

The Synthesis and Functionalisation of Porphyrins and Related Systems



Submitted by

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Under the supervision of Prof. Dr. Mathias O. Senge

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Declaration

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Publications

- D. Larowska, **J. M. O'Brien**, M. O. Senge, G. Burdzinski, B. Marciniak, A. Lewandowska-Andralojc, Graphene Oxide Functionalized with Cationic Porphyrins as Materials for the Photodegradation of Rhodamine B, *J. Phys. Chem. C*, **2020**, *124*, 15769–15780.
- A. Wiehe, **J. M. O'Brien**, M. O. Senge, Trends and targets in antiviral phototherapy, *Photochem. Photobiol. Sci.*, **2019**, *18*, 2565–2612.
- **J. M. O'Brien**, E. Sitte, K. J. Flanagan, K. Kühner, L. J. Hallen, D. Gibbons, M. O. Senge, Functionalization of Deutero- and Protoporphyrin IX Dimethyl Esters via Palladium-Catalyzed Coupling Reactions, *J. Org. Chem.*, **2019**, *10*, 6158–6173.
- S. Belali, H. Savoie, **J. M. O'Brien**, A. A. Cafolla, B. O'Connell, A. R. Karimi, R. W. Boyle, M. O. Senge, Synthesis and Characterization of Temperature-Sensitive and Chemically Cross-Linked Poly(*N*-isopropylacrylamide)/Photosensitizer Hydrogels for Applications in Photodynamic Therapy, *Biomacromolecules*, **2018**, *19*, 1592–1601.
- G. Emandi, Y. M. Shaker, K. J. Flanagan, **J. M. O'Brien**, M. O. Senge, Merging Triptycene, BODIPY and Porphyrin Chemistry: Synthesis and Properties of Mono- and Trisubstituted Triptycene Dye Arrays, *Eur. J. Org. Chem.*, **2017**, 6680–6692.
- M. O. Senge, S. A. MacGowan, **J. M. O'Brien**, Conformational control of cofactors in nature – the influence of protein-induced macrocycle distortion on the biological function of tetrapyrroles, *Chem. Commun.*, **2015**, *51*, 17031–17063.

Conference Abstracts

- **J. M. O'Brien**, M. O. Senge, "The Preparation of Symmetrical Porphyrin Derivatives Related to Naturally Occurring Pigments for Photomedical Applications" at the 151st GDCh Science Forum Chemistry: WiFo, (15.09.19–18.09.19), Aachen, Germany, Poster ORG036.
- **J. M. O'Brien**, S. Belali, H. Savoie, A. A. Cafolla, B. S. O'Connell, A. R. Karimi, R. W. Boyle, M. O. Senge, "Synthesis and Characterization of Temperature-Sensitive and Chemically Cross-Linked Poly(*N*-isopropylacryamide)/Photosensitizer Hydrogels for Applications in Photodynamic Therapy" at the 11th International Cancer Conference (24.09.19–25.09.19), Dublin, Ireland, Poster 14.
- **J. M. O'Brien**, E. Sitte, M. O. Senge, "Classical Organometallic Chemistry Breathing New Life into Natural Porphyrin Functionalization" in the 27th Photo IUPAC Symposium, (08.07.18–13.07.18), Dublin, Ireland, Abstract book P187.
- S. Belali, H. Savoie, **J. M. O'Brien**, A. A. Cafolla, B. S. O'Connell, A. R. Karimi, R. W. Boyle, M. O. Senge, "Synthesis and Characterization of Temperature-Sensitive and Chemically Cross-Linked Poly(*N*-isopropylacryamide)/Photosensitizer Hydrogels for Applications in Photodynamic Therapy" in the 5th ESP Photobiology School, (11.06.18–17.06.18), Brixen, Italy, Abstract book P15.
- **J. M. O'Brien**, E. Sitte, K. J. Flanagan, C. M. Moylan, M. O. Senge, "Classical Organometallic Chemistry Breathing New Life into Natural Porphyrin Functionalization" in the 40th Tetrapyrrole Discussion Group Meeting, (11.09.17–13.09.17), University of Sheffield, Sheffield, United Kingdom, Abstract P35.
- S. Belali, **J. M. O'Brien**, H. Savoie, R. W. Boyle, B. S. O'Connell, A. A. Cafolla, A. R. Karimi, M. O. Senge, "Revitalizing the Application of Protoporphyrin IX as a Photosensitizer via Conjugation in Hydrogel Networks" in the 40th Tetrapyrrole Discussion Group Meeting, (11.09.17–13.09.17), University of Sheffield, Sheffield, United Kingdom, Abstract P36.
- **J. M. O'Brien**, L. Rogers, C. M. Moylan, E. M. Scanlan, M. O. Senge, "Synthetic Strategies Towards Unsymmetrical Porphyrins for Application as Photosensitizers in Photodynamic Therapy (PDT)" in the 16th International Photodynamic

Association World Congress, (08.06.17–13.06.17), Coimbra, Portugal, Abstract P77.

- **J. M. O'Brien**, L. Schmidt, G. Emandi, M. Browne, M. E. Lyons, C. Prior, M. O. Senge, “Triptycene scaffolds: Synthesis and properties of triptycene-derived Schiff base compounds for the selective and sensitive detection of CN^- and Cu^{2+} ” in the 15th Annual Symposium of the Centre for Synthesis and Chemical Biology, (09.12.16), Trinity College Dublin, Dublin, Ireland, Abstract P40.

Oral Presentation

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Abbreviations

aPDT	Antiviral photodynamic therapy
aq.	Aqueous
Ar	Aryl
BAD	BODIPY-anthracene dyad
B ₂ pin ₂	Bis(pinacolato)diboron
calcd.	Calculated
Conc.	Concentrated
d	doublet
dd	double of doublets
DOSY	Diffusion-ordered NMR spectroscopy
DPBF	1,3-Diphenylisobenzofuran
DPM	Dipyrromethane
dppe	1,2-Bis(diphenylphosphino)ethane
dppf	1,1'-Ferrocenediyl-bis(diphenylphosphine)
equiv.	Equivalents
ESI	Electrospray ionisation
FCV	Feline corona virus
FHV	Feline herpes virus
GO	Graphene oxide
h	hour
HA	Haemagglutinin
HCoV-HKU1	Human coronavirus Hong Kong University-1

HPD	Haematoporphyrin derivative
HRMS	High resolution mass spectrometry
HSQC	Heteronuclear single quantum coherence spectroscopy
IAV	Influenza A virus
Lit.	Literature value
LSP	Least-squares plane
m	multiplet
MALDI	Matrix assisted laser desorption ionisation
M.p.	Melting point
MDCK cells	Madin-Darby Canine Kidney cells
MERS-CoV	Middle East respiratory syndrome-related coronavirus
m/z	mass/charge
NMR	Nuclear magnetic resonance
Pd(dppe)Cl ₂	[1,2-Bis(diphenylphosphino)ethane]palladium(II) dichloride
Pd(dppf)Cl ₂	[1,1'-Bis(diphenylphosphino)ferrocene]palladium(II) dichloride
Pd(OAc) ₂	Palladium(II) acetate
PDI	Photodynamic inactivation
Pd(PPh ₃) ₄	Tetrakis(triphenylphosphine)palladium(0)
PDT	Photodynamic therapy
PEPPSI-IPr	Pyridine-enhanced precatalyst preparation stabilisation and initiation, NHC ligand
PMNP	Polymyxin nonapeptide
ppm	Parts per million

PS	Photosensitiser
q	quartet
R_f	Retention factor
RGO	Reduced graphene oxide
RhB	Rhodamine B
ROS	Reactive oxygen species
RT	Room temperature
SARS-CoV	Severe acute respiratory syndrome coronavirus
SARS-CoV-2	Severe acute respiratory syndrome coronavirus-2
sat.	Saturated
soln.	Solution
SPhos	2-Dicyclohexylphosphino-2',6'-dimethoxybiphenyl
t	triplet
TBAF	Tetra- <i>n</i> -butylammonium fluoride
TLC	Thin layer chromatography
TPP	Tetraphenylporphyrin
UV	Ultraviolet
UV/Vis	Ultraviolet-visible spectroscopy
vac.	vacuum
°C	Degree Celsius

Table of Contents

Declaration	ii
Publications	iii
Conference Abstracts	iv
Acknowledgements	vi
Abbreviations	vii
 Chapter 1: Introduction – Porphyrin Synthesis and Functionalisation	
1.1 Tetrapyrroles – Introduction and Nomenclature	1
1.2 The Synthesis of Porphyrins – Condensation Reactions	2
1.3 Functionalisation of the Porphyrin Periphery	7
1.4.1 BODIPYs	10
1.4.2 <i>C</i> - and <i>E</i> -BODIPYs	11
1.4.3 <i>O</i> -BODIPYs	12
1.5.1 An Introduction to the Relationship between Tetrapyrroles and Human Health	14
1.5.2 Modern Photodynamic Therapy (PDT)	16
1.5.3 Photosensitiser Development	20
1.6 Deuteroporphyrin IX	22
 Chapter 2: Antiviral Photodynamic Therapy and COVID-19	
2.1 COVID-19	25
2.2 The PDI of Viruses as a Viable Treatment Option	26
2.3 PDI in Relation to SARS-CoV-2	30
2.4 Objectives	31
 Chapter 3: Functionalisation of Deuteroporphyrin IX Dimethyl Ester	
3.1 Introduction – Functionalisation of Deuteroporphyrin IX	33
3.2 Objectives	34
3.3 Results and Discussion	35

3.4	Conclusion and Future Work	59
 Chapter 4: Photosensitisers for Organic Dye Degradation		
4.1	Introduction	60
4.2	Objectives	61
4.3	Results and Discussion	62
4.4	Conclusion and Future Work	68
 Chapter 5: Preparation of <i>O</i>-BODIPYs		
5.1	Introduction	69
5.2	Objectives	71
5.3	Results and Discussion	72
5.4	Conclusion and Future Work	92
Chapter 6: Experimental		94
Chapter 7: References		123

1 Introduction

1.1 Tetrapyrroles – Introduction and Nomenclature:

In the (bio)chemical world, porphyrins and their tetrapyrrole relatives are the life and soul of the party. These brightly coloured pigments are responsible for the red colour of our blood (heme b, **1.1**, Fig. 1.1),¹ the various shades of green seen in nature (chlorophyll a, **2**, Fig. 1),² and even in some cases fabulous the plumage of birds (turacoverdin and turacin).³ From photosynthesis to respiration, life as we know it would not be possible if tetrapyrroles were not on the scene.¹

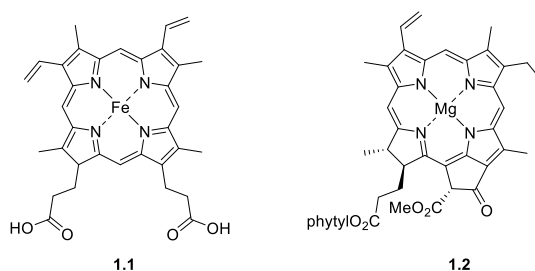


Figure 1.1: Heme b **1** and chlorophyll a **2**.

The elucidation of the structures shown in Fig. 1 led to Nobel Prizes for Hans Fischer and Richard Willstätter, respectively, although the structure of **1.1** was first correctly proposed back in 1912 by Küster.^{4–7} Throughout the 1920s, Fischer worked extensively on the chemistry of porphyrins, synthesising deuteroporphyrin (DPIX, **1.3**, Fig. 1.2), protoporphyrin (PPIX, **1.4**, Fig. 1.2), hematoporphyrin and hemin, and also created an easy-to-follow nomenclature which has since been updated by the IUPAC to the universal porphyrin nomenclature we follow today (Fig. 1.2, **1.5**).^{5,8,9} The basic porphyrin structure as shown in **1.5** is a macrocycle consisting of four pyrrole units connected by four methine bridges. The macrocycle has 22 π -electrons; 18 of which are part of the aromatic system, thereby obeying Hückel's rule for aromaticity ($4n+2$), with the remaining 4 π -electrons taking on more of a double bond character.¹⁰

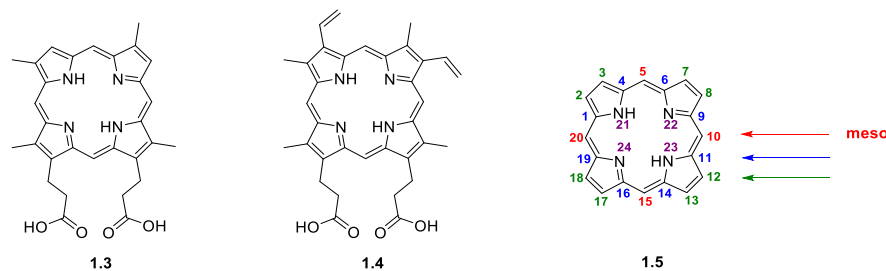
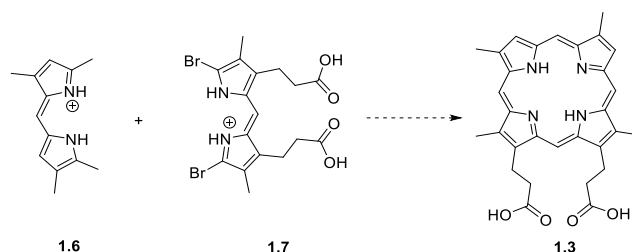


Figure 1.2: Left, Deuterioporphyrin IX **1.3**; centre, protoporphyrin IX **1.4**; right, IUPAC numbering of porphyrin and labelling of the meso-, α -, and β -positions.

Not only do tetrapyrroles add colour to our daily lives, they are one of the most fundamental classes of enzymes in Nature. In many cases, chemically identical tetrapyrrole cofactors are involved in chemically distinct processes. For example, heme b **1.1** has multifaceted roles from the transport and storage of oxygen (hemoglobin, myoglobin), to drug and H₂O₂ metabolism (cytochrome P450 and catalases, peroxidases, respectively) as well as electron transfer (cytochrome c).¹¹

1.2 The Synthesis of Porphyrins – Condensation Reactions:

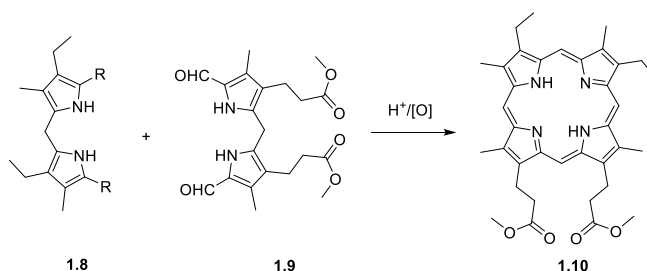
Taking into account the multitude of functions linked to just one tetrapyrrole, it comes as no surprise that today porphyrins are one of the most widely studied classes of natural products, with applications in such diverse areas as photomedicine, in photodynamic therapy (PDT), and in industry, as optical materials and sensors.^{12,13} However, they are far from the most facile of compounds to prepare synthetically. Fischer's initial work on the synthesis of β -substituted porphyrins catalysed a wealth of contributions to the field, such as those of Rothmund,^{14,15} MacDonald,¹⁶ and Lindsey.^{17,18} Work towards the conventional syntheses used today began when Fischer combined two dipyrromethene components, synthesised from a series of substituted pyrrole precursors, at high temperatures in molten organic acid to form DPIX **1.3** (Scheme 1.1).⁵ To avoid a mixture of products, one of the components used, in this case **1.7**, is symmetrical.



Scheme 1.1: An excerpt from Fischer's total synthesis of hemin.

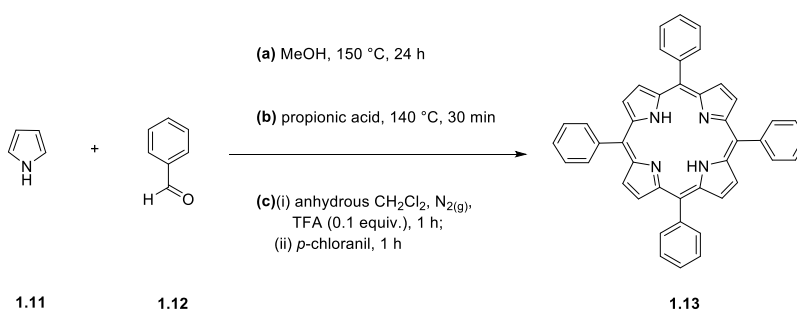
MacDonald was the first to use reduced dipyrromethanes (DPMs) in porphyrin synthesis; he demonstrated the reaction of either a 1,9-di-unsubstituted DPM or its corresponding 1,9-dicarboxylic acid with a 1,9-diformyl DPM, in the presence of hydriodic acid as catalyst, to produce the respective porphyrin in good yields (Scheme 1.2).¹⁶ As with Fischer's total synthesis route, here one DPM moiety is kept symmetrical, and as both of the "linking" substituents are on opposite coupling partners, mixtures are avoided as the two halves are unable to react with themselves. This has remained one of the popular routes in porphyrin

synthesis to-date, although now *p*-toluenesulfonic acid is the more commonly chosen acid catalyst.^{19,20}



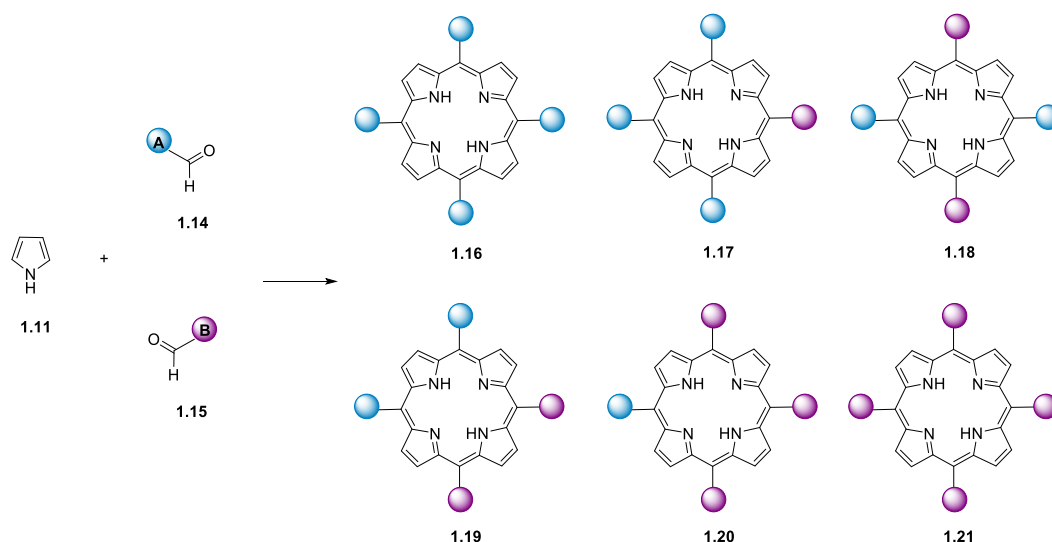
Scheme 1.2: MacDonald condensation to form mesoporphyrin IX dimethyl ester **1.10**.

The classical route towards meso-substituted porphyrins is that initially developed by Rothmund, shown below in Scheme 1.3 (conditions a) for the preparation of well-known 5,10,15,20-tetraphenylporphyrin (TPP) **1.13**.¹⁵ These meso-aryl substituted compounds are very stable and can easily be prepared on multi-gram scales with good yields.²¹ The Adler-Longo method provided more convenient reaction conditions, reacting pyrrole and benzaldehyde in refluxing propionic acid for 30 min (Scheme 1.3, conditions b).²² However, this method again had its deficiencies seen in the difficult to near impossible purification of mixed substituted porphyrins which did not readily crystallise or precipitate from the acid solution, as well as failure to produce the desired porphyrin when using aldehydes with acid-sensitive functional groups. Lindsey refined this method to produce the desired porphyrins using only trace acid catalysis, thereby opening up a whole new scope of functional group tolerability in the synthesis of meso-aryl substituted porphyrins, with yields of 30-40% obtained.²³ Here, pyrrole and benzaldehyde are reacted at room temperature in anhydrous CH_2Cl_2 under N_2 for 1 h, followed by the addition of *p*-chloranil to convert the porphyrinogen to TPP (Scheme 1.3, conditions c). Purification *via* column chromatography separated the product from any polypyrrole side-products. Overall, while the purification is more involved than that of Rothmund and Adler-Longo, wherein the porphyrin simply crystallises or precipitates out of solution, the Lindsey method provides much milder conditions which can tolerate a wide variety of functional groups with improved yields.²⁴



Scheme 1.3: Synthesis of 5,10,15,20-tetraphenylporphyrin (TPP) **1.13**.

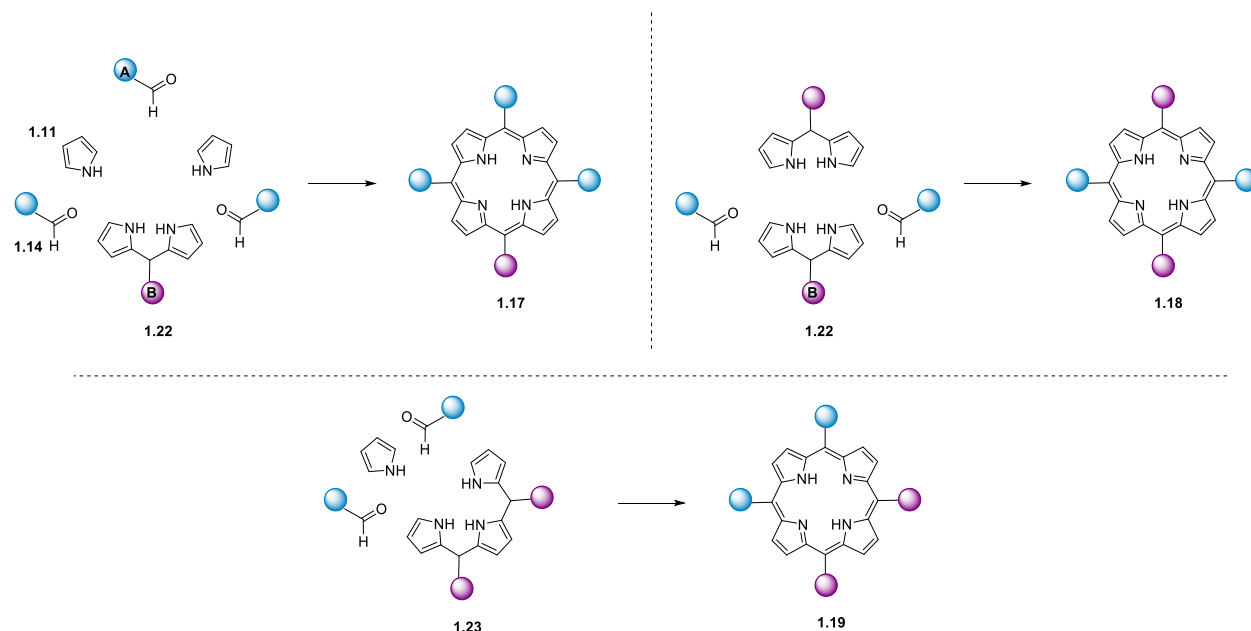
Synthetically, symmetrical meso-substituted porphyrins such as TPP are the most easily achieved. However, these condensation conditions can also be applied to the synthesis of unsymmetrical meso-substituted porphyrins *via* mixed condensations. In this case synthesis involves the mixing of two or more different aldehydes with pyrrole (unsubstituted **1.11** or substituted) to yield a mixture of porphyrin derivatives normally separated by some form of chromatography (Scheme 1.4).²¹



Scheme 1.4: Mixed condensation method yielding both symmetrical and unsymmetrical porphyrin derivatives.

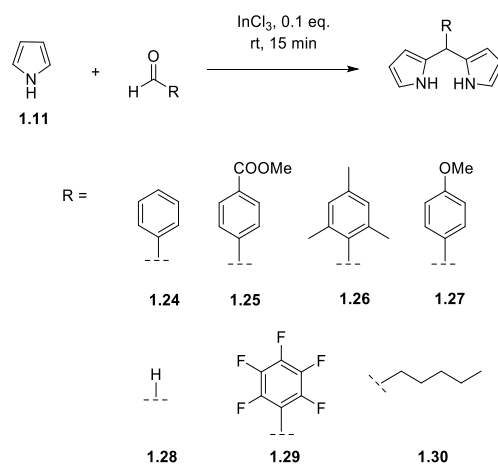
Unsurprisingly, there can be quite tedious purification depending on the ratio of derivatives formed, therefore statistical control of the products is normally attempted.²⁵ For example, a 3:1 ratio of aldehydes would favour the A₃B derivative **1.17**. However, low yields are generally observed due to the formation of multiple porphyrin side-products such as those illustrated in Scheme 1.4.²⁶ Refinement of this method involving di- and tripyrrolic intermediates such as those illustrated in Scheme 1.5 can help in overcoming the pitfalls of

the mixed condensation. Although, as before, the carefully planned ratio of reactants is paramount to the final products observed.^{18,24,25,27,28}



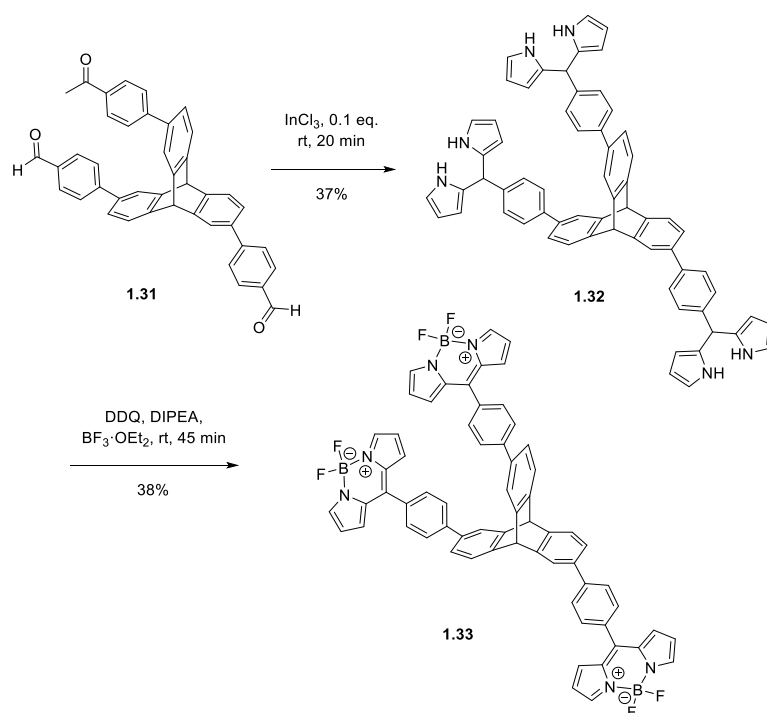
Scheme 1.5: [2+2] and [3+1] condensations using dipyrromethane and tripyrrane moieties.

Dipyrromethanes (DPMs) are important building blocks not only in the synthesis of porphyrins, but also members of the wider tetrapyrrole family – chlorins, corroles and phthalocyanines. The synthesis of simple meso-functionalised DPMs can be achieved *via* condensation of the appropriate aldehyde with pyrrole in the presence of an acid catalyst.²⁹ Laha and co-workers developed a scalable one-flask, solventless synthesis of DPMs using InCl_3 as the acid catalyst. This room temperature reaction was successful in synthesising a broad range of meso-substituted DPMs as much cleaner colourless solids as compared to the same reaction carried out using TFA (Scheme 1.6).²⁷



Scheme 1.6: Synthesis of various meso-substituted DPMs.

The Senge Group adapted this method to the synthesis of trisubstituted triptycene derivatives in 2017. Using trisubstituted triptycene **1.31** as the aldehyde, 2,6,14-tris[(4-phenyl-5-dipyrromethyl)]triptycene **1.32** was synthesized following the procedure of Laha *et al.* in 37% yield, and was then converted to the corresponding threefold BODIPY-substituted (4,4'-difluoro-4-bora-3a,4a-diaza-*s*-indacene) triptycene **1.33** in 38% yield (Scheme 1.7).³⁰

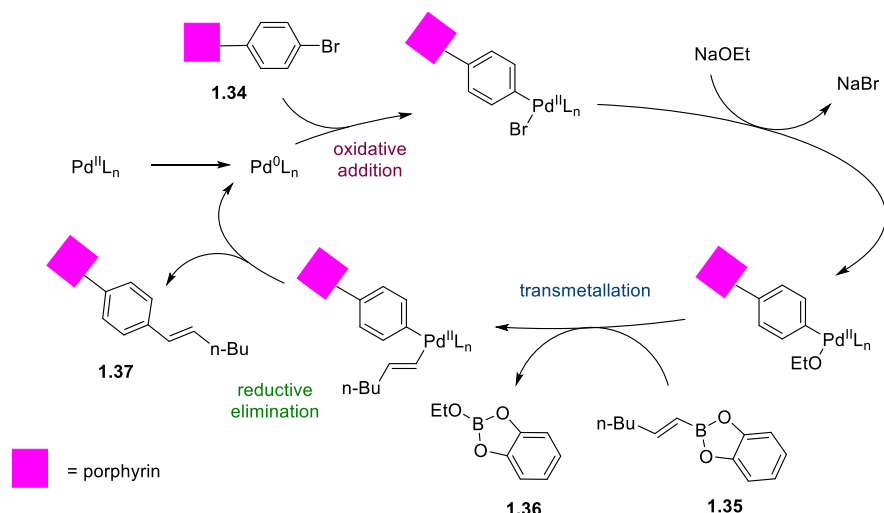


Scheme 1.7: Synthesis of trifunctionalised triptycene derivatives.

1.3 Functionalisation of the Porphyrin Periphery:

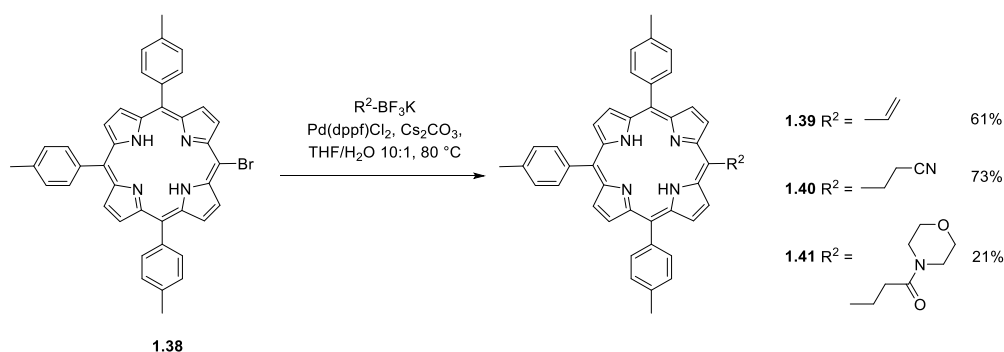
Due to their inherent aromaticity, porphyrins are open to manipulation by the various electrophilic and nucleophilic substitution reactions commonly seen on all other aromatic systems such as halogenation, nitration, sulfonation and acylation.^{21,31} Reactions occur at either the meso- or β -positions, if available, and careful planning allows tuning of the compounds aqueous solubility, optical imaging capabilities and cellular uptake, whatever is necessary for the desired function. The possibilities are near endless, with a wealth of literature available covering all manner of reactions and organometallic coupling methodologies.^{32,33}

One of the most widely used methods for functionalising the porphyrin periphery remains the use of palladium-catalysed cross-coupling reactions. First reported by Heck in 1972 who demonstrated the reactivity between aryl, benzyl and styryl halides with terminal alkenes in the presence of palladium salts to form a new carbon-carbon bond.³⁴ This seminal paper paved the way for an outburst of research into C-C bond forming reactions using transition metal catalysts, which are now a common avenue for functionalisation and derivatisation in any synthetic chemistry lab.^{33,35} Various reactions came next; from Sonogashira couplings in 1975, between an organohalide and an alkyne,³⁶ to Suzuki-Miyaura couplings, between an organohalide and an organoboron compound,³⁷ to more recently the Buchwald-Hartwig aminations, between an organohalide and an amine.^{38,39} Each of these staple reactions follow a general catalytic scheme, as illustrated in Scheme 1.8 with the Suzuki-Miyaura coupling reaction, composed of three main events: oxidative addition, transmetallation, and reductive elimination.^{40,41} Functionalisation in this manner usually proceeds through halogenated precursors, most commonly either brominated or iodinated species.^{21,42–44} The general order of reactivity for the Suzuki-Miyaura and similar Pd-catalysed coupling reactions is as follow: $I > Br \geq OTf \gg Cl$.⁴⁵ This reaction is a useful method of introducing aryl functional groups in reasonable yields.³⁷ Standard conditions employ a Pd-catalyst such as $Pd(PPh_3)_4$ and base to couple a brominated or iodinated precursor with a boronic acid/ester under an inert atmosphere (Scheme 1.8).^{46,47}



Scheme 1.8: General Suzuki-Miyaura coupling mechanism.

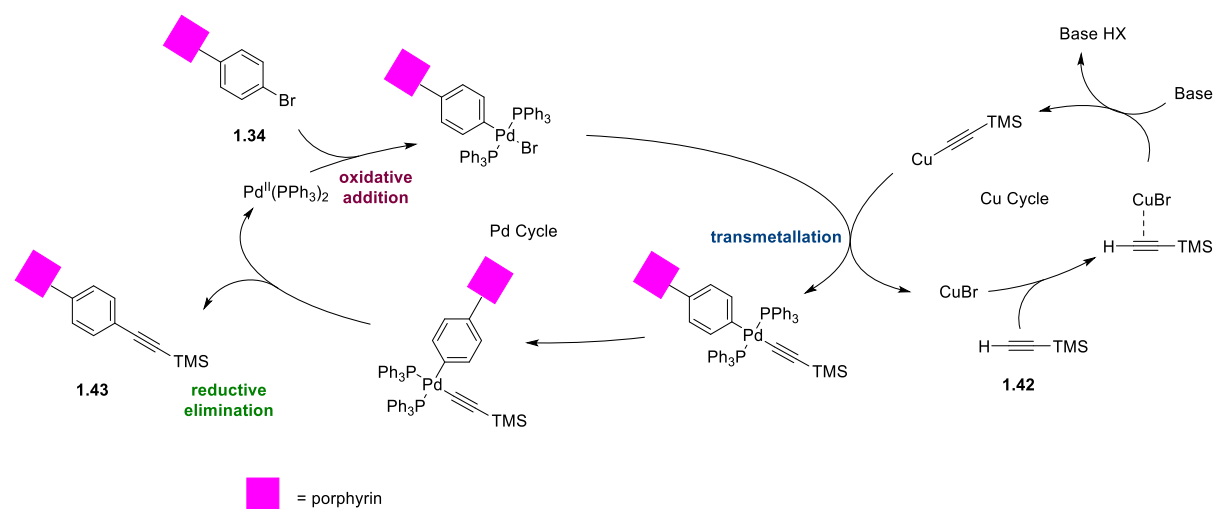
The versatility of this reaction has even been expanded to accommodate alkyl couplings as well as the employment of reagents such as the potassium organotrifluoroborates. Senge and co-workers demonstrated the coupling of such potassium organotrifluoroborates with 5-bromo-10,15,20-*tris*(4-methylphenyl)porphyrin (Scheme 1.9).⁴⁸ These reagents offer advantages over the traditional boronic acids and esters in that due to their increased air-stability there are more commercially available derivatives not found amongst their readily available boronic-counterparts.⁴⁹



Scheme 1.9: Examples of Suzuki-Miyaura coupling using potassium organotrifluoroborates.

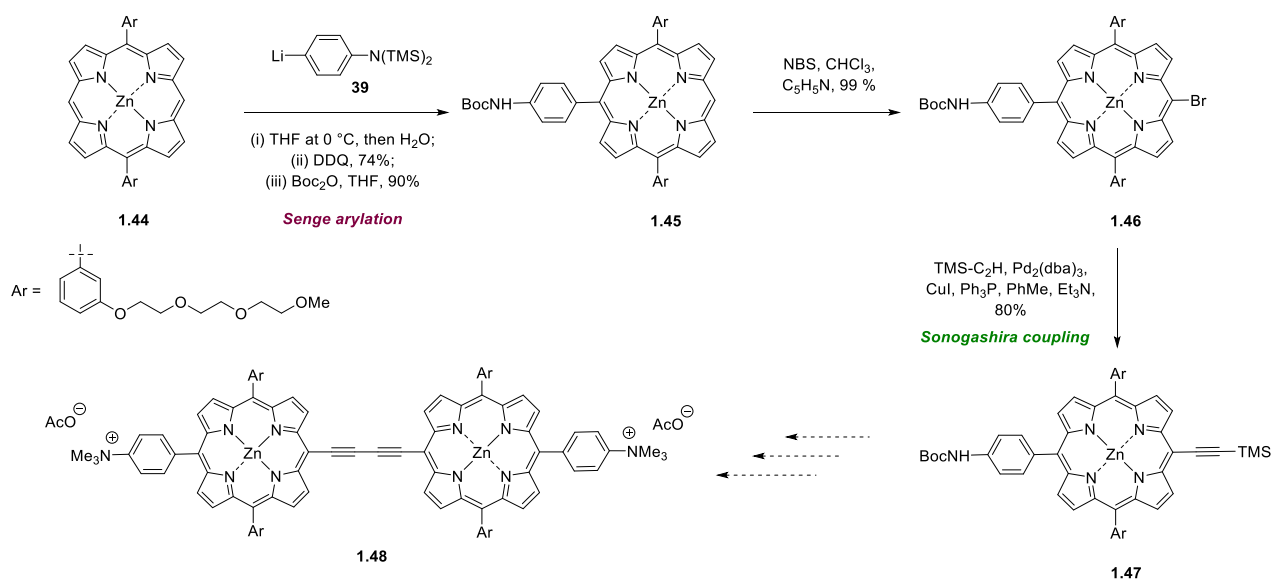
The Sonogashira coupling reaction is most commonly used to prepare alkynyl-substituted derivatives for further follow-up modifications (Scheme 1.10).³⁶ Here, Pd-catalysis as well as Cu-catalysis is used leading to the formation of the carbon-carbon bond between a terminal alkyne and the respective halogenated starting material. In more recent years, the reaction has been successfully performed in the absence of a Cu-catalyst. Fukoyama *et al.* used $\text{PdCl}_2(\text{PPh}_3)_2$ as the sole catalyst and found that in the presence of either

diisopropylamine or piperidine as base, the reaction proceeded in moderate to high yields without any co-catalysis necessary.⁵⁰



Scheme 1.10: General Sonogashira coupling mechanism.

This reaction was first demonstrated on the porphyrin skeleton by Ali and van Lier in 1994 who substituted the β -positions of various metallated deuteroporphyrin derivatives.⁵¹ Since then, it has become one of the most widely applied Pd-catalysed reactions with regards to porphyrin functionalisation. For example, Anderson and co-workers used the Sonogashira coupling in their synthesis of hydrophilic butadiyne-linked conjugated zinc porphyrin dimers (Scheme 1.11).⁵² The target compounds featured high two-photo absorption and red-shifted absorption spectra, making them promising candidates for one-photon and two-photon excited photodynamic therapy (PDT). Their synthesis also featured the Senge arylation to directly substituted the free meso-position of their porphyrin with an aniline moiety.⁵³ The Senge arylation is an example of a highly regioselective nucleophilic substitution, resulting in a high yield of just the mono-substituted compound.^{54,55}



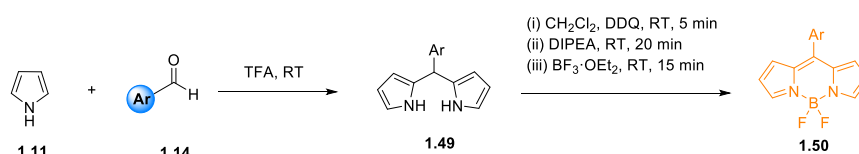
Scheme 1.11: Sonogashira coupling and the Senge arylation featuring in the synthesis of potential photosensitisers for PDT.

1.4.1 BODIPYs:

While an abundance of highly fluorescent organic compounds are known, the difluoroboraindacene “BODIPY”⁵⁶ family has been credited with being one of the more versatile fluorophores, and its popularity has only been growing in recent decades. While the first member of this fluorescent family was discovered by Treibs and Kreuzer in 1968,⁵⁷ this class of compounds failed to receive much attention before the 1980s. Since then, many BODIPY-based dyes have been designed and commercialized for biological labelling.^{58–60} For example, BODIPYs became known as photostable substitutes for fluorescein, giving the fluorophore applications in cell imaging, and by the mid-1990s an abundance of research was undergoing into what became known affectionately as “porphyrin’s little sister”.⁶¹

BODIPYs are usually bright-yellow compounds, containing a conjugated π -electron system, and demonstrate high molar absorptivities with intense long-wavelength UV-vis absorption at approximately 400 nm as well as high fluorescence quantum yields.^{60,62} The optical properties can be fine-tuned in a myriad of functionalisation routes, whether by modification of the pyrrole unit, the meso- or bridge-position, or as will be discussed later, substitution of the fluoride ligands.^{63–65} Direct synthesis of meso-functionalised BODIPYs can be carried out *via* the respective DPM precursor. In a four-step one-pot synthesis, condensation of pyrrole and the respective aldehyde is catalysed by TFA, DDQ oxidizes the dipyrromethane to the dipyrromethene, DIPEA abstracts protons from the pyrrolic

units, and finally complexation with $\text{BF}_3 \cdot \text{OEt}_2$ results in the target BODIPY (Scheme 1.12).²⁹



Scheme 1.12: One-pot BODIPY synthesis.

Today, there is a vast range of BODIPY-type molecules readily available through convenient syntheses including non-fluorinated derivatives such that new terminology has been introduced to identify the nature of the 4,4'-substituents: *F* – fluoro; *C* – alkyl/aryl; *E* – ethynyl; and *O* – oxygen, *i.e.*, *O*-BODIPY.⁶¹

1.4.2 *C*- and *E*-BODIPYs:

Ziessel and co-workers developed a straightforward method to substitute the fluoro ligands of the central boron atom with alkyl and aryl residues, and were also the first to achieve substitution with alkynyl groups.^{66,67} Alkyl and aryl moieties were introduced *via* alkyl-lithium and Grignard reagents under mild conditions (0 – 20 °C), with the products retaining their strongly luminescent and redox-active natures. BODIPYs usually suffer from quite small Stokes shifts ($\Delta\lambda \approx 600 \text{ cm}^{-1}$) and exhibit fluorescence quenching upon conjugation to groups such as proteins.⁶⁸ To alleviate these deficiencies, Ulrich *et al.* displaced the fluoride atoms with 1-lithioethynylpyrene, and found that irradiation of the pyrene chromophore resulted in exclusive emission from the BODIPY core due to the intramolecular energy transfer.⁶⁶ These so-called “cascatelle” systems were expanded by the group to create more complex donor-acceptor systems which exhibited Stokes shifts above $16,000 \text{ cm}^{-1}$ and efficiently fluoresce in the near IR (Fig. 1.3).^{65,69}

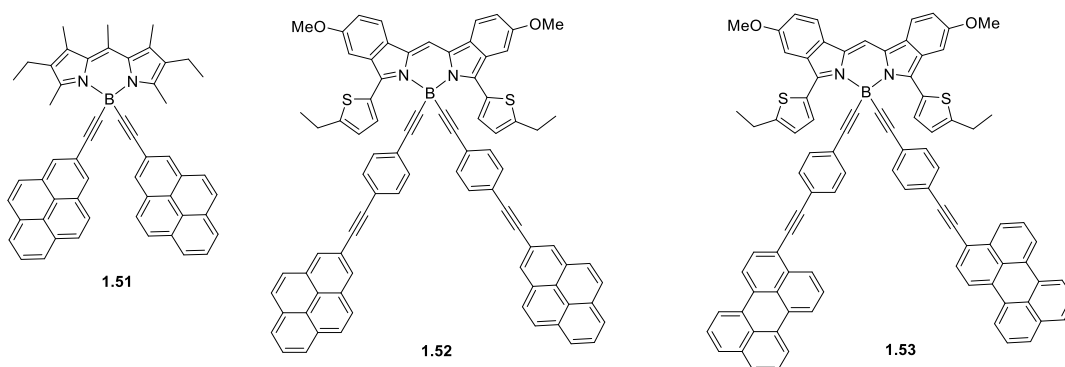
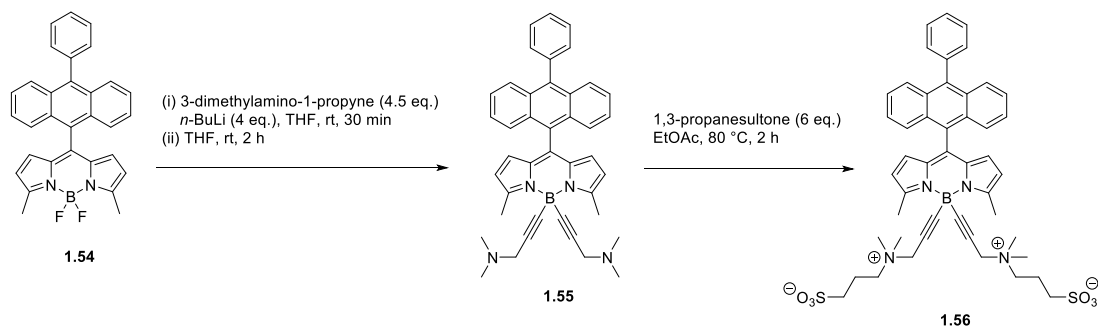


Figure 1.3: Examples of *E*-BODIPYs, so-called “cascatelle” systems synthesised by Ziessel and co-workers.

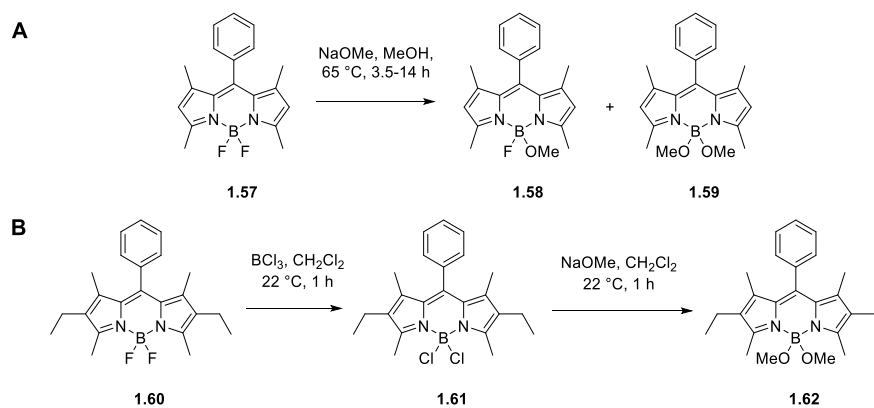
The Senge Group recently designed a library of heavy atom-free water-soluble *E*-BODIPYs for PDT applications (Scheme 1.13).^{70,71} The fluoride ligands were substituted with 3-dimethylamino-1-propyne which was followed by quaternisation of the amine *via* 1,3-propanesultone substitution to achieve the water-soluble derivatives. These BODIPY-anthracene dyads (BADs) were then tested for photosensitising activity against human breast cancer (MDA-MB-468) cells and were found to be capable of $^1\text{O}_2$ production. In particular, BAD **51** was found to exhibit significant photocytotoxicity (15% cell viability) at a concentration of 5×10^{-7} M with minimal dark toxicity.



Scheme 1.13: Synthesis of water-soluble BADs.

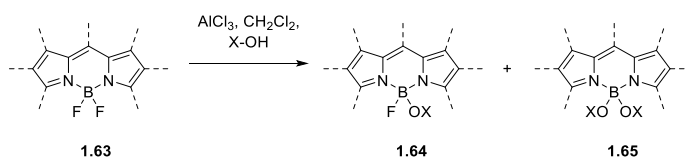
1.4.3 *O*-BODIPYs:

Multiple synthetic routes to *O*-BODIPYs have been developed, motivated by the fact that the resulting compounds tend to be much less lipophilic than their *F*-BODIPY precursors and can exhibit more improved photophysical properties.⁶⁵ Initially, Gabe *et al.* prepared both mono- and di-substituted *O*-BODIPYs by heating the parent *F*-BODIPY to 65 °C in NaOMe and MeOH (Scheme 1.14, a).⁷² Lundrigan and Thompson later reported the synthesis of *O*-BODIPYs *via* *Cl*-BODIPY intermediates (Scheme 1.14, b).⁷³



Scheme 1.14: (a) Synthesis of *O*-BODIPYs; (b) Synthesis of *O*-BODIPYs via *Cl*-BODIPYs.

The fluoride ligands are substituted for chloride ligands using 1 equiv. of BCl_3 . As the B-Cl bond is more labile than that of its *F*-BODIPY counterpart, the reaction with NaOMe to isolate the *O*-BODIPY could be performed under much milder conditions as well as shorter reaction times. However, the most commonly seen synthesis is that developed by Tahtaoui *et al.* in which the B-F bond is activated using a Lewis acid, AlCl_3 , and then stirred in the presence of an excess of the respective alcohol to obtain both mono- and di-substituted *O*-BODIPYs (Scheme 1.15).⁷⁴ This synthesis has proved to be very compatible with a wide range of alcohols and phenols, leading to quite elaborate structures such as those in Fig. 1.4.



Scheme 1.15: Synthesis of *O*-BODIPYs as developed by Tahtaoui *et al.*

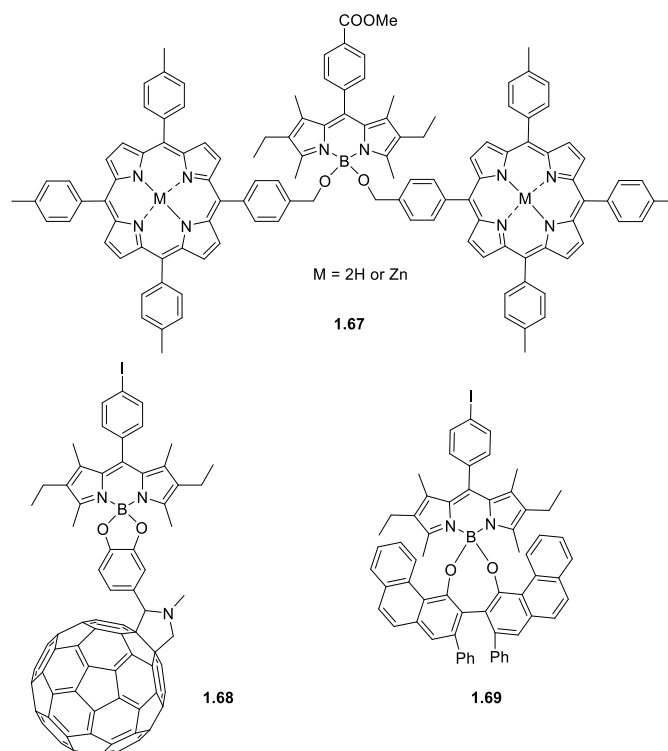


Figure 1.4: Examples of *O*-BODIPYs synthesized *via* AlCl_3 activation pathway.^{75–77}

1.5.1 An Introduction to the Relationship between Tetrapyrroles and Human Health

While unidentified at the time, retrospective diagnoses of disorders related to porphyrins, called porphyrias, have been made throughout history, such as that of King George III and what is known as the “Royal Malady”. Mother-and-son duo Macalpine and Hunter have proposed the King suffered from porphyria, of which his myriad of health problems both mental and physical are compatible.^{78,79} Meticulously trawling through archives they in fact traced the disease back to Mary, Queen of Scots. They even found incredibly descriptive notes from Sir Theodore Turquet de Mayerne, one of the Royal physicians to Mary’s son, James VI, on the condition:

*“On his return he passed blood red urine... red like Alicante wine”*⁸⁰

Röhl, Warren and Hunt undertook a more medical investigation, carrying out DNA analysis of available bones of various members of House of Tudor, finding evidence that the disorder descended to the Duke of Kent, who died in a plane crash in the 1940s. Their

findings also suggested that Queen Victoria and Princess Margaret were also affected by porphyria.⁸¹

Vincent Van Gogh is also suspected to have been a sufferer of the condition. Arnold's depiction of his descent into psychiatric illness align with symptoms of acute porphyria which may have been a consequence of the solvents and materials he worked with in conjunction with his potential genetic predisposition to the disease.⁸²

Today, we know that the porphyrias are a group of inherited metabolic disorders of the heme biosynthetic pathway.^{83–85} Accumulation of the responsible parties, 5-aminolaevulinic acid, porphobilinogen and porphyrins, result in skin lesions, severe abdominal pain, vomiting and an increased heart rate, although patients can present with any number of combinations of these and other symptoms.^{86,87} As previously discussed, heme has multifaceted roles in the body as seen in respiration as well as oxidation-reduction reactions. However, it is mostly produced in red blood cells in relation to the production of haemoglobin, and in the hepatocyte cells of the liver where it is used in the synthesis of cytochromes and haemoproteins.⁸⁵ Granick discovered that the rate-limiting or control point in the heme biosynthetic pathway is the formation of ALA by ALA synthase,⁸⁸ and this differs in the two tissues. ALAS1 is the enzyme involved in the synthesis of heme in the liver, controlled by a negative-feedback loop with the intracellular heme pool, while ALAS2 in red blood cells is only induced during active haem biosynthesis which relies on the availability of iron.^{89–91} This “error in biosynthesis” was first described in the late 19th century by Baumstark who investigated the urine of a patient afflicted with skin photosensitivity. His was the first association of porphyrins isolated from urine with human disease, and the autopsy also records red-brown discolouration of the skin, another characteristic of porphyria.⁹² Not too long after, Günther described a total of 70 cases in which acute symptoms of porphyria arose either spontaneously or following the ingestion of various medications.^{93,94}

For his research on porphyrins and their photosensitising abilities, Meyer-Betz famously injected himself with 200 mg of hematoporphyrin in 1913. Although wary of the intense photodynamic effect of this substance from the work carried out by Hausmann,^{95,96} he found himself obliged to visit a sick patient and unfortunately was unable to prevent himself from direct sun exposure.⁹⁷ He developed an extreme reaction on his hands and face, most prominently on one side as he had been sitting by the window on the train (Fig. 1.5).

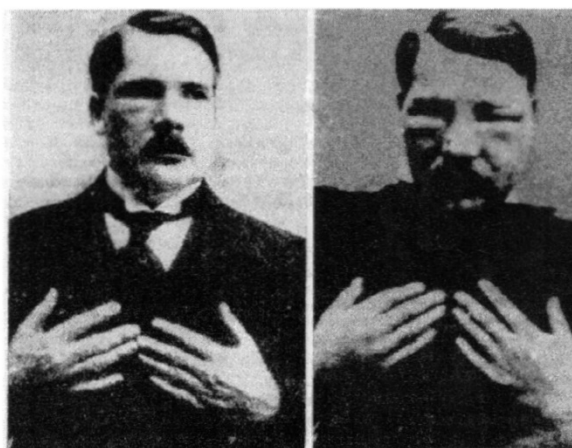


Figure 1.5: Photos Meyer-Betz published documenting his resultant skin photosensitivity.⁹⁷

Meyer-Betz quite clearly demonstrated that the effect that porphyrins and light exposure has on health human tissue, and from there grew the idea what this photoreaction may be used in a beneficial manner to kill pathological tissue. The uptake of hematoporphyrin into the cancerous tissue of a rat was demonstrated by Policard in 1924, and this was followed by Körbler who observed the accumulation of injected porphyrins in tumor tissue.^{98,99} The work of both Schwartz and Rassmussen-Taxdal paved the way for future application of this concept in humans by showing the enhanced fluorescence of lymphatic and cancer tissues as compared to normal tissues in human subjects after intravenous infusion of haematoporphyrin.^{100,101} Importantly, the fact that tumor tissue will preferentially accumulate porphyrins has led to their use not only in phototherapy but also in diagnostics and the identification of cancerous tissues.

1.5.2 Modern Photodynamic Therapy (PDT):

In theory, photodynamic therapy (PDT) is a facile, straight-forward, non-surgical treatment option for various cancers, dermatological conditions, and antimicrobial applications.^{102–105} The field began at the turn of the 20th century with the publication of Finsen's book, *La Photothérapie*.¹⁰⁶ Finsen suffered from Pick's disease, and knew that sun exposure alleviated his symptoms, and so he began research into the role of light in different biological processes. He treated *Lupus vulgaris* using the photosensitising effect of coproporphyrin III to kill *Mycobacterium tuberculosis*.^{107,108} Raab, working under von Tappeiner, found that an acridine dye in combination with light irradiation killed *Paramecium caudatum* cells. von Tappeiner coined the term "photodynamic effect" from

these results and went on to study various dermatological conditions such as *Lupus vulgaris* and basal cell carcinoma with dermatologist Jesionek.^{109,110} The pair even demonstrated what we would now call “translational medicine” when they treated a skin cancer with topical eosin and white light.^{111,112} The work of these scientists defined the principles on which all current photomedical treatments are based upon. The alarming results of Meyer-Betz’s self-experimentation were published soon after,⁹⁷ followed by *in vitro* experiments in the 1940s,^{113,114} with *in vivo* potential realised later by Schwartz, Rassmussen-Taxdal and Lipson.^{100,101,115} PDT as we know it today is due to the seminal advancements made by Dougherty and Kessel in the 1970s.^{102,116} It involves the administration of a photosensitizer (PS) which can accumulate in target tissue and produce cytotoxic singlet oxygen upon activation with light (Fig. 6).

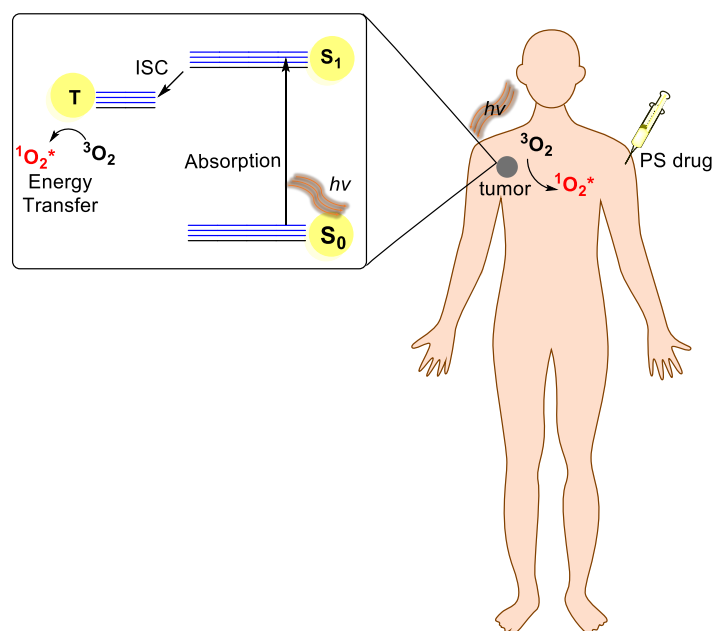


Figure 1.6: Photodynamic therapy with simplified Jablonski diagram.

As seen in the simplified Jablonski diagram above (Fig. 1.6), excitation of the PS with light of an appropriate wavelength results in population of the first excited singlet stage (S_1). From here, intersystem crossing (ISC) occurs enabling population of the longer-lived triplet state (T). This is the key step in the production of reactive oxygen species (ROS), illustrated here in the production of $^1O_2$ from cellular oxygen. Of course, there are many factors involved which can influence the rate of PDT-action, such as the PS dose and PS localisation.^{117,118} Those that target cellular mitochondria induce apoptosis, while PSs designed to sit within the plasma membrane results in necrosis after light exposure.^{102,119}

The most important requirement for a potential PS is that it is capable of producing $^1\text{O}_2$ in a sufficiently high quantum yield.^{120,121} It is $^1\text{O}_2$ that plays the role of the pharmacological agent, and its presence is controlled by the careful balance of PS and light dose.¹²² While aqueous solubility is certainly advantageous, there is now such a large abundance of delivery mechanisms from liposomes and bioconjugates to nanocarriers and hydrogels that even the more lipophilic of target molecules can be trialled.^{123–126}

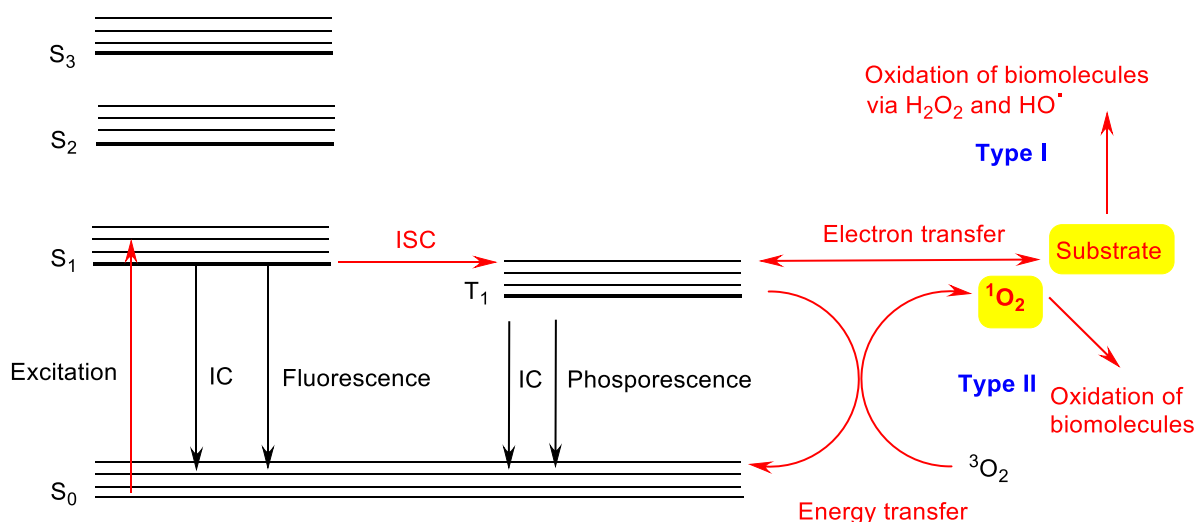


Figure 1.7: Modified Jablonski diagram with ROS generation and oxidative damage highlighted in red.

Looking at the photochemical processes involved in more detail, a modified Jablonski diagram is illustrated in Fig. 1.7. As previously described, excitation with a suitable wavelength of light corresponding to the absorption spectrum of the respective PS results in the formation of the S_1 state.¹²⁷ If white light or sunlight is the light used to irradiate the PS, as is the case in daylight PDT, excitation not only to the S_1 state but also higher singlet excited states occurs.^{128,129} Usually this is followed by rapid relaxation back to the S_1 state in agreement with Kasha's rule.¹³⁰ From the S_1 state the PS has two options – (i) return to the ground state *via* emission of a photon (fluorescence) or by radiationless relaxation *via* internal conversion (IC); or (ii) the PS can form an excited triplet state, T_1 , *via* intersystem crossing (ISC). In the case of the latter, the return to the ground state is spin-forbidden thereby resulting in a longer-lived excited state. Two options are now available for the return to the ground state – phosphorescence, *via* photon emission, or radiationless decay *via* IC.¹²⁷

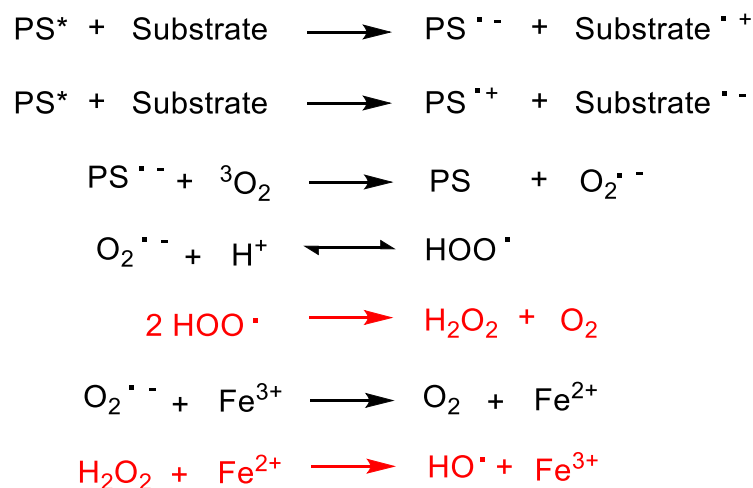


Figure 1.8: Type I photoreactions, with those resulting in the generation of ROS highlighted in red.

It is this longer-lived T_1 state that makes possible the reactions with neighbouring molecules for which the photodynamic effect is known for. For example, a PS in the T_1 excited state can transfer an electron to another substrate, *e.g.*, nearby biomolecules, in what is known as a Type I photoreaction. This results in the formation of reactive radicals, most commonly the superoxide anion radical (Fig. 1.8).^{131,132} The superoxide anion radical can then be converted to the much more cytotoxic H_2O_2 , or it can reduce Fe^{3+} found in cells to form Fe^{2+} and H_2O_2 . This results in the formation of highly reactive and cytotoxic hydroxyl radicals *via* the Haber-Weiss/Fenton reaction.^{133,134} Direct charge transfer to oxygen is only a minor possibility with regards to Type I photosensitisations.¹³² Type II photoreactions, on the other hand, involve reaction of the PS with molecular oxygen (${}^3\text{O}_2$) in an energy transfer process. In this manner, the PS returns to its ground state (S_1), while the ground state ${}^3\text{O}_2$ is excited to its singlet state, ${}^1\text{O}_2$.^{127,135} The PS can continue to be excited and undergo the same sequence generating more and more ${}^1\text{O}_2$ until the reserves of molecular oxygen in the vicinity have been depleted. Both Type I and Type II photoreactions result in the formation of reactive oxygen species (ROS) which, as previously described, are the true cytotoxic or therapeutic agents. The rate of PDT depends on the various quantum yields for singlet state excitation, ISC and energy transfer that the PS possesses, as well as the local availability of molecular oxygen.^{120,121,136} ${}^1\text{O}_2$ has a very short lifetime in biological environments, from $0.4 \pm 0.2 \mu\text{s}$ in the vicinity of cellular membranes to $1.2 \pm 0.3 \mu\text{s}$ in blood vessels.^{137,138} Thus, amphiphilic or slightly lipophilic PSs can be more effective than those readily soluble in aqueous media as they can preferentially localize in cellular

membranes causing more harm than those which would reside in the nearby aqueous environment.^{139–143}

1.5.3 Photosensitiser Development

Porphyrins as photosensitising agents began with derivatives of hematoporphyrin (HpD) being used as tumour imaging agents.¹⁴⁴ As hematoporphyrin was one of the most commonly used photosensitising agents up until this point, HpD was the obvious choice to being work on what would become known as the first generation PSs (Fig. 7, left).^{145,146} This water-soluble mixture of porphyrins had many drawbacks, however, mainly in that it is a complicated mixture of hematoporphyrin derivatives, some of which are not even active as a PS, which varied batch to batch.^{146–148} These components could undergo degradation reactions in the body, and only 0.1–3% accumulated preferentially in tumor tissue resulting in long-term generalized photosensitivity for the patient.^{149–152} purified version of this, porfimer sodium known commercially as Photofrin, was later released and still is a widely used PS, it also suffers from similar prolonged photosensitivity issues (Fig. 1.9, right).^{102,153,154}

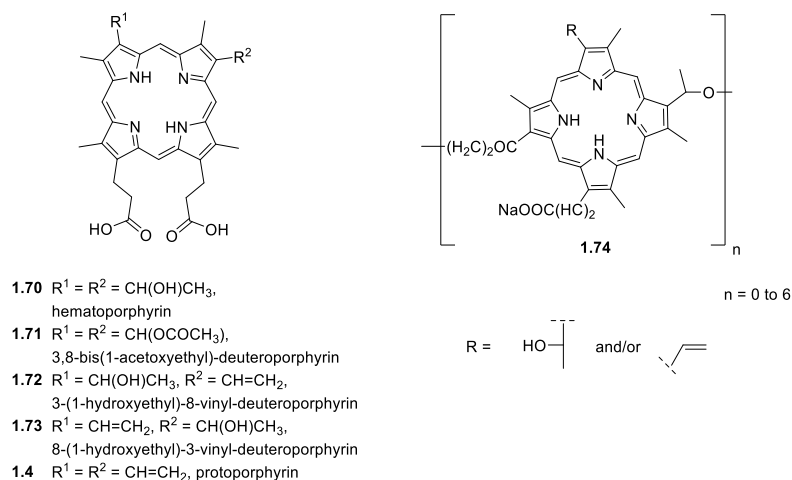


Figure 1.9: Left, components of HpD; right, Photofrin **1.68**.

The second generation PSs were designed to absorb light at longer wavelengths to facilitate deeper light penetration into tissues.^{147,155} Many of the syntheses now focused on improved ¹O₂ generation potential as well as lack of dark toxicity, in addition to being a single compound and not a mixture as seen for the first generation PSs.^{145,147,156,157} An example of a second generation PS treatment is that of 5-aminolevulinic acid (5-ALA), the biosynthetic precursor to PpIX **1.4**.^{158,159} However, due to its hydrophilic nature 5-ALA has limited diffusion and requires high doses over long periods of time in order to ensure

sufficient levels of PpIX.¹⁶⁰ Our group developed a hydrogel-based formulation to instead improve the biocompatibility of the parent PS PpIX using poly(*N*-isopropylacrylamide).¹⁶¹ This method prevented aggregation of PpIX, normally a drawback to direct application of the PS in biological systems, and at a concentration of 75 nM 90% of HT-29 cells were killed *in vitro*.

One of the most well-known examples in the second generation class of PSs is 5,10,15,20-tetrakis(3-hydroxyphenyl)chlorin (*m*THPC, **1.75**), commercially known as Foscan.^{162,163} From this compound, many modifications have been carried out in the search for an ideal so-called third generation PS (Fig. 1.10).^{164,165}

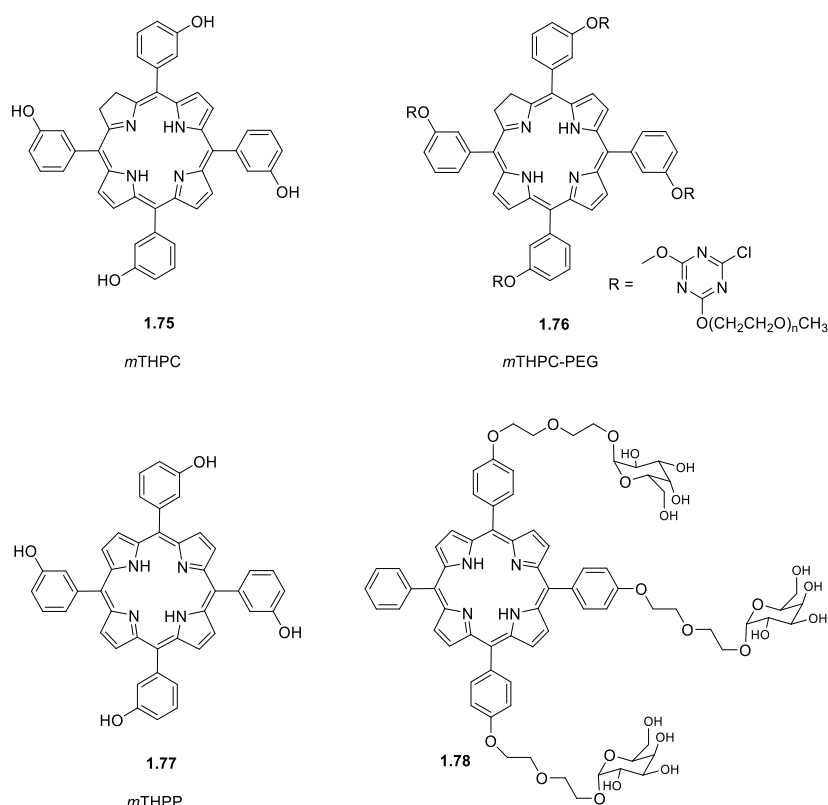


Figure 1.10: *m*THPC **1.75** and various modified third generation PSs.

As seen from the above examples, porphyrins have become a popular target of research for the design of potential successful candidates for application as new PSs.¹⁶⁶ Work carried out in collaboration between the Senge and Scanlan groups at Trinity College in particular has focused on the development of synthetic methods for unsymmetrical porphyrins²¹ and the preparation of respective bioconjugates with moieties such as bile acids, anti-inflammatory units, and carbohydrates.^{167–169} For example, the regioselective introduction of lipid and carbohydrate moieties was used to tune the lipophilicity and solubility in aqueous media (Fig. 1.11).¹⁷⁰

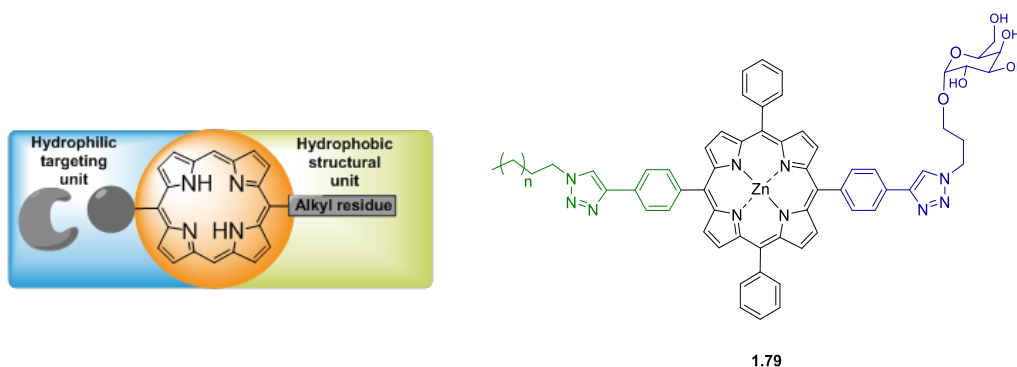


Figure 1.11: Unsymmetric amphiphilic PS system.

1.6 Deuteroporphyrin IX

Another amphiphilic porphyrin that has been investigated for photosensitising activity is Dimegin, the disodium salt of 2,4-di(α -methoxyethyl)-deuteroporphyrin IX (**1.80**, Fig. 1.12).¹⁷¹ Fickweiler *et al.* carried out studies into its cellular uptake and localization as well as photosensitising ability using squamous cell carcinoma, keratinocyte and fibroblast cells. The PS was found to localize in cellular mitochondria and with all cell lines a significant phototoxic effect was observed at concentrations >15 mM, and it was determined that **1.80** is an effective PS with rapid action *in vitro*, disrupting cell membrane integrity upon light irradiation. More recently, Ponomarev and co-workers compared Dimegin with Photodithazine (**1.81**, Fig. 1.12) and Radachlorin (**1.82a** and **1.82b**, Fig. 1.12), two chlorin e6 PSs.^{172–174} Four *in vitro* cell lines were tested – two human (*U87*, primary glioblastoma, and *HT1376*, bladder cancer) and two rat (*RG2*, glioma, and *AY27*, bladder carcinoma). The $^1\text{O}_2$ quantum yield was determined to be 0.65, thus very promising for future PS applications. Dimegin was found to have a slightly higher fluorescence intensity and $^1\text{O}_2$ generation under green light irradiation, and lower under irradiation with red light as compared to the other two PSs. However, it was determined that its higher photostability compensates and allows for an overall higher dose of photons being delivered. Dimegin was also found to have a faster clearance rate from tissues and a lower systemic toxicity, thereby potentially reducing long-term photosensitivity *in vivo*.^{172,173}

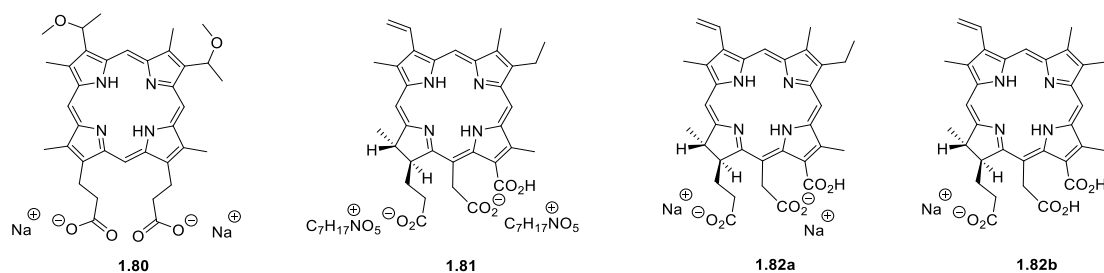


Figure 1.12: Structure of Dimegin **1.80**, Photodithazine **1.81**, and the major **1.82a** and minor **1.82b** components of Radachlorin.

As noted above, Dimegin is a derivative of deuteroporphyrin IX. This porphyrin as well as the structurally related protoporphyrin IX were initially synthesised as intermediates in the form of their dimethyl ester counterparts (**1.83** and **1.84**, Fig. 1.13) during Fischer and Zeile's total synthesis of hemin in 1929.⁵ Protoporphyrin IX (PpIX) has a well-established career as a PS, with it and its derivatives finding applications across such varied areas as medicine, chemical biology, catalysis and even optical materials.¹⁷⁵ With its structural similarity to the widely-applied PS PpIX, as well as the clear photosensitising activity demonstrated by Dimegin, the potential of deuteroporphyrin IX with its multiple free points for functionalisation and tuning of photochemical properties need not be overlooked.

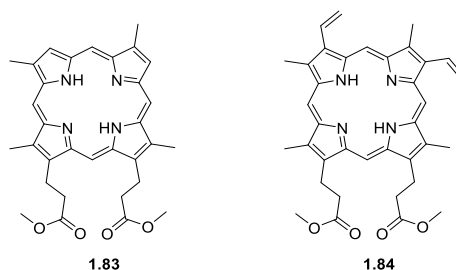


Figure 1.13: Deuteroporphyrin IX and protoporphyrin IX dimethyl ester.

An abundance of both biological and industrial applications have been reported which utilise derivatives of **1.77**, a few of which shall be discussed now to give a broader insight into its versatility. Teng *et al.* synthesized a novel chemiluminescence system using an iron-inserted deuteroporphyrin IX derivative.¹⁷⁶ This FeDP-polymer dot system was capable of creating ROS such as $^1\text{O}_2$ and demonstrated high tumor inhibition in HeLa cell tumor-bearing mice, making it a suitable candidate for PDT. Malik *et al.* demonstrated the cytotoxicity of a deuteroporphyrin-hemin compound against various Gram-positive bacteria in 1990, in a follow-up study to their earlier work on anti-bacterial PDT.^{177,178} The Gram-positive bacteria chosen for the study included *Bacillus cereus*, *Streptococcus faecalis*, and *Staphylococcus aureus*, with treatment against the latter resulting in just 0.005% of the initial population surviving after 2 h. The group later demonstrated photodynamic inactivation (PDI) of Gram-negative bacterial cells, *Escherichia coli* and

Pseudomonas aeruginosa, using a combination of deuteroporphyrin and the positively charged polymyxin nonapeptide (PMNP) in the presence of light.¹⁷⁹ PMNP acts to expand the outer membrane, allowing PSs to penetrate and facilitate photodynamic inactivation (PDI). In this manner, the authors have infiltrated the negatively charged Gram-negative cell wall *via* the use of the PMNP conjugate. In their search for more simple and efficient procedures for the synthesis of cationic photosensitisers (PSs) for PDT, Smith *et al.* functionalised deuteroporphyrin IX dimethyl ester with tertiary amine groups at the β -positions using Eschenmoser's salt, and subsequently quaternised the amine with methyl iodide in quantitative yield (Fig. 1.14).¹⁸⁰ The zinc analogue **1.87** was later used as part of a study into the binding mechanism of cationic porphyrins with DNA.¹⁸¹

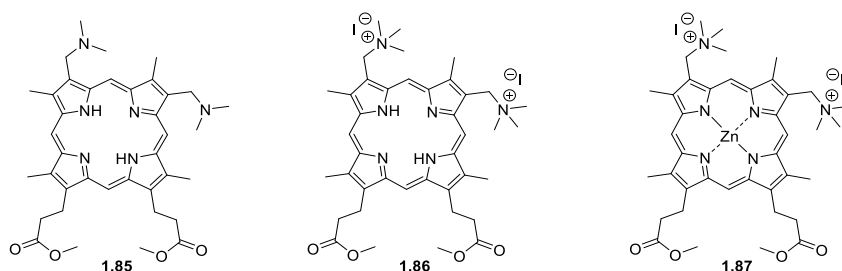


Figure 1.14: 3,8-Bis-[(*N,N*-dimethylamino)methyl]deuteroporphyrin dimethyl ester, **1.85**, 3,8-bis-[(*N,N,N*-trimethylamino)methyl]deuteroporphyrin diiodide dimethyl ester, **1.86**, and (3,8-bis-[(*N,N,N*-trimethylamino)methyl]deuteroporphyrinato IX)zinc(II) diiodide dimethyl ester, **1.87**.

2 Antiviral Photodynamic Therapy and COVID-19

2.1 COVID-19

As has already been discussed, PDT is a well-established treatment option for various types of cancer and cancerous lesions. Though it is now mostly associated with its application in tumor therapy, the photodynamic effect was originally demonstrated against bacteria at the beginning of the 20th century (see previous discussion on the work of Finsen, Raab, von Tappeiner, and Jesionek, section 1.5.1).^{106,109–112} Today, this facet of PDT is increasing in its popularity once more in response to the spreading of antibiotic resistance and the rise of new infections – in particular, the photodynamic inactivation (PDI) of microbes such as bacteria, fungi and viruses. In 2019 we published a review entitled “Trends and targets in antiviral phototherapy” which focused on the PDI of viruses as an alternative treatment in antiviral therapy, but also as a means of viral decontamination.¹²⁷ However, on writing this review we of course had no idea just how relevant the subject matter would become mere months later with the beginning of the COVID-19 pandemic. In December 2019, there were a number of patient and hospital treatment clusters in Wuhan, China reporting similar symptoms – fever, severe respiratory tract infections and pneumonia of unknown origin.^{182,183} Shortly thereafter, a novel coronavirus (severe acute respiratory syndrome coronavirus 2, SARS-CoV-2) was isolated and the disease outbreak became known as COVID-19.^{182–184} It has since spread to 219 countries and territories, with 108,006,680 confirmed cases and 2,378,115 deaths (Table 2.1).^{185–187}

Table 2.1 Global spread of COVID-19 as of 14th February 2021.

Row Labels	Sum of Cases - cumulative total	Sum of Deaths - cumulative total
Global	108006680	2378115
Africa	2713855	68043
Americas	48137377	1131524
Eastern Mediterranean	5998998	139468
Europe	36436128	809441
Other	745	13
South-East Asia	13188211	202607
Western Pacific	1531366	27019
Grand Total	216013360	4756230

Coronaviruses (Coronaviridae) are a family of positive-sense, single-stranded RNA viruses first discovered in 1960.^{188–190} Before the outbreak of COVID-19, there were six reported species of coronaviruses associated with respiratory tract infections – HCoV-229E, HCoV-

OC43, HCoV-Hong Kong University 1 (HCoV-HKU1), HCoV-NL63, severe acute respiratory syndrome (SARS-CoV), and Middle East respiratory syndrome (MERS-CoV).¹⁹¹ The first four cause milder infections that usually don't require medical intervention. However, the latter two as well as COVID-19 are highly pathogenic, capable of causing fatal respiratory diseases.¹⁹⁰ It is believed that SARS-CoV-2 (Fig. 2.1) binds to host cell angiotensin-converting enzyme 2 (ACE-2) receptors using a spike protein. After cell entry, the viral RNA attaches to the host cell ribosomes and produces two polyproteins essential for the replication of new mature virions.^{192,193}

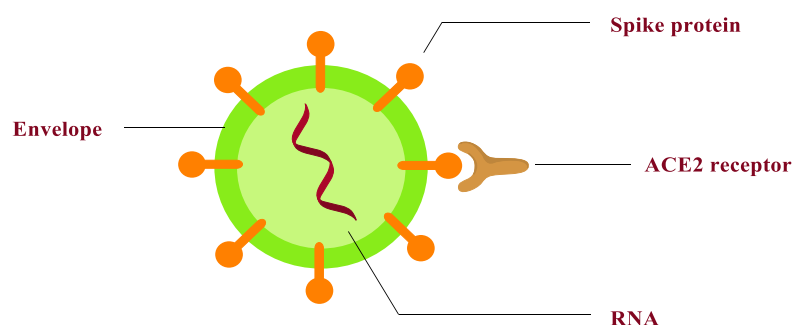


Figure 2.1: Simplified schematic representation of SARS-CoV-2.

2.2 The PDI of Viruses as a Treatment Option

As previously discussed, PSs are capable of generating ROS and are used to destroy malignant cells and tissues *via* PDT, as well as viruses and bacteria *via* PDI.^{102,104,194–196} We are constantly seeing more instances of antibiotic and antiviral drug resistance, the emergence of new infections, and risks to global security (*i.e.*, bioterrorism and disaster scenarios) (Fig. 2.2).^{197–200} Thus, the PDI of viruses is becoming a topic of wider interest in the search for alternative anti-viral treatment methodologies, especially now considering the current state of the world and the battle to overcome the COVID-19 pandemic.^{136, 201,}

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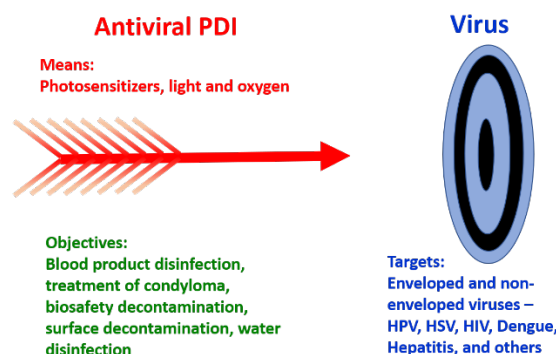


Figure 2.2: An overview of the objectives, targets, and means of designing antiviral PDT.

The PDI of viruses benefits from the same features described previously with regards to the design of an ideal PS for PDT – namely, those that enhance the production of ROS resulting in more efficient and extensive damage to the treatment target. Although a disadvantage with respect to prolonged photosensitivity post-PDT, the ‘unspecificity’ of photodynamic damage is actually of benefit when it comes to PDI. Given the genetic flexibility of viruses, this untargeted mechanism of action is less prone to the development of resistance.²⁰³ As photodynamic effect is only observed (see section 1.5.1) when light of an appropriate wavelength, a PS and oxygen are present at the same time, the PDI of viruses has mostly been applied to the treatment of localised viral lesions, *e.g.*, herpes and warts.^{105,204–206}

Taking into account the basic structure of viruses, there are three principal molecular targets for viral PDI and the reaction with generated ROS: nucleic acids (DNA or RNA), viral proteins, and viral lipids (Fig. 2.3).^{136,201} Viral lipids are an additional target for the generated ROS, and viruses that have either lipids or a viral envelope tend to be more sensitive to viral PDI than those that do not.^{207–209} In the case of SARS-CoV-2, obvious treatment targets include the spike protein, the viral envelope, and the viral RNA.¹⁹⁰

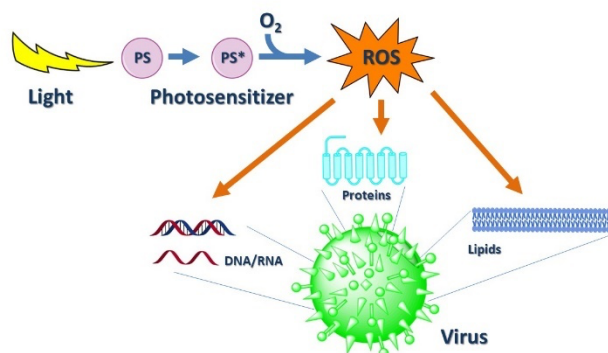


Figure 2.3: Targets in the PDI of viruses: nucleic acids, proteins, and lipids.

Photodamage to viral structures occurs *via* Type 1 and Type 2 photoreactions. Both mechanisms can be active at the same time, and are dependent on the PS itself, its concentration, and the concentration of oxygen present.^{210–212} PS binding or intercalation to nucleic acids is not always needed for effective photosensitisation, though cationic compounds such as methylene blue have been observed to cross the outer membranes of viruses and intercalate into their DNA/RNA.^{213–215} Some PSs (*e.g.*, 5-ALA, PpIX, HPD, see section 1.3.2) have a high affinity to proteins and lipids, and have been used to target the outer structures of viruses, *i.e.*, unsaturated lipids and envelope proteins.^{132,136,216,217} In particular, this damage is seen at oxidation-sensitive amino acids such as tryptophan, methionine, cysteine, histidine and tyrosine. Direct interaction such as intercalation may also influence protein folding and thereby inhibit viral function.^{132,136}

A wide range of chemically quite distinct classes of molecules have been evaluated for their use in PDI, from plant extracts such as psoralen to natural PSs and those already used in PDT.¹²⁷ Those related specifically to various classes of coronaviruses will now be discussed, starting with curcumin (2.1, Fig. 2.4). Curcumin is a polyphenolic compound isolated from turmeric which has been found to be a photocytotoxic agent with activity against various viruses.^{218–220}

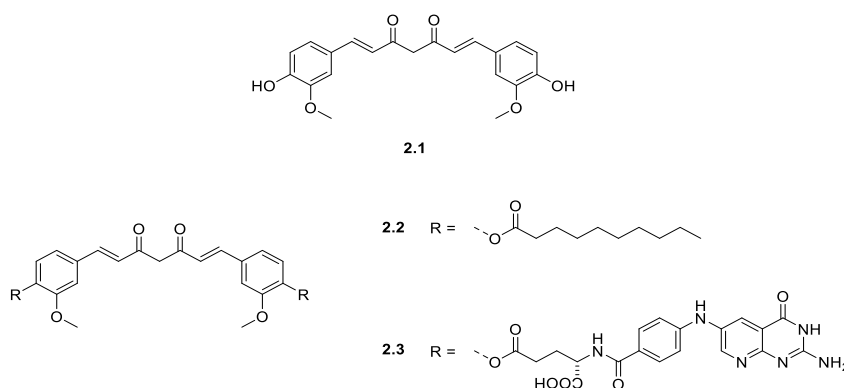
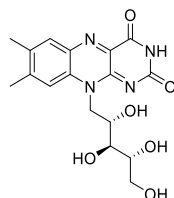


Figure 2.4: Curcumin and selected bioconjugates.

De Clercq and co-workers designed curcumin-based bioconjugates (2.2 and 2.3, Fig. 2.4) with improved bioavailability which showed good activity against VSV, feline corona (FVC) and feline herpes viruses (FHV).²²¹ Curcumin was also found to be a strong inhibitor of NF-κB signalling, its potential against influenza A virus (IAV) propagation was investigated. Treatment of MDCK cells with curcumin significantly reduced the viral titer

at sub-cytotoxic doses (EC_{50} value of $0.47\ \mu\text{M}$), and the synthesis of viral proteins such as haemagglutinin (HA) and neuraminidase was disrupted. That these proteins were inhibited indicated that curcumin is active against the early stages of viral infection and this was confirmed *via* a plaque reduction assay.²²²



2.4

Figure 2.5: Riboflavin.

Riboflavin, or vitamin B2, (**2.4**, Fig. 2.5) is an essential vitamin for humans which acts as a co-factor for flavin coenzymes, playing an essential role in human cell metabolism.^{223,224} Its potential role in the photoinactivation of microorganisms has been known for over half a century.^{202,225} Its application in PACT and the PDI of viruses have found the most interest, as is its role in the decontamination of blood products.^{202,226–228} Riboflavin has been shown to be effective against enveloped as well as a number of non-enveloped viruses, including the MERS coronavirus.²²⁹ The Mirasol Pathogen Reduction Technology (PRT) System was developed as a broad-spectrum pathogen-reduction process which uses a combination of riboflavin and UV light to cause irreversible damage to nucleic acids in blood products.^{230,231} The aim was to provide an extra layer of protection to help prevent transmission of pathogens *via* blood transfusions, and was shown to effectively reduce the MERS-CoV viral titer in blood plasma.²²⁹

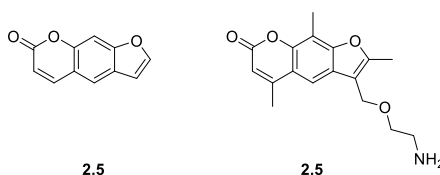


Figure 2.6: Psoralen **2.5** and amotosalen **2.6**.

Psoralen and its derivatives have long been known for their photosensitising properties and in the phototherapy of viruses.^{232,233} This heterocyclic, tricyclic compound consists of a furan and a pyrone ring (**2.5**, Fig. 2.6), and has an affinity to both DNA and RNA, with the ability to intercalate between nucleic acids.^{234–236} Amotosalen **2.6** has been shown to be active against a large number of both enveloped and non-enveloped viruses, including MERS-CoV. The INTERCEPT™ Blood System technology inactivates a broad-spectrum

of pathogens in platelet concentrates prepared for transfusion. It uses amotosalen and UVA light to irreversibly cross-link viral genomic strands, thereby preventing transcription and replication.²²⁶ Hindawi and co-workers used this system to reduce the viral titer of MERS-CoV in plasma and platelet concentrates, thus minimising the risk of transfusion-related MERS-CoV transmission.^{237,238}

2.3 PDI in Relation to SARS-CoV-2

Though various PDI strategies have been employed to either treat or prevent CoV infections, in what way can this methodology be used to tackle the fallout of the COVID-19 pandemic? Though assumptions have been made as to the precise route of infection, respiratory droplets are widely considered the main mode of transmission, and people have been recommended to keep at least a 1 m distance from those with an unknown infection status to minimize the risk of contracting SARS-CoV-2.²³⁹ However, evidence suggests that these microdroplets can in fact be airborne and under the right circumstances can travel up to 8 m.^{240,241} SARS-CoV-2 has been detected in the air approximately 4 m from infected patients in hospital wards, and has been shown to retain its infectivity in aerosols for up to 16 h.^{242–244} It has even been found to remain infectious after being deposited on surfaces such as steel, plastic and copper, and has been found in liquid media such as untreated wastewater.^{243,245,246} Thus, while treatment of the viral infection is certainly the first port-of-call for dealing with the global pandemic, there is also huge potential for PDI in controlling the spread of infection, especially in areas with a high density of “people-traffic”, such as hospitals, public transport services and shopping centres.²³⁹

Other more localised treatment options have also been investigated. Hindawi and co-workers expanded their INTERCEPT™ system to efficiently inactivate SARS-2-CoV in inoculated human plasma.²⁴⁷ As it works so well for blood plasma and platelets, this combination of amotosalen and UVA could have potential in the PDI of viral fragments in other media such as surface decontamination, for example. Indeed, many examples of UV-PDI have found ever-increasing popularity since the rise of the COVID-19 pandemic. For example, here at Trinity College Dublin the group of Conor McGinn have designed a state-of-the-art UV-sanitation robot called Violet. This portable robot has been shown to effectively decontaminate surfaces from coronaviruses, methicillin-resistant *Staphylococcus aureus* (MRSA) and *Clostridium difficile* using UV-C irradiation.^{248,249} Biotech company UVM Systems have designed a UVMask (UVM95A) which uses UV-C light to filter and purify air, inactivating viral particles in less than 0.1 s. The system can be

used for 8 h before a recharge is required, and replaceable air filters are available to change as often as needed.²⁵⁰

2.4 Objectives

As indicated so far in this thesis, there are many pathways one can take when designing a porphyrin, and the design itself has a huge impact on the potential properties and therefore function of that porphyrin. In section 1.6, the photosensitising potential of deuteroporphyrin IX was discussed, however very little derivatisation has been explored to-date. One of the main topics of work in this thesis is the functionalisation of the pre-formed deuteroporphyrin IX skeleton. Due to its unsymmetrical nature, total synthesis of new derivatives would be far more complex, so the focus for this work was on the utilisation of the highly successful transition metal catalysed reactions discussed in section 1.3. This will be discussed in Chapter 3, and one of the main goals of this work was the synthesis of cationic derivatives which could be tested for photosensitising effects for antimicrobial PDT. Positive results were previously reported by Malik and Smith, and the method of introducing quaternised amine groups was adopted for the compounds prepared in this work also.^{177–181}

Following on from the work on deuteroporphyrin IX, a short study into the photodegradation of Rhodamine B is discussed in Chapter 4. Here, cationic derivatives of tetramethylpyridylporphyrin were prepared and conjugated to graphene oxide. The resultant nanohybrids were tested for their ability to break down the dye in an attempt to find an efficient way to remove these waste-water contaminants. The method of quaternising the amines on the porphyrin periphery was used here again, and the resulting cationic charge enabled electrostatic interactions with the graphene oxide sheets in water.

Finally, a study into the standard tetrapyrrole condensation chemistry described in Chapter 1 will be discussed in Chapter 5. Specifically, the *O*-BODIPYs introduced in section 1.4.3 will be utilized as the parent compounds – *via* the preparation of an aldehyde functionality to act as the reaction partner with various pyrrole moieties. To-date, these compounds have not been reported in the direct construction of chromophores and tetrapyrroles. The aim of this project was to determine how feasible these molecules could be as building blocks for porphyrins and porphyrin derivatives. Initial investigations were carried out on symmetrical systems for ease of purification, however a long-term goal of

this study is the development of asymmetric systems for the preparation of more complex systems.

Chapter 3: Functionalization of Deuteroporphyrin IX Dimethyl Ester

3.1 Introduction – Functionalization of Deuteroporphyrin IX

Deuteroporphyrin IX (**1.83**) and protoporphyrin IX (**1.84**), both non-natural and natural porphyrin derivatives, respectively, were initially synthesised as intermediates in the form of their dimethyl ester counterparts (**3.1** and **3.2**, Figure 3.1) during Hans Fischer's total synthesis of hemin in 1929.⁵ As shown in Figure 1, both deuterio- and protoporphyrin IX offer multiple points of functionalisation, be it the vinyl groups of the latter or the free β -positions of the former, as well as the protected carboxylic acid moieties of each, all of which can be manipulated to tune properties such as cellular uptake, aqueous solubility, and optical imaging capabilities.

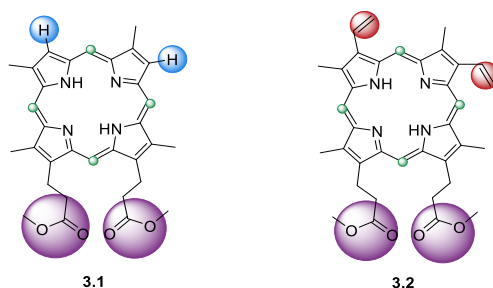


Figure 3.1: Individually addressable functionalisation points in deuteroporphyrin IX **3.1** (left) and protoporphyrin IX dimethyl ester **3.2** (right).

Various functionalisation routes have been reported, such as Pd-catalysed Heck coupling reactions utilising a derivative of **3.1** and methyl acrylate, performed by Smith and Langry in 1983.^{251,252} Smith *et al.* later demonstrated both Heck and Stille couplings at the β -positions, synthesising a variety of alkenyl- and styryl-substituted deuterio- and protoporphyrin IX derivatives.^{253,254} Numerous Heck couplings have been reported since,^{51,255–257} as well as Sonogashira couplings more recently.^{36,258} The vinyl groups of both **3.2** and the corresponding zinc derivative have been directly functionalised *via* a Heck reaction by Castella *et al.*, yielding mixtures of four regioisomers.²⁵⁷ Olefin cross-metathesis reactions have been investigated for several derivatives of protoporphyrin IX and found to give high yields for electron-rich substrates, whilst being less efficient for electron-deficient alkenes.^{259,260}

Though much progress has been made with regards to the functionalisation of **3.1**, the previously described couplings have proceeded through mercurated β -positions, which for any biological studies is far from optimal and poses environmental issues.^{251,254} Additionally, previous endeavors to modify **3.1** and **3.2** have been limited by the

availability of halogenated precursors, coupling substrate scope and/or formation of product mixtures. Various halogenations of the β -positions of **3.1** have been reported, including brominations, iodinations and chlorinations.^{261–264} Further functionalisation examples report the use of both halogenated and formylated derivatives in the synthesis of porphyrin dimers and trimers,^{256,265–267} while others describe later modifications using formylated products, for example, subsequent Wittig reactions on **3.1**.²⁶⁸

3.2 Objectives

When devising a synthetic plan for the functionalisation of a porphyrin, there are many avenues that can be taken, some albeit easier than others. With regards to **3.1**, both β - and meso-positions are available (Fig. 3.1), and in theory synthesis can be based either on a total synthesis approach, or a partial synthesis approach – functionalisation of the pre-formed porphyrin.¹³ However, the lack of symmetry and difficulty of synthesis hinders **3.1** from being used in more general methods of porphyrin functionalisation.²¹ The majority of reported syntheses focus on 3,8-disubstitution products from **3.1** *via* aromatic electrophilic substitution.²⁶⁹ Thus, the starting point for any investigation into the functionalisation of **3.1** must begin with the development of more efficient methods for the halogenation of the β -positions (Fig. 3.2). This will enable a study into facile and versatile methods for peripheral functionalisation of this type IX substituted porphyrin derivative, with a focus on application of the highly versatile Suzuki-Miyaura cross-coupling reaction.^{37,269}

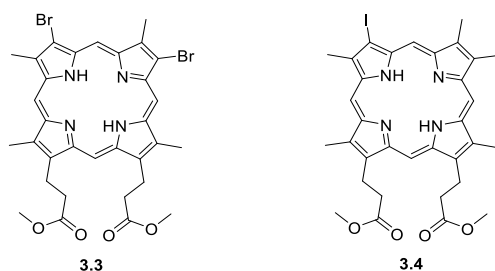


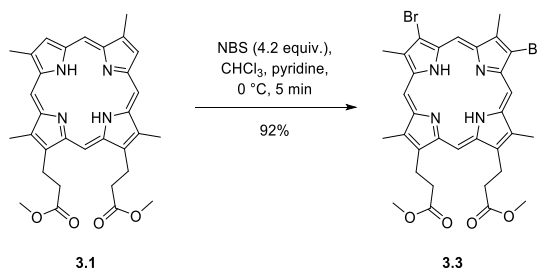
Figure 3.2: 3,8-Dibromo-deuterioporphyrin IX dimethyl ester **3.3** and 3,8-diiodo-deuterioporphyrin IX dimethyl ester **3.4**.

It is hoped that these derivatives may prove to be useful biologically active candidates for treatments such as photodynamic therapy (PDT), as seen for deuterio- and protoporphyrin IX.^{102,104,157,161} As previously discussed in section 1.3.4, cationic porphyrin derivatives have been found to be effective PSs in the field of antimicrobial photodynamic therapy (aPDT) and the PDI of viruses, and so a series of cationic derivatives are planned once reaction conditions have been optimised.¹⁰⁴ Malik *et al.* have already obtained positive results from

the application of **2.1** in aPDT.^{177–179} While successful results against Gram-negative bacteria were achieved *via* conjugation to polymyxin nonapeptide (PMNP), another option is the use of cationic PSs.²⁷⁰ As Gram-negative bacteria are encapsulated within a negatively charged cell wall, due to the presence of teichoic acid residues, the application of cationic PSs may demonstrate more efficient binding and thereby inactivation of these infectious strains.²⁷¹ If successful, the ¹O₂-producing capability of these compounds will be investigated, and potentially *in vitro* testing will be carried out. As **3.1** is not intrinsically water-soluble, the quaternisation of easily introducible amine groups should be an efficient method of altering the solubility in biological media.

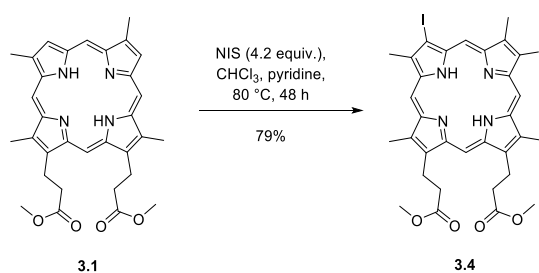
3.3 Results & Discussion

3.3.1 Halogenation of deuteroporphyrin IX dimethyl ester



Scheme 3.1: The dibromination of the β -positions of **3.1**.

The dibromination of the β -positions of **3.1** was carried out according to an adapted literature procedure (Scheme 3.1).^{264,272} The product was obtained in 92% yield, an improvement on both procedures referenced, which reported yields of 45% and 40%, respectively. In the case of Caughey *et al.*,²⁷² 3.27 equiv. of pyridinium bromide perbromide was employed as the brominating agent. NBS was instead chosen as the brominating agent in this synthesis; however, the reaction time of 5 min, temperature of 0 °C and work-up procedure were adopted. NBS was also the brominating agent chosen by Gazzano *et al.*,²⁶⁴ in 4.2 equiv. However, reaction conditions differed in that the bromination was carried out at RT as opposed to 0 °C. Additionally, in both reported procedures purification *via* column chromatography was required, whereas in the synthesis carried out for this project a recrystallisation from MeOH after washing steps with deionised H₂O yielded the product not only in high yield (92%), but also high purity.



Scheme 3.2: The diiodination of the β -positions of **3.1**.

The diiodination of **3.1** was, unfortunately, not as straightforward (Scheme 3.2, Table 3.1). Initially, a mirrored reaction of the bromination was attempted, with NIS acting as the iodinating agent in 4.2 equiv. After 20 min, the starting material appeared to have been used up and the reaction was quenched. However, NMR analysis showed an approximately 50/50 ratio of product and starting material. The reaction time was increased; however, this again was unsuccessful. A procedure reported by Smith *et al.*²⁶⁷ iodinated a bis-bromomercurated deuteroporphyrin IX, which had zinc(II) inserted into its core, with I₂ and NaI in THF and CHCl₃. The reaction gave the product in a 96% yield after 15 min at RT. A similar procedure was attempted on **3.1**; however, no iodination took place at either of the β -positions.

Table 3.1: Optimisation of the diiodination of **3.1**.

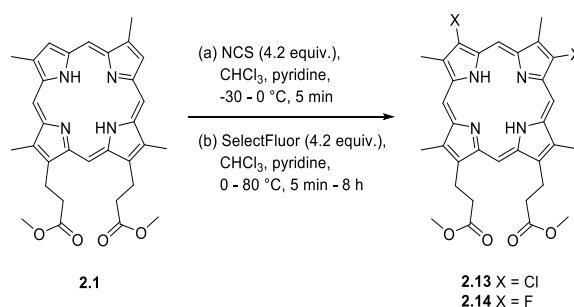
Entry	Iodinating agent (equiv.)	Solvent	Temp (°C)	Time (h)	Yield (%)
1	NIS (4.2)	CHCl ₃	0	0.33	N/A
2	NIS (4.2)	CHCl ₃	0	0.66	N/A
3	NIS (4.2)	CHCl ₃	0	18	N/A
4	I ₂ (2.1)	THF/CHCl ₃ (1:2.5)	20	0.25	N/A
5	I ₂ (2.1) + NaI (0.2)	THF/CHCl ₃ (1:4)	20	0.33	—
6	NIS (4.2)	CHCl ₃	80	21	46
7	NIS (4.2)	CHCl ₃	80	35	70
8	NIS (4.2)	CHCl ₃	80	48	76

Reaction conditions: All reactions were performed in the presence of pyridine. Yields were isolated after recrystallisation from MeOH.

“—” indicates starting material collected only; “N/A” indicates that it was not possible to determine a yield due to the mixture of products obtained.

The procedure using NIS was revisited and on this attempt it was decided to reflux at 80 °C. A recrystallisation from MeOH yielded the desired product in an overall yield of 46%. The experiment was repeated, this time with a longer reflux time of 35 h and recrystallisation from MeOH, to afford the desired diiodinated product **3.4** in a 70% yield. Finally, the reaction was up-scaled and the reflux time increased to 48 h, yielding **3.4** in 76%.

To complete the series, the chlorination and fluorination of **3.1** were also attempted (Scheme 3.3). The dichlorination of the β -positions of **3.1** has been reported previously by Smith *et al.*; however, the reaction proceeded *via* the mercuric salt derivative.²⁶¹ An attempt was made to optimise this procedure in a manner similar to the synthesis of **3.3** and **3.4** using NCS. However, while the dichlorinated product was observed, an inseparable mixture of multiply halogenated compounds was obtained. The same was observed for the difluorination of **3.1**, over-fluorination occurred in all attempts, regardless of temperature or time, employing SelectFluor as the fluorinating agent.

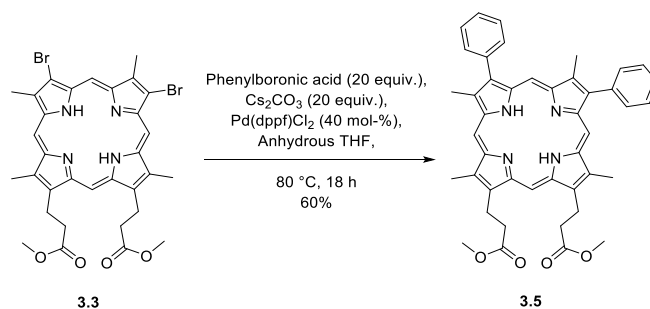


Scheme 3.3: Attempted chlorination and fluorination of **3.1**.

3.3.2 Synthesis of 3,8-diphenyl-deuteroporphyrin IX dimethyl ester

Initially, the procedure for the Suzuki coupling of **3.3** and phenylboronic acid (Scheme 3.4) followed one reported by Senge and co-workers. in which the porphyrin is reacted with 10 equiv. of the boronic acid in THF with 20 equiv. of K₃PO₄ and 10 mol-% Pd(PPh₃)₄ at 60 °C (Table 3.2).²⁷³ After work-up and recrystallisation, however, only starting material was collected. A second procedure published by Senge *et al.* was followed which utilised 10 equiv. of boronic acid per position to be substituted, 20 equiv. of Cs₂CO₃ and 40 mol-% Pd(dppf)Cl₂ in THF at 80 °C.²⁷⁴ Compound **3.5** was obtained in a 60% yield

after recrystallisation from MeOH and confirmed *via* ^1H NMR and mass spectrometry analysis.



Scheme 3.4: Suzuki coupling of **3.3** and phenylboronic acid.

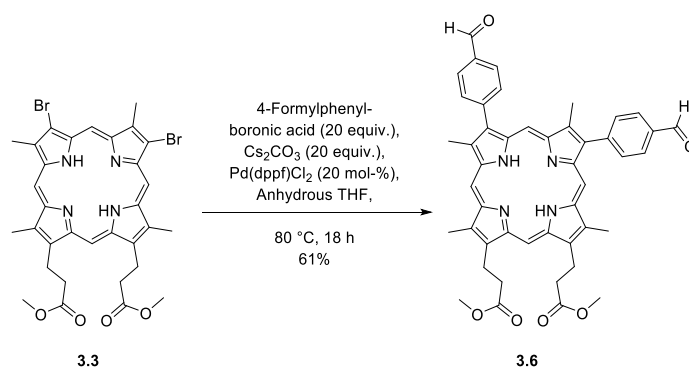
Table 3.2: Optimisation of Suzuki coupling between **3.3** and phenylboronic acid.

Entry	Pd catalyst (mol-%)	Base (equiv.)	Boronic acid (equiv.)	Solvent (mL)	Temp (°C)	Yield (%)
1	Pd(PPh ₃) ₄ (10)	K ₃ PO ₄ (20)	10	THF (10)	60	—
2	Pd(dppf)Cl ₂ (40)	Cs ₂ CO ₃ (20)	20	THF (10)	80	60

“—” indicates starting material collected only.

3.3.3 Synthesis of 3,8-bis(4-formylphenyl)-deuterioporphyrin IX dimethyl ester

As the formyl functional group is one of the most important for further porphyrin modification and functionalisation,^{21,275} this reaction to introduce an aryl-formyl moiety was chosen to be optimised in order to establish the best-yielding conditions for future Suzuki coupling reactions (Table 3.3). Initially, identical conditions to those which gave a 60% yield of the diphenyl-substituted product (**3.5**) were utilised (entry 1, Table 3.3). This afforded the desired product (**3.6**) in a 60% yield after recrystallisation from MeOH. To improve up this, and to reduce the amount of catalyst loading, the amount of [1,1'-bis(diphenylphosphino)ferrocene]palladium(II) dichloride, Pd(dppf)Cl₂, was decreased from 40 mol-% to 20 mol-% (entry 2, Table 3.3). The reaction was repeated on a 20 mg scale, and with all other conditions kept constant from the previous reaction, **3.6** was obtained in a 61% yield (Scheme 3.5).



Scheme 3.5: Suzuki coupling of **3.3** and 4-formylphenylboronic acid.

The reaction conditions were revisited, retaining a catalyst loading of 20 mol-% in each case. Concentration effects were explored, with any reduction in the amount of anhydrous THF resulting in a detrimental effect on the yield (entries 3 and 4, Table 3.3). Thus, the volume of solvent was kept at 10 mL for 20–25 mg scale reactions, and investigations moved to the catalyst. Both pyridine-enhanced precatalyst preparation stabilisation and initiation, NHC ligand (PEPPSI-IPr) and [1,2-bis(diphenylphosphino)ethane]palladium(II) dichloride, Pd(dppe)Cl₂, were employed in 20 mol-% (entries 5 and 6).

Table 3.3: Optimisation of Suzuki reaction between **3.3** and 4-formylphenylboronic acid.

Entry	Pd catalyst (mol-%)	Base (equiv.)	Solvent (mL)	Temp (°C)	Yield (%)
1	Pd(dppf)Cl ₂ (40)	Cs ₂ CO ₃ (20)	THF (10)	80	60
2	Pd(dppf)Cl ₂ (20)	Cs ₂ CO ₃ (20)	THF (10)	80	61
3	Pd(dppf)Cl ₂ (20)	Cs ₂ CO ₃ (20)	THF (5)	80	35
4	Pd(dppf)Cl ₂ (20)	Cs ₂ CO ₃ (20)	THF (7.5)	80	37
5	PEPPSI- <i>i</i> Pr (20)	Cs ₂ CO ₃ (20)	THF (10)	80	—
6	Pd(dppe)Cl ₂ (20)	Cs ₂ CO ₃ (20)	THF (10)	80	46

Reaction conditions: All reactions were performed using 20 equiv. of 4-formylphenylboronic acid under argon for 18 h. Yields were determined after recrystallisation from MeOH.

“—” indicates starting material collected only.

However, as neither catalyst demonstrated even close comparability in efficiency to earlier attempts, Pd(dppf)Cl₂ was employed as the catalyst for future coupling reactions. As optimisation attempts were unsuccessful in achieving higher yields than those of the earlier entries, the conditions described in entry 2 were chosen as optimal for future Suzuki–Miyaura couplings.

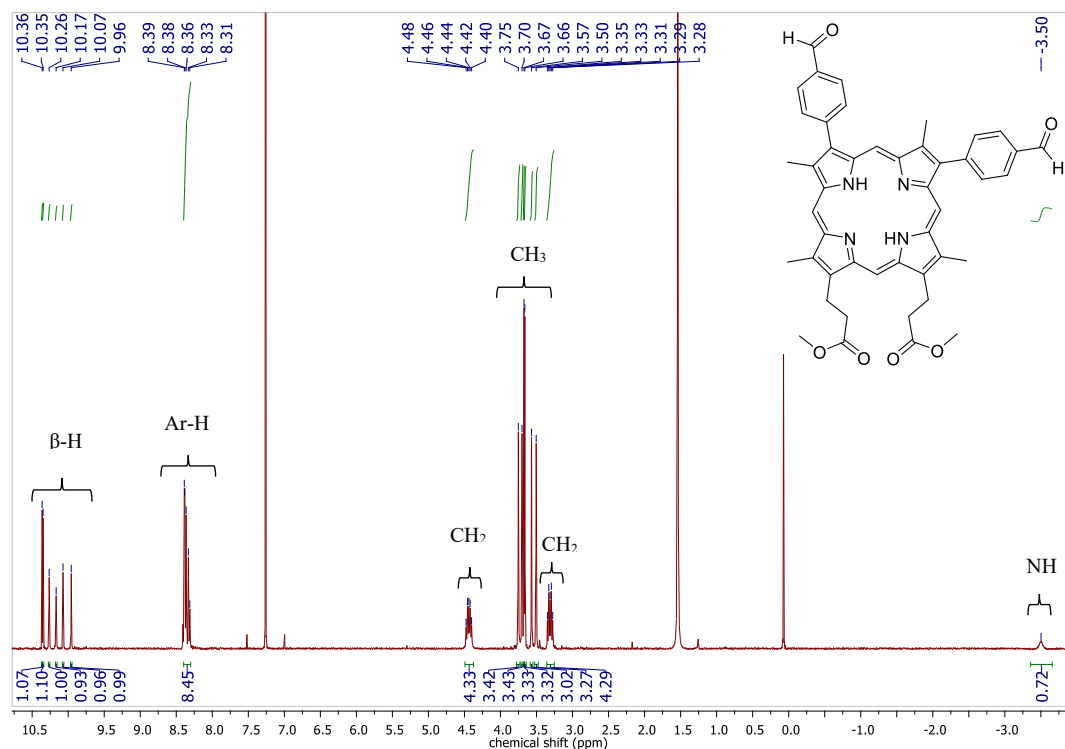
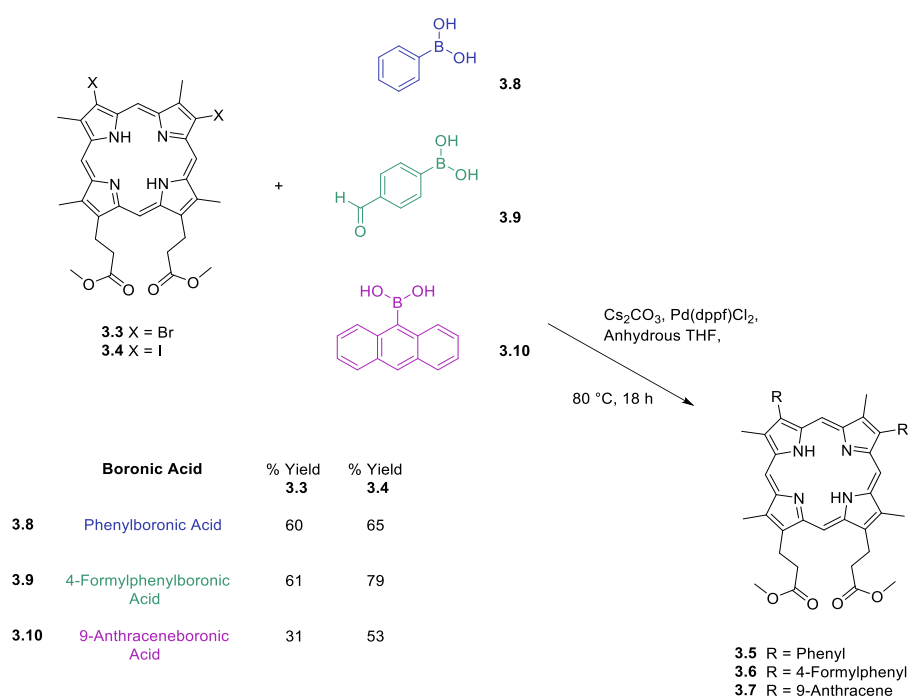


Figure 3.3: ¹H NMR of **3.6** in CDCl₃, 400 MHz.

3.3.4 Synthesis of 3,8-dianthracenyl-deuterioporphyrin IX dimethyl ester

This reaction followed the conditions from the previous Suzuki coupling of **3.3** and 4-formylphenylboronic acid (entry 2, Table 3.3). Compound **3.3** was coupled with 9-anthraceneboronic acid, affording **3.7** in a yield of 31% (Scheme 3.6). TLC analysis indicated a large amount of material on the baseline, which suggested that there may be decomposition occurring, resulting in a much lower yield than that obtained in previous coupling reactions. In addition, by comparison the anthracene moiety is larger than the groups coupled previously, and so steric factors may also be inhibiting conversion from starting material.

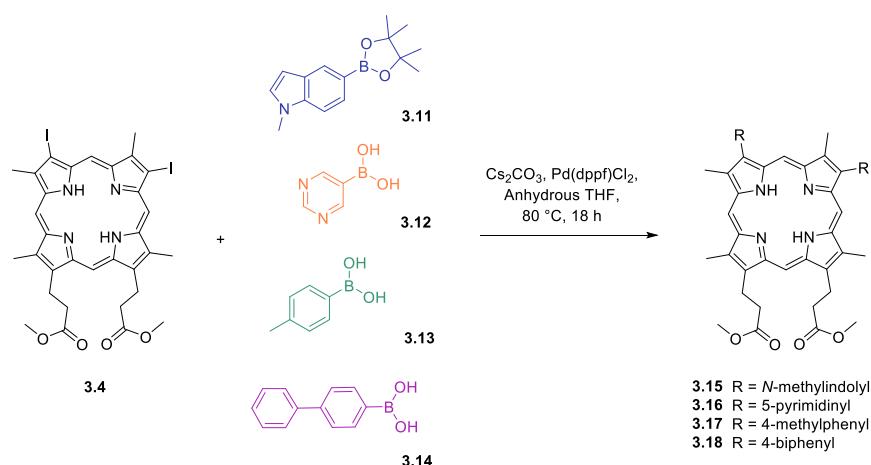
significantly more efficient than the reaction utilizing **3.3**. Finally, **3.4** was coupled with 9-anthraceneboronic acid **3.10**. The desired product **3.7** was obtained in 53% yield, again significantly higher than that utilising the dibromo-analogue. The results obtained confirmed expectations that the Suzuki reactions utilising **3.4** would be more efficient than those of **3.3**, possibly due to the larger size of iodine making it a much better leaving group than bromine in the catalytic cycle.



Scheme 3.7: Comparison of **3.3** vs. **3.4** in Suzuki coupling reactions.

3.3.6 Suzuki couplings with various aromatic systems

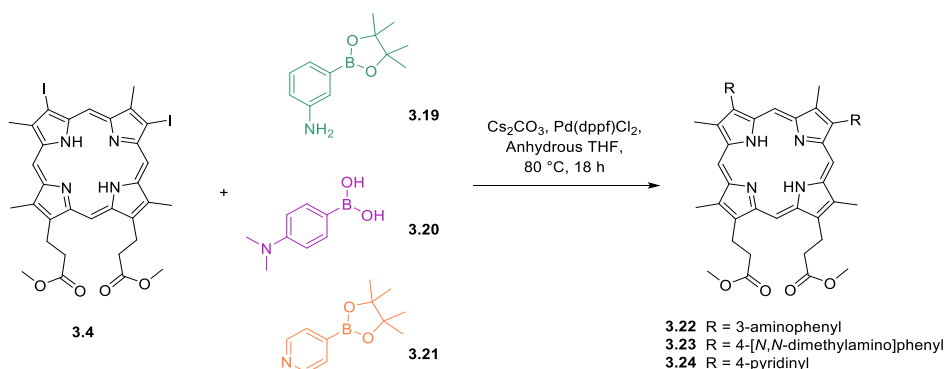
To investigate the efficiency of the coupling reaction with different types of aromatic systems, Suzuki-Miyaura couplings were carried out using *N*-methylindole-5-boronic acid pinacol ester, pyrimidine-5-boronic acid, *p*-tolylboronic acid and 4-biphenylboronic acid (Scheme 3.8). The first coupling to be carried out was that of **3.4** and 1-methylindole-5-boronic acid pinacol ester **3.11**, with a yield of 72% obtained for **3.15**. The reaction with pyrimidine-5-boronic acid **3.12** yielded 52% of **3.16**. Utilising *p*-tolylboronic acid, **3.17** was achieved in a yield of 77%, and a yield of 87% was obtained for **3.18** from the coupling with 4-biphenylboronic acid. In comparison with the bis(anthracenyl)-derivative **3.7**, these less bulky aromatic substituents resulted in significantly more efficient outcomes. This could possibly be due to the large bulk of the anthracene moiety being so close to the porphyrin periphery, as compared to the previously used aromatic substituents.



Scheme 3.8: Comparison of various aromatic systems in Suzuki coupling reactions.

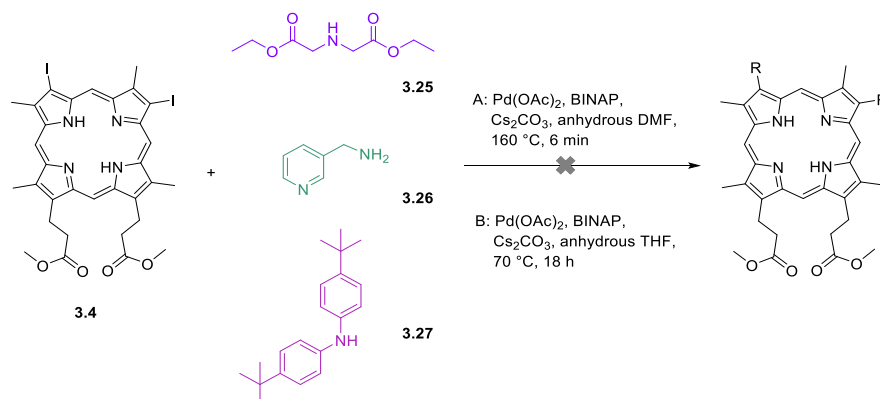
3.3.7 Suzuki couplings of 2.12 towards the preparation of cationic derivatives

As previously described, a series of cationic derivatives of deuterioporphyrin was planned in order to both follow-up the initial work of Smith *et al.*,¹⁸⁰ and also to investigate the potential of the target compounds in antimicrobial PDT. To that end, boronic acids were chosen which would incorporate groups containing nitrogen atoms for subsequent quaternisation *via* *N*-methylations (Scheme 3.9). First, coupling with 3-aminophenylboronic acid pinacol ester **3.19** synthesised **3.22** in 25% yield. The coupling with 4-(*N,N*-dimethylamino)phenylboronic acid **3.20** was more satisfactory, with **3.23** collected in a yield of 48% while that with 4-pyridineboronic acid pinacol ester **3.21** yielded 54% of **3.24**. Though the yields here are lower than those obtained for the couplings with other aromatic systems, although on par with that of the related **3.12**, these compounds will be used in the synthesis of cationic derivatives and if successful results are obtained from singlet oxygen measurement studies efforts to optimise the synthesis will be undertaken.



Scheme 3.9: Suzuki couplings of **3.4** with amine-functionalised boronic acids to prepare precursors for cationic derivatives.

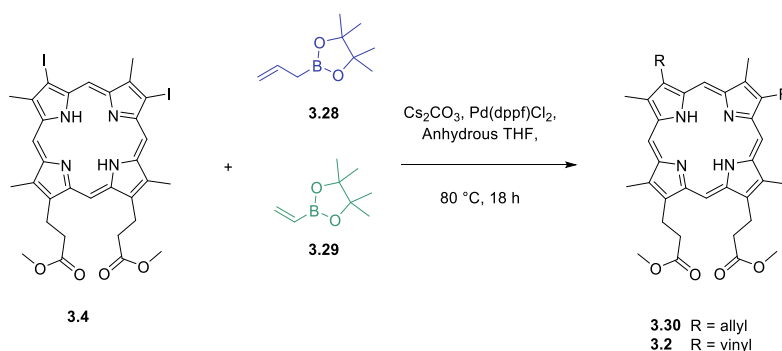
material was collected and due to low availability of the starting material, priority was given to the Suzuki-Miyaura coupling reactions.



Scheme 3.10: Attempted Buchwald-Hartwig aminations (condition A: microwave reaction, condition B: bench reaction).

3.3.9 Alkenyl Suzuki coupling reactions

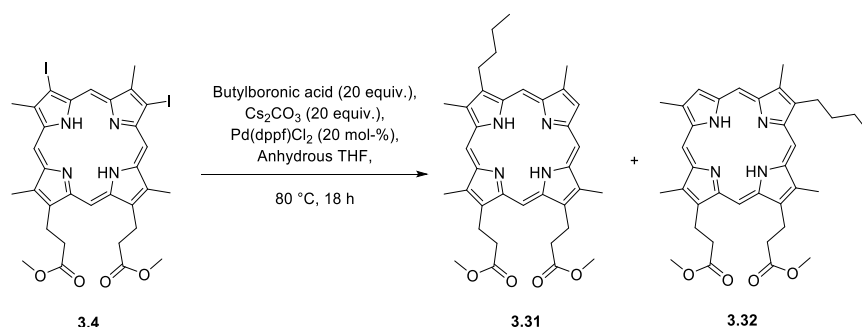
As Suzuki couplings of aromatic functionalities had been successfully demonstrated thus far, an investigation into the efficiency of alkenyl couplings was undertaken (Scheme 3.11). Due to the significantly higher yields associated with the diiodo-derivative observed previously, **3.4** was utilised in these examples. First, a Suzuki coupling with allylboronic acid pinacol ester **3.28** was carried out, affording **3.30** in a yield of 34%. Subsequently, a coupling reaction between **3.4** and vinylboronic acid pinacol ester **3.29** led to the synthesis of protoporphyrin IX dimethyl ester **3.2** in a yield of 38%. This reaction demonstrated the ease at which **3.1** can be transformed into another of the natural porphyrin derivatives *via* the use of standard Pd-catalysed coupling chemistry, albeit if slightly less cost-efficient.



Scheme 3.11: Suzuki coupling reactions with alkenylboronic acids.

3.3.10 Alkyl Suzuki coupling reactions

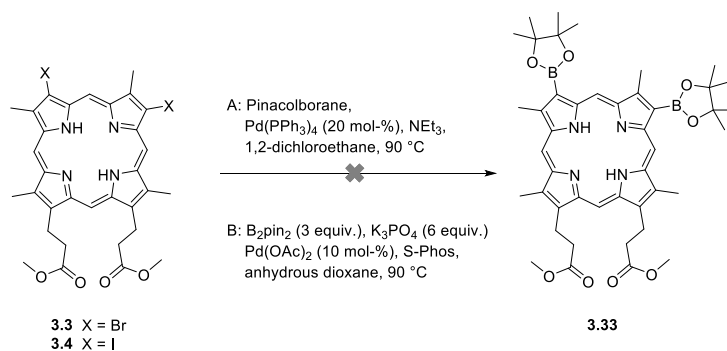
Alkyl coupling reactions were also investigated with isopropylboronic acid pinacol ester and butylboronic acid. Only starting material was collected in the case of the former, and as for the latter, monosubstitution and partial dehalogenation occurred, the products of which were determined to be a mixture of mono- β -substituted dehalogenated deuteroporphyrin, the regioisomers of which have proven to be inseparable (Scheme 3.12).



Scheme 3.12: Suzuki coupling of **3.4** and butylboronic acid.

3.3.11 Attempted Masuda borylation

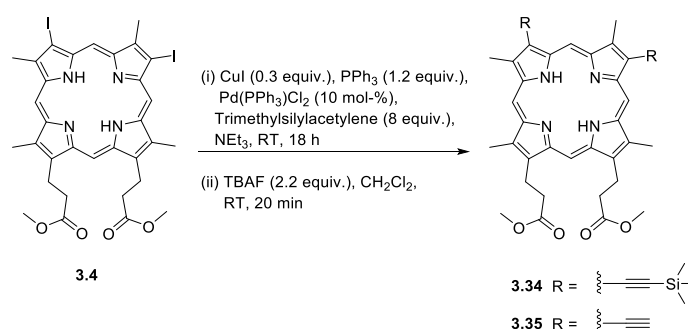
With such successful results obtained from the previous Suzuki-Miyaura couplings using both **3.3** and **3.4**, a comparison of the reversed reactivity using the diborylated derivative *via* the Masuda borylation was an interesting target.²⁷⁶ Initially, **3.3** and **3.4** were reacted with pinacolborane in the presence of tetrakis(triphenylphosphine)palladium(0) [Pd(PPh₃)₄], and NEt₃ in 1,2-dichloroethane at 90 °C (Scheme 3.13, condition A). However, TLC analysis - even after leaving the reaction overnight - did not indicate the formation of any product. The conditions were changed, reacting **3.3** and **3.4** with bis(pinacolato)diboron (B₂pin₂) in the presence of K₃PO₄, 2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl (S-Phos), palladium(II) acetate [Pd(OAc)₂] in anhydrous dioxane (Scheme 3.13, condition B). Unfortunately, no product was observed on this occasion either and this synthetic route was not continued.



Scheme 3.13: Attempted Masuda borylation.

3.3.12 Sonogashira coupling with trimethylsilylacetylene

Sonogashira coupling reactions were investigated using **3.3** and **3.4** in order to introduce another synthetic handle in the form of an acetylene moiety for the facile synthesis of more complex synthetic targets. No coupling was observed using **3.3**, consistent with the results reported by Brunner and Shellerer.²⁵⁸ A 14% yield was obtained upon reacting **3.4** and trimethylsilylacetylene. Further investigation found that room temperature conditions, instead of heating to 70 °C, gave a considerably higher yield of 57%. Deprotection *via* tetra-*n*-butylammonium fluoride (TBAF) produced **3.35** in 87% yield (Scheme 3.14).



Scheme 3.14: Sonogashira coupling of **3.4** with trimethylsilylacetylene and subsequent deprotection *via* TBAF.

The ¹H NMR spectrum of **3.34** gave a strong indication that oligomerisation was occurring in solution, as evidenced by the broad peaks. Therefore, a standard ¹³C NMR spectrum proved impossible; however, a ¹³C HSQC provided partial identification of carbon atoms of the alkyl groups, highlighted in red below (Fig. 3.6).

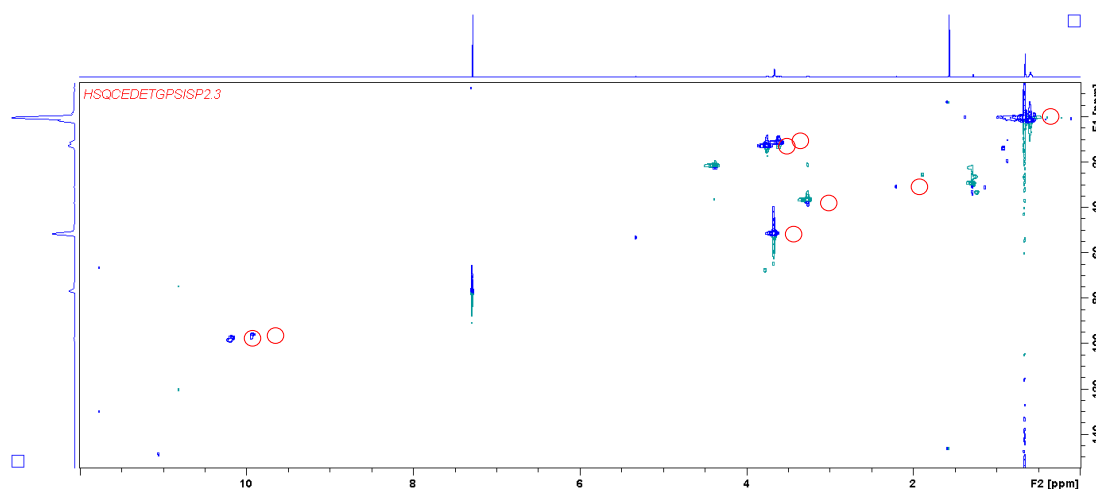
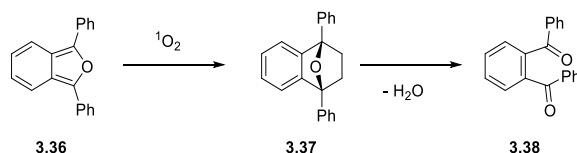


Figure 3.6: ¹³C HSQC of **3.34** in CDCl₃, 25 °C.

3.3.13 Synthesis of Water-Soluble Porphyrins for $^1\text{O}_2$ Studiesⁱ

Another objective of this work was an exploratory investigation into the $^1\text{O}_2$ production capabilities of deuteroporphyrin IX derivatives for potential application in antimicrobial PDT. The generation of $^1\text{O}_2$ was measured by analysis of the degradation of 1,3-diphenylisobenzofuran (DPBF) under UV light. The process is as follows: a solution of the respective PS and DPBF are irradiated with light (halogen lamp, Philips, 15V–150W lamp) at 3 s intervals, with UV-vis spectra obtained in the interim. DPBF acts as a $^1\text{O}_2$ trap, undergoing a [4+2] cycloaddition reaction to produce a species which is inactive under UV irradiation. The decrease in the absorption band of DPBF over time directly corresponds to the amount of $^1\text{O}_2$ produced (Scheme 3.15).^{277,278}



Scheme 3.15: Degradation of DPBF.

The $^1\text{O}_2$ generation of two compounds were measured – **3.23** and **3.24**. The decrease in the UV-vis absorption of DPBF in the presence of each was measured in $\text{CH}_2\text{Cl}_2:\text{CH}_3\text{OH}$ (1:1) at a concentration of 0.15 mol L^{-1} . Rose Bengal (RB) in CH_2Cl_2 at a concentration of 0.15 mol L^{-1} was used as a standard. The respective solutions were irradiated over a period of 1 h, with UV-vis absorption spectra obtained at $t = 0 \text{ s}$ and at intervals of 100 s after initial irradiation. $^1\text{O}_2$ measurements were repeated twice, and Φ_{BHP} values were observed in a standard deviation range of ± 0.04 . The relative $^1\text{O}_2$ quantum yields were calculated with respect to RB ($\Phi_{\text{RB}} = 0.76$ in CH_3OH).²⁷⁹ The slope of the curves of the absorbance maxima of DPBF at 410 nm vs. irradiation time for each compound were calculated. The $^1\text{O}_2$ quantum yield ($\Phi_{\text{deutporp-nhet}}$) for each PS using RB as a reference was calculated using the following equation:

$$\text{Equation 3.1: } \Phi_{\text{deutporp-nhet}} = \Phi_{\text{RB}} \times S_{\text{deutporp-nhet}} / S_{\text{RB}}$$

where Φ represents the quantum yield, S represents the slope, and deutporp-nhet represents the deuteroporphyrin IX derivative, respectively.²⁸⁰

ⁱ Singlet oxygen measurements performed by Bhavya Khurana at TCD.

The results of the DPBF quenching studies for **3.23** and **3.24** are shown in Fig. 3.7. The pyridine-substituted derivative **3.24** exhibited more enhanced DPBF degradation than **3.23**. Using equation 3.1 the relative $^1\text{O}_2$ quantum yields were calculated as 0.19 and 0.32, respectively (Fig. 3.8). To prepare PSs more suited to biological media, cationic derivatives of **3.23** and **3.24** were prepared.

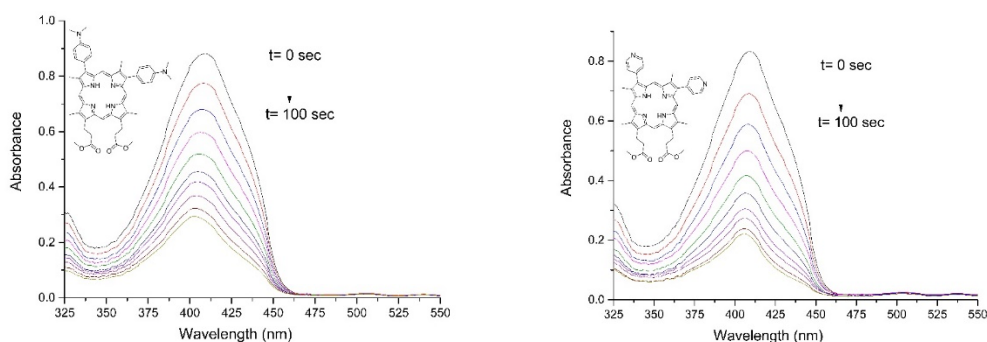


Figure 3.7: DPBF quenching with (left) **3.23** and (right) **3.24**.

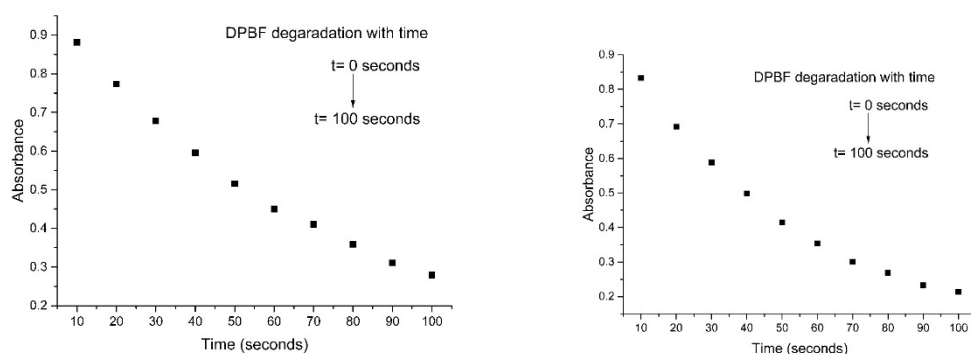
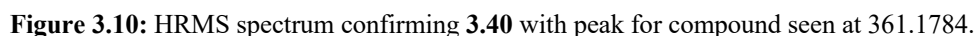


Figure 3.8: Absorption of DPBF vs time (s) in the presence of (left) **3.23** and (right) **3.24**.

Compound **3.23** was *N*-methylated *via* stirring in *N*-methyl-2-pyrrolidone with an excess of MeI (400 equiv.) at RT for 48 h (Scheme 3.16). The product was precipitated with diethyl ether and collected *via* filtration, with **3.39** collected in a yield of 92%.



Page | 51

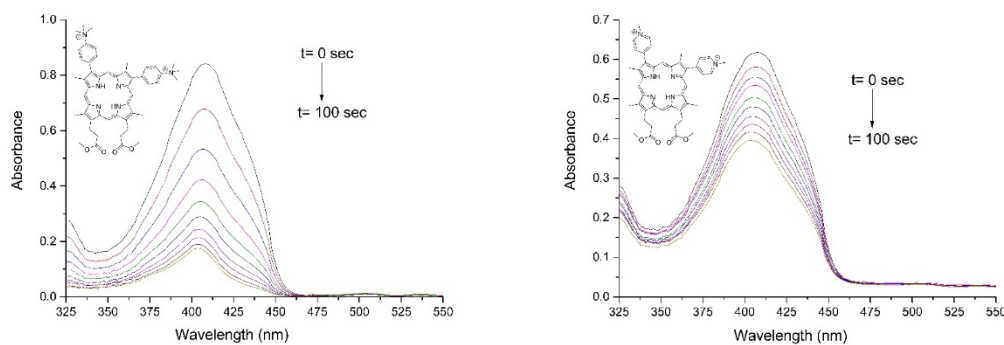


Figure 3.11: DPBF quenching with (left) **3.39** and (right) **3.40**.

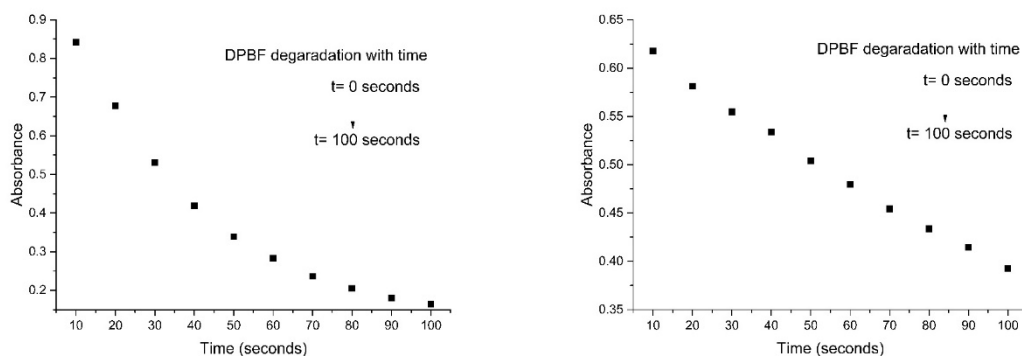
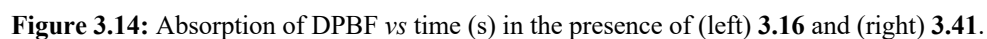
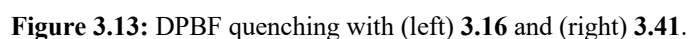
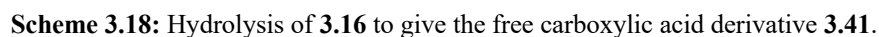


Figure 3.12: Absorption of DPBF vs time (s) in the presence of (left) **3.39** and (right) **3.40**.

To investigate the $^1\text{O}_2$ production of an anionic species, the pyrimidinyl-derivative **3.16** was compared with its carboxylic acid counterpart **3.41** (Scheme 3.18). Again, there was a stark difference seen between the activities of both compounds. While for **3.16**, very little DPBF degradation was observed over the course of the experiment, **3.41** resulted in similar degradation as compared to **3.39** (Fig. 3.13). The $^1\text{O}_2$ quantum yields were determined to be 0.05 and 0.36, respectively, the largest difference observed from the three sets of compounds (Fig. 3.14).



Page | 53

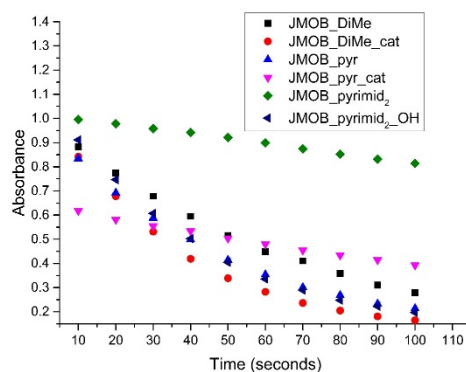


Figure 3.15: Comparison of the DPBF degradation plots for the six deuteroporphyrin IX derivatives. JMOB_DiMe – **3.23**, JMOB_DiMe_cat – **3.39**, JMOB_pyr – **3.24**, JMOB_pyr_cat – **3.40**, JMOB_pyrimid₂ – **3.16**, JMOB_pyrimid₂_OH – **3.41**.

3.3.13 X-ray Crystallographyⁱⁱ

X-ray crystallographic analyses were undertaken on suitable crystals of **3.5**, **3.23** and **3.30**, the structures of which were confirmed *via* single-crystal X-ray diffraction (Figures 3.16–3.22). Crystals were grown following the protocol developed by Hope, by dissolving the compounds in CDCl₃ and allowing for slow evaporation over time.²⁸² Details of data refinements can be found in Table 6.1 (Chapter 6 – Experimental). All images were prepared using Olex2.²⁸³ All three of the structures consist of a flat macrocycle with an average atom deviation from the least-squares plane (LSP) of the 24-atom ring of 0.062 Å and 0.035 Å, respectively.

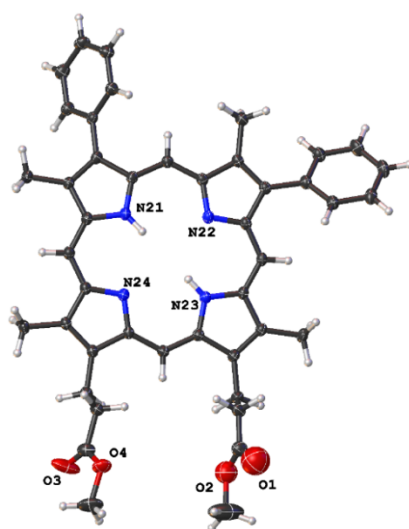


Figure 3.16: X-ray crystal structure of **3.5**.

ⁱⁱ X-Ray Crystallography in this Chapter performed by Dr. Keith J. Flanagan at TCD.

This is comparable to literary examples of deuteroporphyrin IX samples in which the atom deviation from the LSP of the macrocycle ranges from 0.029 to 0.086 Å.^{284–288} The structure of **2.15** illustrates two packing patterns: the first is the offset head-to-tail stacking pattern, aided by a C–H···O interaction between the methyl ester moieties at O1···H13F at distances of 2.746(8) and 2.664(7) Å, respectively (Fig. 3.17A). The second packing motif is the head-to-tail overlap caused by the interaction of the methyl ester group with the hydrogen atoms of the phenyl groups (O3···H36) at a distance of 2.606(8) Å (Fig. 3.17B). This results in the zig-zag pattern seen in Figure 3.9, which is unique compared to the reference examples and is most likely a result of the additional aromatic ring present. **3.5** was modelled with a 0.1% Pd-contamination in the centre of the porphyrin ring, which is a common result of using free base porphyrins in transition metal catalysed reactions. The open space is a prime cavity for conjugation of metal atoms and can be prevented by prior metal coordination in the centre of the porphyrin ring. This metal (for e.g. zinc (II)) can then be removed at a later stage in the target compound synthesis.^{18,273,274}

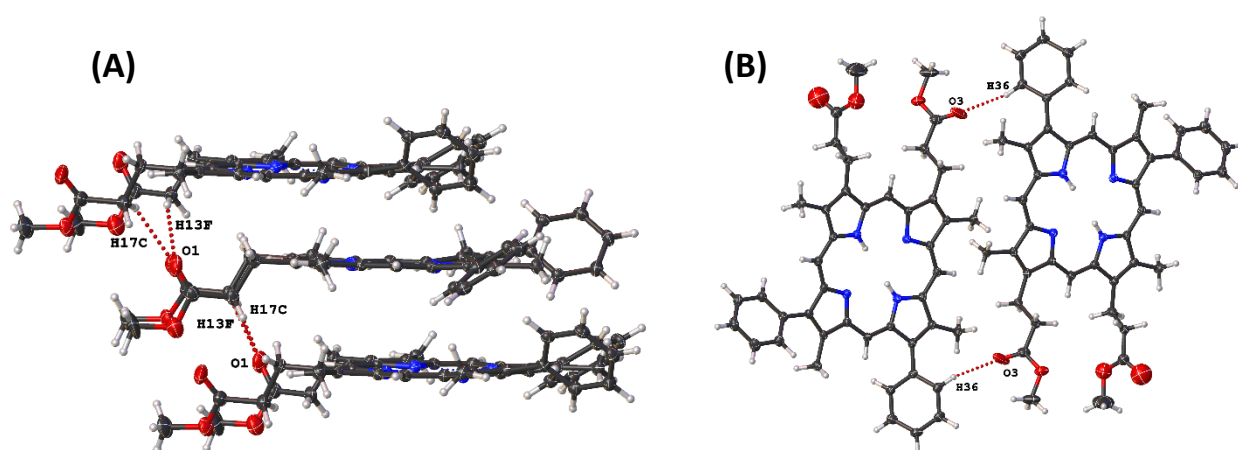


Figure 3.17: Molecular structure of **3.5** showing the head-to-head stacking pattern (A) and the head-to-tail stacking pattern (B). O···H interactions are indicated by the red dashed lines. Thermal displacement is given at 50% probability.

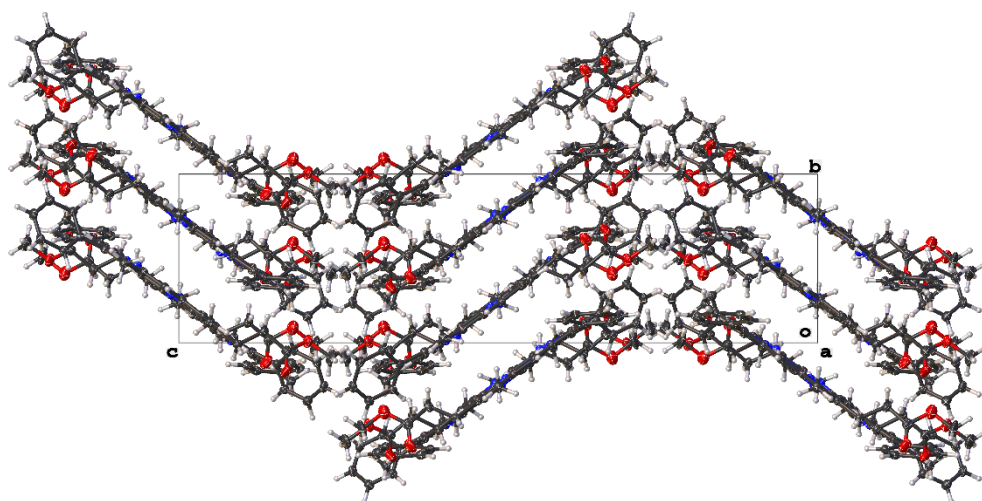


Figure 3.18: Crystal packing of **3.5** looking down the *a*-axis. Thermal displacement is given at 50% probability.

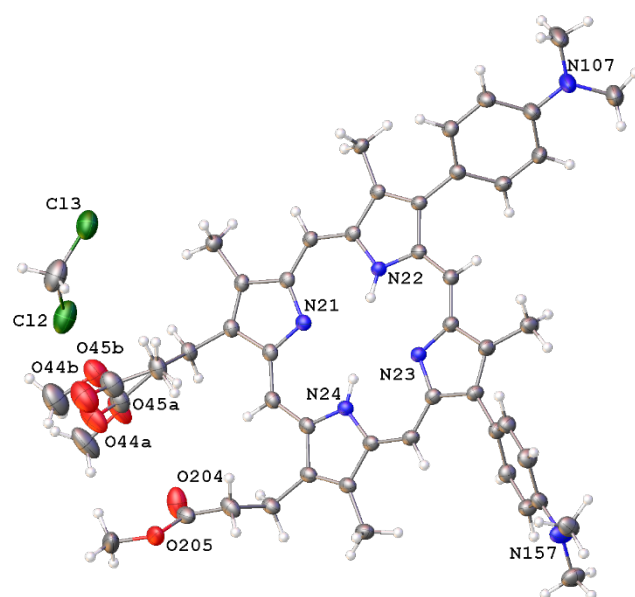


Figure 3.19: View of the molecular structure of **3.23** in the crystal.

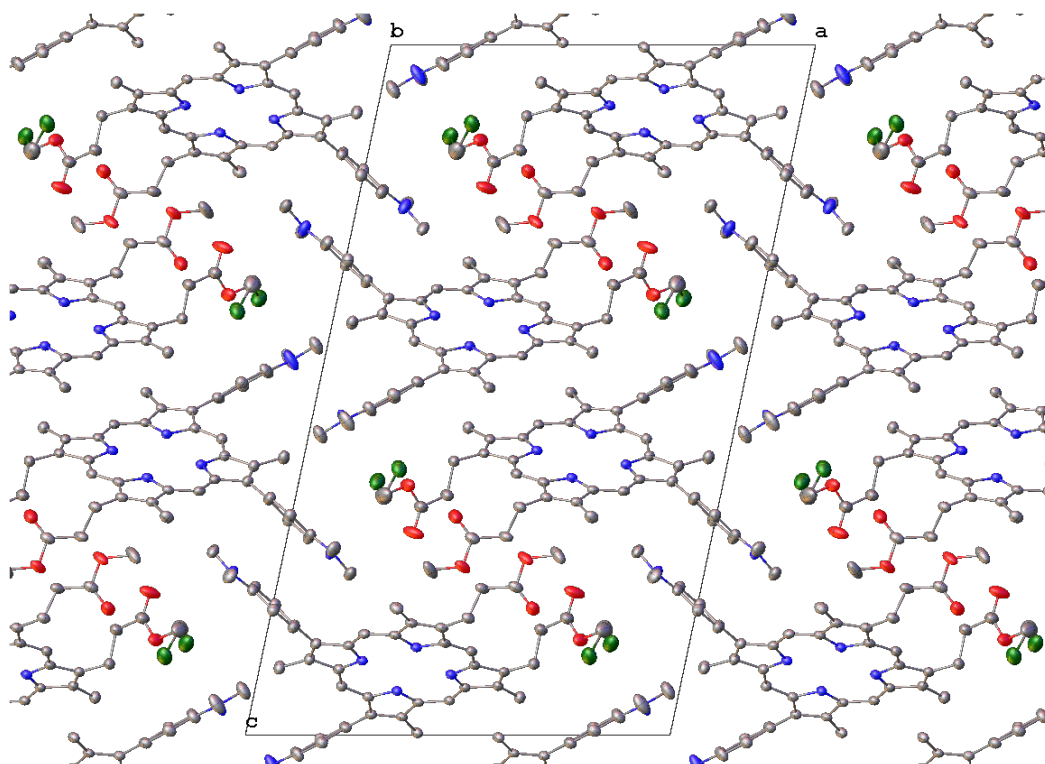


Figure 3.20: Packing diagram of **3.23** viewed normal to (010) showing the major occupied moiety and partial occupancy solvent only. Hydrogen atoms omitted and atomic displacement shown at 50% probability.

Compound **3.30** exhibits head-to-head interactions between the methyl ester moieties, connected by C–H···O short contacts between O1···H17C and O1···H13C at distances of 2.649(3) and 2.606(4) Å, respectively (Fig. 3.21).

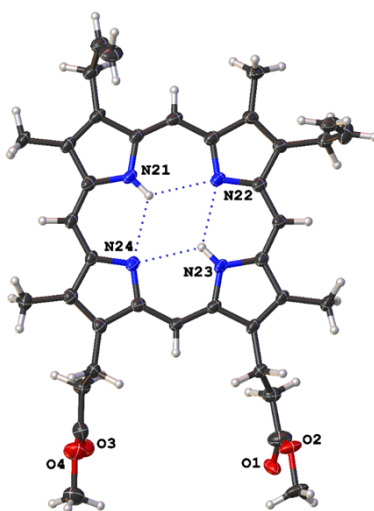


Figure 3.21: X-ray crystal structure of **3.30**.

Another head-to-head overlap aided by a C–H···O short contact between the methyl ester groups (O1···H17E) is observed at a distance of 2.425(3) Å (Fig. 3.22). This results in the stepwise packing pattern seen in Figure 3.14. The introduction of the carbon between the

vinyl group and β -carbon of the porphyrin scaffold forces the side-chain into being more out-of-plane than that of the naturally occurring PpIX.²⁸⁹

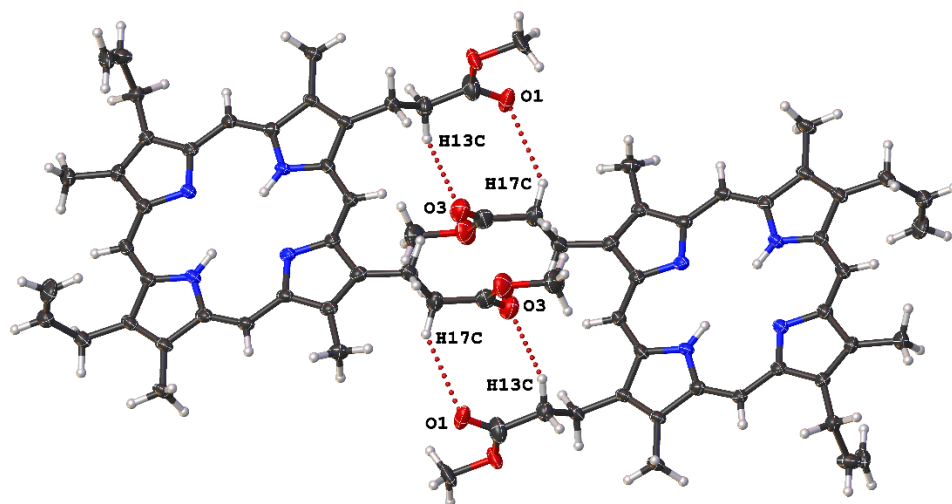


Figure 3.22: Molecular structure of **3.30** showing the head-to-head interaction between the methyl ester moieties. O...H interactions are indicated by the red dashed lines. Thermal displacement is given at 50% probability.

3.4 Conclusions & Future Work

To conclude, new methods for the functionalization of the β -positions of deuteroporphyrin IX dimethyl ester have been presented.²⁹⁰ While previous manipulation of **3.1** and **3.2** has been practiced since the early 1900s, the work described brings the synthetic chemistry of **3.1** into the 21st century and is of importance given the wide scope of applications for these molecules, *e.g.*, in the field of PDT. Initial halogenations were carried out with vastly optimized yields obtained as compared to literature procedures in the case of **3.3** and **3.4**. The described Suzuki and Sonogashira reactions demonstrate the facile manner in which the deuteroporphyrin periphery can be manipulated. The dibrominated derivative **3.3** was compared with the diiodinated derivative **3.4** as a coupling partner in terms of efficiency. Notably, the coupling reaction between **3.4** and 4-formylphenylboronic acid afforded **3.6** in a yield of 79%, and higher yields were observed across the board for all couplings. Aryl couplings tended to give higher yields than those with amine, alkenyl or alkyl substituents. To compare the effects of various aromatic systems, couplings with 9-anthraceneboronic acid, *N*-methylindoleboronic acid, 4-tolylboronic acid, and biphenylboronic acid resulted in yields of 53–87%. Higher yields were achieved with less bulky aromatic substituents, with that of **3.7** being the lowest. A

Suzuki coupling between **3.4** and vinylboronic acid pinacol ester led to the synthesis of protoporphyrin IX dimethyl ester **3.2** in a yield of 38%, illustrating the possibility of alkenyl couplings as well as the interchangeability of **3.1** into various other natural porphyrin derivatives *via* Pd-catalyzed coupling chemistry. Alkyl couplings were unsuccessful in producing disubstituted derivatives, resulting only in an inseparable mixture of isomers after the attempted coupling with butylboronic acid. Sonogashira coupling reactions were investigated, yielded an acetylene-substituted derivative in 57%. This leaves the option to work towards the synthesis of more complex synthetic targets in the future. X-ray crystallographic analysis successfully determined the structure of three derivatives synthesized. Results identified a unique head-to-tail stacking pattern for 3,8-diphenyldeuteroporphyrin IX dimethyl ester **3.5**, most likely due to the presence of additional aromatic moieties on the periphery of the porphyrin. This project was expanded into the synthesis of cationic and anionic deuteroporphyrin derivatives *via* *N*-methylation and facile ester hydrolysis. $^1\text{O}_2$ measurements were taken relative to DPBF degradation, with the most promising compounds identified as **3.39** and **3.41**, with $^1\text{O}_2$ quantum yields of 0.37 and 0.36, respectively. Expansion of these compounds into a larger library for comparison is needed, antimicrobial PDT investigations to ascertain whether they are viable PSs. However, preliminary results reported here support the argument for the photosensitizing ability of DpIX derivatives. Finally, one avenue which wasn't explored was the photosensitising potential of the "parent" compounds, **3.3** and **3.4**. Due to the heavy atom effect described in Chapter 1, the presence of either two bromine or two iodine residues could have a huge impact on the singlet oxygen producing capability of deuteroporphyrin. An idea for a future project for this work could be an investigation into these two compounds to see if they could be applied in PDT.

Chapter 4: Photosensitisers for Organic Dye Degradation

4.1 Introduction

Rhodamine dyes are one of the oldest synthetic dyes used for the colouring of fabrics. They are members of the xanthene family of fluorophores (Fig. 4.1), and have excellent photophysical properties (high extinction coefficients, excellent quantum yields), high photostability and relatively long emission wavelengths. Such desirable properties in a fluorophore have given the rhodamine dyes myriad applications which include, but are not limited to, their use as fluorescence probes and standards, photosensitisers, laser dyes, and chemosensors.^{291–295}

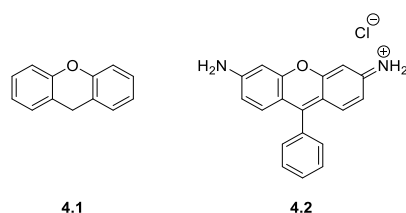
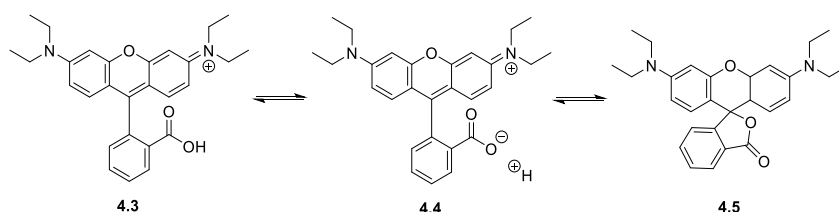


Figure 4.1: Xanthene **4.1** and the Rhodamine core structure **4.2**.

Rhodamine was first synthesised in 1905 by Noeltling and Dziewonsky,²⁹⁶ but it was only in 1997 with the discovery of its ring-opening reaction and the effects of solvent polarity on photophysical properties did the applications previously mentioned really take off (Scheme 4.1).^{68,297,298} When in an acidic solution, the carboxyl group of Rhodamine B (RhB) is protonated; when in a basic solution, dissociation occurs converting RhB into its zwitterionic form. In each of these forms, the chromophore is shared and there is a hypsochromic shift of both the absorption and fluorescence maxima. However, in less polar organic solvents, a reversible conversion to the colourless spirolactone occurs. The π -conjugation has been disturbed, the absorption occurs in the UV spectral region, and the fluorescence quantum yield and lifetime is now very low.^{293,299,300}



Scheme 4.1: Solvent effects on structure of Rhodamine B; cationic **4.3** in acidic solution, zwitterionic **4.4** in basic solution, reversible formation of the lactone **4.5** in organic solvent.

Unfortunately, organic dyes, including the rhodamine family of xanthenes, are regularly found to contaminate wastewater, and are in fact one of the most significant pollutants identified due to their inherent toxicity and long-lasting stability. RhB has been found to cause not only irritation of the skin, eyes, and respiratory tract, but can also be carcinogenic and mutagenic to living organisms.^{301,302} Due to their high stability, traditional methods such as biological or chemical oxidation are not applicable. A photocatalytic degradation process would be ideal, especially one which utilises visible light for enhanced ease and efficiency.³⁰³ Porphyrin derivatives possess the desired photophysical properties, however their inherent hydrophobicity and tendency to aggregate in aqueous media limits their application.^{304,305} The addition of the desired porphyrin to a support surface can limit this aggregation, thereby preventing the decrease in photocatalytic activity. Graphene is one such potential support surface, as it has a conjugated aromatic system, large surface area and good optical transmittance.^{306–309} However, due to the poor solubility of graphene in aqueous media, its hydrophilic derivative graphene oxide (GO) which can form stable aqueous suspensions is more suitable.

4.2 Objectives

Non-covalent nanohybrids consisting of cationic porphyrins and GO will be synthesized and investigated for applicability in the photodegradation of RhB. The porphyrins which will be used are 5,10,15,20-tetrakis(*N*-methylpyridinium-4-yl)porphyrin (TMPyP) and 5,10,15,20-tetrakis(*N*-methylpyridinium-4-yl)porphyrinato]zinc(II) (ZnTMPyP) (Figure 4.2).

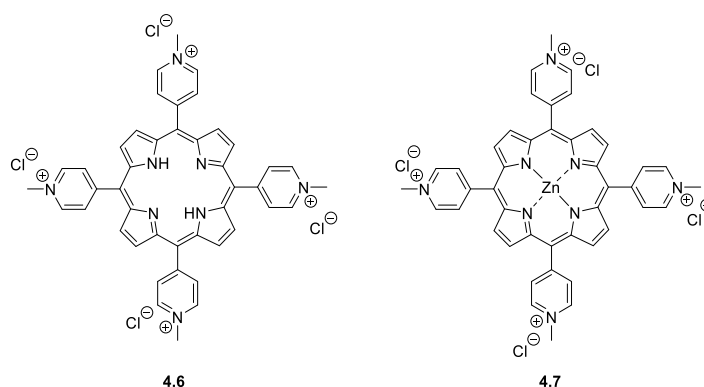
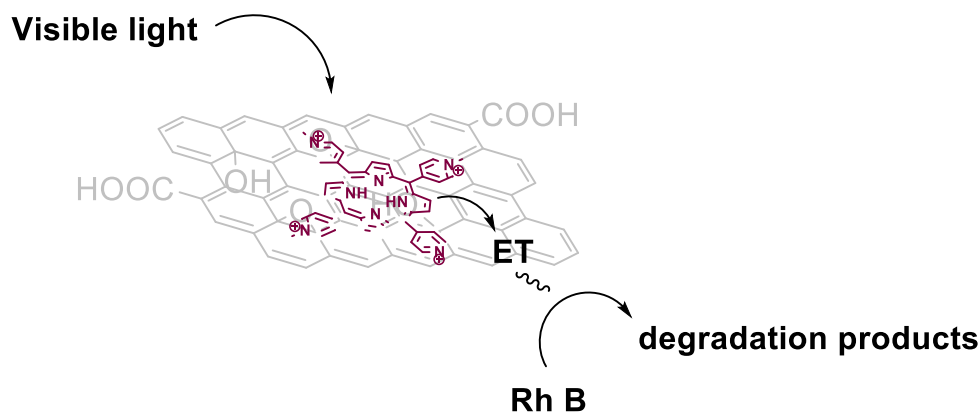


Figure 4.2: Porphyrins to be used for the functionalisation of graphene oxide, TMPyP **4.6** and ZnTMPyP **4.7**.

In aqueous solutions just under neutral pH, GO sheets carry a negative charge due to the presence of oxygen-containing functional groups, and it is hoped that the electrostatic

interaction between these anionic and cationic charges, as well as the π - π interactions between the two conjugated systems, will increase the affinity of the photosensitisers to the GO surface (Scheme 4.2).



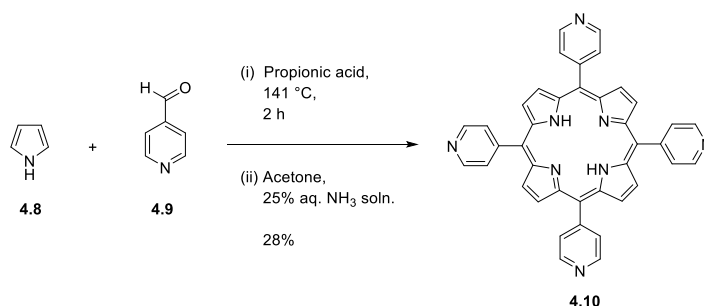
Scheme 4.2: Photodegradation of Rhodamine B *via* porphyrin-GO nanohybrid and visible light.

Whilst there is a wealth of literature on the construction of porphyrin- and graphene-based hybrid materials,³¹⁰ this study aims to thoroughly compare the spectroscopic properties of two water-soluble nanohybrid materials, and provide an analysis of how these properties affect the photocatalytic degradation of RhB.

4.3 Results & Discussion

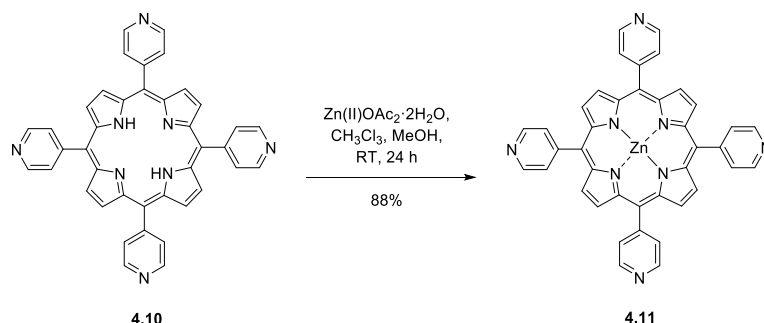
4.3.1 Synthesis of 5,10,15,20-tetrakis(4-pyridyl)porphyrin and metalation with zinc(II)

Compound **4.10** was synthesised according to a literature procedure.³¹¹ After condensation of pyrrole **4.8** and the appropriate aldehyde **4.9**, the reaction mixture was cooled to RT before being treated with acetone and 25% aq. ammonia solution. This mixture was then left in the freezer for 48 h. Purple crystals were collected and washed with MeOH, affording **4.10** in a yield of 28% (Scheme 4.3).



Scheme 4.3: Synthesis of TPyP **4.10**.

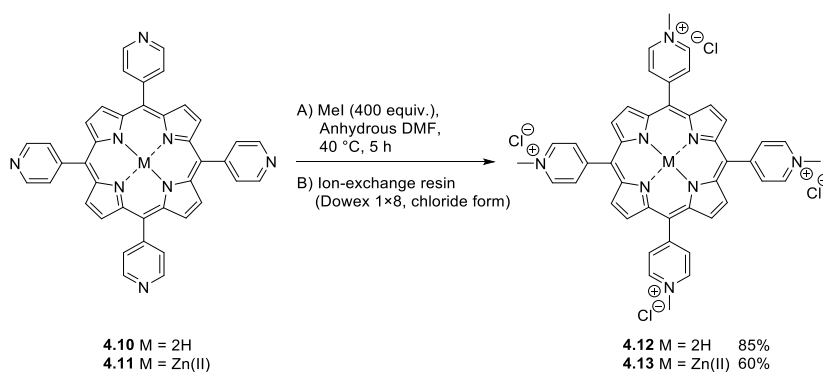
TPyP was then dissolved in CH_3Cl_3 and stirred for 24 h at RT in the presence of zinc(II)acetate dihydrate dissolved in the minimum amount of MeOH to obtain ZnTPyP **4.11** in a yield of 88% (Scheme 4.4).



Scheme 4.4: Synthesis of ZnTPyP **4.11**.

4.3.2 Synthesis of cationic derivatives

The *N*-methylations of compounds **4.10** and **4.11** were carried out according to an adapted literature procedure (Scheme 4.5).³¹² The porphyrin was dissolved in anhydrous DMF and stirred at 40 °C for 5 h in the presence of a large excess of MeI. The reaction mixture was then cooled to RT and an excess of diethyl ether was added to precipitate the *N*-methylated compound. This was then collected *via* filtration and washed with additional diethyl ether. Finally, the porphyrins were passed through an ion-exchange resin (Dowex 1×8, chloride form) using deionised H_2O as eluent. After the removal of solvent *in vacuo* the desired compounds were collected in yields of 85% and 60%, respectively.



Scheme 4.5: Methylation of compounds **4.10** and **4.11**.

4.3.3 Preparation of porphyrin-GO nanohybridsⁱⁱⁱ

The TMPyP-GO and ZnTMPyP-GO nanohybrids were prepared according to the following procedure: a layer of SnO_2 was added to a fluorine-doped tin oxide (FTO) glass electrode *via* a doctor blading method and received thermal treatment. The prepared samples were

ⁱⁱⁱ Prepared by D. Larowska at the Adam Mickiewicz University, Poznan, Poland

covered with GO *via* electrophoretic deposition. The electrodes were then left overnight in the respective porphyrin baths (at a PS concentration of 60 μM) before being air-dried. For the photochemical measurements, the prepared electrodes (TMPyP-GO-SnO₂-FTO, ZnTMPyP-GO-SnO₂-FTO, and GO-SnO₂-FTO as a control) acted as the working electrodes to be analysed, a platinum electrode acted as the counter electrode, and a saturated calomel electrode (SCE) as the reference. The measurements were taken on an electrochemical workstation (Keithley model 617 programmable electrometer) using a 0.1 M LiI acetonitrile solution and a three-electrode configuration quartz cell. Photocurrents of the working electrodes with and without light irradiation were measured at 0 V using a Fiber optic illuminator as the light source.

4.3.4 Steady-state absorption measurements

The UV-vis absorption spectra for TMPyP and ZnTMPyP were as expected and in agreement with the literature (Fig. 4.3).^{312,313} The presence of Zn(II) in the core of the molecule causes a 15 nm red-shift of the Soret band as well as a decrease in the molar absorption coefficient due to a reduction in the HOMO-LUMO gap within the porphyrin macrocycle.³¹⁴ There is also a reduction in the number of visible Q-bands, with two observed at 566 and 613 nm, due to the increase in symmetry of the macrocycle upon metalation.^{315,316}

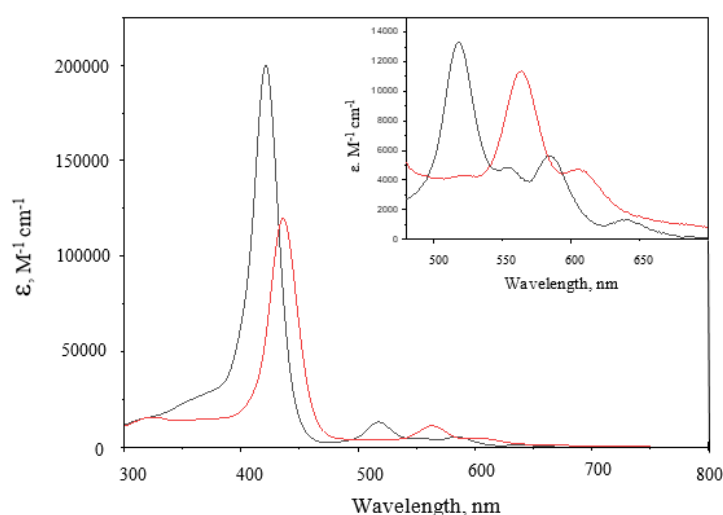


Figure 4.3: Absorption spectra of TMPyP (black) and ZnTMPyP (red) in water (inset: expanded Q-band region).

Ground state interactions between GO and the PSs were investigated *via* UV-vis spectroscopy (Fig. 4.4A). Upon gradual addition of GO to an aqueous solution of TMPyP,

a decrease in the absorbance at 422 nm was accompanied by the appearance of a new band at 440 nm. This is due to the decreasing concentration of the free PS, and an increasing concentration of GO-bound PS. Similar results were observed for that of ZnTMPyP, in which a bathochromic shift of 16 nm was observed upon addition of GO (Fig. 4.4B). This red-shift in the absorbance observed for both PSs upon binding to GO can be explained by the flattening of the porphyrin macrocycles when adhered to the GO surface.

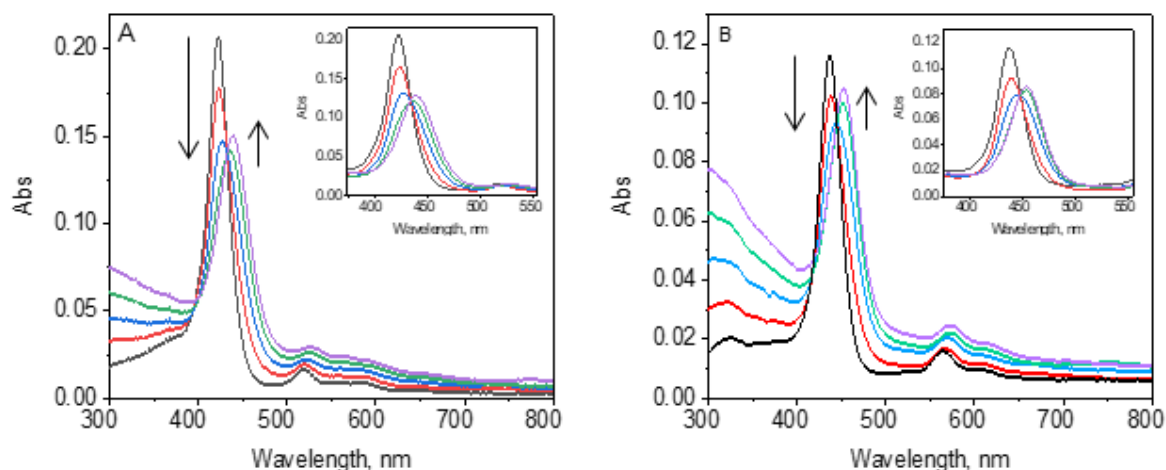


Figure 4.4: A) Absorption spectra recorded in the presence of Rhodamine B with the gradual addition of an aqueous solution of GO ($0\text{--}6.67 \times 10^{-3} \text{ mg mL}^{-1}$) to a $1.0 \mu\text{M}$ aqueous TMPyP solution; B) absorption spectra recorded during the gradual addition of an aqueous solution of GO ($0\text{--}6.67 \times 10^{-3} \text{ mg mL}^{-1}$) to a $1.0 \mu\text{M}$ aqueous ZnTMPyP solution; black: 0 mg mL^{-1} ; red: $1.67 \times 10^{-3} \text{ mg mL}^{-1}$; blue: $3.33 \times 10^{-3} \text{ mg mL}^{-1}$; green: $4.99 \times 10^{-3} \text{ mg mL}^{-1}$; purple: $6.67 \times 10^{-3} \text{ mg mL}^{-1}$.

4.3.5 Photocatalytic activity of the PS-GO composites:

Experiments were carried out in water at pH 6.5 and RT according to the following procedure: 3.448 mL of the respective aqueous catalyst sample [TMPyP-GO (0.42 mg, TMPyP 3.7% wt), ZnTMPyP-GO (0.41 mg, ZnTMPyP 4.9%), GO (0.4 mg)] was mixed with 8.34 mL of Rhodamine B (5 mg mL^{-1}) solution and 13.212 mL of deionised H₂O. The mixtures were stirred in the absence of light until the adsorption-desorption equilibrium was reached, when 3 mL of each of the solutions were placed in a quartz cuvette and irradiated using a halogen lamp light source (150 W with a cut-off filter $\lambda > 400 \text{ nm}$). The

decrease in Rhodamine B concentration was measured at 554 nm. Experiments were recorded in triplicate.^{iv}

The photocatalytic activity towards RhB degradation was investigated under visible light irradiation for the two materials (TMPyP-GO and ZnTMPyP) as well as GO alone (control). Suspensions of the respective samples and RhB were irradiated for 2 h with constant stirring. The decrease in concentration of RhB was measured following changes in the absorbance maxima at 554 nm (Fig. 4.5). For the experiment using GO alone, only a small amount of degradation (3.7% after 2 h) was observed. ZnTMPyP-GO resulted in the highest rate of RhB degradation, at 19% after 2 h visible light irradiation.

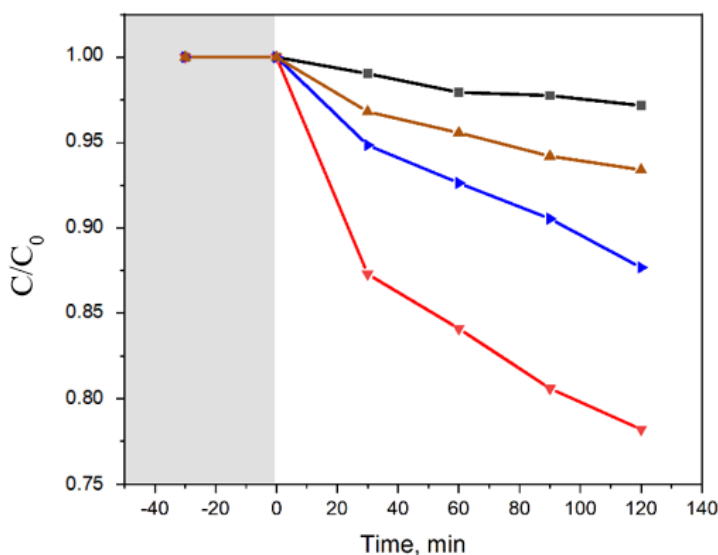


Figure 4.5: Rhodamine B degradation under visible light irradiation ($\lambda > 400$ nm): control (black ■), GO (brown, ▲), TMPyP-GO composite (blue, ►) and ZnTMPyP-GO composite (red, ▼).

The unbound porphyrins did not result in any photocatalytic activity towards RhB degradation, possibly due to their instability under light irradiation as well as the resulting significant decrease in light absorption after decomposition. In addition, adsorption of TMPyP and ZnTMPyP onto GO improved their photostability, as seen by the negligible amount of decomposition seen after even 2 h light irradiation (Fig. 4.6).

^{iv} Experiments carried out by D. Larowska at the Adam Mickiewicz University, Poznan, Poland

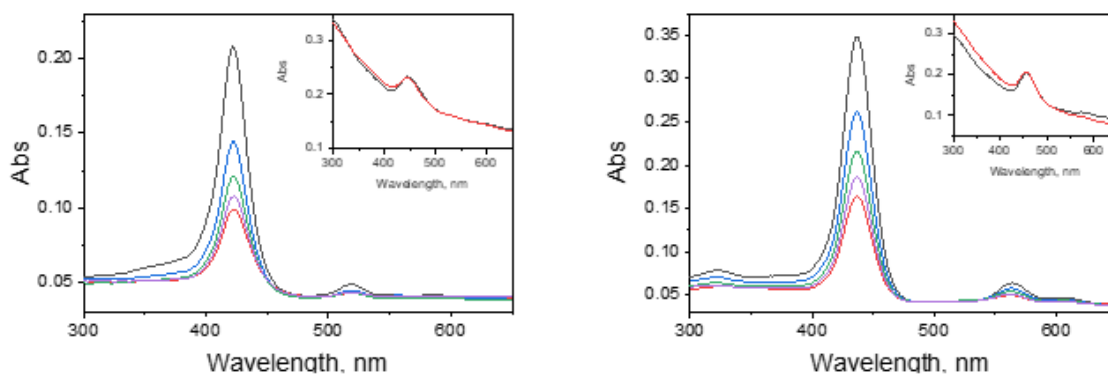
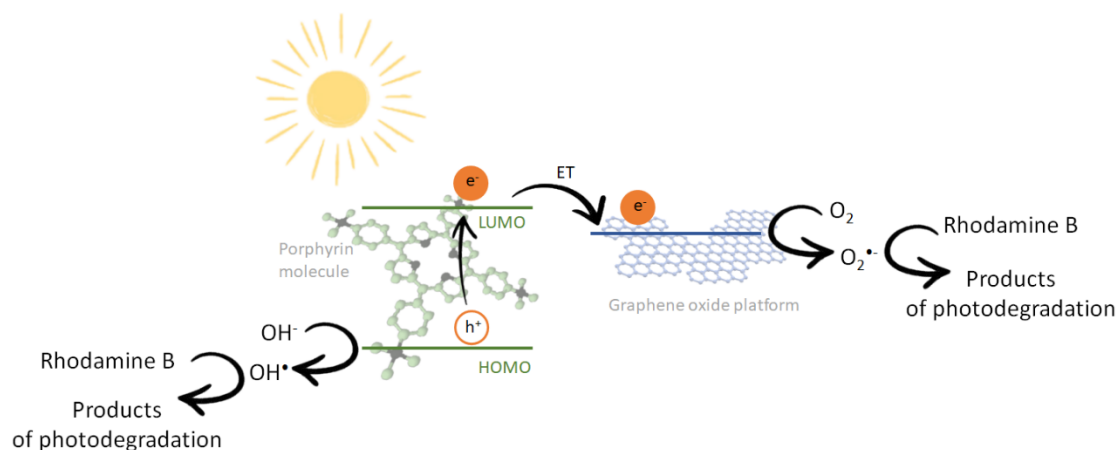


Figure 4.6: UV-vis spectra of TMPyP (left) and ZnTMPyP (right) aqueous solutions under visible light irradiation for 2 h (inset: PS solutions with addition of GO under the same conditions).

4.3.6 Proposed mechanism for photodegradation of Rhodamine B:

RhB photodegradation process has been described previously, and only occurs in the presence of oxygen.^{317,318} As has been discussed in previous chapters, irradiation of a PS with light of an appropriate wavelength results in the formation of various reactive oxygen species (ROS), such as hydroxyl radicals, superoxide radicals, and $^1\text{O}_2$.¹²⁷ The suggested mechanism for the work described herein is illustrated in Scheme 4.6. Upon excitation of the respective porphyrin-GO nanohybrid with visible light, electrons are transferred to the GO sheet creating electron-hole pairs (e^-/h^+). A reaction occurs between the photogenerated holes (h^+) on the surface of either TMPyP or ZnTMPyP and H_2O or OH^- , forming hydroxyl radicals. These radicals can degrade RhB *via* oxidation reactions. Meanwhile, the photogenerated electron (e^-) can react with oxygen to form the superoxide anion $\text{O}_2^{\cdot-}$.



Scheme 4.6: Proposed mechanism for Rhodamine B photodegradation.

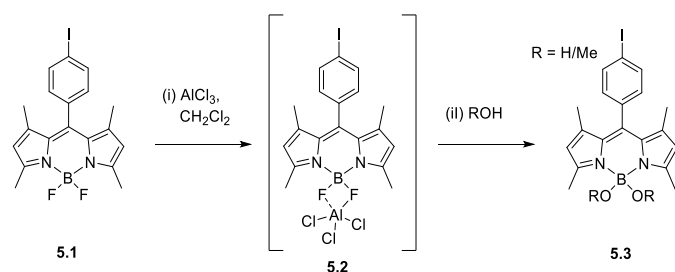
4.4 Conclusion

Two nanohybrids TMPyP-GO and ZnTMPyP-GO were prepared *via* non-covalent adhesion of the cationic PSs to the surface of GO. These were then used in an investigation into the photocatalytic degradation of RhB. Metalation of TMPyP with Zn(II) increased the affinity of the porphyrin towards the GO surface, and while both materials demonstrated significant photocatalytic activity, that of ZnTMPyP-GO was much more efficient. The photodegradation of RhB is believed to occur *via* the excitation of the porphyrin PSs and subsequent transfer of electrons to the GO sheet, forming electron-hole pairs. The photogenerated holes in turn result in the formation of hydroxyl and superoxide radicals, which oxidize RhB and result in the photodegraded products.

Chapter 5: Preparation of *O*-BODIPYs

5.1 Introduction

As discussed in section 1.4, the BODIPY family is one of the more versatile classes of fluorophores, brightly coloured compounds with conjugated π -electron systems which demonstrate high molar absorptivities and high fluorescence quantum yields.^{60–62} Functionalisation routes include modification of the pyrrole units, the meso-position or substitution of the fluoride ligands.^{63–65} Tahtaoui *et al.* developed a straight-forward, low-cost method for the synthesis of *O*-BODIPYs whereby the B-F bond of the parent BODIPY is activated using a Lewis acid, AlCl_3 , followed by nucleophilic substitution with the desired alcohol (Scheme 5.1).⁷⁴ They propose that the AlCl_3 activates the B-F bonds, allowing subsequent nucleophilic substitution with an alcohol.



Scheme 5.1: *O*-BODIPY synthesis and proposed mechanism by Tahtaoui *et al.*⁷⁴

O-BODIPYs have been found to possess enhanced optical properties and aqueous solubility than their “parent” *F*-BODIPY counterparts.^{65,319,320} Blázquez-Moraleja *et al.*, for example, designed *B*-spiranic *O*-BODIPY systems which featured solubility-tagging moieties (Fig. 5.1). The conformational rigidity of the *O*-BODIPY systems not only enhanced both fluorescence quantum yield and photochemical stability, but the orthogonal disposition of the *B*-chelated substituent with regards to the boradiazaindacene skeleton prevented intermolecular π -stacking aggregation, a common issue for *F*-BODIPYs in aqueous media.^{321,322}

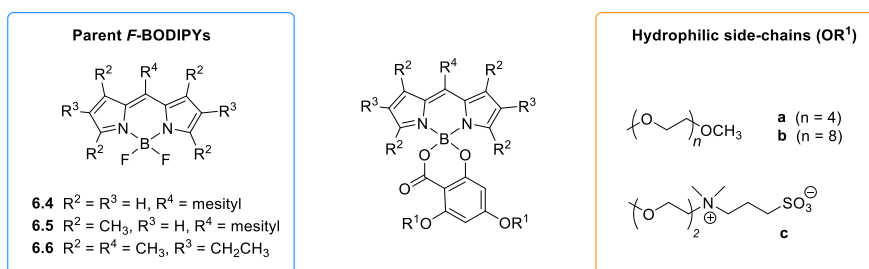


Figure 5.1: Spiranic *O*-BODIPY systems by Blázquez-Moraleja *et al.*³²¹

It was observed that in the solid-state, BODIPYs undergo fluorescence quenching, especially when tightly packed in crystalline form due to the increased π - π stacking. Zhang and co-workers used the $AlCl_3$ activation pathway to couple *F*-BODIPYs with 3,4-dihydroxybenzaldehyde to produce the respective *O*-BODIPYs which were emissive in the solid-state and also had high cell permeability, successfully sensing lysosomes in HeLa cells.³²³

Sánchez-Carnerero *et al.* designed a new method for the preparation of circularly polarised luminescence (CPL) organic molecules from achiral BODIPY chromophores.³²⁴ The “parent” BODIPY was coupled with (*R*)- and (*S*)-1,1'-bi(2-naphthol) (BINOL), respectively. Similar systems were prepared by Zhang *et al.* which also included an aggregation-induced emission (AIE) chromophore, tetraphenylethene (TPE) (Fig. 5.2).³²⁵ These compounds exhibited red-colour CPL signals *via* intramolecular energy transfer from the TPE unit to the BODIPY.

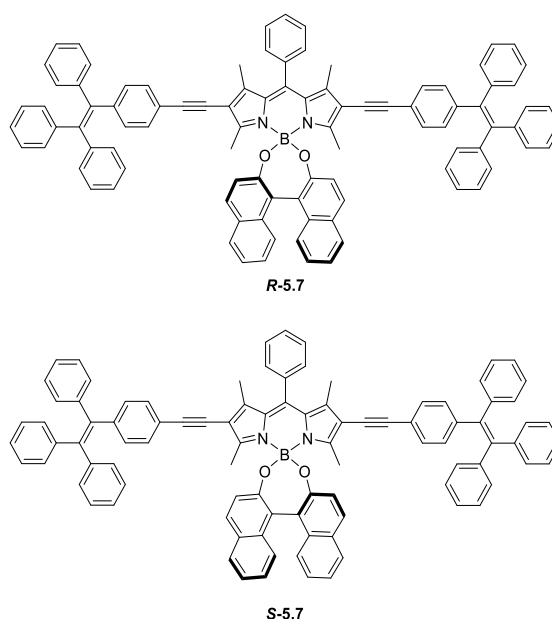


Figure 5.2: AIE-active chiral *O*-BODIPYs.

As noted in section 1.4.2, quite elaborate structures have been made possible by the facile procedure developed by Tahtaoui *et al.*, such as the porphyrin-conjugated system designed by Harvey and co-workers.^{74,75} Here, 5-(4-(hydroxymethyl)phenyl)-10,15,20-tris(4-methylphenyl)porphyrin was used as the nucleophilic alcohol reagent after activation of the BODIPY with AlCl_3 .

5.2 Objectives

The aim of this project is to prepare a series of *O*-BODIPYs which contained an aldehyde functionality. The resulting compounds will then be investigated to test if they can withstand standard tetrapyrrole condensation chemistry. Previously, all manner of compounds and chromophores have been coupled to BODIPYs, including *O*-BODIPYs, as described above. However, to-date these compounds have not been reported in the direct construction of chromophores and tetrapyrroles. Thus, the practicality of these *O*-BODIPYs as building blocks to prepare porphyrin and porphyrin derivatives immediately conjugated to fluorescent dye moieties will be determined. The respective DPM, BODIPY and porphyrin analogues are planned as initial target molecules (Fig. 5.3). If successful, asymmetric systems are also an interesting target, *i.e.*, preparation of asymmetric mono-substituted *O,F*-BODIPYs, whereby one “arm” can be used to construct the desired porphyrin system and a separate system can be built in a follow-up step.

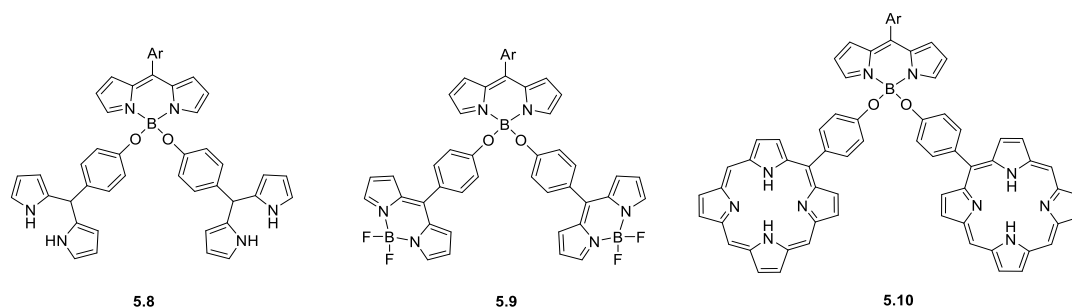


Figure 5.3: Planned target molecules following *O*-BODIPY synthesis.

5.3 Results & Discussion

5.3.1 Synthesis of initial starting materials

The starting materials chosen for initial investigations are shown below in Fig. 5.4. The bromo- and trimethylsilylacetylene-functionalities leave a wide range of synthetic routes open for further modifications once the target molecules have been achieved, as well as the free α -positions on the dipyrromethene skeleton.^{63–65} Synthesis involves a straight-forward two step-procedure, first isolating the DPM followed by complexation with $\text{BF}_3 \cdot \text{OEt}_2$.

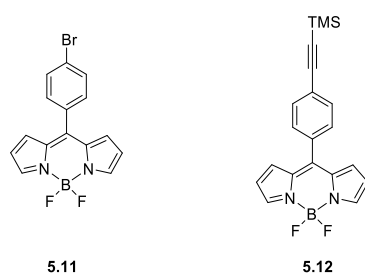
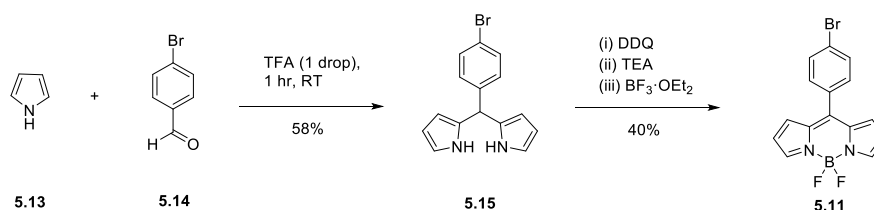


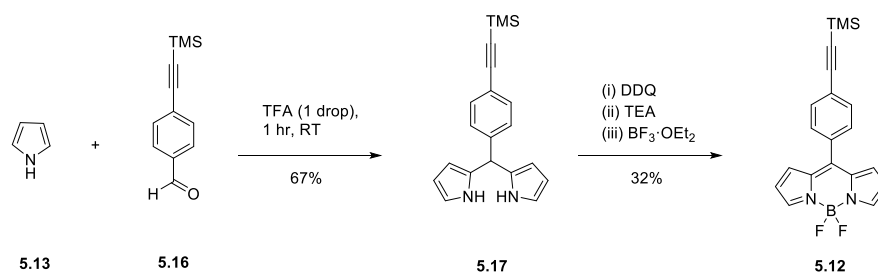
Figure 5.4: Initial starting materials.

For the synthesis of the bromo-functionalised BODIPY **5.11**, the DPM was isolated after reaction of unsubstituted pyrrole with 4-bromobenzaldehyde in the presence of TFA at RT. Compound **5.15** was collected in a 58% yield after flash column chromatography on silica gel. This was then oxidised *via* the addition of DDQ in anhydrous CHCl_3 , deprotonated by TEA, with the desired BODIPY formed following the addition of $\text{BF}_3 \cdot \text{OEt}_2$ (Scheme 5.2). Compound **5.11** was collected as a red-green crystalline solid in 40% yield after work-up and column chromatography.



Scheme 5.2: Synthesis of **5.11**.

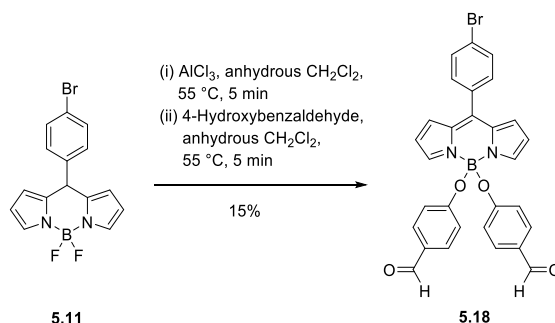
The procedure for the TMS-acetylene substituted BODIPY followed the exact same approach, using 4-[(trimethylsilyl)ethynyl]benzaldehyde in the first-step (Scheme 5.3). The desired BODIPY was collected in a yield of 32% after column chromatography on silica gel.



Scheme 5.3: Synthesis of **5.12**.

5.3.2 Synthesis of *O*-BODIPYs:

To prepare the respective *O*-BODIPYs, the procedure published by Amamoto *et al.* was employed.³²⁶ BODIPY **5.11** was dissolved in anhydrous CH₂Cl₂ and heated to 55 °C in the presence of AlCl₃ for 5 min (Scheme 5.4). A colour change of red-orange to bright pink was observed. A suspension of 4-hydroxybenzaldehyde in anhydrous CH₂Cl₂ was added and the reaction was stirred at 55 °C for a further 5 min. The reaction mixture was filtered through Al₂O₃ and then purified *via* column chromatography.



Scheme 5.4: Synthesis of **5.18**.

Multiple fractions were collected however all were of negligible yield bar a large amount of unreacted 4-hydroxybenzaldehyde. The reaction was repeated with a slightly reduced amount of aldehyde (Table 5.1, entry 2), however there were again multiple fractions and the product was not isolated. The scale of the reaction was increased to see if the compound was being formed in such a low yield that on the previous attempts it was difficult to collect. On this attempt (Table 5.1, entry 3), the crude reaction mixture was washed with water (×2) to remove residual AlCl₃ and dried over MgSO₄ instead of filtered through Al₂O₃ as on the

previous attempts it seemed as though a lot of material was getting lost at this step. Column chromatography was carried out on silica gel using neat *n*-hexanes as eluent initially, increasing polarity up to 20% EtOAc in *n*-hexanes to collect the desired compound in a yield of 15%. A recrystallisation was successful in obtaining a crystal suitable for X-ray crystallography which confirmed the structure (Fig. 5.5).

Table 5.1 – Synthesis of aldehyde-functionalised *O*-BODIPY **5.18**.

Entry	BODIPY	AlCl ₃	4-Hydroxybenzaldehyde	Yield
1	95 mg, 0.275 mmol	1.5 equiv.	5 equiv.	N/A
2	100 mg, 0.290 mmol	1.5 equiv.	4 equiv.	N/A
3	250 mg, 0.725 mmol	1.5 equiv.	4 equiv.	15%

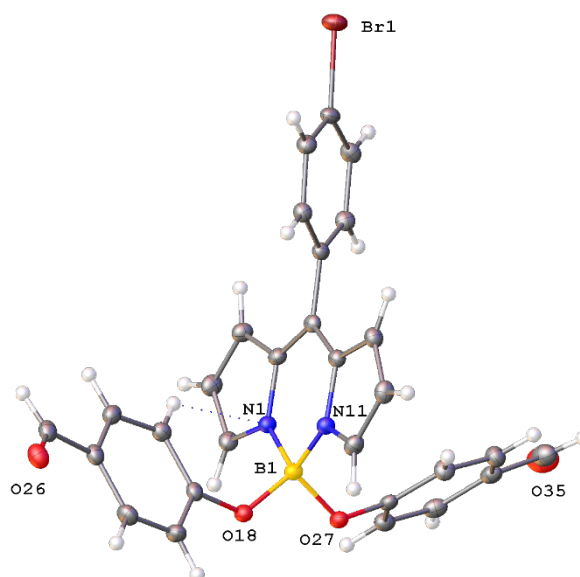
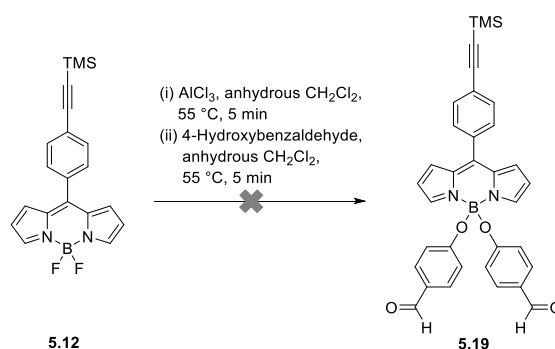


Figure 5.5: X-ray molecular structure of **5.18**, with atomic displacement shown at 50% probability.
Heteroatoms labelled only.^v

Synthesis towards the 4-[(trimethylsilyl)ethynyl]benzaldehyde-substituted *O*-BODIPY was even less successful. Following the same procedure, BODIPY **5.12** was reacted with

^v X-Ray Crystallography carried out by Dr. Brendan Twamley at TCD.

4-hydroxybenzaldehyde (Scheme 5.5). The same colour change was observed, red-orange to bright pink, after heating with AlCl_3 prior to the addition of the aldehyde. Again, multiple fractions were observed in the crude material, all of which were quite polar. Column chromatography on silica gel was carried out to purify the mixture, eluting first with *n*-hexanes and then increasing polarity to 10% EtOAc in *n*-hexanes. Even this seemed too polar and the material had to be re-purified as many fractions eluted together. The reaction was repeated on a larger scale with increased equivalents of AlCl_3 (Table 5.2, entry 2), however this again was unsuccessful. A large amount of 4-hydroxybenzaldehyde was collected from the column, and so the equivalents were reduced as per a procedure by Vicente and co-workers (Table 5.2, entry 3).³²⁷ Unfortunately, the compound was not isolated on any of the attempts.



Scheme 5.5: Attempted synthesis of **5.19**.

Table 5.2 – Attempts to synthesise the aldehyde-functionalised *O*-BODIPY **5.19**.

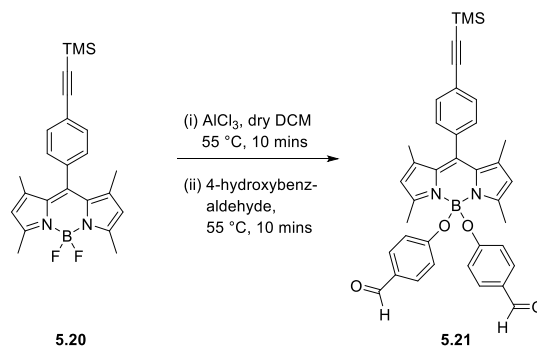
Entry	BODIPY	AlCl_3	4-Hydroxybenzaldehyde	Yield
1	170 mg, 0.434 mmol	1.5 equiv.	4 equiv.	N/A
2	250 mg, 0.638 mmol	3 equiv.	4 equiv.	N/A
3	100 mg, 0.138 mmol	1.5 equiv.	2 equiv.	N/A

At this point it was difficult to plan any forward synthetic investigations as the yield of **5.18** was quite low for potential condensation reactions which in themselves can be subject to low yields and difficult purification.²¹ As there were multiple side-products observed in both cases on every attempt, it was thought that potential reactivity at the free-alpha

positions was impacting the synthesis. There were a few alpha-substituted BODIPYs available for test reactions in the lab, and these gave much more promising results.

5.3.3 Reactions with alpha-substituted BODIPYs

Four BODIPYs were available for test reactions which had been prepared by other group members. Each of these were trialled under the same conditions as described in section 5.3.2 except that the reaction time was increased to 10 min for each step. The first was the reaction with 1,3,5,7-tetramethyl-8-[4-(trimethylsilyl)ethynylphenyl]-4,4'-difluoro-4-bora-3a,4a-diaza-*s*-indacene to prepare **5.21** (Scheme 5.6). Immediately from the crude reaction mixture it was clear that the reaction was much cleaner, with a small amount of starting material remaining and two other fractions which were assumed to be the mono- and di-substituted derivatives.



Scheme 5.6: Synthesis of **5.21**.

Purification *via* column chromatography was carried out, eluting first with neat *n*-hexanes followed by 10% EtOAc in *n*-hexanes to collect the desired compound. As this reaction was carried out on quite a small scale (50 mg, 0.119 mmol), the yield was too low to be determined. However, the ^1H NMR was as expected and overall the reaction was much more promising than that of the alpha-free derivative.

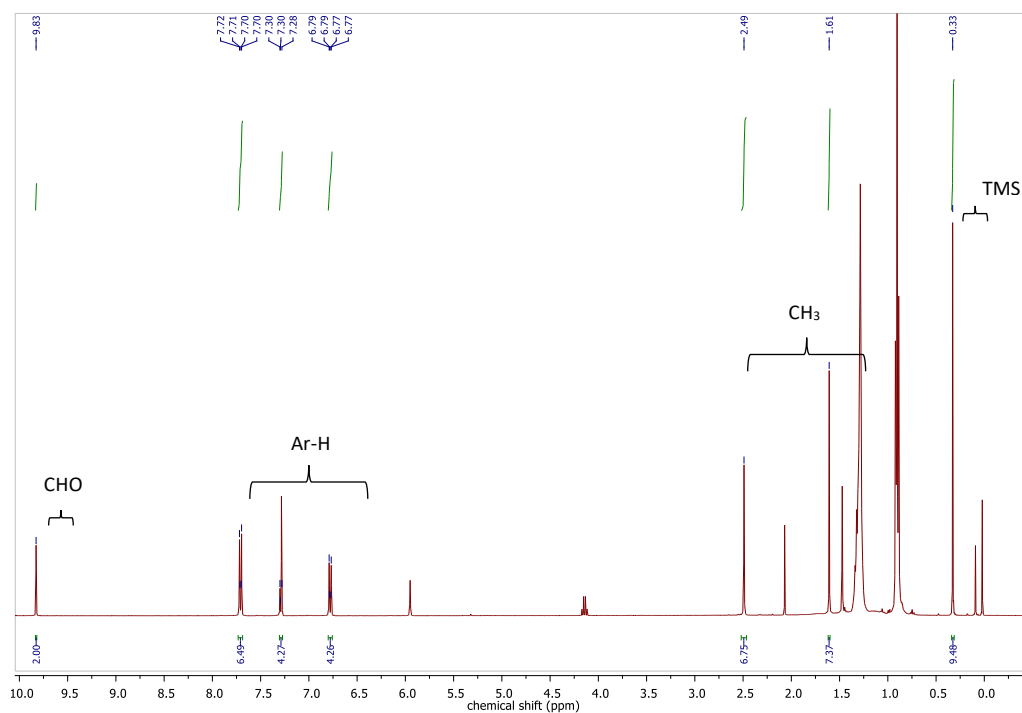
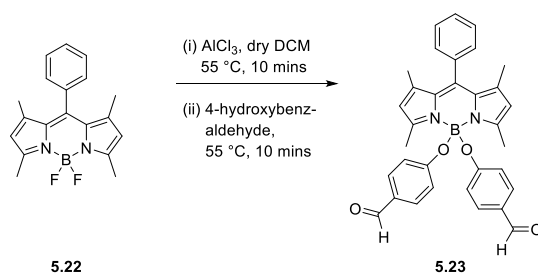


Figure 5.6: ^1H NMR of **5.21** in CDCl_3 (400 MHz, 25 $^\circ\text{C}$).

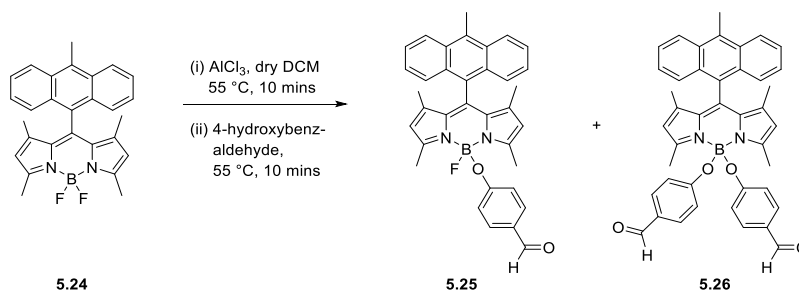
Another reaction was tested using 1,3,5,7-tetramethyl-8-phenyl-4,4'-difluoro-4-bora-3a,4a-diaza-*s*-indacene to prepare **5.23** (Scheme 5.7). The crude material contained multiple fractions, including a small amount of unreacted starting material. Purification *via* column chromatography was unsuccessful in separating out the many side-products. The starting material was removed, however, and so purification was repeated to try to isolate the product. The only compound that could be identified was unreacted 4-hydroxybenzaldehyde. As the previous reaction had much less tedious purification, this derivative was not brought forward for further optimisations.



Scheme 5.7: Synthesis of **5.23**.

The third BODIPY tested was one of the BODIPY-anthracene dyads prepared by Callaghan *et al.* for application in PDT (Scheme 5.8).⁷⁰ The crude reaction mixture was purified *via* column chromatography – two fractions were collected, the mono-substituted derivative

5.25 (Fig. 5.7) and the di-substituted product **5.26** (Fig. 5.8) in 25% and 26% yields, respectively.



Scheme 5.8: Synthesis of **5.25** and **5.26**.

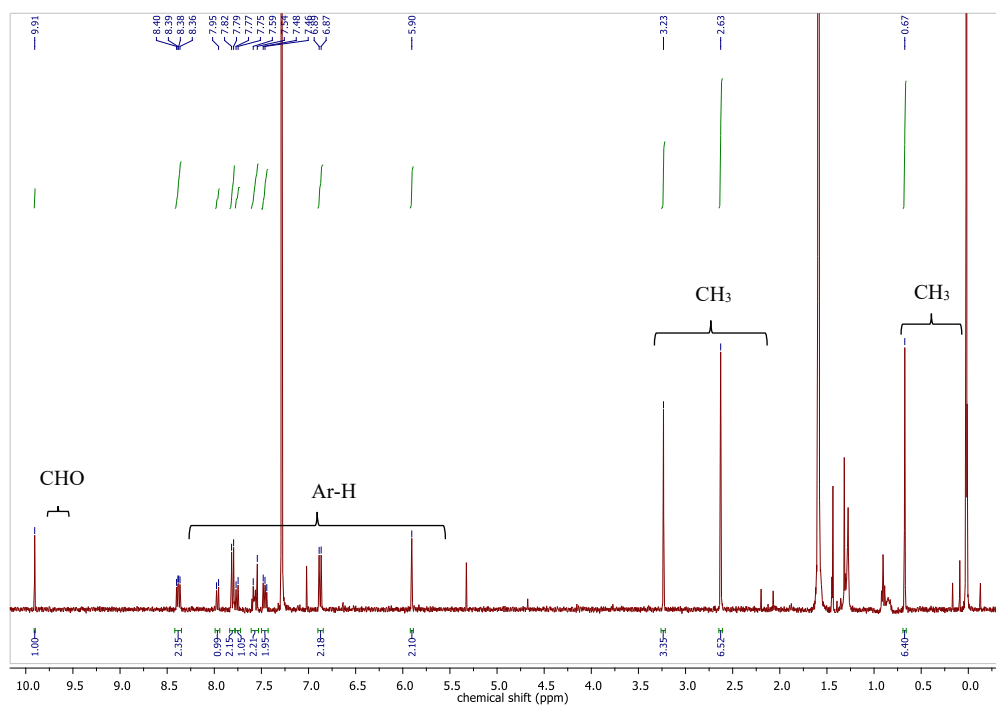


Figure 5.7: ^1H NMR of **5.25** in CDCl_3 (400 MHz, 25 °C).

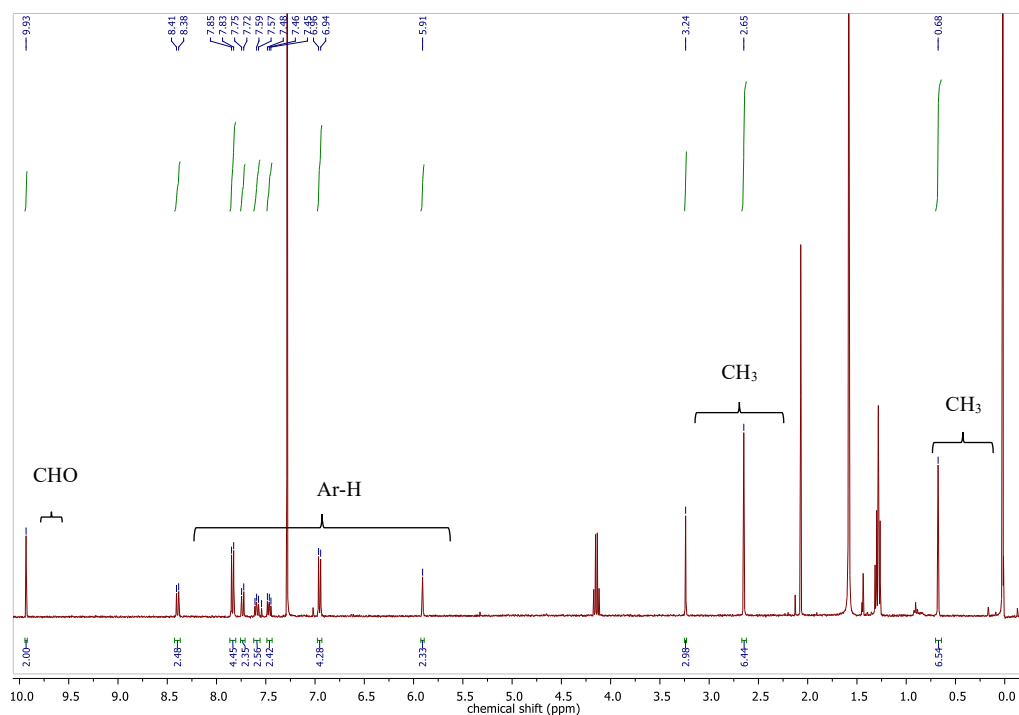
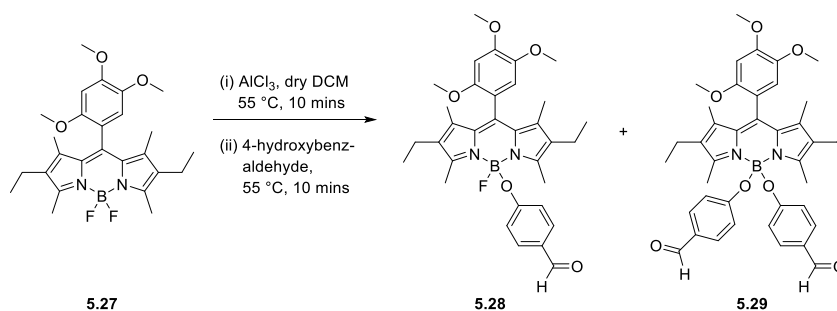


Figure 5.8: ^1H NMR of **5.26** in CDCl_3 (400 mHz, 25 °C).

The fourth trial reaction was with 2,4-diethyl-1,3,5,7-tetramethyl-8-(2,4,5-trimethoxy)phenyl-4,4'-difluoro-4-bora-3a,4a-diaza-*s*-indacene to prepare **5.29** (Scheme 5.9). Purification *via* column chromatography eluting first with neat *n*-hexanes, increasing up to 20% EtOAc in *n*-hexanes isolated both the mono-substituted **5.28** and di-substituted **5.29** derivatives in 7% and 29% yields, respectively.

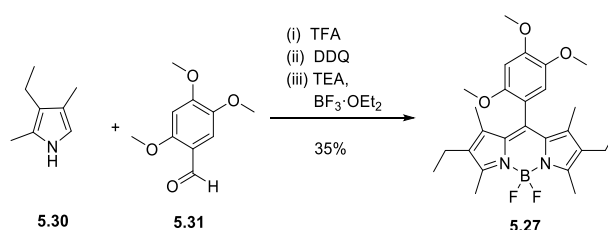


Scheme 5.9: Synthesis of **5.28** and **5.29**.

From these trial reactions, **5.20** and **5.27** were chosen to move forward, the former due to the TMS-acetylene group providing a route for further functionalisation once the target compounds have been achieved, and the latter due to the ease of synthesis of the starting material and the apparent preference for formation of the disubstituted product which would allow more straight-forward investigations due to its more symmetrical nature.

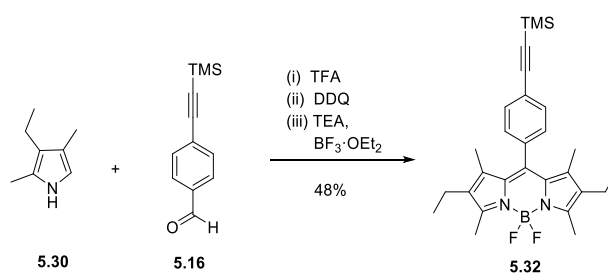
5.3.4 Optimization of the O-BODIPY Synthesis

The synthesis of **5.20** and **5.27** was very straight-forward, even more-so than that of the alpha-free BODIPYs as in this case a one-pot reaction leads directly to the desired compound starting from the respective BODIPY. For the trimethoxy-derivative **5.27**, 3-ethyl-2,4-dimethylpyrrole was reacted with 2,4,5-trimethoxybenzaldehyde in anhydrous CH_2Cl_2 at RT in the presence of TFA overnight. DDQ was then added to oxidise the DPM formed *in situ*, followed by deprotonation *via* TEA and complexation with $\text{BF}_3 \cdot \text{OEt}_2$. Work-up and column chromatography led to the isolation of the desired BODIPY **5.27** as a bright red-green crystalline solid in a yield of 35%.



Scheme 5.10: Synthesis of **5.27**.

5.32 was synthesised in the same manner and there was greater yield as compared to **5.20**, and so this compound was brought forward instead. The same procedure was used as described above using **5.30**, collecting the desired BODIPY in a yield of 48% (Scheme 5.11).



Scheme 5.11: Synthesis of **5.32**.

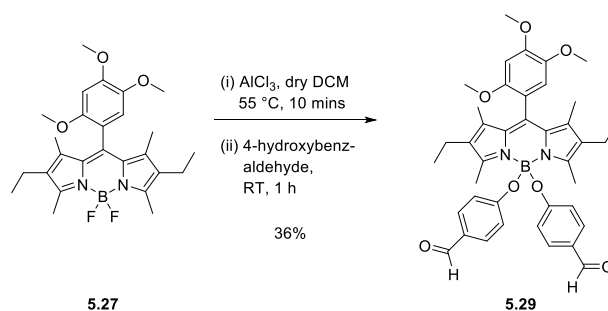
In order to have a sufficient amount of the BODIPY-aldehydes to move forward with an investigation into standard porphyrin condensation chemistry, some optimisations were required. Previously, the procedure involved heating both the BODIPY starting material and AlCl_3 in anhydrous CH_2Cl_2 to 55 °C for 10 min, followed by addition of the aldehyde in CH_2Cl_2 with further heating for 10 min (Scheme 5.9). After numerous attempts, it was difficult to optimise the yield to above the initial result of 29%, and even at that it was not

always reproducible. The initial reaction procedure published by Tahtaoui *et al.* described heating to reflux in the first step, and then cooling of the reaction mixture to RT before the addition of the respective aldehyde.⁷⁴ Thus, **5.27** was dissolved in anhydrous CH₂Cl₂, AlCl₃ (3 equiv.) was added and the mixture was stirred at 55 °C for 10 min and the reaction mixture was then cooled to RT. 4-Hydroxybenzaldehyde (5 equiv.) was added and the reaction mixture was stirred for 30 min at RT. The crude material was washed with water (×2) and dried over MgSO₄. Purification *via* column chromatography led to the isolation of **5.29** in 18% yield (Table 5.3, entry 1). The reaction time of the second step was increased to 60 min, however a reduction in the yield to 13% was observed (entry 2). The equivalents of AlCl₃ were halved, and a yield of 29% was obtained (entry 3). A large amount of unreacted 4-hydroxybenzaldehyde was observed during purification in all cases, and so the equivalents were reduced (entry 4). There was not much difference to the yield in this case and so on the next attempt the reaction was followed *via* TLC leading to an increase in the time of the second step to 60 min (entry 5). Purification isolated **5.29** in a yield of 36%, and these conditions were used going forward (Scheme 5.12). The mono-substituted compound was only observed in minute amounts during purification and was never isolated in any determinable yield under any of these conditions.

Table 5.3 – Optimisations for the synthesis of **5.29**.

Entry	AlCl ₃ (equiv.)	Aldehyde (equiv.)	Stirring at RT	Yield (%) disubstituted	Yield (%) monosubstituted
1	3	5	30	18	-
2	3	5	60	13	-
3	1.5	5	30	29	-
4	1.5	3	30	30	-
5	1.5	3	60	36	-

“-” indicates yield was too low to be determined.



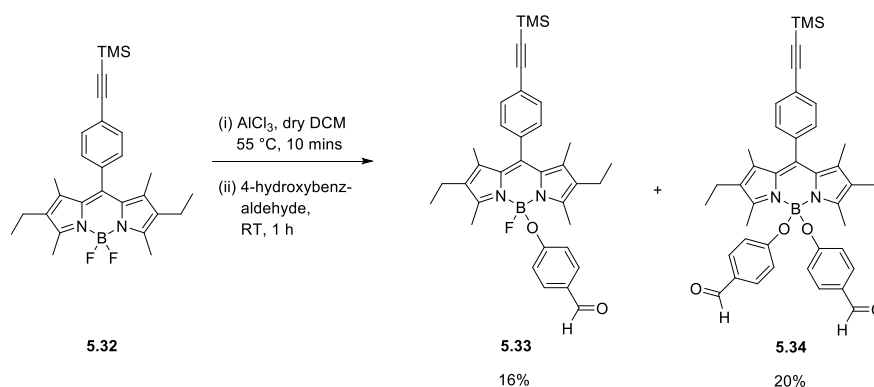
Scheme 5.12: Optimised reaction conditions for the synthesis of **5.29**.

For the TMS-acetylene derivative, optimisations were ongoing in parallel but followed a similar pattern (Table 5.4). Initially, AlCl₃ (3 equiv.), 4-hydroxybenzaldehyde (5 equiv.) and 60 min stirring at RT gave **5.34** in a yield of 14% (entry 1). An increase in the reaction time only resulted in a minor increase to the yield (entry 2). The equivalents of both the AlCl₃ and aldehyde were reduced (entry 3), leading to a yield of 20% for the disubstituted derivative, and 16% for the monosubstituted derivative. Further increase in stirring time to 90 min did not result in any beneficial effect to the yield (entry 4), and so the conditions of entry 3 was used going forward (Scheme 5.13).

Table 5.4 – Optimisations for the synthesis of **5.32**.

Entry	AlCl ₃ (equiv.)	Aldehyde (equiv.)	Stirring at RT	Yield (%) disubstituted	Yield (%) monosubstituted
1	3	5	30	14	-
2	3	5	60	16	-
3	1.5	3	60	20	16
4	1.5	5	90	17	6

“-” indicates yield was too low to be determined.



Scheme 5.13: Synthesis of **5.33** and **5.34**.

5.3.5 One-pot BODIPY Condensation Reaction

The same procedure used for the preparation of the BODIPYs themselves was trialled in the synthesis of BODIPY moieties using the aldehyde functionalities of the *O*-BODIPYs. While optimisations for the *O*-BODIPYs were ongoing, it was thought that purification of the target BODIPYs might be more straight-forward than the aldehyde groups due to their polarity. Thus, initially, a crude mixture of **5.28** and **5.29** was used; this

was dissolved in anhydrous CH_2Cl_2 and reacted with 2,4-dimethylpyrrole in the presence of TFA overnight. This was followed by oxidation by DDQ, deprotonation with TEA, and complexation with $\text{BF}_3 \cdot \text{OEt}_2$. Work-up and purification *via* column chromatography on silica gel eluted two fractions. NMR analysis of the first fraction suggests that the starting material was in fact deborylated and subsequently reborylated by BF_3 (Fig. 5.9). The entire benzaldehyde moiety is no longer visible, with just the 2 protons of the trimethoxy group present in the aromatic region (Scheme 5.14).

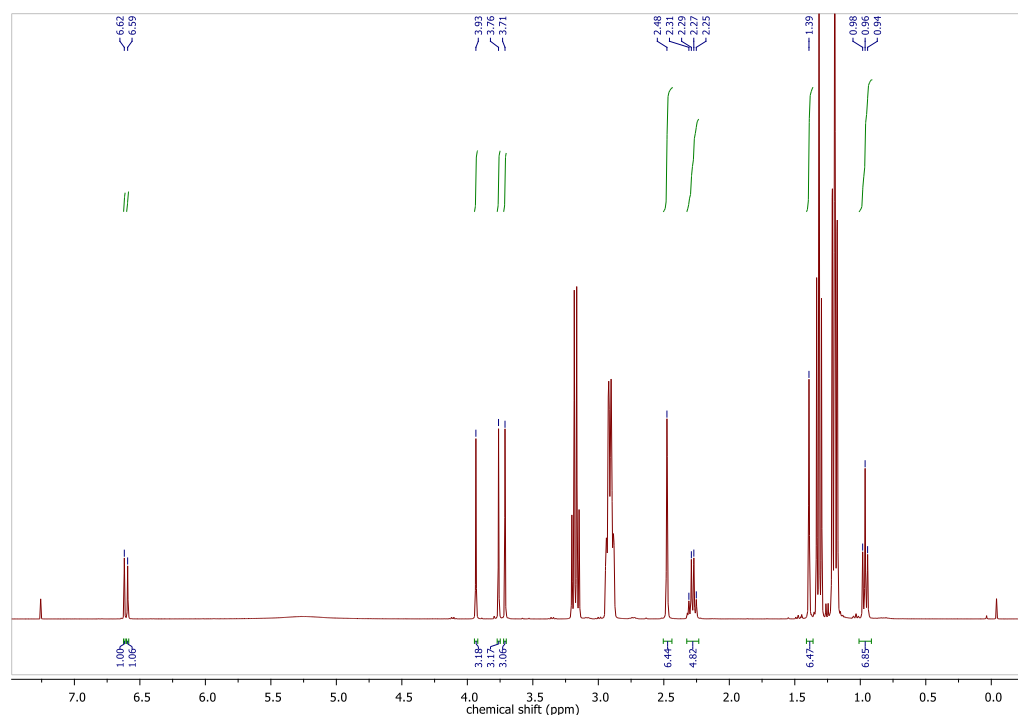
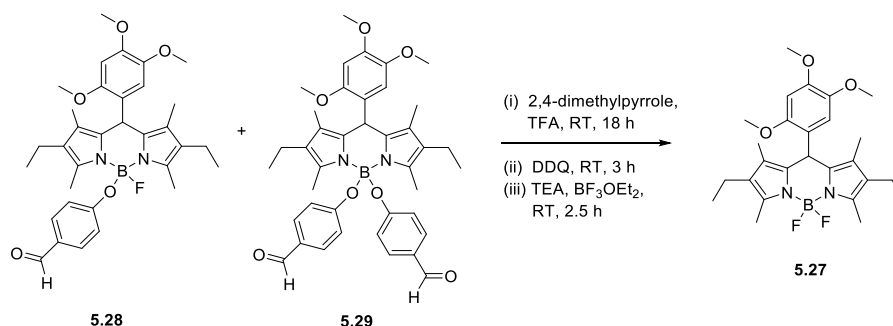


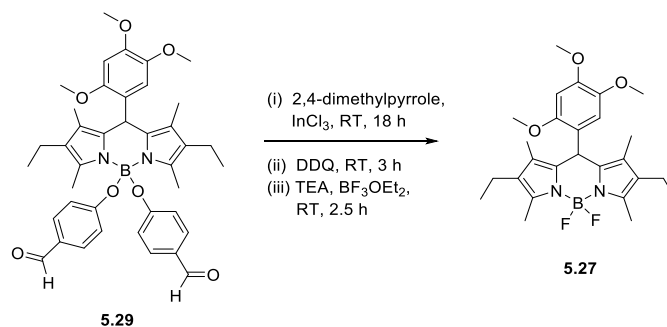
Figure 5.9: ^1H NMR of **5.27** in CDCl_3 (400 MHz, 25 °C).



Scheme 5.14: Attempted BODIPY synthesis using **5.28** and **5.29**.

The second fraction was a quite a mix of compounds, however nothing was observed in the aromatic region and therefore the desired compound was most likely not formed at all. It was assumed that TFA was too harsh an acid catalyst for the B-O bond, and so the reaction was repeated using InCl_3 instead.

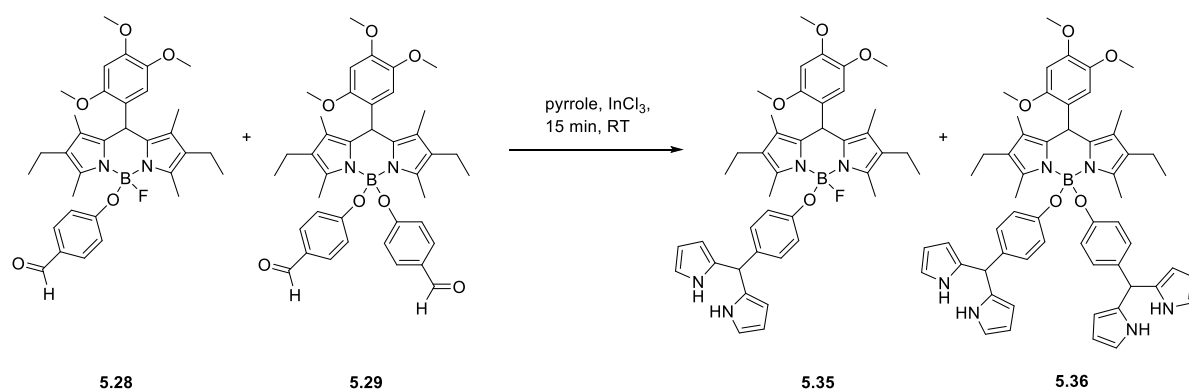
The disubstituted derivative **5.29** was dissolved in anhydrous CH_2Cl_2 and reacted with 3-ethyl-2,4-dimethylpyrrole in the presence of InCl_3 . The reaction was stirred overnight and then the procedure followed the same steps as before: (i) DDQ; (ii) TEA; (iii) $\text{BF}_3 \cdot \text{OEt}_2$. Work-up and purification *via* column chromatography isolated the same compound **5.27** as described before. Thus, it was determined that it was in fact the $\text{BF}_3 \cdot \text{OEt}_2$ that was the issue, as the B-F bond was much stronger than the B-O bond and therefore displacement of the *O*-BODIPY functionality readily occurred over the course of the reaction (Scheme 5.15).



Scheme 5.15: Attempted BODIPY synthesis using **5.29**.

5.3.6 DPM Condensation Reaction

For a test reaction, a crude mixture of **5.28** and **5.29** was dissolved in unsubstituted pyrrole and degassed with argon, as per the procedure by Laha *et al.*²⁷ The reaction mixture was stirred for 15 min at RT, followed by work-up which included washing with NaOH (1 M) and water (Scheme 5.16). The crude material was extracted into CH₂Cl₂ and dried over MgSO₄, followed by purification *via* column chromatography on silica gel. The material was very polar, and the solvent was increased from 10% EtOAc in *n*-hexanes to 50% EtOAc in *n*-hexanes. The two fractions collected were found to be mixtures of compounds.



Scheme 5.16: Attempted DPM synthesis using a crude mixture of **5.28** and **5.29**.

TLC analysis of the first fraction indicated DPM formation after staining in a bromine chamber, and further purification *via* column chromatography was carried out using 2% CH₃OH in CH₂Cl₂ as eluent. ¹⁹F NMR indicated the presence of one fluorine atom present, suggesting the formation of the mono-DPM **5.35**. There was too little of the material to continue characterization. Purification of the second more polar fraction was carried out on silica gel using the same solvent system. While still impure, there were signals in the ¹H NMR spectrum that suggested DPM formation, the ¹¹B spectrum revealed a singlet (Fig. 5.10), indicating the disubstituted product **5.36**, but overall there was too little of the material to be sure. HRMS analysis identified **5.36** at *m/z* = 906.4701 (calcd. 906.4640).

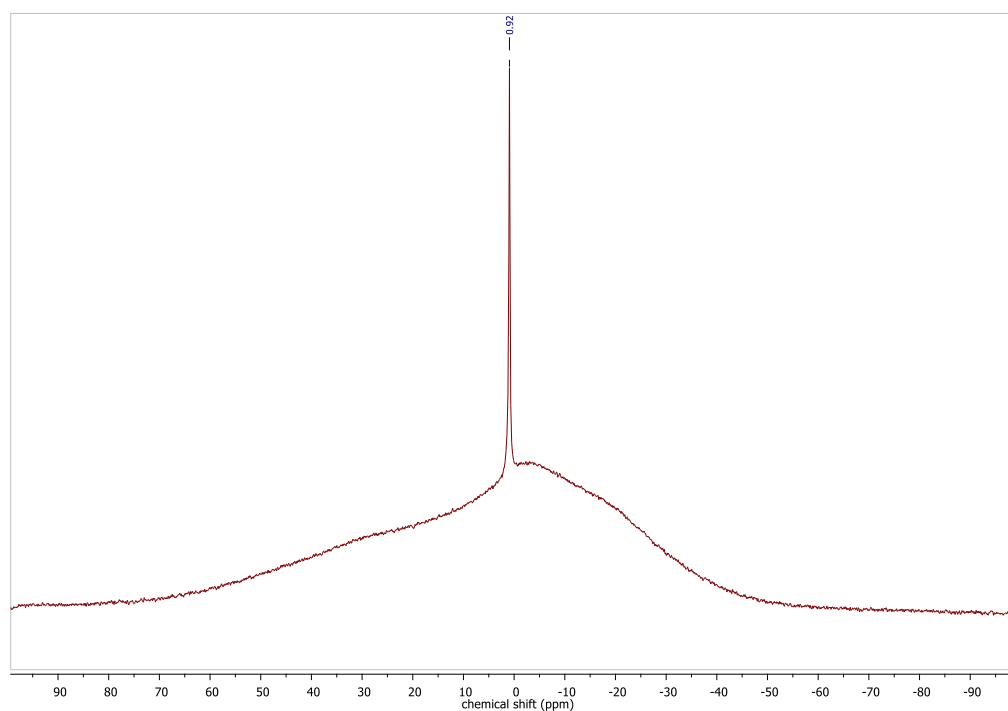
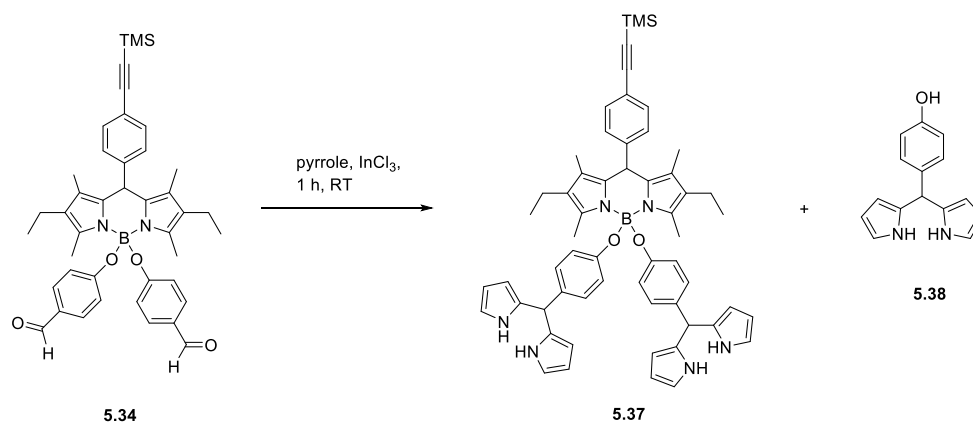


Figure 5.10: ^{11}B NMR of **5.36** in CDCl_3 (600 MHz, 25 °C).

In parallel, investigations with the TMS-acetylene derivative **5.34** were ongoing. **5.34** was dissolved in 40 equiv. of unsubstituted pyrrole and stirred at RT in the presence of InCl_3 (Scheme 5.17). TLC analysis indicated DPM formation after staining in a bromine chamber, and so after 1 h the reaction mixture was directly purified on silica gel without any other work-up procedures to prevent loss of material due to the small scale (0.117 mmol). Excess pyrrole was removed *via* elution with neat *n*-hexanes, and the polarity was increased to 5% EtOAc in *n*-hexanes to remove the starting material. The final fraction was removed using 10% EtOAc in *n*-hexanes, however this was found to be a mixture of two compounds, both of which stained pink in a bromine chamber indicating the presence of two DPMs. Another column was carried out to separate the two fractions, one of which appears to be a hydroxyphenyl-DPM **5.38** (Fig. 5.12) and the second the target DPM **5.37** (Fig. 5.13).



Scheme 5.17: Attempted DPM synthesis using **5.34**.

This procedure was then used for the trimethoxy-*O*-BODIPY **5.29**. Purification *via* column chromatography was carried out on silica gel eluting with 10% EtOAc in *n*-hexanes to collect the hydroxyphenyl-DPM first, followed by the target DPM **5.36** at 50% EtOAc in *n*-hexanes. This was confirmed by HRMS with the compound found at $m/z = 669.3702$ (calcd. 695.3753) (Fig. 5.13).

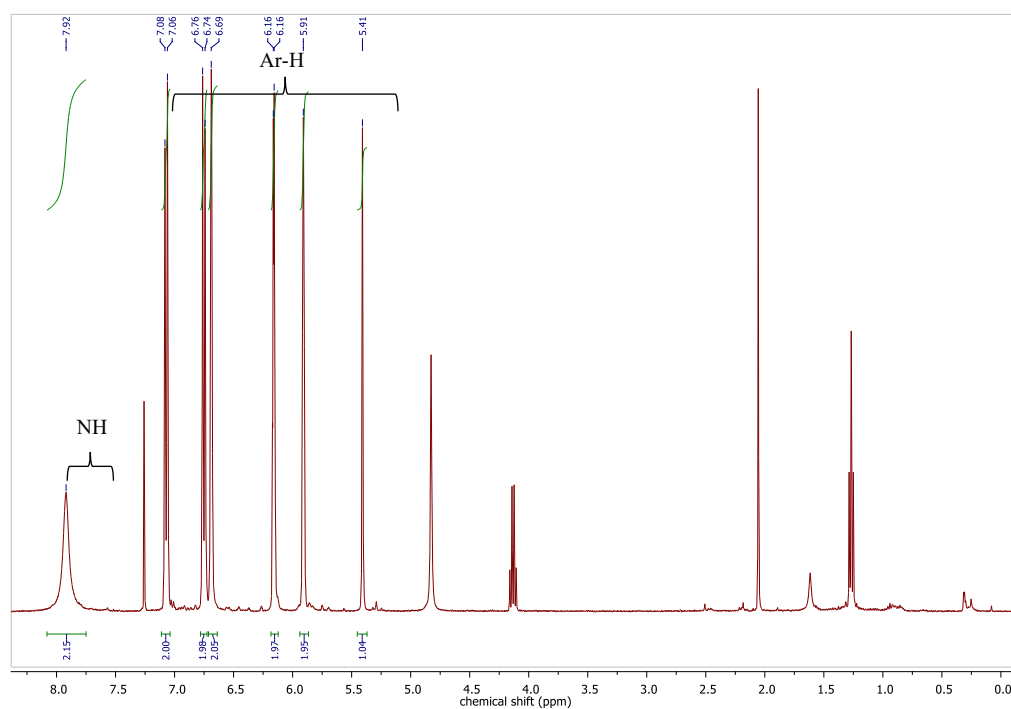


Figure 5.11: ^1H NMR spectrum of **5.38** in CDCl_3 (400 MHz, 25 $^\circ\text{C}$).

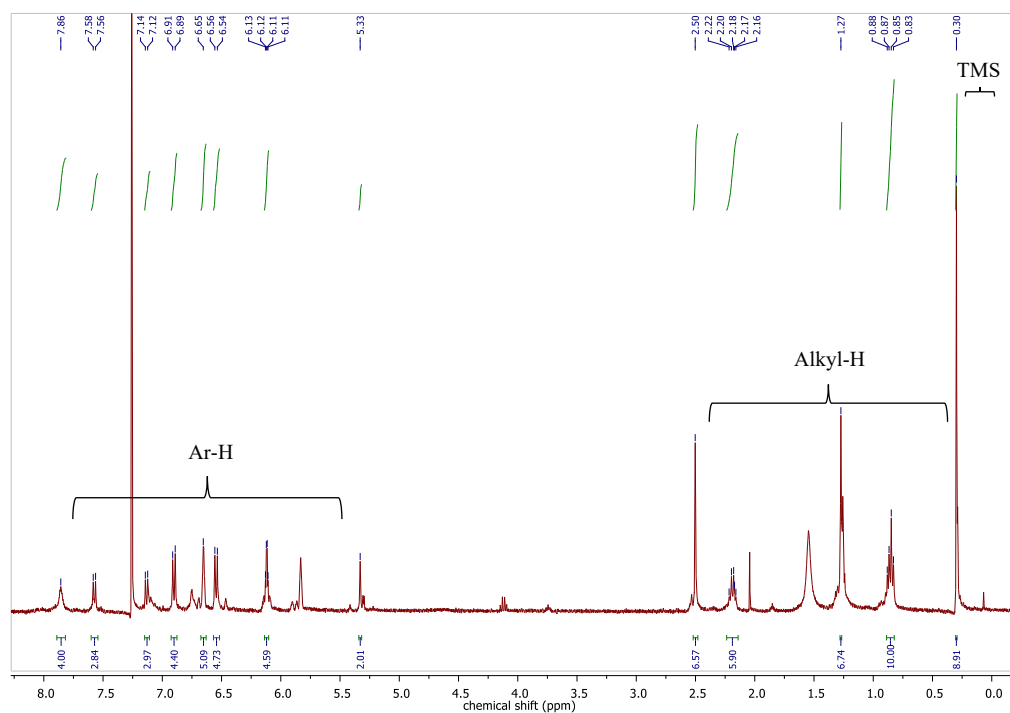


Figure 5.12: ¹H NMR spectrum of **5.37** in CDCl₃ (400 MHz, 25 °C).

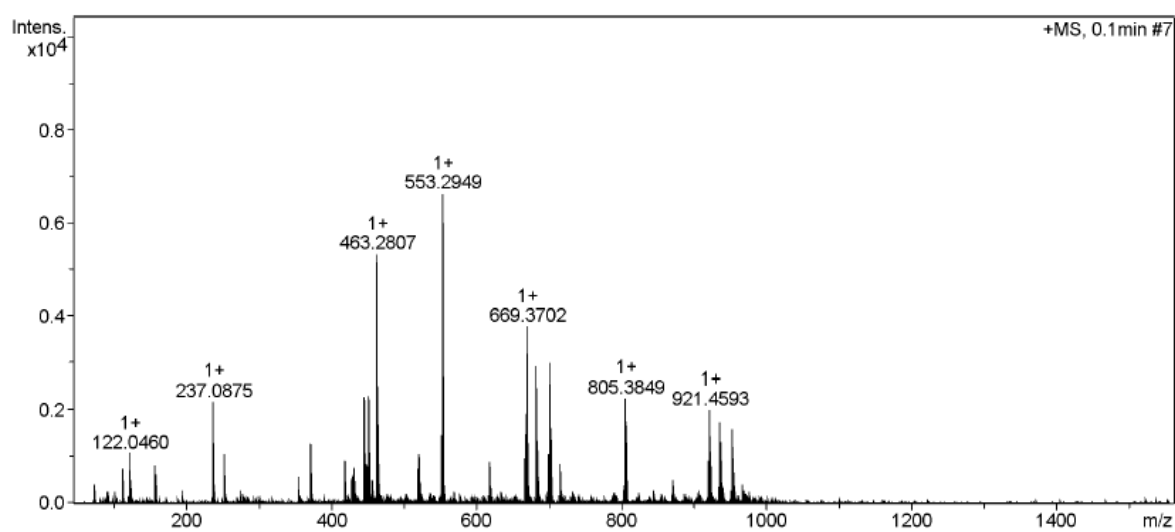
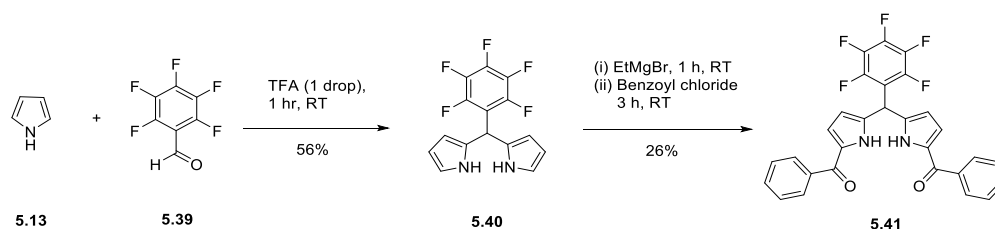


Figure 5.13: HRMS spectrum of the DPM condensation reaction depicted in Scheme 5.16, with the mono-substituted derivative **5.36** found at 669.3702.

5.3.5 Porphyrin Condensation Reaction:

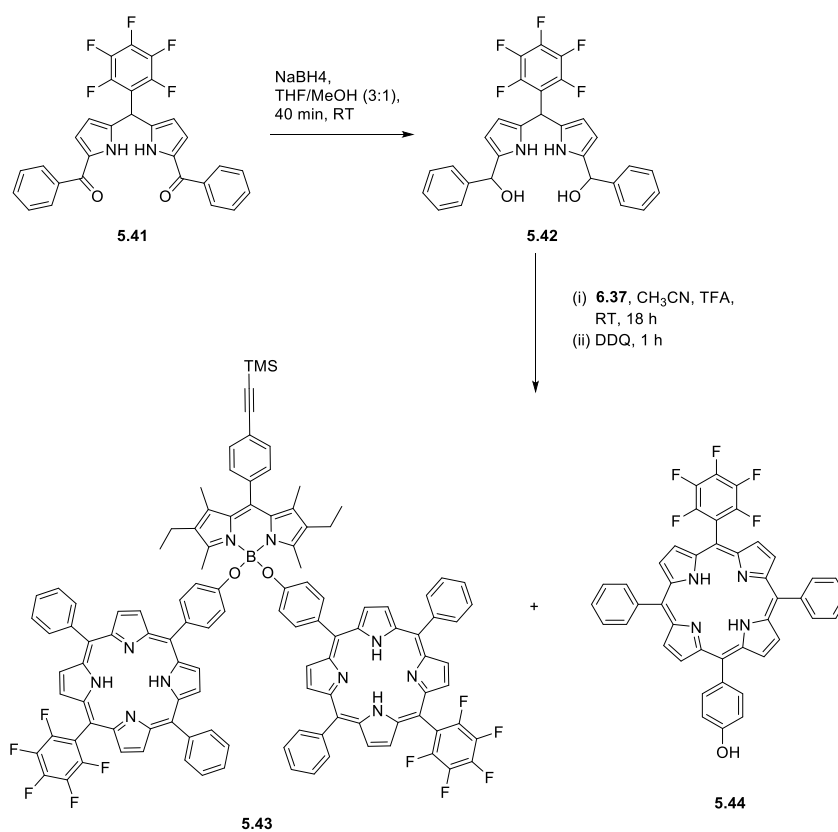
Purification of **5.37** tended to be quite tedious, requiring very slow separation *via* chromatography and even then, a small amount of the suspected side-product, **5.38**, tended to elute with the product. Thus, to prevent any further loss of material as it was difficult to fully remove all of the compound from the silica, a test condensation reaction was attempted with this slight mix of products. DPM **5.41** was chosen for the condensation reaction with **5.37**. Due to its symmetry only one porphyrin product is expected if the reaction with **5.37** is successful, self-coupling of **5.41** is prevented due to the two aldehyde functionalities, and the pentafluorophenyl-moiety is hoped to aid in the polarity of the potential product, aiding purification. This DPM was readily synthesised as per literature procedures,^{vi} starting with the synthesis of 5-(pentafluorophenyl)dipyrromethane **5.40** (Scheme 5.18).^{328–330}



Scheme 5.18: Synthesis of **5.41**.

5.41 was then reduced to the corresponding dipyrromethanediol immediately before use in the condensation reaction with **5.37**. The reaction was carried out using equal equivalents of **5.37** and **5.42**, following the procedures previously described (Scheme 5.19). Purification *via* column chromatography isolated two fractions, one of which was porphyrin expected after reaction with the minor side-product **5.44** (Fig. 5.14) and another which was suspected to be the desired compound. However, there was so little of the material that nothing could be determined from the ¹H NMR, and the compound was not identified *via* HRMS.

^{vi} Synthesised by E. Sitte at TCD.



Scheme 5.19: Attempted synthesis of **5.43**.

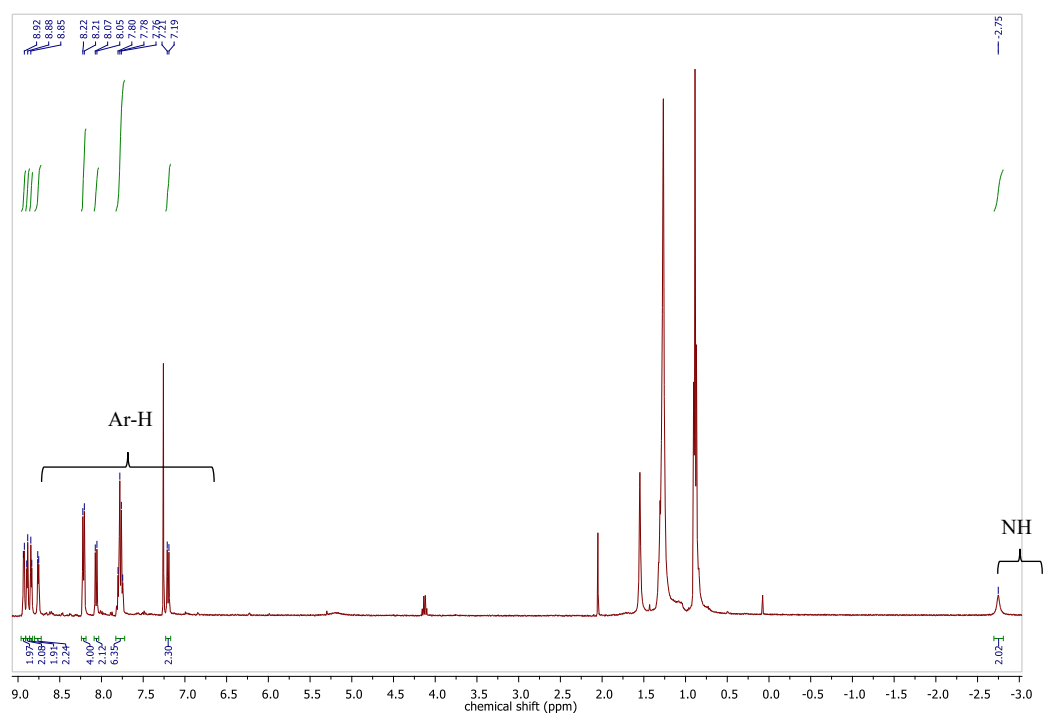
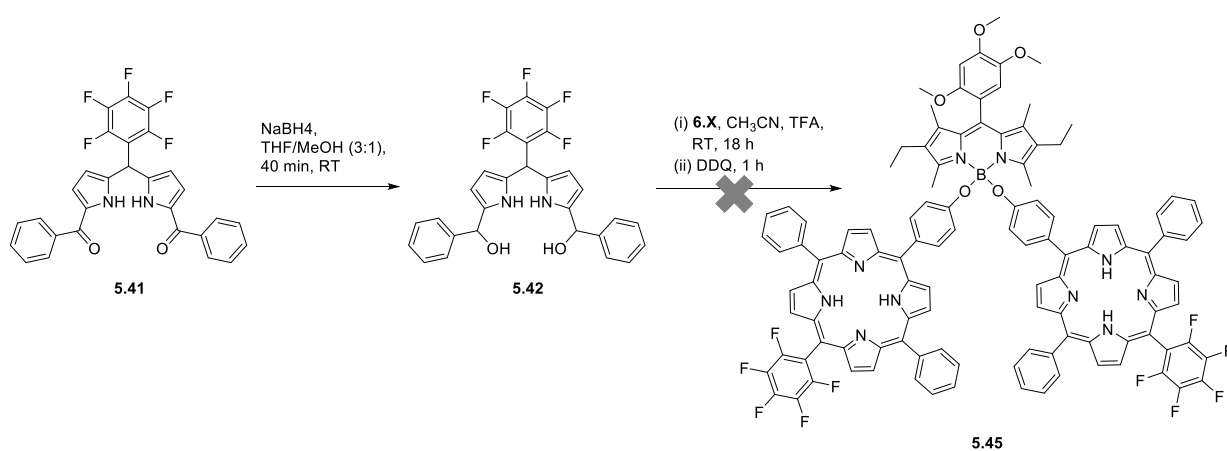


Figure 5.14: ¹H NMR spectrum of **5.44** in CDCl_3 (400 MHz, 25 °C).

Purification of **5.36** was much more successful than **5.37**, and so there was a pure sample for a test reaction with **5.42**. The same procedure was followed (Scheme 5.20) and after work-up TLC analysis indicated a small amount of starting material remaining as well as another major fraction on the baseline. The first fraction collected appeared to be the starting BODIPY **5.27**, indicating that through the course of the reaction the B-O bonds had been cleaved. There was also a broad singlet at 10.39 ppm for 1 proton, possibly a B-OH bond was formed after cleavage but there was so little of the material further follow-up was difficult (Fig. 5.15). The solvent polarity was increased up to 60% EtOAc in *n*-hexanes, but the rest of the material could not be removed from the silica.



Scheme 5.20: Attempted synthesis of **5.45**.

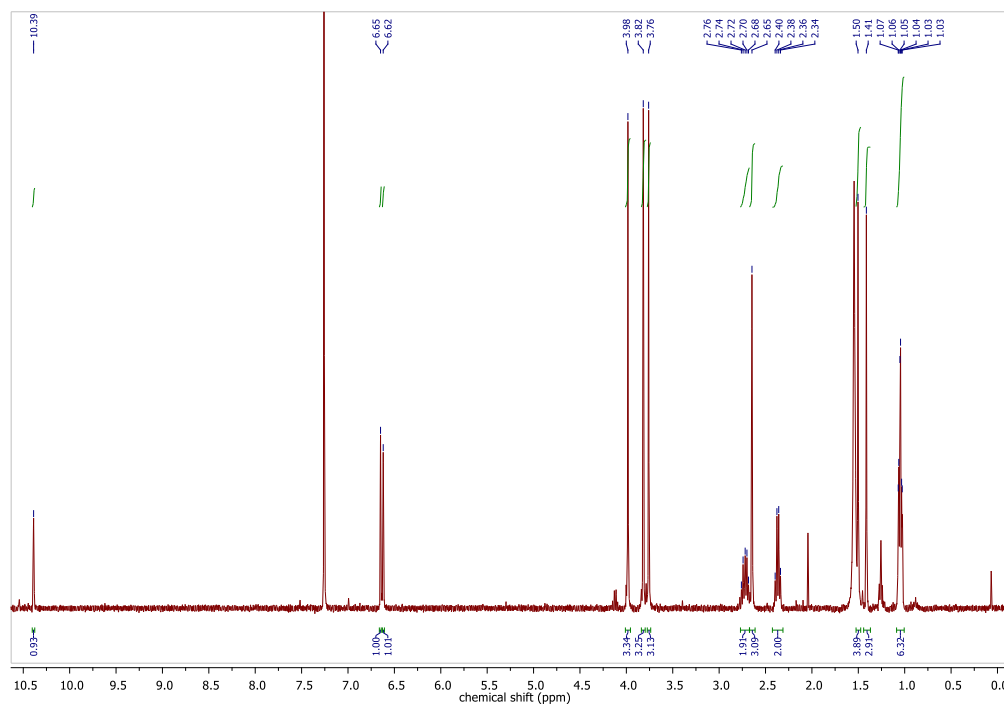


Figure 5.15: ^1H NMR spectrum of **5.27** in CDCl_3 (400 MHz, 25 °C).

5.4 Conclusions and Future Work

It was unfortunate that this project was under such intense time-pressures and severely impacted by the COVID-19 pandemic, as although the respective porphyrins were not isolated before submission of this thesis, only a couple of test reactions were able to be completed and conditions could not be optimised. There is potential for these syntheses to be successful, and given the time there are many steps that could be taken to ensure isolation of the desired products. The reactions described were hindered by tedious purification of in general small amounts of material which limited in-depth follow-up as porphyrin condensation reactions tend to be low yielding.²¹ The reactions to synthesise **5.36** and **5.37** were carried out on a maximum scale of 0.266 mmol for the reaction towards **5.36**, which was achieved in a yield of 13%. This was partly due to trialling of the reaction conditions, but also due to the limited amount of material available due to the time constraints preventing larger batch-syntheses. Going forward, these reactions could be easily up-scaled once the starting material is available in sufficient quantities, and this would leave significant scope for thorough optimisation of the conditions towards **5.43** and **5.45**. As the B-O bonds seem to have been cleaved in the reaction towards **5.45**, InCl₃ could be used as a comparison. Both **5.43** and **5.45** were difficult to remove from the silica gel, and solid phases such as molecular sieves in size-exclusion chromatography could be much more efficient. There is certainly much that could be done to optimise these reactions to conclusively determine the viability of these compounds as standard “porphyrin building blocks”.

However, while the porphyrins were not achieved, significant success was seen in the synthesis of the respective DPMs. Once the correct conditions were found, the synthesis was actually quite straight-forward and as mentioned above, could be easily optimised and up-scaled given the time. A major hindrance to this project overall was the isolation of the aldehydes **5.29** and **5.34**. Now that these syntheses have been optimised and give reliable reproducible yields, there should not be as much of a backlog in the preparation of starting materials moving forward.

One project that is currently ongoing is the application of the BAD-derivatives **5.25** and **5.26**. As the parent is a known ¹O₂ producer and its photosensitising ability has been demonstrated, this is an interesting target for exploratory reactions in follow-up to this project. The effects on the ¹O₂-producing capabilities upon transformation to the *O*-BODIPY will be investigated, and the mono-substituted derivative leaves open the

possibility for more interesting asymmetric systems with various chromophoric units attached.

In conclusion, the synthesis of *O*-BODIPYs *via* activation by AlCl_3 and subsequent reaction with 4-hydroxybenzaldehyde was successful in achieving molecules featuring an aldehyde functionality. The aim of this project was to investigate whether or not these *O*-BODIPYs could tolerate standard “tetrapyrrole” condensation reaction conditions, and in the case of transformation to the respective DPM, this was successful. Using the aldehyde moiety to synthesize a BODIPY was unsuccessful and is most likely not possible under any standard conditions due to the cleaving of the B-O bond upon treatment with $\text{BF}_3 \cdot \text{OEt}_2$ for the more favourable B-F bond. However, given the success seen with the DPM synthesis, it is quite likely that with a few optimisations isolation of the respective porphyrins is possible. This project is continuing within the Senge group, as it unfortunately could not be finished within the given deadline.

6 Experimental

6.1 General Methods and Instrumentation

Deuteroporphyrin IX dimethyl ester was purchased from InoChem Ltd. and used as received. All other reagents were obtained from commercial sources and used as received, with the exception of pyrrole which was filtered through a plug of silica prior to use. All air and/or water-sensitive materials were handled using standard high vac. procedures. Anhydrous THF was obtained *via* passing through alumina under N_{2(g)} in a solvent purification system and then further dried over activated molecular sieves. Reactions at elevated temperatures were carried out using a hot plate with an oil bath as the heat source. Flash chromatography was carried out using either silica gel Florisil (200 mesh; Aldrich) or Al₂O₃ (neutral, particle size 0.05–0.15 mm; Aldrich), as indicated for each synthesis. In some incidences, as indicated for the respective syntheses, Al₂O₃ was treated with the addition of water (6% w/v) prior to use in order to obtain Brockmann activity grade III. Analytical thin-layer chromatography was carried out either on precoated 60 F254 silica plates (0.2 mm thick, 20 × 20 cm) or precoated 60 F254 (neutral) Al₂O₃ plates and visualised by UV irradiation on a Shimadadzu Multispec-1501. Bruker DPX 400 and Agilent 400 were used to obtain ¹H (400.13 MHz), ¹³C{H} (100.61 MHz), ¹⁹F (376.60 MHz) and ¹¹B (128.40 MHz) NMR spectra and a Bruker AV 600 was employed for ¹H (600.13 MHz) and ¹³C{H} (150.90 MHz) NMR spectra. NMR spectroscopy was carried out at room temperature using deuterated solvent, as indicated for each synthesis. All melting points are uncorrected and determined with a Digital Stuart SMP10 melting point apparatus. UV/Vis spectra were recorded in solutions using a Specord 250 spectrophotometer from Analytik Jena (1 cm path length quartz cell). Mass spectrometry analysis (HRMS) was performed with a Q-ToF Premier Waters MALDI quadrupole time-of-flight (Q-TOF) mass spectrometer equipped with Z-spray electrospray ionization (ESI) and matrix assisted laser desorption ionisation (MALDI) sources in positive mode with *trans*-2-[3-(4-*tert*-butylphenyl)-2-methyl-2-propenylidene]malononitrile as the matrix. For ¹O₂ measurements, the photo-irradiation of the samples were performed in quartz cuvettes (2×1×1 cm) under irradiation *via* a polychromatic light source (Philips, 15V-150W lamp), equipped with a 400 nm cut-off filter (Schott GG 400) and a 532 nm diode pumped solid state green laser system (CW532-04, average intensity of 10 mW·cm⁻²). The temperature of the sample was maintained at 18 °C using a Peltier element (Cary Peltier 1×1 Cell

Holder). Absorption spectra were recorded every 100 s. Relative $^1\text{O}_2$ yields ($\Phi_{\text{deutporp-nhet}}$) were calculated from the degradation slopes of DPBF in the presence of different PSs.

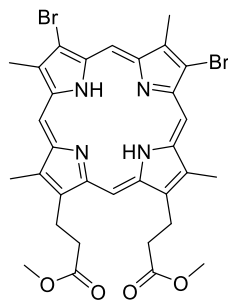
General Procedure A: Suzuki-Miyaura Cross Coupling: Respective brominated or iodinated species (1 equiv.), the desired boronic acid or boronic acid pinacol ester (20 equiv.), Cs_2CO_3 (20 equiv.), and $\text{Pd}(\text{dppf})\text{Cl}_2$ (20 mol%) were dried under high vac. for 1 h. Anhydrous THF was added under $\text{Ar}_{(\text{g})}$ and the solution was degassed *via* three freeze-pump-thaw cycles. The reaction mixture was then heated to 80 °C for 18 h. The solvent was removed *in vacuo* and the residue redissolved in CH_2Cl_2 . This was washed sequentially with sat. aq. NaHCO_3 solution, deionised H_2O , and brine. The organic layer was dried over MgSO_4 , the solvent removed *in vacuo* and the residue recrystallised *via* the two-layer diffusion recrystallisation method.

General Procedure B: F-BODIPY Condensation: The respective pyrrole (2 equiv.) and aldehyde (1 equiv.) were dissolved in anhydrous CH_2Cl_2 and the solution was degassed with $\text{Ar}_{(\text{g})}$ for 1 h. TFA (1 drop) was added and the reaction was stirred at RT for 18 h. DDQ (1 equiv.) was added and the reaction mixture was stirred for 2.5 h. TEA (0.02 equiv.) was added, followed by 15 min stirring at RT. $\text{BF}_3 \cdot \text{OEt}_2$ (0.02 equiv.) was added followed by stirring for 2 h. The reaction mixture was washed with NaHCO_3 and water, sequentially, and the organic phase was dried over anhydrous MgSO_4 . The solvent was removed *in vacuo* and the crude material purified *via* column chromatography on silica gel using *n*-hexanes/EtOAc as eluent.

General Procedure C: O-BODIPY Synthesis: The respective F-BODIPY (1 equiv.) and AlCl_3 (1.5 equiv.) were dissolved in anhydrous CH_2Cl_2 and stirred at 55 °C for 10 min. The reaction mixture was cooled to RT. 4-Hydroxybenzaldehyde (3 equiv.) was added followed by stirring at RT for 1 h. The reaction mixture was washed with water ($\times 2$), the organic phase dried over MgSO_4 , and the solvent removed *in vacuo*. The crude material was purified *via* column chromatography on silica gel using *n*-hexanes/EtOAc as eluent.

6.2 Functionalisation of Deuterioporphyrin IX Dimethyl Ester Derivatives

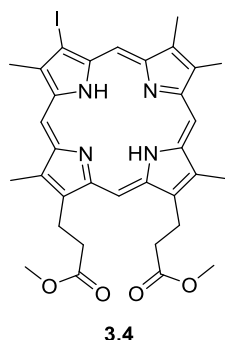
3,8-Dibromo-deuterioporphyrin IX dimethyl ester (3.3)



3.3

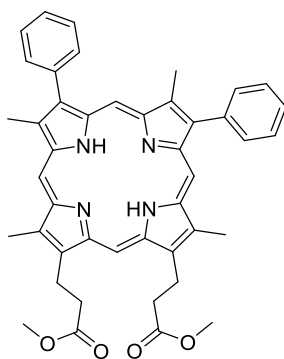
Compound **3.1** (100 mg, 0.186 mmol) was dissolved in CHCl_3 (20 mL) and the solution was cooled to 0 °C in an ice-bath. NBS (130 mg, 0.730 mmol, 4.2 equiv.) and pyridine (0.20 mL) were added over 2 min, with the reaction mixture being stirred vigorously at 0 °C for a total of 5 min. The reaction was quenched with acetone (12 mL), with stirring continued for 5 min. Deionised H_2O (25 mL) was added, with stirring for a further 5 min at 0 °C. The organic layer was extracted with CHCl_3 and washed twice with deionised H_2O . The organic layer was dried over MgSO_4 , the solvent removed *in vacuo*, and the residue recrystallised from MeOH to yield a purple crystalline solid (118 mg, 0.169 mmol, 91%). M.p. = 270–272 °C (lit. 274–277 °C)²⁸; R_f = 0.73 (Al_2O_3 , CH_2Cl_2); ^1H NMR (400 MHz, CDCl_3): δ = −4.40 (s, 2H, NH), 3.23–3.26 (m, 4H, CH_2), 3.56 (s, 3H, CH_3), 3.57 (s, 3H, CH_3), 3.58 (s, 3H, CH_3), 3.60 (s, 3H, CH_3), 3.63 (s, 3H, CH_3), 3.64 (s, 3H, CH_3), 4.36–4.39 (m, 4H, CH_2), 9.83 (s, 1H, meso H), 9.91 (s, 1H, meso H), 9.92 (s, 1H, meso H) and 9.99 (s, 1H, meso H) ppm; ^{13}C NMR (600 MHz, CDCl_3): δ = 11.8, 13.3, 13.3, 21.9, 36.9, 36.9, 51.9, 97.1, 97.7, 98.1, 98.5 and 173.6 ppm; UV-vis (CH_2Cl_2) λ_{max} (log ϵ) = 402 (5.62), 504 (5.70), 536 (5.73), 572 (5.78) and 625 nm (5.79); HRMS (MALDI) $[\text{C}_{32}\text{H}_{32}\text{N}_4\text{O}_4\text{Br}_2] [\text{M}]^+$: m/z calcd. 694.0790; found 694.0817.

3,8-Diiodo-deuteroporphyrin IX dimethyl ester (3.4)



Compound **3.1** (250 mg, 0.463 mmol), NIS (440 mg, 1.945 mmol) and pyridine (0.5 mL) were added to CHCl_3 (50 mL) and the reaction mixture was heated to reflux at 80 °C for 48 h. The reaction was quenched with acetone (50 mL), and deionized H_2O (50 mL) was added, with the resulting mixture stirred for 5 min. The organic layer was extracted with CHCl_3 and washed twice with deionised H_2O . The organic layer was dried over MgSO_4 , the solvent removed *in vacuo*, and the residue recrystallised from MeOH to yield a purple crystalline solid (279 mg, 0.352 mmol, 76%). M.p. = 236 °C (lit. 238 °C)²⁸; R_f = 0.66 (Al_2O_3 , CH_2Cl_2); ^1H NMR (400 MHz, CDCl_3): δ = −4.07 (s, 2H, NH), 3.24–3.28 (m, 4H, CH_2), 3.59 (s, 3H, CH_3), 3.64 (s, 3H, CH_3), 3.65 (s, 6H, CH_3), 3.67 (s, 3H, CH_3), 3.68 (s, 3H, CH_3), 4.37–4.41 (m, 4H, CH_2), 9.95 (s, 1H, meso H), 9.99 (s, 1H, meso H), 10.02 (s, 1H, meso H) and 10.04 (s, 1H, meso H) ppm; ^{13}C NMR (600 MHz, CDCl_3): δ = 11.7, 11.8, 16.1, 16.2, 21.9, 36.0, 51.9, 96.6, 97.1, 100.0, 100.4 and 173.6 ppm; UV-vis (CH_2Cl_2) λ_{max} (log ϵ) = 404 (5.46), 504 (5.56), 538 (5.59), 573 (5.62) and 626 nm (5.65); HRMS (MALDI) $[\text{C}_{32}\text{H}_{32}\text{N}_4\text{O}_4\text{I}_2]$ $[\text{M}]^+$: m/z calcd. 790.0542; found 790.0513.

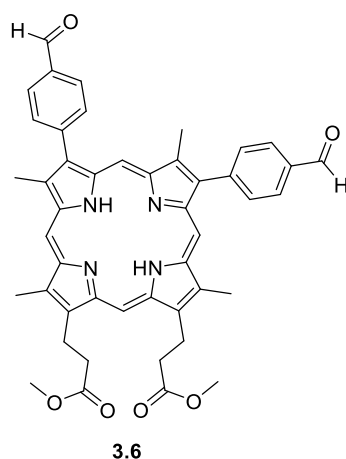
3,8-Diphenyl-deuteroporphyrin IX dimethyl ester (3.5)



3.5

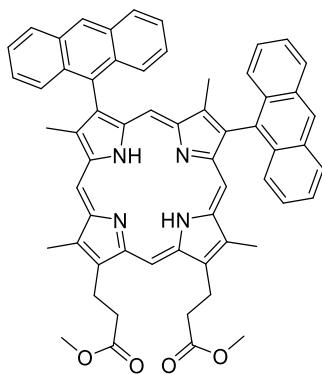
Compound **3.5** was synthesised in accordance with general procedure A, utilising **3.3** (25 mg, 0.0359 mmol), phenylboronic acid (88 mg, 0.722 mmol), Cs₂CO₃ (234 mg, 0.718 mmol) and Pd(dppf)Cl₂ (10.5 mg, 0.0144 mmol, 40 mol%) in anhydrous THF (10 mL) to yield large purple crystals (15 mg, 0.0217 mmol, 60%). Compound **3.5** was also synthesised from **3.4** in accordance with general procedure A, utilising **3.4** (20 mg, 0.0253 mmol), phenylboronic acid (62 mg, 0.506 mmol), Cs₂CO₃ (165 mg, 0.506 mmol) and Pd(dppf)Cl₂ (4 mg, 5.06 × 10⁻³ mmol) in anhydrous THF (10 mL) to yield large purple crystals (12.3 mg, 0.0178 mmol, 70%). M.p. = 226 °C; *R*_f = 0.77 (Al₂O₃, CH₂Cl₂); ¹H NMR (400 MHz, CDCl₃): δ = -3.58 (s, 2H, NH), 3.27–3.34 (m, 4H, CH₂), 3.51 (s, 3H, CH₃), 3.56 (s, 3H, CH₃), 3.66 (s, 3H, CH₃), 3.67 (s, 3H, CH₃), 3.70 (s, 3H, CH₃), 3.73 (s, 3H, CH₃), 4.40–4.48 (m, 4H, CH₂), 7.70–7.75 (m, 2H, Ar-H), 7.83–7.89 (m, 4H, Ar-H), 8.17 (d, 2H, Ar-H, *J* = 7.2 Hz), 8.22 (d, 2H, Ar-H, *J* = 7.2 Hz), 10.06 (s, 1H, meso H), 10.15 (s, 1H, meso H), 10.16 (s, 1H, meso H) and 10.27 (s, 1H, meso H) ppm; ¹³C NMR (100 MHz, CDCl₃): δ = 11.7, 11.8, 12.3, 12.4, 21.4, 36.9, 37.0, 51.8, 96.3, 97.3, 99.3, 100.0, 105.0, 127.5, 128.7, 128.7, 132.3, 132.4, 136.1, 173.6 and 173.7 ppm; UV-vis (CH₂Cl₂) λ_{max} (log ε) = 403 (5.85), 502 (4.75), 536 (4.63), 570 (4.47) and 623 nm (4.31); HRMS (MALDI) [C₄₄H₄₂N₄O₄] [M]⁺: *m/z* calcd. 690.3206; found 690.3207.

3,8-Bis(4-formylphenyl)-deuteroporphyrin IX dimethyl ester (3.6)



Compound **3.6** was synthesised in accordance with general procedure A, utilising **3.3** (20 mg, 0.0287 mmol), 4-formylphenylboronic acid (86 mg, 0.574 mmol), Cs₂CO₃ (187 mg, 0.574 mmol) and Pd(dppf)Cl₂ (4.2 mg, 5.74 × 10⁻³ mmol) in anhydrous THF (10 mL) to yield a purple crystalline solid (13 mg, 0.0174 mmol, 61%). Compound **3.6** was also synthesized from **3.4** in accordance with general procedure A, utilising **3.4** (20 mg, 0.0253 mmol), 4-formylphenylboronic acid (76 mg, 0.506 mmol), Cs₂CO₃ (165 mg, 0.506 mmol) and Pd(dppf)Cl₂ (4 mg, 5.06 × 10⁻³ mmol) in anhydrous THF (10 mL) to yield a purple crystalline solid (15 mg, 0.0201 mmol, 81%). M.p. = 262 °C; *R_f* = 0.35 (Al₂O₃, CH₂Cl₂); ¹H NMR (400 MHz, CDCl₃): δ = -3.50 (br s, 2H, NH), 3.50 (s, 3H, CH₃), 3.67 (s, 3H, CH₃), 3.70 (s, 3H, CH₃), 3.75 (s, 3H, CH₃), 3.57 (s, 3H, CH₃), 3.66 (s, 3H, CH₃), 3.28–3.35 (m, 4H, CH₂), 4.40–4.48 (m, 4H, CH₂), 8.31–8.39 (m, 8H, Ar-H), 9.96 (s, 1H, meso H), 10.07 (s, 1H, meso H), 10.17 (s, 1H, meso H), 10.26 (s, 1H, meso H), 10.35 (s, 1H, CHO) and 10.36 (s, 1H, CHO) ppm; ¹³C NMR (100 MHz, CDCl₃): δ = 11.7, 11.8, 12.4, 12.5, 21.8, 21.9, 36.8, 36.9, 51.8, 96.7, 97.7, 98.9, 99.8, 128.0, 130.1, 130.4, 132.8, 132.9, 135.4, 173.5, 173.5 and 192.3 ppm; UV-vis (CH₂Cl₂) λ_{max} (log ε) = 411 (5.11), 505 (4.05), 539 (3.94), 573 (3.74) and 626 nm (3.60); HRMS (MALDI) [C₄₆H₄₂N₄O₆] [M]⁺: *m/z* calcd. 746.3104; found 746.3134.

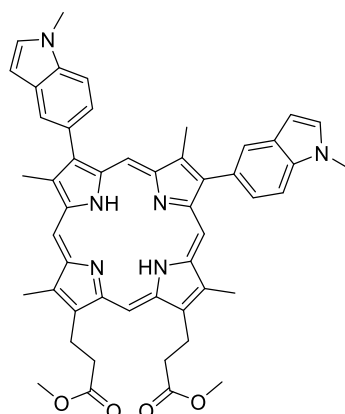
3,8-Bis(9-anthracenyl)-deuterioporphyrin IX dimethyl ester (**3.7**)



3.7

Compound **3.7** was synthesised in accordance with general procedure A, utilising **3.3** (21.5 mg, 0.0309 mmol), 9-anthraceneboronic acid (160 mg, 0.721 mmol), Cs₂CO₃ (238 mg, 0.730 mmol) and Pd(dppf)Cl₂ (5 mg, 7.02 × 10⁻³ mmol) in anhydrous THF (10 mL) to yield a purple crystalline solid (8.4 mg, 0.00943 mmol, 31%). Compound **3.7** was also synthesised from **3.4** in accordance with general procedure A, utilising **3.4** (20 mg, 0.0253 mmol), 9-anthraceneboronic acid (112 mg, 0.506 mmol), Cs₂CO₃ (165 mg, 0.506 mmol) and Pd(dppf)Cl₂ (4 mg, 5.06 × 10⁻³ mmol) in anhydrous THF (10 mL) to yield a purple crystalline solid (12 mg, 0.0135 mmol, 53%). M.p. = 267 °C; *R*_f = 0.75 (Al₂O₃, CH₂Cl₂); ¹H NMR (400 MHz, CDCl₃): δ = -3.25 (s, 2H, NH), 3.44 (s, 3H, CH₃), 3.75 (s, 9H, CH₃), 3.63 (s, 3H, CH₃), 3.19–3.25 (m, 2H, CH₂), 4.34–4.39 (m, 4H, CH₂), 3.67 (s, 3H, CH₃), 3.07–3.35 (m, 2H, CH₂), 4.44–4.49 (m, 2H, CH₂), 7.09–7.13 (m, 2H, Ar-H), 7.47–7.53 (m, 2H, Ar-H), 7.65 (d, 2H, Ar-H, *J* = 8.4 Hz), 8.25 (d, 2H, Ar-H, *J* = 8.4 Hz), 8.82 (s, 1H, Ar-H), 7.22–7.24 (m, 2H, Ar-H), 7.51–7.57 (m, 2H, Ar-H), 7.84 (d, 2H, Ar-H, *J* = 9.1 Hz), 8.30 (d, 2H, Ar-H, *J* = 9.1 Hz), 8.88 (s, 1H, Ar-H), 9.40 (s, 1H, meso H), 9.63 (s, 1H, meso H), 10.14 (s, 1H, meso H) and 10.39 (s, 1H, meso H) ppm; ¹³C NMR (100 MHz, CDCl₃): δ = 11.5, 11.8, 12.2, 12.5, 36.8, 37.0, 40.0, 41.5, 51.7, 51.8, 96.4, 97.5, 98.5, 99.4, 100.1, 125.3, 125.4, 125.6, 125.8, 127.5, 127.6, 128.6, 128.7, 131.6, 131.7, 132.6, 132.7, 173.5 and 173.6 ppm; UV-vis (CH₂Cl₂) λ_{max} (log ε) = 407 (5.86), 504 (5.95), 538 (5.98), 571 (5.01) and 624 nm (5.05); HRMS: (MALDI) [C₆₀H₅₀N₄O₄] [M]⁺: *m/z* calcd. 890.3832; found 890.3801.

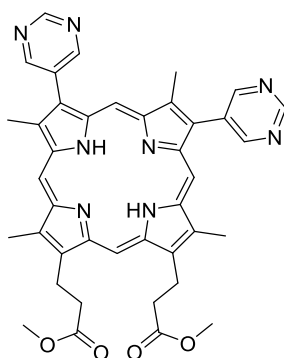
3,8-Bis(*N*-methylindolyl)-deuteroporphyrin IX dimethyl ester (3.15)



3.15

Compound **3.15** was synthesised in accordance with general procedure A, utilising **3.4** (20 mg, 0.0253 mmol), 1-methylindole-5-boronic acid pinacol ester (130 mg, 0.506 mmol), Cs₂CO₃ (165 mg, 0.506 mmol) and Pd(dppf)Cl₂ (4 mg, 5.06 × 10⁻³ mmol) in anhydrous THF (10 mL) to yield a purple crystalline solid (14.5 mg, 0.0182 mmol, 72%). M.p. >300 °C; *R*_f = 0.54 (Al₂O₃, CH₂Cl₂); ¹H NMR (400 MHz, CDCl₃): δ = −3.53 (s, 2H, NH), 3.47 (s, 3H, CH₃), 3.68 (s, 3H, CH₃), 3.71 (s, 3H, CH₃), 3.74 (s, 3H, CH₃), 3.52 (s, 3H, CH₃), 3.66 (s, 3H, CH₃), 3.27–3.35 (m, 4H, CH₂), 4.40–4.49 (m, 4H, CH₂), 4.05 (s, 3H, *N*-CH₃), 4.06 (s, 3H, *N*-CH₃), 6.78 (d, 1H, Ar-H, *J* = 3.0 Hz), 7.29–7.31 (m, 2H, Ar-H), 7.76–7.79 (m, 1H, Ar-H), 7.99–8.03 (m, 1H, Ar-H), 8.35 (s, 1H, Ar-H), 6.80 (d, 1H, Ar-H, *J* = 2.9 Hz), 7.81–7.89 (m, 1H, Ar-H), 8.05–8.10 (m, 1H, Ar-H), 8.42 (s, 1H, Ar-H), 10.10 (s, 1H, meso H), 10.12 (s, 1H, meso H), 10.22 (s, 1H, meso H) and 10.25 (s, 1H, meso H) ppm; ¹³C NMR (100 MHz, CDCl₃): δ = 11.7, 11.8, 12.4, 12.5, 24.9, 33.2, 37.0, 37.1, 51.7, 95.9, 97.0, 99.7, 100.4, 101.5, 109.3, 109.4, 124.6, 124.7, 126.3, 126.4, 128.9, 130.0, 129.6, 136.4 and 173.7 ppm; UV-vis (CH₂Cl₂) λ_{max} (log ε) = 403 (5.86), 504 (5.96), 539 (5.99), 570 (5.01) and 624 nm (5.05); HRMS: (ESI) [C₅₀H₄₈N₆O₄] [M]⁺: *m/z* calcd. 796.3737; found 796.3745.

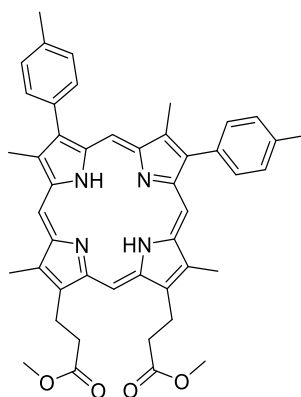
3,8-Bis(5-pyrimidinyl)-deuterioporphyrin IX dimethyl ester (3.16)



3.16

Compound **3.16** was synthesised in accordance with general procedure A, utilising **3.4** (18 mg, 0.023 mmol), pyrimidine-5-boronic acid (63 mg, 0.506 mmol), Cs_2CO_3 (165 mg, 0.506 mmol) and $\text{Pd}(\text{dppf})\text{Cl}_2$ (4 mg, 5.06×10^{-3} mmol) in anhydrous THF (10 mL) to yield a purple crystalline solid (8.4 mg, 0.012 mmol, 52%). M.p. $>300^\circ\text{C}$; $R_f = 0.42$ (Al_2O_3 , CH_2Cl_2); ^1H NMR (400 MHz, CDCl_3): $\delta = -3.51$ (br s, 2H, NH), 3.27–3.35 (m, 4H, CH_2), 3.52 (s, 3H, CH_3), 3.61 (s, 3H, CH_3), 3.66 (s, 3H, CH_3), 3.67 (s, 3H, CH_3), 3.70 (s, 3H, CH_3), 3.76 (s, 3H, CH_3), 4.40–4.47 (m, 4H, CH_2), 9.52–9.58 (m, 6H, Ar-H), 9.82 (s, 1H, meso H), 9.93 (s, 1H, meso H), 10.20 (s, 1H, meso H) and 10.28 (s, 1H, meso H) ppm; ^{13}C NMR (100 MHz, CDCl_3): $\delta = 11.6, 11.8, 12.6, 20.9, 21.5, 21.7, 22.2, 35.6, 36.1, 51.8, 52.1, 96.4, 97.2, 99.3, 102.0, 129.4, 129.5, 131.2, 132.1, 132.5, 132.8, 137.1, 137.2, 173.7$ and 174.9 ppm; UV-vis (CH_2Cl_2) λ_{max} (log ϵ) = 409 (5.48), 507 (5.56), 539 (5.59), 576 (5.63) and 630 nm (5.68); HRMS: (MALDI) $[\text{C}_{40}\text{H}_{438}\text{N}_8\text{O}_4]$ $[\text{M}]^+$: m/z calcd. 694.3016; found 694.3486.

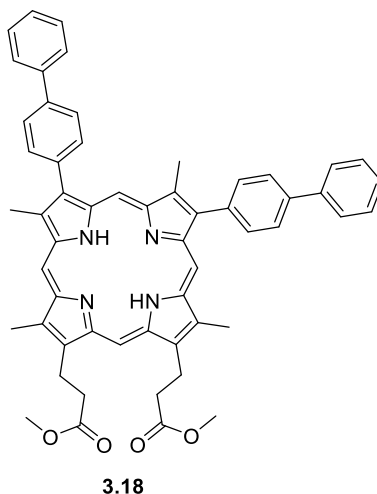
3,8-Bis(4-methylphenyl)-deuterioporphyrin IX dimethyl ester (3.17)



3.17

Compound **3.17** was synthesised in accordance with general procedure A, utilising **3.4** (20 mg, 0.0253 mmol), 4-tolylboronic acid (69 mg, 0.506 mmol), Cs₂CO₃ (165 mg, 0.506 mmol) and Pd(dppf)Cl₂ (4 mg, 5.06 × 10⁻³ mmol) in anhydrous THF (10 mL) to yield a purple crystalline solid (14 mg, 0.0195 mmol, 77%). M.p. >300 °C; *R_f* = 0.80 (Al₂O₃, CH₂Cl₂); ¹H NMR (400 MHz, CDCl₃): δ = -3.57 (s, 2H, NH), 2.68 (s, 3H, CH₃), 2.69 (s, 3H, CH₃), 3.27–3.34 (m, 4H, CH₂), 3.52 (s, 3H, CH₃), 3.55 (s, 3H, CH₃), 3.66 (s, 3H, CH₃), 3.67 (s, 3H, CH₃), 3.70 (s, 3H, CH₃), 3.72 (s, 3H, CH₃), 4.40–4.48 (m, 4H, CH₂), 7.67 (t, 4H, *J* = 8.03 Hz, Ar-H), 8.04 (d, 2H, *J* = 8.03 Hz, Ar-H), 8.08 (d, 2H, *J* = 8.03 Hz, Ar-H), 10.04 (s, 1H, meso H), 10.12 (s, 1H, meso H), 10.13 (s, 1H, meso H) and 10.23 (s, 1H, meso H) ppm; ¹³C NMR (100 MHz, CDCl₃): δ = 11.7, 11.8, 12.3, 12.4, 21.5, 21.6, 21.9, 22.0, 36.9, 37.0, 51.7, 51.8, 96.1, 97.2, 99.3, 100.0, 129.4, 129.5, 129.6, 132.1, 132.1, 132.2, 137.1, 137.2, 173.6 and 173.7 ppm; UV-vis (CH₂Cl₂) λ_{max} (log ε) = 404 (5.03), 503 (3.89), 538 (3.78), 571 (3.65) and 625 nm (3.43); HRMS: (MALDI) [C₄₆H₄₆N₄O₄] [M]⁺: *m/z* calcd. 718.3519; found 718.3493.

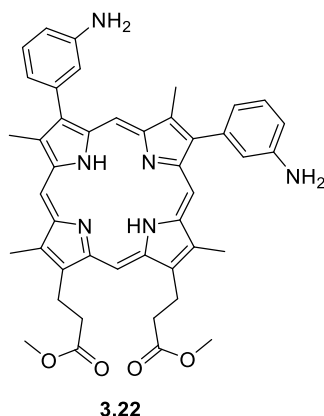
3,8-Bis(4-biphenyl)-deuteroporphyrin IX dimethyl ester (**3.18**)



Compound **3.18** was synthesised in accordance with general procedure A, utilising **3.4** (20 mg, 0.0253 mmol), 4-biphenylboronic acid (100 mg, 0.506 mmol), Cs₂CO₃ (165 mg, 0.506 mmol) and Pd(dppf)Cl₂ (4 mg, 5.06 × 10⁻³ mmol) in anhydrous THF (10 mL) to yield a purple solid (18.5 mg, 0.0219 mmol, 87%). M.p. >300 °C; *R_f* = 0.81 (Al₂O₃, CH₂Cl₂); ¹H NMR (400 MHz, CDCl₃): δ = -3.54 (br s, 2H, NH), 3.27–3.34 (m, 4H, CH₂), 3.53 (s, 3H, CH₃), 3.62 (s, 3H, CH₃), 3.67 (s, 3H, CH₃), 3.68 (s, 3H, CH₃), 3.69 (s, 3H, CH₃), 3.77 (s, 3H, CH₃), 4.40–4.47 (m, 4H, CH₂), 7.47–7.61 (m, 4H, Ar-H), 7.60–7.72 (m, 4H, Ar-H), 7.92 (t, 4H, *J* = 7.08 Hz, Ar-H), 8.08–8.12 (m, 4H, Ar-H), 8.24 (d, 2H, *J* = 7.86 Hz, Ar-

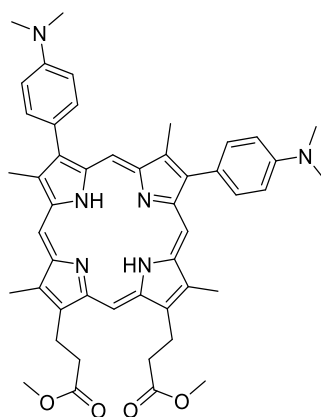
H), 8.29 (d, 2H, $J = 7.86$ Hz), 10.08 (s, 1H, meso H), 10.13 (s, 1H, meso H), 10.20 (s, 1H, meso H) and 10.24 (s, 1H, meso H) ppm; ^{13}C NMR (100 MHz, CDCl_3): $\delta = 11.6, 11.7, 11.7, 21.9, 30.8, 36.6, 36.9, 37.0, 51.6, 51.7, 53.4, 96.3, 96.8, 97.0, 97.2, 115.8, 137.9, 173.6$ and 206.8 ppm; UV-vis (CH_2Cl_2) λ_{max} ($\log \epsilon$) = 406 (4.98), 504 (3.84), 539 (3.74), 572 (3.59) and 626 nm (3.35); HRMS: (MALDI) $[\text{C}_{56}\text{H}_{50}\text{N}_4\text{O}_4]$ $[\text{M}]^+$: m/z calcd. 842.3832; found 842.3803.

3,8-Bis(3-aminophenyl)-deuteroporphyrin IX dimethyl ester (3.22)



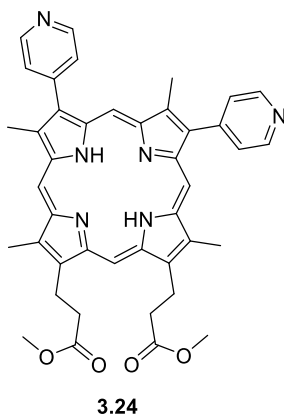
Compound **3.22** was synthesised in accordance with general procedure A, utilising **3.4** (21.3 mg, 0.0269 mmol), 3-aminophenylboronic acid pinacol ester (111 mg, 0.506 mmol), Cs_2CO_3 (165 mg, 0.506 mmol) and $\text{Pd}(\text{dppf})\text{Cl}_2$ (4 mg, 5.06×10^{-3} mmol) in anhydrous THF (10 mL). Work-up procedures were followed as previously described, however, column chromatography on Grade III neutral Al_2O_3 ($\text{CH}_2\text{Cl}_2/n$ -hexane, 7:3, v/v) was required to yield a purple solid (4.8 mg, 6.66×10^{-3} mmol, 25%). M.p. >300 °C; $R_f = 0.88$ (Al_2O_3 , CH_2Cl_2); ^1H NMR (400 MHz, CDCl_3): $\delta = -3.59$ (s, 2H, NH), 3.27–3.34 (m, 4H, CH_2), 3.52 (s, 3H, CH_3), 3.56 (s, 3H, CH_3), 3.66 (s, 3H, CH_3), 3.67 (s, 3H, CH_3), 3.69 (s, 3H, CH_3), 3.72 (s, 3H, CH_3), 3.99–4.01 (m, 4H, NH_2), 4.40–4.48 (m, 4H, CH_2), 7.02–7.06 (m, 2H, Ar-H), 7.43–7.49 (m, 2H, Ar-H), 7.52–7.66 (m, 6H, Ar-H), 10.06 (s, 1H, meso H), 10.12 (s, 1H, meso H), 10.16 (s, 1H, meso H) and 10.22 (s, 1H, meso H) ppm; ^{13}C NMR (100 MHz, CDCl_3): $\delta = 14.1, 19.7, 21.9, 22.7, 24.6, 24.8, 29.4, 29.7, 30.3, 31.9, 33.2, 37.0, 40.1, 40.7, 40.8, 51.7, 53.4, 83.2, 111.2, 112.7, 112.9, 113.1, 118.5, 125.5, 126.9, 129.4, 133.1, 136.1, 201.7, 205.1$ and 212.7 ppm; UV-vis (CH_2Cl_2) λ_{max} ($\log \epsilon$) = 401 (5.10), 507 (5.20), 546 (5.23), 572 (5.30) and 627 nm (5.29); HRMS: (MALDI) $[\text{C}_{44}\text{H}_{44}\text{N}_6\text{O}_4]$ $[\text{M}]^+$: m/z calcd. 720.3424; found 720.3441.

3,8-Bis(4-*N,N*-dimethylaminophenyl)-deuterioporphyrin IX dimethyl ester (3.23)



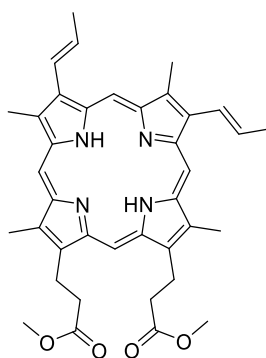
3.23

Compound **3.23** was synthesised in accordance with general procedure A, utilising **3.4** (18.5 mg, 0.0234 mmol), 4-(*N,N*-dimethylamino)phenylboronic acid (83 mg, 0.505 mmol), Cs₂CO₃ (165 mg, 0.506 mmol) and Pd(dppf)Cl₂ (4 mg, 5.06 × 10⁻³ mmol) in anhydrous THF (10 mL) to yield the title compound in a yield of 48% (1 mg, 5.28 × 10⁻³ mmol). M.p. >300 °C; *R_f* = 0.66 (Al₂O₃, CH₂Cl₂); ¹H NMR (400 MHz, CDCl₃): δ = −3.74 (br s, 2H, NH), 3.31–3.34 (m, 4H, CH₂), 3.52 (s, 3H, CH₃), 3.55 (s, 6H, CH₃), 3.65 (s, 6H, CH₃), 3.67 (s, 3H, CH₃), 3.70 (s, 3H, CH₃), 3.82 (s, 3H, CH₃), 3.99 (s, 3H, CH₃), 4.39–4.42 (m, 4H, CH₂), 7.79–7.84 (m, 4H, Ar-H), 7.64–7.69 (m, 4H, Ar-H), 10.08 (s, 1H, meso H), 10.09 (s, 1H, meso H), 10.14 (s, 1H, meso H) and 10.17 (s, 1H, meso H) ppm; ¹³C NMR (100 MHz, CDCl₃): δ = 11.7, 11.7, 12.3, 12.4, 14.1, 21.9, 22.7, 24.8, 29.1, 29.7, 30.0, 31.9, 36.9, 37.0, 37.1, 51.7, 69.7, 83.3, 96.0, 97.0, 99.3, 99.9, 114.1, 115.4, 115.4, 115.5, 126.1, 127.3, 129.7, 131.4, 133.2, 133.2, 133.3, 136.4, 145.8, 145.9, 149.3, 173.6 and 174.7 ppm; UV-vis (CH₂Cl₂) λ_{max} (log ε) = 401 (5.79), 505 (5.89), 538 (5.92), 570 (5.95) and 625 nm (5.99); HRMS: (MALDI) [C₄₈H₅₂N₆O₄] [M]⁺: *m/z* calcd. 776.4050; found 776.4073.



Compound **3.24** was synthesised in accordance with general procedure A, utilising **3.4** (18.5 mg, 0.0234 mmol), 4-pyridine-boric acid pinacol ester (83 mg, 0.505 mmol), Cs₂CO₃ (165 mg, 0.506 mmol) and Pd(dppf)Cl₂ (4 mg, 5.06 × 10⁻³ mmol) in anhydrous THF (10 mL) to yield a crystalline solid in a yield of 54% (4.1 mg, 5.28 × 10⁻³ mmol). M.p. >300 °C; *R*_f = 0.66 (Al₂O₃, CH₂Cl₂); ¹H NMR (400 MHz, CDCl₃): δ = −3.54 (br s, 2H, NH), 3.27–3.34 (m, 4H, CH₂), 3.51 (s, 3H, CH₃), 3.58 (s, 3H, CH₃), 3.65 (s, 3H, CH₃), 3.66 (s, 3H, CH₃), 3.69 (s, 3H, CH₃), 3.74 (s, 3H, CH₃), 4.39–4.46 (m, 4H, CH₂), 8.07 (d, 2H, Ar-H, *J* = 5.7 Hz), 8.12 (d, 2H, Ar-H, *J* = 5.7 Hz), 9.08–9.91 (m, 4H, Ar-H), 9.94 (s, 1H, meso H), 10.05 (s, 1H, meso H), 10.16 (s, 1H, meso H) and 10.25 (s, 1H, meso H) ppm; ¹³C NMR (100 MHz, CDCl₃): δ = 11.7, 12.4, 14.1, 21.7, 21.9, 22.7, 24.8, 29.1, 29.7, 30.0, 31.9, 36.9, 37.0, 37.1, 51.7, 69.7, 83.3, 96.0, 97.0, 99.3, 99.9, 114.1, 115.4, 115.4, 115.5, 126.1, 127.0, 127.1, 129.7, 131.4, 133.2, 133.2, 133.3, 136.4, 145.8, 145.9, 149.3, 150.2, 150.3, and 173.4 ppm; UV-vis (CH₂Cl₂) λ_{max} (log ε) = 410 (5.72), 513 (5.78), 543 (5.83), 579 (5.88) and 627 nm (5.91); HRMS: (MALDI) [C₄₈H₅₂N₆O₄] [M]⁺: *m/z* calcd. 692.3111; found 692.3133.

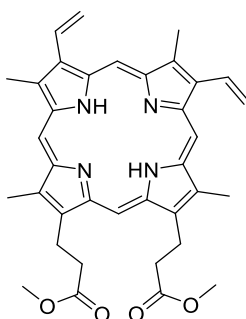
3,8-Diallyl-deuterioporphyrin IX dimethyl ester (3.30)



3.30

Compound **3.30** was synthesised in accordance with general procedure A, utilising **3.4** (15 mg, 0.0190 mmol), allylboronic acid pinacol ester (0.07 mL, 63 mg, 0.375 mmol), Cs₂CO₃ (122 mg, 0.375 mmol) and Pd(dppf)Cl₂ (3 mg, 3.75 × 10⁻³ mmol) in anhydrous THF (10 mL) to yield a purple crystalline solid (4 mg, 6.46 × 10⁻³ mmol, 34%). M.p. = 196 °C; *R*_f = 0.91 (Al₂O₃, CH₂Cl₂); ¹H NMR (400 MHz, CDCl₃): δ = -3.71 (s, 2H, NH), 3.28–3.31 (m, 4H, CH₂), 3.60 (s, 3H, CH₃), 3.62 (s, 3H, CH₃), 3.63 (s, 3H, CH₃), 3.65 (s, 3H, CH₃), 3.66 (s, 6H, CH₃), 4.41–4.46 (m, 4H, CH₂), 4.83–4.85 (m, 4H, CH₂), 5.23–5.25 (m, 1H, CH₂(*trans*)), 5.31–5.34 (m, 1H, CH₂(*cis*)), 5.26–5.28 (m, 1H, CH₂(*trans*)), 5.35–5.37 (m, 1H, CH₂(*cis*)), 6.54–6.65 (m, 2H, CH₂), 10.09 (s, 1H, meso H), 10.10 (s, 1H, meso H), 10.11 (s, 1H, meso H) and 10.12 (s, 1H, meso H) ppm; ¹³C NMR (100 MHz, CDCl₃): δ = 11.6, 11.7, 11.7, 21.9, 30.8, 36.6, 36.9, 37.0, 51.6, 51.7, 53.4, 96.3, 96.8, 97.0, 97.2, 115.8, 137.9, 173.6 and 206.8 ppm; UV-vis (CH₂Cl₂) λ_{max} (log ε) = 400 (5.69), 500 (5.79), 534 (5.82), 569 (5.85) and 622 nm (5.89); HRMS: (MALDI) [C₃₈H₄₂N₄O₄] [M]⁺: *m/z* calcd. 618.3206; found 618.3224.

Protoporphyrin IX dimethyl ester (3.2)

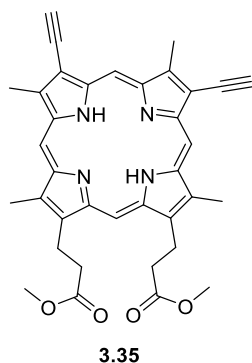


2.2

Compound **3.2** was synthesised in accordance with general procedure A, utilising **3.4** (14.2 mg, 0.0180 mmol), vinylboronic acid pinacol ester (0.06 mL, 58 mg, 0.375 mmol), Cs₂CO₃

(122 mg, 0.375 mmol) and Pd(dppf)Cl₂ (3 mg, 3.75 × 10⁻³ mmol) in anhydrous THF (10 mL) to yield a purple crystalline solid (4 mg, 6.77 × 10⁻³ mmol, 38%). M.p. = 205 °C (lit. 215 °C)²⁸; *R_f* = 0.89 (Al₂O₃, CH₂Cl₂); ¹H NMR (400 MHz, CDCl₃): δ = -3.61 (br s, 2H, NH), 3.63 (s, 3H, CH₃), 3.65 (s, 3H, CH₃), 3.73 (s, 3H, CH₃), 3.74 (s, 3H, CH₃), 3.66 (s, 6H, CH₃), 3.25–3.33 (m, 4H, CH₂), 4.38–4.46 (m, 4H, CH₂), 6.17–6.20 (m, 1H, CH_{2(trans)}), 6.35–6.39 (m, 1H, CH_{2(cis)}), 6.20–6.23 (m, 1H, CH_{2(trans)}), 6.39–6.43 (m, 1H, CH_{2(cis)}), 6.75–6.87 (m, 2H, CH), 10.07 (s, 1H, meso H), 10.12 (s, 1H, meso H), 10.20 (s, 1H, meso H) and 10.26 (s, 1H, meso H) ppm; UV-vis (CH₂Cl₂) λ_{max} (log ε) = 408 (5.30), 506 (5.39), 542 (5.43), 577 (5.45) and 631 nm (5.49); HRMS: (MALDI) [C₃₆H₃₈N₄O₄] [M]⁺: *m/z* calcd. 590.2893; found 590.2883.

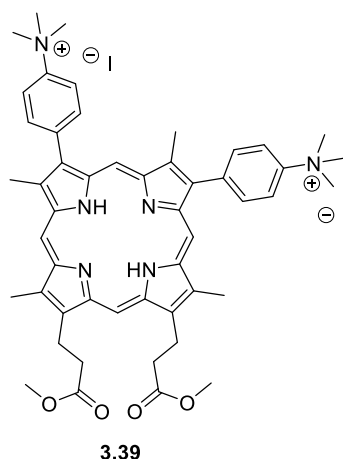
3,8-Diacetylenyl-deuteroporphyrin IX dimethyl ester (3.35)



Compound **3.4** (20 mg, 0.0253 mmol), CuI (1.4 mg, 0.008 mmol), PPh₃ (8 mg, 0.030 mmol) and Pd(PPh₃)₂Cl₂ (3.5 mg, 0.005 mmol) were dried under high vac. for 1.5 h. TEA (5 mL) and trimethylsilylacetylene (0.3 mL) were degassed *via* three freeze-pump-thaw cycles before being added to the reaction vessel under argon. The reaction mixture was then degassed *via* three freeze-pump-thaw cycles and then stirred at room temperature for 18 h. The solvent was removed *in vacuo* and the residue dissolved in CH₂Cl₂. This was then purified on a plug of Al₂O₃ using CH₂Cl₂ as eluent. The solvent was removed *in vacuo* and the residue recrystallised from hexane to yield **3.34** as purple crystals (9.9 mg, 0.013 mmol, 57%). This was then dissolved in CH₂Cl₂ (5 mL) and stirred in the presence of TBAF (1 M solution in THF, 0.05 mL, 0.018 mmol) at RT for 20 min. The reaction mixture was washed sequentially with deionised H₂O and brine, dried over anhydrous MgSO₄ and the solvent removed *in vacuo*. Recrystallisation from MeOH yielded the desired compound **3.35** in 87% (6.6 mg, 0.011 mmol). M.p. = 222 °C; *R_f* = 0.54 (Al₂O₃, CH₂Cl₂); ¹H NMR (600 MHz, CDCl₃): δ = -4.43 (br s, 2H), 3.21 (br s, 4H, CH₂), 3.37–3.40 (m, 6H, CH₃), 3.50 (br s, 2H, CH), 3.57 (br s, 6H, CH₃), 3.64 (s, 6H, CH₃), 4.31 (br s, 4H, CH₂) and 9.81 ppm (br s, 4H,

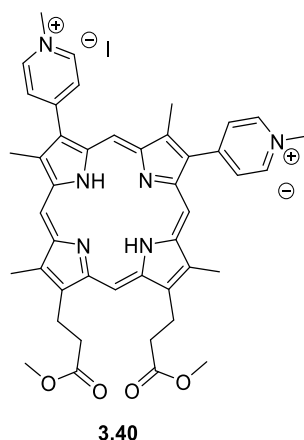
meso H); UV-vis (CH₂Cl₂) λ_{max} (log ϵ) = 414 (5.38), 511 (5.47), 545 (5.50), 578 (5.53) and 636 nm (5.57); HRMS: (MALDI) [C₃₆H₃₄N₄O₄] [M]⁺: m/z calcd. 586.2580; found 586.2592. [¹³C NMR spectrum could not be obtained due to oligomerization occurring in solution]

3,8-Bis(4-*N,N,N*-trimethylaminophenyl)-deuterioporphyrin IX dimethyl ester (3.39)



Compound **3.23** (10 mg, 0.013 mmol) was added to *N*-methyl-2-pyrrolidine (2 mL) and stirred in the presence of an excess of MeI (0.5 mL, 400 equiv.) for 48 h. Diethyl ether was added to precipitate the desired product which was collected *via* filtration (10 mg, 0.012 mmol, 92%). M.p. >300 °C; R_f = 0.25 (Al₂O₃, CH₂Cl₂); UV-vis (CH₃OH) λ_{max} (log ϵ) = 403 (5.71), 503 (5.77), 537 (5.82), 573 (5.83) and 627 nm (5.89); HRMS: (ESI) [C₅₀H₅₈N₆O₄] [M]²⁺: m/z calcd. 806.4509; found 403.2264.

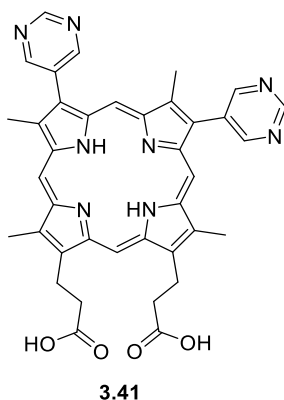
3,8-Bis(4-*N*-methylpyridinyl)-deuterioporphyrin IX dimethyl ester (3.40)



Compound **3.24** (10 mg, 0.014 mmol) was added to *N*-methyl-2-pyrrolidine (2 mL) and stirred in the presence of an excess of MeI (0.5 mL, 400 equiv.) for 48 h. Diethyl ether was

added to precipitate the desired product which was collected *via* filtration (10.5 mg, 0.013 mmol, 94%). M.p. >300 °C; R_f = 0.30 (Al₂O₃, CH₂Cl₂); UV-vis (CH₃OH) λ_{max} (log ϵ) = 398 (5.68), 504 (5.75), 540 (5.79), 575 (5.80) and 625 nm (5.89); HRMS: (ESI) [C₄₄H₄₆N₆O₄] [M]²⁺: m/z calcd. 806.4509; found 361.1794.

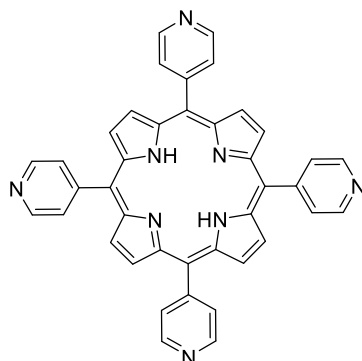
3,8-Bis(pyrimidinyl)-deuteroporphyrin IX (3.41)



3.16 (10 mg, 0.014 mmol) was dissolved in the minimum amount of THF (2 mL) and heated to 70 °C for 2 h in the presence of NaOH (1 M). The reaction mixture was diluted with water, unreacted starting material removed by washed the aqueous layer with CH₂Cl₂. The aqueous layer was then acidified with HCl (1 M) to precipitate the product which was collected *via* filtration (6.9 mg, 0.010 mmol, 71%). M.p. 275 °C; R_f = 0.15 (Al₂O₃, CH₂Cl₂); UV-vis (CH₃OH) λ_{max} (log ϵ) = 403 (5.74), 505 (5.76), 539 (5.83), 590 (5.85) and 626 nm (5.82); HRMS: (ESI) [C₃₈H₃₄N₈O₄] [M]⁻: m/z calcd. 666.2703; found 332.2104.

6.4 Photosensitisers for Organic Dye Degradation

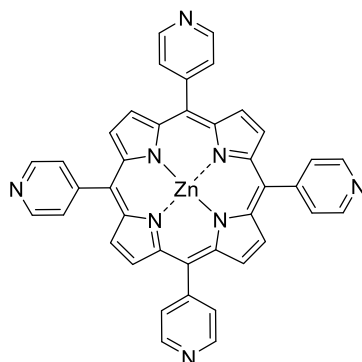
5,10,15,20-Tetrakis(4-pyridyl)porphyrin (4.10)³¹¹



4.10

Pyrrole (2.5 mL, 36 mmol), previously filtered through a plug of silica, and 4-pyridinecarboxaldehyde (2.8 mL, 30 mmol) were added to refluxing propionic acid (100 mL) and the resulting solution was refluxed for 2 h. The reaction mixture was then cooled in an ice-bath and treated with acetone (400 mL) and 25% aq. ammonia solution (100 mL). The resulting solution was stored in the freezer overnight. The crystallised solid was filtered and washed with cold MeOH. Purple crystals (0.758 g, 1.236 mmol, 17%) were obtained. M.p. = >300 °C; ¹H NMR (CDCl₃ + pyridine-d₅, 400 MHz): δ = −1.86 (br s, 2H, NH), 8.12 (d, 8H, Ar-H, *J* = 5.7 Hz), 8.83 (s, 8H, βH), 8.93 ppm (d, 8H, Ar-H, *J* = 5.7 Hz); UV-vis (DMSO) λ_{max} (log ε) = 416 (5.82), 512 (4.55) and 546 nm (4.10); HRMS: (MALDI) [C₄₀H₂₆N₈]: *m/z* calcd. 618.2280; found 618.2284.

[5,10,15,20-Tetrakis(4-pyridyl)porphyrinato]zinc(II) (4.11)³³¹

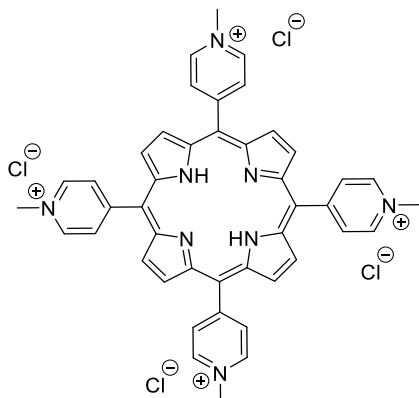


4.11

5,10,15,20-Tetrakis(4-pyridyl)porphyrin (0.1 g, 0.162 mmol) in chloroform (38 mL) was treated with an excess of Zn(II) acetate dihydrate (0.106 g, 0.049 mmol) dissolved in the minimum amount of MeOH. The reaction mixture was stirred at RT for 24 h. The reaction mixture was concentrated *in vacuo*, and MeOH was added to precipitate a violet solid. This

was filtered and washed with MeOH, and dried *in vacuo*. A purple solid (0.126 g, 0.185 mmol, 88%) was collected. M.p. = >300 °C; ^1H NMR ($\text{CDCl}_3 + \text{pyridine-d}_5$, 400 MHz): δ = 8.05 (d, 8H, Ar-H, J = 5.8 Hz), 8.81 (s, 8H, βH), 8.93 (d, 8H Ar-H, J = 5.8 Hz); UV-vis (DMSO) λ_{max} ($\log \epsilon$) = 428 (5.84), 560 (4.49) and 599 nm (4.10); HRMS: (MALDI) $[\text{C}_{40}\text{H}_{26}\text{N}_8\text{Zn}]$: m/z calcd. 680.1415; found 680.1411.

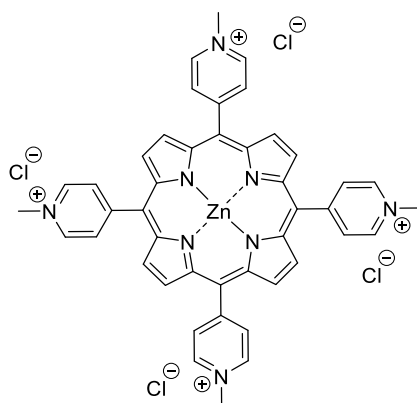
5,10,15,20-Tetrakis(*N*-methylpyridinium-4-yl)porphyrin tetrachloride (**4.12**)³¹²



4.12

An excess of MeI (6.04 mL, 96.8 mmol) was added to a suspension of **4.10** (0.150 g, 0.242 mmol) in dry DMF (20 mL). The reaction was stirred for 5 h at 40 °C under $\text{Ar}_{(\text{g})}$. The resulting brown-red solution was cooled to RT and diethyl ether was added to precipitate a dark brown solid. This was filtered and washed with diethyl ether. A dark brown solid was collected (0.262 g, 0.221 mmol, 91%). The solid was dissolved in the minimum amount of deionised H_2O and passed through an ion-exchange resin (Dowex 1×8 chloride form, 200-400 mesh size, eluent = deionised H_2O). The solvent was removed *in vacuo* and the resulting purple solid dried in an oven at 80 °C overnight. A purple solid was obtained (0.165 g, 0.187 mmol, 85%). M.p. = >300 °C; ^1H NMR (DMSO-d_6 , 400 MHz): δ = −3.10 (br s, 2H, NH), 4.70 (s, 12H, CH_3), 8.96 (d, 8H, Ar-H, J = 6.4 Hz), 9.15 (s, 8H, βH), 9.48 (d, 8H, Ar-H, J = 6.4 Hz); UV-vis (DMSO) λ_{max} ($\log \epsilon$) = 425 (5.36), 516 (4.12), 570 (3.57) and 589 nm (3.44); HRMS: (MALDI) $[\text{C}_{44}\text{H}_{40}\text{N}_8]$: m/z calcd. 680.3376; found 680.3405.

[5,10,15,20-Tetrakis(*N*-methylpyridinium-4-yl)porphyrinato]zinc(II) tetrachloride (4.13)³¹³

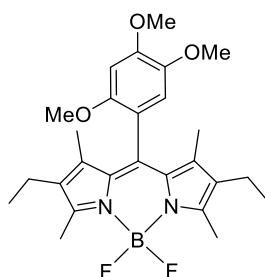


4.13

An excess of MeI (5.2 mL, 83.27 mmol) was added to a suspension of **4.11** (0.142 g, 0.208 mmol) in dry DMF (20 mL). The reaction was stirred for 5 h at 40 °C under Ar(g). The resulting green solution was cooled to RT and diethyl ether was added to precipitate a dark green solid. This was filtered and washed with diethyl ether. A dark green solid was collected (0.156 g, 0.125 mmol, 60%). The solid was dissolved in the minimum amount of deionised H₂O and passed through an ion-exchange resin (Dowex 1×8 chloride form, 200-400 mesh size, eluent = deionised H₂O). The solvent was removed *in vacuo* and the resulting green solid dried in an oven at 80 °C overnight. M.p. = >300 °C; ¹H NMR (DMSO-d₆, 400 MHz): δ = 4.68 (s, 12H, CH₃), 8.84 (d, 8H, Ar-H, *J* = 6.4 Hz), 8.97 (s, 8H, βH), 9.39 (d, 8H, Ar-H, *J* = 6.4 Hz); UV-vis (DMSO) λ_{max} (log ε) = 438 (5.15), 564 (4.10) and 607 nm (3.73); HRMS: (MALDI) [C₄₀H₃₆N₈Zn]: *m/z* calcd. 740.2354; found 740.2375.

6.5 Preparation of *O*-BODIPYs

1,3,5,7-Tetramethyl-8-(2,4,5-trimethoxyphenyl)-4,4'-difluoro-4-bora-3a,4a-diaza-s-indacence (5.27)

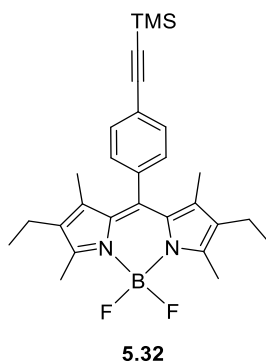


5.27

Synthesised according to General Procedure B: 3-Ethyl-2,4-dimethyl pyrrole (1.08 mL, 8 mmol) and 2,4,5-trimethoxybenzaldehyde (785 mg, 4 mmol) were dissolved in anhydrous

CH₂Cl₂ (160 mL) and the solution was degassed with Ar_(g) for 1 h. TFA (1 drop) was added and the reaction was stirred at RT overnight. DDQ (906 mg, 4 mmol) was added and the reaction mixture was stirred for 2.5 h. TEA (9 mL) was added, followed by stirring for 15 min. BF₃·OEt₂ (9 mL) was then added followed by stirring for 2 h. The reaction mixture was washed with NaHCO₃ and water, sequentially, and the organic layer was dried over anhydrous MgSO₄. The solvent was removed *in vacuo* and the crude material purified *via* column chromatography on silica gel using *n*-hexanes as eluent, increasing polarity up to 25% EtOAc in *n*-hexanes to collect the compound in a yield of 35% (657 mg, 1.4 mmol). M.p. = 190 °C; R_f = 0.65 (SiO₂, CH₂Cl₂); ¹H NMR (CDCl₃, 400 MHz): δ = 0.98–1.02 (t, 6H, CH₂CH₃, *J* = 7.5 Hz), 1.42 (s, 6H, CH₃), 2.28–2.34 (q, 4H, CH₂CH₃, *J* = 7.5 Hz), 2.52 (s, 6H, CH₃), 3.74 (s, 3H, OCH₃), 3.80 (s, 6H, OCH₃), 3.97 (s, 3H, OCH₃), 6.60 (s, 1H, Ar-H) and 6.67 (s, 1H, Ar-H) ppm; ¹³C NMR (100 MHz, CDCl₃): δ = 11.7, 12.6, 12.9, 15.1, 15.8, 16.5, 21.6, 43.4, 57.4, 93.2, 103.1, 110.0, 123.4, 130.4, 131.4, 132.4, 136.1, 138.4, 140.2 and 151.0 ppm; UV-vis (CH₂Cl₂) λ_{max} (log ε) = 376 (3.86) and 526 (4.77) nm; HRMS: (ESI) [C₂₆H₃₃BF₂N₂O₃]: *m/z* calcd. 470.2552; found 470.2712.

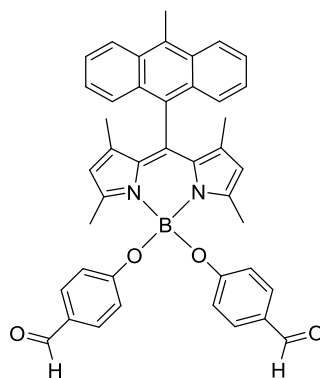
2,6-Diethyl-1,3,5,7-tetramethyl-8-[4-(trimethylsilyl)ethynyl]phenyl]-4,4'-difluoro-4-bora-3a,4a-diaza-s-indacene (5.32)



Synthesised according to General Procedure B: 3-Ethyl-2,4-dimethyl pyrrole (1.08 mL, 8 mmol) and TMS-acetylenebenzaldehyde (804 mg, 4 mmol) were dissolved in anhydrous CH₂Cl₂ (160 mL) and the solution was degassed with Ar_(g) for 1 h. TFA (1 drop) was added and the reaction was stirred at RT overnight. DDQ (906 mg, 4 mmol) was added and the reaction mixture was stirred for 2.5 h. TEA (9 mL) was added, followed by stirring for 15 min. BF₃·OEt₂ (9 mL) was then added followed by stirring for 2 h. The reaction mixture was washed with NaHCO₃ and water, sequentially, and the organic layer was dried over

anhydrous MgSO₄. The solvent was removed *in vacuo* and the crude material purified *via* column chromatography on silica gel using *n*-hexanes as eluent, increasing polarity up to 10% EtOAc in *n*-hexanes to collect the compound in a yield of 48% (900 mg, 1.9 mmol). M.p. = 246–248 °C; R_f = 0.70 (SiO₂, CH₂Cl₂); ¹H NMR (CDCl₃, 400 MHz): δ = 0.98 (s, 9H, TMS), 0.96–0.99 (t, 6H, CH₂CH₃, *J* = 7.5 Hz), 1.29 (s, 6H, CH₃), 2.27–2.32 (q, 4H, CH₂CH₃, *J* = 7.5 Hz), 2.52 (s, 6H, CH₃), 7.23–7.25 (d, 2H, Ar-H, *J* = 8.2 Hz) and 7.58–7.60 (d, 2H, Ar-H, *J* = 8.2 Hz) ppm; ¹³C NMR (100 MHz, CDCl₃): δ = 11.9, 12.6, 14.9, 16.8, 57.4, 95.0, 103.8, 123.4, 128.8, 130.4, 132.8, 133.0, 137.2, 137.8, 139.3 and 152.7 ppm; UV-vis (CH₂Cl₂) λ_{max} (log ε) = 381 (4.38) and 529 (4.92) nm; HRMS: (ESI) [C₂₈H₃₅BF₂N₂Si]: *m/z* calcd. 476.2631; found 476.3051.

1,3,5,7-Tetramethyl-8-(9-methylanthracenyl)-4,4'-bis(4-formylphenyl)-4-bora-3a,4a-diaza-s-indacence (5.26)

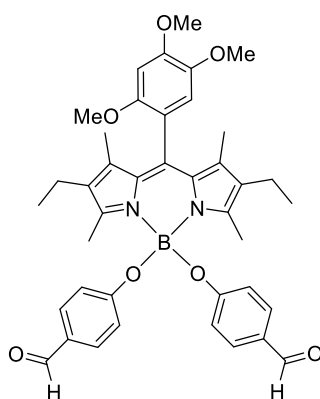


5.26

5.24 (100 mg, 0.228 mmol) and AlCl₃ (45 mg, 0.342 mmol) were dissolved in anhydrous CH₂Cl₂ (10 mL) and the solution was heated to 55 °C for 10 min. The reaction mixture was cooled to RT and 4-hydroxybenzaldehyde (111 mg, 0.912 mmol) in CH₂Cl₂ (10 mL) was added followed by stirring at 55 °C for 10 min. The reaction mixture was washed with water (× 3), the organic phase dried over MgSO₄, and the solvent removed *in vacuo*. The crude material was purified *via* column chromatography on silica gel using *n*-hexanes as eluent, increasing up to 15% EtOAc in *n*-hexanes to collect the title compound **5.26** in a yield of 26% (42 mg, 0.059 mmol). M.p. = 184 °C; R_f = 0.52 (SiO₂, CH₂Cl₂); ¹H NMR (CDCl₃, 400 MHz): δ = 0.68 (s, 6H, CH₃), 2.65 (s, 6H, CH₃), 3.24 (s, 3H, CH₃), 5.91 (s, 2H, Ar-H), 6.94–6.96 (m, 4H, Ar-H), 7.45–7.47 (m, 2H, Ar-H), 7.48–7.59 (m, 2H, Ar-H), 7.72–7.75 (m, 2H, Ar-H), 7.83–7.85 (d, 4H, Ar-H, *J* = 8.2 Hz), 8.38–8.41 (m, 3H, Ar-H)

and 9.93 (s, 2H, CHO) ppm; ^{13}C NMR (100 MHz, CDCl_3): δ = 159.1, 138.9, 137.3, 131.0, 130.8, 130.0, 127.6, 126.2, 126.0, 125.9, 125.6, 125.2, 120.8, 27.1, and 14.98 ppm; UV-vis (CH_2Cl_2) λ_{max} (log ϵ) = 351 (4.12), 372 (4.29), 392 (4.20) and 498 (4.52) nm; HRMS: (ESI) $[\text{C}_{42}\text{H}_{35}\text{BN}_2\text{O}_4]$: m/z calcd. 642.2690; found 643.2925.

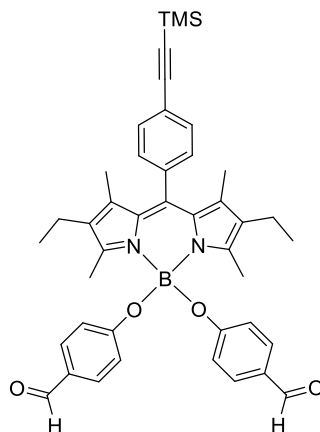
2,6-Diethyl-1,3,5,7-tetramethyl-8-(2,4,5-trimethoxyphenyl)-4,4'-bis(4-formylphenyl)-4-bora-3a,4a-diaza-s-indacence (5.29)



5.29

Synthesised according to General Procedure C: **5.27** (150 mg, 0.319 mmol) and AlCl_3 (85 mg, 0.068 mmol) were dissolved in anhydrous CH_2Cl_2 (15 mL) and the solution was heated to 55 °C for 30 min. The reaction mixture was cooled to RT and 4-hydroxybenzaldehyde (117 mg, 0.957 mmol) was added followed by stirring for 1 h. The reaction mixture was washed with water ($\times 3$), the organic phase dried over MgSO_4 , and the solvent removed *in vacuo*. The crude material was purified *via* column chromatography on silica gel using *n*-hexanes as eluent, increasing up to 10% EtOAc in *n*-hexanes to collect **5.29** in a yield of 36% (77 mg, 0.113 mmol). M.p. = 210 °C; R_f = 0.45 (SiO_2 , CH_2Cl_2); ^1H NMR (CDCl_3 , 400 MHz): δ = 1.22–1.26 (t, 6H, CH_2CH_3 , J = 7.1 Hz), 1.45 (s, 6H, CH_3), 2.14–2.19 (q, 4H, CH_2CH_3 , J = 7.4 Hz), 2.40 (s, 6H, CH_3), 6.63 (s, 1H, Ar-H), 6.68 (s, 1H, Ar-H), 6.73–6.75 (d, 2H, Ar-H, J = 8.6 Hz), 6.82–6.84 (d, 2H, Ar-H, J = 8.7 Hz), 7.60–7.62 (d, 2H, Ar-H, J = 8.7 Hz), 7.63–7.65 (d, 2H, Ar-H, J = 8.7 Hz), 9.76 (s, 1H, CHO), and 9.77 (s, 1H, CHO) ppm; ^{13}C NMR (CDCl_3 , 600 MHz): δ = 11.3, 11.5, 12.7, 12.9, 14.5, 14.6, 17.1, 17.2, 56.1, 56.2, 56.9, 57.7, 97.7, 97.8, 118.7, 128.6, 128.8, 162.6, 162.7, 190.8 and 191.1 ppm; UV-vis (CH_2Cl_2) λ_{max} (log ϵ) = 502 (4.10), 385 (4.22), 371 (4.35) and 342 (4.11) nm; HRMS: (ESI) $[\text{C}_{40}\text{H}_{43}\text{BN}_2\text{O}_7]$: m/z calcd. 674.3163; found 674.2905.

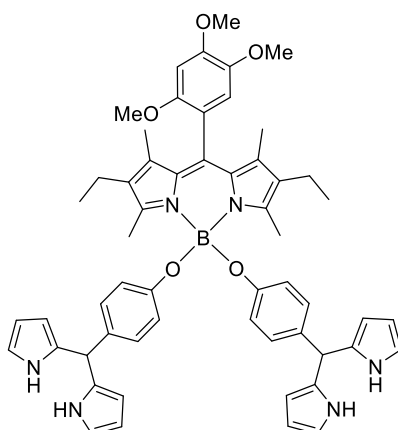
2,6-Diethyl-1,3,5,7-tetramethyl-8-[4-(trimethylsilyl)ethynyl]phenyl]-4,4'-bis(4-formylphenyl)-4-bora-3a,4a-diaza-s-indacence (5.34)



5.34

Synthesised according to General Procedure C: **5.32** (150 mg, 0.32 mmol) and AlCl_3 (63 mg, 0.47 mmol) were dissolved in anhydrous CH_2Cl_2 (20 mL) and the solution was heated to 55 °C for 30 min. The reaction mixture was cooled to RT and 4-hydroxybenzaldehyde (115 mg, 0.95 mmol) was added followed by stirring for 1 h. The reaction mixture was washed with water ($\times 3$), the organic phase dried over MgSO_4 , and the solvent removed *in vacuo*. The crude material was purified *via* column chromatography on silica gel using *n*-hexanes as eluent, increasing up to 10% EtOAc in *n*-hexanes to collect the title compound **5.34** in a yield of 25% (54 mg, 0.079 mmol). M.p. = 190–193 °C; R_f = 0.69 (SiO_2 , CH_2Cl_2); ^1H NMR (CDCl_3 , 400 MHz): δ = 0.30 (s, 9H, TMS), 1.22–1.26 (t, 6H, CH_2CH_3 , J = 7.1 Hz), 1.33 (s, 6H, CH_3), 2.13–2.19 (q, 4H, CH_2CH_3 , J = 7.4 Hz), 2.43 (s, 6H, CH_3), 6.71–6.73 (d, 4H, Ar-H, J = 8.6 Hz), 7.25–7.27 (d, 2H, Ar-H, J = 8.6 Hz), 7.64–7.66 (d, 4H, Ar-H, J = 8.6 Hz) and 9.78 (s, 2H, CHO) ppm; ^{13}C NMR (CDCl_3 , 600 MHz): δ = 11.2, 12.9, 14.5, 14.6, 17.1, 17.9, 43.1, 56.1, 56.9, 105.7, 112.1, 125.2, 128.7, 130.2, 132.9, 149.3, 150.9, 162.6, 162.8, 190.5 and 190.8 ppm; UV-vis (CH_2Cl_2) λ_{max} (log ϵ) = 499 (4.31), 379 (4.22), 362 (4.26) and 349 (4.12) nm; HRMS: (ESI) $[\text{C}_{42}\text{H}_{44}\text{BN}_2\text{O}_4\text{Si}]$: m/z calcd. 679.3189; found 679.3176.

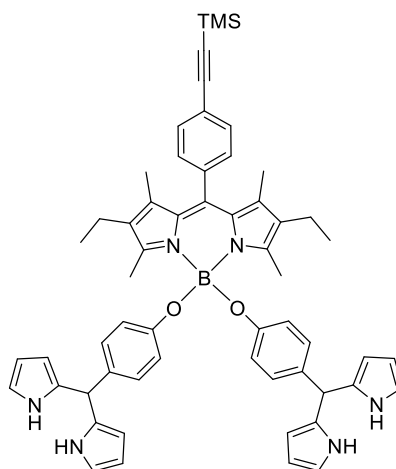
2,6-Diethyl-1,3,5,7-tetramethyl-8-(2,4,5-trimethoxyphenyl)-4,4'-bis(4-formylphenyl-dipyrromethane)-4-bora-3a,4a-diaza-s-indacence (5.36)



5.36

5.29 (200 mg, 0.266 mmol) and InCl_3 (6 mg, 0.027 mmol) were dissolved in pyrrole (0.4 mL, 5.36 mmol) and the solution was stirred at RT for 1 h under $\text{Ar}_{(\text{g})}$. The reaction mixture was directly dry-loaded on silica gel and purified *via* column chromatography using *n*-hexanes as eluent, increasing up to 50% EtOAc to collect the desired compound in a yield of 13% (32.5 mg, 0.036 mmol). M.p. = 240–244 °C; R_f = 0.30 (SiO_2 , CH_2Cl_2); ^1H NMR (CD_3OD , 400 MHz): δ = 0.86–0.89 (t, 6H, CH_2CH_3 , J = 7.5 Hz), 1.43 (s, 6H, CH_3), 2.21–2.27 (q, 4H, CH_2CH_3 , J = 7.5 Hz), 2.47 (s, 6H, CH_3), 3.60 (s, 3H, OCH_3), 3.66 (s, 3H, OCH_3), 3.91 (s, 3H, CH_3), 5.22 (s, 1H, Ar-H), 5.24 (s, 1H, Ar-H), 5.64–5.68 (m, 4H, Ar-H), 5.89–5.97 (m, 2H, Ar-H), 6.39–6.41 (d, 2H, Ar-H, J = 8.4 Hz), 6.55–6.61 (m, 6H, Ar-H), 6.64–6.69 (m, 2H, Ar-H), 6.79–6.85 (m, 4H, Ar-H), 6.94–7.00 (m, 2H, Ar-H) and 9.73 (br s, 4H, NH) ppm; ^{13}C NMR (CD_3OD , 600 MHz): δ = 10.1, 10.2, 11.1, 11.7, 13.1, 13.7, 13.8, 16.4, 16.5, 19.5, 43.1, 43.2, 43.3, 53.4, 55.3, 55.4, 55.6, 55.9, 56.1, 56.3, 60.2, 98.3, 98.4, 105.6, 105.8, 105.9, 106.0, 106.1, 106.4, 106.5, 106.6, 113.3, 114.1, 114.3, 114.4, 115.4, 116.3, 116.4, 116.5, 117.3, 118.4, 128.6, 128.7, 129.0, 129.1, 131.9, 132.1, 132.7, 132.8, 133.7, 133.8, 133.9, 134.5, 134.6, 136.6, 137.5, 137.7, 138.0, 144.2, 144.3, 151.0, 151.1, 151.2, 152.7, 153.2, 154.7, 154.9, 155.3, 155.4 and 155.5 ppm; UV-vis (CH_2Cl_2) λ_{max} (log ϵ) = 391 (4.94), 423 (4.86), 466 (4.70) and 482 (4.74) nm; HRMS: (ESI) $[\text{C}_{56}\text{H}_{59}\text{BN}_6\text{O}_5]$: m/z calcd. 906.4640; found 906.4701.

2,6-Diethyl-1,3,5,7-tetramethyl-8-[4-(trimethylsilyl)ethynyl]phenyl]-4,4'-bis(4-formylphenyl-dipyrromethane)-4-bora-3a,4a-diaza-s-indacence (5.37)



5.37

5.34 (80 mg, 0.117 mmol) and InCl_3 (5 mg, 0.023 mmol) were dissolved in pyrrole (0.35 mL, 4.69 mmol) and the solution was stirred at RT for 1 h under $\text{Ar}_{(\text{g})}$. The reaction mixture was directly dry-loaded on silica gel and purified *via* column chromatography using *n*-hexanes as eluent, increasing up to 10% EtOAc to collect the desired compound as a mixture with a side product. Further column chromatography was carried out using the same conditions, and the desired compound was collected in 10% yield (11 mg, 0.012 mmol). M.p. = 247 °C (degraded); R_f = 0.31 (SiO_2 , CH_2Cl_2); ^1H NMR (CDCl_3 , 400 MHz): δ = 0.30 (s, 9H, TMS), 0.83–0.88 (m, 6H, CH_2CH_3), 1.27 (s, 6H, CH_3), 2.18–2.20 (m, 4H, CH_2CH_3), 2.50 (s, 6H, CH_3), 5.33 (s, 2H, Ar-H), 5.83 (s, 4H, Ar-H), 6.11–6.13 (m, 6H, Ar-H), 6.54–6.56 (d, 4H, Ar-H, J = 8.5 Hz), 6.65 (s, 4H, Ar-H), 6.89–6.91 (d, 4H, Ar-H, J = 8.5 Hz), 7.12–7.14 (d, 2H, Ar-H, J = 7.9 Hz), 7.56–7.58 (d, 2H, Ar-H, J = 7.9 Hz) and 7.86 (br s, 4H, NH) ppm; ^{13}C NMR (CDCl_3 , 600 MHz): δ = 12.0, 12.9, 14.1, 14.2, 14.6, 17.0, 17.1, 21.1, 22.6, 22.7, 25.6, 29.4, 29.7, 31.6, 31.9, 42.5, 43.2, 60.4, 67.9, 115.1, 115.4, 116.0, 116.4, 116.9, 117.1, 117.7, 117.9, 118.1, 118.8, 128.4, 128.9, 129.6, 130.6, 131.1, 132.6, 132.8, 133.0, 133.2, 154.2, 154.7 and 154.8 ppm; UV-vis (CH_2Cl_2) λ_{max} (log ϵ) = 387 (4.88), 417 (4.70), 468 (4.62) and 486 (4.71) nm; HRMS: (ESI) $[\text{C}_{28}\text{H}_{25}\text{BF}_2\text{N}_2]$: $[\text{M}]^+$ m/z calcd. 913.4797; found 669.3702.

6.6 X-Ray Crystallography

Single crystal X-ray diffraction data for all compounds were collected on a Bruker APEX 2 DUO CCD diffractometer by using graphite-monochromated MoK α ($\lambda = 0.71073$ Å) radiation. Crystals were mounted on a MiTeGen MicroMount and collected at 100(2) K by using an Oxford Cryosystems Cobra low-temperature device. Data were collected using omega and phi scans and were corrected for Lorentz and polarisation effects by using the APEX software suite.^{332–334} Using Olex2, the structure was solved with the XT structure solution program, using the intrinsic phasing solution method and refined against $|F^2|$ with XL using least squares minimisation.^{283,335} The C and N bound H atoms were placed in their expected calculated positions and refined as riding model: N–H = 0.88 Å, C–H = 0.95–0.98 Å, with U_{iso} (H) = 1.5 U_{eq} (C) for methyl H atoms and 1.2 U_{eq} (C, N) for all other atoms other H atoms. In the structure of compound **3.23**, the methyl ester at C13 was modelled over two positions using restraints (SADI, SIMU, and ISOR) and constraints (EADP) in an 80:20% occupancy. A 1% inclusion of the palladium(II) derivative was modelled in the structure. In the structure of compound **2.30**, both allyl groups were modelled over two positions using the restraints DFIX in a 55:45% occupancy. The methyl ester at C13 was modelled over two positions using restraints (SIMU) in a 54:46% occupancy.

Table 6.1: Details of XRD data collection and refinement.

Compound	3.5	3.23	3.30
Empirical formula	C ₄₄ H _{41.99} N ₄ O ₄ Pd _{0.01}	C _{48.03} H _{52.06} Cl _{0.06} N ₆ O ₄	C ₃₈ H ₄₂ N ₄ O ₄
Formula weight	691.87	779.50	618.75
Temperature/K	99.98	100(2)	100(2)
Crystal system	orthorhombic	Monoclinic	triclinic
Space group	Pbca	P2 ₁ /C	P $\bar{1}$
a/Å	25.8161(10)	16.7032(10)	8.7165(15)
b/Å	8.5863(3)	7.2160(4)	14.056(3)
c/Å	32.5051(12)	31.0724(16)	14.557(3)
α /°	90	90	72.555(7)

$\beta/^\circ$	90	101.9100(10)	74.384(5)
$\gamma/^\circ$	90	90	75.547(4)
Volume/ $\text{\AA}^3$	7205.2(5)	4103.3(4)	1610.8(5)
Z	8	4	2
$D_{\text{calc}} \text{ g/cm}^3$	1.276	1.262	1.276
μ/mm^{-1}	0.087	0.085	0.083
F(000)	2932.0	1661	660.0
Crystal size/ mm^3	0.56×0.27×0.07	0.52×0.199×0.086	0.30×0.18×0.02
Radiation	MoK α	MoK α	MoK α
Wavelength/ $\text{\AA}$	$\lambda = 0.71073$	$\lambda = 0.71073$	$\lambda = 0.71073$
$2\theta/^\circ$	2.962–56.606	2.680–27.280	3.000–51.066
Reflections collected	89421	60005	35315
Independent reflections	8957	9184	5921
R_{int}	0.0588	0.0408	0.0771
R_{sigma}	0.0326	0.0262	0.0711
Restraints	40	135	15
Parameters	524	603	467
GooF	1.046	1.026	1.046
$R_1 [I > 2\sigma(I)]$	0.0555	0.0593	0.0838
$wR_2 [I > 2\sigma(I)]$	0.1211	0.1571	0.2295
$R_1 [\text{all data}]$	0.0873	0.0745	0.1305
$wR_2 [\text{all data}]$	0.1362	0.1702	0.2582
Largest peak/ $e \text{ \AA}^{-3}$	0.52	0.524	0.64
Deepest hole/ $e \text{ \AA}^{-3}$	-0.44	-0.342	-0.39

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