Attempts Toward An Improved Synthesis of Aza-Dipyrrins

by

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Dalhousie University is located in Mi'kma'ki,
the  ancestral and unceded territory of the
Mi'kmaq. We are all Treaty people.

# DEDICATION

To my children and all the African young women in a dark place with no hope of a better tomorrow. If I could do it, SO CAN YOU.

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# ABSTRACT

Compounds built on the 4,4-difluoro-4-bora-3a,4a-diaza-*s*-indacene (*F*-BODIPY) framework have a wide range of uses stemming from their highly tunable electronic properties. The versatility of this class of compound affords them applications as probes in biological systems and as dyes. Aza-dipyrrins and respective boron compounds (aza-BODIPYs) are direct analogues of BODIPYs in which a carbon *meso*-atom is replaced with nitrogen. This change leads to a large red-shift in their absorption spectra making these compounds effective for applications such as biological imaging and photodynamic therapy (PDT). This thesis aims to develop new methodologies for the effective, eco-friendly and cost-effective synthesis of *F*-BODIPYs and aza-BODIPYs. Attempts to avert the challenges faced by the current synthesis of *F*-BODIPYs are described. These involve using only 1 equiv. of $BF_3 \cdot Et_2O$ in a continuous flow operation. The design of alternative synthetic routes toward aza-dipyrrins is described, where the generation of unstable intermediates that render traditional methods inflexible are avoided. Details of preliminary experimentation to validate these methods are included, as are considerations for future development. Further attempts towards the synthesis of aza-dipyrrins are described. One new route takes advantage of the reductive power of tetravalent phosphorus reagents in C−N coupling. It also describes a new route towards the nitrosylation of pyrroles that is fast, effective and avoids the use of acidic conditions and can thus be potentially applied to less stable pyrroles.

# LIST OF ABBREVIATIONS USED

| | |
|---|---|
| AcOH | Acetic acid |
| Ar | Aromatic |
| $BF_3 \cdot OEt_2$ | Boron trifluoride diethyl etherate |
| $BH_3 \cdot THF$ | Borane tetrahydrofuran |
| BODIPY | 4-Bora-3a,4a-diaza-*s*-indacene |
| br s | Broad singlet |
| $CDCl_3$ | Chloroform |
| d | Doublet |
| DBU | 1,8-Diazabicyclo[5.4.0]undec-7-ene |
| DDQ | 2,2-Dichloro-5,6-dicyano-1,4-benzoquinone |
| DEATMS | N,N-Diethylamino trimethylsilane |
| DIPEA | N,N-Diisopropylethylamine |
| EDC.HCl | 1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide |
| Equiv | Equivalents |
| $Et_2O$ | Diethyl ether |
| EtOAc | Ethyl acetate |
| EtOH | Ethanol |
| *F*-BODIPY | 4,4-Difluoro-4-bora-3a,4a-diaza-*s*-indacene |
| g | Gram |
| GP | General procedure |
| h | Hour |
| HMDS | Hexamethyldisilazane |
| HRMS | High resolution mass spectrometry |
| Hz | Hertz |

| | |
|---|---|
| IUPAC | International Union of Pure and Applied Chemistry |
| $J$ | Coupling constant |
| LiHMDS | Lithium hexamethyldisilazide |
| m | Multiplet |
| MeOH | Methanol |
| mg | Milligram |
| min | Minute |
| mL | Millilitre |
| NIR | Near infrared region |
| NMR | Nuclear Magnetic Resonance |
| °C | Degrees Celsius |
| $p$-chloranil | Tetrachloro-1,4-benzoquinone |
| PDT | Photodynamic therapy |
| Ph | Phenyl |
| PFP | Pentafluorophenylphenol |
| PFA | Perfluoroalkoxyalkane |
| q | Quartet |
| rt | Room temperature |
| $R_f$ | Retention time factor |
| s | Singlet |
| sec | Second |
| t | Triplet |
| THF | Tetrahydrofuran |
| TLC | Thin-layer chromatography |
| TMSPa | Tris(trimethylsilyl)phosphate |
| $t_R$ | Residence time |

| | |
|---|---|
| wt% | Weight percent |
| $\delta$ | Chemical shift |
| $\Delta$ | Heat |
| $\mu L$ | Microlitre |

# ACKNOWLEDGEMENTS

Firstly, I would like to sincerely appreciate the SASEP scholarship committee for awarding me a fully funded scholarship to study here at Dalhousie and for bringing me from Zimbabwe to Canada. I would also like to express my sincere gratitude to my supervisor Prof. Alison Thompson. I would like to thank her for taking a chance on me and accepting me into her research group. Her dedication towards the research program and students is admirable and it has been a real privilege to observe and participate in. She allowed me to freely explore chemistry, to make mistakes and most importantly to learn. She has been an exceptional mentor, who has been supportive throughout this experience. It has been my pleasure to experience your creativity, enthusiasm and passion for chemistry and research. I would also like to sincerely thank my supervisory committee, Dr. Speed, Dr. Chitnis and Dr. Cozens for their time in reviewing my work throughout the years. Their support throughout is greatly appreciated. None of this work would have been possible without the excellent support of exceptional past and present group members of the Thompson laboratory. Their assistance, ideas and friendship will forever be cherished. To my family and friends who supported me morally during this journey, I thank you. Lastly to my husband Amos and my daughter Hailey, I would like to express my immense gratitude for holding my hand in the ups and downs of this journey. For pushing me and believing in me. Above all for coming halfway around the world with me so I can pursue my dream.

# Chapter 1 - Introduction

## 1.1- Pyrrole.

This thesis is centred around the chemistry of pyrrole and pyrrole-containing compounds. Pyrrole is a heterocycle containing a nitrogen atom within the ring.[1] Due to the dominance of pyrrolic components in natural compounds and medicines,[2,3] pyrrole (**Figure 1**) stands out as one of the most well-known heterocycles. Indeed, the biological significance of pyrrole and its derivatives cannot be overstated given that the pyrrolic motif constitutes part of many naturally occurring substances, for example, tetrapyrroles and porphyrins, which serve as active moieties in chlorophyll, heme, vitamin B12, bile pigments. Other examples involve the tripyrrolic prodigiosin skeleton,[4] and many pyrrole-containing alkaloid natural products of varying complexity and biological activity.
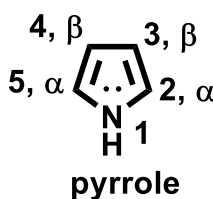
*Figure 1: Structure and numbering of pyrrole.*

A description of the various positions in the pyrrole ring is achieved either by the use of numbers or by the use of Greek letters as shown in **Figure 1**. The nitrogen atom is commonly referred to as the 1-position. The 2- and 5- positions are known as the α-positions. Positions 3- and 4 positions are referred to as the β-positions. The presence of the lone pair of electrons on the nitrogen atom of the pyrrole construct results in the delocalization of six π-electrons over five atoms such that pyrrole is classified as a π-excessive aromatic system.[5] The pyrrolic system is thus susceptible to

electrophilic substitution reactions. In fact, pyrrole is more reactive than benzene in this respect[2] because the 5-membered 6π-system results in the stability of pentacyclic intermediate (δ-complexes) relative to the isoelectronic cyclopentadiene (**Figure 2**). The 6π system formed as a result of the conjugation of the nitrogen lone pair makes pyrrole aromatic as it follows the 4n + 2 Huckle's rule of aromaticity.
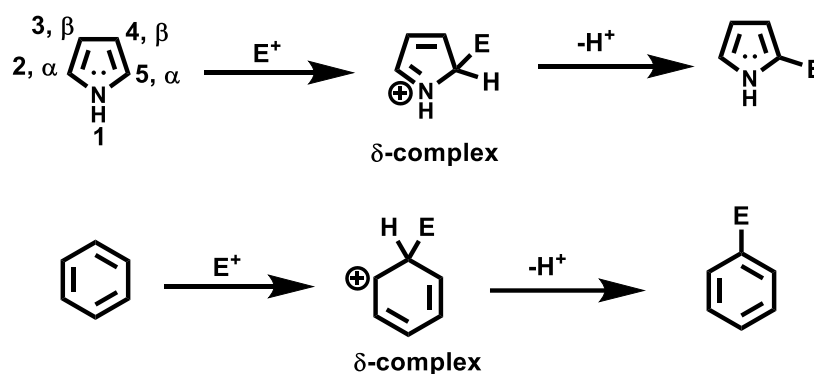


*Figure 2: Electrophilic addition of electrophiles to pyrrole and benzene.*

The delocalization of the nitrogen lone pair also gives rise to resonance forms bearing formal charges with significant electron density at both the α- and β-positions of pyrrole. As a result, electrophilic addition occurs at both the α- and β-positions, with the α-position strongly favoured as shown in **Figure 2**. This result can be explained by theoretical means through the calculation of electron densities,[6] and through resonance stabilization and/or HOMO/LUMO coefficients, which reveal that electrophilic addition at the β-positions results in an intermediate that is cross conjugated.[7,8]

## 1.2 - Dipyrrins and Aza dipyrrins.

The connection of two pyrrolic units by a methine bridge through the 2-positions results in a planar dipyrrin (**Figure 3**) that exhibits strong absorbance bands in the visible region of the electromagnetic spectrum. Dipyrrins are fully conjugated compounds with $12\pi$ electrons delocalized across the dipyrrin core. The conjugation is responsible for strong absorbance bands in the visible region of the electromagnetic spectrum; of these intensely coloured compounds.[9] The IUPAC nomencleture used to label dipyrrins follows that used in pyrroles with the 1- and 9- positions known as the $\alpha$-positions, and the 2-, 3-, 7- and 8-positions as the $\beta$-positions. The 5- position of the dipyrrins is known as the *meso*-position given that it is located centrally within the framework shown in **Figure 3**.[10] Dipyrrins are prone to both electrophilic and nucleophilic attack on unsubstituted ring positions, such that the fully unsubstituted dipyrrin is unstable.[11] Enhanced stability is achieved with the presence of alkyl groups on the $\alpha$- and $\beta$- positions about the dipyrrin core. Therefore, dipyrrins are typically isolated as their hydrobromide or hydrochloride salts both of which are more stable than the corresponding free bases.[12] However, aryl-substitution in the *meso*-position of the dipyrrin framework results in significantly enhanced stability and these dipyrrins can be isolated as the free bases under room conditions. A common modification to the dipyrrin framework is the replacement of the central carbon atom of the dipyrrin with a nitrogen atom. This yields a related but distinct class of compounds called aza dipyrrins (**Figure 3**).[13] Although much less studied than dipyrrins on account of challenging synthetic approaches, aza dipyrrins are gaining interest due to their red-shifted absorptions compared to those of the parent dipyrrins.
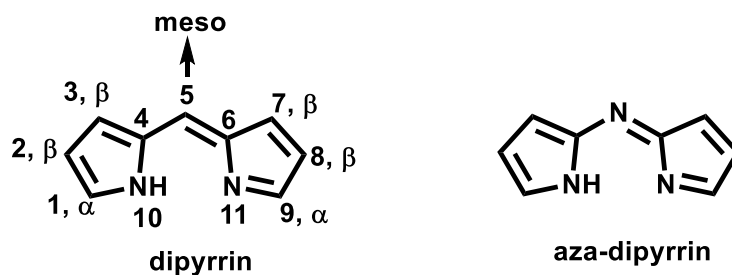
*Figure 3: Numbering system for dipyrrins (left) and aza dipyrrin core (right).*

Adopting from porphyrin chemistry, the construction of the dipyrrin framework can be achieved through one of several generalized methods. The first general approach (**Scheme 1, route I**) involves the condensation of an α-free pyrrole with an α-formyl pyrrole, under acidic conditions, and enables the formation of dipyrrin salts bearing different substituents about the two pyrrolic units.[14] The other approach (**Scheme 1, route II**) involves condensation of two equiv. of an α-unsubstituted pyrrole with an aldehyde to provide a symmetric dipyrromethane. Oxidation then provides the dipyrrin. This route often utilizes aryl aldehydes, thus placing an aryl group in the *meso*-position, although alkyl variants are also known.[15] A variation of this strategy utilizes a carboxylic acid[14] or an acid chloride,[16,17] rather than an aldehyde, thus generating the dipyrrin directly and negating the need for later oxidation across the *meso*-position.
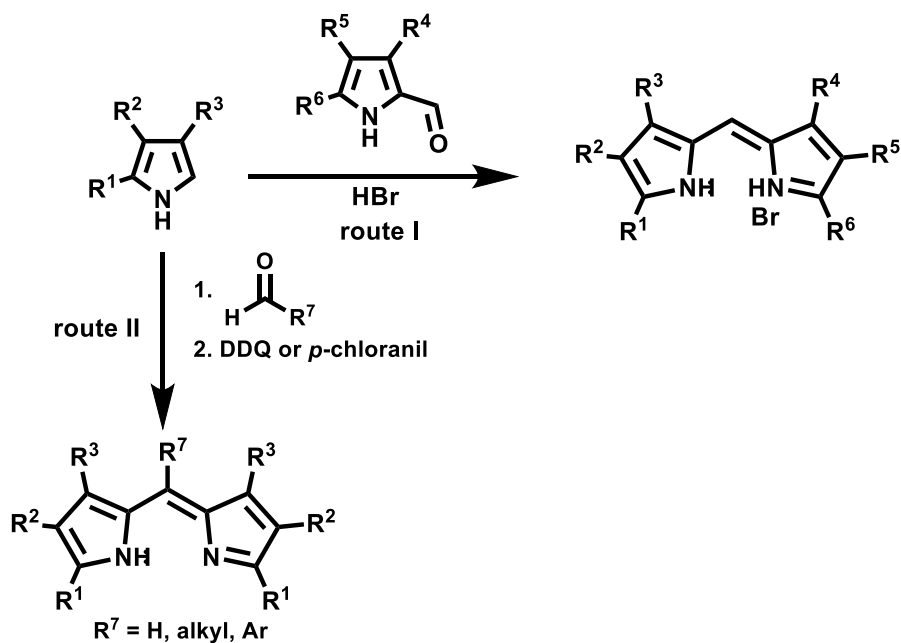
*Scheme 1: Synthetic strategies to dipyrrins.*

Oxidation of dipyrromethanes to dipyrrins is achieved with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) or the milder 2,3,5,6-tetrachloro-1,4-benzoquinone (*p*-chloranil), as indicated in **Scheme 1.** These oxidants were originally borrowed from the shelves of chemists familiar with the oxidation of cyclic tetrapyrroles to make porphyrins, with little variation published since that early work. The oxidation is typically a messy business and is further complicated by challenging chromatographic requirements. As such, incorporation of the -BF$_2$ moeity, chelating both nitrogen atoms, is often effected in situ as the formation of the apolar boron complex significantly improves the outlook for isolation of purified material. The so-formed BODIPYs are the subject of Chapter 2 in this thesis.

Dipyrrrins and aza dipyrrins were traditionally used as synthetic intermediates for the construction of porphyrins and aza porphyrins (aka phthocyanines). However, recent interest in the dipyrrinato framework has since increased due to the ability of dipyrrins to act as metal-chelating ligands for various metal cations. This strategy has shown potential to form charge-neutral complexes with striking optical properties, as well as tunable functionality.[14] The versatility of dipyrrinato ligands as chelating agents for various main group elements and in various applications also is well documented.[18–21] Deprotonation of the dipyrrin gives a resonance-stabilized monoanionic ligand (**Figure 4**) allowing dipyrrins to act as bidentate chelating ligands which can easily be complexed with transition metal ions through the two nucleophilic nitrogen atoms to form isolable complexes of different conformations.[14] As such complexes of dipyrrins with cations such as Ti(IV),[22] Mn(III),[23] Fe(II),[24,25] Co(III),[26] Rh(I),[27] Rh(III),[28] Ir(III),[28] Sn(IV)[22], Pd(II)[29] etc. have been reported, along with their various optical, electronic and catalytic capabilities.
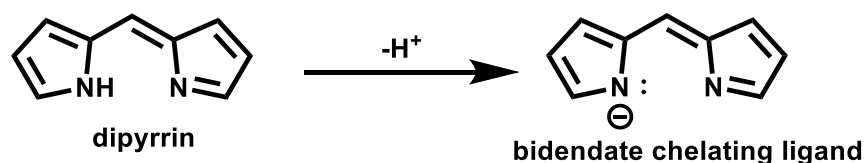


*Figure 4: Complexation of dipyrrins to different types of elements via the nucleophilic nitrogens.*

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## 1.3 - *F*-BODIPYs and aza BODIPYs.

The most common and intensively studied dipyrrinato complexes are the boron difluoride (–BF$_2$) chelated complexes known as *F*-BODIPYs (**Figure 5**).[30,31] The generally highly fluorescent *F*-BODIPY framework was unintentionally discovered in 1968 by Treibs and Kreuzer but has since found increasing applications in a large variety of scientific fields.[20] The IUPAC numbering system for *F*-BODIPYs is different than dipyrrins, but the term α-, β- and *meso*-positions are utilized for both frameworks.[32] Chelation of dipyrrins with -BF$_2$ facilitates tetrahedral geometry at boron. This essentially acts as the "glue" that restricts motion such that the typically non-fluorescent dipyrrin skeleton is rigidified to result in sharp absorption and emission bands.[33,34] Such (photo)electronic properties have been intensely studied, with fine-tuning resulting in highly capable BODIPYs, e.g. bespoke emission, redox properties and/or (photo)sensitization to generate singlet oxygen, and beyond. Many BODIPY-based fluorescent probes have been developed for use in fluorescence imaging.[35]
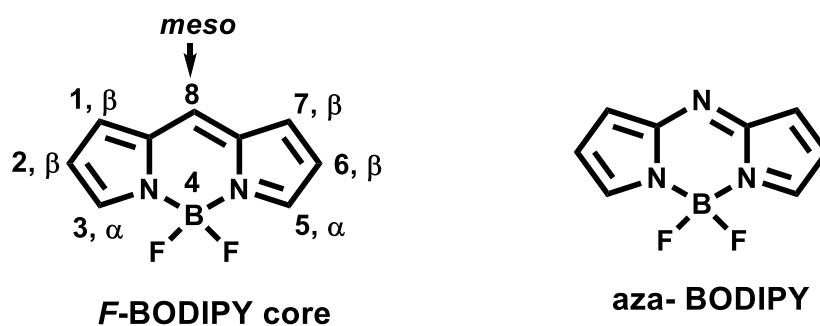


*Figure 5: Structure and IUPAC labelling of F-BODIPYs (left) and the structure of aza BODIPY (right).*

Beyond their use as fluorescent bioprobes, the electronic tunability of BODIPYs has led to utility as photosensitizers for photodynamic therapy[36] and in dye-sensitized solar cells for photovoltaic technology.[37] The planar core, facile functionalization and tunable HOMO–LUMO gap of BODIPYs offer significant promise in this regard.[38] Furthermore, the replacement of the carbon atom with a nitrogen atom at the meso-position forms the aza *F*-BODIPY framework (**Figure 5**). This change lowers the energy of both absorption and emission transitions by reducing the HOMO–LUMO energy gap compared to *F*-BODIPYs with similar substituents. As such, aza BODIPY dyes typically absorb and emit at 600–750 nm and beyond,[39] i.e. significantly red-shifted compared to their equivalent BODIPYs.

*F*-BODIPYs are synthesized from dipyrrins or aza dipyrrins by treatment with a base (triethylamine, DIEA, DBU etc.) and boron trifluoride diethyl etherate (BF$_3$•OEt$_2$) (**Scheme 2**). For meso aryl-substituted BODIPYs, the dipyrrin is made in situ from the reaction of an aldehyde with excess pyrrole under acid conditions and subsequent oxidation with DDQ or p-chloranil as mentioned before (**Scheme 1**). Without being isolated, the dipyrrin is often treated with excess base and boron trifluoride diethyl etherate to give the *F*-BODIPY (**Scheme 2**).
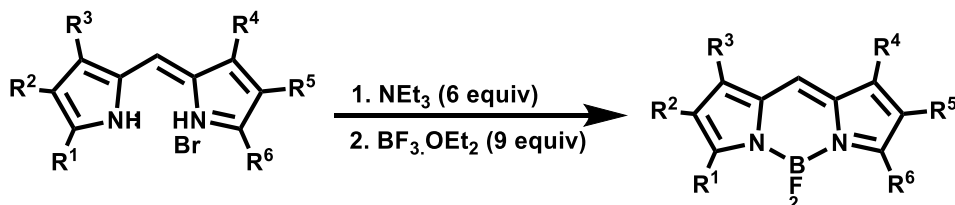


*Scheme 2: General synthetic strategy to F-BODIPYs.*

## 1.4 - Thesis Overview.

Considering the importance of -BF$_2$ complexes of the dipyrrinato and aza dipyrrinato units, economical and versatile access to these constructs is required. This thesis research aims to develop new methodologies for the effective, eco-friendly and cost-effective synthesis of *F*-BODIPYs and aza BODIPYs. Chapter 2 describes attempts to avert the challenges faced in the current synthesis of *F*-BODIPYs by using only 1 equiv of BF$_3$•Et$_2$O in a continuous flow operation. Chapter 3 describes attempts towards a new synthetic route to aza dipyrrins, precursors to aza BODIPYs. The route described is based on the use of acyclic precursors to the aza dipyrrin construct that thus avoids the unstable intermediates encountered in the current synthesis of these compounds. Chapter 4 also describes attempts towards the synthesis of aza dipyrrins, in this case via a new route that takes advantage of the reductive power of tetravalent phosphorus reagents in C−N coupling. Chapter 4 further describes a new route toward the nitrosylation of pyrroles that is fast, effective and avoids the use of acidic conditions. Chapter 5 of this thesis consists of a review[40] reproduced in its entirety and with permission (see Appendix A) from the Royal Society of Chemistry. This published review highlights the various approaches to effecting substitution at the boron atom of BODIPYs. The thesis concludes with Chapter 6 comprising of conclusions from Chapters 2-5.

## Chapter 2: Attempts Towards an Economic Synthesis of *F*-BODIPYS.

## 2.1 – Introduction.

This chapter describes efforts towards the synthesis of *F*-BODIPYs using 1 equiv. of $BF_3 \cdot OEt_2$. For decades, the chemistry of BODIPYs rested with *F*-BODIPYs via chelation of the dipyrrin unit with $-BF_2$. Although new strategies[41,42] have emerged for the synthesis of *F*-BODIPYs, the treatment of a solution of dipyrrin, or its HX salt, with excess base (typically 6 equiv. $NEt_3$ or DIPEA) and $BF_3 \cdot OEt_2$ (typically 9 equiv.) has provided the traditional route to *F*-BODIPYs in generally quite high yields.[43] Despite the obvious excesses of reagents, yields generally decrease upon decreasing the stoichiometry.[44,45] Furthermore, the yields vary significantly with the use of compromised ''anhydrous'' conditions. This is unsurprising, given the anticipated behaviour of $BF_3 \cdot OEt_2$ in the presence of alternative donors, yet to an extent implying complications beyond simple quenching and instead consequent to the complexity of various equilibria involving Lewis acidic boron in the presence of $NEt_3$, $H_2O$, $Et_2O$ and the chelating ligand. With the goal of simplifying synthetic protocol, a general method for *F*-BODIPY synthesis was published,[43] that involves a second aliquot of excess $NEt_3$ and $BF_3 \cdot OEt_2$ in an open-air environment (hydrous conditions).[43] While this synthesis of *F*-BODIPYs removes the need for anhydrous conditions, the use of further reagent excesses is far from ideal. Furthermore, the separation of the $BF_3 \cdot NEt_3$ byproduct from the desired *F*-BODIPY, on scale, is non-trivial.[43] These problems highlight the need for the development of a new synthetic approach to *F*-BODIPYs that is high-yielding and environmentally acceptable. Due to the favourable optical and physical properties inherent to *F*-BODIPYs, a staggering number of these compounds have been synthesized. Conversely, little investigative research has been performed examining the fundamental nature of dipyrrin

complexation of boron. The work reported herein explores the stoichiometric addition of BF$_3$•Et$_2$O to dipyrrins in the absence of a base.

## 2.2 – Synthetic strategy.

Exploration by a previous researcher in the Thompson Lab [46] attempted to synthesize the popular *F*-BODIPY **2.2** from the free base dipyrrin **2.1** using just one equiv of BF$_3$•OEt$_2$, conducting the reaction in the absence of the base revealed that the ligation of the free-base dipyrrin to BF$_3$•OEt$_2$ formally liberates fluoride ion, which presumably binds with the unreacted BF$_3$•OEt$_2$ resulting in 50% ratio of the desired *F*-BODIPY **2.2** and 50% ratio of non BF$_2$ complexed material of the dipyrrin **2.3** (**Scheme 3**).[46] The F$^-$ readily binds with the unreacted BF$_3$•OEt$_2$, generating anionic BF$_4^-$ making BF$_3$•OEt$_2$ unavailable to react with the remaining free-base dipyrrin to make the desired *F*-BODIPY. Although the yield of the *F*-BODIPY is lower than that achieved using some other approaches, these preliminary investigations offer a rationale for the synthetic work described in this chapter. While this new methodology represents a high atom economic use of the BF$_3$•OEt$_2$, the formation of the unwanted HBF$_4$ salt needs to be addressed in order for higher yields of the desired *F*-BODIPY to be attained.
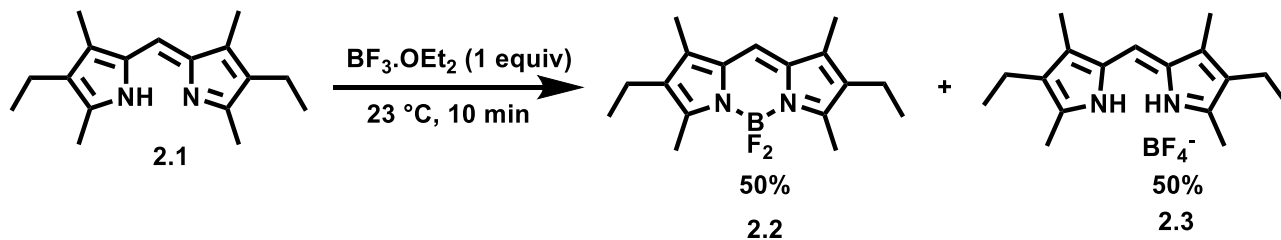


*Scheme 3: Addition of BF$_3$•Et$_2$O (1 equivalent) to free-base 2.1 in toluene.*

Importantly, the stoichiometric by-products of the reaction are a proton and fluoride. There is, therefore, a need to minimize contact between the ejected $F^-$ and the unreacted $BF_3 \cdot OEt_2$. This encouraged the exploration of the use of a continuous flow process for this transformation, to prevent the produced fluoride from interacting with the as-yet unreacted $BF_3 \cdot OEt_2$. This strategy would hopefully minimize the formation of the non-complexed material and thus maximize the yield of the *F*-BODIPY.

## 2.2 - Continuous flow process.

Continuous flow processes involve performing chemical reactions in a tube or a pipe (reactor coil).[47] In a continuous flow set-up, reagents are continuously pumped through different streams, combined through the mixer upon passing into the reactor coil, and the product then continuously collected downstream. There is, therefore, no interaction between the incoming reagents (upstream) and the products formed downstream (**Figure 6**). Having such a setup, introducing the free base dipyrrin **2.1** and $BF_3 \cdot OEt_2$ from different streams, would hopefully of avoid the interaction of the ejected $F^-$ with the unreacted $BF_3$. The use of flow chemistry has been shown to improve control of reaction parameters such as heat and mass transfer, mixing and residence time which leads to improved robustness compared with related batch processes.[48] The overall time a chemical species spends in the reactor coil is equivalent to the total reaction time and is known as the residence time. The residence time can be fluctuated based on the flow rate of reagents and the internal volume of the reactor coil.
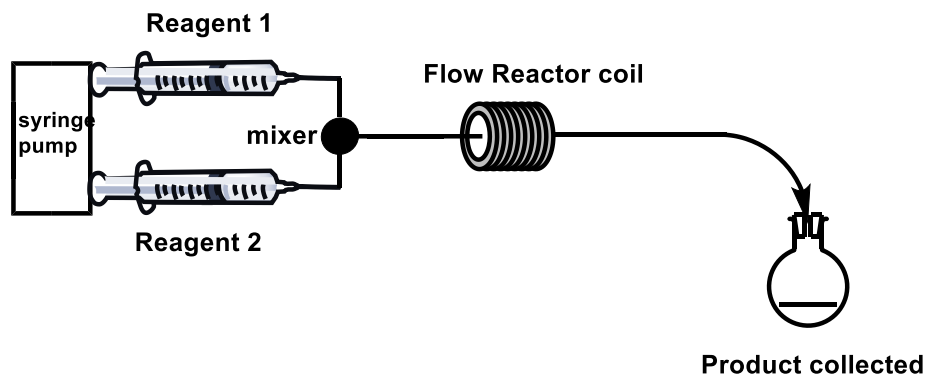
*Figure 6: A generic continuous flow set-up.*

## 2.3 - Project Goals.

This project aims to develop a new methodology for the synthesis of *F*-BODIPYs using a continuous flow setup that uses only one equiv of $BF_3 \cdot OEt_2$ and eliminates, reduces or optimizes the use of a base. As mentioned, in a continuous flow process, reagents are pumped from different streams and then mixed at a common point (T or Y mixer) before moving into the reactor coil where the reaction continues to form products which are then collected downstream (**Figure 7**). The hypothesis, therefore, is that using flow chemistry to pump the free base and the $BF_3 \cdot OEt_2$ through different streams would enable mixing at a common point, formation of the *F*-BODIPY and generation of fluoride and proton by-products. All would be continuously pumped downstream, thus divorcing the (by)products from the incoming $BF_3 \cdot OEt_2$. In this way, it was anticipated that the formation of the $HBF_4$ salt would be averted and, in turn, the yield of the desired *F*-BODIPY increased. This method will ideally increase the availability of $BF_3 \cdot OEt_2$ for reaction with the free-base dipyrrin, thus potentially increasing the yield of the desired *F*-BODIPY product. The use of just one equiv of $BF_3 \cdot OEt_2$ in the absence of $NEt_3$ will avert the formation of Lewis adducts such as $BF_3 \cdot NEt_3$, enhancing purification procedures as well as product yields,

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thereby producing an overall increase in efficiency thus addressing the challenges encountered in the traditional synthesis of *F*-BODIPYs.
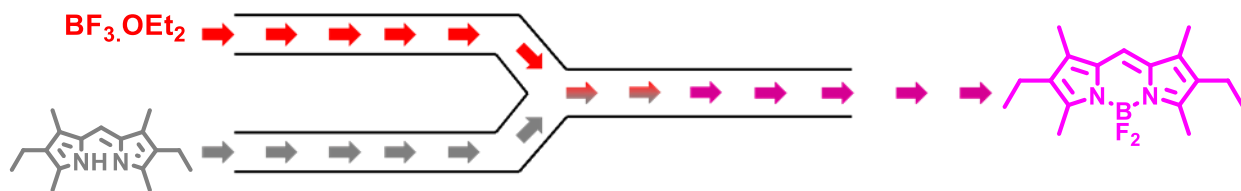


*Figure 7: Stream-flow mechanism in a continuous flow operation.*

## 2.4 - Results and Discussion.

## 2.4.1 - Reaction Optimization and Understanding of Batch Operation.

Prior to performing the synthesis of an *F*-BODIPY using flow chemistry, there was a need to understand the synthesis using the batch method. As a first trial, the published conditions leading to the discovery of this reactivity were repeated.[46] Prior to performing the synthesis of the *F*-BODIPY, free dipyrrin **2.1** was prepared from its HBr salt **2.0** as this is generally a more stable and isolable form of dipyrrins.[49] To prepare the dipyrrin salt **2.0**, pyrrole **2.4** was synthesized first. Following a published procedure, pyrrole **2.4** was prepared via the reaction of ethyl acetoacetate with sodium nitrite in the presence of acetic acid to produce ethyl 2-aminoacetoacetate which then reacted with 2,4-pentanedione to give ethyl 4-acetyl-3,5-dimethylpyrrole-2-carboxylate **2.4** as a white solid after recrystallization from ethyl acetate (**Scheme 4**).[50]

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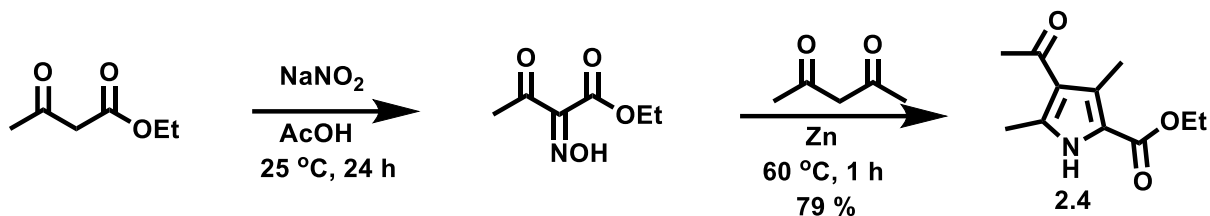
*Scheme 4: Synthesis of pyrrole 2.4.*

Once isolated, pyrrole **2.4** was reduced with BH₃•THF to yield pyrrole **2.5** as a white solid after

purification by column chromatography.[51] Dipyrrin **2.0** was then synthesized in 85% isolated yield

from pyrrole **2.5** via one-pot acid-catalyzed hydrolysis, decarboxylation, and condensation in the

presence of formic acid and HBr (**Scheme 5**).[52]
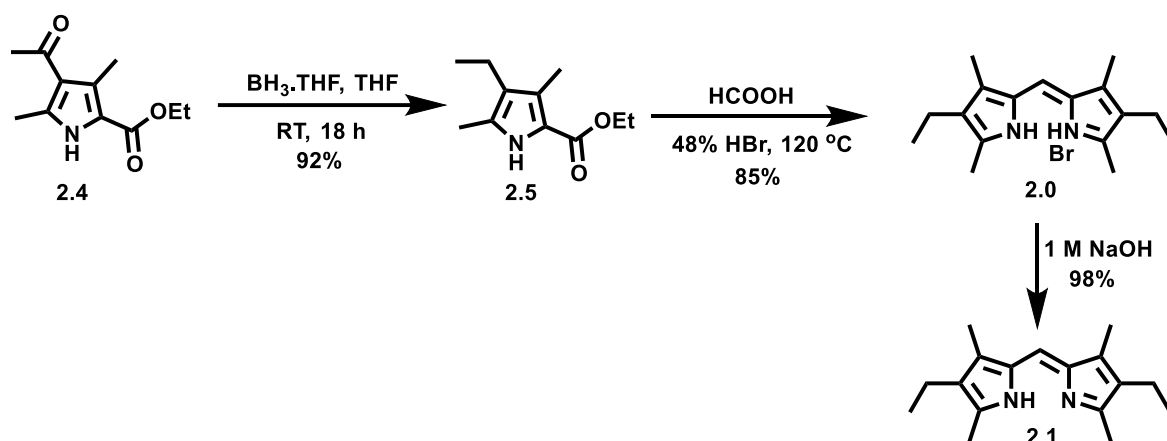


*Scheme 5: Synthesis of free base dipyrrin 2.1.*

For each run, the bromide salt was dissolved in CH₂Cl₂ and washed with aqueous NaOH (1M).

The organic layer was then dried over anhydrous Na₂SO₄ and the solvent was removed to yield

dipyrrin **2.1** as a brown, crystalline solid.[9] With the desired substrate in hand, the formation of the

*F*-BODIPY **2.2** on the bench top (batch mode) was explored by screening solvents, equivalents,

temperature, and reaction time for the addition of 1 equiv of BF₃•OEt₂ to the free-base dipyrrin in

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the absence of base. For each entry, the free base dipyrrin **2.1**, was dissolved in anhydrous toluene in a round bottom flask under a nitrogen atmosphere, and 1 equiv. of $BF_3 \cdot OEt_2$ was added with stirring. After stirring for 10 minutes, the reaction mixture was filtered over celite. The *F*-BODIPY **2.2** was collected first by flushing with hexanes in a 49% yield. The $HBF_4$ dipyrrin salt **2.3**, was then collected in a 46% yield from the celite pad by flushing with $CH_2Cl_2$ followed by removal of the solvent in vacuo.

To minimize operations and to make future exploration more efficient by avoiding the need for work-up and isolation of the reaction products after each trial, ^{1}H NMR spectroscopic analysis of a crude reaction mixture was utilized to determine the amount of each component present in the reaction mixture after the completion of the reaction. To identify and/or quantify all the components of a given mixture, the amounts of specific (known) components were determined using an internal standard. Ideally, the internal standard must be present in a known amount and its spectrum must have at least one well-resolved assignable and integrable peak that does not overlap with other peaks in the spectrum of the sample.[53] Benzene was chosen for this investigation because it is soluble in the NMR solvent $CDCl_3$ and has a ^{1}H NMR resonance separate from those of the analyte being quantified.[54] To determine conversion, upon completion of the reaction according to TLC analysis, the reaction solvent was removed *in vacuo* and the crude material was dissolved in a known volume of deuterated chloroform ($CDCl_3$). A known volume of benzene was added. A known aliquot of the product mixture, now containing benzene, was added to an NMR tube, and then diluted with a known amount of $CDCl_3$ to reach a volume suitable for ^{1}H NMR analysis. Figure 8 compares ^{1}H NMR spectra for the *F*-BODIPY (**2.2**, middle), the $HBF_4$ salt (**2.3**, top) and the crude reaction mixture containing both the *F*-BODIPY and the dipyrrin salt. The crude mixture clearly contains F-BODIPY and non-complexed material. The non-complexed material

presumably consists of an NMR-averaged mixture of starting dipyrrin and dipyrrin salts, including

the $BF_4^-$ salt of the protonated dipyrrin.
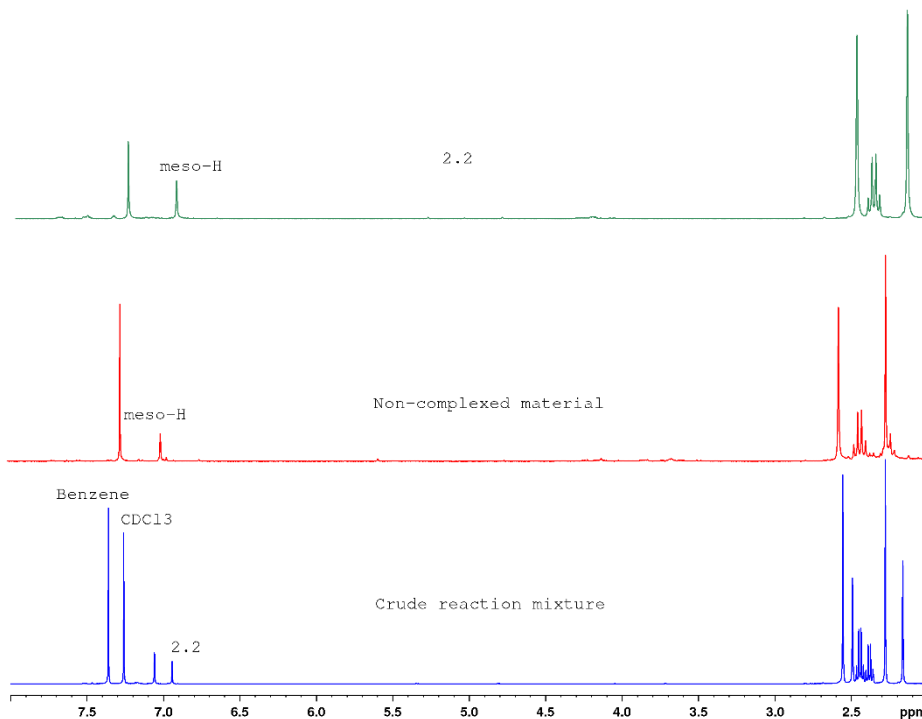


*Figure 8:* $^1$*H-NMR (CDCl₃) spectra of 2.2 (top), Non-complexed material (middle) and a crude mixture (bottom) with benzene as an internal standard.*

By setting the integral of benzene to 6, the integral for the meso-H of the *F*-BODIPY and the non-

complexed material were determined for the crude product mixture. Since a known amount of

benzene had been added, the number of moles of benzene could, therefore, be calculated. The

number of moles of each component present in the crude reaction mixture (analyte, **A**) was then

calculated from the molar amount of internal standard and the molar ratio:

$$nA = nIS \text{ x } rA/IS$$

The mass of the sample does not factor into the calculation because the method relies solely on the

molar ratio of the internal standard to the compound to be determined. Once the number of moles

present at the end of the reaction are known, the percentage conversion for each product could be calculated using the initial number of moles of the free base **2.1** used in the reaction. After several rounds of optimization for the batch synthesis process, it was found that the highest yields and conversions of the desired *F*-BODIPY could be achieved using 3 mL (for 50 mg of free-base dipyrrin) of toluene for 10 minutes at 23°C as shown in (**Table 1, entry 1**).
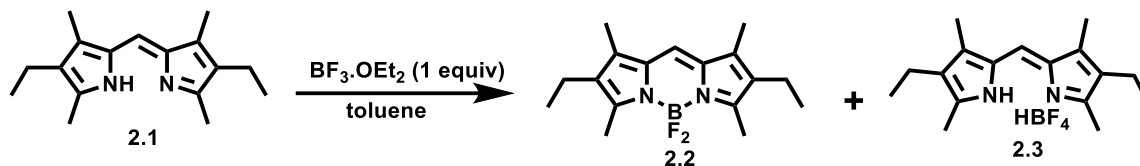
| Entry | Volume (mL | Time (min) | Temp (°C) | 2.2[a] | Non-complexed material[a] |
|-------|-----------|------------|-----------|--------|---------------------------|
| 1 | 3 | 10 | 23 | 49 | 46 |
| 2 | 30 | 60 | 23 | 20 | 65 |
| 3 | 3 | 5 | 150 | 34 | 48 |
| 4 | 30 | 18 h | 23 | 17 | 74 |
| 5 | 3 | 24 h | 23 | 0 | 75 |

*Table 1: Batch process optimization.* [a] **ratio of 2.2 and non-complexed material present in the reaction mixture.** Based on these results, the conditions associated with **entry 1** were selected for exploration in a continuous flow operation for the synthesis of the desired *F*-BODIPY **2.2**.

## 2.4.2 - Reaction Optimization in Flow Operation.

As mentioned before, in a continuous flow setup, reagents are introduced upstream and products are collected downstream. It was hypothesized that introducing the free base **2.1** from one stream

and the $BF_3 \cdot OEt_2$ from another stream would avert the reaction of the components of HF, supposedly produced downstream, from reacting with the unreacted $BF_3$ upstream. To study this concept, a rudimentary continuous flow setup was assembled from affordable and commercially available components to give the reactor shown in (**Figure 9**) harnessing two syringes to one syringe pump to allow the syringes to be pumped at the same rate.
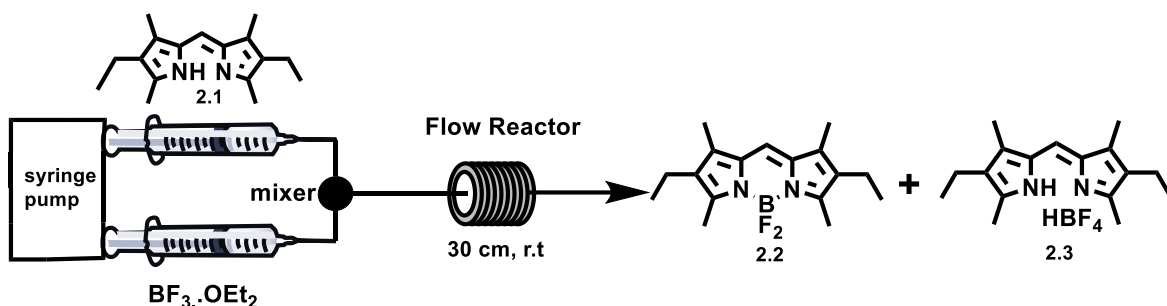


*Figure 9: Lab-scale flow reactor setup.*

To begin the study for the synthesis of *F*-BODIPY **2.2** using a flow method, the equivalents previously investigated in the batch method were used in the continuous flow reactor setup as shown in **Figure 9**. Solutions of starting materials were prepared just like in the batch syntheses i.e., 50 mg of **2.1** was placed in a pear-shaped flask, purged with nitrogen and then 3 mL of anhydrous toluene was added into the flask. In another pear-shaped flask, $BF_3 \cdot OEt_2$ was treated in the same manner. Each solution was loaded, under nitrogen, into a gas-tight syringe. Both syringes were then filled up with nitrogen to keep the reaction mixture anhydrous and ensure that the nitrogen gas pushes the reaction mixture through the flow reactor and thus no solution is left in the tubing. The solutions were pumped by a syringe pump, through a 0.02-inch internal diameter tee mixer into perfluoroalkoxyalkane (PFA) tubing also 0.02-inch internal diameter. The length of the reactor coil determines the length of time (residence time $t_R$) it takes for a fluid to pass through the reactor coil. Changing the flow rate of fluid through the reactor coil, or the length of the coil,

changes the residence time.[55] Since the hypothesis is that the reaction of the free base dipyrrin and BF$_3$•OEt$_2$ is essentially spontaneous, the length of the PFA flow reactor loop was made short and kept constant at 30 cm. To test the hypothesis, the flow rate was varied to adjust the residence time ($t_R$). It was noted that when the two streams came into contact, an immediate colour change from orange to deep red was observed, indicating the formation of the *F*-BODIPY. The reaction mixture was collected in a vial downstream. The reaction was immediately quenched upon exit using a solution of saturated NaHCO$_3$. The solvent was removed in *vacuo* and the reaction mixture was placed under vacuum to remove residual solvent. To determine the reaction conversion, the crude reaction mixture was evaluated, just like for the batch reaction described above, using an internal standard and ^{1}H NMR spectroscopy. A total of five runs were performed and the results are shown in **Table 2**.

| Entry | Flow Rate/mLmin$^{-1}$ | $t_R$/sec | T/°C | 2.2[a] | Non-complexed material[a] |
|:---:|:---:|:---:|:---:|:---:|:---:|
| 1 | 0.2 | 18.3 | 0 | 29 | 71 |
| 2 | 0.5 | 7.31 | 0 | 41 | 59 |
| 3 | 1.0 | 3.65 | 0 | 39 | 61 |
| 4 | 2.0 | 1.83 | 0 | 40 | 60 |
| 5 | 5.0 | 0.73 | 0 | 24 | 76 |

*Table 2: Optimization of the continuous flow process with a reactor coil of 30 cm. [a]ratio of 2.2 vs non-complexed material.*

The residence time ($t_R$) was calculated using the equation:

**Residence time = Reactor Volume/ Flow Rate**

And Reactor Volume = cross section X Length

$$= \pi r^2 L$$
$$= 3.1416(0.0254 \text{ cm})^2 \text{ X } 30 \text{ cm}$$
$$= 0.061 \text{ cm}^3$$

This reactor volume was constant for this investigation since the reactor length was kept constant at 30 cm. The residence time for each flow rate was calculated using the above equation. The flow rate was plotted against the percentage conversion for both the *F*-BODIPY **2.2** and the non-complexed material. It was observed that generally the complexation was always limited, suggesting that the $BF_3 \cdot OEt_2$ has a greater affinity for the $F^-$ produced in situ than for the free base dipyrrin coming through from a different stream. As the flow rate increases the residence time decreases and so does the yield of both the *F*-BODIPY. Furthermore, the 5 mL/min flow rate was too fast i.e. $t_R$ was too short to achieve optimal conversion to the desired *F*-BODIPY, whilst the 0.5 mL/min (7.31-sec) gave the greatest conversion. Further decreasing the flow rate to 0.2 mL/min, thus increasing the residence time to 18.3 sec, resulted in a decrease in conversion to the desired *F*-BODIPY (**Figure 10**): this can be attributed to less efficient mixing when using lower flow rates.[56]
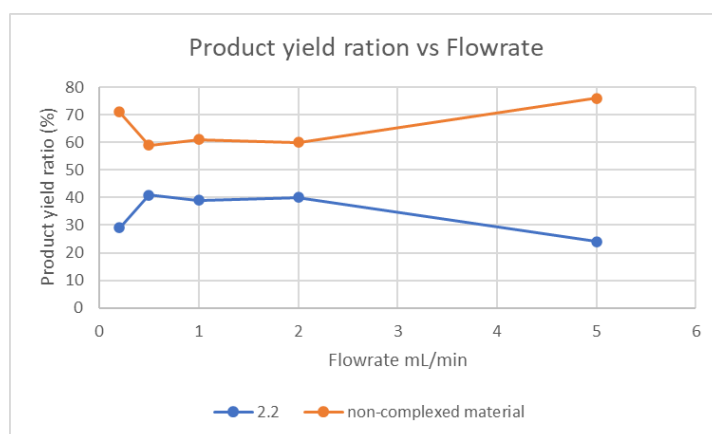
*Figure 10: Relationship between flow rate and product yield.*

The results confirmed that the reaction is rapid as shown by the colour change of the free base dipyrrin upon contact with $BF_3 \cdot OEt_2$. Both the results obtained in continuous flow and batch reactions did not vary significantly, with the formation of the non-complexed material limiting the yields of F-BODIPY. Also, when operating a continuous flow system using highly air-sensitive reagents, it should be noted that PFA tubing allows slow permeation of air and moisture, which could lead to poor yields.[55] These disappointing results encouraged us to return to exploring the reaction in batch in the presence of HF scavengers to attempt to mop up the proton and fluoride produced in situ.

## 2.5 - Hydrogen fluoride scavengers.

It was speculated that the moderate yield of the *F*-BODIPY **2.2** in both the batch and flow setups might be attributed to the HF reacting with unreacted $BF_3 \cdot OEt_2$ to form $HBF_4$ and thus the $HBF_4$ dipyrrin salt. The continuous flow setup was ineffective at preventing $HBF_4$ dipyrrin salt formation, and therefore the addition of a scavenger to the reaction mixture to mop up the proton and fluoride formally produced in situ was envisioned. HF scavengers[57] such as bases like $Na_2CO_3$, $K_2CO_3$ and $CaCO_3$ have been reported to be effective in mopping up HF in reactions where the presence of HF could potentially interfere with the formation of the desired products. Furthermore, mopping up the HF produced will serve to drive the reaction equilibrium towards the product, and thus increase yields of the desired product.

Therefore, a quick and simple potential solution to avert the formation of $HBF_4$ salt was to add an organic or inorganic base (>1.0 equiv) to the reaction mixture to neutralize HF. Inorganic bases ($K_2CO_3$,[58] $Na_2CO_3$, $CaCO_3$[59]) were chosen as the first scavengers with hopes of producing an inorganic base-HF salt, potentially beneficial in that this approach to scavenge HF offered a

possible non-chromatographic approach to purify **2.2** from an inorganic base-HF salt. This is based

on reports that solubilities of alkali-metal are very limited in organic solvents [60] The effectiveness

of these scavengers, in the reaction of **2.1** with $BF_3 \cdot OEt_2$, was thus investigated. To this end, 1.5

equiv of each scavenger was added to a stirring solution of free base **2.1**. The mixture was then

treated with 1 equiv $BF_3 \cdot OEt_2$ in a dropwise manner. In each run, the heterogeneous reaction

mixture reached completion after 10 minutes, as monitored by TLC. After completion of the

reaction, the reaction mixture was filtered, and the solvent was removed *in vacuo*. The resulting

crude reaction mixture was dissolved in chloroform and the ${}^1$H NMR spectrum recorded. As

before, the ratio of integration of the meso-H peaks was used as a measure of conversion for the

products shown in **Table 3** (entry 1-4). In all these runs, the yield of the non-complexed material

was higher than that of the desired BODIPY **2.2**. This shows that the inorganic bases were

unsuccessful at scavenging such as to improve desired yields.
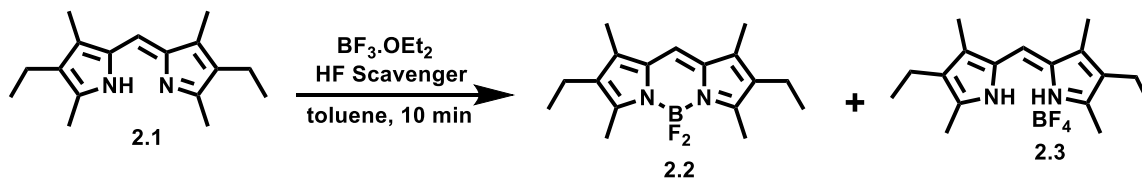


| Entry | HF Scavenger | 2.2 | Non-complexed material |
|---|---|---|---|
| 1 | $K_2CO_3$ | 28 | 72 |
| 2 | $NaCO_3$ | 30 | 70 |
| 3 | $CaCO_3$ | 27 | 73 |
| 4 | $CaCl_2$ | 0 | 100 |
| 5 | Calcium 2-ethylhexanoate | 0 | 100 |
| 6[a] | DEATMS | 4 | 79 |

| Entry | HF Scavenger | 2.2 | Non-complexed material |
|-------|--------------|-----|------------------------|
| 7 | HMDS | 28 | 72 |
| 8 | TMSPa | 39 | 0 |
| 9 | 2,6-Di-tert-butyl-4-methyl-pyridine | 31 | 69 |
| 10 | DABCO | Trace | 100 |
| 11 | DBU | Trace | 100 |
| 12 | *N,N*-dimethyl-1-naphthylamine | 0 | 100 |
| 13[a] | Proton sponge | 34 | 56 |
| 14 | BH$_3$•THF | 35 | 65 |
| 15 | Triethylborane | 23 | 77 |
| 16 | Triphenylborane | 28 | 72 |
| 17 | 2,6-Lutidine | 43 | 57 |

***Table 3: Synthesis of F-BODIPY in the presence of HF scavengers, [a]Isolated yield***

Attention was thus turned to the use of organic HF scavengers. In lithium-ion battery research, HF is notorious for causing the electrochemical decomposition of electrolytes by attacking cathode materials that contain transition metal components affording metal-fluoride species.[61,62] This not only destroys the cathode structure but also seriously impedes the electrochemical reaction of the anode.[63,64] To improve lifetime and decrease impedance build-up in lithium-ion batteries, several additives have been successfully introduced to scavenge HF and avoid undesired surface reactions. In light of this, attention was thus turned to the additives that have been shown to be effective in this regard. *N,N*-diethylamino trimethylsilane (DEATMS) and hexamethyldisilazane (HMDS) have the ability to form a strong Si-N bond which effects the H$_2$O/HF-scavenging.[65,66] The basicity of the nitrogen atom and the fluorophilicity of the Si atom work in tandem to scavenge HF.[67] It

was anticipated that this matched chemical reactivity between the Si-N functional group and the HF species would be effective for reducing the HF concentration in the reaction of **2.1** and BF$_3$•OEt$_2$. Tris(trimethylsilyl)phosphate (TMSPa)[68] has also been used successfully in the scavenging of HF in Li batteries, with this ability attributed to the -SiMe$_3$ moieties. In all the runs performed, when the free-base **2.1** was treated with BF$_3$•OEt$_2$ in the presence of these HF scavenging additives, the formation of the desired *F*-BODIPY **2.2** occured in trace amounts (**Table 3, entry 6 to 9**). These disappointing results encouraged the exploration of proton trapping approaches.

Triethylamine and DIPEA are nucleophilic bases used in the traditional synthesis of BODIPYs. Attention was therefore turned to the use of non-nucleophilic bases that are usually employed in proton scavenging with hopes of mopping up proton but not interfering with other functions in the reaction.[69] It was postulated that sterically hindered bases like DABCO, DBU, *N,N*-dimethyl-1-naphthylamine could be employed to trap the proton and suppress, if not eliminate, the reaction of HF with BF$_3$ to minimize the formation of the undesired non-complexed material. Thus, the stage was set to commence experimentation with proton traps, to determine whether the formation of BODIPY **2.2** was possible in the presence of sterically hindered bases. With the above thoughts, the free-base dipyrrin was treated with BF$_3$•OEt$_2$ in the presence of the hindered bases. Unfortunately, only trace amounts of *F*-BODIPY were formed in the presence of the hindered bases, as confirmed by TLC (**Table 3, entries 10 to 13**). It was postulated that the presence of the bulky bases might also hinder the BF$_3$•OEt$_2$ from reacting with the free base and hence no product was formed. In the case of the proton sponge, 34% of the desired *F*-BODIPY was isolated, which is less than the yield obtained in the absence of HF scavengers. Attention was turned to an alternative approach.

According to previous studies,[70] the formation of *F*-BODIPY is initiated by the donor-acceptor interaction of the lone electron pair of the pyrroline nitrogen atom of the free base and the vacant orbital of the boron atom in $BF_3$, followed by the formation of a hydrogen bond between the hydrogen atom of the NH group of the free base and the nearest fluorine atom in $BF_3$ adduct. It is this bonding that promotes the formal elimination of HF in the last step of the synthesis of BODIPY. It was therefore speculated that having another boron source in the reaction mixture, which could scavenge the ejected fluoride, could potentially prevent the formation of non-complexed material and possibly increase the yield of the desired BODIPY **2.2**. In light of this, the use of boranes was explored **(entry 14 to entry 16)**. The free base was reacted with the $BF_3 \cdot OEt_2$ in the presence of each borane but formation of  the desired product **2.2** was not enhanced. Given the lack of success thus far, attention was turned to varying solvents and other reaction conditions for the F-BODIPY synthesis utilizing 1 equiv. of $BF_3 \cdot OEt_2$ in the absence of a base.


## 2.6 - Effect of solvent and temperature on the reaction.

To gauge the effect of the reaction solvent on the synthesis of BODIPY using 1 equiv of $BF_3 \cdot OEt_2$, the reaction according to **Table 1** was performed multiple times with variations in solvents and temperature in pursuit of securing the best yielding conditions. To this end, the free base **2.1** was dissolved in the anhydrous solvent and the solution was treated with 1 equiv of $BF_3 \cdot OEt_2$ for the allocated reaction time. The reaction solvent was removed *in vacuo* and the crude residue was analyzed using $^1$H NMR spectroscopy in the presence of benzene as an internal standard. The *F*-BODIPY was formed in trace amounts in most of the solvents. However, 50% conversion was observed for the reaction conducted in toluene. However, when toluene was used, the TLC before

concentration in vacuo had a vibrant red/orange spot with a green hue that is typical for *F*-BODIPYs but after concentration in vacuo, the TLC analysis reviewed a much paler spot at the same $r_f$ value. We speculated that because the toluene has a very high boiling point, the product was decomposing to the non-complexed material during evaporation of the solvent in vacuo. The suitability of other solvents and solvent mixtures for this reaction were thus explored (**Table 4**).

| Entry | Solvent/s | Volume/mL | Time/min | Temp. | 2.2[a] | Non-complexed material[a] |
|:---:|:---:|:---:|:---:|:---:|:---:|:---:|
| 1 | $CH_2Cl_2$ | 3 | 10 | rt | 21 | 79 |
| 2 | $Et_2O$ | 3 | 10 | rt | 0 | 100 |
| 3 | $CH_3CN$ | 3 | 10 | rt | 0 | 100 |
| 4 | THF | 3 | 10 | rt | 0 | 100 |
| 5 | hexanes | 3 | 10 | 30 | 33 | 67 |
| 6 | $CH_2Cl_2$:THF | 5:1 | 3 | 30 | trace | 88 |
| 7 | $CH_2Cl_2$:hexanes | 5:1 | 3 | 30 | **69** | **31** |
| 8 | toluene:$CH_2Cl_2$ | 5:1 | 60 | 30 | 25 | 75 |

*Table 4: Screening of different reaction conditions for the synthesis of F-BODIPYs. [a]ratio.*

For the various reaction conditions screened, the use of hexanes (**Table 4, entry 5**) resulted in a, enhanced conversion, even though the free base **2.1** did not fully dissolve but was suspended in

the hexanes. This result was encouraging, hence it was speculated that the complete dissolution of the free base **2.1** would increase conversion to the desired *F*-BODIPY **2.2**. The free base (50 mg) was therefore dissolved in 1 mL of anhydrous $CH_2Cl_2$. Anhydrous hexanes (5 mL) was then added to this solution (**Table 4, entry 7**). Treatment of the reaction mixture with 1 equiv. of $BF_3 \cdot OEt_2$ gratifyingly resulted in the formation of the desired product in 69% yield and these conditions showed promise for the general synthesis of *F*-BODIPYs. To demonstrate the utility of these newly established conditions, a variety of *F*-BODIPYs with various substitution patterns were synthesized. The starting dipyrrins were synthesized as HBr salts and then deprotonated to their free bases by washing with aq. NaOH. The dipyrrin substituted at the meso position with the toluyl substituent was isolated as its free base, as meso-aryl-substituted dipyrrins are generally isolated as such. In each case, the free base was subsequently dissolved in 1 mL of anhydrous $CH_2Cl_2$, and 5 mL of hexanes was then added. In each case, the reaction mixture was treated with 1 equiv. of $BF_3 \cdot OEt_2$ and stirred for 1-10 minutes, depending on the substrate. After completion of the reaction, as confirmed by TLC, the reaction mixture was then quenched with water and extracted with $CH_2Cl_2$. The organic layers were combined and dried with $Na_2SO_4$, concentrated in vacuo and the crude reaction mixture was dissolved in $CH_2Cl_2$ followed by filtration through a pad of silica to afford the desired *F*-BODIPY. After the BODIPY had been collected, the silica was then washed with ethyl acetate to afford the $HBF_4$ salt after removal of solvent from the resulting filtrate.
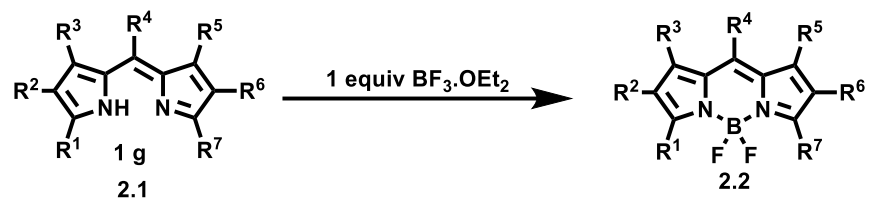
| Entry | BODIPY Product | Yield |
|-------|---------------|-------|
| 1 | | 51 |
| 2 | | 39, 58[a] |
| 3 | | 21 |
| 4 | | 25 |
| 5 | | 38 |

**Table 5: Synthesis of F-BODIPYs using 1 equiv BF₃.OEt₂, *[a]In the presence of 1 equiv NEt₃.***

The new method was tolerated by the alkyl-substituted substrates, for which $F$-BODIPYs were isolated in 51% and 39% yield, and the toluyl substituted dipyrrin **(entry 5)** which was isolated in 38% yield. However, dipyrrins containing alkanoate **(entry 3)** and conjugate ester **(entry 4)** functionalities were isolated in only 21% and 25 % yield, respectively. Although the yields were lower than for the traditional $F$-BODIPYs synthesis (9 equiv of $BF_3$•$OEt_2$ and 6 equiv of $NEt_3$) obtaining 20-50% yield of the product with just 1 equiv of $BF_3$ in the absence of base, accompanied by a facile purification and isolation of the free base starting material as its $HBF_4$ salt, is a satisfactory result. On a small scale, the traditional methodology for the synthesis of $F$-BODIPY and the hydrous method established in the Thompson lab[43] poses no problems as the workup and purification are somewhat simple. However, on a larger scale, above 1 g, the unwanted $BF_3$•$NEt_3$ adduct is formed in significant amounts, particularly considering the excess reagents used. As such, the workup becomes more difficult as complex emulsions are usually witnessed.[71] Since the synthesis with 1 equiv of $BF_3$•$OEt_2$ does not include the use of a base, no unwanted adduct would be formed and thus the workup would be relatively simple and thereby making it a method of choice for larger-scale syntheses. To this end, the three methods were compared on a 1 g scale, making note of reaction time, the total amount of solvent required for workup and the total amount of waste solvent during purification. The use of 1 equiv of $BF_3$•$OEt_2$ in the absence of base proved to be advantageous as the reaction only took up to 10 minutes and the workup was also fast as no emulsions were observed – unlike for the other methods where mild emulsions were observed. Overall waste was the least for the method involving 1 equiv $BF_3$•$OEt_2$ in toluene, and the absence of base or scavenger, because purification only required filtration through a pad of silica, eluting with $CH_2Cl_2$ to provide the $F$-BODIPY product followed by elution with hexanes to obtain the $HBF_4$ dipyrrin salt.

| Method | Total reaction time | | | Total waste | | |
| | Reaction/ hr | Work up/ min | Purification/ min | Work up/mL | Purification/ mL | 2.2 yield |
| --- | --- | --- | --- | --- | --- | --- |
| Traditional method (anhydrous)[30] | 2.5 | 26 | 35 | 1440 | 358 | 53[a] |
| Hydrous method[43] | 2.5 | 37 | 58 | 1730 | 620 | 86[b] |
| 1 equiv method (developed herein) | 10 min | 23 | 19 | 1320 | 234 | 30[c] |

*[a]NEt₃, CH₂Cl₂, N₂ atmosphere, [b]NEt₃, CH₂Cl₂, air, [c]CH₂Cl₂:Hexanes (1:5), N₂ atmosphere*

*Table 6: Comparison of the synthesis of F-BODIPY using 9 equiv BF₃.OEt₂ and 6 equiv NEt₃ (anhydrous), 18 equiv BF₃•OEt₂ and 12 equiv NEt₃ (hydrous method) and 1 equiv BF₃.OEt₂ (1 equiv method).*

## 2.7 - Conclusion.

We have investigated the synthesis of *F*-BODIPY in a continuous flow operation using 1 equiv of $BF_3 \cdot OEt_2$ in the absence of a base. The results confirmed that the reaction of the free-base dipyrrin and $BF_3 \cdot OEt_2$ is rapid at the point of mixing. Indeed, by comparing results obtained in batch to those obtained in flow, it was found that there was no significant change in the yields obtained. This suggests that the continuous flow operation failed to eliminate the interaction between the HF produced in situ, with the unreacted $BF_3 \cdot OEt_2$ to form $BF_4^-$ and thus the dipyrrin $HBF_4$ salt. We then introduced HF scavengers in batch mode with the hope of counteracting the formation of the

HBF$_4$ salt and thus the desired *F*-BODIPY would be generated in higher yields. To this end, the use of a variety of additives was explored but none resulted in the generation of the desired product in high yields. Some additives, like TMSPa, resulted in the elimination of the HBF$_4$ salt but the yield of the BODIPY did not change. We then studied the reaction of the free-base dipyrrin and 1 equiv of BF$_3$•OEt$_2$ in the presence of various solvents and at various temperatures to discover that the reaction performed moderately well in 1:5 CH$_2$Cl$_2$: hexanes at 30 °C. This was however only optimal for the alkyl-substituted *F*-BODIPYs, which were formed in moderate yields. A comparison of this new method with the traditional anhydrous method[30] and the hydrous method[43] on a 1 g scale of free base **2.1** showed that this new method is advantageous from an economic point of view as it requires only 1 equiv of BF$_3$ and reduced volume of solvent for purification. This method only takes 10 min for the reaction to reach completion, unlike for the other methodologies which take 2.5 and 3 hours.[43]

## 2.8 – Experimental.

All chemicals were used as received unless otherwise indicated. All NMR spectra were recorded using 500 MHz or 300 MHz spectrometers. [1]H chemical shifts are reported in ppm relative to tetramethylsilane using chloroform solvent residual at δ = 7.26 ppm as an internal standard. [13] C spectra were recorded using UDEFT pulse sequence with chemical shifts reported in ppm referenced to CDCl$_3$ resonance at δ = 77.2 ppm. Splitting patterns are indicated as follows: br, broad; s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet. All coupling constants (*J*) are reported in Hertz (Hz). High-resolution mass spectra were obtained using TOFMS experiments operating in both positive and negative modes. Column chromatography, as indicated, was

performed using 230-400 mesh ultra-pure silica. Pyrrole **2.4**,[50] **2.5**,[51] and dipyrrin **2.0**,[52] **2.1**,[9] were prepared according to literature procedures.

## General Procedure for the synthesis of *F*-BODIPY with 1 equiv. of BF$_3$•OEt$_2$ in a batch process (GP1).

The free-base dipyrrin **2.1** (50 mg, 0.20 mmol) was dissolved in anhydrous toluene (3 mL) under a nitrogen atmosphere and BF$_3$•OEt$_2$ (25 μL, 0.20 mmol) was added to the solution. The reaction mixture was then stirred for 10 min at room temperature. The crude reaction mixture was quenched by the addition of H$_2$O, followed by an extraction with CH$_2$Cl$_2$ (30 mL, x 3). The combined organic fractions were then washed with aqueous NaHCO$_3$ (x 3), resulting in the dissolution of the crude product in the organic layer which was then dried over Na$_2$SO$_4$ and concentrated in vacuo. Hexane was added to the concentrated crude product to form a suspension which was then filtered over a pad of celite. Rinsing with excess hexanes and concentration of the resulting fraction in vacuo afforded the *F*-BODIPY **2.2** as a deep red solid. The celite pad was re-washed with excess CH$_2$Cl$_2$ and the resulting fraction was concentrated in vacuo to isolate the HBF4 dipyrrin salt **2.3** as a bright orange solid.

## General Procedure for the synthesis of *F*-BODIPY with 1 eq. of BF$_3$·OEt$_2$ in a continuous flow process (GP2).

The free-base dipyrrin **2.1** (50 mg, 0.20 mmol) was dissolved in anhydrous CH$_2$Cl$_2$ (1.5 mL) under a nitrogen atmosphere in a pear-shaped bottom flask. In another pear-shaped flask, BF$_3$•OEt$_2$ (25 μL, 0.20 mmol) was dissolved in anhydrous CH$_2$Cl$_2$ (1.5 mL) under a nitrogen atmosphere. The

solutions were each loaded into 3 mL syringes and nitrogen gas was then used to fill the extra volume of the syringe to keep the mixture under a nitrogen gas environment. This was done by pulling some of the nitrogen gas from the bottle of anhydrous solvent which was placed under a nitrogen gas environment. Both reagents were then pumped, at the same flow rate, and combined at a T-piece mixer. The combined stream was directed to a 30 cm (0.06 mL) PFA flow reactor coil at room temperature. The crude reaction mixture was quenched in $H_2O$ followed by an extraction with $CH_2Cl_2$ (30 mL, x 3). The combined organic fractions were then washed with aqueous $NaHCO_3$ (x 3), resulting in the dissolution of the crude product in the organic layer which was then dried over $Na_2SO_4$ and concentrated *in vacuo*. The resulting residue was dissolved in $CDCl_3$ (4 mL), and benzene (4 mL) was added, with stirring. An aliquot (200 μL) of this solution was added to an NMR sample tube and then diluted with $CDCl_3$ (400 μL). A $^1H$ NMR spectrum of the sample was collected, and the NMR-based yield was determined.

## Chapter 3 – Towards an Improved Synthesis of Aza Dipyrrins.

## 3.1 - Introduction.

As mentioned in Chapter 2, one essential requirement for fluorescence bioimaging/detection is a high-performance organic material (fluorophore) with good absorption and emission that is located in the red to deep red region of the electromagnetic spectrum (near-infra-red, NIR, 650–900 nm). When light enters body tissues it is either scattered or absorbed, and the extent of both processes depends on tissue type and wavelength of the light. The light absorption characteristics of tissues decrease with increasing wavelength, hence longer wavelengths of light penetrate more efficiently through tissue.[72,73] The shorter wavelengths (<650 nm) have less tissue penetration and are mostly absorbed, resulting in a variety of physiological damage. Therefore, ideal tissue permeability of light occurs within the wavelength range of approximately 650-900 nm, known as the "phototherapeutic window".[74] A good fluorophore should preferably have strong absorbance in this phototherapeutic window, where light penetration into the body tissue is maximized. Therefore for bio-imaging in living organisms, the BODIPY framework offers significant potential.[75,76,77,78] Though BODIPY dyes are promising for use in bio-imaging, the absorption maxima of conventional BODIPY dyes are generally below 700 nm. For BODIPY dyes to be more useful as fluorescent probes and sensors in bioapplications, their absorption should lie in the near-infrared region (650-900 nm).[79,80] In recent years, studies regarding the BODIPY family have enabled several promising strategies to efficiently push the absorption and emission of BODIPYs to the far-red and NIR regions. One such strategy involves increasing the extent of conjugation of the BODIPY core. Generally, increasing molecular conjugation enhances $\pi$-electron delocalization, which facilitates a shift of absorption and emission maxima into the NIR

regions.[81,82] An alternative strategy to designing systems capable of absorbing in the NIR region involves the use of aza BODIPYs. Aza BODIPYs are a class of BODIPYs that derives from conventional BODIPYs by replacement of the *meso*-carbon with a nitrogen atom (N). Incorporation of the *meso*-nitrogen atom in aza BODIPYs results in a LUMO that is significantly stabilized compared to that in BODIPYs.[83,39]
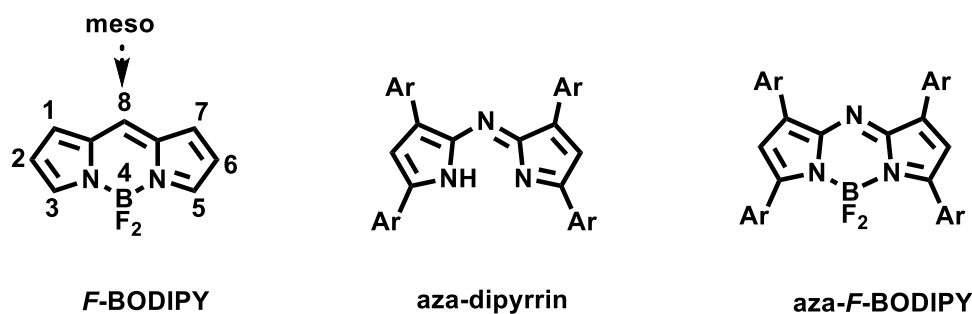


*Figure 11: Structures of F-BODIPY, aza dipyrrin and aza F-BODIPY cores.*

The HOMO–LUMO energy gap in aza BODIPYs is significantly smaller than that in BODIPYs, which leads to absorption and emission at longer wavelengths. Indeed, aza BODIPYs generally absorb and emit bathochromically, with a significant increase of about 100 nm, compared to the parent BODIPY bearing an equivalent substitution pattern. Modest fluorescence quantum yields[84] and excellent photostability generally accompany these desirable properties of aza BODIPYs.[33,85,86,87,13] Consequently, the aza BODIPY framework is promising for use in fluorescence bioimaging. Furthermore, the long absorption wavelengths and good photostability make aza BODIPYs suitable for use as sensitizers for photodynamic therapy (PDT) applications.[88] Photovoltaic applications also benefit from long wavelength absorbance, allowing for harvesting a large portion of solar energy.[89]

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## 3.2 - Synthesis of aza BODIPYs.

Applications utilizing aza BODIPYs rely on the availability of aza dipyrrins, which were first reported in 1943 as unexpected deep blue, coloured products.[89] There are two classes of aza dipyrrins, differing in their substitution patterns about the pyrrolic rings. The most common class features a tetra-aryl substitution pattern. The synthesis of aza dipyrrins bearing a tetra-aryl substitution pattern begins with the aldol condensation of benzaldehydes and acetophenones to form the chalcones **3.1** (**Scheme 6**).[90] Subsequent 1,4-Michael addition of nitromethane to chalcones yields the nitrobutanone derivatives **3.2**, which are the common precursors of the two known routes to this class of aza dipyrrins. The first route involves the condensation of the nitrobutanone derivatives **3.2** in the presence of an excess of an ammonium source (up to 40 equiv), heated at reflux temperature in ethanol for reaction times of up to 48 h resulting in the formation of the aza dipyrrin **3.3a** (**Scheme 6, Route I**). Generally, the aza dipyrrin precipitates from the reaction mixture and can be easily collected by filtration, or purified by chromatography. This route results in symmetrical aza dipyrrins with yields usually around 20-50%.[90]
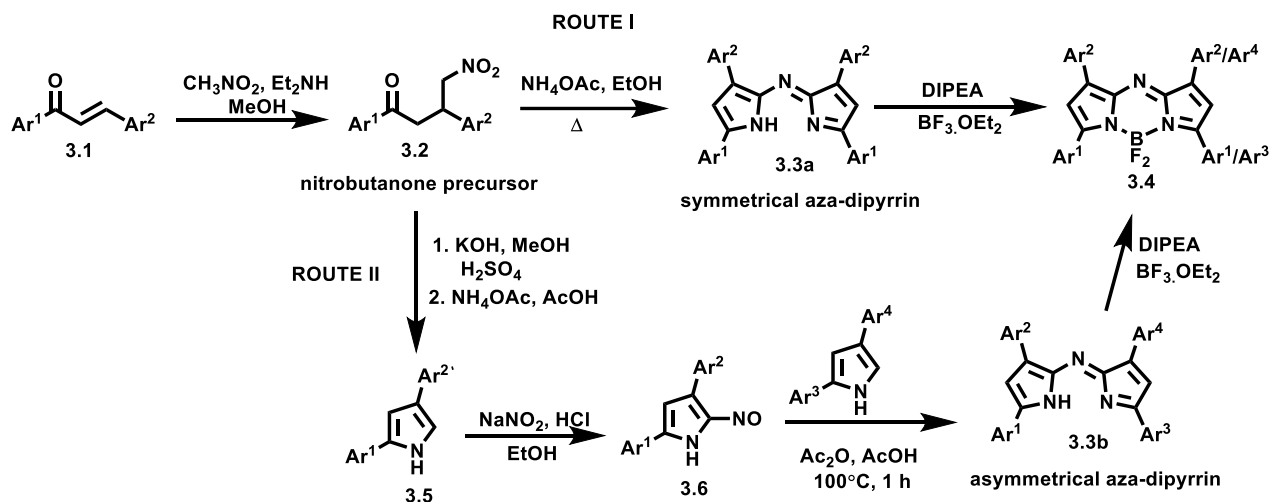


Scheme 6: Synthesis of aza dipyrrins 3.3a, 33b and aza BODIPY 3.4.

To accommodate different functional groups in the aza dipyrrin framework, for fine-tuning both spectroscopic and solubility properties of the compounds and allowing the introduction of specific functional groups for molecular sensors and bioconjugated analogs, the asymmetric route is often utilized (**Scheme 6, Route II**).[91] In this approach, 2,4-diaryl pyrrole **3.5** is synthesized first from the same nitrobutanone precursor **3.2,** followed by a subsequent reaction with sodium nitrite in the presence of ethanolic HCl to form nitroso pyrroles **3.6** (**Scheme 6**). These conditions do not allow alkyl-substituted pyrroles to be nitrosylated. Cross-condensation of pyrroles **3.5** and nitroso pyrroles **3.6**, under elevated temperature in acetic acid and acetic anhydride, results in the formation of the asymmetric aza dipyrrin **3.3b**. Prefunctionalization of the pyrroles offers access to both symmetrical and non-symmetrical aza dipyrrins in moderate to high yields.[91] The popular boron derivatives aza BODIPYs (**3.4**) can be synthesized from **3.3a** and **3.3b**, using boron trifluoride etherate in the presence of a base.[89] The two routes, I and II, have been widely employed to prepare tetra-aryl aza BODIPYs.

Another class of the aza dipyrrin family is the β,β- (**3.7**) or β,α- (**3.8**) ring-fused annulated framework as shown in **Figure 12**. This type of aza dipyrrin framework absorbs further bathochromically compared to the tetra-aryl aza dipyrrins shown in **Scheme 6**.[81] This is due to the higher coplanarity and higher rigidity, causing enhanced conjugation.[13]
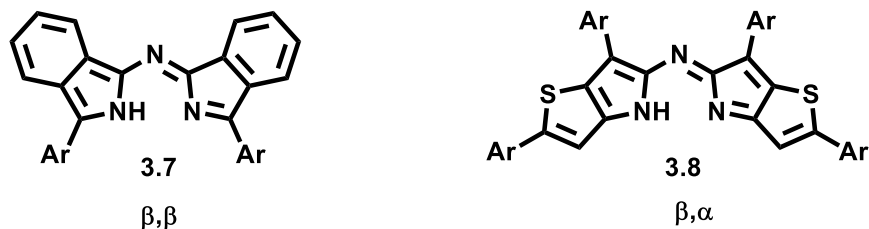
*Figure 12: Conformationally restricted β,β aza dipyrrins 3.7 (left) and β,α aza dipyrrin 3.8 (right).*

Synthesis of the annulated aza dipyrrins **3.7** involves the addition of aryl Grignard reagents to dinitriles (phthalonitriles) **3.9** (**Scheme 7, A**),[92] followed by the addition of excess aqueous ammonium chloride. This route is inefficient in most cases, leaving starting materials unconsumed, observation of complex mixtures of by-products, and low aza dipyrrin yields.[93] An adaptation of the approach involving condensation of an α-free pyrrole and a nitroso pyrrole has been reported for producing conformationally restricted aza dipyrrins,[84] e.g. symmetric aza dipyrrin **3.12** and asymmetric aza dipyrrin **3.14** (**Scheme 7**, **B** and **C**). For the synthesis of the symmetric aza dipyrrin **3.12**, a one-pot reaction of the aryl-constrained pyrrole **3.11** with 0.5 eq of $NaNO_2$ in acidic media is utilized.[90] In this approach (**Scheme 7, B**), half of the pyrrole **3.11** is converted, under acidic conditions, to the nitrosopyrrole in situ, and then immediately condenses with the original pyrrole to yield the aza dipyrrin **3.12**. On the contrary, the asymmetric synthesis of aza dipyrrin **3.14** (**Scheme 7, C**), involves first the generation and isolation of nitrosopyrrole **3.13**, followed by the addition of a second pyrrole bearing different substituents.[90]
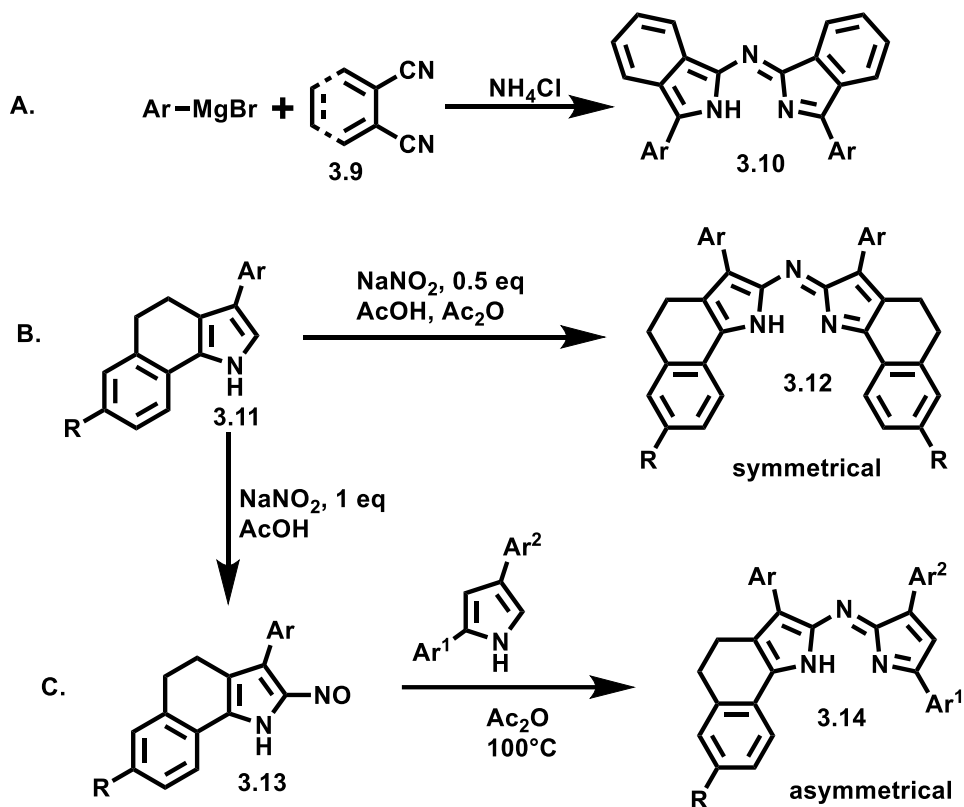
*Scheme 7: Synthesis of conformationally restricted aza dipyrrins 3.10, 3.12 and 3.14.*

Despite the growing importance of aza BODIPYs, all the synthetic methods to the parent aza dipyrrins only support arylated systems.[94] Unfortunately, the presence of numerous aromatic rings in the aza BODIPYs causes aggregation. The presence of $\pi$-stacking in these multi-aryl systems results in poor water solubility that limits their application in bioapplications and clinical translation despite their good photochemical properties.[88] Indeed, the conventional aza BODIPY is hydrophobic. For use in biological systems, the size and hydrophilicity of aza BODIPYs need to be improved without significant loss of valuable photophysical characteristics.[94] The rotation of the bulky aryl groups in aza BODIPYs and BODIPYs, in the excited states results in the dissipation of energy via thermal relaxation. This leads to low fluorescent $\Phi_f$ values when compared with those of many conventional alkyl-substituted BODIPYs.[95] For instance, alkyl-substituted BODIPYs

such as **3.15** are well-known (**Figure 13**).[96] These emit strongly in the 510 nm region. However, complementary aryl-substituted BODIPYs **3.16** absorb at longer wavelengths (588-626 nm) (**Figure 13**) with extinction coefficients and the fluorescence quantum yields are significantly lower than that of the alkyl-substituted variant **3.15**. A possible rationale for the reduced quantum yields of the aryl-substituted variants such as **3.16** relative to the alkyl-substituted systems (**3.15**), is that energy is lost from the excited state via thermal pathways involving rotation of the aryl substituents. The ability to tune substitution about the dipyrrin framework is highly advantageous for improving the applicability of the aza BODIPYs. For instance, introducing the alkyl substitution to the aza BODIPY framework will reduce the thermal relaxation pathways brought about by the free rotation of the aryl substituents, and reduce $\pi$-stacking which would serve to reduce the aggregation and solubility problems.



**3.15**

$\lambda_{max}$. **fluor = 510 nm**

$\phi$ **= 0.64 (CHCl$_3$)**

**3.16**

**Ar = Ph, Naph, 4-MeOC$_6$H$_4$,**
**4-FC$_6$H$_4$, 2-MeOC$_6$H$_4$**

$\lambda_{max}$. **fluor = 588 - 626 nm**

$\phi$ **= 0.08 - 0.42 (CHCl$_3$)**

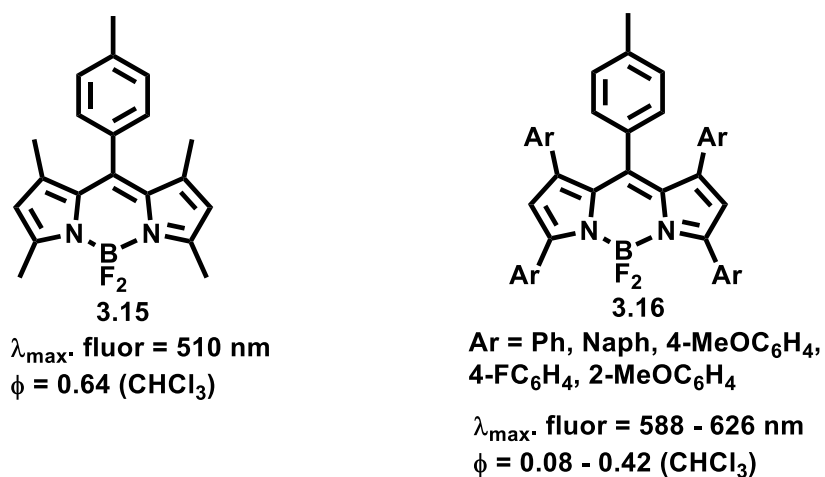*Figure 13: Chemical structure and photophysical properties of representative BODIPYs 3.15 and 3.16.*

Attempts to synthesize alkyl-substituted aza dipyrrins such as **3.17** (**Figure 14**) have been reported though all have been unsuccessful.[97] Polyalkylated aza dipyrrins cannot be synthesized by any known methods. There is only one reported aza dipyrrin that is not exclusively aryl-substituted. It

features methyl groups on the β-positions of the pyrrolic units **3.18** (**Figure 14**) and phenyl rings on the α-positions, as demanded by synthetic routes. Leaving the α-positions unsubstituted or with non-aryl substituents results in the failure of the aldol condensation that is key to the synthesis of aza dipyrrins (**Scheme 6**).[97]
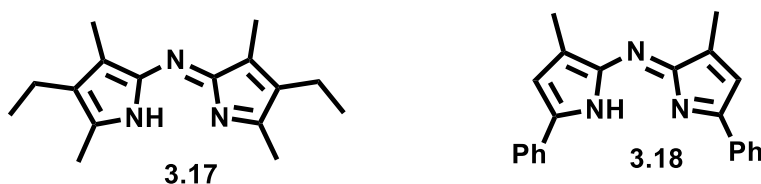


*Figure 14: Hypothetical exclusively alkyl-substituted aza dipyrrin 3.17 (left) and β,β methyl-aza dipyrrin 3.18 (right).*

The lack of derivatives beyond the extensively arylated aza dipyrrins, a consequence of the limited synthetic approaches, substantially limits the applications of aza BODIPYs in bioapplications. The installation of the *meso* aza N atom is a major challenge. The high temperatures and acidic media along with long reaction times and excess ammonia used in the described approaches (**Scheme 6** and **Scheme 7**), only allow for aryl substituted starting materials, particularly on the α-positions. Furthermore, the α-nitrogenated pyrrole intermediates lack stability, potentially leading to unproductive pathways that are most detrimental in the very reactive alkyl-substituted pyrroles. A new pathway, that avoids the generation of these unstable α-nitrogenated pyrroles for the installation of the *meso* N-atom, is highly desirable. Ideally, a new pathway would allow for variation of substitution about the pyrrolic units of the aza dipyrrin.

Taken together, the methods described above (**Scheme 6** and **Scheme 7**) provide a foundation for synthesizing the majority of aza dipyrrin derivatives with the preferred route being the condensation of nitrobutanones with excess ammonium acetate (**Scheme 6, Route I**). A comprehensive mechanistic study[98] of this route indicates the formation of a mixture of mono-, di-

, and tri-labeled species representative of a more complex process which has been shown to be non-viable in alkyl-substituted aza dipyrrins. Furthermore, the high-yielding route to aza dipyrrins through nitroso pyrroles and α-free pyrroles, though simple, cannot be translated to alkyl-substituted pyrroles as the acid-mediated nitrosylation is only successful in pyrroles bearing aryl substituents. However, and as motivation for this thesis, complexation of the alkyl-bearing aza dipyrrin **3.18** (**Scheme 8**) with BF$_3$.OEt$_2$ and *N, N*-diisopropylethylamine (DIPEA) in CH$_2$Cl$_2$ led to aza BODIPY **3.19** with improved solubility and excellent NIR photophysical properties in organic and aqueous solutions compared to its all aryl-substituted counterparts. These results are encouraging indications that alkyl-substituted aza BODIPYs could be adapted for in vitro and in vivo NIR fluorescence imaging.[87] Development of synthetic routes to enable the preparation of aza dipyrrins with a wide variety of substitution patterns is therefore desirable.
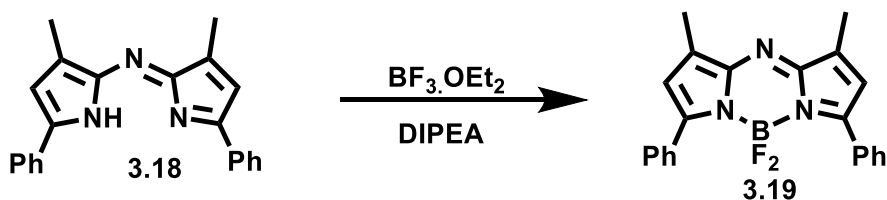


*Scheme 8: Synthesis of alkyl-substituted aza BODIPY 3.19.*

## 3.3 - Project goals.

This project aims to explore synthetic routes toward aza dipyrrins that accommodate the introduction of a variety of substituents about the pyrrolic units. This study focuses on the development of synthetic methodology toward aza dipyrrins with a particular interest in less and non-arylated aza dipyrrins i.e. alkyl-substituted aza dipyrrins. If successful, this study will provide a route for the synthesis of aza dipyrrins of various substitution patterns which will then be used to synthesize aza BODIPY complexes. Photophysical properties of these aza BODIPYs will then be investigated, including solubility, aggregation, and optical properties and the suitability thereof for future clinical translation.

## 3.4 - Synthetic strategy for aza dipyrrins.

Retrosynthetic analysis of the tetraaryl aza dipyrrins through the routes shown in **Scheme 6** reveals that the *meso*-N atom is installed onto already-made pyrroles in- or ex-situ. In the approach described in **Scheme 6, Route I**, two molecules of the nitrobutanone **3.2** undergo intramolecular cyclization in situ to form pyrroles. Ammonia from NH$_4$OAc (the source of the *meso*-N atom) and an α-free pyrrole (**Scheme 9, A**) react to produce the amino pyrrole **3.20**, which reacts with another equivalent of the α-free pyrrole to furnish the aza dipyrrin.[98] On the other hand, in **Scheme 6**, **Route II**, the nitrobutanone **3.2** also undergoes intramolecular cyclization to form pyrrole, which is then isolated and separately reacted with NaNO$_2$ to install the *meso*-N via the isolated an α-nitrogenated nitrosopyrrole **3.6** (**Scheme 9, B**). The nitrosopyrrole then reacts with another equivalent of α-free pyrrole to afford the aza dipyrrin. Clearly, the late-stage installation of the *meso*-N atom, after pyrrole formation, is a limitation in these routes to aza dipyrrins. The conditions required to produce unstable α-nitrogenated pyrroles are harsh and non-selective, and cannot be translated to non-aryl substitution patterns. Preinstallation of the *meso*-N atom before the formation of the pyrrolic units offers an alternative approach to the synthesis of aza dipyrrins.
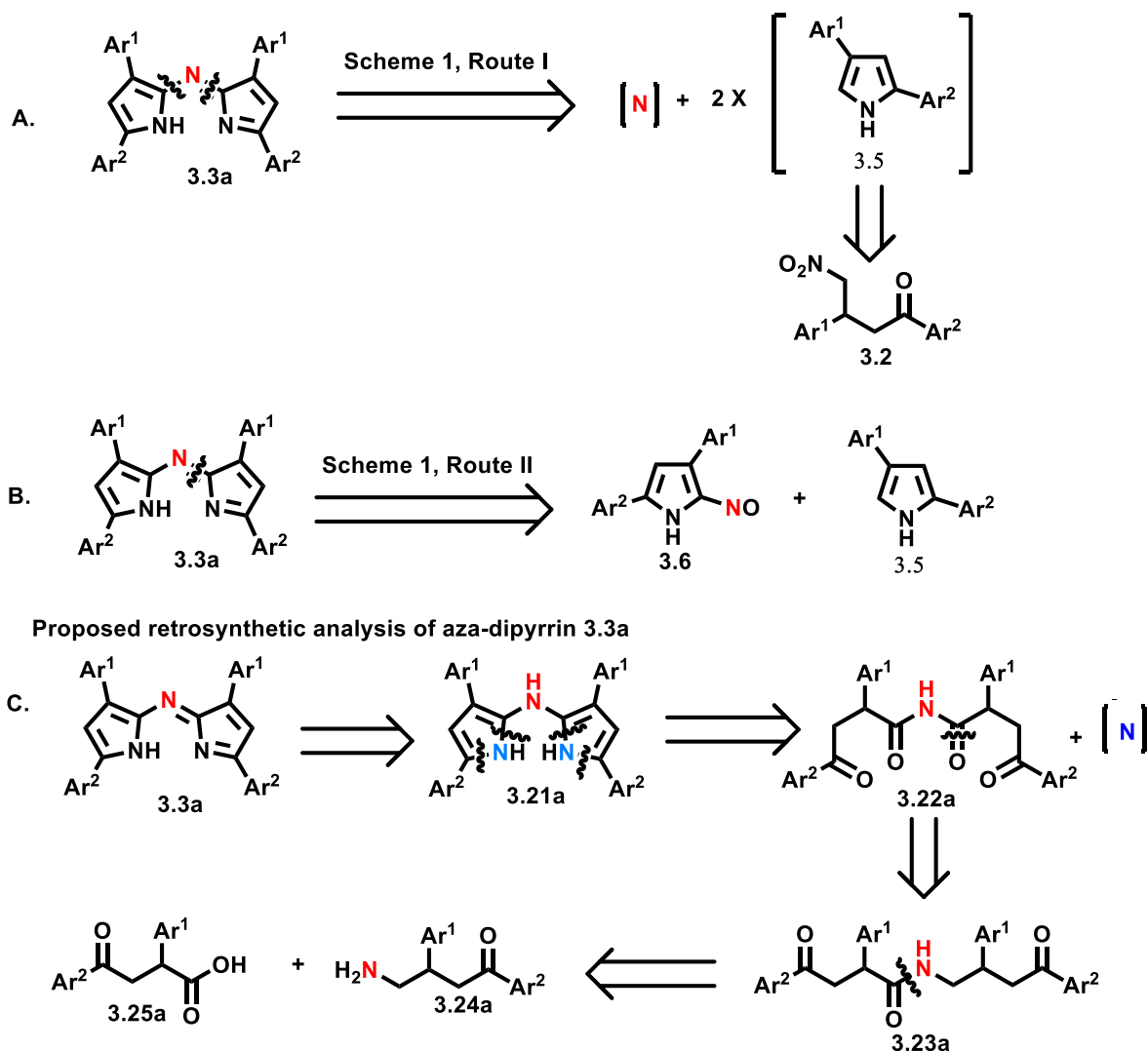
*Scheme 9: Retrosynthetic analysis of tetraaryl aza dipyrrin 3.3a.*

Cognizant of this possibility, a previous researcher in the Thompson group proposed a strategy wherein an appropriately substituted 4,4'-diketomide **3.22a** (**Scheme 9, C**), prepared from the oxoacid **3.25a** and oxoamine **3.24a**, might be converted to a dipyrolamine **3.21a** via a double Paal-Knorr cyclization. The dipyrolamine **3.21a** could then be oxidized to aza dipyrrin **3.3a**, either in air or via the use of a supplementary oxidant such as DDQ or *p*-chloranil. Using this disconnection strategy, strategic insertion of the meso-N atom would be achieved prior to the formation of the

pyrrolic framework courtesy of imide **3.22a**. This strategy takes advantage of the Paal- Knorr cyclization, an extremely robust method already demonstrated to convert almost all 1,4-diketones to their corresponding heterocycles.[99,100] In this strategy, the source of the meso-N atom is the central imide within **3.22a** (**Scheme 9, C**), therefore, avoiding the unstable α-nitrogenated pyrroles that currently limit the pathways to aza dipyrrins. Furthermore, the two halves of the imide may be functionalized separately and then coupled to result in asymmetric aza dipyrrins.

There are several possible routes to imides depending on the desired substitution patterns. Synthetically, **3.24a** and **3.25a** become targets. For the synthesis of **3.24a** and **3.25a** (**Scheme 10**), diaryl chalcone **3.26a** was chosen as the starting point, given reports[91] of successful hydrolytic Nef oxidation and Micheal addition chemistry. As discussed in section **3.2**, chalcones are readily prepared by an aldol/dehydration reaction of the corresponding benzaldehyde and acetophenone.[90] As shown in **Scheme 10**, the chalcone **3.26a** can readily undergo oxidation to the oxoacid **3.25a** and nitromethylation gives nitrobutanone **3.27a**. For the disconnection in **Scheme 9**, **C** to be feasible, nitrobutanone **3.27a** might then be reduced to oxo-amine **3.24a**. The oxoacid **3.25a** and the oxo-amine **3.24a** could then be coupled to give the amide **3.23a**, then oxidized to the target imide **3.22a**.[101,102] The imide **3.22a** might then be cyclized under Paal-Knorr conditions to produce the dipyrrolamine **3.21a**, ready for oxidation to provide the target aza dipyrrin **3.3a**.
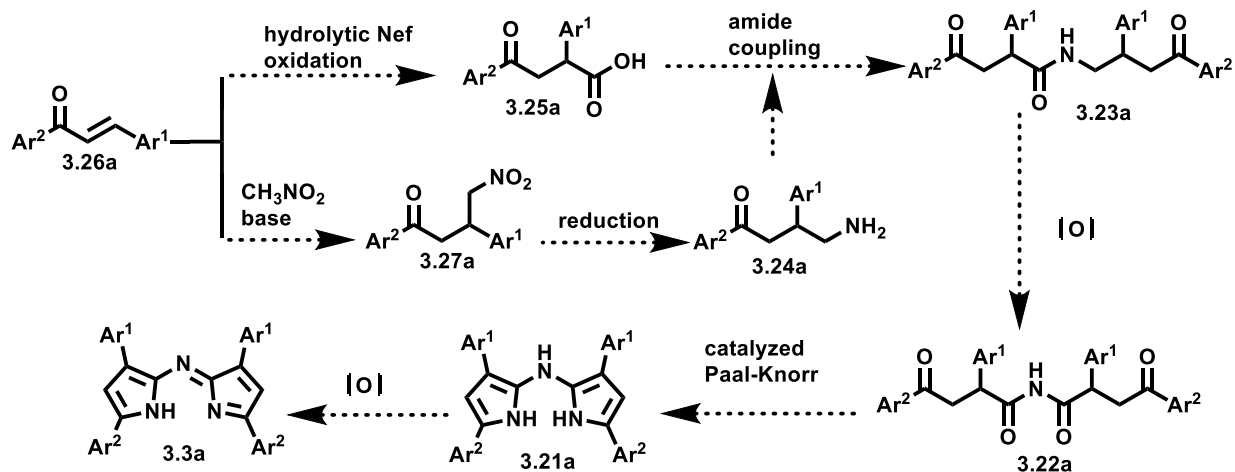
*Scheme 10: Proposed synthesis of aza dipyrrins 3.3a via imide 3.22a.*

## 3.5 - Exploration of the proposed strategy.

To investigate the viability of this proposed strategy, the initial target was the stable tetraphenyl-substituted aza dipyrrin **3.3b** (**Figure 15**), so that the new route could be explored without fear of product instability hampering success.
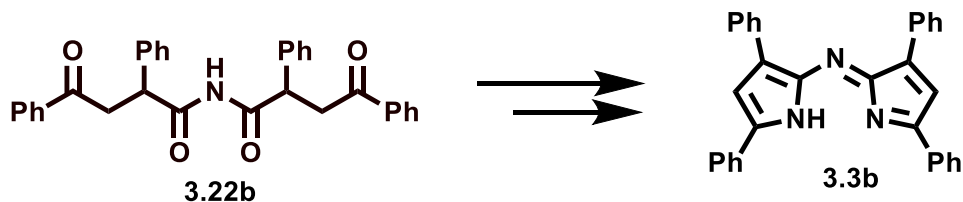


*Figure 15: Target aza dipyrrin 3.3b for proof of concept via synthesis of imide 3.22b.*

To prepare the target imide **3.22b** according to the proposed route in **Scheme 10**, the starting point was chalcone **3.26b** (**Scheme 11**). Chalcone **3.26b** was smoothly converted to oxoacid **3.25b** via the Michael addition of ethyl nitroacetate followed by Nef oxidation under hydrolytic conditions.[103] The oxoacid was isolated in a 38% yield as a white solid, and characterized

according to $^1$H NMR spectroscopic analysis. The chalcone **3.26b** was then converted to

nitrobutanone **3.27b**, via the Michael addition of nitromethane, and was isolated in a 58% yield.

The next step required the reduction of nitrobutanone **3.27b** to oxoamine **3.24b**. For this reduction,

the mild, metal-free, HSiCl$_3$-mediated protocol presented by Orlandi et al., was chosen as this was

reported to be successful and highly selective for aliphatic nitro compounds.[104] However, treatment

of nitrobutanone **3.27b** with HSiCl$_3$ in the presence of DIPEA did not result in the formation of

the desired oxoamine **3.24b**.
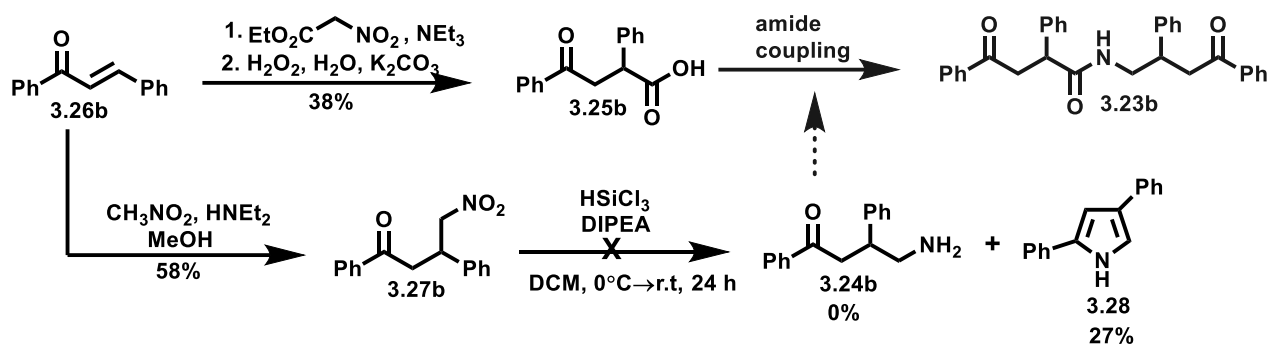


**Scheme 11**: *Attempted coupling of oxoacid 3.25b and oxoamine 3.24b to amide 3.23b.*

Instead, the reaction resulted in a complex mixture with no spectroscopic evidence of the presence

of the desired oxo-amine. Further analysis of the mixture showed the presence of 2,4-diphenyl

pyrrole **3.28** (**Scheme 11**), which was isolated in a 27% yield. The presence of 2,4-diphenyl pyrrole

suggested that the nitro group was indeed reduced to the desired oxoamine **3.24b**, and that this

material underwent in-situ intramolecular cyclization to provide the pyrrole. To avoid this

intramolecular cyclization, attempts were made to protect the ketone of **3.27b** before the reduction

of the nitro group. Attempts to form the propylene glycol acetal **3.29** (**Scheme 12**), catalyzed by

hydrochloric acid or triethyl orthoformate/tetrabutyl ammonium tribromide,[105] and attempts to

form dimethyl acetal **3.30** using methanol and *p*-toluenesulfonic acid, were unfruitful and instead resulted in the recovery of starting material. The protection of the ketone was unsuccessful, presumably because the ketone is insufficiently electrophilic.[105]
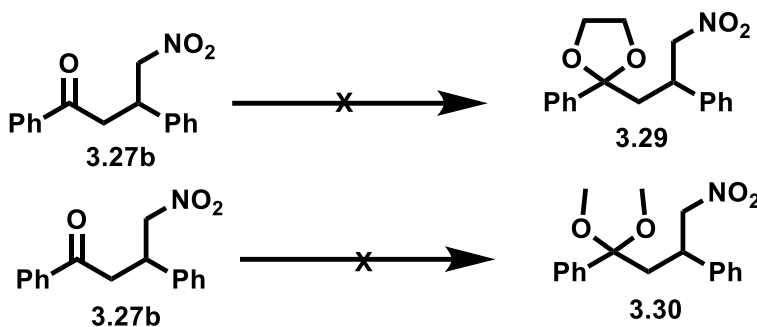


***Scheme 12: Attempted protection of nitrobutanone 3.27b by the generation of the acetal 3.29 and dimethyl acetal 3.30.***

Given that the oxoamine **3.24b** could not be isolated, the proposed strategy (**Scheme 11**) wherein the oxoacid **3.25b** is coupled with the oxoamine **3.34b** could not be pursued. Therefore, a new strategy was proposed wherein the oxoamine **3.24b** would be trapped in situ by a more reactive carboxylic acid surrogate, such as an activated ester, thus avoiding intramolecular cyclization to form the pyrrole. Various carboxylic acid surrogates have been used as acylating substrates to enhance the atom- and step-economies of amidation.[106,107] Among them, activated aryl esters are common since they are often crystalline stable materials, and more electrophilic towards amines, than are the parent carboxylic acids, producing fewer side reactions during coupling.[107] To evaluate this strategy, the pentafluorophenyl (PFP) active ester **3.31** (**Scheme 13**) was chosen, as it is readily synthesizable, stable, has good organic solubility and has been useful for making amides (**Scheme 13**).[108,109,110] The presence of active ester **3.31** in the reaction mixture undergoing reduction of nitrobutanone **3.27b** would hopefully limit intramolecular cyclization to form pyrrole **3.28**.

instead, **3.27b** which would react in situ, with excess active ester **3.31** to form amide **3.23b**, thus potentially outcompeting the unproductive intramolecular cyclization.[109]

The desired pentaflourophenyl-activated ester **3.31** (**Scheme 13**) was synthesized by treatment of oxoacid **3.25b** with EDC.HCl and pentafluorophenol.[111] Ester **3.31** was isolated in a 96% yield after purification via column chromatography. The colourless oil solidified to a white solid upon standing,. Confirmation of structure was achieved by NMR analysis and X-ray crystallography. The crystal structure of the active ester is shown in **Figure 16**, clearly demonstrating incorporation of the pentafluoro moiety.
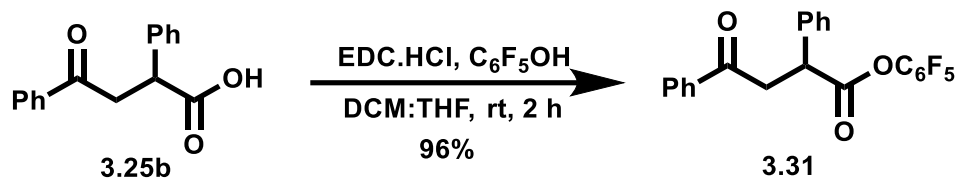


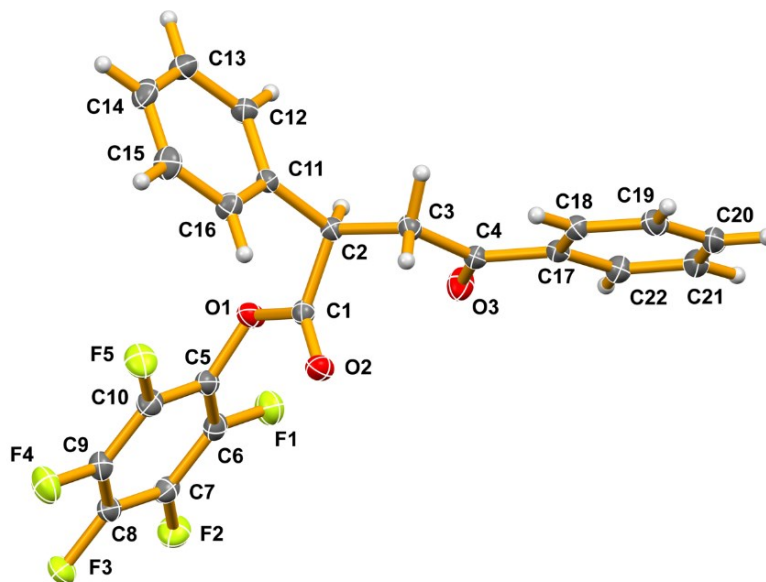*Scheme 13: Synthesis of active ester 3.31.*



*Figure 16: ORTEP diagram of ester 3.31. Thermal ellipsoids are shown at 50% probability.*

The reduction of nitrobutanone **3.27b** was repeated, this time in the presence of the active ester **3.31**. Reduction using HSiCl₃ conditions was again employed, given that these conditions had been successful in reducing the nitrobutanone **3.27b** to the oxoamine **3.24b** (**Scheme 11**), even though intramolecular cyclization was observed. The reaction of nitrobutanone **3.27b** (**Scheme 14**) with HSiCl₃ in the presence of the active ester **3.31** resulted in partial consumption of both starting materials, as observed by TLC analysis. A new vibrant yellow spot was observed on the baseline of the TLC plate when stained with bromocresol green. A white precipitate was formed upon quenching the reaction mixture with NaHCO₃, and this was affiliated with the aqueous layer during work-up. The white precipitate was collected via filtration. Efforts to identify this material were unsuccessful because this solid was not soluble in common organic solvents (CH₂Cl₂, CDCl₃, DMSO, CH₃CN, MeOH, EtOAc, and Et₂O). The filtrate was concentrated and purified by column chromatography to recover both the starting materials **3.27b** and **3.31** in 93% and 38% yield, respectively. It was hypothesized that the use of HSiCl₃ was the likely source of the white solid, possibly a polysiloxane, presumably by reaction with the active ester **3.31** and hence the 38% recovery of this active ester. Polysiloxanes are generally insoluble in organic solvents, thereby explaining the insolubility of the isolated white solid.[112] The nitrobutanone was recovered quantitatively, suggesting that the HSiCl₃ was not available to react with the nitrobutanone **3.27b**.
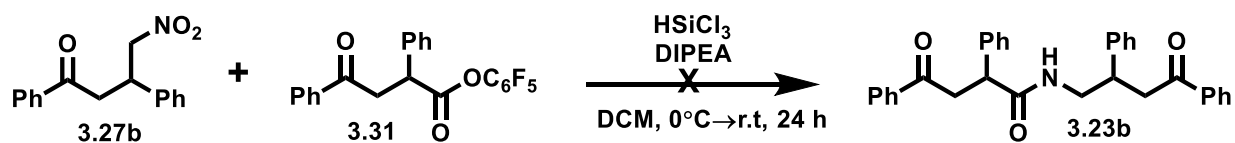


*Scheme 14: Attempted synthesis of amide 3.23b by coupling of nitrobutanone 3.27b and active ester 3.31.*

The consumption of the active ester **3.31** under the HSiCl₃ reduction conditions, suggests that the active ester is not stable under the reduction conditions. Given this challenge, a new system was required in order to perform the chemoselective reduction of nitrobutanone **3.27b** in the presence of other functional groups. To this end, a range of alternative conditions for the selective reduction of the nitro group were screened. Identification of a useful reduction protocol, even if accompanied by cyclization of the resulting oxoamine and formation of the corresponding pyrrole, would enable further attempts to trap the oxoamine with the active ester. Firstly, the reduction of nitrobutanone **3.27** was attempted using hydrogenation in the presence of 10% palladium on carbon, as successfully utilized for the reduction of other nitro groups.[113] Under these conditions, starting material was consumed and the presence of two new spots as confirmed by TLC analysis. Filtration and purification of the reaction mixture afforded two white solids which, upon analysis, were not any of the expected products. The first spot (with a lower $R_f$ relative to the second spot) stained vibrant dark purple with vanillin. Following quenching and workup, the compound corresponding to the first spot was isolated via column chromatography on silica. After analysis via ¹H NMR spectroscopy, the isolated compound was characterized as alcohol **3.32** (**Scheme 15**). Interestingly, instead of reduction of the nitro group of nitrobutanone **3.27b**, the ketone was partially reduced to an alcohol, generating nitrobutanol **3.32** in a 38% yield.
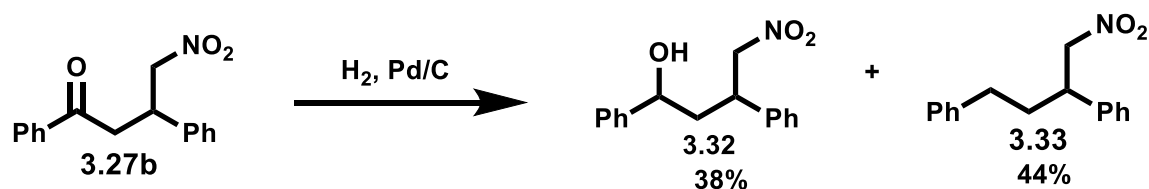


*Scheme 15: Reduction of nitrobutanone 3.27b to nitrobutanol 3.32 and compound 3.33.*

A crystal of compound **3.32** was submitted for X-ray crystallography. The structure is shown in **Figure 17**, confirming the presence of the hydroxyl moiety in the compound.
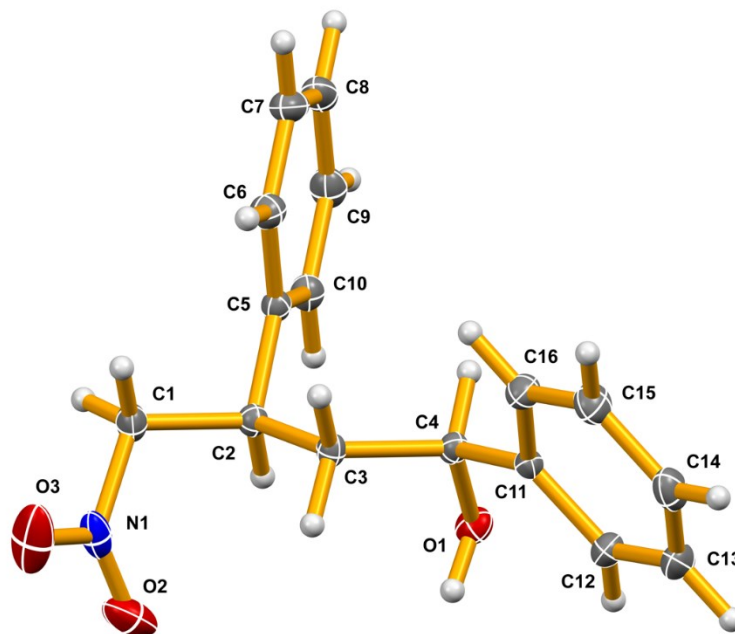


*Figure 17: ORTEP diagram of ester alcohol. Thermal ellipsoids are shown at 50% probability.*

Analysis of the material corresponding to the second spot (with a higher $R_f$ relative to the first spot) with $^1$H NMR spectroscopy and MS spectrometry, revealed compound **3.33** (**Scheme 15**). Interestingly, this was formed through the complete reduction of the ketone. The ortho hydrogen atoms on the phenyl group adjacent to the ketone moiety in **3.2b** are the most deshielded in the $^1$H NMR spectrum, but in the isolated product **3.33**, these are less deshielded. Furthermore, the chemical shift for two hydrogen atoms adjacent to the nitro group stayed consistent in the starting material **3.27b** (4.64-4.82 ppm) and the product **3.33** (4.53-4.60 ppm).[114] The complete reduction of the ketone was also confirmed by MS spectrometry. Clearly, the ketone was chemoselectively reduced, rather than the nitro group, despite evidence to the contrary. This is not overly surprising

as catalytic hydrogenation using transition metals, though it has received high interest, can exhibit limited selectivity in the presence of other reducible functional groups.[113]

Due to the lack of selectivity of the hydrogenation for the nitro group, the reduction of the nitrobutanone **3.27b** was then attempted under other conditions that have been successfully utilized in the chemoselective reduction of nitro in the presence of ketones (**Table 7**).
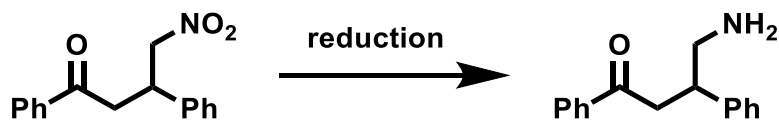


| Conditions | Solvent | Time/ h | Temperature/°C | Outcome |
|---|---|---|---|---|
| Fe, $CaCl_2$[115] | EtOH | 6 | 60 | No conversion |
| $SnCl_2.2H_2O$[116] | EtOAc | 24 | 50 | No conversion |
| $Na_2S_2O_4$[117] | DMF | 5 | 90 | No conversion |
| $NH_2-NH_2$[118] | EtOH | 6 | 78 | No conversion |

*Table 7: Attempts to reduce the nitro group in nitrobutanone 3.27b.*

However, most of these attempts did not result in the consumption of starting materials and/or did not result in the formation of any of the expected products. However, the protocol involving the use of elemental zinc powder in the presence of ammonium chloride as a proton source (**Scheme 16**), did result in reactivity. Chemoselectivity for this protocol is impressively high, with the conversion of aliphatic nitro compounds to amines.[119,120] Reaction of nitrobutanone **3.27b** with zinc and ammonium chloride in MeOH resulted in the complete consumption of nitrobutanone **3.27b**. A single new product was formed, according to TLC analysis. Workup and column

chromatography of the resulting reaction mixture furnished a white product characterized as the pyrroline **3.34** (**Scheme 16**).[121]
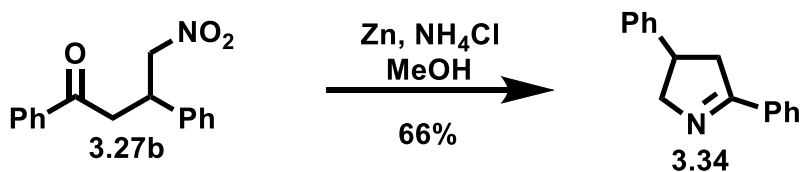


*Scheme 16: Reduction of nitobutanone 3.27b to pyrroline 3.34.*

This result suggests that nitrobutanone **3.27b** was indeed reduced to oxoamine **3.24b**, which subsequently underwent intramolecular cyclization, generating pyrroline **3.34** in a 66% yield. The reduction of the nitro group in Michael adducts, using zinc and ammonium chloride, has been reported to produce pyrrolines and in some cases pyrroline-N-oxides through the formation of hydroxylamine.[121,122,123] The reaction of pyrroline-N-oxides in acidic media has been reported to result in the formation of pyrrole.[124,125] However, the reduction protocol using zinc results in the formation of only the pyrroline **3.34** which does not undergo oxidation to form pyrrole under these conditions.[125] This contradicts the results for the $HSiCl_3$-mediated reduction of **3.27b** (**Scheme 11**), where pyrrole was isolated. Presumably, in this case (**Scheme 16**), the nitro group is reduced to hydroxylamine, which undergoes intramolecular cyclization to the pyrroline-N-oxide. The $HSiCl_3$ then undergoes nucleophilic substitution at silicon, forming a strong bond with oxygen resulting in the formation of silanol and then the pyrroline-N-oxide forms the pyrrole.[125]

The success of the reductive cyclization promoted conditions to explore the viability of trapping nitrobutanone **3.27b** with active ester **3.31** to provide the amide **3.23b** according to **Scheme 14**. In light of this, the nitrobutanone **3.27b** and the active ester **3.31** were treated with zinc dust and

NH$_4$Cl at 60 °C (**Scheme 17**). However, analysis of the product mixture revealed the presence of pyrroline **3.34**, as before, and a new compound that was characterized as amide **3.35** (**Scheme 17**). The formation of amide **3.35** suggests that the active ester **3.31** reacted with NH$_4$Cl generating the corresponding primary amide **3.35**. A crystal of the amide suitable for X-ray analysis was obtained from the slow evaporation of a solution of this material in CH$_2$Cl$_2$ and pentane. The resulting crystal structure diagram for the amide is shown in **Figure 18**, confirming the presence of the -NH$_2$ moiety in the compound.
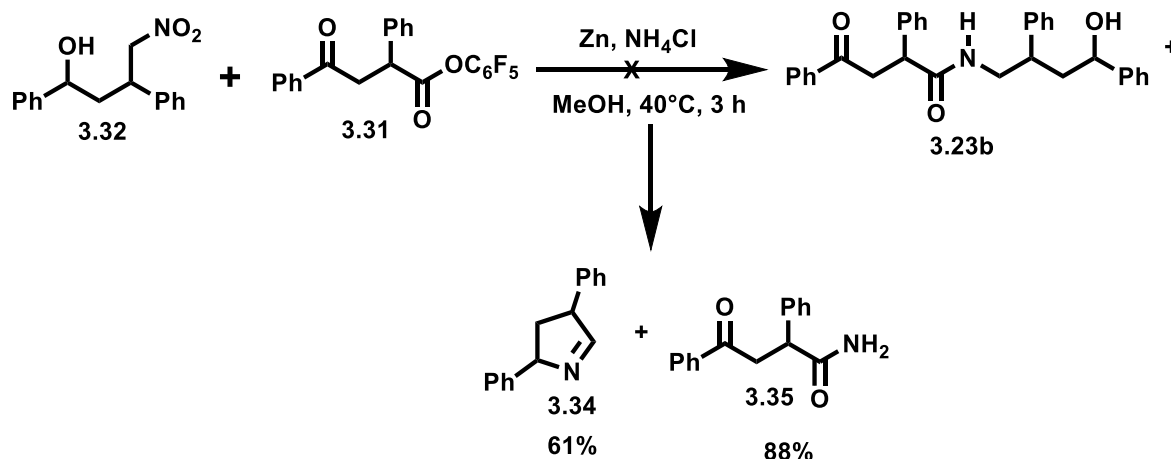


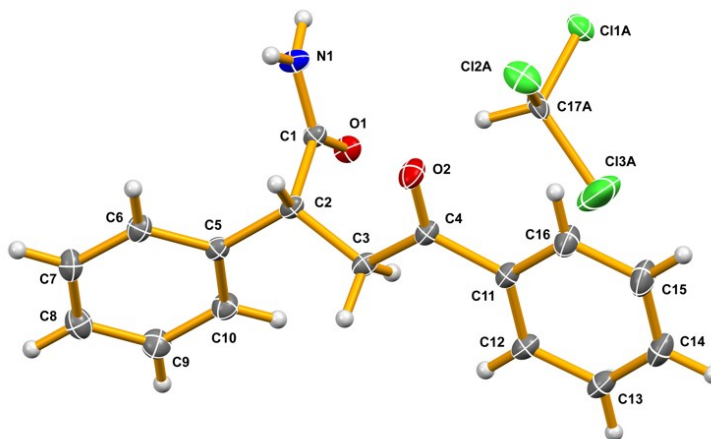*Scheme 17: Attempted coupling of the nitrobutanone 3.27b and active ester 3.31.*



*Figure 18: ORTEP diagram of amide 3.35 with solvent. Thermal ellipsoids are shown at 50% probability.*

The trapping of the nitrobutanone with the active ester was unsuccessful as the active ester reacted with an ammonia equivalent present in the solution, and was thus unavailable to couple with the formed oxoamine. The reduction itself was however successful, as indicated by the isolation of the pyrroline **3.34**. Cognizant of these results, the use of ammonium chloride for the reduction of the nitrobutanone **3.27b** needed to be avoided and the use of zinc powder maintained to avoid the conversion of the active ester **3.31** to the amide **3.35**.

Rather than ammonia providing the hydrogen atoms, the reduction of nitro groups with zinc can be achieved in acidic media, though yield and chemoselectivity are often compromised.[120] This protocol is familiar as it is frequently utilized within the Thompson lab for the Knorr pyrrole synthesis.[77] The Knorr pyrrole synthesis involves a zinc-induced exothermic reduction of ethyl 2-aminoacetoacetate to form an α-amino ketone, which immediately reacts in situ to form pyrrole, as discussed in Chapter 1. Given the instability of the active ester **3.31** in the presence of $NH_4Cl$, the Knorr pyrrole synthesis conditions were mimicked for the reduction of **3.25**, with hopes of avoiding the conversion of the active ester to its primary amide **3.35**. However, when nitrobutanone **3.27b** was reacted with the active ester **3.31** in the presence of zinc in AcOH, the expected amide product (**3.23b**) was not formed. Instead, the active ester **3.31** was recovered in an 89% yield and the pyrroline **3.34** was again isolated. This result suggests that the reduction of nitrobutanone **3.27b** to oxoamine **3.24b** was successful under these conditions. Intramolecular cyclization of the oxoamine **3.24b** to the pyrroline **3.34** is, however, again favoured over coupling with the active ester. Therefore, the proposed trapping of the oxoamine with the active ester was unsuccessful.

Given that the oxoamine trapping strategy was unsuccessful, a new strategy was explored wherein the nitrobutanol **3.32** obtained from the hydrogenation of nitrobutanone **3.27b** (**Scheme 15**), could be subjected to the Zn/NH4Cl conditions for the reduction of the amine **3.36** (**Scheme 18**). The desired carbonyl functionality would then be installed from the alcohol later in the approach. Without the carbonyl moiety, the nitro group would hopefully be reduced without intramolecular cyclization, to afford the amine **3.36**. The amine **3.36** could then be coupled with the active ester **3.31** to yield the amide **3.37**. Oxidation would then install the desired ketone in **3.22b** (**Scheme 18**). With this amide in hand, the pathway would be anticipated to continue as proposed in **Scheme 10** to yield the desired aza dipyrrin **3.3a**.
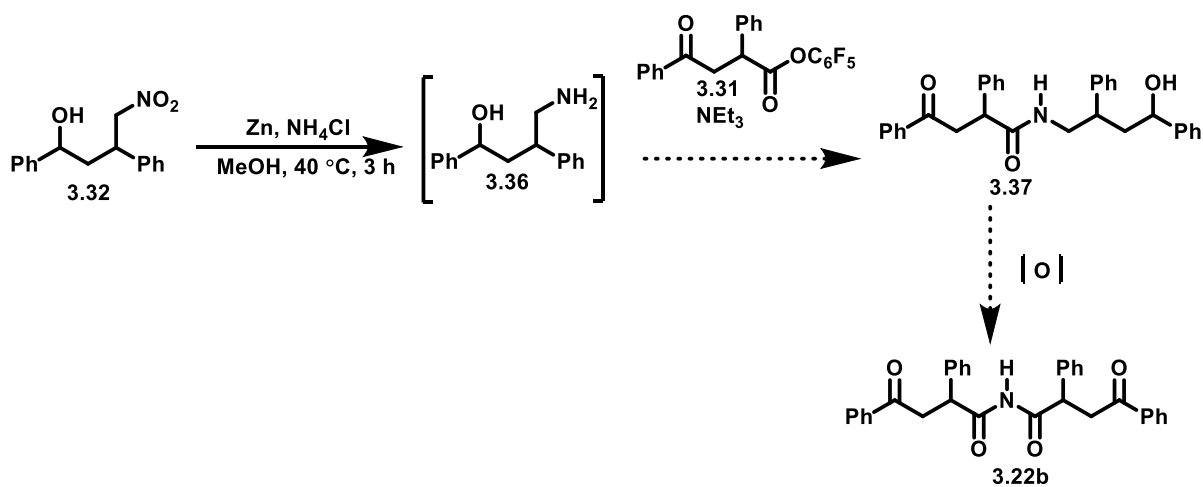


*Scheme 18: Proposed route to 3.22b, with the late-stage installation of the ketone.*

The nitrobutanol **3.32** was therefore dissolved in AcOH and subjected to reduction with zinc dust in the presence of an excess of active ester **3.31** (**Scheme 19**). Following workup and purification via column chromatography, active ester **3.31** was recovered in an 85% yield together with two new compounds. Gratifyingly, the product corresponding to the spot with the lowest $R_f$ on the TLC

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plate was characterized as the desired amide **3.37** by analysis of the $^1$H NMR spectrum and with support from mass spectrometry. The identity of the other compound isolated (spot with higher $R_f$ on the TLC), has not been successfully elucidated. The success in synthesizing **3.37**, despite the 6%, crude yield, is exciting and still warrants further development to determine the viability of this pathway. The isolated product was not clean according to TLC and $^1$H NMR spectroscopy.
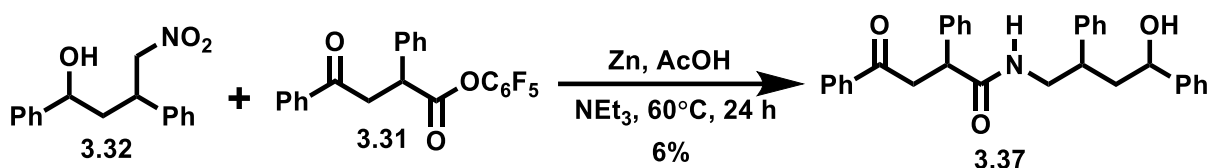


*Scheme 19: Attempted coupling of nitrobutanol 3.32 and active ester 3.31.*

The focus thus returned to the amide **3.35** in

Scheme *17*. A method of formation of imides was explored wherein an acid chloride is coupled with an amide in the presence of sodium hydride.[126] Since the primary amide **3.35** was available, coupling with the acid chloride **3.38** would hopefully provide the desired amide **3.22b** (**Scheme 20**).[126]
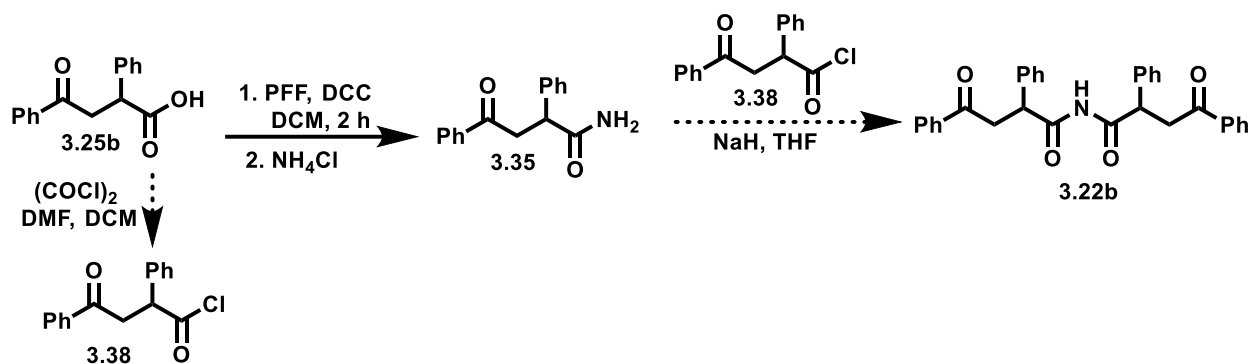
*Scheme 20: Proposed strategy for the synthesis of amide 3.22b via acid chloride 3.38.*

To this end, oxoacid **3.25b** was reacted with oxalyl chloride in the presence of catalytic amounts of DMF. The mixture was stirred at 0 °C for 10 min, and then at room temperature for two hours. The solvent and excess oxalyl chloride were removed *in vacuo*. Analysis of the spectral data revealed furanol **3.39** (**Scheme 21**). The presence of this product suggested that the desired acid chloride **3.38** indeed formed under the reaction conditions but underwent intramolecular cyclization to generate product **3.39** (**Scheme 21**). This cyclization was a major drawback and meant that we could not proceed with the proposed pathway in **Scheme 20.**
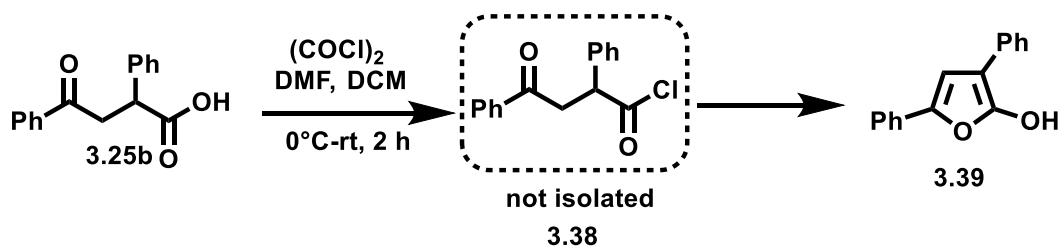


*Scheme 21: Cyclization of acid chloride 3.38 to furanol 3.39.*

## 3.6 - Future Work.

The hint of success from the formation of amine 3.23b (**Scheme 19**) from the reaction of nitrobutanone **3.27b** and active ester **3.31**, though in a low yield, means we can undertake optimization of this reaction to further investigate this method for the synthesis of aza dipyrrins. Another possible alternative to synthesize aza dipyrrins might involve the use of the amide **3.35** ( **Scheme 17**) which can be converted to phosphinimidic amide **3.40** (**Scheme 22**) by treatment with stoichiometric quantities of phosphines and diethyl azodicarboxylate (DEAD).[127,128] The phosphinimidic amide **3.40** might then be coupled with the oxoacid **3.25b** to give the hydroxyl amide **3.41**, ready for oxidation to the desired imide **3.22b** enabling the pathway to continue as proposed in **Scheme 10**.
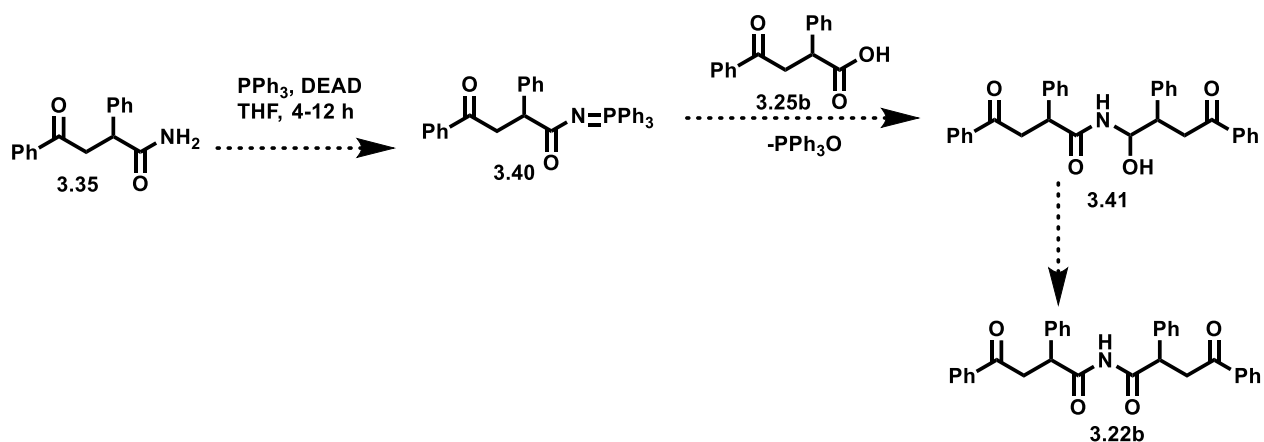


*Scheme 22: Proposed synthesis of imide 3.22b via coupling of phosphinimidic amide 3.40 and oxoacid 3.25b.*

## 3.7 - Experimental.

All chemicals were used as received unless otherwise indicated. All NMR spectra were recorded using 500 MHz or 300 MHz spectrometers. $^1$H chemical shifts are reported in ppm relative to tetramethylsilane using chloroform solvent residual at $\delta$ = 7.26 ppm as an internal standard. $^{13}$ C spectra were recorded using UDEFT pulse sequence with chemical shifts reported in ppm

referenced to CDCl$_3$ resonance at $\delta$ = 77.2 ppm. Splitting patterns are indicated as follows: br, broad; s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet. All coupling constants ($J$) are reported in Hertz (Hz). High-resolution mass spectra were obtained using TOFMS experiments operating in both positive and negative modes. Column chromatography, as indicated, was performed using 230-400 mesh ultra-pure silica. 4-Oxo-2,4-diphenylbutanoic acid **3.25b**[103] and 4-Nitro-1,3-diphenylbutanone **3.27b**[91] were synthesized according to reported procedures.

**4-Oxo-2,4-diphenylbutanoic acid pentafluorophenyl ester, (3.31).**
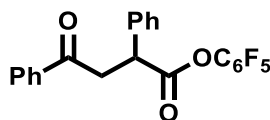


4-Oxo-2,4-diphenylbutanoic acid **3.25b** (9.6 mmol, 1 equiv.), EDC.HCl (1.25 equiv.) and pentafluorophenol (1.25) were dissolved in THF:CH$_2$Cl$_2$ 1:1 (2 mL) and stirred at room temperature for 2 hours. The reaction was diluted to 10 mL with CH$_2$Cl$_2$ and washed with water and brine. The organics were dried over Na$_2$SO$_4$ and concentrated in vacuo. Purification over silica eluting with 17% EtOAc/hexanes gave **3.31** as a white solid (3.86g, 96%). $^1$H NMR (500 MHz; CDCl$_3$) $\delta$: 8.00 (d, $J$ = 7.28 Hz, 2H), 7.56-7.60 (m, 1H), 7.41.-7.48 (m, 6H), 7.35-7.38 (m, 1H), 4.65-4.68 (dd, $J$ = 3.9, 10.2 Hz, 1H), 3.98-4.05 (m, 1H), 3.45-3.49 (dd, $J$ = 3.9, 10.6 Hz, 1H). $^{13}$C NMR (CDCl$_3$) $\delta$: 196.7, 169.6, 136.5, 136.0, 133.5, 129.2, 128.7, 128.3, 128.1, 127.9, 46.1, 42.8, 4 carbon signals missing. $^{19}$F NMR (471 MHz, CDCl$_3$) $\delta$: -152.0 (d, $J$ = 17.7 Hz, 2F), -158.7 (t, $J$ = 21.6Hz, 1F), -162.6 (dt, $J$ = 4.7, 17.7 Hz, 2F). NMR data were found to be in accordance with literature.[129]

**4-Nitro-1,3-diphenylbutan-1-ol, (3.32).**
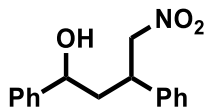


A mixture of **3.27b** (300 mg, 1.11 mmol), 10% Pd/C (30 mg), and NEt$_3$ (few drops) was dissolved in THF (0.08 M). Following repeated evacuation under vacuum and re-filling the atmosphere with nitrogen, the reaction vessel was again evacuated and then placed under an atmosphere of hydrogen. The reaction mixture was stirred under an atmosphere of hydrogen for 24 h. Upon completion of the reaction, the mixture was flushed with nitrogen and then filtered over a pad of Celite, flushing with THF. Concentration of the solution *in vacuo* gave the crude product. Purification of the crude product over silica eluting with 5% EtOAc/hexanes gave **3.32** as a white solid (108 mg, 36%). $^1$H NMR (500 MHz; CDCl$_3$) $\delta$: 7.30-7.35 (m, 4H), 7.24-7.29 (m, 2H), 7.20-7.23 (m, 2H), 7.14-7.16 (m, 2H), 4.53-4.62 (m, 2H), 4.48-4.52 (m, 1H), 3.34-3.40 (m, 1H), 2.23-2.29 (m, 1H), 2.06-2.11 (m, 1H), OH (br, 1.82). $^{13}$C NMR (CDCl$_3$) $\delta$:143.1, 139.1, 129.1, 128.8, 128.2, 127.8, 127.6, 126.2, 80.4, 72.1, 41.6, 40.9. HRMS-ESI (*m/z*): [M+Na]$^+$ calc'd for C$_{16}$H$_{17}$NNaO$_3$: 294.1101, found 294.1089.

**1,1'-(4-Nitrobutane-1,3-diyl)dibenzene, (3.33).**
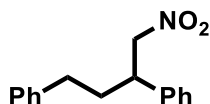


Nitrobutanone **3.27b** (300 mg, 1.11 mmol), 10% Pd/C (30 mg), and NEt$_3$ (few drops) were dissolved in THF (0.08 M). Following repeated evacuation under vacuum and re-filling the atmosphere with nitrogen, the reaction vessel was again evacuated and then placed under an atmosphere of hydrogen. The reaction mixture was stirred under an atmosphere of hydrogen for

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24 h. Upon completion of the reaction, the mixture was flushed with nitrogen and then filtered over a pad of Celite flushing with THF. Concentration of the solution *in vacuo* gave the crude product. Purification of the crude material over silica eluting with 5% EtOAc/hexanes gave **3.33** as a colourless oil (125 mg, 44%). $^1$H NMR (500 MHz; CDCl$_3$) δ: 7.36-7.39 (m, 2H), 7.25-7.32 (m, 3H), 7.18-7.23 (m, 3H), 7.09 (d, $J$ = 7.28 Hz, 2H), 4.52-4.59 (m, 2H), 3.45-3.51 (m, 1H), 2.44-2.57 (m, 2H), 2.01-2.06 (m, 2H). $^{13}$C NMR (CDCl$_3$) δ: 140.9, 139.0, 129.1, 128.5, 128.3, 127.8, 127.7, 126.2, 80.9, 43.8, 34.5, 33.0. HRMS-ESI (*m/z*): [M+Na]$^+$ calc'd for C$_{16}$H$_{17}$NNaO$_2$: 278.1151; found 278.1151.

**3,5-Diphenyl-3,4-dihydro-2H-pyrrole, (3.34).**
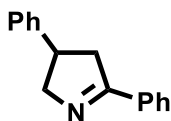


Nitrobutanone **3.27b** (50 mg, 0.19 mmol) and NH$_4$Cl (41 mg, 0.76 mmol) were dissolved in MeOH. Zinc dust (38 mg, 0.57 mmol) was added portion-wise over 30 min and the mixture was stirred at 60°C for 3 h. Upon completion, the reaction mixture was allowed to cool to room temperature then diluted to 15 mL with water and extracted with CH$_2$Cl$_2$. The organic layer was washed with brine, dried over Na$_2$SO$_4$ and the solvent was removed *in vacuo* to give the crude product. Purification of the crude product over silica eluting with 20% EtOAc/hexanes gave **3.34** as a white solid (27 mg, 66%). $^1$H NMR (500 MHz; CDCl$_3$) δ: 7.87-7.89 (m, 2H), 7.42-7.50 (m, 3H), 7.31-7.34 (m, 2H), 7.23-7.26 (m, 3H), 4.51-4.57 (m, 1H), 4.10-4.15 (m, 1H), 3.65-3.71 (m, 1H), 3.46-3.52 (m, 1H), 3.08-3.13 (m, 1H). $^{13}$C NMR (CDCl$_3$) δ: 174.2, 144.1, 133.2, 131.3, 128.8,

128.6, 128.0, 126.7, 68.3, 44.3, 42.4, 1 signal missing. HRMS-ESI (*m/z*): [M+H]$^+$ calc'd for C$_{16}$H$_{16}$N 222.127726, found 222.127962.

**4-Oxo-2,4 diphenylbutanamide, (3.35).**
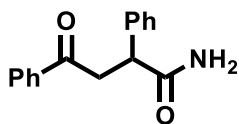


Oxoacid **3.25b** (50 mg, 0.19 mmol) and NH$_4$Cl (41 mg, 0.76 mmol) were dissolved in MeOH. Zinc dust (38 mg, 0.57 mmol) was added portion-wise over 30 min and the reaction was stirred at 60°C for 3 h. Upon completion, the reaction mixture was allowed to cool to room temperature and thn diluted to 15 mL with water and extracted with CH$_2$Cl$_2$. The organics were washed with brine, dried over Na$_2$SO$_4$ and the solvent was removed *in vacuo* to give the crude product. Purification of the crude product over silica eluting with 40% EtOAc/hexanes gave **3.35** as a white solid (29 mg, 58%). $^1$H NMR (500 MHz; CDCl$_3$) *δ*: 7.95-7.97 (m, 2H), 7.52-7.55 (m, 1H), 7.41-7.45 (m, 2H), 7.38-7.40 (m, 2H), 7.32-7.36 (m, 2H), 7.26-7.29 (m, 1H), 5.59-5.68 (d, *J* = 46.7 Hz, 2H), 4.22-4.25 (m, 1H), 4.02-4.08 (m, 1H), 3.19-3.24 (m, 1H). $^{13}$C NMR (CDCl$_3$) *δ*: 198.1, 174.9, 139.5, 136.6, 133.2, 129.0, 128.5, 128.1, 127.9, 127.6, 47.2, 42.5. HRMS-ESI (*m/z*): [M+Na]$^+$ calc'd for C$_{16}$H$_{15}$NNaO$_2$ 276.0995; found 276.0986.

**N-(2-Hydroxy-4-phenylbutyl)-4-Oxo-2,4-diphenylbutanamide, (3.37).**
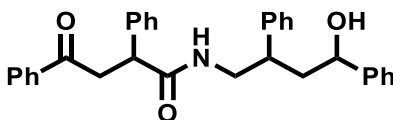
Nitrobutanol **3.32** (388 mg, 1.43 mmol), NEt$_3$ (200 μL, 1.43 mmol) and active ester **3.31** (3.58 mmol) were dissolved in 3 mL of AcOH and the mixture stirred at 60°C. Zinc dust was added slowly over 30 min and the reaction mixture was stirred for 3 h. After **3.32** was consumed as monitored by TLC, the reaction mixture was cooled to room temperature. The mixture was then filtered over a pad of celite and the resulting mixture was extracted with CHCl$_3$. The organic layer was dried over anhydrous Na$_2$SO$_4$ and concentrated *in vacuo* to give the crude product. Purification over silica gave **3.37** as a brown oil (6 mg, 1%). $^1$H NMR (500 MHz; CDCl$_3$) $\delta$: 8.01 (d, 2H), 7.61 (t, 3H), 7.50 (m, 3H), 7.31-7.43 (m, 14H), 4.57-4.70 (m, 3H), 4.36-4.39 (m, 1H), 3.93-3.99 (m, 1H), 3.43-3.47 (m, 1H), 3.31-3.36 (m, 1H), 2.27-2.38 (m, 2H), 2.14-2.19 (m, 1H). HRMS-ESI (*m/z*): [M+Na]$^+$ calc'd for C$_{32}$H$_{31}$NNaO$_3$ 500.2196; found 500.2189.

**3,5-Diphenyl-2-furanol, (3.39).**
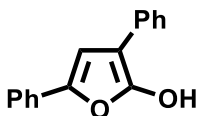


Oxoacid **3.25b** (1 g, 3.93 mmol) was dissolved in anhydrous CH$_2$Cl$_2$ (15 mL) and the resulting solution cooled to 0 °C. Oxalyl chloride (4.72 mmol, 1.2 equiv.) was added dropwise followed by the addition of a drop of DMF. The mixture was stirred at 0 °C, coming to room temperature over 2 h. The solvent and excess oxalyl chloride were removed *in vacuo* to give a yellow oil. The yellow oil was dissolved in a small amount of CH$_2$Cl$_2$ and excess hexanes to effect precipitation. The resultant white crystalline solid was collected by filtration, (890 mg, 96%). $^1$H NMR (500 MHz; CDCl$_3$) $\delta$: 7.89-7.91 (m, 2H), 7.63 (d, $J$ = 2.14 Hz, 1H), 7.39-7.44 (m, 6H), 37.33-7.35 (m, 2H), 6.03-6.03 (m, 1H). $^{13}$C NMR (CDCl$_3$) $\delta$: 171.7, 147.3, 134.8, 130.9, 129.5, 129.2, 128.7, 127.1, 126.6, 81.5. HRMS-ESI (*m/z*): [M+Na]$^+$ calc'd. for C$_{16}$H$_{12}$NaO$_2$ 259.0730; found 259.0728.

# Chapter 4 – Attempted PPh$_3$-Mediated C−N Coupling of Nitrosoarenes.

## 4.1 – Introduction.

The work in Chapter 3 aimed to form aza dipyrrins in an acyclic manner through the preinstallation of the linking C-N bond, before the formation of the pyrrolic rings, but to no avail. Perhaps exploring other methods for the installation of the C-N bond in pyrroles would provide a desirable synthesis of aza dipyrrins. As mentioned in Chapter 3, the most direct synthetic route for the generation of aza dipyrrins involves heating nitrobutanones with an ammonium source, in alcohol. Despite the practical simplicity, the reaction pathway(s) for this conversion is complex. However, the proposed mechanism (**Scheme 23**) for this transformation suggests, first, the multi-step generation of a nitroso pyrrole. This material then, upon reaction with an alpha-free pyrrole, condenses to form the aza dipyrrin. Given the large number of steps, many of which are likely reversible, no wonder the yields for this route are low and typically less than 50%.[130] Another strategy for the synthesis of aza dipyrrins, again leveraging early-stage C-N bond formation, is the use of nitroso-pyrroles as described in Chapter 3. The reported[91] route to nitroso pyrroles involves the reaction of an α-free pyrrole with NaNO$_2$ in acidic media, but this cannot be applied to the more electron-rich alkyl-substituted pyrroles. This warrants the need to consider other C-N bond formation strategies in pyrrolic systems.[91] Perhaps, the most viable alternative for the synthesis of aza dipyrrins, that can hopefully be applied to non-aryl substituted starting materials, requires exploration of other, mild, C-N bond formation strategies.
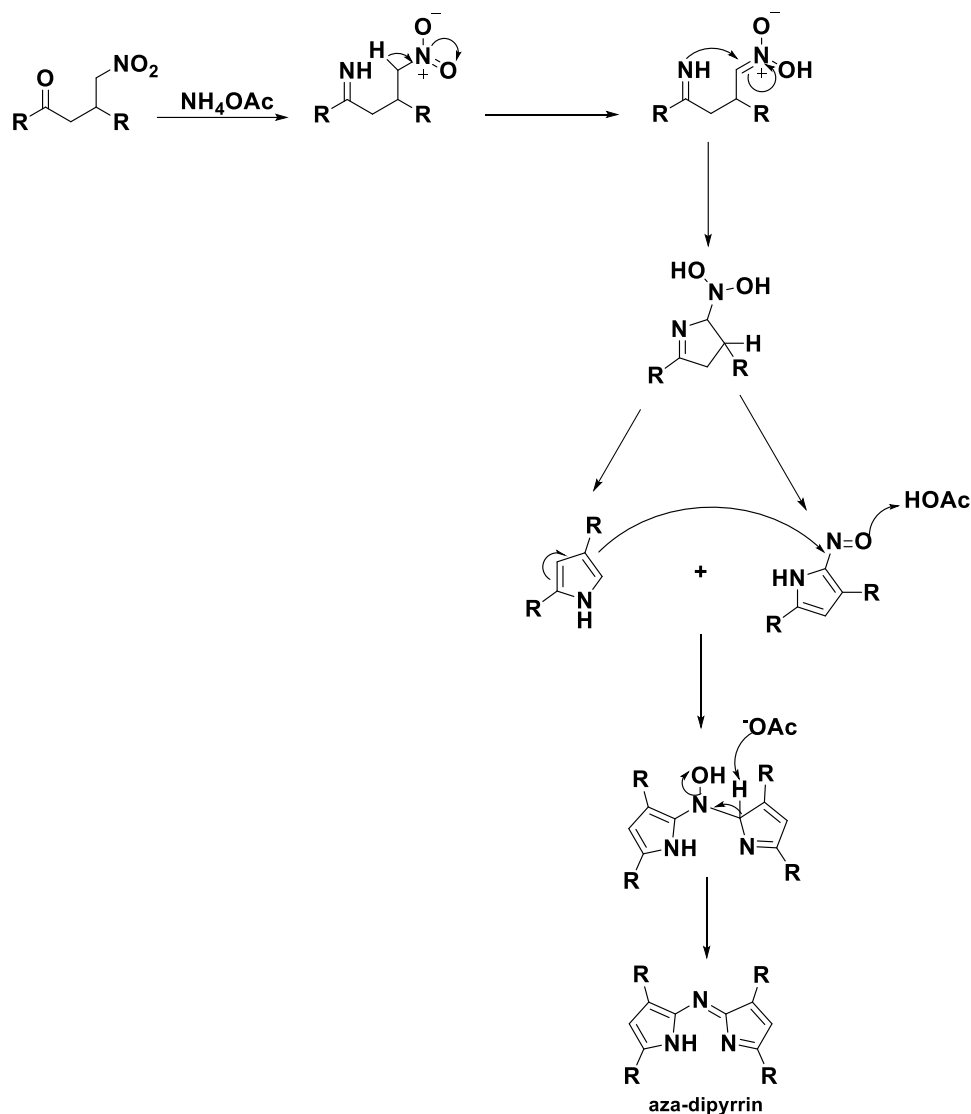
*Scheme 23: A suggested mechanistic pathway for the formation of aza dipyrrins from nitrobutanones.*

Most prevailing C-N bond-forming strategies involve transition metal (TM) catalysis.[131] TM-catalyzed C-N cross-coupling involves an electrophile-nucleophile approach, characterized by the Buchwald-Hartwig[132,133] and Ullmann-Goldberg[134,135] reactions in which aryl halides react with an amine or amide using stoichiometric or catalytic amounts of a Cu promoter (**Figure 19, A**). This has since been overshadowed by developments in Pd (**Figure 19, A**) catalysis due to low yields and harsh conditions.[134] Pd-catalyzed C-N cross-coupling, one of the primary methods used for

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catalytic C-N bond formation from aryl (pseudo)halides, still has persistent limitations. These include the requirement for elevated temperatures, strong bases, and expensive Pd (pre)catalysts.[136] Improved turnover, and the advantages of a reduced cost of base metal, encouraged the development of Ni-catalyzed C-N cross-coupling[137,138] (**Figure 19, A**) but these still face limitations such as the use of air-sensitive Ni(0) catalysts or customized ligand systems. An alternative approach to TM-catalyzed C-N bond formation involves the oxidative copper-catalyzed intermolecular C-N cross-coupling of N-nucleophiles with aryl-boron reagents (**Figure 19, B**)[131] In addition to the synthetic simplicity, this approach is supported by an impressive catalogue of aryl-boron derivatives now available both commercially and synthetically.[139] This protocol requires only mild reaction conditions, generally inexpensive reagents and tolerates a vast scope of coupling partners.
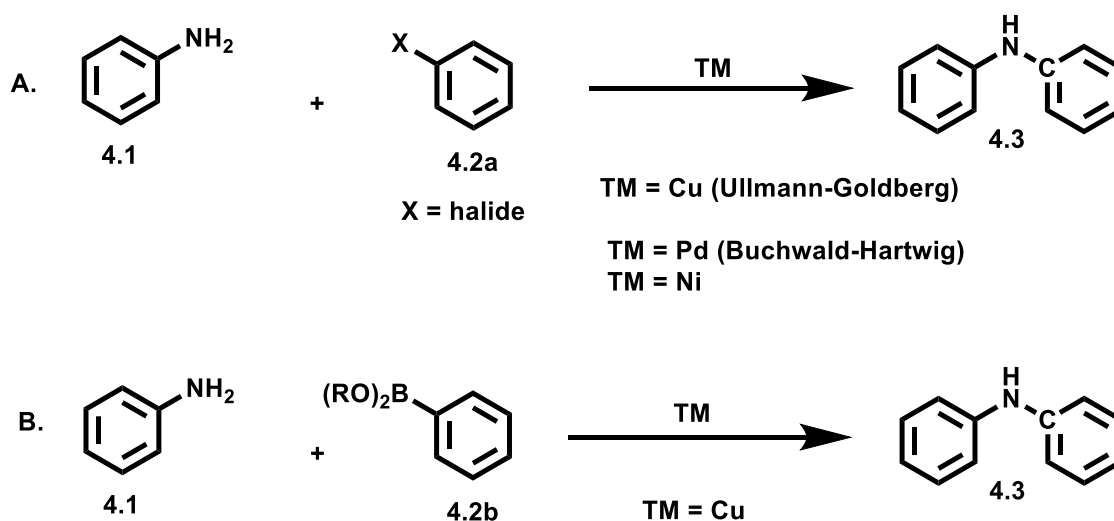


*Figure 19: Classic C-N coupling protocols.*

While these strategies allow for facile C-N bond formations, replacing to an extent harsher methods (Goldberg reaction, nucleophilic aromatic substitution, etc.),[135] and significantly expanding the repertoire of C-N bond formation, transition metal-based catalysts are often toxic, costly to make and/or require complicated ligands. Their removal from the final product can be cumbersome. Therefore, metal-free routes to C-N bond formation for application to the synthesis of aza dipyrrins are more desirable.

Recently, the Radosevich group reported a reductive strategy for C-N coupling that does not rely on transition metals, thereby enabling a complementary route from readily accessible nitro compounds and boronic acids (**Figure 20**).[140] Specifically, this organophosphorus-based strategy relies on an all-main-group system composed of an organophosphorus P(III)/P(V) redox catalyst and hydrosilane as a reducing agent. This protocol requires in situ activation of the phosphine(V) oxide to form an active P(III) intermediate, which reacts with nitro substrates and regenerates phosphine(V) oxide. This method uses nitroarene substrates that are distinct from, but generally no less accessible than, those used in established C-N cross-coupling methods. The method also offers unique chemoselectivities and functional group tolerance.[141]
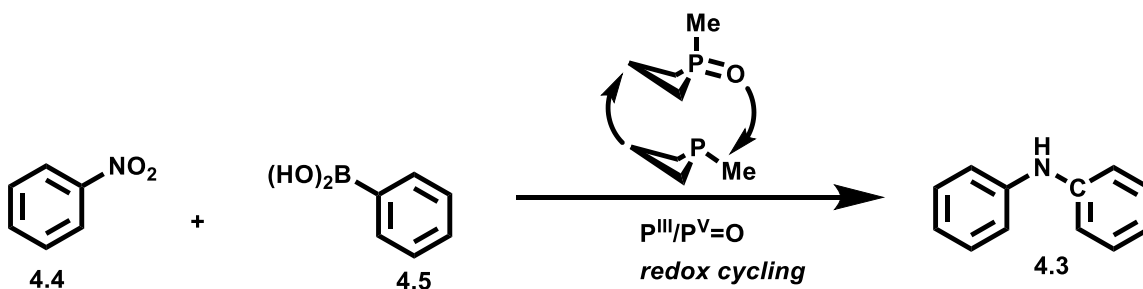


*Figure 20: Reductive C-N coupling (PIII/PV) redox catalysis.*

Given the challenges described in Chapter 3 involving the intramolecular cyclization of oxoamines in the attempted synthesis of the 4'4-diketoimides (**3.22b**), this P(III)/P(V) redox catalysis (**Figure 21, A**) presented an attractive approach for pyrroles. Synthesis of aza dipyrrins was envisioned via the phosphorus-based catalyst C-N coupling of α-nitro pyrroles and 2-pyrrole-boronic acids (**Figure 21, B**) in the presence of the silane reductant as reported by the Radosevich group.[140]

The hope was that the corresponding amino bispyrrole would undergo facile oxidation to form the desired aza dipyrrin. This approach is attractive as it relies on the availability of α-nitro pyrroles. These can be accessed via the reaction of an α-free pyrrole with nitric acid/sulfuric acid, with a variety of functionalized pyrroles. Similarly, aryl-boronic acids are generally bench-stable reagents that can be handled with no special precautions against air or humidity. Their toxicity is low, they present limited documented environmental issues and produce boric acid upon consumption in the Radosevich chemistry. Furthermore, there are lots of reported methods for their preparation.[142]
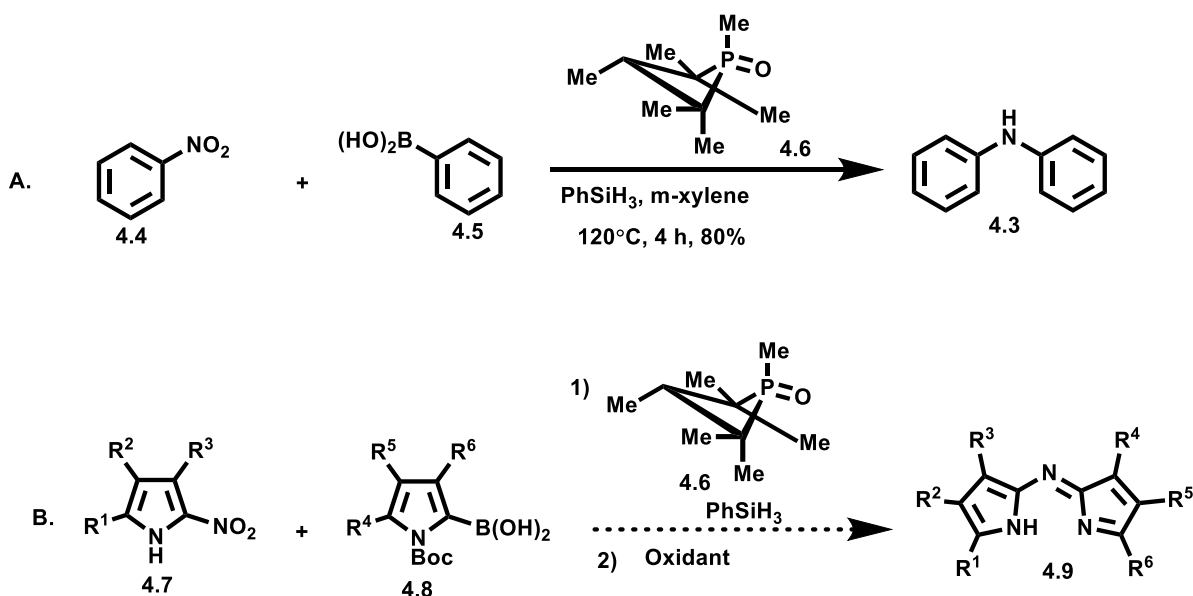


*Figure 21: Organophosphorus-Catalyzed Reductive C−N Coupling of nitro aryls and boronic acids.*

## 4.2 - Project Goals.

This project aims to develop a new method for the synthesis of aza dipyrrins by making use of Radosevich-inspired C-N phosphine-based catalysis, using nitropyrroles and 2-pyrrole boronic acids. The proposed coupling is mild, with no use of acid or excess reagents, and thus should offer potential with non-aryl-substituted pyrroles for the synthesis of novel non-aryl-substituted aza dipyrrins.

## 4.3 - Results and Discussion.

## 4.3.1 - Attempted coupling of nitropyrroles with boronic acids using Radosevich catalyst.

To investigate the viability of the proposed Radosevich-inspired C-N coupling for the synthesis of aza dipyrrins, diphenyl nitropyrrole **4.7a** (**Figure 22**) was chosen, as diphenyl pyrrole precursor can be readily synthesized. Boronic acid **4.8a** was chosen as the coupling partner, as it is commercially available. Successful coupling of these partners, followed by oxidation, would result in the formation of the aza dipyrrin **4.10a** (**Figure 22**).
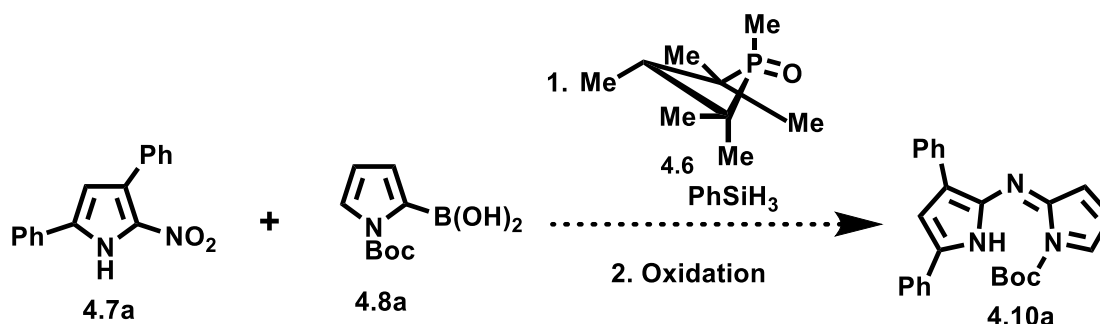


*Figure 22: Proposed coupling of nitropyrrole 4.7a and boronic acid 4.8a to aza dipyrrin 4.10a.*

In order to synthesize the nitro-substituted pyrrole **4.7a**, the previously described chalcone chemistry was utilized.[91] To this end, the chalcone **3.26b** was converted, via Micheal addition of nitromethane, to nitrobutanone **3.27b**. This transformation proceeds via deprotonation of nitrobutanone **3.27b** with KOH in MeOH to generate a nitro-stabilized anion. Hydrolysis in the presence of $H_2SO_4$ gave the 1-keto-4-dimethyl acetal intermediate, which was converted directly to the diphenyl pyrrole **3.28** using $NH_4OAc$.[143] The pyrrole was isolated in a 41% yield (**Scheme 24**). Nitration of diphenyl pyrrole **3.28** was then accomplished by reaction with nitric acid and sulfuric acid[144] to afford **4.7a** in a 24% yield.[12] Isolation and purification of the nitropyrrole was

difficult as nitration also occurred on the phenyl rings, providing a somewhat complex product mixture that requires careful chromatography in order to achieve the desired purity of product. Despite the low yield, the successful isolation of **4.7a** enabled the exploration of the proposed strategy.
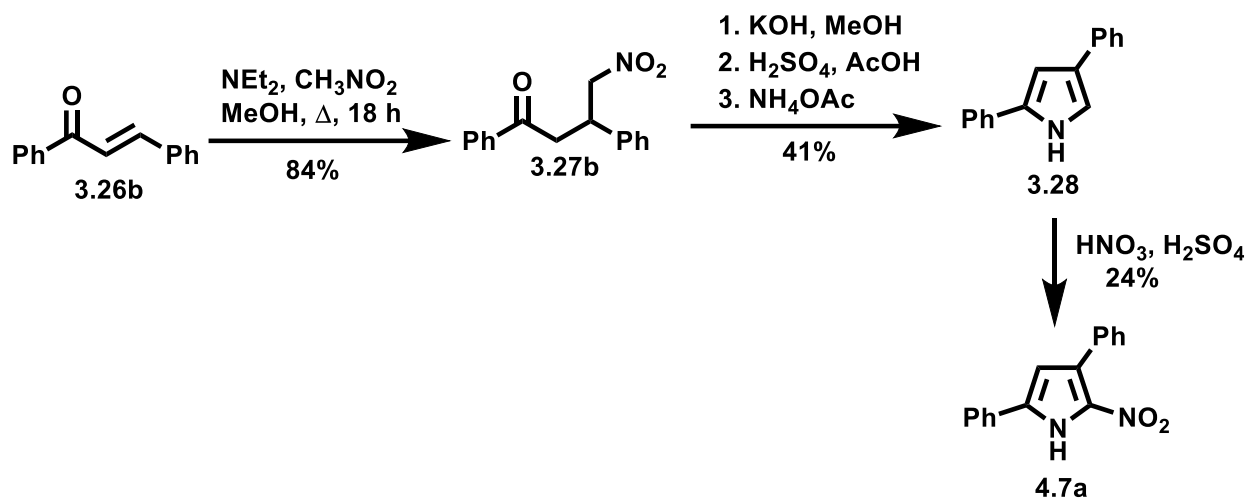


*Scheme 24: Synthesis of diphenyl nitropyrrole 4.7a.*

To evaluate the utility of the Radosevich chemistry, the diphenyl nitro-pyrrole **4.7a** was dissolved in *m*-xylene, then subjected to the coupling conditions with N-boc-2-pyrrole boronic acid **4.8a** in the presence of the phosphorus catalyst **4.6 (**which was obtained from Dr. Speed's lab) and PhSiH$_3$ as reductant (**Scheme 25**). According to the literature method, the reaction mixture was stirred for 18 hours at 120 °C, using an oil bath. Disappointingly, analysis of the reaction mixture by TLC revealed a mixture consisting of multiple components. Further analysis of the reaction mixture using MS analysis did not show evidence of dipyrrolic materials. The anticipated C-N coupling of the diphenyl-nitro pyrrole **4.7a** with the N-boc-2-pyrrole boronic acid **4.8a** was thus deemed unsuccessful under these conditions. It was speculated that stirring pyrroles at such high temperatures for long periods would likely result in decomposition, and hence the complex

mixtures obtained. To enable further exploration of this phosphorus-based coupling, extending it to pyrroles, further work turned to heating using microwave irradiation in order to shorten the reaction times.
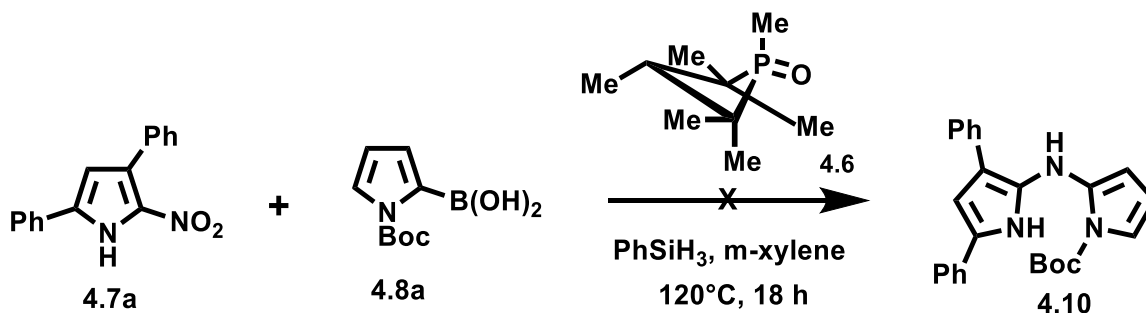


*Scheme 25: Attempted coupling of diphenyl nitropyrrole 4.7a and N-boc-2-pyrrole boronic acid 4.8a.*

Furthermore, given the failed C-N coupling involving two pyrrolic substrates, the procedure was repeated with phenyl substrates as reported by Radosevich's group,[140] so as to both confirm the feasibility of the original chemistry in our hands and to evaluate the feasibility of using microwave-promoted heating. To this end, nitrobenzene **4.4** and 4-chloro-phenylboronic acid **4.11** (**Scheme 26, A**) were subjected to C-N coupling in the presence of the phosphorus catalyst **4.6** and PhSiH₃. The reaction was heated using microwave irradiation. Analysis using TLC revealed the complete disappearance of starting material after 2 hours. Reassuringly, the desired arylamine **4.12** was successfully formed as the major product as shown by the formation of a single product according to analysis using TLC. Analysis of the crude reaction mixture using MS confirmed that the singular product was the expected material. Given that the method was successful for the synthesis of arylamine **4.12**, efforts returned to the incorporation of pyrroles. To that end, the coupling partners were varied so as to investigate the ability of diphenyl nitropyrrole (**4.7a**) to react with 4-chloro-phenylboronic **4.11** (**Scheme 26, B**) under the phosphorus-catalyzed conditions. The ability of the

N-boc-2-pyrrole boronic acid (**4.8a**) to act as a coupling partner with nitrobenzene was also explored **4.4** (**Scheme 26, C**). However, when either of the pyrrole-based substrates was subjected to the C-N coupling conditions with the corresponding phenyl substrate, the desired product was not identified via MS analysis of the reaction mixture. The reactions resulted in complex reaction mixtures with no evidence of expected products,
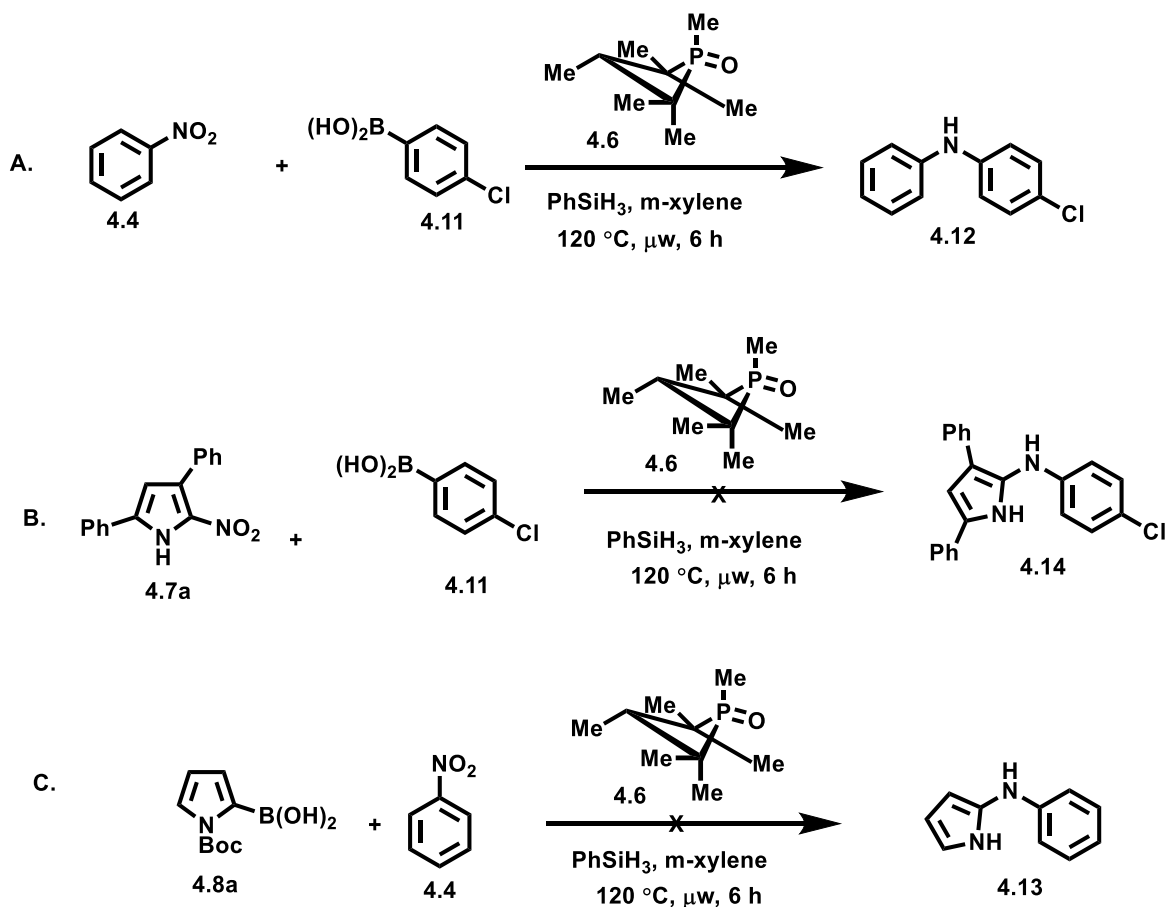


*Scheme 26: (A) Coupling of nitrobenzene 4.4 with boronic acid 4.11. (B) Attempted coupling of nitropyrrole 4.7a and boronic acid 4.11. (C) Attempted coupling of nitrobenzene 4.4 and boronic acid 4.8a.*

Based on these results it was concluded that these pyrrole-based substrates could not participate in the C-N coupling using Radosevich's catalyst **4.6**. This result was a major setback that prompted us to explore alternate organophosphorus compounds for the catalysis of this transformation. Tervalent organophosphorus compounds (PR$_3$) are potent nucleophiles that are used as catalysts in many reactions and react with a wide variety of oxygen-containing compounds to yield the corresponding quinquevalent derivatives (O=PR$_3$).[145] The major driving force behind these reactions is the great strength of the P=O bond formed.[143] Furthermore, experimental, spectroscopic, and computational data[141] suggest that P(III)/P(V)=O catalysis results in the reductive deoxygenation of nitro substrates to the corresponding nitroso compound in the first catalytic cycle (**Scheme 27**). Once formed, nitrosylated material **4.15** then undergoes a reaction with PR$_3$ to give an oxazaphosphirane intermediate **4.16**. This is postulated to coordinate with the boronic acid, followed by 1,2-migration of the organoboron residue to nitrogen, and final hydrolysis to afford the coupling product **4.19** (**Scheme 27**).[141]
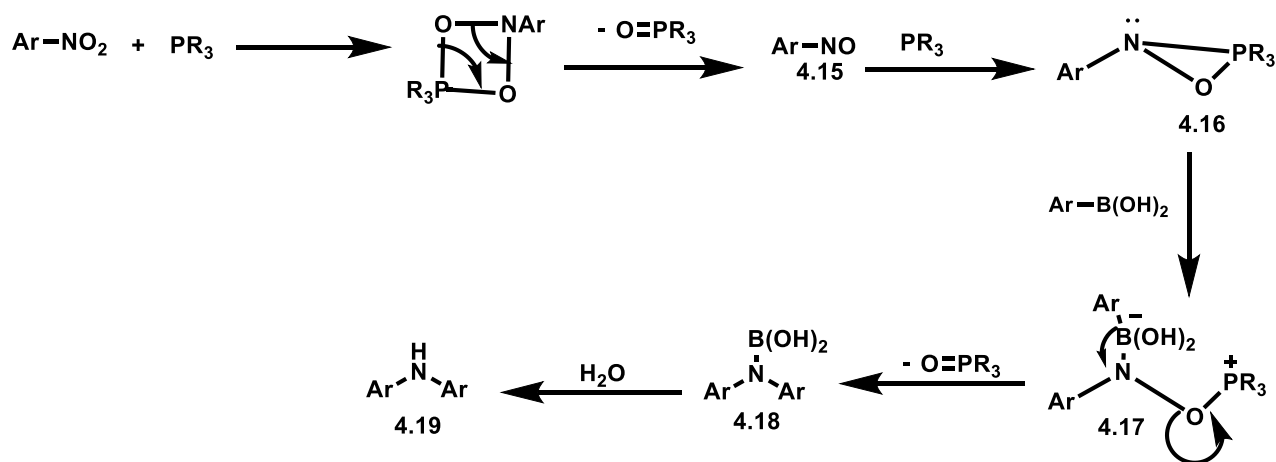


*Scheme 27: Reaction of boronic acids with nitro (hetero)arenes.*

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The realization that the nitro-aryl substrate shown in **Scheme 27** undergoes reduction, in the first catalytic cycle, to form a corresponding nitroso compound was beneficial because aryl nitroso pyrroles can be synthesized in much higher yield and with easier purification than their nitro-counterparts. Using nitroso pyrroles as starting materials would eradicate the first catalytic cycle and hopefully shorten the reaction time as nitroso compounds are deoxygenated by phosphines and phosphites much more rapidly than nitro compounds.[146] The protection of the N-atom of the nitroso pyrrole was deemed necessary before commencing the coupling. In this way, the reactivity of the N-atom could not interfere with the desired coupling chemistry. To prepare the nitroso-pyrrole, the pyrrole precursor was protected before the installation of the nitroso group. To this end, diphenyl-pyrrole **3.28** was reacted with iodomethane in the presence of sodium hydride[147] to yield the N-methyl pyrrole **4.20** in a 73% yield (**Scheme 28**). The N-methyl pyrrole **4.20** was then subjected to nitrosylation via treatment with NaNO$_2$ in ethanolic HCl to afford the novel N-methyl nitroso pyrrole **4.21** as a green solid in a 61% yield (**Scheme 28**).[148]
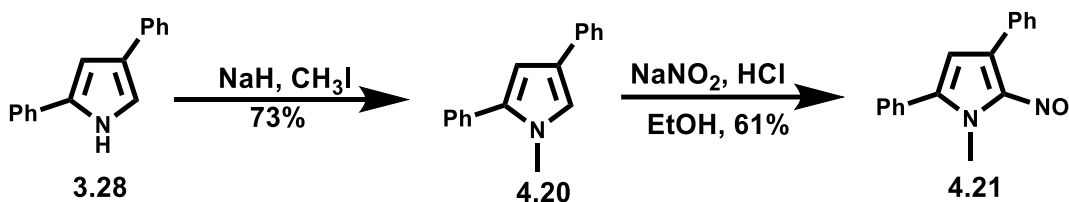


*Scheme 28: Synthesis of N-methyl protected diphenyl nitroso-pyrrole 4.21.*

Triphenylphosphine (PPh$_3$) was chosen for the first exploration of phosphorus(III)-based catalysts since it has been reported[149] to aid the deoxygenative coupling of nitroarenes and boronic acids. The N-methylated nitroso pyrrole **4.21** was therefore subjected to attempted deoxygenative C-N coupling with N-Boc-2 pyrrole boronic acid **4.11** using PPh$_3$ as the catalyst in the presence of

PhSiH$_3$ as reductant (**Scheme 29**). The reaction was stirred at 120 °C under microwave irradiation. Sequential analysis of the reaction mixture after heating for 10 minutes to 1 hour did not show any change in the reaction mixture. However, analysis of the reaction mixture after heating for 2 hours did not show consumption of nitrosopyrrole **4.21** but did reveal the disappearance of the boronic acid **4.11** and the generation of a new spot. Further analysis of the compound corresponding to the new spot revealed the presence of N-H pyrrole. It was speculated that the very high temperatures utilized might be causing the boronic acid **4.11** to decompose and hence exploration of alternating energy sources was deemed necessary.
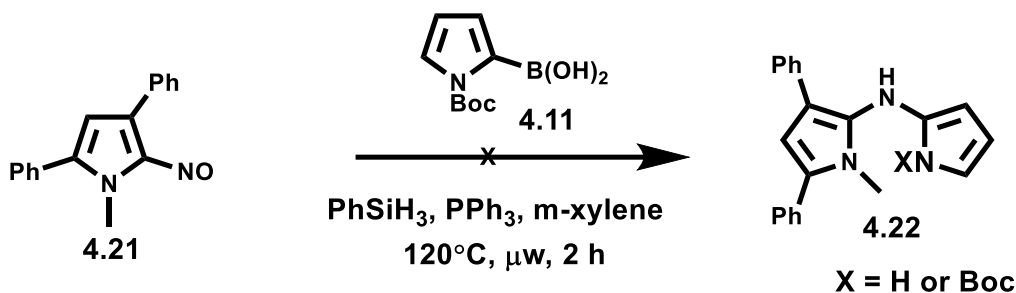


*Scheme 29: Attempted coupling of N-methyl nitroso-pyrrole 4.21 with boronic acid 4.11.*

## 4.3.2 - Attempted visible light and coupling of nitroso pyrroles with boronic acids.

Given that the N-boc-2-pyrrole boronic acid **4.8a** decomposed under the phosphorus-based catalysis conditions, other non-heat energy sources were considered for activation of the desired transformation. Recently, Manna and coworkers reported[150] a metal-free, visible-light- mediated reductive amination between nitroarenes and boronic acids involving triphenylphosphine (**Scheme 30, A**). This approach is performed at ambient temperature without any photocatalyst. In this synthesis, the nitroarenes are activated under the irradiation of visible light facilitating

deoxygenation through single-electron oxidation of triphenylphosphine. A nitroso-arene is formed that is readily converted to a nitrene intermediate which subsequently engages in C-N coupling with boronic acids.[150] Given that this approach does not require heating of the starting materials, it presents an attractive approach to aza dipyrrins via coupling of α-nitroso pyrroles and 2-pyrrole-boronic acids (**Scheme 30, B**) under CFL light irradiation. The hope was that, without heat, the boronic acid **4.8a** would survive and thus couple with the nitroso substrate **4.21** to form the desired amino bispyrrole **4.22**.
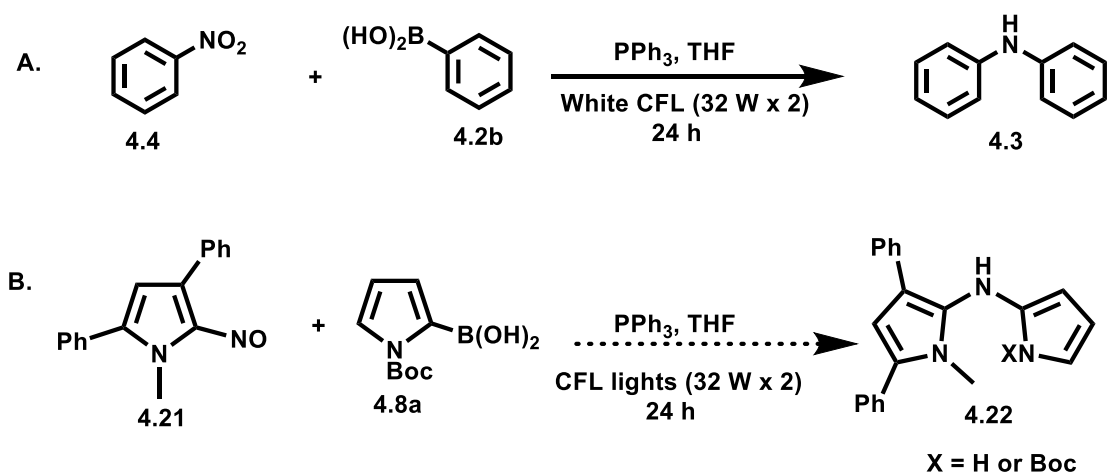


*Scheme 30: A: Photochemical PPh₃-mediated coupling of nitrobenzene and phenylboronic acid. B: Proposed photochemical PPh₃-mediated coupling of nitrosopyrrole and boronic acids.*

To evaluate the utility of this photochemistry in a pyrrole-based system, diphenyl-nitroso pyrrole **4.21** and N-boc-2 pyrrole boronic acid **4.8a** were dissolved in dry THF in the presence of PPh₃ and the reaction mixture placed under a nitrogen atmosphere. Irradiation with 64 W (2 × 32 W) CFL lamps for 24 hours (**Scheme 31**) and analysis of the reaction mixture using TLC after, revealed the complete consumption of the nitroso substrate and formation of three new spots. However, the boronic acid was not consumed based on the TLC analysis and was recovered quantitatively.

Spectroscopic analysis of the compounds corresponding to the three compounds formed suggested the carbazole-type product **4.23**, azoxy-type product **4.24** and azo dye **4.25** (**Scheme 31**). It was speculated that upon photoirradiation with the CFL lights, the nitroso substrate **4.21** undergoes reductive deoxygenation by reaction with the PPh₃ to form a nitrene intermediate which reacts differently forming the three obtained compounds.

One of the compounds formed is a carbazole type of product **4.23**. Research into this class of compounds revealed they are a known product of the Cardogan cyclization reaction of 2-nitrophenyl derivatives in the presence of suitable organophosphorus reagents.[145]
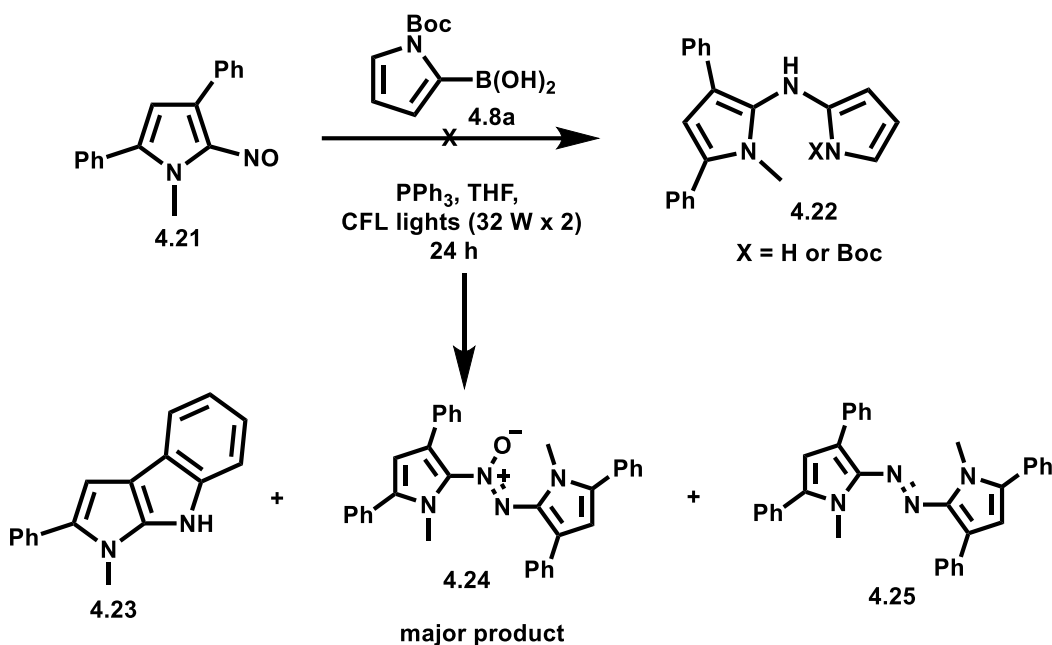


*Scheme 31: Attempted photochemical PPh₃ -mediated coupling of nitroso pyrrole 4.21 and boronic acids 4.8a.*

It was speculated that the formation of **4.23** is a result of a nitrene insertion into the proximal C-H position on the adjacent phenyl ring, rather than coupling with the boronic acid partner **4.8a**.[151–153] Based on this hypothesis, we postulated that to avoid the formation of the carbazole product **4.23**

and form the desired product **4.22**, the boronic acid **4.8a** should be present in excess. However, when the reaction was repeated in the presence of excess boronic acid **4.8a**, the carbazole product was still observed and the boronic acid was recovered quantitatively with no evidence of the desired product.

Another reaction product observed during the reaction of diphenyl-nitroso pyrrole **4.21** with PPh[3] under CFL light irradiation is the azoxy-type product **4.24**, analogous to azoxybenzenes (also known as N-oxides of azo compounds).[154] This type of product has been shown as an intermediate in the reduction of nitrobenzene to aniline with an unexpected level of stability.[155] The formation of this product suggests a reduction of nitroso pyrrole **4.21** to hydroxylamine **4.26** (**Figure 23**), which condenses with another molecule of nitroso pyrrole **4.21** to form the novel azoxytetraphenylpyrrole **4.24**.[156]
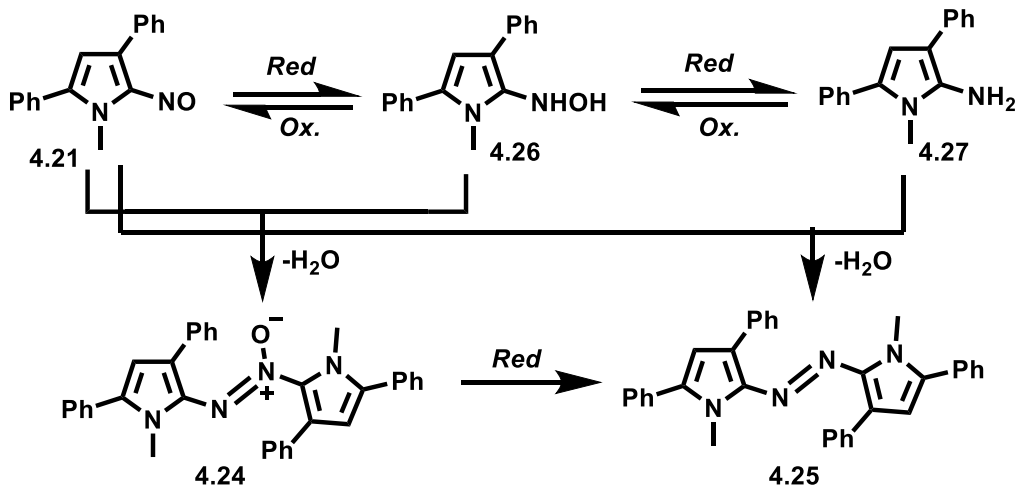


*Figure 23: Proposed reaction sequence to form azoxy-bis pyrrole 4.24 and azo bispyrrole 4.54 via hydroxylamine pyrrole 4.26 and amino pyrrole 4.27.*

Compounds containing an azoxy functionality are known to have broad applications in industry such as for dying and reducing agents,[157,158] chemical stabilizers,[159] chemical intermediates,[160]

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polymerization inhibitors,[161] and therapeutic agents.[162] Traditional industrial syntheses of azoxy compounds are often costly, inefficient, and environmentally unfriendly.[154,163] The discovery of these pyrrole-based azoxy compounds **4.24** can complement and meet the need for new sustainable azoxy compounds in industry.

The third product formed from the reaction of the nitroso pyrrole with boronic acid **4.8a** in the presence of PPh$_3$ and irradiation with white CFL lights appeared as an intense non-polar red spot upon analysis via TLC. The spot displayed bright orange fluorescence under long-wave ultraviolet light. A small amount of the red material was collected from the crude reaction mixture following chromatographic separation. Spectroscopic analysis of the red material and the LRMS-ESI$^+$ showed a [M+ H]$^+$ peak at *m/z* =493.23 The NMR data further suggested that the red material was diphenyl-azo bispyrrole **4.25** (**Scheme 31**). It was speculated that the hydroxylamine **4.26** (**Figure 23**) undergoes further reduction to form the amino pyrrole **4.27**, which then condenses with another nitroso pyrrole **4.21** forming the azo bis pyrrole **4.25**. Azo bispyrroles were accidentally discovered[129] in the Thompson lab by a previous researcher in their attempt to synthesize aza dipyrrins. These featured rotationally constrained β-aryl substituents and were prepared using NH$_4$OAc in glacial acetic acid under microwave irradiation. However, the yields for these syntheses of azo bispyrroles are very low. Another researcher from the Thompson group attempted[46] the development of a methodology to afford azo bispyrroles with improved yields, following the traditional way through which azo dyes are made i.e., via diazonium salts.[164] This traditional route demanded the use of amino pyrrole **4.27** which is very unstable and is notoriously known for self-condensing to the aza dipyrrin.[90] This resulted in the adoption of stringent anhydrous conditions for this synthesis with no ultimate reaction of the diazonium salts to the azo bispyrroles. The discovery of azo bispyrroles from the reductive deoxygenation of nitroso pyrroles

with PPh₃ under CFL light irradiation provides an alternative route to these pyrrole-based azo-dyes. The azo dye features the substitution pattern of the starting materials, presumably enabling the synthesis of variously substituted azo dyes. This will in turn allow further solid-state absorbance and emission studies on these compounds. Azo dyes often display spectacular photophysical properties and are key to dyes such as methyl orange, commonly known as the pH indicator and so have earned utility in textile, food, rubber, and plastic industries.[165] Besides their characteristic colouring function, azo compounds are reported[20] as antibacterial, antiviral, antifungal and cytotoxic agents. They can be used as drug carriers and are currently being screened for their potential biomedical use, including cancer diagnosis and therapy.[166]

Despite the exciting discovery of new classes of pyrrolic compounds, the aim of this project is to find an improved alternative synthesis of aza dipyrrins. Given the unsuccessful attempts thus far, other alternative conditions were thus explored.

## 4.3.3 - Attempted PPh₃/NaI photochemical reduction of nitroso pyrroles under blue LED irradiation.

Given the recovery of boronic acid **4.8a** in the attempted coupling with nitroso pyrrole **4.21** under photo irradiation with CFL lights, it was concluded that N-boc-2-pyrrole boronic acid **4.8a** is not reactive under these conditions. Therefore, efforts focused in the use of the nitroso pyrroles **4.21b**. Nitroso pyrroles are known to undergo reduction with Adams catalyst or by hydrogenation with palladium on carbon catalyst to provide amino pyrrole **4.27** which undergoes dimerization upon exposure to air to form aza dipyrrins, with loss of ammonia, in very low yield.[90,98,167]
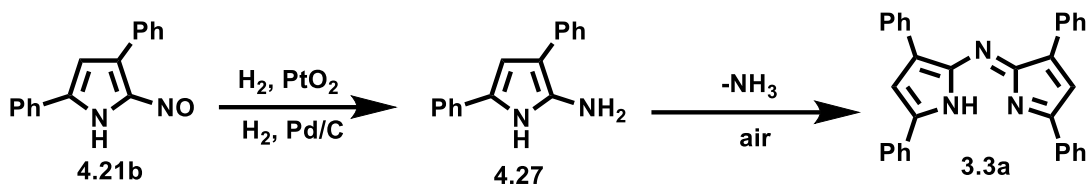
*Scheme 32: TM-catalyzed reduction of nitroso pyrrole 4.21b to amino pyrrole 4.27 and condensation of 4.27 to aza dipyrrin 3.3a.*

Recently, Qu and co-workers reported[168] a mild, highly selective transition-metal-free photo redox system based on the combination of NaI and PPh$_3$ for the reduction of nitroarenes (**Scheme 33, A**). In this system, the combination of nitroarenes with NaI and PPh$_3$ was found to generate an electron-donor-acceptor (EDA) complex under blue LED light irradiation. This EDA complex absorbs photons to enable reductive hydrogenation of nitroarenes with a variety of functional groups. Mechanistic insight on this NaI/PPh$_3$-mediated reduction of nitroarenes suggested the reduction of nitrosoarenes to the nitroso intermediate and then the hydroxylamine intermediate which is then decomposed by the EDA complex to provide the amine product.[169] From this system, a new pathway to the aza dipyrrins using the NaI/PPh$_3$ mediated reduction of nitroso pyrroles under blue LED light irradiation was envisioned (**Scheme 33, B**).
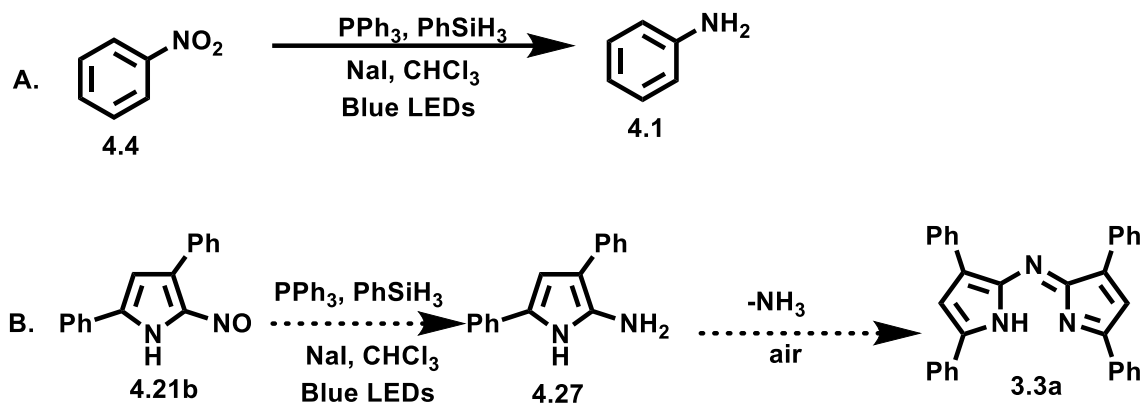
*Scheme 33: A: NaI/PPh₃-mediated photochemically reductive amination of nitrobenzene 4.4. B: Proposed synthesis of aza dipyrrin 3.3a via NaI/PPh₃-mediated photochemically reductive amination of nitroso pyrrole 4.21b.*

The hope was that the nitroso pyrrole **4.21b** would undergo reduction under the blue LED light irradiation to form the amino pyrrole **4.27** in situ. The amino pyrrole would then dimerize to form the desired aza dipyrrin **3.3a**. To evaluate the feasibility of this proposed hydrogenative amination approach, nitroso pyrrole **4.21b**, PPh₃, NaI and PhSiH₃ were dissolved in anhydrous CHCl₃ and the reaction mixture was stirred under blue LED irradiation for 18 hours (**Scheme 34**). Pleasingly, the reaction mixture changed from the green nitroso colour to a vibrant blue colour typical for aza dipyrrins. The crude reaction mixture showed two spots on TLC analysis and when the crude sample was submitted for MS analysis, it revealed that the spots were that of the aza dipyrrin and the pyrrolehydroxylamine **4.26**. The blue compound was isolated by column chromatography in a 44% yield and ¹H NMR showed that it was indeed the tetraphenyl aza dipyrrin **3.3a**. This was a satisfying result which meant that a new method for the synthesis of aza dipyrrin was successfully developed, with a comparative yield to the current chalcone route towards aza dipyrrins.[90] The disappearance of the methyl group in the final product is baffling as it is a rigid protecting group

for pyrroles, we hypothesized that the presence of triphenylphosphine might have led to the deprotection of pyrrole. Attempts to isolate the pyrrolehydroxylamine **4.26** were unfruitful as it
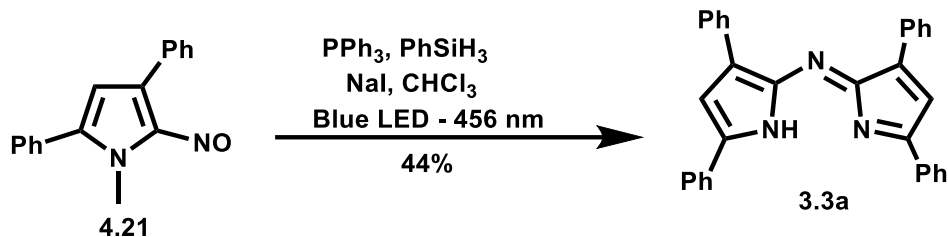


**Scheme 34: Synthesis of aza dipyrrin 3.3a via NaI/PPh₃-mediated photochemical reductive amination of nitroso pyrrole 4.21.**

decomposed upon exposure to air. The presence of the pyrrole hydroxylamine provides evidence that the NaI/PPh$_3$ reductive amination under blue LED irradiation indeed follows the mechanism described by Qu and co-workers[168] where the nitroarenes are reduced to the nitroso intermediate, which is then reduced to the hydroxylamine intermediate which is further reduced to the aminopyrrole, which dimerizes to the aza dipyrrin. Based on this hypothesis, we speculated that the addition of excess PhSiH$_3$ would prompt the full conversion of hydroxylamine **4.26** to amino pyrrole **4.27** and hence lead to an increase in the yield of the aza dipyrrin **3.3a**. However, repeating the reaction in the presence of excess PhSiH$_3$ resulted in the complex reaction mixture based on TLC analysis and a drastic decrease in the yield of the desired aza dipyrrin **3.3a**.

Given the salient features of the present reduction protocol including no need for transition-metal catalysts, mild reaction conditions, ample potential substrate scope with broad functional group tolerance, and high chemoselectivities. Application to non-aryl substituted pyrroles for the synthesis of particularly alkyl-substituted aza dipyrrins was envisioned. With the established reductive amination by the blue LED irradiation-induced NaI/PPh$_3$ catalytic system, it was

postulated that other substrates, including alkyl-substituted nitroso pyrroles, would survive under these conditions. In order to explore the tolerance of the reaction when utilizing alkyl-substituted nitroso pyrroles, the starting materials were to be synthesized. Nitroso pyrroles are generally synthesized by the direct nitrosylation of pyrroles using sodium nitrite in ethanolic HCl. Even though reports[170] show that this approach cannot be applied to alkyl-substituted pyrroles, a decision was made to try this nitrosylation in our own hands. To this end, pyrroles stabilized by electron-withdrawing groups were chosen ahead of any attempts to synthesize nitroso pyrroles bearing exclusively alkylated substitution. To start, dimethyl acetal-pyrrole **4.28** (**Scheme 35, A**) was subjected to a reaction with $NaNO_2$ in ethanol in the presence of concentrated HCl following reported conditions.[148] Analysis of the reaction with TLC showed a complex product mixture with multiple spots. MS results for the reaction mixture did not show the peak for the desired product **4.29**. Faced with this challenge another substrate was chosen. The Knorr-type pyrrole **4.30** (**Scheme 35, B**), featuring a benzyl ester and an ethyl ester in the 2- and 3-positions, respectively, is prepared in large quantities within the Thompson group and is hence readily available for use. In order to prepare the α-free pyrrole **4.32**, first the benzyl ester was cleaved to the carboxylic acid **4.31** via hydrogenolysis. Decarboxylation of **4.31**, facilitated by the treatment with TFA, generated the α-free pyrrole **4.32**(**Scheme 35, A**). The α-free pyrrole was then subjected to nitrosylation conditions with $NaNO_2$ in ethanolic HCl. Just as with the previous substrate, the desired nitroso product **4.33** was not identified in the reaction mixture, based on the MS results of the crude reaction mixture. Before giving up on the nitrosylation of alkyl-substituted pyrroles, another substrate was chosen. The pyrrole **4.34** also available in the Thompson group, was deprotected by reaction with HCl in ethanol to provide the α-free pyrrole **4.35** which was subjected to nitrosylation conditions with $NaNO_2$ but to no avail (**Scheme 35, C**). The reaction resulted in a complex mixture

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as with the previous substrates. At this point, it was concluded that alkyl-substituted pyrroles could not be nitrosylated using the current method used for the aryl-substituted pyrroles.[148]
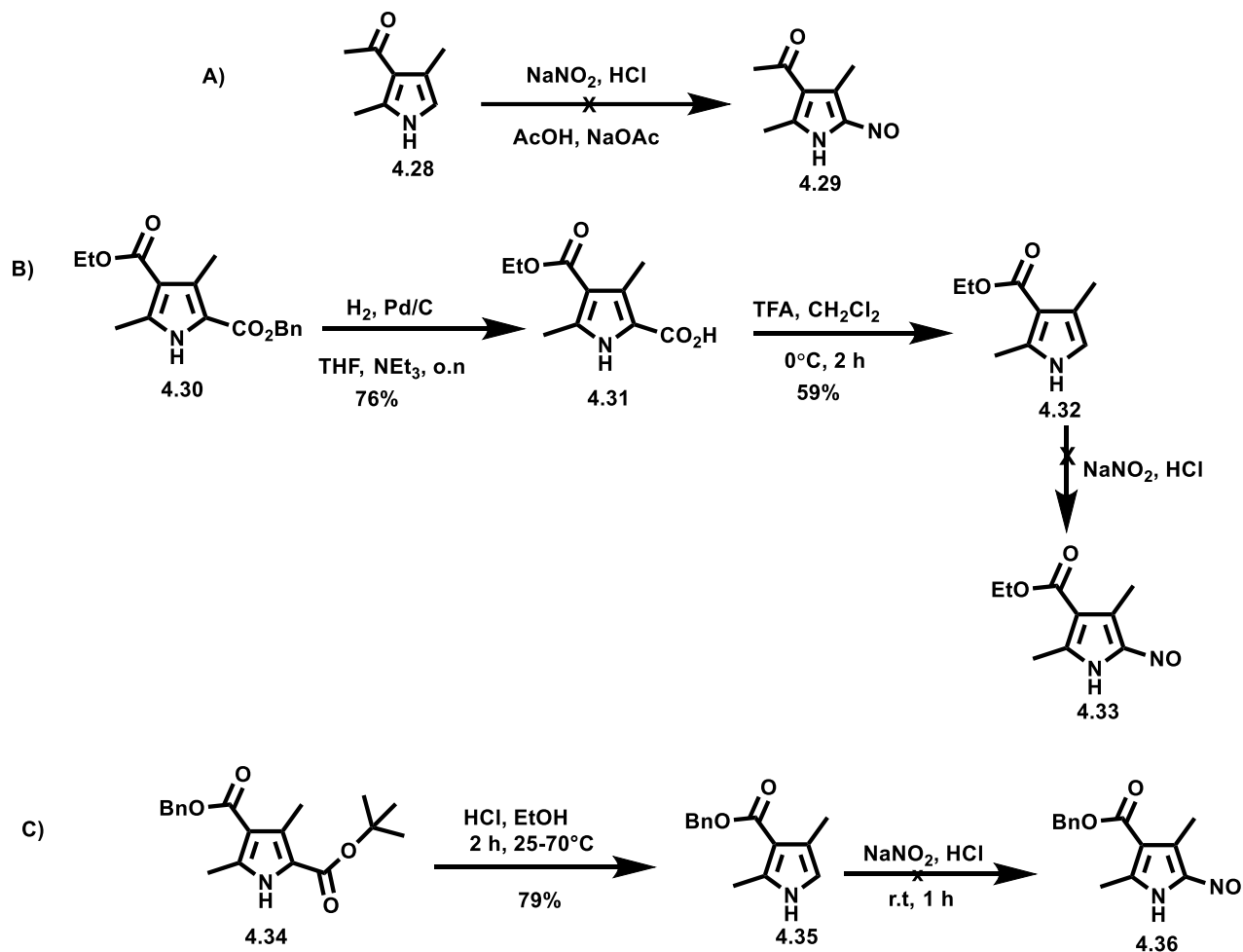


*Scheme 35: Attempted nitrosylation of alkyl-substituted pyrroles.*

While this approach has been well-established for aryl-substituted pyrroles, the nitrosylation of alkyl-substituted pyrroles clearly remains a challenge.[148,171] Possibly the acidic conditions induce polymerization of the highly reactive alkyl-substituted pyrroles.[172] This necessitates the development of an efficient and selective method for the nitrosylation of non-aryl-substituted pyrroles for the synthesis of non-aryl-substituted aza dipyrrins.

## 4.3.4 - An alternative route to α-nitroso pyrroles.

The encountered challenges in the synthesis of non-aryl substituted nitroso pyrroles warrant the need for the development of a new approach requiring only mild and preferably non-acidic conditions. A common route to α-nitroso pyrroles, as mentioned before, involves the *in situ* generation of nitrosonium ions by treatment of α-free pyrroles with sodium nitrite under acidic conditions.[173] Evidently, this method for the nitrosylation of pyrroles cannot be applied to non-aryl substituted derivatives. The first nitroso compound to be synthesized was nitrosobenzene published by Baeyer over a century ago.[174] Since then, several methods have been published for the synthesis of nitrosoarenes[173] via nitrosonium ions generated in-situ from salts with different counterions (e.g. $BF_4$ , $PF_6$, $HSO_4$, $ClO_4$ etc ). Starting materials e.g. $NO_x$, $N_2O_3$, $N_2O_4$, nitrites and prefunctionalized ionic liquids, and reactions involve numerous protocols.[173]

Attention was thus turned to the use of nitrosonium salts, rather than $NaNO_2$, for nitrosylation. Nitrosonium salts are generally inexpensive, stable and safe in handling, which makes them attractive reagents in organic chemistry. Molender et al.[175] showed that nitrosoarenes can be synthesized by a mild direct nitrosylation procedure using the $NOBF_4$ nitrosonium salt (**Scheme 36, left**).  In this synthesis, the authors used the potassium trifluoroborate aryl system **4.37** with the trifluoroboryl moiety acting as a directing group for the introduction of the nitroso electrophile at the ipso-position. The procedure led to the formation of a nitrosoarenes **4.38** with defined regioselectivity and with compatibility with various functional groups including challenging heteroarenes.[175] Hilt et al.[176] also reported the use of $NOBF_4$ as a nitrosylating reagent for the synthesis of nitrosobenzene derivatives from trimethylsilyl-substituted benzene derivatives **4.39** (**Scheme 36, right**). The synthesis was shown to be effective for both electron-rich, electron-deficient and bulky starting materials.[176] A shared feature of both methods is the fast reaction rate,

with the formation of products occurring within the first few minutes. According to the proposed mechanism for the two approaches, a shared pathway for the nitrosylation exists. This involves initial electrophilic ipso addition of nitrosyl and subsequent loss of -BF$_3$ or -SiMe$_3$ moieties. While these methods have been efficient for nitrosylation of other heteroarenes such as substituted pyridines, they have not been demonstrated in heteroaromatics such as pyrrole.
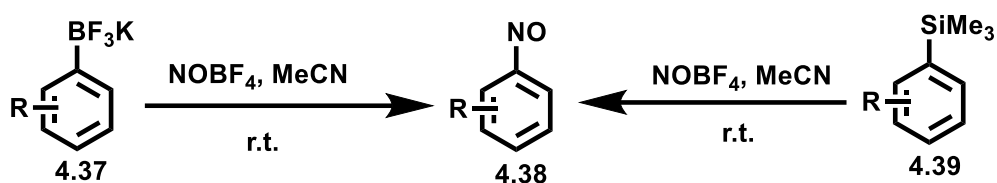


*Scheme 36: Use of leaving groups for aryl nitrosylation using NOBF$_4$.*

Based on the simplicity of this protocol it was desirable for application in pyrroles, particularly alkyl-substituted pyrroles. Pyrroles are known as electron-rich heterocycles, and functionalization of the pyrrole core generally occurs at the α-position.[7,8] Based on this reactivity, it was hypothesized that pyrroles would react directly with NOBF$_4$ for the introduction of the nitroso group on the α-position (**Scheme 37**).
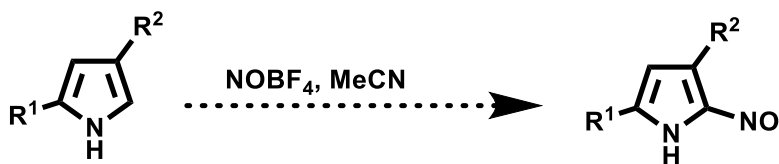


*Scheme 37: Proposed nitrosylation of pyrroles using NOBF$_4$ salt.*

To evaluate the utility of the proposed nitrosylation of pyrroles using $NOBF_4$, diphenyl-pyrrole **3.28** was chosen as the model substrate given that the corresponding product **4.40** is stable and well described.[90,91] Pyrrole **3.28** was synthesized according to a reported procedure.[148] The investigation of the nitrosylation of **3.28** with $NOBF_4$ was evaluated under various conditions (via varying solvents, temperature, equivalents and order of addition) as shown in **Table 8**. Initially, the reaction was carried out open to air in MeCN at room temperature (**Table 8, entry 1**), stirring the reaction mixture at room temperature as described by Molander et al.[175] Unfortunately, the desired product **4.40** was not detected. However, all starting material was consumed, as confirmed by TLC analysis and MS spectrometry data corresponding to the reaction mixture. Instead, a complex mixture was obtained. Repeating the attempted reaction at a reduced temperature of 0°C did not result in the detection of the expected product, nor did stirring for 24 hours (**Table 8**, **entry 2**). Fortunately, the portion-wise addition of $NOBF_4$ to the solution of **3.28** in MeCN under nitrogen at 0°C proved to be efficient for this transformation, affording the required nitroso product **4.40** in a 30% (**entry 3**). A by-product was also isolated. This material was characterized by $^1$H NMR spectroscopy and MS spectrometry as compound **4.41**, which is an intermediate to the tetraphenyl aza dipyrrin **3.3a** (**Table 8**, **entry 4**). Attempts to obtain a crystal structure for compound **4.41** were unfruitful as it forms the tetraphenyl aza dipyrrin **3.3a** upon sitting for a few days. It was speculated that the occurrence of this intermediate could be a result of the reaction of the desired nitroso pyrrole product **4.40** with some unreacted starting material **3.28**, a known reaction of nitroso compounds.[90,173] The reduced temperature was thus advantageous to formation of the desired nitroso pyrrole.
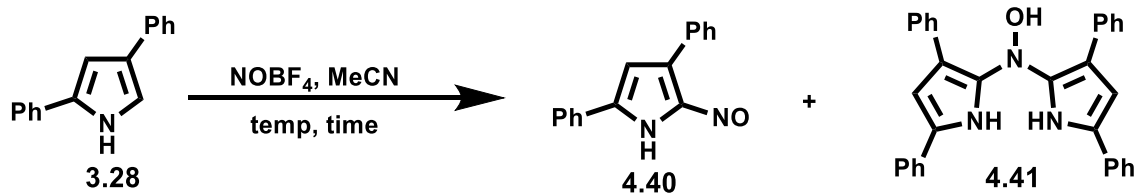
| Run | NOBF$_4$ (equiv) | Temp (°C) | Time (min) | Base | 3.28[a] | 4.40[a] | 4.41[a] |
|---|---|---|---|---|---|---|---|
| 1[b] | 1.5 | rt | 120 | none | ND | Trace | ND |
| 2[b] | 1.5 | 0 | 24 h | none | ND | 9% | ND |
| 3 | 1.5 | 0 | 5 | none | 42% | 30% | 18% |
| 4 | 2 | 0 | 5 | none | ND | 31% | 29% |
| 5 | 2 | 0 | 60 | none | ND | 40% | ND |
| 6[c] | 2 | 0 | 5 | none | ND | 17% | ND |
| 7 | 1.8 | -5 | 10 | none | 10% | 65% | ND |
| 8 | 1 | -5 | 24 h | none | 8 | 40% | ND |
| 9 | 0.9 | -5 | 5 | none | ND | 60% | ND |
| 10 | 0.5 | r.t | 6 h | none | 57% | 27% | 13% |
| 11 | 1.8 | -5 | 4 h | none | trace | 59% | 18% |
| 12 | 1.8 | -5 | 5 | NaHCO$_3$ | None | 49% | trace |
| 13 | 1.8 | -5 | 5 | Et$_3$SiH | None | 61% | trace |
| 14 | 1.8 | -5 | 5 | NaH | None | 58% | trace |
| 15[d] | 1.8 | -5 | 15 | None | None | 52% | ND |

*Table 8: Optimization of Nitrosylation reaction of 3.28 to 4.40. [a]Isolated yield, [b]Open to air, [c] Addition of pyrrole to the NOBF$_4$ in MeCN, [d] 1 g scale.*

In an attempt to further increase the yields of the nitroso pyrrole, the order of addition was reversed. Thus the pyrrole was added to a solution of NOBF$_4$ in anhydrous MeCN. Unfortunately, this resulted in a reduction in the yield of the desired nitroso product (**Table 8**, **entry 6**), suggesting that the nitroso product **4.40** is not stable in the presence of excess NOBF$_4$. Therefore, all reactions that followed were performed with the addition of the NOBF$_4$ to the solution of **3.28** in MeCN, to limit exposure of the product to NOBF$_4$. To improve the yields of the nitroso product and reduce the production of the intermediate **4.41**, the equivalents of the NOBF$_4$ were increased. However, this did not change the yield of the desired product, even when the reaction mixture was stirred for longer times (**entry 5**). Further screening revealed that a reduction in temperature to the -5 to -10°C range, by using a combination of an ice bath and acetone, is essential in slowing down if not eradicating the formation of the intermediate **4.41** (**Table 8, entry 8**). This makes sense as nitroso pyrroles have been reported to react with α-free pyrroles to generate the aza dipyrrins at elevated temperatures.[91] Furthermore, because the reaction of α-free pyrroles and NOBF$_4$ results in the formation of HBF$_4$, a strong acid, the use of additives (**entry 12 to entry 15**) to quench the HBF$_4$ was explored. Unfortunately, the use of bases to quench the HBF$_4$ did not have a positive effect on the yield of the nitroso product. In all the runs conducted, traces of the tetraphenyl aza dipyrrin **3.3a** were observed. And so I settled on utilizing 50 mg of **3.28** and 1.8 equiv of NOBF$_4$ in the absence of additives for all optimizations. When the reaction was scaled up from 50 mg to 1 g scale, the desired product was isolated in a 52% yield as shown in **Table 8** (**entry 14**). Although the yield is within the same margin as the original NaNO$_2$/HCl protocol, the new NOBF$_4$-mediated nitrosylation is faster as the latter requires three steps that run for over 2 hours.[91] Furthermore, the NOBF$_4$ approach does not involve the use of acidic conditions and requires simple workup and purification procedures.

Although a marginally improved yield was obtained using 1.8 equiv of $NOBF_4$ at -5°C using an ice bath and acetone as shown in **Table 8** (**entry 8**), the use of 0.9 equiv (**Table 8, entry 9**) was selected for application in other pyrrole derivatives based on stoichiometric reasons, and the desire to not promote dinitrosylation and to limit exposure of the nitroso product to excess $NOBF_4$. With the selected optimization conditions in hand (**Table 8, entry 9**), the protocol was extended to other pyrroles. Firstly, the generality of this transformation with respect to aryl-substituted pyrroles was evaluated. To do this, pyrroles with a variety of aryl-substitutions were synthesized to enable the study of how different functional groups behave under the new nitrosylation conditions. The synthesis of the pyrroles started with the synthesis of the chalcones **4.42(a-l)**, prepared from the corresponding benzaldehydes and acetophenones utilizing reported[90] conditions. The chalcones prepared are shown in **Figure 24**.
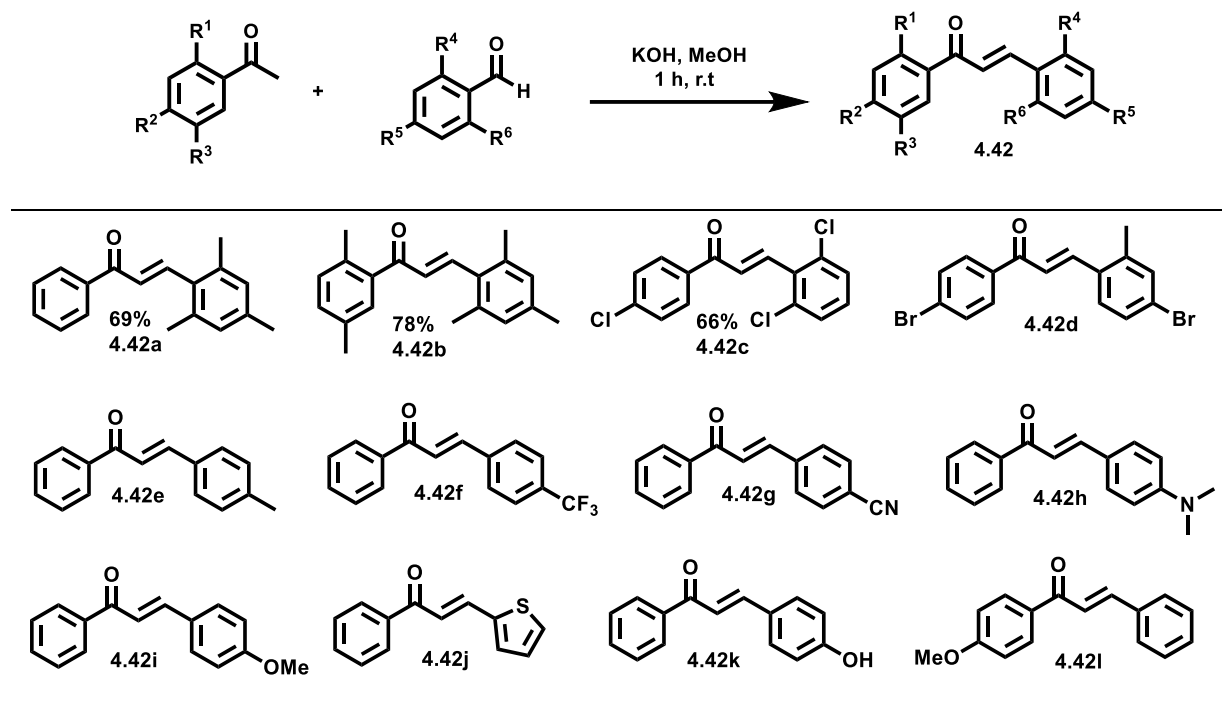
*Figure 24: Synthesis of chalcones 4.42 (a-l)*

The chalcones **4.42(a-l)** were then reacted with nitromethane under basic conditions and the reaction mixture was stirred at reflux temperature for 1h (**Figure 25**). In each case, the reaction mixture was then quenched via the addition of 1M HCl until pH 2 was achieved. At pH 2, each product precipitated as a white solid and was then isolated via filtration. In order to purify the white solids, each precipitate was dissolved in minimal dichloromethane and an excess of 20% ethyl acetate/hexane was added, and the resulting mixture was allowed to stand until a precipitate formed. The precipitate was then isolated via filtration and dried to afford the nitrobutanones **4.43** **(a-l)**. Although a literature procedure was used as a template for this synthesis,[148] DBU was identified as a superior alternative to diethylamine which was the reported base for this Michael

addition. Nitrobutanones **4.43(f-l)** were prepared with the help of Jacob Campbell, Emily brown and Adil Alkas from the Thompson group.
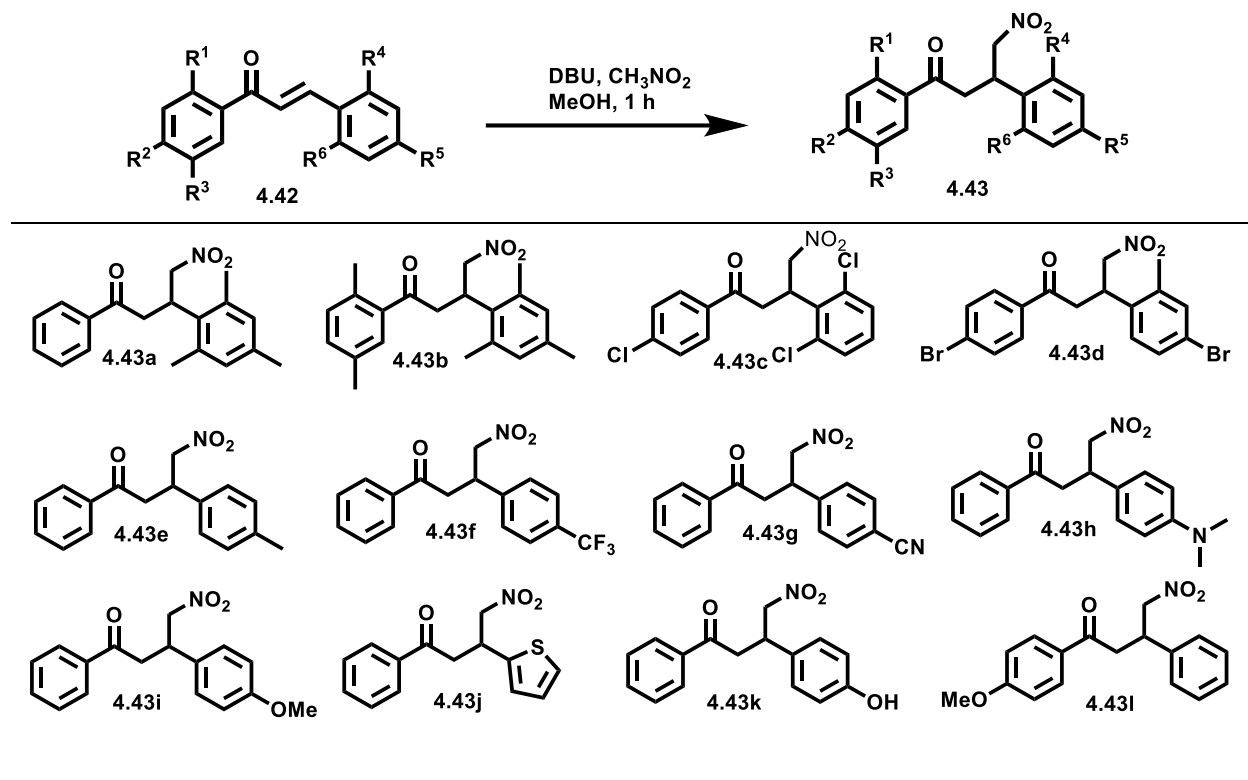


**Figure 25:** *Synthesis of nitrobutanones 4.43 (a-l) from chalcones 4.42.*

Following a published procedure,[148] the nitrobutanones were converted into pyrroles via a three-step procedure (**Figure 26**). Thus, the nitrobutanones **4.43(a-l)** were treated with a solution of KOH in anhydrous MeOH. The reaction mixture was stirred at room temperature for 1h and then the colourless solution was added dropwise into a solution of concentrated $H_2SO_4$ in anhydrous MeOH at 0°C. The reaction mixture was then allowed to slowly warm up to room temperature and further stirred for 1h. The reaction was quenched by the addition of water and ice, then neutralized to pH 7 with 4M NaOH. The mixture was then filtered, and the white solid thus obtained was dissolved in acetic acid and $NH_4OAc$ was then added. The mixture was stirred at reflux

temperature (100°C) for 1h. The mixture was cooled, poured over ice, and neutralized to pH 7 with 4M NaOH. The resulting precipitate was isolated via filtration and then dried. The solid was dissolved in minimal dichloromethane and upon the addition of excess cold pentane, a solid precipitated which was isolated via filtration and washed with cold pentane and dried to afford the pyrroles **4.44(a-l)** as a free flowing-solids (**Figure 26**). Pyrroles **4.44(f-l)** were prepared with the help of members from the Thompson group.
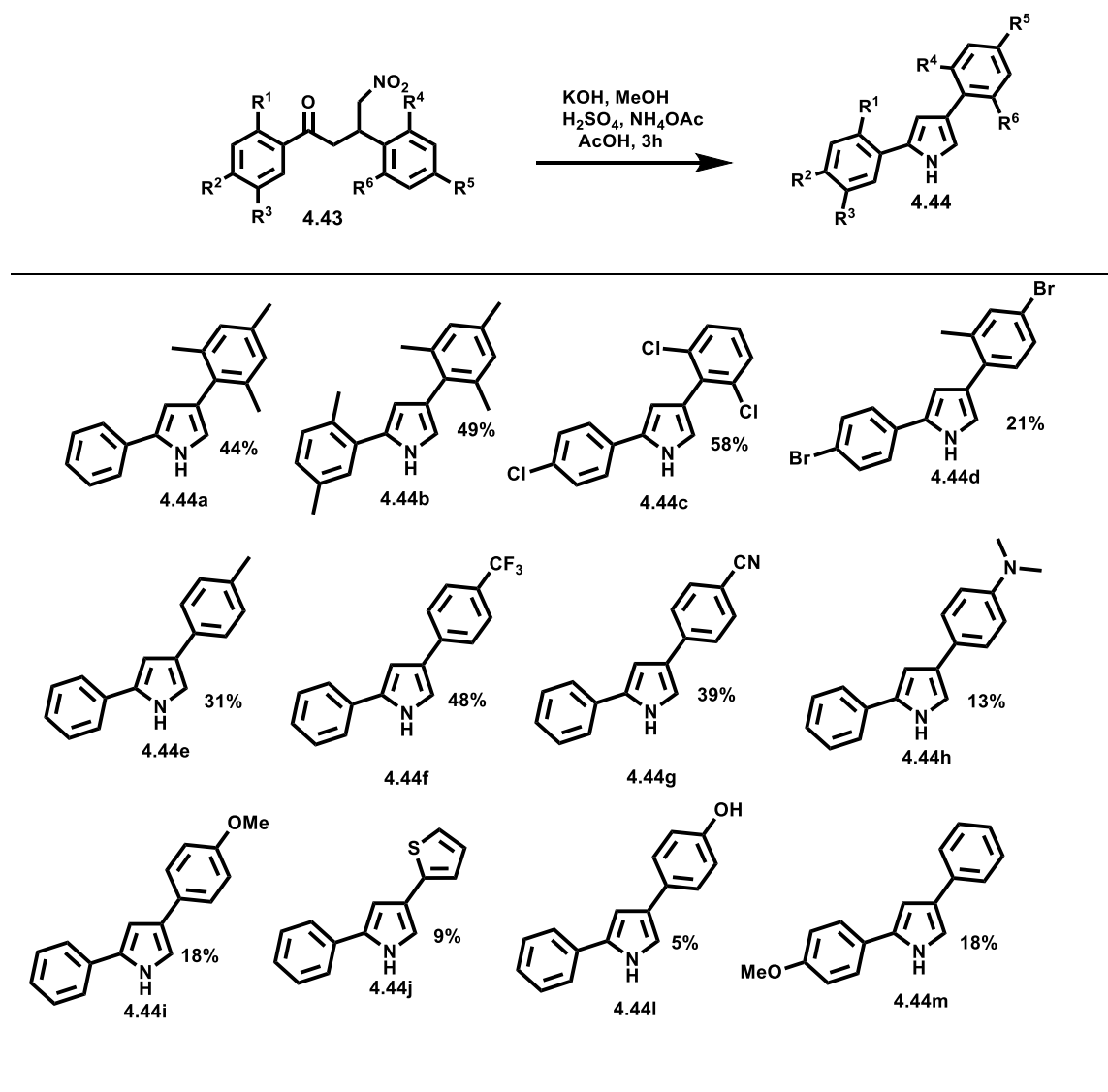


*Figure 26: Synthesis of pyrroles 4.44 from nitrobutanones 4.43.*

With the pyrroles in hand, the newly established nitrosylation conditions using NOBF4 were applied to other pyrrole derivatives. To this end, the aryl-substituted pyrroles **4.44(a-l)** containing a wide array of substrates were each dissolved in anhydrous MeCN under a nitrogen atmosphere at -5 to -10°C (achieved using an ice/acetone bath). Solid NOBF$_4$ (0.9 eq) was then added in 3 portions. The resulting solution was stirred for 5-10 minutes, in the cold bath, at which point all starting material was consumed according to analysis by TLC. The reaction mixture was added to water and extracted into CH$_2$Cl$_2$. The combined organic fractions were dried over anhydrous Na$_2$SO$_4$ and then concentrated *in vacuo*. The resulting solid was purified using column chromatography column to afford the desired 2-nitroso pyrroles. Pyrroles **4.44(a-h)** reacted successfully under the nitrosylation conditions to form each nitroso pyrrole in satisfactory yields (46-79%, **Figure 27**). These yields are within the same range as those obtained using NaNO$_2$/HCl.[90]
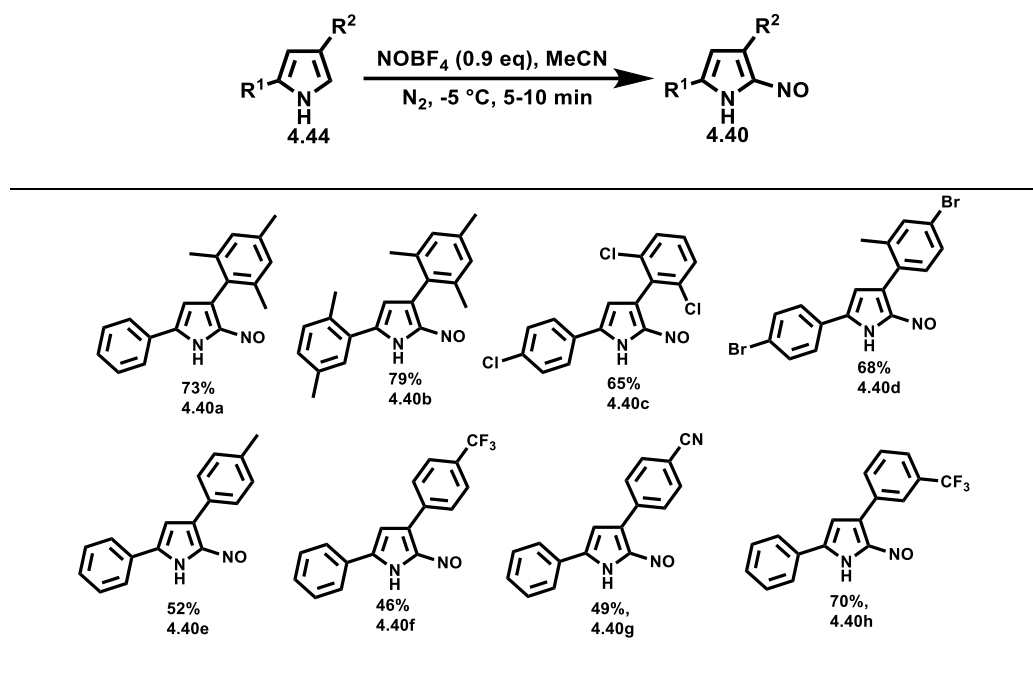


*Figure 27: Synthesis of aryl-nitroso pyrroles on a variety of pyrrole substrates.*

Despite success with pyrroles 4.44(a-h), analogues **4.44(i-m)** did not form the desired nitroso product under the optimal conditions for nitrosylation using NOBF$_4$ (**Figure 28**). These pyrroles all bear some electron-donating groups on the aryl rings.
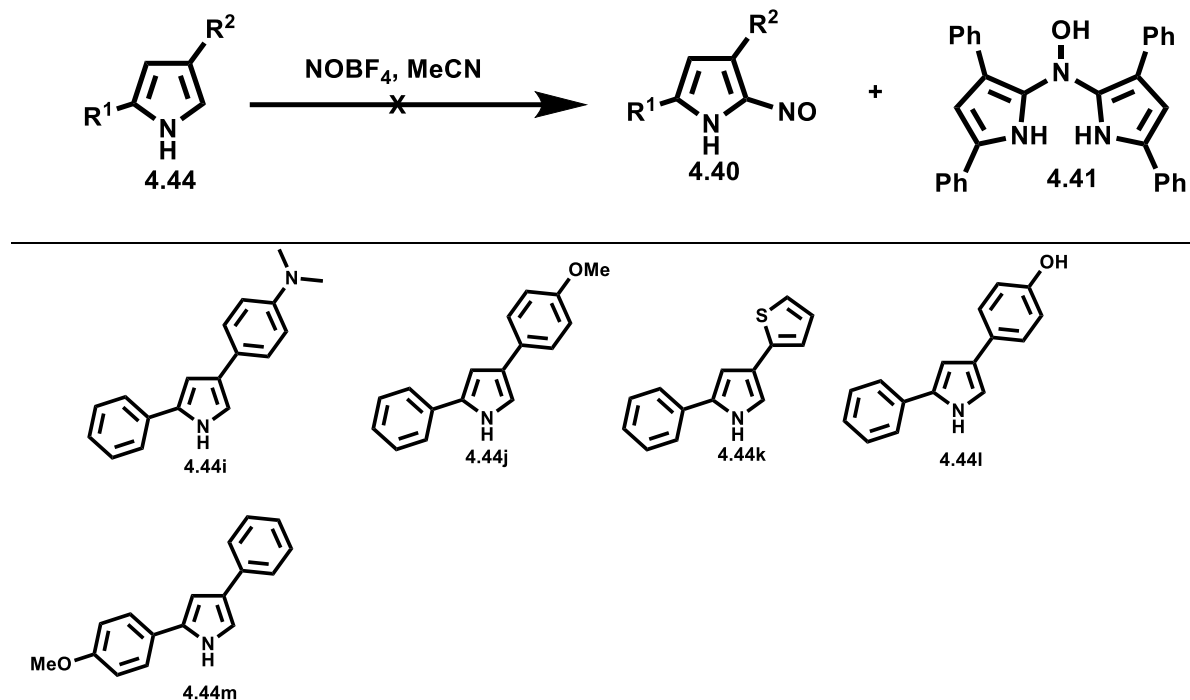


*Figure 28: Failed attempted nitrosylation of pyrroles bearing electron-donating groups on the phenyl rings.*

Although expending no efforts to isolate the material, based on MS analysis of the crude reaction mixtures the mass for the N-hydroxyl intermediate **4.41** was found in all runs, particularly for substrates bearing substituents featuring electron donating groups (**Figure 28**). Based on this observation, it was hypothesized that the increased electron density prompts the α-free pyrrole still present in the solution to immediately attack the nitroso pyrrole once formed to form the N-hydroxyl intermediate **4.41**. This is a positive result for the ultimate goal of the project which is the synthesis of aza dipyrrins, as the N-hydroxyl intermediate **4.41** is only one step away from the

aza dipyrrin. Based on this hypothesis and having established a broad scope for aryl-substituted

pyrroles, attention was then turned to alkyl-substituted pyrroles. Attempts towards the nitrosylation

of the dimethylpyrrole **4.45** (**Scheme 38**), using the optimal protocol involving NOBF$_4$, resulted

in a complex reaction mixture, based on TLC and $^1$H NMR analysis of the crude reaction mixture.

The desired nitroso product was not detected. The stoichiometry was reduced to as low as 0.5 equiv

NOBF$_4$, given the electron-rich nature of the pyrrole, yet without detection of the desired product.
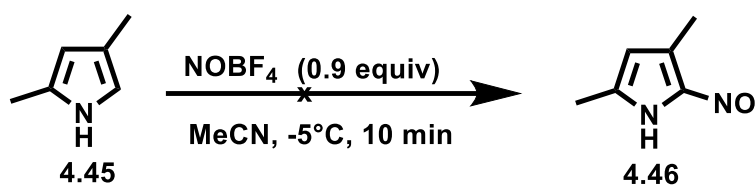


*Scheme 38: Attempted nitrosylation of dimethyl pyrrole 4.45.*

It was reasoned that since the pyrrole has two potential reactive sites that can potentially be

nitrosylated, coupled with the high reactivity of alkyl-substituted pyrroles, it might be over-

nitrosylated and/or prompt further reaction of the nitroso product with components of the reaction

mixture. With this in mind, efforts turned to the evaluation of stabilized alkyl-substituted pyrrole

**4.47** (**Scheme 39**), i.e. those bearing electron-withdrawing groups and with only one reactive

position. In this way, it was anticipated that any potential side reactions would be minimized.

Subjecting **4.47** to the optimal NOBF$_4$ conditions resulted in the formation of product **4.48**

(**Scheme 39**), which was isolated after column chromatography in a 53% yield, verified by NMR

and MS analysis. This result was particularly pleasing as it suggests that the desired nitroso product

did form but immediately reacted with the unreacted α-free pyrrole to make the hydroxyl

intermediate **4.48**. Leaving product **4.48** in an open-air environment for a couple of days did not

result in the formation of the aza dipyrrin as observed with the diphenyl nitroso pyrrole reaction.
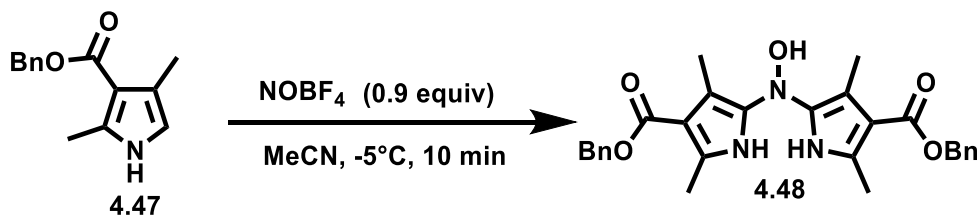
*Scheme 39: Synthesis of hydroxyl intermediate 4.48 from the nitrosylation of pyrrole 4.47.*

According to the proposed mechanism by Loudet et al. (**Scheme 23**)[130] for the formation of aza dipyrrins involving the condensation of a nitroso pyrrole and another α-free pyrrole, the hydroxyl aza dipyrrin intermediate is protonated by acetic acid, losing a molecule of water to produce an aza dipyrrin.[177] In light of this mechanism, it was hypothesized that subjecting **4.48** to acidic media would result in the formation of the alkyl-substituted aza dipyrrin. However, when **4.48** was stirred in acetic acid/acetic anhydride at 60°C, the desired aza dipyrrin was not detected. Instead, product **4.49** (**Scheme 40**) was isolated**.** Presumably, compound **4.40b** dissociated under the acidic conditions to make α-free pyrrole which reacted with a molecule of acetic anhydride to form pyrrole **4.49**. The X-ray structure of **4.49** is shown in **Figure 29**.
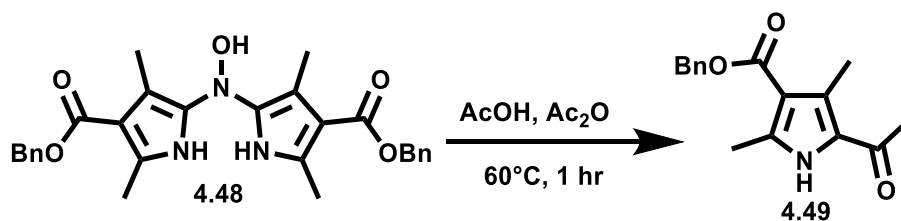


*Scheme 40: Attempted protonation of hydroxyl intermediate 4.48.*
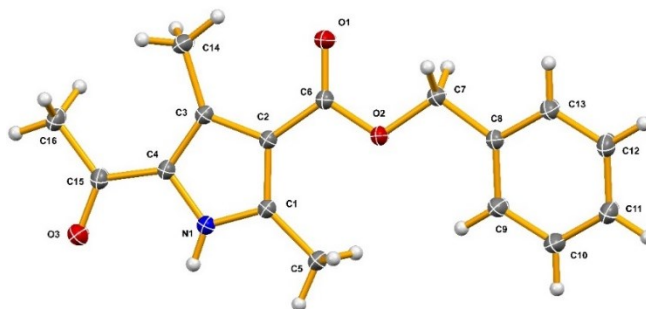
*Figure 29: OTREP diagram of pyrrole 4.49. Thermal ellipsoids are shown at 50% probability.*

The formation of the hydroxyl intermediate **4.48** prompted the evaluation of the protocol on an exclusively alkylated substrate **4.51** (**Scheme 41**). When **4.51** was treated with $NOBF_4$, the starting material disappeared 5 minutes after the addition of $NOBF_4$, according to TLC analysis. However, when subjected to aqueous workup, the colour of the crude reaction mixture changed from light brown to green, and then to black upon evaporation of the solvent in *vacuo*.
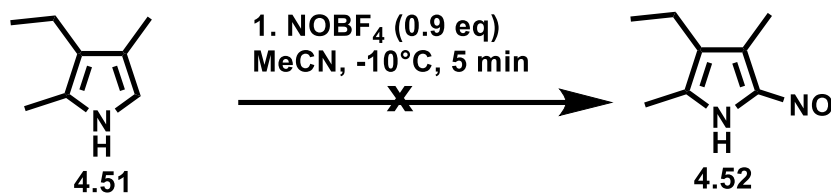


*Scheme 41: Attempted nitrosylation of pyrrole 4.51*

Analysis of the crude product mixture using TLC, after the workup, revealed many new spots and the corresponding NMR spectrum did not exhibit any peaks characteristics of the expected product. To avoid the aqueous workup and heat, the solvent (MeCN) was removed under a high vacuum. The sample was submitted for NMR spectroscopy. Although shimming was challenging due to the product methyl peaks lying under the MeCN solvent peak, the spectrum shows that the α-proton of the starting material **4.51** disappeared, indicating the presence of another species other

than a proton on the α-position of the pyrrole. Furthermore, the peaks in the product slightly shifted compared to the starting material **4.51** as shown in **Figure 30**.
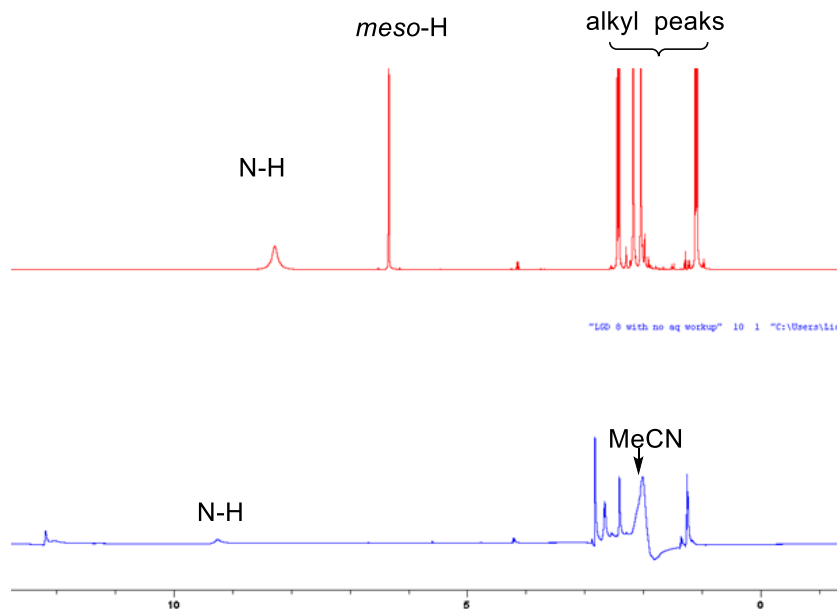


*Figure 30: Top: $^1$H NMR spectrum of pyrrole 4.51. Bottom: $^1$H NMR of the reaction mixture in MeCN showing disappearance of meso-H peak.*

The desired nitroso product was detected by MS analysis. This, together with the NMR data, suggests that the nitroso product forms under these nitrosylation conditions but is not stable in aqueous conditions and under heat. Based on this result, it was hypothesized that if the nitroso product formed, the addition of a second equivalent of **4.51** to the reaction mixture upon consumption of starting material, would result in the formation of the aza dipyrrin **4.53** (**Scheme 42**). However, the addition of a second equivalent of **4.51** resulted in a complex reaction mixture.
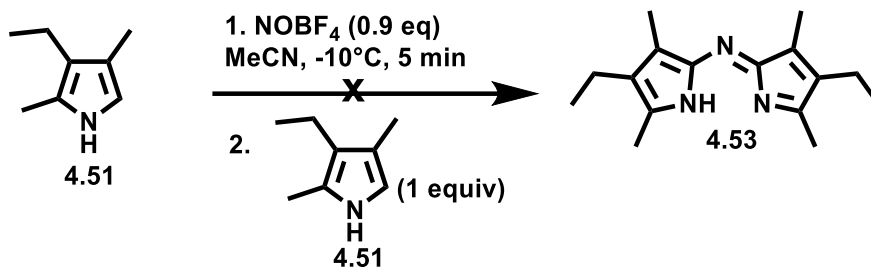
*Scheme 42: Attempted synthesis of aza dipyrrin 4.53 from the second addition of 4.51 to a solution of 4.51 and NOBF₄.*

Given the intense reactivity of the pyrrole **4.51**, it was hypothesized that the formation of HBF₄ would interfere with **4.51**, and/or with reaction products. Therefore, *in-situ* quenching of HBF₄ could potentially irradicate any side reactions. To quench the HBF₄, a variety of additives (**Scheme 43**) were added to the solution of pyrrole before the addition of NOBF₄. Addition of Et₃SiH and NaH still resulted in complicated reaction mixtures but, interestingly, the addition of NaHCO₃ to the reaction mixture resulted in the formation of the N-hydroxyl intermediate **4.54** (**Scheme 43**), confirmed by MS and ¹H NMR analysis. The corresponding ¹H NMR spectrum is shown in **Figure 31**, showing the sets of peaks for the product **4.54**. However, attempts toward acquiring a carbon NMR for **4.54** were unfruitful as the material decomposed.
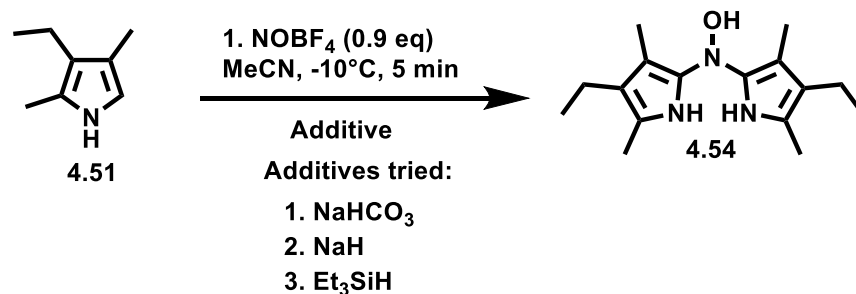
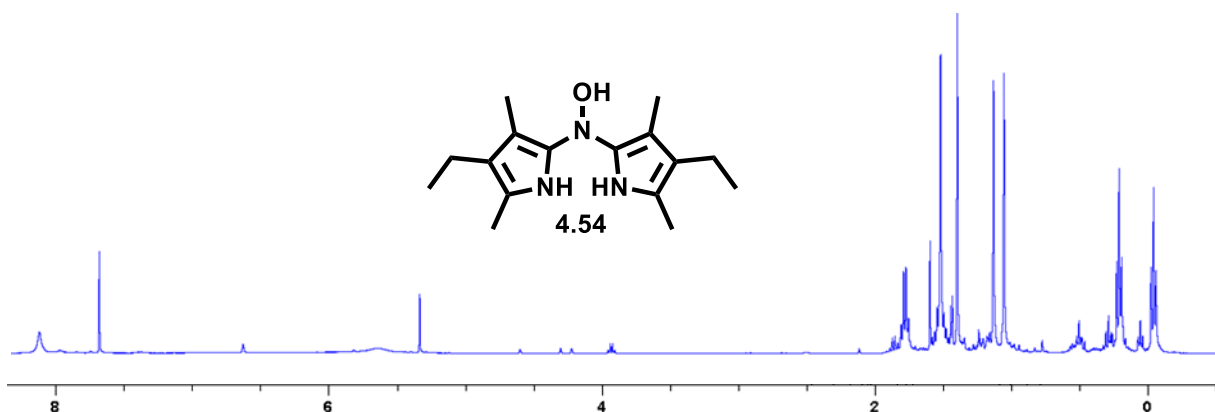Scheme 43: Synthesis of N-hydroxyl intermediate 4.54 in the presence of additives to quench HBF₄ in situ.



Figure 31: ¹H NMR spectrum of compound 4.54.

With the insight that product **4.54** was presumably being formed, but is not stable, it was hypothesized that trapping this material as an *F*-BODIPY **4.55** would enhance stability and allow further study and/or manipulations of this compound. To this end, pyrrole **4.51** was reacted with NOBF₄ in the presence of NaHCO₃. Instead of quenching the reaction, 6 equivalents of anhydrous NEt₃ were added and the reaction mixture was allowed to stir for 10 minutes before the addition of 9 equivalents of BF₃•OEt₂ (**Scheme 44**). A drastic colour change from brown to a deep purple fluorescent hue was observed upon addition of BF₃•OEt₂. TLC analysis of the reaction mixture showed the disappearance of the starting material after about 5 minutes of stirring, and the presence of a significant baseline spot plus two very fluorescent spots as shown in (**Figure 32, left**). The reaction was quenched with water and extracted with CH₂Cl₂. TLC analysis of the crude product

mixture showed the presence of multiple new spots. Purification to obtain the two compounds corresponding to the spots was achieved using column chromatography. The two isolated materials were submitted for NMR and MS analysis. The spectra obtained were complex but the boron and fluorine NMR spectra suggested the presence of a -BF$_2$ moiety in the two samples. Efforts toward the characterization of the fluorescent species obtained from this study are underway. The TLC plate shows a red fluorescent spot: although isolated, the amount was insufficient to allow for characterization.
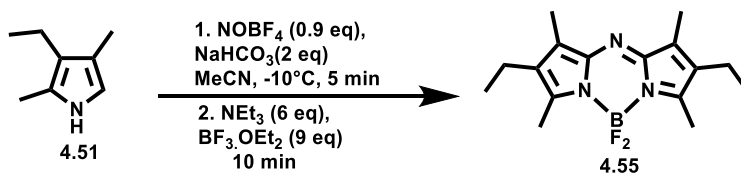


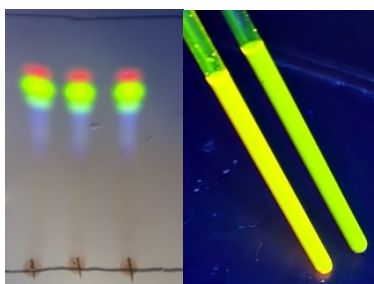*Scheme 44: Attempted synthesis of aza-F-BODIPY 4.55 from 4.51.*



*Figure 32:TLC analysis of the reaction of 4.51 with NEt$_3$ and BF$_3$•OEt$_2$ before work-up (left), NMR samples for the two fluorescent compounds isolated (right).*

The incorporation of a -BF$_2$ moiety into the dipyrrin and aza-dipyrrin framework causes these compounds to fluoresce. The evidence of the presence of the -BF$_2$ moiety, according to NMR analysis, and the fluorescence is an exciting indication of some kind *F*-BODIPY formed. However, pyrrole **4.51** might not have reacted in the expected way, as the expected products were not detected via MS analysis of the product materials.

## 4.4.1 - Conclusion.

This chapter discusses the development of a potential alternative route to the synthesis of aza dipyrrins, ideally to overcome limitations in the current methods of synthesis. Several pathways have been proposed herein wherein α-nitro or α-nitroso pyrroles bearing desired substituents are synthesized and then coupled with 2-boc-pyrrole boronic acid **4.11** under catalysis with tetravalent phosphorus reagents in the presence of phenylsilane as a reductant. Investigations of this coupling revealed multiple challenges, with complex mixtures obtained. This prompted the reaction of nitroso pyrroles with 2-boc-pyrrole boronic acid **4.11** under light-promoted triphenylphosphine-induced catalysis. The use of blue LED lights resulted in the formation of the desired aza dipyrrin in a 44% yield, an achievement comparable to the current routes to aza dipyrrins.[90] Given this success, attempts to synthesize alkyl-substituted nitroso-pyrroles for subjection to the blue LED-mediated methods using the nitrosylation conditions with $NaNO_2$ in ethanolic HCl were unsuccessful. This prompted the exploration of alternative nitrosylation conditions for pyrroles. The reaction of α-free pyrroles with $NOBF_4$ in acetonitrile resulted in the formation of nitroso pyrroles and several novel nitroso pyrroles were synthesized in reasonable yields. Application of this nitrosylation to alkyl-substituted systems did not proceed as expected but provided evidence for the formation of N-hydroxyl intermediates. This provides intriguing evidence that aza-dipyrrins are possibly just a step away. Further development is necessary to determine the viability of the pathway.

## 4.4.2 - Future work.

The synthesis of the fluorescent material from the reaction of the alkyl-substituted pyrrole with NOBF$_4$ and subsequently with BF$_3$•OEt$_2$ in the presence of NEt$_3$, excitingly suggests the presence of incorporation of the -BF$_2$ moiety within the product compounds. Efforts towards elucidation and characterization of the fluorescent compounds should be pursued. If successfully characterized, a possible mechanism for the reactivity of alkyl pyrrole derivatives with NOBF$_4$ can be proposed. This will allow further study of the reactivity of alkyl-substituted pyrroles in the synthesis of aza dipyrrins. The discovery of the new pyrrole-based carbazole provides a new class of pyrrolic compounds. Varying the substitution around the pyrrolic frame will allow for the synthesis of a variety of novel compounds of this kind. Solid-state absorbance and emission spectra of the compounds should then be studied and their optical properties elucidated.
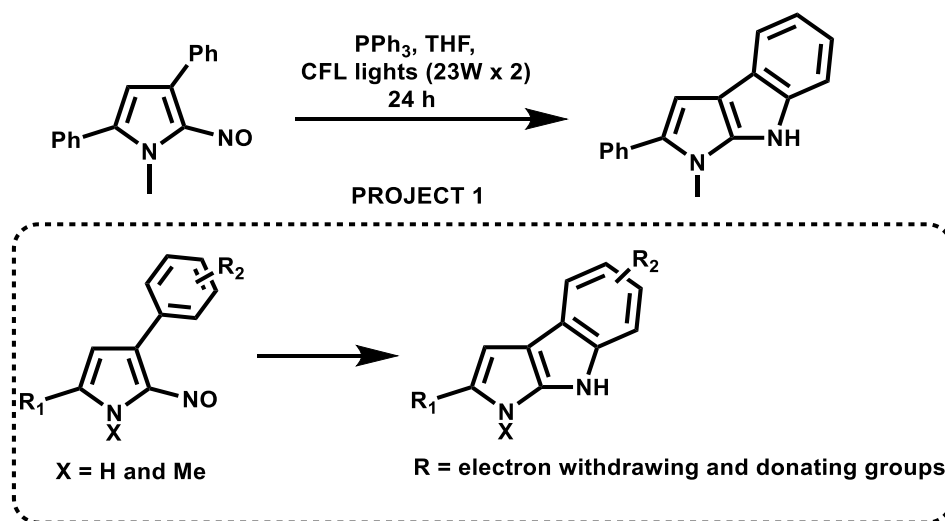
The azoxy class of compounds carries uncommon 1,3-dipolar O−N=N linkage with charges distributed over the three-atom set which is a valuable building block in the preparation of dyes and pigments, potential for drug delivery,[178] and promising anticancer activities. The discovery of a pyrrole-based azoxy compound can complement and meet the needs of new azoxy compounds and potentially provide a sustainable option as the traditional industrial syntheses of azoxy compounds are often costly, inefficient, and environmentally unfriendly.[160,163] It follows that practical, accessible methods for the synthesis of azoxybenzene and functional azoxy derivatives are urgently needed. We speculate that azoxy pyrrole was formed as a result of the condensation of the nitroso pyrroles and hydroxyl pyrrole formed as a result of the reduction of nitrosopyrrole with the PhSiH$_3$ reductant.[179,180] This work should give a strong impulse to new research efforts for this important transformation. Broadening the range of substitution about the pyrrolic rings will allow for the synthesis of novel azoxypyrroles which will stimulate further investigation into this unique and interesting class of products.
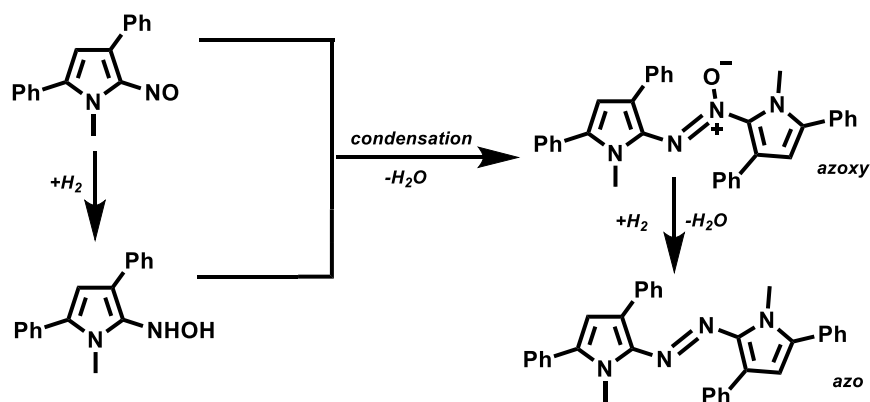


*Scheme 45: The proposed pathway to the pyrrole-based azoxy and azo compounds.*

The presence of azo dyes suggests that the further reduction of the azoxy compound and loss of water results in the formation of the azobispyrrole. The low yields suggest that this process is a slow process or less amount of reductant was used there was not enough reductant to reduce all the azoxy compound to the azo dye. Further optimization of the transformation of the azoxypyrrole to the azobispyrrole is needed to provide a new route to the azobispyrroles which are a new class of azo compounds. The current route being explored for the synthesis of these compounds relies on harsh reaction conditions, such as high temperature and excess amounts of ammonium reagents (up to 35 equiv) that lead to the formation of hazardous or undesirable byproducts following the over oxidation/reduction of the starting materials and the competing formation of aza dipyrrins.[181] With an optimized, efficient route to azobispyrroles from the azoxypyrroles, azobispyrroles can be synthesized in higher amounts enough for characterization.

## 4.5 - Experimental.

All $^1$H NMR (500 MHz), $^{13}$C NMR (125 MHz) and $^{11}$B NMR (160 MHz) spectra were recorded using a Bruker AV 500 MHz spectrometer. All $^{19}$F NMR (282 MHz) spectra were recorded using a Bruker AV 300 MHz spectrometer. $^1$H chemical shifts are reported in ppm relative to tetramethylsilane using chloroform solvent residual at $\delta$ = 7.26 ppm as an internal standard. $^{13}$C spectra were recorded using the UDEFT pulse sequence with chemical shifts reported in ppm referenced to CDCl$_3$ resonance at $\delta$ = 77.2 ppm. Splitting patterns are indicated as follows: br, broad; s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet. All coupling constants ($J$) are reported in Hertz (Hz). High-resolution mass spectra were obtained using TOFMS experiments with electrospray ionization operating in both positive and negative modes as indicated eg. [M + H]$^+$, [M - H]$^-$. Column chromatography was performed in glass tubes using 230-400 mesh ultra

pure silica or via a Biotage chromatograph. Chalcones were prepared according to literature procedures,[90,95,182] except for **4.42b**, **4.42c**, and **4.42d**. Nitrobutanones were prepared according to literature procedures except for **4.43b**, **4.43c**, and **4.43d**. Nitroso pyrrole **4.21**[148] was synthesized according to a reported procedure.

## 4.5.1 - General procedure 1 (GP1) for the synthesis of chalcones, 4.42b-d

Following a published procedure[148] for the synthesis of aza-BODIPYs, to synthesize the chalcones **4.42b-d**, KOH (2.5 equiv.) was added to a stirring solution of a benzaldehyde (23.3 mmol, 1 equiv.) and acetophenone (23.3 mmol, 1 equiv.) in MeOH (20 mL). The reaction mixture was stirred at r.t. for 1 h. The precipitate formed was isolated via filtration, washed with MeOH and cold pentane, and then dried under vacuum to afford the desired chalcone.

## 4.5.2 - General procedure 2 (GP2) for the synthesis of nitrobutanones, 4.43a-d

To a solution of chalcone, **4.42a-d** (6 mmol, 1 equiv.) in MeOH (20 mL) was added 1,8-diazabicyclo(5.4.0)undec-7-ene (DBU) (30 mmol, 5 equiv.) and nitromethane (30 mmol, 5 equiv.). The mixture was heated at reflux temperature for 1 h, then allowed to cool to room temperature. The solution was acidified to pH 2 with 1 M HCl and then extracted with $CH_2Cl_2$ (2 x100 mL). The combined organics were washed with water (100 mL) and brine (100 mL), then dried over $Na_2SO_4$. The solvent was removed in vacuo, and the resulting oil was purified by column chromatography on silica (5→100% ethyl acetate/hexanes) to provide the desired product.

### 4.5.3 - General procedure 3 (GP3) for the synthesis of 2,4-diaryl-1Hpyrroles, 4.44a-d

To a solution of KOH (40 mmol) in MeOH (124 mL) was added nitrobutanone **4.43a-d** (8 mmol) and the mixture was stirred for 1 h at room temperature. The mixture was then added dropwise to a solution of conc. $H_2SO_4$ (12 mL) in MeOH (20 mL) at 0 °C. The solution was allowed to warm to room temperature and then stirred for a further 1 h. Water (100 mL) and ice (100 mL) were added, and the mixture was neutralized with aqueous 4 M NaOH and then extracted with $CH_2Cl_2$ (2 x 250 mL). The combined organics were washed with water (100 mL) and brine (50 mL), then dried over $Na_2SO_4$. The solvent was removed *in vacuo* to provide a crude oil, which was carried into the next stage without further purification. To the intermediate compound was added acetic acid (27 mL) and $NH_4OAc$ (40 mmol), and the resulting mixture was heated at 100 °C for 1 h. The reaction mixture was allowed to cool to room temperature, and ice (100 mL), was then added. The mixture was carefully neutralized with aqueous 4 M NaOH to result in the generation of a precipitate which was isolated by filtration. The crude product was further purified by the dissolution of the solid in a small amount of $CH_2Cl_2$, followed by the addition of pentane and isolation of the resulting precipitate *via* filtration.

### 4.5.4 - General procedure 4 (GP4) for the synthesis of nitroso pyrroles 4.21a-h

To a stirred solution of pyrrole **4.44a-h** (50 mg) in anhydrous MeCN (5 mL) under a nitrogen atmosphere at -5 to -10°C (achieved using an ice/acetone bath) was added solid $NOBF_4$ (0.9 eq) in 3 portions, with a flow of nitrogen maintained during the additions. The resulting solution was stirred for 5-10 minutes, in the cold bath, at which point all pyrrole starting material was consumed

according to analysis by TLC. The reaction mixture was added to water (20 mL) at room temperature, and extracted into $CH_2Cl_2$ (2 x 20 mL). The combined organics were dried over $Na_2SO_4$, then concentrated *in vacuo*. The resulting solid was dry-loaded onto a silica chromatography column, aided by dissolution in $CH_2Cl_2$, and purified using a gradient of ethyl acetate/hexanes (0→60% ethyl acetate) as eluent to afford the desired 2-nitroso pyrrole as a green solid that stained orange on silica TLC plates visualized with vanillin stain and heat.

## 4.5.5 - Synthesis of compounds

**(2*E*)-1-(2,5-Dimethylphenyl)-3-(2,4,6-trimethylphenyl)prop-2-en-1-one, (4.42b).**
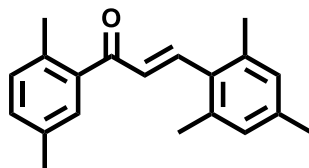


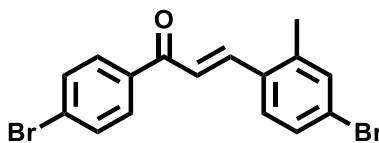The title compound was synthesized from 2,4,6-trimethylbenzaldehyde and 2,5-dimethylacetophenon according to **GP1** and was isolated as a yellow solid (5.1 g, 78%). ^{1}H NMR (500 MHz, CDCl3) δ: 7.65 (d, *J* = 17 Hz, 1H), 7.29 (s, 1H), 7.15-7.19 (m, 2H), 6.90 (s, 2H), 6.76 (d, *J* = 16 Hz, 1H), .2.43 (s, 3H), 2.35 (s, 3H), 2.34 (s, 6H), 2.29 (s, 3H). ^{13}C NMR δ: 197.1, 144.8, 139.2, 138.9, 137.3, 135.3, 134.1, 132.1, 131.5, 129.6, 129.0, 21.5, 21.4, 21.2, 20.1, 2 carbon signals missing. HRMS-ESI (*m/z*): [M+Na]$^+$ calc'd for $C_{20}H_{22}NaO$ 301.1563, found 301.1559.

**(2*E*)-1-(4-Chlorophenyl)-3-(2,6-dichlorophenyl)prop-2-en-1-one, (4.42c).**
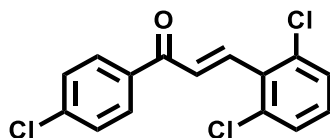
The title compound was synthesized from 2,6-dichlorobenzaldehyde and 4- chloroacetophenone according to **GP1** and was isolated as a yellow solid (4.79 g, 66%).^{1}H NMR (CDCl$_3$): δ = 7.95 (m, 2H), 7.85 (d, $J$ = 16 Hz, 1H), 7.61 (d, J = 16 Hz, 1H), 7.47 (d, $J$ = 10 Hz, 2H), 7.38 (d, $J$ = 10 Hz, 2H), 7.21 (t, $J$ = 5.0 Hz, 1H); ^{13}C NMR (CDCl$_3$) δ: 188.9, 139.6, 138.3, 135.9, 135.2, 132.4, 130.1, 129.9, 129.0, 128.8, 1 carbon signal missing. HRMS-ESI (*m/z*): [M+Na]$^+$ calc'd for C$_{15}$H$_9$Cl$_3$NaO 332.9617, found 332.9611.

**(2*E*)-3-(4-Bromo-2-methylphenyl)-1-(4-bromophenyl)prop-2-en-1-one, (4.42d).**



According to a modified version of **GP1**, the title compound was synthesized from 4-bromo-2-methylbenzaldehyde (5.02 mmol) and 4-bromoacetophenone (5.02 mmol), and was isolated as a yellow solid (1.71 g, 89%).^{1}H NMR (CDCl$_3$) δ: 8.03 (d, $J$ = 15 Hz, 1H), 7.64-7.88 (dd, $J$ = 110 Hz, 7.0 Hz, 4H), 7.54 (d, 8.1 Hz, 1H), 7.37-7.40 (m, 3H), 2.45 (s, 3H). ^{13}C NMR δ: 189.2, 141.9, 140.5, 139.1, 136.9, 134.0, 132.8, 132.2, 130.2, 129.7, 128.0, 124.8, 123.0, 19.8. HRMS-ESI (*m/z*): [M+Na]$^+$ calc'd for C$_{16}$H$_{12}$Br$_2$NaO 400.9147, found 400.9150.

**4-Nitro-1-phenyl-3-(2,4,6-trimethylphenyl)butan-1-one, (4.43a).**
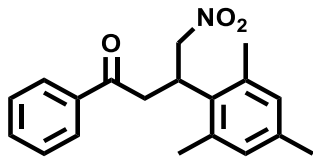


The title compound was synthesized from **4.42a**, according to **GP2**, and was isolated as an orange

oil (1.37 g, 74%). $^1$H NMR (CDCl$_3$) δ: 7.95 (d, $J$ = 7.6 Hz, 2H), 7.55-7.58 (m, 1H), 7.44-7.47 (m,

2H), 6.86 (s, 2H), 4.85-4.96 (m, 2H), 4.77 (m, 1H), 3.49-3.59 (m, 2H), 2.47 (s, 6H), 2.26 (s, 3H).

$^{13}$C NMR (CDCl$_3$) δ: 197.2, 136.8, 136.4, 133.4, 132.9, 131.3, 129.9, 128.7, 128.1, 78.2, 40.5,

33.9, 21.3, 20.6, in accordance with literature.[95]

**1-(2,5-Dimethylphenyl)-4-nitro-3-(2,4,6-trimethylphenyl)butan-1-one, (4.43b).**
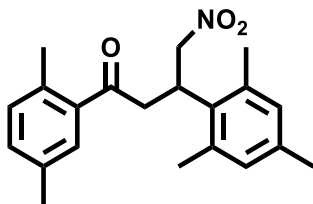

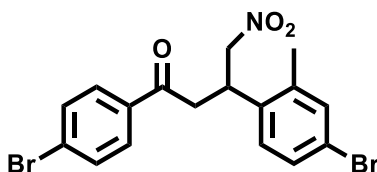
The title compound was synthesized from **4.42b**, according to **GP2**, and was isolated as a white

crystalline solid (1.28 g, 63%). $^1$H NMR (CDCl$_3$) δ: 7.31 (s, 1H), 7.18 (d, $J$ = 7.9 Hz, 1H), 7.10 (d,

$J$ = 8.1 Hz, 1H) 6.82 (s, 2H), 4.83-4.86 (m, 1H), 4.75-4.80 (m, 1H), 4.68-4.72 (m, 1H), 3.36-3.46

(m, 2H), 2.41 (s, 3H), 2.33 (s, 3H), 2.29 (s, 3H), 2.25 (s, 3H), 2.22 (s, 3H). $^{13}$C NMR (CDCl$_3$) δ:

201.3, 137.6, 137.0, 135.7, 135.3, 135.2, 132.2, 131.9, 131.2, 129.8, 128.7, 78.1, 43.3, 34.4, 21.5,

21.0, 20.8, 20.6, 20.3. HRMS-ESI (*m/z*): [M+Na]$^+$ calc'd. for C$_{21}$H$_{25}$NNaO$_3$: 362.1724; found

362.1727.

**3-(2,6-Dichloro-phenyl)-4-nitro-1-(4-chloro-phenyl)-butan-1-one, (4.43c).**
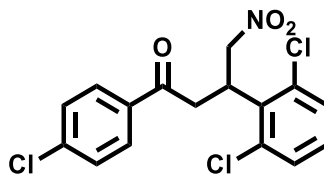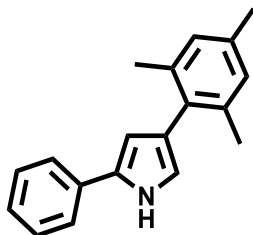


The title compound was synthesized from **4.42c**, according to **GP2**, and was isolated as a yellow

solid (1.51 g, 67%). $^1$H NMR (CDCl$_3$) δ: 7.86-7.88 (m, 2H), 7.41-7.43 (m, 2H), 7.37-7.38 (d, $J$ =

8.6 Hz, 1H), 7.27-7.29 (d, $J$ = 9.0 Hz, 1H), 7.14 (t, $J$ = 6.0 Hz, 1H), 5.26-5.31 (m, 1H), 4.95-5.05

(m, 2H), 2.68 (d, $J$ = 7.9 Hz, 2H). $^{13}$C NMR (CDCl$_3$) δ: 195.3, 140.1, 137.0, 134.4, 134.2, 130.0,

129.4, 129.3, 129.0, 76.2, 38.9, 35.3, 1 carbon signal missing. HRMS-ESI (*m/z*): [M+Na]$^+$ cal'd

for C$_{16}$H$_{12}$Cl$_3$NNaO$_3$: 393.9772; found 393.9775.

**3-(2-Methyl-4-bromo-phenyl)-4-nitro-1- (4-bromo-phenyl)-butan-1-one, (4.43d).**
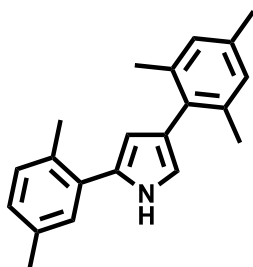


The title compound was synthesized from **4.42d**, according to **GP2**, and was isolated as a yellow

oil (1.69 0 g, 64%). $^1$H NMR (CDCl$_3$) δ: 7.76 (d, $J$ = 8.5 Hz, 2H), 7.60 (d, $J$ = 8.5 Hz, 2H), 7.35

(s, 1H), 7.28-7.31 (m, 1H), 7.02 (d, $J$ = 7.1 Hz, 1H), 4.71-4.75 (m, 1H), 4.58-4.62 (m, 1H), 4.42-

4.48 (m, 1H), 3.31-3.43 (m, 2H), 2.45 (s, 3H). $^{13}$C NMR (CDCl$_3$) δ: 195.7, 139.1, 136.4, 135.0,

134.2, 132.3, 129.8, 129.6, 129.2, 127.1, 121.6, 78.9, 41.5, 34.1, 19.6. HRMS-ESI (*m/z*): [M-H]$^-$

calc'd. for C$_{17}$H$_{14}$Br$_2$NO$_3$: 437.9346; found 437.9333.

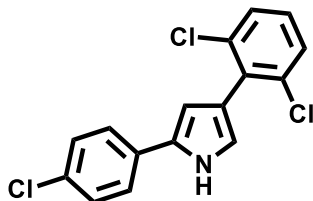**2-Phenyl-4-(2,4,6-trimethylphenyl)-1*H*-pyrrole, (4.44a).**



The title compound was synthesized from **4.43a**, according to **GP3**, and was isolated as a purple solid (920 mg, 44%). $^1$H NMR (CDCl$_3$) δ: 8.45 (br, 1H), 7.55-7.56 (m, 2H), 7.42-7.45 (m, 2H), 7.26-7.29 (m, 1H), 7.02 (s, 2H), 6.71-6.72 (m, 1H), 6.48-6.50 (m, 1H), 2.39 (s, 3H), 2.26 (s, 6H). $^{13}$C NMR (CDCl$_3$) δ: 137.6, 136.1, 133.1, 132.7, 131.6, 128.9, 127.9, 126.0, 123.9, 123.5, 117.5, 107.7. 21.1, 21.0. HRMS-ESI (*m/z*): [M+H]$^+$ calc'd. for C$_{19}$H$_{20}$N: 262.1590; found 262.1591.

**2-(2,5-Dimethylphenyl)-4-(2,4,6-trimethylphenyl)-1*H*-pyrrole, (4.44b).**
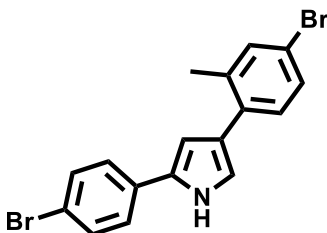


The title compound was synthesized from **4.43b**, according to **GP3** and was isolated as a purple solid (1.13 mg, 49%). $^1$H NMR (CDCl$_3$) δ: 8.52 (br, 1H), 7.52-7.53 (m, 1H), 7.45-7.62 (d, *J* = 8.5 Hz, 1H), 7.30-7.32 (d, *J* = 8.6 Hz, 1H), 7.25 (s, 2H), 6.95-6.96 (m, 1H), 6.52-6.53 (m, 1H), 2.74 (s, 3H), 2.66 (s, 6H), 2.52 (s, 6H). $^{13}$C NMR (CDCl$_3$) δ: 137.6, 136.0, 135.4, 133.4, 132.7, 131.8, 131.1, 130.9, 128.0, 127.9, 127.3, 123.0, 116.4, 110.7, 21.2, 21.1, 20.9, 1 signal missing. HRMS-ESI (*m/z*): [M+H]$^+$ calc'd. for C$_{21}$H$_{24}$N: 290.1903, found 290.1903.

**4-(2,6-Dichloro-phenyl)- 2-(4-chloro-phenyl)-1H-pyrrole, (4.44c).**



The title compound was synthesized from **4.43c**, according to **GP3**, and was isolated as a purple solid (1.31 g, 51%). $^1$H NMR (CD$_3$NO$_2$) δ: 8.22 (br, 1H), 7.95 (d, $J$ = 7.1 Hz, 2H), 7.44 (m, 1H), 7.32 (d, $J$ = 7.1 Hz, 2H), 7.16 (m, 1H), 7.06 (m, 1H), 6.94 (m, 1H), 6.69 (m, 1H). $^{13}$C NMR (CDCl$_3$) δ: 137.6, 136.0, 135.4, 133.4, 132.7, 131.8, 131.1, 130.9, 128.0, 127.9, 127.3, 123.0. HRMS-ESI (*m/z*): [M+H]$^+$ calc'd. for C$_{16}$H$_{11}$Cl$_3$N: 323.6130; found 323.3133.

**4-(4-Bromo-2-methylphenyl)-2-(4-bromophenyl)-1*H*-pyrrole, (4.44d).**



The title compound was synthesized from **4.43d**, according to **GP3**, and was isolated as a purple solid (657 mg, 21%). $^1$H NMR (CDCl$_3$) δ: 8.49 (br, 1H), 7.54 (d, $J$ = 9.4 Hz, 2H), 7.43-7.44 (m, 1H), 7.41 (d, $J$ = 8.9 Hz, 2H), 7.35-7.37 (m, 1H), 7.28 (s, 1H), 6.97-6.98 (m, 1H), 6.66-6.67 (m, 1H), 2.46 (s, 3H). $^{13}$C NMR (CDCl$_3$) *δ:* 137.6, 133.4, 132.2, 131.5, 131.2, 130.8, 129.0, 128.1, 127.7, 125.5, 120.2, 120.0, 118.3, 107.4, 21.4. HRMS-ESI (*m/z*): [M+H]$^+$ calc'd. C$_{17}$H$_{14}$Br$_2$N for 389.9488, found 389.9499

**4-(4-Methylphenyl)-2-phenyl-1H-pyrrole, (4.44e).**
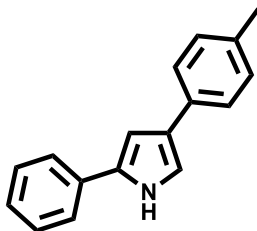


The title compound was synthesized from **4.43e**, according to a literature peocedure,[183] and was isolated as a crystalline silver solid (490 g, 31%). $^1$H NMR (CDCl$_3$) $\delta$: 8.32 (br, 1H), 7.52 (d, $J$ = 6.9 Hz, 2H), 7.47 (d, $J$ = 8.3 Hz, 2H), 7.39 (t, $J$ = 6.9 Hz, 2H), 7.24 (t, $J$ = 6.9 Hz, 1H), 7.18 (d, $J$ = 8.3 Hz, 2H), 7.12 (bs, 1H), 6.80 (bs, 1H), 2.36 (s, 3H). $^{13}$C NMR (CDCl$_3$) $\delta$: 135.5, 133.1, 132.8, 132.7, 129.5, 129.1, 126.8, 126.6, 125.3, 124.0, 115.4, 104.1, 21.3. NMR data were found to be in accordance with literature.[183]

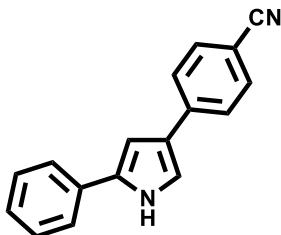**2-Phenyl-4-[4-(trifluoromethyl)phenyl]-1H-pyrrole, (4.44f).**
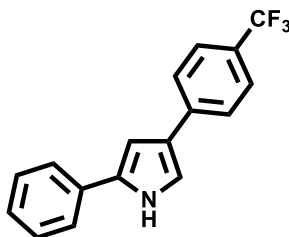


The title compound was synthesized from **4.43f**, according to a literature procedure,[184] and was isolated as an off white crystalline solid (0.54 g, 48%). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$: 8.54 (bs, 1H), 7.66 (d, $J$ = 8.0 Hz, 2H), 7.60 (d, $J$ = 8.0 Hz, 2H), 7.53 (dd, $J$ = 7.7, 1.3 Hz, 2H), 7.41 (t, $J$ = 7.7 Hz, 2H), 7.27 (t, $J$ = 7.7 Hz, 1H), 7.20-7.23 (m, 1H), 6.82-6.85 (m, 1H). $^{19}$F{$^1$H} NMR (377 MHz, CDCl$_3$) $\delta$: -62.2 (s). $^{13}$C NMR (CDCl$_3$) $\delta$: 139.2, 133.8, 133.0, 129.2, 127.0, 126.0, 125.8,

125.7, 125.4, 125.2, 124.1, 116.5, 104.1. NMR data were found to be in accordance with literature.[184]

## 4-(4-Cyanophenyl)-2-phenyl-1H-pyrrole (4.44g)



The title compound was synthesized from **4.43g** according to a literature procedure[185] and was isolated as a yellow solid (190 mg, 39%). $^1$H NMR (DMSO-d$_6$) δ: 11.69 (s, 1H), 7.81 (d, $J$ = 8 Hz 2H), 7.75 (d, $J$ = 8.1 Hz 2H), 7.69 (d, $J$ = 7.3 Hz 1H), 7.58 (dd, $J$ = 3.2, 1.7 Hz, 1H), 7.39 (t, $J$ = 7.2 Hz, 2H), 7.20 (t, $J$ = 7.1 Hz, 1H), 7.09 (dd, $J$ = 2.7, 1.7 Hz, 1H), 1 signal missing. $^{13}$C NMR (DMSO-d$_6$) δ: 140.7, 133.0, 132.6, 132.3, 128.8, 126.1, 124.8, 123.6, 123.1, 119.5, 118.9, 106.7, 103.5. NMR data were found to be in accordance with literature.[185]

## 2-Phenyl-4-[3-(trifluoromethyl)phenyl]-1H-pyrrole, (4.44h).
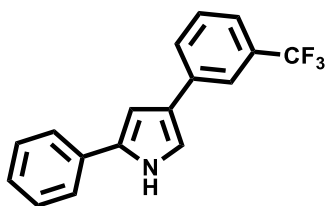


According to an amended version of **GP3**, nitrobutanone **4.43h**,[186] (7.09 mmol) was reacted with KOH (35.6 mmol) in MeOH (60 mL). After 1 hour, the mixture was then added dropwise to a solution of conc. $H_2SO_4$ (9.3 mL) in MeOH (50 mL) at 0 °C. After the mixture was neutralized with aqueous 4 M KOH, the intermediate product was isolated by filtration and dried overnight in

a vacuum desiccator. To the intermediate compound was added acetic acid (27 mL) and NH₄OAc

(17.7 mmol), and the resulting mixture was heated at 100 °C for 1 h. After the mixture was

neutralised with aqueous 4 M KOH, the crude material was extracted with $CH_2Cl_2$ (50 mL) and

the organics were later washed with water and brine, and then dried over $Na_2SO_4$. The solvent was

removed *in vacuo*, and the resulting material was purified by dissolution in a small amount of

$CH_2Cl_2$, followed by the addition of hexanes and isolation of the precipitate *via* filtration to provide

the desired compound as a crystalline silver solid (0.27 g, 13%). $^1$H NMR (CDCl₃) $\delta$: 8.52 (br,

1H), 7.80 (s, 1H), 7.73 (d, $J$ = 6.1 Hz, 1H), 7.53 (d, $J$ = 6.3 Hz, 2H), 7.37-7.50 (m, 4H), 7.27 (t, $J$

= 6.1 Hz, CDCl₃ shoulder), 7.16-7.22 (m, 1H), 6.81-6.87 (m, 1H). $^{19}$FNMR (CDCl₃) $\delta$: -62.7 (s).

$^{13}$C NMR (CDCl₃) $\delta$: 136.5, 133.7, 132.3, 131.3, 131.0, 129.2, 128.4, 126.9, 125.5, 124.1, 123.2,

122.4, 121.9, 116.1, 104.0.

**N,N-Dimethyl-4-(5-phenyl-1H-pyrrol-3-yl)benzenamine, (4.44i).**
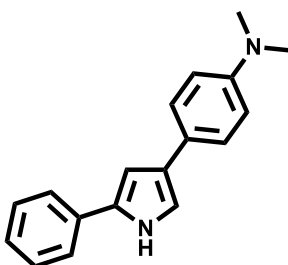


The title compound was synthesized according to an a literature procedure[182] and was isolated as

a crystalline silver solid (80 mg, 18%). $^1$H NMR (400 MHz, CDCl₃) $\delta$: 8.39 (br, 1H), 7.51 (d, $J$ =

7.3 Hz, 2H), 7.47 (d, $J$ = 7.9 Hz, 2H), 7.38 (t, $J$ = 7.9 Hz, 2H), 7.22 (t, $J$ = 7.4Hz, 1H), 7.03-7.07

(m, 1H), 6.84 (br, 2H), 6.75-6.78 (m, 1H), 2.98 (s, 6H). $^{13}$C NMR (CDCl₃) $\delta$: 132.9, 132.8, 129.0,

127.0, 126.4, 126.3, 123.9, 114.6, 113.6, 103.9, 41.2, 2 signals missing. NMR data were found to be in accordance with literature.[182]

**4-(4-Methoxyphenyl)-2-phenyl-1H-pyrrole, (4.44j).**
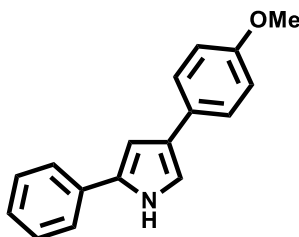
The title compound was synthesized from **4.43j** according to a literature procedure,[183] [62]and was isolated as a crystalline silver solid (0.15 g, 9%). ^{1}H NMR (DMSO-$d_6$) $\delta$: 11.33 (bs, 1H), 7.67 (d, $J$ = 8.0 Hz, 2H), 7.52 (d, $J$ = 9.1 Hz, 2H), 7.36 (t, $J$ = 8.0 Hz, 2H), 7.20-7.23 (m, 1H), 7.16 (t, $J$ = 8.0 Hz, 1H), 6.90 (d, $J$ = 9.1 Hz, 2H), 6.85-6.88 (m, 1H), 3.75 (s, 3H). ^{13}C NMR (DMSO-$d_6$) $\delta$: 157.1, 132.7, 132.0, 128.7, 128.4, 125.5, 124.6, 123.3, 115.7, 114.0, 103.0, 55.0 (one signal missing). NMR data were found to be in accordance with literature.[183]

**4-(4-Hydroxyphenyl)-2-phenyl-1H-pyrrole, (4.44l).**
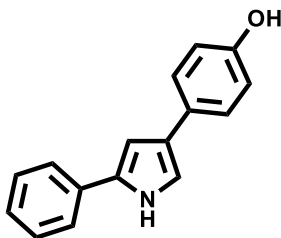
The tittle compound was synthesized from **4.43l** according to **GP3**, and was isolated as a light yellow solid (90 mg, 5%). $^1$H NMR (DMSO-d$_6$) δ: 11.27 (s, 1H), 9.17 (s, 1H), 7.66 (d, $J$ = 7.1 Hz 2H), 7.40 (d, $J$ = 8.5 Hz, 2H), 7.26 (t, $J$ = 7.8 Hz, 2H), 7.19-7.12 (m, 2H), 6.82 (dd, $J$ = 2.7, 1.7 Hz 1H), 6.73 (d, $J$ = 8.6 Hz, 2H). $^{13}$C NMR (DMSO-d$_6$) δ: 155.6, 133.3, 132.3, 129.1, 127.3, 126.1, 126.0, 125.5, 123.8, 115.8, 115.7, 103.4. HRMS-ESI$^-$ $m/z$ [M$^+$ - H] calc'd for C$_{16}$H$_{12}$NO: 234.0924; found 234.0918.
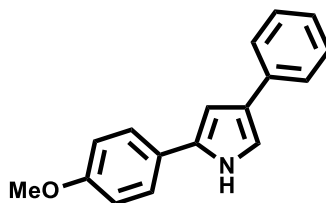
**2-(4-Methoxyphenyl)-4-phenyl-1H-pyrrole, (4.44m).**



The title compound was synthesized from **4.43m** according to a literature procedure,[183] and was isolated as a crystalline silver solid (0.37 g, 18%). $^1$H NMR (DMSO-d$_6$) δ: 11.28 (br, 1H), 7.56-7.64 (m, 4H), 7.31 (t, $J$ = 7.7 Hz, 2H), 7.25-7.28 (m, 1H), 7.11 (t, $J$ = 7.7 Hz, 1H), 6.95 (d, $J$ = 8.9 Hz, 2H), 6.78-6.82 (m, 1H), 3.77 (s, 3H). $^{13}$C NMR (DMSO-d$_6$) δ: 157.6, 135.9, 132.3, 128.5, 125.6, 124.9, 124.8, 124.5, 124.4, 115.7, 114.2, 102.0, 55.1. NMR data were found to be in accordance with literature.[183]

**2-Nitroso-3,5-diphenyl-1H-pyrrole, (4.40).**
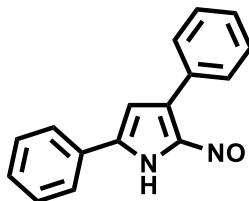


The title compound was synthesized from **3.28b** according to **GP4** and was isolated as a green solid (37 mg, 65%). $^1$H NMR (CDCl$_3$) δ: 8.16-8.19 (m, 2H), 7.80-7.83 (m, 2H), 7.47-7.51 (m, 6H), 7.14 (s, 1H). $^{13}$C NMR (CDCl$_3$) δ: 162.7, 147.6, 141.8, 132.1, 131.2, 130.2, 129.8, 129.5, 129.3, 129.0, 2 signals missing. HRMS-ESI (*m/z*): [M+Na]$^+$calc'd for C$_{16}$H$_{12}$N$_2$NaO: 271.0843; found 271.0842. NMR data were found to be in accordance with literature.[182]
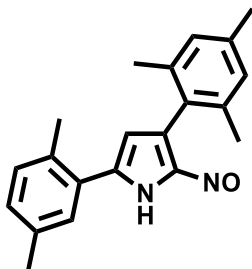
**2-Nitroso-5-phenyl-3-(2,4,6-trimethylphenyl)-1*H*-pyrrole, (4.40a).**
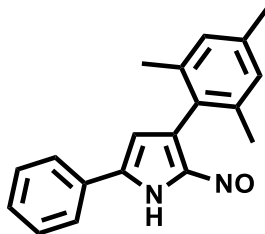


The title compound was synthesized from **4.44a** according to **GP4** and was isolated as a green solid (41 mg, 73%). $^1$H NMR (CDCl$_3$) δ: 7.85 (m, 2H), 7.44-7.51 (m, 3H), 7.0 (s, 2H), 6.84 (s,

1H), 2.35 (s, 3H), 2.23 (s, 6H). $^{13}$C NMR (CDCl$_3$) δ: 163.0, 143.8, 138.1, 137.1, 131.2, 129.3, 128.8, 128.3, 126.9, 116.4, 21.1, 21.0, 2 signals missing. HRMS-ESI (*m/z*): [M+Na]$^+$ calc'd. for C$_{19}$H$_{18}$N$_2$NaO: 313.1309; found 313.1311.

**5-(2,5-Dimethylphenyl)-2-nitroso-3-(2,4,6-trimethylphenyl)-1*H*-pyrrole, (4.40b).**



The title compound was synthesized from **4.44b** according to **GP4** and was isolated as a green solid (43 mg, 79%). $^1$H NMR (CDCl$_3$) δ: 7.35 (s, 1H), 7.18-7.22 (m, 2H), 7.01 (s, 2H), 6.62 (s, 1H), 2.48 (s, 3H), 2.37 (s, 3H), 2.35 (s, 3H), 2.25 (s, 6H). $^{13}$C NMR (CDCl$_3$) δ: 137.6, 137.1, 135.8, 135.3, 135.2, 132.3, 132.2, 131.9, 131.2, 129.9, 128.7, 78.2, 43.4, 34.4, 20.9, 3 signals missing. HRMS-ESI (*m/z*): [M+Na]$^+$ calc'd. for C$_{21}$H$_{22}$N$_2$NaO: 341.1621; found 341.1624.
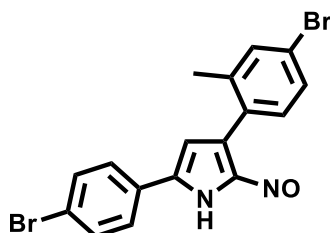
**2-Nitroso-3-(2,6-diclorobenzene)-5-(4-chlorobenzene)-1H-pyrrole, (4.40c).**
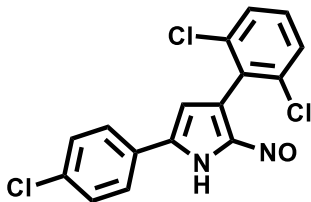


The title compound was synthesized from **4.44c** according to **GP4** and was isolated as a green solid (35 mg, 65%). $^1$H NMR (CDCl$_3$) δ: 8.16-8.19 (m, 2H), 7.80-7.83 (m, 2H), 7.47-7.51 (m, 2H), 7.14 (s, 1H), 6.77-6.78 (m, 1H), 1 signal missing. $^{13}$C NMR (CDCl$_3$) $^{13}$C NMR (CDCl$_3$) δ: 147.6,

145.0, 139.4, 137.4, 136.7, 134.8, 133.4, 132.7, 131.1, 130.9, 128.0, 127.9. HRMS-ESI (*m/z*): [M+H]$^+$ calc'd. for C$_{16}$H$_{10}$Cl$_3$N$_2$O: 352.;6110 found 352.6113.

**3-(4-Bromo-2-methylphenyl)-5-(4-bromophenyl)-2-nitroso-1*H*-pyrrole, (4.40d).**



The title compound was synthesized from **4.44d** according to **GP4** and was isolated as a green solid (37 mg, 68%). $^1$H NMR (CDCl$_3$) δ: 7.71 (d, J = 7.9 Hz, 2H), 7.61 (d, *J* = 7.9 Hz, 2H), 7.50-7.52 (m, 2H), 7.43-7.45 (m, 1H), 6.94 (s, 1H), 2.45 (s, 3H), 1 signal missing. $^{13}$C NMR (CDCl$_3$) δ: 163.0, 142.4, 139.0, 133.5, 133.2, 132.7, 130.4, 128.9, 128.4, 128.2, 126.1, 123.3, 20.9, 2 signals missing. HRMS-ESI (*m/z*): [M+H]$^+$ calc'd. for C$_{17}$H$_{13}$Br$_2$N$_2$O: 418.9390; found 418.9389.
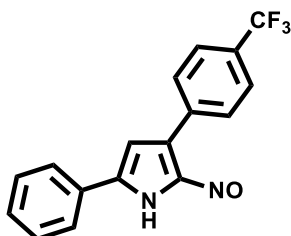
**3-(4-Methylphenyl)-2-nitroso-5-phenyl-1*H*-pyrrole, (4.40e).**
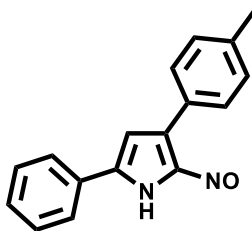


The title compound was synthesized from **4.44e** according to **GP4** and was isolated as a green solid (38 mg, 68%). $^1$H NMR (CDCl$_3$) δ: 8.01 (d, *J* = 8.52 Hz, 2H), 7.78-7.80 (m, 2H), 7.50-7.52

(m, 3H), 7.30 (d, $J$ = 8.47 Hz, 2H), 7.12 (s, 1H), 2.43 (s, 3H). $^{13}$C NMR (CDCl$_3$) $\delta$: 135.5, 133.1, 132.8, 132.7, 129.5, 129.1, 126.8, 126.6, 125.3, 124.0, 115.4, 104.1, 21.3. HRMS-ESI (*m/z*): [M+H]$^+$ calc'd. for C$_{17}$H$_{15}$N$_2$O 263.1179, found, 263.1187.

**2-Nitroso-5-phenyl-3-[4-(trifluoromethyl)phenyl]-1H-pyrrole, (4.40f).**



The title compound was synthesized from **4.44f** (80 mg) according to **GP4**, and was isolated as a green solid (41 mg, 46%). $^1$H NMR (CDCl$_3$) $\delta$: 8.30 (d, $J$ = 8.1 Hz, 2H), 7.78-7.85 (m, 2H), 7.75 (d, $J$ = 8.2 Hz, 2H), 7.49-7.55 (m, 3H), 7.19 (s, 1H). $^{13}$C NMR (CDCl$_3$) $\delta$: 162.5, 135.3, 131.5, 131.4, 129.8, 129.6, 128.9, 126.8, 125.8, 125.7, 125.4, 113.0, 1 signal missing. $^{19}$F NMR (CDCl$_3$) $\delta$: 62.77. HRMS-ESI$^-$ (m/z): [M$^+$ - H] calc'd for C$_{17}$H$_{10}$F$_3$N$_2$O: 315.0751; found 315.0740.
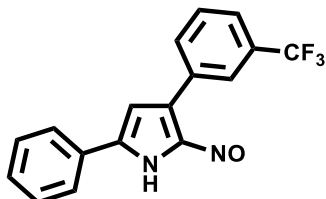
**2-Nitroso 4-(4-Cyanophenyl)-2-phenyl-1H-pyrrole, (4.40g).**
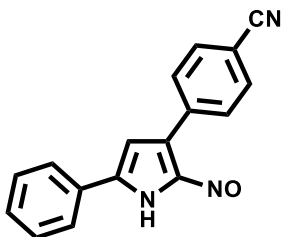


The title compound was synthesized from **4.44g** according to **GP4** and was isolated as a green solid (38 mg, 68%). $^1$H NMR (MeCN) $\delta$: 8.32 (d, $J$ = 8 Hz, 2H), 7.78-7.81 (m, 3H), 7.52-7.55 (m, 3H), 7.28 (s, 1H), 7.20 (s, 1H), 1 signal missing. $^{13}$C NMR (DMSO-d$_6$) $\delta$: 140.7, 133.0, 132.6,

132.3, 128.8, 126.1, 124.8, 123.6, 123.1, 119.5, 118.9, 106.7, 103.5. HRMS-ESI (*m/z*): [M+H]$^+$ calc'd. for $C_{17}H_{12}N_3O$ 274.0975, found 274.0984.

**2-Nitroso-5-phenyl-3-[3-(trifluoromethyl)phenyl]-1H-pyrrole, (4.40h).**



The title compound was synthesized from **4.44h** according to **GP4** and was isolated as a green solid, (39 mg, 70%). $^1$H NMR (CDCl$_3$) δ: 8.44 (d, *J* = 8.0 Hz, 1H), 8.37 (s, 1H), 7.78-7.84 (m, 2H), 7.72 (d, *J* = 7.6 Hz, 1H), 7.63 (t, *J* = 8.0 Hz, 1H), 7.49-7.57 (m, 3H), 7.19 (s, 1H), 1 signal missing. $^{13}$C NMR (CDCl$_3$) δ: 133.0, 132.6, 131.8, 131.6, 131.4, 130.2, 129.6, 129.4, 128.9, 126.8, 126.1, 126.0, 125.8, 125.9. $^{19}$F NMR (CDCl$_3$) δ: 62.67. HRMS-ESI (m/z): [M-H]$^-$ cal'd. for $C_{17}H_{10}F_3N_2O$ 315.0751, found 315.0741.

***N*-(3,5-diphenyl-1*H*-pyrrol-2-yl)-*N*-hydroxy-3,5-diphenyl-1*H*-pyrrol-2-amine, (4.41).**
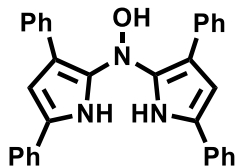


The title compound was synthesized as a by-product from **3.28b** (50 mg) and NOBF$_4$ (1 equiv), according to **GP4**, and was isolated as a green solid, (18 mg, 34%). $^1$H NMR (CDCl$_3$) δ: 8.84 (br, 1H), 7.50-7.52 (m, 5H), 7.34-7.38 (m, 5H), 7.28-7.30 (m, 5H), 7.18-7.15 (m, 5H), 6.75 (s, 1H),

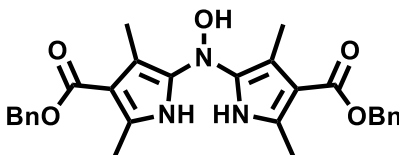6.56-6.58 (m, 1H), 6.24 (br, 1H), 1 signal missing. $^{13}$C NMR (CDCl$_3$) δ: 171.4, 135.5, 133.1, 132.5, 131.8, 131.3, 129.6, 129.6, 129.4, 129.2, 129.0, 128.9, 128.6, 128.2, 126.8, 126.5, 125.7, 125.2, 123.9, 115.5, 104.0, 3 signals missing. HRMS-ESI (m/z): [M+H]$^+$, calc'd for C$_{32}$H$_{26}$N$_3$O 468.2070, found 468.2071.

**Dibenzyl 5-(hydroxyamino)-2,4-dimethyl-1*H*-pyrrole-3-carboxylate, (4.48).**



The title compound was synthesized from **4.47** (100 mg) and NOBF$_4$ (1.8 equiv), according to **GP4**, and was isolated as a white solid, (50 mg, 47%). $^1$H NMR (CDCl$_3$) δ: 8.12 (br, 1H), 7.31-7.42 (m, 2H), 7.33-7.37 (m, 2H), 7.29-7.33 (m, 4H), 7.18-7.20 (m, 2H), 5.61 (br, 1H), 5.26 (s, 2H), 5.20 (d, *J* = 11.3 Hz, 1H), 5.08 (d, *J* = 11.3 Hz, 1H), 2.35 (s, 3H), 2.19 (s, 3H), 2.13 (s, 3H), 1.86 (s, 3H), 1 signal missing. $^{13}$C NMR (CDCl$_3$) δ: 165.9, 163.3, 157.1, 141.7, 139.2, 137.1, 135.3, 134.6, 128.8, 128.5, 128.3, 128.2, 127.9, 124.3, 118.7, 111.8, 66.9, 65.4, 26.6, 14.2, 11.0, 10.9 2 signals missing. HRMS-ESI (m/z): [M+H]$^+$ calc'd for C$_{28}$H$_{30}$N$_3$O$_5$ 488.2180, found 488.2179.

**Benzyl 5-acetyl-2,4-dimethyl-1*H*-pyrrole-3-carboxylate, (4.49).**
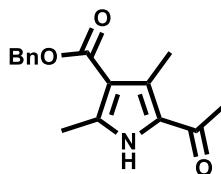
To a solution of pyrrole **4.47** (100 mg) in AcOH (1 mL) and Ac₂O (1mL) under a nitrogen atmosphere was added solid NOBF₄ (1.8 equiv) in three portions. The mixture was stirred at 100°C for 1 h. The mixture was added to a saturated NaHCO₃ solution (10 mL), and extracted into CH₂Cl₂ (2 x 10 mL). The combined organics were dried over Na₂SO₄, then concentrated *in vacuo*. The resulting solid was dry-loaded onto a silica chromatography column, aided by dissolution in CH₂Cl₂, and purified using a gradient of ethyl acetate/hexanes (20→60% ethyl acetate) as eluent to afford the desired product as a brown solid (21 mg, 18%). ¹H NMR (CDCl₃) δ: 9.48 (br, 1H), 7.41-7.43 (m, 2H), 7.35-7.39 (m, 2H), 7.32-7.34 (m, 1H), 5.30 (s, 2H), 2.62 (s, 3H), 2.49 (s, 3H), 2.47 (s, 3H). ¹³C NMR (CDCl₃) δ: 188.0, 165.3, 140.5, 136.6, 130.2, 128.7, 128.3, 128.2, 113.8, 65.7, 28.6, 14.8, 13.0, 1 signal missing. HRMS-ESI (m/z): [M+Na]⁺, calc'd for C₁₆H₁₇NNaO₃ 294.1101, found 294.1104.

**2,2'-diazenediyl-oxide-bis(3,5-diphenyl-1-methyl-pyrrole), (4.24).**
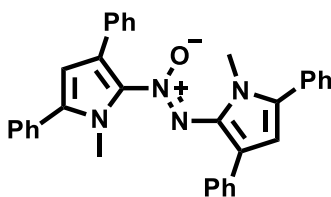


A 2 dram vial was charged with pyrrole **4.21** (30 mg, 1 equiv.) and PPh₃ (1.2 equiv.) under a nitrogen atmosphere. The mixture was then dissolved in anhydrous THF (2 mL). The resulting mixture was stirred for 22 h under irradiation with 2 x 23 W CFL lamps. The reaction was monitored by TLC. When pyrrole **4.21** was fully consumed, the reaction was diluted with 10 mL of EtOAc and washed with 10 mL of water. The organics were combined and dried over Na₂SO₄ and concentrated *in vacuo*. The crude material was purified on the Biotage using 40%

CH$_2$Cl$_2$/Hexanes to afford the desired product as a purple solid (14 mg, 24%). $^1$H NMR (CDCl$_3$) δ: 7.55-7.57 (m, 2H), 7.45-7.51 (m, 8H), 7.35-7.38 (m, 6H), 7.18-7.21 (m, 2H), 7.08 (s, 2H), 6.55 (s, 2H), 3.73 (m, 6H). $^{13}$C NMR (CDCl$_3$) δ: 135.7, 133.6, 133.1, 128.9, 128.6, 128.4, 128.3, 126.9, 124.6, 120.5, 2 signals missing.

**2,2'-Diazenediyl]bis(3,5-diphenyl-1-methyl-pyrrole), (4.25).**
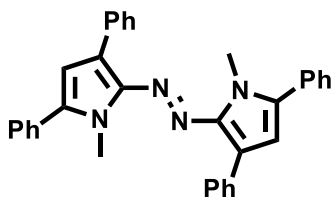


The reaction and work-up used to provided **4.24** also afforded **4.25** as a red solid (20 mg, 19%). $^1$H NMR (CDCl$_3$) δ: 8.06 (d, $J$ = 6.4 Hz, 4H), 7.95 (d, $J$ = 6.4 Hz, 4H), 7.52-7.56 (m, 4H), 7.41-7.44 (m, 6H), 7.34-7.37 (m, 2H), 7.21 (s, 2H), 3.69 (s, 3H). HRMS-ESI (m/z): [M+H]$^+$, calc'd for C$_{34}$H$_{29}$N$_4$ 493.238673, found 493.237809.

**N-(3,5-Diphenyl-2H-pyrrol-2-ylidene)-3,5-diphenyl-1H-pyrrol-2-amine 2 (3.3a)**
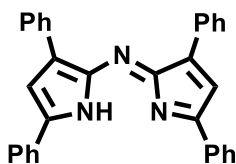
A 2 dram vial was charged with nitroso pyrrole **4.21** (52 mg, 1 equiv.), NaI (0.5 equiv.), and PPh$_3$ (1 equiv.) under a nitrogen atmosphere. The mixture was then dissolved in 2 mL of anhydrous CHCl$_3$. To this was added PhSiH$_3$ (2 equiv.). The resulting mixture was stirred for 18 h under irradiation with a 456 nm blue LED lamp. The reaction was monitored by TLC. When nitroso pyrrole **4.21** was fully consumed, the reaction was quenched with saturated Na$_2$CO$_3$ (10 mL) and extracted with CH$_2$Cl$_2$ (3 x 10 mL). The organics were combined and dried over Na$_2$SO$_4$ and concentrated *in vacuo*. The crude material was purified on the Biotage using 40% CH$_2$Cl$_2$/Hexanes to afford the desired product as a blue solid (20 mg, 44%). $^1$H NMR (CDCl$_3$) δ: 8.06 (d, $J$ = 7.4 Hz, 4H), 7.96 (d, $J$ = 7.5 Hz, 4H), 7.57-7.51 (m, 4H), 7.50-7.41 (m, 6H), 7.39-7.34 (m, 2H), 7.21 (s, 2H), 1 signal missing. NMR data were found to be in accordance with literature.[98]

**1-Methyl-2,4-diphenyl-1*H*-pyrrole, (4.20).**
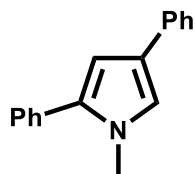


To a solution of pyrrole **3.28** (1.88 g, 1 equiv) in THF (18 mL) was added NaH (2 equiv.) and CH$_3$I (3 equiv.). The resulting mixture was stirred at 0°C overnight. When pyrrole **3.28** was fully consumed, the reaction mixture was diluted with EtOAc (10 mL) and washed with saturated NaCl (10 mL), then with water (10 mL). The organics were then dried over Na$_2$SO$_4$ and concentrated in vacuo. The crude material was dissolved in MeOH in which the desired product precipitated and was collected as a pale purple solid after filtration (1.14 g, 57%). $^1$H NMR (CDCl$_3$) δ: 7.53 (d, $J$ = 8.1 Hz, 2H), 7.40-7.46 (m, 4H), 7.32-7.35 (m, 3H), 7.15-7.18 (m, 1H), 7.01 (m, 1H), 6.53 (m, 1H),

3.97 (s, 3H). $^{13}$C NMR (CDCl$_3$) δ: 135.6, 133.1, 128.7, 128.6, 128.4, 127.0, 125.4, 125.0, 124.3, 120.4, 106.6, 35.2, 1 signal missing.

**1-Methyl-2-phenyl-1,8-dihydropyrrolo[2,3-*b*]indole, (4.23).**
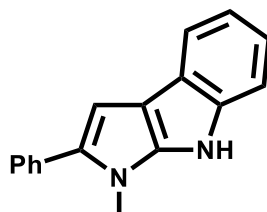


A 2 dram vial was charged with pyrrole **4.21** (30 mg, 1 equiv.) and PPh$_3$ (1.2 equiv.) under a nitrogen atmosphere. The mixture was then dissolved in anhydrous THF (2 mL). The resulting mixture was stirred for 22 h under irradiation with 2 x 23 W CFL lamps. The reaction was monitored by TLC. When pyrrole **4.21** was fully consumed, the reaction was diluted with EtOAc and washed with water. The organics were combined and dried over Na$_2$SO$_4$ and concentrated *in vacuo*. The crude material was purified on the Biotage instrument using 40% CH$_2$Cl$_2$/Hexanes to afford the desired product as a yellow oil (3.1 mg, 11%). $^1$H NMR (CDCl$_3$) δ: 7.60-7.62 (m, 2H), 7.43-7.49 (m, 3H), 7.28-7.33 (m, 4H), 6.47 (s, 1H), 3.68 (s, 3H), 1 signal missing. Sample too small to acquire a carbon spectrum. HRMS-ESI$^-$ (m/z): [M +H]$^+$, calc'd for C$_{17}$H$_{15}$N$_2$ 247.1230, found 247.1236.

# Chapter 5 - Substitution at Boron in BODIPYs.

The material in this chapter was published as a peer-reviewed invited article in the journal Chemical Communications.[40] Copyright information is included in the Appendix of this thesis. Liandrah Gapare's contributions to this published review include the completion of a thorough literature review regarding substitution at the boron atom of BODIPYs, collation of all relevant material, creating the first draft for all sections, and working with Dr. Alison Thompson (graduate supervisor) to effect edits prior to submission.

The chemistry of boron has a long history, from its elemental isolation in the early nineteenth century to modern-day utility with an impact that transcends all the chemical disciplines.[187,188] Boron is used extensively in synthesis, playing a key functional role in organic transformations ranging from classic hydroboration-oxidation to modern metal-catalyzed coupling reactions.[189] The utility of boron stems from the electronic properties of this Group 3 element, with its ground-state electronic configuration of $1s^2 2s^2 2p^1$. The study of boron, which adopts $sp^2$ hybridization and trivalency in compounds such as boron trifluoride ($BF_3$), presents an informative learning experience at all educational levels. The electron-deficient (six valence electron) atom, with its empty p-orbital, accepts electrons from donors to enable $sp^3$ hybridization at boron. In this way, boron readily interconverts between generally neutral $sp^2$ trigonal planar and charged $sp^3$ tetrahedral hybridization states upon coordination to heteroatoms such as oxygen and nitrogen and halogens. This apparently simple interconversion is at the heart of a wide range of applications across synthesis, materials science, sensing probes and drug discovery.[190,191,192] Boronic acid $B(OH)_3$ was used as a component in a mild antiseptic in the early twentieth century.[193] However, perhaps on account of unwarranted toxicity concerns, it took more than five decades for boron to

be unreservedly adopted by the medicinal chemistry community. It is conceivably this same concern regarding toxicity that was responsible for the slow development of synthetic methods by which to manipulate boron-containing compounds and/or that exploit the reactivity offered by compounds containing this element. However, since the discovery of Suzuki–Miyaura coupling, the developing interest in organoboron chemistry has led to boron now being seen as mainstream across catalysis and structural modification. In 2003, FDA approval of the first boron-containing medicine (Bortezomib, marketed as Velcade® for the treatment of cancer) paved the way for the development of new boron-containing drugs.[194,195]

Our adventures with boron in the Thompson group at Dalhousie University in Halifax, Canada originate with the chemistry of pyrroles. Given that Hans Fischer's unveiling of pyrrole as the major building block for porphyrins arguably constituted one of the first complete works of synthetic chemistry, this heterocycle is perhaps one of the most-studied.[196,197] The work discussed herein focuses on molecular scaffolds composed of two pyrrolic units, namely dipyrrins and the corresponding 4,4-disubstituted-4-bora-3a,4a-diaza-s-indacene complexes of boron known as BODIPYs. **Figure 33** shows the IUPAC numbering of these systems. The structural similarities of BODIPYs and s-indacenes is at the origin of the numbering system used for BODIPYs. In keeping with journal guidelines, this Feature article highlights our contributions to this area, melding our published results with applications across a wider context. Readers interested in a comprehensive review of dipyrrins and/or BODIPYs should explore works dedicated to extensive content reviews.[198,199,200,201,202,203,204]

Connection of two pyrrolic units through the 2-positions by a methine bridge results in a fully conjugated, planar dipyrrin that exhibits strong absorbance bands in the visible region of the electromagnetic spectrum. Aza-dipyrrins and aza-BODIPYs, whereby the central carbon atom of

the dipyrrin skeleton is replaced by nitrogen, also feature two pyrrolic units (**Figure 33**).[205] Although much less studied than dipyrrins on account of challenging synthetic approaches, and although not a focus of this review, aza-dipyrrins are gaining interest due to their red-shifted absorptions compared to the parent dipyrrins. The versatility of dipyrrinato ligands as chelating agents for various main group elements and in various applications is well documented.[206,207,208,209]
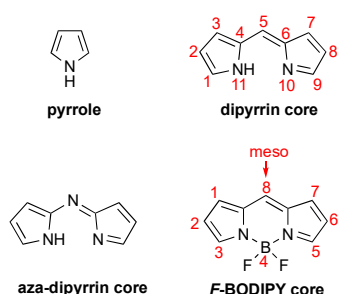


*Figure 33: Core frameworks of pyrrole, dipyrrin, F-BODIPY and aza-dipyrrin.*

The most common and intensively studied dipyrrinato complexes are the boron difluoride (-BF$_2$) chelated complexes known as *F*-BODIPYs. Boron-dipyrrinato complexes with oxygen-based substitution at boron are often denoted as *O*-BODIPYs, with variants featuring carbon substitution at boron referred to as *C*-BODIPYs. However, adherence to these naming conventions is far from absolute and the term "BODIPYs" is often used without consideration of the nature of the substituent at boron. The generally highly fluorescent *F*-BODIPY framework was unintentionally discovered in 1968 by Treibs and Kreuzer upon attempts to acylate 2,4-dimethylpyrrole with excess acetic anhydride in the presence of boron trifluoride as the Lewis acid catalyst. Instead of the desired 2-acyl-pyrrole **2** (**Scheme 46**), the two brightly coloured compounds **4** and **5** were isolated in < 10% yields.[210] Chelation of dipyrrin **3** with –BF$_2$ facilitates tetrahedral geometry at boron. This essentially acts as the "glue" that restricts motion such that the typically non-fluorescent dipyrrinato skeleton is rigidified to result in sharp absorption and emission bands.[199,211]

Such (photo)electronic properties have been intensely studied, with fine-tuning resulting in highly capable BODIPYs, e.g. bespoke emission, redox properties and/or (photo)sensitization to generate singlet oxygen and beyond.
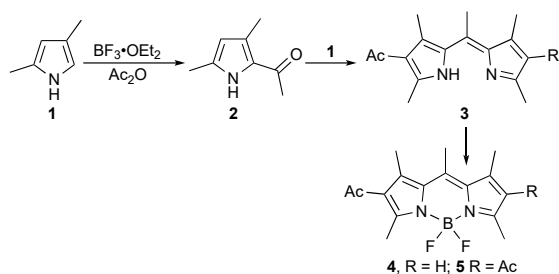


*Scheme 46: Synthesis of the first F-BODIPYs.*

Visualization of cellular biochemical activity is critical to understanding fundamental biology, with fluorescence imaging serving as an integral tool for labelling and for probing intracellular change. Fluorescence imaging relies upon the interplay of the probe (fluorophore) and the detection technique. In the presence of a desired interaction in the biological system, or upon occurrence of a biochemical change of interest, an ideal probe must itself exhibit a property, or a change in property, that is measurable by the detection method in use. The ideal probe should have optimal chemical and physical characteristics such as absorption and fluorescence emission in the visible or near-infrared (NIR) region, a large Stokes shift, high fluorescence quantum yield, useful lipophilicity, facile structural tunability and accessible synthesis. Given these requirements, many BODIPY-based fluorescent probes have been developed.[212] Some of the commercially available probes are, just to mention a few, LysoTracker[TM] Red DND-99,[213] which is selective for acidic organelles, and BODIPY[TM] FL-C$_5$,[214] used for label primary amines (R-NH$_2$) of proteins, amine-modified oligonucleotides and other amine-containing (bio)molecules (**Figure 34**)[215,216,217] While these BODIPY-based probes are used for labelling, others report on intracellular events such as

hypoxia, a common feature of solid cancer tumours. As approx. 30% of cancer deaths are related to late diagnosis, accurate and early monitoring may be the most accessible route to increasing cancer survival rates thus lending urgency to the development of robust diagnostic probes.[218,219,220]



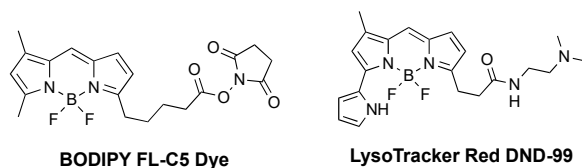**BODIPY FL-C5 Dye**          **LysoTracker Red DND-99**

*Figure 34: Two commercially available BODIPY probes used in molecular biology.*

Beyond their use as fluorescent bioprobes, the electronic tunability of BODIPYs has led to utility as photosensitizers for photodynamic therapy[221] and in dye-sensitized solar cells for photovoltaic technology.[222] The planar core, facile functionalization and tunable HOMO-LUMO gap of BODIPYs offer significant promise in this regard.[223] Furthermore, the presence of nitrogen at the meso-position of the aza-*F*-BODIPY framework lowers the energy of both absorption and emission transitions by reducing the HOMO–LUMO energy gap compared to *F*-BODIDYs with similar substituents. As such aza-BODIPY dyes typically absorb and emit at 600-750 nm and beyond.[224]

The tunability of dipyrrins is courtesy of the ability to vary substitution. Building on the various approaches by which to vary substitution about the dipyrrinato core, many of which require variation of the starting material pyrroles, work in our group has focussed on substitution at boron.

Construction of the boron-containing BODIPY framework necessitates prior synthesis of the corresponding dipyrrin, achieved through one of two generalized approaches. One approach (**Scheme 47**) involves the condensation of an a-free pyrrole **6** with an a-formyl pyrrole **7**, under

acidic conditions, and enables formation of dipyrrin salts **8** bearing different substituents about the two pyrrolic units.[200] The other approach involves condensation of two equiv of an α-unsubstituted pyrrole **6** with an aldehyde to provide a symmetric dipyrromethane. Oxidation then provides the dipyrrin **9**. This route often utilizes aryl aldehydes, thus placing an aryl group in the meso position, although alkyl variants are also known.[225] A variation of this strategy utilizes a carboxylic acid[200] or an acid chloride,[226,227] rather than an aldehyde, thus generating the dipyrrin directly and negating the need for later oxidation across the meso-position.
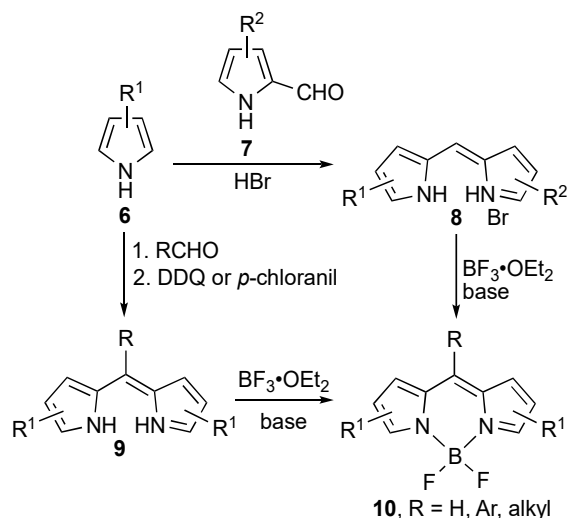


*Scheme 47: Synthetic approaches to F-BODIPYs.*

Oxidation of dipyrromethanes to dipyrrins is achieved with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) or the milder 2,3,5,6-tetrachloro-1,4-benzoquinone (*p*-chloranil), as indicated in **Scheme 47**. These oxidants were originally borrowed from the shelves of chemists familiar with the oxidation of cyclic tetrapyrroles to make porphyrins, with little variation published since that early work. The oxidation is typically a messy business, and is further complicated by challenging chromatographic requirements. As such, -BF$_2$ incorporation is often effected in situ as the formation of the apolar boron complex significantly improves the outlook

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for isolation of purified material. For decades, the chemistry of BODIPYs rested with *F*-BODIPYs via chelation of the dipyrrinato unit with -BF$_2$. Although new strategies[228,229] have emerged for the synthesis of *F*-BODIPYs, the treatment of a solution of dipyrrin, or its HX salt, with excess base (typically 6 equiv NEt$_3$ or DIPEA) and BF$_3$•OEt$_2$ (typically 9 equiv) has provided the traditional route to *F*-BODIPYs in generally quite high yields (**Scheme 47**).[230] Despite the obvious excesses of reagents, yields generally decrease upon decreasing the stoichiometry.[231,232] Furthermore, the yields vary significantly with compromised "anhydrous" conditions. This is unsurprising, given the anticipated behaviour of BF$_3$•OEt$_2$ in the presence of alternative donors, yet to an extent implying complications beyond simple quenching and instead consequent to the complexity of various equilibria involving Lewis acidic boron in the presence of NEt$_3$, H$_2$O, Et$_2$O and the chelating ligand. With the goal of simplifying synthetic protocol, we published a general method for *F*-BODIPY synthesis utilizing a hydrous, open-air environment and involving a second aliquot of excess NEt$_3$ and BF$_3$•OEt$_2$.[230] While this synthesis of *F*-BODIPYs removes the need for anhydrous conditions, the use of further reagent excesses is far from ideal.

While synthesis of dipyrrins is often facile the free-bases are typically unstable, especially when lacking substituents in the meso-position. For this reason dipyrrins are commonly isolated as the brick-red hydrobromide (or sometimes hydrochloride) salts, which are more stable than the corresponding free-bases. The instability of free-base dipyrrins is problematic when derivatizing the dipyrrinato core. As such, consideration of the –BF$_2$ unit of *F*-BODIPYs as a protecting group for dipyrrins holds considerable appeal. However, the reliability of deprotection is key to the utility of all potential protecting groups. Our unsuccessful attempts to remove the -BF$_2$ moiety from *F*-BODIPYs had, again borrowing from porphyrin chemistry, involved harsh treatments with strong acids. The premise of this approach was to protonate the N atoms of the dipyrrinato unit,

akin to the method used to demetallate porphyrins. We then instead leaned on the chemistry of boron, and relied on the strength of the B–O bond as a driving force for deprotection. Indeed, it is well documented that treatment of *F*-BODIPY with methoxide under forcing conditions results in substitution of fluoride to generate the corresponding *O*-BODIPY featuring two methoxy groups at boron.[233] We hypothesized that B–O bond formation could be achieved with tert-butoxide, with steric bulk preventing formation of the corresponding bis-tert-butoxy *O*-BODIPY analogue and instead resulting in decomplexation at boron. Heating *F*-BODIPYs in wet *t*-BuOH under microwave irradiation in the presence of KOH, thus generating *t*-BuOK in situ, resulted in removal of the –BF$_2$ moiety and liberation of the deprotected dipyrrins in generally high-quantitative yields, although lower for systems bearing electron-withdrawing groups such as acyl (**Scheme 48**).[231,234] During optimization of this work, a small amount of the intermediate 4-*tert*-butoxide-4-fluoro-BODIPY was isolated, supporting the anticipated role of tert-butoxide as a bulky nucleophile at boron and providing our first glimpse of the ability to activate, and thereby derivitise, BODIPYs at boron. Similarly, treatment of *F*-BODIPYs with KO$^i$Pr provided the corresponding di(isopropoxy) *O*-BODIPYs. The dihydroxy *O*-BODIPY was also isolated in the course of this work. There are limited reports of boron complexes of this type, in which the boron atom bears two hydroxyl substituents, as decomposition to boric acid prevails under aqueous/acidic conditions.[235,236,237,227] Observation of the dihydroxy *O*-BODIPY inspired subsequent development of the Lewis acid-activated deprotection of *F*-BODIPYs and *Cl*-BODIPYs discussed later in this article.
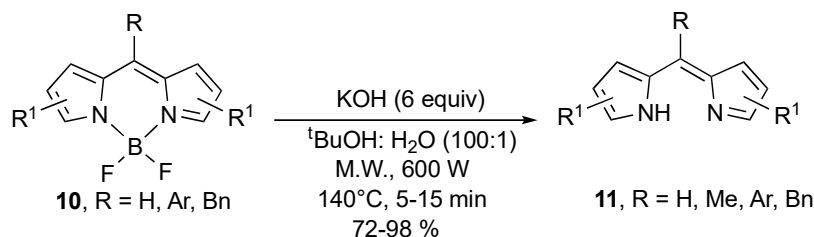
*Scheme 48: Microwave-assisted deborylation of F-BODIPYs using tertbutoxide.*

Returning to the synthesis of *F*-BODIPYs from dipyrrins, the use of excess base and BF$_3$ reagents inevitably results in unwanted boron-containing by-products such as BF$_3$•Et$_3$N, a material that results in the formation of emulsions during extractive work-up procedures, and complicates purification/isolation on a large scale. To improve upon this environmentally and economically unfavourable approach, we developed methodology that utilises stoichiometric quantities of BF$_3$•OEt$_2$. To do so, we relied upon our synthesis of lithium dipyrrinato salts[232] (**Scheme 49**, top left) through treatment of dipyrrins with LiHMDS or nBuLi). We also investigated sodium and potassium salts, identifying complementary reactivity of the dipyrrinato unit and the ability to generate heteroleptic metal complexes of transition metals.[238,239] Lithium salts have since been used to generate the first gallium and phosphorus dipyrrinato complexes[240] (**Scheme 49**, bottom). The isolation of the lithium dipyrrinato salt **12**, followed by treatment with [PPh$_4$][GaCl$_4$], gave the corresponding GADIPY. Furthermore, the reaction of PhPCl$_2$ and TMSOTf produced a [PhPOTf]$^+$ fragment which then reacted with the lithium dipyrrinato salt **12** to give the thermally unstable phenylphosphenium (PHODIPY). The alkali dipyrrinato salts were key to extending the range of dipyrrinato complexes reported, as it is challenging to imagine success such as that depicted in **Scheme 49** if limited to using the previous approach to dipyrrinato complexes which essentially involved stirring HBr salts of dipyrrins with metal chloride/other salts.[200] As a caution,
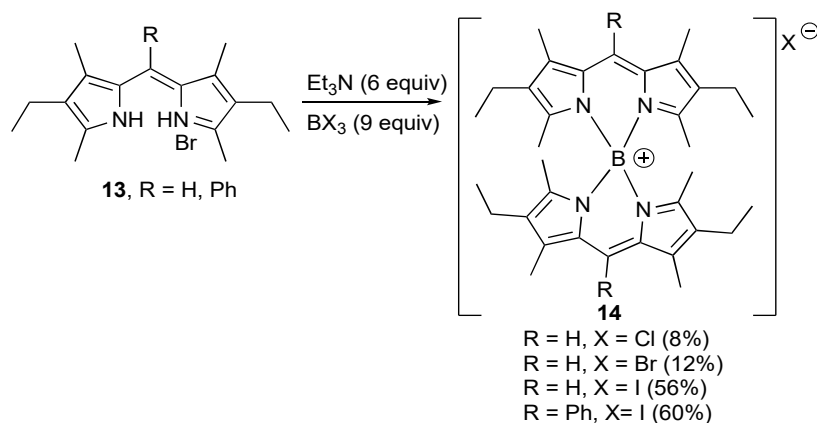
we note that the tetramethyl free-base dipyrrin starting material for the GADIPY and PHODIPY shown in **Scheme 49** is a potent sternutator with the ability to sensitize users to its presence in even trace amounts.
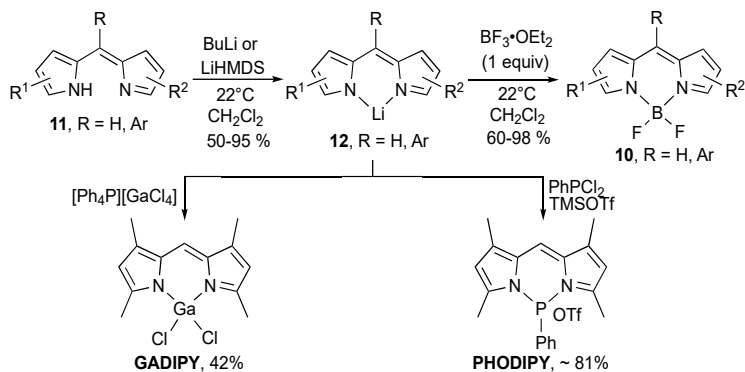


*Scheme 49: Synthesis and use of Li dipyrrinato salts.*

Given the success of lithium dipyrrinato salts as synthetic precursors, we extended their reactivity to complexation with boron with hopes of developing a route to *F*-BODIPYs that utilised stoichiometric amounts of reagents. The free-base dipyrrin was thus treated with 1.1 equiv LiHMDS, resulting in formation of the corresponding Li salt which then reacted in situ with 1 equiv BF$_3$•OEt$_2$ to give the *F*-BODIPY in 60-98% yields (**Scheme 49** (top)).[232] This method proved equally effective in averting the use of NEt$_3$/DIPEA and excess BF$_3$•OEt$_2$, and eases purification challenges by avoiding the formation of unwanted Lewis adducts. A variety of *F*-BODIPYs, including both meso-H and meso-aryl substituents, were synthesized in quantitative yields. *F*-BODIPYs involving various pyrrolic substitution patterns, including a-free, b-free and fully unsubstituted dipyrrins, as well as conjugated alkanate esters, were synthesized in this way. Furthermore, bis(*F*-BODIPYs) that had proven elusive via traditional approaches using NEt$_3$/DIPEA and BF$_3$•OEt$_2$ were obtained via treatment of the corresponding bis(lithium

dipyrrinato) salts with a stoichiometric amount of BF$_3$•OEt$_2$.[232] Although many transition metal dipyrrinato complexes have been synthesized, BODIPYs featuring halogens other than fluoride at boron had yet to be reported: certainly the traditional route to *F*-BODIPYs involving excess NEt$_3$/DIPEA and BF$_3$•OEt$_2$ was unsuited for reactions involving the more reactive boron trihalides. Furthermore, although the stability of *F*-BODIPYs provides a thermodynamic driving force for reaction success, this could not be relied upon for desired dipyrrinato products involving B–Cl, B–Br and/or B–I bonds. Nevertheless, to explore the possibility of non-fluoro *X*-BODIPYs, we treated dipyrrins **13** with 6 equiv NEt$_3$ and 9 equiv of either BCl$_3$, BBr$_3$ or BI$_3$ (**Scheme 50**). Characterization of the resultant products did not reveal *X*-BODIPYs but instead provided the first dipyrrinato salts **14** featuring a boronium cation isolated with a counter-anion corresponding to the boron trihalide used. The yield of the boronium cations increased as the size of the halogen increased, corresponding to the improved leaving group ability and the susceptibility of the boron centre to nucleophilic attack. Of note, dipyrrinato-based boronium cations are large, and have the potential to be rendered (homo)chiral.

**13**, R = H, Ph

Et₃N (6 equiv)
BX₃ (9 equiv)

**14**
R = H, X = Cl (8%)
R = H, X = Br (12%)
R = H, X = I (56%)
R = Ph, X= I (60%)

*Scheme 50: Synthesis of first dipyrrinato boronium salts.*

Failure of this approach to form *X*-BODIPYs (X = halogen where X ≠ F) fueled our consequent

exploration of a salt metathesis approach to *Cl*-BODIPYs **15**. This approach was highly successful,

with treatment of lithium dipyrrinato complexes with 1 equiv BCl₃ providing *Cl*-BODIPYs in very

high yields (**Scheme 51**, top left).[241] The quantum yields for *Cl*-BODIPYs are unsurprisingly lower

than those of the corresponding *F*-BODIPYs, yet still exhibit considerable fluorescence (e.g. $\phi_F \approx$

0.4 vrs. 0.9). These *Cl*-BODIPYs were unstable to moisture, thereby regenerating dipyrrins and

indicating complementary reactivity for *Cl*- and *F*-BODIPYs.
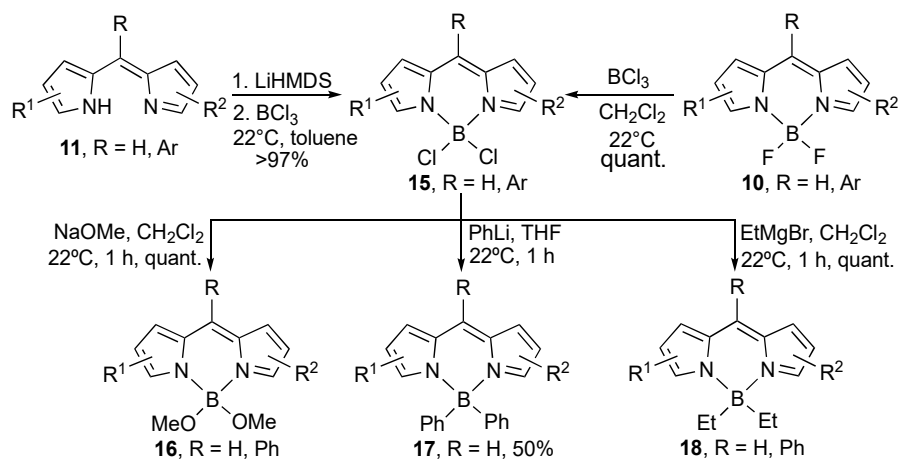
***Scheme 51: Synthesis of Cl-BODIPYs – synthetic intermediates for substitution at boron.***

Although attempts to isolate *Br*-BODIPYs and *I*-BODIPYs using this methodology were unsuccessful we speculated that these compounds do form, as evident by the deep red colour and hints of fluorescence associated with addition of BBr$_3$ and BI$_3$ to lithium dipyrrinato salts. However, these BODIPYs are presumably insufficiently stable, under the conditions we explored, to enable isolation. There are reports of the reactions of the dipyrinnato motif with BCl$_3$[242] and BBr$_3$.[243] In these reports, the heavy atom BODIPYs were not isolated but were used as intermediates and underwent substitution with alkoxides, demonstrating their reactivity under ambient conditions. As a consequence of sequentially reacting bis(dipyrrins) with BF$_3$ and then BCl$_3$ in attempts to prepare unsymmetrical bis(BODIPYs), we established that *F*-BODIPYs can be smoothly converted into *Cl*-BODIPYs upon treatment with 1 equiv BCl$_3$ (**Scheme 51**, top right).[244] As well as providing another reliable route to *Cl*-BODIPYs, this discovery prompted a mechanistic investigation. Through labelling the boron in *F*-BODIPYs, achieved via derivitisation of isotopically labeled B(OMe)$_3$, halogen exchange (rather than –BX$_2$ exchange) was confirmed

upon treatment of *F*-BODIPYs with $BCl_3$.[245] At first sight the loss of the strong B–F bond, and formation of the weaker B–Cl bond, in the BODIPY unit seems to conflict with thermodynamic principles,[246] but a more thorough analysis reveals $BClF_2$ as the formal byproduct. Given somewhat rapid exchange in $BX_3$ Lewis acids,[247] formation and loss of uncoordinated $BClF_2$ and $BF_3$ from the system is envisaged to drive the quantitative transformation of *F*-BODIPYs into *Cl*-BODIPYs. A *Br*-BODIPY was isolated using this strategy,[248] i.e. treatment of *F*-BODIPY with $BBr_3$, as confirmed via $^{11}B$ NMR spectroscopy. Although the weaker Br–B bond offers intriguing reactivity, the reactivity of *Br*-BODIPYs was not extensively investigated.

With halogen exchange at boron now firmly established, we turned our attention to other forms of substitution at boron and thus explored the reactivity of the new *Cl*-BODIPYs. We postulated that the weaker B–Cl bond would allow for more facile substitutions at the boron centre than had been possible when *F*-BODIPYs were the only starting materials available. To investigate this hypothesis, isolated *Cl*-BODIPYs were treated with alkoxides, aryl lithium reagents and Grignard reagents (**Scheme 51**, bottom).[241] Nucleophilic substitution at the boron center was found to be facile providing dialkoxy (*O*-BODIPYs), dialkyl and diaryl BODIPYs (*C*-BODIPYs) in high yields using stoichiometric amounts of reagents and under mild reaction conditions. Such substitution compares favourably to the harsh conditions and long reaction times necessary to effect the same substitution at boron in *F*-BODIPYs. For example, conversion of *F*-BODIPYs into the corresponding dimethoxy *O*-BODIPY had typically required reflux temperatures and reaction times reaching 18 h. Recent improvements demonstrated the use of other Lewis acids such as $AlCl_3$ to promote substitution at boron.[235,237]

Uniting the ability to prepare *Cl*-BODIPYs, through halogen exchange of *F*-BODIPYs, with the facile substitution of *Cl*-BODIPYs at boron provided opportunities for substitutions beginning

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with the air-/moisture-stable *F*-BODIPYs. This one-pot approach utilizes *Cl*-BODIPY as a synthetic intermediate for substitution at boron. *F*-BODIPYs were treated with 1 equiv $BCl_3$ at room temperature. After 1 h, solid NaOMe was added to the solution under inert conditions to give *O*-BODIPYs in quantitative yield.[244] Successful synthesis of *O*-BODIPYs via this route contrasts with the trace amounts observed when *F*-BODIPYs are treated directly with NaOMe under the same mild conditions. Similarly, in situ generation of *Cl*-BODIPYs and treatment with Grignard reagents provides *C*-BODIPYs in quantitative yield from *F*-BODIPYs.

The advantages of using *Cl*-BODIPYs as situ intermediates were also demonstrated through the synthesis of **19** (**Scheme 52**). Such spirocyclic-at-boron *O*-BODIPYs had previously proven to be elusive when *F*-BODIPYs were reacted with alcohols in the presence of $AlCl_3$. This approach, proceeding via in situ formation of a B-F-Al-F chelate, had resulted in a range of *O*-BODIPYs and demonstrated the ability to activate the B–F bond through treatment with Lewis acid.[237] However, under these conditions, attempted substitution of the fluoro substituents with 1,3-propanediol did not provide the corresponding spirocyclic derivative. Our methodology involving in situ generation of *Cl*-BODIPY, followed by treatment with the lithium dienolate of 1,3-propanediol in a stoichiometric amount and under mild conditions, provided the desired O-BODIPY **19**.
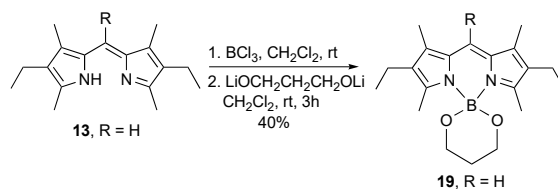


*Scheme 52: Chelated O-BODIPY utilizing Cl-BODIPY as a synthetic intermediate.*

The BCl₃-mediated route to substitution of *F*-BODIPYs at boron has gained some popularity. For example, BODIPYs bearing carboxyl functionality at boron are of interest for use in biological settings as they can be rendered much less lipophilic than the corresponding *F*-BODIPYs and can be modified to present a red-shifted sharp emission band with rich fluorescence properties. The first such *COO*-BODIPYs were synthesized in low-moderate yields through treatment of *F*-BODIPYs at 90ºC for 40 h with a pre-mixed solution containing TMSCl and acetic acid: the authors proposed the presence of TMSOAc, generated in situ, to be responsible for reactivity at boron.[249] More recently, a milder and higher yielding synthesis of *COO*-BODIPYs was reported (**Scheme 53**).[250] This involved activation of *F*-BODIPYs with BCl₃, and was applied to a range of mono- and bis-carboxylic acids. This approach enabled chiral auxiliaries to be appended at boron, leading to *COO*-BODIPYs that exhibited circularly polarized luminescence in the visible region.[251,252,253] This Lewis-acid mediated approach offers considerable convergency and improved yields.
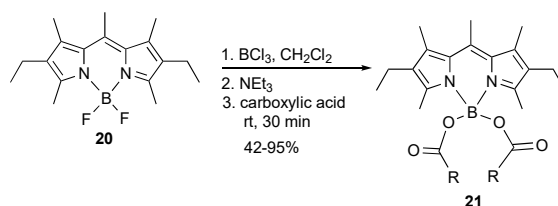


*Scheme 53: BCl₃-activated synthesis of COO-BODIPYs from F-BODIPY.*

Activation of *F*-BODIPYs through treatment with BCl₃ was also used for the synthesis of *N*-BODIPYs **23** (**Scheme 54**),[254] with the Lewis donicity of the chelating diamines tempered through their incorporation as sulfonamides: use of simple amines such as ethylenediamine failed to produce *N*-BODIPYs. BODIPYs and aza-BODIPYs featuring both carboxyl and amino-functionality at boron, e.g. aza-BODIPY **25** (**Scheme 55**), were obtained via treatment of *Cl*-(aza)-

BODIPYs, prepared in situ from the corresponding *F*-(aza)-BODIPYs, with glycines protected with a variety of carbonyl-based electron-withdrawing protecting groups (PG) at nitrogen.[255,256] In this way, water-soluble BODIPYs bearing amino acids at boron have been prepared, and investigated as regards cellular uptake and cytotoxicity.[257]
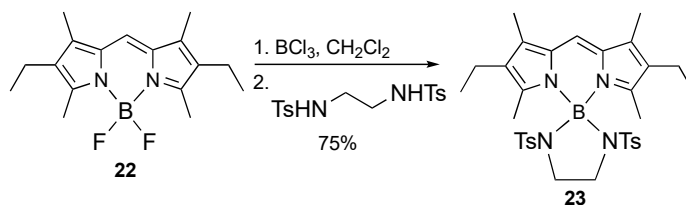


*Scheme 54: Synthesis of N-BODIPY via BCl₃ activation of F-BODIPY.*
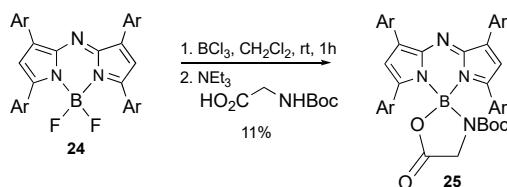


*Scheme 55: Glycine-based N,O-aza-BODIPY via Cl-aza-BODIPY.*

Applying the utility of *Cl*-BODIPYs led to the first *O*-BODIPY:glucose conjugates featuring sugar moieties attached at the boron atom through covalent B–O–C bonds.[258] Treatment of the meso-aryl *F*-BODIPY **26** with BCl₃ generated the corresponding *Cl*-BODIPY, which was used as the precursor for three fluorescent BODIPY-glucose conjugates: i.e., 1:1 α-glucofuranose BODIPY **27**, alongside 1:2 α-glucofuranose and 1:2 α-glucoseptanose BODIPYs which are both shown schematically as **28** (**Scheme 56**). Complexation between the boron atom of the BODIPYs and the C1, C2 *cis*-1,2 diol sites of glucose was observed, with binding to the C3, C5 1,3-diol most likely for the second BODIPY unit in the 1:2 constructs. This synthetic route melds the capabilities of the BODIPY and boronic acid moieties to enable *O*-BODIPY–sugar binding to occur: given the harsh conditions and extended reaction times necessary for substitution at boron in *F*-BODIPYs,

the reactivity of the newly available *Cl*-BODIPY motif must surely have been critical to this early success. More recent work conjugating BODIPYs to sugars through complexation at boron used *O*-BODIPYs bearing methoxy groups at boron, themselves prepared from the corresponding *Cl*-BODIPYs. Use of the *O*-BODIPYs provided only methanol as by-product, rather than production of HCl when *Cl*-BODIPYs were used. These milder conditions enabled improved yields courtesy of the increased stability of fragile sugar-BODIPY conjugates of glucose, xylose and ribose under these less acidic reaction conditions.[259] Other Lewis acids have been used to activate *F*-BODIPYs. For example, AlCl$_3$ activates *F*-BODIPYs to enable substitution at boron with perfluoro-alkoxy groups.[260]
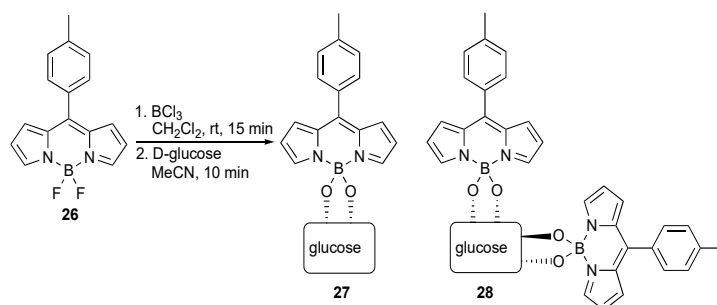


***Scheme 56: BODIPY-sugar conjugates utilizing Cl-BODIPY as synthetic intermediate.***

Our adventures modifying substituents at the boron atom of BODIPYs had led us to understand that the reactivity of the integral X–B bond could be tuned. While seemingly obvious in retrospect, we must remember that BODIPYs were celebrated for several decades in only their difluoro form. Such *F*-BODIPYs were applauded for their desirable photophysical properties and, critically, for their stability, i.e. their ability to tolerate a broad range of chemical and physiological conditions. With our new knowledge regarding substitution of boron in BODIPYs we realized that deprotection (i.e., removal of the -BF$_2$ unit from *F*-BODIPYs) could be revisited. Whilst the

alkoxy-promoted deprotection of *F*-BODIPYs was successful (**Scheme 48**), the use of these basic

conditions to remove the -BF$_2$ motif was less than ideal. However, as previously mentioned, we

had learned that the Cl–B bonds within *Cl*-BODIPYs are susceptible to attack by water such as to

generate the dihydroxy *O*-BODIPY – which decomposes to provide boric acid and the parent

dipyrrin as its stable HCl salt.[234] Combined with the newly discovered and reliable transformation

of *F*-BODIPYs into *Cl*-BODIPYs, this reactivity provided a new strategy for the deborylative

deprotection of *F*-BODIPYs. Indeed, the reaction of *F*-BODIPYs with 1 equiv BCl$_3$, and

subsequent dissolution in excess acetone: water (10:1), afforded a quantitative yield of the dipyrrin

salt (**Scheme 57**). This approach was demonstrated using *F*-BODIPYs featuring unsubstituted,

alkyl-substituted and keto-substituted pyrrolic units. Similarly, meso-H and meso-aryl *F*-

BODIPYs were successfully deprotected. Treatment of *F*-BODIPYs with BBr$_3$ was equally

successful, with reaction of the corresponding *Br*-BODIPY with wet acetone providing the parent

dipyrrin as its HBr salt.[248] Alternative methods for deprotection of *F*-BODIPYs, including via use

of other Lewis acids,[261,262] Brønsted acids[263] and via treatment with methylboronic acid and TFA

are also known.[264] This approach has been key to generating prodigiosene-type complexes

whereby a pyrrolide flanks the dipyrrinato unit to create an effective chelation pocket.[265,266]
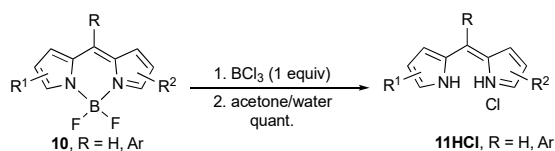


*Scheme 57: Deprotection of F-BODIPYs via Cl-BODIPYs.*

Deprotection of *F*-BODIPYs via *Cl*-BODIPYs has proven to be reliable, gaining use such as in

the synthesis of some tripyrrolic natural products. For example, a concise metal-free method for

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the facile synthesis of synthetic and natural prodigiosenes utilized the -BF$_2$ unit as a protective

motif for the dipyrrinato construct **31**, enabling isolation of these stable and non-polar synthetic

intermediates. Deprotection at boron via hydrolysis of the corresponding *Cl*-BODIPYs provided

the desired prodigiosenes **33** as their HCl salts with purification merely requiring crystallisation

(**Scheme 58**).[267] Removal of the -BF$_2$ unit was also achieved with *tert*-butoxide to give the required

prodigiosene as its free base, but in a reduced yield and after necessary chromatography.
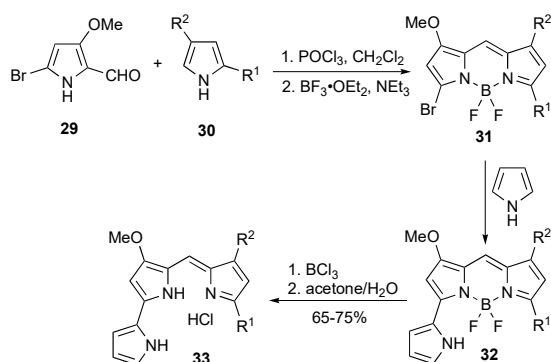


***Scheme 58: Synthesis of prodigiosenes using F-BODIPYs as protected***

***dipyrrins.***

Returning to the synthesis of *F*-BODIPYs, we found ourselves in an ideal position to probe the

somewhat capricious yields obtained when applying the traditional synthetic conditions involving

treatment of dipyrrins, and/or their HX salts, with base (typically 6 equiv NEt$_3$ or DIPEA) and

BF$_3$•OEt$_2$ (typically 9 equiv).[230] One rationale for the variation in BODIPY yields rests with

interactions between the Lewis acid BF$_3$ and adventitious water which may be present if strict

anhydrous conditions are not adhered to. Indeed, even trace amounts of water can cause significant

reductions in product yield. However, the effect of water on yields seems to go beyond simple

deactivation of BF$_3$.[268] Our insight gained from reacting *F*-BODIPYs with Lewis acids such as

BCl$_3$ and BBr$_3$ led us to question whether treatment with BF$_3$•OEt$_2$ would similarly result in

activation. If so, we envisaged that treatment with water may serve to effect nucleophilic attack at the boron atom of BODIPYs and thereby lead to ultimate formation of boric acid and liberated dipyrrin. We were encouraged by published work that showed that BODIPYs were activated at boron through treatment with Lewis acids such as $SnCl_4$, enabling substitution of $^{19}F$ for radioactive $^{18}F$ at boron.[269] In our investigations, we mixed *F*-BODIPYs with 1 equiv $BF_3 \cdot OEt_2$ and were delighted to observe new $^{19}F$ and $^{11}B$ NMR signals c.f. the starting materials.[248] This activated intermediate (**Scheme 59**), featuring reversible interaction of the fluoro substituents of the *F*-BODIPY with the Lewis acidic boron of the added $BF_3 \cdot OEt_2$, presents an opportunity to achieve direct substitution at the boron atom of *F*-BODIPYs.

Treatment of the activated intermediate with excess water, such as would be encountered during a typical aqueous /work-up, returned the original *F*-BODIPY in quantitative yields.[248] Presumably, the added $BF_3 \cdot OEt_2$ is quenched in the presence of excess water. In contrast, upon the addition of just 3 equiv water to the activated intermediate, the boron atom of the BODIPY is nucleophilically attacked to form first the hydroxy O-BODIPY, followed by complete hydrolysis to liberate boric acid and the parent dipyrrin isolated as its $HBF_4$ salt **34** (**Scheme 59**). These salts are intensely crystalline, although subject to loss of $BF_3$ over extended periods of time in air, and easily converted to the corresponding HBr salts. This deprotection strategy was successful for several *F*-BODIPYs bearing alkyl-substituted pyrrolic units. However, the incorporation of an aryl substituent at the meso-position resulted in significantly reduced yield for the deprotection, and suggests opportunities for chemoselective removal of the $-BF_2$ unit from *F*-BODIPYs. The use of 3 equiv water is critical to hydrolysis at the boron atom of the *F*-BODIPY, with the use of excess water instead quenching the F---B interaction involving the added $BF_3 \cdot OEt_2$ and thus quenching the activated intermediate.
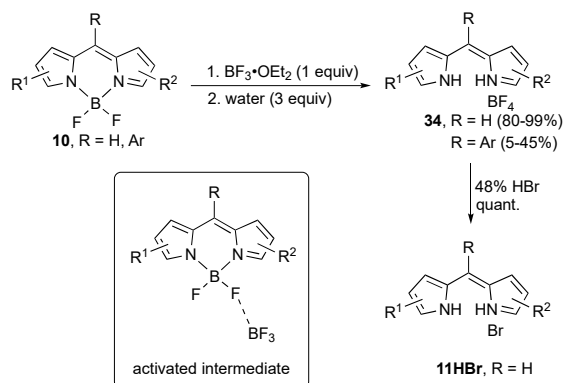
*Scheme 59: Activation and deprotection of F-BODIPYs using BF₃.*

to the corresponding HBr salts. This deprotection strategy was successful for several *F*-BODIPYs bearing alkyl-substituted pyrrolic units. However, the incorporation of an aryl substituent at the meso-position resulted in significantly reduced yield for the deprotection, and suggests opportunities for chemoselective removal of the -BF$_2$ unit from *F*-BODIPYs. The use of 3 equiv water is critical to hydrolysis at the boron atom of the *F*-BODIPY, with the use of excess water instead quenching the F---B interaction involving the added BF$_3$•OEt$_2$ and thus quenching the activated intermediate.
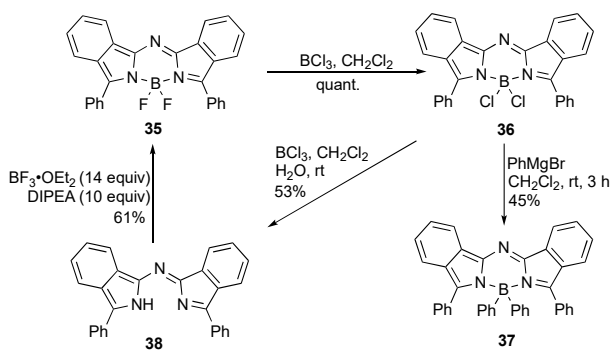


*Scheme 60: Synthesis and utility of Cl-aza-BODIPYs.*

Alkali salts of the aza-dipyrrinato complex[270] enabled substitution at boron, as perhaps rationalized through appreciation of the donicity of the dipyrrin and aza-dipyrrin constructs, deduced via $^{13}$C NMR spectroscopy.[271] Furthermore, the archetypal aza-dipyrrin subtypes were found to successfully undergo complexation to -$BCl_2$ when treated with $BCl_3$ (**Scheme 60**). For example, formation of the *Cl*-aza-BODIPYs **36** occurs through stepwise halogen exchange and a mixed halogen BODIPY intermediate featuring a -BClF unit.[272] *Cl*-aza-BODIPYs such as **36** were found to be unstable after a few days of exposure to air, decomposing to the aza-dipyrrin HCl salts. The utility of the Cl-aza-BODIPY scaffold, as contained within the subphthalocyanine motif,[273] extends to substitution at boron under mild conditions through treatment with aryl Grignard reagents, courtesy of the lability of the B–Cl bond. Unlike in *F*-BODIPYs, the addition of a nucleophile immediately after in situ formation of the *Cl*-aza-BODIPY **36** from the *F*-aza-BODIPY **35** failed to effect B-substitution, and instead returned either the *F*-aza-BODIPY or the parent free-base (i.e., deborylated) dipyrrin **38**. Rather, removal of the solvent and by-products such as $BF_2Cl$, prior to addition of the nucleophile, is essential to quenching the halogen exchange reaction and achieving complete substitution at boron. As for *F*-BODIPYs, *F*-aza-BODIPYs are also amenable to deprotection through formation of the corresponding *Cl*-aza-BODIPY. The chemistry of boron in aza-BODIPYs remains largely unexplored.

**Conclusions**

In conclusion, we have highlighted the utility and reactivity of boron in our work with BODIPYs and, briefly, with aza-BODIPYs. Installation of the -$BR_2$ moiety offers enhanced rigidity to the conjugated dipyrrinato framework and therefore highly desirable photophysical properties. We have explored the reactivity at boron within BODIPYs such as to enable convergent substitution

at this position, as well as render the -BX$_2$ unit (X = halogen) effective as a useful protecting group that can be removed under highly specific conditions.

# Chapter 6 – Conclusions.

## Chapter 2 - Conclusion.

This chapter discusses the investigation of the synthesis of *F*-BODIPY in a continuous flow operation using 1 equiv of BF$_3$•OEt$_2$ in the absence of a base. The results confirmed that the reaction of the free-base dipyrrin and BF$_3$•OEt$_2$ is rapid at the point of mixing. Indeed, by comparing results obtained in batch to those obtained in flow, it was found that there was no significant change in the yields obtained. This suggests that the continuous flow operation failed to eliminate the interaction between the HF produced in situ, with the unreacted BF$_3$•OEt$_2$ to form BF$_4$$^-$ and thus the dipyrrin HBF$_4$ salt. We then introduced HF scavengers in batch mode with the hope of counteracting the formation of the non-complexed materail and thus the desired *F*-BODIPY would be generated in higher yields. To this end, the use of a variety of additives was explored but none resulted in the generation of the desired product in high yields. Some additives, like TMSPa, resulted in the elimination of the HBF$_4$ salt but the yield of the BODIPY did not change. We then studied the reaction of the free-base dipyrrin and 1 equiv of BF$_3$•OEt$_2$ in the presence of various solvents and at various temperatures to discover that the reaction performed moderately well in 1:5 CH$_2$Cl$_2$: hexanes at 30 °C. This was however only optimal for the alkyl-substituted *F*-BODIPYs, which were formed in moderate yields. A comparison of this new method with the traditional anhydrous method[30] and the hydrous method[43] on a 1 g scale of free base **2.1** showed that this new method is advantageous from an economic point of view as it requires only 1 equiv of BF$_3$ and reduced volume of solvent for purification. This method only takes 10 min for the reaction to reach completion, unlike for the other methodologies which take 2.5 and 3 hours.[43]

## Chapter 3 - Conclusion.

This chapter discusses the development of potential alternative syntheses of aza dipyrrins wherein an acyclic diketoimde is synthesized, then converted to dipyrrolamine via Paal-knorr cyclization then oxidation to aza dipyrrin. Preliminary investigation of this pathway revealed challenges with undesired side reactions. However, the hint of success from the formation of amine **3.23b** from the reaction of nitrobutanone **3.27b** and active ester **3.31**, though in a low yield, means further optimization and development of this method is possible to determine the viability of this method for the synthesis of aza dipyrrins.

## Chapter 4 - Conclusion.

This chapter discusses the development of a potential alternative route to the synthesis of aza dipyrrins, ideally to overcome limitations in the current methods of synthesis. Several pathways have been proposed herein wherein α-nitro or α-nitroso pyrroles bearing desired substituents are synthesized and then coupled with 2-boc-pyrrole boronic acid **4.11** under catalysis with tetravalent phosphorus reagents in the presence of phenylsilane as a reductant. Investigations of this coupling revealed multiple challenges, with complex mixtures obtained. This prompted the reaction of nitroso pyrroles with 2-boc-pyrrole boronic acid **4.11** under light-promoted triphenylphosphine-induced catalysis. The use of blue LED lights resulted in the formation of the desired aza dipyrrin in a 44% yield, an achievement comparable to the current routes to aza dipyrrins.[90] Given this success, attempts to synthesize alkyl-substituted nitroso-pyrroles for subjection to the blue LED-mediated methods using the nitrosylation conditions with $NaNO_2$ in ethanolic HCl were unsuccessful. This prompted the exploration of alternative nitrosylation conditions for pyrroles. The reaction of α-free pyrroles with $NOBF_4$ in acetonitrile resulted in the formation of nitroso

pyrroles and several novel nitroso pyrroles were synthesized in reasonable yields. Application of this nitrosylation to alkyl-substituted systems did not proceed as expected but provided evidence for the formation of N-hydroxyl intermediates. This provides intriguing evidence that aza-dipyrrins are possibly just a step away. Further development is necessary to determine the viability of the pathway.

## Chapter 5 - Conclusion.

This chapter highlighted the utility and reactivity of boron in our work with BODIPYs and, briefly, with aza-BODIPYs. Installation of the -BR$_2$ moiety offers enhanced rigidity to the conjugated dipyrrinato framework and therefore highly desirable photophysical properties. We have explored the reactivity at boron within BODIPYs such as to enable convergent substitution at this position, as well as render the -BX$_2$ unit (X = halogen) effective as a useful protecting group that can be removed under highly specific conditions.

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# Appendix A.

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# Appendix B: X-Ray Crystallographic Analysis Data.

**4-Oxo-2,4-diphenylbutanoic acid pentafluorophenyl ester, (3.31).**
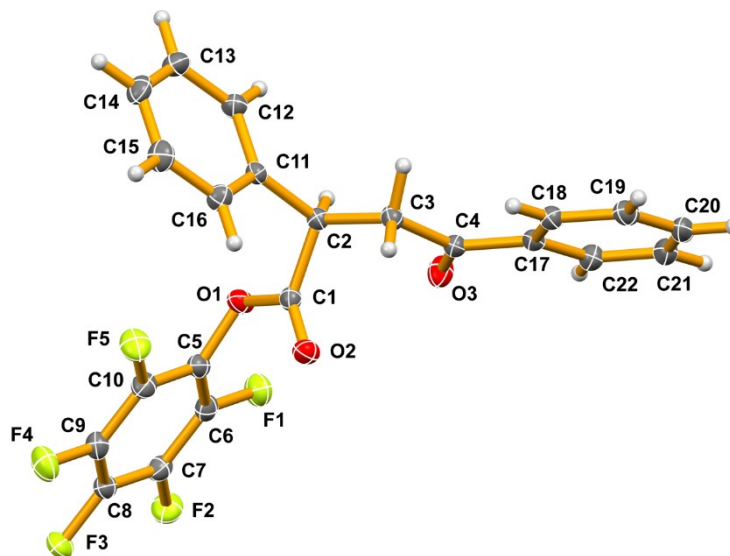


*Figure 35: ORTEP diagram of ester 3.31. Thermal ellipsoids are shown at 50% probability.*

| | |
|---|---|
| Empirical formula | $C_{22}H_{13}F_5O_3$ |
| Formula weight | 420.32 |
| Temperature | 125(2) K |
| Wavelength | 0.71073 Å |
| Crystal system | Monoclinic |
| Space group | $P2_1/c$ |
| Unit cell dimensions | $a$ = 7.3358(3) Å          a= 90° |
| | $b$ = 18.2998(7) Å        b= 101.609(2)° |
| | $c$ = 13.8963(6) Å        g= 90° |
| Volume | 1827.33(13) Å$^3$ |
| $Z$ | 4 |
| Density (calculated) | 1.528 Mg/m$^3$ |
| Absorption coefficient | 0.135 mm$^{-1}$ |
| F(000) | 856 |

| Crystal size | 0.088 x 0.076 x 0.062 mm$^3$ |
| Theta range for data collection | 2.226 to 30.998° |
| Index ranges | -10<=h<=10, -26<=k<=26, -20<=l<=20 |
| Reflections collected | 129550 |
| Independent reflections | 5827 [R(int) = 0.0624] |
| Completeness to theta = 25.242° | 99.9 % |
| Absorption correction | Semi-empirical from equivalents |
| Max. and min. transmission | 0.7432 and 0.7162 |
| Refinement method | Full-matrix least-squares on $F^2$ |
| Data / restraints / parameters | 5827 / 0 / 271 |
| Goodness-of-fit on $F^2$ | 1.033 |
| Final R indices [I>2sigma(I)] | R1 = 0.0411, wR2 = 0.0990 |
| R indices (all data) | R1 = 0.0581, wR2 = 0.1114 |
| Extinction coefficient | n/a |
| Largest diff. peak and hole | 0.415 and -0.244 e.Å$^{-3}$ |

**4-Nitro-1,3-diphenylbutan-1-ol, (3.32).**
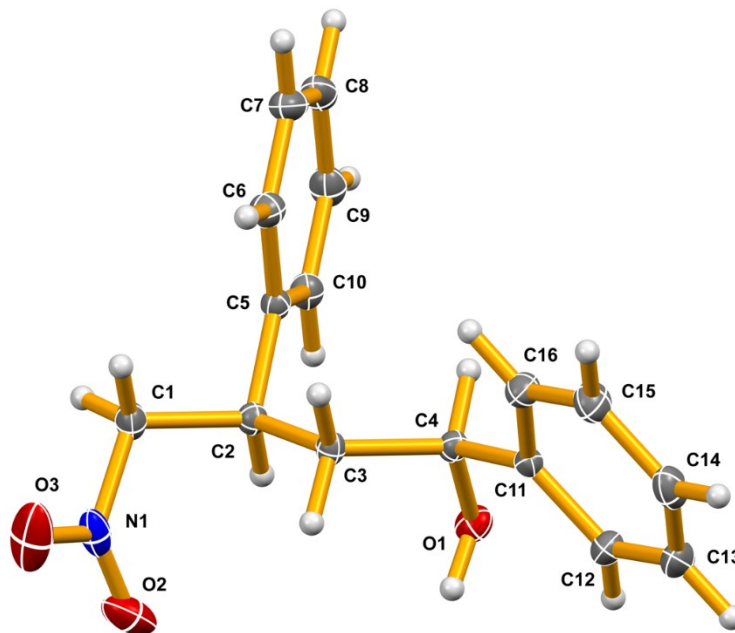


*Figure 36: ORTEP diagram of alcohol 3.32. Thermal ellipsoids are shown at 50% probability.*

| | |
|---|---|
| Empirical formula | $C_{16}H_{17}NO_3$ |
| Formula weight | 271.30 |
| Temperature | 125(2) K |
| Wavelength | 0.71073 Å |
| Crystal system | Triclinic |
| Space group | *P*-1 |
| Unit cell dimensions | *a* = 5.7796(2) Å  a= 76.2853(16)° |
| | *b* = 9.8634(4) Å  b= 88.5992(17)° |
| | *c* = 12.2495(5) Å  g = 83.5883(16)° |
| Volume | 674.15(5) Å$^3$ |
| *Z* | 2 |
| Density (calculated) | 1.337 Mg/m$^3$ |
| Absorption coefficient | 0.092 mm$^{-1}$ |
| F(000) | 288 |
| Crystal size | 0.414 x 0.108 x 0.024 mm$^3$ |
| Theta range for data collection | 1.711 to 36.316° |
| Index ranges | -9<=h<=9, -16<=k<=16, -20<=l<=20 |
| Reflections collected | 89515 |
| Independent reflections | 6537 [R(int) = 0.0721] |
| Completeness to theta = 25.242° | 100.0 % |
| Absorption correction | Semi-empirical from equivalents |
| Max. and min. transmission | 0.7489 and 0.6378 |
| Refinement method | Full-matrix least-squares on F$^2$ |
| Data / restraints / parameters | 6537 / 0 / 185 |
| Goodness-of-fit on F$^2$ | 1.031 |
| Final R indices [I>2sigma(I)] | R1 = 0.0460, wR2 = 0.1213 |
| R indices (all data) | R1 = 0.0641, wR2 = 0.1359 |
| Extinction coefficient | n/a |
| Largest diff. peak and hole | 0.516 and -0.219 e.Å$^{-3}$ |

**4-Oxo-2,4 diphenylbutanamide, (3.35).**
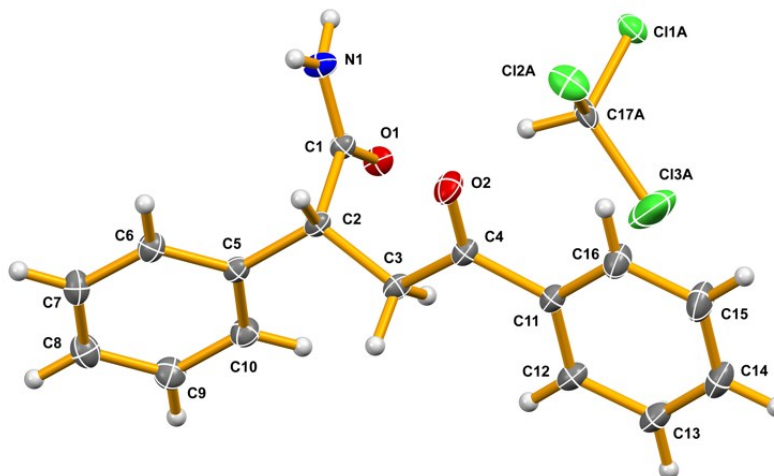


*Figure 37: ORTEP diagram of amide 3.35 with solvent. Thermal ellipsoids are shown at 50% probability.*

| | |
|---|---|
| Empirical formula | $C_{17}H_{16}Cl_3NO_2$ |
| Formula weight | 372.66 |
| Temperature | 125(2) K |
| Wavelength | 0.71073 Å |
| Crystal system | Monoclinic |
| Space group | $P2_1/c$ |
| Unit cell dimensions | $a = 10.9411(4)$ Å      a= 90° |
| | $b = 20.1946(6)$ Å      b= 102.081(1)° |
| | $c = 8.1906(2)$ Å      g = 90° |
| Volume | 1769.64(9) Å$^3$ |
| Z | 4 |
| Density (calculated) | 1.399 Mg/m$^3$ |
| Absorption coefficient | 0.525 mm$^{-1}$ |
| F(000) | 768 |
| Crystal size | 0.180 x 0.104 x 0.085 mm$^3$ |
| Theta range for data collection | 2.017 to 45.342° |
| Index ranges | -21<=h<=21, -40<=k<=40, -16<=l<=16 |

Reflections collected 244944

Independent reflections 14858 [R(int) = 0.0448]

Completeness to theta = 25.242° 99.9 %

Absorption correction Semi-empirical from equivalents

Max. and min. transmission 0.7489 and 0.6976

Refinement method Full-matrix least-squares on $F^2$

Data / restraints / parameters 14858 / 93 / 291

Goodness-of-fit on $F^2$ 1.027

Final R indices [I>2sigma(I)] R1 = 0.0365, wR2 = 0.0995

R indices (all data) R1 = 0.0566, wR2 = 0.1134

Extinction coefficient n/a

Largest diff. peak and hole 0.523 and -0.366 e.Å$^{-3}$

# Appendix C: NMR data for synthesized compounds.

**4-Oxo-2,4-diphenylbutanoic acid pentafluorophenyl ester, (3.31).**
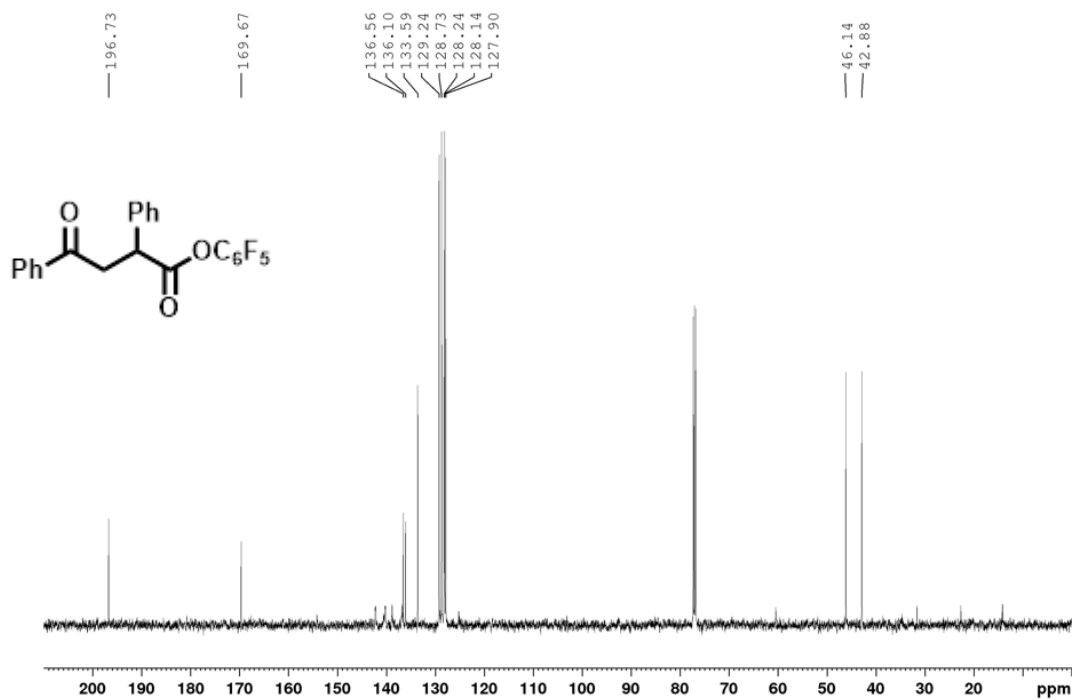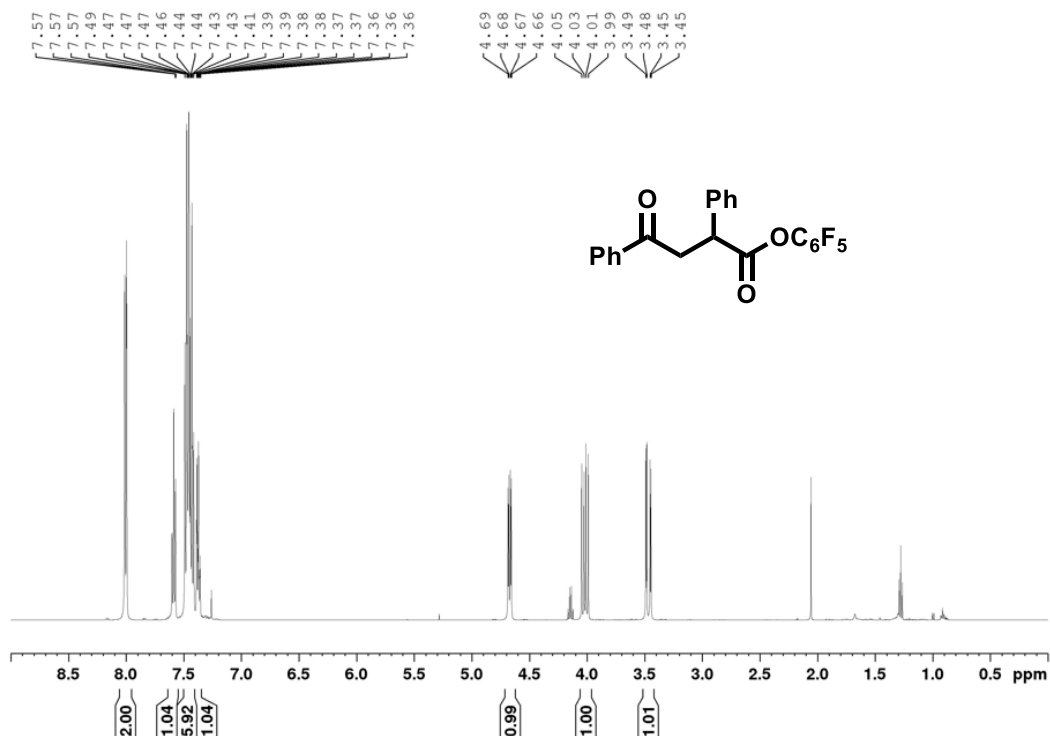
## 4-Nitro-1,3-diphenylbutan-1-ol, (3.32).
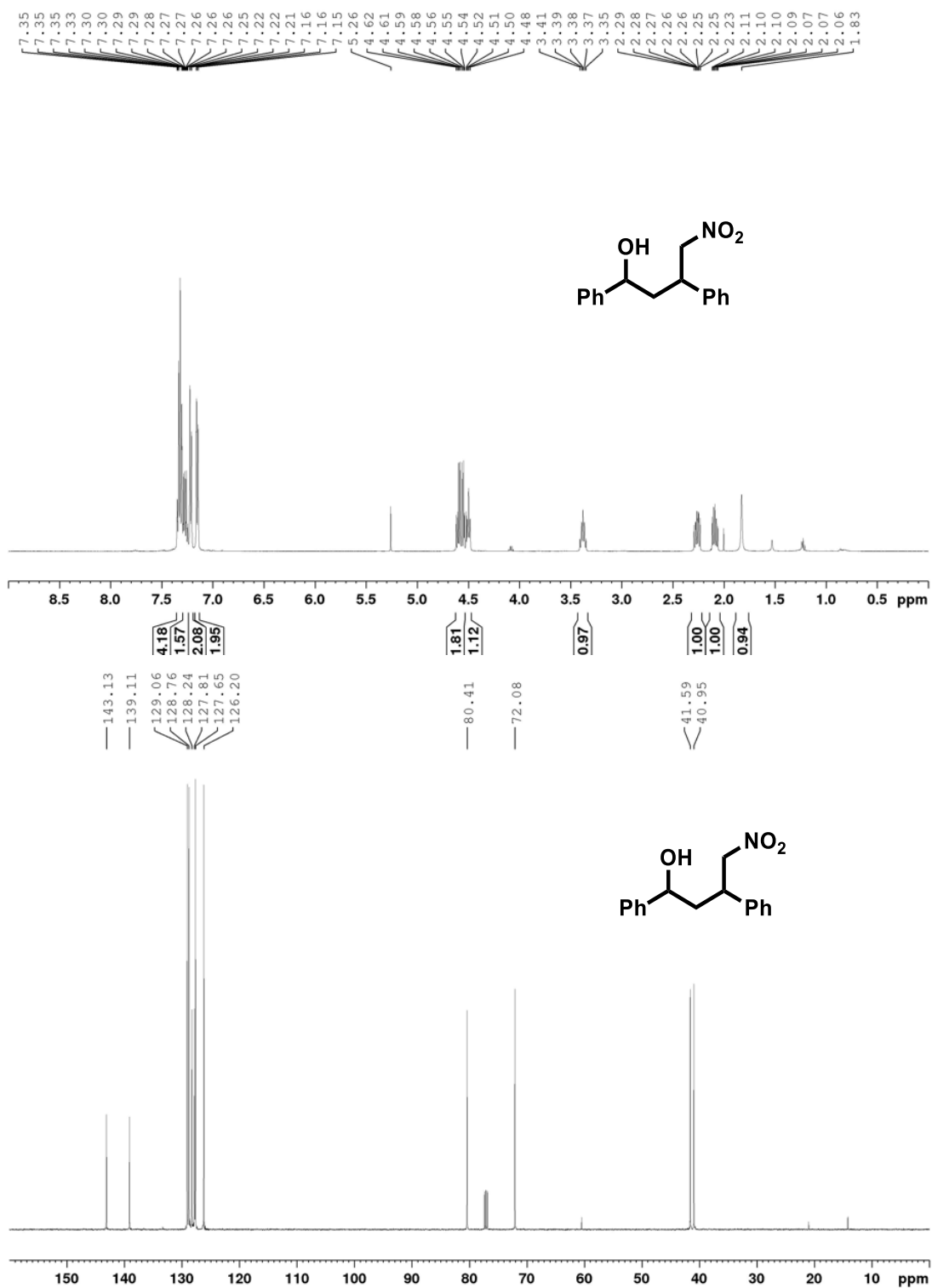
# 1,1'-(4-Nitrobutane-1,3-diyl)dibenzene, (3.33).
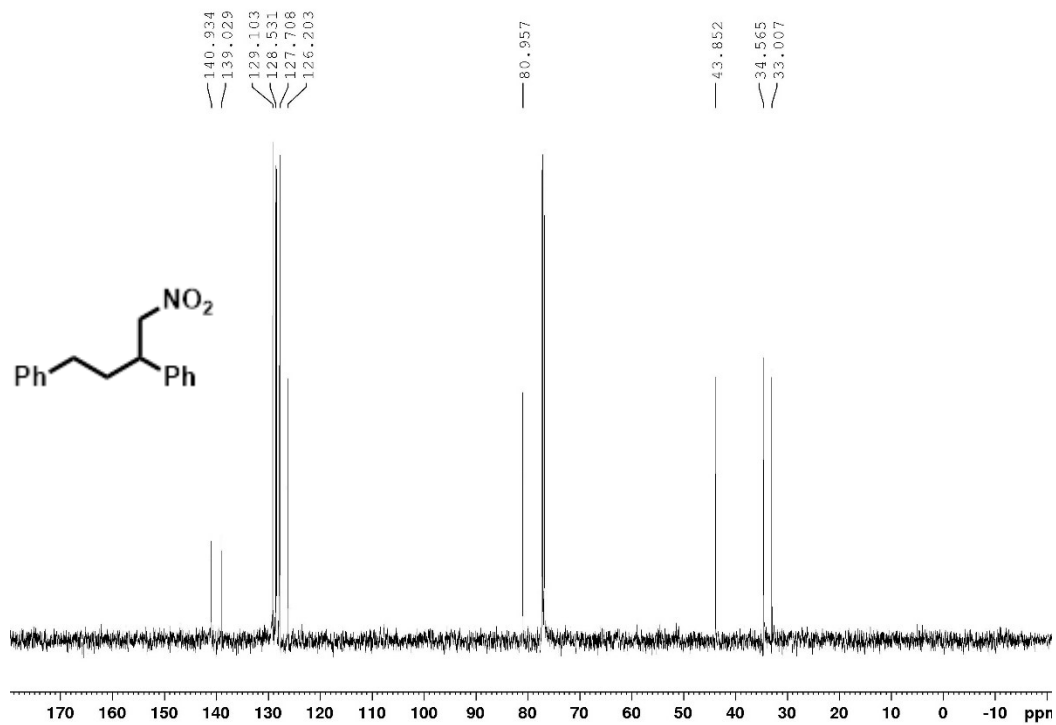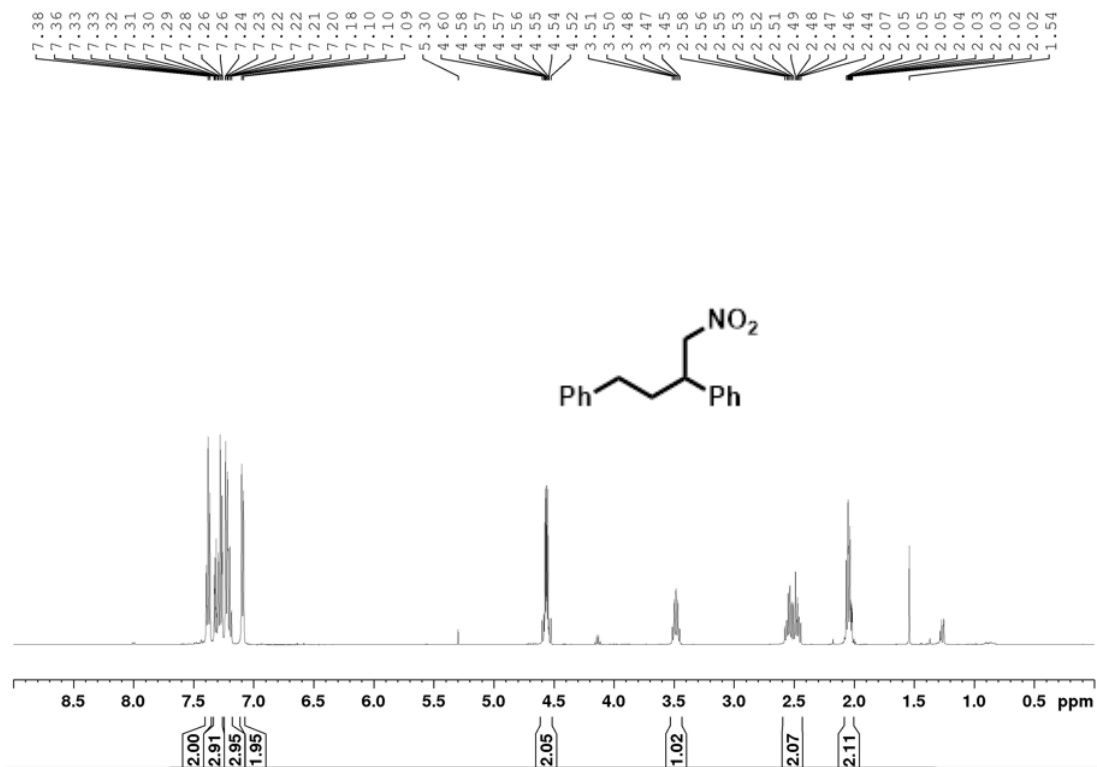
**3,5-Diphenyl-3,4-dihydro-2H-pyrrole, (3.34).**
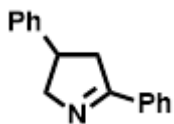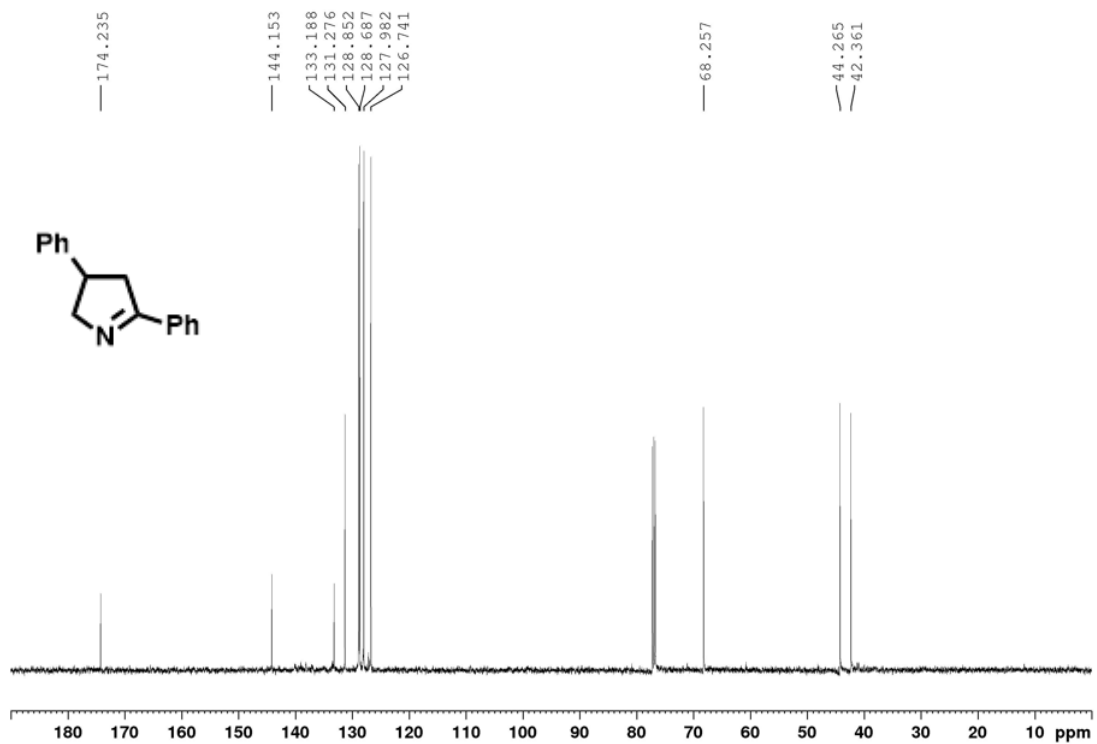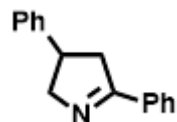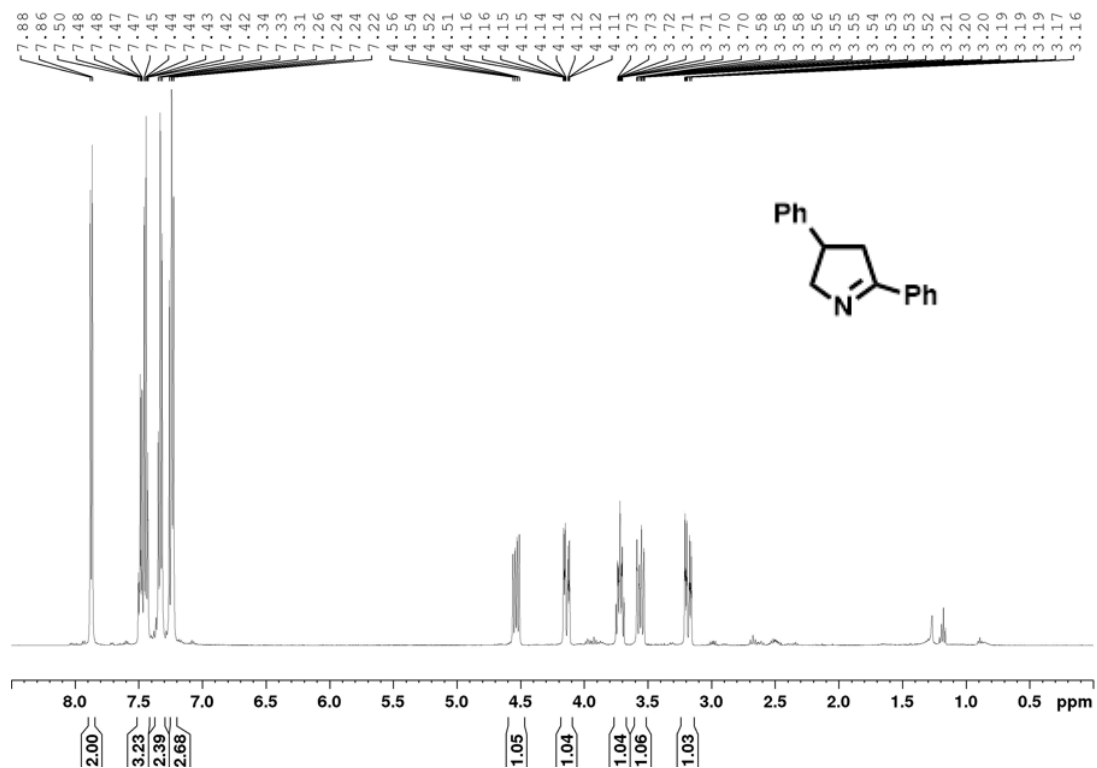
**4-Oxo-2,4 diphenylbutanamide, (3.35).**
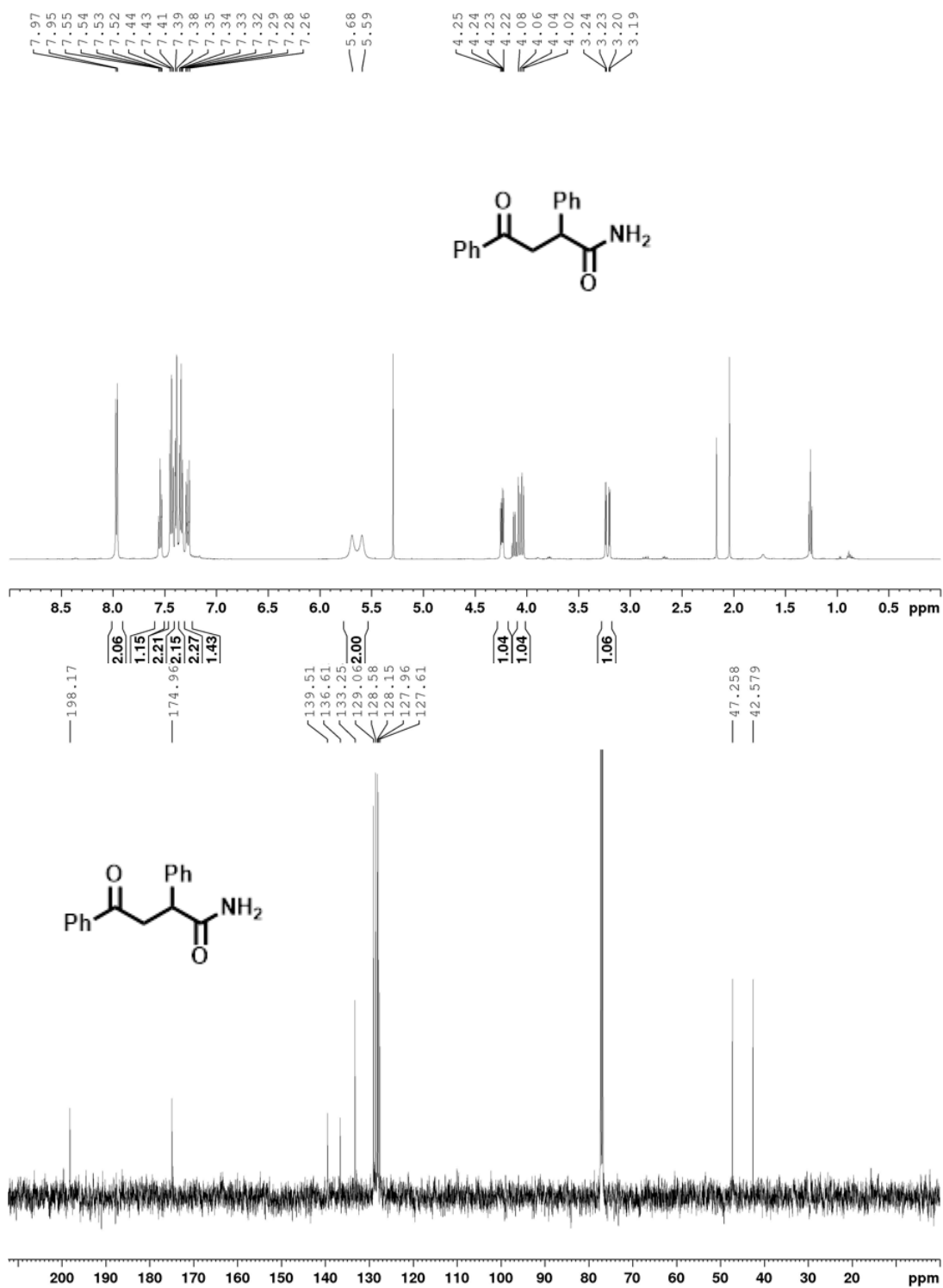
**N-(2-hydroxy-4-phenylbutyl)-4-Oxo-2,4-diphenylbutanamide, (3.37).**

## 3,5-Diphenyl-2-furanol, (3.39).

7.91, 7.91, 7.90, 7.64, 7.63, 7.44, 7.42, 7.42, 7.42, 7.41, 7.41, 7.40, 7.40, 7.35, 7.34, 7.33

6.04, 6.03



2.04  1.00  6.05  2.04    0.98

171.73

147.31

134.82, 130.96, 129.53, 129.29, 129.07, 128.72, 127.18, 126.62

81.55
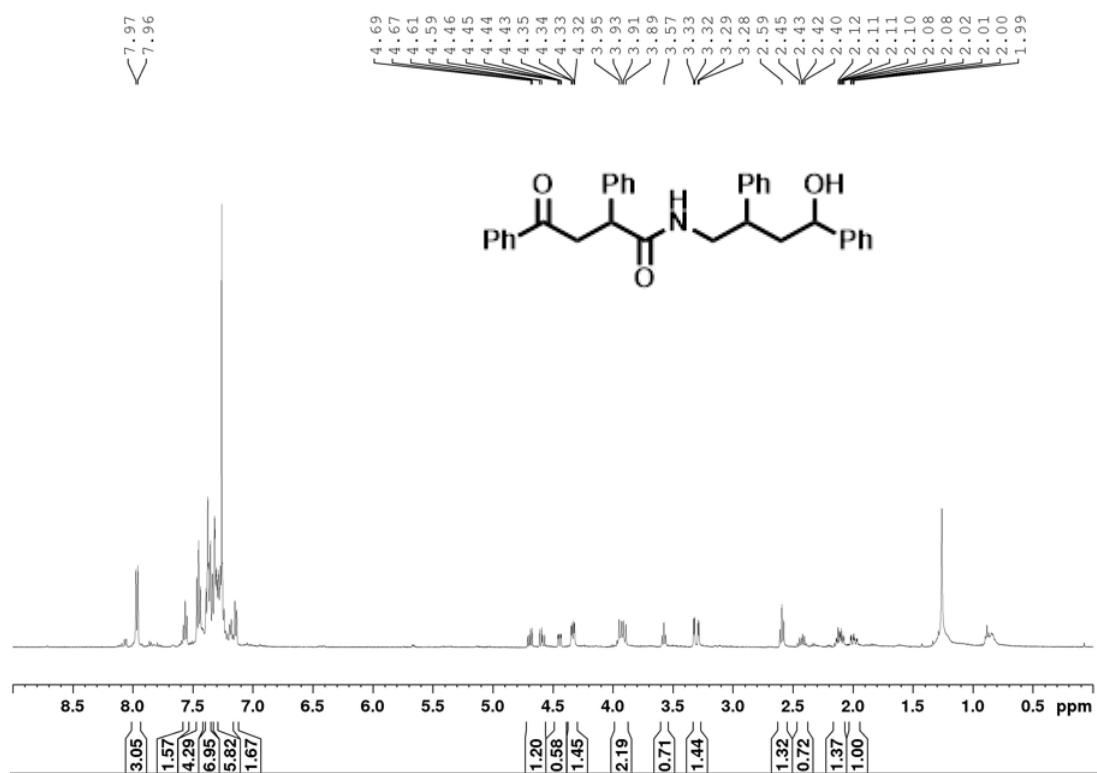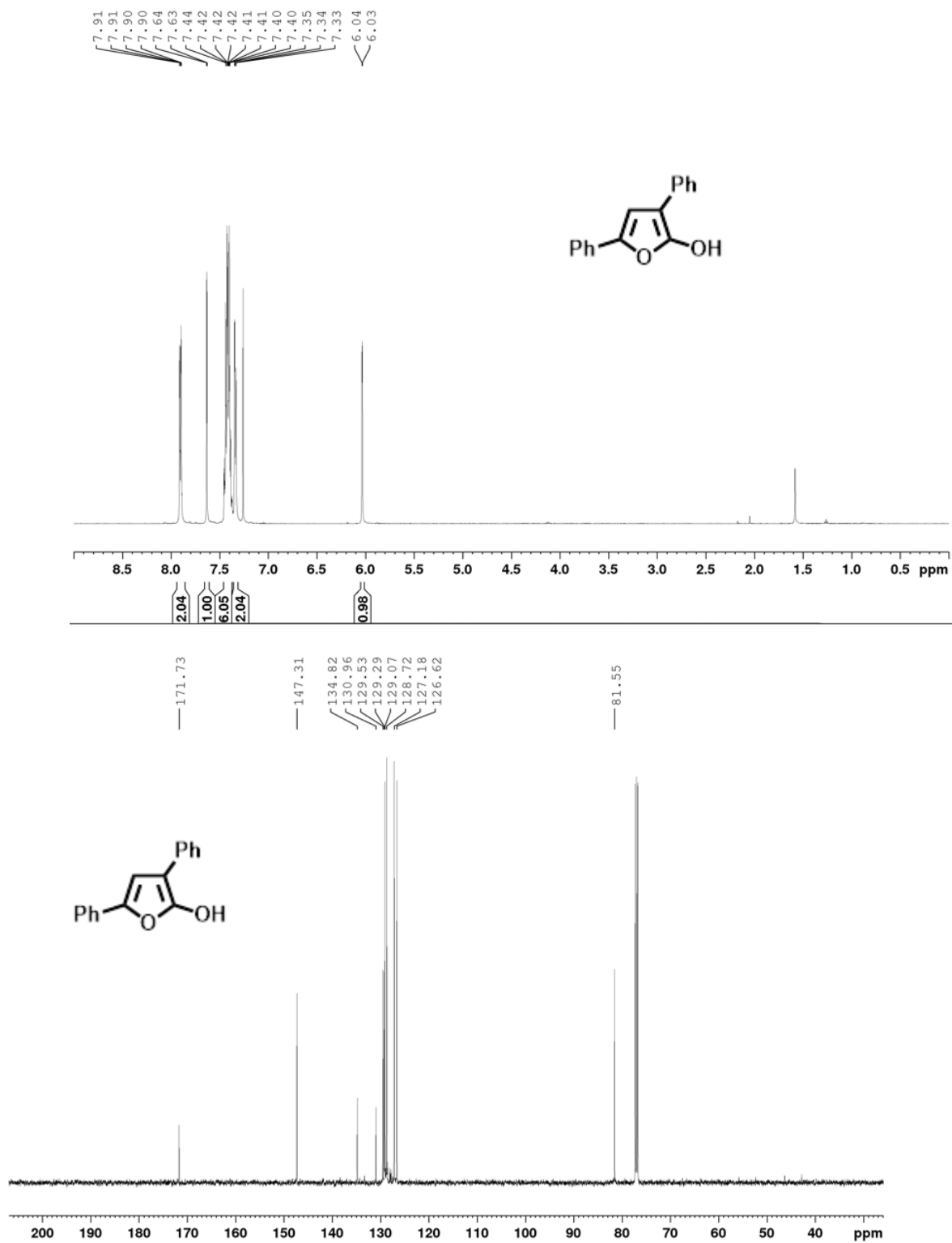
**(2*E*)-1-(2,5-Dimethylphenyl)-3-(2,4,6-trimethylphenyl)prop-2-en-1-one, (4.42b)**
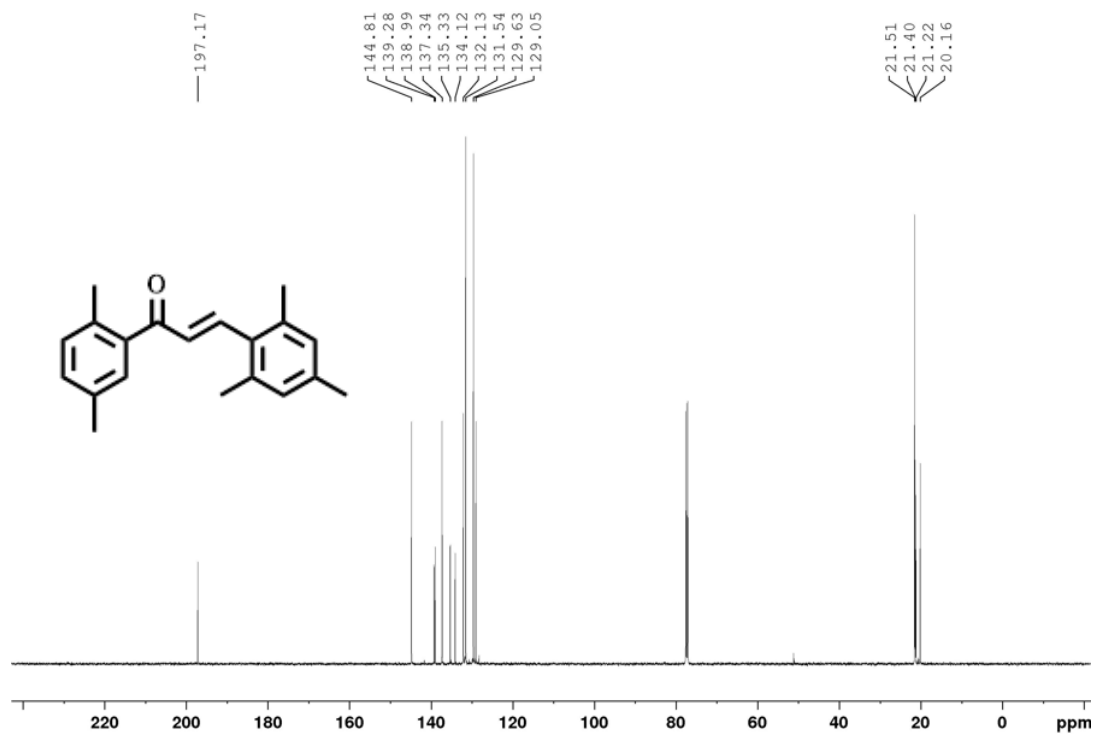
**(2*E*)-1-(4-Chlorophenyl)-3-(2,6-dichlorophenyl)prop-2-en-1-one, (4.42c).**
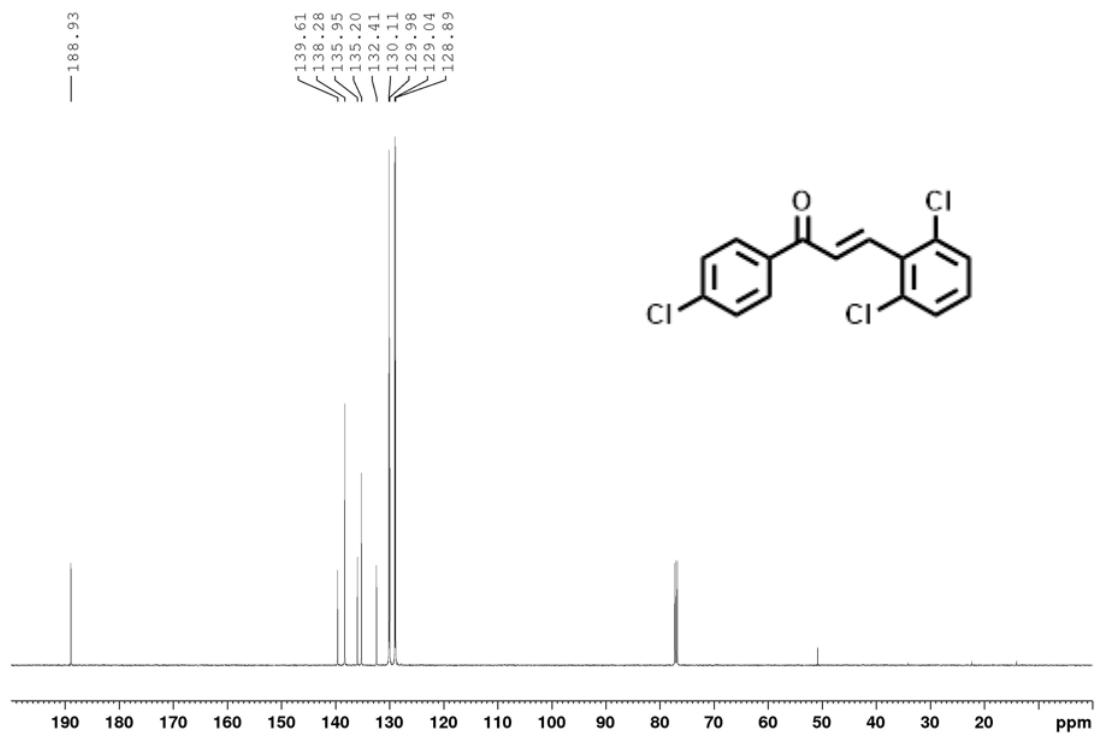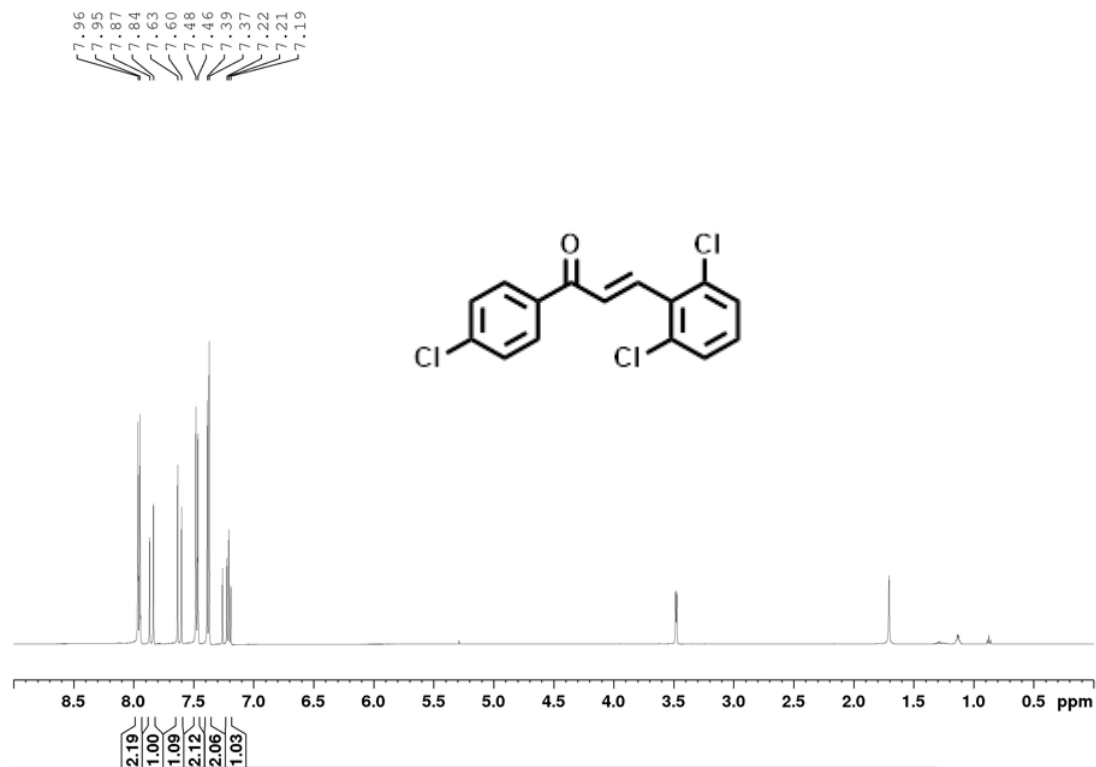
**(2*E*)-3-(4-Bromo-2-methylphenyl)-1-(4-bromophenyl)prop-2-en-1-one, (4.42d)**
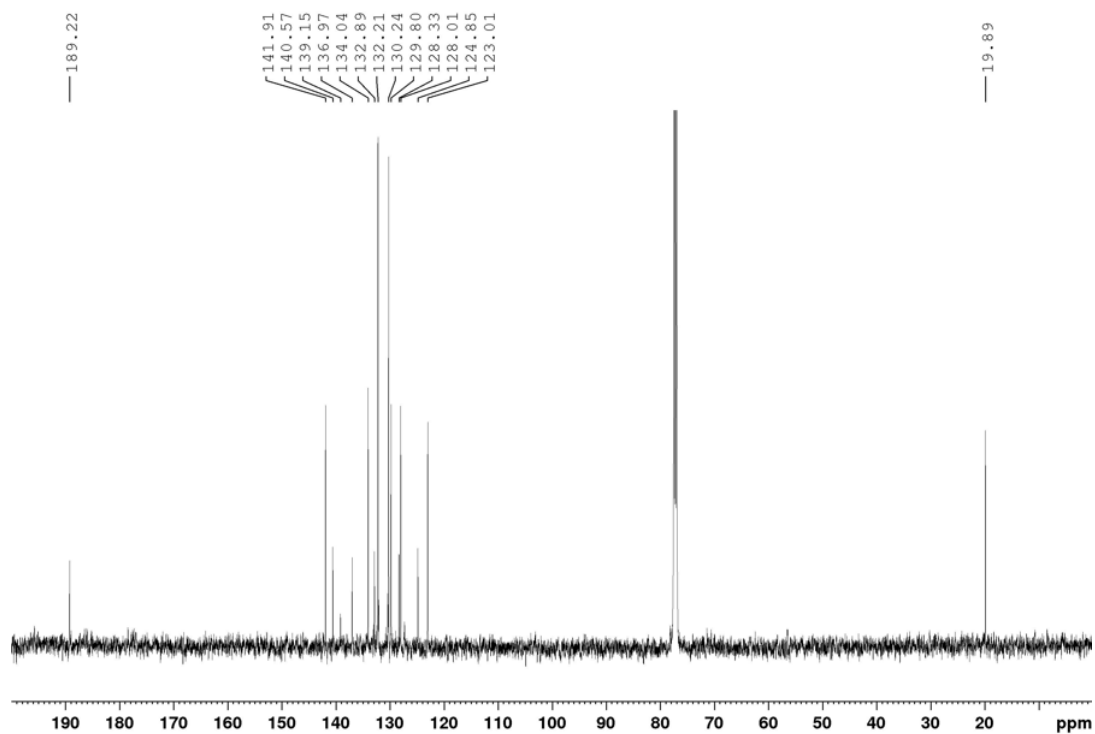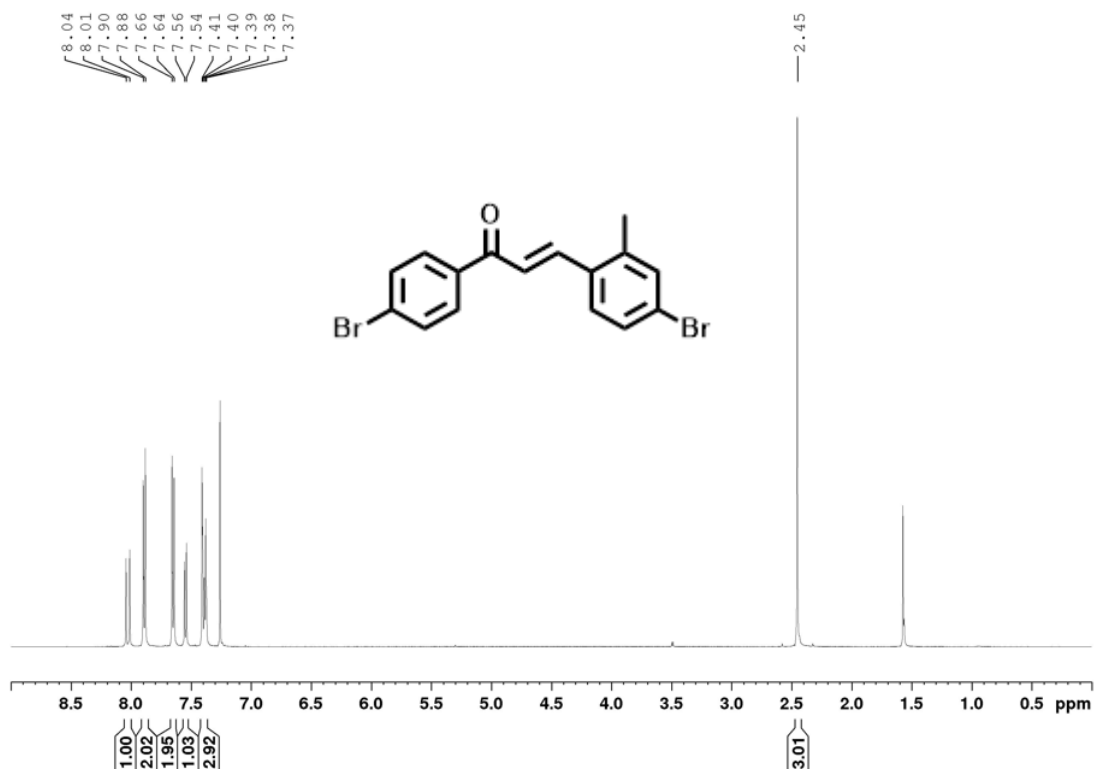
**4-Nitro-1-phenyl-3-(2,4,6-trimethylphenyl)butan-1-one, (4.43a).**
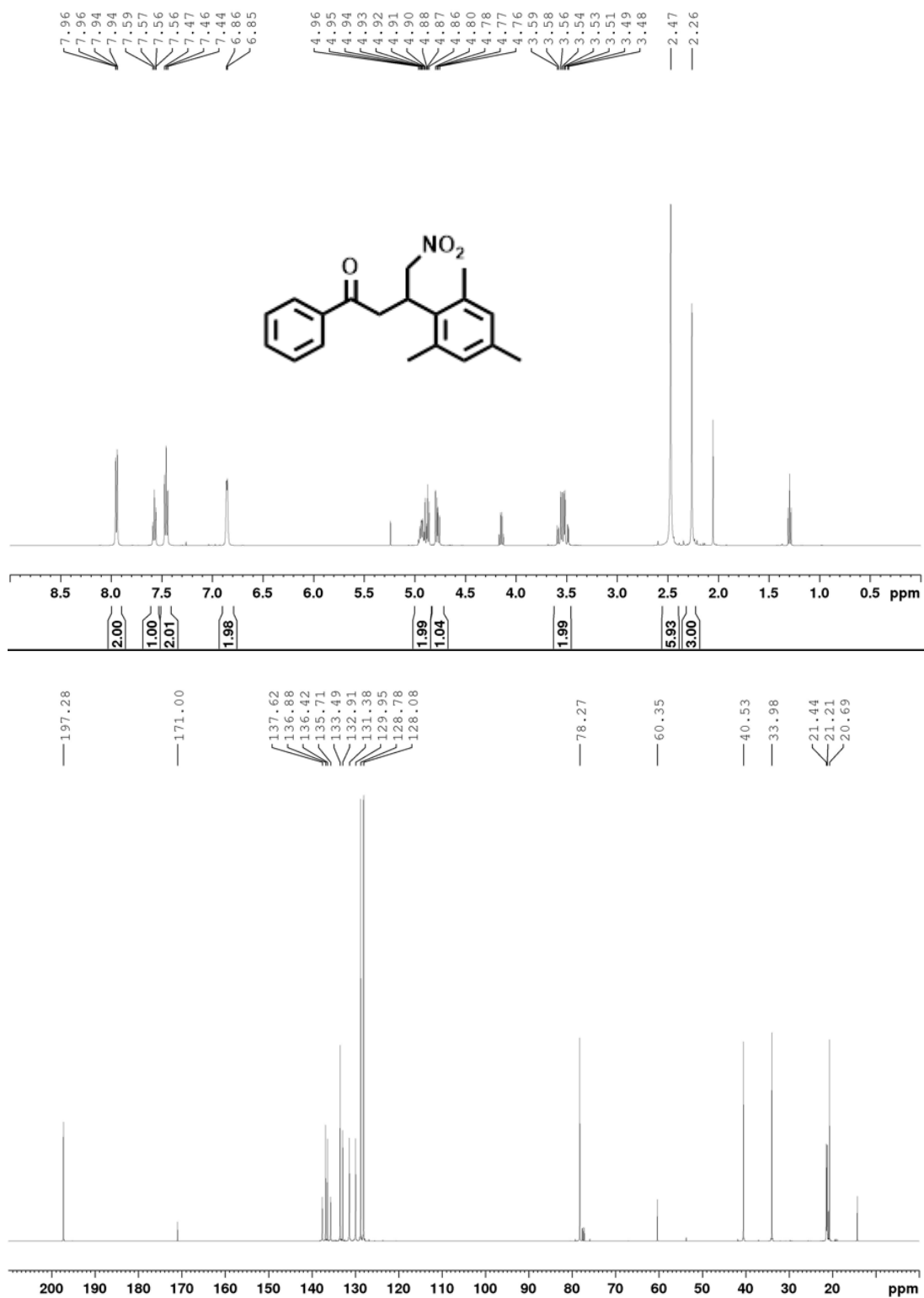
# 1-(2,5-Dimethylphenyl)-4-nitro-3-(2,4,6-trimethylphenyl)butan-1-one, (4.43b).
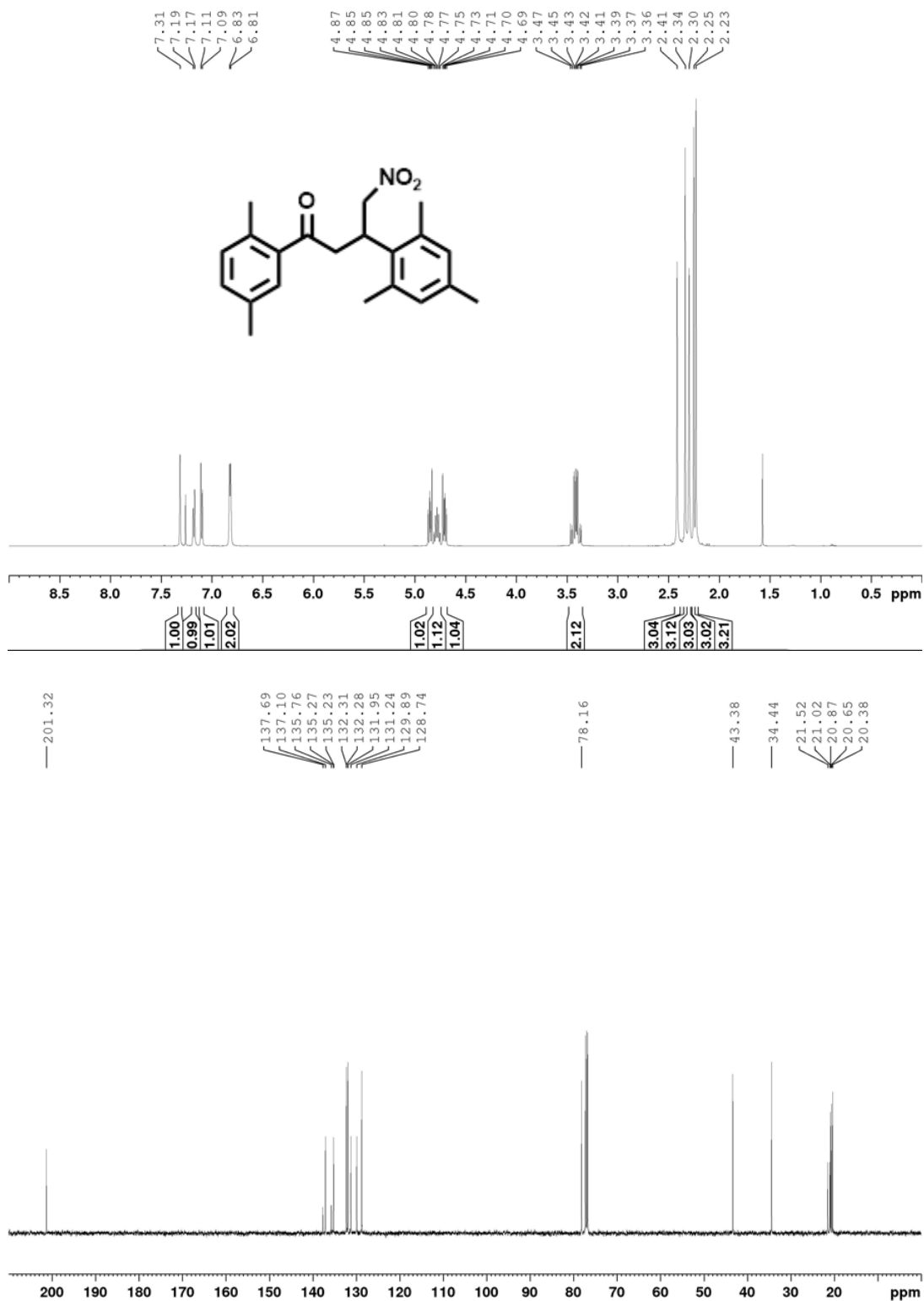
**3-(2,6-Dichloro-phenyl)-4-nitro-1-(4-chloro-phenyl)-butan-1-one, (4.43c).**
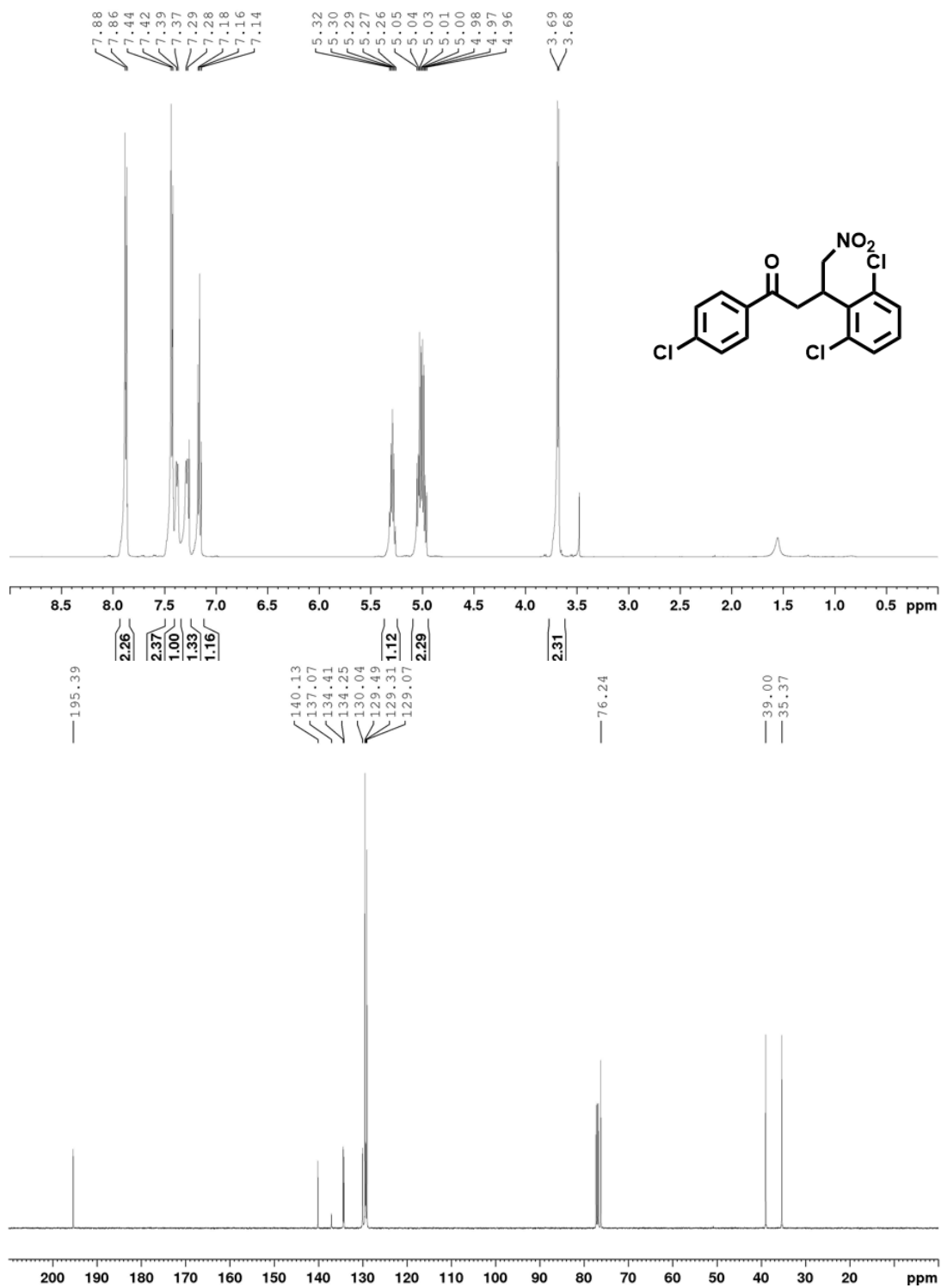
# 3-(2-Methyl-4-bromo-phenyl)-4-nitro-1- (4-bromo-phenyl)-butan-1-one, (4.43d).
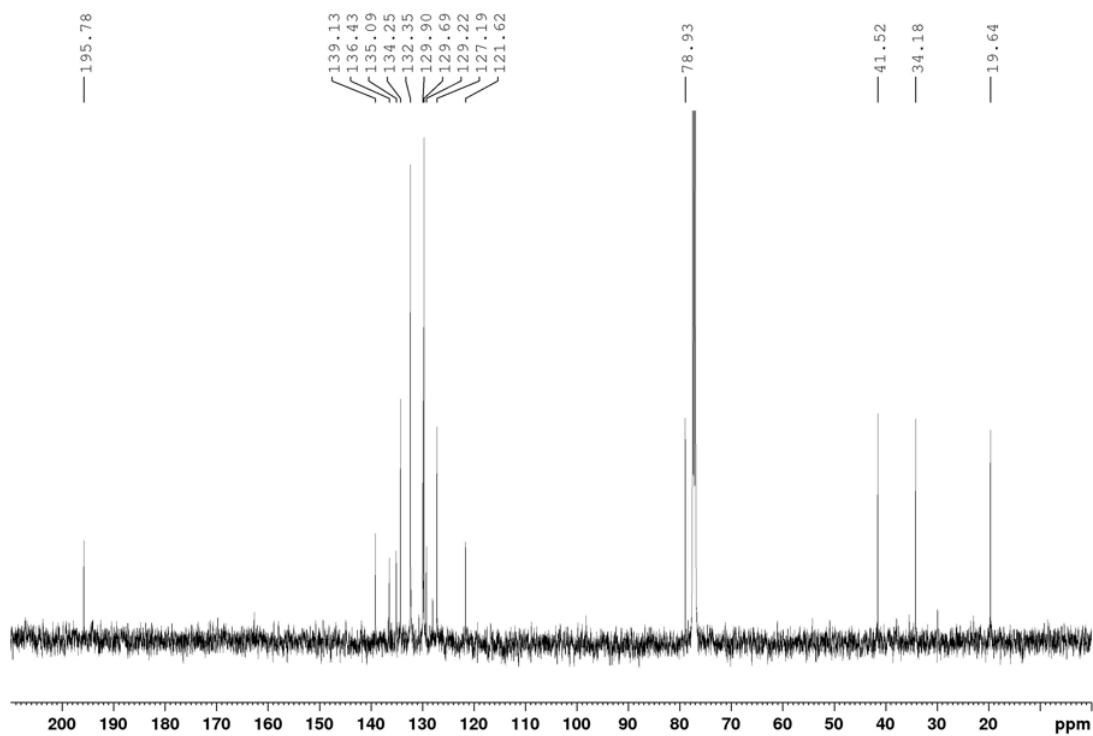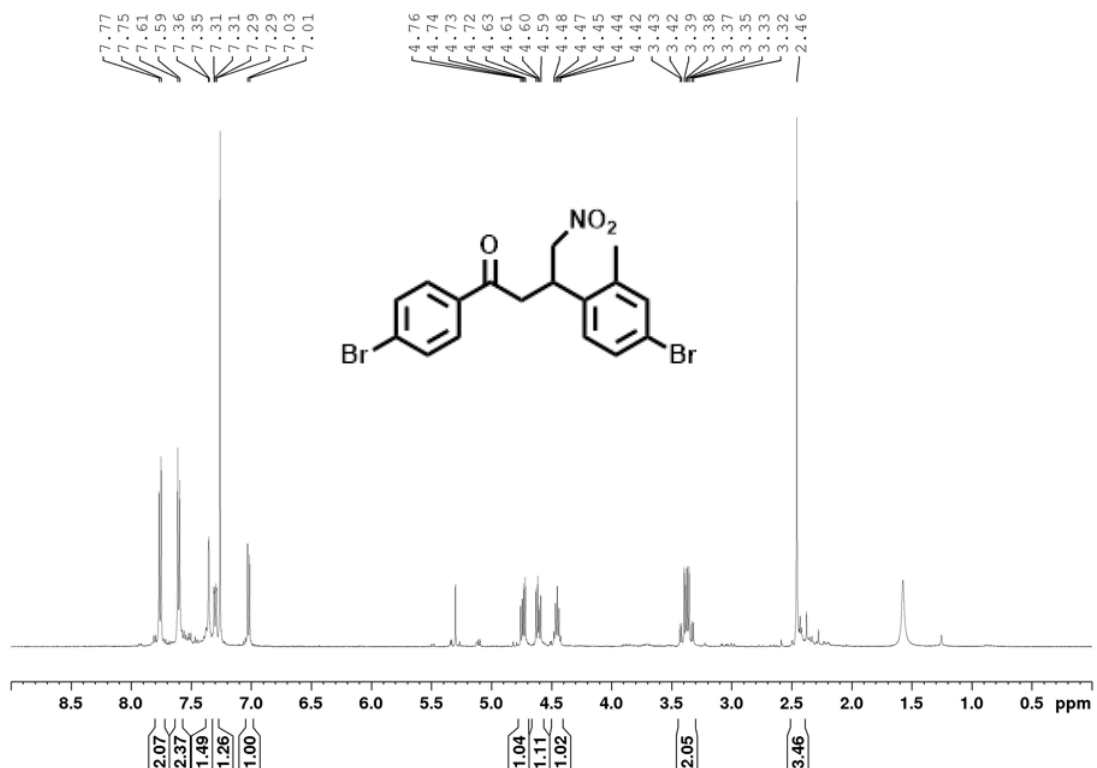
**2-Phenyl-4-(2,4,6-trimethylphenyl)-1*H*-pyrrole, (4.44a).**
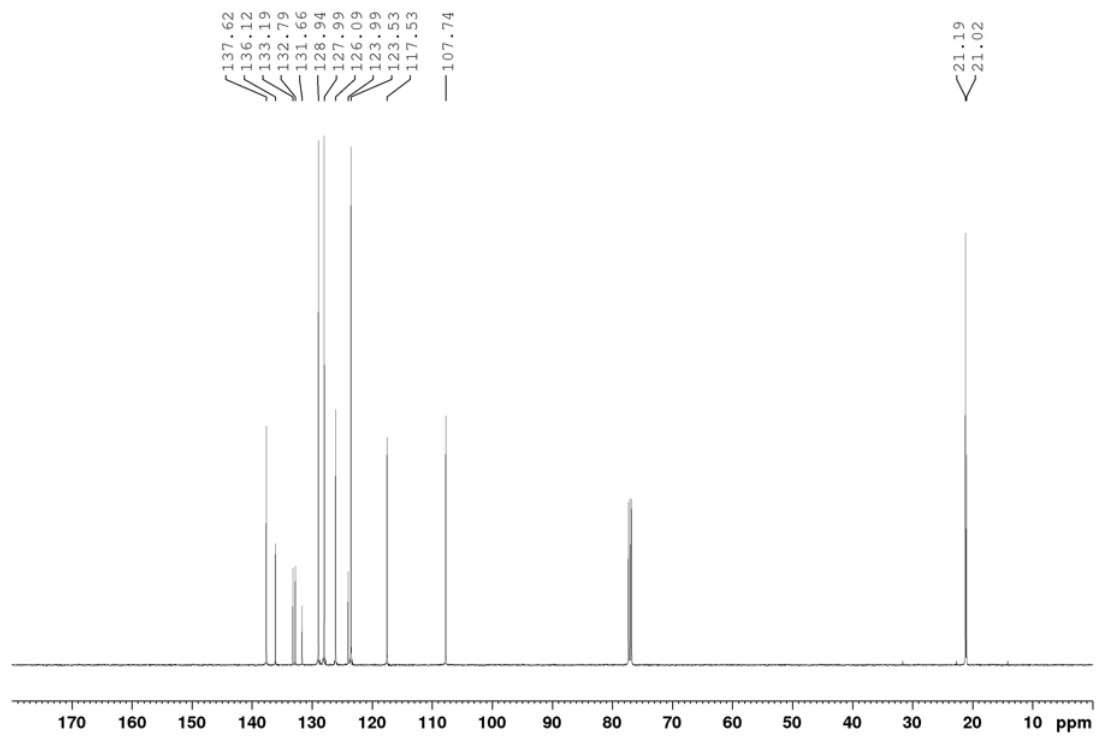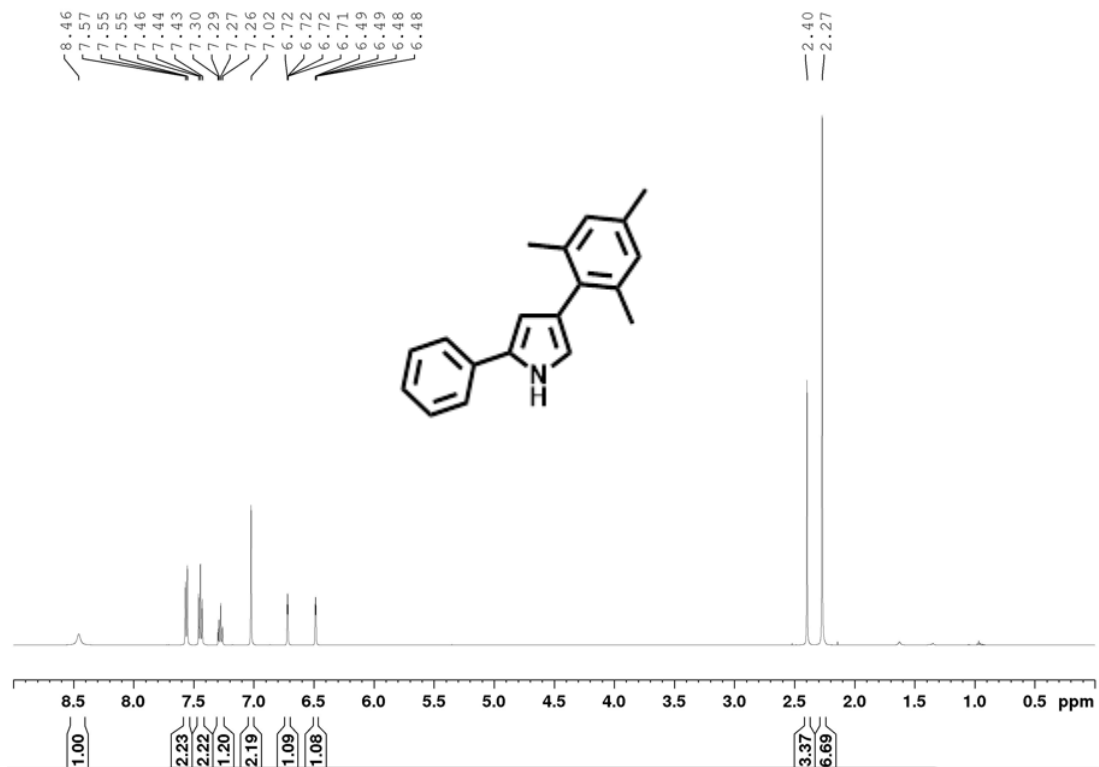
**2-(2,5-Dimethylphenyl)-4-(2,4,6-trimethylphenyl)-1_H_-pyrrole, (4.44b).**
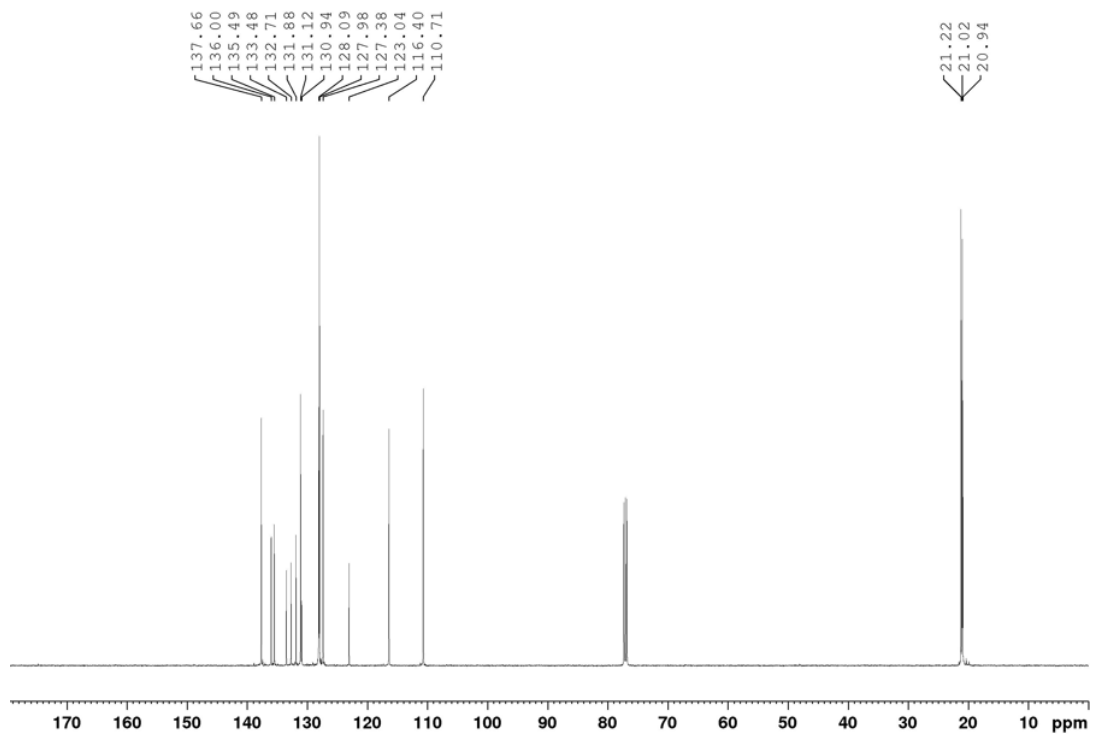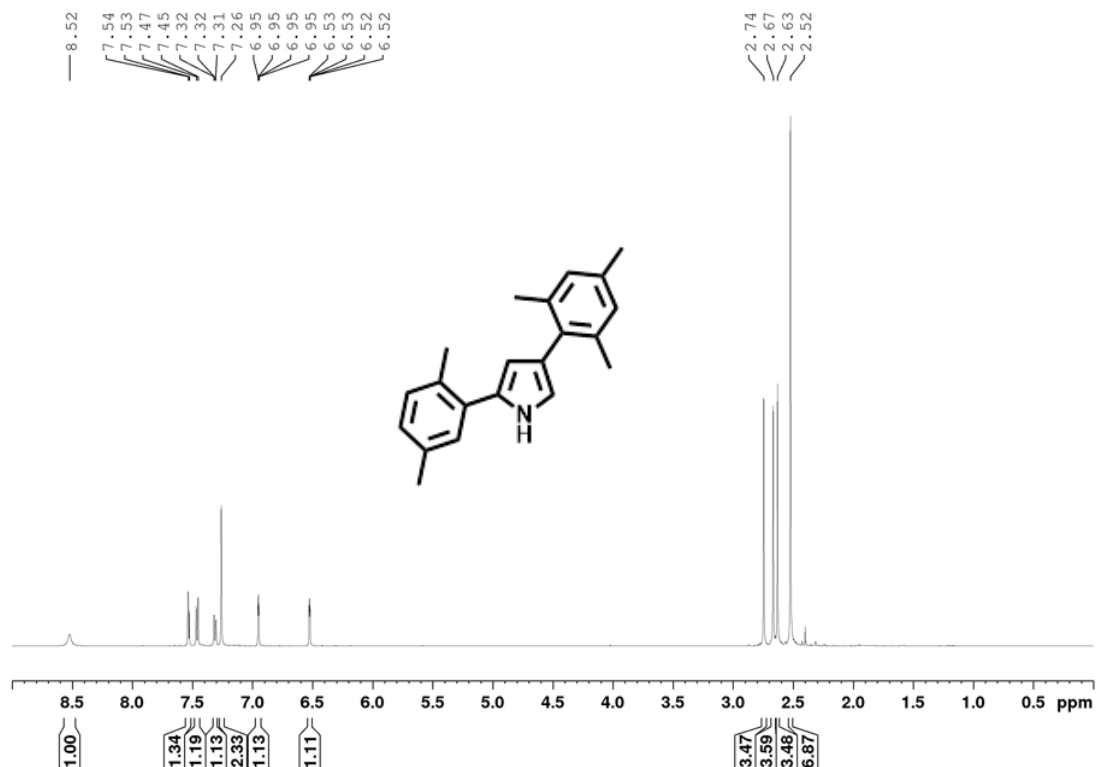
**4-(4-Bromo-2-methylphenyl)-2-(4-bromophenyl)-1*H*-pyrrole, (4.44d).**
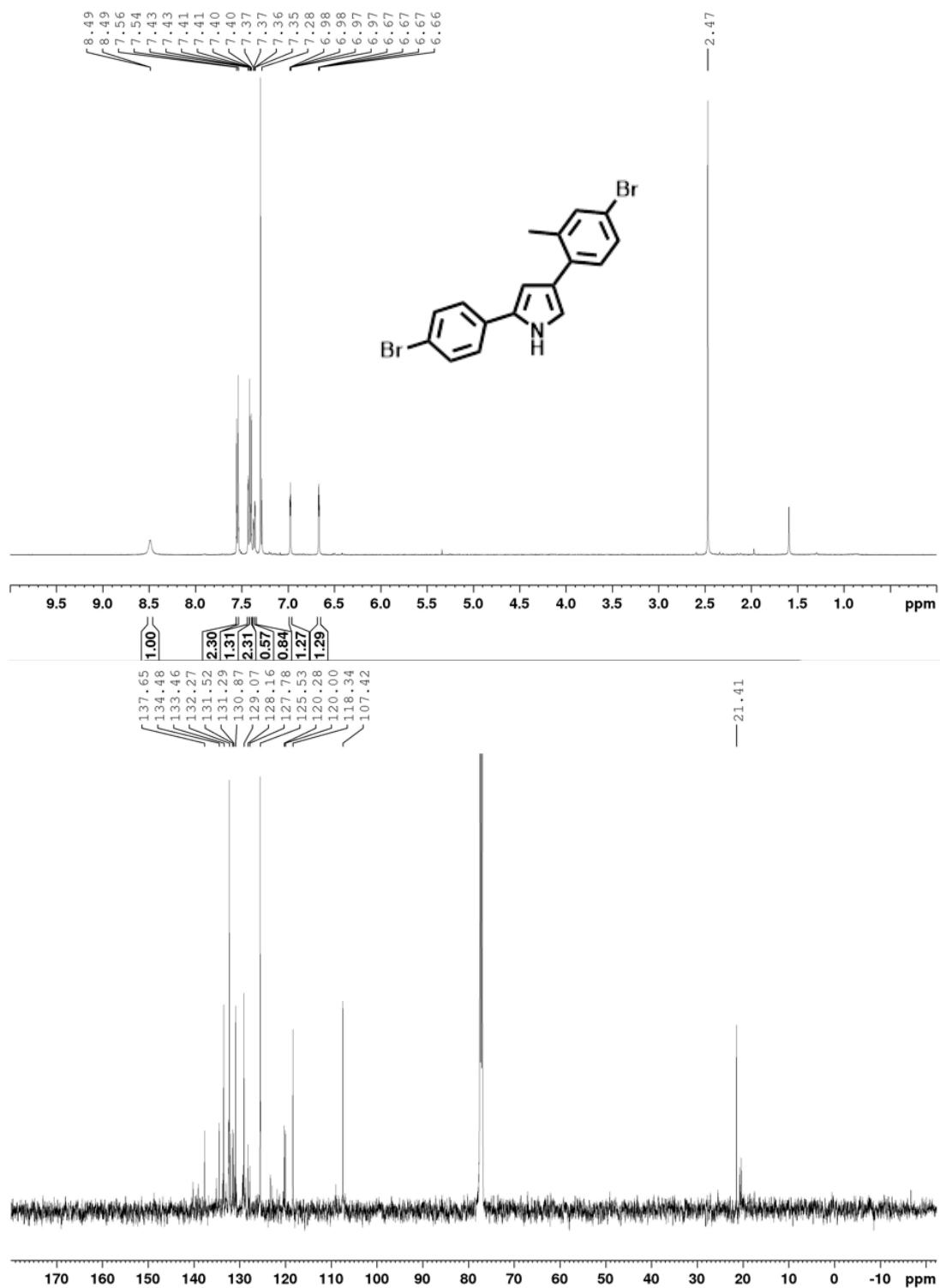
**4-(4-Methylphenyl)-2-phenyl-1H-pyrrole, (4.44e)**.
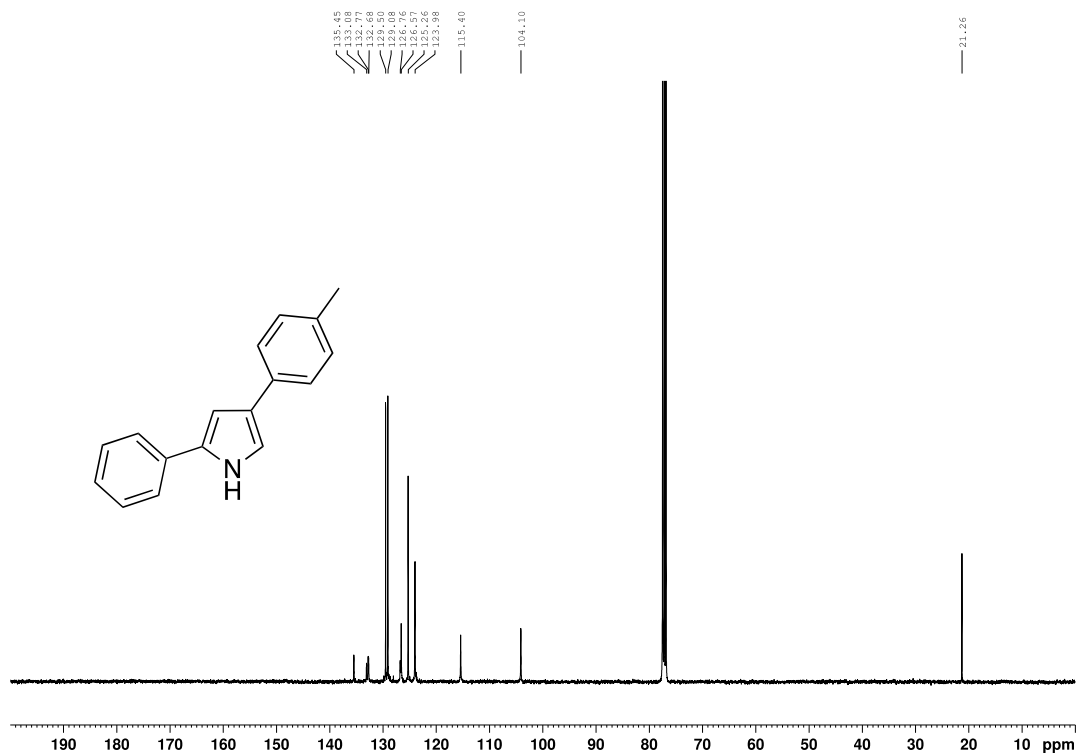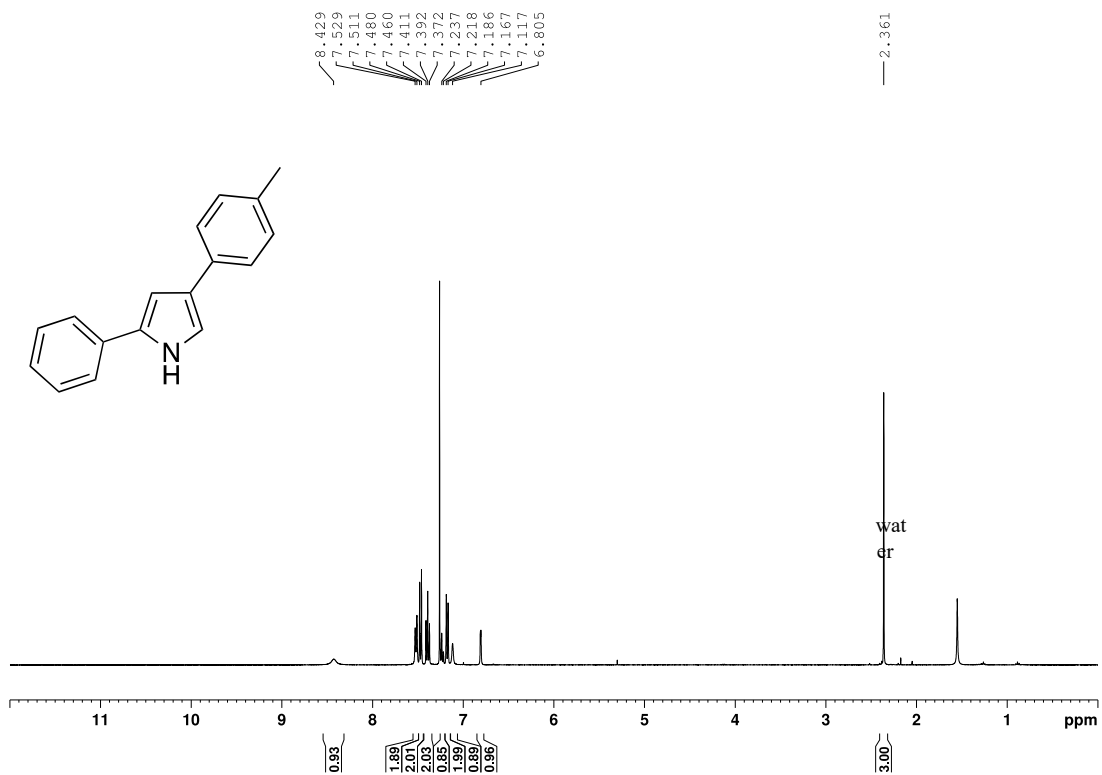
## 2-Phenyl-4-[4-(trifluoromethyl)phenyl]-1H-pyrrole, (4.44f).
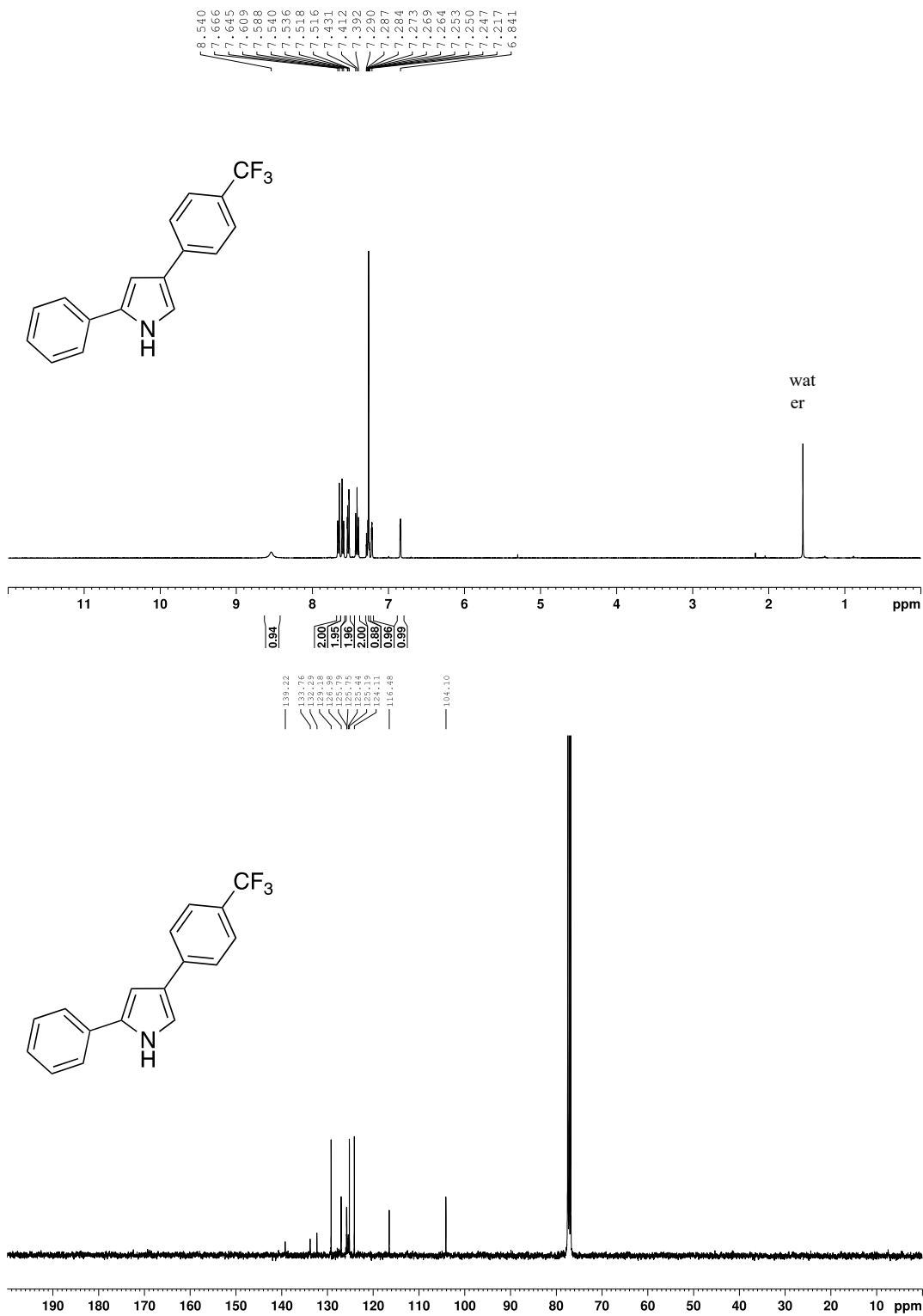
# 4-(4-Cyanophenyl)-2-phenyl-1H-pyrrole (4.44g).
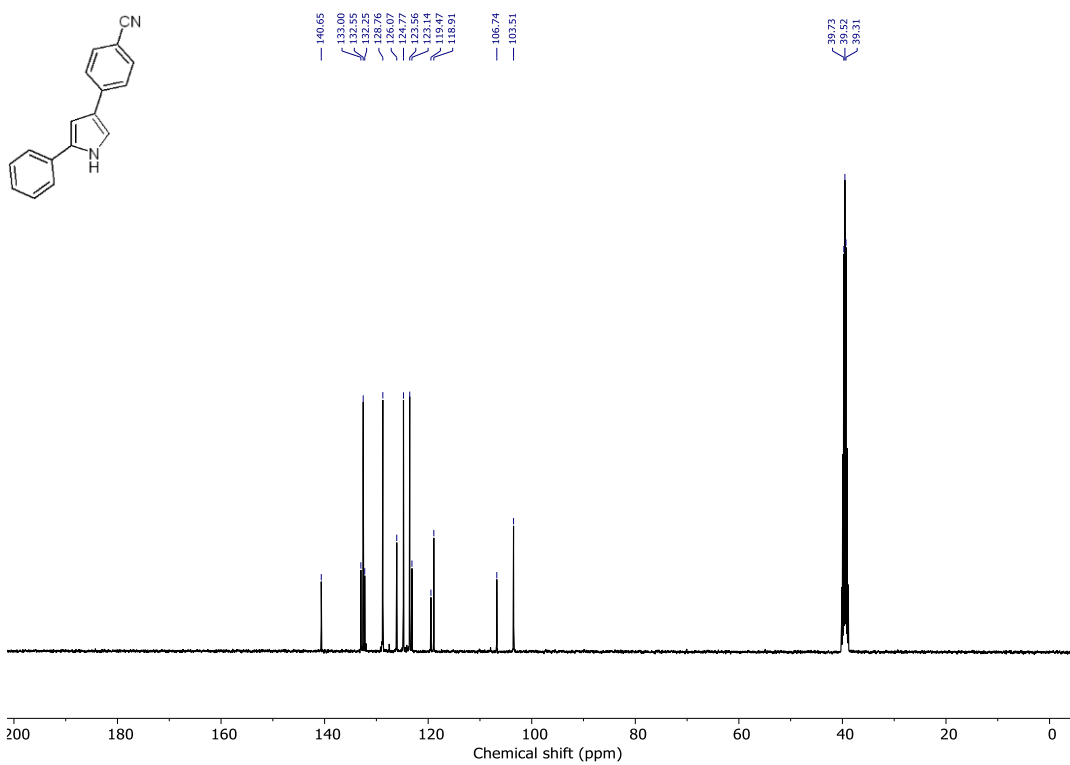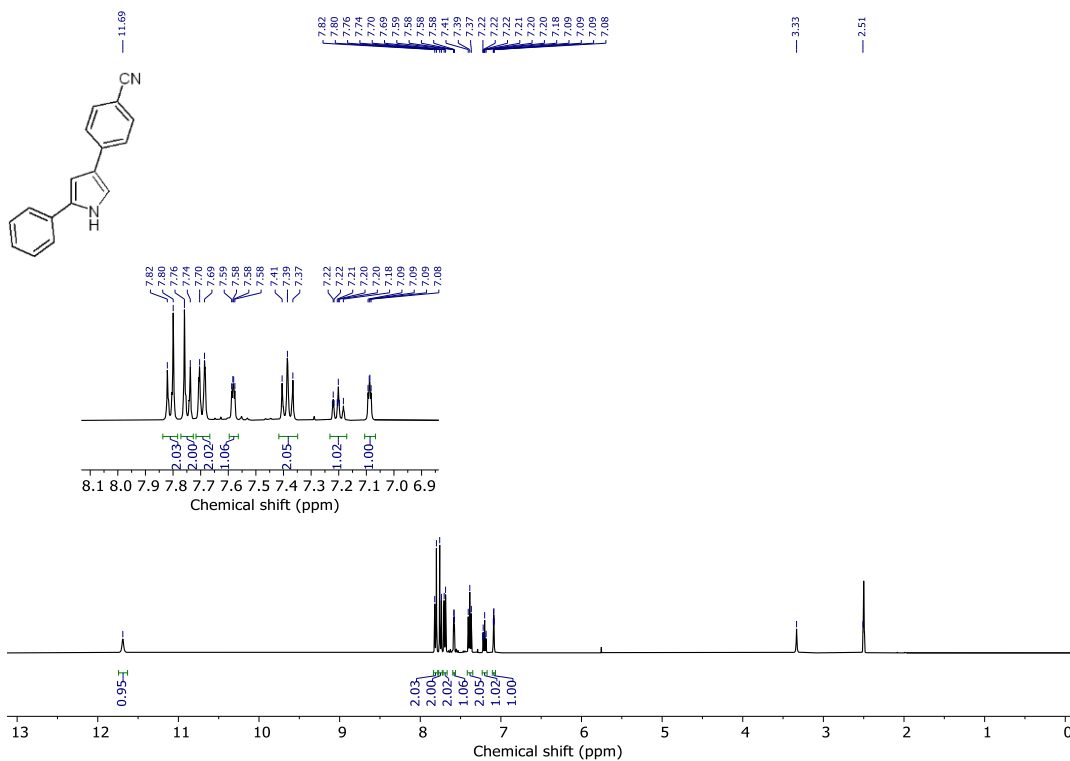
## 2-Phenyl-4-[3-(trifluoromethyl)phenyl]-1H-pyrrole, (4.44h).
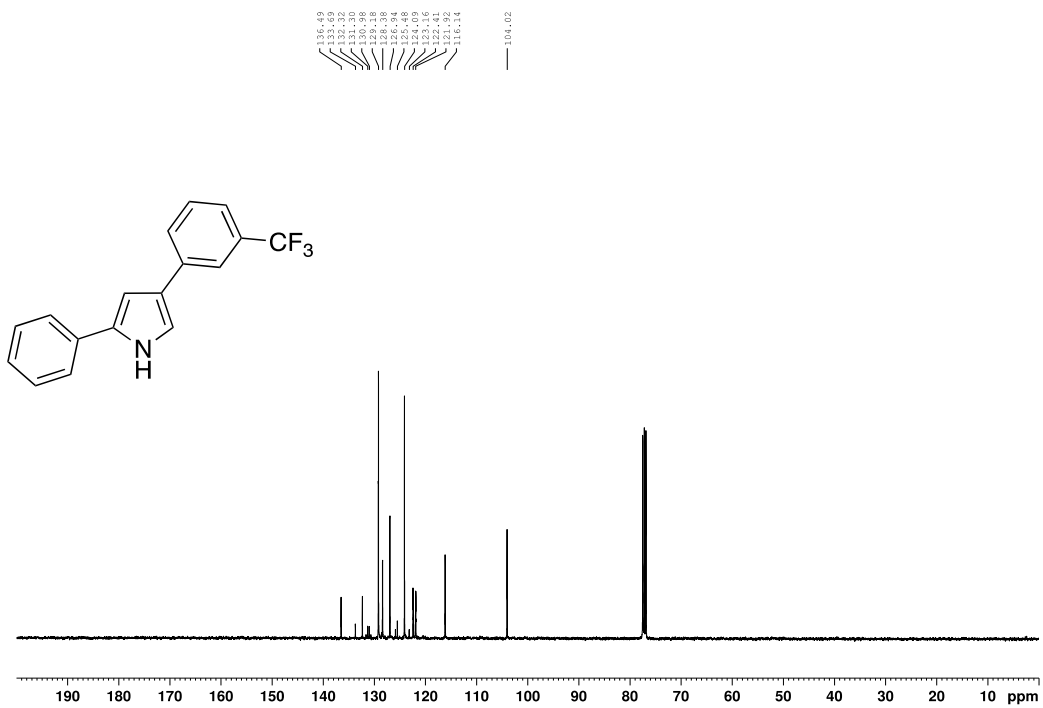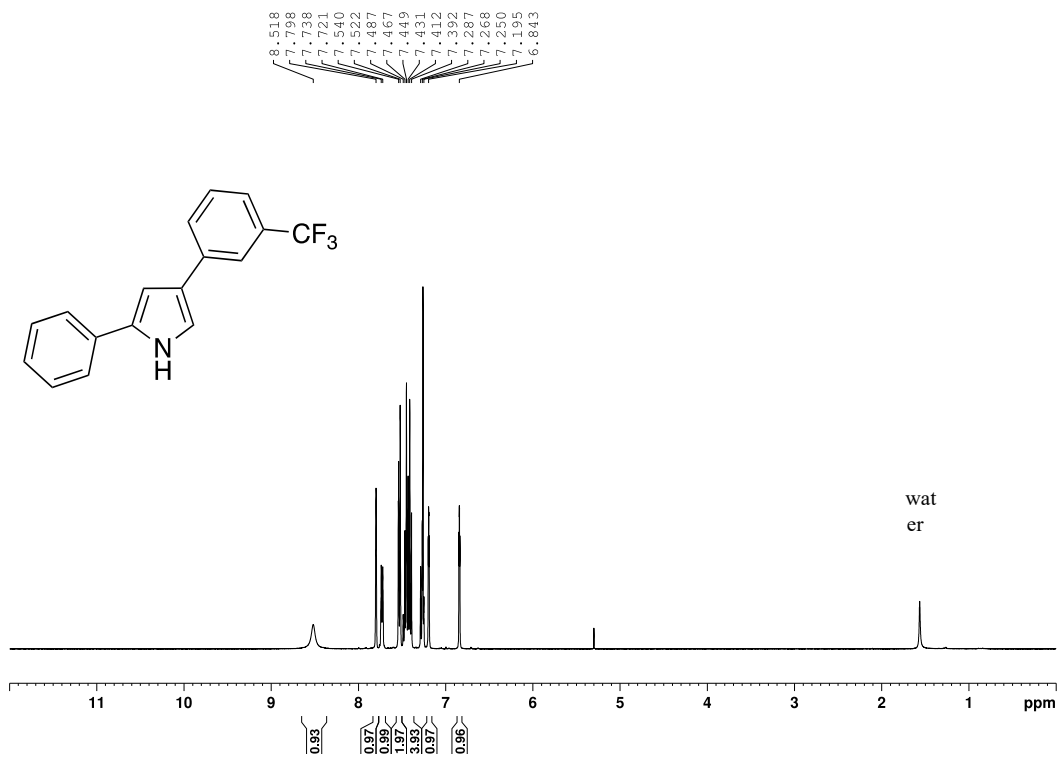
**N,N-Dimethyl-4-(5-phenyl-1H-pyrrol-3-yl)benzenamine, (4.44i).**
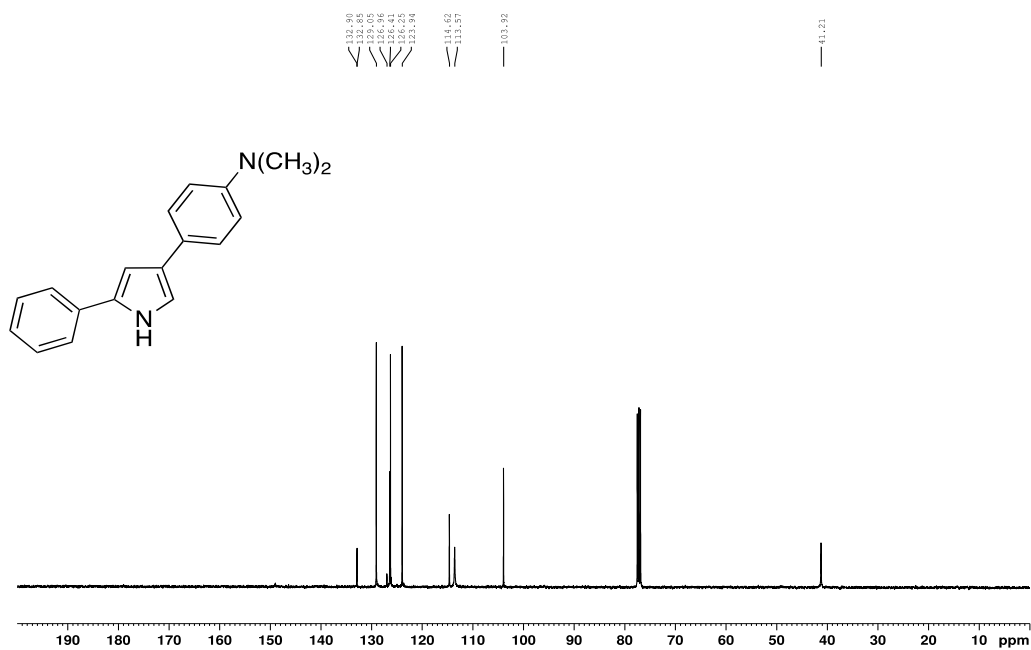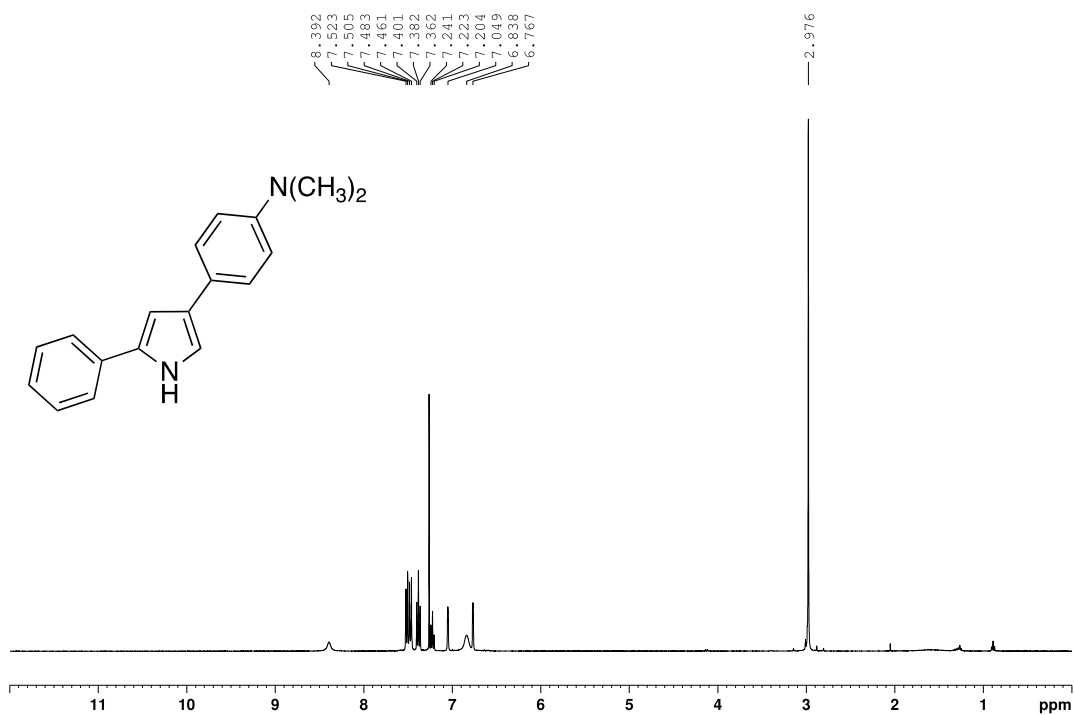
**4-(4-Methoxyphenyl)-2-phenyl-1H-pyrrole, (4.44j).**
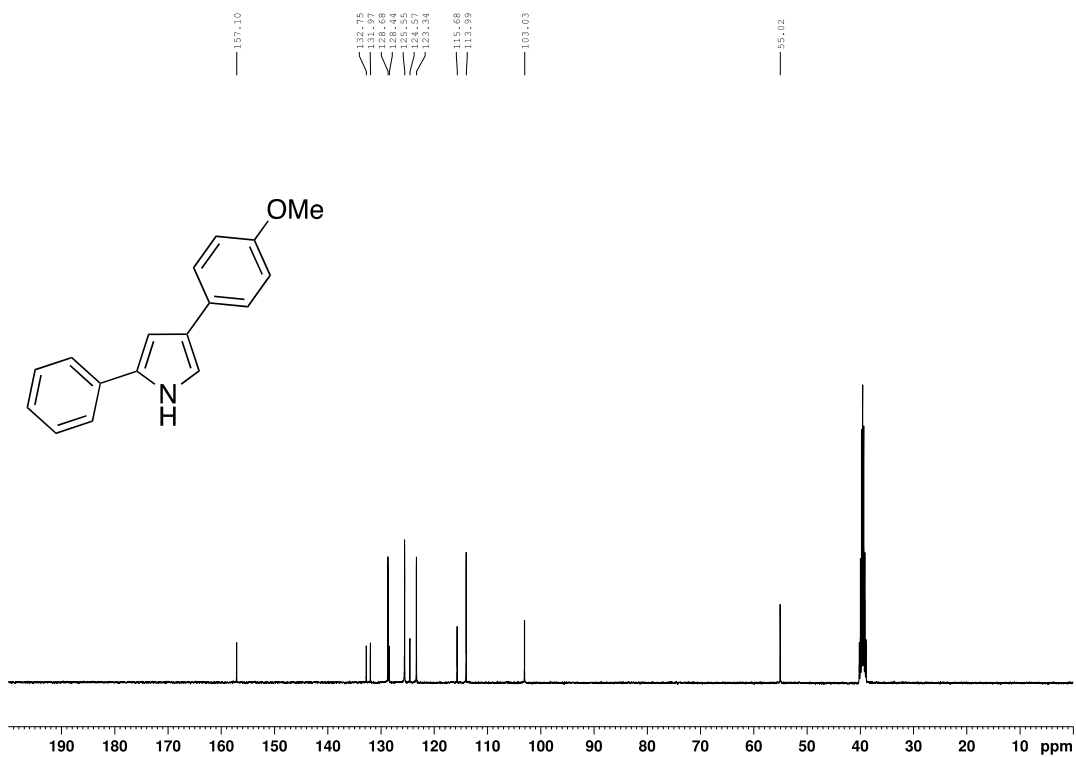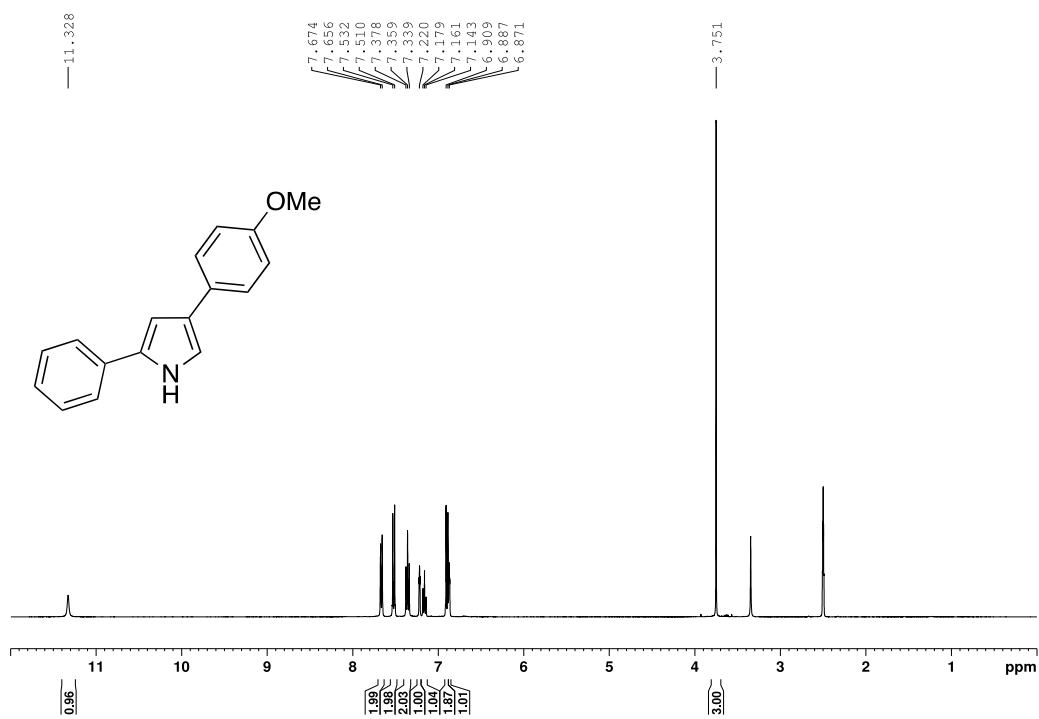
# 4-(4-Hydroxyphenyl)-2-phenyl-1H-pyrrole, (4.44l).
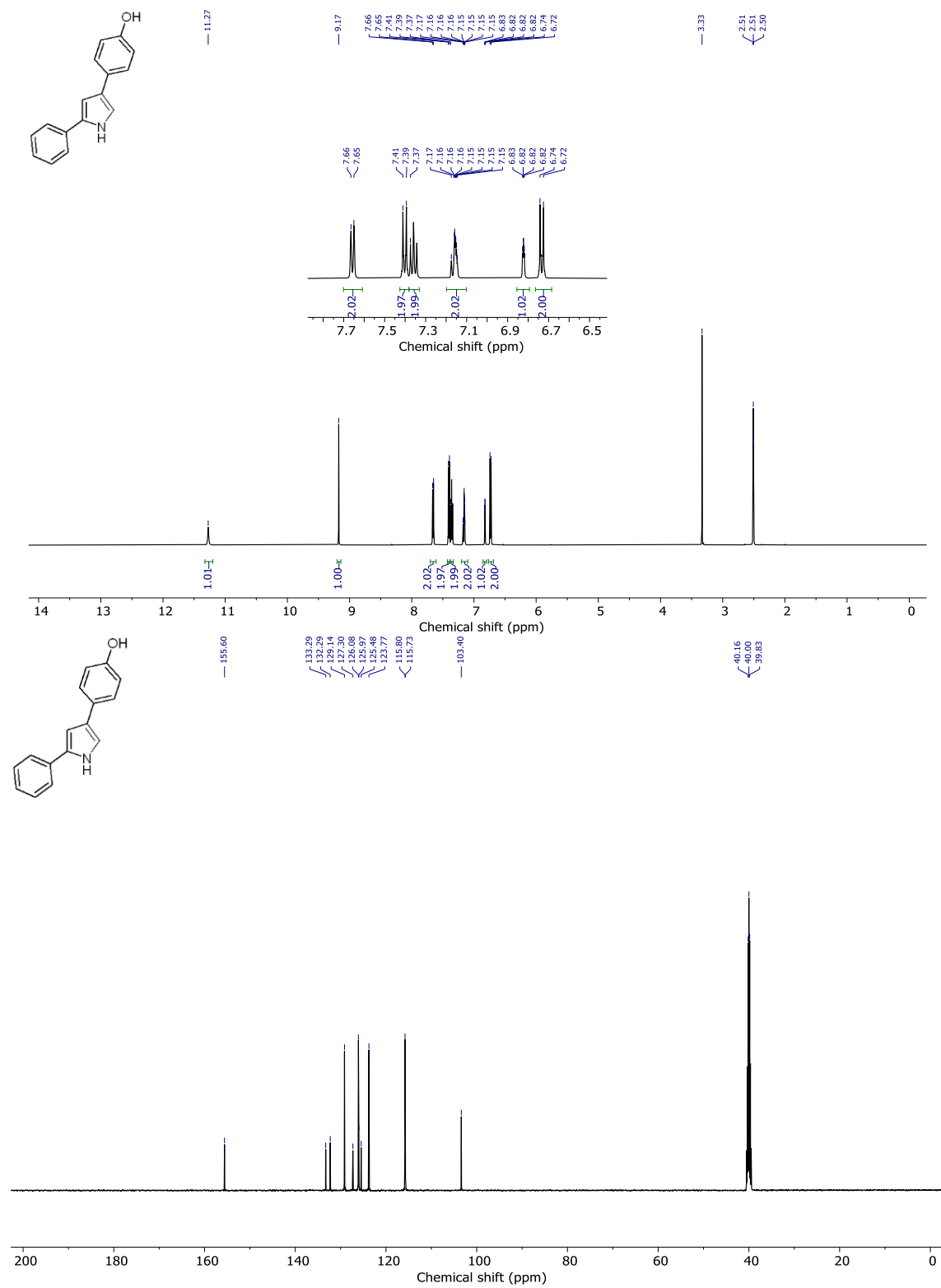
## 2-(4-Methoxyphenyl)-4-phenyl-1H-pyrrole, (4.44m).
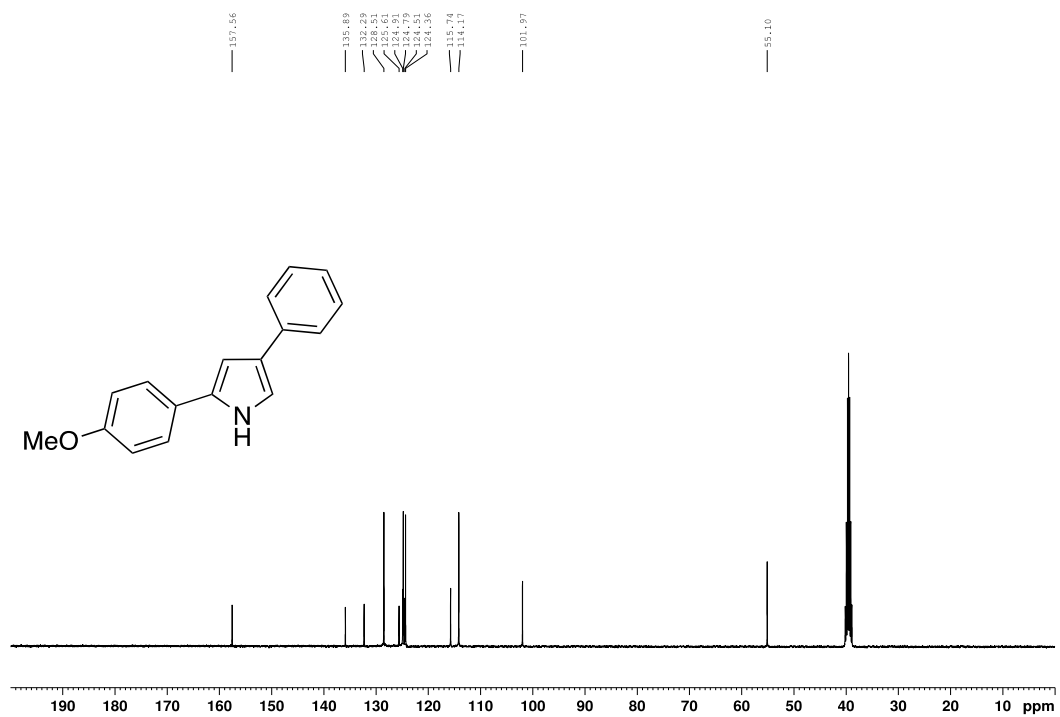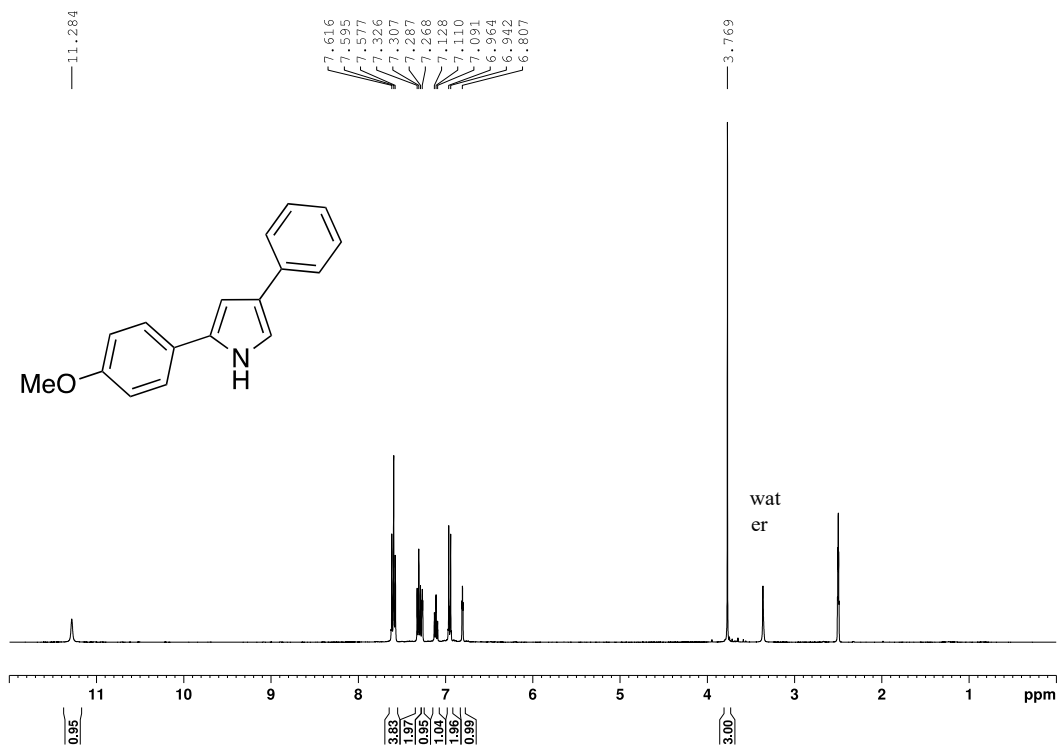
**2-Nitroso-5-phenyl-3-(2,4,6-trimethylphenyl)-1*H*-pyrrole, (4.21a).**
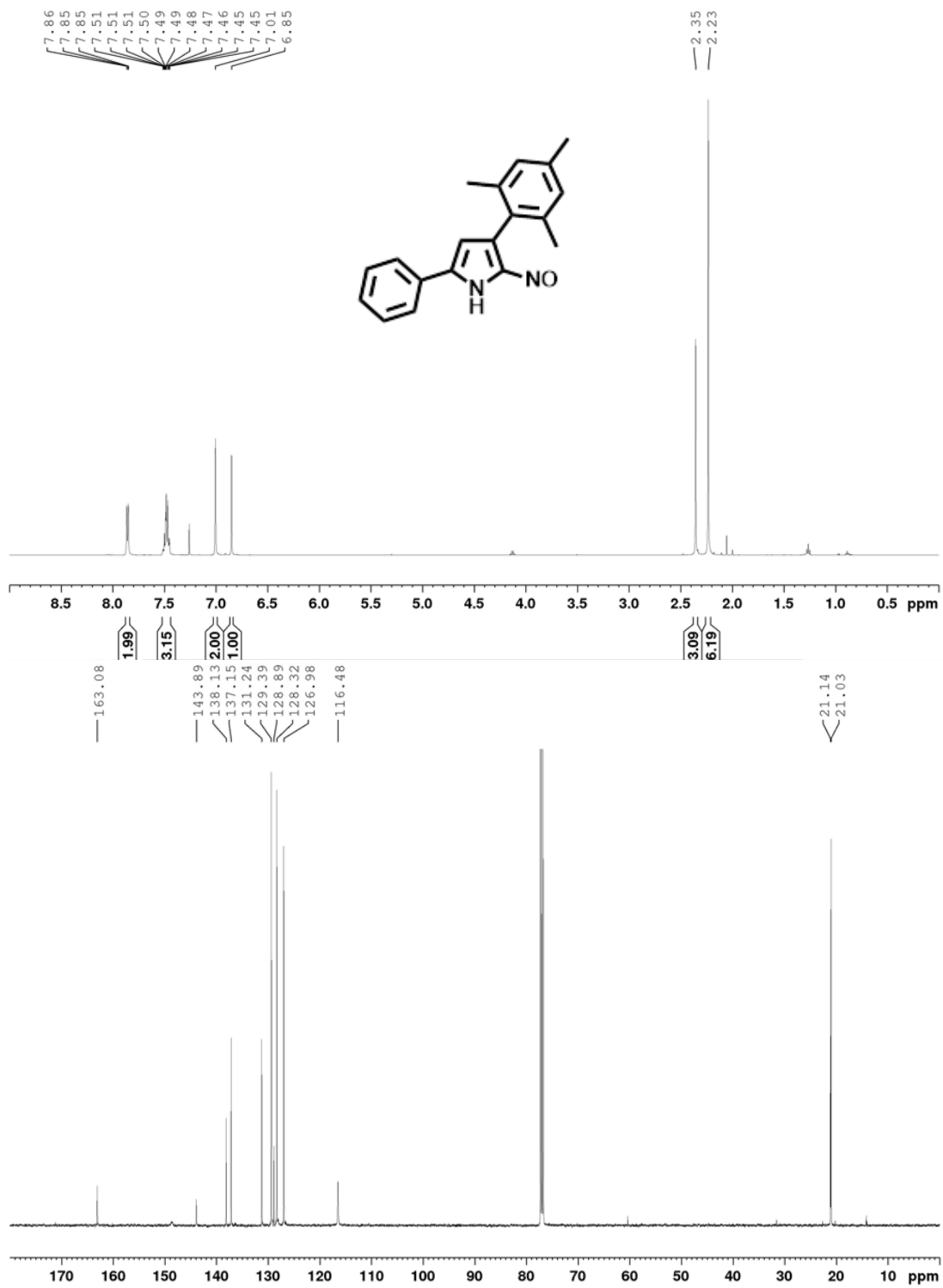
**5-(2,5-Dimethylphenyl)-2-nitroso-3-(2,4,6-trimethylphenyl)-1*H*-pyrrole, (4.21b).**
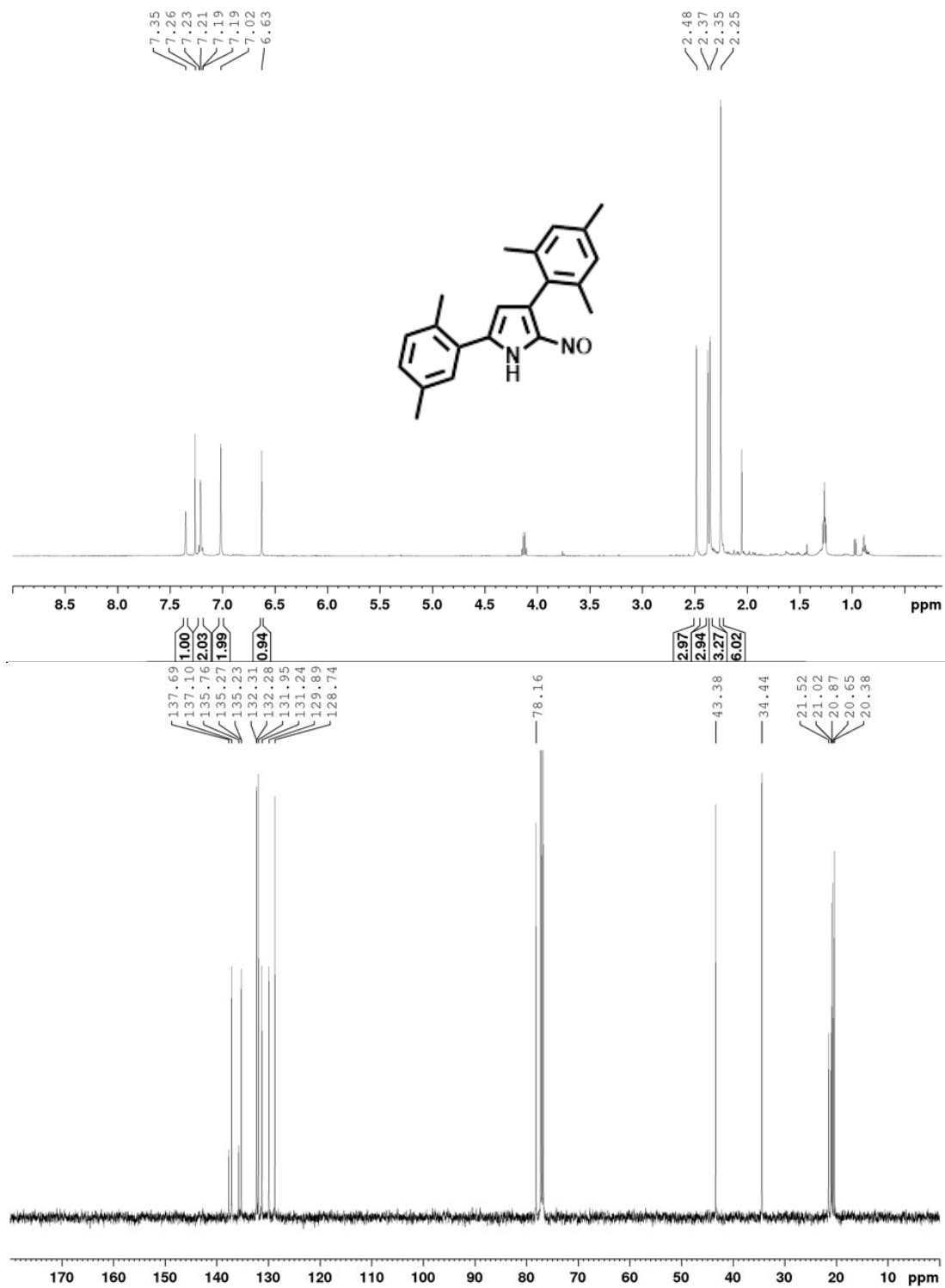
**3-(4-Bromo-2-methylphenyl)-5-(4-bromophenyl)-2-nitroso-1*H*-pyrrole, (4.21d).**
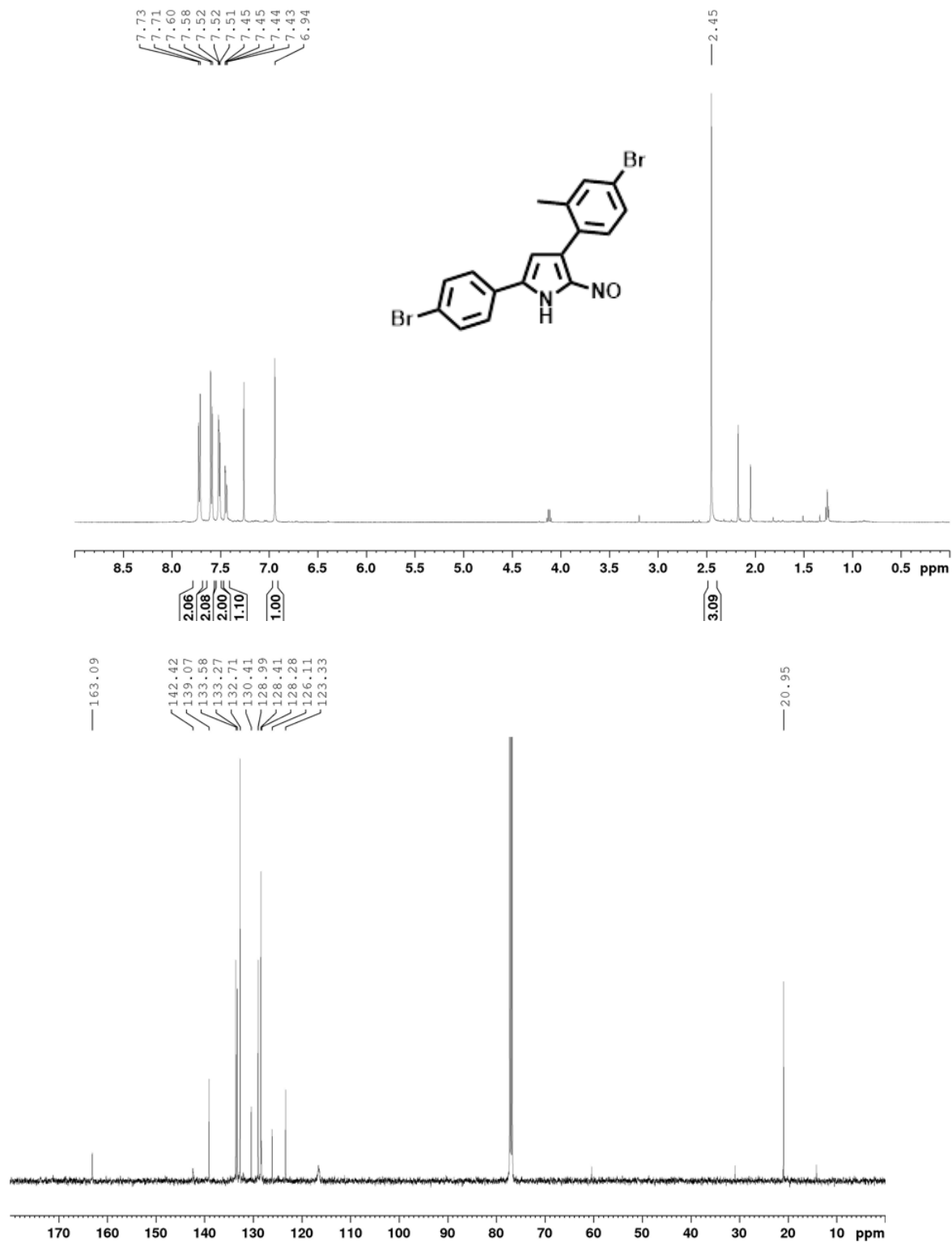
**3-(4-Methylphenyl)-2-nitroso-5-phenyl-1*H*-pyrrole, (4.21e).**
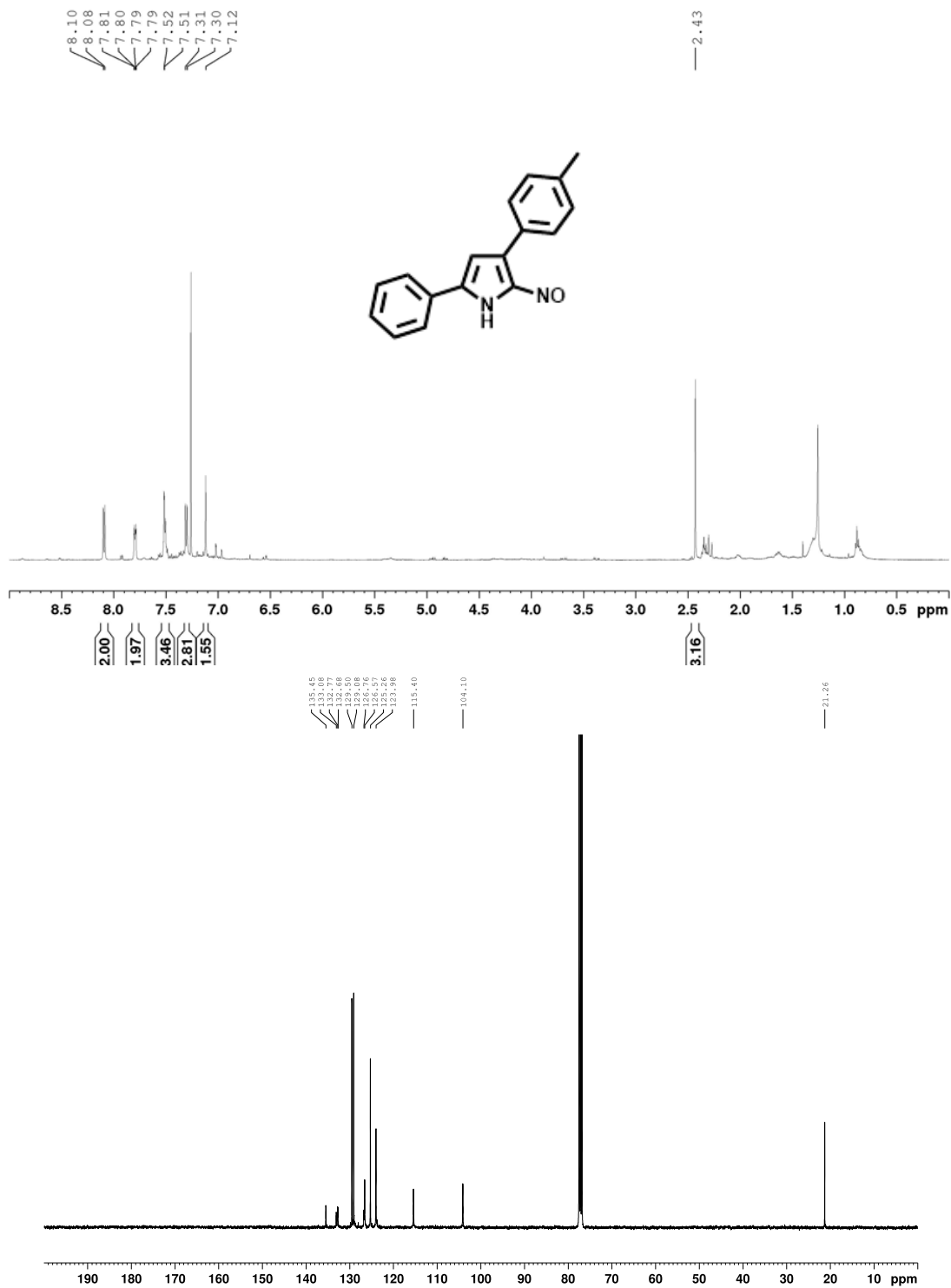
**2-Nitroso-5-phenyl-3-[4-(trifluoromethyl)phenyl]-1H-pyrrole, (4.21f).**
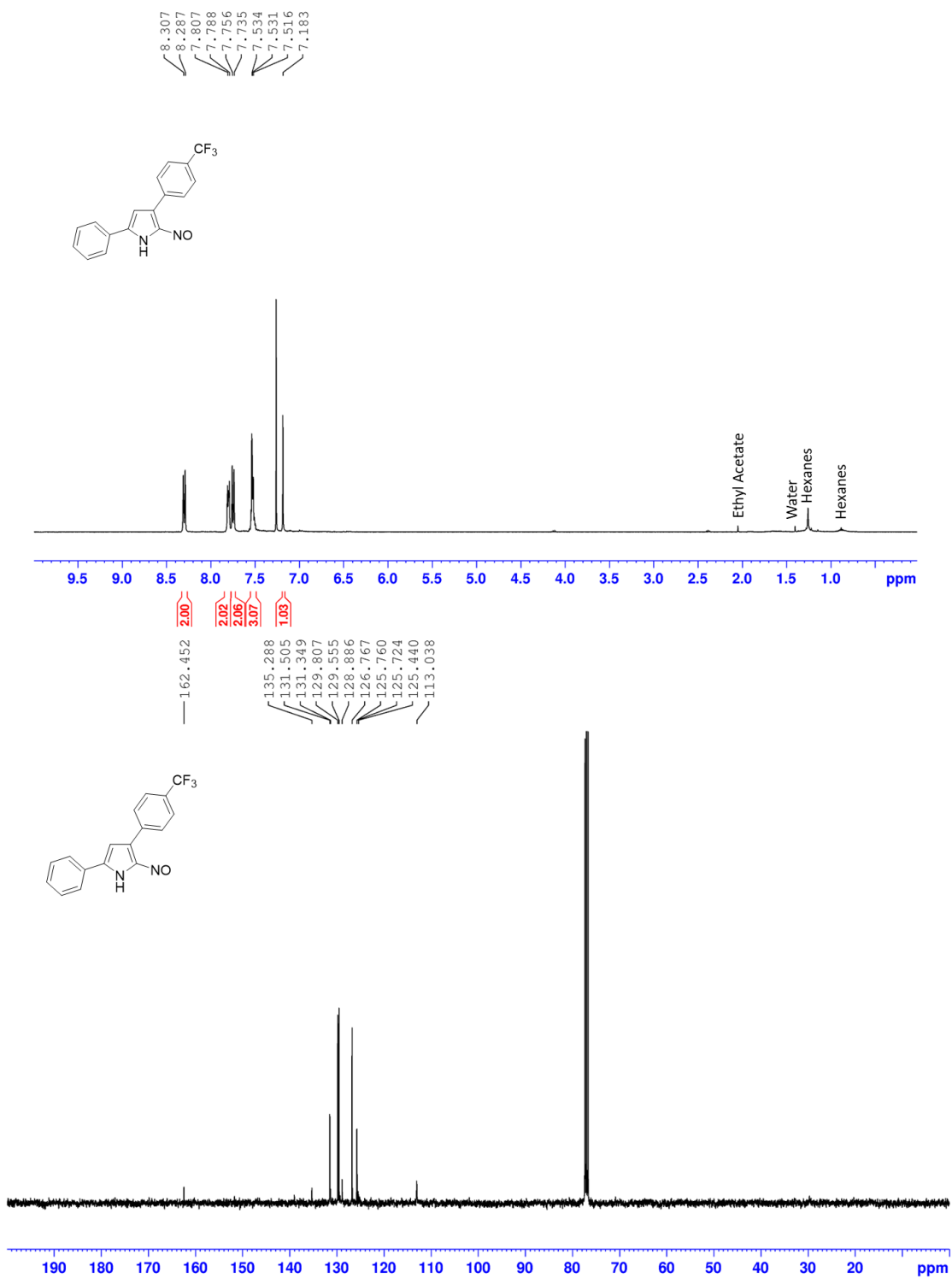
## 2-Nitroso 4-(4-Cyanophenyl)-2-phenyl-1H-pyrrole, (4.40g).
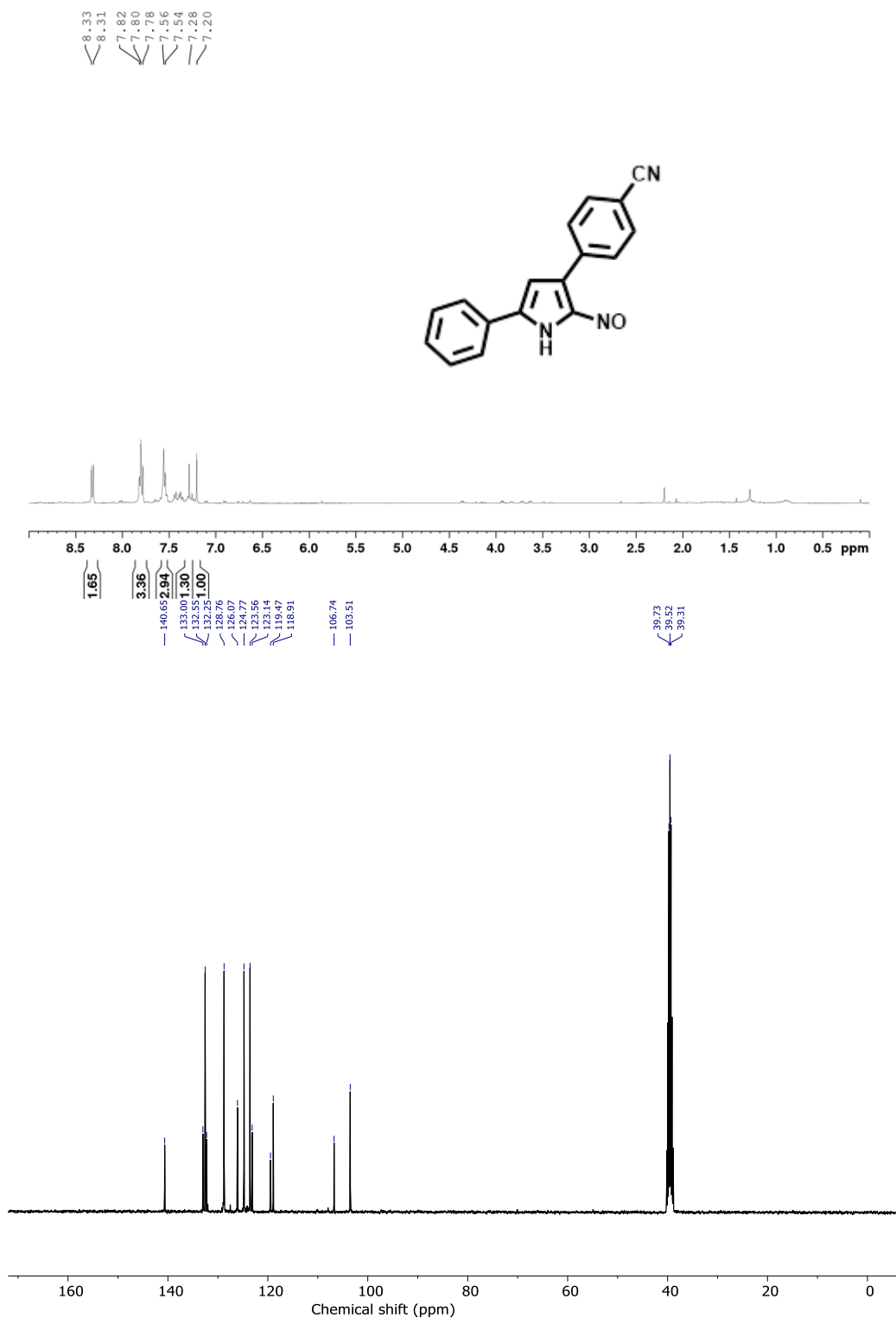
**2-Nitroso-5-phenyl-3-[3-(trifluoromethyl)phenyl]-1H-pyrrole, (4.21h).**
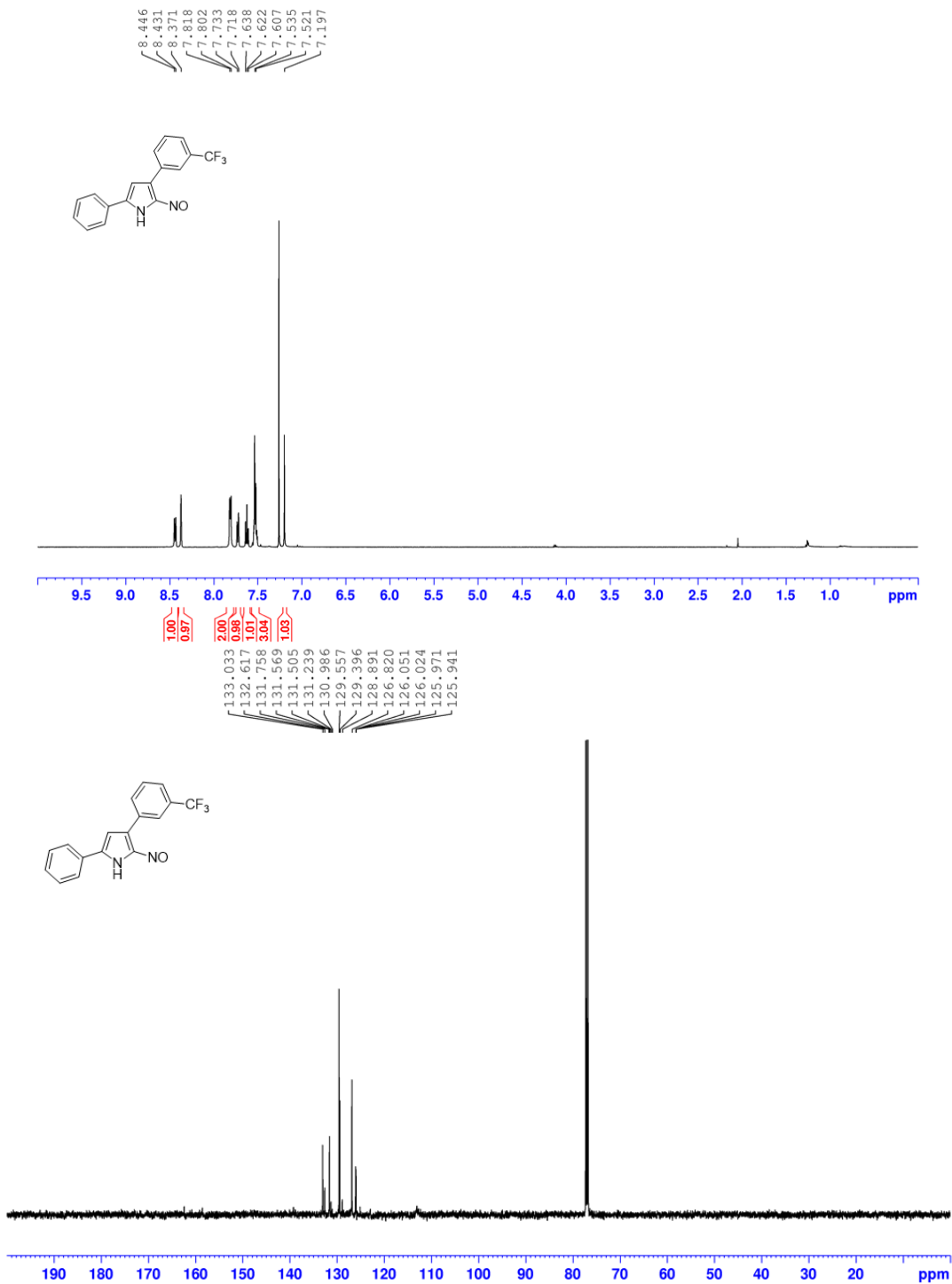
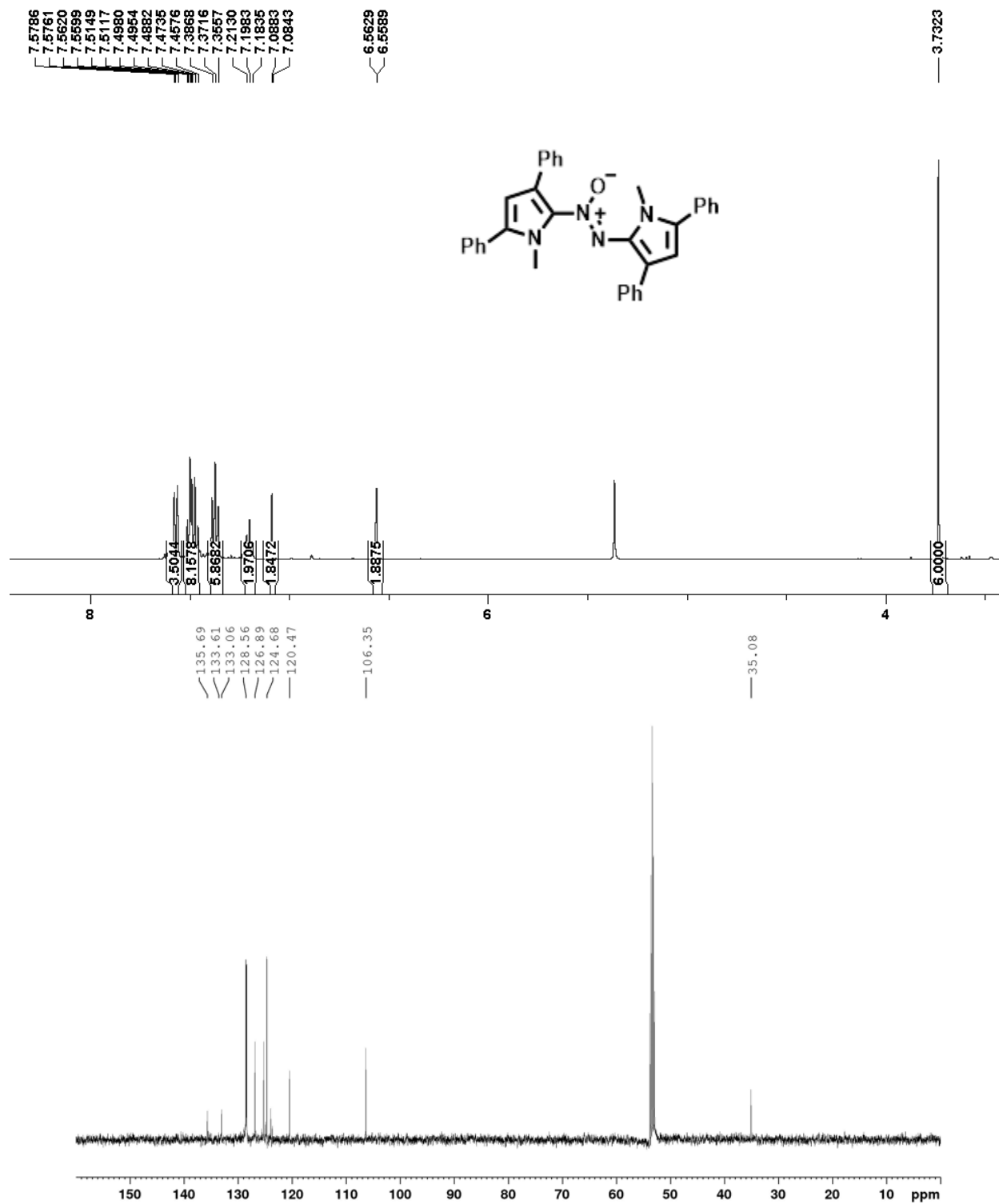**N-(3,5-diphenyl-1H-pyrrol-2-yl)-N-hydroxy-3,5-diphenyl-1H-pyrrol-2-amine, (4.41).**
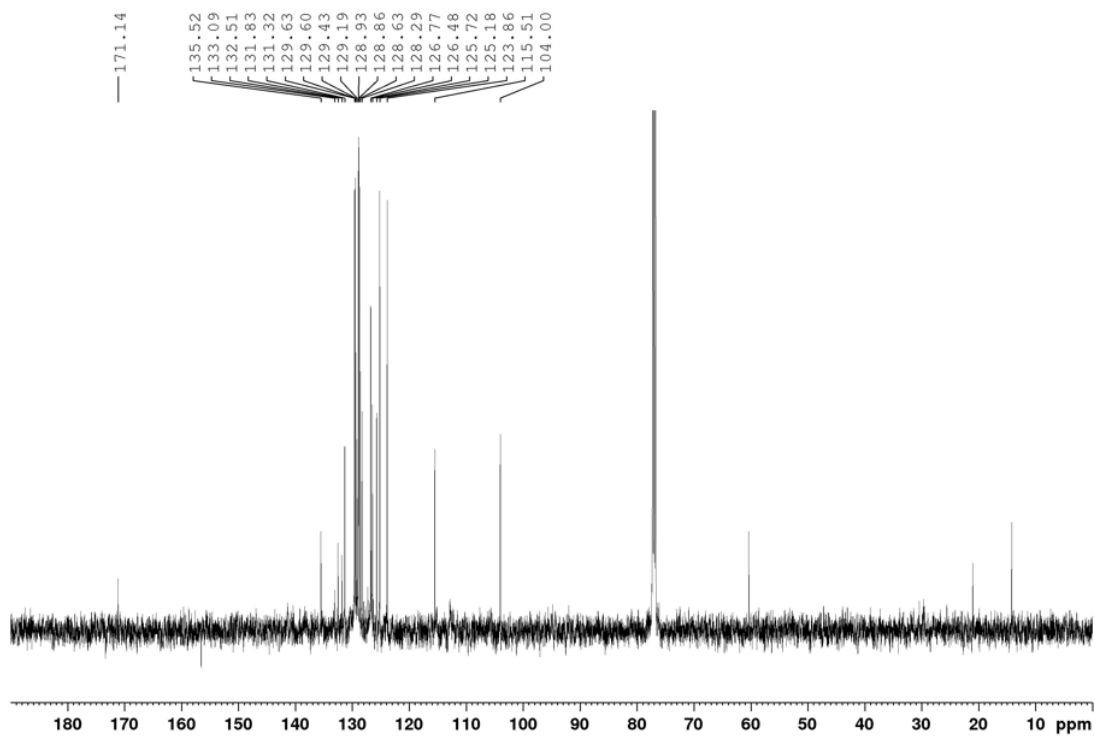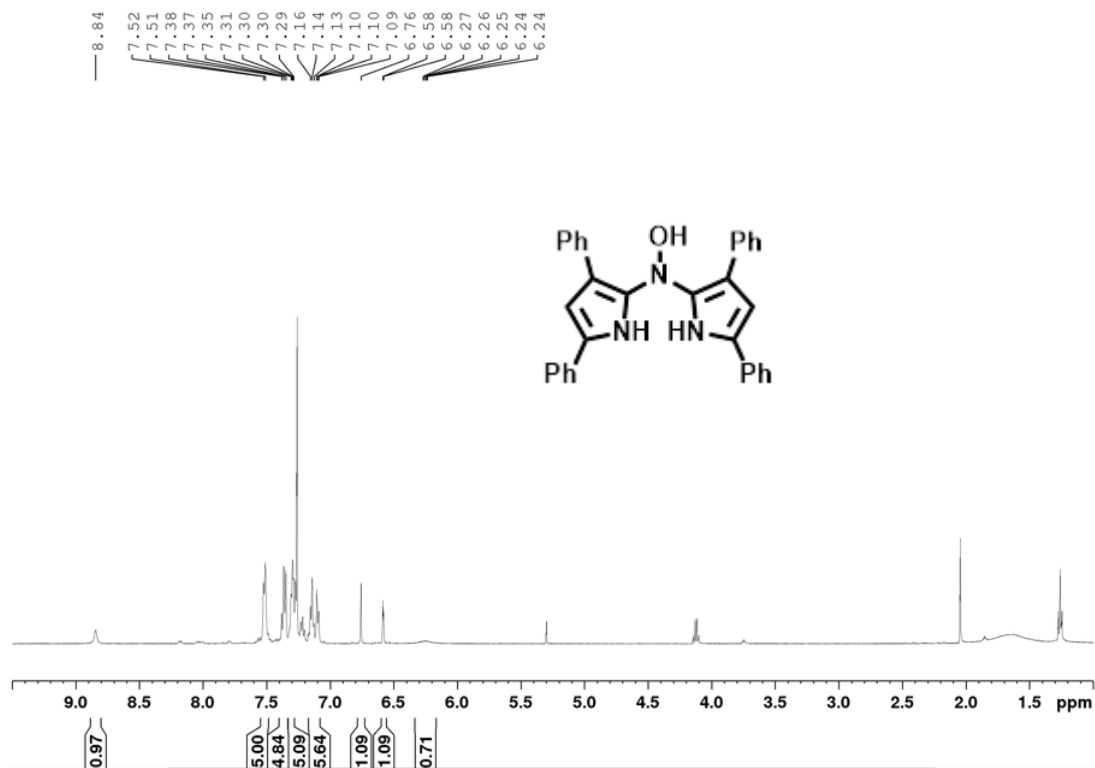
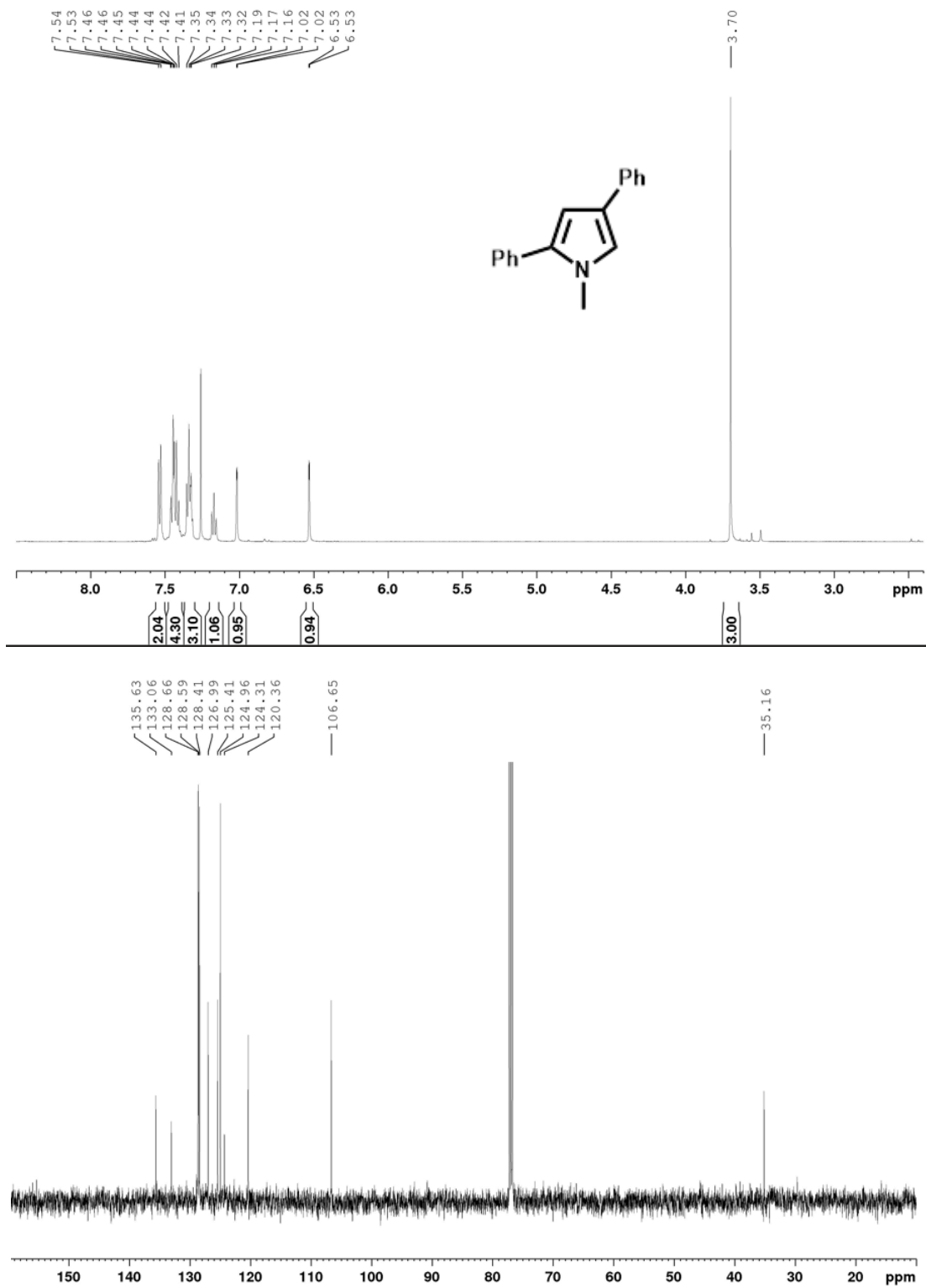**Dibenzyl 5-(hydroxyamino)-2,4-dimethyl-1*H*-pyrrole-3-carboxylate, (4.48).**
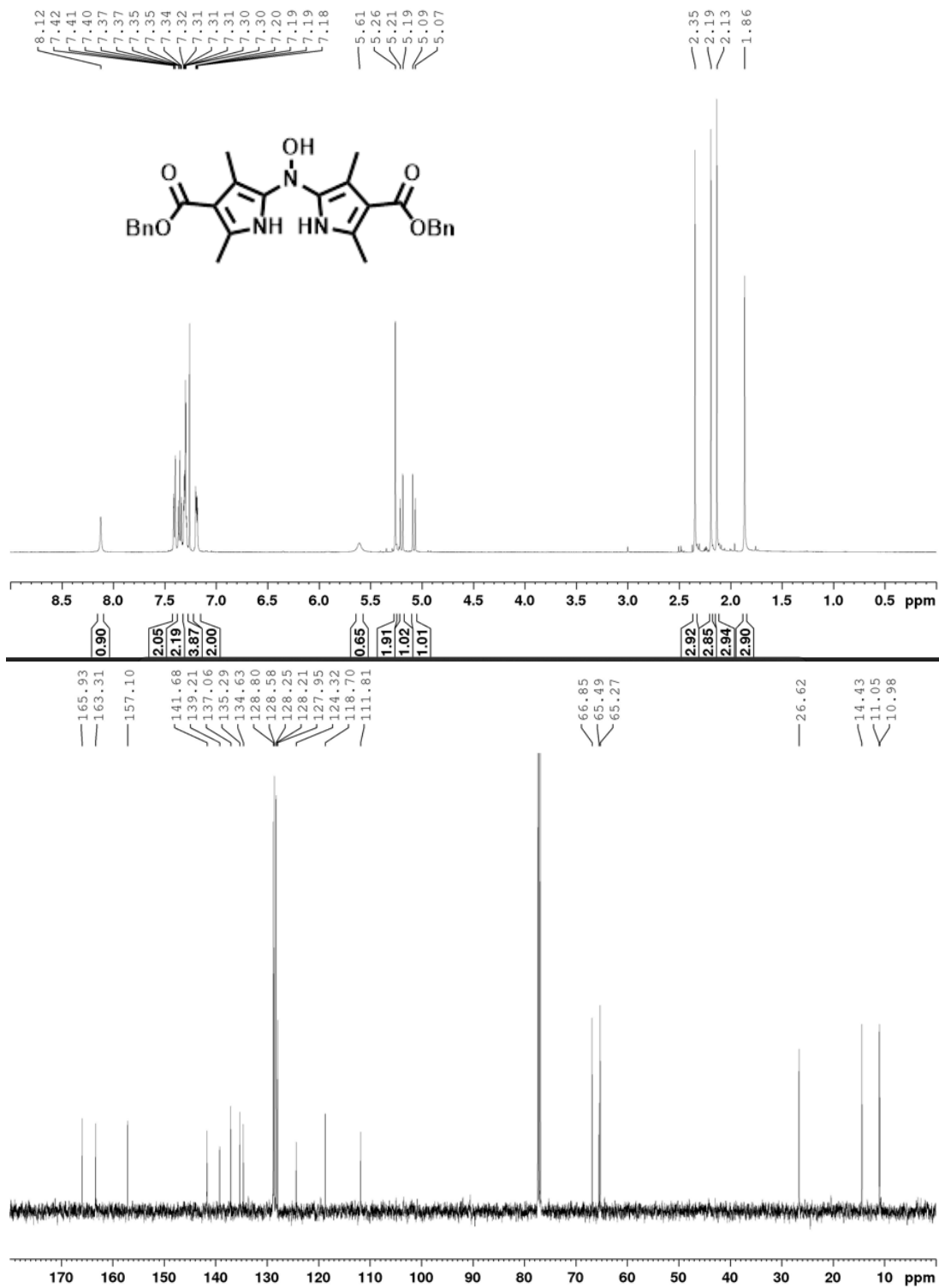
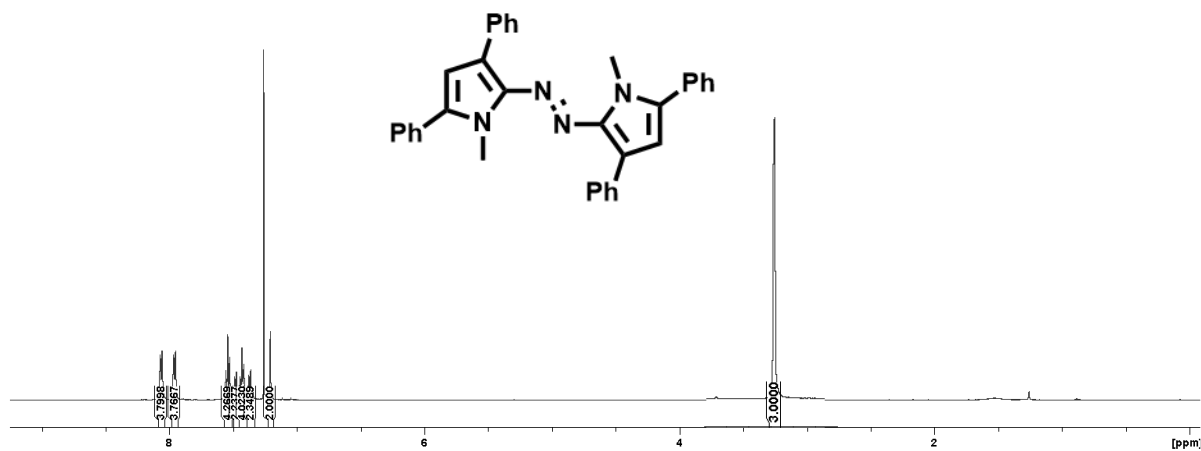**Benzyl 5-acetyl-2,4-dimethyl-1*H*-pyrrole-3-carboxylate, (4.49).**
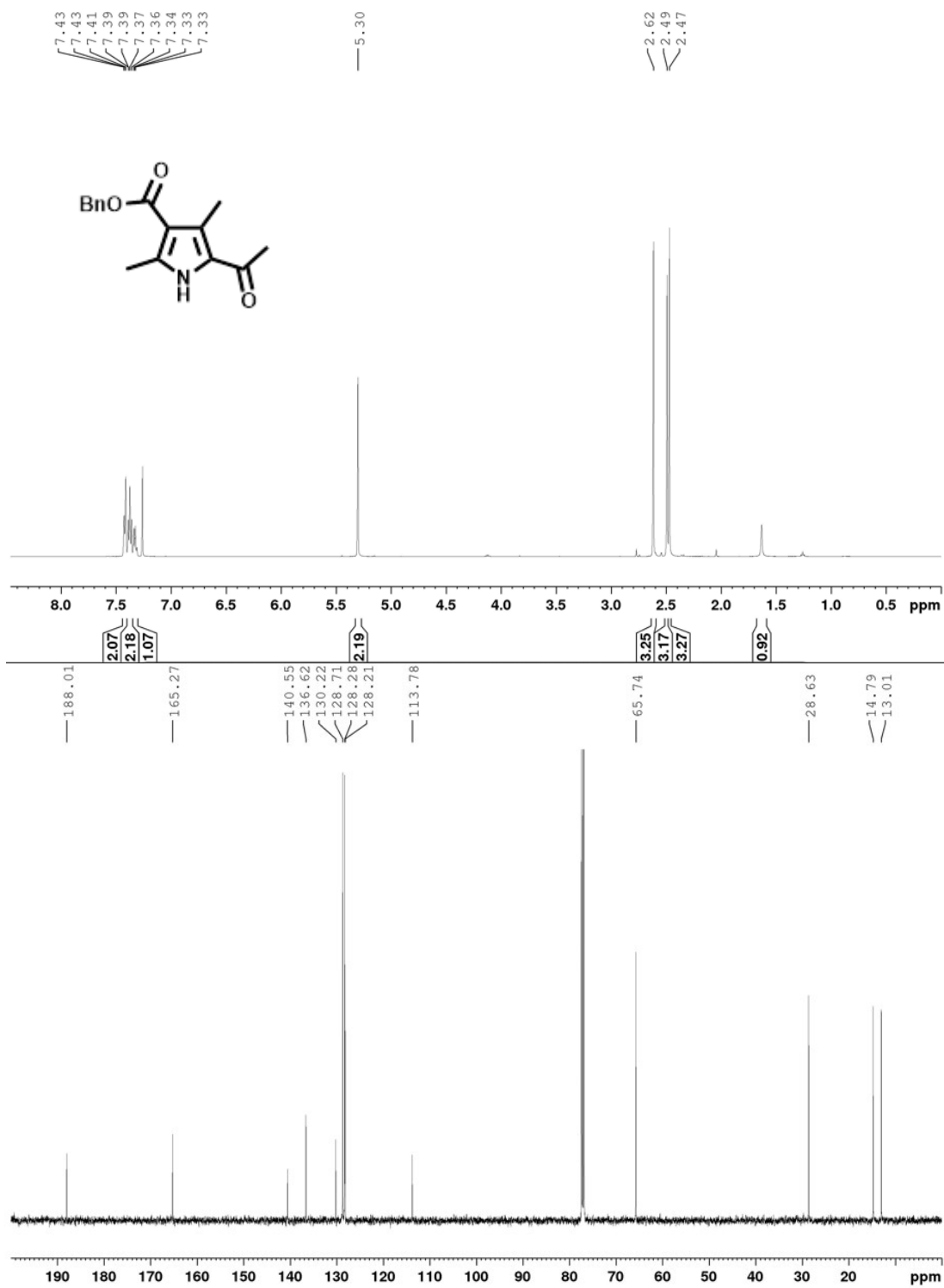
## 2,2'-diazenediyl-oxide-bis(3,5-diphenyl-1-methyl-pyrrole), (4.24).

**1-methyl-2,4-diphenyl-1*H*-pyrrole, (4.20).**

**2,2'-diazenediyl]bis(3,5-diphenyl-1-methyl-pyrrole), (4.25).**



**1-methyl-2-phenyl-1,8-dihydropyrrolo[2,3-*b*]indole, (4.23).**