Boron Functionalization of BODIPY Dyes, and Their Evaluation as Bioimaging Agents

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BORON FUNCTIONALIZATION OF BODIPY DYES, AND THEIR EVALUATION AS BIOIMAGING AGENTS

A Dissertation

Submitted to the Graduate Faculty of the
Louisiana State University and
Agricultural and Mechanical College
in partial fulfillment of the
requirements for the degree of
Doctor of Philosophy

in

The Department of Chemistry

by
Alex Long Nguyen
B.S., Louisiana State University, 2011
May 2016
As I close another important chapter of my life, I would like to dedicate this dissertation to my wonderful and supporting parents, Ngo V. Nguyen and Huynh M. Doan for their encouragement and motivation. My extraordinary sisters, Cynthia, Ashlee, Ally, and Oanh with their supports and advices. And of course, to my fiancee, Trang T. H. Nguyen for her undying love and patience through my long and challenging journey.
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GLOSSARY OF ABBREVIATIONS

<table>
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<tr>
<th>Abbreviation</th>
<th>Description</th>
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</thead>
<tbody>
<tr>
<td>δ</td>
<td>Chemical shift</td>
</tr>
<tr>
<td>ε</td>
<td>Extinction coefficient</td>
</tr>
<tr>
<td>$\lambda_{\text{max}}$</td>
<td>Maximum wavelength</td>
</tr>
<tr>
<td>$^{11}\text{B NMR}$</td>
<td>Boron 11 Nuclear Magnetic Resonance</td>
</tr>
<tr>
<td>BL</td>
<td>Bladder</td>
</tr>
<tr>
<td>BODIPY</td>
<td>Boron Dipyrrromethene</td>
</tr>
<tr>
<td>Bz</td>
<td>Benzyl</td>
</tr>
<tr>
<td>$^{13}\text{C NMR}$</td>
<td>Carbon 13 Nuclear Magnetic Resonance</td>
</tr>
<tr>
<td>CuTc</td>
<td>Copper(I) thiethyl-2-carboxylate</td>
</tr>
<tr>
<td>d</td>
<td>Doublet</td>
</tr>
<tr>
<td>DCM</td>
<td>Dichloromethane</td>
</tr>
<tr>
<td>DDQ</td>
<td>2,3-Dichloro-5,6-dicyano-1,4-benzoquinone</td>
</tr>
<tr>
<td>DFT</td>
<td>Density functional calculation</td>
</tr>
<tr>
<td>DNA</td>
<td>Deoxyribonucleic acid</td>
</tr>
<tr>
<td>EMA</td>
<td>European Medicines Agency</td>
</tr>
<tr>
<td>Et</td>
<td>Ethyl</td>
</tr>
<tr>
<td>EtOAc</td>
<td>Ethyl acetate</td>
</tr>
<tr>
<td>FDA</td>
<td>Food and Drug Administration</td>
</tr>
<tr>
<td>FRET</td>
<td>Förster Resonance Energy Transfer</td>
</tr>
<tr>
<td>GB</td>
<td>Gall bladder</td>
</tr>
<tr>
<td>$^{1}\text{H NMR}$</td>
<td>Proton Nuclear Magnetic Resonance</td>
</tr>
<tr>
<td>HRMS-ESI</td>
<td>High Resolution Mass Spectrometry Electrospray Ionization</td>
</tr>
<tr>
<td>h</td>
<td>Hours</td>
</tr>
<tr>
<td>HOMO</td>
<td>Highest Occupied Molecular Orbital</td>
</tr>
<tr>
<td>HPLC</td>
<td>High-Performance Liquid Chromatography</td>
</tr>
<tr>
<td>Hz</td>
<td>Hertz</td>
</tr>
<tr>
<td>ICT</td>
<td>Intramolecular Charge Transfer</td>
</tr>
<tr>
<td>IDG</td>
<td>Indocyanine Green</td>
</tr>
<tr>
<td>J</td>
<td>Coupling constant (Hz)</td>
</tr>
<tr>
<td>LUMO</td>
<td>Lowest Unoccupied Molecular Orbital</td>
</tr>
</tbody>
</table>
M      Molarity
m/z    Mass to charge ratio
Me     Methyl
mg     Milligram
MHz    Megahertz
min    Minutes
mL     Milliliter
NIR    Near-infrared
nm     Nanometer
PDT    Photodynamic therapy
PEG    Polyethylene glycol
PET    Positron Emission Tomography
Ph     Phenyl
ppm    Parts per million
rDA    Retro-Diels-Alder
RNA    Ribonucleic Acid
rt     Room temperature
s      Singlet
SI     Small intestine
S_NAr  Nucleophilic Aromatic Substitution
SNR    Signal to Noise Ratio
SPL    Sphingosine-1-phosphate
SPECT  Single-Photo Emission Computed Tomography
t     Triplet
THF    Tetrahydrofuran
TLC    Thin Layer Chromatography
UV-Vis Ultra violet-visible
ABSTRACT

BODIPY, also known as “porphyrin’s little sister,” belongs to a class of fluorescent dyes. It contains a dipyrromethene π-system with a disubstituted boron atom. The basic 4,4-difluoro-4-bora-3a,4a-diaza-s-indacene (BODIPY) is known for its numerous useful applications in the fields of biology and materials. Modification of this well-known fluorophore has been shown to change its photophysical and chemical properties. There has been great interest in the modification at the boron center in recent years for synthesizing new dyads and cascade-type dyes. This work focuses on functionalization at the boron center with carbon and oxygen nucleophiles for further investigation as bioimaging agents.

Chapter 1 of this dissertation describes an overview of BODIPYs including synthetic development, post-synthetic functionalization strategies, and how BODIPYs can be involved in many biological applications.

Chapter 2 discusses the synthesis, characterization, and computational studies of 4,4-dialkoxy BODIPY and its derivatives. Preliminary studies with various Lewis acids and alcohols will be investigated and discussed. In collaboration with Dr. Petia Bobadova-Parvanova of Rockhurst University, the photophysical properties were studied using computational analysis. The structural, spectroscopic and fluorescence properties of all the synthesized BODIPYs will be studied and be compared.

Chapter 3 presents the synthesis and characterization of 4,4′-dicyano-BODIPYs. A novel route for preparation of 4,4′-difunctionalized BODIPYs bearing phenyl and various substituents at the boron center was developed. These compounds were synthesized in a three step one-pot reaction between dipyrromethenes and dichlorophenylborane, followed by replacement of chloride
with fluoride and various carbon- and oxygen-centered nucleophiles. These BODIPYs’ structural, spectroscopic, and fluorescence properties are reported and discussed.

Chapter 4 represents the investigation of six 1,2,3-triazole-BODIPYs under the Cu(I)-catalyzed Huisgen cycloaddition reaction conditions. A novel BODIPY bearing a chiral moiety was synthesized using method C and X-ray crystallography confirmed its identity.

Chapter 5 reports the synthesis of chloroalcohol compounds via triphosgene-triethylamine activation. An asymmetric $S_N1$ reaction was investigated through the use of an oxazolidinone.
CHAPTER 1: INTRODUCTION

1.1 Structure of BODIPY® Dyes

In the last two decades, biomedical scientists have continued to search for new organic dyes for medicinal therapies in order to visualize intracellular processes.¹ New fluorophores that are capable of being excited and emitting within the “biological window” of 600-800 nm became an attractive and versatile tool as theranostic agents for various cancer treatments. Compounds in this red or near-infrared (NIR) region of the spectrum typically provided minimal interference from the endogenous chromophores, reduced light scattering, and prevented damage to cells and tissues.²⁻⁵ The boron dipyrromethene (designated BODIPY) family of dyes have the desired framework for facile modification, making them tunable probes and sensors for many biological applications, in comparison to other alternative nonradioactive fluorophores, such as rhodamines, cyanines, and fluorescein (Figure 1.1).

Figure 1.1: Structural framework of selected common fluorophores.
4,4-Difluoro-4-bora-3a,4a-diaza-s-indacene, or BODIPY, is often recognized as “porphyrin’s little sister”. This family of fluorophores consists of a dipyrrromethene framework complexed to a disubstituted boron unit. The dipyrrromethene structure consists of two pyrrole units linked via an interpyrrolic methine bridge. The complexation system of dipyrrromethene with a BF$_2$ unit provides a “constrained” conjugated system, giving planarity to the BODIPY conjugated π-system. The advantage of complexation with the BF$_2$ moiety is to increase the rigidity of the tricyclic system and to prevent cis/trans isomerization of the dipyrrromethene core. This restricted conformation allows for π-electron delocalization along the carbon-nitrogen backbone, which provides high fluorescence quantum yields. The overall charge of BODIPY is neutral due to the zwitterionic species involving the boron and nitrogen atoms.

The systematic naming for the dipyrrromethene and BODIPY cores are shown in Figure 1.2. In the BODIPY, positions 3 and 5 are denoted as alpha (α) while positions 1, 2, 6, and 7 are referred as beta (β) similar to the pyrrolic system. The meso-position is located at the 8-carbon, while positions 4 and 4’ are the two fluoride atoms connected to the boron center.

Figure 1.2: Numbering system for dipyrrin and BODIPY frameworks.

A single crystal structure analysis of the BODIPY core shows the three fused rings framework which consisting of a central six-membered ring and two five-membered pyrrolic rings.
with a π-electron delocalization backbone (Figure 1.3).\textsuperscript{10} The presence of B-N bonds interrupts the π-conjugation which shows that the BF\textsubscript{2} moiety does not play a significance role in extending the backbone delocalization. The approximate tetrahedral geometry of the boron atom (BF\textsubscript{2}N\textsubscript{2}) can be confirmed by the N\textsubscript{1}-B\textsubscript{1}-N\textsubscript{2} and F\textsubscript{1}-B\textsubscript{1}-F\textsubscript{2} bond angles.\textsuperscript{11} The approximate bond length of N\textsubscript{1}-C\textsubscript{4} shows a single bond, while N\textsubscript{1}-C\textsubscript{3} indicates double bond characteristic. BODIPY was initially thought to resemble a monomethine cyanine dye by having 6π electrons equally delocalized over five atoms but found to be isoelectronic with heptamine cyanine having 12π distributed over eleven atoms.\textsuperscript{12}

![Image](image.png)

Figure 1.3: The X-ray crystal structure of unsubstituted BODIPY with atoms labeled and 50% probability displacement ellipsoids.\textsuperscript{10}

The monoclinic unit cell of the BODIPY comprises of four molecules arranged head-to-tail geometry, which utilities the π-π interactions between adjacent hydrophobic fragments and avoids the variation from the fluorine dipole moments.\textsuperscript{13} Little differences in heteroatoms dipole moment of BODIPY core provide modification at various positions via electrophilic and nucleophilic additions. The functionalization at the substituent-free positions unlocks new tunable routes to numerous novel BODIPY derivatives.\textsuperscript{14}
BODIPY and its derivatives show remarkable photophysical characteristics. The characteristics are intense absorption and emission in the visible region ($\lambda_{\text{max}} \geq 450$ nm), high fluorescence quantum yields, high molar absorption coefficients (around 40,000 to 80,000 M$^{-1}$ cm$^{-1}$), and relatively small Stokes shifts (~15 nm). Various properties of BODIPYs include excellent photophysical stability, thermal- and photochemical stability in solution and solid states, high solubility in many organic solvents, and resistance to changes in pH and solvent polarity.$^{15-17}$

The typically strong intense absorption band of the BODIPY fluorophore in the visible region comes from the $S_0$-$S_1$ ($\pi-\pi^*$) transition containing a shoulder of high energy around 480 nm from the 0-1 vibrational transition, while a broad weaker band around 350 nm is assigned to the $S_0$-$S_2$ ($\pi-\pi^*$) transition.$^{12,18}$ Excitation of an electron in either the $S_1$ or $S_2$ states, an equally narrow band from the absorption and emission spectra is perceived from the $S_1$ state. BODIPYs that have emission around 500-590 nm typically have a yellow to green color. Small Stokes shifts are often observed in many BODIPY compounds, which indicate that the $S_0$-$S_1$ transition and vibrational relaxation make no significant changes in the core structure.$^{19}$

Addition of functional groups to the carbon atoms at the $\alpha$-, $\beta$-, and meso-positions as well as the boron atom of BODIPY can alter its photophysical properties. The BODIPY absorption band can be shifted into the red or near-IR region by increasing the degree of $\pi$-electron delocalization. Having functional groups that are electron-withdrawing or -donating on the BODIPY core as well as intramolecular rotation can significantly affect the absorption and emission properties.$^{20}$

Investigation of BODIPY’s functionalization will further research development in the synthesis of new fluorophores for multi-purpose applications. By altering the spectroscopic properties and functionalities of BODIPY dyes, there are boundless possibilities for designing
novel, challenging and versatile fluorescent compounds. Throughout this Dissertation, various synthetic methodologies and investigation techniques will be described.

1.2 Synthetic Methodologies

In 1968, Treibs and Kreuzer were the first to synthesize a BODIPY by mixing 2,4-dimethylpyrrole, acetic anhydride, and BF$_3$·OEt$_2$, and found this robust class of compound could have potential application as tunable laser dyes.²¹ This fluorophore was not fully explored until the late 1980s, where BODIPYs were found to be useful for biological applications, such as cellular imaging and probe sensors. For example, Wories and coworkers²² reported the first water-soluble BODIPYs for cellular visualization. Since the mid-1990s, publications and patents reported on BODIPYs have increased tremendously. Extensive modifications to the BODIPY framework have led to many BODIPY derivatives with numerous applications: biomolecular imaging,²³-²⁶ photosensitizers,²⁷-³⁰ fluorescent switches,³¹-³⁴ chemosensors,³⁵-⁴⁰ electroluminescence devices, laser dyes,⁴¹-⁴³ drug delivery agents,²⁸,⁴⁴ and in photodynamic therapy.⁴⁵-⁴⁶

1.2.1 Synthesis of the BODIPY Core

There are many routes toward the synthesis of BODIPY using well-known pyrrole chemistry. First, a highly reactive electrophilic ketopyrrole and readily nucleophilic 2-unsubstituted-pyrrole afford the corresponding dipyrrromethene compounds. Using a non-nucleophilic base, either a secondary or tertiary amine, followed by complexation using boron trifluoride etherate (BF$_3$·OEt$_2$) gives the desired BODIPY in moderate yields. Even though there are numerous reports of BODIPY syntheses in the literature, the fully unsubstituted BODIPY 1 remained a challenge due to the compound’s reactivity. However, three independent research groups have reported successful routes to the fully unsubstituted BODIPY 1. The first method was
reported by Bruce and coworkers (Scheme 1.1, Method A),¹⁰ where dipyromethane 3 was oxidized to the corresponding dipyromethene by using DDQ or chloranil as the oxidizing agent. To avoid undesired side products, the oxidation step was carried out under inert conditions and at low temperature (-78 °C). The complexation step with BF₃⋅OEt₂ was performed in situ using DBU as an additive to yield the desired compound in 5-10% yield. This unsubstituted compound 1 was characterized by ¹H-, ¹³C-, ¹¹B-, and ¹⁹F-NMR spectroscopy and its structure was confirmed by single crystal X-ray analysis.

Scheme 1.1: Methods for syntheses of unsubstituted BODIPY 1.

Another approach to the unsubstituted BODIPY 1 was through a classic acid-catalyzed condensation method between pyrrole-2-carbaldehyde 5 and unsubstituted pyrrole 4, followed by complexation with BF₃⋅OEt₂ in the presence of a base to afford the desired product 1 in 8% yield (Scheme 1.1, Method B).¹⁴ However, the unsubstituted BODIPY can be synthesized in 98% yield from the most efficient method developed by Pena-Cabrera and coworkers,¹³ where a meso-thiomethyl BODIPY 1 was treated with trimethylsilane under mild conditions using copper(I)
thienyl-2-carboxylate (CuTc) and palladium in THF for 45 min at reflux temperature (Scheme 1.1, Method C). No reaction was observed in the absence of CuTc or palladium. The impressive characteristic of BODIPY 1 is a high quantum yield (93%) in non-polar and polar solvents.

1.2.2 Synthesis of Symmetric BODIPY Dyes

8-Substituted symmetrical BODIPYs can be synthesized by acid-catalyzed condensation between acid chlorides, aldehydes, or anhydrides with α-free pyrroles to give the corresponding dipyrromethene (or dipyrromethane in the case of aldehyde). Polymerization of pyrrole typically occurs when both α-positions of the pyrroles are unsubstituted. To avoid this polymerization, only one α-position (C2) is usually unsubstituted. The most popular route consists of a “one-pot three step” reaction and has become the most efficient way to synthesize a wide range of meso-substituted BODIPYs with the desired appendages (Scheme 1.2).

Symmetrical BODIPY syntheses typically involve self-condensation between two equivalents of an α-free pyrrole with an aryl aldehyde to give a dipyrromethane (Scheme 1.2). A recent report shows that aldehydes and pyrroles can also react under neat conditions (no solvent required) to afford dipyrromethanes.47 The dipyrromethanes are subsequently oxidized to give dipyrromethenes which then undergo complexation with BF$_3$·OEt$_2$. Alternatively, another method to synthesize BODIPYs requires treating the same two units of an α-free pyrrole with acyl chloride to directly give dipyrromethene. The advantage of this method is that no oxidation step is necessary, which usually increases the reaction yields and eases purification. Similar to acyl chlorides, anhydrides also react with an α-free pyrrole to give the corresponding dipyrromethene. Although introducing aromatic groups onto the BODIPY core is expected to extend the π-conjugation delocalization, the nearly perpendicular geometry of the groups at the meso-position prevent significant interaction of the two π-systems, but increases BODIPY stability.6,11,16,48
Scheme 1.2: General procedures for symmetrical BODIPY synthesis via condensation.

The approach using a cyclic anhydride provides the corresponding BODIPY bearing a terminal carboxylic acid, which are receptive to coupling to biological molecules such as proteins, DNA and lipids.\textsuperscript{15,49} meso-Unsubstituted BODIPY can generally be prepared from pyrrole-2-carbaldehyde and an \( \alpha \)-free pyrrole in an acid-catalyzed condensation reaction. An acid catalyst, such as \( p \)-toluenesulfonic acid or Montmorillonite clay, is often used in order to generate the pyrrole carbinyl cation which reacts with the \( \alpha \)-free pyrrole to give dipyrromethane.\textsuperscript{50-51} Symmetric and unsymmetric BODIPYs can also be synthesized from dipyroketones.\textsuperscript{52}

1.2.3 Synthesis of Unsymmetrical BODIPY Dyes

The approach to synthesize unsymmetrical BODIPYs relies on the use of two different pyrroles, for example by reacting the ketopyrrole (carbonyl-containing pyrrole) with a different \( \alpha \)-
free pyrrole via Lewis acid mediated condensation (Scheme 1.3).\textsuperscript{53-54} The ketopyrrole precursor fragment can be synthesized from an α-free pyrrole and Grignard reagents and an acid chloride.\textsuperscript{53,55-56} The use of electron-rich and electron-deficient pyrroles determines the percent yields of the desired BODIPY product. Electron-rich pyrrole usually gives a high yield while electron-poor pyrrole usually gives a low yield due to self-condensation which results in the undesired symmetrical product. The dipyrrromethene salt then reacts with BF\(_3\)·OEt\(_2\) in the presence of a base to give a BODIPY scaffold with two different pyrrolic units for further functionalization. In addition, Zhao and coworkers\textsuperscript{57} recently reported that unsymmetric BODIPYs can be synthesized from dipyrroketone precursors.

### 1.3 Derivatization of the BODIPY Core

Although BODIPYs have many advantages, some of their limitations are the typical absorption and emission wavelength maxima around 500 nm, relatively small Stokes shifts, poor solubility in an aqueous environment, and inability to directly conjugate to biomolecules. To overcome these drawbacks, functional groups can be attached directly to the BODIPY core via the use of a substituted pyrrolic precursor, substituted aldehyde, or by post-functionalization of the BODIPY dyes. The tunable properties of BODIPY allow the synthesis of derivatives that absorb and emit in the span over the desired wavelength in the visible and NIR ranges.

Many research groups (including Vicente,\textsuperscript{48,58-59} Burgess,\textsuperscript{60} Ziessel,\textsuperscript{44} Boens,\textsuperscript{1,61} Nagano,\textsuperscript{30} Akkaya,\textsuperscript{62} O’Shea,\textsuperscript{63} Rurack and Daub,\textsuperscript{64} and Carreira\textsuperscript{65}) are currently exploring new methods to optimize the photophysical properties of these dyes while retaining their stabilities. BODIPY dyes can be derived from various approaches: i) nucleophilic substitutions or additions of styryl or alkynyl groups at the 3,5-positions, ii) electrophilic substitutions at the 2,6-positions, iii) cross-coupling reactions with palladium(0) on halogenated BODIPYs, iv) nucleophilic substitution at
the boron center. Metal-mediated cross-coupling reactions provide one of the most convenient methods to incorporate functionalities directly into the BODIPY core with halogens at the 2,3,5,6,8-positions. Typical palladium-mediated cross-coupling reactions can be accomplished through the Suzuki, Sonagashira, Heck, and Stille methods.

Scheme 1.3: General procedure for unsymmetrical BODIPY via ketopyrrole and dipyrroketone.

1.3.1 Functionalization at the 8-position

The meso-position (or 8-position) is the easiest position to introduce various “handles” on the BODIPY from the initial condensation step (examples are shown in Figure 1.4). This position can be functionalized with a variety of aromatic groups via acid-catalyzed condensation, using either an aldehyde or acyl chloride. The introduction of useful groups on the 8-position for specialized purposes, such as incorporation of metal ion binding ligands, functionality for donor-acceptor cassettes, water-soluble groups, and biomolecules for biological applications, including as pH probes and chemical sensors. For example, probes with aliphatic ester 8-aryl BODIPYs are being used to investigate dynamic effects in membranes (Figure 1.4,
structure 9). Boens and coworkers\textsuperscript{1,61,80} studied the effect of electron-donating and electron-withdrawing groups at the \textit{meso}-position. BODIPYs with substituents at the 1,7-positions or bulky substituents on the 8-aryl group show restricted rotation of the \textit{meso}-aryl group, which in turn increases the fluorescence quantum yields (Figure 1.4, structure 9). In addition, replacing the \textit{meso}-aryl group with a trifluoromethyl unit also increases quantum yields due to the reduction in the nonradiative decay through rotation.\textsuperscript{1,15}

Substitution of the carbon atom at the 8-position with a nitrogen atom generates a new class of fluorophore called “aza-BODIPYs,” which were not reported until 1994 (Figure 1.4, structure 11).\textsuperscript{81-84} The important characteristics of aza-BODIPYs are sharp absorption and emission wavelengths in the NIR (650-850 nm) range, high molar extinction coefficients, and moderate to good fluorescence quantum yields.\textsuperscript{85} The \textit{meso}-nitrogen with the lone pair can dramatically decrease the HOMO-LUMO energy gap through stabilization,\textsuperscript{6} which induces a large red-shift in the absorption and fluorescence emission maxima (~100 nm). These aza-dipyrrmethenes can be prepared by condensation between nitrosopyrrole and an \textit{α}-free pyrrole or Michael addition product (reaction from chalcones and nitromethane) with formamide.\textsuperscript{81-83} This class of fluorophore has found its usefulness in various applications: as photosensitizers for PDT,\textsuperscript{72,86} NIR-emitting chemosensors, bioimaging probes,\textsuperscript{32,65,87} and fluorescent biological labels.\textsuperscript{88-89}

\textbf{1.3.2 Modification at the 1,3,5,7-Positions}

The photoelectronic properties of the BODIPY core can be fine-tuned by varying the substituents on the carbon framework. Analogous to other heteroaromatic systems, the methyl groups at the 1, 3, 5, and 7-positions are the most nucleophilic sites. The 3,5-methyl groups are considered relatively acidic due to being next to the pyrrolic nitrogen atom. In order to extend the \textit{π}-conjugation, the methyl groups can be deprotonated and undergo condensation with electron-
rich aromatic aldehydes through Knoevenagel reactions to generate trans-stryryl groups (Figure 1.5).

![Chemical structures](image)

Figure 1.4: Selected examples of 8-substituted BODIPY structures: 6, 7, 8, 9, 10, 11, 12, and 13. Some groups, such as dimethylamino on the 3,5-aryls induce high quantum yields only in the protonated form by disfavoring intramolecular charge transfer (ICT) in the excited state. Post-functionalization using various aryl-aldehyde groups provides a methodology for introducing “handle” through a simple modification, producing long-wavelength absorbing and emitting BODIPYs. Addition of halogens such as chloride or iodide at the 3,5-positions allows BODIPY to
become reactive toward nucleophilic aromatic substitutions (S\textsubscript{N}Ar) and palladium-catalyzed cross-coupling.

![Chemical structures](image)

Figure 1.5: Selected examples of 3,5-substituted BODIPY structures: 14,\textsuperscript{94} 15,\textsuperscript{95} 16,\textsuperscript{96} 17,\textsuperscript{97} and 18,\textsuperscript{97}

While carbon- and oxygen-based nucleophiles produce BODIPYs with largely unchanged $\lambda_{\text{max}}$ in the absorbance and emission spectral properties, nitrogen and sulfur with various substituents on the 3,5-positions have been demonstrated to red-shift the emission spectra. All these nucleophiles provided additional functionalities and extended conjugation.\textsuperscript{15} Incorporation
of ethynyl, aryl, and styryl groups can be accomplished through palladium-mediated cross-coupling reactions, providing fluorescent probes for a variety of applications.

1.3.3 Functionalization at the 2,6-Positions

The reactivity of the BODIPY core can be predicted based on the resonance structure, as shown in Figure 1.6, where positions 2 and 6 contain the least positive charge. For this reason, they undergo electrophilic aromatic substitution. Different functional groups have been introduced at the 2- and 6-positions via halogenation,\textsuperscript{30,98} nitration,\textsuperscript{99-100} sulfonation,\textsuperscript{15,49,101,22} and formylation.\textsuperscript{73} Particularly, the introduction of sulfonate groups increase the BODIPY’s water solubility properties for biological purposes (Figure 1.7, structure 19). Even though sulfonate groups do not make a significance change in the absorption and emission spectra, BODIPYs containing these groups are strongly fluorescent in polar solvents and more stable than their precursors. On the other hand, addition of nitro groups at the 2,6-positions reduces the BODIPY fluorescence quantum yields (Figure 1.7, structure 21).\textsuperscript{99}

![Figure 1.6: Resonance structures of positive charge delocalization through BODIPY core.](image)

Addition of halogen groups (bromide or iodide) at the 2- and 6-positions can cause a significant red shift in the absorption and fluorescence emission maxima of BODIPYs but quench the quantum yield due to the heavy atom effect\textsuperscript{16} (Figure 1.7, structure 20). Furthermore, post-modification on these 2,6-halogenated BODIPYs typically involves through palladium-mediated cross-couplings, such as Suzuki,\textsuperscript{102} Stille,\textsuperscript{71} Sonagashira,\textsuperscript{103} and Heck reactions.\textsuperscript{104}
1.3.4 Modifications at the Boron Center

Boron-substituted BODIPYs have been of increased interest in the past few years. Many researches have investigated the increase in stability of BODIPYs, their redox properties, Stokes shifts, and development of donor-acceptor systems. There are many demonstrations using carbon nucleophiles to replace the fluoride atoms (Figure 1.8). The first example of 4,4-dialkyl-BODIPYs were synthesized via the reaction of dipyrromethenes with boron-alkyl compounds. Alternatively, Ziessel and coworkers investigated the synthesis of 4,4-dialkyl-, 4,4-diaryl-, and 4,4-diethynyl-BODIPYs by Grignard and organolithium methods. These modifications at the boron center can be used for synthesizing new BODIPY-based dyads and cascade-type dyes. These $B$-aryl BODIPYs have larger Stokes shifts compared to their BF$_2$ parents. Cyano groups can replace the fluoride atoms using trimethylsilyl cyanide in high yields in the presence of a Lewis acid. Cyano substituents on the boron center enhance the fluorescence quantum yields and stability of BODIPYs. Recently, Ankush and coworkers reported a new method to introduce ethyl groups directly onto the boron center in high yields via treating BODIPY with Et$_2$AlCl (Figure 1.8, structure 26). They also compared their method to the Grignard method and reported that their method is more efficient.
While carbon-substituted BODIPYs are used for increasing the Stokes shift and stability, oxygen groups on the boron atom increase the BODIPY aqueous solubility. In 1999, Burgess and coworkers demonstrated the first oxygen substitution on the boron center by intramolecular cyclization of 3,5-dihydroxy-ortho phenyl. Since then, a series of 4,4-dialkoxy- and diaryloxy-BODIPYs were synthesized either by refluxing with sodium alkoxide in alcohol or with alcohols mediated by Lewis acid (Figure 1.9, 28 and 29). On the other hand, Courtis and coworkers focused on the synthesis of mono-alkoxy BODIPYs to be used for bioimaging application.
1.3.5 Ring Fusion to the BODIPY core

In the last few decades, the development of compounds emitting in the red and NIR ranges became a focus of research for bioanalytical and optoelectrical imaging applications. Fluorescent organic dyes in the red and near-IR regions are important biomarker tools in DNA sequencing, gel electrophoresis, in vivo imaging, and tissue perfusion. In order to reach this longer wavelength (lower energy), extended conjugation via ring fusion became an efficient way to move forward. Different approaches were applied for formation of the ring such as aryl-fused pyrroles, 2-acetylphenols, and retro-Diels-Alder (rDA) syntheses of norbornane pyrroles (Figure 1.10). Recently, Uppal and coworkers demonstrated aromatization of bicyclohexanyl BODIPY using DDQ as the oxidant agent. Ring fusion provides a red-shifted, sharper fluorescence emission and high fluorescence quantum yields due to the rigidification, which inhibits the rotation of the aromatic groups.

1.4 Applications of BODIPY Dyes

There is a growing demand for new organic fluorophores that are capable of improving the luminescence, electrochemical, and fluorescence properties in all aspects of life sciences. BODIPY dyes have the desired framework and photophysical properties to meet those demands. There are many attractive applications that BODIPYs are involved in, including tunable dyes, environmental
fluorescent indicators, enzyme substrates, fluorescent pH probes, bioimaging, electroluminescent devices, donor-acceptor energy transfer cassettes, fluorescent chemosensors, light-emitting and ion signaling devices, and photosensitizer agents for photodynamic therapy (PDT) of cancer (Figure 1.11).

1.4.1 Biological Applications

BODIPY compounds, as fluorophores, have become versatile visualization dyes in recent years due to the capability for biological tagging to various desired analytes (proton and metal-bind ions) and to enzymes, polypeptides, proteins, and nucleic acids in DNA. For example, many organic fluorescent dyes have been used for in vivo imaging and for binding with a non-radioactive ligand in biological intracellular processes. Due to the recent advancement in bioanalytical and
optoelectrical imaging, rising effort for development of fluorescence dyes in the red and NIR region (600-900 nm) has become more important than ever for application in molecular imaging.

Fluorophores excited and emitting in the red/NIR region of the spectrum provided many advantages. One advantage is that fluorescent dyes in this region can afford significant light penetration and elimination of light scattering, typically caused by endogenous chromophores found in the biological issues. For example, many endogenous chromophores such as nucleic acids, aromatic amino acids, oxy- and deoxy-hemoglobin and chemicals in fluorescene microscopy faced a phenomenon known as tissue autofluorescence. These chromophores usually absorb and emit at short wavelengths, in turn resulting in only minimal penetration depth (Figure 1.12). By introducing fluorophores that can absorb and emit at longer wavelengths, a majority of background

Figure 1.11: Several biological applications of molecular fluorescent probes.\textsuperscript{124} Reprint with permission from \cite{124} Copyright (2008) American Chemical Society.
noise can be eliminated, minimizing the autofluorescence which causes problems in the detection and quantification of biological signals. Another advantage is the absorption coefficient, which for NIR dyes is drastically lower than other shorter wavelength dyes. As a result, it helps deeper penetration in tissues up to several centimeters.

The low background noise and light scattering in the NIR region are significantly reduced based on the equation describing that the scattering intensity is proportional to the inverse fourth power of the wavelength. This also results in high signal to noise ratio (SNR) thus affording highly sensitivity in detection. In addition, long wavelength light also provides low interference in the Raman scattering and prevents degradation of the sample. There are numerous features for an ideal NIR absorber to be constructed as a fluorescent probe and indicator: photo- and chemo-stability, high molar absorption coefficients, high fluorescence quantum yields, high solubility in aqueous media, and resistance to self-quenching.

Figure 1.12: Mouse’s vital organs and BODIPY fluids autofluorescence with different excitation/emission filters. a) no filter; b) blue/green (460-500nm/505-560nm) filter; c) green/red (525-555nm/590-650 nm) filter; d) NIR (725-775nm/790-830nm) filter. GB = gall bladder, SI = small intestine, BL = bladder. Reprinted with permission from [125] Copyright (2002) Elsevier.
In addition to BODIPYs, other organic dyes such as porphyrin, phthalocyanine, cyanine, fluorescein, and squaraine with high photostability and long wavelength absorption and emission maxima have been extensively investigated and have made great contributions to the science field in the last several decades (Table 1.1). However, these fluorophore dyes have a few limitations, including low fluorescence quantum yields, poor photo- and chemo-stabilities, and also low solubility in aqueous media. To date, only indocyanine green (depited as IDG in Table 1.1) is FDA and EMA-approved as a NIR bioimaging dye to be used for biomedical purposes due to its nontoxic and minimal side effects, as an angiographic contrast agent. However, this dye has a low quantum yield, similar to its parent cyanine dye, and lacks functionalization for additional conjugation to biomolecules. On the other hand, one emerging promising NIR-fluorescent imaging dye is IR Dye®800CW (Table 1.1). This dye has an activated CO$_2$H group that has the ability to react with biomolecules. This dye is currently in pre-clinical trials.

While many other organic fluorophore dyes have shortcomings, BODIPY dyes process a number of interesting characteristics that make them suitable for applications as indicators, probe sensors, biolabels and stains. Thus, distinct features such as sharp, narrow absorption and emission spectra (for multicolor imaging), not prone to solvent polarity, high molar absorption coefficients, tunability, solubility, and stability make BODIPY the potential fluorophore.

Table 1.1: Commercially available NIR compounds for biomolecular conjugation with absorption and emission wavelength in the NIR region.

<table>
<thead>
<tr>
<th>Dye name (Manufacturer)</th>
<th>Chemical Structure</th>
<th>Absorption Max (nm)</th>
<th>Emission Max (nm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICG (Sigma Aldrich)</td>
<td><img src="image" alt="Chemical Structure" /></td>
<td>800</td>
<td>810</td>
</tr>
<tr>
<td>Dye name (Manufacturer)</td>
<td>Chemical Structure</td>
<td>Absorption Max (nm)</td>
<td>Emission Max (nm)</td>
</tr>
<tr>
<td>-------------------------</td>
<td>--------------------</td>
<td>---------------------</td>
<td>------------------</td>
</tr>
<tr>
<td>IRDye 800CW NHS Ester (LI-COR Biosciences)</td>
<td><img src="image" alt="Chemical Structure" /></td>
<td>778</td>
<td>794</td>
</tr>
<tr>
<td>Dye 783 NHS Ester (Dyomics GmbH.)</td>
<td><img src="image" alt="Chemical Structure" /></td>
<td>783</td>
<td>800</td>
</tr>
<tr>
<td>La Jolla Blue (Hyperion, Inc.)</td>
<td><img src="image" alt="Chemical Structure" /></td>
<td>680</td>
<td>700</td>
</tr>
<tr>
<td>BODIPY 630/650-X Succinimidy1 Ester (Life Technologies Inc.)</td>
<td><img src="image" alt="Chemical Structure" /></td>
<td>625</td>
<td>640</td>
</tr>
<tr>
<td>BODIPY 650/665-X Succinimidy1 Ester (Life Technologies, Inc.)</td>
<td><img src="image" alt="Chemical Structure" /></td>
<td>646</td>
<td>660</td>
</tr>
</tbody>
</table>

### 1.4.2 Cellular Stains

In the microbial world, cellular visualization is an important tool that can provide significant information in studying the physiological and pathological processes of organelles.
Cells that are inked with specific stains have the ability to permeate through cell membranes and allow visibility under the lens of a high powered microscope. Numerous BODIPYs conjugated to various biomolecules have been used for in vivo and in vitro visualization of intracellular processes. These are commercially available BODIPYs from Life Technologies, Inc, being used for imaging of the endoplasmic reticulum and Golgi apparatus (Table 1.1).

1.4.3 Environmental Indicators

In the last few years, there has been a wide range of development fluorescent chemosensors to use as probes for intracellular pH and metal ions probes (Figure 1.13). The design factors for selective and sensitive sensors are: i) fluorophore-spacer-chelator or ii) intrinsic fluorescent chelators. The two processes that contribute to the fluorophore-spacer-chelator are photoinduced electron transfer (PET) and photoinduced intramolecular charge transfer (ICT). The fluorescent probes are designed based on the idea that the fluorophore and chelator are separated by a short aliphatic spacer in order to diminish the electronic interaction between the fluorophore and the chelator. For example, a chelator on the meso-aryl substituent does not interact with the fluorophore due to its perpendicular orientation geometry. PET is the process where the electron-transfer from the electron-donor chelator in the HOMO to the lower HOMO level of the electron-acceptor fluorophore. ICT is the process of internal charge transfer (upon photo-excitation) between an electron-withdrawing group that is conjugated to an electron-donating group of the fluorophore.

1.4.4 Enzyme Substrates

There are strategies for investigating enzymatic activity in live cells. Numerous systems and conjugates have been developed consisting of a BODIPY fluorescent dye conjugated to fatty acids, phospholipids, receptor ligands, and cholesterol for investigating enzymatic activities in
fluorometric assays. The BODIPY fluorophore has been investigated in fluorometric assays to study proteases using a useful tool, fluorescence resonance energy transfer (FRET). When the fluorescent dye binds to protease, it results in a no fluorescence due to the “self-quenching” effect. In the presence of the protease enzyme, it hydrolyzes the conjugated fragments and the fluorescence is restored due to the disruption from intramolecular FRET quenching. The enzymatic cleavage is correlated to the simple on/off fluorescent phenomenon, which in turn results in providing the simple and continuum assays for various proteases.

\[ M = \text{Hg}^{2+}, \text{Ag}^+, \text{Cu}^{2+} \]

![Chemical structures](image)

Figure 1.13: Selected examples of meso-functionalized BODIPYs as pH and metal ions probes.

Jones and coworkers\(^{128}\) in 1997 reported two BODIPYs conjugated with casein to study protease enzymatic activity. Recently in 2009, Saba and coworkers\(^{129}\) demonstrated that BODIPY conjugated to a sphingosine-1-phosphate lyase (SPL) substrate is able to replace the standard radioactive SPL assays (Figure 1.14, 38 and 39). The BODIPY-labeled SPL provided an efficient way to measure SPL activity in cell tissues.
1.4.5 Biological Labels

Biological labeling has become one of the most common methods used for bioanalytical techniques, particularly in using fluorescent compounds with excellent electronic properties in the UV to the NIR regions. The search for new fluorescent dyes that are capable of easing the way to visualize the function of enzymes, proteins, DNA, and other biomolecules in intracellular processes is undergoing rapid development. BODIPY dyes are a promising target for fluorescent probes and labels due to their remarkable photophysical properties and low cellular toxicities. The small framework size and low molecular weight of BODIPY makes it a good candidate to increase cell permeability for intracellular studies without drastic changes in their biological functions. There are many reports indicating that BODIPYs are used as fluorescent labels to conjugate to specific biological components, such as polylipids, various amino acids, DNA and RNA, dextran, polystyrene micropheres, and proteins. In order to attach to a particular biomolecule, the BODIPY dyes must contain a reactive functionalized group: terminal carboxylic acid and sulfonic acids (Figure 1.15). One of the most useful applications of BODIPY dyes is in gel electrophoresis and DNA sequencing, in which BODIPY is conjugated to oligonucleotides and it displays a minimal effect on the DNA fragment mobility. BODIPY-based fluorescent compounds have found uses in HPLC and capillary electrophoresis, especially when it is bound to cysteine residues in proteins.

Figure 1.14: BODIPY-S1P 38 and NBD-S1P 39 containing sphingosine.\textsuperscript{129}
1.5 Research Outlook

There are numerous efforts on the synthesis and development of functionalized BODIPYs for various applications, as biological probes in the NIR region (>700 nm), and as radioactive agents for positron emission tomography (PET) or SPECT. Thus, there is still much work needed to be done on improving the electronic properties of BODIPY dyes. In addition, there are still new demands for versatile fluorophores with enhanced water solubility and high quantum yields for cellular studies.

![Soraphen A derivatives 40 and 41 conjugated to BODIPY](image)

Figure 1.15: Soraphen A derivatives 40 and 41 conjugated to BODIPY.\(^7^8\)

1.6 References


30


CHAPTER 2: SYNTHESIS, SPECTROSCOPIC STUDIES, AND COMPUTATIONAL MODELING OF 4,4-DIALKOXY-BODIPYS

2.1 Introduction

Boron-substituted BODIPYs have been explored in the last decade due to their ease of synthetic post-modification, increased aqueous hydrophilic solubility, decreased oxidation/reduction potentials, use as biological probes for bioimaging, and development as cassette devices with donor-acceptor systems.\textsuperscript{1-2} Even though replacements of the fluoride atoms with carbon or oxygen nucleophiles have shown no substantial changes on the absorption or emission properties, there are potential enhancements on the Stokes shift and fluorescence quantum yields. Development in boron functionalization has been slow compared to carbon modification of the dipyrromethene core. Nevertheless, nucleophilic substitution at the boron atom remains a tremendous synthetic challenge for further functionalization with various groups.

There are several methods for BODIPY boron-functionalization with oxygen nucleophiles: i) post-modification of F-BODIPYs and ii) complexation of dipyrromethenes with reactive boron compounds.\textsuperscript{3-4} Derivatization of B-F can be done in a variety of ways: elevated temperature\textsuperscript{5,6} with alkoxide or Lewis acid mediated\textsuperscript{7-16} with alcohols. For example, Nagano and coworkers\textsuperscript{5} demonstrated that refluxing a mixture of 8-phenyl-BODIPY with sodium methoxide in methanol for 14 hours can afford the mono- and di-methoxyl BODIPYs (up to 52% yield). Alternatively, BODIPYs can be heated in a microwave-assisted reactor with alkoxide.\textsuperscript{6} However, a milder method\textsuperscript{7} was developed via activating of B-F bonds with Lewis acid (aluminum trichloride) followed by addition of various alcohols. The Lewis acid was an essential part for cleavage of fluoride atoms, which led to nucleophilic attack of weak oxygen nucleophiles. Various alcohols

have been demonstrated to directly replace the fluorine atoms, including methanol, ethanol, benzyl alcohol, polyethylene glycol, and phenol. However, the yields for the corresponding 4,4-dialkoxy- and diaryloxy-BODIPYs are often low (ranging from 20% to quantitative) due to difficulty in removal of large excesses of alcohols. Using latter methodologies, antenna-containing BODIPY with donor-acceptor-acceptor triad components and BODIPY-oxazine dyads were developed.\textsuperscript{9-11} Furthermore, these mild conditions are being used extensively and found to be compatible with amine, ester, and aldehyde groups.\textsuperscript{12} In the last few years, several O-BODIPYs have been used in circularly polarized luminescence spectroscopy using the latter methodology.\textsuperscript{13-14}

Recently, Thompson and coworkers\textsuperscript{17} developed a milder strategy which involves a two step one-pot reaction using boron trichloride with F-BODIPYs to afford a reactive intermediate 4,4-dichloro-BODIPY, which readily undergoes reaction with alkoxides or alkyls to give the corresponding 4,4-dialkoxy- and dialkyl-BODIPYs in relatively high yields. Another mild method was reported for the synthesis of 4-monoalkoxy-BODIPYs in moderate yields (38-70%), which involves activation of the BODIPY using trimethylsilyltrifluoromethanesulfonate (TMSOTf) followed by addition of an alcohols.\textsuperscript{18} Similar methodology was used previously for boron functionalization in subphthalocyanines via a triflate-subphthalocyanine intermediate.\textsuperscript{19} There are several ways for complexation of dipyrromethenes with halogenated boron compounds.\textsuperscript{3-4,20} The usefulness of dipyrromethenes as a platform is that many 4,4-functionalized BODIPYs can be synthesized via a one-step reaction.

### 2.1.1 Radioactive 18-Fluoride Imaging

The use of radioactively labeled atoms (\textsuperscript{123}I, \textsuperscript{18}F, etc.) for nuclear imaging has become a promising tool for physicians to diagnose many diseased patients. The ability to produce images of particular parts in the body using a trace amount of radioactive nuclei is tremendously
advantageous in the biomedical field. Positron emission tomography (PET) and single photon emission computed tomography (SPECT) have been utilized in many bioimaging applications. The practical uses of PET include creating a three dimensional image upon radiation using the radioactive fluoride to allow mapping of uptake in vivo. For imaging of endogenous antibodies and polypeptides, SPECT is preferred over PET due to the slow kinetic measurements and relatively long isotope half-life. Many FDA-approved radiotracers have been used exclusively for clinical theranostic treatments. Moreover, iodinated compounds have emerged as potential radiotherapy candidates in PET and SPECT imaging for bioimaging applications.\textsuperscript{21-22} However, the use of \textsuperscript{[18}F]-radionabelling of BODIPYs as PET/fluorescence dual imaging probes has been extensively studied recently.\textsuperscript{23-28} Incorporation of 4-mono-radioactive fluorine onto the boron center of BODIPY can provide PET and fluorescence components for a faster and effective diagnosis in organic and aqueous environments.

### 2.1.2 Research Prospective

Although several boron functionalization methods have been developed, alternative functionalization strategies must be explored due to low yields and difficult purifications. This chapter aims to report further investigation of these boron-functionalization methodologies and extend them to the synthesis of 4,4-dialkoxy-BODIPYs. In addition, we also explored using Cu(I)-catalyzed alkyne-azide click conditions using 4,4-dipropargyloxy-BODIPY in order to produce the first boron-\textit{bis}(1,2,3)triazole-functionalized BODIPY. In our study, the structural, spectroscopic and fluorescence properties of all the synthesized BODIPYs were investigated and are compared using computational and experimental methods.
2.2 Results and Discussion

2.2.1 Syntheses

Three 8-aryl-1,3,5,7-tetramethyl-BODIPYs 1-3 were synthesized through a classical BODIPY synthetic routes (Scheme 2.1). The route was a 3-step-1-pot synthesis, which began with acid-catalyzed condensation\textsuperscript{29-30} of the commercially available 2,4-dimethylpyrrole with the corresponding aryl aldehydes in dichloromethane. An acid catalyst, boron trifluoride etherate (BF\textsubscript{3}•OEt\textsubscript{2}), was used in order make the carbonyl more electrophilic toward nucleophilic attack. After stirring the reaction mixture under inert argon at room temperature for 48 hours, 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) was used as the oxidant to oxidize the dipyrromethanes to dipyrromethenes. The dipyrromethenes were deprotonated under basic conditions with triethylamine (Et\textsubscript{3}N), followed by complexation with boron trifluoride etherate (BF\textsubscript{3}•OEt\textsubscript{2}) to give BODIPYs 1-3 in yields ranging from 6-26%. Electron-donating groups (3,4-dimethoxy BODIPY 2) and electron-withdrawing groups (4-methoxycarbonyl BODIPY 3) were introduced at the meso-phenyl positions to study the effect on the boron-substitution reaction.

\textbf{Scheme 2.1: Synthesis of BODIPY 1-3 from acid-catalyzed condensation between 2,4-dimethylpyrrole with aryl aldehydes.}

We first began our methodology investigation by employing conditions as previously described by Nagano and coworkers\textsuperscript{5} to synthesize 4,4-dimethoxy-BODIPY 1a. Method A is a one-step reaction between BODIPY 1 with 6 equiv. of sodium methoxide in methanol and the reaction mixture was refluxed for 12 hours to afford the corresponding 4,4-dimethoxy-BODIPY
1a in 66% yield (Scheme 2.2). In addition, TLC also indicated the 4-monoalkoxy-BODIPY intermediate under these conditions. Next, we investigated BODIPYs with electron-donating and electron-withdrawing groups on the 8-phenyl. When BODIPY 2, containing two electron-donating methoxy groups (positions 3 and 4 of the 8-phenyl group), was exposed to the above reaction conditions, the corresponding 4,4-dimethoxy-BODIPY 2a was afforded in a yield of 50%. On the other hand, BODIPY 3, containing an electron-withdrawing (4-methoxycarbonyl), produced the corresponding 4,4-dimethoxy-BODIPY 3a in poor yield of 4% although 53% of the starting material was recovered.

![Scheme 2.2: Synthesis of BODIPYS 1a-3a from Method A-C.](image)

DFT calculations at the B3LYP/6-31+G(d,p) level for evaluation of the atomic charges on BODIPYs 1-3 indicate that there are no significance differences between the charges on the 12-atom BODIPY core. This shows that the electron donating or withdrawing nature of the 8-aryl group does not greatly affect the dipyrromethene core. This could be explained by the loss of electronic communication between the meso-aryl and 1,7-dimethyl substituent on the BODIPY core (Figure 2.1) due to the large dihedral angles. With the aim to increase the yields of the substitution reaction in the presence of electron-withdrawing groups, such as in BODIPY 3, since
the methoxycarbonyl group can be used as a precursor to carboxyl-substituted BODIPYs for further derivatization, we decided to explore alternative methodologies using milder reaction conditions (at lower temperature and with milder nucleophiles).

Table 2.1: Methods A, B, and C for synthesis of 4,4-dimethoxy-BODIPYs 1a, 2a, and 3a with isolated yields.

<table>
<thead>
<tr>
<th>BODIPY</th>
<th>Method A</th>
<th>Method B</th>
<th>Method C</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a</td>
<td>66%</td>
<td>52%</td>
<td>98%</td>
</tr>
<tr>
<td>2a</td>
<td>50%</td>
<td>11%</td>
<td>8%</td>
</tr>
<tr>
<td>3a</td>
<td>4%</td>
<td>58%</td>
<td>70%</td>
</tr>
</tbody>
</table>

Our approach was to optimize the conditions as reported by Tahtaoui and coworkers in order to synthesize 4,4-dimethoxy-BODIPY 1a. Our preliminary investigation began with the absence of and changing Lewis acids as shown on Table 2.2. In the absence of a Lewis acid, the reaction did not proceed and resulted in re-isolation of the starting material BODIPY 1, which was in agreement with Tahtaoui and coworkers. This indicates that BODIPY 1 requires chelation of a Lewis acid in order to make the B-F bonds more labile toward nucleophilic substitution. Lewis acids such as Zn(OAc)$_2$, TiCl$_4$, SnCl$_2$, SnCl$_4$, and BCl$_3$ did not produce the desired 4,4-dimethoxy-BODIPY 1a. Also, the reaction with TiCl$_4$ led to decomposition of the starting material. Indeed, AlCl$_3$ as Lewis acid gave BODIPY 1a in an isolated 52% yield at reflux temperature after 15 min with excess amount of methanol (278 equiv), which is in agreement with previous reports (entry 6). However, the excess of alcohol were difficult to remove and the product was hard to purify.

At room temperature and with longer reaction time (12 h), the desired BODIPY 1a was obtained in 44% yield (entry 7). When reducing the amount of methanol equivalent from 278 to 5, BODIPY 1a was afforded in a lower yield of 19% (entry 8). These preliminary data show that
AlCl_3 and an excess of alcohol were necessary for the synthesis of 4,4-dimethoxy-BODIPY 1a in good yield.\textsuperscript{7}

Table 2.2: Preliminary studies for synthesis of 4,4-Dimethoxy-BODIPY 1a using methanol as nucleophile.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Lewis Acid</th>
<th>Temp</th>
<th>Product, Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>---</td>
<td>25 °C</td>
<td>1</td>
</tr>
<tr>
<td>2</td>
<td>Zn(OAc)_2</td>
<td>40 °C</td>
<td>1</td>
</tr>
<tr>
<td>3</td>
<td>TiCl_4</td>
<td>25 °C</td>
<td>decomp</td>
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<tr>
<td>4</td>
<td>SnCl_4</td>
<td>40 °C</td>
<td>1</td>
</tr>
<tr>
<td>5</td>
<td>SnCl_4</td>
<td>40 °C</td>
<td>1</td>
</tr>
<tr>
<td>6</td>
<td>AlCl_3</td>
<td>40 °C</td>
<td>1a, 52%</td>
</tr>
<tr>
<td>7</td>
<td>AlCl_3</td>
<td>25 °C</td>
<td>1a, 44%</td>
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<td>8\textsuperscript{a}</td>
<td>AlCl_3</td>
<td>40 °C</td>
<td>1a, 19%</td>
</tr>
<tr>
<td>9</td>
<td>BCl_3</td>
<td>25 °C</td>
<td>1</td>
</tr>
</tbody>
</table>

\textsuperscript{a}: 5.0 equiv of MeOH was used

To further explore the scope of our reaction, we also investigated variation of the solvents at room temperature (Table 2.3). Using acetonitrile, compound 1a was obtained in 16% yield, which is due to the possible competition reaction between the nitrile and methanol as nucleophiles toward the boron center. With tetrahydrofuran, the oxygen could possible poison the aluminum catalyst to give the starting material 1 before the addition of methanol. Similar to when using methanol, dipyrrromethene was the only product due to the possible competing reaction between
methanol and the Lewis acid. These results demonstrated that dichloromethane is the best solvent to use for method B.

Table 2.3: Synthesis of BODIPY 1a in various solvents using Method B at reflux temperature.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Product, Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>dichloromethane</td>
<td>1a, 44%</td>
</tr>
<tr>
<td>2</td>
<td>acetonitrile</td>
<td>1a, 16%</td>
</tr>
<tr>
<td>3</td>
<td>methanol</td>
<td>dipyrromethene</td>
</tr>
<tr>
<td>4</td>
<td>tetrahydrofuran</td>
<td>1</td>
</tr>
</tbody>
</table>

The next step was replacing methanol with a stronger nucleophile, sodium methoxide. As shown on Table 2.4, aluminum chloride as the Lewis acid gave the desired product 1a in 46% yield. However, these conditions were not reproducible (Table 2.4, entry 1). Similar to Table 2.1, varying the Lewis acids resulted in the recovery of starting material, except for boron trichloride.

Under these conditions (2 equiv. of AlCl₃, 278 equiv. of alcohol, reflux in dichloromethane for 15 min), BODIPYs 1a (52%), 2a (11%) and 3a (58%) were afforded in moderate yields (Method B, Scheme 2.2). Notably, BODIPY 3a was obtained in 58% yield, a remarkable increase in the yield obtained using method A. While method B gave the desired 4,4-dimethoxy-BODIPY in moderate yield, we further investigated the optimization of the conditions and developed new method C. This novel method consists of activating the BODIPY with TMSOTf at elevated temperature, followed by addition of alcohols (5.0 equiv.) and a non-nucleophilic base (DIPEA) at room temperature.
Table 2.4: Preliminary studies for synthesis of 4,4-Dimethoxy-BODIPY 1a using sodium methoxide as nucleophile.

![Chemical structure]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Lewis Acid</th>
<th>Temp</th>
<th>Product, Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>AlCl₃</td>
<td>50 °C</td>
<td>1a, 46%</td>
</tr>
<tr>
<td>2</td>
<td>ZnCl₂</td>
<td>50 °C</td>
<td>1</td>
</tr>
<tr>
<td>3</td>
<td>MgCl₂</td>
<td>50 °C</td>
<td>1</td>
</tr>
<tr>
<td>4</td>
<td>SnCl₄</td>
<td>50 °C</td>
<td>1</td>
</tr>
<tr>
<td>5</td>
<td>InCl₃</td>
<td>50 °C</td>
<td>1</td>
</tr>
<tr>
<td>6</td>
<td>FeCl₃</td>
<td>50 °C</td>
<td>1</td>
</tr>
<tr>
<td>7</td>
<td>BCl₃</td>
<td>25 °C</td>
<td>1a, 19%</td>
</tr>
</tbody>
</table>

Similar to method B, we also screened various solvents (toluene, dichloromethane, tetrahydrofuran, and chloroform) at room temperature to afford BODIPY 1a (Table 2.5). The desired BODIPY 1a yields were obtained at room temperature with toluene (50%), dichloromethane (25%), chloroform (29%), and tetrahydrofuran (0% and 100% of starting material was recovered). The conditions with dichloromethane also gave the starting material 1 (20%) and the mono-substituted (17%) product. Notably, toluene and dichloromethane gave the yields within 2 hours while chloroform required overnight. In addition, silver triflate (AgOTf) was used in place of TMSOTf and resulted in isolation of the starting material. These results indicated that the reaction yields were dependent on the solvent used and reaction temperature.
With Method C using toluene at elevated temperature, compound 1a was remarkably synthesized in high yield (98%). As expected, compound 3a was also isolated in high yield (70%) compared to method B (58%). However, compound 2a with an electron donating group at the meso-phenyl afforded a low yield (8%) with uncomplexed dipyromethene as a by-product. The three methodologies were used for synthesis of 4,4-dimethoxy-BODIPYs 1a-3a as summarized in Table 2.1 with yields ranging from 4% to 98%. Therefore, BODIPYs 1a and 3a were accessed in high yield using the newly developed method C, providing an efficient and convenient synthetic route for boron functionalization.

Table 2.5: Synthesis of 4,4-dimethoxy-BODIPY 1a in various solvents using Method C at room temperature.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Product, Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>dichloromethane</td>
<td>1a, 25%</td>
</tr>
<tr>
<td>2</td>
<td>toluene</td>
<td>1a, 50%</td>
</tr>
<tr>
<td>3</td>
<td>chloroform</td>
<td>1a, 29%</td>
</tr>
<tr>
<td>4</td>
<td>tetrahydrofuran</td>
<td>1</td>
</tr>
</tbody>
</table>

Since there is wide range of yields obtained for BODIPYs 1a-3a under the three methods, we suspected that the intermediates formed upon fluoride dissociation from boron under these reaction conditions can be investigated using computational modeling. All these reactions likely undergo the same boronium cation intermediate INT1 formation (Scheme 2.3) and $^{19}$F-NMR and X-ray crystallography have confirmed the existent of these cations. DFT modeling showed the
Scheme 2.3: Synthesis of BODIPYs 1a-e using Methods B and C via Boronium Intermediate \textbf{INT1}.

calculated Gibbs free energies for the formation of \textbf{INT1} from BODIPY 1 (Table 2.6). The intermediates were computationally modeled for method A (in methanol), method B (in dichloromethane), and method C (in toluene). Indeed, fluoride dissociation from BODIPY 1 in method A requires the least amount of energy (37 kcal/mol) in methanol, followed by 56 kcal/mol in dichloromethane, and the largest amount of energy (92 kcal/mol) in toluene. This tendency can be explained by the three solvents’ relative dielectric permittivities: methanol (\(\varepsilon = 32.6\)), dichloromethane (\(\varepsilon = 8.93\)), and toluene (\(\varepsilon = 2.37\)). From these values, the direct dissociation of fluoride ion from BODIPY 1 is likely to occur in method A, since the reaction barrier for the formation of \textbf{INT1} can be overcome by refluxing the mixture in methanol at 70-75 °C. This is unlikely to happen in method B since a larger amount of energy (56 kcal/mol) is required to overcome this barrier. However, computational calculations show that the addition of Lewis acid \(\text{AlCl}_3\), followed by fluoride dissociation to form the counter ion \(\text{AlCl}_3\text{F}^-\) significantly stabilizes the boronium cation \textbf{INT1}. Indeed, this is in agreement with the milder conditions required for method B. Furthermore, the calculations also suggest that the milder reaction can occur at a lower temperature. While performing the reaction entirely at room temperature, BODIPY 1a was afforded in lower yield (44 vs. 52%) after 12 hours.

For method C, the potential energy barrier of 25 kcal/mol for the fluoride abstraction with triflate anion to give trimethylsilyl fluoride can be easily overcome by refluxing in toluene at 110
°C. Indeed, NMR spectroscopy and X-ray crystallography have shown that such a boronium species bearing a triflate ligand exists.\textsuperscript{32} Moreover, our calculations for method A also show similar Gibbs free energies and stabilities for INT1 from all starting BODIPYs 1-3: for BODIPY 1 ($\Delta G = 37.4 \text{ kcal/mol}$), for BODIPY 2 ($\Delta G = 37.5 \text{ kcal/mol}$), and for BODIPY 3 ($\Delta G = 38.7 \text{ kcal/mol}$).

Table 2.6: Calculated $\Delta G$ energies for formation of INT1 through methods A, B, and C.

<table>
<thead>
<tr>
<th>Method</th>
<th>modeled solvent</th>
<th>Anion</th>
<th>$\Delta G$ (kcal/mol)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>CH$_3$OH</td>
<td>F-</td>
<td>37</td>
</tr>
<tr>
<td>B</td>
<td>CH$_2$Cl$_2$</td>
<td>F-</td>
<td>56</td>
</tr>
<tr>
<td>B</td>
<td>CH$_2$Cl$_2$</td>
<td>AlCl$_3$F-</td>
<td>-22</td>
</tr>
<tr>
<td>C</td>
<td>PhCH$_3$</td>
<td>F-</td>
<td>92</td>
</tr>
<tr>
<td>C</td>
<td>PhCH$_3$</td>
<td>OTf-</td>
<td>25</td>
</tr>
</tbody>
</table>

Various alcohols were investigated for the synthesis of new 4,4-diethoxy-BODIPYs 1a-e using the milder methods B and C, as shown in Scheme 2.3 with the isolated yields given in Table 2.7. In method B, all desired BODIPYs were obtained in moderate yields (21-64%) while method C was highly sensitive to the steric of the alcohol. This is likely due to the close distance of the triflate anion to the boron center.\textsuperscript{33} Indeed, no product was obtained for method C when isopropanol was used. It has shown previously that the use of tert-butanol/tert-butoxide has resulted in BODIPY deboronation.\textsuperscript{6} When a larger excess of ethanol was used for BODIPY 1b using method C, the yield could be increased to 37% and the mono-4-ethoxy-BODIPY was also
afforded in 20% yield. In addition, we also investigated the addition sequence of DIPEA. When we added the DIPEA before addition of alcohols, a 35% yield of BODIPY 1b resulted. Therefore, in order to obtain the highest yield of the desired 4,4-dialkoxy-BODIPYs, the starting BODIPY and various alcohol nucleophile with selected methods must be considered.

Table 2.7: Synthesis of BODIPYs 1a-e with isolated yields using Method B and C.

<table>
<thead>
<tr>
<th>BODIPY</th>
<th>R</th>
<th>Method B (%)</th>
<th>Method C (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a</td>
<td>Me</td>
<td>52</td>
<td>98</td>
</tr>
<tr>
<td>1b</td>
<td>Et</td>
<td>64</td>
<td>18</td>
</tr>
<tr>
<td>1c</td>
<td>iPr</td>
<td>26</td>
<td>0</td>
</tr>
<tr>
<td>1d</td>
<td>allyl</td>
<td>57</td>
<td>30</td>
</tr>
<tr>
<td>1e</td>
<td>propargyl</td>
<td>52</td>
<td>40</td>
</tr>
</tbody>
</table>

We also investigated the tolerance of 4,4-dipropargyloxy-BODIPY 1e toward further functionalization by using the Cu(I)-catalyzed Huisgen cycloaddition conditions as previously reported for the click reaction of alkyne-functionalized BODIPYs with azide containing carbohydrate and folate moieties (Scheme 2.4). As a result, the 4,4-bis(N-benzyl-1,2,3-triazole)-BODIPY 4 was obtained in 78% yield from BODIPY 1e. The click conditions consist of using \textit{in situ} generated copper(I) catalyst from copper(0) and copper (II) sulfate, in the presence of sodium ascorbate and benzyl azide in an aqueous water/THF mixture. To the best of our knowledge this is the first report demonstrated that post-modification of a BODIPY boron functionalized bearing an alkyne group can occur with the click cycloaddition reaction.
2.2.2 Structural Characterization

All BODIPYs were characterized by $^1$H-, $^{13}$C-, and $^{11}$B-NMR, HRMS, UV-Vis, fluorescence, and in the case of 1a-c, 1e, 3a and 4 also by X-ray crystallography. The disappearance of the triplet for the BF$_2$ (at ca. 0.6 ppm) and the appearance of the singlet attributed to B(OR)$_2$ (at ca. 2 ppm) in the $^{11}$B-NMR spectra clearly showed the formation of the targeted 4,4-dialkoxy-BODIPY. The $^1$H-NMR spectrum clearly indicated the formation of the 1,2,3-triazoles of BODIPY 4 with two singlets at 7.50 ppm (triazole) and 5.43 ppm (benzyl CH$_2$) protons, respectively.

Full structural confirmation of all compounds was obtained from the X-ray crystal structures. Crystals suitable for X-ray analysis were grown from slow evaporation of hexane diffused in dichloromethane (for 1a-c), and acetone (for 1e and 3a). As expected, the meso-aryl groups are oriented perpendicular to the dipyrrromethene core to avoid steric congestion caused by the 1,7-dimethyl groups. In addition, the alkoxy groups on the boron center adopt a nearly tetrahedral geometry. BODIPYs 1a-c, e, and 3a structures as shown in Figure 2.1, have at least approximate two-fold symmetry. BODIPY 1b has crystallographic C$_2$ symmetry, and BODIPY 1a has one molecule on a two-fold axis and another in a general position. The central six-membered C$_3$N$_2$B rings of all five compounds deviate little from planarity, with mean and maximum deviations of 0.021 and 0.057 Å respectively for 1a, 0.024 and 0.037 Å for 1b, 0.003 and 0.005 Å.
for 1c, 0.008 and 0.021 Å for 1e, 0.035 and 0.075 Å for 3a, and 0.014 and 0.032 Å for 4. In all cases, the phenyl plane forms a large dihedral angle with the best plane of the C₉N₂B BODIPY core; these dihedral angles are 84.2 and 83.8° (2 independent molecules) for 1a, 86.5° for 1b, 84.7° for 1c, 79.8 and 82.1° (2 independent molecules) for 1e, 84.0 and 84.6° (2 independent molecules) for 3a, and 78.9 and 79.1° (two independent molecules) for 4. The geometry of the boron atoms is tetrahedral, and 18 B-O bond distances over the six compounds have lengths in the range 1.420(4) – 1.444(5) Å, with an average value of 1.432 Å. These distances are in good agreement with those in the p-iodo-aryl analogue of BODIPY 1a, 1.420(4) and 1.437(3) Å. As in that compound, the conformations of the B-OR groups in all six compounds have the alpha C atoms of both alkyl groups folded symmetrically toward the BODIPY core.

In addition, the geometries of BODIPYs 1a-e and 4 were also investigated and confirmed computationally. The computational results show that the boron atom adopted a nearly tetrahedral geometry and the 8-aryl groups were oriented nearly perpendicular to the BODIPY plane, which is in agreement with the X-ray data. Surprisingly, there exist two conformers for all BODIPYs, as revealed by the computational optimization of the structures. As shown in Figure 2.2, the most stable conformer 1a is symmetric (the two B-OR groups symmetrically oriented on both sides of the BODIPY plane, see Figure 2.2a) and in the other conformer 1a’ the B(OR)₂ groups positioned sideways, as shown in Figure 2.2b.

The data given in Table 2.8 suggest that there are deviations from planarity (ranging between 15 and 17°) for the non-symmetric conformers of the BODIPYs and there no significant differences in the relative Gibbs free energies between the two conformers. At room temperature,
Figure 2.1: Molecular structures of BODIPYs 1a-c, e, 3a, and 4 from X-ray crystal analysis, with 50% probability ellipsoids. Only one of the independent molecules is shown for those structures with Z’ > 1.

The two conformers interconvert rapidly in THF solution since the Gibbs energy differences are very small. However, only the symmetric conformer is depicted in the crystal structures shown in Figure 2.1 while the unsymmetric BODIPY conformer with the boron lying out of the C₃N₂ plane for related BF₂ systems has previously been observed.
Figure 2.2: Molecular structures of (a) the symmetric conformer 1a and (b) the unsymmetric conformer 1a’ from B3LYP/6-31+G(d,p) optimization.

Table 2.8: Calculated relative Gibbs free energies, HOMO and LUMO energies, and HOMO-LUMO gap in THF for the symmetric (1a-e, 4) and unsymmetric (1a’-e’, 4’) BODIPY conformers.

<table>
<thead>
<tr>
<th>BODIPY</th>
<th>HOMO (a.u.)</th>
<th>LUMO (a.u.)</th>
<th>Gap (eV)</th>
<th>Δ G (kcal/mol)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a</td>
<td>-0.20599</td>
<td>-0.09520</td>
<td>3.01</td>
<td>0</td>
</tr>
<tr>
<td>1a’</td>
<td>-0.2044</td>
<td>-0.09280</td>
<td>3.04</td>
<td>6.76</td>
</tr>
<tr>
<td>1b</td>
<td>-0.20542</td>
<td>-0.09440</td>
<td>3.02</td>
<td>0</td>
</tr>
<tr>
<td>1b’</td>
<td>-0.20393</td>
<td>-0.09245</td>
<td>3.03</td>
<td>8.39</td>
</tr>
<tr>
<td>1c</td>
<td>-0.20548</td>
<td>-0.09436</td>
<td>3.02</td>
<td>0</td>
</tr>
<tr>
<td>1c’</td>
<td>-0.20315</td>
<td>-0.09117</td>
<td>3.05</td>
<td>9.92</td>
</tr>
<tr>
<td>1d</td>
<td>-0.20694</td>
<td>-0.09608</td>
<td>3.02</td>
<td>0</td>
</tr>
<tr>
<td>1d’</td>
<td>-0.20143</td>
<td>-0.09077</td>
<td>3.01</td>
<td>7.82</td>
</tr>
<tr>
<td>1e</td>
<td>-0.21009</td>
<td>-0.09941</td>
<td>3.01</td>
<td>0</td>
</tr>
<tr>
<td>1e’</td>
<td>-0.20776</td>
<td>-0.09635</td>
<td>3.03</td>
<td>7.45</td>
</tr>
<tr>
<td>4</td>
<td>-0.20686</td>
<td>-0.09602</td>
<td>3.02</td>
<td>0</td>
</tr>
<tr>
<td>4’</td>
<td>-0.20778</td>
<td>-0.09638</td>
<td>3.03</td>
<td>6.55</td>
</tr>
</tbody>
</table>
2.2.3 Spectroscopic Study

The spectroscopic properties of BODIPYs 1-1e, 2-2a, 3-3a, and 4 were investigated in tetrahydrofuran and toluene and the results are shown in Table 2.9. All BODIPYs showed absorption bands between 501 and 506 nm and emission bands between 505 and 517 nm in THF and toluene with strong absorption bands (log $\varepsilon = 4.4$-5.7). Indeed, previous studies have showed that replacement of fluorides of BODIPY dyes with alkoxy groups afford only small changes in the absorption and emission wavelengths, which is in agreement with these results.\textsuperscript{7-8,12} Moreover, the bis(1,2,3-triazole)-BODIPY 4 in THF and toluene indicated a slight blue-shifted absorption ($\lambda_{\text{max}}$ ca. 495 nm) and thus the largest Stokes shift. The observed experimental data are in agreement with the computational modeling data (Table 2.8), showing similar HOMO-LUMO gaps for BODIPYs 1a-e and 4. Interestingly, it is impossible to distinguish spectroscopically between the two conformers since the HOMO-LUMO gaps are very similar as shown in Figure 2.2.

In both solvents, the 4,4-dimethoxy-BODIPY derivatives 1a, 2a and 3a bearing flexible methoxy groups show decreased fluorescence quantum yields due to the increased rotational energy lost in non-radiative decay to the ground state. BODIPY derivative 1b (in THF) and all 4,4-alkoxy-BODIPYs (in toluene) demonstrated this trend in decreased fluorescence quantum yields. Interestingly, BODIPYs 1c and 1e bearing the isopropoxy and progargyloxy groups showed significant enhancements in fluorescence quantum yield in THF. This result is in agreement with previous reports showing BODIPY derivatives bearing isopropoxy and benzyloxy groups also have increased fluorescence quantum yields compared to its $F$-BODIPY precursor.\textsuperscript{7} In addition, the bis(1,2,3-triazole)-BODIPY 4 also showed enhancement of the fluorescence quantum yield in THF, but not in toluene. Furthermore, bis(1,2,3-triazole)-BODIPY 4 has a larger Stokes shift in
both solvents. These results conclude that substitution at the boron center with alkoxy groups is likely to decrease the quantum yields in toluene, but in a more polar solvent such as THF, certain BODIPYs have shown enhancement of the quantum yields.

Table 2.9: Absorption and emission spectral properties of BODIPYs 1-1e, 2-2a, 3-3a, and 4 in THF and PhMe (in parentheses) at room temperature.

<table>
<thead>
<tr>
<th>BODIPY</th>
<th>Absorption ( \lambda_{\text{max}} / \text{nm} )</th>
<th>Emission ( \lambda_{\text{max}} / \text{nm} )</th>
<th>( \log \varepsilon (\text{M}^{-1} \cdot \text{cm}^{-1}) )</th>
<th>( \Phi_f )</th>
<th>Stokes’ shift (nm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>501 (504)</td>
<td>505 (511)</td>
<td>4.96 (5.33)</td>
<td>0.56 (0.96)</td>
<td>4 (7)</td>
</tr>
<tr>
<td>1a</td>
<td>502 (504)</td>
<td>507 (512)</td>
<td>4.86 (5.38)</td>
<td>0.44 (0.73)</td>
<td>5 (8)</td>
</tr>
<tr>
<td>1b</td>
<td>502 (504)</td>
<td>507 (512)</td>
<td>4.54 (5.24)</td>
<td>0.46 (0.70)</td>
<td>5 (8)</td>
</tr>
<tr>
<td>1c</td>
<td>501 (504)</td>
<td>505 (509)</td>
<td>4.70 (5.48)</td>
<td>0.63 (0.70)</td>
<td>4 (5)</td>
</tr>
<tr>
<td>1d</td>
<td>503 (505)</td>
<td>507 (511)</td>
<td>4.66 (5.47)</td>
<td>0.56 (0.57)</td>
<td>4 (6)</td>
</tr>
<tr>
<td>1e</td>
<td>504 (506)</td>
<td>508 (513)</td>
<td>4.74 (5.04)</td>
<td>0.62 (0.82)</td>
<td>4 (7)</td>
</tr>
<tr>
<td>2</td>
<td>501 (505)</td>
<td>505 (509)</td>
<td>5.00 (5.66)</td>
<td>0.93 (0.87)</td>
<td>4 (4)</td>
</tr>
<tr>
<td>2a</td>
<td>503 (505)</td>
<td>507 (512)</td>
<td>4.38 (5.06)</td>
<td>0.42 (0.57)</td>
<td>4 (7)</td>
</tr>
<tr>
<td>3</td>
<td>503 (506)</td>
<td>508 (515)</td>
<td>4.42 (5.62)</td>
<td>0.43 (0.51)</td>
<td>5 (9)</td>
</tr>
<tr>
<td>3a</td>
<td>504 (506)</td>
<td>510 (517)</td>
<td>4.73 (5.48)</td>
<td>0.31 (0.34)</td>
<td>6 (11)</td>
</tr>
<tr>
<td>4</td>
<td>494 (496)</td>
<td>511 (512)</td>
<td>4.80 (4.94)</td>
<td>0.72 (0.56)</td>
<td>17 (16)</td>
</tr>
</tbody>
</table>

\( \varepsilon \) = extinction coefficient; \( \Phi_f \) = fluorescence quantum yield

2.3 Conclusions

In summary, we have investigated three different methods for the synthesis of 4,4-dimethoxy-BODIPYs containing electron-withdrawing and electron-donating meso-aryl groups. Method A consists of heating NaOMe in refluxing methanol at 80 °C for 12 hours, and gave
BODIPY 2a (8-(3,4-dimethoxyphenyl)) with the highest yield of 50%. Method B involves treating BODIPYs with AlCl$_3$ in refluxing dichloromethane, followed by large excess of alcohol, and afforded the desired 4,4-dialkoxy-BODIPYs 1a-f in moderate yields ranging from 26% to 64%.

On the other hand, method C was the most effective way to synthesize BODIPYs 1a and 3a in 98 and 70% yields, respectively. Method C employs TMSOTf in refluxing toluene, followed by addition of 5 equiv. of methanol and DIPEA. However, methanol was best used in method C since all other alcohols as nucleophiles gave lower yields of the targeted 4,4-disubstituted BODIPYs. The 4,4-progargyloxy-BODIPY 1e was subjected under the Cu(I)-catalyzed Huisgen cycloaddition reaction conditions and produced the corresponding bis-(1,2,3-triazole)-BODIPY 4.

These 4,4-dialkoxy-BODIPYs showed minor changes in absorption and emission spectra in THF and toluene. However, BODIPY 4 with two large $N$-benzyl-(1,2,3-triazole) groups on the boron center resulted blue-shifted absorption maxima in both solvents (THF and toluene). All 4,4-
dialkoxy-BODIPYs 1a-e have shown a decrease in fluorescence quantum yields compared to BODIPY 1 likely due to the higher rotational freedom of the alkoxy groups, therefore increasing the amount of energy lost to non-radiative decay to the ground state. In contrast, BODIPYs 1c,e and 4 showed enhancements in the fluorescence quantum yields in THF. Furthermore, BODIPY 4 displayed the largest Stokes shifts in both solvents.

2.4 Experimental

2.4.1 General Information

All the reagents and solvents were purchased from Sigma-Aldrich and were used without further purification. All reactions were carried out with oven-dried glassware under a dry argon atmosphere. All the reactions were monitored using Sorbent Technologies 0.2 mm silica gel TLC plates with UV-254 nm indicator. Flash column chromatography was performed using Sorbent Technologies 60 Å silica gel (230-400 mesh). Prep-TLC 60 Å silica gel 20 x 20 cm (210-270 μm) was used. All 1H-, 13C-, 11B-NMR spectra were collected on a Bruker AV-400 spectrometer in deuterated chloroform. The CDCl3 chemical shifts (δ) are reported in ppm using as reference 7.27 for proton and 77.16 for carbon and BF3•OEt2 was used as reference (0.00 δ) for boron NMR. Coupling constants are reported in Hertz (Hz). All the mass spectra were collected using a Agilent 6210 ESI-TOF mass spectrometer. All melting points were recorded using a MEL-TEMP electrothermal instrument.

2.4.2 Syntheses

General procedure for synthesis of BODIPYs 1-3.29-30,37-38 Aryl aldehyde (9.81 mmol) was suspended in anhydrous CH2Cl2 (300 mL). 2,4-Dimethylpyrrole (2.12 mL, 20.6 mmol) was added, followed by 6 drops of BF3•OEt2 to the reaction mixture. After stirring for 48 h, TLC indicated no more aryl aldehyde in the reaction mixture, and DDQ (1.113 g, 4.91 mmol) in CH2Cl2 was then
added. After 1.5 h stirring at room temperature, NEt₃ (10.3 mL, 73.58 mmol) was added and after another 1 h BF₃·OEt₂ (12.1 mL, 98.1 mmol) was added. The final mixture was stirred at room temperature for 6 h and then poured into water (50 mL). The organic layer was washed with water (2 x 50 mL). The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The product was purified by silica gel flash column chromatography using mixtures of petroleum ether and dichloromethane for elution.

4,4-Difluoro-8-phenyl-1,3,5,7-tetramethyl-BODIPY (1). Obtained as a green/orange solid (20% yield, 650 mg), mp: 168-169 °C; ¹H NMR (CDCl₃, 400 MHz) δ 7.47-7.26 (m, 5H), 5.98 (s, 2H), 2.56 (s, 6H), 1.38 (s, 6H); ¹³C NMR (CDCl₃, 100 MHz) δ 155.57, 143.29, 141.87, 135.14, 131.57, 129.26, 129.26, 128.08, 121.34, 14.71, 14.46; ¹¹B NMR (CDCl₃, 128 MHz) δ 0.65 (t, J = 33.4 Hz); HRMS (ESI-TOF) m/z 324.1718 [M + H]+ calculated for C₁₉H₂₀BF₂N₂: 324.1728. These data are in agreement with those previously reported.²⁹-³⁰

4,4-Difluoro-8-(3,4-dimethoxyphenyl)-1,3,5,7-tetramethyl-BODIPY (2). Obtained as a red solid (6% yield, 229 mg), mp: 182-183 °C; ¹H NMR (CDCl₃, 400 MHz) δ 6.97 (d, J = 8.1 Hz, 1H), 6.84 (d, J = 8.1 Hz, 1H), 5.60 (s, 2H), 3.96 (s, 3H), 3.86 (s, 3H), 2.56 (s, 6H), 1.49 (s, 6H); ¹³C NMR (CDCl₃, 100 MHz) δ 155.35, 149.80, 149.53, 143.14, 141.59, 131.71, 127.09, 121.12, 120.44, 111.57, 111.10, 56.10, 55.88, 14.53, 14.42; ¹¹B NMR (CDCl₃, 128 MHz) δ 0.62 (t, J = 33.0 Hz); HRMS (ESI-TOF) m/z 384.1930 [M + H]+ calculated for C₂₁H₂₄BF₂N₂O₂: 384.1939. These data are in agreement with those previously reported.²⁹,³⁷
4,4-Difluoro-8-(4-methoxycarbonylphenyl)-1,3,5,7-tetramethyl-BODIPY (3). Obtained as a bright red solid (26% yield, 483 mg) mp: 181-183 °C; $^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ 8.19 (d, $J$ = 8.5 Hz, 2H), $\delta$ 7.42 (d, $J$ = 8.1 Hz, 2H), 5.99 (s, 2H), 3.98 (s, 3H), 2.57 (s, 6H), 1.37 (s, 6H); $^{13}$C NMR (CDCl$_3$, 100 MHz) $\delta$ 166.58, 156.10, 143.01, 140.35, 139.94, 131.04, 130.94, 130.48, 128.50, 121.62, 52.50, 14.71, 14.61; $^{11}$B NMR (CDCl$_3$, 128 MHz) $\delta$ 0.61 (t, $J$ = 32.8 Hz); HRMS (ESI-TOF) $m/z$ 382.1773 [M + H]$^+$ calculated for C$_{21}$H$_{22}$BF$_2$N$_2$O$_2$: 382.1752. These data are in agreement with those previously reported.$^{29,38}$

General procedure for synthesis of O-BODIPYs using method A. In an oven-dried flask, BODIPY (20.0 mg, 0.062 mmol) and NaOMe (21.0 mg, 0.389 mmol) were dissolved in anhydrous methanol (2 mL). The mixture was refluxed for 12 h and then cooled down to room temperature. The reaction mixture was poured into ice water (5.0 mL), extracted with CH$_2$Cl$_2$ (3 x 5.0 mL), washed with brine (1 x 5.0 mL), and dried over anhydrous Na$_2$SO$_4$. The crude product was concentrated under reduced pressure and the resulting residue was purified by TLC, using ethyl acetate for elution.

General procedure for synthesis of O-BODIPYs using method B. In an oven-dried flask, BODIPY (20.0 mg, 0.062 mmol) and AlCl$_3$ (16.4 mg, 0.123 mmol) were dissolved in anhydrous CH$_2$Cl$_2$ (5 mL). The mixture was refluxed for 15 min before alcohol (17.15 mmol, 278.0 equiv) was added. The final reaction mixture was refluxed for 15 min. The mixture was allowed to cool down to room temperature and then concentrated under reduced pressure. The resulting residue was purified by TLC, using the eluents indicated below.
General procedure for synthesis of O-BODIPYs using method C. In an oven-dried flask, BODIPY (20 mg, 0.06 mmol) and TMSOTf (28.0 µL, 0.154 mmol) were dissolved in anhydrous toluene (5 mL) and the mixture was refluxed for 30 min. The solution was allowed to cool down to room temperature and alcohol (0.308 mmol, 5.0 equiv) was added, followed by DIPEA (27.0 µL, 0.154 mmol, 2.5 equiv.). After 1 h stirring at room temperature, the crude product was concentrated under reduced pressure and purified by TLC, using the eluents indicated below.

4,4-Dimethoxy-8-phenyl-1,3,5,7-tetramethyl-BODIPY (1a). This BODIPY was produced in 66% yield by method A, 58% by method B and 98% by method C. The crude product was purified by TLC (eluent EtOAc) to give an orange solid that was recrystallized from 1:1 hexane/dichloromethane. Mp: 125-130 °C; \(^1\)H NMR (CDCl\(_3\), 400 MHz) \(\delta\) 7.50-7.30 (m, 5H), 5.97 (s, 2H), 2.97 (s, 6H), 2.54 (s, 6H), 1.39 (s, 6H); \(^{13}\)C NMR (CDCl\(_3\), 100 MHz) \(\delta\) 155.77, 141.71, 141.38, 135.81, 133.01, 129.10, 128.82, 128.35, 121.05, 49.24, 14.70, 14.58; \(^{11}\)B NMR (CDCl\(_3\), 128 MHz) \(\delta\) 2.52 (s); HRMS (ESI-TOF) m/z 370.1938 [M + Na]\(^+\) calculated for C\(_{21}\)H\(_{25}\)BN\(_2\)NaO\(_2\): 370.1923. These data are in agreement with literature.\(^5\)

4,4-Dimethoxy-8-(3,4-dimethoxyphenyl)-1,3,5,7-tetramethyl-BODIPY (2a). This BODIPY was produced in 50% yield by method A, 11% by method B and 8% by method C. The crude product was purified by TLC (eluent 50:50 hexane/EtOAc) to afford a dark orange/red solid, that was recrystallized from acetone. Mp: 100-105 °C (decomposes); \(^1\)H NMR (CDCl\(_3\), 400 MHz) \(\delta\) 6.97 (d, \(J = 8.1\) Hz, 1H), 6.84 (d, \(J = 8.1\) Hz, 1H), 6.78 (s, 1H), 5.98 (s, 2H), 3.96 (s, 3H), 3.89 (s, 3H), 2.97 (d, \(J = 12.5\) Hz, 6H), 2.54 (s, 6H), 1.49 (s, 6H); \(^{13}\)C NMR (CDCl\(_3\), 100 MHz) \(\delta\) 155.79, 149.85, 149.53, 141.54, 141.37, 133.30, 128.02, 120.96, 120.86, 111.58, 111.53, 56.31,
56.06, 49.33, 49.26, 14.72; $^{11}$B NMR (CDCl$_3$, 128 MHz) δ 2.52 (s); HRMS (ESI-TOF) m/z 430.2149 [M + Na]$^+$ calculated for C$_{23}$H$_{29}$BN$_2$NaO$_4$: 430.2136.

4,4-Dimethoxy-8-(4-methoxycarbonylphenyl)-1,3,5,7-tetramethyl-BODIPY (3a). This BODIPY was produced in 4% yield by method A, 58% by method B and 70% by method C. The crude product was purified by TLC (eluent EtOAc) to afford an orange solid that was recrystallized from acetone. Mp: 100-105 °C (decomposed). $^1$H NMR (CDCl$_3$, 400 MHz) δ 8.19 (d, $J$ = 8.5 Hz, 2H), δ 7.42 (d, $J$ = 8.1 Hz, 2H), 5.99 (s, 2H), 3.98 (s, 3H), 2.97 (s, 6H), 2.57 (s, 6H), 1.37 (s, 6H); $^{13}$C NMR (CDCl$_3$, 100 MHz) δ 166.70, 156.34, 141.17, 140.70, 140.21, 132.48, 130.72, 130.37, 128.79, 121.40, 52.50, 49.24, 14.76, 14.73; $^{11}$B NMR (CDCl$_3$, 128 MHz) δ 2.51 (s); HRMS (ESI-TOF) m/z 428.1992 [M + Na]$^+$ calculated for C$_{23}$H$_{27}$BN$_2$NaO$_4$: 428.1981.

4,4-Diethoxy-8-phenyl-1,3,5,7-tetramethyl-BODIPY (1b). This BODIPY was produced in 64% yield by method B and 37% by method C. The crude product was purified via TLC (eluent 80:20 hexane/EtOAc) to give an orange solid, that was recrystallized from 1:1 hexane/dichloromethane. Mp: 140-145 °C; $^1$H NMR (CDCl$_3$, 400 MHz) δ 7.48-7.29 (m, 5H), 5.95 (s, 2H), 3.07 (q, $J$ = 7.0 Hz, 4H), 2.58 (s, 6H), 1.38 (s, 6H), 1.07 (t, $J$ = 7.0 Hz, 6H); $^{13}$C NMR (CDCl$_3$, 100 MHz) δ 155.87, 141.61, 141.25, 135.85, 132.84, 129.09, 128.80, 128.37, 121.00, 56.64, 17.83, 14.94, 14.59; $^{11}$B NMR (CDCl$_3$, 128 MHz) δ 1.82 (s); HRMS (ESI-TOF) m/z 398.2251 [M + Na]$^+$ calculated for C$_{23}$H$_{27}$BN$_2$NaO$_2$: 398.2264.

4,4-Diisopropoxy-8-phenyl-1,3,5,7-tetramethyl-BODIPY (1c). This BODIPY was produced in 26% yield by method B and could not be obtained by method C. The crude product
was purified via TLC (eluent 80:20 hexane/EtOAc) to give an orange solid, that was recrystallized from 1:1 hexane/dichloromethane. Mp: 140-145 °C; ¹H NMR (CDCl₃, 400 MHz) δ 7.49-7.30 (m, 5H), 5.96 (s, 2H), 3.40-3.34 (septuplet, J = 6.24 Hz, 2H), 2.61 (s, 6H), 1.39 (s, 6H), 0.89 (d, J = 6.08 Hz, 12H); ¹³C NMR (CDCl₃, 100 MHz) δ 156.26, 141.50, 141.42, 135.96, 132.28, 129.06, 128.78, 128.46, 121.16, 63.01, 24.93, 15.76, 14.65; ¹¹B NMR (CDCl₃, 128 MHz) δ 1.30 (s); HRMS (ESI-TOF) m/z 426.2654 [M + Na]⁺ calculated for C₂₅H₃₃BN₂NaO₂: 426.2575.

4,4-Diallyloxy-8-phenyl-1,3,5,7-tetramethyl-BODIPY (1d). This BODIPY was produced in 57% yield by method B and 30% by method C. The crude product was purified by TLC (eluent 80:20 hexane/EtOAc) to give an orange solid that was recrystallized from 1:1 hexane/dichloromethane. Mp: 70-73 °C; ¹H NMR (CDCl₃, 400 MHz) δ 7.52-7.29 (m, 5H), 5.95 (s, 2H), 5.92-5.82 (m, 2H), 5.15 (d, J = 1.84 Hz, 1H), 5.11 (d, J = 1.88 Hz, 1H), 4.92 (d, 1H), 4.89 (d, 1H), 3.63 (d, J = 5.24 Hz, 4H), 2.56 (s, 6H), 1.38 (s, 6H); ¹³C NMR (CDCl₃, 100 MHz) δ 156.06, 141.53, 138.70, 135.77, 132.78, 129.13, 128.85, 128.34, 128.23, 121.18, 113.42, 63.41, 15.03, 14.59; ¹¹B NMR (CDCl₃, 128 MHz) δ 2.01 (s); HRMS (ESI-TOF) m/z 422.2251 [M + Na]⁺ calculated for C₂₅H₂₉BN₂NaO₂: 422.2254.

4,4-(Diprop-2-yn-1-yloxy)-8-phenyl-1,3,5,7-tetramethyl-BODIPY (1e). This BODIPY was produced in 52% yield by method B and 40% by method C. The crude product was purified via TLC (eluent 80:20 hexane/EtOAc) to give an orange solid, that was recrystallized from 1:1 hexane/dichloromethane. Mp: 70-73 °C; ¹H NMR (CDCl₃, 400 MHz) δ 7.49-7.27 (m, 5H), 5.97 (s, 2H), 3.86 (s, 4H), 2.61 (s, 6H), 1.52 (s, 2H), 1.40 (s, 6H); ¹³C NMR (CDCl₃, 100 MHz) δ 156.62, 142.22, 141.42, 135.58, 132.79, 129.16, 128.92, 128.26, 121.52, 83.16, 70.83, 49.96,
15.19, 14.58; \(^{11}\)B NMR (CDCl\(_3\), 128 MHz) \(\delta\) 1.78 (s); HRMS (ESI-TOF) \(m/z\) 418.1938 [M + Na]\(^+\) calculated for C\(_{25}\)H\(_{25}\)BN\(_2\)NaO\(_2\): 418.1934.

4,4’-(Di-N-Benzyl,-1,2,3, triazoloxy)-8-phenyl-1,3,5,7-tetramethyl-BODIPY (4). 4,4-Dipropargyloxy-BODIPY 1e (15.7 mg, 0.040 mmol, 1.0 equiv.) and Cu(0) (10.1 mg, 0.158 mmol, 4.0 equiv.) were dissolved in a mixture of THF/water (8 mL, 3:1) under inert gas atmosphere. Benzyl azide (0.074 mL, 0.594 mmol, 5.0 equiv.) was added dropwise to the reaction mixture. A solution of CuSO\(_4\)·5H\(_2\)O (7.4 mg, 0.030 mmol, 0.75 equiv.) and sodium ascorbate (15.7 mg, 0.079 mmol, 2.0 equiv.) in THF/water (8 mL, 3:1) was added (after sonication for 30 min) and the reaction mixture was heated for 1.5 h at 70 °C. Once TLC indicated reaction completion the mixture was cooled to room temperature and partitioned between ethyl acetate (30 mL) and water (30 mL). The combined organic layers were dried over Na\(_2\)SO\(_4\) and then concentrated under reduced pressure. The crude product was purified via prep-TLC eluted with 20:80 hexane/EtOAc and recrystallized from 3:1 hexane/dichloromethane to afford the bis(1,2,3-triazole)-BODIPY 4 as a dark orange solid (20.4 mg, 78% yield). \(^1\)H NMR (CDCl\(_3\), 400 MHz) \(\delta\) 7.50 (s, 2H), 7.36-7.27 (m, 15H), 5.84 (s, 2H), 5.43 (s, 4H), 4.28 (s, 4H), 2.40 (s, 6H), 1.36 (s, 6H); \(^{13}\)C NMR (CDCl\(_3\), 100 MHz) \(\delta\) 155.63, 149.42, 142.17, 135.48, 134.93, 129.21, 129.15, 128.75, 128.35, 128.30, 121.68, 121.48, 56.80, 54.15, 31.06, 29.84, 29.41, 14.96, 14.57; \(^{11}\)B NMR (CDCl\(_3\), 128 MHz) \(\delta\) 2.06 (s); HRMS (ESI-TOF) \(m/z\) 684.3218 [M + Na]\(^+\) calculated for C\(_{39}\)H\(_{39}\)BN\(_8\)NaO\(_2\): 684.3229.

2.4.3 X-ray Determined Molecular Structures

Crystal structures were determined using low-temperature data from a Bruker Kappa APEX-II DUO diffractometer with either MoK\(_{\alpha}\) or CuK\(_{\alpha}\) radiation. For all structures, H atoms
were located from difference maps but constrained in calculated positions during refinement. For 
1a, \(Z' = 3/2\), for 1b, \(Z' = 1/2\), and for 1e, 3a and 4, \(Z' = 2\). 3a was the hemihydrate and a 
nonmerohedral twin, and 4 was also a nonmerohedral twin.

Crystal data 1a: \(\text{C}_{21}\text{H}_{25}\text{BN}_2\text{O}_2\), \(M = 348.24\), monoclinic, \(a = 20.2592(14)\), \(b = 11.2886(8)\), 
\(c = 12.7820(8) \, \text{Å}, \beta = 93.968(3)^\circ, U = 2916.2(3) \, \text{Å}^3, T = 100 \, \text{K}, \) space group \(P2/c\), \(Z = 6\), \(D_c = 
1.190 \, \text{g cm}^{-3}, \mu(\text{Cu K}\alpha) = 0.597 \, \text{mm}^{-1}, 24457 \) reflections measured, \(\theta_{\text{max}} = 68.8^\circ\), 5251 unique \( (R_{\text{int}} = 0.032). \) The final \(R = 0.040 \) \((4321 \, I > 2\sigma(I) \) data), \(wR(F^2) = 0.105 \) \( \) (all \( \) data), CCDC 1035578.

Crystal data 1b: \(\text{C}_{23}\text{H}_{29}\text{BN}_2\text{O}_2\), \(M = 376.29\), monoclinic, \(a = 9.1588(4)\), \(b = 11.4850(7)\), 
\(c = 10.1066(4) \, \text{Å}, \beta = 96.860(2)^\circ, U = 1055.49(9) \, \text{Å}^3, T = 100 \, \text{K}, \) space group \(P2/n\), \(Z = 2\), \(D_c = 
1.184 \, \text{g cm}^{-3}, \mu(\text{Mo K}\alpha) = 0.075 \, \text{mm}^{-1}, 33635 \) reflections measured, \(\theta_{\text{max}} = 29.4^\circ\), 3096 unique \( (R_{\text{int}} = 0.045). \) The final \(R = 0.043 \) \((2411 \, I > 2\sigma(I) \) data), \(wR(F^2) = 0.119 \) \( \) (all \( \) data), CCDC 1035579.

Crystal data 1c: \(\text{C}_{25}\text{H}_{33}\text{BN}_2\text{O}_2\), \(M = 404.34\), monoclinic, \(a = 9.0299(11)\), \(b = 16.252(2)\), 
\(c = 16.2554(19) \, \text{Å}, \beta = 102.241(7)^\circ, U = 2331.3(5) \, \text{Å}^3, T = 100 \, \text{K}, \) space group \(P2_1/c\), \(Z = 4\), \(D_c = 
1.152 \, \text{g cm}^{-3}, \mu(\text{Mo K}\alpha) = 0.072 \, \text{mm}^{-1}, 12118 \) reflections measured, \(\theta_{\text{max}} = 25.9^\circ\), 4417 unique \( (R_{\text{int}} = 0.091). \) The final \(R = 0.058 \) \((2457 \, I > 2\sigma(I) \) data), \(wR(F^2) = 0.134 \) \( \) (all \( \) data), CCDC 1035580.

Crystal data 1e: \(\text{C}_{25}\text{H}_{25}\text{BN}_2\text{O}_2\), \(M = 396.28\), monoclinic, \(a = 7.9474(8)\), \(b = 11.8269(10)\), 
\(c = 45.453(4) \, \text{Å}, \beta = 92.521(6)^\circ, U = 4268.2(7) \, \text{Å}^3, T = 100 \, \text{K}, \) space group \(P2_1/n\), \(Z = 8\), \(D_c = 1.233 \, \text{g cm}^{-3}, \mu(\text{Cu K}\alpha) = 0.611 \, \text{mm}^{-1}, 18058 \) reflections measured, \(\theta_{\text{max}} = 67.4^\circ\), 7057 unique \( (R_{\text{int}} = 0.045). \) The final \(R = 0.080 \) \((5633 \, I > 2\sigma(I) \) data), \(wR(F^2) = 0.180 \) \( \) (all \( \) data), CCDC 1035581.
Crystal data 3a: C$_{23}$H$_{27}$BN$_2$O$_4$•0.5(H$_2$O), \( M = 415.28 \), triclinic, \( a = 7.6310(6) \), \( b = 15.4871(12) \), \( c = 19.4805(16) \) Å, \( \alpha = 72.585(4) \), \( \beta = 84.215(4) \), \( \gamma = 89.809(4) \), \( U = 2184.7(3) \) Å$^3$, \( T = 100 \) K, space group P-1, \( Z = 4 \), \( D_c = 1.263 \) g cm$^{-3}$, \( \mu(Cu K\alpha) = 0.703 \) mm$^{-1}$, 15119 reflections measured, \( \theta_{\text{max}} = 66.9^\circ \), 7555 unique (\( R_{\text{int}} = 0.108 \)). The final \( R = 0.067 \) (5951 \( I>2\sigma(I) \) data), \( wR(F^2) = 0.196 \) (all data), CCDC 1035582.

Crystal data 4: C$_{39}$H$_{39}$BN$_8$O$_2$, \( M = 662.59 \), triclinic, \( a = 11.1659(8) \), \( b = 16.0899(12) \), \( c = 19.5309(13) \) Å, \( \alpha = 90.127(5) \), \( \beta = 92.245(5) \), \( \gamma = 96.332(5) \), \( U = 3484.7(4) \) Å$^3$, \( T = 90 \) K, space group P-1, \( Z = 4 \), \( D_c = 1.263 \) g cm$^{-3}$, \( \mu(Cu K\alpha) = 0.639 \) mm$^{-1}$, 33229 reflections measured, \( \theta_{\text{max}} = 67.7^\circ \), 11371 unique (\( R_{\text{int}} = 0.062 \)). The final \( R = 0.049 \) (8767 \( I>2\sigma(I) \) data), \( wR(F^2) = 0.123 \) (all data), CCDC 1051095.

### 2.4.4 Steady-state Absorption and Fluorescence Spectroscopy

The photophysical properties of compounds 1, 1a-e, 2, 2a, 3, 3a and 4 were determined by preparing a stock solution with a concentration of \( 5 \times 10^{-5} \) M and diluting it to appropriate concentrations for absorbance and emission spectra measurements. All the absorption spectra were obtained using a Varian Cary 50 UV/visible spectrophotometer. The optical density, \( \varepsilon \), were taken by preparing solution concentrations between \( 7.5 \times 10^{-6} \) and \( 2.5 \times 10^{-5} \) M in order to get \( \lambda_{\text{max}} \) between 0.5 and 1.0. Emission spectra were measured on a PTI QuantaMaster4/2006SE spectrofluorometer with the slit width set at 3 nm. All absorbance and emission spectra were acquired within 3 h of fresh solution preparation, at room temperature. BODIPYs 1, 2, and 3 were used as a standard in THF for calculating the fluorescence quantum yields with an excitation at 480 nm (BODIPY 1 \( \Phi_f = 0.56 \), BODIPY 2 \( \Phi_f = 0.93 \), BODIPY 3 \( \Phi_f = 0.43 \)), as previously
reported. Rhodamine 6G ($\Phi_r = 0.95$ in EtOH) was used as the reference for compounds 1, 1a-e, 2, 2a, 3, 3a, and 4 in toluene. A spectrophotometric cell with a path length of 10 mm was used.

2.4.5 Computational Modeling

The reaction mechanism was studied by electronic structure calculations at the B3LYP/6-31+G(d,p) level. The hybrid Becke’s Three Parameter DFT Functional was used.\textsuperscript{39-40} The solvent effects were taken into account using the Polarized Continuum Model (PCM).\textsuperscript{41-42} Atomic charges were calculated following the NPA method.\textsuperscript{43-44} The geometries of all structures were optimized without symmetry constraints. The stationary points on the potential energy surface were confirmed with frequency calculations. All calculations were performed using the Gaussian 09 program package.

2.5 References


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CHAPTER 3: SYNTHESIS AND CHARACTERIZATION OF 4,4-DICYANO- AND 4,4-
FUNCTIONALIZED BODIPYS[a]

3.1 Introduction

Recent growth in fluorescence labeling for bioanalytical purposes has provided new developments in cellular biology, bioimaging, medicine, and pharmacy fields. One of the most promising fluorophores to be used for these applications is boron dipyrrmethene (also known as BODIPY). The distinct characteristics of BODIPY are high photochemical and thermal stabilities, large molar extinction coefficients, high fluorescence quantum yields, and ease of modification.

Postmodification of the BODIPY core has been an appealing topic in the past years. Functionalization at various positions of the BODIPY core provides new robust organic dyes with fascinating optical properties such as with fluorescence quantum yield, moderate Stokes shifts, and large molar extinction coefficients. However, one of the limitation is the moderate Stokes shift (~20 nm) generally displayed by many known BODIPY dyes. One particular position on the BODIPY framework that is being investigated is the boron center for its potential enhancement of the Stokes shifts and fluorescence quantum yields of BODIPYS.

There are a few boron functionalization approaches toward synthesis of C- and E-BODIPYS. C-BODIPYS have an aryl or alkyl group chelated to the boron center while E-BODIPYS have ethynyl groups. The first approach consists of reaction between dipyrrromethenes with haloborane compounds. Holten and coworkers reported the first 4,4-dialkyl-BODIPYS via dipyrrromethene complexation with dialkyboron analogues such as bromodimethylborane, dibutylboron triflate, or 9-BBN triflate. Using the latter methodology, BODIPYS bearing 4-monosubstituents and 4,4'-substituents have been reported. Several groups have reported the use of halogenated

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boranes to introduce oxygen substituents on boron in one step.\textsuperscript{6-8} On the other hand, more constrained BODIPYs were synthesized through cyclization of 3,5-diaryl-substituted groups with boron-containing compounds.\textsuperscript{9-12}

Another approach is the direct substitution of the fluoride atoms at the boron center with carbon nucleophiles. Using Grignard or organolithium reagents, several $C$- and $E$-BODIPYs were synthesized in one or two steps with dialkyl, diaryl, and dialkynyl groups.\textsuperscript{13-21} These $E$-BODIPYs have been shown to induce large Stokes shifts and found to be relatively stable under strong basic and acidic conditions. Using the latter method, dimeric dialkynyl-BODIPYs were reported.\textsuperscript{17} A similar strategy was previously employed for the synthesis of a 4,4’-dicyano-BODIPY using trimethylsilylcyanoide in the presence of BF$_3$•OEt$_2$ or SnCl$_4$ as catalyst.\textsuperscript{18} Carbon nucleophiles chelating to the boron center provides a more stable BODIPY compared to its BF$_2$ precursor.\textsuperscript{22}

In order to broaden the scope of boron functionalization, development of milder carbon nucleophiles and unsymmetric substitution on the boron center must be studied. In this chapter, we investigated the reactivity of Lewis acid mediated boron functionalizations and extend this methodology to the synthesis of new 4,4-dicyano-BODIPYs. In addition, we also explored and prepared a series of novel functionalized BODIPYs bearing phenyl and various substituents at the boron center. These compounds 7a-g and 8a-g were synthesized in a three step one-pot reaction between dipyrromethenes and dichlorophenylborane, followed by replacement of chloride atom with fluoride and various carbon- and oxygen-centered nucleophiles. These BODIPYs’ structural, spectroscopic, and fluorescence properties are reported and discussed in this chapter.
3.2 Results and Discussion

3.2.1 Syntheses

Five BODIPYs 1-5 were synthesized according to previous reports. We begin by following a previously reported procedure from Burgess and coworkers for the synthesis of 4,4'-dicyano-BODIPYs. Our preliminary investigation began with various Lewis acids (Table 3.1). Using tin tetrachloride (SnCl4) and shorter amount of time (10 min) at ambient temperature, BODIPY 1a can be synthesized and isolated with 79% yield while boron trifluoride etherate (BF3·OEt2) and longer time (2 hours) gave 84% yield. Indeed, the product yield decreased to 39% yield when a milder Lewis acid (AlCl3) was used. However, the isolated yield increased up to 49% at reflux temperature. This is in agreement with our previous studies of reaction conditions at room temperature reflux conditions.

Table 3.1: Preliminary studies for synthesis of Lewis acid mediated 4,4'-dicyano-BODIPY.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Lewis acid</th>
<th>Temp</th>
<th>Time</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>SnCl4</td>
<td>25 °C</td>
<td>10 min</td>
<td>79</td>
</tr>
<tr>
<td>2</td>
<td>BF3·OEt2</td>
<td>25 °C</td>
<td>2 h</td>
<td>84</td>
</tr>
<tr>
<td>3</td>
<td>AlCl3</td>
<td>40 °C</td>
<td>2 h</td>
<td>49</td>
</tr>
<tr>
<td>4</td>
<td>AlCl3</td>
<td>25 °C</td>
<td>1 h</td>
<td>39</td>
</tr>
</tbody>
</table>

To further investigate and optimize the scope of our reaction, we subjected BODIPYs 1-5 to Lewis acid mediated substitutions using TMSCN as nucleophile to study their reactivity toward boron functionalization (Table 3.2). When BODIPY 2 containing two electron-donating groups on
the 8-aryl substituent was subjected to above conditions, the corresponding 4,4’-dicyano-BODIPY 2a was obtained in 37% yield. On the other hand, BODIPY 3 with an electron-withdrawing methoxycarbonyl group on the 8-aryl produced BODIPY 3a in 65% yield. BODIPYs 4a and 5a with meso-free and meso-phenyl substituent, respectively were obtained in 51% and 81% yields.

Table 3.2: Synthesis of 4,4’-dicyano-BODIPYs 1a-5a with isolated yields.

<table>
<thead>
<tr>
<th>BODIPY</th>
<th>R</th>
<th>Ar</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a</td>
<td>H</td>
<td>Ph</td>
<td>79</td>
</tr>
<tr>
<td>2a</td>
<td>H</td>
<td>3,4-(OMe)₂Ph</td>
<td>37</td>
</tr>
<tr>
<td>3a</td>
<td>H</td>
<td>4-CO₂MePh</td>
<td>65</td>
</tr>
<tr>
<td>4a</td>
<td>Et</td>
<td>Ph</td>
<td>81</td>
</tr>
<tr>
<td>5a</td>
<td>Et</td>
<td>H</td>
<td>51</td>
</tr>
</tbody>
</table>

In the presence of a Lewis acid (AlCl₃, BF₃·OEt₂, BCl₃ and SnCl₄), these methods can afford either the 4-mono- or 4,4’-disubstituted BODIPYs depending on the reaction conditions. In order to prepare 4,4’-difunctionalized BODIPYs containing two different substituents on the boron center, additional synthetic steps are required. The aim of our work is to synthesize 4,4’-difunctionalized BODIPYs in one pot. Our initial synthetic approach was to treat BODIPY 4 with triethylamine and dichlorophenylborane to produce BODIPY 7b, as previously reported. Unfortunately, thin layer chromatography (TLC) indicated presence of the starting material. It has
been recently reported that BODIPYs can react with boron trichloride followed by a Grignard reagent or alkoxide to afford the corresponding difunctionalized BODIPYs.\textsuperscript{26}

![Scheme 3.1: Attempted reaction for synthesis of 4,4-difunctionalized-BODIPY 7b.](image)

Alternatively, we also attempted to use the commercially available 2,4-dimethyl pyrrole in a three-step one-pot reaction BODIPY synthesis with dichlorophenylborane, followed by sodium methoxide to give BODIPY 6 with phenyl and methoxy substituents with an overall yield of 4%. Due to the low overall percent yield, we investigated the use of dipyrromethenes as our starting material for further functionalization with various nucleophiles.

![Scheme 3.2: Synthesis of 4,4-difunctionalized-BODIPY 6 from 2,4-dimethyl pyrrole.](image)

The starting dipyrren hydrochloride salts 7 and 8 were synthesized from ketopyrrole and the corresponding pyrroles as previously reported.\textsuperscript{27} The three-step one-pot reaction consists of treating dipyrren 7 or 8 in anhydrous dichloromethane with 5 equiv of triethylamine (TEA). After 30 min, phenylboron dichloride (5 equiv) was added dropwise to the mixture, followed by 10 equiv of a nucleophile, and the reaction was stirred at room temperature for an additional 1-2 hours to afford the corresponding 4,4-difunctionalized BODIPYs 7a-g and 8a-g.
Scheme 3.3: One-pot synthesis of BODIPYs from dipyrrins.

For comparison purposes between various substituents on the boron center, dipyrrins 7 and 8 were also reacted with triethylamine and complexation with BF₃•OEt₂ to give F-BODIPYs 4 and 9 in 68 and 41% yields, respectively.²⁸ The isolated yields (14-63%) obtained for the target 4,4’-difunctionalized BODIPYs 7a-g and 8a-g are given in Table 3.3. Some nucleophiles resulted in lower yields due to the competing reaction with water to give the hydroxide derivatives as by-products, which have been previously isolated and characterized.⁶,²⁹ Using tetrabutylammonium fluoride (TBAF) as the fluoride source, 4-phenyl-BODIPYs 7a and 8a were obtained in 52% and 41% yields, respectively which are milder conditions than those reported in the literature.⁶,²⁹-³⁰ This indicates that the B-Cl bond strength is weaker and more easily displaced than the B-F bond, and thus the reaction does not require elevated temperature or the presence of Lewis acid activators.

Scheme 3.4: Synthesis of F-BODIPYs 4 and 9 from dipyrrins.

Hard and soft nucleophiles were screened under our above milder reaction conditions. Soft nucleophile such as trimethylsilyl cyanide (TMSCN) has been used previously for boron
functionalization through Lewis acid mediation (tin tetrachloride or boron trifluoride).\textsuperscript{18} However, hard nucleophiles such as alkoxides and acetate also produced the target BODIPYs in moderate yields (Table 3.3). Other nucleophiles containing amine, ester and acetylene functionalities can be employed under our milder conditions, thus allowing for further functionalization or conjugation to the BODIPY through the boron atom.\textsuperscript{18,25,31}

Table 3.3: Yields and \textsuperscript{11}B NMR chemical shifts (128 MHz, CDCl\textsubscript{3}, all singlets) for BODIPYs 7a-g and 8a-g.

<table>
<thead>
<tr>
<th>BODIPY</th>
<th>R</th>
<th>R\textsuperscript{1}</th>
<th>Yield (%)</th>
<th>δ (ppm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>7a</td>
<td>Et</td>
<td>F</td>
<td>52</td>
<td>2.43</td>
</tr>
<tr>
<td>7b</td>
<td>Et</td>
<td>OMe</td>
<td>63</td>
<td>2.18</td>
</tr>
<tr>
<td>7c</td>
<td>Et</td>
<td>CN</td>
<td>17</td>
<td>-9.42</td>
</tr>
<tr>
<td>7d</td>
<td>Et</td>
<td>OAc</td>
<td>25</td>
<td>-0.48</td>
</tr>
<tr>
<td>7e</td>
<td>Et</td>
<td>OCH\textsubscript{2}CH\textsubscript{2}NHBoc</td>
<td>32</td>
<td>1.54</td>
</tr>
<tr>
<td>7f</td>
<td>Et</td>
<td>O(CH\textsubscript{2}CH\textsubscript{2}O)\textsubscript{3}Me</td>
<td>21</td>
<td>1.63</td>
</tr>
<tr>
<td>7g</td>
<td>Et</td>
<td>OCH\textsubscript{2}C≡CH</td>
<td>25</td>
<td>1.73</td>
</tr>
<tr>
<td>8a</td>
<td>H</td>
<td>F</td>
<td>41</td>
<td>2.23</td>
</tr>
<tr>
<td>8b</td>
<td>H</td>
<td>OMe</td>
<td>49</td>
<td>2.10</td>
</tr>
<tr>
<td>8c</td>
<td>H</td>
<td>CN</td>
<td>18</td>
<td>-7.43</td>
</tr>
<tr>
<td>8d</td>
<td>H</td>
<td>OAc</td>
<td>16</td>
<td>-0.34</td>
</tr>
<tr>
<td>8e</td>
<td>H</td>
<td>OCH\textsubscript{2}CH\textsubscript{2}NHBoc</td>
<td>14</td>
<td>1.10</td>
</tr>
<tr>
<td>8f</td>
<td>H</td>
<td>O(CH\textsubscript{2}CH\textsubscript{2}O)\textsubscript{3}Me</td>
<td>15</td>
<td>1.21</td>
</tr>
<tr>
<td>8g</td>
<td>H</td>
<td>OCH\textsubscript{2}C≡CH</td>
<td>31</td>
<td>1.65</td>
</tr>
</tbody>
</table>

The addition of a polyethylene glycol group is used for increasing solubility of BODIPY without changing the absorption and emission wavelengths. We also attempted to deprotect the
Boc group in BODIPY 7e to give BODIPY 7h, but the deprotection failed and resulted in BODIPY 7j. We suspected that the B-O bond is reactive toward TFA conditions as previously reported.22

Scheme 3.5: Attempt Boc deprotection reaction of BODIPY 7e.

3.2.2 Structural Characterization

All BODIPYs were characterized by $^1$H, $^{13}$C, and $^{11}$B NMR, HRMS (ESI-TOF), and UV-Vis absorbance and fluorescence spectrophotometry. BODIPYs 1a, 3a-5a, 7b, 7c, and 8c were also characterized by X-ray crystallography (see Figure 3.1). Different substituents on the boron center have no substantial effect on the 3,5-dimethyl and 2,6-diethyl chemical shifts. Indeed, the $^1$H NMR spectra clearly show that the 3,5-methyl groups appear as a singlet around 2.2 ppm and the 1,7-methyl groups at 1.3 ppm for BODIPYs 7a-g. However, the 1,3,5,7-methyl groups for BODIPYs 8a-g consist of 4 singlets at 2.2, 2.1, 1.4 and 1.3 ppm. Significant differences were observed in the $^{11}$B NMR of the BODIPYs using BF$_3$•OEt$_2$ as reference ($\delta = 0$ ppm), as shown in Table 3.3. The $^{11}$B NMR spectra clearly shows the 4,4′-dicyano-BODIPYs 1a-5a via the singlet peaks attributed to B(CN)$_2$ at ca. -16.9 ppm. Indeed, the $^{11}$B NMR spectra showed that the chemical shifts are influenced by the electron density of the substituents bound to boron, which is greater for BODIPYs 1a-5a and less for the 4-phenyl-BODIPYs 7c and 8c, and lowest for the mono-fluorides 7a and 8a. BODIPYs 4 and 9 bearing two fluorides, have a triplet peak at 0.7 ppm with ca. $J(^{11}$B-$^{19}$F) = 33 Hz. The $^{11}$B NMR spectra clearly shows a singlet for all BODIPYs 7a-g and 8a-g with chemical shifts ranging from the mono-fluoride 7a (2.43 ppm) to the cyano derivative
7c (9.42 ppm). For the case of 7a and 8a, the lack of boron-fluorine coupling might be due to quadrupolar broadening, as previously observed.6,14

Crystals suitable for X-ray analysis were grown by slow diffusion of hexane in dichloromethane (for BODIPYs 7c and 8c) or in ethyl acetate (for BODIPY 7b) and slow diffusion in dichloromethane for BODIPYs 1a-5a. Structures are shown in Figure 3.1. The C3N2B cores of both of the two independent molecules of 1a (only one shown in Fig. 1) are nearly planar, with mean deviations 0.012 and 0.017 Å.

Figure 3.1: Molecular structures of BODIPYs 1a and 3a-5a from X-ray crystal analysis, with 50% probability ellipsoids.

The phenyl groups form dihedral angle of 75.8 and 78.8° with those planes. In 3a, the central ring is nonplanar, with the B(CN)2 substituent tilted such that the B atom is 0.157 Å out of
the plane of the other five atoms. The phenyl group of the meso substituent is nearly orthogonal to the central plane, with a dihedral angle of 88.1°. The central ring of 4a has a similar conformation to that of 3a, but with a smaller out-of-plane deviation for the B atom, 0.057 Å and a 77.6° dihedral angle for the phenyl ring. In 5a, the out-of-plane deviation for the B atom is somewhat larger, 0.205 Å. In all cases, the central BN$_2$C$_3$ ring is fairly planar, with mean deviation of 0.020 Å for both 7b and 7c and 0.056 Å for 8c (Figure 3.2). The 8-mesophenyl is oriented approximately perpendicular to the BODIPY core plane, to avoid steric hindrance from the 1,7-dimethyl substituents, the dihedral angles being 84.1° for 7b, 85.3° for 7c, and 87.6° for 8c. Likewise, the phenyl group on boron forms dihedral angles with the central ring of 86.1° for 7b, 85.9° for 7c, and 83.2° for 8c.

![Figure 3.2: Molecular structures of BODIPYs 7b-c, and 8c from X-ray crystal analysis, with 50% probability ellipsoids.](image)

3.2.3 Spectroscopic Study

The spectroscopic properties of BODIPYs 7a-g, 8a-g, 4 and 9 were determined in dichloromethane at room temperature and the results are summarized in Table 3.4. All BODIPYs show absorptions (511-524 nm) in the visible range that correspond to the S$_0$-S$_1$ (π-π*) transition. The symmetric BODIPYs 7a-g showed strong absorption bonds with high molar absorption
coefficients (log $\varepsilon = 4.6$-$4.9$) in the range of 521-524 nm and emission bands between 533-537 nm.

The asymmetric BODIPYs 8a-g also showed strong absorption bonds with high molar absorption coefficients (log $\varepsilon = 4.7$-$5.0$) and blue-shifted absorption bands (511-513 nm) and emission bands (521-523 nm). All BODIPYs showed Stokes shift ranging from 9 to 15 nm.

Table 3.4: Absorption and emission spectroscopic properties of BODIPYs 7a-g, 8a-g, 4, and 9 in CH$_2$Cl$_2$ at room temperature.

<table>
<thead>
<tr>
<th>BODIPYs</th>
<th>Absorption $\lambda_{\text{max}}$ (nm)</th>
<th>Emission $\lambda_{\text{max}}$ (nm)</th>
<th>log $\varepsilon$ (M$^{-1}$ cm$^{-1}$)</th>
<th>$\Phi_f$</th>
<th>Stokes’ shift (nm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>7a</td>
<td>524</td>
<td>535</td>
<td>4.86</td>
<td>0.53</td>
<td>11</td>
</tr>
<tr>
<td>7b</td>
<td>522</td>
<td>537</td>
<td>4.77</td>
<td>0.42</td>
<td>15</td>
</tr>
<tr>
<td>7c</td>
<td>521</td>
<td>533</td>
<td>4.63</td>
<td>0.65</td>
<td>12</td>
</tr>
<tr>
<td>7d</td>
<td>522</td>
<td>533</td>
<td>4.63</td>
<td>0.64</td>
<td>11</td>
</tr>
<tr>
<td>7e</td>
<td>523</td>
<td>533</td>
<td>4.73</td>
<td>0.60</td>
<td>11</td>
</tr>
<tr>
<td>7f</td>
<td>523</td>
<td>534</td>
<td>4.82</td>
<td>0.48</td>
<td>11</td>
</tr>
<tr>
<td>7g</td>
<td>523</td>
<td>534</td>
<td>4.61</td>
<td>0.51</td>
<td>11</td>
</tr>
<tr>
<td>8a</td>
<td>513</td>
<td>523</td>
<td>4.85</td>
<td>0.61</td>
<td>10</td>
</tr>
<tr>
<td>8b</td>
<td>512</td>
<td>523</td>
<td>4.92</td>
<td>0.50</td>
<td>11</td>
</tr>
<tr>
<td>8c</td>
<td>511</td>
<td>521</td>
<td>4.97</td>
<td>0.78</td>
<td>10</td>
</tr>
<tr>
<td>8d</td>
<td>512</td>
<td>522</td>
<td>4.81</td>
<td>0.68</td>
<td>10</td>
</tr>
<tr>
<td>8e</td>
<td>513</td>
<td>523</td>
<td>4.76</td>
<td>0.60</td>
<td>10</td>
</tr>
<tr>
<td>8f</td>
<td>512</td>
<td>521</td>
<td>4.72</td>
<td>0.51</td>
<td>9</td>
</tr>
<tr>
<td>8g</td>
<td>513</td>
<td>523</td>
<td>4.78</td>
<td>0.64</td>
<td>10</td>
</tr>
<tr>
<td>4</td>
<td>526</td>
<td>536</td>
<td>4.68</td>
<td>0.74</td>
<td>10</td>
</tr>
<tr>
<td>9</td>
<td>514</td>
<td>524</td>
<td>4.49</td>
<td>0.82</td>
<td>10</td>
</tr>
</tbody>
</table>

$\varepsilon = $ extinction coefficient; $\Phi_f = $ fluorescence quantum yield

BODIPYs bearing flexible groups show decreased fluorescence quantum yields due to increased energy lost to non-radiative decay to the ground state, which is in agreement with
previous observations. BODIPYs bearing cyano substituents showed the largest fluorescence quantum yields, 0.65 for 7c and 0.78 for 8c when compared to other 4-phenyl-BODIPYs.

3.3 Conclusions

A series of new 4,4’-dicyano-BODIPYs 1a-5a were investigated and synthesized following a previous procedure. Lewis acid tin tetrachloride provided a convenient and robust methodology for functionalization at the boron center with cyano nucleophile. In addition, a novel route for the preparation of 4,4’-difunctionalized BODIPYs 7a-g and 8a-g bearing two different substituents at the boron center was developed. A three step one-pot reaction between dipyrrins with phenylboron dichloride, followed by addition with a nucleophile produced the target BODIPYs in moderate yields ranging from 14% to 63%. BODIPYs 7b and 8b containing a methoxide substituent were obtained in the highest yields while lower yields were achieved for milder nucleophiles (alcohols, TMSCN, acetate ion) due to the competing formation of the corresponding 4-hydroxyl-BODIPY derivatives. BODIPYs 7c and 8c containing cyano groups on boron exhibit the highest quantum yields compared to other substituents.

3.4 Experimental

3.4.1 General Information

All commercially available reagents were purchased from Sigma-Aldrich and were used without further purification. All anhydrous reactions were carried out with oven-dried glassware under a dry argon atmosphere. All the reactions were monitored by using Sorbent Technologies pre-coated polyester backed TLC (200 μm silica gel with indicator UV-254 nm). Flash column chromatography was performed using Sorbent Technologies 60 Å silica gel (230-400 mesh). Prep-TLC 60 Å silica gel 20 x 20 cm (210-270 μm) was used. All 1H-, 13C-, and 11B-NMR spectral were collected using a Bruker AV-400 spectrometer in deuterated dichloromethane or chloroform as
solvents. The CDCl₃ chemical shifts (δ) are reported in ppm with 7.27 for proton and 77.16 for carbon NMR as reference. The CD₂Cl₂ chemical shifts (δ) are reported in ppm with 5.23 for proton and 54.00 for carbon NMR as reference. The BF₃•OEt₂ was used as an external reference (δ 0.00) for boron NMR. Coupling constants are reported in hertz (Hz). All the mass spectra were collected using an Agilent 6210 ESI-TOF mass spectrometer. All melting points were recorded using a MEL-TEMP electrothermal instrument.

3.4.2 Syntheses

General procedure for synthesis of 4,4-dicyano-BODIPYs 1a-5a. BODIPYs 1-5 were dissolved in anhydrous dichloromethane (3 mL). Tin tetrachloride (1 M in dichloromethane, 0.5 equiv) solution was added dropwise, followed by trimethylsilyl cyanide (7.0 equiv). After 10 min, the reaction was quenched with water and extracted with dichloromethane (2 x 5 mL). The organic layers were washed with sat. NaHCO₃ (2 x 5 mL). The combined organic layers were washed with water (2 x 5 mL), dried over Na₂SO₄, and concentrated under reduced pressure.

4,4-Dicyano-8-phenyl-1,3,5,7-tetramethyl-BODIPY (1a). The crude product was purified via TLC (eluent 80/20 hexane/ethyl acetate) to give a bright orange solid BODIPY 1a (16.5 mg, 79%) that was recrystallized from 100% dichloromethane: ¹H NMR (CDCl₃, 400 MHz) δ 7.49-7.40 (m, 3H), 7.25-7.17 (m, 3H), 6.09 (s, 2H), 2.66 (s, 6H), 1.34 (s, 6H); ¹³C NMR (CDCl₃, 100 MHz) δ 155.91, 144.47, 142.66, 133.97, 129.73, 129.49, 129.45, 127.67, 126.07, 125.33, 122.61, 122.58, 15.43, 14.59; ¹¹B NMR (CDCl₃, 128 MHz) δ -16.92 (s); HRMS (ESI-TOF) m/z 360.1631 [M + Na]⁺ calculated for C₂₁H₁₉BN₄: 360.1645.
4,4-Dicyano-8-(3,4-dimethoxyphenyl)-1,3,5,7-tetramethyl-BODIPY (2a). The crude product was purified via TLC (eluent 50/50 hexane/ethyl acetate) to give a bright orange solid BODIPY 2a (10.8 mg, 37%) that was recrystallized from 100% acetone: $^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ 7.02 (d, $J = 8.2$ Hz, 1H), 6.84 (dd, $J = 8.2$, 2.0 Hz, 1H), 6.79 (d, $J = 2.0$ Hz, 1H), 6.17 (s, 2H), 3.97 (s, 3H), 3.89 (s, 3H), 2.73 (s, 6H), 1.53 (s, 6H); $^{13}$C NMR (CDCl$_3$, 100 MHz) $\delta$ 155.83, 150.08, 149.90, 144.46, 142.56, 130.07, 126.05, 122.50, 120.20, 111.71, 110.72, 56.21, 55.97, 15.44, 14.71; $^{11}$B NMR (CDCl$_3$, 128 MHz) $\delta$ -16.93 (s); HRMS (ESI-TOF) m/z 420.1843 [M + Na]$^+$ calculated for C$_{23}$H$_{23}$BN$_4$O$_2$: 420.1828.

4,4-Dicyano-8-(4-methoxycarbonylphenyl)-1,3,5,7-tetramethyl-BODIPY (3a). The crude product was purified via TLC (eluent 30/70 hexane/dichloromethane) to give a bright orange solid BODIPY 3a (18.0 mg, 65%) that was recrystallized from 100% acetone: $^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ 8.23 (d, $J = 7.9$ Hz, 2H), 7.42 (d, $J = 7.9$ Hz, 2H), 6.18 (s, 2H), 3.99 (s, 3H), 2.74 (s, 6H), 1.41 (s, 6H); $^{13}$C NMR (CDCl$_3$, 100 MHz) $\delta$ 166.22, 156.51, 144.21, 138.65, 131.35, 130.64, 128.13, 122.89, 52.49, 15.48, 14.76; $^{11}$B NMR (CDCl$_3$, 128 MHz) $\delta$ -16.94 (s); HRMS (ESI-TOF) m/z 396.1867 [M + H]$^+$ calculated for C$_{23}$H$_{21}$BN$_4$O$_2$: 396.1869.

4,4-Dicyano-8-phenyl-2,6-diethyl-1,3,5,7-tetramethyl-BODIPY (4a). The crude product was purified via TLC (eluent 80/20 hexane/ethyl acetate) to give a bright orange solid BODIPY 4a (17.5 mg, 81%) that was recrystallized from 1:1 acetone/dichloromethane: $^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ 7.45 (p, $J = 3.5$ Hz, 3H), 7.20 (dd, $J = 6.8$, 3.1 Hz, 3H), 2.62 (s, 6H), 2.28 (q, $J = 7.6$ Hz, 4H), 1.24 (s, 6H), 0.93 (t, $J = 7.6$ Hz, 6H); $^{13}$C NMR (CDCl$_3$, 100 MHz) $\delta$ 153.97, 141.04, 139.85, 134.78, 134.21, 129.32, 129.27, 127.98, 17.21, 14.51, 13.39, 11.85; $^{11}$B NMR (CDCl$_3$,
128 MHz) δ -16.84 (s); HRMS (ESI-TOF) m/z 416.2257 [M + Na]^+ calculated for C_{25}H_{27}BN_4: 416.2264.

4,4-Dicyano-2,6-diethyl-1,3,5,7-tetramethyl-BODIPY (5a). The crude product was purified via TLC (eluent 80/20 hexane/ethyl acetate) to give a bright orange solid BODIPY 5a (12.3 mg, 51%) that was recrystallized from 1:1 acetone/dichloromethane: ^1H NMR (CDCl$_3$, 400 MHz) δ 7.07 (s, 1H), 2.66 (s, 6H), 2.45 (q, J = 7.5 Hz, 4H), 2.22 (s, 6H), 1.10 (t, J = 7.5 Hz, 6H); ^13C NMR (101 MHz, Chloroform-d) δ 155.15, 138.11, 133.23, 130.74, 119.34, 17.40, 14.48, 13.28, 9.49; ^11B NMR (CDCl$_3$, 128 MHz) δ -16.93 (s); HRMS (ESI-TOF) m/z 340.1944 [M + Na]^+ calculated for C_{19}H_{23}BN_4: 340.1949.

General procedure for synthesis of dipyrrins 7 and 8. 27 2,4-dimethyl ketopyrrole (1.0 equiv) was dissolved in anhydrous 8:1 pentane/dichloromethane at 0 °C. 2,4-dimethyl pyrrole or 3-ethyl-2,4-dimethyl pyrrole (1.0 equiv) was added dropwise to the stirred mixture and warmed to room temperature. After 24 h, Et$_3$N (1.0 equiv) was added dropwise to the reaction mixture for an hour and quenched with water (10 mL) and extracted with dichloromethane (10 mL). The combined organic layers were dried over MgSO$_4$ and concentrated under reduced pressure. The crude products were purified by column chromatography (eluent EtOAc to 5% MeOH/ EtOAc to 30% MeOH/ EtOAc) to afford the corresponding dipyrrins 7 and 8.

Dipyrrin (7). 27% yield: ^1H NMR (CDCl$_3$, 400 MHz) δ 7.37 (s, 3H), 7.27-7.21 (m, 2H), 2.28 (s, 6H), 2.24 (q, 4H, J = 7.32 Hz) 1.15 (s, 6H), 0.93 (t, 6H, J = 7.16 Hz); ^13C NMR (CDCl$_3$, 100 MHz) δ 150.25, 138.92, 137.65, 136.08, 134.88, 131.39, 129.73, 128.53, 128.10, 17.69, 15.00,
14.50, 11.85; HRMS (ESI-TOF) m/z 333.2325 [M + H]^+ calculated for C_{23}H_{28}N_2: 333.2335. These data are in agreement with previous reported.\textsuperscript{33}

Dipyrrin (8). 31% yield: \textsuperscript{1}H NMR (CDCl\textsubscript{3}, 400 MHz) \(\delta\) 7.61 (t, 1H, \(J = 7.36\) Hz), 7.51 (t, 2H, \(J = 7.80\) Hz), 7.32 (d, 2H, \(J = 7.20\) Hz), 6.17 (s, 1H), 2.71 (s, 3H), 2.68 (s, 3H), 2.39 (q, 2H, \(J = 7.52\) Hz), 1.41 (s, 3H), 1.34 (s, 3H), 1.04 (t, 3H, \(J = 7.48\) Hz); \textsuperscript{13}C NMR (CDCl\textsubscript{3}, 100 MHz) \(\delta\) 139.35, 137.74, 134.40, 130.65, 130.33, 129.88, 129.54, 128.86, 118.19, 50.45, 17.61, 14.67, 14.52, 14.34, 12.29; HRMS (ESI-TOF) m/z 305.2012 [M + H]^+ calculated for C\textsubscript{21}H\textsubscript{24}N\textsubscript{2}: 305.2024.

General procedure for synthesis of BODIPYs 7a-g and 8a-g. Dipyrrins 7 or 8 (1.0 equiv.) were dissolved in anhydrous CH\textsubscript{2}Cl\textsubscript{2} (5 mL). Et\textsubscript{3}N (5.0 equiv) was added dropwise to the solution at room temperature. Dichlorophenylborane (5.0 equiv) was added dropwise and the mixture was stirred for 1 h. Nucleophile (10.0 equiv) was added dropwise and the final mixture stirred for an additional 1-2 h while followed by TLC. All crude products were concentrated under reduced pressure and purified as described below to afford BODIPYs 7a-g and 8a-g.

4-Fluoro-4-phenyl-8-phenyl-2,6-diethyl-1,3,5,7-tetramethyl-BODIPY (7a). The crude product was purified via TLC (eluent 50/50 hexane/dichloromethane) to give an orange solid BODIPY 7a (11.4 mg, 52%) that was recrystallized from 50/50 hexane/EtOAc: mp 210-215 °C; \textsuperscript{1}H NMR (CD\textsubscript{2}Cl\textsubscript{2}, 400 MHz) \(\delta\) 7.57-7.51 (m, 3H), 7.43-7.40 (m, 3H), 7.37-7.35 (m, 1H), 7.20 (t, 2H, \(J = 6.9\) Hz), 7.15-7.11 (m, 1H), 2.23 (q, 4H, \(J = 7.6\) Hz), 2.17 (s, 6H), 1.32 (s, 6H), 0.91 (t, 3H, \(J = 7.5\) Hz); \textsuperscript{13}C NMR (CDCl\textsubscript{3}, 100 MHz) \(\delta\) 153.91, 140.55, 137.07, 136.54, 132.81, 132.10, 132.07, 130.48, 129.11, 129.05, 128.80, 128.73, 128.58, 127.00, 126.09, 17.25, 14.78, 13.20,
13.16, 11.89; \(^{11}\)B NMR (CDCl\(_3\), 128 MHz) \(\delta\) 2.43 (s); HRMS (ESI-TOF) \(m/z\) 438.2752 [M + H]\(^+\) calculated for C\(_{29}\)H\(_{32}\)BFN\(_2\): 438.2740.

4-Methoxy-4-phenyl-8-phenyl-2,6-diethyl-1,3,5,7-tetramethyl-BODIPY (7b). The crude product was purified via TLC (eluent 50/50 hexane/dichloromethane) to give an orange solid BODIPY 7b (29.3 mg, 63%) that was recrystallized from 50/50 hexane/EtOAc: mp 160-165 °C; \(^1\)H NMR (CD\(_2\)Cl\(_2\), 400 MHz) \(\delta\) 7.56-7.50 (m, 3H), 7.43-7.36 (m, 4H), 7.15 (t, 2H, \(J = 7.4\) Hz), 7.10-7.05 (m, 1H), 3.09 (s, 3H), 2.23 (q, 4H, \(J = 7.6\) Hz), 2.16 (s, 6H), 1.32 (s, 6H), 0.90 (t, 3H, \(J = 7.6\) Hz); \(^{13}\)C NMR (CDCl\(_3\), 100 MHz) \(\delta\) 153.66, 140.51, 136.91, 136.00, 132.51, 132.36, 131.32, 129.08, 128.89, 128.83, 128.82, 128.58, 126.79, 125.59, 49.20, 17.31, 14.85, 12.86, 11.93; \(^{11}\)B NMR (CDCl\(_3\), 128 MHz) \(\delta\) 2.18 (s); HRMS (ESI-TOF) \(m/z\) 472.2771 [M + Na]\(^+\) calculated for C\(_{30}\)H\(_{35}\)BN\(_2\)O: 472.2775.

4-Cyano-4-phenyl-8-phenyl-2,6-diethyl-1,3,5,7-tetramethyl-BODIPY (7c). The crude product was purified via TLC (eluent 80/20 hexane/EtOAc) to give an orange solid BODIPY 7c (8.6 mg, 17%) that was recrystallized from 50/50 hexane/dichloromethane: mp 110-115 °C; \(^1\)H NMR (CD\(_2\)Cl\(_2\), 400 MHz) \(\delta\) 7.56-7.54 (m, 3H), 7.49 (d, 2H, \(J = 6.6\) Hz), 7.42-7.38 (m, 1H), 7.25 (t, 2H, \(J = 6.9\) Hz), 7.21-7.17 (m, 1H), 2.25 (q, 4H, \(J = 7.6\) Hz), 2.15 (s, 6H), 1.34 (s, 6H), 0.91 (t, 3H, \(J = 7.6\) Hz); \(^{13}\)C NMR (CDCl\(_3\), 100 MHz) \(\delta\) 154.0, 140.43, 136.89, 136.18, 132.76, 132.29, 130.57, 129.11, 128.99, 128.78, 128.73, 128.64, 126.90, 125.70, 17.30, 14.83, 13.55, 11.89; \(^{11}\)B NMR (CDCl\(_3\), 128 MHz) \(\delta\) -9.42 (s); HRMS (ESI-TOF) \(m/z\) 467.2618 [M + Na]\(^+\) calculated for C\(_{30}\)H\(_{32}\)BN\(_3\): 467.2613.
4-Acetoxy-4-phenyl-8-phenyl-2,6-diethyl-1,3,5,7-tetramethyl-BODIPY (7d). The crude product was purified via TLC (elucent 80/20 hexane/EtOAc) to give an orange solid BODIPY 7d (9.5 mg, 25%) that was recrystallized from 50/50 hexane/EtOAc: mp 150-155 °C; 1H NMR (CD₂Cl₂, 400 MHz) δ 7.56-7.48 (m, 3H), 7.44-7.41 (m, 2H), 7.39-7.36 (m, 1H), 7.21 (t, 2H, J = 6.8 Hz), 7.17-7.12 (m, 1H), 2.22 (q, 4H, J = 7.6 Hz), 2.07 (s, 3H), 2.04 (s, 6H), 1.33 (s, 6H), 0.89 (t, 6H, J = 7.6 Hz); 13C NMR (CDCl₃, 100 MHz) δ 172.40, 152.41, 140.88, 136.76, 136.71, 132.47, 131.25, 129.10, 129.06, 128.89, 128.60, 126.94, 126.06, 23.19, 17.38, 14.75, 13.12, 12.09; 11B NMR (CDCl₃, 128 MHz) δ -0.48 (s); HRMS (ESI-TOF) m/z 500.2720 [M + Na]+ calculated for C₃₁H₃₅BN₂O₂: 500.2737.

4-(N-Boc-ethanolyl)-4-phenyl-8-phenyl-2,6-diethyl-1,3,5,7-tetramethyl-BODIPY (7e). The crude product was purified via TLC (elucent 80/20 Hexane/EtOAc) to give an orange solid BODIPY 7e (15.5 mg, 32%) that was recrystallized from 50/50 hexane/EtOAc: mp 55-60 °C; 1H NMR (CD₂Cl₂, 400 MHz) δ 7.56-7.51 (m, 3H), 7.45-7.36 (m, 3H), 7.37-7.35 (m, 1H), 7.15 (t, 2H, J = 7.4 Hz), 7.10-7.05 (m, 1H), 3.24-3.18 (m, 2H), 3.16-3.15 (m, 2H), 2.21 (q, 4H, J = 7.6 Hz), 2.12 (s, 6H), 1.42 (s, 9H), 1.31 (s, 6H), 0.89 (t, 6H, J = 7.6 Hz); 13C NMR (CDCl₃, 100 MHz) δ 156.34, 153.54, 140.56, 136.81, 136.14, 132.57, 131.21, 129.07, 128.99, 128.83, 128.76, 128.63, 126.71, 125.64, 28.65, 17.30, 14.80, 13.06, 11.93; 11B NMR (CDCl₃, 128 MHz) δ 1.54 (s); HRMS (ESI-TOF) m/z 601.3561 [M + Na]+ calculated for C₃₆H₄₆BN₃O₃: 601.3573.

4-(Triethyleneglycol monomethyl ether)-4-phenyl-8-phenyl-2,6-diethyl-1,3,5,7-tetramethyl-BODIPY (7f). The crude product was purified via TLC (elucent 80/20 hexane/EtOAc) to give an orange/red oil BODIPY 7f (11.4 mg, 21%) that was recrystallized from 50/50...
hexane/EtOAc. $^1$H NMR (CD$_2$Cl$_2$, 400 MHz) $\delta$ 7.56-7.50 (m, 3H), 7.44-7.40 (m, 3H), 7.38-7.36 (m, 1H), 7.15 (t, 2H, $J$ = 8 Hz), 7.10-7.06 (m, 1H), 3.64-3.62 (m, 2H), 3.60-3.57 (m, 6H), 3.51-3.48 (m, 2H), 3.33 (s, 3H), 3.30 (t, 2H, $J$ = 5.6 Hz), 2.22 (q, 4H, $J$ = 7.6 Hz), 2.15 (s, 6H), 1.31 (s, 6H), 0.89 (t, 6H, $J$ = 7.5 Hz); $^{13}$C NMR (CD$_2$Cl$_2$, 100 MHz) $\delta$ 137.26, 136.64, 133.02, 132.64, 131.67, 129.53, 129.41, 129.32, 129.23, 129.00, 127.09, 126.02, 73.21, 72.51, 71.23, 71.14, 70.99, 61.49, 59.18, 17.62, 15.06, 13.21, 12.12; $^{11}$B NMR (CDCl$_3$, 128 MHz) $\delta$ 1.63 (s); HRMS (ESI-TOF) m/z 604.3557 [M + Na]$^+$ calculated for C$_{36}$H$_{47}$BN$_2$O$_4$: 604.3565.

4-(Pro-2-yn-1-yloxy)-4-phenyl-8-phenyl-2,6-diethyl-1,3,5,7-tetramethyl-BODIPY (7g). The crude product was purified via TLC (eluent 50/50 hexane/dichloromethane) to give an orange solid BODIPY 7g (13.9 mg, 25%) that was recrystallized from 50/50 hexane/ethyl acetate: mp 130-135 °C; $^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ 7.56-7.50 (m, 3H), 7.42 (d, 3H, $J$ = 6.6 Hz), 7.38-7.34 (m, 1H), 7.17 (t, 2H, $J$ = 8.1 Hz), 7.10 (t, 1H, $J$ = 7.2 Hz), 3.92 (d, 1H, $J$ = 2.4 Hz), 2.22 (q, 4H, $J$ = 6.6 Hz), 2.21 (s, 3H), 2.17 (s, 3H), 1.32 (s, 3H), 1.31 (s, 3H), 0.90 (t, 6H, $J$ = 7.5 Hz); $^{13}$C NMR (CDCl$_3$, 100 MHz) $\delta$ 154.19, 140.33, 136.79, 136.34, 132.73, 132.55, 131.20, 129.10, 128.96, 128.81, 128.79, 128.64, 126.73, 125.69, 70.92, 50.09, 17.28, 14.80, 13.22, 11.93; $^{11}$B NMR (CDCl$_3$, 128 MHz) $\delta$ 1.73 (s); HRMS (ESI-TOF) m/z 496.2771 [M + Na]$^+$ calculated for C$_{32}$H$_{35}$BN$_2$O: 496.2754.

4-Fluoro-4-phenyl-8-phenyl-6-ethyl-1,3,5,7-tetramethyl-BODIPY (8a). The crude product was purified via TLC (eluent 50/50 hexane/dichloromethane) to give an orange solid BODIPY 8a (11.4 mg, 41%) that was recrystallized from 50/50 hexane/EtOAc: mp 120-125 °C; $^1$H NMR (CD$_2$Cl$_2$, 400 MHz) $\delta$ 7.57-7.51 (m, 3H), 7.43-7.40 (m, 3H), 7.37-7.35 (m, 1H), 7.20 (t, 2H, $J$ =
6.8 Hz), 7.16-7.12 (m, 1H), 5.88 (s, 1H), 2.24 (q, 2H, J = 7.6 Hz), 2.19 (s, 3H), 2.15 (s, 3H), 1.39 (s, 3H), 1.35 (s, 3H), 0.91 (t, 3H, J = 7.6 Hz); \(^{13}\)C NMR (CDCl\(_3\), 100 MHz) \(\delta\) 141.27, 140.64, 136.12, 133.58, 132.06, 132.02, 129.17, 129.11, 128.84, 128.62, 128.43, 127.05, 126.19, 120.85, 17.25, 15.35, 14.68, 14.56, 13.32, 11.94; \(^{11}\)B NMR (CDCl\(_3\), 128 MHz) \(\delta\) 2.23 (s); HRMS (ESI-TOF) \(m/\varepsilon\) 410.2439 [M + H]\(^+\) calculated for C\(_{27}\)H\(_{28}\)BFN\(_2\): 410.2398.

4-Methoxy-4-phenyl-8-phenyl-6-ethyl-1,3,5,7-tetramethyl-BODIPY (8b). The crude product was purified via TLC (eluent dichloromethane) to give an orange solid BODIPY 8b (34.4 mg, 49%) that was recrystallized from 50/50 hexane/EtOAc: mp 120-125 °C; \(^1\)H NMR (CD\(_2\)Cl\(_2\), 400 MHz) \(\delta\) 7.57-7.51 (m, 3H), 7.43-7.36 (m, 4H), 7.15 (t, 2H, J = 7.3 Hz), 7.10-7.06 (m, 1H), 5.86 (s, 1H), 3.10 (s, 3H), 2.24 (q, 2H, J = 7.5 Hz), 2.19 (s, 3H), 2.13 (s, 3H), 1.38 (s, 3H), 1.34 (s, 3H), 0.91 (t, 3H, J = 7.6 Hz); \(^{13}\)C NMR (CDCl\(_3\), 100 MHz) \(\delta\) 155.61, 153.68, 141.30, 139.67, 137.10, 136.54, 133.41, 132.38, 131.94, 131.56, 129.21, 129.03, 128.77, 128.73, 126.91, 125.77, 120.71, 60.59, 49.27, 21.24, 17.37, 15.24, 14.82, 14.71, 14.40, 13.04, 12.06; \(^{11}\)B NMR (CDCl\(_3\), 128 MHz) \(\delta\) 2.10 (s); HRMS (ESI-TOF) \(m/\varepsilon\) 444.2458 [M + Na]\(^+\) calculated for C\(_{28}\)H\(_{31}\)BN\(_2\)O: 444.2468.

4-Cyano-4-phenyl-8-phenyl-6-ethyl-1,3,5,7-tetramethyl-BODIPY (8c). The crude product was purified via TLC (eluent 80/20 hexane/EtOAc) to give an orange solid BODIPY 8c (5.1 mg, 18%) that was recrystallized from 50/50 hexane/dichloromethane: mp 90-95 °C; \(^1\)H NMR (CD\(_2\)Cl\(_2\), 400 MHz) \(\delta\) 7.57-7.53 (m, 3H), 7.50-7.48 (m, 2H), 7.42-7.38 (m, 2H), 7.25 (t, 2H, J = 6.8 Hz), 7.22-7.18 (m, 1H), 5.96 (s, 1H), 2.26 (q, 2H, J = 9.3 Hz), 2.17 (s, 3H), 2.13 (s, 3H), 1.40 (s, 3H), 1.37 (s, 3H), 0.92 (t, 3H, J = 7.5 Hz); \(^{13}\)C NMR (CD\(_2\)Cl\(_2\), 100 MHz) \(\delta\) 141.53, 133.25,
4-Acetoxy-4-phenyl-8-phenyl-6-ethyl-1,3,5,7-tetramethyl-BODIPY (8d). The crude product was purified via TLC (eluent 80/20 hexane/EtOAc) to give an orange solid BODIPY 8d (3.2 mg, 16%) that was recrystallized from 50/50 hexane/EtOAc: mp 100-105 °C; \(^1\)H NMR (CDCl\(_3\), 400 MHz) \(\delta\) 7.55-7.49 (m, 5H), 7.45-7.43 (m, 2H), 7.22 (t, 2H, \(J = 7.1 \) Hz), 7.19-7.16 (m, 1H), 5.82 (s, 1H), 2.24 (q, 2H, \(J = 7.5 \) Hz), 2.11 (s, 3H), 2.05 (s, 3H), 2.02 (s, 3H), 1.38 (s, 3H), 1.33 (s, 3H), 0.88 (t, 3H, \(J = 7.3 \) Hz); \(^{13}\)C NMR (CDCl\(_3\), 100 MHz) \(\delta\) 172.45, 154.27, 152.31, 146.25, 141.63, 140.05, 137.76, 136.32, 133.25, 132.42, 132.21, 131.78, 129.15, 128.95, 128.90, 128.70, 128.43, 127.01, 126.19, 120.86, 29.85, 23.15, 17.35, 15.75, 15.35, 14.69, 14.65, 14.34, 13.66, 13.24, 12.06; \(^{11}\)B NMR (CDCl\(_3\), 128 MHz) \(\delta\) -0.34 (s); HRMS (ESI-TOF) m/z 472.2407 [M + Na]\(^+\) calculated for C\(_{29}\)H\(_{31}\)BN\(_2\)O\(_2\): 472.2397.

4-(N-Boc-ethanoyl)-4-phenyl-8-phenyl-6-ethyl-1,3,5,7-tetramethyl-BODIPY (8e). The crude product was purified via TLC (eluent 80/20 hexane/EtOAc) to give an orange solid BODIPY 8e (5.0 mg, 14%) that was recrystallized from 50/50 hexane/EtOAc: mp 60-65 °C; \(^1\)H NMR (CDCl\(_3\), 400 MHz) \(\delta\) 7.56-7.51 (m, 3H), 7.45-7.41 (m, 3H), 7.37-7.36 (m, 1H), 7.17 (t, 2H, \(J = 6.8 \) Hz), 7.10 (t, 1H, \(J = 7.0 \) Hz), 5.85 (s, 1H), 3.24 (t, 2H, \(J = 5.0 \) Hz), 3.18 (t, 2H, \(J = 4.6 \) Hz), 2.22 (q, 2H, \(J = 7.9 \) Hz), 2.15 (s, 3H), 2.09 (s, 3H), 1.43 (s, 9H), 1.37 (s, 3H), 1.33 (s, 3H), 0.90 (t, 3H, \(J = 7.5 \) Hz); \(^{13}\)C NMR (CD\(_2\)Cl\(_2\), 100 MHz) \(\delta\) 132.78, 129.60, 129.50, 129.15, 129.03, 127.15, 126.21, 120.97, 61.04, 28.74, 28.64, 17.61, 15.46, 14.92, 14.78, 13.38, 12.18; \(^{11}\)B NMR (CDCl\(_3\),
128 MHz) δ 1.10 (s); HRMS (ESI-TOF) m/z 601.3561 [M + Na]+ calculated for C_{36}H_{46}BN_{3}O_{3}: 601.3573.

4-(Tri(ethyleneglycol monomethyl ether)-4-phenyl-8-phenyl-6-ethyl-1,3,5,7-tetramethyl-BODIPY (8f). The crude product was purified via TLC (eluent 80/20 hexane/EtOAc) to give an orange/red oil BODIPY 8f (6.1 mg, 15%) that was recrystallized from 50/50 hexane/EtOAc. \(^1\)H NMR (CD_{2}Cl_{2}, 400 MHz) δ 7.56-7.51 (m, 3H), 7.42 (t, 3H, J = 6.3 Hz), 7.38-7.34 (m, 1H), 7.16 (t, 2H, J = 6.8 Hz), 7.12-7.07 (m, 1H), 5.85 (s, 1H), 3.64-3.61 (m, 2H), 3.60-3.56 (m, 6H), 3.51-3.48 (m, 2H), 3.33 (s, 3H), 3.33-3.28 (m, 2H), 2.23 (q, 2H, J = 7.8 Hz), 2.17 (s, 3H), 2.12 (s, 3H), 1.38 (s, 3H), 1.33 (s, 3H), 0.90 (t, 3H, J = 7.6 Hz); \(^{13}\)C NMR (CD_{2}Cl_{2}, 100 MHz) δ 156.02, 154.00, 141.85, 140.19, 137.69, 136.84, 133.86, 132.81, 132.49, 132.24, 129.58, 129.46, 129.15, 129.10, 127.30, 127.12, 126.21, 126.12, 120.90, 73.22, 73.01, 72.52, 71.23, 71.16, 70.99, 61.54, 59.18, 17.63, 15.43, 14.96, 14.78, 13.34, 12.18; \(^{11}\)BNMR (CDCl_{3}, 128 MHz) δ 1.21 (s); HRMS (ESI-TOF) m/z 576.3244 [M + Na]+ calculated for C_{34}H_{43}BN_{2}O_{4}: 576.3240.

4-(Pro-2-yn-1-yloxy)-4-phenyl-8-phenyl-6-ethyl-1,3,5,7-tetramethyl-BODIPY (8g). The crude product was purified via TLC (eluent 50/50 hexane/dichloromethane) to give an orange solid BODIPY 8g (7.0 mg, 31%) that was recrystallized from 50/50 hexane/EtOAc: mp 120-125 °C; \(^1\)H NMR (CD_{2}Cl_{2}, 400 MHz) δ 7.57-7.51 (m, 3H), 7.43-7.41 (m, 3H), 7.38-7.36 (m, 1H), 7.17 (t, 2H, J = 6.9 Hz), 7.13-7.09 (m, 1H), 5.87 (s, 1H), 3.94 (q, 2H, J = 1.7 Hz), 2.27 (t, ), 2.19 (s, 3H), 2.14 (s, 3H), 1.38 (s, 3H), 1.34 (s, 3H), 0.90 (t, 3H, J = 7.5 Hz); \(^{13}\)C NMR (CD_{2}Cl_{2}, 100 MHz) δ 156.38, 154.17, 141.85, 140.58, 138.17, 136.66, 134.12, 132.70, 132.25, 129.63, 129.51, 129.18, 129.06, 129.02, 127.23, 126.30, 121.09, 84.51, 71.40, 50.35, 17.60, 15.56, 14.90, 14.78, 13.55, 12.20; \(^{11}\)B
NMR (CDCl₃, 128 MHz) δ 1.65 (s); HRMS (ESI-TOF) m/z 468.2458 [M + Na]⁺ calculated for C₃₀H₃₁BN₂O: 468.2449.

General procedure for synthesis of BODIPYs 4 and 9. Dipyrrins 7 or 8 (1.0 equiv.) were dissolved in anhydrous CH₂Cl₂ (5 mL). Et₃N (7.5 equiv) was added dropwise followed by BF₃·OEt₂ (10.0 equiv). The final mixture was stirred for an additional 1 h. The crude products were concentrated under reduced pressure and purified via TLC (eluent 50/50 hexane/dichloromethane) to afford BODIPYs 4 and 9.

4,4-Difluoro-8-phenyl-2,6-diethyl-1,3,5,7-tetramethyl-BODIPY (4). This BODIPY was isolated as an orange solid (41.2 mg, 68%) that was recrystallized from 50/50 hexane/EtOAc: mp 175-180 °C; ¹H NMR (CDCl₃, 400 MHz) δ 7.49-7.47 (m, 3H), 7.30-7.28 (m, 2H), 2.55 (s, 6H), 2.31 (q, 4H, J = 7.6 Hz), 1.29 (s, 6H), 0.99 (t, 3H, J = 7.6 Hz); ¹³C NMR (CDCl₃, 100 MHz) δ 153.80, 140.33, 138.54, 135.94, 132.87, 130.91, 129.14, 128.85, 128.40, 17.20, 14.74, 12.62, 11.74; ¹¹B NMR (CDCl₃, 128 MHz) δ 0.69 (t, J = 33.5 Hz); HRMS (ESI-TOF) m/z 402.2164 [M + Na]⁺ calculated for C₂₃H₂₇BF₂N₂: 402.2143. These data are in agreement with those previously reported.⁸

4,4-Difluoro-8-phenyl-6-ethyl-1,3,5,7-tetramethyl-BODIPY (9). This BODIPY was isolated an orange solid (27.2 mg, 41%) that was recrystallized from 50/50 hexane/EtOAc: mp 195-200 °C; ¹H NMR (CDCl₃, 400 MHz) δ 7.49-7.48 (m, 3H), 7.30-7.27 (m, 2H), 5.95 (s, 1H), 2.56 (s, 6H), 2.32 (q, 2H, J = 7.6 Hz), 1.36 (s, 3H), 1.31 (s, 3H), 0.99 (t, 3H, J = 7.6 Hz); ¹³C NMR (CDCl₃, 100 MHz) δ 155.56, 153.98, 142.07, 141.03, 139.49, 135.55, 133.63, 131.42, 129.20,
128.96, 128.26, 120.70, 29.84, 17.21, 14.67, 14.61, 14.40, 12.77, 11.82; \(^{11}\)B NMR (CDCl\(_3\), 128 MHz) \(\delta\) 0.67 (t, \(J = 33.3\) Hz); HRMS (ESI-TOF) \(m/z\) 352.2031 [M + H]\(^+\) calculated for C\(_{21}\)H\(_{23}\)BF\(_2\)N\(_2\): 352.2034.

### 3.4.3 X-ray Determined Molecular structures

Crystal structures were determined using low-temperature data from a Bruker Kappa APEX-II DUO diffractometer with either Mo K\(\alpha\) or Cu K\(\alpha\) radiation. For all structures, H atoms were located from difference maps but constrained in calculated positions during refinement.

Crystal data 1a: C\(_{21}\)H\(_{19}\)BN\(_4\), \(M = 338.21\), monoclinic, \(a = 23.449(6)\), \(b = 7.1532(18)\), \(c = 21.231(5)\) \(\text{Å}\), \(U = 3561.2(15)\) \(\text{Å}^3\), \(T = 100\) K, space group Pca2\(_1\), \(Z = 8\), \(D_c = 1.262\) g cm\(^{-3}\), \(\mu\) (Cu K\(\alpha\)) = 0.08 mm\(^{-1}\), 9965 reflections measured, \(\theta_{\text{max}} = 26.8^\circ\), 3858 unique (\(R_{\text{int}} = 0.043\)). The final \(R = 0.037\) (3858 \(I>2\sigma(I)\) data), \(wR(F^2) = 0.088\) (all data), CCDC 1457137.

Crystal data 3a: C\(_{23}\)H\(_{21}\)BN\(_4\)O\(_2\), \(M = 396.25\), monoclinic, \(a = 9.6379(6)\), \(b = 29.7309(19)\), \(c = 7.1824(5)\) \(\text{Å}\), \(U = 2009.5(2)\) \(\text{Å}^3\), \(T = 100\) K, space group P2\(_1/c\), \(Z = 4\), \(D_c = 1.310\) g cm\(^{-3}\), \(\mu\) (Cu K\(\alpha\)) = 0.09 mm\(^{-1}\), 1798 reflections measured, \(\theta_{\text{max}} = 26.4^\circ\), 4065 unique (\(R_{\text{int}} = 0.044\)). The final \(R = 0.046\) (2670 \(I>2\sigma(I)\) data), \(wR(F^2) = 0.110\) (all data), CCDC 1457138.

Crystal data 4a: C\(_{25}\)H\(_{27}\)BN\(_4\), \(M = 394.32\), monoclinic, \(a = 20.4760(3)\), \(b = 11.3191(2)\), \(c = 11.2060(2)\) \(\text{Å}\), \(U = 2231.02(6)\) \(\text{Å}^3\), \(T = 100\) K, space group Cc, \(Z = 4\), \(D_c = 1.174\) g cm\(^{-3}\), \(\mu\) (Cu K\(\alpha\)) = 0.07 mm\(^{-1}\), 9990 reflections measured, \(\theta_{\text{max}} = 29.2^\circ\), 3028 unique (\(R_{\text{int}} = 0.034\)). The final \(R = 0.034\) (2878 \(I>2\sigma(I)\) data), \(wR(F^2) = 0.089\) (all data), CCDC 1457139.
Crystal data 5a: C_{19}H_{23}BN_4, M = 318.22, monoclinic, a = 13.8407(4), b = 8.5881(2), c = 16.2914(4) Å, U = 1778.09(8) Å³, T = 100 K, space group P2_1/c, Z = 4, Dc = 1.189 g cm⁻³, μ (Cu Kα) = 0.07 mm⁻¹, 9892 reflections measured, θ_{max} = 30.1°, 5209 unique (R_{int} = 0.043). The final R = 0.045 (3990 I>2σ(I) data), wR(F2) = 0.120 (all data), CCDC 1457139.

Crystal data 7b: C_{30}H_{35}BN_2O, M = 450.41, monoclinic, a = 11.7029(5), b = 13.0834(6), c = 17.1865(7) Å, U = 2502.11(19) Å³, T = 90 K, space group P2_1/n, Z = 4, Dc = 1.196 g cm⁻³, μ (Cu Kα) = 0.55 mm⁻¹, 11723 reflections measured, θ_{max} = 63.7°, 4074 unique (R_{int} = 0.046). The final R = 0.041 (3284 I>2σ(I) data), wR(F2) = 0.115 (all data), CCDC 1415153.

Crystal data 7c: C_{30}H_{32}BN_3, M = 445.40, triclinic, a = 8.0820(5), b = 10.8718(6), c = 15.3444(9) Å, β = 91.560(4)°, U = 1247.30(13) Å³, T = 100 K, space group PI, Z = 2, Dc = 1.186 g cm⁻³, μ(CuKα) = 0.53 mm⁻¹, 11402 reflections measured, θ_{max} = 67.7°, 4208 unique (R_{int} = 0.032). The final R = 0.045 (3469 I>2σ(I) data), wR(F2) = 0.113 (all data), CCDC 1415154.

Crystal data 8c: C_{28}H_{28}BN_3, M = 417.34, orthorhombic, a = 7.4105(5), b = 14.0956(10), c = 22.5059(17) Å, U = 2350.9(3) Å³, T = 90 K, space group P2_12_12_1, Z = 4, Dc = 1.179 g cm⁻³, μ(CuKα) = 0.53 mm⁻¹, 10612 reflections measured, θ_{max} = 68.3°, 4063 unique (R_{int} = 0.051). The final R = 0.045 (3417 I>2σ(I) data), wR(F2) = 0.109 (all data), CCDC 1415155.

3.4.4 Steady-state Absorption and Fluorescence Spectroscopy

The photophysical properties of these compounds 7a-g, 8a-g, 4 and 9 in dichloromethane at room temperature were measured by preparing a stock solution with a concentration of 5 × 10⁻⁵
M and diluting it to appropriate concentrations for absorbance and emission spectra measurements. All the absorption spectra were obtained using a Perkin Elmer Lambda 35 UV/VIS Spectrometer. The optical density, $\varepsilon$, were taken by preparing solution concentrations between $7.5 \times 10^{-6}$ and $2.5 \times 10^{-5} \text{ M}$ in order to get $\lambda_{\text{max}}$ between 0.5 and 1.0. Emission spectra were measured on a Perkin Elmer LS 55 Luminescence spectrometer with the slit width set at 3 nm. All absorbance and emission spectra were acquired within 3 h of fresh solution preparation, at room temperature. A spectrophotometric cell with a path length of 10 nm was used.

3.5 References


33. Crawford, S. M.; Thompson, A., Conversion of 4,4-Difluoro-4-bora-3a,4a-diaza-s-indacenes (F-BODIPYs) to Dipyrrins with a Microwave-Promoted Deprotection Strategy. Org. Lett. 2010, 12, 1424-1427.
CHAPTER 4: SYNTHESIS AND CHARACTERIZATION OF BODIPY-CARBOHYDRATE CONJUGATES AND CHIRAL BODIPYS FOR BIOIMAGING

4.1 Introduction

In the last 10 years, the growth of \textit{in vivo} molecular imaging has progressed rapidly for evaluation of cancer for collaborations among physicians, imaging specialists, chemists, and physicists.\textsuperscript{1} There are three types of molecular imaging: metabolic, targeted, and physiologic. One category of molecular imaging is targeted imaging which consists of fluorophore labeling with a specific ligand that bonds to a receptor. On the other hand, metabolic imaging involves the visualization of metabolic processes of glucose uptake by cells.

The three most common modes of \textit{in vivo} oncologic imaging are nuclear medicine imaging, optical imaging, and magnetic resonance imaging (MRI). Nuclear medicine imaging is a noninvasive treatment that uses a small amount of radioactive tracer with temporal/spatial detection to diagnose a variety of diseases. Positron emission tomography (PET) and single photon emission computed tomographic (SPECT) are the two methods used for \textit{in vivo} nuclear imaging. The advantage of PET and SPECT is their ability to detect the radiotracer amount in a matter of minutes. PET and SPECT are used as imaging techniques that barely disturb the biological system. PET produces higher image resolution than SPECT by using coincident rays to determine radionuclide location. SPECT is a more cost efficient option that produces a broader image range, compared to PET, by using a collimator to select for certain angles of incidence of radionuclide emissions. SPECT imaging modalities, when using advanced equipment, in small animal systems can produce an image resolution better than PET. Although PET and SPECT are advantageous, they do have certain limitations. SPECT has a limit on isotope combinations; so multiple isotopes have to be targeted many times to produce a single image. Both PET and SPECT are more expensive than other imaging methods and they potentially expose patients to more
radioactivity due the ionizing radiation so it is recommended that these tests are performed at a minimum for the safety of the patient.

In metabolic imaging, one particular glucose analog, fluoro-2-deoxy-D-glucose (FDG), has been used extensively for chemotherapeutic uses in order to study the glucose uptake in the body. However, when FDG was injected at therapeutic drug dose, it was found to cause toxicity to the nervous central system and thus was discarded. The alternative analog, $^{18}$F-2-deoxy-D-glucose ($^{18}$F-FDG), which is sensitive in PET and can be used to approximate the amount of glucose uptake during glycolysis. It enters the cell through glucose transporters (GLUTs) and is then phosphorylated. Dephosphorylation by glucose-6-phosphotase allows for a flow of $^{18}$F-FDG in a cell, however the process is extremely slow due to naturally low levels of glucose-6-phosphotase present. It was suggested that $^{18}$F-FDG is much more successful in healthy cells undergoing aerobic respiration than in malignant cells that utilize anaerobic respiration. During aerobic respiration in cells, glycolysis begins to slow down in the presence of oxygen as predicted by the Pasteur effect. The Warburg effect demonstrates that malignant cells use a glycolytic anaerobic respiration pathway even in the presence of oxygen. Although it is less efficient than aerobic respiration; this is a possible adaptation to long-term hypoxia experienced in tumors. The half-life of radioactive $^{18}$F is 110 min, which is long enough to carry out the synthesis and transport it to an imaging laboratory.

4.1.1 Click Chemistry

Nobel Laureate Professor Barry Sharpless first introduced click chemistry in 2001. Since then, it has become a popular method used in many diverse fields. The characteristics of click chemistry are fast reactions and high reaction yields, easy to purify, versatile, and regiospecific. One of the most widely used class of click reaction is copper-catalyzed Huisgen 1,3-dipolar
cycloaddition (HDC) reaction. This reaction does not require high temperature conditions and results in regiospecific 1,4-substituted products. Although “click reactions” was developed in 2001, the utility of click chemistry in BODIPY’s core or 8-phenyl were not reported until the last few years. Approaches to conjugate biomolecules via the meso-phenyl with folate,\(^6\) polyethylene glycol and carbohydrate,\(^7\) and zinc-TPP\(^8-9\) have been reported. The triazole group can directly insert into the dipyrrromethene core at either the 2,6-positions\(^{10}\) or 3,5-positions.\(^{10-11}\) On the other hand, the triazole has also provided a linker between fluorophores for intramolecular resonance energy transfer (RET).\(^{12-14}\) However, having triazole moieties on the boron center for post functionalization of \(F\)-BODIPY has not been reported until recently.\(^{15}\)

![Figure 4.1: Selected examples of (1,2,3-triazole)-BODIPYs.](image-url)
4.1.2 Chiral fluorophore

Chiral recognition has been growing in the last few decades for determination of enantiomeric purity in many chiral functional groups using organic fluorophores.\textsuperscript{16} The study of chiral properties of organic molecules is very important in drug discovery and pharmaceutical chemistry. Fluorophores that are capable of distinguishing one enantiomer from another have an advantage in rapid chiral assays. Some examples of BODIPYs containing a chiral functionality have been reported.\textsuperscript{17-20} Ziessel and coworkers reported the synthesis of 4-mono-aryl BODIPY which has hydrogen bonding between the fluoride atom and 3-aldehyde hydrogen. On the other hand, Sanchez-Carnerero \textit{et al.} demonstrated that a chiral O-BODIPY can be applied in circularly polarized luminescence (CPL) spectroscopy with a 1,1'-binaphthyl moiety on the boron center.

\textbf{Figure 4.2:} Selected examples of chiral BODIPYs.

In order to extend the scope of (1,2,3-triazole)-BODIPYs synthesis, we decided to design and synthesize new fluorophores containing mono-, di-, and tri-(1,2,3-triazole)-BODIPYs bearing a carbohydrate framework in order to study and compare their biological properties. In addition, the synthesis of chiral BODIPY is investigated for chiral recognition applications or stereoselective aldol reactions.
4.2 Results and Discussion

4.2.1 Syntheses of (1,2,3-triazole)-BODIPYs

The goal for this project was to synthesize a series of fluorescent bioconjugates comprising a BODIPY fluorophore bearing a triazole group connected to carbohydrate moiety for target-specific cell accumulation. This has been previously investigated for synthesis of porphyrins and related macrocycles with conjugates for use as photosensitizers for PDT. In addition, mono-radioactive $^{18}$F can be installed on the boron center as a dual-modality fluorescent probe.

![Figure 4.3: Our designed synthetic platform.](image)

Scheme 4.1: Synthesis of BODIPY 1 from 3-ethyl-,2,4-dimethyl pyrrole.

The starting BODIPY 1 was synthesized, as previously reported, by condensation between the commercially available 3-ethyl-2,4-dimethylpyrrole and p-propargyloxy-
benzaldehyde using a 3-step-1-pot reaction in high yield, as shown in Scheme 4.1. The progaryloxy benzaldehyde was synthesized as a crude product via Williamson reaction between propargyl bromide and $p$-hydroxyl benzaldehyde, according to the literature procedure.\textsuperscript{25}

![Scheme 4.2: Synthesis of 4,4-dipropargyl-BODIPY 2.](image)

The progaryloxy groups were introduced at the boron center via activation of BODIPY 1 with aluminum chloride\textsuperscript{15,26} followed by excess propargyl alcohol to afford tri-alkyne BODIPY 2 in 69\% yield (Scheme 4.2). The goal was to provide three terminal alkyne groups for further functionalization using click chemistry.

![Scheme 4.3: Synthesis of BODIPYs 3a and 3b.](image)
BODIPY 2 was subjected to either commercially available benzyl azide or 1-azido-1-deoxy-β-D-glucopyranoside tetraacetate, using solution-phase “click” conditions, which consists of copper(II) sulfate, copper(0) and sodium ascorbate in THF/water (3:1), to give tri-(1,2,3-triazoles)-BODIPYs 3a and 3b. Under an inert gas atmosphere, the mixture were refluxed at 70 °C for 6 h for compounds 3a and 3b. Upon reaction completion, the mixture was cooled to room temperature and partitioned between ethyl acetate and water to remove the generated copper salt by-product. The combined organic layers were dried over Na₂SO₄ and concentrated under reduced pressure. The crude products were purified using preparative-TLC (thin layer chromatography) to give tri-(1,2,3-triazoles)-BODIPYs 3a and 3b in 76% and 64% yields, respectively. Indeed, the click reaction has provided a high yield to conjugate glucose derivate or benzyl to BODIPYs core.

![Scheme 4.4: Fail attempted hydrolysis of BODIPY 3b.](image)

We then attempted to hydrolyze compound 3b under basic condition (NaOMe in MeOH) at 0 °C to give 3c, but the reaction failed. We also attempted various hydrolysis conditions such as
BBr$_3$ or NaOH. The BBr$_3$ conditions gave the corresponding dipyrrromethene while the NaOH conditions replaced the BF$_2$ with B(OH)$_2$.

Scheme 4.5: Synthesis of BODIPYs 4a and 4b.

Having the optimized conditions for the tri-(1,2,3-triazole)-BODIPYs, we turned our attention to the synthesis of mono- and di-(1,2,3-triazole)-BODIPYs. For the mono-azido synthesis, BODIPY 1 was exposed to Cu(I)-catalyzed azide-alkyne cycloaddition with commercially available benzyl azide or 1-azido-1-deoxy-β-D-glucopyranoside tetraacetate to afford BODIPY 4a (93%) and the mono-triazole-tetraacetate-sugar BODIPY 4b (82%) as shown in Scheme 4.5. The mono-triazole-sugar BODIPY 4b was hydrolyzed under basic conditions to give the desired glucose triazole 4c in 93% yield. Surprisingly, the B-(OR)$_2$ moiety was still intact under strong nucleophilic reaction conditions such as NaOMe as confirmed by $^1$H-, $^{13}$C- and $^{11}$B-NMR spectroscopy and also HRMS. Note, when hydrolysis was attempted at room temperature, the B-(OR)$_2$ moiety was removed to give dipyrrromethene.
In order to synthesize the di-triazole-sugar BODIPY, compound 4a was exposed to aluminum chloride (AlCl₃), followed by excess propargyl alcohol to give meso-triazolephenyl BODIPY 5a in 73% yield (Scheme 4.7). The meso-triazolephenyl BODIPY 5a was subjected to Cu(I)-catalyzed azide-alkyne cycloaddition with commercially available 1-azido-1-deoxy-β-D-glucopyranoside tetraacetate to afford compound 6a in 72% yield. BODIPY 6a was purified by silica gel column chromatography but the compound was immobile. Then we decided to use neutral alumina column chromatography and were able to isolate the targeted product in good yield. We also attempted to subject BODIPY 6a to hydrolysis conditions (NaOMe in MeOH at 0 °C) but obtained the 4,4-dihydroxy product. In addition, if we treated BODIPY 5a with the commercially available unprotected glucose azide under the same click reaction conditions, we recovered the starting material and dipyrromethene as a by-product.

4.2.2 Synthesis of chiral BODIPY

We now turned to the synthesis of BODIPY with a boron atom bearing a chiral motif. We began our investigation by introducing a carboxylate group to the boron center through two different methods. Method B consists of treating BODIPY 7 with AlCl₃ and excess addition of
acetic acid to give BODIPY 8b in moderate yield (42%). The conditions were milder and required a shorter time than those previously reported.\textsuperscript{27-28} However, when BODIPY 7 was exposed using method C, a mixture of 4-mono- and 4,4-disubstituted BODIPYs 8a and 8b were obtained with 8% and 14% yields, respectively. Even though method B gave a high yield of the di-substituted product, this method typically required an excess amount of the nucleophile (278 equiv.). For that reason, we decided to use method C for our next investigation.

Scheme 4.7: Synthesis of 4,4-tri(1,2,3-triazole)-BODIPY.
To further explore the extent of this reaction, we used 4-bromobenzoic acid as the nucleophile using method C and were able to obtain the targeted BODIPY 9 in 5% yield (Scheme 4.11). BODIPY 9 was characterized by $^1$H- and $^{11}$B-NMR spectroscopy and X-ray crystallography.

Next, we investigated an amino acid containing carboxylic acid. When we tried tryptophan with Boc-protected amine using method C, we were hoping to isolate the mono- or di-substituted products. Interestingly, the product obtained was the cyclic BODIPY product 10 (Scheme 4.12). To the best of our knowledge, this is the first report of a chiral group and nitrogen atom on the boron center. This compound has a potential for fluorescent chiral recognition. In addition, BODIPY 10 was characterized by $^1$H- and $^{11}$B-NMR spectroscopy and X-ray crystallography.
These results prompted us to further investigate unprotected amino acids. When amino acids without Boc or Fmoc groups were used, the resulting products were dipyrrromethenes. It is possible that electron withdrawing Boc protecting group makes the nitrogen atom less basic. We decided to use ethanolamine as the nucleophile with methods B and C. Similar to acetate, the di-substituted product 11b was obtained in 70% yield with method B while a mixture of mono- and di-products was obtained with method C in 14% and 10% yields, respectively. This indicates that the indole of the tryptophan plays a steric factor and facilitates the cyclization.

Finally, we used ethylene glycol as the nucleophile using methods B and C (Scheme 4.14). We were able to obtain the targeted BODIPY 12 in 21% and 37% yields, respectively.
4.2.3 Structural Characterization

All BODIPYs were characterized by $^1$H-, $^{13}$C-, and $^{11}$B-NMR, and HRMS. BODIPYs 4a-b, 9, 10, 11a and 12 were characterized by X-ray crystallography (see Figures 4.4 and 4.5). The disappearance of the triplet for the BF$_2$ (at ca. 0.6 ppm) and the appearance of the singlet attributed to B(OR)$_2$ (at ca. 2 ppm) in the $^{11}$B-NMR spectra clearly showed the formation of the targeted 4,4-dialkoxy-BODIPY. The $^1$H-NMR spectrum clearly indicated the formation of the 1,2,3-triazoles of BODIPY 3a-b, 4a-c, and 6a with singlets ranging from 7.50-8.12 ppm.

Figure 4.4: Molecular structures of BODIPYs 4a-b from X-ray crystal analysis, with 50% probability ellipsoids.
Figure 4.5: Molecular structures of BODIPYs 9, 10, 11a and 12 from X-ray crystal analysis, with 50% probability ellipsoids.

Full structural confirmation of all compounds was obtained from the X-ray crystal structures. Crystals suitable for X-ray analysis were grown by slow evaporation of dichloromethane diffused in acetone (for 4a-b), hexane in dichloromethane (for 9, 11a, and 12),
and EtOAc in MeOH (for 10). The alkoxy groups on the boron center adopt a nearly tetrahedral geometry.

4.3 Conclusions

A series of six 1,2,3-triazole-BODIPYs were synthesized in high yields under the Cu(I)-catalyzed Huisgen cycloaddition reaction conditions. A BODIPY bearing one triazole group was shown to undergo hydrolysis while two or three triazole resulted in the 4,4-hydroxyl product. Acetyl and 1,2-Boc-aminoalcohol groups were introduced to the boron center through two different methods. Method B was the most effective way to give the di-substituted BODIPYs 8b and 11b in 42% and 70% yields, respectively. Method C gave a mixture of 4-mono-acetyl-BODIPYs 8a (8%) and 4,4-di-acetyl-BODIPY 8b (14%) and 4-mono-alkoxy 11a (14%) and 4,4-dialkoxy 11b (10%). A novel BODIPY bearing a chiral moiety was synthesized using method C and X-ray crystallography confirmed its identity.

4.4 Experimental

4.4.1 General Considerations

All commercially available reagents were purchased from Sigma-Aldrich and were used without further purification. All anhydrous reactions were carried out with oven-dried glassware under a dry argon atmosphere. All the reactions were monitored by using Sorbent Technologies pre-coated polyester backed TLC (200 µm silica gel with indicator UV-254 nm). Flash column chromatography was performed using Sorbent Technologies 60 Å alumina neutral (230-400 mesh). All preparative-TLC were used with Silica Gel 60 Å silica gel 20 x 20 cm (210-270 µm). All 1H-, 13C-, 11B-NMR spectral were collected using AV-400 spectrometer (operating at 400 MHz for 1H NMR and 100 MHz for 13C NMR) and deuterated acetone or chloroform as solvents. The CDCl₃ chemical shifts (δ) are reported ppm with 7.27 for proton and 77.16 for carbon NMR as
reference. The (CD$_3$)$_2$CO chemical shift (δ) are reported ppm with 2.05 for proton and 29.84 and 206.26 for carbon NMR as reference. The BF$_3$•OEt$_2$ chemical shift (δ) is reported with 0.00 for boron NMR as reference. Coupling constants are reported in Hertz (Hz). All the mass spectra were collected using an Agilent 6210 ESI-TOF mass spectrometer.

### 4.4.2 Syntheses

**BODIPY (1).** The BODIPY 1 was synthesized according to the literature.$^{7,25}$ $^1$H NMR (CDCl$_3$, 400 MHz) δ 7.20 (d, J = 8.0 Hz, 2H), 7.09 (d, J = 8.0 Hz, 2H), 4.77 (s, 2H), 2.57 (s, 1H), 2.54 (s, 6H), 2.31 (q, J = 7.3 Hz, 4H), 1.33 (s, 6H), 0.99 (t, J = 7.4 Hz, 6H); $^{13}$C NMR (CDCl$_3$, 100 MHz) δ 158.06, 153.70, 140.04, 138.51, 132.81, 129.60, 128.94, 115.64, 75.97, 56.14, 17.18, 14.75, 12.80, 11.94; $^{11}$B NMR (CDCl$_3$, 128 MHz) δ 0.68 (t, J = 33.3 Hz).

**BODIPY (2).** In an oven-dried flask, *meso*-alkynylphenyl-BODIPY 1 (100 mg, 0.230 mmol, 1.0 equiv.) and AlCl$_3$ (61 mg, 0.460 mmol, 2.0 equiv.) were dissolved in anhydrous CH$_2$Cl$_2$ (20 mL). The mixture was refluxed for 30 min and propargyl alcohol (3.7 mL, 64.007 mmol, 278.0 equiv.) was added for an additional 30 min. After the mixture was cooled to room temperature and stirred for 2 h, the crude product was concentrated under reduced pressure. The crude product was purified via TLC (eluent 80:20 hexane/EtOAc) to afford BODIPY 2 (80.6 mg, 69% yield) as an orange solid, that was recrystallized from 1:1 hexane/dichloromethane. $^1$H NMR (CDCl$_3$, 400 MHz) δ 7.21 (d, J = 8 Hz, 2H), 7.09 (d, J = 8 Hz, 2H), 4.78 (s, 2H), 3.81 (s, 4H), 2.57 (s, 6H), 2.31 (q, J = 7.3 Hz, 4H), 2.04 (s, 2H), 1.33 (s, 6H), 0.98 (t, J = 7.2 Hz, 6H); $^{13}$C NMR (CDCl$_3$, 100 MHz) δ 157.86, 154.72, 139.39, 137.15, 132.71, 132.30, 129.69, 129.38, 115.44, 83.27, 78.15, 75.80, 70.44, 56.06, 49.80, 17.11, 14.71, 12.75, 11.89; $^{11}$B NMR (CDCl$_3$, 128 MHz) δ 1.76 (s); HRMS (ESI-TOF) m/z 528.2669 [M + Na]$^+$ calculated for C$_{32}$H$_{33}$BN$_2$O$_3$: 528.2681.
BODIPY (3a). BODIPY 2 (17.5 mg, 0.035 mmol, 1.0 equiv.) and Cu(0) (2.2 mg, 0.035 mmol, 1.0 equiv.) were dissolved in a mixture of THF/water (8 mL, 3:1) under inert gas atmosphere. Benzyl azide (0.043 mL, 0.346 mmol, 10.0 equiv.) was added dropwise to the reaction mixture. A solution of CuSO₄·5H₂O (1.7 mg, 0.007 mmol, 0.2 equiv.) and sodium-ascorbate (3.4 mg, 0.017 mmol, 0.5 equiv.) in THF/water (8 mL, 3:1) was added (after sonication for 30 min) and the reaction mixture was heated for 22 h at 70 °C. Once TLC indicated complete consumption of starting material, the mixture was cooled to room temperature and partitioned between ethyl acetate (30 mL) and water (30 mL). The combined organic layers were dried over Na₂SO₄ and then concentrated under reduced pressure. The crude product was purified via TLC (eluted 20:80 hexane/EtOAc) to afford triazoles BODIPY 3a (23.8 mg, 76% yield) and was recrystallized from 1:3 acetone/hexanes. ¹H NMR (CDCl₃, 400 MHz) δ 7.59 (s, 1H), 7.38-7.23 (m, 15H), 7.17 (d, J = 8.0 Hz, 2H), 7.07 (d, J = 8 Hz, 2H), 5.57 (s, 2H), 5.42 (s, 4H), 5.25 (s, 2H), 4.22 (s, 4H), 2.39 (s, 6H), 2.22 (q, J = 7.12 Hz, 4H), 1.28 (s, 6H), 0.93 (t, J = 6.8 Hz, 6H); ¹³C NMR (CDCl₃, 100 MHz) δ 158.67, 153.79, 149.71, 144.31, 140.18, 137.32, 134.93, 134.51, 132.72, 132.53, 129.85, 129.31, 129.24, 129.11, 129.00, 128.90, 128.69, 128.27, 128.24, 122.78, 121.65, 115.35, 62.21, 56.84, 54.43, 54.10, 21.15, 17.20, 14.81, 14.30, 12.62, 11.99; ¹¹B NMR (CDCl₃, 128 MHz) δ 2.10 (s); HRMS (ESI-TOF) m/z 927.4589 [M + Na]⁺ calculated for C₅₃H₅₆BN₁O₅: 927.4593.

BODIPY (3b). Tri-alkynyl-BODIPY 2 (27.2 mg, 0.054 mmol, 1.0 equiv.), Cu(0) (13.7 mg, 0.215 mmol, 4.0 equiv.), and 1-azido-1-deoxy-β-D-glucopyranoside tetraacetate (301 mg, 0.806 mmol, 15.0 equiv.) were dissolved in a mixture of THF/water (8 mL, 3:1) under an inert gas atmosphere. A solution of CuSO₄·5H₂O (10.1 mg, 0.040 mmol, 0.75 equiv.) and sodium-ascorbate (21.3 mg, 0.107 mmol, 2.0 equiv.) in THF/water (8 mL, 3:1) was added (after sonication for 30
min) and the reaction mixture was heated for 14 h at 70 °C. Once TLC indicated complete consumption of starting material, the mixture was cooled to room temperature and partitioned between ethyl acetate (30 mL) and water (30 mL). The combined organic layers were dried over Na₂SO₄ and then concentrated under reduced pressure. The crude product was purified via alumina neutral flash chromatography (eluent 100% EtOAc to 95:5 EtOAc/MeOH) to give BODIPY 3b (56.3 mg, 64% yield) and was recrystallized from EtOAc. ¹H NMR ((CD₃)₂CO, 400 MHz) δ 8.43 (s, 1H), 8.12 (s, 1H), 7.98 (d, J = 8.0 Hz, 2H), 7.37 (d, J = 8.0 Hz, 2H), 6.27 (d, J = 8.0 Hz, 1H), 6.22 (d, J = 8.1 Hz, 1H), 6.17 (d, J = 8.1 Hz, 1H), 5.64 (d, J = 8.0 Hz, 2H), 5.62 (s, 6H), 5.54 (d, 2H), 5.29 (d, 2H), 4.36-4.32 (m, 4H), 4.26-4.23 (m, 4H), 4.22-4.19 (m, 4H), 2.54 (s, 6H), 2.35 (q, J = 7.52 Hz, 4H), 2.04 (s, 9H), 2.01 (s, 9H), 1.97 (s, 9H), 1.79 (s, 9H), 1.41 (s, 6H), 0.98 (t, J = 7.44 Hz, 6H); ¹³C NMR (CDCl₃, 100 MHz) δ 170.79, 170.34, 170.14, 169.30, 154.93, 141.63, 137.82, 133.43, 130.86, 123.73, 121.79, 121.42, 116.44, 86.06, 85.88, 75.42, 75.32, 73.65, 71.53, 71.46, 68.93, 68.86, 62.91, 62.8, 57.10, 55.03, 20.71, 20.68, 20.59, 20.28, 20.23, 17.73, 15.14, 12.98, 12.33; ¹¹B NMR (CDCl₃, 128 MHz) δ 2.05 (s); HRMS (ESI-TOF) m/z 1647.6033 [M + Na]+ calculated for C₇₄H₉₂BN₁₁O₃₀: 1647.6019.

BODIPY (4a). BODIPY 1 (30 mg, 0.069 mmol, 1.0 equiv.) and Cu(0) (4.4 mg, 0.069 mmol, 1.0 equiv.) were dissolved in a mixture of THF/water (8 mL, 3:1) under an inert gas atmosphere. Benzyl azide (0.022 mL, 0.180 mmol, 2.6 equiv.) was added dropwise to the reaction mixture. A solution of CuSO₄·5H₂O (3.4 mg, 0.014 mmol, 0.2 equiv.) and sodium-ascorbate (6.8 mg, 0.035 mmol, 0.5 equiv.) in THF/water (8 mL, 3:1) was added (after sonication for 30 min) and the reaction mixture was heated for 6 h at 70 °C. Once TLC indicated complete consumption of starting material, the mixture was cooled to room temperature and partitioned between ethyl
acetate (30 mL) and water (30 mL). The combined organic layers were dried over Na₂SO₄ and then concentrated under reduced pressure. The crude product was purified via TLC (eluent 50:50 hexane/EtOAc) to afford BODIPY 4a (36.4 mg, 93% yield) and was recrystallized from 1:3 dichloromethane/hexane. ¹H NMR (CDCl₃, 400 MHz) δ 7.60 (s, 1H), 7.39-7.28 (m, 5H), 7.18 (d, J = 8.0 Hz, 2H), 7.09 (d, J = 8.0 Hz, 2H), 5.58 (s, 2H), 5.25 (s, 2H), 2.54 (s, 6H), 2.30 (q, J = 7.4 Hz, 4H), 1.31 (s, 6H), 1.00 (t, J = 7.16 Hz, 6H); ¹³C NMR (CDCl₃, 100 MHz) δ 158.75, 153.69, 144.24, 140.11, 138.49, 134.52, 132.81, 131.23, 129.66, 129.30, 129.00, 128.63, 128.26, 122.83, 115.41, 62.18, 54.42, 17.18, 14.74, 12.59, 11.91; ¹¹B NMR (CDCl₃, 128 MHz) δ 0.68 (t, J = 33.7 Hz); HRMS (ESI-TOF) m/z 589.2910 [M + Na]⁺ calculated for C₃₃H₃₆BF₂N₅O: 589.2895.

BODIPY (4b). BODIPY 1 (50 mg, 0.115 mmol, 1.0 equiv.), Cu(0) (14.6 mg, 0.230 mmol, 2.0 equiv.), and 1-azido-1-deoxy-β-D-glucopyranoside tetraacetate (214.9 mg, 0.576 mmol, 5 equiv.) were dissolved in a mixture of THF/water (8 mL, 3:1) under an inert gas atmosphere. A solution of CuSO₄·5H₂O (11.5 mg, 0.046 mmol, 0.4 equiv.) and sodium-ascorbate (22.8 mg, 0.115 mmol, 1.0 equiv.) in THF/water (8 mL, 3:1) was added (after sonication for 30 min) and the reaction mixture was heated for 21 h at 70 °C. Once TLC indicated complete consumption of starting material, the mixture was cooled to room temperature and partitioned between ethyl acetate (30 mL) and water (30 mL). The combined organic layers were dried over Na₂SO₄ and then concentrated under reduced pressure. The crude product was purified via TLC (elucent 50:50 hexane/EtOAc) to afford BODIPY 4b (76.5 mg, 82% yield) and was recrystallized from 1:3 dichloromethane/hexane. ¹H NMR ((CD₃)₂CO, 400 MHz) δ 8.43 (s, 1H), 7.30-7.25 (m, 4H), 6.30 (d, J = 8.1 Hz, 1H), 5.67 (t, J = 9.4 Hz, 1H), 5.57 (t, J = 9.4 Hz, 1H), 5.31 (s, 2H), 4.40-4.36 (m, 1H), 4.30-4.25 (m, 1H), 4.21-4.18 (m, 1H), 2.49 (s, 6H), 2.35 (q, J = 7.5 Hz, 4H), 2.00 (s, 3H),
1.98 (s, 3H), 1.96 (s, 3H), 1.83 (s, 3H), 1.39 (s, 6H), 0.99 (t, \( J = 7.5 \) Hz, 6H); \(^{13}\text{C} \text{NMR} ((\text{CD}_3)_2\text{CO}, 100 \text{ MHz}) \delta 170.76, 170.35, 170.17, 169.40, 160.18, 154.24, 144.92, 141.80, 139.29, 133.58, 131.97, 130.56, 129.01, 123.76, 116.55, 86.07, 75.43, 73.52, 71.53, 68.84, 62.78, 62.63, 20.67, 20.58, 20.27, 17.56, 15.04, 12.66, 12.19; \(^{11}\text{B} \text{NMR} (\text{CDCl}_3, 128 \text{ MHz}) \delta 0.67 (t, \( J = 33.9 \) Hz); HRMS (ESI-TOF) \( m/z \) 829.3391 [M + Na]\(^+\) calculated for C\(_{40}\)H\(_{48}\)BF\(_2\)N\(_5\)O\(_{10}\): 829.3384.

BODIPY (4c). BODIPY 4b (22.5 mg, 0.028 mmol, 1.0 equiv.) and NaOMe (6.3 mg, 0.117 mmol, 4.2 equiv.) were dissolving in MeOH (5 mL) at 0 °C. The mixture was stirred for 30 min and then warmed to room temperature. Once TLC indicated complete consumption of starting material, Dowex 50WX8 H\(^+\) resin was added and stirred until the solution is neutral. The resin was filtered off and crude product was concentrated by reduced pressure. The crude product was purified using alumina column chromatography (eluent 50:50 dichloromethane/acetone) to afford BODIPY 4c (16.5 mg, 93% yield) and was recrystallized from 1:6 water/dichloromethane. \(^{1}\text{H} \text{NMR} ((\text{CD}_3)_2\text{CO}, 400 \text{ MHz}) \delta 8.31 (s, 1H), 7.29 (s, 4H), 5.70 (d, 1H), 5.30 (s, 2H), 4.71 (d, \( J = 4.0 \) Hz, 2H), 4.64 (d, \( J = 4.0 \) Hz, 2H), 4.46 (d, \( J = 4.0 \) Hz, 2H), 4.04-3.98 (m, 1H), 3.89-3.82 (m, 2H), 3.74-3.63 (m, 3H), 3.60-3.54 (m, 1H), 2.49 (s, 6H), 2.35 (q, \( J = 7.56 \) Hz, 4H), 1.39 (s, 6H), 0.99 (t, \( J = 7.5 \) Hz, 6H); \(^{13}\text{C} \text{NMR} ((\text{CD}_3)_2\text{CO}, 100 \text{ MHz}) \delta 160.63, 154.58, 139.65, 133.91, 132.32, 130.92, 129.27, 124.43, 116.81, 89.39, 81.17, 78.92, 74.19, 71.41, 62.98, 62.90, 17.91, 15.39, 13.02, 12.55; \(^{11}\text{B} \text{NMR} (\text{CDCl}_3, 128 \text{ MHz}) \delta 0.60 (t, \( J = 34.3 \) Hz); HRMS (ESI-TOF) \( m/z \) 639.3149 [M + H]\(^+\) calculated for C\(_{32}\)H\(_{40}\)BF\(_2\)N\(_5\)O\(_6\): 639.3109.

BODIPY (5a). In an oven-dried flask, BODIPY 4a (45.2 mg, 0.080 mmol, 1.0 equiv.) with AlCl\(_3\) (21 mg, 0.159 mmol, 2.0 equiv.) were dissolving in anhydrous CH\(_2\)Cl\(_2\) (10 mL). The mixture
was refluxed for 30 min and propargyl alcohol (1.278 mL, 22.143 mmol, 278.0 equiv.) was added for an additional 30 min. After the reaction cooled to room temperature and stirred for 1 h, the crude product was concentrated under reduced pressure. The crude product was purified via TLC (eluent 50:50 hexane/EtOAc) to afford BODIPY 5a (37.3 mg, 73% yield) and was recrystallized from 1:1 hexane/EtOAc. \( ^1\)H NMR (CDCl\(_3\), 400 MHz) \( \delta \) 7.59 (s, 1H), 7.39-7.32 (m, 5H), 7.19 (d, \( J = 8.0 \) Hz, 2H), 7.08 (d, \( J = 8.0 \) Hz, 2H), 5.58 (s, 2H), 5.25 (s, 2H), 3.80 (s, 4H), 2.57 (s, 6H), 2.30 (q, \( J = 7.3 \) Hz, 4H), 2.04 (s, 2H), 1.30 (s, 6H), 0.98 (t, \( J = 6.8 \) Hz, 6H); \( ^{13}\)C NMR (CDCl\(_3\), 100 MHz) \( \delta \) 158.64, 154.75, 144.26, 139.56, 137.21, 134.52, 132.77, 132.40, 129.82, 129.28, 129.11, 128.97, 128.25, 122.80, 115.28, 83.35, 70.55, 62.18, 54.41, 49.88, 17.20, 14.81, 12.83, 11.96; \( ^{11}\)B NMR (CDCl\(_3\), 128 MHz) \( \delta \) 1.77 (s); HRMS (ESI-TOF) \( m/z \) 661.3309 [M + Na]\(^+\) calculated for C\(_{39}\)H\(_{42}\)BN\(_5\)O\(_3\): 661.3318.

BODIPY (6a). BODIPY 5a (7.8 mg, 0.012 mmol, 1.0 equiv.), Cu(0) (3.1 mg, 0.049 mmol, 4.0 equiv.), and 1-azido-1-deoxy-\( \beta \)-D-glucopyranoside tetraacetate (68.3 mg, 0.183 mmol, 15 equiv.) were dissolved in a mixture of THF/water (4 mL, 3:1) under an inert gas atmosphere. A solution of CuSO\(_4\)·5H\(_2\)O (2.3 mg, 0.009 mmol, 0.75 equiv.) and sodium-ascorbate (4.8 mg, 0.024 mmol, 2.0 equiv.) in THF/water (4 mL, 3:1) was added (after sonication for 30 min) and the reaction mixture was heated for 21 h at 70 °C. Once TLC indicated complete consumption of starting material, the mixture was cooled to room temperature and partitioned between ethyl acetate (30 mL) and water (30 mL). The combined organic layers were dried over Na\(_2\)SO\(_4\) and then concentrated under reduced pressure. The crude product was purified via alumina column chromatography (eluent 100% EtOAc to 1:1 EtOAc/acetone) to afford BODIPY 6a (12.1 mg, 72% yield) and was recrystallized from acetone. \( ^1\)H NMR ((CD\(_3\))\(_2\)CO, 400 MHz) \( \delta \) 8.12 (s, 2H), 7.97
BODIPY (7). Benzaldehyde (1.0 mL, 9.81 mmol) was suspended in anhydrous CH$_2$Cl$_2$ (300 mL). 2,4-Dimethylpyrrole (2.12 mL, 20.6 mmol) was added, followed by 6 drops of BF$_3$•OEt$_2$ to the reaction mixture. After stirring for 48 h, TLC indicated no more aryl aldehyde in the reaction mixture, and DDQ (1.113 g, 4.91 mmol) in CH$_2$Cl$_2$ was then added. After 1.5 h stirring at room temperature, NEt$_3$ (10.3 mL, 73.58 mmol) was added and after another 1 h BF$_3$•OEt$_2$ (12.1 mL, 98.1 mmol) was added. The final mixture was stirred at room temperature for 6 h and then poured into water (50 mL). The organic layer was washed with water (2 x 50 mL). The combined organic layers were dried over anhydrous Na$_2$SO$_4$ and concentrated under reduced pressure. The product was purified by silica gel flash column chromatography using mixtures of petroleum ether and dichloromethane to afford BODIPY 7 as a green/orange solid (20% yield, 650 mg). $^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ 7.47-7.26 (m, 5H), 5.98 (s, 2H), 2.56 (s, 6H), 1.38 (s, 6H); $^{13}$C NMR (CDCl$_3$, 100 MHz) $\delta$ 155.57, 143.29, 141.87, 135.14, 131.57, 129.26, 129.26, 128.08, 121.34, 14.71, 14.46; $^{11}$B NMR (CDCl$_3$, 128 MHz) $\delta$ 0.65 (t, $J = 33.4$ Hz); HRMS (ESI-TOF) $m/z$ 324.1718 [M + H]$^+$
calculated for C_{19}H_{20}BF_{2}N_{2}: 324.1728. These data are in agreement with those previously reported.\textsuperscript{29-30}

Synthesis of BODIPY 8b using method B. In an oven-dried flask, BODIPY 7 (20.0 mg, 0.062 mmol, 1.0 equiv.) with AlCl\textsubscript{3} (16.5 mg, 0.123 mmol, 2.0 equiv.) were dissolved in anhydrous CH\textsubscript{2}Cl\textsubscript{2} (5 mL). The mixture was refluxed for 30 min and acetic acid (0.987 mL, 17.236 mmol, 278.0 equiv.) was added for an addition 30 min. After the reaction cooled to room temperature and stirred for 2 h, the crude product was concentrated under reduced pressure. The crude product was purified via TLC (eluent 50:50 hexane/EtOAc) to afford BODIPY 8b (10.4 mg, 42% yield) as an orange solid, that was recrystallized from 1:1 hexane/dichloromethane. \textsuperscript{1}H NMR (CDCl\textsubscript{3}, 400 MHz) \(\delta\) 7.47 (d, \(J = 5.6\) Hz, 3H), 7.39 (d, \(J = 5.7\) Hz, 2H), 5.94 (s, 2H), 2.45 (s, 6H), 2.05 (s, 6H), 1.39 (s, 6H); \textsuperscript{13}C NMR (CDCl\textsubscript{3}, 100 MHz) \(\delta\) 171.61, 152.98, 142.99, 135.36, 133.12, 129.09, 128.86, 128.27, 121.44, 23.09, 14.73; \textsuperscript{11}B NMR (CDCl\textsubscript{3}, 128 MHz) \(\delta\) -0.40 (s); HRMS (ESI-TOF) \(m/z\) 426.1836 [M + Na]\textsuperscript{+} calculated for C\textsubscript{23}H\textsubscript{25}BN\textsubscript{2}O\textsubscript{4}: 426.1851.

Synthesis of BODIPYs 8a and 8b using method C. In an oven-dried flask, BODIPY 7 (20 mg, 0.062 mmol, 1.0 equiv.) and TMSOTf (28.0 \(\mu\)L, 0.154 mmol, 2.5 equiv.) were dissolved in anhydrous toluene (5 mL) and the mixture was refluxed for 30 min. The solution was allowed to cool down to room temperature and acetic acid (18 \(\mu\)L, 0.308 mmol, 5.0 equiv.) was added, followed by DIPEA (27.0 \(\mu\)L, 0.154 mmol, 2.5 equiv.). After 1 h stirring at room temperature, the crude product was concentrated under reduced pressure and was purified via TLC (eluent 50:50 hexane/EtOAc) to afford BODIPYs 8a (1.7 mg, 8% yield) and 8b (3.4 mg, 14% yield).
BODIPY (8a). Recrystallized from 1:1 hexane/dichloromethane. $^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ 7.56-7.36 (m, 3H), 7.31-7.29 (m, 2H), 5.96 (s, 2H), 2.50 (s, 6H), 2.01 (s, 3H), 1.57 (s, 6H); $^{11}$B NMR (CDCl$_3$, 128 MHz) $\delta$ 0.33 (d, $J = 26.88$ Hz); HRMS (ESI-TOF) $m/z$ 386.1687 [M + Na]$^+$ calculated for C$_{21}$H$_{22}$BFN$_2$O$_2$: 386.1697.

BODIPY (8b). Recrystallized from 1:1 hexane/dichloromethane. $^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ 7.47 (d, $J = 5.6$ Hz, 3H), 7.39 (d, $J = 5.7$ Hz, 2H), 5.94 (s, 2H), 2.45 (s, 6H), 2.05 (s, 6H), 1.39 (s, 6H); $^{13}$C NMR (CDCl$_3$, 100 MHz) $\delta$ 171.61, 152.98, 142.99, 135.36, 133.12, 129.09, 128.86, 128.27, 121.44, 23.09, 14.73; $^{11}$B NMR (CDCl$_3$, 128 MHz) $\delta$ -0.40 (s); HRMS (ESI-TOF) $m/z$ 426.1836 [M + Na]$^+$ calculated for C$_{23}$H$_{25}$BN$_2$O$_4$: 426.1851.

BODIPY (9). In an oven-dried flask, BODIPY 7 (20 mg, 0.062 mmol, 1.0 equiv.) and TMSOTf (28.0 µL, 0.154 mmol, 2.5 equiv.) were dissolved in anhydrous toluene (5 mL) and the mixture was refluxed for 30 min. The solution was allowed to cool down to room temperature and 4-bromobenzoic acid (61.9 mg, 0.308 mmol, 5.0 equiv) was added, followed by DIPEA (27.0 µL, 0.154 mmol, 2.5 equiv.). After 1 h stirring at room temperature, the crude product was concentrated under reduced pressure and was purified via TLC (eluent 50:50 hexane/EtOAc) to afford BODIPY 9 (2.1 mg, 5% yield) and was recrystallized from 1:1 hexane/dichloromethane. $^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ 8.05 (d, $J = 8.1$ Hz, 4H), 7.59 (d, $J = 8.1$ Hz, 4H), 7.26 (s, 5H), 5.92 (s, 2H), 2.36 (s, 6H); $^{11}$B NMR (CDCl$_3$, 128 MHz) $\delta$ 0.48 (s).

BODIPY (10). In an oven-dried flask, BODIPY 7 (20 mg, 0.062 mmol, 1.0 equiv.) and TMSOTf (28.0 µL, 0.154 mmol, 2.5 equiv.) were dissolved in anhydrous toluene (5 mL) and the
mixture was refluxed for 30 min. The solution was allowed to cool down to room temperature and Boc-Trp-OH (94.0 mg, 0.308 mmol, 5.0 equiv) was added, followed by DIPEA (54.0 µL, 0.154 mmol, 5.0 equiv.). After 1 h stirring at room temperature, the crude product was concentrated under reduced pressure and was purified via TLC (eluent 50:50 hexane/EtOAc) to afford BODIPY 10 (4.9 mg, 13% yield) and was recrystallized from 1:1 MeOH/EtOAc. \(^1\)H NMR (CDCl\(_3\), 400 MHz) δ 8.13 (s, 1H), 8.07 (s, 1H), 7.53-7.45 (m, 4H), 7.41-7.32 (m, 3H), 7.26 (s, 4H), 7.17 (dd, \(J = 6.6, 3.3\) Hz, 3H), 6.03 (s, 1H), 5.95 (s, 1H), 4.53 (d, \(J = 9.0\) Hz, 1H), 3.72 (d, \(J = 13.8\) Hz, 1H), 3.37 (dd, \(J = 13.6, 9.0\) Hz, 2H), 2.52 (s, 3H), 2.17 (s, 3H), 1.38 (d, \(J = 6.6\) Hz, 6H), 1.25 (s, 9H). \(^{11}\)B NMR (CDCl\(_3\), 128 MHz) δ 1.66 (s); HRMS (ESI-TOF) \(m/z\) 589.2986 [M + H]\(^+\) calculated for C\(_{35}\)H\(_{38}\)BN\(_4\)O\(_4\): 589.3004.

Synthesis of BODIPY 11b using method B. In an oven-dried flask, BODIPY 7 (20.0 mg, 0.062 mmol, 1.0 equiv.) with AlCl\(_3\) (16.5 mg, 0.123 mmol, 2.0 equiv.) were dissolved in anhydrous CH\(_2\)Cl\(_2\) (5 mL). The reaction was refluxed for 30 min and N-Boc-ethanolamine (0.143 mL, 0.925 mmol, 15.0 equiv.) was added for an additional 30 min. After the reaction cooled to room temperature and stirred for 2 h, the crude product was concentrated under reduced pressure. The crude product was purified via TLC (eluent 50:50 hexane/EtOAc) to afford BODIPY 8b (26.2 mg, 70% yield) as an orange solid, that was recrystallized from 1:1 hexane/dichloromethane. \(^1\)H NMR (CDCl\(_3\), 400 MHz) δ 7.54-7.46 (m, 3H), 7.32-7.28 (m, 2H), 5.96 (s, 2H), 3.22-3.12 (m, 4H), 3.12-3.00 (m, 4H), 2.56 (s, 6H), 1.42 (s, 18H), 1.37 (s, 6H); \(^{13}\)C NMR (CDCl\(_3\), 100 MHz) δ 156.95, 156.24, 155.20, 142.12, 135.34, 132.73, 129.18, 128.95, 128.20, 121.44, 79.73, 62.69, 60.99, 43.28, 42.42, 28.55, 28.49, 14.83, 14.56; \(^{11}\)B NMR (CDCl\(_3\), 128 MHz) δ 2.05 (s); HRMS (ESI-TOF) \(m/z\) 628.3517 [M + Na]\(^+\) calculated for C\(_{33}\)H\(_{47}\)BN\(_4\)O\(_6\): 628.3507.
Synthesis of BODIPYs 11a and 11b using method C. In an oven-dried flask, BODIPY 7 (20 mg, 0.062 mmol, 1.0 equiv.) and TMSOTf (28.0 µL, 0.154 mmol, 2.5 equiv.) were dissolved in anhydrous toluene (5 mL) and the mixture was refluxed for 30 min. The solution was allowed to cool down to room temperature and N-Boc-ethanolamine (48 µL, 0.308 mmol, 5.0 equiv) was added, followed by DIPEA (27.0 µL, 0.154 mmol, 2.5 equiv.). After 1 h stirring at room temperature, the crude product was concentrated under reduced pressure and was purified via TLC (eluent 50:50 hexane/EtOAc) to afford BODIPYs 11a (3.9 mg, 14% yield) and 11b (3.8 mg, 10% yield).

BODIPY (11a). Recrystallized from 1:1 hexane/dichloromethane. \(^1\)H NMR (CDCl\(_3\), 400 MHz) δ 7.53-7.45 (m, 3H), 7.36-7.24 (m, 2H), 5.97 (s, 2H), 3.17 (t, \(J = 5.3\) Hz, 2H), 3.09 (t, \(J = 5.0\) Hz, 2H), 2.56 (s, 6H), 1.42 (s, 9H), 1.38 (s, 6H); \(^{13}\)C NMR (CDCl\(_3\), 100 MHz) δ 142.68, 135.26, 132.15, 129.22, 129.02, 128.17, 128.14, 121.42, 28.57, 28.51, 14.84, 14.54; \(^{11}\)B NMR (CDCl\(_3\), 128 MHz) δ 1.47 (d, \(J = 23.04\) Hz); HRMS (ESI-TOF) m/z 487.2540 [M + H]\(^+\) calculated for C\(_{31}\)H\(_{30}\)BN\(_3\)O\(_2\): 487.2535.

BODIPY (11b). Recrystallized from 1:1 hexane/dichloromethane. \(^1\)H NMR (CDCl\(_3\), 400 MHz) δ 7.54-7.46 (m, 3H), 7.36-7.28 (m, 2H), 5.96 (s, 2H), 3.22-3.12 (m, 4H), 3.12-3.00 (m, 4H), 2.56 (s, 6H), 1.42 (s, 18H), 1.37 (s, 6H); \(^{13}\)C NMR (CDCl\(_3\), 100 MHz) δ 156.95, 156.24, 155.20, 142.12, 135.34, 132.73, 129.18, 128.95, 128.20, 121.44, 79.73, 62.69, 60.99, 43.28, 42.42, 28.55, 28.49, 14.83, 14.56; \(^{11}\)B NMR (CDCl\(_3\), 128 MHz) δ 2.05 (s); HRMS (ESI-TOF) m/z 628.3517 [M + Na]\(^+\) calculated for C\(_{33}\)H\(_{47}\)BN\(_4\)O\(_6\): 628.3507.
BODIPY (12). In an oven-dried flask, BODIPY 7 (20 mg, 0.062 mmol, 1.0 equiv.) and TMSOTf (28.0 µL, 0.154 mmol, 2.5 equiv.) were dissolved in anhydrous toluene (5 mL) and the mixture was refluxed for 30 min. The solution was allowed to cool down to room temperature and ethylene glycol (17.0 µL, 0.308 mmol, 5.0 equiv) was added, followed by DIPEA (27.0 µL, 0.154 mmol, 2.5 equiv.). After 1 h stirring at room temperature, the crude product was concentrated under reduced pressure and was purified via TLC (eluent 50:50 hexane/EtOAc) to afford BODIPY 12 (8.0 mg, 37% yield), that was recrystallized from 1:1 hexane/dichloromethane. ^1H NMR (CDCl₃, 400 MHz) δ 7.50 (d, J = 5.7 Hz, 3H), 7.31 (d, J = 4.2 Hz, 3H), 5.97 (s, 2H), 4.30 (s, 4H), 2.57 (s, 6H), 1.38 (s, 6H); ^13C NMR (CDCl₃, 100 MHz) δ 133.32, 129.82, 129.09, 128.75, 128.55, 128.28, 65.89, 29.84, 15.26, 14.66; ^11B NMR (CDCl₃, 128 MHz) δ 5.90 (s); HRMS (ESI-TOF) m/z 346.1962 [M + H]^+ calculated for C₂₁H₂₃BN₂O₂: 346.1959.

4.4.3 X-ray Determined Molecular structures

Crystal structures were determined using low-temperature data from a Bruker Kappa APEX-II DUO diffractometer with either Mo Kα or Cu Kα radiation. For all structures, H atoms were located from difference maps but constrained in calculated positions during refinement.

Crystal data 4a: C₃₃H₃₆BF₂N₅O, M = 567.48, triclinic, a = 11.1039(3), b = 11.3734(3), c = 12.9720(4) Å, U = 1445.82(7) Å³, T = 90 K, space group P1, Z = 2, Dc = 1.304 g cm⁻³, μ (Cu Kα) = 0.09 mm⁻¹, 5542 reflections measured, θ_max = 30.5°, 8843 unique (R_int = 0.040). The final R = 0.053 (8843 I>2σ(I) data), wR(F2) = 0.129 (all data).
Crystal data 4b: C_{40}H_{48}BF_{2}N_{5}O_{10}, M = 807.64, monoclinic, a = 13.3965(15), b = 9.2534(10), c = 17.1816(19) Å, U = 2059.0(4) Å³, T = 90 K, space group P2₁, Z = 2, Dc = 1.303 g cm⁻³, μ (Cu Kα) = 0.83 mm⁻¹, 1814 reflections measured, θ_{max} = 59.0°, 4680 unique (R_{int} = 0.060). The final R = 0.062 (4680 I > 2σ(I) data), wR(F²) = 0.131 (all data).

Crystal data 9: C_{33}H_{27}BBr_{3}N_{2}O_{4}, M = 686.20, Orthorhombic, a = 8.537(1), b = 10.710(2), c = 32.867(5) Å, U = 3005.1(8) Å³, T = 100 K, space group P2₁2₁2₁, Z = 4, Dc = 1.517 g cm⁻³, μ (Cu Kα) = 2.74 mm⁻¹, 3292 reflections measured, θ_{max} = 25.7°, 5682 unique (R_{int} = 0.146). The final R = 0.068 (5682 I > 2σ(I) data), wR(F²) = 0.104 (all data).

Crystal data 10: C_{35}H_{37}BN_{4}O_{4}, M = 588.50, monoclinic, a = 11.4670(8), b = 8.8110(6), c = 15.9543(11) Å, U = 1581.82(19) Å³, T = 90 K, space group P2₁, Z = 2, Dc = 1.236 g cm⁻³, μ (Cu Kα) = 0.65 mm⁻¹, 4547 reflections measured, θ_{max} = 60.1°, 4657 unique (R_{int} = 0.040). The final R = 0.028 (4657 I > 2σ(I) data), wR(F²) = 0.071 (all data).

Crystal data 11a: C_{26}H_{33}BFN_{3}O_{3}, M = 465.36, monoclinic, a = 5.9290(2), b = 25.0122(14), c = 16.4436(8) Å, U = 2429.9(2) Å³, T = 90 K, space group P2₁/c, Z = 4, Dc = 1.272 g cm⁻³, μ (Cu Kα) = 0.09 mm⁻¹, 7361 reflections measured, θ_{max} = 33.2°, 9239 unique (R_{int} = 0.030). The final R = 0.049 (9239 I > 2σ(I) data), wR(F²) = 0.128 (all data).

Crystal data 12: C_{21}H_{23}BN_{2}O_{2}, M = 346.22, monoclinic, a = 11.306(2), b = 8.9098(10), c = 17.990(3) Å, U = 1812.0(5) Å³, T = 100 K, space group P2₁/n, Z = 4, Dc = 1.269 g cm⁻³, μ (Cu
\( K\alpha) = 0.08 \text{ mm}^{-1}, \) 4878 reflections measured, \( \theta_{\text{max}} = 34.8^\circ, \) 7459 unique \( (R_{\text{int}} = 0.051). \) The final \( R = 0.057 \) \( (7459 \ I>2\sigma(I) \ data), \ wR(F2) = 0.153 \) (all data).

4.5 References


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CHAPTER 5: CHLORINATION OF ALCOHOLS AND ASYMMETRIC Sn1 REACTION

5.1 Introduction

5.1.1 Chlorination

Alkyl chlorides are useful building blocks in organic chemistry. Transformation of unreactive alcohols into reactive alkyl halides has proven to produce important intermediates in many organic syntheses. Chlorination reactions have become widespread in organic chemistry and useful in organic synthesis. The chlorination reaction mechanism typically requires the activation of an unreactive alcohol to give a better leaving group. Then in the presence of an excess of chloride anions, Sn2 attack at the adjacent, electropositive carbon atom to give the corresponding alkyl chloride product.

![Structures of chlorosulfolipid natural products](image)

Figure 5.1: Structures of chlorosulfolipid natural products: danicalipin $A_{4-6}$, malhamensilipin $A_{4,7-9}$, hexachlorosulfolipid, $^{10}$ undecachlorosulfolipid $A$ and $B$. $^{11}$

More than 2000 known natural products containing the alkyl chloride motif have displayed enormous antibiotic and cytotoxic activities. $^{12}$ The chlorosulfolipids are one class of polychlorinated natural product and some examples include danicalipin $A_{4-6}$, malhamensilipin $A_{4,7-9}$, hexachlorosulfolipid, $^{10}$ and undecachlorosulfolipid $^{11}$ (Figure 5.1). Malhamensilipin $A$, a

protein tyrosine kinase inhibitor, has antimicrobial activity which can be extracted from *Poterioochromonas malhamensis*.

Classic chlorination methods using chlorinating agents such as thionyl chloride (SOCl₂),¹³ phosphorus chloride (PCls),¹⁴-¹⁷ Lucas’ reagent,¹⁸-¹⁹ and Appel²⁰ reagents have been reported to convert alcohols to the corresponding alkyl chlorides (Scheme 5.1). The use of toxic halogenating agents is unappealing to organic chemists because these chlorinating agents resulted in inseparable or gaseous byproducts. Chlorination using Appel’s reagent typically results in inversion of stereochemistry.

![Scheme 5.1: Classical chlorination methods.](image)

Recently, several new methods have been developed for chlorination reactions (Scheme 5.2). Vilsmeier and Haack’s salt was reported as a reagent to chlorinate primary alcohols.²¹ However, the disadvantage of this method is due to long reaction time, selectivity for only primary alcohols, and low yields (47%-70%). In 2004, Baba and coworkers²² reported a direct chlorination reaction of alcohols under neutral conditions with HSiMe₂Cl and benzil as an additive. The transformation produces moderate yields of alkyl chlorides at high temperature. However, transformation of a primary alcohol such as 2-phenylethanol did not give the chlorinated product. They also reported highly regioselective chlorination for tertiary alcohols over primary alcohols using the HSiMe₂Cl/benzil/cat. InCl₂ conditions. Recently in 2010, Denton et al.²³ demonstrated rapid chlorination of primary and secondary alcohols under phosphine oxide-catalyzed conditions.
Using (COCl)₂ and Ph₃PO conditions have been shown to result in high yield but removal of the phosphine oxides by-products during purification remains a challenge. Jeong and coworkers²⁴ have shown an alternative method towards chlorination by using strong organic base DBU and sulfonylating agents to afford the alkyl chloride product in moderate yields.

![Scheme 5.2: Recent chlorination methods.](image)

5.1.2 A Chiral auxiliary for an Asymmetric S₅1 reaction

Substitution reactions are ubiquitous in many organic chemistry transformations. In organic chemistry, there are many substitution reactions such as nucleophilic, electrophilic, radical, and organometallic reactions. There are two types of nucleophilic substitution reaction: S₅1, and S₅2. The S₅2 reaction gives inversion of stereochemistry while the S₅1 reaction results in a racemic mixture. In order to control enantioselectivity in a S₅1 reaction, the nucleophilic attack must be induced via chirality substrate control such as a chiral auxiliary. Chiral auxiliaries have
become an essential tool for organic chemists to synthesize stereospecific natural products and pharmaceutical drugs. In 1975, Nobel laureate E. J. Corey developed the use of chiral auxiliaries in order to control the stereochemical outcome of a given compound in an organic transformation. There are three steps to induce stereoselective transformation with auxiliary incorporation: i) the chiral auxiliary is coupled to the target substrate; ii) the compound undergoes diastereoselective conversions; and iii) cleavage of the chiral auxiliary to result in an enantioselective product. Evans and coworkers introduced the concept of oxazolidinone auxiliaries and it has been widely used in complex natural synthesis. For example, many stereoselective reactions such as aldol reactions, alkylation reactions, and Diels-Alder reactions have utilized this methodology. Numerous groups have subsequently extended and improved this chiral auxiliary asymmetric induction. For example, Olivo and coworkers particularly focused on indene-based thiazolidinethione as the chiral auxiliary replacement. There are many ways for removal of the oxazolidinone auxiliary and transforming it to other functional groups.

5.2 Results and Discussion

5.2.1 Chlorination Syntheses

To explore mild reaction conditions for chemoselective chlorination of primary alcohols in presence of tertiary alcohols, 3-phenylbutane-1,3-diol (CAS#7133-68-8) was used as a model substrate. There are currently two different pathways to synthesize the 1,3-diol. The first pathway requires acetophenone 1, which is commercially available, to react with allylmagnesium bromide in a Grignard reaction, which resulted in the desired homoallyl alcohol 2 in 93% yield (Scheme 5.3). The alkene product 2 was subjected to reductive ozonolysis gas (O₃) to give the intermediate
molozonide, which was then reduced by NaBH₄ to achieve the 1,3-diol 4 in 77% yield. Although path 1 gave the target compound in good yield, we also investigated an alternative way.

\[
\begin{align*}
\text{Scheme 5.3: Path 1 towards synthesis of 3-phenylbutane-1,3-diol 4.}
\end{align*}
\]

Path 2, the less efficient pathway, began by reacting ethyl acetate and acetophenone through an aldol reaction (Scheme 5.4). Strong base, such as LDA, deprotonates the α proton of ethyl acetate to form the enolate. The anion in the α position of the enolate then attacks the carbonyl of acetophenone 1 to produce ester 3. The crude materials were taken on to the next step without purification. The ester product 3 was reduced by LiAlH₄ in THF to give 1,3-diol 4 in 69% over two steps.

The diol was treated with various chlorinating reagents for preliminary studies, as depicted in Table 5.1. Classical chlorinating agents such as SOCl₂ and PCl₅ have resulted in crude complex mixtures.

\[
\begin{align*}
\text{Scheme 5.4: Path 2 towards synthesis of 3-phenylbutane-1,3-diol 4.}
\end{align*}
\]

Next, CCl₄-PPh₃ and triphosgene-PPh₃ were investigated (entries 1 and 2) and produced the chlorinated product 4a in 30% and 78%, respectively. The triphenylphosphine by-products were responsible for these modest yields. In the presence of triphosgene and triethylamine, the
chloro-alcohol product was obtained rapidly in a yield of 98%. Indeed, when phosgene was used in place of triphosgene, the desired product 4a was still obtained but in a lower yield of 89%. On the other hand, other bases such as pyridine and Hünig’s base (DIPEA) were also investigated and these reactions resulted in cyclic carbonate 8.

Table 5.1: Preliminary studies on chlorination of 1,3-diol 4 with various chlorinate reagents.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Chlorinate reagents</th>
<th>4a, yield (%)</th>
<th>8, yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CCl₄, PPh₃</td>
<td>30</td>
<td>---</td>
</tr>
<tr>
<td>2</td>
<td>Triphosgene, PPh₃</td>
<td>78</td>
<td>---</td>
</tr>
<tr>
<td>3</td>
<td>Triphosgene, TEA</td>
<td>98</td>
<td>---</td>
</tr>
<tr>
<td>4</td>
<td>Phosgene, TEA</td>
<td>89</td>
<td>---</td>
</tr>
<tr>
<td>5</td>
<td>Triphosgene, Pyridine</td>
<td>---</td>
<td>86</td>
</tr>
<tr>
<td>6</td>
<td>Triphosgene, DIPEA</td>
<td>---</td>
<td>45</td>
</tr>
</tbody>
</table>

TEA: triethylamine, CCl₄: carbon tetrachloride, PPh₃: triphenylphosphine

Our typical chlorination protocol includes 0.5 equiv. of triphosgene and 2.5 equiv of triethylamine under anhydrous conditions in dichloromethane. The reaction started at 0 °C and then was warmed to room temperature. Based on TLC, it was shown that the starting material was fully consumed within 5 minutes. However, the reaction was stirred for an additional 3 hours for general purpose for all the diols. The 1,3-diols 4-7 containing primary and tertiary alcohols were converted into their corresponding chloroalcohol products 4a-7a in excellent yield ranging from 85-98%. It was initially suspected that chlorination could possibly occur at the primary and tertiary hydroxyl positions.
Table 5.2: Chemoselective chlorination of aliphatic primary alcohol vs. tertiary alcohol

<table>
<thead>
<tr>
<th>entry</th>
<th>starting material</th>
<th>product</th>
<th>yield</th>
</tr>
</thead>
</table>
| 1     | \[
\begin{array}{c}
\text{Ph} \\
\text{Me} \\
\text{OH}
\end{array}
\] 4 | \[
\begin{array}{c}
\text{Ph} \\
\text{Me} \\
\text{Cl}
\end{array}
\] 4a | 98% |
| 2     | \[
\begin{array}{c}
\text{Ph} \\
\text{OH}
\end{array}
\] 5 | \[
\begin{array}{c}
\text{Ph} \\
\text{Cl}
\end{array}
\] 5a | 85% |
| 3     | \[
\begin{array}{c}
\text{Ph} \\
\text{OH}
\end{array}
\] 6 | \[
\begin{array}{c}
\text{Ph} \\
\text{Cl}
\end{array}
\] 6a | 97% |
| 4     | \[
\begin{array}{c}
\text{OH}
\end{array}
\] 7 | \[
\begin{array}{c}
\text{Cl}
\end{array}
\] 7a | 96% |

However, the chlorination reactions were chemoselective only for primary alcohols in the presence of tertiary alcohols. In addition, non-anhydrous conditions were also performed and effectively resulted in an excellent yield of 98%.

To further our investigation, various groups binding to the tertiary carbon were synthesized and studied. As shown in Table 5.1, highly ionizable tertiary alcohols were unaffected by the activation reagents due to sterically demanding substituents such as phenyl and methyl. In addition, whenever the phenyl and methyl were substituted with larger substituents, primary alcohols were
still converted to its corresponding primary chloride products. My role in the published chlorination paper was to investigate aliphatic alcohols and substitute other bases while other co-authors (Ayala and Villalpando) were to investigate different functional group compatibility, secondary alcohols and α-branched alcohols.

5.2.2 Asymmetric S<sub>N</sub>1 Reaction

![Scheme 5.5: Retrosynthetic analysis of oxazolidinone 17.]

As shown in retrosynthetic Scheme 5.5, the target compound 17 can be derived from acylation between chloroformate 16 and oxazolidone 13. This fragment 16 comes from 1,3-diol 4 through a series steps of protection and deprotection. The diol will be synthesized through two pathways. The first pathway consists of treating acetophenone with Grignard reagent and ozonolysis. Fragment 13 can be made through cyclization of aminoalcohol 12. The amino alcohol 12 can be synthesized from the commercially available indene 9, which was previously reported.\textsuperscript{35}
Our first approach was to treat commercially available indene 9 with osmium tetroxide, N-methylmorpholine-N-oxide (NMO), and water in an Upjohn dihydroxylation reaction to produce racemic diol 10 in 89% yield, as shown in Scheme 5.6. The next step was to treat the diol with acetonitrile and sulfuric acid to form a cyclic imine as an intermediate. By introducing a nucleophile such as water, the heterocycle opened up to give ammonium-alcohol enantiomers 11a and 11b.

Scheme 5.6: Synthesis of oxazolidone 13 from commercially available indene 9.

The next approach was to perform kinetic resolution on the two enantiomers with L-tartaric acid. In order to distinguish between the two amino alcohol enantiomers, methods such as recrystallization and filtration were applied. The targeted amino alcohol 12 was separated as a recrystallized solid. Unfortunately, when comparing the optical rotation for the amino alcohol to the authentic commercially available amino alcohol from Aldrich, the values were significantly different. The optical rotation for our synthesized amino alcohol was +26.13° and for the authentic amino alcohol was -96.6°. Therefore, the authentic commercial amino alcohol was used for the
next step. The amino alcohol 12 was treated with phosgene and triethylamine and afforded oxazolidinone 13 in 96\% yield (Scheme 5.6).

\[
\begin{align*}
\text{OH} & \quad \text{TBSOTf} & \text{OTBS} & \quad p\text{-TsOH} \\
\text{OH} & & \text{OTBS} \\
\text{4} & \quad 2,6\text{-lutidine} & \text{MeOH} & \text{14} \\
(93\%) & & (73\%) \\
\text{13} & & \text{15}
\end{align*}
\]

Scheme 5.7: Protection and selective deprotection of 1,3-diol 4.

With fragment 13 in hand, we next turned our attention to fragment 16. The hydroxyl groups of 1,3-diol 4 were subjected to mixture of tert-butyldimethylsilyl triflate (TBSOTf) and 2,6-lutidine to give 1,3-di-O-TBS compound 14 in an excellent yield of 93\% (Scheme 5.7). Then compound 14 was exposed to selective deprotection of the primary TBS ether with p-toluenesulfonic acid (p-TsOH) in methanol to produce alcohol 15 in 73\% yield. The alcohol was then reacted with phosgene to form chloroformate 16 in 75\% yield as a crude product (Scheme 5.8). No purification was performed on the chloroformate since it is very unstable on silica gel and to moisture. The chloroformate was carried into the next step of the synthesis.

\[
\begin{align*}
\text{OH} & \quad \text{Cl} & \quad \text{Cl} \\
\text{OTBS} & & \text{OTBS} \\
\text{15} & \quad \text{THF, 0 \, ^\circ\text{C}} & \text{16} \\
(75\%) & & 
\end{align*}
\]

Scheme 5.8: Synthesis of chloroformate 16.

As shown in Table 5.3, we explored acylation coupling conditions between chloroformate 16 and oxazolidone 13 in order to synthesize the target oxazolidinone 17. Screening of various bases in THF at different temperature afforded the desired compound 17 with a wide range of yields ranging from no product to 59\% yield. When triethylamine was used as the base, the target compound 17 was obtained in 52\% yield, while no product was produced when 1,8-
diazabicyclo[5.4.0]undec-7-ene (DBU), pyridine and diisopropylethylamine (DIPEA) were used. When a mixture of TEA and DMAP was used, the yield increased to 59%. Surprisingly, stronger bases such as n-BuLi resulted in a yield of 49% while sec-BuLi only gave trace amount of the desired product. The reaction with n-BuLi proceeded in the fastest time when compared to other bases.

Table 5.3: Optimized acylation reaction conditions for synthesis of oxazolidinone 17.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Base</th>
<th>Temp</th>
<th>17, Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Triethylamine</td>
<td>0 °C</td>
<td>52</td>
</tr>
<tr>
<td>2</td>
<td>DBU</td>
<td>0 °C</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>Triethylamine + DMAP</td>
<td>0 °C</td>
<td>59</td>
</tr>
<tr>
<td>4</td>
<td>DIPEA</td>
<td>0 °C</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>NaH</td>
<td>0 °C</td>
<td>23</td>
</tr>
<tr>
<td>6</td>
<td>n-BuLi</td>
<td>-78 °C</td>
<td>49</td>
</tr>
<tr>
<td>7</td>
<td>sec-BuLi</td>
<td>-78 °C</td>
<td>trace</td>
</tr>
<tr>
<td>8</td>
<td>LDA</td>
<td>-78 °C</td>
<td>22</td>
</tr>
<tr>
<td>9</td>
<td>Pyridine</td>
<td>0 °C</td>
<td>0</td>
</tr>
</tbody>
</table>

Next, we explored using n-BuLi at various temperatures and reaction times (Table 5.4). At higher temperature, the yields of compound 17 decreased possibly due to the degradation of THF. The degradation transforms n-butylithium into butane and inhibits the reaction. With longer times (6-8 h), the yields are relatively unchanged and ranged from 37-43%.
Table 5.4: Optimization of coupling conditions between chloroformate 16 and oxazolidone 13.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Time</th>
<th>Temp</th>
<th>17, Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3 h</td>
<td>-78 °C</td>
<td>49</td>
</tr>
<tr>
<td>2</td>
<td>3 h</td>
<td>-40 °C</td>
<td>31</td>
</tr>
<tr>
<td>3</td>
<td>3 h</td>
<td>0 °C</td>
<td>9</td>
</tr>
<tr>
<td>4</td>
<td>6 h</td>
<td>-78 °C</td>
<td>37</td>
</tr>
<tr>
<td>5</td>
<td>8 h</td>
<td>-78 °C</td>
<td>43</td>
</tr>
</tbody>
</table>

With compound 17 in hand, we now turned our attention to perform the asymmetric S_N1 reaction. Oxazolidinone 17 undergoes ionization with BF_3•OEt_2 to form a tertiary carbocation and furan undergoes nucleophilic attack to give oxazolidinone 18 in 96% yield (Scheme 5.9). The optical rotation is [α] = +146.2 for compound 18. Finally, hydrolytic cleavage of the chiral auxiliary is performed with potassium carbonate and methanol to give the alcohol 19. The optical rotation is [α] = +2.3, which shows that the alcohol 19 is enantiopure.

5.3 Conclusions

In summary, a series of chloroalcohol compounds 4a-7a were synthesized in high yields (85-98%) via triphosgene-triethylamine activation conditions. The chlorination reaction was chemoselective only for primary alcohols in the presence of tertiary alcohols due to steric hindrance. Other bases such as pyridine and diisopropylethylamine resulted in the cyclic carbonate 8. Fragment 13 was made through a series of steps from the commercially available indene 9 while fragment 16 was made from the commercially available acetophenone 1. Oxazolidinone 17 was
synthesized in moderate yield from acylation reaction between chloroformate 16 and oxazolidone 13. Compound 17 was ionized with Lewis acid (BF$_3$•OEt$_2$) and undergoes nucleophilic attack with furan in an asymmetric S$_{N}$1 reaction to give compound 18 in excellent yield of 96%. The oxazolidone was cleaved under hydrolysis conditions to produce alcohol 19 in good yield of 48%.

Scheme 5.9: S$_{N}$1 reaction and auxiliary cleavage.

5.4 Experimental

5.4.1 General Information

2-Phenyl-4-penten-2-ol (2). Acetophenone (0.500 g, 4.16 mmol) was dissolved in THF (42 mL) and cooled to -78 °C. AllyMgBr (4.57 mL, 4.51 mmol) was added dropwise to the reaction mixture. After 45 minutes, the reaction was quenched with half saturated NH$_4$Cl (20 mL) and extracted with EtOAc (3 x 20 mL). The combined organic layers were dried over MgSO$_4$, filtered,
and concentrated under reduced pressure. The crude product was purified via silica (90/10 Hex/EtOAc) to afford alcohol 2 (93%, 0.630 g).

(±)-3-Phenylbutane-1,3-diol (4). Path 1: Alcohol 2 (25.0 mg, 0.154 mmol) was dissolved in MeOH (5 mL) and cooled to 0 °C. O₃ was bubbled into the solution until the solution turned blue. NaBH₄ (11.7 mg, 0.308 mmol) was added as solid and warmed to room temperature. The crude product was purified via silica (eluent 60/40 Hex/EtOAc) to afford 1,3-diol 4 (77%, 19.8 mg). ¹H NMR (CDCl₃, 250 MHz) δ 7.47-7.18 (m, 5H), 3.75 (dq, J = 9.5, 4.6 Hz, 1H), 3.62-3.45 (m, 1H), 2.12-2.01 (m, 2H), 1.58 (s, 3H).

(±)-3-Phenylbutane-1,3-diol (4). Path 2: DIPEA (3.9 mL, 27.4 mmol) was suspended in anhydrous THF (100 mL) and cooled to -78 °C. n-butyllithium (11.0 mL, 27.4 mmol) was added dropwise, followed by anhydrous EtOAc (2.5 mL, 25.7 mmol) and then acetophenone (2 mL, 17.1 mmol). After 1.5 hours, the reaction mixture was quenched with half saturated NH₄Cl (20 mL) and extracted with EtOAc (3 x 20 mL). The combined organic layers were dried over MgSO₄, filtered, and concentrated under reduced pressure to afford crude ester 3. The crude ester 3 was taken to next step without purification. The LiAlH₄ (0.715 g, 18.8 mmol) was dissolved in THF (250 mL) and cooled to 0 °C. The ester was added to the reaction mixture and rinsed three times with THF. After 15 min, the mixture was quenched with water (0.72 mL) and then washed with 15% NaOH (0.72 mL) and then water (2.2 mL). The aqeous layers were extracted with EtOAc (200 mL), dried over small amount of MgSO₄, filtered, and concentrated under reduced pressure. The crude product was purified via silica (eluent 60/40 Hex/EtOAc) to afford 1,3 diol 4 (69% over two steps, 1.96 g). ¹H NMR (CDCl₃, 250 MHz) δ 7.47-7.18 (m, 5H), 3.75 (dq, J = 9.5, 4.6 Hz, 1H), 3.62-3.45 (m, 1H), 2.12-2.01 (m, 2H), 1.58 (s, 3H).
General Procedure for Chlorination. In an over-dried flask, diol (2.00 mmol) was dissolved in anhydrous CH$_2$Cl$_2$ (15 mL) and cooled to 0 °C. Triethylamine (5.00 mmol) was added dropwise to the reaction mixture, followed by triphosgene (1.00 mmol). The reaction was warmed up to room temperature and stirred for an addition 3 hours. The mixture was quenched with saturated NaHCO$_3$ (30 mL). The aqueous layer was extracted with CH$_2$Cl$_2$ (2 x 30 mL). The combined organic layers were dried over MgSO$_4$, filtered, and concentrated under reduced pressure.

(±)-4-Chloro-2-phenylbutan-2-ol (4a). Diol 4 (332 mg, 2.00 mmol, CAS #7133-68-8) was utilized along with the requisite amounts of triethylamine and triphosgene. The crude product was purified via silica (eluent 90/10 hexane/EtOAc) to give a colorless oil 4a (98%, 361 mg). $^1$H NMR (CDCl$_3$, 250 MHz) δ 7.46-7.24 (m, 5H), 3.56 (ddd, $J = 10.8, 8.4, 7.8$ Hz, 1H), 3.35 (ddd, $J = 10.7, 8.9, 6.4$ Hz, 1H), 2.35-2.29 (m, 2H), 2.04 (s, 1H), 1.62 (s, 3H); $^{13}$C NMR (CDCl$_3$, 62.5 MHz) δ 146.30, 128.36, 126.94, 124.48, 74.24, 46.54, 40.42, 30.70; IR (cm$^{-1}$): $f = 3553, 3432, 3026, 2928, 1272, 969, 692$; HRMS (ESI-TOF) m/z 167.0622 [M - OH]$^+$ calculated for C$_{10}$H$_{12}$Cl: 167.0626.

(±)-(E)-5-Chloro-3-phenylpent-1-en-3-ol (5a). Diol 5 (385 mg, 2.00 mmol) was utilized along with the requisite amounts of triethylamine and triphosgene. The crude product was purified via silica (eluent 90/10 hexane/EtOAc) to give a yellow oil 5a (85%, 356 mg). $^1$H NMR (CDCl$_3$, 250 MHz) δ 7.42-7.23 (m, 5H), 6.64 (d, $J = 16.1$ Hz, 1H), 6.25 (d, $J = 16.1$ Hz, 1H), 3.74-3.56 (m, 2H), 2.25-2.06 (m, 2H), 1.79 (s, 1H), 1.45 (s, 3H). $^{13}$C NMR (CDCl$_3$, 62.5 MHz,) δ 136.40, 134.92, 128.55, 127.87, 127.61, 126.40, 72.75, 44.94, 40.33, 28.86; IR (cm$^{-1}$): $f = 3553, 3399, 3026, 2928, 1272, 969, 692$; HRMS (ESI-TOF) m/z 193.0779 [M - OH]$^+$ calculated for C$_{12}$H$_{14}$Cl: 193.0787.
2-Benzyl-4-chloro-1-phenylbutan-2-ol (6a). Diol 6 (550 mg, 2.00 mmol, CAS #497845-92-8) was utilized along with the requisite amounts of triethylamine and triphosgene. The crude product was purified via silica (eluqent 90/10 hexane/EtOAc) to give a colorless oil 6a (97%, 532 mg). \(^1\)H NMR (CDCl\(_3\), 250 MHz) \(\delta\) 7.40-7.22 (m, 10H), 3.72-3.66 (m, 2H), 2.83 (s, 4H), 1.99-1.92 (m, 2H), 1.55 (s, 1H); \(^{13}\)C NMR (CDCl\(_3\), 62.5 MHz) \(\delta\) 136.36, 130.59, 128.41, 126.80, 73.74, 45.81, 41.39, 40.25; IR (cm\(^{-1}\)): \(\nu\) = 3561, 3468, 3028, 2923, 1453, 1089, 700; HRMS (ESI-TOF) \(m/z\) 297.1022 [M + Na]\(^+\) calculated for C\(_{17}\)H\(_{19}\)ClNaO: 297.1000.

1-(2-Chloroethyl)cyclopentanol (7a). Diol 7 (260 mg, 2.00 mmol, CAS #73089-93-7) was utilized along with the requisite amounts of triethylamine and triphosgene. The crude product was purified via silica (eluqent 70/30 pentane/Et\(_2\)O) to give a colorless oil 7a (96%, 285 mg). \(^1\)H NMR (CDCl\(_3\), 250 MHz); \(\delta\) 3.72-3.66 (m, 2H), 2.12-2.01 (m, 2H), 1.83-1.55 (m, 8H), 1.41 (s, 1H); \(^{13}\)C NMR (CDCl\(_3\), 62.5 MHz) \(\delta\) 81.47, 44.05, 41.07, 39.70, 23.32; IR (cm\(^{-1}\)): \(\nu\) = 3393, 2961, 2874, 1452, 1211, 731; HRMS (ESI-TOF) \(m/z\) 131.0622 [M - OH]\(^+\) calculated for C\(_7\)H\(_{12}\)Cl: 131.0634.

(±)-4-Methyl-4-phenyl-1,3-dioxan-2-one (8). Diol 4 (332 mg, 2.00 mmol) was utilized along with the requisite amounts of pyridine (0.40 mL, 5.00 mmol) and triphosgene (297 mg, 0.500 mmol). The crude product was purified via silica (eluqent 60/40 hexane/EtOAc) to give a colorless oil 8 (86%, 329 mg). \(^1\)H NMR (CDCl\(_3\), 250 MHz) \(\delta\) 7.40-7.25 (m, 5H), 4.31 (ddd, ddd, \(J = 11.2, 4.7, 4.2\) Hz, 1H), 4.03 (ddd, \(J = 11.2, 10.0, 4.5\) Hz, 1H), 2.46-2.26 (m, 2H), 1.70 (s, 3H); \(^{13}\)C NMR (CDCl\(_3\), 62.5 MHz) \(\delta\) 148.62, 142.24, 128.76, 127.83, 123.80, 84.26, 64.99, 33.16, 29.99; IR (cm\(^{-1}\)): \(\nu\) = 2983, 2917, 1733, 1087, 699; HRMS (ESI-TOF) \(m/z\) 215.0684 [M + Na]\(^+\) calculated for C\(_{11}\)H\(_{12}\)NaO\(_3\): 215.0698.
5.4.2 Asymmetric S_N1 Syntheses

Compound (10). Indene 9 (2mL, 17.15 mmol) was suspended in THF (28.5 mL). After 30 min, tert-butanol (28.5 mL) was added, followed by water (5.67 mL) and NMO (2.05 g, 18.86 mmol). One crystal solid of OsO₄ was added to the reaction mixture. The reaction was stirred overnight, quenched with Na₂S₂O₃ (50 mL), and extracted with ethyl acetate (50 mL). The combined organic layers were dried over MgSO₄, filtered, and concentrated under reduced pressure. The crude product was purified via silica (eluent 50/50 Hex/EtOAc) to afford diol 10 (89% yield, 2.283 g).

Compound (12). Diol 10 (3.88 g, 25.8 mmol) was dissolved in dry acetonitrile (25 mL). The reaction was cooled to 0 °C and H₂SO₄ (2.875 mL) was added dropwise. The reaction mixture was warmed to room temperature. After 6 hours, the mixture was quenched with water (15 mL), diluted with water (15 mL), and concentrated by atmosphere pressure. The reaction residue was refluxed at 100 °C overnight and warmed to room temperature. Then isobutanol (15 mL) was added, followed by NaOH (50% solution, 15 mL) and diluted with tert-butanol (15 mL). The aqueous was extracted with ethyl acetate (5 x 10 mL) and dried over MgSO₄. The crude amino alcohols mixture (4.54 g, 30.44 mmol) were dissolved in MeOH (68 mL). L-tartaric acid (5.05 g, 33.48 mmol) dissolved in MeOH (68 mL) were added to the reaction and refluxed for 3 hours. Then the mixture was cooled to room temperature and recrystallized with methanol to afford amino alcohol 12 (210 mg).

Compound (13). Commercially available amino alcohol 12 (2.5 g, 16.75 mmol) was suspended in CH₂Cl₂ (180 mL). The reaction was cooled to 0 °C and triethylamine (5.84 mL, 41.89
mmol) was added dropwise. Then triphosgene (1.987 g, 6.70 mmol) dissolved in CH₂Cl₂ (10 mL) were cannula over to the reaction mixture. The reaction was quenched with half saturated NH₄Cl (200 mL) after stirring for 2 hours. The mixture was extracted with CH₂Cl₂ (50 mL). The combined organic layers were dried over MgSO₄, filtered, and concentrated under reduced pressure to afford a white yellow solid oxazolidone 13 (96%, 3.048 g).

Compound (14). 1,3 diol 4 (0.9371 g, 5.64 mmol) was dissolved in anhydrous CH₂Cl₂ (33.6 mL) and cooled to -78 °C. Then 2,6-lutidine (2.63 mL, 22.5 mmol) was added dropwise, followed by TBSOTf (3.107 mL, 13.53 mmol). After 1 hour, the reaction was warmed to room temperature and continued stirring for additional 1 hour. The mixture was quenched with half saturated NaHCO₃ (10 mL) and extracted with CH₂Cl₂ (3 x 10 mL). The combined organic layers were dried over MgSO₄, filtered, and concentrated under reduced pressure. The crude product was purified via silica (eluent 100% hexanes to 95/5 Hex/EtOAc) to afford ligh yellow oil TBS ether 14 (93%, 2.0706 g). ¹H NMR (CDCl₃, 250 MHz) δ 7.61-7.22 (m, 6H), 3.85 (td, J = 9.5, 6.1 Hz, 1H), 3.53 (td, J = 9.6, 6.1 Hz, 1H), 2.20 (dt, J = 16.6, 8.4 Hz, 2H), 1.78 (s, 3H), 1.13 (s, 9H), 1.00 (s, 9H), 0.28 (s, 3H), 0.14 (s, 3H), 0.11 (d, J = 3.1 Hz, 6H).

Compound (15). 1,3-TBS ether 14 (0.200 g, 0.507 mmol) was dissolved in anhydrous MeOH (25 mL) and cooled to 0 °C. TsOH (0.012g, 0.06 mmol) was added as solid to the reaction mixture. After 1 hour, the mixture was quenched with a drop of triethylamine and concentrated under reduced pressure. The crude product was purified via silica (eluent 90/10 Hex/EtOAc) to afford a colorless oil compound 15 (73%, 0.104 g). ¹H NMR (CDCl₃, 250 MHz) δ 7.49-7.20 (m, 5H), 3.62 (t, J = 6.1 Hz, 2H), 2.03 (tt, J = 14.1, 7.1 Hz, 2H), 1.73 (s, 3H), 0.98 (s, 9H), 0.14 (s, 3H), -0.04 (s, 3H).
Compound (16). Alcohol 15 (100 mg, 0.357 mmol) was dissolved in THF (6 mL) and cooled to 0 °C. Phosgene (0.256 mL, 15% in toluene, 0.392 mmol) solution was added and the reaction was warmed to room temperature. After 15 minutes, the reaction was quenched with cold saturated NaHCO₃ (5 mL) and extracted with cold pentane (5 mL). The organic layer was dried over MgSO₄, filtered, and concentrated under reduced pressure to afford the crude chloroformate 16 (75%, 92.3 mg). ¹H NMR (CDCl₃, 250 MHz) δ 7.59-7.14 (m, 11H), 4.45-4.26 (m, 2H), 4.09 (ddd, J = 10.6, 9.2, 6.2 Hz, 1H), 2.23 (ddd, J = 16.8, 12.8, 6.8 Hz, 2H), 1.68 (s, 3H), 0.98 (s, 11H), 0.16 (s, 3H), 0.02 (s, 3H).

Compound (17). Oxazolidone 13 (64.6 mg, 0.188 mmol) was dissolved in THF (1 mL) and cooled to -78 °C. n-BuLi (0.088 mL, 2.135 M in hexane, 0.188 mmol) was added dropwise to the reaction. Chloroformate 16 (30.0 mg, 0.171 mmol) dissolved in THF (1 mL) was cannula over the reaction mixture. After 3 hours, the reaction was quenched with half saturated NH₄Cl (5 mL) and extracted with EtOAc (3 x 5 mL). The combined organic layers were dried over MgSO₄, filtered, and concentrated under reduced pressure. The crude product was purified via silica (eluent 80/20 Hex/EtOAc) to afford compound 17 (49%, 40 mg). ¹H NMR (CDCl₃, 250 MHz) δ 7.59-7.40 (m, 3H), 7.40-7.14 (m, 7H), 5.49 (dd, J = 15.4, 7.0 Hz, 1H), 5.20 (dq, J = 8.3, 4.0 Hz, 1H), 4.56-4.36 (m, 1H), 4.27-4.11 (m, 1H), 3.34 (s, 2H), 2.49-2.18 (m, 2H), 1.70 (d, J = 3.6 Hz, 3H), 1.00 (s, 9H), 0.18 (s, 3H), 0.03 (d, J = 1.4 Hz, 3H).

Compound (18). Compound 17 (78.0 mg, 0.162 mmol) was dissolved in anhydrous CH₂Cl₂ (8 mL) and cooled to -78 °C. Furan (0.083 mL, 1.134 mmol) was added, followed by BF₃•OEt₂ (0.080 mL, 0.648 mmol) to the reaction and warmed to room temperature. After 1 hour, the
reaction mixture was quenched with saturated NaHCO₃ (10 mL) and extracted with CH₂Cl₂ (3 x 10 mL). The combined organic layers were dried over MgSO₄, filtered, and concentrated under reduced pressure. The crude product was purified via silica (eluent 80/20 Hex/EtOAc) to afford compound 18 (96%, 64.7 mg). ¹H NMR (CDCl₃, 250 MHz) δ 7.61 (d, J = 7.4 Hz, 1H), 7.42-7.12 (m, 11H), 6.38-6.31 (m, 1H), 6.23 (d, J = 2.9 Hz, 1H), 5.64 (t, J = 6.5 Hz, 1H), 5.32-5.15 (m, 1H), 4.45-4.21 (m, 2H), 3.37 (d, J = 3.3 Hz, 2H), 2.76-2.46 (m, 2H), 1.74 (s, 3H); ¹³C NMR (CDCl₃, 62.5 MHz) δ 159.90, 151.35, 151.02, 145.84, 141.54, 139.57, 138.40, 129.93, 128.29, 127.97, 126.55, 126.40, 126.38, 126.12, 125.27, 109.84, 105.99, 64.78, 63.53, 42.38, 38.61, 37.83, 29.62, 25.92.

Compound (19). Compound 18 (12.3 mg, 0.029 mmol) was dissolved in MeOH (2 mL) and cooled to 0 °C. Potassium carbonate (8.1 mg, 0.059 mmol) was added as solid to the reaction and warmed to room temperature. After 1.5 hours, the reaction was quenched with half saturated NH₄Cl (2 mL) and extracted with EtOAc (3 x 2 mL). The combined organic layers were dried over MgSO₄, filtered, and concentrated under reduced pressure. The crude product was purified via silica (eluent 80/20 Hex/EtOAc) to afford alcohol 19 (48%, 3.0 mg). ¹H NMR (CDCl₃, 250 MHz) δ 7.37-7.11 (m, 7H), 6.34 (dd, J = 3.2, 1.9 Hz, 1H), 6.22-6.14 (m, 1H), 3.69-3.48 (m, 2H), 2.53-2.23 (m, 2H), 1.67 (s, 3H).

5.5 References


APPENDIX A: NMR Characterization of Compounds Found in Chapter 2

Figure A.1: $^1$H NMR of BODIPY 1 in CDCl$_3$ (400 MHz)

Figure A.2: $^{13}$C NMR of BODIPY 1 in CDCl$_3$ (100 MHz)
Figure A.3: $^1$H NMR of BODIPY 1a in CDCl$_3$ (400 MHz)

Figure A.4: $^{13}$C NMR of BODIPY 1a in CDCl$_3$ (100 MHz)
Figure A.5: $^1$H NMR of BODIPY 1b in CDCl$_3$ (400 MHz)

Figure A.6: $^{13}$C NMR of BODIPY 1b in CDCl$_3$ (100 MHz)
Figure A.7: $^1$H NMR of BODIPY 1c in CDCl$_3$ (400 MHz)

Figure A.8: $^{13}$C NMR of BODIPY 1c in CDCl$_3$ (100 MHz)
Figure A.9: $^1$H NMR of BODIPY 1d in CDCl$_3$ (400 MHz)

Figure A.10: $^{13}$C NMR of BODIPY 1d in CDCl$_3$ (100 MHz)
Figure A.11: $^1$H NMR of BODIPY 1e in CDCl$_3$ (400 MHz)

Figure A.12: $^{13}$C NMR of BODIPY 1e in CDCl$_3$ (100 MHz)
**Figure A.13:** $^1$H NMR of BODIPY 2 in CDCl$_3$ (400 MHz)

**Figure A.14:** $^{13}$C NMR of BODIPY 2 in CDCl$_3$ (100 MHz)
**Figure A.15:** $^1$H NMR of BODIPY 2a in CDCl$_3$ (400 MHz)

**Figure A.16:** $^{13}$C NMR of BODIPY 2a in CDCl$_3$ (100 MHz)
Figure A.17: $^1$H NMR of BODIPY 3 in CDCl$_3$ (400 MHz)

Figure A.18: $^{13}$C NMR of BODIPY 3 in CDCl$_3$ (100 MHz)
**Figure A.19:** $^1$H NMR of BODIPY 3a in CDCl$_3$ (400 MHz)

**Figure A.20:** $^{13}$C NMR of BODIPY 3a in CDCl$_3$ (100 MHz)
**Figure A.21:** $^1$H NMR of BODIPY 4 in CDCl$_3$ (400 MHz)

**Figure A.22:** $^{13}$C NMR of BODIPY 4 in CDCl$_3$ (100 MHz)
Figure A.23: $^{11}$B NMR of BODIPY 1 in CDCl$_3$ (128 MHz)

Figure A.24: $^{11}$B NMR of BODIPY 1a in CDCl$_3$ (128 MHz)
Figure A.25: $^{11}$B NMR of BODIPY 1b in CDCl$_3$ (128 MHz)

Figure A.26: $^{11}$B NMR of BODIPY 1c in CDCl$_3$ (128 MHz)
Figure A.27: $^{11}$B NMR of BODIPY 1d in CDCl$_3$ (128 MHz)

Figure A.28: $^{11}$B NMR of BODIPY 1e in CDCl$_3$ (128 MHz)
Figure A.29: $^{11}$B NMR of BODIPY 2 in CDCl$_3$ (128 MHz)

Figure A.30: $^{11}$B NMR of BODIPY 2a in CDCl$_3$ (128 MHz)
**Figure A.31:** $^1$B NMR of BODIPY 3 in CDCl$_3$ (128 MHz)

**Figure A.32:** $^1$B NMR of BODIPY 3a in CDCl$_3$ (128 MHz)
Figure A.33: $^{11}$B NMR of BODIPY 4 in CDCl$_3$ (128 MHz)
APPENDIX B: NMR Characterization of Compounds Found in Chapter 3

Figure B.1: $^1$H NMR of BODIPY 1a in CDCl$_3$ (400 MHz)

Figure B.2: $^{13}$C NMR of BODIPY 1a in CDCl$_3$ (100 MHz)
Figure B.3: $^1$H NMR of BODIPY 2a in CDCl$_3$ (400 MHz)

Figure B.4: $^{13}$C NMR of BODIPY 2a in CDCl$_3$ (100 MHz)
**Figure B.5:** $^1$H NMR of BODIPY 3a in CDCl$_3$ (400 MHz)

**Figure B.6:** $^{13}$C NMR of BODIPY 3a in CDCl$_3$ (100 MHz)
Figure B.7: $^1$H NMR of BODIPY 4a in CDCl$_3$ (400 MHz)

Figure B.8: $^{13}$C NMR of BODIPY 4a in CDCl$_3$ (100 MHz)
**Figure B.9:** $^1$H NMR of BODIPY 5a in CDCl$_3$ (400 MHz)

**Figure B.10:** $^{13}$C NMR of BODIPY 5a in CDCl$_3$ (100 MHz)
Figure B.11: $^1$H NMR of Dipyrrin 7 in CDCl$_3$ (400 MHz)

Figure B.12: $^{13}$C NMR of Dipyrrin 7 in CDCl$_3$ (100 MHz)
Figure B.13: $^1$H NMR of BODIPY 7a in CD$_2$Cl$_2$ (400 MHz)

Figure B.14: $^{13}$C NMR of BODIPY 7a in CDCl$_3$ (100 MHz)
Figure B.15: $^1$H NMR of BODIPY 7b in CD$_2$Cl$_2$ (400 MHz)

Figure B.16: $^{13}$C NMR of BODIPY 7b in CDCl$_3$ (100 MHz)
Figure B.17: $^1$H NMR of BODIPY 7c in CD$_2$Cl$_2$ (400 MHz)

Figure B.18: $^{13}$C NMR of BODIPY 7c in CDCl$_3$ (100 MHz)
**Figure B.19:** $^1$H NMR of BODIPY 7d in CD$_2$Cl$_2$ (400 MHz)

**Figure B.20:** $^{13}$C NMR of BODIPY 7d in CDCl$_3$ (100 MHz)
Figure B.21: $^1$H NMR of BODIPY 7e in CD$_2$Cl$_2$ (400 MHz)

Figure B.22: $^{13}$C NMR of BODIPY 7e in CDCl$_3$ (100 MHz)
Figure B.23: $^1$H NMR of BODIPY 7f in CD$_2$Cl$_2$ (400 MHz)

Figure B.24: $^{13}$C NMR of BODIPY 7f in CD$_2$Cl$_2$ (100 MHz)
**Figure B.25:** $^1$H NMR of BODIPY 7g in CD$_2$Cl$_2$ (400 MHz)

**Figure B.26:** $^{13}$C NMR of BODIPY 7g in CDCl$_3$ (100 MHz)
**Figure B.27:** $^1$H NMR of Dipyrrin 8 in CDCl$_3$ (400 MHz)

**Figure B.28:** $^{13}$C NMR of Dipyrrin 8 in CDCl$_3$ (100 MHz)
Figure B.29: $^1$H NMR of BODIPY 8a in CD$_2$Cl$_2$ (400 MHz)

Figure B.30: $^{13}$C NMR of BODIPY 8a in CDCl$_3$ (100 MHz)
Figure B.31: $^1$H NMR of BODIPY 8b in CD$_2$Cl$_2$ (400 MHz)

Figure B.32: $^{13}$C NMR of BODIPY 8b in CDCl$_3$ (100 MHz)
Figure B.33: $^1$H NMR of BODIPY 8c in CD$_2$Cl$_2$ (400 MHz)

Figure B.34: $^{13}$C NMR of BODIPY 8c in CD$_2$Cl$_2$ (100 MHz)
Figure B.35: $^1$H NMR of BODIPY 8d in CDCl$_3$ (400 MHz)

Figure B.36: $^{13}$C NMR of BODIPY 8d in CDCl$_3$ (100 MHz)
Figure B.37: $^1$H NMR of BODIPY 8e in CD$_2$Cl$_2$ (400 MHz)

Figure B.38: $^{13}$C NMR of BODIPY 8e in CD$_2$Cl$_2$ (100 MHz)
Figure B.39: $^1$H NMR of BODIPY 8f in CD$_2$Cl$_2$ (400 MHz)

Figure B.40: $^{13}$C NMR of BODIPY 8f in CD$_2$Cl$_2$ (100 MHz)
Figure B.41: $^1$H NMR of BODIPY 8g in CD$_2$Cl$_2$ (400 MHz)

Figure B.42: $^{13}$C NMR of BODIPY 8g in CD$_2$Cl$_2$ (100 MHz)
Figure B.43: $^1$H NMR of BODIPY 4 in CDCl$_3$ (400 MHz)

Figure B.44: $^{13}$C NMR of BODIPY 4 in CDCl$_3$ (100 MHz)
Figure B.45: $^1$H NMR of BODIPY 9 in CDCl$_3$ (400 MHz)

Figure B.46: $^{13}$C NMR of BODIPY 9 in CDCl$_3$ (100 MHz)
Figure B.47: $^{11}$B NMR of BODIPY 1a in CDCl$_3$ (128 MHz)

Figure B.48: $^{11}$B NMR of BODIPY 2a in CDCl$_3$ (128 MHz)
Figure B.49: $^{11}$B NMR of BODIPY 3a in CDCl$_3$ (128 MHz)

Figure B.50: $^{11}$B NMR of BODIPY 4a in CDCl$_3$ (128 MHz)
Figure B.51: $^{11}$B NMR of BODIPY 5a in CDCl$_3$ (128 MHz)

Figure B.52: $^{11}$B NMR of BODIPY 7a in CDCl$_3$ (128 MHz)
Figure B.53: $^{11}$B NMR of BODIPY 7b in CDCl$_3$ (128 MHz)

Figure B.54: $^{11}$B NMR of BODIPY 7c in CDCl$_3$ (128 MHz)
Figure B.55: $^{11}$B NMR of BODIPY 7d in CDCl$_3$ (128 MHz)

Figure B.56: $^{11}$B NMR of BODIPY 7e in CDCl$_3$ (128 MHz)
Figure B.57: $^{11}$B NMR of BODIPY 7f in CDCl$_3$ (128 MHz)

Figure B.58: $^{11}$B NMR of BODIPY 7g in CDCl$_3$ (128 MHz)
Figure B.59: $^{11}$B NMR of BODIPY 8a in CDCl$_3$ (128 MHz)

Figure B.60: $^{11}$B NMR of BODIPY 8b in CDCl$_3$ (128 MHz)
Figure B.61: $^{11}$B NMR of BODIPY 8c in CDCl$_3$ (128 MHz)

Figure B.62: $^{11}$B NMR of BODIPY 8d in CDCl$_3$ (128 MHz)
Figure B.63: $^{11}$B NMR of BODIPY 8e in CDCl$_3$ (128 MHz)

Figure B.64: $^{11}$B NMR of BODIPY 8f in CDCl$_3$ (128 MHz)
Figure B.65: $^{11}$B NMR of BODIPY 8g in CDCl$_3$ (128 MHz)

Figure B.66: $^{11}$B NMR of BODIPY 4 in CDCl$_3$ (128 MHz)
Figure B.67: $^{11}$B NMR of BODIPY 9 in CDCl$_3$ (128 MHz)
APPENDIX C: NMR Characterization of Compounds Found in Chapter 4

Figure C.1: $^1$H NMR of BODIPY 1 in CDCl$_3$ (400 MHz)

Figure C.2: $^{13}$C NMR of BODIPY 1 in CDCl$_3$ (100 MHz)
Figure C.3: $^1$H NMR of BODIPY 2 in CDCl$_3$ (400 MHz)

Figure C.4: $^{13}$C NMR of BODIPY 2 in CDCl$_3$ (100 MHz)
Figure C.5: $^1$H NMR of BODIPY 3a in CDCl$_3$ (400 MHz)

Figure C.6: $^{13}$C NMR of BODIPY 3a in CDCl$_3$ (100 MHz)
Figure C.7: $^1$H NMR of BODIPY 3b in acetone (400 MHz)

Figure C.8: $^{13}$C NMR of BODIPY 3b in acetone (100 MHz)
Figure C.9: $^1$H NMR of BODIPY 4a in CDCl$_3$ (400 MHz)

Figure C.10: $^{13}$C NMR of BODIPY 4a in CDCl$_3$ (100 MHz)
Figure C.11: $^1$H NMR of BODIPY 4b in acetone (400 MHz)

Figure C.12: $^{13}$C NMR of BODIPY 4b in acetone (100 MHz)
**Figure C.13:** $^1$H NMR of BODIPY 4c in acetone (400 MHz)

**Figure C.14:** $^{13}$C NMR of BODIPY 4c in CDCl$_3$ (100 MHz)
Figure C.15: $^1$H NMR of BODIPY 5a in CDCl$_3$ (400 MHz)

Figure C.16: $^{13}$C NMR of BODIPY 5a in CDCl$_3$ (100 MHz)
Figure C.17: $^1$H NMR of BODIPY 6a in acetone (400 MHz)

Figure C.18: $^{13}$C NMR of BODIPY 6a in acetone (100 MHz)
**Figure C.19:** $^1$H NMR of BODIPY 7 in acetone (400 MHz)

**Figure C.20:** $^{13}$C NMR of BODIPY 7 in CDCl$_3$ (100 MHz)
Figure C.21: $^1$H NMR of BODIPY 8a in CDCl$_3$ (400 MHz)

Figure C.22: $^1$H NMR of BODIPY 8b in CDCl$_3$ (400 MHz)
Figure C.23: $^{13}$C NMR of BODIPY 8b in CDCl$_3$ (100 MHz)

Figure C.24: $^1$H NMR of BODIPY 9 in CDCl$_3$ (400 MHz)
Figure C.25: $^1$H NMR of BODIPY 10 in CDCl$_3$ (400 MHz)

Figure C.26: $^1$H NMR of BODIPY 11a in CDCl$_3$ (400 MHz)
Figure C.27: $^{13}$C NMR of BODIPY 11a in CDCl$_3$ (100 MHz)

Figure C.28: $^1$H NMR of BODIPY 11b in CDCl$_3$ (400 MHz)
Figure C.29: $^{13}$C NMR of BODIPY 11b in CDCl$_3$ (100 MHz)

Figure C.30: $^1$H NMR of BODIPY 12 in CDCl$_3$ (400 MHz)
Figure C.31: $^{13}$C NMR of BODIPY 12 in CDCl$_3$ (100 MHz)

Figure C.32: $^{11}$B NMR of BODIPY 1 in CDCl$_3$ (128 MHz)
Figure C.33: $^{11}$B NMR of BODIPY 2 in CDCl$_3$ (128 MHz)

Figure C.34: $^{11}$B NMR of BODIPY 3a in CDCl$_3$ (128 MHz)
Figure C.35: $^{11}$B NMR of BODIPY 3b in CDCl$_3$ (128 MHz)

Figure C.36: $^{11}$B NMR of BODIPY 4a in CDCl$_3$ (128 MHz)
Figure C.37. $^{11}$B NMR of BODIPY 4b in CDCl$_3$ (128 MHz)

Figure C.38. $^{11}$B NMR of BODIPY 4c in CDCl$_3$ (128 MHz)
Figure C.39: $^{11}$B NMR of BODIPY 5a in CDCl$_3$ (128 MHz)

Figure C.40: $^{11}$B NMR of BODIPY 6a in ((CD$_3$)$_2$CO (128 MHz)
Figure C.41: $^{11}$B NMR of BODIPY 7 in CDCl$_3$ (128 MHz)

Figure C.42: $^{11}$B NMR of BODIPY 8a in CDCl$_3$ (128 MHz)
Figure C.43: $^{11}$B NMR of BODIPY 8b in CDCl$_3$ (128 MHz)

Figure C.44: $^{11}$B NMR of BODIPY 9 in CDCl$_3$ (128 MHz)
Figure C.45: $^{11}$B NMR of BODIPY 10 in CDCl$_3$ (128 MHz)

Figure C.46: $^{11}$B NMR of BODIPY 11a in CDCl$_3$ (128 MHz)
Figure C.47: $^{11}$B NMR of BODIPY 11b in CDCl$_3$ (128 MHz)

Figure C.48: $^{11}$B NMR of BODIPY 12 in CDCl$_3$ (128 MHz)
APPENDIX D: NMR Characterization of Compounds Found in Chapter 5

Figure D.1: $^1$H NMR of compound 4 in CDCl$_3$ (250 MHz)

Figure D.2: $^1$H NMR of compound 4a in CDCl$_3$ (250 MHz)
Figure D.3: $^{13}$C NMR of compound 4a in CDCl$_3$ (62.5 MHz)

Figure D.4: $^1$H NMR of compound 5a in CDCl$_3$ (250 MHz)
Figure D.5: $^{13}$C NMR of compound 5a in CDCl$_3$ (62.5 MHz)

Figure D.6: $^1$H NMR of compound 6a in CDCl$_3$ (250 MHz)
Figure D.7: $^{13}$C NMR of compound 6a in CDCl$_3$ (62.5 MHz)

Figure D.8: $^1$H NMR of compound 7a in CDCl$_3$ (250 MHz)
Figure D.9: $^{13}$C NMR of compound 7a in CDCl$_3$ (62.5 MHz)

Figure D.10: $^1$H NMR of compound 8 in CDCl$_3$ (250 MHz)
Figure D.11: $^{13}$C NMR of compound 8 in CDCl$_3$ (62.5 MHz)

Figure D.12: $^1$H NMR of compound 14 in CDCl$_3$ (250 MHz)
Figure D.13: $^1$H NMR of compound 15 in CDCl$_3$ (250 MHz)

Figure D.14: $^1$H NMR of compound 16 in CDCl$_3$ (250 MHz)
Figure D.15: $^1$H NMR of compound 17 in CDCl$_3$ (250 MHz)

Figure D.16: $^1$H NMR of compound 18 in CDCl$_3$ (250 MHz)
Figure D.17: $^{13}$C NMR of compound 18 in CDCl$_3$ (62.5 MHz)

Figure D.18: $^1$H NMR of compound 19 in CDCl$_3$ (250 MHz)
Title: Synthesis and Reactivity of 4,4-Dialkoxy-BODIPYs: An Experimental and Computational Study

Author: Alex L. Nguyen, Petia Bobadova-Parvanova, Melissa Hopfinger, et al

Publication: Inorganic Chemistry

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Chlorination of Aliphatic Primary Alcohols via Triphosgene–Triethylamine Activation

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VITA

Alex L. Nguyen was born in Saigon, Vietnam and is engaged to Trang T. H. Nguyen. His family immigrated to the US in 1997 and has resided in Baton Rouge, Louisiana since. After he took Intermediate Organic Chemistry with Dr. Carol Taylor as the instructor, he was fascinated with unique transformations in organic chemistry and joined Taylor’s group the following semester to begin his undergraduate research. He earned a Bachelor of Science degree from Louisiana State University (LSU) in May of 2011. With his continued interests in organic chemistry, he entered the chemistry doctoral program in the Chemistry Department at LSU, Baton Rouge, Louisiana in August 2011. He joined the laboratory of Dr. M. Graça H. Vicente and Dr. Kevin M. Smith shortly afterward. He is currently a candidate for the degree of Doctor of Philosophy at the May 2016 commencement.