A Look into the Reactivity and Functionality of Pyrroles and Dipyrrins

by

Min Joon Kim

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Abstract

The dipyrrin unit formally consists of a pyrrolic unit and an aza-fulvenium unit. Within this thesis, two projects involving pyrroles and dipyrrins will be discussed.

2-Formyl pyrroles play a critical role in pyrrole chemistry because they act as a precursor to multi-pyrrolic compounds including dipyrrins. Herein a new synthetic route to 2-formyl pyrroles from 2-thionoester pyrroles is explored. 2-Thionoester pyrroles, when treated with Raney nickel in acetone, are reduced to their corresponding 2-formyl pyrroles. Along with the optimization process of this desulfurative reduction, mechanistic studies are discussed.

By arylating the α-, β-, and meso-positions of dipyrrins, we wish to establish a synthetic pathway for each position of arylation. Through pre-functionalization of pyrroles and Suzuki coupling, α-Ph and β-Ph dipyrrins were synthesized. Miyaura borylation of dipyrrins were attempted to explore a new synthetic route to introduce an aryl moiety onto the dipyrrin core.

List of Abbreviations and Symbols Used

Ac – Acetate

α – Alpha

Å – Angstrom

Ar – Aryl

Bn – Benzyl

β – Beta

bipy – Bipyridyl

Bpin – Boronic acid pinacol ester

br – Broad

δ – Chemical shift

CoA – Coenzyme A

J – Coupling constants

COD – 1,5-Cyclooctadiene

°C – Degrees Celsius

DDQ – 2,3-Dichloro-5,6-dicyanobenzoquinone

DCM – Dichloromethane

H-DIBAL – Diisobutylaluminum hydride

d – Doublet

ESI – Electrospray ionization

Et – Ethyl

g – Grams

Hz – Hertz

HRMS – High resolution mass spectrometry

HV – Hollingsworth & Vose

h – Hour

IUPAC – International Union of Pure and Applied Chemistry

L – Litre

m/z – Mass-to-charge ratio

MHz – Megahertz

m.p. – Melting point

Me – Methyl

μm – Micrometre

mL – Millilitre

mmol – Millimole

M – Molarity

ε – Molar extinction coefficient

mol – Mole

m – Multiplet

NMR – Nuclear magnetic resonance

ppm – Parts per million

p – Pentet

Ph – Phenyl

q – Quartet

s – Singlet

^{t}Bu – *tert*-Butyl

THF – Tetrahydrofuran

TLC – Thin layer chromatography

t – Triplet

UV – Ultraviolet

USD – United States Dollar

W – Watt

λ – Wavelength

w/w – Weight/weight percent

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Chapter 1. Introduction

1.1 Overview

This thesis composes of two distinct projects. The first one involves the reduction of 2-thionoester pyrroles; the second involves the synthesis of various functionalized dipyrrins, *F*-BODIPYs and α-borylated dipyrrins through Miyaura borylation. The common theme of these projects is to explore the reactivity and the synthetic opportunities presented by pyrrole-containing chemical species.

1.2 Pyrrole

The main focus of research within the Thompson group is on pyrroles. Pyrroles are heterocyclic compounds, containing one nitrogen atom in a five-membered ring system. Pyrrole was first isolated from bone oil in 1857, and its structure was first characterized in 1870.[1] The numbering system of pyrrole, set by the International Union of Pure and Applied Chemistry (IUPAC), is shown in **Figure 1**. Another common system of nomenclature involves denoting the α- and β- positions, where the 2- and 5- positions are referred as α- and α'-positions and the 3- and 4- positions as β- and β'-positions.

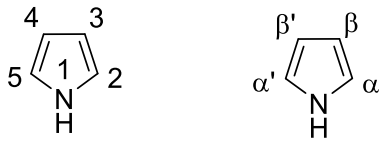


Figure 1. The IUPAC numbering of the pyrrole ring (left); alternative numbering system (right).

Pyrroles, biosynthetic precursors for various natural products, are widely studied for their use in pharmaceutics as anti-inflammatory drugs[2,3] (e.g. Tolmetin and Zomepirac), immunosuppressants[4] (e.g. prodigiosin), and anticancer agents[5,6] (e.g. Roseophilin). One

of the most well-known pyrrole-containing drugs is Lipitor, also known as atorvastatin (**Figure 2**). Lipitor is a cardiovascular drug, and its original form was first discovered in the 1970s[7] after it was isolated as a natural product from fungal strains. Lipitor is used to reduce the level of cholesterol by acting as a competitive inhibitor of HMG CoA enzyme (3-hydroxy-3-methyl-glutaryl-coenzyme A reductase), which plays an important role in transforming acetyl CoA into a cholesterol in our bodies.[8] Lipitor has been the top-selling low-density-lipoprotein drug in history, peaking with total revenue of $130 billion USD by 2011.[9]

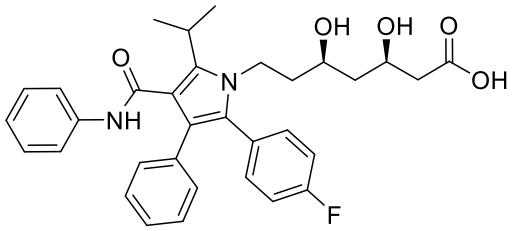


Figure 2. Structure of Lipitor (atorvastatin).

The synthesis of complex pyrrole-containing molecules such as Lipitor is viable courtesy of the electronic properties of the pyrrole unit. Pyrroles are aromatic compounds, given their six pi-electron system, a planar cyclic structure, and a fully conjugated system.[10] Since pyrroles have delocalized pi-electrons, they can be represented by several contributing resonance structures (**Figure 3**). Similarly to appropriately substituted benzene rings, pyrrole can easily undergo electrophilic substitution, particularly as the first such intermediate bears a full octet of electrons of each atom. The ease of electrophilic substitution opens up countless synthetic opportunities.[11]

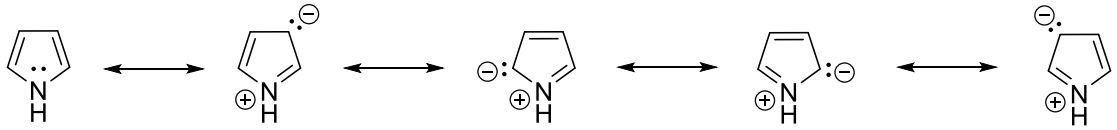


Figure 3. Resonance structures of pyrrole.

The lone pair of electrons on the nitrogen atom of pyrrole is part of the pi-system of a pyrrole ring. The role of this lone pair becomes important when considering the reaction pathways that pyrroles tend to follow. For instance, an ester-bearing pyrrole (i.e. 2-carboxylate pyrrole) has another contributing resonance structure, as shown in **Figure 4**, an appreciation of which reveals why the carbonyl carbon is less reactive towards nucleophilic attack than are typical esters. Given that the lone pair of electrons on nitrogen stabilize through resonance, whenever a conjugated system is introduced onto a pyrrole ring, pyrroles show different reactivity compared to analogous features positioned on an alkyl chain. As exemplified in **Figure 4**, 2-carboxylate pyrrole takes the form of a doubly vinylogous carbamate, meaning that the carbamate functionality is joined by two conjugated bonds.[12] Therefore, the ester functionality present on the 2-position of a pyrrole does not behave as a normal ester but rather more like a carbamate, thereby changing the reactivity of the carbonyl carbon.

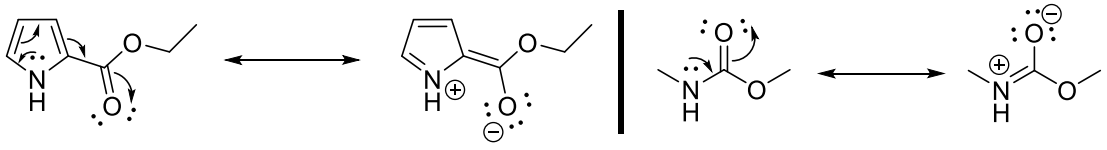


Figure 4. Resonance structures of 2-carboxylate pyrrole (left) and of carbamate (right).

Some of the many pyrrole-containing natural products are illustrated in **Figure 5**. The first one is peramine, an insect antifeedant, and it was isolated from *Acremoium loliae*.

This compound was characterized by Rowan, Hunt, and Gaynor in 1986.[13] The second compound is oroidin, which was first discovered in 1971 following isolation from *Agelas oroides*.[14] Oroidin exhibits anti-biofouling activity, targeting *R. salexigens* in the ocean.[15] The next compound is called pyrrolomycin B, and it was first isolated from *Actinomycete* strain in 1981. It has shown antibacterial activity against both Gram-positive and Gram-negative bacteria.[16] Similar to pyrrolomycin B, sceptrin is also an antimicrobial agent. Sceptrin was isolated from *Agelas sceptrum* by Faulkner and Clardy in 1981, and it has demonstrated its potency against several bacterial strains including *Bacillus subtilis*, *Candida albicans*, and *Pseudomonas aeruginosa*.[17] Lastly, indanomycin shows antibiotic activity and was isolated from *Streptomyces antibioticus* in 1978. It contains a carboxylate on the 2-position of the pyrrole ring, which is the recurring structural feature that is commonly seen in microbial metabolites.[18]

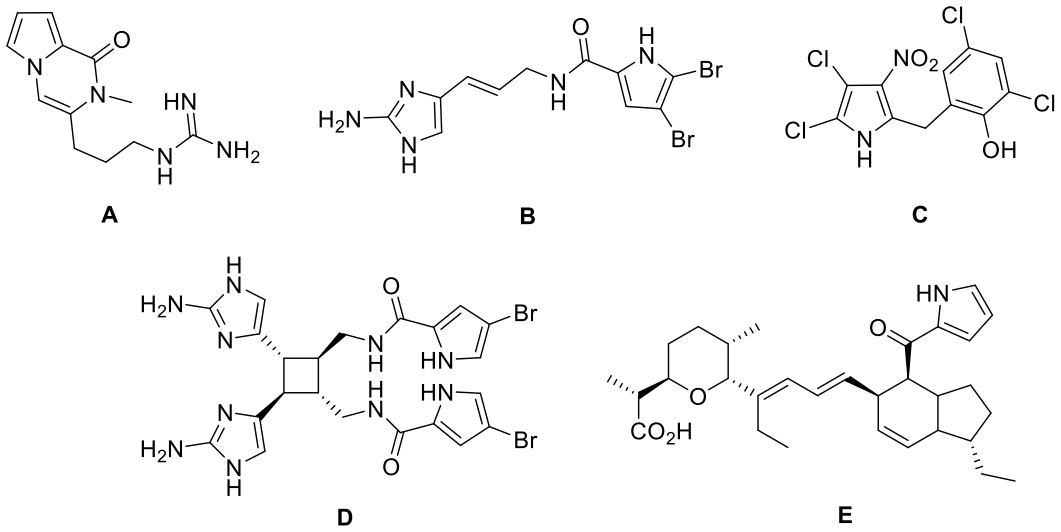


Figure 5. Examples of pyrrole-containing natural products: A-peramine; B-oroidin; C-pyrrolomycin B; D-sceptrin; E-indanomycin.

Along with pyrroles, multi-pyrrolic compounds are known, i.e. natural products and synthesized molecules. Some widely known pyrrole-containing species are shown in **Figure 6**. The shown di-pyrrolic compound is called a dipyrrin, the tri-pyrrolic compound is known as a prodigiosin, and lastly the tetra-pyrrolic structure is known as a porphyrin. Traditionally, most chemistry of pyrroles was related to the goal of synthesizing porphyrins because these tetrapyrroles hold great potential in biomedical application, acting as a precursor to a heme group, which is a carrier of oxygen atoms in our bloodstreams.[19]

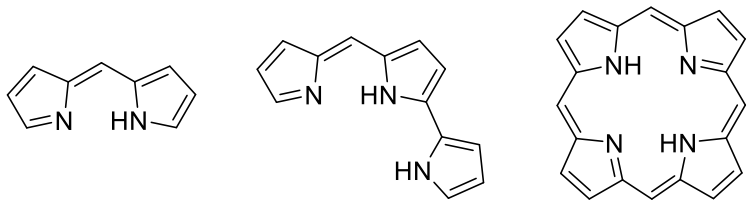


Figure 6. Structures of some di-, tri-, and tetra-pyrrolic compounds.

These multi-pyrrolic compounds are typically synthesized from 2-carboxaldehyde pyrroles which have been a long-standing interest. In an acidic environment, 2-carboxaldehyde pyrroles can self-condense to form dipyrrins (**Figure 7**).[20] Therefore, to probe the chemistry of dipyrrins and other multi-pyrrolic compounds, having a high yielding and reproducible synthetic pathway to 2-carboxaldehyde pyrroles is critical.

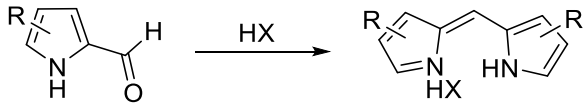
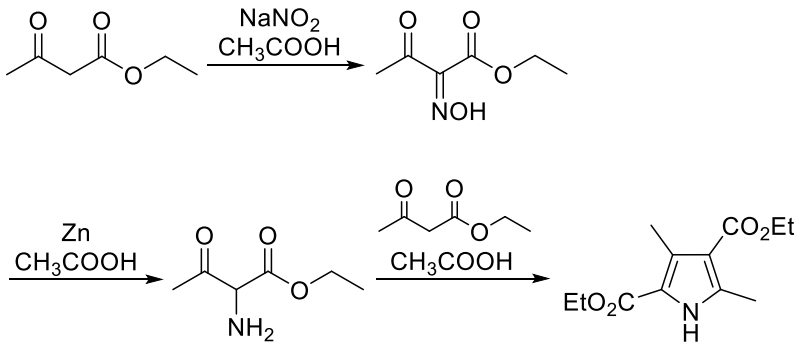


Figure 7. Self-condensation of 2-carboxaldehyde pyrroles to form dipyrrins.

Current synthetic routes to 2-carboxaldehyde pyrroles typically start from the Knorr-pyrrole synthesis. The Knorr-pyrrole synthesis was first published in 1884,[21] and

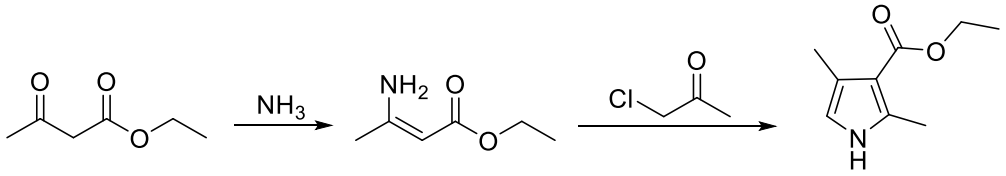
there are now countless variations.[22,23] One of the major strengths of the Knorr-approach is that it uses readily available materials and can be conducted on mole scales in an academic research setting. In the Thompson group, one of the prevailing Knorr-pyrrole syntheses is shown in **Scheme 1**, where β-keto esters form an oxime which then gets reduced to form an amine. Upon the addition of zinc powder, the reaction mixture becomes exothermic, so the temperature has to be monitored and controlled by use of an ice bath as the oxime is reduced to the corresponding amine. Subsequently, condensation with another β-keto ester yields the requisite dicarboxylate pyrrole. Because, as previously mentioned, these esters actually behave as carbamates, treatment of 2-carboxylate pyrrole with a reducing agent such as *H*-DIBAL does not yield aldehydes. Therefore, the final product of a Knorr synthesis has to undergo a rather lengthy synthetic pathway to yield a 2-carboxaldehyde pyrrole.



Scheme 1. Synthesis of Knorr-pyrrole bearing 2-carboxylate groups.

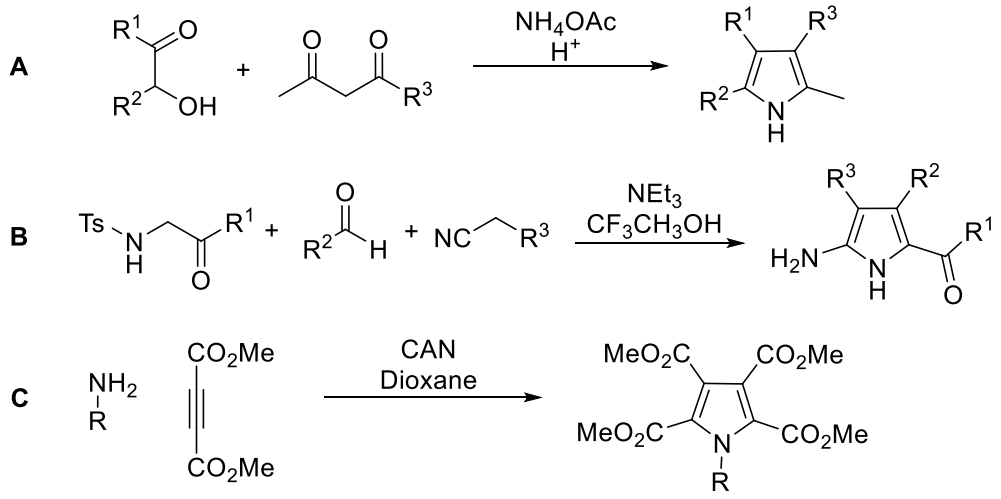
There are also other known routes to synthesize pyrroles.[24-26] Another prominent method is called the Hantzsch pyrrole synthesis where β-keto esters react with ammonia and α-halo ketones (**Scheme 2**). Ammonia readily reacts with β-keto esters to form the corresponding enamine ester. In the presence of α-halo ketones, enamine esters react with

the electrophilic halogenated carbon atom. Consequently, the following intermediate cyclizes to yield 3-carboxylate pyrrole.[25]



Scheme 2. The Hantzsch pyrrole synthesis from β-keto esters.

In **Scheme 3**, other multicomponent syntheses of pyrroles are illustrated. The first method involves dicarbonyl compounds reacting with benzoin derivatives in the presence of ammonium acetate to form tetrasubstituted pyrroles. The second pathway involves reacting activated nitriles with *N*-protected amino acetophenones and aromatic aldehydes. The last route involves two alkynes reacting with primary amine catalyzed by cesium (IV) ammonium nitrate (CAN), undergoing single electron transfer to ultimately yield tetracarboxylate pyrroles.[27]



Scheme 3. Examples of multicomponent pyrrole syntheses.

The Thompson group aims to understand the reactivity of the pyrrole unit to better predict and expand the synthetic scope of the pyrrole core. Understanding the properties of this structural unit enables photophysical and electrochemical properties, as well as synthetic pathways, to be better utilized. Within this thesis, Chapter 2 discusses a new approach of synthesizing 2-carboxaldehyde pyrroles, and Chapter 3 discusses various approaches to introduce an aryl group onto a dipyrrin core.

Chapter 2. Synthesis of 2-Formyl Pyrroles from 2-Thionoester Pyrroles

2.1 Introduction

The ability of pyrroles to react with various electrophiles enables the introduction of diverse functionalities onto the pyrrolic core. Taking advantage of this fact, 2-thionoester pyrroles have recently been synthesized in the Thompson group (**Figure 8**). Pyrroles bearing this functionality have been little studied.[28]

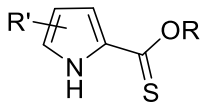


Figure 8. Structure of 2-thionoester pyrrole.

Unlike the 2-thionoester pyrroles (-C(S)OR) of interest here, 2-thioester pyrroles (-C(O)SR) have been thoroughly evaluated as such species are common secondary metabolites in marine bacteria and plants.[29,30] For example, it was recently found that certain tetrabromopyrroles induce larval settlement of corals in response to biofilms generated by marine bacteria called *Pseudoalteromonas*.[31] In order to effectively synthesize tetrabromopyrroles, enzyme catalyzed pathways were investigated where the thioester functionality becomes significant. In the biosynthesis of such halogenated pyrroles, an acyl carrier protein (ACP) was used as a linker to connect proline which then ultimately forms a fully halogenated pyrrole (**Figure 9**). Each step is catalyzed respectively by an adenylation enzyme, a dehydrogenase enzyme, and a halogenation enzyme.[29]

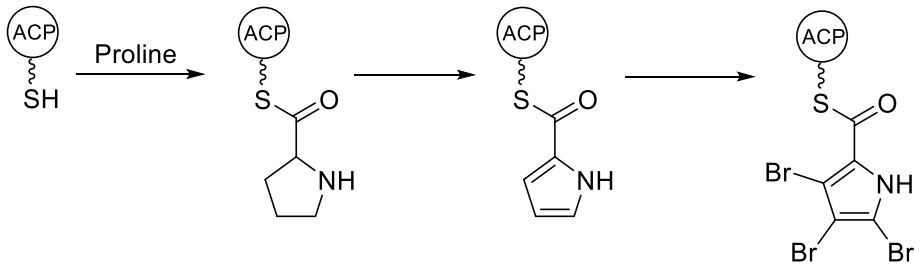


Figure 9. Biosynthetic pathway of halogenated pyrroles.

On the other hand, the reactivity of the 2-thionoester pyrroles (-C(S)OR) of interest herein has not been studied in detail despite the fact that thionoesters are more electrophilic compared to the corresponding all-oxygen ester functional groups (C=S bond length of 1.6 Å cf. C=O bond length of 1.2 Å).[32,33] The potential of utilizing new reactivity at the 2- (or α-) position of pyrroles opens new synthetic opportunities in pyrrole chemistry that build on traditional approaches. 2-Formyl pyrroles typically stem from readily available Knorr-type pyrroles which bear 2-carboxylate (i.e. ester) functionality that exhibit doubly-vinylogous carbamate character, as exemplified in **Figure 10** and discussed in Chapter 1.[12,34] Established procedures use the Knorr protocol to produce pyrroles 2-substituted with ethyl, benzyl, and *tert*-butyl esters. As such, the transformation of 2-carboxylate pyrroles to 2-formyl pyrroles typically requires either hydrolysis, decarboxylation and finally formylation,[35,36] or reduction to the alcohol followed by oxidation back to the desired aldehyde,[37] given that reaction with *H*-DIBAL is unsuccessful. For both Et and ^{t}Bu esters, hydrolysis and decarboxylation could be executed under basic conditions for an extended amount of time, to produce the corresponding α-free pyrrole.[36,38] In contrast, the benzyl ester can be removed via hydrogenolysis, whereupon decarboxylation produces the desired 2-*H* pyrroles.[39] To synthesize 2-formyl pyrroles, 2-*H* pyrroles can either be formylated via a Vilsmeier-Haack reaction[35] or via treatment of 2-carboxylic acid pyrroles (from

hydrolysis and hydrogenolysis of the esters) with trimethyl orthoformate.[40] In addition to the inevitably poor atom economy that results from such circuitousness, these reactions can be low yielding and necessitate harsh conditions. As such, exploring a new methodology for the direct reduction of 2-thionoesters pyrroles to provide 2-formyl pyrroles is appealing.

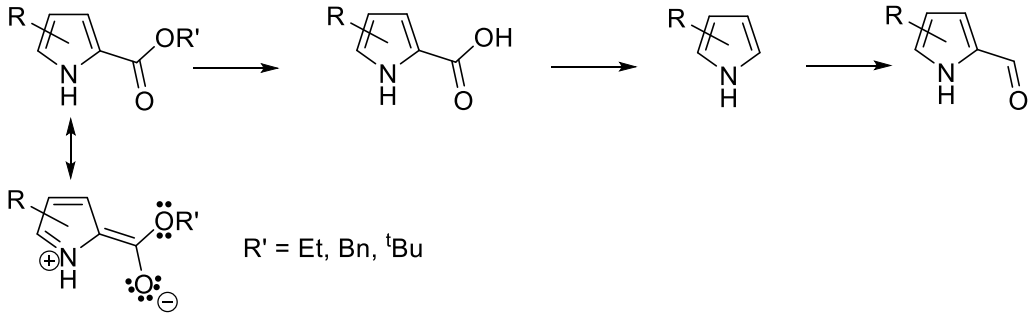


Figure 10. 2-Carboxylate pyrroles, and transformation to 2-formyl pyrroles.

Although the literature is bare of examples featuring the functional group reactivity of 2-thionoester pyrroles, we noticed a role for thiophilic reagents in the reduction of 2-thioester pyrroles. Intriguingly, Raney nickel was shown to react with 2-thioester pyrroles to provide 2-formyl pyrroles and α-free pyrroles (**Figure 11**).[41-43] Raney nickel is a widely known catalysts that has been traditionally used to effect various organic reactions including hydrogenation and desulfurization.[44] It is prepared by removing aluminum from aluminum-nickel alloy by treating with a base (i.e. potassium hydroxide or sodium hydroxide).[45] Therefore, Raney nickel is quite basic, and it decomposes when it is exposed to acids. During preparation step of Raney nickel, dihydrogen gases are evolved, while some are trapped inside the mixture constituting the resulting catalyst, and these remnants of hydrogen gas are used to perform hydrogenation. Furthermore, Raney nickel is highly pyrophoric, so it must be stored in an aqueous solution and should never be allowed to dry.[44] Based on the concentration of the base, and the preparation temperature and time,

different types of Raney nickel can be prepared. In the past, W-type Raney nickel was commercially available, but such types of Raney nickel have now become obsolete.

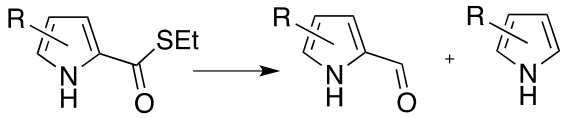


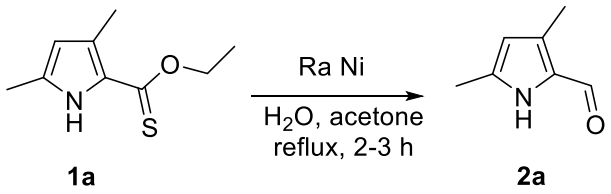
Figure 11. Reduction of 2-thioester pyrroles.

We thus explored the reactivity of 2-thionoester pyrroles with Raney nickel, taking advantage of the commercial availability of Raney nickel as a slurry in water, in the hopes that 2-thionoester pyrroles would follow the precedent set for 2-thioester pyrroles. In order to screen the reactivity of 2-thionoester pyrroles, they were first synthesized, following the literature procedure.[28] 2-Thionoester pyrrole was prepared via treatment of the corresponding 2-carboxylate pyrrole with Lawesson's reagent in a solution in toluene at reflux temperature. Along the synthesis, we were faced with several challenges including the stench of the thionating reagent, poor selectivity of thionation when multiple ester groups are present, and poor yields (~10-20%). Despite these challenges, 2-thionoester pyrroles were successfully synthesized, thus enabling their reactivity with Raney nickel to be evaluated.

As previously mentioned, Raney nickel is commercially available as a slurry in water. Upon standing, the particles within the slurry sink, making it extremely challenging to transfer Raney nickel in a reproducible manner. Therefore, when transferring Raney nickel into a reaction vessel, the container first needs to be shaken up and then the slurry is quickly transferred, via glass pipette into the reaction flask. According to the literature report involving the production of 2-formyl pyrroles from 2-thioester pyrroles upon

treatment with Raney nickel, the catalyst first had to be "activated" by heating at reflux temperature in acetone for 1 hour prior to the addition of the substrate.[41,42]

Following this precedent, our goal was to treat pyrroles bearing 2-thionoester functionality with Raney nickel to hopefully reduce to 2-formyl pyrroles. Therefore, a Raney nickel slurry in water was first activated in acetone by heating at reflux temperature for an hour before 2-thionoester pyrrole **1a** was added. Although current commercially available Raney nickel is different from W2 Raney nickel used in literature reports, which has become obsolete, we found that this activation step was essential for success of our desired reduction using 2800 Raney nickel. After the starting material was fully consumed, the mixture was filtered through a short pad of silica to remove the spent Raney nickel and thus enable isolation of the desired aldehyde in 67% yield (**Scheme 4**).



Scheme 4. Reduction of 2-thionoester via Raney nickel

Executing the reaction under an atmosphere of hydrogen did not improve the yield, supporting the synergy of the thiophilicity of the Raney nickel and an unknown source of hydrogen present in the reaction mixture. The amount of Raney nickel used was in large excess,[41,42,46] and numerous attempts were made to reduce the equivalencies of Raney nickel but, without significant detriment to yield, the stoichiometry could not be minimized (**Table 1**). Similarly, dissolution of the substrate in acetone was key to success, as the use of other water-miscible solvents (methanol, ethanol, tetrahydrofuran and isopropanol)[47]

previously reported as suitable for reactions involving Raney nickel, resulted in only isolation of starting material.

Table 1. Entries of yield of 2-formyl pyrrole using different molar equivalencies of Raney nickel

Entry	Reactant (mmol)	Amount of Raney Nickel (g)[a]	Raney nickel (mmol)	Equiv. Raney Nickel	Yield (%)
1	1.1	2.4	28	25	67
2	1.0	3.4	39	39	53
3	0.88	1.3	15	17	43
4	0.40	0.17	2.0	5	17
5	0.47	2.0	23	49	50

[a]The mass of Raney nickel was calculated following the method provided by the supplier

The work discussed thus far constituted research conducted as part of an Honours research project. Subsequent to that, this Master of Science thesis was designed to explore scope and mechanistic aspects of the reduction of 2-thionoester pyrroles.

2.2 Scope of Reduction with Raney nickel

Following the reaction conditions described in **Scheme 4**, the scope of this reaction was explored (**Table 2**). First, different ester functionalities were manipulated. Indeed, pyrroles **1b**, an ethyl ester, and **1f**, a benzyl ester, were both successfully reduced (entries 2 and 7). In contrast, *tert*-butyl thionoesters were unable to be tested because the substrate did not survive the thionation step. Next, different carbon chains and a phenyl group on the beta position were introduced and with each functionality present, thionoester groups were successfully reduced without any pronounced difficulty. Within the reduction of thionoester **1a**, bearing an unsubstituted carbon atom at the β-position, we expanded the investigation to determine if alkyl substituents could be tolerated. This proved successful (entries 2 and 3), and so a substrate with a phenyl substituent was explored with similar success. Lastly, pyrroles bearing electron-withdrawing (**1e**) and an alkanoate (**1h**) were

tested. Pyrrole **1e** was successfully reduced to give the corresponding aldehyde in 46% isolated yield, but interestingly, the yield of **1h** was relatively low, and the reason behind this is still not known although reduction of the alkanoate functionality may seem to complicate the reactivity.

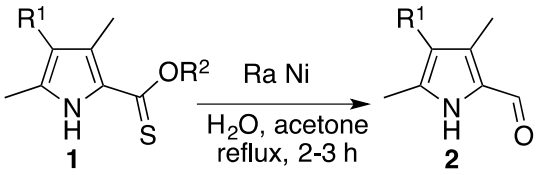


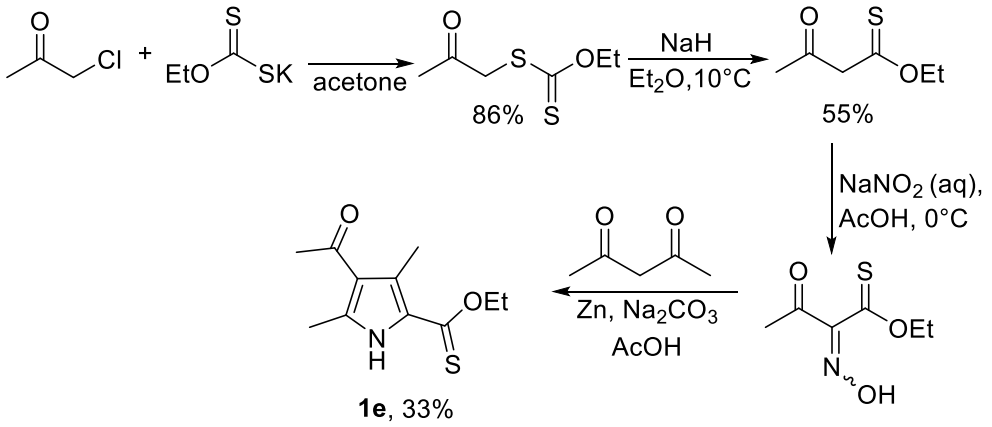
Table 2. Reduction of 2-carboxylate pyrroles to 2-formyl pyrroles using Raney nickel.

Entry	Substrate	R^1	R^2	Yield of 2 (%)
1	**1a**	-H	Et	67
2	**1b**	-Me	Et	52
3	**1c**	-Et	Et	63
4	**1d**	-Ph	Et	45
5	**1e**	$-C(O)CH_3$	Et	44
6	**1e**	$-C(O)CH_3$	Et	46[a]
7	**1f**	-Me	Bn	44[b]
8	**1g**	$-(CH_2)_4CH_3$	Bn	70
9	**1h**	$-(CH_2)_2C(O)OCH_3$	Bn	12

[a]The following product was the deuterated 2-formyl pyrrole (2e'); [b]expected product is **2b**

With a useful method in hand by which to convert 2-thionoester pyrroles into 2-formyl pyrroles, we investigated a direct route to 2-thionoester pyrroles from acyclic materials. Identification of a direct route to 2-thionoester pyrroles would present a direct approach, rather than first having to thionate 2-carboxylate pyrroles. Now, we were interested whether the direct synthesis of 2-thionoesters would be possible by following a traditional Knorr pyrrole synthesis with variation such that a thiocarbonyl moiety would be introduced. From the work from a fellow Thompson group member, Sophie Gaube, a direct synthesis from commercially available reagents to 2-thionoester pyrroles has been

established (**Scheme 5**). The final product of this direct Knorr-pyrrole synthesis is pyrrole **1e**, which was successfully reduced into its corresponding aldehyde via Raney nickel method (**Table 2**, entry 6).



Scheme 5. Knorr-pyrrole synthesis of **1e**.

Now, having a complete synthesis from acyclic compounds to 2-formyl pyrroles via 2-thionoester pyrroles in hand, mechanistic details of the desulfurative reduction were considered in the hopes of better understanding the synthetic pathway.

2.3 Mechanistic Study of Raney Nickel Reduction

To date, a complete mechanism of desulfurization by Raney nickel remains unclear. As previously mentioned, in the past, W-type of Raney nickel had been used for organic reactions including hydrogenation or the reduction of carbonyls. Such reduction pathways involving Raney nickel normally proceed in the presence of dihydrogen but, interestingly, the yields of these reactions declined when more "aged" Raney nickel was used, suggesting the existence of another hydrogen source in Raney nickel, which escapes over time upon standing.[48] Initial consideration by Hauptmann and Walter in 1962 resulted in various desulfurization reactions courtesy of Raney nickel. From these collective works, these

authors concluded that, based on the reactivity of Raney nickel, desulfurization can be either hydrogenolytic desulfurization (**Figure 12**) or become complicated with other side reactions that can allow exchange between oxygen atoms with sulfur atoms.[49] In analysis of this reported work and reflection, a clear mechanism for desulfurative reduction is not forthcoming.

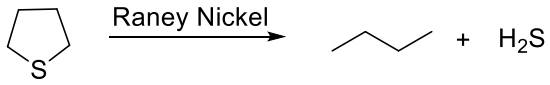
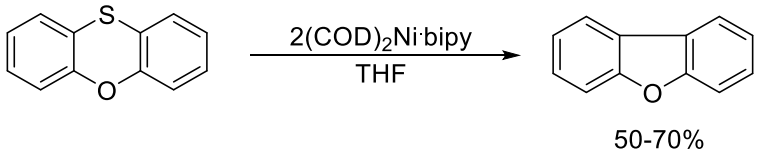


Figure 12. Simple hydrogenolytic desulfurization.

As previously mentioned, Raney nickel contains dihydrogen gases that are trapped inside the mixture. However, it has been demonstrated that these dihydrogen gases are not necessary for certain desulfurization reactions to proceed. For instance, Eisch and Im successfully reduced phenoxathiin with a nickel complex in the absence of dihydrogen gas and proposed that this outcome had resulted from a single electron pathway (**Scheme 6**).[50] This was further supported by thioether cleavage by lithium di-*tert*-butylbiphenylide (LiDBB), a powerful alkyl-lithiating reagent and a radical anion.[51] Stemming from these works as well as other studies, many believe that desulfurization proceeds via a single electron pathway.[52-54]



Scheme 6. Reduction of phenoxathiin in the absence of dihydrogen gas.

Recently, through X-ray photoelectron spectroscopy studies, chemisorption of a sulfur atom (in thiophene or thioether) onto a nickel surface was observed, thereby supporting an important role for the thiophilicity of Raney nickel.[55] We know that the reduction of 2-thionoester pyrroles is not a simple hydrogenolytic desulfurization but a combination of reduction and desulfurization. Therefore, the following reactions were conducted to understand the origins of the oxygen and hydrogen atoms that constitute the aldehyde functional group within the product 2-formyl pyrroles (**Figure 13**). The source of both hydrogen and oxygen atoms are quite limited since there are only few reagents are present in the reaction mixture: the starting material, Raney nickel, water and acetone.

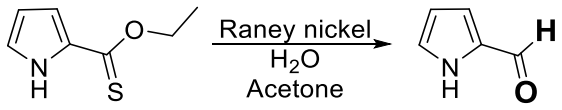
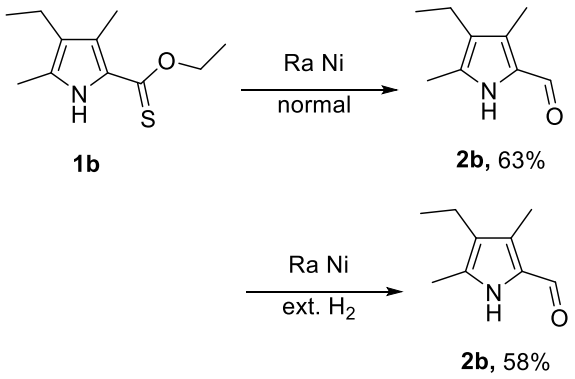


Figure 13. Current reduction of 2-thionoester pyrroles (atoms of interest in bold).

The first hypothesis was that the hydrogen atom in the end-product had derived from hydrogen gas that had been trapped inside the Raney nickel. However, executing the reaction of Raney nickel with pyrrole **1b** in excess hydrogen gas did not improve the yield or decrease the reaction time (**Scheme 7**), supporting the previously mentioned notion that dihydrogen gas is not necessary to drive the desulfurization reaction. Then, it was hypothesized that water may play a role in the reduction of thionoesters being studied herein. Therefore, water from Raney nickel was manually removed by drawing out the liquid from the Raney nickel slurry. Then, acetone was added, and the slurry was shaken and left to settle, and the liquid then drawn out once again. This process was repeated several times. For the final wash, acetone was added to match the desired solvent volume of the reaction for the reduction of pyrrole **1b**. Using this water-reduced Raney nickel, only

a trace amount of 2-formyl pyrrole formed which suggests that either oxygen or hydrogen from water could possibly end up in the aldehyde. Due to the pyrophoricity of Raney nickel, we chose not to completely dry the Raney nickel which may be the reason why the trace amount of the product formed.



Scheme 7. Difference in yields in presence/absence of external hydrogen gas.

It was proposed that if the hydrogen atom that features in the aldehyde unit of our product, 2-formyl pyrrole, actually derived from water, then deuterated 2-formyl pyrroles would be formed when there is deuterium oxide present in the reaction mixture. There have been a few reported examples of isotope exchange reactions with Raney nickel using deuterium oxide. For instance, one report indicates that deuterated Raney nickel was prepared by heating the nickel alloy with heavy water at 100 °C.[56] Other research involved C-H to C-D exchange of carbohydrates using Raney nickel with use of ultrasound or a microwave activation (**Figure 14**).[56]

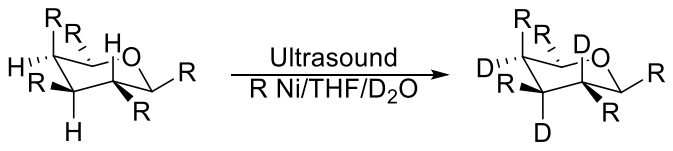
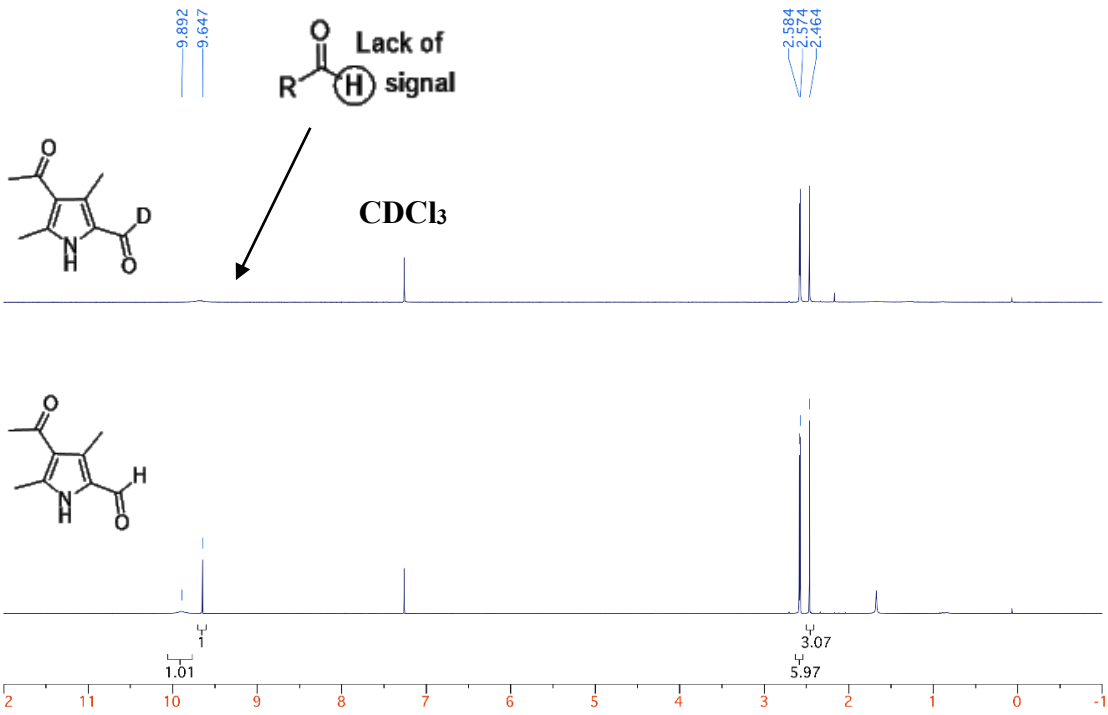


Figure 14. Isotopic exchange of carbohydrates.

As the above preparation of deuterated Raney nickel required deuterated sodium hydroxide, a simple preparation of deuterated Raney nickel was instead attempted. After transferring Raney nickel slurry into a vial or a reaction flask, water was drawn out from the slurry, and the mixture was diluted with deuterium oxide and was agitated by use of a sonicator. Then, the liquid was drawn out from the slurry, and the mixture was again diluted with deuterium oxide and then agitated by use of a sonicator. The dilution and sonication wash cycles were repeated 10 times to ensure efficient exchange from water to deuterium oxide. Reaction of the deuterated slurry with pyrrole **1e** resulted in formation of **2e'** (**Table 2**, entry 6), and the presence of the deuterated product was confirmed by both ^{1}H and ^{13}C NMR spectroscopy (**Figure 15**). Disappearance of the signal at δ 9.65 ppm signal in the ^{1}H NMR spectrum correlated with introduction of deuterium within the aldehyde functional group as a consequence of reacting the deuterium-oxide-prepared Raney nickel with pyrrole **1e**. Likewise, the presence of a triplet in the ^{13}C NMR spectrum due to the coupling between a deuterium and a carbon atom supports the presence of a deuterium atom in the final product. However, without the use of a sonicator for the wash cycles for the exchange of water for deuterium oxide, the conversion to deuterated 2-formyl pyrrole was incomplete such that both deuterated and non-deuterated 2-formyl pyrrole were present in the product mixture. This was confirmed by comparing the integration of the signals in the ^{1}H NMR spectrum where the ratio between an aldehyde hydrogen and the methyl group was found to be 0.3 to 3 (normally it is 1 to 3). Such incomplete exchange could have either resulted from the water molecules trapped inside the Raney nickel or from the facile exchange of deuterium with hydrogen on the nickel surface promoted by external disturbance.

^{1}H NMR; 300 MHz, $CDCl_3$



^{13}C NMR; 125 MHz, $CDCl_3$

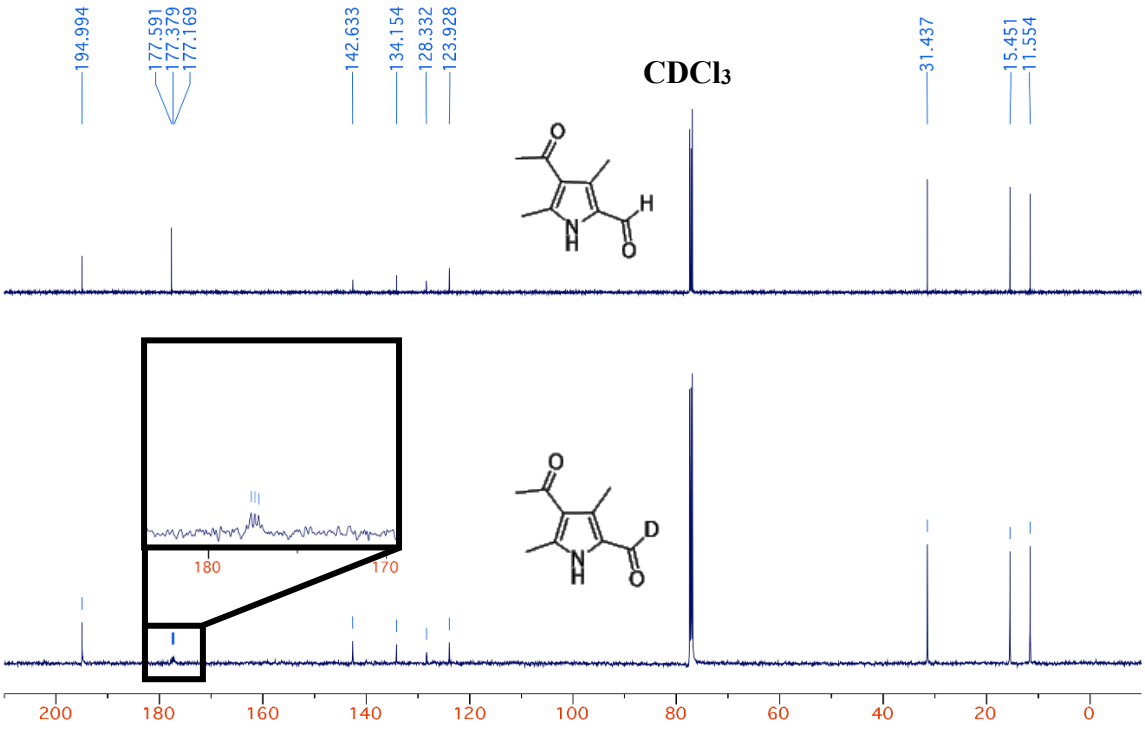


Figure 15. ^{1}H (top) and ^{13}C (bottom) NMR spectra of deuterated 2-formyl pyrrole.

From these results, it is now evident that the hydrogen atom that constitutes the aldehyde of 2-formyl pyrrole derives from water. However, we were still uncertain whether the hydrogen atom was coming directly from water or through an exchange with Raney nickel surface (i.e. being adsorbed and presenting as H_2 or $H\cdot$). Therefore, we wanted to explore more into reaction pathway the desulfurative reduction of 2-thionoester pyrroles takes to yield 2-formyl pyrroles (or how it is acquiring the hydrogen from water).

As previous reports have mentioned, many people believe that desulfurization via Raney nickel is proposed to induce reactivity via a radical pathway.[52-54] To confirm whether the reduction proceeds through a radical pathway, we used a radical clock/trap (**Figure 16**) in the hopes of a ring opening of the radical clocks or other evidence of interception of intermediates along the reaction pathway. Cyclopropyl groups are known for their reactivities against radical species.[57] Because of the constrained ring system, whenever radical species are present, cyclopropyl groups are reduced with ring opening.[58] Therefore, in organic chemistry, these types of radical clocks provide indirect methods to calculate the rate constant of an unknown reaction. Since radical clocks undergo unimolecular radical reaction at a known rate, in the presence of other radical species they will undergo bimolecular radical reactions. Thus, by comparing the ratio of the products from competitive reactions, the rate constant of an unknown reaction can be calculated.[57] TEMPO on the other hand, is a stable radical species and acts as a radical trap by reacting directly with a radical, thus forming alkoxyamine.[59] For reaction of **1a** with Raney nickel in the presence of either diethyl cyclopropane-1,1-dicarboxylate or cyclopropyl phenyl ketone, neither the ring opening of these radical clocks nor any trapped molecules were observed. Also, the yields of 2-formyl pyrrole remained consistent (50-60%) regardless of

the presence or absence of these radical clocks. Interestingly, when the Raney nickel reduction was conducted in the presence of TEMPO, the yield of **1a** decreased drastically (7%), but the trapped product could not be found by use of either mass spectrometry or NMR spectroscopy. Based on these results, the mechanism of the reduction is still inconclusive, but based on the yield of the reaction with TEMPO, it could be hypothesized that the reduction occurs through a radical-based mechanism.

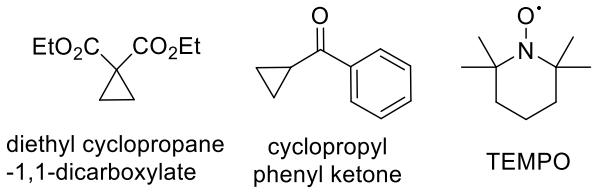
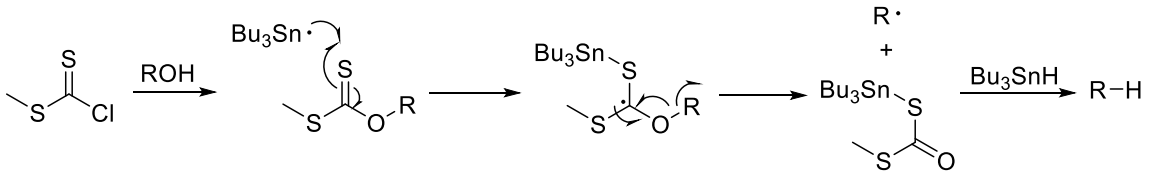


Figure 16. Structures of radical clocks/trap.

Lastly, to explore whether the reaction is undergoing a photochemical pathway, two reactions were set up: one reaction had a light (i.e. household bulb; power = 60 W) shining right into the reaction mixture, while the other was covered in aluminum foil to prevent any light from reaching the reaction. If the reduction proceeds via a photochemically-induced pathway, then the reaction with the light would be expected to provide a higher yield. However, the yields of 2-formyl pyrrole isolated from the two reactions were comparable: the one with light yielded 40% and one without the light yielded 50%.

From all these results, we have found that the following factors play critical roles in the reduction of 2-thionoester pyrroles: thiophilicity of Raney nickel; presence of water; and possibility of radical formation. In order to propose a mechanism for the observed desulfurative reduction, we first considered the widely-known Barton McCombie reaction,

which involves a deoxygenation reaction of an alcohol, where, in our case, the thionoester functionality could act as an intermediate in this process.[60] Although, in the Barton McCombie reaction, Raney nickel is not being used, it was thought to be a suitable starting point since it deals with the extrusion of a sulfur atom via a radical pathway. In this deoxygenation reaction, tributyltin hydride is used to initiate a radical-induced reaction pathway (**Scheme 8**). Ultimately, the R group on the oxygen leaves as a radical (i.e. deoxygenated) which then picks up a hydrogen atom from tributyltin hydride.



Scheme 8. Proposed mechanism for Barton-McCombie deoxygenation.

If a mechanism analogous to that of the Barton McCombie mechanism is implemented with our reduction with Raney nickel, nickel could potentially take over the role of tin (as a radical source) and a hydrogen atom could be from the adsorbed hydrogen on Raney nickel (**Figure 17**). First, courtesy of the thiophilicity of nickel radical formation on the carbonyl carbon could occur. Then, the ethyl group would leave as a radical, which would be highly reactive (or picks up a hydrogen atom from Raney nickel to form ethane). The S-C bond would undergo homolytic cleavage and then form a bond with a hydrogen atom, yielding 2-formyl pyrrole. One downfall of this mechanism would be the formation of ethyl radicals. Although, there will be hydrogen atoms adsorbed on Raney nickel to terminate radical chain reactions, formation of an ethyl radical would require a strong driving force.

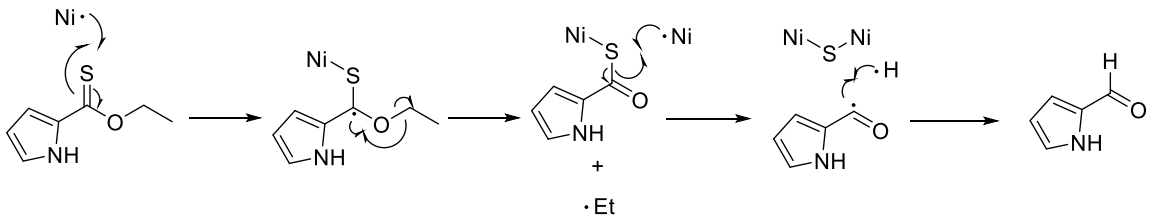


Figure 17. Proposed mechanism in precedent of Barton-McCombie deoxygenation.

Another proposed mechanism is shown in **Figure 18**. In this mechanism, we prioritized the bond formation between nickel (of Raney nickel) and sulfur atoms, recognizing the thiophilicity of Raney nickel. While the sulfur atom of 2-thionoester pyrrole would be activated by Raney nickel, nucleophiles that are present in the reaction mixture could attack an electrophilic centre. In this case, the Raney nickel slurry is basic (pH ~ 9-10), and so high concentration of hydroxide ions would be present in the reaction mixture and could attack the carbonyl carbon. Now, we are still in need of an aldehyde hydrogen atom. Although we are not sure how (directly from water or from the nickel surface) the hydrogen of water ends up in the aldehyde group, many believe the cleavage and the addition of hydrogen atom proceed via single electron transfer. While the whole system is activated by Raney nickel, the C-S bond could undergo homolytic cleavage, leaving with S-Ni radical which could instantly form a bond with other nickel atoms or other sulfur radicals. On the other hand, the radical formed on the carbon atom could pick up a hydrogen atom from the surface of Raney nickel. However, we were uncertain which of these two steps (nucleophilic attack or single electron transfer) would happen first. Lastly, the proton could be picked up by a base (in this case hydroxide), and the ethoxy group thus leaves, with 2-formyl pyrrole as the final product. Although other mechanisms were also considered, including the formation of a thial which ultimately gets hydrolyzed

to yield 2-formyl pyrroles, based on the observation of various reactions, the properties of Raney nickel, and other reactions involving Raney nickel, we concluded that the mechanisms shown in **Figure 17** and **Figure 18** to be preferable.

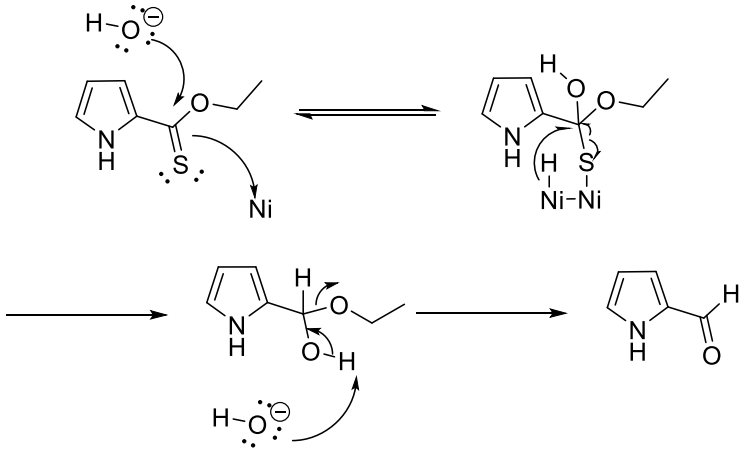


Figure 18. Proposed mechanism of reduction of 2-thionoester pyrrole with Raney nickel.

These potential mechanisms incite the investigation of several factors: the role that a pyrrole ring plays in the reductive desulfurization, and the role of acetone. As discussed in Chapter 1 and 2, the electron rich nature of the pyrrole ring alters the reactivity of functional groups that are present. To test this, we could try to synthesize aliphatic 2-thionoesters and see whether reduction to aldehydes occupies. Secondly, as shown in **Figure 18**, if water treatment with Raney nickel provides hydroxide ions, 2-formyl pyrroles would have been observed in the other solvents that had been tested. However, only the use of acetone provided the corresponding 2-formyl pyrroles, so we are also curious of the role that acetone plays.

Lastly, isotope labelling studies using $H_2{}^{18}O$ were also considered, to track down where the oxygen atom is coming from. However, considering how much water is already

present in the reaction mixture and the cost of $H_2{}^{18}O$, the use of this labelled material was thought to be an ineffective approach that would bring little value to this study.

2.4 Conclusion and Future Work

Along with the work from a summer student, a complete synthetic scheme to enable the conversion of commercially available reagents to 2-formyl pyrroles has been identified. 2-Thionoester pyrroles bearing various alkyl chains and an aryl group were successfully reduced to the corresponding 2-formyl pyrroles. From studies using deuterium oxide, radical clocks and a radical trap, mechanistic considerations have led to two proposed mechanisms. In the attempts to explore the mechanistic details of desulfurative reduction, 2-formyl pyrroles have been successfully deuterated in the presence of deuterium oxide. However, there was no sign of any intercepted molecules upon treatment with the radical traps, so it is still difficult to have a clear idea how this reaction proceeds. Considering the history of desulfurative reduction of Raney nickel and that its mechanism is still not clearly known, new possibilities remain. We are fully aware that taking this route to prepare 2-formyl pyrroles would not be as practical as we would like, so we will continue to explore new strategies to reach these pyrroles.

Chapter 3. Synthesis of Alpha/Beta-Substituted Dipyrrins

3.1 Introduction

Dipyrrins formally consist of a pyrrolic unit and an aza-fulvenium unit made by linking two pyrrolic units by a methene bridge.[61] The numbering system set by IUPAC for dipyrrins, as well as common naming method (alpha/beta/meso) are shown in **Figure 19**. The numbering system of dipyrrins is different from that of pyrroles, as the 1-position of dipyrrins is on a carbon atom rather than a nitrogen atom, and this 1-11 numbering system of dipyrrins follows the numbering system of porphyrins.

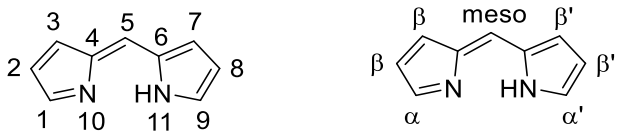


Figure 19. The numbering system of a dipyrrin.

Dipyrrins can exist either in their more stable salt forms (commonly HBr or HCl salts), or in their free base forms.[62] Generally, the stability of dipyrrins is determined based on the number and genre of substitutions on the dipyrrin core. Different functionalities on the α- and β-positions, as well as on the 5-position (which is also commonly referred to the meso-position) can be present on the dipyrrin core. Especially for the meso-position, it was found that the presence of an aryl group greatly increases the stability of a dipyrrin.[63] Similar to pyrroles, dipyrrins have a conjugated pi system, which makes them susceptible to electrophilic and nucleophilic attack.[64,65]

In recent years, dipyrrins have been receiving more attention from chemists because they share both structural and chemical similarities with porphyrins (**Figure 20**).[66] Hemes, which contain the porphyrin backbone, transport and store oxygen atoms in our

bloodstream, and because of this medical reason, they are one of the most researched pyrrole-containing compounds.[67] As researchers explore the synthesis and applications of porphyrins, chemists have also become interested in dipyrrins because dipyrrins can be viewed as a precursor to porphyrins.[66] In our bodies, porphyrins are chelated to an iron atom which have caused some research groups to investigate the chelating abilities of dipyrrins with metals or non-metals.

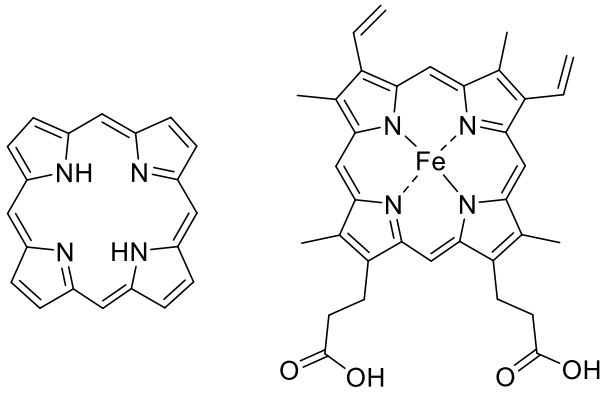


Figure 20. Structure of porphyrin (left) and heme (right).

One of the most well-known form of a chelated dipyrrin is that of 4,4-difluoro-4-bora-3a,4a-diaza-sindacene (commonly known as *F*-BODIPY), where the dipyrrinato ligand is complexed to a -BF_2 unit (**Figure 21**). BODIPY dyes strongly absorb and fluoresce in the visible region with high quantum yield, making them excellent fluorescent probes.[68] Furthermore, BODIPYs have been found to be chemically robust towards the polarity and pH of their surrounding environment. They have found widespread use as probes for physiological systems and models thereof.[69] The stability of BODIPYs makes the -BF_2 unit effective to protect the chelating nitrogen atoms of dipyrrins through the formation of BODIPY. BODIPYs can be synthesized from both the salt and the free base form of dipyrrins.[69]

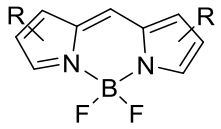


Figure 21. General structure of *F*-BODIPY.

Recently in the Thompson group, robust synthetic methods towards BODIPYs have been discovered, thereby producing these boron-containing complexes in high yields and requiring less complicated synthetic procedures.[70] Normally, *F*-BODIPY (**Figure 21**) can be easily synthesized by treating a dipyrrin with excess amount of $BF_3{\cdot}OEt_2$ and NEt_3 in solution, and this synthesis pathway does not require anhydrous techniques.

As exemplified in numerous reports, even slight differences on the dipyrrinato ligand core greatly alters the photophysical properties.[71-73] BODIPYs have absorption and emission peaks between 450 and 550 nm and, based on the substituents on the BODIPY core, these wavelengths can be easily tuned. In general, the presence of conjugated systems (either double bonds, aromatic rings or both), greatly increases the absorption wavelengths. For example, benzene ring-fused BODIPY derivatives showed intense red-shifted absorption at 629 nm whereas non-fused BODIPY derivatives absorbed at 519 nm.[72] As shown in **Figure 22**, increasing the number of styryl units altered the photophysical properties of the BODIPY derivatives, shifting towards the red region.[74] Therefore, by varying the substituents on the BODIPY unit, we can sensitively alter the absorbances and emission wavelengths of the dye. As human cells interact with light and cytotoxicity is induced by either UV or visible light (phototoxcitiy), use of a light-activated probe has the potential to cause undesirable damage.[75] BODIPYs are often used as a fluorescent probe in cells, and by introducing conjugated systems onto the dipyrrinato ligand core, we can

increase the emission wavelength of BODIPYs, avoiding the wavelength window which may be toxic to human cells. Indeed, in general the capability of dyes to emit at higher wavelengths (red-shift) is highly favourable in terms of medical applications. Furthermore, BODIPYs emitting in the far-red and near-IR range have potential for use in electronics industries.[76]

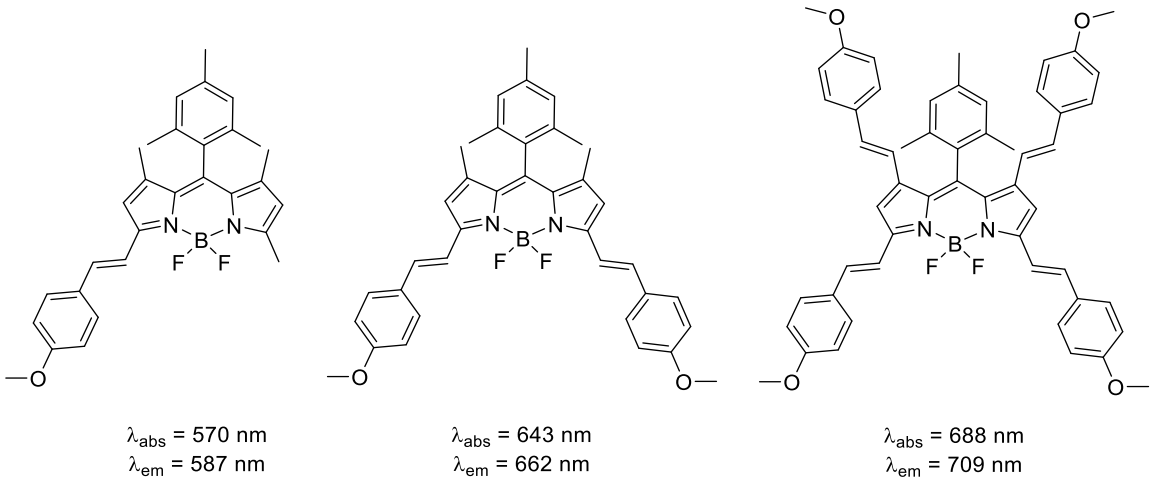


Figure 22. Effects of having increasing number of styryl groups on the BODIPY core on their Increasing number of styryl groups A, B (643 nm), and C (688 nm).

Along with iron (heme) and boron complex (e.g. BODIPYs), there have been numerous studies on other metal atoms complexed with the dipyrrinato framework. These atoms include, but are not limited to, Zn, Ga, Sn, Rh, In, Re, and Al, and each of these complexes shows unique properties in terms of properties such as reactivity, catalytic activity and luminescence.[77-80] One key feature of dipyrrinato complexes is the capability of harvesting light (e.g. *F*-BODIPYs).[81] Although metal-complexed dipyrrins are generally non-emissive, one interesting example involves a double helix of a zinc(II) dipyrrinato complex which was found to be highly fluorescent, exhibiting quantum yields (0.91 in cyclohexane) comparable to those of BODIPYs (**Figure 23**).[78,82] From this finding, other

fluorescent metal-complexed dipyrrins were synthesized and tested for their value in biological environments.

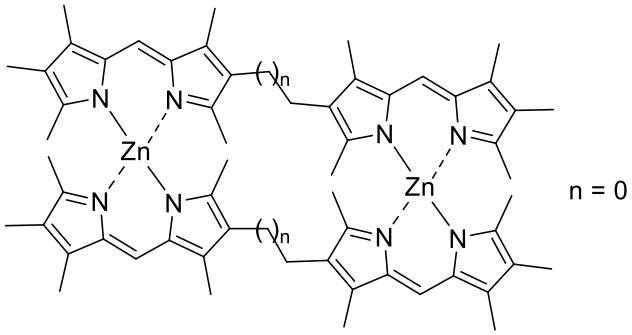


Figure 23. A double helix of zinc(II) dipyrrinato complex.

There have been several cases where these dipyrrin-metal complexes exhibit medicinal potential. One example of gallium, indium, iron, and ruthenium complexed dipyrrins showed phototoxicity activity against tumour cells and against bacteria cells (i.e. *S. aureus*) as the pentafluorophenyl groups form a covalent bond with either alcohols or thiocarbohydrates (**Figure 24**).[83] Tumour cells and bacterial cells uptake nutrients from their environments via glycosylation, an efficient process in which proteins or DNA is coupled to glucose by enzymatic activities. Therefore, through glycosylation, bacterial cells acquire carbohydrates that are post-functionalized with ruthenium-complexed dipyrrins from their surroundings. Then, once the ruthenium-complexed dipyrrins are irradiated, the tumour cells and bacterial cells undergo apoptosis.[83]

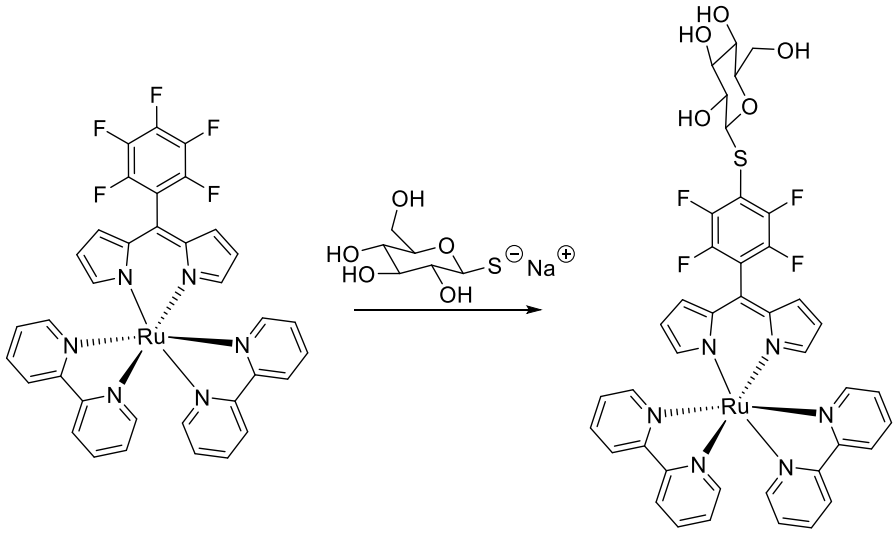
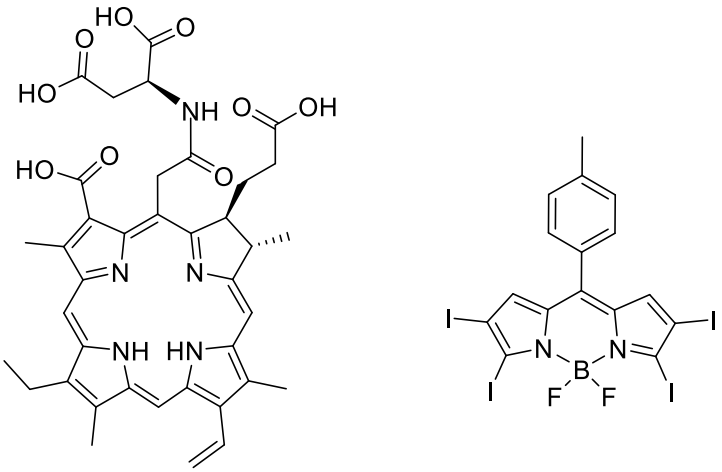


Figure 24. Interaction of ruthenium complexed dipyrrins against thiocarbohydrates of bacterial cells.

A rising application of a dipyrrinato network is photodynamic therapy (PDT).[84] In PDT, photosensitizers are delivered to the target cells, and upon illumination, photosensitizers are activated, producing reactive and cytotoxic singlet oxygen, $^1O_2$, in the region that is illuminated. These highly reactive oxygen species then trigger apoptosis and necrotic cell deaths. Since the photosensitizers are generally non-toxic when they are not irradiated, by only illuminating the tumour cells, PDT can selectively target highly localized non-malignant lesions.[85] There have been many attempts to alter the BODIPY unit to enhance the ability to produce singlet oxygen by incorporating heavy substituents (e.g. iodine and alkyl chain).[84,86] For example, an iodinated BODIPY showed a potential as a PDT agent, by yielding a single oxygen quantum yield of 93%, which is comparable to that of clinically approved photosensitizers for photodynamic therapy (**Figure 25**).[84]



Talaporfin
λ_{max} = 654 nm
ε = 40000 M^{-1} cm^{-1}
$^1O_2$ = 0.48

λ_{max} = 581 nm
ε = 116000 M^{-1} cm^{-1}
$^1O_2$ = 0.87

Figure 25. Clinically approved photosensitizer (left) and iodinated BODIPY as a potential PDT agent (right).

As well as their photophysical properties and medicinal applications, the abilities of dipyrrins as a ligand are appealing. Dipyrrins have demonstrated the ability to form dynamic chemical bonds – both labile coordination bonds and covalent bonds.[87] One advantage that comes from this characteristic is that dipyrrinato ligands can accommodate metals with various valencies, creating more favourable interactions and enabling tuning for a range of applications. According to the Covalent Bond Classification (CBC) method, 3 types of ligands, L, X, and Z are present, and each corresponds to the ability to donate two, one and zero electrons, respectively, to a metal centre. The L ligand presents two electrons to a metal centre, forming a dative covalent bond with the metal. The X ligand provides one electron, acting as a radical and forms a normal covalent bond with the metal. Lastly, the Z ligand accepts two electrons from the metal centre, forming a dative covalent bond.[88] For example, 2,2'-bipyridine acts as a neutral bidentate ligand (two L ligands). The

dipyrrinato unit acts as a monovalent bidentate ligand as exemplified in **Figure 26** – meaning that one nitrogen formally donates two electrons to the metal centre while the other forms a coordination bond (one L ligand and one X ligand).

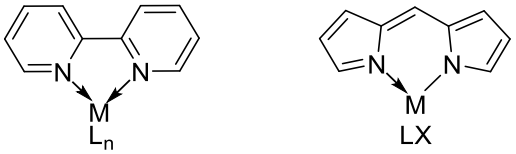


Figure 26. 2,2'-bipyridine (left) and dipyrrin (right) complexation to a metal.

A recent publication from the Thompson group investigated how changing the ligand core affects the donor strength of dipyrrinato ligands.[89] Using a palladium complex containing the 1,3-diisopropylbenzimidazolin-2-ylidene ligand, the donating capability was measured by comparing the chemical shift of the ^{13}C NMR signal of the carbene carbon in each complex (**Figure 27**).

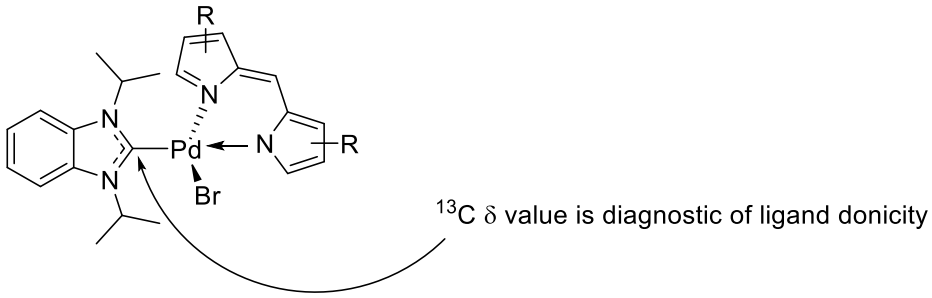
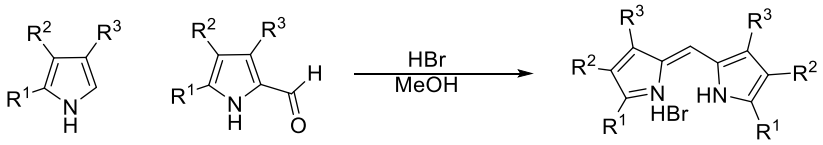


Figure 27. Palladium complex with a dipyrrin as a ligand.

By the trans influence, stronger donating ligands would localize the electron density towards themselves, decreasing the electron density of the metal trans to the ligand, which ultimately results in a higher chemical shift on the carbene carbon (down-field shifted). The presence and nature of electron-donating substituents and functionality on the meso-position greatly influence the donor strength of the dipyrrins. It was reported that increased

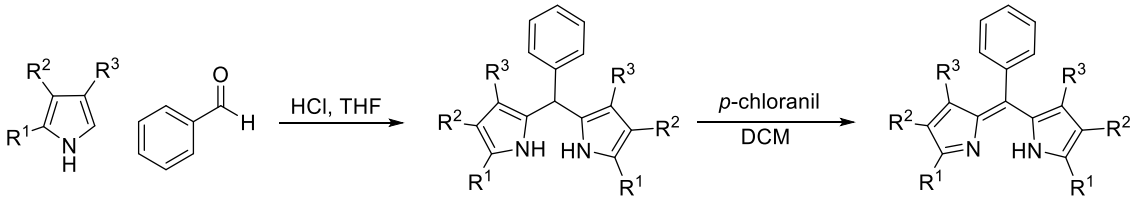
conjugation about the dipyrrin core influences the electron density on the nitrogen atoms of the dipyrrin. Therefore, introducing tunable conjugated systems onto the dipyrrin core would be a method by which to favourably enhance interaction with the metal. Now, studying dipyrrins as a ligand and considering how functionalities on a dipyrrin core would affect their photophysical and chemical characteristics, we desire to synthesize dipyrrins bearing various functional groups. In particular, we were interested in seeing how substitution at the α- and β-positions would affect the ability of the relevant dipyrrinato system to complex to metals such as those occupying early transition and/or lanthanide positions in the periodic table.

To introduce new moieties to a dipyrrin core, we first need to understand how dipyrrins are made. Indeed, there are two traditional ways of synthesizing dipyrrins. The first method involves condensation. As shown in **Scheme 9**, acid-catalyzed condensation of a 2-formyl pyrrole and a 2-*H* pyrrole yields the salt form of dipyrrins. This condition is widely known as MacDonald coupling due to a formation of an asymmetric dipyrrin and following methods used for the synthesis of dipyrrins embedded within porphyrins.[90] Aqueous hydrobromic acid is usually employed to provide the necessary acid catalysis. One of the advantages of this reaction is that the product usually precipitates, as its HBr salt, and so isolation and purification are generally facile.



Scheme 9. MacDonald coupling of 2-H pyrrole and 2-formyl pyrrole.

The second method, illustrated in **Scheme 10**, is usually used when we want to incorporate functionality onto the meso-position (e.g. an aryl group). This method involves condensation of pyrroles with appropriately substituted aldehydes, in an acidic solution, to synthesize dipyrromethanes which are then oxidized to form dipyrrins. Unlike **Scheme 9**, the product dipyrrin forms as a free base, and purification and isolation usually require multiple steps. Curiously, protonation of meso-aryl substituted dipyrrins is more challenging than when the meso-position is unsubstituted, and so purification via salt formation is not generally useful for these dipyrrins. Such concern becomes prominent in the oxidation step as the solution often turns to black upon the addition of oxidant. The fact that the typical oxidants used for this step, *p*-chloranil and DDQ, are not highly soluble in both dichloromethane and water makes work-up extraction extremely challenging. Therefore, in the Thompson group, various attempts have been made to improve the oxidation step which includes testing different oxidants, solvents, and purification methods. However, after extensive effort, we found only the quinone-based oxidants usefully oxidized dipyrromethanes to dipyrrins. Despite these obvious challenges, the method shown in **Scheme 10** represents the accepted approach in the field.[91,92]



Scheme 10. Dipyrrin synthesis from oxidation of dipyrromethane.

As appreciated by analysis of both approaches (**Scheme 9** & **10**), we can synthesize dipyrrins by utilizing functionalized pyrroles, or we can first synthesize dipyrrins and then

introduce various moieties onto the dipyrrin core. In this project, taking advantage of the reactivity of dipyrrins and pyrroles, different methods by which to incorporate aryl groups onto the dipyrrin unit will be discussed. We are particularly interested in determining an arylation route for the substitution of each position around the dipyrrin (**Figure 28**), as the presence of an extended conjugated system alters the electronic and photophysical properties of dipyrrins. Although it will not be discussed within this thesis, we ultimately wish to complex these arylated dipyrrins with a series of lanthanides and test their potential as ligands.

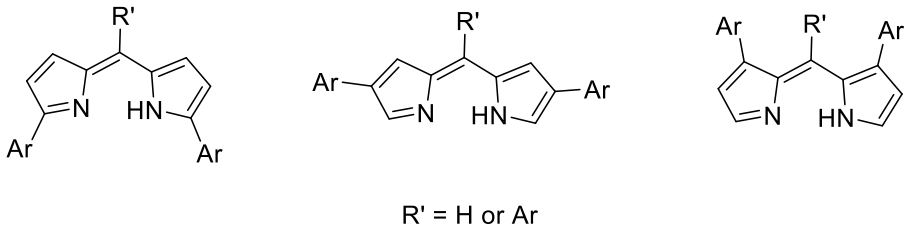
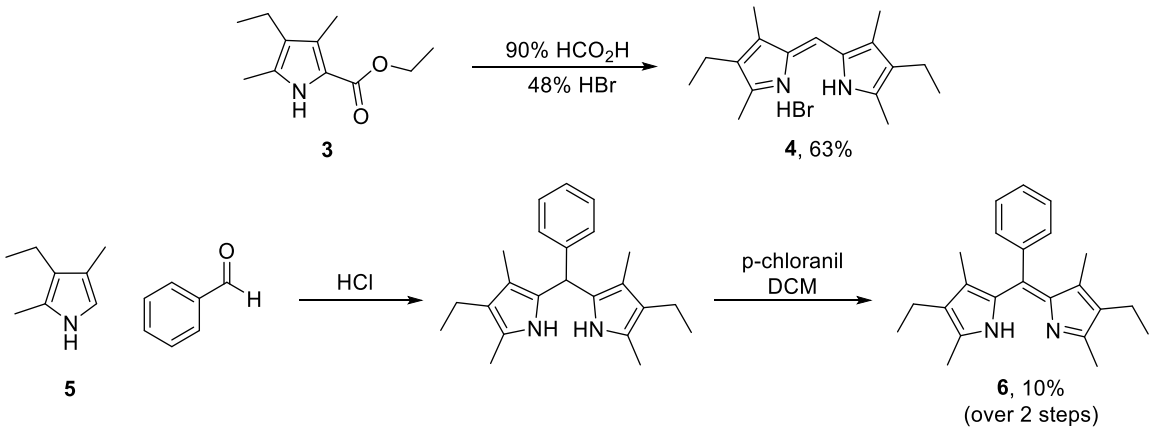


Figure 28. Proposed dipyrrins bearing aryl groups on different position with either meso-*H* or meso-Ar.

3.2 Synthesis of the Unsubstituted Dipyrrins

As previously discussed, the ultimate goal of this project is to synthesize aryl-substituted dipyrrins to enable comparison of the effect that the position of the aryl group has on the electronic properties. Therefore, it was logical to first synthesize reference, unsubstituted, compounds where there is no aryl group present. In this way, we can minimize variables when we evaluate arylated dipyrrins for their abilities as a ligand. Therefore, two dipyrrins were selected where the dipyrrin core is substituted with alkyl chains (**Scheme 11**). Dipyrrin salt **4** features a methyl-, ethyl- and methyl- substitution pattern around the pyrrole units. This grouping of alkyl substitution follows from the facile

synthesis of **3**, subsequent to reduction of 4-acetyl-3,5-dimethyl-1*H*-pyrrole-2-carboxylic acid ethyl ester formed as a result of a Knorr reaction on large scale.[93,94] Dipyrrin **6** features the same alkyl substituents and bears a phenyl substitution in the meso-position.



Scheme 11. Synthetic schemes of dipyrrins **4** and **6**.

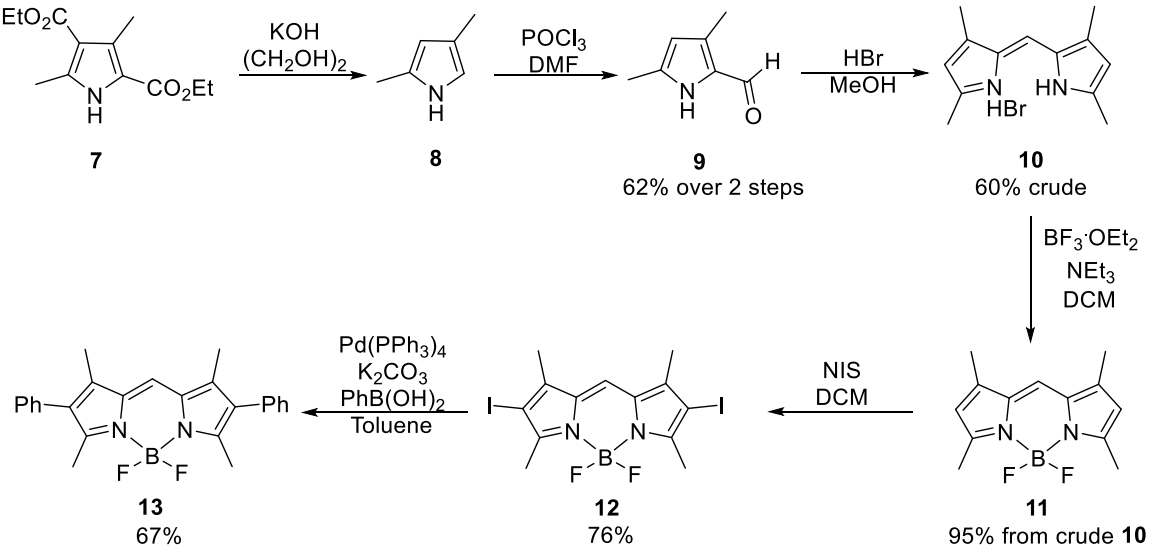
From the Knorr synthesis, one common end product is 4-acetyl-3,5-dimethyl-1*H*-pyrrole-2-carboxylic acid ethyl ester in which acetyl functionality is easily reduced by treatment with borane tetrahydrofuran complex to yield **3**.[93] Pyrrole **3**, through treatment with formic acid and hydrobromic acid, underwent hydrolysis and acid-catalyzed decarboxylation in the presence of acid, followed by formylation by formic acid.[94] As such, 2-*H* pyrrole self-condensed to yield dipyrrin **4** in the presence of hydrobromic acid to produce the salt (63%). Unlike dipyrrin **4**, synthesis of dipyrrin **6**, requires incorporation of an aryl group on the meso-position. As discussed earlier, to introduce an aryl group, the starting material had to be changed to 2-*H* pyrroles (**5**) alongside use of a reagent that provides the meso-position. For meso-*H* dipyrrins, the meso-carbon atom originates with a carboxylic acid (e.g. formic acid), whereas for meso-aryl dipyrrins, the meso-carbon atom originates from an aldehyde. This is because the α-keto pyrroles, that would otherwise

result, would be extremely unreactive. Because the two starting materials, 2-*H* pyrroles and 2-formyl pyrroles, differ in oxidation state, the use of two 2-*H* pyrroles plus an aldehyde necessitates the use of an oxidant. As shown in **Scheme 11**, synthesis and purification of dipyrrin **6** are not ideal, resulting in a low isolated yield of 10% (over 2 steps). Both dipyrrins have no extended-conjugated system on the pyrrolic core, but dipyrrin **6** has an aryl group on the meso-position. Therefore, when we compare these dipyrrins complexed to either -BF_2 or metal atoms, we will be able to distinguish the effect of an aryl group on the meso-position.

As previously mentioned, increasingly unsubstituted dipyrrins are known to be increasingly unstable, and they are known to be sternutators (i.e. cause respiratory issues).[95] Therefore, within this project, alkylated dipyrrins were selected for screening to avoid such health-related issues and because alkyl substituted-pyrroles are easily accessible from the Knorr approach.

3.3 Synthetic Route for Incorporating a Phenyl Moiety onto the Dipyrrin Core

We wish to introduce an extended conjugated pi system onto a dipyrrinato complex, through incorporation of aryl units about the core. In order to do so, we could take two routes: condensation of an aryl-substituted pyrrole or arylation of either α-free or β-free dipyrrins. At first, it was presumed that incorporating an aryl functionality early on, at the pyrrole stage of the synthetic route, may become problematic later in the pathway due to the bulkiness of an aryl group. Moreover, it has been observed that dipyrrins and BODIPYs favour the addition of electrophiles at the β-position.[96,97] With this in mind, a synthetic route to introduce an aryl group on the beta position of a dipyrrin was considered (**Scheme 12**).



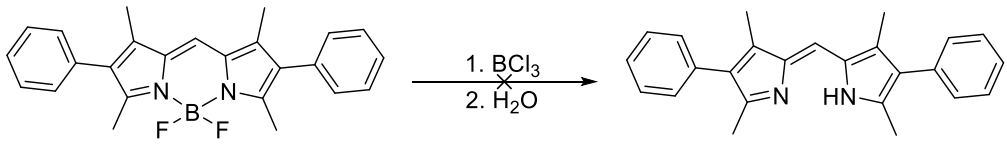
Scheme 12. Synthesis of meso-*H* β-Ph dipyrrin.

Starting from another prominent product of the Knorr approach, 3,5-dimethyl-1*H*-pyrrole-2,4-dicarboxylic acid ethyl ester[98] underwent base-catalyzed decarboxylation, to give the corresponding α-free pyrrole **8**, formylation of which, via the Vilsmeier approach, reliably gave the 2-formyl pyrrole **9** (62% over 2 steps). Following the MacDonald coupling, the HBr salt of β-free dipyrrin **10** was synthesized in 60%.[20] As this compound is a sternutator, it was carried onto the next step without further purification or characterization. Therefore, the nitrogen atom of the dipyrrin **10** was protected via BODIPY synthesis to yield **11** (95%).

The goal was then to incorporate an aryl group onto the β-position of **11** through Suzuki coupling. Suzuki coupling unites one halogenated species and one borylated species in the presence of palladium catalyst.[99] Since the synthesis of halogenated BODIPYs generally is high-yielding and less complicated, rather than borylating the BODIPY, we decided to halogenate **11** using *N*-iodosuccinimide following the literature method (76%).[100] Of course, regioselectivity of the halogenation was not an issue because of the

presence of methyl groups on the other positions. Nevertheless, in an excess of halogenating species, halogenation of such α-methyl group has been observed.[101] The iodinated BODIPY **12** was successfully di-arylated through Suzuki coupling, acquiring the two aryl moieties from phenyl boronic acid (67%).[102]

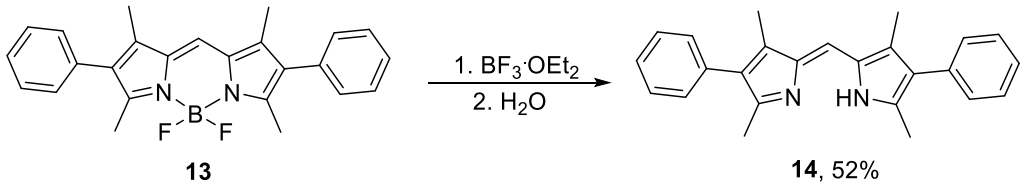
Since our ultimate goal is to test the activity of β-Ph substituted dipyrrins as ligands not as -BF_2 complexed ligand, BODIPY **13** needed to be deprotected. In the Thompson group, several methods have been discovered to deprotect BODIPYs. For this process, the reactivity of either nitrogen or boron atoms are targeted, ultimately releasing the -BF_2 moiety and returning the unprotected dipyrrin.[103] This process could be easily achieved in the presence of a nucleophile, if the boron atom is activated, and even water can do the job. From the work of a fellow Thompson group member, Dr. Travis Lundrigan, it was found that *Cl*-BODIPYs are far more sensitive to water than are *F*-BODIPYs.[104] Therefore, in the first step of the deprotection, boron trichloride is used to effect halogen exchange, which is then followed by the addition of water. The boron centre of *Cl*-BODIPYs becomes susceptible to a nucleophilic attack by water, ultimately yielding boric acid, $B(OH)_3$, and the free-base dipyrrins.[104] However, this method did not yield the free base form of the BODIPY and only yielded unreacted starting materials (**Scheme 13**).



13 **14**

Scheme 13. Attempted deprotection of BODIPY **13** via halogen exchange at the boron centre.

Therefore, another attempt was made using a slightly different method (**Scheme 14**). This time, BODIPY **13** was treated with boron trifluoride diethyl etherate ($BF_3{\cdot}OEt_2$). The addition of water successfully deprotected BODIPY **13** and yielded the required dipyrrin **14** (52%). The main contribution to this success was the enhanced activation of the boron atom by a stronger Lewis acid ($BF_3{\cdot}OEt_2$). From the previous work in the Thompson group, it was observed that whenever $BF_3{\cdot}OEt_2$ is used to deprotect BODIPY, the HBF_4 salt of the dipyrrin can be isolated. However, analysis of the product recovered from the reaction shown in **Scheme 14** (^{11}B and ^{19}F NMR spectroscopy), the BF_4^- anion was absent, meaning that HBF_4 salt had likely been washed with excess amount of water the work-up extraction.

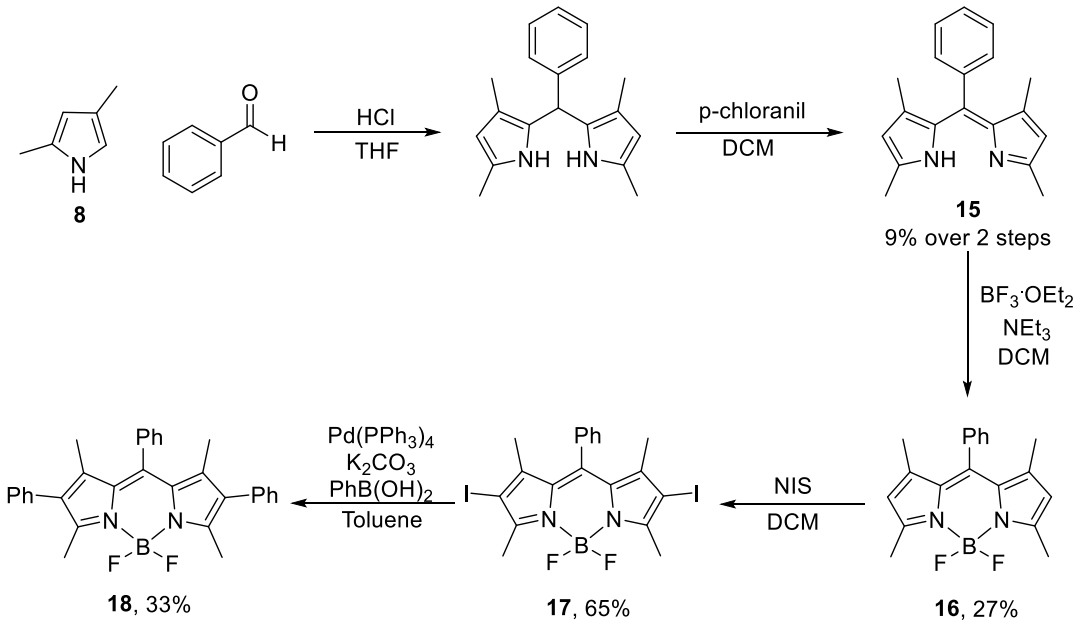


13 **14**, 52%

Scheme 14. Successful deprotection of BODIPY **13** by activation with boron trifluoride diethyl etherate.

To compare the effect of the substituent on the meso-position of dipyrrin ligands, the meso-aryl version of **14** was synthesized (i.e. the dipyrrin contained within BODIPY **18**, **Scheme 15**). As previously described for dipyrrin **14**, pyrrole **8** was prepared through decarboxylation of 3,5-dimethyl-1*H*-pyrrole-2,4-dicarboxylic acid ethyl ester. In order to place an aryl group on the meso-position of the required dipyrrin, pyrrole **8** condensed with benzaldehyde, followed by oxidation to yield dipyrrin **15** in 9% isolated yield over two steps. Since purification following the oxidation step is cumbersome, it is common to effect condensation, oxidation, and BODIPY synthesis proceed in one-pot, yielding BODIPY **16**

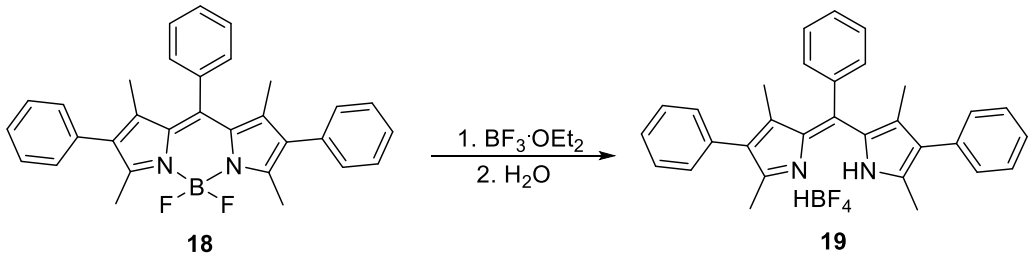
as the isolated product. Unfortunately, when dipyrrin **15** was treated with boron trifluoride diethyl etherate, the yield of the isolated BODIPY was only 27% (from dipyrrin **15**). Moreover, the subsequent reactions (iodination and Suzuki coupling) yielded 65% and 33%, respectively which are lower when compared to the yields for the analysis reactions involving the dipyrrin **14**. One contributing factor for such outcome is that the presence of an aryl group (in synergy with electron-donating alkyl groups) increases the electron density of the dipyrrin core, allowing other side reactions to proceed at a higher rate. Especially for the iodination step, formation of another product was observed, which had not been noted for meso-*H* BODIPY **11**.



Scheme 15. Synthesis of meso-Ph β-Ph dipyrrin.

Deprotection of BODIPY **18** was attempted by first activating it with boron trifluoride diethyl etherate, followed by the addition of water (**Scheme 16**). Unfortunately, the activation step of BODIPY **18** had not been as effective compared to BODIPY **13**, and even when large excess of $BF_3{\cdot}OEt_2$ was added, both unreacted starting material and the

HBF_4 salt were observed by TLC. Since only 20 mg of BODIPY **18** underwent deprotection, not enough salt **19** had formed to be collected through Millipore frit (0.45 μm HV). Therefore, synthesis of β-Ph meso-Ph dipyrrin is still in progress by preparing more of BODIPY **18** to precipitate the HBF_4 salt.



18 **19**

Scheme 16. Attempted deprotection of BODIPY **18**.

As seen in the example involving the formation of dipyrrin **15**, the oxidation step is detrimental to the yield. Despite this low-yielding method, as previously mentioned, quinone-based reagents including quinone, 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ), or *p*-chloranil are the most accepted reagents for the oxidation step. One can make an effort to avoid the oxidation step by synthesizing a pyrrole that contains a phenyl ketone functionality in the α-position. Coupling of this species with 2-*H* pyrrole may be a viable route to synthesis meso-Ph dipyrrin, rather than coupling two pyrroles with a benzaldehyde. However, α-Ph ketone pyrroles are insufficiently reactive, because of the pyrrole unit, thus the electrophilicity of the carbonyl carbon of the ketone is greatly reduced (**Figure 29**).

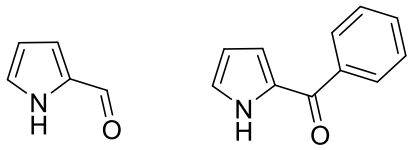


Figure 29. α-Formyl and α-Ph ketone pyrroles.

The synthesis of dipyrrins bearing aryl groups at the α-position was next attempted. Although placing a halogen on the beta position may be viable at the dipyrrin stage, as seen in **Schemes 12** and **15**, placing a halogen on the alpha position only occurs as a minor product via this approach (**Figure 30**). For this reason, we needed a way to perform halogenation onto the alpha position of the dipyrrin unit. Nevertheless, halogenation on the alpha position only occurs when other positions are substituted with other functionalities. Therefore, an alternative strategy was required.

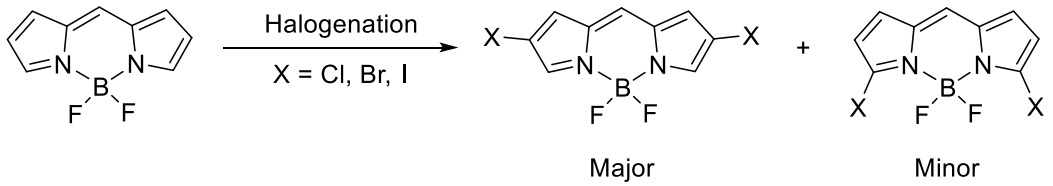
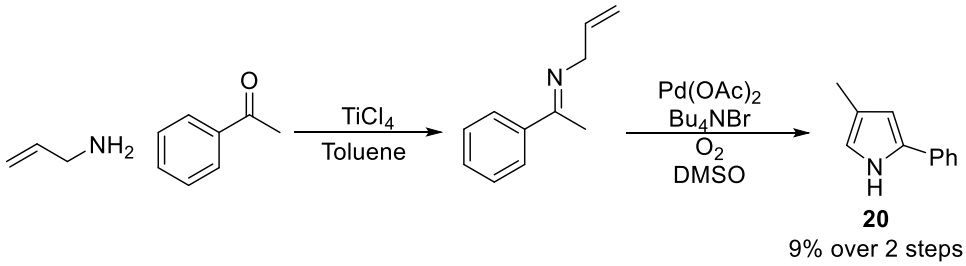


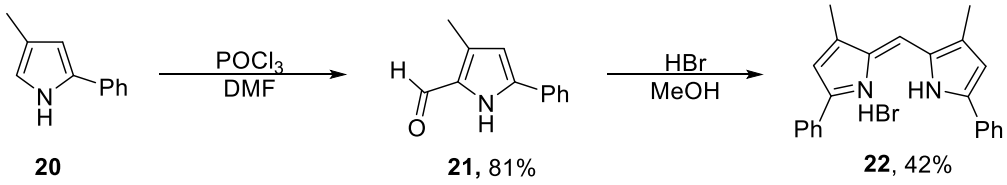
Figure 30. Regioselectivity of halogenation on BODIPY.

Then, we wondered if, rather than going through halogenation and Suzuki-coupling, whether a direct introduction of aryl moieties would be feasible. Following this idea, two options were present: incorporating an aryl moiety either prior to pyrrole synthesis or via Suzuki coupling when the synthetic sequence is at the pyrrole stage. However, 2-halogenated pyrroles are not generally stable,[105] so we chose to incorporate an aryl moiety prior to pyrrole synthesis (**Scheme 17**). Although there have been numerous precedents of synthesizing α-Ph substituted pyrroles from ethyl benzoylacetate,[106,107] the routes shown in **Scheme 17** were chosen because the desired products are only two steps away from the commercially available reagents. Pyrrole **20** was thus synthesized from allylamine and acetophenone via the corresponding imine in the presence of a catalyst, titanium (IV) chloride.[108,109] The following imine cyclizes to form a pyrrole by undergoing α-palladation, intramolecular alkene insertion and β-hydride elimination.



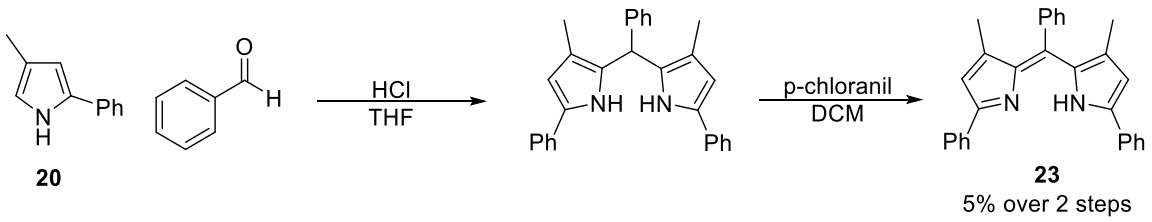
Scheme 17. Synthesis of a pyrrole bearing an aryl group on the α-position**.**

After pyrrole **20** was isolated, we wish to synthesize the formylated version (**21**, **Scheme 18**) so we can couple these two pyrroles via MacDonald coupling to synthesize a meso-*H* α-Ph dipyrrin (**22**, **Scheme 18**). Therefore, pyrrole **20** was formylated via Vilsmeier reaction to yield pyrrole **21** (81%). Then pyrrole **21** and **20** were coupled together via MacDonald coupling in the presence of an acid to yield dipyrrin **22**, which was isolated as HBr salt in 42% yield.



Scheme 18. Synthesis of meso-H α-Ar dipyrrin.

Thus, we now have the α-Ph dipyrrins **22** and the β-Ph dipyrrins **14** available for analysis as ligands. The next goal was to prepare the meso-Ph variant of **22** (i.e. dipyrrin **23**, **Scheme 19**). In order to introduce an aryl group to the meso-position, pyrrole **20** was coupled with benzaldehyde in the presence of hydrochloric acid followed by oxidation to yield dipyrrin **23** (5% over 2 steps).



Scheme 19. Synthesis of meso-Ph α-Ph dipyrrin.

Along with the two reference dipyrrins **4** and **6**, three dipyrrins and one BODIPY bearing aryl moieties on different positions have been synthesized and routes towards them have been demonstrated (**Figure 31**). With these five dipyrrins and one BODIPY in hands, we will be able to compare correlations between the properties of interest (either electronic properties as ligands or photophysical properties) and the presence and/or position of the aryl groups.

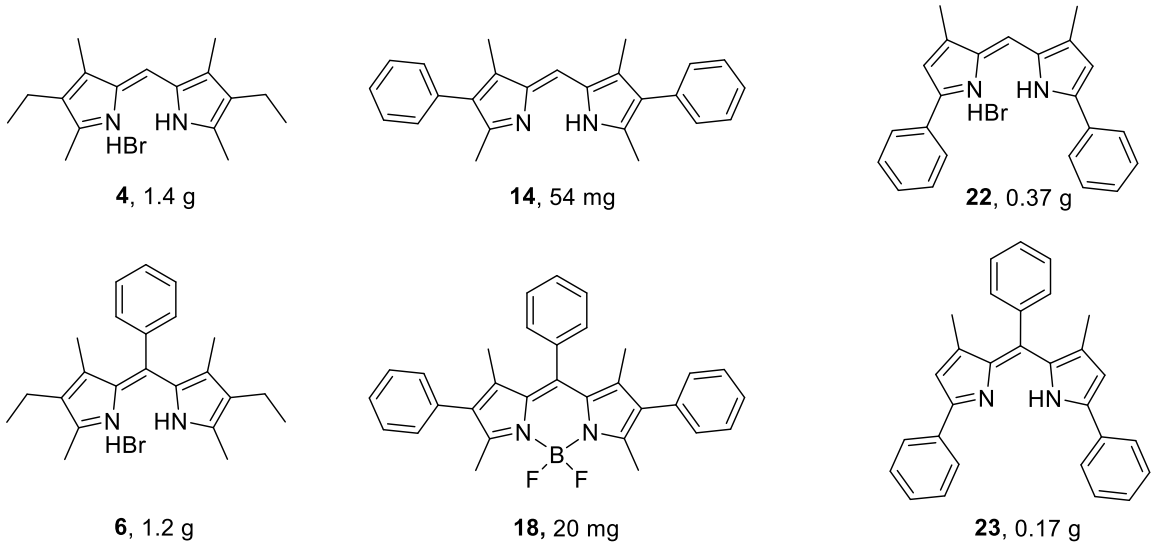


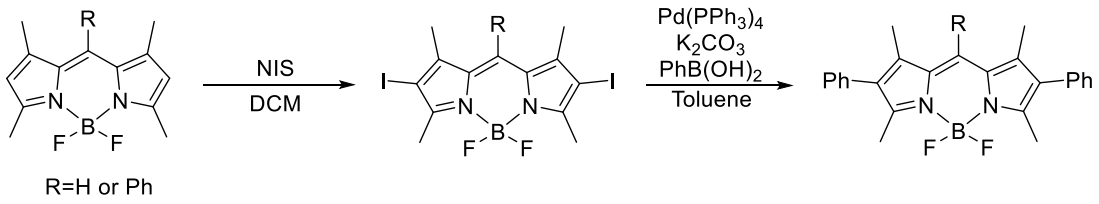
Figure 31. Two reference dipyrrins, three dipyrrins and one BODIPY synthesized with various position of a phenyl group.

Because of the regioselectivity of halogenation on dipyrrins, we have neglected Suzuki coupling approach to introduce an aryl group for α-Ar dipyrrins. Although the

discussed method (**Scheme 18** and **Scheme 19**) works without any prominent problem, we wished to explore a different route to incorporate an aryl moiety (i.e. via Suzuki coupling).

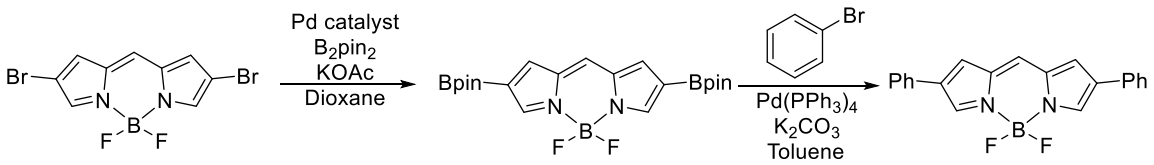
3.4 Synthetic Route to Miyaura Borylation on Dipyrrins

So far, the dipyrrins bearing phenyl substituents at β-positions have acquired the aryl moieties through halogenation, followed by Suzuki coupling. In terms of Suzuki coupling, two reactants are generally needed: one bearing a halogen atom (Cl, Br, or I) and the other bearing a boronate moiety (boronic acid or Bpin).[99] The two β-Ph dipyrrins that have been synthesized bore iodo-substitution and acquired the phenyl functionality from the use of phenylboronic acid (**Scheme 20**).



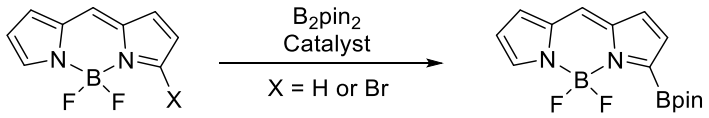
Scheme 20. Current approach to β-Ph BODIPYs from β-I BODIPYs.

We wanted to find out whether this method could be achieved from the opposite pairing, i.e. dipyrrins bearing a boronic acid unit and a phenyl group bearing a halo-substituent (**Scheme 21**). Two advantages that can come from this method are that aryl halides can sometimes be more readily available than their corresponding aryl-$B(OR)_2$ units, and that diverse aryl halides are more accessible than boronic acids (both on the market and with respect to synthesis).



Scheme 21. Proposed approach to β-Ph BODIPYs from β-Br BODIPYs.

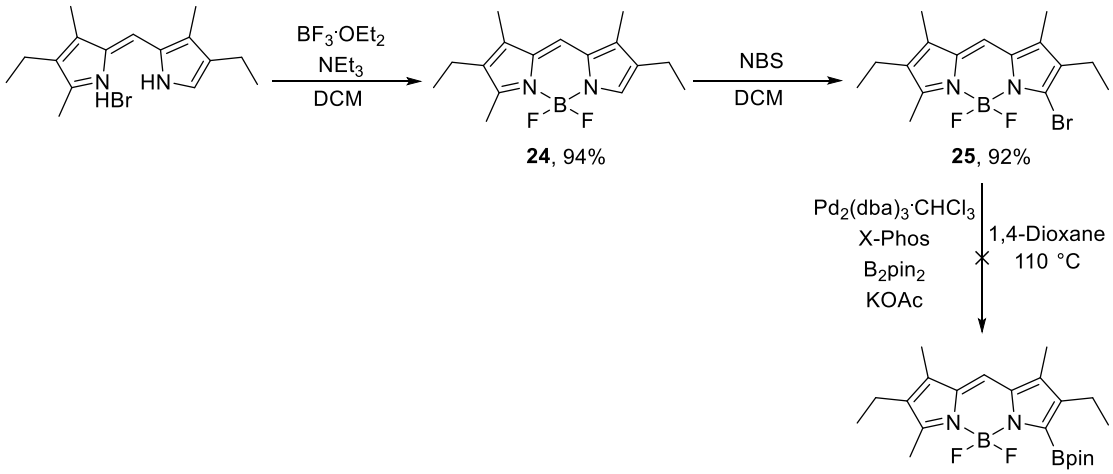
Since there was already a known method for Miyaura borylation on the beta position of the dipyrrins,[110,111] a new method by which to effect borylation at the alpha position was investigated. The ultimate goal of this approach would be forming a C-B bond on the α-position directly from a C-H bond (**Scheme 22**).



Scheme 22. Miyaura borylation on the α-position of a dipyrrin.

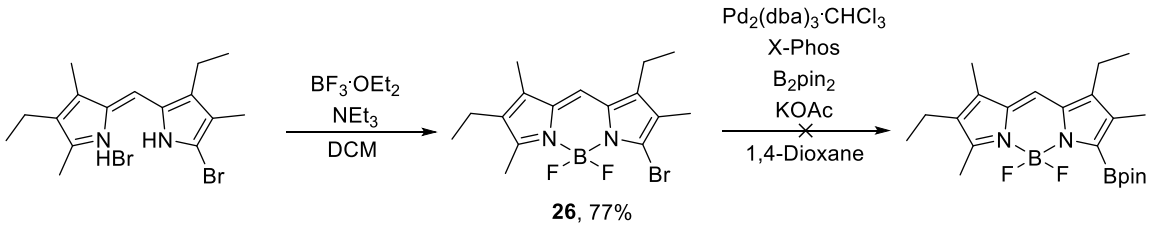
To implement the method illustrated in **Scheme 22**, a BODIPY **25** bearing a bromo-substituent on the α-position was needed. Therefore, the α-*H* dipyrrin that was available in the Thompson group was transformed into the corresponding BODIPY **24** in 92% isolated yield, which was then brominated using *N*-bromosuccinimide to yield BODIPY **25** in 94% yield. Attempted borylation of **25**, following the literature method, was then attempted.[111] Along with BODIPY **25**, tris(dibenzylideneacetone)dipalladium(0), X-Phos, bis(pinacolato)diboron, and potassium acetate were thus charged into a vial, which then was heated to reflux temperature and stirred for 90 minutes. However, the desired result was not obtained as the starting materials simply decomposed (**Scheme 23**). The proposed challenge was the steric bulk present on the dipyrrin core. Because of the bulky ethyl group adjacent to the desired reactive position, the reagent may have not been easily accessible

to the dipyrrin. Therefore, different classes of dipyrrins were proposed to ease this challenge.



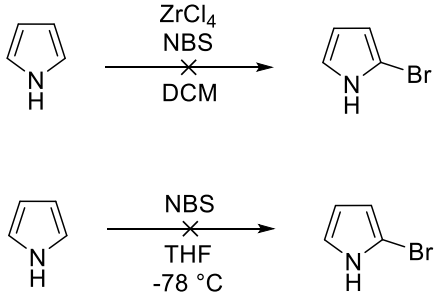
Scheme 23. Attempted borylation of α-Br BODIPY.

As previously mentioned, the less-substituted dipyrrins are generally less stable, and so dipyrrins bearing alkyl chains were desired. Therefore, instead of an ethyl group on the β-position adjacent to the desired reactive site, a methyl group was used in this position within dipyrrin salt (**Scheme 24**). The α-Br dipyrrin salt was converted into the corresponding BODIPY **26** in 77% yield. However, BODIPY **26** did not undergo borylation, and when the starting materials had been fully consumed, only decomposition was observed according to analysis using NMR spectroscopy.



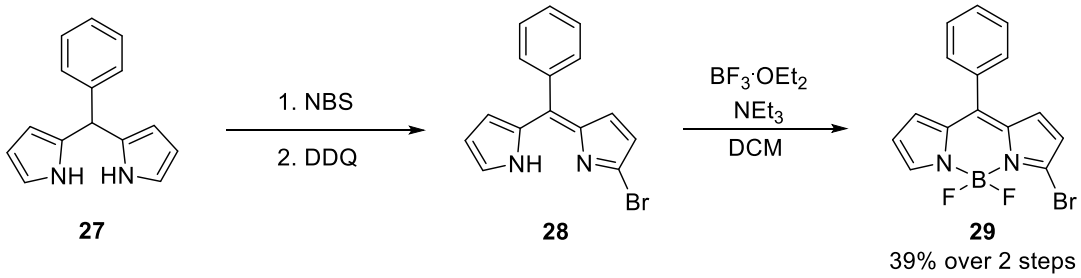
Scheme 24. Synthesis of β-Me BODIPY **26** and attempted borylation.

Decomposition of BODIPYs **25** and **26** led us to consider β-free dipyrrins because we believed that such our unsuccessful results were mainly due to the steric bulk provided by the β-position. In order to achieve this, there is one barrier that needs to be overcome: this involves the regioselectivity of halogenation. In previous cases (**Schemes 23** & **24**), all but the desired α-position had been occupied by alkyl substituents, meaning that there was no competition for halogenation. If dipyrrins unsubstituted at α- and β-positions were to be used, we would need to selectively halogenate the α-position. Both dipyrrins and BODIPYs, however, favour halogenation at the β-position, so di-halogens could form but there is no known method to specifically halogenate only on the α-position.[97] As shown in **Scheme 25**, several attempts were made to synthesize 2-bromopyrrole following literature methods,[112,113] but one reported that the 2-bromopyrrole readily decomposes at room temperature.[105] When pyrrole was treated with zirconium (IV) chloride and NBS, the resulting white solid was analyzed by NMR spectroscopy, but it was found that the isolated solid was not the desired α-Br pyrrole. The second reaction shown in **Scheme 25**, the crude reaction mixture was stirred at -78 °C for 2 hours, but after work-up, decomposition was observed, yielding black solids.



Scheme 25. Attempted α-bromination of pyrroles.

Interestingly though, dipyrromethanes favour halogenation at the alpha addition.[114] If successful, this would allow us to halogenate prior to the oxidation step to acquire the desired α-Br dipyrromethane ready for oxidation to provide the desired α-Br dipyrrin **28** (**Scheme 27**). Subsequently, dipyrrin **28** underwent the BODIPY synthesis to yield BODIPY **29** in 39% yield (over 2 steps).



27 **28** **29**
39% over 2 steps

Scheme 26. Synthesis of α-Br meso-Ph BODIPY.

Alongside, another α-Br BODIPY was synthesized from a pyrrolinone, which is a precursor to prodigiosin, readily available in the Thompson group. As discussed in Chapter 1, prodigiosin is a tri-pyrrolic compound, and it is widely known for its anticancer activity. To synthesize prodigiosin, Suzuki coupling generally employs: a dipyrrin bearing a halogen and a pyrrole bearing a boronic acid (**Figure 32**). Boc-protected 2-boronic acid pyrroles can be purchased, and the requisite α-Br dipyrrins can be synthesized from pyrrolinone.

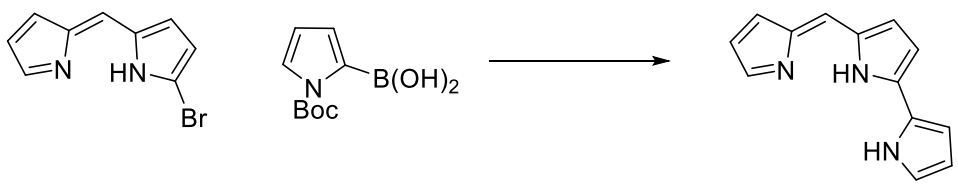
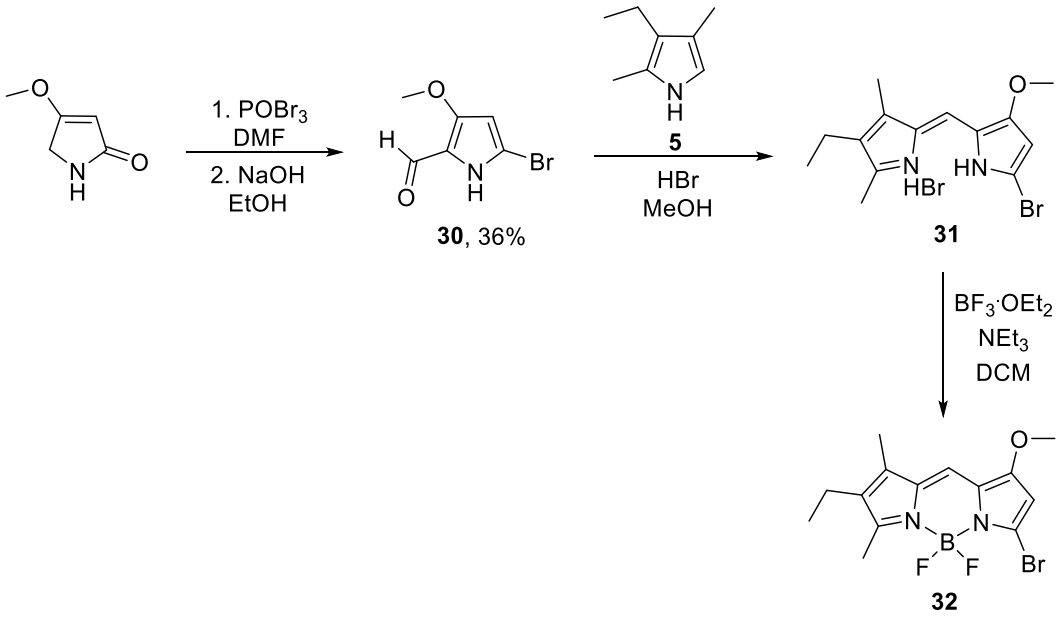


Figure 32. Synthetic route to prodigiosin.

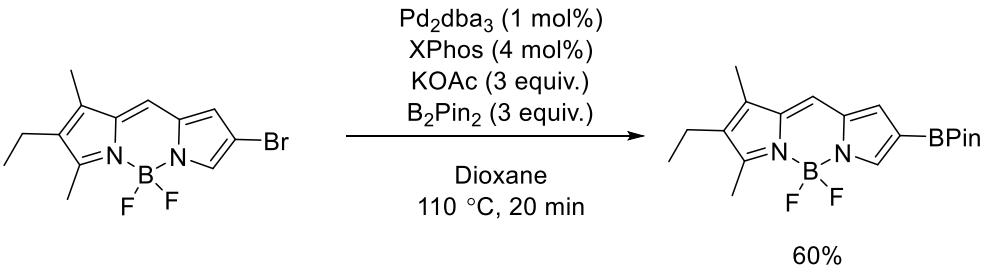
Therefore, synthesis of α-Br dipyrrin **31** was attempted (**Scheme 27**). Pyrrolinone was treated with phosphoryl bromide followed by formylation to successfully produce the α-Br pyrrole **30** (36%), which then was coupled with pyrrole **5** under acidic conditions to obtain the HBr salt of the dipyrrin **31**. Then, the following salt was connected into the corresponding BODIPY via treatment with triethylamine and boron trifluoride diethyrate in 97% yield.



Scheme 27. α-Br BODIPY synthesis.

The above BODIPYs (**29** and **32**) were exposed to several attempts to borylate, varying different Pd catalysts, ligands, base and temperature. A fellow Thompson group member, Dr. Craig Smith, optimized a method for the beta borylation of brominated BODIPYs (**Scheme 28**). His optimized method involved the same condition as indicated in **Scheme 23**, and successfully enabled various aryl groups to be coupled onto borylated dipyrrins via Suzuki coupling. Challenges incurred during optimization because the borylated BODIPYs tend to decompose on silica, so the crude mixtures were instead

pushed through a short column on silica to remove baseline materials before crystallization enabled purification.



Scheme 28. Optimized reaction conditions for borylation of β-Br BODIPY according to work completed by Dr. Craig Smith (unpublished).

In an initial attempt to borylate **29** and **32**, these BODIPYs were treated under the optimized conditions shown in **Scheme 28**. After 20 minutes, starting materials were still present, so the reaction was extended to 2 hours until all the starting materials had been consumed. After work-up and purification (quick column on silica and crystallization), only trace amounts of the borylated species were found using mass spectrometry, and by NMR spectroscopy most was decomposed material (**Table 3**, entry 3). It was suspected that the borylated product may not be too stable and that the bromo substituent can serve as a good leaving group to result in protodebromination rather than borylation. Therefore, BODIPY **29** was treated under the same conditions as before but at a lower temperature (60 °C): by TLC analysis, most of the starting materials remained unreacted after 2 hours. Therefore, the temperature was increased to 80 °C (2 hours), and when the starting materials had been consumed, the desired product could not be identified by mass spectrometry and NMR spectroscopy upon work-up and purification (**Table 3**, entry 4). Given the lack of success when exposing BODIPYs **29** and **32** to the conditions used in the

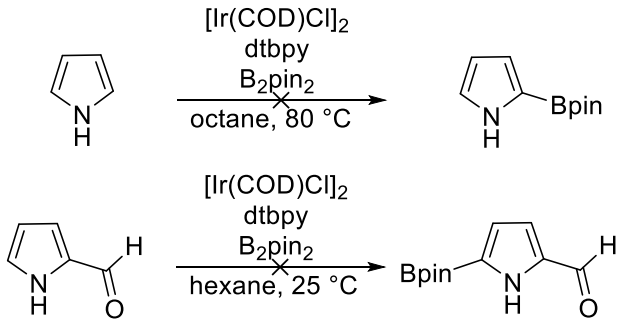
lab to effect borylation, we altered the catalysts, the ligands, and the base. For example, in entry 5, we changed the catalyst from [1,1′-tris(dibenzylideneacetone)dipalladium(0) to bis(diphenylphosphino)ferrocene]dichloropalladium(II), while the base was changed from potassium acetate to triethylamine.[115] For entry 6, palladium (II) acetate was chosen for the palladium catalyst, triphenylphosphine as the ligand, and triethylamine for the base. Similar with the previous attempts, however, no desired product could be isolated or characterized.

Table 3. Attempted borylation of BODIPY **28** and **32** varying catalyst, temperature, and ligand.

Entry	Sub-strate	Pd Catalyst	Ligand	Base	Temper-ature	Time	Pro-duct
1	**32**	$Pd_2(dba)_3{\cdot}CHCl_3$	X-Phos	KOAc	110 °C	20 min	-
2	**32**	$Pd_2(dba)_3{\cdot}CHCl_3$	X-Phos	KOAc	110 °C	2 h	-
3	**29**	$Pd_2(dba)_3{\cdot}CHCl_3$	X-Phos	KOAc	110 °C	2 h	trace
4	**29**	$Pd_2(dba)_3{\cdot}CHCl_3$	X-Phos	KOAc	60 → 80 °C	4 h	-
5	**29**	$Pd(dppf)Cl_2{\cdot}DCM$	-	NEt_3	80 °C	20 h	-
6	**29**	$Pd(OAc)_2$	PPh_3	NEt_3	80 °C	6 h	-

Without any success from the borylation step of dipyrrins, a new approach was considered, this time involving a direct borylation from a C-H bond. Following the literature method, 2-formyl pyrrole and pyrrole were subjected to an iridium catalyst and 4,4’-di-tert-butyl-2,2’-dipyridyl (**Scheme 29**), The reported procedures confirmed the identity of the product by gas chromatography without any purification.[116,117] However, in our hands, in the case of 2-formyl pyrrole, only the starting materials were isolated when conducted manually. The required 2-borylated pyrrole also seemed to decompose upon

distillation. Analysis of the distilled material using NMR spectroscopy and mass spectrometry did not reveal the desired compounds.



Scheme 29. Attempted borylation of pyrrole and 2-formyl pyrrole.

Disappointingly, many attempted efforts did not yield the desired α-borylated pyrroles/dipyrrins/BODIPYs. The main contributing factor of such outcomes was the differences in reactivity at the α- and β-positions of pyrroles and dipyrrins. For example, the β-positions of BODIPYs/dipyrrins bear the least positive charge, favouring an electrophilic addition at these sites.[97] Therefore, due to the difference in electron density within the dipyrrinato core, α-borylation was found to be particularly challenging as the α-positions are not the most reactive centre of the dipyrrin/BODIPY. Considering such factors, we are still in need of other routes by which to synthesize α-borylated dipyrrins/BODIPYs.

3.5 Conclusion and Future Work

In the first part of this project, five dipyrrins and one BODIPY were synthesized, differing in the position of aryl substituents. Introducing an aryl group was achieved via Suzuki coupling where the dipyrrins bear halo-substituents and the boronic moiety bear an aryl group. In the second part of the project, the opposite route was considered thereby

placing a Bpin substituent onto the dipyrrin/BODIPY core. After several attempts varying reaction conditions for borylation, we were not able to isolate the desired product.

Future work for this project includes synthesizing the last class of dipyrrin (i.e. deprotecting β-Ph meso-Ph BODIPY **18**), screening catalysts and ligands for Miyaura borylation at the α-position of BODIPYs, and exploring different starting points. For example, rather than borylating dipyrrins, we could potentially functionalize pyrroles (i.e. Bpin) and condense them to synthesize borylated dipyrrins. The concern with this approach is the uncertain stability of the Bpin moiety through the required condensation and oxidation en route to dipyrrin. Also, there has been an example of placing a Bpin group directly onto the meso-mesityl position of a dipyrromethane.[118] Although, we are skeptical whether the following product would survive oxidation to the desired dipyrrin, we could attempt a one-pot reaction (i.e. borylation and Suzuki coupling) to see whether dipyrrins bearing aryl groups could be isolated. Such a route would be only viable for meso-aryl dipyrrins as the MacDonald coupling directly forms dipyrrin, skipping the dipyrromethane stage. Therefore, we are still in need of a new method for the alpha-borylation of meso-*H* dipyrrins.

Chapter 4. Experimental

4.1 General Information

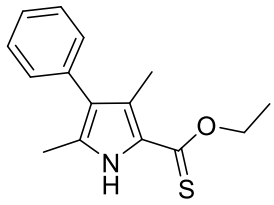
Anhydrous solvents, silica 40-63 μm 60 Å, 150 mesh Brockmann III activated neutral aluminum oxide and reagents were purchased and used as received. All NMR spectra were obtained using 300 or 500 MHz spectrometers. Chemical shifts for NMR spectroscopy are reported in parts per million (ppm) using the solvent signal [$CDCl_3$ (^{1}H 7.26 ppm; ^{13}C 77.16 ppm); DMSO (1H 2.50 ppm; 13C 39.52 ppm)] as the internal reference. All coupling constants (*J*) are reported in Hertz (Hz). All mass spectra were obtained through use of a time-of-flight mass spectrometer operating in positive electrospray ionization mode. Melting points were determined using a Fisher-Johns melting point apparatus.

From Chapter 2, pyrroles **1a**, **1b**, **1e**, and **1f** were prepared according to the literature procedure involving Lawesson's reagent.[28] Raney nickel is W. R. Grace Grade 2800 (CAS# 7440-02-0), purchased from Sigma Aldrich in the form of a slurry in water with the nickel composition stated as equal to or greater than 89% (Cat. # 221678-100G). Before each use, the bottle containing the Raney nickel slurry was thoroughly shaken before aliquots were drawn out quickly with a pipette in order to enable efficient transfer of the slurried material to a reaction flask.

From Chapter 3, 3,5-dimethyl-1*H*-pyrrole-2,4-dicarboxylic acid ethyl ester,[98] 4-acetyl-3,5-dimethyl-1*H*-pyrrole-2-carboxylic acid ethyl ester,[119] and 4-methoxy-3-pyrrolin-2-one[120] were prepared according to literature procedures. Duapore membrane filters (0.45 μm HV) used for Millipore filtration were purchased from MilliporeSigma and used as received.

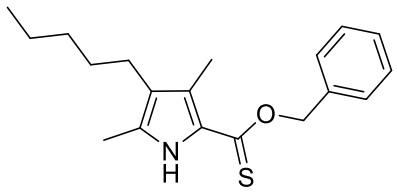
4.2 Experimental Procedures for Chapter 2

O-Ethyl 3,5-dimethyl-4-phenyl-1*H*-pyrrole-2-carbothioate (1d)



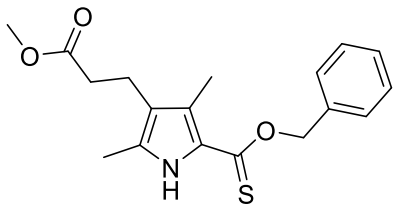
According to the literature method,[28] the title compound was obtained as a yellow solid (0.76 g, 39 %). M.p. 89-92°C; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 9.31 (1H, br s), 7.39-7.45 (2H, m), 7.29-7.34 (1H, m), 7.22-7.25 (2H, m), 4.71 (2H, q, *J*=6.9 Hz), 2.30 (3H, s), 2.26 (3H, s), 1.49 (3H, t, *J*=6.9 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 200.0, 134.5, 134.3, 130.2, 129.0, 128.4, 126.6., 124.8, 66.8, 14.3, 12.9, 12.5, one carbon signal missing; HRMS-ESI (*m/z*): $[M+Na]^+$ calculated for $C_{15}H_{17}NNaOS$, 282.0923; found 282.0923.

O-Benzyl 3,5-dimethyl-4-pentyl-1*H*-pyrrole-2-carbothioate (1g)



According to the literature method,[28] the title compound was obtained as a yellow oil (0.53 g, 50 %). ^{1}H-NMR (300 MHz, $CDCl_3$): δ 9.13 (1H, br s), 7.35-7.49 (5H, m), 5.70 (2H, s), 2.34 (2H, t, *J*=7.2 Hz), 2.24 (3H, s), 2.22 (3H, s), 1.42 (2H, p, *J*=7.2 Hz), 1.28-1.35 (4H, m), 0.91 (3H, t, *J*=7.2 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 198.7, 136.2, 135.0, 129.1, 128.6, 128.4, 128.2, 127.0, 124.7, 72.0, 31.7, 30.5, 23.9, 22.7, 14.2, 12.4, 12.0; HRMS-ESI (*m/z*): $[M+Na]^+$ calculated for $C_{19}H_{25}NNaOS$, 338.1549; found 338.1545.

***O*-Benzyl 3,5-dimethyl-4-methylpropionic-1*H*-pyrrole-2-carbothioate (1h)**



According to the literature method,[28] the title compound was obtained as a yellow solid (0.45 g, 43 %). M.p. 98-100°C; ^{1}H-NMR (500 MHz, $CDCl_3$): δ 9.11 (1H, br s), 7.33-7.45 (5H, m), 5.67 (2H, s), 3.65 (3H, s), 2.69 (2H, t, J=7.5 Hz), 2.41 (2H, t, J=7.5 Hz), 2.23 (3H, s), 2.23 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$): δ 198.9, 173.4, 136.1, 135.0, 128.6, 128.4, 128.3, 126.1, 122.2, 72.2, 51.7, 34.8, 19.5, 12.3, 11.9, one carbon signal missing; HRMS-ESI (*m/z*): $[M+Na]^+$ calculated for $C_{18}H_{21}NNaO_3S$, 354.1134; found 354.1127.

General Procedure for Synthesizing 2-Formyl Pyrroles from 2-Thionoester Pyrroles (GP1)

Slurried Raney nickel (2 mL containing water and Raney nickel) was suspended in acetone, and the mixture was heated at reflux temperature for 1 hour. 2-Thionoester pyrrole **1** (100 mg, 0.47 mmol) was dissolved in acetone (10 mL), and the resulting solution was added to the reaction mixture containing Raney nickel in acetone held at reflux temperature. The reaction mixture was heated at reflux temperature for 2 hours, with stirring under nitrogen gas. Analysis using thin layer chromatography showed the complete consumption of starting material and the appearance of the product at lower R_f. The reaction mixture was allowed to cool to room temperature and filtered through a short pad of silica, washing with acetone (500 mL). The filtrate was concentrated under vacuum, diluted with ethyl acetate and washed with brine. The organic layer was then dried using anhydrous sodium

sulfate, and the solvent was removed through rotary evaporation to yield a dark greenish brown solid. The crude product was purified via column chromatography over silica, eluting with 40% ethyl acetate/hexanes.

General Procedure for Radical Studies (GP2)

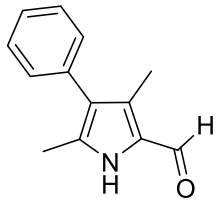
Following GP1, radical clock was added along with 2-thionoester pyrrole **1a**. Each reaction was run in parallel with a reference reaction prepared by GP1.

Cyclopropyl phenyl ketone: 500 equivalencies of the radical clock were added with **1a**, and the product **2a** was isolated in 55% (in absence of a radical clock: 53%).

Diethyl cyclopropane-1,1-dicarboxylate: 200 equivalencies of the radical clock were added with **1a**, and the product **2a** was isolated in 64% (in absence of a radical clock: 58%).

TEMPO: 50 equivalencies of TEMPO were added with **1a**, and the product **2a** was isolated in 7% (in absence of a radical trap: 37%).

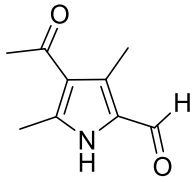
2-Formyl-3,5,-dimethyl-4-phenylpyrrole (2d)



Following GP1, the title compound was obtained as a beige solid (69 mg, 45%). M.p. 148-150 °C; ^{1}H-NMR (300 MHz, DMSO-d_6): δ 11.77 (1H, br s), 9.56 (1H, s), 7.39-7.44 (2H, m), 7.25-7.31 (3H, m), 2.25 (3H, s), 2.21 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$): δ 176.6, 135.6, 134.3, 131.7, 130.0, 128.5, 128.4, 126.7, 125.6, 12.4, 9.6; HRMS-ESI (*m/z*):

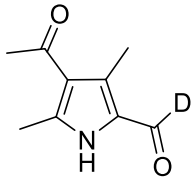
$[M+Na]^+$ calculated for $C_{13}H_{13}NNaO$, 222.0889; found 222.0887; it is a newly synthesized compound.

4-Acetyl-2-formyl-3,5-dimethylpyrrole (2e)



Following GP1, the title was compound was prepared as a beige solid (65 mg, 44 %). M.p. 168-170 °C; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 9.89 (1H, br s), 9.65 (1H, s), 2.58 (3H, s), 2.57 (3H, s), 2.46 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$): δ 195.0, 177.7, 142.6, 134.2, 128.4, 123.9, 31.4, 15.4, 11.5; HRMS-ESI (*m/z*): $[M+Na]^+$ calculated for $C_9H_{11}NNaO_2$ 188.0682; found 188.0681; data in accordance with literature.[121]

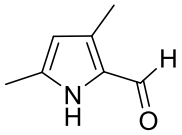
4-Acetyl-2-formyl-d-3,5-dimethylpyrrole (2e')



To a slurried Raney nickel (2 mL containing water and Raney nickel) deuterium oxide (5 mL portion) was added. The reaction vessel was stirred and sonicated at room temperature for 30 seconds, and the solvent was decanted. The following wash was repeated for 10 times. After a final wash, deuterium oxide (2 mL) and acetone (10 mL) were added. GP1 was followed to obtain the title compound as a beige solid (68 mg, 46%). M.p. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 9.69 (1H, br s), 2.58 (3H, s), 2.57 (3H, s), 2.47 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$): δ 195.0, 177.4 (t), 142.6, 134.2, 128.3, 123.9, 31.4, 15.5, 11.6; HRMS-

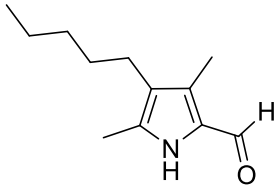
ESI (*m/z*): $[M+Na]^+$ calculated for $C_9H_{10}DNNaO_2$ 189.0745; found 189.0736; it is a newly synthesized compound.

2-Formyl-3,5-dimethylpyrrole (2b) from 1f



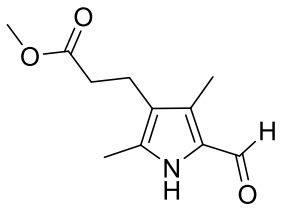
Following GP1, the title compound was prepared (69 mg, 45%). ^{1}H-NMR (300 MHz, $CDCl_3$): δ 10.16 (1H, br s), 9.43 (1H, s), 5.82 (1H, s), 2.29 (6H, s), 2.27 (3H, s); data in accordance with literature.[122]

2-Formyl-3,5-dimethyl-4-pentylpyrrole (2g)



Following GP1, the title compound was obtained as a beige solid (45 mg, 70 %). M.p. 70-71 °C; ^{1}H-NMR (500 MHz, $CDCl_3$): δ 9.87 (1H, br s), 9.47 (1H, s), 2.37 (2H, t, *J*=7.5 Hz), 2.28 (3H, s), 2.27 (3H, s), 1.45 (2H, p, *J*=7.5. Hz), 1.28-1.38 (4H, m), 0.92 (3H, t, *J*=7.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 175.8, 135.6, 132.3, 128.0, 123.6, 31.8, 30.4, 23.9, 22.7, 14.2, 11.8, 9.0; HRMS-ESI (*m/z*): $[M+Na]^+$ calculated for $C_{12}H_{19}NNaO$, 216.1359; found 216.1362; data in accordance with literature.[123]

2-Formyl-3,5-dimethyl-4-methylpropionic pyrrole (2h)



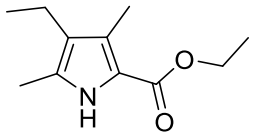
Following GP1, the title was compound was obtained as a beige solid (15 mg, 12 %). M.p. 128-129 °C; ^{1}H-NMR (500 MHz, $CDCl_3$): δ 9.82 (1H, br s), 9.45 (1H, s), 3.66 (3H, s), 2.71 (2H, t, *J*=7.5 Hz), 2.44 (2H, t, *J*=7.5 Hz), 2.27 (3H, s), 2.26 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$): δ 176.0, 173.4, 135.9, 132.3, 128.1, 121.1, 51.8, 34.7, 19.4, 11.7, 8.9; HRMS-ESI (*m/z*): $[M+Na]^+$ calculated for $C_{11}H_{15}NNaO_3$, 232.0944; found 232.0946; data in accordance with literature.

Quantifying Raney Nickel in Slurry

To quantify pyrophoric Raney nickel, which is available as a slurry in water, density factors were considered. Equivalences of Raney nickel are calculated from the dry mass of Raney nickel which can be calculated from the following method: (weight of slurry reagent – weight of water of the same volume) * density factor (1.2). Through a personal communication with a technical service representative from Sigma-Aldrich, the document containing the density factor and the calculation of the dry mass of Raney nickel was received on March 10th, 2017.

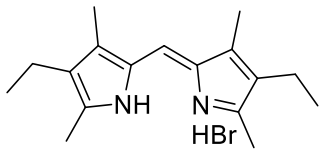
4.3 Experimental Procedures for Chapter 3

4-Ethyl-3,5-dimethyl-1*H*-pyrrole-2-carboxylic acid ethyl ester (3)



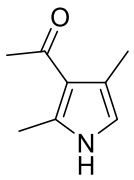
Following a literature procedure,[124] 4-acetyl-3,5-dimethyl-1*H*-pyrrole-2-carboxylic acid ethyl ester[119] (3 g, 14 mmol) was dissolved in anhydrous tetrahydrofuran (100 mL). While magnetically stirring, borane tetrahydrofuran complex solution (28 mL, 1 M) was added drop-wise to the solution in an ice bath (0 °C), and the reaction mixture was stirred at room temperature for 18 hours under nitrogen. Water (15 mL) and aqueous hydrochloric acid (90 mL, 5% wt) was added to the reaction mixture. The reaction mixture was extracted with ethyl acetate (100 mL x 3), and the combined organic layers were washed with saturated solution of sodium bicarbonate (100 mL), dried over anhydrous sodium sulfate, and concentrated *in vacuo* to obtain white solids (2.5 g, 93%). No further purification was necessary. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 8.54 (1H, br s), 4.29 (2H, q, J=7.1 Hz), 2.38 (2H, q, J=7.5 Hz), 2.28 (3H, s), 2.20 (3H, s), 1.34 (2H, t, J=7.1 Hz), 1.05 (2H, t, J=7.5 Hz); data in accordance with literature.[125]

3-Ethyl-5-((4-ethyl-3,5-dimethyl-2*H*-pyrrol-2-ylidene)methyl)-2,4-dimethyl-1*H*-pyrrole hydrobromide (4)



Following a literature method,[94] 4-ethyl-3,5-dimethyl-1*H*-pyrrole-2-carboxylic acid ethyl ester (**3**) (2.5 g, 13 mmol) was dissolved in formic acid (12 mL, 90% wt.). The reaction mixture was heated to reflux temperature in an oil bath (120 °C) with stirring. To a stirring solution, hydrobromic acid (4 mL, 48% wt.) was added, and the reaction mixture was stirred for 1 hour. The reaction mixture was taken out of the oil bath and allowed to cool to room temperature. The reaction mixture was kept in the fridge for 2 days, and the resulting precipitate was collected and washed with ether to obtain the title compound as a red-orange solid (1.4 g, 63%). ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.02 (1H, s), 2.66 (6H, s), 2.42 (4H, q, J=7.5 Hz), 2.26 (6H, s), 1.07 (6H, t, J=7.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 153.70, 141.16, 130.49, 126.04, 118.54, 17.20, 14.41, 12.74, 9.94; HRMS-ESI (*m/z*): $[M+H]^+$ calculated for $C_{17}H_{25}N_2$, 257.2012; found 257.2021; data in accordance with literature.[20]

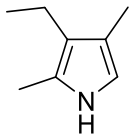
4-Acetyl-3,5-dimethyl-1*H*-pyrrole



Following a literature procedure,[119] 4-acetyl-3,5-dimethyl-1*H*-pyrrole-2-carboxylic acid ethyl ester[119] (50 g, 240 mmol) was dissolved in ethylene glycol. Potassium hydroxide pellets (27 g, 480 mmol) were added to the reaction mixture which was then heated to reflux temperature in an oil bath (160 °C) with stirring for 19 hours. The reaction was allowed to cool down to room temperature before the addition of water (200 mL). Extraction with chloroform (200 mL x 3), followed by drying of the organic fractions with anhydrous sodium sulfate and removal of the solvent *in vacuo* gave the crude product. The

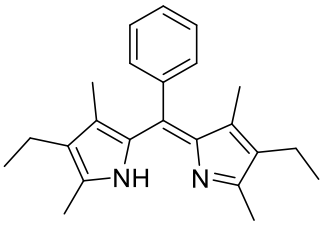
crude product was crystallized from ethyl acetate to obtain the title compound as a yellow solid (23.5 g, 71%). ^{1}H-NMR (300 MHz, $CDCl_3$): δ 8.65 (1H, br s), 6.36 (1H, q, J=1.1), 2.50 (3H, s), 2.43 (3H, s), 2.28 (3H, d, J=1.1 Hz); data in accordance with literature.[119]

3-Ethyl-2,4-dimethyl-1*H*-pyrrole (5)



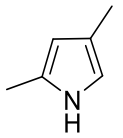
Following a modified literature procedure,[126] lithium aluminum hydride (6.5 g, 175 mmol) was suspended in anhydrous tetrahydrofuran (400 mL). To the suspension, a solution of 4-acetyl-3,5-dimethyl-1*H*-pyrrole[119] (20 g) in anhydrous tetrahydrofuran (200 mL) was added drop-wise at 0 °C. The reaction mixture was heated to reflux temperature in an oil bath (66 °C) with stirring for 2 hours under nitrogen. The reaction was allowed to cool down to room temperature before the addition of saturated sodium sulfate solution (200 mL). The reaction mixture was filtered off and extracted with dichloromethane (300 mL x 3). The organic layers were combined, washed with brine, dried over anhydrous sodium sulfate, and concentrated *in vacuo* to give the crude product. The crude product was distilled *in vacuo* to obtain a colourless oil (9.5 g, 53%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.47 (1H, br s), 6.40 (1H, s), 2.41 (2H, q, J=7.6 Hz), 2.19 (3H, s), 2.06 (3H, s), 1.10 (3H, t, J=7.6 Hz), in accordance with literature.[119]

3-Ethyl-5-[(4-ethyl-3,5-dimethyl-2*H*-pyrrol-2-ylidene)phenylmethyl]-2,4-dimethyl-1*H*-pyrrole (6)



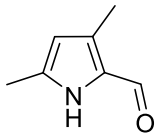
Following a literature procedure,[127] 3-ethyl-2,4-dimethyl-1*H*-pyrrole (**5**) (3 g, 24 mmol) was dissolved in anhydrous dichloromethane (450 mL). While magnetically stirring, benzaldehyde (1.2 g, 12 mmol) was added to the reaction mixture followed by trifluoroacetic acid (3 drops). The reaction mixture was stirred at room temperature for 2 hours under nitrogen. The reaction progress was monitored via use of thin layer chromatography. When all the starting materials were consumed, *p*-chloranil (3 g, 12 mmol) was added to the reaction mixture. The following reaction mixture was stirred for 30 minutes. Water (200 mL) was added, and the reaction mixture was extracted with dichloromethane (200 mL x 3). The combined organic layers were dried over anhydrous sodium sulfate, concentrated *in vacuo* to give the crude product. The crude product was purified on alumina column chromatography (100% dichloromethane) to obtain the title compound as a dark red solid (130 mg, 20%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.40-7.42 (3H, m), 7.29-7.32 (2H, m), 2.32 (6H, s), 2.28 (4H, q, J=7.5 Hz), 1.19 (6H, s), 0.97 (6H, t, J=7.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 150.25, 138.95, 137.6, 136.1, 134.9, 131.4, 129.8, 128.5, 128.1, 17.7, 15.0, 14.5, 11.9; HRMS-ESI (*m/z*): $[M+H]^+$ calculated for $C_{23}H_{29}N_2$, 333.4989; found 333.2325, data in accordance with literature.[127]

2,4-Dimethyl-1*H*-pyrrole (8)



Following a literature procedure,[126] 3,5-dimethyl-1*H*-pyrrole-2,4-dicarboxylic acid diethyl ester[98] (20 g, 84 mmol) was dissolved in ethylene glycol (100 mL). Potassium hydroxide pellets (24 g, 418 mmol) were added to the reaction mixture. The reaction mixture was heated to reflux temperature by use of an oil bath (160 °C) with stirring for 19 hours. The reaction mixture was allowed to cool to room temperature before the addition of water (200 mL). Extraction with chloroform (200 mL x 3), followed by drying of the combined organic fractions with anhydrous sodium sulfate and removal of the solvent *in vacuo* gave the crude product. The crude product was distilled *in vacuo* to obtain a colourless oil (5.9 g, 74%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.61 (1H, br s), 6.41 (1H, s), 5.76 (1H, s), 2.24 (3H, s), 2.09 (3H, s), in accordance with literature.[126]

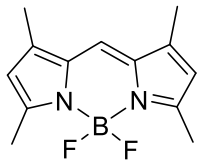
3,5-Dimethyl-1*H*-pyrrole-2-carboxaldehyde (9)



Following a literature procedure,[128] 2,4-dimethyl-1*H*-pyrrole (**8**) (6 g, 62 mmol) was dissolved in *N,N*-dimethylformamide (41 mL). While magnetically stirring, phosphorus oxychloride (8 mL, 81 mmol) was added drop-wise to the solution at 0 °C by use of an ice bath (0 °C). The reaction was stirred for 1 hour at room temperature. The reaction mixture was poured into water (190 mL), and aqueous potassium hydroxide solution (120 mL, 20%

by wt.) was added to the reaction mixture. The precipitate was isolated by a suction filtration. The mother liquor was kept and concentrated in vacuo to obtain the crude product. The material was purified by silica gel column chromatography (30% ethyl acetate in hexane) to obtain the title compound as a brown solid (6.7 g, 84%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.96 (1H, br s), 9.46 (1H, s), 5.85 (1H, s), 2.32 (3H, s), 2.30 (3H, s), in accordance with literature.[128]

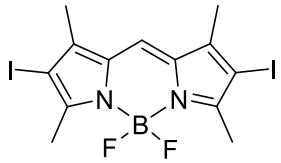
4,4-Difluoro-1,3,5,7-tetramethyl-4-bora-3a,4a-diaza-s-indacene (11)



Following a modified literature procedure,[20,70] 3,5-dimethyl-1*H*-pyrrole-2-carboxaldehyde (**9**) (0.25 g, 2 mmol) was dissolved in methanol (5 mL). While magnetically stirring, hydrobromic acid (2.5 mL, 2 mmol) was added, and the reaction mixture was heated to reflux temperature (70 °C) for 1 hour. The reaction mixture was allowed to cool down to room temperature, and the precipitate was collected by filtration with use of Millipore frit to obtain red-brown solid (Caution: this material is a sternutator). The solid was dissolved in dichloromethane (10 mL) and, while stirring, triethylamine (0.5 mL, 4 mmol) was added. After 10 minutes of stirring, boron trifluoride diethyl etherate (0.7 mL, 6 mmol) was added. The reaction was stirred for 1.5 hour. While stirring, further triethylamine (0.5 mL, 4 mmol) was added. After 5 minutes of stirring, further boron trifluoride diethyl etherate (0.7 mL, 6 mmol) was added. The resulting reaction mixture was stirred until the starting materials were fully consumed shown according to analysis via TLC. The reaction mixture was washed with aqueous hydrochloric acid (10 mL x 5, 1 M). The combined organic layers

were washed with brine, dried over anhydrous sodium sulfate, and concentrated *in vacuo*. The resulting crude material was purified by column chromatography on alumina (10% ethyl acetate in hexane) to obtain the title compound as a bright red solid (140 mg, 52%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.05 (1H, s), 6.06 (2H, s), 2.54 (6H, s), 2.26 (6H, s); ^{13}C NMR (125 MHz, $CDCl_3$): δ 156.6, 141.2, 133.4, 120.1, 119.0, 14.6, 11.2; ^{19}F NMR (282 MHz, $CDCl_3$): δ -146.41 (q, J=33 Hz); ^{11}B NMR (160 MHz, $CDCl_3$): δ 0.89 (t, J=33 Hz); HRMS-ESI (m/z): $[M+Na]^+$ calculated for $C_{13}H_{15}BF_2N_2Na$, 271.0736; found 271.1189; data in accordance with literature.[129]

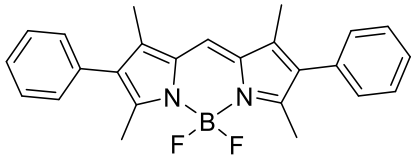
4,4-Difluoro-2,6-diiodo-1,3,5,7-tetramethyl-4-bora-3a,4a-diaza-s-indacene (12)



Following a literature procedure,[100] 4,4-difluoro-1,3,5,7-tetramethyl-4-bora-3a,4a-diaza-s-indacene (**11**) (0.5 g, 2 mmol) was dissolved in dichloromethane (20 mL). While magnetically stirring, *N*-iodosuccinimide (1 g, 4.4 mmol) was added at 0 °C. The reaction mixture was stirred at room temperature. The reaction progress was checked by use of thin layer chromatography. When all the starting material were consumed, aqueous sodium hydroxide solution (50 mL, 2 M) was added. Extraction with dichloromethane (20 mL x 3), followed by drying of the combined organic fractions with anhydrous sodium sulfate and removal of the solvent *in vacuo* gave the crude product. The crude product was purified by column chromatography on alumina (20% ethyl acetate in hexane) to obtain the title compound as a bright red solid (770 mg, 76%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.09 (1H, s), 2.59 (6H, s), 2.21 (6H, s); ^{19}F NMR (282 MHz, $CDCl_3$): δ -146.05 (q, J=32 Hz); ^{11}B

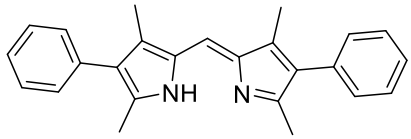
NMR (160 MHz, $CDCl_3$): δ 0.63 (t, J=32 Hz); HRMS-ESI (m/z): $[M+Na]^+$ calculated for $C_{13}H_{13}BF_2I_2N_2Na$, 522.9121; found 522.9124; data in accordance with literature.[102]

4,4-Difluoro-1,3,5,7-tetramethyl-2,6-diphenyl-4-bora-3a,4a-diaza-s-indacene (13)



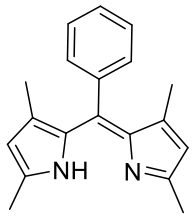
Following a literature procedure,[102] 4,4-difluoro-2,6-diiodo-1,3,5,7-tetramethyl-4-bora-3a,4a-diaza-s-indacene (**12**) (700 mg, 1.4 mmol) and phenylboronic acid (0.4 g, 3.5 mmol) were charged to a round-bottom flask, and anhydrous toluene (300 mL) was added. To the stirring solution, potassium carbonate solution (50 mL, 2 M) and ethanol (50 mL) were added, and the reaction mixture was stirred for 40 minutes at room temperature under nitrogen. Tetrakis(triphenylphosphine)palladium(0) (0.2 g, 0.14 mmol) was added to the reaction mixture, and the reaction mixture was heated to 80 °C and stirred for 16 hours. After being allowed to cool to room temperature, the reaction mixture was concentrated *in vacuo* and extracted with dichloromethane (150 mL x 3). The combined organic layers were dried over anhydrous sodium sulfate, concentrated *in vacuo*. The resulting crude material was purified by column chromatography on alumina (60% dichloromethane in hexanes) to obtain the title compound as a bright orange solid (470 mg, 84%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.26-7.48 (10H, m), 7.19 (1H, s), 2.56 (6H, s), 2.25 (6H, s); ^{13}C NMR (125 MHz, $CDCl_3$): δ 155.5, 137.5, 133.7, 133.2, 132.3, 129.9, 128.6, 127.2, 120.5, 13.6, 10.4; ^{19}F NMR (282 MHz, $CDCl_3$): δ -120.54 (q, J=33 Hz); ^{11}B NMR (160 MHz, $CDCl_3$): δ 1.08 (t, J=34 Hz); HRMS-ESI (m/z): $[M+Na]^+$ calculated for $C_{25}H_{23}BF_2N_2Na$, 423.1815; found 423.1799; data in accordance with literature.[102]

2-[(3,5-Dimethyl-4-phenyl-2*H*-pyrrol-2-ylidene)methyl]-3,5-dimethyl-4-phenyl-1*H*-pyrrole (14)



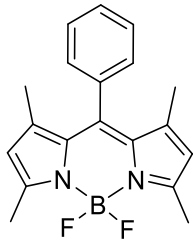
Following a modified literature procedure,[130] 4,4-difluoro-1,3,5,7-tetramethyl-2,6-diphenyl-4-bora-3a,4a-diaza-s-indacene (**13**) (300 mg, 1.1 mmol) was dissolved in anhydrous dichloromethane (50 mL). While magnetically stirring, boron trifluoride diethyl etherate (0.2 mL, 1.1 mmol) was added. The reaction mixture was stirred for 1 hour at room temperature under nitrogen. Water (0.06 mL, 3.3 mmol) was added, and the reaction mixture was stirred for 10 minutes. Water (10 mL) was again added, and the reaction mixture was extracted with dichloromethane (50 mL x 3), washed with brine, and concentrated *in vacuo*. The crude material was purified on alumina column chromatography (30% dichloromethane in hexanes) to obtain the title compound as a brown solid (200 mg, 52%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.41-7.44 (4H, m), 7.27-7.32 (6H, m), 6.86 (1H, s), 2.38 (6H, s), 2.23 (6H, s); ^{13}C NMR (125 MHz, $CDCl_3$): δ 151.7, 137.5, 135.5, 134.5, 130.5, 129.7, 128.4, 126.4, 117.1, 15.5 10.5; HRMS-ESI (*m/z*): $[M+H]^+$ calculated for $C_{25}H_{25}N_2$, 353.2012; found 353.2008; it is a newly synthesize compound.

2-[(3,5-Dimethyl-2*H*-pyrrol-2-ylidene)phenylmethyl]-3,5-dimethyl-1*H*-pyrrole (15)



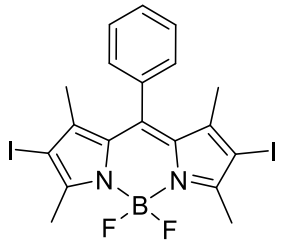
Following a modified literature procedure,[131] 2,4-dimethyl-1*H*-pyrrole (**7**) (1 g, 11 mmol) was dissolved in aqueous hydrochloric acid (19 mL, 0.2 M). While magnetically stirring, benzaldehyde (2.8 mL, 5.3 mmol) was added to the reaction mixture. The reaction mixture was stirred for 4 hours at room temperature. The reaction progress was monitored by thin layer chromatography. When all the starting materials were consumed (1 hour), *p*-chloranil (1.3 g, 5.3 mmol) was added to the reaction. The following reaction mixture was stirred for 30 minutes. Water (50 mL) was added, and the reaction mixture was extracted with dichloromethane (50 mL x 3). The combined organic layers were dried over anhydrous sodium sulfate, concentrated *in vacuo*, and purified by column chromatography on alumina (100% dichloromethane) to obtain the title compound as a dark red solid (130 mg, 9%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.42-7.44 (3H, m), 7.27-7.30 (2H, m), 5.95 (2H, s), 2.40 (6H, s), 1.33 (6H, s), in accordance with literature.[132]

4,4-Difluoro-1,3,5,7-tetramethyl-8-phenyl-4-bora-3a,4a-diaza-s-indacene (16)



Following a modified literature method,[70] 2-[(3,5-Dimethyl-2*H*-pyrrol-2-ylidene) phenylmethyl]-3,5-dimethyl-1*H*-pyrrole (**15**) (150 mg, 0.6 mmol) was dissolved in dichloromethane (10 mL). To a stirring solution, triethylamine (0.5 mL, 3.3 mmol) was added, and the reaction mixture was stirred for 10 minutes. Boron trifluoride diethyl etherate (0.7 mL, 5.0 mmol) was added, and the reaction mixture was stirred until consumption of the starting materials was shown by TLC. The reaction mixture was washed with aqueous hydrochloric acid (20 mL x 5, 1 M). The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, and concentrated *in vacuo*. The crude material was purified by silica gel column chromatography (5% ethyl acetate in hexane) to obtain the title compound as a bright red solid (41 mg, 27%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.46-7.47 (3H, m), 7.25-7.27 (2H, m), 5.96 (2H, s), 2.54 (6H, s), 1.36 (6H, s); ^{13}C NMR (125 MHz, $CDCl_3$): δ 155.5, 143.3, 141.9, 135.1, 131.6, 129.2, 129.1, 128.1, 121.3, 14.7, 14.4; ^{19}F NMR (282 MHz, $CDCl_3$): δ -146.29 (q, J=33 Hz); ^{11}B NMR (160 MHz, $CDCl_3$): δ 0.79 (t, J=33 Hz); HRMS-ESI (m/z): $[M+Na]^+$ calculated for $C_{19}H_{19}BF_2N_2Na$, 347.1502; found 347.1490, in accordance with literature.[132]

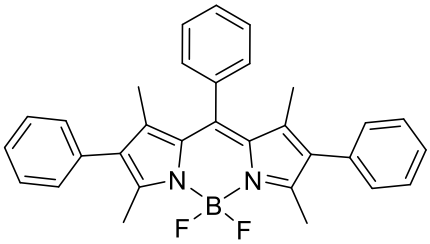
4,4-Difluoro-2,6-diiodo-1,3,5,7-tetramethyl-8-phenyl-4-bora-3a,4a-diaza-s-indacene (17)



Following a literature method,[100] 4,4-difluoro-1,3,5,7-tetramethyl-8-phenyl-4-bora-3a,4a-diaza-s-indacene (**16**) (80 mg, 0.2 mmol) was dissolved in dichloromethane (20 mL). While

magnetically stirring, *N*-iodosuccinimide (0.2 g, 0.9 mmol) was added at 0 °C. The reaction mixture was stirred at room temperature. The reaction progress was monitored by use of thin layer chromatography. When all the starting material had been consumed, aqueous sodium hydroxide solution (50 mL, 2 M) was added. Extraction with dichloromethane (20 mL x 3), followed by drying the combined organic fractions with anhydrous sodium sulfate and removal of the solvent *in vacuo* gave the crude material. Purification by alumina column chromatography (20% ethyl acetate in hexane) gave the title compound as a bright red solid (14 mg, 16%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.51-7.53 (3H, m), 7.24-7.27 (2H, m), 2.65 (6H, s), 1.39 (6H, s); ^{13}C NMR (125 MHz, $CDCl_3$): δ 156.9, 145.5, 141.5, 134.9, 131.5, 129.7, 129.6, 129.0, 128.0, 17.1, 16.2; ^{19}F NMR (282 MHz, $CDCl_3$): δ -119.79 (q, J=32 Hz); ^{11}B NMR (160 MHz, $CDCl_3$): δ 0.57 (t, J=32 Hz); HRMS-ESI (*m/z*): $[M+Na]^+$ calculated for $C_{19}H_{17}BF_2I_2N_2Na$, 598.9434; found 598.9419; data in accordance with literature.[133]

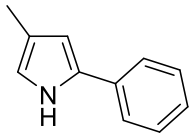
4,4-Difluoro-1,3,5,7-tetramethyl-2,6,8-triphenyl-4-bora-3a,4a-diaza-s-indacene (18)



Following a literature method, 4,4-difluoro-2,6-diiodo-1,3,5,7-tetramethyl-8-phenyl-4-bora-3a,4a-diaza-s-indacene (**17**) (75 mg, 0.13 mmol) and phenylboronic acid (0.04 g, 0.33 mmol) were charged to a round-bottom flask, and anhydrous toluene (30 mL) was added. To a stirring solution, potassium carbonate solution (5 mL, 2 M) and ethanol (5 mL) were added, and the reaction was stirred for 40 minutes at room temperature under nitrogen.

After 40 minutes, tetrakis(triphenylphosphine)palladium(0) (0.02 g, 0.13 mmol) was added to the reaction mixture, and the reaction mixture was heated to 80 °C and stirred for 16 hours under nitrogen. The reaction mixture was allowed to cool down to room temperature, concentrated *in vacuo* and extracted with dichloromethane (25 mL x 3). The combined organic layers were dried over anhydrous sodium sulfate, concentrated under vacuum, and purified by silica gel column chromatography (25% dichloromethane in hexane) to obtain the title compound as a bright orange solid (20 mg, 33%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.48-7.50 (3H, m), 7.36-7.40 (6H, m), 7.29-7.32 (2H, m), 7.16-7.17 (4H, m), 2.54 (6H, s), 1.31 (6H, s); ^{13}C NMR (125 MHz, $CDCl_3$): δ 154.4, 142.3, 139.4, 135.6, 133.9, 130.3, 129.4, 129.2, 128.4, 128.2, 127.2, 13.5, 12.9, two carbon signals missing; ^{19}F NMR (282 MHz, $CDCl_3$): δ -120.17 (q, J=32 Hz); ^{11}B NMR (160 MHz, $CDCl_3$): δ 1.01 (t, J=34 Hz); HRMS-ESI (*m/z*): $[M+Na]^+$ calculated for $C_{31}H_{27}BF_2N_2Na$, 499.2128; found 499.2131; this is a newly synthesized compound.

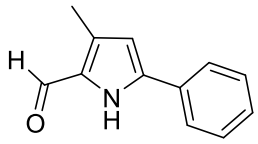
4-Methyl-2-phenyl-1*H*-pyrrole (20)



Following a modified literature method,[109,134] allylamine (6 mL, 83 mmol) and acetophenone (1.9 mL, 17 mmol) were added to a round-bottom flask. Anhydrous toluene (35 mL) was added, and the reaction mixture was cooled in an ice bath to 0 °C. While magnetically stirring, titanium(IV) chloride solution (1M in dichloromethane, 11 mL, 11 mmol) was added drop-wise over 40 minutes. Then, the ice bath was removed, and the reaction mixture was stirred for 2 hours at room temperature. The resulting mixture was

suction filtered, and the filtrate was washed with brine (50 mL), and the combined organic fractions were dried over anhydrous sodium sulfate, and concentrated *in vacuo* to give the crude imine. 3 Å molecular sieves, palladium(II) acetate (0.2 g, 0.9 mmol) tetrabutylammonium bromide (8 g, 25 mmol), and the imine (2 g, 13 mmol) were then charged to a round-bottom flask. The flask was flushed with oxygen, and dimethyl sulfoxide (70 mL) was added. The reaction mixture was stirred at room temperature for 24 hours under oxygen. Ethyl acetate (100 mL) was added, and the mixture then filtered through silica and washed with ethyl acetate (300 mL). The solvent was removed *in vacuo* and the crude material purified by silica gel column chromatography (10% ethyl acetate in hexanes) to obtain the title compound as a white solid (170 mg, 9%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.17 (1H, br s), 7.43-7.48 (2H, m), 7.32-7.38 (2H, m), 7.16-7.22 (1H, m), 6.62-6.63 (1H, m), 6.37-6.39 (1H, m), 2.17 (3H, s), in accordance with literature.[134]

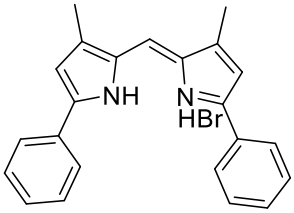
3-Methyl-5-phenyl-1*H*-pyrrole-2-carboxaldehyde (21)



Following a modified literature procedure,[128] 4-methyl-2-phenyl-1*H*-pyrrole (**20**) (120 mg, 0.8 mmol) was dissolved in *N,N*-dimethylformamide (5 mL). While magnetically stirring, phosphorus oxychloride (0.1 mL, 1 mmol) was added drop-wise to the reaction mixture at 0 °C, and the reaction was stirred for 1 hour at room temperature under nitrogen. The reaction mixture was poured into water (80 mL), and aqueous potassium hydroxide solution (40 mL, 20% by wt.) was added to the reaction mixture. The resulting precipitate was isolated via suction filtration without need for further purification (120 mg, 81%). ^{1}H

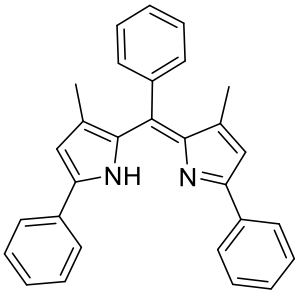
NMR (300 MHz, $CDCl_3$): δ 9.64 (1H, s), 7.57-7.60 (2H, d), 7.34-7.45 (3H, m), 6.44 (1H, d), 2.41 (3H, s); this is a newly synthesized compound.

3-Methyl-2-((3-methyl-5-phenyl-2*H*-pyrrol-2-ylidene)methyl)-5-phenyl-1*H*-pyrrole hydrobromide (22)



Following a modified literature method,[20] 3-methyl-5-phenyl-1*H*-pyrrole-2-carboxaldehyde (**21**) (450 mg, 2.4 mmol) was dissolved in methanol (50 mL). While magnetically stirring, aqueous hydrobromic acid (48% w/w, 0.7 mL, 2.4 mmol) was added to the reaction mixture. The reaction mixture was heated to reflux temperature (70 °C) and stirred for 1 hour. The reaction mixture was allowed to cool down to room temperature, and the resulting precipitate was collected by filtration with use of Millipore frit to obtain the title compound as a purple solid (418 mg, 42%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.33-8.36 (4H, m), 7.47-7.55 (6H, m), 7.24 (1H, s), 6.78 (2H, s), 2.46 (6H, s); ^{13}C NMR (125 MHz, $CDCl_3$): δ 154.8, 147.2, 131.5, 129.4, 129.2, 129.1, 128.5, 120.3, 116.3, 12.8; HRMS-ESI (*m/z*): $[M+H]^+$ calculated for $C_{23}H_{21}N_2$, 325.1699; found 325.1692; this is a newly synthesized compound.

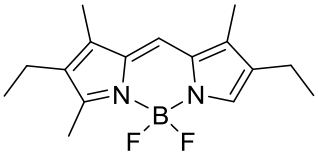
2-((3,5-Diphenyl-2*H*-pyrrol-2-ylidene)methyl)-3,5-diphenyl-1*H*-pyrrole (23)



Following a modified literature procedure,[131] 4-methyl-2-phenyl-1*H*-pyrrole (**20**) (1.5 g, 9.5 mmol) was dissolved in aqueous hydrochloric acid (20 mL, 0.5 M). While magnetically stirring, benzaldehyde (0.5 mL, 4.8 mmol) was added to the reaction mixture. The reaction mixture was stirred for 4 hours at room temperature. The reaction progress was monitored by use of thin layer chromatography. When all the starting materials were consumed, dichloromethane (50 mL) was added. The reaction mixture was dried over anhydrous sodium sulfate and concentrated *in vacuo*. The crude product was filtered through a short pad of alumina with dichloromethane to remove the baseline material. The crude product (300 mg, 0.75 mmol) was dissolved in dichloroethane (5 mL), and DDQ (340 mg, 1.5 mmol) was then added. The reaction mixture was stirred for 30 minutes. Water (20 mL) was added, and the reaction mixture was extracted with dichloromethane (20 mL x 3). The combined organic layers were dried over anhydrous sodium sulfate, and concentrated *in vacuo*. The crude material was purified by column chromatography on alumina (20% dichloromethane) to obtain the title compound as a dark red solid (170 mg, 57%). M.p.: 181-182 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 14.62 (1H, br s), 7.89-7.90 (4H, d, J=4.5 Hz), 7.46-7.49 (7H, m), 7.36-7.42 (4H, m), 6.58 (2H, s), 1.45 (6H, s); ^{13}C NMR (125 MHz, $CDCl_3$): δ 152.0, 141.7, 140.2, 139.0, 137.8, 133.3, 129.3, 129.0, 128.9, 128.6, 128.6, 126.2,

117.5, 14.9; HRMS-ESI (*m/z*): $[M+H]^+$ calculated for $C_{29}H_{25}N_2$, 401.2012; found 401.2019; this is a newly synthesized compound.

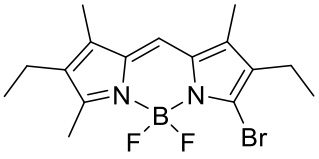
4,4-Difluoro-2,6-diethyl-1,3,7-trimethyl-4-bora-3a,4a-diaza-s-indacene (24)



Following a literature method,[70] 3-ethyl-5-((4-ethyl-3,5-dimethyl-2*H*-pyrrol-2-ylidene)methyl)-4-methyl-1*H*-pyrrole hydrobromide (1 g, 3.1 mmol) was dissolved in dichloromethane (100 mL). While magnetically stirring, triethylamine (2.6 mL, 19 mmol) was added. After 10 minutes of stirring, boron trifluoride diethyl etherate (3.5 mL, 28 mmol) was added. The reaction was stirred for 1.5 hour. While stirring, further triethylamine (2.6 mL, 19 mmol) was added. After 5 minutes of stirring, further boron trifluoride diethyl etherate (3.5 mL, 28 mmol) was added. The resulting reaction mixture was stirred until the starting materials were fully consumed according to analysis via TLC. The reaction mixture was washed with aqueous hydrochloric acid (50 mL x 5, 1 M). The combined organic layers were washed with brine (50 mL), dried over anhydrous sodium sulfate, and concentrated *in vacuo.* Purification of the crude material by column chromatography on alumina gave the title compound as a bright red solid (850 mg, 94%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.42 (1H, s), 7.06 (1H, s), 2.52 (3H, s), 2.42 (2H, q, *J*=7.5 Hz), 2.39 (2H, q, *J*=7.5 Hz), 2.19 (3H, s), 2.18 (3H, s), 1.18 (2H, t, *J*=7.5 Hz), 1.07 (2H, t, *J*=7.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 159.4, 139.3, 138.5, 135.4, 134.6, 133.3, 132.5, 132.2, 120.6, 18.3, 17.4, 14.5, 14.3, 13.1, 9.6, one alkyl carbon signal missing; ^{19}F NMR (282 MHz, $CDCl_3$): δ -120.38 (q, *J*=32 Hz); ^{11}B NMR (160 MHz, $CDCl_3$): δ 0.49 (t, *J*=32 Hz); HRMS-

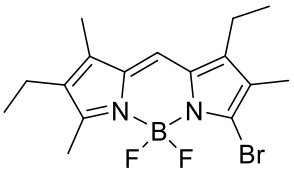
ESI (*m/z*): $[M+Na]^+$ calculated for $C_{16}H_{21}BF_2N_2Na$, 313.1658; found 313.1660; this is a newly synthesized compound.

4,4-Difluoro-1-bromo-2,6-diethyl-3,5,7-trimethyl-4-bora-3a,4a-diaza-s-indacene (25)



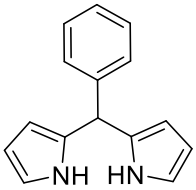
Following a modified literature method,[100] 4,4-difluoro-2,6-diethyl-1,3,7-tetramethyl-8-phenyl-4-bora-3a,4a-diaza-s-indacene (**24**) (200 mg, 0.7 mmol) was dissolved in dichloromethane (10 mL). While magnetically stirring, *N*-bromosuccinimide (130 mg, 0.7 mmol) was added at 0 °C. The reaction mixture was stirred at room temperature. The reaction progress was monitored by use of thin layer chromatography. When all the starting material had been consumed (2 hours), aqueous sodium hydroxide solution (20 mL, 2 M) was added. Extraction with dichloromethane (50 mL x 3), followed by drying the combined organic fractions with anhydrous sodium sulfate and removal of the solvent *in vacuo* gave the crude material. Purification by alumina column chromatography (20% ethyl acetate in hexane) gave the title compound as a bright red solid (240 mg, 92%).^{1}H NMR (500 MHz, $CDCl_3$): δ 6.95 (1H, s), 2.53 (3H, s), 2.43 (2H, q, *J*=7.5 Hz), 2.39 (2H, q, *J*=7.5 Hz), 2.21 (3H, s), 2.17 (3H, s), 1.09 (3H, t, *J*=7.5 Hz), 1.08 (3H, t, *J*=7.5 Hz); HRMS-ESI (*m/z*): $[M+Na]^+$ calculated for $C_{16}H_{20}BBrF_2N_2Na$, 391.0763; found 391.0748; this is a newly synthesized compound.

4,4-Difluoro-1-bromo-3,6-diethyl-2,5,7-trimethyl-4-bora-3a,4a-diaza-s-indacene (26)



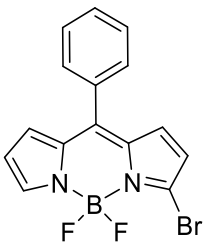
Following a modified literature method,[70] 2-bromo-4-ethyl-5-((4-ethyl-3,5-dimethyl-2*H*-pyrrol-2-ylidene)methyl)-3-methyl-1*H*-pyrrole hydrobromide (50 mg, 0.12 mmol) was dissolved in dichloromethane (5 mL). While magnetically stirring, triethylamine (0.1 mL, 0.75 mmol) was added. After 10 minutes of stirring, boron trifluoride diethyl etherate (0.14 mL, 1.1 mmol) was added. The reaction was stirred for 1.5 hour. While stirring, further triethylamine (0.1 mL, 0.75 mmol) was added. After 5 minutes of stirring, further boron trifluoride diethyl etherate (0.14 mL, 1.1 mmol) was added. The resulting reaction mixture was stirred until the starting materials were fully consumed shown by TLC (1 hour). The reaction mixture was washed with aqueous hydrochloric acid (10 mL x 5, 1 M). The organic layer was washed with brine (10 mL), dried over anhydrous sodium sulfate, and concentrated *in vacuo*. The crude material was purified via column chromatography on alumina (10% ethyl acetate in hexanes) to yield the title compound as a bright red solid (34 mg, 77%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.93 (1H, s), 2.59 (2H, q, J=7.5 Hz), 2.52 (3H, s), 2.38 (2H, q, J=7.5 Hz), 2.17 (3H, s), 2.00 (3H, s), 1.15 (3H, t, J=7.5 Hz), 1.07 (3H, t, J=7.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 160.4, 142.1, 139.4, 134.5, 134.0, 131.7, 127.8, 125.1, 118.7, 18.4, 17.4, 16.1, 14.4, 13.2, 9.9, 9.6; ^{19}F NMR (282 MHz, $CDCl_3$): δ -120.51 (q, J=31 Hz); ^{11}B NMR (160 MHz, $CDCl_3$): δ 0.64 (t, J=30 Hz); HRMS-ESI (*m/z*): $[M+Na]^+$ calculated for $C_{16}H_{20}BBrF_2N_2Na$, 391.0763; found 391.0766; this is a newly synthesized compound.

5-Phenyldipyrromethane (27)



Following a modified literature procedure,[135] pyrrole (70 mL, 1.1 mol) and benzaldehyde (1.1 mL, 11 mmol) were added to a round-bottom flask. The flask was purged with nitrogen. Magnesium bromide (0.99 g, 5.4 mmol) was added to the reaction mixture. The reaction mixture was stirred for 1.5 hour at room temperature under nitrogen. The mixture was treated with powdered sodium hydroxide pellets (2.2 g, 54 mmol) and stirred for 1 hour. The resulting mixture was filtered, and the filtrate was concentrated *in vacuo* to recover excess pyrrole and provide the crude product. The crude product was dissolved in 20% ethyl acetate/hexanes solution (100 mL), and water (50 mL) was added. Extraction with 20% ethyl acetate/hexanes, drying of the organic fraction over anhydrous sodium sulfate and concentrated *in vacuo* gave the crude product which was crystallized from 20% water/ethanol to give the title compound as a pale beige solid (1.9 g, 78%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.89 (2H, br s), 7.22-7.36 (5H, m), 6.68-6.70 (2H, m), 6.18 (2H, q, J=3.0 Hz), 5.93-5.95 (2H, m), 5.48 (1H, s), in accordance with literature.[135]

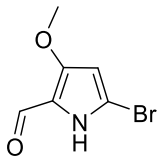
4,4-Difluoro-2-bromo-8-phenyl-4-bora-3a,4a-diaza-s-indacene (29)



Following a modified literature procedure,[70,136] 5-phenyldipyrromethane (**27**) (2.0 g, 9.0 mmol) was dissolved in anhydrous tetrahydrofuran (200 mL). The reaction mixture was cooled in an acetone-dry ice bath (-78 °C), and *N*-bromosuccinimide (1.6 g, 9.0 mmol) was added. The reaction mixture was stirred at -78 °C for 1 hour under nitrogen. The reaction mixture was allowed to warm to room temperature, and DDQ (2.0 g, 9.0 mmol) was added. The resulting mixture was stirred for 30 minutes, and the solvent was removed *in vacuo.* The resulting material was filtered through a short pad of alumina with 25% dichloromethane in hexanes, and the filtrate was concentrated *in vacuo*. The crude product was dissolved in dichloromethane (100 mL). While magnetically stirring, triethylamine (4.0 mL, 28 mmol) was added. After 10 minutes of stirring, boron trifluoride diethyl etherate (5.2 mL, 42 mmol) was added. The reaction was stirred for 1.5 hour. While stirring, further triethylamine (4.0 mL, 28 mmol) was added. After 5 minutes of stirring, further boron trifluoride diethyl etherate (5.2 mL, 42 mmol) was added. The resulting reaction mixture was stirred until the starting materials were fully consumed shown by TLC (1 hour). The reaction mixture was washed with aqueous hydrochloric acid (100 mL x 5, 1 M). The organic layer was washed with brine (50 mL), dried over anhydrous sodium sulfate, and concentrated *in vacuo*. The crude material was purified by column chromatography on alumina (10% dichloromethane in hexanes) to yield the title compound as a bright red solid (1.23 g, 39 %). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.95 (1H, s), 7.57-7.60 (1H, m), 7.49-7.53 (4H, m), 6.93 (1H, d, *J*=4.1 Hz), 6.84 (1H, d, *J*=4.3 Hz), 6.58 (1H, d, *J*=3.6 Hz), 6.53 (1H, d, *J*=4.3 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 145.5, 144.9, 144.3, 133.3, 132.0, 131.9, 131.8, 131.0, 130.6, 128.7, 122.2, 119.2, 118.7; ^{19}F NMR (282 MHz, $CDCl_3$): δ -120.51 (q, *J*=28 Hz); ^{11}B NMR (160 MHz, $CDCl_3$): δ 0.64 (t, *J*=27 Hz); HRMS-ESI (*m/z*):

$[M+Na]^+$ calculated for $C_{15}H_{10}BBrF_2N_2Na$, 368.9981; found 368.9989; this is a newly synthesized compound.

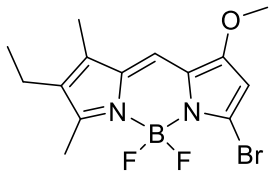
5-Bromo-3-methoxy-1*H*-pyrrole-2-carboxaldehyde (30)



Following a literature procedure,[137] *N,N*-diethylformamide (3 mL, 27 mmol) and anhydrous dichloromoethane (3 mL) were added to a round-bottom flask. The reaction mixture was stirred in an ice bath (0 °C) for 10 minutes under nitrogen. To the stirring solution, phosphoryl bromide (6.3 g, 22 mmol) in anhydrous dichloromethane (8 mL) was added. The ice bath was removed, and the reaction mixture was stirred for 30 minutes at room temperature. The resulting mixture was concentrated *in vacuo* to give the crude intermediate as a white powder. The intermediate was dissolved in anhydrous dichloromethane (10 mL) and was stirred in an ice bath (0 °C) for 10 minutes under nitrogen. To a stirring solution, 4-methoxy-3-pyrrolin-2-one (1 g, 8.8 mmol) in anhydrous dichloromethane (10 mL) was added drop-wise. The reaction mixture was stirred for 3 hours at 40 °C. The reaction was monitored by use of thin layer chromatography. When all the starting material were consumed, the reaction mixture was allowed to cool to room temperature. Saturated sodium carbonate solution was added to the reaction mixture to adjust pH to 7-8. Then, the reaction mixture was extracted with dichloromethane (x mL x 3), and the combined organic fractions were dried over anhydrous sodium sulfate and concentrated *in vacuo*. The crude product was dissolved in 95% ethanol (50 mL). While magnetically stirring, sodium hydroxide (4 M, 5 mL) solution was added. The reaction

mixture was heated to reflux temperature (78 °C) and stirred for 4 hours. The reaction progress was monitored by use of thin layer chromatography. When all the starting material were consumed, the reaction mixture was allowed to cool to room temperature, and then concentrated *in vacuo*. Then, hydrochloric acid (2 M) was added to adjust pH to 7-8. The reaction mixture was poured into water (70 mL), extracted with dichloromethane (100 mL x 3), and the combined organic fractions dried over anhydrous sodium sulfate, and concentrated *in vacuo* to give the title compound as a white solid (650 mg, 36%). Without need for further purification. ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.99 (1H, br s), 9.40 (1H, s), 5.94 (1H, s), 3.87 (3H, s), in accordance with literature.[137]

4,4-Difluoro-5-bromo-2-ethyl-7-methoxy-1,3-diamethyl-4-bora-3a,4a-diaza-s-indacene (32)



Following a modified literature procedure,[20,70] 5-bromo-3-methoxy-1*H*-pyrrole-2-carboxaldehyde (**30**) (500 mg, 2.5 mmol) and 3-ethyl-2,4-dimethyl-1*H*-pyrrole (**5**) (300 mg, 2.5 mmol) were dissolved in methanol (10 mL). While magnetically stirring, 48% hydrobromic acid (5 mL, 2.5 mmol) was added, and the reaction mixture was heated to reflux temperature (70 °C) for 1 hour. The reaction mixture was allowed to cool down to room temperature, and water (10 mL) was added. The mixture was extracted with dichloromethane (20 mL x 3). The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, and concentrated *in vacuo*. The crude dipyrrin (180 mg, 0.6 mmol) was dissolved in dichloromethane (50 mL) and, while stirring, triethylamine

(0.5 mL, 3.5 mmol) was added. After 10 minutes of stirring, boron trifluoride diethyl etherate (0.6 mL, 5.2 mmol) was added. The reaction was stirred for 1.5 hour. While stirring, further triethylamine (0.5 mL, 3.5 mmol) was added. After 5 minutes of stirring, further boron trifluoride diethyl etherate (0.6 mL, 5.2 mmol) was added. The resulting reaction mixture was stirred until the starting materials were fully consumed according to analysis using TLC (1 hour). The reaction mixture was washed with aqueous hydrochloric acid (50 mL x 5, 1 M). The organic layer was washed with brine (50 mL), dried over anhydrous sodium sulfate, and concentrated *in vacuo*. Purification of the crude material by column chromatography on alumina (5% dichloromethane in hexanes) gave the title compound as a dark red solid (200 mg, 97%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.08 (1H, s), 5.89 (1H, s), 3.88 (3H, s), 2.50 (3H, s), 2.38 (2H, q, J=7.5 Hz), 2.14 (3H, s), 1.06 (3H, t, J=7.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 160.8, 158.2, 138.5, 133.4, 133.0, 126.3, 123.6, 117.2, 101.5, 58.6, 17.4, 14.5, 13.0, 9.5; ^{19}F NMR (282 MHz, $CDCl_3$): δ -118.65 (q, J=31 Hz); ^{11}B NMR (160 MHz, $CDCl_3$): δ 0.64 (t, J=32 Hz); HRMS-ESI (*m/z*): $[M+Na]^+$ calculated for $C_{14}H_{16}BBrF_2N_2NaO$, 379.0399; found 379.0416; this is a newly synthesized compound.

Chapter 5. Conclusion and Future Work

Within this thesis, the reactivity and functionality of the pyrrolic core and the dipyrrinato core have been explored. The goal of the first project was to reduce 2-thionoester pyrroles into 2-formyl pyrroles using Raney nickel. 2-Thionoester pyrroles bearing alkyl and ester functionalities have successfully been reduced in moderate to good yields. Moreover, deuterated 2-formyl pyrroles were successfully synthesized in the presence of deuterium oxide and Raney nickel. Stemming from this result, a mechanistic pathway for the desulfurative reduction using Raney nickel has been investigated. Using observations from a radical clock/trap reaction and a water-free reduction, a mechanism for the desulfurative reduction of 2-thionoester pyrroles is proposed. Although a complete mechanism is still unknown, we have identified that the hydrogen atom that becomes integral to the aldehyde comes from water, and that the reaction is likely to proceed via single electron transfer. Now, we have a complete route from commercially available agents to 2-formyl pyrroles, with 2-thionoester pyrroles being the intermediate product. Although such route is advantageous, in terms of atom economy, than the currently known method to synthesize 2-formyl pyrroles, it still presents some of downfalls (e.g. stench of the sulfur-containing reagents, or a customized approach from 2-carboxylate pyrroles). Therefore, we are still in need for a practical direct route to 2-formyl pyrroles from 2-carboxylate pyrroles.

The goal of the second project was to synthesize dipyrrins bearing phenyl groups on different positions (i.e. α-, β-, and meso-positions). Depending on the position of the aryl groups, a specific synthetic route was employed. For example, for the preparation of β-Ph dipyrrins, the aryl substituents were introduced via Suzuki coupling, while the α-Ph

dipyrrins were pre-functionalized in the pyrrole stage. The second part of the project explored a different approach to synthesize α-Ph dipyrrins. Rather than dipyrrins bearing halogen atoms being coupled with phenyl boronic acids, we wished to synthesize α-borylated dipyrrins. Modified literature procedure for borylation β-halogenated dipyrrins and pyrroles were implemented, but the desired products could not be produced and/or isolated.

Future work involves screening different catalysts that are known to effect borylation of pyrrole-containing chemical species. Ultimately, we wish to couple α-borylated dipyrrins with halogenated aryl groups and test whether α-Ph dipyrrins could be synthesized.

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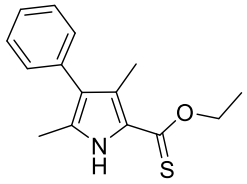
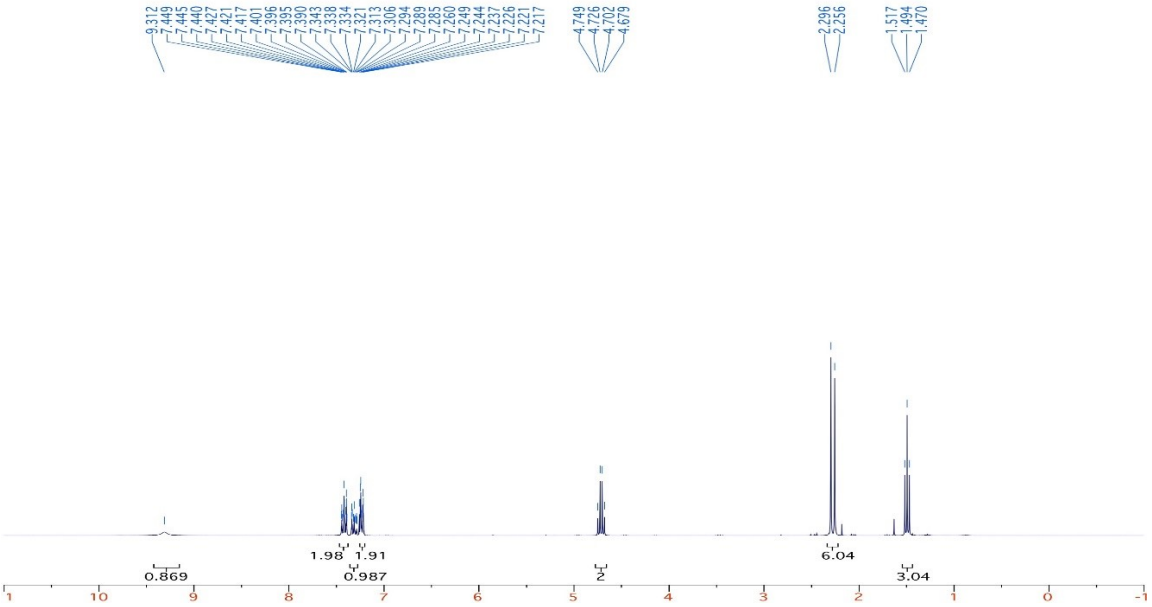
Appendix 1. NMR Spectra for Chapter 2

O-Ethyl-3,5-dimethyl-4-phenyl-1*H*-pyrrole-2-carbothioate (1d)



^{1}H NMR; 300 MHz, $CDCl_3$



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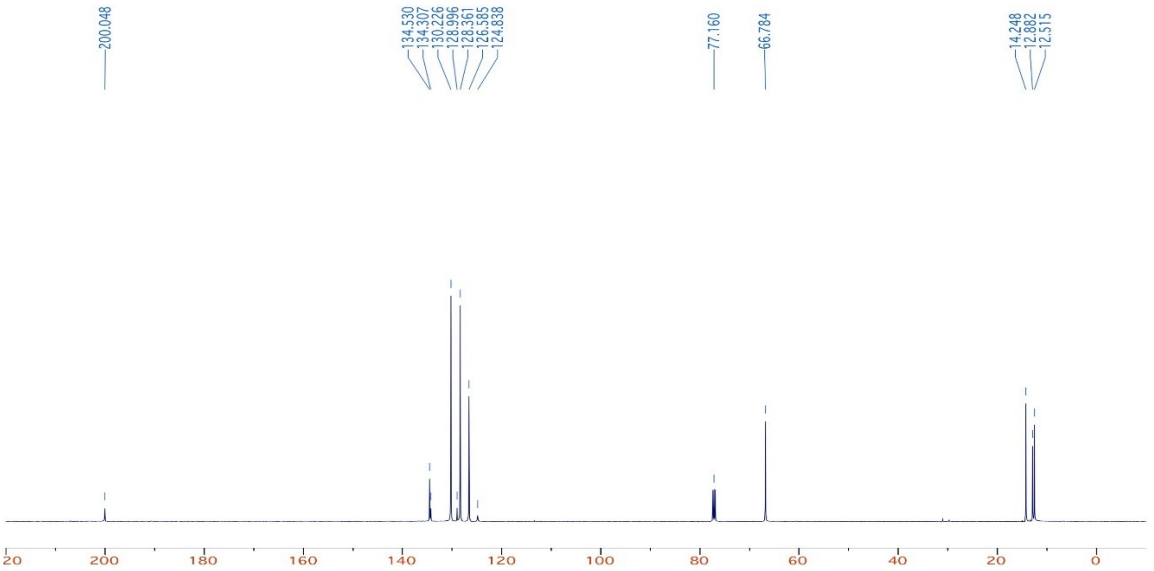
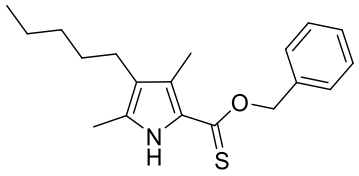


_O_-Benzyl-3,5-dimethyl-4-pentyl-1_H_-pyrrole-2-carbothioate (1g)



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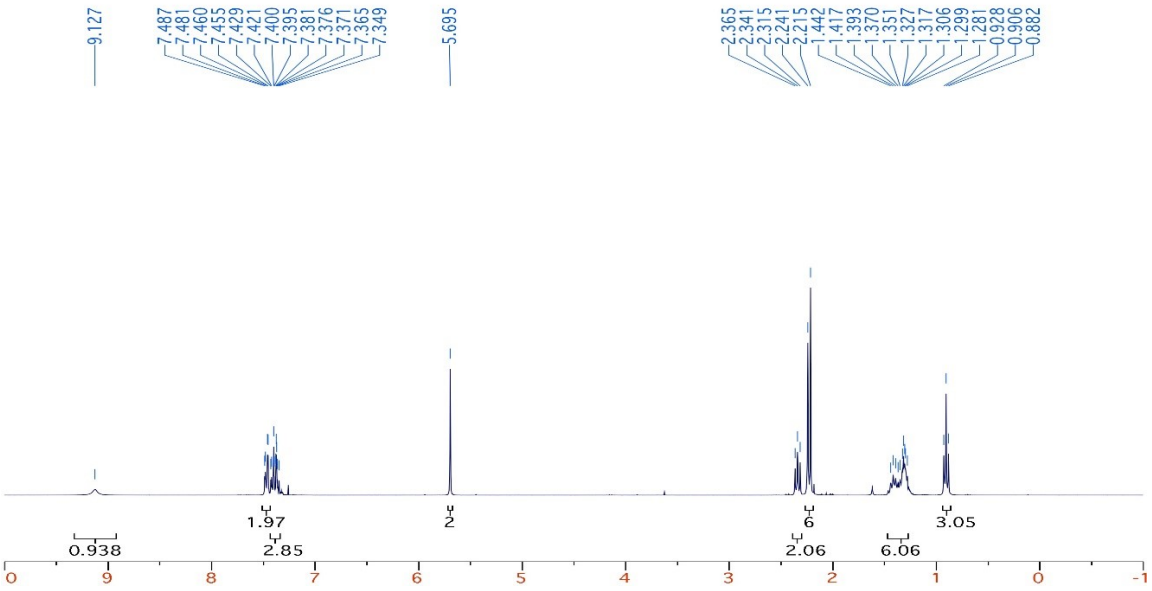

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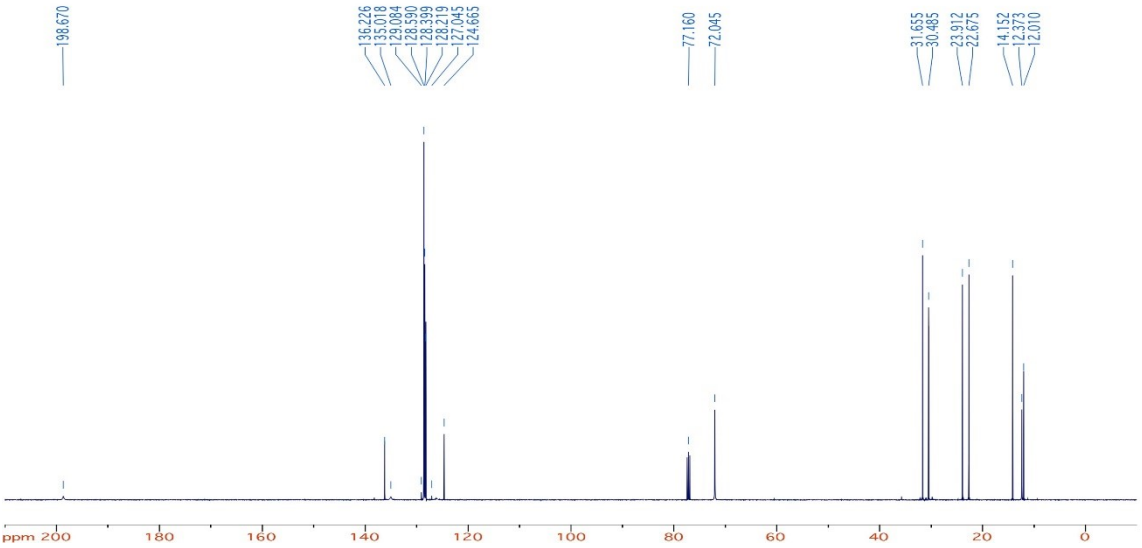
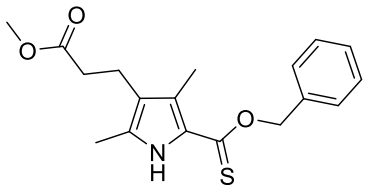
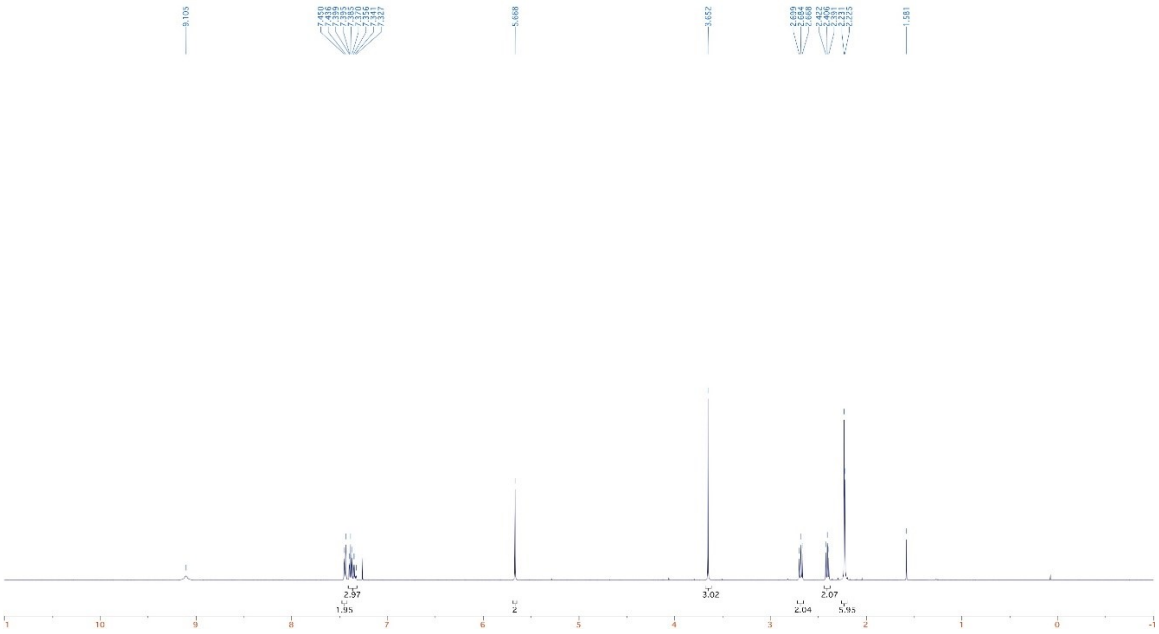


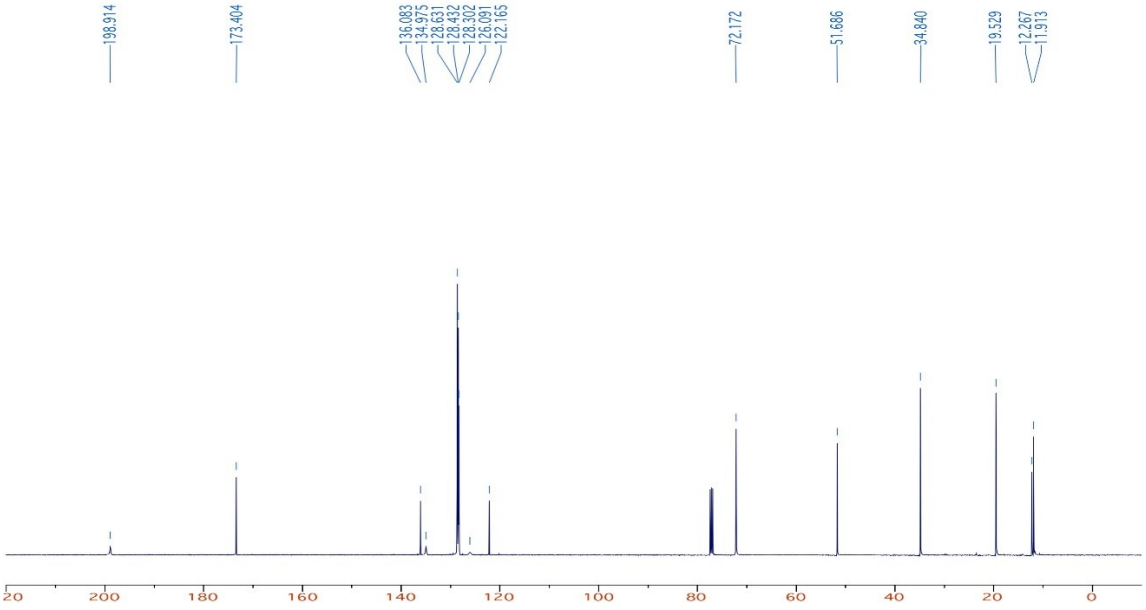
***O*-Benzyl-3,5-dimethyl-4-methylpropionic-1*H*-pyrrole-2-carbothioate (1h)**



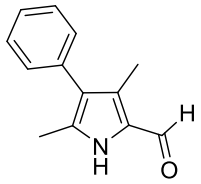
^{1}H NMR; 500 MHz, $CDCl_3$



^{13}C NMR; 125 MHz, $CDCl_3$



2-Formyl-3,5,-dimethyl-4-phenylpyrrole (2d)



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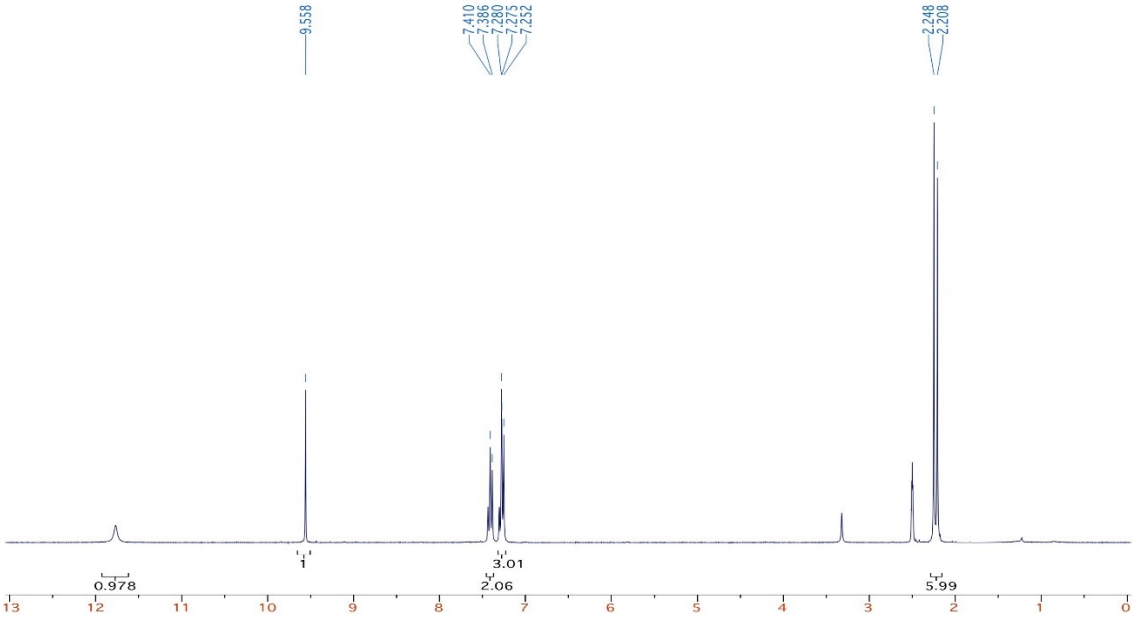

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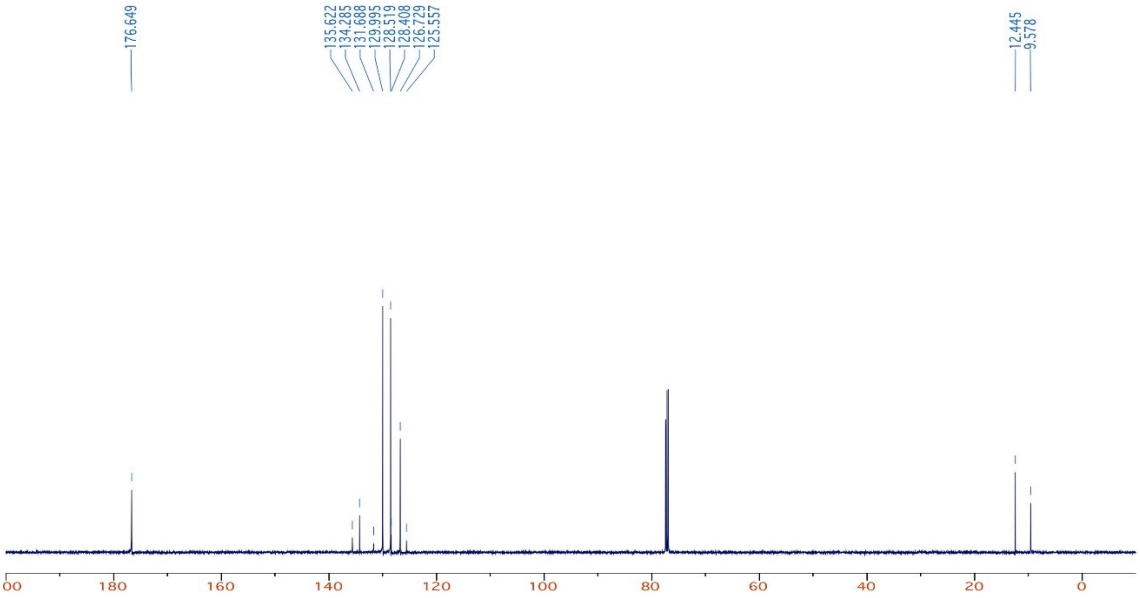
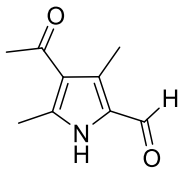
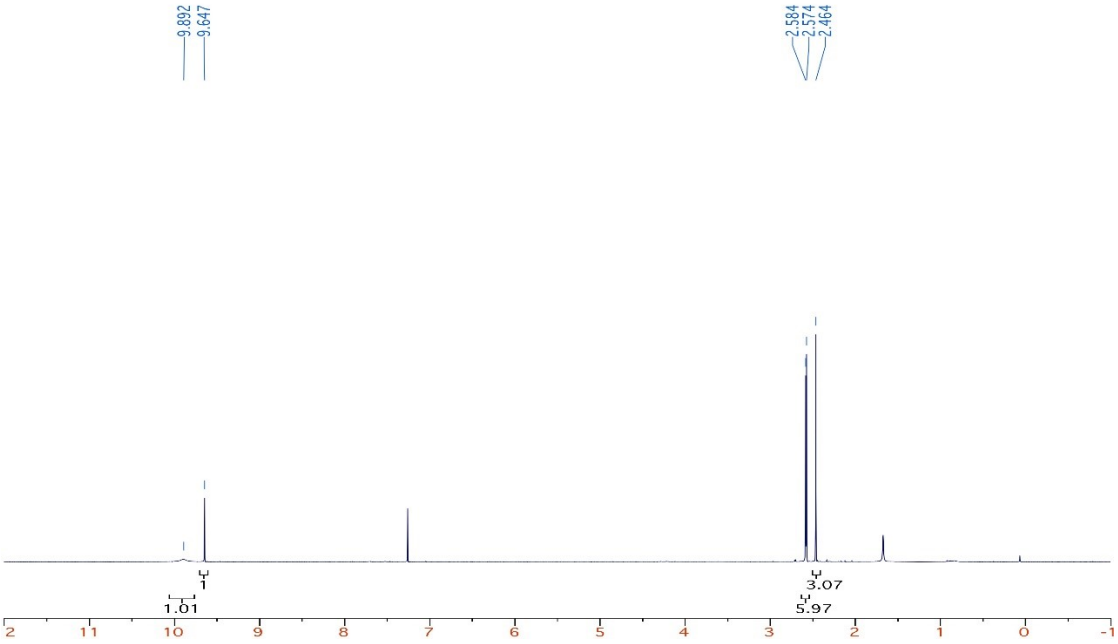


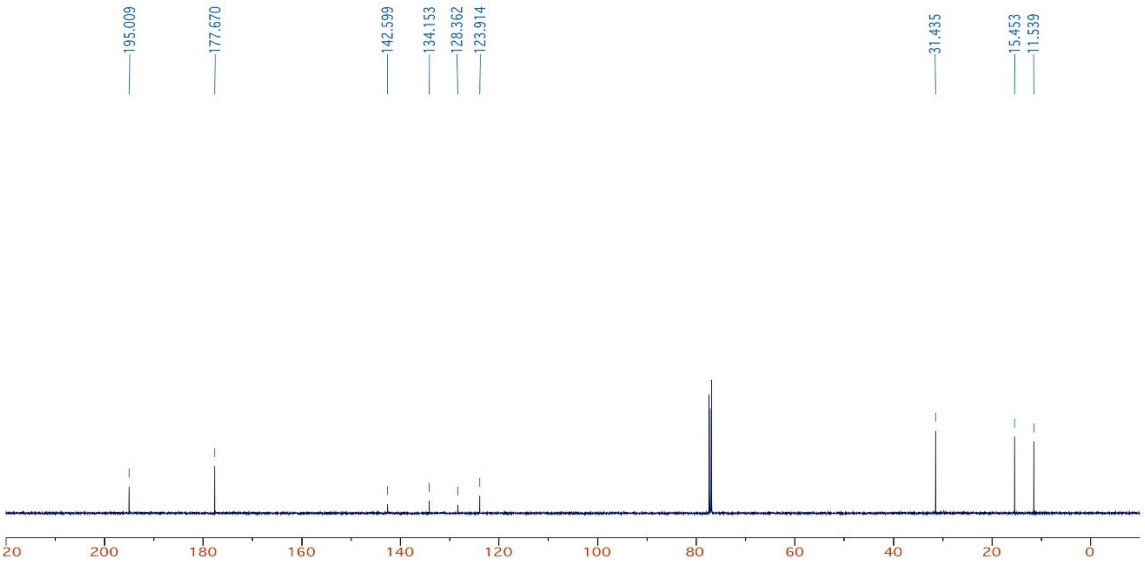
4-Acetyl-2-formyl-3,5-dimethylpyrrole (2e)



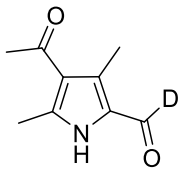
^{1}H NMR; 300 MHz, $CDCl_3$



^{13}C NMR; 125 MHz, $CDCl_3$



4-Acetyl-2-formyl-*d*-3,5-dimethylpyrrole (2e')



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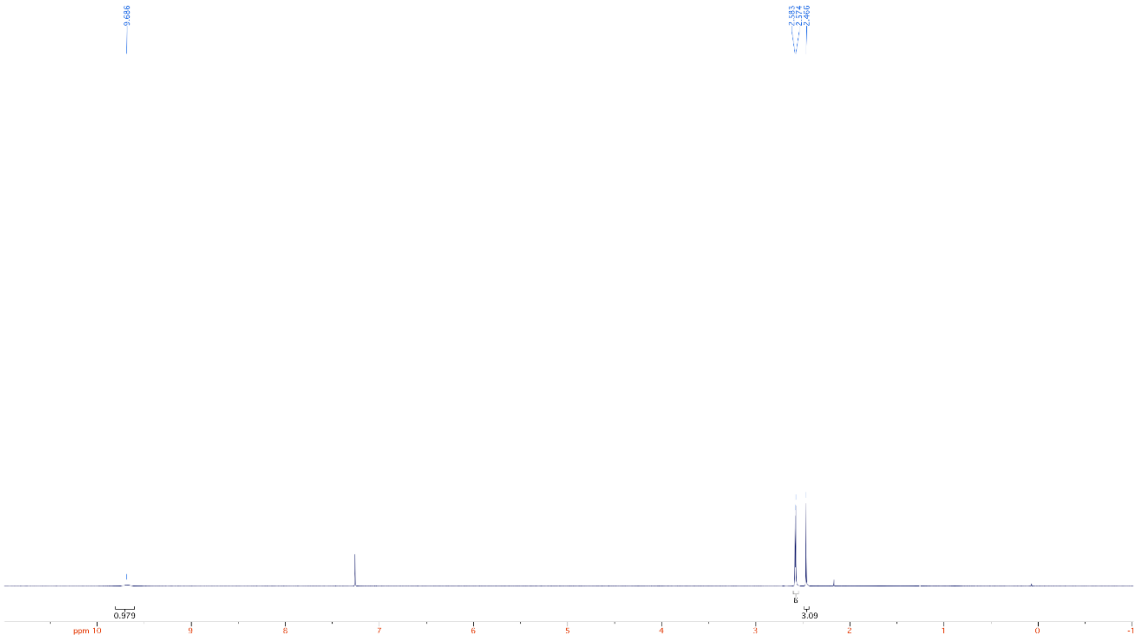
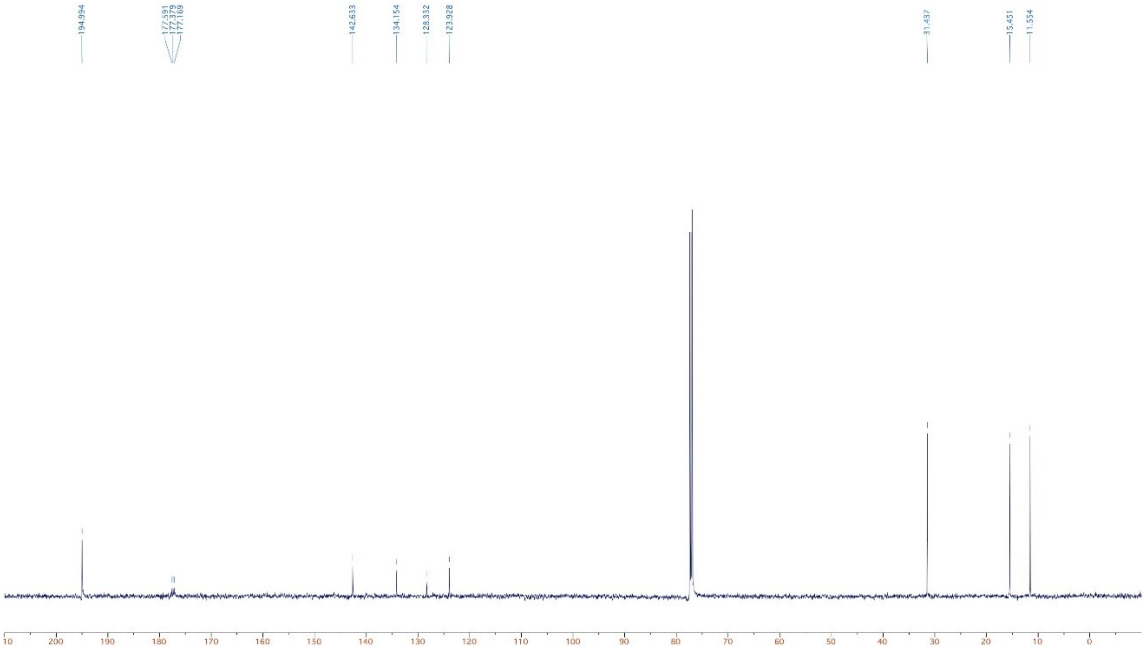
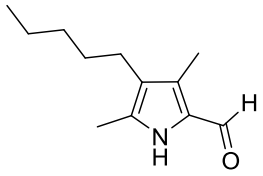


^{13}C NMR; 125 MHz, $CDCl_3$



2-Formyl-3,5-dimethyl-4-pentylpyrrole (2g)



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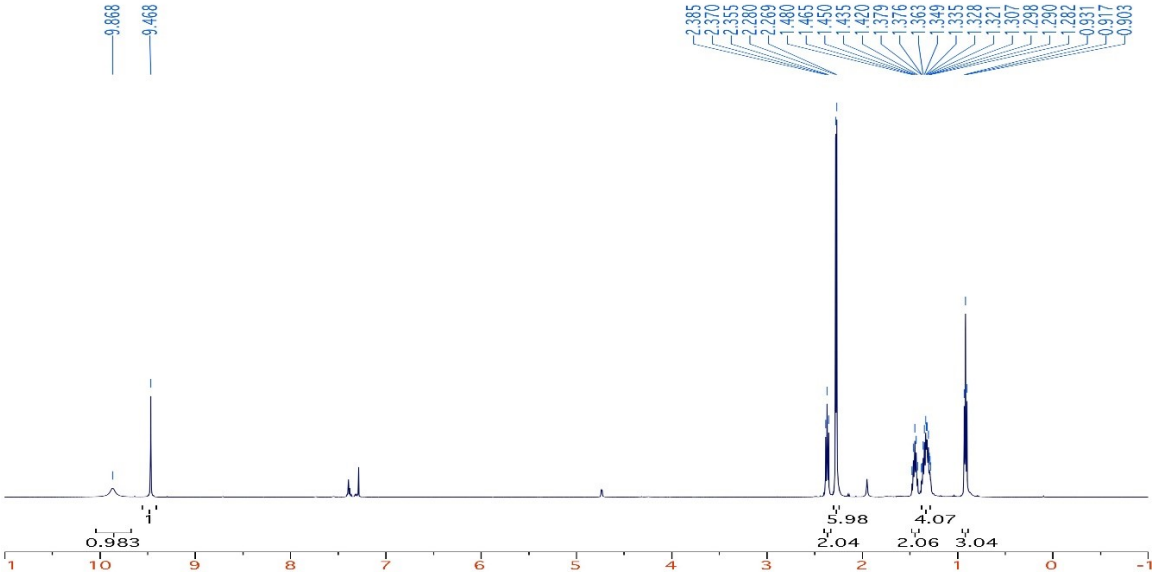
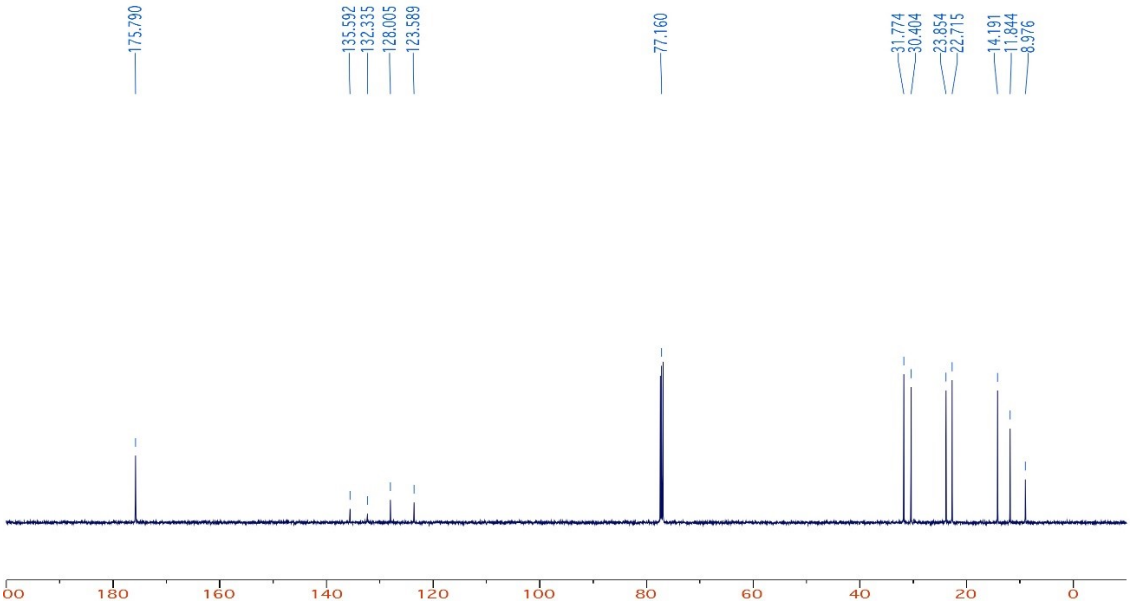
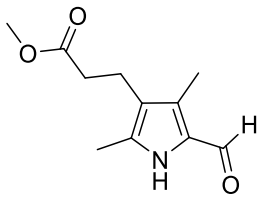


^{13}C NMR; 125 MHz, $CDCl_3$



2-Formyl-3,5-dimethyl-4-methylpropionic pyrrole (2h)



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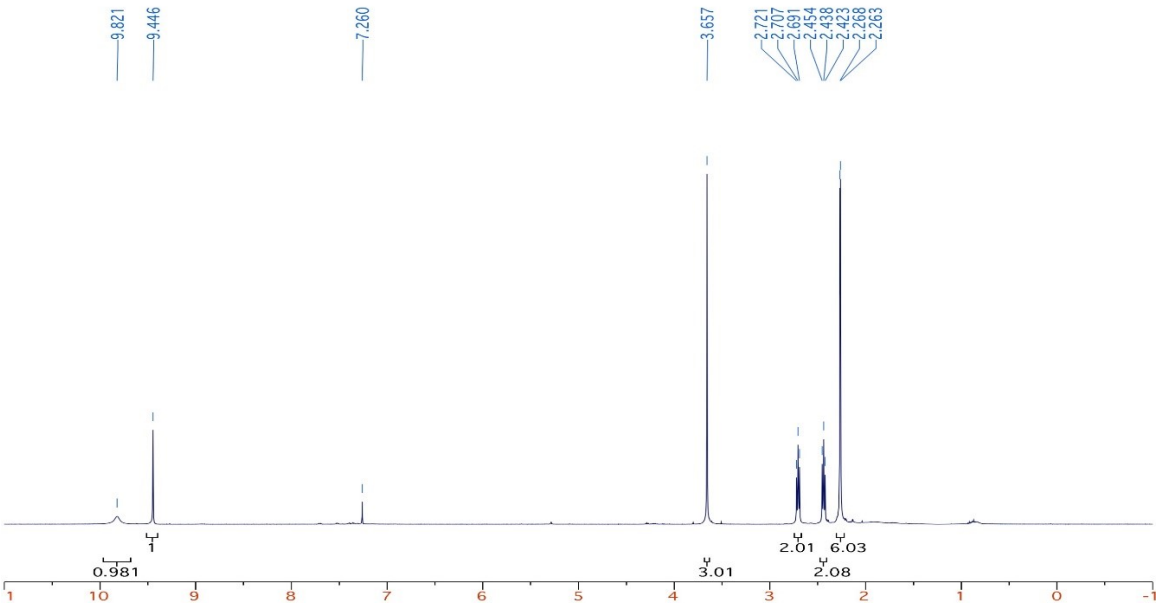

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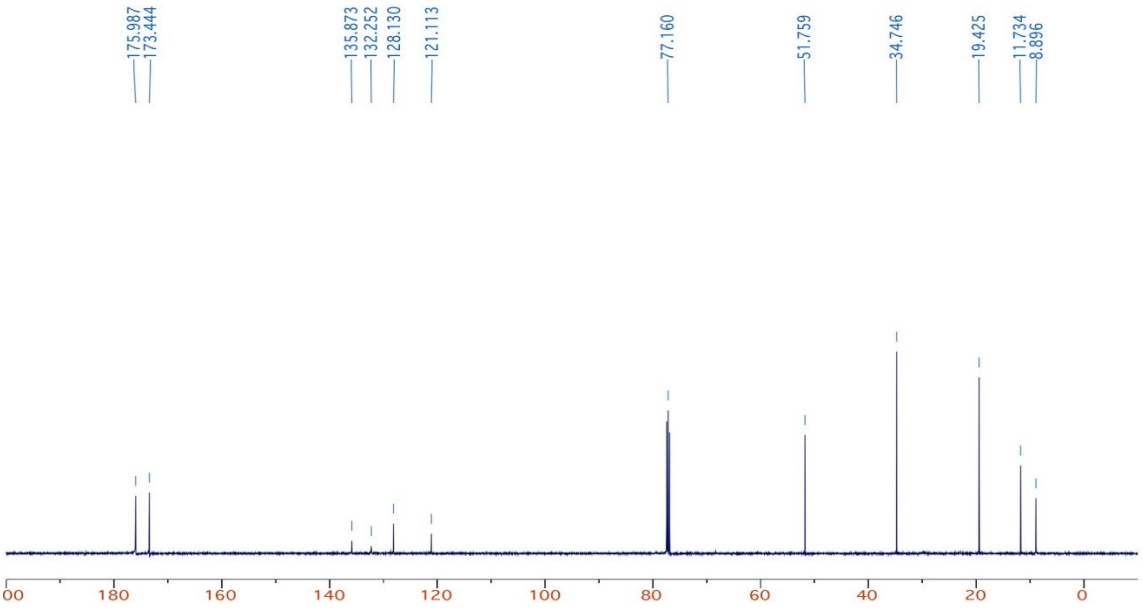
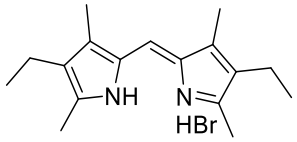


Appendix 2. NMR Spectra for Chapter 3

3-Ethyl-5-((4-ethyl-3,5-dimethyl-2*H*-pyrrol-2-ylidene)methyl)-2,4-dimethyl-1*H*-pyrrole hydrobromide (4)



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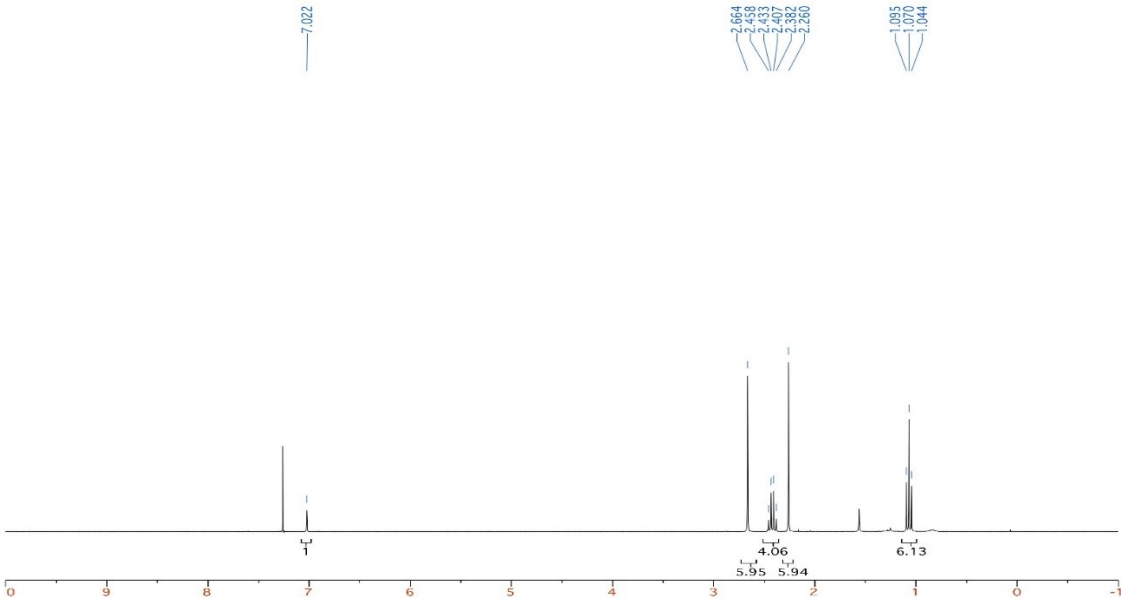
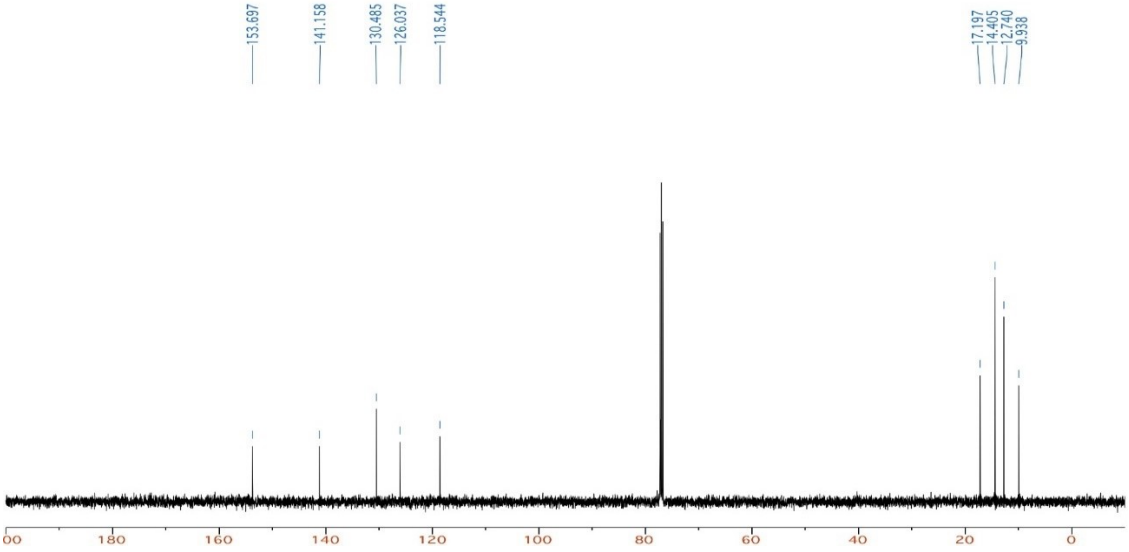
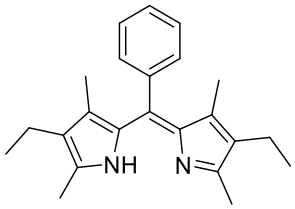


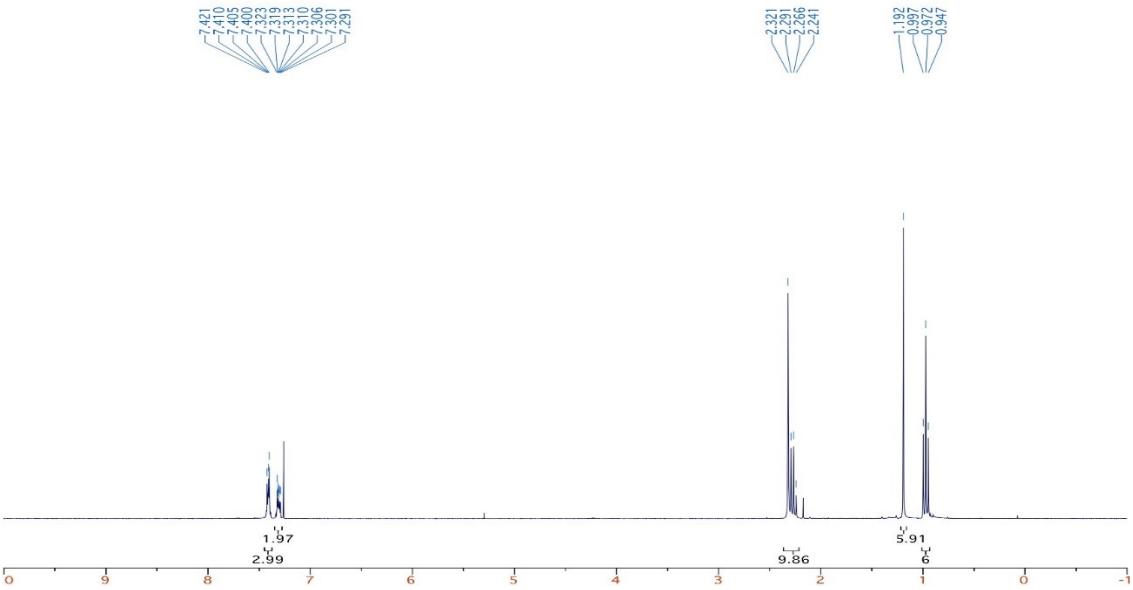
^{13}C NMR; 125 MHz, $CDCl_3$



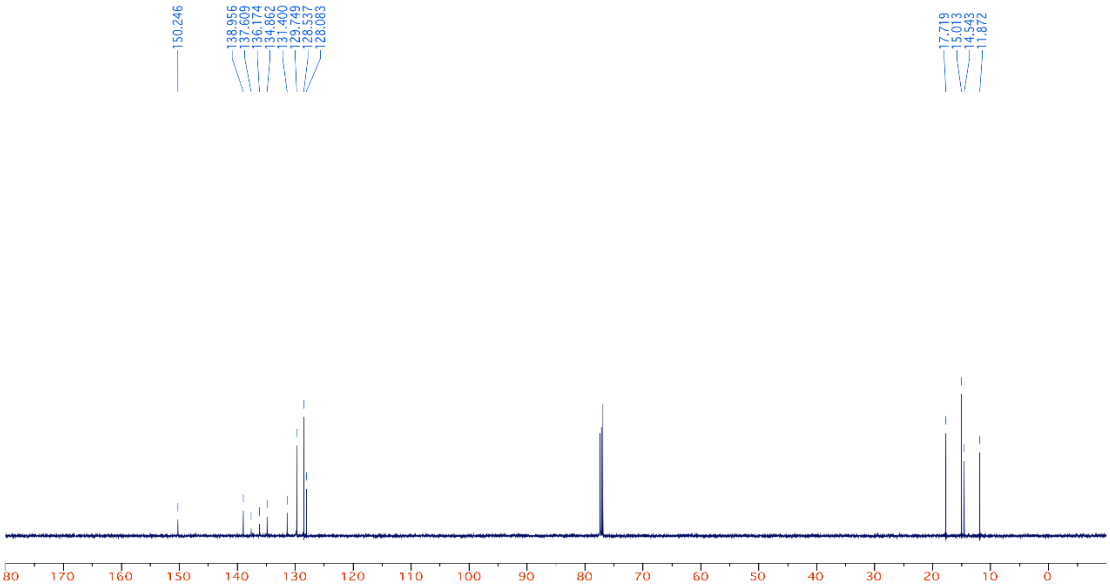
3-Ethyl-5-[(4-ethyl-3,5-dimethyl-2*H*-pyrrol-2-ylidene)phenylmethyl]-2,4-dimethyl-1*H*-pyrrole (6)



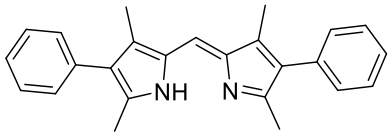
^{1}H NMR; 300 MHz, $CDCl_3$



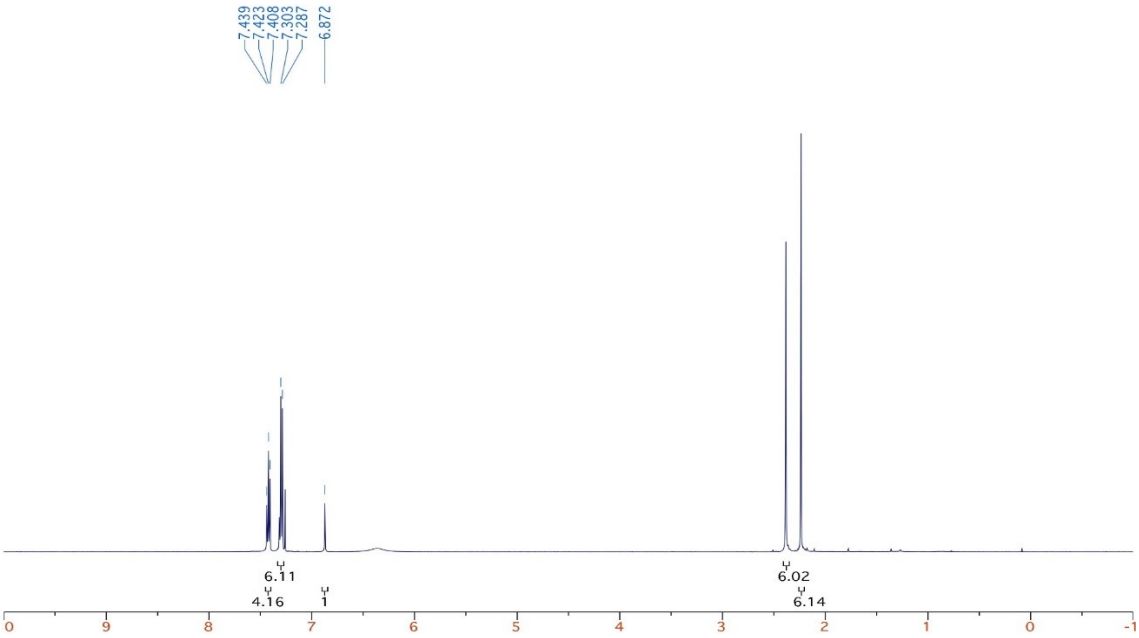
^{13}C NMR; 125 MHz, $CDCl_3$



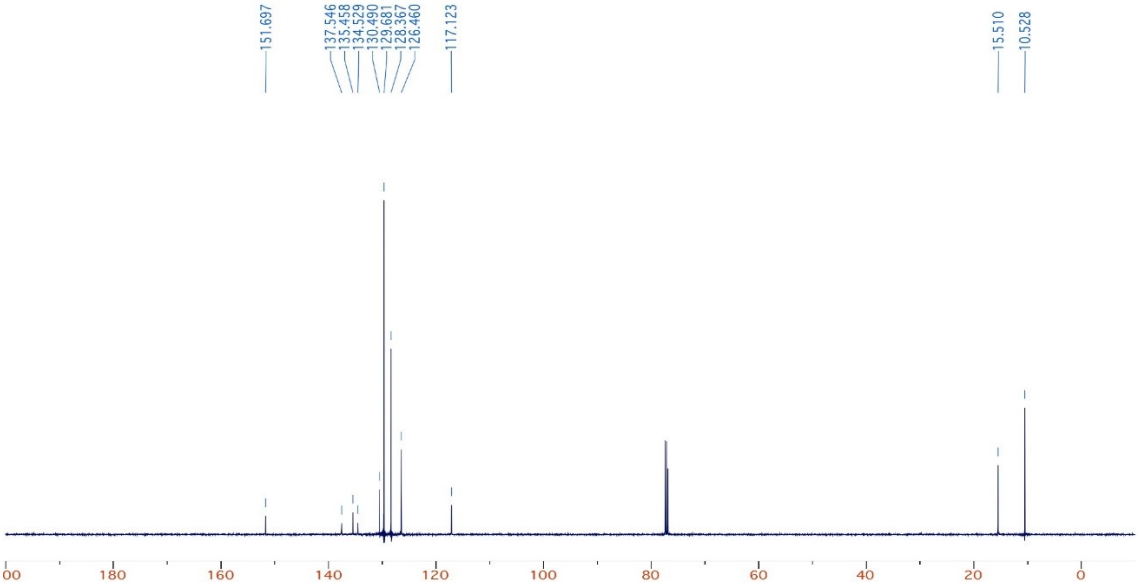
4,4-Difluoro-1,3,5,7-tetramethyl-2,6-diphenyl-4-bora-3a,4a-diaza-s-indacene (14)



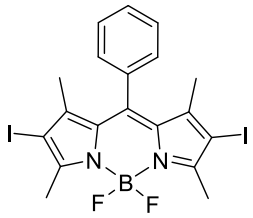
^{1}H NMR; 300 MHz, $CDCl_3$



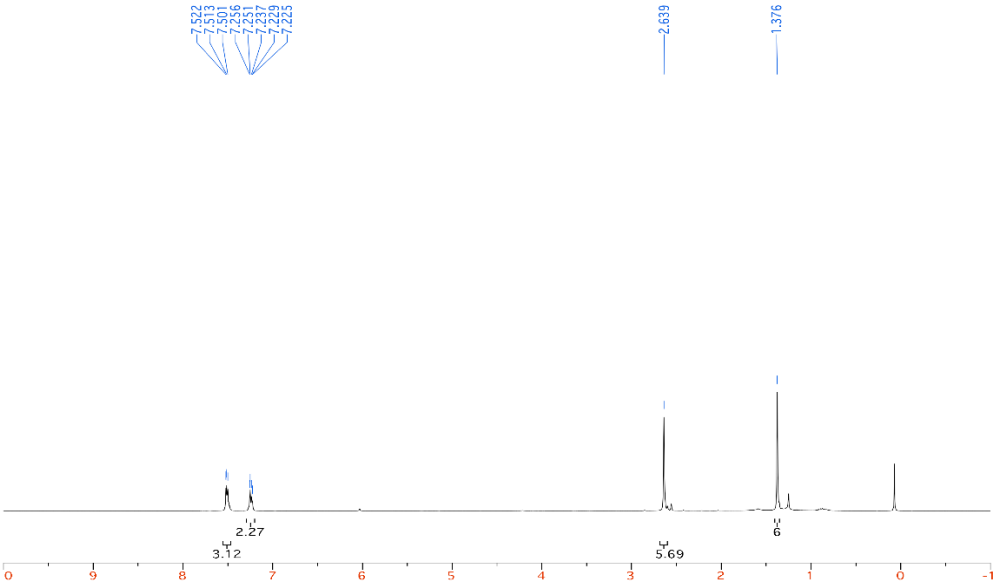
^{13}C NMR; 125 MHz, $CDCl_3$



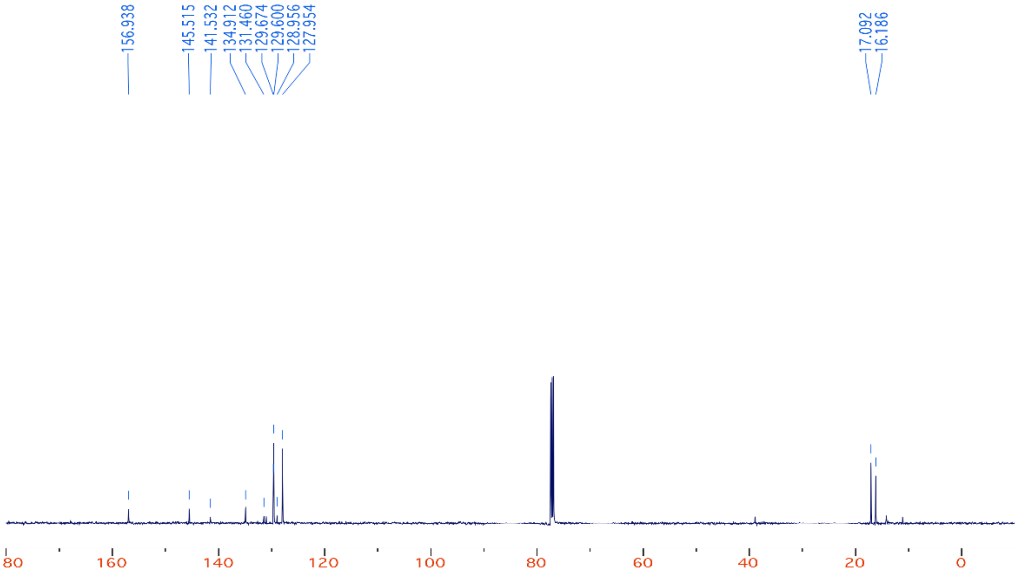
4,4-Difluoro-2,6-diiodo-1,3,5,7-tetramethyl-8-phenyl-4-bora-3a,4a-diaza-s-indacene (17)



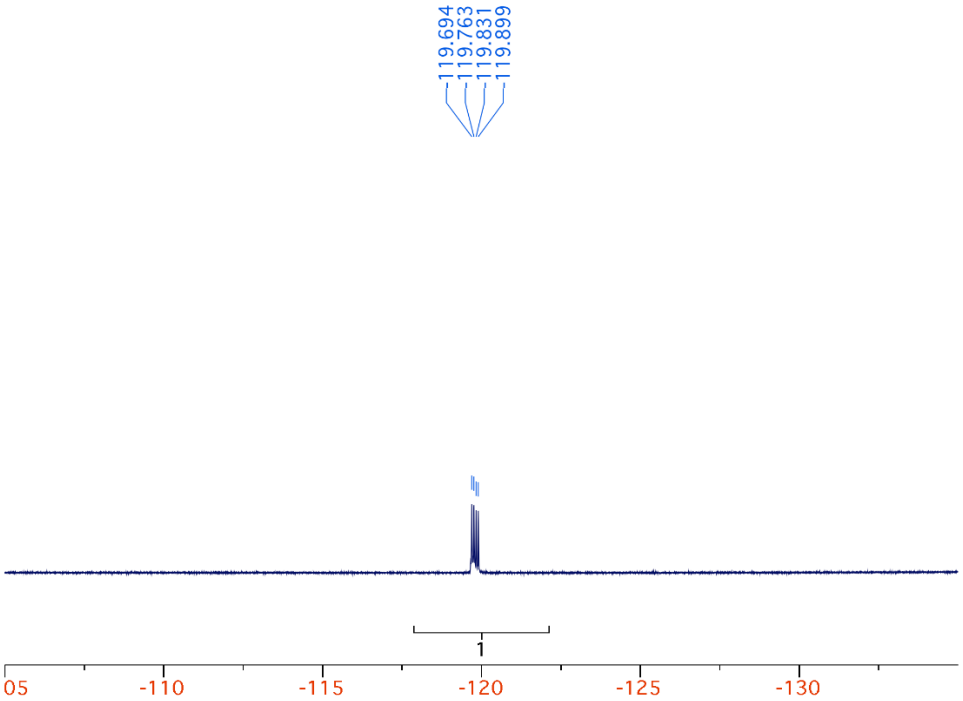
^{1}H NMR; 300 MHz, $CDCl_3$



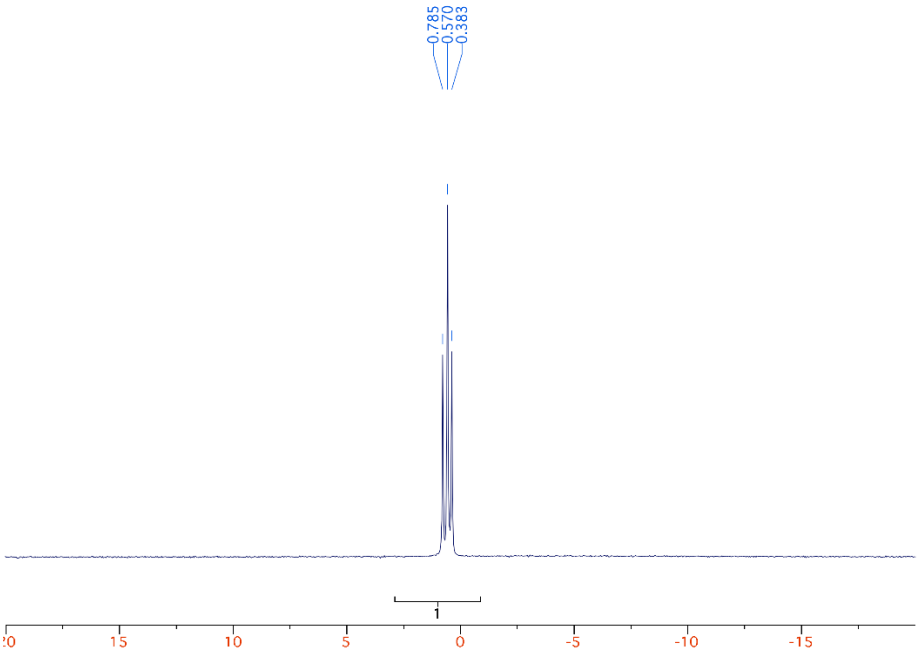
^{13}C NMR; 125 MHz, $CDCl_3$



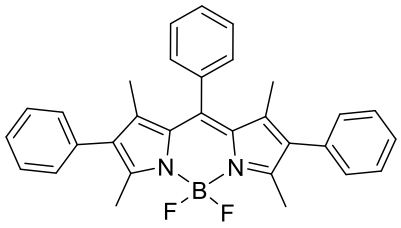
^{19}F NMR; 282 MHz, $CDCl_3$



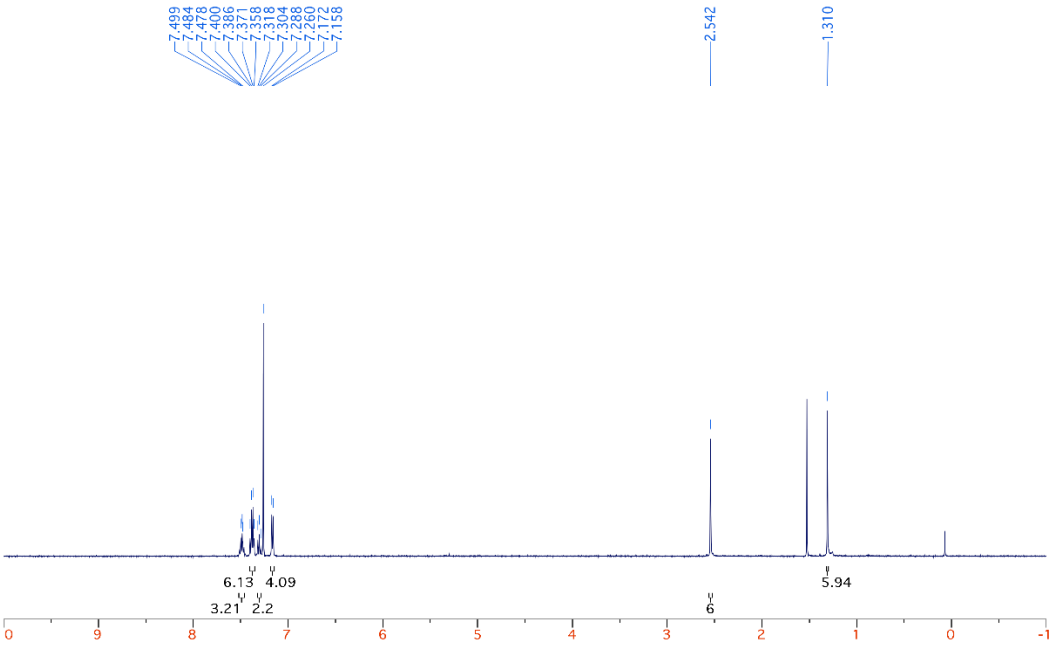
^{11}B NMR; 160 MHz, $CDCl_3$



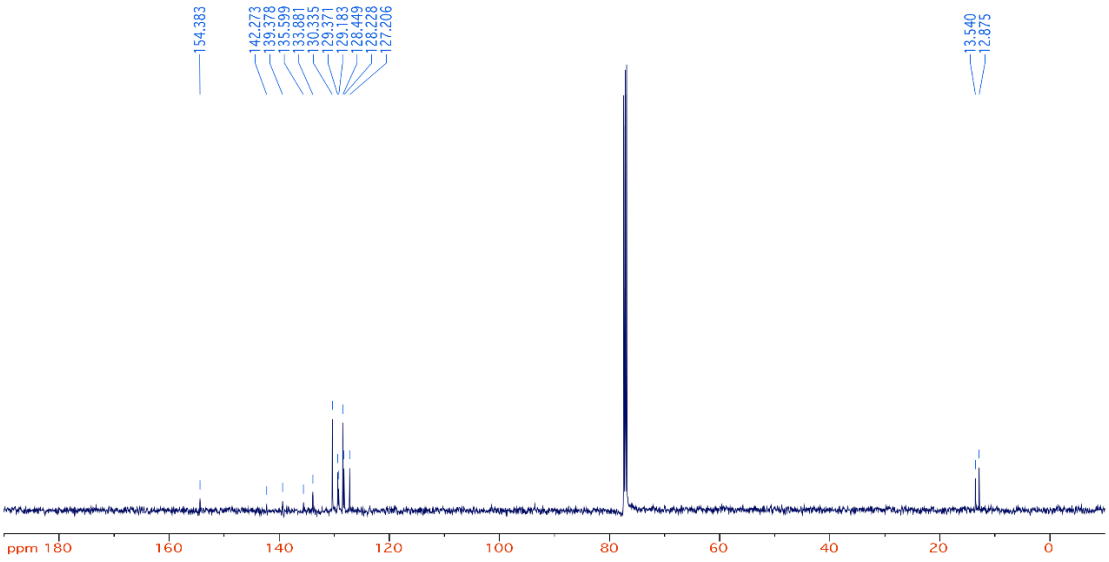
4,4-Difluoro-1,3,5,7-tetramethyl-2,6,8-triphenyl-4-bora-3a,4a-diaza-s-indacene (18)



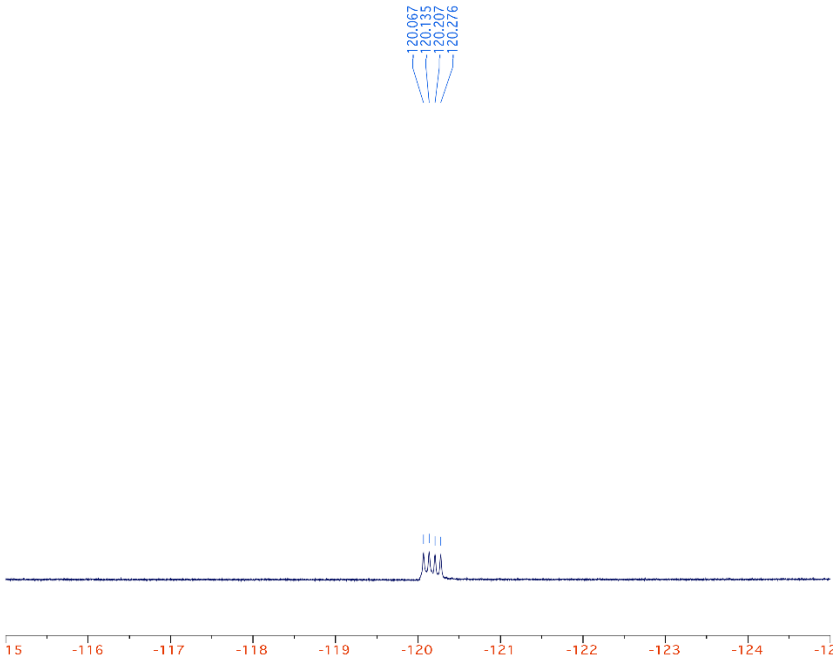
^{1}H NMR; 300 MHz, $CDCl_3$



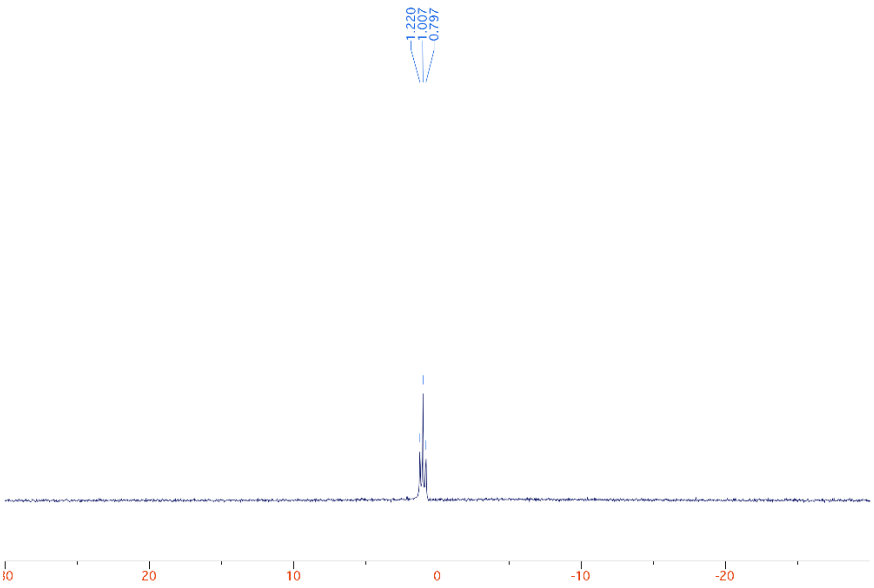
^{13}C NMR; 125 MHz, $CDCl_3$



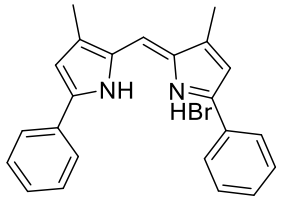
^{19}F NMR; 282 MHz, $CDCl_3$



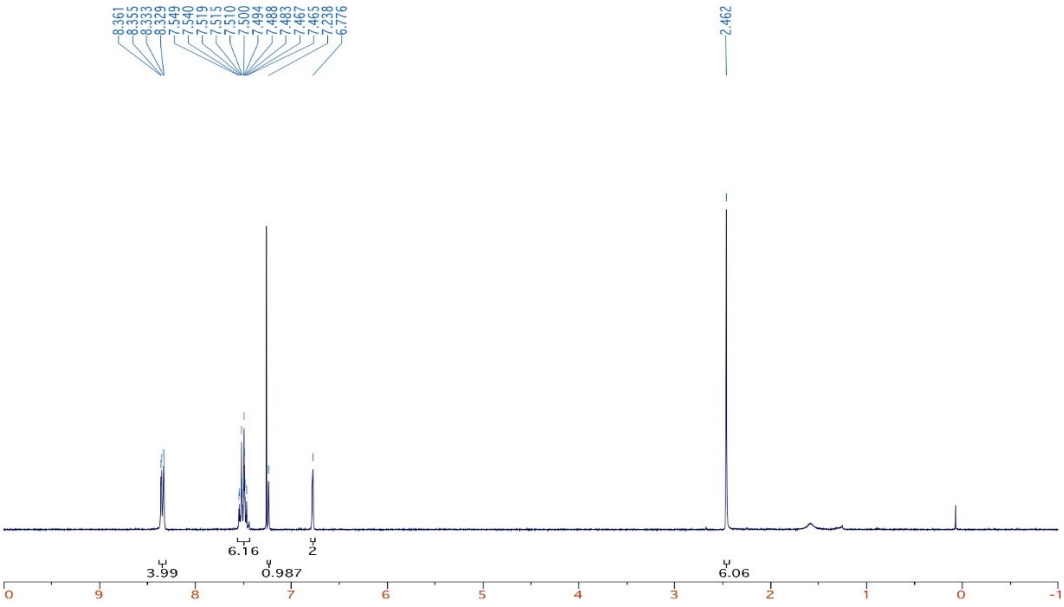
^{11}B NMR; 160 MHz, $CDCl_3$



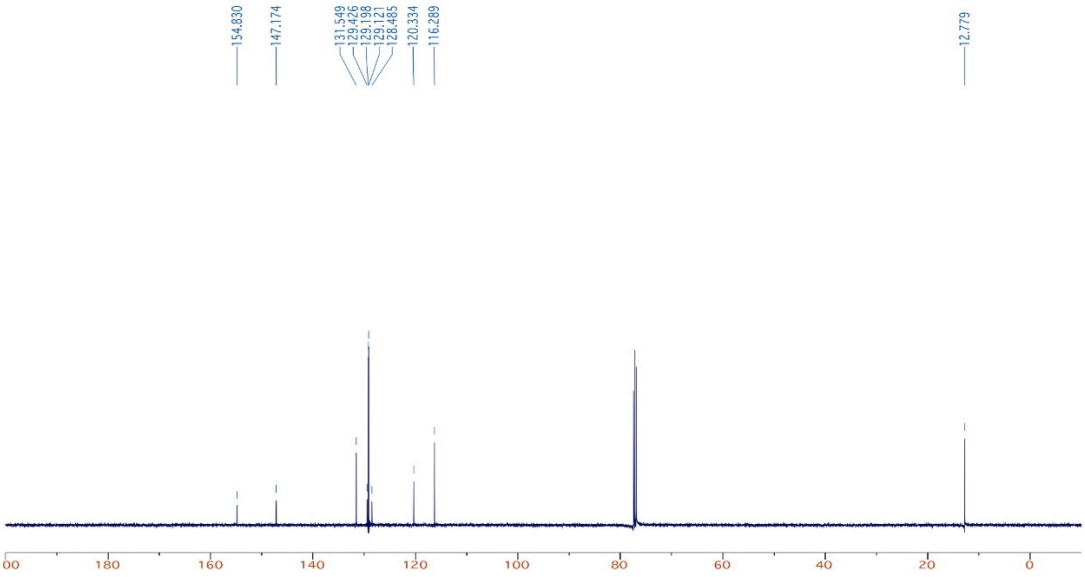
3-Methyl-2-((3-methyl-5-phenyl-2*H*-pyrrol-2-ylidene)methyl)-5-phenyl-1*H*-pyrrole hydrobromide (22)



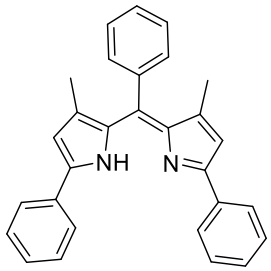
^{1}H NMR; 300 MHz, $CDCl_3$



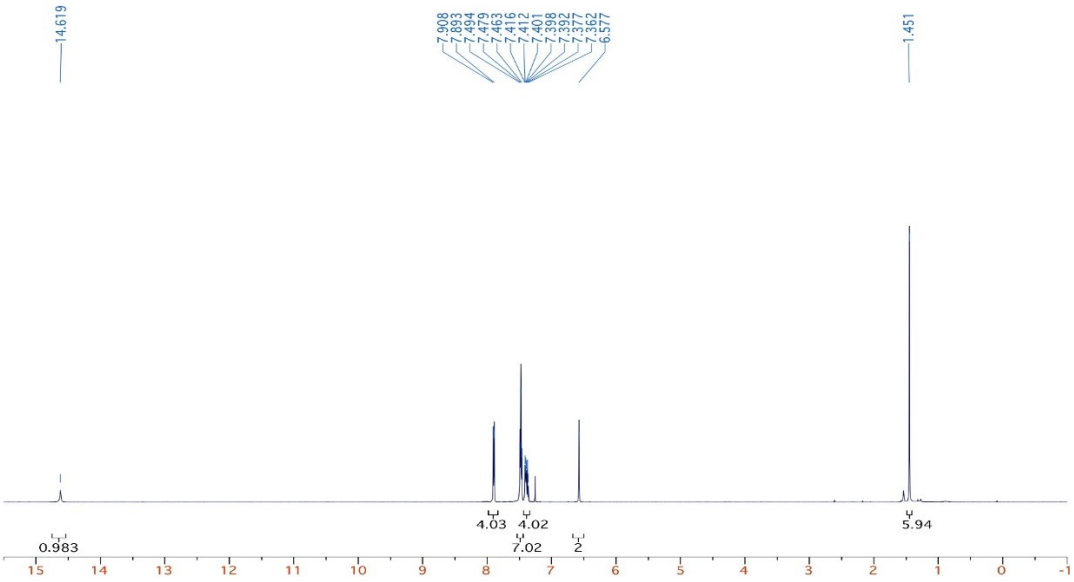
^{13}C NMR; 125 MHz, $CDCl_3$



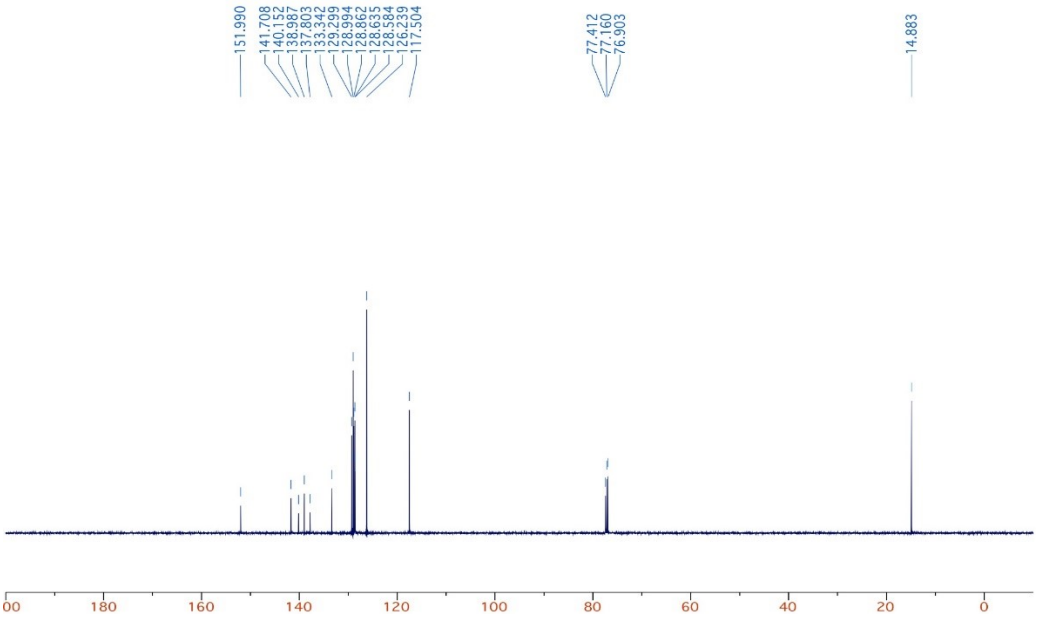
2-((3,5-Diphenyl-2*H*-pyrrol-2-ylidene)methyl)-3,5-diphenyl-1*H*-pyrrole (23)



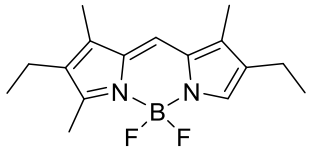
^{1}H NMR; 300 MHz, $CDCl_3$



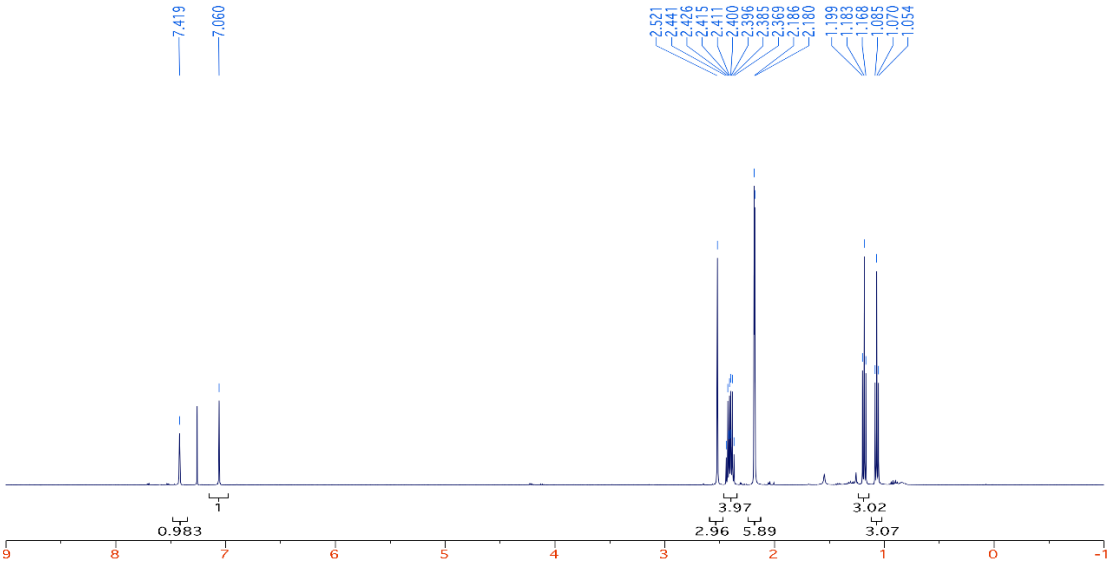
^{13}C NMR; 125 MHz, $CDCl_3$



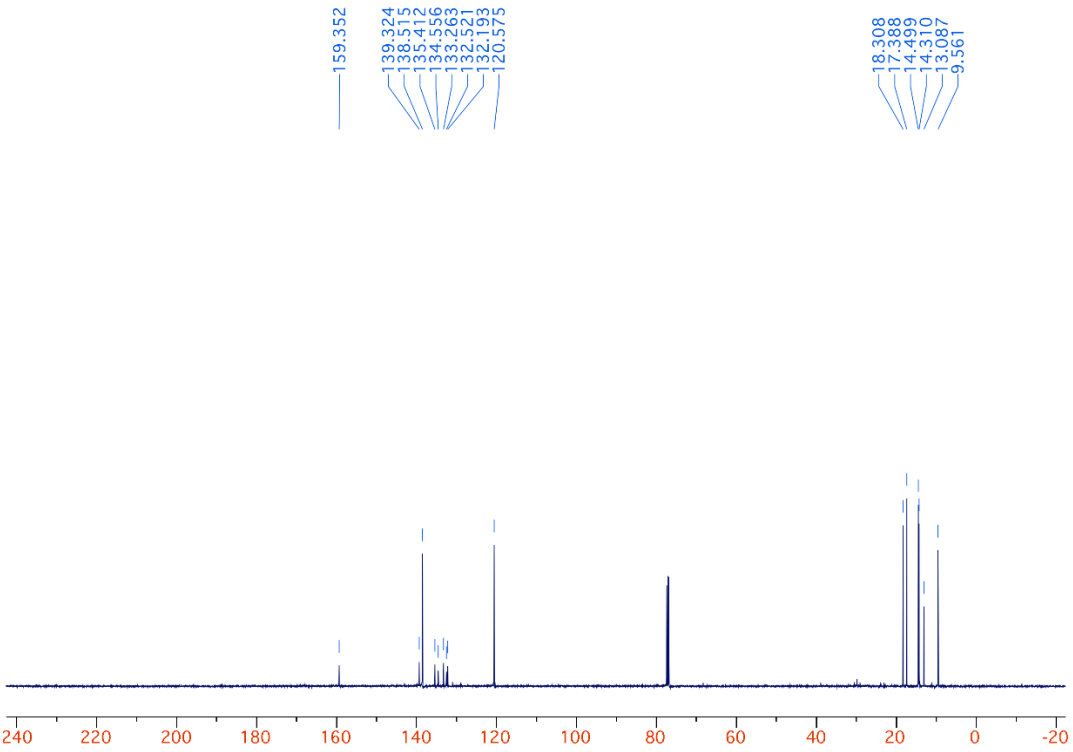
4,4-Difluoro-1-bromo-2,6-diethyl-3,5,7-trimethyl-4-bora-3a,4a-diaza-s-indacene (24)



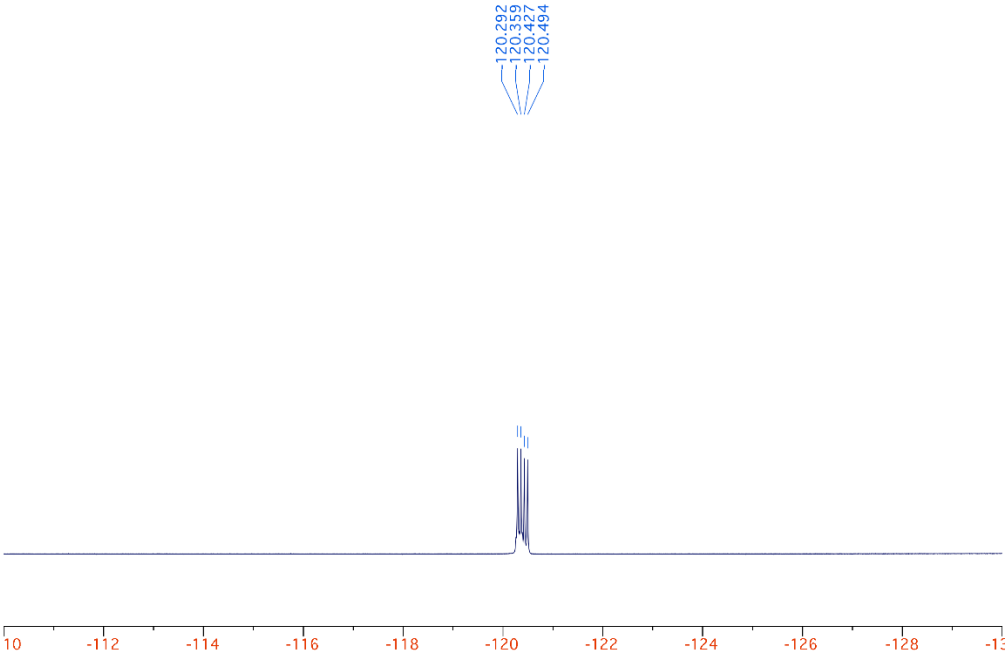
^{1}H NMR; 500 MHz, $CDCl_3$



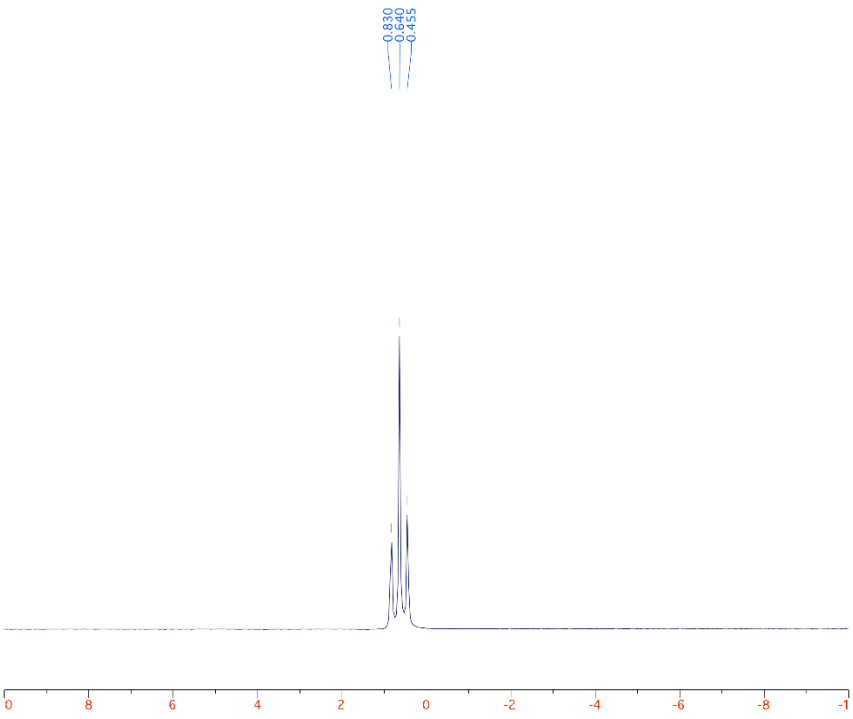
^{13}C NMR; 125 MHz, $CDCl_3$



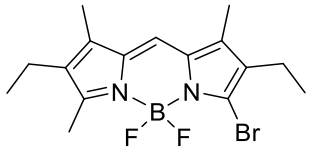
^{19}F NMR; 282 MHz, $CDCl_3$



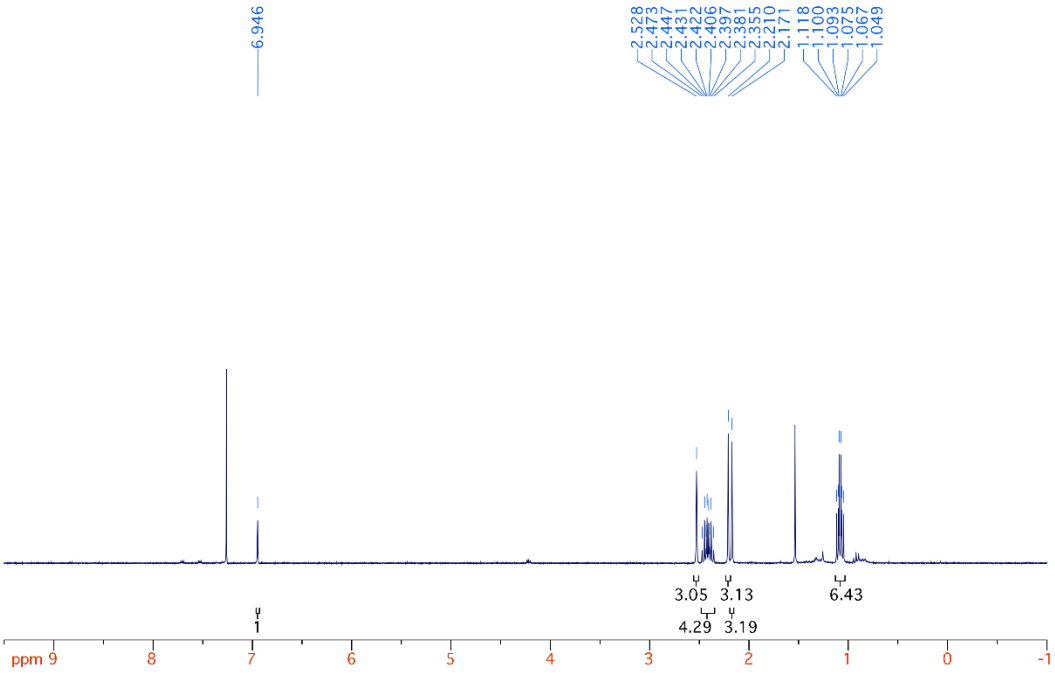
^{11}B NMR; 160 MHz, $CDCl_3$



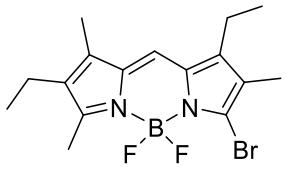
4,4-Difluoro-1-bromo-2,6-diethyl-3,5,7-trimethyl-4-bora-3a,4a-diaza-s-indacene (25)



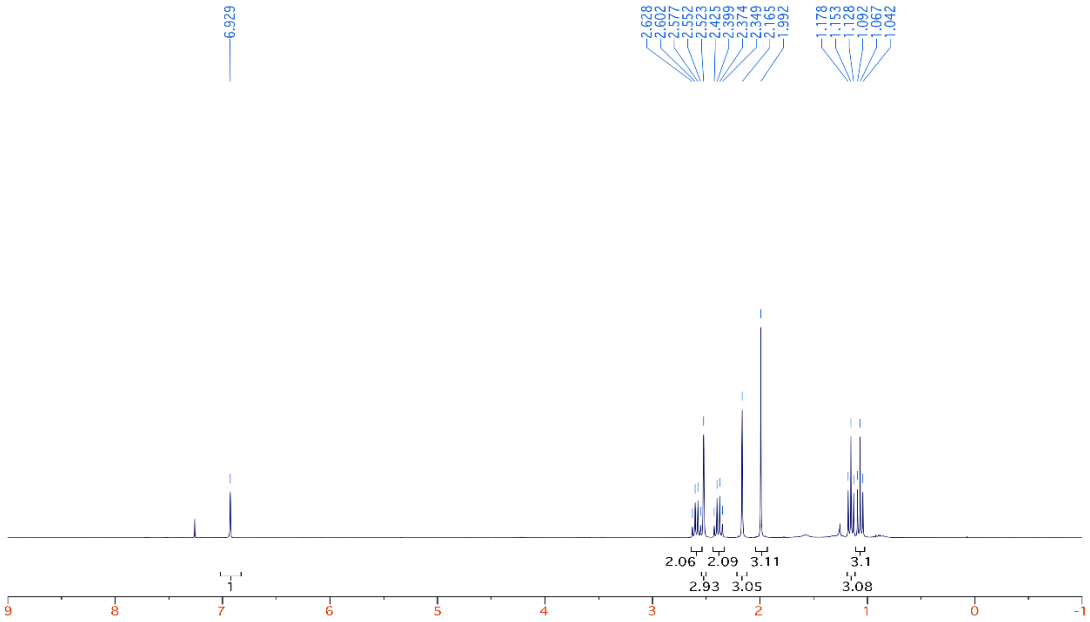
^{1}H NMR; 300 MHz, $CDCl_3$



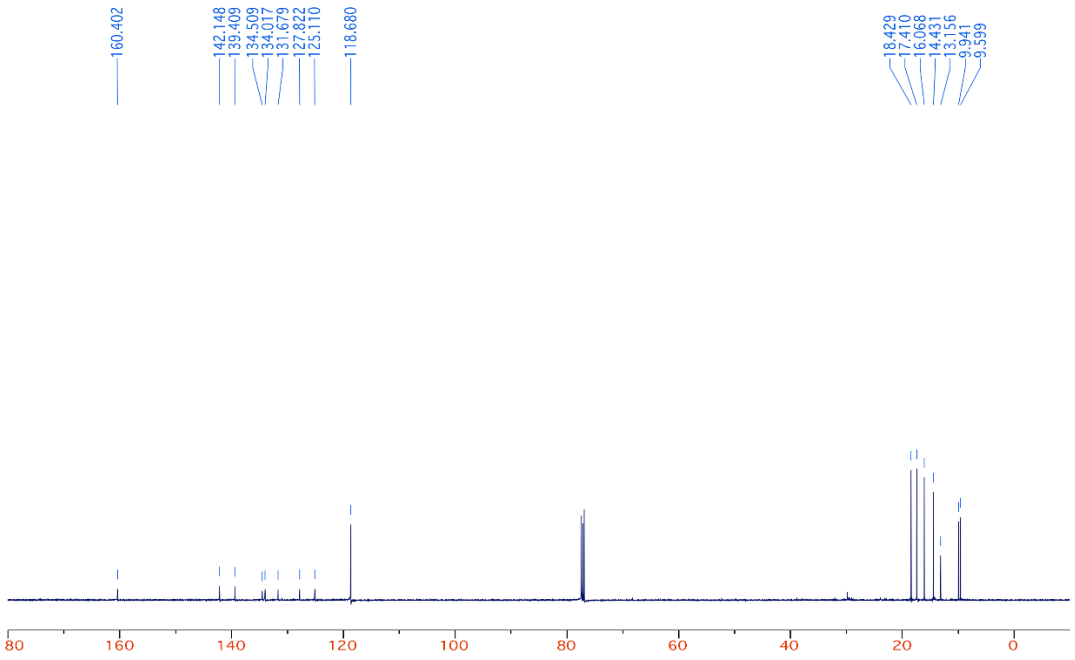
4,4-Difluoro-1-bromo-3,6-diethyl-2,5,7-trimethyl-4-bora-3a,4a-diaza-s-indacene (26)



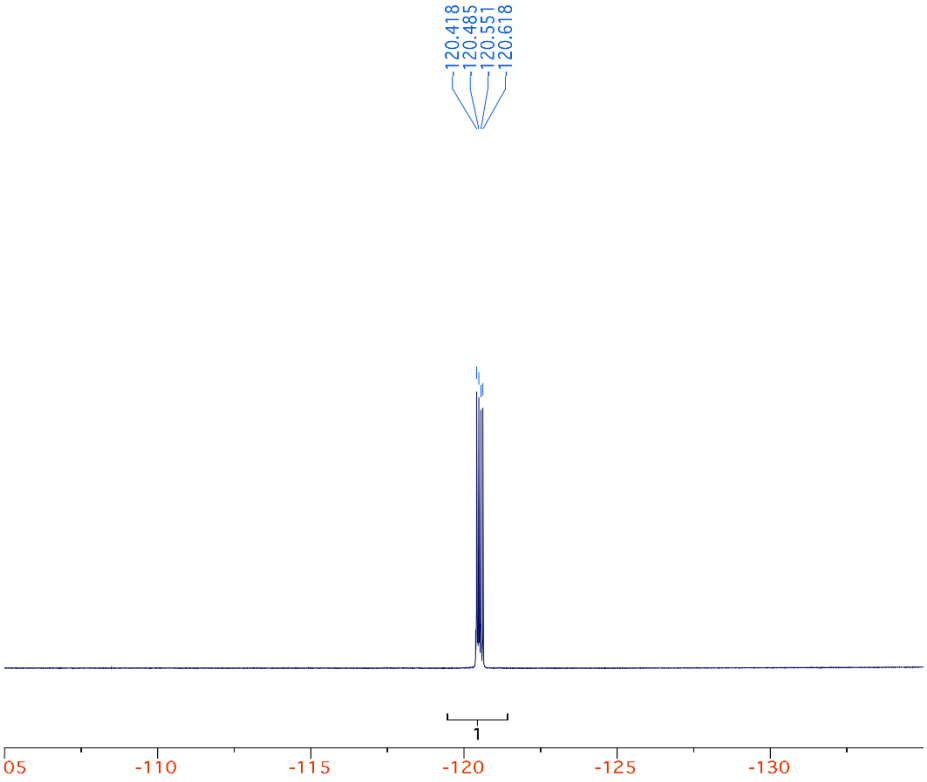
^{1}H NMR; 300 MHz, $CDCl_3$



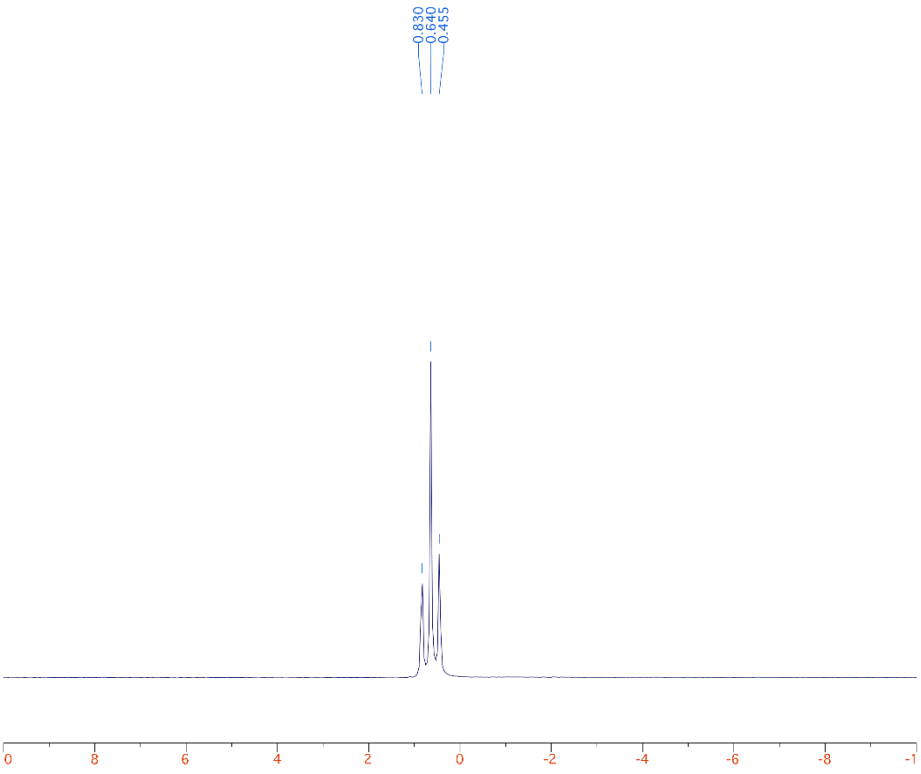
^{13}C NMR; 125 MHz, $CDCl_3$



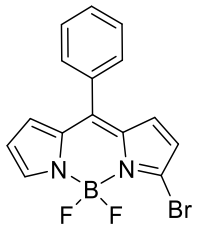
^{19}F NMR; 282 MHz, $CDCl_3$



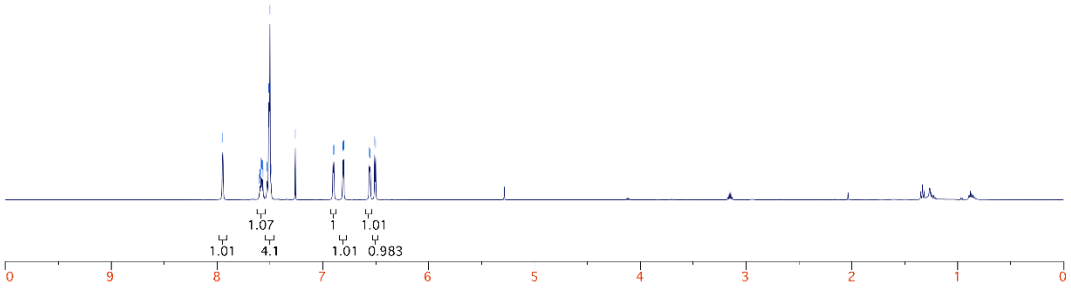
^{11}B NMR; 160 MHz, $CDCl_3$



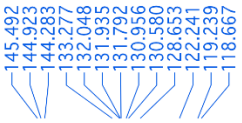
4,4-Difluoro-2-bromo-8-phenyl-4-bora-3a,4a-diaza-s-indacene (29)

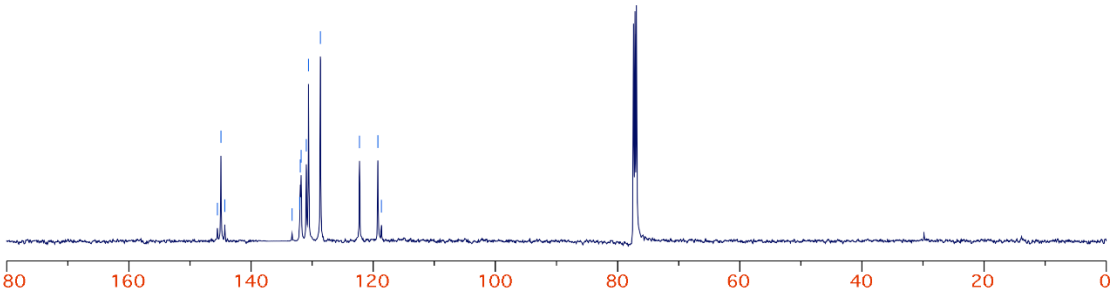


^{1}H NMR; 300 MHz, $CDCl_3$

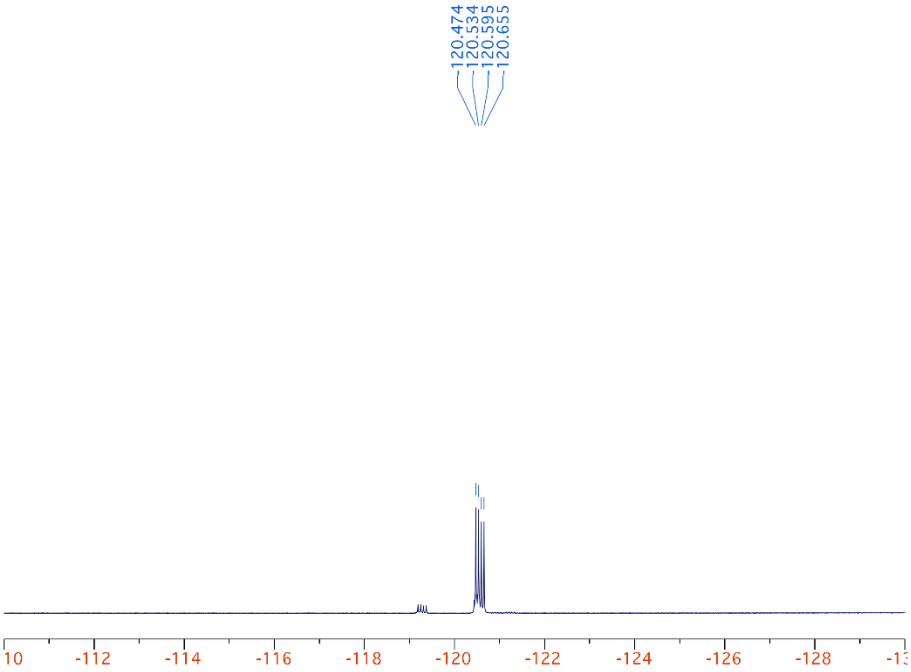


^{13}C NMR; 125 MHz, $CDCl_3$

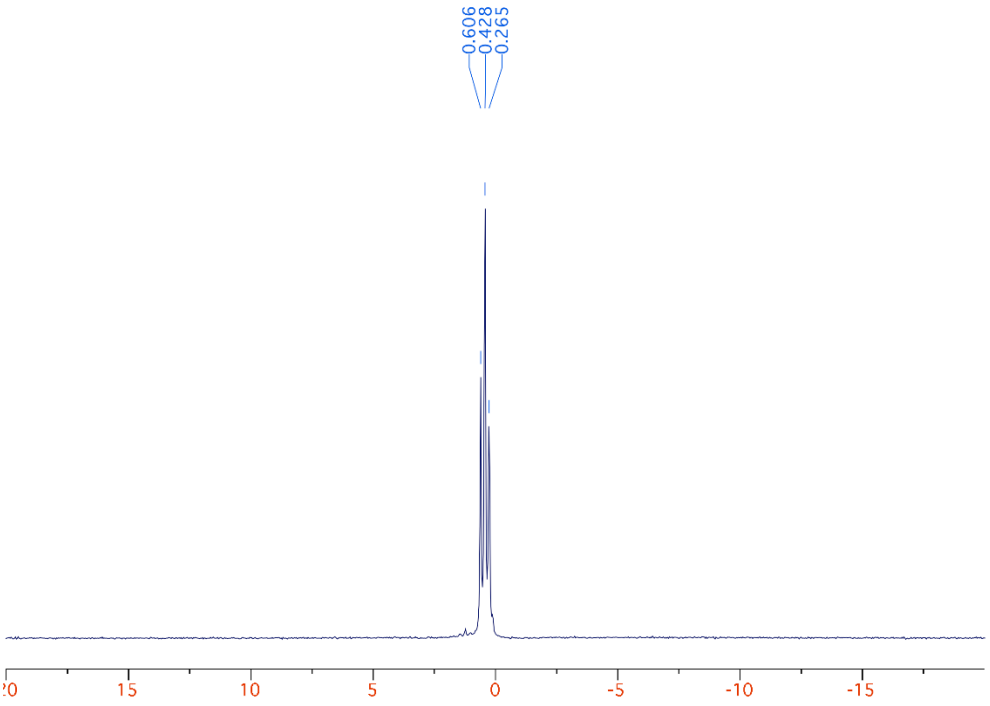




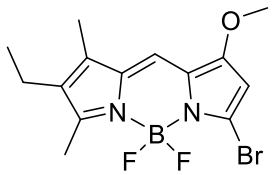
^{19}F NMR; 282 MHz, $CDCl_3$



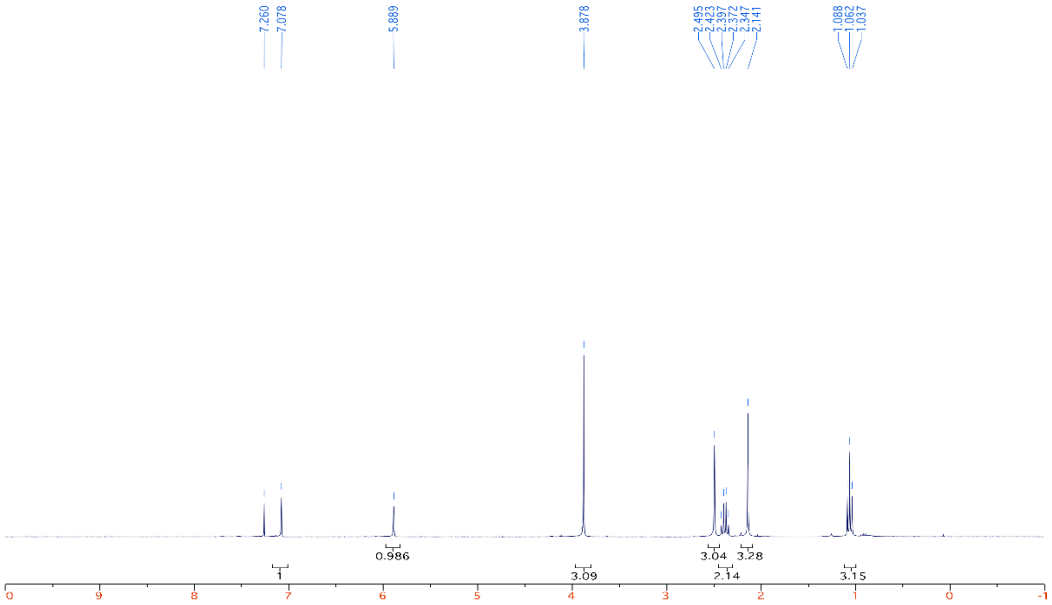
^{11}B NMR; 160 MHz, $CDCl_3$



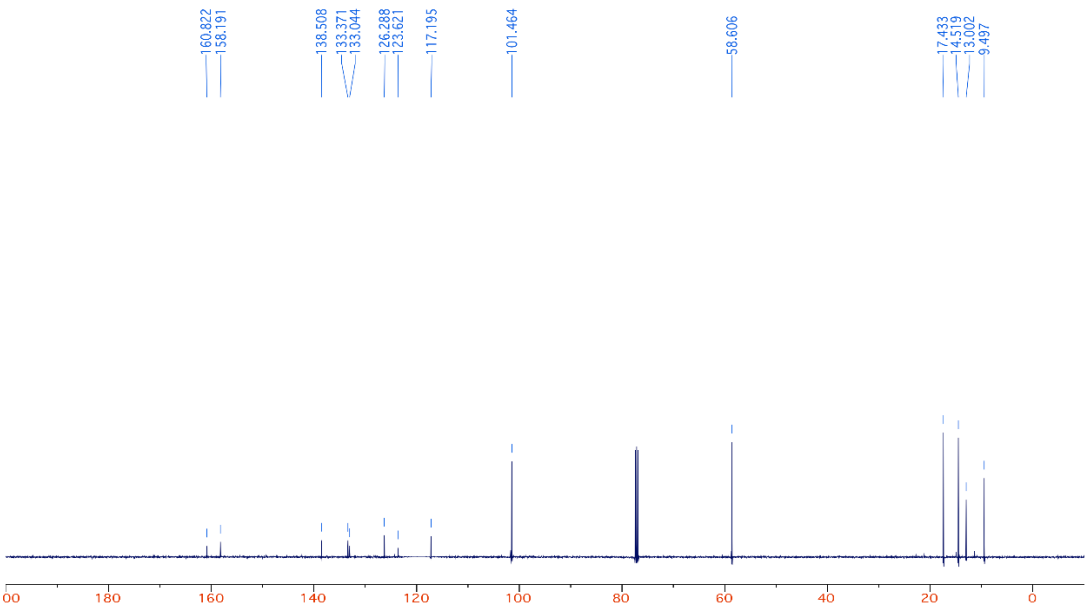
4,4-Difluoro-5-bromo-2-ethyl-7-methoxy-1,3-diamethyl-4-bora-3a,4a-diaza-s-indacene (32)



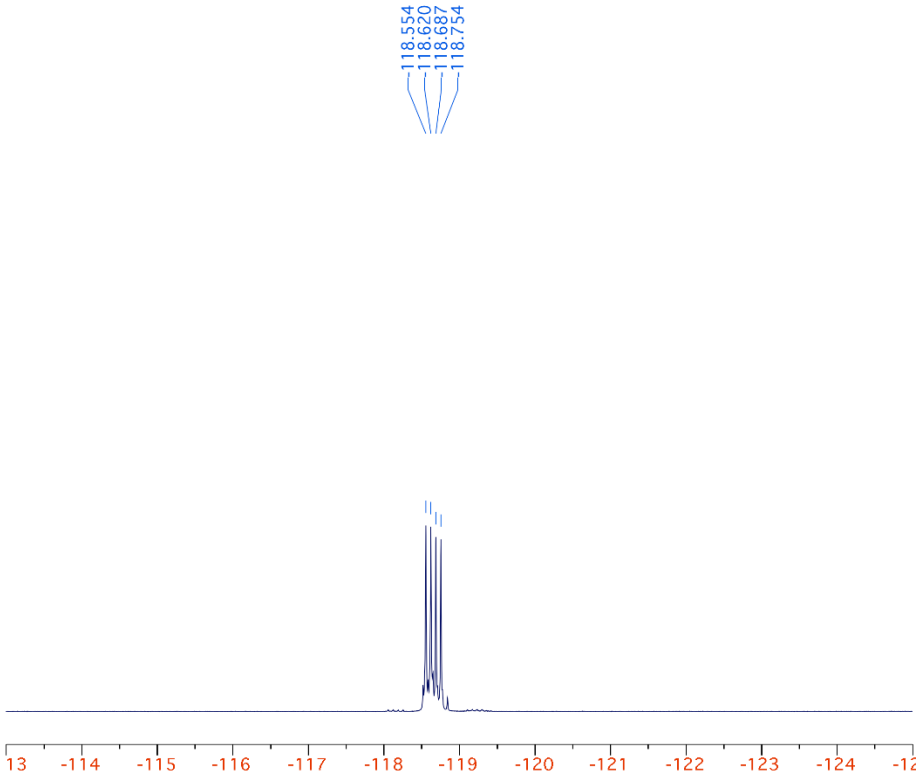
^{1}H NMR; 300 MHz, $CDCl_3$



^{13}C NMR; 125 MHz, $CDCl_3$



^{19}F NMR; 282 MHz, $CDCl_3$



^{11}B NMR; 160 MHz, $CDCl_3$