STUDIES TOWARDS THE SYNTHESIS OF 2,5-DISUBSTITUTED-3-
FLUOROTHIOPHENES USING A DIRECTED ORTHO-METALATION/NICKEL-
CATALYZED CROSS-COUPLING APPROACH

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# TABLE OF CONTENTS

LIST OF FIGURES...........................................................................................................v

ACKNOWLEDGMENTS........................................................................................................ix

ABBREVIATIONS USED....................................................................................................xi

CHAPTER

1. **INTRODUCTION** ................................................................. 1
   1.1: Introduction to Liquid Crystals................................................. 1
   1.2: Liquid Crystal Phases.............................................................. 3
   1.3: Interactions of Liquid Crystalline Materials with Electric Fields and Polarized Light.............................................................................. 8
      *Interactions of Liquid Crystals with Electric Fields* ................. 8
      *Fundamental Properties of Light* ............................................. 9
      *Interactions of Liquid Crystals with Light* ............................ 11
   1.4: The Use of Ferroelectric Liquid Crystals in Displays............... 13
   1.5: Structure of Liquid Crystal Phase Forming Materials.............. 15
   1.6: Fluorinated Liquid Crystals.................................................... 17
   1.7: Thiophene-based Liquid Crystals........................................... 19
   1.8: Previous Work Toward the Synthesis of 3-Fluorothiophene Moieties......................................................................................... 22
   1.9 Thesis Goals............................................................................ 30
      *Development of Nickel-catalyzed Cross-Couplings Using Thienyl Pseudohalides* ................................................................. 31
      *Synthesis of 2-alkoxy-3-fluorothiophenes* .............................. 34

2. **RESULTS AND EXPERIMENTAL DISCUSSION** .................... 36
   2.1: Synthesis of p-Tolyl O-carbamate Model Compound **17** .... 36
2.2: Studies Towards Ni-catalyzed Cross-couplings using p-Tolyl O-carbamate Model Compound 17………………………………………………..43

2.3: Synthesis of 5-Methyl-2-O-carbamate Model Compound 36……….49

2.4: Directed Ortho-metalation Experiments Involving O-carbamate 36……………………………………………………………………54

2.5: Attempted Synthesis of 2-thienyl-O-sulfamates and O-thiocarbamates…………………………………………………………………………61

3.  FUTURE DIRECTIONS………………………………………………………..67

4.  EXPERIMENTAL DETAILS………………………………………………….69

5.  REFERENCES……………………………………………………………………84
LIST OF FIGURES

Figure 1.1.1. Structure of cholesteryl benzoate ......................................................... 2

Figure 1.2.1. “Rod” phase representations of solids, liquids, and the nematic liquid crystal phase ........................................................................................................... 3

Figure 1.2.2. Simulated macromolecular structure of a chiral nematic phase (Reproduced from the Barrett Group of McGill University) ........................................ 4

Figure 1.2.3. Simulated macromolecular structure of the chiral smectic C phase (Reproduced from the Barrett Group of McGill University) .................................. 6

Figure 1.2.4. Pictorial representation of the basic differences between discussed liquid crystal phases ........................................................................................................... 7

Figure 1.3.1. Illustration of an example electromagnetic wave (Reproduced from the University of California -Davis) ................................................................. 9

Figure 1.3.2. The effect of polarizers on polarized and plane polarized light .................. 10

Figure 1.3.3. Helical geometry of the chiral smectic C phase in the absence of an external electric field ........................................................................................................... 12

Figure 1.4.1. The off (a) and on (b) states of a SSFLC display ..................................... 14

Figure 1.4.2. The on (a) and off (b) states of a TN display cell .................................... 15

Figure 1.5.1. Generalized structure of ferroelectric LC materials ............................... 16

Figure 1.5.2. Influence of the identity of central and terminal mesogen linkages on the ability to form smectic phases ................................................................. 17

Figure 1.6.1. The effects of various lateral core substituents on transition temperatures in an example mesogen based on a phenyl core .......................................... 18

Figure 1.7.1. Structure of thiophene .............................................................................. 19

Figure 1.7.2. Dipole moment, bond angles, and numbering conventions within thiophene ................................................................................................................. 19

Figure 1.7.3. Differences in phase behavior and melting points as a consequence of electronic conjugation in 2,5-disubstituted thiophene cores versus 2,4-disubstituted thiophene cores (reproduced from ref. 16) ................................. 20
Figure 1.7.4. Representative fluorothiophene-containing mesogens synthesized by the Seed-Sampson group……………………………………………………………………………21

Figure 1.8.1. Balz-Schiemann approach towards 3-fluorothiophenes developed by Kiryanov……………………………………………………………………………………………………23

Figure 1.8.2. Commercially available electrophilic fluorination agents…………………………………………………………………………………………………………………………….23

Figure 1.8.3. Direct fluorination of the thiazole core as developed by Grubb……………………………………………………………………………………………………………………………24

Figure 1.8.4. Attempts at 3-fluorination of 2-alkoxythiophene cores by Subramanian…………………………………………………………………………………………………………24

Figure 1.8.5. The basic mechanism of the directed ortho metalation process as well as common directing groups (DMG), and installable functionalities (E) using this method…………………………………………………………………………………………….26

Figure 1.8.6. Attempted 3-position deprotonation of a 2-alkoxythiophene derivative and subsequent trapping using NFSI…………………………………………………………………………………..27

Figure 1.8.7. Proposed mechanism for single electron transfer in N-F agent-based fluorinations…………………………………………………………………………………………………….28

Figure 1.8.8. 3-fluorination of 3-bromo-2-alkoxythiophene derivatives using halogen-metal exchange………………………………………………………………………………………………29

Figure 1.8.9. Mercuration of the undesired protodehalogenated side product of halogen-metal exchange………………………………………………………………………………………………..30

Figure 1.9.1. Previously prepared directing group–containing thiophene cores……………………………………………………………………………………………………………………………………31

Figure 1.9.2. The use of carbonates, sulfamates and O-carbamates as “pseudo-halide” cross-coupling partners in the presence of a nickel catalyst………………………………………………………32

Figure 1.9.3. Proposed tandem DOM-fluorination/Ni-catalyzed cross-coupling approach to the 2,5-disubstituted-3-fluorothiophene core……………………………………………………………………….33

Figure 1.9.4. Oxidation/etherification of thienyl BF₃K salts as developed by Tietz…………………………………………………………………………………………………………………………34

Figure 1.9.5. Proposed synthetic pathway to the 2-alkoxy-3-fluorothiophene core utilizing DOM-fluorination and reductive cleavage with Schwartz’ reagent followed by Mitsunobu etherification ………………………………………………………………………………………………………35

Figure 2.1.1. Competitive deprotonation at the 3- and 5-positions of the thiophene ring in the presence of a directing group (DMG)………………………………………………………………………………………………36

Figure 2.1.2. Retrosynthetic cleavage of the O-C carbamate bond and subsequent tracing to the parent thienone (18) and trifluoroborate salt (21)………………………………………………………………………………………………………………………….37
Figure 2.1.3. Synthesis of 5-(p-Tolyl)-2-O,N,N-diethyl thienyl carbamate (17) .................38
Figure 2.1.4. Literature report of the oxidative dimerization of thienones .........................40
Figure 2.1.5. Proposed oxidative dimerization during the oxidation of trifluoroborate salt (21) .................................................................................................................................41
Figure 2.1.6. The comparative deprotonations/enolization of generalized thiophene-2(3H)-one and thiophene-2(5H)-one by bis-hexamethyldisilazide base .....................42
Figure 2.2.1. Attempted Ni-catalyzed cross-coupling of thienyl O-carbamate 17 ............44
Figure 2.2.2. Accepted mechanism for Ni-catalyzed Suzuki cross-couplings .............45
Figure 2.2.3. Proposed mechanism for Pd(0)-catalyzed “homo-coupling” of boronic acids in the presence of molecular oxygen .........................................................46
Figure 2.2.4. Free energy profile for the Ni-catalyzed cross-coupling of phenyl N,N-dimethyl phenyl o-carbamate and phenyl boronic acid (Reproduced from Garg et al) ............................................................................................................................47
Figure 2.2.5. Partial conversion of boronic acid 23 into boronic acid anhydride 31 through thermal dehydration ....................................................................................49
Figure 2.3.1. Synthesis of 2-methyl-5-O-thienyl carbamate derivative (36) .............50
Figure 2.3.2. Literature preparation of potassium phenyltrifluoroborate using KF and an organic acid ................................................................................................................51
Figure 2.3.3. Preparation of compound 37 using KF/L-tartaric acid ......................52
Figure 2.3.4. Systematic comparison of KF/Tartaric acid and KHF₂ preparations of trifluoroborate salt 34 ................................................................................................................53
Figure 2.4.1. Selected directed ortho metalation experiments using O-carbamate 36 ....55
Figure 2.4.2. Mechanism of the anionic ortho-Fries rearrangement .......................56
Figure 2.4.3. General tetrameric and hexameric aggregates of organolithiums (Reproduced from Rathman et al) ......................................................................................57
Figure 2.4.4. TMEDA/n-butyllithium complex ................................................................58
Figure 2.4.5. Keto-enol tautomerization of 2-hydroxythiophenes ..........................59
Figure 2.4.6. Proposed mechanism for potential iterative intermolecular Michael-type additions following ortho-Fries rearrangement ........................................60
Figure 2.5.1. Structure of target compounds 43 and 44 ........................................61
Figure 2.5.2. Proposed mechanism for formation of 43 via O-sulfanation

Figure 2.5.3. Screened reaction conditions for the attempted preparation of compound 43

Figure 2.5.4. Proposed mechanism for the intermolecular Michael-type oligomerization of compound 35a,b upon deprotonation

Figure 2.5.5. Structure of Lawesson’s reagent (45)

Figure 2.5.6. Mechanism of Lawesson’s reagent (45) mediated thiation of carbonyl containing compounds

Figure 2.5.7. Literature precedents for the thiation of cyclic O-carbamates

Figure 2.5.8. Attempted thiation of compound 36

Figure 3.1.1 Proposed Michael trapping using butanethiolate
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ABBREVIATIONS USED

\( \vec{B} \)  
Magnetic field vector

\( \vec{E} \)  
Electric field vector

[O]  
General oxidation reaction

Aq.  
Aqueous

Ar  
Aromatic group

B(OMe)\(_3\)  
Trimethyl borate

c  
Speed of light

C  
Crystalline phase

c.a.  
"Circa" - Approximately

CDCl\(_3\)  
Deuterated chloroform

CH\(_2\)Cl\(_2\)  
Dichloromethane

d  
NMR doublet

DIAD  
Diisopropyl azodicarboxylate

DMG  
Directed metalation group

DMSO-d\(_6\)  
Deuterated dimethylsulfoxide

DOM  
Directed ortho metalation

Et\(_2\)O  
Diethyl ether

EtOH  
Ethanol
<table>
<thead>
<tr>
<th>Acronym</th>
<th>Full Form</th>
</tr>
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<tbody>
<tr>
<td>FLC</td>
<td>Ferroelectric liquid crystal</td>
</tr>
<tr>
<td>HA</td>
<td>General weak acid</td>
</tr>
<tr>
<td>HCl</td>
<td>Hydrochloric Acid</td>
</tr>
<tr>
<td>Hg(OCOCF$_3$)$_2$</td>
<td>Mercury (II) trifluoroacetate</td>
</tr>
<tr>
<td>HPF$_6$</td>
<td>Hexafluorophosphoric acid</td>
</tr>
<tr>
<td>I</td>
<td>Isotropic liquid</td>
</tr>
<tr>
<td>K$_2$PO$_4$</td>
<td>Potassium phosphate</td>
</tr>
<tr>
<td>KHF$_2$</td>
<td>Potassium bifluoride</td>
</tr>
<tr>
<td>LC</td>
<td>Liquid crystal</td>
</tr>
<tr>
<td>LCD</td>
<td>Liquid crystal display</td>
</tr>
<tr>
<td>m</td>
<td>NMR multiplet</td>
</tr>
<tr>
<td>MeCN</td>
<td>Acetonitrile</td>
</tr>
<tr>
<td>MeOH</td>
<td>Methanol</td>
</tr>
<tr>
<td>MgSO$_4$</td>
<td>Magnesium sulfate</td>
</tr>
<tr>
<td>N</td>
<td>Nematic phase</td>
</tr>
<tr>
<td>NaHMDS</td>
<td>Sodium bis-(trimethylsilyl)amide</td>
</tr>
<tr>
<td>NaNO$_2$</td>
<td>Sodium nitrite</td>
</tr>
<tr>
<td>NaOH</td>
<td>Sodium hydroxide</td>
</tr>
<tr>
<td>$n$-BuLi</td>
<td>$n$-Butyllithium</td>
</tr>
<tr>
<td>NFSI</td>
<td>N-Fluorobenzenesulfonylimide</td>
</tr>
<tr>
<td>PCy$_3$</td>
<td>Tricyclohexylphosphine</td>
</tr>
</tbody>
</table>
Pd(PPh₃)₄  *Tetrakis*(triphenylphosphine)palladium(0)
PPh₃  Triphenylphosphine
RT  Room temperature
s  NMR singlet
s-BuLi  *sec*-Butyllithium
SET  Single electron transfer
Sm  Smectic liquid crystal phase
SSFLC  Surface stabilized ferroelectric liquid crystal display
t  NMR triplet
THF  Tetrahydrofuran
TLC  Thin layer chromatography
TMEDA  Tetramethylethlenediamine
TN  Twisted nematic liquid crystal phase
CHAPTER 1: INTRODUCTION

1.1: Introduction to Liquid Crystals

In addition to the three most commonly known phases of matter (solids, liquids, and gases) there exists an unusual phase of matter known as the “liquid crystalline” (LC) phase. As the superficially oxymoronic name suggests, this phase envelops molecular behaviors that mimic crystalline solids and liquids simultaneously. In a solid, intermolecular forces hold molecules together retaining both positional and orientational order. In contrast to this highly ordered state, liquids lack either specific orientational or directional order. Molecules in the liquid phase are in constant diffuse motion, constantly changing directions and shifting in position. The most common measurement of this molecular movement is temperature, which measures the average kinetic energy of molecules within matter. At a substance specific temperature, the kinetic energy of individual molecules exceeds the intermolecular forces between groupings of molecules. This phenomena is known as a phase transition, and the temperature at which it occurs is known as the phase transition temperature. For the aforementioned case of a phase change from solid to liquid, this transition temperature is referred to as the “melting point” of a substance. The intermolecular forces constraining these types of transitions are influenced by the structural properties of molecules. For a good portion of the known scientific timeline, this three-membered description of the phase behavior of matter was sufficient. However, in 1888 an Austrian scientist, Friedrich Reinitzer,\(^1\) noted that specific cholesterol derivatives, in particular cholesteryl benzoate (Figure 1.1.1), exhibited what appeared to
be two separate melting points: melting into a cloudy liquid at 145 °C and melting into a clear liquid at 178.5 °C.

Figure 1.1.1: Structure of cholesteryl benzoate

Furthermore, it was noted that in this “cloudy” state, the material was able to rotate plane polarized light. Although not recognized until later, this was the first recorded example of a material exhibiting liquid crystalline phase behavior.

In liquid crystalline phases, the strong positional ordering of a crystal lattice seen in many solids is mostly lost, but some of the average orientational order exhibited by solids remains. The most common type of liquid crystalline materials are “thermotropic” LCs, which exhibit temperature dependent phase behavior. Depending on the degree of positional and orientational order present in a liquid crystal phase, different phase designations are assigned.
1.2 Liquid Crystal Phases

For the sake of phase comparisons, molecules that form liquid crystalline phases will be considered to behave as long, slender rods (Figure 1.2.1).

Figure 1.2.1: “Rod” phase representations of solids, liquids, and the nematic liquid crystal phase

In the liquid crystalline phase, molecules orient themselves, on average, pointing in a specific direction. This direction is aptly referred to as the “director” of a LC material. Molecules that exhibit LC phases are known as “mesogens”. While maintaining this directional order, molecules are free to diffuse in three-dimensional space. The LC phase in which molecules possess this basic orientational order is known as the “nematic” phase, and is the simplest liquid crystal phase. In addition to possessing a director, some varieties of nematic LCs possess a rotational structural motif (Figure 1.2.2).
Figure 1.2.2: Simulated macromolecular structure of a chiral nematic phase

(Reproduced from the Barrett Group of McGill University)³

These types of liquid crystal phases are known as “chiral nematic” phases or “cholesteric” phases.² Chiral nematic phases are formed by liquid crystal molecules that contain a chiral center or another element that makes them chiral. In a macromolecular view, these molecules form helical structures that rotate with a specific “pitch” – the distance required for one full rotation of the director. As one might imagine, the defined stereochemistry of chiral liquid crystals is directly responsible for this type of “stereospecific” rotation – a result of their molecular packing being influenced by their chirality.

The last common class of liquid crystal phase behaviors encompasses phases known as “smectic” phases. Unlike the nematic phases, which possess primarily orientational order, smectic phases also have a degree of positional order, with molecules in smectic phases forming layered substructures. Similar to the nematic phases, smectic
phases also possess a general orientational director. How this director is oriented with respect to the aforementioned molecular layers gives rise to the designation of the smectic A phase – a phase in which the director is perpendicular to the molecular planes – and the smectic C phase – a phase in which the director makes an angle other than 90° with respect to the molecular planes.² Further molecular order within these planes gives rise to other types of smectic phases, which will not be discussed here.

Both McMillan⁴ and Wulf⁵ have developed models that describe the behavior of the smectic C phase in comparison to the behavior of the smectic A phase. According to McMillan, molecules in the smectic A phase may be considered to have free rotation around their axis which is “frozen out” during a transition to the smectic C phase. As the rotational energy of molecules within the smectic A phase decreases (e.g. with temperature), dipole-dipole interactions between molecules become more prevalent and the observed “tilting” of molecules to form the smectic C phase is the result of these interactions. In contrast, Wulf’s model asserts that steric repulsions between “zig-zag” shaped tails of liquid crystals, a common structural motif, stabilizes the slanted orientation of molecules within the smectic C phase.

In close analogy to the chiral nematic phase formed by some classes of liquid crystalline materials, chiral mesogens may form a chiral smectic C phase. Within this type of phase, molecules are ordered into planes with the director oriented at an angle to the plane. However, unlike the conventional smectic C phase, the director rotates in a helical fashion throughout this plane (Figure 1.2.3).²
Chiral smectic C materials have seen applications in a variety of electronic devices such as, but not limited to, image scanners, image processing devices and liquid crystal displays (LCDs). In order to better understand the importance of liquid crystals in the field of optical electronics, a brief overview of the behavior of liquid crystals in electric fields and their interactions with light will be presented.

The figure below summarizes the discussed liquid crystal phases visually (Figure 1.2.4).
Figure 1.2.4: Pictorial representation of the basic differences between discussed liquid crystal phases.
1.3: Interactions of Liquid Crystalline Materials with Electric Fields and Polarized Light

*Interactions of Liquid Crystals with Electric Fields*: One of the four fundamental forces within the natural world is the electrostatic force. Simply put, objects possessing electric charges of opposite sign will experience an attractive force while objects possessing electric charges of identical sign experience a repulsive force. This is further manifested in the observation that charges within an electric field will experience a corresponding electric force that depends on the sign and magnitude of the charge and the strength of the external electric field. While discrete charges rarely exist within molecules, dipoles, or centers with partial negative or positive charge character, are a common feature that exists as the result of deformation of electron density. This is often observed in polar chemical bonds – i.e., bonds between atoms of differing electronegativity. Like discrete charges, molecular dipoles also interact with electric fields.\(^2\)

For polar liquid crystals in the absence of an electric field, there is no overall orientation of dipoles, in spite of the overall positional and rotational order parameters assigned to liquid crystalline phases. However, in the presence of an electric field, molecules reorient themselves to align their dipole moments with the external field. Depending on the degree of charge separation (i.e., polarity) in a molecule and the strength of the applied field, the force causing polar molecules to adopt this orientational change varies. In the case of liquid crystals, the director of the material can be aligned with this external applied electric field. In a liquid phase, the inherent disorder of molecules prevents this alignment. In a solid, the intermolecular forces maintaining the high degree of
orientational and positional order overcome the influence of an electric field. Thus, the response of liquid crystals to external electric fields is a behavior that is unique to this phase of matter.\textsuperscript{2} In general, the net electric dipole per unit volume (during the application of an external field) within a material is called the “polarization” of a material.

**Fundamental Properties of Light:** At this point, it should be noted that this definition of polarization is fundamentally different from the definition of polarization of electromagnetic waves. Thanks to the tireless work of James Clerk Maxwell in the late 1800s, it was realized that visible light is, in fact, an electromagnetic wave – that is, it consists of both an electric field component and a magnetic field component which propagate through space perpendicular to each other (Figure 1.3.1).

![Illustration of a representative electromagnetic wave](image)

**Figure 1.3.1:** Illustration of a representative electromagnetic wave (Reproduced from the University of California – Davis)\textsuperscript{8}

Since the magnetic and electric fields in the above example each oscillate within a single plane, this type of electromagnetic wave represents a “plane-polarized” wave of radiation.
Light of mixed polarizations (also known as “unpolarized light”) can be filtered to transmit plane polarized light by passing it through materials known as “polarizers”. Light that is already plane-polarized will pass through a second polarizer, to some degree, provided that the two distinct polarizations are at an angle less than 90° with respect to each other. When light with a 90° difference in polarization with respect to a polarizer strikes the polarizer, zero light is transmitted. This is the fundamental principle that allows liquid crystal displays to function (Figure 1.3.2).

Figure 1.3.2: The effect of polarizers on polarized and plane polarized light
Interactions of Liquid Crystals with Light: A material that has different properties when acted upon from different directions is defined as being “anisotropic”. An anisotropic material possess different indices of refraction depending on the polarization of light that passes through it. This phenomenon is known commonly as “birefringence”. In fact, polarizers are a textbook example of this type of material. Liquid crystals, additionally, exhibit anisotropic properties. In the smectic C phase, the symmetry of the phase prevents the formation of a net polarization vector. Chiral smectic C phases, due to their natural helical structure, also have a net polarization of zero in the absence of an external electric field (Figure 1.3.3).
It is well known that plane-polarized light is rotated by samples of optically pure chiral materials. In the case of chiral liquid crystalline materials, light is rotated by the macrostructural chirality of the material. In the presence of an external electric field, this helical structure is unwound and a net polarization develops. Types of liquid crystals that
are able to be polarized by an electric field are known as “ferroelectric LCs”. In the case of ferroelectric LCs, some degree of polarization exists even after the removal of the external electric field. Such materials are utilized in the construction of so-called “surface-stabilized” ferroelectric liquid crystal displays (SSFLCs).

### 1.4: The Use of Ferroelectric Liquid Crystals in Displays

In a typical SSFLC, liquid crystalline material is sandwiched between two pieces of glass that are fit with perpendicular polarizers, preventing light from being transmitted. By applying an electric field to the material, the liquid crystalline material will twist the incoming light 90° after it exits the first polarizer, allowing it to pass through the second polarizer. This is the “on” or “bright state” of a liquid crystal display. When the orientation of the electric field is reversed, the liquid crystalline material does not twist the light, and the incoming light is completely blocked by the second polarizer. This is the “off” or “dark state” of a liquid crystal display. A diagram of these two types of states is given below (Figure 1.4.1).
In a conventional twisted nematic (TN) cell, the glass surfaces are rubbed with an alignment material to create some degree of rotational order in the nematic liquid crystal that is pressed between the surfaces. In the “on” state, no electric field is applied and the natural twist of the LC material allows light to pass through both polarizers. When a field is applied, this helical twisting is undone and light can no longer pass through – this is the “off” state (Figure 1.4.2).
In TN cells, the natural (and relatively slow) relaxation of liquid crystal molecules is responsible for the transition between the light and dark states, whereas in a SSFLC display, the electric field is entirely responsible for the transition between light and dark states. As a result, SSFLC displays possess much faster switching times than their TN counterparts.\textsuperscript{10}

1.5: Structure of Liquid Crystal Phase Forming Materials

Goodby\textsuperscript{11} defines the general qualities of materials that form tilted and ferroelectric liquid crystals as the following:

1.) Possess an alkyl-aryl-alkyl system
2.) Has a strong terminal lateral dipole

3.) Has at least two aromatic rings

4.) Has a chiral center, which serves to reduce the symmetry of the phase, leading to ferroelectric behavior.

Additionally, the presence of a strongly polarizable core (often aromatic) increases the intensity of ferroelectric behavior in a liquid crystalline material. These qualities are generalized in the figure given below (Figure 1.5.1).

![Figure 1.5.1: Generalized structure of ferroelectric LC materials](image)

The tendency to form smectic LC phases is strongly influenced by the identities of the central and terminal linkages, as identified by Goodby (Figure 1.5.2). \(^6\)
Figure 1.5.2: Influence of the identity of central and terminal mesogen linkages on the ability to form smectic phases

1.6: Fluorinated Liquid Crystals

As previously mentioned, the incorporation of a lateral dipole moment in liquid crystalline target molecules increases ferroelectric properties. More recently, fluorinated liquid crystals have received increasing attention in the literature, and are a primary focus of the Seed-Sampson group.\textsuperscript{12–14} The high electronegativity of fluorine allows for drastic changes in the dipole of the core without imparting a significant steric impact on intermolecular packing (in most cases). The incorporation of fluorine as a lateral substituent on the aromatic core of a liquid crystal often results in significantly lowered melting points and the reduction of higher order smectic phases which are not suitable for use in displays. This is ideal for display applications of LC materials where it is best for the ferroelectric phase to form close to room temperature. Figure 1.6.1 illustrates the
effects of various lateral core substituents on melting temperatures and phase formation with comparison to the relative van der Waals radii of the substituents.

<table>
<thead>
<tr>
<th>Compound</th>
<th>Transition Temperatures (°C)</th>
<th>van der Waals Volume (Å³)</th>
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<td>Sm</td>
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<tr>
<td>H</td>
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</tbody>
</table>

Figure 1.6.1: The effects of various lateral core substituents on transition temperatures in an example mesogen based on a phenyl core

As seen above, the incorporation of fluorine into the LC leads to the formation of desirable smectic phases while decreasing the transition temperature into these phases versus a hydrogen substituent. Additionally, fluorine maintains a minimal steric effect, as indicated by its small van der Waals volume (H = 3.4 Å, F = 5.8 Å).
1.7: Thiophene-based Liquid Crystals

One of the major research interests of the Seed-Sampson group is the development of liquid crystalline materials containing an S-heterocycle core. Thiophene is a 5-membered, aromatic, sulfur-containing heterocycle (Figure 1.7.1).

![Figure 1.7.1: Structure of thiophene](image)

Thiophene possesses a significant inherent lateral dipole moment as well as a natural molecular bend which aids in the reduction of transition temperatures in LC materials containing thiophene cores (Figure 1.7.2).\(^\text{15}\)

![Figure 1.7.2: Dipole moment, bond angles and numbering conventions within thiophene](image)

Both 2,5- and 2,4-disubstituted thiophene derivatives have been shown to exhibit liquid crystalline behavior.\(^\text{16,17}\) However, 2,4-disubstituted thiophenes often exhibit depressed or eliminated mesophase behavior versus analogous 2,5-disubstituted thiophenes. This may best be explained by the comparative electronic relay in each type of molecule. This
reduction of conjugation and its effect on phase behavior is shown in Figure 1.7.3. The reduction of electronic relay affects the polarizability along the molecular axis, ultimately affecting the anisotropy of molecular polarizability.

**Figure 1.7.3:** Differences in phase behavior and melting points as a consequence of electronic conjugation in 2,5-disubstituted thiophene cores versus 2,4-disubstituted thiophene cores (reproduced from ref. 16).
As noted in Figure 1.7.3, a 2,4-disubstitution pattern in the thiophene core of thiophene esters reduces the degree of conjugation (by resonance) through the molecule, resulting in a loss of desirable phase behavior in some cases.

As a consequence, the focus of the Seed-Sampson group has been on the synthesis of LCs containing the 2,5-disubstituted thiophene (or otherwise sulfur-containing) core, which has more desirable phase behavior. Some examples of LCs synthesized by the Seed-Sampson group are given below (Figure 1.7.4).

![Chemical structures](Image)

Figure 1.7.4: Representative fluorothiophene-containing mesogens synthesized by the Seed-Sampson group
Additionally, the pursuit of fluorinated thiophene core LCs has remained a continual goal for the group (cf. 1.7.4) – particularly materials containing the 2,5-disubstituted-3-fluorothiophene moiety or 3-fluorinated alkoxythiophenes.9,18

1.8: Previous Work Toward the Synthesis of 3-Fluorothiophene Moieties

The incorporation of fluorine onto the thiophene ring presents a unique challenge. Several recent articles have been dedicated to the fluorination of thiophene.19,20 Outside of LC applications, fluorinated molecules (including fluorinated thiophenes) have seen impact in both medicinal and materials chemistry, provoking intense interest in novel and synthetically useful fluorination methodologies.21–24 Direct fluorination of thiophene using F₂ is non-ideal due to the low selectivity of fluorination as well as the extreme danger of F₂ gas. Literature attempts at direct fluorination using 5% F₂ in He led to a mixture of 2-fluorothiophene and 3-fluorothiophene products.25 As an alternative to traditional F₂ fluorination, the Seed-Sampson group has a long-standing interest in mild, regioselective and chemoselective fluorination methodologies.

One of the preliminary methodologies employed by the group utilized the known Balz-Schiemann reaction to fluorinate the 3-position of the thiophene ring (Figure 1.8.1).12
Diazotization of 3-aminothiophene 1 proceeded in outstanding yield to give diazonium salt 2. Thermal treatment of 2 using a sand bath followed by trapping of the desired product using a cold finger yielded the desired 3-fluorinated product (3) in moderate yield. In spite of the success of this method, the use of harsh conditions and unconventional purification limits the application of this method to more complex systems.

A variety of commercially available electrophilic fluorination agents have also seen use within our group (Figure 1.8.2).

Previously, Alan Grubb, a former member of the Seed-Sampson group, utilized Selectfluor™ in an electrophilic aromatic substitution type reaction for the fluorination of thiazole cores (Figure 1.8.3), affording the desired products in moderate yields.\textsuperscript{26}
Figure 1.8.3: Direct fluorination of the thiazole core as developed by Grubb

Although this is a mild and therefore desirable method, the modest yields and requirement of a resonance-donating alkoxy group limit the scope of this transformation.

Attempts by group member Pritha Subramanian to fluorinate the 3-position of 2-alkoxythiophene derivatives 4 and 5 failed to yield the desired product under identical conditions to Grubb’s method (Figure 1.8.4).

Figure 1.8.4: Attempts at 3-fluorination of 2-alkoxythiophene cores by Subramanian

The use of NFSI as an alternative fluorination agent produced a marked increase in yields of the desired product (4 – 19%). However, a large quantity of difficult to remove starting material often remained and was not separable using conventional column
chromatography. With this information in hand, it was determined that direct 3-fluorination of thiophene cores was not an ideal late-stage route towards 3-fluorothiophene derivatives.

A common strategy for fluorination is direct deprotonation followed by electrophilic trapping using one of the aforementioned electrophilic fluorination agents (Figure 1.8.2). Directed ortho metalation (DOM) is a method commonly used for the functionalization of a typically unreactive site adjacent to a so-called “directing group” (DMG). An ideal directing group has the ability to coordinate strongly to organolithium reagents while simultaneously resisting nucleophilic addition by the organolithium. During the addition of an organolithium reagent to the substrate, coordination between the directing group and the organolithium facilitates lithiation “ortho” to the directing group. After lithiation, a wide variety of electrophiles may be added to trap the lithiated intermediate, allowing for a broad range of functionalization to be performed (Figure 1.8.5).\textsuperscript{27–29} This process ranges in efficiency based upon the relative strength of the directing group, which is related to its structure and electron density.
Figure 1.8.5: The basic mechanism of the directed ortho metalation process as well as common directing groups (DMG), and installable functionalities (E) using this method

Aryl alkoxy groups are known DMGs for ortho-metalation processes, and it was therefore postulated that the 3-position of a 2-alkoxythiophene derivative may be amenable to this type of deprotonation and trapping using NFSI. Deprotonation of 2-alkoxythiophene 6 at
$0 \, ^\circ C$ followed by trapping using a solution of NFSI in THF led to a mixture of monofluorinated (7) and difluorinated (8) products in low yields (Figure 1.8.6).

Figure 1.8.6: Attempted 3-position deprotonation of a 2-alkoxythiophene derivative and subsequent trapping using NFSI

The low yields of the desired product (7) are likely the result of protodemetalation side reactions. While the mechanism of the reaction between N-F based fluorination agents and organolithium reagents is still not completely understood, it is accepted that a single-electron transfer (SET) reaction may result in the reformation of the protonated starting material (6) after lithiation (Figure 1.8.7).\textsuperscript{30,31,32}
As illustrated above, upon treatment of the substrate with an organolithium reagent, organolithium reagent 9 is generated in situ. Under the SET byproduct formation pathway, a single electron transfer results in the formation of radical intermediate 11. Subsequent hydrogen abstraction from THF (which is used as the solvent in many deprotonations) regenerates starting material 12.

Outside of direct deprotonation, halogen-metal exchange is another popular method for the in situ generation of organolithium reagents. A halogen on the substrate is readily displaced by lithium, provided by an organolithium reagent. This generated lithio-
intermediate may then be allowed to react with the desired electrophile, NFSI in this case.

Attempts by Pritha Subramanian to utilize halogen-metal exchange in 3-bromothiophene derivatives were met with success, generating the desired 3-fluorothiophenes in 68 – 74% yield (Figure 1.8.8).

This being said, this method was marred by the formation of sometimes significant quantities (ca. 4 – 36% of the reaction product) of the undesired protodebrominated product (through the SET mechanism detailed in Figure 1.8.7). Separation of the desired fluorinated product from the protodebrominated side product required careful chromatographic separations, often via multiple purifications by column chromatography, in order to generate the desired product in synthetically useful purity.

To remedy this problem, the group sought to develop a method of derivatization that would allow the protodehalogenated material (13) to be easily and efficiently separated from the desired fluorinated product. C-3 Mercuration and precipitation as the mercuric chloride salt (14) through treatment of the crude reaction mixture with Hg(OCOCF$_3$)$_2$ in
ethanol/THF and subsequent salting with sodium chloride allowed for the undesired byproduct to be easily separated from the fluorinated product using filtration (Figure 1.8.9). Following this step, the desired product was purified using a single column chromatographic separation.

![Figure 1.8.9: Mercuration of the undesired protodehalogenated side product of halogen-metal exchange](image)

Although this method allowed for the eventual synthesis of several fluorinated chiral liquid crystal targets, competition from a SET side reaction and the subsequent need for the mercuration/separation process represents an inconvenient step that also reduces the overall yield of the fluorination process significantly. We postulate that, through the development of more efficient electrophilic fluorination processes, the need for this type of derivatization chemistry may be eliminated.

1.9: Thesis Goals

During the end of her time with the Seed-Sampson group, Pritha Subramanian made preliminary attempts towards the synthesis of thiophene derivatives containing a more powerful directing group
than the previously utilized alkoxy directing group, culminating in the preparation of two
directing group-containing targets, specifically \( O \)-phosphorodiamidate 15 and \( O \)-
carbamate 16 (Figure 1.9.1).

![Chemical structures of 15 and 16](image)

**Figure 1.9.1: Previously prepared directing group-containing thiophene cores**

Unfortunately, due to time constraints, the ability of these groups to act as highly efficient
directing groups in electrophilic DOM-fluorination (see section 1.8 for previous
experiments) was not investigated. We hypothesize that, the greater propensity of these
groups to act as directing groups will decrease the degree of protodemetalation encountered
previously and hence eliminate the need for the previously developed mercuration
chemistry (see Figure 1.8.9) which utilizes hazardous mercury salts and adds an additional
synthetic step.

*Development of Nickel-catalyzed Cross-Couplings Using Thienyl Pseudohalides:*

Interestingly, these types of C-O-linked directing groups (ex. 15 and 16) have been
shown to act as coupling partners in nickel-catalyzed Suzuki-couplings. Nickel-catalyzed
reactions are a recently expanding sub-discipline of catalysis. Nickel-based catalysts are
often far less expensive than their more well-developed transition metal counterparts (e.g.
Pd, Rh, Ru) and have increased stability to air and moisture. Using nickel catalysts,

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2 See section 1.8 for more background information on directed ortho metalation
transformations such as Suzuki-type cross-couplings, aminations, polymerizations, borylations and cycloadditions are accessible. Particularly interesting is the use of so-called “pseudo-halides” as cross-coupling partners with boronic acids in the place of traditionally used bromides, chlorides and iodides. While the coupling of triflate ($R' = \text{SO}_2\text{CF}_3$) and nonaflate ($R' = \text{SO}_2\text{C}_4\text{F}_9$) phenol derivatives such as $Z$ are common in Pd-catalyzed cross-couplings, the most examined classes of pseudo-halides within Ni-catalyzed cross-couplings are esters, $O$-carbamates, and sulfamates (Figure 1.9.2).

![Figure 1.9.2: The use of esters, $O$-carbamates, and sulfamates as “pseudo-halide” cross-coupling partners in the presence of a nickel catalyst](image)

Interestingly, many groups that are amenable to Ni-catalyzed cross-couplings are also capable of acting as strong directing groups in DOM, as noted in recent literature.

In spite of their growing popularity within the literature, there are no examples of these types of couplings utilizing thienyl $O$-carbamates or thienyl $O$-sulfamates as pseudohalide partners and no examples of DOM chemistry utilizing these groups within thienyl systems. It was envisioned that, utilizing a tandem DOM fluorination/Ni-catalyzed cross-coupling approach, the 3-position of the thiophene ring might be sequentially fluorinated (using an electrophilic fluorine source such as NFSI) and then subjected to
cross-coupling, providing a divergent approach to a family of potentially mesogenic 2,5-disubstituted 3-fluorothiophene derivatives (Figure 1.9.3).

![Diagram of proposed tandem DOM fluorination/Ni-catalyzed cross-coupling approach to the 2,5-disubstituted 3-fluorothiophene core]

**Figure 1.9.3: Proposed tandem DOM fluorination/Ni-catalyzed cross-coupling approach to the 2,5-disubstituted 3-fluorothiophene core**

With this knowledge, we set out with the goal of evaluating the ability of thienyl O-carbamates and O-sulfamates to act as efficient directing groups in DOM fluorination in an attempt to reduce the quantity of protodemetalated/protodehalogenated byproducts present after lithiation and trapping using NFSI. Furthermore, we wished to probe the ability of these systems to act as pseudohalide coupling partners in Ni-catalyzed couplings following fluorination. If such a method was accessible, it would allow for the development of a divergent approach to a variety of 2,5-disubstituted 3-fluorothiophene derivatives – prime candidates for incorporation into liquid crystalline materials.
Synthesis of 2-alkoxy-3-fluorothiophenes:

As previously stated (see Figure 1.7.4), 2-alkoxy-3-fluorothiophene derivatives are common targets within the Seed-Sampson group. Most recently, Jonathan Tietz developed a very efficient route towards 2-alkoxythiophenes through the oxidation of thienyl BF$_3$K salts to their corresponding thienone derivatives and subsequent elaboration to 2-alkoxythiophenes through Mitsunobu etherification (Figure 1.9.4).

Additionally, recent literature reports indicate that, in the presence of Schwartz’s reagent (Cp$_2$Zr(H)Cl), O-carbamates may be cleaved to yield their corresponding phenolic parent. Therefore, we envisioned the possible fluorination of the 3-position of the thiophene ring using DOM-type chemistry (see Figure 1.9.3) and subsequent cleavage using Schwartz’s reagent to yield the corresponding thienone. This fluorinated thienone derivative could then potentially be efficiently elaborated to 2-alkoxy-3-fluorothiophene derivatives using the chemistry developed by Tietz. This proposed synthetic route is summarized in the scheme below (Figure 1.9.5).
Figure 1.9.5: Proposed synthetic pathway to the 2-alkoxy-3-fluorothiophene core utilizing DOM fluorination and reductive cleavage with Schwartz’ reagent followed by Mitsunobu etherification

In this thesis, an account of the synthesis of two thienyl $O$-carbamate derivatives, and investigations into their behavior in DOM fluorinations and Ni-catalyzed cross-couplings, is presented. An efficient route to these types of 2-hydroxythiophene derivatives (which might be extended to other DMGs) has been developed and synthetic complications and pitfalls of this route have been thoroughly investigated.
CHAPTER 2: RESULTS AND EXPERIMENTAL DISCUSSION

1.) Synthesis of \( p \)-Tolyl \( O \)-Carbamate Model Compound (17)

In order to probe the synthetic utility of the \( N,N \)-diethyl \( O \)-carbamate moiety in thiophene systems, a suitable model compound was needed. Initially, a 5-(\( p \)-tolyl)thiophene-2-carbamate model (17) was selected as a first target. Blocking of the 5-position of the thiophene ring with a chemically inert “dummy group” was crucial to ensure that the reasonably acidic 5-position was not in competition with deprotonation at the 3-position facilitated by the directed ortho-metalation group (Figure 2.1.1). Additionally, this substituent would simplify the \(^1\)H NMR spectrum of the desired product.

![Potential mixture of 2,5-substituted and 2,3-substituted products]

**Figure 2.1.1:** Competitive deprotonation at the 3- and 5-positions of the thiophene ring in the presence of a directing group (DMG)

With model substrate 17 selected, retrosynthetic cleavage of the O-C bond of the carbamate (17), separating to an O-centered thiophene enolate (20) and carbamoyl chloride-type
synthon (19), prompted the use of the trifluoroborate oxidation chemistry developed by Jonathan Tietz, a previous member of the Seed-Sampson group, as a method to access the appropriate parent thienone (18) (Figure 2.1.2).43

![Chemical structure](image)

Figure 2.1.2: Retrosynthetic cleavage of the O-C carbamate bond and subsequent tracing to the parent thienone (18) and trifluoroborate salt (21)
Figure 2.1.3: Synthesis of 5-(p-Tolyl)-2-O,N-diethyl thienyl carbamate (17)

With this route (Figure 2.1.3) in mind, 4-methylphenylboronic acid (23) was prepared through halogen-metal exchange between 4-bromotoluene (22) and n-butyllithium with subsequent trapping of the generated organolithium intermediate using trimethylborate followed by acidic hydrolysis. Boronic acids, by nature, are present as a mixture of free acids and mixed anhydrides, making analysis of purity and yield by $^1$H NMR difficult. This material was used crude, and a two-step yield was calculated after subsequent Suzuki coupling with 2-bromothiophene in a mixed solvent system of toluene, acetone, and water. Tetrakis(triphenylphosphine)palladium(0) itself was prepared in-house through the reaction of palladium (II) chloride with triphenylphosphine in the presence of hydrazine.
monohydrate and was used shortly after preparation.\textsuperscript{45} This cross-coupling led to the desired compound, 2-\((p\text{-tolyl})\)thiophene \((24)\), in 92\% yield from 4-bromotoluene after purification by elution through a silica plug using petroleum ether. Direct lithiation at the 2-position of the thiophene ring proceeded smoothly at \(-78 °C\) using \(n\)-butyllithium. The \textit{in situ} generated organolithium intermediate was trapped using trimethylborate. After washing the crude product with petroleum ether to remove any unreacted, highly non-polar starting material, the desired boronic acid \((25)\) was obtained in 77\% yield as a pale green solid. Interestingly, \(^1\text{H}\) NMR analysis shows this boronic acid to exist entirely as the free acid in DMSO-\(d_6\), with no evidence of anhydride formation. 5-\((p\text{-Tolyl})\)-2-thienylboronic acid \((25)\) was smoothly converted to the corresponding trifluoroborate salt \((21)\) through conventional reaction with KHF\(_2\) in a methanol/water solvent system according to the method originally developed by Molander \textit{et al.}\textsuperscript{46} Extraction of the crude reaction mixture with boiling acetone followed by dissolution of the crude product in the minimal amount of acetone and subsequent “crashing-out” of the product \textit{via} the addition of diethyl ether with vigorous stirring was needed to separate the trifluoroborate salt \((21)\) from insoluble potassium salt byproducts. The trifluoroborate salt was obtained as a light grey solid in 86\% yield. Oxidation of this salt using Oxone, a process that was well-documented within our group,\textsuperscript{43} became exceedingly challenging due to the formation of a pervasive, blue impurity during oxidation. Attempts at separation of the target thienone product \((18a,b)\) from this blue impurity by flash column chromatography and recrystallization failed to yield a significant reduction in the concentration of the impurity. Although this highly colored impurity was not visible in the \(^1\text{H}\) NMR spectrum of the product, solutions of the
compound were blue at high dilution with the color becoming more intensely purple at higher concentrations of the crude compound. This compound readily stained glassware purple, as well. Inspection of the literature yielded one interesting report by the Evans group at Imperial College London. During an attempted preparation of 2,2'-bithiophene-5-boronic acid, samples of crude material spotted onto TLC plates were observed turning deep blue when exposed to air. The group hypothesized that this deep blue color was the result of spontaneous oxidation to the corresponding thienone in air, and oxidative coupling of this thienone to yield a highly conjugated dimer (Figure 2.1.4).

![Chemical structure of 2,2'-bithiophene-5-boronic acid](image_url)

**Figure 2.1.4: Literature report of the oxidative dimerization of thienones**

Some dyes of this class were prepared in 9-22% yield by the Evans group and characterized by absorbance measurements. In light of this information, it was believed that this
pervasive blue impurity (27) observed during the preparation of thienone 18a, b may be the result of this type of oxidative dimerization (Figure 2.1.5).

![Chemical structure](image)

**Figure 2.1.5: Proposed oxidative dimerization during the oxidation of trifluoroborate salt (21)**

In support of this, MALDI-MS of the crude material showed a peak corresponding to the mass of the dimerization product (27). Dimerizations of this type have also been observed by other members of the group under similar conditions. Performing oxidations to the trifluoroborate salt under an argon atmosphere and with fewer equivalents of Oxone oxidant still led to the formation of this byproduct. Additionally, it was observed that the presence of any amount of residual sodium chloride after the isolation of the product resulted in a complete decomposition of the desired thienone product. The literature suggests that this may be the result of the generation of Cl₂ or hypochlorites *in situ* through the reaction of Oxone and chloride ion.⁴⁸,⁴⁹ This was not noted by previous members of the
Seed-Sampson group in their work with thienones. In the future, optimization of this dimerization process may prove to be synthetically useful for the construction of thiophene-based dyes, but it currently stands in the way of the desired synthetic transformation. In spite of this side reaction, a quantity of pure thienone (18a,b) was obtained as a grey solid in 63% yield after purification by flash chromatography. After this material was characterized by $^1$H NMR spectroscopy, it was discovered that the two regioisomeric forms of the thienone, 5-(p-tolyl)thiophene-2(3H)-one (18b) and 5-(p-tolyl)thiophene-2(5H)-one (18a), were formed in a 9:1 ratio. However, both regioisomeric forms of the desired product thienone will react in an identical manner upon treatment with a base to form the corresponding enolate (Figure 2.1.6), so their separation was not required.

![Figure 2.1.6: The comparative deprotonations/enolization of generalized thiophene-2(3H)-one and thiophene-2(5H)-one by bis-hexamethylsilylamide base](image)

With the desired thienone derivative(s) (18a,b) in hand, conversion to the corresponding N,N-diethyl O-carbamate (17) through deprotonation/enolization using NaHMDS and subsequent trapping of the enolate by diethyl carbamoyl chloride in anhydrous THF was achieved in 52% yield after purification by flash chromatography. This represents one of the few examples of thienyl O-carbamates synthesized, and the first synthesized by this type of route. At the time of writing of this thesis, only one group had synthesized a 2-thienyl O-carbamate. Furthermore, in their experiments with directed ortho metalation, they had failed to account for the reasonably acidic 5-position hydrogen, and consequently experienced deprotonation at the 5-position exclusively instead of at the desired 3-position when using the appropriate organolithium base, s-butyllithium. Our work represents the first experiments performed on a 2-thienyl O-carbamate with the acidic 5-position of the thiophene blocked with an inert group, ensuring that deprotonation occurs exclusively at the 3-position of the thiophene ring. No literature examples of 2-thienyl O-carbamates as pseudohalide partners for nickel catalyzed cross-couplings were available at the time of this writing. Therefore, we began to explore the use of thienyl O-carbamate 17 in such cross-coupling reactions.

2.) Studies Towards Ni-catalyzed Cross-couplings using p-Tolyl O-carbamate

Model Compound 17

According to a recent series of reports by Garg et al.,\textsuperscript{38} NiCl$_2$(PC$_3$)$_2$ (28) has been identified as a suitable catalyst for the cross-coupling of aryl O-carbamates as so-called
“pseudo-halide” substrates with boronic acids. No literature examples of 2-thienyl O-carbamates as pseudohalide partners for nickel catalyzed cross-couplings were available at the time of this writing. Therefore, we began to explore the use of thienyl O-carbamate 17 in such cross-coupling reactions. The catalyst (28) was prepared by refluxing NiCl₂·6H₂O with the appropriate ligand, tricyclohexylphosphine, in ethanol according to a literature precedent.51 p-Tolylboronic acid (23) was selected as a trial coupling partner due to the simplicity of the desired product in ¹H NMR analysis. Following published conditions, the O-carbamate substrate (17) was refluxed in toluene with the catalyst (28), boronic acid (23) and potassium phosphate (Figure 2.2.1).

Figure 2.2.1: Attempted Ni-catalyzed cross-coupling of thienyl O-carbamate 17

Using these conditions, the product 29 resulting from the desired Suzuki-type coupling of the O-carbamate 17 and boronic acid 23 was not observed. Instead, only homo-coupling between two equivalents of boronic acid, yielding 4,4’-dimethyl-1,1’-biphenyl (30), was observed after work-up. Generally, it is assumed that nickel-catalyzed Suzuki-type cross-
couplings proceed through a Ni(0)/Ni(II) catalytic cycle, analogous to the accepted Pd(0)/Pd(II) catalytic cycle for conventional palladium-catalyzed Suzuki couplings except that excess boronic acid acts as a reducing agent, reducing the initial Ni(II) complex to the catalytically active Ni(0) species (Figure 2.2.2).\textsuperscript{52}

Figure 2.2.2: Accepted mechanism for Ni-catalyzed Suzuki cross-couplings

It has been previously proven that, in the presence of molecular oxygen, two boronic acid partners may be cross-coupled in the presence of a palladium catalyst leading to the aforementioned “homo-coupled” type-product (Figure 2.2.3).
Figure 2.2.3: Proposed mechanism for Pd(0)-catalyzed “homo-coupling” of boronic acids in the presence of molecular oxygen

A study by Lakmini et al.\textsuperscript{53} determined that the formation of a peroxy-Pd\textsuperscript{0} complex through reaction with molecular oxygen is a key step in this process. Interestingly, this compound exists as an isolatable solid which may be prepared through the reaction of zero-valent palladium phosphine complexes with O\textsubscript{2} in benzene.\textsuperscript{54} In the presence of this peroxy-Pd complex, aryl boronic acids were homo-coupled to furnish the corresponding biaryl adducts in 40-59\% yields. Due to this discovery and the previous evidence that Ni(0) complexes behave similarly to Pd(0) complexes in Suzuki-type reactions, it is possible that the formation of a similar peroxy-Ni\textsuperscript{0} complex leads to the observed homo-coupled product 30 in the attempted reaction.
A reexamination of the literature indicated that the Ni(0) species generated by the reduction of the Ni(II) catalysis by excess boronic acid may be sensitive to water. However, it was additionally proposed that some amount of water is needed in order to generate hydroxide ions for the activation of the boronic acid prior to oxidative addition across the nickel center. The effect of water on the success of Ni-catalyzed cross-couplings of aryl carbamates and aryl boronic acids was closely examined through density functional theory (DFT) modeling by the Garg group (Figure 2.2.4).41

Figure 2.2.4: Free energy profile for the Ni-catalyzed cross-coupling of phenyl N,N-dimethyl phenyl O-carbamate and phenyl boronic acid (Reproduced from Garg et al)41
The above Gibbs free energy profile shows that, following transmetalation of the O-carbamate onto the Ni(0) center (A in Figure 2.2.4), the addition of water forms a 6-membered water-Ni(II)-carbamate complex (B in Figure 2.2.4) that is 1.1 kcal/mol more stable than compound A. This process consequently increases the energetic barrier for the next required transmetalation reaction in the cycle, indicating that the reactivity of O-carbamates with respect to Ni cross-couplings is reduced in the presence of excess water.

In a bid to remove any adventitious water from the Ni(0)-catalyzed coupling reaction, toluene was distilled over Na/benzophenone and K₃PO₄ was dried in a vacuum oven prior to use. Otherwise, identical reaction conditions were employed. However, this modification still failed to yield the desired product. Some literature reports indicated that inconsistent results were obtained during such coupling reactions with K₃PO₄ obtained from different vendors,⁵¹ indicating that this reaction may not be as robust as original reports seemed to indicate. One report indicated that a 1:10 ratio of free boronic acid to boronic anhydride formed prior to coupling led to greatly increased yields.⁴¹ By heating a sample of p-tolylboronic acid (23) to 80 °C under vacuum for 24 hours using a Kugelrohr apparatus and monitoring changes in composition by ¹H NMR spectroscopy, the desired ratio of boronic acid to boronic anhydride (31) was obtained (Scheme 2.2.5).
Figure 2.2.5: Partial conversion of boronic acid 23 into boronic acid anhydride 31 through thermal dehydration

Unfortunately, use of this “optimized composition” boronic acid/boronic anhydride mixture in the cross-coupling still failed to give the desired product. Although most studies cite tricyclohexylphosphine as the most synthetically useful ligand for Ni-catalyzed Suzuki-couplings, other phosphine ligands have also seen use. Since no thiophene-based Ni-catalyzed cross-couplings have been published, this variation has not yet been explored. In future work, attention should be diverted to the optimization of these types of reactions through variations in ligand types, solvent selection, and the exploration of other types of installable pseudohalide groups which are known to be susceptible to Ni(0) C-O insertion and cross-coupling in phenyl systems.

3.) Synthesis of 5-Methyl-2-0-carbamate Model Compound 36

As detailed above, the use of a $p$-tolyl-substituted thiophene moiety as a model compound for the exploration of the chemistry of thienyl $O$-carbamates proved to be less
than ideal due to synthetic complications during the preparation of the O-carbamate substrate 17. It was thought that by decreasing the electron density of the thiophene system, the oxidative dimerization (Figure 2.1.5) encountered during oxidation of the $p$-tolyl BF$_3$K salt (21) may be eliminated. Additionally, a simple 2-alkylated thiophene starting material would eliminate the need for the costly and time consuming attachment of the 5-($p$-tolyl) group through Suzuki coupling. With this in mind, 2-methylthiophene, an inexpensive and commercially available alkylthiophene, was selected as an attractive alternative starting material.

**Figure 2.3.1: Synthesis of 2-methyl-5-$O$-thienyl carbamate derivative (36)**

Following a similar synthetic design (Figure 2.3.1), 2-methylthiophene (32) was treated with $n$-butyllithium in anhydrous THF at -78 °C and the resulting lithiated intermediate was trapped using trimethyl borate. 5-Methyl-2-thiopheneboronic acid (33) was isolated as a white solid after acid hydrolysis. This material protodeboronated at room temperature in the presence of oxygen in under 24 hours, resulting in the regeneration of the starting 2-methylthiophene. However, this material can be safely stored under vacuum for several weeks. The boronic acid (33) was suspended in methanol and reacted with KHF$_2$ in the
presence of water to yield the corresponding BF₃K salt (34) in 61% yield from 2-methylthiophene after hot acetone extraction and precipitation from acetone through the addition of diethyl ether.

A recent literature report by Lennox et al. stated that trifluoroborate salts may be prepared in high purity and excellent yields by the reaction of a boronic acid with KF in the presence of an organic acid, L-tartaric acid.⁵⁵ Reportedly, the addition of an organic acid shifts the equilibrium favoring nucleophilic addition of fluoride ions to the boron center by consuming hydroxide ions that are produced as a result of fluoride substitution (Figure 2.3.2).

![Figure 2.3.2: Literature preparation of potassium phenyltrifluoroborate using KF and an organic acid](image)

According to this report, the target aryltrifluoroborate salt is isolated by simple filtration and evaporation when an acetonitrile/THF/H₂O mixture is used as the solvent. In our hands, this chemistry was utilized to convert 4-methylphenylboronic acid to the corresponding trifluoroborate salt (37) in 54% yield (Figure 2.3.3).
Although this yield was significantly lower than the yields reported by Lennox, the synthetic ease of this process prompted an investigation of the applicability of this method to thiophene-containing boronic acids, a subset of reactivity not explored in the literature. In a systematic comparison of this KF-based method to a conventional KHF\textsubscript{2} method for the generation of thienyl trifluoroborate salts (Figure 2.3.4), it was found that the yield of these reactions was highly dependent on reaction scale, with reactions on greater than a 3 g scale failing to yield any significant organic products after work up. Method B fails completely on scales larger than 1 g, yielding no organic products. Presumably, protodeboronation occurs and the volatile product, 2-methylthiophene, is lost during rotary evaporation. Method A yields the desired product in synthetically useful amounts, although yields are substantially reduced as the reaction scale is increased. Although various trifluoroborate salts have seen extensive use in our group, this type of yield/scale dependence has never previously been observed during their preparation.
Generally speaking, for this model system, the KHF$_2$ method was found to be superior to the newly discovered literature method in spite of the moderate isolated yields. With this knowledge, the subsequent preparation of all trifluoroborate salts was pursued on a 1 g scale and utilized the KHF$_2$ method (Method A).

Oxidation of the 5-methylthienyl trifluoroborate 34 proceeded in moderate yields giving the desired product (35a, b) as a red oil after solvent evaporation. After this material was characterized by $^1$H NMR spectroscopy, it was noted that the two regioisomeric forms of the thienone, 35a and 35b, were formed in a 2:3 ratio. This particular thienone was quite volatile and was handled carefully during concentration in vacuo. Inverse addition of a
solution of the two regioisomeric thienones 35a and 35b in distilled THF to a stirred solution of diethyl carbamoyl chloride and NaHMDS in THF at -10 °C furnished the 5-methylthienyl-2-O-carbamate derivative (36) in 35% yield after purification by silica flash column chromatography (10% ethyl acetate, 90% petroleum ether).

4.) Directed Ortho-metalation Experiments Involving O-carbamate 36

With the targeted O-carbamate model substrate (36) in hand, a variety of experiments were designed in order to probe the ideal reaction conditions for ortho-metalation and trapping (Figure 2.4.1).
Following the seminal work of Victor Snieckus, several synthetically important transformations were envisioned: (i) the desired 3-position fluorination to yield compound 39, (ii) trapping by trimethyl borate to yield a 3-boronic acid (38) which could be further subjected to the Ag-mediated fluorinations developed Ritter et al to yield the desired 3-fluorinated material 39, and (iii) an anionic ortho-Fries rearrangement to yield the corresponding amide (40).
The ortho-Fries rearrangement (Figure 2.4.2) is a widely used method for the generation of aromatic ortho-hydroxy amides. Following lithiation ortho to a dialkyl $O$-carbamate moiety (41) at $-78 \, ^\circ C$, an intramolecular amide migration occurs upon warming to room temperature to yield compound 42. However, no examples of this reaction have been reported in thiophene systems.

![Figure 2.4.2: Mechanism of the anionic ortho-Fries rearrangement](image)

As previously stated (Section 1.8), the generation of organolithium intermediates followed by trapping using an electrophilic fluorine source (such as NFSI) can be an efficient method for the introduction of fluorine into an aromatic ring. Treatment of $O$-carbamate 36 with $s$-BuLi at $-78 \, ^\circ C$ (allowing an hour for lithiation) followed by treatment with a THF solution of NFSI yielded an intractable mixture of aromatic products and starting material after warming to room temperature. These identified products could not be separated using column chromatography. $^{19}$F NMR analysis of the crude reaction mixture did not indicate the introduction of fluorine.
Examination of the literature indicated that the inclusion of a disaggregation reagent may be necessary for lithiation to occur. Tetramethylethylenediamine (TMEDA) is a common additive in organolithium chemistry. Without the presence of any external chelating ligands, organolithiums exist in tetrameric and hexameric forms (Figure 2.4.3). 

![Figure 2.4.3: General tetrameric and hexameric aggregates of organolithiums](image)

The extent of this aggregation behavior depends on the identity of the organolithium reagent in question and the solvent system in which it is dissolved. The number of lithium atoms included in each aggregate is known as the aggregation number. The addition of a chelating ligand, such as TMEDA, reduces this aggregation number through the formation of lithium chelates (Figure 2.4.4).
The reduction of aggregation number also leads to an increase in the effective base strength of organolithium reagents and can cause drastic changes in reactivity.

The previously described directed ortho-metalation of 36 was repeated in the presence of TMEDA. After lithiation, attempted trapping with NFSI and warming to room temperature yielded a viscous brown oil that appeared as a single baseline spot during TLC analysis (10% ethyl acetate, 90% petroleum ether). $^1$H NMR spectroscopic analysis of this material showed a complex spectrum containing a large prevalence of aliphatic signals in the 0.0 – 4.5 ppm range (in CDCl$_3$). An identical result was obtained during an attempt to trap the lithiated intermediate using trimethyl borate. Lithiation followed by warming to room temperature, in the absence of any external electrophiles, resulted in a similar result.

Although the anionic ortho-Fries rearrangement has never been reported in thiophene systems, it was postulated that this rearrangement is occurring at a rate that is greater than that of nucleophilic attack of the lithio-intermediate on the desired electrophile. It has been previously observed by our group and others that 2-hydroxythiophenes tautomerize spontaneously to yield the corresponding keto form (Figure 2.4.5). $^{43,60,61}$
The 2(5\(H\))-tautomer of these thienone derivatives may considered to be analogous to conventional \(\alpha,\beta\)-unsaturated ketones in terms of reactivity. With this in mind, a mechanistic examination of the proposed rearrangement shows that there is potential for a series of subsequent iterative Michael-type additions leadings to oligomerization (Figure 2.4.6).
Figure 2.4.6: Proposed mechanism for potential iterative intermolecular Michael-type additions following ortho-Fries rearrangement

The requisite proton that is donated to form the 2-hydroxythiophene-3-amide derivative may originate from water that is added during the quenching of the reaction mixture or from deprotonation of the methyl group in the 5-position.
Depending on the size of the formed oligomers, this type of process could easily be envisioned as producing a product mixture that would exhibit a $^1$H NMR spectrum rich in varied aliphatic proton signals in the 0 – 5 ppm range, like those obtained for the crude products of the above reactions. The ortho-Fries rearrangement is exclusive to O-carbamate containing substrates. To avoid this rearrangement, we targeted alternative directing groups; namely the O-sulfamate and O-thiocarbamate groups, both of which are powerful directing groups that may be amenable to Ni-catalyzed cross-coupling.

5.) **Attempted Synthesis of 2-thienyl-O-sulfamates and O-thiocarbamates**

While the DOM and Ni-catalyzed cross-coupling chemistry have proved problematic to date for 2-thienyl O-carbamates, we recognized that many other directing groups have seen use within the literature for both cross-couplings and DOM. We directed our attention to the corresponding $N,N$-dimethyl sulfamate (43) and thiocarbamate (44) analogs of compound 36 (Figure 2.5.1), both of which are known and powerful directing groups.\(^{28}\) Interestingly, no analogous 2-thienyl O-sulfamates or O-thiocarbamates have been previously reported.

![Figure 2.5.1: Structure of target compounds 43 and 44](image)

It was postulated that compound 43 should be easily accessible through deprotonation/enolization of thienone 35a,b and subsequent trapping using $N,N$-dimethylsulfamoyl chloride (Figure 2.5.2).
However, under several different sets of conditions, varying temperature, base, and order of addition of reagents, formation of the desired product (43) was not achieved. Attempted conditions are illustrated below (Figure 2.5.3).

Figure 2.5.2: Proposed mechanism for formation of 43 via O-sulfanation

Figure 2.5.3: Screened reaction conditions for the attempted preparation of compound 43
In the above inverse addition experiments, a solution of the thienone 35a,b in THF (anhydrous) was added dropwise to a stirred solution of the appropriate base and N,N-dimethylsulfamoyl chloride in THF under an argon atmosphere. After stirring overnight, the reaction mixtures were quenched with a small amount of water, extracted with ether and concentrated. A $^1$H NMR spectrum of this crude material was taken to evaluate the success of the reaction. A second set of experiments was performed under identical temperature/base conditions using a direct addition order (i.e. the substrate was directly deprotonated, and a solution of electrophile in THF was then added). In all of the attempted experiments, a red-brown oil was obtained. $^1$H NMR analysis of these oils yielded, in each case, spectra rich in signals in the 0 – 5 ppm range with no significant aromatic products. These spectra suggest a similar type of oligomerization to that described in Figure 2.4.6. A possible iterative Michael-addition type mechanism operating in these reactions is given below (Figure 2.5.4).

![Figure 2.5.4: Proposed mechanism for the intermolecular Michael-type oligomerization of compound 35a,b upon deprotonation](image-url)
It is unclear why the $O$-carbamate adduct 36 could be readily prepared, while the corresponding $O$-sulfamate 43 proved inaccessible under similar conditions. Due to the difficulties experienced during the attempted preparation of compound 43, this route was abandoned and will be subject to further investigation in the future.

To prepare thienylthiocarbamate 44, we considered that compound 36 could be directly thionated using Lawesson’s reagent (Figure 2.5.5).

![Figure 2.5.5: Structure of Lawesson’s reagent (45)](image)

In the presence of carbonyl compounds such as esters, amides, and ketones, Lawesson’s reagent (45) leads to the formation of the corresponding thiocarbonyl compounds. The generalized mechanism for these types of transformations is given below (Figure 2.5.6).
With this general pattern of reactivity in mind, it was expected that treatment of 36 with Lawesson’s reagent should readily furnish the desired thiocarbonyl product, 44. Similar transformations were reported in the literature using cyclic O-carbamate moieties (Figure 2.5.7), although no examples were found utilizing acyclic O-carbamates.
Disappointingly, preliminary attempts at direct thiation of 36 (Figure 2.5.8) using Lawesson’s reagent in either THF or toluene failed to yield the desired product, leaving only unreacted starting material and what are presumably the byproducts of the degradation of Lawesson’s reagent.

Figure 2.5.7: Literature precedents for the thiation of cyclic O-carbamates
Using $^{13}$C NMR spectroscopy to analyze the crude reaction product, no NMR signals were observed above 165 ppm. According to the literature, the chemical shift of the thiocarbonyl carbon within the desired $O$-thiocarbamate product should lie at or above 185 ppm. In spite of this, these experiments represent only preliminary attempts at direct thiation and further work is required before this approach may be dismissed as unsuccessful.

**CHAPTER 3: FUTURE DIRECTIONS**

As previously stated, the complications encountered during the utilization of compound 36 (see Figure 2.4.6) for fluorination through DOM and nickel-catalyzed cross-couplings do not represent the end of this synthetic pathway. To unambiguously prove that a thienone intermediate formed by an ortho-Fries rearrangement and subsequent protonation is the true cause of the failure of this DOM chemistry, work is currently
underway to trap the proposed formed Michael acceptor using butanethiolate \textit{in situ} (Figure 3.1.1).

\begin{equation}
\begin{array}{c}
36 \\
\text{s-BuLi, TMEDA, THF, -78 °C} \\
\text{ortho-Fries rearrangement}
\end{array}
\end{equation}

\textbf{Figure 3.1.1: Proposed Michael trapping using butanethiolate}

Many other directing groups have been well-researched in the literature within phenyl systems but not within thiophene systems.\textsuperscript{28} Groups that are not amenable to anionic rearrangements but are still susceptible to Ni-couplings (such as sulfamates, carbonates, and pivalates) are ideal candidates for future synthetic explorations. Furthermore, the actual conditions of the cross-coupling reaction were not thoroughly probed with respect to the identity of the catalyst ligands and solvent. Changing one or both of these factors may lead to marked differences in the efficiency of the reaction. Additionally, the conditions for the preparation of \textit{O}-sulfamate 43 (see Figure 2.5.3) require further investigation by a future researcher. Additionally, although preliminary attempts at the
direct thiation of \textbf{36} using Lawesson’s reagent were unsuccessful (see \textbf{Figure 2.5.8}), further optimization is required before this chemistry may be dismissed completely.

In conclusion, efficient synthetic approaches to two \textit{N,N}-diethyl \textit{O}-thienyl carbamates \textbf{17} and \textbf{36} and been developed. Unfortunately, attempts to utilize the \textit{N,N}-diethyl \textit{O}-thienyl carbamate as a directing group and Ni-catalyzed cross-coupling partner have failed, an efficient route towards other types of directing group equipped thiophenes has been outlined, and possible synthetic difficulties in intermediate steps have been thoroughly investigated. Future research will easily be able to build on this body of work in order to create a library of other directing group equipped thiophenes containing \textit{O}-sulfamates, pivalates, and carbonates.

\textbf{CHAPTER 4: EXPERIMENTAL DETAILS}

\textbf{General Considerations:}

\textbf{Solvents}

\textit{Tetrahydrofuran}. THF was dried by refluxing over sodium metal under argon with benzophenone as an indicator.

\textit{Toluene}. Toluene was dried by refluxing over sodium metal under argon with benzophenone as an indicator.

\textit{Petroleum ether}. Petroleum ether was distilled from commercially available sources and stored in amber bottles.
Ethyl acetate. Ethyl acetate was distilled from commercially available sources and stored in amber bottles.

Diethyl ether. Diethyl ether was used directly from a commercially purchased drum.

Reagents

Organolithiums. All organolithium reagents were titrated before use using a solution of 1,3-diphenyl-2-propanone \( p \)-tosylhydrazone\(^{64} \) in THF and were stored in a refrigerator while not in use.

TMEDA. TMEDA was used as received and stored under argon.

NFSI. NFSI was dried in a vacuum desiccator with \( \text{P}_2\text{O}_5 \) overnight before use.

Trimethyl Borate. Trimethyl borate was used as received and was stored in a freezer under argon or in a Sure-Seal bottle.

Acid chlorides: All acid chlorides were used as received and were stored under argon.

Product Purification and Analysis

NMR spectra. Spectra were obtained using a 400 MHz Bruker Avance 400 MHz spectrometer running Topspin version 2.1 software and with TMS as an internal standard.

Thin layer chromatographic analysis. TLC analysis was performed using aluminum-backed silica gel plates (Sigma-Aldrich), 200 µm layer thickness, 2-25 µm particle size, 60 Å pore size, and were examined under UV light.

Flash column chromatography. Flash column chromatography was carried out using Fisher Scientific silica gel (Davisil\textsuperscript{TM},170-400 Mesh, Type 60A, Grade 1740) using pressure applied from house air.
Experimental Details

Preparation of 4-methylphenylboronic acid (23)

4-Bromotoluene (2.21 g, 12.9 mmol) was stirred under nitrogen with THF (60 mL, distilled over Na/benzophenone) and cooled to -78 °C with an acetone and dry ice bath. n-BuLi (8.75 mL, 2.0 M in pentane, 18 mmol) was added dropwise over 3 minutes between -70 °C and -75 °C. The reaction mixture was stirred for 30 minutes at -78 °C. A small sample of the reaction mixture was placed in a test tube, and then worked up by the addition of Et₂O and H₂O. The ether layer was separated and analyzed by gas chromatography to reveal that all starting material had been consumed. B(OMe)₃ (1.77 g, 17.0 mmol) was added dropwise to the reaction mixture over 5 minutes between -70 °C and -75 °C. The reaction mixture was left to stir and warmed to room temperature overnight under nitrogen. Aq. HCl (1.5 M, 16 mL) was added and the reaction mixture was stirred for 15 minutes. The reaction mixture was then concentrated in vacuo to yield a white crystalline residue and some water. The residue was extracted with Et₂O (3 x 20 mL) and the combined organic washings were washed with brine (20 mL). The combined organic washings were then dried with MgSO₄ and filtered. The combined organic washings were concentrated in vacuo to yield a white solid (1.78 g). ¹H NMR analysis revealed that the solid contained
primarily the desired product (~95% pure). The product was used in the next step without further purification.

23: $^1$H NMR (400 MHz, DMSO-d$_6$): $\delta$ 2.30 (s, 3H), 7.15 (d, $J$ = 7.6 Hz, 2H), 7.68 (d, $J$ = 8.0 Hz, 2H), 7.90 (s, 2H)

**Preparation of 2-(p-tolyl)thiophene (24)**

\[ \text{4-Methylphenylboronic acid (23) (3.05 g) was mixed with toluene (48 mL) and 2-bromothiophene (2.64 g, 16.2 mmol) under nitrogen and stirred. Pd(PPh$_3$)$_4$ (2.2 g, 1.9 mmol), K$_2$CO$_3$ (6.2 g, 45 mmol), acetone (12 mL) and water (6 mL) were each sequentially added in one portion to the reaction mixture. Additional acetone (10 mL) and H$_2$O (10 mL) were used to wash powdered reactants into the reaction mixture that were stuck to the sides of the flask. The resulting yellow reaction mixture was refluxed overnight. The next day, the reaction mixture was checked by TLC to reveal that all 2-bromothiophene had been consumed. The reaction mixture was allowed to cool to room temperature before H$_2$O (15 mL) was added and the reaction mixture stirred. The reaction mixture was extracted with Et$_2$O (3 x 30 mL) and the combined organic washings were dried with MgSO$_4$, filtered, and concentrated *in vacuo* to yield a pale yellow oil which turned dark red quickly upon exposure to the air. TLC analysis (100% petroleum ether) showed 3 spots. Petroleum ether was used to purify the product by passing it through a silica plug. Fractions which were} \]
determined to contain the desired product by TLC analysis were combined. A red powder suspended in the combined fractions was separated by filtration and discarded. The filtrate was concentrated in vacuo to yield 24 as a light brown solid that showed only very minor impurities by NMR analysis. (2.75 g, 97%, 95% pure)

24: $^1$H NMR (400 MHz, DMSO-d$_6$): $\delta$ 2.32 (s, 3H), 7.10 (dd, $J = 5.2, 3.6$ Hz, 1H), 7.22 (d, $J = 8.4$ Hz, 2H), 7.45 (dd, $J = 3.6, 1.2$ Hz, 1H), 7.49 (dd, $J = 4.8, 1.2$ Hz, 1H), 7.54 (d, $J = 8.0$ Hz, 2H).

Preparation of 5-(p-tolyl)-2-thienylboronic acid (25)

2-(p-Tolyl)thiophene (24) (3.37 g, 19.3 mmol) was mixed with anhydrous THF (40 mL) under nitrogen at room temperature and stirred to yield a faint brown which was cooled to -78 °C using a dry ice/acetone bath. $n$-BuLi (13.0 mL, 2.0 M in pentane, 26 mmol) was added dropwise between -78 °C and -65 °C over 15 minutes. The mixture was allowed to stir for one hour at -78 °C. A pale white precipitate was visible in the reaction mixture. B(OMe)$_3$ (2.82 g, 27.1 mmol) was added dropwise over 5 minutes between -78 °C and -65 °C. As the reaction was stirred, the pale white precipitate dissolved. The reaction mixture

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$^5$ The spot was observed quickly evaporating. It is likely that this spot was unconsumed 2-bromo thiophene that was not observed due to evaporation when the reaction was checked for completion using TLC analysis previously
was allowed to stir overnight under nitrogen and slowly warmed to room temperature. The final reaction mixture was a pale brown color. Aq. HCl (5.4 mL, 6.0 M) was added and a white precipitate formed. The reaction mixture was allowed to stir for 10 minutes before being extracted with dichloromethane (5 x 20 mL). The combined organic washings were dried with MgSO₄, filtered and concentrated in vacuo to yield a pale green solid (5.12 g). This solid was stored under argon in a freezer until further use. An ¹H NMR spectrum taken the next day revealed that some starting material was present. The sample was again placed in a freezer under argon. The next day, the crystals were dried in vacuo and then washed with petroleum ether to yield a pale green solid and dark blue washings. The washings were concentrated in vacuo to yield dark blue crystals which were shown by ¹H NMR analysis to contain unreacted starting material. The title product (25) was isolated as a green crystalline solid (3.52 g).

25: ¹H NMR (400 MHz, DMSO-d₆): δ 2.32 (s, 3H), 7.22 (d, J = 6.8 Hz, 2H), 7.46 (m, 1H), 7.56 (d, J = 8.0 Hz, 2H), 7.64 (m, 1H), 8.22 (s, 2H).

**Preparation of 5-(p-tolyl)-2-thienyl trifluoroborate (21)**

Boronic acid 25 (1.56 g) and MeOH (20 mL) were stirred together and cooled with an ice and water bath. The resulting solution was a pale brown color. KHF₂ (1.80 g, 23.0 mmol) was added in one portion and the reaction mixture was stirred for 5 minutes. H₂O (5 mL)
was added dropwise over 2 minutes with no change in temperature and the cooling bath was removed. The reaction mixture was allowed to warm to room temperature and was stirred vigorously for one hour. After stirring, some white precipitate was visible in the reaction mixture. Some green crystals remained stuck to the flask, so they were washed into the reaction mixture with acetone (2 mL). The reaction mixture was concentrated \textit{in vacuo} to yield pale white crystals which were left to dry under high vacuum in a vacuum desiccator in the presence of P$_2$O$_5$. Drying yielded a grey white crude solid (2.69 g). The solid was washed with petroleum ether to remove any possible non-polar impurities, and the solid was dried to afford the title compound 21 as a grey solid. (1.73 g, 83% from 24).

21: $^1$H NMR (400 MHz, DMSO-$d_6$): $\delta$ 2.30 (s, 3H), 6.79 (d, $J = 3.2$ Hz, 1 H), 7.15 (d, $J = 8.4$ Hz, 2H), 7.20 (m, 1H), 7.45 (d, $J = 8.4$ Hz, 2H).

**Preparation of 5-(p-tolyl)-2(3H)-thienone (18b) and 5-(p-tolyl)-2(5H)-thienone (18a)**

![Chemical structure of 21, 18a, and 18b with reaction conditions: KF$_3$B, Oxone, acetone, water]

5-(p-Tolyl)-2-thienyl trifluoroborate (21) (0.56 g, 2.0 mmol) was vigorously stirred with acetone (9 mL) under ambient atmosphere to form a grey solution. Oxone (1.27 g, 4.13 mmol) dissolved in water (9 mL) was added to the solution in one portion. Upon addition, the reaction mixture became pink and gradually turned purple. After stirring for 5 minutes
at room temperature, aq. HCl (0.02 M, 17 mL) was added. The reaction mixture was extracted with dichloromethane (5 x 10 mL). The combined organic washings were dried with MgSO₄, filtered and concentrated *in vacuo* to yield a metallic red-grey solid (0.31 g). ¹H NMR analysis showed that product was present, along with only small impurities. The product was purified via flash chromatography (20% DCM, 80% PE, 15 g silica) to yield a green-grey solid (0.24 g, 63%) which contained a 1:9 mixture of thienones 18a and 18b.

18b: ¹H NMR (400 MHz, CDCl₃): δ 2.42 (s, 3H), 3.68 (d, J = 3.2 Hz, 2H), 6.08 (app. t, J = 6.0 Hz, 1H), 7.20 (d, J = 8.4 Hz, 2H), 7.35 (d, J = 8.0 Hz, 2H) (major product).

18a: ¹H NMR (400 MHz, CDCl₃): δ 2.34 (s, 3H), 5.53 (app t, J = 2.4 Hz, 1H), 6.39 (dd, J = 6.0, 2.0 Hz, 1H), 7.15 (m, 2H) (overlapped with benzene ring protons of major product 18b), 7.45 (dd, J = 6.0, 2.0 Hz, 2H) (minor product).

All column fractions contained blue spots when analyzed by TLC. Fractions showing a single fluorescent spot when visualized with a UV lamp along with a blue spot were combined and concentrated to yield grey-green crystals. ¹H NMR analysis of the combined fractions shows that products 18a,b were present (two possible regioisomers), together with some aliphatic impurities. The product was used in the next step (preparation of 17) without further purification.
Conversion of Thienone Derivatives (18a,b) to 5-(4-methylphenyl)thien-2-yl N,N-diethylcarbamate (17)

\[
s_1 \xrightarrow{\text{NaHMDS, THF}} \text{17} \quad \Delta^2,3: \Delta^3,4 = 1:9
\]

Diethyl carbamoyl chloride (0.22 g, 1.6 mmol) was stirred with anhydrous THF (6 mL) under N\textsubscript{2} and cooled to 0 °C using a brine/ice bath. NaHMDS (2.0 M in THF, 0.45 mL, 0.9 mmol) was added dropwise between 0 °C – 5 °C over 5 minutes. The thienones 18a and 18b (0.1386 g, 0.7285 mmol) were dissolved in anhydrous THF (4 mL) and added dropwise between 0 °C and 5 °C over 10 minutes. The resulting reaction mixture was a deep purple color. The cooling bath was removed and the reaction mixture was allowed to stir overnight at room temperature. Aq. NaOH (10 mL, 1.0 M) was added and the reaction mixture was allowed to stir overnight at room temperature. The next day, the reaction mixture was concentrated in vacuo, and then extracted with Et\textsubscript{2}O (3 x 10mL). The combined organic washings were washed with deionized H\textsubscript{2}O (10 mL) and brine (10 mL), and concentrated in vacuo to yield a deep purple oil (0.17 g). \textsuperscript{1}H NMR analysis showed the desired product to be present along with some undetermined impurities. The product was purified by flash chromatography (10% ethyl acetate, 90% petroleum ether, 9 g silica). Fractions showing a purple spot that increased in intensity under UV were combined and concentrated to yield the title product 17 as a purple oil (0.11 g, 52%).
17: $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 1.22 (m, 6H), 2.34 (s, 3H), 3.40 (m, 4H), 6.58 (d, $J = 4.0$ Hz, 1H), 6.95 (d, $J = 4.0$ Hz, 1H), 7.15 (d, $J = 8.0$ Hz, 2H), 7.43 (d, $J = 8.0$ Hz, 2H).

**Preparation of NiCl$_2$(PCy$_3$)$_2$ Catalyst (28)**

EtOH (40 mL) was degassed by bubbling N$_2$ through it for 15 minutes. NiCl$_2$·6H$_2$O (0.82 g, 3.5 mmol) was dissolved in degassed EtOH (20 mL) in a nitrogen flushed flask and stirred to produce a light green solution. PCy$_3$ (2.39 g, 8.52 mmol) was weighed into a nitrogen flushed flask and dissolved in degassed EtOH (20 mL) to produce a colorless solution. The NiCl$_2$·6H$_2$O solution was transferred to the same flask containing the PCy$_3$ solution using a cannula at room temperature. Upon mixing, the reaction mixture took on a purple-red color. The reaction mixture was stirred and refluxed for one hour under nitrogen. After one hour, the reaction mixture was allowed to cool to room temperature and filtered under nitrogen to yield a purple-red solid. The flask and solid were washed with ice-cold EtOH (40 mL) and Et$_2$O (2 x 40 mL) and the solid was dried under vacuum overnight to yield 28 as a fine purple-red powder (2.22 g, 93%) (m.p. 225 – 228°C, Lit. m.p. = 235°C$^{65}$)
Preparation of 5-methyl-2-thienylboronic acid (33)

2-Methylthiophene (32) (9.75 mL, d = 1.014 g/mL at 25 °C, 0.101 mol) was stirred with THF (200 mL, distilled over Na/benzophenone) under an argon atmosphere and cooled to -78 °C using a dry ice/acetone bath. n-BuLi (10.0 mL, 10.5 M in hexanes, 0.105 mol) was added dropwise over 35 minutes between -78 °C and -70 °C. As the first few drops of n-BuLi were added, the reaction mixture became a deep purple-red color. The reaction mixture was allowed to stir for 30 minutes at this temperature before being warmed to -20 °C over 15 minutes. The reaction mixture was then cooled back to -78 °C over 15 minutes with no change in physical appearance. B(OMe)₃ (14.5 mL, d = 0.932 g/mL at 20 °C, 0.130 mol) was added dropwise over 32 minutes between -78 °C and -68 °C. After addition was complete, the reaction mixture had become an opaque pale white color. The reaction mixture was allowed to stir and warm to room temperature overnight. Aq. HCl (180 mL, 1M, 0.2 mol) was added the next morning and the white precipitates within the reaction mixture disappeared. The reaction mixture was allowed to stir for 1 hour. The reaction mixture was partially concentrated in vacuo and was then partitioned between diethyl ether (50 mL) and brine (50 mL). The aqueous and organic layers were separated and the aqueous layer was extracted with diethyl ether (2 x 50 mL). The combined organic washings were dried with MgSO₄ and filtered. The filtrate was concentrated in vacuo to yield the title compound 33 as a white solid (15.48 g). This solid was used without further purification.
in future reactions. A precise NMR spectra could not be captured due to the presence of mixed boronic anhydrides in the crude reaction product.

33: $^1$H NMR (400 MHz, DMSO-$_d$$^6$) $\delta$ 8.03 (diagnostic boronic acid O-H signal)

Preparation of 5-methyl-2-thienyl trifluoroborate (34)

5-Methylthiophene-2-boronic acid (33) (1.00 g, crude, ~7.04 mmol) and methanol (10 mL) were stirred together under an ambient atmosphere in a round bottom flask to yield a clear yellow solution. The reaction mixture was cooled using an ice/water bath to ~5 °C. KHF$_2$ (1.65 g, 21.1 mmol) was added in one portion and water (5 mL, $d = 1.000 \text{ g/mL at } 25 \degree \text{C}$, 0.3 mol) was added dropwise over 3 minutes (temperature was not monitored). The cooling bath was removed and the reaction mixture was vigorously stirred for 1 hour at room temperature. As the reaction mixture was stirred, it gradually became more opaque until it eventually became an opaque yellow solution with some visible white precipitate. The resulting mixture was concentrated in vacuo to yield a wet white-yellow pearlescent solid. This solid was dried in a vacuum desiccator with P$_2$O$_5$. The crude solid was suspended in acetone (20 mL) and heated to boiling before being filtered. This process was repeated 3 times with the residual solids left in the reaction flask. The filtrate was concentrated in vacuo to yield a yellow-orange solid (3.02 g). The solid was dissolved in
the minimal volume of acetone (10-20 mL) and diethyl ether was added (~60 mL) while stirring until a precipitate began to form. The mixture was then cooled using an ice bath before being filtered to isolate the precipitated solids. The filtrate was a yellow solution. The filtrate was concentrated in vacuo to yield a pale yellow solid. This crystalization process was repeated 3 additional times (1:3 ratio of acetone to diethyl ether) with vigorous stirring. The title compound 34 was obtained as a white grey solid (1.60 g, 56% from 2-methylthiophene).

34: $^1$H NMR (400 MHz, DMSO-$_d$6) δ 2.35 (broad s, 3H), 6.53 (m, 1H), 6.56 (d, $J = 3.2$ Hz, 1H).

**Preparation of 5-methyl-2(5H)-thienone (35a) and 5-methyl-2(3H)-thienone (35b)**

The 2-thienyl BF$_3$K salt (34) (0.97 g, 4.8 mmol) was stirred with acetone (24 mL) under an ambient atmosphere to form a pale yellow solution. Oxone (3.0 g, 9.8 mmol) was dissolved in H$_2$O (24 mL) and added to the reaction mixture in one portion (temperature not monitored). The reaction mixture instantly became opaque and gradually became slightly pink as the reaction mixture was allowed to stir for 5 minutes at room temperature. After 5 minutes, aq. HCl (42 mL, 0.02 M, 0.84 mmol) was added and the reaction mixture
became more transparent. The reaction mixture was extracted with dichloromethane (3 x 20 mL). The combined organic washings were dried with MgSO$_4$ and concentrated in vacuo to yield a red oil (0.60 g). This oil was eluted through a 2 cm silica plug using dichloromethane and was concentrated to yield a red oil (0.21 g after drying under high vacuum, 38.9%). The silica retained a slightly yellow coloration.

(35b, $\beta,\gamma$-unsaturated, 60%): $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 5.18 (m, 1H), 3.43 (m, 2H), 2.13 (m, 3H)

(35a, $\alpha,\beta$-unsaturated, 40%): $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.40 (dd, $J = 6.0$, 2.8 Hz, 1H, 6.27 (dd, $J = 6.0$, 2.0 Hz, 1H), 4.50 (ddq, $J = 7.2$, 2.8, 2.2 Hz, 1H), 1.60 (d, $J = 7.2$ Hz, 3H)

Conversion of Thienone Derivatives 35a,b to 5-methylthien-2-yl N,N-diethylcarbamate (36)

THF (40 mL, distilled over Na/benzophenone) was stirred with diethyl carbamoyl chloride (1.3023 g, 9.6047 mmol) under a nitrogen atmosphere and cooled to 0 °C using an ice/brine bath. NaHMDS (5.5 mL, 2.0 M in THF, 11 mmol) was added over 5 minutes between 0-5 °C. The solution was a pale yellow color due to the NaHMDS. The thienones 35a,b (0.85 g, 7.5 mmol) were dissolved in anhydrous THF (10 mL) and added dropwise over 27
minutes, maintaining the reaction temperature between 0 – 5 °C. As the solution was added, the reaction mixture became dark brown. The cooling bath was removed and the reaction mixture was allowed to warm to room temperature overnight. The next day, aq. NaOH (40 mL 1 M, 0.04 mol) was added and the reaction mixture was allowed to stir for 4 hours. The reaction mixture was then extracted with diethyl ether (4 x 30 mL) and the combined organic washings were washed with brine (80 mL). The combined organic washings were dried with MgSO₄ and concentrated in vacuo to yield a red-brown oil (1.73 g). The reaction mixture was dried overnight under high vacuum in a desiccator with P₂O₅ to yield a red-brown oil (1.09 g). Crude ¹H NMR analysis revealed that the product was not yet entirely pure. It was postulated that the impurity may be residual diethylamine from the decomposition of diethyl carbamoyl chloride. After attempts to purify via (i) distillation with a Kugelrohr and (ii) washing with mild acid (10% v/v aq. HCl), the ¹H NMR spectra remained unchanged. The crude mixture was purified using flash column chromatography (10:90 ethyl acetate/petroleum ether, 50 g silica). After concentration and drying in a high vacuum desiccator with P₂O₅, the title compound 36 was isolated as a clear pale yellow oil (0.55 g, 35%).

36: ¹H NMR (400 MHz, CDCl₃) δ 6.43 (m, 1H), 6.39 (d, J = 3.6 Hz, 1H), 3.38 (m, 4H), 2.38 (broad s, 3H), 1.20 (m, 6H).
CHAPTER 5: REFERENCES

(1) Discovery of liquid crystals


(8) University of California - Davis. Electromagnetic Radiation

(9) Subramanian, P. Development of Synthetic Approaches Towards 2- Substituted 3- and 4-Fluorothiophene Building Blocks and Their Application in Liquid Crystal Synthesis.


(26) Grubb, A. M. Preparation of heteroatom-substituted 1,3-thiazoles as building blocks for liquid crystal synthesis., Kent State University, 2011.


