

FUNCTIONALIZATION OF MONO- AND DIPYRROLIC COMPOUNDS

by

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TO MOM AND DAD,
WITH LOVE

*“At the end of the day,
the most overwhelming key to a child’s success
is the involvement of parents”*

– J. D. Hull

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Abstract

Chemical manipulations of pyrrolic compounds can often prove to be difficult. This is especially true for dipyrrens. As a result of this, methodology development for the chemical manipulation of pyrrolic compounds is of particular interest. The graduate work presented herein involves three projects dedicated to developing such methodologies.

Based on microwave-promoted deprotection of *F*-BODIPYs previously developed by the Thompson group, an *F*-BODIPY was probed for use as a protecting group option for the manipulation of the parent dipyrren. Rather than isolating the expected functional group interconversion product, the *F*-BODIPY was deprotected and the resulting dipyrren was reduced to form its corresponding dipyrromethane in moderate yield. A series of reactions using similar conditions and substrates were performed to explore the scope of this reaction.

Methodologies for the manipulation of functional groups can also prove useful when trying to improve the stability of a molecule. Porphomethenes suffer from auto-oxidation due to the inherent stability of their oxidized counterparts, porphyrins. Oxidation of the susceptible bridgehead carbon atoms may be prevented *via* an isosteric replacement (by replacing C-H with C-F). However, while developing model *meso*-difluorodipyrromethane systems for study, complications arose due to the interesting electronic properties of pyrrole. These complications were studied instead, in the hopes of eventually correcting the methodology.

In addition, the choice of substitution on a pyrrole can affect the success or failure of a reaction. While attempting to expand upon a known series of bis(ruthenium-pyrrolyl) complexes, ligand synthesis proved to be more challenging than anticipated as a result of choice in substitution on the pyrrolic moiety. Again, a study of these complications was pursued with the intention of developing a successful methodology.

As a whole, this thesis portrays some of the trials and tribulations often involved when working towards the successful chemical manipulation of pyrrolic compounds. It is with the hope of the author to both educate on some of the intricacies involved when handling pyrrolic compounds, and inspire others to aid in the quest towards easier and more reliable ways to chemically manipulate pyrroles.

List of Abbreviations and Symbols Used

Å	angstrom
δ	chemical shift <i>or</i> partial charge
ε	molar absorptivity
η	hapticity (contiguous donor atoms)
κ	hapticity (non-contiguous donor atoms)
μ	micro
μW	microwave
π	pi bonding orbital
π*	pi antibonding orbital
ρ	Hammett reaction constant
σ	Hammett substituent constants
A	CH ₂ CO ₂ H
Ac	acetyl
AcO	acetoxy
ad	apparent doublet
AIBN	azobisisobutyronitrile
A ^{Me}	CH ₂ CO ₂ Me
aq	aqueous
Ar	aryl moiety
as	apparent singlet
Asp	aspartic acid
at	apparent triplet
bipy	bipyridyl
Bn	benzyl
Boc	<i>tert</i> -butyloxycarbonyl
BODIPY	boron-dipyrromethene
br	broad
Calcd.	calculated

CAN	ceric ammonium nitrate
Cbz	carboxybenzyl
CCDC	Cambridge Crystallographic Data Centre
cm	centimetre
d	doublet(s)
DAST	(diethylamino)sulfur trifluoride
1,2-DCE	1,2-dichloroethane
DCM	dichloromethane
dd	doublet of doublets
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DMAP	4-(<i>N,N</i> -dimethylamino)pyridine
DMF	<i>N,N</i> -dimethylformamide
DMSO	dimethylsulfoxide
DNA	deoxyribonucleic acid
DNP	2,4-dinitrophenylhydrazone
DNPH	2,4-dinitrophenylhydrazine
DTT	dithiothreitol
E	active enzyme site <i>or</i> electrophile
EDG	electron donating group
EI	enzyme-inhibitor complex
equiv.	equivalent
ES	enzyme-substrate complex
ESI	electrospray ionization
Et	ethyl
EWG	electron withdrawing group
FGI	functional group interconversion
g	gram
GHz	gigahertz
GP	general procedure
h	hour(s)
HMDS	hexamethyldisilazane

{ ¹ H}	proton decoupled NMR experiment
HRMS	high-resolution mass spectrometry
Hz	hertz
I	inhibitor
<i>i</i> Pr	iso-propyl
IUPAC	International Union of Pure and Applied Chemistry
$J_{XX'}$	bond coupling constant between atom X and atom X'
k	rate constant
L	neutral 2-electron donor ligand
LDA	lithium diisopropylamide
Leu	leucine
LG	leaving group
L_n	generic ligand set
M	generic transition metal <i>or</i> molecular ion <i>or</i> mol/L (molar)
m	multiplet <i>or meta</i>
m/z	mass-to-charge ratio
Me	methyl
mg	milligram
MHz	megahertz
min	minute
mL	millilitre
MLCT	metal-to-ligand charge transfer
MM	Molar Mass
mol	mole(s)
m.p.	melting point
N	normal (equivalents per litre)
<i>n</i>	normal (straight chain)
NBS	<i>N</i> -bromosuccinimide
<i>n</i> Bu	normal-butyl
NFSI	<i>N</i> -fluorobenzenesulfonimide
NIS	<i>N</i> -iodosuccinimide

nm	nanometre
NMR	nuclear magnetic resonance
nosyl or Ns	nitrobenzenesulfonyl
Nu	nucleophile
<i>o</i>	<i>ortho</i>
OAc	acetate
OMe	methoxy group
OTf	triflate (trifluoromethanesulfonate)
OTs	tosylate (<i>p</i> -toluenesulfonate)
P	product, or (CH ₂) ₂ CO ₂ H
<i>p</i>	<i>para</i>
<i>p</i> -tosyl or Ts	<i>p</i> -toluenesulfonyl
PG	protecting group
pH	measure of acidity/basicity
Ph	phenyl
p ^{Me}	(CH ₂) ₂ CO ₂ Me
ppm	parts per million
PTFE	poly(tetrafluoroethylene)
q	quartet
r.t.	room temperature
redox	reduction-oxidation
R _f	retention factor
S	substrate
s	singlet
S _N 2	bimolecular nucleophilic substitution
SPSS	Statistical Package for the Social Sciences
t	triplet
TBAB	tetrabutylammonium bromide
tert	tertiary
TFA	trifluoroacetic acid
THF	tetrahydrofuran

TIPS	triisopropylsilyl
TLC	thin-layer chromatography
TMS	trimethylsilyl
TOF	time of flight
URO-D	uroporphyrinogen decarboxylase
UV	ultraviolet
W	watts
X	generic anion <i>or</i> anionic ligand
Zn(DFMS)	bis(((difluoromethyl)sulfinyl)oxy)zinc

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“Gratitude is the heart’s memory” – French Proverb

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“Only a life lived for others is a life worthwhile.” – Albert Einstein

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Here’s to many more memories with you all!

Chapter 1 Introduction

1.1 Pyrrolic Compounds: Historical Aspects, Syntheses, and Applications of Interest

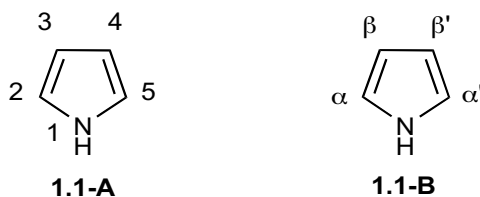
1.1.1 Monopyrroles

Pyrroles are a class of heterocyclic compounds comprised of five-membered aromatic rings, whereby one atom of the cyclic structure is nitrogen. They are a particularly important class of heterocycle and are ubiquitous across all six¹ taxonomic kingdoms: bacteria,² protozoans,³ the photosynthetic chromista,⁴ plants,⁵ marine fungi,⁶ and animals^{7,8} all biosynthesize their own pyrrole-containing metabolites.

In addition to having important biological relevance for animal and plant survival (in oxygen transport⁸ and photosynthesis,⁵ respectively), pyrrole-containing compounds have also been found to exhibit antibacterial, antiviral, antihypertensive, anticonvulsant, antimalarial, antidepressant, antipsychotic, antiprotozoal, antitumor, antifungal, anti-inflammatory, antioxidant, and immunosuppressant activity.^{7,9-13} Furthermore, they have been shown to be useful scaffolds for functional materials.^{14,15}

The nomenclature of pyrrolic compounds has seen significant revision since the structure of pyrrole was first elucidated in 1870.¹⁶ The current IUPAC nomenclature recommendations are depicted in Figure 1 - 1. Arabic numeral (**1.1-A**) and Greek letter (**1.1-B**) labeling are used interchangeably when referring to positions on the pyrrolic compound.¹⁷ However, the exclusive use of numerals is recommended for the proper naming of pyrrolic compounds in supplemental materials.¹⁷

Figure 1 - 1: IUPAC Nomenclature of Pyrrole

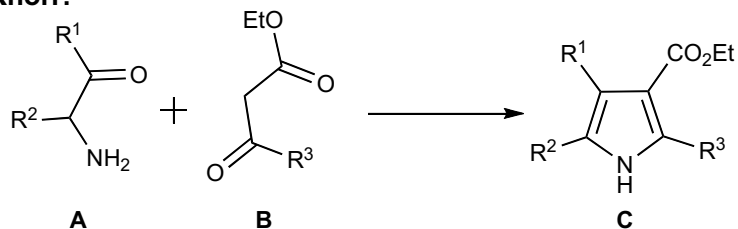


The traditional pyrrole syntheses are the Knorr¹⁸ reaction and Paal-Knorr^{19,20} condensation. The Knorr reaction involves the condensation of an α -aminocarbonyl

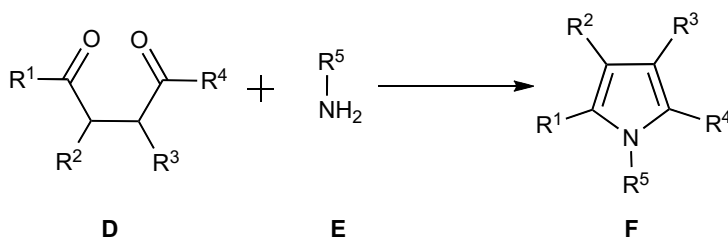
compound (**A**, as shown in Scheme 1 - 1) with another dicarbonyl compound (**B**). In contrast, Paal-Knorr condensations employ γ -dicarbonyl compounds (**D**) and primary amines (**E**).

Scheme 1 - 1: Knorr and Paal-Knorr Pyrrole Syntheses

Knorr:



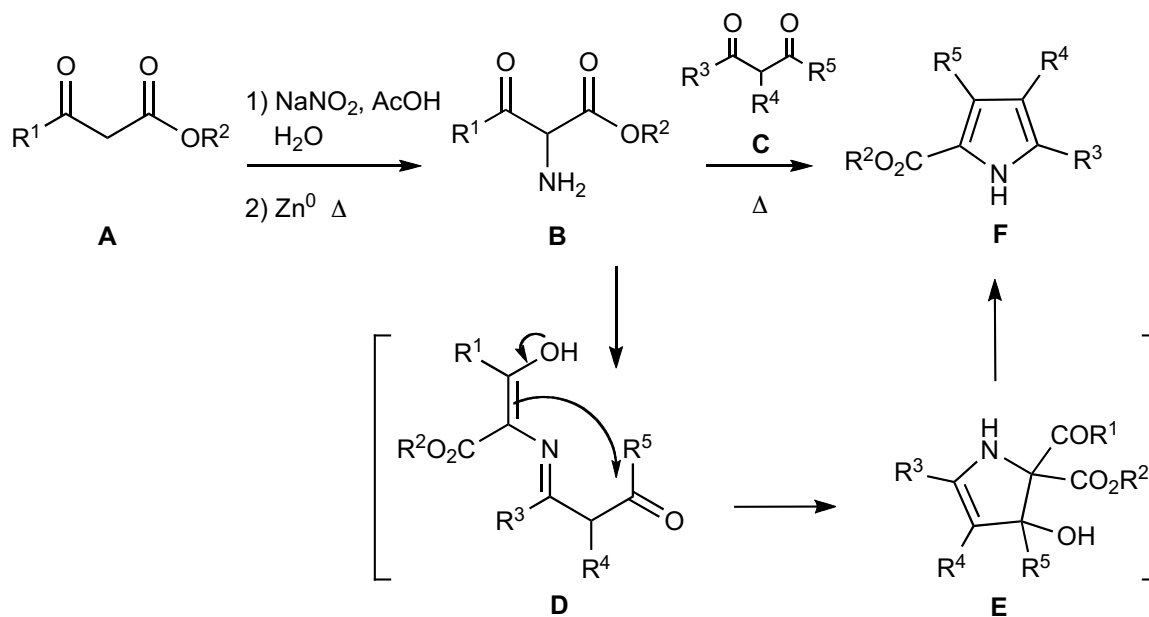
Paal-Knorr:



The Knorr reaction is most commonly used in the Thompson group for the preparation of pyrroles. This reaction proceeds *via* condensation of the amino functionality of **A** (Scheme 1 - 1) with the carbonyl functionality of **B**, linking the two compounds by an imine moiety. The imine then tautomerizes to an enamine, which allows for cyclization by an intramolecular Knoevenagel condensation. This is followed by subsequent elimination of water to form the pyrrole (**C**).

There are many possible modifications to the Knorr reaction, but the modification that the Thompson group typically employs is the Fischer-Fink variant (Scheme 1 - 2).²¹⁻²³ This method involves the *in situ* formation and reduction of an oxime to form amine **B** (Scheme 1 - 2), which subsequently reacts with dicarbonyl **C** form an imine intermediate (**D**). Imine **D** can then undergo an intramolecular Knoevenagel condensation to form **E**, followed by aromatization to form pyrrole **F** by means of elimination. Employing a symmetrical dicarbonyl compound (**C**, where $R^3 = R^5$, $R^4 \neq H$) ensures a major structural isomer, but varying the terminal substituents of **C** will yield a mixture of isomers.²³

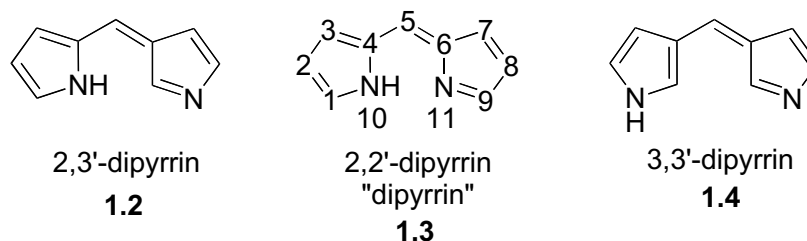
Scheme 1 - 2: Fischer-Fink Variant of the Knorr Pyrrole Synthesis



1.1.2 Polypyrroles

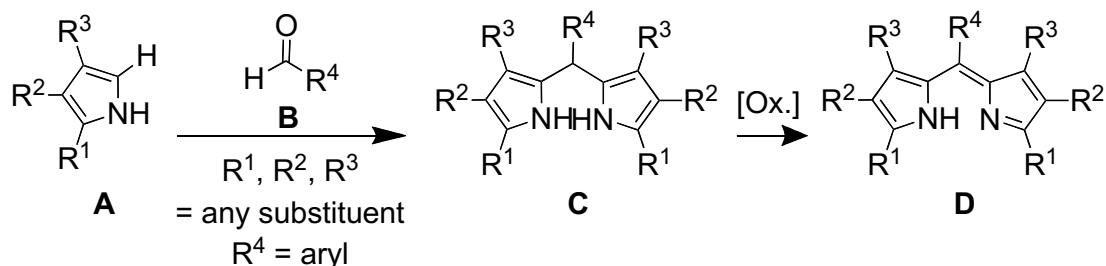
Monopyrroles can be reacted further to form di-, tri-, tetra- and pentamers, due to the inherent lone pair delocalization of the nitrogen atom of pyrroles. Dipyrrins are a prominent type of dipyrrole, and were classically synthesized as precursors to porphyrins and porphyrin derivatives.²⁴ Dipyrrins have three structural isomers, with 2,3'- (**1.2**, Figure 1 - 2), 2,2'- (**1.3**), and 3,3'-connectivities (**1.4**).^{25,26} The term “dipyrrin” can be used to refer to all three isomers, but this term is generally applied to the most common 2,2'- isomer (**1.3**) and will be used as such in this document. IUPAC recommendation for the nomenclature of dipyrrins is presented in Figure 1 - 2, structure 1.3.²⁷

Figure 1 - 2: Isomers of Dipyrrin



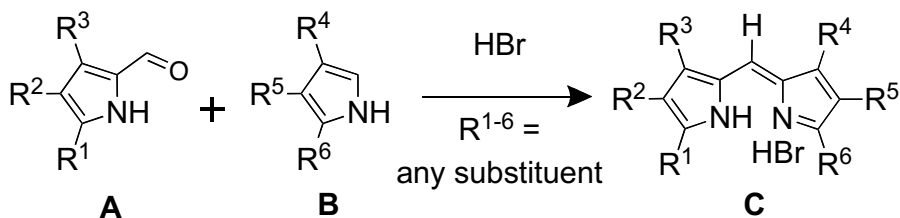
There is a vast catalogue of reported dipyrrens, and many are substituted at the 5- or *meso*- position. A standard procedure for synthesizing *meso*-substituted dipyrrens is to first prepare the dipyrromethane (**C**, Scheme 1 - 3) and then perform an oxidation reaction. Two equiv. of an α -free pyrrole (**A**) can be condensed with an aldehyde (**B**) to form a dipyrromethane (**C**).²⁸⁻³¹

Scheme 1 - 3: Synthesis of Dipyrromethanes and their Respective Dipyrrens



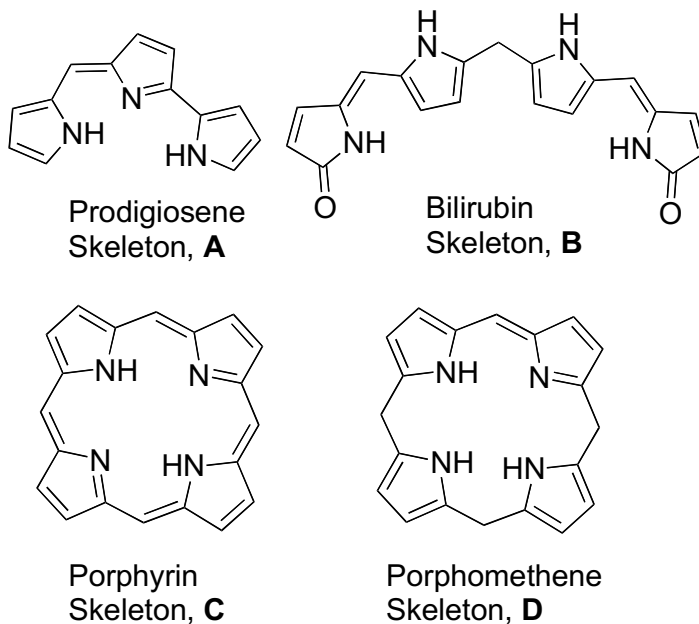
DDQ or *p*-chloranil is typically used for the oxidation of dipyrromethanes (**C**, Scheme 1 - 3) to their respective dipyrrens (**D**).^{32,33} *Meso*-unsubstituted dipyrrens (as shown Scheme 1 - 4, compound **C**) may be formed *via* MacDonald coupling, through the condensation of an α -unsubstituted pyrrole (**A**) with an α -formyl pyrrole (**B**).^{34,35}

Scheme 1 - 4: MacDonald Coupling



Dipyrrens can also be used to form tri-, tetra-, and pentapyrrolic compounds. Prodigiosenes are a class of tripyrrolic compounds that are of interest, particularly for their antimicrobial,³⁶ antitumor,³⁷⁻⁴⁰ and antimalarial⁴¹ properties (**A**, Figure 1 - 3). These compounds will not be discussed in any further detail, as they are not an area of focus in this thesis.

Figure 1 - 3: General Skeletons of Representative Tri- and Tetrapyrrolic Compounds



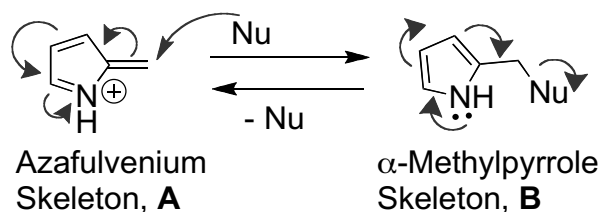
Linear and macrocyclic tetrapyrrolic compounds (i.e. **B** and **C/D**, respectively, as shown in Figure 1 - 3) are also of interest. There are many uses for tetrapyrrolic compounds, including as sensitizers in solar cells,⁴² as photodynamic therapy agents,⁴³ or as catalysts.⁴⁴ They have also been the subject of study owing to their antioxidant properties^{45,46} and as bioconjugates.⁴⁰ In Chapter 3 of this thesis, a chemically modified porphomethene (**D**, Figure 1 - 3) is proposed as a potential inhibitor of the enzyme uroporphyrinogen decarboxylase (URO-D), which is part of a biosynthetic pathway that results in the formation of heme (a naturally occurring porphyrin found in hemoproteins).⁴⁷

1.2 *N*-Functionalization of Pyrrolic Compounds

1.2.1 *N*-Functionalization of Monopyrroles

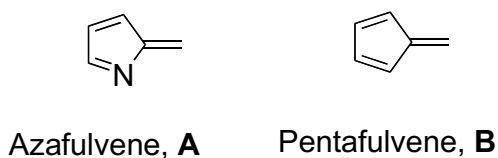
The chemical manipulation of pyrrolic compounds can be challenging. This is especially true when an α -methyl substituent is present on the pyrrolic substrate that is of interest for manipulation. This is due to the inherent propensity of an α -methylpyrrole (**A**, Scheme 1 - 5) to form an azafulvenium intermediate (**B**).

Scheme 1 - 5: General Skeletons of Azafulvenium and α -Methylpyrroles



The homoaromatic equivalents of azafulvenes (**A**, Figure 1 - 4) are called pentafulvenes (**B**). Pentafulvenes are antiaromatic with $4n$ electrons,⁴⁸ since the cross-conjugated exocyclic double bond cannot participate in aromaticity, and azafulvenes can be thought of in the same manner.

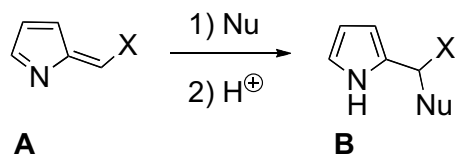
Figure 1 - 4: General Structure of Pentafulvenes and Azafulvenes



Azafulvenes are quite reactive to nucleophilic additions to the exocyclic carbon atom (**A** to **B**, Scheme 1 - 6), electrophilic additions at the α -position (**C** to **D**), as well as cycloaddition reactions to form bicyclic systems (**E** to **G**).⁴⁹⁻⁵³ The acid-catalyzed polymerization of pyrrolic compounds results from the formation of the azafulvenium cation.⁵⁴ This undesired reactivity can be prevented by the incorporation of an *N*-protecting group.

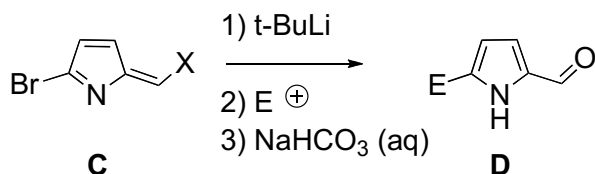
Scheme 1 - 6: Examples of Azafulvene Reactivity

Nucleophilic Addition:

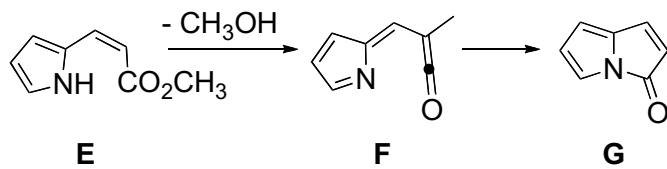


X = OH, NR₂
Nu = NR₂, SR, R
E = RI, R₃SiCl, RSSR,
R = alkyl and aryl

Electrophilic Addition:



Electrocyclization:

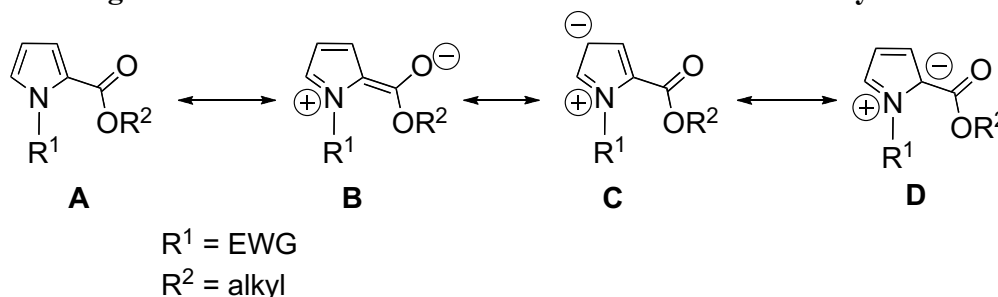


N-Protecting groups mask the nitrogen atom of the pyrrole, aiding difficult transformations by directing and controlling reactivity.⁵⁵⁻⁵⁷ *N*-protecting groups can have either electron-donating or electron-withdrawing character. Both types of *N*-protecting group have their respective benefits. Protecting groups with electron-donating character such as *N*-benzyl groups are generally robust, accommodating hydride-mediated reductions (using NaBH₄ or LiAlH₄), cross-couplings, and electrocyclizations, as well as Wittig, aldol, and alkylation reactions (among others).⁵⁴ *N*-Silyl protecting groups are employed to direct electrophilic substitution to the β-position,^{58,59} since an *N*-unprotected pyrrole will tend to direct substitution preferentially to the α-position. In contrast, electron-withdrawing *N*-protecting groups can direct substitution to the α-position⁵⁹⁻⁶¹ or the β-position,⁶⁰⁻⁶³ depending on the reaction conditions employed.

Electron-withdrawing *N*-protecting groups act by drawing electron density out of the pyrrole ring, favoring resonance structure **A** (as shown in Figure 1 - 5); this chemical modification makes the nitrogen lone pair less available, decreasing aromatic character

and inherent nucleophilicity.^{52,64} Effectively, either electron-donating or electron-withdrawing *N*-protecting groups will allow for chemical control *via* manipulation of sterics and/or electronics.

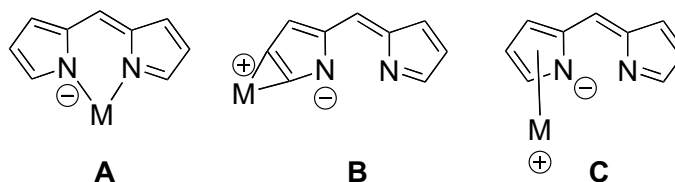
Figure 1 - 5: Resonance Structures of an *N*-Substituted Pyrrole



1.2.2 *N*-Protection and Metal Complexation of Dipyrins

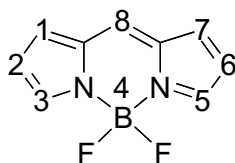
N-Protection can also be performed on deprotonated free-base dipyrins, by means of complexation to a metal as dipyrinato ligands.^{65,66} This is a particularly useful technique, as straightforward functional group manipulations of dipyrins have been described as “messy and often ruinous manipulations”.⁶⁷ Dipyrinato complexes can be prepared using a range of metals and ancillary ligands, with the most common examples being derived from iron(III),⁶⁸⁻⁷² copper(II)⁷³⁻⁷⁵ and zinc(II)⁷⁶⁻⁸³ metal ions. Dipyrinato ligands typically chelate in a κ^2 manner (A, Figure 1 - 6). On rare occasion, they have also been shown to bind to pyrrolic units in η^2 (B)⁸⁴ or η^5 (C)⁸⁵ fashion.

Figure 1 - 6: Binding Modes of Dipyrin Ligands



Dipyrinato ligands are also known to coordinate to boron.⁶⁵ For example, borondifluoride dipyrinato complexes, or *F*-BODIPYs (Figure 1 - 7), coordinate in a κ^2 manner (A, Figure 1 - 6).

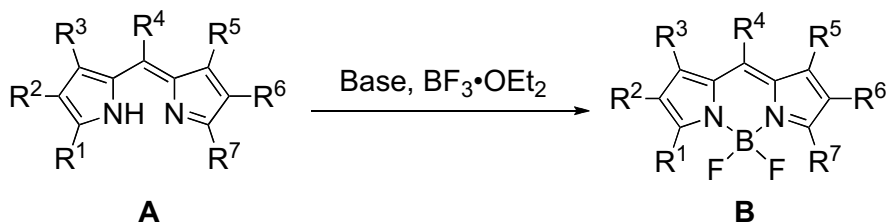
Figure 1 - 7: General Skeleton of an *F*-BODIPY



F-BODIPYs are a popular area of study in many fields owing to their high stability, intense fluorescence,^{86,87} high absorption coefficients and delocalized molecular orbitals.⁶⁵ *F*-BODIPYs have been employed as dyes for the labeling of proteins⁸⁸⁻⁹¹ and DNA,^{92,93} and are emerging as useful protecting groups for functional group interconversion (FGI) on dipyrins.^{94,95} The chemical manipulation of an *N*-protected dipyrin is described in Chapter 2. *F*-BODIPYs have been assigned IUPAC numbering different to that of the parent dipyrin (as shown in Scheme 1 - 7).⁶⁵

Meso-substituted *F*-BODIPYs can be obtained in a one-pot process, beginning with the use of the desired substituted pyrrole to form a dipyrin (as pictured in Scheme 1 - 3). Subsequent addition of excess triethylamine (NEt₃, 6 equiv.) and borontrifluoride diethyletherate (BF₃•OEt₂, 9 equiv.) to the dipyrin (**A**, Scheme 1 - 7) affords the respective *F*-BODIPY (**B**).^{65,96-99} However, the non-nucleophilic base employed in *F*-BODIPY formation is not limited to NEt₃ (Scheme 1 - 7). *F*-BODIPYs have also been synthesized by employing lithium hexamethyldisilazide (LiHMDS, 1.1 equiv.; BF₃•OEt₂, 1 equiv.).¹⁰⁰ Employing LiHMDS in place of NEt₃ generally results in higher yields of the *F*-BODIPY.

Scheme 1 - 7: Synthesis of an *F*-BODIPY



1.3 Thesis Overview

The work included in this thesis focuses on the functionalization of pyrroles and dipyrrolic compounds. Chapter 2 describes the chemical manipulation of substituted dipyrrens. This is of particular interest given that there are few examples of the chemical manipulation of dipyrrens. The ability to manipulate functional groups that are incorporated into the dipyrren core will allow for tunable solubility. Chapter 3 focuses on the fluorination of pyrroles and dipyrromethanes, for which there is also little information available. Chapter 4 focuses on novel ruthenium-pyrrolide complexes for use in photodynamic therapy, with relevant methodology development towards these systems discussed therein. Chapter 5 is a summary of the three experimental projects that have been presented in this thesis. As a whole, this document is a body of work dedicated towards increasing the ease of handling of pyrrolic compounds, in the hopes of allowing these heterocycles to be more accessible to the general organic chemist.

1.4 References for Chapter 1

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Chapter 2 Microwave-Assisted Deprotection of *F*-BODIPYs, and *In Situ* Reduction of Dipyrrens to Dipyrromethanes

This chapter includes content that has previously appeared in:

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Declaration of Authorship:

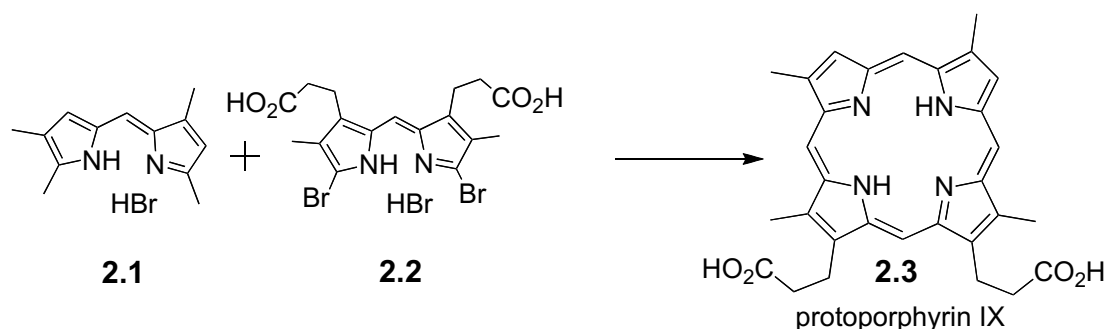
I completed the body of work that is presented in this chapter, with the exceptions being the preparation of compounds **2.38**, **2.39**, and **2.56 free base** (performed by Dr. Deb Smithen), and the crystallographic analysis of compound **2.14** (performed Dr. T. Stanley Cameron).

2.1 Background

2.1.1 Literature Precedence for the Modification of a Dipyrren

There are limited reports regarding the chemical manipulation of dipyrrens.¹ Those that do exist are the result of studies working towards the formation of porphyrins e.g., the total synthesis of heme by Fisher.² The formation of a porphyrin is a thermodynamically favorable process, due to the inherent stability that arises from building a conjugated macrocycle. Scheme 2 - 1 depicts the C-C coupling of two dipyrrolic units to form protoporphyrin IX (**2.3**).

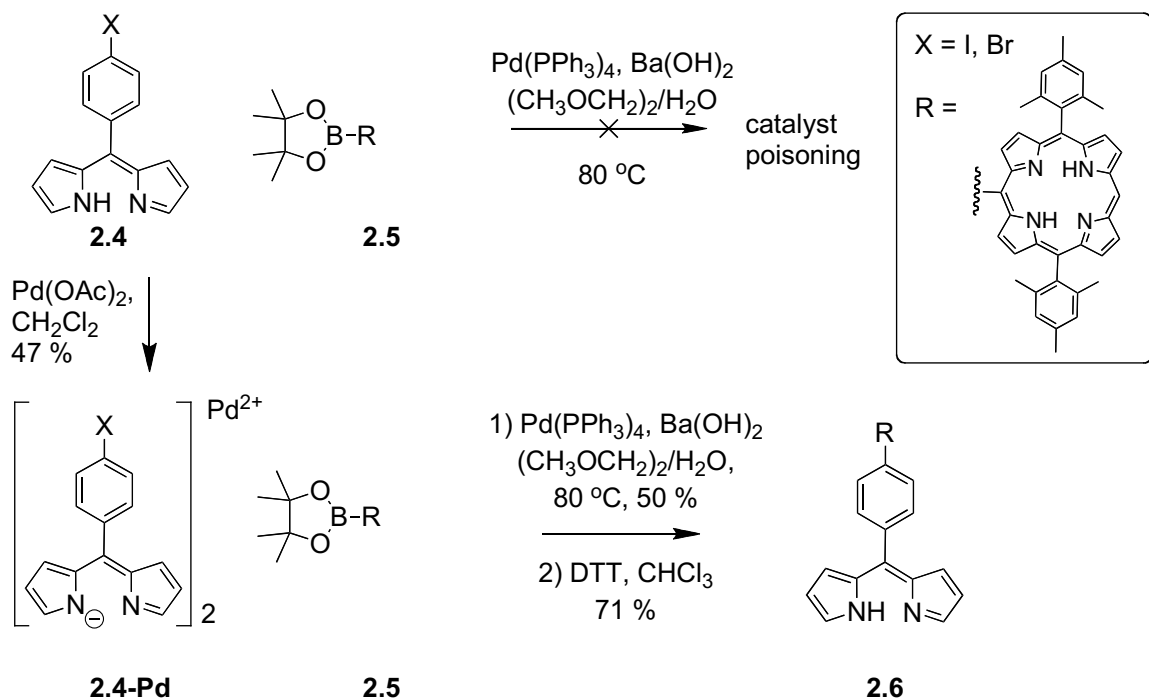
Scheme 2 - 1: Formation of Porphyrin 2.3



Working with dipyrrens can be intimidating for newcomers to pyrrole chemistry, especially since relatively straightforward functional group interconversion (FGI) on dipyrrens have been described as “messy and often ruinous manipulations.”³ Free-base dipyrrens are prone to slow decomposition,⁴ which is expedited by exposure to acid.⁵ Once synthesized, dipyrrens require immediate purification to ensure stability. Nevertheless, chemical manipulations on dipyrrens can be performed by employing *N*-protecting groups, in the form of metal complexation.^{1,6}

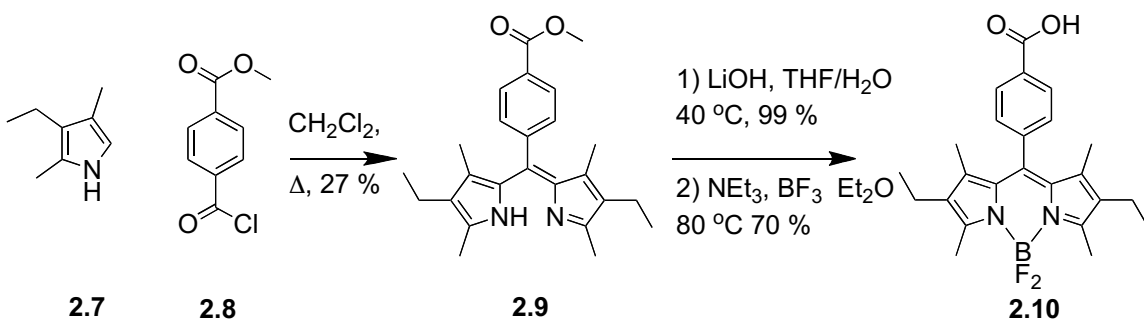
The Suzuki cross-coupling of an aryl halide and an arylboronic acid is a fairly robust carbon-carbon bond forming reaction. However, when a free-base dipyrren was used as a substrate (**2.4**, Scheme 2 - 2), catalyst poisoning can occur.⁷ This problem was overcome by the protection of the free-base dipyrren (**2.4**) by the formation of the corresponding dipyrrenato palladium(II) complex (**2.4-Pd**), which can be decomplexed by use of dithiothreitol (DTT) after successful cross-coupling has taken place (Scheme 2 - 2).⁷ Catalyst poisoning can also be circumvented by employing the respective *F*-BODIPY as the Suzuki cross-coupling substrate in place of the free-base dipyrren.⁸

Scheme 2 - 2: Suzuki Cross-Coupling on a Palladium Complexed *meso*-Aryl Dipyrren



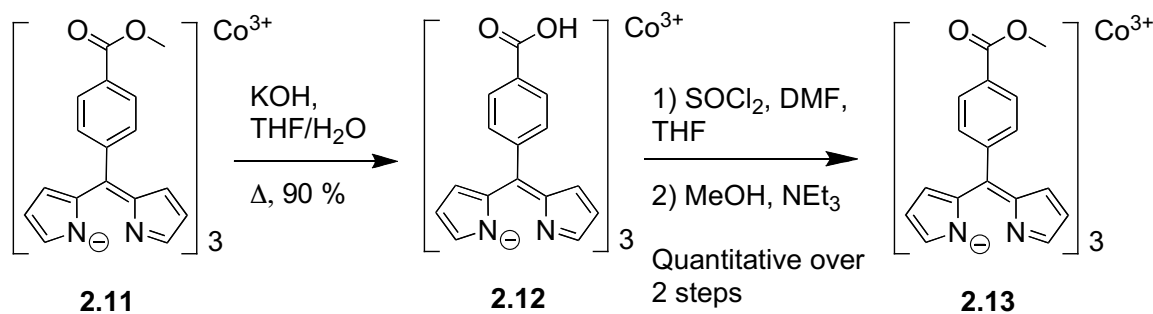
The formation of esters or amides are two additional examples of useful chemical manipulations that prove to be more difficult than expected when performed on free-base dipyrrens. In general, both ester and amide bond formation requires the presence of a carboxylic acid. If the free-base dipyrren is not synthesized with a carboxylic acid moiety already appended, then the compound bearing the ester group is prepared by hydrolysis. There is one report of ester hydrolysis performed on a free-base *meso*-aryl dipyrren (Scheme 2 - 3).⁹ Although this reaction is successful, the results are specific to the completely substituted free-base dipyrren **2.9** (Scheme 2 - 3), which bears the ester functionality on the *meso*-aryl moiety.

Scheme 2 - 3: Ester Hydrolysis on a Fully-Substituted, Free-Base Dipyrren



In order to circumvent this challenge, ester hydrolysis is routinely performed on dipyrrenato complexes rather than on their respective free-base dipyrrens. *F*-BODIPYs,¹⁰⁻²⁵ and *C*-BODIPYs,²⁶⁻²⁸ as well as ruthenium(II),^{29,30} ruthenium(III),³¹ iridium(III),³² rhodium(III),³¹ and cobalt(III)³³⁻³⁵ dipyrrenato complexes are all amenable to ester hydrolysis. The substrate scope for ester hydrolysis is much greater when employing a dipyrrenato complex. In addition to substrates that bear the *meso*-aryl appended ester group (comparable to **2.11** in Scheme 2 - 4^{10-14,26-35}), dipyrrenato complexes of substrates that bear ester functionalities at the α -¹⁶ or β - position^{15,17,18} of the pyrrole, as well substrates with esters¹⁹ and alkyl esters²⁰⁻²² in the *meso*-position can also successfully undergo ester hydrolysis. Subsequent re-esterification (**2.12** to **2.13**, Scheme 2 - 4)^{23,24,35} or amidation^{9,21,24,25} on the resulting carboxylic acid group is also performed with relative ease.

Scheme 2 - 4: Employing Cobalt(III) as a Protecting Group Strategy



F-BODIPYs are stable under a wide range of reaction conditions. In addition to the reactions mentioned above, *F*-BODIPYs can tolerate chemical manipulations such as electrophilic (i.e., sulfonation,^{36,37} nitration,^{36,37} halogenation,³⁸ and Vilmeyer-Haack^{39,40} reactions), and nucleophilic substitution reactions,⁴¹⁻⁴⁵ oxidations,^{23,45,46} and hydrogenations.^{24,47-49} *F*-BODIPYs display intense color and fluorescent properties, and also exhibit increased motility on silica when purifying using column chromatography, making them much easier to isolate than their respective free-base dipyrrens.

2.1.2 *F*-BODIPY Formation as a Protection Strategy

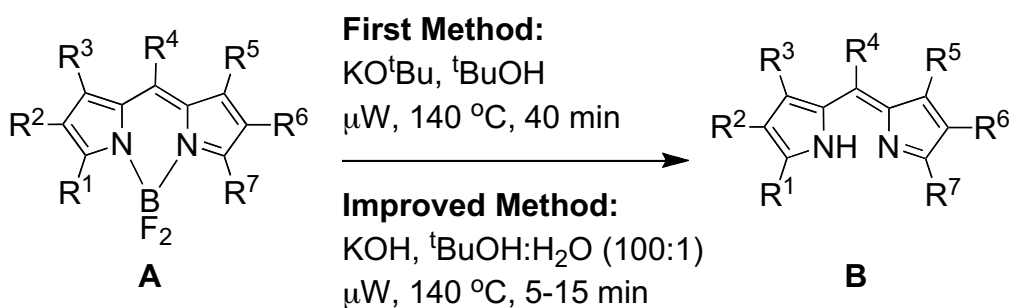
The formation of *F*-BODIPYs prior to chemical manipulation of dipyrrens is a promising protection strategy. It is generally anticipated when employing a protection strategy that the protecting group utilized can be removed once it is no longer necessary. This removal is preferred to be facile and high yielding. Fortunately, the Thompson group has communicated three general methods for the deprotection of *F*-BODIPYs.

The first method developed to access deprotection involved reacting an *F*-BODIPY with 6 equiv. of potassium *tert*-butoxide using microwave heating (92 °C) in a sealed system for 40 minutes (employing *tert*-butanol as solvent).⁵⁰ The yields received from this deprotection are typically between 80-90 %.⁵⁰

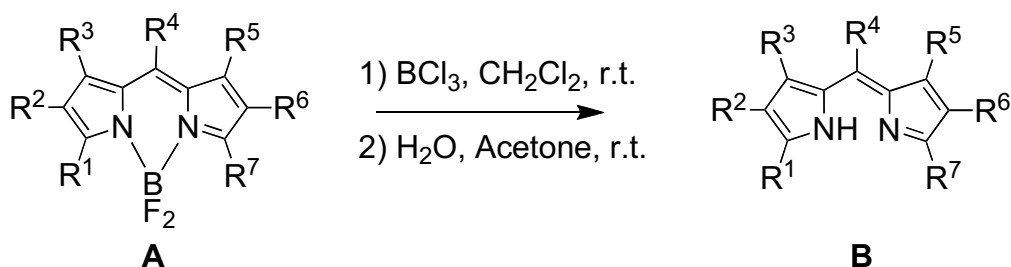
The second microwave-assisted method improved upon the original deprotection by using KOH in place of potassium *tert*-butoxide (as shown in Scheme 2 - 5).⁵¹ In addition, the reaction time was decreased from 40 minutes to 5 minutes by increasing the reaction temperature from 92 °C to 140 °C.

Scheme 2 - 5: Microwave-Assisted Deprotection of *F*-BODIPYs

Microwave-Assisted Methods:



Newest Method:



The most recently reported deprotection strategy is also the most facile method developed to date. This method employs boron trihalides, such as BCl₃, to activate the borondifluoride moiety of the *F*-BODIPY (**A**) for nucleophilic attack. Water is employed as the nucleophile to facilitate deprotection without use of conventional or microwave heating, unmasking the parent dipyrrolic (**B**) with quantitative conversion.⁵² This method does not employ the use of microwave heating, as the deprotection proceeds at room temperature.

2.1.3 Project Direction

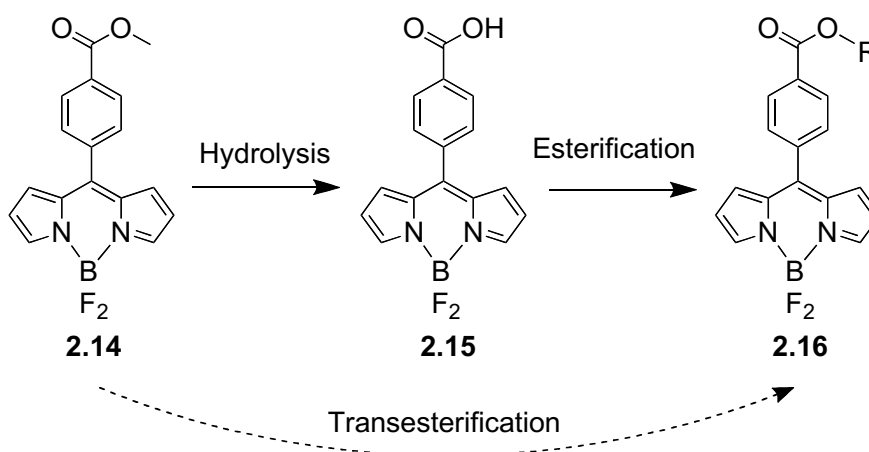
At the onset of this project, the goal was to employ *F*-BODIPYs in place of their parent dipyrrolics for the chemical manipulation of their appended functional groups. Once the desired functionalities had been chemically installed, *F*-BODIPY substrates could then be deprotected using one of the above strategies to unmask the respective functionalized dipyrrolics. However, an unusual reaction occurred, and the goal of this chapter was changed so as to investigate this deleterious transformation.

2.2 Results and Discussion

2.2.1 Preliminary Observations

Since *F*-BODIPY deprotection is available and high yielding, an attempt was made to mask the parent dipyrin as an *F*-BODIPY during chemical manipulation. An *F*-BODIPY featuring an ester moiety was employed, as this substituent could be chemically modified in order to impart water solubility. Ethylene glycol was chosen as the alcohol to be employed in esterification, as a water-solubilizing moiety could be appended to the free hydroxyl group. In the interest of streamlining the synthesis, a transesterification route (2.14 to 2.16, Scheme 2 - 6) was proposed in place of the stepwise hydrolysis (2.14 to 2.15) and re-esterification (2.15 to 2.16).

Scheme 2 - 6: Stepwise Chemical Modification versus Transesterification

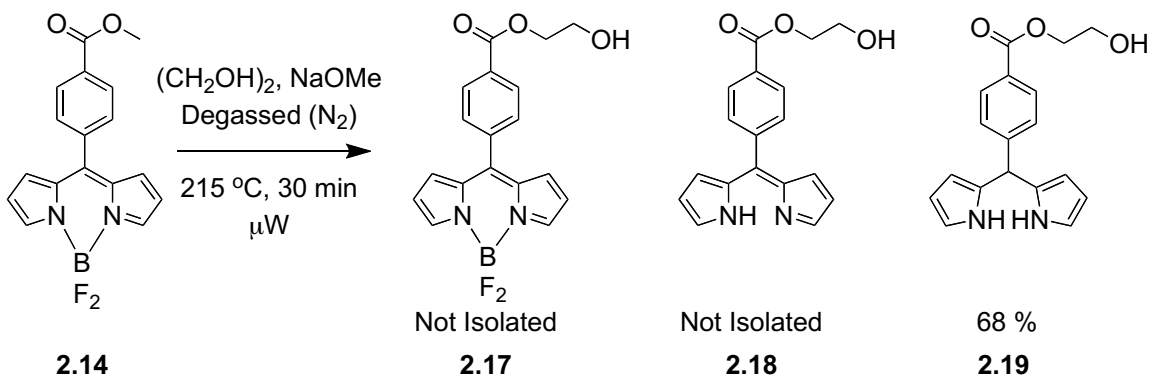


Many methodologies that have been designed for use on monopyrroles have also been successfully applied to BODIPY substrates, such as the oxidation of α -methyl substituents on pyrroles⁵³ and *F*-BODIPYs⁵⁴ using bromine. Following a transesterification procedure that had been developed for pyrrolic starting materials,⁵⁵ 4,4-difluoro-8-(4-methoxycarbonylphenyl)-4-bora-3a,4a-diaza-*s*-indacene (**2.14**, Scheme 2 - 7) was submitted to microwave-assisted transesterification conditions, using reagent-grade ethylene glycol in excess and 3 equiv. of sodium methoxide.⁵⁵

It was expected that the methyl ester moiety of **2.14** (Scheme 2 - 7) would be transesterified under these conditions, exchanging the methoxy group for a 2-hydroxyethoxy group to produce 4,4-difluoro-8-(4-(2-hydroxyethoxy)carbonylphenyl)-

4-bora-3a,4-diaza-s-indacene (**2.17**). The deprotection of **2.17** to give **2.18** was also expected, especially since the conditions employed are similar to those used previously for deprotection.^{50,51}

Scheme 2 - 7: Formation of 2.19

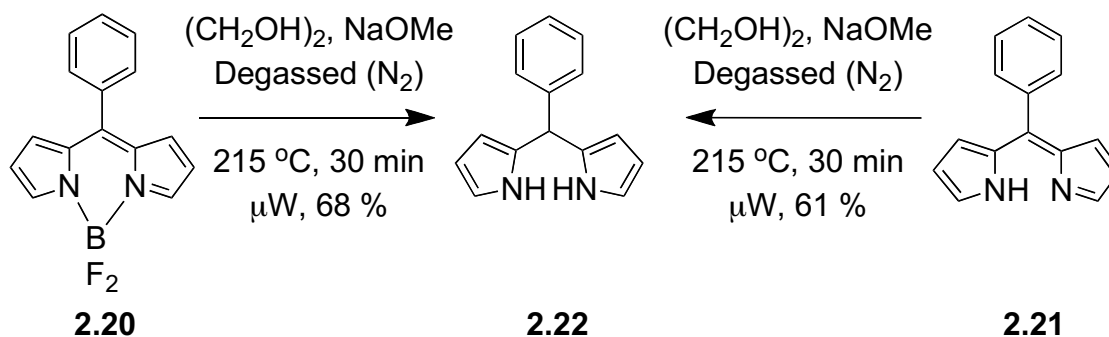


Under the conditions employed, both transesterification and deprotection occurred. In addition, the dipyrromethane unit was reduced to produce 5-((4-(2-hydroxy)ethoxycarbonyl)phenyl)dipyrromethane (**2.19**) in a 68 % yield, with no traces of the expected transesterified *F*-BODIPY product (**2.17**) nor the corresponding dipyrromethane (**2.18**). Dipyrromethane **2.19** was most likely produced from the reduction of the analogous dipyrromethane (**2.18**), which would have been deprotected during the course of the reaction. Given this interesting finding, the reaction was explored further in an attempt to understand its scope and limitations, and to reveal the redox partner in the reaction.

2.2.2 Generation of Dipyrromethanes from Dipyrromethanes

The *F*-BODIPY of 5-phenyldipyrromethane (**2.20**) and the respective dipyrromethane (**2.21**) were employed as substrates using the microwave-assisted reaction conditions described in Scheme 2 - 7. These substrates were used to probe the roles of the ester functionality and borondifluoride moiety featured in **2.14**, so as to determine if either of these moieties are required for the reduction to proceed. The corresponding reduced, deprotected dipyrromethane (5-phenyldipyrromethane, **2.22**) was isolated in 68 % yield when *F*-BODIPY **2.20** was submitted to the original conditions. Additionally, the reaction proceeded comparably for the transformation of dipyrromethane **2.21** to dipyrromethane **2.22**.

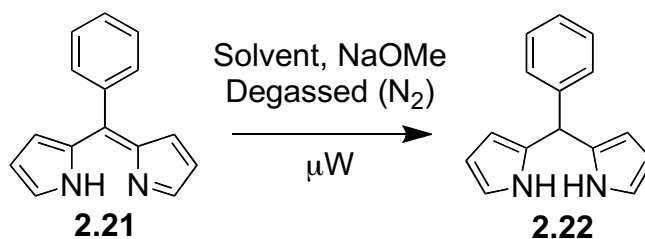
Scheme 2 - 8: Deprotection and Reduction of an *F*-BODIPY and a Dipyrin



Given that the yield of the reduction reaction was modest, the dipyrromethane **2.22** was resubmitted to the reaction conditions in order to ensure that it would be stable once formed. This test of stability was performed both with and without sodium methoxide present. In both cases, the starting material (**2.22**) was recollectd quantitatively. This suggests that the dipyrromethane **2.22** was indeed stable once formed. With the knowledge that the dipyrromethane was stable to the microwave-assisted reaction conditions, the role of the solvent in this reduction reaction was investigated.

2.2.3 Methodology Optimization

Multiple solvents were explored in order to determine whether the observed reduction of a dipyrin to a dipyrromethane specifically required the use of ethylene glycol. Ethylene glycol has two hydroxyl groups present, but it was uncertain whether this property was essential for either deprotection or reduction. Selected reactions exploring the effects of various solvents are summarized in Table 2 - 1.

Table 2 - 1: The Role of the Solvent on the Deprotection and Reduction of 2.21^a

Entry	Solvent	Boiling Point of Solvent Employed	Yield of 2.22(%)
1	ethylene glycol	198 °C	68 ^b
2	2-methoxyethanol	125 °C	59 ^b
3	1,2-dimethoxyethane	85 °C	0 ^c
4	ethanol	78 °C	0 ^c
5	<i>n</i> -butanol	118 °C	0 ^c
6	benzyl alcohol	205 °C	59 ^b
7	4-methoxybenzyl alcohol	259 °C	47 ^b
8	DMF	153 °C	16 ^b

^aReaction conditions: 215 °C, 30 min, MW, 50 mg of **2.21**, 3 equiv. sodium methoxide;
^byields of isolated **2.22**; ^conly decomposition products observed

Of the eight solvents investigated, the majority were found to afford the reduction product **2.22** successfully. 2-Methoxyethanol and 1,2-dimethoxyethane (entries 2 and 3, Table 2 - 1) were utilized as a means of determining whether or not the presence of hydroxy groups on the solvent were required. Under identical conditions to those previously employed, the use of 2-methoxyethanol as a solvent afforded the expected product (**2.22**) in a modest yield. Benzyl alcohols were employed as simple alcohols with high boiling points. Employing benzyl alcohol (entry 6) or 4-methoxybenzyl alcohol (entry 7) resulted in comparable yields of **2.22** (59 % and 47 %, respectively). DMF was explored as a non-protic solvent: though the formation of **2.22** was observed, the yield was much lower (16 %).

In contrast, the use of low boiling solvents such 1,2-dimethoxyethane (entry 3), ethanol (entry 4) or *n*-butanol (entry 5) resulted only in decomposition. However, these solvents were heated far beyond their respective boiling points. This may have promoted decomposition of any product that may have formed, as the solid components of the

reaction mixture may no longer have been dissolved due to significant phase change of the solvent. Given that the reduction occurred using higher boiling point alcohols (2-methoxyethanol, benzyl alcohol and 4-methoxybenzyl alcohol) as solvents, only one hydroxy group appears to be required for the expected transformation to proceed.

In an attempt to make the reaction conditions less caustic, the amount of sodium methoxide in the reaction mixture was altered to 0, 0.1, 0.5, 1, and 2 equiv., with the results compared to those obtained using 3 equiv. (Table 2 - 2). The yields of **2.22** were essentially the same when using 1, 2, and 3 equiv. (entries 4-6), with much lower yields observed with <1 equiv. (entries 1-3). No change to the reaction conditions were made going forward, as the original amount of 3 equiv. of sodium methoxide was the highest yielding trial in this series.

Table 2 - 2: The Effects of Sodium Methoxide on Yield^a

Entry	Equiv. of NaOMe	Yield of 2.22 (%)
1	0	0 ^b
2	0.1	33 ^c
3	0.5	38 ^c
4	1	61 ^c
5	2	67 ^c
6	3	71 ^c

^aReaction conditions: 10 min, 215°C MW, 50 mg substrate, (CH₂OH)₂ as solvent; ^bonly decomposition products observed; ^cyield of isolated **2.22**

Prior to investigating substrate scope, both temperature and time were optimized (Table 2 - 3). Lowering temperature as a means of increasing yield proved unsuccessful, resulting largely in decomposition (entries 5-7). However, when conducting the reaction at 215 °C, it was found that reducing reaction times to 10 minutes (entry 3) afforded slightly elevated yields of **2.22** in comparison to 30 minutes (entry 1) or 20 minutes (entry 2). As such, the optimized reaction conditions emerged as 215 °C for 10 minutes.

Table 2 - 3: The Effects of Temperature and Time on Yield and Consumption of Starting Material^a

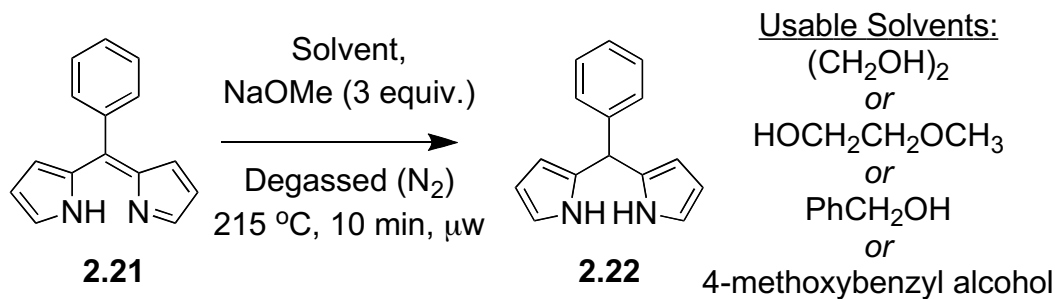
Entry	Time (min)	Temperature (°C)	Consumption of 2.21 (%) ^b	Yield of 2.22 (%) ^c
1	30	215	100	61
2	20	215	100	63
3	10	215	100	71
4	5	215	89	54
5	10	200	80	34
6	10	150	5	2
7	15	200	87	34

^aReaction conditions: MW, 50 mg substrate, 3 equiv. sodium methoxide, (CH₂OH)₂ as solvent;

^bobtained from the ratio of 2.21 to 2.22 *via* integration of NMR signals ^cyields of isolated 2.22

Overall, the optimal reaction conditions for the transformation of *F*-BODIPYs and dipyrins to dipyrromethanes under microwave-assisted conditions were found to be 215°C for 10 minutes in the presence of 3 equiv. of sodium methoxide and excess ethylene glycol, although the transformation was also able to be successfully conducted in 2-methoxyethanol, benzyl alcohol and 4-methoxybenzyl alcohol as solvents (Scheme 2 - 9).

Scheme 2 - 9: Optimized Microwave-Assisted Reduction Conditions

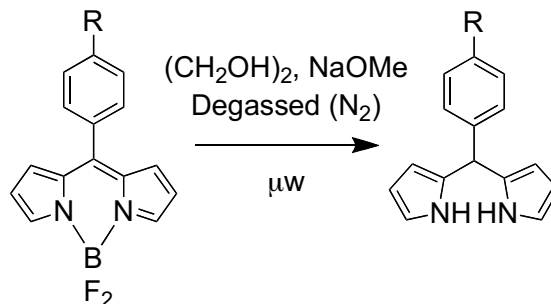


2.2.4 Exploration of Substrate Scope

With optimized conditions in hand, an investigation into substrate tolerance was launched. To begin with, substrates substituted at the *para*-position of the *meso*-aryl

moiety were tested using the optimized microwave-assisted reduction conditions (Table 2 - 4). Both electron-withdrawing and electron-donating functionalities were tolerated, and each substrate produced comparable yields of their respective dipyrromethanes (entries 1-7). In the case of the nitro-functionalized substrate (**2.28**, entry 8), only products resulting from decomposition were obtained.

Table 2 - 4: The Effects of Changing the Electronic Influence at the *p*-Position^a



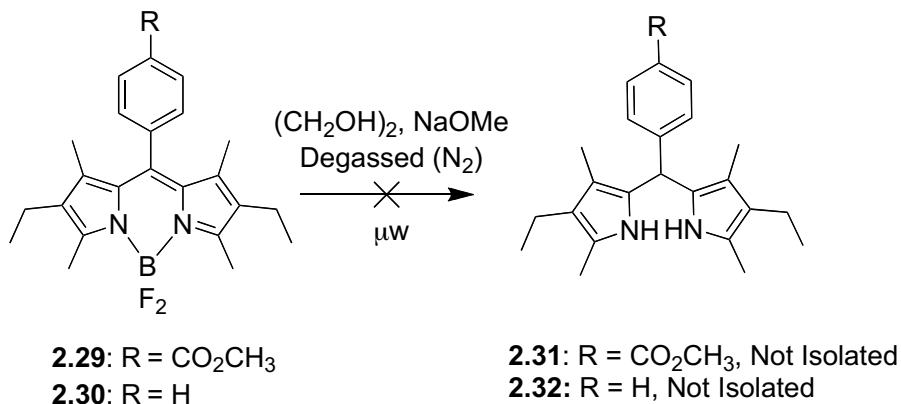
Entry	R (Compound #)	Yield (%)
1	-NMe ₂ (2.23)	47 ^b
2	-OCH ₃ (2.24)	76 ^b
3	-CH ₃ (2.25)	63 ^b
4	-H (2.20)	68 ^b
5	-Br (2.26)	61 ^b
6	-CO ₂ CH ₃ (2.14)	68 ^b
7	-CF ₃ (2.27)	53 ^b
8	-NO ₂ (2.28)	0 ^c

^aReaction conditions: 10 min, 215°C MW, 50 mg substrate, 3 equiv. sodium methoxide, (CH₂OH)₂ as solvent; ^b yields of isolated dipyrromethane; ^conly decomposition products observed

Substrates with substitution on the pyrrolic moieties were also investigated. The first two *F*-BODIPYs of this series were employed as fully-substituted mimics of **2.14** and **2.20** (as **2.29** and **2.30** respectively, Scheme 2 - 10). When ester-bearing *F*-BODIPY **2.29** was submitted to the microwave-assisted reduction conditions (3 equiv. sodium methoxide, ethylene glycol, 10 min, 215 °C), decomposition was primarily observed and only 1 % of the starting material was recovered. Likewise, decomposition was also

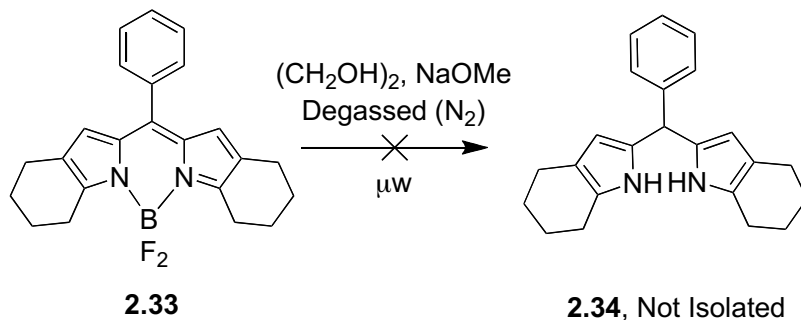
observed when *F*-BODIPY **2.30** was employed, albeit with slightly higher recovery of starting material (23 %).

Scheme 2 - 10: Attempted Reduction of 2.29 and 2.30



The third substrate employed was unsubstituted adjacent to the *meso*-position (**2.33**, Scheme 2 - 11). This also predominantly afforded decomposition after being submitted to the microwave-assisted reduction conditions, and only 4 % of the starting material was recovered.

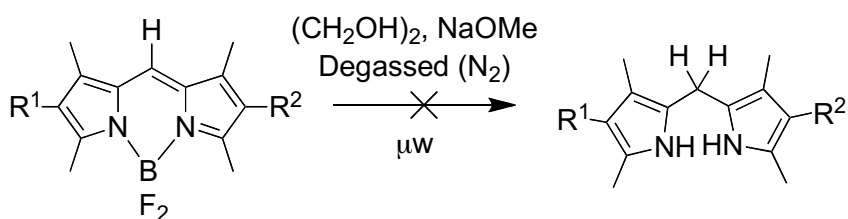
Scheme 2 - 11: Attempted Reduction of 2.33



As a final investigation into substrate scope, a series of *meso*-H substrates (Table 2 - 5) were also submitted to the microwave-assisted reduction conditions. These substrates had varying chain lengths and functional groups on the pyrrolic units, but lacked substitution at the *meso*-position. Entries 1-3 (Table 2 - 5) displayed symmetric substitution patterns and entries 4 and 5 had asymmetric substitution. None of the *meso*-H substrates yielded their respective dipyrromethanes upon exposure to the microwave-

assisted reduction conditions, returning only decomposition with a minor amount of starting material. The only substrates that yielded anything other than recovered starting material or decomposition products were **2.36** and **2.37** (entries 2 and 3), for which a small amount of the deprotected dipyrin was isolated (**2.40** and **2.41**, respectively).

Table 2 - 5: Further Exploration of Substrate Tolerance^a



2.35: R¹, R² = ethyl R³ = H

2.36: R¹, R² = (CH₂)₃OH R³ = H

2.37: R¹, R² = *n*-pentyl R³ = H

2.38: R¹ = CF₃(CH-)OH R² = ethyl R³ = H

2.39: R¹ = H R² = *n*-hexyl R³ = H

Entry	Recovered BODIPY (%) ^b	Deprotected Dipyrin (%) ^b	Deprotected and Reduced Dipyrromethane (%) ^b
1	8 (2.35)	0	0
2	0 (2.36)	Trace (2.40)	0
3	34 (2.37)	18 (2.41)	0
4	8 (2.38)	0	0
5	10 (2.39)	0	0

^aReaction conditions: 10 min, 215°C MW, 50 mg substrate, 3 equiv. sodium methoxide, (CH₂OH)₂ as solvent ^byields of isolated products

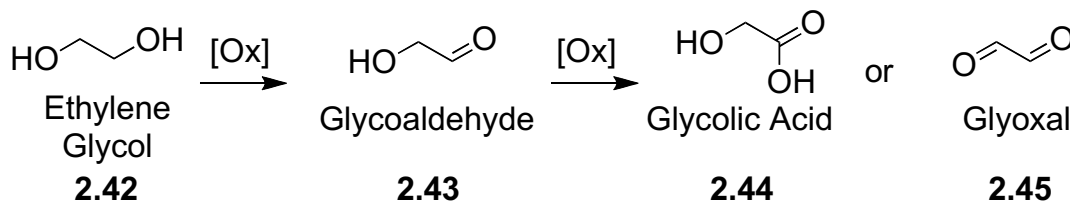
This series of experiments has shed light on the scope of the reduction and deprotection reaction. Substrates substituted at the *meso*-position, but not at the pyrrolic units, were successfully transformed into their respective dipyrromethanes. In contrast, substrates with substitution on the dipyrrolic unit were unable to withstand the reaction conditions.

2.2.5 Mechanistic Insight

As the transformation from the *F*-BODIPY or dipyrin to its respective dipyrromethane is a reductive process, in which the dipyrin is reduced to the dipyrromethane, there must also be an oxidation reaction occurring. The redox partner was hypothesized to be ethylene glycol (**2.42**), which would be oxidized to 2-hydroxyacetaldehyde (glycoaldehyde, **2.43**, Scheme 2 - 12). Similarly, benzaldehydes are predicted as the resulting byproduct from the redox reaction when employing benzyl alcohols as the reaction solvent.

Glycoaldehyde (**2.43**) has been reported to be a product of the air-oxidation of **2.42** at high temperatures (Scheme 2 - 12).⁵⁶ Glycoaldehyde (**2.43**) can be further oxidized to form glycolic acid (**2.44**) and glyoxal (**2.45**) under oxidative conditions.⁵⁷ In this regard, the microwave-assisted reduction procedure incorporates a degassing step (N₂) to remove oxygen from the reaction mixture. As oxygen was not present in the reaction mixture during the course transformation of *F*-BODIPYs and dipyrins to dipyrromethanes, this eliminated the possibility of **2.43** being generated by this alternative mechanism.

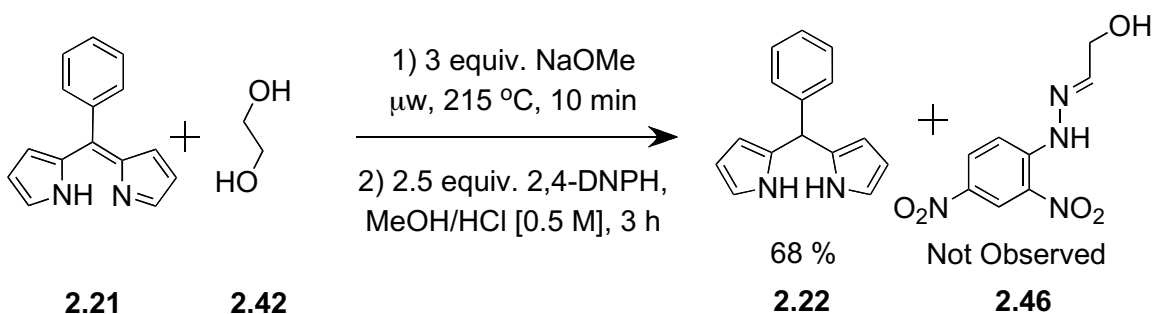
Scheme 2 - 12: Oxidation Progression of Ethylene Glycol



Hydrazines, such as 2,4-dinitrophenylhydrazine (2,4-DNPH), react with aldehydes to form hydrazones.⁵⁸ The formation of a hydrazone from the reaction mixture by *in situ* trapping would indicate that the solvent was the redox partner (Scheme 2 - 13). In fact, a hydrazone has previously been demonstrated to be an *in situ* trap for aldehyde **2.43**.⁵⁹ After microwave irradiation (10 min, 215 °C) of 5-phenyldipyrromethene (**2.21**) and sodium methoxide (3 equiv.) in ethylene glycol, a solution of 2,4-DNPH (2.5 equiv.) in acidic methanol was added directly to the reaction mixture. After stirring at room

temperature for 3 hours, the use of TLC analysis, ^1H NMR and mass spectrometry showed no sign of the formation of hydrazone **2.46** in the crude reaction mixture.

Scheme 2 - 13: Attempted Hydrazone Formation with Glycoaldehyde



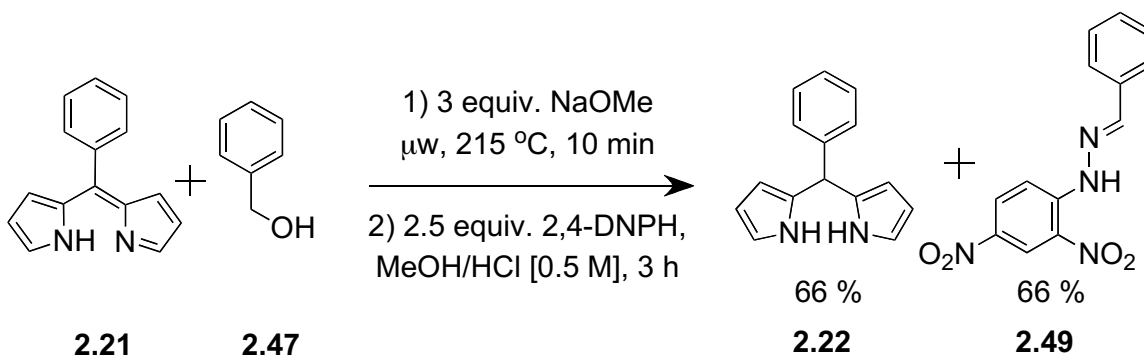
A second attempt was made to form the hydrazone of glycoaldehyde, this time employing 80 equiv. of 2,4-DNPH at room temperature for an hour.⁶⁰ After microwave irradiation, the reaction mixture was acidified to pH 4 using 1 M acidic (HCl) methanol, followed by the addition of 2,4-DNPH (80 equiv.) was added directly to the reaction mixture in one portion. Once again, the formation of the 2,4-DNP derivative of glycoaldehyde in the reaction mixture was not observed by the use of TLC analysis, ^1H NMR or mass spectrometry.

It is possible that acid **2.44** (Scheme 2 - 12) was present instead of aldehyde **2.43** in the reaction mixture. As aldehyde **2.43** is a better reducing agent than ethylene glycol (**2.42**),⁶¹ it could continue to act as the reducing agent to form the acid **2.44**. As such, a simpler system was selected to prove (or disprove) that the solvent was behaving as a redox partner.

Benzyl alcohol (**2.47**) was substituted for ethylene glycol (**2.42**), since the use of these solvents gave comparable yields in Table 2 - 1. It was hypothesized that benzaldehyde (**2.48**) would form during the course of the microwave-assisted reduction, in addition to producing the dipyrromethane **2.22**. The hydrazone of benzaldehyde **2.49** (Scheme 2 - 14) is well known.^{58,62} Furthermore, **2.48** would be easily detected in the reaction mixture by use of TLC analysis (by visualization under a UV lamp). After the addition of 2,4-DNPH post-microwave irradiation of **2.21** (Scheme 2 - 14), the reaction mixture produced dipyrromethane **2.22** and 1-benzylidene-2-(2,4-

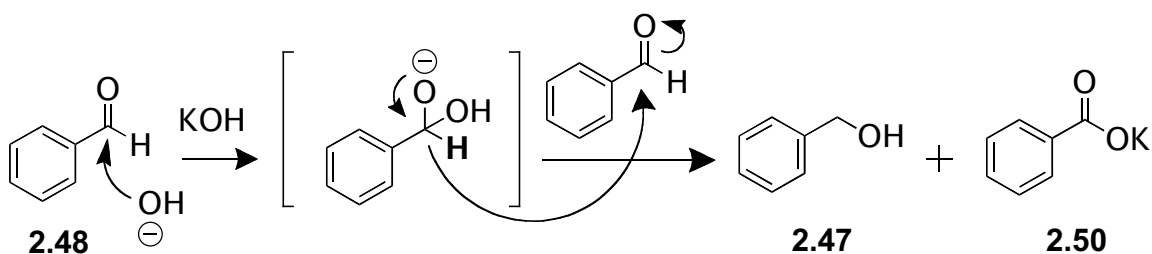
dinitrophenyl)hydrazone (**2.49**) in equal proportions (66 % yield). In a parallel reaction that did not make use of the *in situ* hydrazone formation, benzaldehyde was isolated in a comparable yield.

Scheme 2 - 14: Formation of 2.49



Satisfied that the redox partner was indeed the solvent, the mechanism of hydride delivery was investigated. The alcohol formally transfers a hydride to the dipyrriato core under the reaction conditions. Due to the high temperatures and the presence of base, interference *via* a Cannizzaro⁶³ hydride transfer cannot be ruled out once benzaldehyde (**2.48**) has formed (Scheme 2 - 15).

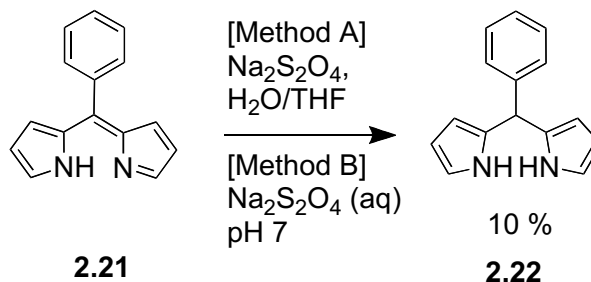
Scheme 2 - 15: The Cannizzaro Reaction



The transformation of a dipyrriin to a dipyrromethane is not novel. Dipyrriins can be reduced to dipyrromethanes using NaBH_4 , or by hydrogenolysis (H_2/Pd), and substrates typically bear a stabilizing group such as a *meso*-aryl or *meso*-acetyl group.⁶⁴⁻⁶⁶ Dipyrriins have also been reported to lose their stereotypical yellow color when exposed to a solution of sodium dithionite ($\text{Na}_2\text{S}_2\text{O}_4$), implying the formation of the respective

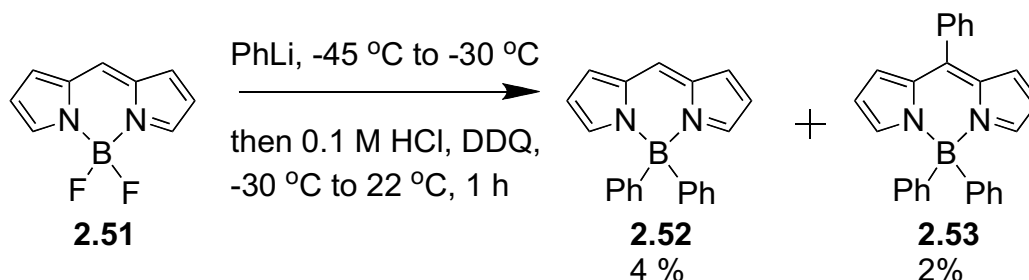
colourless dipyrromethane.⁶⁷ Unfortunately, this reaction was not as straightforward as it initially appeared. When **2.21** was exposed to an aqueous-THF solution⁶⁷ of Na₂S₂O₄ (Scheme 2 - 16), significant baseline decomposition was observed by TLC analysis, and only 10 % of the reduction product (**2.22**) was obtained. Use of a pH 7.0 phosphate-buffered sodium dithionite system achieved the same result. Prolonged exposure resulted in complete decomposition of **2.22** within 20 minutes when using a 0.2 M solution of dithionite and within only 5 minutes when using a saturated solution.

Scheme 2 - 16: Sodium Dithionite-Mediated Reduction of 2.21



Indeed, the *meso*-position of an *F*-BODIPY has also been noted to display electrophilicity. Phenyl lithium was employed for the modification of completely unsubstituted *F*-BODIPY (Scheme 2 - 17).⁶⁸ The reaction afforded a mixture of products, where *F*-BODIPY **2.51** (Scheme 2 - 17) was substituted at the *meso*-position and the boron centre to form *C*-BODIPY **2.53**.⁶⁸

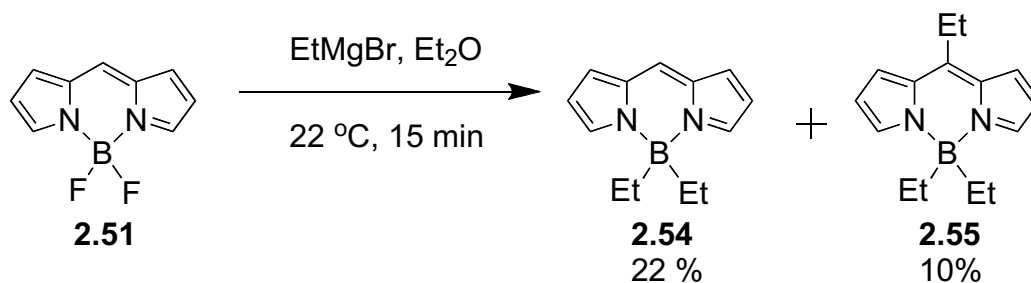
Scheme 2 - 17: Meso-Modification of an F-BODIPY using PhLi



The use of Grignard reagents on *F*-BODIPYs further highlights the electrophilicity of the *meso*-position. The use of ethylmagnesium bromide with *F*-

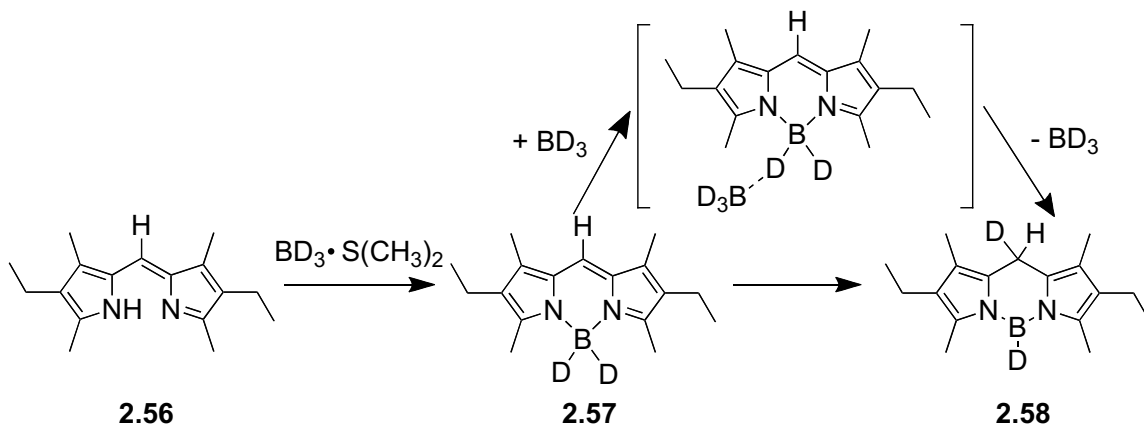
BODIPY **2.51** (Scheme 2 - 18) formed *C*-BODIPY **2.55**, where the *meso*-position and boron centre have been alkylated.⁶⁹

Scheme 2 - 18: *Meso*-Modification of an *F*-BODIPY using a Grignard Reagent



Similarly, the isomerization of a *D*-BODIPY effectively transfers a deuteride to the *meso*-position of the parent dipyrroin, showing another display of electrophilicity at this position (Scheme 2 - 19).^{70,71} The deuterium was abstracted from *D*-BODIPY **2.57** by use of borane-*d*₃-dimethylsulfide ($\text{BD}_3 \cdot \text{S}(\text{CH}_3)_2$) and subsequently delivered to the *meso*-position to form borane-dipyrroinato complex **2.58**.

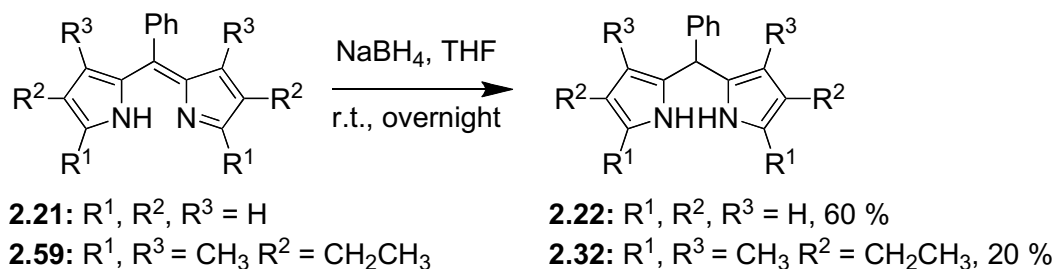
Scheme 2 - 19: Isomerization Resulting in Formal Deuteride Transfer



Polypyrrolic systems have also been demonstrated to tolerate reduction *via* use of NaBH_4 . The conversion of biliverdins to bilirubins,⁷²⁻⁷⁵ tripyrrenes to tripyrranes,⁷⁶ and conjugated tetrapyrrolic systems to phlorins^{77,78} have been reported to proceed by use of NaBH_4 .

For the purpose of comparing the microwave-assisted methodology described in this chapter to the reduction of dipyrins using a hydride source, dipyrins **2.21**, **2.56**, **2.56•HBr**, and **2.59**, were reacted with 1 equiv. of NaBH₄. *Meso*-phenyl substituted substrates were successfully reduced, although a much lower yield was observed when employing the fully substituted substrate **2.59** (Scheme 2 - 20). This was likely due to the relative instability of the resulting dipyrromethane, which auto-oxidized back to the dipyrin starting material in air. Working quickly during purification *via* column chromatography allowed for isolation of the dipyrromethane.

Scheme 2 - 20: NaBH₄ Mediated Reduction of *meso*-Phenyl Dipyrins



When employing 1 equiv. of NaBD₄ to reduce **2.21** to **2.22-d₁** (Scheme 2 - 21), it was found that hydride delivery exclusively occurs at the *meso*-position. The signal at 5.48 ppm in the ¹H NMR spectrum of **2.22-d₁** was decreased from the expected integration of 1H to only an integration of 0.03H (Figure 2 - 1) This confirms that this is the most electrophilic position on the dipyrin structure.

Scheme 2 - 21: Selective Deuteration of 2.21 using NaBD₄

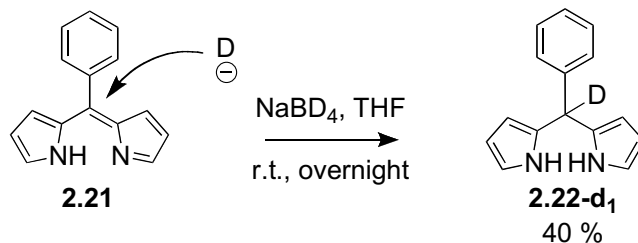
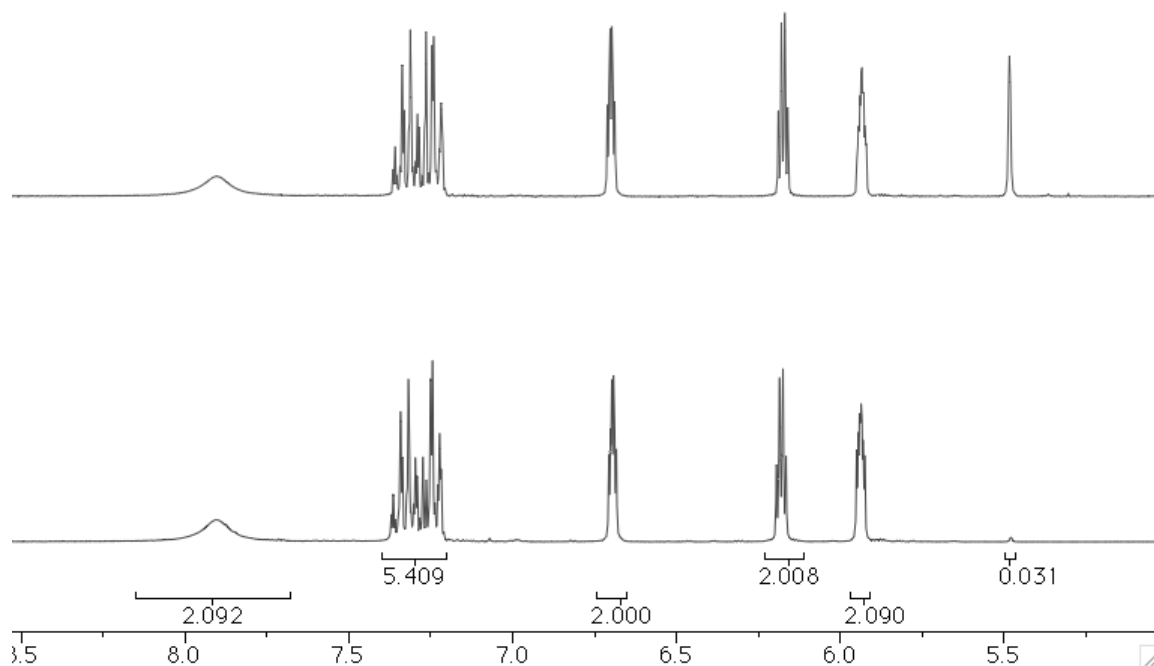


Figure 2 - 1: ^1H NMR Spectrum Showing Deuteration of 2.22 Using NaBD_4

TOP = *meso*-Phenyldipyrromethane (2.22)

BOTTOM = Deuterated *meso*-Phenyldipyrromethane (2.22- D_1)

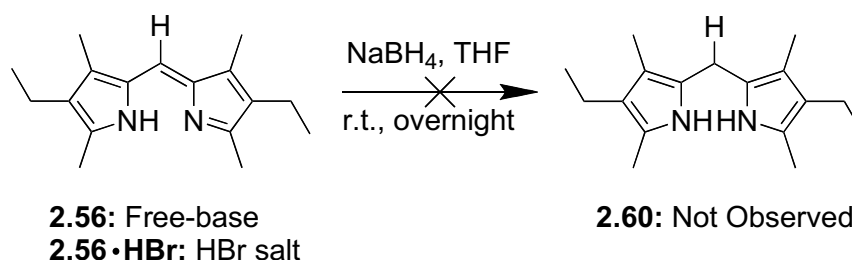


TOP: [shift (integration): δ 7.93 (2H), 7.20-7.35 (5H), 6.70 (2H), 6.17 (2H) 5.92 (2H), 5.48 (1H) ppm]

BOTTOM: [note ^1H signals reduced due to the incorporation of ^2H : δ 5.48 ppm]

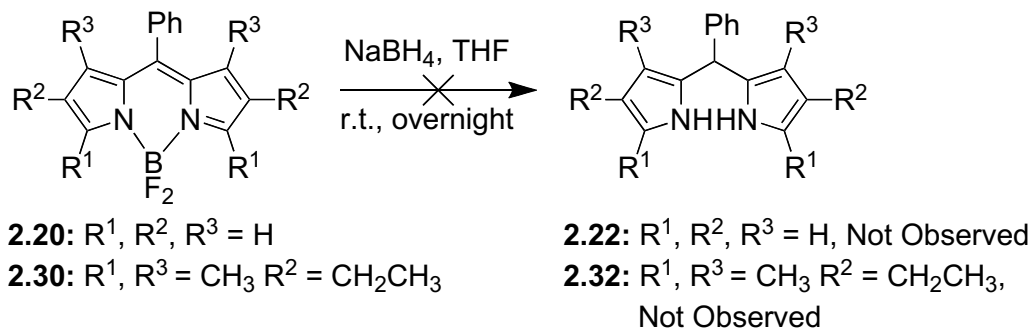
The NaBH_4 mediated reduction of a *meso*-H dipyrin was also investigated. The *meso*-H substrate (as its free-base **2.56**, or its HBr salt **2.56•HBr**, Scheme 2 - 22) was not successfully reduced by use of NaBH_4 , but that may be explained by the reduced electrophilicity of the *meso*-position. The anionic intermediate resulting from hydridic attack may not be as stabilized without the presence of a *meso*-phenyl group. In both cases, no reaction was observed and the majority of starting material (88 %) was recovered.

Scheme 2 - 22: Attempted NaBH₄ Mediated Reduction of *meso*-H Dipyrrens



F-BODIPYs **2.20** and **2.30** were also submitted to NaBH₄ reduction conditions (Scheme 2 - 23). The *F*-BODIPYs were anticipated to behave similarly to their parent dipyrrens, as was observed during reduction by use of the microwave-assisted conditions (ethylene glycol or benzyl alcohol with 3 equiv. sodium methoxide, 10 minutes, 215 °C). It was therefore surprising to discover that the reaction of an *F*-BODIPY with NaBH₄ resulted primarily in decomposition.

Scheme 2 - 23: Attempted NaBH₄ Mediated Reduction of *F*-BODIPYs

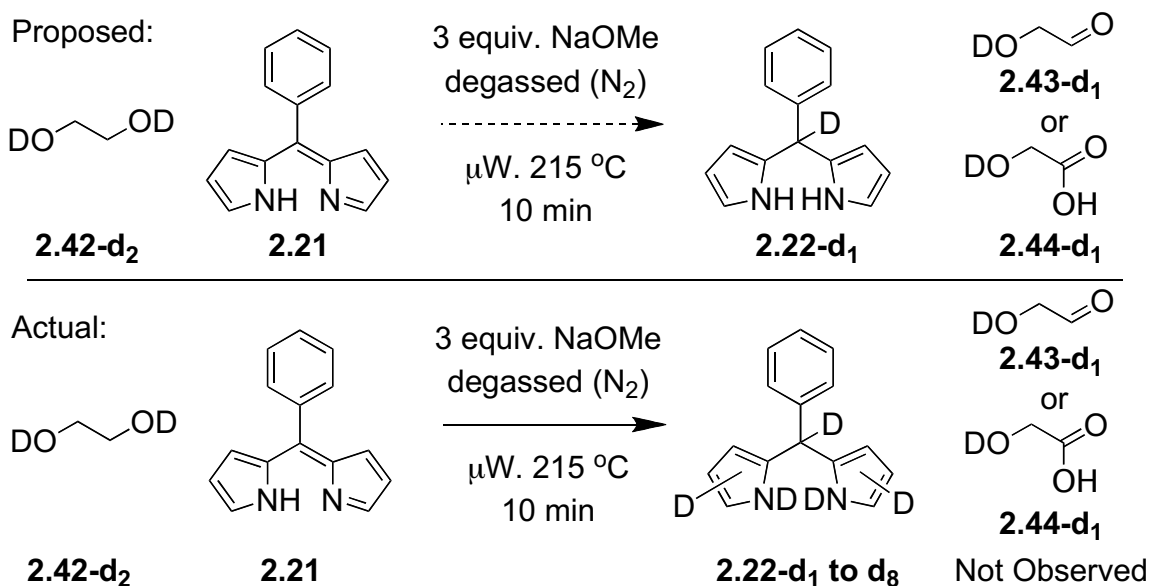


To rule out the possibility of radical delivery of a hydrogen atom to the dipyrren core during the microwave-assisted reduction reaction, 10 equiv. of 2-propanol-2-D₁ was added to the reaction mixture (**2.21**, DMF, NaOMe, 215 °C, 10 min). The deuterated *iso*-propanol would be more stabilized than ethylene glycol as a radical delivery agent, since it would form a tertiary radical byproduct and the ethylene glycol radical byproduct would be secondary. DMF was used in place of ethylene glycol to reduce competition of the dipyrromethane forming by means of the solvent, rather than the added *iso*-propanol. This experiment resulted in undeuterated **2.22** in a 10 % yield, which was actually lower

than what is achieved by employing DMF by itself (16 %, Table 2 - 1). This indicates that the reduction goes by hydride delivery rather than a radical mechanism.

When deuterated ethylene glycol (**2.42-d₂**, (DOCH₂)₂) was employed as solvent using the optimized methodology, deuterium was incorporated throughout the dipyrromethane skeleton. The deuterium incorporation displayed in the product mirrored deuterium/hydrogen exchange as seen in pyrrolic compounds.⁷⁹ Deuteration occurred throughout the dipyrin framework without appreciable selectivity, including at the *meso*-position (Scheme 2 - 24).

Scheme 2 - 24: Employing Ethylene Glycol-OD-d₂ as Solvent



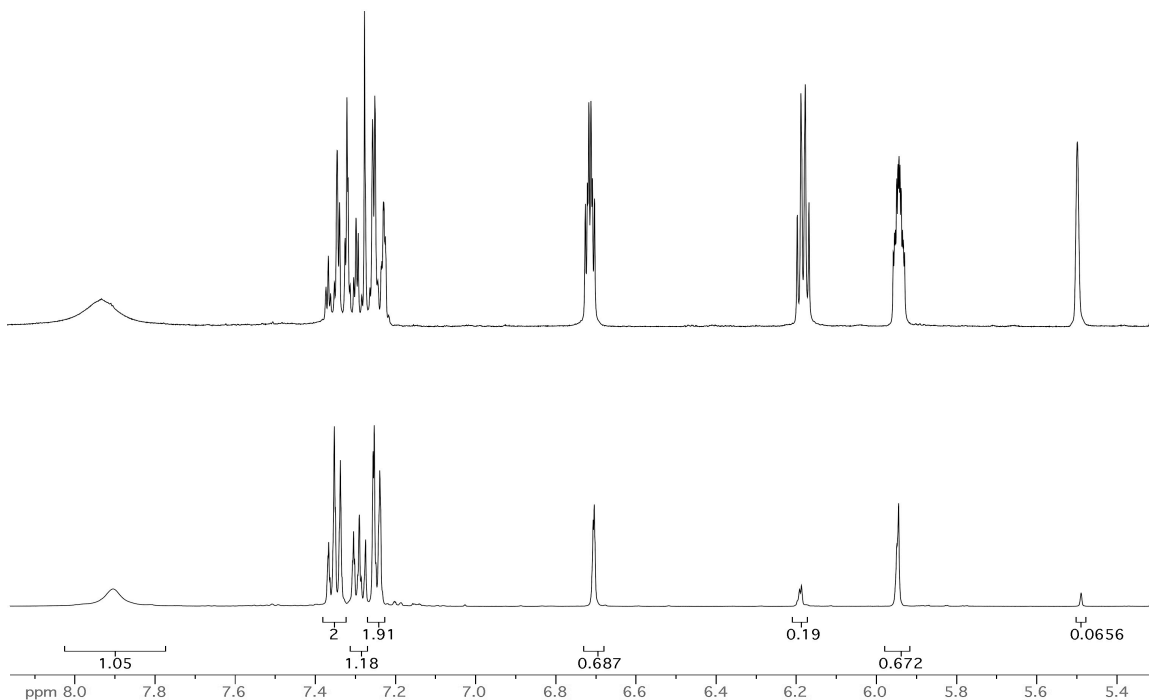
Given that the isomers were inseparable by column chromatography, ¹H NMR data was used to determine which isomers were present. Preferential incorporation was observed at the *meso*- (5.49 ppm) and β- (6.19 ppm) positions (5, and 2 / 8 respectively) of the dipyrromethane (Figure 2 - 2). The yield for the reaction employing deuterated solvent was relatively lower than that of the undeuterated reaction involving 3 equiv. of sodium methoxide in reagent grade ethylene glycol. The reaction employing non-deuterated solvent produced 35 mg of **2.22** from the reduction of 50 mg of **2.21**. In contrast, 23 mg of the collective dipyrromethane-d_x (**2.22-d_x**) isomers were obtained from the reduction of 50 mg of **2.21** in the presence of deuterated solvent. As a result,

deuterated benzyl alcohol was used instead as the solvent for the microwave assisted-reduction reaction.

Figure 2 - 2: ^1H NMR Spectrum Showing Deuteration of 2.22 by means of 2.42-d₂

TOP = *meso*-Phenyldipyrromethane (2.22)

BOTTOM = Deuterated *meso*-Phenyldipyrromethane (2.22-D_x)



TOP: [shift (integration): δ 7.93 (2H), 7.20-7.35 (5H), 6.70 (2H), 6.17 (2H), 5.92 (2H), 5.48 (1H) ppm]

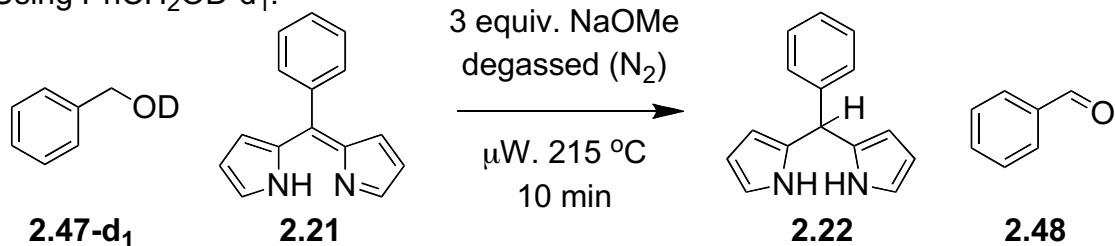
BOTTOM: [note ^1H signals reduced due to the incorporation of ^2H : δ 7.93, 6.70, 6.17, 5.92, 5.48 ppm]

Two structural isomers of deuterated benzyl alcohol were employed (Scheme 2 - 25). The effects of deuteration at the hydroxyl position of benzyl alcohol (PhCH₂OD, **2.47-d₁**) were compared with the effects of deuteration at the α -carbon (PhCD₂OH, **2.47-d₂**) while using both solvents under the optimized microwave-assisted reaction conditions. When benzyl alcohol-OD-d₁ (PhCH₂OD, **2.47-d₁**) was employed as the solvent using the optimized reduction methodology (**2.21**, NaOMe, 215 °C, 10 min), no incorporation of deuterium was observed (60 % yield of **2.22**). However, when benzyl alcohol-d₂ (PhCD₂OH, **2.47-d₂**) was used as the solvent, incorporation of deuterium was seen exclusively at the *meso*-position (37 % yield of compound **2.22-d₁**, Scheme 2 - 25).

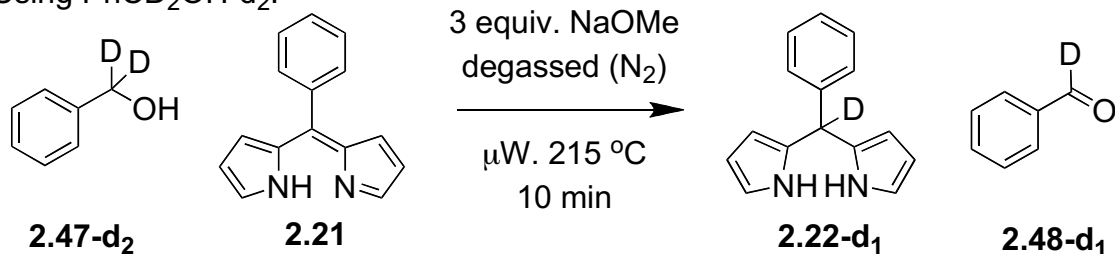
Incorporation of deuterium at the *meso*-position was comparable to that of the reduction of **2.21** with NaBD₄, and is the expected result of a nucleophilic hydride attack.

Scheme 2 - 25: Employing Benzyl Alcohol-d₁ or -d₂ as Solvent

Using PhCH₂OD-d₁:



Using PhCD₂OH-d₂:



All evidence thus far support the mechanistic hypothesis that the solvent is the redox partner in the reduction of a dipyririn or *F*-BODIPY to its corresponding dipyrromethane. In addition, hydride delivery was achieved *via* transfer of a hydrogen atom from the α -carbon of the solvent rather than from the hydroxyl moiety.

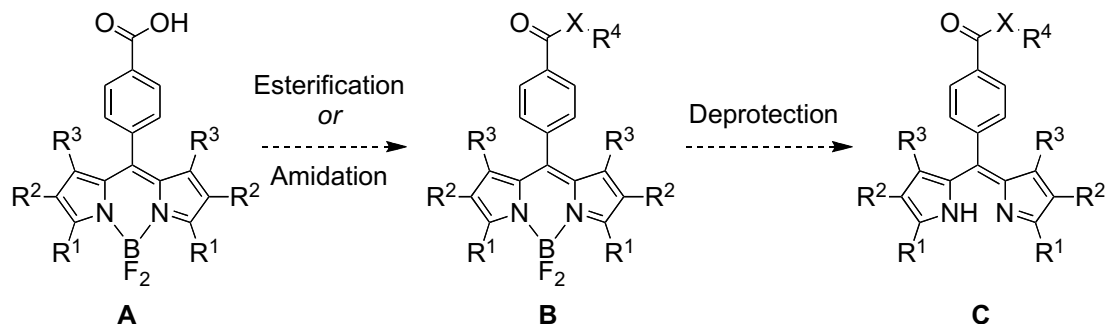
2.3 Conclusions and Future Directions

It has been demonstrated that *meso*-aryl *F*-BODIPYs and dipyrrens undergo reduction to produce their corresponding dipyrromethanes under basic, microwave-assisted conditions in the presence of excess ethylene glycol, benzyl alcohol, 4-methoxybenzyl alcohol, or 2-methoxyethanol at 215 °C. The redox partner appears to be the hydroxyl-containing solvent, which generates the corresponding aldehyde. Although the formation of dipyrromethanes *via* the condensation of pyrrole with aryl aldehydes can be high-yielding,⁸⁰ a viscous and difficult-to-manipulate reaction mixture is often received, which is complicated by the fact that pyrrole is often used as the reaction solvent.⁸¹⁻⁸³ These procedures often require cumbersome purification methods (high temperature vacuum distillation, multiple column chromatography purifications, unsuccessful recrystallizations, etc.). Alternatively, given that *F*-BODIPYs can be prepared using a simple one-pot process;^{6,84} the method described herein can be used as a synthetic strategy to produce dipyrromethanes *via* the respective *F*-BODIPY. This chapter also serves as a caution towards previously unobserved deleterious reactivity of BODIPYs and dipyrrens.

As the initial goal of this project was to check the viability of the use of *F*-BODIPYs as *N*-protected dipyrrens during a microwave-assisted transesterification, future work could involve the synthesis of a series of ester- and amide-appended *F*-BODIPYs (**A** to **B**, Scheme 2 - 26). With these substrates in hand, one of the deprotection strategies described in section 2.1.2 could be applied to afford the desired dipyrren (**B** to **C**). Relevant optimization of the chosen reaction would be required for efficient deprotection.

Scheme 2 - 26: Future Work

R¹ - R³ = H, alkyl, aryl, etc.
R⁴ = H, alkyl, aryl, etc.
X = O, N



Upon optimization, a wide variety of substituents could be screened for tolerance to the *N*-deprotection reaction. Any potential undesired reactivity that occurs during *N*-deprotection would be noted, to determine which substituents cannot be present on the parent dipyrroin during use of this strategy. After the tolerance is determined, efforts could be directed towards first using an *F*-BODIPY to establish the target substituent(s), followed by deprotection to reveal the parent dipyrroin.

2.4 Experimental

2.4.1 General Considerations

NMR spectra were recorded at the Atlantic Region Magnetic Resonance Centre (ARMRC). All ^1H and $^{13}\text{C}\{^1\text{H}\}$ NMR spectra were obtained using a 500 MHz NMR spectrometer (operating at 500 MHz and 125 MHz, respectively) and CDCl_3 as solvent, unless otherwise stated. Chemical shifts were recorded in parts per million (ppm) with internal reference to CDCl_3 (^1H NMR at 7.26 ppm, $^{13}\text{C}\{^1\text{H}\}$ NMR at 77.16 ppm), unless stated otherwise. $^{11}\text{B}\{^1\text{H}\}$ NMR spectra were obtained using a 500 MHz NMR instrument (operating at 160 MHz). Splitting patterns are indicated as follows: ad, apparent doublet; as, apparent singlet; br, broad; s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet. Coupling constants (J) are reported in units of Hertz (Hz). High and low resolution ESI⁺ mass spectra were recorded by Mr. Xiao Feng from ion trap (ESI TOF) instruments. All microwave-promoted reactions were performed using a Biotage Initiator 8 laboratory microwave apparatus. 0-400 W power, 2.45 GHz. Column chromatography was performed using Silicycle 230-400 mesh ultra pure silica or Brockman (III) basic alumina, as indicated. Crude solvents for column chromatography and extractions were distilled under 1 atm of pressure prior to use. All other chemicals were used as received. TLC analysis was performed on silica gel or neutral aluminum oxide plates, visualized using UV light (254 nm) and/or developed with Vanillin stain. Melting points were uncorrected, and are exclusively reported for novel compounds. Measurements for the crystal structure of **2.14** were made on a Rigaku RAXIS RAPID imaging plate area detector with graphite monochromated Mo-K_α radiation. The structures were solved by direct method⁸⁵ and expanded using Fourier techniques⁸⁶. Calculations were performed using the CrystalStructure^{87,88} crystallographic software package.

The following compounds were prepared according to literature procedures: 5-(4-methoxycarbonyl)phenyldipyrin,³⁵ 5-(4-trifluoromethyl)phenyldipyrromethane,⁸⁹ **2.20**,⁵⁰ **2.23**,⁹¹ **2.24**,⁹² **2.25**,⁹³ **2.26**,⁹¹ **2.28**,⁹³ **2.29**,⁹⁴ **2.30**,⁵¹ **2.35**,⁵⁰ **2.37**,⁹⁵ **2.40**,⁹⁴ **2.41**,⁹⁵ **2.56**•HBr,⁹⁶ and **2.59**.⁵⁰ The following compounds were prepared by other Thompson group members: **2.38**,⁵¹ **2.39**,⁵¹ and **2.56**.⁹⁷

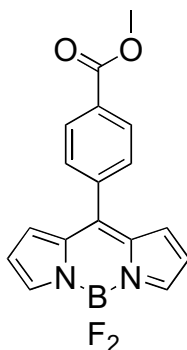
2.4.2 General Procedure (GP1) for the Synthesis of F-BODIPYs

The appropriate dipyrin or HBr/HCl dipyrin salt (1 equiv.) was treated with NEt₃ (6 equiv.) and BF₃•OEt₂ (9 equiv.) while stirring at room temperature in anhydrous dichloromethane [~0.04 M]. Upon complete consumption of the dipyrin, according to TLC analysis, the solvent was removed from the reaction mixture *in vacuo*. The crude dark red solid was dissolved in diethyl ether and washed twice with equal volume of 1 M HCl (to remove excess BF₃•OEt₂), followed by distilled water and then brine. The organic fraction was then reduced *in vacuo*, and the compound was purified using column chromatography (silica). Removal of the organic solvent *in vacuo* gave the product as a red/orange solid.

2.4.3 General Procedure (GP2) for the Synthesis of F-BODIPYs

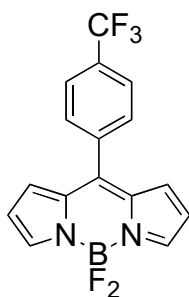
The appropriate dipyrromethane (1 equiv.) was treated with DDQ (1.1 equiv.) while stirring at room temperature in anhydrous dichloromethane [~0.12 M]. Upon complete consumption of the dipyrromethane according to analysis using TLC (i.e., conversion to the dipyrin, typically within 30-45 minutes), the reaction mixture was treated with NEt₃ (6 equiv.) and BF₃•OEt₂ (9 equiv.). Upon complete consumption of the dipyrin, according to analysis using TLC, the solvent was removed from the reaction mixture *in vacuo*. The crude dark red solid was dissolved in diethyl ether and washed twice with 1 M HCl (equal parts, to remove excess BF₃•OEt₂), followed by distilled water and then brine. The organic fraction was then reduced *in vacuo*, and the compound was purified using column chromatography (silica). Removal of the organic solvent *in vacuo* gave the product as a red/orange solid.

4,4-Difluoro-8-(4-methoxycarbonylphenyl)-4-bora-3a,4a-diaza-s-indacene (2.14)



Using GP1, the title compound was synthesized from 5-(4-methoxycarbonylphenyl) phenyldipyrin (0.542 g, 1.94 mmol) in 5.5 hours. The title compound was isolated as a red solid (0.483 g, 76 % yield) after column chromatography (silica – CH₂Cl₂). m.p.: 208–209 °C; ¹H (500 MHz, CDCl₃): δ 8.19 (d, 2H, *J* = 8), 7.96 (as, 2H), 7.64 (d, 2H, *J* = 8), 6.88 (ad, 2H), 6.56 (ad, 2H), 3.98 (s, 3H) ppm; ¹³C{¹H} (125 MHz, CDCl₃): δ 166.3, 145.9, 145.0, 138.1, 134.8, 132.3, 131.6, 130.5, 129.7, 119.1, 52.7 ppm; ¹¹B{¹H} (160 MHz, CDCl₃): δ 0.24 (t, *J* = 27) ppm; HRMS-ESI (*m/z*): [M + Na]⁺ Calcd 349.0936 for C₁₇H₁₃B₁F₂N₂O₂Na; found 349.0930. Crystal data for **2.14**: C₁₇H₁₃N₂BF₂O₂, MM = 326.11 g/mol, dark red needle 0.90 x 0.33 x 0.15 mm; primitive triclinic, space group P-1 (#2), a = 7.5380(7) Å, b = 7.8407(7) Å, c = 13.3682(7) Å, β = 77.62(4) °, V = 740.0 (2) Å³, Z = 2, ρ = 1.463 g/cm³, μ(MoKα) = 1.127 cm⁻¹, 53727 reflections (20535 unique, R_{int} = 0.029), R(F) = 0.0350, R_w(F) = 0.0487, GOF = 0.933. (“CCDC 949267” contains the X-ray data in CIF format for this manuscript. These data can be obtained, free of charge, via <http://www.ccdc.cam.ac.uk/products/csd/request>)

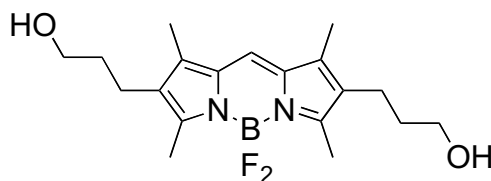
4,4-Difluoro-8-(4-trifluoromethylphenyl)-4-bora-3a,4a-diaza-s-indacene (2.27)



Using GP2, the title compound was synthesized from 5-(4-

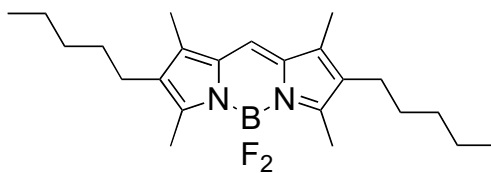
trifluoromethyl)phenyldipyrromethane (0.300 g, 1.03 mmol). The title compound was isolated as a red solid (0.166 g, 48 % yield) after column chromatography (silica – 20 % Et₂O/hexanes). m.p.: 188-190 °C; ¹H (500 MHz, CDCl₃): δ 7.94 (as, 2H), 7.77 (d, 2H, *J* = 8), 7.65 (d, 2H, *J* = 8), 6.83 (ad, 2H), 6.53 (ad, 2H) ppm; ¹³C {¹H} (125 MHz, CDCl₃): δ 145.2, 137.4, 134.9, 132.7 (q, *J* = 32), 131.5, 130.8, 130.1, 123.8 (q, *J* = 270, C-F), 125.6, 119.2 ppm; ¹¹B {¹H} (160 MHz, CDCl₃): δ 1.20 (t, *J* = 28) ppm; HRMS-ESI (*m/z*): [M + Na]⁺ Calcd 359.0755 for C₁₆H₁₀B₁F₅N₂O₂Na; found 359.0749.

4,4-Difluoro-1,3,5,7-tetramethyl-2,6-di-3-hydroxypropyl-4-bora-3a,4a-diaza-s-indacene (2.36)



Using GP1, the title compound was synthesized from **2.40** (0.450 g, 1.29 mmol) in 3 hours. The title compound was isolated as a red solid (0.090 g, 18 % yield) after column chromatography (silica – 5 % MeOH/CH₂Cl₂). m.p.: 164-165 °C; ¹H (500 MHz, CDCl₃): δ 6.92 (s, 1H), 3.62 (t, 4H, *J* = 6.5), 2.46 (s, 6H), 2.43 (t, 4H, *J* = 7.5), 2.14 (s, 6H), 1.64-1.70 (m, 4H), 1.24 (br s, 2H) ppm; ¹³C {¹H} (125 MHz, CDCl₃): δ 155.6, 137.9, 133.0, 129.8, 119.4, 62.7, 33.4, 20.7, 13.2, 10.2 ppm; ¹¹B {¹H} (160 MHz, CDCl₃): δ 0.86 (t, *J* = 34) ppm; HRMS-ESI (*m/z*): [M + Na]⁺ Calcd 387.2031 for C₁₉H₂₇B₁F₂N₂O₂Na; found 387.2026.

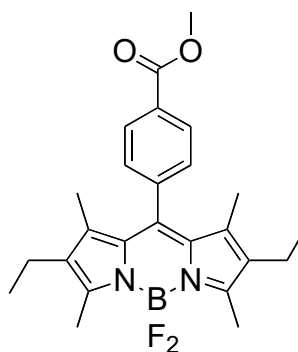
4,4-Difluoro-1,3,5,7-tetramethyl-2,6-dipentyl-4-bora-3a,4a-diaza-s-indacene (2.37)⁹⁶



Using GP1, the title compound was synthesized from **2.41** (0.250 g, 0.59 mmol) in 4 hours. The title compound was isolated as a red solid (0.122 g, 71 % yield) after column chromatography (silica – CH₂Cl₂). m.p.: 122-123 °C; ¹H (500 MHz, CDCl₃): δ ppm: 6.94

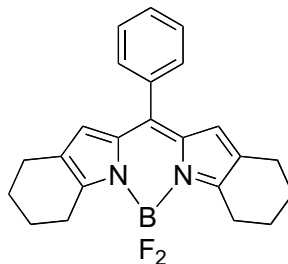
(s, 1H), 2.48 (s, 6H), 2.34 (t, 4H, $J = 4.5$), 2.15 (s, 6H), 1.40-1.46 (m, 4H), 1.27-1.36 (m, 8H), 0.90 (t, 6H, $J = 4$) ppm; $^{13}\text{C}\{^1\text{H}\}$ (125 MHz, CDCl_3): δ 155.0, 137.1, 132.6, 130.4, 118.7, 31.8, 30.0, 24.2, 22.7, 14.2, 12.8, 9.7 ppm; $^{11}\text{B}\{^1\text{H}\}$ (160 MHz, CDCl_3): δ 0.76 (t, $J = 35$) ppm; HRMS-ESI (m/z): $[\text{M} + \text{Na}]^+$ Calcd 411.2759 for $\text{C}_{23}\text{H}_{35}\text{B}_1\text{F}_2\text{N}_2\text{Na}$; found 411.2754.

4,4-Difluoro-1,3,5,7-tetramethyl-2,6-diethyl-8-(4-methoxycarbonylphenyl)-4-bora-3a,4a-diaza-s-indacene (2.29)⁹⁴



Using GP2, the title compound was synthesized from 1,3,7,9-tetramethyl-2,8-diethyl-5-(4-methoxycarbonylphenyl)dipyrromethane (2.39 g, 6.10 mmol) stepwise. Following GP2, the dipyrin formed in 45 minutes and was converted to the *F*-BODIPY in an additional 2 hrs. The title compound was isolated as a dark green solid (0.589 g, 22 % yield) after column chromatography (silica – CH_2Cl_2). m.p.: 225-227 °C; ^1H (500 MHz, CDCl_3): δ 8.17 (d, 2H, $J = 8$), 7.40 (d, 2H, $J = 8$), 3.98 (s, 3H), 2.53 (s, 6H), 2.29 (q, 4H, $J = 4.5$), 1.25 (s, 6H), 0.98 (t, 6H, $J = 4.5$) ppm; $^{13}\text{C}\{^1\text{H}\}$ (125 MHz, CDCl_3): δ 166.7, 154.4, 140.8, 138.8, 138.2, 133.2, 130.7, 130.4, 128.8, 52.5, 17.2, 14.7, 12.7, 12.0 (1 x C missing) ppm; $^{11}\text{B}\{^1\text{H}\}$ (160 MHz, CDCl_3): δ 0.65 (t, $J = 33$) ppm; HRMS-ESI (m/z): $[\text{M} + \text{Na}]^+$ Calcd 461.2188 for $\text{C}_{25}\text{H}_{29}\text{B}_1\text{F}_2\text{N}_2\text{Na}$; found 461.2182.

5,5-Difluoro-11-phenyl-5-bora-4b,5a-diaza-s-1,2,3,4,6,7,8,9-octahydroindeno[2,1-b]fluorene (2.33)

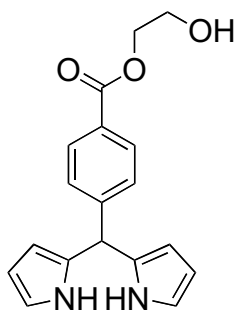


Tetrahydroindole (0.429 g, 3.54 mmol) and benzoyl chloride (0.205 mL, 1.77 mmol) were heated and stirred at reflux temperature in anhydrous 1,2-DCE (55 mL) for 48 hours. The solution was allowed to cool to room temperature, and then the *in situ* generated dipyrin was treated with NEt₃ (6 equiv.) and BF₃•OEt₂ (9 equiv.). Upon consumption of the dipyrin (monitored *via* TLC analysis, 1 hour), the solvent was removed from the reaction mixture *in vacuo*. The crude dark red solid was dissolved in diethyl ether and washed twice with 1M HCl (equal parts) to remove excess BF₃•OEt₂, followed by distilled water and then brine. The organic solvent volume was then reduced *in vacuo*, and the compound was purified using column chromatography (silica – 2 % Et₂O/hexanes). Removal of the organic solvent *in vacuo* gave the title compound as a red/orange solid (0.106 g, 16 % yield). Upon NMR analysis, it was noted that the compound was not pure. Purification was attempted *via* column chromatography (silica – 10 % EtOAc/hexanes, alumina – 10 % CH₂Cl₂/hexanes): these attempts proved to be unsuccessful and the sample was used without further purification. m.p.: 183-187 °C; ¹H (500 MHz, CDCl₃): δ 7.45-7.50 (m, 5H), 6.42 (s, 2H), 3.09 (t, 4H, *J* = 4), 2.50 (t, 4H, *J* = 4), 1.83-1.88 (m, 4H), 1.71-1.76 (m, 4H) ppm; ¹³C{¹H} (125 MHz, CDCl₃): δ 157.5, 141.1, 134.8, 133.9, 130.4, 129.7, 129.4, 128.2, 126.6, 24.8, 23.3, 23.0, 22.5 ppm; ¹¹B {¹H} (160 MHz, CDCl₃): δ 0.58 (t, *J* = 33) ppm; HRMS-ESI (*m/z*): [M + Na]⁺ Calcd 399.1820 for C₂₃H₂₃B₁F₂N₂Na; found 399.1815.

2.4.4 General Procedure (GP3) for the Microwave-Assisted Deprotection and Reduction of *F*-BODIPYs

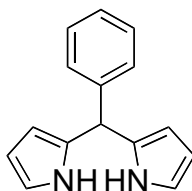
F-BODIPY (0.050 g, 1 equiv.) was added to a solution of NaOMe (3 equiv.) and ethylene glycol (3 mL) in a Biotage microwave vial with 2-5 mL capacity, and was sealed using a crimper on a cap that featured a septum. The reaction mixture was degassed by bubbling with N₂ for 15 minutes, and then it was heated and stirred at 215 °C for 10 minutes in a Biotage microwave system. Since the system employed was computer automated, the parameters were defined using the provided software for vial size (2-5 mL), solvent absorbance level (high), magnetic stirring (on), time (10 minutes) and temperature (215 °C). After cooling to room temperature, the reaction mixture was dissolved in CH₂Cl₂ (50 mL) and washed with water (50 mL x 3). The organic layer was dried with anhydrous Na₂SO₄, concentrated *in vacuo* and purified *via* column chromatography (alumina), to give a (semi-)solid.

5-((4-(2-Hydroxy)ethoxycarboxy)phenyl)dipyrrromethane (2.19)



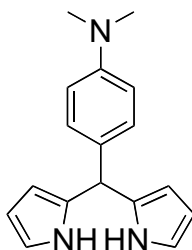
Using GP3, the title compound was synthesized from 4,4-difluoro-8-(4-methoxycarbonylphenyl)-4-bora-3a,4adiaza-s-indacene (**2.14**). The title compound was isolated as a dark semi-solid (0.029 g, 68 % yield) after column chromatography (alumina – 0→10 % MeOH/CH₂Cl₂). m.p.: 55-57 °C; ¹H (500 MHz, CDCl₃): δ 8.02 (br s, 2H), 7.89 (d, 2H, *J* = 9), 7.19 (d, 2H, *J* = 9), 6.62-6.64 (m, 2H), 6.07-6.08 (m, 2H), 5.79 (as, 2H), 5.43 (s, 1H), 4.33-4.35 (m, 2H), 3.83-3.85 (m, 2H) ppm; ¹³C{¹H} (125 MHz, CDCl₃): δ 166.9, 147.9, 131.7, 130.1, 128.60, 128.56, 117.7, 108.6, 107.6, 66.7, 61.4, 44.1 ppm; HRMS-ESI (*m/z*): [M + Na]⁺ Calcd 333.1215 for C₁₈H₁₈N₂O₃Na; found 333.1210.

5-Phenyldipyrromethane (2.22)



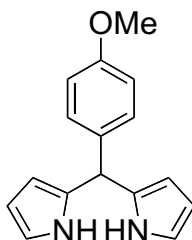
Using GP3, the title compound was synthesized from 4,4-difluoro-8-phenyl-4-bora-3a,4a-diaza-s-indacene (**2.20**). The title compound was isolated as a dark beige solid (0.028 g, 68 % yield) after column chromatography (alumina – 10 % Et₂O/hexanes). ¹H (500 MHz, CDCl₃): δ 7.93 (br s, 2H), 7.20-7.35 (m, 5H), 6.70 (d, 2H, *J* = 6), 6.17 (d, 2H, *J* = 7) 5.92 (d, 2H, *J* = 6), 5.48 (s, 1H) ppm. Spectral and physical properties were in agreement with previously reported data.⁸⁰

5-(4-Dimethylamino)dipyrromethane



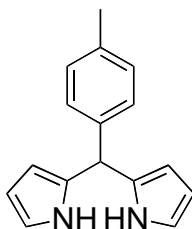
Using GP3, the title compound was synthesized from 4,4-difluoro-8-(4-dimethylaminophenyl)-4-bora-3a,4a-diaza-s-indacene (**2.23**). The title compound was isolated as a dark beige solid (0.020 g, 47 % yield) after column chromatography (alumina – 10→20 % EtOAc/hexanes). ¹H (500 MHz, CDCl₃): δ 7.90 (br s, 2H), 7.09 (d, 2H, *J* = 9), 6.70 (d, 2H, *J* = 9), 6.66-6.72 (m, 2H), 6.15-6.17 (m, 2H), 5.93-5.96 (m, 2H), 5.39 (s, 1H), 2.94 (s, 6H) ppm. Spectral and physical properties were in agreement with previously reported data.⁹⁸

5-(4-Methoxyphenyl)dipyrromethane



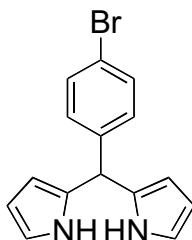
Using GP3, the title compound was synthesized from 4,4-difluoro-8-(4-methoxyphenyl)-4-bora-3a,4adiazas-indacene (**2.24**). The title compound was isolated as a dark beige solid (0.034 g, 76 % yield) after column chromatography (alumina – 10 % EtOAc/hexanes). ^1H (500 MHz, CDCl_3): δ 7.89 (br s, 2H), 7.14 (d, 2H, $J = 9$), 6.86 (d, 2H, $J = 9$), 6.68 (ad, 2H), 6.16 (ad, 2H), 5.92 (as, 2H), 5.42 (s, 1H), 3.80 (s, 3H) ppm. Spectral and physical properties were in agreement with previously reported data.⁸⁰

5-(4-Methylphenyl)dipyrromethane



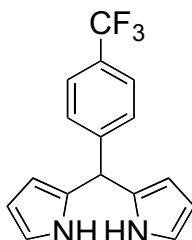
Using GP3, the title compound was synthesized from 4,4-difluoro-8-(4-methylphenyl)-4-bora-3a,4adiazas-indacene (**2.25**). The title compound was isolated as a dark beige solid (0.026 g, 63 % yield) after column chromatography (alumina – 5→10 % EtOAc/hexanes). ^1H (500 MHz, CDCl_3): δ 7.89 (br s, 2H), 7.08-7.15 (m, 4H), 6.66-6.69 (m, 2H), 6.15 (q, 2H), 5.91-5.93 (as, 2H), 5.43 (s, 1H), 2.34 (s, 3H) ppm. Spectral and physical properties were in agreement with previously reported data.⁸⁰

5-(4-Bromophenyl)dipyrromethane



Using GP3, the title compound was synthesized from 4,4-difluoro-8-(4-bromophenyl)-4-bora-3a,4-diaza-s-indacene (**2.26**). The title compound was isolated as a dark beige solid (0.023 g, 61 % yield) after column chromatography (alumina – 10→20 % EtOAc/hexanes). ^1H (500 MHz, CDCl_3): δ 7.92 (br s, 2H), 7.44 (d, 2H, $J = 9$), 7.19 (d, 2H, $J = 9$), 6.70-6.72 (m, 2H), 6.16-6.19 (m, 2H), 5.87-5.91 (m, 2H), 5.43 (s, 1H) ppm. Spectral and physical properties were in agreement with previously reported data.⁸⁹

5-(4-Trifluoromethylphenyl)dipyrromethane



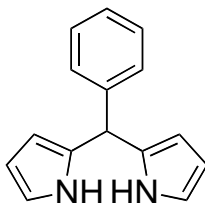
Using GP3, the title compound was synthesized from 4,4-difluoro-8-(4-trifluoromethylphenyl)-4-bora-3a,4-diaza-s-indacene (**2.27**). The title compound was isolated as a dark beige semi-solid (0.021 g, 53 % yield) after column chromatography (alumina – CH_2Cl_2). ^1H (500 MHz, CDCl_3): δ 7.97 (br s, 2H), 7.59 (d, 2H, $J = 8$), 7.35 (d, 2H, $J = 8$), 6.74 (as, 2H), 6.17-6.19 (m, 2H), 5.90 (as, 2H), 5.53 (s, 1H) ppm. Spectral and physical properties were in agreement with previously reported data.⁸⁹

5.2.4 General Procedure (GP4) for the NaBH_4 Mediated Reduction of Dipyrins to Dipyrromethanes

Sodium borohydride (1 equiv.) was added under a flow of N_2 to a solution of dipyrin (0.050 g, 1 equiv.) and anhydrous THF (1.5 mL). The reaction mixture was stirred at

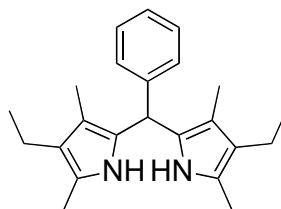
room temperature overnight and quenched with dilute aqueous HCl (30 mL). The resulting solution was extracted with CH₂Cl₂ (3 x 30 mL) and the combined organic phase was washed with water (90 mL), brine (90 mL), dried with anhydrous NaSO₄ and concentrated *in vacuo*. Purification was achieved *via* column chromatography to produce a solid.

5-Phenyldipyrromethane (2.22)



Using GP4, the title compound was synthesized from 5-phenyldipyrin (**2.21**). The title compound was isolated as a beige solid (0.030 g, 60 % yield) after column chromatography (silica – CH₂Cl₂). ¹H (500 MHz, CDCl₃): δ 7.93 (br s, 2H), 7.20-7.35 (m, 5H), 6.70 (d, 2H, *J* = 6), 6.17 (d, 2H, *J* = 7) 5.92 (d, 2H, *J* = 6), 5.48 (s, 1H) ppm. Spectral and physical properties were in agreement with previously reported data.⁸⁰

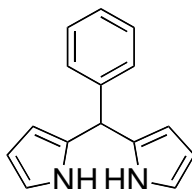
2,8-Diethyl-5-phenyl-1,3,7,9-tetramethyl-dipyrromethane (2.32)⁹⁹



Using GP4, the title compound was synthesized from 2,8-diethyl-5-phenyl-1,3,7,9-tetramethyl-dipyrin (**2.59**). The title compound was isolated as a pink solid (0.010 g, 20 % yield) after column chromatography (silica – CH₂Cl₂). ¹H (300 MHz, CDCl₃): δ 7.13-7.30 (m, 5H), 7.04 (br s, 2H), 5.42 (s, 1H) 2.36 (q, 4H, *J* = 8), 2.08 (s, 6H), 1.77 (s, 6H), 1.05 (t, 6H, *J* = 8) ppm. HRMS-ESI (*m/z*): [M + Na]⁺ calcd. for C₂₃H₃₀N₂Na: 357.2301; found: 357.2305. Note: this compound readily oxidizes to the corresponding dipyrin (orange/red solid) and therefore, full characterization was not possible.

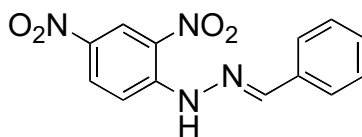
2.4.5 Miscellaneous

5-Phenyldipyrromethane (2.22)



5-Phenyldipyrin (**6**, 0.050 g, 0.227 mmol) was added under a flow of N₂ to a stirring solution of aqueous Na₂S₂O₄/THF (0.395 g in 1 mL of H₂O and 3 mL of THF). The reaction mixture was allowed to stir at room temperature for 10 minutes, where the solvent was removed azeotropically using toluene (2 × 50 mL) and the resulting oil was separated between CH₂Cl₂ (50 mL) and water (50 mL). The aqueous layer was extracted using CH₂Cl₂ (50 mL × 2) and then the combined organic layers were dried over Na₂SO₄ and concentrated in vacuo. The crude mixture was then purified over neutral Brockman III alumina – 10 % → 20 % Et₂O/hexanes. 5-Phenyldipyrromethane was isolated as a beige solid (0.005 g, 10 % yield). ¹H NMR (500 MHz, CDCl₃) δ: 7.93 (br s, 2H), 7.20–7.35 (m, 5H), 6.70 (d, 2H, *J* = 6), 6.17 (d, 2H, *J* = 7), 5.92 (d, 2H, *J* = 6), 5.48 (s, 1H). Spectral and physical properties were in agreement with previously reported data.⁸⁰

1-Benzylidene-2-(2,4-dinitrophenyl)hydrazone (2.49)



After microwave irradiation (10 minutes, 215 °C) of 5-phenyldipyrin (**2.21**) (0.050 g, 0.23 mmol) and NaOMe (0.037 g, 0.68 mmol) in benzyl alcohol (**2.47**), a solution of 2,4-DNPH (2.5 equiv.) in acidic methanol (25:1 MeOH/sulfuric acid) was added directly to the reaction mixture, which was then stirred at room temperature for 3 hours. The resulting yellow precipitate was isolated *via* suction filtration (0.035 g, 66 % yield). ¹H (500 MHz, CDCl₃): δ 11.32 (s, 1H), 9.16 (s, 1H), 8.37 (d, 1H, *J* = 10), 8.13 (d, 1H, *J* =

10), 8.09 (s, 1H), 7.75-7.80 (m, 2H), 7.46-7.50 (m, 3H) ppm. Spectral and physical properties were in agreement with previously reported data.⁶²

2.5 References for Chapter 2

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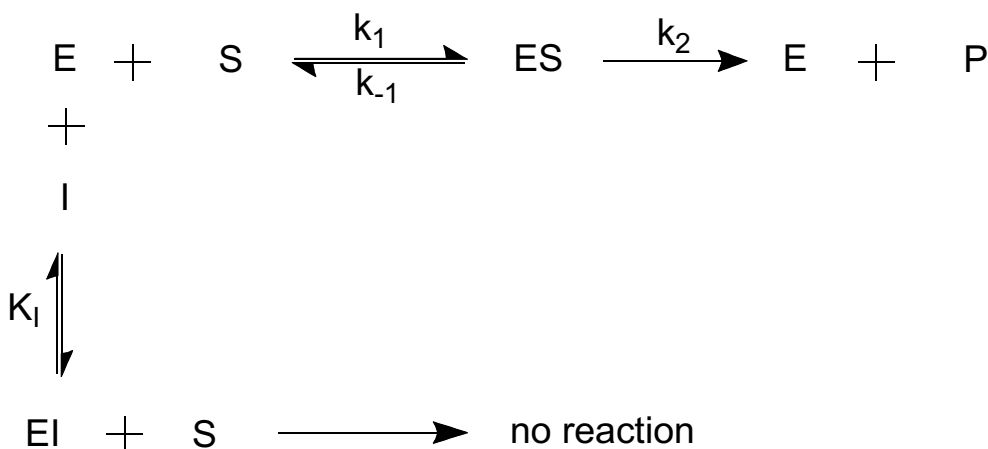
Chapter 3 An Investigation of the Stability of α -Difluoromethyl Pyrroles

3.1 Background

3.1.1 URO-D Enzyme Function and Inhibition

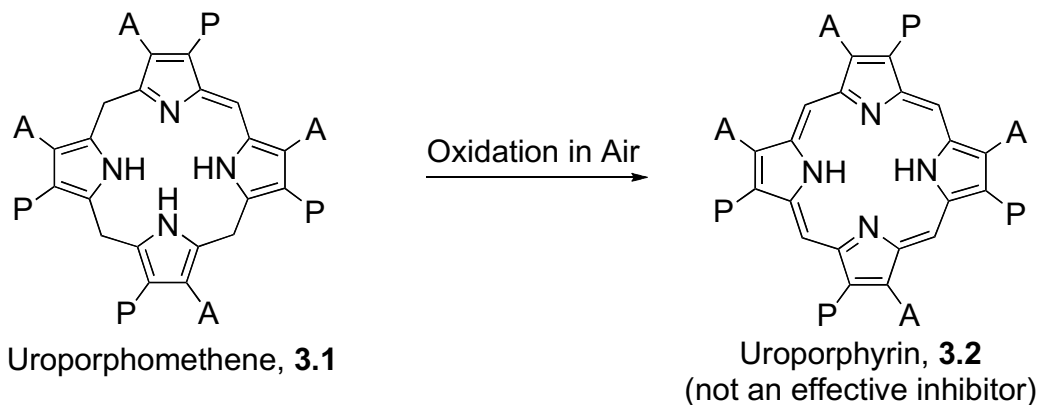
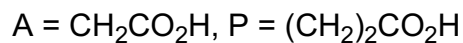
Competitive inhibition occurs when the inhibitor (**I**, Scheme 3 - 1) has an affinity for the active enzyme site (**E**) and thereby competes with the native substrate (**S**).¹ This interaction creates a competing pathway that prevents the native substrate from forming the expected enzyme-substrate complex (**ES**) or the product (**P**), as an enzyme-inhibitor complex (**EI**) forms instead.

Scheme 3 - 1: General Pathway of Competitive Inhibition



The inhibitor of interest for this chapter is uroporphomethene (**3.1**, Scheme 3 - 2). Uroporphomethene is a known competitive inhibitor of the enzyme uroporphyrinogen decarboxylase (URO-D), which is involved in the biosynthesis of heme.² This tetrapyrrolic compound possesses a double bond on one of the bridgehead carbons. Further oxidation of **3.1** leads to uroporphyrin (**3.2**, Scheme 3 - 2), which displays no inhibition of URO-D.² It has been reported that inhibition of URO-D is linked to increased response of cancerous cells to radiotherapy.³ Therefore, inhibitors of this enzyme have potential in the development of cancer treatments, along with treatments of other physiological complaints that involve abnormal heme biosynthesis.

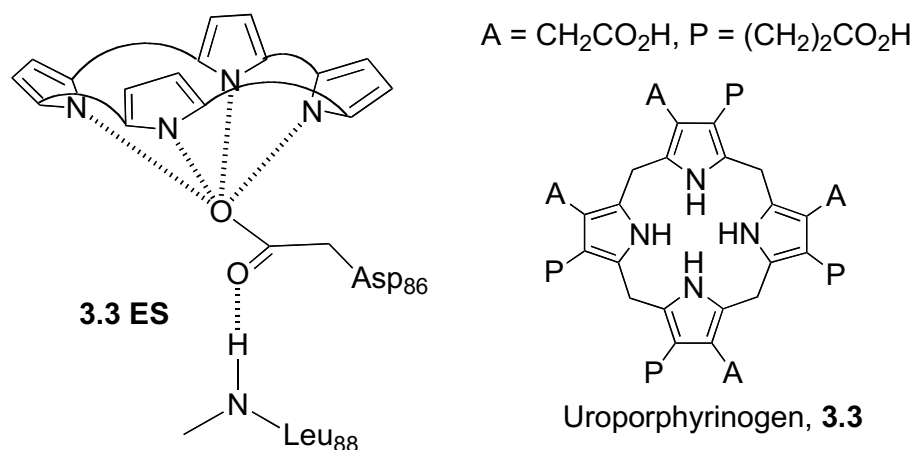
Scheme 3 - 2: Unwanted Oxidation of Uroporphomethene in Air



The oxidation of **3.1** occurs spontaneously in air.² This auto-oxidation process is grounded in the thermodynamic drive towards aromaticity.⁴ This is a longstanding challenge among scientists studying tetrapyrrolic systems saturated at the bridgehead positions. Porphomethene intermediates (like **3.1**) auto-oxidize to their inherently more stable conjugated systems (like porphyrin **3.2**), making the intermediates extremely difficult to isolate.

One strategy to overcome unwanted auto-oxidation is to replace the -CH₂- bridgehead hydrogen atoms of **3.1** with atoms or groups that cannot easily be removed. In addition to possessing stability in air, the modified porphomethene must also bind to the enzyme active site to act as a competitive inhibitor of URO-D. The native enzymatic substrate of URO-D, uroporphyrinogen I/III (**3.3**), adopts a 3-dimensional structure whereby the four pyrrolic units face downwards to interact with aspartic acid 86 (Asp86) and leucine 88 (Leu88) in the enzyme active site (as shown in Figure 3 - 1).⁵ This conformational ability must be maintained in any potential inhibitor.

Figure 3 - 1: Schematic of Uroporphyrinogen III Interacting with URO-D

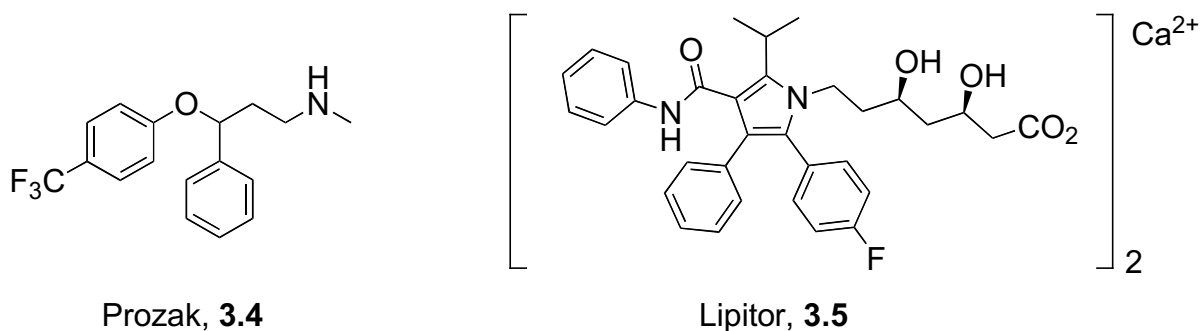


3.1.2 Isosteric Replacements in Biologically Relevant Molecules

There are many functional groups that qualify as a biologically tolerated replacement for a hydrogen atom substituent, but some discernment was required to select the ideal candidate. The notion of effecting substitution *via* tuning physical and biological properties is well documented, as the concept has been widespread across chemistry for almost a century. In 1919, Langmuir predicted the physical properties of the ketene functionality two decades before it was isolated based on its resemblance to a diazomethyl group, stating that the two functionalities were “isosteres”.⁶ A decade later, Erlenmeyer noted that antibodies had difficulty discerning between phenyl and thienyl rings, as well as between -CH₂- as a methylene moiety, oxygen as an ether moiety, and -NH- as an amine moiety.^{7,8} Based on this idea that a biological system cannot discern equivocally among certain functionalities, an entire field has developed.

There are several functionalities that can be used as a hydrogen isostere: D, F, Cl, Br, and methyl are the most common.⁹ In medicinal chemistry, fluorine has proved to be a very useful hydrogen isostere. Fluorine is the most electronegative element. Consequently, carbon-fluorine bonds are very strong. A carbon-fluorine bond has a bond energy of 485 kJ/mol, versus a carbon-carbon bond or a carbon-hydrogen bond which are 346 kJ/mol or 411 kJ/mol, respectively.¹⁰ Two examples of fluorinated compounds developed through the pharmaceutical industry are Prozac (3.4)¹¹ and Lipitor (3.5).¹²

Figure 3 - 2: Fluorinated Pharmaceuticals

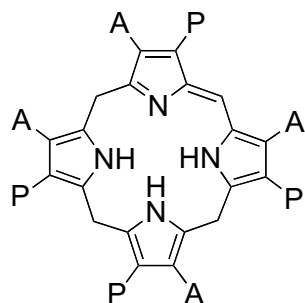


Fluorine is a relatively small atom in comparison to the other halogens, or to a methyl group. This is especially important to note in cases where the 3-dimensional structure of the isostere needs to remain consistent with the original compound. However, fluorine is not a perfect hydrogen replacement. The carbon-fluorine bond (1.41 Å) is longer than the carbon-hydrogen bond (1.09 Å), and the electronic properties between the two atoms are vastly different.¹³ Despite these differences, fluorine is still generally well-tolerated as a hydrogen isostere.

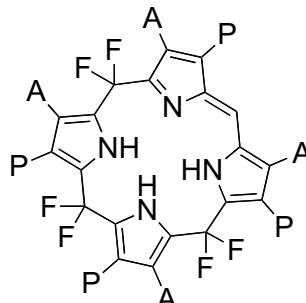
The installation of a difluoromethyl group (-CF₂H)¹⁴⁻¹⁶ or a difluoromethylene moiety (-CF₂-)¹⁷ was of particular interest with respect to the project described within this thesis, as these moieties are isosteres to a methyl group and a methylene moiety, respectively. Indeed, interchanging the -CH₂- bridgehead hydrogen atoms in **3.1** for fluorine atoms was predicted to produce an isosteric inhibitor (**3.6**, Figure 3 - 3). Additionally, the proposed -CF₂- bridgehead linkers should also stabilize uroporphomethene from the unwanted oxidation that would result in the corresponding uroporphyrin.

Figure 3 - 3: Uroporphomethene Isostere

A = CH₂CO₂H, P = (CH₂)₂CO₂H



Uroporphomethene, **3.1**



Uroporphomethene Isostere, **3.6**

3.1.3 Fluorinating Agents

Although there are many fluorinating agents, this report will focus on the generation of *gem*-difluoro substituents. Such difluoromethyl groups can be produced by, but are not limited to, one of the following methods (Figure 3 - 4): (i) difluorination of an aldehyde using popular nucleophilic deoxofluorination agents such as DAST (**3.7**, (diethylamino)sulfur trifluoride, Figure 3 - 5),^{18,19} Xtalfluor-E® (**3.8** (diethylamino)difluorosulfonium tetrafluoroborate, Figure 3 - 5),²⁰ Xtalfluor-M® (**3.9**, morpholinodifluorosulfonium tetrafluoroborate)²⁰ or Deoxo-Fluor® (**3.10**, bis(2-methoxyethyl)aminosulfur trifluoride),²¹ (ii) copper-catalyzed cross-coupling, followed by decarboxylation;²² (iii) radical debromination of a bromodifluoromethyl group (-CF₂Br);^{22,23} and (iv) direct difluoromethylation using bis(((difluoromethyl)sulfinyl)oxy)zinc (**3.11**, Zn(DFMS)).²⁴

Figure 3 - 4: Strategies Towards Installing a -CF₂H Group

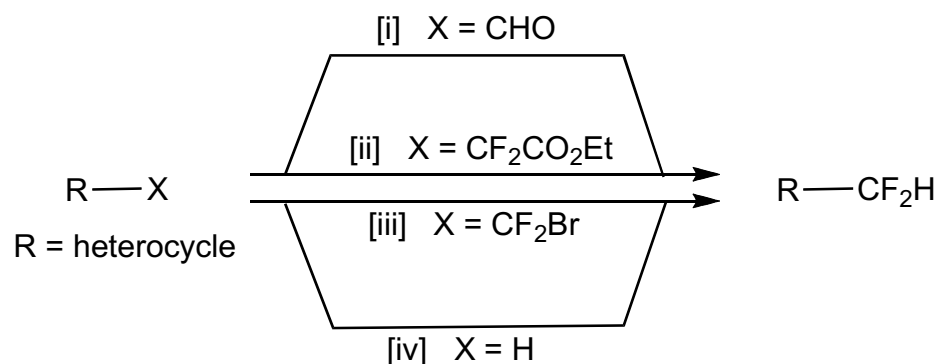
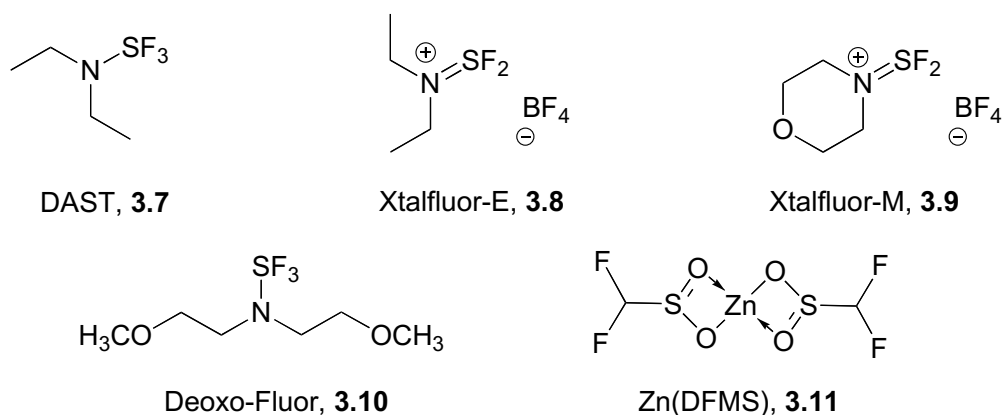


Figure 3 - 5: Examples of Deoxofluorinating Agents



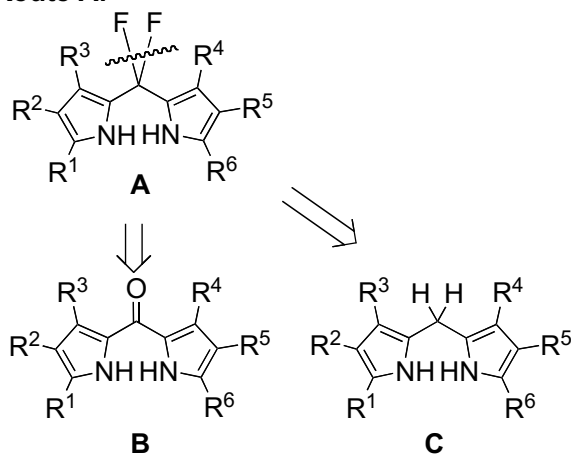
3.1.4 Disconnection Strategies Towards a Porphomethene Isostere

Two strategies were employed in attempt to assemble a model dipyrrolic system (**A**, Scheme 3 - 3). Route A uses dipyrrolic starting material to build the model system **A**. Using this strategy, a dipyrrolylketone (**B**) was reacted with a nucleophilic source of fluorine. Alternatively, an electrophilic source of fluorine was reacted with a dipyrromethane (**C**) in attempt to build difluorodipyrromethane **A**.

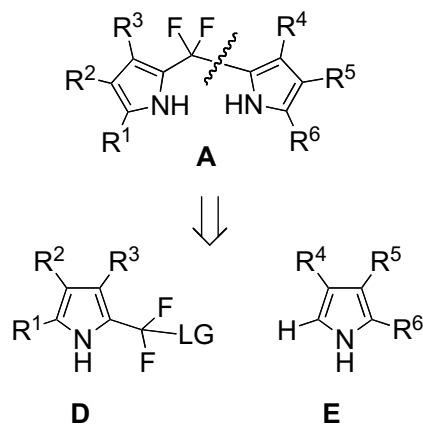
In contrast, route B employs a monopyrrole for fluorination in place of a dipyrrole. The difluorodipyrromethane (**A**) was proposed to subsequently form by reacting fluorinated pyrrole **D** with α -free pyrrole **E**. The uroporphomethene isostere was to be built using the route that saw the most success in building the model system.

Scheme 3 - 3: Disconnection Strategies Towards a Model Difluorodipyrromethane

Route A:



Route B:

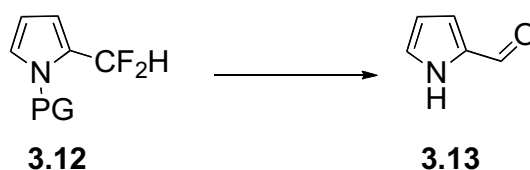


R¹⁻⁶ = H, alkyl, aryl, acyl, ester, etc.

3.1.5 Project Direction

The initial goal of the work presented within this chapter was to develop a methodology that could be applied to the installation of *gem*-difluoromethylene moieties in porphomethenes related to heme. The synthesis of a tetrapyrrolic system containing the desired *gem*-difluoromethylene moieties proved to be difficult, due to the inherent electronic properties of pyrroles and the resultant instability of the fluoro-substituted pyrrolic skeleton. In short, the difluoromethyl group, when substituted onto the α -position of pyrroles, proved only to be stable when an *N*-protecting group was in place (3.12). Removal of the protecting group resulted in hydrolysis of the difluoromethyl group to give 2-formyl pyrrole (3.13). Presented herein are the results pertaining to the study of this reactivity.

Scheme 3 - 4: Hydrolysis of the -CF₂H Upon Removal of the *N*-Protecting Group



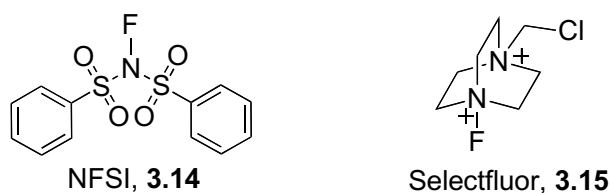
PG = *N*-protecting group

3.2 Results and Discussion

3.2.1 Attempted Synthesis of a Difluorodipyrromethane from Dipyrrolic Compounds

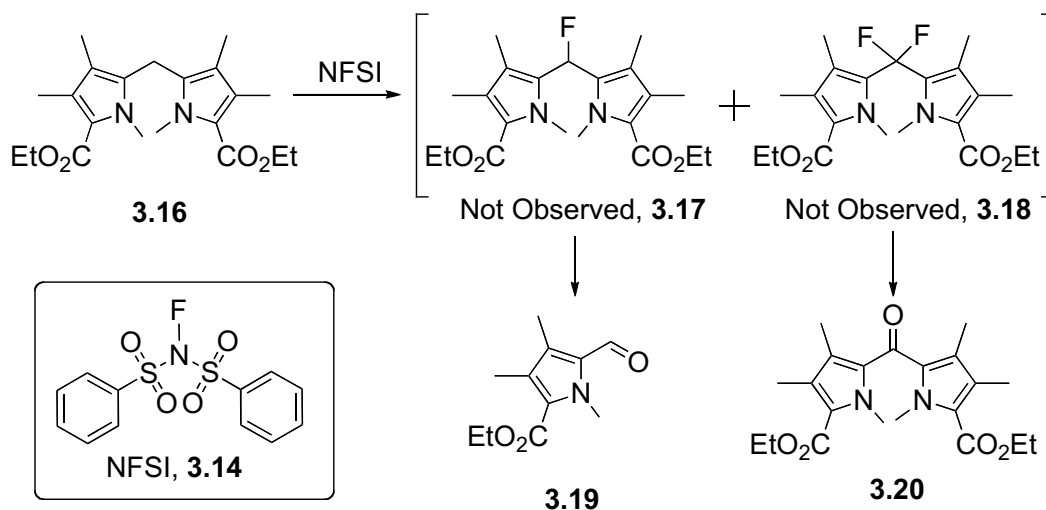
Previous attempts in the Thompson group to build the model difluorodipyrromethane used two strategies.²⁵ The first approach was to employ electrophilic fluorinating reagents on dipyrromethanes (Scheme 3 - 5).²⁵ Attempts to install a -CF₂- moiety by use of electrophilic fluorinating reagents such as *N*-fluorobenzenesulfonimide (NFSI, **3.14**, Figure 3 - 6) or Selectfluor® (**3.15**) on a *meso*-unsubstituted dipyrromethane resulted in the generation of multiple unisolated products and/or decomposition.²⁵

Figure 3 - 6: Two Examples of Electrophilic Fluorinating Agents



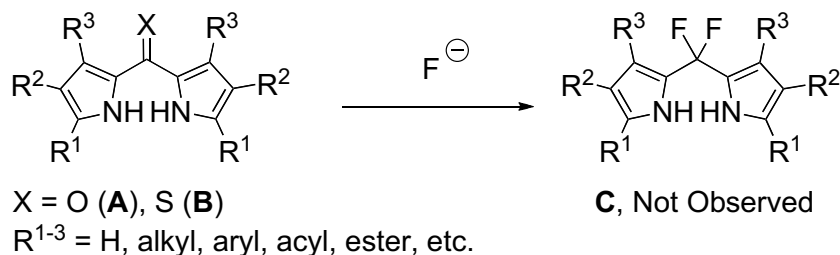
However, incorporating *N*-protecting groups on the *meso*-unsubstituted dipyrromethane (**3.16**) allowed for the isolation of oxidation products. These products could have formed first as the mono- (**3.17**) and difluorinated (**3.18**) intermediates, and then undergone hydrolysis resulting in the isolation of aldehyde **3.19** and dipyrrolylketone **3.20**, respectively (Scheme 3 - 5).²⁵

Scheme 3 - 5: Attempted Electrophilic Fluorination of *N*-Protected Dipyrromethane using NFSI



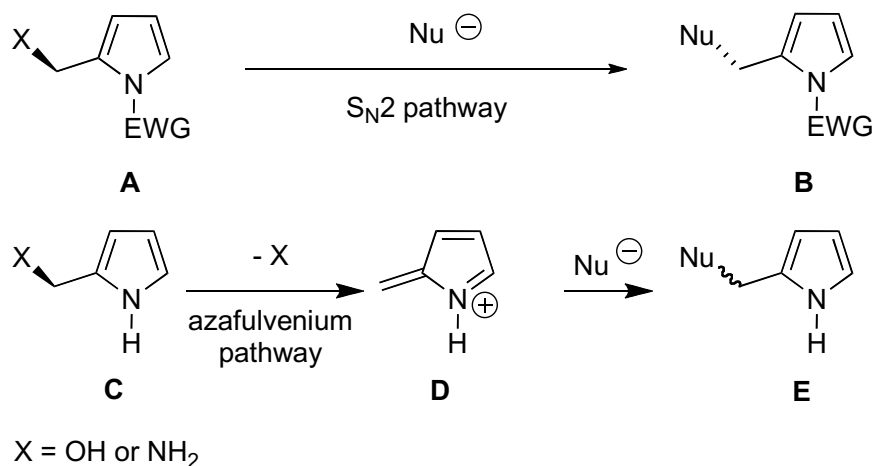
The second approach was to employ nucleophilic fluorinating agents on dipyrrolylketones or thioketones. Attempts to produce the -CF₂- moiety *via* nucleophilic fluorinating reagents such as Deoxo-Fluor® (3.10), DAST (3.7), and Xtalfluor-E® resulted in the recovery of starting material and/or decomposition products in all cases (Scheme 3 - 6).²⁵

Scheme 3 - 6: Attempted Nucleophilic Fluorination of Dipyrrolylketones or Thioketones



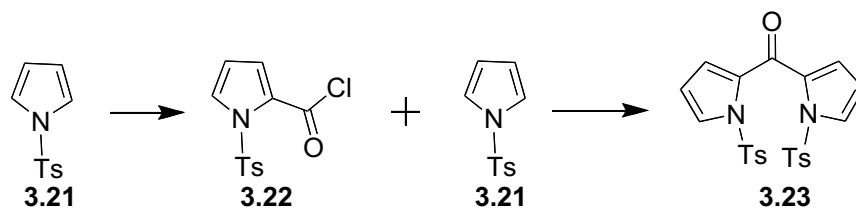
As stated in chapter 1, the use of *N*-protecting groups can often aid difficult transformations on pyrroles, as masking the nitrogen atom of the pyrrole can help direct and control reactivity.²⁶⁻²⁸ Specifically, the incorporation of an electron-withdrawing group at the nitrogen atom can deactivate the pyrrole by pulling electron density out of the ring, decreasing aromatic character and inherent nucleophilicity.^{29,30} When the nitrogen atom of pyrrole is unprotected (C, Scheme 3 - 7), nucleophilic substitution is postulated to proceed through an azafulvenium intermediate (D) to give a racemic mixture of products (E, Scheme 3 - 7).³⁰ In contrast, the use of an electron-withdrawing (EWG) *N*-protecting group employed allowed for higher enantiomeric selectivity (Scheme 3 - 7, EWG = triflyl > mesyl > *tert*-butyloxycarbonyl (Boc) ≈ acetyl).³¹ The azafulvenium pathway becomes increasingly disfavored as the strength of the electron withdrawing group increased, since the *N*-EWG directs substitution to proceed primarily by an S_N2 pathway.³¹

Scheme 3 - 7: Postulated Pathways for Nucleophilic Substitution on an α -Methyl Pyrrole



As such, the nucleophilic fluorination of dipyrrolyketones was revisited using *N*-protected analogues. It was hypothesized that the incorporation of an *N*-EWG would prevent enolization of the ketone moiety, which would arise from an azafulvenium-type tautomerism. The first *N*-EWG employed for this strategy was an *N*-tosyl group (*p*-toluenesulfonyl). Ditosyl-protected dipyrrolyketone (**3.23**, Scheme 3 - 9) was reported to form as a by-product in the synthesis of *N*-tosyl-1*H*-pyrrole-2-carbonyl chloride (**3.22**).³² Attempts were made to improve the modest yield (24 %), but all optimization trials resulted in a decrease in yield.

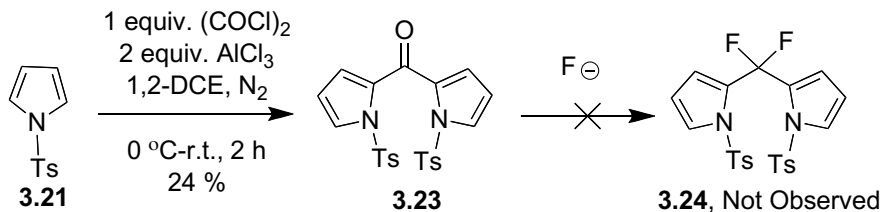
Scheme 3 - 8: Formation of 3.23 from 3.21



The first optimization attempt intended to promote conversion of **3.21** to **3.22** by control of stoichiometry of the reagents (1 equiv. **3.21**, 2 equiv. oxalyl chloride (COCl)₂, 1 hr, 0 °C). Once **3.22** had formed according to analysis using TLC (appeared as a spot with low R_f, as the acyl chloride is hydrolyzed to an acid on contact with silica or alumina), a second portion of **3.21** was added (1 equiv., 2 hr, 0 °C to r.t.). Performing the

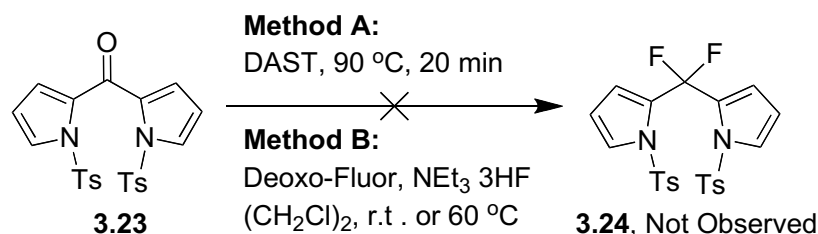
proposed stepwise formation of **3.23** resulted mainly in decomposition products, with a 26 % recovery of starting material. Changing the Lewis acid to SnCl₄ produced only trace amounts of product, with significant decomposition (TLC analysis). In the interest of time, the procedure was thus followed as written without modification (Scheme 3 - 9), with a 24 % yield obtained.

Scheme 3 - 9: Synthesis and Attempted Fluorination of 3.23



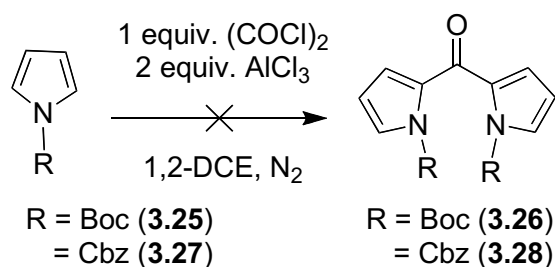
Previous attempts²⁵ to fluorinate **3.23** using Xtalfluor-E® had resulted in near quantitative return of starting material, with (80 °C) or without heating (Scheme 3 - 9). Having noted that DAST had achieved oxidation of an aldehyde group to achieve a difluoromethyl group where Xtalfluor-E® had failed (*vide infra*, section 3.2.2, Table 3 - 2), **3.23** was submitted to routine conditions¹⁹ for DAST-mediated fluorination (neat, 20 min, 90 °C, Scheme 3 - 10). Yet again, quantitative return of starting material was observed. The fluorination of **3.23** was also attempted using Deoxo-Fluor®. Reported procedures typically use Deoxo-Fluor® either neat, or as a solution in 1,2-DCE with 0.2 equiv. of HF,²¹ but for safety reasons, NEt₃•3HF was substituted for HF. Again, quantitative return of **3.23** was achieved, with no reaction over 24 hours at room temperature, or after heating at 60 °C (Scheme 3 - 10).

Scheme 3 - 10: Attempted Synthesis of 3.24



The *N*-Boc or *N*-carboxybenzyl protecting groups possess less electron withdrawing character than the *N*-tosyl group employed in **3.23**, and were also pursued as protecting group options in forming a dipyrrolylketone. However, attempts to synthesize either the *tert*-butyloxycarbonyl-protected dipyrrolylketone (*N*-Boc, **3.33**) or the dicarboxybenzyl-protected dipyrrolylketone (*N*-Cbz, **3.35**) were unsuccessful when applying the same procedure that had been used to synthesize **3.29** (Scheme 3 - 11) and resulted in decomposition. As such, the synthesis of a difluoromethyl pyrrole *via* dipyrrolic starting material was ultimately unsuccessful.

Scheme 3 - 11: Attempted Synthesis of Boc- or Cbz-Protected Dipyrrolylketones



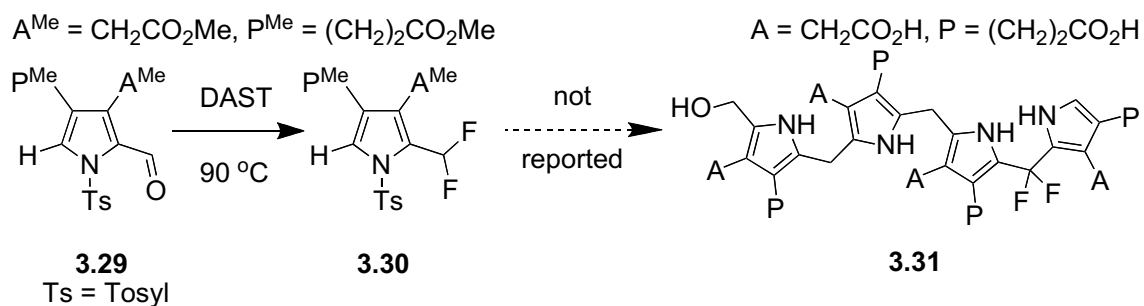
3.2.2 Synthesis of Fluorinated Pyrroles

Given that the attempts to install the $-\text{CF}_2-$ moiety in a dipyrrolic system had failed, the second strategy, involving monopyrroles, was pursued. Monopyrroles were fluorinated to synthesize their respective 2-difluoromethylpyrroles. Upon oxidation of the difluoromethyl moiety, these pyrroles could be used as building blocks for difluorinated dipyrromethanes and larger $-\text{CF}_2-$ linked polypyrroles. The stability of difluoromethyl pyrroles was also investigated, hopeful that this information would help to solve the challenges encountered when attempting to produce and isolate difluorinated dipyrroles, as described above.

Scott and co-workers¹⁹ reported that α -difluoromethyl pyrroles could be used as building blocks in the formation of a tetrapyrrole (**3.29**, Scheme 3 - 12). However, this study focused on the preparation of these difluoromethyl-containing pyrrolic building blocks. The report described the need for *N*-protection when fluorinating 2-formylpyrroles using DAST, and that use of *N*-unprotected substrates resulted in a

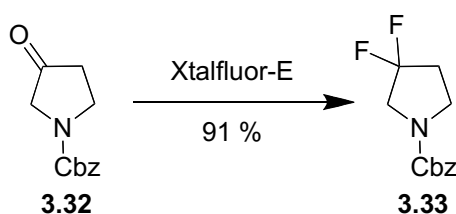
“black tar”.¹⁹ In contrast, the fluorination of *N*-tosyl α -formylpyrrole **3.29** was high yielding (87 %, Scheme 3 - 12).¹⁹

Scheme 3 - 12: Literature Example of Installing a Difluoromethyl Group on a Pyrrole

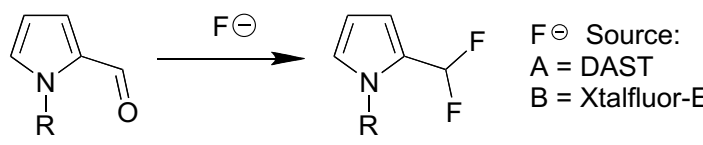


Due to the hazardous nature of DAST at temperatures greater than 80 °C (explosive: blast shield required; highly corrosive HF species produced *in situ*), the current work also explored the use of XtalFluor-E® as a less hazardous alternative.²⁰ Like DAST, XtalFluor-E® has been shown to be effective in the conversion of a carbonyl group to a *gem*-difluoride moiety (Scheme 3 - 13).²⁰ However, there are no reported examples of the use of this reagent to fluorinate 2-formylpyrroles.

Scheme 3 - 13: Literature Example of Fluorination of Carbonyl Group using XtalFluor-E®



A series of various *N*-protected 2-formylpyrroles was reacted with the deoxofluorination reagents XtalFluor-E® and DAST (Table 3 - 1). The goal of this brief survey was to identify suitable reaction conditions for the deoxofluorination reaction, as well as the required properties of the *N*-protecting group.

Table 3 - 1: Deoxofluorination of *N*-Protected 2-Formylpyrrole

Entry	R	F- Source	% Yield (#)
1	Me	A	0 ^a
2	Me	B	0 ^a
3	Cbz	A	0 ^{a,b}
4	Cbz	B	0 ^{a,b}
5	Tosyl	A	76 ^{b,c} (3.34)
6	Tosyl	B	81 ^c (3.34)
7	SO ₂ Ph	B	92 ^c (3.35)
8	C(O)Ph	A	54 ^c (3.36)
9	SO ₂ NMe ₂	A	0 ^a
10	SO ₂ NMe ₂	B	0 ^a
11	CH ₂ Ph	A	0 ^a
12	CH ₂ Ph	B	0 ^a
13	Ph	B	0 ^a

^aNo product formed, only return of starting material and decomposition;

^bReactions performed by Dr. Smithen; ^cYields of isolated products

In order for fluorination to proceed with high yields, the *N*-protecting group utilized on the pyrrole substrate required strong electron withdrawing character, like that seen in *N*-benzenesulfonyl or *N*-tosyl protecting groups (entries 5-7, Table 3 - 1). A modest yield was observed when employing a benzoyl protecting group (entry 8) which is only moderately electron withdrawing.³³ Consequently, it was unexpected that use of either the *N*-carboxybenzyl (entries 3 and 4) or *N*-dimethylsulfamoyl (entries 9 and 10) was not tolerated, as these groups are also moderately electron withdrawing. *N*-Methyl (entries 1 and 2), *N*-benzyl (entries 11 and 12) and *N*-phenyl (entry 13) 2-formylpyrroles did not react with either DAST or Xtalfluor-E®, even at elevated temperatures (90-100 °C) and with the use of prolonged reaction times. This may have been a result of the weakly electron donating character of these *N*-protecting groups.³³

In addition, a series of *N*-protected 2-formylpyrroles bearing substitution on the

pyrrolic periphery were submitted to the DAST or Xtalfluor-E® mediated deoxofluorination reactions (Table 3 - 2). Employing a substituted *N*-benzoyl protected pyrrole (entry 1, Table 3 - 2) gave a comparable yield to the same reaction involving the respective unsubstituted substrate (entry 8, Table 3 - 1). It appeared that the presence of an additional ester substituent on substrates employing the *N*-carboxybenzyl protecting group (entry 2, Table 3 - 2) allowed the fluorination to proceed in a modest yield (50 %).

Table 3 - 2: Deoxofluorination of Substituted 2-Formylpyrroles

Entry	R ¹	R ²	R ³	R ⁴	F-Source	% Yield (#)
1	C(O)Ph	CO ₂ Et	Me	Et	B	59 ^a (3.37)
2	Cbz	CO ₂ Bn	Me	Me	B	50 ^{a,b} (3.38)
3	SO ₂ Ph	H	(CH ₂) ₂ CO ₂ Me	CH ₂ CO ₂ Me	B	0 ^c
4	SO ₂ Ph	H	(CH ₂) ₂ CO ₂ Me	CH ₂ CO ₂ Me	A	84 ^a (3.39)
5	SO ₂ Ph	H	Me	(CH ₂) ₂ CO ₂ Me	A	0 ^c
6	SO ₂ Ph	H	Me	Me	A	0 ^c

^aYields of isolated products; ^bReaction performed by Dr. Smithen; ²⁵

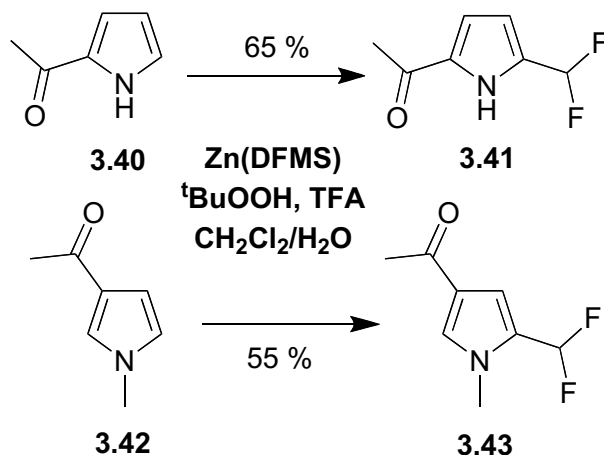
^cNo product formed, return of starting material and decomposition

Interestingly, the deoxofluorination reaction synthesizing the tosyl-protected diester **3.39** (entries 3 and 4) was only successful using DAST. This may be a result of the concentration of the reaction mixture, where DAST is employed under neat conditions¹⁹ and Xtalfluor-E® is used in a 0.25 M solution solvated in 1,2-DCE.²⁰ Analogues of the pyrrole featured in entries 3 and 4 were also submitted to the reaction conditions, containing either one (entry 5) or two (entry 6) methyl substituents in place of the alkyl esters. Unfortunately, neither analogue was fluorinated under the conditions utilized.

Another method to install a α -difluoromethyl group onto a pyrrole employs Zn(DFMS) (**3.11**, Figure 3 - 4), which is a commercially-available fluorinating reagent developed by the Baran group.²⁴ This reagent is intended for the difluoromethylation of nitrogen-containing heteroaromatic compounds *via* a $-CF_2H$ radical.²⁴ The reported

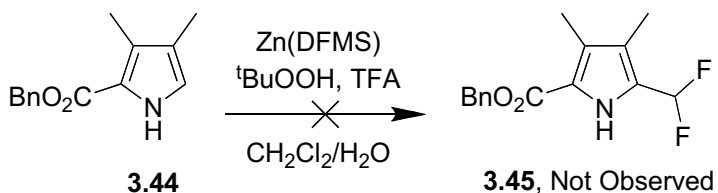
substrate scope included two pyrrolic examples (Scheme 3 - 14);²⁴ one unprotected substrate (3.40 to 3.41), and one *N*-methyl protected substrate (3.42 to 3.43)

Scheme 3 - 14: Literature Example of Difluoromethylation of Pyrroles using Zn(DFMS)



As the end goal was to form a substituted difluorodipyrromethane to model the uroporphomethene isostere (3.6, Figure 3 - 3), a pyrrole displaying substitution in the β -positions (3.44) was selected to investigate substrate tolerance. Submission of pyrrole 3.44 to the reaction conditions (Scheme 3 - 15) resulted in a near-quantitative return of the starting material (98 % of 3.44). Longer reaction times and additional portions of the reagents gave the same result. Further investigation was not pursued due to the expense of the Zn(DFMS) and the ready availability of other deoxofluorination reagents that afforded more success (as shown in Table 3 - 1 and Table 3 - 2).

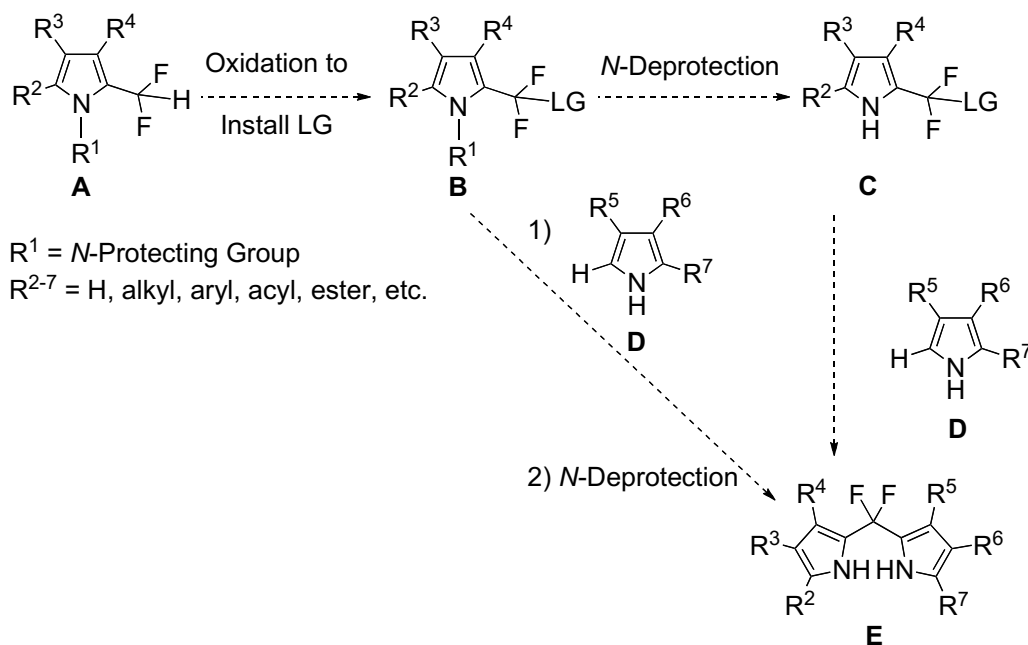
Scheme 3 - 15: Attempts to Install a Difluoromethyl Group



3.2.3 Attempted Oxidation of a Difluoromethyl Group

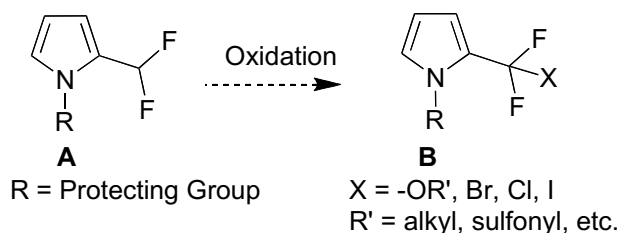
In order to use the 2-difluoromethylpyrroles (as shown in Table 3 - 1 and Table 3 - 2) as building blocks to form larger fluorinated polypyrroles (such as **3.6** in Figure 3 - 3, or **3.31** in Scheme 3 - 12), a good leaving group must be introduced through oxidation of the difluoromethyl carbon atom (**B** or **C**, Scheme 3 - 16). This transformation is required to couple the fluorinated pyrrole **C** (or **B**) to the α -free pyrrole **D** form the desired dipyrrolic model **E**.

Scheme 3 - 16: Towards Fluorinated Monopyrrolic Building Blocks from 2-Difluoromethylpyrroles



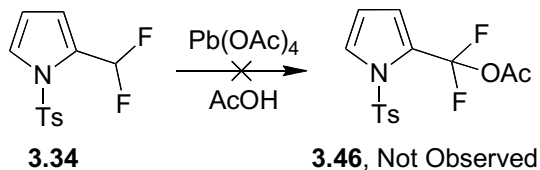
It was decided that a bromide, chloride or alkoxy substituent (**B**, Scheme 3 - 17) would be introduced into pyrrolic difluoromethyl groups *via* radical or oxidation processes. Introduction of such groups are fairly routine in the synthesis of analogous 2-methylpyrroles, and so the traditional reaction conditions were investigated first.

Scheme 3 - 17: Proposed Oxidation of 2-Difluoromethylpyrroles



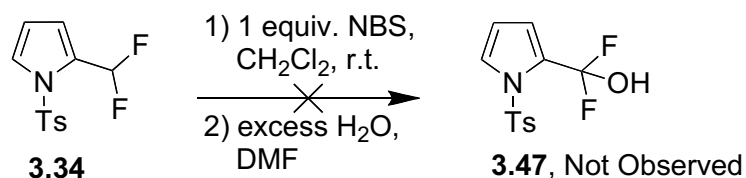
One method of installing a leaving group at the α -methyl position involved oxidation using lead tetraacetate and acetic acid.³⁴⁻³⁶ However, TLC analysis showed only starting material after submitting **3.34** (from Table 3 - 1) to the Pb(IV)-mediated oxidation conditions (Scheme 3 - 18). Cognizant that the targeted carbon atom ($-\text{CF}_2\text{H}$) is electron poor relative to the usual substrate of this transformation ($-\text{CH}_3$), the reaction was heated at 40 °C for 48 hours. While monitoring this process using TLC analysis, it seemed that decomposition was favored over the desired oxidation reaction (i.e., the formation of **3.46**). Neither additional heating time, nor heating at a higher temperature afforded any product.

Scheme 3 - 18: Attempted Oxidation of 3.34 Using $\text{Pd}(\text{OAc})_4$



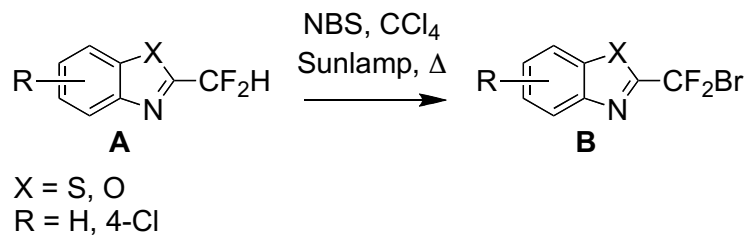
Another method of installing an oxygen-connective substituent was to perform a stepwise reaction of **3.34** with *N*-bromosuccinimide (NBS), followed by the addition of $\text{H}_2\text{O}/\text{DMF}$ (Scheme 3 - 19).³⁷ When monitoring the bromination step of this reaction by use of ^1H NMR spectroscopy, no change was observed after reacting for 24 hours or with the introduction of heating (40 °C, additional 24 hours). Consequently, the bromination reaction was investigated before pursuing this route any further.

Scheme 3 - 19: Attempted Bromination of a α -Difluoromethyl Group



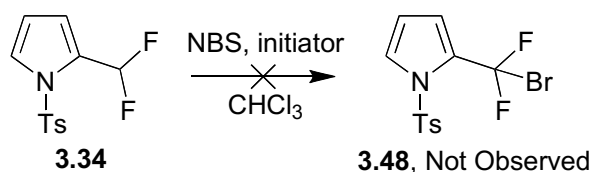
In many traditional synthetic routes towards the preparation of porphyrin, the oxidation of α -methyl substituents are achieved using bromine.^{38,39} A more modern way of achieving this pyrrolic transformation proceeds *via* the Wohl-Ziegler reaction.^{40,41} The Wohl-Ziegler reaction uses radical initiators and NBS to form Br_2 and HBr *in situ*, which controls the concentration of these reactive species to maximize the selectivity of the reaction. There is precedence for brominating a difluoromethyl group (**A**, Scheme 3 - 20) to form a bromodifluoromethyl group (**B**),⁷⁴ and so **3.34** was submitted to the Wohl-Ziegler reaction.

Scheme 3 - 20: Literature Example of a Wohl-Ziegler Performed on a Difluoromethyl Group



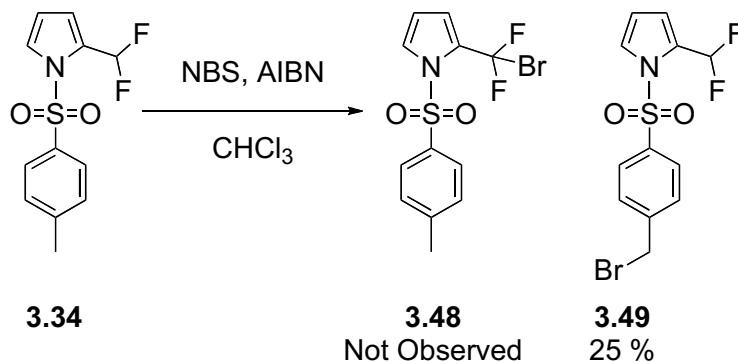
The ^1H NMR and ^{19}F NMR signals of the difluoromethyl group were used to follow the bromination of pyrrole **3.34**. The difluoromethyl proton of **3.34** appeared as a triplet with chemical shift of 7.12 ppm in the ^1H NMR spectrum, with a $J_{\text{H-F}}$ coupling constant of 55 Hz. In the ^{19}F NMR spectrum, a doublet appeared at -110.7 ppm with the corresponding coupling constant ($J_{\text{F-H}} = 55$ Hz). If the difluoromethyl group were to be successfully brominated, the characteristic triplet in the ^1H NMR spectrum would disappear and the ^{19}F NMR spectrum would no longer exhibit the characteristic doublet. When attempting to brominate **3.34**, either azobisisobutyronitrile (AIBN) or a microwave reactor was used for radical initiation (Scheme 3 - 21).

Scheme 3 - 21: Attempted Bromination of 3.34



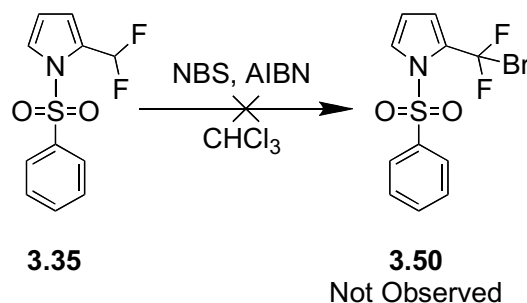
The reaction was unsuccessful under microwave-assisted conditions, leading to quantitative return of starting material. When employing AIBN as a radical initiator, the desired product (**3.48**) was not observed. Instead, the *p*-methyl group of the tosyl moiety was brominated to result a 25 % yield of **3.49** (Scheme 3 - 22), with a 70 % recovery of starting material. It became clear that the presence of this additional benzylic position within the *N*-tosyl group was detrimental to bromination at the desired pseudo-benzylic position of the 2-difluoromethyl group.

Scheme 3 - 22: Bromination of 3.34



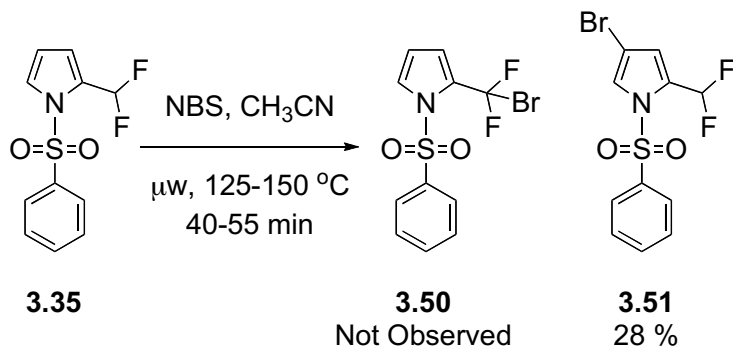
In attempt to avoid the alternative bromination product **3.49**, *N*-benzenesulfonyl protected pyrrole (**3.35**, Table 3 - 1) was used in place of **3.34**. However, when pyrrole **3.35** was submitted to NBS-mediated bromination in the presence of AIBN, a quantitative return of starting material was recovered (Scheme 3 - 23).

Scheme 3 - 23: Attempted Bromination of 3.35 using NBS and AIBN



Given the known reactivity of chloroform during radical processes,⁴²⁻⁴⁴ the reaction was repeated using acetonitrile (CH₃CN) as the solvent. The difluoromethyl group was left unreacted when employing AIBN as the radical initiator, as determined by use of ¹H NMR spectroscopy. When a microwave reactor was used to heat and initiate (40 min, 150 °C) the bromination of **3.35**, one major product was observed *via* use of TLC analysis (along with significant decomposition). Again, the desired product (**3.50**) was not observed and instead the bromination occurred at the 4-position on the pyrrole (**3.51**, Scheme 3 - 24). As a result, a new model substrate was chosen.

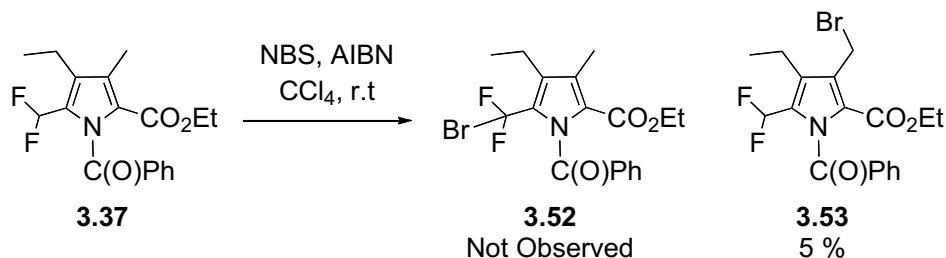
Scheme 3 - 24: Microwave-Assisted Bromination of 3.35 using NBS



Pyrrole **3.37** (Table 3 - 2) was chosen for its fully substituted framework, in an attempt to prevent direct bromination on the pyrrole skeleton rather than the α -difluoromethyl group. Reaction of **3.37** with NBS and AIBN led to moderate recovery of starting material (60 %), even when using CCl₄ as solvent rather than CHCl₃ or CH₃CN (Scheme 3 - 25). The remainder of the reaction mixture was composed of multiple co-eluting products, as well as decomposition products that were fixed to the

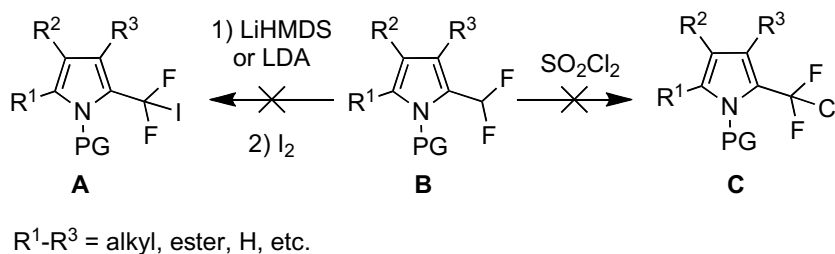
baseline of the chromatography column. Isolation of the various products proved to be extremely difficult using both silica and alumina chromatography, due to the small scale of these reactions. However, one product was isolated in a measurable amount (i.e. >1 mg). Once again, undesired bromination was observed, this time targeting the substituted 3-position of the pyrrole (**3.53**, Scheme 25).

Scheme 3 - 25: Bromination of 3.37



Iodination *via* the stepwise deprotonation and reaction of the difluoromethyl group with iodine (**B** to **A**, Scheme 3 - 26) and chlorination by use of sulfonyl chloride (SO_2Cl_2 , **B** to **C**, Scheme 3 - 26) were also pursued within the Thompson group, but both strategies were found to be unfruitful at oxidizing the difluoromethyl group, resulting in decomposition and/or a return of starting material.²⁵

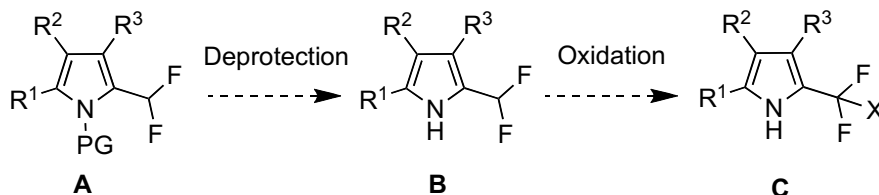
Scheme 3 - 26: Attempted Halogenations of *N*-Protected α -Difluoromethyl Pyrroles



The oxidation of an α -methyl group of a pyrrole is traditionally performed on an *N*-unsubstituted substrate. The next step was to investigate the stability of *N*-deprotected α -difluoromethyl pyrroles (**B**, Scheme 3 - 27), as well as identify a substrate that tolerated the removal of the *N*-protecting group. Employing *N*-unprotected pyrroles (**B**) as substrates in the oxidation reactions described in this section, in place of *N*-protected

pyrroles (A), were hypothesized to be able to produce the desired products of oxidation (C).

Scheme 3 - 27: Proposed Synthesis of Oxidized α -Difluoromethyl Pyrroles



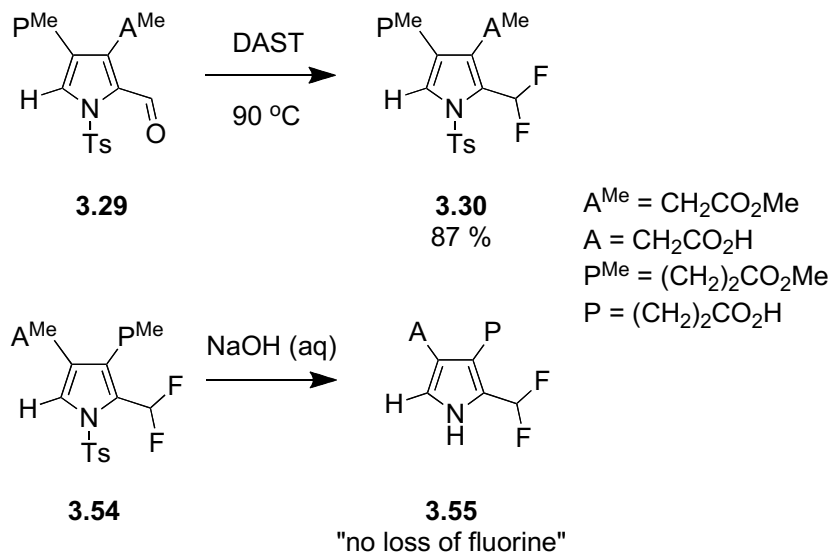
R¹-R³ = alkyl, ester, H, etc.

X = Br, Cl, I, etc.

3.2.4 Deprotection of α -Difluoromethylpyrroles

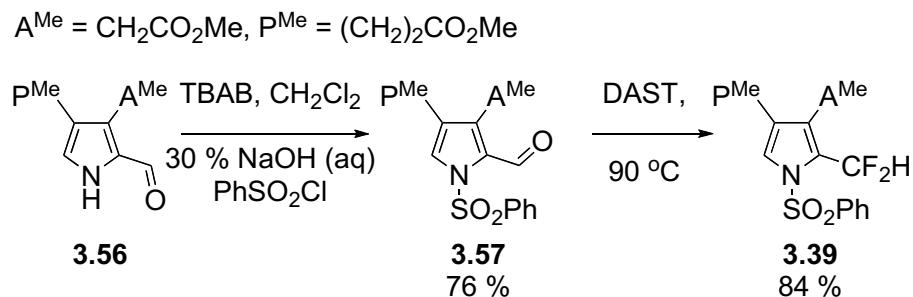
Scott and co-workers¹⁹ report that an α -difluoromethyl pyrrole tolerated the removal of an *N*-tosyl group. The reported *N*-deprotection reaction employed an aqueous sodium hydroxide solution (Scheme 3 - 28).¹⁹ The reaction conditions for the *N*-deprotection reaction was not elaborated, upon nor was a yield reported, but the authors claim that there was no loss of fluorine from the *N*-deprotected pyrrole.¹⁹ No follow-up study was ever published. In addition, there was some confusion in discerning the substitution pattern on the pyrrole used in the study. In contrast to the α -difluoromethyl pyrrole synthesized in the Scott work (3.30, Scheme 3 - 28), the acetic and propionic esters are reported as reversed in the substrate that was employed for deprotection (3.54).

Scheme 3 - 28: Fluorination of 3.29 and Deprotection of 3.54, as Reported by Scott et al.



In an attempt to replicate these findings, the diester **3.56** was prepared following a previously reported procedure.⁴⁵ The *N*-protected pyrrole **3.57** was prepared *via* the reaction of **3.56** with benzenesulfonyl chloride, and subsequently fluorinated to form **3.39** using DAST (Table 3 - 2, entry 4; Scheme 3 - 29). Pyrrole **3.39** was synthesized for comparison with pyrrole **3.30** (Scheme 3 - 28) during *N*-deprotection, and other Thompson group members are currently pursuing the synthesis of the alternate pyrrole **3.54**.

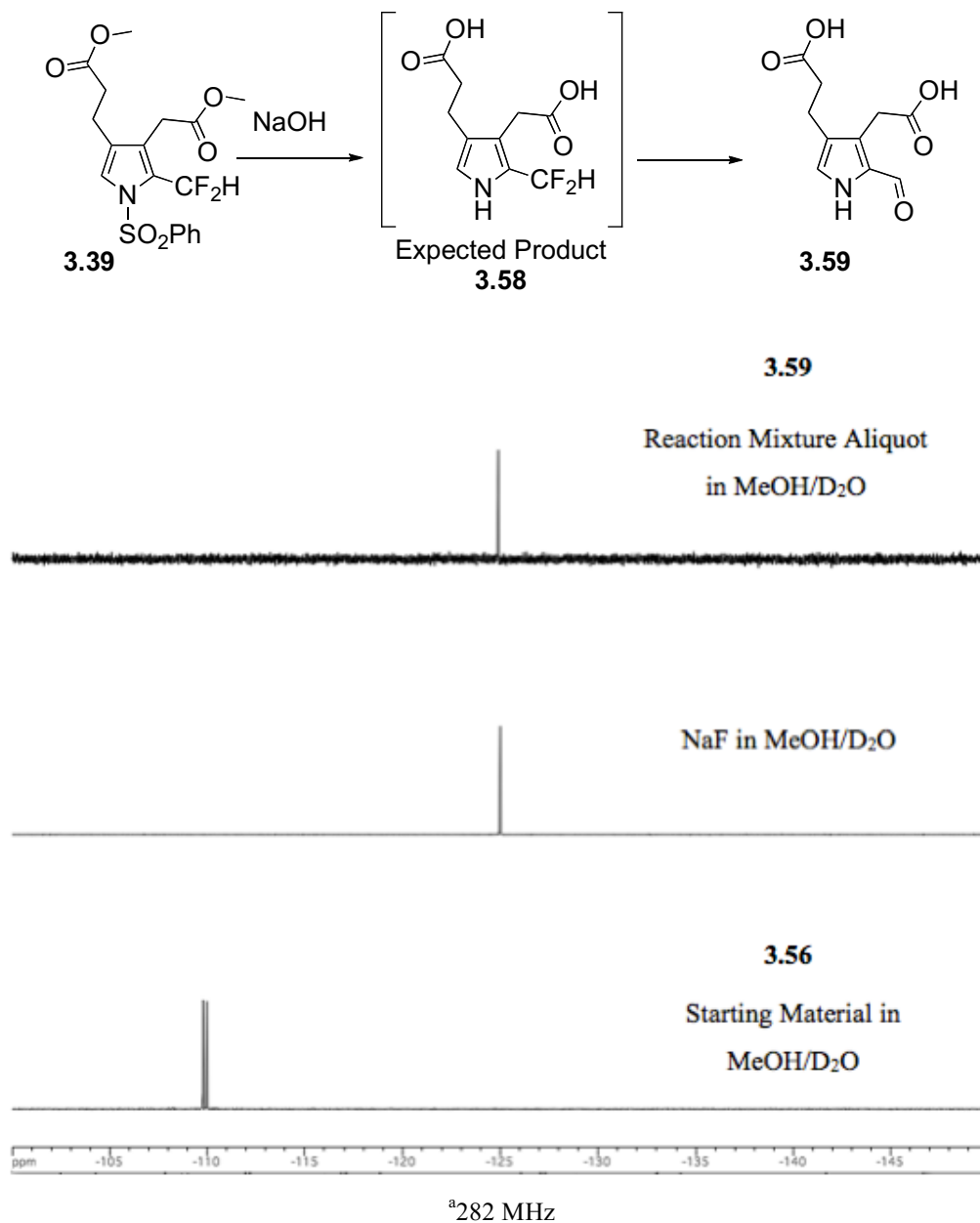
Scheme 3 - 29: Synthesis of 3.39



Removal of the *N*-benzenesulfonyl group from **3.39** was attempted using reported deprotection conditions referenced in Scott's study, which employed 2N $\text{NaOH}_{(\text{aq})}$.^{19,46}

Methanol was added as a co-solvent, as the starting pyrrole was insoluble in water at room temperature (50 °C, 1M NaOH in 1:1 MeOH/H₂O). An aliquot of the reaction mixture was submitted for ¹⁹F NMR analysis in D₂O; the experiment resulted in a single signal corresponding to a fluoride anion (F⁻, -125 ppm), rather than the expected doublet resulting from a difluoromethyl substituent (Figure 3 - 7).

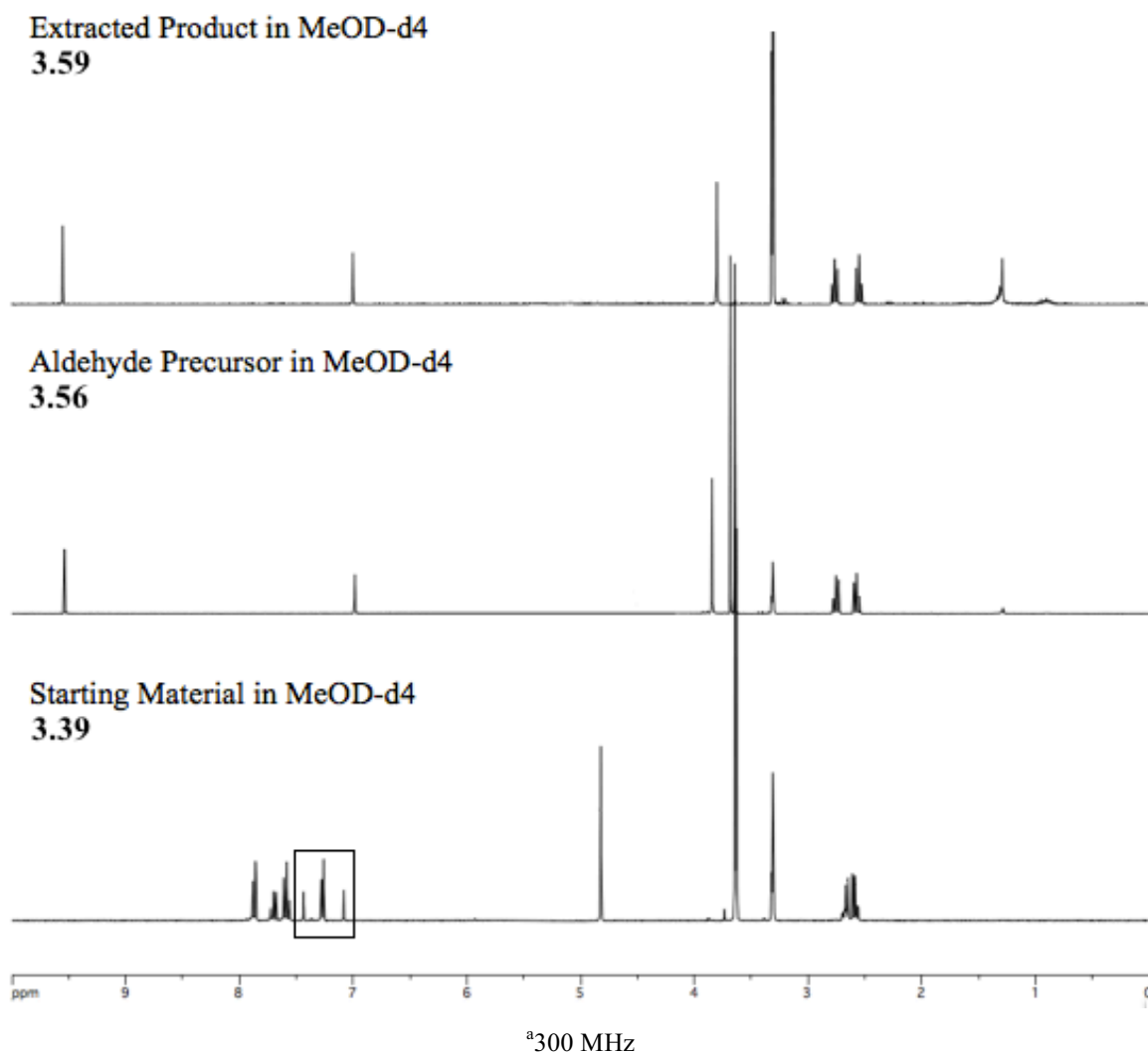
Figure 3 - 7: ¹⁹F NMR Spectra of Before and After the Deprotection of 3.39^a



Due to the poor solubility of the product in D₂O, the ¹H NMR spectrum collected had very poor resolution and the analysis was repeated in a different solvent. The reaction

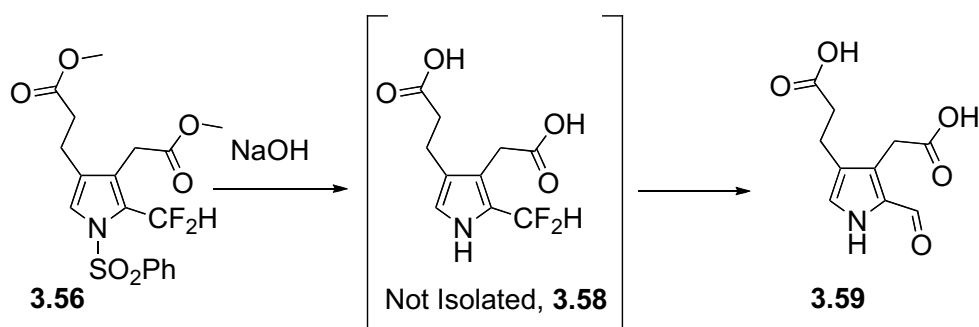
mixture was extracted into ethyl acetate (EtOAc), concentrated and then dissolved in MeOD-d4 for ^1H NMR analysis without further purification. The starting material **3.39** displayed the characteristic triplet signal in the ^1H NMR spectrum, which arose from the difluoromethyl group (highlighted with a box in Figure 3 - 8). This characteristic triplet signal results from $J_{\text{H-F}}$ coupling,²⁰ and is featured in all of the ^1H NMR spectra for the α -difluoromethyl pyrroles synthesized (Table 3 - 1 and Table 3 - 2). After deprotection, the triplet signal was replaced by a sharp singlet at $\delta 9.55$ ppm, comparable to the chemical shift of the aldehyde signal observed in aldehyde **3.56**.

Figure 3 - 8: ^1H NMR Spectra of Before and After the Deprotection of **3.39^a**



This result suggested the loss of fluorine by hydrolysis to form the 2-formylpyrrole **3.59** (Scheme 3 - 30). The two singlets that arise from the methyl ester substituents are also missing from the extracted product of the deprotection reaction, suggesting that the two esters have also hydrolyzed to form the diacid-bearing pyrrole due to the basic aqueous conditions employed during deprotection (**3.59**, as shown in Scheme 3 - 30). The reaction was repeated (50 °C, 1M NaOH 1:1 MeOH/H₂O) in order to report a yield. The reaction was worked up by slowly titrating to pH 4 using 2M HCl_(aq). After extracting the organic material using EtOAc and concentrating the organic layer *in vacuo*, the crude mixture was purified using column chromatography. This resulted in the isolation of **3.59** in a 27 % yield. The deprotection of **3.39** was repeated a third time, this time using 2N NaOH_(aq) at 50 °C, and **3.59** was isolated again in a 23 % yield. The alkyl esters in the β-position of pyrrole **3.39** undergo hydrolysis in each case.

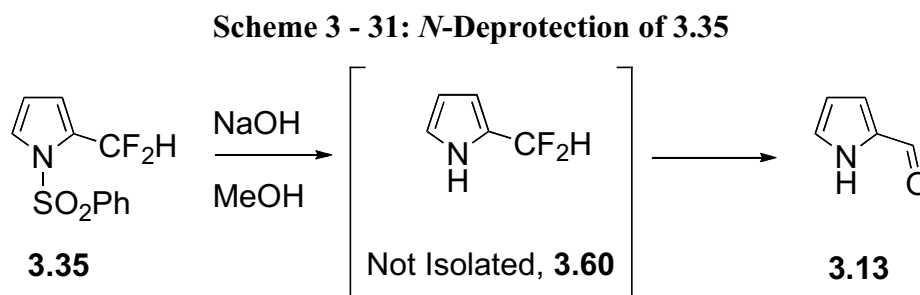
Scheme 3 - 30: Synthesis of 3.59



The reaction was repeated, again using NaOH but this time employing MeOH as solvent. The solvent was removed *in vacuo* upon consumption of starting material by use of TLC analysis. Again, ¹⁹F and ¹H NMR spectral analysis indicated free fluoride and the aldehyde (**3.59**) were present in the reaction mixture with no signs of the α-difluoromethyl group remaining intact.

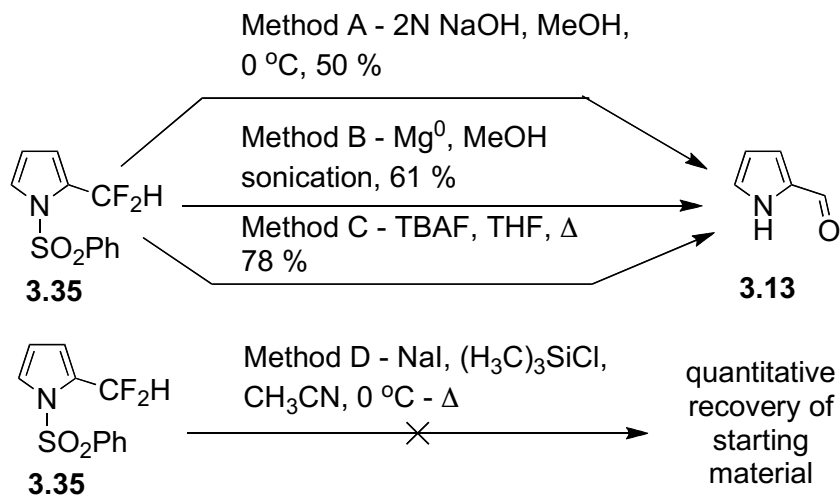
Going forward, simpler substrates were explored for studying the loss of fluorine upon *N*-deprotection. The study of the loss of fluorine upon *N*-deprotection was continued using pyrrole **3.35** (entry 7, Table 3 - 1). Given that employing an elevated temperature continued to afford low yield (30 % of **3.35** at 50 °C), the reaction temperature was decreased to 0 °C. Upon deprotection using methanolic NaOH at 0 °C,⁴⁶ 2-formylpyrrole

(**3.13**) was isolated in a 50 % yield (Scheme 3 - 31). Pyrrole **3.13** was the hydrolysis product of the desired α -difluoromethyl pyrrole **3.60**, as shown in Scheme 3 - 31.



Previously in the Thompson group, pyrrole **3.60** (Scheme 3 - 31) was noted to appear stable in solution during basic work-up conditions. Unfortunately, this compound decomposed while concentrating the organic phase *in vacuo*.²⁵ As a result of this observation, several alternative conditions for deprotection of *N*-protected pyrrole **3.35** were explored (Scheme 3 - 32).

Scheme 3 - 32: Survey of Deprotection Conditions for Use in Deprotecting 3.35

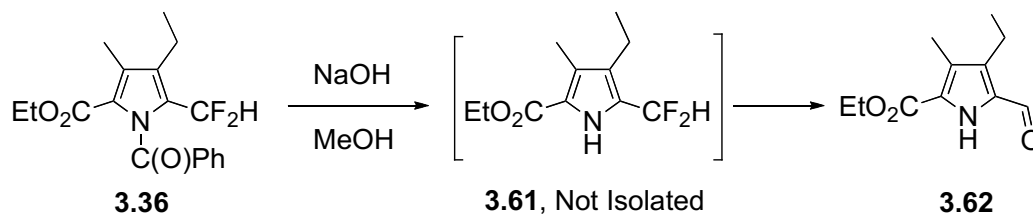


After purification using column chromatography, a quantitative return of starting material (**3.57**) was isolated using method D (Scheme 3 - 32).⁴⁷ Pyrrole **3.13** was isolated when employing methods B⁴⁸ or C.⁴⁹

An *N*-benzoyl protecting group was also employed in Scott's study,¹⁹ and so substrate **3.37** was selected to undergo deprotection using sodium hydroxide in methanol

at 0 °C. The corresponding formylpyrrole (**3.62**) was isolated once again, in 52 % yield.

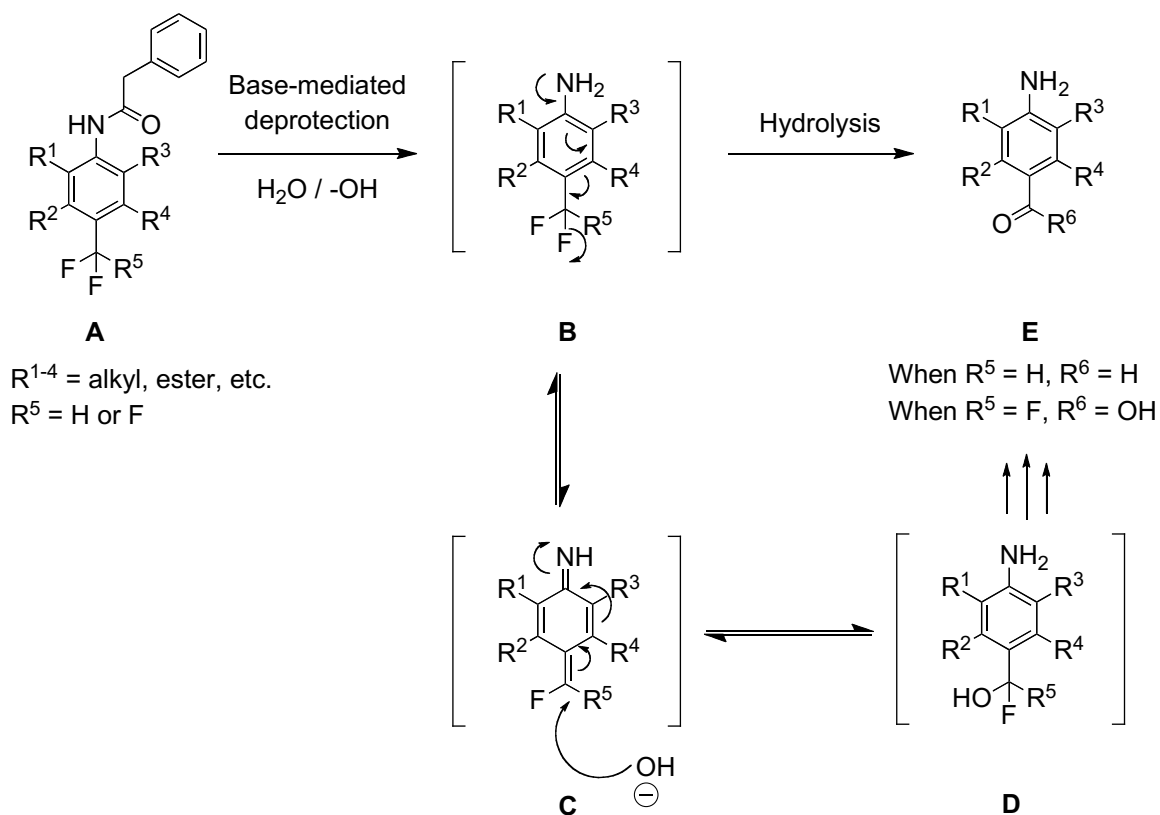
Scheme 3 - 33: *N*-Deprotection of **3.36**



The results indicate that the α -difluoromethyl group was hydrolyzed during the course of the work-up. Due to insufficient supporting information in regards to Scott's study, elaboration was required to pinpoint at which stage of the deprotection reaction the hydrolysis of α -difluoromethyl group occurred.

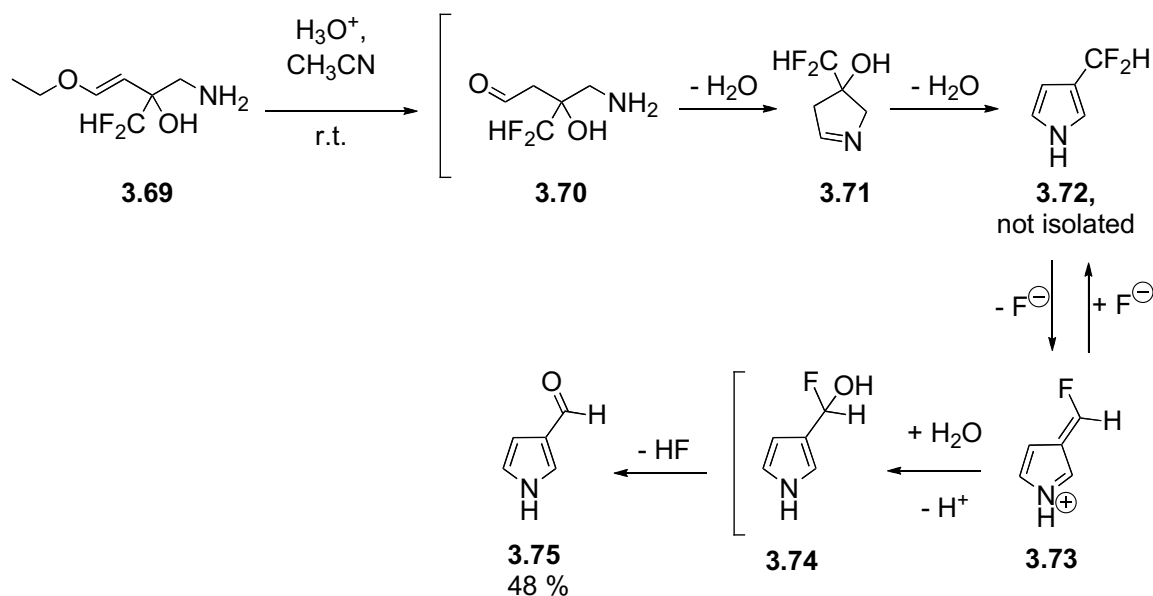
Given that *N*-deprotection was accompanied by hydrolysis of the difluoromethyl moiety, it would seem that a protecting group is required to stabilize the difluoromethyl group. This reactivity is analogous to 1,4-substituted benzenes that bear an electron donating group and a difluoro⁵⁰ or trifluoromethyl^{51,52} group (Scheme 3 - 34). Employment of a protecting group on the electron-donating moiety was found to prevent hydrolysis (**A**, Scheme 3 - 34) and removal of the protecting group was noted to cause the appended polyfluoromethyl group to suffer from hydrolysis (**B** to **E**), which was consistent with the results seen thus far. Hydrolysis was achieved by the formation of a quinone-like intermediate (**C**) *via* electron-donation into the benzene ring, which resulted in the ejection of fluoride (**B**).⁵⁰ This process would repeat until the polyfluoromethyl group was hydrolyzed to species **E**. This reactivity has been documented to occur in basic conditions, which were prescribed for the removal of the group in question (i.e., base-mediated *N*-deprotection to remove a benzyl carbamate group).^{50,51}

Scheme 3 - 34: Hydrolysis of a Polyfluoromethyl Group



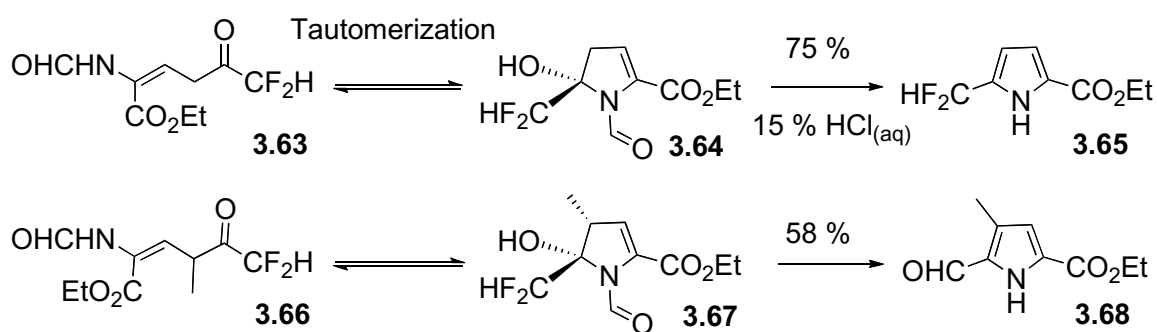
Likewise, hydrolysis is observed in β -difluoromethyl pyrroles (Scheme 3 - 35).⁵³ The authors propose a mechanism by which the desired product **3.72** is hydrolyzed to the isolated product **3.75**, and that this hydrolysis was mediated by the formation of an azafulvenium intermediate **3.73**.⁵³ This azafulvenium intermediate was suspected to arise during the course of the hydrolysis reaction that was observed with α -difluoromethyl pyrroles herein.

Scheme 3 - 35: Literature Attempt of the Formation of 3-Difluoromethylpyrrole



There are very few isolations of an *N*-H α -difluoromethyl pyrrole.^{24,54} In each case, substitution on the pyrrole is important in preventing the hydrolysis of the difluoromethyl group. Although α -difluoromethyl pyrrole **3.65** was isolated from **3.63** in 75 % yield, the incorporation of an additional methyl group in **3.66** afforded aldehyde **3.68** instead of the corresponding difluoromethyl pyrrole (Scheme 3 - 36).⁵⁴

Scheme 3 - 36: Synthesis of 2-Formyl and 2-Difluoromethylpyrroles



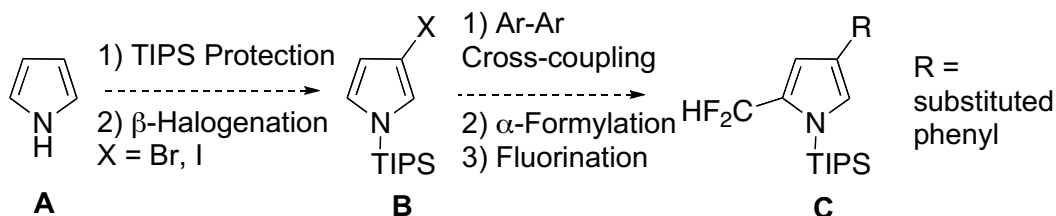
It was then hypothesized that if a stabilizing group was to be introduced into the framework of the α -difluoromethyl pyrroles, then perhaps delocalization of electron cloud through this moiety would offer competition to the formation of the problematic azafulvenium intermediate.

3.2.5 Towards the Synthesis of 4-Aryl-2-Difluoromethylpyrroles

The results thus far have demonstrated that pyrroles containing an α -difluoromethyl substituent will undergo hydrolysis of the α -difluoromethyl group during the course of *N*-deprotection. This differs from the results reported during the Scott study, which stated that an *N*-protected α -difluoromethyl pyrrole was deprotected without loss of fluorine.¹⁹ In each case, the respective formyl pyrroles were isolated in place of the expected *N*-deprotected α -difluoromethyl pyrroles. It was then hypothesized that the installation of a stabilizing group on the *N*-protected 2-difluoromethylpyrroles may allow for the study of the hydrolysis of the difluoromethyl group. If the deprotected species resisted hydrolysis, then the mechanism for the loss of fluorine could be studied.

The installation of a phenyl substituent in the 4-position of a 2-difluoromethylpyrrole would extend the conjugation of the π -system. The added conjugation would stabilize the substrate during the deprotection. A five-step sequence towards the target 4-substituted-2-difluoromethylpyrrole was proposed (Scheme 3 - 37).

Scheme 3 - 37: Proposed Synthesis of Aryl-Substituted 2-Difluoromethylpyrroles

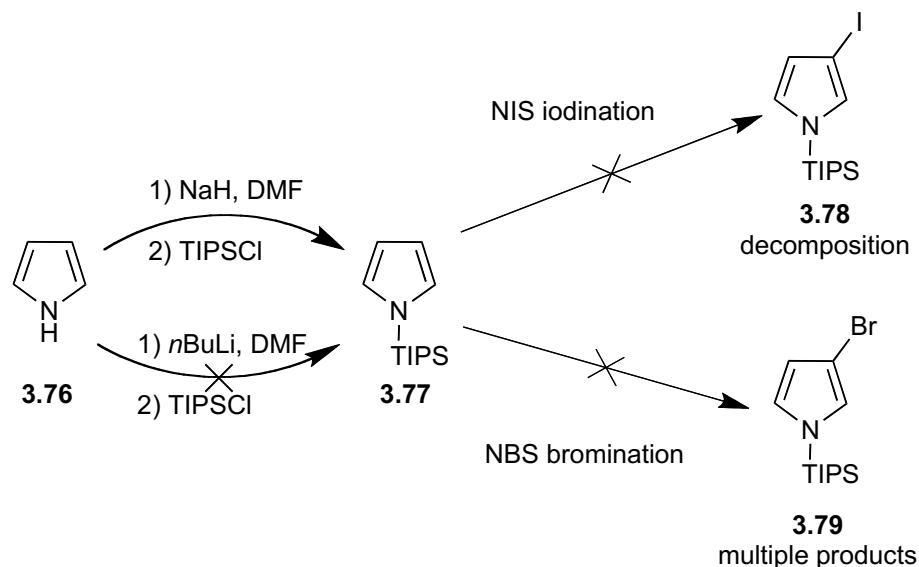


An *N*-triisopropylsilyl ether (TIPS) protecting group would be used to promote β -bromination⁵⁵ to form substrate **B** for use in Suzuki cross-coupling (Scheme 3 - 37). The resulting product could then be formylated and subsequently fluorinated to give the desired pyrrole **C**.

The *N*-TIPS protection⁵⁶ of **3.76** proceeded in moderate yield, forming **3.77** in a 63 % yield on a multi-gram scale. Complications arose while attempting the β -halogenation reaction on **3.77** (Scheme 3 - 38). The synthesis of pyrrole **3.78** by *N*-iodosuccinimide (NIS) mediated iodination of *N*-TIPS protected pyrrole (**3.77**) is a known transformation.^{56,57} However, the reaction of NIS with pyrrole **3.77** resulted in decomposition, which was not entirely surprising as NIS is known to deprotect certain

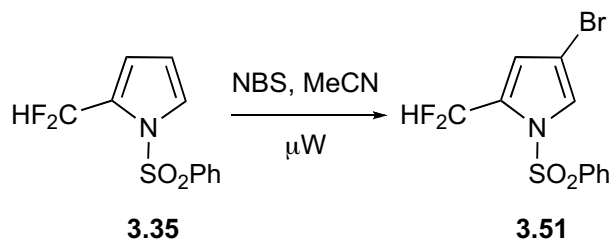
silyl ethers.⁵⁸ Similarly, the bromination of pyrrole **3.77** using NBS is reported to produce **3.79** in high yield,^{56,59,60} but was found to be unselective and resulted in multiple products even at low temperatures (-78 °C) in my hands.

Scheme 3 - 38: Attempted Synthesis of β -Halogenated Pyrroles



Given that the β -halogenation of pyrrole **3.77** resulted in repeated failures, a different pyrrole was selected for use in producing 4-aryl-2-difluoromethyl pyrroles. Pyrrole **3.51** was found to be useful for this purpose, and so the NBS-mediated bromination of **3.35** was revisited (Scheme 3 - 39).

Scheme 3 - 39: β -Bromination of **3.35**



The brominated pyrrole **3.51** was initially isolated in poor yield after treatment of **3.35** with NBS at 125 °C for 40 minutes (microwave-assisted, 28 % yield, Table 3 - 3). Unsatisfied with the modest yield afforded initially, it was decided that this reaction should undergo optimization. The reaction was found to progress more effectively at

100 °C, resulting in a slightly improved 37 % yield. Increasing the scale of the reaction ten-fold increased the yield by ~10 % (46 % yield).

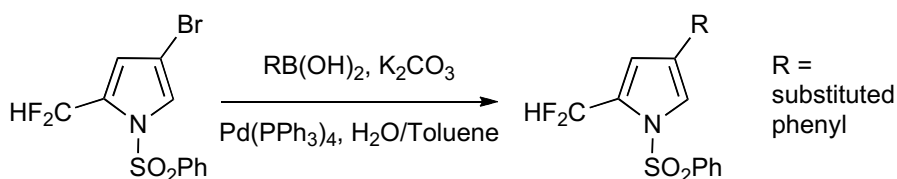
Table 3 - 3: Optimization of the β -bromination of N-benzenesulfonyldifluoromethylpyrrole (3.35)

Entry	Time (min)	Temperature (°C)	Yield ^a
1	30	150	12
2	40	125	28
3	60	100	37

^aYields of isolated **3.51**

When submitted to Suzuki cross-coupling conditions (sealed reaction under N₂, 90 °C, overnight),⁶¹ **3.51** was transformed into the respective 4-phenyl substituted pyrrole (**3.81**) in quantitative yield (entry 1, Table 3 - 4). Boronic acids with either electron withdrawing (entries 2) or electron donating character (entry 3) were tolerated as cross-coupling substrates, but the yields of isolated product were modest in comparison to **3.81** (R = H).

Table 3 - 4: Suzuki Cross-Coupling of N-Protected Difluoromethylpyrroles



Entry	R	% Yield (#) ^a
1	phenyl	<99 (3.81)
2	<i>p</i> -trifluoromethylphenyl	57 (3.82)
3	<i>p</i> -anisole	52 (3.83)

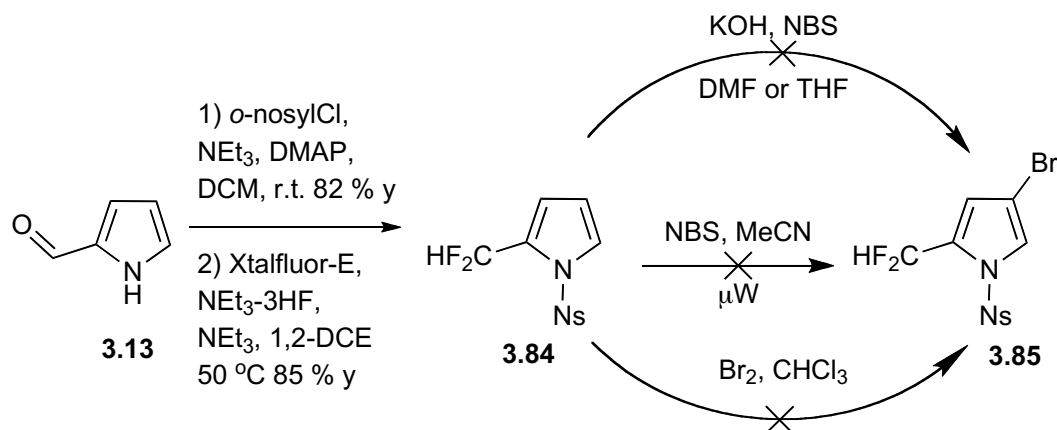
^aYields of isolated product

A series of difluoromethylpyrroles bearing the 2-nitrobenzenesulfonyl protecting group (*o*-nosyl) was also proposed due to the anhydrous deprotection conditions necessary for *N*-*o*-nosyl removal. Since the deprotection of an *o*-nosyl protecting group

was achieved under anhydrous conditions, two complimentary strategies were available for use in investigating the stability of the α -difluoromethyl moiety. In particular, use of anhydrous *N*-deprotection conditions would not allow for hydrolysis of the α -difluoromethyl group until the anhydrous conditions are intentionally compromised with H₂O.

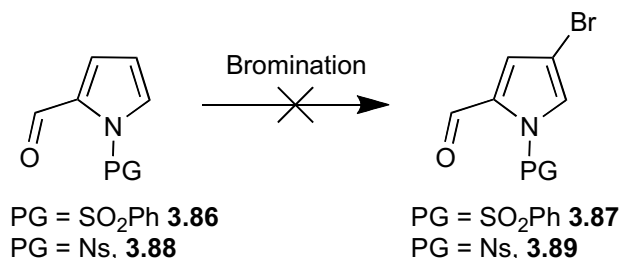
The *N*-*o*-nosyl protected 2-difluoromethylpyrrole (**3.84**) was synthesized from 2-formyl pyrrole (**3.13**), and then subsequently submitted to the microwave-assisted bromination condition. However, bromination was not achieved with this substrate using the microwave-assisted conditions (NBS, CH₃CN, 60 min, 100 °C). Alternate methods of bromination were explored but ultimately resulted in decomposition and/or recovery of starting material (Scheme 3 - 40).

Scheme 3 - 40: Attempted Synthesis of 3.85



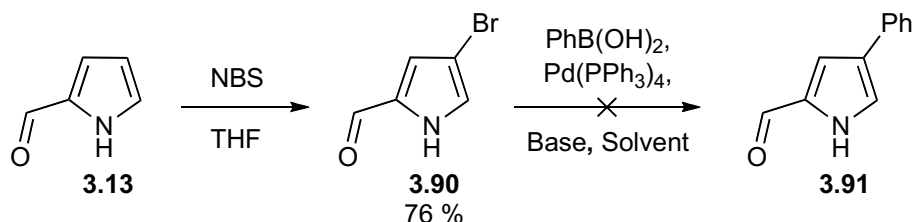
Since the overall yield was 14 to 17 % over 4 steps to achieve **3.81** from pyrrole **3.13**, a new route towards the *o*-nosyl (Ns) protected series was needed, and the synthesis of the conjugated 2-difluoromethylpyrroles was altered accordingly. Bromination was attempted on the *N*-protected 2-formylpyrroles (Scheme 3 - 41). Neither of the protected 2-formylpyrroles were brominated by use of NBS or Br₂, resulting in a quantitative return of starting material. However, the bromination of *N*-unprotected 2-formylpyrrole is a known transformation,⁶² and proceeded in a 76 % yield (Scheme 3 - 42).

Scheme 3 - 41: Attempted Bromination of 3.86 and 3.88



Two reports were followed for the Suzuki cross-coupling reaction, but neither method met success (Scheme 3 - 42). In a report by Townsend *et al.*,⁶³ the Suzuki product **3.91** was synthesized from 4-bromo-2-formyl pyrrole (**3.90**) in a 40 % yield (Pd(PPh₃)₄, PhB(OH)₂, Na₂CO₃, dioxane, 105 °C, 24 hours), but this result was not reproducible and led to 65 % recovery of starting material.

Scheme 3 - 42: Attempted Synthesis of 3.91



The Suzuki methodology⁶¹ previously employed was revisited for use in this transformation (Pd(PPh₃)₄, PhB(OH)₂, K₂CO₃, H₂O/Toluene, 90 °C, Table 3 - 4). The reaction proceeded for 5 days while monitoring using TLC analysis, despite overnight being sufficient time for previous substrates (Table 3 - 4). The reaction mixture was purified to recover 18 % of the starting material.

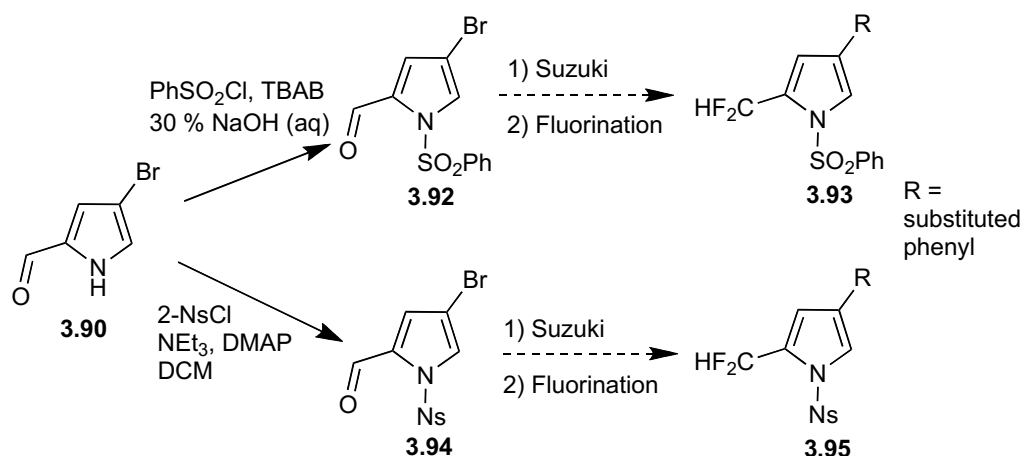
Catalyst poisoning may have resulted from the formation of a bidentate pyrrolide palladium complex. The 2-formylpyrrole construct is known to bind in a bidentate fashion by the nitrogen and oxygen atoms to Re(I),⁶⁴ Ru(II),⁶⁵ Cu(II)⁶⁶⁻⁶⁸ Sn(II),⁶⁹ Ge(II),⁶⁹ Pb(II)⁶⁹ Pd(II),^{68,70} Pt(II),⁶⁸ Ni(II),⁶⁸ In(III),⁷¹ Cr(III)⁷² and Co(III).⁶⁷

Since cross-coupling **3.90** proved to be unsuccessful, a protecting group strategy must be considered. There are three protecting strategies: the nitrogen atom, the aldehyde group, or both functionalities can be protected. *N*-substituted pyrroles⁷³⁻⁸³ are more

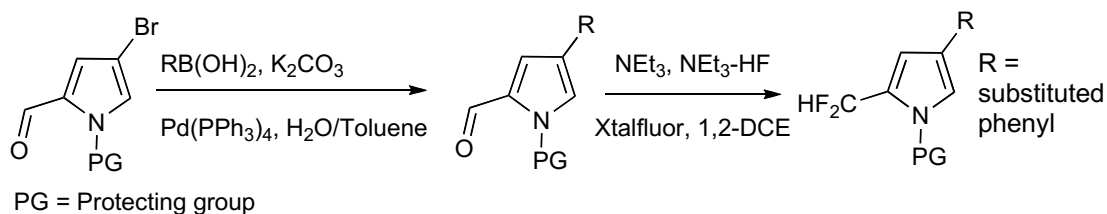
commonly employed as Suzuki substrates than *N*-H pyrroles.^{63,84,85} In addition, there is precedence for the tolerance of *N*-protected-2-formylpyrroles in Suzuki cross-coupling reactions.^{63,74,78,83}

The *N*-benzenesulfonyl and *N*-*o*-nosyl protected pyrroles were selected for their success in the fluorination of the aldehyde moiety (Scheme 3 - 43). In the case of the Suzuki cross-coupling reaction, both **3.92** and **3.94** bore electron-withdrawing groups. This made these bromopyrroles good participants in the oxidative addition step of the catalytic cycle since the electron density was drawn towards the electron-withdrawing group, weakening the carbon-halide bond for metal insertion.⁸⁶

Scheme 3 - 43: Route Towards *N*-Protected Difluoromethylpyrroles



The results of the Suzuki cross-coupling reactions are presented in Table 3 - 5. The yields presented are unoptimized. Reacting *N*-benzenesulfonyl protected pyrrole **3.92** under Suzuki conditions was a higher yielding reaction than employing *N*-*o*-nosyl protected pyrrole **3.94** as a substrate under the same conditions. In contrast, there no was apparent trend seen from varying the *p*-substituent on the aryl moiety of the Suzuki products.

Table 3 - 5: Suzuki Cross-Coupling and Fluorination Towards Target Substrates

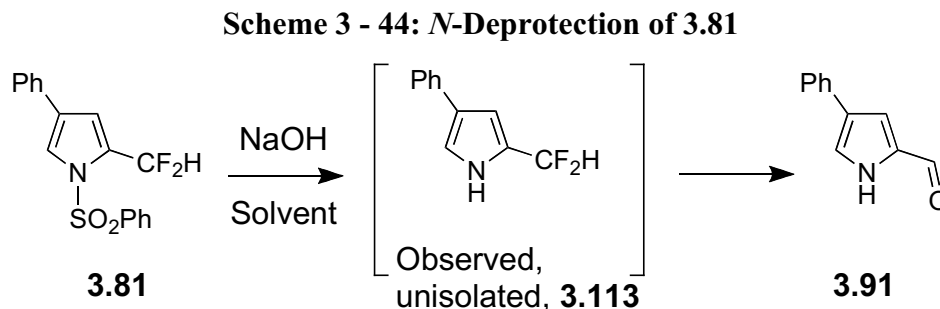
Entry	R	Suzuki Yield (%) ^a (compound #)		Fluorination Yield (%) ^a (compound #)	
		PG: PhSO ₂	<i>o</i> -Nosyl	PhSO ₂	<i>o</i> -Nosyl
1	CF ₃	77 (3.96)	62 (3.101)	73 (3.82)	85 (3.108)
2	F	82 (3.97)	86 (3.102)	47 (3.106)	61 (3.109)
3	H	91 (3.98)	66 (3.103)	54 (3.81)	90 (3.110)
4	CH ₃	88 (3.99)	61 (3.104)	57 (3.107)	70 (3.111)
5	OCH ₃	91 (3.100)	65 (3.105)	47 (3.83)	62 (3.112)

^aYields of isolated products

The results of the fluorination reaction are also presented in the table, and are dependent on inherent electrophilicity of the formyl pyrrole in question. The *N*-*o*-nosyl protecting group has stronger electron withdrawing character, which delocalizes electron density away from the aldehyde moiety through the pyrrole ring. This induced a better electrophile for the attack of the nucleophilic fluoride. The *N*-benzenesulfonyl protecting group acted similarly, but to a lesser extent than the *o*-nosyl group did. This was demonstrated by higher yields observed in the *o*-nosyl protected series than in the benzenesulfonyl-protected series. Having an additional withdrawing moiety seemed to be beneficial in the fluorination of benzenesulfonyl-protected series, as **3.82** was isolated in a much higher yield than the other substrates (entry 1, Table 3 - 5). The *o*-nosyl group has such strong withdrawing capacity that all substrates produced moderate to high yields for the fluorination reaction. Lower yields were seen when isolating derivatives bearing *p*-donating groups (entry 4 and 5), as well as for *p*-fluorine derivative **3.109** (entry 2). With these 10 substrates in hand, the investigation of the stability of the difluoromethyl group was continued.

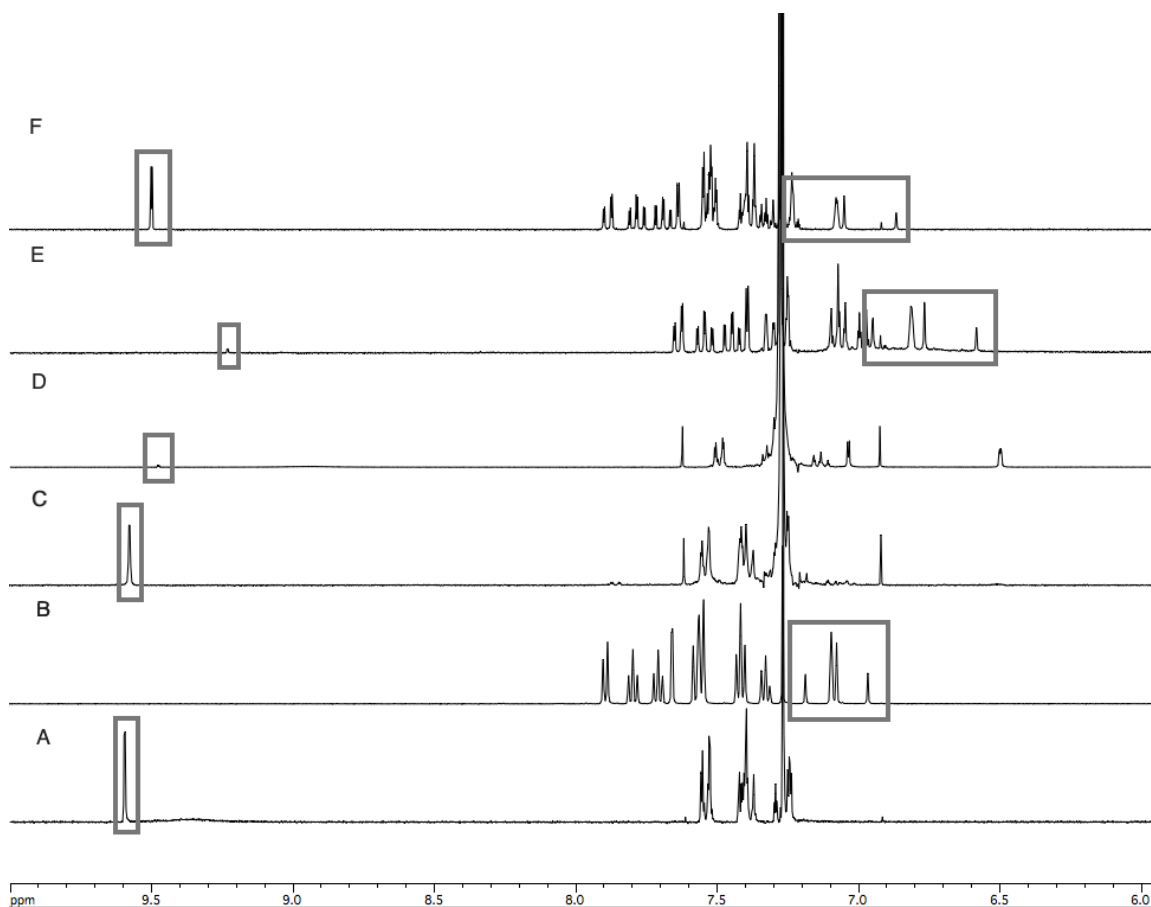
3.2.6 An Investigation of the Hydrolysis of α -Difluoromethyl Groups

All described attempts to remove the *N*-benzenesulfonyl protecting group from a difluoromethylated pyrrole have resulted in the isolation of the respective aldehyde. Even when employing β -substituted pyrrole **3.81** in the methanolic NaOH-mediated deprotection reaction,⁴⁶ it was found that only the aldehyde could be isolated (Scheme 3 - 44). The added conjugation did not provide stabilization for the difluoromethyl group under the reaction conditions provided.



To this regard, the nature of the solvent was explored for its effect on stabilizing the difluoromethyl group and preventing the formation of the aldehyde (Figure 3 - 9). To investigate the effects of the solvent employed, the deprotection reaction was performed in a series of solutions using polar protic or aprotic solvents and aqueous NaOH on β -substituted pyrrole **3.81** at 50 °C. Upon consumption of the starting *N*-benzenesulfonyl protected pyrrole, monitored by use of TLC analysis, a small scale extraction was performed on the reaction mixture. The reaction mixture was diluted with CDCl₃, was quickly washed with water, and the organic layer was studied using ¹H NMR spectroscopy after drying over Na₂SO₄.

Figure 3 - 9: ^1H NMR Spectra of the Deprotection of 3.118 in Various Solvents^a



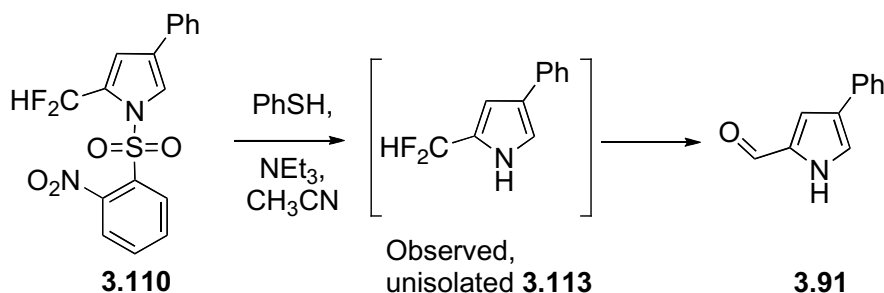
^aA = **3.91**, B = **3.81**, C = deprotection in H_2O , D = deprotection in CH_3OH , E = deprotection in THF, F = deprotection in *iso*-propanol; all spectra collected using CDCl_3 as the deuterated solvent.

The *N*-deprotected difluoromethyl pyrrole was noted using ^1H NMR spectroscopy when employing THF or *iso*-propanol (spectra E and F, respectively, as shown in Figure 3 - 9) as the reaction solvent, but not when employing water or methanol (spectra C and D respectively). Unfortunately, the difluoromethyl pyrrole **3.113** still was not isolated, and the aldehyde **3.91** was isolated in its place (48 %). The deprotected difluoromethyl pyrrole appeared to be the major product when employing THF as the reaction solvent, but trace aldehyde had begun to form *in situ*. This showed that the difluoromethyl group was sensitive to NaOH-mediated hydrolysis.

It was then decided that *N*-deprotection should be performed under anhydrous reaction conditions as a strategy to avoid the deleterious hydrolysis reaction. The *N*-*o*-nosyl protected substrates were found to be appropriate for this purpose as this group can be *N*-deprotected under anhydrous conditions using 2.5 equiv. triethylamine and 1.8

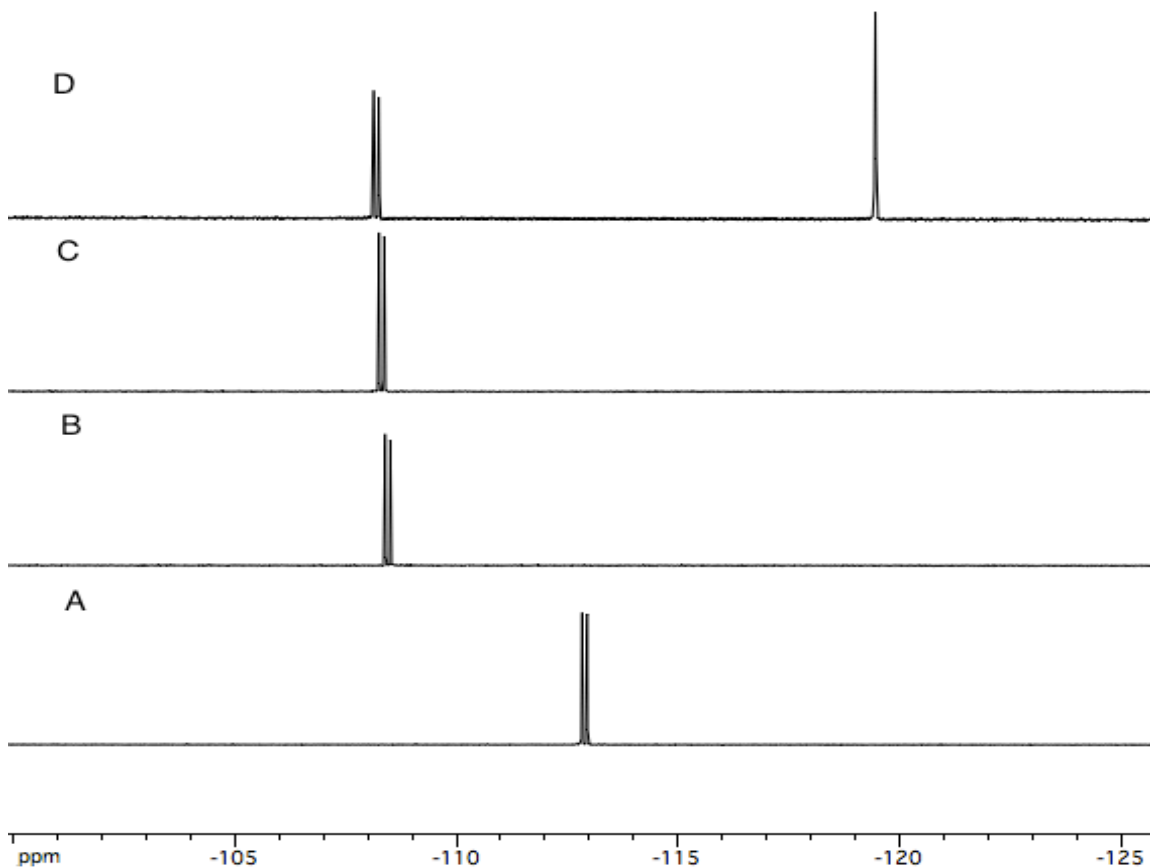
equiv. of thiophenol.⁸⁷ Unfortunately, the use of this strategy to *N*-deprotect **3.110** also resulted in the isolation of aldehyde **3.91**, albeit in a much higher yield (93 %, Scheme 3 - 45).

Scheme 3 - 45: Deprotection of 3.110



The deprotection of *N*-nosyl protected pyrrole **3.110** was also monitored by use of ¹H and ¹⁹F NMR spectroscopy, initiated by the addition of 1.8 equiv. PhSH and 2.5 equiv. NEt₃ in CH₃CN through a septum. The doublet signal that arose from the α-difluoromethyl group of the *N*-deprotected pyrrole **3.110** (spectrum A, Figure 3 - 10) was noted to shift downfield from the *N*-protected pyrrole (**3.113**, spectrum B) in the ¹⁹F NMR spectrum. The *N*-deprotected pyrrole (**3.113**) was found to persist as long as the reaction vessel remained under an inert, anhydrous environment (as demonstrated in spectrum C, Figure 3 - 10, 24 hours post-deprotection). The hydrolysis of the α-difluoromethyl group began immediately after the intentional introduction of water through a septum causing a second signal to arise upfield from the *N*-deprotected pyrrole signal, owing to the presence of free fluoride (singlet, spectrum D). This observation allowed for the delineation of the *N*-deprotection producing **3.113**, and subsequent hydrolysis reactions in producing **3.91**. An anhydrous environment was key to studying the two reactions separately.

Figure 3 - 10: *N*-Deprotection and Hydrolysis of 3.110, as Monitored by ¹⁹F NMR Spectroscopy^a



^aA=3.110, B = 3.113, C = 3.113 24 hours post-deprotection, D = 3.113 5 min after addition of H₂O; all spectra collected using CD₃CN as the deuterated solvent.

Five *N*-protected difluoromethyl pyrroles (**3.108** to **3.112**, Table 3 - 5) were used to study the substituent effects upon the rates of *N*-deprotection and of the hydrolysis of the difluoromethyl group. A Hammett plot was felt to be suitable to show this relationship in a quantifiable manner.

Louis Plack Hammett first developed Hammett relationships in 1937.⁸⁸ The nature of the substituents were found to play a role on the activation energy of a reaction, which directly affected the reaction constant. Using the relative calculated rate constants of this two-step process, the Hammett linear free energy relationships can be determined using the Hammett equation (Equation 3 - 1). The reaction mechanisms were proposed by use of these results.

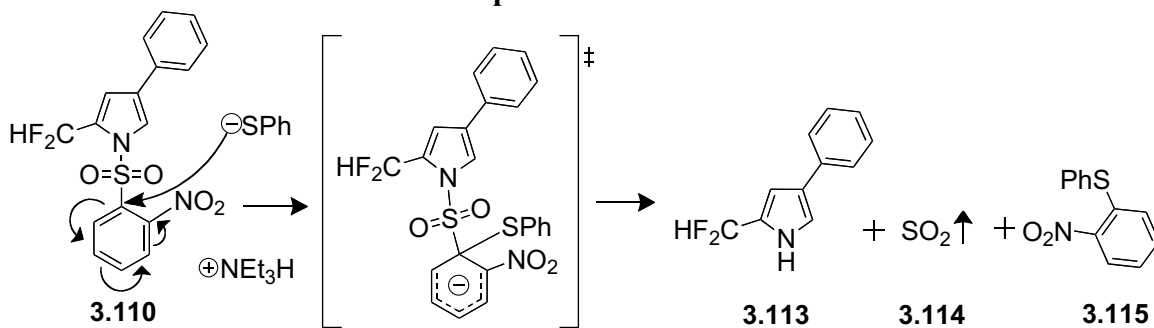
Equation 3 - 1: Hammett Equation

$$\log\left(\frac{k_R}{k_H}\right) = \rho\sigma$$

3.2.7 A Kinetic Study of the *N*-Deprotection of α -Difluoromethyl Pyrroles

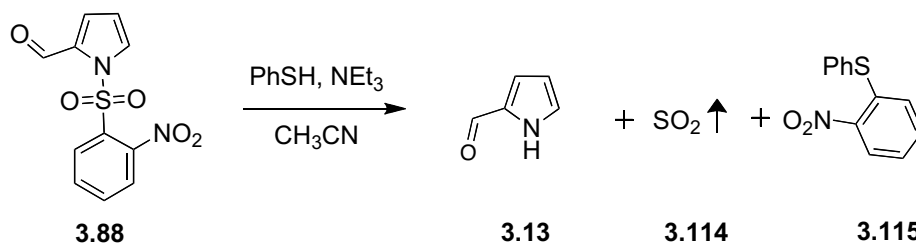
The deprotection reaction involved in this study was monitored using absorption spectrophotometry. Absorption spectrophotometry was chosen over NMR spectroscopy, due to the increased rate of the reaction when using pseudo-first order reaction conditions (equilibrium <1 min at 0 °C, $\sim 4 \times 10^{-4}$ M, exact concentrations *vide infra*). Data was collected at 1×10^{-1} s time points using absorption spectrophotometry, which was much faster than NMR spectroscopy (1.2 min per data point). Furthermore, deprotection of the *N*-*o*-nosyl pyrroles produced a yellow byproduct, thioether **3.115**. The deprotection of **3.110** was therefore monitored by the formation of **3.115** (Scheme 3 - 46).

Scheme 3 - 46: Deprotection Mechanism of **3.110**



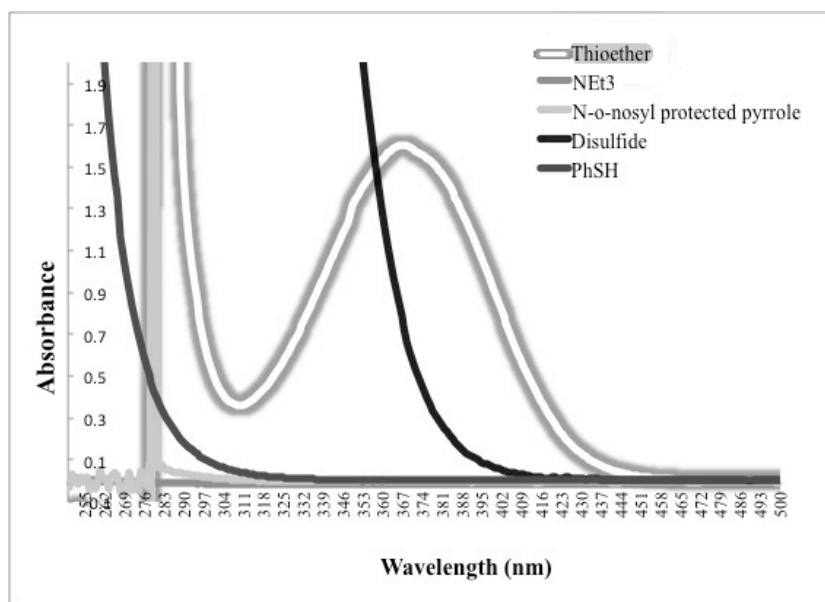
The thioether **3.115** is a known compound, but finding its extinction coefficient in CH_3CN proved to be unfruitful ($\epsilon_{\text{EtOH}} = 4500 \text{ L mol}^{-1} \text{ cm}^{-1}$, reported as $\log \epsilon$).⁸⁹ The compound **3.115** was prepared from the intentional deprotection of *N*-*o*-nosyl protected formyl pyrrole (**3.88**) using PhSH and NEt_3 , and was isolated in quantitative yield (Scheme 3 - 47). After confirming the structure using ^1H NMR spectroscopy, the absorption spectrum was collected in CH_3CN . The thioether **3.115** exhibited an absorption maximum at 368 nm (as previously reported⁸⁹), with an extinction coefficient of $4000 \text{ L mol}^{-1} \text{ cm}^{-1}$ in CH_3CN .

Scheme 3 - 47: Synthesis of 3.115



The absorbance maximum that was produced by thioether **3.115** does not incur interference from any of the five *N*-*o*-nosyl protected pyrroles or PhSH, which all displayed intense absorbance below 290 nm (Figure 3 - 11).

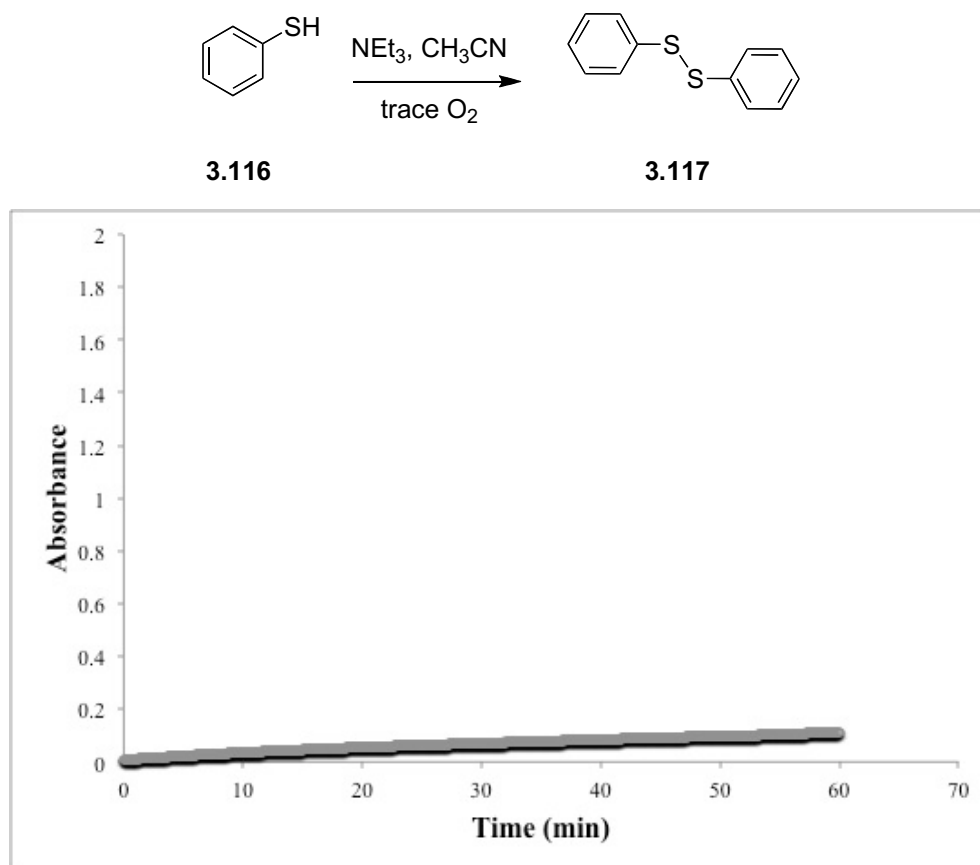
Figure 3 - 11: Absorbance Data for the Deprotection Reaction Starting Materials and Thioether Product^a



^a Spectra collected at the maximum concentrations present in the reaction studied:
3.110 = 4.0×10^{-4} M, **3.115** = 4.0×10^{-4} M, NEt_3 = 2.2×10^{-1} M, PhSH = 1.6×10^{-1} M, **3.117** = 1.9×10^{-2} M

A mixture of NEt_3 and PhSH in CH_3CN was analyzed over a period of 1 hour to probe for interference at the monitored wavelength (368 nm). No interference occurred within the first minute of this experiment, but gradual formation of disulfide **3.117** formed within the hour ($A = 0.112$, 2.83×10^{-3} M). Perhaps, this resulted from unintentional introduction of oxygen into the system.⁹⁰⁻⁹² Fortunately, this side reaction occurred outside of the time scale of the experiment.

Figure 3 - 12: Formation of Disulfide 3.117, as Monitored at 368 nm

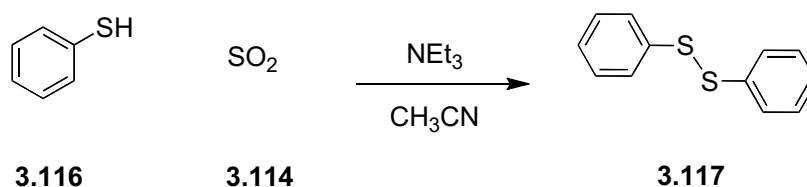


To safeguard against the formation of **3.117** during the *N*-deprotection experiment *via* oxygen-mediated oxidation, a steady flow of dry nitrogen gas was introduced into the collection chamber of the UV-Vis spectrophotometer. However, upon careful inspection of the *N*-deprotection of **3.110** under pseudo-first order conditions (400 equiv. PhSH, 560 equiv. NEt₃, CH₃CN, 0 °C, N₂) using TLC analysis, the reaction mixture was found to contain disulfide **3.117**, in addition to the expected reaction mixture (**3.115**, **3.116**, hydrolysis product **3.91** from exposure to silica, and a compound that was presumed to be **3.113**). Given that the reaction was performed anhydrously and the atmosphere of the collection chamber of the spectrometer was also nitrogen gas, the formation of **3.117** should have been prevented. In addition, the quantity of **3.117** that formed in the background of the *N*-deprotection reaction in a single minute (1.9×10^{-2} M in reaction mixture) was an order of magnitude larger than the quantity produced in an hour by oxygen (2.83×10^{-3} M, as depicted in Figure 3 - 12). Therefore, one or more alternative

oxidation pathways toward the formation of **3.117** were occurring during the *N*-deprotection reaction.

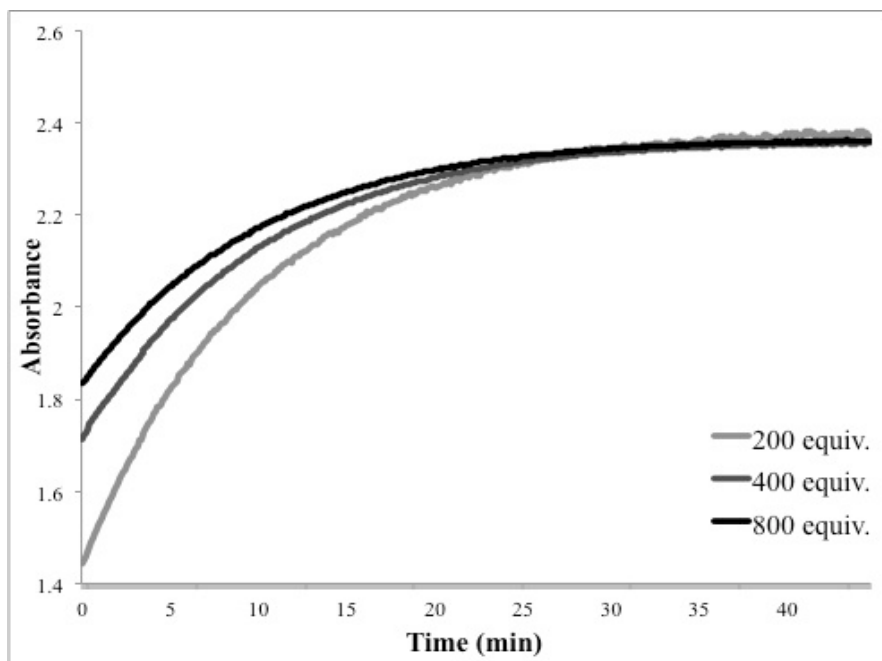
There are many reactions that afford **3.117**; e.g., thiophenol **3.116** is known to afford disulfide **3.117** in the presence of an oxidizing agent and a base.^{90,91,93,94} Sulfur dioxide is also known to act as an oxidizing agent.⁹⁵⁻⁹⁷ As sulfur dioxide (**3.114**) was produced as a byproduct of *N*-*o*-nosyl deprotection, it may have been participating in one or more of these additional oxidation pathways as the oxidizing agent (Scheme 3 - 48).

Scheme 3 - 48: Example of Potential Background Oxidation Occurring During *N*-Deprotection



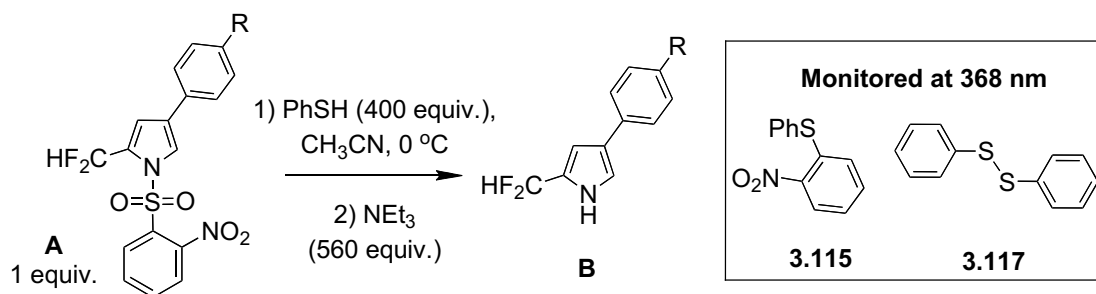
As a qualitative analysis, the deprotection reaction was conducted on **3.110** at a concentration of 4.078×10^{-4} M under anhydrous conditions in CH₃CN at 0 °C (Figure 3 - 13). The deprotection was varied by adding 200, 400, or 800 equiv. of PhSH to the solution. To initiate deprotection, 280, 560, or 1200 equiv. of NEt₃ (respectively) was added under anhydrous conditions *via* a septum of a cuvette. The deprotection reaction reached equilibrium within 45 seconds at 200 equiv. of PhSH, and within 35 seconds at 400 equiv. of PhSH. The reaction reached equilibrium at approximately the same time when employing 800 equiv. of PhSH as with 400 equiv. of PhSH, qualitatively showing saturation of the rate constant was achieved when employing 400 equiv. of PhSH. It was decided to go forward using 400 equiv. of PhSH and 560 equiv. of NEt₃.

Figure 3 - 13: Qualitative Saturation of the Rate Constant of the Deprotection of 3.110



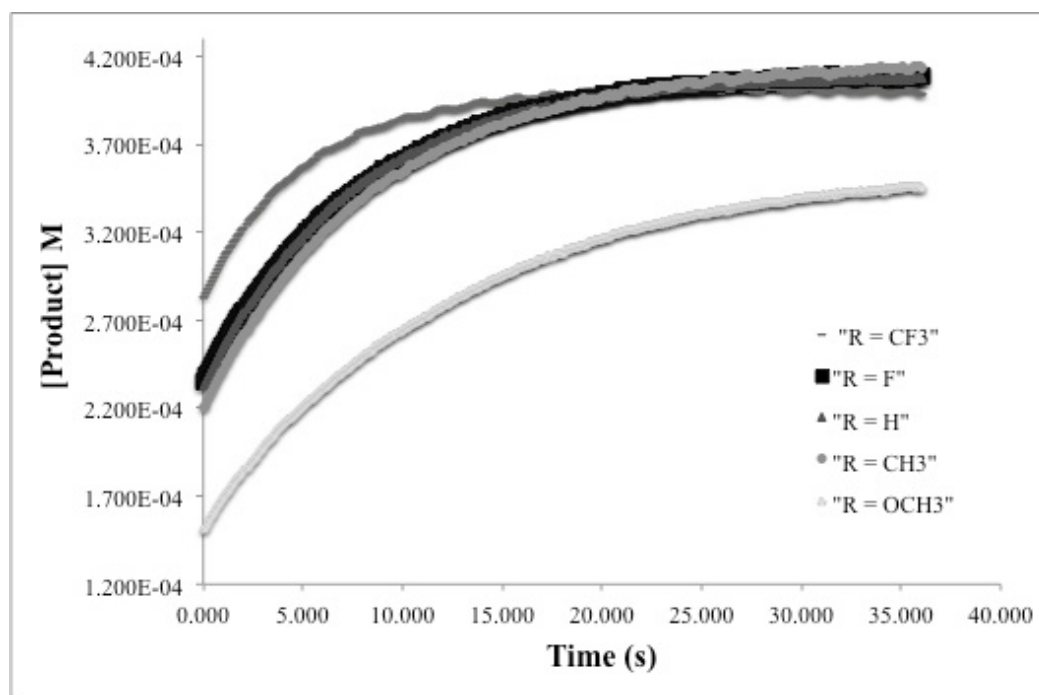
The deprotection of the *N*-*o*-nosyl protected series (A, Scheme 3 - 49) was performed at the concentrations indicated for each substrate. Cuvettes equipped with a septum cover were charged with an anhydrous solution of the pyrrole (1 equiv.) and PhSH (400 equiv.) in CH₃CN at 0 °C (Scheme 3 - 49). The deprotection reaction was initiated by the injection of an anhydrous solution of NEt₃ (560 equiv.) through the septum of the cuvette.

Scheme 3 - 49: Pseudo-First Order Deprotection of *N*-*o*-Nosyl Protected α -Difluoromethyl Pyrroles, As Monitored by 3.115



By the application of the Beer-Lambert law using the respective calculated extinction coefficient of the multichromophore system to relate absorbance to concentration, the evolution of *N*-deprotected difluoromethyl pyrrole over time was plotted graphically (Figure 3 - 14).

Figure 3 - 14: Evolution of *N*-Deprotected α -Difluoromethyl Pyrroles Over Time



The formation of disulfide **3.117** caused interference to the absorbance reading at 368 nm during the kinetic study, which arose from the presence of thioether **3.115**. The interference incurred by **3.117** caused the artificial overproduction of **3.115** (i.e. >100 % conversion). However, overproduction was consistent across the sample set (Table 3 - 6). Given that **3.117** may have formed by a variety of mechanisms, the reaction constants reported herein were not accurate and were exclusively for use in determining a trend within this sample set.

Table 3 - 6: Theoretical Change in Absorbance at 368 nm Produced by 100 % Conversion of Fluorinated *N*-*o*-Nosyl Protected Pyrroles to Thioether 3.115 Compared to the Experimental Absorbance

R	Final Concentration of Pyrrole (M)	Expected Absorbance Achieved by 100 % Conversion to 3.115	Average^a Final Absorbance Value at Equilibrium (Discrepancy)	% Overproduction
CF₃	4.033X10 ⁻⁴	1.613	2.378 (0.765)	47
F	4.109X10 ⁻⁴	1.644	2.456 (0.812)	49
H	4.078X10 ⁻⁴	1.631	2.370 (0.739)	45
CH₃	4.150X10 ⁻⁴	1.660	2.360 (0.700)	42
OCH₃	3.568X10 ⁻⁴ ^b	1.427	2.094 (0.667)	47

^a Average absorbance reading at equilibrium in the duplicated experiments;

^b This concentration was lower due to measurement error in preparing the stock solution

As the concentration of PhSH (reactant ‘B’) was in great excess relative to the fluorinated *N*-*o*-nosyl pyrroles (reactant ‘A’), we can assume that the concentration ‘B’ remained constant through the experiment. The relative rate constants were calculated from (Equation 3 - 2) for each substrate.

Equation 3 - 2: Pseudo-first Order Rate Equation

$$rate = \frac{d[A]}{dt} = -k[A][B] = -k'[A]; \text{ where } k' = k[B]$$

The reaction was monitored *via* the evolution of product, rather than the consumption of starting material. The concentration of **3.110** or ‘A’ decreases at the same rate as the monitored product **3.115** forms (henceforth called ‘P’). The amount of starting material remaining at any time ‘[A]_{*t*}’ will be equal to the amount of starting material in the reaction mixture initially present in the reaction mixture ‘[A]_{*i*}’ less the amount of product present in the reaction mixture at that same time ‘[P]_{*t*}’. Since this deprotection reaction was quantitative under anhydrous conditions, an assumption can be made that the

concentration of the starting material initially present $[A]_i$ in the reaction mixture was the same concentration of product formed upon completion of the reaction $[P]_\infty$. This relationship was demonstrated through Equation 3 - 3.

Equation 3 - 3: The Mathematical Relationship Between Product and Starting Material at Any Time During the Course of the Reaction

$$[A]_t = [A]_i - [P]_t$$

$$[A]_t = [P]_\infty - [P]_t$$

Please note that the amount of starting material present initially was defined as $[A]_i$, rather than $[A]_0$; this was due an unavoidable delay caused by the manual injection of NEt_3 and manual start of data collection resulting in about 5 seconds of missed data. Again, the data collected was meant to be for qualitative observation only. Since this error was consistent across all samples, the discrepancy was accounted for mathematically. The amount of starting material present when the instrument began the recording absorbance values $[A]_0$ (rather than the reaction time zero, $[A]_i$) was equal to the amount of starting material at the reaction time zero $[A]_i$ less the amount of product that had already formed by instrument time zero $[P]_0$. Again, an assumption was made that the concentration of the starting material initially present $[A]_i$ was the same concentration of product formed $[P]_\infty$ upon completion of the reaction, since this reaction proceeds at a quantitative yield (Equation 3 - 4).

Equation 3 - 4: The Mathematical Relationship Between Product and Starting Material at the Beginning of Data Collection

$$[A]_0 = [A]_i - [P]_0$$

$$[A]_0 = [P]_\infty - [P]_0$$

By substituting this relationship into the integrated first order rate law, the equation employed to solve for the rate constant 'k' was manipulated to monitor the formation of product 'P' as a means of observing the consumption of starting material 'A' (Equation 3 - 5).

Equation 3 - 5: Derivation of the Rate Law for Formation of Product from the Integrated First Order Rate Equation

$$\ln[A]_t = -kt + \ln[A]_0$$

$$\ln[A]_t - \ln[A]_0 = -kt$$

$$\ln \frac{[A]_t}{[A]_0} = -kt$$

$$\frac{[A]_t}{[A]_0} = e^{-kt}$$

$$\frac{[P]_\infty - [P]_t}{[P]_\infty - [P]_0} = e^{-kt}$$

$$-[P]_t = ([P]_\infty - [P]_0)e^{-kt} - [P]_\infty$$

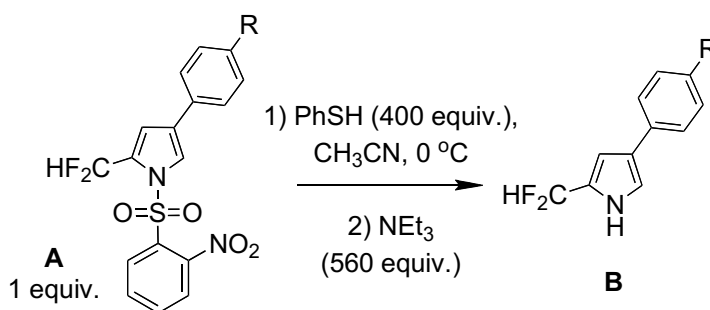
$$[P]_t = -([P]_\infty - [P]_0)e^{-kt} + [P]_\infty; \text{ where } k = k'$$

Each substrate was analyzed in triplicate. Experimental error was unavoidable and some substrates were limited to duplicate experiments due to error in the collection of data. As such, the results are analyzed with two replicates. Since each population (group of replicates for each substrate) was an extremely small sample size ($n = 2$), extensive statistical analysis was not pursued. Levene's test was used to probe if the variances across two or more groups are equal, or if the groups are different.⁹⁸ This test is usually done as a preliminary comparison of means, but can also be used to answer the stand-alone question of "are my populations heterogeneous or equal?" as it tests a null hypothesis that the variances are equal across a population.⁹⁸ In my case, the resulting p-value was less than 0.05 (p-value = <0.0001 , using SPSS Levene's Test on XLSTAT for Mac) and the null hypothesis was rejected; this is to say that the variances observed are unlikely to have occurred from a equal population and so the differences recorded between the samples were very likely to have been real.⁹⁸ That said, with only two replicates of each population it may be more accurate to say that the data was trending towards statistical significance than to boldly claim statistical significance from one low-level test.

Regardless, the results reported were analyzed as relative rate constants within this substrate set at the concentrations employed, and not as absolute rate constants for the reported deprotection reaction. More replicates would have been required to confirm the

absolute individual rates of each reaction, and the previously noted discrepancies would need to be corrected experimentally. The presented analysis, however, was sufficient for my purposes, as the results herein have demonstrated that there was a relative substituent effect on the rate of reaction. No further analysis was felt necessary for the purpose of this study. After confirming the rate constants of each substrate, the rates were digested into a linear free-energy relationship by using the Hammett equation (Equation 3 - 1). As hypothesized, the varying β -aryl moieties induced differences in the relative rate constants for this deprotection reaction (Table 3 - 7).

Table 3 - 7: Rate Constants and Relevant Hammett Parameters for the Deprotection of *N*-Nosyl Protected Pyrroles



Entry (#)	Substituent (R)	[Starting Material] (M)	Rate Constants (s^{-1}) ^a	σ^b	$\log\left(\frac{K_R}{K_H}\right)$
1 (3.108-A)	CF_3	4.033×10^{-4}	$(1.962 \pm 0.001) \times 10^{-2}$	0.54	0.19
2 (3.109-A)	F	4.109×10^{-4}	$(1.230 \pm 0.038) \times 10^{-2}$	0.06	-0.01
3 (3.110-A)	H	4.078×10^{-4}	$(1.236 \pm 0.077) \times 10^{-2}$	0	0.000
4 (3.111-A)	CH_3	4.150×10^{-4}	$(1.193 \pm 0.026) \times 10^{-2}$	-0.17	-0.02
5 (3.112-A)	OCH_3	3.568×10^{-4} ^c	$(0.807 \pm 0.016) \times 10^{-2}$	-0.27	-0.19

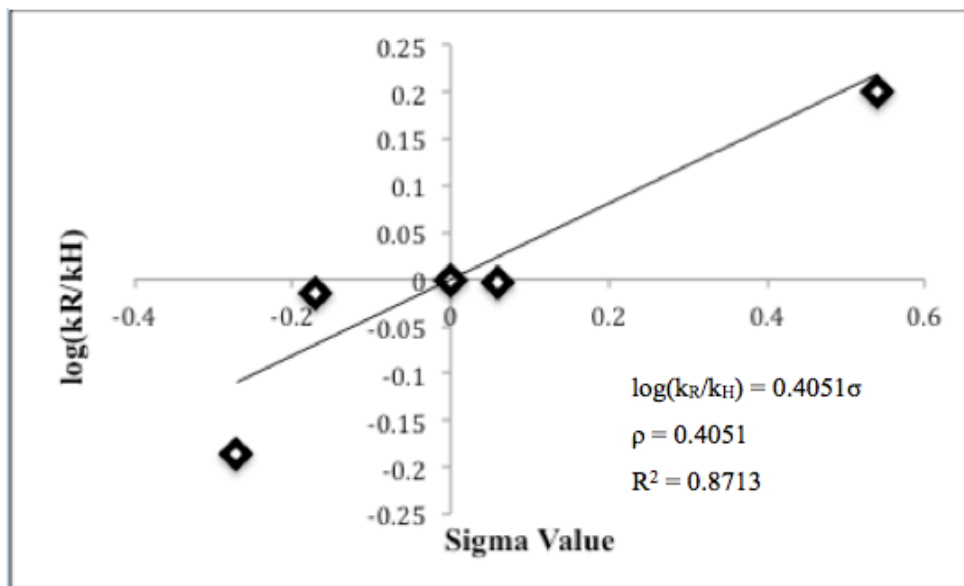
^a rate constants calculated on two replicates of each substrate using Kaleidagraph v 4.1.3 and error on replicates calculated using XLSTAT v 2015.4.01.21576; ^bAs reported in a review by Taft et. al⁹⁹;

^cThis concentration is lower due to a measurement error in preparing the stock solution

The presence of strong electron-withdrawing character was found to be an asset for inducing a faster rate of deprotection (entry 1, **3.108**). Weakly donating (entry 4, **3.111**) and weakly withdrawing character (entry 2, **3.109**) both impeded the rate of the reaction only slightly from the standard compound (entry 3, **3.110**). However, strong

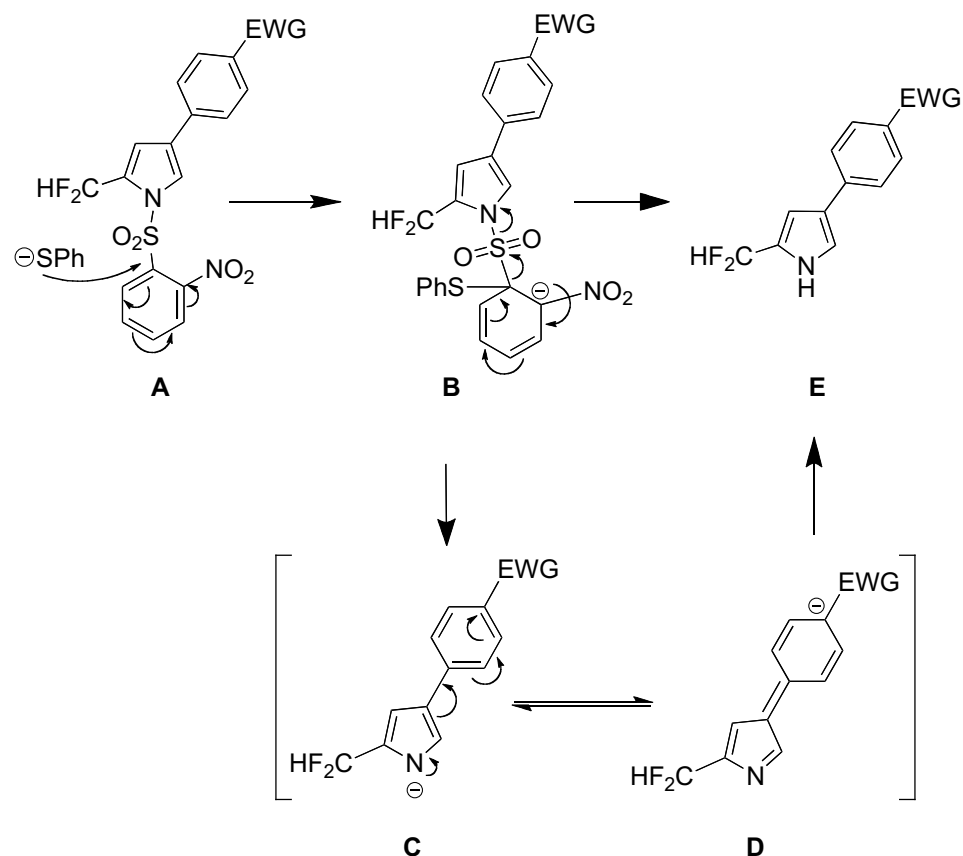
electron-donating character was found to impede the rate significantly (entry 5, **3.112**). The rho value was found to be 0.4, suggesting that there was a build up of negative charge in the reaction intermediate (Figure 3 - 15).

Figure 3 - 15: Deprotection Hammett Plot



These results suggest that electron-withdrawing groups were able to stabilize the negative charge that was formally deposited on the nitrogen atom of **C** (Scheme 3 - 50) after the Meisenheimer-like intermediate **B** has collapsed to *N*-deprotect the pyrrole. Although negative charge character resulting from this *N*-deprotection can be delocalized within all five of the aromatic pyrrolic systems, substrates bearing electron-withdrawing groups have an additional stabilization pathway by resonance *via* the phenyl ring (**C** to **D**, Scheme 3 - 50). This additional pathway allowed for ready acceptance of electronic density resulting from the elimination of the thioether **3.115** and sulfur dioxide **3.114**. As such, it was beneficial for the substituent present on the β -phenyl group of the difluoromethyl pyrrole to have the capacity to stabilize negative charge character (i.e., electron-withdrawing).

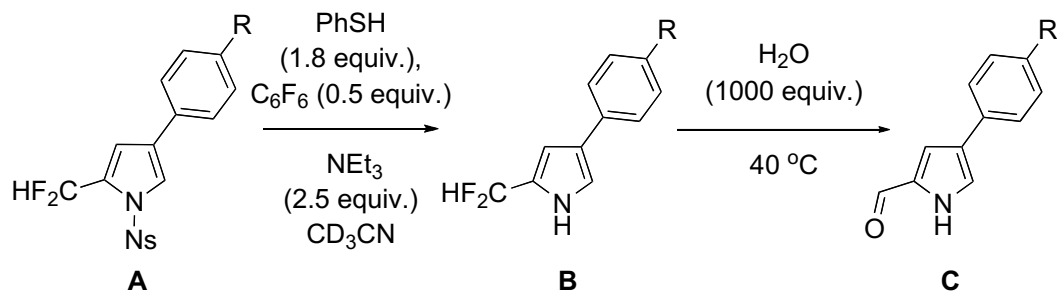
Scheme 3 - 50: Proposed Deprotection Mechanism



3.2.8 A Kinetic Study of the Hydrolysis of α -Difluoromethyl Groups

The absorption spectrophotometry technique employed had facilitated a kinetic study of the first step of this two-part hydrolysis of a CF_2H group; by monitoring the formation of the thioester byproduct **3.115/3.117** (and deprotected pyrrole), rate constants for each reaction was determined for the *N*-deprotection each of the five fluorinated *N*-*o*-nosyl protected pyrroles. The Hammett relationship was then established from the rate constants and showed that there was a negative charge build up in the transition state, which was consistent with the proposed mechanism. The second part of the transformation in question was the actual loss of fluoride by hydrolysis (**B** to **C**, Scheme 3 - 51). The Hammett relationship was then determined, to make inferences towards the mechanism.

**Scheme 3 - 51: The Hydrolysis of the Difluoromethyl Group,
As Monitored by ^{19}F NMR Spectroscopy**



The kinetics of the hydrolysis reaction was monitored using ^{19}F NMR spectrometry. The loss of fluoride through hydrolysis was readily observed by employing a fluorinated internal standard. As the reaction progressed, the signal arising from the pyrrole difluoromethyl group reduced in intensity with respect to the inert internal standard (hexafluorobenzene).

This reaction also followed pseudo-first order rate law with respect to the pyrrole, where 1000 equiv. of water was added to an NMR tube through a septum. The NMR tube contained a freshly deprotected fluorinated pyrrole (2.5 equiv. NEt_3 ; 1.8 equiv. PhSH), with 0.5 equiv. of hexafluorobenzene (to create an initial 2:3 ratio between the ^{19}F NMR signals of the pyrrole to the internal standard), as well as the reaction mixture that arose from the deprotection reaction (NEt_3 , PhSH , **3.150**), at a total concentration of $\sim 1.4 \times 10^{-2}$ M in CD_3CN .

Before initiating the experiment, ^1H and ^{19}F NMR spectroscopy was used to confirm that the reaction mixture contained only the fluorinated $N\text{-H}$ pyrrole and not the hydrolyzed final product, which formed if due care was not taken to ensure that the sealed NMR tube was dry and purged completely with N_2 gas. The ^{19}F NMR spectrum was also used for the purpose of comparing the initial integration of the internal standard to the starting material **B** (Scheme 3 - 51), as a time of zero data point. The initial concentration of the N -deprotected pyrrole was confirmed by calculation of the theoretical concentration. This calculation was performed by use of the integration values of the ^{19}F NMR signals arising from **B** and hexafluorobenzene, as well as the known concentration of hexafluorobenzene.

Water was administered through the septum of the NMR tube to initiate the hydrolysis of the difluoromethyl group. The consumption of **B** (Scheme 3 - 51) was monitored until the reaction reached equilibrium. However, equilibrium in this case does not mean that the reaction has gone to completion, as seen in the deprotection reaction. In the case of the hydrolysis reaction, the amount of water required to drive the reaction to 100 % consumption of the starting pyrrole **B** caused the standard hexafluorobenzene to form a second layer in the reaction mixture and, consequently, caused a massive decrease in its signal from the ^{19}F NMR spectrum. As such, 1000 equiv. of water was chosen to initiate hydrolysis of the deprotected pyrrole because it was still present in great excess with respect to the starting material, but did not disturb the homogeneity of the reaction mixture.

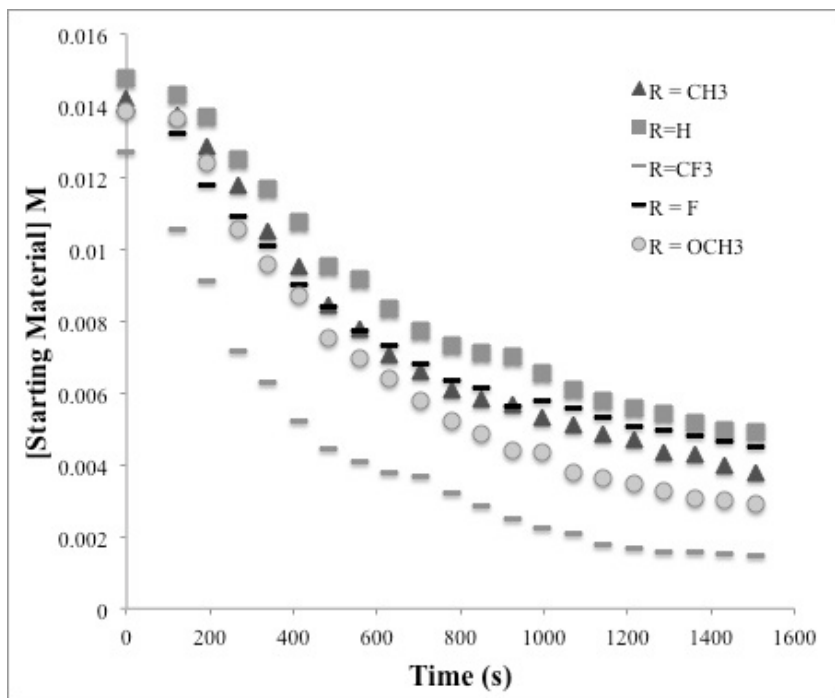
The time required to inject the water into the NMR tube through a septum, ensure homogeneity of the sample (agitation by vortex mixer) and insert the sample into the NMR spectrometer was measured with a stopwatch and accounted for in the first data point. The hydrolysis reaction reached equilibrium 25 minutes after the introduction of water into the previously anhydrous system when monitoring using ^{19}F NMR at room temperature (25 °C) for most substrates. The temperature was thus increased to 40 °C so that all substrates had reached equilibrium after 25 minutes of monitoring the hydrolysis of the difluoromethyl group. The internal standard was used to integrate the ^{19}F NMR peak evolving from the difluoromethyl group and this value was used to calculate the associated concentration, using Equation 3 - 6. The concentration of the starting material at any point in time ' $[A]_t$ ' was directly proportional to the ratio between the peak integral resulting from the starting material that was present at the time in question ' $\int A_t$ ' and the peak integral that was collected before the reaction began ' $\int A_0$ ' (which are both calculated using the internal standard), multiplied by the concentration of the starting material present before the reaction began ' $[A]_0$ '.

Equation 3 - 6: Calculating the Concentration of Starting Material Remaining Using the Integrations of the ^{19}F NMR signal

$$[A]_t = \frac{\int A_t}{\int A_0} [A]_0$$

Using this information, the consumption of *N*-deprotected difluoromethyl pyrrole was plotted graphically over time (Figure 3 - 16).

Figure 3 - 16: Hydrolysis of *N*-Deprotected Difluoromethyl Pyrroles Over Time



Since this technique monitors the consumption of starting material, rather than the evolution of product as in the first step, the first order rate law can be used without modification (Equation 3 - 7).

Equation 3 - 7: Rate Law for the Hydrolysis of the Difluoromethyl Group, from the Integrated First Order Rate Equation

$$\ln[A]_t = -kt + \ln[A]_0$$

$$\ln[A]_t - \ln[A]_0 = -kt$$

$$\ln \frac{[A]_t}{[A]_0} = -kt$$

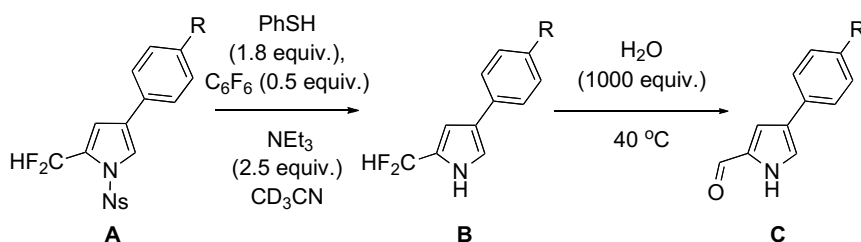
$$\frac{[A]_t}{[A]_0} = e^{-kt}$$

$$[A]_t = [A]_0 e^{-kt}$$

Each substrate was analyzed in triplicate, and the data was treated as a small sample size ($n = 3$). As before, extensive statistical analysis was not pursued due to sample size, but a Levene's test was performed to demonstrate heterogeneity across the substrates.⁹⁸ In my case, the resulting p-value was less than 0.05 (p-value = 0.020, using SPSS Levene's Test on XLSTAT for Mac) and the null hypothesis was rejected; this is to say that the differences noted in the reaction constants of each substrates are likely to have been real.⁹⁸

The reported rate constants are relative within this sample set at the concentrations employed, and are not absolute constants. However, the data provided was sufficient to demonstrate that there was a substituent effect on the rate of reaction and no further analysis was felt necessary. After confirming the rate constants of each substrate, the relative rates were digested into a linear free-energy relationship by using (Equation 3 - 1) and then presented in the form of a Hammett plot.

Table 3 - 8: Rate Constants and Relevant Hammett Parameters for the Hydrolysis of the Difluoromethyl Group



Entry (#)	Substituent	[Starting Material] M	Rate Constant (s^{-1}) ^a	σ^b	$\log\left(\frac{K_R}{K_H}\right)$
1 (3.108-B)	CF ₃	1.400X10 ⁻²	(1.712 ± 0.092) X10 ⁻³	0.54	0.27
2 (3.109-B)	F	1.408X10 ⁻²	(0.966 ± 0.108) X10 ⁻³	0.06	0.02
3 (3.110-B)	H	1.501X10 ⁻²	(0.914 ± 0.094) X10 ⁻³	0	0
4 (3.111-B)	CH ₃	1.422X10 ⁻²	(1.021 ± 0.013) X10 ⁻³	-0.17	0.05
5 (3.112-B)	OCH ₃	1.450X10 ⁻²	(1.195 ± 0.025) X10 ⁻³	-0.27	0.12

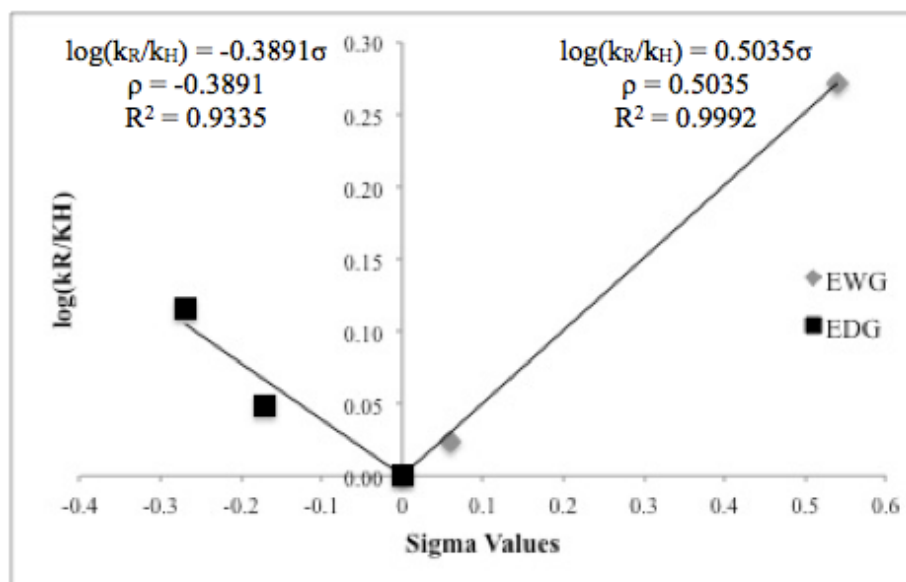
^a rate constants calculated using Kaleidagraph v 4.1.3 and error is calculated using XLSTAT v 2015.4.01.21576; ^bAs reported in a review by Taft et. al⁹⁹

As shown in the data, varying the β -aryl moieties on the difluoromethyl pyrrole induced subtle differences in the rate constants for the hydrolysis reaction (Table 3 - 8).

Pyrrole **3.108-B** displayed the fastest rate constant of the series ($R = CF_3$). That said, all of the substrates bearing substitution were faster than the control substrate **3.110-B** ($R = H$). The data bears resemblance to a concave up parabola with a minimum at $R = H$ when plotted using the Hammett equation.

Non-linear relationships were found to be known in Hammett plots,^{100,101} and simply implied the existence of two differing mechanisms. The mechanism that was followed by each particular substrate depended on the electronic character of the substituent effect in each case. The rho value for electron-donating groups was found to be -0.4, suggesting that there was a build up of positive charge or neutralization of negative charge in the reaction intermediate for substrates bearing an electron-donating group (left-hand slope, Figure 3 - 17). In contrast, the rho value for electron-withdrawing groups was found to be 0.5, suggesting that there was a build up of negative charge in the reaction intermediate (right-hand slope, Figure 3 - 17).

Figure 3 - 17: Hydrolysis Hammett Plot

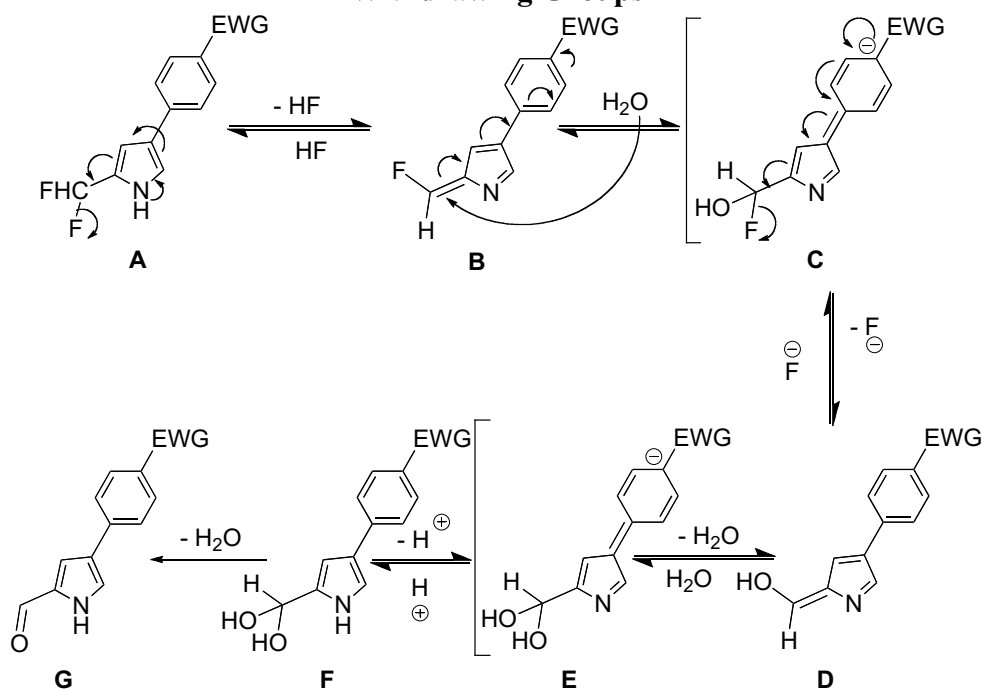


When proposing the mechanisms for this reaction, one must remember that the only difference in structure between these substrates was the *p*-substituent residing on the β -aryl moieties on the difluoromethyl pyrrole. The nature of the *p*-substituent was therefore responsible for inducing two different mechanisms, which are based on each

substituent's respective electronic character and the substituent's capacity to stabilize the type of charge character that was implied by the sign of the rho value.

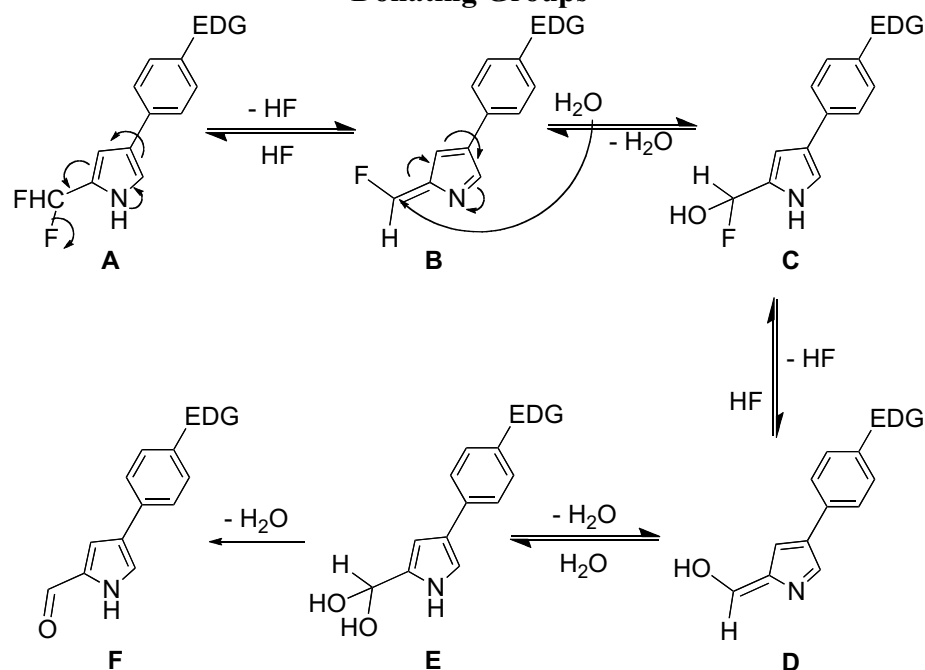
The β -aryl moieties presumably participated in the delocalization of electron density when subjecting substrates bearing electron-withdrawing groups to the hydrolysis reaction (Scheme 3 - 52), since this type of substituent could have helped to stabilize negative charge character. The proposed mechanism began by the ejection of a fluoride anion (**A**), under aqueous conditions, forming an azafulvene intermediate (**B** to **E**), followed by nucleophilic attack of water on the fluoromethene moiety (such as in **B**). The electron cloud can delocalize into the appended aryl group, stabilizing the resulting negative charge. This reaction also produced HF, but there was 2.5 equiv. of NEt_3 present in the reaction mixture from the *N*-deprotection reaction to produce the starting material. This reagent will participate in acid-base equilibrium with the remaining 0.8 equiv. of excess PhSH from the *N*-deprotection reaction, but some base was available for reaction with HF. This process would repeat until the difluoromethyl group was hydrolyzed to aldehyde (**G**).

Scheme 3 - 52: Proposed Hydrolysis Mechanism for Pyrroles Bearing Electron-Withdrawing Groups



The substrates bearing electron-donating groups could not have followed the same mechanism. Each nucleophilic attack on the fluoromethene moiety resulted in the reprotonation of the pyrrolic nitrogen (**B** to **C** or **D** to **E**, Scheme 3 - 53), rather than remaining as the azafulvene intermediate (**B**) throughout the course of hydrolysis.

Scheme 3 - 53: Proposed Hydrolysis Mechanism for Pyrroles Bearing Electron-Donating Groups



The potential for non-covalent interaction between the fluorine atom of the difluoromethyl group and water should also be noted, which could have acted as an initial step to the mechanism. There is precedence for benzylic fluorine bonds being activated by a hydroxyl functionality to make the fluorine atom a better leaving group in an S_N2 reaction.¹⁰² Indeed, both mechanisms proposed could be compared to an S_N2 ' nucleophilic conjugate substitution reaction with fluorine acting as the leaving group, which also has precedence.¹⁰³

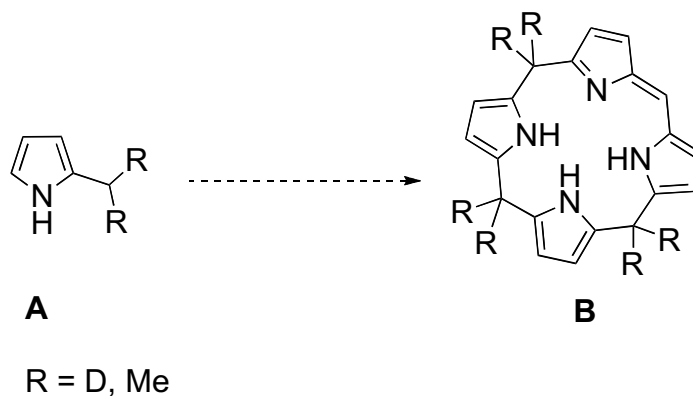
Fluorine would also be sequestered in water, as the anion is highly solvated by hydrogen bonding with the water molecules present in the reaction mixture.¹⁰⁴ This drives the equilibrium towards formyl pyrrole **F** (Scheme 3 - 53) as the fluoride anion was unavailable for nucleophilic substitution to promote the reverse reaction.

3.3 Conclusions and Future Directions

This study sought out a synthetic strategy through which to chemically trap porphomethenes en route to heme, in a manner that prevented auto-oxidation of the porphomethenes to the corresponding heme. Due to the propensity of pyrroles to access azafulvenium-like intermediates, the C-F bonds of an α -difluoromethyl substituent were found to be labile under hydrolytic conditions. As such, pyrrole building blocks containing α -difluoromethyl substituents were found to be unsuitable for use in the preparation of air-stable porphomethenes. A study was performed to investigate the apparent lability of the C-F bond in α -difluoromethyl pyrroles. The presence of an electron-withdrawing group tended to accelerate this process, as determined through the kinetics of the deprotection and subsequent hydrolysis reactions of *N*-protected β -aryl α -difluoromethyl pyrroles.

Given that α -difluoromethyl groups were determined as unstable isosteric replacements for α -methyl substituents of pyrrole, the choice of substituent replacement would have to be reconsidered to ensure stable pyrroles and dipyrromethanes *en route* to the target isostere **B** (previously R = F, Scheme 3 - 54). As mentioned in section 3.1.2, there are other isosteric replacement options that could be explored instead of fluorine atoms. Other examples of replacements for hydrogen atoms include deuterium atoms, or methyl groups. Future work could focus on the incorporation of either moiety as an isosteric replacement for two out of three hydrogen atoms on the α -methyl group of pyrroles (**A**, Scheme 3 - 54).

Scheme 3 - 54: Future Work



3.4 Experimental Procedures and Data for Chapter 3

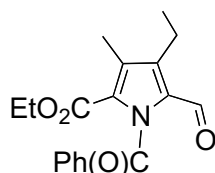
NMR spectra were recorded at the Atlantic Region Magnetic Resonance Centre (ARMRC). All ^1H and ^{13}C NMR spectra were obtained using a 500 MHz NMR spectrometer (operating at 500 MHz and 125 MHz, respectively) and CDCl_3 as solvent, unless otherwise stated. Chemical shifts were recorded in parts per million (ppm) with internal reference to CDCl_3 (^1H NMR at 7.26 ppm, ^{13}C NMR at 77.16 ppm), unless otherwise specified. ^{19}F NMR spectra were obtained using a 500 MHz NMR instrument (operating at 470 MHz) using trifluoroacetic acid (TFA, ^{19}F NMR at -76.55 ppm) as an external reference. Splitting patterns are indicated as follows: ad, apparent doublet; as, apparent singlet; at, apparent triplet; br, broad; s, singlet; d, doublet; dd, doublet of doublets; t, triplet; q, quartet; m, multiplet. Coupling constants (J) are reported in units of Hertz (Hz). High and low resolution ESI+ mass spectra were recorded by Mr. Xiao Feng from ion trap (ESI TOF) instruments. All microwave-promoted reactions were performed using a Biotage Initiator 8 laboratory microwave apparatus. 0-400 W power, 2.45 GHz. Melting points were uncorrected, and are exclusively reported for novel compounds. Column chromatography was performed using Silicycle 230-400 mesh ultra pure silica or Brockman (III) basic alumina, as indicated. Celite® 454 was used as a filtering agent, where indicated. Crude solvents for column chromatography and extractions were distilled under 1 atm of pressure prior to use. All other chemicals were used as received. TLC analysis was performed on silica gel or neutral alumina plates, visualized using UV light (254 nm) and/or developed with Vanillin stain. UV analysis was carried out using a Varian CARY 100 BIO UV-Visible spectrophotometer, with the baseline manually corrected for the solvent used and the wavelength measured in nm.

The following compounds were prepared according to literature procedures: **3.13**,¹⁰⁵ **3.23**,³² **3.25**,¹⁰⁶ **3.27**,¹⁰⁷ **3.36**,¹⁹ **3.77**,¹⁰⁸ **3.86**,¹⁰⁹ **3.88**,¹¹⁰ **3.90**,⁶² 1-phenyl-1*H*-pyrrole-2-carbaldehyde,¹¹¹ 1-benzyl-1*H*-pyrrole-2-carbaldehyde,¹¹² *N,N*-dimethyl 2-formyl-1*H*-pyrrole-1-sulfonamide,¹¹³ ethyl 4-ethyl-5-formyl-3-methyl-1*H*-pyrrole-2-carboxylate,¹¹⁴ 1-tosyl-1*H*-pyrrole-2-carbaldehyde,¹¹⁵ 3,4-dimethyl-1-(phenylsulfonyl)-1*H*-pyrrole-2-carbaldehyde,¹¹⁶ 3-(2-methoxycarbonyl-ethyl)-4-methyl-1*H*-pyrrole-2-carbaldehyde,¹¹⁷ benzyl 3-(2-methoxycarbonyl-ethyl)-4-(methoxycarbonylmethyl)-5-methyl-1*H*-pyrrole-2-

carboxylate⁴⁵ ; The following compounds were prepared by other Thompson group members: 1-methyl-1*H*-pyrrole-2-carbaldehyde,¹¹⁵ benzyl 2-formyl-1*H*-pyrrole-1-carboxylate,²⁵ **3.38**,²⁵ **3.44**.¹¹⁸

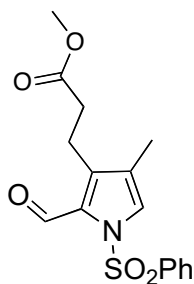
3.4.1 Synthesis of *N*-Protected 2-Formylpyrroles

Ethyl 1-benzoyl-4-ethyl-5-formyl-3-methyl-1*H*-pyrrole-2-carboxylate



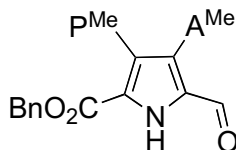
NEt₃ (1.03 mL, 7.4 mmol) and DMAP (0.090 g, 0.74 mmol) were added under N₂ to a stirring solution of **3.62**¹¹⁴ (2.092 g, 10 mmol) in anhydrous CH₂Cl₂ (4 mL). Benzoyl chloride (0.860 mL, 7.4 mmol) was added dropwise and the reaction was allowed to stir overnight at room temperature. The reaction mixture was diluted with 100 mL Et₂O, and then washed with aqueous sodium bicarbonate solution (100 mL), water (100 mL) and brine (100 mL). The organic phase was dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The title compound was isolated as a colourless solid (0.907 g, 40 % yield) after column chromatography (silica – 10 % Et₂O/hexanes). m.p.: 66-68 °C; ¹H NMR (CDCl₃, 500 MHz): δ 9.75 (s, 1H), 7.68 (d, 2H, *J* = 8), 7.58 (t, 1H, *J* = 8), 7.43 (t, 2H, *J* = 8), 4.11 (q, 2H, *J* = 7), 2.82 (q, 2H, *J* = 8), 2.34 (s, 3H), 1.24 (t, 3H, *J* = 8), 1.08 ppm (t, 3H, *J* = 7); ¹³C{¹H} NMR (CDCl₃, 125 MHz): δ 178.8, 169.9, 160.5, 137.9, 134.1, 131.5, 129.8, 128.9, 127.8, 127.3, 61.4, 17.3, 16.1, 13.9, 10.0 (1 x C missing) ppm; HRMS-ESI (*m/z*): [M + Na]⁺ Calcd 336.1206 for C₁₈H₁₉NNaO₄; found 336.1202.

3-(2-Methoxycarbonyl-ethyl)-4-methyl-1-(phenylsulfonyl)-1*H*-pyrrole-2-carbaldehyde



Benzenesulfonyl chloride (0.304 mL, 2.382 mmol) was added to an aggressively stirring solution of 3-(2-methoxycarbonylethyl)-4-methyl-1*H*-pyrrole-2-carbaldehyde¹¹⁷ (0.310 g, 1.588 mmol) and tetrabutylammonium bromide (0.015 g, 0.048 mmol) in a mixed solvent system of CH₂Cl₂ (1 mL) and 30 % aqueous NaOH (0.5 mL) at 0 °C. The reaction was stirred overnight, gradually warming to room temperature. Upon complete consumption of the starting pyrrole by TLC analysis, the reaction mixture was diluted with CH₂Cl₂ (30 mL) and H₂O (30 mL). The aqueous layer was extracted with CH₂Cl₂ and the combined organic layers were dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The title compound was isolated as a colourless solid (0.236 g, 44 % yield) after column chromatography (silica – 10 % Et₂O/hexanes). m.p.: 70-71 °C; ¹H NMR (CDCl₃, 500 MHz): δ 10.18 (s, 1H), 7.82-7.84 (m, 2H), 7.64 (t, 1H, *J* = 8), 7.53 (t, 2H, *J* = 8), 7.31 (s, 1H), 3.61 (s, 3H), 2.98 (t, 2H, *J* = 8), 2.50 (t, 2H, *J* = 8), 2.05 ppm (s, 3H); ¹³C{¹H} NMR (CDCl₃, 125 MHz): δ 180.6, 173.1, 139.7, 138.7, 134.4, 129.7, 129.6, 127.0, 126.4, 123.9, 51.7, 33.4, 20.8, 9.7 ppm; HRMS-ESI (*m/z*): [M + Na]⁺ Calcd 358.0720 for C₁₆H₁₇NNaO₅S; found 358.0719.

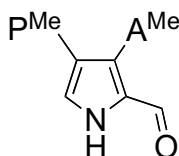
Benzyl 5-formyl-3-(2-methoxycarbonylethyl)-4-(methoxycarbonylmethyl)-1*H*-pyrrole-2-carboxylate



Cerium ammonium nitrate (CAN, 15.050 g, 27.450 mmol) was added to a stirring solution of benzyl 3-(2-methoxycarbonylethyl)-4-(methoxycarbonylmethyl)-5-methyl-1*H*-pyrrole-2-carboxylate (2.500 g, 6.695 mmol) in H₂O (100 mL), THF (100 mL), and acetic acid (25 mL) at 0 °C. The icebath was removed after CAN was fully dissolved. The reaction was stirred for 2 hours and then diluted with 300 mL of H₂O. The aqueous layer was extracted into CH₂Cl₂ and then the combined organic layers were washed with saturated aqueous sodium bicarbonate, followed by brine. The organic layer was dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The title compound was isolated as a colourless solid (2.594 g, 98 % yield) after column chromatography (silica – 20 %

EtOAc/hexanes). ^1H NMR (CDCl_3 , 500 MHz): δ 9.79 (br s, 1H), 9.76 (s, 1H) 7.32-7.41 (m, 5H), 5.33 (s, 2H), 3.83 (s, 2H), 3.70 (s, 3H), 3.62 (s, 3H), 3.03 (t, 2H, $J = 8$), 2.56 ppm (t, 2H, $J = 8$); $^{13}\text{C}\{^1\text{H}\}$ NMR (CDCl_3 , 125 MHz): δ 179.6, 173.4, 171.1, 160.1, 135.2, 130.8, 128.9, 128.8, 125.4, 124.1, 67.2, 52.6, 51.7, 34.5, 29.3, 19.9 ppm; HRMS-ESI (m/z): $[\text{M} + \text{Na}]^+$ Calcd 410.1210 for $\text{C}_{20}\text{H}_{21}\text{NNaO}_7$; found 410.1219. Spectral and physical properties were in agreement with previously reported data.⁴⁵

4-(2-Methoxycarbonylethyl)-3-(methoxycarbonylmethyl)-1H-pyrrole-2-carbaldehyde (3.56)



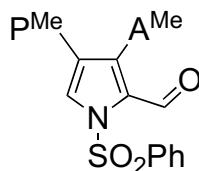
H_2SO_4 (3 mL) in TFA (10 mL) was added to a stirring solution of benzyl 5-formyl-3-(2-methoxycarbonylethyl)-4-(methoxycarbonylmethyl)-1H-pyrrole-2-carboxylate (2.500 g, 6.454 mmol) in TFA (5 mL). The reaction mixture was concentrated *in vacuo* after stirring for 30 minutes. The crude product was dissolved in 150 mL of EtOAc and extracted with 5 % aqueous sodium bicarbonate (4 x 20 mL). The combined aqueous layers were extracted once with EtOAc (100 mL), and then acidified to pH 2 using H_2SO_4 at 0 °C. The aqueous layer was extracted with EtOAc (3 x 100 mL). The organic layer was then concentrated *in vacuo* and subsequently dissolved in boiling H_2O with a small amount of charcoal. The charcoal was then filtered and the aqueous solution was concentrated *in vacuo*. The resulting colourless solid, 5-formyl-3-(2-methoxycarbonylethyl)-4-(methoxycarbonylmethyl)-1H-pyrrole-2-carboxylic acid (1.335 g, 70 %), was used without further purification for the next step.

5-formyl-3-(2-methoxycarbonylethyl)-4-(methoxycarbonylmethyl)-1H-pyrrole-2-carboxylic acid (1 g, 3.364 mmol) and sodium bicarbonate (0.848 g, 10.092 mmol) were dissolved in a mixed solvent system of CHCl_3 (12 mL) and H_2O (12 mL) and heated to reflux temperature with stirring. Once the reaction mixture had reached reflux temperature, a solution of KI (1.229 g, 7.401 mmol) and I_2 (1.025 g, 4.037 mmol) in H_2O (8 mL) was added dropwise. The reaction mixture was heated at reflux temperature for an additional 5 minutes, where the residual I_2 was quenched with sodium bisulfite (0.510 g).

After cooling, the reaction mixture was diluted with brine (120 mL) and CH₂Cl₂ (75 mL), and separated. The aqueous layer was then extracted with CH₂Cl₂ (3 x 60 mL), and the combined organic layers were dried over Na₂SO₄ and concentrated *in vacuo*. The resulting crude 5-iodo-4-(2-methoxycarbonylethyl)-3-(methoxycarbonylmethyl)-1*H*-pyrrole-2-carbaldehyde was dissolved in MeOH (80 mL) and bubbled with N₂ for 15 minutes before adding PtO₂ (0.153 g, 0.673 mmol) and sodium acetate (1.131 g, 13.456 mmol) under N₂. The atmosphere was purged and reestablished with H₂. After stirring for 1 hour, the catalyst was filtered using Celite® as a filtering agent, sodium bicarbonate (0.310 g) was added to the filtrate and the filtrate was concentrated *in vacuo*. The crude product was dissolved in CH₂Cl₂ (60 mL) and extracted with H₂O (200 mL). The aqueous layer was extracted with CH₂Cl₂ (5 x 60 mL), and the combined organic layers were dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The title compound was isolated as a colourless solid (0.852 g, 90 % yield) after column chromatography (silica – 1 % MeOH/CH₂Cl₂). ¹H NMR (CDCl₃, 500 MHz): δ 9.62 (br s, 2H, NH/aldehyde overlapping), 6.92 (s, 1H), 3.77 (s, 2H), 3.70 (s, 3H), 3.67 (s, 3H), 2.79 (t, 2H, *J* = 7), 2.58 ppm (t, 2H, *J* = 7); ¹³C{¹H} NMR (CDCl₃, 125 MHz): δ 178.1, 173.4, 171.2, 130.1, 125.6, 124.9, 124.2, 52.6, 51.8, 34.7, 29.6, 20.0 ppm; HRMS-ESI (*m/z*): [M + Na]⁺ Calcd 276.0842 for C₁₂H₁₅NNaO₅; found 276.0844. Spectral and physical properties were in agreement with previously reported data.⁴⁵

Note: each step of this procedure must be done in quick succession, or the overall yield will be significantly lower.

4-(2-Methoxycarbonylethyl)-3-(methoxycarbonylmethyl)-1-(phenylsulfonyl)-1*H*-pyrrole-2-carbaldehyde (3.57)

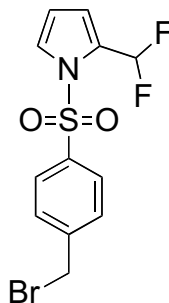


Benzenesulfonyl chloride (0.574 mL, 4.501 mmol) was added to an aggressively stirring solution of **3.56** (0.760 g, 3.001 mmol) and tetrabutylammonium bromide (0.029 g, 0.090

mmol) in a mixed solvent system of CH₂Cl₂ (1 mL) and 30 % aqueous NaOH (0.5 mL) at 0 °C. The reaction was stirred overnight, gradually warming to room temperature. Upon complete consumption of the starting pyrrole by TLC analysis, the reaction mixture was diluted with CH₂Cl₂ (30 mL) and H₂O (30 mL). The aqueous layer was extracted with CH₂Cl₂ and the combined organic layers were dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The title compound was isolated as a colourless solid (0.894 g, 76 % yield) after column chromatography (silica – 10 % Et₂O/hexanes). m.p.: 170-172 °C; ¹H NMR (CDCl₃, 500 MHz): δ 10.21 (s, 1H), 7.83 (d, 2H, *J* = 8), 7.65 (t, 1H, *J* = 8), 7.54 (t, 2H, *J* = 8), 7.35 (s, 1H), 3.83 (s, 2H), 3.67 (s, 3H), 3.65 (s, 3H), 2.72 (t, 2H, *J* = 7), 2.58 (t, 2H, *J* = 7) ppm; ¹³C{¹H} NMR (CDCl₃, 125 MHz): 181.0, 172.8, 170.3, 138.6, 134.7, 131.5, 130.2, 129.9, 127.4, 127.1, 125.7, 52.3, 51.9, 33.7, 30.7, 19.8 δ ppm; HRMS-ESI (*m/z*): [M + Na]⁺ Calcd 416.0774 for C₁₈H₁₉NNaO₇S; found 416.0777.

3.4.2 Synthesis of Brominated Pyrroles

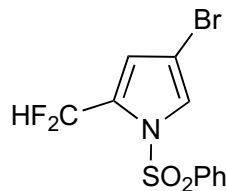
1-(4-(Bromomethyl)phenylsulfonyl)-2-(difluoromethyl)-1H-pyrrole (3.49)



A stirring solution of **3.34** (0.040 g, 0.147 mmol) in anhydrous CHCl₃ (2 mL) was treated with *N*-bromosuccinimide (0.026 g, 0.147 mmol) and AIBN (0.002 g, 0.015 mmol) under N₂. The reaction mixture was heated to 75 °C overnight with stirring, at which point TLC analysis showed only partial consumption of starting material and no remaining NBS. Additional NBS (0.013 g, 0.074 mmol) was added to the reaction mixture after cooling, and the solution was allowed to stir at 75 °C for another 24 hours. The reaction mixture was partitioned between water (30 mL) and CH₂Cl₂ (3 x 30 mL), and the combined organic phase was washed with brine (90 mL), dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. NOTE: compound was unable to be purified from other minor isomers. The title compound was isolated as a dominant product in a mixture of compounds (0.013 g, 25 % crude yield) after column chromatography (silica – 8 %

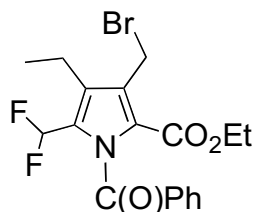
EtOAc/hexanes, 0-8 % EtOAc/hexanes, 0-4 % EtOAc/hexanes; further purification was not pursued). ^1H NMR (CDCl_3 , 500 MHz): δ 7.85 (d, 2H, $J = 8$), 7.52 (d, 2H, $J = 8$), 7.31 (s, 1H), 7.11 (t, 1H, $J = 55$, CF_2H), 6.66 (s, 1H), 6.31-6.33 (m, 1H), 4.45 (s, 2H) ppm; ^{19}F NMR (CDCl_3 , 470 MHz): δ -111.4 (d, $J = 55$, CF_2H) ppm.

4-Bromo-2-(difluoromethyl)-1-(phenylsulfonyl)-1H-pyrrole (3.51)



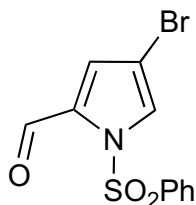
3.35 (0.490 g, 1.905 mmol) and *N*-bromosuccinimide (0.340 g, 1.905 mmol) were dissolved in anhydrous CH_3CN (10 mL) under N_2 , and the reaction mixture was heated and stirred at 100 °C for 1 hour using a Biotage microwave system. Since the system employed was computer automated, the parameters were defined using the provided software for vial size (10-20 mL), solvent absorbance level (medium), magnetic stirring (on), time (60 minutes) and temperature (100 °C). The reaction mixture was then partitioned between water (150 mL) and CH_2Cl_2 (3 x 150 mL), and the combined organic phase was washed with brine (450 mL), dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The title compound was isolated as a colourless solid (0.291 g, 46 % yield) after column chromatography (silica – 5 % CH_2Cl_2 /hexanes). m.p.: 83-86 °C; ^1H NMR (CDCl_3 , 300 MHz): δ 7.89-7.92 (m, 2H), 7.64-7.70 (m, 1H), 7.53-7.59 (m, 2H), 7.32 (ad, 1H), 7.09 (t, 1H, $J = 55$, CF_2H , overlaps with CDCl_3), 6.64 (as, 1H) ppm; ^{19}F NMR (CDCl_3 , 282 MHz): δ -112.1 (d, $J = 55$, CF_2H) ppm; $^{13}\text{C}\{^1\text{H}\}$ NMR (CDCl_3 , 125 MHz): δ 138.1, 134.9, 129.8, 129.7, 127.6, 123.7, 117.8, 108.1 (t, $J = 235$, C-F), 101.1 ppm; HRMS-ESI (m/z): $[\text{M} + \text{Na}]^+$ Calcd 357.9319 for $\text{C}_{11}\text{H}_8\text{BrF}_2\text{NNaO}_2\text{S}$; found 357.9306

Ethyl 1-benzoyl-3-(bromomethyl)-5-(difluoromethyl)-4-ethyl-1H-pyrrole-2-carboxylate (3.53)



A solution of **3.37** (0.050 g, 0.149 mmol) in anhydrous CCl_4 (2 mL) was treated with *N*-bromosuccinimide (0.027 g, 0.149 mmol) and benzoyl peroxide (0.036 g, 0.015 mmol) under N_2 at room temperature. The reaction was allowed to stir at room temperature for 72 hours, at which point the reaction mixture was partitioned between water (30 mL) and CH_2Cl_2 (3 x 30 mL). The combined organic phase was washed with brine (90 mL), dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The title compound was isolated as a colourless solid (0.003 g, 5 % yield) after column chromatography (silica – 15 % CH_2Cl_2 /hexanes). m.p.: 92-93 °C; ^1H NMR (CDCl_3 , 500 MHz): δ 7.60-7.62 (m, 3H), 7.46 (t, 2H, $J = 8$), 6.78 (t, 1H, $J = 54$, CF_2H), 4.74 (s, 2H), 4.02 (q, 2H, $J = 7$), 2.74 (q, 2H, $J = 8$), 1.29 (t, 3H, $J = 8$), 1.08 (t, 3H, $J = 7$) ppm; ^{19}F NMR (CDCl_3 , 470 MHz): δ -111.3 (d, $J = 54$, CF_2H) ppm; $^{13}\text{C}\{^1\text{H}\}$ NMR (CDCl_3 , 125 MHz): δ 169.0, 159.6, 134.6, 133.9, 129.8, 129.6, 129.1, 127.9, 109.3 (t, $J = 235$, C-F), 61.6, 22.0, 17.2, 16.1, 13.9 ppm (2XC missing); HRMS-ESI (m/z): $[\text{M} + \text{Na}]^+$ Calcd 436.0330 for $\text{C}_{18}\text{H}_{18}\text{BrF}_2\text{NNaO}_3$; found 436.0329

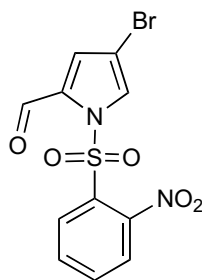
4-Bromo-1-(phenylsulfonyl)-1H-pyrrole-2-carbaldehyde (3.92)



3.90 (4.000 g, 22.989 mmol), benzenesulfonylchloride (4.40 mL, 34.483 mmol), and tetrabutylammonium bromide (0.230 g, 0.690 mmol) were dissolved into CH_2Cl_2 (17.6 mL). A 30 % $\text{NaOH}_{(\text{aq})}$ solution (9.6 mL) was added to the reaction mixture with stirring at 0 °C. The reaction mixture was allowed to warm to room temperature and continued to

stir overnight. The reaction mixture was diluted with H₂O (30 mL), was allowed to separate and then the organic layer was removed. The aqueous layer was extracted with CH₂Cl₂ (3X 30 mL) and then the combined organic layers were dried over Na₂SO₄. The organic layer was filtered, concentrated *in vacuo*, and then purified *via* column chromatography (silica – 50 % CH₂Cl₂/hexanes). The title compound was isolated as a colourless solid (3.685 g, 51 % yield). m.p.: 103-104 °C; ¹H NMR (CDCl₃, 500 MHz): δ 9.93 (s, 1H), 7.94 (d, 2H, J = 8 Hz), 7.68 (t, 1H, J = 7 Hz), 7.55-7.60 (m, 3H), 7.10 (s, 1H) ppm; ¹³C{¹H} NMR (CDCl₃, 125 MHz): δ 178.1, 137.9, 135.1, 133.6, 129.9, 127.9, 127.7, 125.7, 101.9 ppm; HRMS-ESI (*m/z*): [M + H]⁺ Calcd 335.9306 for C₁₁H₉BrN₂O₃S; found 313.9470

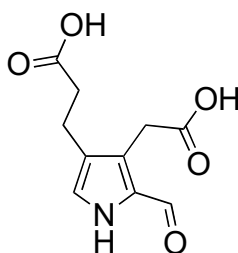
4-Bromo-1-(2-nitrophenylsulfonyl)-1H-pyrrole-2-carbaldehyde (3.94)



3.90 (2.720 g, 15.632 mmol), 2-nitrobenzenesulfonylchloride (3.149 g, 14.211 mmol), and NEt₃ (2.97 mL, 21.317 mmol) were dissolved into CH₂Cl₂ (55 mL). Dimethylaminopyridine (0.174 g, 1.421 mmol) was added to the stirring reaction mixture, and the solution continued to stir overnight. The reaction mixture was extracted with H₂O (60 mL) and brine (60 mL), and the organic layer was dried over Na₂SO₄. The organic layer was filtered, concentrated *in vacuo*, and then purified *via* column chromatography (silica – 50 % CH₂Cl₂/hexanes). The title compound was isolated as a beige solid (4.171 g, 82 % yield). m.p.: 143-145 °C; ¹H NMR (CDCl₃, 500 MHz): δ 9.57 (s, 1H), 8.47-8.49 (m, 1H), 7.83-7.85 (m, 3H), 7.71 (s, 1H), 7.16 (s, 1H) ppm; ¹³C{¹H} NMR (CDCl₃, 125 MHz): δ 176.9, 148.2, 136.0, 133.8, 133.5, 132.7, 131.1, 130.7, 129.5, 125.3, 100.9 ppm; HRMS-ESI (*m/z*): [M + H]⁺ Calcd 358.9337 for C₁₁H₈BrN₂O₅S; found 358.9325

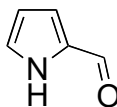
3.4.3 Deprotection of *N*-Benzoyl or *N*-Benzenesulfonyl Protecting Groups

4-(2-Carboxyethyl)-3-(Carboxymethyl)-1*H*-pyrrole-2-carbaldehyde (3.59)



3.39 (0.050 g, 0.120 mmol) was added to a solution of 1M NaOH in 1:1 H₂O/MeOH (1 mL) while stirring. The reaction mixture was heated to 50 °C with stirring, until TLC analysis showed complete consumption of starting material. The reaction mixture was diluted with H₂O (50 mL) and acidified to pH 4 by use of 2M HCl_(aq) at 0 °C. The reaction mixture was then extracted with CH₂Cl₂ (3 x 50 mL), and then the combined organic phase was washed with brine, dried over anhydrous Na₂SO₄, concentrated *in vacuo* and purified *via* column chromatography (silica – 50 % EtOAc/hexanes). The title compound was isolated as a colourless solid (0.012 g, 27 % yield). ¹H (300 MHz, C(O)(CD₃)₂): δ 10.81 (br s, 1H), 9.70 (s, 1H), 7.07 (as, 1H), 3.85 (s, 2H), 2.78 (t, *J* = 8, expected 2H but overlaps with water peak), 2.59 (t, *J* = 8, expected 2H but overlaps with water peak) ppm; HRMS-ESI (*m/z*): [M + H]⁺ Calcd 248.0529 for C₁₁H₈BrN₂O₅S; found 248.0528. Unstable in CDCl₃, C(O)(CD₃)₂, and CD₃OD for prolonged periods of time and precipitates from THF-*d*8 and CD₃CN.

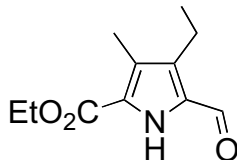
1*H*-Pyrrole-2-carbaldehyde (3.13)



3.35 (0.050 g, 0.194 mmol) was treated with anhydrous 1M TBAF in THF (0.194 mL, 0.194 mmol) while stirring at room temperature in anhydrous THF (8 mL). The reaction mixture was heated at reflux temperature for 1.5 hours, at which point TLC analysis showed complete consumption of starting material. Upon cooling the reaction mixture, the solution was concentrated *in vacuo* and purified directly *via* column chromatography (silica – CH₂Cl₂). The title compound was isolated as a colourless solid (0.014 g, 78 % yield). ¹H (500 MHz, CDCl₃): δ 9.97 (br s, 1H), 9.54 (s, 1H), 7.17 (s, 1H), 7.02 (s, 1H),

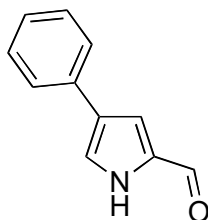
6.36-6.38 (m, 1H). Spectral and physical properties were in agreement with previously reported data.¹¹⁹

Ethyl 5-(formyl)-4-ethyl-3-methyl-1H-pyrrole-2-carboxylate (3.62)



3.37 (0.050 g, 0.149 mmol) was added to a chilled (0 °C) solution of 2M NaOH in MeOH (1 mL) while stirring. The reaction mixture was allowed to stir at 0 °C for 30 minutes, at which point TLC analysis showed complete consumption of starting material. The reaction mixture was partitioned between CH₂Cl₂ and water, and then the organic phase was washed with brine, dried over anhydrous Na₂SO₄, concentrated *in vacuo* and purified *via* column chromatography (silica – 10 % EtOAc/hexanes). The title compound was isolated as a colourless solid (0.016 g, 52 % yield). ¹H (500 MHz, CDCl₃): δ 9.76 (s, 1H), 9.44 (br s, 1H), 4.35 (q, 2H, *J* = 7), 2.74 (q, 2H, *J* = 8), 2.29 (s, 3H), 1.37 (t, 3H, *J* = 7), 1.20 (t, 3H, *J* = 8). Spectral and physical properties were in agreement with previously reported data.¹²⁰

4-Phenyl-1H-pyrrole-2-carbaldehyde (3.91)



A 1M solution of NaOH in MeOH (2.5 mL) containing **3.81** (0.050 g, 0.150 mmol) was heated and stirred at 50 °C, until TLC analysis showed complete consumption of starting material. The reaction mixture was concentrated *in vacuo* to a residue and then suspended in EtOAc (25 mL). The diluted reaction mixture was then extracted with dilute HCl (3 x 30 mL), and brine (50 mL). The organic layer was dried over anhydrous Na₂SO₄, concentrated *in vacuo* and purified *via* column chromatography (silica – 10 % acetone/hexanes). The title compound was isolated as a beige solid (0.013 g, 48 % yield).

Alternatively:

A solution of PhSH (0.049 mL, 0.477 mmol) and **3.110** (0.100 g, 0.264 mmol) in CH₃CN (13 mL) was bubbled with N₂ for 10 minutes, after which anhydrous NEt₃ (0.092 mL, 0.660 mmol) was added under N₂. The reaction was allowed to stir for 30 minutes before diluting with EtOAc (50 mL). The diluted reaction mixture was then extracted with 2M NaOH (3 x 50 mL), followed by 1M HCl (3 x 50 mL), and brine (50 mL). The organic layer was dried over anhydrous Na₂SO₄, concentrated *in vacuo* and purified *via* column chromatography (silica – 10 % acetone/hexanes). The title compound was isolated as a beige solid (0.042 g, 93 % yield).

¹H NMR (500 MHz, THF-d₈): δ 11.44 (br s, 1H), 9.53 (s, 1H), 7.57 (d, 2H, *J* = 8 Hz), 7.49 (as, 1H), 7.30 (t, 2H, *J* = 8), 7.24 (as, 1H), 7.14 (t, 1H, *J* = 8 Hz) ppm; ¹³C{¹H} NMR (125 MHz, THF-d₈): δ 179.1, 135.8, 135.3, 129.4, 127.7, 126.7, 125.8, 123.6, 117.2 ppm; HRMS-ESI (*m/z*): [M + Na]⁺ Calcd for C₁₁H₉NONa 194.0576; Found 194.0576. ¹H NMR spectrum previously reported in acetone-d₆.⁶³

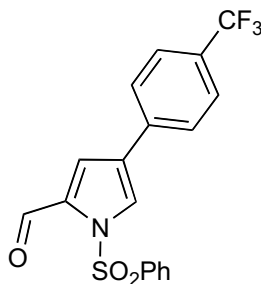
Thioether **3.115** can also be isolated as a yellow solid (0.049 g, 80 %) when employing the latter methodology that uses pyrrole **3.110**. ¹H (500 MHz, CDCl₃): δ 8.20-8.24 (dd, 1H, *J* = 1.5, 8), 7.56-7.60 (m, 2H), 7.46-7.51 (m, 3H), 7.31-7.36 (m, 1H), 7.18-7.24 (m, 1H), 6.87 (dd, 1H, *J* = 1, 8), Spectral and physical properties were in agreement with previously reported data;¹²¹ HRMS-ESI (*m/z*): [M + Na]⁺ Calcd 254.0246 for C₁₂H₉NNaO₂S; found 254.0239; ε_{368nm} = 4000 L mol⁻¹ cm⁻¹ in CH₃CN.

3.4.4 General Procedure (GP1) for the Suzuki Cross-Coupling of 4-Bromopyrroles

A 4-bromo-1-protected-1*H*-pyrrole (1 equiv.) was dissolved in toluene [0.1 M], along with a phenylboronic acid (1.2 equiv.), and Pd(PPh₃)₄ (0.1 equiv.) under an inert atmosphere with stirring. Potassium carbonate (4 equiv.) was dissolved as an aqueous solution [1.1 M], and then purged with N₂ for 15 minutes. The K₂CO₃ aqueous solution was then added to the stirring reaction mixture, sealed under N₂, and heated with stirring at 90°C overnight. The reaction mixture was then partitioned and the aqueous layer was extracted with CH₂Cl₂ (equivalent volume to aqueous layer x 3). The combined organic

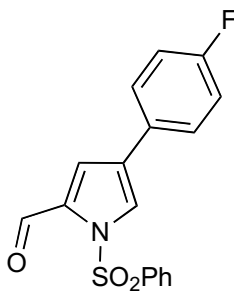
layers were dried over Na₂SO₄, filtered, concentrated *in vacuo* and then purified *via* column chromatography.

1-(Phenylsulfonyl)-4-(4-(trifluoromethyl)phenyl)-1H-pyrrole-2-carbaldehyde (3.96)



Using GP1 with 4-(trifluoromethyl)phenylboronic acid, the title compound was synthesized from **3.92** (0.500 g, 1.592 mmol). The title compound was isolated as a colourless solid (0.465 g, 77 % yield) after column chromatography (silica – 50 % CH₂Cl₂/hexanes). m.p.: 175-177 °C; ¹H NMR (CDCl₃, 500 MHz): δ 10.06 (s, 1H), 7.99 (d, 2H, J = 8 Hz), 7.94 (s, 1H), 7.64-7.71 (m, 5H), 7.58 (t, 2H, J = 8 Hz), 7.47 (s, 1H) ppm; ¹³C{¹H} NMR (CDCl₃, 125 MHz): δ 179.1, 138.1, 135.5, 135.0, 134.4, 130.2, 129.9, 127.7, 126.9, 126.2 (2XC), 126.1, 125.0, 121.6 ppm, (CF₃ coupling not observed); HRMS-ESI (*m/z*): [M + Na]⁺ Calcd 402.0388 for C₁₈H₁₂F₃NNaO₃S; found 402.0385.

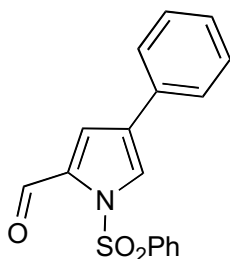
4-(4-Fluorophenyl)-1-(phenylsulfonyl)-1H-pyrrole-2-carbaldehyde (3.97)



Using GP1 with 4-fluorophenylboronic acid, the title compound was synthesized from **3.92** (0.500 g, 1.592 mmol). The title compound was isolated as a colourless solid (0.431 g, 82 % yield) after column chromatography (silica – 50 % CH₂Cl₂/hexanes). m.p.: 164-165 °C; ¹H NMR (CDCl₃, 500 MHz): δ 10.0 (s, 1H), 7.95 (d, 2H, J = 8 Hz), 7.807-7.812 (m, 1H), 7.66 (t, 1H, J = 8 Hz), 7.56 (t, 2H, J = 8 Hz), 7.47-7.50 (m, 2H), 7.38-7.39 (m,

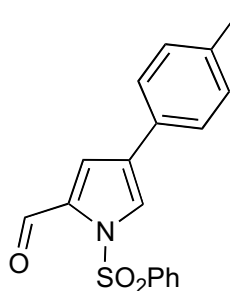
1H), 7.10 (t, J = 9 Hz) ppm; $^{13}\text{C}\{^1\text{H}\}$ NMR (CDCl_3 , 125 MHz): δ 179.2, 138.3, 134.9, 134.3, 129.8, 127.6 (2XC), 124.7, 121.8, 116.3, 116.2 (2 X C missing) ppm; HRMS-ESI (m/z): $[\text{M} + \text{Na}]^+$ Calcd 352.0420 for $\text{C}_{17}\text{H}_{12}\text{FNNaO}_3\text{S}$; found 352.0418

4-Phenyl-1-(phenylsulfonyl)-1H-pyrrole-2-carbaldehyde (3.98)



Using GP1 with phenylboronic acid, the title compound was synthesized from **3.92** (0.874 g, 2.784 mmol). The title compound was isolated as a colourless solid (0.867 g, 91 % yield) after column chromatography (silica – 50 % CH_2Cl_2 /hexanes). m.p.: 108-110 °C; ^1H NMR (CDCl_3 , 500 MHz): δ 10.0, 7.95 (d, 2 H, J = 7 Hz), 7.87 (s, 1H), 7.66 (t, 1H, 7 Hz), 7.52-7.57 (m, 4H), 7.45 (s, 1H), 7.41(t, 2H, J = 8 Hz), 7.32 (t, 1H, J = 7 Hz) ppm; $^{13}\text{C}\{^1\text{H}\}$ NMR (CDCl_3 , 125 MHz): δ 179.2, 138.3, 134.8, 134.3, 131.9, 128.5, 128.1, 125.0, 122.0 ppm; HRMS-ESI (m/z): $[\text{M} + \text{H}]^+$ Calcd 312.0694 for $\text{C}_{17}\text{H}_{14}\text{NO}_3\text{S}$; found 312.0676.

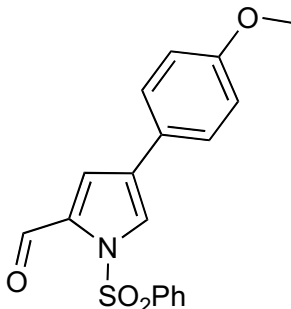
1-(Phenylsulfonyl)-4-*p*-tolyl-1H-pyrrole-2-carbaldehyde (3.99)



Using GP1 with 4-tolueneboronic acid, the title compound was synthesized from **3.92** (0.500 g, 1.592 mmol). The title compound was isolated as a colourless solid (0.457 g, 88 % yield) after column chromatography (silica – 50 % CH_2Cl_2 /hexanes). m.p.: 155-156 °C; ^1H NMR (CDCl_3 , 500 MHz): δ 10.0 (s, 1H), 7.95 (d, 2H, J = 8 Hz), 7.84 (s, 1H), 7.66

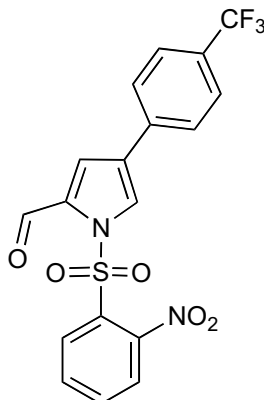
(t, 1H, J = 8 Hz), 7.54 (t, 2H, J = 8 Hz), 7.42 (d, 3H), J = 8 Hz), 7.21 (d, 2H, J = 8 Hz), 2.37 (s, 3H) ppm; $^{13}\text{C}\{^1\text{H}\}$ NMR (CDCl_3 , 125 MHz): δ 179.4, 138.5, 138.2, 134.9, 134.3, 130.0, 129.9, 129.1, 128.6, 127.6, 125.8, 124.8, 122.1, 21.4 ppm; HRMS-ESI (m/z): $[\text{M} + \text{Na}]^+$ Calcd 348.0670 for $\text{C}_{18}\text{H}_{15}\text{NNaO}_3\text{S}$; found 348.0660

4-(4-Methoxyphenyl)-1-(phenylsulfonyl)-1H-pyrrole-2-carbaldehyde (3.100)



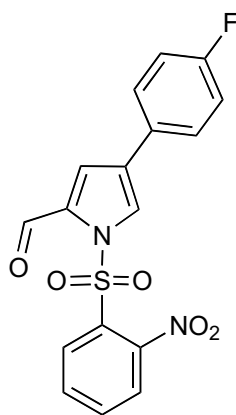
Using GP1 with 4-methoxyphenylboronic acid, the title compound was synthesized from **3.92** (0.500 g, 1.592 mmol). The title compound was isolated as a colourless solid (0.493 g, 91 % yield) after column chromatography (silica – 50 % CH_2Cl_2 /hexanes). m.p.: 150-151 °C; ^1H NMR (CDCl_3 , 500 MHz): δ 10.0 (s, 1H), 7.94 (d, 2H, J = 8 Hz), 7.78 (s, 1H), 7.65 (t, 1H, J = 7 Hz), 7.54 (t, 2H, J = 8 Hz), 7.45 (d, 2H, J = 9 Hz), 7.39 (s, 1H), 6.94 (d, 2H, J = 9 Hz) ppm; $^{13}\text{C}\{^1\text{H}\}$ NMR (CDCl_3 , 125 MHz): δ 179.3, 159.7, 138.4, 134.7, 134.2, 129.8, 128.4, 127.5, 127.1, 124.4, 124.2, 121.8, 114.7, 55.5 ppm; HRMS-ESI (m/z): $[\text{M} + \text{Na}]^+$ Calcd 364.0619 for $\text{C}_{18}\text{H}_{15}\text{FNNaO}_4\text{S}$; found 364.0629

1-(2-Nitrophenylsulfonyl)-4-(4-(trifluoromethyl)phenyl)-1H-pyrrole-2-carbaldehyde (3.101)



Using GP1 with 4-(trifluoromethyl)phenylboronic acid, the title compound was synthesized from **3.94** (0.500 g, 1.392 mmol). The title compound was isolated as an off-colourless solid (0.364 g, 62 % yield) after column chromatography (silica – CH₂Cl₂). m.p.: 187-189 °C; ¹H NMR (CDCl₃, 500 MHz): δ 9.70 (s, 1H), 8.56-8.59 (m, 1H), 8.03 (as, 1H), 7.85-7.89 (m, 3H), 7.68-7.72 (m, 3H), 7.49-7.50 (as, 1H) ppm; ¹³C{¹H} NMR (CDCl₃, 125 MHz): δ 177.6, 135.9, 134.2, 134.0, 132.6, 128.4, 126.3 (2xC), 126.2, 126.1 (3xC), 125.8, 125.3 (2xC missing) ppm; HRMS-ESI (*m/z*): [M + Na]⁺ Calcd 447.0238 for C₁₈H₁₁F₃N₂NaO₅S; found 447.0235

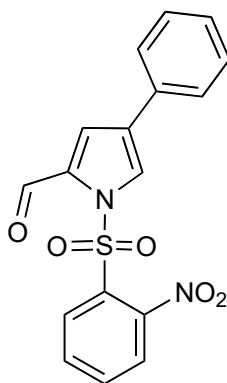
4-(4-Fluorophenyl)-1-(2-nitrophenylsulfonyl)-1H-pyrrole-2-carbaldehyde (3.102)



Using GP1 with 4-fluorophenylboronic acid, the title compound was synthesized from **3.94** (0.500 g, 1.392 mmol). The title compound was isolated as a beige solid (0.446 g, 86 % yield) after column chromatography (silica – CH₂Cl₂). m.p.: 172-175 °C;

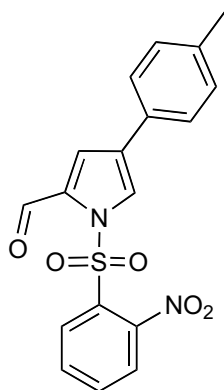
^1H NMR (CDCl_3 , 500 MHz): δ 9.68 (s, 1H), 8.51-8.53 (m, 1H), 7.90 (s, 1H), 7.83-7.85 (m, 3H), 7.53-7.55 (m, 2H), 7.419-7.423 (m, 1H), 7.12 (t, 2H, $J = 9$ Hz) ppm; $^{13}\text{C}\{^1\text{H}\}$ NMR (CDCl_3 , 125 MHz): δ 177.6, 135.7, 134.1, 133.7, 132.6, 131.5, 128.0, 127.8, 127.7, 127.5, 126.8, 126.0, 125.2, 116.3, 116.2 ppm, (CF coupling not observed); HRMS-ESI (m/z): $[\text{M} + \text{Na}]^+$ Calcd 397.0270 for $\text{C}_{17}\text{H}_{11}\text{FN}_2\text{NaO}_5\text{S}$; found 397.0271

1-(2-Nitrophenylsulfonyl)-4-phenyl-1H-pyrrole-2-carbaldehyde (3.103)



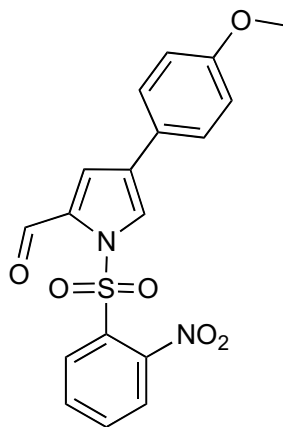
Using GP1 with phenylboronic acid, the title compound was synthesized from **3.94** (0.874 g, 2.784 mmol). The title compound was isolated as a beige solid (0.650 g, 66 % yield) after column chromatography (silica – CH_2Cl_2). m.p.: 177-178 °C; ^1H NMR (CDCl_3 , 500 MHz): δ 9.69 (s, 1H), 8.48-8.50 (m, 1H), 7.96 (s, 1H), 7.83 (ad, 3H), 7.58 (d, 2H, $J = 8$ Hz), 7.49 (s, 1H), 7.43 (t, 2H, $J = 8$ Hz), 7.34 (t, 1H, $J = 7$ Hz) ppm; $^{13}\text{C}\{^1\text{H}\}$ NMR (CDCl_3 , 125 MHz): δ 177.7, 135.7, 134.1, 133.5, 132.6, 131.7, 131.5, 129.3, 128.2, 127.7, 127.7, 126.2, 126.0, 125.2 ppm; HRMS-ESI (m/z): $[\text{M} + \text{Na}]^+$ Calcd 379.0365 for $\text{C}_{17}\text{H}_{12}\text{N}_2\text{NaO}_5\text{S}$; found 357.0553.

1-(2-Nitrophenylsulfonyl)-4-*p*-tolyl-1*H*-pyrrole-2-carbaldehyde (3.104)



Using GP1 with 4-tolueneboronic acid, the title compound was synthesized from **3.94** (0.500 g, 1.392 mmol). The title compound was isolated as a beige solid (0.315 g, 61 % yield) after column chromatography (silica – CH₂Cl₂). m.p.: 171-172 °C; ¹H NMR (CDCl₃, 500 MHz): δ 9.68 (s, 1H), 8.44-8.46 (m, 1H), 7.917-7.919 (m, 1H), 7.81-7.82 (m, 3H), 7.46-7.47 (m, 3H), 7.23 (d, 2H, J = 8 Hz), 2.38 (s, 3H) ppm; ¹³C{¹H} NMR (CDCl₃, 125 MHz): δ 177.7, 148.2, 138.1, 135.6, 134.0, 133.4, 132.6, 131.6, 129.9, 128.8, 127.8, 127.3, 126.1, 125.9, 125.2, 21.3 ppm; HRMS-ESI (*m/z*): [M + Na]⁺ Calcd 393.0521 for C₁₈H₁₄N₂NaO₅S; found 393.0508

4-(4-Methoxyphenyl)-1-(2-nitrophenylsulfonyl)-1*H*-pyrrole-2-carbaldehyde (3.105)



Using GP1 with 4-methoxyphenylboronic acid, the title compound was synthesized from **3.94** (0.500 g, 1.392 mmol). The title compound was isolated as a beige solid (0.348 g, 65 % yield) after column chromatography (silica – CH₂Cl₂). m.p.: 165-166 °C; ¹H NMR (CDCl₃, 500 MHz): δ 9.68 (s, 1H), 8.43-8.45 (m, 1H), 7.87 (s, 1H), 7.80-7.82 (m, 3H),

7.49 (d, 2H, J = 9 Hz), 7.43 (s, 1H), 6.96 (d, 2H, J = 9 Hz) ppm; $^{13}\text{C}\{^1\text{H}\}$ NMR (CDCl_3 , 125 MHz): δ 177.7, 159.7, 148.2, 135.6, 134.0, 133.3, 132.6, 131.6, 127.6, 127.2, 126.8, 126.0, 125.1, 124.3, 114.7, 55.5 ppm; HRMS-ESI (m/z): $[\text{M} + \text{Na}]^+$ Calcd 409.0470 for $\text{C}_{18}\text{H}_{14}\text{FN}_2\text{NaO}_6\text{S}$; found 409.0464.

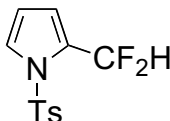
3.4.5 General Procedure (GP2) for Fluorination using XtalFluor®

XtalFluor-E® or XtalFluor-M® (3 equiv., as indicated) was added to a solution of $\text{NEt}_3 \cdot 3\text{HF}$ (4 equiv.) and NEt_3 (2 equiv.) in CH_2Cl_2 or 1,2-DCE (if heating above 40 °C) [0.3 M], with stirring at room temperature under N_2 . The 2-formylpyrrole substrate (1 equiv.) was then added in one portion and the reaction mixture was stirred under N_2 at room temperature overnight, unless otherwise specified, before quenching with aqueous sodium bicarbonate solution (10 mL) and stirring for 15 minutes. The reaction mixture was then diluted with CH_2Cl_2 (30 mL) and washed with water (30 mL) and brine (30 mL). The organic phase was dried over anhydrous Na_2SO_4 , concentrated *in vacuo* and purified *via* column chromatography (silica).

3.4.6 General Procedure (GP3) for Fluorination using DAST

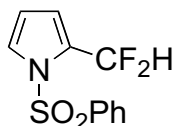
DAST (2 equiv.) was added neat to the 2-formylpyrrole substrate (1 equiv.) at room temperature under N_2 . The slurry was heated at 90 °C for until TLC analysis showed complete consumption of the starting formyl pyrrole (typically after 20 minutes), at which point the reaction mixture was cooled to room temperature and diluted with CH_2Cl_2 (30 mL). The reaction mixture was then washed with aqueous sodium bicarbonate solution (30 mL), water (30 mL) and brine (30 mL). The organic phase was dried over anhydrous Na_2SO_4 , concentrated *in vacuo* and purified *via* column chromatography (silica).

2-(Difluoromethyl)-1-(tosyl)-1H-pyrrole (3.34)



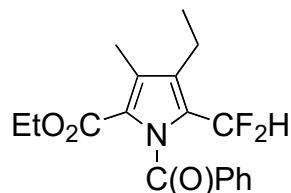
Using GP2 in CH₂Cl₂ at room temperature, the title compound was synthesized from 1-tosyl-1*H*-pyrrole-2-carbaldehyde¹¹⁵ (0.200 g, 0.802 mmol). The title compound was isolated as a colourless solid (0.176 g, 81 % yield) after column chromatography (silica – 20 → 25 % EtOAc/hexanes). m.p.: 71-73 °C; ¹H NMR (CDCl₃, 500 MHz): δ 7.77 (d, 2H, *J* = 8), 7.31 (d, 2H, *J* = 8), 7.12 (t, 1H, *J* = 55, CF₂H), 6.64 (as, 1H), 6.30 (at, 1H) ppm; ¹⁹F NMR (CDCl₃, 470 MHz) δ -110.7 (d, *J* = 55.0, CF₂H) ppm; ¹³C{¹H} NMR (CDCl₃, 125 MHz): δ 145.7, 135.7, 130.2, 127.5, 125.0, 115.4, 112.0, 108.9 (t, *J* = 234, C-F), 21.8 (1 x C missing) ppm; HRMS-ESI (*m/z*): [M + Na]⁺ Calcd 294.0371 for C₁₂H₁₁F₂NNaO₂S; found 294.0380

2-(Difluoromethyl)-1-(phenylsulfonyl)-1*H*-pyrrole (3.35)



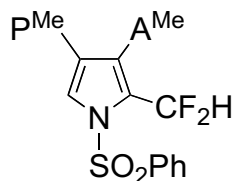
Using GP2 with gentle heating (35 °C) in CH₂Cl₂, the title compound was synthesized from 1-(phenylsulfonyl)-1*H*-pyrrole-2-carbaldehyde¹⁰⁹ (0.133 g, 0.565 mmol). The title compound was isolated as a colourless solid (0.133 g, 92 % yield) after column chromatography (silica – 10 % Et₂O/hexanes). m.p.: 64-66 °C; ¹H NMR (CDCl₃, 500 MHz): δ 7.89 (d, 2H, *J* = 8), 7.63 (t, 2H, *J* = 8), 7.53 (t, 2H, *J* = 8), 7.32 (br s, 1H), 7.12 (t, 1H, *J* = 55, CF₂H), 6.66 (br s, 1H), 6.31 (at, 1H) ppm; ¹⁹F NMR (CDCl₃, 470 MHz) δ -110.8 (d, *J* = 55.0, CF₂H) ppm; ¹³C{¹H} NMR (CDCl₃, 125 MHz): δ 138.6, 134.5, 129.6, 127.9, 127.4, 125.1 (t, *J* = 3), 115.6 (t, *J* = 5), 112.2, 108.8 (t, *J* = 233, C-F) ppm; HRMS-ESI (*m/z*): [M + Na]⁺ Calcd 280.0214 for C₁₁H₉F₂NNaO₂S; found 280.0201

Ethyl 1-benzoyl-5-(difluoromethyl)-4-ethyl-3-methyl-1*H*-pyrrole-2-carboxylate (3.37)



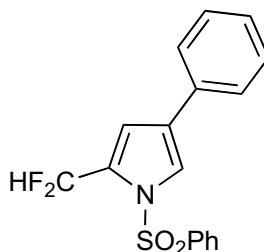
Using GP2 at reflux temperature in 1,2-DCE, the title compound was synthesized from Ethyl 1-benzoyl-4-ethyl-5-formyl-3-methyl-1*H*-pyrrole-2-carboxylate (0.400 g, 1.276 mmol). The title compound was isolated as a colourless solid (0.254 g, 59 % yield) after column chromatography (silica - 30 % CH₂Cl₂/hexanes). m.p.: 42-45 °C; ¹H NMR (CDCl₃, 500 MHz): δ 7.56-7.62 (m, 3H), 7.43 (t, 2H, *J* = 8), 6.83 (t, 1H, *J* = 54, CF₂H), 3.87 (q, 2H, *J* = 7), 2.64 (q, 2H, *J* = 8) 2.30 (s, 3H), 1.16 (t, 3H, *J* = 8), 1.00 (t, 3H, *J* = 7) ppm; ¹⁹F NMR (CDCl₃, 470 MHz) δ -110.3 (d, *J* = 54, CF₂H) ppm; ¹³C{¹H} NMR (CDCl₃, 125 MHz): δ 169.4, 160.6, 134.7, 134.0, 129.9, 129.6, 129.3, 128.9, 126.6, 124.0, 109.7 (t, *J* = 233.3, C-F) ppm; HRMS-ESI (*m/z*): [M + Na]⁺ Calcd 358.1225 for C₁₈H₁₉F₂NNaO₃; found 358.1227

2-(Difluoromethyl)-4-(2-methoxycarbonyl-ethyl)-3-(methoxycarbonylmethyl)-1-(phenylsulfonyl)-1*H*-pyrrole (3.39)



Using GP3, the title compound was synthesized from **3.57** (0.650 g, 1.652 mmol). The title compound was isolated as a colourless solid (0.574 g, 84 % yield) after column chromatography (0 → 0.05 % MeOH/CH₂Cl₂). m.p.: 85-86 °C; ¹H NMR (CDCl₃, 500 MHz): δ 7.80 (d, 2H, *J* = 8), 7.62 (t, 1H, *J* = 8), 7.51 (t, 2H, *J* = 8), 7.25 (t, 1H, *J* = 54, CF₂H), 7.12 (s, 1H), 3.66 (s, 3H), 3.65 (s, 3H), 3.60 (s, 2H), 2.67 (t, 2H, *J* = 7), 2.56 (t, 3H, *J* = 7) ppm; ¹⁹F NMR (CDCl₃, 470 MHz): δ -109.9 (d, *J* = 54, CF₂H, overlaps with CDCl₃) ppm; ¹³C{¹H} NMR (CDCl₃, 125 MHz): δ 173.0, 170.7, 138.7, 134.4, 129.6, 127.1, 124.7 (t, *J* = 10), 124.1, 121.7, 109.6 (t, *J* = 231.9, C-F), 52.3, 51.9, 33.6, 30.0, 20.1 (1 x C missing) ppm; HRMS-ESI (*m/z*): [M + Na]⁺ Calcd 438.0793 for C₁₈H₁₉F₂NNaO₆S; found 438.0779.

2-(Difluoromethyl)-4-phenyl-1-(phenylsulfonyl)-1H-pyrrole (3.81)

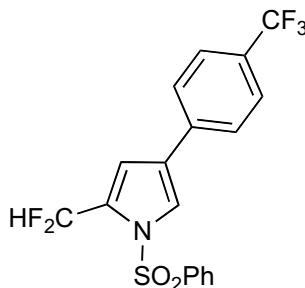


Using GP2, the title compound was synthesized from **3.98** (0.785 g, 2.521 mmol). The title compound was isolated as a colourless solid (0.720 g, 86 % yield) after column chromatography (silica – 20→50 % CH₂Cl₂/hexanes).

Alternatively:

Using GP1 with phenylboronic acid, the title compound was synthesized from **3.51** (0.040 g, 0.120 mmol). The title compound was isolated as a colourless solid (0.040 g, 100 % yield) after column chromatography (silica – 5 % CH₂Cl₂/hexanes). m.p.: 103-104 °C; ¹H NMR (CDCl₃, 500 MHz): δ 7.93 (d, 2H, J = 8 Hz), 7.63 (t, 2H, J = 7 Hz), 7.52-7.56 (m, 3H), 7.48 (d, 2H, J = 8 Hz), 7.37 (t, 2H, J = 8 Hz), 7.29 (d, 1H, 7 Hz), 7.16 (t, 1H, J = 55 Hz, CF₂H) ppm; ¹⁹F NMR (CDCl₃, 470 MHz) δ -112.2 (d, J = 55 Hz, CF₂H) ppm; ¹³C{¹H} NMR (CDCl₃, 125 MHz): δ 138.7, 134.6, 133.1, 132.6, 129.7, 129.2, 127.8, 127.6, 125.9, 120.4, 114.1, 114.1, 108.9 (t, J = 234 Hz, C-F) ppm; HRMS-ESI (m/z): [M + Na]⁺ Calcd 356.0527 for C₁₇H₁₃F₂NO₂S; found 356.0536.

2-(Difluoromethyl)-1-(phenylsulfonyl)-4-(4-(trifluoromethyl)phenyl)-1H-pyrrole (3.82)

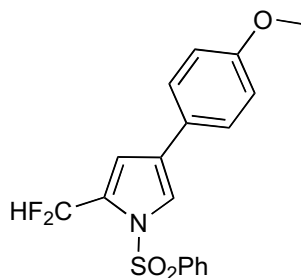


Using GP2 with Xtalfluor-M®, the title compound was synthesized from **3.96** (0.379 g, 1.000 mmol). The title compound was isolated as a colourless solid (0.291 g, 73 % yield) after column chromatography (silica – 20 → 50 % CH₂Cl₂/hexanes).

Alternatively:

Using GP1 with 4-trifluoromethylphenylboronic acid, the title compound was synthesized from **3.51** (0.050 g, 0.149 mmol). The title compound was isolated as a colourless solid (0.034 g, 57 % yield) after column chromatography (silica – 5 % CH₂Cl₂/hexanes). m.p.: 68-69 °C; ¹H NMR (CDCl₃, 500 MHz): δ 7.95 (d, 2H, J = 8 Hz), 7.54-7.67 (m, 8H), 7.16 (t, 1H, J = 55 Hz, CF₂H), 6.98 (s, 1H) ppm; ¹⁹F NMR (CDCl₃, 470 MHz) δ -63.6 (CF₃), -112.5 (d, J = 52 Hz, CF₂H) ppm; ¹³C{¹H} NMR (CDCl₃, 125 MHz): δ 138.3, 136.1, 134.8, 129.7, 129.2, 127.6, 126.6, 126.1, 125.9, 125.3, 123.2, 121.1, 113.6, 108.6 (t, J = 234 Hz, CF₂H) ppm; HRMS-ESI (*m/z*): [M + Na]⁺ Calcd 424.0407 for C₁₈H₁₂F₅NNaO₂S; found 424.0417

2-(Difluoromethyl)-4-(4-methoxyphenyl)-1-(phenylsulfonyl)-1H-pyrrole (3.83)

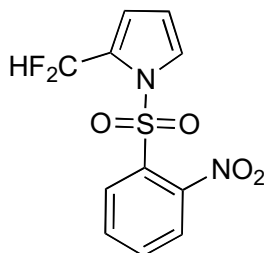


Using GP2 with Xtalfluor-M®, the title compound was synthesized from **3.100** (0.341 g, 1.000 mmol). The title compound was isolated as a colourless solid (0.171 g, 47 % yield) after column chromatography (silica – 20 → 50 % CH₂Cl₂/hexanes).

Alternatively:

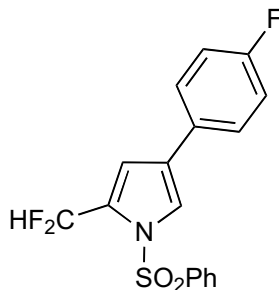
Using GP1 with 4-methoxyphenylboronic acid, the title compound was synthesized from **3.51** (0.050 g, 0.149 mmol). The title compound was isolated as a colourless solid (0.039 g, 52 % yield) after column chromatography (silica – 5 % CH₂Cl₂/hexanes). m.p.: 58-59 °C; ¹H NMR (CDCl₃, 300 MHz): δ 7.92 (m, 2H), 7.60-7.66 (m, 1H), 7.50-7.56 (m, 2H), 7.47-7.48 (m, 1H), 7.38-7.43 (m, 2H), 7.15 (t, 1H, J = 55 Hz, CF₂H), 6.88-6.93 (m, 3H), 3.82 (s, 3H) ppm; ¹⁹F NMR (CDCl₃, 282 MHz) δ -113.9 (d, J = 55 Hz, CF₂H) ppm; ¹³C{¹H} NMR (CDCl₃, 125 MHz): δ 159.4, 138.7, 134.5, 129.8, 129.6, 127.9, 127.4, 127.0, 125.2, 119.4, 114.5, 114.5, 114.0, 108.8 (t, J = 234, C-F), 55.5 ppm; HRMS-ESI (*m/z*): [M + Na]⁺ Calcd 386.0638 for C₁₈H₁₅F₂NNaO₃S; found 386.0646

2-(Difluoromethyl)-1-(2-nitrophenylsulfonyl)-1*H*-pyrrole (3.84)



Using GP2 with Xtalfluor-E®, the title compound was synthesized from **3.88**¹¹⁰ (0.877 g, 3.103 mmol). The title compound was isolated as a colourless solid (0.800 g, 85 % yield) after column chromatography (silica – 70 → 100 % CH₂Cl₂/hexanes). m.p.: 83-85 °C; ¹H NMR (CDCl₃, 500 MHz): δ 7.88 (d, 1H, *J* = 8 Hz), 7.81 (t, 1H, *J* = 8 Hz), 7.69 (t, 1H, *J* = 8 Hz), 7.44 (d, 1 H, *J* = 9), 7.40 (as, 1H), 7.02 (t, 1H, *J* = 55 Hz, CF₂H), 6.77 (as, 1H), 6.41 (at, 1H) ppm; ¹⁹F NMR (CDCl₃, 470 MHz) δ -112.3 (d, *J* = 55 Hz, CF₂H) ppm; ¹³C {¹H} NMR (CDCl₃, 125 MHz): δ 135.2, 133.1, 133.0, 129.6, 128.6, 126.6, 125.4, 116.3 (t, *J* = 6), 112.0, 110.8, 108.9 (t, *J* = 234 Hz, CF₂H) (1xC missing) ppm; HRMS-ESI (*m/z*): [M + Na]⁺ Calcd 325.0065 for C₁₁H₈F₂N₂NaO₄S; found 325.0055.

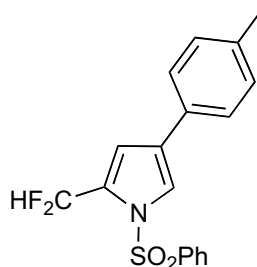
2-(Difluoromethyl)-4-(4-fluorophenyl)-1-(phenylsulfonyl)-1*H*-pyrrole (3.106)



Using GP2 with Xtalfluor-M®, the title compound was synthesized from **3.97** (0.329 g, 1.000 mmol). The title compound was isolated as a colourless solid (0.164 g, 47 % yield) after column chromatography (silica – 20 → 50 % CH₂Cl₂/hexanes). m.p.: 106-107 °C; ¹H NMR (CDCl₃, 500 MHz): δ 7.93 (d, 2H, *J* = 8 Hz), 7.64 (t, 1H, *J* = 7 Hz), 7.54 (t, 2H, *J* = 8 Hz), 7.50 (s, 1 H), 7.42-7.45 (m, 2H), 7.15 (-CF₂H group signal overlapped: 7.26, 7.15, 7.04, *J* = 55 Hz), 7.06 (t, 2H, 8 Hz), 6.91 (s, 1H) ppm; ¹⁹F NMR (CDCl₃, 470 MHz)

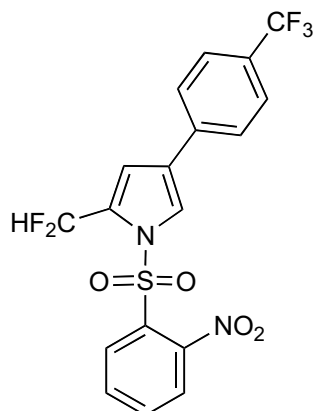
δ -112.3 (d, $J = 55$ Hz, CF_2H), -(115.5-115.6) (m) ppm; $^{13}\text{C} \{^1\text{H}\}$ NMR (CDCl_3 , 125 MHz): δ 162.4 (d, $J = 248$ Hz, C-F), 138.5, 134.6, 129.7, 128.7, 127.5, 127.4, 127.1, 120.0, 116.1, 116.0, 113.9, 108.7 (t, $J = 234$ Hz, CF_2H) ppm; HRMS-ESI (m/z): $[\text{M} + \text{Na}]^+$ Calcd 374.0439 for $\text{C}_{17}\text{H}_{12}\text{F}_3\text{NNaO}_2\text{S}$; found 374.0443.

2-(Difluoromethyl)-1-(phenylsulfonyl)-4-*p*-tolyl-1*H*-pyrrole (3.107)



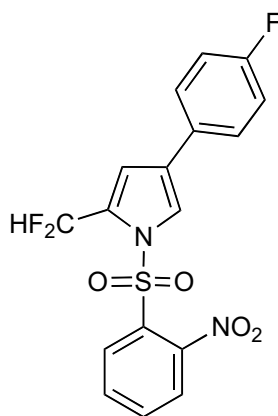
Using GP2 with Xtalfluor-M®, the title compound was synthesized from **3.99** (0.325 g, 1.000 mmol). The title compound was isolated as a colourless solid (0.198 g, 57 % yield) after column chromatography (silica – 20 → 50 % CH_2Cl_2 /hexanes). m.p.: 97-98 °C; ^1H NMR (CDCl_3 , 500 MHz): δ 7.92 (d, 2H, $J = 8$ Hz), 7.63 (t, 1H, 7 Hz), 7.53 (at, 3H), 7.37 (d, 2H, $J = 8$ Hz), 7.18 (d, 2H, $J = 8$ Hz), 7.15 (t, 7.26, 7.15, 7.04, one shoulder under chloroform peak, $J = 55$ Hz, 1H, CF_2H), 6.95 (s, 1H) ppm; ^{19}F NMR (CDCl_3 , 470 MHz) δ -112.1 (d, $J = 55$ Hz, CF_2H) ppm; $^{13}\text{C} \{^1\text{H}\}$ NMR (CDCl_3 , 125 MHz): δ 138.6, 137.6, 134.5, 129.7, 129.6, 128.9, 128.7, 128.4, 128.1, 127.4, 125.7, 119.9, 114.0, 108.8 (t, $J = 235$ Hz, C-F), 21.3 ppm; HRMS-ESI (m/z): $[\text{M} + \text{Na}]^+$ Calcd 370.0689 for $\text{C}_{18}\text{H}_{15}\text{F}_2\text{NNaO}_2\text{S}$; found 370.0671.

2-(Difluoromethyl)-1-(2-nitrophenylsulfonyl)-4-(4-(trifluoromethyl)phenyl)-1H-pyrrole (3.108)



Using GP2 with Xtalfluor-M®, the title compound was synthesized from **3.101** (0.320 g, 0.754 mmol). The title compound was isolated as a beige solid (0.286 g, 85 % yield) after column chromatography (silica – 50 % CH₂Cl₂/hexanes). m.p.: 80-81 °C; ¹H NMR (CDCl₃, 500 MHz): δ 7.88 (ad, 1H), 7.81-7.85 (m, 1H), 7.72-7.77 (m, 3H), 7.64-7.68 (m, 4H), 6.98-7.20 (m, 2H, CF₂H and one pyrrolic peak included) ppm; ¹⁹F NMR (CDCl₃, 470 MHz) δ -63.7, -113.1 (t, J = 55 Hz, CF₂H) ppm; ¹³C {¹H} NMR (CDCl₃, 125 MHz): δ 147.9, 135.8, 135.6, 133.1, 132.5, 130.3, 130.1, 129.8, 129.6, 126.2, 126.0, 125.5, 122.6, 114.3, 108.7 (t, J = 235 Hz, CF₂H) ppm; HRMS-ESI (*m/z*): [M + Na]⁺ Calcd 469.0257 for C₁₈H₁₁F₅N₂NaO₄S; found 469.0241.

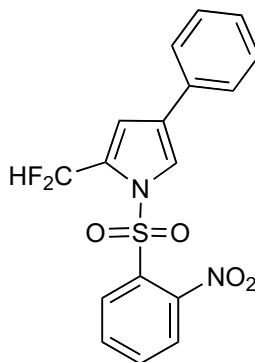
2-(Difluoromethyl)-4-(4-fluorophenyl)-1-(2-nitrophenylsulfonyl)-1H-pyrrole (3.109)



Using GP2 with Xtalfluor-E®, the title compound was synthesized from **3.102** (0.290 g, 0.776 mmol). The title compound was isolated as a beige solid (0.186 g, 61 % yield) after

column chromatography (silica – 50 % CH₂Cl₂/hexanes). m.p.: 86-88 °C; ¹H NMR (CDCl₃, 500 MHz): δ 7.88 (d, 1H, J = 8 Hz), 7.80 (t, 1H, J = 8 Hz), 7.71 (t, 1H, J = 8 Hz), 7.63 (d, 1H, J = 8 Hz), 7.59 (as, 1H), 7.49-7.52 (m, 2H), 7.09 (t, 2H, J = 9 Hz), 7.06 (-CF₂H group signal overlapped: 7.17, 7.06, 6.95, J = 55 Hz, 1H), 7.02 (s, 1H) ppm; ¹⁹F NMR (CDCl₃, 470 MHz) δ -113.0 (d, J = 55 Hz), -(115.0-115.1) (m) ppm; ¹³C{¹H} NMR (CDCl₃, 125 MHz): δ 162.6 (d, J = 250 Hz, C-F), 147.8, 135.4, 133.1, 132.8, 130.0, 129.4, 128.0 (d, J = 89 Hz), 127.2 (d, J = 102), 125.4, 121.4, 116.2, 116.1, 114.6, 108.8 (t, J = 235 Hz, CF₂H) ppm; HRMS-ESI (m/z): [M + Na]⁺ Calcd 419.0289 for C₁₇H₁₁F₃N₂NaO₄S; found 419.0287

2-(Difluoromethyl)-1-(2-nitrophenylsulfonyl)-4-phenyl-1H-pyrrole (3.110)



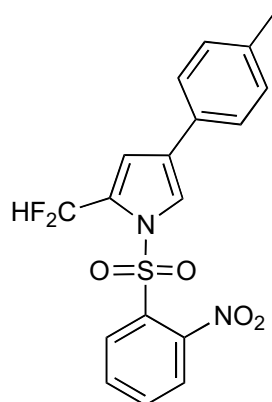
Using GP2 with Xtalfluor-E®, the title compound was synthesized from **3.103** (0.230 g, 0.645 mmol). The title compound was isolated as a beige solid (0.221 g, 90 % yield) after column chromatography (silica – 50 % CH₂Cl₂/hexanes).

Alternatively:

Using GP3, the title compound was synthesized from **3.103** (0.650 g, 1.824 mmol). The title compound was isolated as a beige solid (0.513 g, 74 % yield) after column chromatography (silica – 50 % CH₂Cl₂/hexanes). m.p.: 100-103 °C; ¹H NMR (CDCl₃, 500 MHz): δ 7.89 (d, 1H, J = 8 Hz), 7.79 (t, 1H, J = 8 Hz), 7.70 (t, 1H, J = 8 Hz), 7.65 (as, 1H), 7.54-7.57 (m, 3H), 7.41 (t, 2H, J = 8 Hz), 7.32 (t, 1H, J = 7 Hz), 7.09 (s, 1H), 7.07 (t, 7.18, 7.07, 6.96, 1H, J = 55 Hz, CF₂H) ppm; ¹⁹F NMR (CDCl₃, 470 MHz) δ -113.0 (d, J = 55 Hz, CF₂H) ppm; ¹³C{¹H} NMR (CDCl₃, 125 MHz): δ 135.3, 133.1, 133.0, 132.1, 129.8, 129.2 (2xC), 128.0, 127.8, 127.7, 125.9, 125.5, 121.7, 114.7, 108.8

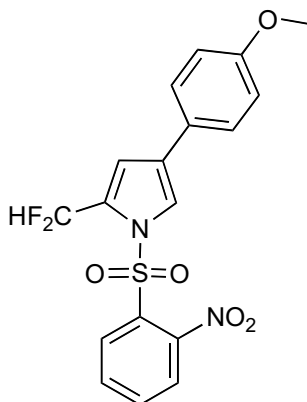
(t, J = 235 Hz, C-F) (1 X C missing) ppm; HRMS-ESI (*m/z*): [M + H]⁺ Calcd 379.0564 for C₁₇H₁₃F₂N₂O₄S; found 379.0544

2-(Difluoromethyl)-1-(2-nitrophenylsulfonyl)-4-*p*-tolyl-1*H*-pyrrole (3.111)



Using GP2 with Xtalfluor-E®, the title compound was synthesized from **3.104** (0.240 g, 0.648 mmol). The title compound was isolated as a beige solid (0.177 g, 70 % yield) after column chromatography (silica – 50 % CH₂Cl₂/hexanes). m.p.: 114-115 °C; ¹H NMR (CDCl₃, 500 MHz): δ 7.88 (d, 1H, J = 8 Hz), 7.78 (t, 1H, J = 8 Hz), 7.68 (t, 1H, J = 8 Hz), 7.61 (as, 1H), 7.53 (d, 1H, J = 8 Hz), 7.43 (d, 2H, J = 8 Hz), 7.21 (d, 2H, J = 8 Hz), 6.95-7.17 (m, 2H, CF₂H and pyrrolic peak included) ppm; ¹⁹F NMR (CDCl₃, 470 MHz) δ -113.0 (d, J = 55 Hz, CF₂H) ppm; ¹³C{¹H} NMR (CDCl₃, 125 MHz): δ 137.9, 135.2, 133.1, 129.9, 129.7, 129.3, 129.2, 127.8, 125.8, 125.4, 121.3, 114.7, 108.8 (t, J = 235 Hz, C-F) ppm; HRMS-ESI (*m/z*): [M + Na]⁺ Calcd 415.0540 for C₁₈H₁₄F₂N₂NaO₄S; found 415.0522

**2-(Difluoromethyl)-4-(4-methoxyphenyl)-1-(2-nitrophenylsulfonyl)-1H-pyrrole
(3.112)**



Using GP2 with Xtalfluor-E®, the title compound was synthesized from **3.105** (0.300 g, 0.776 mmol). The title compound was isolated as a beige solid (0.196 g, 62 % yield) after column chromatography (silica – 50 % CH₂Cl₂/hexanes). m.p.: 145-148 °C; ¹H NMR (CDCl₃, 500 MHz): δ 7.88 (d, 1H J = 8 Hz), 7.78 (t, 1H, J = 8 Hz), 7.69 (t, 1H, J = 8 Hz), 7.52-7.55 (m, 2H), 7.46 (d, 2H, J = 9 Hz), 6.92-7.16 (m, 4H, CF₂H and pyrrolic peak included), 3.83 (s, 3H) ppm; ¹⁹F NMR (CDCl₃, 470 MHz) δ -113.0 (d, J = 55 Hz, CF₂H) ppm; ¹³C{¹H} NMR (CDCl₃, 125 MHz): δ 159.6, 147.7, 135.2, 133.1 (2xC), 129.6, 129.3 (t, J = 31), 127.5, 127.1, 125.4, 124.6, 120.7, 114.7 (t, J = 5), 114.6, 108.8 (t, J = 235, CF₂H) 55.5 ppm; HRMS-ESI (m/z): [M + Na]⁺ Calcd 431.0489 for C₁₈H₁₄F₂N₂NaO₅S; found 431.0491.

3.4.7 General Procedure (GP4) for the Kinetics of N-Deprotection

The deprotection of *N*-*o*-nosyl α-difluoromethyl pyrroles was performed at the concentrations indicated for each substrate (*vide infra*) in a Varian CARY 100 BIO UV-Visible spectrophotometer. The cuvette holders were equipped with a circulating cooling bath set at -10 °C. A steady flow of dry N₂ gas was piped into the sample chamber to prevent condensation forming on the cuvette during data collection, and to also prevent oxygen from inadvertently causing excess disulfide formation. The cuvette holders were allowed to cool for 3 hours before testing their refrigeration capacity on a blank sample. It was found that the temperature of a blank sample containing CH₃CN took 10 minutes to equilibrate to 0 °C.

Cuvettes were equipped with a septum cover, which employs both Teflon tape on the thread of the cuvette and parafilm around the septum cover to ensure a sealed system (CAUTION: thiophenol is fatal upon inhalation or if in contact with skin). The sealed cuvette was flushed with N₂ for 10 minutes, and then charged with 3 mL an anhydrous solution of the pyrrole (1 equiv.) and thiophenol (~400 equiv.) in acetonitrile. The charged cuvette was allowed to cool to 0 °C over 10 minutes, and manual baseline correction was performed. The deprotection reaction was initiated by the injection of an anhydrous solution of NEt₃ (0.5 mL, containing ~560 equiv.) through the septum of the cuvette.

The reaction was monitored for 60 seconds at a wavelength of 368 nm, collecting data points at 1X10⁻¹ second intervals. The concentration of deprotected pyrrole forming was calculated from each absorbance value over time, to produce relative rate constants. UV-absorbing compounds **3.115** and **3.117** were treated as forming at the same rate with a combined bimolecular extinction coefficient of 5850 L mol⁻¹ cm⁻¹, whilst fully aware that background oxidation may be occurring *via* multiple mechanisms (making this assumption possibly untrue). Kinetic analysis was run in triplicates, but 1 out of 3 replicates contained unusable data. Therefore, the rate constants achieved by analysis in this manner resulted in relative data, with respect to this unique experiment, and are not to be reported absolute rate constants.

Line of Best Fit in Relation to the Rate Equation

Rate constants of each substrate are calculated using Kaleidagraph v 4.1.3 by plotting concentration of product over time.

Rate Equation: $[P]_t = [-([P]_{\infty} - [P]_o)e^{-kt}] + [P]_{\infty}$

Line of Best Fit: $y = [(m1) * \exp (-m2 * m0)] + m3$

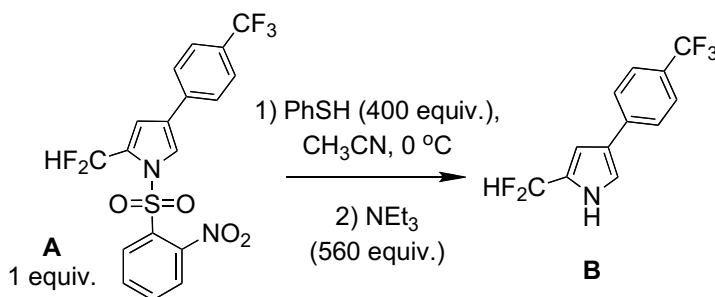
Variable 'm2' is the relative rate constant 'k' at the concentrations employed.

NEt₃ Stock Solution

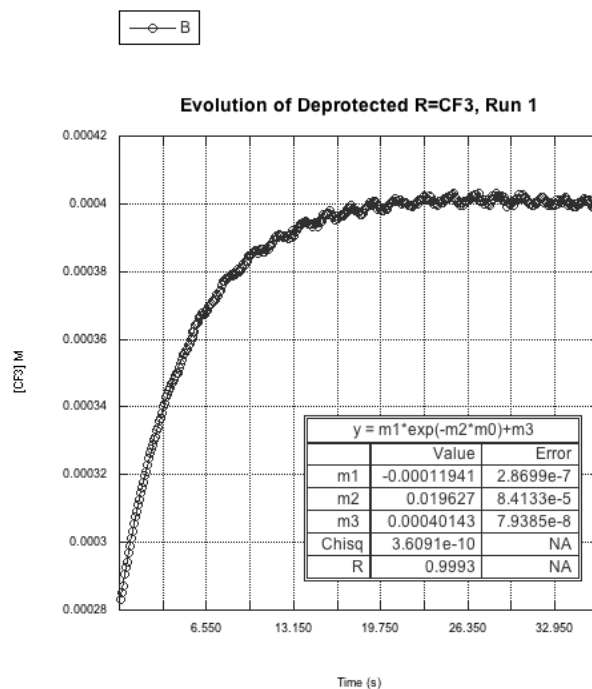
A stock solution was prepared using NEt₃ (2.185 mL, 1.568X10⁻² mol) in CH₃CN using a 10.000 mL volumetric flask equipped with a septum under N₂. The solution was bubbled with N₂ for 10 minutes for mixing purposes and the removal of any residual oxygen. To

initiate *N*-deprotection, an aliquot (0.5 mL, 7.840×10^{-4} mol) was added to a cuvette charged with 3 mL of a solution containing protected pyrrole and PhSH, resulting in a final concentration of 2.240×10^{-1} M of NEt_3 in the monitored reaction. The same stock solution was used across all samples; exact equivalents of NEt_3 vary per sample.

Rate Constant Afforded from the Production of **3.108B**



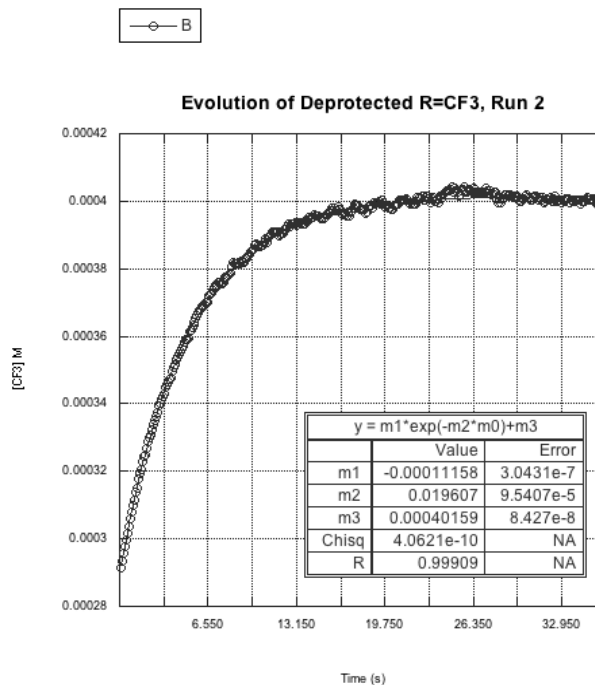
An initial stock was prepared using **3.108** (0.021 g, 4.705×10^{-5} mol) in CH_3CN using a 10.000 mL volumetric flask equipped with a septum under N_2 . After bubbling the solution with N_2 for 10 minutes, an aliquot of the first stock (1.000 mL, 4.705×10^{-6} mol) was transferred to a second 10.000 mL volumetric flask equipped with a septum under N_2 . The second stock was then charged with PhSH (0.195 mL, 404 equiv., 1.903×10^{-3} mmol) and the remaining volume consisted of CH_3CN . After bubbling the solution with N_2 for 10 minutes, an aliquot of the second stock (3.000 mL, 1.411×10^{-6} mol of **3.108**, 5.709×10^{-4} mol of PhSH) was transferred to a sealed cuvette equipped with a septum cover. To initiate *N*-deprotection, an aliquot (0.5 mL, 555 equiv., 7.840×10^{-4} mol) of the NEt_3 stock solution was added to a cuvette charged with **3.108** and PhSH, resulting in a final concentration of 1.631×10^{-1} M of NEt_3 , 2.240×10^{-1} M of NEt_3 and 4.033×10^{-4} M of **3.108** in the monitored reaction. The reaction was monitored until it reached equilibrium (36 seconds).



$$k = 1.963 \times 10^{-2} \text{ s}^{-1}$$

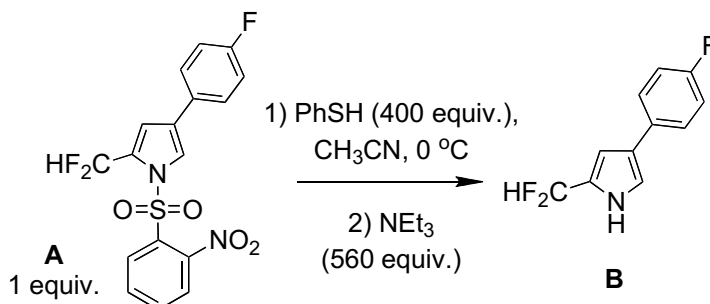
Rate Constant Afforded from the Production of 3.108B, Replicate #2

Followed procedure for replicate # 1. The reaction was monitored until it reached equilibrium (36 seconds).

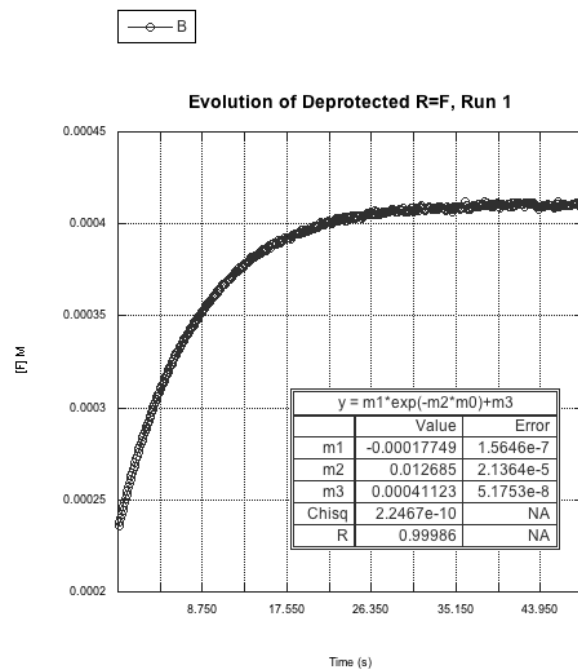


$$k = 1.961 \times 10^{-2} \text{ s}^{-1}$$

Rate Constant Afforded from the Production of 3.109B



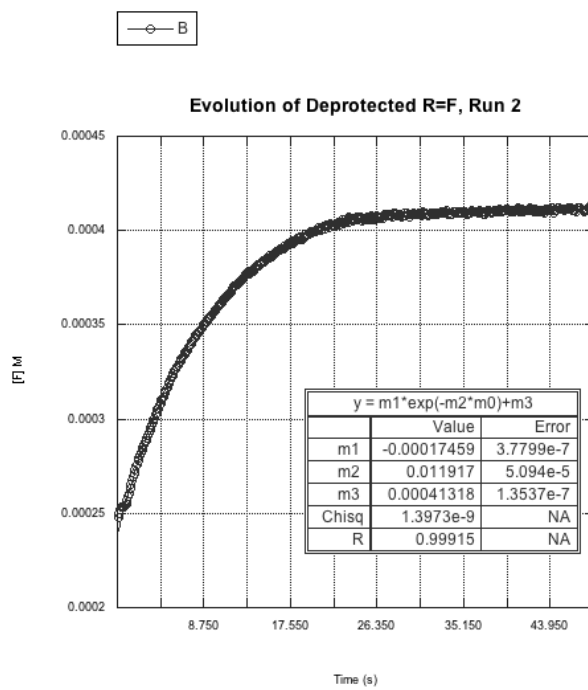
An initial stock was prepared using **3.109** (0.019 g, 4.794×10^{-5} mol) in CH_3CN using a 10.000 mL volumetric flask equipped with a septum under N_2 . After bubbling the solution with N_2 for 10 minutes, an aliquot of the first stock (1.000 mL, 4.794×10^{-6} mol) was transferred to a second 10.000 mL volumetric flask equipped with a septum under N_2 . The second stock was then charged with PhSH (0.195 mL, 397 equiv., 1.903×10^{-3} mol) and the remaining volume consisted of CH_3CN . After bubbling the solution with N_2 for 10 minutes, an aliquot of the second stock (3.000 mL, 1.438×10^{-6} mol of **3.109**, 5.709×10^{-4} mol of PhSH) was transferred to a sealed cuvette equipped with a septum cover. To initiate *N*-deprotection, an aliquot (0.5 mL, 545 equiv., 7.840×10^{-4} mol) of the NEt_3 stock solution was added to a cuvette charged with **3.109** and PhSH, resulting in a final concentration of $1.631 \times 10^{-1} \text{ M}$ of NEt_3 , $2.240 \times 10^{-1} \text{ M}$ of PhSH and $4.109 \times 10^{-4} \text{ M}$ of **3.109** in the monitored reaction. The reaction was monitored until it reached equilibrium (48 seconds).



$$k = 1.269 \times 10^{-2} \text{ s}^{-1}$$

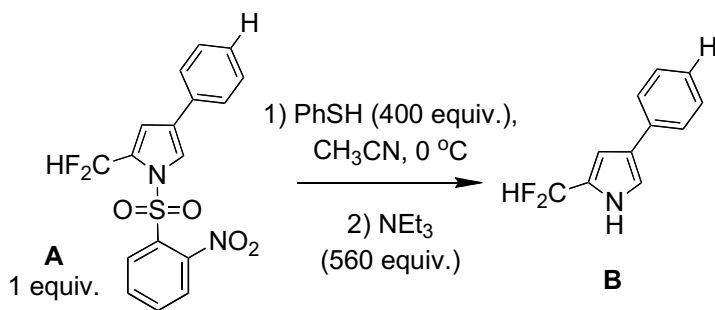
Rate Constant Afforded from the Production of 3.109B, Replicate #2

Followed procedure for replicate # 1. The reaction was monitored until it reached equilibrium (48 seconds).

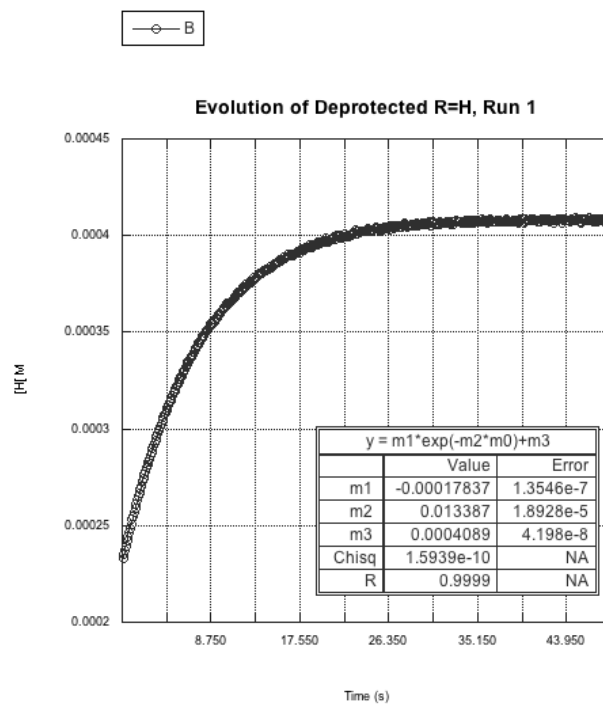


$$k = 1.192 \times 10^{-2} \text{ s}^{-1}$$

Rate Constant Afforded from the Production of 3.110B



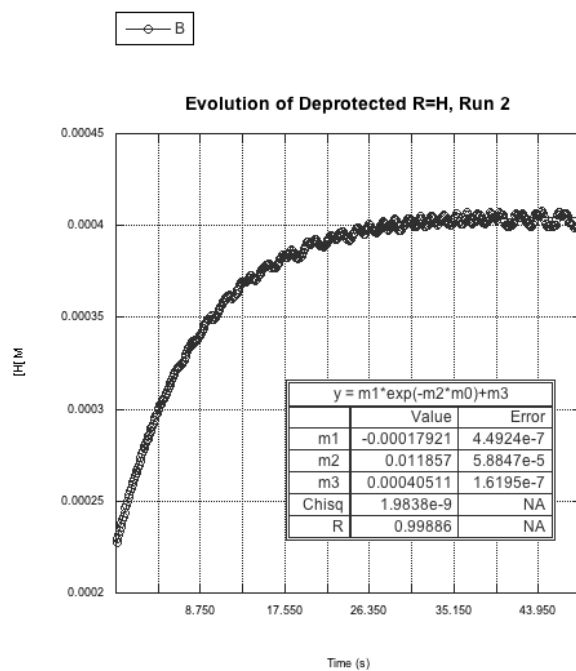
An initial stock was prepared using **3.110** (0.018 g, 4.757×10^{-5} mol) in CH₃CN using a 10.000 mL volumetric flask equipped with a septum under N₂. After bubbling the solution with N₂ for 10 minutes, an aliquot of the first stock (1.000 mL, 4.757×10^{-6} mol) was transferred to a second 10.000 mL volumetric flask equipped with a septum under N₂. The second stock was then charged with PhSH (0.195 mL, 400 equiv., 1.903×10^{-3} mol) and the remaining volume consisted of CH₃CN. After bubbling the solution with N₂ for 10 minutes, an aliquot of the second stock (3.000 mL, 1.427×10^{-6} mol of **3.110**, 5.709×10^{-4} mol of PhSH) was transferred to a sealed cuvette equipped with a septum cover. To initiate *N*-deprotection, an aliquot (0.5 mL, 550 equiv., 7.840×10^{-4} mol) of the NEt₃ stock solution was added to a cuvette charged with **3.110** and PhSH, resulting in a final concentration of 1.631×10^{-1} M of NEt₃, 2.240×10^{-1} M of NEt₃ and 4.078×10^{-4} M of **3.110** in the monitored reaction. The reaction was monitored until it reached equilibrium (48 seconds).



$$k = 1.339 \times 10^{-2} \text{ s}^{-1}$$

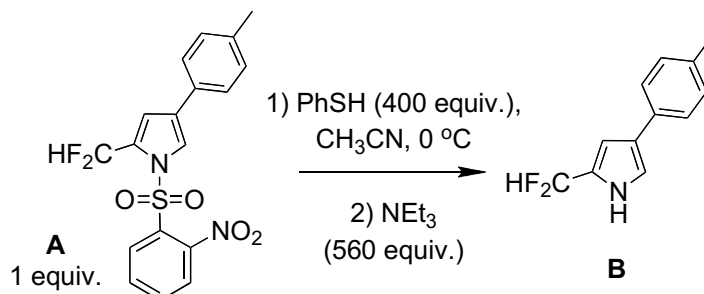
Rate Constant Afforded from the Production of 3.110B, Replicate #2

Followed procedure for replicate # 1. The reaction was monitored until it reached equilibrium (48 seconds).

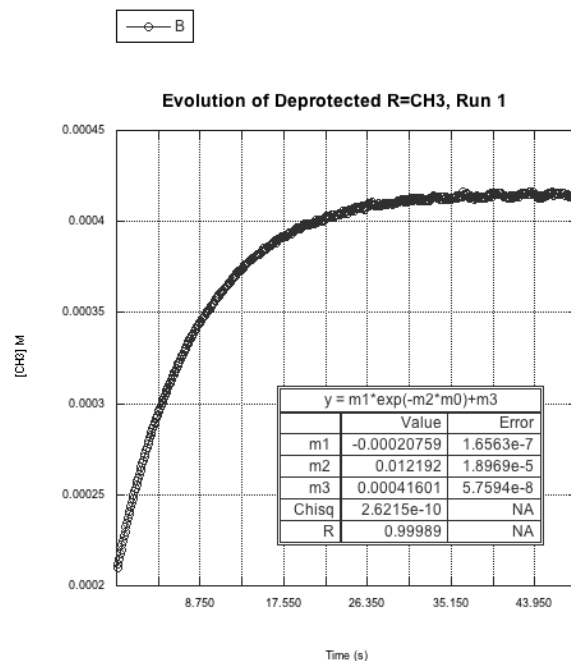


$$k = 1.186 \times 10^{-2} \text{ s}^{-1}$$

Rate Constant Afforded from the Production of 3.111B



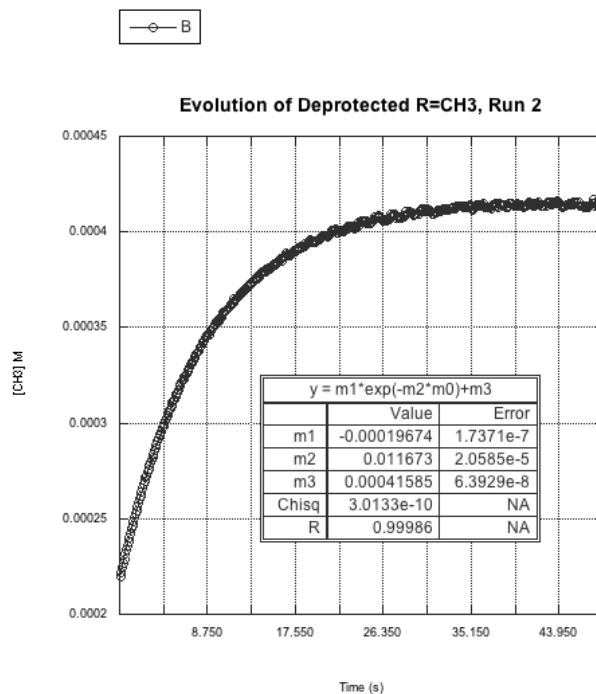
An initial stock was prepared using **3.111** (0.019 g, 4.842×10^{-5} mol) in CH₃CN using a 10.000 mL volumetric flask equipped with a septum under N₂. After bubbling the solution with N₂ for 10 minutes, an aliquot of the first stock (1.000 mL, 4.842×10^{-6} mol) was transferred to a second 10.000 mL volumetric flask equipped with a septum under N₂. The second stock was then charged with PhSH (0.195 mL, 395 equiv., 1.903×10^{-3} mol) and the remaining volume consisted of CH₃CN. After bubbling the solution with N₂ for 10 minutes, an aliquot of the second stock (3.000 mL, 1.453×10^{-6} mol of **3.111**, 5.709×10^{-4} mol of PhSH) was transferred to a sealed cuvette equipped with a septum cover. To initiate *N*-deprotection, an aliquot (0.5 mL, 540 equiv., 7.840×10^{-4} mol) of the NEt₃ stock solution was added to a cuvette charged with **3.111** and PhSH, resulting in a final concentration of 1.631×10^{-1} M of NEt₃, 2.240×10^{-1} M of NEt₃ and 4.150×10^{-4} M of **3.111** in the monitored reaction. The reaction was monitored until it reached equilibrium (48 seconds).



$$k = 1.219 \times 10^{-2} \text{ s}^{-1}$$

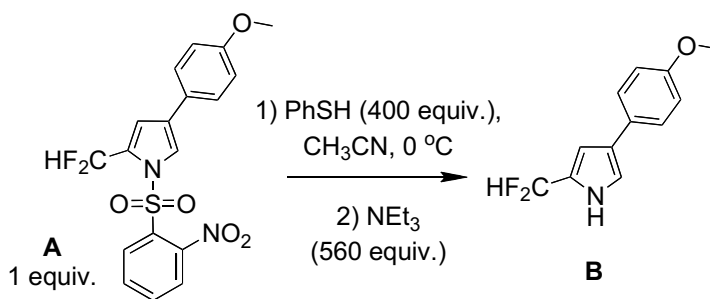
Rate Constant Afforded from the Production of 3.111B, Replicate #2

Followed procedure for replicate # 1. The reaction was monitored until it reached equilibrium (48 seconds).

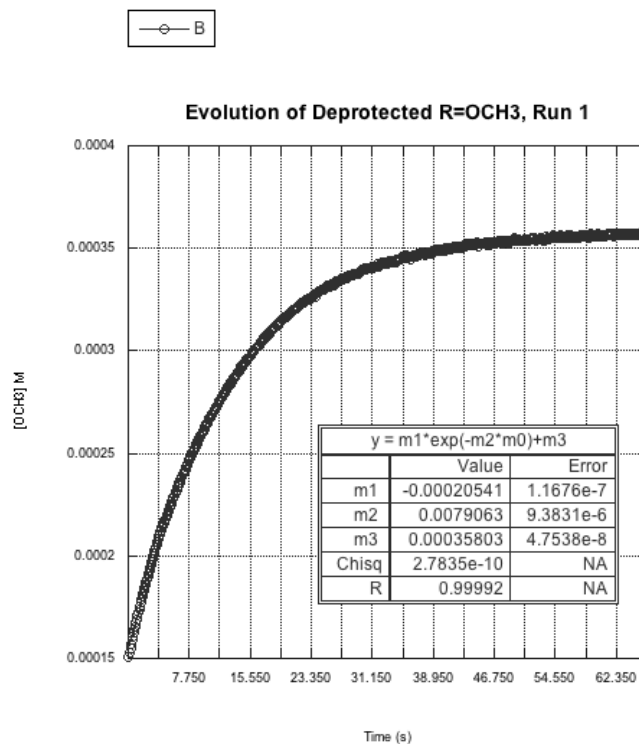


$$k = 1.167 \times 10^{-2} \text{ s}^{-1}$$

Rate Constant Afforded from the Production of 3.112B



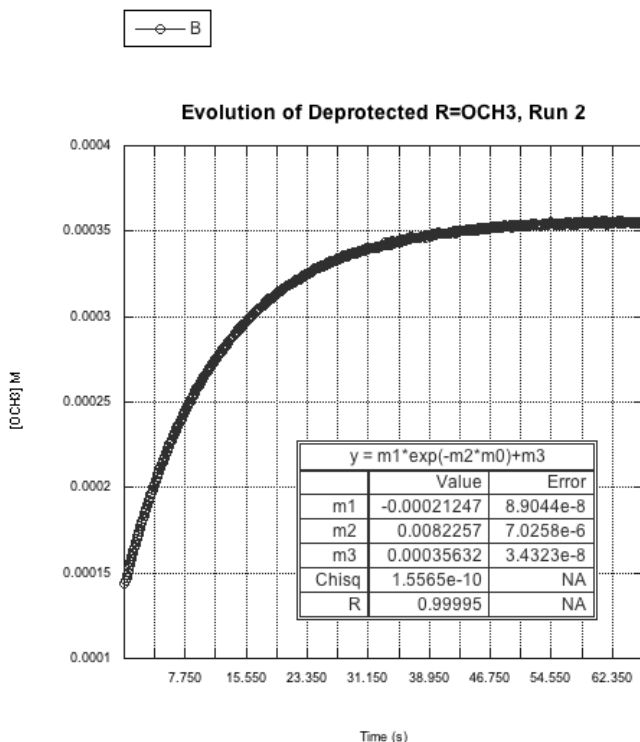
An initial stock was prepared using **3.112** (0.017 g, 4.163×10^{-5} mol) in CH₃CN using a 10.000 mL volumetric flask equipped with a septum under N₂. After bubbling the solution with N₂ for 10 minutes, an aliquot of the first stock (1.000 mL, 4.163×10^{-6} mol) was transferred to a second 10.000 mL volumetric flask equipped with a septum under N₂. The second stock was then charged with PhSH (0.195 mL, 457 equiv., 1.903×10^{-3} mol) and the remaining volume consisted of CH₃CN. After bubbling the solution with N₂ for 10 minutes, an aliquot of the second stock (3.000 mL, 1.249×10^{-6} mol of **3.112**, 5.709×10^{-4} mol of PhSH) was transferred to a sealed cuvette equipped with a septum cover. To initiate *N*-deprotection, an aliquot (0.5 mL, 627 equiv., 7.840×10^{-4} mol) of the NEt₃ stock solution was added to a cuvette charged with **3.112** and PhSH, resulting in a final concentration of 1.631×10^{-1} M of NEt₃, 2.240×10^{-1} M of PhSH and 3.568×10^{-4} M of **3.112** in the monitored reaction. The reaction was monitored until it reached equilibrium (66 seconds).



$$k = 7.906 \times 10^{-3} \text{ s}^{-1}$$

Rate Constant Afforded from the Production of 3.112B, Replicate #2

Followed procedure for replicate # 1. The reaction was monitored until it reached equilibrium (66 seconds).



$$k = 8.226 \times 10^{-3} \text{ s}^{-1}$$

3.4.8 General Procedure (GP5) for the Kinetics of α -Difluoromethyl Group Hydrolysis

The deprotection of each *N*-*o*-nosyl α -difluoromethyl pyrrole was performed as a stock solution, at the concentrations indicated for each substrate (*vide infra*), using PhSH (1.8 equiv.) and NEt₃ (2.5 equiv.) in CD₃CN (purging and bubbling with N₂ as before). Hexafluorobenzene was added as an internal standard at a known concentration. Upon complete deprotection as noted by use of ¹H and ¹⁹F NMR spectroscopy, the stock solution was transferred to three separate dry and N₂-flushed NMR tubes (0.500 mL each). The NMR tubes were equipped with septum cap that were sealed with both Teflon tape and parafilm, taking care in applying the tapes evenly.

The starting concentration of deprotected pyrrole was confirmed by use of the internal standard before beginning hydrolysis. The instrument bore temperature was increased to 40 °C and the sample was allowed to equilibrate for 5 minutes, at which point a *t*₀ spectrum was collected. The sample was ejected from the bore, and hydrolysis was initiated by the injection of H₂O (1000 equiv.) through the septum cap. The sample was

then briefly agitated using a vortex mixer and re-inserted into the probe. The first spectrum was collected immediately (^{19}F NMR, $t = 2$ minutes). Subsequent data points were collected at 1 minute and 13 second intervals (32 scans), to a total collection time of 25 minutes and 7 seconds. The decreasing concentration of fluorinated pyrrole was calculated by use of the integration of the peaks arising from the internal standard and the α -difluoromethyl group. Samples were run in triplicates, and the relative rate constants were calculated.

Due to time constraints applied to instrument usage, the analysis of the series was performed over several days. Each experiment began with analyzing the hydrolysis of **3.110B** to ensure that the handling of samples was identical throughout this study. If the hydrolysis of **3.100B** did not yield results that were replicate to the standardized data, the data for that series was rejected. Likewise, if preemptive hydrolysis had occurred due to human error in the preparation of a sample, the data was rejected.

Line of Best Fit in Relation to the Rate Equation

Rate constants of each substrate are calculated using Kaleidagraph v 4.1.3 by plotting concentration of starting material over time.

Rate Equation: $[A]_t = [A]_0 e^{-kt}$

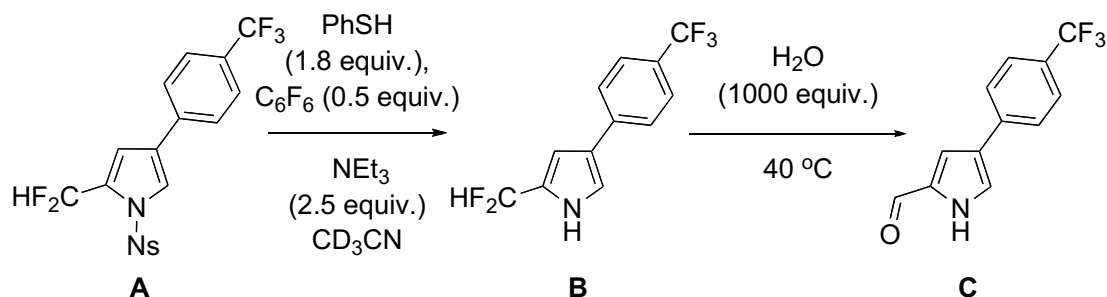
Line of Best Fit: $y = [(m1) * \exp(-m2 * m0)]$

Variable 'm2' is the relative rate constant 'k' at the concentrations employed.

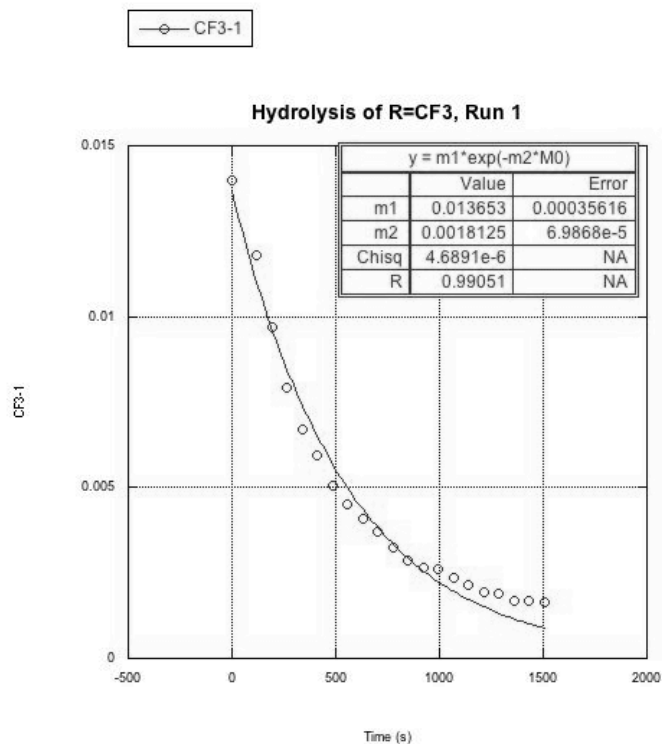
Hexafluorobenzene Stock Solution

A stock solution was freshly prepared prior to *N*-deprotection of the samples. The stock solution was produced at a concentration of ~ 0.4 M. Between 0.5 mL and 1 mL of stock solution was prepared at a time; e.g., a solution of hexafluorobenzene (2.185 mL, 1.568×10^{-2} mol) in CD_3CN (0.5 mL) was equipped with a septum under N_2 . The solution was bubbled with N_2 for 10 minutes for the removal of any residual oxygen. The amount of the hexafluorobenzene stock solution added to each sample stock solution is indicated in the procedures below.

Rate Constant Afforded from the Hydrolysis of **3.108B**, Replicate #1



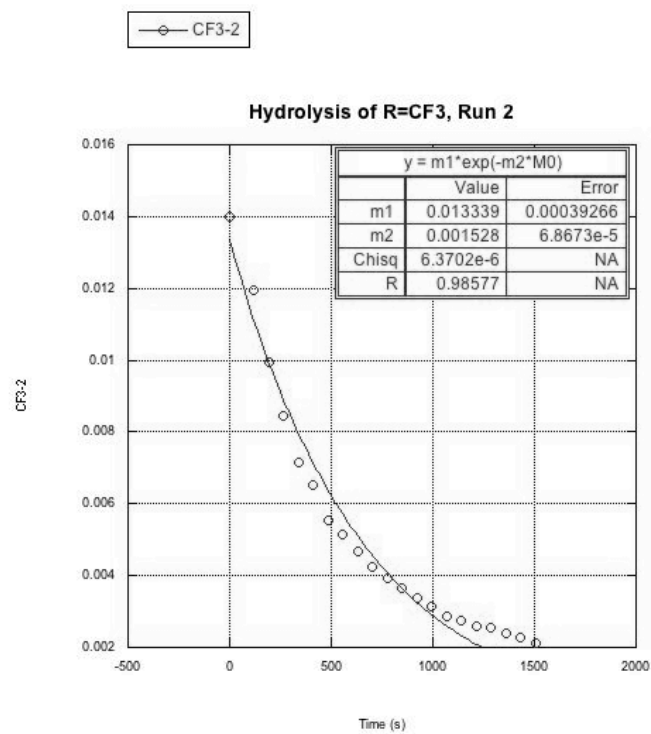
An initial stock was prepared using **3.108** (0.022 g, 4.929×10^{-5} mol) and PhSH (0.010 mL, 9.739×10^{-5} mol) in CD₃CN (2.500 mL) under N₂. After bubbling the solution with N₂ for 10 minutes, anhydrous NEt₃ (0.018 mL, 1.291×10^{-4} mol) and hexafluorobenzene stock (0.060 mL, containing 2.595×10^{-5} mol of hexafluorobenzene) were added, resulting in 1.904×10^{-2} M concentration of **3.108B**. An aliquot of the reaction mixture (0.500 mL, containing 9.519×10^{-6} mol of **3.108B**) was transferred to a dry and N₂-flushed NMR tube equipped with septum cap once *N*-deprotection was complete. Hydrolysis was initiated by the injection of H₂O (0.180 mL, 1050 equiv.) through the septum cap, resulting in a final concentration of 1.400×10^{-2} M of **3.108B** in the monitored reaction. The reaction was monitored by use of ¹⁹F NMR spectroscopy for 25 minutes and 7 seconds.



$$k_{\text{CF3-1}} = 1.813 \times 10^{-3} \text{ s}^{-1}$$

Rate Constant Afforded from the Hydrolysis of 3.108B, Replicate #2

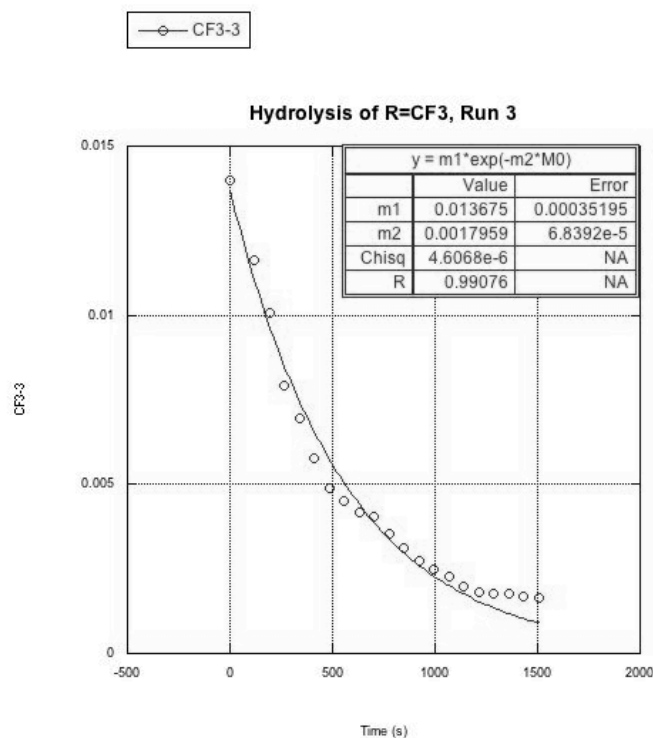
Followed procedure for replicate # 1. The reaction was monitored until it reached equilibrium (25 minutes and 7 seconds).



$$k_{CF3-2} = 1.528 \times 10^{-3} \text{ s}^{-1}$$

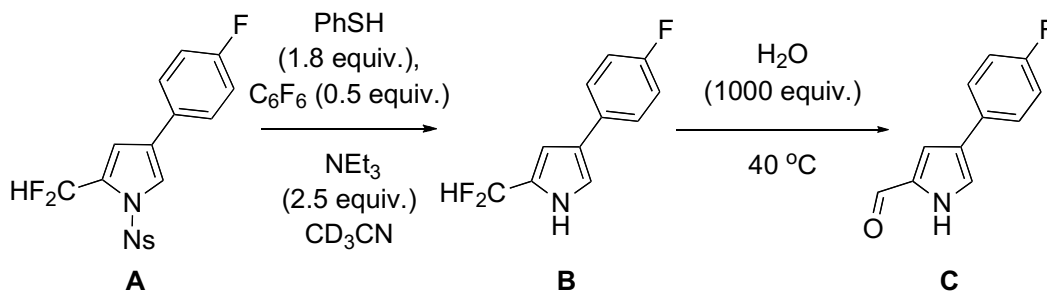
Rate Constant Afforded from the Hydrolysis of 3.108B, Replicate #3

Followed procedure for replicate # 1. The reaction was monitored until it reached equilibrium (25 minutes and 7 seconds).



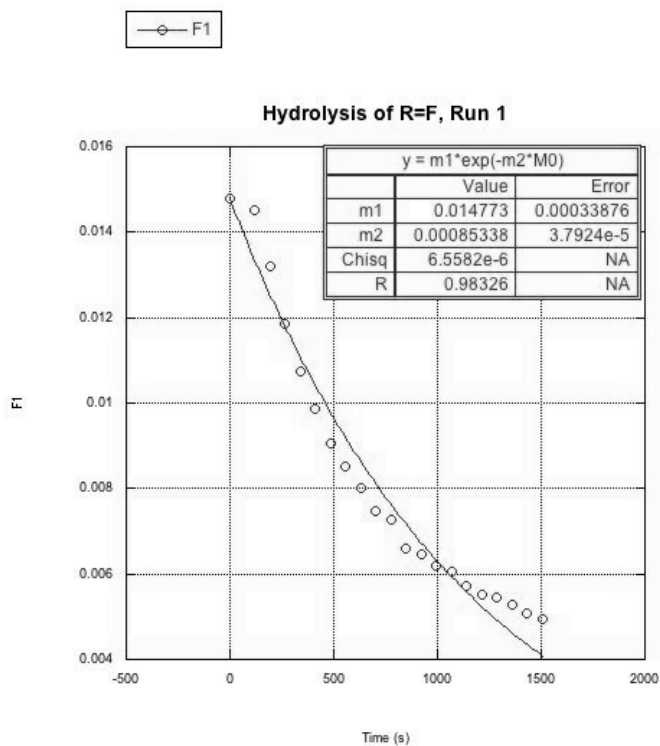
$$k_{\text{CF3-3}} = 1.796 \times 10^{-3} \text{ s}^{-1}$$

Rate Constant Afforded from the Hydrolysis of **3.109B**, Replicate #1



An initial stock was prepared using **3.109** (0.022 g, 5.551×10^{-5} mol) and PhSH (0.010 mL, 9.739×10^{-5} mol) in CD_3CN (2.800 mL) under N_2 . After bubbling the solution with N_2 for 10 minutes, anhydrous NEt_3 (0.019 mL, 1.363×10^{-4} mol) and hexafluorobenzene stock (0.070 mL, containing 3.023×10^{-5} mol of hexafluorobenzene) were added, resulting in 1.915×10^{-2} M concentration of **3.109B**. An aliquot of the reaction mixture (0.500 mL, containing 9.574×10^{-6} mol of **3.109B**) was transferred to a dry and N_2 -flushed NMR tube equipped with septum cap once *N*-deprotection was complete. Hydrolysis was initiated by the injection of H_2O (0.180 mL, 1044 equiv.)

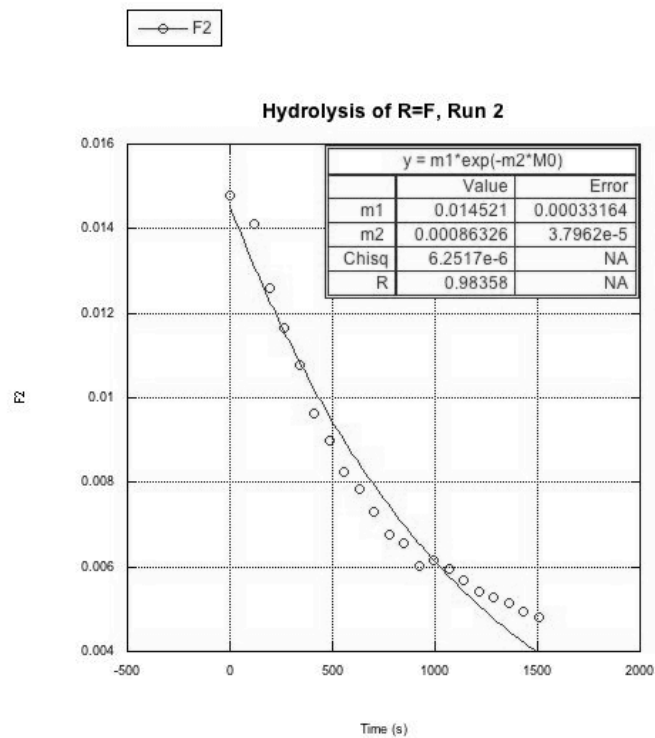
through the septum cap, resulting in a final concentration of 1.408×10^{-2} M of **3.109B** in the monitored reaction. The reaction was monitored by use of ^{19}F NMR spectroscopy for 25 minutes and 7 seconds.



$$k_{F-1} = 8.534 \times 10^{-4} \text{ s}^{-1}$$

Rate Constant Afforded from the Hydrolysis of 3.109B, Replicate #2

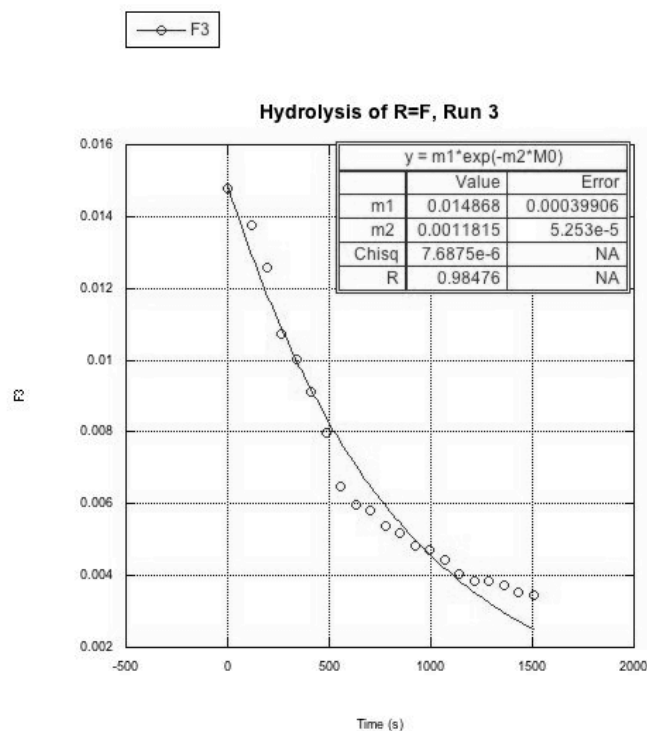
Followed procedure for replicate # 1. The reaction was monitored until it reached equilibrium (25 minutes and 7 seconds).



$$k_{F-2} = 8.633 \times 10^{-4} \text{ s}^{-1}$$

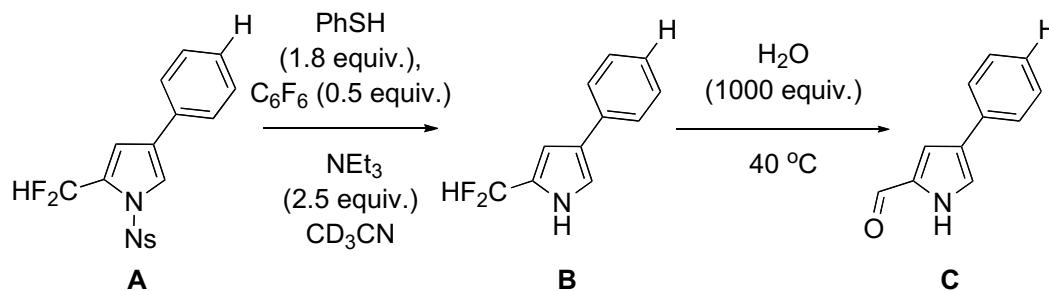
Rate Constant Afforded from the Hydrolysis of 3.109B, Replicate #3

Followed procedure for replicate # 1. The reaction was monitored until it reached equilibrium (25 minutes and 7 seconds).



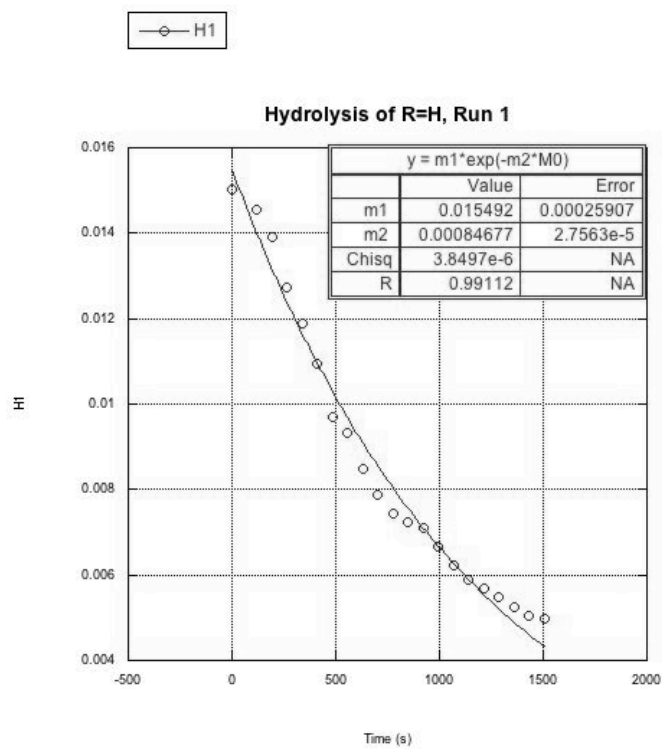
$$k_{F-3} = 1.182 \times 10^{-3} \text{ s}^{-1}$$

Rate Constant Afforded from the Hydrolysis of **3.110B**, Replicate #1



An initial stock was prepared using **3.110** (0.020 g, 5.286×10^{-5} mol) and PhSH (0.010 mL, 9.739×10^{-5} mol) in CD_3CN (2.500 mL) under N_2 . After bubbling the solution with N_2 for 10 minutes, anhydrous NEt_3 (0.018 mL, 1.291×10^{-4} mol) and hexafluorobenzene stock (0.062 mL, containing 2.682×10^{-5} mol of hexafluorobenzene) were added, resulting in 2.041×10^{-2} M concentration of **3.110B**. An aliquot of the reaction mixture (0.500 mL, containing 1.020×10^{-5} mol of **3.110B**) was transferred to a dry and N_2 -flushed NMR tube equipped with septum cap once *N*-deprotection was complete. Hydrolysis was initiated by the injection of H_2O (0.180 mL, 979 equiv.) through the septum cap, resulting in a final concentration of 1.501×10^{-2} M of **3.110B** in

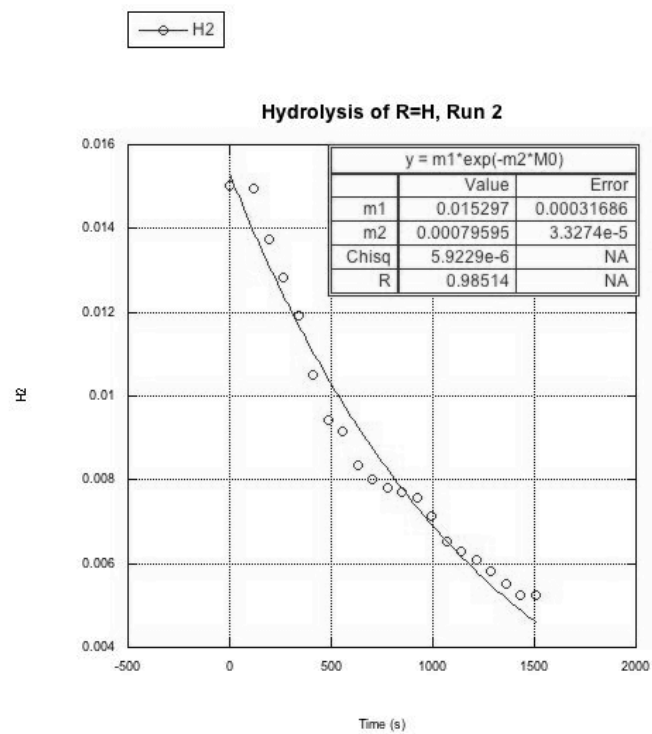
the monitored reaction. The reaction was monitored by use of ^{19}F NMR spectroscopy for 25 minutes and 7 seconds.



$$k_{\text{H-1}} = 8.468 \times 10^{-4} \text{ s}^{-1}$$

Rate Constant Afforded from the Hydrolysis of 3.110B, Replicate #2

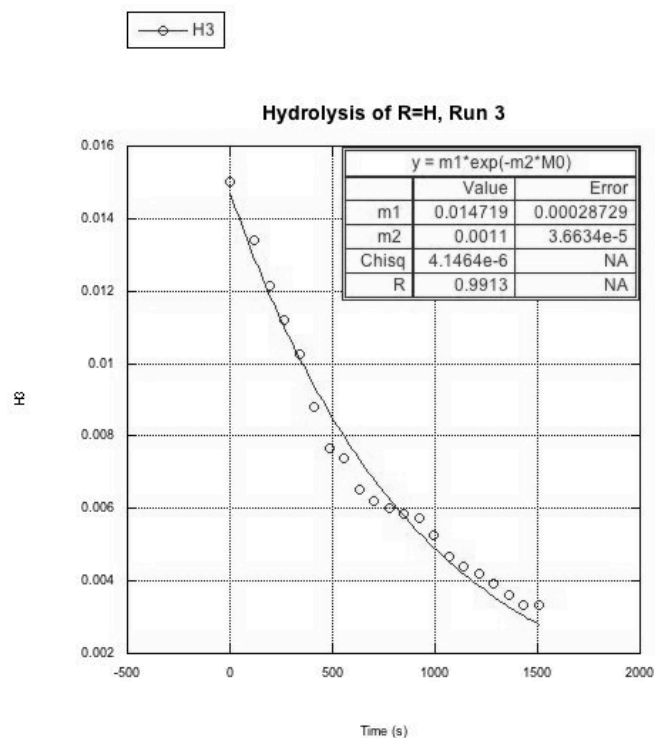
Followed procedure for replicate # 1. The reaction was monitored until it reached equilibrium (25 minutes and 7 seconds).



$$k_{H-2} = 7.960 \times 10^{-4} \text{ s}^{-1}$$

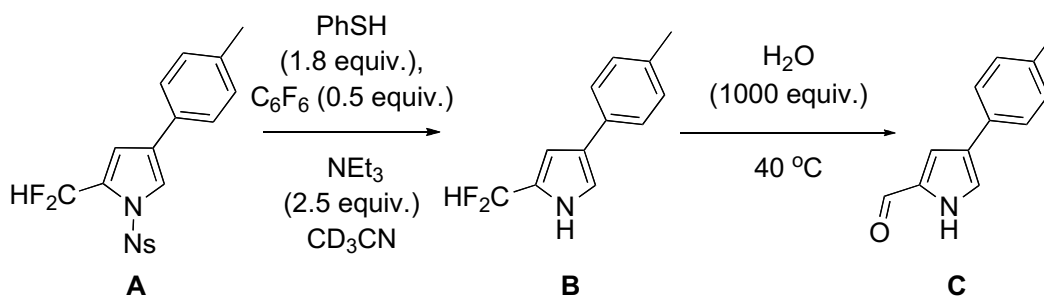
Rate Constant Afforded from the Hydrolysis of 3.110B, Replicate #3

Followed procedure for replicate # 1. The reaction was monitored until it reached equilibrium (25 minutes and 7 seconds).



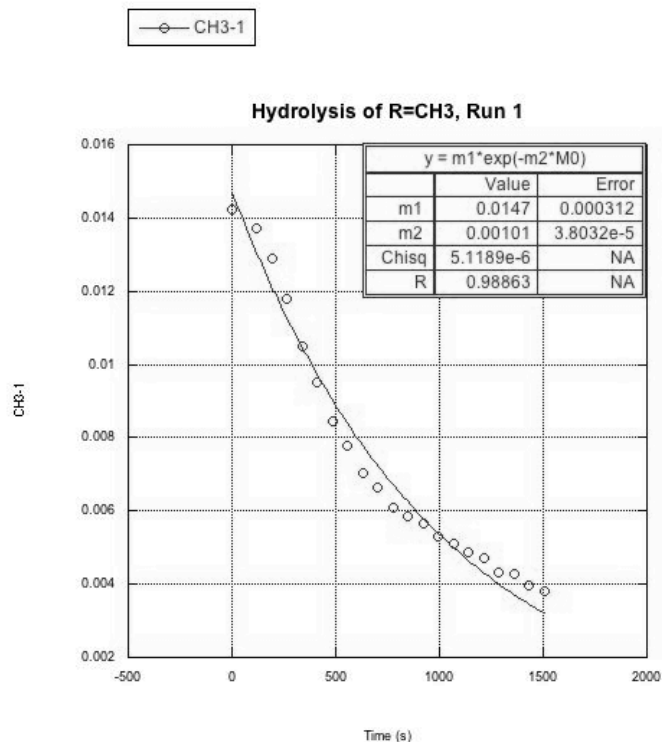
$$k_{H-3} = 1.100 \times 10^{-3} \text{ s}^{-1}$$

Rate Constant Afforded from the Hydrolysis of **3.111B**, Replicate #1



An initial stock was prepared using **3.111** (0.022 g, 5.607×10^{-5} mol) and PhSH (0.010 mL, 9.739×10^{-5} mol) in CD_3CN (2.800 mL) under N_2 . After bubbling the solution with N_2 for 10 minutes, anhydrous NEt_3 (0.019 mL, 1.363×10^{-4} mol) and hexafluorobenzene stock (0.070 mL, containing 3.023×10^{-5} mol of hexafluorobenzene) were added, resulting in 1.934×10^{-2} M concentration of **3.111B**. An aliquot of the reaction mixture (0.500 mL, containing 9.670×10^{-6} mol of **3.111B**) was transferred to a dry and N_2 -flushed NMR tube equipped with septum cap once *N*-deprotection was complete. Hydrolysis was initiated by the injection of H_2O (0.180 mL, 1032 equiv.)

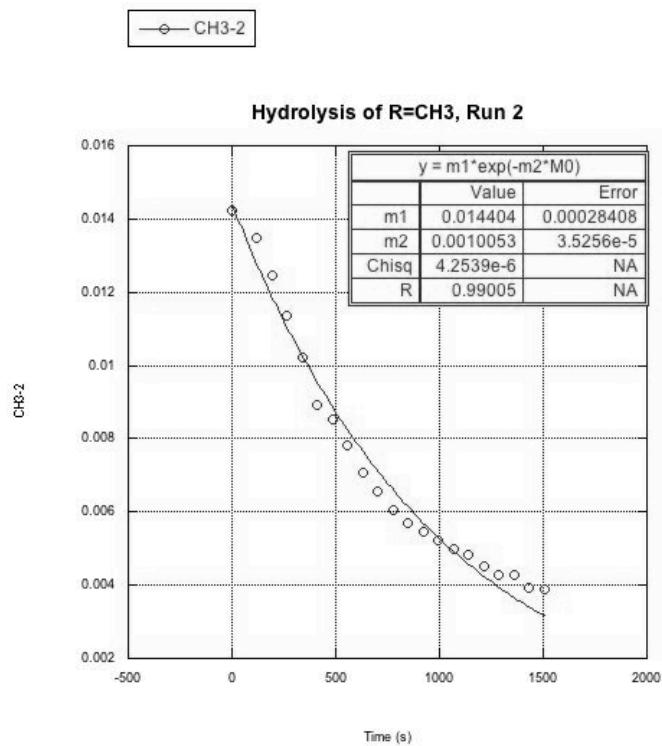
through the septum cap, resulting in a final concentration of 1.422×10^{-2} M of **3.111B** in the monitored reaction. The reaction was monitored by use of ^{19}F NMR spectroscopy for 25 minutes and 7 seconds.



$$k_{\text{CH3-1}} = 1.010 \times 10^{-3} \text{ s}^{-1}$$

Rate Constant Afforded from the Hydrolysis of 3.111B, Replicate #2

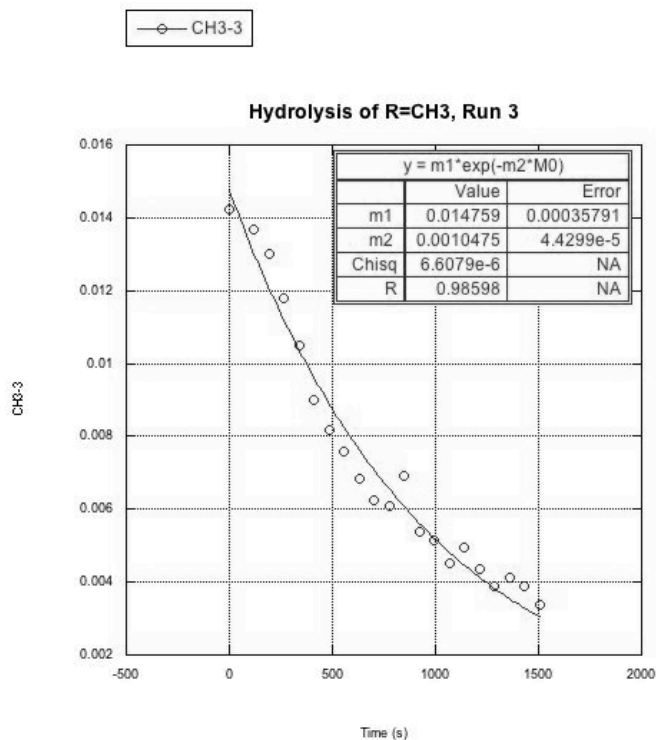
Followed procedure for replicate # 1. The reaction was monitored until it reached equilibrium (25 minutes and 7 seconds).



$$k_{\text{CH}_3-2} = 1.005 \times 10^{-3} \text{ s}^{-1}$$

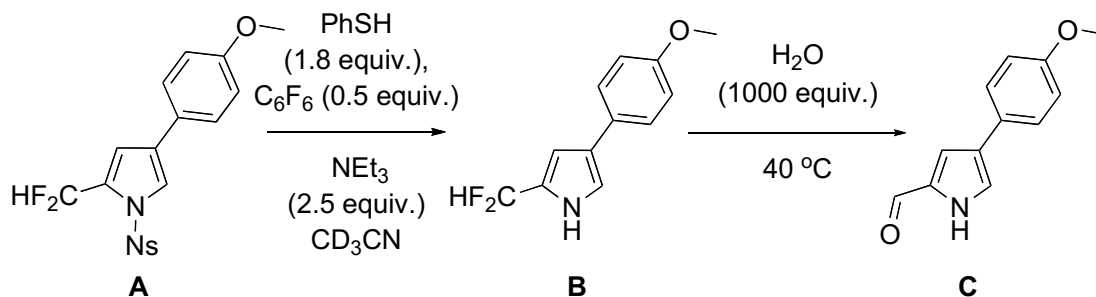
Rate Constant Afforded from the Hydrolysis of 3.111B, Replicate #3

Followed procedure for replicate # 1. The reaction was monitored until it reached equilibrium (25 minutes and 7 seconds).



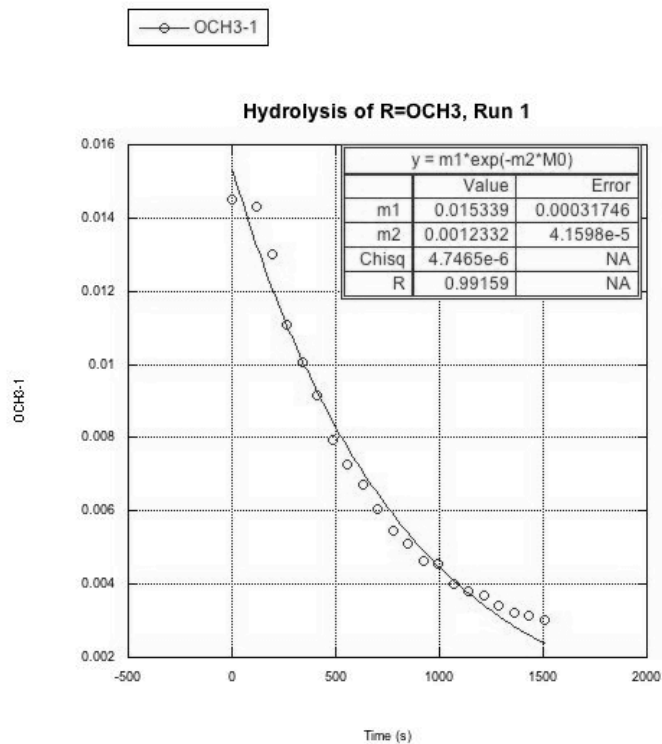
$$k_{\text{CH3-3}} = 1.048 \times 10^{-3} \text{ s}^{-1}$$

Rate Constant Afforded from the Hydrolysis of 3.112B, Replicate #1



An initial stock was prepared using **3.112** (0.025 g, 6.122×10^{-5} mol) and PhSH (0.011 mL, 1.071×10^{-4} mol) in CD_3CN (3.000 mL) under N_2 . After bubbling the solution with N_2 for 10 minutes, anhydrous NEt_3 (0.021 mL, 1.507×10^{-4} mol) and hexafluorobenzene stock (0.072 mL, containing 3.114×10^{-5} mol of hexafluorobenzene) were added, resulting in 1.972×10^{-2} M concentration of **3.112B**. An aliquot of the reaction mixture (0.500 mL, containing 9.861×10^{-6} mol of **3.112B**) was transferred to a dry and N_2 -flushed NMR tube equipped with septum cap once *N*-deprotection was complete. Hydrolysis was initiated by the injection of H_2O (0.180 mL, 1013 equiv.)

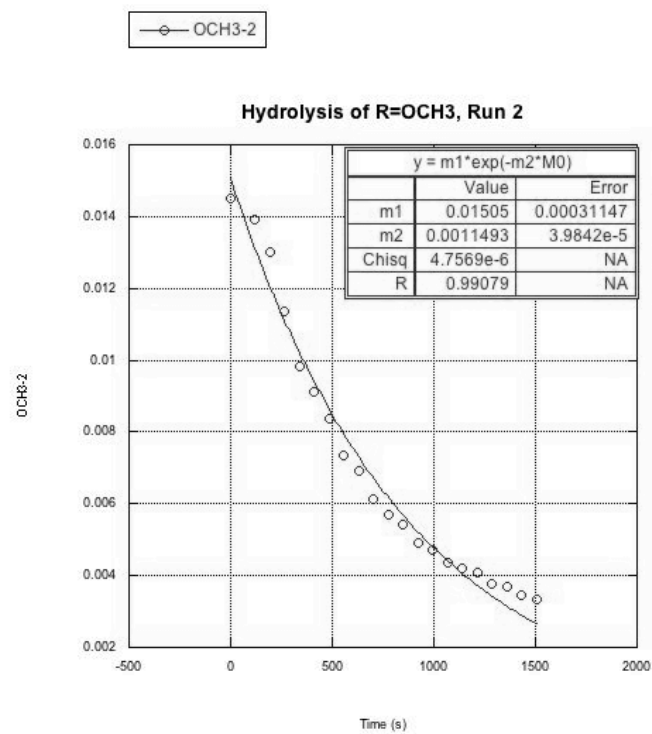
through the septum cap, resulting in a final concentration of 1.450×10^{-2} M of **3.112B** in the monitored reaction. The reaction was monitored by use of ^{19}F NMR spectroscopy for 25 minutes and 7 seconds.



$$k_{\text{OCH}_3-1} = 1.233 \times 10^{-3} \text{ s}^{-1}$$

Rate Constant Afforded from the Hydrolysis of 3.112B, Replicate #2

Followed procedure for replicate # 1. The reaction was monitored until it reached equilibrium (25 minutes and 7 seconds).



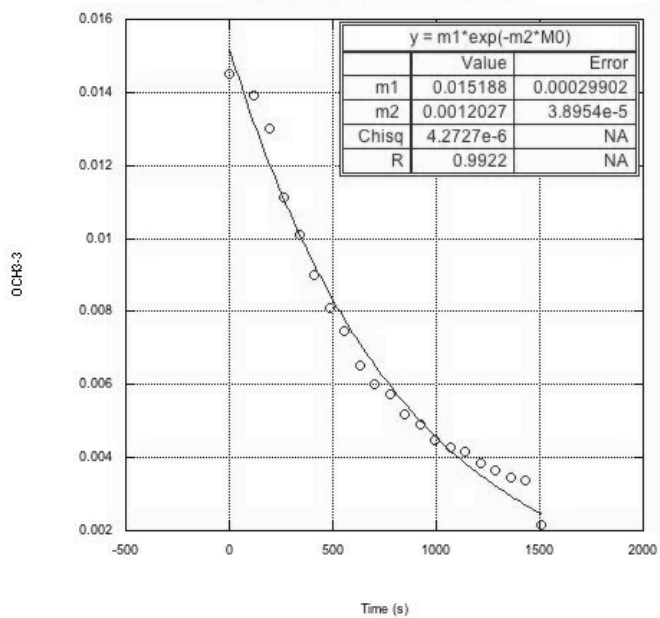
$$k_{\text{OCH}_3-2} = 1.149 \times 10^{-3} \text{ s}^{-1}$$

Rate Constant Afforded from the Hydrolysis of 3.112B, Replicate #3

Followed procedure for replicate # 1. The reaction was monitored until it reached equilibrium (25 minutes and 7 seconds).

—○— OCH3-3

Hydrolysis of R=OCH3, Run 3



$$k_{\text{OCH}_3-3} = 1.203 \times 10^{-3} \text{ s}^{-1}$$

3.5

References for Chapter 3

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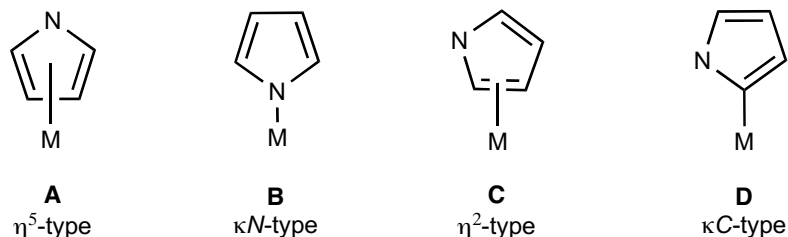
Chapter 4 Ligand Design Towards Conjugated Bis(Pyrrolyl Ruthenium) Complex Salts

4.1 Background

4.1.1 The Pyrrolide Ligand

Pyrrolide ligands are heteroaromatic analogues of the cyclopentadienyl ligand. Although it was previously believed that pyrrolide-metal complexes were unstable,¹ the study of pyrrolide ligand has recently been receiving more attention since their discovery in the early 1960s.^{2,3} Like their homoaromatic counterparts, pyrrolide ligands can display more than one binding mode. The binding modes most commonly displayed by pyrrolide ligands bound to metals are the η^5 -type coordination mode (i.e., azaferrocenes, **A**, Figure 4 - 1),⁴⁻⁷ and the κN -type mode (**B**).^{6,8-19} However, η^2 -type coordination (**C**)²⁰ and κC -type coordination (**D**)^{21,22} have also been reported.

Figure 4 - 1: Binding Modes of Pyrrolide Ligands

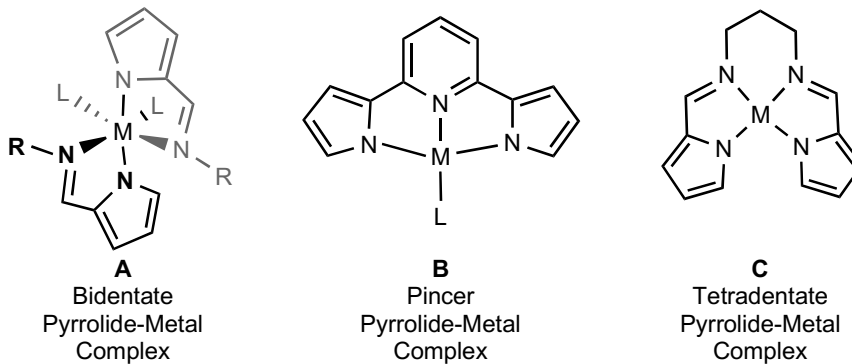


Pyrrolide ligands exhibiting κN -type bonding are known to display monodentate^{6,11,15-17} or polydentate^{8-10,12,13,18,19} binding to metal centres, depending on the substitution of the ligand prior to complexation. Schrock has recently incorporated κN -type monodentate ancillary pyrrolide ligands into molybdenum and tungsten complexes,^{6,11,14-17} and the majority these complexes have displayed good catalytic activity in metathesis reactions. Monodentate κN -type binding has also been reported in a Ti(III)-pyrrolide complex.²³

Appending electron-donating groups to the pyrrolyl moiety can result in polydentate binding to the metal centre. Formyl-pyrrolide^{13,24-31} and pyrrolide-imine (**A**, Figure 4 - 2)^{18,19} ligands are both known to participate in metal binding as bidentate ligands. In addition, there are also examples of pyrrolide moieties as part of a pincer (or tridentate) ligand (see **B** in Figure 4 - 2),^{8,9,12} and as part of a tetradentate ligand (**C**).¹⁰

Metal-chelates of porphyrins and linear tetrapyrroles can also be categorized as tetradentate ligand-metal complexes.

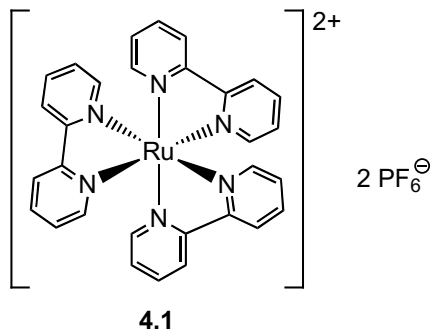
Figure 4 - 2: General Skeletons of Representative Ligands



4.1.2 Heteroleptic Pyrrolyl Ruthenium Complexes

Ruthenium complexes containing bipyridyl (bipy) ligands (e.g., **4.1**, Figure 4 - 3) have received additional attention in more recent years, with an average of about 160 publications a year reported since 2010 (according to a search for “Ruthenium Bipyridyl Complexes” in Scifinder). Some of this growing popularity can be attributed to their chemiluminescence properties, which can be achieved in an aqueous medium and do not require deoxygenation of the solvent medium.³² These attributes have allowed bipy-containing ruthenium complexes to be employed as sensors in bioassays (e.g, immunoassays and DNA analysis).³³

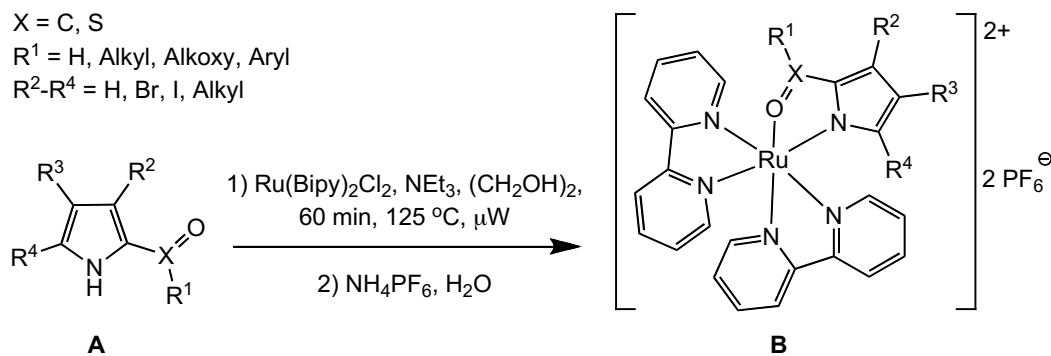
Figure 4 - 3: Tris(2,2'-bipyridyl- κ N, κ N) Ruthenium(II) Di(hexafluorophosphate)



The Thompson group has previously studied air- and moisture-stable Ru(II) complexes, with emphasis on the incorporation of a κ^2 -*N,O*-bound pyrrolide ligand

(Scheme 4 - 1).¹³ The syntheses of these Ru(II) salts are generally high yielding,¹³ and their anions can undergo salt-exchange (PF_6^- to Cl^-) to allow for greater water-solubility.³⁴ These complexes can be synthesized using a microwave-assisted procedure, which employs pyrroles that are substituted in the α -position with an oxygen-containing moiety that is available for binding (Scheme 4 - 1).¹³

Scheme 4 - 1: Synthesis of κ^2 -*N,O*-Pyrrolyl Ru(II) Complexes



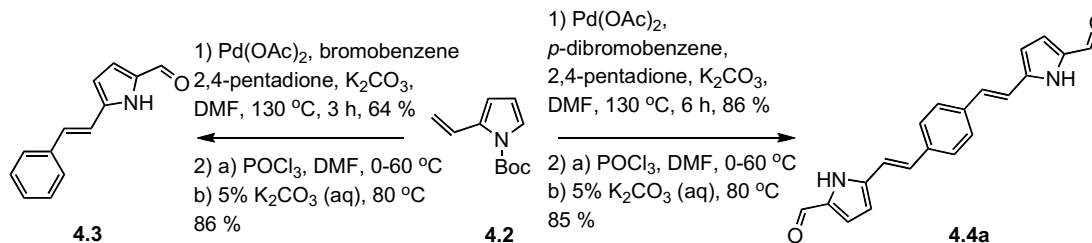
In addition, the complexes depicted in Scheme 4 - 1 display a broad absorbance range from ~250-570 nm, resulting from overlapping absorptions arising from bipy-localized transitions ($\pi \rightarrow \pi^*$, <300 nm), lower energy transfers ($\pi \rightarrow \pi^*$, 300-400 nm), and metal-to-ligand charge transfer transitions (MLCT, $d\pi(\text{Ru}) \rightarrow \pi^*(\text{Ligand})$, 400-570 nm).¹³ These transitions are characteristic to bipy-containing ruthenium complexes.^{35,36} However, what is unique to the pyrrolide/bipy ruthenium complexes is the very broad MLCT absorption range, which is caused by the overlapping absorptions from metal-to-bipy and metal-to-pyrrolide transitions.²¹

4.1.3 Heteroleptic Bis(Pyrrolyl Ruthenium) Complexes

Building on the study described in section 4.1.2, the Thompson group desired to explore the effects of varying the level of conjugation present in the pyrrolide ligand system. The study began with the synthesis of a mono-pyrrolic ligand (**4.3**, Scheme 4 - 2) from vinyl-pyrrole **4.2** as a means to optimize the synthetic protocol.³⁴ The dipyrrolic ligand (**4.4a**, Scheme 4 - 2) was also prepared in a similar manner, by use of 2 equiv. of vinyl-pyrrole

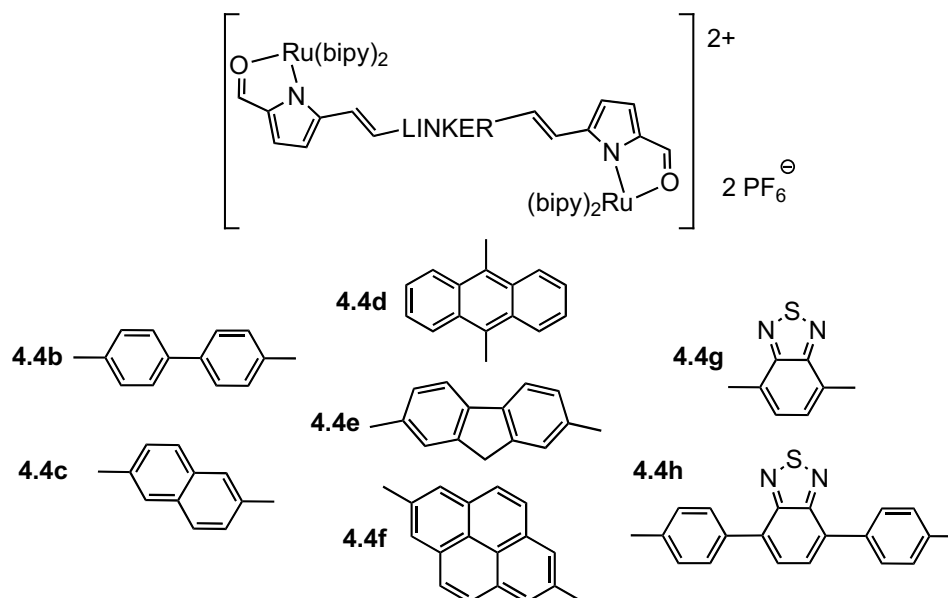
4.2 and an extended reaction time (6 hours).³⁴ Once synthesized, the ligands can be bound to Ru(II) as shown in Scheme 4 - 1.

Scheme 4 - 2: Synthesis of Mono and Bis(Pyrrrolyl) Ligands



Upon preparation of the mono- and bis(ruthenium) complexes, it was found that the dimer displayed a significantly more intense MLTC absorbance.³⁴ In order to probe this further, the linker incorporated into the symmetric di(formyl-pyrrolyl) ligand was varied.³⁴ Of the variants explored, linkers **4.4e** (pyrene, Figure 4 - 4) and **4.4f** (benzothiadiazole) displayed continuous absorbance over the broadest wavelength ranges (~250-650 nm).

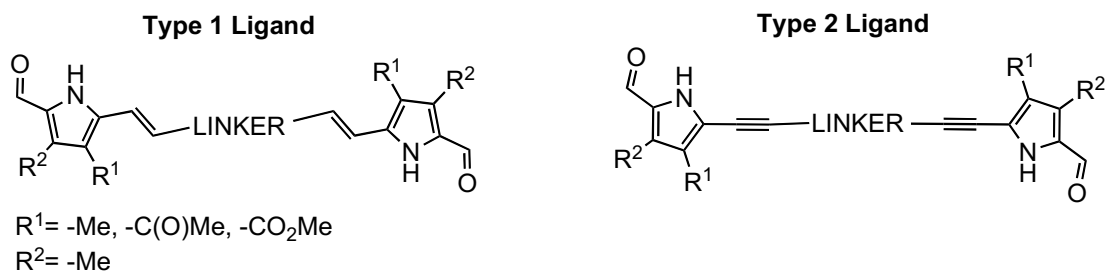
Figure 4 - 4: Conjugated, Symmetric Bis(Ruthenium) Hexafluorophosphate Salts



4.1.4 Strategies For the Preparation of Bis(Pyrrolyl) Ligands

The initial goal of the project described herein was to broaden the known array of bis(ruthenium-pyrrolyl) complexes using two proposed ligand frameworks (Figure 4 - 5): Type 1 ligands would incorporate substitution on the β -positions of the pyrrolyl moiety, while Type 2 ligands would incorporate the same β -substitution, and replace the alkene moieties with alkyne moieties. The linkers used for these ligands would mirror those depicted in section 4.1.3.

Figure 4 - 5: Proposed Type 1 and Type 2 Ligands for Use in Bis(Pyrrolyl Ruthenium) Complexes



A secondary goal of this study was to explore the effects of ligand substitution (i.e., $R^1 = R^2 = \text{Me}$ vs. $R^1 = R^2 = \text{H}$) on the photophysical properties of Type 1 and 2 ligands and their corresponding bis(ruthenium) complexes. The introduction of cross-conjugation *via* R^1 was also to be explored ($R^1 = \text{C}(\text{O})\text{Me}, \text{CO}_2\text{Me}$; $R^2 = \text{Me}$).

4.1.5 Project Direction

The initial goal of the work presented within this chapter was to synthesize a series of symmetric bis(ruthenium) complexes as an extension to a study previously initiated in the Thompson group. However, developing a synthetic protocol for the synthesis of Type 1 ligands proved to be problematic, and the preparation of Type 2 ligands were pursued instead. A protocol for the synthesis of a Type 2 monomer ligand was achieved, but the methodology was not transferable to the preparation of a dimer ligand, and thus had to be modified. Described herein are the challenges and successes relating to the development of a viable synthetic methodology.

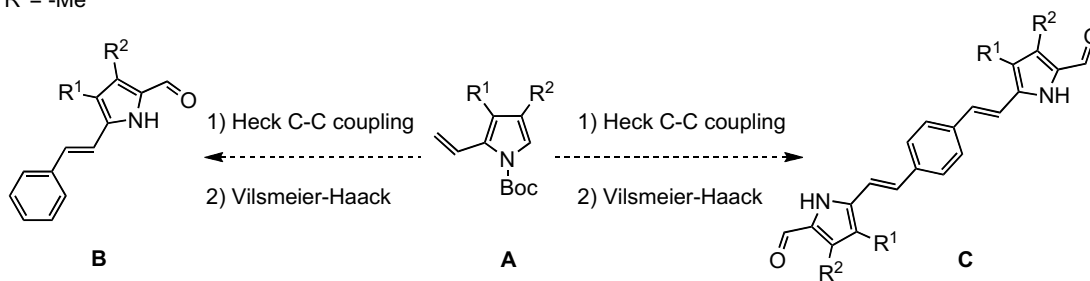
4.2 Results and Discussion

4.2.1 Attempted Synthesis of Type 1 Bis(Pyrrolyl) Ligand

Previously, *N*-Boc-2-vinyl pyrrole (**4.2**) was employed in a two-step procedure involving a modified Heck cross-coupling³⁷ and Vilsmeier-Haack reactions³⁸ to form monomer (i.e., **4.3**) and dimer (i.e., **4.4a**) Type 1 ligands depicted in Scheme 4 - 2. Ideally, this strategy would also be transferable to the β -substituted series as well (Scheme 4 - 3), forming monomer **B** and dimer **C**, beginning from *N*-Boc- α -vinyl pyrrole **A**.

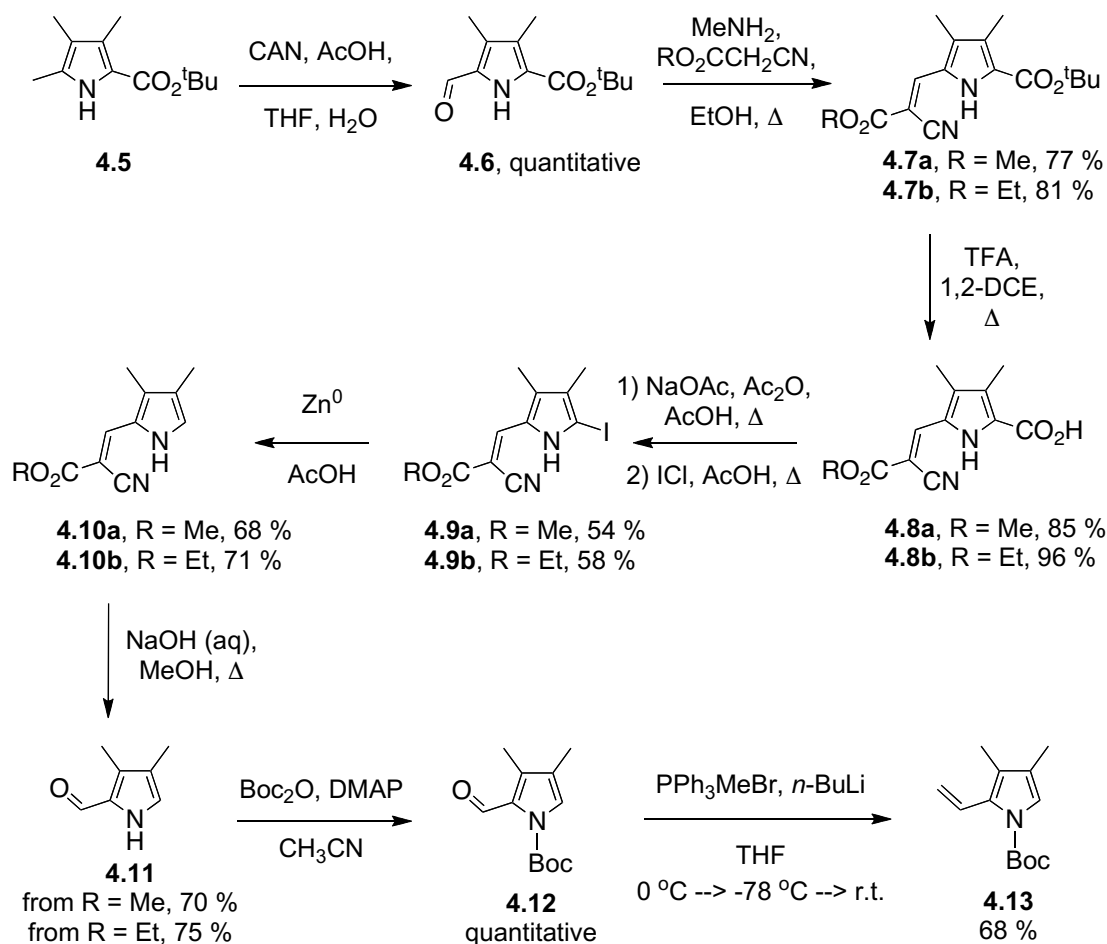
Scheme 4 - 3: Proposed Synthesis of β -Substituted Type 1 Dimer Ligands

R¹= -Me, -C(O)Me, -CO₂Me
R²= -Me



Pyrrole **4.2** (previous work, Scheme 4 - 2; or **A** in Scheme 4 - 3, R¹ = R² = H) was accessible from a 2-step procedure beginning with 2-formyl pyrrole.³⁹ In contrast, the formation of the β -methyl substituted analogue (studied in this thesis, **A**, Scheme 4 - 3, R¹ = R² = Me) was much more laborious (Scheme 4 - 4).

Scheme 4 - 4: Synthesis of *N*-Boc Protected 2-Vinyl Pyrrole 4.13



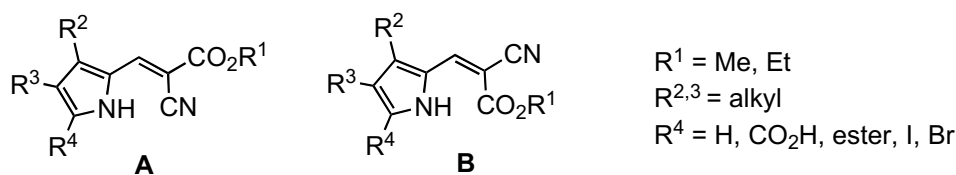
By use of a cyanovinyl protecting group,^{40,41} the desired α -formyl pyrrole **4.13** was synthesized in 9 steps from pyrrole **4.5** (Scheme 4 - 4). The use of either the methyl ester or ethyl ester of the cyanovinyl protecting group was found to provide the desired pyrrole, but some steps worked better with one protecting group over the other, as demonstrated by the yields.

The sequence began by oxidation of the α -methyl group of pyrrole **4.5** by use of cerium ammonium nitrate to form formyl pyrrole **4.6** (Scheme 4 - 4).⁴² This oxidation was also performed using $\text{Pb}(\text{OAc})_4$ in acetic acid,⁴¹ albeit in a more modest yield (63 %). The formyl group of **4.6** was protected as the cyanovinyl methyl ester **4.7a** or the cyanovinyl ethyl ester **4.7b**, by a Knoevenagel condensation with the respective cyanoacetate. The yields were comparable when either protecting group was employed (**4.7a** = 77 %; **4.7b** = 81 %).

Pyrroles **4.7a** and **4.7b** were deprotected to α -acids, and subsequently submitted to decarboxylative iodination to form their corresponding α -iodo pyrrole, **4.9a** and **4.9b**. The decarboxylative iodination reaction afforded comparable yields for both substrates (**4.9a** = 54 %; **4.9b** = 58 %). However, pyrrole **4.7b** was found to afford a higher yield of **4.8b** from the *t*-butyl deprotection reaction (96 %, vs. **4.8a** = 85 %) due to greater solubility of both the starting pyrrole **4.7b** and the product **4.8b** in the reaction solvent. Prolonged reaction times (100 min instead of 80 min) and modest dilution of the reaction mixture afforded a decrease in yield (70 % of **4.8a**). No further optimization was pursued.

The reduction of pyrroles **4.9a** and **4.9b**, and subsequent deprotection to form pyrrole **4.11**, were comparable with either protecting group. As a final note on the reactivity of cyanovinyl protected pyrroles, both *E*- (**A**, Scheme 4 - 5) and *Z*-isomers (**B**) of the protecting group were found to form upon formyl group protection (i.e., to form **4.7a** and **4.7b**),^{41,43,44} with further isomerization noted to occur in acidic reactions.⁴⁴ The minor isomer was noted by the appearance of an additional NH signal and cyanoacrylate vinyl signal in the ¹H NMR spectrum downfield from the major isomer.⁴⁴ This minor isomer was found to typically comprise < 20 % of the total isolated material and can be removed by fractional recrystallization, if necessary. The major isomer was proven to be the *E*-isomer by use of the crystal structures (**A**, Scheme 4 - 5).^{40,44,45} This is unsurprising as this isomer is less sterically hindered than the *Z*-isomer. As the ultimate goal was to deprotect the masked formyl group to form pyrrole **4.11**, both isomers were carried forward through the reaction sequence featured in Scheme 4 - 4, and the yields reported are of the isomeric mixture.

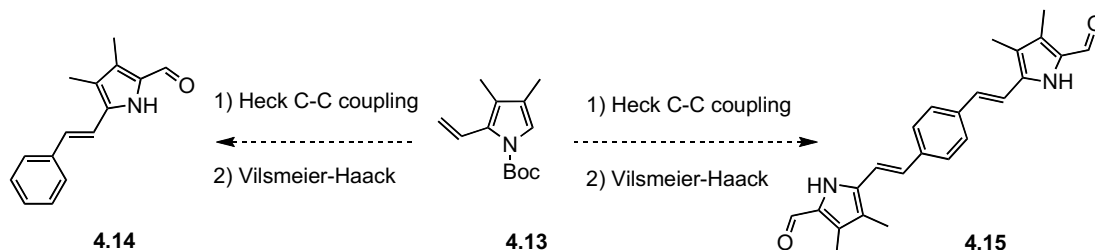
Scheme 4 - 5: *E*- and *Z*-Isomers of Cyanovinyl Protected Pyrroles



The *N*-Boc protection of pyrrole **4.11** to form pyrrole **4.12** was quantitative. Finally, applying the Wittig reaction³⁹ to pyrrole **4.12** afforded target pyrrole **4.13** in a 68 % yield. This yield was slightly lower, but comparable, to the synthesis of pyrrole **4.2**

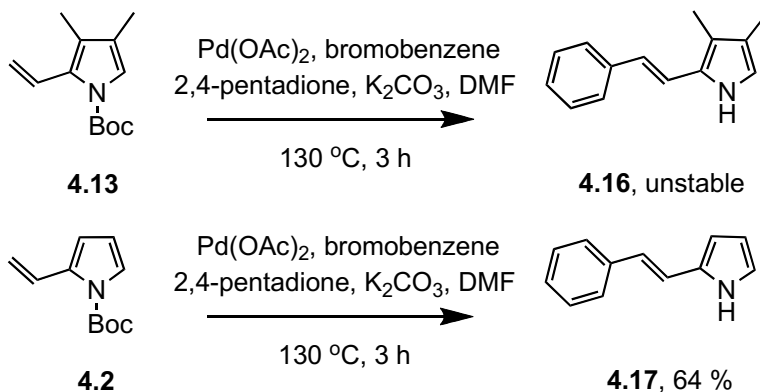
(80 % for the Wittig reaction). With target pyrrole **4.13** in hand, a protocol for the synthesis of the monomer ligand **4.14** (Scheme 4 - 6) was targeted. If successful, this protocol was to be used for the proposed synthesis of the dimer ligand **4.15**.

Scheme 4 - 6: Proposed Synthesis of 4.14 and 4.15 from *N*-Boc Protected 4.13



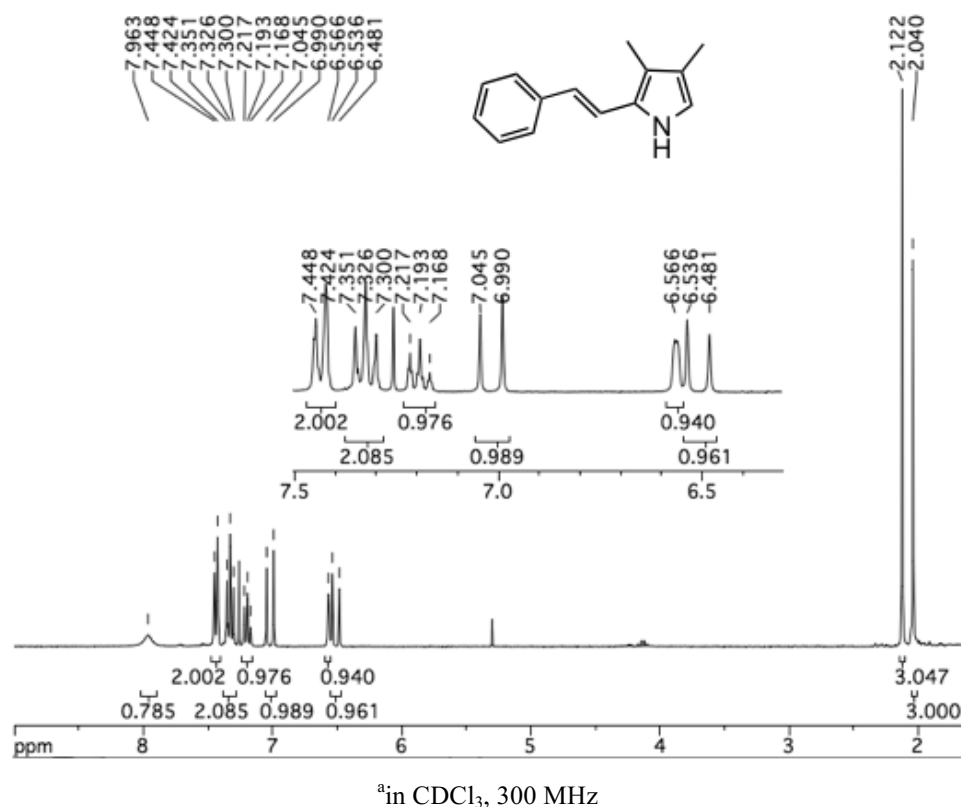
The attempted synthesis of the Heck coupling product **4.16** (Scheme 4 - 7) was performed using the same reaction conditions previously employed when applying pyrrole **4.2** as a Heck substrate.³⁷ *N*-Boc deprotection is known to occur *in situ* during the course of the Heck coupling reaction, forming **4.17** (Scheme 4 - 7).³⁴ Fortunately, this did not cause any difficulties for the isolation of **4.17**, as the product was stable to the employed reaction and purification conditions (which featured an extraction, concentration *in vacuo*, and purification using silica column chromatography).

Scheme 4 - 7: Synthesis of 4.16 and 4.17



In contrast, the *N*-deprotected product **4.16** appears to be unstable. Although its formation was indicated by ¹H NMR spectroscopy following purification by column chromatography (Figure 4 - 6), it had already begun to decompose over a short timespan and did not survive repurification.

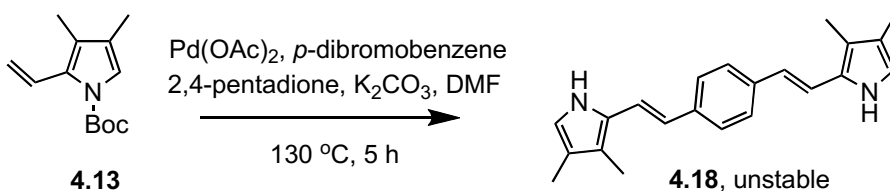
Figure 4 - 6: ^1H NMR Spectrum of Pyrrole 4.16^a



Efforts were made to ensure that the product remained *N*-Boc protected by reducing the reaction time to 2 hours. The solid phase for column chromatography purification was also switched to basic alumina (Brock type III) in attempt to prevent *N*-deprotection during purification. Unfortunately, even when both techniques were employed in succession, the deprotected product was still isolated (10 %), and quickly decomposed. The reaction was also scaled up, once again taking the previously described precautions, but decomposition was still observed.

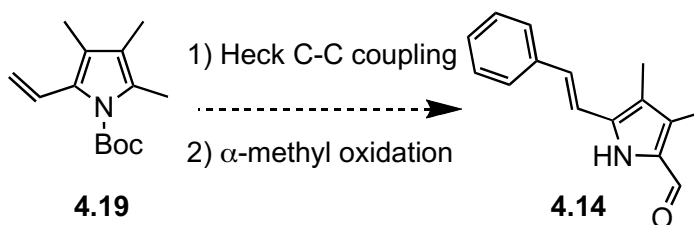
The synthesis of the dimer ligand **4.18** was attempted regardless, under the hypothesis that extension of the conjugation system might promote stability of the *N*-deprotected product (Scheme 4 - 8). Although TLC analysis initially indicated product formation, decomposition was observed once again.

Scheme 4 - 8: Synthesis of 4.18



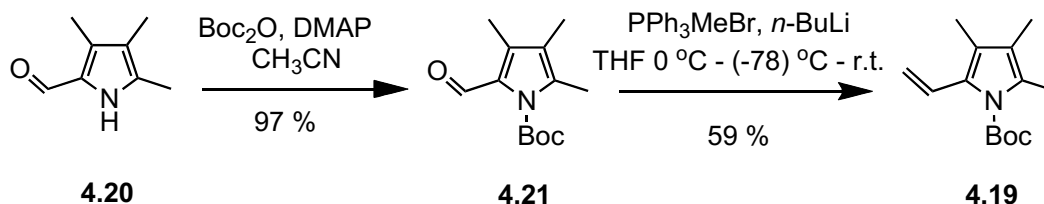
Instead, a fully-substituted pyrrole was employed (4.19, Scheme 4 - 9). The rationale behind choosing a fully-substituted pyrrole was to mask the α -position, thus reducing alternative decomposition pathways by means of polymerization.⁴⁶ The use of this pyrrole would require a different synthetic protocol for the target monomer, as depicted in Scheme 4 - 9.

Scheme 4 - 9: Alternate Proposed Synthesis of 4.14



Fully-substituted pyrrole 4.19 was prepared from 4.20 (Scheme 4 - 10), using a similar strategy to that used for the preparation of 4.13. The *N*-Boc protection reaction was found to be straightforward and high yielding (97 %). However, the order of addition was found to be important for the Wittig reaction when preparing the vinyl pyrrole 4.19 from *N*-Boc pyrrole 4.21, which was not observed in the preparation of 4.13, or in 4.2. Pyrrole 4.20 was recovered (40 %) if the pyrrole was added drop-wise to the Wittig reagent. In contrast, pyrrole 4.19 was afforded in 59 % yield when the order of addition was reversed.

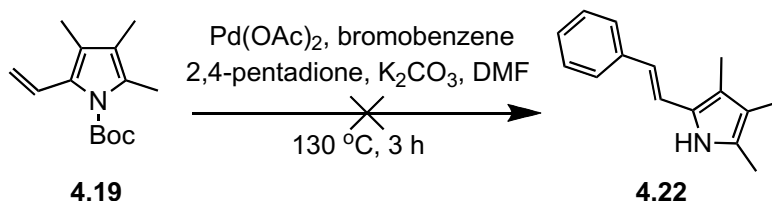
Scheme 4 - 10: Synthesis of Fully-Substituted Vinyl-Pyrrole 4.19



Indeed, pyrrole **4.21** does appear to be sensitive to strong bases. When exposing pyrrole **4.21** to *n*-BuLi at -78 °C, significant decomposition was observed *via* TLC analysis, and only 45 % of the starting material was recovered. On the basis of this result, it was thought that the α -methyl group underwent deprotonation in the presence of excess base, offering an alternative pathway for the Wittig reagent.

Pyrrole **4.19** was submitted to the previously utilized Heck cross-coupling conditions in attempt to synthesize pyrrole **4.22** (Scheme 4 - 11). The reaction was halted after 3 hours, as significant amounts of decomposition product had steadily formed over the course of the reaction (as indicated by use of TLC analysis). However, a partial recovery of *N*-protected starting material was noted (52 %).

Scheme 4 - 11: Attempted Synthesis of 4.22

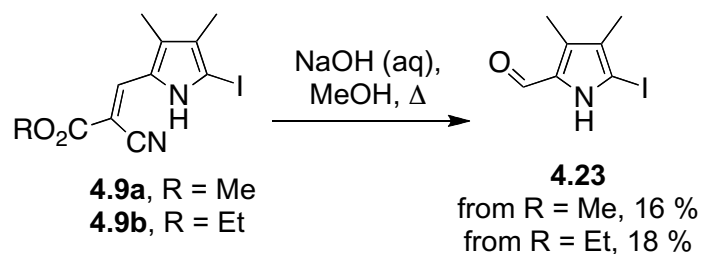


Given that the pursuit of synthesizing Type 1 ligands had not resulted in any successes, an alternative strategy was pursued.

4.2.2 Attempted Synthesis of Type 2 Bis(Pyrrolyl) Ligands *via* the Use of Unprotected Pyrrole

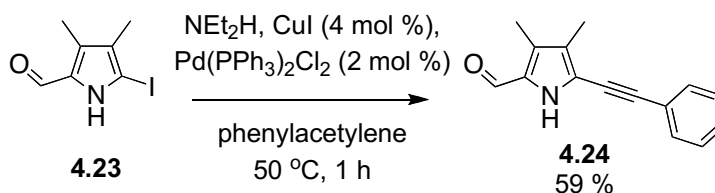
The fundamental approach to preparing Type 2 ligands, which bear alkyne moieties, is very similar to the preparation that was used for Type 1 ligands. Firstly, an appropriate pyrrole cross-coupling partner must be prepared. Given that the Sonogashira reaction is utilized here, the pyrrole must bear an iodo or alkynyl group. Using the sequence of reactions depicted in Scheme 4 - 4, pyrroles **4.9a** and **4.9b** were found to be suitable for this purpose. The cyanovinyl pyrroles were deprotected, as before, using methanolic NaOH and heating at reflux temperature. This deprotection afforded the iodopyrrole **4.23**, albeit in a much lower yield than that observed when deprotecting **4.10a** and **4.10b**.

Scheme 4 - 12: Synthesis of 4.23

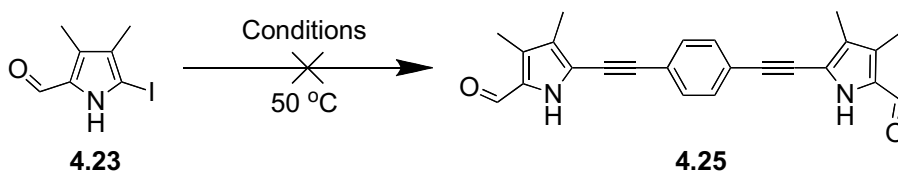


Iodopyrrole **4.23** was then used to prepare the monomer (**4.24**) using a modified procedure,⁴⁷ which was isolated in a 59 % yield (Scheme 4 - 13). The synthesis of the dimer was then attempted following a similar protocol without additional optimization.

Scheme 4 - 13: Synthesis of Monomer Ligand 4.24



Using 1 equiv. of *p*-diethynylbenzene, and 2 equiv. of the pyrrole, the modified procedure was found to be unsuccessful in producing dimer **4.25** (Table 4 - 1, entry 1). Rather than forming the expected product, as seen in the synthesis of monomer **4.24**, a slow evolution of baseline material was noted *via* TLC analysis. Furthermore, analysis of the crude reaction mixture by use of ¹H NMR spectroscopy showed that the signal resulting from the aldehyde was missing from the spectrum. As a result, additional reaction conditions were explored in attempt to synthesize the dimer (Table 4 - 1).

Table 4 - 1: Screening for a Protocol to Produce Dimer Ligand 4.25

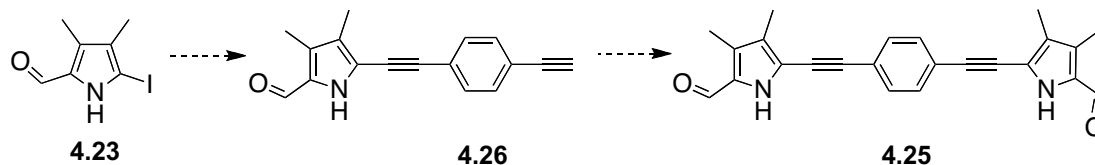
Entry	Solvents (M)	Time (days)	Catalyst	CuI	Observation
1	4:1 NEt ₂ H/1,2-DCE (0.08) ^a	3	Pd(Ph ₃) ₂ Cl ₂ (2 mol %)	4 mol %	No Product ^c
2	1:1 NEt ₂ H/THF (0.1) ^a	3	Pd(Ph ₃) ₂ Cl ₂ (2 mol %)	4 mol %	No Product ^c
3	5:2 NEt ₃ /THF (0.06) ^b	1	Pd(Ph ₃) ₄ (10 mol %)	4 mol %	Insoluble precipitate
4	5:2 NEt ₃ /THF (0.006) ^b	1	Pd(Ph ₃) ₄ (10 mol %)	4 mol %	No Product ^{c, d}

^a1 equiv. *p*-diethynylbenzene, 2 equiv. pyrrole **4.23**; ^b1 equiv. *p*-diethynylbenzene, 3 equiv. pyrrole **4.23**; ^cformyl group not present (¹H NMR spectroscopy); ^dsparingly soluble in DMSO

The mixed solvent system was modified in order to concentrate the reaction mixture further (Table 4 - 1, entry 2). Unfortunately, this resulted in the same evolution of baseline material noted previously, with loss of the aldehyde signal observed in the ¹H NMR spectrum. Instead, a different procedure for the Sonogashira cross-coupling was employed,⁴⁸ using a higher loading of both catalyst and copper iodide at a more dilute concentration (Table 4 - 1, entry 3). This reaction resulted in an insoluble precipitate that could not be characterized, as well as recovered starting material (**4.23**, 12 %). The procedure was modified by dilution, in which the reaction concentration was decreased ten-fold (Table 4 - 1, entry 4). This reaction produced a solid that was sparingly soluble in DMSO. The precipitate was filtered (washing with THF), and the resulting brown solid was analyzed by use of ¹H NMR spectroscopy without further purification. Again, the disappearance of the aldehyde signal was noted, suggesting that the additional reactivity of this functional group was causing difficulty in the synthesis and isolation of the desired

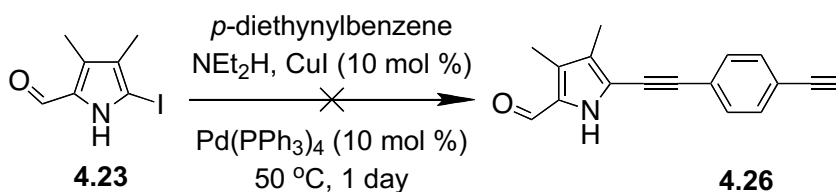
product. Following this result, the synthesis of the dimer was approached using a stepwise protocol (Scheme 4 - 14).

Scheme 4 - 14: A Stepwise Strategy Towards 4.25



The Sonogashira reaction was repeated using equimolar amounts of *p*-diethynylbenzene and pyrrole **4.23** (Scheme 4 - 15), with the goal of isolating the mono-pyrrole **4.26** and then resubmitting the product to the form the dimer (**4.25**).⁴⁸ After 24 hours, the crude reaction mixture displayed complete consumption of *p*-diethynylbenzene by use of TLC analysis. Unfortunately, the only material afforded from purification using column chromatography was the starting pyrrole (**4.23**, 80 %).

Scheme 4 - 15: Attempted Synthesis of 4.26



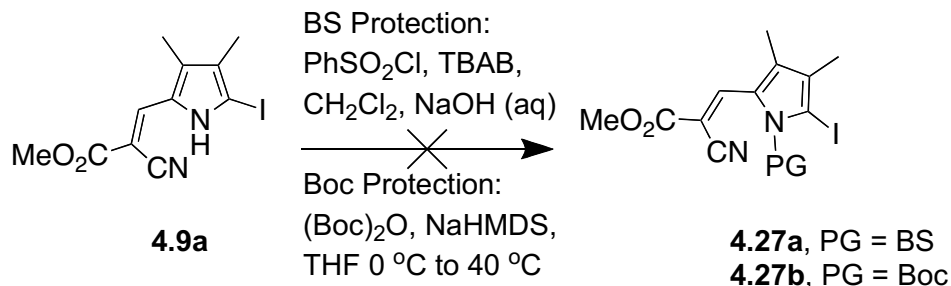
There appears to be multiple reactions occurring under the conditions described above. Although the desired dimer ligand **4.25** may have been forming during the course of this study, the species could have been transitory under the conditions employed.

4.2.3 Attempted Synthesis of Type 2 Bis(Pyrrolyl) Ligand *via* Protected Pyrrole

It was then decided that a protection strategy should be considered to prevent undesired reactivity. In this case, the functionalities on iodopyrrole **4.23** that could be protected are the nitrogen atom and/or the formyl group. Formyl group protection has already been incorporated onto pyrrole **4.9a**, which was found to be suitable for this purpose. In

addition, the introduction of an *N*-protecting group was also attempted using pyrrole **4.9a** (Scheme 4 - 16).

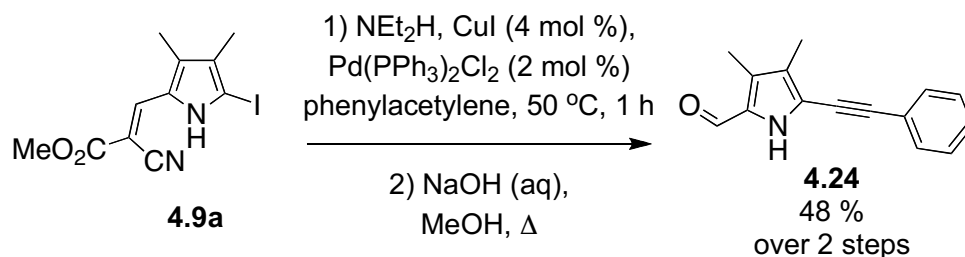
Scheme 4 - 16: Attempted *N*-Protection of 4.9a



Attempting to *N*-protect pyrrole **4.9a** with either a benzenesulfonyl group (BS) or Boc group was found to be unsuccessful, with a return of starting material noted in each case. The attempted *N*-benzenesulfonyl protection reaction afforded a larger return of starting material (91 %), but this was unsurprising due to the milder reaction conditions employed for this protection in contrast to the *N*-Boc protection conditions (40 % recovery of **4.9a**).

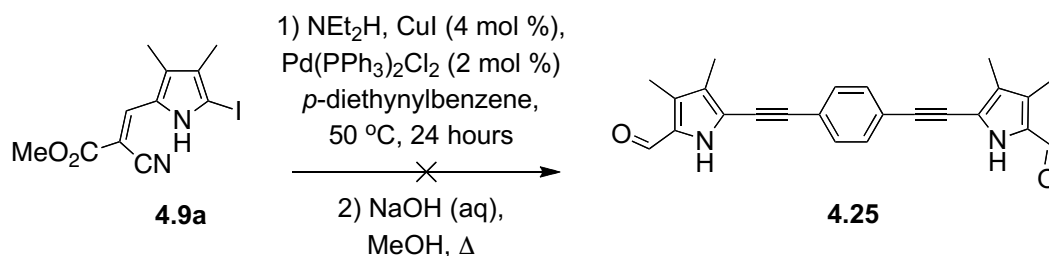
N-substitution of a pyrrole can be very mild (catalytic DMAP,⁴⁹ or NaOH⁵⁰ as base), or can employ a strong base (e.g. *n*BuLi,^{51,52} or NaH^{53,54}) and use of low temperatures (0 to -78 °C). In addition, solvolysis of the *N*-protecting group during the protection reaction was a possible side-reaction.⁵⁵ *N*-substitution sometimes requires significant optimization.⁴⁶ In the interest of time, the *N*-protection strategy was not pursued any further, and pyrrole **4.9a** was chosen for use in the Sonogashira cross-coupling reaction (Scheme 4 - 17).

Scheme 4 - 17: Alternative Synthesis of 4.24



The conditions for achieving the monomer from pyrrole **4.23** were repeated, this time using pyrrole **4.9a** as a cross-coupling substrate. After filtration through Celite®, the reaction mixture was carried forward for deprotection of the formyl group (Scheme 4 - 17, part 2). The monomer was afforded in 48 % yield over two steps. Once again, the reaction conditions were applied with intention of forming the dimer ligand **4.25**, by use of 2 equiv. of pyrrole **4.9a** and 1 equiv. of *p*-diethynylbenzene.

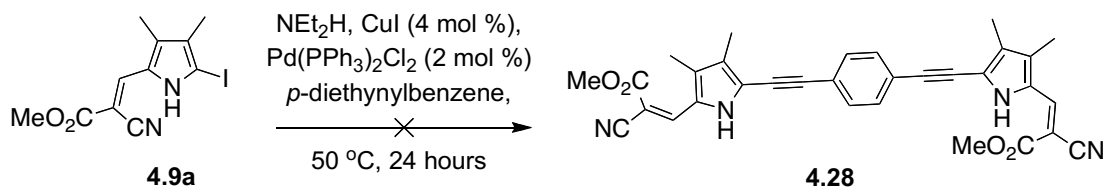
Scheme 4 - 18: Attempted Synthesis of 4.25 via 4.9a



TLC analysis of the crude reaction mixture showed complete consumption of *p*-diethynylbenzene after 24 hours and some starting material remaining. After filtration through Celite®, the reaction mixture was carried forward for the removal of the cyanovinyl group. The reaction afforded only a return of *N*-deprotected starting material (**4.23**, 10 %).

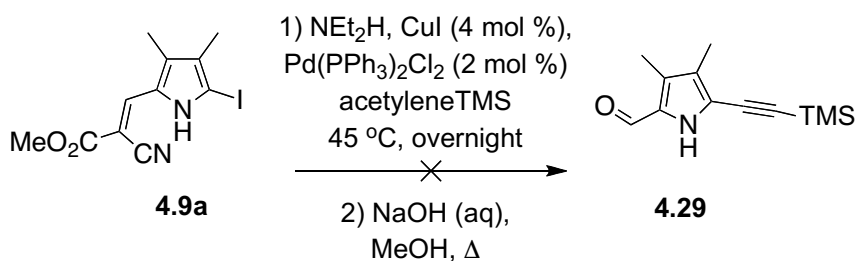
The reaction was repeated, monitored until the complete consumption of *p*-diethynylbenzene, and then purified without deprotection of the cyanovinyl groups. Unfortunately, the two main yellow spots seen by use of TLC analysis were each composed of multiple co-eluting compounds. Due to the complexity of the reaction mixture, and the lack of success in the deprotection of the cyanovinyl group, this methodology was not pursued any further.

Scheme 4 - 19: Attempted Synthesis of 4.28



A final attempt was made to prepare a suitable pyrrole for cross-coupling by appending the alkyne moiety to the pyrrole. Following a known procedure,⁴⁸ the synthesis of the alkynyl-appended pyrrole was attempted from the cyanovinyl protected pyrrole **4.9a**. Significant decomposition product was observed by use of TLC analysis. After removing the catalyst and decomposition products *via* filtration through alumina (Brock Type II basic), the remaining crude reaction mixture (1 mg after concentration *in vacuo*) appeared to be a mixture of TMS-deprotected product and starting material (¹H NMR spectroscopy the crude reaction mixture).

Scheme 4 - 20: Attempted Synthesis of 4.29

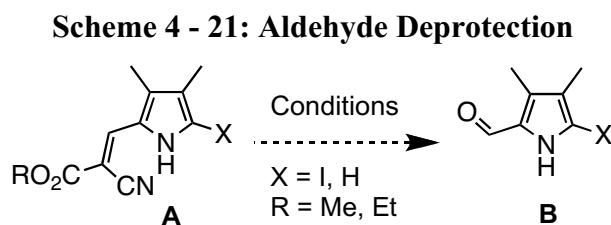


4.3 Conclusions and Future Directions

The initial goal of this project was to expand upon the known series of bis(ruthenium-pyrrolyl) complexes. Although ligand synthesis proved to be more challenging than anticipated, there were still some successful outcomes and knowledge gained. Notably, substitution in the β -position of the pyrrolic skeleton decreases the stability of the molecule and ease of isolation of Type 1 ligands. Dimers of the β -unsubstituted Type 1 ligands described in section 4.1.3 were isolated *via* filtration, and were found to be stable to air and moisture, regardless of the presence of an *N*-Boc protecting group. Substitution may still be tolerated at the β -positions of the pyrrole in Type 1 ligands, but the incorporation of an additional electron-withdrawing group on the pyrrolic skeleton could be necessary to improve the stability of the cross-coupling product.

This project was still in its preliminary stages, and there are many future directions it could take. It is possible that both cross-coupling reactions presented in this chapter (Heck and Sonogashira) could have benefited from optimization of conditions, allowing for the detection and/or isolation of the corresponding target dimers, 4.15 and 4.25. To begin, all experiments should be repeated in the glove box to ensure rigorously anhydrous conditions.⁵⁶ Milder cross-coupling conditions should be sought out to combat the apparent instability seen under the reaction conditions employed.

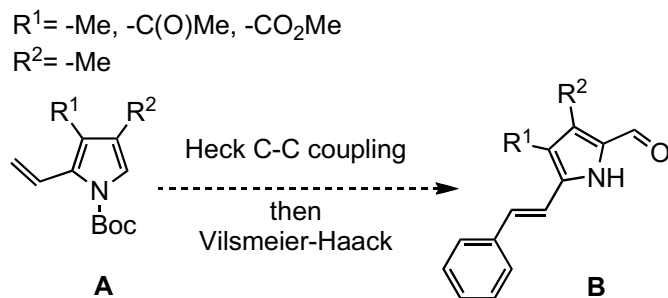
In addition, efforts should be made to optimize the deprotection of the cyanovinyl group (Scheme 4 - 21). This step of the synthetic sequence was low yielding and this resulted in a loss of material.



Finally, should the synthesis of the model Type 1 ligand still prove difficult, it is suggested that the product be submitted to a subsequent Vilsmeier-Haack reaction immediately after removal of the catalyst by filtering through Celite®. Perhaps the

incorporation of a formyl group (**B**, Scheme 4 - 22), as a result of the Vilsmeier-Haack reaction, will offer stabilizing properties to the molecule as a whole.

Scheme 4 - 22: Towards Type 1 Monomer Ligands



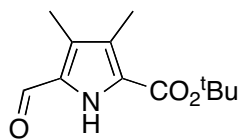
4.4 Experimental Procedures and Data for Chapter 4

4.4.1 General Considerations

NMR spectra were recorded at the Atlantic Region Magnetic Resonance Centre (ARMRC). All ^1H and $^{13}\text{C}\{^1\text{H}\}$ NMR spectra were obtained using a 500 MHz NMR spectrometer (operating at 500 MHz and 125 MHz, respectively) and CDCl_3 as solvent, unless stated otherwise. Chemical shifts were recorded in parts per million (ppm) with internal reference to CDCl_3 (^1H NMR at 7.26 ppm, $^{13}\text{C}\{^1\text{H}\}$ NMR at 77.16 ppm). ^{19}F NMR spectra were obtained using a 500 MHz NMR instrument (operating at 470 MHz) using TFA (^{19}F NMR at -76.55 ppm) as an external reference. Splitting patterns are indicated as follows: ad, apparent doublet; as, apparent singlet; br, broad; s, singlet; d, doublet; dd, doublet of doublets; t, triplet; q, quartet; m, multiplet. Coupling constants (J) are reported in units of Hertz (Hz). High and low resolution ESI^+ mass spectra were recorded by Mr. Xiao Feng from ion trap (ESI TOF) instruments. Column chromatography was performed using Silicycle 230-400 mesh ultra pure silica or Brockman (III) basic alumina, as indicated. Celite® 454 was used as a filtering agent, where indicated. Crude solvents for column chromatography and extractions were distilled under 1 atm of pressure prior to use. All other chemicals were used as received. TLC analysis was performed on silica gel or neutral aluminum oxide plates, visualized using UV light (254 nm) and/or developed with Vanillin stain. Melting points were uncorrected, and are exclusively reported for novel compounds.

The following compounds were prepared according to literature procedures: **4.7a**,⁴¹ **4.7b**,⁴¹ **4.8a**,⁴⁴ **4.8b**,⁴⁴ **4.9a**,⁴⁴ **4.9b**,⁴⁴ **4.10a**,⁴⁴ and **4.10b**.⁴⁴ The following compounds were prepared by other Thompson group members: **4.5**⁵⁷ and **4.20**.⁴¹

***tert*-Butyl 5-formyl-3,4-dimethyl-1*H*-pyrrole-2-carboxylate (4.6)**



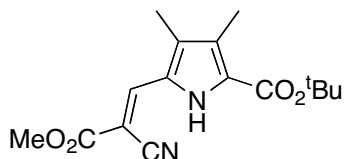
CAN (21.480 g, 39.182 mmol) was added to a stirring solution of **4.5**⁵⁷ (2.000 g, 9.557 mmol) in THF:AcOH:H₂O (96 mL : 24 mL : 96 mL) at 0 °C. The reaction mixture was allowed to warm to room temperature and stirred for 2 hours, at which point CAN (5.239 g, 9.557 mmol) was added and the reaction mixture was stirred for an additional 30 minutes. The reaction mixture was poured into water (400 mL) and extracted with CH₂Cl₂ (3 x 400 mL). The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated *in vacuo*.⁴⁷ The residue was purified *via* column chromatography (silica – 25 % EtOAc/hexanes) to afford the title compound as a colourless solid (2.134 g, 100 %).

Alternatively:

Pb(OAc)₄ (35.50 g, 80.07 mmol) was added in several portions to a stirring solution of **4.5**⁵⁷ (7.617 g, 36.395 mmol) in AcOH (36 mL). The reaction mixture was heated to 80 °C for 30 minutes. After cooling the reaction mixture to room temperature, ethylene glycol (1.5 mL) was added to quench the reaction, and then the slow addition of H₂O (210 mL) was added to incur precipitation. The resulting precipitate was collected *via* filtration and dissolved in CH₂Cl₂, filtering a second time to remove any insoluble impurities.⁴¹ The solvent was removed *in vacuo*, and the crude product recrystallized from MeOH/H₂O to give the title compound as a colourless solid (5.141 g, 63 %).

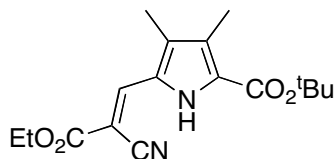
¹H NMR (300 MHz, CDCl₃) δ: 9.76 (s, 1H), 9.30 (br s, 1H), 2.28 (s, 3H), 2.24 (s, 3H), 1.58 (s, 9H) ppm. Spectral and physical properties were in agreement with previously reported data.^{41,58} ¹³C{¹H} NMR (500 MHz, CDCl₃) δ: 179.1, 160.4, 130.4, 129.6, 126.6, 126.0, 82.3, 28.5, 9.9, 8.7 ppm.

***tert*-Butyl 5-(2-cyano-2-methoxycarbonylvinyl)-3,4-dimethyl-1*H*-pyrrole-2-carboxylate (4.7a)**



A mixture of pyrrole **4.6** (2.000 g, 8.958 mmol) and methyl cyanoacetate (1.190 mL, 13.437 mmol) was heated at reflux temperature in EtOH (4.5 mL). When the reaction mixture reached reflux temperature, NH₂Me (2M in THF, 0.314 mL, 0.627 mmol) was added. The reaction mixture was cooled to room temperature and the resulting crystals were isolated *via* filtration (washing with cold EtOH, followed by hexanes)⁴¹ to give the title compound as a yellow solid (1.985 g, 73 %). Both *E/Z* isomers had formed during the course of the reaction (88 % *E* isomer by ¹H NMR spectroscopy). An analytical sample (0.5 g) was recrystallized using EtOH/CH₂Cl₂ to obtain exclusively the *E* isomer for spectral analysis: ¹H NMR (500 MHz, CDCl₃) δ: 10.18 (br s, 1H), 8.04 (s, 1H), 3.89 (s, 3H), 2.26 (s, 3H), 2.17 (s, 3H), 1.59 (s, 9H) ppm. Spectral and physical properties were in agreement with previously reported data.⁴⁴ ¹³C{¹H} NMR (125 MHz, CDCl₃) δ: 163.8, 159.5, 139.5, 133.8, 128.0, 126.6, 125.0, 118.3, 93.6, 82.7, 53.2, 28.4, 10.0, 9.5 ppm.

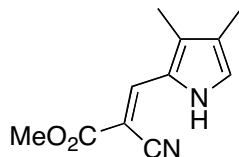
***tert*-Butyl 5-(2-cyano-2-ethoxycarbonylvinyl)-3,4-dimethyl-1*H*-pyrrole-2-carboxylate (4.7b)**



A mixture of pyrrole **4.6** (5.000 g, 22.394 mmol) and ethyl cyanoacetate (3.600 mL, 33.592 mmol) was heated at reflux temperature in EtOH (22.4 mL). When the reaction mixture reached reflux temperature, NH₂Me (2M in THF, 0.800 mL, 1.568 mmol) was added to the solution. The reaction mixture was cooled to room temperature and the resulting crystals were isolated *via* filtration (washing with cold EtOH, followed by hexanes)⁴¹ to give the title compound as a yellow solid (5.808 g, 81 %). Both *E/Z* isomers had formed during the course of the reaction (91 % *E* isomer by ¹H NMR spectroscopy). An analytical sample (0.7 g) was recrystallized using EtOH/CH₂Cl₂ to obtain exclusively the *E* isomer for spectral analysis: ¹H NMR (500 MHz, CDCl₃) δ: 10.19 (br s, 1H), 8.04 (s, 1H), 4.34 (q, 2H, *J* = 7), 2.29 (s, 3H), 2.19 (s, 3H), 1.62 (s, 9H), 1.40 (t, 3H, *J* = 7) ppm. Spectral and physical properties were in agreement with previously reported data.⁴¹;

$^{13}\text{C}\{^1\text{H}\}$ NMR (125 MHz, CDCl_3) δ : 163.3, 159.6, 139.4, 133.5, 127.8, 126.5, 125.1, 118.3, 94.2, 82.6, 62.4, 28.4, 14.4, 10.0, 9.5 ppm.

2-(2-Cyano-2-methoxycarbonylvinyl)-3,4-dimethyl-1H-pyrrole (4.10a)



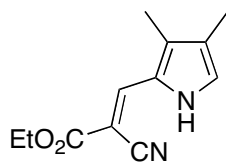
Both isomers of **4.7a** (3.00 g, 9.857 mmol) were dissolved in 1,2-DCE (10.6 mL). The dissolved pyrrole was then heated to reflux temperature with stirring, at which point TFA (1.1 mL) was added. The reaction mixture was heated, with stirring, for another 45 minutes at reflux temperature. A second portion of TFA (1.1 mL) was added, and the reaction mixture was heated and stirred for an additional 35 minutes. Upon cooling to 0 °C, a yellow precipitate formed and was isolated by filtration. The precipitate was washed with cold 1,2-DCE, followed by hexanes.⁴⁴ The resulting yellow solid (**4.8a**, 2.082 g, 85 %) was used without further purification for the next step (77 % *E* isomer by ^1H NMR spectroscopy).

Both isomers of **4.8a** (2.000 g, 8.057 mmol) and sodium acetate (0.661 g, 8.057 mmol) were dissolved in a mixed solvent system of 9 % Ac_2O in AcOH (17.9 mL) and heated to 105 °C with stirring, at which point 1M ICl in AcOH (16.2 mL 16.2 mmol) was added to the reaction mixture. After 5 minutes, NaHSO_3 (0.838 g, 8.057 mmol) in H_2O (105 mL) was added to quench any unreacted iodine. Upon cooling to room temperature, a lime green precipitate had formed and was isolated by filtration (washing with H_2O). The precipitate was dissolved in CH_2Cl_2 and filtered again to remove any insoluble impurities. The filtrate was collected and the solvent was removed *in vacuo*. The resulting crude residue was precipitated from MeOH, the precipitate was collected by filtration and washed with hexanes.⁴⁴ The resulting pale green solid (**4.9a**, 1.426 g, 54 %) was used without further purification for the next step (74 % *E* isomer by ^1H NMR spectroscopy).

Both isomers of **4.9a** (0.434 g, 1.82 mmol) and zinc dust (0.438 g, 6.705 mmol) were dissolved in AcOH (3 mL) and manually stirred until the reaction mixture began to self-heat. The reaction was then magnetically stirred for an additional 20 minutes, at which point the zinc dust was removed *via* filtration, washing the zinc dust with small portions

of MeOH (4 x 0.5 mL) until the rinsings became clear. The zinc dust (still on the filter paper in the Büchner funnel) was washed with H₂O (5 mL), causing precipitation of a dark yellow precipitate in the filtrate. The precipitate that formed from the filtrate of the first filtration was collected *via* a second filtration, washing with copious amounts of H₂O, and then dried in air.⁴⁴ The title compound was isolated as a golden yellow solid (**4.10a**, 0.182 g, 68 % yield). Both *E/Z* isomers were present, as stated previously. The sample was recrystallized using MeOH/CH₂Cl₂ to obtain exclusively the *E* isomer for spectral analysis: ¹H NMR (CDCl₃, 500 MHz): δ 9.65 (br s, 1H), 8.00 (s, 1H), 6.99 (as, 1H), 3.87 (s, 3H), 2.18 (s, 3H), 2.04 (s, 3H) ppm. Spectral and physical properties were in agreement with previously reported data⁴⁴; ¹³C{¹H} NMR (CDCl₃, 125 MHz): δ 164.8, 139.6, 134.7, 127.8, 125.0, 122.2, 119.7, 88.2, 52.8, 10.0, 9.6 ppm.

2-(2-Cyano-2-ethoxycarbonylvinyl)-3,4-dimethyl-1H-pyrrole (**4.10b**)



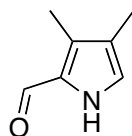
Both isomers of **4.7b** (10.0 g, 31.4 mmol) were dissolved in 1,2-DCE (31.4 mL). The dissolved pyrrole was then heated to reflux temperature with stirring, at which point TFA (3.4 mL) was added. The reaction mixture was heated, with stirring, for another 45 minutes at reflux temperature. A second portion of TFA (3.4 mL) was added, and the reaction mixture was heated and stirred for an additional 35 minutes. Upon cooling to 0 °C, a yellow precipitate formed and was isolated *via* filtration. The precipitate was washed with cold 1,2-DCE, followed by hexanes.⁴⁴ The resulting yellow solid (**4.8b**, 7.924 g, 96 %) was used without further purification for the next step (82 % *E* isomer by ¹H NMR spectroscopy).

Both isomers of **4.8b** (7.824 g, 29.833 mmol) and sodium acetate (2.447 g, 29.833 mmol) were dissolved in a mixed solvent system of 9 % Ac₂O in AcOH (66 mL) and heated to 105 °C with stirring, at which point 1M ICl in AcOH (60 mL, 60 mmol) was added to the reaction mixture. After 5 minutes, NaHSO₃ (2.5 g, 24.0 mmol) in H₂O (400 mL) was added to quench any unreacted iodine. Upon cooling to room temperature, a lime green

precipitate formed and was isolated *via* filtration (washing with H₂O). The precipitate was dissolved in CH₂Cl₂ and filtered again. The filtrate was collected and the solvent was removed *in vacuo*. The resulting crude residue was precipitated from MeOH, the precipitate was collected *via* filtration and washed with hexanes.⁴⁴ The resulting pale green solid (**4.9b**, 5.954 g, 58 %) was used without further purification for the next step (72 % *E* isomer by ¹H NMR spectroscopy).

Both isomers of **4.9b** (1.907 g, 5.541 mmol) and zinc dust (1.848 g, 28.260 mmol) were dissolved in AcOH (12 mL) and manually stirred until the reaction mixture began to self-heat. The reaction was magnetically stirred for an additional 20 minutes, at which point the zinc dust was removed *via* filtration, washing the zinc dust with small portions of MeOH (4 x 1.5 mL) until the rinsings became clear. The zinc dust (still on the filter paper in the Büchner funnel) was washed with H₂O (18 mL), causing precipitation of a dark yellow precipitate in the filtrate. The precipitate that formed from the filtrate was collected *via* a second filtration, washing with copious amounts of H₂O, and then dried in air.⁴⁴ The title compound was isolated as a golden yellow solid (**4.10b**, 0.855 g, 71 % yield). Both *E/Z* isomers were present, as previously stated. The sample was recrystallized using MeOH/CH₂Cl₂ to obtain exclusively the *E* isomer for spectral analysis: ¹H NMR (CDCl₃, 500 MHz): δ 9.66 (br s, 1H), 8.00 (s, 1H), 6.98 (as, 1H), 4.32 (q, 2H, *J* = 7), 2.18 (s, 3H), 2.04 (s, 3H), 1.36 (t, 3H, *J* = 7) ppm. Spectral and physical properties were in agreement with previously reported data.⁴⁴; ¹³C{¹H} NMR (CDCl₃, 125 MHz): δ 164.3, 139.5, 134.5, 127.6, 125.0, 122.1, 119.8, 88.7, 61.9, 14.5, 10.0, 9.6 ppm.

3,4-Dimethyl-1*H*-pyrrole-2-carbaldehyde (**4.11**)



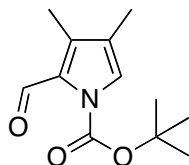
A solution of pyrrole **4.10a** (0.182 g, 0.891 mmol) in MeOH (5.6 mL) was heated to reflux temperature with stirring under N₂, at which point 4 M aqueous NaOH (1.1 mL) was added dropwise. The reaction mixture was heated and stirred for 20 minutes before H₂O (5.6 mL) was added. MeOH was then removed *in vacuo*. The reaction mixture was

heated to reflux temperature with stirring for an additional 2 hours, and then cooled to room temperature. The reaction mixture was diluted with H₂O (20 mL), and the crude product was extracted with CH₂Cl₂ (3 x 25 mL), and the combined organic layers were dried over anhydrous Na₂SO₄ and concentrated *in vacuo*.⁴⁴ The title compound was isolated as a colourless solid (0.077 g, 70 %) after purification *via* column chromatography (silica – 20 % EtOAc/hexanes).

Or:

A solution of pyrrole **4.10b** (0.855 g, 3.918 mmol) in MeOH (24.5 mL) was heated to reflux temperature with stirring under N₂, at which point 4 M aqueous NaOH (4.9 mL) was added dropwise. The reaction mixture was heated and stirred for 20 minutes before H₂O (24.5 mL) was added. MeOH was then removed *in vacuo*. The reaction mixture was heated to reflux temperature with stirring for an additional 2 hours, and then cooled to room temperature. The reaction mixture was diluted with H₂O (20 mL). The crude product was extracted with CH₂Cl₂ (3 x 50 mL), and the combined organic layers were dried over anhydrous Na₂SO₄ and concentrated *in vacuo*.⁴⁴ The title compound was isolated as a colourless solid (0.364 g, 75 %) after purification *via* column chromatography (silica – 20 % EtOAc/hexanes). ¹H NMR (500 MHz, MeOD-*d*₄) δ: 10.95 (br s, 1H, exchangeable - not always present), 9.47 (s, 1H), 6.89 (s, 1H), 2.55 (s, 3H), 1.99 (s, 3H) ppm. Spectral and physical properties were in agreement with previously reported data.⁵⁹

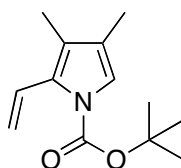
***tert*-Butyl 2-formyl-3,4-dimethyl-1*H*-pyrrole-1-carboxylate (4.12)**



Pyrrole **4.11** (0.410 g, 3.329 mmol) and DMAP (0.052 g, 0.430 mmol) were dissolved in anhydrous CH₃CN (39 mL) under N₂. To the stirring solution was added a solution of Boc₂O (2.110 g, 9.669 mmol) in anhydrous CH₃CN (10 mL). The solvent was removed *in vacuo* after 30 minutes and the residue was dissolved in CH₂Cl₂ (50 mL) and washed with H₂O (3 x 50 mL). The organic layer was dried over Na₂SO₄, concentrated *in vacuo* and

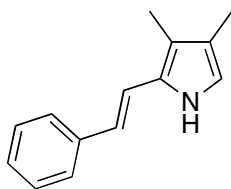
purified *via* column chromatography (alumina type III basic – 10 % EtOAc/hexanes). The title compound was afforded as a translucent, colourless semi-solid (0.742 g, 100 %). ¹H NMR (500 MHz, MeOD-*d*4) δ: 10.39 (s, 1H), 7.14 (s, 1H), 2.32 (s, 3H), 1.99 (s, 3H), 1.61 (s, 9H) ppm. Spectral and physical properties were in agreement with previously reported data.⁶⁰

***tert*-Butyl 3,4-dimethyl-2-vinyl-1*H*-pyrrole-1-carboxylate (4.13)**



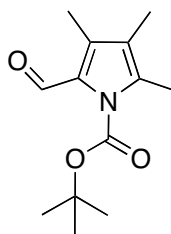
A 1.6 M solution of *n*-BuLi in hexanes (0.616 mL, 0.986 mmol) was added to a stirring suspension of methyltriphenylphosphonium bromide (0.384 g, 1.075 mmol) anhydrous THF (9 mL) at 0 °C under N₂. After stirring for 2 hours, the solution was cooled to -78 °C and a solution containing pyrrole **4.12** (0.200 g, 0.896 mmol) in anhydrous THF (1.7) was added dropwise. The reaction mixture was allowed to slowly warm to room temperature, and was then stirred overnight. The reaction was quenched by the dropwise addition H₂O (1 mL), at which point the reaction mixture was opened to air and poured into H₂O (25 mL). The crude organic mixture was extracted with CH₂Cl₂ (3 x 25 mL), and then the combined organic layers were dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The crude residue was purified *via* column chromatography (alumina type III basic – 10 % EtOAc/hexanes) to provide the title compound as a translucent, colourless solid (0.135 g, 68 %). m.p.: 32-34 °C; ¹H NMR (500 MHz, CDCl₃) δ: 7.04 (dd, 1H, *J* = 18, 12), 6.96 (s, 1H), 5.31 (dd, 1H, *J* = 12, 2), 5.24 (dd, 1H, *J* = 18, 2), 2.05 (s, 3H), 1.97 (s, 3H), 1.57 (s, 9H) ppm; ¹³C{¹H} NMR (CDCl₃, 125 MHz): δ 149.6, 129.7, 128.7, 122.5, 122.1, 117.9, 115.4, 83.1, 28.2, 10.9, 10.4 ppm; HRMS-ESI (*m/z*): [M + Na]⁺ Calcd 244.1308 for C₁₃H₁₉NO₂Na; found 244.1310.

(E)-3,4-Dimethyl-2-styryl-1H-pyrrole (4.16)



$\text{Pd}(\text{OAc})_2$ (0.001 g, 0.005 mmol) and 2,4-pentandione (1 drop) were stirred in anhydrous DMF under N_2 for 10 minutes, at which point bromobenzene (0.052 mL, 0.490 mmol) and a solution of pyrrole **4.13** (0.130 g, 0.587 mmol) in anhydrous DMF (1.5 mL) were added. The reaction mixture was cycled with N_2 twice before adding anhydrous K_2CO_3 (0.135 g, 0.980 mmol), and cycling an additional 3 times with N_2 . The reaction mixture was then heated to 130 °C for 3 hours with stirring. The reaction mixture was cooled to room temperature and the catalyst was removed *via* filtration through a small quantity of Celite®.³⁷ The title compound was received as an oil (0.010 g, 10 %), albeit briefly, after purification *via* column chromatography (0→10 % EtOAc/hexanes – alumina type III basic). ^1H NMR (300 MHz, CDCl_3) δ : 7.96 (br s, 1H), 7.44 (ad, 2H, $J = 8$), 7.33 (at, 2H, $J = 7$), 7.19 (at, 1H, $J = 7$), 7.02 (d, 1 H, $J = 17$), 6.57 (as, 1H), 6.51 (d, 1H, $J = 17$), 2.12 (s, 3H), 2.04 (s, 3H) ppm. Unstable species.

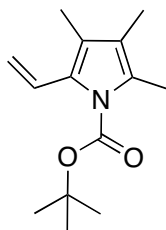
***tert*-Butyl 2-formyl-3,4,5-trimethyl-1H-pyrrole-1-carboxylate (4.21)**



Pyrrole **4.20** (0.200 g, 1.458 mmol) and DMAP (0.023 g, 0.190 mmol) were dissolved in anhydrous CH_3CN (16 mL) under N_2 . To the stirring solution was added a solution containing Boc_2O (0.859 g, 3.936 mmol) in anhydrous CH_3CN (4 mL). The solvent was removed *in vacuo* after 30 minutes and the residue was dissolved in CH_2Cl_2 (50 mL) and washed with H_2O (3 x 50 mL). The organic layer was dried over Na_2SO_4 , concentrated *in vacuo* and purified *via* column chromatography (alumina type III basic – 10 % EtOAc/hexanes). The title compound was afforded as a yellow oil (0.337 g, 97 %). ^1H NMR (500 MHz, CDCl_3) δ : 9.99 (s, 1H), 2.35 (s, 3H), 2.28 (s, 3H), 1.92 (s, 3H), 1.61 (s,

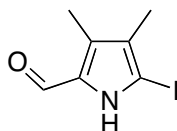
9H) ppm; $^{13}\text{C}\{^1\text{H}\}$ NMR (CDCl_3 , 125 MHz): δ 180.9, 149.7, 134.8, 134.7, 129.4, 120.6, 85.1, 28.1, 12.9, 10.8, 8.8 ppm; HRMS-ESI (m/z): $[\text{M} + \text{Na}]^+$ Calcd 260.1267 for $\text{C}_{13}\text{H}_{19}\text{NO}_3\text{Na}$; found 260.1267.

***tert*-Butyl 2,3,4-trimethyl-5-vinyl-1*H*-pyrrole-1-carboxylate (4.19)**



A 1.6 M solution of *n*-BuLi in hexanes (0.290 mL, 0.464 mmol) was added to a stirring suspension of methyltriphenylphosphonium bromide (0.181g, 0.506 mmol) anhydrous THF (4.2 mL) at 0 °C under N_2 . After stirring for 2 hours, the solution was cooled to -78 °C and was added dropwise to a solution containing pyrrole **4.21** (0.100 g, 0.421 mmol) in anhydrous THF (0.8 mL) at -78 °C. The reaction mixture was allowed to slowly warm to room temperature, and then stirred overnight. The reaction was quenched by the dropwise addition H_2O (1 mL), at which point the reaction mixture was opened to air and poured into H_2O (20 mL). The crude organic mixture was extracted with CH_2Cl_2 (3 x 25 mL), the combined organic layers were dried over anhydrous Na_2SO_4 , and concentrated *in vacuo*. The crude residue was purified *via* column chromatography (alumina type III basic – 3 % EtOAc/hexanes) to provide the title compound as a pale yellow oil (0.058 g, 59 %). ^1H NMR (500 MHz, CDCl_3) δ : 6.80 (dd, 1H, $J = 18, 11$), 5.24 (dd, 1H, $J = 11, 2$), 5.15 (dd, 1H, $J = 18, 2$), 2.31 (s, 3H), 2.03 (s, 3H), 1.92 (s, 3H), 1.58 (s, 9H) ppm; $^{13}\text{C}\{^1\text{H}\}$ NMR (CDCl_3 , 125 MHz): δ 150.6, 129.1, 128.4, 126.6, 121.2, 119.6, 114.1, 83.4, 28.3, 13.4, 11.0, 9.5 ppm; HRMS-ESI (m/z): $[\text{M} + \text{Na}]^+$ Calcd 258.1465 for $\text{C}_{14}\text{H}_{21}\text{NO}_2\text{Na}$; found 258.1465.

5-Iodo-3,4-dimethyl-1*H*-pyrrole-2-carbaldehyde (4.23)



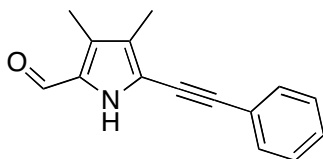
A solution of pyrrole **4.8a** (0.500 g, 1.515 mmol) in MeOH (3.8 mL) was heated to reflux temperature with stirring under N₂, at which point 4 M aqueous NaOH (1.9 mL) was added dropwise. The reaction mixture was heated and stirred for 20 minutes before H₂O (6 mL) was added. MeOH was then removed *in vacuo*. The reaction mixture was heated to reflux temperature with stirring for an additional 2 hours, at which point the reaction mixture was cooled to room temperature. The reaction mixture was diluted with H₂O (20 mL), and the crude product was extracted with CH₂Cl₂ (3 x 25 mL). The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated *in vacuo*.⁴⁴ The title compound was isolated as a colourless solid (0.062 g, 16 %) after purification *via* column chromatography (silica – 20 % EtOAc/hexanes).

Alternatively:

A solution of pyrrole **4.8b** (2 g, 5.811 mmol) in MeOH (15 mL) was heated to reflux temperature with stirring under N₂, at which point 4 M aqueous NaOH (7.3 mL) was added dropwise. The reaction mixture was heated and stirred for 20 minutes before H₂O (15 mL) was added. MeOH was then removed *in vacuo*. The reaction mixture was heated to reflux temperature with stirring for an additional 2 hours, and then cooled to room temperature. The reaction mixture was diluted with H₂O (50 mL), and the crude product was extracted with CH₂Cl₂ (3 x 75 mL). The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated *in vacuo*.⁴⁴ The title compound was isolated as a colourless solid (0.259 g, 18 %) after purification *via* column chromatography (silica – 20 % EtOAc/hexanes).

¹H NMR (500 MHz, CDCl₃) δ: 9.60 (br s, 1H), 9.40 (s, 1H), 2.29 (s, 3H), 1.97 (s, 3H) ppm. Spectral and physical properties were in agreement with previously reported data.⁴⁷

3,4-Dimethyl-5-(phenylethynyl)-1H-pyrrole-2-carbaldehyde (4.24)



Pyrrole **4.23** (0.100 g, 0.402 mmol), Pd(PPh₃)₂Cl₂ (0.006 g, 0.008 mmol) and CuI (0.003 g, 0.016 mmol) were suspended in NEt₂H (4 mL) and cycled with N₂ 5 times before

adding phenyl acetylene (0.066 mL, 0.603 mmol). The reaction mixture was then heated to 50 °C for an hour with stirring. The reaction mixture was cooled to room temperature and the catalyst was removed *via* filtration through a small quantity of Celite®.⁴⁷ The filtrate was concentrated *in vacuo* and then purified *via* column chromatography (silica – CH₂Cl₂), to afford the title compound as a pale yellow solid (0.053 g, 59 %).

Alternatively:

Pyrrole **4.9a** (0.100 g, 0.291 mmol), Pd(PPh₃)₂Cl₂ (0.004 g, 0.006 mmol) and CuI (0.002 g, 0.012 mmol) were suspended in NEt₂H (3 mL) and cycled with N₂ 5 times before adding phenyl acetylene (0.048 mL, 0.436 mmol). The reaction mixture was then heated to 50 °C for an hour with stirring. The reaction mixture was cooled to room temperature and the catalyst was removed *via* filtration through a small quantity of Celite®.⁴⁷ The filtrate was concentrated *in vacuo* and used for the next step without further purification. The crude residue was dissolved in MeOH (1.5 mL) was heated to reflux temperature with stirring under N₂, at which point 6 M aqueous NaOH (0.15 mL) was added dropwise. The reaction mixture was heated and stirred for 20 minutes before H₂O (1.8 mL) was added. MeOH was then removed *in vacuo*. The reaction mixture was heated to reflux temperature with stirring for an additional 2 hours, and then cooled to room temperature. The reaction mixture was diluted with H₂O (20 mL). The crude product was extracted with CH₂Cl₂ (3x 25 mL), and the combined organic layers were dried over anhydrous Na₂SO₄ and concentrated *in vacuo*.⁴⁴ The title compound was isolated as a pale yellow solid (0.031 g, 48 %) after purification *via* column chromatography (silica – 10 % EtOAc/hexanes). m.p.: 164-165 °C; ¹H NMR (500 MHz, CDCl₃) δ: 9.61 (s, 1H), 9.09 (br s, 1H), 7.50-7.53 (m, 2H), 7.35- 7.38 (m, 3H), 2.28 (s, 3H), 2.13 (s, 3H) ppm; ¹³C{¹H} NMR (CDCl₃, 125 MHz): δ 117.0, 131.6, 130.4, 129.6, 128.9, 128.6, 126.4, 122.5, 119.2, 96.3, 80.1, 9.6, 8.9 ppm; HRMS-ESI (*m/z*): [M + Na]⁺ Calcd 246.0889 for C₁₅H₁₃NONa; found 246.0891.

4.5 References for Chapter 4

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Chapter 5 Conclusions

Each project presented herein can be linked back to a general theme, which was the chemical manipulation of functional groups on pyrroles. Chapters 3 and 4 focused heavily on the chemical manipulation of monopyrroles, with brief discussions on work towards synthesizing and chemically manipulating dipyrrolic compounds. In comparison, Chapter 2 focused on the chemical manipulation of dipyrrens and their metal complexes.

In Chapter 2, we learned that *F*-BODIPYs aren't quite as robust as originally reported. The reaction conditions employed for the microwave-assisted transesterification reaction are, admittedly, a bit harsh. Nevertheless, it was important to explore reactivity under different reaction conditions in order to discover the limitations of compounds. This was especially true for compounds that are being developed for industrial applications. Often times, deleterious reactivity is difficult to find, or is left unreported. Knowledge pertaining to undesired reactivity is equally as useful as information pertaining to reactions that are successful, so as to offer "cautionary tales" for the benefit of the chemical community.

Indeed, Chapters 3 and 4 can be offered as similar knowledge gained. Protecting groups can be incredibly important towards the success (or failure) of the chemical manipulation of a monopyrrole. Although α -difluoromethyl pyrroles are very stable in the presence of air and moisture whilst *N*-protected, the removal of the *N*-protecting group promptly initiates the ejection of fluoride by means of an azafulvenium-mediated hydrolysis reaction.

In addition, substitution on the pyrrole skeleton played a role in reactivity. In Chapter 3, it was found that changing the electronics of a pyrrole (*via* substitution) affected the relative rates of deprotection. In Chapter 4, β -unsubstituted Type 1 dimer ligands were found to be air and moisture stable, but reactions towards their β -methyl analogues were found to be more sensitive. These are two examples, but there are others within in the body of this text that also illustrate unexpected reactivity where there had previously been success (and *vice versa*), as a result of a change in substrate. This offers an important lesson for newcomers to pyrrole chemistry; please don't be discouraged if a reaction is initially unsuccessful. Careful planning can allow for the chemical manipulation of an alternate pyrrole substrate after the offending reaction is achieved.

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Appendices

Appendix 1. License Agreement for Chapter 2

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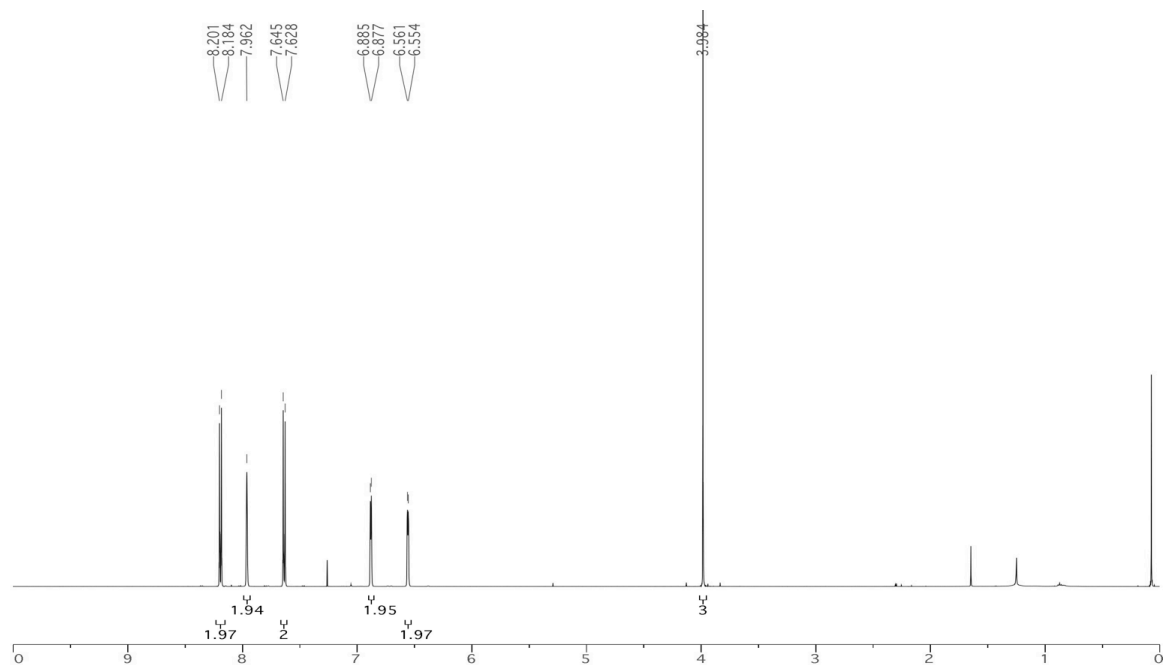
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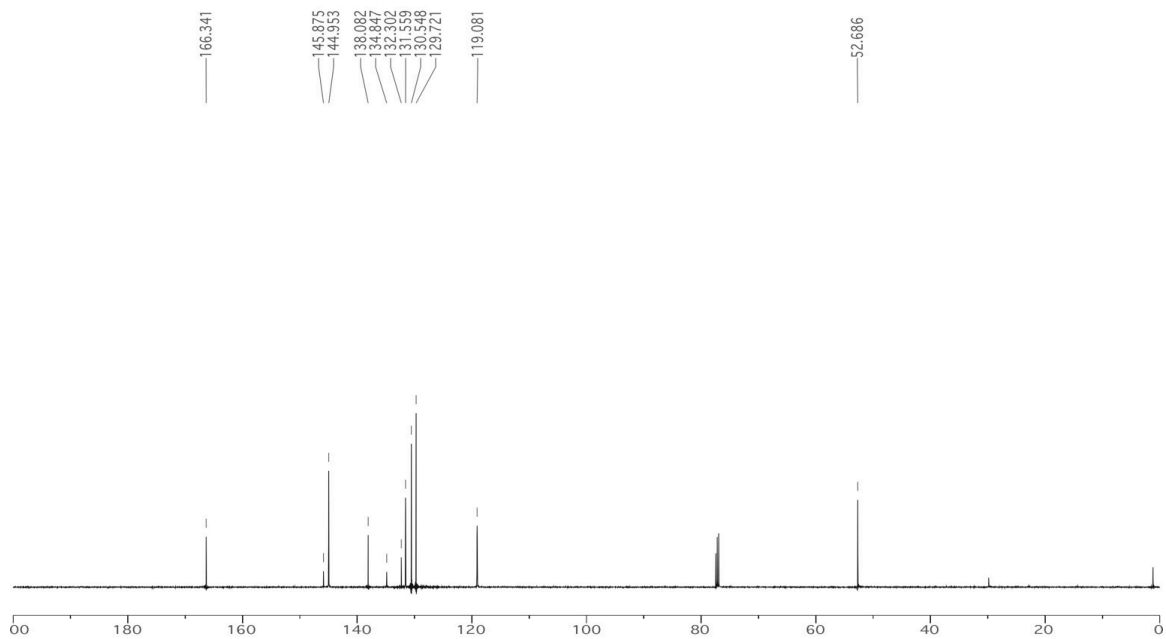
Appendix 2. NMR Spectra for Chapter 2

4,4-Difluoro-8-(4-methoxycarbonylphenyl)-4-bora-3a,4a-diaza-*s*-indacene (2.14)

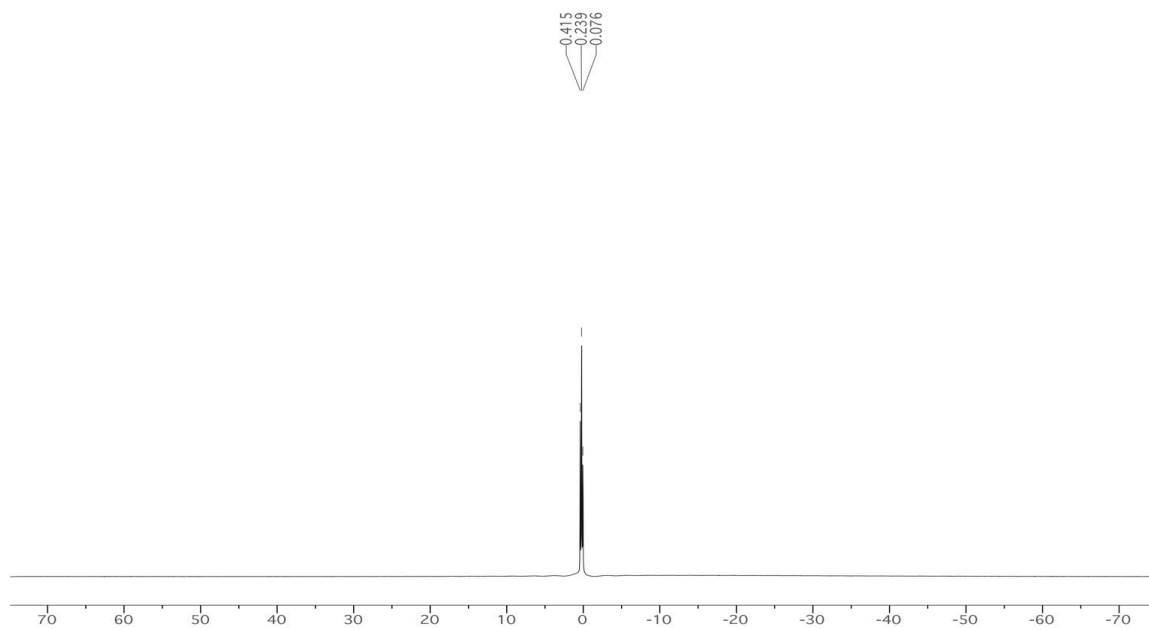
^1H NMR spectrum in CDCl_3 , 500 MHz



^{13}C NMR spectrum in CDCl_3 , 125 MHz



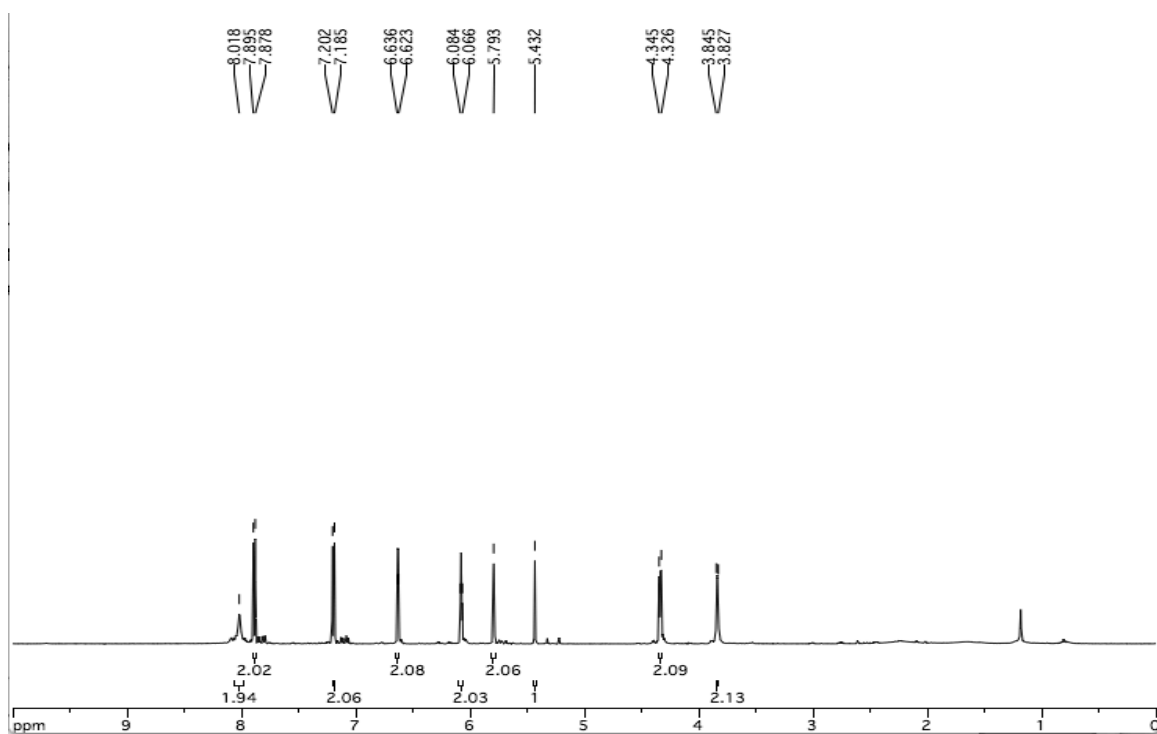
^{11}B NMR spectrum in CDCl_3 , 160 MHz



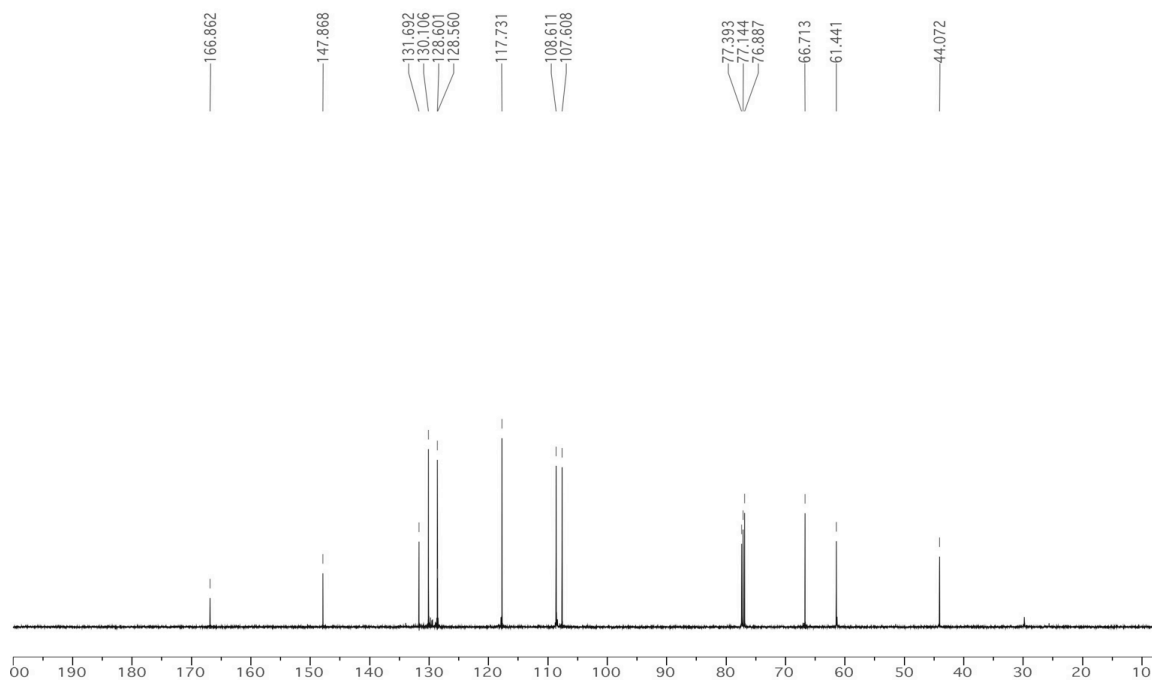
5-((4-(2-Hydroxy)ethoxy)carboxy)phenyl)dipyrromethane (2.19)

^1H NMR spectrum in CDCl_3 , 500 MHz

*minor impurities

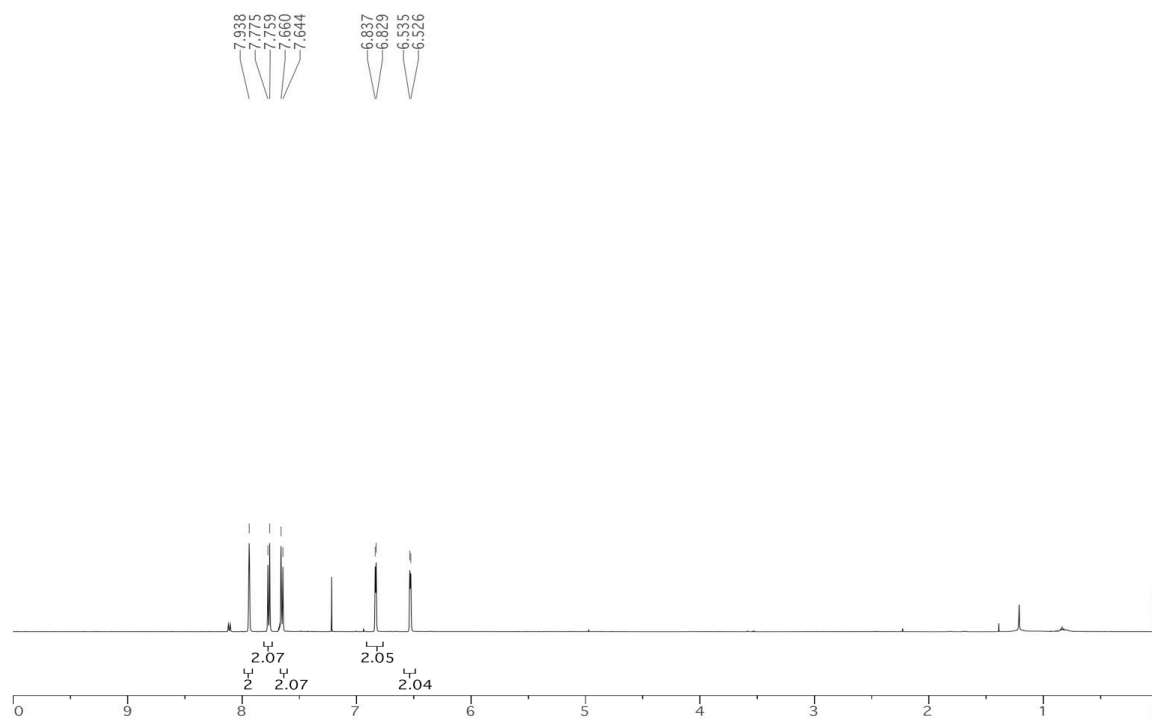


^{13}C NMR spectrum in CDCl_3 , 125 MHz

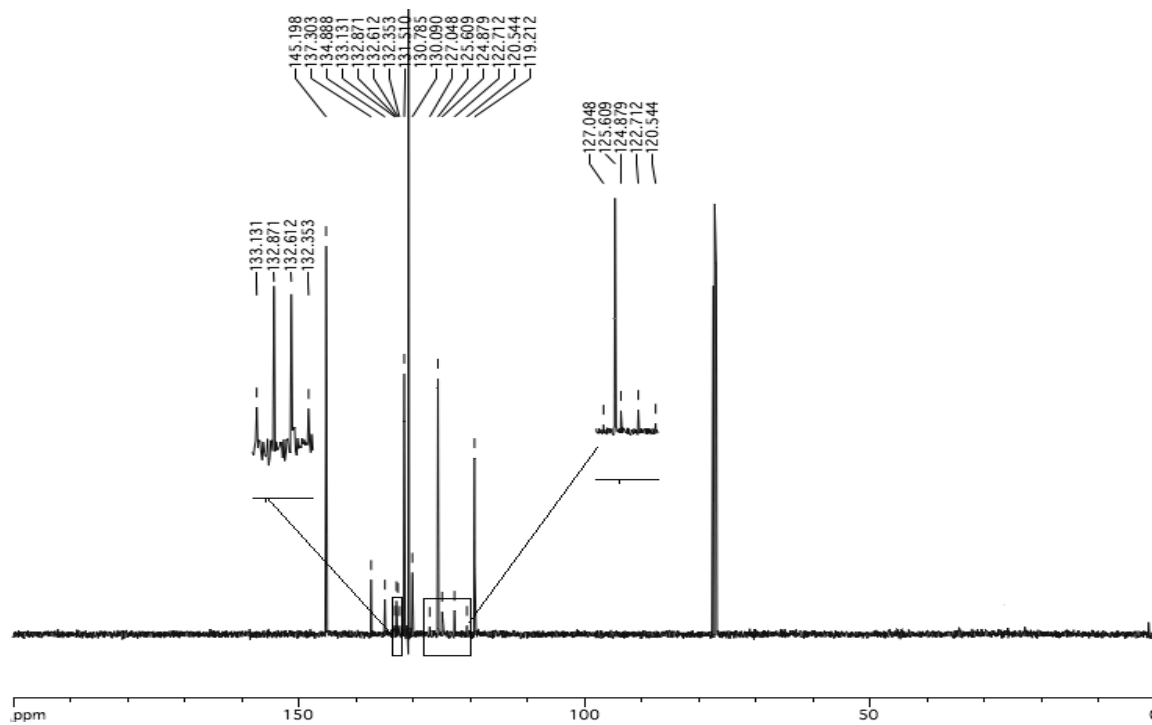


4,4-Difluoro-8-(4-trifluoromethylphenyl)-4-bora-3a,4a-diaza-s-indacene (2.27)

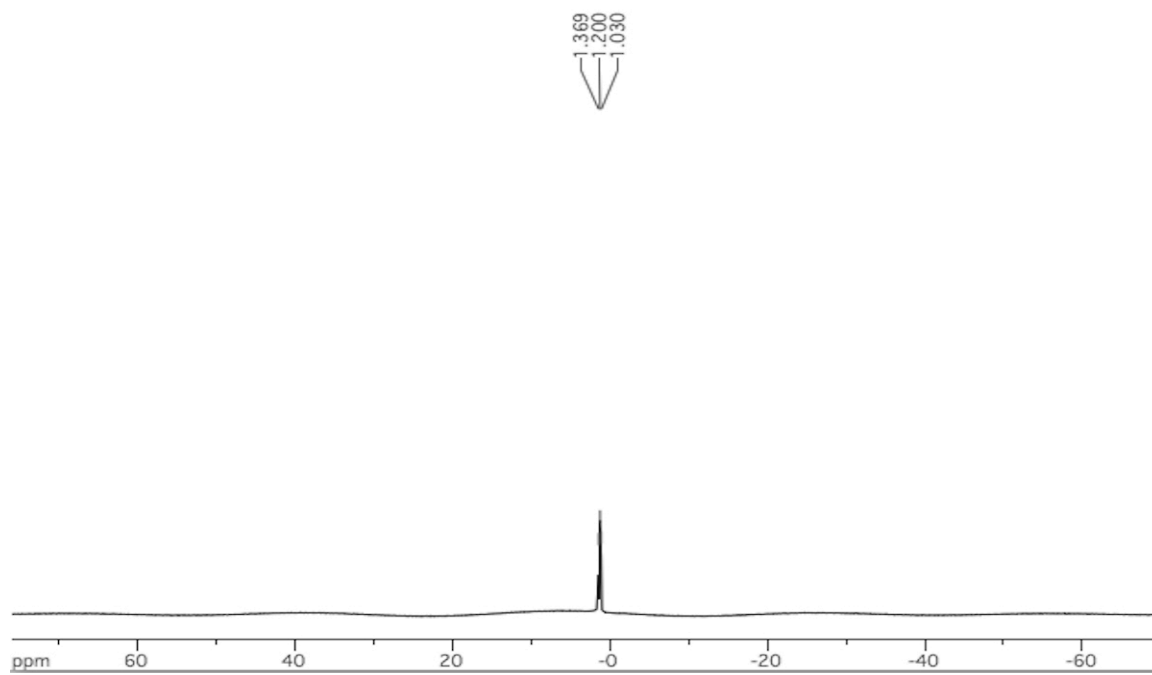
^1H NMR spectrum in CDCl_3 , 500 MHz



^{13}C NMR spectrum in CDCl_3 , 125 MHz

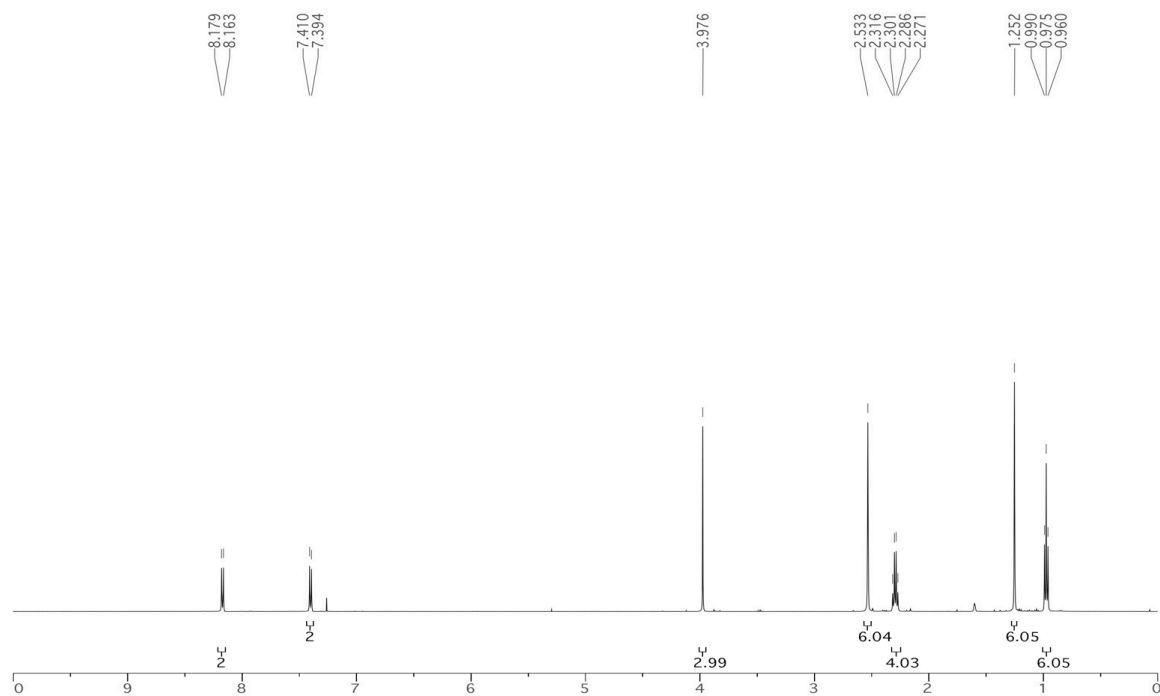


^{11}B NMR spectrum in CDCl_3 , 160 MHz

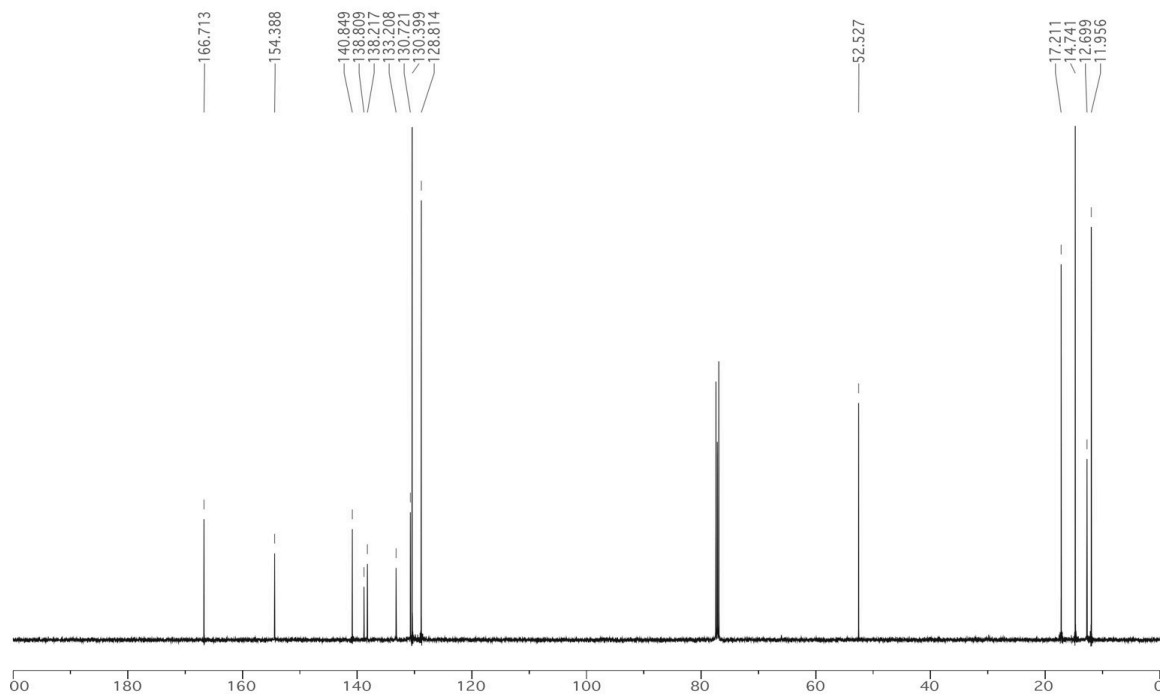


4,4-Difluoro-1,3,5,7-tetramethyl-2,6-diethyl-8-(4-methoxycarbonylphenyl)-4-bora-3a,4a-diaza-s-indacene (2.29)

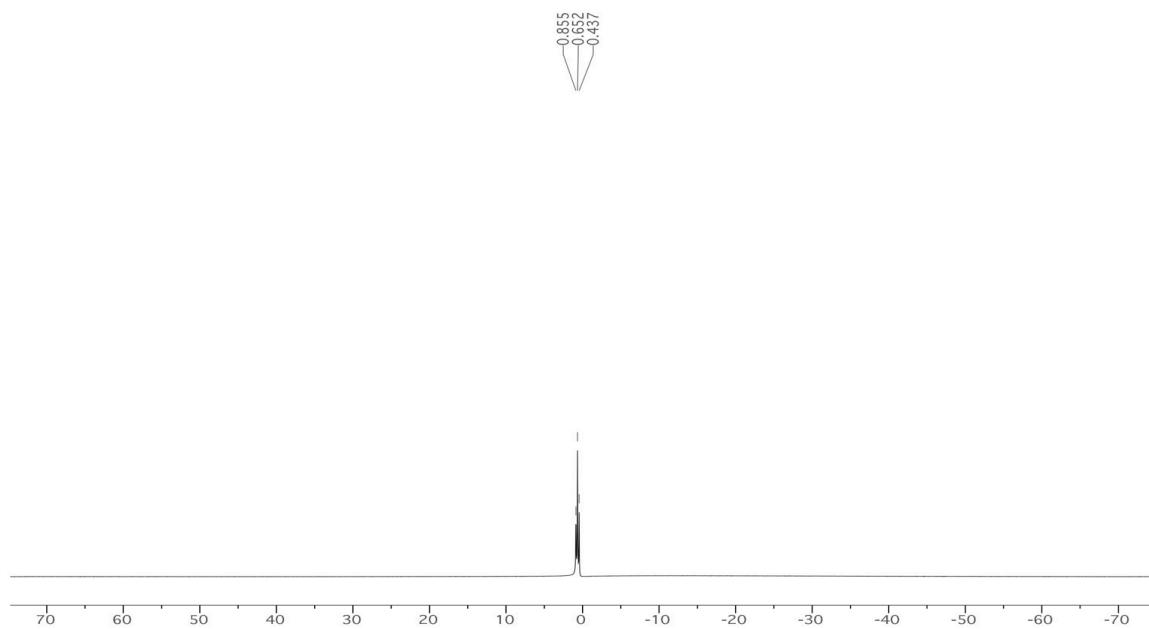
^1H NMR spectrum in CDCl_3 , 500 MHz



^{13}C NMR spectrum in CDCl_3 , 125 MHz



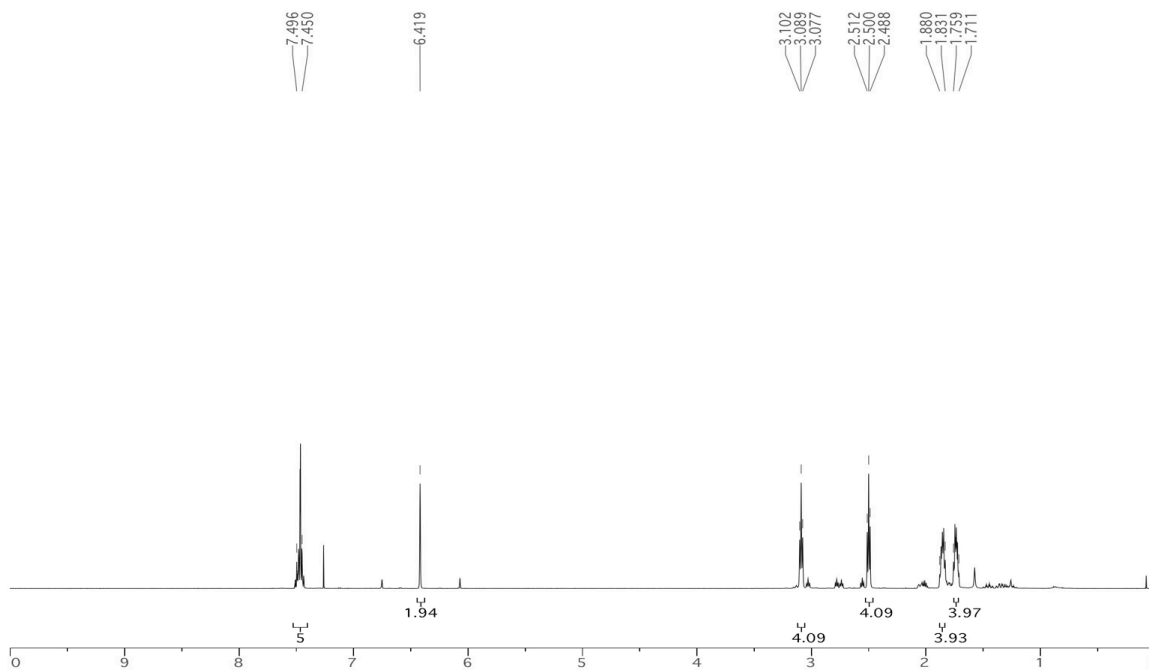
^{11}B NMR spectrum in CDCl_3 , 160 MHz



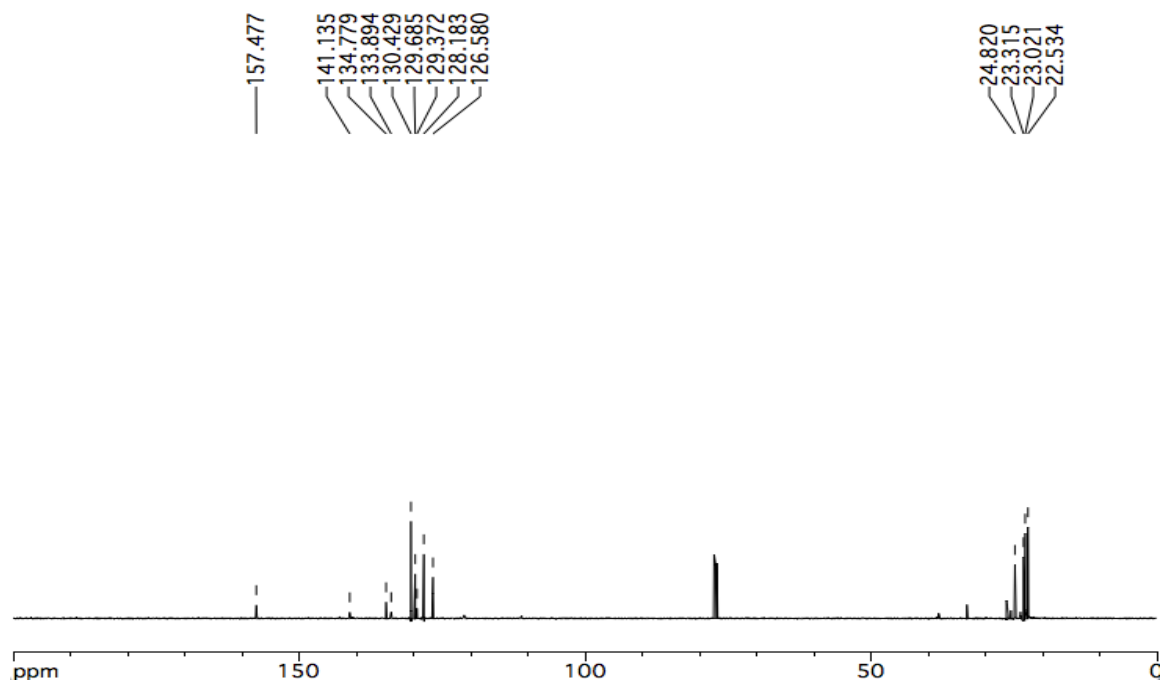
5,5-Difluoro-11-phenyl-5-bora-4b,5a-diaza-s-1,2,3,4,6,7,8,9-octahydroindeno[2,1-b]fluorene (2.33)

^1H NMR spectrum in CDCl_3 , 500 MHz

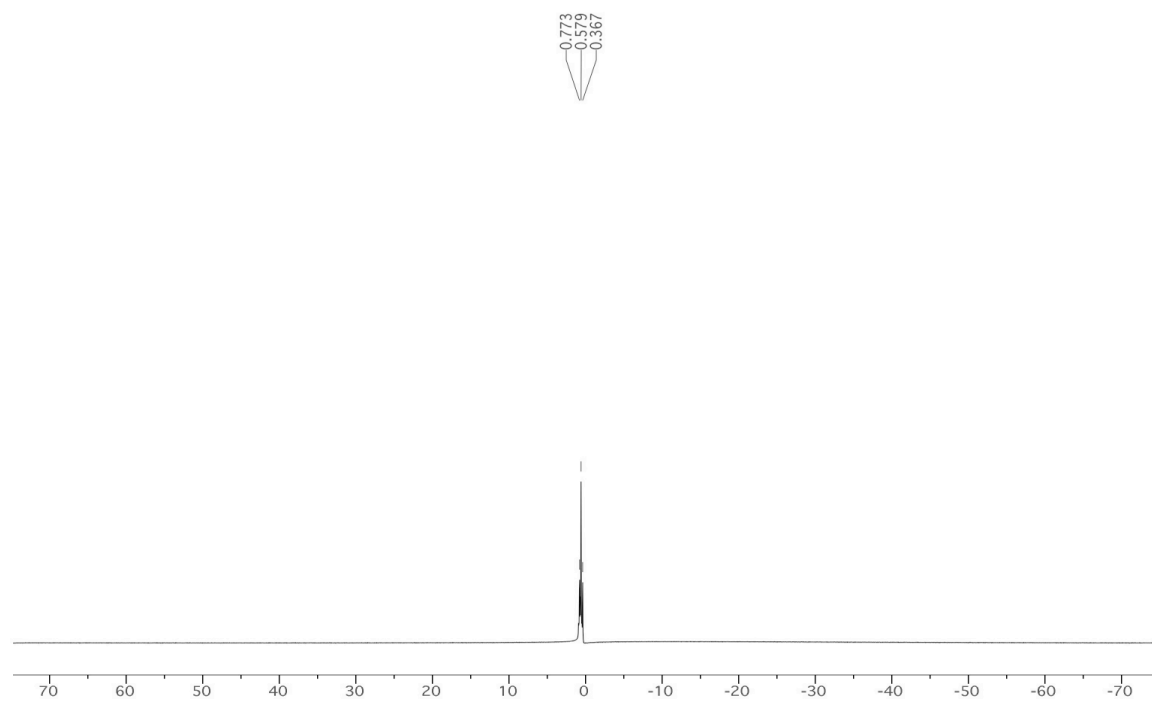
*minor impurities



^{13}C NMR spectrum in CDCl_3 , 125 MHz

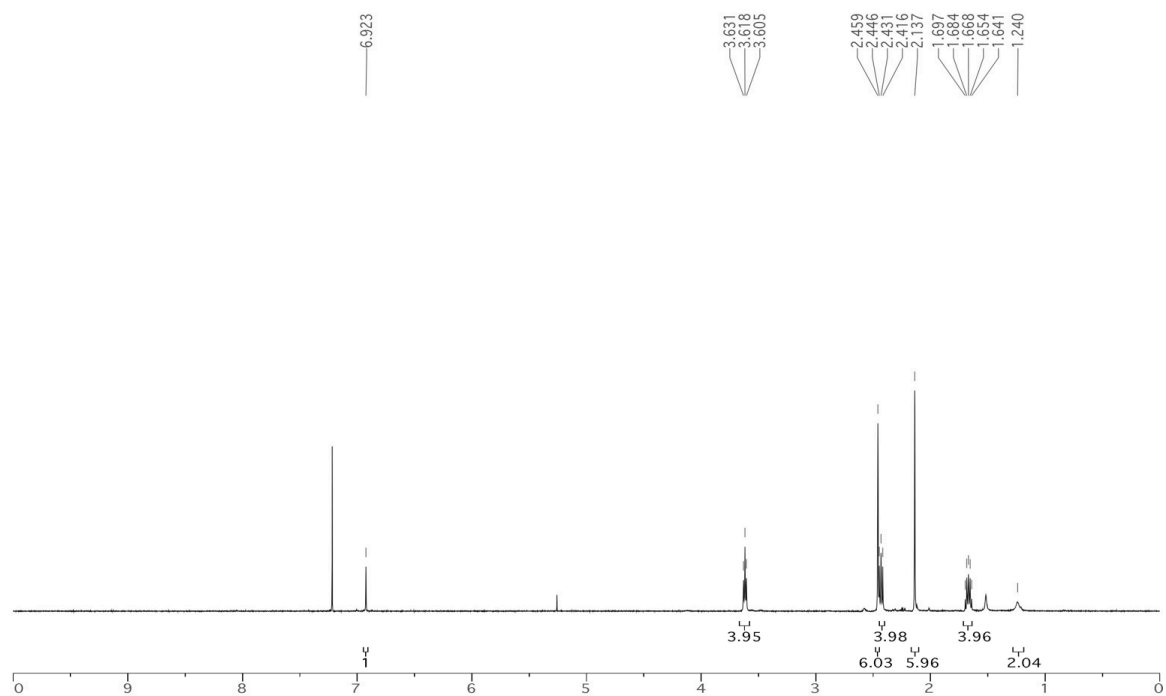


^{11}B NMR spectrum in CDCl_3 , 160 MHz

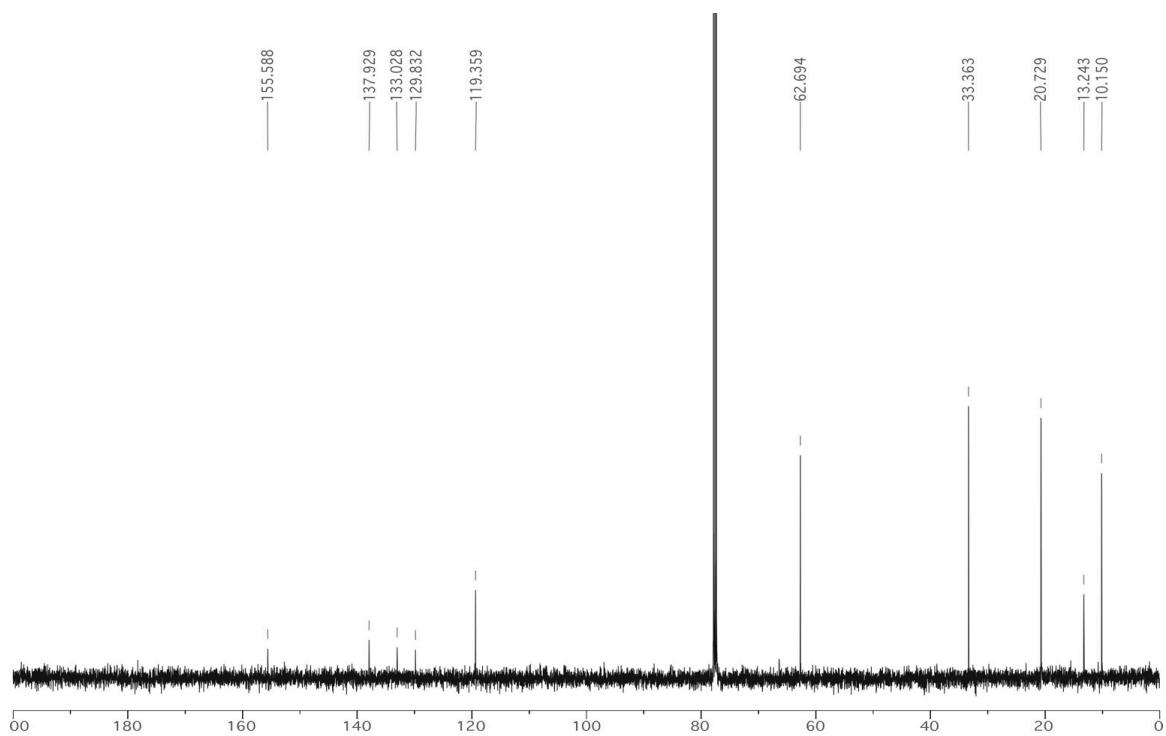


4,4-Difluoro-1,3,5,7-tetramethyl-2,6-di-3-hydroxypropyl-4-bora-3a,4a-diaza-s-indacene (2.36)

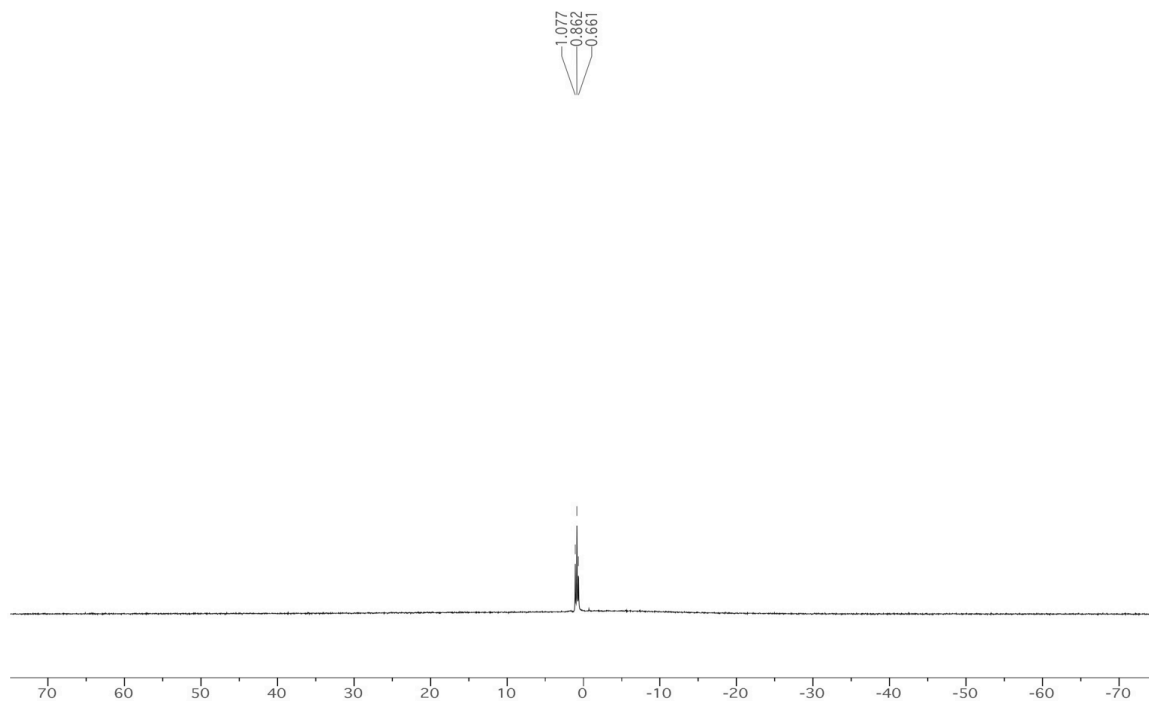
^1H NMR spectrum in CDCl_3 , 500 MHz



^{13}C NMR spectrum in CDCl_3 , 125 MHz

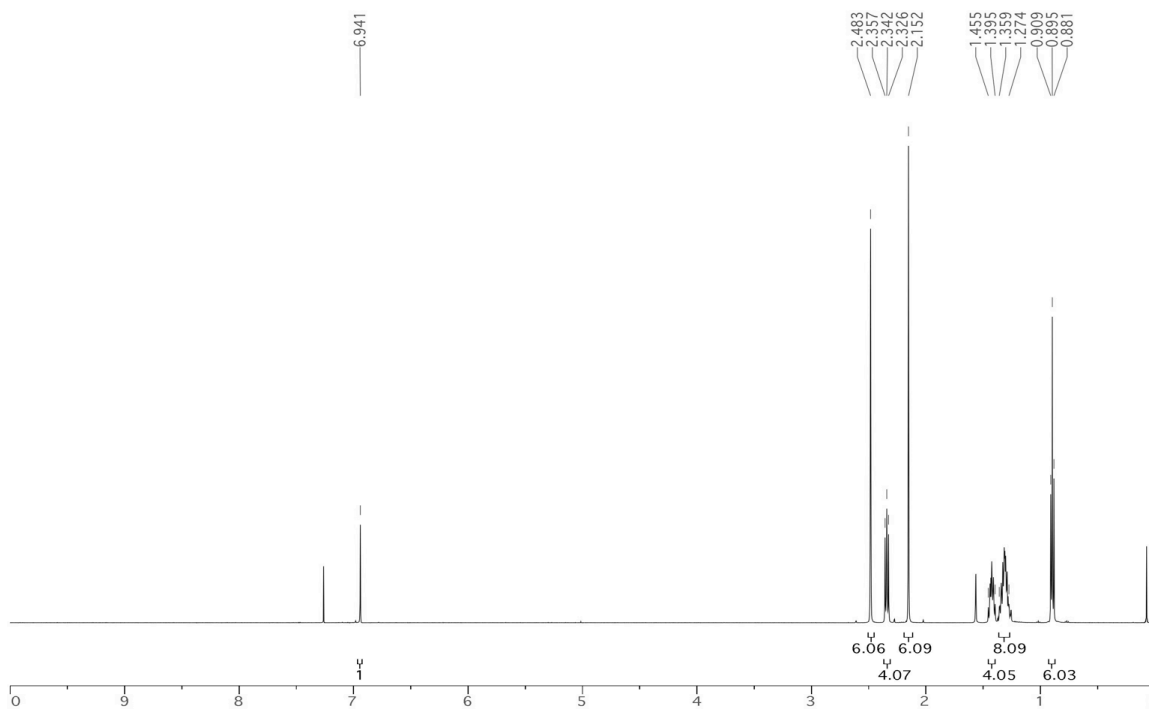


^{11}B NMR spectrum in CDCl_3 , 160 MHz

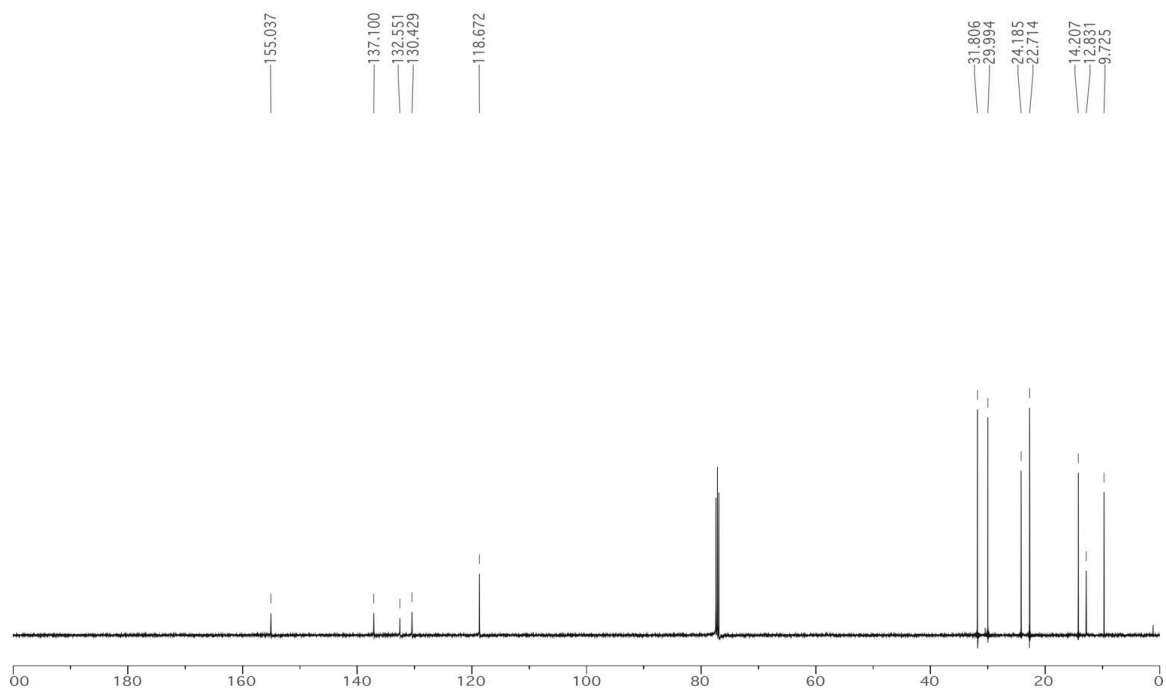


4,4-Difluoro-1,3,5,7-tetramethyl-2,6-dipentyl-4-bora-3a,4a-diaza-s-indacene (2.37)

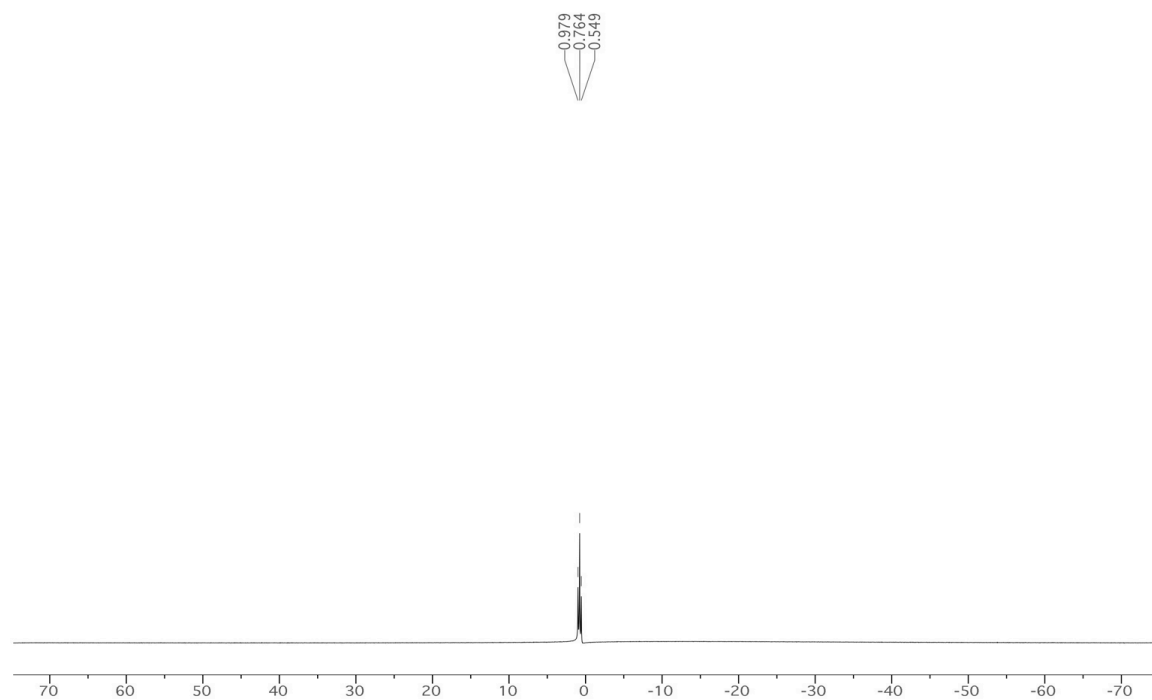
^1H NMR spectrum in CDCl_3 , 500 MHz



^{13}C NMR spectrum in CDCl_3 , 125 MHz



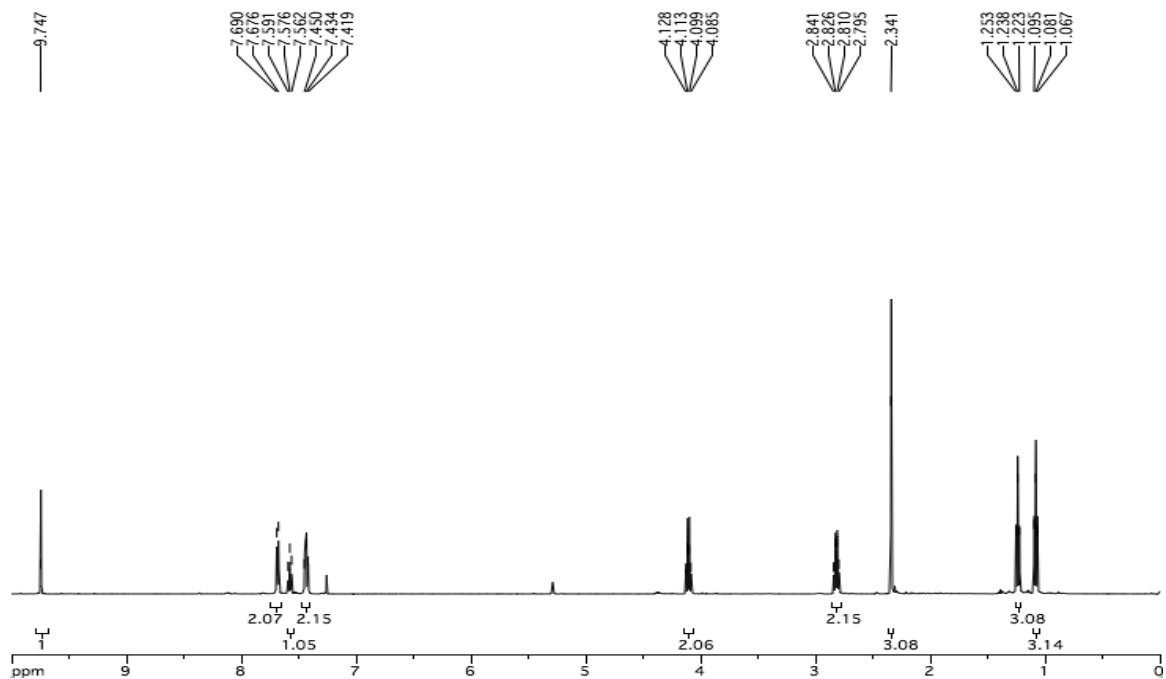
^{11}B NMR spectrum in CDCl_3 , 160 MHz



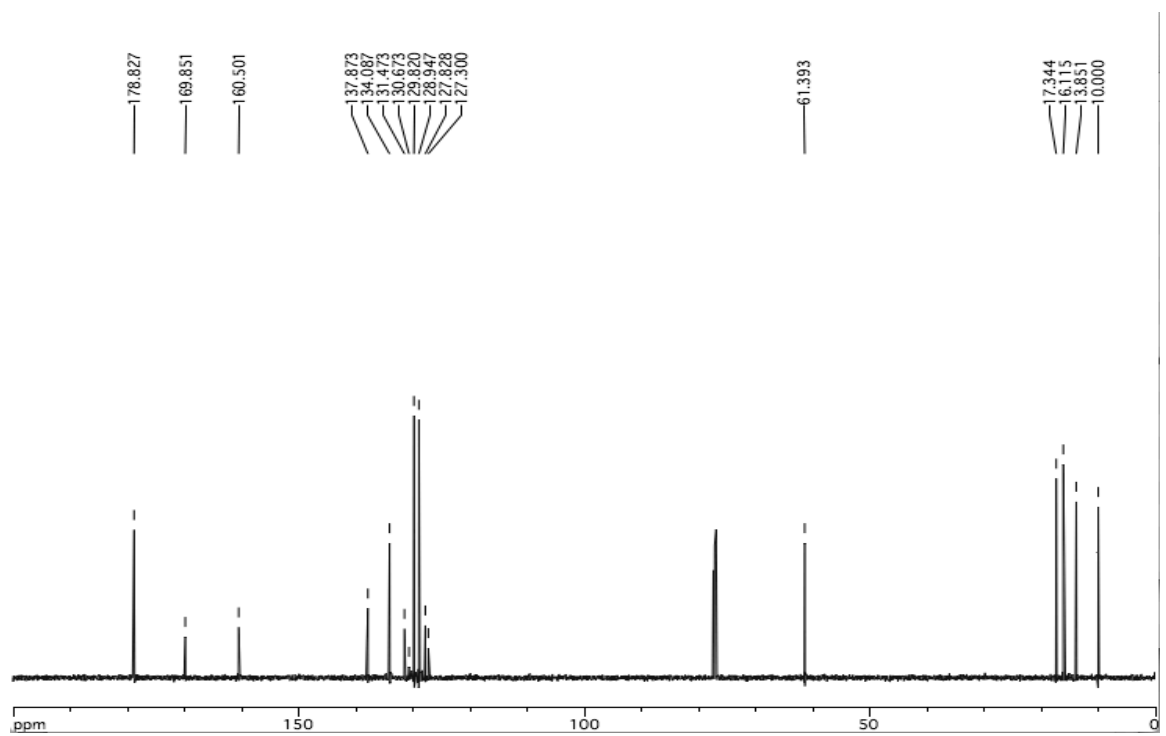
Appendix 3. NMR Spectra for Chapter 3

Ethyl 1-benzoyl-4-ethyl-5-formyl-3-methyl-1*H*-pyrrole-2-carboxylate

^1H NMR spectrum in CDCl_3 , 500 MHz

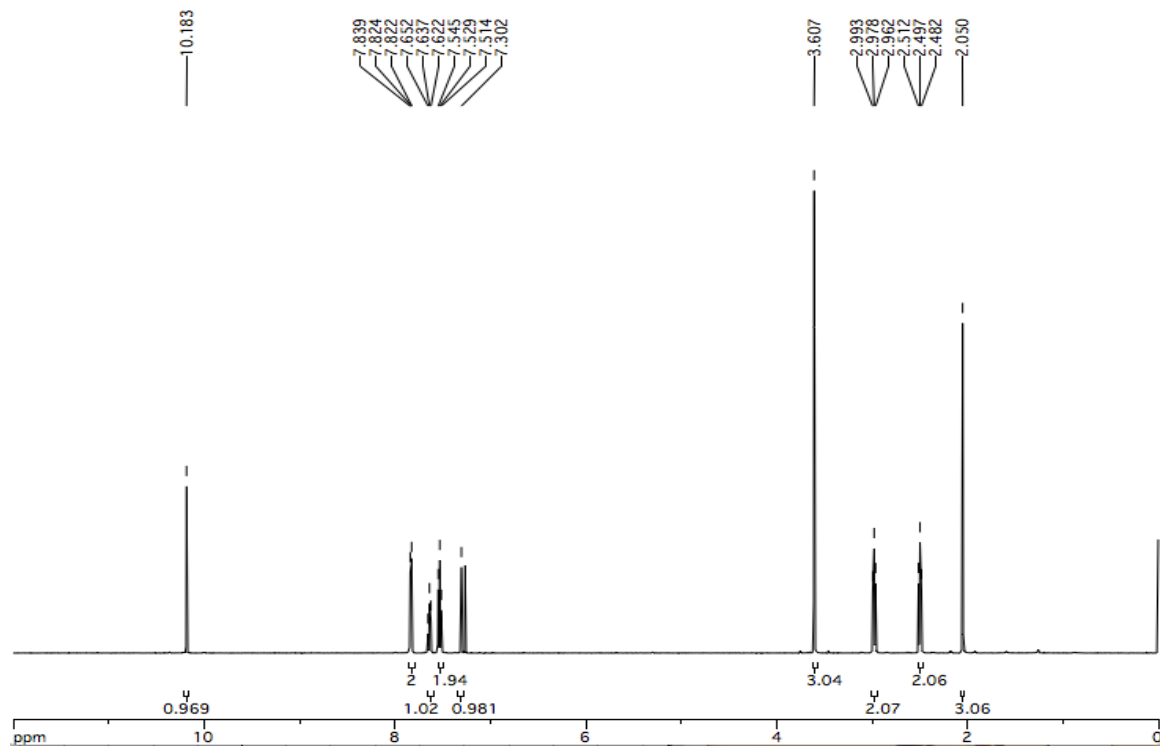


^{13}C NMR spectrum in CDCl_3 , 125 MHz

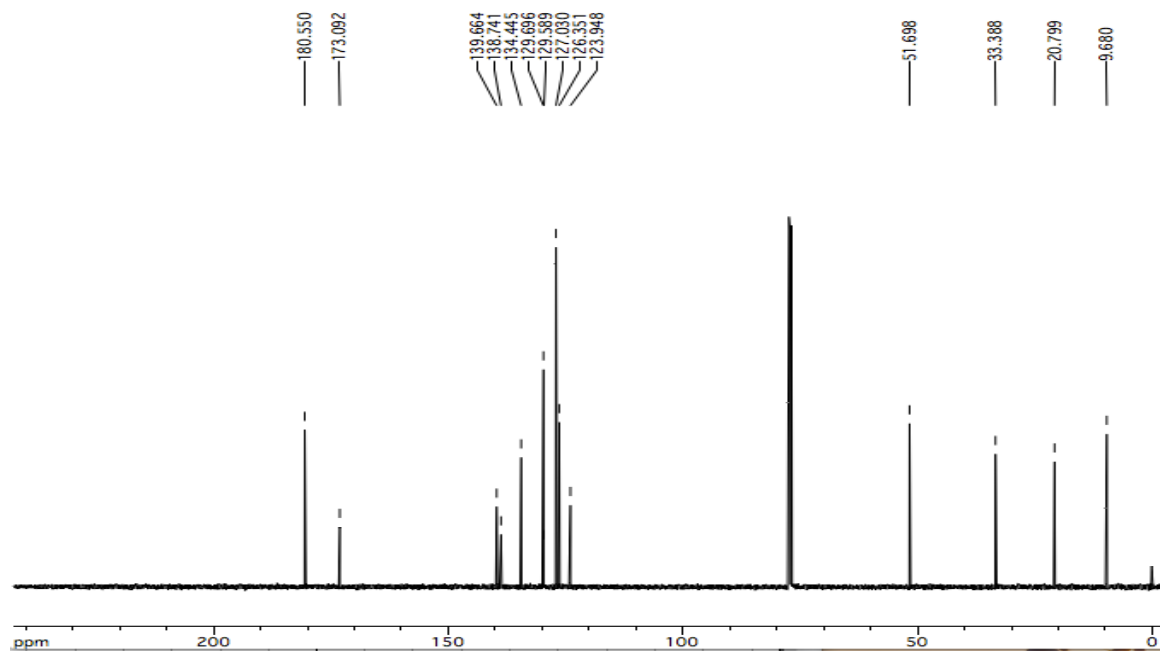


3-(2-Methoxycarbonylethyl)-4-methyl-1-(phenylsulfonyl)-1*H*-pyrrole-2-carbaldehyde

¹H NMR spectrum in CDCl₃, 500 MHz

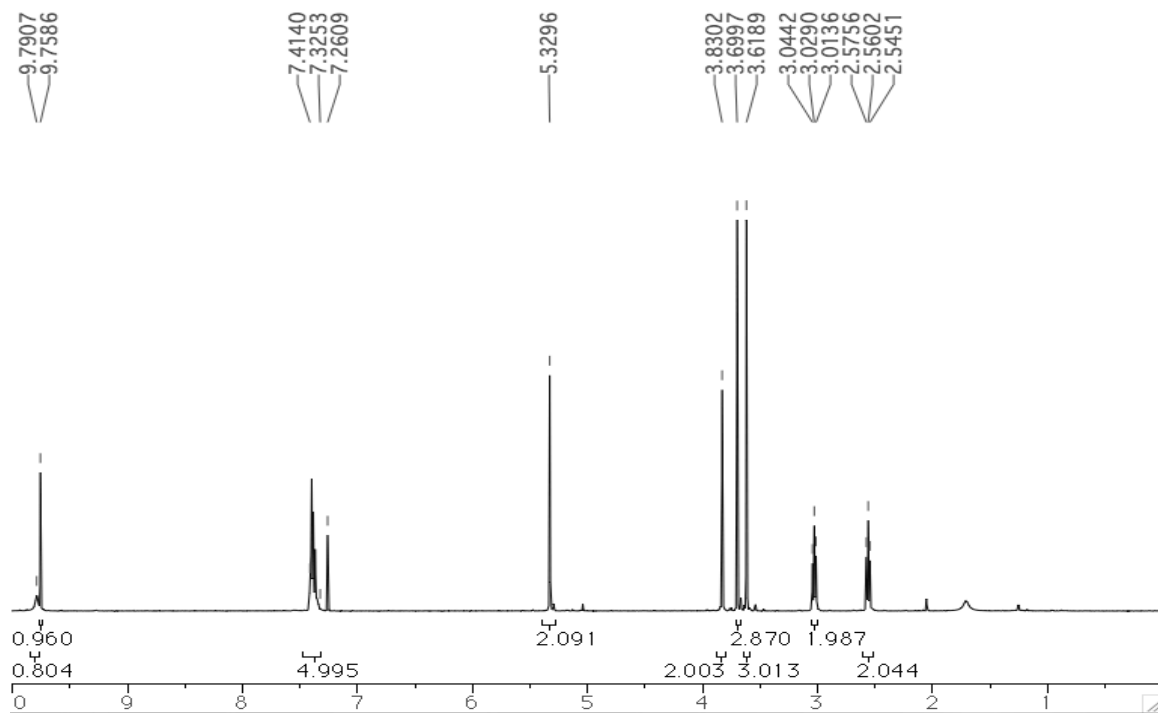


¹³C NMR spectrum in CDCl₃, 125 MHz

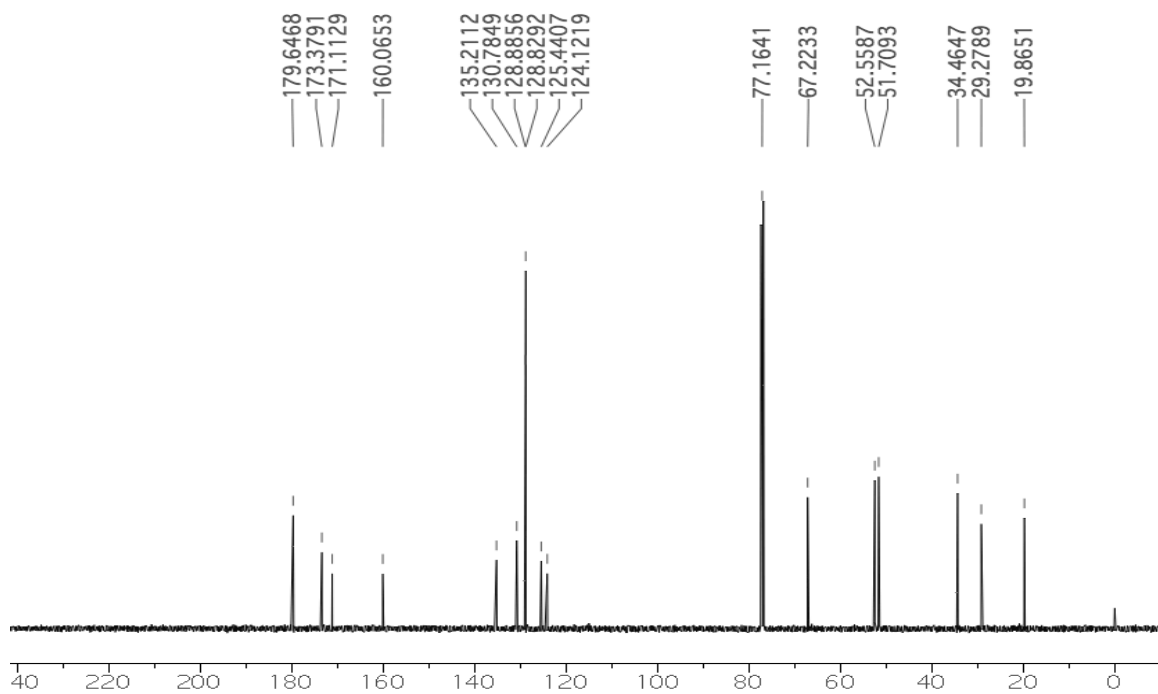


Benzyl 5-formyl-3-(2-methoxycarbonyl-ethyl)-4-(methoxycarbonylmethyl)-1H-pyrrole-2-carboxylate

^1H NMR spectrum in CDCl_3 , 500 MHz

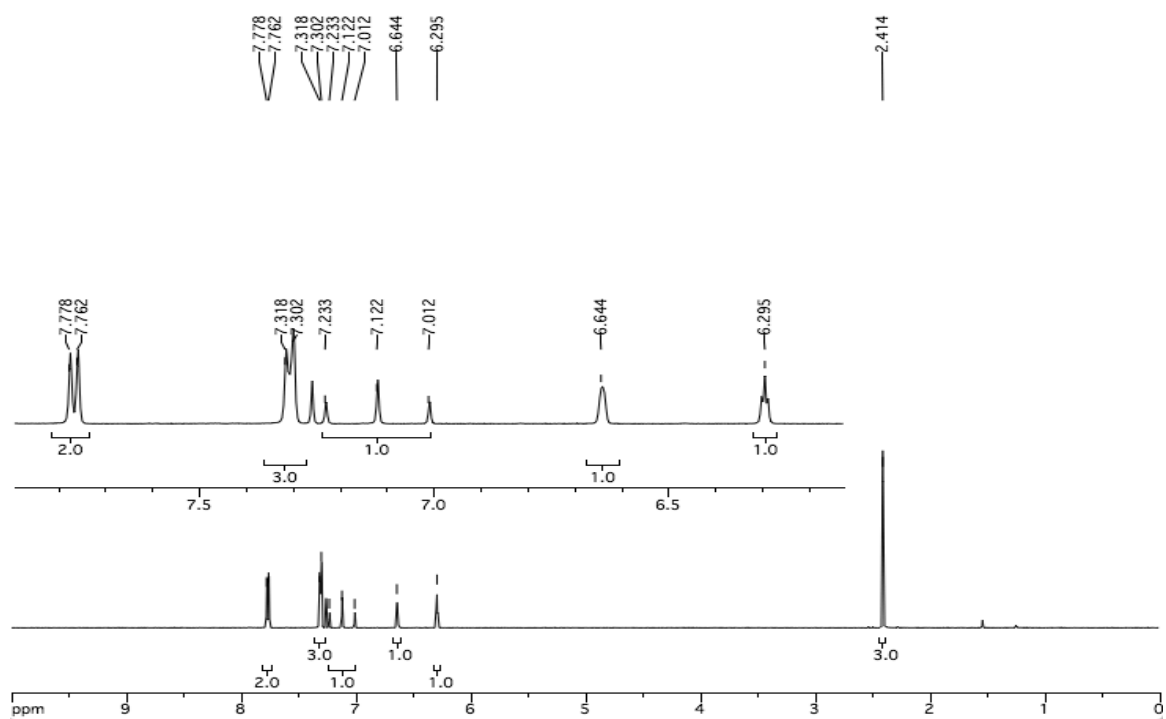


^{13}C NMR spectrum in CDCl_3 , 125 MHz

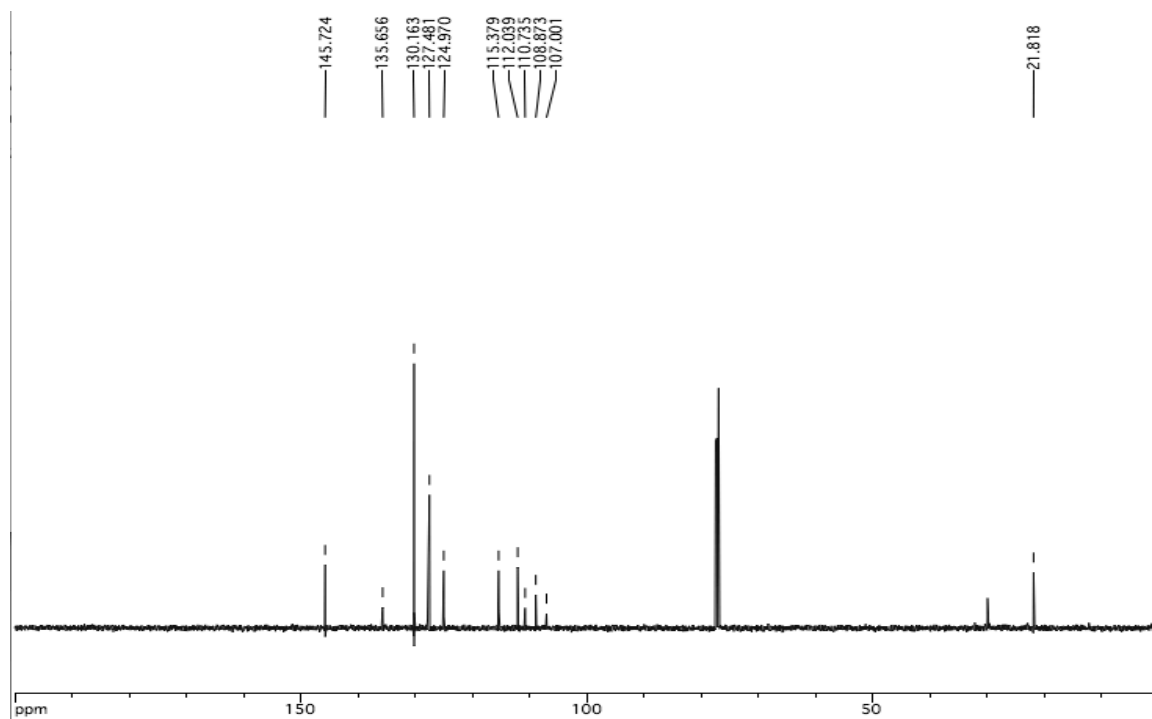


2-(Difluoromethyl)-1-(tosyl)-1H-pyrrole (3.34)

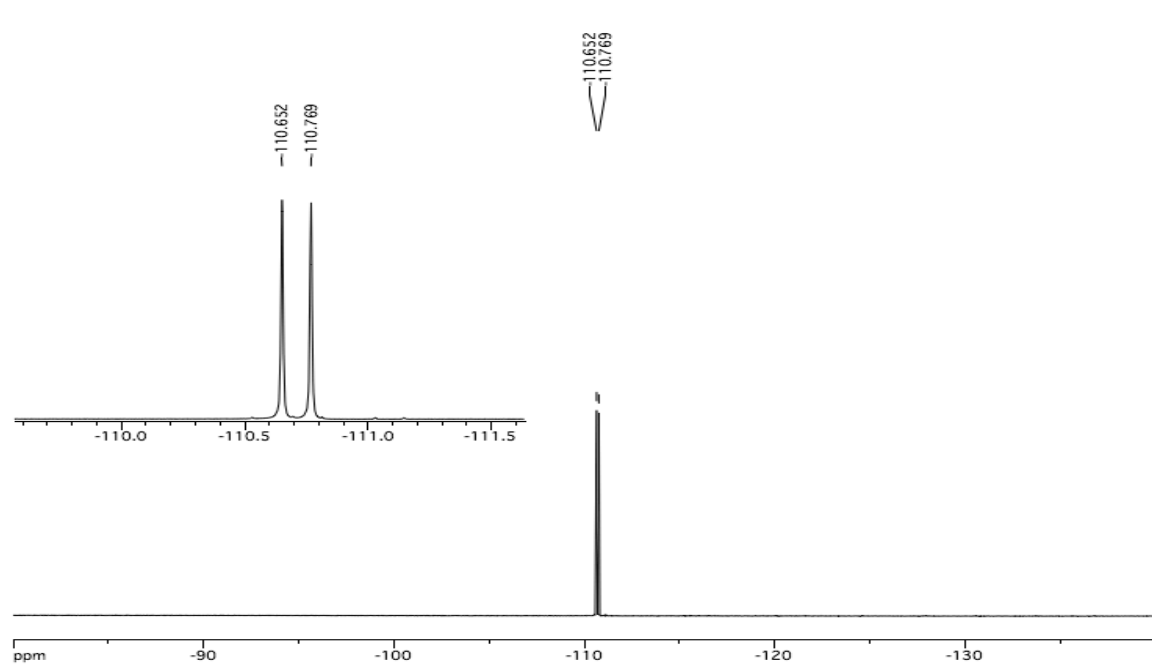
^1H NMR spectrum in CDCl_3 , 500 MHz



^{13}C NMR spectrum in CDCl_3 , 125 MHz

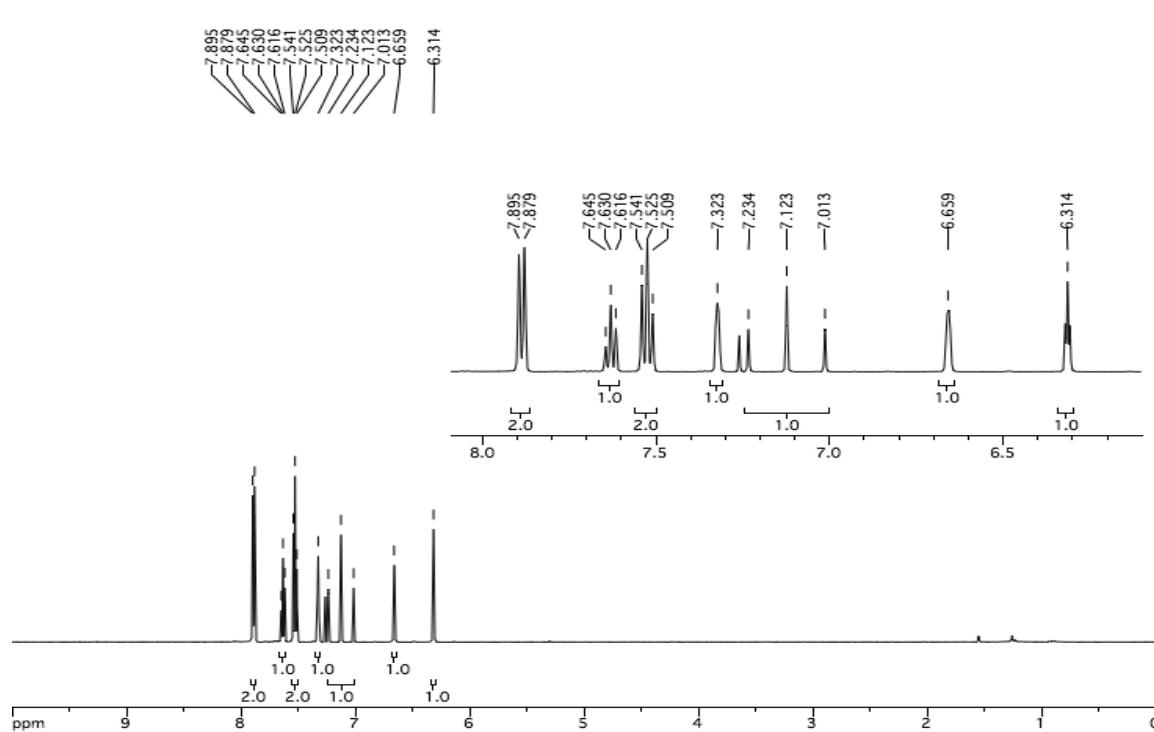


^{19}F NMR spectrum in CDCl_3 , 470 MHz

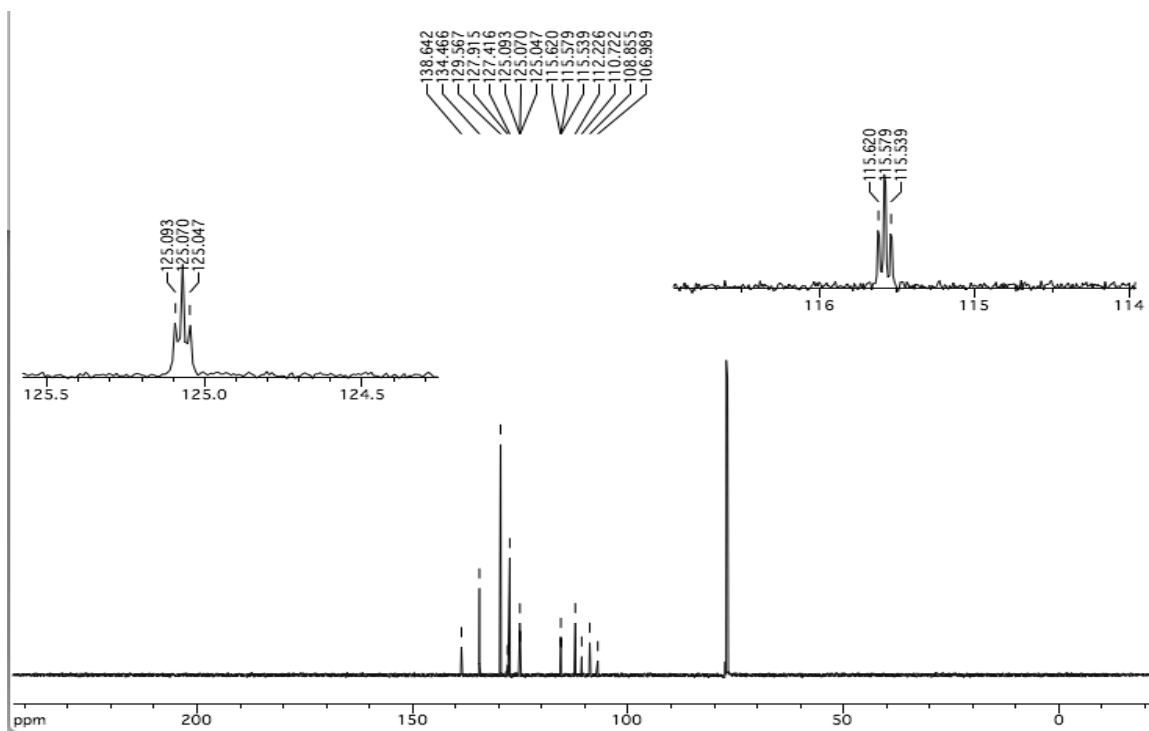


2-(Difluoromethyl)-1-(phenylsulfonyl)-1H-pyrrole (3.35)

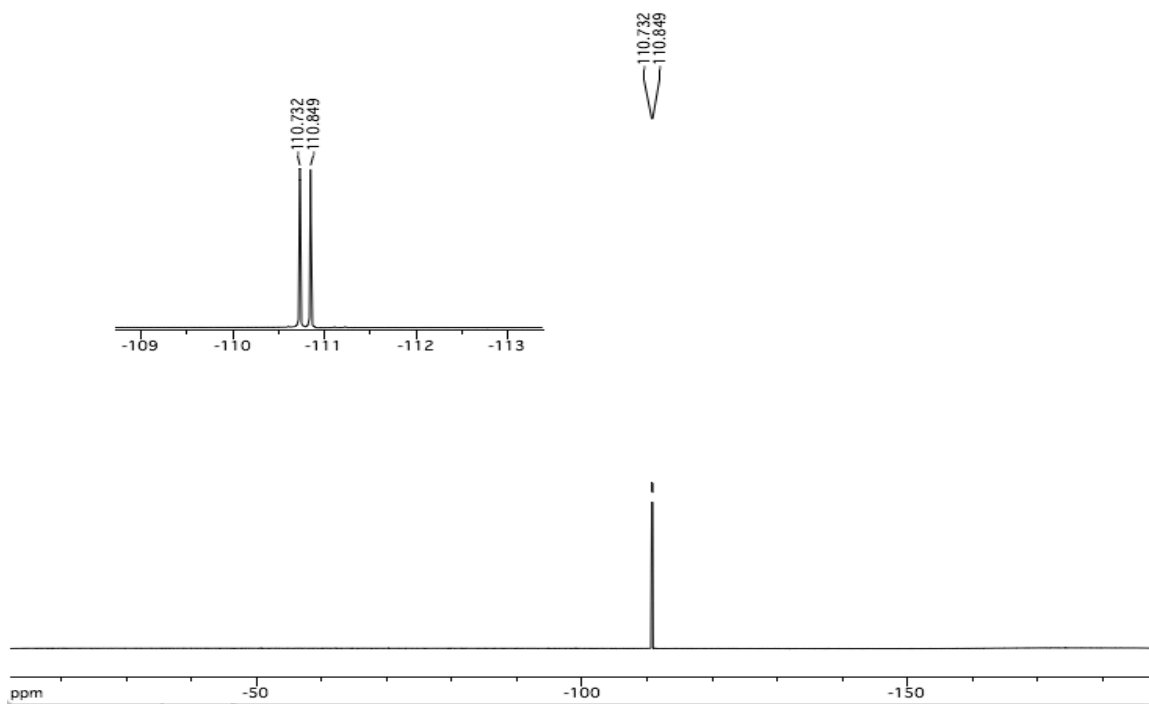
^1H NMR spectrum in CDCl_3 , 500 MHz



^{13}C NMR spectrum in CDCl_3 , 125 MHz

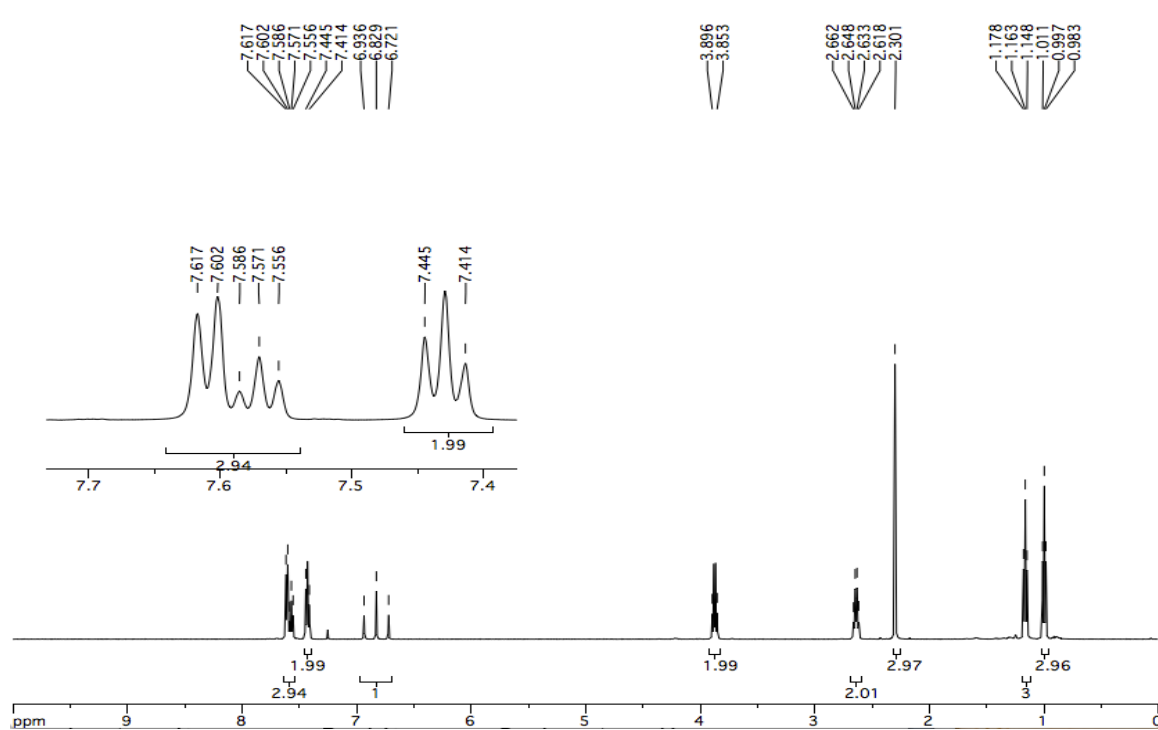


^{19}F NMR spectrum in CDCl_3 , 470 MHz

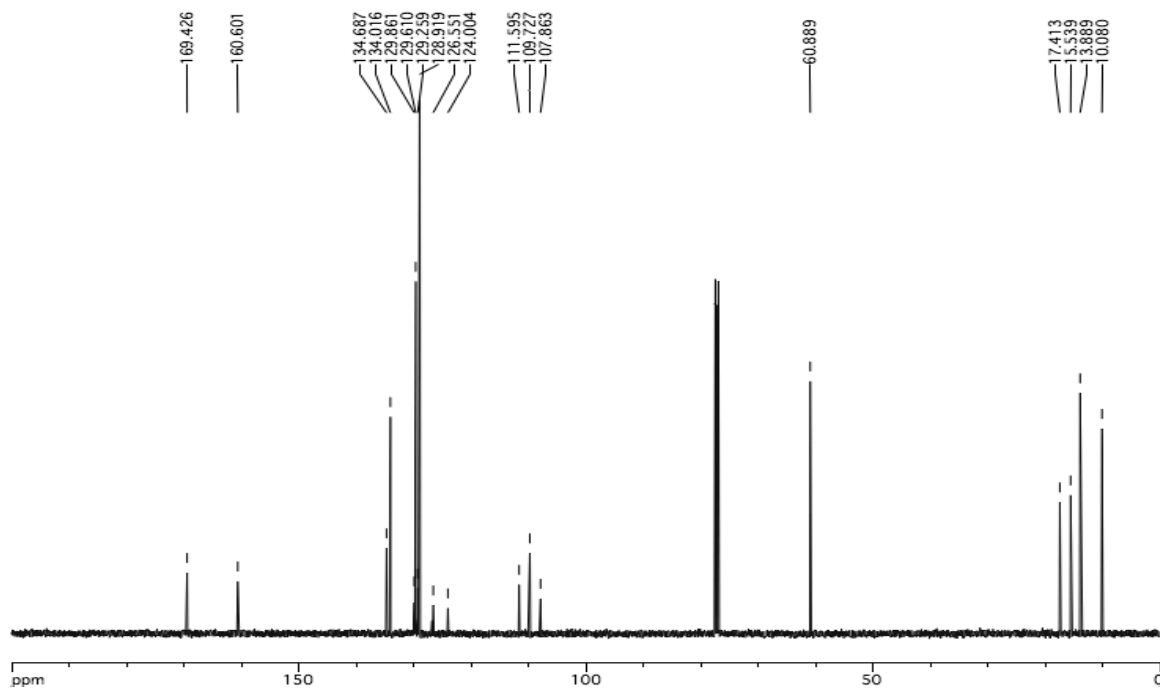


Ethyl 1-benzoyl-5-(difluoromethyl)-4-ethyl-3-methyl-1H-pyrrole-2-carboxylate (3.37)

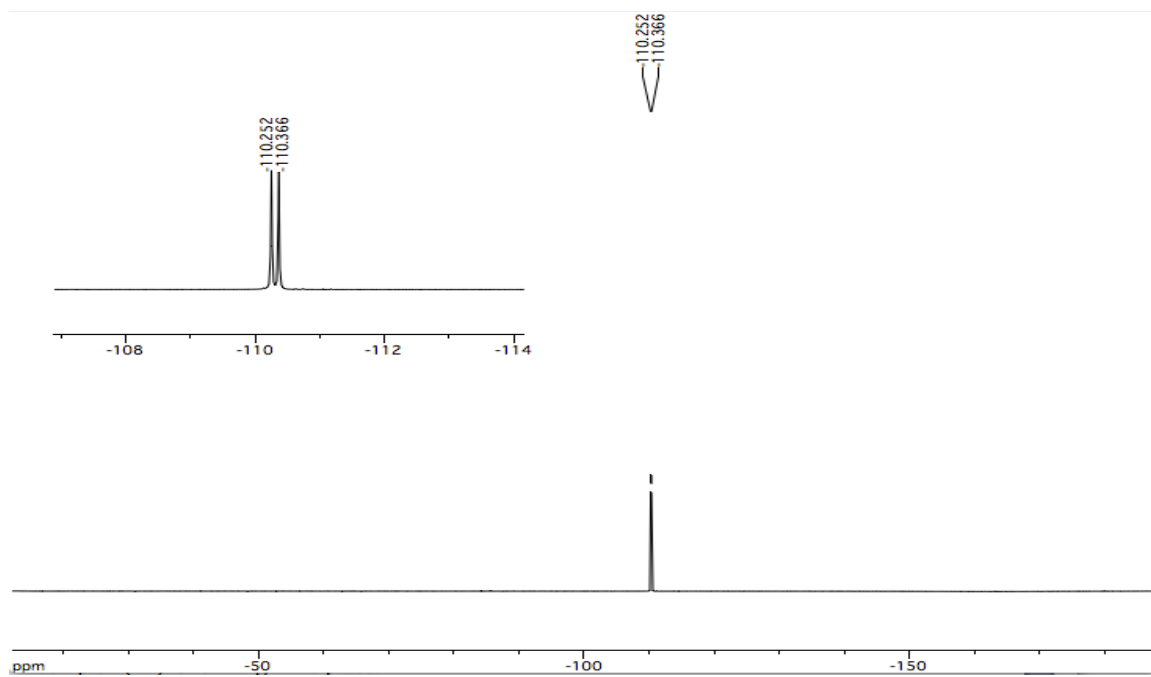
¹H NMR spectrum in CDCl₃, 500 MHz



¹³C NMR spectrum in CDCl₃, 125 MHz

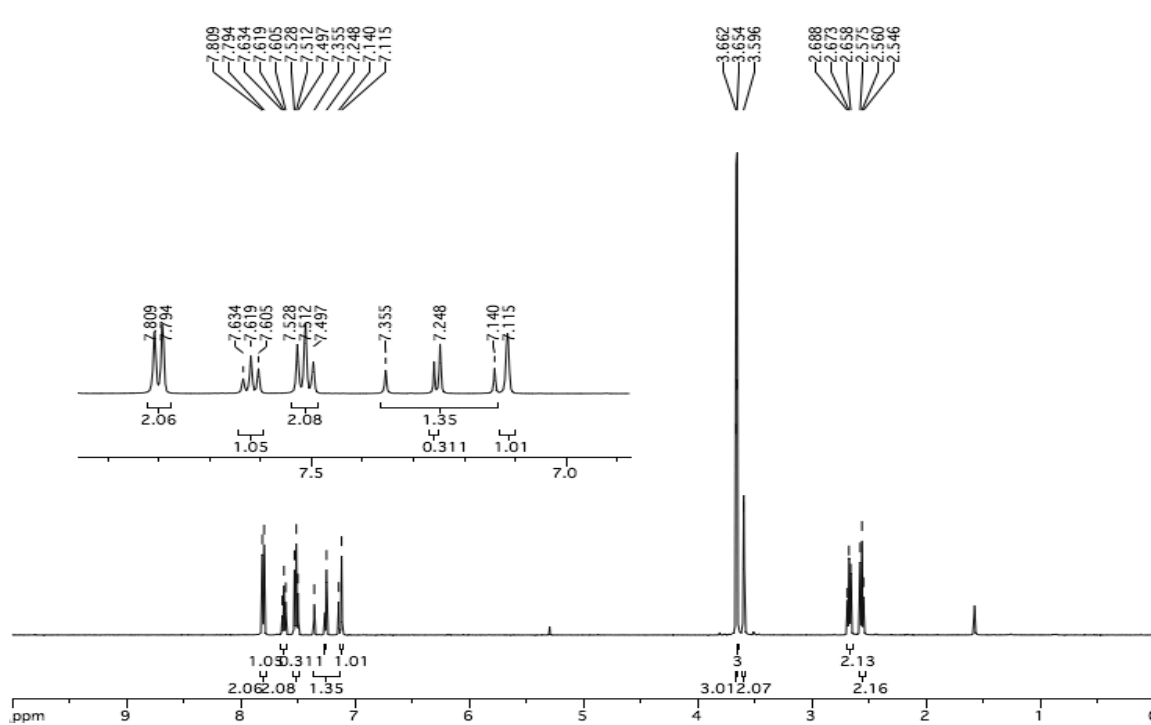


^{19}F NMR spectrum in CDCl_3 , 470 MHz

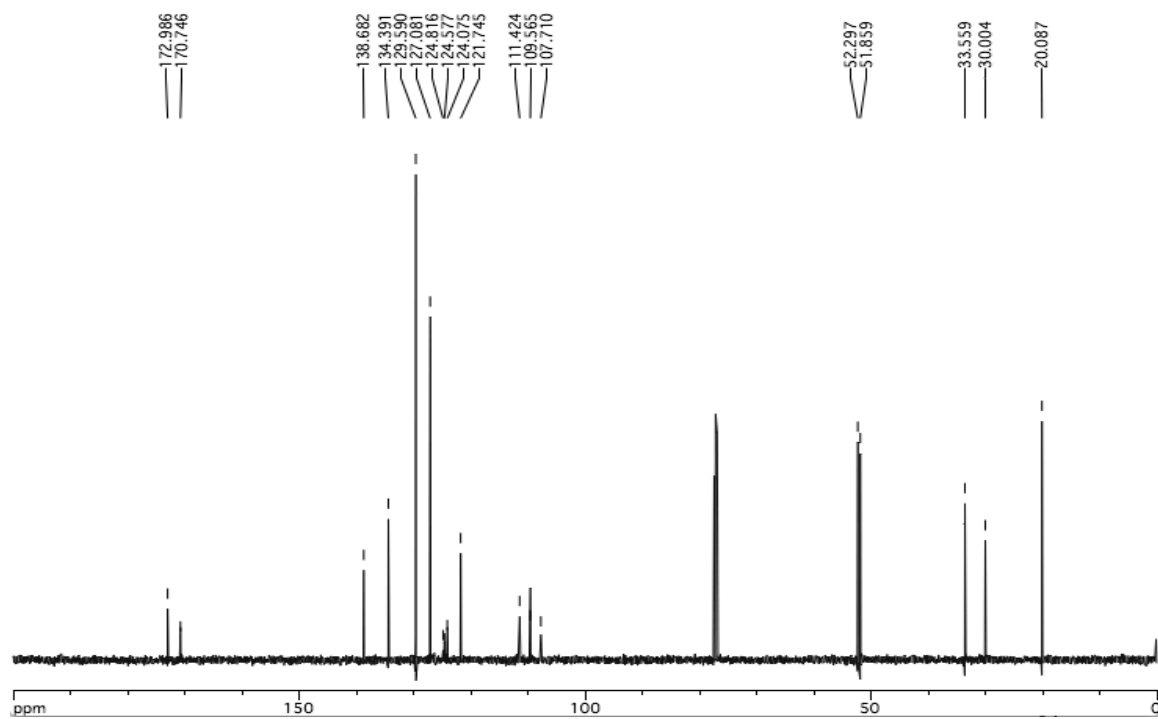


2-(Difluoromethyl)-4-(2-methoxycarbonyl-ethyl)-3-(methoxycarbonylmethyl)-1-(phenylsulfonyl)-1H-pyrrole (3.39)

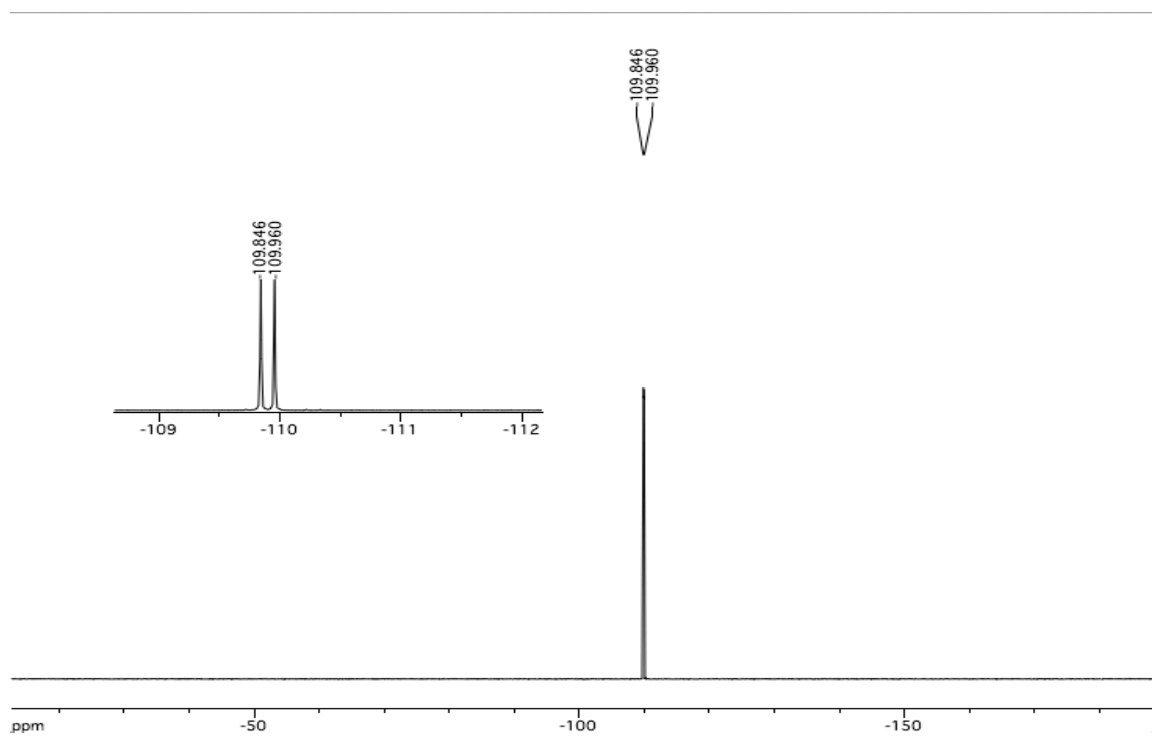
^1H NMR spectrum in CDCl_3 , 500 MHz



^{13}C NMR spectrum in CDCl_3 , 125 MHz

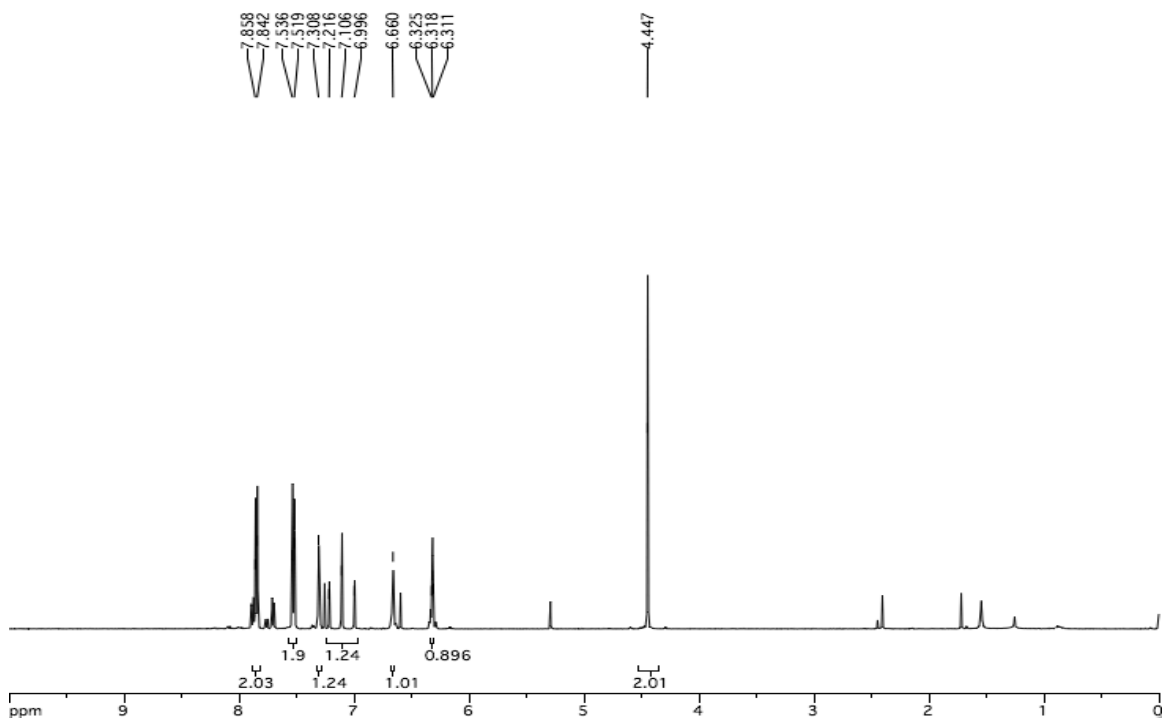


^{19}F NMR spectrum in CDCl_3 , 470 MHz



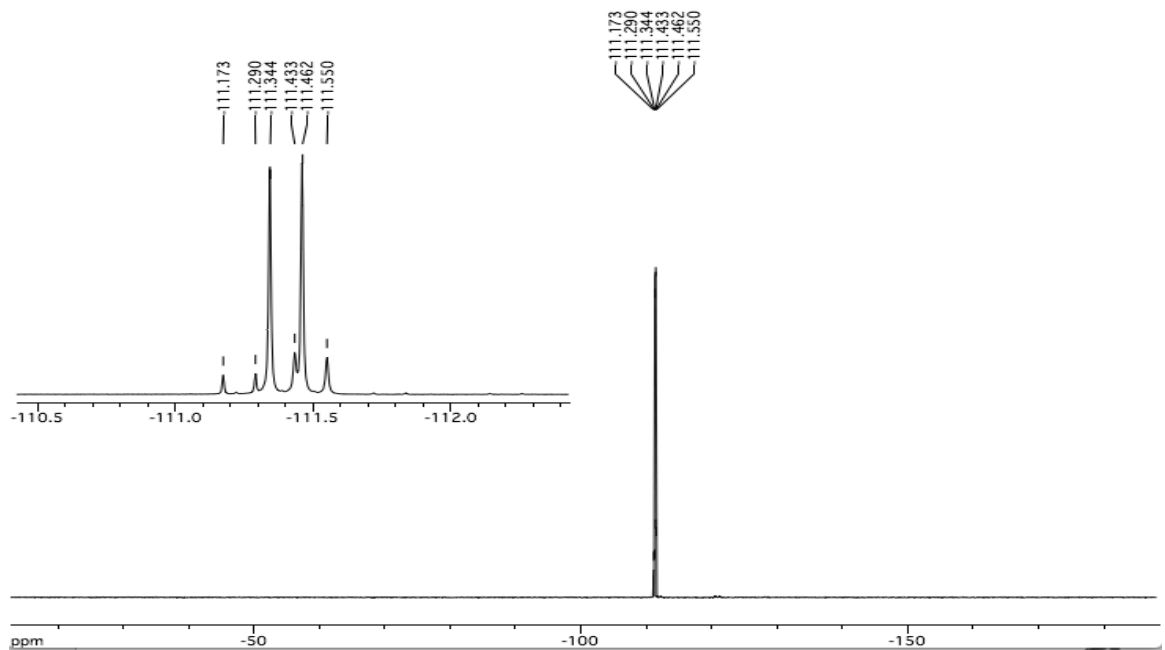
1-(4-(Bromomethyl)phenylsulfonyl)-2-(difluoromethyl)-1H-pyrrole (3.49)

^1H NMR spectrum in CDCl_3 , 500 MHz



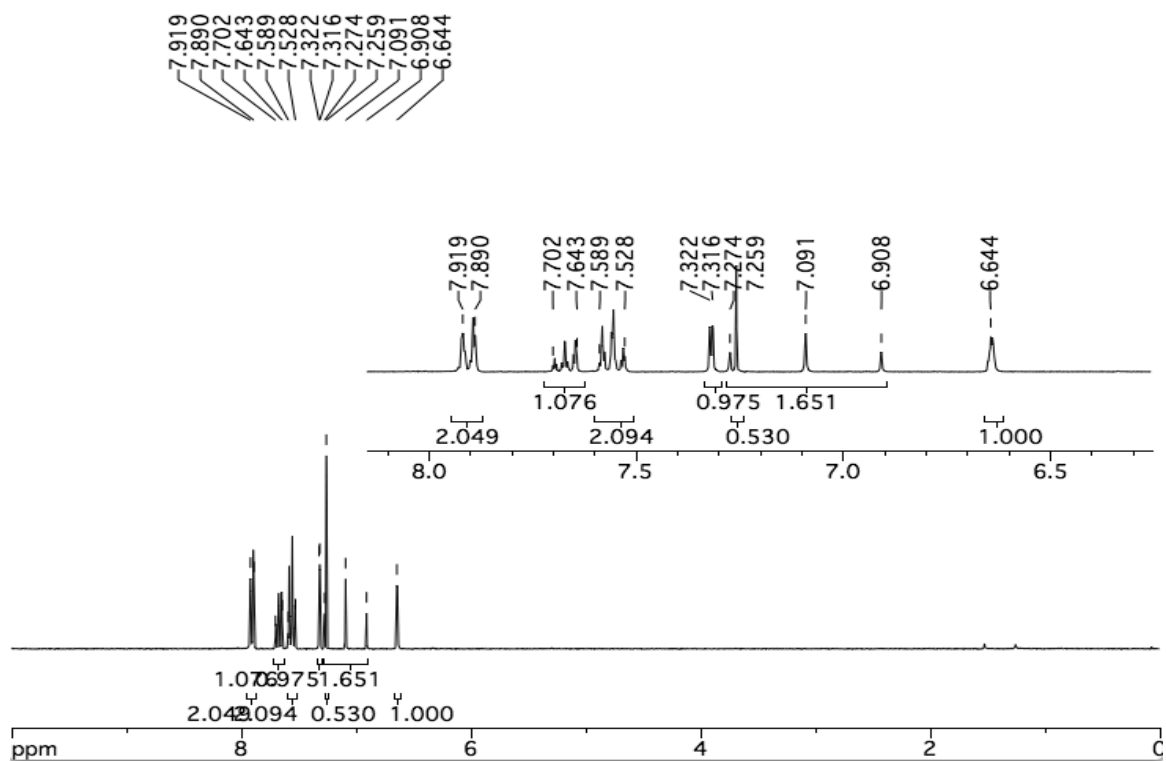
^{19}F NMR spectrum in CDCl_3 , 470 MHz

*Note other minor products that afford signals at -111.2 (d, $J = 55$) and -111.5 (d, $J = 55$)

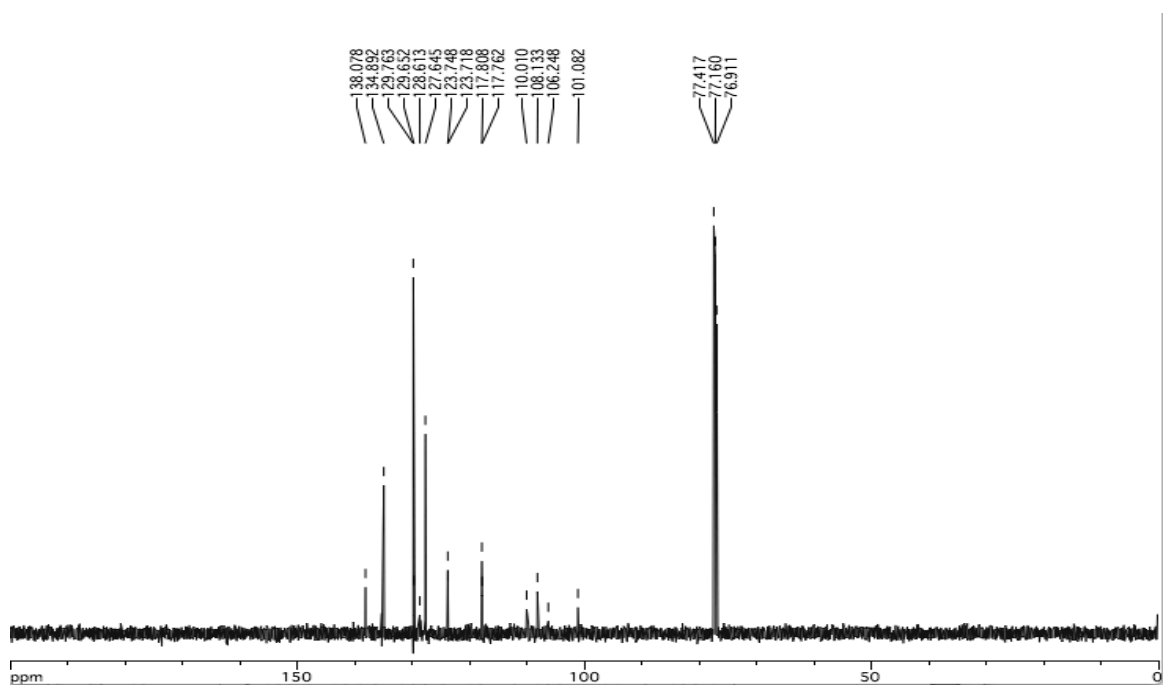


4-Bromo-2-(difluoromethyl)-1-(phenylsulfonyl)-1H-pyrrole (3.51)

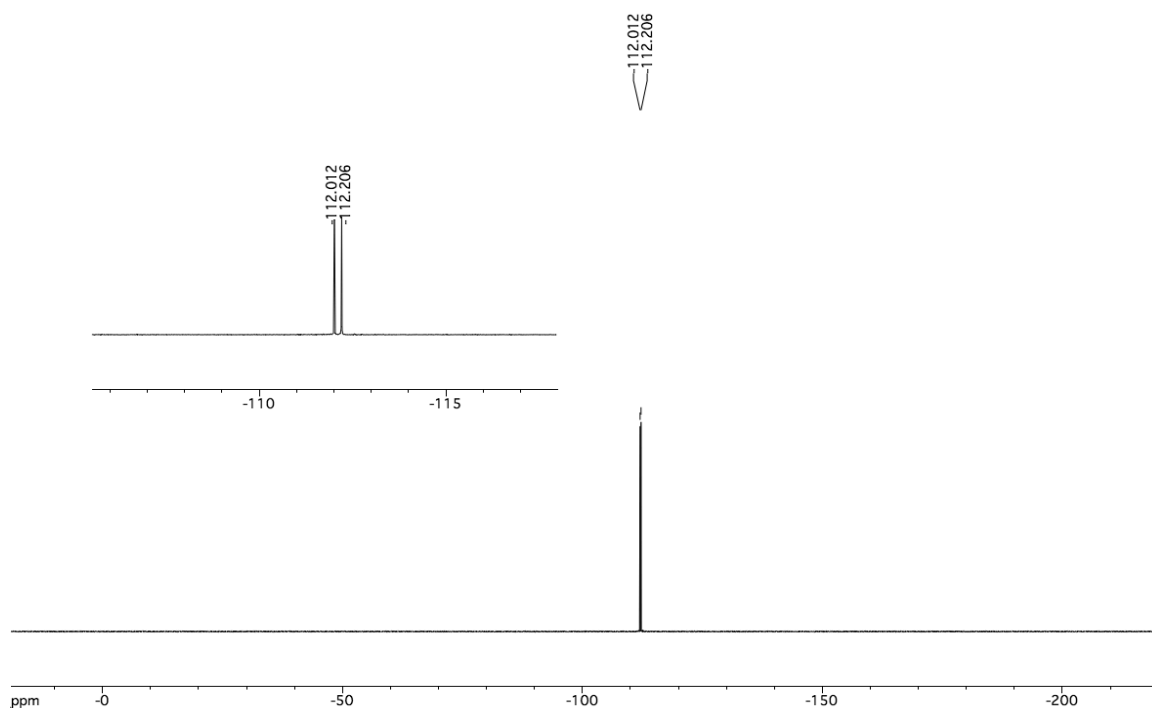
^1H NMR spectrum in CDCl_3 , 300 MHz



^{13}C NMR spectrum in CDCl_3 , 125 MHz

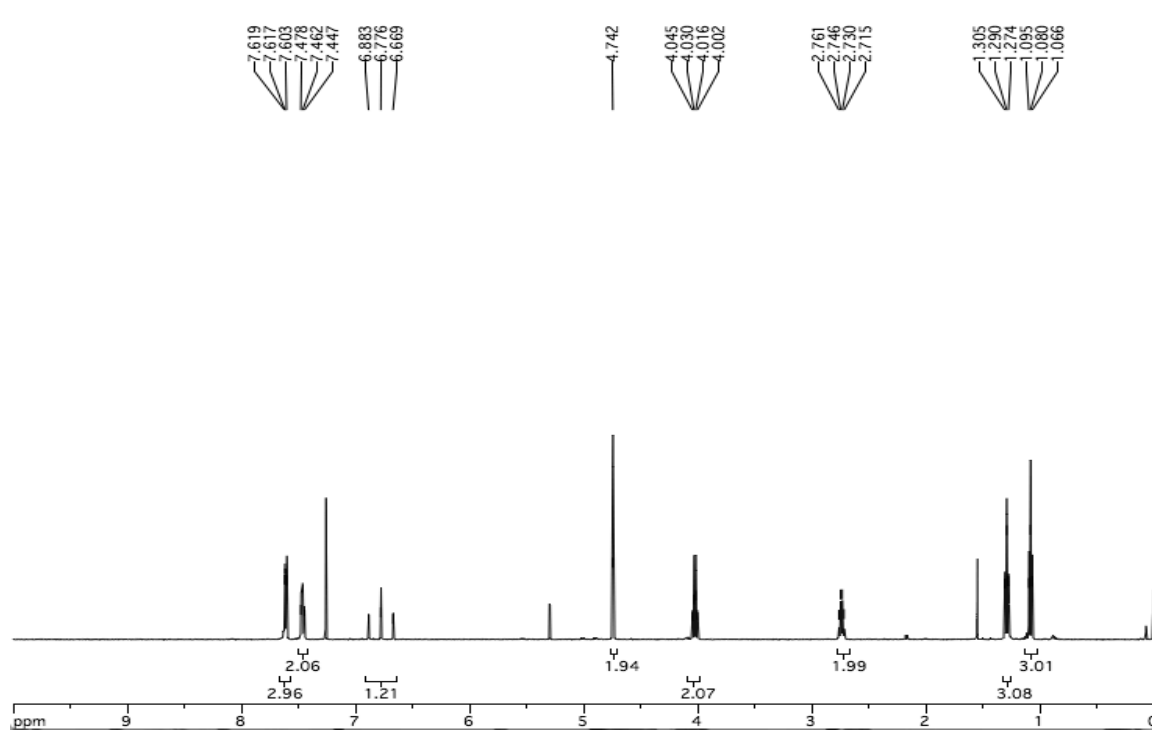


^{19}F NMR spectrum in CDCl_3 , 282 MHz

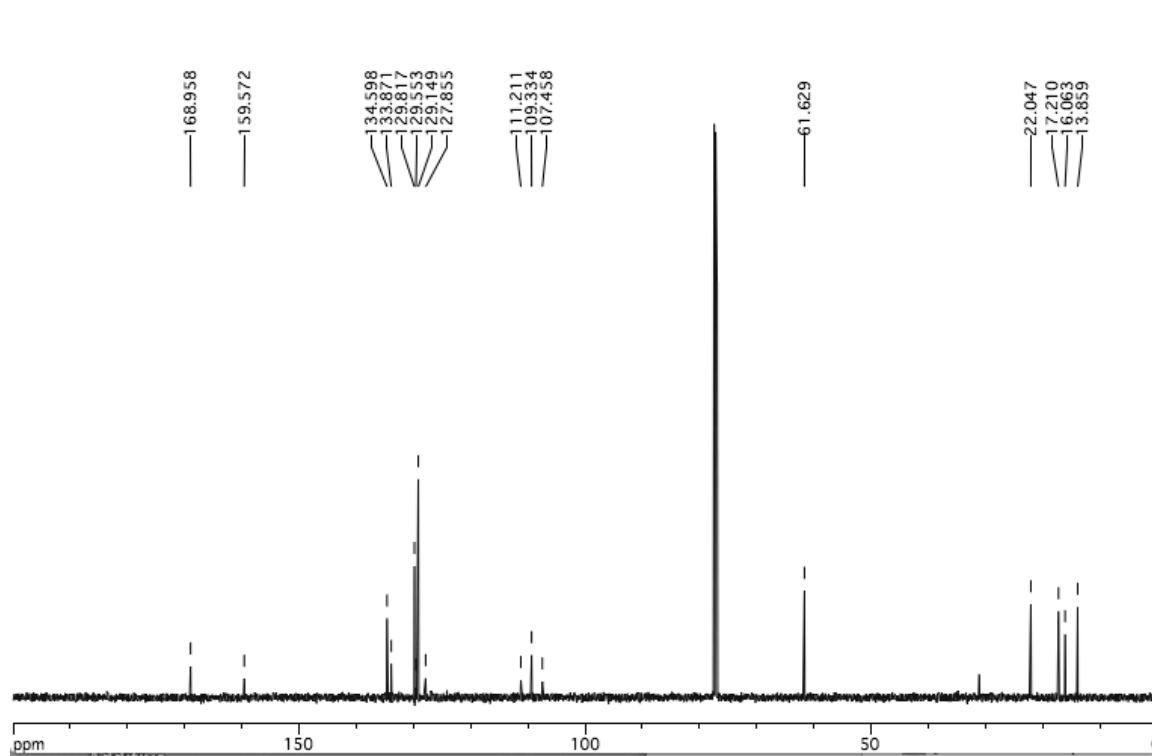


Ethyl 1-benzoyl-3-(bromomethyl)-5-(difluoromethyl)-4-ethyl-1H-pyrrole-2-carboxylate (3.53)

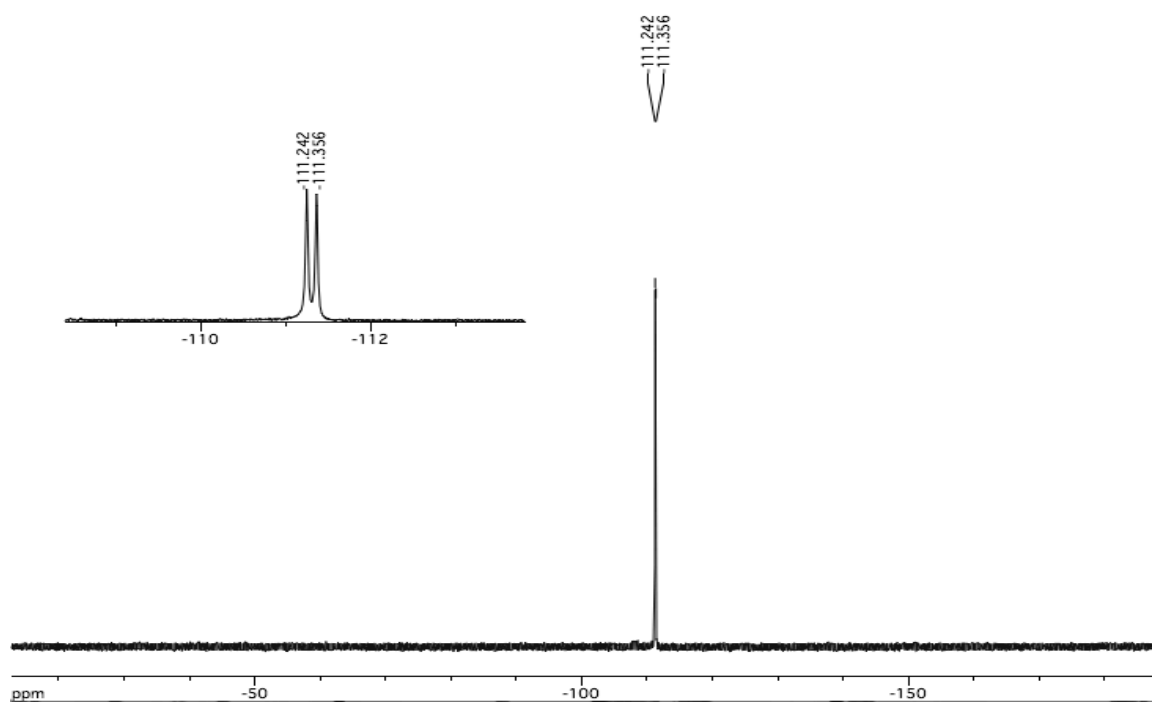
^1H NMR spectrum in CDCl_3 , 500 MHz



^{13}C NMR spectrum in CDCl_3 , 125 MHz

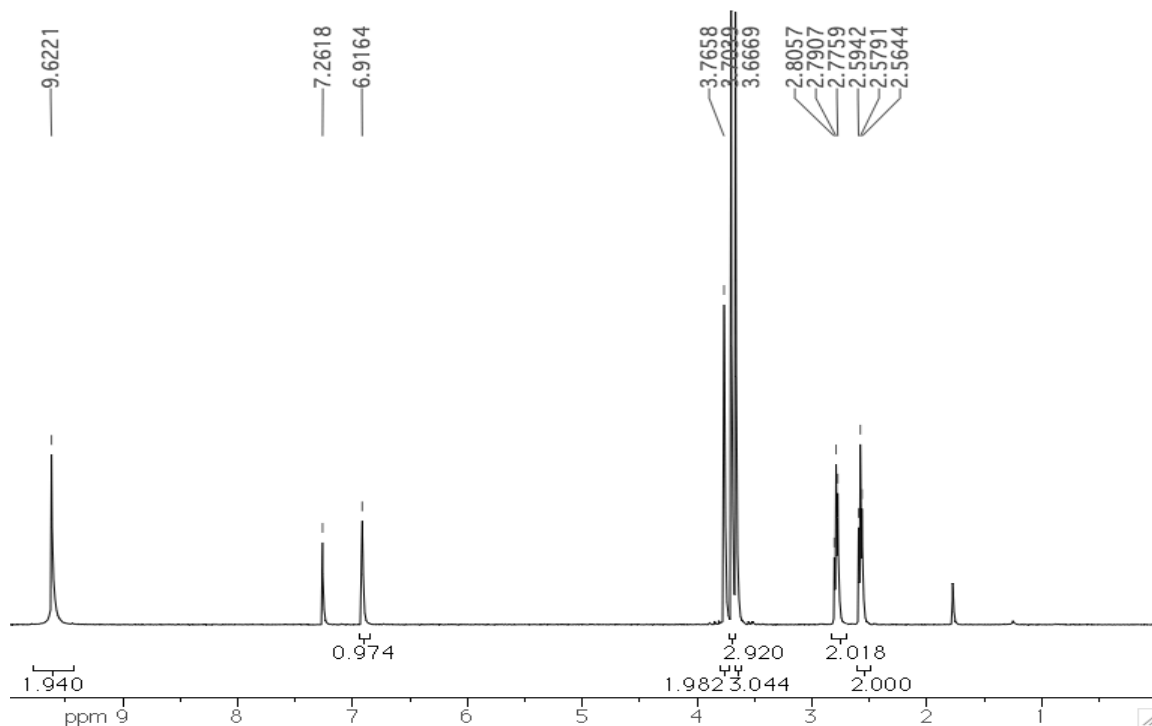


^{19}F NMR spectrum in CDCl_3 , 470 MHz

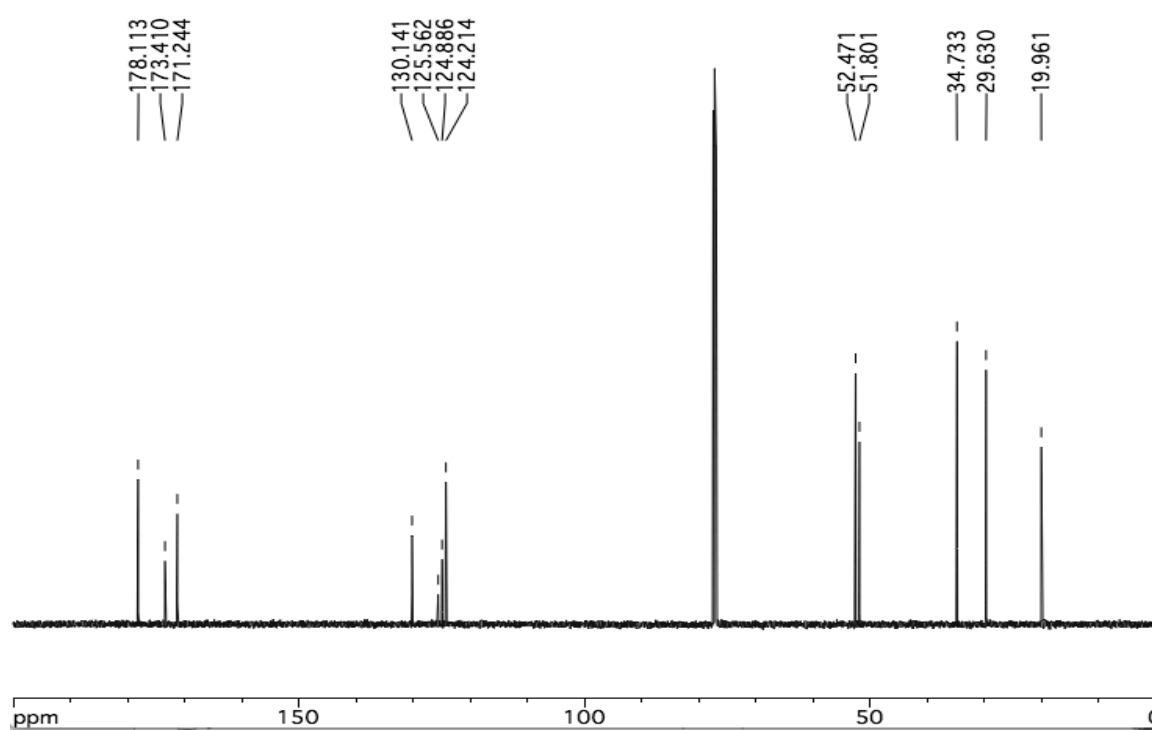


4-(2-Methoxycarbonyl-ethyl)-3-(methoxycarbonylmethyl)-1H-pyrrole-2-carbaldehyde (3.56)

^1H NMR spectrum in CDCl_3 , 500 MHz

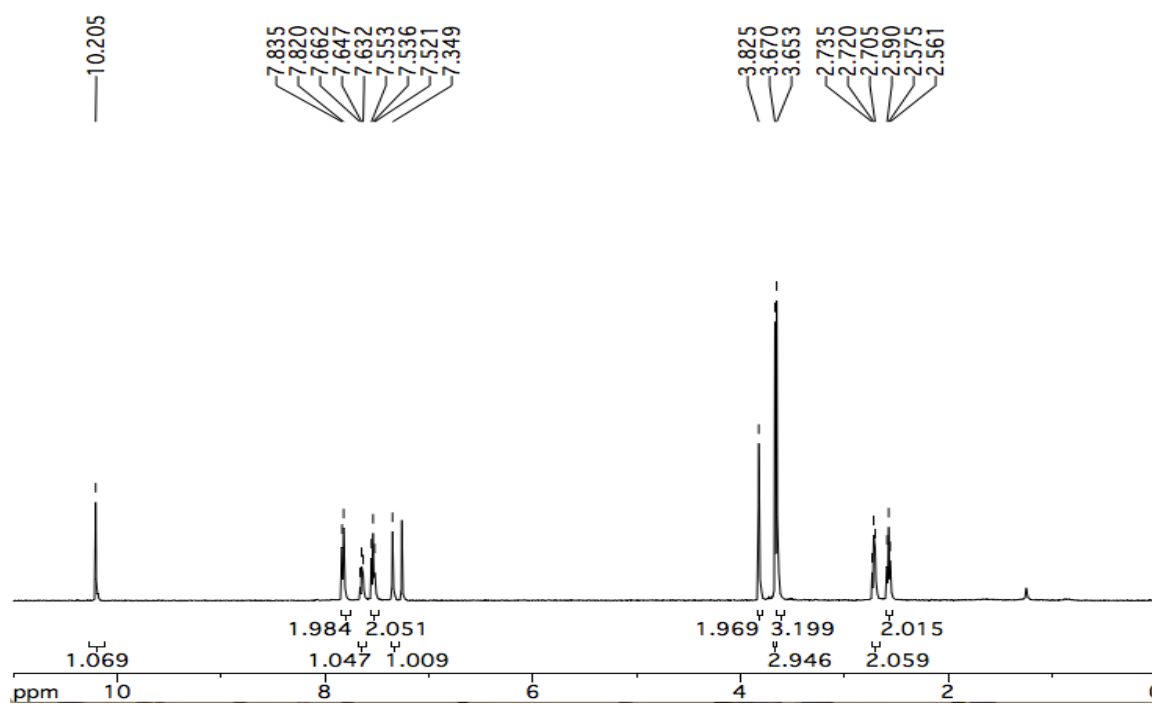


^{13}C NMR spectrum in CDCl_3 , 125 MHz

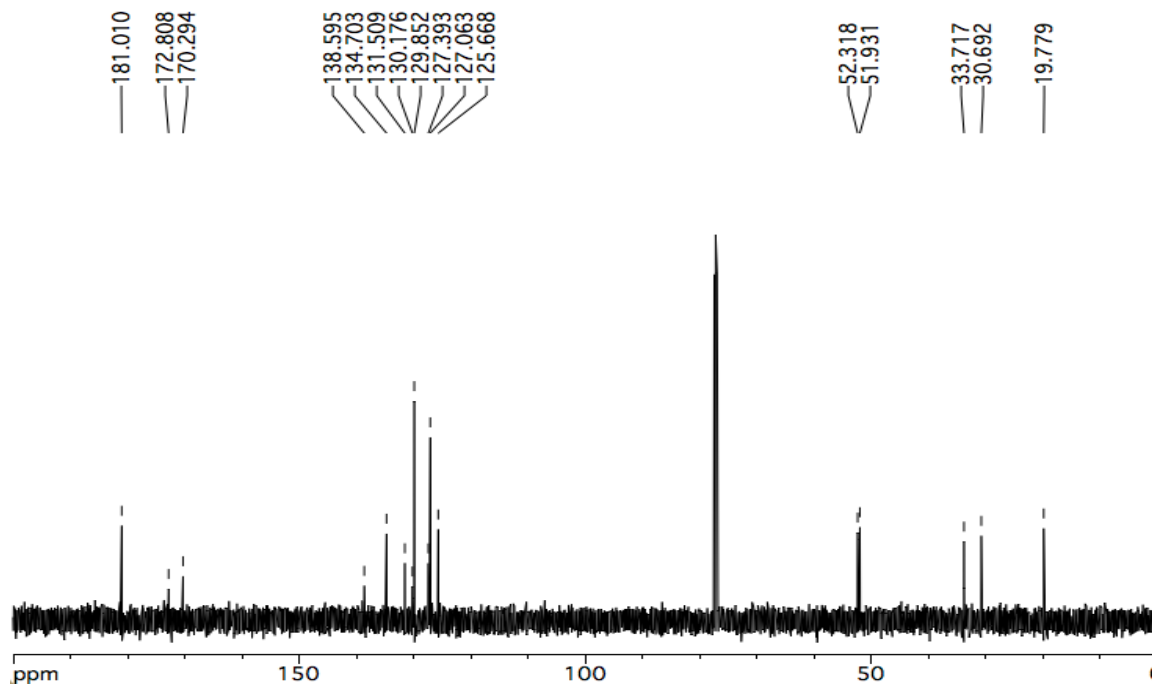


4-(2-Methoxycarboylethyl)-3-(methoxycarbonylmethyl)-1-(phenylsulfonyl)-1*H*-pyrrole-2-carbaldehyde (3.57)

¹H NMR spectrum in CDCl₃, 500 MHz

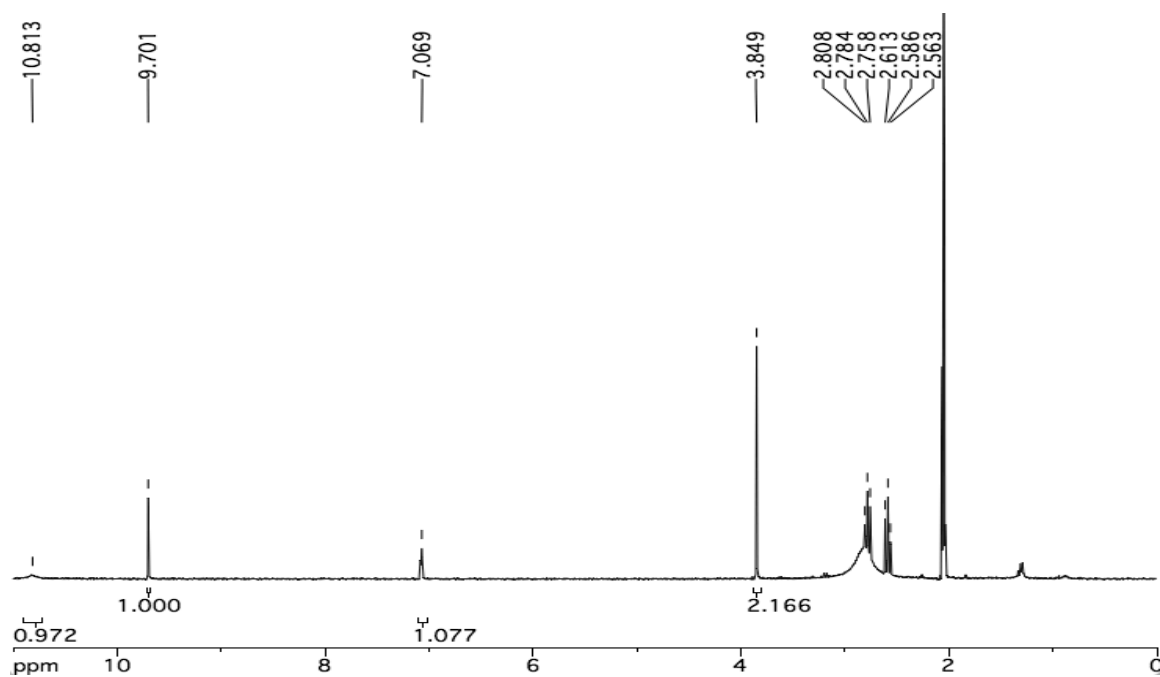


¹³C NMR spectrum in CDCl₃, 125 MHz



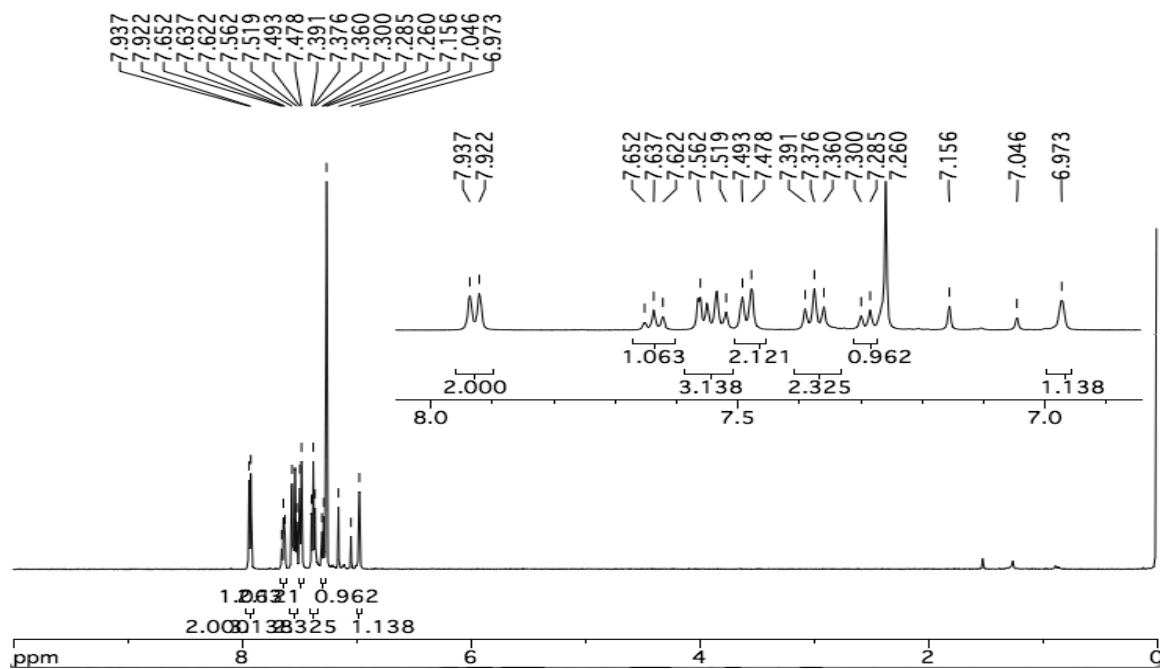
4-(2-Methoxycarbonyl-ethyl)-3-(methoxycarbonylmethyl)-1H-pyrrole-2-carbaldehyde (3.59)

¹H NMR spectrum in C(O)(CD₃)₂, 300 MHz

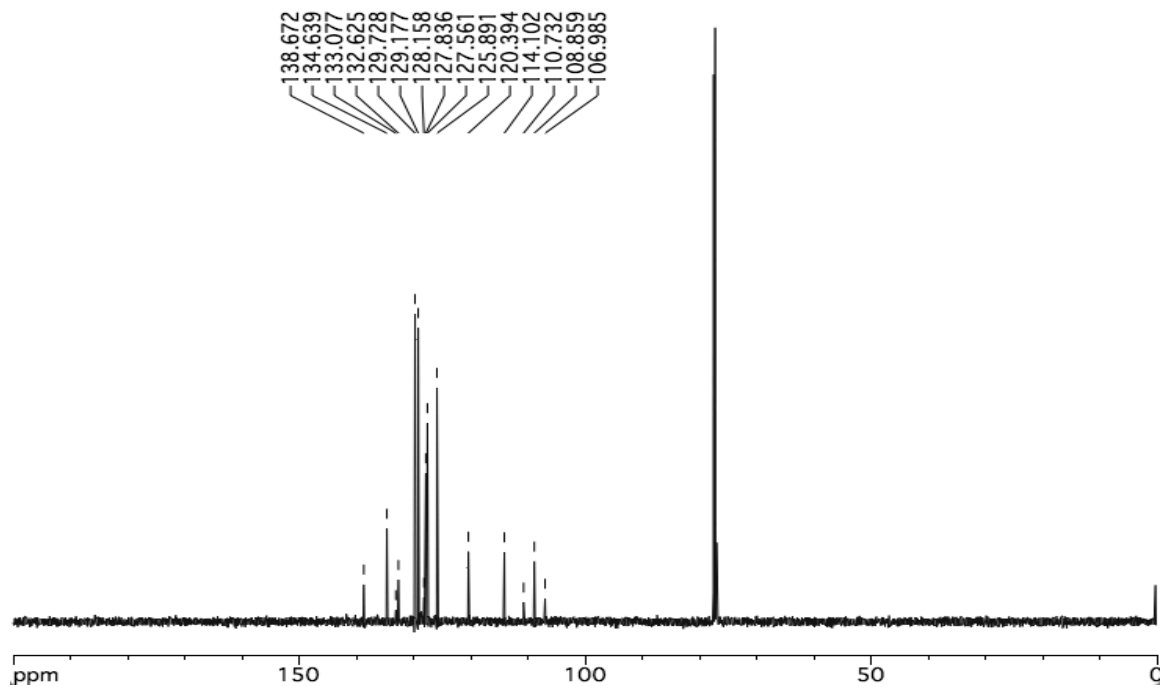


2-(Difluoromethyl)-4-phenyl-1-(phenylsulfonyl)-1H-pyrrole (3.81)

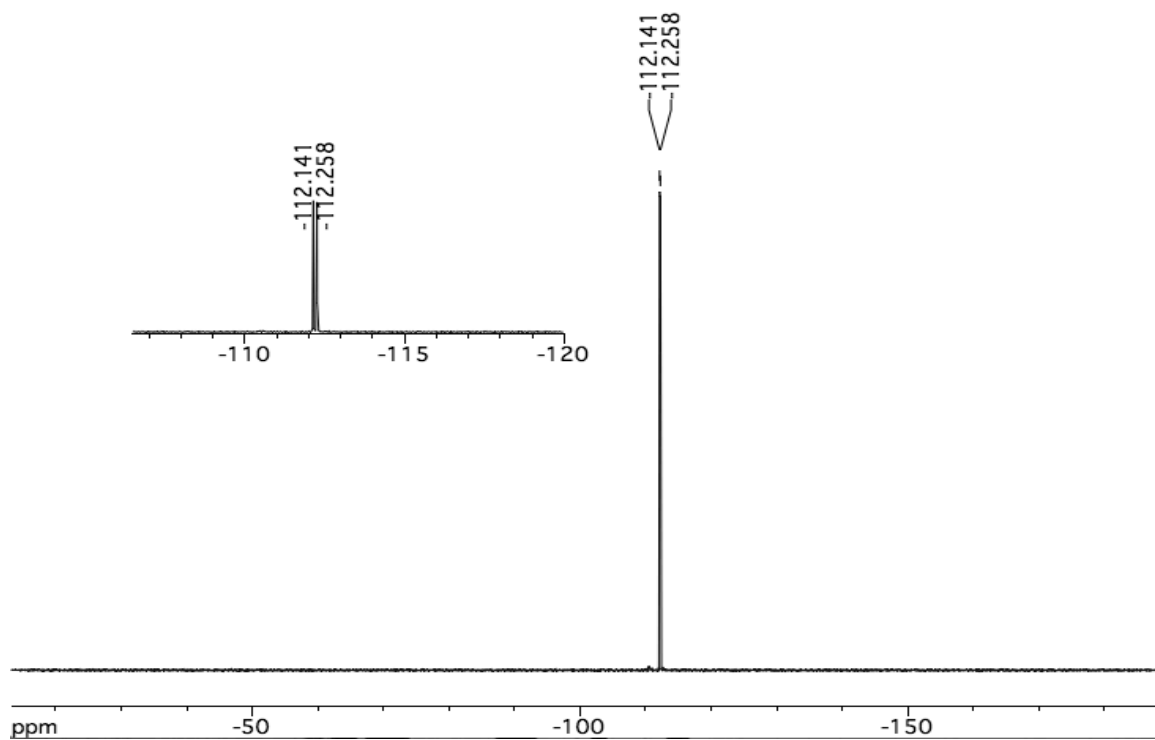
¹H NMR spectrum in CDCl₃, 500 MHz



^{13}C NMR spectrum in CDCl_3 , 125 MHz

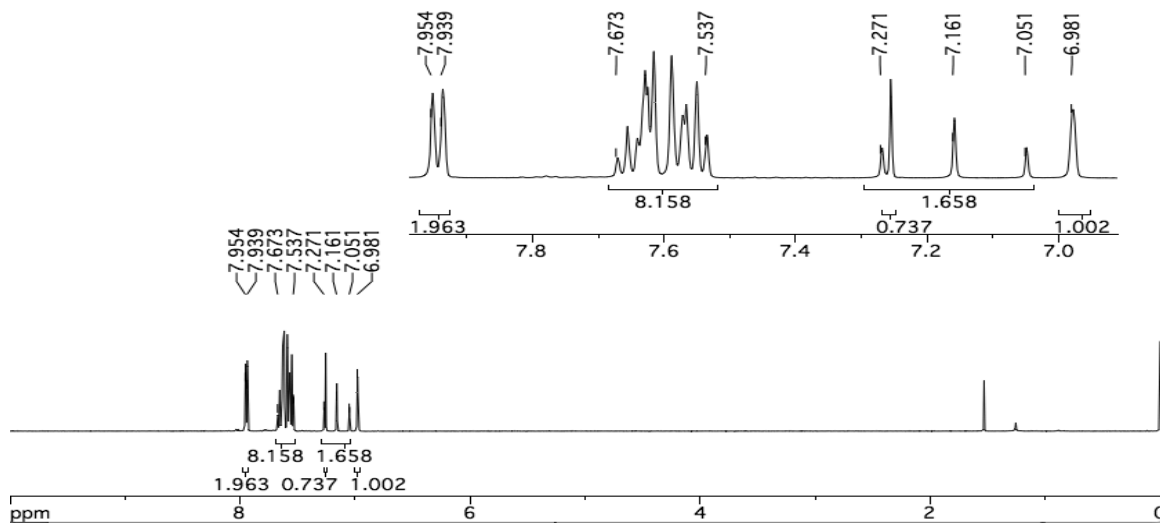


^{19}F NMR spectrum in CDCl_3 , 470 MHz

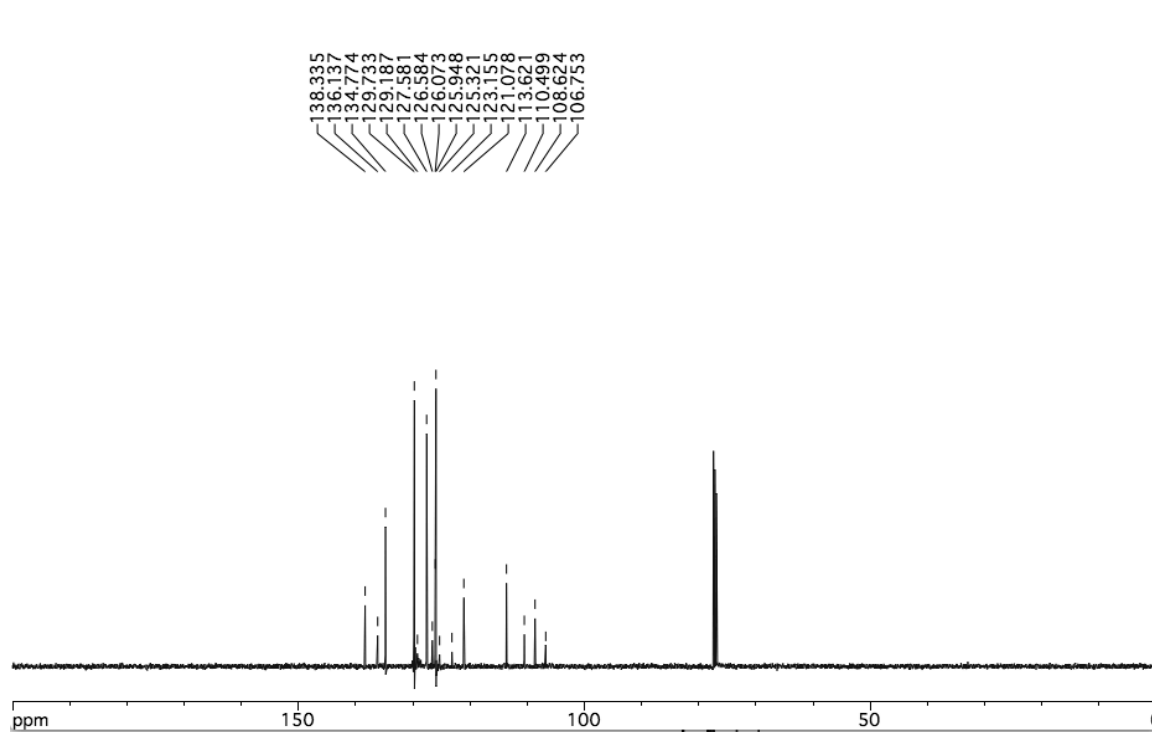


2-(Difluoromethyl)-1-(phenylsulfonyl)-4-(4-(trifluoromethyl)phenyl)-1*H*-pyrrole (3.82)

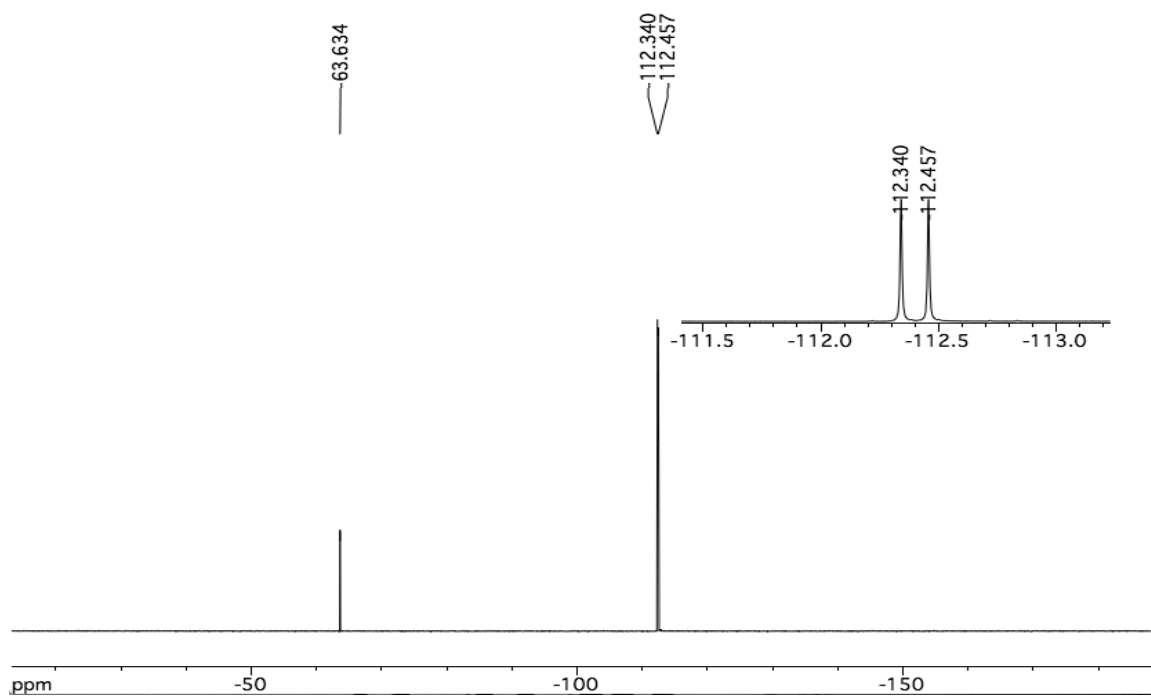
¹H NMR spectrum in CDCl₃, 500 MHz



¹³C NMR spectrum in CDCl₃, 125 MHz

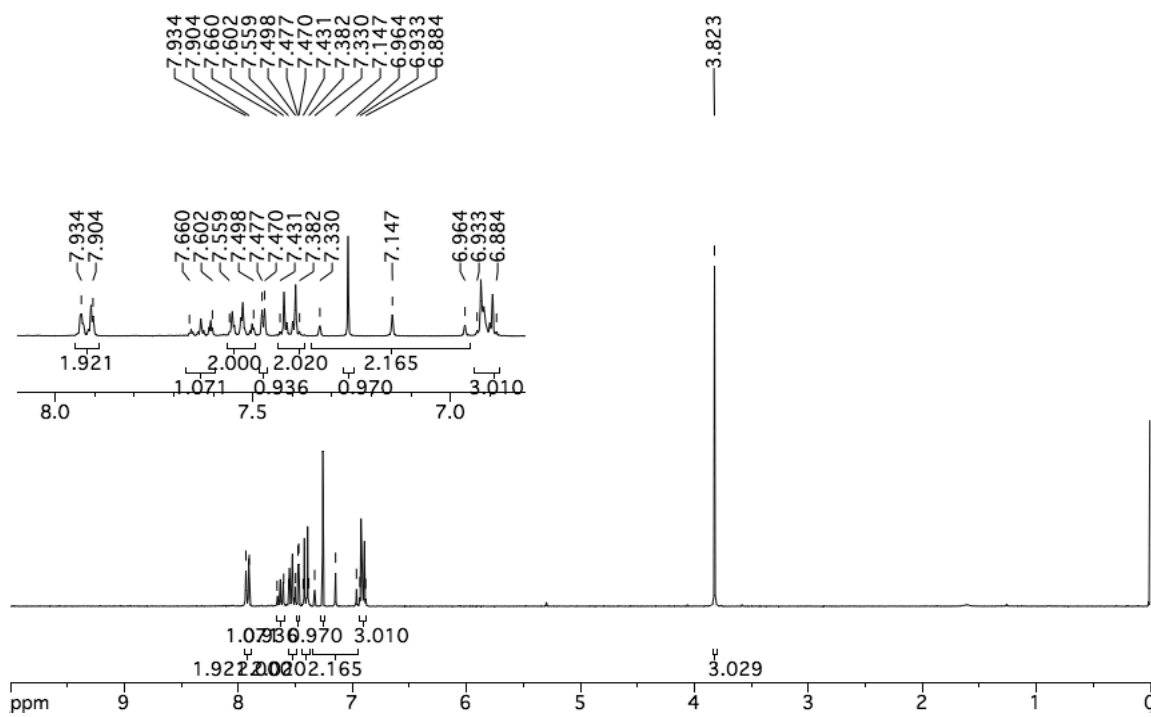


^{19}F NMR spectrum in CDCl_3 , 470 MHz

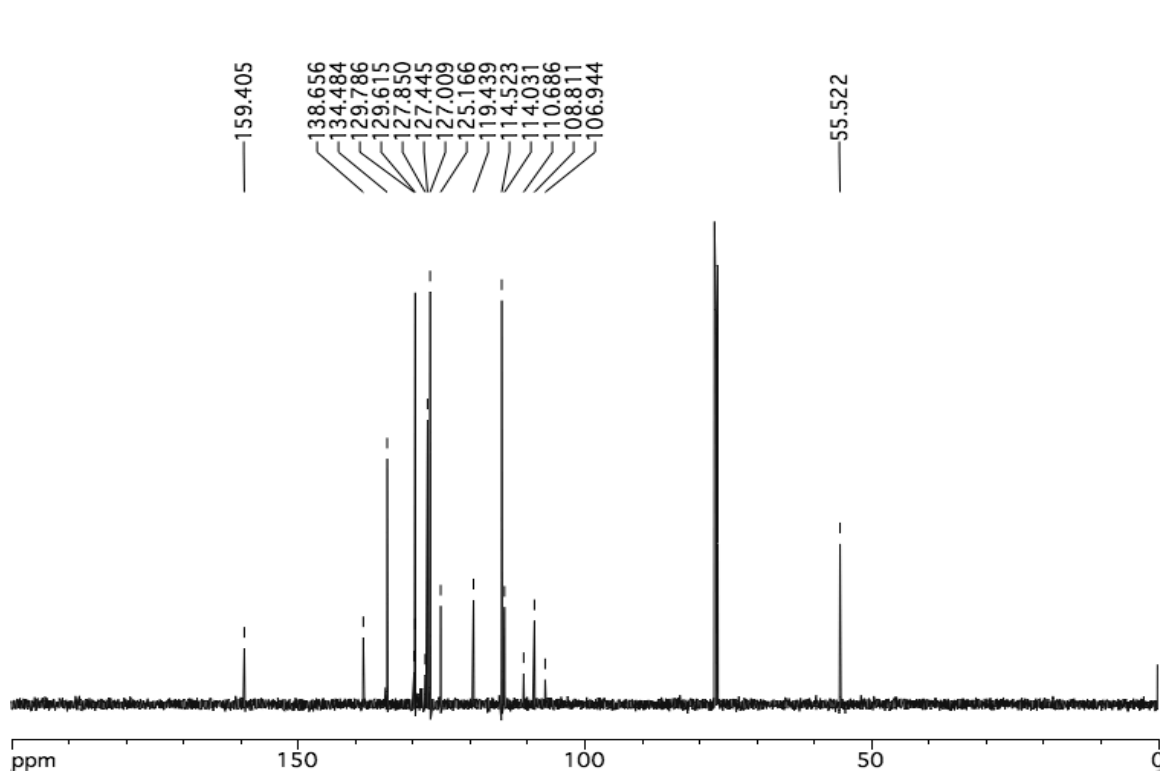


2-(Difluoromethyl)-4-(4-methoxyphenyl)-1-(phenylsulfonyl)-1*H*-pyrrole (3.83)

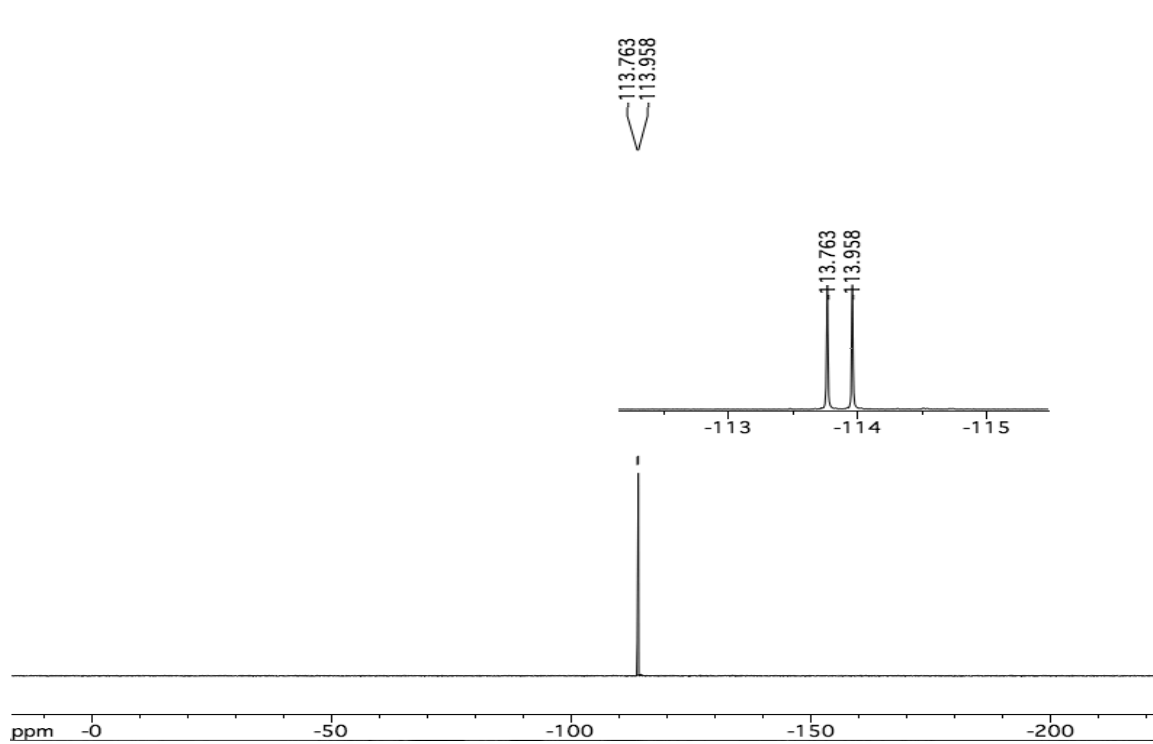
^1H NMR spectrum in CDCl_3 , 300 MHz



^{13}C NMR spectrum in CDCl_3 , 125 MHz

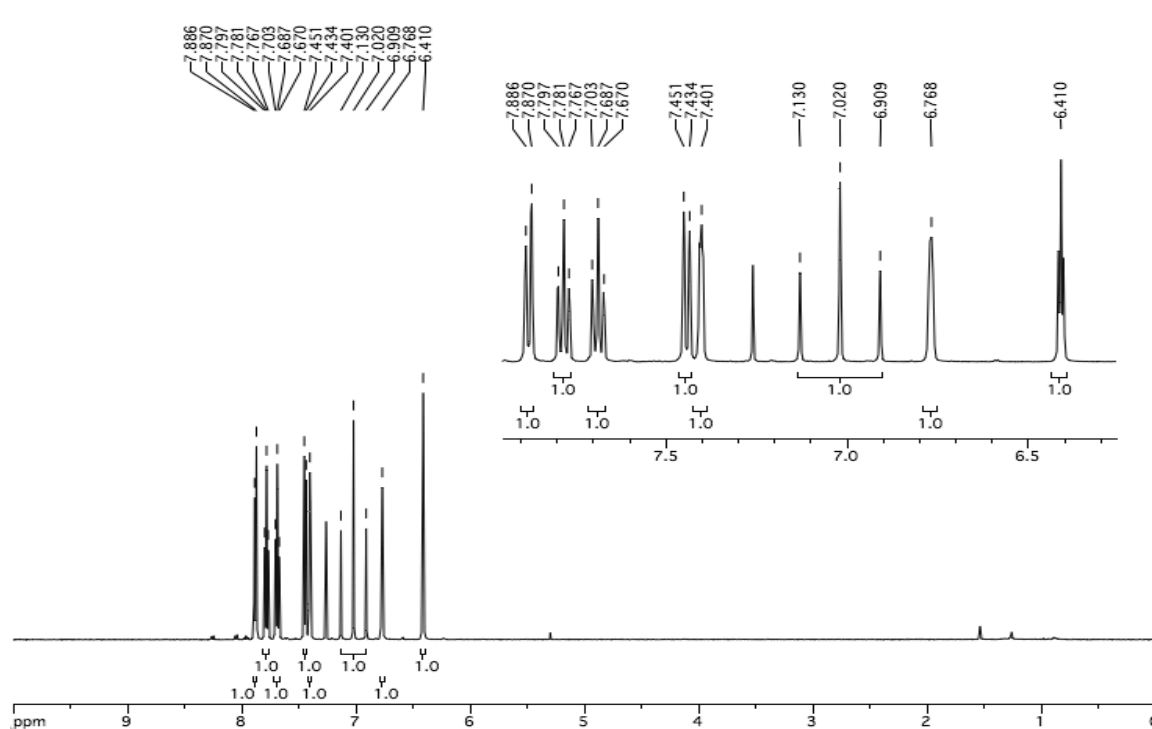


^{19}F NMR spectrum in CDCl_3 , 282 MHz

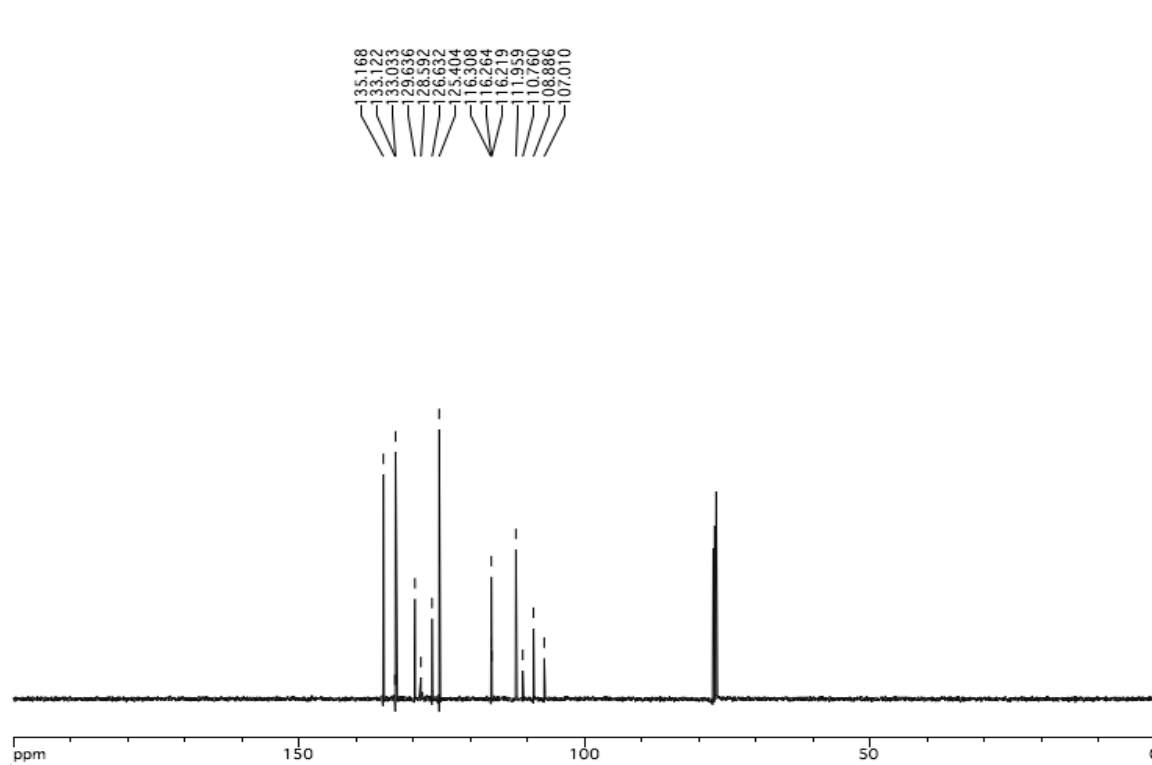


2-(Difluoromethyl)-1-(2-nitrophenylsulfonyl)-1*H*-pyrrole (3.84)

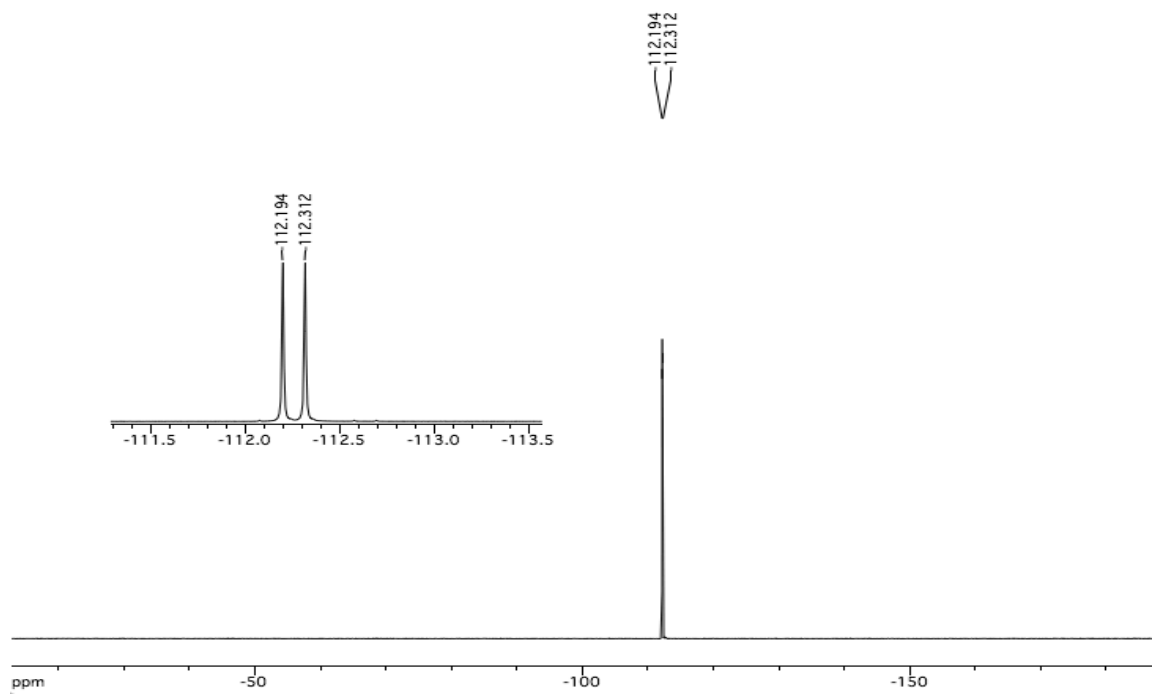
^1H NMR spectrum in CDCl_3 , 500 MHz



^{13}C NMR spectrum in CDCl_3 , 125 MHz

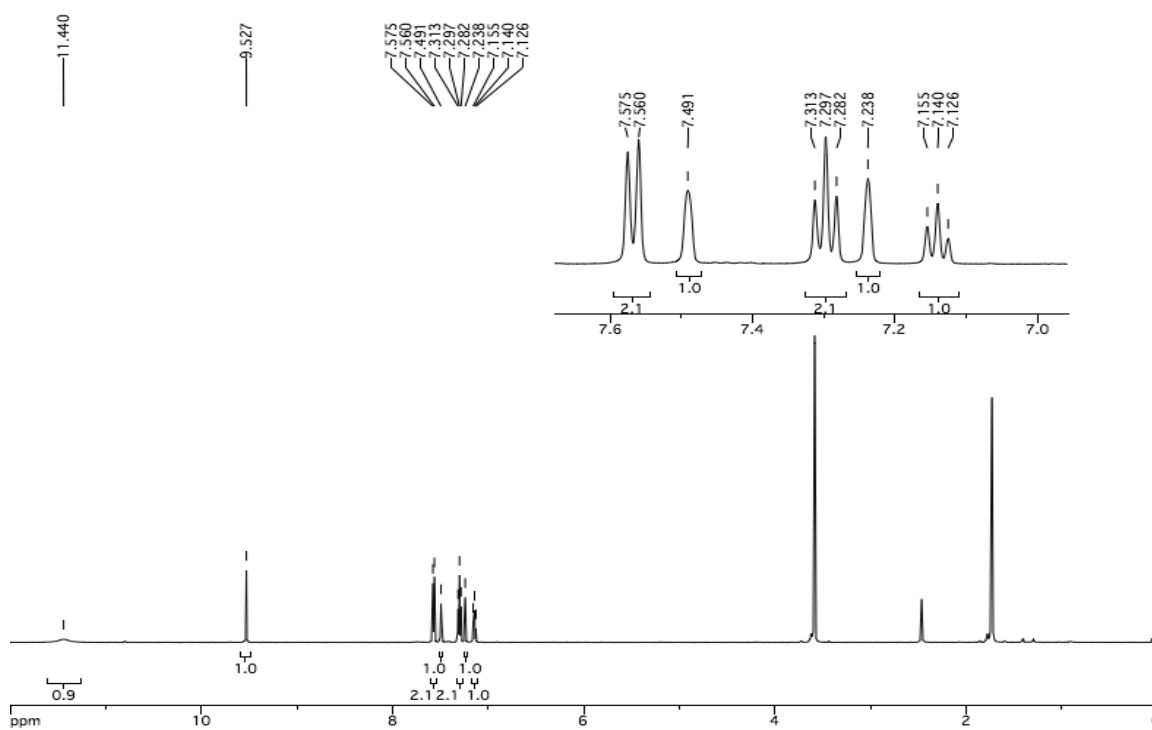


^{19}F NMR spectrum in CDCl_3 , 470 MHz

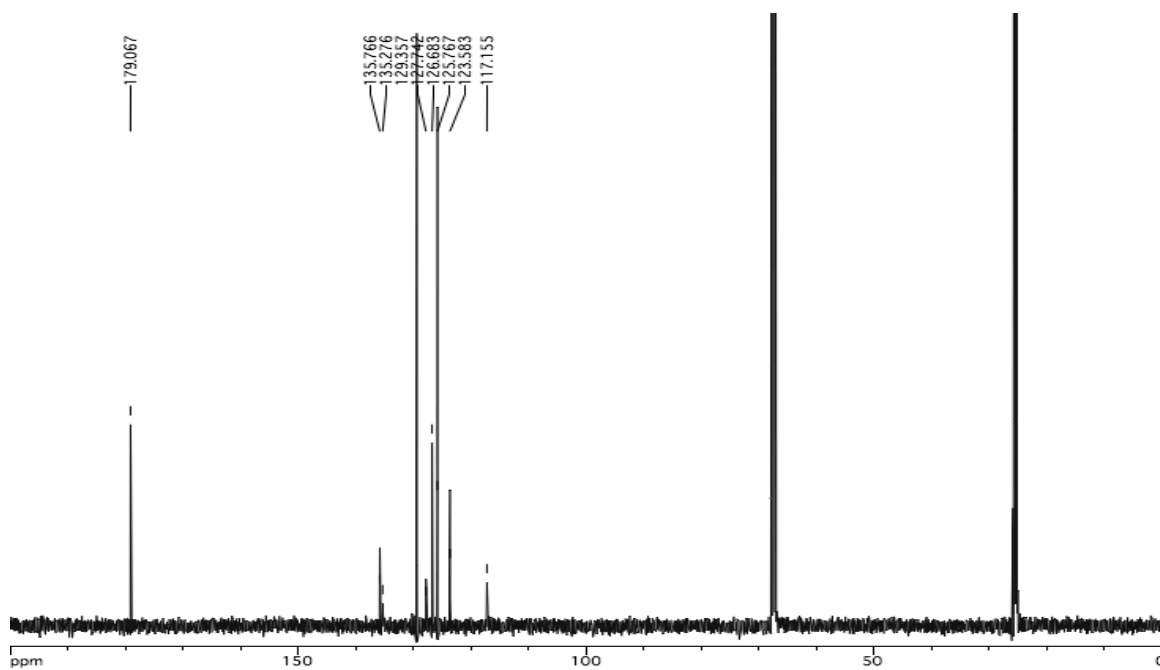


4-Phenyl-1H-pyrrole-2-carbaldehyde (3.91)

^1H NMR spectrum in $\text{THF-}d_8$, 500 MHz

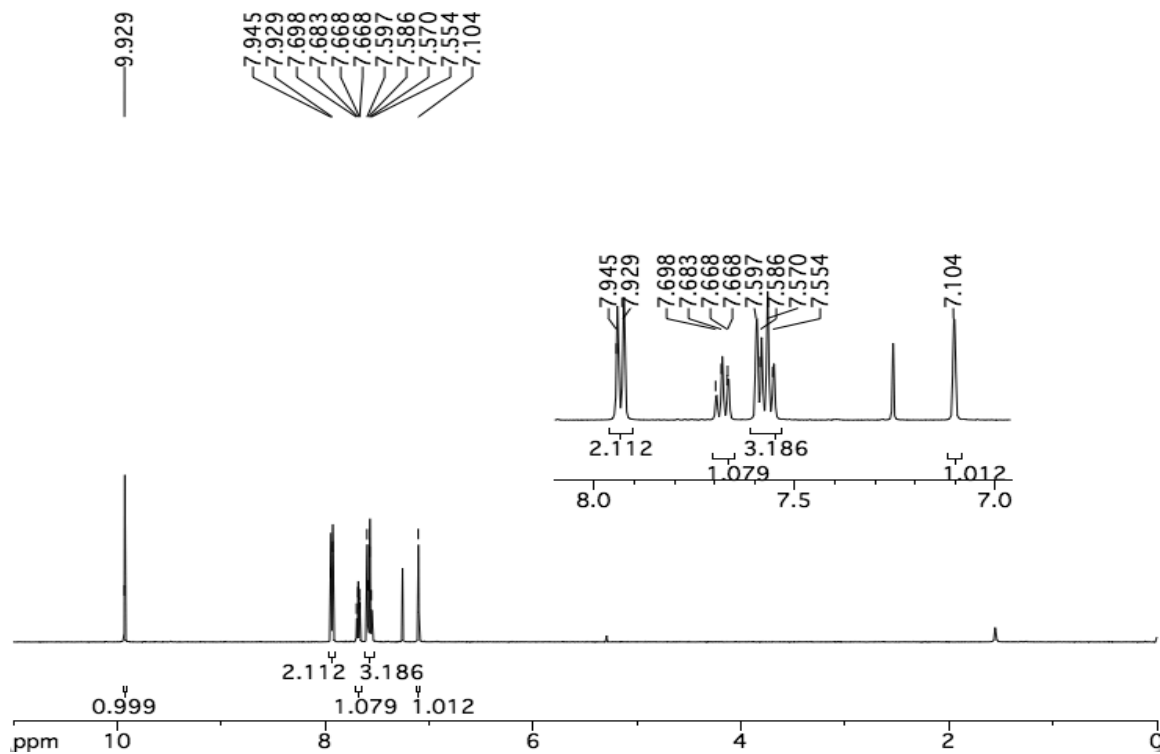


^{13}C NMR spectrum in THF-*d*8, 125 MHz

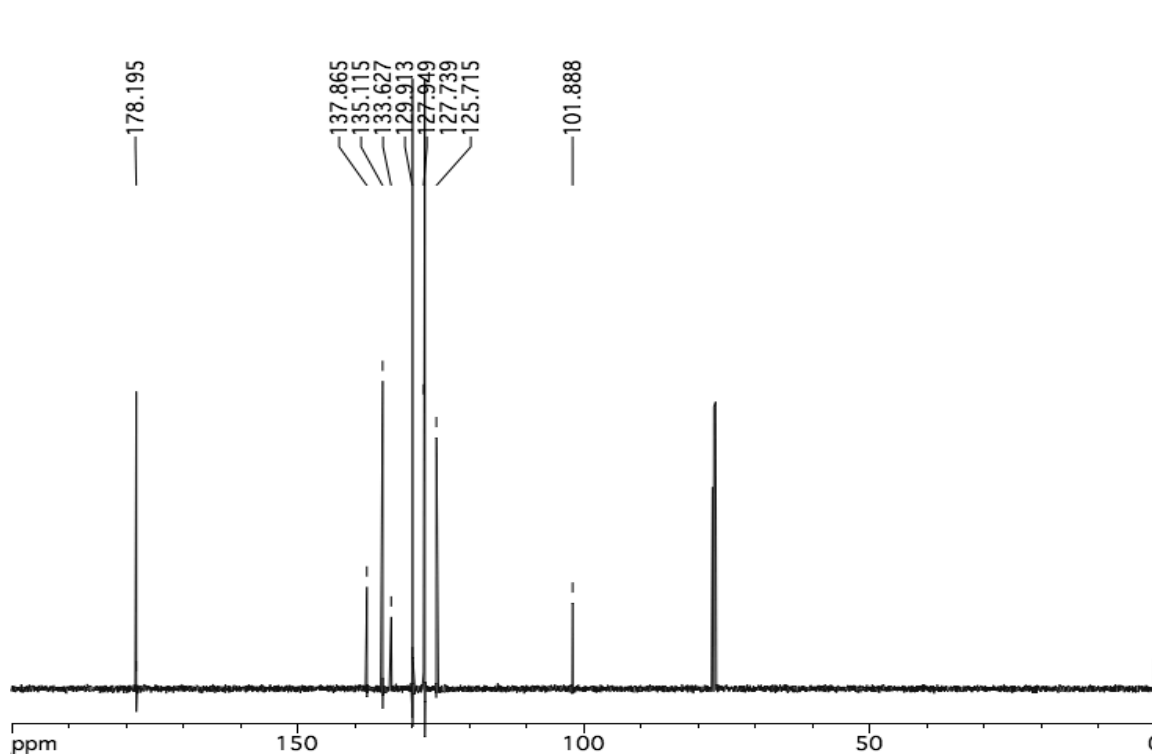


4-Bromo-1-(phenylsulfonyl)-1H-pyrrole-2-carbaldehyde (3.92)

^1H NMR spectrum in CDCl_3 , 500 MHz

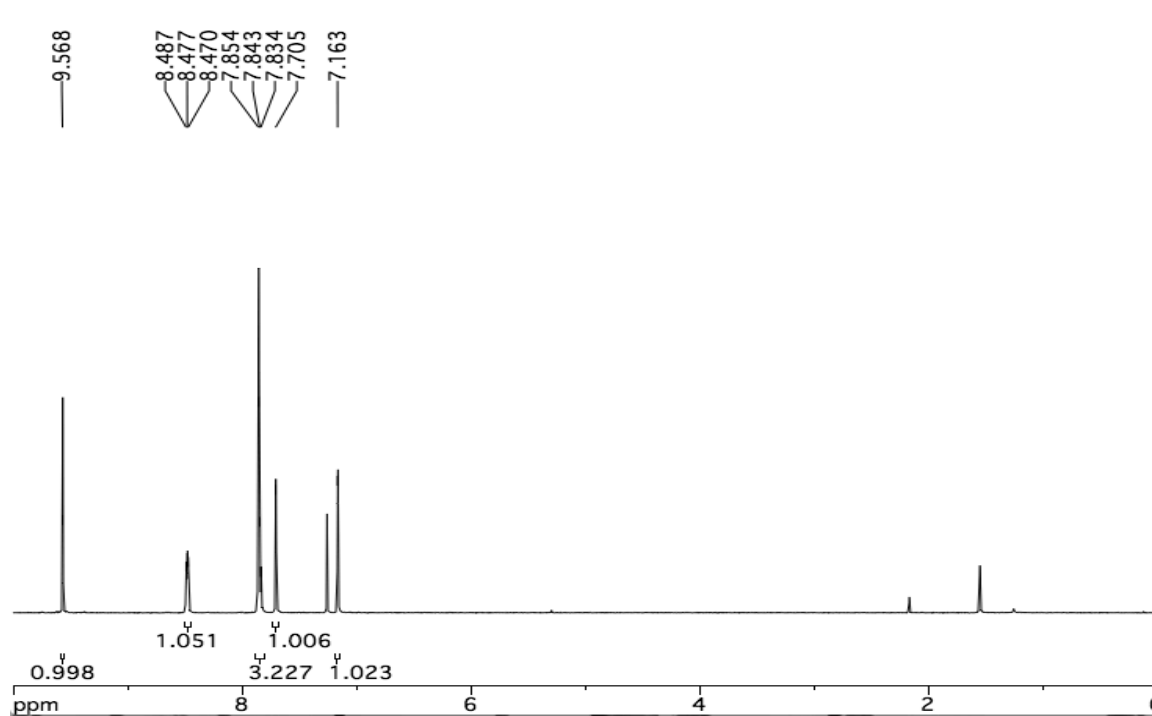


^{13}C NMR spectrum in CDCl_3 , 125 MHz

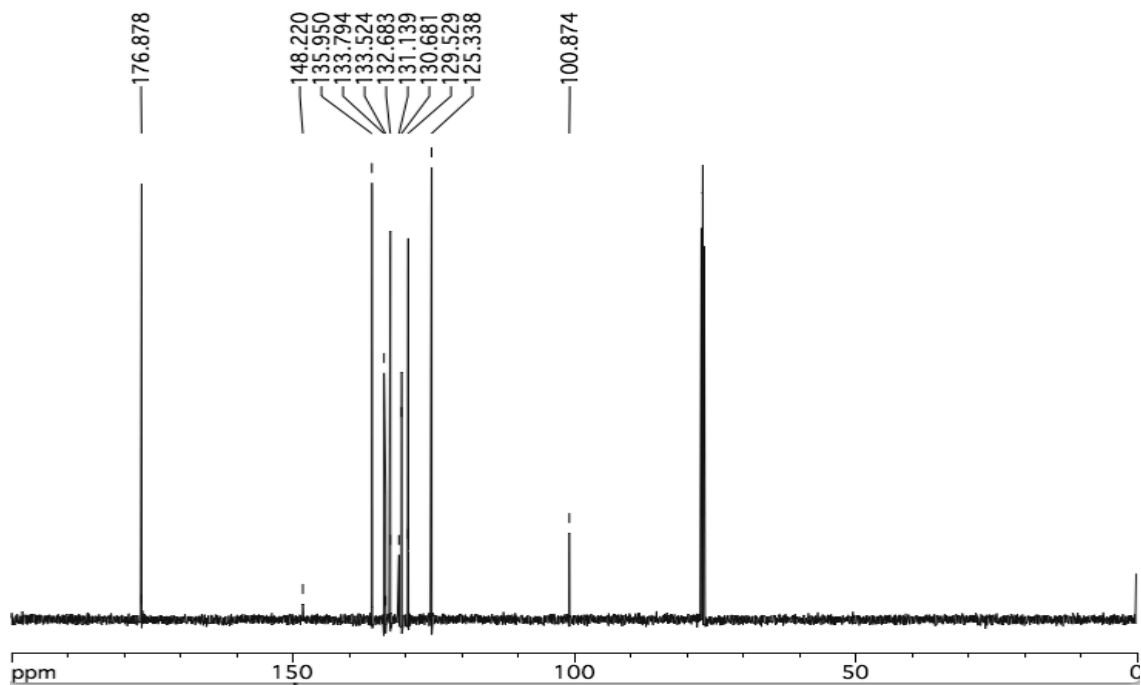


4-Bromo-1-(2-nitrophenylsulfonyl)-1H-pyrrole-2-carbaldehyde (3.94)

^1H NMR spectrum in CDCl_3 , 500 MHz

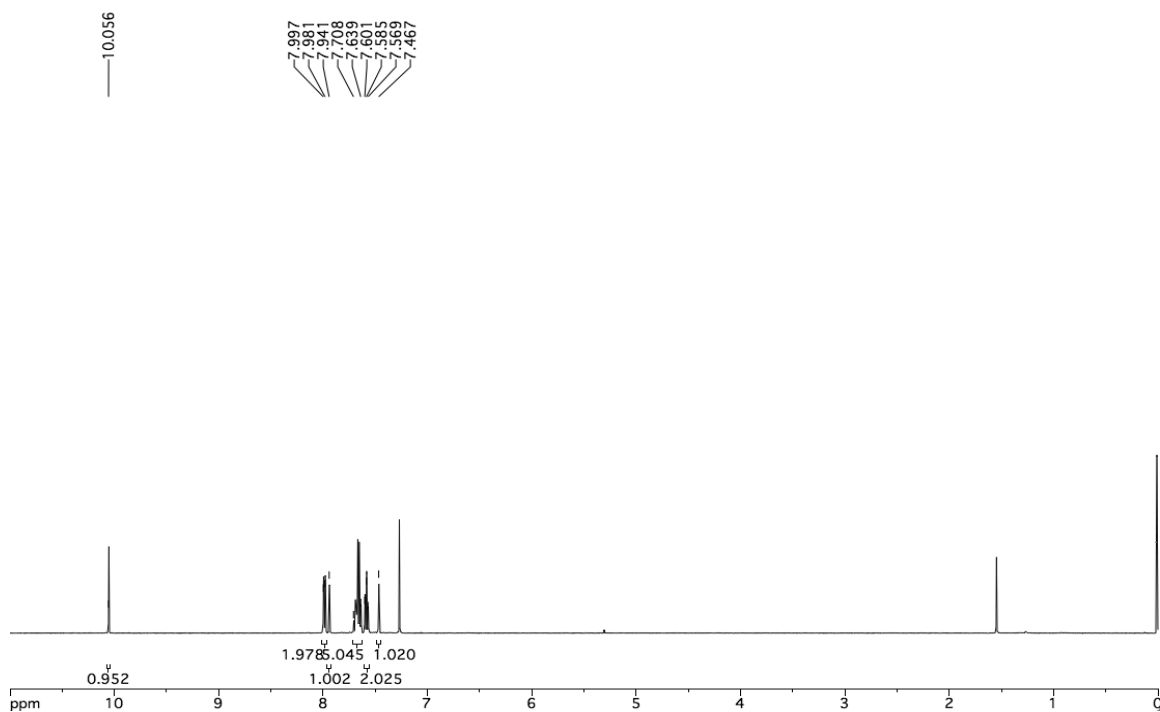


^{13}C NMR spectrum in CDCl_3 , 125 MHz

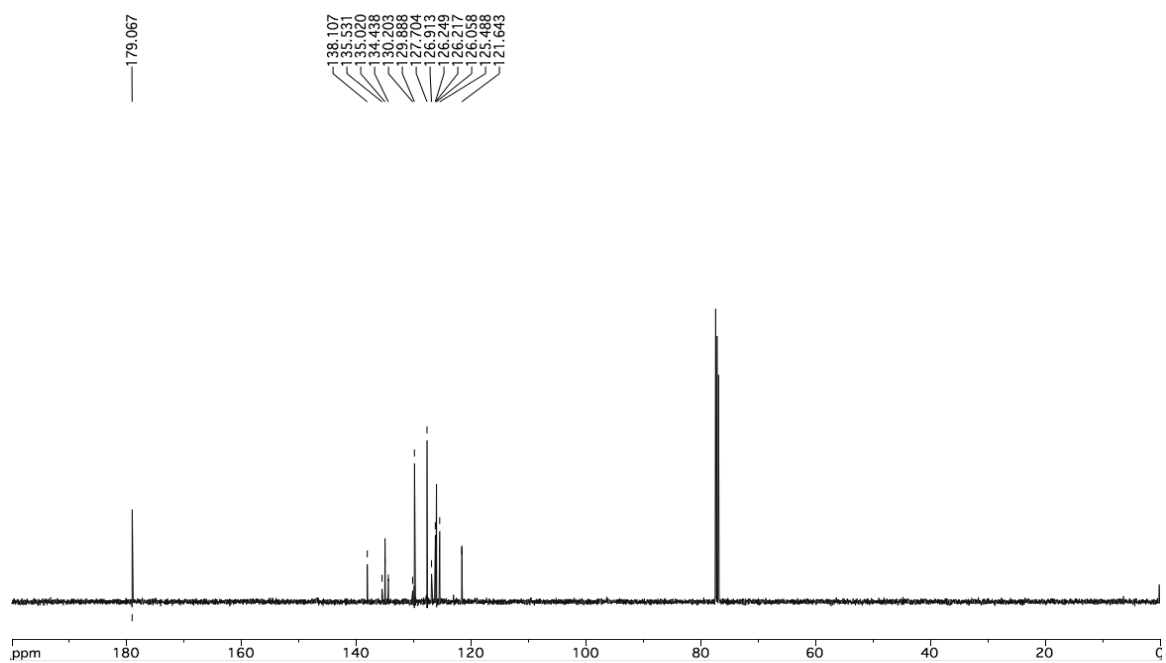


1-(Phenylsulfonyl)-4-(4-(trifluoromethyl)phenyl)-1H-pyrrole-2-carbaldehyde (3.96)

^1H NMR spectrum in CDCl_3 , 500 MHz

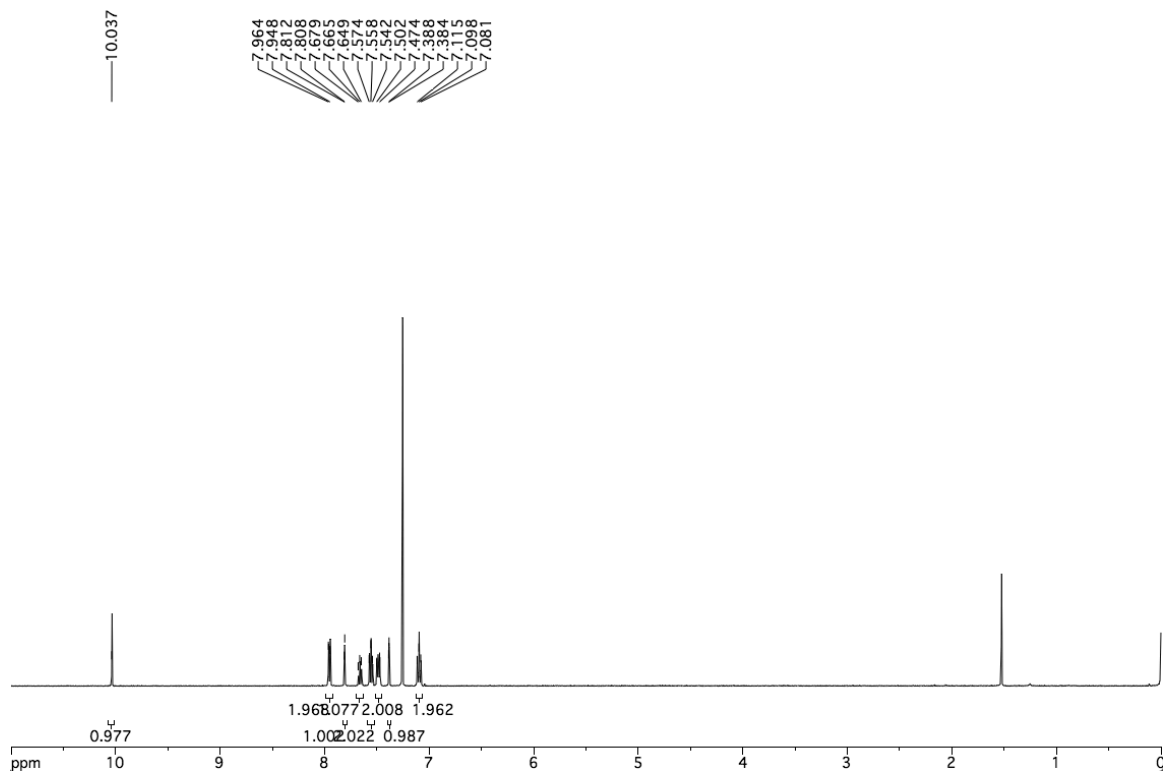


^{13}C NMR spectrum in CDCl_3 , 125 MHz

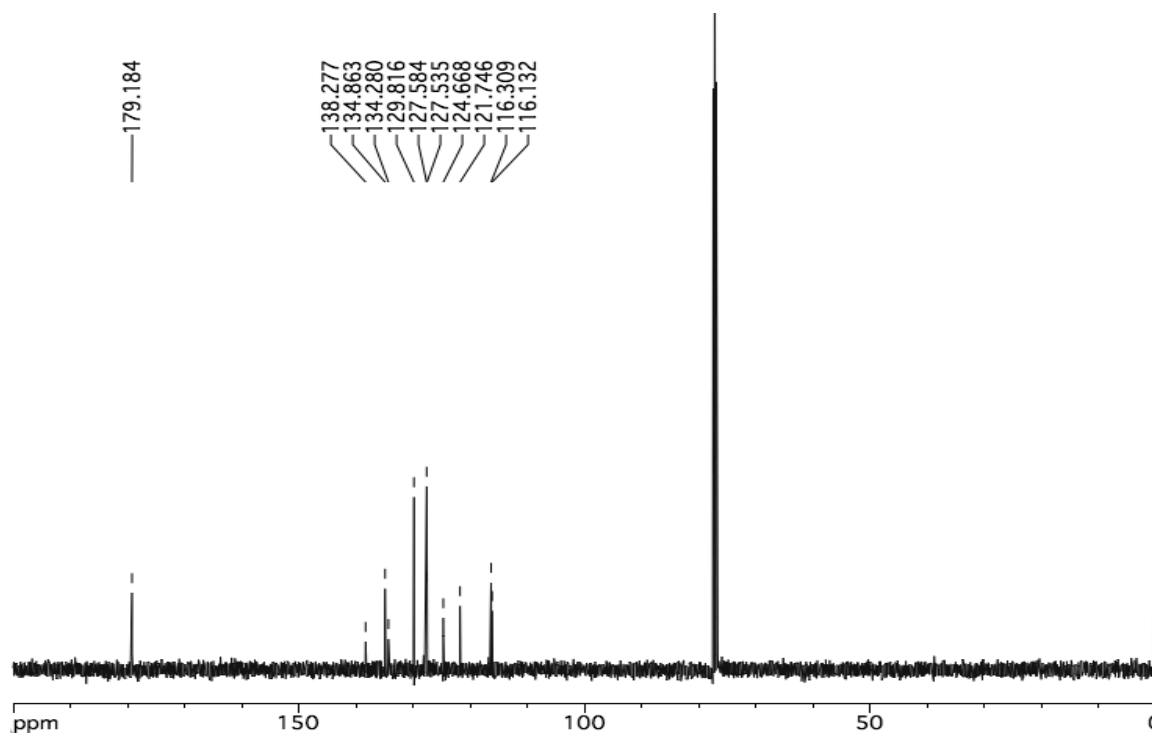


4-(4-Fluorophenyl)-1-(phenylsulfonyl)-1H-pyrrole-2-carbaldehyde (3.97)

^1H NMR spectrum in CDCl_3 , 500 MHz

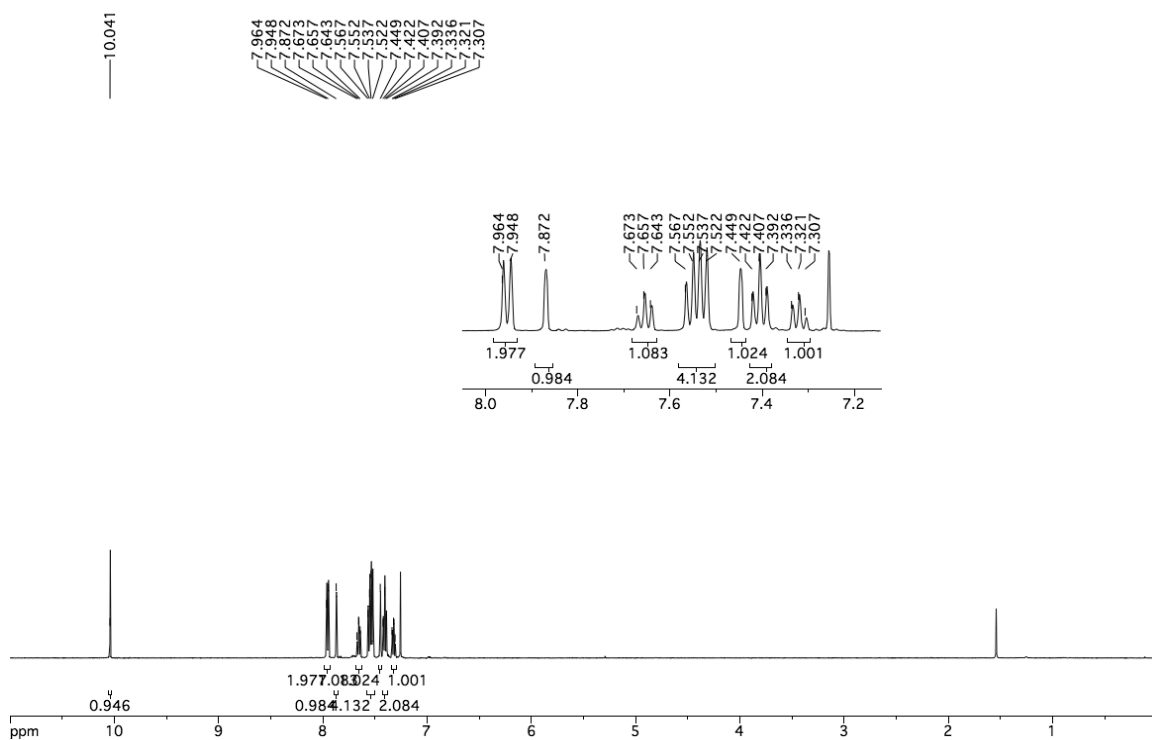


^{13}C NMR spectrum in CDCl_3 , 125 MHz

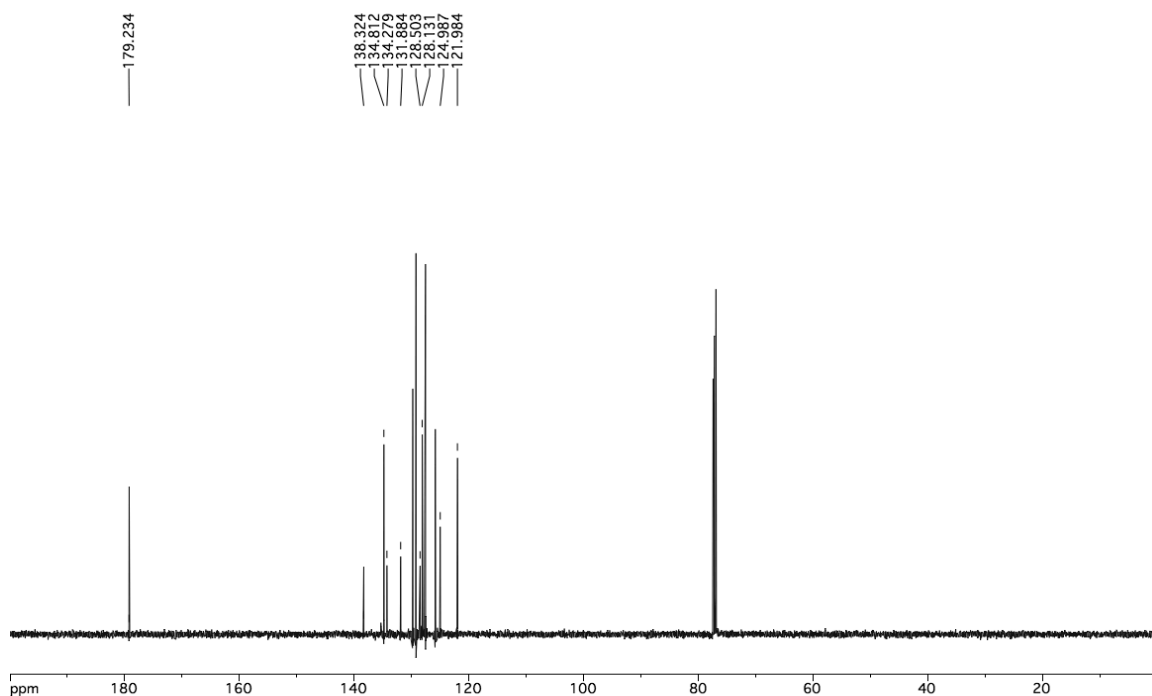


4-Phenyl-1-(phenylsulfonyl)-1H-pyrrole-2-carbaldehyde (3.98)

^1H NMR spectrum in CDCl_3 , 500 MHz

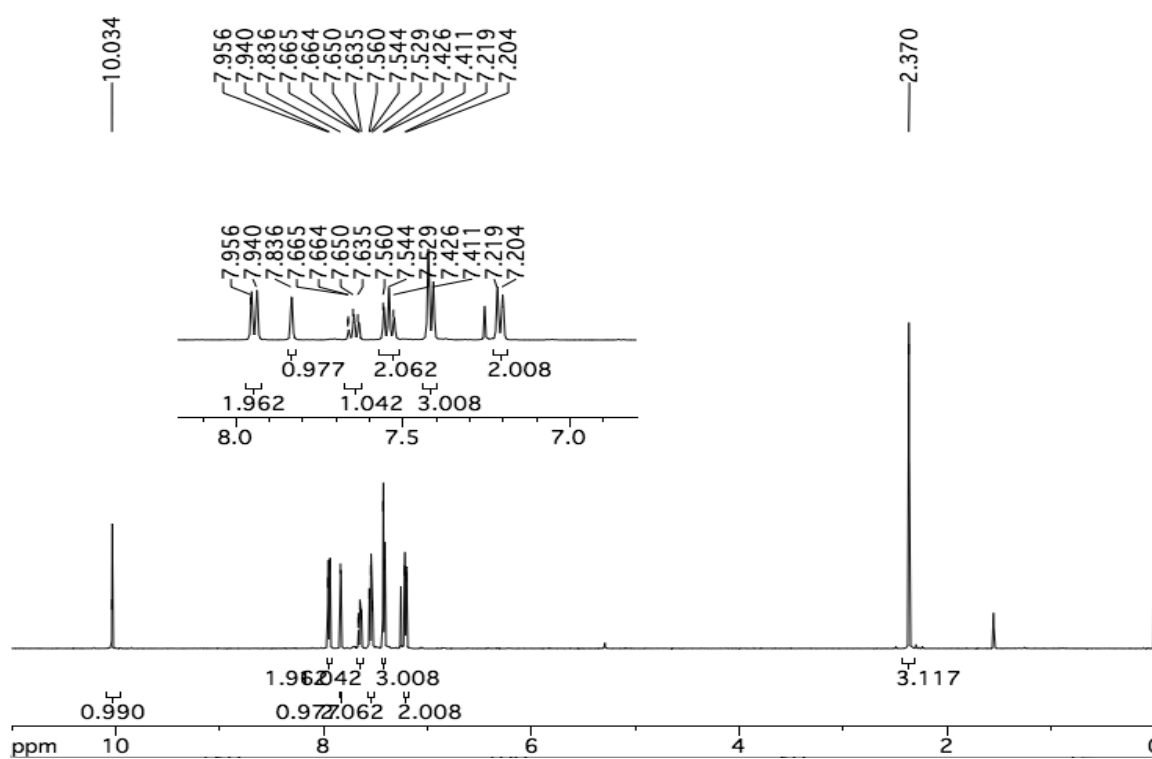


^{13}C NMR spectrum in CDCl_3 , 125 MHz

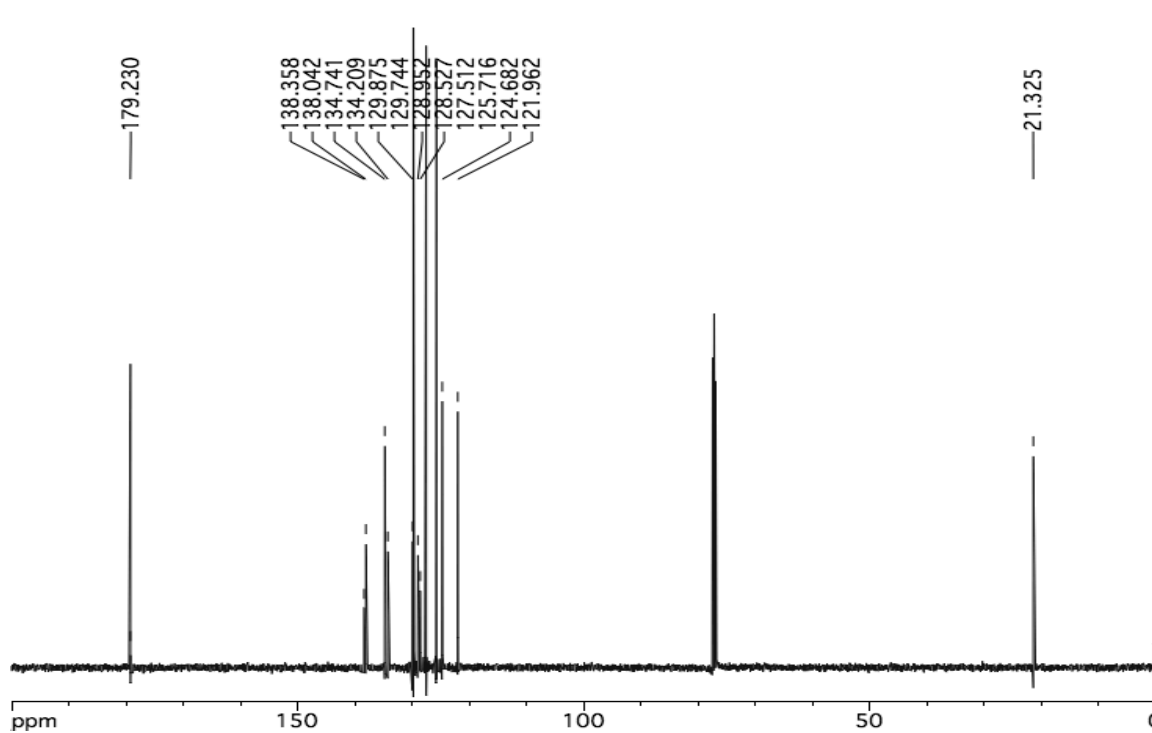


1-(Phenylsulfonyl)-4-p-tolyl-1H-pyrrole-2-carbaldehyde (3.99)

^1H NMR spectrum in CDCl_3 , 500 MHz

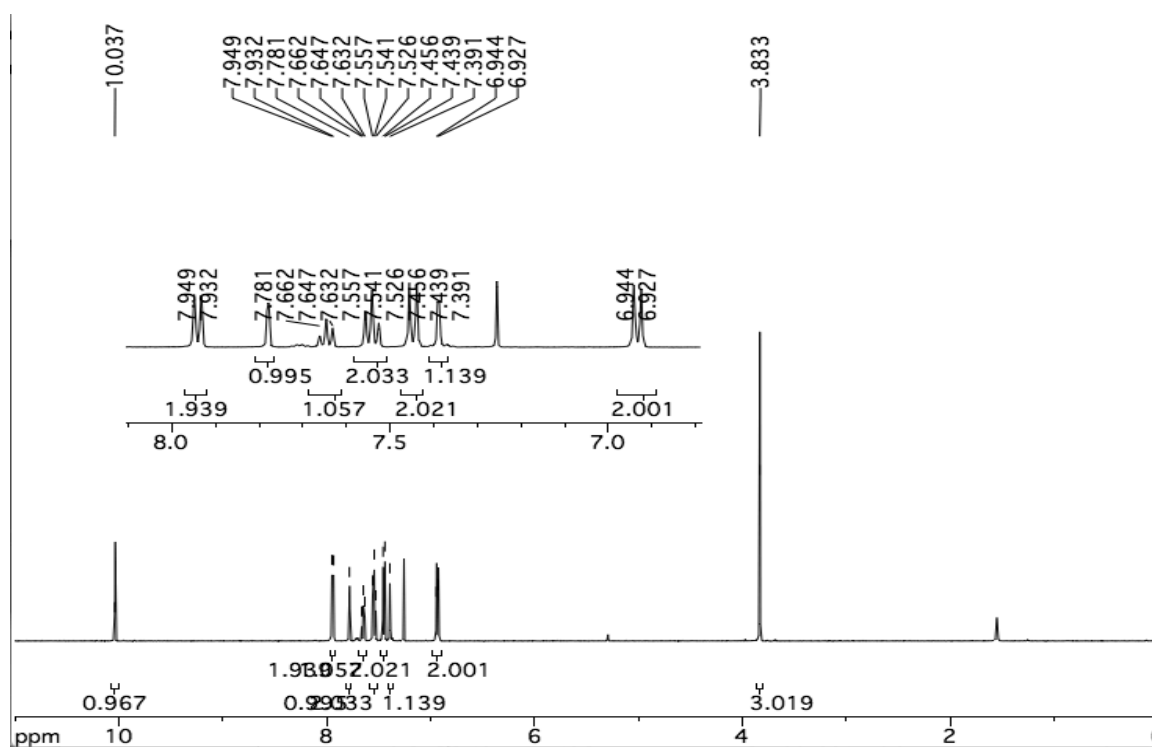


^{13}C NMR spectrum in CDCl_3 , 125 MHz

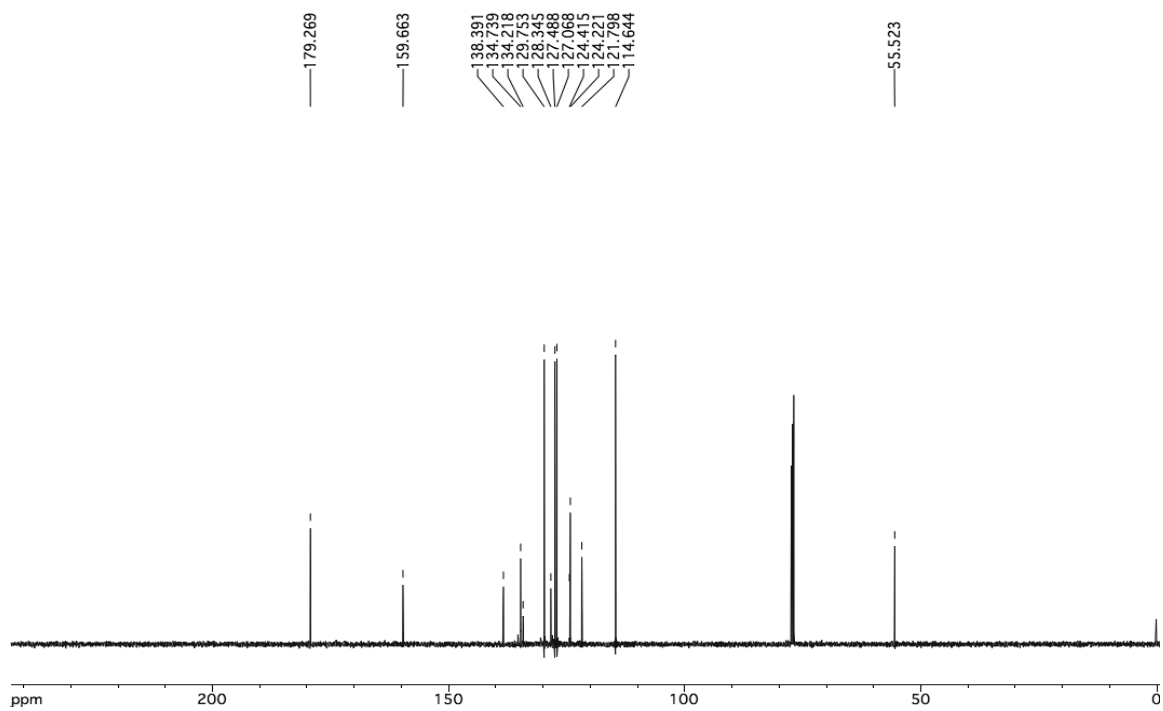


4-(4-Methoxyphenyl)-1-(phenylsulfonyl)-1H-pyrrole-2-carbaldehyde (3.100)

^1H NMR spectrum in CDCl_3 , 500 MHz

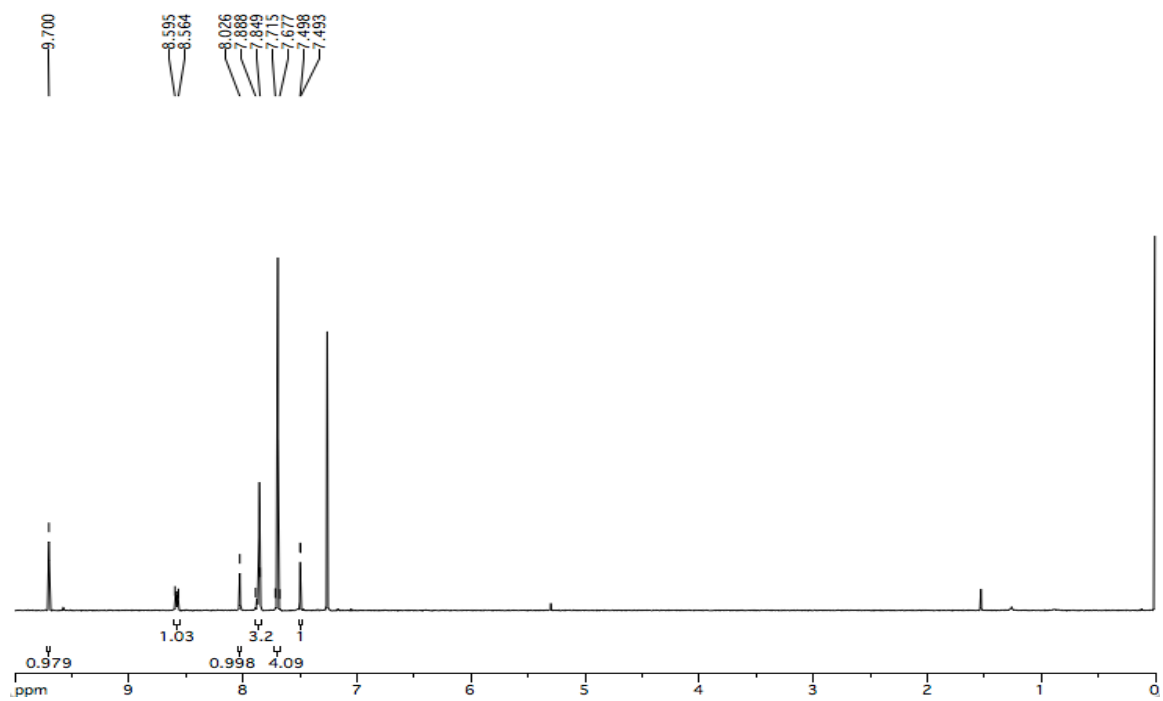


^{13}C NMR spectrum in CDCl_3 , 125 MHz

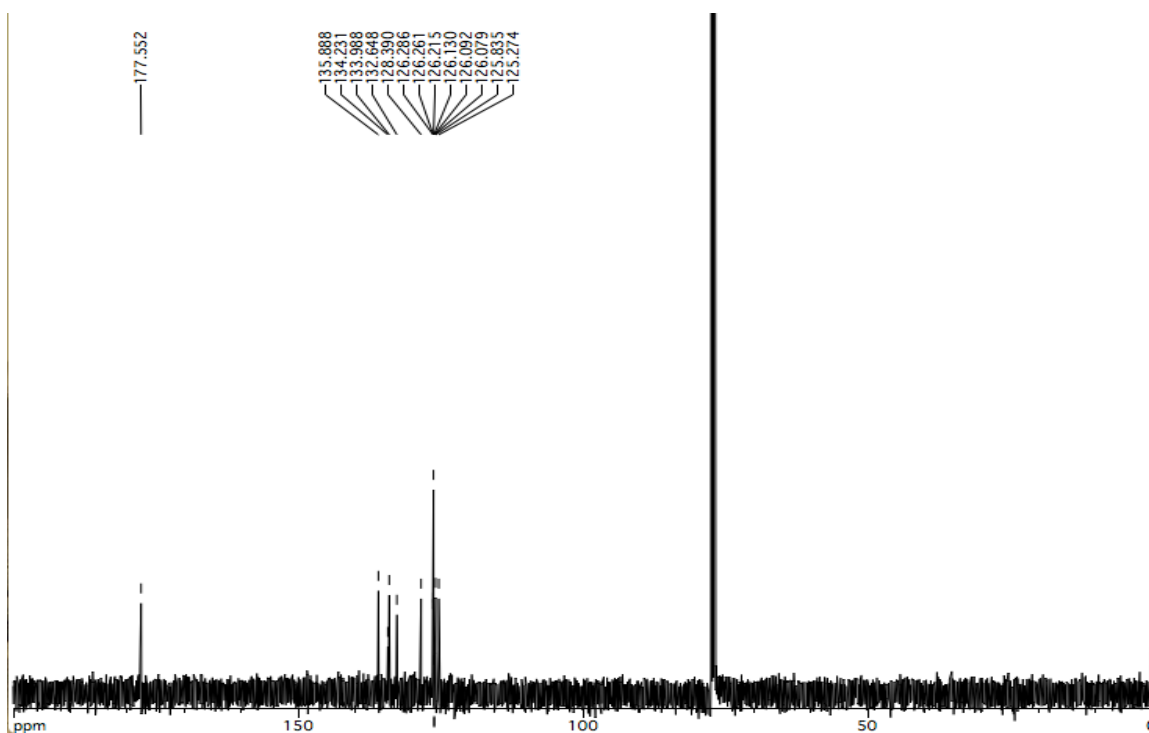


1-(2-Nitrophenylsulfonyl)-4-(4-(trifluoromethyl)phenyl)-1H-pyrrole-2-carbaldehyde (3.101)

^1H NMR spectrum in CDCl_3 , 500 MHz

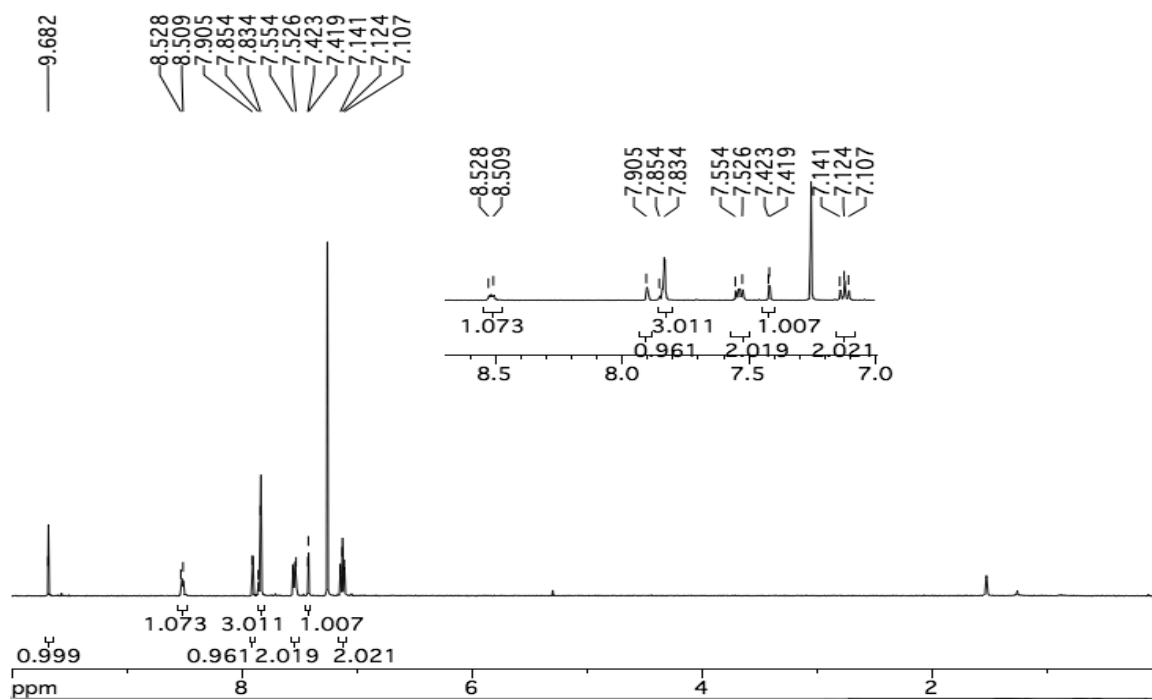


^{13}C NMR spectrum in CDCl_3 , 125 MHz

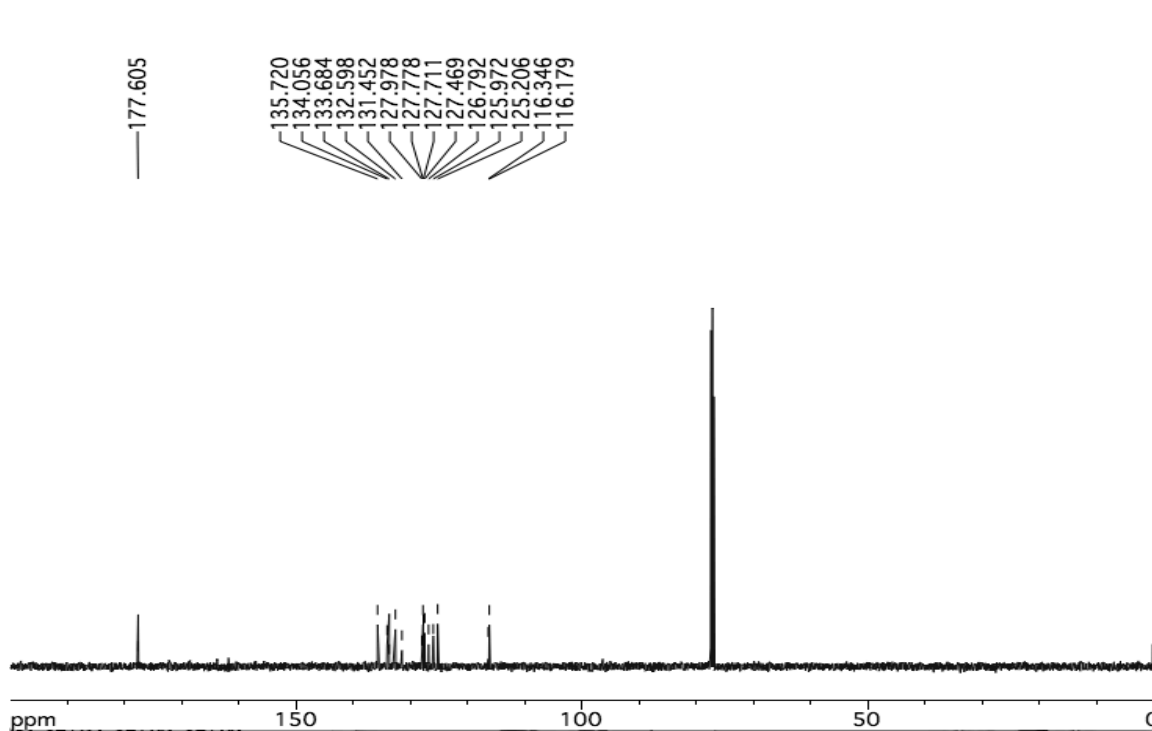


4-(4-Fluorophenyl)-1-(2-nitrophenylsulfonyl)-1H-pyrrole-2-carbaldehyde (3.102)

^1H NMR spectrum in CDCl_3 , 500 MHz

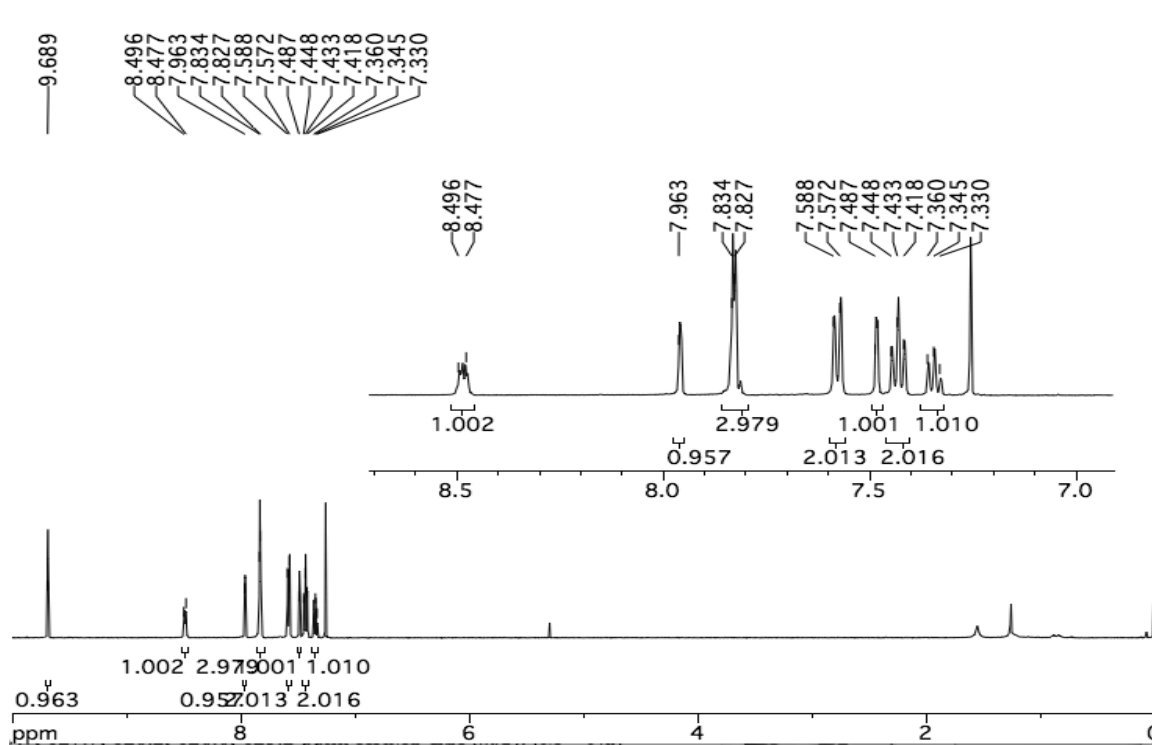


^{13}C NMR spectrum in CDCl_3 , 125 MHz

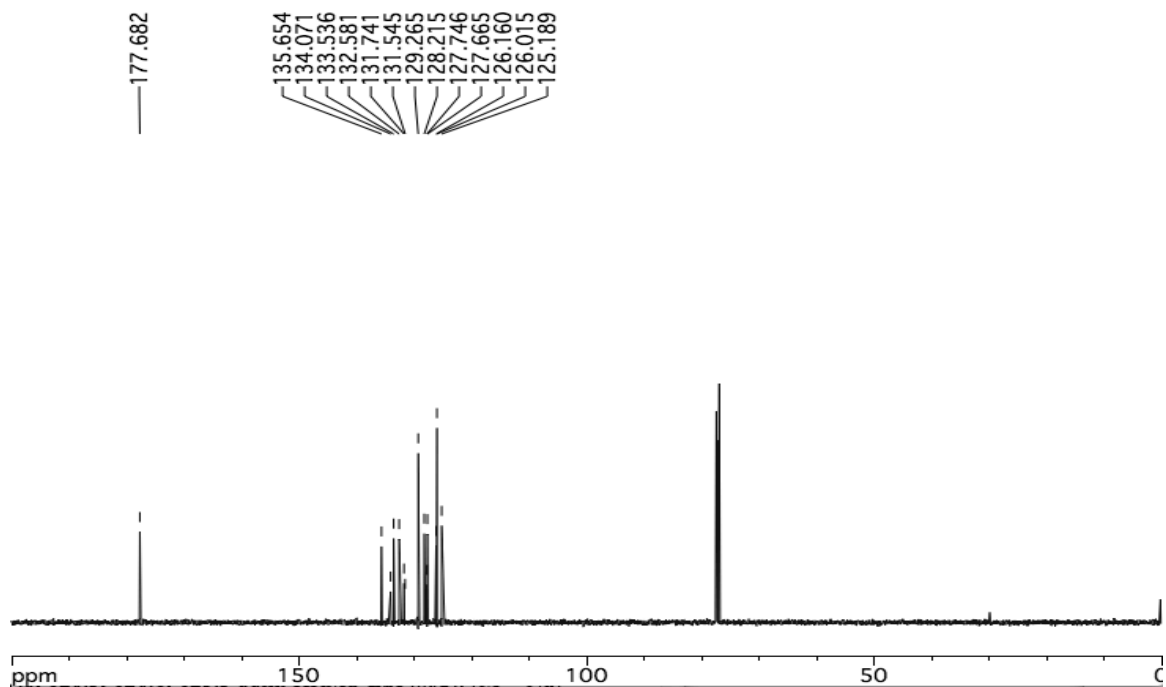


1-(2-Nitrophenylsulfonyl)-4-phenyl-1H-pyrrole-2-carbaldehyde (3.103)

^1H NMR spectrum in CDCl_3 , 500 MHz

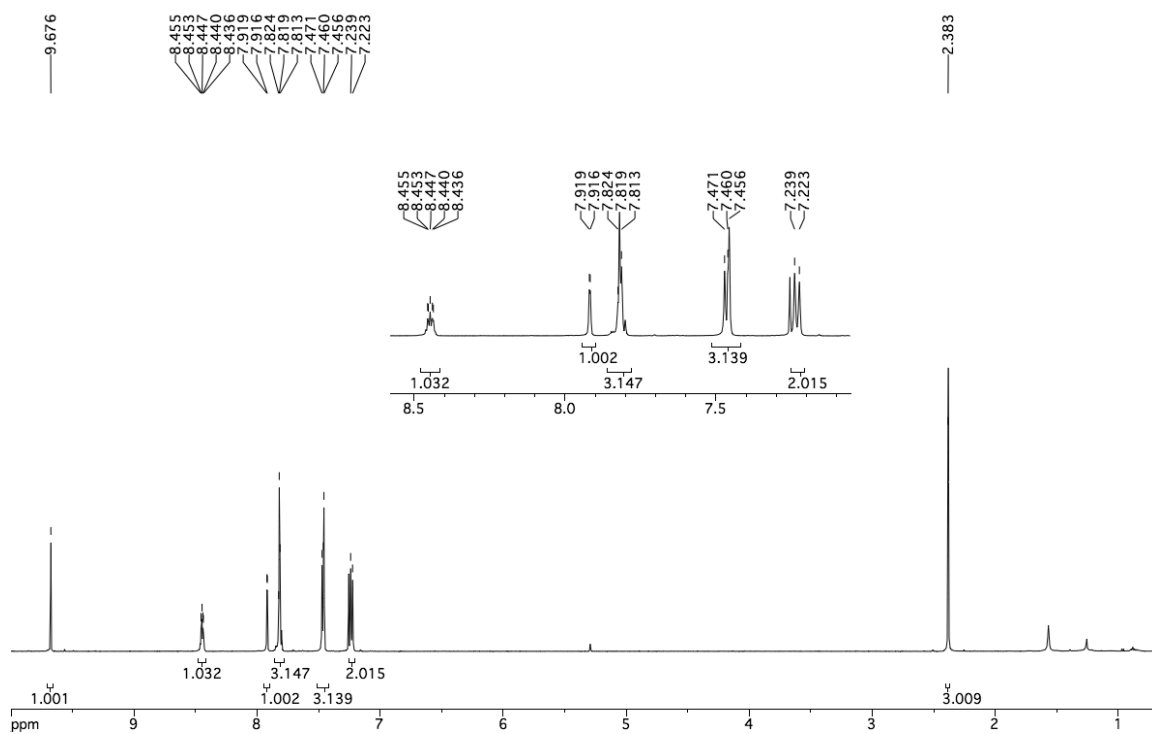


^{13}C NMR spectrum in CDCl_3 , 125 MHz

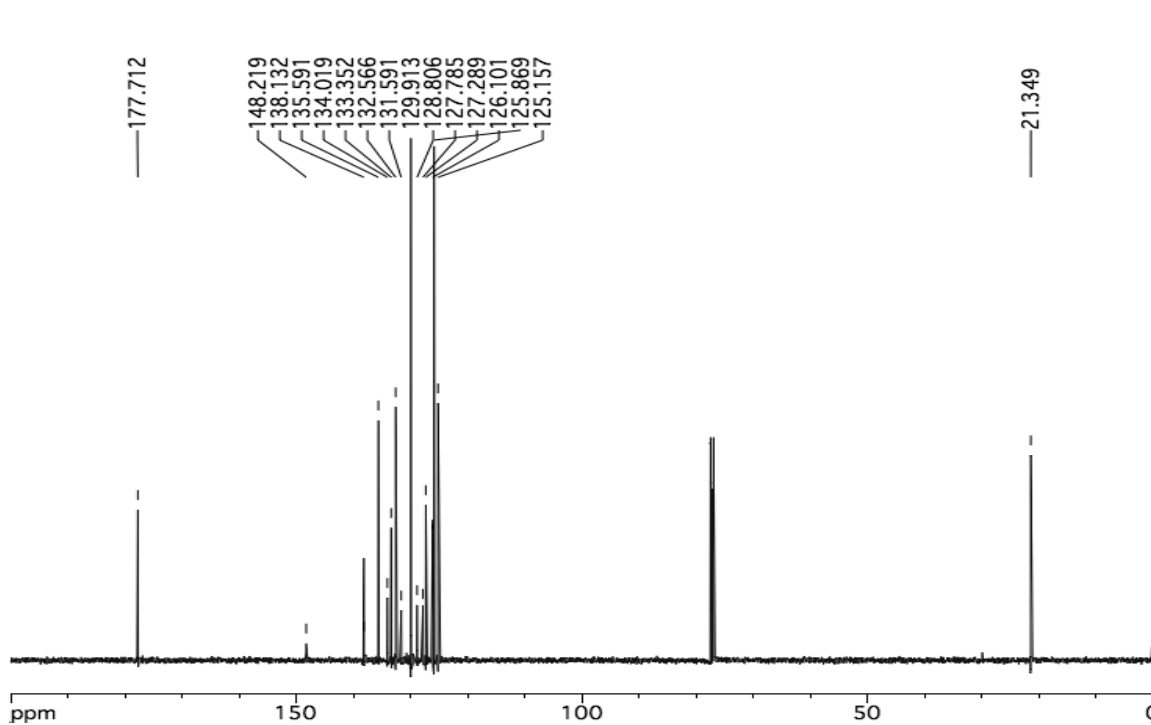


1-(2-Nitrophenylsulfonyl)-4-*p*-tolyl-1H-pyrrole-2-carbaldehyde (3.104)

^1H NMR spectrum in CDCl_3 , 500 MHz

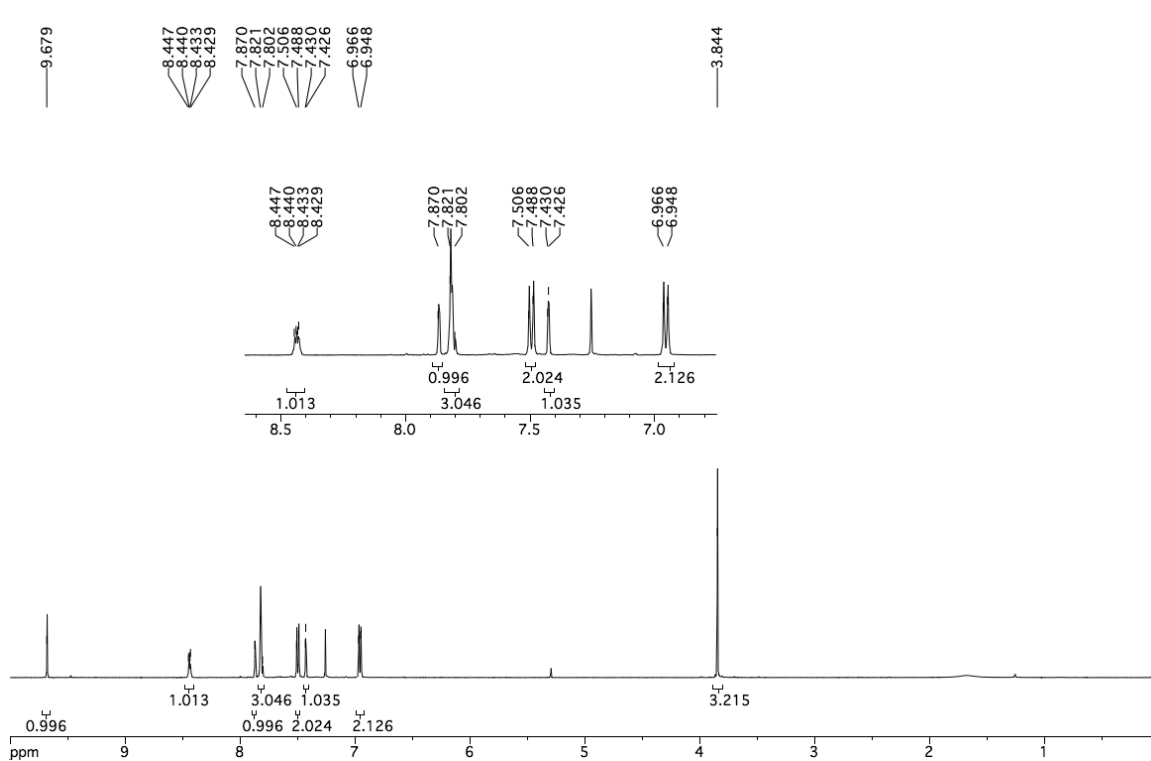


^{13}C NMR spectrum in CDCl_3 , 125 MHz

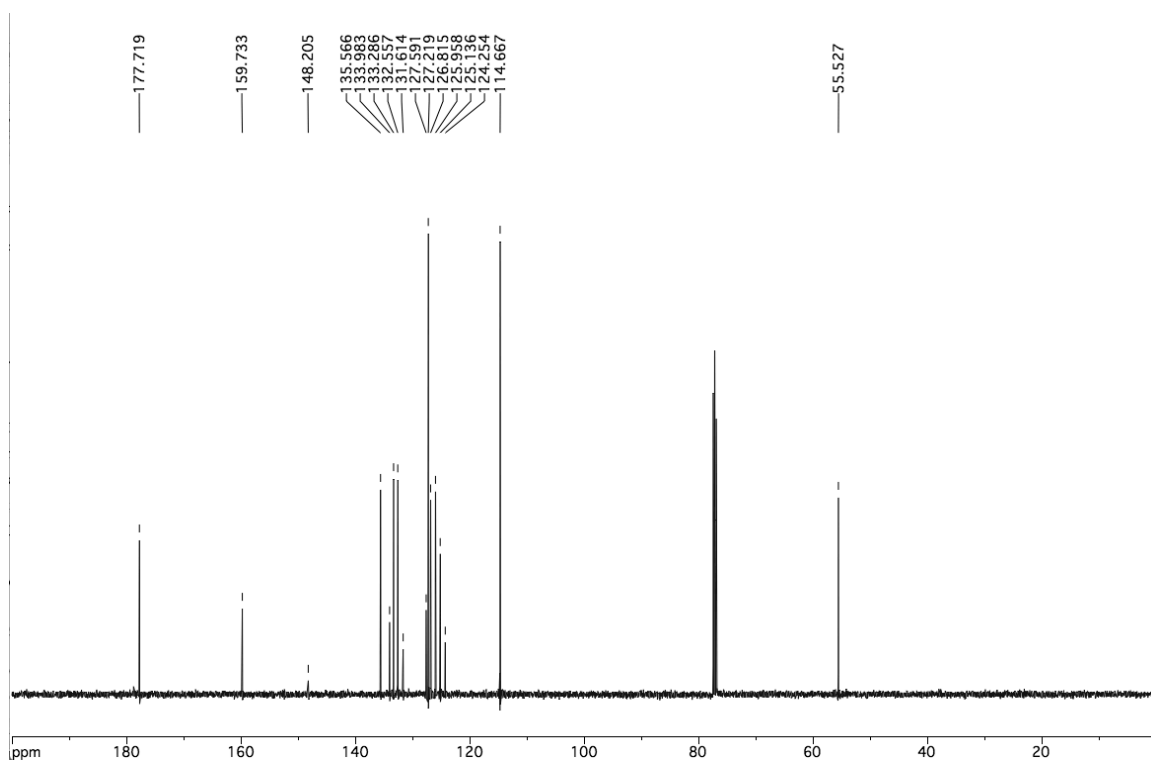


4-(4-Methoxyphenyl)-1-(2-nitrophenylsulfonyl)-1H-pyrrole-2-carbaldehyde (3.105)

^1H NMR spectrum in CDCl_3 , 500 MHz

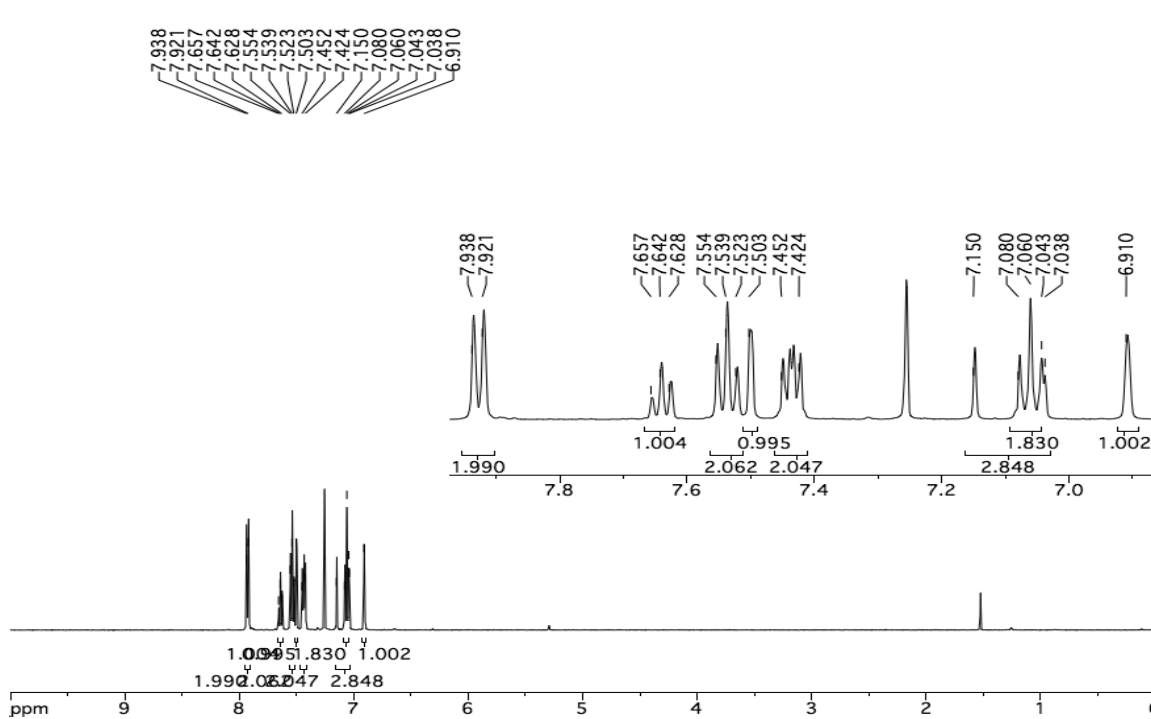


^{13}C NMR spectrum in CDCl_3 , 125 MHz

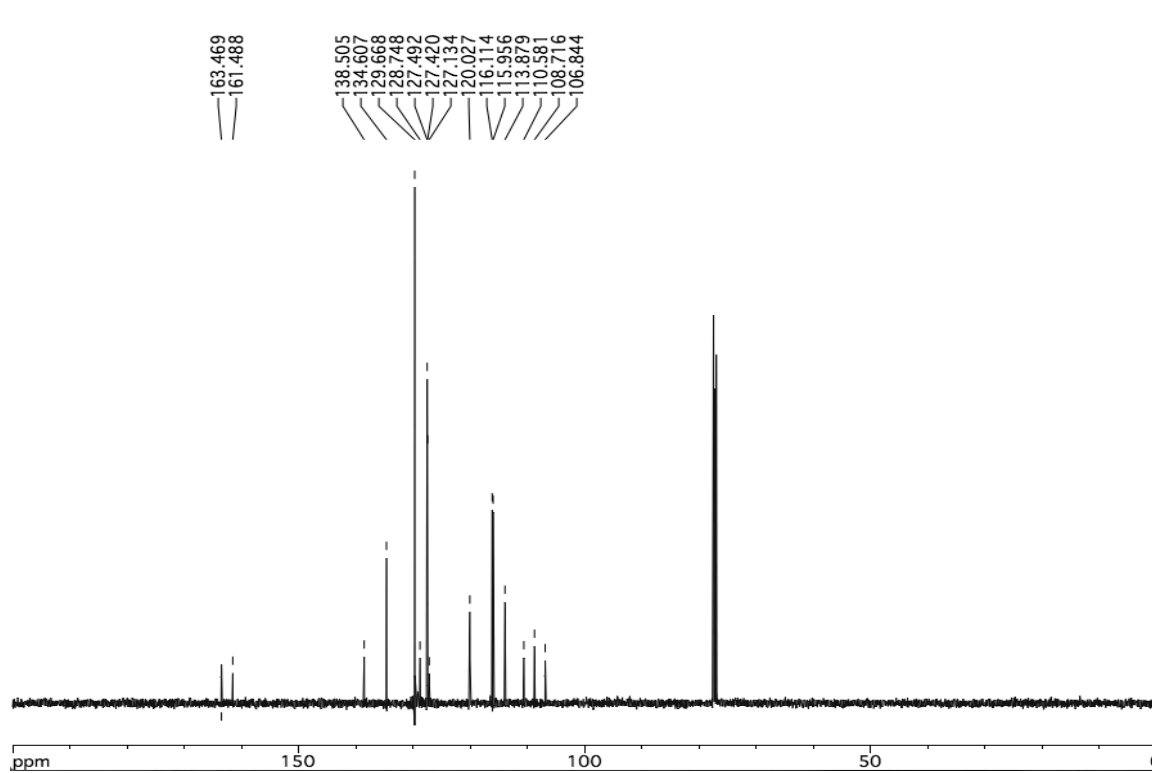


2-(Difluoromethyl)-4-(4-fluorophenyl)-1-(phenylsulfonyl)-1H-pyrrole (3.106)

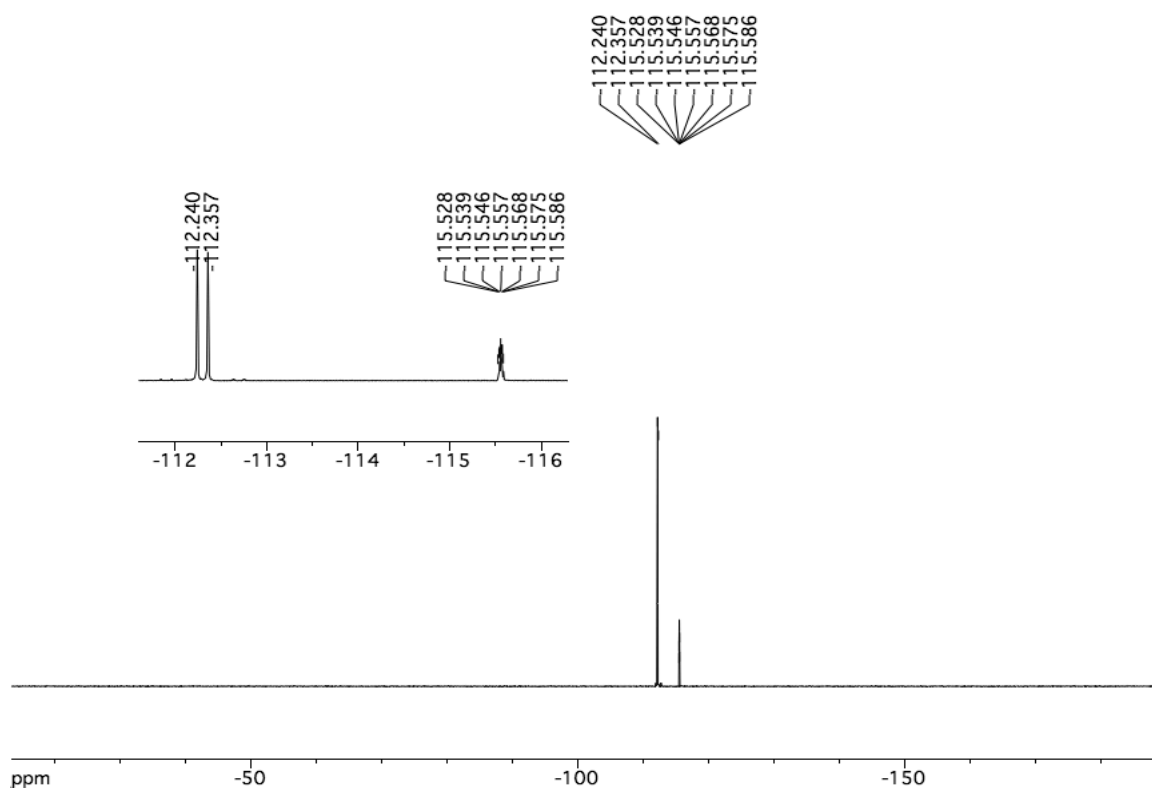
^1H NMR spectrum in CDCl_3 , 500 MHz



^{13}C NMR spectrum in CDCl_3 , 125 MHz

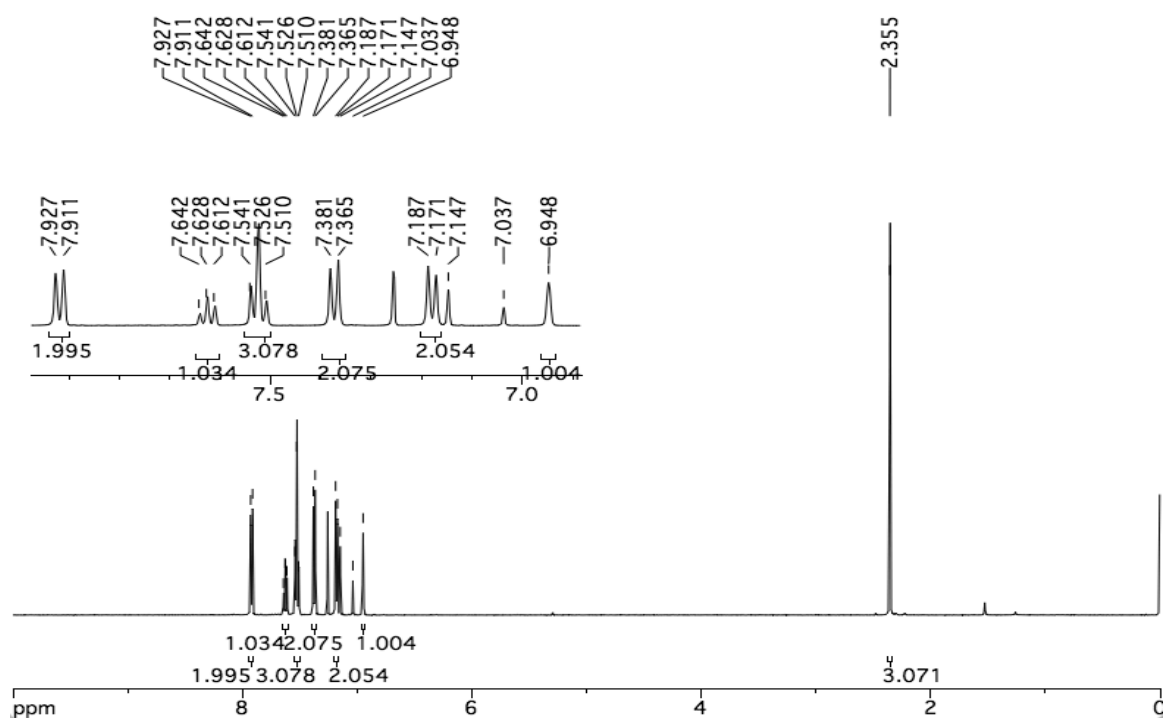


^{19}F NMR spectrum in CDCl_3 , 470 MHz

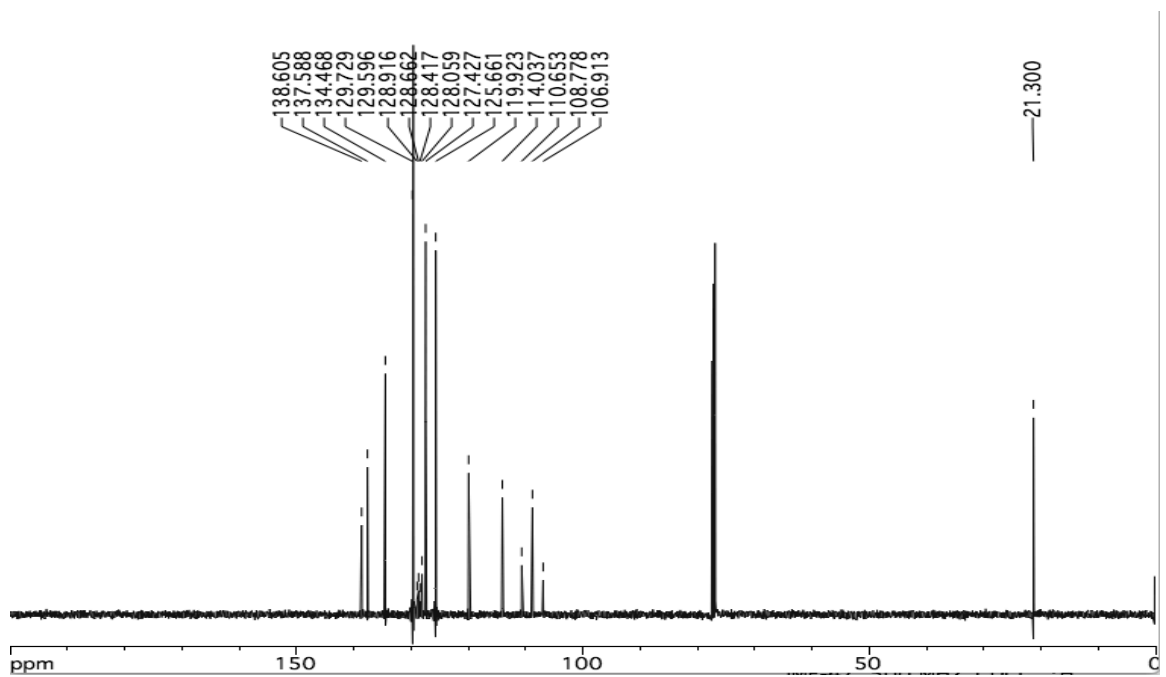


2-(Difluoromethyl)-1-(phenylsulfonyl)-4-*p*-tolyl-1*H*-pyrrole (3.107)

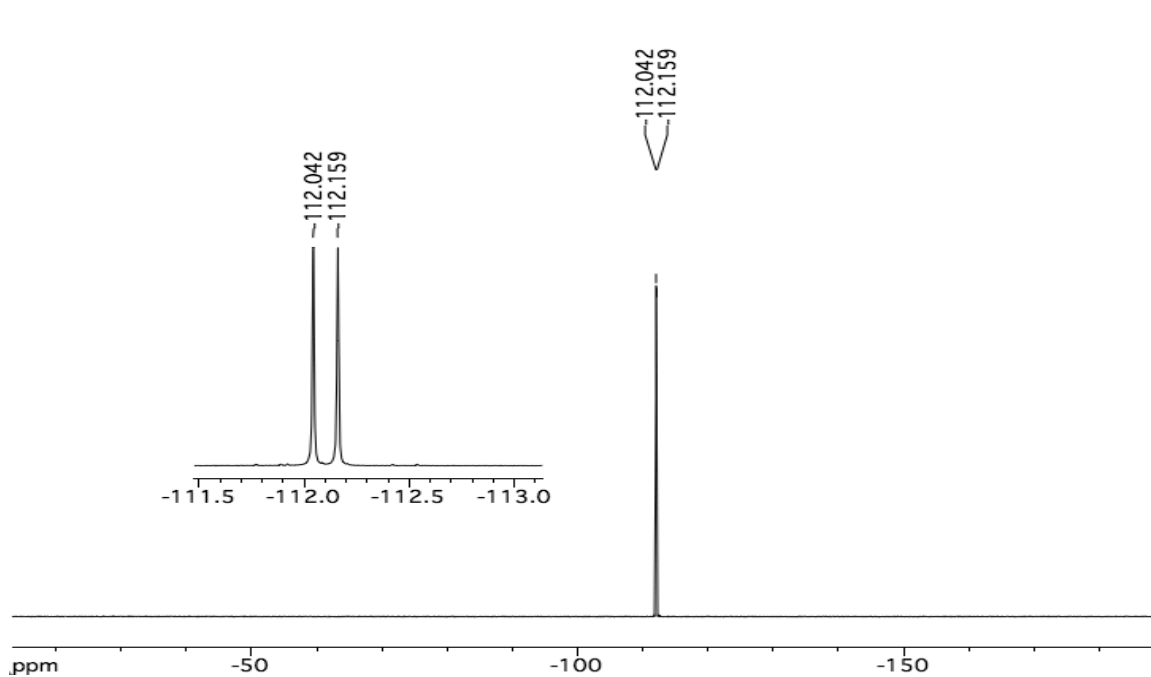
¹H NMR spectrum in CDCl₃, 500 MHz



¹³C NMR spectrum in CDCl₃, 125 MHz

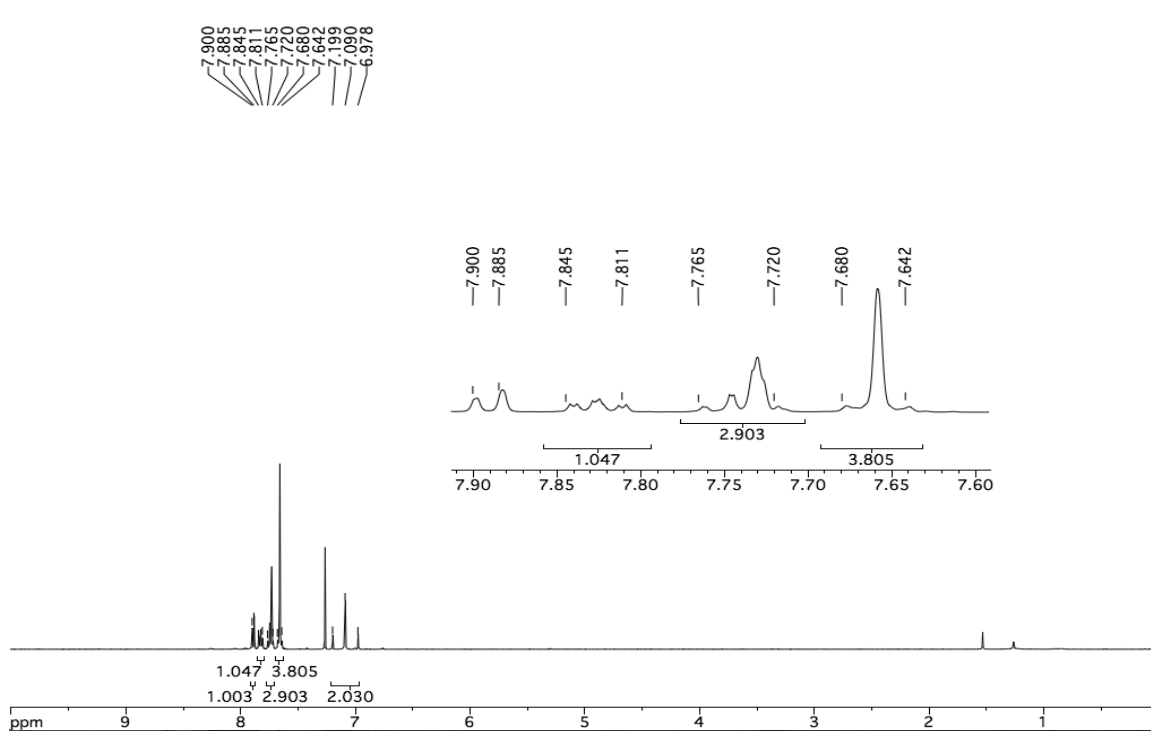


^{19}F NMR spectrum in CDCl_3 , 470 MHz

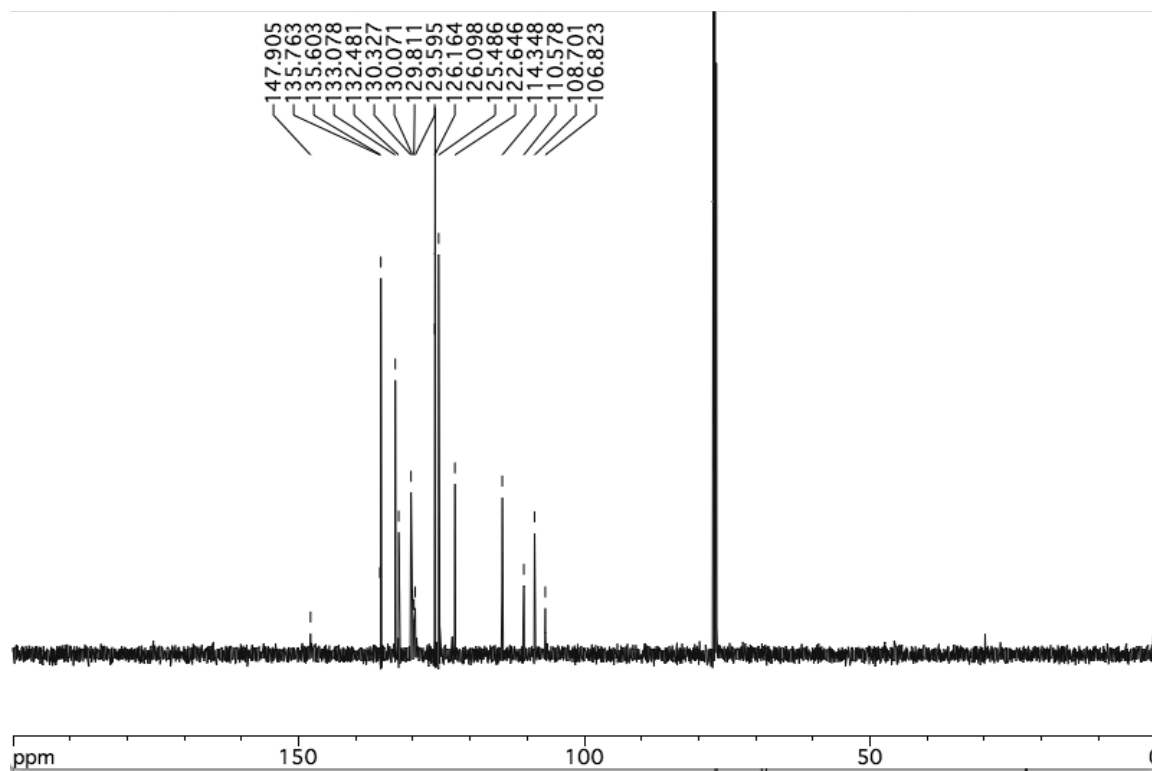


2-(Difluoromethyl)-1-(2-nitrophenylsulfonyl)-4-(4-(trifluoromethyl)phenyl)-1H-pyrrole (3.108)

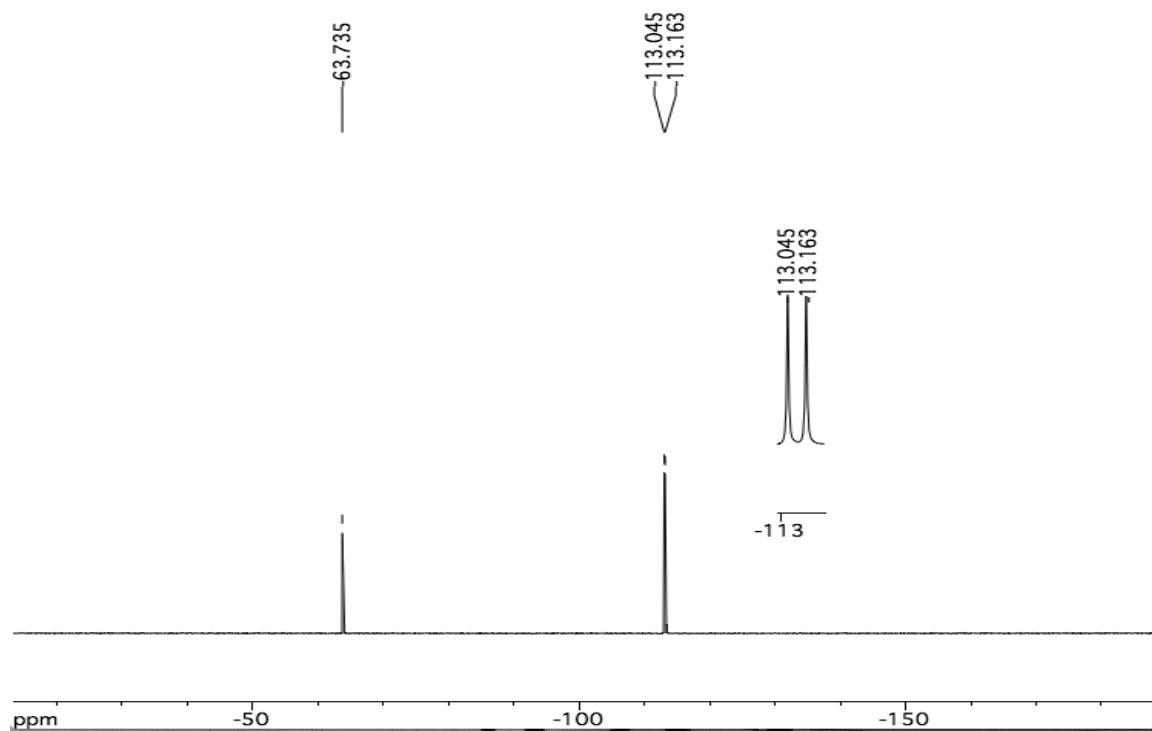
^1H NMR spectrum in CDCl_3 , 500 MHz



^{13}C NMR spectrum in CDCl_3 , 125 MHz

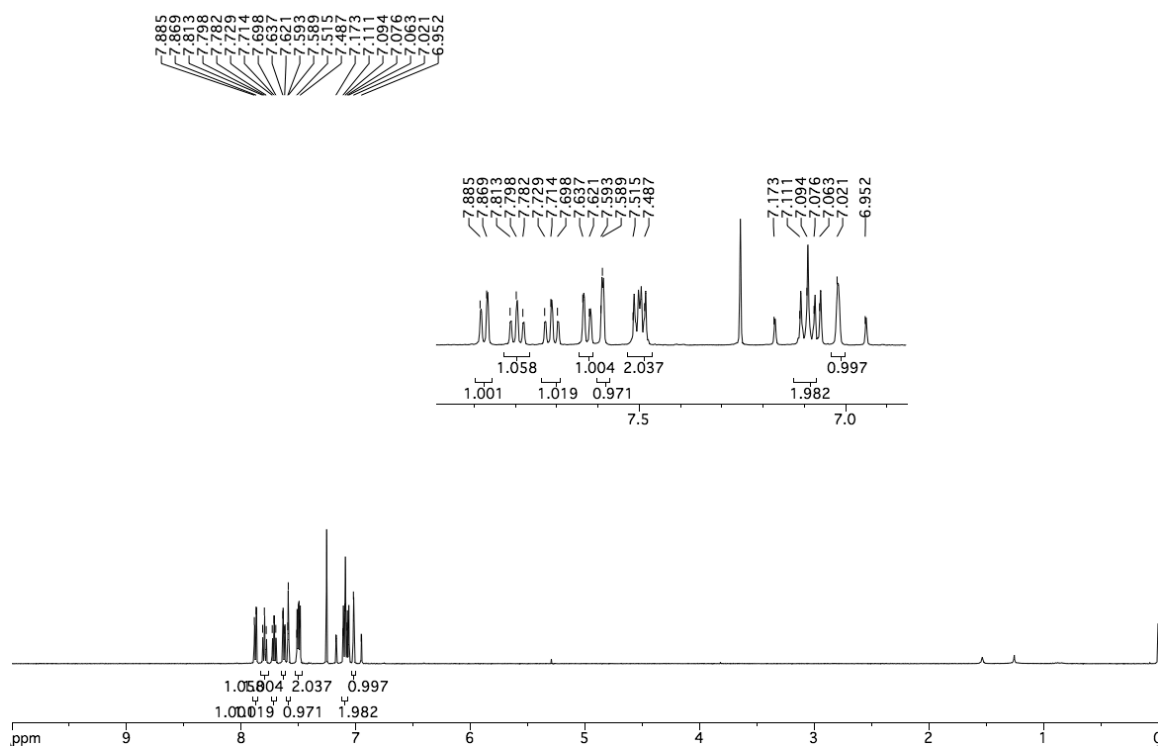


^{19}F NMR spectrum in CDCl_3 , 470 MHz

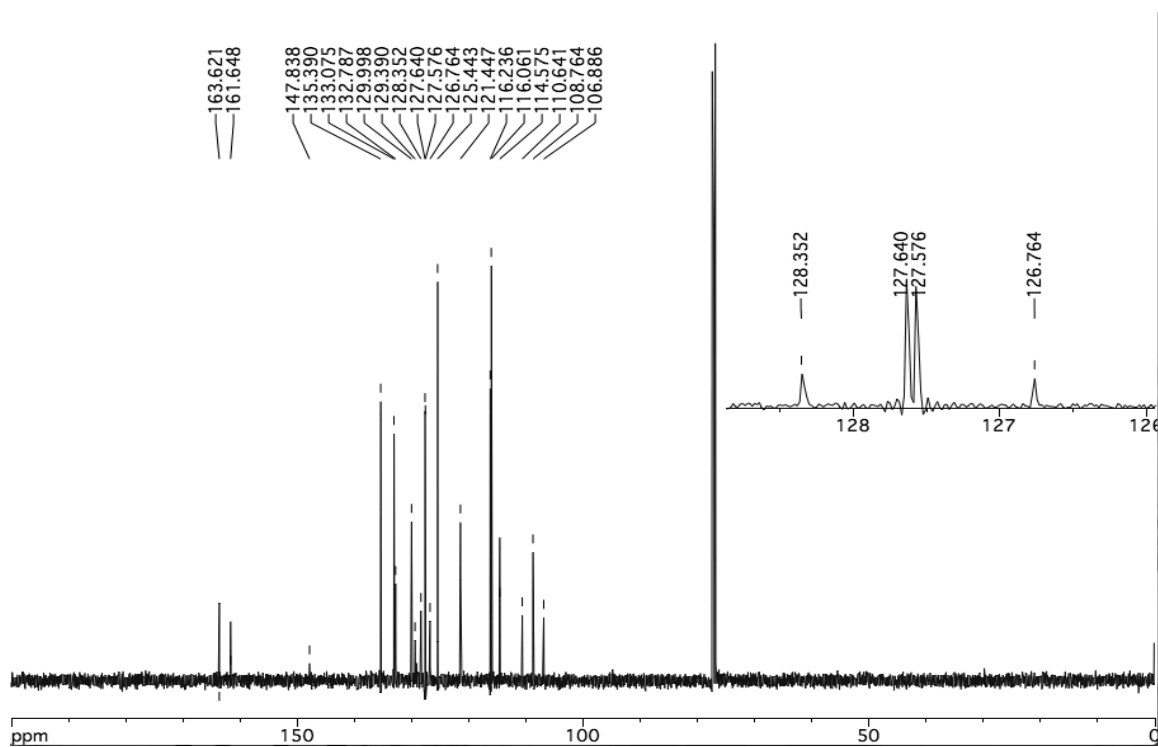


2-(Difluoromethyl)-4-(4-fluorophenyl)-1-(2-nitrophenylsulfonyl)-1H-pyrrole (3.109)

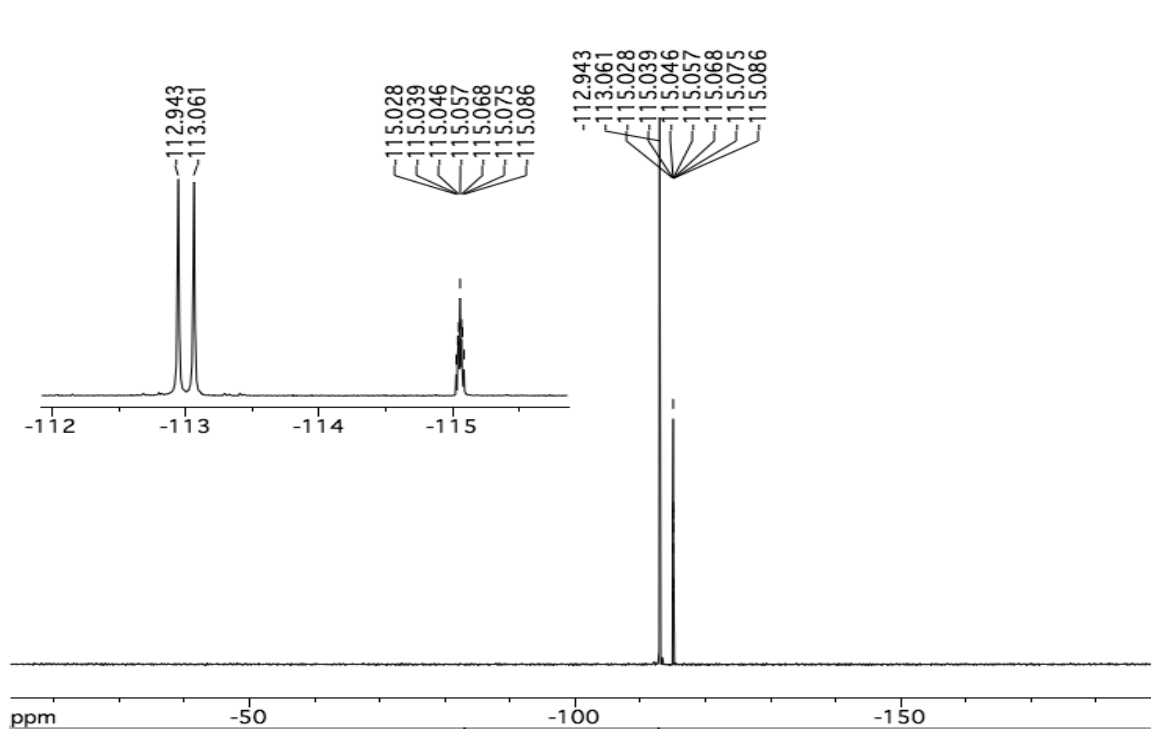
^1H NMR spectrum in CDCl_3 , 500 MHz



^{13}C NMR spectrum in CDCl_3 , 125 MHz

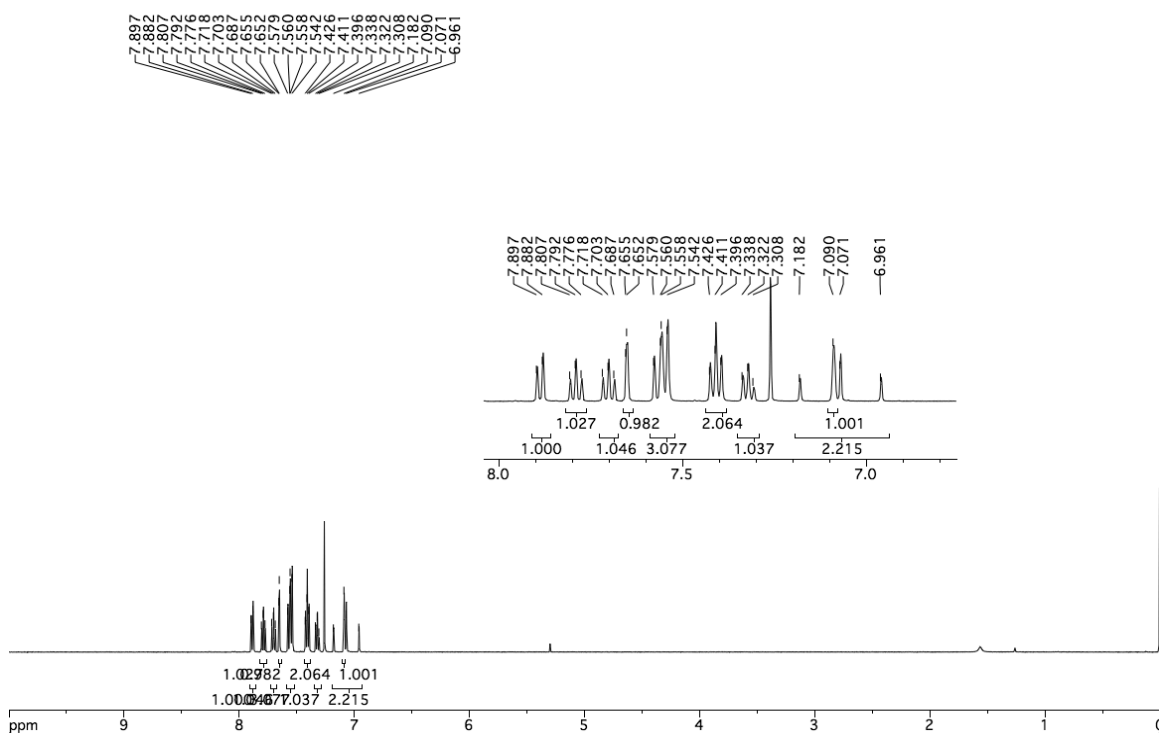


^{19}F NMR spectrum in CDCl_3 , 470 MHz

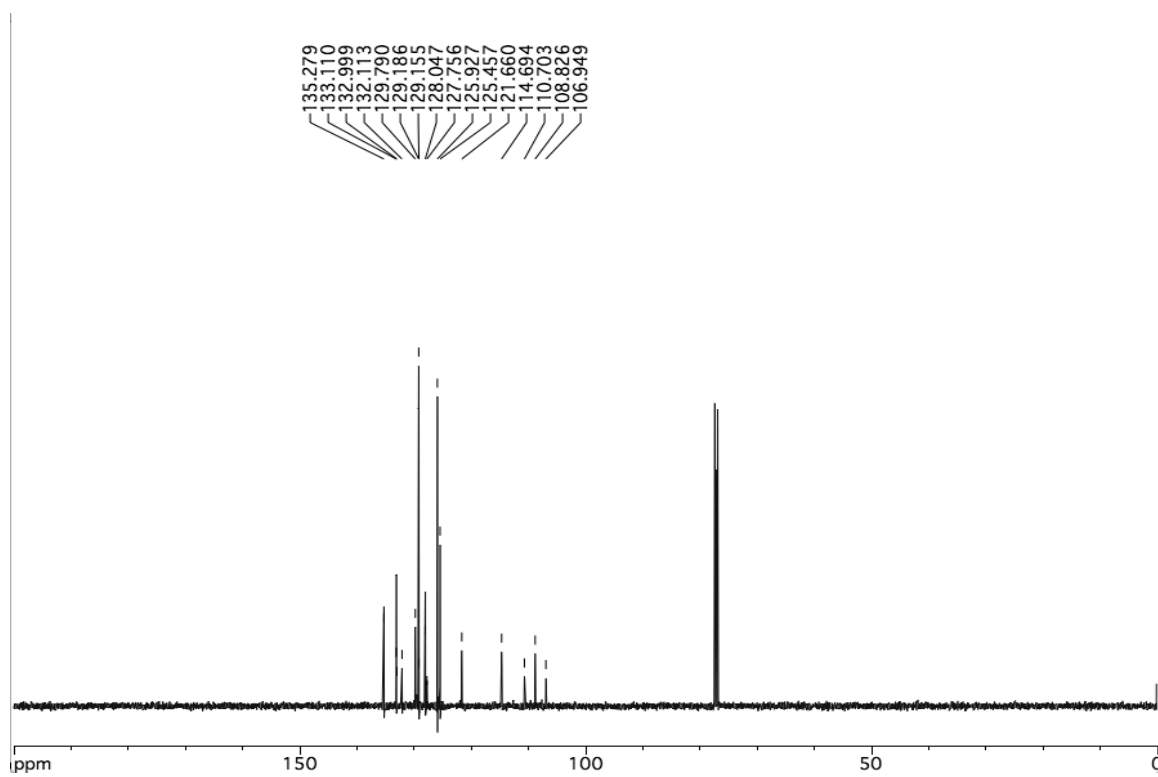


2-(Difluoromethyl)-1-(2-nitrophenylsulfonyl)-4-phenyl-1H-pyrrole (3.110)

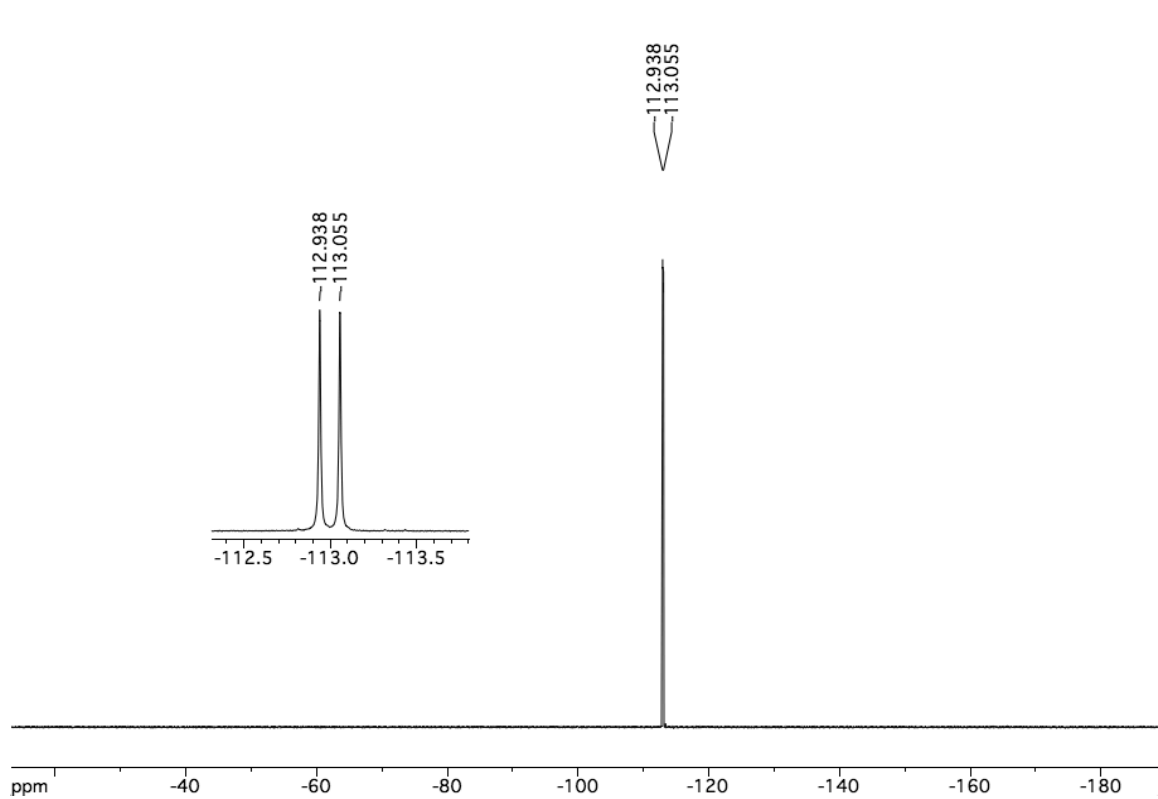
^1H NMR spectrum in CDCl_3 , 500 MHz



^{13}C NMR spectrum in CDCl_3 , 125 MHz

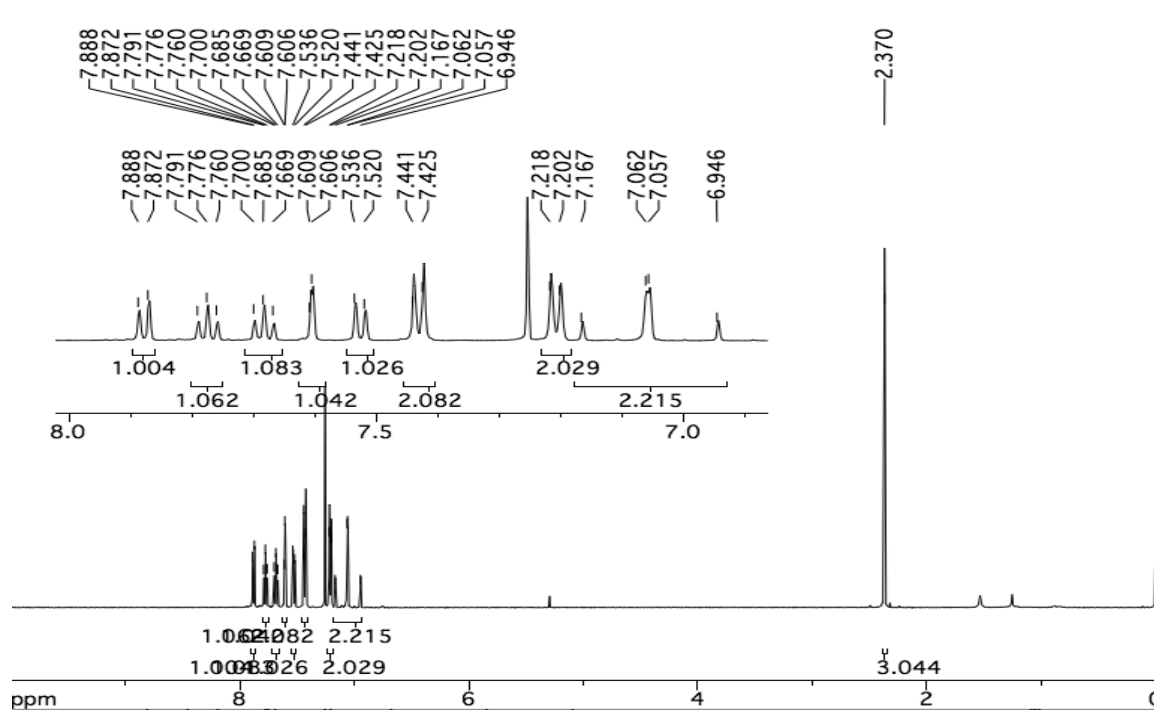


^{19}F NMR spectrum in CDCl_3 , 470 MHz

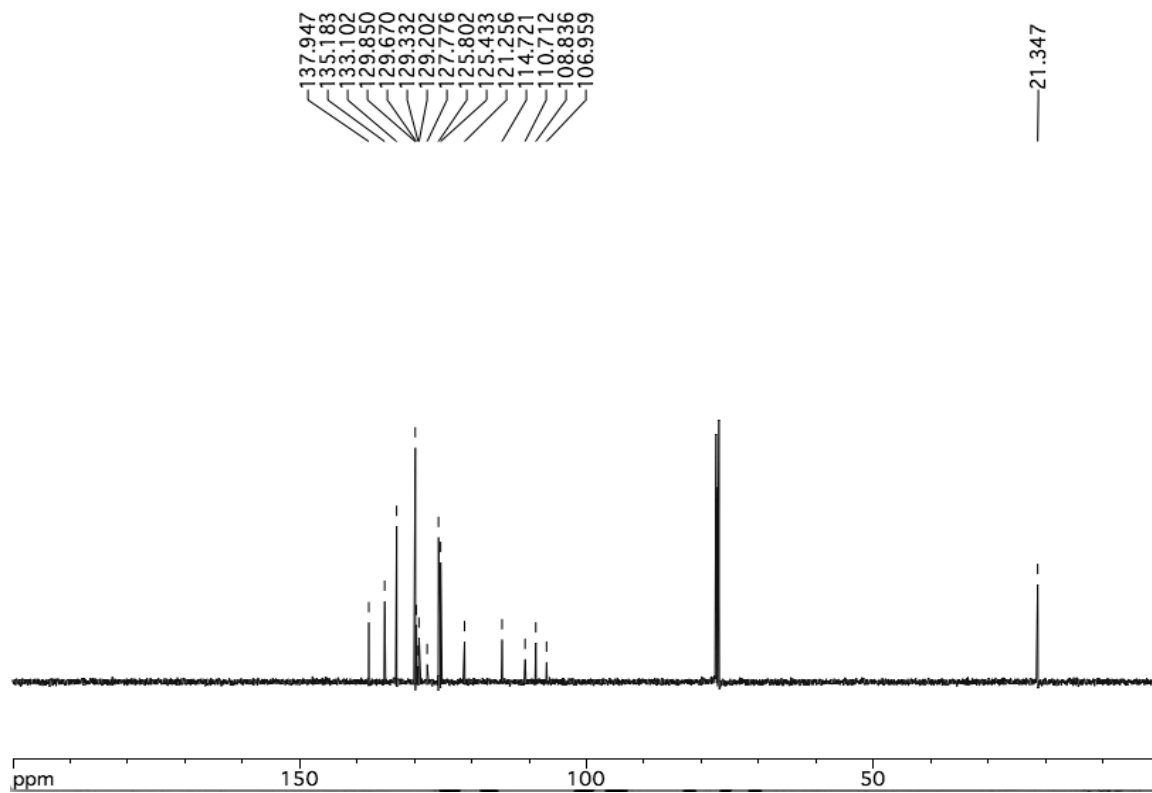


2-(Difluoromethyl)-1-(2-nitrophenylsulfonyl)-4-*p*-tolyl-1*H*-pyrrole (3.111)

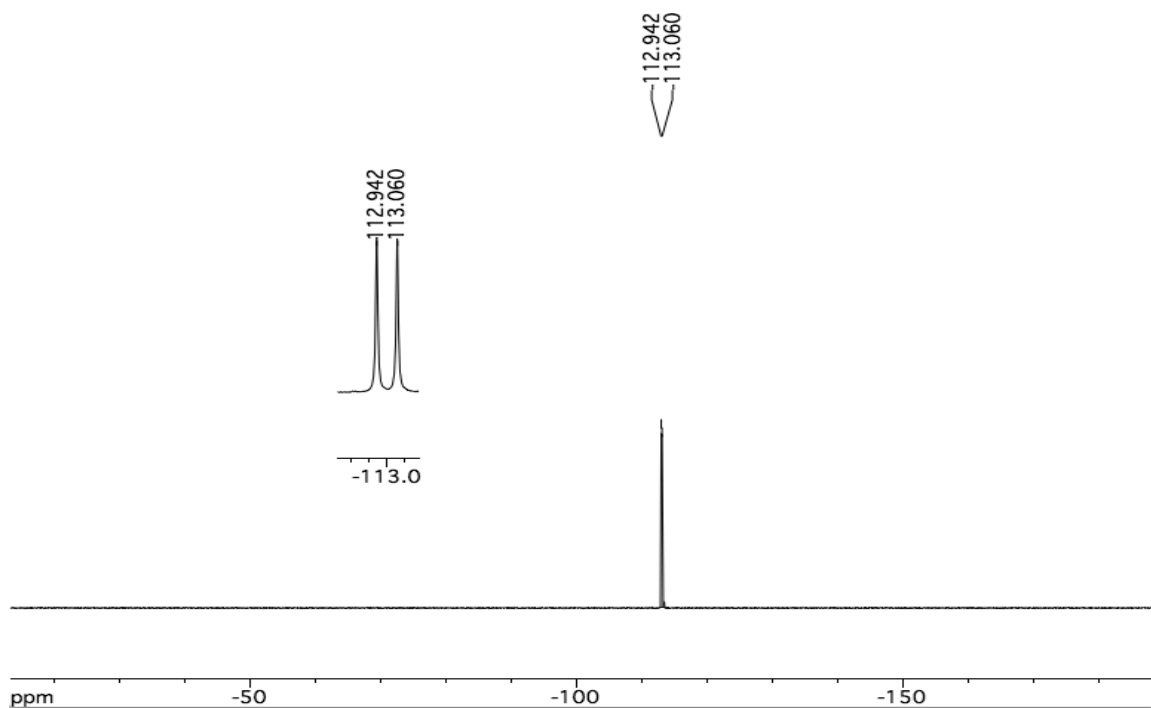
¹H NMR spectrum in CDCl₃, 500 MHz



¹³C NMR spectrum in CDCl₃, 125 MHz

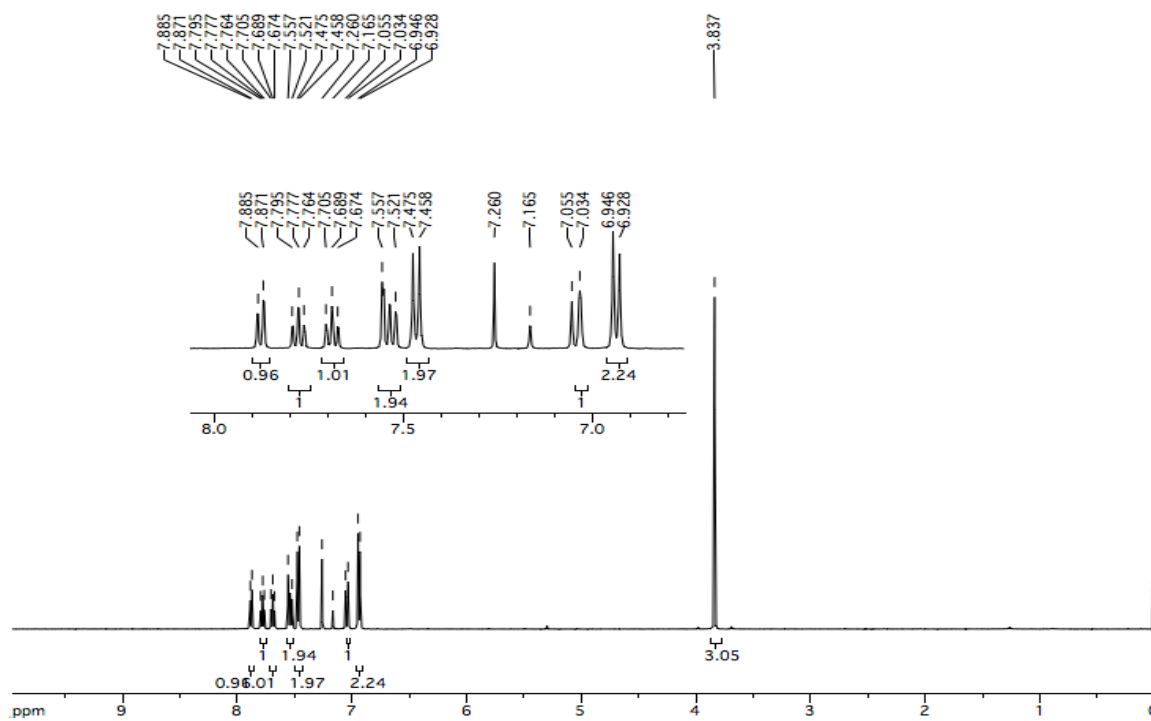


^{19}F NMR spectrum in CDCl_3 , 470 MHz

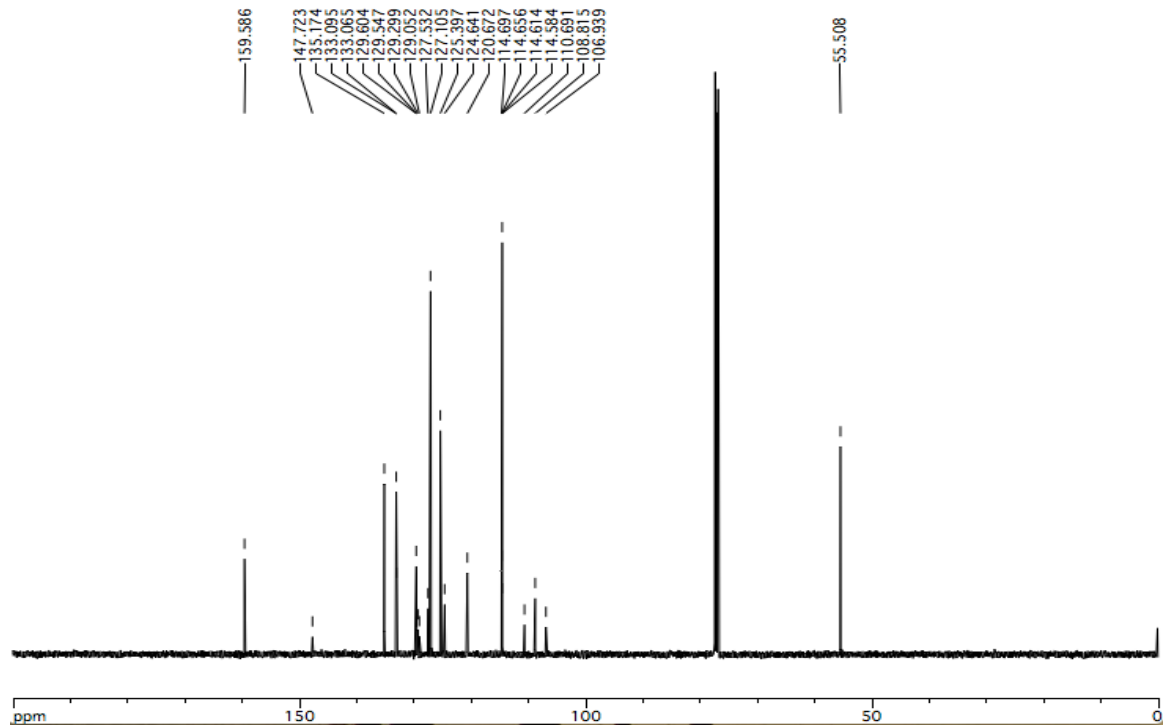


2-(Difluoromethyl)-4-(4-methoxyphenyl)-1-(2-nitrophenylsulfonyl)-1H-pyrrole (3.112)

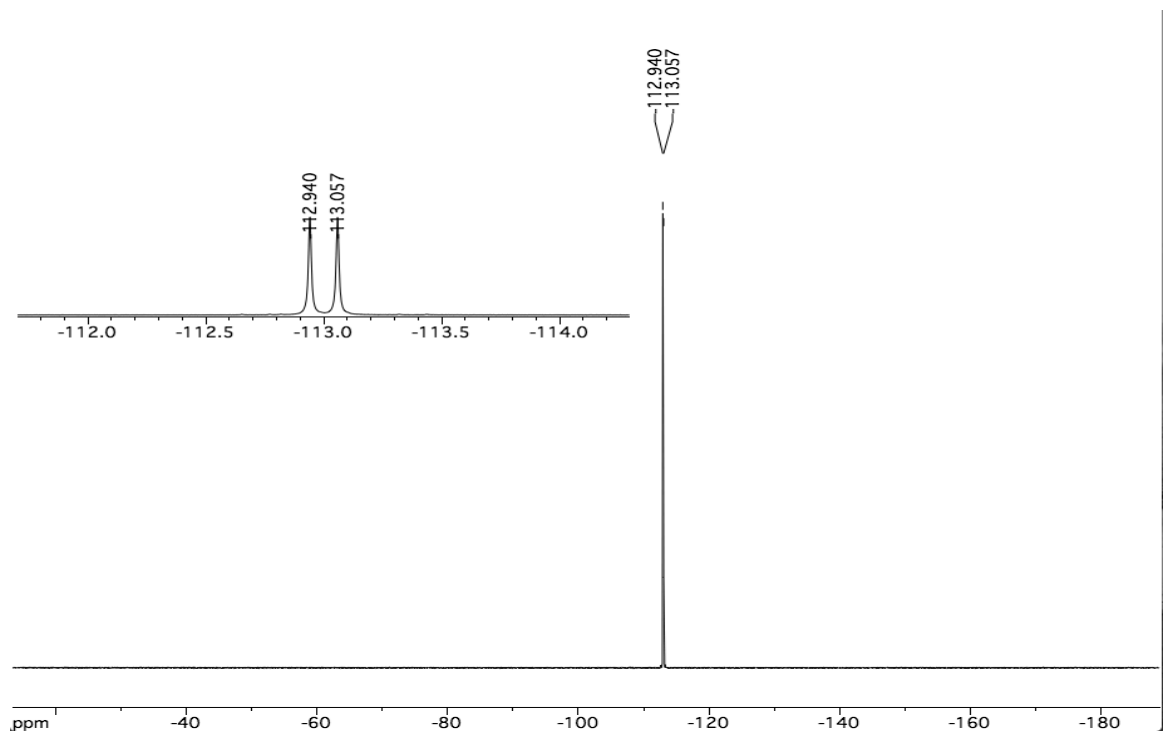
^1H NMR spectrum in CDCl_3 , 500 MHz



^{13}C NMR spectrum in CDCl_3 , 125 MHz



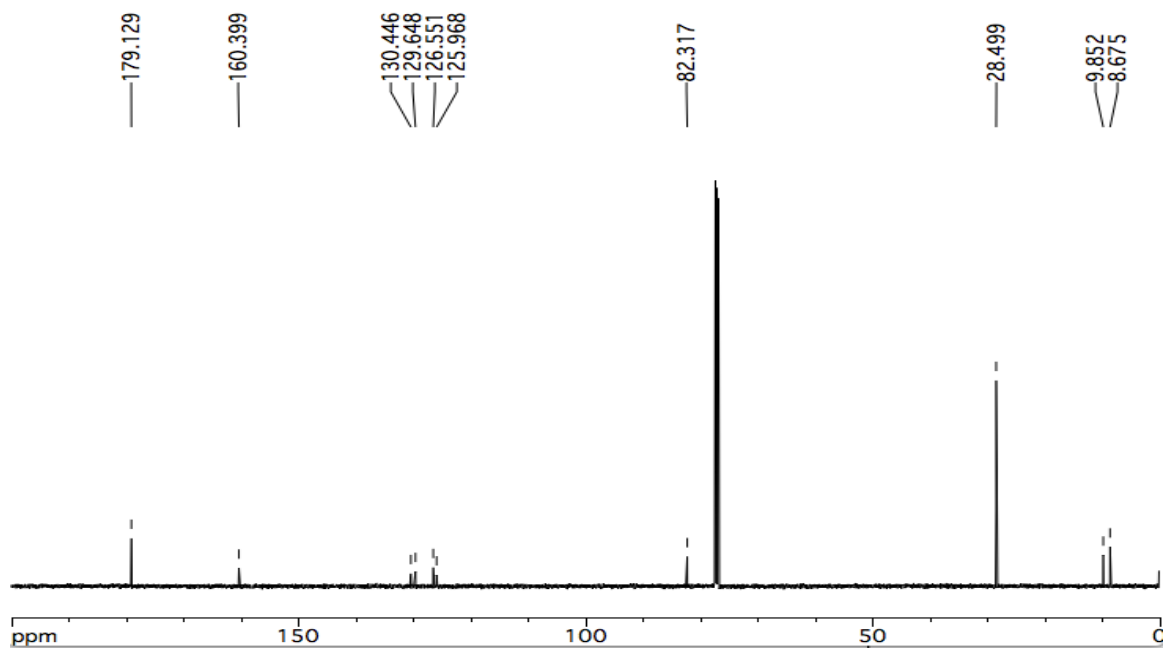
^{19}F NMR spectrum in CDCl_3 , 470 MHz



Appendix 4. NMR Spectra for Chapter 4

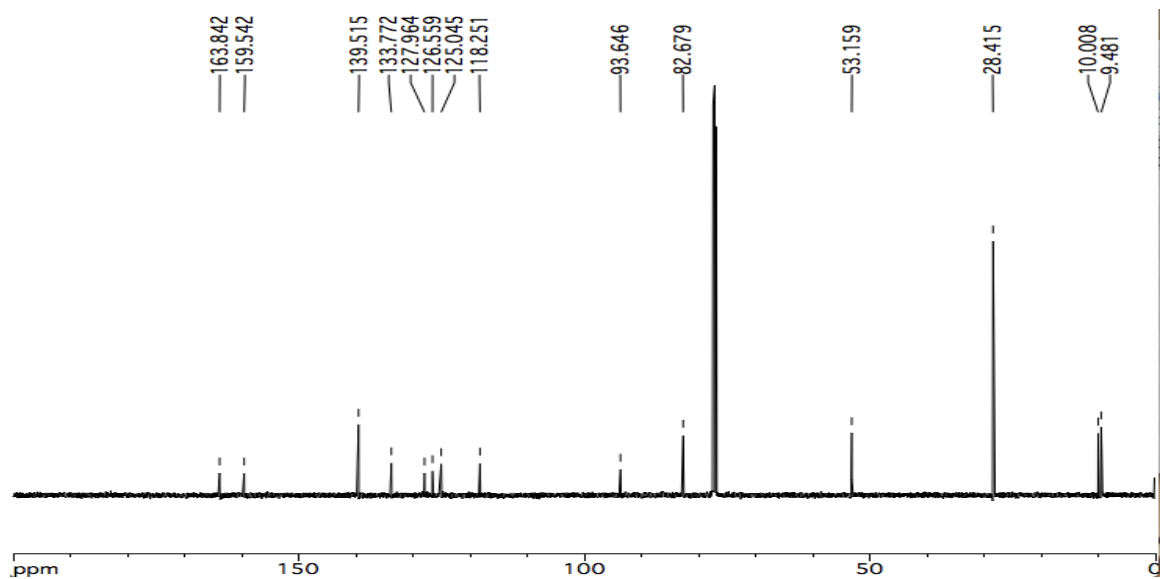
tert-Butyl 5-formyl-3,4-dimethyl-1*H*-pyrrole-2-carboxylate (4.6)

^{13}C NMR spectrum in CDCl_3 , 125 MHz



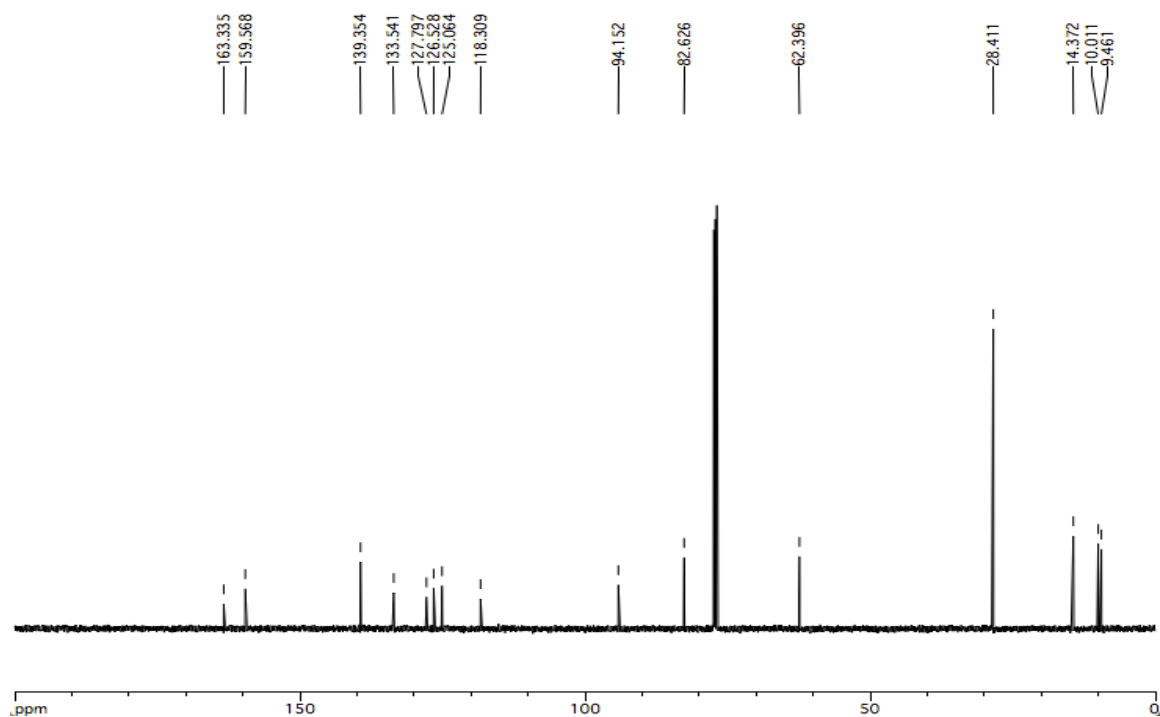
tert-Butyl 5-(2-cyano-2-methoxycarbonylvinyl)-3,4-dimethyl-1*H*-pyrrole-2-carboxylate (4.7a)

^{13}C NMR spectrum in CDCl_3 , 125 MHz



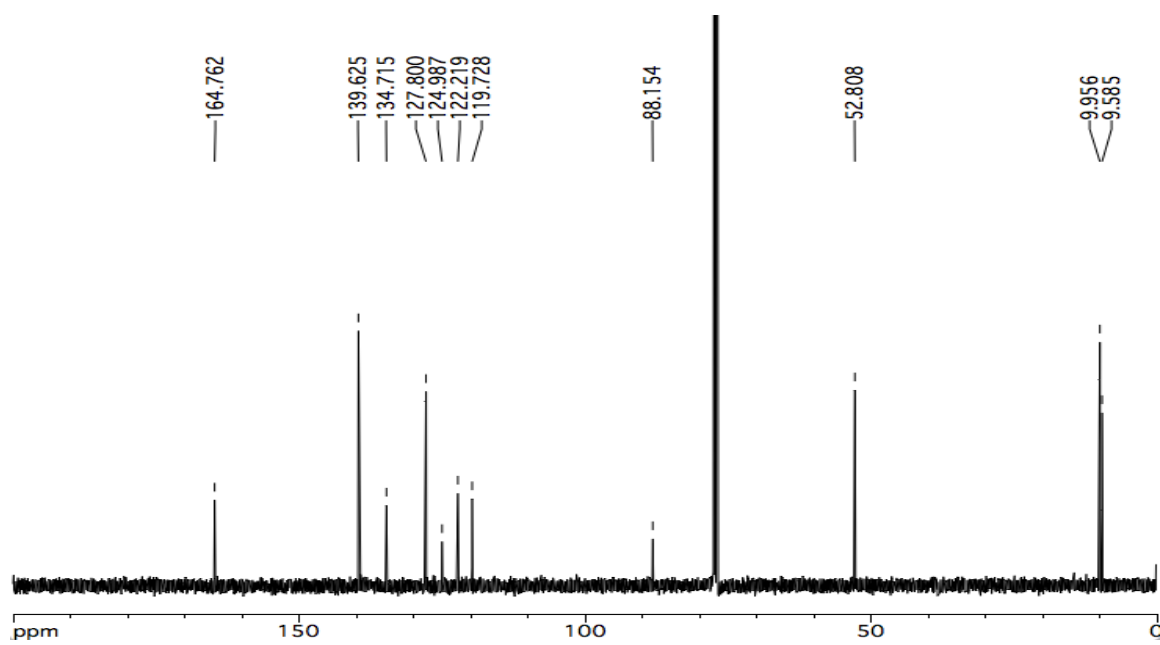
***tert*-Butyl 5-(2-cyano-2-ethoxycarbonylvinyl)-3,4-dimethyl-1*H*-pyrrole-2-carboxylate (4.7b)**

¹³C NMR spectrum in CDCl₃, 125 MHz



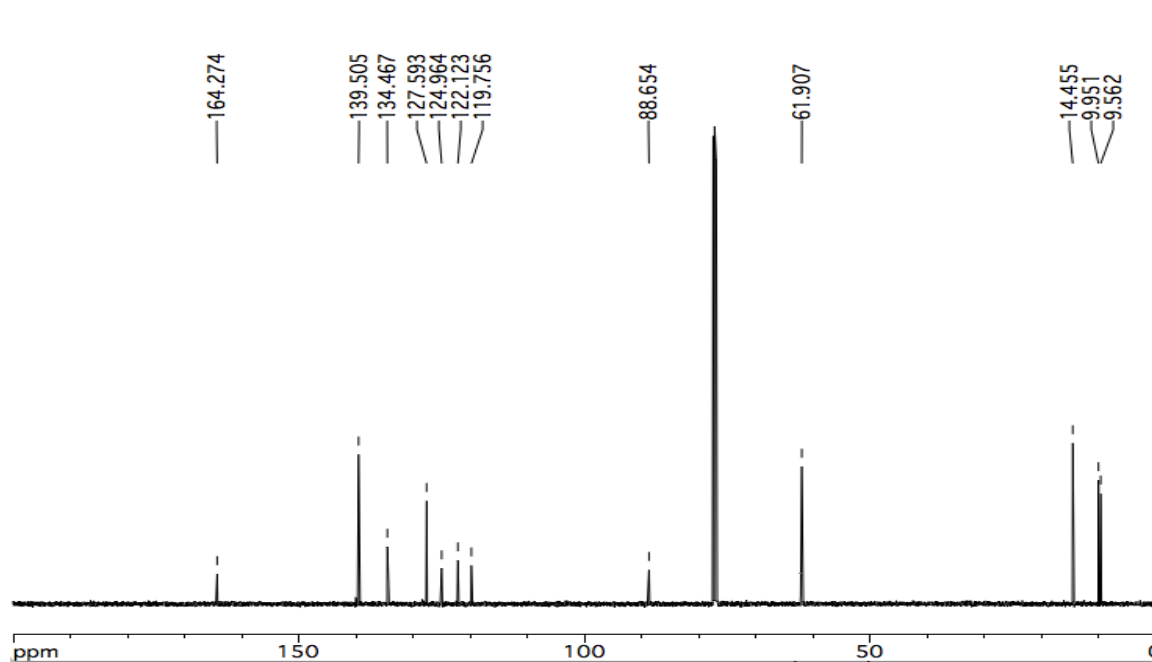
2-(2-Cyano-2-methoxycarbonylvinyl)-3,4-dimethyl-1*H*-pyrrole (4.10a)

¹³C NMR spectrum in CDCl₃, 125 MHz



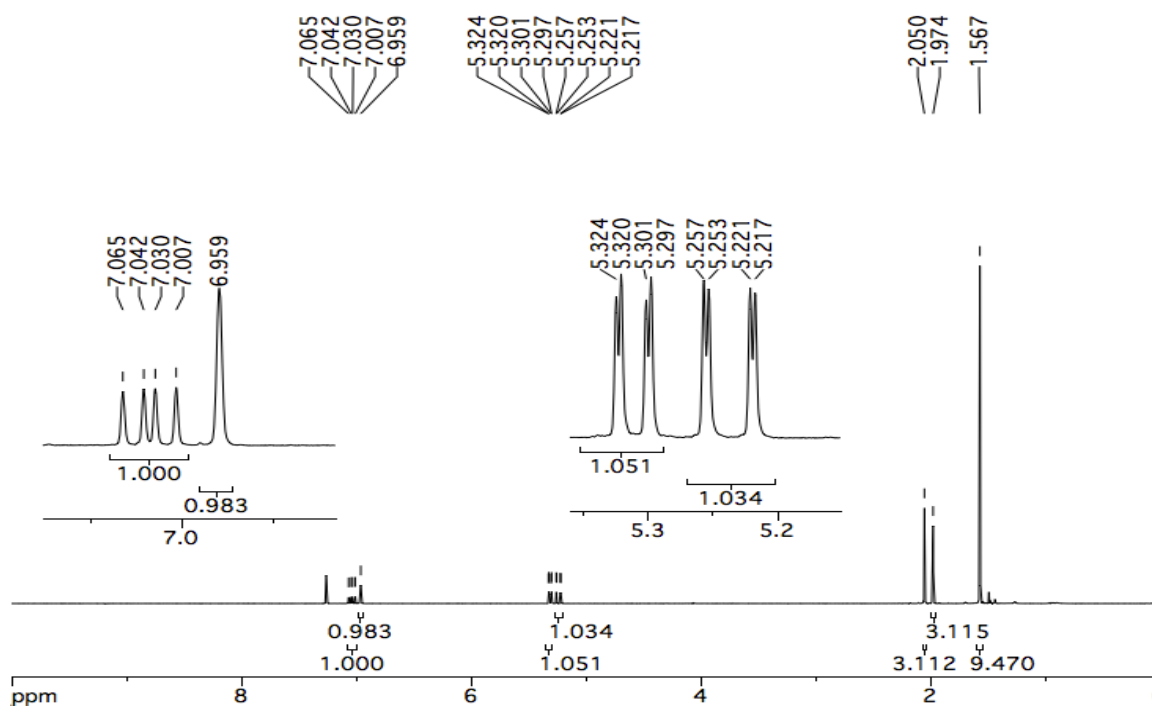
2-(2-Cyano-2-ethoxycarbonylvinyl)-3,4-dimethyl-1H-pyrrole (4.10b)

^{13}C NMR spectrum in CDCl_3 , 125 MHz

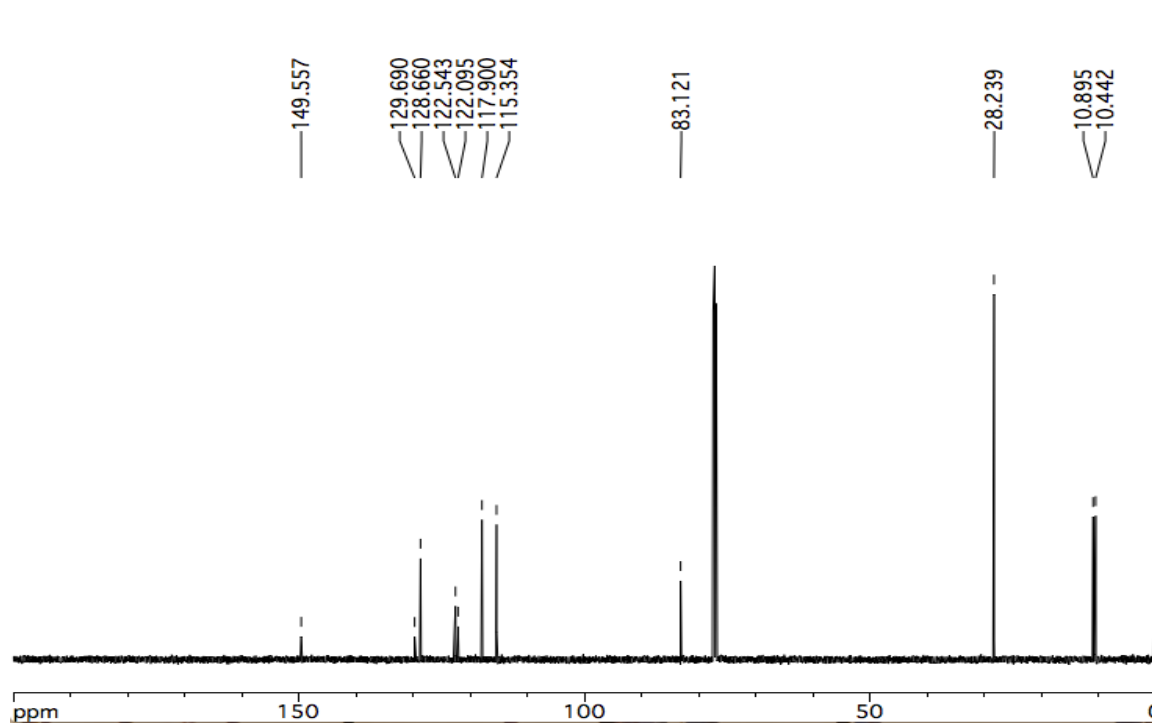


***tert*-Butyl 3,4-dimethyl-2-vinyl-1H-pyrrole-1-carboxylate (4.13)**

^1H NMR spectrum in CDCl_3 , 500 MHz

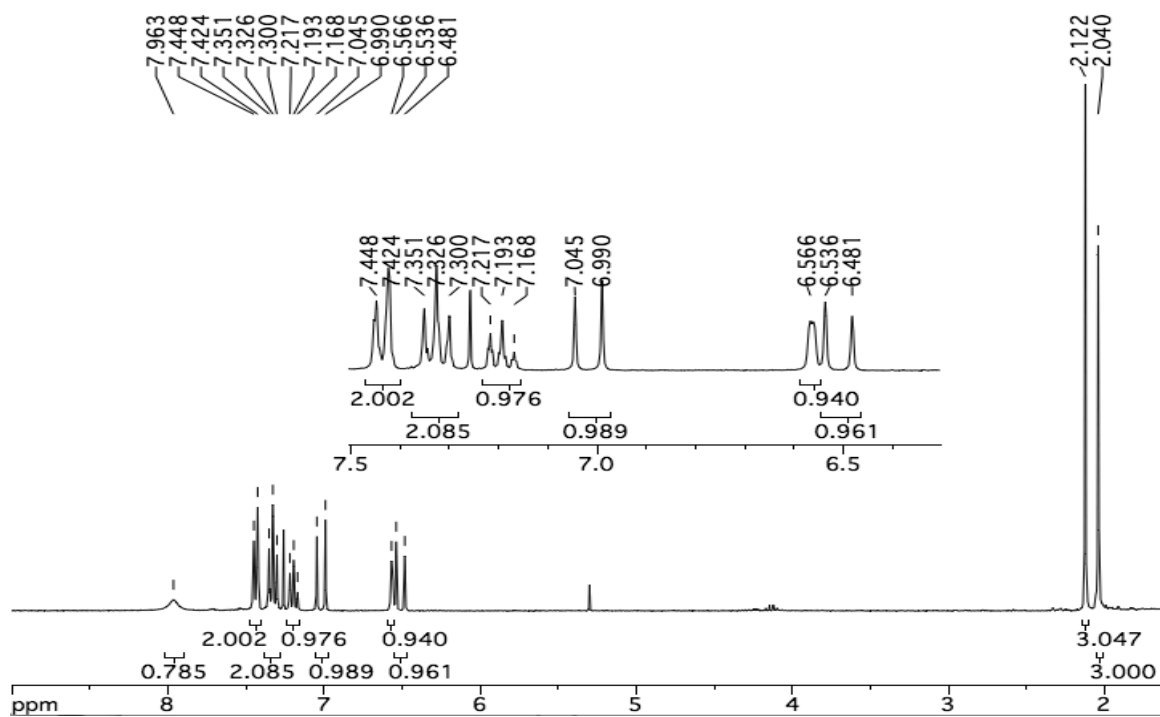


^{13}C NMR spectrum in CDCl_3 , 125 MHz



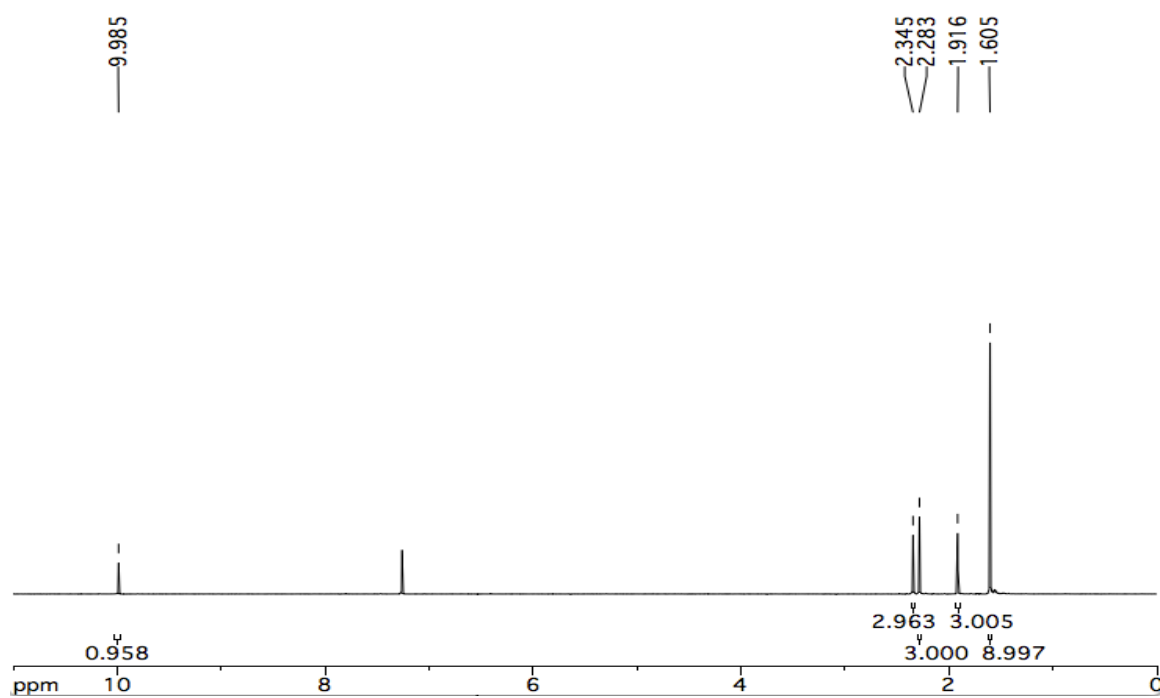
(E)-3,4-Dimethyl-2-styryl-1H-pyrrole (4.16)

^1H NMR spectrum in CDCl_3 , 300 MHz

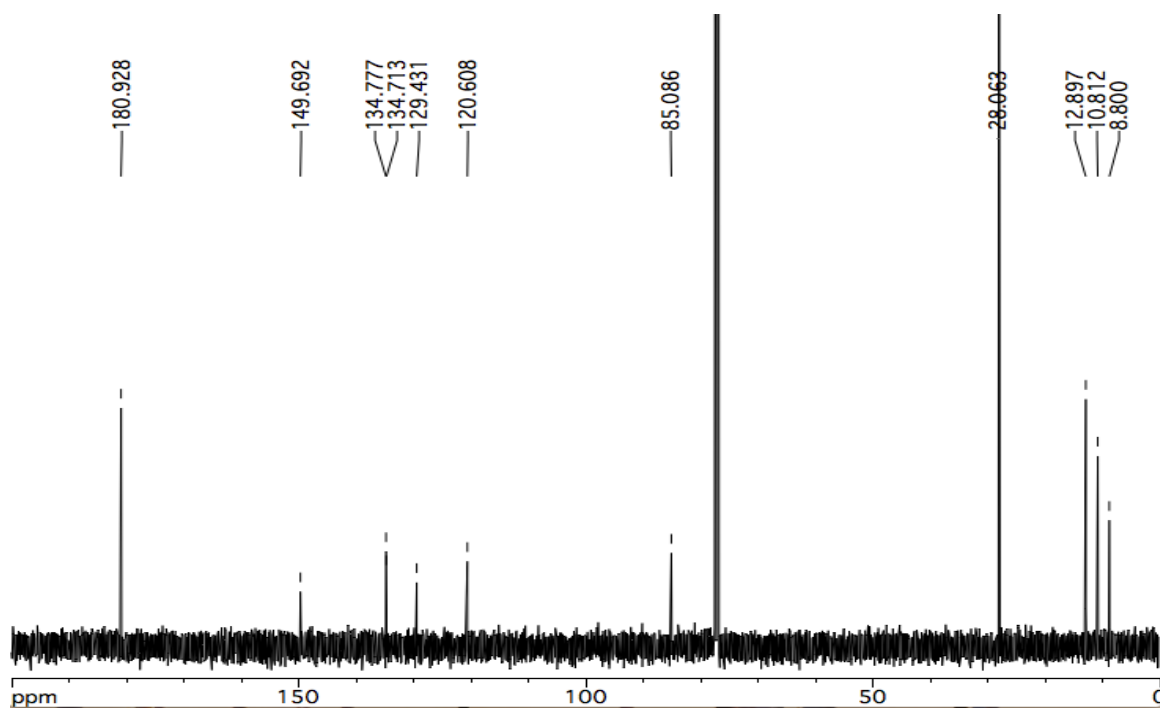


***tert*-Butyl 2-formyl-3,4,5-trimethyl-1*H*-pyrrole-1-carboxylate (4.21)**

^1H NMR spectrum in CDCl_3 , 500 MHz

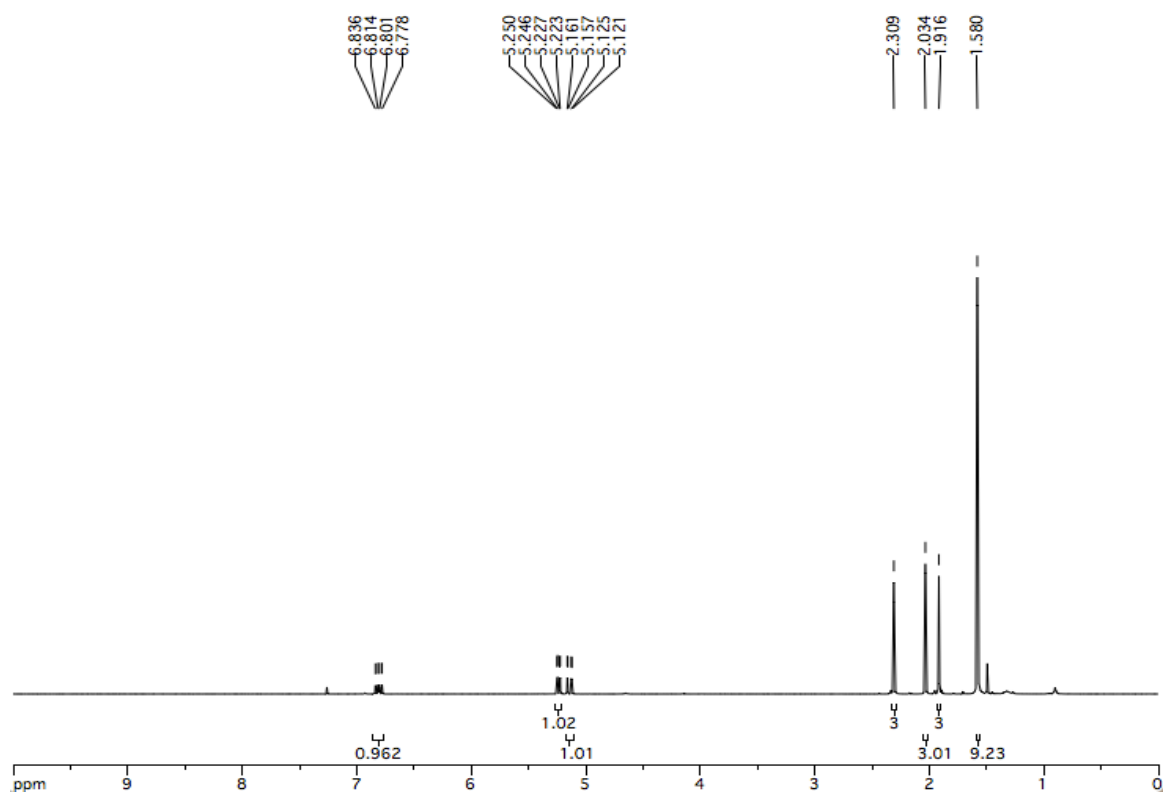


^{13}C NMR spectrum in CDCl_3 , 125 MHz

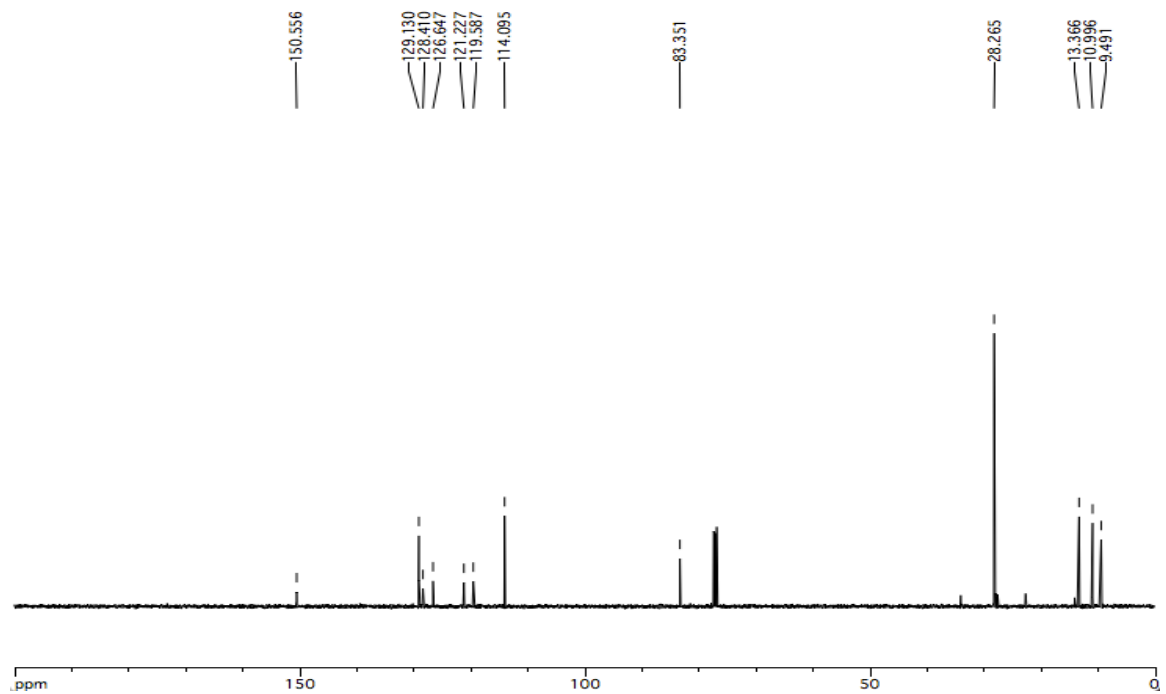


***tert*-Butyl 2,3,4-trimethyl-5-vinyl-1*H*-pyrrole-1-carboxylate (4.19)**

¹H NMR spectrum in CDCl₃, 500 MHz

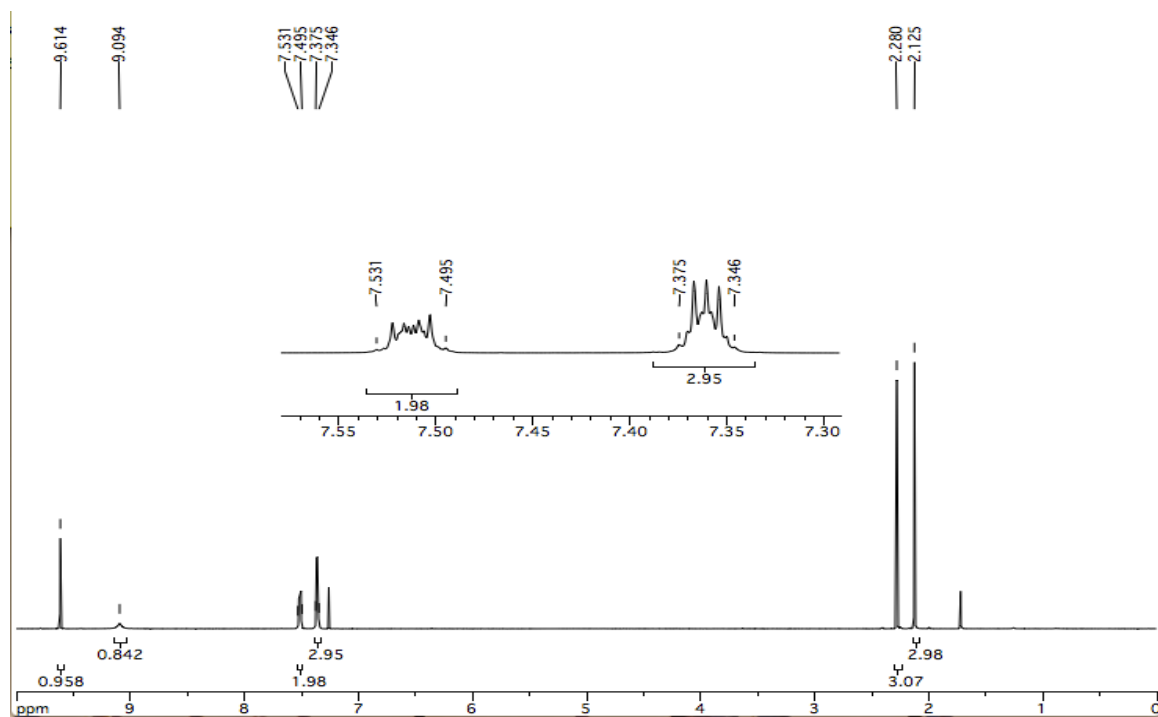


¹³C NMR spectrum in CDCl₃, 125 MHz



3,4-Dimethyl-5-(phenylethynyl)-1H-pyrrole-2-carbaldehyde (4.24)

^1H NMR spectrum in CDCl_3 , 500 MHz



^{13}C NMR spectrum in CDCl_3 , 125 MHz

