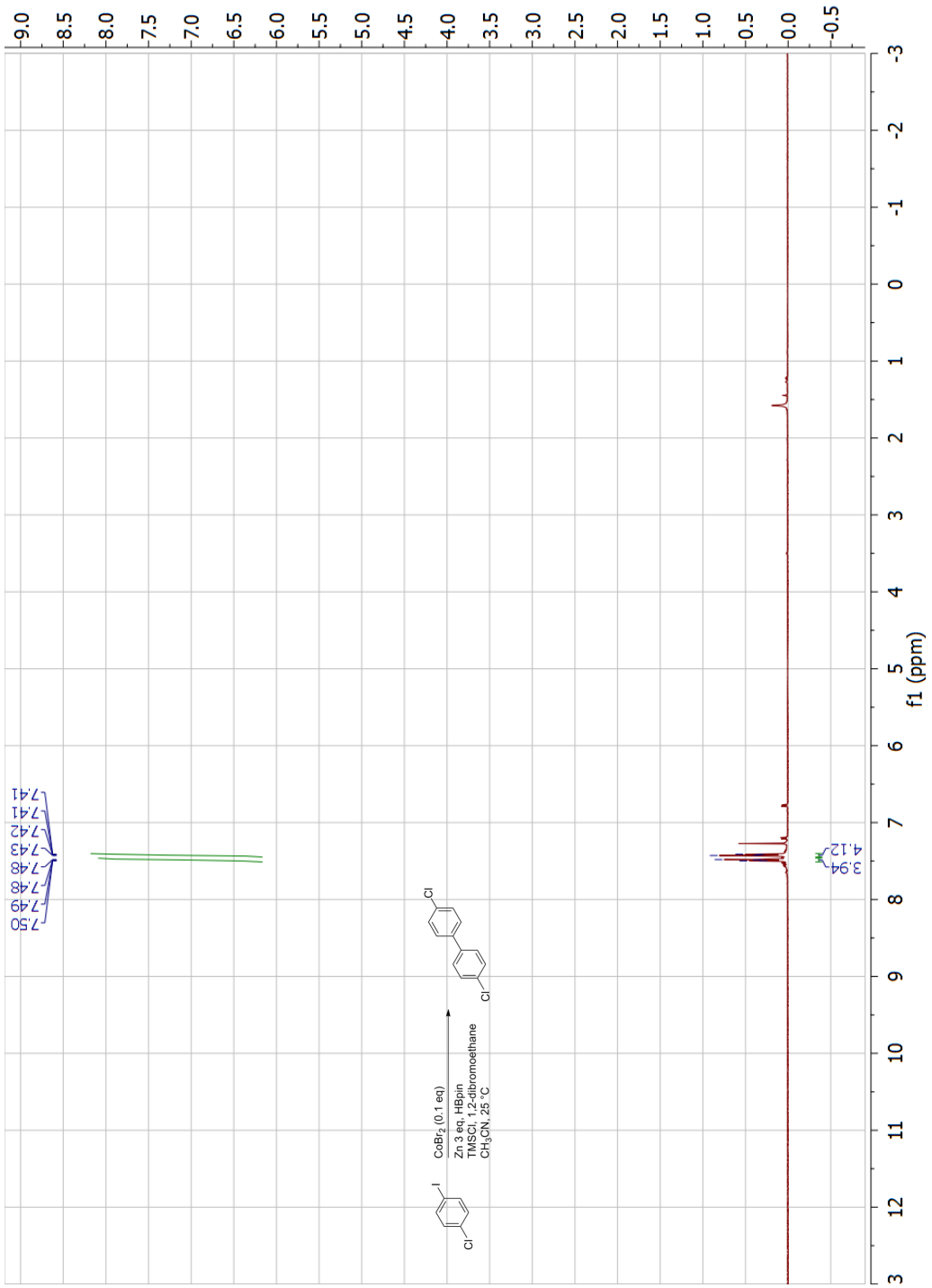

Cl
I
Zn, LiCl, THF
TMSCl
Br
Br
50 °C, 24 h
HBpin, THF
25 °C, 1 h
Cl
pinB
7.75
7.73
7.36
7.34
1.35
12.00
2.06
2.00
f1 (ppm)


23.67
f1 (ppm)
Zn, LiCl, THF
TMSCl
Br
Br
50 °C, 24 h
HBpin, THF
-78 to 25 °C, 1 h
pinB


f1 (ppm)
1.23
1.25
7.44
7.45
7.47
7.54
7.55
7.57
7.94
7.96
2.00
1.12
2.10
Zn, LiCl, THF
TMSCl
50 °C, 24 h
HBpin, THF
-78 to 25 °C, 1 h
pinB

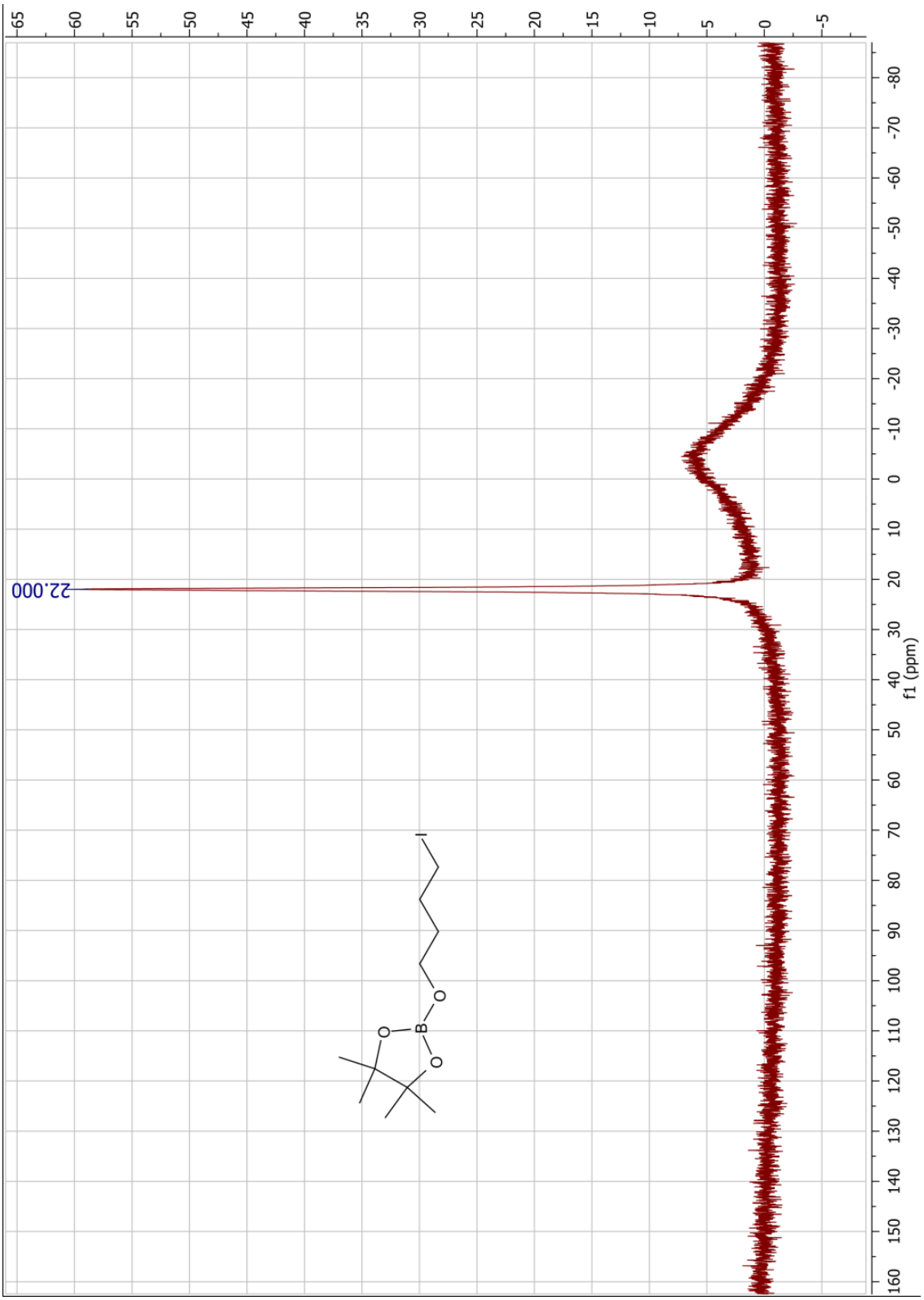

29.79
28.71
22.42
COOMe
I
Zn, HBpin, THF
TMSCl
Br
Br
50 °C, 24 h
99% HBpin remained unreacted
f1 (ppm)

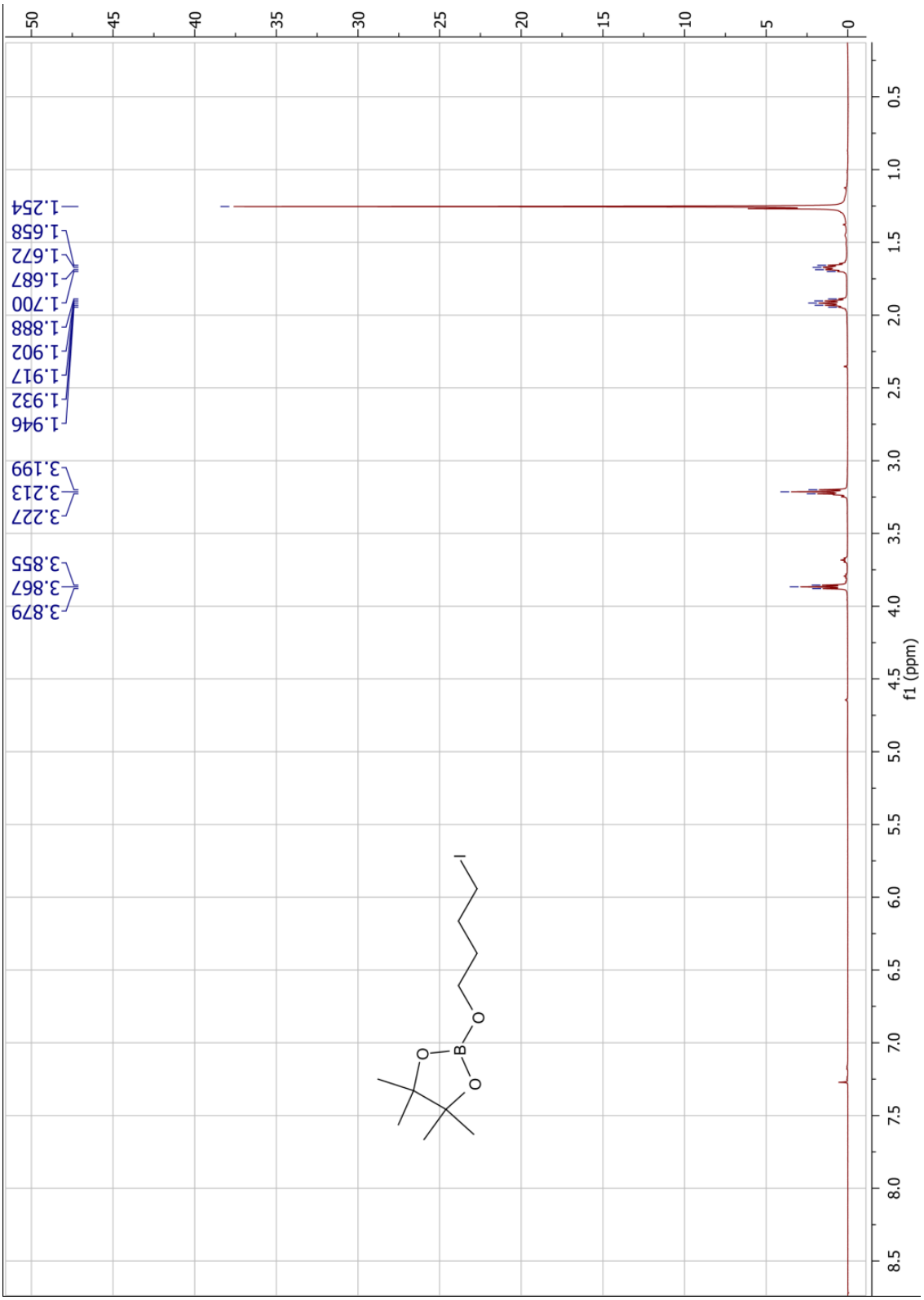

29.04
27.96
22.74
18.88
0.83
0.17
f1 (ppm)
COOMe
Zn, HBpin, THF
TMSCl
50 °C, 24 h
Br
Br
I
99% HBpin remained unreacted

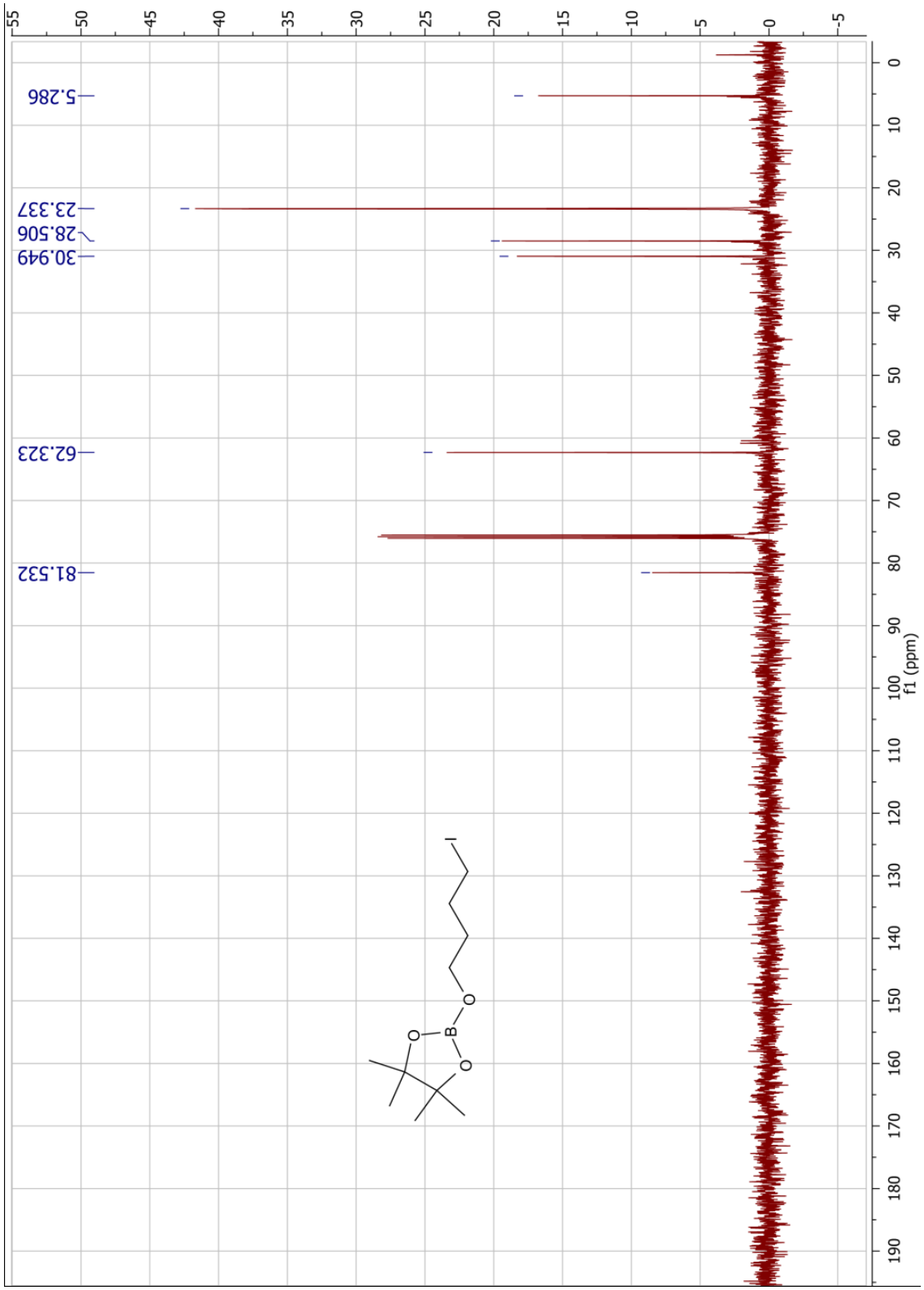

7.50
7.49
7.48
7.48
7.43
7.42
7.41
7.41
3.94
4.12
CoBr2 (0.1 eq)
Zn 3 eq, HBpin
TMSCl, 1,2-dibromoethane
CH3CN, 25 °C
Cl
Cl
Cl
f1 (ppm)

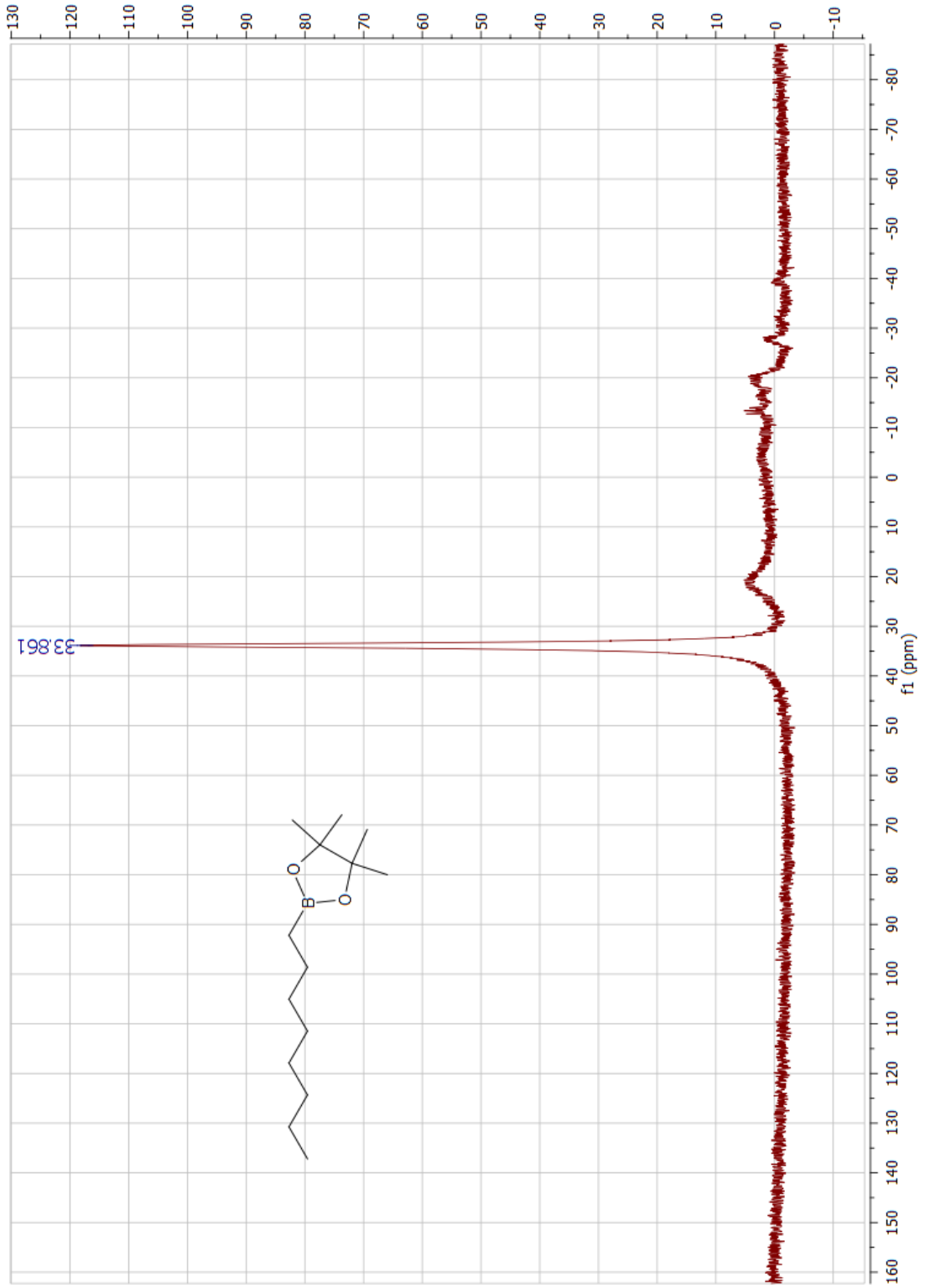
Appendix C

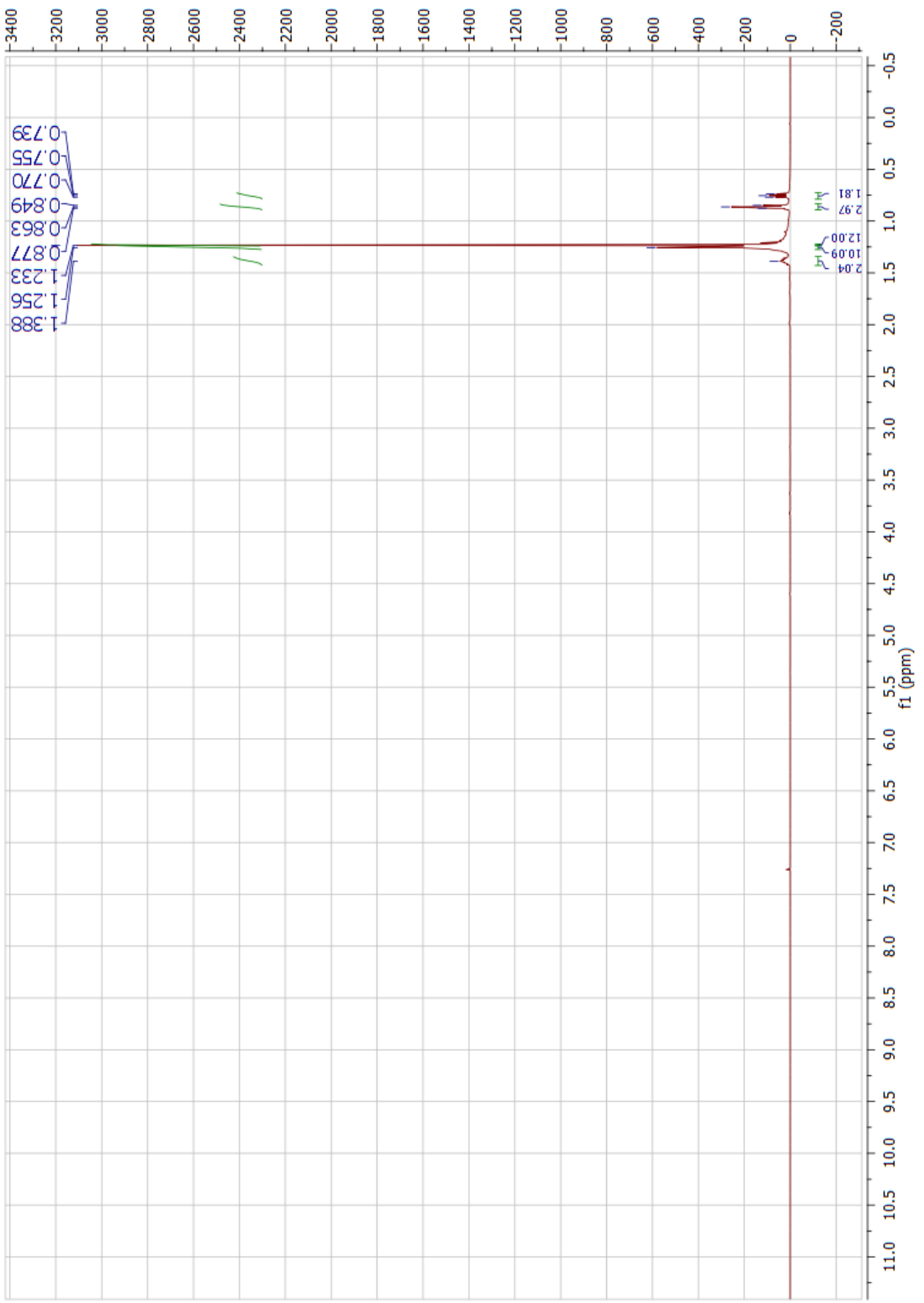
CHAPTER 4. ^{1}H, ^{11}B, and ^{13}C NMR Spectra

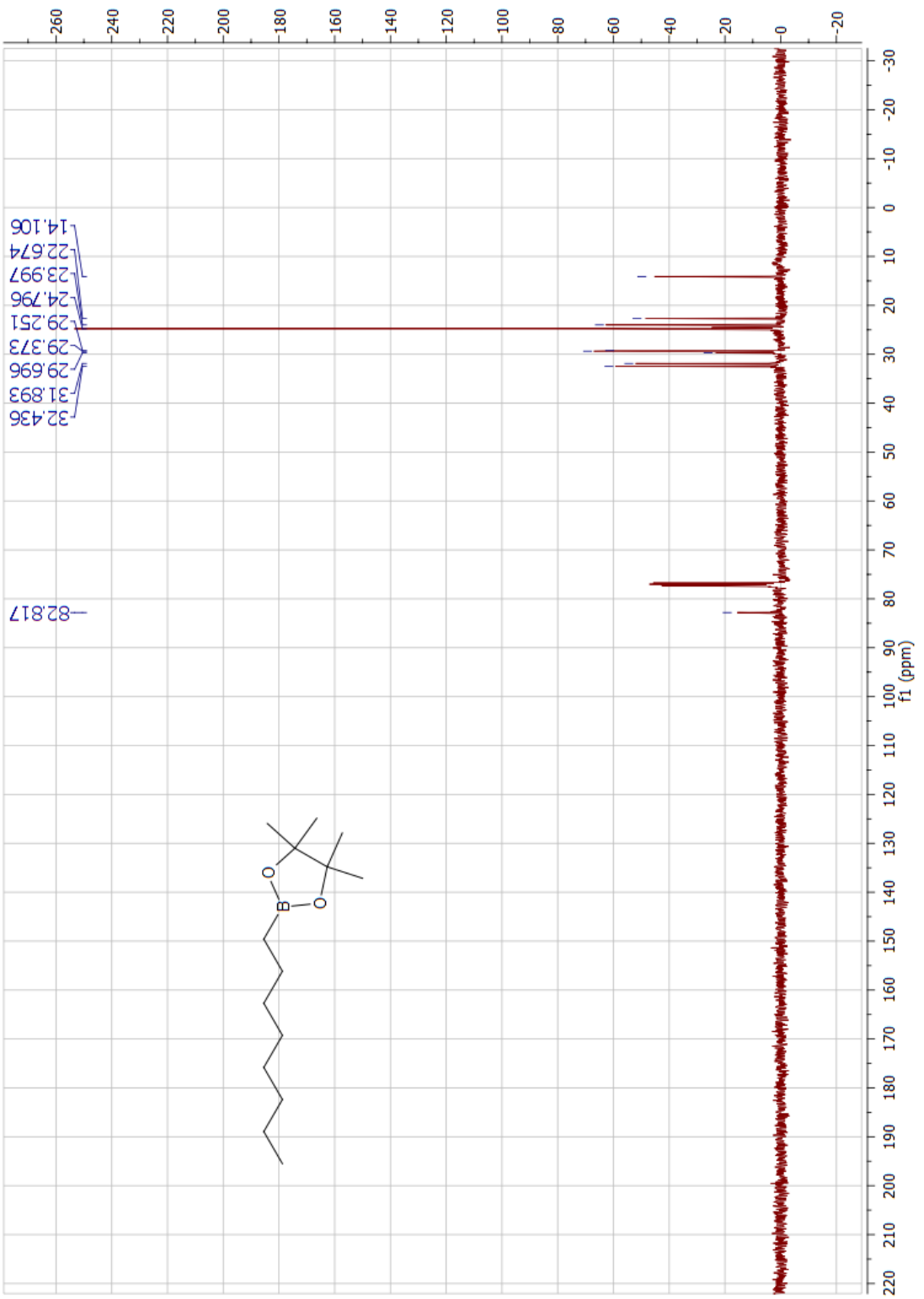

22.000
f1 (ppm)

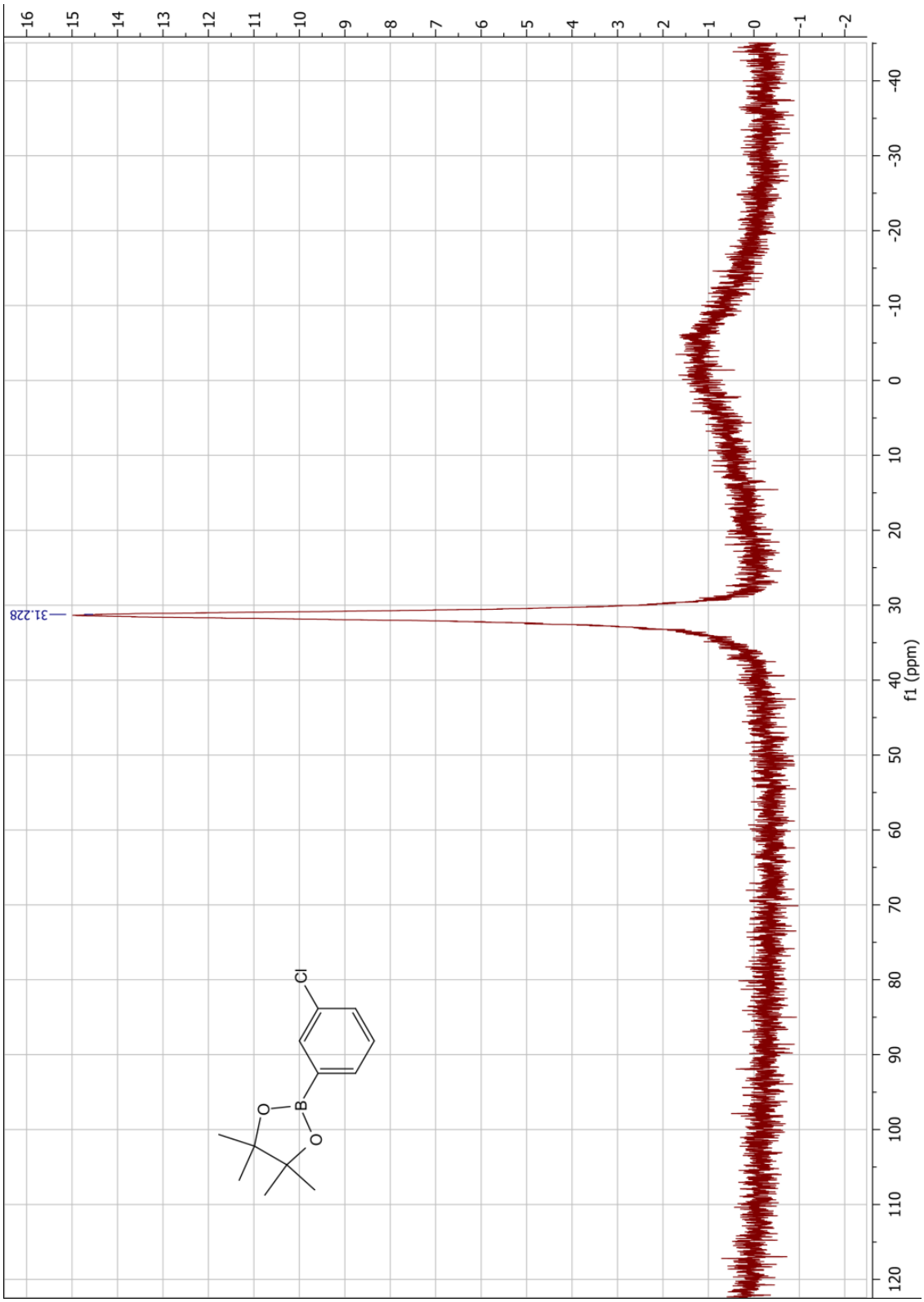

1.254
1.658
1.672
1.687
1.700
1.888
1.902
1.917
1.932
1.946
3.199
3.213
3.227
3.855
3.867
3.879
f1 (ppm)

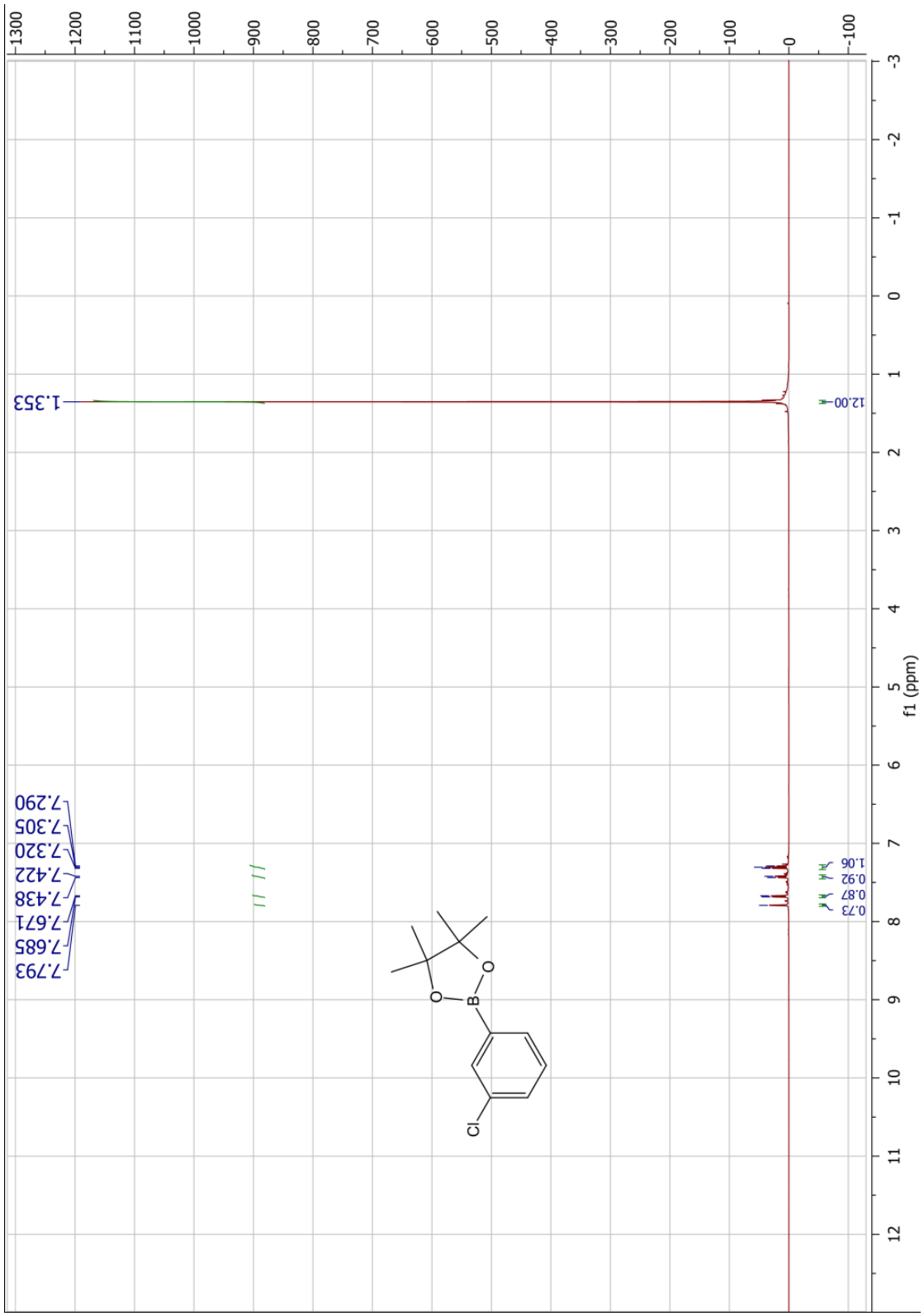

5.286
23.337
28.506
30.949
62.323
81.532
f1 (ppm)

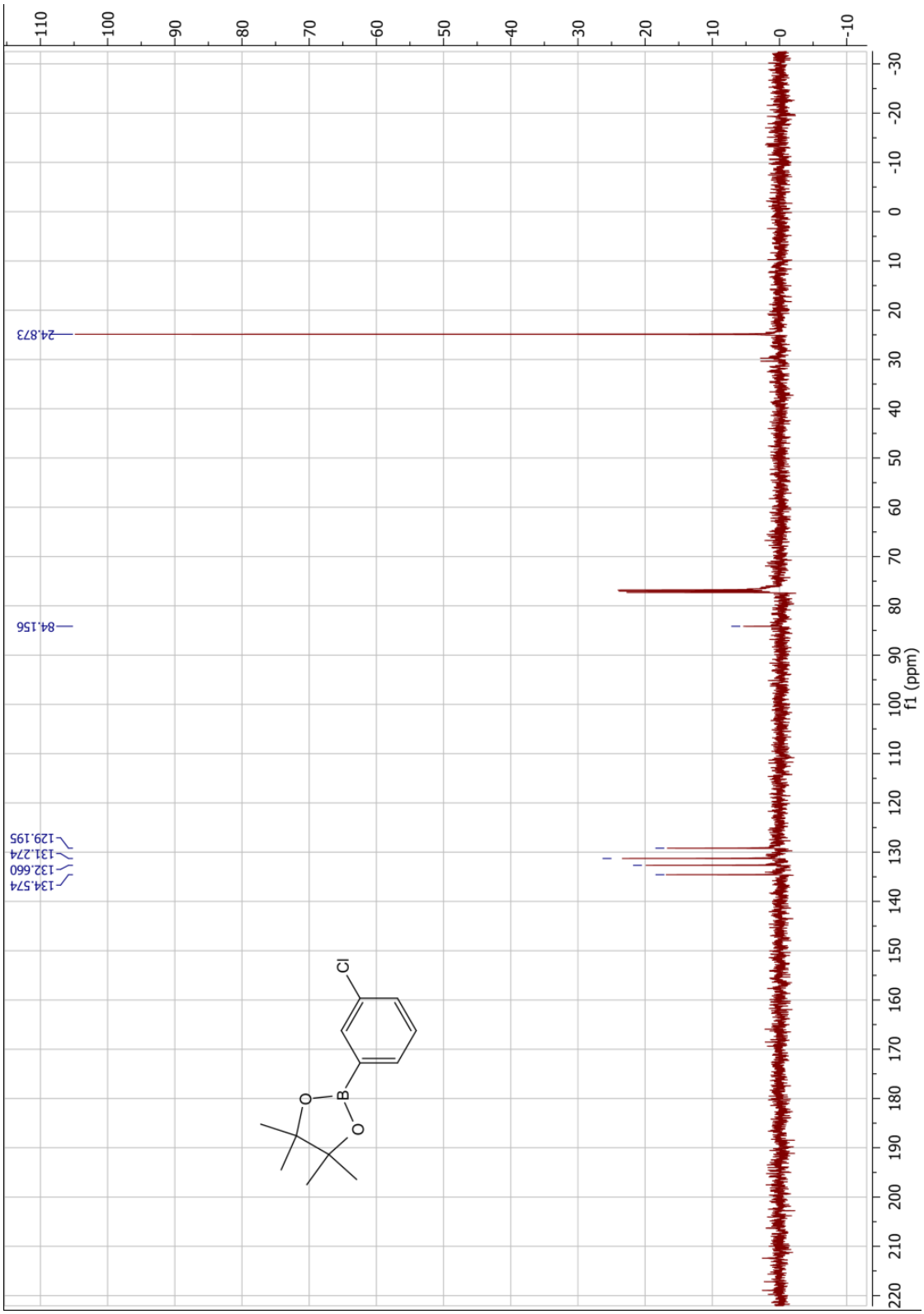

33.861
f1 (ppm)

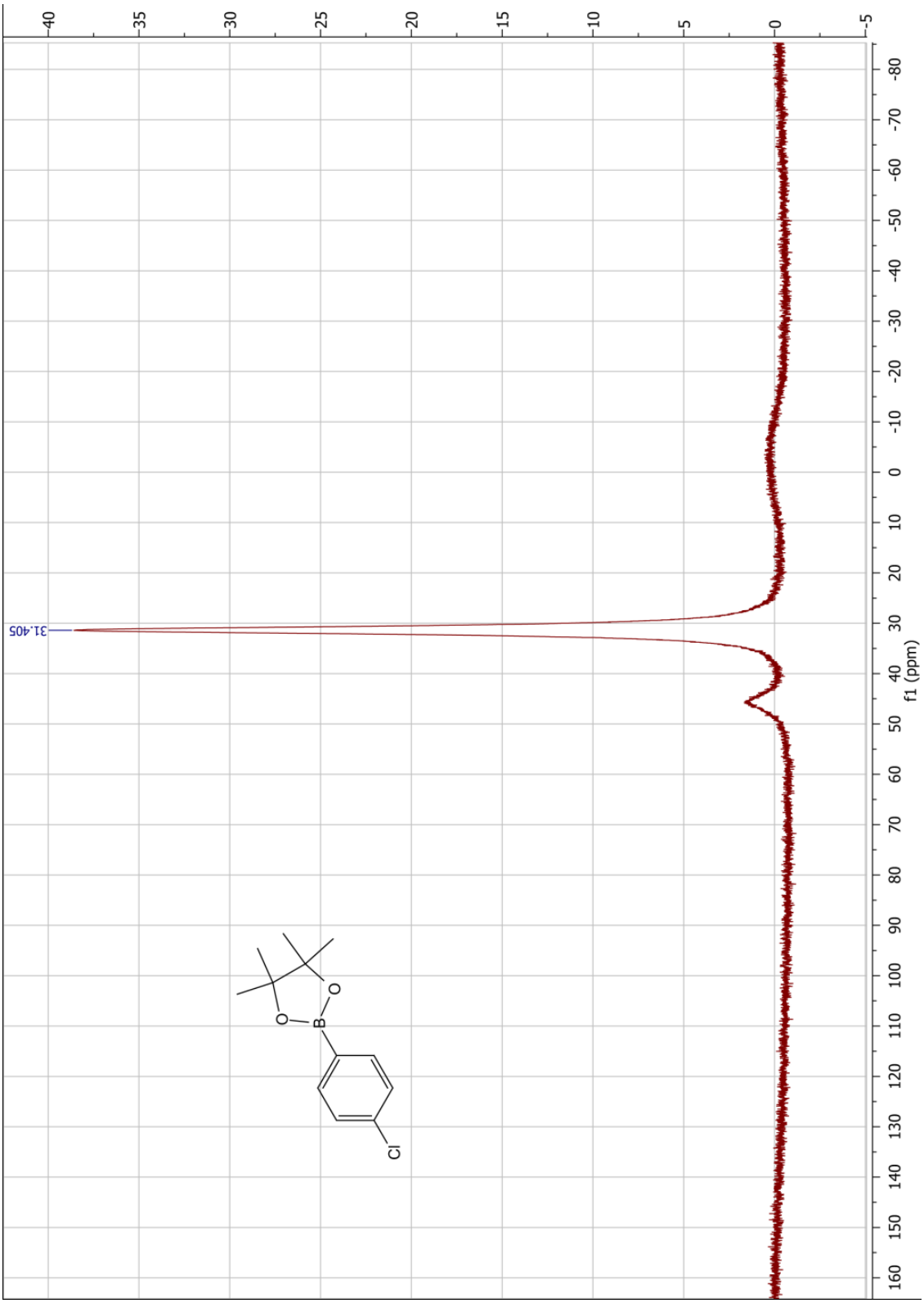

0.739
0.755
0.770
0.849
0.863
0.877
1.233
1.256
1.388
1.81
2.97
12.00
10.09
2.04
f1 (ppm)

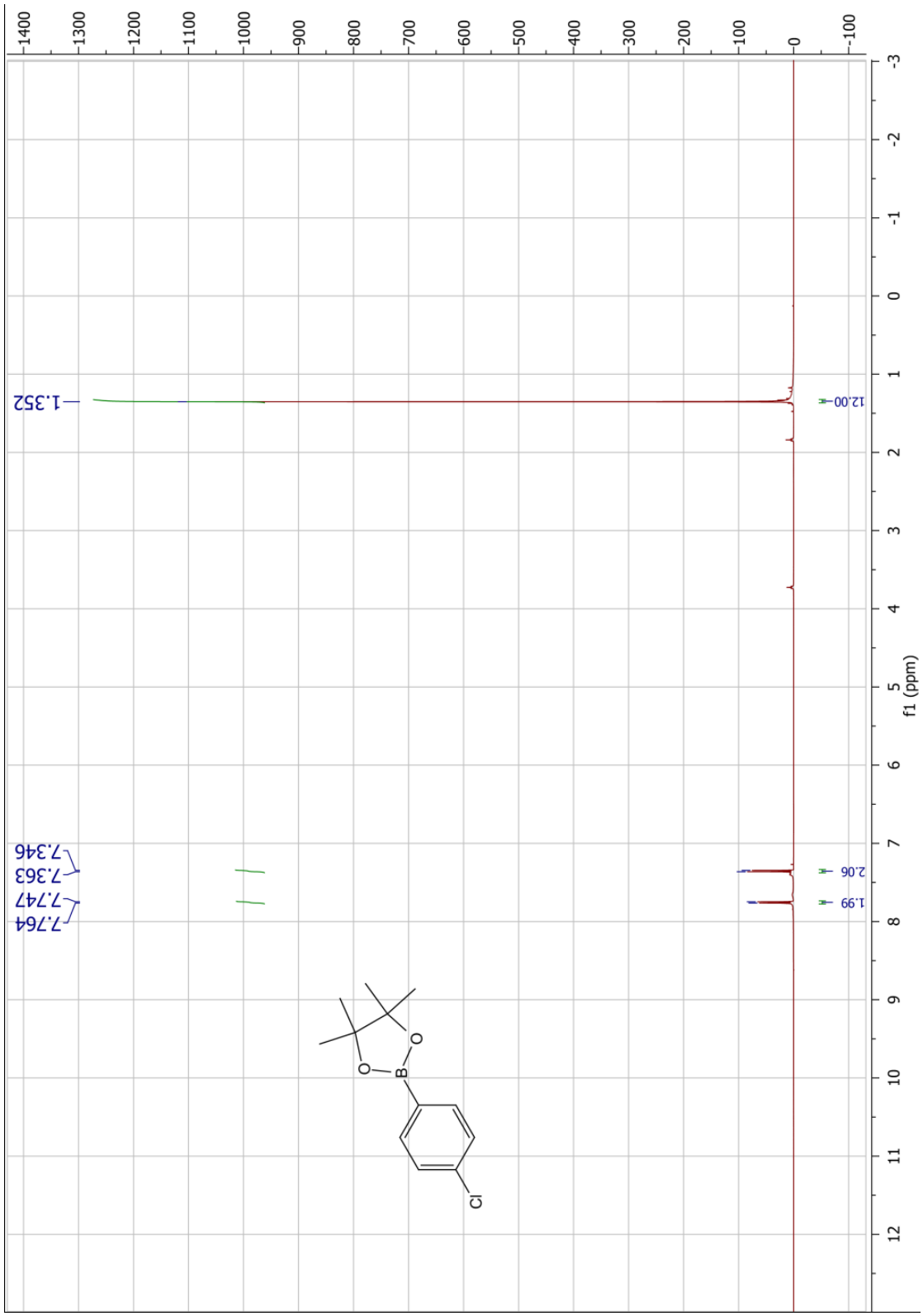

82.817
32.436
31.893
29.696
29.373
29.251
24.796
23.997
22.674
14.106
f1 (ppm)

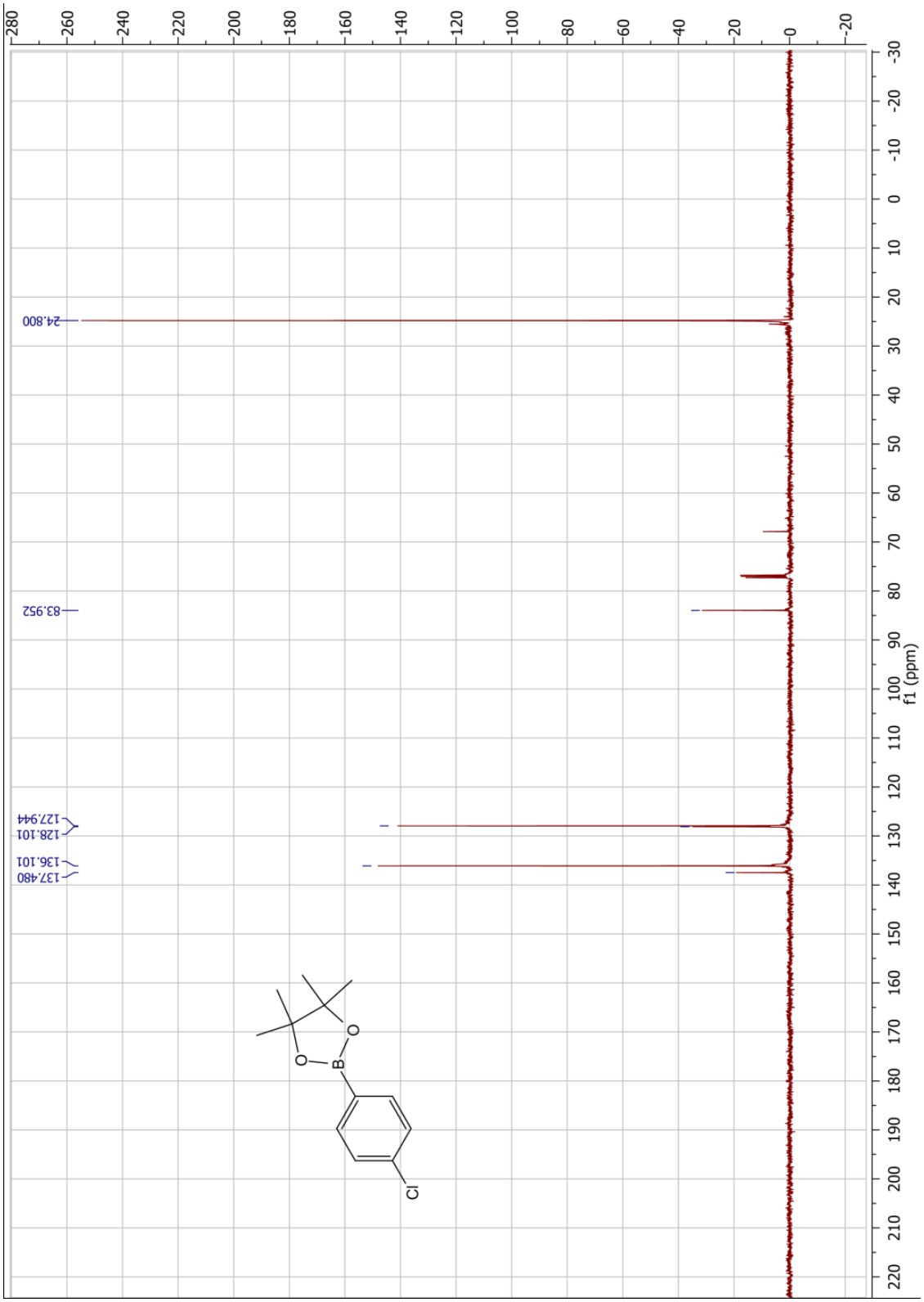

31.228
f1 (ppm)
Cl
B
O
O

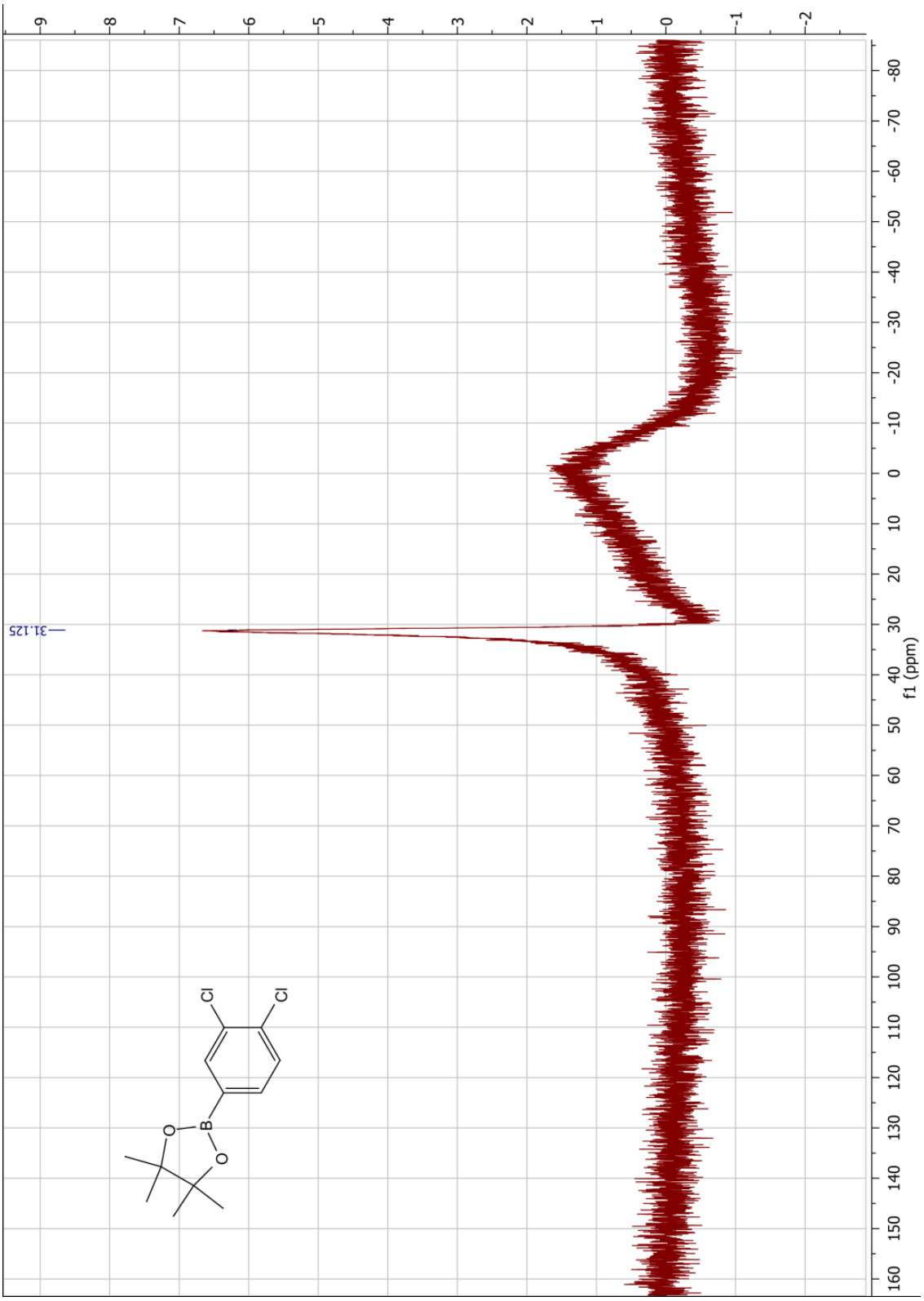

1.353
12.00
1.06
0.92
0.87
0.73
7.793
7.685
7.671
7.438
7.422
7.320
7.305
7.290
B
O
O
Cl
f1 (ppm)

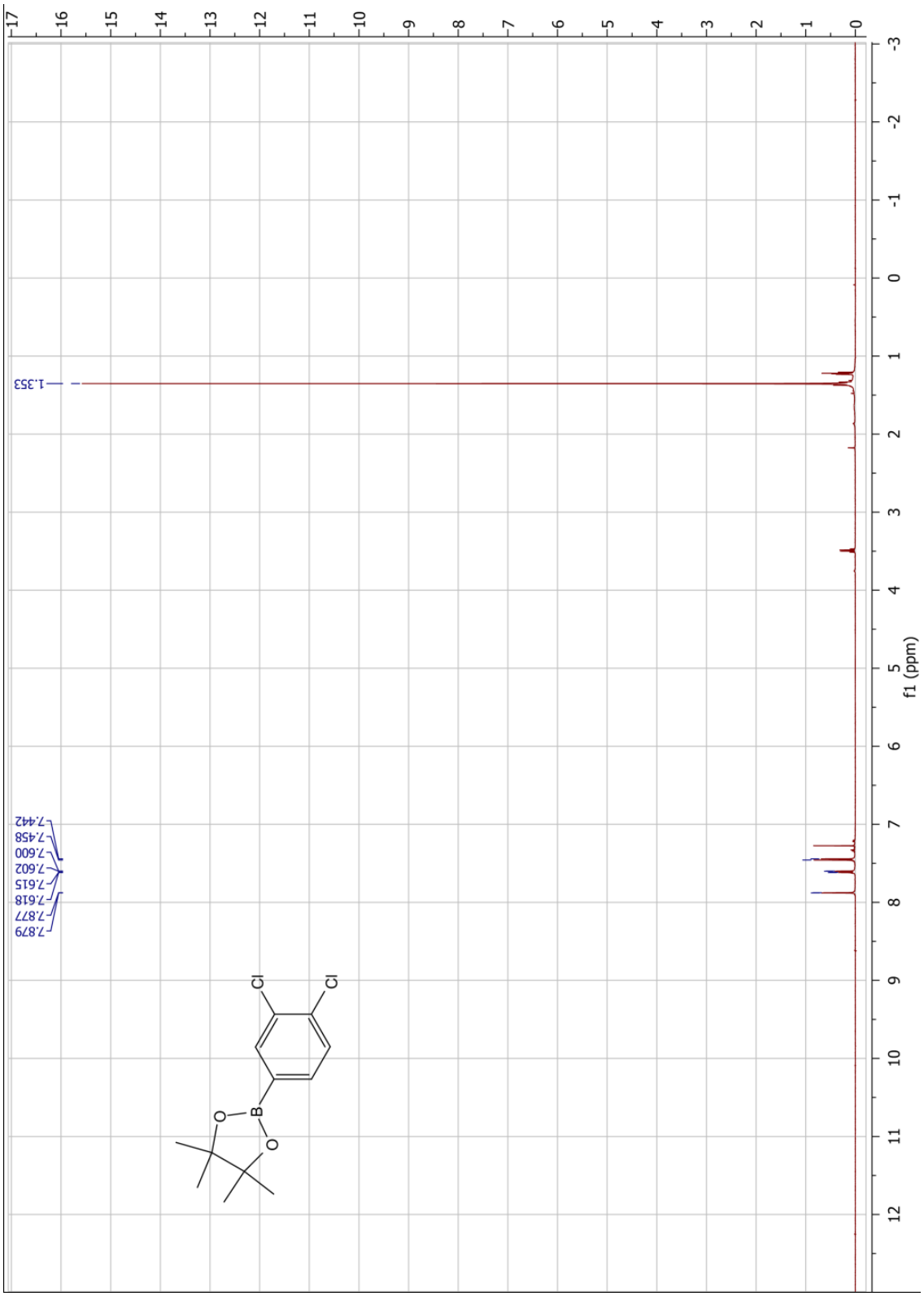

24.873
84.156
134.574
132.660
131.274
129.195
Cl
B
O
O
f1 (ppm)

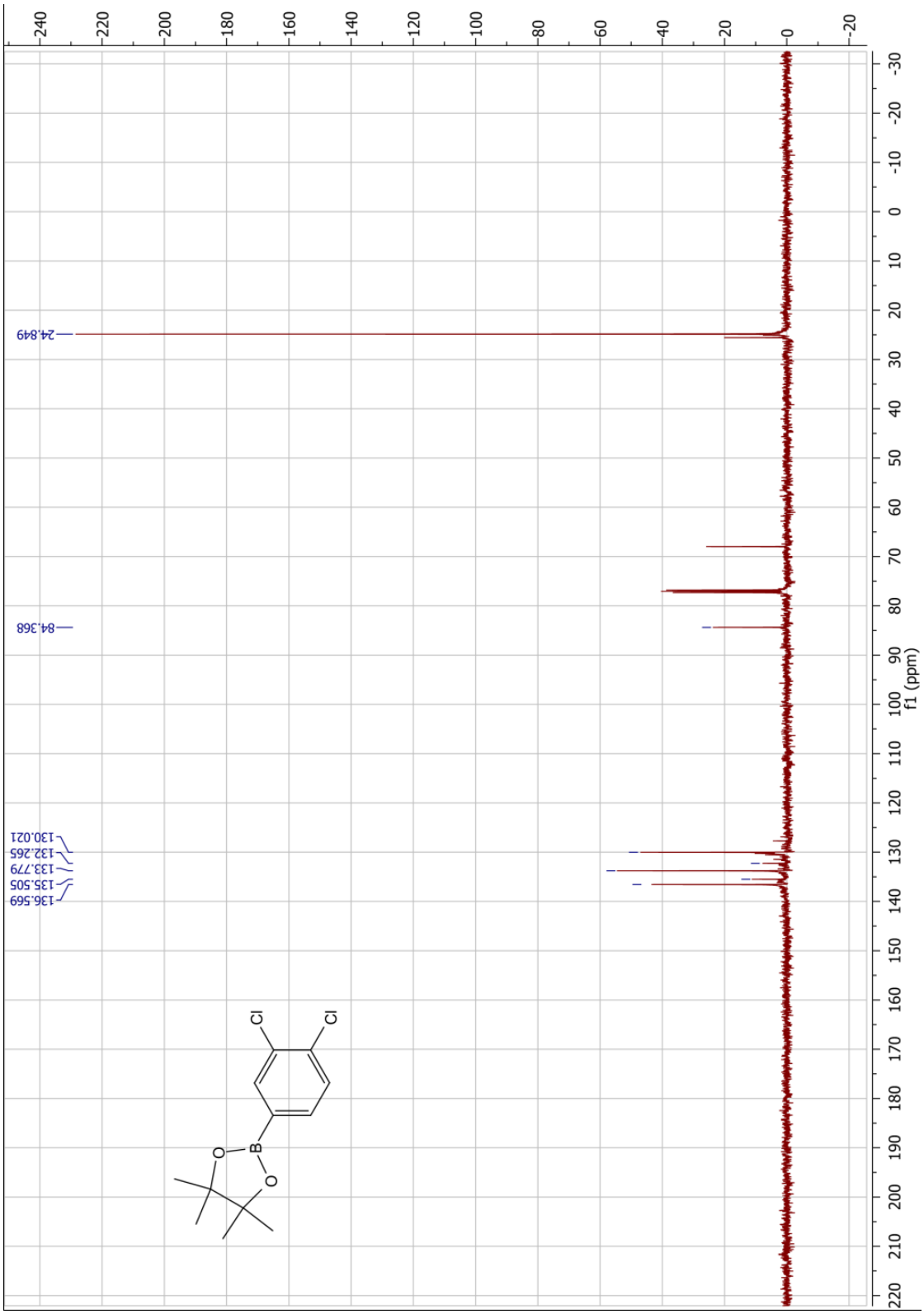

31.405
f1 (ppm)
B
O
O
Cl

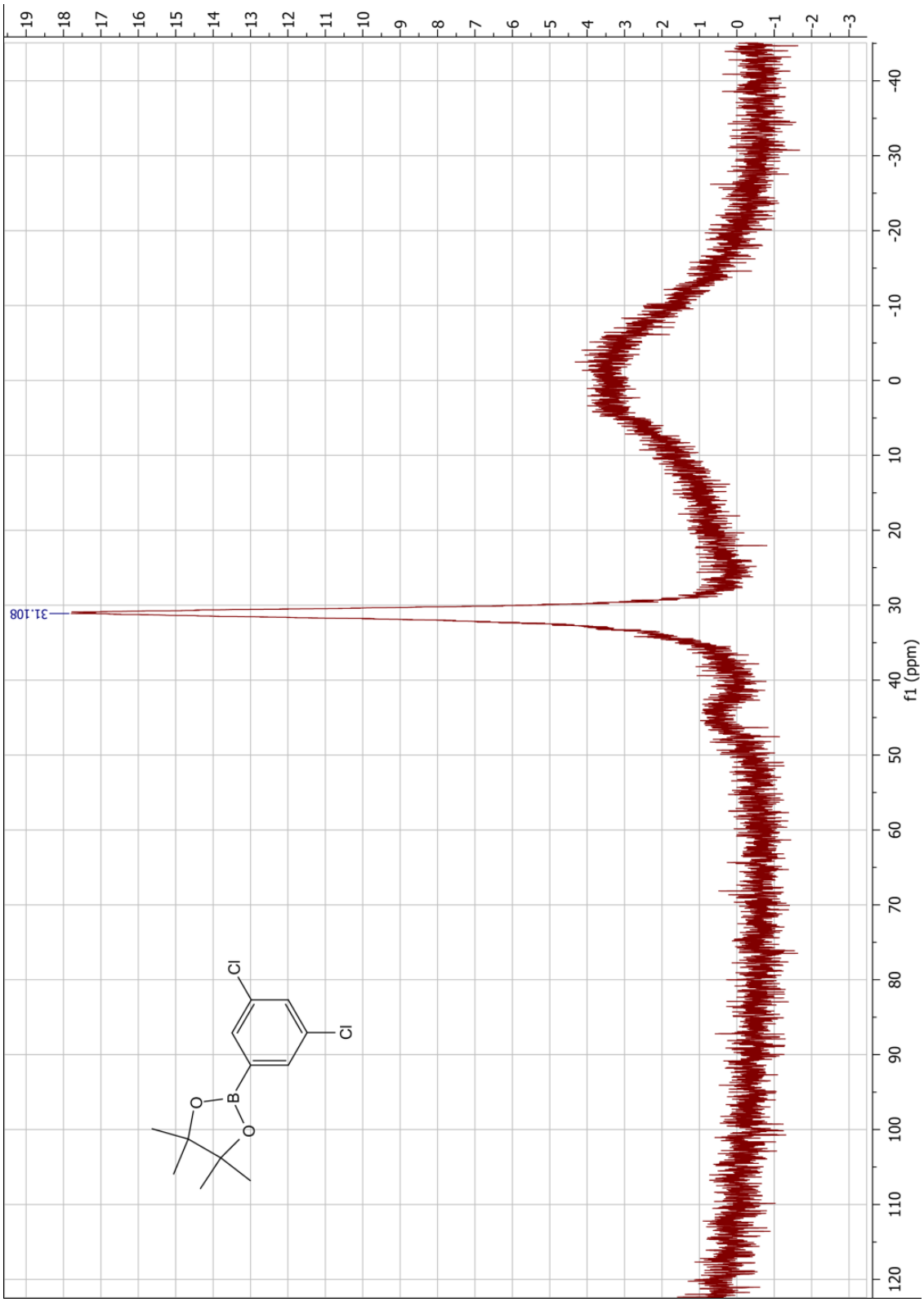

1.352
12.00
7.764
7.747
7.363
7.346
2.06
1.99
B
O
O
Cl
f1 (ppm)

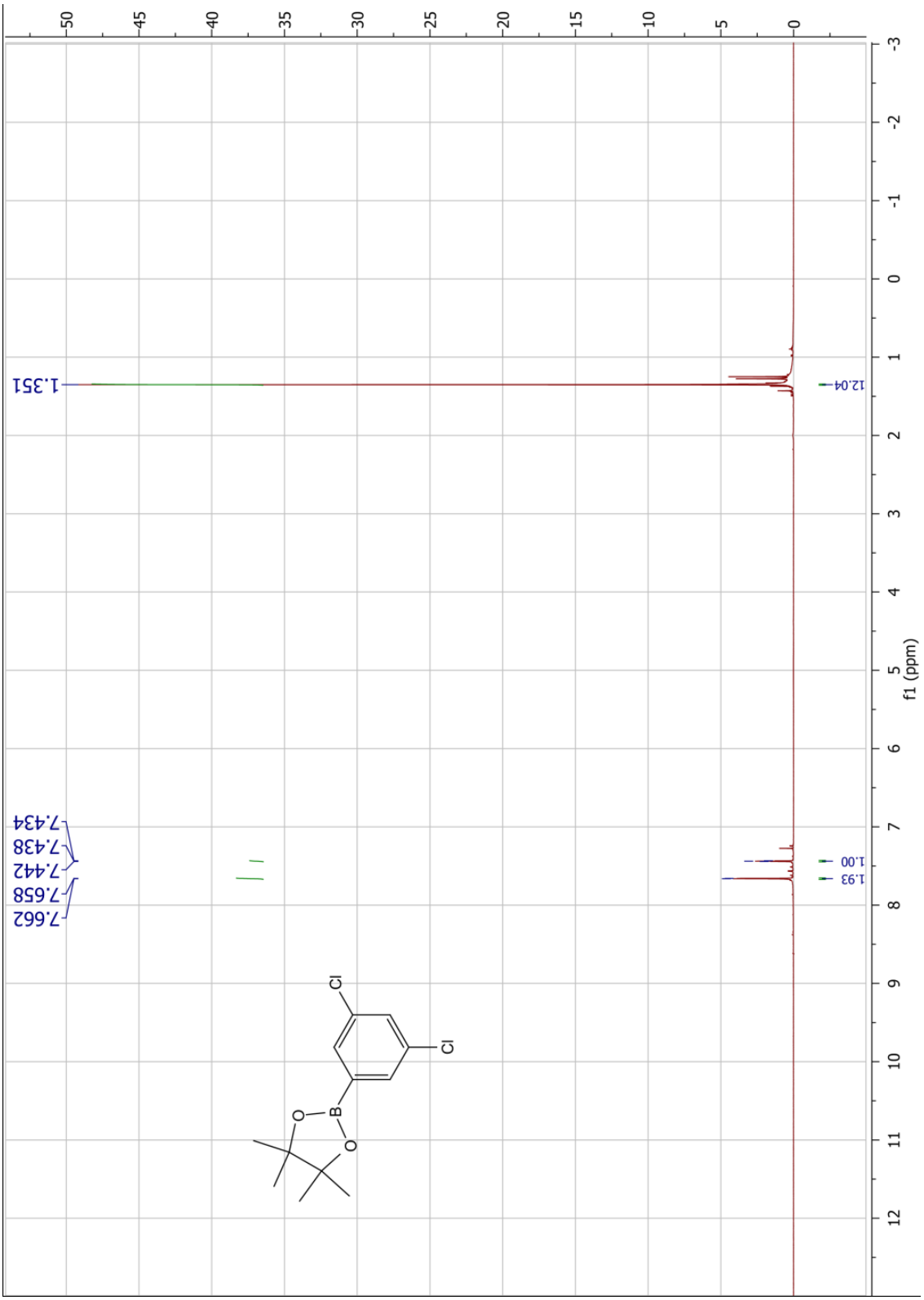

24.800
83.952
127.944
128.101
136.101
137.480
f1 (ppm)
O
O
B
Cl

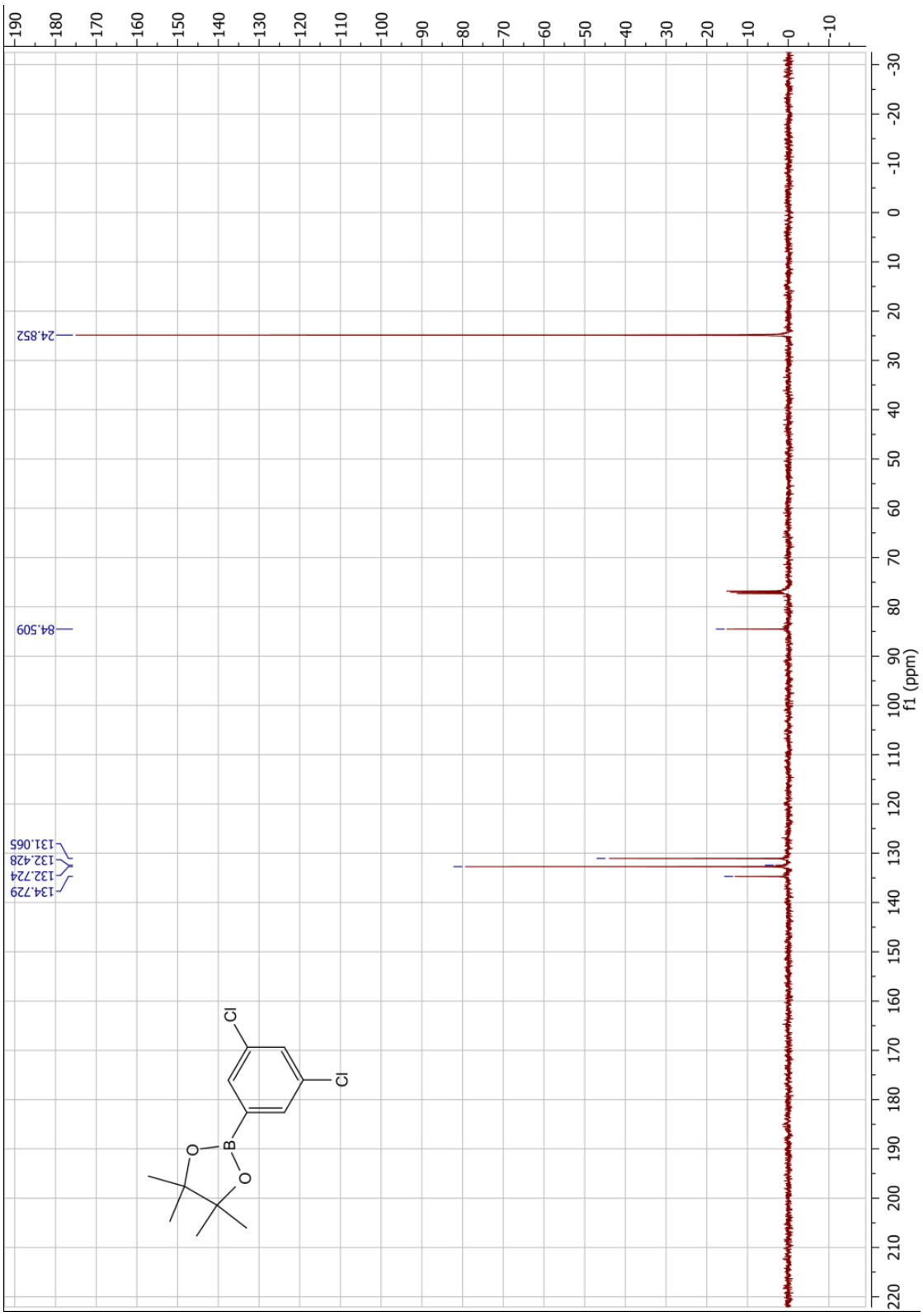

31.125
f1 (ppm)
Cl
Cl
B
O
O

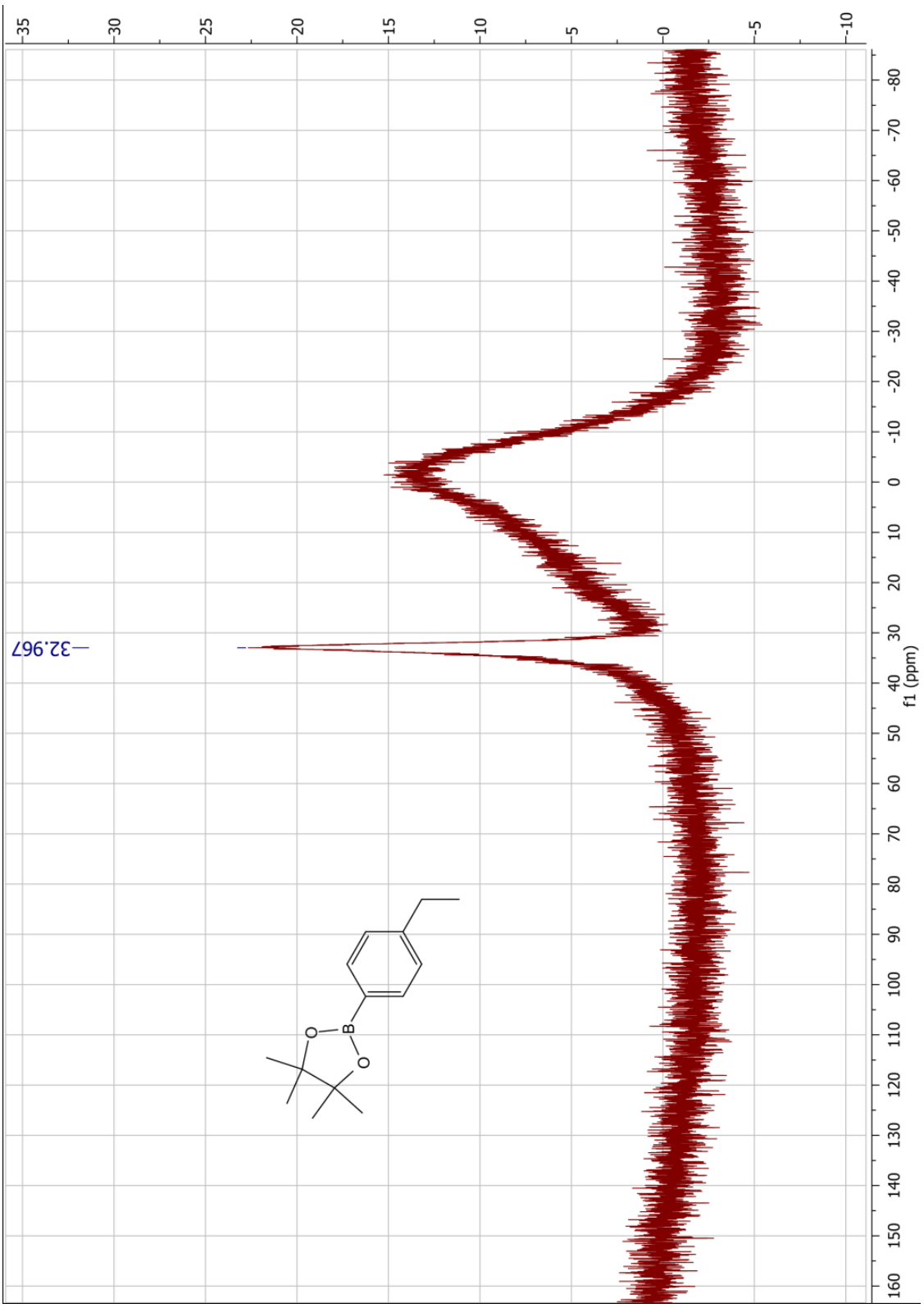

1.353
7.879
7.877
7.618
7.615
7.602
7.600
7.458
7.442
Cl
Cl
B
O
O
f1 (ppm)

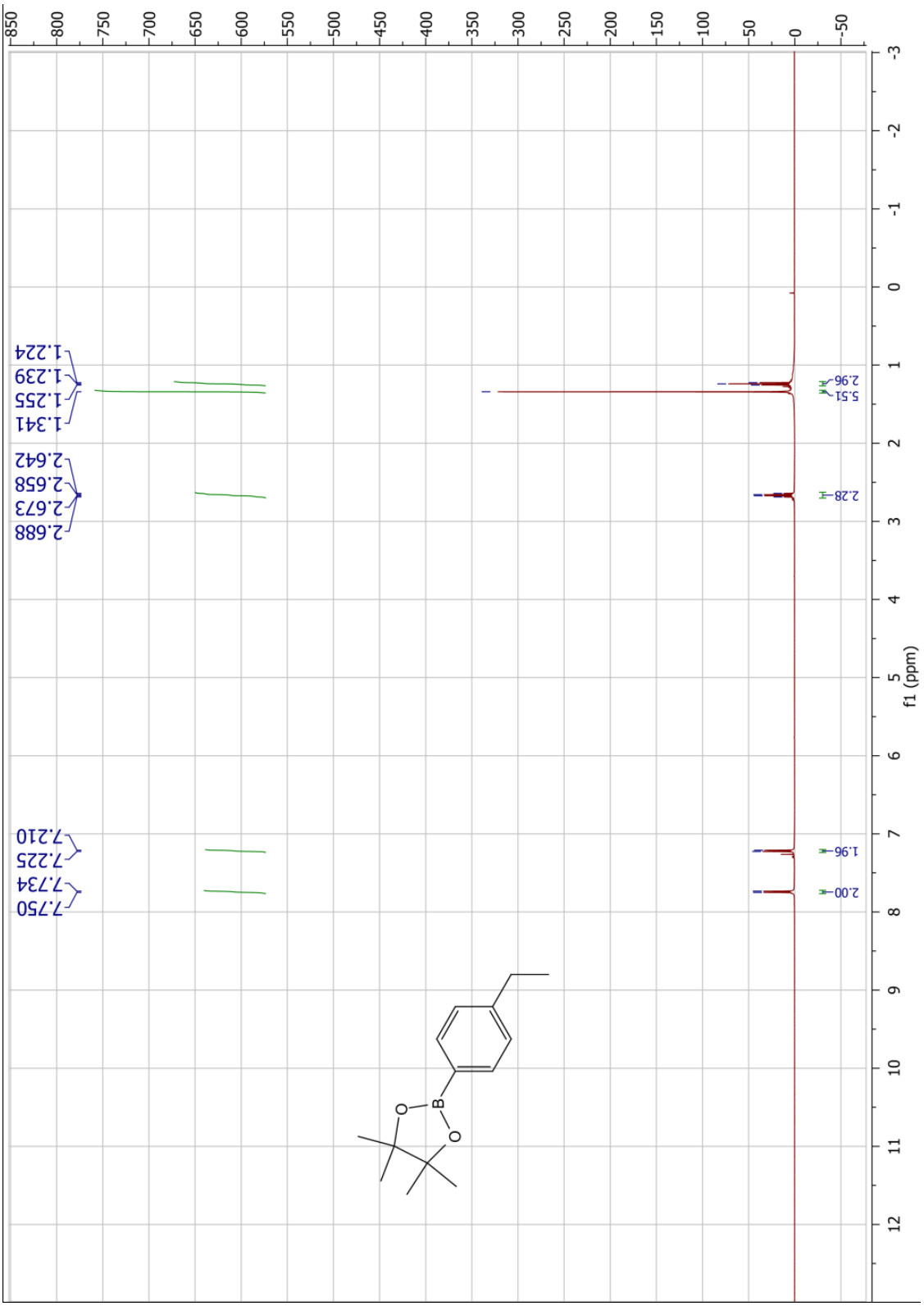

24.849
84.368
136.569
135.505
133.779
132.265
130.021
Cl
Cl
O
B
O
f1 (ppm)

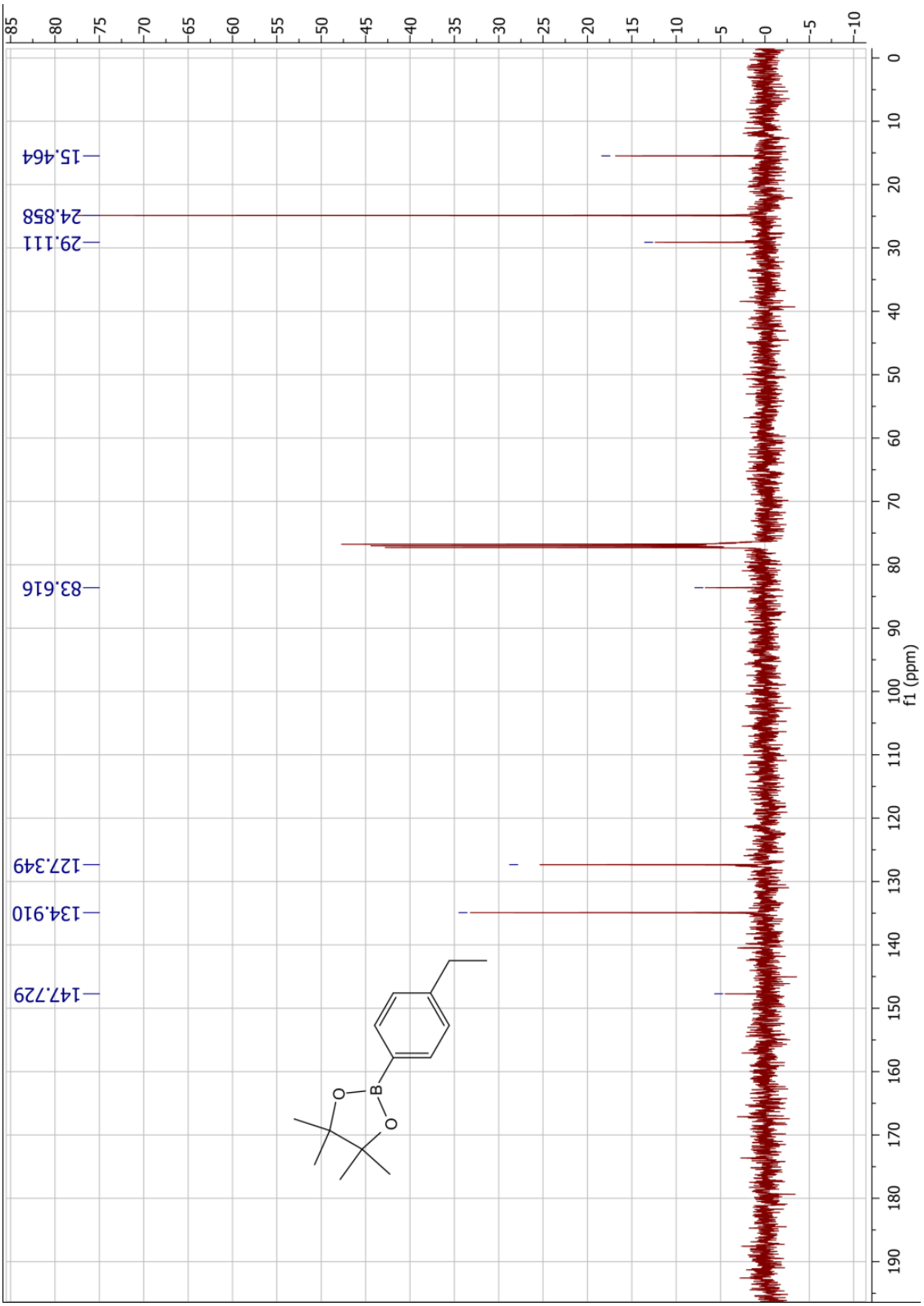

31.108
f1 (ppm)
Cl
Cl
O
B
O

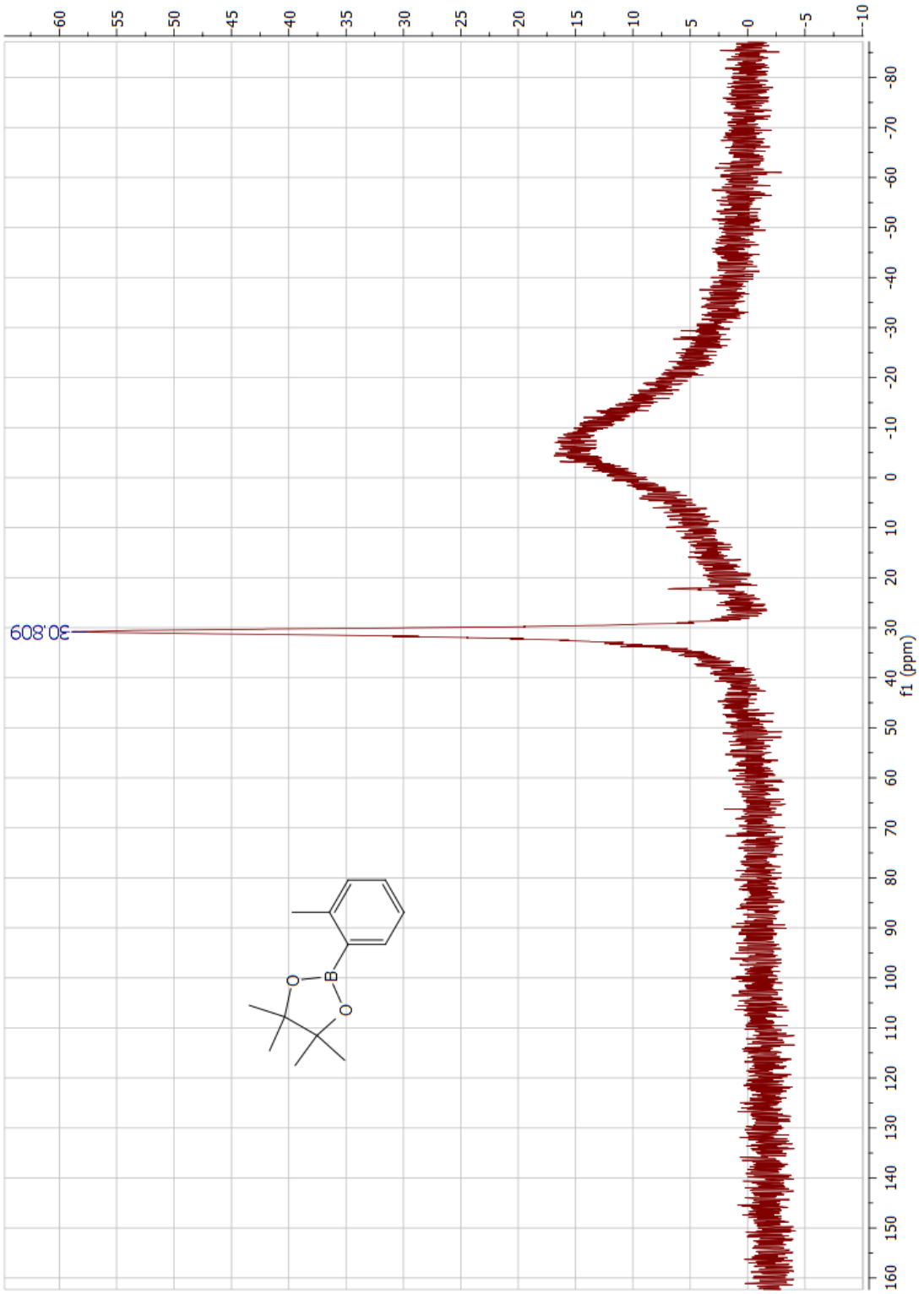

1.351
7.434
7.438
7.442
7.658
7.662
12.04
1.93
1.00
Cl
Cl
B
O
O
f1 (ppm)

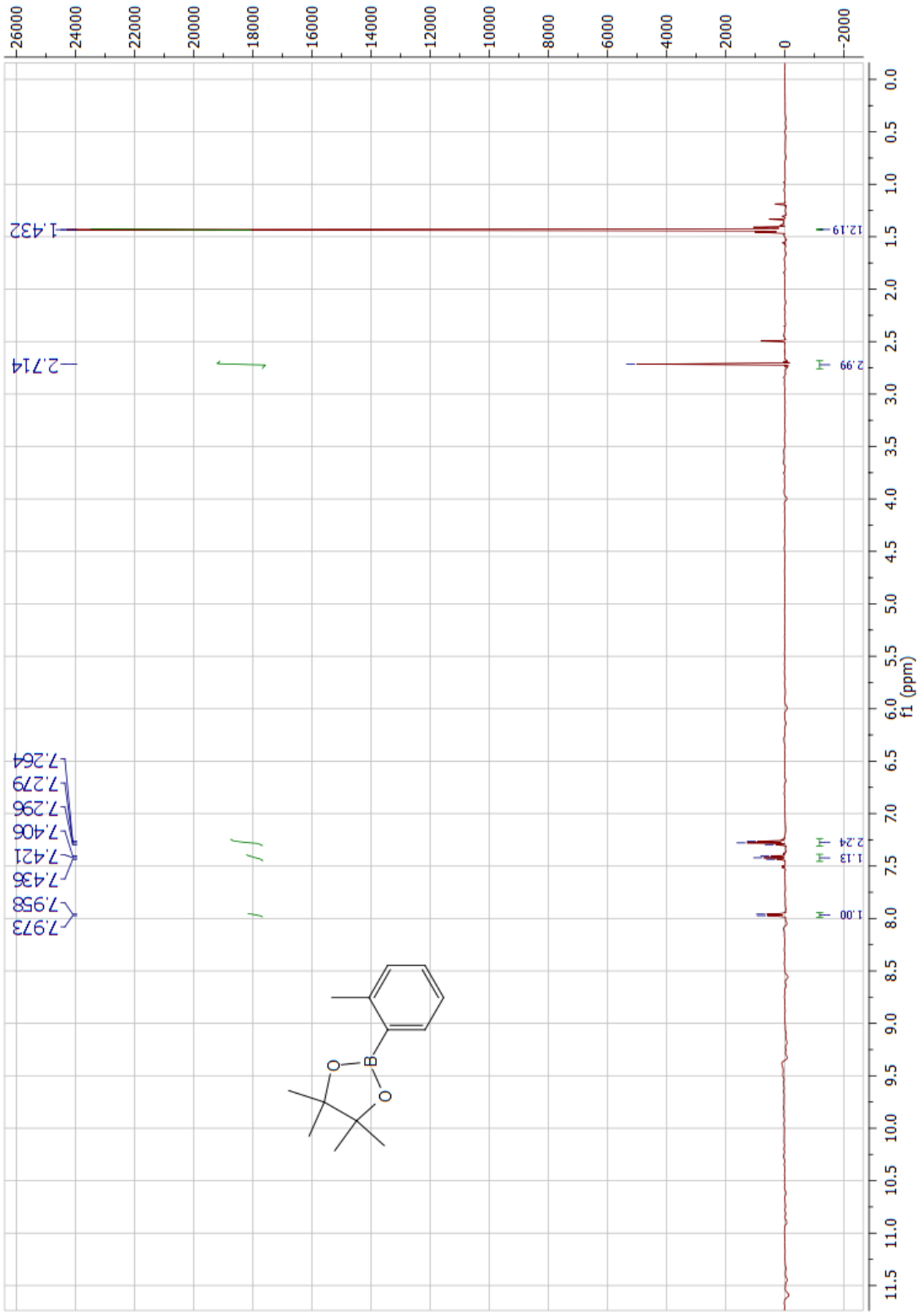

24.852
84.509
131.065
132.428
132.724
134.729
Cl
Cl
O
B
O
f1 (ppm)

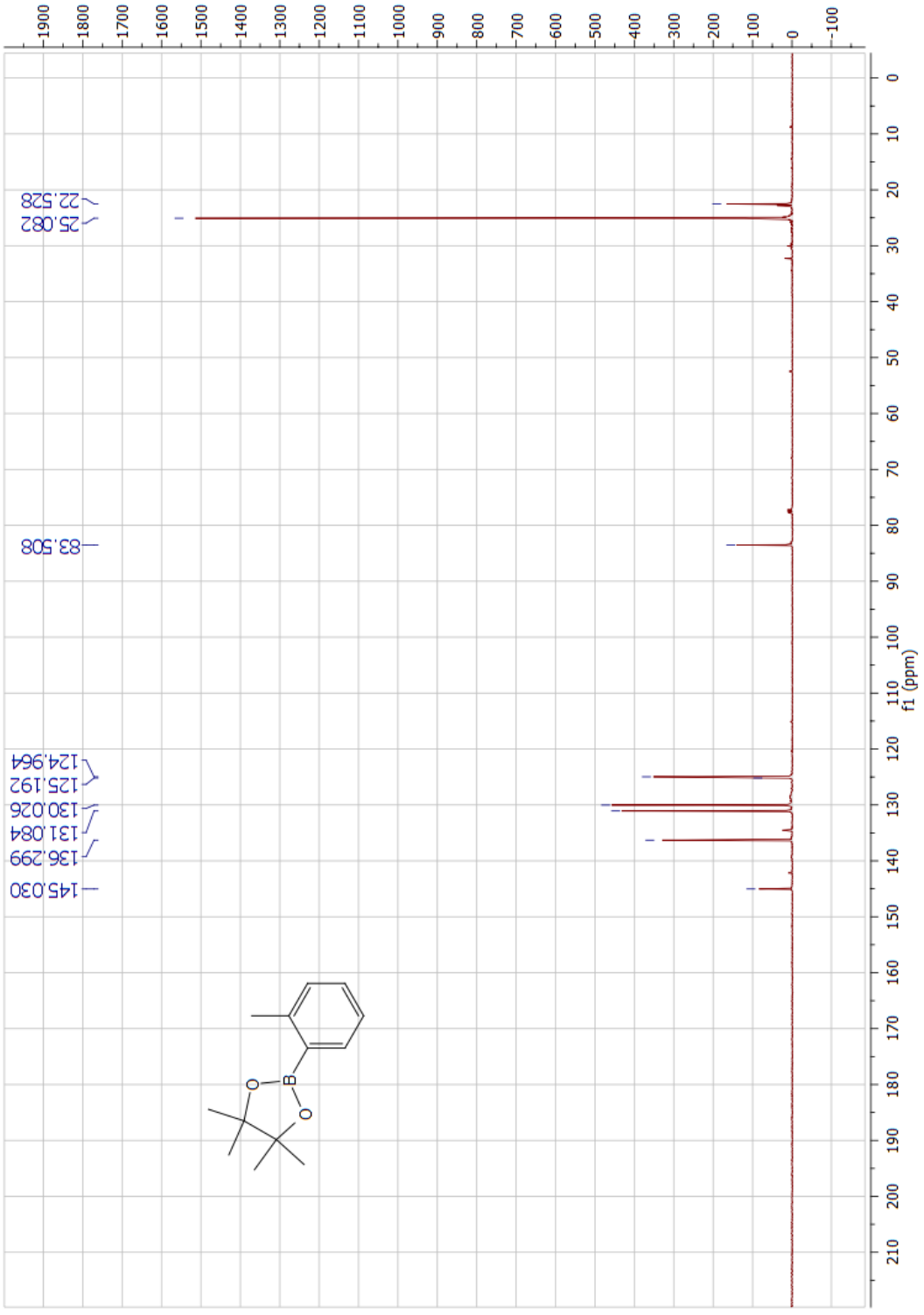

32.967
f1 (ppm)

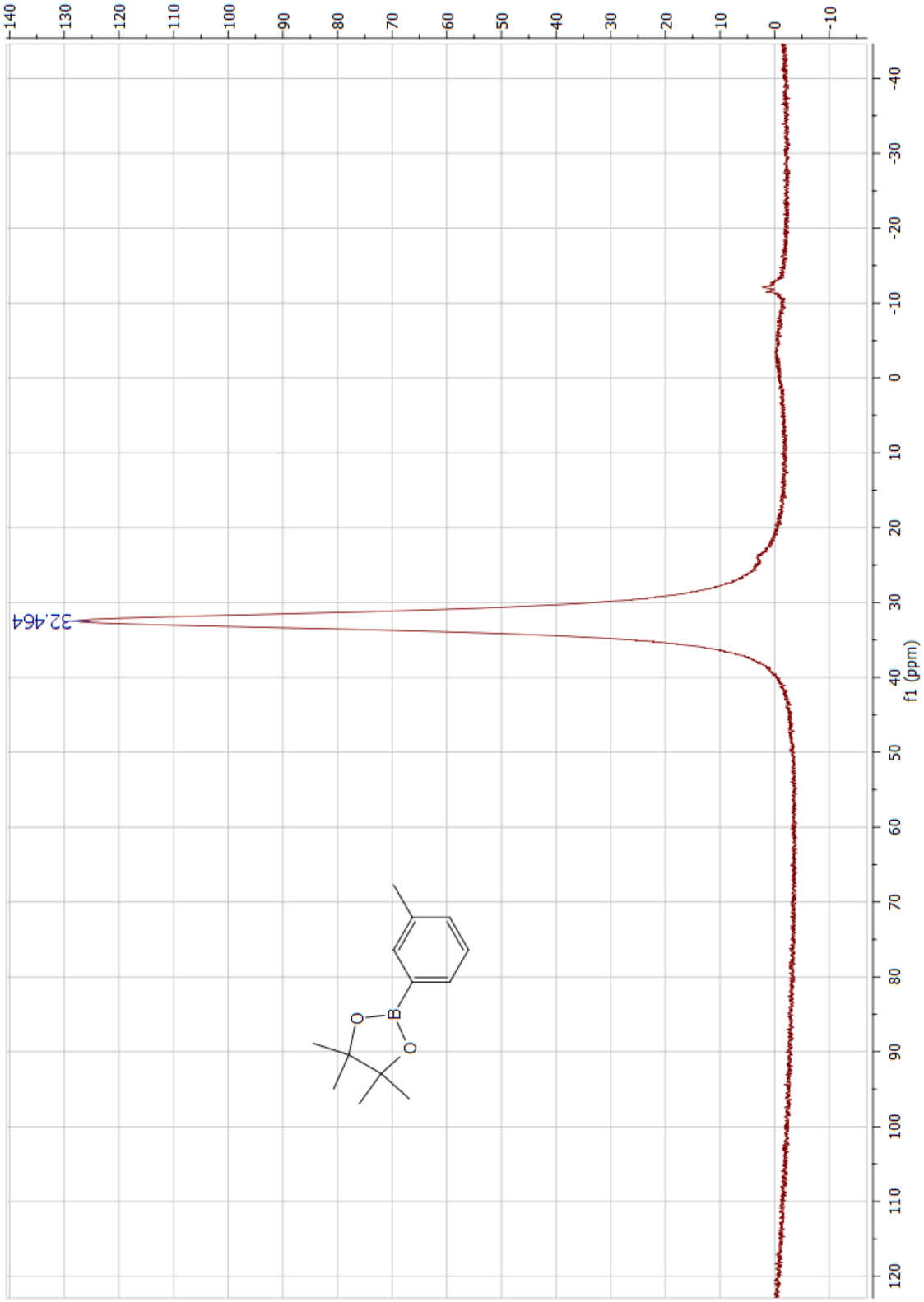

7.750
7.734
7.225
7.210
2.688
2.673
2.658
2.642
1.341
1.255
1.239
1.224
2.00
1.96
2.28
5.51
2.96
f1 (ppm)

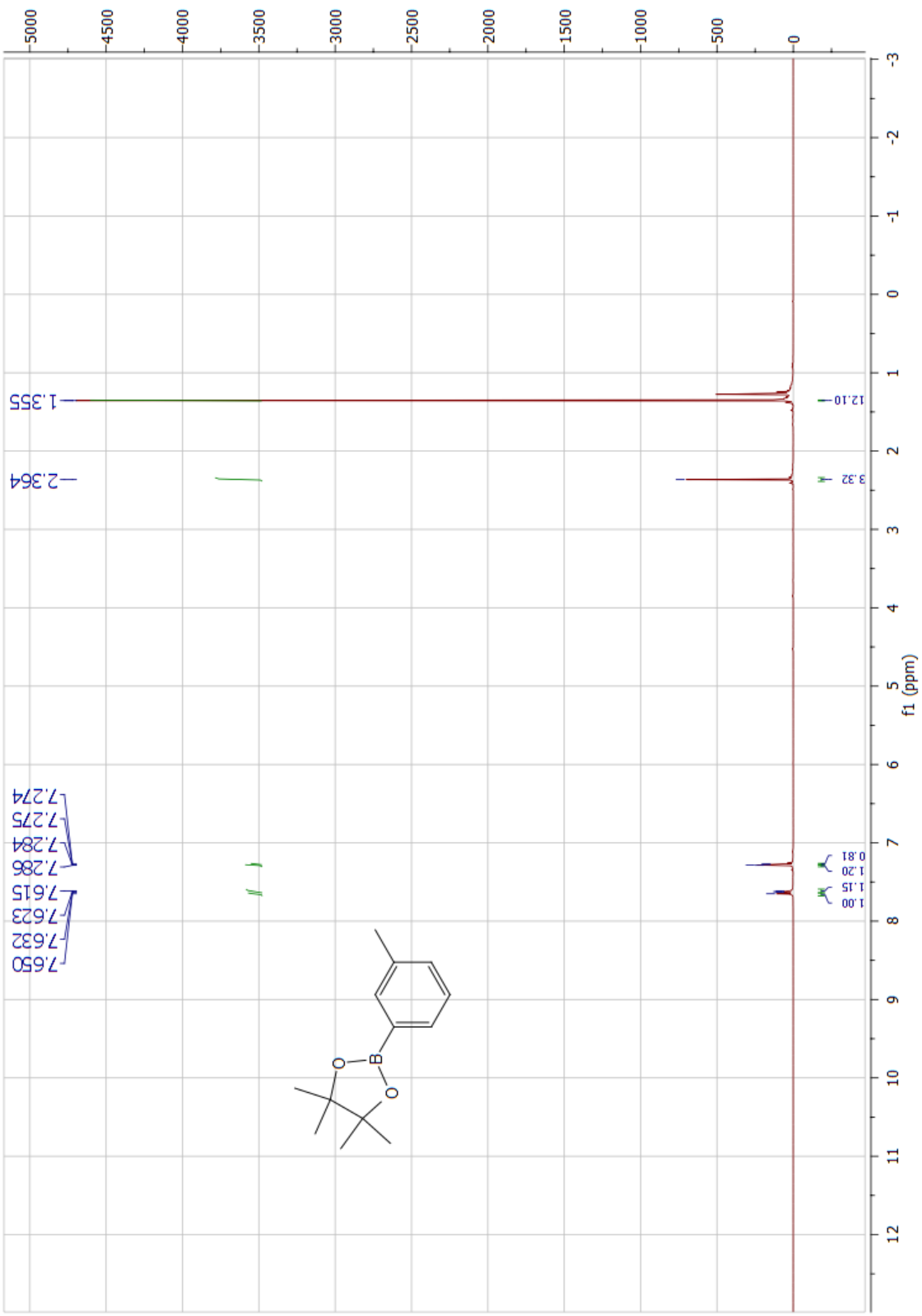

15.464
24.858
29.111
83.616
127.349
134.910
147.729
f1 (ppm)

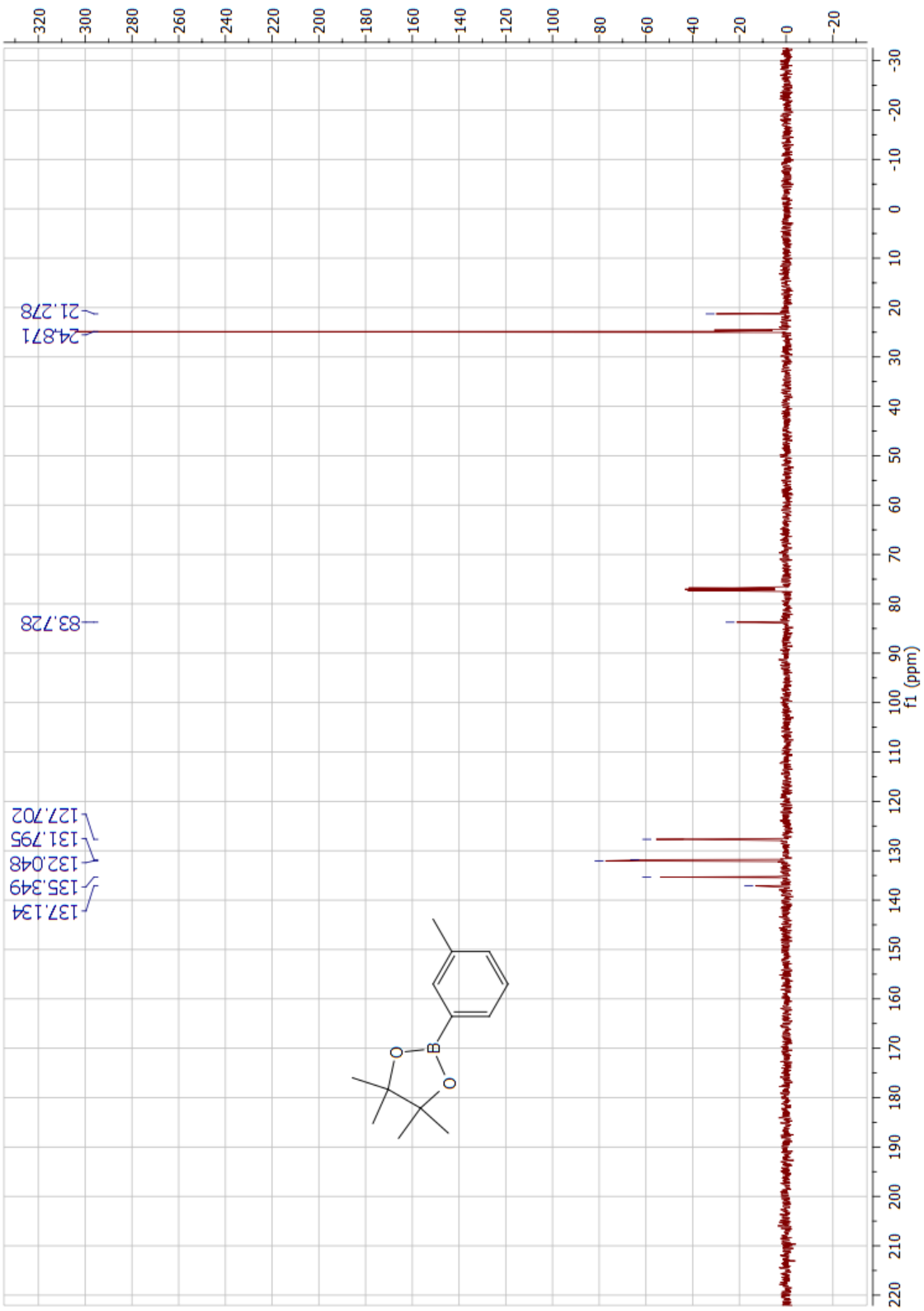

30.809
f1 (ppm)

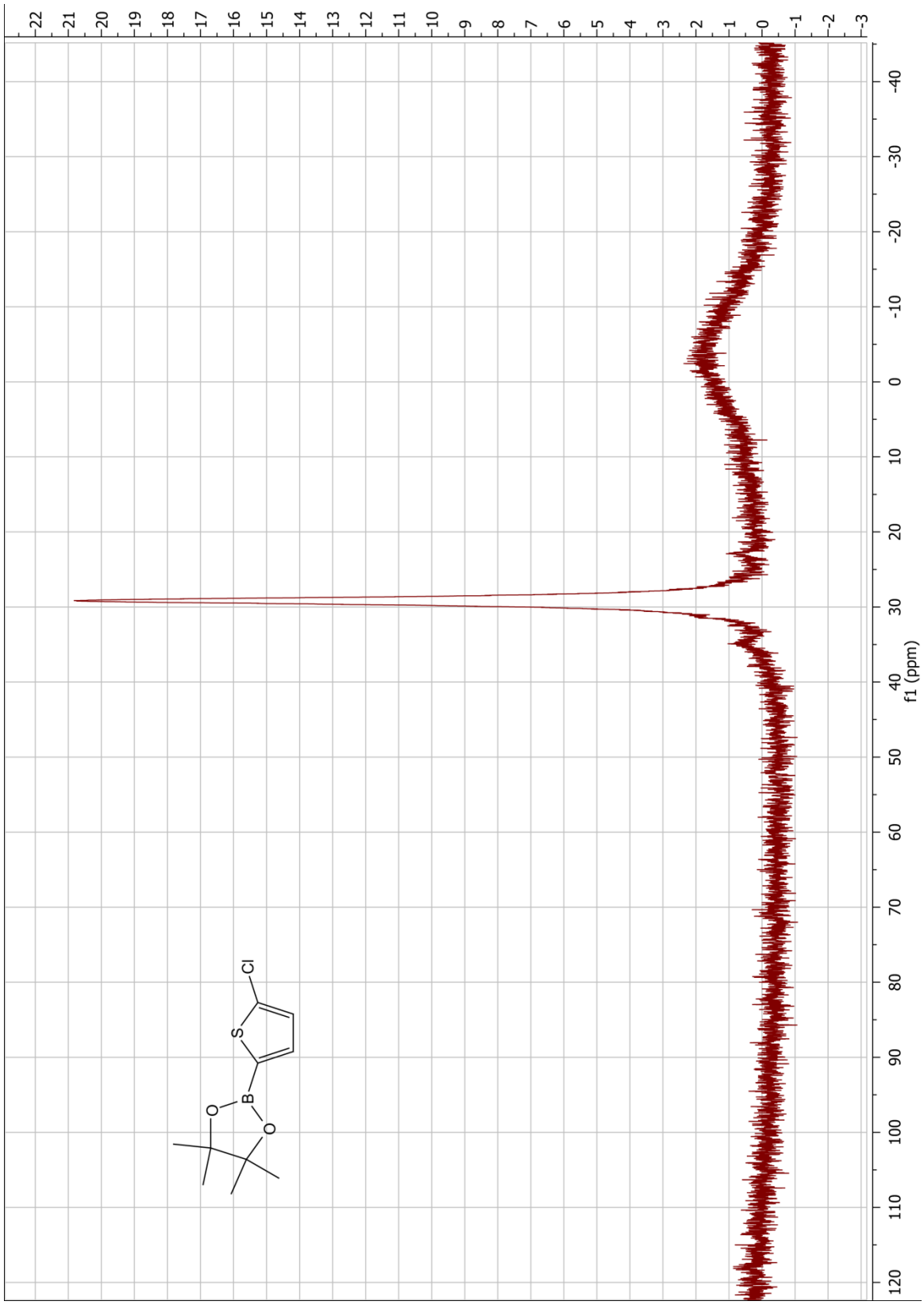

1.432
2.714
7.973
7.958
7.436
7.421
7.406
7.296
7.279
7.264
12.19
2.99
2.24
1.13
1.00
f1 (ppm)

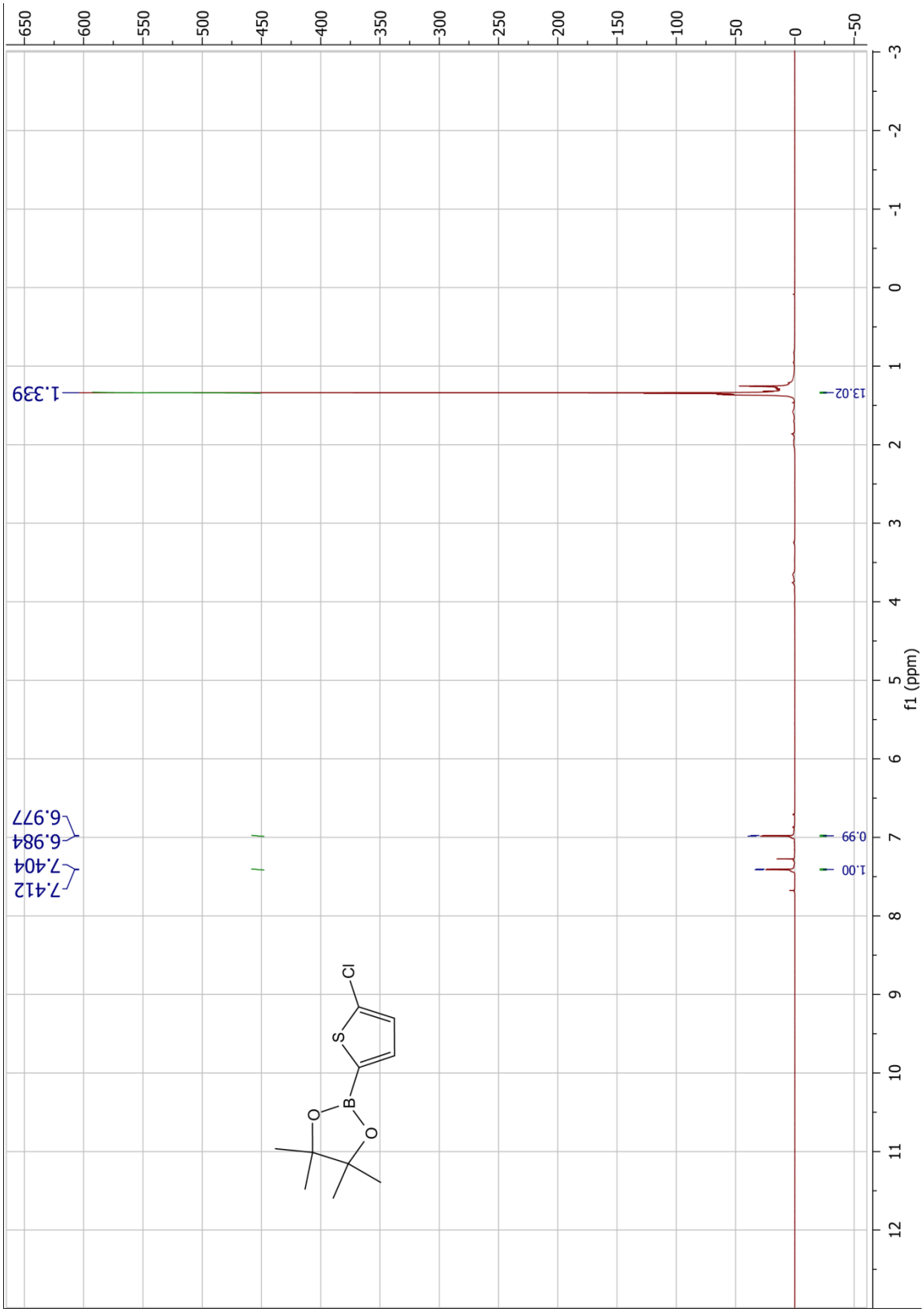

22.528
25.082
83.508
124.964
125.192
130.026
131.084
136.299
145.030
f1 (ppm)

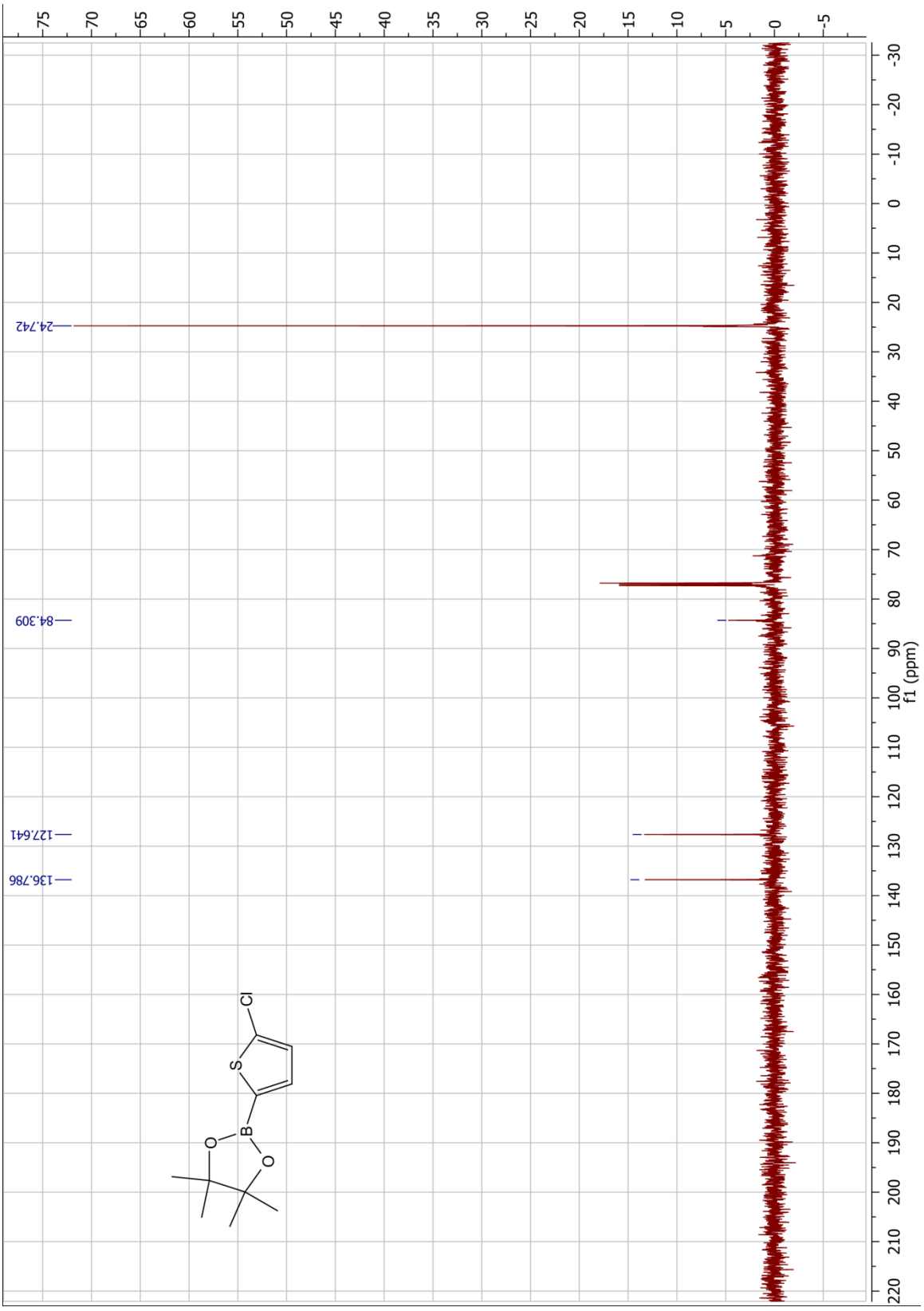

32.464
f1 (ppm)

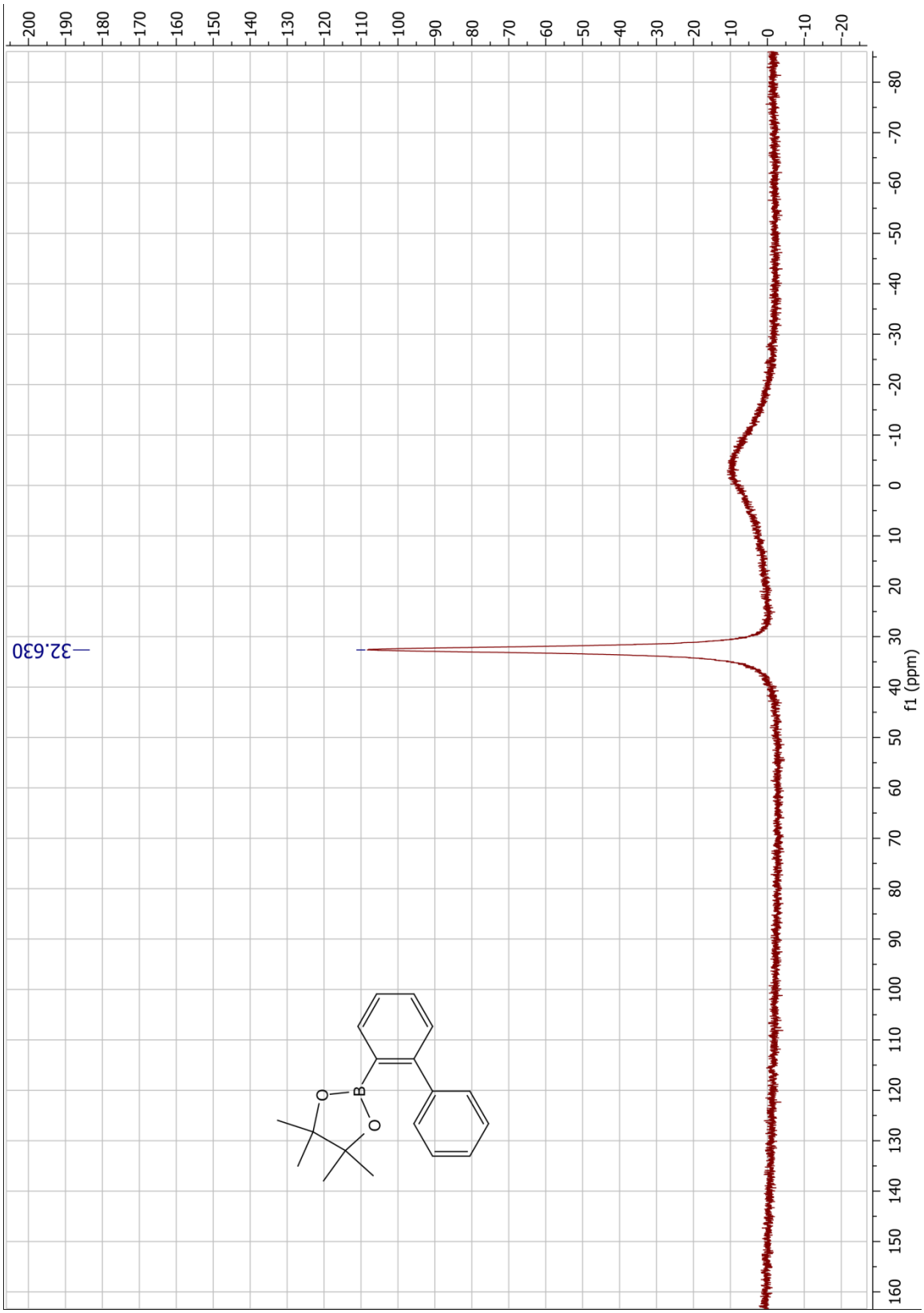

1.355
2.364
7.274
7.275
7.284
7.286
7.615
7.623
7.632
7.650
12.10
3.32
1.00
1.15
1.20
0.81
f1 (ppm)

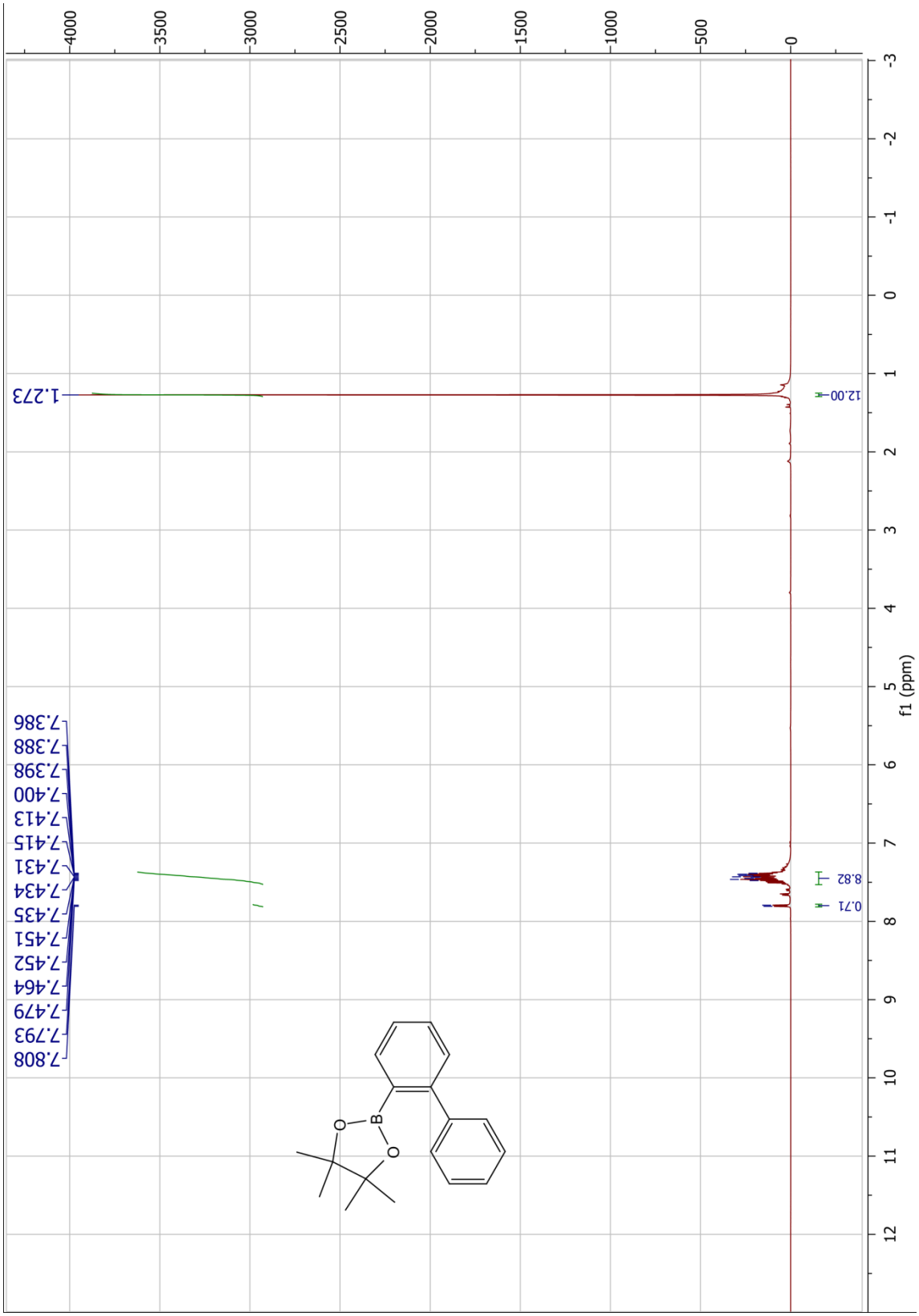

21.278
24.871
83.728
127.702
131.795
132.048
135.349
137.134
f1 (ppm)

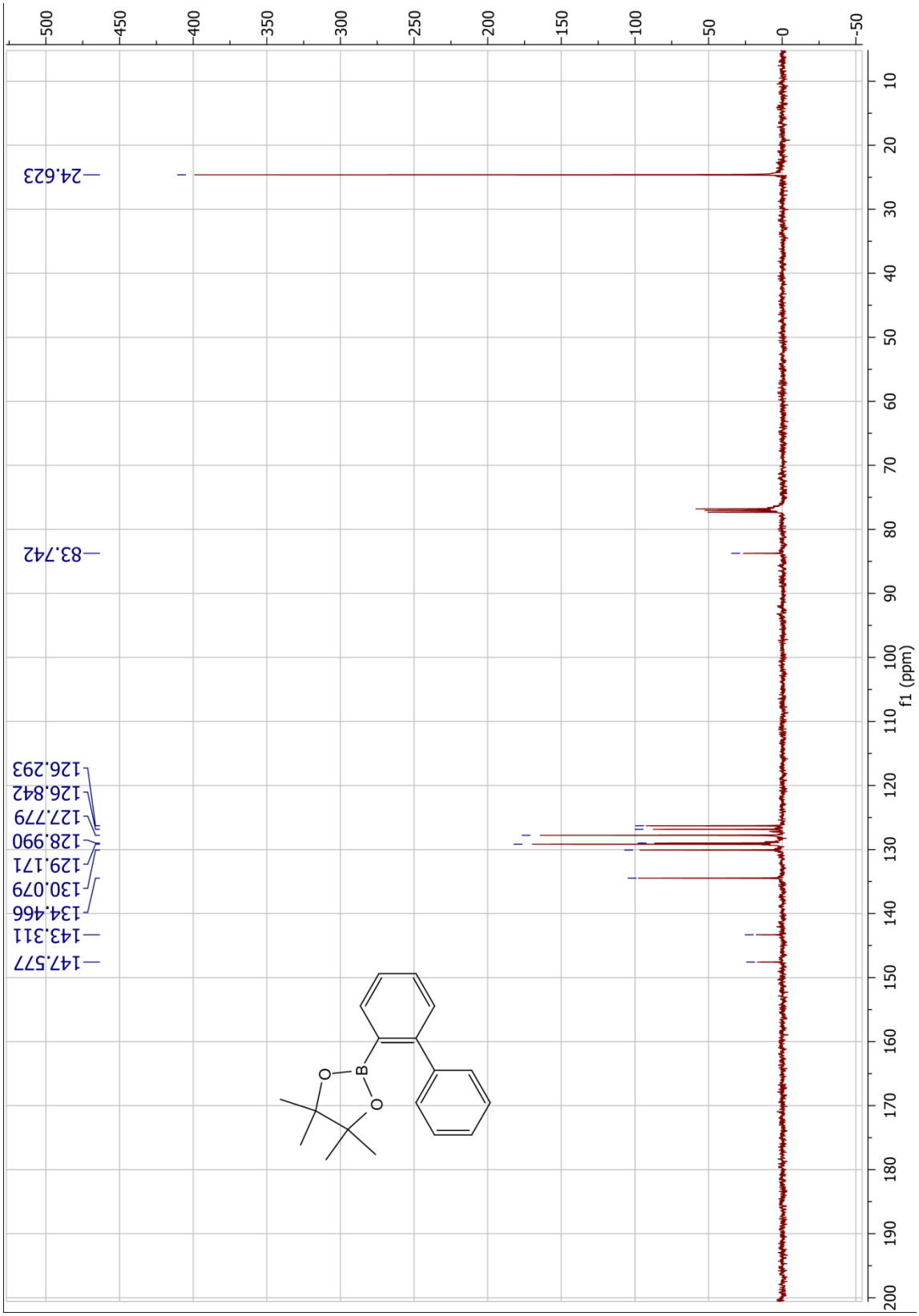

Cl
S
B
O
O
f1 (ppm)

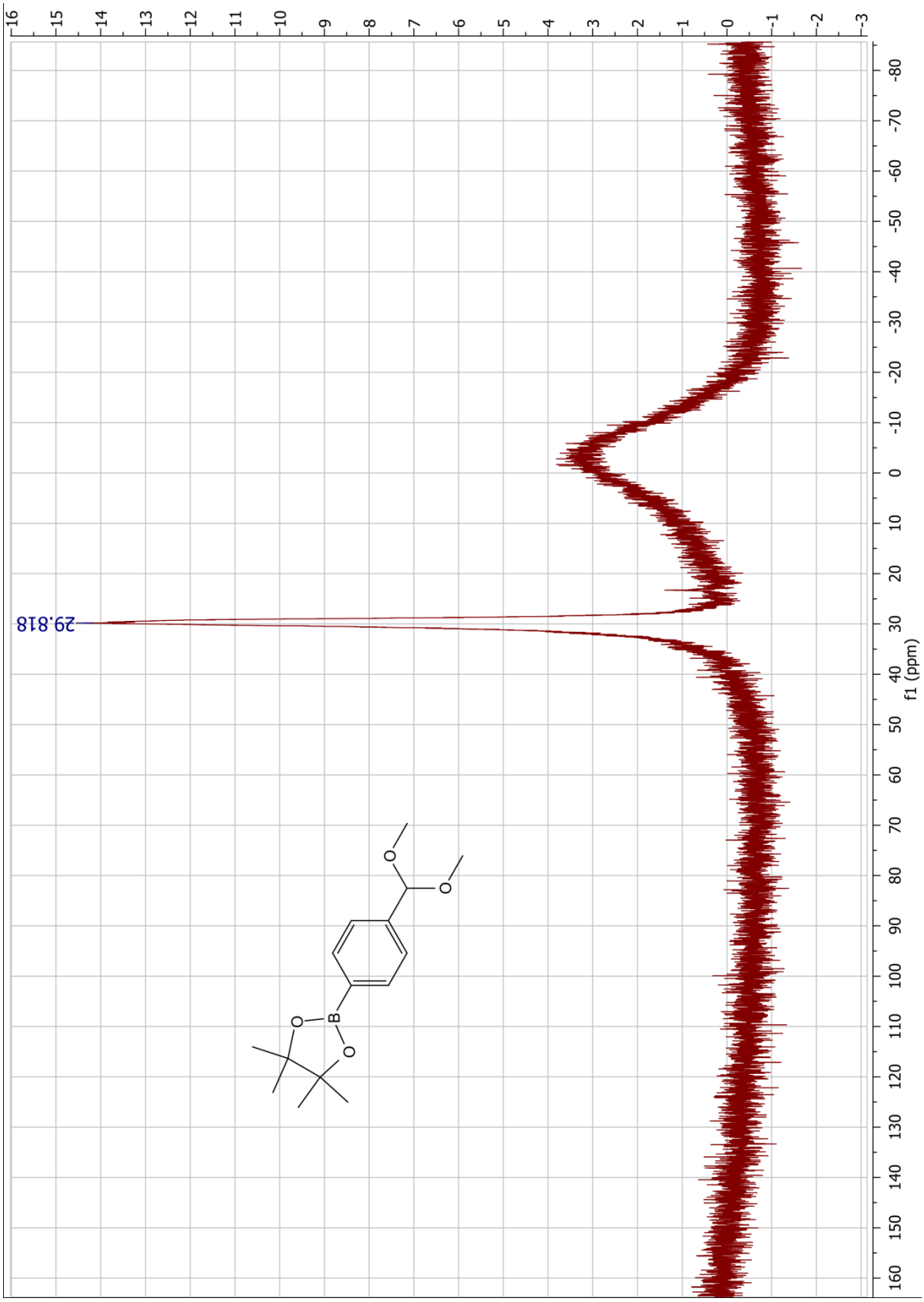

1.339
7.412
7.404
6.984
6.977
13.02
0.99
1.00
f1 (ppm)
Cl
S
B
O
O

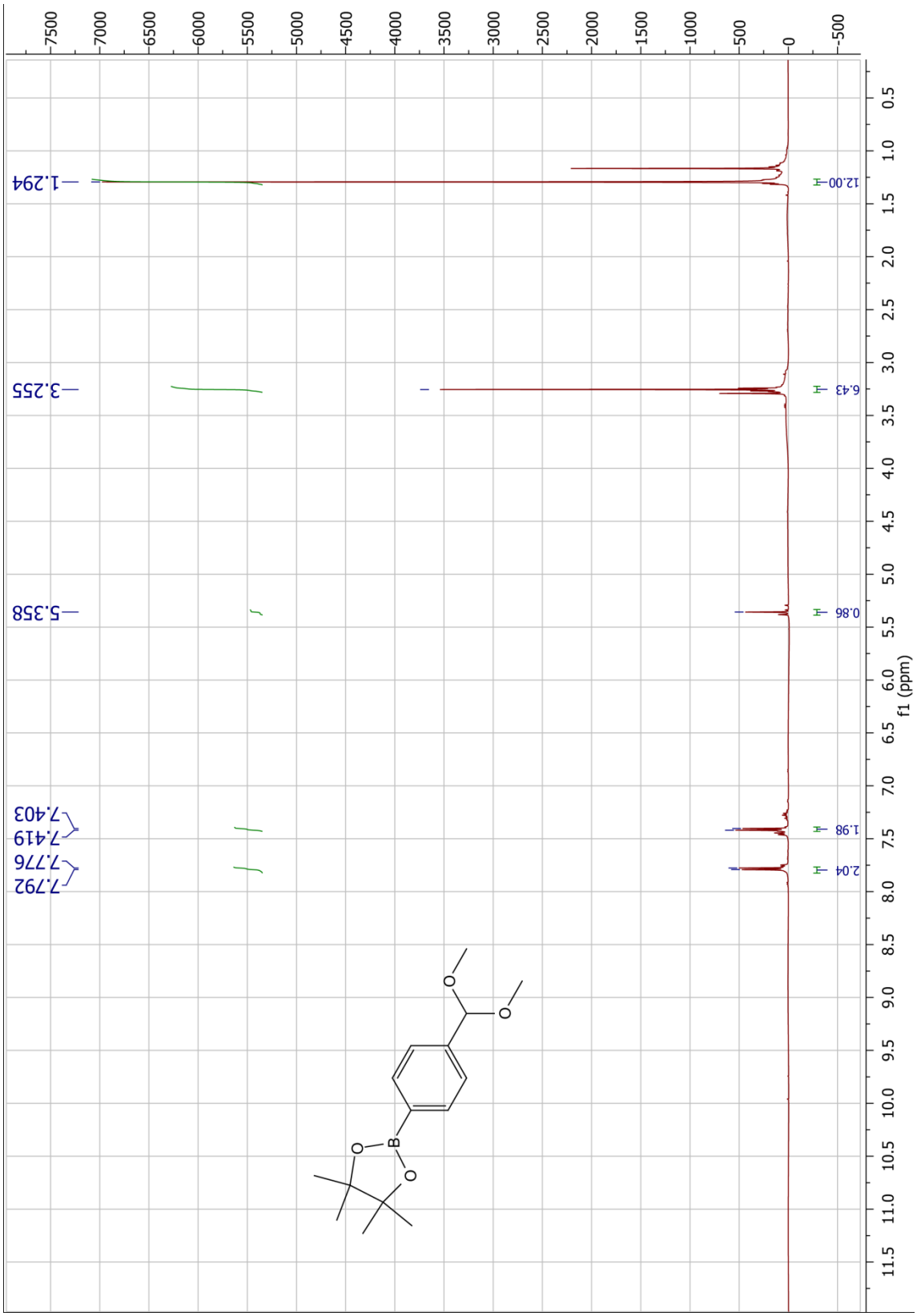

24.742
84.309
127.641
136.786
f1 (ppm)
Cl
S
B
O
O

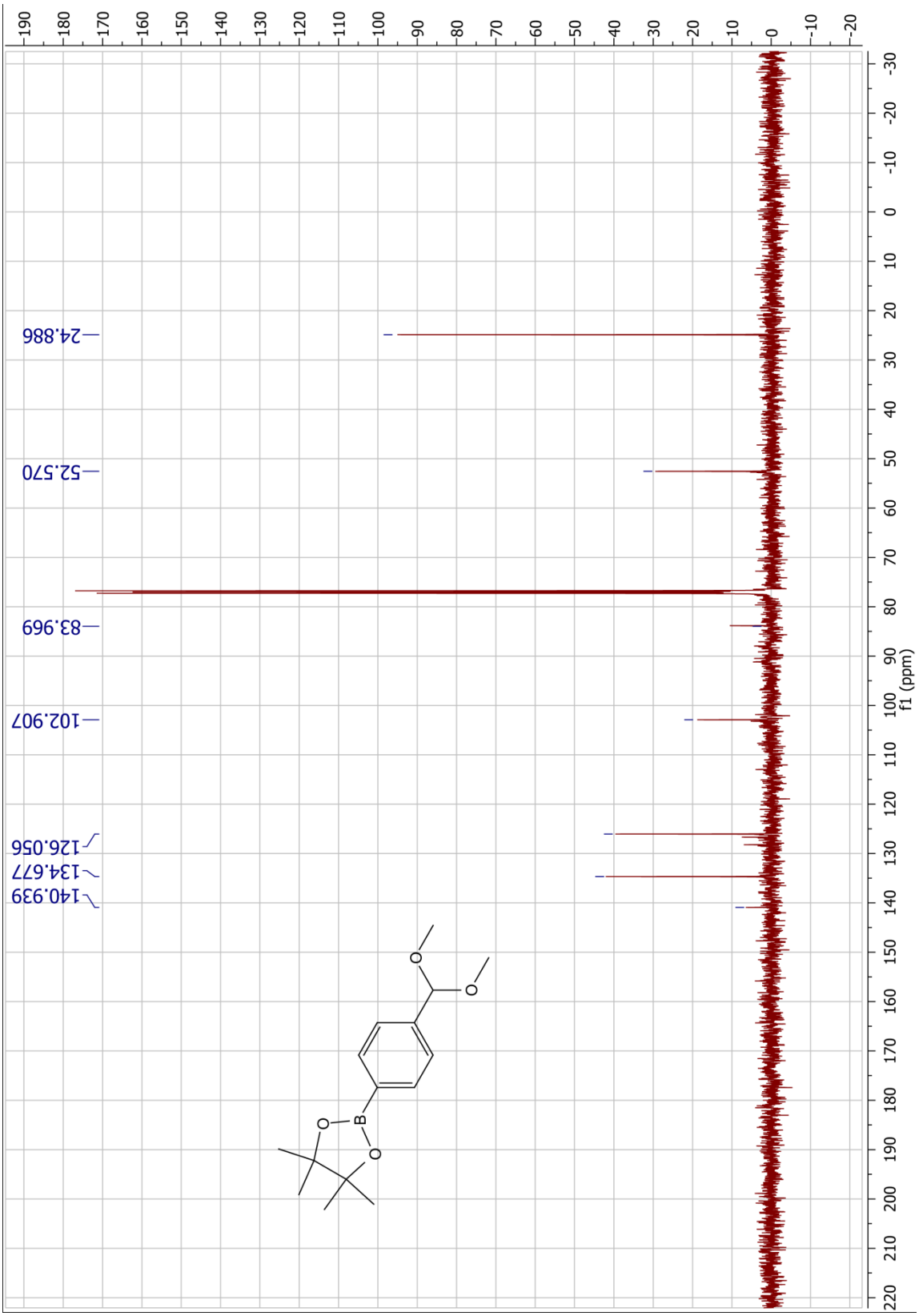

32.630
f1 (ppm)

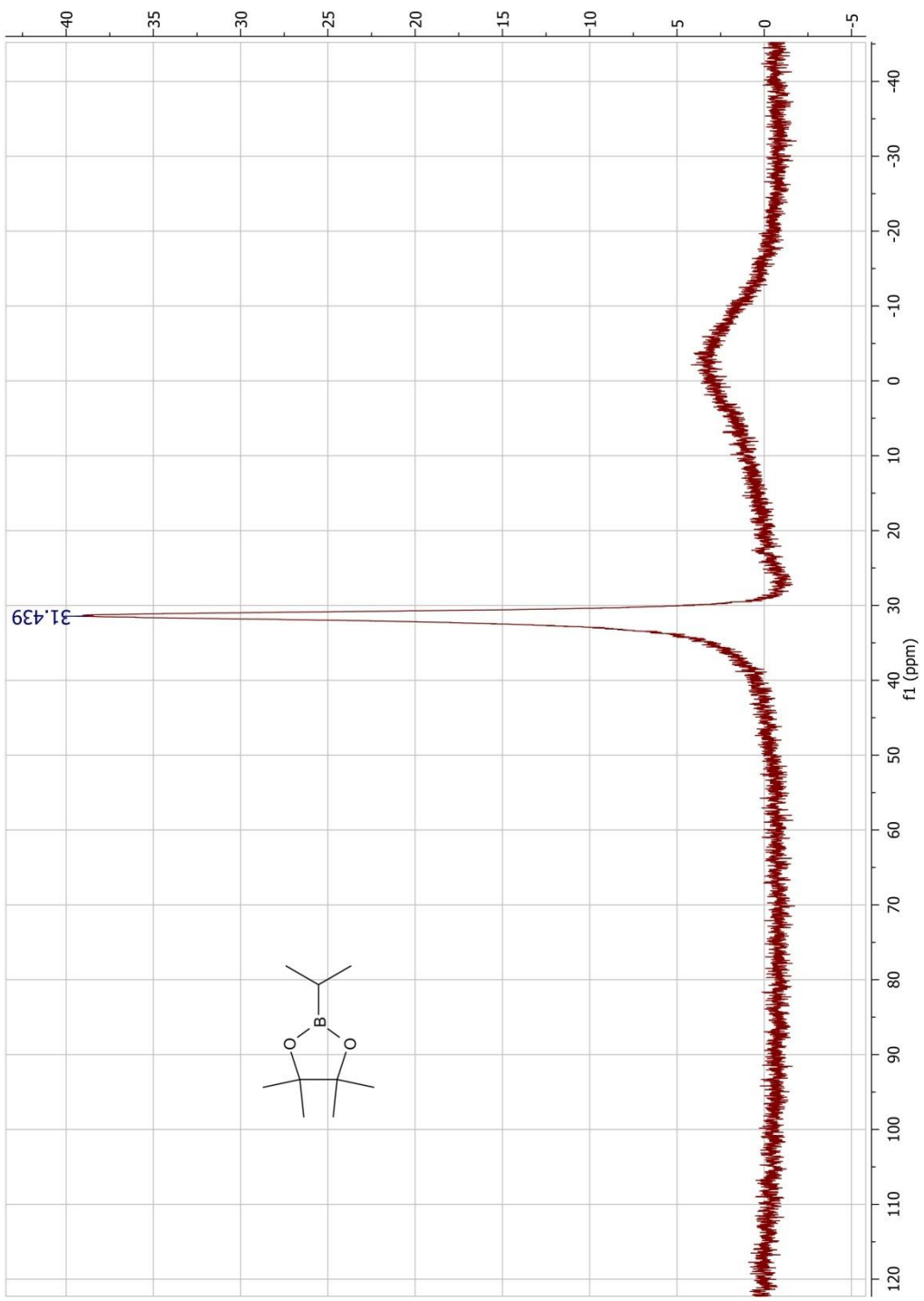

4000
3500
3000
2500
2000
1500
1000
500
0
-3
-2
-1
0
1
2
3
4
5
6
7
8
9
10
11
12
f1 (ppm)
1.273
12.00
8.82
0.71
7.808
7.793
7.479
7.464
7.452
7.451
7.435
7.434
7.431
7.415
7.413
7.400
7.398
7.388
7.386
O
B
O

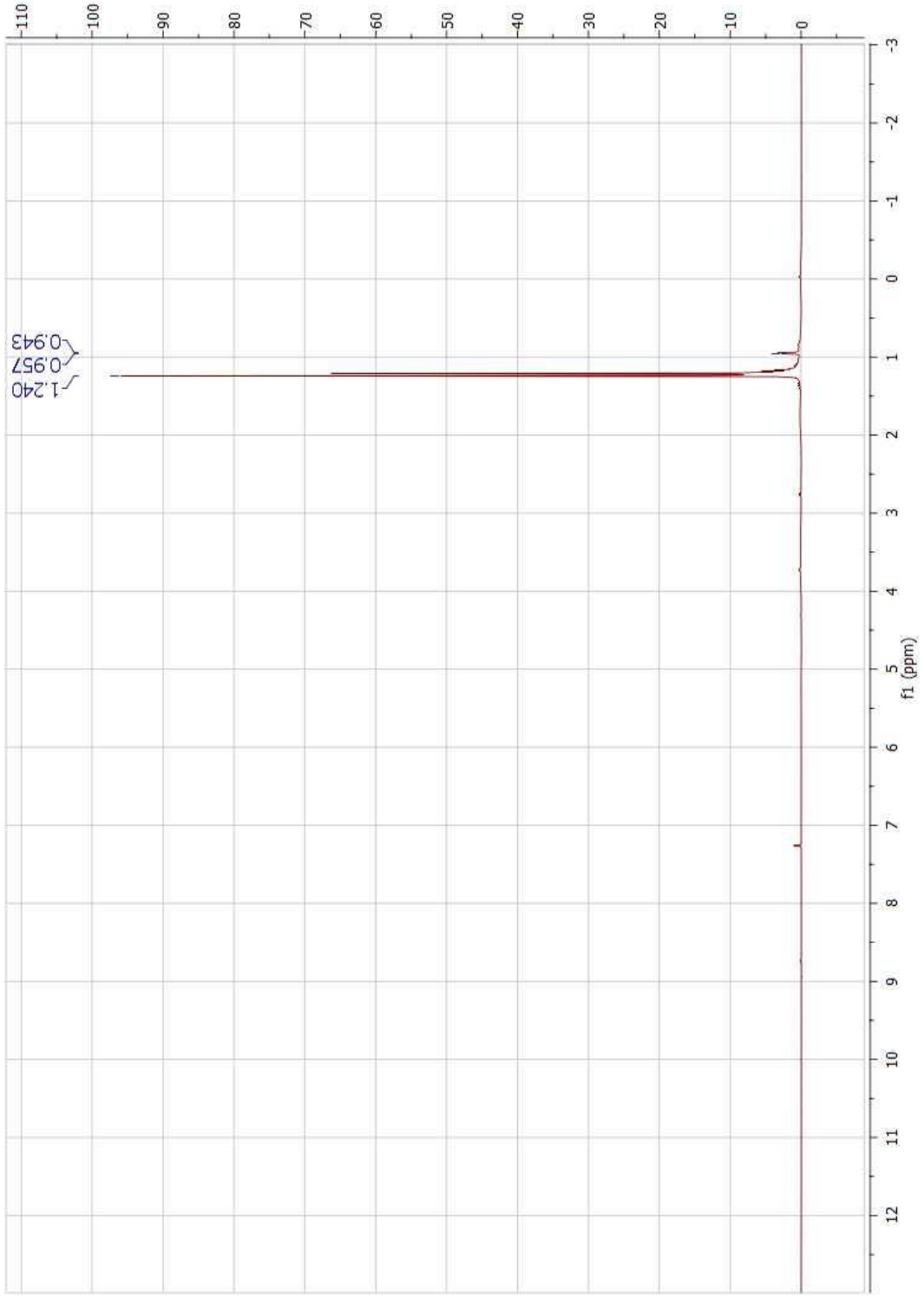

24.623
83.742
147.577
143.311
134.466
130.079
129.171
128.990
127.779
126.842
126.293
O
B
O
f1 (ppm)

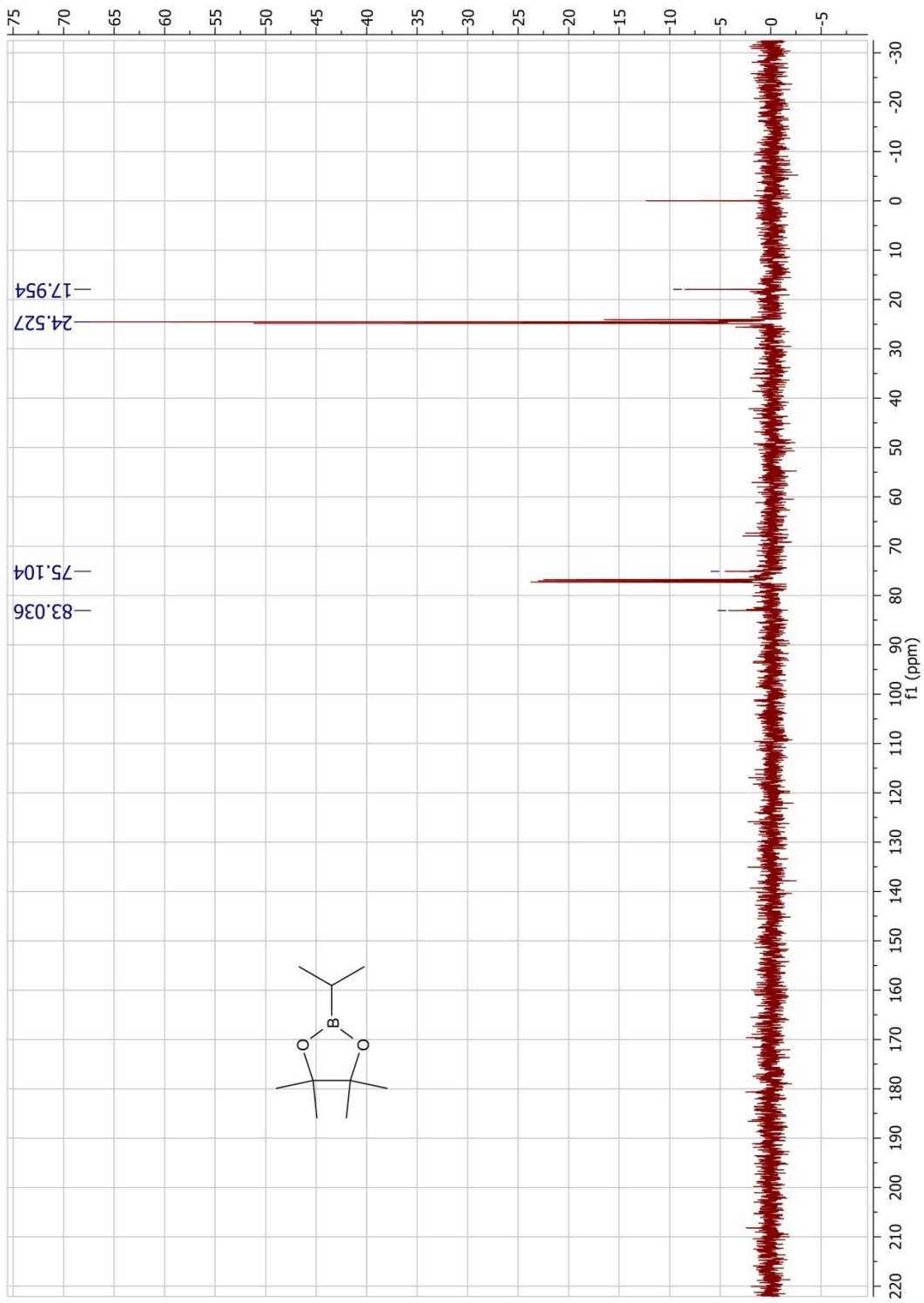

29.818
f1 (ppm)

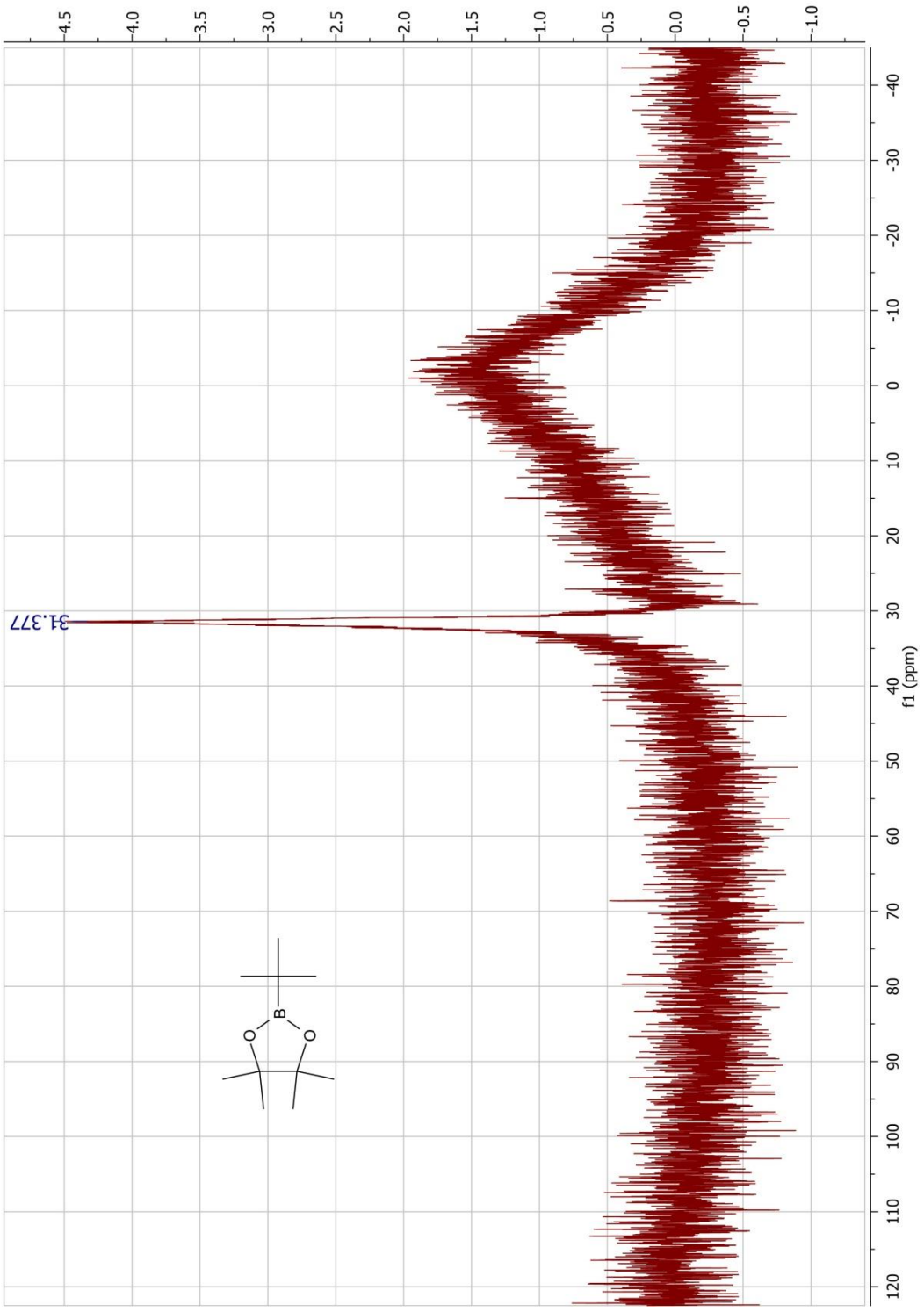

7.792
7.776
7.419
7.403
5.358
3.255
1.294
2.04
1.98
0.86
6.43
12.00
f1 (ppm)

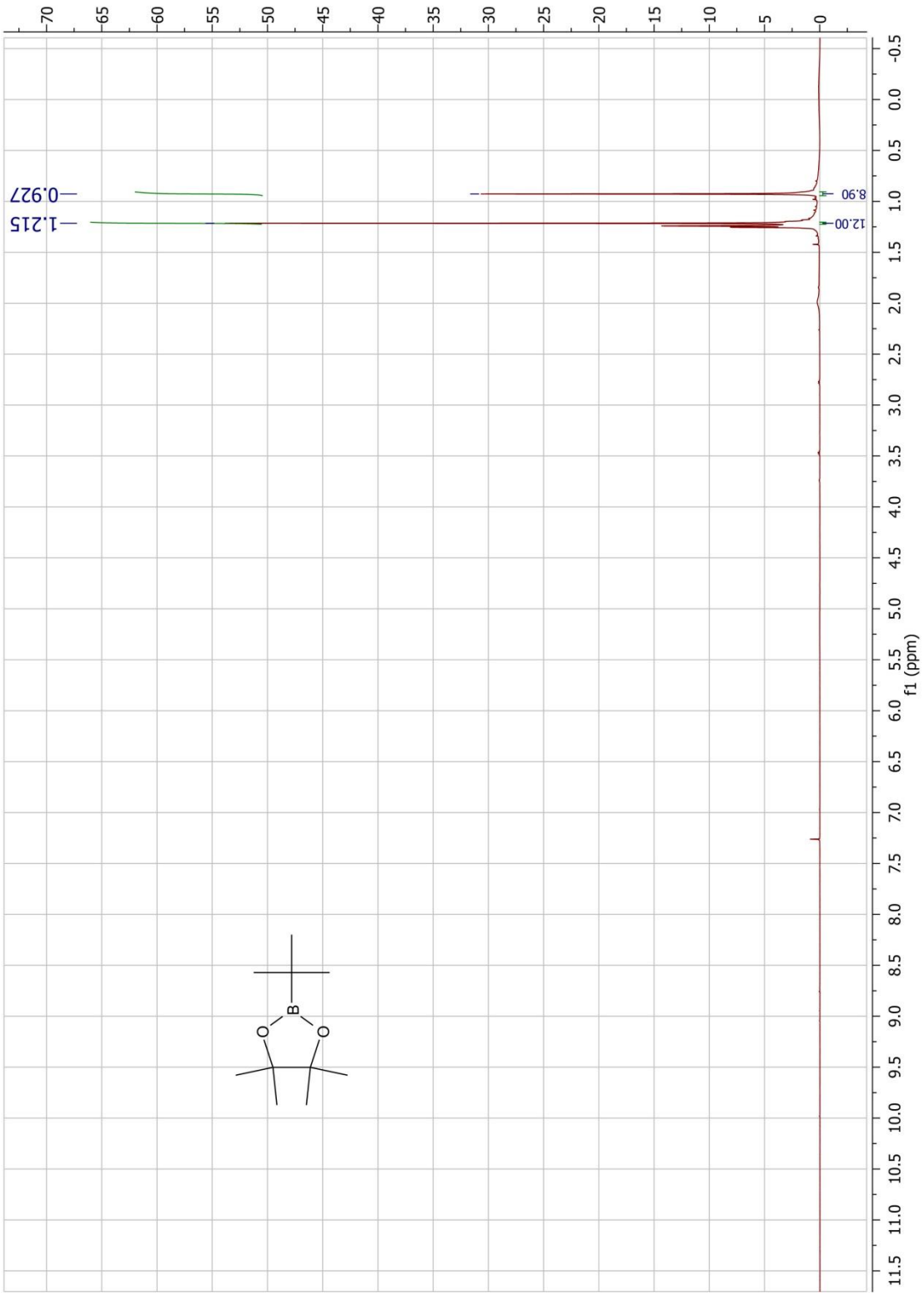

24.886
52.570
83.969
102.907
126.056
134.677
140.939
f1 (ppm)

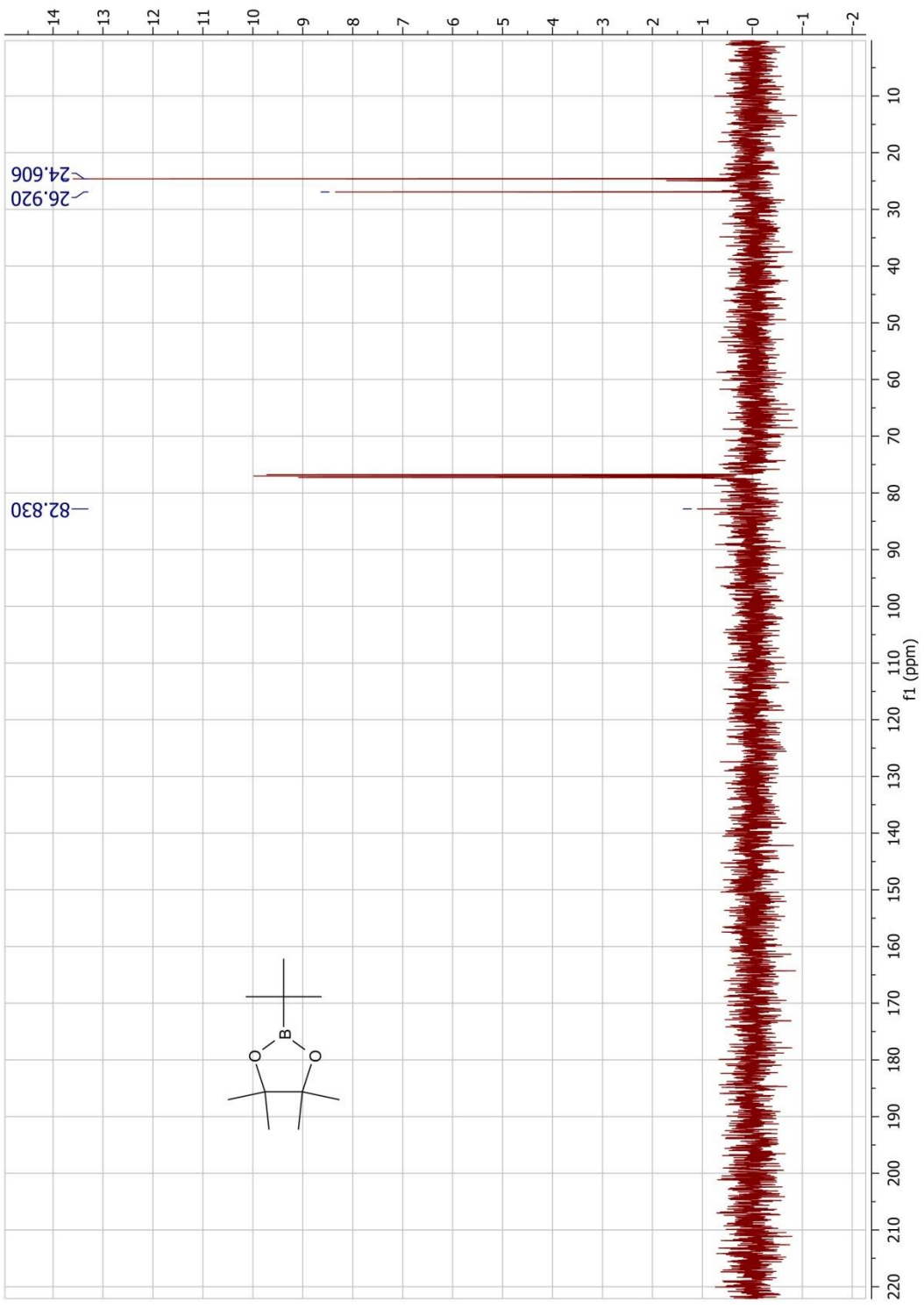

31.439
f1 (ppm)
B
O
O

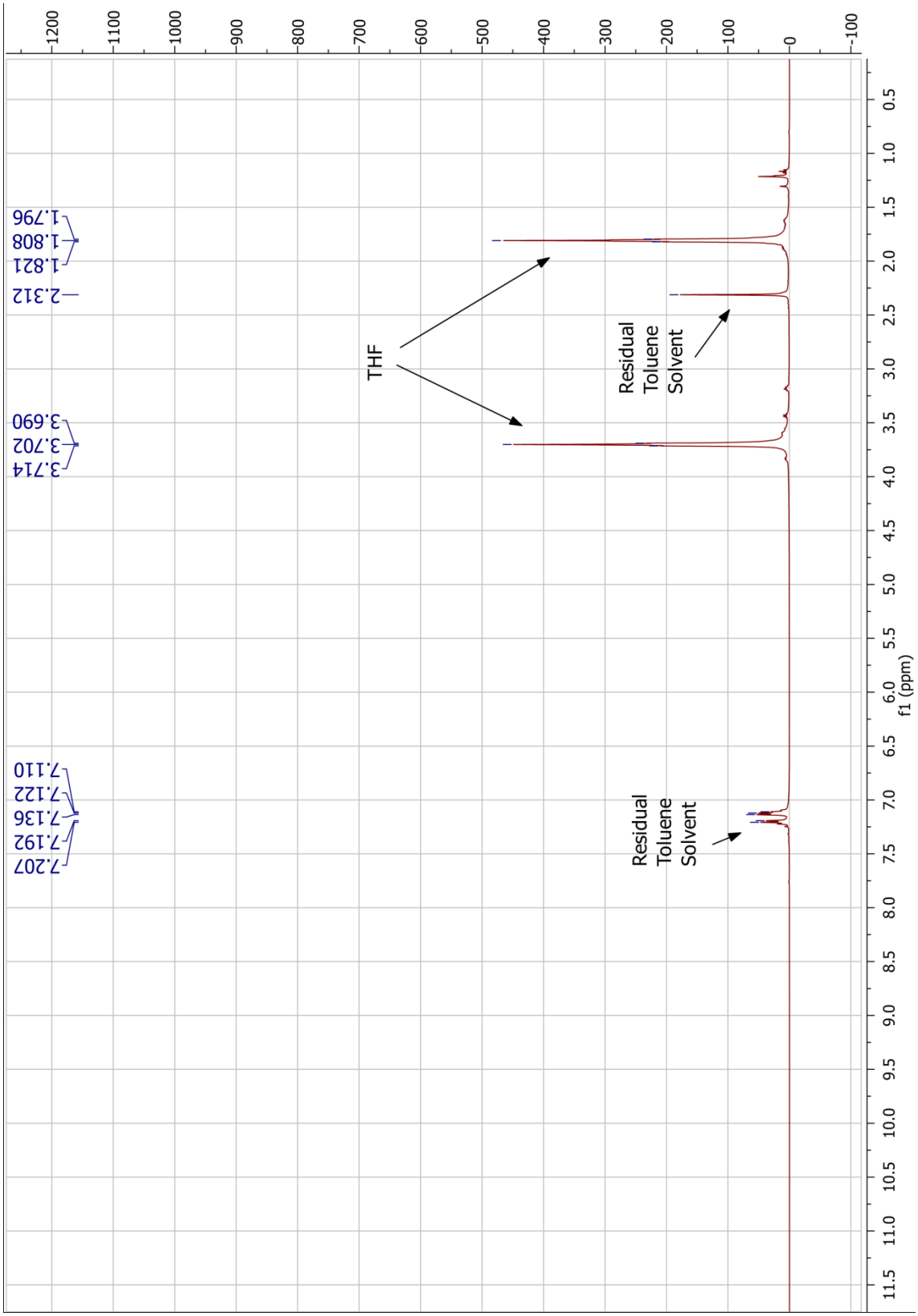

1.240
0.957
0.943
f1 (ppm)

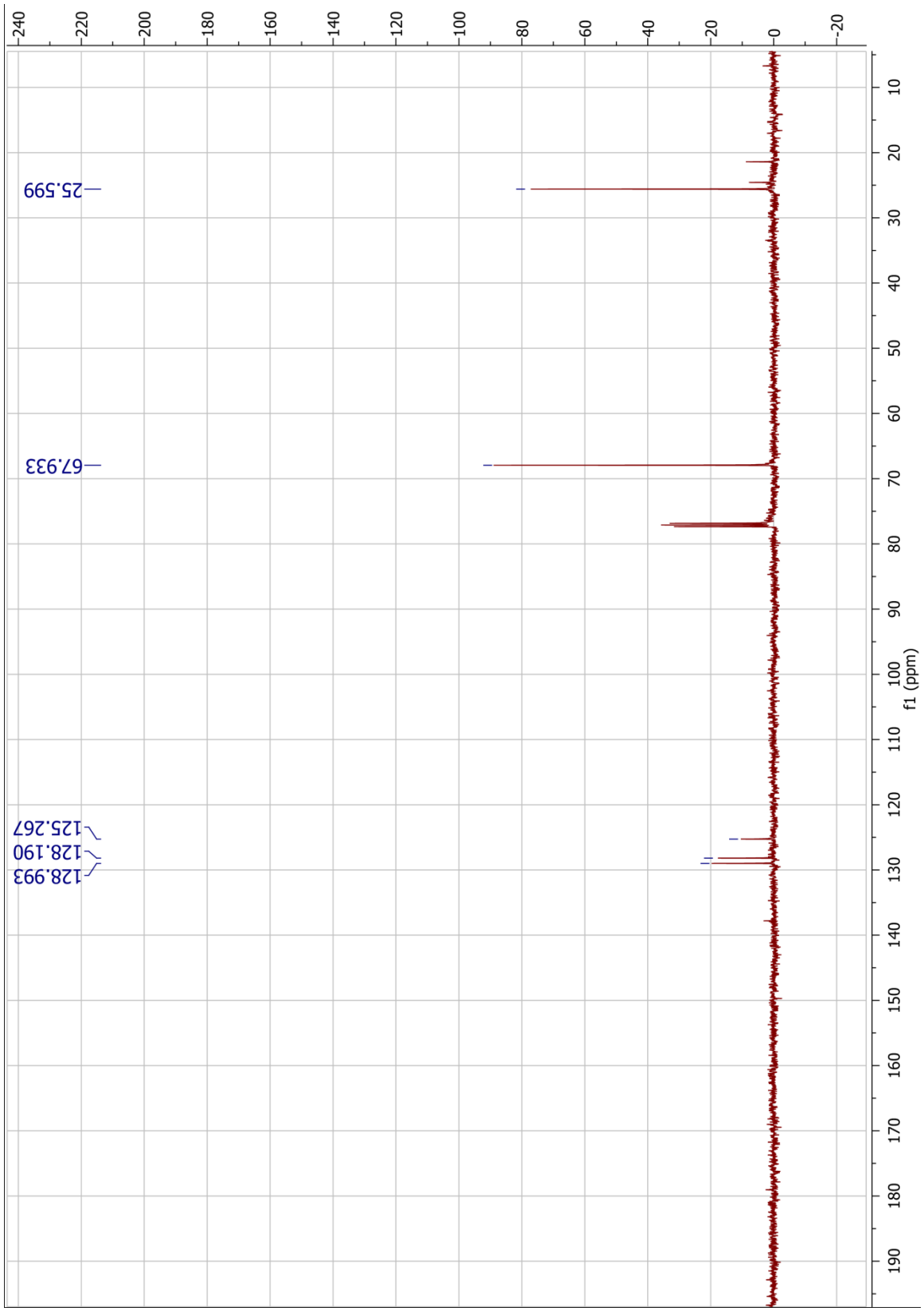

83.036
75.104
24.527
17.954
f1 (ppm)


31.377
f1 (ppm)
B
O
O


0.927
1.215
8.90
12.00
f1 (ppm)
B
O
O


82.830
26.920
24.606
B
O
O
f1 (ppm)


7.207
7.192
7.136
7.122
7.110
3.714
3.702
3.690
2.312
1.821
1.808
1.796
THF
Residual
Toluene
Solvent
Residual
Toluene
Solvent
f1 (ppm)


25.599
67.933
128.993
128.190
125.267
f1 (ppm)

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