# Metal-Catalyzed Cross-Coupling Reactions with Dithiolanes and Dithianes

By

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## Abstract

Creating new carbon-carbon bonds is one of the most important and challenging reactions in organic synthesis. Metal-catalyzed cross-coupling reactions have emerged as one of the preferred methods of producing new carbon-carbon bonds, and this work led to the 2010 Nobel Prize in Chemistry.

This thesis was aimed at expanding the current research in the area of metal-catalyzed cross-coupling reactions to include new applications with dithiolane and dithiane protecting groups. 1,3-Dithiolane and 1,3-dithiane derivatives are particularly interesting molecules in that they can be deprotonated by a strong base to form anions, which can then be used for carbon-carbon bond synthesis. This thesis describes the investigation into the use of dithiolanes and dithianes in metal-catalyzed cross-coupling reactions, as well as some of the challenges faced in performing this sulfur-based chemistry.

## Acknowledgements

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Lastly, I would like acknowledge my wonderful family for all of their love and support through the years.

## Dedication

*For Ainsley and Rachel*

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## List of Abbreviations

| | |
|---|---|
| © | Copyright sign |
| $^{o}$ | Degrees |
| $^{o}$C | Degrees Celsius |
| Ac | Acetyl |
| Ar | Aryl |
| Bu | Butyl |
| ca. | Circa |
| Cy | Cyclohexyl |
| DavePhos | 2-Dicyclohexylphosphino-2'-(N,Ndimethylamino)biphenyl |
| dba | Dibenzylideneacetone |
| DCM | Dichloromethane |
| DMSO | Dimethylsulfoxide |
| DPEphos | Bis(2-diphenylphosphinophenyl)ether |
| DPPB | 1,4-Bis(diphenylphosphino)butane |
| DPPF | 1,1'-Bis(diphenylphosphino)ferrocene |
| Eq. | Equivalents |
| Et | Ethyl |
| FID | Flame ionization detector |
| Fig. | Figure |
| g | Gram |
| GC | Gas chromatography |

| | |
|---|---|
| Hex | Hexyl |
| Hz | Hertz |
| LDA | Lithium diisopropylamide |
| $L_n$ | Ligand |
| min | Minute |
| m/z | Mass-to-charge ratio |
| mg | Milligram |
| mL | Millilitre |
| mmol | Millimole |
| MS | Mass spectrometry |
| NBS | *N*-Bromosuccinimide |
| *n*-BuLi | *n*-Butyllithium |
| NCS | *N*-Chlorosuccinimide |
| NMR | Nuclear magnetic resonance |
| Ph | Phenyl |
| ppm | Parts per million |
| Pr | Propyl |
| s | Second |
| SPhos | 2-Dicyclohexylphosphino-2',6'-dimethoxybiphenyl |
| TLC | Thin-layer chromatography |
| TMS | Trimethylsilane |
| UV | Ultraviolet |
| Xantphos | 9,9-Dimethyl-4,5-bis(diphenylphosphino)xanthenes |

# Chapter 1: Introduction

## 1.1 General introduction

Metal-catalyzed cross-coupling reactions are used in many applications of organic chemistry.[1-3] A general metal-catalyzed cross-coupling reaction is described by the joining of two hydrocarbon fragments with the aid of a metal catalyst. This is a powerful technique for creating new carbon-carbon bonds that leads to increasing the molecular complexity of an organic synthesis product. Research in this area has led to numerous accolades, including the 2010 Nobel Prize in Chemistry.[4]

The purpose of the research in this dissertation was to broaden the scope of current metal-catalyzed cross coupling methods, to include new reactions involving dithiolanes and dithianes. To the best of my knowledge, a metal-catalyzed cross-coupling reaction between a dithiolane/dithiane and an organohalide has not previously been described. There is a precedent for this work, as other acyl anions have been used in similar cross-coupling reactions. It was proposed by Hartwig *et al.* that acyl anion equivalents such as dithianes and cyanohydrins have potential for these types of reactions.[5] My thesis project had three main objectives:

1) To determine the conditions required for a successful cross-coupling reaction between a dithiolane/dithiane and an organohalide
2) Optimization of the reaction conditions
3) Testing the scope of the reaction by varying either the dithiolane/dithiane or the organohalide

The general approach was to use previously published procedures for other acyl anion equivalents in metal-catalyzed cross-coupling reactions. This involved preparing acyl anion

equivalents from dithiolanes/dithianes under basic conditions; separately combining catalyst, ligand, and organohalide and solvating with heat; then finally combining everything at the reaction temperature. The reaction progress was monitored using gas chromatography (GC). Optimization of the reaction was attempted by varying the reaction temperature, transmetalating, and altering the starting materials. Control reactions were then performed to test the reactivity and stability of the acyl anion equivalent.

The aim of this research was to demonstrate that the acyl anion equivalent of a dithiolane or a dithiane could be used in cross-coupling reactions. This would broaden the range of applications for current metal-catalyzed cross-coupling reactions.

## 1.2 Dithiane and dithiolane chemistry

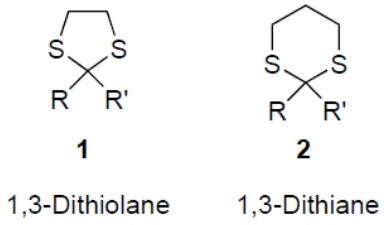
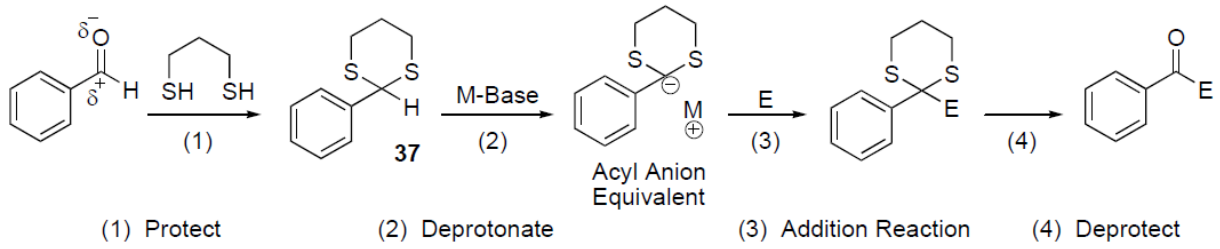



**Fig. 1.1.** Thioacetal protecting group. 1,3-Dithiolane derivative (left). 1,3-Dithiane derivative (right).

Protecting groups are used in organic chemistry to temporarily block a reactive site in a multifunctional compound in order to achieve chemoselectivity in a successive reaction.[6,7] When performing an organic synthesis, it may be necessary to selectively protect one carbonyl group of a molecule in the presence of another less reactive one. This is possible due to the order of reactivity of carbonyls: [aldehydes (aliphatic > aromatic) > acyclic ketones and cyclohexanones > cyclopentanones > α,β-unsaturated ketones or α,α-disubstituted ketones >>

aromatic ketones]. The most useful protecting groups for carbonyl groups are the acyclic and cyclic acetals or ketals, and the acyclic or cyclic thioacetals or ketals. Incorporation of the protecting group into the molecule is obtained by the treatment of the carbonyl group with an alcohol, diol, thiol, or dithiol in the presence of acid. The carbonyl derivatives are stable toward a number of reagents and can be cleaved by acid hydrolysis in the case of the oxygen derivatives, or under neutral conditions by oxidants for the sulfur derivatives.[6,7]

1,3-Dithiane and 1,3-dithiolane derivatives are particularly useful in that they can be deprotonated by a strong base such as *n*-BuLi to form anions, which can then be used for carbon-carbon bond synthesis.[8-10] The formation of an acyl anion equivalent creates a reversal of polarity for the carbonyl group and is referred to as "umpolung" chemistry. This type of chemistry has a wide variety of applications in synthetic organic chemistry, thus demonstrating the usefulness of these protecting group molecules.[11]



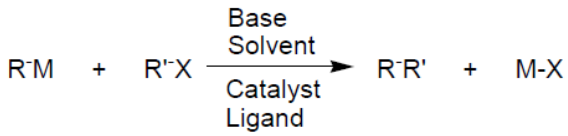

**Scheme 1.1.** Example of Umpolung chemistry with benzaldehyde using 1,3-propanedithiol.

1,3-Dithianes are generally produced by acid-catalyzed condensation of carbonyl compounds with 1,3-propanedithiol. This can be accomplished with a number of Lewis acid catalysts, such as $BF_3 \cdot Et_2O$, $SOCl_2$-$SiO_2$, $SmI_3$, or $TeCl_4$.[6,7] Similarly, 1,3-dithiolanes are produced by acid-catalyzed condensation of carbonyl compounds with 1,2-ethanedithiol. Lewis acid catalysts used in this case include $BF_3 \cdot Et_2O$, $TiCl_4$, $ZnCl_2$, and $SiCl_4$.[7] Regeneration of the

carbonyl can be achieved by treating the dithiolane or dithiane derivative with $Hg^{2+}$ or $Ag^{+}$ salts under neutral conditions.[6,7]

### 1.3 Metal-catalyzed cross-coupling

Metal-catalyzed cross-coupling reactions are very powerful techniques for creating new carbon-carbon bonds in organic syntheses.[1-3] The general reaction scheme involves combining an organometallic fragment, RM, with an organohalide, R′X, to produce a new organic compound $R^1$-$R^2$ and salt M-X as a byproduct (Scheme 1.1). A cross-coupling reaction involves the coupling of two different starting materials, which differs from a homocoupling reaction where two identical molecules react to form a product. This is often an undesired by-product in cross-coupling reactions.




**Scheme 1.2.** General scheme for a metal-catalyzed cross-coupling reaction.

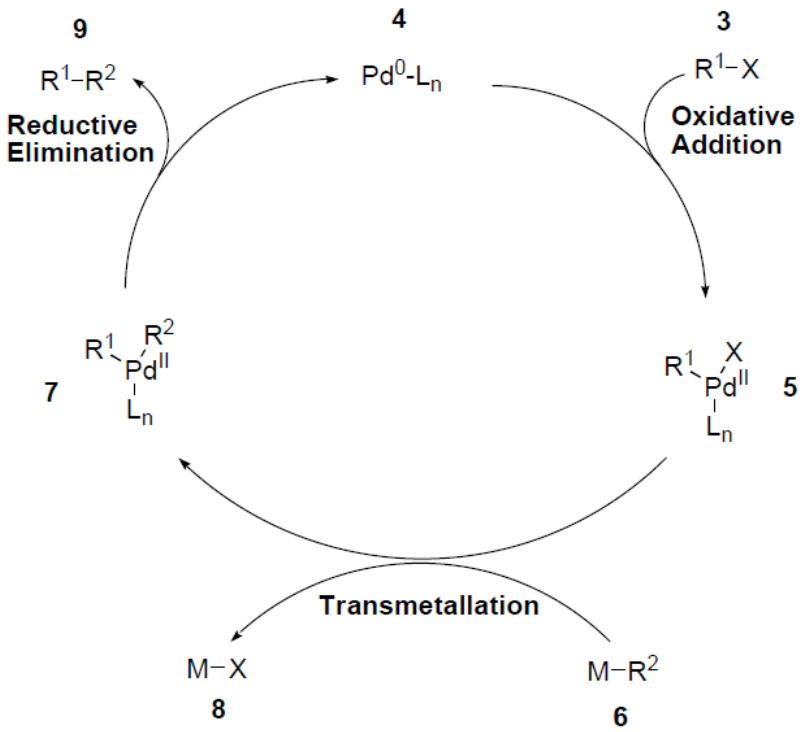
#### 1.3.1 The Nobel Prize and C-C bond formation

The formation of carbon-carbon bonds is an essential part of organic synthesis. Research in this area has led to a number of Nobel Prizes in Chemistry, including the Grignard reaction in 1912, the Diels-Alder reaction in 1950, and the Wittig reaction in 1979. Prior to the 1960s, the techniques available for C-C bond formation were limited. The development of reactions using transition metals as catalysts for C-C bond formation in the 1960s and 1970s was a major advancement in the field of organic synthesis.[12] The 2010 Nobel Prize in Chemistry was awarded to three scientists: Richard Heck, Ei-ichi Negishi and Akira Suzuki, for their work on palladium-catalyzed cross-coupling reactions for C-C bond formation.[13] The Heck, Negishi, and

Suzuki reactions are fundamental reactions used in organic synthesis and have a wide variety of applications, including the development of pharmaceuticals and the industrial preparation of fine chemicals.[14]

### 1.3.2 Organometallic cross-coupling mechanism

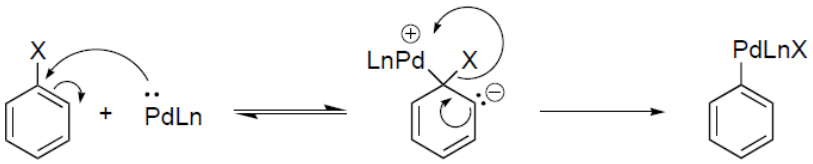
In palladium-catalyzed cross-coupling reactions, the general mechanism begins with oxidative addition of an organic halide **3** to a $Pd^0$-ligand complex **4**, which gives $Pd^{II}$ compound **5**. The second step is a transmetallation with **6** to give intermediate **7** and byproduct **8**, followed by a reductive elimination giving the cross-coupled product **9** and regenerating $Pd^0$ **4** (Scheme 1.2). In these reactions, the $Pd^0$ species is usually complexed to a ligand, $L_n$, with the most common ligands being either monodentate or bidentate phosphines.[15]




**Scheme 1.3.** General mechanistic scheme for a Pd-catalyzed cross-coupling reaction.

The first step in the cross-coupling reaction is an oxidative addition, for which a number of mechanisms have been proposed. The most common organic electrophiles in cross-coupling reactions are aryl and alkenyl halides and triflates, and their mechanisms of oxidative addition have been extensively studied.[16] In the concerted oxidative addition reaction, the mechanism follows an associative bimolecular process. It begins with nucleophilic attack from the metal centre on the σ-bond of the substrate making a 3-membered σ-complex. Subsequent intramolecular ligand bond cleavage forms the oxidized complex with a *cis* geometry, however isomerization can occur. The concerted oxidative addition mechanism is typical for non-polar substrates and homonuclear diatomics, such as $H_2$.[17]

A second important mechanism of oxidative addition is the $S_NAr$ type, shown below in Scheme 1.4. This mechanism is similar to the $S_N2$ pathway for simple organic reactions and is applicable to the aryl halides used in this thesis. The process begins as the $Pd^0$ source acts as a nucleophile attacking the more electrophilic side of the substrate; which produces an anti-aromatic intermediate. The resulting intermediate then returns to aromaticity, the carbon to halogen bond is cleaved, and then the halogen coordinates to the cationic metal to form the product.[15,16]




**Scheme 1.4.** Oxidative addition of an aryl halide onto palladium by an SnAr mechanism.

Oxidative addition by the SnAr mechanism can be promoted with the use of an electron withdrawing group.[16] An electron withdrawling group on the correct position of the aryl ring can

offer resonance stabilization for the anti-aromatic intermediate. Additionally, the choice of the aryl halide will have an impact on the rate of oxidative addition. The rate of oxidative addition is determined by bond energy between the carbon and the leaving group on the substrate; the lower the bond energy the faster the oxidative addition process.[18] The C-I bond has an average energy of 210 kJ/mol, the C-Br bond has an average energy of 280 kJ/mol, and the C-Cl bond has an average energy of 330 kJ/mol.[19] Reductive elimination is the opposite process from oxidative addition. It occurs more readily when the bond being formed is more stable, such as a C-C σ-bond. Reductive elimination occurs when the bonding carbons are adjacent to each on the metal centre.

The ligand used in a cross-coupling reaction has a profound impact on the metal atom and the rates of both oxidative addition and reductive elimination. Ligands are typically monodentate (such as triphenylphosphine) or bidentate (such as Xantphos). Amine ligands (N type) act as a hard Lewis base and phosphine ligands (P type) act as a soft Lewis base. The most common ligands are P type, while hemilabile monophosphine-monoamine (P-N type) ligands are beginning to grow in popularity. P-N Type ligands have an ability to bind soft metal centers, such as platinum and palladium. The phosphorus can bind strongly while the nitrogen can bind weakly, allowing for easy displacement of the nitrogen moiety. This allows more flexibility for the geometry around the metal atom and promotes easier isomerization and reductive elimination processes, since the nitrogen atom can release and re-bind to the metal atom.[20,21]

The effect of a ligand on a cross-coupling reaction can be generalized into two categories; the electronic and the steric influences.[22] The electronic aspect has to do with the distribution of electron density over the metal atom. All phosphine ligands are π-acceptors, but phosphines containing electron-withdrawing substituents are less basic and therefore poorer σ-donors.

Contrarily phosphine ligands containing electron-donating groups are more basic and therefore better σ-donors.[23-25] An increased electron density on the metal atom will stabilize higher oxidation states and therefore increase the rate of oxidative addition.[17] The steric effect of a ligand can have a great influence on the reactivity of the metal catalyst. A ligand with more steric bulk will promote a faster reductive elimination, however if the ligand is too bulky it may impede the oxidative addition process.[26,27]

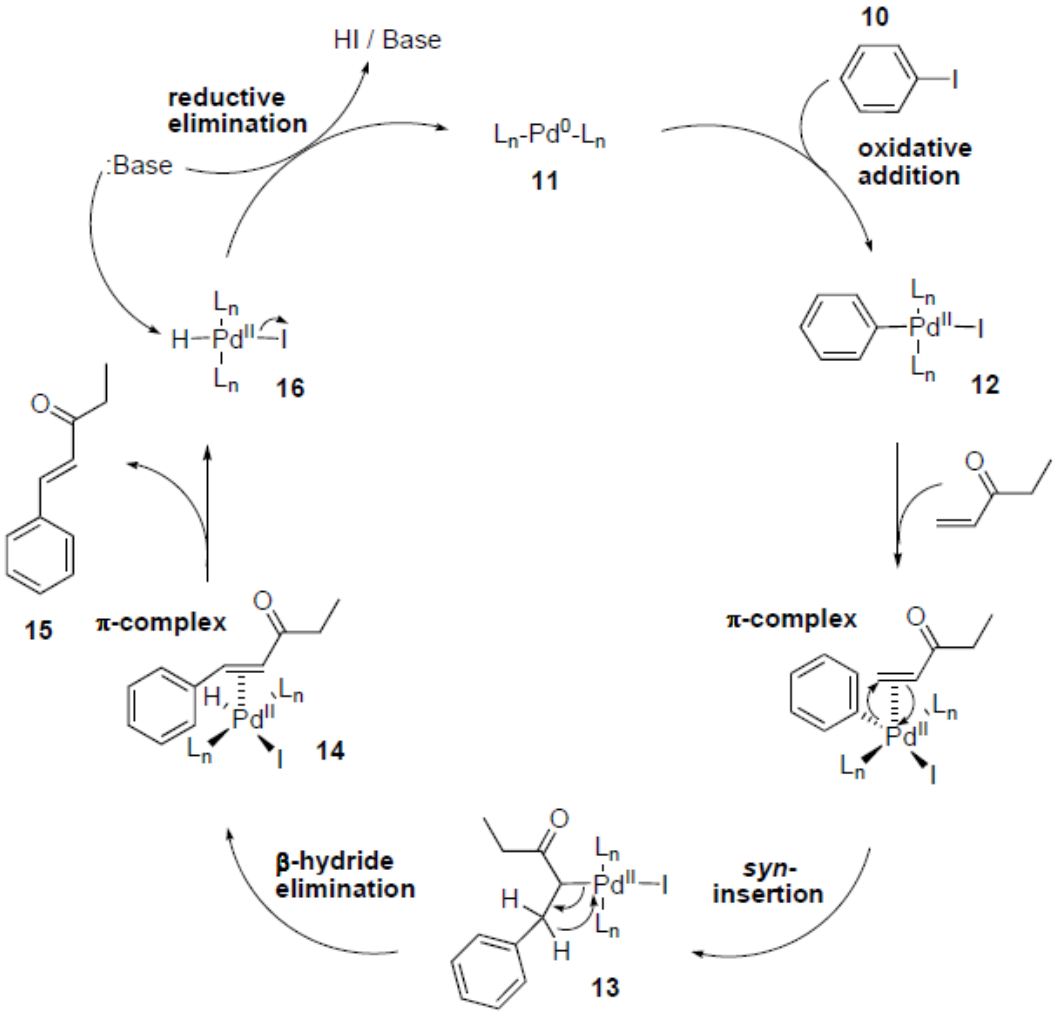
There are many common named reactions involving Pd-catalyzed cross-couplings. The Heck alkenylation of organic electrophiles is often grouped together with Pd-catalyzed cross-coupling reactions as the first step in both mechanisms is the same; however no transmetallation step occurs in the Heck reaction. The following sections of this thesis will discuss the Heck, Negishi, and Suzuki reactions and their mechanisms as these reactions are named for the scientists who shared the 2010 Nobel Prize in Chemistry.

### 1.3.3 Heck reaction

A series of papers by Richard Heck in 1968 described the first reactions involving alkenylation of organic electrophiles.[28-34] The Heck reaction begins with an oxidative addition step, as is found with the Pd-catalyzed cross-coupling reactions. However, the second step does not proceed with a transmetallation. Instead, a syn-insertion occurs followed by a β-hydride elimination to form the substituted alkene product.[15]

The electrophiles used in traditional Heck reactions were typically aryl or vinyl halides, however a wide variety of other compounds have now been used. The generally accepted mechanism is based on a $Pd^0/Pd^{II}$ redox system (Scheme 1.3). The first step is an oxidative addition of **10** to $Pd^0$ **11**, which creates intermediate **12**. The next step involves a *syn*-insertion,

which gives the σ-organopalladium complex **13**, with regioselectivity being determined by steric and electronic factors. The third step is a β-hydride elimination of an accessible β-hydrogen to generate intermediate **14**, which then undergoes reductive elimination to yield the final product **15** and the hydridopalladium complex **16**. The $Pd^0$ catalyst, **11**, can be regenerated through treatment of the hydridopalladium complex **16** with base.[35]

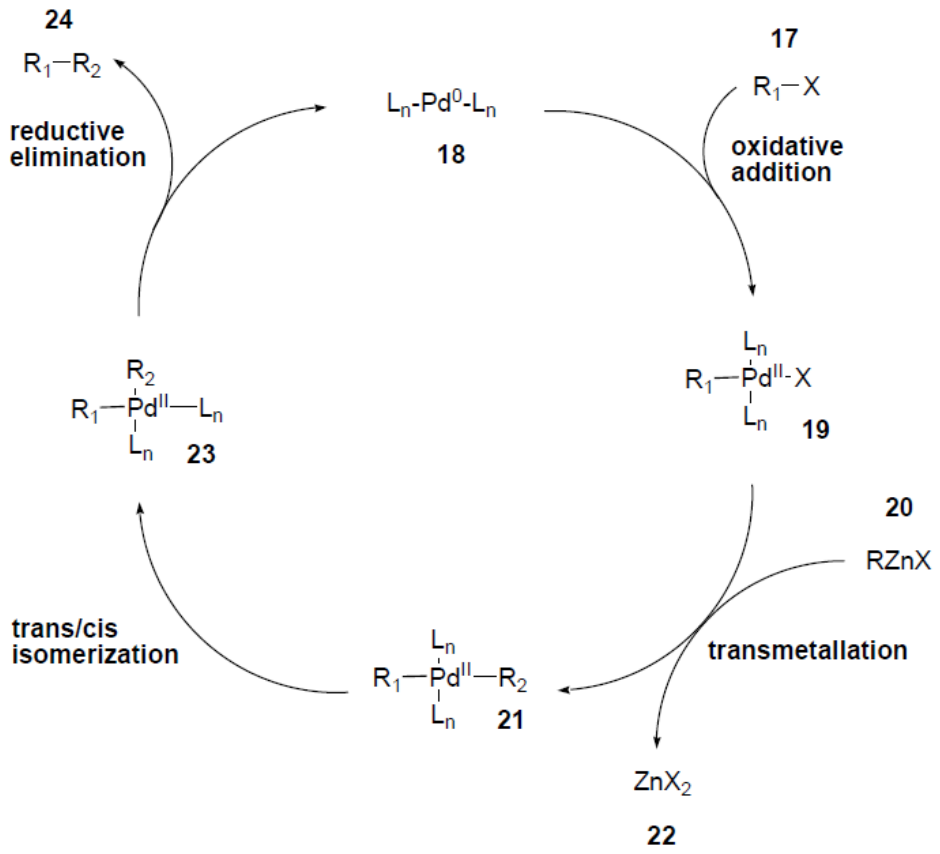



**Scheme 1.5.** General mechanism for a Heck reaction.

### 1.3.4 Negishi coupling

A Negishi cross-coupling reaction uses a nickel or palladium catalyst to cross-couple an organozinc compound with an organic halide. Negishi first demonstrated this type of reaction in 1977.[36] Negishi cross-couplings can also include reactions with organoaluminums and organozirconiums, as well as those utilizing metal salt cocatalysts such as $ZnCl_2$ and $ZnBr_2$.[37,38] The organohalide used can be an alkenyl, aryl, allyl, benzyl, or propargyl halide or pseudohalide (a compound that is similar to a halide in reactivity and charge), and the organozinc can be alkenyl, aryl, allyl, benzyl, or alkynyl. The most favourable cross-couplings are aryl-aryl, aryl-alkenyl, alkenyl-aryl, and alkenyl-alkenyl.[38]

The mechanism for Negishi cross-coupling reactions essentially follows that of the general Pd-catalyzed cross-coupling reaction (Scheme 1.4). The first step is an oxidative addition of organic halide **17** to $Pd^0$ species **18** to give intermediate **19.** This is followed by transmetallation with organozinc compound **20** to yield intermediate **21** and the zinc salt byproduct **22.** Next a cis-trans isomerisation takes place to produce intermediate **23**, which then allows for the terminating step of reductive elimination to produce the final product **24** and the regeneration of the $Pd^0$ catalyst **18**. Negishi couplings are particularly useful due to their high catalytic reactivity and high chemoselectivity. These reactions are widely used for cross-coupling carbon-carbon bonds and have a large variety of synthetic applications.[38]




**Scheme 1.6.** General mechanism for a Negishi coupling.

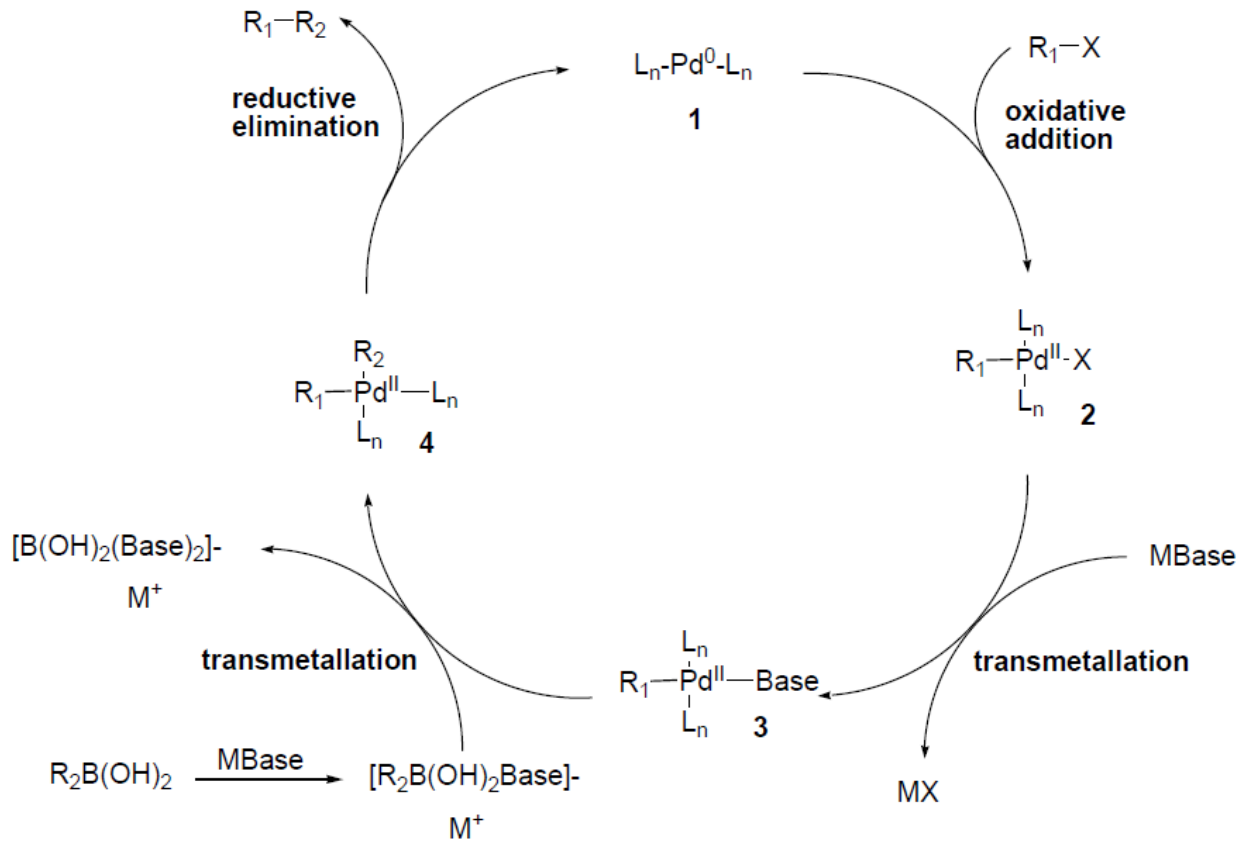
### 1.3.5 Suzuki coupling

The Suzuki cross-coupling reaction is the reaction between organoboronic acids and organic halides, catalyzed by a Pd catalyst. This reaction was first demonstrated by Suzuki in 1979,[39] and is also sometimes referred to as the Suzuki-Miyaura reaction. Suzuki couplings have been applied to aryl-, alkyl-, alkenyl-, and alkynlboranes. Triflates have also been used as electrophiles in the reaction.

The mechanism for the Suzuki reaction is very similar to the general mechanism for Pd-catalyzed cross-couplings (Scheme 1.2). One major difference is that the boronic acid requires activation by a nucleophile in order to complete the reaction due to the low nucleophilicity of

boronic acids. Coordination of hydroxide to boron increases its reactivity towards Pd.[15] The catalytic cycle begins with oxidative addition of the organic halide **25** to the $Pd^0$ catalyst **26** to give intermediate **27** (Scheme 1.5). Next, a transmetallation process occurs where a nucleophile displaces the halogen atom to provide intermediate **28**. This is followed by another transmetallation, this time with the boron-ate complex to give the organopalladium intermediate **29**. Reductive elimination then generates the final cross-coupled product **30** as well as regenerating the original Pd catalyst **26**.[40]

Suzuki couplings are particularly powerful reactions due to their good regioselectivity and stereoselectivity. Suzuki couplings also utilize readily-available reagents, the reagents are stable in water, and the reaction requires only mild conditions. For these reasons, Suzuki couplings are among the most widely-used cross-coupling reactions and have a broad range of applications, including being especially useful in polymer chemistry.[40]




**Scheme 1.7.** General mechanism for a Suzuki coupling.

### 1.4 Catalyst poisoning

The success of a metal-catalyzed cross-coupling reaction is largely dependent on the functionality of the metal catalyst. Metal catalysts are known to be highly sensitive, and susceptible to many factors that can reduce their catalytic ability. Catalyst poisoning is an effect that can occur in organic reactions in which the effectiveness of a catalyst is reduced by another compound. This can be a reactant or product of the reaction, or a contaminant in the reaction medium, that binds to the catalytic active sites, causing these sites to become inaccessible and unable to catalyze the reaction. In large-scale industrial reactions, steps must be taken to ensure removal of potential poisons or to replenish the active catalyst.[41]

Catalyst poisoning can be used advantageously in certain reactions to reduce the efficiency of a strong catalyst prior to reaction. This has been seen in the Rosenmund reduction of acyl chlorides to aldehydes. This reaction utilizes a Pd catalyst on $BaSO_4$, which if left unregulated will over reduce the reactants. The catalyst is poisoned with quinoline-S or other S-containing compounds in order to moderate the catalysis and prevent overreduction.[42] The selective poisoning of a palladium catalyst to fine tune a reaction is well established.[43,44] However, it is a delicate balance of helpful and harmful effects. The poisoning effect has been shown to be dependent on the temperature of the reaction,[45] as well as the solvent used in the reaction.[46]

One of the most common and best-studied catalyst poisons is sulfur. The work presented in this thesis utilized sulfur-containing compounds, dithiolanes and dithianes, in metal-catalyzed cross-coupling reactions; therefore it is important to understand any potential for catalyst poisoning.

Sulfur can have a significant effect on the catalytic properties of palladium, even at very low concentrations.[45,47,48] Sulfur species such as $H_2S$, RSH, and RSSR are poisons for all reduced metal catalysts due to the formation of strong metal-S bonds.[49,50] This has been observed extensively in catalytic hydrogenation reactions where $H_2S$ and $SO_2$ readily poison nickel catalysts.[51]

The poisoning effect sulfur has on a palladium catalyst can be either temporary or permanent. When a catalyst is temporarily inactivated the catalytic properties can be restored by eliminating the poison source or by cleaning the surface of the catalyst. Permanent poisoning results from a poison that cannot be effectively removed from the active site of the catalyst.

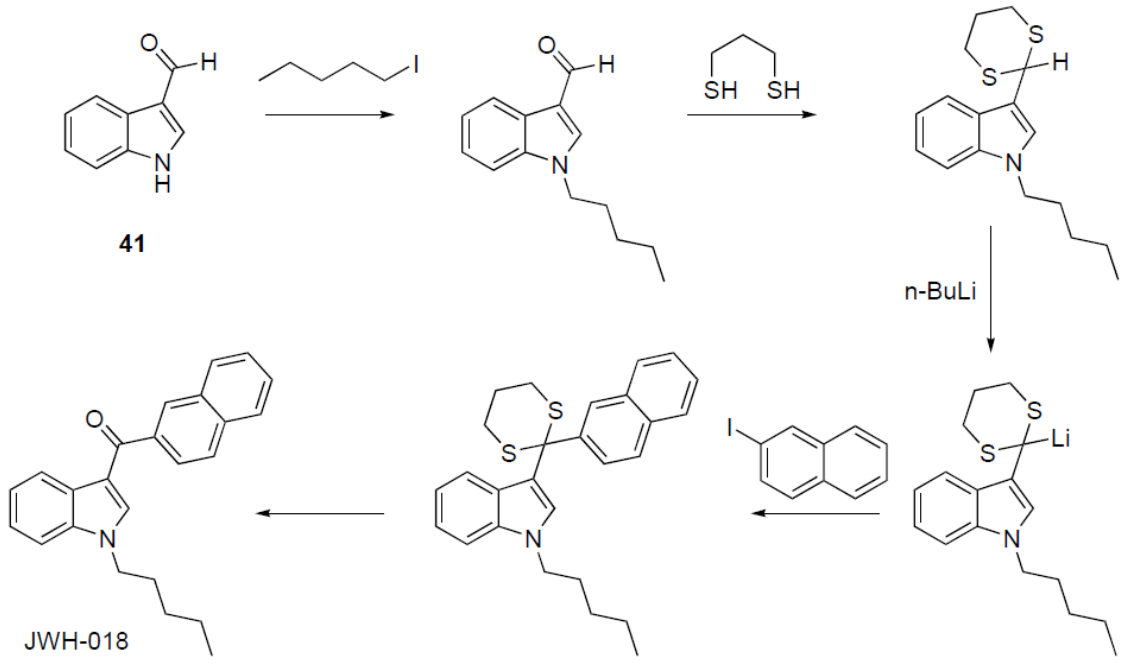
When experiencing permanent poisoning, more catalyst could be added to the reaction to increase the degree of conversion.[47]

There is potential for sulfur containing compounds to poison a catalyst; however there remains a precedent for metal-catalyzed reactions with dithiolanes and dithianes. There are several examples of successful metal-catalyzed reactions in the presence of thioethers. Successful hydrogenation reactions have been demonstrated in the presence of phosphine-thioether ligands by Le Roux *et al.* with Ir and Guimet *et al.* with both Ir and Rh.[52,53] Meindertsma *et al.* was able to do hydrogenation reactions on vinylthioethers with 5 mol% of a Rh catalyst.[54] Thioethers have also been used specifically in metal-catalyzed cross-coupling reactions. Examples include thioether-imidazolinium ligands used in Pd catalyzed Suzuki cross-coupling reactions,[55] and arylthioethers used as a directing group in Pd catalyzed olefination reactions of arenes.[56]

## Chapter 2: Thesis Objectives

### 2.1 Thesis objectives

The objective of this thesis project was to develop conditions to cross-couple dithiolanes/dithianes with aryl halides and to use these techniques for the construction of complex polycyclic biologically relevant structures. An example synthesis of a biologically relevant compound is shown below in Scheme 2.1. It begins with indole-3-carbaldehyde **41**, which was synthesized in this thesis, and follows several steps, including one metal-catalyzed cross-coupling reaction with a dithiane and an aryl halide, to produce a cannabinoid agonist naphthalen-1-yl-(1-pentylindol-3-yl)methanone, also known as JWH-018.




**Scheme 2.1.** Example synthesis of JWH-018 involving a metal-catalyzed cross-coupling reaction between a dithiane and an aryl halide.

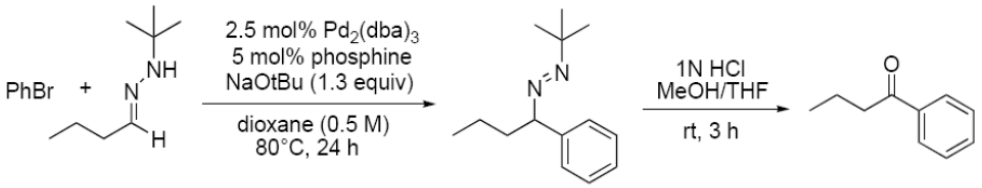
The first challenge was to successfully cross-couple a dithiolane/dithiane in a metal-catalyzed cross-coupling reaction with an aryl halide, next was to optimize these conditions, and then finally to measure the scope of applicability over other ditholane/dithiane-based structures. In optimizing the reaction conditions there were several factors taken into consideration: the base, ligand, catalyst, temperature, and solvent. The goal of this research project was to eventually apply the optimized method to the construction of large, complex ring systems and biologically active molecules.

## 2.2 Premise for research

As stated previously in Chapter 1, **c**reating new carbon-carbon bonds is crucial in organic synthesis; therefore the design of new techniques to do so is of great importance. To the best of my knowledge there have been no previous attempts to create a new carbon-carbon bond between a ditholane/dithiane and an aryl halide in a metal-catalyzed cross-coupling reaction. As was discussed in Chapter 1.2, the protection of carbonyl groups with dithiols is an excellent approach for umpolung chemistry and the acyl anion produced has the potential to be used for cross-coupling. This application has been discussed previously by Takemiya and Hartwig.[57]

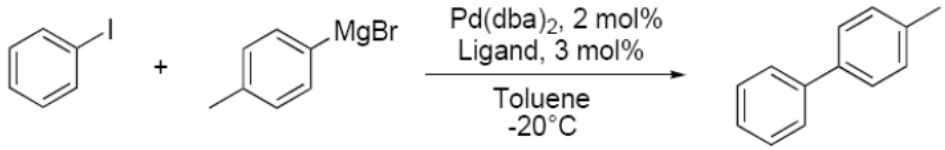
The use of acyl anions in metal-catalyzed cross-coupling reactions has been shown.[57,58] Takemiya and Hartwig demonstrated that a hydrazone acyl anion equivalent did not cross-couple at high yields on their initial attempts. Through optimization of their methods, they were able to identify specific conditions that would reproducibly generate the desired product in high yield.[57] This is illustrated below in Table 2.1. Martin and Buchwald performed similar experiments utilizing a Kumadu-Corriu cross-coupling reaction.[58] These data is summarized in Table 2.2.

**Table 2.1.** Summary of Pd-catalyzed cross-coupling reactions with a hydrazone acyl anion equivalent.[57]

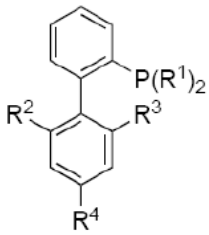



| Entry | Phosphine | Conversion of PhBr (%) | Yield of ketone (%) |
|---|---|---|---|
| 1 | DPPF | 54 | trace |
| 2 | $PPh_3$ (10 mol %) | 77 | 7 |
| 3 | DPPB | 59 | 28 |
| 4 | Q-phos | 100 | 37 |
| 5 | $PtBu_3$ | 100 | 56 |
| 6 | BINAP | 91 | 61 |
| 7 | Xantphos | 100 | 93 |
| 8 | DPEphos | 100 | 99 |

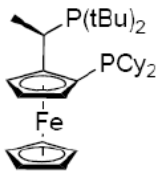
**Table 2.2.** Summary of Kumada-Corriu cross-coupling reaction results by Martin and Buchwald.[58]



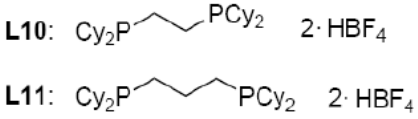

| Entry | Halide/pseudohalide | Ligand | Time (hrs) | Yield (%) | Entry | Halide/pseudohalide | Ligand | Time (hrs) | Yield (%) |
|---|---|---|---|---|---|---|---|---|---|
| 1 | I | $PPh_3$ | 14 | 3 | 13 | I | L4 | 10 | 55 |
| 2 | I | L8 | 14 | 7 | 14 | I | L1 | 10 | 82 |
| 3 | I | L5 | 14 | 9 | 15 | I | L2 | 10 | 93 |
| 4 | I | $P(tBu)_3$ | 14 | 10 | 16 | I | L3 | 6 | 98 |
| 5 | I | L11 | 14 | 17 | 17 | I | None | 6 | 1 |
| 6 | I | L10 | 14 | 19 | 18 | OTf | L5 | 10 | 3 |
| 7 | I | $PCy_3$ | 14 | 21 | 19 | OTf | $PCy_3$ | 10 | 26 |
| 8 | I | L7 | 14 | 21 | 20 | OTf | L2 | 10 | 27 |
| 9 | I | L6 | 14 | 26 | 21 | OTf | L1 | 10 | 34 |
| 10 | I | L9 | 14 | 30 | 22 | OTf | Xantphos | 10 | 41 |
| 11 | I | dppf | 14 | 37 | 23 | OTf | L4 | 10 | 53 |
| 12 | I | Xantphos | 12 | 54 | 24 | OTf | L3 | 10 | 79 |




**L1**: $R^1$=Cy; $R^2$=$R^3$=$R^4$=iPr
**L2**: $R^1$=Cy; $R^2$=$R^3$=OMe; $R^4$=H
**L3**: $R^1$=Cy; $R^2$=$NMe_2$; $R^3$=$R^4$=H
**L4**: $R^1$=tBu; $R^2$=$NMe_2$; $R^3$=$R^4$=H
**L6**: $R^1$=Cy; $R^2$=$R^3$=$R^4$=H
**L7**: $R^1$=tBu; $R^2$=$R^3$=$R^4$=iPr
**L8**: $R^1$=tBu; $R^2$=$R^3$=$R^4$=H
**L9**: $R^1$=tBu; $R^2$=$R^3$=OMe; $R^4$=H




**L5**




As will be presented in Chapter 3, my first attempts did not produce the desired product in high yield, however it was anticipated that we could find suitable conditions and hopefully optimize them to produce the desired product in high yields. The results of this research and a detailed discussion can be found in Chapter 3.

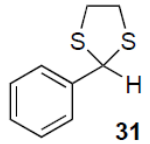
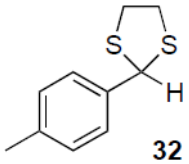
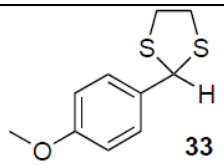
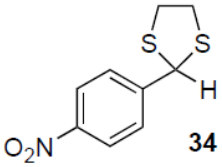
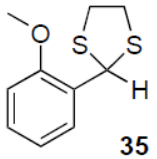
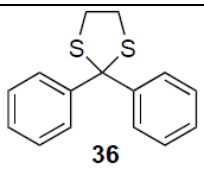
# Chapter 3: Results and discussion

## 3.1 Synthesis of dithiolanes and dithianes

It has been hypothesized that dithiolanes and dithianes would be suitable candidates for metal-catalyzed cross-coupling reactions.[57] Dithiolanes and dithianes have 2 sulfur atoms that help to stabilize carbanions – an acyl anion equivalent. This is an example of umpolung chemistry that inverts the natural reactivity of a carbonyl carbon and allows it to participate in reactions that would not have been possible otherwise.[11]

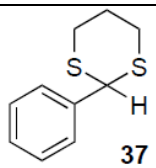
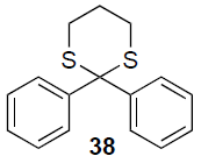
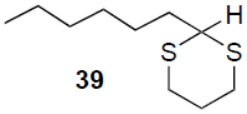
This thesis project was focused on the use of dithiolanes and dithianes for metal-catalyzed cross-coupling reactions. To the best of my knowledge, this has not been accomplished previously. The first step was to synthesize the dithiolanes and dithianes according to General Procedure I (see Chapter 5 – Experimental Procedures). The compounds that were prepared are summarized below in Tables 3.1 and 3.2.

**Table 3.1.** List of dithiolane molecules synthesized.

| Molecule | Structure | Reference Number |
|---|---|---|
| 2-Phenyl-1,3-dithiolane |  **31** | 59 |
| 2-*p*-Tolyl-1,3-dithiolane |  **32** | 59 |
| 2-(4-Methoxyphenyl)-1,3-dithiolane |  **33** | 59 |
| 2-(4-Nitrophenyl)-1,3-dithiolane |  **34** | 60 |
| 2-(2-Methoxyphenyl)-1,3-dithiolane |  **35** | 59 |
| 2,2-Diphenyl-1,3-dithiolane |  **36** | 60 |

Aryl-nitro compounds are prone to decomposition by light, oxygen, and water. This product, structure **34** from table 3.1, was stored under argon and in a vessel that was encased in aluminum foil to prevent decomposition.

**Table 3.2.** List of dithiane molecules synthesized.

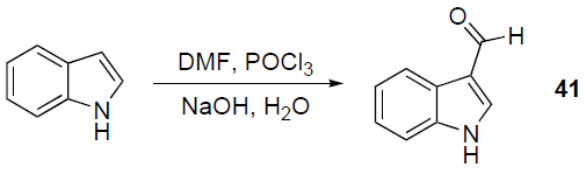
| Molecule | Structure | Reference Number |
|---|---|---|
| 2-Phenyl-1,3-dithiane |  **37** | 59, 61 |
| 2,2-Diphenyl-1,3-dithiane |  **38** | 62 |
| 2-Hexyl-1,3-dithiane |  **39** | 63 |
| 1,3-Dithiane |  **40** | 64 |

We planned to use the Pd-catalyzed reaction between bromobenzene and **31** or **37** to develop conditions for the desired cross-coupling. The expected products 2,2-diphenyl-1,3-dithiolane **36** and 2,2-diphenyl-1,3-dithiane **38** were therefore also prepared according to General Procedure I. They were used in the development of reaction monitoring techniques. It was determined that TLC was unable to demonstrate a difference in $R_f$ value between the starting material and product dithiolane/dithiane using a variety of eluting conditions. Attempts with TLC included the following eluents: 50:1 Hex:EtOAc, 100:1 Hex:EtOAc and re-running the plate several times, hexanes with 5% acetone, hexanes with 5% dichloromethane, hexanes with 5% toluene, hexanes with 5% iso-propanol, petroleum ether with 5% toluene, pure toluene, and pure dichloromethane. As there is no detectable change in polarity between starting material and

product, the affinities of the molecules for the stationary phase and/or mobile phase did not differ. Therefore TLC was not a suitable method to track the reaction progress of a metal-catalyzed cross-coupling reaction of an aryl-halide with 2-phenyl-1,3-dithiolane or with 2-phenyl-1,3-dithiane.

An alternative method for monitoring the reaction progress was needed, and it was determined that using GC-FID would be suitable for this purpose. GC-FID has a number of advantages that makes it an effective technique for studying the progress of an organic synthesis reaction. Running standards and a mixture of standards through the GC-FID instrument can be used to develop a method. Aliquots of reaction mixture quenched, worked up, and then analyzed by GC-FID allow the comparison of their retention times to the standards. These data can also be used to determine the ideal reaction timeline. Finally the results can be reproduced on a full-scale reaction, using an internal standard to quantify reaction progress. The method development for the GC-FID monitoring of metal-catalyzed cross-coupling reactions will be described in detail in section 3.3.

It was anticipated that the attempts at cross-coupling a dithiolane and/or a dithiane would be successful and therefore the next step would be to prepare other aldehydes that are biologically relevant. This would allow the application of this cross-coupling system to complex polycyclic heterocycles. Indole-3-carbaldehyde **41** was chosen as indole compounds are important biological molecules.[65] They are precursors to many pharmaceuticals, including anticancer and antitumor therapeutics.[66] Indole-3-carbaldehyde **41** was prepared using a Vilsmeier-Haack reaction, as described in Chapter 5.[67] Scheme 3.1 below summarizes the reaction.




**41**

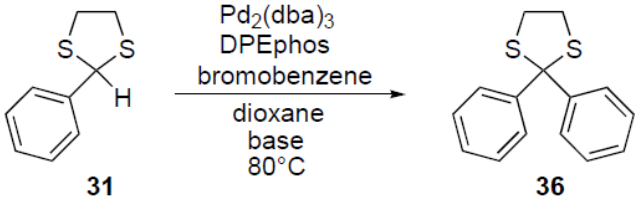
**Scheme 3.1.** Synthesis of indole-3-carbaldehyde.

### 3.2 Dithiolanes in metal-catalyzed cross-coupling reactions

Dithiolanes are attractive candidates for use in metal-catalyzed cross-coupling reactions. The use of this functional group in these types of reactions has not previously been demonstrated. This would offer a new tool for organic chemists to use in synthesis; therefore successful completion of this reaction would be highly desirable.

The expected mechanism would follow a typical metal-catalyzed cross-coupling reaction as described in Chapter 1, Scheme 1.2. Numerous attempts were made to cross-couple 2-phenyl-1,3-dithiolane **31** with bromobenzene. These attempts are summarized below in Table 3.3. In each reaction no desired product was observed. The crude NMR spectrum that was collected from reaction entry 1 in Table 3.3 is displayed. along with the NMR spectrum of the starting material in Fig. 3.1. Crude NMR and GC-MS results confirmed that the majority of extracted reaction material was unreacted starting material and a trace amount of impurities.

**Table 3.3.** Cross-coupling reaction attempts with 2-phenyl-1,3-dithiolane **31** and bromobenzene.




**31** **36**

| Entry | Base | Temperature (°C) | Time (hrs) | Result of the Reaction |
|---|---|---|---|---|
| 1 | NaOtBu | 80 | 16 | No Reaction |
| 2 | LiTMDS | 80 | 16 | No Reaction |
| 3 | LDA | 80 | 16 | No Reaction |
| 4 | NaOtBu | 80 | 8 | No Reaction |
| 5 | LiTMDS | 80 | 8 | No Reaction |

* See experimental procedure 5.11.1, page 90.

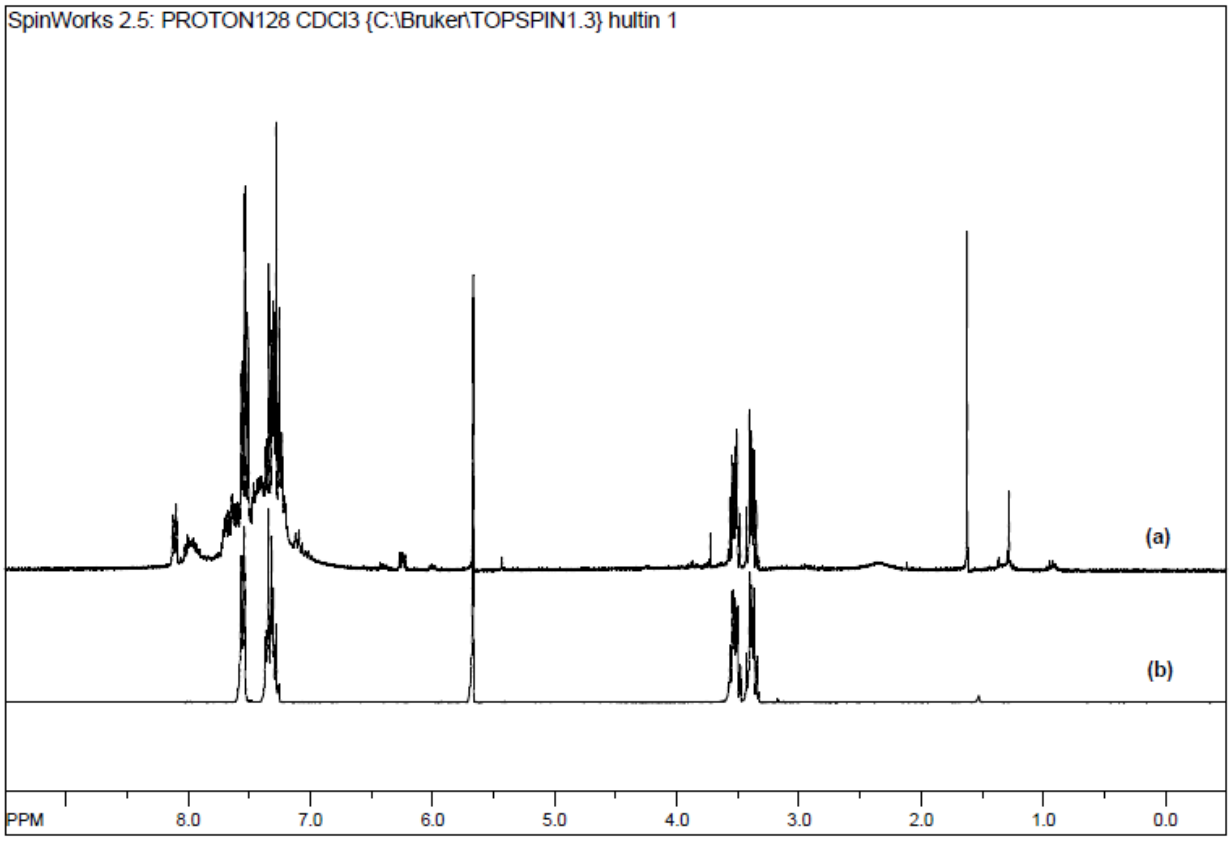
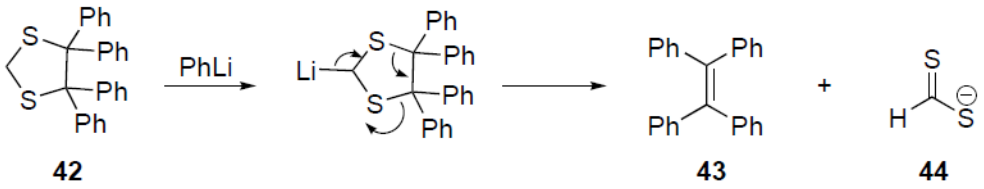



**Fig. 3.1.** $^{1}$H-NMR spectra of cross-coupling reaction attempts with 2-phenyl-1,3-dithiolane and bromobenzene. **(a)** Crude spectrum from entry 1 of Table 3.3. **(b)** Spectrum of starting material.

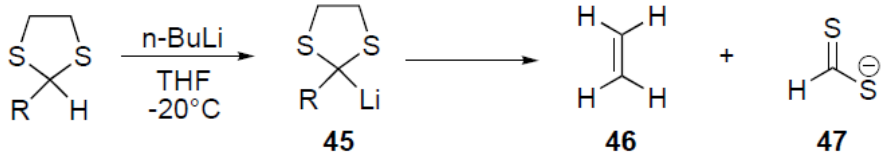
Attempts were made to complete this reaction; however they were unsuccessful. It was discovered that other researchers had used the anion derived from **31** in reactions and found that dithiolane carbanions were prone to decomposition. It was originally proposed by Schönberg *et al.* in 1931 that the decomposition was occurring through facile elimination pathways (Scheme 3.2[68]). Schönberg *et al.* reacted 4,4,5,5-tetraphenyl-1,3-dithiolane **42** with phenyllithium and found that 1,1,2,2-tetraphenylethene **43** and methanedithioate **44** were produced.




**42** **43** **44**

**Scheme 3.2.** The reaction of 4,4,5,5-tetraphenyl-1,3-dithiolane with phenyllithium to produce 1,1,2,2-tetraphenylethene and methanedithioate, as demonstrated by Schönberg *et al.*[68]

Dithiolanes were later used by Seebach and Corey in 1975[(69)] when they tried to use them as nucleophilic acylating agents. They quickly observed the reactions failed because the dithiolane was undergoing facile elimination to yield ethylene **46** and dithiocarbonate **47**.[69] This decomposition of the dithiolane is shown below in Scheme 3.3.

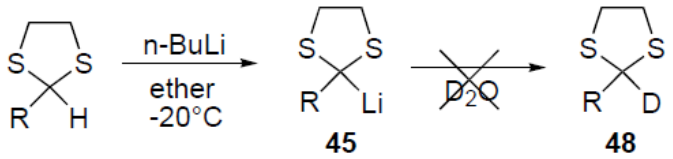



**45** **46** **47**

**Scheme 3.3.** Decomposition of dithiolane as determined by Seebach and Corey.[69]

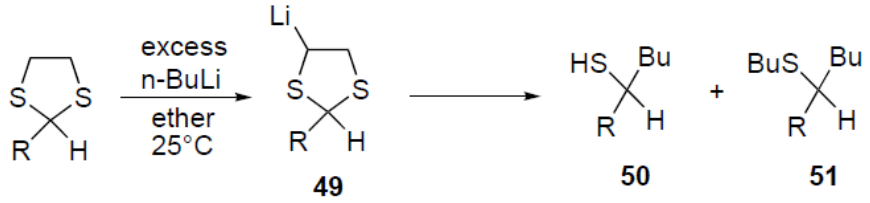
The proposed mechanism of decomposition by elimination was later investigated by Wilson *et al.*[70] in 1980. They observed that when a dithiolane was treated with *n*-BuLi in ether

at -20° and then quenched with $D_2O$ that the deuterated dithiolane **48** was not observed by GC-MS.[70] This is shown below in Scheme 3.4.




**Scheme 3.4.** $D_2O$ quench of dithiolane as shown by Wilson *et al.*[70]

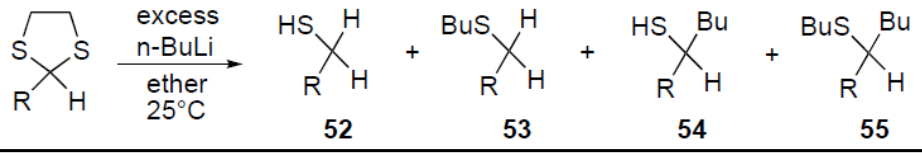
Using an excess of *n*-BuLi in ether at 25°C, Wilson *et al.* again did not observe the predicted deuterated dithiolane **48** but instead observed a mixture of thiol **50** and thiolane **51**. This is illustrated below in Scheme 3.5. This led Wilson *et al.* to conclude that 2-lithio-1,3-dithiane **45** was not produced under these conditions but rather that the reaction progressed through the proposed intermediate 5-lithio-1,3-dithiane **49** shown in Scheme 3.5.[70]




**Scheme 3.5.** Reaction of dithiolane with excess *n*-BuLi as performed by Wilson *et al.*[70]

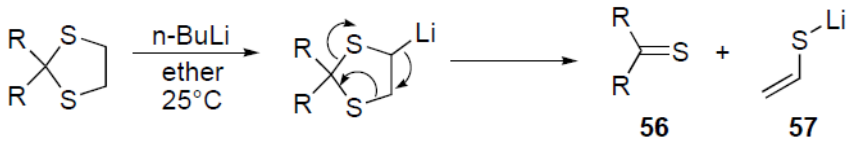
Wilson *et al.* hypothesized that if the initial cleavage formed a thiocarbonyl intermediate it would explain how the impurities formed. These observations influenced Wilson *et al.* to perform more experiments and determine if the results could be controlled, if they were reproducible, and if there were promising applications for these methods.[70] Their attempts are summarized below in Table 3.4.

**Table 3.4.** Summary of experiments by Wilson *et al.* cleaving dithiolane with *n*-BuLi.[70]




| R group | Molar Equivalent | Temperature (°C) | Time (min) | Solvent | % of unreacted starting material | % of product **52** | % of product **53** | % of product **54** | % of product **55** |
|---|---|---|---|---|---|---|---|---|---|
| $C_6H_{13}$ | 1.0 | -20 | 30 | ether | 86 | 0.3 | 2 | 7 | 2 |
| $C_6H_{13}$ | 1.0 | 0 | 30 | ether | 74 | 1 | 4 | 17 | 2 |
| $C_6H_{13}$ | 1.0 | 0 | 30 | THF | 92 | 1 | 4 | 2 | 0 |
| $C_6H_{13}$ | 4.0 | 25 | 240 | ether | 0 | 3 | 4 | 73 | 19 |
| $C_5H_{11}$ | 4.0 | 25 | 240 | ether | 0 | 2 | 7 | 67 | 22 |

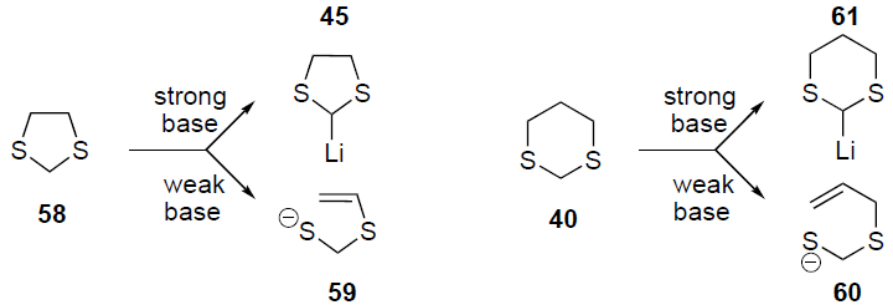
This work culminated with success as Wilson *et al.* were able to use their results to demonstrate that this method allowed dithiolanes to be synthesized into non-trivial secondary mercaptans, and separately that dithiolanes could be used to execute carbonyl transposition.[70] Further work from Wilson *et al.* proposed a mechanism for the formation of the thiocarbonyl intermediate **56** and lithium ethenethiolate **57**.[71] This mechanism is shown in Scheme 3.6.




**Scheme 3.6.** Mechanism for the cleavage/reduction of dithiolane as proposed by Wilson *et al.*[71]

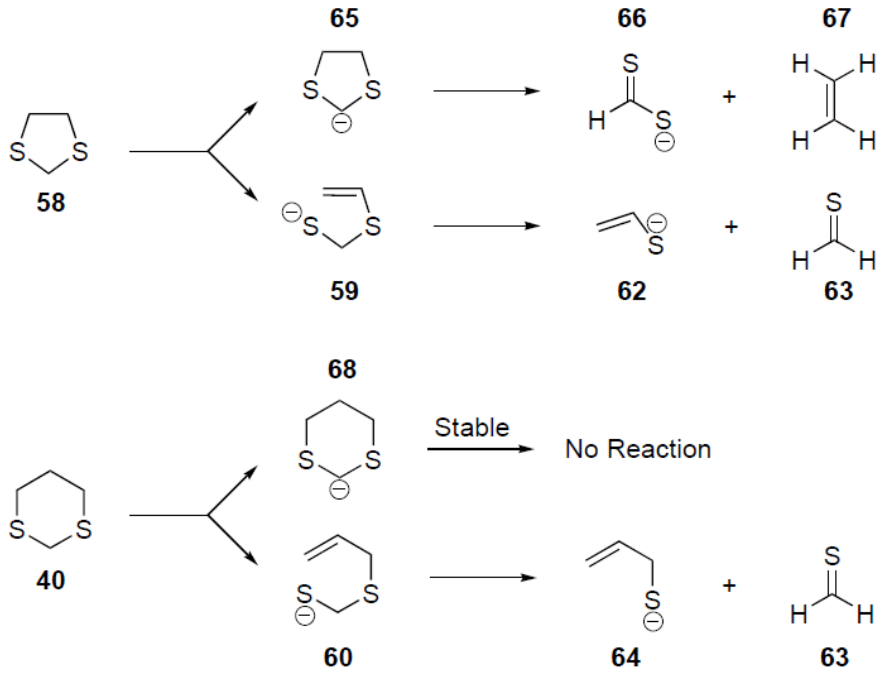
The study supporting the above mechanism was conducted on both 1,3-dithiolane **58** and 1,3-dithiane **40**. It was demonstrated that the anion formed from the deprotonation of **58** and **40** could be controlled by the strength of base that was used. A weaker base was shown to produce the E2-type elimination products **59** and **60** that were observed by Seebach and Corey,[69] while a

stronger base deprotonated at the C-2 position providing the desired 2-lithio-1,3-dithiolane **45** and 2-lithio-1,3-dithiane **61**. This is illustrated in Scheme 3.7.




**Scheme 3.7.** Mode of deprotonation for 1,3-dithiolane and 1,3-dithiane as proposed by Wilson *et al.*[71]

The experiments completed by Wilson *et al.* provided direct evidence for the E2-type intermediates and their subsequent decomposition: vinylthiomethanethiolate **59** broke down into ethenethiolate **62** and methanethial, **63,** and allylthiomethanethiolate **60** gave 2-propene-1-thiolate **64** and methanethial **63**. Wilson *et al.* were able to provide evidence that 1,3-dithiolan-2-ide **65** was not stable to a [2 + 4] cycloreversion and therefore decomposed to form methanedithioate **66** and ethylene **67**. Another important conclusion from this research was that 1,3-dithian-2-ide **68** was reasonably stable and could therefore be used for subsequent reactions.[71] These results are summarized below in Scheme 3.8.




**Scheme 3.8.** Deprotonation of dithiolane and dithiane as shown by Wilson *et al.*[71]

This led me to conclude that dithiolanes, such as 1,3-dithiolane **58**, are not suitable candidates for metal-catalyzed cross-coupling reactions. I was also able to conclude that dithianes, such as 1,3-dithiane **40**, are reasonably stable and have the potential to react successfully in metal-catalyzed cross-coupling reactions. I therefore continued to explore palladium-catalyzed metal cross-coupling reactions exclusively with dithianes.

### 3.3 Monitoring reaction progress

Initial attempts to monitor reaction progress of the metal-catalyzed cross-coupling reactions utilized thin-layer chromatography (TLC). The resolution was extremely poor; therefore a new technique was needed to monitor reaction progress.

In order to expedite the collection of results, an analysis method using GC-FID was developed. This method included conducting micro-workups of aliquots removed from reactions

in progress at given time intervals, extracting and then analyzing the crude material by GC-FID to determine the reaction progress. Pure standard samples of starting compounds and products were run through the GC-FID to determine their retention times for a given GC-FID method. Next they were run through in a mixture to give evidence of their retention times in a complex mixture and to demonstrate that each peak was properly resolved from one another. Multiple GC-FID methods were developed at different times for different applications. The list of structures and their retention times are summarized in the following 3 tables, Table 3.5, Table 3.6, and Table 3.7.

**Table 3.5.** Summary of retention times for starting materials, products, and possible byproducts using standard GC-FID method # 1. Gradient Programming: 70°C, 2 min; 20°C/min, 5 min → 170°C; 30°C/min, 3 min → 260°C; 260°C, 15 min.

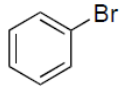
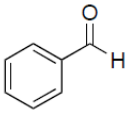
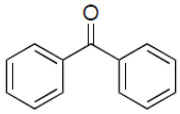
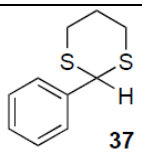
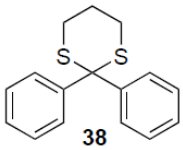
| Structure | Name | Retention Time (min) |
|---|---|---|
|  | Bromobenzene | 5.4 |
|  | Benzaldehyde | 6.7 |
|  | Benzophenone | 11.8 |
|  **37** | 2-phenyl-1,3-dithiane | 13.6 |
|  **38** | 2,2-diphenyl-1,3-dithiane | 22.7 |

**Table 3.6.** Summary of retention times for starting materials, products, and possible byproducts using standard GC-FID method # 2. Gradient Programming: 70°C, 7 min; 10°C/min, 10 min → 170°C; 20°C, 4.5 min → 260°C; 260°C, 7 min.

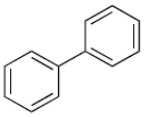
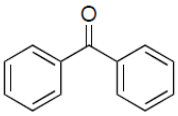
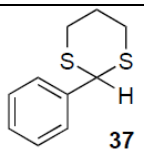
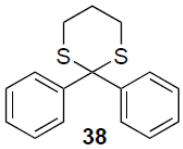
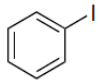
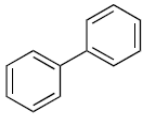
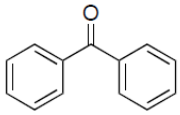
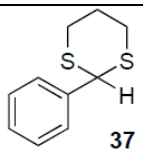
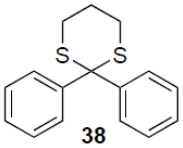
| Structure | Name | Retention Time (min) |
|---|---|---|
|  | Toluene | 2.9 |
|  | Iodobenzene | 12.5 |
|  | Biphenyl | 16.1 |
|  | Benzophenone | 18.4 |
|  **37** | 2-Phenyl-1,3-dithiane | 19.6 |
|  **38** | 2,2-Diphenyl-1,3-dithiane | 26.8 |

**Table 3.7.** Summary of retention times for starting materials, products, and possible byproducts using standard GC-FID method # 3. Gradient Programming: 70°C; 40°C/min, 4.75 min → 260°C; 260°C, 11 min.

| Structure | Name | Retention Time (min) |
|---|---|---|
|  | Iodobenzene | 3.1 |
|  | Biphenyl | 4.4 |
|  | Benzophenone | 5.8 |
|  37 | 2-Phenyl-1,3-dithiane | 6.7 |
|  38 | 2,2-Diphenyl-1,3-dithiane | 13.9 |

In the development of standard GC-FID method # 1 the aryl-halide being used was bromobenzene. In all reactions that were analyzed with this GC-FID method there was no evidence of trace amounts of benzaldehyde and therefore it was not included in the later-developed GC methods. It was hypothesized that one trace impurity observed in standard GC-FID method # 1 might result from the homocoupling of bromobenzene to produce biphenyl. Once this material was acquired it was added as a standard to be run in the GC-FID method.

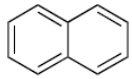
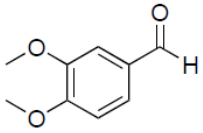
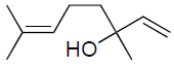
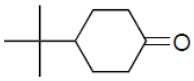
Acquisition of this did not take place until standard GC-FID method # 2 was created and being used to monitor reaction progress.

Standard GC-FID method # 2 was developed because it was anticipated that the GC-FID method would become used as a quantitative method of analysis using an internal standard. As such it was desirable to have all possible components of interest coming off the column after the solvent front had finished eluting. To achieve this result, gradient thermal programming was used to slowly increase the column temperature. This would allow the less volatile materials to be retained in the column for a longer period of time. During the development of standard GC-FID method # 2, the aryl-halide was switched from bromobenzene to iodobenzene. This meant that iodobenzene was the most volatile component of interest and standard GC-FID method # 2 was developed to have iodobenzene elute after the solvent front.

Standard GC-FID method # 3 was created to expedite the collection of results. Since several reactions were being run simultaneously and the time required to collect the GC-FID data for a single reaction was slightly longer than 30 minutes, it was necessary to reduce the experiment time in order to collect meaningful results while the reaction was still in progress.

The following compounds were tested for their suitability as internal standards: naphthalene, 3,4-dimethoxybenzaldehyde, linalool, and 4-tert-butyl-cyclohexanone. These potential internal standards, their structures, and their corresponding retention times in standard GC-FID method # 3 are summarized in Table 3.8. It was determined that naphthalene was the best candidate for an internal standard because it was believed that naphthalene would not react under the reaction conditions, it would not interfere with the desired reaction, and its retention time in the GC-FID methods was well resolved from all of the starting and product materials as well as any expected impurities.

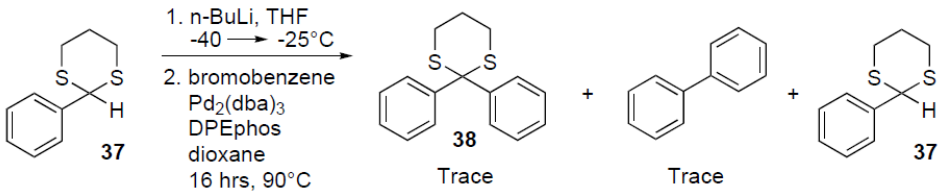
**Table 3.8.** Summary of retention times for possible internal standards according to standard GC-FID method # 3.

| Structure | Name | Retention Time (min) |
|---|---|---|
|  | Naphthalene | 8.1 |
|  | 3,4-<br>Dimethoxybenzaldehyde | 11.2 |
|  | Linalool | 6.7 |
|  | 4-Tert-butyl-cyclohexanone | 7.5 |

### 3.4 Dithianes in metal-catalyzed cross-coupling reactions

We next examined whether 2-phenyl-1,3-dithiane **37** could be used in a cross-coupling reaction with bromobenzene. To accomplish this 2-phenyl-1,3-dithiane **37** was placed in THF and then trerated with *n*-BuLi. An aliquot of this reaction mixture was removed and quenched with $D_2O$ to verify the formation of 2-lithio-2-phenyl-1,3-dithiane, this will be discussed in more detail in section 3.4.3. The remainder was used in an attempt at a metal-catalyzed cross-coupling reaction. Aliquots of the reaction were removed periodically and subsequent workup and analysis by GC-FID determined that a trace amount of the desired product **38** and a trace amount of biphenyl, the homocoupling product of bromobenzene, had formed. A final aliquot was analyzed and it was seen that over the course reaction there was no change in the percent conversion of forming either the desired product or biphenyl. The remainder of the reaction

material was assumed to be unreacted starting material, 2-phenyl-1,3-dithiane **37**, due to having the same retention time in the GC-FID analysis as the standard starting material did. This is summarized below in Scheme 3.9.

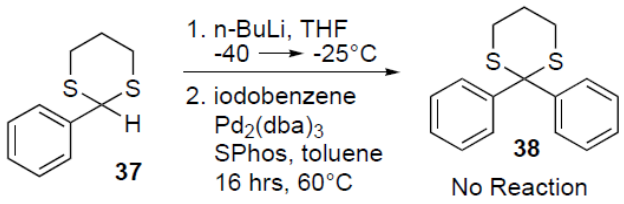



**Scheme 3.9.** 2-Phenyl-1,3-dithiane cross-coupling reaction. See experimental procedure 5.11.2, page 91.

Since a trace amount of product was observed, this indicated a positive result and reinforced the original objective, which was to determine the viability of a metal-catalyzed cross-coupling reaction with dithianes. Repeated attempts under the same and similar reaction conditions were unable to provide more than a trace amount of the desired product **38**.

Next, the reaction conditions were varied to try to optimize the reaction. The procedure remained the same for producing 2-lithio-2-phenyl-1,3-dithiane in THF and used the same Pd catalyst, however the aryl halide was changed to iodobenzene, the ligand was changed to SPhos, and the co-solvent was changed from dioxane to toluene. Iodobenzene being more electrophilic and reactive than bromobenzene was predicted to be able to increase the yield of product. Also, by varying the ligand from the bidentate DPEphos to the monodentate SPhos, this would decrease the steric hindrance effect of the ligand and increase the rate of transmetallation. These reaction conditions were chosen based on previous work.[58] The reaction was also only heated to 60$^{o}$C as we hypothesized that higher temperatures may have decomposed the reacting materials.

The reaction scheme is shown below in Scheme 3.10. No desired product was observed from these attempts. Only unreacted starting material was observed, as determined by the retention times measured in the GC-FID analysis.




**Scheme 3.10.** 2-Phenyl-1,3-dithiane cross-coupling reaction, attempted optimization conditions. See experimental procedure 5.11.3, page 91.

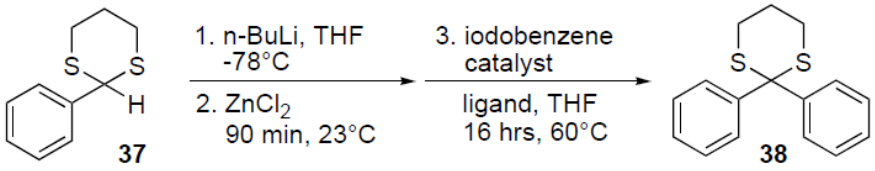
Attempts at improving this reaction were unsuccessful, and therefore I proceeded forward with Negishi cross-coupling reactions. It was expected that the reaction would more successful due to the fact that Negishi cross-couplings reactions make use of a more stable metallating agent.

### 3.4.1 Negishi reactions

As described in section 1.3.4, a Negishi cross-coupling reaction uses a nickel or palladium catalyst to cross-couple an organozinc compound with an organic halide. There are several advantages of the Negishi cross-coupling reaction. One advantage is transmetallating the organolithium species into an organozinc species. This is because organozinc compounds are more stable than the organolithium species, since they are less basic, and therefore might provide a higher prospect for a successful reaction.[72] It is expected that the organozinc species will be stable at higher temperatures and for a longer period of time.[38,72] Another advantage is that the

Negishi cross-coupling reaction has been demonstrated to be tolerant of steric bulk.[73] Creating a polycyclic product such as 2,2-diphenyl-1,3-dithiane will be bulky; therefore Negishi cross-couplings are advantageous in this regard. The Negishi cross-coupling reaction is the most versatile method for aryl-aryl c-c bond formation.[74]

In order to execute a Negishi cross-coupling with 2-phenyl-1,3-dithiane and iodobenzene transmetallation must occur. Once formed, 2-Lithio-2-phenyl-1,3-dithiane was treated with $ZnCl_2$ to produce (2-phenyl-1,3-dithian-2-yl)zinc(II) chloride, which was then used in Negishi cross-coupling attempts. This procedure was performed as previously described.[75] The reaction scheme is summarized below in Scheme 3.11.




**Scheme 3.11.** Negishi coupling of 2-phenyl-1,3-dithiane.

Several attempts were made at Negishi cross-coupling reactions. These data are summarized below in Table 3.9.

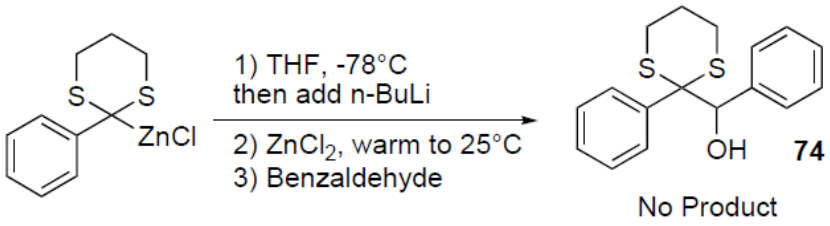
**Table 3.9.** Summary of Negishi coupling reaction attempts with varied reaction conditions.

| Entry | Catalyst | Ligand | Temperature (°C) | Time (hrs) | Result |
|---|---|---|---|---|---|
| 1 | $Pd_2(dba)_3$ | DPEphos | 60 | 16 | No Product |
| 2 | $Pd_2(dba)_3$ | $PCy_3 \cdot HBF_4$ | 60 | 16 | No Product |
| 3 | $Pd_2(dba)_3$ | Xantphos | 60 | 16 | No Product |
| 4 | $Pd_2(dba)_3$ | DPPF | 60 | 16 | No Product |
| 5 | $Pd_2(dba)_3$ | DPPB | 60 | 16 | Trace Product |
| 6 | $Pd(PPh_3)_4$ | | 60 | 16 | Trace Product |

* See experimental procedure 5.11.4, page 92.

Entries 1 – 5 all used $Pd_2(dba)_3$ as the catalyst source but varied the ligand that was used. Entry 6 used $Pd(PPh_3)_4$ as the catalyst and ligand. Every attempt was analyzed by GC-FID and the bulk of the reaction material in each case was unreacted starting material. When using $Pd_2(dba)_3$ and DPPB a trace amount of product was observed, and when using $Pd(PPh_3)_4$ a trace amount of product was again observed. In all other attempts no evidence of the desired product was detected.

Due to the poor results obtained from attempts at Negishi cross-coupling reactions I attempted to demonstrate the reactive potential of the organozinc complex. This control reaction was done by adding an electrophile, such as benzaldehyde, to the solution containing the organozinc complex. A positive reaction would have provided evidence that 2-lithio-2-phenyl-1,3-dithiane was being transmetallated to the organozinc complex successfully; since it has been demonstrated that organozinc reagents readily react with electrophilic carbonyl groups.[76] Unfortunately no reaction was observed and therefore I could not confirm that the organozinc complex was formed properly. This is summarized below in Scheme 3.12. This and other control reactions will be discussed in greater detail in section 3.4.3.




**Scheme 3.12.** Control reaction with (2-phenyl-1,3-dithian-2-yl)zinc(II) chloride and benzaldehyde.

The failure of this reaction was not scrutinized, however there are some theories that suggest reasons why the reaction did not progress as expected. Recall that Scheme 1.4 showed a typical mechanism of the Negishi reaction. There may have been a steric effect from 2-lithio-2-phenyl-1,3-dithiane that prevented the transmetallation to (2-phenyl-1,3-dithian-2-yl)zinc(II) chloride. Additionally, steric effects may have obstructed the ability of the cis-trans isomerization process. This would then prevent reductive elimination of the desired product. Lastly, all attempts at this reaction used monodentate phosphine ligands or bidentate bis-phosphine ligands. There were no attempts that used a bidentate-N,P ligand. A bidentate-N,P ligand could have promoted reductive elimination because of the greater flexibility in the chelation of the ligand.

Of all the attempts at the Negishi reaction, the best result was the GC-FID observation of a suspected trace amount of desired product. This was shown in Table 3.9 entries 5 and 6. Aside from these attempts no other reaction was able to produce any evidence that the desired product was forming. As well, an attempt at a control reaction of simply adding the organozinc compound to an electrophile failed to produce that desired product, **74**. At this point it was

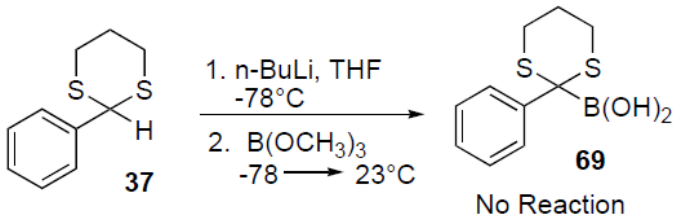
assumed that the Negishi reaction was not going to be a viable option and my attention moved towards other metal-catalyzed cross-coupling reactions, such as the Suzuki reaction.

### 3.4.2 Suzuki reactions

As was discussed in section 1.3.5, the Suzuki cross-coupling reaction is a Pd-catalyzed reaction between organoboronic acids and organic halides. This reaction was attempted because there are numerous advantages of Suzuki reactions, such as the availability of reagents and the mild reaction conditions. Suzuki reactions are generally unaffected by water, applicable to a broad range of functional groups, and the inorganic byproduct is non-toxic and easily removed from the reaction mixture.[77]

#### 3.4.2.1 Synthesizing 2-phenyl-1,3-dithian-2-ylboronic acid

The first approach to Suzuki cross-coupling reactions began by attempting to prepare 2-phenyl-1,3-dithian-2-ylboronic acid **69**. For this, 2-phenyl-1,3-dithiane **37** was treated with *n*-BuLi to form the corresponding anion, and then $B(OCH_3)_3$ was added. This is summarized below in Scheme 3.13.




**Scheme 3.13.** Suzuki cross-coupling of 2-phenyl-1,3-dithiane. See experimental procedure 5.11.5, page 93.

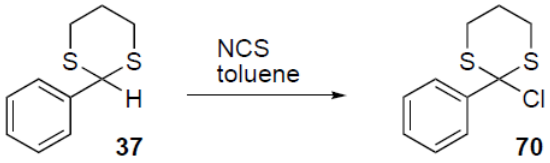
Upon workup the only material that was isolated was unreacted starting material **37**. This reaction was attempted multiple times without success. In one attempt more time was given for 2-lithio-2-phenyl-1,3-dithiane to mix with the boron ester at –78°C prior to slowly warming to room temperature. Another type of control reaction was attempted to prove that 2-lithio-2-phenyl-1,3-dithiane formed quantitatively, which is necessary for boronic acid **69** to form properly. This was done by treating 2-phenyl-1,3-dithiane **37** with *n*-BuLi and then removing an aliquot and quenching with $D_2O$. This control reaction will be discussed in greater detail in Section 3.4.3. 2-Lithio-2-phenyl-1,3-dithiane was shown to be created successfully; however boronic acid **69** was not synthesized successfully. As such, 2-phenyl-1,3-dithian-2-ylboronic acid **69** was not used in Suzuki cross-coupling.

Since 2-lithio-2-phenyl-1,3-dithiane was created successfully there must have been a factor that prevented the formation of boronic acid **69**. This was likely due to steric effects. The dithianyl anion is quasi-tertiary and displacement from the borate would proceed by an addition then elimination sequence; therefore one would expect there to be strain energy in the transformation. This reaction could have been promoted through the use of a chloroborate, a more reactive electrophile. Using $BCl_3$ may have promoted the reaction, and then subsequent workup in aqueous conditions would then produce the desired product, 2-phenyl-1,3-dithian-2-ylboronic acid **69**.

#### 3.4.2.2 Synthesizing 2-halo-2-phenyl-1,3-dithianes

Since boronic acid **69** was unable to be synthesized correctly I attempted the Suzuki reaction from the opposite strategy. I tried to prepare a 2-halo-2-phenyl-1,3-dithiane for the purpose of combining it with a commercially purchased aryl boronic acid in a Suzuki cross-

coupling reaction. The attempted synthesis of 2-chloro-2-phenyl-1,3-dithiane is outlined below in Scheme 3.14.




**Scheme 3.14.** Synthesis of 2-chloro-2-phenyl-1,3-dithiane. See experimental procedure 5.11.6, page 94.

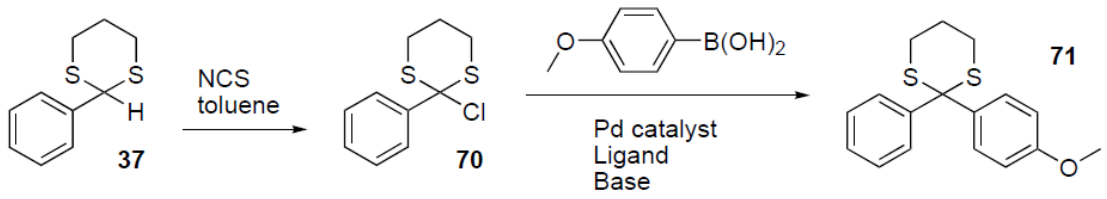
A method to prepare 2-chloro-1,3-dithiane has previously been published[78] and has been shown to be used in many applications[79,80]. It was thought that this method would be suitable to prepare 2-chloro-2-phenyl-1,3-dithiane.

Under an argon atmosphere N-chlorosuccinimide was slowly added over a period of 1 hour to a solution of 2-phenyl-1,3-dithiane **37** in toluene. The reaction progressed for another hour while the temperature was maintained between 20–25°C by intermittent external cooling of the reaction vessel. While still under an argon atmosphere the crude reaction mixture was submitted for NMR analysis.

The results of the NMR analysis on the crude mixture suggested that **37** had been quantitatively converted to the desired product **70**. This was interpreted from the disappearance of the 2-hydrogen signal that was previously found at approximately 5.19 ppm in the $^{1}$H-NMR spectrum.

Assuming that 2-chloro-2-phenyl-1,3-dithiane was synthesized quantitatively this material was then carried into the next step of the Suzuki cross-coupling reaction. 2-Chloro-2-phenyl-1,3-dithiane was prepared *in situ* and then added to a solution containing the remainder of

the Suzuki reaction materials; catalyst, ligand, base, and aryl boronic acid. This attempt is summarized below in Scheme 3.15.




**Scheme 3.15.** *In situ* synthesis of 2-chloro-2-phenyl-1,3-dithiane for Suzuki cross-coupling reactions.

Numerous attempts were made at the synthesis described in Scheme 3.15. The ligand and/or catalyst were varied using 5 different sets of conditions, and the base was varied between $Cs_2CO_3$ and CsF for each condition, for a total of 10 different attempts at the Suzuki cross-coupling reaction. The results are summarized below in Table 3.10. Analysis by GC-FID did not show any evidence of the desired product in all of the attempts. The only material detected was assumed to be unreacted starting material **37**, as determined by the retention time in the GC-FID analysis.

**Table 3.10.** Summary of Suzuki cross-coupling attempts with 2-chloro-2-phenyl-1,3-dithiane and 4-methoxyphenylboronic acid.

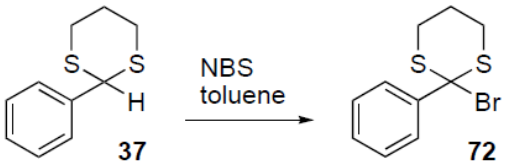
| Entry | Catalyst | Ligand | Base | Time (hrs) | Result |
|---|---|---|---|---|---|
| 1 | $Pd_2(dba)_3$ | DPEPhos | | 16 | No Product |
| 2 | $Pd_2(dba)_3$ | $PCy_3{\cdot}HBF_4$ | | 16 | No Product |
| 3 | $Pd_2(dba)_3$ | Sphos | $Cs_2CO_3$ | 16 | No Product |
| 4 | $Pd_2(dba)_3$ | DPPF | | 16 | No Product |
| 5 | $Pd(PPh_3)_4$ | | | 16 | No Product |
| 6 | $Pd_2(dba)_3$ | DPEPhos | | 16 | No Product |
| 7 | $Pd_2(dba)_3$ | $PCy_3{\cdot}HBF_4$ | | 16 | No Product |
| 8 | $Pd_2(dba)_3$ | Sphos | CsF | 16 | No Product |
| 9 | $Pd_2(dba)_3$ | DPPF | | 16 | No Product |
| 10 | $Pd(PPh_3)_4$ | | | 16 | No Product |

* See experimental procedure 5.11.7, page 94.

The failure to produce the desired product **71** led to speculation that 2-chloro-2-phenyl-1,3-dithiane **70** was not being synthesized correctly and more analysis was needed. Therefore the synthesis of **70** was repeated and subjected to more scrutiny.

The reaction described in Scheme 3.14 was performed directly in an NMR tube in order to collect live data on the reaction progress. It was shown that after only 40 minutes the entire 2-hydrogen peak at approximately 5.19 ppm in the $^1$H-NMR had disappeared. At that point the crude reaction material was immediately subjected to GC-MS analysis. The analysis of the entire GC-MS spectrum demonstrated that the exact mass of **70** (m/z = 230/232 g/mol) did not appear in any of the peaks. A detailed analysis of the MS data from each peak separated by GC suggested the formation of several byproducts; including benzaldehyde, benzoyl chloride, (dichloromethyl)benzene, (trichloromethyl)benzene, 1,2-dithiolane, 1,2-dithiolane-1-oxide, and 1,2-dithiolane-1,1-dioxide (For data see Appendix II: pg 134 – 140).

Upon closer analysis using NMR and GC-MS it was determined that **70** was not being formed properly and therefore the Suzuki cross-coupling reaction would not be able to work as expected. This concluded the attempts at preparing 2-chloro-2-phenyl-1,3-dithiane and it was then attempted to prepare the 2-bromo analogue. This is shown below in Scheme 3.16.




**37** **72**

**Scheme 3.16.** Synthesis of 2-bromo-2-phenyl-1,3-dithiane. See experimental procedure 5.11.8, page 95.

Initially attempts at this reaction were prepared in an NMR tube to monitor the reaction progress. Once the peak for the 2-hydrogen from **37** at approximately 5.19 ppm in the $^{1}$H-NMR had disappeared the reaction mixture was submitted directly for GC-MS analysis. GC-MS data demonstrated that desired product **72** was not formed. A detailed analysis of the MS data from each peak separated by GC suggested the formation of several byproducts; including (dibromomethyl)benzene, 1,2-dithiolane, and unreacted starting material **37** (For data see Appendix II: pg 141 – 144).

2-Bromo-2-phenyl-1,3-dithiane **72** could not be properly synthesized and therefore it was not attempted to be cross-coupled with an aryl boronic acid in a Suzuki reaction.

The failure of these reactions could be attributed to poor purity of the halogenating agents, NCS and NBS. These succinimides were several years old and were not purified prior to their use. A contamination in this material could have protonated 2-lithio-2-phenyl-1,3-dithiane back into the starting material, 2-phenyl-1,3-dithiane **37**. Additionally, the succinimides were

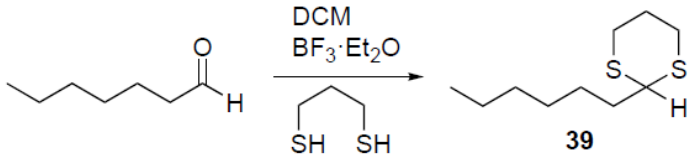
used in great excess therefore increasing the total amount of contamination in the reaction mixture. To test the theory that contamination was causing the reaction to fail the succinimides should be purified prior to starting the reaction. This can be done by recrystallization. NCS can be recrystallized with benzene or toluene,[81] and NBS can be recrystallized with water.[82]

### 3.4.3 Control reactions

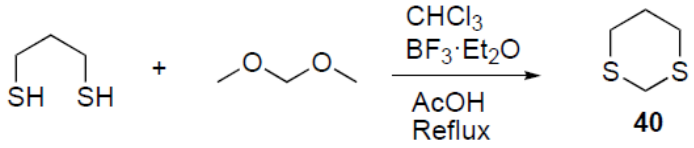
Three types of control reactions were performed while investigating the formation, reactivity, and stability of a 2-lithio-1,3dithiane:

1. A $D_2O$ quench of the anionic solution to ensure that the 2-lithio-1,3-dithiane was being produced quantitatively
2. Addition of an electrophile to the anionic solution to react and form an expected product
3. Increasing the temperature of the anionic solution in order to measure its thermal stability.

In anticipation of desirable cross-coupling conditions being found, other dithianes such as 2-hexyl-2-phenyl-1,3-dithiane **39** and 1,3-dithiane **40** were synthesized. Their syntheses are shown below in Schemes 3.17 and 3.18, respectively. These dithianes were tested in one of the control reactions to ensure anion formation and reactivity. Specifically, **39** and **40** were treated with *n*-BuLi to form their respective 2-lithio analogue, and then an electrophile was added to this solution. These reactions will be discussed in Section 3.4.3.2.



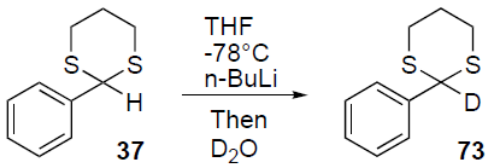

**Scheme 3.17.** Synthesis of 2-hexyl-2-phenyl-1,3-dithiane.




**Scheme 3.18.** Synthesis of 1,3-dithiane.

### 3.4.3.1 Anion stability: $D_2O$ quench

The first control reaction was done to ensure that the anion was being produced quantitatively. The 2-hydrogen on 2-phenyl-1,3dithiane produces a unique signal in $^1$H-NMR at approximately 5.19 ppm. I was able to use this signal to calculate the approximate degree of conversion from 2-phenyl-1,3-dithiane **37** to 2-lithio-2-phenyl-1,3-dithiane. Following a standard procedure,[83] 2-phenyl-1,3-dithiane **37** in THF was treated with *n*-BuLi and then an aliquot of the reaction was removed and immediately quenched in $D_2O$ producing 2-deutero-2-phenyl-1,3-dithiane. 2-Deutero-2-phenyl-1,3-dithiane does not have a hydrogen in the 2-position and therefore no signal should be visible at 5.19 ppm in the $^1$H-NMR. This reaction is summarized below in Scheme 3.19 and the $^1$H-NMR result is shown below in Fig. 3.2.




**Scheme 3.19.** Synthesis of 2-deutero-2-phenyl-1,3-dithiane.

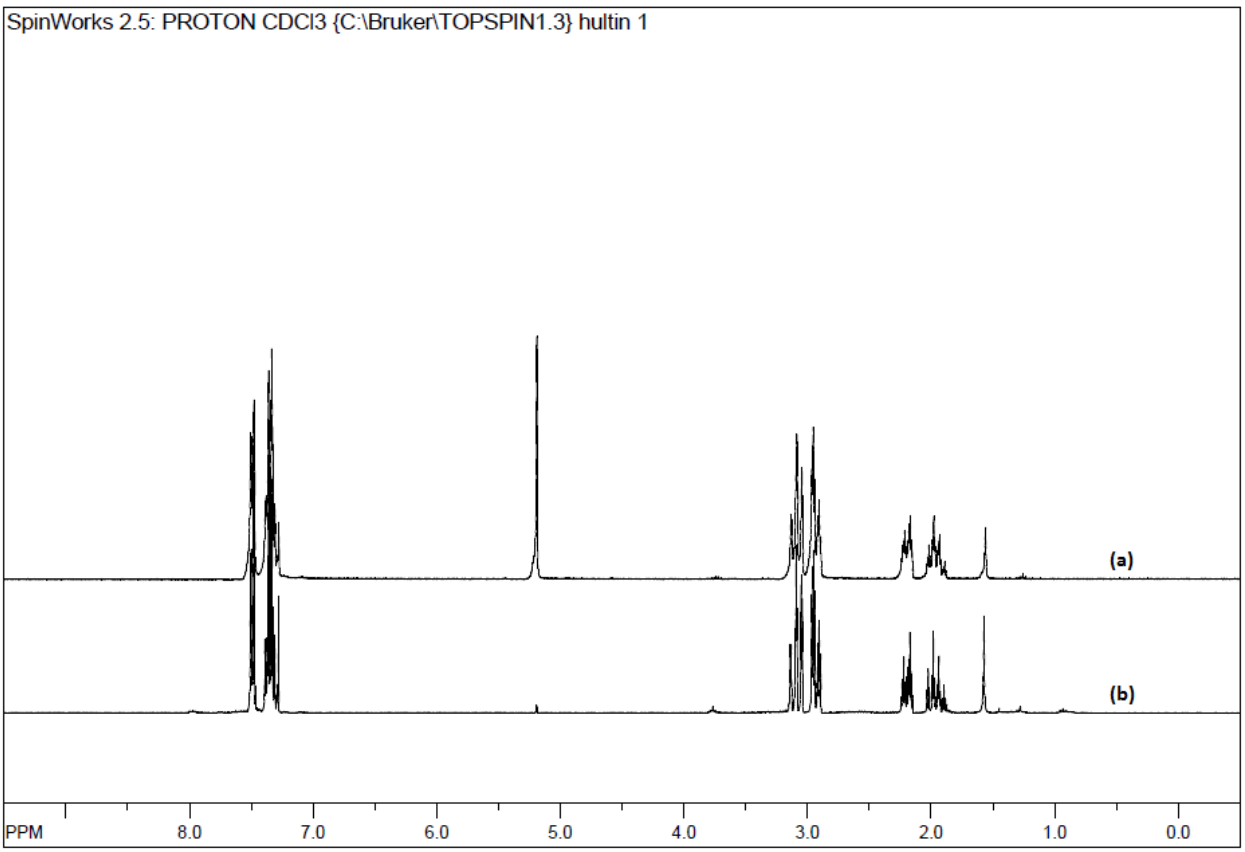
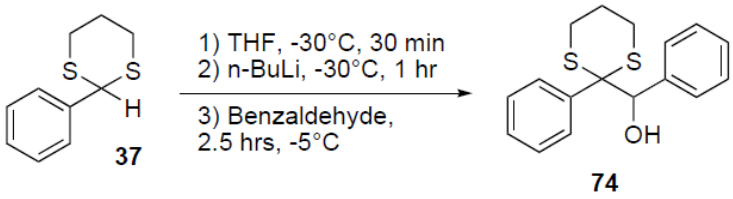



**Fig. 3.2.** $^{1}$H-NMR spectra of: (a) 2-phenyl-1,3-dithiane, (b) 2-deutero-2-phenyl-1,3-dithiane.

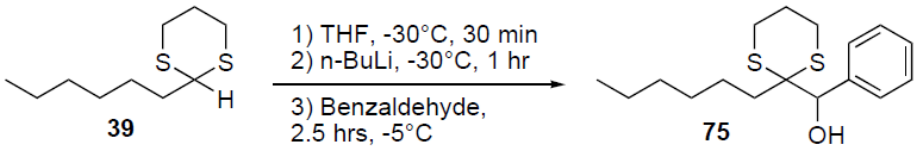
This control reaction was done successfully and demonstrated that 2-deutero-2-phenyl-1,3-dithiane was produced quantitatively. According to the integration of the $^{1}$H-NMR spectra 97.75% of the material was 2-deutero-2-phenyl-1,3-dithiane. This was not 100% 2-deutero-2-phenyl-1,3-dithiane primarily due to the quality of the $D_2O$ that was used. The $D_2O$ was labelled as being only 99% from Sigma-Aldrich, and this particular bottle was quite aged. Therefore the result of 97.75% of 2-deutero-2-phenyl-1,3-dithiane is regarded as being quantitative. 2-Hexyl-1,3-dithiane **39** and 1,3-dithiane **40** were not subjected to this experiment.

### 3.4.3.2 Adding to electrophiles

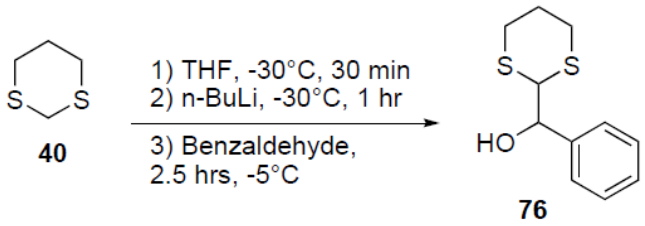
In order to demonstrate that a particular 2-lithio-1,3-dithiane was reactive and a good candidate for a cross-coupling reaction it must first be subjected to predictable reaction conditions and able to form an expected product. Since the 2-carbon of a 2-lithio-1,3-dithiane has anionic properties it should readily react with electrophiles, such as aldehydes, that would then form a new carbon-carbon bond. 2-Phenyl-1,3-dithiane **37**, 2-hexyl-1,3-dithiane **39**, and 1,3-dithiane **40** were each tested by this method. Each dithiane in THF was treated with *n*-BuLi and then benzaldehyde was added and the reaction mixture was slowly warmed to –5°C and maintained for 2.5 hours. The three reaction schemes are illustrated below in Schemes 3.20, 3.21, and 3.22, respectively. Each of these attempts was successful and generated reasonable yields of the expected products.




**Scheme 3.20.** Synthesis of phenyl(2-phenyl-1,3-dithian-2-yl)methanol. This reaction resulted in a 76% yield of purified product.




**Scheme 3.21.** Synthesis of (2-hexyl-1,3-dithian-2-yl)(phenyl)methanol. This reaction resulted in a 73% yield of purified product.




**Scheme 3.22.** Synthesis of (1,3-dithian-2-yl)(phenyl)methanol. This reaction resulted in a 73% yield of purified product.

### 3.4.3.3 Anion thermal stability

In order to push the cross-coupling reaction to its limit I needed to determine how thermally stable 2-lithio-2-phenyl-1,3-dithiane is. In order to accomplish this I heated 2-lithio-2-phenyl-1,3-dithiane to a specific temperature and then proceeded with the previously discussed control reactions; the $D_2O$ quench and the adding of a reactive electrophile. The highest temperature that demonstrated the survival of 2-lithio-2-phenyl-1,3-dithiane would then be the temperature used in cross-coupling reaction attempts.

2-Phenyl-1,3-dithiane **37** and internal standard naphthalene in THF were treated with *n*-BuLi. This was placed in an ice bath and allowed to slowly warm to 0°C and then stirred for 30 minutes. Since the reaction vessel appeared to have not changed in colour or turbidity the reaction was therefore allowed to slowly warm to room temperature, where it was stirred for another 30 minutes. Again there was no observed change in colour or turbidity, therefore the reaction was slowly heated to 55°C and stirred for another 30 minutes. At this point an aliquot was taken at 55°C and immediately quenched in $D_2O$. $^1$H-NMR analysis showed that 2-deutero-2-phenyl-1,3-dithiane **73** was produced, this is shown below in Fig. 3.3.

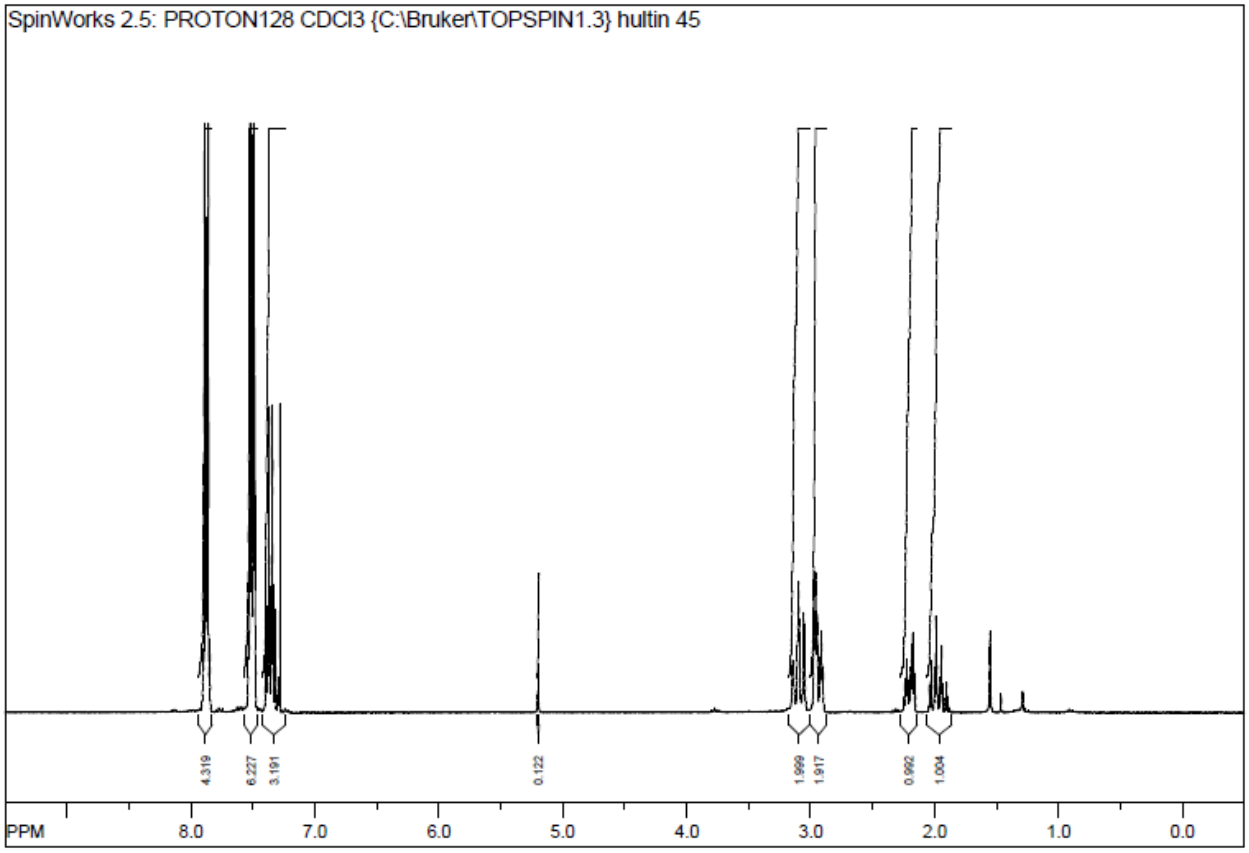



**Fig. 3.3.** NMR from quenching 2-lithio-2-phenyl-1,3-dithiane at 55°C with $D_2O$ to produce 2-deutero-2-phenyl-1,3-dithiane.

2-Lithio-2-phenyl-1,3-dithiane was demonstrated to be stable up to 55°C as shown in Figure 3.3. The peak at approximately 5.19 ppm was integrated with respect to the alkyl peaks at 3 ppm and it was determined that approximately 12% of the material was 2-phenyl-1,3-dithiane, and that 88% of the material was then 2-deuterio-2-phenyl-1,3-dithiane. This is roughly consistent with what was expected for stable 2-lithio-2-phenyl-1,3-dithiane, since the $D_2O$ used to quench the anion was significantly old.

The visual appearance, colour and turbidity, appeared to be normal up to 55°C, a pale yellow transparent solution. I continued to heat this solution attempting to determine if 2-lithio-

2-phenyl-1,3-dithiane was stable at higher temperatures. Upon further heating of this solution I observed a quick discolouration as the solution began to turn black and then became opaque. It was assumed that this observation demonstrated that 2-lithio-2-phenyl-1,3-dithiane had decomposed and no further analysis at this point was done.

The same thermal stability reaction was conducted on 2-lithio-2-phenyl-1,3-dithiane with o-xylene as the solvent. No $D_2O$ quench was performed, but qualitative observations of the reaction were documented. The solution appeared as expected up to 60°C; a pale yellow transparent solution. Further heating quickly led to a black and opaque mixture. Again, it was assumed that this observation demonstrated that 2-lithio-2-phenyl-1,3-dithiane had decomposed. Therefore, o-xylene or other high boiling solvent are not necessary for metal-catalyzed cross-coupling reactions with 2-lithio-2-phenyl-1,3-dithiane, since it appears to decompose at temperatures above 60°C. As such, my attempts at metal-catalyzed cross-coupling reactions with 2-lithio-2-phenyl-1,3-dithiane will begin with THF as the solvent. Attempts at optimizing this reaction could explore the use of other solvents. The desired properties of the reaction solvent require the solvent to be a liquid at both the cool temperature where the anion is formed, -30°C, as well as the high temperature that the reaction will proceed at, 55°C.

A final set of experiments was conducted to assess the thermal stability of 2-lithio-2-phenyl-1,3-dithiane. For these experiments I created 2-lithio-2-phenyl-1,3-dithiane in both THF and separately in o-xylene. Both flasks were slowly heated up to 60°C, and at this temperature both flasks contained a pale yellow transparent solution. The flask containing 2-lithio-2-phenyl-1,3-dithiane in THF had benzaldehyde added to it, and it immediately turned to an opaque yellow solution and upon workup I observed the expected product, phenyl(2-phenyl-1,3-dithian-2-yl)methanol **74**. The flask with 2-lithio-2-phenyl-1,3-dithiane in o-xylene was heated further

to 100°C. Upon heating past 60°C I observed the formation of a white opaque solution that slowly turned red as it approached 100°C. Once at 100°C I added benzaldehyde and the solution turned to an opaque yellow-orange solution. Workup and then $^{1}$H-NMR analysis revealed a complicated mixture that appeared to contained some unreacted starting material, benzaldehyde and a variety of byproducts or decomposition products. This mixture was not further analyzed and the desired product was not observed.

It was concluded from the above experiments that 2-lithio-2-phenyl-1,3-dithiane is stable up to 60°C, however complications are observed at higher temperatures. Therefore, following this analysis cross-coupling reactions with 2-lithio-2-phenyl-1,3-dithiane were heated to approximately 60°C.

### 3.5 Metal-catalyzed cross-coupling 2-lithio-2-phenyl-1,3-dithiane with iodobenzene

The $D_2O$ quench reaction discussed in Section 3.4.3.1 demonstrated that 2-lithio-2-phenyl-1,3-dithiane was formed quantitatively. As discussed in Section 3.4.3.2, the addition of 2-lithio-2-phenyl-1,3-dithiane to an electrophile demonstrated that 2-lithio-2-phenyl-1,3-dithiane was able to react as expected. These control reactions were done prior to the attempts of cross-coupling 2-lithio-2-phenyl-1,3-dithiane with iodobenzene.

As will be discussed in Section 3.5.1, the results of the initial attempts to cross-couple 2-lithio-2-phenyl-1,3-dithiane with iodobenzene were not optimal. In order to begin optimizing the reaction conditions the thermal stability of 2-lithio-2-phenyl-1,3-dithiane was tested, which was previous discussed in Section 3.4.3.3. Once those experiments had demonstrated that 2-lithio-2-phenyl-1,3-dithiane was stable up to 60°C, but not at higher temperatures, a new procedure was employed. These reactions will now be discussed in more detail.

### 3.5.1 Initial attempts at cross-coupling 2-lithio-2-phenyl-1,3-dithiane with iodobenzene

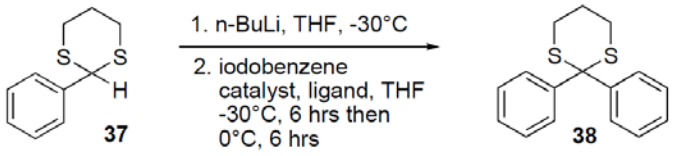
This section is going to discuss the results from my initial experiments to cross-couple 2-lithio-2-phenyl-1,3-dithiane with iodobenzene in a metal-catalyzed reaction. I will begin by briefly discussing the procedure for the reaction, how aliquots were sampled from the reaction, and how the aliquots were worked up for GC-FID analysis. Next I will present and discuss the results that were obtained from numerous reactions. Then I will discuss some of the attempts to troubleshoot the reaction, and finally I will discuss some of the unanswered questions that arose as a result of this work.

Following a standard procedure,[83] 2-phenyl-1,3-dithiane was converted into 2-lithio-2-phenyl-1,3-dithiane. Following another standard procedure the palladium catalyst, ligand, and iodobenzene were solvated in toluene. Once both reaction vessels were at –30°C they were combined and the cross-coupling reaction began. In these initial attempts an aliquot of the reaction was removed every 1.5 hours, treated to a micro-workup, and then analysed by GC-FID. Each aliquot of a reaction was taken with a needle and syringe. The needle and syringe were first purged with Ar gas three times, and then the needle was inserted through a septum on the reaction flask and 0.10 mL of the reaction mixture was withdrawn into the syringe. The 0.10 mL aliquot was quickly dispensed into a 5 mL beaker that contained approximately 1 mL of DCM and 1 mL of $H_2O$. This mixture was stirred briefly before extracting the DCM layer and placing into a separate beaker containing $MgSO_4$. This mixture was then filtered directly into a 2 mL GC vial and submitted for GC-FID analysis.

The reaction temperature was originally maintained at –30°C for a total of 6 hours, and thus four aliquots were taken at this temperature. The temperature was then slowly increased to 0°C and held constant for another 6 hours, during which time another four aliquots were

removed, worked up, and analysed by GC-FID. Since none of the reactions provided evidence that starting material **37** was completely consumed they were all reacted overnight at room temperature before a final aliquot was taken. The motivation for sampling and analysing aliquots over a timeframe was to determine the reaction conversion as a function of time. Therefore once all the starting material **37** was consumed the reaction could be stopped, worked up, and analyzed. Table 3.11 below summarizes all of the results from the attempts that followed this procedure and method of analysis.

**Table 3.11.** Summary of initial cross-coupling reactions with iodobenzene and 2-lithio-2-phenyl-1,3-dithiane.




| Entry | Catalyst | Ligand | Result |
|---|---|---|---|
| 1 | $Pd_2(dba)_3$ | Sphos | No Product |
| 2 | $Pd_2(dba)_3$ | JohnPhos | No Product |
| 3 | $Pd_2(dba)_3$ | DavePhos | No Product |
| 4 | $Pd_2(dba)_3$ | $PCy_3 \cdot HBF_4$ | No Product |
| 5 | $Pd_2(dba)_3$ | DPEPhos | No Product |
| 6 | $Pd_2(dba)_3$ | Sphos | No Product, Trace Homocoupling |
| 7 | $Pd_2(dba)_3$ | DavePhos | 11.7% Yield of Desired Product |
| 8 | $Pd_2(dba)_3$ | *t*-$Bu_3 \cdot$HBF4 | No Product |
| 9 | $Pd_2(dba)_3$ | Xantphos | Trace Product |
| 10 | $Pd_2(dba)_3$ | DPPF | No Product |
| 11 | $Pd(PPh_3)_4$ | | No Product, Trace Homocoupling |

The results for each reaction in Table 3.11 were determined by GC-FID. A higher level of certainty was not obtained by using other methods to confirm the GC-FID evidence, and

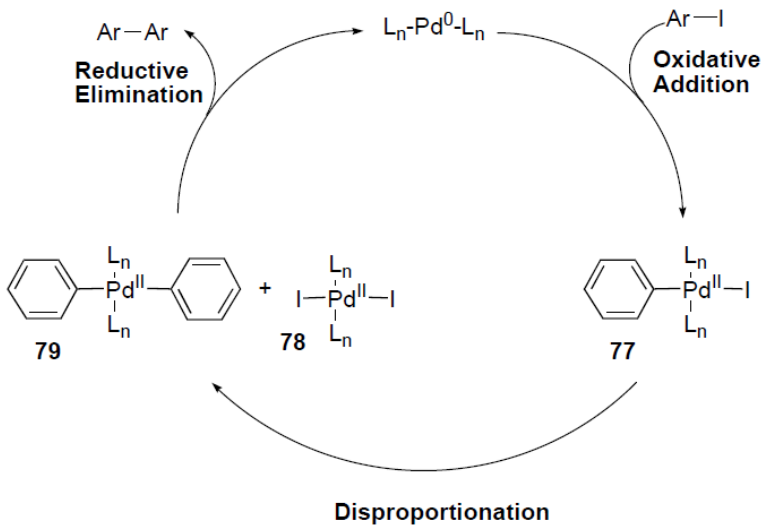
therefore the following discussions are based solely on the evidence of retention times. Only for entry 7 of Table 3.11 was the desired product isolated and fully characterized by NMR analysis. This will be discussed in more detail shortly. For now, the major components from each attempted reaction were hypothesized to be unreacted starting material **37**, iodobenzene, and toluene. A peak was observed at approximately 18.4 minutes in the GC-FID analysis for every reaction attempted, providing some evidence for trace amounts of benzophenone. It is noteworthy to mention that a standard for 2-butyl-2-phenyl-1,3-dithiane was not prepared and its retention time was not determined. 2-Butyl-2-phenyl-1,3-dithiane would be the cross-coupling product for *n*-BuLi and 2-phenyl-1,3-dithiane, another reasonable outcome from this reaction mixture. The presence of 2-butyl-2-phenyl-1,3-dithiane may explain the peak at 18.4 min that was assumed to belong to benzophenone. This was not investigated further.

2-Phenyl-1,3-dithiane **37** in THF was a clear transparent solution that slowly turned into a transparent pale yellow solution once the addition of *n*-BuLi began. For all attempted reactions this would remain a transparent pale yellow solution until the toluene solution was added, except for one attempt. The first attempt using DavePhos as a ligand, shown above as entry 3 in Table 3.11, the 2-lithio-2-phenyl-1,3-dithiane solution turned green and opaque. It was assumed that 2-lithio-2-phenyl-1,3-dithiane had decomposed and that the reaction should be stopped and repeated. Instead, this reaction was allowed to continue and no product was observed. Eventually the reaction was repeated to ensure that the result was meaningful. The results of repeating the experiment are shown as entry 7 of Table 3.11, and the result was different. In the second attempt the 2-lithio-2-phenyl-1,3-dithiane solution was again a transparent pale yellow, and this attempt successfully produced a measurable amount of the desired product. This

provided evidence that when the 2-lithio-2-phenyl-1,3-dithiane solution had turned green and turbid that it was a signal of decomposition.

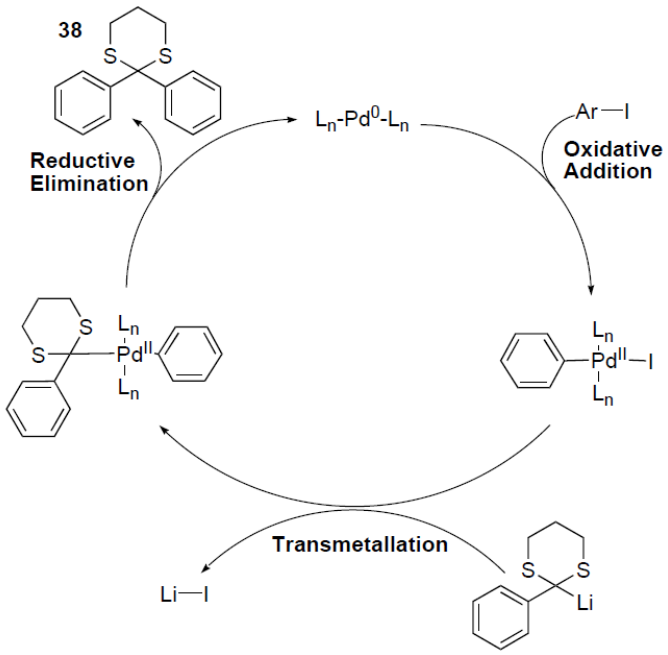
The toluene solution containing the catalyst, ligand, and iodobenzene was typically dark red and turbid prior to heating. Following heating it became a transparent light red solution. This was assumed to be an indication that the catalyst was ligated with the ligand and fully solvated in the solvent. An exception to these observations was when DPEphos was used as the ligand. In this case, the toluene solution was green and turbid prior to heating and then turned into a transparent yellow/orange solution following heating. The important concept from preparing these catalyst solutions was that I needed to achieve a transparent solution to indicate that a reactive catalyst is solvated.

The GC-FID data for the reactions summarized by entries 6 and 11 of Table 3.11 provides some evidence that biphenyl may have been produced in the reaction. A trace amount of material was detected at an approximate retention time of 16.10 min. It was anticipated that biphenyl could be a homocoupling byproduct of the reaction and it was therefore obtained as a standard and ran through the GC-FID method to obtain its retention time; which was determined to be 16.10 min and was shown in Table 3.6. A simple description for the mechanism of a metal-catalyzed homocoupling reaction of an aryl halide is outlined below in Scheme 3.23. It begins with two separate oxidative additions of iodobenzene onto two separate $Pd^0$ complexes, producing two monoorganylpalladium species **77**. Next a disproportionation of **77** forms **78** and diorganylpalladium species **79**. Finally reductive elimination of **79** forms the homocoupling product, biphenyl, and regenerates the $Pd^0$ complex to re-enter the catalytic cycle.[84-87]




**Scheme 3.23.** Mechanism for the homocoupling reaction of iodobenezene.

Evidence that the desired product **38** was produced was seen in the GC-FID results for two reactions, entries 7 and 9 from Table 3.11. Entry 9 used Xantphos as the ligand and the GC-FID data contained evidence that a trace amount of the desired product had formed. Attempts were made to isolate the desired product and then properly characterize it with NMR analysis; unfortunately this was not accomplished successfully. Entry 7 used DavePhos as the ligand and GC-FID provided evidence that a measurable amount of the desired product had been formed. This reaction was quenched, worked up, purified by flash column chromatography, and then characterized by NMR. The NMR analysis proved the presence of the desired product **38**, 2,2-diphenyl-1,3-dithiane, and unreacted starting material **37**, 2-phenyl-1,3-dithiane. The desired product was isolated in an 11.7% yield. Scheme 3.24 below summarizes the mechanism for the formation of 2,2-diphenyl-1,3-dithiane **38**.




**Scheme 3.24.** Cross-coupling mechanism for the formation of 2,2-diphenyl-1,3-dithiane.

It is possible that the starting material **37** was being consumed by another process during the reaction. This seems evident as percent conversion of the reaction as determined by GC-FID was much greater than that of the isolated percent yield. The area of a peak calculated from GC-FID can be used as a tool to predict the approximate percent conversion of the reaction. In this reaction, entry 7 from Table 3.11, the GC-FID data was used to calculate a 41% conversion of starting material into the desired product, much greater than the 11.7 % isolated yield. The percent conversion result was arrived at by dividing the percent area of the desired product by the sum of the percent areas of the starting material and the desired product (8.986 / 21.968 = 0.409 or 41%). This method of using the percent area of starting material and product will be revisited in Sections 3.5.2 and 3.5.3 to discuss the approximate percent conversion of other reactions. However, in order to properly rely on this information the addition of an internal standard in the reaction mixture is required. By removing an aliquot of known volume from the

reaction mixture, the exact amount of internal standard in that aliquot would be known and this could be compared to the amount of starting material and desired product to calculate the percent conversion of the reaction. Table 3.8 summarized the retention times of some internal standard candidates. During the course of my experimentation it was anticipated that this type of approach would be used, however it was deemed unwarranted until meaningful results were first obtained.

### 3.5.2 Revised attempts at cross-coupling 2-lithio-2-phenyl-1,3-dithiane with iodobenzene

The next series of reactions was designed to improve on the already positive result of an 11.7% isolated yield of desired product; entry 7 from Table 3.11. Due to the low yields it was hypothesized that higher temperatures would produce a higher yield of the desired product. The next series of reactions followed the same initial procedure as previous attempts; however the reaction mixture was kept at –30°C for 4.5 hours, then slowly warmed to room temperature for 3 hours, and then finally heated to 60°C for 3 hours. Aliquots were removed every 1.5 hours and were analyzed immediately using GC-FID method # 3 from Table 3.7. The results from this approach are summarized below in Table 3.12.

**Table 3.12.** Summary of cross-coupling reactions with iodobenzene and 2-lithio-2-phenyl-1,3-dithiane that began at –30°C and then incrementally heated to 80°C.

| Entry | Ligand | Result |
|---|---|---|
| 1 | DavePhos | No Product |
| 2 | 2-Diphenylphosphino-2'-(N,N-dimethylamino)biphenyl | No Product |
| 3 | 2-Di-t-butylphosphino-2'-(N,N-dimethylamino)biphenyl | No Product |
| 4 | Tri-2-furylphosphine | No Product |
| 5 | 1,1'-Bis(di-t-butylphosphino)ferrocene | No Product |
| 6 | Tris(2,4-di-t-butylphenyl)phosphite | No Product |
| 7 | 2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl | Trace Desired, New Peak @ 8.85 min |

Entry 1 from Table 3.12 shows that no reaction was observed, which is a different result than what was seen using the same conditions in entry 7 from Table 3.11. This is a concern for reproducibility; a reaction is only useful as long as it is reproducible. If I were able to determine and eliminate any sources of error that should improve the reproducibility of the reaction and the yield of the desired product. Additionally it would provide more confidence in results obtained from other similar experiments. In fact, the same conditions produced the desired product in one attempt and then not in another attempt. This suggests that other attempts that did not produce the desired product may have been a result of an unknown source of error rather than a unacceptable experimental design/condition.

The next series of reactions followed the procedure as described in earlier attempts; however it was modified to achieve the reaction temperature in the fastest time possible. As such the solution of 2-lithio-2-phenyl-1,3dithiane in THF was slowly warmed from –30°C to room temperature. The catalyst, ligand, and iodobenzene solution was only cooled to room temperature. The two solutions were combined at room temperature and then immediately warmed to the reaction temperature of 60°C. Table 3.13 below summarizes the results from this series of reactions.

**Table 3.13.** Summary of heated cross-coupling reactions with iodobenzene and 2-lithio-2-phenyl-1,3-dithiane.

| Entry | Ligand | Result |
|---|---|---|
| 1 | DavePhos | No Product |
| 2 | 2-Diphenylphosphino-2'-(N,N-dimethylamino)biphenyl | No Product |
| 3 | 2-Di-t-butylphosphino-2'-(N,N-dimethylamino)biphenyl | No Product |

Entry 1 from Table 3.13 shows that no product was observed when DavePhos was used as the ligand. Yet DavePhos is the same ligand as the previously successful reaction, entry 7 from Table 3.11. It is noteworthy to mention that in each attempt summarized in Table 3.13 the 2-lithio-2-phenyl-1,3-dithiane solution was observed to be a transparent light yellow solution and therefore I believe that it was stable prior to its combination with the catalytic solution. The only difference between entry 7 from Table 3.11 and entry 1 from Table 3.13 was that the former was limited to room temperature, while the latter was heated to 60°C. Recall that 2-lithio-2-phenyl-1,3-dithiane solution was determined to be stable up to 60°C, as discussed in Section 3.4.3.3. Since the reaction failed to be reproducible I turned my attention to analyzing this problem. To do this, the reaction with DavePhos was repeated in triplicate while holding all experimental parameters constant and paying meticulous attention to the detail of each step within the procedure. Table 3.14 below summarizes the results of three attempts.

**Table 3.14.** Summary of reproducibility trials for the cross-coupling reaction of iodobenzene and 2-lithio-2-phenyl-1,3-dithiane.

| Entry | Ligand | Result |
|---|---|---|
| 1 | DavePhos | ≈ 16 % Conversion |
| 2 | DavePhos | ≈ 13 % Conversion |
| 3 | DavePhos | ≈ 13 % Conversion |

The data in Table 3.14 suggests that with meticulous attention the reaction proceeded in a reproducible manner. This was a positive result, therefore I repeated the same experimental conditions using the other monophosphine-monoamine ligands from entry 2 and entry 3 of Table 3.13; using 2-diphenylphosphino-2'-(N,N-dimethylamino)biphenyl and 2-di-t-butylphosphino-

2'-(N,N-dimethylamino)biphenyl, respectively. These results are summarized below in Table 3.15.

**Table 3.15.** Summary of cross-coupling reaction attempts of iodobenzene and 2-lithio-2-phenyl-1,3-dithiane with different monophosphine-monoamine ligands.

| Entry | Ligand | Result |
|---|---|---|
| 1 | 2-Diphenylphosphino-2'-(N,N-dimethylamino)biphenyl | ≈ 2.5 % Conversion |
| 2 | 2-Di-t-butylphosphino-2'-(N,N-dimethylamino)biphenyl | ≈ 1.6 % Conversion |

As shown in Table 3.15 different monophosphine-monoamine ligands were able to generate trace amounts of the desired product. This is a good result and demonstrates again that meticulous attention to every detail allowed the reaction to proceed. However, other experimental parameters were then studied in an attempt to optimize such Pd catalyzed cross-coupling reactions with dithianes. Since the reaction with the highest yield of the desired product used DavePhos as the ligand, future experiments will hold this variable constant and use only DavePhos as the ligand.

### 3.5.3 Catalyst loading conditions

As was discussed in Section 1.4, some sulfur species are known to be catalyst poisons. Sulfur species such as $H_2S$, RSH, and RSSR have been confirmed to poison reduced metal catalysts due to the formation of strong metal-S bonds.[45] As such, it was hypothesized that the palladium catalyst could be subjected to poisoning from the use of a dithiane functional group. Since strong metal-S bonds are likely to form in the presence of sulfur containing compounds, such as a dithiane, it is reasonable to expect that catalyst poisoning may be occurring.[46] In order

to test this hypothesis, the next series of reactions varied the loading capacity of the catalyst to investigate the percent yield response. The catalyst loading for all reactions up to this point was 10 mol %. We varied the catalyst loading, using 5, 10, and 100 mol %. Table 3.16 below summarizes the results of the first attempts at varying the catalyst loading.

**Table 3.16.** Summary of cross-coupling reaction attempts of iodobenzene and 2-lithio-2-phenyl-1,3-dithiane while varying the catalyst loading.

| Entry | Catalyst Loading (mol %) | Result |
|---|---|---|
| 1 | 5 | ≈ 13 % Conversion |
| 2 | 10 | ≈ 25 % Conversion |
| 3 | 100 | No Reaction |

Comparing entry 1 and entry 2 of Table 3.16 it seems that there may be some evidence that the Pd catalyst is being inactivated and the reaction is halting. When using 5 mol % of catalyst, approximately half of the percent conversion was observed as compared to using 10 mol % of catalyst. Further, since aliquots were analyzed as a function of time it was observed that there was no increase in product following the first aliquot. This observation is consistent with what one would expect in a reaction mixture where the catalyst is being inactivated, or poisoned. This theory could have been more reliable if the reaction that used 100 mol % produced a higher yield than that using 10 mol %. Unfortunately, entry 3 of Table 3.16 shows that no product was observed, and this suggests that there was a problem with reproducibility. Since these reactions were conducted simultaneously there were minimal variables that could be responsible for this reaction failing. It is noteworthy to mention that in all three reactions the visual observations were consistent with those from previous successful attempts at this reaction. Specifically, prior

to being combined with each other, the 2-lithio-2-phenyl-1,3-dithiane solution was a light pale yellow transparent solution and the toluene-catalyst solution was a light red transparent solution.

At this point I decided that I cannot yet trust my data and my attention was focused on resolving sources of error and improving reproducibility. To do this I repeated the experiments from Table 3.16. They were conducted simultaneously, exactly as they were previously. The results are summarized below in table 3.17.

**Table 3.17.** Summary of the second series of cross-coupling reaction attempts with iodobenzene and 2-lithio-2-phenyl-1,3-dithiane while varying the catalyst loading.

| Entry | Catalyst Loading (mol %) | Result |
|---|---|---|
| 1 | 5 | ≈ 14 % Conversion |
| 2 | 10 | No Reaction |
| 3 | 100 | No Reaction |

Comparing the results from entry 1 of Table 3.16, 13 % conversion, to entry 1 of Table 3.17, 14 % conversion, provides evidence that this reaction can be performed reproducibly. Unfortunately, entry 2 and entry 3 in Table 3.17 show that no product was observed when 10 mol % and 100 mol % of catalyst were used. Again the reproducibility of the reaction seems to be a pronounced complication.

Throughout all of the Pd-catalyzed cross-coupling reaction attempts there were several measures taken to address sources of error and poor reproducibility. This included but was not limited to the following:

1. Verified the purity of 2-phenyl-1,3-dithiane by NMR
2. Titrated diphenylacetic acid with *n*-BuLi to determine the exact concentration of *n*-BuLi

3. Purchased a new bottle of catalyst, $Pd_2(dba)_3$
4. Freshly distilled THF from $LiAlH_4$ immediately prior to each reaction
5. Performed control reactions to ensure the potential for a successful reaction
    a. Ensured quantitative production of 2-lithio-2-phenyl-1,3-dithiane by quenching with $D_2O$
    b. Ensured 2-lithio-2-phenyl-1,3-dithiane was able to react and form expected products by the addition to an electrophile
    c. Determined the highest reaction temperature by assessing the thermal stability of 2-lithio-2-phenyl-1,3-dithiane.

Following each of the above measures, another round of attempts was made with careful meticulous preparation. These attempts were identical to those described in tables 3.16 and 3.17, and their results are summarized below in table 3.18.

**Table 3.18.** Summary of the third series of cross-coupling reaction attempts with iodobenzene and 2-lithio-2-phenyl-1,3-dithiane while varying the catalyst loading.

| Entry | Catalyst Loading (mol %) | Result |
|---|---|---|
| 1 | 5 | No Reaction |
| 2 | 10 | No Reaction |
| 3 | 100 | No Reaction |

As Table 3.18 shows, no reaction was observed in any of the trials. A fourth and final attempt was made and the results are summarized below in table 3.19.

**Table 3.19.** Summary of the fourth series of cross-coupling reaction attempts with iodobenzene and 2-lithio-2-phenyl-1,3-dithiane while varying the catalyst loading.

| Entry | Catalyst Loading (mol %) | Result |
|---|---|---|
| 1 | 5 | No Reaction |
| 2 | 10 | No Reaction |
| 3 | 50 | No Reaction |
| 4 | 100 | No Reaction |

In the final attempt I again observed no reaction for all attempts to cross-coupling iodobenzene with 2-lithio-2-phenyl-1,3-dithiane while varying the catalyst loading. At this point it was decided that this specific reaction was particularly sensitive and prone to sources of error that could not be identified or corrected for. As such experimentation was abandoned and conclusions were drawn.

### 3.6 Discussion

There were some instances where a reaction could have been subjected to greater scrutiny. Some of these issues could have received a more detailed analysis however it was deemed to be a distraction from the main focus of this project at the time. Therefore these items were not investigated in greater detail.

A peak was observed in the GC-FID analysis of most experiments at approximately 19.33 min. As shown in Table 3.6, 2-phenyl-1,3-dithiane was found to elute at approximately 19.55 min with this particular GC-FID method. At first glance it was thought that the GC experiment may have degraded 2-phenyl-1,3-dithiane, however when 2-phenyl-1,3-dithiane was run as a pure standard material it did not suffer any such degradation. Therefore this material was likely not starting material **37** that had degraded.

The only other suggestion to explain this sizable peak was that it must have formed during the reaction. In order to investigate the identity of this material more work would be required. None of the expected byproducts matched the retention time of 19.33 min. TLC analysis on the crude reaction mixture did not show any evidence of any UV-absorbing species other than the starting material and desired product. Since this material was observed using GC-FID I would expect that preparative HPLC would resolve this peak from other peaks and therefore this material could then be collected and analyzed. Using any two of the following techniques could provide sufficient evidence: GC-MS, GC-IR, NMR, or high resolution mass spectrometry (HRMS). Ideally NMR could help to elucidate the structure and then another technique could provide complimentary data. At this point of experimentation this was deemed to be a distraction from the main focus of this project. Therefore this material was not isolated and characterized.

The peak found at approximately 19.33 min in the GC-FID analysis was not the only peak whose material required characterization. Every GC-FID peak from each experiment should have had more techniques to confirm the identity. The GC-FID peak at 18.40 minutes suggested benzophenone but it did not provide conclusive confirmation of this molecule. The GC-FID peak at 19.55 minutes suggests unreacted starting material, 2-phenyl-1,3-dithiane, but again this cannot be confirmed by this method alone. In order to conclusively solve this dilemma more evidence would be required. Assuming that the material of interest has been isolated from the mixture a complete analysis would require more than one technique to properly determine its identity. According to the Scientific Working Group for the Analysis of Seized Drugs (SWGDRUG) recommendations, in order to confirm the structure a minimum of one category A technique and then at least one other from either category A, B, or C. If a category

A technique is not used, at least 3 different techniques should be used with two of the three from category B.[88] Table 3.20 below summarizes the SWGDRUG description of the categories for various techniques.

**Table 3.20.** Table of SWGDRUG categories.

| Category A | Category B | Category C |
|---|---|---|
| Infrared Spectroscopy | Capillary Electrophoresis | Color Tests |
| Mass Spectrometry | Gas Chromatography | Fluorescence Spectroscopy |
| Raman Spectroscopy | Ion Mobility Spectrometry | Immunoassay |
| X-ray Diffractometry | Liquid Chormatography | Melting Point |
| Nuclear Magnetic Resonance Spectroscopy | Microcystalline Tests | Ultraviolet Spectroscopy |
| | Pharmaceutical Identifiers | |
| | Thin Layer Chromatography | |

The standard analysis for each reaction was GC-FID, and is therefore a category B technique. To confirm the identity of each material I would still need to isolate each material and then subject it to either a category A technique or two other techniques with at least one of the two being a category B. It should be noted that GC can be coupled with other techniques to satisfy this demand, specifically GC-MS and GC-IR. An MS detector is more sensitive than an IR detector and therefore GC-MS could have been the category A technique of choice for these experiments.

## Chapter 4: Conclusions and Future Work

The purpose of the research in this dissertation was to broaden the scope of current metal-catalyzed cross-coupling methods, by including new reactions involving dithiolanes and dithianes. This was done by producing the acyl anion equivalent of a dithiolane or a dithiane and then studying the results of adding them into conditions for various metal-catalyzed cross-coupling reactions. Successful reactions would then broaden the range of applications for current metal-catalyzed cross-coupling reactions. My thesis project had three main objectives:

1) To determine the conditions required for a successful cross-coupling reaction between a dithiolane/dithiane and an organohalide
2) To optimize the reaction conditions
3) To test the scope of the reaction by varying either the dithiolane/dithiane or the organohalide

In order to meet the outlined objectives experimentation began with a general approach that used previously published procedures for other acyl anion equivalents in metal-catalyzed cross-coupling reactions. The acyl anion equivalents studied in this thesis were prepared from dithiolanes/dithianes under basic conditions. Separately, the catalyst, ligand, and organohalide were combined and heated to achieve full solvation. Finally the reaction was initiated by combining this mixture with the acyl-anion equivalent and then warming the reaction to the desired temperature. The reaction progress was monitored using GC-FID. Initial attempts produced evidence that trace amounts of the desired cross-coupling product had formed. Optimization of the reaction was attempted by systematically varying the reaction temperature, solvent, and ligand, as well as trying different cross-coupling strategies such as Negishi and

Suzuki reactions. Three types of control reactions were performed to test the formation, reactivity, and stability of the acyl anion equivalent.

A control reaction, involving the addition of $D_2O$ to the acyl anion equivalent, was able to demonstrate that the corresponding 2-lithio dithiane species was being generated in high yield. Further to this, a separate control reaction, involving the addition of an electrophile to the acyl anion equivalent, was able to prove the reactive potential of the 2-lithio dithiane species as the expected adduct was obtained. Finally, a third control reaction was able to demonstrate that the acyl anion equivalent was stable up to approximately 55°C. This was done by heating the acyl anion equivalent to fixed temperatures and then quenching with $D_2O$. These control reactions lead to the conclusion that 2-phenyl-1,3-dithiane will form 2-lithio-2-phenyl-1,3-dithiane in high yield and remain stable up to 55°C.

From numerous iterations at attempting metal-catalyzed cross-coupling reactions with dithiolanes, and reviewing work by Wilson *et al.*[70,71], it was concluded that 2-phenyl-1,3-dithiolane was not a good candidate for metal-catalyzed cross-coupling reactions. Similar cross-coupling reaction conditions with 2-phenyl-1,3-dithiane produced evidence of the desired product, 2,2-diphenyl-1,3-dithiane; which was isolated in a 12% yield and characterized by GC-FID and NMR. This satisfied the first objective of my work; to determine conditions for a successful cross-coupling reaction between a dithiane and an organohalide. Additionally, this positive result demonstrated that there is potential to optimize the cross-coupling reaction; my second objective. Attempts at optimization began with varying the ligand. During these optimization experiments it was observed that the reproducibility was poor, and as such these reactions were said to be particularly sensitive. The source of error responsible was not identified in this study.

Attempts were made to determine any sources of error that were leading to the reaction being non-reproducible. The purity of starting materials were verified, solvents were freshly distilled, and control reactions were performed. Despite all these efforts the reaction of 2-phenyl-1,3-dithiane in metal-catalyzed cross-coupling reactions was still found to be non-reproducible. It was hypothesized that the palladium catalyst was being poisoned by the dithiane starting material, which is a sulfur containing compound and may be able to form strong S-metal bonds inactivating the Pd catalyst. This hypothesis was tested by varying the amount of catalyst in otherwise identical reaction conditions. Unfortunately inconsistent results were observed from these attempts. In one case it was seen that the percent of catalyst present was proportional to the amount of product observed, while in other cases the reactions failed completely regardless of the amount of catalyst used. This was an indication that catalyst poisoning may be an issue, however there are other sources of error preventing the reaction from progressing as desired.

Despite the difficulties associated with sulfur species in metal-catalyzed cross-coupling reactions I believe that there is potential for optimization of such reactions with dithianes. This interesting reaction would prove to be a useful and appealing tool for the organic chemist. It could also prove to be applicable to wide range of substrates and therefore offering a synthetic route to several product analogues.

Future work should focus on determining the sources of error and increasing the reproducibility of the reaction. It has been noted that bimetallic interactions in Pd-Pt systems improved the resistance to irreversible sulfur poisoning of the catalyst.[45,89] Conceivably, using a bimetallic catalytic system could improve the productivity of these reactions. Other future work could involve another control reaction designed to confirm the chemist's technique. This could

be done by performing known cross-coupling reactions that are comparatively sensitive and then confirming that the correct desired product was produced and in the expected yield. If known cross-coupling reactions were to fail, or be non-reproducible, it would signify that there was an issue with the chemist's technique.

Once the reaction has been demonstrated to be reproducible it could then be further optimized. This study would involve varying the reaction parameters systematically to achieve the optimal conditions. This could include varying the solvent, temperature, concentration, catalyst, ligand, the ratio of ligand to catalyst, the starting dithiane, and the cross-coupling partner.

Other future work could include the synthesis and application of 2-chloro-1,3-dithiane. I was unable to successfully synthesize 2-chloro-2-phenyl-1,3-dithiane, however, the synthesis of 2-chloro-1,3-dithiane is a literature procedure and reproducing this experiment could be beneficial. Firstly, 2-chloro-1,3-dithiane could be studied in metal-catalyzed cross-coupling reactions, such as the Suzuki reaction. Secondly, treating 2-chloro-1,3-dithiane with strong base could produce a stable carbene. This carbene could then be used in subsequent reactions, such as additions to alkenes to form cyclopropyldithianes.

# Chapter 5: Experimental Procedures

## 5.1 General introduction

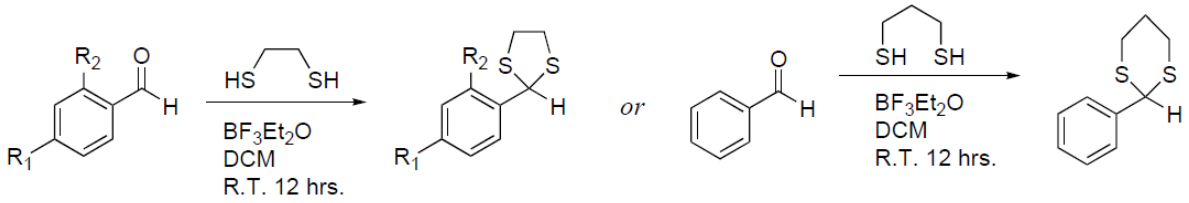
$^{1}$H-NMR (300 MHz) and $^{13}$C-NMR (75 MHz) spectra was recorded on a Bruker Avance 300 MHz spectrometer in $CDCl_3$ solution, unless otherwise noted. Chemical shifts for $^{1}$H and $^{13}$C are reported in parts per million (ppm) down field from TMS, using residual $CDCl_3$ (7.28 ppm and triplet at 77.2 ppm, respectively) as an internal standard. High resolution mass spectra were recorded on a VG-7070E instrument of E-B geometry. All GC data was collected on a CP Varian 3900 with autosampler CP8400 series, 1 μL injection, split 10:1, supel cowax-10 column (15 m x 0.32 mm column and a 0.5 μm film), with a constant flow (25 mL/min of helium). All GC-MS data was collected with direct injection using a CP Varian 3800 GC and a VF-5MS column (30 m x 0.25 mm column and a 0.25 μm film) coupled with a triple quadrupole Varian 320-MS detector. Recorded GC-MS data was compared to NIST libraries to identify structures.

Flash chromatography was performed using Silicycle Silica-P flash silica gel (230-400 mesh). $R_f$ values refer to TLC performed on pre-coated (0.2 mm) Alugram® Sil G/UV silica gel plates visualized with UV light. All reactions were performed in an inert argon atmosphere with glassware that was oven dried at 140°C overnight and cooled in a desiccator before use. All reactions were magnetically stirred and carried out with standard syringe techniques.

THF and toluene were obtained from a solvent purifier (Innovative Technology Inc.), purified by passage through two columns of activated alumina under argon pressure, then they were degassed via sparging with argon immediately before use. Iodobenzene was passed through a short column of activated alumina immediately before use. All palladium reagents and phosphine ligands were used as purchased from Strem Chemicals. Cesium fluoride, cesium

carbonate, and potassium tert-butoxide were used as received from Sigma Aldrich. Butyl lithium was used as received from Sigma Aldrich, although it was titrated with diphenylacetic acid to calculate its molarity prior to calculating the amount needed for a reaction.

### 5.2 General Procedure I: preparation of dithiolanes and dithianes




**Scheme 5.1.** Synthesis of dithiolanes (left) and dithianes (right).[6]

Benzaldehyde (1.0 eq.) was added to a round bottom flask containing DCM (ca. 1.5 mL per mmol of aldehyde). The flask was capped with a rubber septum and purged with argon gas while stirring. To this 1,2-ethanedithiol or 1,3-propanedithiol (0.95 eq.) was added and the mixture was stirred for 5 minutes. $BF_3{\cdot}Et_2O$ (0.2 eq.) was then added dropwise while stirring, and the reaction was allowed to continue for 12 hours. The reaction mixture was diluted with $Et_2O$ and quenched with saturated aqueous $NaHCO_3$. These phases were separated and the aqueous layer was extracted once more with $Et_2O$. The organic fractions were combined and washed with cold distilled water, and then washed with brine. The organic layer was dried with $MgSO_4$, filtered, and then concentrated on a rotary evaporator.

### 5.2.1 Synthesis of 2-phenyl-1,3-dithiolane

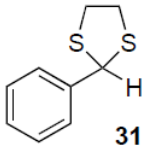



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**Fig. 5.1.** 2-Phenyl-1,3-dithiolane.

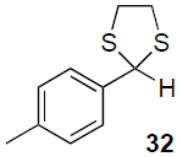
2-Phenyl-1,3-dithiolane was prepared on a 10 mmol scale according to General Procedure I. The product was purified by flash column chromatography eluting with 50:1 Hex:EtOAc to yield 1.56 g of clear liquid (90% yield). This is a known compound, recorded NMR spectra match those previously published.[59]

**$R_f$ =** 0.24 (50:1 Hex:EtOAc).

**$^1$H-NMR** (300 MHz, $CDCl_3$) δ 7.57-7.54 (2H, m), 7.34-7.30 (3H, m), 5.67 (1H, s), 3.54-3.50 (2H, m), 3.40-3.36 (2H, m).

**$^{13}$C-NMR** (75 MHz, $CDCl_3$) δ 140.35, 128.52, 128.07, 127.98, 56.32, 40.28.

### 5.2.2 Synthesis of 2-*p*-tolyl-1,3-dithiolane




**32**

**Fig. 5.2.** 2-*p*-Tolyl-1,3-dithiolane.

2-*p*-Tolyl-1,3-dithiolane was prepared on a 10 mmol scale according to General Procedure I. The product was purified by flash column chromatography eluting with 50:1

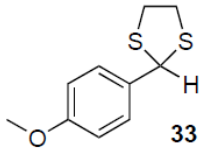
Hex:EtOAc to yield 1.88 g of white powder (100% yield). This is a known compound, recorded NMR spectra match those previously published.[59]

**$R_f$** = 0.23 (50:1 Hex:EtOAc).

**$^1$H-NMR** (300 MHz, $CDCl_3$) δ 7.45-7.42 (2H, d), 7.16-7.13 (2H, d), 5.65 (1H, s), 3.53-3.50 (2H, m), 3.39-3.35 (2H, m), 2.35 (3H, s).

**$^{13}$C-NMR** (75 MHz, $CDCl_3$) δ 137.90, 137.16, 129.20, 127.85, 56.19, 40.23, 21.14.

### 5.2.3 Synthesis of 2-(4-methoxyphenyl)-1,3-dithiolane




33

**Fig. 5.3.** 2-(4-Methoxyphenyl)-1,3-dithiolane.

2-(4-Methoxyphenyl)-1,3-dithiolane was prepared on a 10 mmol scale according to General Procedure I. The product was purified by flash column chromatography eluting with 19:1 Hex:EtOAc to yield 1.67 g of white powder (82% yield). This is a known compound, recorded NMR spectra match those previously published.[59]

**$R_f$** = 0.24 (19:1 Hex:EtOAc).

**$^1$H-NMR** (300 MHz, $CDCl_3$) δ 7.49-7.46 (2H, d), 6.88-6.85 (2H, d) 5.66 (1H, s), 3.81 (3H, s), 3.53-3.50 (2H, m), 3.39-3.35 (2H, m).

**$^{13}$C-NMR** (75 MHz, $CDCl_3$) δ 159.44, 131.84, 129.17, 113.90, 56.09, 55.35, 40.23.

### 5.2.4 Synthesis of 2-(4-nitrophenyl)-1,3-dithiolane

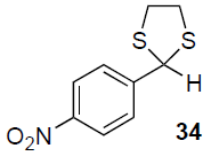



**Fig. 5.4.** 2-(4-Nitrophenyl)-1,3-dithiolane.

2-(4-Nitrophenyl)-1,3-dithiolane was prepared on a 6 mmol scale according to General Procedure I. The product was purified by flash column chromatography eluting with 9:1 Hex:EtOAc to yield 1.08 g of white powder (83% yield). This product was light sensitive. Upon exposure to light it turned bright orange. The final product was stored in a cold and dark place. This is a known compound, recorded NMR spectra match those previously published.[60]

**$R_f$** = 0.26 (9:1 Hex:EtOAc).

**$^1$H-NMR** (300 MHz, $CDCl_3$) δ 8.20-8.17 (2H, d), 7.71-7.68 (2H, d), 5.67 (1H, s), 3.57-3.49 (2H, m), 3.47-3.39 (2H, m).

**$^{13}$C-NMR** (75 MHz, $CDCl_3$) δ 148.66, 147.46, 128.87, 123.78, 54.95, 40.52.

### 5.2.5 Synthesis of 2-(2-methoxyphenyl)-1,3-dithiolane

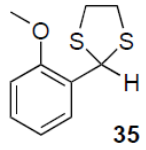



**Fig. 5.5.** 2-(2-Methoxyphenyl)-1,3-dithiolane.

2-(2-Methoxyphenyl)-1,3-dithiolane was prepared on a 10 mmol scale according to General Procedure I. The product was purified by flash column chromatography eluting with

50:1 Hex:EtOAc to yield 1.84 g of white powder (91% yield). This is a known compound, recorded NMR spectra match those previously published.[59]

**$R_f$ =** 0.15 (50:1 Hex:EtOAc).

**$^1$H-NMR** (300 MHz, $CDCl_3$) δ 7.77-7.74 (1H, dd), 7.29-7.23 (1H, dt), 7.00-6.95 (1H, dt), 6.89-6.86 (1H, dd), 6.10 (1H, s), 3.89 (3H, s), 3.48-3.40 (2H, m), 3.39-3.31 (2H, m).

**$^{13}$C-NMR** (75 MHz, $CDCl_3$) δ 156.60, 129.27, 128.83, 128.15, 120.64, 110.52, 55.68, 49.11, 39.42.

### 5.2.6 Synthesis of 2,2-diphenyl-1,3-dithiolane

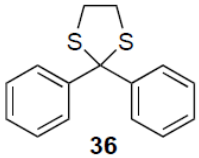



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**Fig. 5.6.** 2,2-Diphenyl-1,3-dithiolane.

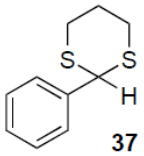
2,2-Diphenyl-1,3-dithiolane was prepared on a 5 mmol scale according to General Procedure I. The product was purified by flash column chromatography eluting with 50:1 Hex:EtOAc to yield 0.96 g of white crystals (74% yield). This is a known compound, recorded NMR spectra match those previously published.[60]

**$R_f$ =** 0.22 (50:1 Hex:EtOAc).

**$^1$H-NMR** (300 MHz, $CDCl_3$) δ 7.66-7.62 (4H, m), 7.34-7.22 (6H, m), 3.44 (4H, s).

**$^{13}$C-NMR** (75 MHz, $CDCl_3$) δ 144.64, 128.23, 127.99, 127.24, 76.91, 40.20.

### 5.2.7 Synthesis of 2-phenyl-1,3-dithiane




37

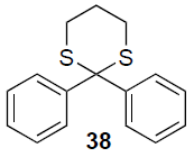
**Fig. 5.7.** 2-Phenyl-1,3-dithiane.

2-Phenyl-1,3-dithiane was prepared on a 50 mmol scale according to General Procedure I. The product was purified by recrystallization with 95% EtOH to yield 1.88 g of white crystals (93% yield). This is a known compound, recorded NMR spectra match those previously published.[59,61]

**$^{1}$H-NMR** (300 MHz, $CDCl_3$) δ 7.50-7.47 (2H, m), 7.39-7.27 (3H, m), 5.19 (1H, s), 3.13-3.04 (2H, m), 2.96-2.89 (2H, m), 2.24-2.14 (1H, m), 2.03-1.88 (1H, m).

**$^{13}$C-NMR** (75 MHz, $CDCl_3$) δ 139.14, 128.76, 128.46, 127.78, 51.52, 32.14, 25.15.

### 5.2.8 Synthesis of 2,2-diphenyl-1,3-dithiane




38

**Fig. 5.8.** 2,2-Diphenyl-1,3-dithiane.

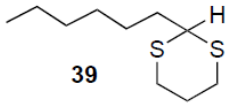
2,2-Diphenyl-1,3-dithiane was prepared on a 10 mmol scale according to General Procedure I. The product was purified by recrystallization with 95% EtOH to yield 2.67 g of white powder (95% yield). This is a known compound, recorded NMR spectra match those previously published.[62]

**$R_f$** = 0.25 (50:1 Hex:EtOAc).

**$^1$H-NMR** (300 MHz, $CDCl_3$) δ 7.75-7.72 (4H, d), 7.39-7.27 (6H, m), 2.83-2.80 (4H, m), 2.07-1.99 (2H, m).

**$^{13}$C-NMR** (75 MHz, $CDCl_3$) δ 142.59, 129.36, 128.45, 127.60, 62.81, 29.42, 24.52.

### 5.2.9 Synthesis of 2-hexyl-1,3-dithiane




39

**Fig. 5.9.** 2-Hexyl-1,3-dithiane.

2-Hexyl-1,3-dithiane was prepared on a 22.5 mmol scale according to General Procedure I. The product was purified by vacuum distillation to yield 2.71 g of clear liquid (59% yield). This is a known compound, recorded NMR spectra match those previously published.[63]

**$^1$H-NMR** (300 MHz, $CDCl_3$) δ 4.05 (1H, t), 2.94-2.78 (4H, m), 2.17-2.08 (1H, m), 1.94-1.82 (1H, m), 1.80-1.71 (2H, m), 1.55-1.46 (2H, quin), 1.36-1.26 (6H, m), 0.89 (3H, t).

**$^{13}$C-NMR** (75 MHz, $CDCl_3$) δ 47.70, 35.49, 31.58, 30.52, 28.90, 26.59, 26.09, 22.56, 14.06.

## 5.3 Synthesis of 2,2-diphenyl-1,3-dithiane

The procedure was performed as described previously.[57] $Pd_2(dba)_3$ (23.3 mg, 0.025 mmol) and DavePhos (36.1 mg, 0.092 mmol) were added to a reaction vessel and the headspace was purged with argon gas. To this toluene (3 mL) and iodobenzene (62.4 μL, 0.56 mmol) were added and the mixture was heated to 45°C for 30 min while stirring. Heating continued until the solution was transparent and then it was cooled to room temperature.

In a separate argon-purged vessel, 1,3-dithiane (100 mg, 0.51 mmol) was added and purged with argon gas. This was then dissolved in THF (1 mL) and the solution was cooled to -30°C. After mixing for 30 min at -30°C, *n*-BuLi (1.6 M in hexanes, 0.32 mL, 0.51 mmol) was added dropwise while stirring. This mixture was slowly warmed to room temperature over 1 hour. At room temperature the basic solution was transferred via a cannula to the reaction vessel. The reaction was then slowly heated to 50°C for 24 hours. The reaction was cooled to room temperature and diluted with $Et_2O$ then filtered through Celite. The mixture was then washed with 1 M HCl, then washed with distilled $H_2O$, and finally washed with brine. The organic layer was dried with anhydrous $MgSO_4$, filtered and concentrated to dryness. The crude product was purified by flash column chromatography eluting with 50:1 Hex:EtOAc to yield 16.3 mg of white powder (12% yield).

### 5.4 Synthesis of indole-3-carbaldehyde

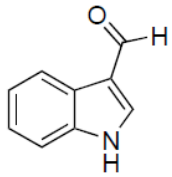



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**Fig. 5.10.** Indole-3-carbaldehyde.

The procedure was performed as described previously.[67] DMF (29.4 mL, 380.2 mmol) was placed in a three-necked round bottom flask. A drying tube filled with drierite was used on one neck of the flask, a dropping funnel was used on the centre neck, and a glass stopper on the third. The reaction vessel was placed in an ice-acetone-water bath for 30 min. Using the dropping funnel $POCl_3$ (9.55 mL, 15.7 g, 102.4 mmol) was slowly added while stirring, a pink

colour was observed as the Vilsmeier-Hack complex was formed. Using the dropping funnel indole (10.0 g, 85.4 mmol) dissolved in DMF (10 mL, 132 mmol) was slowly added being careful to ensure the temperature did not rise above 10°C. Once the addition was complete a digital thermometer was inserted and the reaction was slowly heated to 35°C while mixing. Heating continued for 1 hour and an opaque yellow solution was observed. Following the reaction 65 g of crushed ice was added turning the solution to a transparent bright red. NaOH (37.56 g, 939 mmol) was dissolved in $H_2O$ (100 mL) and added to the reaction vessel very slowly using a dropping funnel until one third of the solution has been added. The remainder of the solution was then added very quickly. The solution was rapidly heated to the boiling point and maintained for 20 minutes then slowly cooled to room temperature and finally placed in a refrigerator overnight. The precipitate was collected by filtration and then washed with a large excess of cold distilled water. The final material was collected as an off-white (pale yellow) powder. After drying to completeness on a high-vac it was determined that the reaction was quantitative (100% yield). This is a known compound, recorded NMR spectra match those previously published.[65]

**$^{1}$H-NMR** (300 MHz, DMSO-d6) δ 12.12 (1H, s), 9.95 (1H, s), 8.28 (1H, s), 8.12-8.09 (1H, dd), 7.54-7.51 (1H, dd), 7.29-7.19 (2H, dquintet).

**$^{13}$C-NMR** (75 MHz, DMSO-d6) δ 184.91, 138.39, 137.02, 124.09, 123.41, 122.08, 120.79, 118.14, 112.38.

### 5.5 Synthesis of 1,3-dithiane

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**Fig. 5.11.** 1,3-Dithiane.

The procedure was performed as described previously.[8] $BF_3 \cdot Et_2O$ (4.2 mL, 33.4 mmol), AcOH (8.4 mL, 146.7 mmol), and $CHCl_3$ (67.2 mL) were combined in a round bottom flask and brought to reflux. To this mixture 1,3-propanedithiol (3.5 mL, 34.9 mmol) and dimethoxymethane (3.4 mL, 38.4 mmol) were slowly added dropwise over several hours. Reflux was continued for one more hour and then cooled to room temperature. The reaction was quenched with distilled water and separated. The organic layer was washed with water (3 x 20 mL), washed with 10% KOH (2 x 20 mL) and then washed again with water (2 x 20 mL). The organic layer was dried with $K_2CO_3$ and then concentrated. The crude material was recrystallized from MeOH to yield 2.89 g (24 mmol) of white powder (69% yield). This is a known compound, recorded NMR spectra match those previously published.[64]

**$^1$H-NMR** (300 MHz, $CDCl_3$) δ 3.79 (2H, s), 2.86-2.82 (4H, t), 2.12-2.05 (2H, quintet).

**$^{13}$C-NMR** (75 MHz, $CDCl_3$) δ 31.98, 29.95, 26.60.

### 5.6. $D_2O$ quench reaction on 2-phenyl-1,3-dithiane

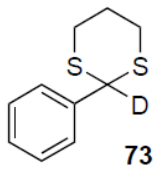

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**Fig. 5.12.** 2-Phenyl-2-deutero-1,3-dithiane.

The procedure was performed as described previously.[83] 2-phenyl-1,3-dithiane (100 mg, 0.51 mmol) was placed in a reaction flask and purged with argon. To this THF (1.5 mL) was added and cooled to -30°C and then stirred for 30 min. *n*-BuLi (2.0 M in hexanes, 0.28 mL, 0.56 mmol) was added dropwise while stirring. Mixing continued at -30°C for 1 hour and then an aliquot of the reaction was removed via syringe and injected into $D_2O$. DCM was used to extract the product, which was then dried with $MgSO_4$, filtered and concentrated. The crude material was a white needle-shaped crystal.

**$^1$H-NMR** (300 MHz, $CDCl_3$) δ 7.51-7.47 (2H, m), 7.39-7.29 (3H, m), 3.14-3.04 (2H, m), 2.97-2.89 (2H, m), 2.24-2.15 (1H, m), 2.03-1.88 (1H, m).

**$^{13}$C-NMR** (75 MHz, $CDCl_3$) δ 139.08, 128.76, 128.46, 127.76, 51.11 (t, J = 23.7 Hz), 32.10, 25.15.

### 5.7 Synthesis of phenyl(2-phenyl-1,3-dithian-2-yl)methanol:

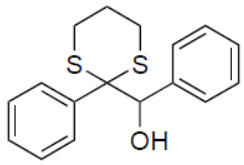


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**Fig. 5.13.** Phenyl(2-phenyl-1,3-dithian-2-yl)methanol.

The procedure was performed as described previously.[90] 2-phenyl-1,3-dithiane (100 mg, 0.51 mmol) was placed in a reaction flask and purged with argon. To this THF (1.5 mL) was added and the mixture was cooled to -30°C and stirred for 30 min. *n*-BuLi (2.0 M in hexanes, 0.28 mL, 0.56 mmol) was added dropwise while stirring. The reaction was kept at -30°C for 1 hour and then benzaldehyde (62.4 µL, 0.61 mmol) was added. Next the reaction was slowly

warmed to -5°C and maintained for 2.5 hours, and then quenched with saturated aqueous $NH_4Cl$ and extracted with $CHCl_3$. The crude mixture was concentrated and then purified by recrystallization with from MeOH to yield 120 mg (78% yield) of white crystals.

**$R_f$**: 0.12 in 19:1 Hex:EtOAc.

**$^1$H-NMR** (300 MHz, $CDCl_3$) δ 7.72-7.69 (2H, m), 7.35-7.29 (3H, m), 7.25-7.12 (3H, m), 6.90-6.87 (2H, d), 5.01 (1H, s), 2.93 (1H, bs), 2.80-2.62 (4H, m), 1.99-1.91 (2H, m).

**$^{13}$C-NMR** (75 MHz, $CDCl_3$) δ 137.42, 137.26, 130.55, 128.21, 128.18, 128.11, 127.58, 127.02, 81.11, 66.52, 27.31, 27.00, 24.80.

### 5.8 Synthesis of (2-hexyl-1,3-dithian-2-yl)(phenyl)methanol

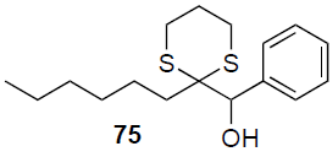


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**Fig. 5.14.** (2-Hexyl-1,3-dithian-2-yl)(phenyl)methanol.

The procedure was performed as described previously.[90] 2-hexyl-1,3-dithiane (100 mg, 0.49 mmol) was placed in a reaction flask and purged with argon. To this THF (1 mL) was added then cooled to -30°C and stirred for 30 min. *n*-BuLi (1.6 M in hexanes, 0.31 mL, 0.49 mmol) was added dropwise while stirring. The reaction was kept at -30°C for 1 hour and then benzaldehyde (62.3 μL, 0.59 mmol) was added. Next the reaction was brought to -5°C and maintained for 2.5 hours. Then the reaction was quenched with saturated aqueous $NH_4Cl$ and extracted with $CHCl_3$. The crude mixture was concentrated and then purified by vacuum distillation to yield 107 mg (73% yield) of a clear oil. This is a new compound. High-resolution MS data to support its structure determination is given below.

**$R_f$**: 0.20 in 10:1 Hex:EtOAc.

**$^1$H-NMR** (300 MHz, $CDCl_3$) δ 7.46-7.32 (5H, m), 5.17 (1H, s), 3.27-3.19 (2H, m), 3.12-3.02 (2H, m), 2.79-2.71 (2H, m), 2.75-2.67 (2H, m), 2.18-2.09 (2H, m), 1.97-1.83 (2H, m), 1.86-1.78 (2H, m), 1.57-1.48 (2H, m), 1.26 (1H, bs), 0.88 (3H, t).

**$^{13}$C-NMR** (75 MHz, $CDCl_3$) δ 137.86, 128.73, 127.64, 127.28, 73.84, 59.34, 34.71, 31.67, 29.74, 26.61, 25.50, 24.37, 24.30, 22.59, 14.07.

**HRMS:** Calculated for $C_{17}H_{26}NaOS_2$: 333.1322, Found: 333.1317.

### 5.9 Synthesis of (1,3-dithian-2-yl)(phenyl)methanol

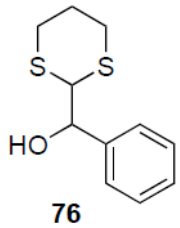


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**Fig. 5.15.** (1,3-Dithian-2-yl)(phenyl)methanol.

The procedure was performed as described previously.[90] 1,3-dithiane (150 mg, 1.25 mmol) was placed in a reaction flask and purged with argon. To this THF (2.5 mL) was added then cooled to -30°C and stirred for 30 min. *n*-BuLi (1.6 M in hexanes, 0.78 mL, 1.25 mmol) was added dropwise while stirring. The reaction was kept at -30°C for 1 hour and then benzaldehyde (152.5 µL, 1.50 mmol) was added. Next the reaction was brought to -5°C and maintained for 2.5 hours. Then the reaction was quenched with saturated aqueous $NH_4Cl$ and extracted with $CHCl_3$. The crude mixture was concentrated and then purified by flash column chromatography eluting with 4:1 Hex:EtOAc to yield 206 mg (73% yield) of a viscous white oil.

**$R_f$**: 0.21 in 4:1 Hex:EtOAc.

**$^{1}$H-NMR** (300 MHz, $CDCl_3$) δ 7.46-7.32 (5H, m), 4.95-4.92 (1H, d), 4.12-4.09 (1H, d), 3.02-2.91 (2H, m), 2.90 (1H, bs), 2.79-2.69 (2H, m).

**$^{13}$C-NMR** (75 MHz, $CDCl_3$) δ 140.19, 128.45, 128.31, 126.86, 74.77, 52.84, 28.26, 27.63, 25.40.

### 5.10 Thermal stability of a 2-phenyl-1,3-dithiane anion by $D_2O$ quench reaction:

The procedure was performed as described previously.[83] 2-phenyl-1,3-dithiane (50 mg, 0.26 mmol) was placed in a reaction flask and purged with argon. To this THF (1 mL) was added and cooled to -30°C and then stirred for 30 min. *n*-BuLi (1.6 M in hexanes, 0.16 mL, 0.28 mmol) was added dropwise while stirring. Mixing continued at -30°C for 1 hour and then the reaction was slowly warmed to 55°C. At 55°C an aliquot was removed from the reaction via a syringe and injected into $D_2O$. DCM was used to extract the product, which was then dried with $MgSO_4$, filtered and concentrated. The crude material was a white needle shaped crystal.

### 5.11 Data specific experimental procedures:

#### 5.11.1 Experimental procedure pertaining to the data summarized in Table 3.3.

This series of experiments tested the following different bases: NaOtBu, LiTMDS, and LDA. 2-Phenyl-1,3-dithiolane (150 mg, 0.823 mmol), $Pd_2(dba)_3$ (19 mg, 0.021 mmol), DPEphos (22 mg, 0.041 mmol), and base (1.07 mmol) were combined in a reaction vessel within a glove box. Once removed from the glove box the reaction vessel was placed under positive pressure with Ar gas. To this dioxane (1 mL) and bromobenzene (0.095 mL, 0.905 mmol) were added and then the reaction was heated to 80°C. After 16 hrs of heating the temperature was reduced to room temperature and a 0.1 mL aliquot was taken. This aliquot was quenched with distilled

$H_2O$, extracted with DCM, dried with $MgSO_4$, and concentrated to dryness. Then this crude material was submitted for NMR analysis, which showed that the bulk of the material was unreacted starting material.

### 5.11.2 Experimental procedure pertaining to the data summarized in Scheme 3.9.

$Pd_2(dba)_3$ (21.0 mg, 0.023 mmol) and DPEphos (24.4 mg, 0.045 mmol) were added to a reaction vessel and the headspace was purged with argon gas. To this dioxane (2 mL) and bromobenzene (95 μL, 0.905 mmol) were added.

2-Phenyl-1,3-dithiane (195 mg, 0.999 mmol) was placed in a separate vessel and purged with argon gas. To this THF (2 mL) was added and the solution was cooled to -40°C. After mixing for 30 min at -40°C, *n*-BuLi (1.6 M in hexanes, 0.68 mL, 1.36 mmol) was added dropwise while stirring. This mixture was slowly warmed to room temperature over a period of 1 hour. At room temperature this basic solution was transferred via cannula into the other reaction vessel. The resulting mixture was then slowly heated to 90°C and maintained for 16 hours. The reaction was then cooled to room temperature, then diluted with $Et_2O$ and filtered through Celite. The mixture was then washed with 1 M HCl, then washed with distilled $H_2O$, and finally washed with brine. The organic layer was separated and dried with anhydrous $MgSO_4$, then filtered and concentrated to dryness. The crude product was analyzed by GC-FID. The results showed evidence of a trace amount of desired product, a trace amount of biphenyl, and the bulk of the material to be unreacted 2-phenyl-1,3-dithiane.

### 5.11.3 Experimental procedure pertaining to the data summarized in Scheme 3.10.

$Pd_2(dba)_3$ (23.3 mg, 0.025 mmol) and SPhos (15.7 mg, 0.038 mmol) were added to a reaction vessel and the headspace was purged with argon gas. To this toluene (4 mL) and iodobenzene (95 μL, 0.905 mmol) were added.

2-Phenyl-1,3-dithiane (195 mg, 0.999 mmol) was placed in a separate vessel and purged with argon gas. To this THF (3 mL) was added and the solution was cooled to -40°C. After mixing for 30 min at -40°C, *n*-BuLi (1.6 M in hexanes, 0.68 mL, 1.36 mmol) was added dropwise while stirring. This mixture was slowly warmed to room temperature over a period of 1 hour. At room temperature this basic solution was transferred via cannula into the other reaction vessel. The resulting mixture was then slowly heated to 60°C and maintained for 16 hours. The reaction was then cooled to room temperature, then diluted with $Et_2O$ and filtered through Celite. The mixture was then washed with 1 M HCl, then washed with distilled $H_2O$, and finally washed with brine. The organic layer was separated and dried with anhydrous $MgSO_4$, then filtered and concentrated to dryness. The crude product was then analyzed by GC-. The results showed evidence of unreacted starting material; 2-phenyl-1,3-dithiane.

### 5.11.4 Experimental procedure pertaining to the data summarized in Scheme 3.11 and Table 3.9.

This series of experiments tested the following different ligands: DPEphos, $PCy_3 \cdot HBF_4$, Xantphos, DPPF, and DPPB. One experiment used $Pd(PPh_3)_4$ as the ligand and catalyst source.

Catalyst and ligand [$Pd_2(dba)_3$ (21.0 mg, 0.023 mmol) and ligand (0.045 mmol) or $Pd(PPh_3)_4$ (26.6 mg, 0.023 mmol)] were added to a reaction vessel and the headspace was purged with argon gas. To this THF (3 mL) and bromobenzene (142 μL, 0.905 mmol) were added.

2-Phenyl-1,3-dithiane (195 mg, 0.999 mmol) was placed in a separate vessel and purged with argon gas. To this THF (3 mL) was added and the solution was cooled to -78°C. After mixing for 30 min at -78°C, *n*-BuLi (1.6 M in hexanes, 0.68 mL, 1.36 mmol) was added dropwise while stirring. Following an additional 30 min at -78°C, $ZnCl_2$ (1.0 M in $Et_2O$, 1.45 mL, 1.45 mmol) was added dropwise while stirring. Next, this mixture was slowly warmed to room temperature over a period of 1 hour. At room temperature the organozinc solution was transferred via cannula into the reaction vessel. The resulting mixture was then slowly heated to 60°C and maintained for 16 hours. Then the reaction was cooled to room temperature, diluted with $Et_2O$ and then filtered through Celite. The resulting mixture was washed with 1 M HCl, then washed with distilled $H_2O$, and finally washed with brine. The organic layer was separated and dried with anhydrous $MgSO_4$, then filtered and concentrated to dryness. The crude product was analyzed by GC-FID. The results of entries 1 – 4 showed evidence of only unreacted starting material; 2-phenyl-1,3-dithiane. The results of entries 5 and 6 showed trace evidence of the desired product, 2,2-diphenyl-1,3-dithiane, while the bulk of the material was unreacted starting material.

### 5.11.5 Experimental procedure pertaining to the data summarized in Scheme 3.13.

2-Phenyl-1,3-dithiane (100 mg, 0.509 mmol) was placed in a reaction vessel and purged with argon gas. To this THF (1.5 mL) was added and the solution was cooled to -78°C. After

mixing for 30 min at -78°C, *n*-BuLi (1.6 M in hexanes, 0.28 mL, 0.560 mmol) was added dropwise while stirring. After mixing for an additional 15 min $B(OCH_3)_3$ (0.62 μL, 0.560 mmol) was added and the mixture was allowed to slowly warm to room temperature and then mixed for an additional 4 hours. The reaction was quenched with distilled $H_2O$, acidified with 1 M HCl, and then extracted with EtOAc. The organic layer was washed with brine, dried with $MgSO_4$, and then concentrated to dryness. This material was then submitted for NMR analysis, which provided evidence of unreacted starting material; 2-phenyl-1,3-dithiane.

### 5.11.6 Experimental procedure pertaining to the data summarized in Scheme 3.14.

2-Phenyl-1,3-dithiane (20 mg, 0.102 mmol) was placed in an NMR tube and purged with argon gas. To this benzene-$d_6$ (0.75 mL) and NCS (28 mg, 0.210 mmol) were added and the reaction was monitored with $^1$H-NMR and $^{13}$C-NMR. The $^1$H-NMR was collected in 16 scans and the $^{13}$C-NMR was collected in 32 scans. Once the peak at approximately 5.19 ppm in the $^1$H-NMR disappeared the sample was immediately submitted for GC-MS analysis; which provided evidence of several byproducts, but no evidence of the desired product or starting material.

### 5.11.7 Experimental procedure pertaining to the data summarized in Table 3.10.

This series of experiments tested $Pd_2(dba)_3$ with the following different ligands: $PCy_3 \cdot HBF_4$, DPPF, DPEphos, and Sphos. Another experiment used $Pd(PPh_3)_4$ as the ligand and catalyst source. These conditions were repeated using two different bases: $Cs_2CO_3$ and CsF.

2-Phenyl-1,3-dithiane (100 mg, 0.509 mmol) was placed in a reaction vessel and purged with argon gas. To this toluene (0.7 mL) was added and the mixture was stirred. Next, while the temperature was maintained at 20-25°C with external cooling, NCS (122 mg, 0.916 mmol) was added very slowly over a period of 1 hour and then stirred for an additional hour.

In a separate reaction vessel catalyst and ligand [$Pd_2(dba)_3$ (11.7 mg, 0.013 mmol) and ligand (0.025 mmol) or $Pd(PPh_3)_4$ (15.0 mg, 0.013 mmol)] were combined with phenylboronic acid (68.3 mg, .560 mmol) and base (1.53 mmol). This vessel was purged with argon and then toluene (0.8 mL) was added. The two reaction vessels were combined and heated to 60°C for 8 hours. Analysis by GC-FID did not provide any evidence of the desired product.

### 5.11.8 Experimental procedure pertaining to the data summarized in Scheme 3.16.

2-Phenyl-1,3-dithiane (20 mg, 0.102 mmol) was placed in an NMR tube and purged with argon gas. To this benzene-$d_6$ (0.75 mL) and NBS (32.6 mg, 0.183 mmol) were added and the reaction was monitored with $^1$H-NMR and $^{13}$C-NMR. The $^1$H-NMR was collected in 16 scans and the $^{13}$C-NMR was collected in 32 scans. Once the peak at approximately 5.19 ppm in the $^1$H-NMR disappeared the sample was immediately submitted for GC-MS analysis; which provided evidence of several byproducts, unreacted starting material, and no evidence of the desired product.

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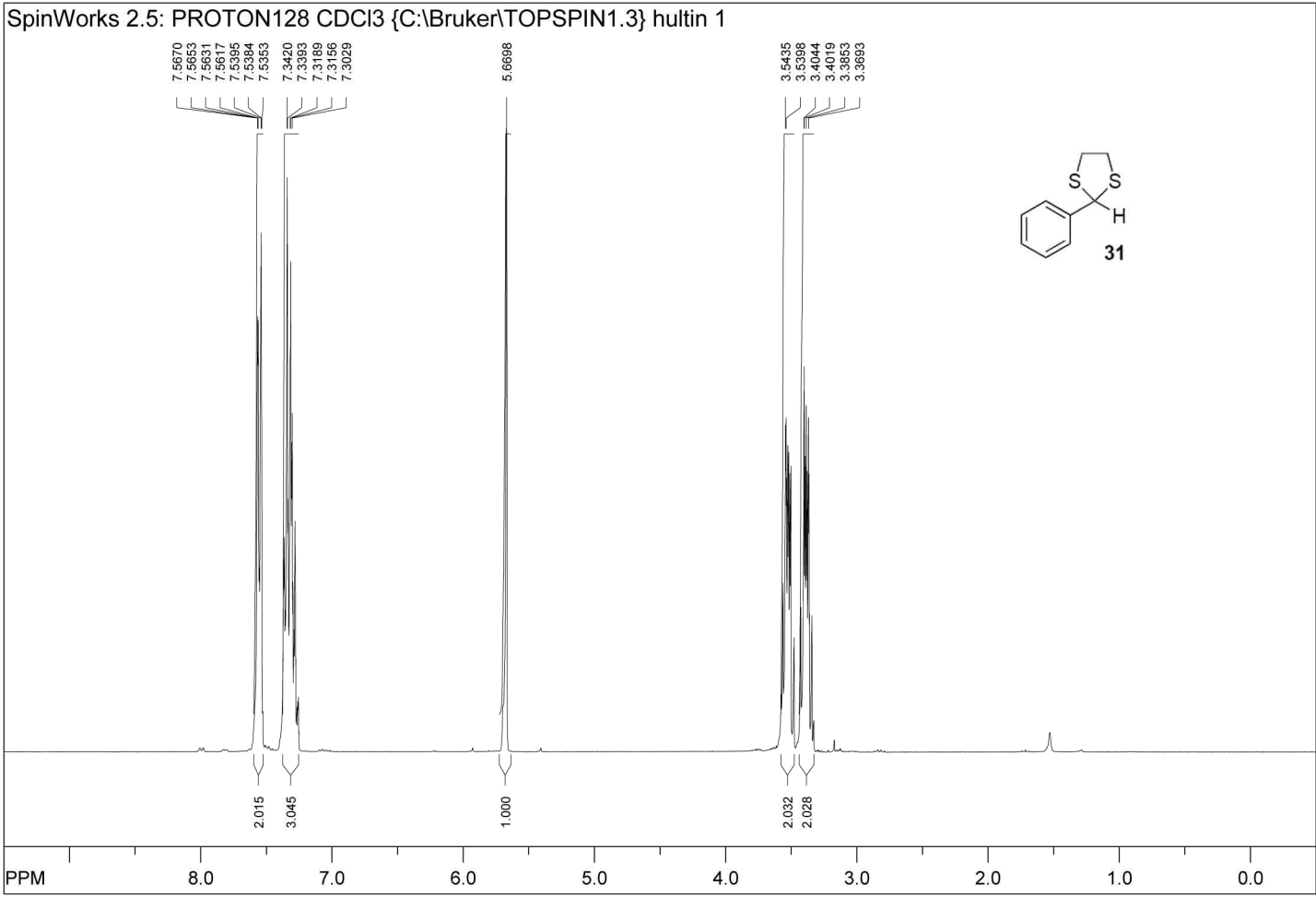
# Appendix I

## NMR Spectra

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number of scans: 128
processed size: 32768 complex points
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Hz/cm: 120.052 ppm/cm: 0.40000

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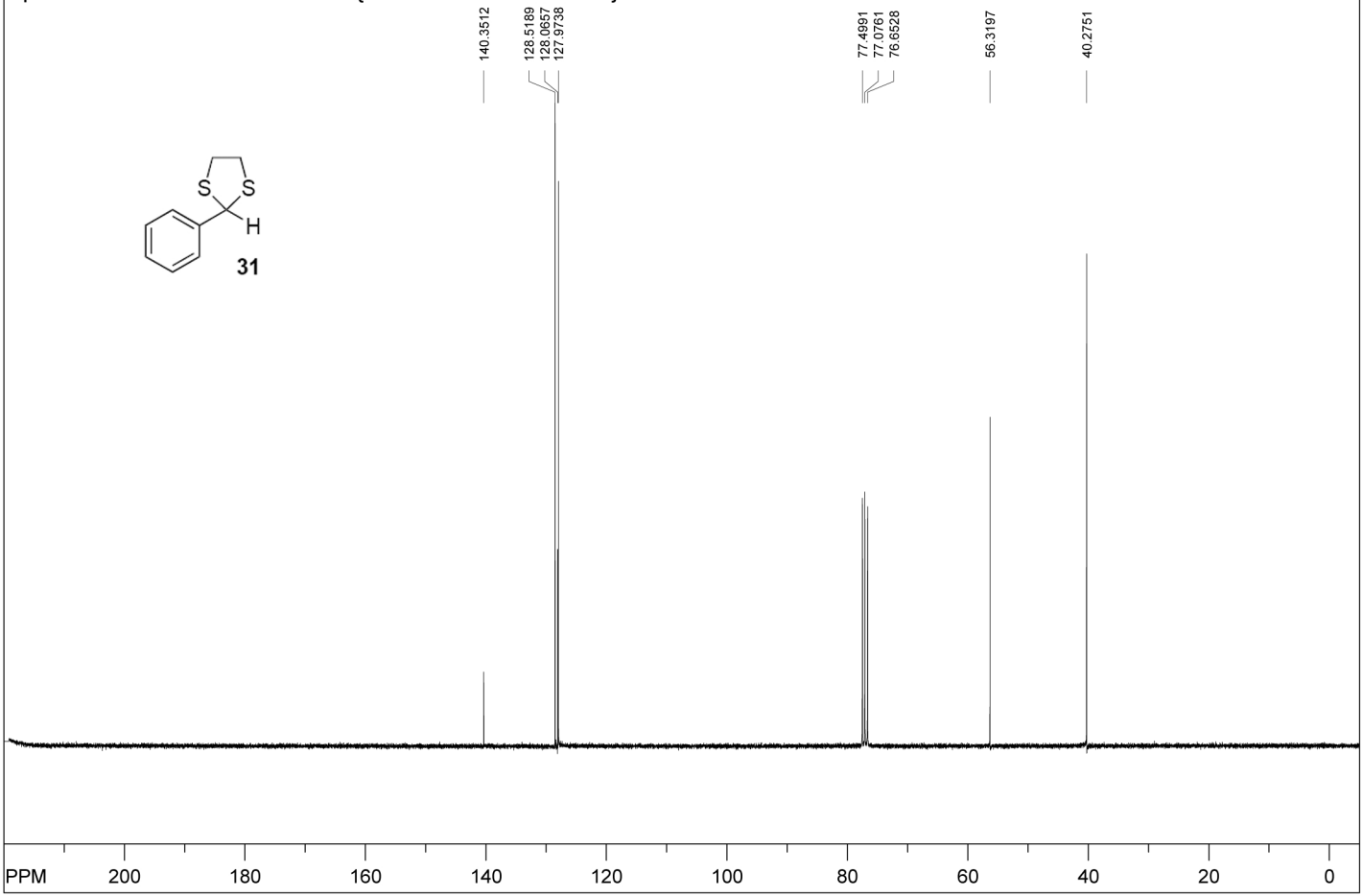


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width: 17985.61 Hz = 238.297995 ppm = 0.274439 Hz/pt
number of scans: 3072
processed size: 32768 complex points
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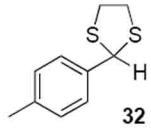


32

2.000 2.000 1.000 2.034 2.029

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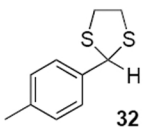


**32**

137.9008
137.1588
129.2024
127.8499
77.4728
77.0491
76.6262
56.1891
40.2327
21.1404

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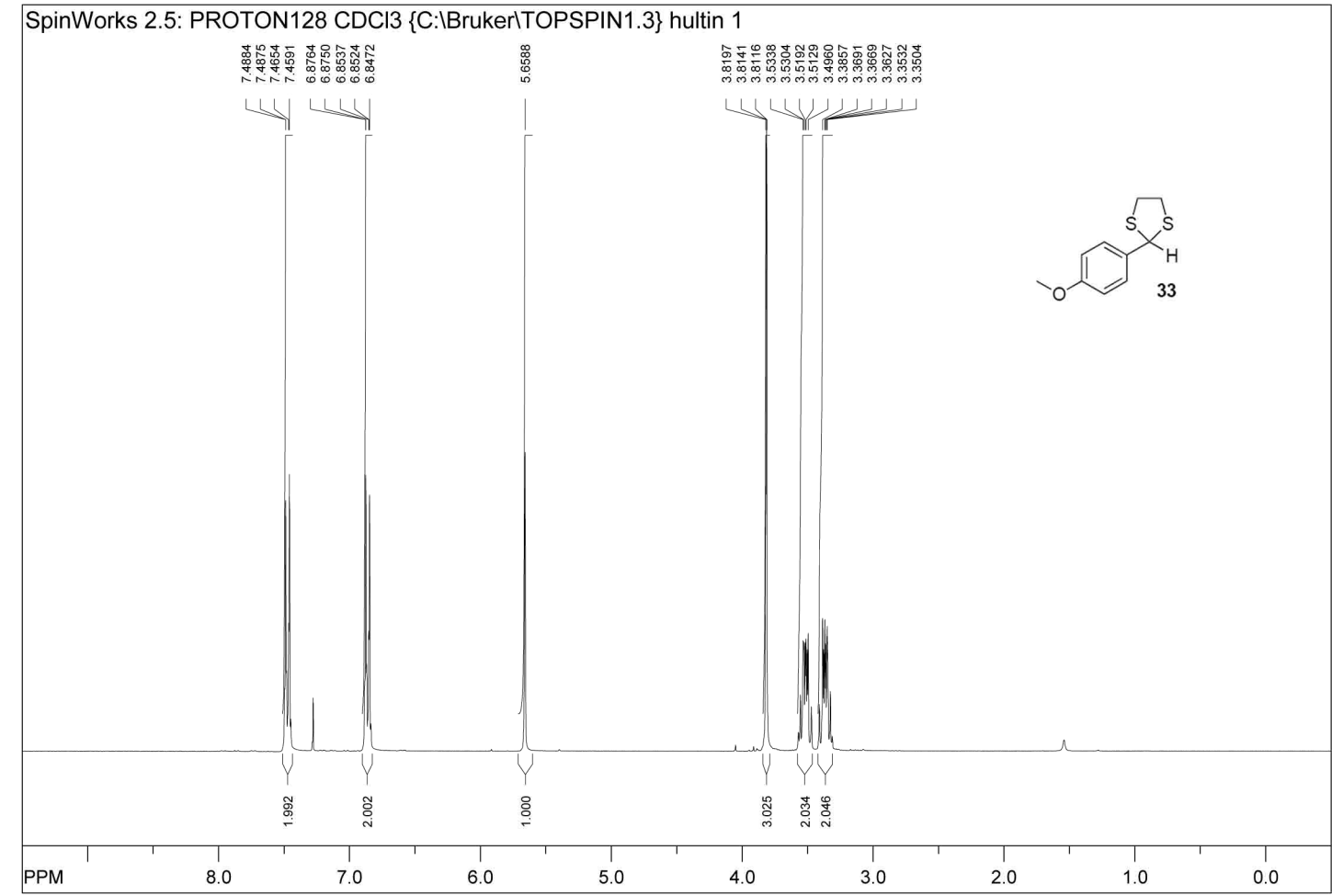





33

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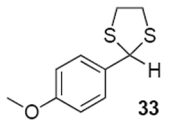


33

159.4362
131.8422
129.1677
113.8994
77.4772
77.0543
76.6311
56.0940
55.3523
40.2319

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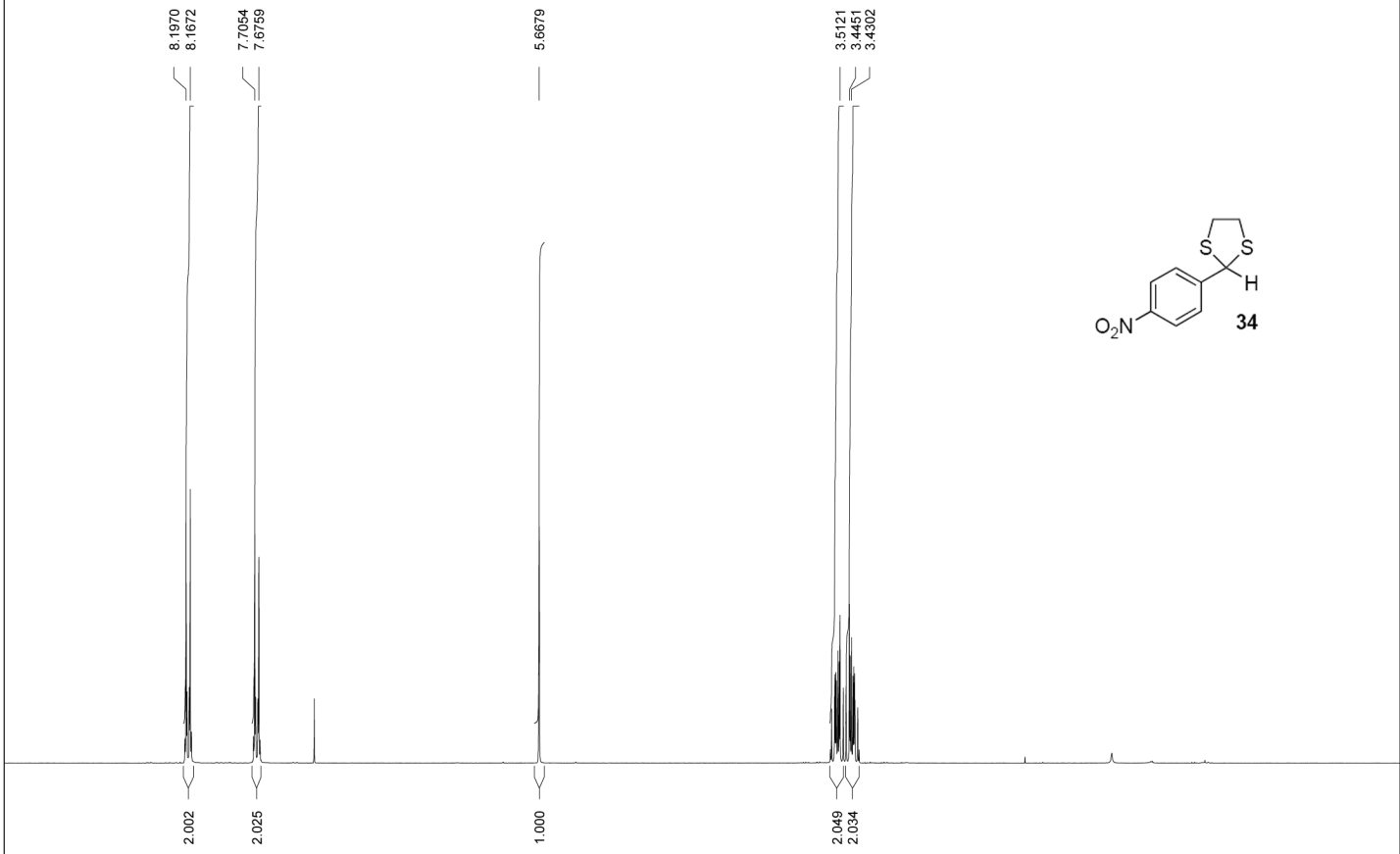





**34**

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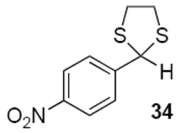


34

148.6576
147.4643
128.8676
123.7763
77.4748
77.0512
76.6272
54.9519
40.5224

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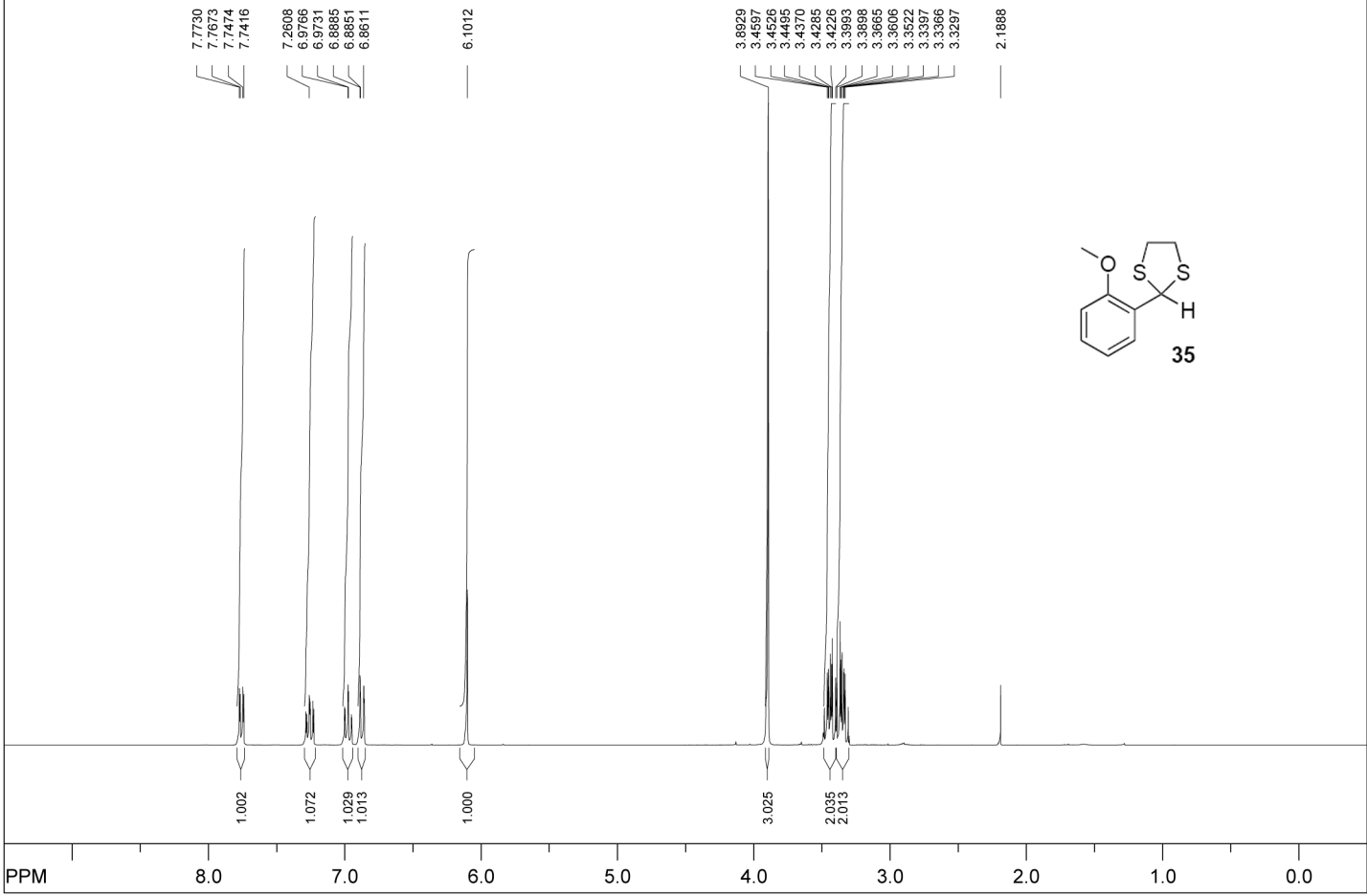





35

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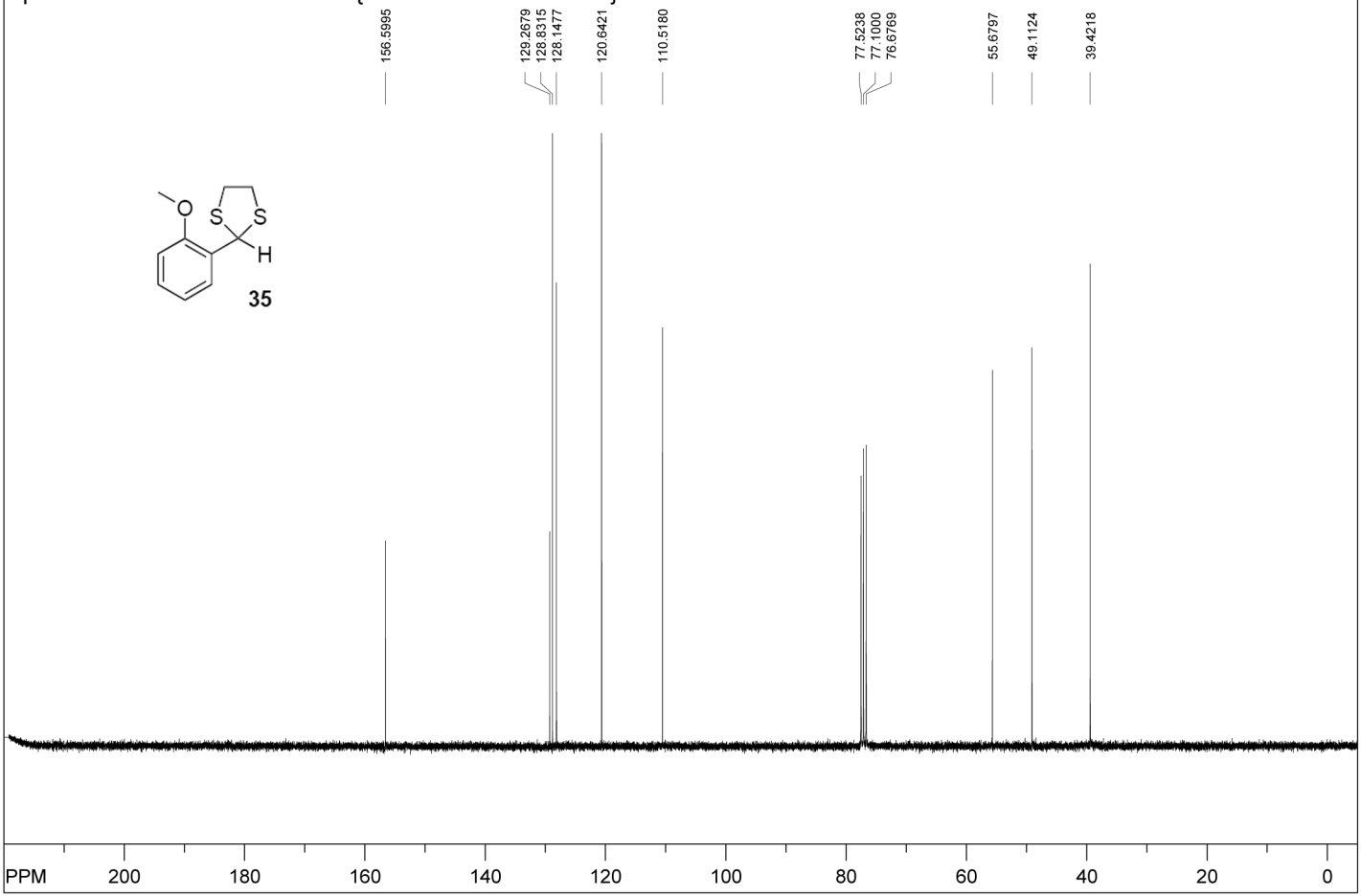


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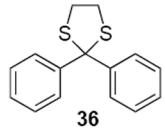


**36**

3.993 6.124 3.996

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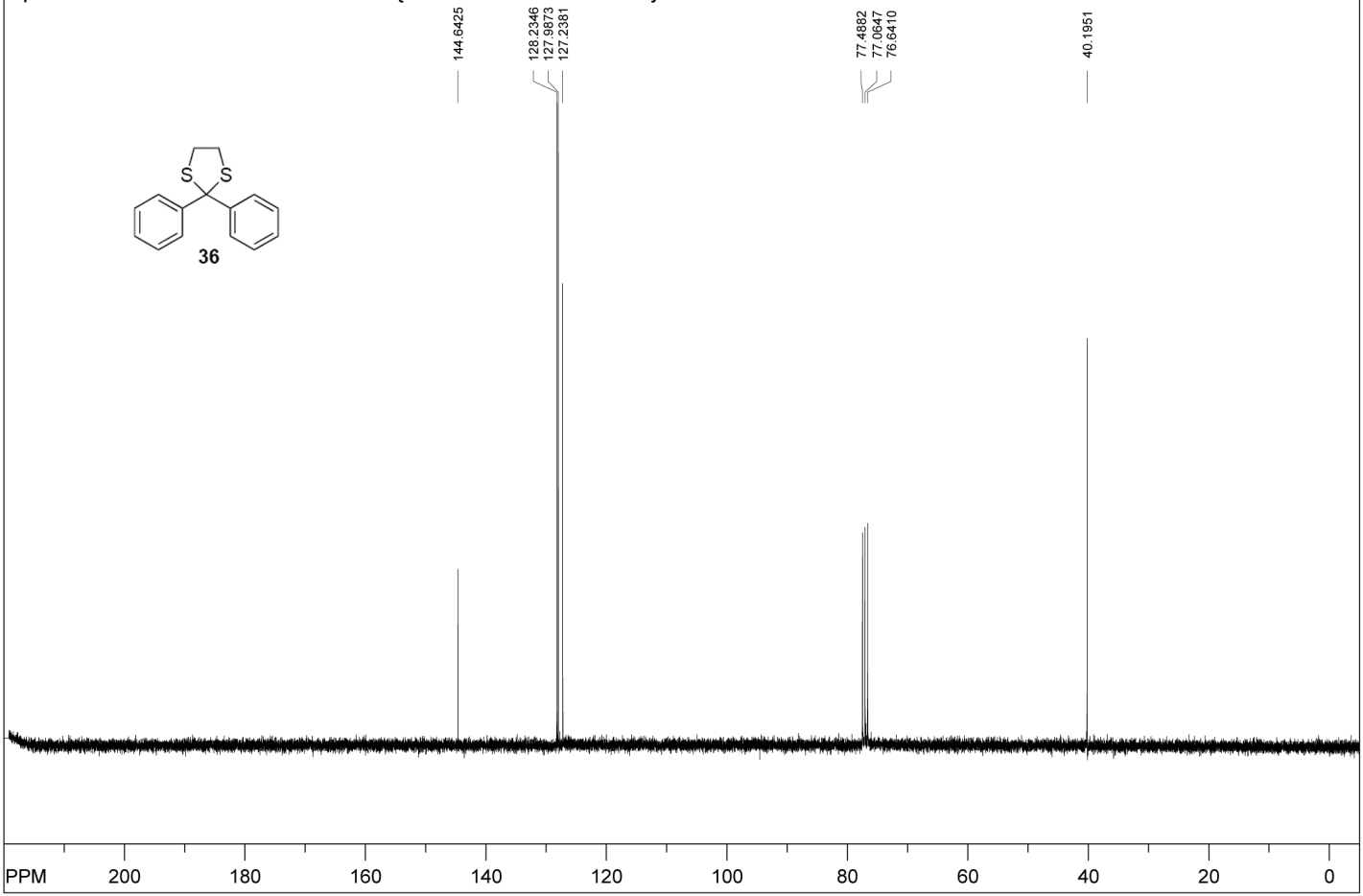


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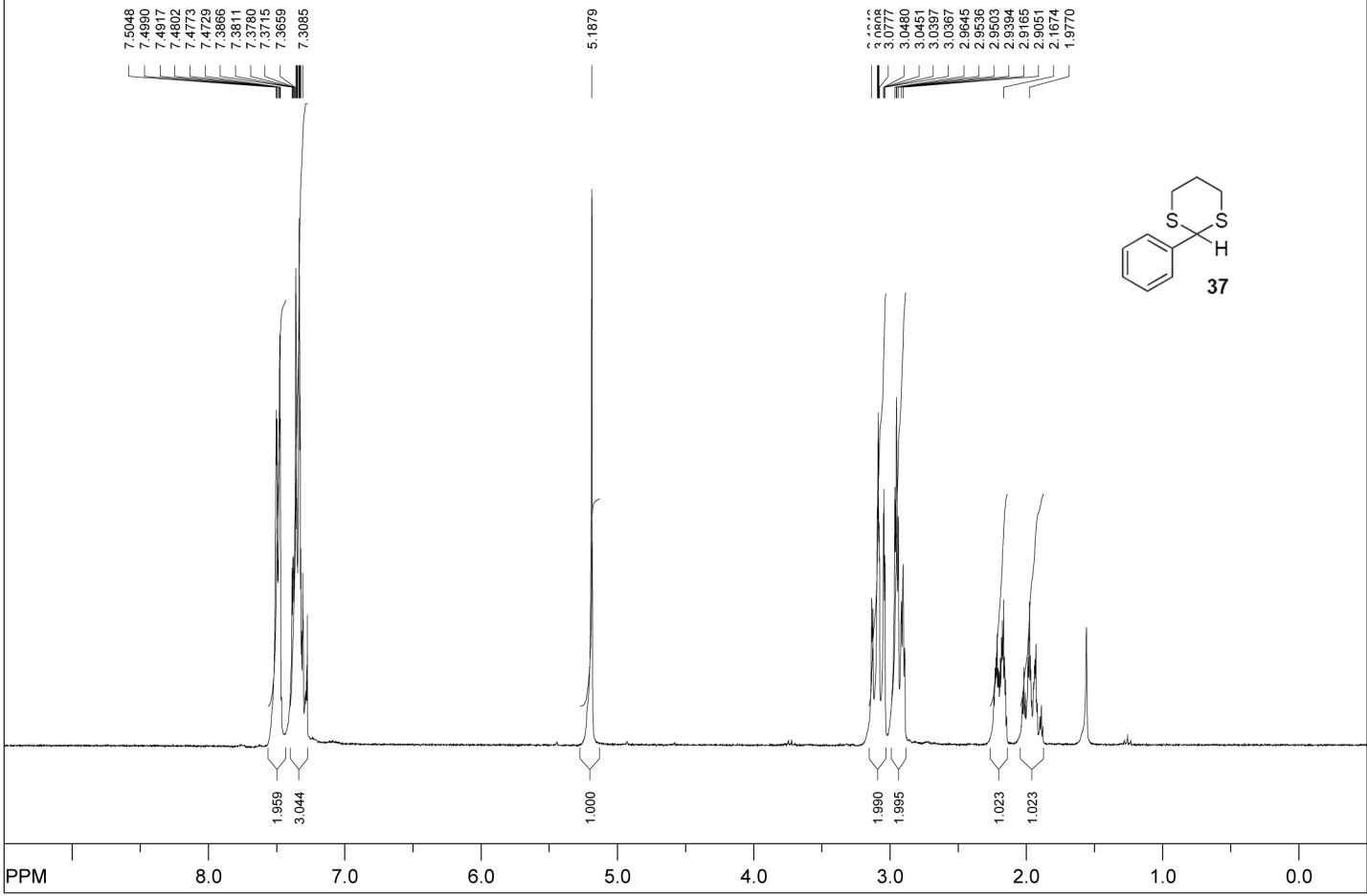


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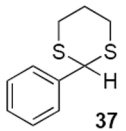


37

139.1429
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77.4778
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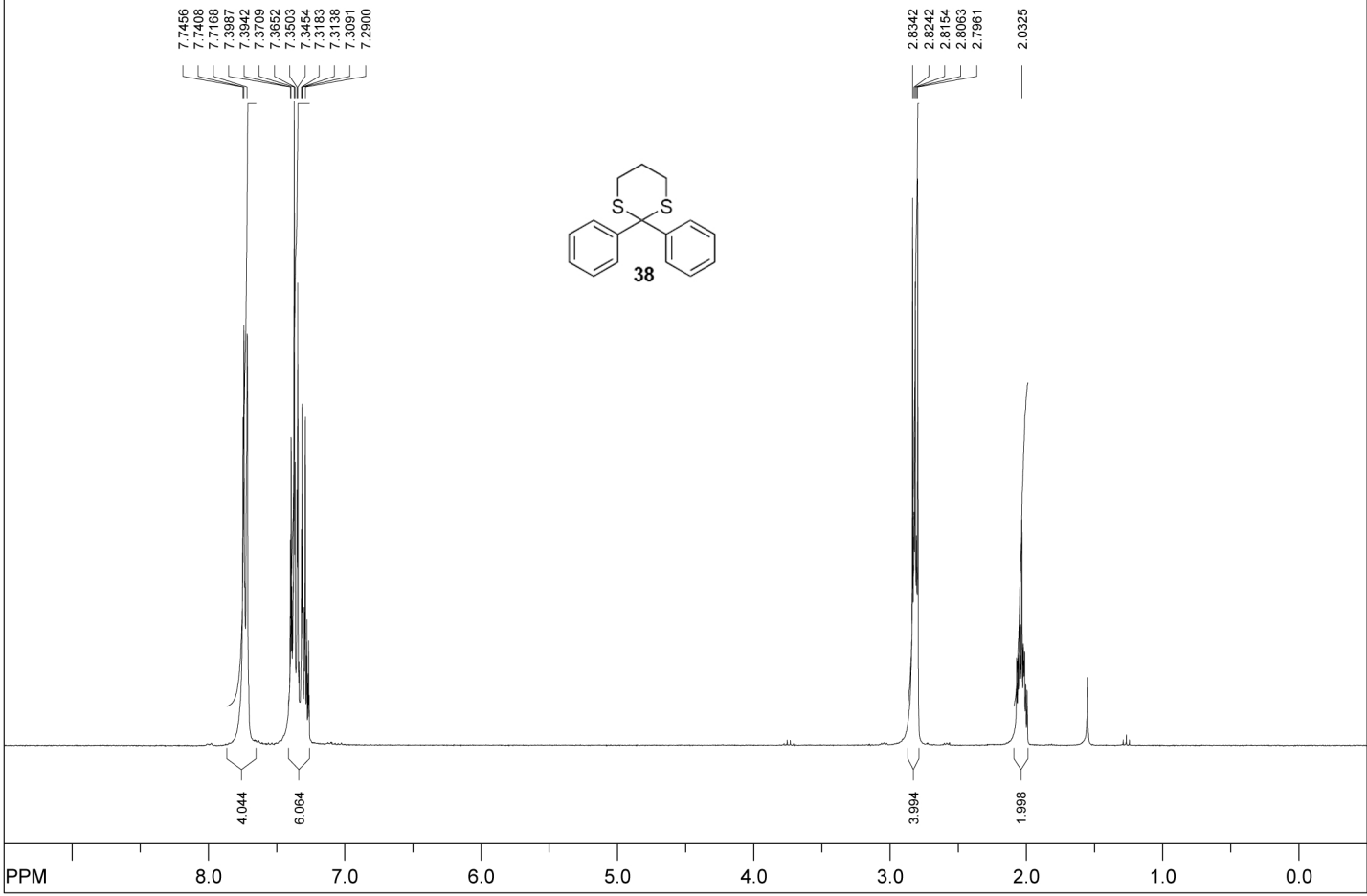
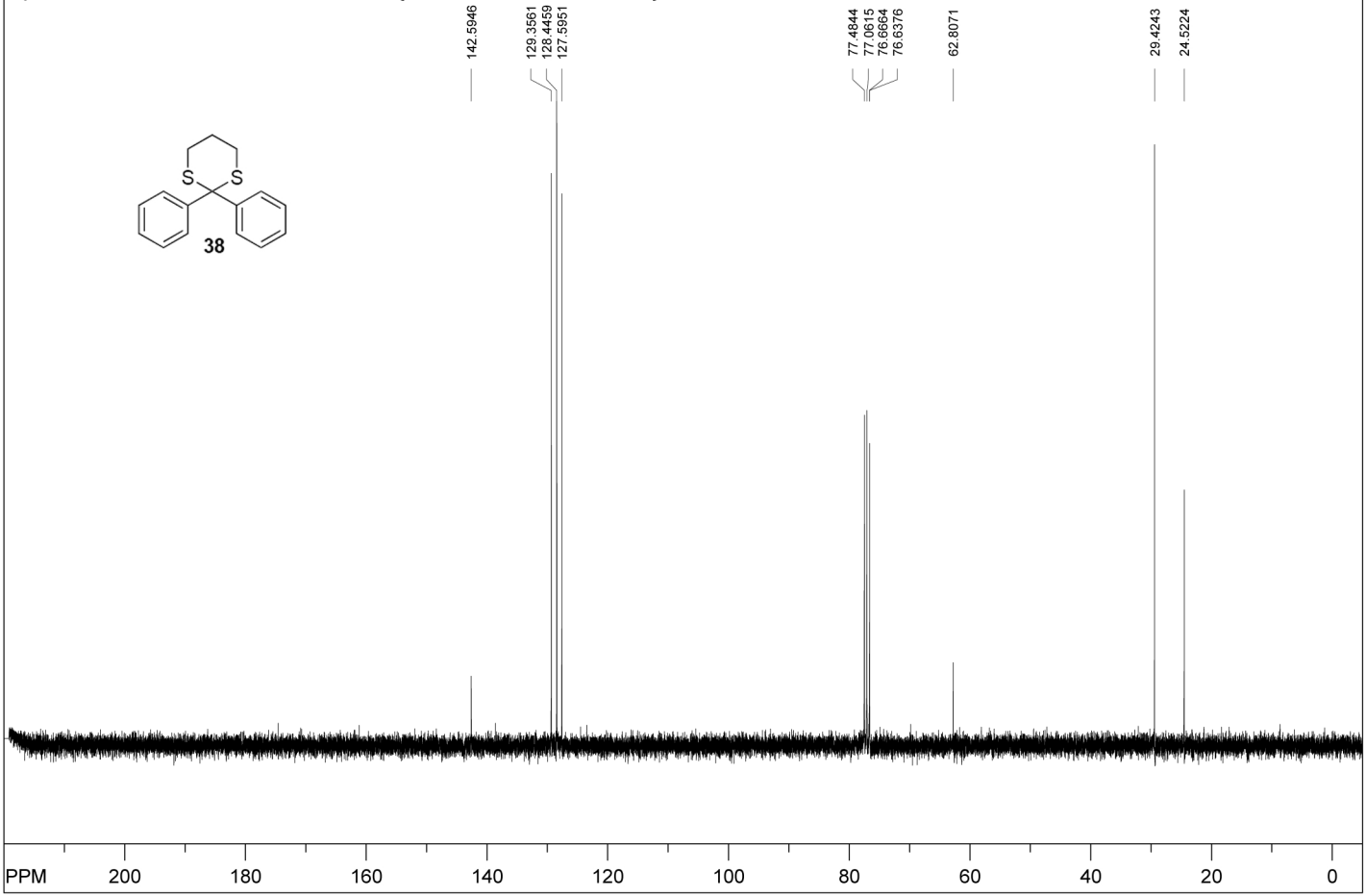
Hz/cm: 679.210 ppm/cm: 8.99910

SpinWorks 2.5: PROTON CDCl3 {C:\Bruker\TOPSPIN1.3} hultin 1



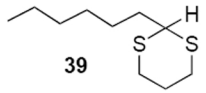

file: C:\Users\Michael\Desktop\Thesis\Data\Lab Computer and NMR\NMR\MM-B2-121P\1\fid expt: <zg3(freq. of 0 ppm: 300.130006 MHz
transmitter freq.: 300.131853 MHz
time domain size: 65536 points
width: 6172.84 Hz = 20.567092 ppm = 0.094190 Hz/pt
number of scans: 16
processed size: 32768 complex points
LB: 0.000 GB: 0.0000
Hz/cm: 120.052 ppm/cm: 0.40000

SpinWorks 2.5: C13CPD256 CDCl3 {C:\Bruker\TOPSPIN1.3} hultin 1




file: C:\Users\Michael\Desktop\Thesis\Data\Lab Computer and NMR\NMR\MM-B2-121P\2\fid expt: <zgpg> freq. of 0 ppm: 75.467749 MHz
transmitter freq.: 75.475295 MHz
time domain size: 65536 points
width: 17985.61 Hz = 238.297995 ppm = 0.274439 Hz/pt
number of scans: 219
processed size: 32768 complex points
LB: 0.000 GB: 0.0000
Hz/cm: 679.210 ppm/cm: 8.99910

SpinWorks 2.5: PROTON CDCl3 {C:\Bruker\TOPSPIN1.3} hultin 13




39

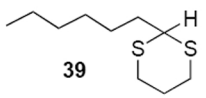
4.0735 4.0507 4.0277 2.8898 2.8804 2.8542 2.8427 2.8280 2.0982 1.8856 1.7846 1.7608 1.7392 1.7333 1.7102 1.5031 1.4779 1.3306 1.3180 1.3130 1.3003 1.2919 1.2860 0.9076 0.9017 0.8947 0.8855 0.8622

1.000 4.069 1.033 1.025 2.026 2.029 6.009 3.004

PPM 8.0 7.0 6.0 5.0 4.0 3.0 2.0 1.0 0.0

file: C:\Users\Michael\Desktop\Thesis\Data\Lab Computer and NMR\NMR\MM-B3-45P\1\fid expt: <zg30> freq. of 0 ppm: 300.130006 MHz
transmitter freq.: 300.131853 MHz
time domain size: 65536 points
width: 6172.84 Hz = 20.567092 ppm = 0.094190 Hz/pt
number of scans: 16
processed size: 32768 complex points
LB: 0.000 GB: 0.0000
Hz/cm: 120.052 ppm/cm: 0.40000

SpinWorks 2.5: C13CPD32 CDCl3 {C:\Bruker\TOPSPIN1.3} hultin 13



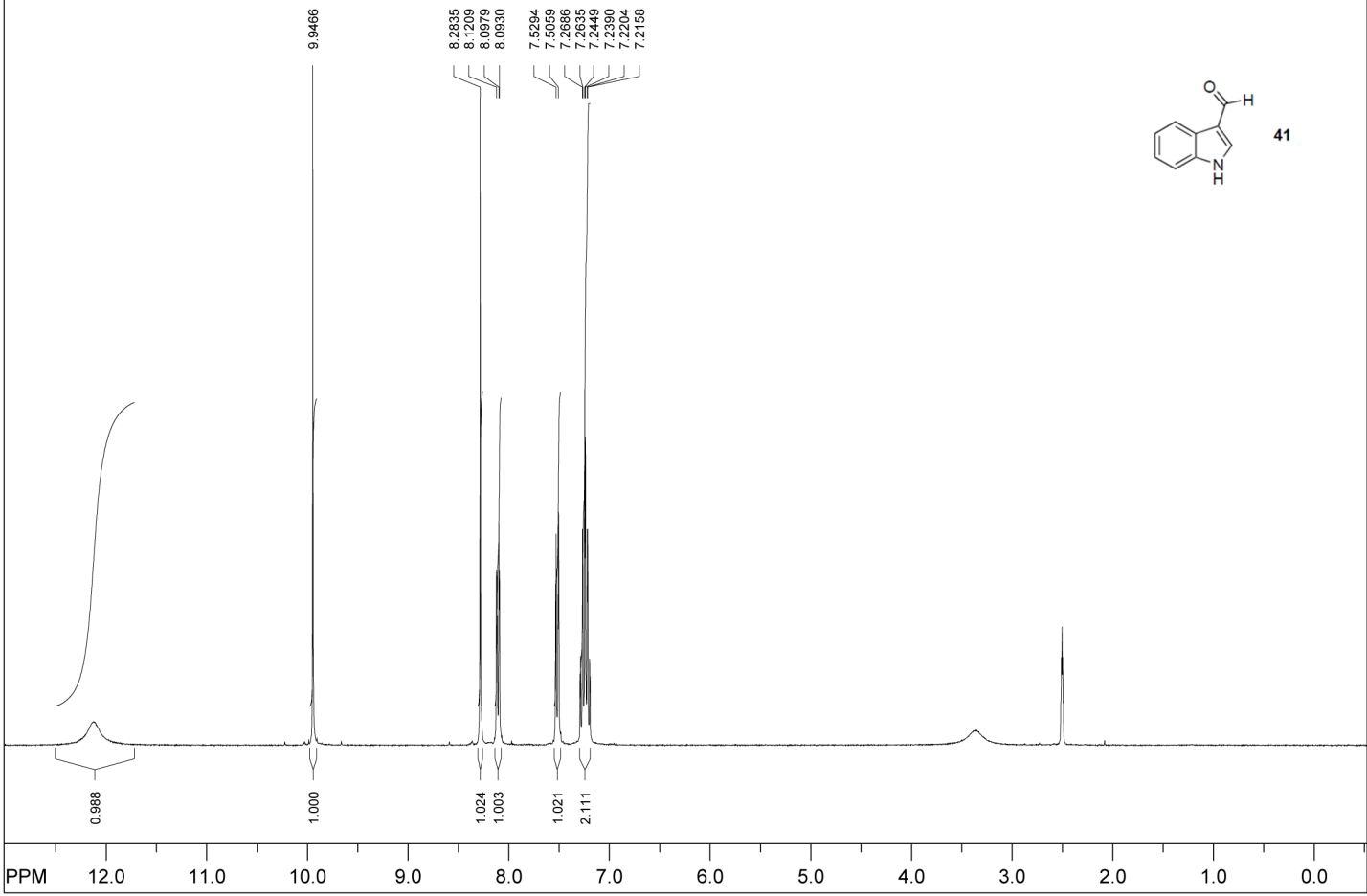

39

77.4857
77.0626
76.6395
47.7006
35.4928
31.5767
30.5220
28.9073
26.5947
26.0945
22.5578
14.0633

PPM 200 180 160 140 120 100 80 60 40 20 0

file: C:\Users\Michael\Desktop\Thesis\Data\Lab Computer and NMR\NMR\MM-B3-45P\2\fid expt: <zgpg> freq. of 0 ppm: 75.467749 MHz
transmitter freq.: 75.475295 MHz
time domain size: 65536 points
width: 17985.61 Hz = 238.297995 ppm = 0.274439 Hz/pt
number of scans: 200
processed size: 32768 complex points
LB: 0.000 GB: 0.0000
Hz/cm: 679.210 ppm/cm: 8.99910

SpinWorks 2.5: PROTON DMSO {C:\Bruker\TOPSPIN1.3} hultin 2



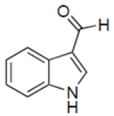




41

file: C:\Users\Michael\Desktop\Thesis\Data\Lab Computer and NMR\NMR\MM-B1-125-dmso\1\fid expt: <freq. of 0 ppm: 300.130000 MHz
transmitter freq.: 300.131853 MHz
processed size: 32768 complex points
time domain size: 65536 points
LB: 0.000 GB: 0.0000
width: 6172.84 Hz = 20.567092 ppm = 0.094190 Hz/pt
Hz/cm: 162.553 ppm/cm: 0.54161
number of scans: 16

SpinWorks 2.5: C13CPD256 DMSO {C:\Bruker\TOPSPIN1.3} hultin 2



41

184.9145
138.3877
137.0219
124.0929
123.4148
122.0771
120.7889
118.1414
112.3768
40.3215
40.0473
39.7689
39.4910
39.2131
38.9346

PPM 200 180 160 140 120 100 80 60 40 20 0

file: C:\Users\Michael\Desktop\Thesis\Data\Lab Computer and NMR\NMR\MM-B1-125-dmso\2\fid expt: <freq. of 0 ppm: 75.467787 MHz
transmitter freq.: 75.475295 MHz processed size: 32768 complex points
time domain size: 65536 points LB: 0.000 GB: 0.0000
width: 17985.61 Hz = 238.297995 ppm = 0.274439 Hz/pt Hz/cm: 679.210 ppm/cm: 8.99910
number of scans: 256

SpinWorks 2.5: PROTON CDCl3 {C:\Bruker\TOPSPIN1.3} hultin 1

**40**




file: C:\Users\Michael\Desktop\Thesis\Data\Lab Computer and NMR\NMR\MM-B3-65P2\1\fid expt: <zg3(freq. of 0 ppm: 300.130006 MHz
transmitter freq.: 300.131853 MHz
time domain size: 65536 points
width: 6172.84 Hz = 20.567092 ppm = 0.094190 Hz/pt
number of scans: 16
processed size: 32768 complex points
LB: 0.000 GB: 0.0000
Hz/cm: 120.052 ppm/cm: 0.40000

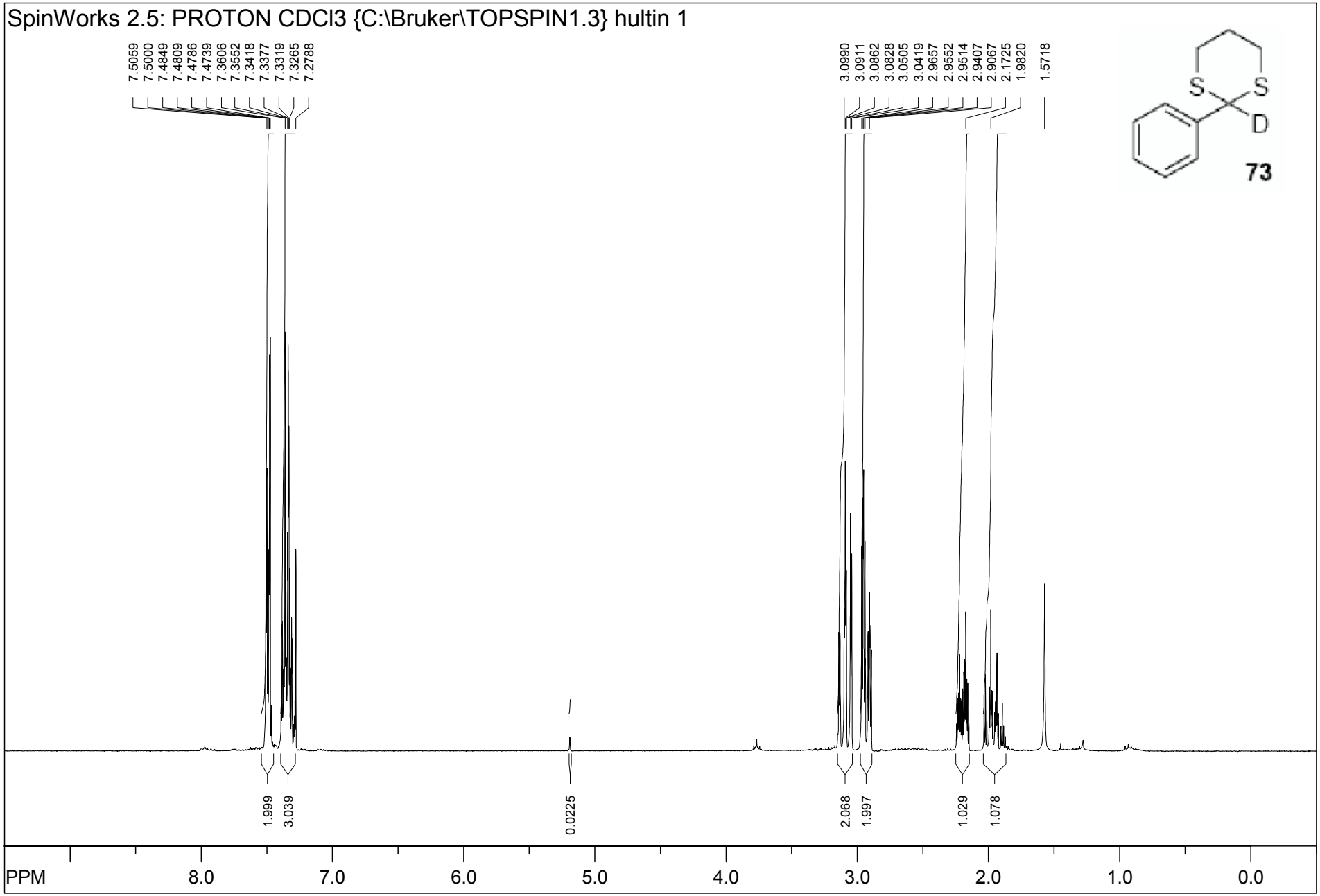
SpinWorks 2.5: C13CPD32 CDCl3 {C:\Bruker\TOPSPIN1.3} hultin 1

40




file: C:\Users\Michael\Desktop\Thesis\Data\Lab Computer and NMR\NMR\MM-B3-65P2\2\fid expt: <zgpg> freq. of 0 ppm: 75.467749 MHz
transmitter freq.: 75.475295 MHz
time domain size: 65536 points
width: 17985.61 Hz = 238.297995 ppm = 0.274439 Hz/pt
number of scans: 512
processed size: 32768 complex points
LB: 0.000 GB: 0.0000
Hz/cm: 719.353 ppm/cm: 9.53097

SpinWorks 2.5: PROTON CDCl3 {C:\Bruker\TOPSPIN1.3} hultin 1




file: C:\Users\Michael\Desktop\Thesis\Data\Lab Computer and NMR\NMR\MM-B2-127-D2O Quench\1\fid freq. of 0 ppm: 300.130006 MHz

transmitter freq.: 300.131853 MHz

time domain size: 65536 points

width: 6172.84 Hz = 20.567092 ppm = 0.094190 Hz/pt

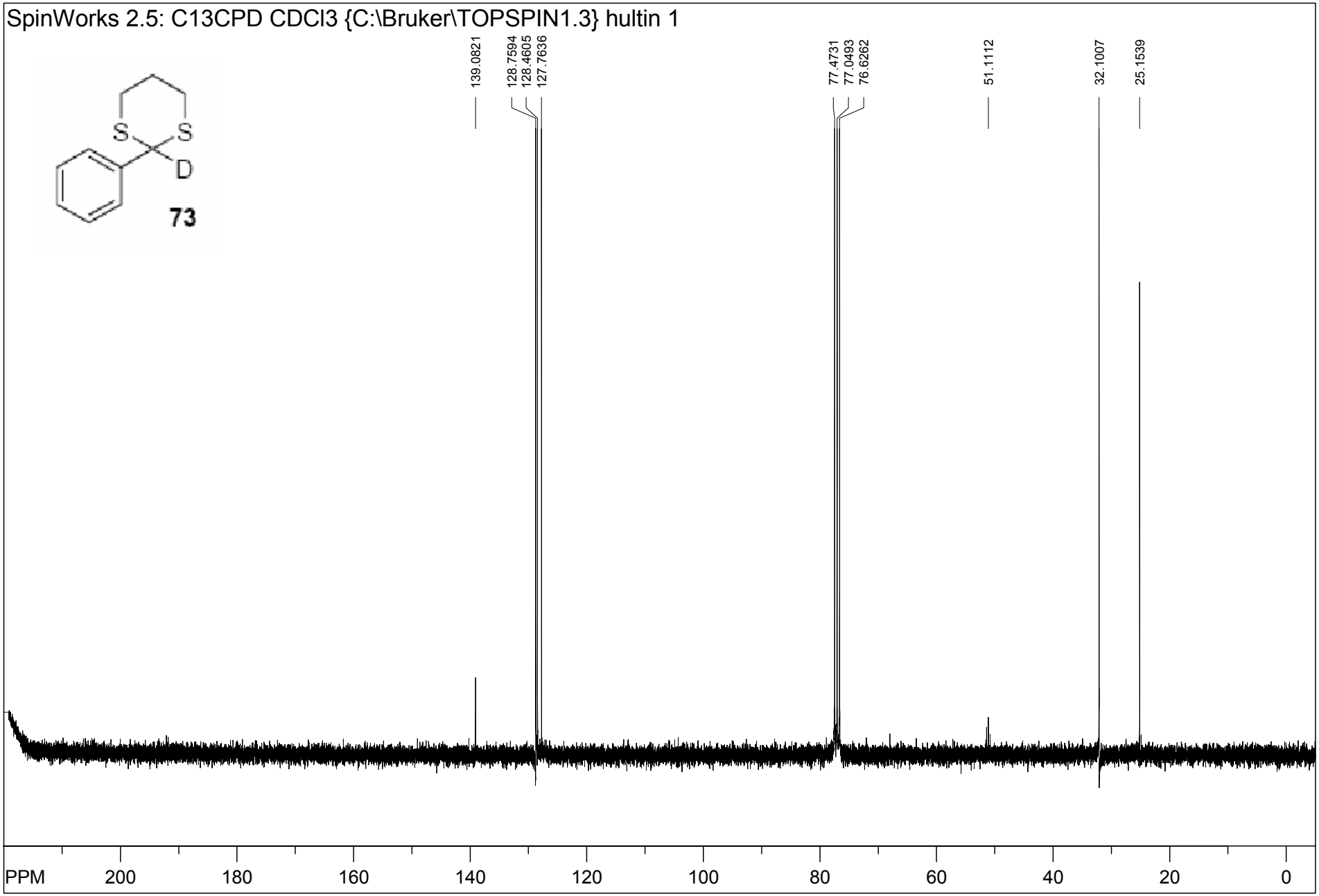
number of scans: 64

processed size: 32768 complex points

LB: 0.000 GB: 0.0000

Hz/cm: 120.052 ppm/cm: 0.40000

SpinWorks 2.5: C13CPD CDCl3 {C:\Bruker\TOPSPIN1.3} hultin 1




file: C:\Users\Michael\Desktop\Thesis\Data\Lab Computer and NMR\NMR\MM-B2-127-D2O Quench\2\fid freq. of 0 ppm: 75.467749 MHz

transmitter freq.: 75.475295 MHz

time domain size: 65536 points

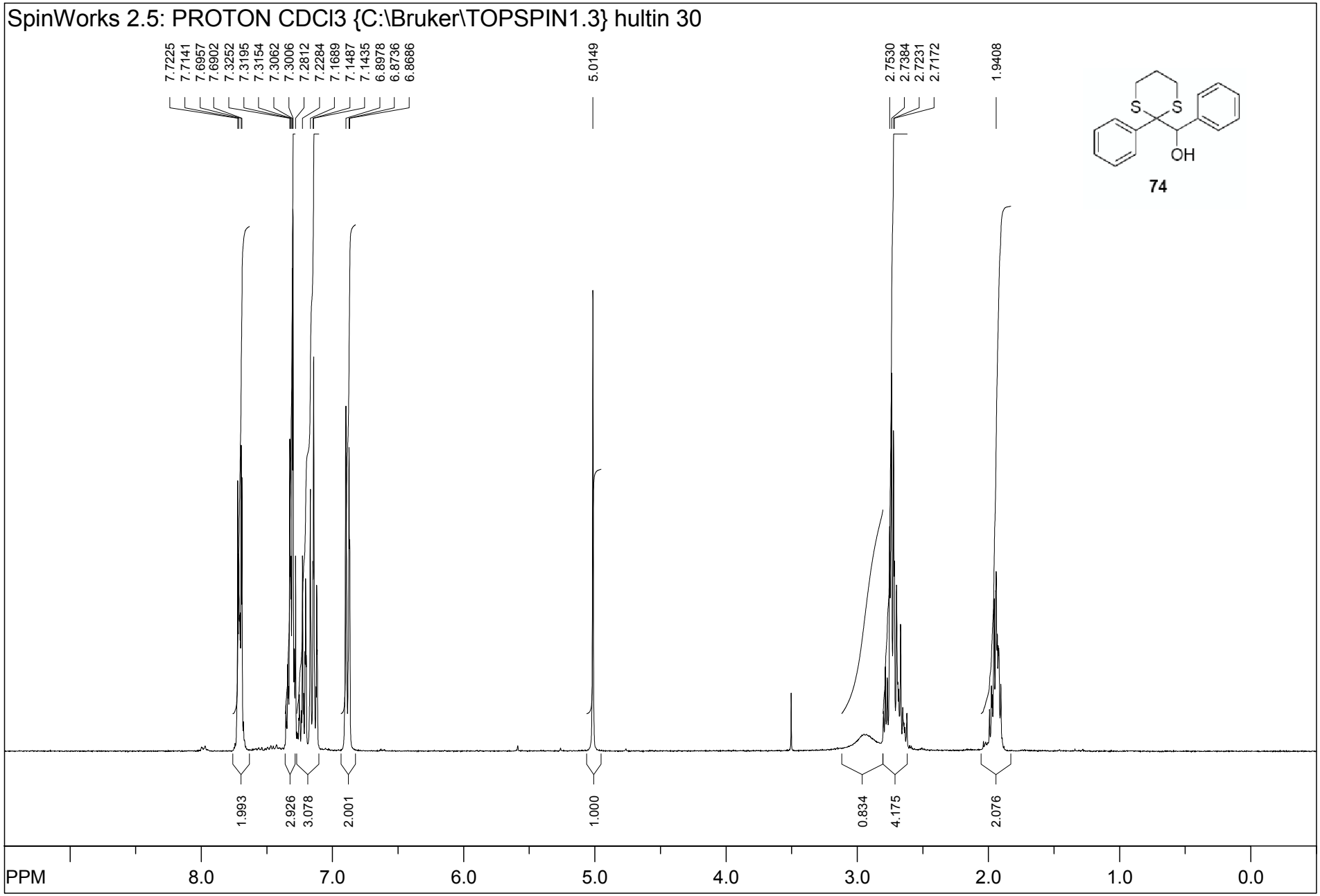
width: 17985.61 Hz = 238.297995 ppm = 0.274439 Hz/pt

number of scans: 4096

processed size: 32768 complex points

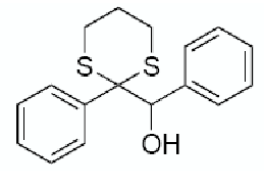
LB: 0.000 GB: 0.0000

Hz/cm: 679.210 ppm/cm: 8.99910




file: C:\Users\Michael\Desktop\Thesis\Data\Lab Computer and NMR\NMR\MM-B3-93P2\2\fid expt: <zg3(freq. of 0 ppm: 300.130006 MHz
transmitter freq.: 300.131853 MHz
time domain size: 65536 points
width: 6172.84 Hz = 20.567092 ppm = 0.094190 Hz/pt
number of scans: 32
processed size: 32768 complex points
LB: 0.000 GB: 0.0000
Hz/cm: 120.052 ppm/cm: 0.40000

SpinWorks 2.5: C13CPD CDCl3 {C:\Bruker\TOPSPIN1.3} hultin 30




74




file: C:\Users\Michael\Desktop\Thesis\Data\Lab Computer and NMR\NMR\MM-B3-93P2\1\fid expt: <zgpg> freq. of 0 ppm: 75.467749 MHz

transmitter freq.: 75.475295 MHz

time domain size: 65536 points

width: 17985.61 Hz = 238.297995 ppm = 0.274439 Hz/pt

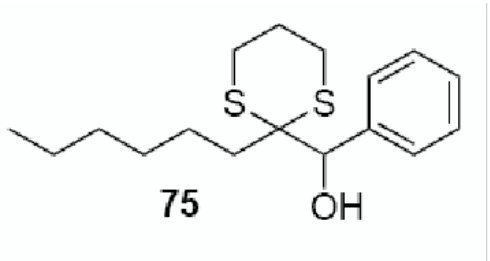
number of scans: 1024

processed size: 32768 complex points

LB: 0.000 GB: 0.0000

Hz/cm: 679.210 ppm/cm: 8.99910

PROTON CDCl3 {C:\Bruker\TOPSPIN1.3} student 42







BRUKER

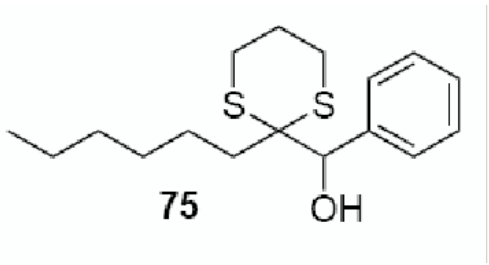
Current Data Parameters
NAME MM-B3-59P
EXPNO 1
PROCNO 1

F2 - Acquisition Parameters
Date_ 20101003
Time 13.15
INSTRUM spect
PROBHD 5 mm QNP 1H/1
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 16
DS 2
SWH 6172.839 Hz
FIDRES 0.094190 Hz
AQ 5.3084660 sec
RG 114
DW 81.000 usec
DE 6.00 usec
TE 298.2 K
D1 1.00000000 sec
TD0 1

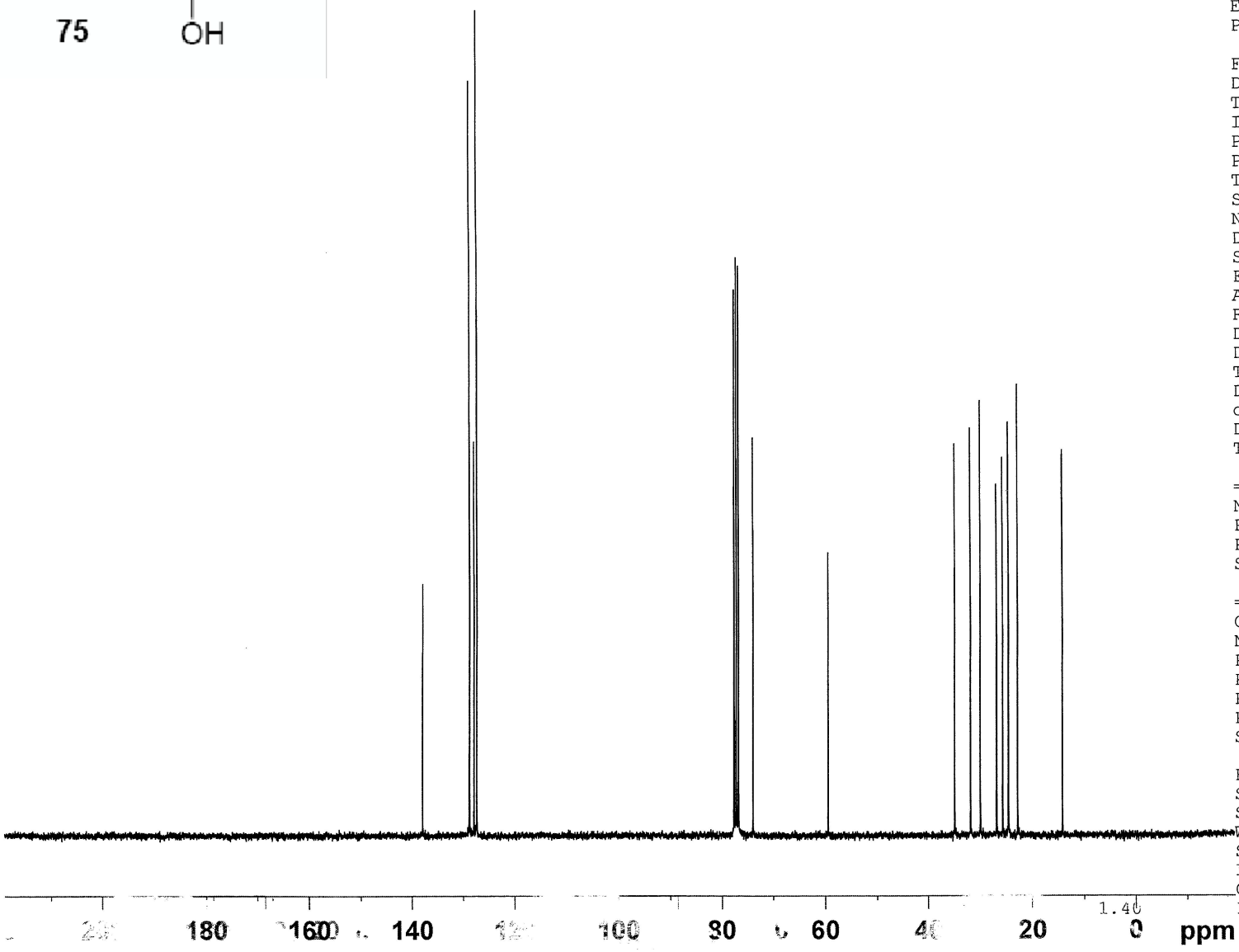
======== CHANNEL f1 ========
NUC1 1H
P1 10.00 usec
PL1 0.00 dB
SFO1 300.1318534 MHz

F2 - Processing parameters
SI 32768
SF 300.1300060 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00

C13CPD CDCl3 {C:\Bruker\TOPSPIN1.3} student 42




137.86
129.08
128.73
128.43
127.85
127.64
127.28
77.50
77.28
77.08
76.65
73.84
59.34
34.71
31.67
29.74
26.61
25.50
24.37
24.30
22.59
14.07




Current Data Parameters
NAME MM-B3-59P
EXPNO 2
PROCNO 1

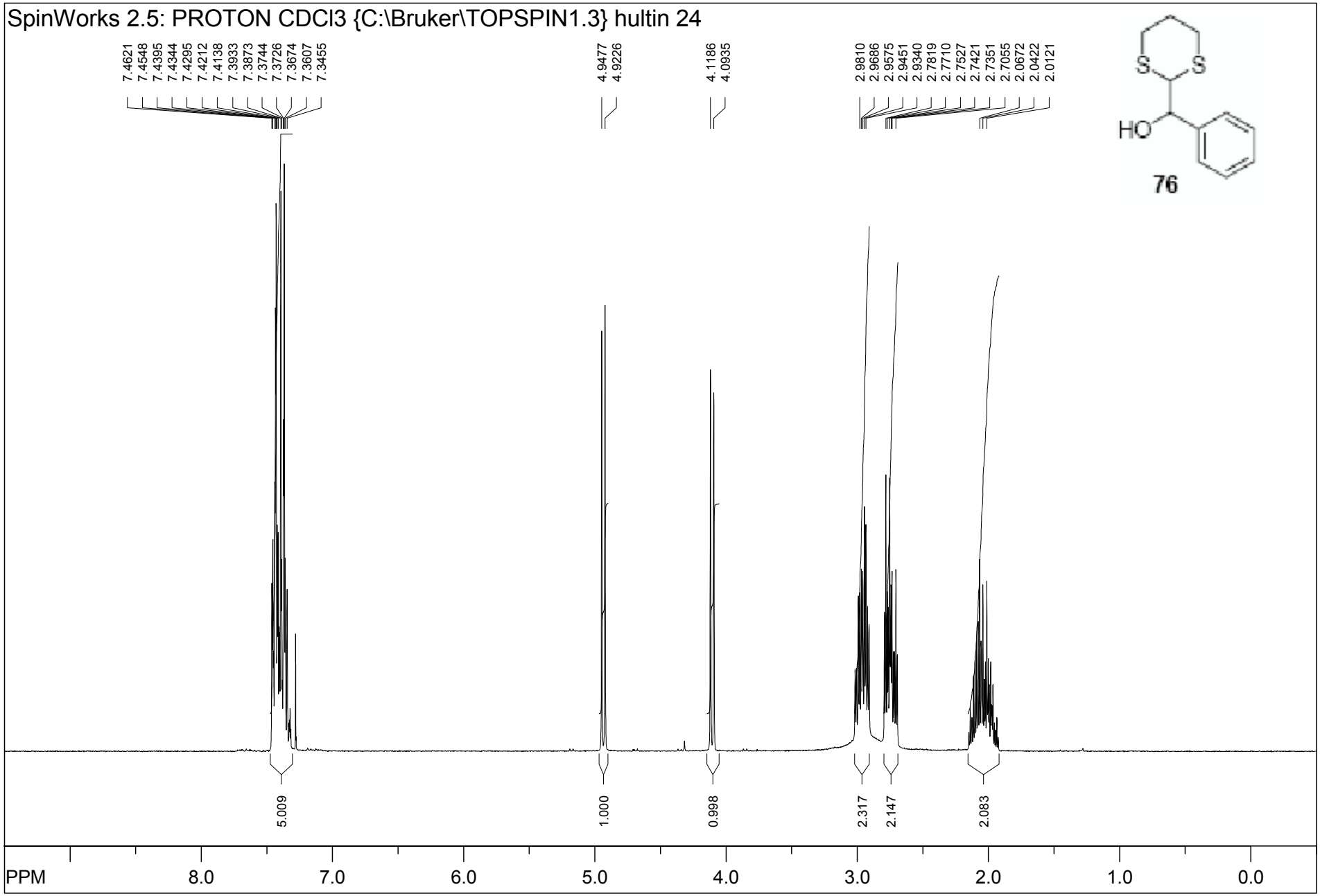
F2 - Acquisition Parameters
Date_ 20101003
Time 14.22
INSTRUM spect
PROBHD 5 mm QNP 1H/1
PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 1024
DS 4
SWH 17985.611 Hz
FIDRES 0.274439 Hz
AQ 1.8219508 sec
RG 1625.5
DW 27.800 usec
DE 6.00 usec
TE 298.2 K
D1 2.00000000 sec
d11 0.03000000 sec
DELTA 1.89999998 sec
TD0 1

======== CHANNEL f1 ========
NUC1 13C
P1 5.60 usec
PL1 -6.00 dB
SFO1 75.4752953 MHz

======== CHANNEL f2 ========
CPDPRG2 waltz16
NUC2 1H
PCPD2 80.00 usec
PL2 0.00 dB
PL12 18.06 dB
PL13 24.00 dB
SFO2 300.1312005 MHz

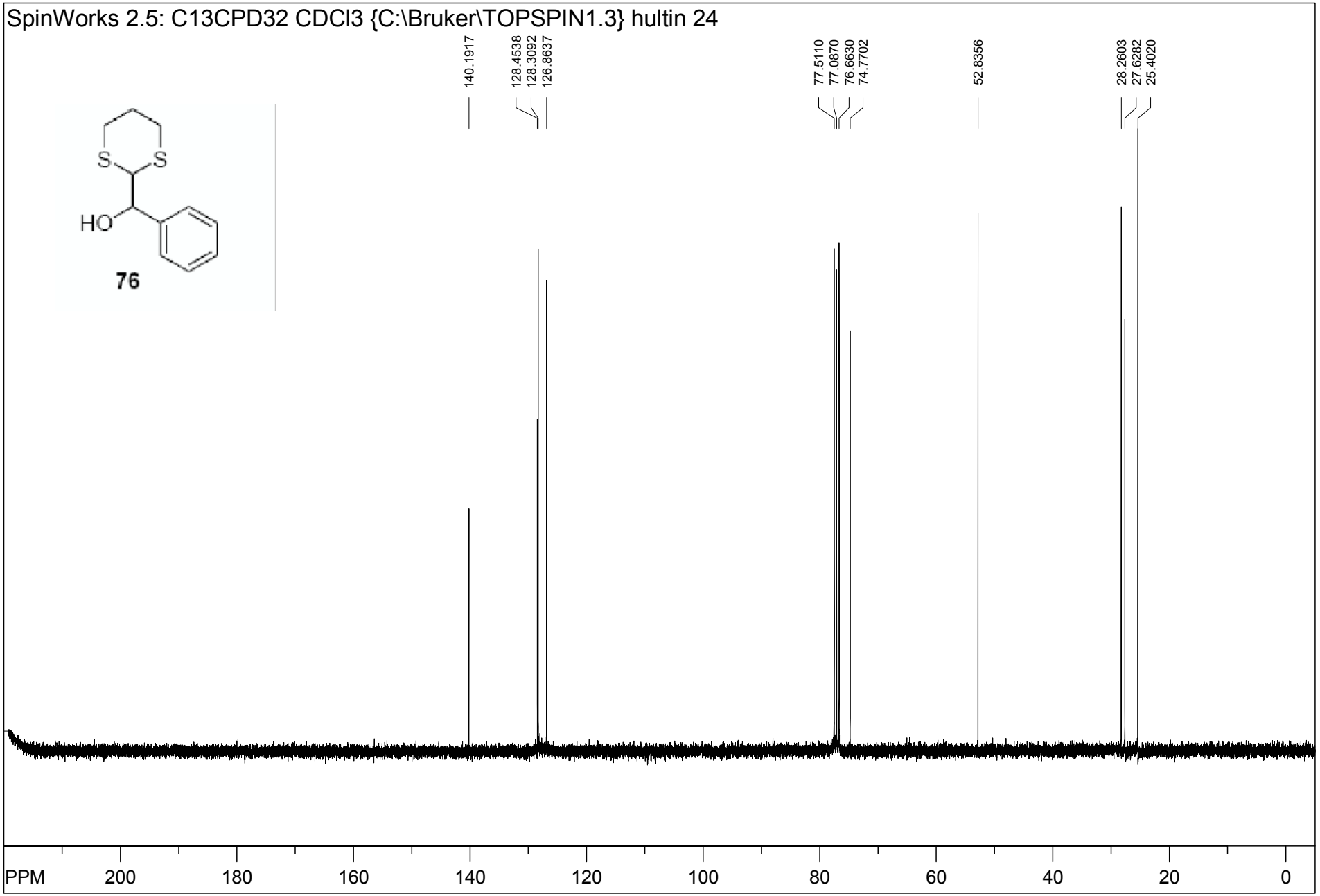
F2 - Processing parameters
SI 32768
SF 75.4677490 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC

SpinWorks 2.5: PROTON CDCl3 {C:\Bruker\TOPSPIN1.3} hultin 24




file: C:\Users\Michael\Desktop\Thesis\Data\Lab Computer and NMR\NMR\MM-B3-79P2\2\fid expt: <zg3(freq. of 0 ppm: 300.130006 MHz
transmitter freq.: 300.131853 MHz
time domain size: 65536 points
width: 6172.84 Hz = 20.567092 ppm = 0.094190 Hz/pt
number of scans: 16
processed size: 32768 complex points
LB: 0.000 GB: 0.0000
Hz/cm: 120.052 ppm/cm: 0.40000

SpinWorks 2.5: C13CPD32 CDCl3 {C:\Bruker\TOPSPIN1.3} hultin 24

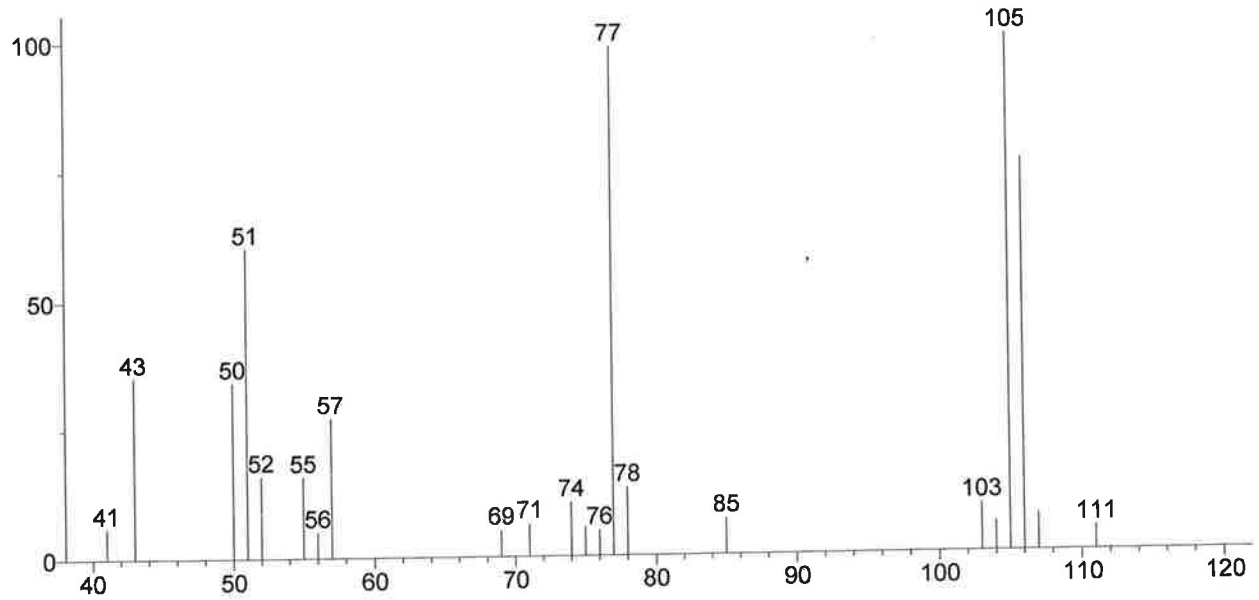



file: C:\Users\Michael\Desktop\Thesis\Data\Lab Computer and NMR\NMR\MM-B3-79P2\1\fid expt: <zgpg>
transmitter freq.: 75.475295 MHz
time domain size: 65536 points
width: 17985.61 Hz = 238.297995 ppm = 0.274439 Hz/pt
number of scans: 1024

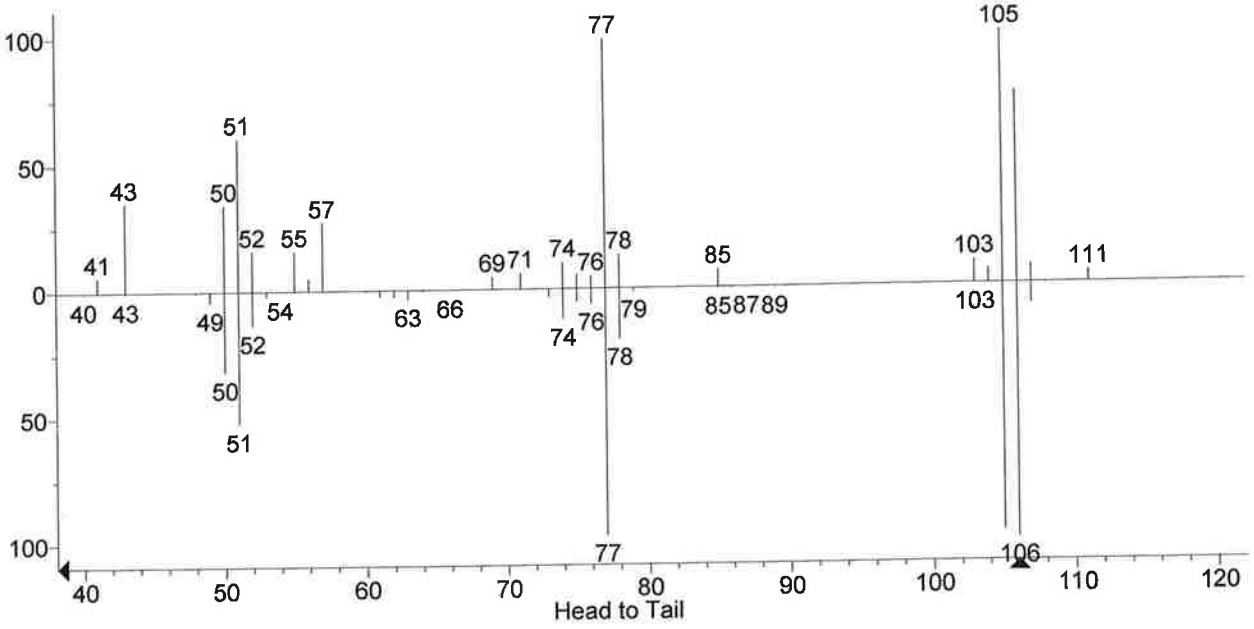
freq. of 0 ppm: 75.467749 MHz
processed size: 32768 complex points
LB: 0.000 GB: 0.0000
Hz/cm: 679.210 ppm/cm: 8.99910

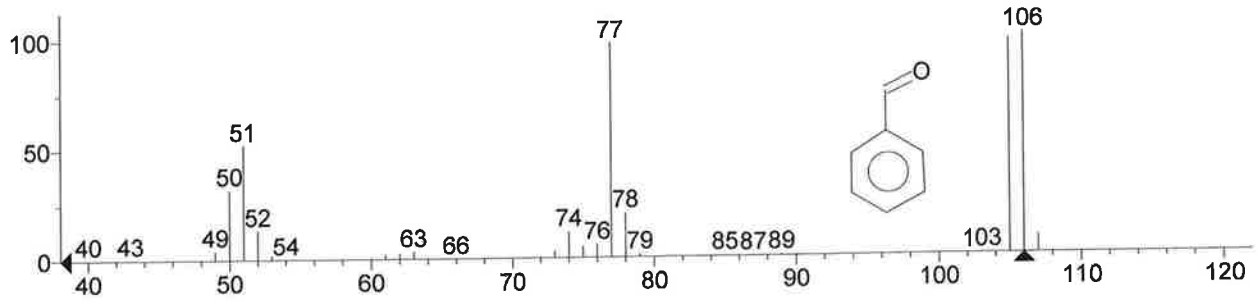
# Appendix II

## GC-MS Spectra

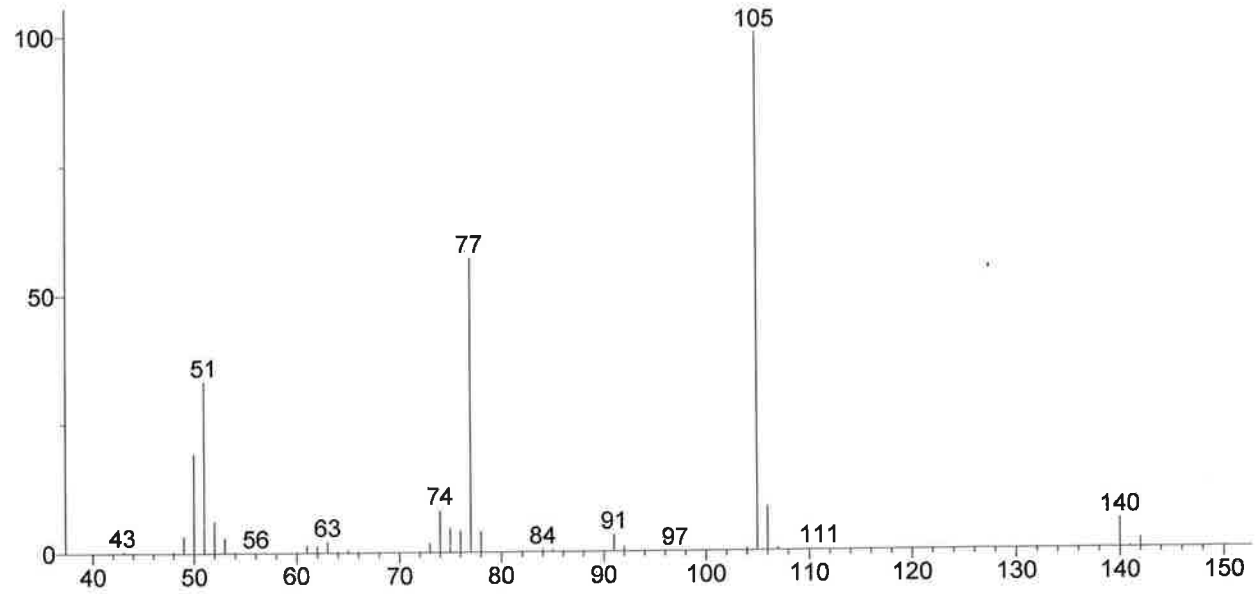



(Text File) 2.979 min, Scan: 102

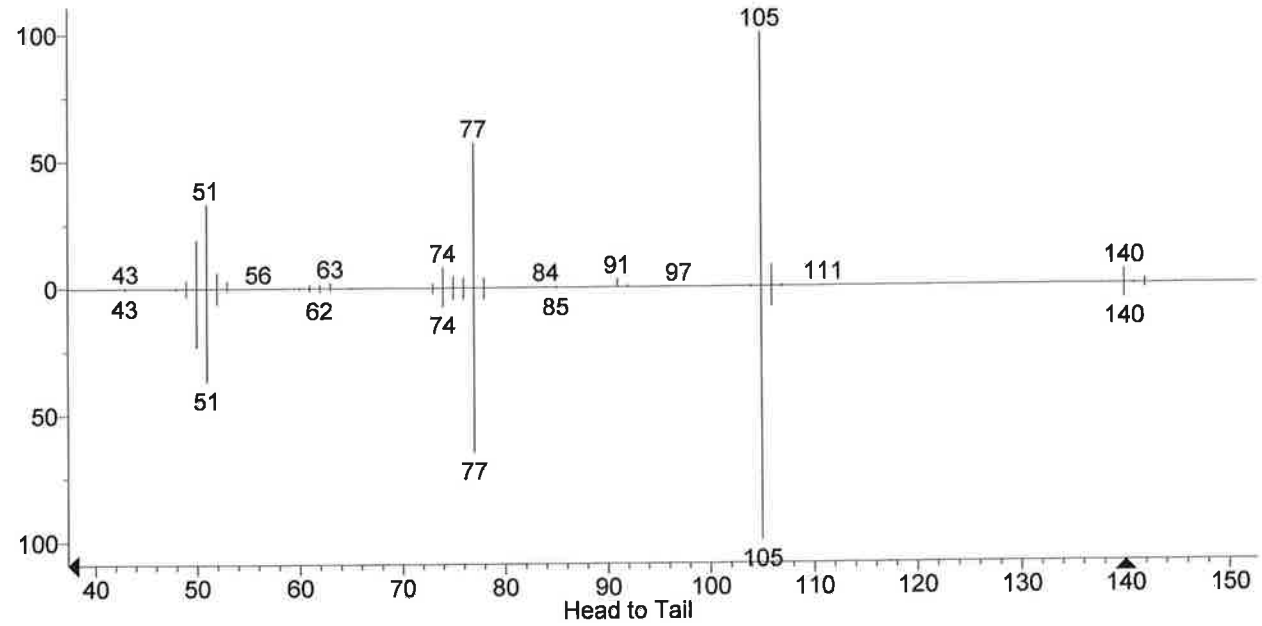


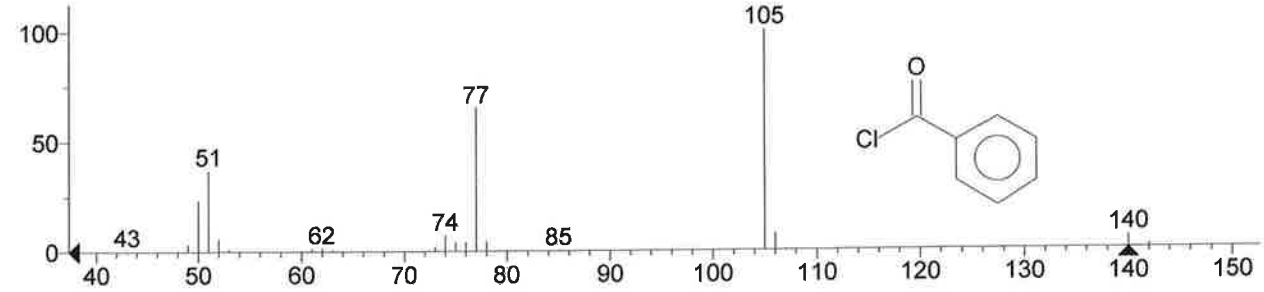

(replib) Benzaldehyde



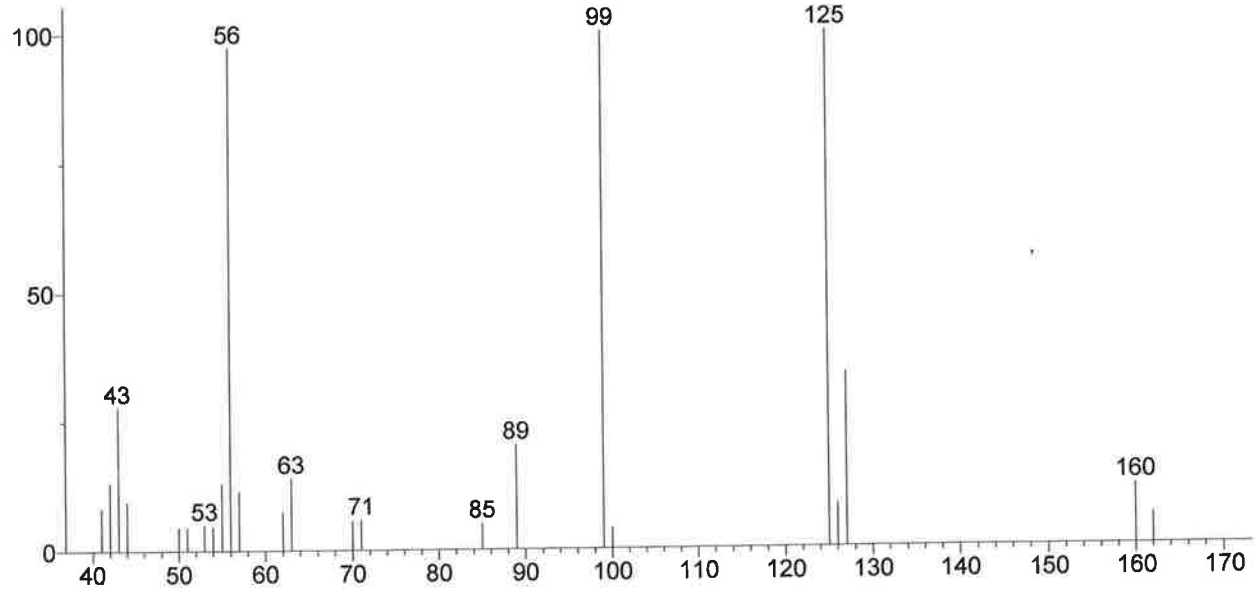

(Text File) 3.756 min, Scan: 462



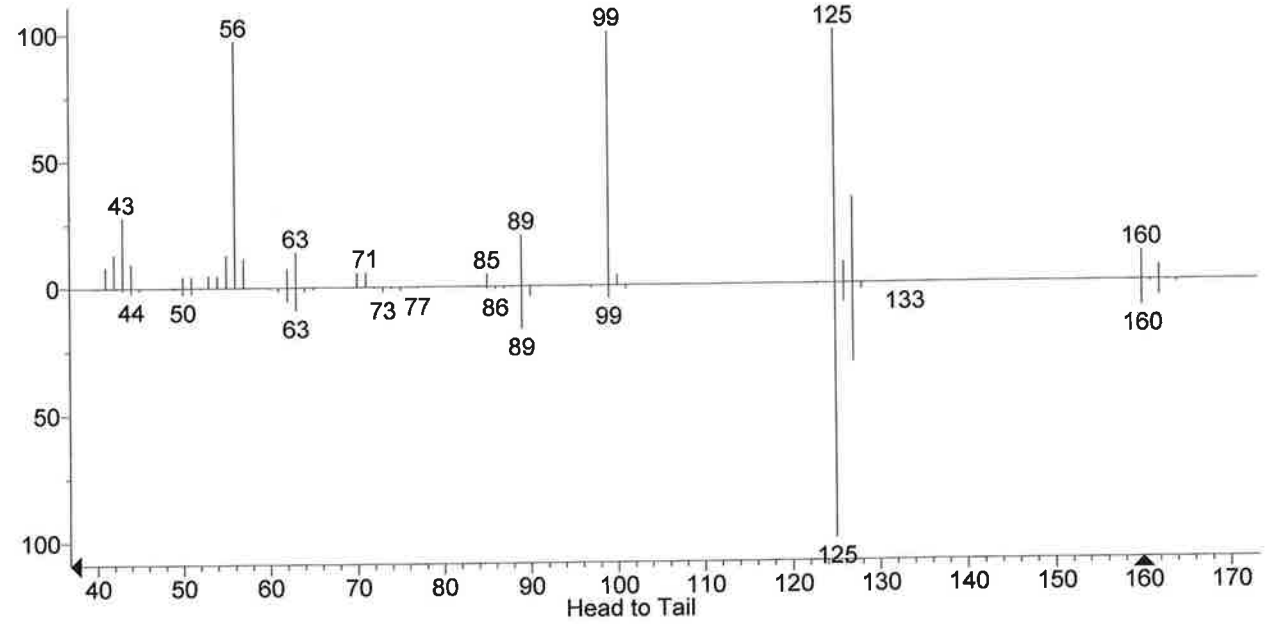

Head to Tail

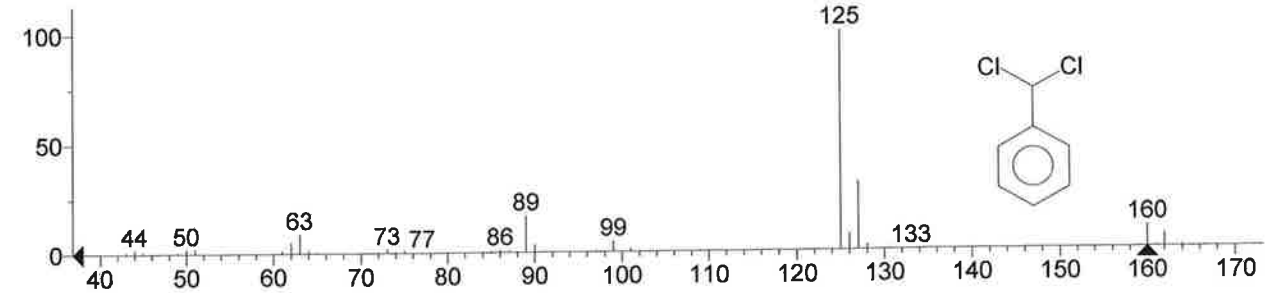



(replib) Benzoyl chloride

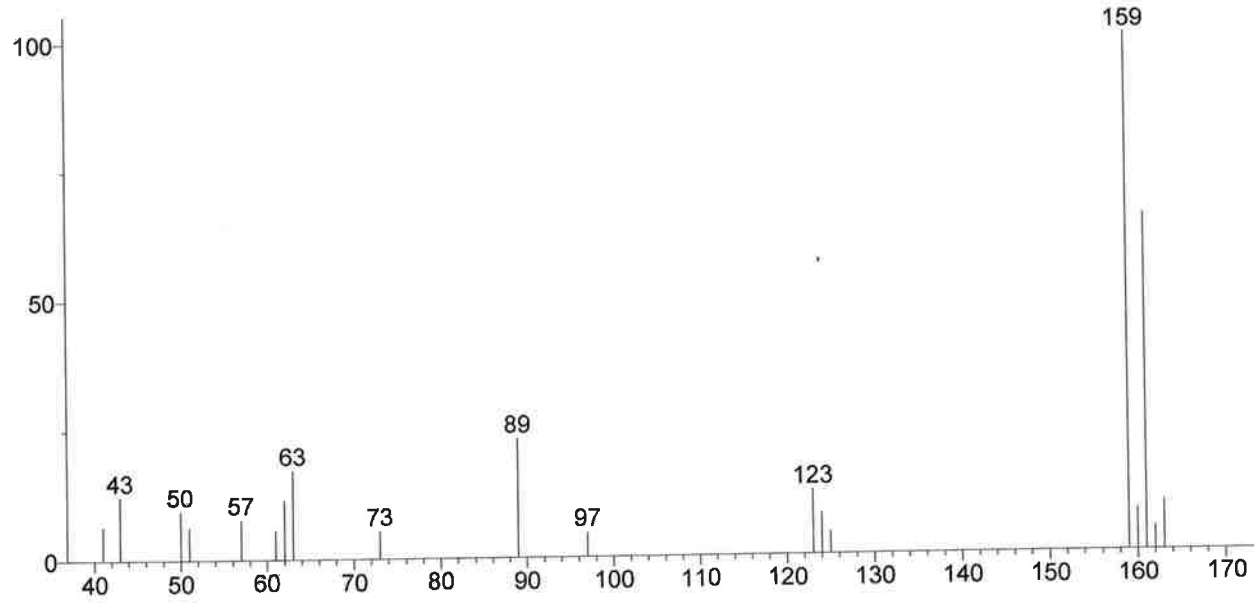



(Text File) 4.044 min, Scan: 402

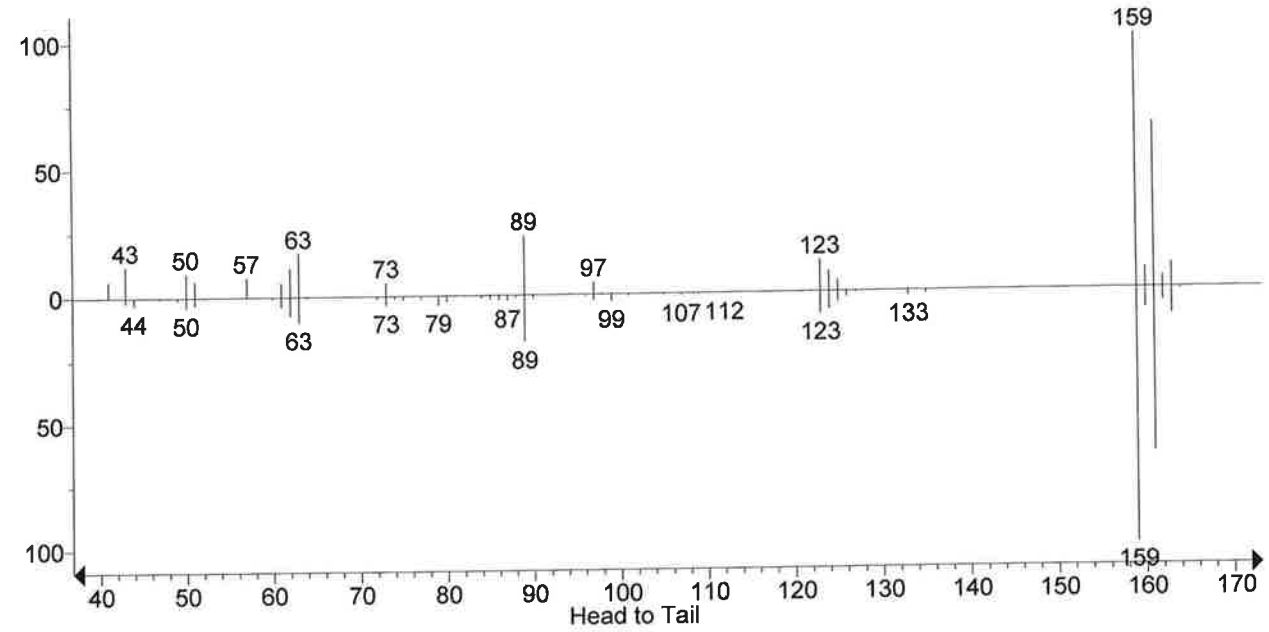


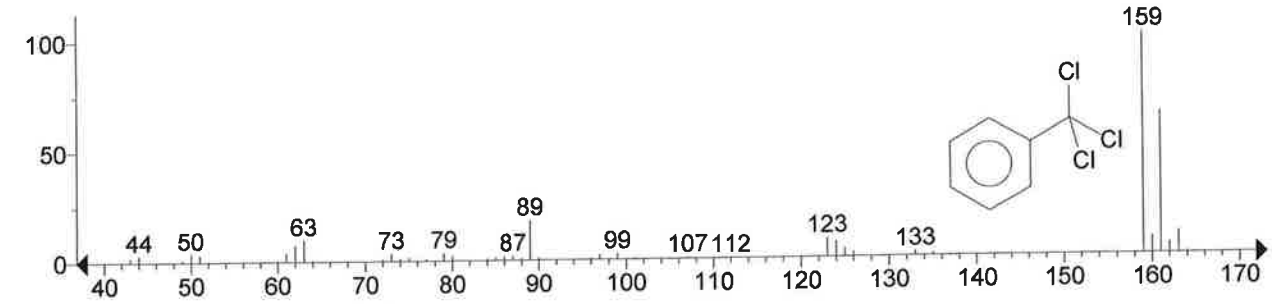




(replib) Benzene, (dichloromethyl)-

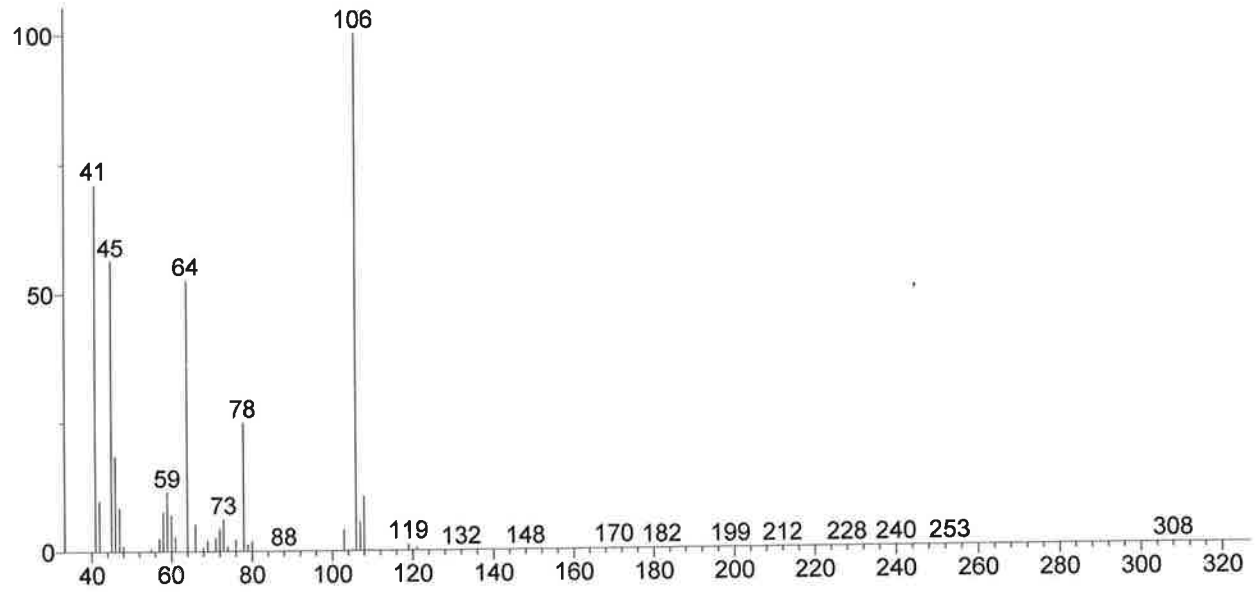



(Text File) 4.613 min, Scan: 562

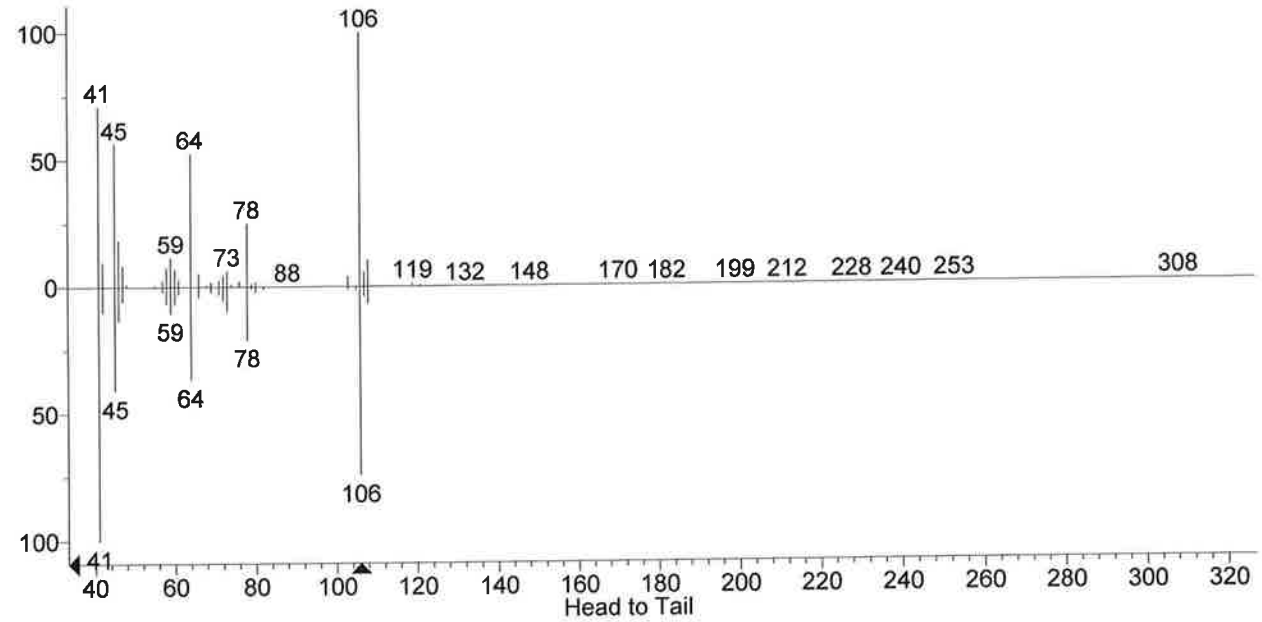


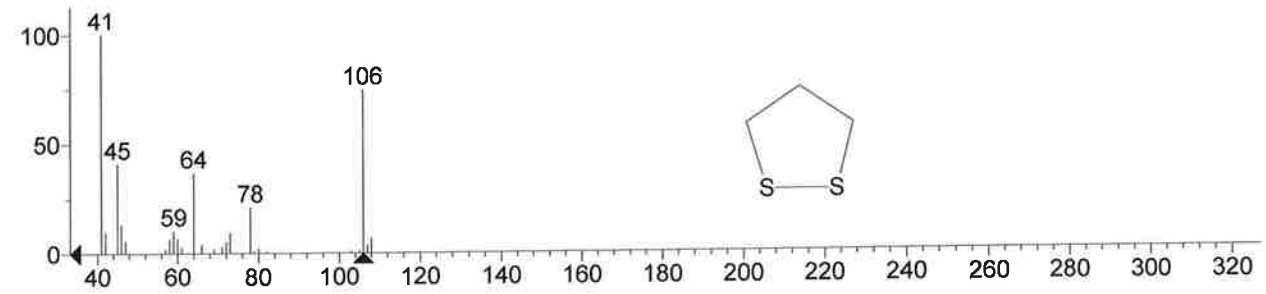




(mainlib) Benzene, (trichloromethyl)-

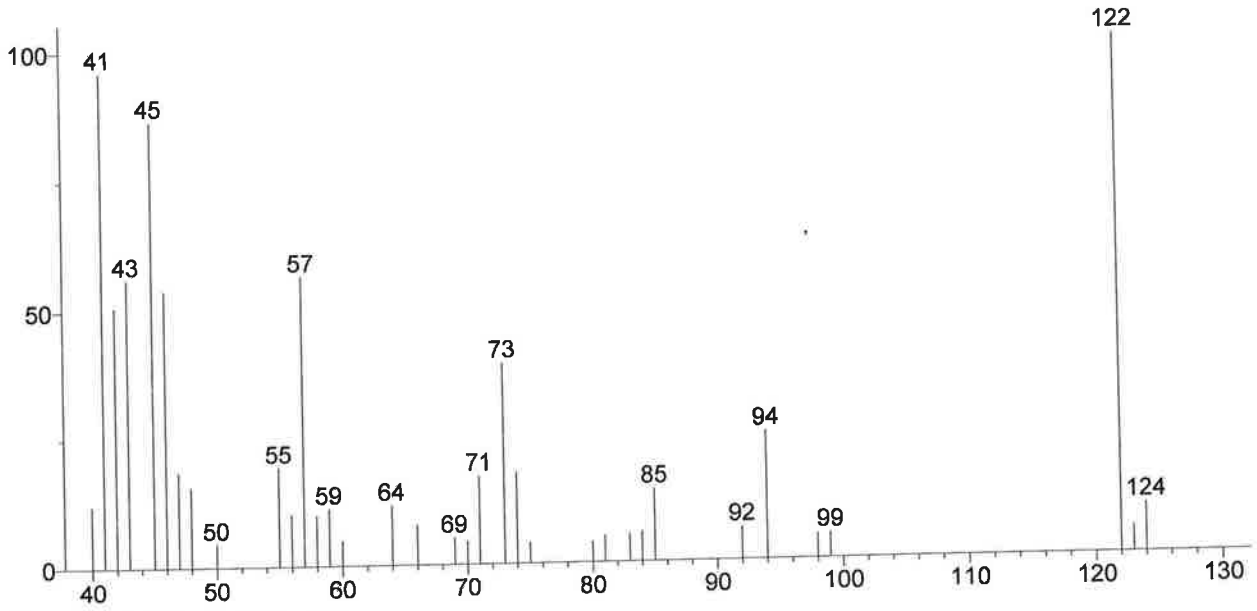



(Text File) 3.333 min, Scan: 343

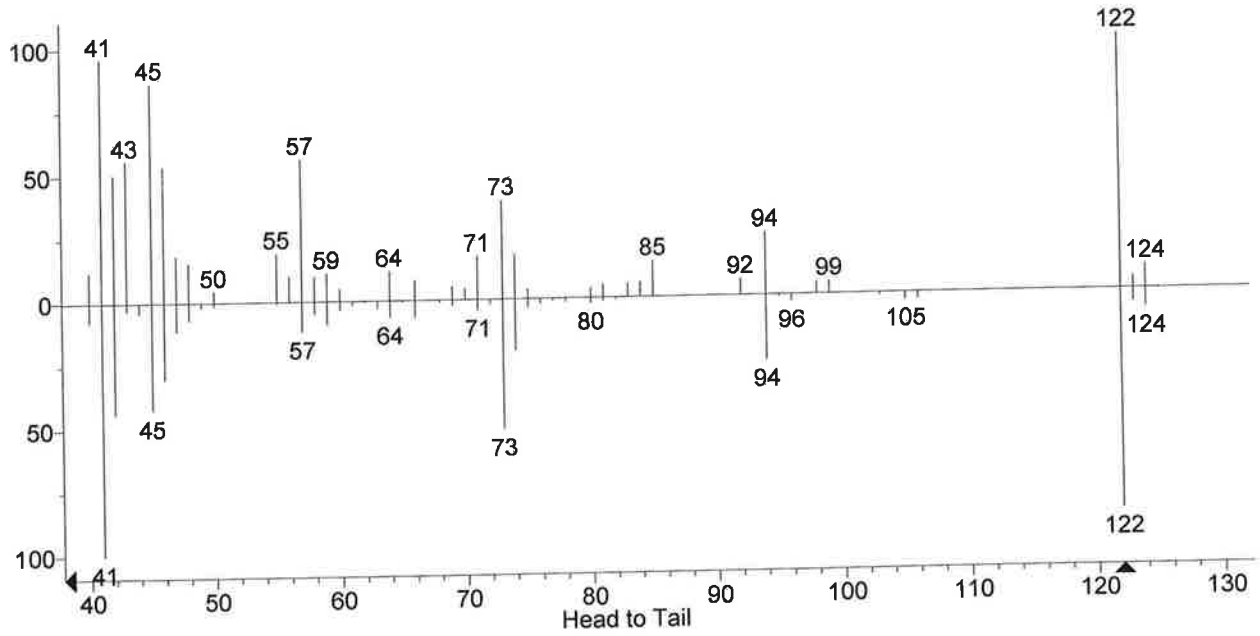


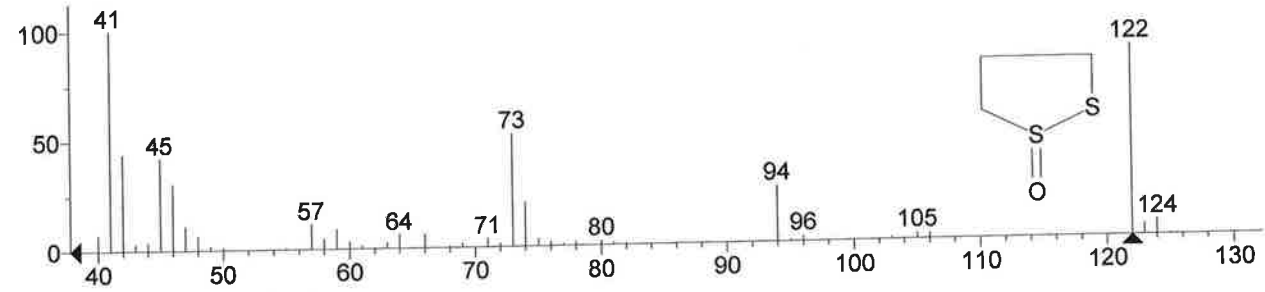




(replib) 1,2-Dithiolane

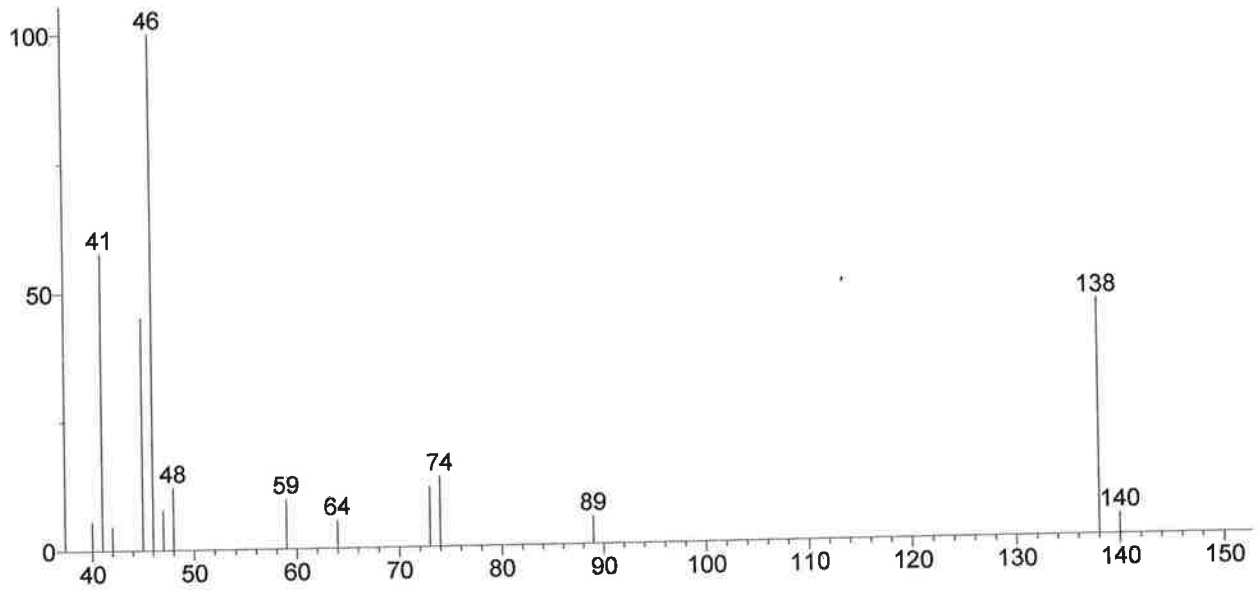



(Text File) 4.912 min, Scan: 646

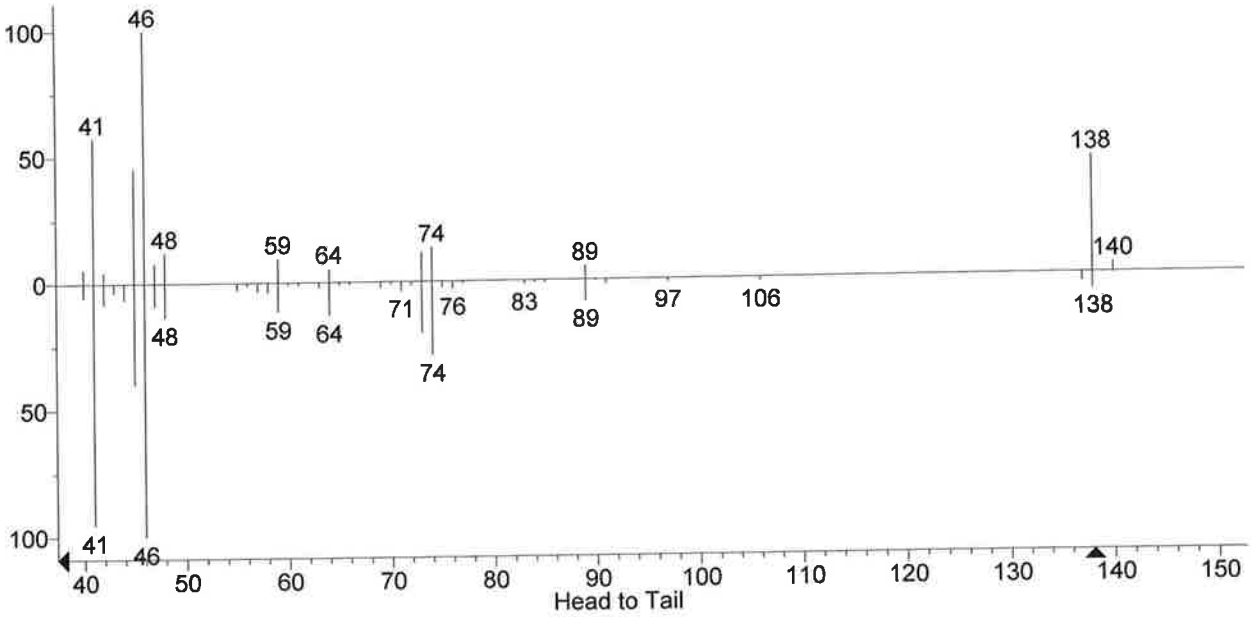


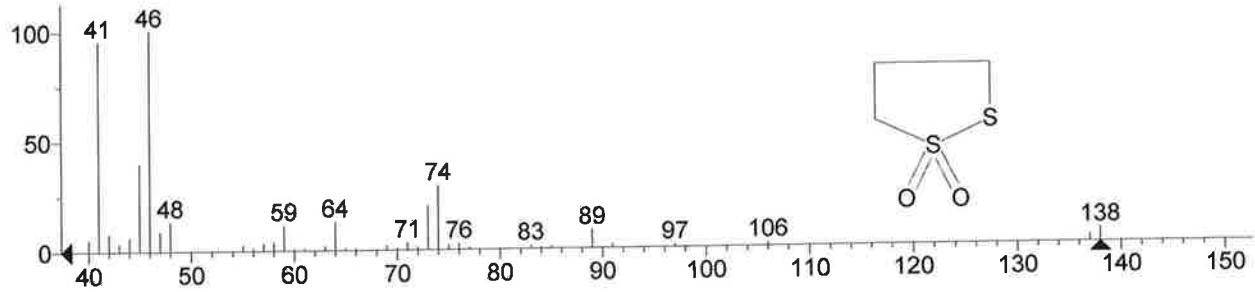




(mainlib) 1,2-Dithiolane-1-oxide

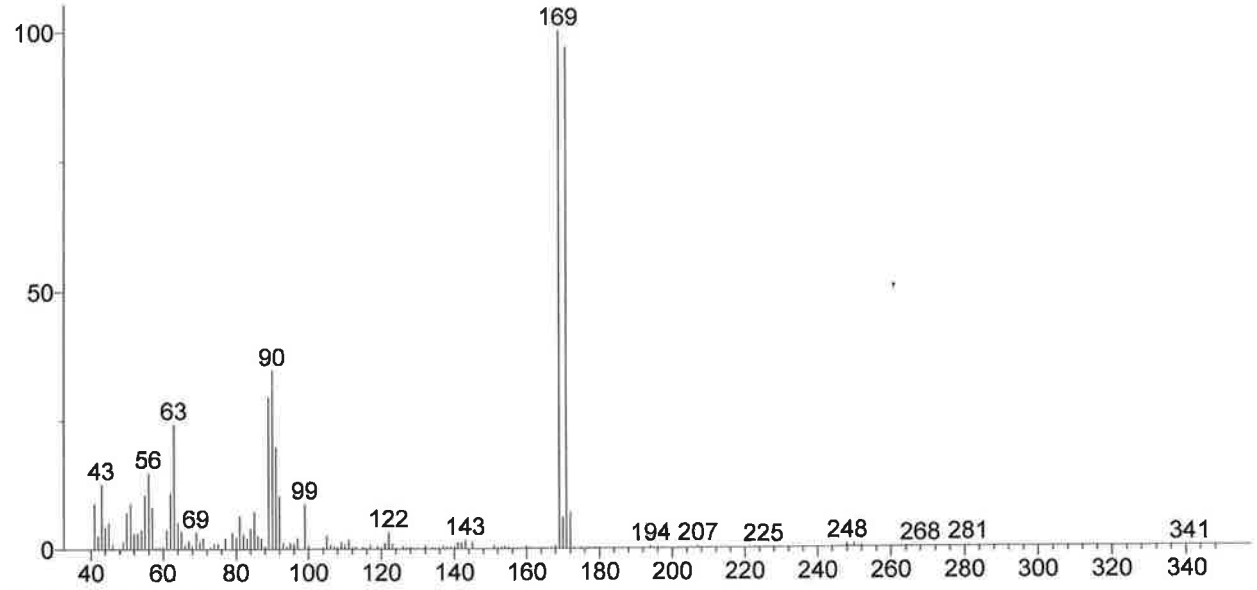



(Text File) 5.701 min, Scan: 868




(mainlib) 1,2-Dithiolane, 1,1-dioxide

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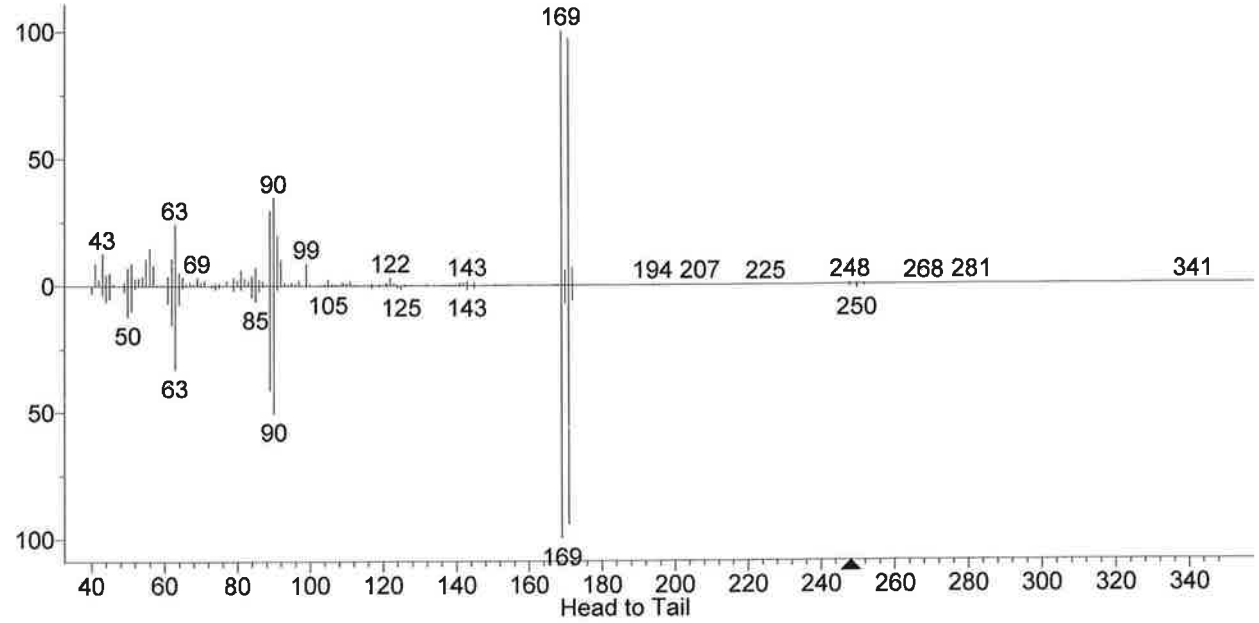
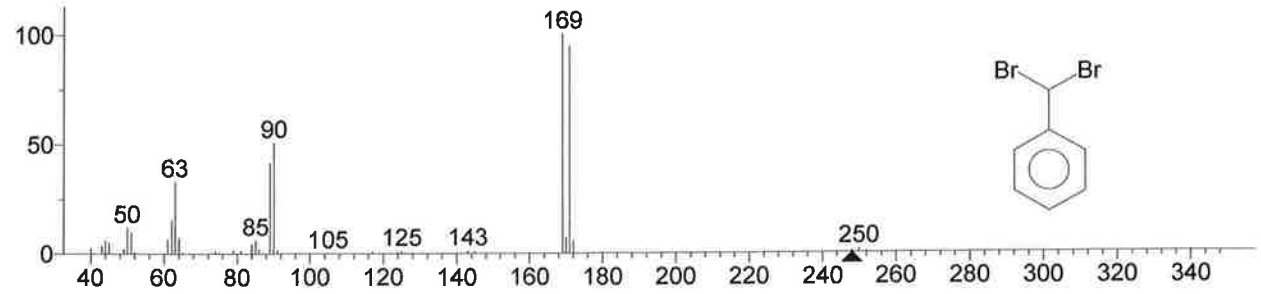
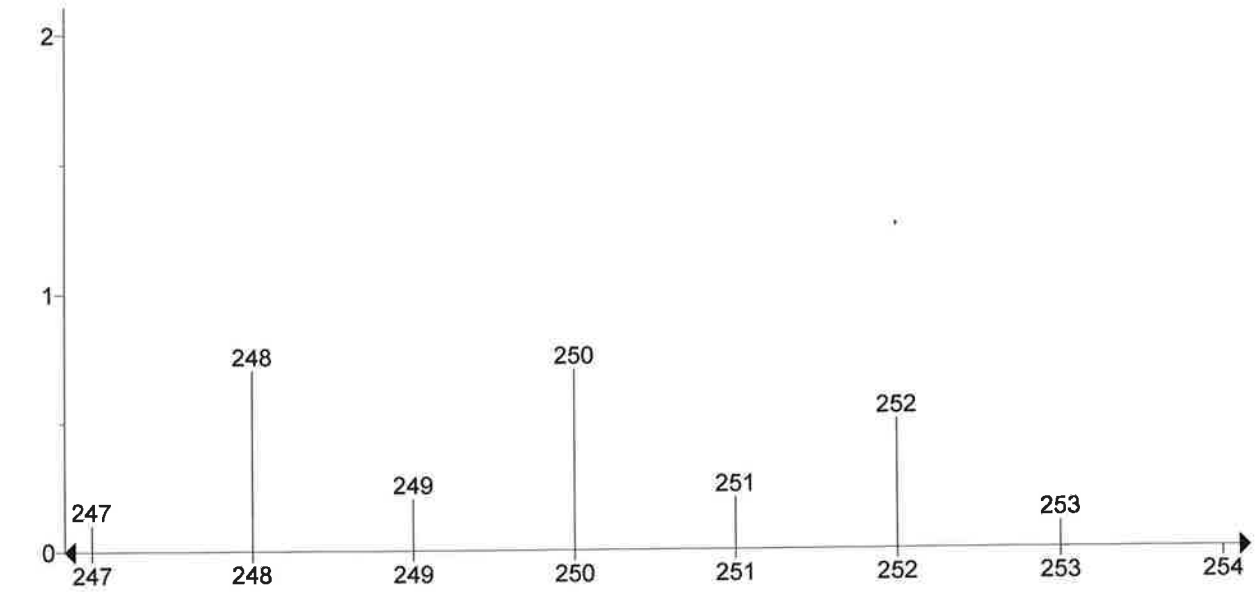



(replib) Benzene, (dibromomethyl)-

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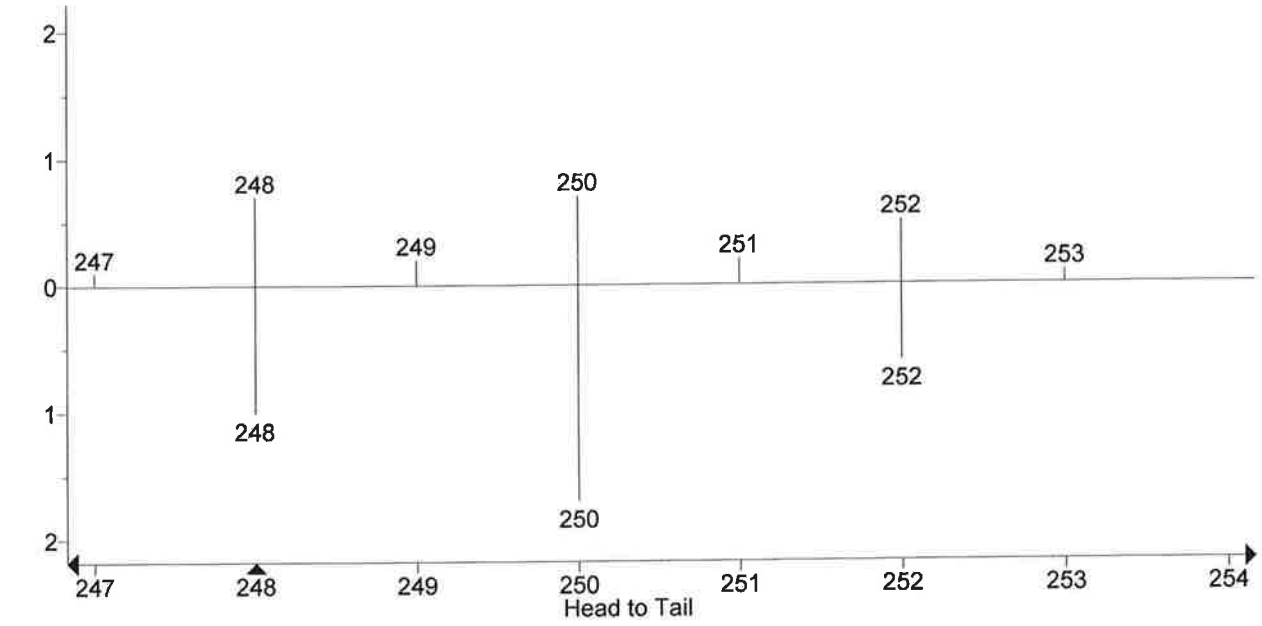
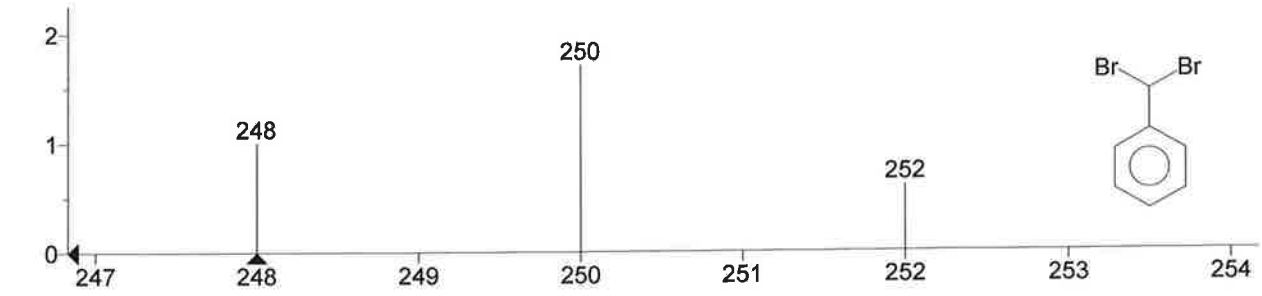
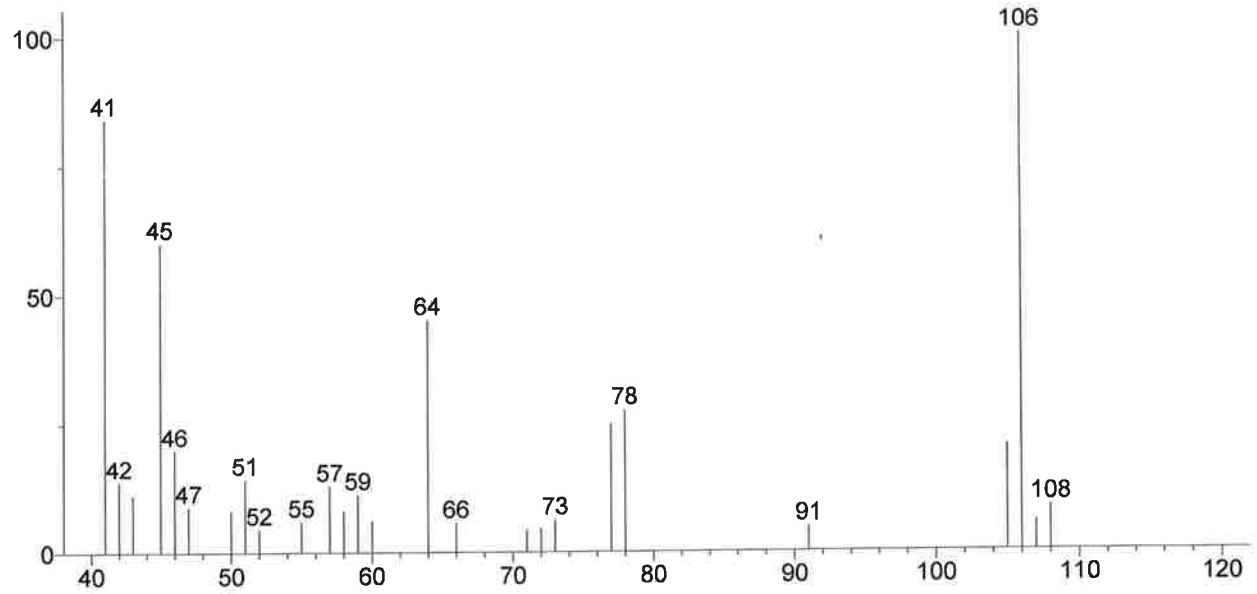
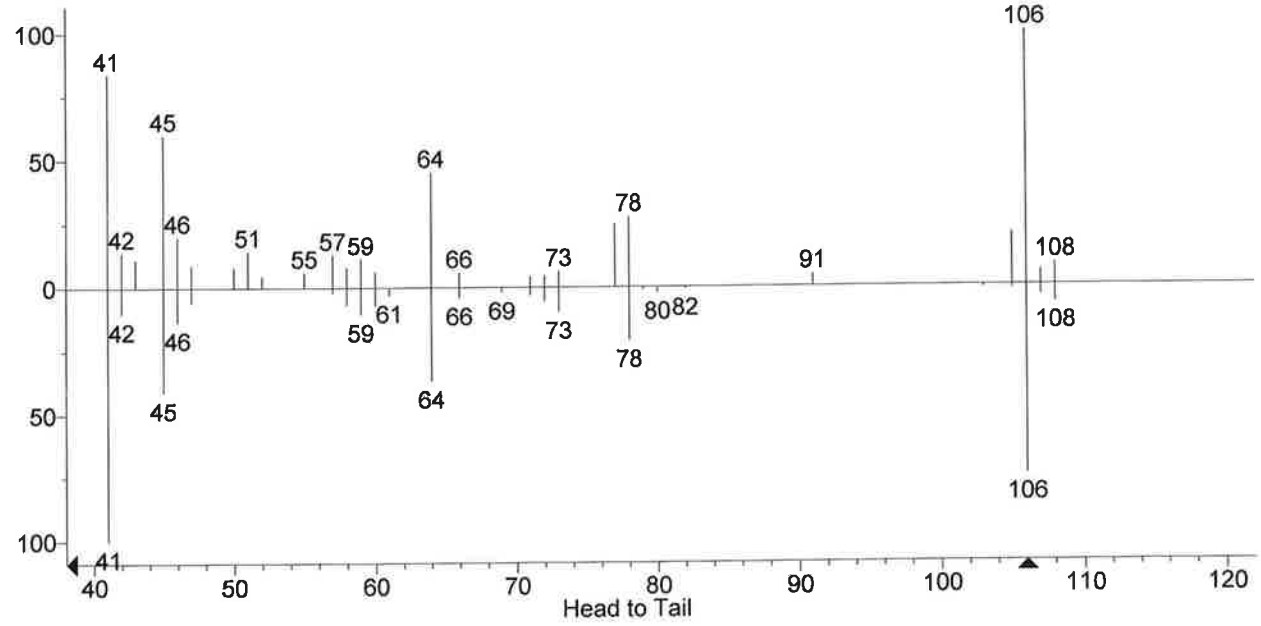


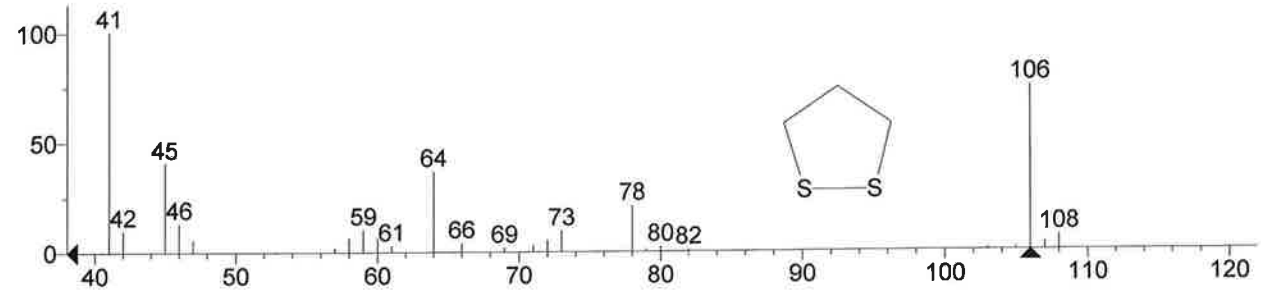




(replib) Benzene, (dibromomethyl)-

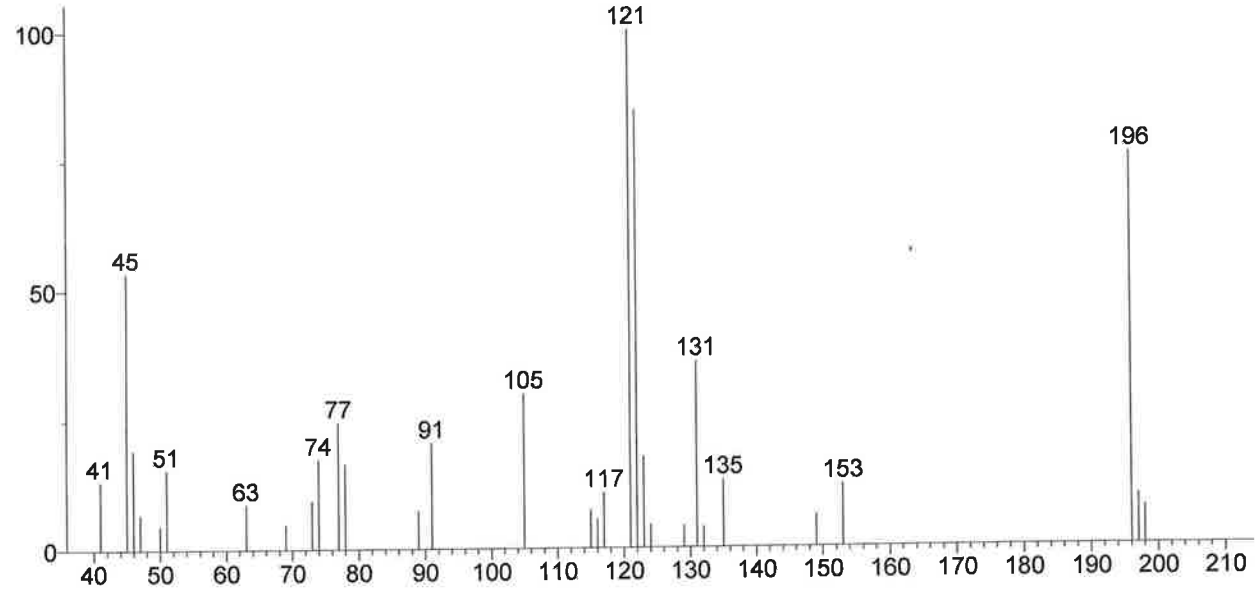



(Text File) 3.232 min, Scan: 28




(replib) 1,2-Dithiolane

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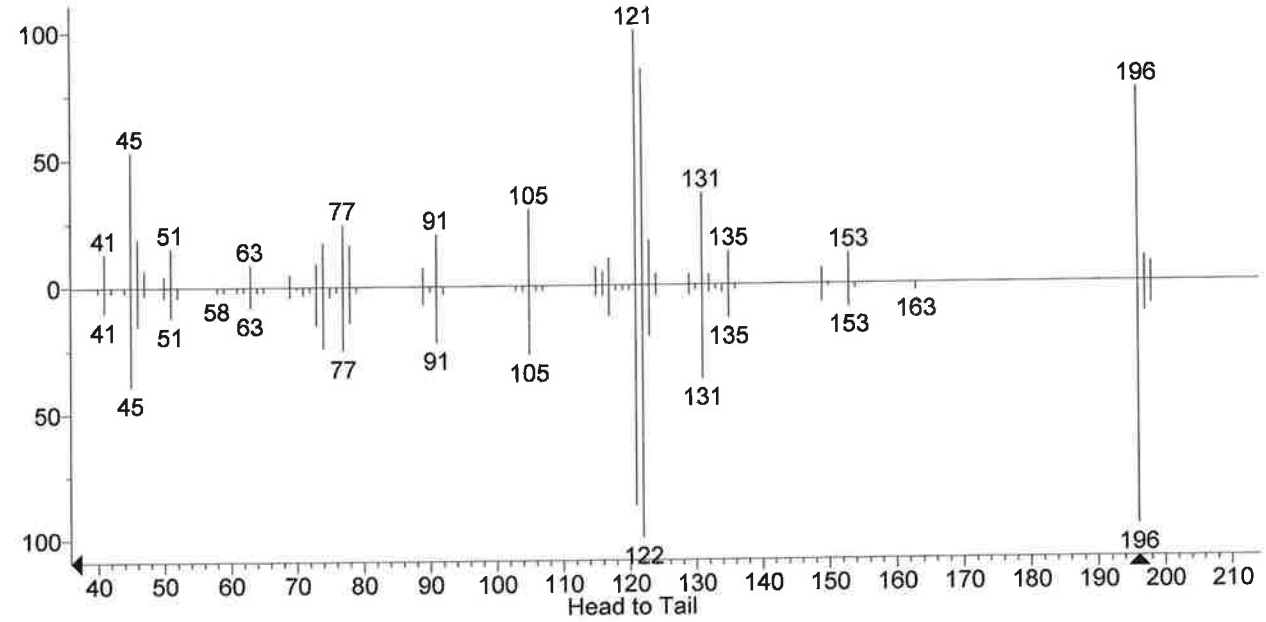


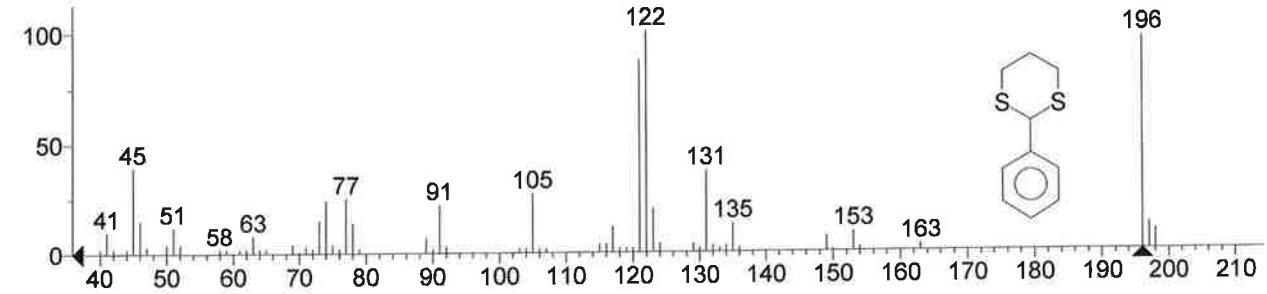


(replib) 1,3-Dithiane, 2-phenyl-