JOC The Journal of Organic Chemistry

Article

Functionalization of Deutero- and Protoporphyrin IX Dimethyl Ester via Palladium-catalyzed Coupling Reactions

Jessica M. O'Brien, Elisabeth Sitte, Keith J. Flanagan, Hannes Kühner, Lukas J. Hallen, Dáire Gibbons, and Mathias O. Senge

J. Org. Chem., **Just Accepted Manuscript** • DOI: 10.1021/acs.joc.9b00350 • Publication Date (Web): 16 Apr 2019

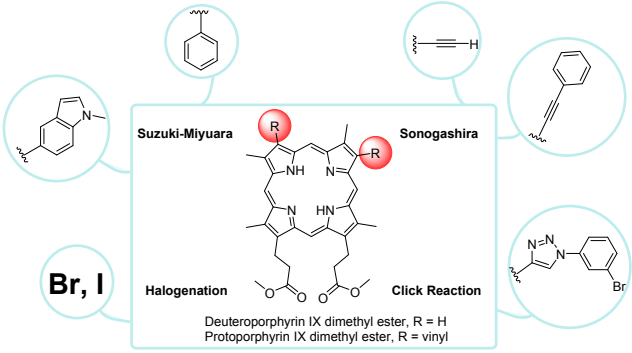
ACS Publications

is published by the American Chemical Society. 1155 Sixteenth Street N.W., Washington, DC 20036

Functionalization of Deutero- and Protoporphyrin IX Dimethyl Ester via Palladium-catalyzed Coupling Reactions

*Jessica M. O'Brien,[§] Elisabeth Sitte,[§] Keith J. Flanagan, Hannes Kühner, Lukas J. Hallen, Dáire Gibbons, and Mathias O. Senge**

School of Chemistry, SFI Tetrapyrrole Laboratory, Trinity Biomedical Sciences Institute, 152–160 Pearse Street, Trinity College Dublin, The University of Dublin, Dublin 2, Ireland



ABSTRACT Herein, we report the functionalization of the *β*-positions of deutero- and protoporphyrin IX dimethyl ester. Initial halogenations were carried out on both deutero- and protoporphyrin IX dimethyl ester. While previously reported, vastly optimized yields with respect to deuteroporphyrin halogenation were obtained. Methods were developed for the bromination of the vinyl groups of protoporphyin IX dimethyl ester. Subsequent palladium-

catalyzed coupling reactions were utilized to modify the periphery of these naturally occurring porphyrin derivatives with a variety of functionalities. The described Suzuki, Sonogashira, as well as "Click" reactions demonstrate the ease at which these porphyrins may be manipulated and even interchangeable, as will be discussed for one example. X-ray crystallographic analysis successfully determined the structure of two derivatives synthesized. Results identified a unique head-to-tail stacking pattern for 3,8-diphenyldeuteroporphyrin IX dimethyl ester, most likely due to the presence of additional aromatic moieties on the periphery of the porphyrin.

INTRODUCTION

Deuteroporphyrin IX and protoporphyrin IX, both non-natural and natural porphyrin derivatives, respectively, were initially synthesized as intermediates in the form of their dimethyl ester counterparts (**1** and **2**, Figure 1) during Hans Fischer's total synthesis of hemin in 1929.[1] As shown in Figure 1, both deutero- and protoporphyrin IX offer multiple points of functionalization, 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.

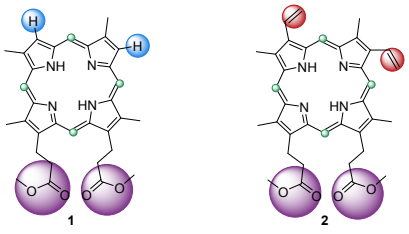


Figure 1. Individually addressable functionalization points in deuteroporphyrin IX dimethyl ester **1** (left) and protoporphyrin IX dimethyl ester **2** (right).

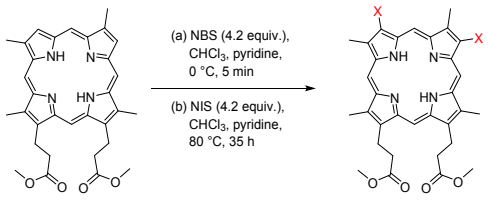
Various functionalization routes have been reported, such as Pd-catalyzed Heck coupling reactions utilizing a derivative of **1** and methyl acrylate, performed by Smith and Langry in 1983.[2] Smith *et al.* later demonstrated both Heck and Stille couplings at the *β*-positions, synthesizing a variety of alkenyl- and styryl-substituted deutero- and protoporphyrin IX derivatives.[3] Numerous Heck couplings have been reported since,[4] as well as Sonogashira couplings more recently.[5] The vinyl groups of both **2** and the corresponding zinc derivative have been directly functionalized *via* a Heck reaction by Castella *et al*., yielding mixtures of four regioisomers.[4d] 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.[6]

Though much progress has been made with regards to the functionalization of **1**, the previously described couplings have proceeded through mercurated *β*-positions, which for any biological studies is far from optimal.[2a,3b] Additionally, previous endeavors to modify **1** and **2** have been limited by the availability of halogenated precursors, coupling substrate scope and/or formation of product mixtures. Thus, we have developed more efficient methods for the halogenation of **1** and **2**. This enabled our investigation into an efficient and versatile method for peripheral functionalization of these natural type IX substituted porphyrin derivatives – most notably the development of methods for application of the highly versatile Suzuki-Miyaura cross-coupling.[7,8] It is hoped that these derivatives may prove to be useful biologically active candidates for treatments such as photodynamic therapy (PDT), as are their parent compounds.[9] The use of protoporphyrin-containing nanomaterials as photosensitizers[10] evokes the demand for methods of covalent conjugation of these compounds, e.g. *via* newly introduced functional groups. In addition, derivatives of **1** and **2** could serve as bactericidal agents against heme-iron dependent

pathogenic bacteria such as *Mycobacterium tuberculosis*, *Staphylococcus aureus* and *Porphyromonas gingivalis*, either by disruption of the heme uptake pathway or by delivery of a drug[11] and analogs of the natural tetrapyrroles are important tools for the elucidation of their biosynthetic pathways.[12] Furthermore, protoporphyrin IX and its derivatives promise usefulness as parts of sensors for toxins and volatile organic compounds (VOCs), *e.g.*, for food safety control.[13] The tuning of properties such as solubility could broaden the porphyrins' spectrum of applicability in this field.

RESULTS AND DISCUSSION

The *β*-halogenation of **1** began with the bromination, which followed an adapted literature procedure (Scheme 1, a).[14] The product was obtained in a 92% yield, an improvement on both procedures referenced, which reported yields of 45% and 40%, respectively. Amalgamation of both procedures, utilizing NBS as brominating agent, and a temperature of 0 °C for the course of the reaction and work-up markedly enhanced the efficiency of the reaction. Additionally, in both reported procedures purification *via* column chromatography was required, whereas in the synthesis reported a washing step followed by recrystallization from MeOH afforded **3** not only in high yield but also high purity. The iodination followed, although reaction conditions were altered considerably to afford the diiodinated product. Literature procedures were explored.[15] However, the best results were obtained upon treatment with NIS with reflux at 80 °C for 48 h, giving **4** in a yield of 76%.



1

3 X = Br 92%
4 X = I 79%

Scheme 1. Halogenation of deuteroporphyrin IX dimethylester **1**.

The Suzuki-Miyaura Pd-catalyzed coupling reaction was chosen for our initial investigations.[8] The first attempt at the Suzuki coupling of **3** and phenylboronic acid (Scheme 2) followed one reported previously by us[16a] in which the porphyrin is reacted with 10 equiv. of the boronic acid in THF with 20 equiv. of K_3PO_4 and 10 mol% $Pd(PPh_3)_4$ at 60 °C. In this case, the procedure was unsuccessful in synthesizing the desired product. A second procedure[16b] was followed which utilized 10 equiv. of boronic acid per position to be substituted, 20 equiv. of Cs_2CO_3 and 40 mol% Pd(dppf)Cl_2 in THF at 80 °C. **5** was obtained in a 60% yield after recrystallization from MeOH and confirmed *via* ^{1}H NMR and mass spectrometry analysis.

As the formyl functional group is one of the most important for further porphyrin modification and functionalization,[17] the coupling of **3** and 4-formylphenylboronic acid was chosen to be optimized to establish the best-yielding conditions for future Suzuki-Miyaura coupling reactions. Initially, identical conditions to those which gave a 60% yield of the diphenyl-substituted product (**5**) were utilized (Table 1). This afforded the desired product (**6**) in a 60% yield after recrystallization from MeOH. To improve upon this, and to reduce the amount of catalyst loading, the amount of Pd(dppf)Cl_2 was decreased from 40 mol% to 20 mol% (entry 2), yielding **6** in 61%. 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 solvent resulting in a detrimental effect to the yield of the reaction (entries 3 and 4). Thus, the volume of solvent was kept at 10 mL for 20–25 mg scale reactions, and investigations moved to the catalyst. Both PEPPSI-*i*Pr and Pd(dppe)Cl_2 were employed in 20 mol% (entries 5 and 6). However, as neither catalyst demonstrated even close comparability in efficiency to earlier attempts, Pd(dppf)Cl_2 was employed as the catalyst for future coupling reactions. As optimization attempts were

unsuccessful in achieving higher yields than that of the earlier entries, the conditions detailed in entry 2 were chosen as optimal for future Suzuki-Miyaura couplings.

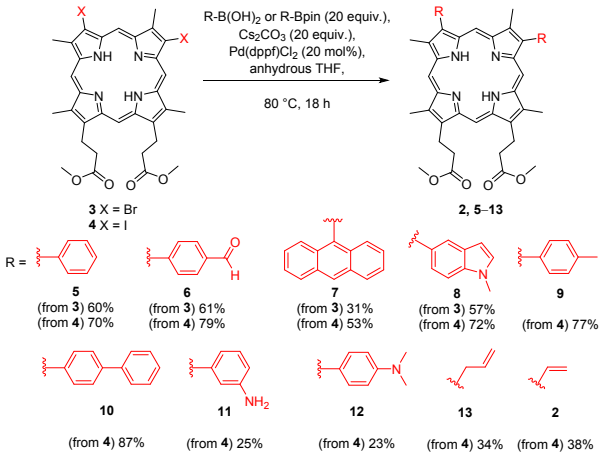
Table 1. Optimization of Suzuki-Miyaura coupling reaction (reactions carried out on a 20 mg scale of **3**).

Entry	Pd catalyst (mol%)	Base (equiv.)	Solvent (mL)	Temp (˚C)	Yield (%)
1	$Pd(dppf)Cl_2$ (40)	Cs_2CO_3 (20)	THF (10)	80	60
2	$Pd(dppf)Cl_2$ (20)	"	"	"	61
3	"	"	THF (5)	"	35
4	"	"	THF (7.5)	"	37
5	PEPPSI-*i*Pr (20)	"	THF (10)	"	–[a]
6	$Pd(dppe)Cl_2$ (20)	"	"	"	46

Reaction conditions: All reactions were performed utilizing 10 equiv. of 4-formylphenylboronic acid under argon for 18 h. Yields were determined after recrystallization from MeOH. [a]Indicates starting material collected only. " Indicates "same as above".

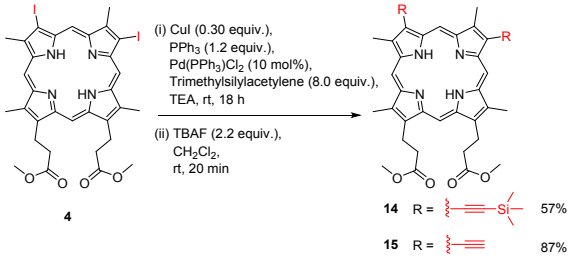
The coupling reaction was repeated using a wide variety of substrates to demonstrate the facile way the deuteroporphyrin periphery can be manipulated (Scheme 2). The dibrominated derivative **3** was compared with the diiodinated derivative **4** as a coupling partner. Notably, the coupling reaction between **4** and 4-formylphenylboronic acid afforded **6** in 79% yield, and higher yields were observed across the board for all couplings. This indicated that iodinated derivative was a more efficient coupling partner in these syntheses, and so **4** was used for future reactions. Aryl couplings tended to give higher yields than those with amine or alkenyl substituents. To compare the effects of various aromatic systems, coupling of **4** with 9-anthraceneboronic acid,

N-methylindolylboronic acid, 4-tolylboronic acid and biphenylboronic acid gave **7**, **8**, **9**, and **10** in yields of 53% to 87% (Scheme 2). Higher yields were obtained with less bulky aromatic substituents, with that of **7** being the lowest, possibly due to the large bulk of the anthracene moiety so close to the porphyrin macrocycle. Amine couplings were by far the poorest yielding. Coupling of **4** with 3-aminophenylboronic acid and 4-dimethylaminophenylboronic acid gave **11** and **12** in yields of 25% and 23%, respectively. A Suzuki coupling between **4** and vinylboronic acid pinacol ester led to the synthesis of protoporphyrin IX dimethyl ester **2** in a yield of 38%. This reaction demonstrated the ease at which **1** can be transformed into another of the natural porphyrin derivatives *via* the use of standard Pd-catalyzed coupling chemistry, albeit if slightly less cost-efficient. In addition, a coupling with allylboronic acid pinacol ester gave **13** in 34% yield. An alkyl coupling was also attempted, using butylboronic acid. However, only mono-substitution and partial dehalogenation occurred, the products of which were determined to be a mixture of mono-β-substituted dehalogenated deuteroporphyrin, the isomers of which have proven to be inseparable.



Scheme 2. Suzuki-Miyaura coupling reactions between **3** or **4** and a variety of boronic acids and boronic acid pinacol esters (**2**, **5**–**13**).

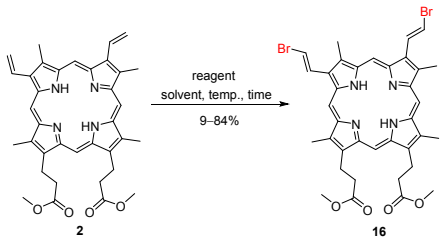
Sonogashira coupling reactions were investigated using both **1** and **2** in order to optimize procedures for more complex synthetic targets, broaden the scope of known derivatives, and compare with other Pd-catalyzed coupling reactions. No coupling was observed when **3** was employed as the coupling partner, consistent with the results reported by Brunner and Schellerer.[5b] However, a 14% yield was obtained upon reaction of **4** and trimethylsilylacetylene. Further investigation found that carrying out the reaction at room temperature, instead of 70 °C, gave a considerably higher yield of **14**, 57% (Scheme 3). Deprotection *via* TBAF gave **15** in 87%.



Scheme 3. Sonogashira coupling of diiododeuteroporphyrin dimethyl ester **4** and subsequent deprotection to give **15**.

Following *β*-functionalization of **1**, the scope of palladium-catalyzed coupling reactions was expanded to **2**. While C-H bond halogenations of chlorin vinyl groups have been reported previously,[18] equivalent bromovinyl or iodovinyl derivatives of protoporphyrin IX have been unknown so far. Attempts to iodinate the vinyl moieties of **2** using either NIS or I_2 and PIFA did not yield the desired product. Conversely, bromination with NBS in DCE at 84 °C afforded the dibrominated product **18** in 9% (Scheme 4, Table 2, entry 1). Various reaction conditions were screened for the bromination of **2**. As a general trend, it was ascertained that a decrease in reaction time reduced decomposition of the porphyrin and the use of a minimal amount of NBS lowered the formation of side products with multiply brominated vinyl groups (entry 2–4). A

yield of 40% was the highest obtained when **2** was reacted with 2.2 equiv. NBS in DCE at 84 °C for 2.5 h. Change of solvent to DCM and decrease in the reaction temperature to 40 °C resulted in no product formation at all (entry 5). Finally, pyridinium bromide perbromide (PBPB) was employed as a brominating agent (2.2 equivalents) and the reaction was carried out in $CHCl_3$ at 61 °C for 3 h and formation of the desired product increased significantly giving 84% yield (entry 6).



Scheme 4. Bromination of the vinyl groups of **2**. Reaction conditions used are given in Table 2.

Table 2. Optimization of protoporphyrin IX dimethyl ester (**2**) bromination to yield **16**.

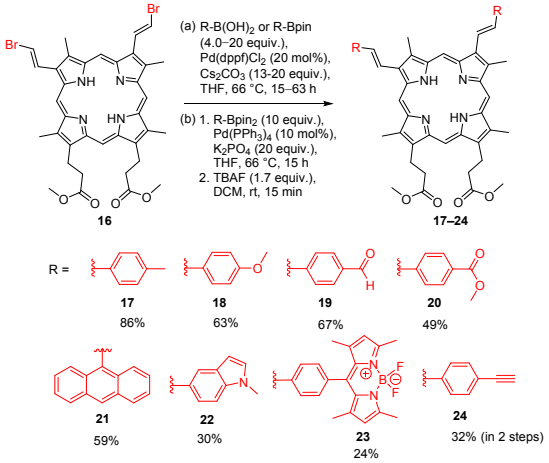
Entry	Brominating agent (equiv.)	Reaction time (h)	Solvent	Temp. (˚C)	Yield (%)
1	NBS (2.2)	18	DCE	84	9
2	NBS (3.0)	5.5	“	“	22
3	“	3	“	“	25
4	NBS (2.2)	2.5	“	“	40
5	“	5	DCM	40	–
6	PBPB (2.2)	3	$CHCl_3$	61	84

“ Indicates “same as above”

– Indicates no product formation.

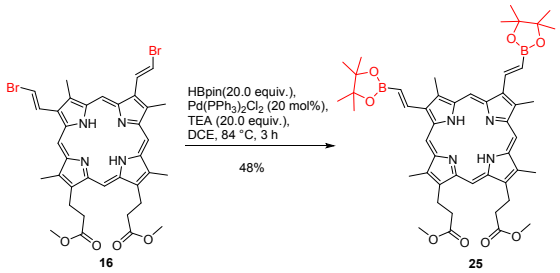
With an efficient procedure for the synthesis of precursor **16** at hand, we sought to devise protocols for Suzuki-Miyaura cross coupling reactions at the vinyl positions. After obtaining good results for the respective reactions at the *β*-positions of **1** using a modified literature

procedure,[16b] similar reaction conditions were applied for Suzuki-Miyaura coupling reactions of **16** with different substrates to afford **17**–**23** (Scheme 5). **16** was reacted with 20 equiv. of aryl boronic acid or boronic acid pinacol ester in THF at 66 °C, with Pd(dppf)Cl_2 employed as the catalyst and Cs_2CO_3 as the base (Scheme 5, a). A notable high yield of 86% was obtained in the coupling reaction with 4-tolylboronic acid to give **17**. Usage of substrates with functional groups such as 4-methoxyphenyl- and 4-formylphenylboronic acid decreased the product yields (**18** and **19**) to 63% and 67%, respectively. Methyl benzoate substituted porphyrin **20** was isolated in 49% yield which was mainly attributed to the low solubility of the boronate ester used, thus incomplete conversion of the starting material. An anthracene substituent could be introduced in a moderate yield of 59% (**21**) whereas coupling reactions with other bulky units such as 1-methylindole and a BODIPY dye afforded **22** and **23** in only 30% and 24% yield, respectively. Different coupling conditions were employed for the reaction of **16** with 4-[(trimethylsilyl)ethynyl]phenylboronic acid pinacol ester. In order to preserve the silyl protecting groups, thereby preventing side reactions and allowing full characterization of the material, the base was changed to K_3PO_4 (20 equiv.) and Pd(PPh_3)$_4$ (10 mol%) was used as a catalyst (Scheme 5, b). Subsequent deprotection with TBAF gave **24** in 32% overall yield.



Scheme 5. Suzuki-Miyaura coupling reactions of **16** with different boronic acids and boronic acid pinacol esters to yield **17**–**24**.

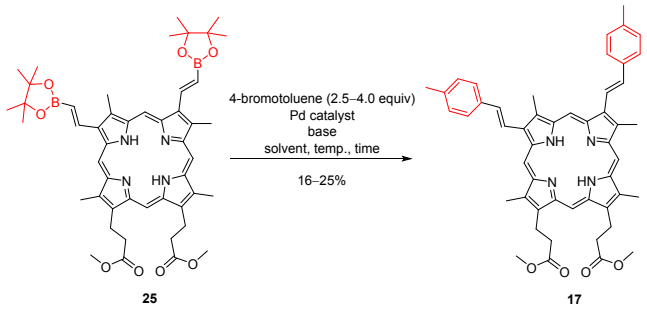
A Masuda borylation[19a] of **16** using pinacolborane was carried out adapting a procedure by Hyslop *et al.*[19b] which uses $Pd(PPh_3)_2Cl_2$ (10 mol%) as a catalyst and TEA (20 equiv.) as a base (Scheme 6). The reaction yielded the bisborylated porphyrin (**25**) in a yield of 48%, as well as observed but unisolated monoborylated products and recovered starting material.



Scheme 6. Masuda borylation of **16** to give **25**.

After the promising results obtained from Suzuki-Miyaura coupling on **16**, further investigations in the reactivity of protoporphyrin IX dimethyl ester derivatives were made by testing the utility of the reversed coupling reaction using **25**. Establishing procedures for Suzuki-Miyaura reactions on protoporphyrin IX dimethyl ester using both reactant combinations would broaden the range of possible coupling substrates. Exploratory reactions of **25** with 4-bromotoluene were carried out with optimization of the procedure being attempted (Scheme 7). Based on a method by Bakar *et al.*[20a] that was applied for coupling reactions with meso-borylated porphyrins, 20 mol% of catalyst $Pd(PPh_3)_4$ and 4.0 equiv. of Cs_2CO_3 were used in THF (Table 3, entry 1). Coupling product **17** was obtained in only 16% yield. Another procedure was employed that had been reported by Hata *et al.*[20b] for coupling reactions with *β*-borylated porphyrins. Use of 10 mol% of $Pd_2(dba)_3$, 0.40 equiv. of PPh_3 and 3.0 equiv. of Cs_2CO_3 in a toluene/DMSO 2:1 mixture led to complete decomposition of the porphyrin within 2 h (entry 2).

The conditions that had previously been applied for Suzuki-Miyaura coupling reactions with brominated protoporphyrin IX derivative **16**, using 20 mol% of $Pd(dppf)Cl_2$ and 20 equiv. of Cs_2CO_3, yielded compound **17** in 25% (entry 3), a low figure compared to the 86% yield when **17** was prepared from **16**. Clearly, dibrominated precursor **16** proved to be more useful for Suzuki-Miyaura coupling reactions than diborylated precursor **25**.



Scheme 7. Suzuki-Miyaura cross-coupling reactions of **25** with 4-bromotoluene to give **17**. Reaction conditions used are given in Table 3.

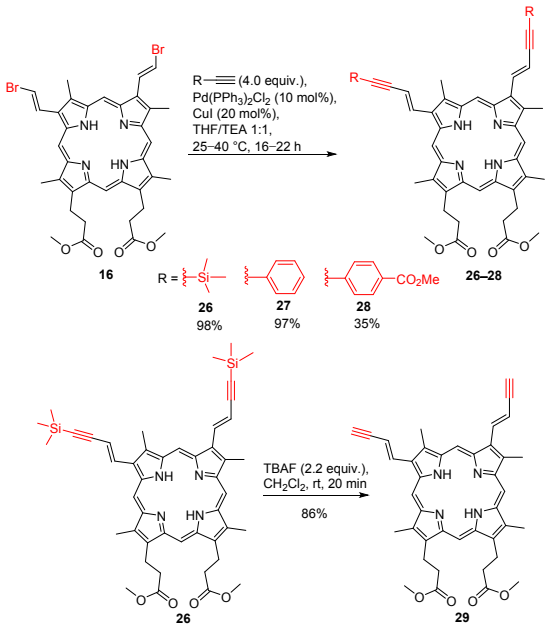
Table 3. Optimization of Suzuki-Miyaura cross-coupling reactions with borylated protoporphyrin IX dimethyl ester (**25**).

Entry	Reagents (equiv.)	Time (h)	Solvent	Temp. (˚C)	Yield (%)
1	4-bromotoluene (2.5) $Pd(PPh_3)_4$ (0.20) Cs_2CO_3 (4.0)	17	THF	66	16
2	4-bromotoluene (4.0) $Pd_2(dba)_3$ (0.10) PPh_3 (0.40) Cs_2CO_3 (3.0)	2	Toluene/DMSO 2:1	80	–
3	4-bromotoluene (4.0) $Pd(dppf)Cl_2$ (0.20)	16	THF	66	25

Cs_2CO_3 (20)

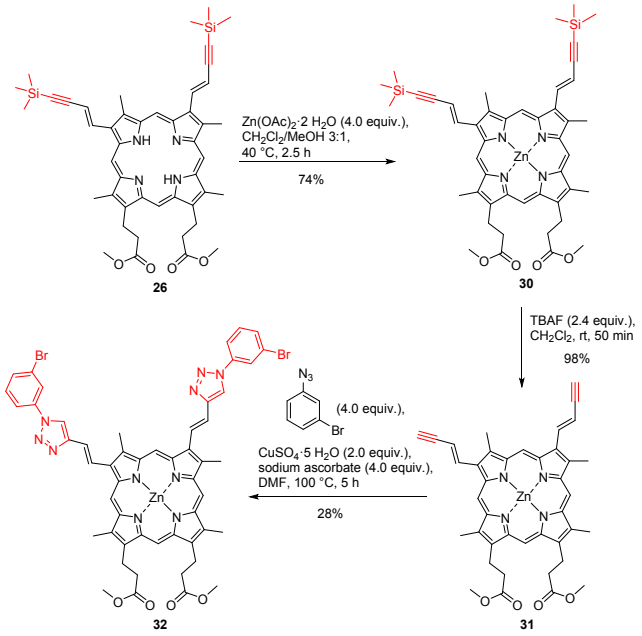
– Indicates no product formation.

Following the study of the scope of Suzuki-Miyaura reactions, Sonogashira couplings using **16** were investigated as well. No product formation in a coupling with trimethylsilylacetylene was observed when copper-free conditions were applied. However, use of $Pd(PPh_3)_2Cl_2$ (10 mol%) with CuI (20 mol%) as a co-catalyst in THF/TEA following a procedure by Fujimoto *et al.*[21] afforded acetylene-appended porphyrin **26** in 98% yield (Scheme 8). A similarly high yield of 97% was obtained when phenylacetylene was used as a coupling partner to form **27**. Conversely, reaction with the more electron-deficient methyl 4-ethynylbenzoate did not lead to complete conversion to the disubstituted product **28**, resulting in only 35% yield of desired compound and a significant amount of recovered starting material. An interchanging cationic and anionic pathway of the Sonogashira reaction mediated by the electron-rich or electron-poor nature of the alkyne was proposed by Ljungdahl *et al.*[22] The reaction conditions applied in our studies may promote the cationic pathway, thereby disfavoring the reaction with electron-poor substrates. The removal of the trimethylsilyl protection groups of **26** using TBAF proceeded in 86% yield.



Scheme 8. Sonogashira coupling reactions between **16** and different ethynyl substrates to give **26**–**28** and deprotection of **26** with TBAF to give **29**.

The ease of appending **16** with an acetylene moiety delivers a readily available starting material for cycloaddition reactions, such as copper-catalyzed 1,3-dipolar cycloadditions of azides and alkynes ("Click reaction").[23] The feasibility of this reaction for acetylene-appended protoporphyrin IX derivatives was tested after insertion of zinc(II) in **26** and subsequent TMS-deprotection to yield **31** (Scheme 9). This was followed by cycloaddition of **31** with 1-azido-3-bromobenzene (4.0 equiv.) using $CuSO_4 \cdot 5\ H_2O$ (2.2 equiv.) and sodium ascorbate (4.0 equiv.) in DMF to obtain **32** in 28% yield. The *meta*-bromophenyl substituent introduced to the porphyrin can be used as a synthetic handle for further arm extensions. This provides acetylene-appended protoporphyrin IX derivatives as new compounds for Click reactions, possibly adding to the recently investigated applications of protoporphyrin IX in bioactive materials, biorthogonal reactions and drug delivery systems.[10a,24]



Scheme 9. Functionalization of a protoporphyrin IX derivative (**31**) by azide-alkyne 1,3-dipolar cycloaddition to give **32**.

The optical properties of synthesized porphyrin derivatives studied were in range of expected parameters. Appending protoporphyrin IX dimethyl ester with aromatic moieties generally led to a 8–10 nm shift of the last Q band absorption maximum. Ethynyl-substituted free base derivatives **26**–**29** showed slightly higher shifts of 9–13 nm, the porphyrin with the largest change being **28**. While the ethynyl moiety extends the conjugation of the porphyrin macrocycle, the electron-withdrawing carbonyl group in **28** also contributes to the bathochromic shift in absorption.

X-ray crystallographic analyses were undertaken on suitable crystals of **5** and **13**, the structures of which were confirmed *via* single crystal X-ray diffraction (Figure 2). Both 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 (**5**) and 0.035 Å (**13**), respectively. This is comparable to literary examples of deuteroporphyrin IX samples (Figure 3), in which the atom deviation from the LSP of the macrocycle ranges from 0.029–0.086 Å.[25]

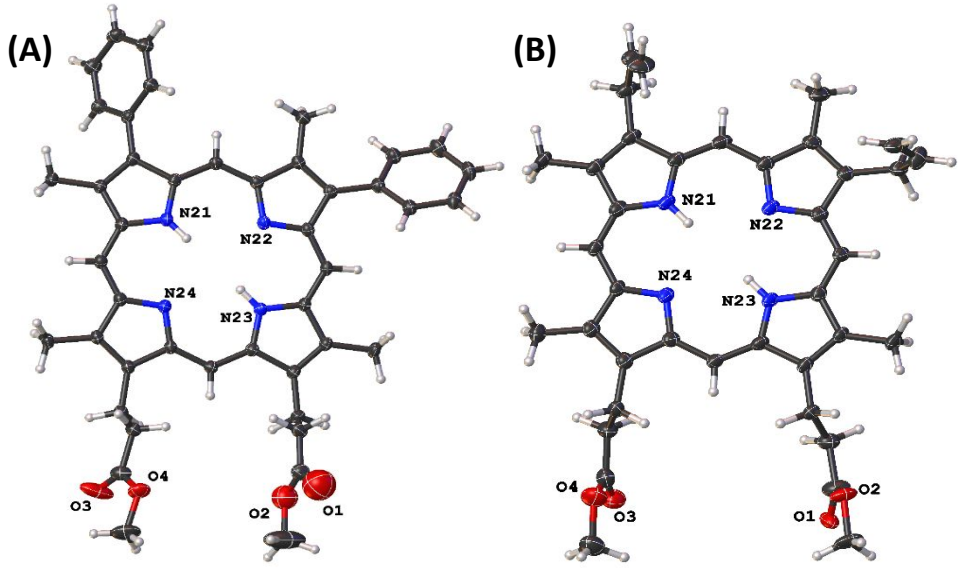


Figure 2. The molecular structure of compounds **5** (A) and **13** (B). Thermal displacement is given at 50% probability.

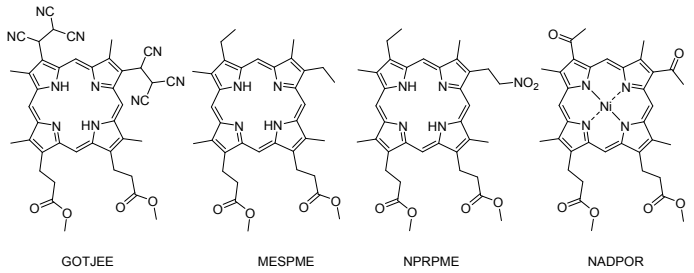


Figure 3. Literary samples of deuteroporphyrin IX dimethyl ester derivatives obtained from the CCDC database (updated August 2018).[25e]

The structure of **5** illustrates two packing patterns; the first is the offset head-to-head stacking pattern, aided by a C–H···O interaction between the methyl ester moiety at O1···H17C and O1···H13F at a distance of 2.764(8) and 2.664(7) Å, respectively (Figure 4A). The second packing motif is the head-to-tail overlap caused by interaction of the methyl ester moiety with the phenyl hydrogen atoms (O3···H36) at a distance of 2.606(8) Å (Figure 4B). This results in the zig-zag pattern observed for the packing of compound **5** (Figure 5).

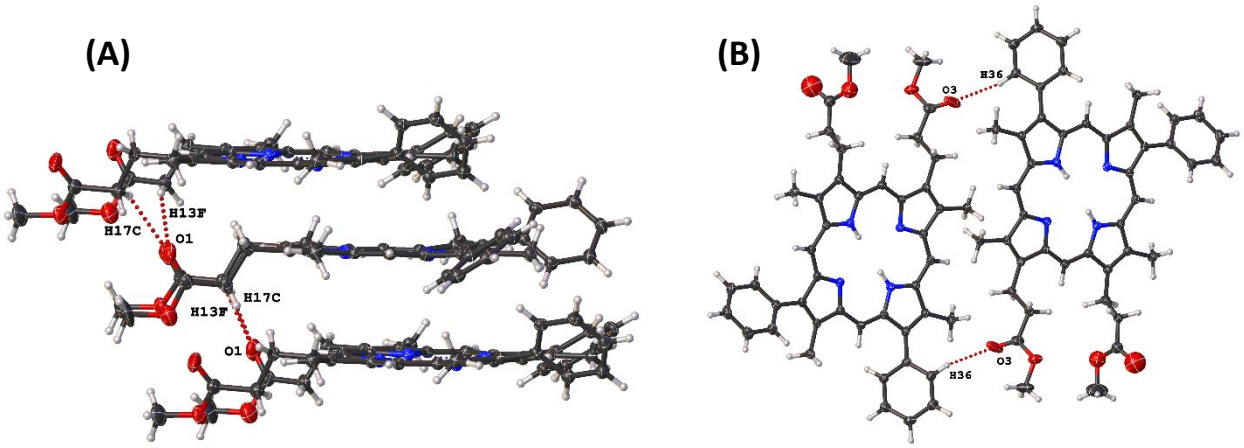


Figure 4. Molecular structure of compound **5** showing the head-to-head stacking pattern (A) and

the head-to-tail stacking pattern (B). O···H interactions are indicated by the red dashed lines. Thermal displacement is given at 50% probability.

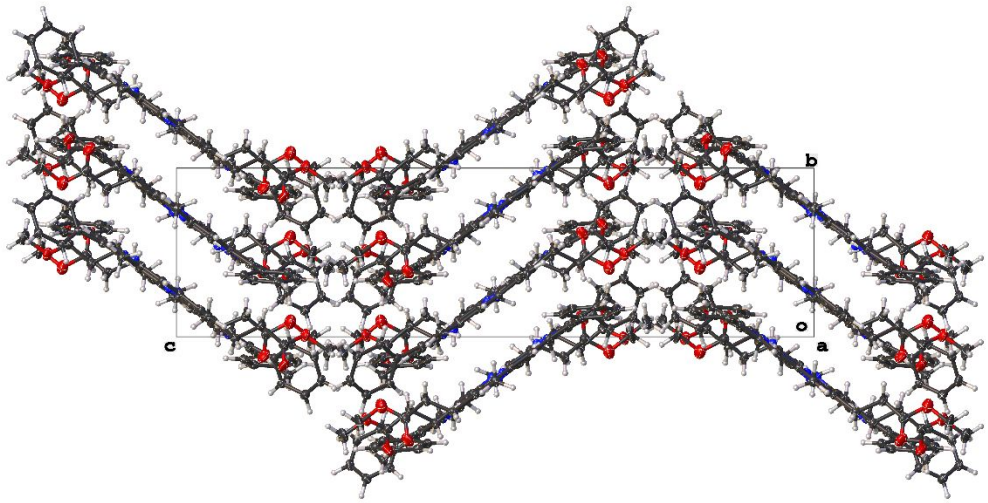


Figure 5. Crystal packing of compound **5** looking down the *a*-axis. Thermal displacement is given at 50% probability.

Compound **13** exhibits a head-to-head interaction 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 (Figure 6). Additionally, a head-to-head overlap aided by a C–H···O short contact between the methyl ester moieties (O1···H17E) is observed, at a distance of 2.425(3) Å (Figure 7). This results in the stepwise packing pattern, as illustrated in Figure 8. The introduction of the carbon between the vinyl group and the *β*-carbon of the porphyrin scaffold perturbs the side chain more out-of-plane than that of the naturally occurring protoporphyrin IX dimethyl ester.[26]

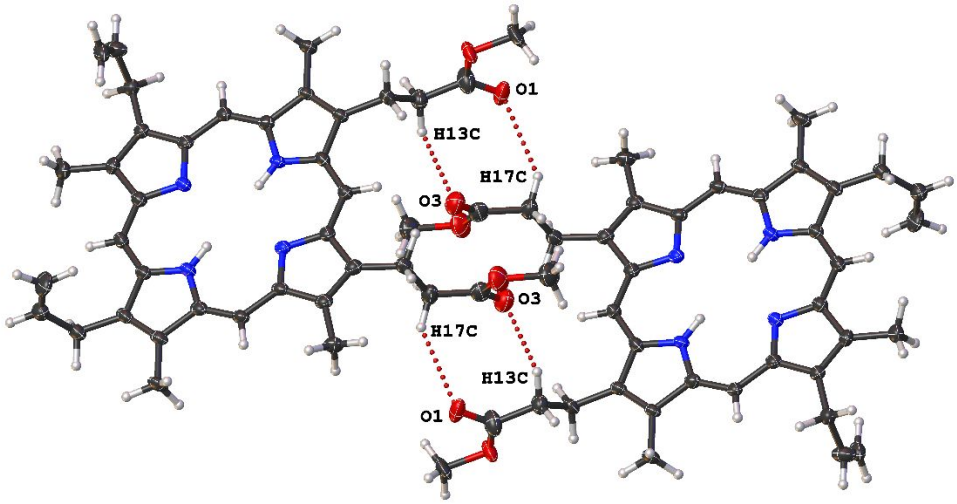


Figure 6. Molecular structure of compound **13** showing the head-to-head interaction between the methyl ester moieties. O···H interactions are indicated by the red dashed lines. Thermal displacement is given at 50% probability.

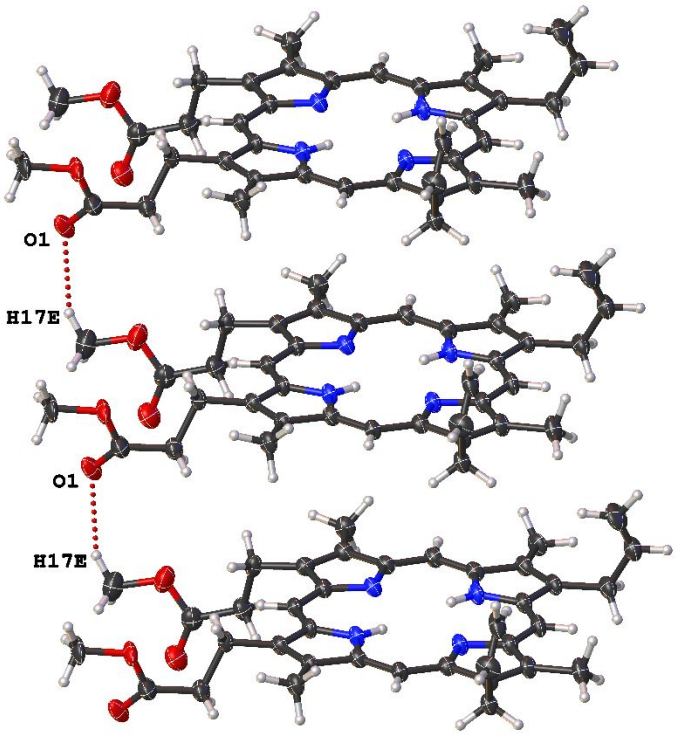


Figure 7. Molecular structure of compound **13** showing the head-to-head stacking pattern. O···H interactions are indicated by the red dashed lines. Thermal displacement is given at 50% probability.

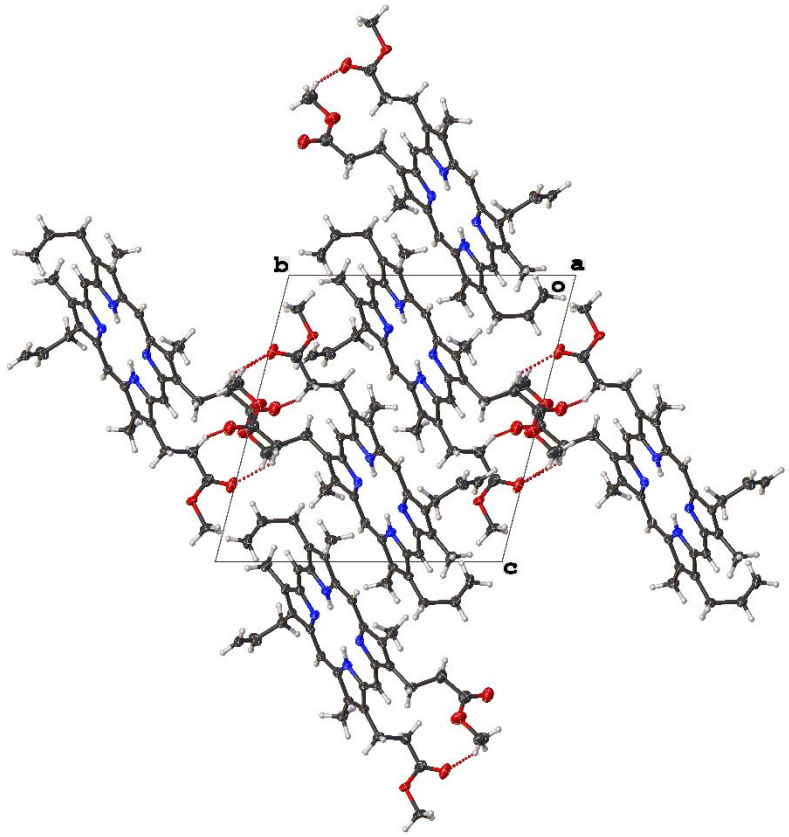


Figure 8. Crystal packing of compound **13** looking down the *a*-axis. Thermal displacement is given at 50% probability.

In comparison to the aforementioned literary samples (Figure 3), the head-to-head stacking and overlap is the most common packing motif formed. Thus, the head-to-tail stacking featured in **5** is unique, and most likely a result of the additional aromatic ring present.

CONCLUSIONS In conclusion, we have demonstrated the ease at which deutero- and protoporphyrin IX dimethyl ester can be functionalized *via* the use of classical palladium-catalyzed coupling reactions. The optimized conditions will allow further manipulation of optical

properties, due to the scope of functionalities introduced. The porphyrin derivatives synthesized herein are promising candidates for apoprotein reconstitution studies to investigate cofactor binding and possible enhancement of the catalytic activity of enzymes.[27] Furthermore, it was shown that the devised reaction procedures enable the facile attachment of functional molecules such as fluorophores to the porphyrin periphery. In future, this methodology may also be applied for the introduction of linker groups to produce useful bio-probes.

EXPERIMENTAL SECTION

General Information. 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, apart from pyrrole which was filtered through a plug of silica before 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 oil bath as a heat source. Flash chromatography was carried out using either silica gel Florisil (200 mesh; Aldrich) or ALOX (neutral, particle size 0.05–0.15 mm; Aldrich), as indicated for each synthesis. ALOX was treated by addition of 6% water prior to use to obtain Brockmann activity grade III. Preparative thin layer chromatography was performed on precoated preparative Uniplates (silica, 2000 μm, 20 × 20 cm, Analtech). 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) ALOX plates and visualized by UV irradiation on a Shimadadzu Multispec-1501. Bruker DPX 400 and Agilent 400 were used to obtain ^{1}H (400.13 MHz), ^{13}C{H} (100.61 MHz), ^{19}F{H} (376.60 MHz) and ^{11}B (128.40 MHz) NMR spectra and a Bruker AV 600 was employed for ^{1}H (600.13 MHz) and ^{13}C{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 ionization (MALDI) sources in positive mode with *trans*-2-[3-(4-*tert*-butylphenyl)-2-methyl-2-propenylidene]malononitrile as the matrix.

General procedure A: Compound **3** or **4** (1.0 equiv.), the appropriate boronic acid or boronic acid pinacol ester (20 equiv.), Cs_2CO_3 (20 equiv.), and Pd(dppf)Cl_2 (20 mol%) were dried under high vac. for 1 h. Anhydrous THF was added under $Ar_{(g)}$ 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 saturated aqueous $NaHCO_3$ solution, deionized H_2O, and brine. The organic layer was dried over $MgSO_4$, the solvent removed *in vacuo* and the residue recrystallized from MeOH.

General Procedure B: Compound **16** and Cs_2CO_3 (13–20 equiv.) were dried under high vac. for 1 h. Anhydrous THF was added under $Ar_{(g)}$ and the solution was purged with $Ar_{(g)}$ for 20 min. The appropriate boronic acid or boronic acid pinacol ester (4.0–20 equiv.) and Pd(dppf)Cl_2 (20 mol%) were added and the mixture was purged with $Ar_{(g)}$ for another 5 min. The reaction mixture was then heated to 66 °C for 15–63 h. The solvent was removed *in vacuo* and the residue redissolved in CH_2Cl_2. This was washed sequentially with saturated aqueous $NaHCO_3$ solution, deionized H_2O, and brine. The organic layer was dried over $MgSO_4$, the solvent was removed *in vacuo* and the residue was purified as indicated in the respective section.

General Procedure C: Compound **16**, $Pd(PPh_3)_2Cl_2$ (10 mol%), CuI (20 mol%) and, if solid, the ethynyl substrate (4.0 equiv.) were dried under high vac. for 30 min. To a separate sealed tube, anhydrous THF and anhydrous TEA were added in a 1:1 ratio under $Ar_{(g)}$, followed by, if liquid, the ethynyl substrate (4.0 equiv.). The mixture was purged with $Ar_{(g)}$ for 15 min and then transferred to the reaction vessel *via* a syringe. The reaction was then stirred at 25–40 °C for 16 h. The solvent was removed *in vacuo* and the residue was purified as indicated in the respective section.

3,8-Dibromo-deuteroporphyrin IX dimethyl ester (**3**) Compound **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. Deionized 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 deionized H_2O. The organic layer was dried over $MgSO_4$, the solvent removed *in vacuo*, and the residue recrystallized 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 (ALOX, CH_2Cl_2); ^{1}H 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) $[C_{32}H_{32}N_4O_4Br_2]$ $[M]^+$: *m/z* calcd. 694.0790; found 694.0817.

3,8-Diiodo-deuteroporphyrin IX dimethyl ester (**4**) Compound **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 deionized H_2O. The organic layer was dried over $MgSO_4$, the solvent removed *in vacuo*, and the residue recrystallized 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 (ALOX, CH_2Cl_2); ^{1}H 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) $[C_{32}H_{32}N_4O_4I_2]$ $[M]^+$: *m/z* calcd. 790.0542; found 790.0513.

3,8-Diphenyl-deuteroporphyrin IX dimethyl ester (**5**) Compound **5** was synthesized in accordance with general procedure A, utilizing **3** (25 mg, 0.0359 mmol), phenylboronic acid (88 mg, 0.722 mmol), Cs_2CO_3 (234 mg, 0.718 mmol) and Pd(dppf)Cl_2 (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 **5** was also synthesized from **4** in accordance with general procedure A, utilizing **4** (20 mg, 0.0253 mmol), phenylboronic acid (62 mg, 0.506 mmol), Cs_2CO_3 (165 mg, 0.506 mmol) and Pd(dppf)Cl_2 (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 (ALOX, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ = –3.58 (s, 2H, NH), 3.27–3.34 (m, 4H, CH_2), 3.51 (s, 3H, CH_3), 3.56 (s,

3H, CH_3), 3.66 (s, 3H, CH_3), 3.67 (s, 3H, CH_3), 3.70 (s, 3H, CH_3), 3.73(s, 3H, CH_3), 4.40–4.48 (m, 4H, CH_2), 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; ^{13}C NMR (100 MHz, $CDCl_3$): 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 (CH_2Cl_2) λ_{max} (log ε) = 403 (5.85), 502 (4.75), 536 (4.63), 570 (4.47) and 623 nm (4.31); HRMS (MALDI) [$C_{44}H_{42}N_4O_4$] $[M]^+$: *m/z* calcd. 690.3206; found 690.3207.

3,8-Bis(4-formylphenyl)-deuteroporphyrin IX dimethyl ester (**6**) Compound **6** was synthesized in accordance with general procedure A, utilizing **3** (20 mg, 0.0287 mmol), 4-formylphenylboronic acid (86 mg, 0.574 mmol), Cs_2CO_3 (187 mg, 0.574 mmol) and Pd(dppf)Cl_2 (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 **6** was also synthesized from **4** in accordance with general procedure A, utilizing **4** (20 mg, 0.0253 mmol), 4-formylphenylboronic acid (76 mg, 0.506 mmol), Cs_2CO_3 (165 mg, 0.506 mmol) and Pd(dppf)Cl_2 (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 (ALOX, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ = –3.50 (br s, 2H, NH), 3.50 (s, 3H, CH_3), 3.67 (s, 3H, CH_3), 3.70 (s, 3H, CH_3), 3.75 (s, 3H, CH_3), 3.57 (s, 3H, CH_3), 3.66 (s, 3H, CH_3), 3.28–3.35 (m, 4H, CH_2), 4.40–4.48 (m, 4H, CH_2), 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; ^{13}C NMR (100 MHZ, $CDCl_3$): 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 (CH_2Cl_2) λ_{max} (log ε) = 411 (5.11), 505 (4.05), 539 (3.94),

573 (3.74) and 626 nm (3.60); HRMS (MALDI) $[C_{46}H_{42}N_4O_6]$ $[M]^+$: *m/z* calcd. 746.3104; found 746.3134.

3,8-Bis(9-anthracenyl)-deuteroporphyrin IX dimethyl ester (**7**) Compound **7** was synthesized in accordance with general procedure A, utilizing **3** (21.5 mg, 0.0309 mmol), 9-anthraceneboronic acid (160 mg, 0.721 mmol), Cs_2CO_3 (238 mg, 0.730 mmol) and Pd(dppf)Cl_2 (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 **7** was also synthesized from **4** in accordance with general procedure A, utilizing **4** (20 mg, 0.0253 mmol), 9-anthraceneboronic acid (112 mg, 0.506 mmol), Cs_2CO_3 (165 mg, 0.506 mmol) and Pd(dppf)Cl_2 (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 (ALOX, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ = –3.25 (s, 2H, NH), 3.44 (s, 3H, CH_3), 3.75 (s, 9H, CH_3), 3.63 (s, 3H, CH_3), 3.19–3.25 (m, 2H, CH_2), 4.34–4.39 (m, 4H, CH_2), 3.67 (s, 3H, CH_3), 3.07–3.35 (m, 2H, CH_2), 4.44–4.49 (m, 2H, CH_2), 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; ^{13}C NMR (100 MHz, $CDCl_3$): 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 (CH_2Cl_2) λ_{max} (log ε) = 407 (5.86), 504 (5.95), 538 (5.98), 571 (5.01) and 624 nm (5.05); HRMS: (MALDI) $[C_{60}H_{50}N_4O_4]$ $[M]^+$: *m/z* calcd. 890.3832; found 890.3801.

3,8-Bis(N-methylindolyl)-deuteroporphyrin IX dimethyl ester (**8**) Compound **8** was synthesized in accordance with general procedure A, utilizing **3** (20 mg, 0.0287 mmol), 1-methylindole-5-

boronic acid pinacol ester (148 mg, 0.574 mmol), Cs_2CO_3 (187 mg, 0.574 mmol) and Pd(dppf)Cl_2 (4.2 mg, 5.74×10^{-3} mmol) in anhydrous THF (10 mL) to yield a purple crystalline solid (13 mg, 0.0163 mmol, 57%). Compound **8** was also synthesized from **4** in accordance with general procedure A, utilizing **4** (20 mg, 0.0253 mmol), 1-methylindole-5-boronic acid pinacol ester (130 mg, 0.506 mmol), Cs_2CO_3 (165 mg, 0.506 mmol) and Pd(dppf)Cl_2 (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 (ALOX, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ = –3.53 (s, 2H, NH), 3.47 (s, 3H, CH_3), 3.68 (s, 3H, CH_3), 3.71 (s, 3H, CH_3), 3.74 (s, 3H, CH_3), 3.52 (s, 3H, CH_3), 3.66 (s, 3H, CH_3), 3.27–3.35 (m, 4H, CH_2), 4.40–4.49 (m, 4H, CH_2), 4.05 (s, 3H, *N*-CH_3), 4.06 (s, 3H, *N*-CH_3), 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; ^{13}C NMR (100 MHz, $CDCl_3$): 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 (CH_2Cl_2) λ_{max} (log ε) = 403 (5.86), 504 (5.96), 539 (5.99), 570 (5.01) and 624 nm (5.05); HRMS: (ESI) [$C_{50}H_{48}N_6O_4$] $[M]^+$: *m/z* calcd. 796.3737; found 796.3745.

3,8-Bis(4-methylphenyl)-deuteroporphyrin IX dimethyl ester (**9**) Compound **9** was synthesized in accordance with general procedure A, utilizing **4** (20 mg, 0.0253 mmol), 4-tolylboronic acid (69 mg, 0.506 mmol), Cs_2CO_3 (165 mg, 0.506 mmol) and Pd(dppf)Cl_2 (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 (ALOX, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ = –3.57 (s, 2H, NH), 2.68 (s, 3H, CH_3), 2.69 (s, 3H, CH_3), 3.27–3.34 (m, 4H, CH_2), 3.52 (s, 3H, CH_3), 3.55 (s, 3H, CH_3),

3.66 (s, 3H, CH_3), 3.67 (s, 3H, CH_3), 3.70 (s, 3H, CH_3), 3.72 (s, 3H, CH_3), 4.40–4.48 (m, 4H, CH_2), 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; ^{13}C NMR (100 MHz, $CDCl_3$): 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 (CH_2Cl_2) λ_{max} (log ε) = 404 (5.03), 503 (3.89), 538 (3.78), 571 (3.65) and 625 nm (3.43); HRMS: (MALDI) [$C_{46}H_{46}N_4O_4$] $[M]^+$: *m/z* calcd. 718.3519; found 718.3493.

3,8-Bis(4-biphenyl)-deuteroporphyrin IX dimethyl ester (**10**) Compound **10** was synthesized in accordance with general procedure A, utilizing **4** (20 mg, 0.0253 mmol), 4-biphenylboronic acid (100 mg, 0.506 mmol), Cs_2CO_3 (165 mg, 0.506 mmol) and Pd(dppf)Cl_2 (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 (ALOX, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ = –3.54 (br s, 2H, NH), 3.27–3.34 (m, 4H, CH_2), 3.53 (s, 3H, CH_3), 3.62 (s, 3H, CH_3), 3.67 (s, 3H, CH_3), 3.68 (s, 3H, CH_3), 3.69 (s, 3H, CH_3), 3.77 (s, 3H, CH_3), 4.40–4.47 (m, 4H, CH_2), 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, $CDCl_3$): 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 (CH_2Cl_2) λ_{max} (log ε) = 406 (4.98), 504 (3.84), 539 (3.74), 572 (3.59) and 626 nm (3.35); HRMS: (MALDI) [$C_{56}H_{50}N_4O_4$] $[M]^+$: *m/z* calcd. 842.3832; found 842.3803.

3,8-Bis(3-aminophenyl)-deuteroporphyrin IX dimethyl ester (**11**) Compound **11** was synthesized in accordance with general procedure A, utilizing **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 Pd(dppf)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 ALOX (CH_2Cl_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 (ALOX, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ = –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, $CDCl_3$): δ = 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 ε) = 401 (5.10), 507 (5.20), 546 (5.23), 572 (5.30) and 627 nm (5.29); HRMS: (MALDI) [$C_{44}H_{44}N_6O_4$] $[M]^+$: *m/z* calcd. 720.3424; found 720.3441.

3,8-Bis(4-dimethylaminophenyl)-deuteroporphyrin IX dimethyl ester (**12**) Compound **12** was synthesized in accordance with general procedure A, utilizing **4** (18.5 mg, 0.0234 mmol), 4-(*N*,*N*-dimethylamino)phenylboronic acid (83 mg, 0.505 mmol), Cs_2CO_3 (165 mg, 0.506 mmol) and Pd(dppf)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 ALOX (CH_2Cl_2/*n*-hexane, 7:3, v/v) was required to yield a purple solid (4.1 mg, 5.28×10^{-3} mmol, 23%). M.p. >300 °C; R_f = 0.66 (ALOX, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ = –3.74

(br s, 2H, NH), 3.31–3.34 (m, 4H, CH_2), 3.52 (s, 3H, CH_3), 3.55 (s, 6H, CH_3), 3.65 (s, 6H, CH_3), 3.67 (s, 3H, CH_3), 3.70 (s, 3H, CH_3), 3.82 (s, 3H, CH_3), 3.99 (s, 3H, CH_3), 4.39–4.42 (m, 4H, CH_2), 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; ^{13}C NMR (100 MHz, $CDCl_3$): 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 (CH_2Cl_2) λ_{max} (log ε) = 401 (5.79), 505 (5.89), 538 (5.92), 570 (5.95) and 625 nm (5.99); HRMS: (MALDI) [$C_{48}H_{52}N_6O_4$] $[M]^+$: *m/z* calcd. 776.4050; found 776.4073.

3,8-Diallyl-deuteroporphyrin IX dimethyl ester (**13**) Compound **13** was synthesized in accordance with general procedure A, utilizing **4** (15 mg, 0.0190 mmol), allylboronic acid pinacol ester (0.07 mL, 63 mg, 0.375 mmol), Cs_2CO_3 (122 mg, 0.375 mmol) and Pd(dppf)Cl_2 (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 (ALOX, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ = –3.71 (s, 2H, NH), 3.28–3.31 (m, 4H, CH_2), 3.60 (s, 3H, CH_3), 3.62 (s, 3H, CH_3), 3.63 (s, 3H, CH_3), 3.65 (s, 3H, CH_3), 3.66 (s, 6H, CH_3), 4.41–4.46 (m, 4H, CH_2), 4.83–4.85 (m, 4H, CH_2), 5.23–5.25 (m, 1H, $CH_{2(trans)}$), 5.31–5.34 (m, 1H, $CH_{2(cis)}$), 5.26–5.28 (m, 1H, $CH_{2(trans)}$), 5.35–5.37 (m, 1H, $CH_{2(cis)}$), 6.54–6.65 (m, 2H, CH_2), 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; ^{13}C NMR (100 MHz, $CDCl_3$): 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 (CH_2Cl_2) λ_{max} (log ε) = 400 (5.69), 500 (5.79), 534 (5.82), 569 (5.85) and 622 nm (5.89); HRMS: (MALDI) [$C_{38}H_{42}N_4O_4$] $[M]^+$: *m/z* calcd. 618.3206; found 618.3224.

Protoporphyrin IX dimethyl ester (**2**) Compound **2** was synthesized in accordance with general procedure A, utilizing **4** (14.2 mg, 0.0180 mmol), vinylboronic acid pinacol ester (0.06 mL, 58 mg, 0.375 mmol), Cs_2CO_3 (122 mg, 0.375 mmol) and Pd(dppf)Cl_2 (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 (ALOX, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ = –3.61 (br s, 2H, NH), 3.63 (s, 3H, CH_3), 3.65 (s, 3H, CH_3), 3.73 (s, 3H, CH_3), 3.74 (s, 3H, CH_3), 3.66 (s, 6H, CH_3), 3.25–3.33 (m, 4H, CH_2), 4.38–4.46 (m, 4H, CH_2), 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 (CH_2Cl_2) λ_{max} (log ε) = 408 (5.30), 506 (5.39), 542 (5.43), 577 (5.45) and 631 nm (5.49); HRMS: (MALDI) [$C_{36}H_{38}N_4O_4$] $[M]^+$: *m/z* calcd. 590.2893; found 590.2883.

3,8-Diacetylenyl-deuteroporphyrin IX dimethyl ester (**15**) Compound **4** (20 mg, 0.0253 mmol), CuI (1.4 mg, 0.008 mmol), PPh_3 (8 mg, 0.030 mmol) and Pd(PPh_3)$_2Cl_2$ (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 CH_2Cl_2. This was then purified on a plug of ALOX using CH_2Cl_2 as eluent. The solvent was removed *in vacuo* and the residue recrystallized from hexane to yield **14** as purple crystals (9.9 mg, 0.013 mmol, 57%). This was then dissolved in CH_2Cl_2 (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 deionized H_2O and brine, dried over anhydrous $MgSO_4$ and the solvent removed *in vacuo*. Recrystallization from MeOH yielded the desired compound

15 in 87% (6.6 mg, 0.011 mmol). M.p. = 222 °C; R_f = 0.54 (ALOX, CH_2Cl_2); ^{1}H NMR (600 MHz, $CDCl_3$): δ = –4.43 (br s, 2H), 3.21 (br s, 4H, CH_2), 3.37–3.40 (m, 6H, CH_3), 3.50 (br s, 2H, CH), 3.57 (br s, 6H, CH_3), 3.64 (s, 6H, CH_3), 4.31 (br s, 4H, CH_2) and 9.81 ppm (br s, 4H, meso H); UV-vis (CH_2Cl_2) λ_{max} (log ε) = 414 (5.38), 511 (5.47), 545 (5.50), 578 (5.53) and 636 nm (5.57); HRMS: (MALDI) [$C_{36}H_{34}N_4O_4$] $[M]^+$: *m/z* calcd. 586.2580; found 586.2592. [^{13}C NMR spectrum could not be obtained due to oligomerization occurring in solution]

(E,E)-3^2,8^2-Dibromo-protoporphyrin IX dimethyl ester (**16**) Compound **2** was synthesized from protoporphyrin IX disodium salt following a standard procedure.[29] In a 100 mL 3-necked round-bottomed flask with attached reflux condenser, compound **2** (100 mg, 0.169 mmol) was dissolved in $CHCl_3$ (40 mL). Pyridinium bromide perbromide (119 mg, 0.372 mmol) was added and the reaction mixture was stirred at 61 °C for 3 h. The mixture was cooled to room temperature and washed with saturated aqueous $Na_2S_2O_3$ solution (2 ×), deionized H_2O (1 ×) and brine (1 ×). The organic layer was dried over $MgSO_4$, filtered and the solvent was removed *in vacuo*. The crude product was purified by silica gel column chromatography (SiO_2, CH_2Cl_2/EtOAc, 40:1, v/v) to give **16** as a purple powder (106 mg, 0.142 mmol, 84%); M.p. >300 °C; R_f = 0.71 (SiO_2, CH_2Cl_2/EtOAc, 40:1, v/v); ^{1}H NMR (400 MHz, $CDCl_3$): δ = –4.82 (br s, 2H, NH), 2.70 (s, 3H, CH_3), 3.20 (s, 3H, CH_3), 3.21–3.29 (m, 4H, CH_2), 3.40 (s, 3H, CH_3), 3.48 (s, 3H, CH_3), 3.70 (s, 6H, CH_3), 4.25–4.36 (m, 4H, CH_2), 6.89 (d, J = 14.0, 1H, β-vinyl-H), 6.90 (d, J = 14.0, 1H, β-vinyl-H), 7.88 (d, J = 14.0 Hz, 1H, α-vinyl-H), 8.04 (d, J = 14.0 Hz, 1H, α-vinyl-H), 8.70 (s, 1H, meso H), 9.31 (s, 1H, meso H), 9.51 (s, 1H, meso H) and 9.82 (s, 1H, meso H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 11.7, 11.7, 12.3, 12.8, 21.9, 29.9, 37.0, 37.0, 51.9, 96.2, 96.4, 96.7, 97.0, 110.0, 110.1, 130.2 and 173.6 ppm; UV-vis (CH_2Cl_2) λ_{max} (log ε) =

410 (5.13), 508 (4.06), 544 (4.00), 578 (3.76) and 632 (3.66) nm; HRMS (APCI) $[C_{36}H_{37}Br_2N_4O_4]$ $[M+H]^+$: *m/z* calcd. 747.1176; found 747.1177.

(E,E)-3²,8²-Bis(4-methylphenyl)-protoporphyrin IX dimethyl ester (**17**) Compound **16** (28.0 mg, 0.0375 mmol), Cs_2CO_3 (245 mg, 0.751 mmol), 4-tolylboronic acid (102 mg, 0.751 mmol) and Pd(dppf)Cl_2 (5.50 mg, 7.51×10^{-3} mmol) were reacted in anhydrous THF (15 mL) for 18 h in accordance with general procedure B. The crude product was purified by silica gel column chromatography (CH_2Cl_2/MeOH eluent of increasing polarity up to CH_2Cl_2/MeOH, 100:0.175, v/v) to yield **17** as a purple powder (25.0 mg, 0.0324 mmol, 86%); M.p. = 294–296 °C; R_f = 0.56 (SiO_2, CH_2Cl_2/MeOH, 80:1, v/v); ^{1}H NMR (400 MHz, $CDCl_3$): δ = –4.18, (br s, 2H, NH), 2.55 (s, 6H, CH_3), 3.22 (t, *J* = 7.8 Hz, 4H, CH_2), 3.36 (s, 3H, CH_3), 3.44–3.47 (m, 9H, CH_3), 3.68 (s, 6H, CH_3), 4.29 (t *J* = 7.5 Hz, 2H, CH_2), 4.29 (t, *J* = 7.5 Hz, 2H, CH_2), 7.39–7.44 (m, 4H, Ar-H), 7.47 (d, *J* = 16.4 Hz, 1H, *β*-vinyl-H), 7.54 (d, *J* = 16.4 Hz, 1H, *β*-vinyl-H), 7.76 (d, *J* = 7.9 Hz, 2 H, Ar-H), 7.81 (d, *J* = 7.9 Hz, 2H, Ar-H), 8.21 (d, *J* = 16.4 Hz, 1H, *α*-vinyl-H), 8.35 (d, *J* =16.4 Hz, 1H, *α*-vinyl-H), 9.66 (s, 1H, meso H), 9.67 (s, 1H, meso H), 9.81 (s, 1H, meso H) and 9.86 (s, 1H, meso H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 11.6, 11.7, 12.8, 12.9, 21.6, 21.9, 37.0, 51.9, 95.8, 96.7, 97.0, 97.3, 120.8, 121.0, 126.8, 129.8, 129.8, 134.7, 134.8 135.7, 135.8, 137.9, 138.0 and 173.7 ppm; UV-vis (CH_2Cl_2) λ_{max} (log *ε*) = 414 (4.51), 513 (3.46), 553 (3.53), 582 (3.27), 639 (3.18) nm; HRMS (MALDI) $[C_{50}H_{50}N_4O_4]$ $[M^+]$: *m/z* calcd. 770.3832; found 770.3866.

(E,E)-3²,8²-Bis(4-methoxyphenyl)-protoporphyrin IX dimethyl ester (**18**) Compound **16** (20.0 mg, 0.0267 mmol), Cs_2CO_3 (174 mg, 0.534 mmol), 2-(4-methoxyphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (81.2 mg, 0.534 mmol) and Pd(dppf)Cl_2 (3.90 mg, 5.34×10^{-3} mmol) were reacted in anhydrous THF (5 mL) for 17 h in accordance with general procedure B.

The crude product was passed through a plug of Grade III neutral ALOX using CH_2Cl_2 for elution and then further purified by silica gel column chromatography (CH_2Cl_2) to yield compound **18** as a purple solid (13.6 mg, 0.0169 mmol, 63%); M.p. = 248–250 °C (lit. 252–255 °C)[30]; R_f = 0.23 (SiO_2, CH_2Cl_2/MeOH, 100:0.25, v/v). ^{1}H NMR (400 MHz, $CDCl_3$ + TFA-d): δ = –3.28 (br s, 1H, NH), –3.10 (s, 1H, NH), 3.11–3.19 (m, 4H, CH_2), 3.62 (s, 3H, CH_3), 3.63 (s, 3H, CH_3), 3.64 (s, 3H, CH_3), 3.67 (s, 3H, CH_3), 3.74 (s, 3H, CH_3), 3.78 (s, 3H, CH_3), 3.98 (s, 3H, CH_3), 3.98 (s, 3H, CH_3), 4.41–4.51 (m, 4H, CH_2), 7.17–7.12 (m, 4H, Ar-H), 7.54 (d, J = 16.4 Hz, 1H, β-vinyl-H), 7.58 (d, J = 16.4 Hz, 1H, β-vinyl-H), 7.91–7.86 (m, 4 H, Ar-H), 8.36 (d, J = 16.4 Hz, 1H, α-vinyl-H), 8.39 (d, J = 16.4 Hz, 1H, α-vinyl-H), 10.63 (s, 1H, meso H), 10.69 (s, 1H, meso H), 10.76 (s, 1H, meso H) and 10.87 (s, 1H, meso H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$ + TFA-d): δ = 12.0, 12.1, 13.1, 21.6, 21.7, 35.5, 35.6, 52.7, 55.8, 98.7, 99.0, 99.6, 100.2, 114.9, 116.9, 129.1, 130.2, 137.5, 137.5, 138.8, 139.0, 139.0, 139.1, 140.0, 140.3, 142.6, 142.7, 160.8, 160.8 and 174.9 ppm; UV-vis (CH_2Cl_2): λ_{max} (log ε) = 414 (5.10), 516 (4.07), 554 (4.16), 583 (3.91), 640 (3.80) nm; HRMS (MALDI) [$C_{50}H_{50}N_4O_6$] $[M]^+$: calcd. 802.3730; found 802.3766.

(E,E)-3^2,8^2-Bisformyl-protoporphyrin IX dimethyl ester (**19**) Compound **16** (60.0 mg, 0.0802 mmol), Cs_2CO_3 (523 mg, 1.60 mmol), 4-formylphenylboronic acid (240 mg, 1.60 mmol) and Pd(dppf)Cl_2 (11.7 mg, 0.0160 mmol) were reacted in anhydrous THF (50 mL) for 15 h in accordance with general procedure B. The crude product was purified by silica gel column chromatography (CH_2Cl_2/MeOH/TEA eluent of increasing polarity up to CH_2Cl_2/MeOH/TEA, 100:0.375:0.5, v/v/v). Recrystallization from CH_2Cl_2/*n*-hexane gave **19** as a purple powder (43.0 mg, 0.0538 mmol, 67%); M.p. >300 °C; R_f = 0.29 (SiO_2, CH_2Cl_2/MeOH, 80:1, v/v); ^{1}H NMR (600 MHz, $CDCl_3$): δ = –4.00 (br s, 2H, NH), 3.24 (t, J = 7.7 Hz, 2H, CH_2), 3.25 (t, J = 7.7

Hz, 2H, CH_2), 3.27 (s, 3H, CH_3), 3.43 (s, 6H, CH_3), 3.50 (s, 3H, CH_3), 3.67–3.68 (m, 6H, CH_3), 4.30 (t, J = 7.7 Hz, 2H, CH_2), 4.32 (t, J = 7.7 Hz, 2H, CH_2), 7.38 (d, J = 16.4 Hz, 1H, β-vinyl-H), 7.43 (d, J = 16.4 Hz, 1H, β-vinyl-H), 7.83 (d, J = 7.7 Hz, 2H, Ar-H), 7.88 (d, J = 7.7 Hz, 2H, Ar-H), 8.00–8.04 (m, 4H, Ar-H), 8.27 (d, J = 16.4 Hz, 1H, α-vinyl-H), 8.37 (d, J = 16.4 Hz, 1H, α-vinyl-H), 9.56 (s, 1H, meso H), 9.74 (s, 1H, meso H), 9.76 (s, 1H, meso H) and 9.90 (s, 1H, meso H), 10.12 (s, 1H, CHO) and 10.33 (s, 1H, CHO) ppm; ^{13}C NMR (150 MHz, $CDCl_3$): δ = 11.8, 13.0, 13.3, 14.3, 21.9, 29.8, 36.9, 51.9, 96.4, 96.9, 97.4, 97.5, 125.1, 127.1, 130.6, 133.1, 133.2, 135.7, 144.1, 173.6 and 191.8 ppm; UV-vis (CH_2Cl_2) λ_{max} (log ε) = 424 (4.38), 515 (3.48), 555 (3.52), 585 (3.31), 641 (3.20) nm; HRMS (MALDI) [$C_{50}H_{46}N_4O_6$] [M^+]: *m/z* calcd. 798.3417, found 798.3403.

(E,E)-3^2,8^2-Bis(4-methoxycarbonylphenyl)-protoporphyrin IX dimethyl ester (**20**) Compound **16** (20.0 mg, 0.0267 mmol), Cs_2CO_3 (174 mg, 0.534 mmol), 3-methoxycarbonylphenylboronic acid pinacol ester (140 mg, 0.534 mmol) and Pd(dppf)Cl_2 (3.90 mg, 5.34×10^{-3} mmol) were reacted in anhydrous THF (13 mL) for 63 h in accordance with general procedure B. The crude product was passed through a plug of silica gel (CH_2Cl_2/MeOH, 100:1, v/v) and then further purified by preparative TLC (CH_2Cl_2/MeOH, 100:0.5, v/v) to give compound **20** as a purple solid (11.2 mg, 0.0130 mmol, 49%); M.p. >300 °C (lit. 187–189 °C)[30]; R_f = 0.24 (SiO_2, CH_2Cl_2/MeOH, 100:1, v/v); ^{1}H NMR (400 MHz, $CDCl_3$): δ = –4.35 (br s, 2H, NH), 3.03 (s, 3H, CH_3), 3.24–3.16 (m, 7H, CH_2, CH_3), 3.34 (s, 3 H, CH_3), 3.39 (s, 3H, CH_3), 3.67 (s, 6H, CH_3), 4.06 (s, 3H, CH_3), 4.06 (s, 3H, CH_3), 4.20–4.27 (m, 4H, CH_2), 7.18 (d, J = 16.4 Hz, 1H, β-vinyl-H), 7.31 (d, J = 16.4 Hz, 1H, β-vinyl-H), 7.69 (d, J = 8.0 Hz, 2H, Ar-H), 7.79 (d, J = 8.0 Hz, 2H, Ar-H), 7.98 (d, J = 16.4 Hz, 1H, α-vinyl-H), 8.24–8.16 (m, 5H, Ar-H, α-vinyl-H), 9.21 (s, 1H, meso H), 9.49 (s, 1H, meso H), 9.57 (s, 1H, meso H), 9.76 (s, 1H, meso H) ppm; ^{13}C NMR (100

MHz, $CDCl_3$): δ = 11.6, 11.7, 12.8, 12.9, 21.8, 36.9, 51.9, 52.4, 96.1, 96.7, 97.0, 97.2, 123.9, 124.0, 126.5, 126.5, 129.2, 129.3, 130.4, 130.4, 133.0, 133.2, 142.6, 142.6, 167.1, 167.2 and173.6 ppm; UV/Vis (CH_2Cl_2) λ_{max} (log ε) = 424 (5.25), 517 (4.25), 555 (4.34), 585 (4.09), 641 (3.97) nm; HRMS (MALDI) [$C_{52}H_{50}N_4O_8$] $[M]^+$: *m/z* calcd. 858.3629; found 858.3652.

(E,E)-3²,8²-Bis(anthracen-9-yl)-protoporphyrin IX dimethyl ester (**21**) Compound **16** (47.0 mg, 0.0628 mmol), Cs_2CO_3 (409 mg, 1.26 mmol), 9-anthracenylboronic acid (279 mg, 1.26 mmol) and Pd(dppf)Cl_2 (9.20 mg, 0.0126 mmol) were reacted in anhydrous THF (20 mL) for 18 h in accordance with general procedure B. The crude product was purified by silica gel column chromatography (CH_2Cl_2/MeOH eluent of increasing polarity up to CH_2Cl_2/MeOH, 100:0.2, v/v). The obtained fraction was recrystallized from CH_2Cl_2/MeOH to yield **21** as a purple powder (35.0 mg, 0.0366 mmol, 59%); M.p. = 153 °C (lit. 145–148 °C)[30]; R_f = 0.65 (SiO_2, CH_2Cl_2/MeOH, 80:1, v/v); ^{1}H NMR (400 MHz, $CDCl_3$): δ = –3.58 (br s, 1H, NH), 3.24 (t, J = 7.8 Hz, 2H, CH_2), 3.29 (t, J = 7.8 Hz, 2H, CH_2), 3.45 (s, 3H, CH_3), 3.60 (s, 3 H, CH_3), 3.64 (s, 3 H, CH_3), 3.67 (s, 3 H, CH_3), 3.70 (s, 3H, CH_3), 3.75 (s, 3H, CH_3), 4.29–4.34 (m, 2H, CH_2), 4.34–4.39 (m, 2H, CH_2) 7.56–7.64 (m, 8H, Ar-H), 8.11–8.19 (m, 6H, Ar-*H*), 8.20–8.29 (m, 2H, α-vinyl-H), 8.57 (s, 2H, Ar-H), 8.71–8.79 (m, 4H, Ar-H, β-vinyl-H), 9.99 (s, 1H, meso H), 10.04 (s, 1H, meso H), 10.08 (s, 1H, meso H), and 10.14 (s, 1H, meso H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$): δ = 11.3, 11.5, 12.0, 12.3, 14.0, 21.7, 21.8, 29.9, 36.9, 37.0, 51.9, 51.9 96.0, 96.9, 97.0, 97.3, 125.3, 125.3, 125.5, 125.5, 126.0, 126.1, 126.6, 126.6, 127.3, 128.9, 128.9, 129.5, 131.7, 131.7, 133.5, 134.1, 173.7, 173.7 and 183.2 ppm; UV-vis (CH_2Cl_2) λ_{max} (log ε) = 416 (4.50), 512 (3.53), 548 (3.49), 580 (3.31), 635 (3.11) nm; HRMS (MALDI) [$C_{64}H_{54}N_4O_4$] [M^+]: *m/z* 942.4145, found 942.4162.

(E,E)-3²,8²-Bis(1-methylindol-5-yl)-protoporphyrin IX dimethyl ester (**22**) Compound **16** (20.0 mg, 0.0267 mmol), Cs_2CO_3 (174 mg, 0.534 mmol), 1-methyl-1H-indol-5-boronic acid (137 mg, 0.534 mmol) and Pd(dppf)Cl_2 (3.90 mg, 5.34×10^{-3} mmol) were reacted in anhydrous THF (5 mL) for 15 h in accordance with general procedure B. The crude product was passed through a plug of Grade III neutral ALOX using CH_2Cl_2 for elution and then further purified by column chromatography on Grade III neutral ALOX (CH_2Cl_2/*n*-hexane, 1:1, 3:2, v/v). The product containing fraction was passed through a plug of silica gel using CH_2Cl_2 and CH_2Cl_2/MeOH (100:0.3, v/v) to remove any remaining boronic acid. Compound **22** was isolated as a purple solid (6.90 mg, 8.13×10^{-3} mmol, 30%); M.p. >300 °C; R_f = 0.18 (SiO_2, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$ + TFA-d): δ = –3.85 (br s, 1H, NH), 3.26 (t, J = 7.7 Hz, 4H, CH_2), 3.56 (s, 6H, CH_3), 3.62 (s, 3 H, CH_3), 3.65 (s, 3H, CH_3), 3.68 (s, 6H, CH_3), 3.91 (s, 6H, CH_3), 4.32–4.40 (m, 4H, CH_2), 6.67–6.69 (m, 2H, Ar-H), 7.16–7.18 (m, 2H, Ar-H), 7.53 (d, J = 8.4 Hz, 2H, Ar-H), 7.79 (d, J = 16.3 Hz, 1H, β-vinyl-H), 7.82 (d, J = 16.3 Hz, 1H, β-vinyl-H), 7.88–7.94 (m, 2H, Ar-H), 8.14 (d, J = 6.1 Hz, 2H, Ar-H), 8.46 (d, J =16.4 Hz, 1H, α-vinyl-H), 8.53 (d, J = 16.4 Hz, 1H, α-vinyl-H), 9.89 (s, 1H, meso H), 9.92 (s, 1H, meso H), 10.07 (s, 1H, meso H) and 10.13 (s, 1H, meso H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$ + TFA-d): δ =11.8, 11.9, 13.1, 13.2, 22.0, 33.2, 37.1, 51.9, 96.0, 96.9, 97.5, 97.9, 101.8, 109.9, 119.2, 119.3, 120.1, 120.6, 129.2, 129.8, 130.3, 130.3, 137.0, and 173.8 ppm; UV-vis (CH_2Cl_2) λ_{max} (log ε) = 413 (5.20), 515 (4.19), 556 (4.27), 582 (4.09), 641 (3.94), 675 (3.74) nm; HRMS (MALDI) [$C_{54}H_{52}N_6O_4$] $[M]^+$: calcd. 848.4050; found 848.4059.

(E,E)-3²,8²-Bis(1,3,5,7-tetramethyl-8-(phen-4-ylene)-4,4-difluoro-4-bora-3a,4a-diaza-s-indacene)-protoporphyrin IX dimethyl ester (**23**) 1,3,5,7-Tetramethyl-8-(4-phenylboronic acid)-4,4-difluoro-4-bora-3a,4a-diaza-s-indacene was prepared according to a procedure by Bai *et al*.[31]

Compound **16** (25.0 mg, 0.0334 mmol), Cs_2CO_3 (145 mg, 0.445 mmol), 1,3,5,7-tetramethyl-8-(4-phenylboronic acid)-4,4-difluoro-4-bora-3a,4a-diaza-s-indacene (49.2 mg, 0.134 mmol) and Pd(dppf)Cl_2 (4.90 mg, 6.68×10^{-3} mmol) were reacted in anhydrous THF (10 mL) for 18 h in accordance with general procedure B. The crude product was purified by silica gel column chromatography (*n*-hexane/EtOAc, 2:1, 1:1, v/v) to give **23** as light-red crystals (10.0 mg, 8.10×10^{-3} mmol, 24%); M.p. = 244 °C dec.; R_f = 0.51 (SiO_2, EtOAc/*n*-hexane, 1:1, v/v); ^{1}H NMR (600 MHz, $CDCl_3$): δ = –3.71 (br s, 2H, NH), 1.65 (s, 6H, CH_3), 1.66 (s, 6H, CH_3), 2.63 (s, 12H, CH_3), 3.28 (t, J = 7.7 Hz, 4H, CH_2), 3.60 (s, 3H, CH_3), 3.61 (s, 3H, CH_3), 3.67 (s, 6H, CH_3), 3.76 (s, 3H, CH_3), 3.77 (s, 3H, CH_3), 4.36–4.40 (m, 4H, CH_2), 6.08 (s, 4H, pyrrole-H), 7.53–7.50 (m, 4H, Ar-*H*), 7.80 (d, J = 16.4 Hz, 1H, β-vinyl-H), 7.79 (d, J = 16.4 Hz, 1H, β-vinyl-H), 8.09 (d, J = 7.8 Hz, 4H, Ar-H), 8.75 (d, J = 16.5 Hz, 1H, α-vinyl-H), 8.76 (d, J = 16.4 Hz, 1H, α-vinyl-H), 9.99 (s, 1H, meso H), 10.00 (s, 1H, meso H), 10.16 (s, 1H, meso H) and 10.17 (s, 1H, meso H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$): δ = 11.7, 11.8, 13.3, 13.4, 14.7, 14.9, 21.8, 36.9, 51.8, 96.4, 97.2, 97.3, 97.8, 121.4, 122.9, 127.4, 128.8, 131.6, 134.0, 134.6, 138.9, 141.6, 143.2, 155.7 and 173.6 ppm; ^{19}F NMR (377 MHz, $CDCl_3$): δ =-146.13 ppm (q, $^2J_{F,B}$ = 32.6 Hz);^{11}B NMR(128 MHz, $CDCl_3$): δ = 0.88 ppm (t, $^2J_{B,F}$ = 33.3 Hz); UV-vis (CH_2Cl_2): λ_{max} (log ε) = 419 (5.86), 502 (5.91), 553 (4.96), 583 (4.66), 639 (4.60) nm; HRMS (MALDI) [$C_{74}H_{72}B_2F_4N_8O_4$] $[M]^+$: *m/z* calcd. 1234.5799; found 1234.5824.

(E,E)-3^2,8^2-Bis(4-ethynylphenyl)-protoporphyrin IX dimethyl ester (**24**) Compound **16** (50.0 mg, 0.0668 mmol) and K_3PO_4 (284 mg, 1.34 mmol) were dried under high vac. for 1 h. Anhydrous THF (20 mL) was added and the solution was purged with $Ar_{(g)}$ for 30 minutes. 4-[(Trimethylsilyl)ethynyl]phenylboronic acid pinacol ester (201 mg, 0.668 mmol) and $Pd(PPh_3)_4$ (7.70 mg, 6.68 μmol) were added, the solution was purged with $Ar_{(g)}$ for 10 minutes and the

mixture was heated to 66 °C for 15 h. The solvent was removed *in vacuo* and the residue was purified by silica gel column chromatography (CH_2Cl_2/CH_3OH, 100:0.25, v/v). A mixture of TMS-protected and partially deprotected porphyrins (28.4 mg, 0.0322 mmol) was isolated. This mixture was used for the subsequent deprotection step. The residue was dissolved in anhydrous CH_2Cl_2 (15 mL) and a 1 M solution of TBAF in THF (54 µL, 0.054 mmol) was added under $Ar_{(g)}$. The mixture was stirred at room temperature for 15 min and subsequently passed through a plug of Grade III neutral ALOX and eluted with CH_2Cl_2. Recrystallization from CH_2Cl_2/MeOH yielded **24** as a purple powder (16.7 mg, 0.0211 mmol, 32%); M.p. = 168 °C dec.; R_f = 0.38 (ALOX, CH_2Cl_2/*n*-hexane, 3:1, v/v); ^{1}H NMR (600 MHz, $CDCl_3$ + TFA-d): δ = 3.11–3.19 (m, 4H, CH_2), 3.26 (s, 1H, acetylene-H), 3.27 (s, 1H, acetylene-H), 3.58 (s, 3H, CH_3), 3.59 (s, 3H, CH_3), 3.60 (s, 3H, CH_3), 3.65 (s, 3H, CH_3), 3.69 (s, 3H, CH_3), 3.76 (s, 3H, CH_3), 4.37–4.46 (m, 4H, CH_2), 7.50–7.60 (m, 2H, β-vinyl-H), 7.68–7.74 (m, 4H, Ar-H), 7.83–7.90 (m, 4H, Ar-H), 8.48 (d, J = 16.2 Hz, 1H, α-vinyl-H), 8.49 (d, J = 16.2 Hz, 1H, α-vinyl-H), 10.54 (s, 1H, meso H), 10.56 (s, 1H, meso H),10.64 (s, 1H, meso H) and 10.81 (s, 1H, meso H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$): δ = 12.2, 12.2, 13.2, 13.2, 21.8, 21.9, 35.6, 35.7, 52.0, 79.1, 83.6, 98.9, 99.1, 100.0, 112.1, 115.0, 120.7, 123.0, 123.0, 127.3, 133.0, 136.6, 136.8, 136.9, 137.1, 137.5, 138.0, 138.0, 139.7, 139.7, 140.6, 140.7, 141.1, 142.1, 142.1, 142.4, 142.5, 143.0 and 173.1 ppm; UV-vis (CH_2Cl_2): λ_{max} (log ε) = 421 (5.24), 515 (4.23), 555 (4.29), 584 (4.07), 640 (3.99), 671 (3.79) nm; HRMS (MALDI) $[C_{52}H_{46}N_4O_4]$ $[M]^+$: *m/z* calcd. 790.3519; found 790.3531.

(E,E)-3^2,8^2-Bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-protoporphyrin IX dimethyl ester (**25**) Compound **16** (20.0 mg, 0.0267 mmol) and $Pd(PPh_3)_2Cl_2$ (3.8 mg, 5.34×10^{-3} mmol) were dried under high vac. for 30 min. Anhydrous 1,2-dichloroethane (1 mL), TEA (70 µL, 0.534 mmol) and pinacolborane (80 µmL, 0.534 mmol) were added under $Ar_{(g)}$ and the solution was

purged with $Ar_{(g)}$ for 10 min. The reaction mixture was heated to 84 °C for 3 h. The solvent was removed under reduced pressure and the crude product was purified by silica gel column chromatography (CH_2Cl_2/EtOAc, 20:1, v/v). Recrystallization from CH_2Cl_2/*n*-hexane yielded **25** as a purple powder (10.7 mg, 0.0127 mmol, 48%); M.p. >300 °C; R_f = 0.28 (SiO_2, CH_2Cl_2/EtOAc, 20:1, v/v); ^{1}H NMR (600 MHz, $CDCl_3$): δ = –3.96 (br s, 1H, NH), 1.57 (s, 24H, boryl-CH_3), 3.20–3.29 (m, 4H, CH_2), 3.54 (s, 3H, CH_3), 3.61 (s, 3H, CH_3), 3.64 (s, 3H, CH_3), 3.67 (s, 3H, CH_3), 3.70 (s, 3H, CH_3), 3.75 (s, 3H, CH_3), 4.29–4.39 (m, 4H, CH_2), 6.86 (d, J = 18.6, 1H, β-vinyl-H), 6.88 (d, J = 18.6, 1H, β -vinyl-H), 8.99 (d, J = 18.6, 1H, α-vinyl-H), 9.02 (d, J = 18.6, 1H, α-vinyl-H), 9.86 (s, 1H, meso H), 9.90 (s, 1H, meso H), 10.12 (s, 1H, meso H), 10.16 (s, 1H, meso H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$): δ = 11.7, 12.0, 13.3, 13.6, 21.9, 22.0, 25.2, 4.0, 51.9, 83.9, 96.0, 97.4, 97.6, 98.5, 142.7, 142.8, 173.7 and 173.7 ppm; UV-vis (CH_2Cl_2): λ_{max} (log ε) = 416 (5.34), 512 (4.29), 548 (4.27), 581 (4.01), 636 (3.92) nm; HRMS (MALDI) $[C_{48}H_{60}B_2N_4O_8]$ $[M]^+$: *m/z* calcd. 842.4597, found 842.4633.

(E,E)-3^2,8^2-Bis(trimethylsilylethynyl)-protoporphyrin IX dimethyl ester (**26**) Compound **16** (152 mg, 0.203 mmol), (triisopropylsilyl)acetylene (0.11 mL, 0.800 mmol), $PdCl_2(PPh_3)_2$ (19.0 mg, 0.0271 mmol) and CuI (9.60 mg, 0.0399 mmol) were reacted in a mixture of THF (2.5 mL) and Et_3N (2.5 mL) for 15 h in accordance with general procedure B. The crude product was purified by silica gel column chromatography (CH_2Cl_2/MeOH eluent of increasing polarity from 100:0.1, v/v, to 100:0.5, v/v) to yield **26** as a purple powder (178 mg, 0.200 mmol, 98%); M.p. >300 °C; R_f = 0.37 (SiO_2, CH_2Cl_2/MeOH 100:0.1, v/v); ^{1}H NMR (400 MHz, $CDCl_3$ + TFA-d): δ = 0.39 (s, 18H, TMS-CH_3), 3.10–3.18 (m, 4H, CH_2), 3.56 (s, 6H, CH_3), 3.64 (s, 3H, CH_3), 3.64 (s, 3H, CH_3), 3.71 (s, 3H, CH_3), 3.72 (s, 3H, CH_3), 4.38–4.46 (m, 4H, CH_2), 6.72 (d, J = 16.3 Hz, 2H, β-vinyl-H), 6.72 (d, J = 16.4 Hz, 2H, β-vinyl-H), 8.40 (d, J = 16.4 Hz, 2H, α-vinyl-H), 10.53

(s, 1H, meso H), 10.57 (s, 1H, meso H), 10.61 (s, 1H, meso H) and 10.87 (s, 1H, meso H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$ +TFA-d): δ = 0.0, 12.1, 12.3, 13.2, 13.4, 21.8, 35.5, 35.5, 52.1, 98.9, 99.2, 99.6, 100.1, 102.2, 102.3, 103.9, 120.9, 121.0, 132.4, 132.4, 135.5, 135.8, 137.5, 137.8, 138.8, 138.9, 140.3 and 173.4 ppm; UV-vis (CH_2Cl_2): λ_{max} (log ε) = 420 (5.71), 517 (4.60), 553 (4.69), 584 (4.65), 641 (4.25) nm. HRMS (MALDI) [$C_{46}H_{54}N_4O_4Si_2$] [M]$^+$: *m/z* calcd. 782.3684, found 782.3682.

(E,E)-3^2,8^2-Bis(4-phenylethynyl)-protoporphyrin IX dimethyl ester (**27**) Compound **16** (15.0 mg, 0.020 mmol), phenylacetylene (10 µL, 0.0912 mmol), $PdCl_2(PPh_3)_2$ (1.4 mg, 2.00×10^{-3} mmol) and CuI (0.80 mg, 4.01×10^{-3} mmol) were reacted in a mixture of THF (2.5 mL) and Et_3N (2.5 mL) for 3 h in accordance with general procedure B. The solvents were removed under reduced pressure and the crude solids were passed through a plug of silica gel (CH_2Cl_2/MeOH, 100:0.2, v/v). Compound **27** (15.3 mg, 0.0193 mmol, 97%) was obtained as a purple powder. M.p. >300 °C; R_f = 0.37 (ALOX, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$ + TFA-d): δ = 3.11–3.18 (m, 4H, CH_2), 3.58 (s, 6H, CH_3), 3.65 (s, 3H, CH_3), 3.66 (s, 3H, CH_3), 3.76 (s, 3H, CH_3), 3.77 (s, 3H, CH_3), 4.47–4.40 (m, 4H, CH_2), 6.95 (d, J = 16.2 Hz, 1H, β-vinyl-H), 6.97 (d, J = 16.2 Hz, 1H, β-vinyl-H), 7.44–7.48 (m, 6H, Ar-H), 7.72–7.67 (m, 4H, Ar-*H*), 8.46 (d, J = 16.2 Hz, 1H, α-vinyl-H), 8.47 (d, J = 16.2 Hz, 1H, α-vinyl-H), 10.60 (s, 2H, meso H), 10.68 (s, 1H, meso H) and 10.88 (s, 1H, meso H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$ + TFA-d): δ = 12.1, 12.3, 13.2, 13.4, 21.8, 35.5, 35.5 52.2, 90.0, 90.0, 96.4, 96.4, 98.9, 99.3, 99.6, 100.1, 121.2, 121.3, 122.9, 128.8, 129.3, 131.3, 132.1, 132.1, 135.9, 136.3, 137.5, 137.8, 138.9, 139.0, 140.4, 140.4 and 173.6 ppm; UV-vis (CH_2Cl_2): λ_{max} (log ε) = 422 (5.59), 518 (4.55), 556 (4.64), 586 (4.56), 642 (4.28) nm; HRMS (MALDI) [$C_{52}H_{46}N_4O_4$] [M$^+$]: *m/z* calcd. 790.3528; found 790.3519.

(E,E)-3²,8²-Bis(4-methoxycarbonylphenylethynyl)-protoporphyrin IX dimethyl ester (**28**) Compound **16** (20.0 mg, 0.0267 mmol), methyl 4-ethynylbenzoate (17.0 mg, 0.107 mmol), $Pd(PPh_3)_2Cl_2$ (3.90 mg, 2.67×10^{-3} mmol) and CuI (1.0 mg, 5.34×10^{-3} mmol) were reacted in a mixture of anhydrous THF (0.5 mL) and TEA (0.5 mL) for 22 h in accordance with general procedure C. The crude product was passed through a plug of silica gel (CH_2Cl_2, CH_2Cl_2/MeOH,100:1, v/v). The crude product was further purified by column chromatography on Grade III neutral ALOX (CH_2Cl_2/*n*-hexane, 1:1, 3:2, v/v, and CH_2Cl_2/MeOH, 100:0.5, v/v) and on silica gel (CH_2Cl_2, CH_2Cl_2/MeOH, 100:0.5, 100:1, v/v) to yield compound **28** as a purple powder (8.50 mg, 9.37×10^{-3} mmol, 35%); M.p. >300 °C; R_f = 0.16 (SiO_2, CH_2Cl_2/MeOH, 100:1, v/v); ^{1}H NMR (400 MHz, $CDCl_3$ + TFA-d): δ = 3.11–3.19 (m, 4H, CH_2), 3.59 (s, 6H, CO_2CH_3), 3.66 (s, 6H, CH_3), 3.78 (s, 3 H, CH_3), 3.78 (s, 3H, CH_3), 4.00 (s, 6H, CH_3), 4.40–4.48 (m, 4H, CH_2), 6.96 (d, J = 16.2 Hz, 1H, β-vinyl-H), 6.98 (d, J = 16.2 Hz, 1H, β-vinyl-H), 7.75 (d, J = 8.1 Hz, 2H, Ar-*H*), 7.76 (d, J = 8.1 Hz, 2H, Ar-*H*), 8.13 (d, J = 8.1 Hz, 4H, Ar-*H*), 8.51 (d, J = 16.2 Hz, 1H, α-vinyl-H), 8.52 (d, J = 16.2 Hz, 1H, α-vinyl-H), 10.61 (s, 1H, meso H), 10.64 (s, 1H, meso H), 10.70 (s, 1H, meso H), 10.91 (s, 1H, meso H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$ + TFA-d): δ = 12.1, 12.2, 13.2, 13.4, 21.7, 35.5, 35.5, 52.4, 52.9, 91.6, 95.2, 98.6, 99.0, 99.4, 99.7, 120.6, 127.8, 130.0, 132.1, 132.1, 132.3, 135.8, 136.1, 138.0, 139.3, 140.6, 167.5, 174.0 and 174.0 ppm; UV-vis (CH_2Cl_2): λ_{max} (log ε) = 429 (4.85), 520 (3.89), 559 (3.98), 587 (3.76), 644 (3.65) nm; HRMS (MALDI) $[C_{56}H_{50}N_4O_8]$ $[M]^+$: *m/z* calcd. 906.3629; found 906.3612.

(E,E)-3²,8²-Bisethynyl-protoporphyrin IX dimethyl ester (**29**) Compound **26** (59.2 mg, 0.0756 mmol) was dissolved in anhydrous CH_2Cl_2 (30 mL) under $Ar_{(g)}$, a 1 M solution of TBAF in THF (0.17 mL, 0.170 mmol) was added and the mixture was stirred for 20 min at room temperature. The reaction mixture was washed with water (2 ×) and brine (1 ×), the organic layer was dried

over $MgSO_4$, filtered and the solvent was removed *in vacuo* to give **29** as a purple powder (41.1 mg, 0.0649 mmol, 86%); M.p. >300 °C; R_f = 0.25 (SiO_2, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$ + TFA-d): δ = 3.10–3.18 (m, 4H, CH_2), 3.54 (br s, 2H, acetylene-H), 3.56 (s, 3H, CH_3), 3.57 (s, 3H, CH_3), 3.63 (s, 3H, CH_3), 3.64 (s, 3H, CH_3), 3.72 (s, 3H, CH_3), 4.37–4.46 (m, 4H, CH_2), 6.65–6.71 (m, 2H, β-vinyl-H), 8.46 (d, J = 16.4 Hz, 1H, α-vinyl-H), 8.47 (d, J = 16.4 Hz, 1H, α-vinyl-H), 10.50 (s, 1H, meso H), 10.56 (s, 1H, meso H), 10.59 (s, 1H, meso H) and 10.87 (s, 1H, meso H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$ + TFA-d): δ = 12.1, 12.2, 13.2, 13.3, 21.8, 35.5, 35.6, 52.0, 82.6, 83.3, 83.4, 98.8, 99.3, 99.6, 100.0, 119.5, 119.6, 133.6, 134.9, 135.2, 137.4, 137.8, 138.6, 138.7, 140.0, 140.2, 140.3, 140.8, 141.6, 141.7, 142.4, 142.7, 142.8, 143.1 and 173.1 ppm; UV-vis (CH_2Cl_2): λ_{max} (log ε) = 417 (5.69), 515 (4.61), 550 (4.65), 582 (4.61), 640 (4.24) nm; HRMS (MALDI) [$C_{40}H_{38}N_4O_4$] $[M]^+$: *m/z* calcd. 638.2893, found 638.2924.

((E,E)-3²,8²-Bis(trimethylsilylethynyl)-protoporphyrinato IX dimethyl ester)zinc(II) (**30**) Compound **26** (25.0 mg, 0.0319 mmol) was dissolved in CH_2Cl_2 (9 mL) and $ZnOAc_2$•$2H_2O$ (21.0 mg, 0.0958 mmol) dissolved in MeOH (3 mL) was added. The mixture was heated to 40 °C for 1.5 h. Additional $ZnOAc_2$•$2H_2O$ (7.00 mg, 0.0319 mmol) was added and the mixture was heated to 40 °C for 1 h more. The solvent was removed *in vacuo* and the residue was purified by column chromatography on Grade III neutral ALOX (CH_2Cl_2/*n*-hexane 1:1, 2:1, v/v, CH_2Cl_2/MeOH, 100:0.3, v/v) to yield **30** as a green solid (19.9 mg, 0.0235 mmol, 74%); M.p. >300 °C; R_f = 0.62 (SiO_2, CH_2Cl_2/MeOH, 100:0.25, v/v); ^{1}H NMR (600 MHz, $CDCl_3$): δ = 0.57 (s, 18H, TMS), 2.15 (s, 3H, CH_3), 2.61 (s, 3H, CH_3), 2.95–3.03 (m, 7H, CH_3, CH_2), 3.11 (s, 3 H, CH_3), 3.70 (s, 3H, CH_3), 3.73 (s, 3H, CH_3), 3.82–3.91 (br m, 4H, CH_2), 5.93 (d, J = 14.9 Hz, 1H, β-vinyl-H), 6.05 (d, J = 14.9 Hz, 1H, β-vinyl-H), 6.95–7.18 (br m, 2H, α-vinyl-H, meso H), 7.59 (d, J = 13.7 Hz, 1H, α-vinyl-H), 8.09 (s, 1H, meso H), 8.36 (s, 1H, meso H) and 8.70 (s, 1H,

meso H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$): δ = 0.6, 11.2, 11.5, 12.0, 12.4, 21.6, 36.9, 36.9, 51.9, 95.3, 95.7, 96.2, 97.2, 97.2, 106.3, 106.4, 110.7, 111.0, 132.6, 132.8, 134.7, 135.2, 135.3, 136.0, 136.5, 136.9, 137.9, 138.1, 142.7, 143.9, 144.4, 145.0, 146.2, 146.6, 146.6, 147.0, 173.6 and 173.6 ppm; UV-vis (CH_2Cl_2): λ_{max} (log ε) = 426 (5.59), 549 (4.52), 590 (4.78) nm; HRMS (MALDI) $[C_{46}H_{52}N_4O_4Si_2Zn]$ $[M]^+$: *m/z* calcd. 844.2819; found 844.2797.

((E,E)-3^2,8^2-Bisethynyl-protoporphyrinato IX dimethyl ester)zinc(II) (**31**) Compound **30** (31.8 mg, 0.0375 mmol) was dissolved in anhydrous CH_2Cl_2 (20 mL) under $Ar_{(g)}$, a 1 M solution of TBAF in THF (90 µL, 0.0900 mmol) was added and the mixture was stirred for 50 min at room temperature. The reaction mixture was passed through a plug of Grade III neutral ALOX (CH_2Cl_2/MeOH, 100:0.2, v/v) to give **31** as a green solid (25.9 mg, 0.0369 mmol, 98%); M.p. >300 °C; R_f = 0.41 (SiO_2, CH_2Cl_2/MeOH, 100:0.25, v/v); ^{1}H NMR (600 MHz, THF-d_8): δ = 3.24–3.29 (m, 4H, CH_2), 3.57 (s, 3H, CH_3), 3.57 (s, 6H, CH_3), 3.60 (s, 6H, CH_3), 3.68 (s, 3 H, CH_3), 3.81–3.79 (m, 2H, acetylene-H), 4.34–4.40 (m,4H, CH_2), 6.79 (d, J = 16.5 Hz, 2H, β-vinyl-H), 8.63–8.73 (m, 2H, α-vinyl-H), 9.95 (s, 3H, meso H) and 9.99 (s, 1H, meso H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$): δ = 11.8, 11.8, 13.5, 13.5, 22.8, 37.9, 51.7, 81.1, 81.2, 85.4, 97.8, 97.9, 98.6, 98.8, 112.0, 112.0, 135.7, 136.0, 137.7, 138.1, 138.5, 138.7, 138.8, 140.6, 140.7, 146.9, 147.9, 148.3, 148.8, 149.6, 149.6, 149.7, 150.1 and 173.8 ppm; UV-vis (THF): λ_{max} (log ε) = 431 (5.43), 555 (4.43), 594 (4.54) nm; HRMS (MALDI) $[C_{40}H_{36}N_4O_4Zn]$ $[M]^+$: *m/z* calcd. 700.2028; found 700.2049.

((E,E)-3^2,8^2-Bis(2-(1-(3-bromophenyl)-1H-1,2,3-triazol-4-yl))-protoporphyrinato IX dimethyl ester) zinc(II) (**32**) 1-Azido-3-bromobenzene was synthesized according to a procedure by Matoba *et al*.[32] Compound **31** (24.5 mg, 0.0348 mmol), sodium ascorbate (27.5 mg, 0.139 mmol) and $CuSO_4$•$5H_2O$ (19.0 mg, 0.0761 mmol) were dissolved in anhydrous DMF. (5 mL), 1-azido-

3-bromobenzene (34.8 mg, 0.175 mmol) was added and the reaction mixture was heated to 100 °C for 5 h. EtOAC was added and the mixture was washed with saturated aqueous $NaHCO_3$ solution (3 ×). The organic layer was dried over $MgSO_4$, filtered and the solvent was removed *in vacuo*. The residue was purified by silica gel column chromatography (CH_2Cl_2, CH_2Cl_2/MeOH, 100:2, v/v). The collected product was dissolved in a minimal amount of CH_2Cl_2, a few drops of pyridine were added and the solution was layered with methanol. A precipitate formed that was collected by suction filtration and washed with methanol. Compound **32** was obtained as a purple powder (10.7 mg, 9.74 × 10^{-3} mmol, 28%); M.p. = 259–264 °C; R_f = 0.27 (ALOX, CH_2Cl_2/MeOH, 100:1, v/v); ^{1}H NMR (600 MHz, DMSO-d_6): δ = 3.28–3.31 (m, 4H, CH_2), 3.59 (s, 3H, CH_3), 3.60 (s, 3H, CH_3), 3.64 (s, 3H, CH_3), 3.65 (s, 3H, CH_3), 3.88 (s, 3H, CH_3), 3.91 (s, 3H, CH_3), 4.34–4.40 (m, 4H, CH_2), 7.69 (t, J = 8.1 Hz, 2H, Ar-H), 7.81 (d, J = 8.0 Hz, 2H, Ar-H), 7.86 (d, J = 15.9 Hz, 2H, β-vinyl-H), 8.15 (d, J = 7.7 Hz, 2H, Ar-H), 8.34–8.38 (m, 2H, Ar-H), 9.13–9.22 (m, 2H, α-vinyl-H), 9.58 (s, 1H, triazole-H), 9.59 (s, 1H, triazole-H), 10.08 (s, 1H, meso H), 10.21 (s, 1H, meso H), 10.27 (s, 1H, meso H) and 10.39 (s, 1H, meso H) ppm; ^{13}C NMR (150 MHz, DMSO-d_6): δ = 11.4, 11.5, 13.3, 13.4, 21.4, 36.8, 51.3, 97.0, 97.1, 97.9, 98.0, 119.2, 119.2, 120.4, 120.4, 121.2, 121.3, 122.6, 122.7, 122.7, 124.6, 124.7, 131.5, 132.1, 135.4, 135.6, 136.8, 137.1, 137.6, 137.7, 137.9, 139.4, 139.6, 146.2, 146.8, 147.4, 147.7, 147.8, 147.8, 147.9, 148.0, 148.1, 148.4 and 173.1 ppm; UV-vis (THF): λ_{max} (log ε) = 431 (5.16), 555 (4.18), 594 (4.36) nm; HRMS (MALDI) [$C_{52}H_{44}Br_2N_{10}O_4Zn$] $[M]^+$: *m/z* calcd. 1094.1205; found 1094.1213.

Crystallography. *Crystal Structure Determinations.* Crystals were grown following the protocol developed by Hope, by dissolving the compounds in $CDCl_3$ and allowing for slow evaporation over time.[33] 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 (λ = 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 polarization effects by using the APEX software suite.[34] Using Olex[2], 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 minimization.[35] 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 Uiso (H) = 1.5Ueq (C) for methyl H atoms and 1.2Ueq (C, N) for all other atoms other H atoms.

*Crystal Data for 3,8-Diphenyl-deuteroporphyrin IX dimethyl ester (**5**).* $C_{44}H_{42}N_4O_4$, M = 690.3206, orthorhombic, Pbca, a = 25.8161(10) Å, b = 8.5863(3) Å, c = 32.5051(12) Å, $\alpha = \beta = \gamma$ = 90°, V = 7205.2(5) Å^3, T = 99.98 K, Z = 8, $\mu(MoK_\alpha)$ = 0.087, 89421 reflections measured, 8957 unique (R_{int} = 0.0588) which were used in all calculations. The final wR_2 was 0.1362 ($I > 2\sigma(I)$). The methyl ester at C13 was modeled 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.

*Crystal Data for 3,8-Diallyl-deuteroporphyrin IX dimethyl ester (**13**).* $C_{38}H_{42}N_4O_4$, M = 618.3206, triclinic, $P\bar{1}$, a = 8.7165(15) Å, b = 14.056(3) Å, c = 14.557(3) Å, α = 72.557(3)°, β = 74.384(5)°, γ = 75.574(4)°, V = 1610.8(5) Å^3, T = 100(2) K, Z = 2, $\mu(MoK_\alpha)$ = 0.083, 35315 reflections measured, 5921 unique (R_{int} = 0.0771) which were used in all calculations. The final wR_2 was 0.2295 ($I > 2\sigma(I)$). Both allyl groups were modeled over two positions using the restraints DFIX in a 55:45% occupancy. The methyl ester at C13 was modeled over two positions using restraints (SIMU) in a 54:46% occupancy.

ASSOCIATED CONTENT

Supporting Information. The supporting information is available free of charge on the ACS publications website. The following files are available free of charge.

Additional experimental studies, X-ray crystallography data and NMR spectra (pdf).

AUTHOR INFORMATION

Corresponding Author

* E-mail: sengem@tcd.ie

Author Contributions

§These authors contributed equally.

Funding Sources

This work was supported by a grant from Science Foundation Ireland (SFI IvP 13/IA/1894), the Sydney E. Auchinleck Foundation and Trinity College Dublin.

Notes

The authors declared no competing financial interest.

ACKNOWLEDGMENT

This work was supported by a grant from Science Foundation Ireland (SFI IvP 13/IA/1894), the Sydney E. Auchinleck Foundation, and Trinity College Dublin.

REFERENCES

(1) Fischer, H.; Zeile, K. Synthese des Hämatoporphyrins, Protoporphyrins und Hämins. *Ann. Chem.* **1929**, *468*, 98–116.

(2) (a) Heck, R. F. Acylation, Methylation, and Carboxyalkylation of Olefins by Group VIII Metal Derivatives. *J. Am. Chem. Soc.* **1968**, *90*, 5518–5526. (b) Smith, K. M.; Langry, K. C. Electrophilic Mercuration Reactions of Derivatives of Deuteroporphyrin IX: New Syntheses of Coproporphyrin III, Harderoporphyrin, Isoharderoporphyrin, and S-411 Porphyrin (Dehydrocoproporphyrin). *J. Org. Chem.* **1983**, *48*, 500–506.

(3) (a) Stille, J. K. The Palladium-Catalyzed Cross-Coupling Reactions of Organotin Reagents with Organic Electrophiles. *Angew. Chem. Int. Ed. Engl.* **1986**, *25*, 508–524. (b) Morris, I. K.; Snow, K. M.; Smith, N. W.; Smith, K. M. Syntheses of Novel Substituted Porphyrins by the Mercuration and Palladium/Olefin Methodology. *J. Org. Chem.* **1990**, *55*, 1231–1236.

(4) (a) Ali, H.; van Lier, J. E. Synthesis of β-Substituted Porphyrins Using Palladium Catalysed Reactions. *Tetrahedron*. **1994**, *50*, 11933–11944. (b) Gauler, R.; Risch, N. New Heck-Type Coupling Reactions of Natural Tetrapyrroles− Synthesis of Porphyrinoligomers Bridged by Divinyl-and Trivinylbenzene. *Eur. J. Org. Chem.* **1998**, 1193–1200. (c) Risch, N.; Gauler, R.; Keuper, R. Synthesis of Porphyrin Dimers Using a Heck-Type Coupling Reaction with Bisacrylates. *Tetrahedron Lett.* **1999**, *40*, 2925–2926. (d) Castella, M.; Trull, F. R.; López Calahorra, L.; Velasco, D.; González, M. M. Synthesis of Porphyrins β-Tetrasubstituted by Flexible Hydrocarbon Chains. *Org. Lett.* **2001**, *3*, 541–544.

(5) (a) Sonogashira, K.; Tohda, Y.; Hagihara, N. A Convenient Synthesis of Acetylenes: Catalytic Substitutions of Acetylenic Hydrogen with Bromoalkenes, Iodoarenes and Bromopyridines. *Tetrahedron Lett.* **1975**, *50*, 4467–4470. (b) Brunner, H.; Shellerer, K.–M. Benzoporphyrins and Acetylene-Substituted Porphyrins as Improved Photosensitizers in the

Photodynamic Tumor Therapy with Porphyrin Platinum Conjugates. *Monatsh. Chem.* **2002**, *133*, 679–705.

(6) (a) Liu, X.; Sternberg, E.; Dolphin, D. Cross-Metathesis Reactions of Vinyl-Chlorins and-Porphyrins Catalyzed by a "Second Generation" Grubbs' Catalyst. *Chem. Commun.* **2004**, 35, 852–853. (b) Liu, X.; Sternberg, E.; Dolphin, D. Cross-Metathesis of the Vinyl Group on Tetrapyrrolic Macrocycles: Reactivity, Selectivity, and Mechanism. *J. Org. Chem.* **2008**, *73*, 6542–6550.

(7) Smith, K. M. in *Heme, Chlorophyll, and Bilins*, Smith, A. G.; Witty, M., (Eds); Humana Press: New Jersey, **2002**, pp. 13–38.

(8) Miyaura, N.; Yamada, K.; Suzuki, A. A New Stereospecific Cross-Coupling by the Palladium-Catalyzed Reaction of 1-Alkenylboranes with 1-Alkenyl or 1-Alkynyl Halides. *Tetrahedron Lett.* **1979**, *20*, 3437–3440.

(9) (a) Dougherty, T. J.; Gomer, C. J.; Henderson, B. W.; Jori, G.; Kessel, D.; Korbelik, M.; Moan, J.; Peng, Q. Photodynamic Therapy. *J. Natl. Cancer Inst.* **1998**, *90*, 889–905. (b) Hamblin, M. R.; Hasan, T. Photodynamic Therapy: a New Antimicrobial Approach to Infectious Disease? *Photochem. Photobiol. Sci.* **2004**, *3*, 436–450. (c) Ethirajan, M.; Chen, Y.; Joshi, P.; Pandey, R. K. The Role of Porphyrin Chemistry in Tumor Imaging and Photodynamic Therapy. *Chem. Soc. Rev.* **2011**, *40*, 340–362. (d) Belali, S.; Savoie, H.; O'Brien, J.; Cafolla, A. A.; O'Connell, B.; Karimi, A. R.; Boyle, R. W.; Senge, M. O. 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.

(10) (a) Dong, J.; Ghiladi, R. A.; Wang, Q.; Cai, Y.; Wei, Q. Protoporphyrin-IX Conjugated Cellulose Nanofibers that Exhibit High Antibacterial Photodynamic Inactivation Efficacy. *Nanotechnology* **2018**, *29*, 265601. (b) Fadavi, F.; Abdulkhani, A.; Hamazeh, Y.; Bacher, M.; Gorfer, M.; Bandian, D.; Rosenau, T.; Hettegger, H. J. Photodynamic Antimicrobial Cellulosic Material Through Covalent Linkage of Protoporphyrin IX onto Lyocell Fibers. *J. Wood Chem. Technol.* **2018**, *0*, 0–18.

(11) (a) Tullius, M. V.; Harmston, C. A.; Owens, C. P.; Chim, N.; Morse, R. P.; McMath, L. M.; Iniguez, A.; Kimmey, J. M.; Sawaya, M. R.; Whitelegge, J. P.; Horwitz, M. A.; Goulding, C. W. Discovery and Characterization of a Unique Mycobacterial Heme Acquisition System. *Proc. Natl. Acad. Sci. U. S. A.* **2011**, *108*, 5061–5056. (b) Mazmanian, S. K.; Skaar, E. P.; Gaspar, A. H.; Humayun, M.; Gornicki, P.; Jelenska, J.; Joachmiak, A.; Missiakas, D. M.; Schneewind, O. Passage of Heme-Iron Across the Envelope of *Staphylococcus aureus*. *Science* **2003**, *299*, 906–909. (c) Lewis, J. P.; Dawson, J. A.; Hannis, J. C.; Muddiman, D.; Macrina, F. L. Hemoglobinase Activity of the Lysine Gingipain Protease (Kgp) of Porphyromonas Gingivalis W83. *J. Bacteriol.* **1999**, *181*, 4905–4913. (d) Owens, C. P.; Chim, N.; Goulding, C. W. Insights on How the *Mycobacterium tuberculosis* Heme Uptake Pathway Can Be Used as a Drug Target. *Future Med. Chem.* **2013**, *5*, 1391–1403.

(12) (a) Battersby, A. R.; Fookes, C. J. R.; Pandey, P. S. Linear Tetrapyrrolic Intermediates for Biosynthesis of the Natural Porphyrins: Experiments with Modified Substrates. *Tetrahedron* **1983**, *39*, 1919–1926. (b) Battersby, A. R.; Fookes, C. J. R.; Matchan, G. W. J.; Pandey, P. S. Biosynthesis of Natural Porphyrins: Studies with Isomeric Hydroxymethylbilanes on the Specificity and Action of Cosynthetase. *Angew. Chem. Int. Ed.* **1981**, *20*, 293–295. (c) Battersby, A. R.; Fookes, C. J. R.; Hart, G.; Matcham, G. W. J.; Pandey, P. S. Biosynthesis of Porphyrins

and Related Macrocycles. Part 21. The Interaction of Deaminase and Its Product (Hydroxymethylbilane) and the Relationship between Deaminase and Cosynthetase. *J. Chem. Soc., Perkin Trans. 1* **1983**, 3041–3047. (d) Haufschildt, K.; Schmalz, S.; Kriegler, T. M.; Neumann, A.; Streif, J.; Arai, H.; Heinz, D. W.; Layer, G. The Crystal Structure of Siroheme Decarboxylase in Complex with Iron-Uroporphyrin III Reveals Two Essential Histidine Residues. *J. Mol. Biol.* **2014**, *426*, 3272–3286.

(13) (a) Liu, F.; Ding, A.; Zheng, J.; Chen, J.; Wang, B. A Label-Free Aptasensor for Ochratoxin a Detection Based on the Structure Switch of Aptamer. *Sensors* **2018**, *18*, 1769. (b) Li, Z.; Zhou, X.; Shi, J.; Zou, X.; Huang, X.; Tahir, H. E. Preparation of Conducting Polyaniline/Protoporphyrin Composites and Their Application for Sensing VOCs. *Food Chem.* **2019**, *276*, 291–297.

(14) (a) Caughey, W. S.; Alben, J. O.; Fujimoto, W. Y.; York, J. L. Substituted Deuteroporphyrins. I. Reactions at the Periphery of the Porphyrin Ring. *J. Org. Chem.* **1966**, *31*. 2631–2640. (b) Gazzano, E. R.; Lázaro-Martínez, J. M.; Buldain, G. Y. A New Look at the Halogenation of Porphyrins. *Curr. Org. Chem.* **2017**, *21*, 177–182.

(15) Minnetian, O. M.; Morris, I. K.; Snow, K. M.; Smith, K. M. New Syntheses and Reactions of Some Halogenated Porphyrins. *J. Org. Chem.* **1989**, *54*, 5567–5574.

(16) (a) Ryan, A.; Gehrold; A.; Perusitti, R.; Pintea, M.; Fazekas, M.; Locos, O. B.; Blaikie, F.; Senge, M. O. Porphyrin Dimers and Arrays. *Eur. J. Org. Chem.* **2011**, 5817–5844. (b) Moylan, C.; Rogers, L.; Shaker, Y. M.; Davis, M.; Eckhardt, H. G.; Eckert, R.; Ryan, A. A.; Senge, M. O. Preparation of Tri-and Hexasubstituted Triptycene Synthons by Transition Metal Catalyzed Cross-Coupling Reactions for Post-Modifications. *Eur. J. Org. Chem.* **2016**, 185–195.

(17) (a) Senge, M. O. Stirring the Porphyrin Alphabet Soup—Functionalization Reactions for Porphyrins. *Chem. Commun.* **2011**, *47*, 1943–1960. (b) Dahms, K.; Senge, M. O.; Bakar, M. B. Exploration of *meso*-Substituted Formylporphyrins and Their Grignard and Wittig Reactions. *Eur. J. Org. Chem.* **2007**, 3833–3848.

(18) (a) Khadira, A.; de Coene, Y.; Gawal, P.; Roche, C.; Clays, K.; Anderson, H. L. Push–Pull Pyropheophorbides for Nonlinear Optical Imaging. *Org. Biomol. Chem.* **2017**, *15*, 947–965. (b) Cao, L.; Guo, X.; Wang, L.; Wang, S.; Li, Y.; Zhao, W. Synthesis and in Vitro Phototoxicity of Novel π-Extension Derivatives of Chlorin e6. *New J. Chem.* **2017**, *41*, 14279–14287.

(19) (a) Muruta, M.; Watanabe, S.; Masuda, Y. Novel Palladium (0)-Catalyzed Coupling Reaction of Dialkoxyborane with Aryl Halides: Convenient Synthetic Route to Arylboronates. *J. Org. Chem.* **1997**, *62*, 6458–6459. (b) Hyslon, A. G.; Kellett, M. A.; Iovine, P. M.; Therien, M. J. Suzuki Porphyrins: New Synthons for the Fabrication of Porphyrin-Containing Supramolecular Assemblies. *J. Am. Chem. Soc.* **1998**, *120*, 12676–12677.

(20) (a) Bakar, M. A.; Sergeeva, N. N.; Juillard, T.; Senge, M. O. Synthesis of Ferrocenyl Porphyrins via Suzuki Coupling and Their Photophysical Properties. *Organometallics* **2011**, *30*, 3225–3228. (b) Hata, H.; Shinokubo, H.; Osuka, A. Highly Regioselective Ir-Catalyzed β-Borylation of Porphyrins via C−H Bond Activation and Construction of β−β-Linked Diporphyrin. *J. Am. Chem. Soc.* **2005**, *127*, 8264–8265.

(21) Fujimoto, K.; Yorimitsu, H.; Osuka, A. Facile Preparation of β-Haloporphyrins as Useful Precursors of β-Substituted Porphyrins. *Org. Lett.* **2014**, *16*, 972–975.

(22) Liungdahl, T.; Bennur, T.; Dallas, A.; Emtenäs, H.; Mårtensson, J. Two Competing Mechanisms for the Copper-Free Sonogashira Cross-Coupling Reaction. *Organometallics* **2008**, *27*, 2490–2498.

(23) (a) Tornøe, C. W.; Christensen, C.; Meldal, M. Peptidotriazoles on Solid Phase: [1, 2, 3]-Triazoles by Regiospecific Copper (I)-Catalyzed 1, 3-Dipolar Cycloadditions of Terminal Alkynes to Azides. *J. Org. Chem*. **2002**, *67*, 3057–3064. (b) Rostovtsev, V. V.; Green, L. G.; Fokin, V. V.; Sharpless, K. B. A Stepwise Huisgen Cycloaddition Process: Copper(I)-Catalyzed Regioselective "Ligation" of Azides and Terminal Alkynes. *Angew. Chem. Int. Ed.* **2002**, *41*, 2596–2599.

(24) (a) Romine, M. F.; Rodionov, D. A.; Maezato, Y.; Anderson, L. N.; Nandhikonda, P.; Rodionova, I. A.; Carre, A.; Li, X.; Xu, C.; Clauss, T. R. W.; Kim, Y.-M.; Metz, T. O.; Wright, A. T. Elucidation of Roles for Vitamin B12 in Regulation of Folate, Ubiquinone, and Methionine Metabolism. *Proc. Natl. Acad. Sci. U. S. A.* **2017**, *114*, E1205–E1214. (b) Amirshaghaghi, A.; Altun, B.; New, K.; Yan, L.; Stein, J. M.; Cheng, Z.; Tsourkas, A. Site-Specific Labeling of Cyanine and Porphyrin Dye-Stabilized Nanoemulsions with Affibodies for Cellular Targeting. *J. Am Chem. Soc.* **2018**, *140*, 13550–13553.

(25) (a) Little, R. G.; Ibers, J. A. Crystal and Molecular Structure of the Free Base Porphyrin, Mesoporphyrin IX Dimethyl Ester. *J. Am. Chem. Soc.* **1975**, *97*, 5363–5369. (b) Hamor, T. A.; Caughey, W. S.; Hoard, J. L. The Crystal and Molecular Structure of Nickel (II) 2,4-Diacetyldeuteroporphyrin-IX Dimethyl Ester. *J. Am. Chem. Soc.* **1965**, *87*, 2305–2312. (c) Bonnett, R.; Hursthouse, P. A.; Trotter, J. Nitrosation and Nitrosylation of Haemoproteins and Related Compounds. Part 3. Attack at the Vinyl Groups of Protoporphyrin Dimethyl Ester. X-

Ray Analysis of 8^1(*E*)-8^2-Nitroprotoporphyrin Dimethyl Ester. *J. Chem. Soc., Perkin Trans. 1* **1980**, 490–494. (d) Senge, M. O.; Fuhrhop, J.–H. CSD *Communication (Private Communication)* **1999**, CCDC 121724. (e) Groom, C. R.; Bruno, I. J.; Lightfoot, M. P.; Ward, S. C. The Cambridge Structural Database. *Acta Cryst. Sect. B* **2016**, *72*, 171–179.

(26) Caughey, W. S.; Ibers, J. A. Crystal and Molecular Structure of the Free Base Porphyrin, Protoporphyrin IX Dimethyl Ester. *J. Am. Chem. Soc.* **1977**, *99*, 6639–6645.

(27) Fruk, L.; Kuo, C.-H.; Torres, E.; Niemeyer, C. M. Apoenzyme Reconstitution as a Chemical Tool for Structural Enzymology and Biotechnology. *Angew. Chem. Int. Ed.* **2009**, *48*, 1550–1574.

(28) Caughey, W. S.; Alben, J. O.; Fujimoto, W. Y.; York, J. L. Substituted Deuteroporphyrins. I. Reactions at the Periphery of the Porphyrin Ring. *J. Org. Chem.* **1966**, *31*. 2631–2640.

(29) Hultquist, D. E.; Morrison, M. Lactoperoxidase I. The Prosthetic Group of Lactoperoxidase. *J. Biol. Chem.* **1963**, *238*, 2843–2846.

(30) Morris, I. K.; Snow, K. M.; Smith, N. W.; Smith, K. M. Syntheses of Novel Substituted Porphyrins by the Mercuration and Palladium/Olefin Methodology. *J. Org. Chem.* **1990**, *55*, 1231–1236.

(31) Bai, M.; Huang, J.; Zheng, X.; Song, Z.; Tang, M.; Mao, W.; Yuan, L.; Wu, J.; Weng, X.; Zhou, X. Highly Selective Suppression of Melanoma Cells by Inducible DNA Cross-Linking Agents: Bis(catechol) Derivatives. *J. Am. Chem. Soc.* **2010**, *132*, 15321–15327.

(32) Matoba, M.; Kajimoto, T.; Nishide, K.; Node, M. Preparation and Application of Odorless 1,3-Propanedithiol Reagents. *Chem. Pharm. Bull.* **2006**, 54, 141–146.

(33) Hope, H. X-Ray Crystallography: A Fast, First-Resort Analytical Tool. *Prog. Inorg. Chem.* **2007**, *41*, 1–19.

(33) (a) *Saint*, Version 8.37a, Bruker AXS, Inc., Madison, WI, **2013**. (b) *SADABS*, version 2016/2, Bruker AXS, Inc., Madison, WI, **2014**. (c) *APEX3*, Version 2016.9–0, Bruker AXS, Inc., Madison, WI, **2016**.

(34) (a) Dolomanov, O. V.; Bourhis, L. J.; Gildea, R. J.; Howard, J. A. K.; Puschmann, H. *OLEX2*: A Complete Structure Solution, Refinement and Analysis Program. *J. Appl. Crystallogr.* **2009**, *42*, 339–341. (b) Sheldrick, G. *SHELXT* – Integrated Space-Group and Crystal-Structure Determination. *Acta Cryst. Sect. A* **2015**, *71*, 3–8.