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Advances in Modern Synthetic Porphyrin Chemistry

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1. Introduction

Porphyrin chemistry has undergone a renaissance over the past ten years due to potential applications of these compounds in areas including photodynamic therapy, solar energy conversion and catalysis. It seems an appropriate time, therefore, to review modern contributions in this field. The area, prior to 1978, has been widely reviewed in the series of books 'The Porphyrins' edited by Dolphin.[1a] Historical and synthetic aspects to that date are well covered and so this review will focus on synthetic porphyrin chemistry of the last twenty years. More recent porphyrin syntheses have also been covered by Dolphin et al.[1b] This review will be divided into two main parts: firstly the preparation of compounds where functionality is introduced during the formation of the porphyrin; secondly functionalisation of the preformed porphyrin macrocycle.

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2. Part 1—Synthesis of Functionalised Porphyrins from Non-Porphyrin Precursors

2.1. Adler–Longo method

Tetraphenylporphyrin (TPP) was first synthesised using benzaldehyde and pyrrole in 1936 by Rothmund[2] (Scheme 1). The reaction was carried out in a sealed tube at 150°C for 24 h. The yields however were low and the harsh conditions meant that only a limited number of aromatic aldehydes survived the procedure. Improvements to this method were made by Adler and Longo[3] in 1967 who reacted benzaldehyde and pyrrole in refluxing propionic acid for 30 min, open to air. Using these conditions, a greater variety of substituted benzaldehydes were converted into the corresponding 5,10,15,20-tetraphenylporphyrins. The reactions could also be scaled up to give multi-gram quantities of porphyrin, and in some cases yields of up to 20% were obtained. This method is still used widely when large quantities of porphyrin are needed and where the aldehydes

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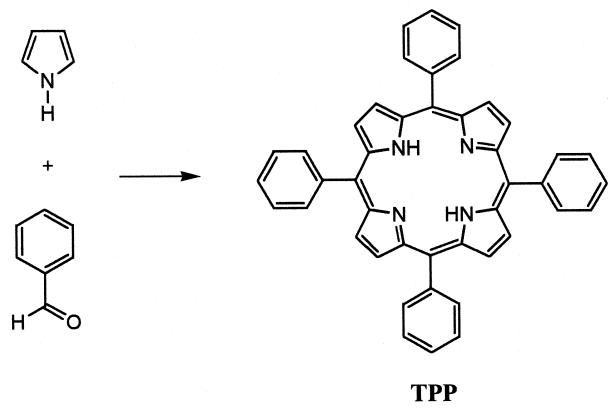


Scheme 1. Formation of tetraphenylporphyrin.

are capable of withstanding acidic conditions. Examples of this method[4–10] include the synthesis of basket handle porphyrins[11] by Chandrashekar et al.[12] using a preformed dialdehyde and pyrrole in propionic acid.

Differentially functionalised porphyrins can also be prepared by using two different aldehydes under essentially the same conditions. This type of reaction is often used for the preparation of porphyrins containing three substituted phenyl rings derived from one aldehyde and one substituted phenyl ring derived from the other. The obvious problem is the separation of the mixture of products, which can include up to six different compounds. However, by varying the stoichiometry of the reagents, yields of the desired product can be maximised.

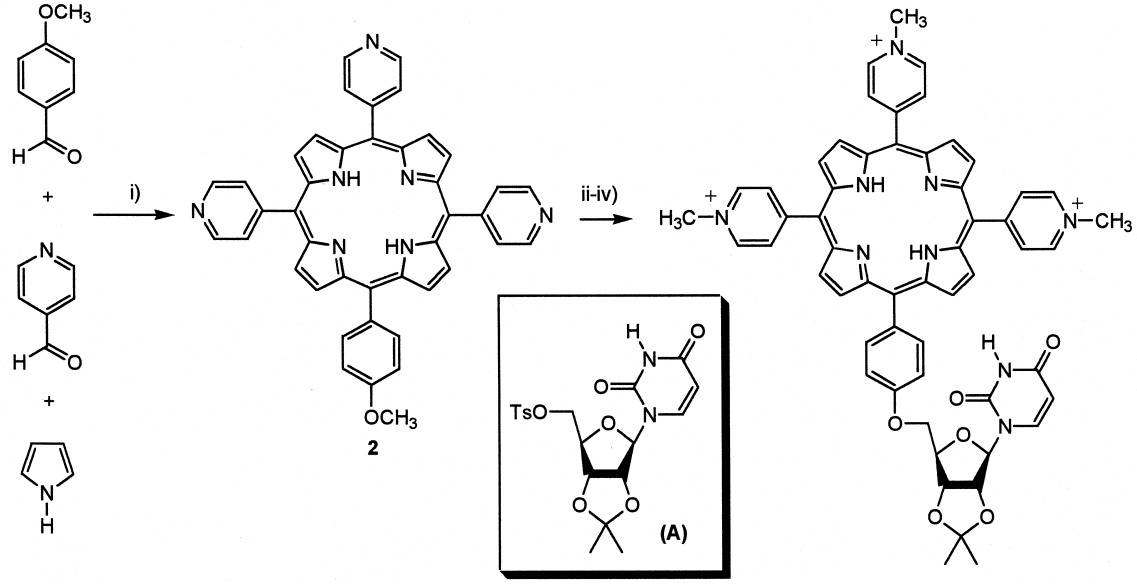
The Adler–Longo method is often used to obtain unsymmetrically substituted tetraphenylporphyrins with groups suitable for further modification. An elegant example of this is the recent synthesis of water soluble porphyrinyl nucleosides by Czuchajowski and co-workers.[13] In this synthesis 4-methoxybenzaldehyde and 4-pyridinecarboxaldehyde were condensed with pyrrole under Adler–Longo conditions.[14,15] The mixture of products contained porphyrins with up to three 4-methoxyphenyl groups at the *meso*-positions, the remaining *meso*-positions being occupied by 4-pyridyl rings. These products were separated by silica gel chromatography. The three compounds were further functionalised on the 4-methoxyphenyl rings to give the porphyrinyl nucleosides (Scheme 2, only the porphyrin containing one 4-methoxyphenyl group is shown for clarity).

Other porphyrins made using the propionic acid procedure include *meso*-tetra(4-methoxynaphthyl)porphyrin which was subsequently demethylated and investigated as a potential tumour localiser.[16] Lavalle et al.[17] have used the Adler–Longo[3] method to synthesise cationic porphyrins which could be used for DNA binding studies. In this case a protected amino aldehyde was prepared and used to form the porphyrin, before removal of the protecting group to reveal a tetraaminomethylporphyrin (Scheme 3). The latter was protonated in the pH range suitable for DNA binding.

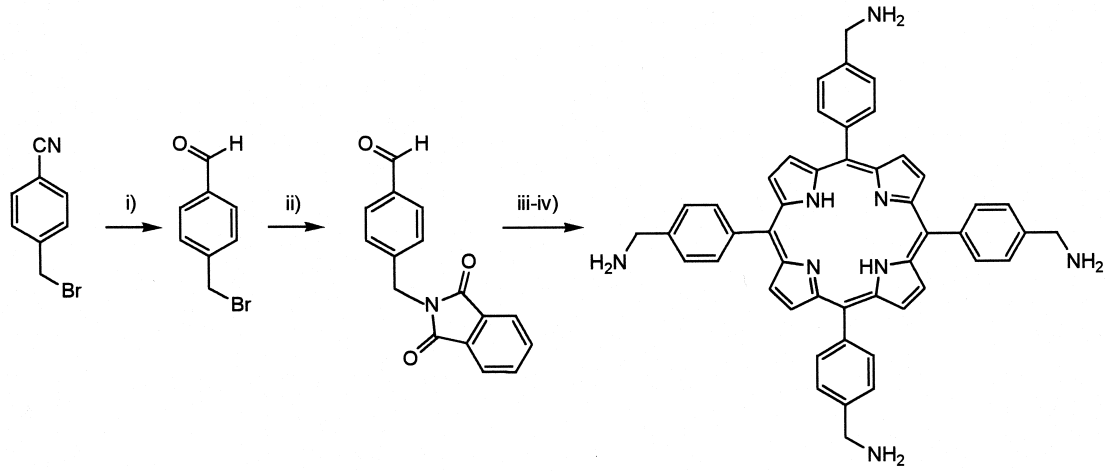
While the above methods show the utility of the propionic acid method, there are several drawbacks. The formation of the reduced porphyrin (chlorin) invariably contaminates the product and a high percentage of tarry by-products are also formed. Another problem is the failure of the reaction with aldehydes containing acid sensitive functional groups.

2.2. Lindsey method

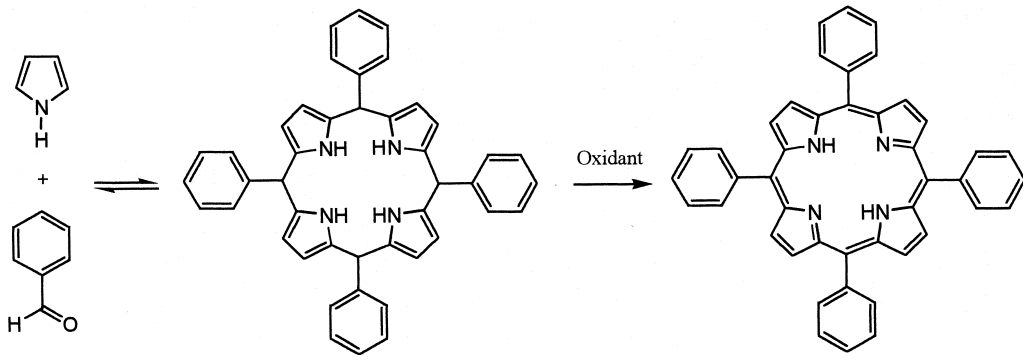
Many of the problems associated with the rather harsh conditions of the Adler–Longo method can be overcome using methodology developed by Lindsey et al.[18] The Lindsey method relies on the formation of porphyrinogen as an intermediate in porphyrin synthesis. The existence of this intermediate has previously been shown by Dolphin,[19] who isolated β-octamethyl-*meso*-tetraphenylporphyrinogen under Adler–Longo conditions. The advantage of this method is that it allows the formation of porphyrins from sensitive aldehydes, in higher yields, with more facile



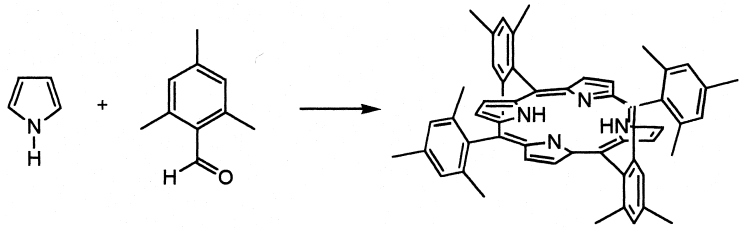
Scheme 2. Reaction conditions: (i) Propionic acid; (ii) Pyridine hydrochloride, 220°C, 2.5 h; (iii) (**A**), Cs_2CO_3, NaH, DMF, 65°C, 42–36 h; (iv) CH_3I/CH_3NO_2 (4:3), 70°C, 12 h.



Scheme 3. Reaction conditions: (i) DiBAL-H, CH_2Cl_2, 0°C, then 45°C, 4 h, 60%; (ii) Potassium phthalimide, DMF, reflux, 4 h, 90%; (iii) Pyrrole, acid; (iv) NaOH, heat, then 70% H_2SO_4, heat.



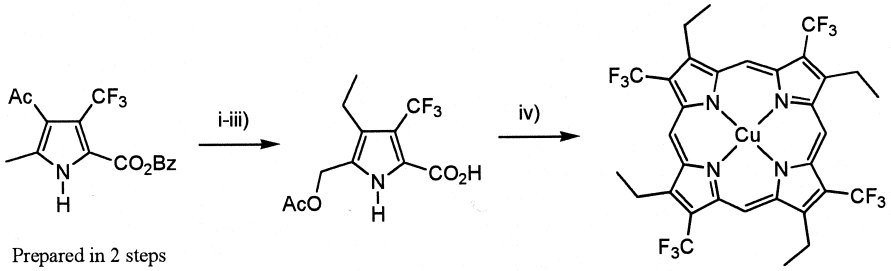
Scheme 4. Formation of porphyrin from porphyrinogen.



Scheme 5. Formation of tetramesitylporphyrin.

purification. A drawback, however, is the need for higher dilution conditions (typically 10^{-2} M), which means that the reaction is not amenable to scale-up. The methodology relies on the fact that pyrrole and benzaldehyde under acid catalysis will establish an equilibrium with tetraphenylporphyrinogen. The dilution conditions are important to optimise formation of the porphyrinogen at the expense of open chain polypyrrylmethanes. After the equilibrium has been established, an oxidant is added which irreversibly converts the porphyrinogen to the corresponding porphyrin (Scheme 4). It was found using TPP as a model, that equimolar concentrations of pyrrole, benzaldehyde and triethylorthoacetate (water scavenger), with boron trifluoride, at room temperature, produced optimal results. The reaction is carried out under inert conditions in dichloromethane for 1 h, followed by addition of 2,3,5,6-tetrachlorobenzoquinone (*p*-chloranil) and a further hour at reflux. Lindsey and co-workers[18] have used this method to synthesise over 30 porphyrins, with average yields around 30–40%, using boron trifluoride or trifluoroacetic acid as the catalyst.

The Lindsey conditions were later modified to allow the formation of *o*-substituted tetraphenylporphyrins which, due to their sterically hindered nature, are difficult to prepare.[20] Sterically hindered porphyrins are useful as crowding around the macrocycle can lead to a non-planar conformation, which in turn can lead to modified optical properties.[21a,b] Using tetramesitylporphyrin as an example (which had previously been prepared in yields of



Scheme 6. Reaction conditions: (i) $NaBH_4$, BF_3, THF, 3 h, 94%; (ii) $Pb(OAc)_4$, AcOH, 60°C, 3 h, 72%; (iii) H_2, Pd–C (5%), Et_3N, THF, 3 h, 88%; iv) $Cu(OAc)_2$, AcOH, reflux.

1–6%),[22a–c] it was found that adding ethanol as a co-catalyst in the presence of BF_3, resulted in the formation of tetramesitylporphyrin in 30% yield (Scheme 5). The need for ethanol was attributed to its ability to dissociate the mesitaldehyde–BF_3 complex.

The general utility of these optimised conditions was explored using various *o*-substituted benzaldehydes. The results showed that 2-alkoxy, 2-alkyl and 2,6-dialkoxybenzaldehydes gave improved yields with the addition of ethanol but *o*-substituted halogens showed no improvement.[20] Other examples of sterically hindered porphyrins which have been prepared using this methodology include dodecaphenylporphyrin,[23] which was prepared using 3,4-diphenylpyrrole and benzaldehyde in 5.7% yield. The Lindsey group has also prepared hindered porphyrins using derivatised benzaldehydes and pyrrole. Octa- and dodecabenzyloxyporphyrins have also been synthesised in 9–52% yield[24] in this way, as have *meso*-tetraglycosylporphyrins[25] and *meso*-tetraalkynylporphyrins.[26] The use of diversely functionalised aldehydes for building 24 porphyrin-based model systems has been described by Lindsey et al.[27] The effects of the addition of salts[28] such as NaCl or benzyltributylammonium chloride on the Lindsey procedure has been studied recently and it has been shown that, depending on the salt, porphyrin yield can be increased by up to two-fold.

A noteworthy modification of the Lindsey procedure is the use of clays for porphyrin synthesis.[29] Initial work in this area by Pinnavaia[30] showed that TPP formed on the surface of montmorillonites. Using this concept for the synthesis of *meso*-tetraalkylporphyrins, Onaka and co-workers[29] used various acidic clays in place of BF_3. It was found that montmorillonite K10 gave the highest yield of porphyrin (46% yield for *meso*-tetrapentylporphyrin, compared to 20% yield using BF_3).

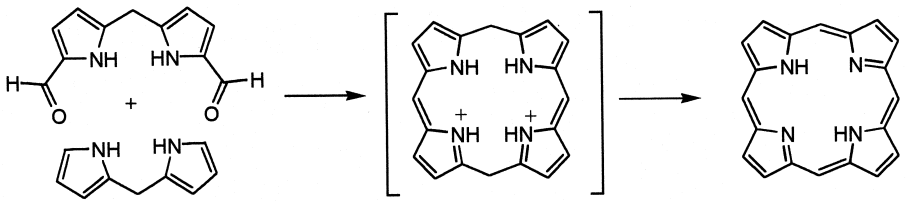
Another method for tetraarylporphyrin synthesis involves the use of transition metal salts. Llama et al.[31] have used vanadium (V), titanium (IV) and manganese (III) salts to synthesise a variety of porphyrins in good yields (68% yield of TPP with $VOCl_3$) and at higher concentrations than the Lindsey method. It was reported that the high valent metal salt, acting as an oxidant, converts the porphyrinogen to the porphyrin *via* a radical process.

2.3. Porphyrins from 2-substituted pyrroles

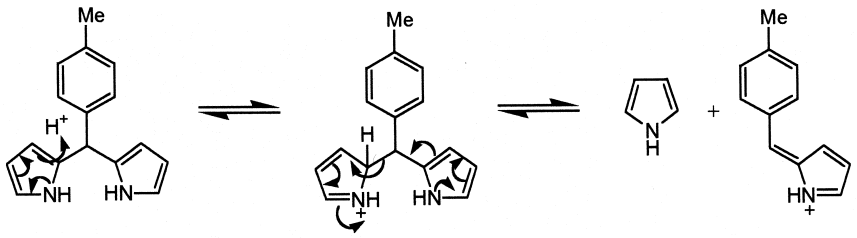
This method relies upon the 'head-to-tail' cyclocondensation of four molecules of a pyrrole under acidic conditions. The requirements are: (a) that the 2- or 5-position of the pyrrole bears a substituted methyl group which will encourage formation of a highly electrophilic azafulvene in acid; and (b) that the remaining 2- or 5-position should be unsubstituted or have a group which is easily eliminated (carboxyl group) under acidic conditions. This method is useful in the synthesis of porphyrins containing non-equivalent β-positions. A drawback is that several steps are usually required to prepare the highly substituted pyrrole precursor, and also that the 'head-to-tail' nature of the reaction precludes its use in the synthesis of most naturally occurring porphyrins where the D ring is inverted.[32] A recent example of this method is the synthesis of an electron deficient porphyrin containing four trifluoromethyl groups, by Ogoshi et al.[33] (Scheme 6). The same porphyrin was later prepared using the hydroxymethylpyrrole derivative and ethanol as the solvent in 30% yield, at room temperature and without the addition of metal salts.[34]

2.4. 2+2 Porphyrin synthesis

Porphyrins can also be prepared from dipyrromethanes using what are commonly called 2+2 syntheses. The term 2+2 arises because the porphyrin is formed by the condensation of two dipyrromethanes (fragments containing two pyrrole units). Early work in this area was pioneered by MacDonald[35] and the basic synthetic route is shown in Scheme 7. The original MacDonald method involves the



Scheme 7. 2+2 Porphyrin synthesis.



Scheme 8. Acid catalysed cleavage of dipyrromethane.

use of one dipyrromethane bearing two formyl groups alpha to the pyrrolic nitrogen and another dipyrromethane with no α-substitution.

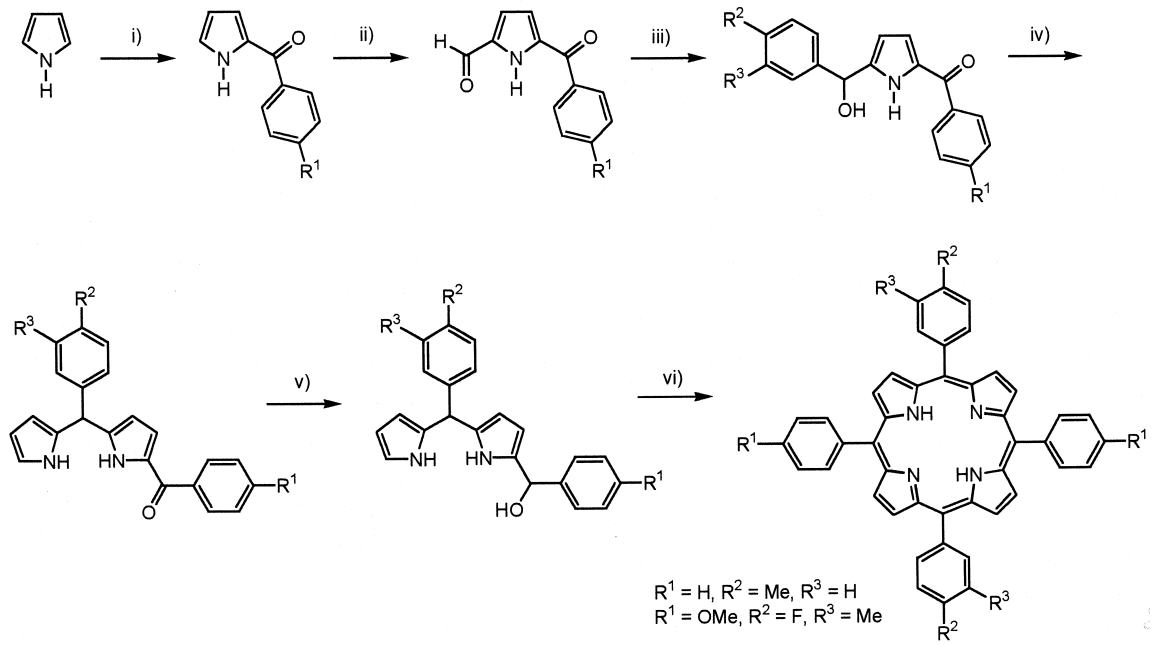
There is obvious scope for the preparation of a large variety of functionalised porphyrins using this route and a greater degree of regioselectivity can be attained relative to the Adler and Lindsey methods. The β-positions can be differentially functionalised on the pyrrole rings and the bridging carbon in the dipyrromethane can also be substituted. Honeybourne et al.[36] used a modified MacDonald synthesis for the preparation of models of naturally occurring porphyrins, for studying the enzyme ferrochelatase. They prepared dipyrromethanes containing differentially substituted β-positions and formyl groups at the terminal α-positions. The coupling resulted in the formation of porphyrins in 10% yield.

Although the original MacDonald 2+2 method requires bisformylation of one dipyrromethane, two α-free dipyrromethanes can also be condensed with 'one carbon equivalents' to supply the two incipient *meso*-positions. Strapped porphyrins which are bridged between opposing *meso*-positions have been made by Baldwin et al.[37] using a bisdipyrromethane and trimethylorthoformate as the one carbon unit.

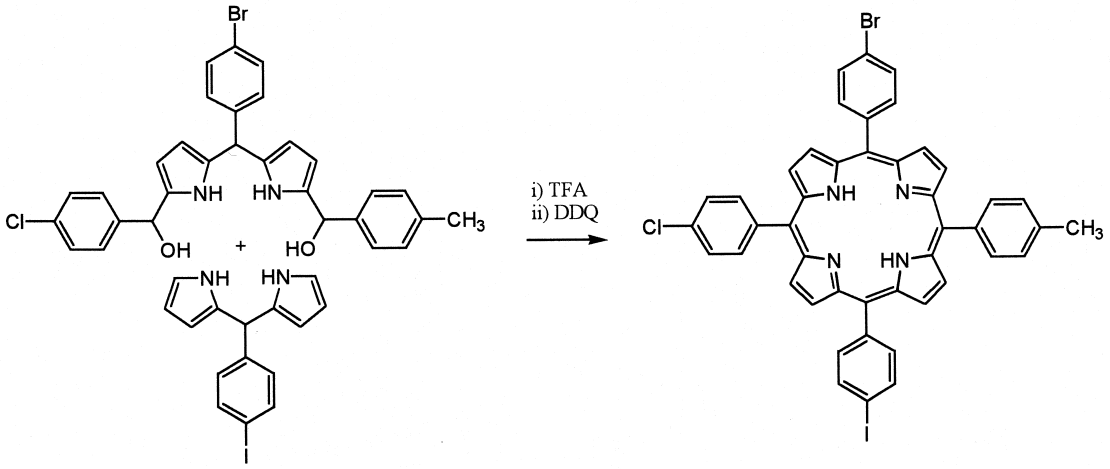
The use of dipyrromethanes and one carbon fragments, however, also has its drawbacks. The Smith group[38] have reported that the self-condensation of dipyrromethane in the presence of 'one carbon' fragments leads to a mixture of products. This was attributed to the acid catalysed cleavage of the dipyrromethane, resulting in the expulsion of pyrrole (Scheme 8).

Tetraarylporphyrins have also been synthesised by other modifications of 2+2 methodology. Smith et al.[39] have prepared *meso*-tetraarylporphyrins containing two-fold rotational symmetry (Scheme 9) and extended this procedure to allow the formation of a tetraarylporphyrin with four different aryl substituents. 5,15-Di(4-tolyl)-10,20-diphenylporphyrin was prepared in 31% yield and 5,15-bis(4-fluoro-3-methylphenyl)-10,20-bis(4-methoxyphenyl)-porphyrin was made in 24% yield. It was proposed that attaching the 'one carbon' fragment to the dipyrromethane would disfavour the acid catalysed cleavage of the dipyrromethane.[38]

Lindsey et al.[40] have also synthesised porphyrins containing four different *meso*-substituents. One of these compounds contains three different halogens attached to the phenyl rings and was prepared in 14% yield (Scheme 10).



Scheme 9. Reaction conditions: (i) EtMgBr, then $R^1C_6H_4COCl$; (ii) $POCl_3$, DMF; (iii) $R^2R^3C_6H_3MgBr$; (iv) Pyrrole, AcOH; (v) $LiAlH_4$; (vi) $CH_3CH_2CO_2H$.



Scheme 10. Differentially substituted porphyrin.

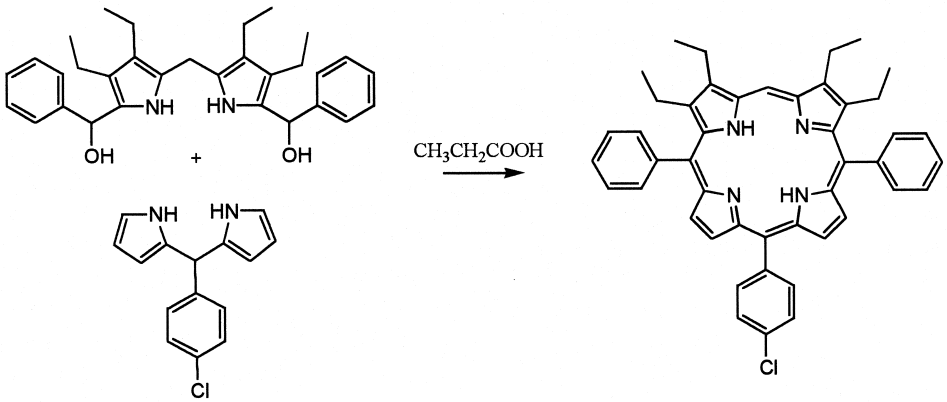
Maruyama and co-workers[41] have used 5,5′-bis(hydroxymethyl)dipyrromethanes to prepare unsymmetric porphyrin dimers using similar methodology. Anderson[42] has synthesised porphyrin dimers using substituted dipyrromethane and trimethylsilylpropynal as the one carbon fragment. Unsymmetrical *meso*-arylporphyrins with substituted β-positions have also been synthesised. Ogoshi et al.[43] prepared their 5,15-diphenyl-10-*p*-chlorophenyl-2,3,17,18-tetraethylporphine as the single product in 9% yield (Scheme 11). Diphenylporphyrins have been synthesised by 2+2 methodology as shown by Rose et al.[44] who reacted 3,3′-diethyl-4,4′-dimethyl-2,2′-dipyrromethane with substituted benzaldehydes. They produced the 5,15-di(*o*-nitrophenyl)porphyrin analogue in 45% yield. Other syntheses of diphenylporphyrins include those of Manka and Lawrence,[45] Maruyama and co-workers[46] and Boyle et al.[47,48]

The substituent pattern of the porphyrins formed from 2+2 reactions can be broadly classed into four categories: (a) all β- and all *meso*-substituted, (b) all β- and two *meso*-substituted, (c) no β-substituted and two *meso*-substituted, (d) no β-substituted and four *meso*-substituted. The 2+2 route[49–77] has become very popular in recent years due to its flexibility, and there are many reports of porphyrin synthesis based on this methodology. It is, however, very dependent on the availability of suitable dipyrromethane building blocks, and the preparation of dipyrromethanes has also been the subject of several recent studies, but this area lies outside the scope of this review.[78]

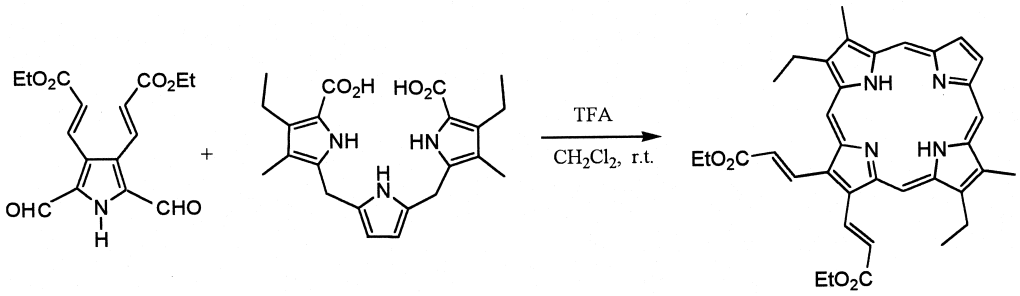
2.5. 3+1 Porphyrin synthesis

The 3+1 synthetic route involves the condensation of a tripyrrane (compound containing three pyrrole groups linked alpha to the ring nitrogens by two saturated carbons) with a diformyl pyrrole. This area has seen much activity in the last five years, although the methodology has been used previously for the synthesis of expanded porphyrins and oxa- and thiaporphyrins.[79] Momenteau et al.[80,81] have used this procedure to prepare a porphyrin containing two acrylic acid units on the same pyrrole, in 33% yield as shown in Scheme 12.

Lash [82] has used pyrrole dialdehyde and tripyrrane to prepare an octaalkylporphyrin in 60% yield. The porphyrinogen forms under acid catalysis and is then oxidised as shown in Scheme 13. More complex porphyrins such as acenaphthoporphyrins[83] and phenanthrolinoporphyrins[84] containing fused 1,10-phenanthroline subunits have also been synthesised by Lash et al.[83,84] Sessler[85] and co-workers have used this approach to produce mono-functionalised



Scheme 11. Formation of 5,15-diphenyl-10-*p*-chloro-2,3,17,18-tetraethylporphine.



Scheme 12.

alkylporphyrins. The 3+1 route has been used to create many exotic porphyrinoid structures such as oxybenzaporphyrins[86] and carbachlorins.[87] Other work[88–92] includes the synthesis of porphyrin analogues containing cycloheptatriene[88,89] and pyridine[90] subunits.

2.6. Porphyrins from linear tetrapyrroles

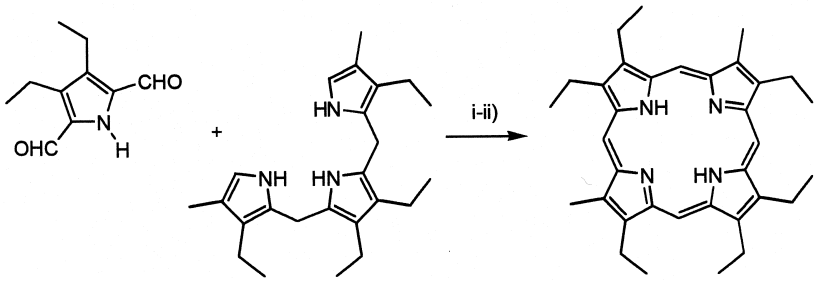
Linear tetrapyrroles or bilanes can be cyclised to produce porphyrins. This strategy is used when there is a need to synthesise porphyrins which are unsymmetrical and contain a variety of substituents at the β-position. *b*-Bilenes bearing an iminium group at the 1-position and a methyl at the 19-position have been used, via an oxidative cyclisation strategy, to prepare porphyrins. Clezy et al.[93] have used ^{13}C-labelled *b*-bilenes to show that the final carbon required to complete the ring system originates from the methyl group (Scheme 14).

The most common tetrapyrroles used for porphyrin synthesis are *a*,*c*-biladienes. The use of 1-bromo-19-*a*,*c*-methylbiladienes as porphyrin precursors has been reviewed by Dolphin et al.[94] It has been shown[95] that vinylporphyrins can be prepared from 1-bromo-19-methyl-*a*,*c*-biladienes. Using this intermediate, Dolphin et al.[95] carried out the cyclisation step using DMSO–pyridine at room temperature (Scheme 15). The bisacetate was then converted to the corresponding chloro compound in two steps, which in turn was dehydrochlorinated.

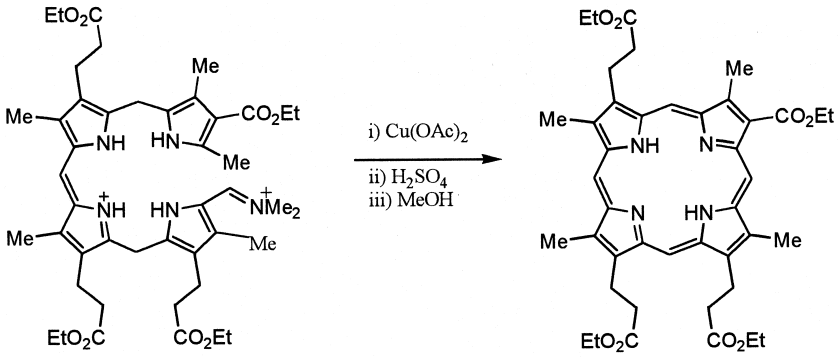
Smith et al.[96] have also prepared porphyrins from *a*,*c*-biladienes for use in photodynamic therapy. More recently, Lash et al.[97] have synthesised dinaphthoporphyrins from *a*,*c*-biladienes. Smith et al.[98] have also carried out the cyclisation of *a*,*c*-biladiene salts with 1,19-arylmethyl substituents.

3. Part 2—Synthesis of Functionalised Porphyrins by Reactions on Preformed Porphyrins

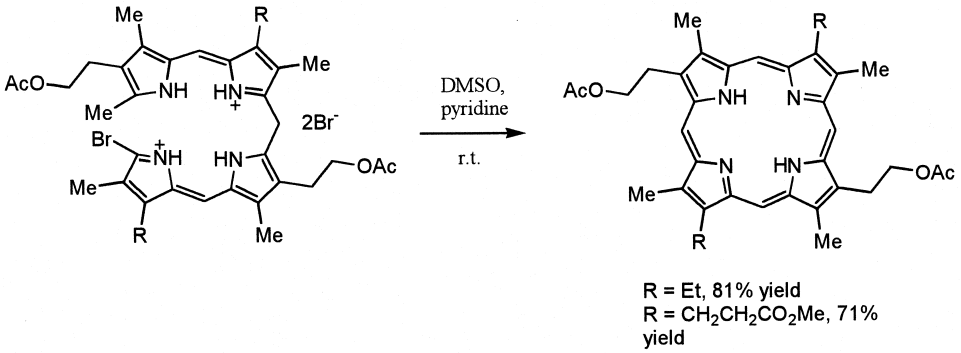
Reactions on the porphyrin macrocycle can be categorized



Scheme 13. Reaction conditions: (i) TFA; (ii) Et_3N, DDQ.



Scheme 14. Porphyrin formation from *b*-bilanes.



Scheme 15.

in several different ways; for the purposes of this survey we will separate them by the reaction site on the porphyrin and nature of reaction as follows: (1) reactions at the *meso*-position, (2) reactions at the β-position, (3) cyclisation reactions, (4) functional group interconversions, (5) phenyl ring transformations of arylporphyrins.

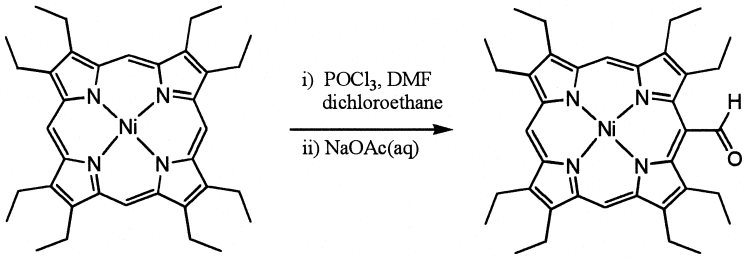
3.1. Reactions at the *meso*-position

The *meso*- and β-positions of the porphyrin macrocycle have similar reactivity towards electrophilic substitution and so the selective introduction of substituents at the *meso*-positions commonly requires the use of β-substituted porphyrins. Formylation at the *meso*-position is one of the most common reactions and is carried out by the Vilsmeier formylation reaction on the corresponding copper or nickel complex of the porphyrin[99,100a–c] to give porphyrins of the type shown in Scheme 16. The aldehyde functionality on the porphyrin can then be subjected to many conventional functional group transformations, but these will be covered in a later section of this review.

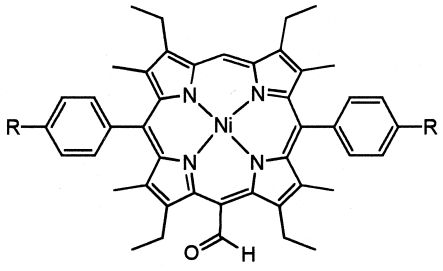
Gunter et al.[101] have also prepared *meso*-formylated 5,15-diphenyloctaalkylporphyrins bearing substituents on the phenyl rings which were used as intermediates in the preparation of purpurins. The mono formylated products of the various phenyl-substituted porphyrins are shown in Fig. 1.

A modification of the Vilsmeier formylation reaction has also been carried out by Smith et al.[102] on the nickel complex of octaethylporphyrin (OEP). This involved replacement of dimethylformamide with dimethylamino-acrolein, resulting in the introduction of a 2-formylvinyl group. The 2-formylvinyl group introduced by this method, upon treatment with strong acid, cyclised onto the adjacent β-pyrrolic position to give a benzochlorin. A similar reaction was carried out by Maruyama et al.[103] using 5,15-di-*p*-tolyloctaethylporphyrin to give the corresponding *meso*-(2-formylvinyl)porphyrin, which was then cyclised.

Nitration of the porphyrin at a *meso*-position by electrophilic aromatic substitution using $PhSeNO_2$ has been performed by van Lier et al.[104] Using PhSeCl and $AgNO_2$,

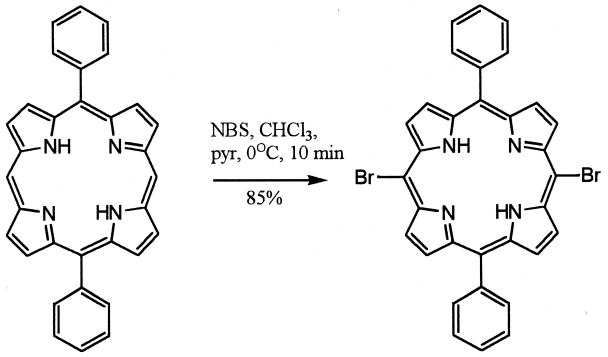


Scheme 16. Ni(II) *meso*-formyloctaethylporphyrin.



R	Me	NMe_2	NO_2	OTs
Yield (%)	90	60	44	90

Figure 1. Formylation products of substituted diphenyloctaalkylporphyrins.

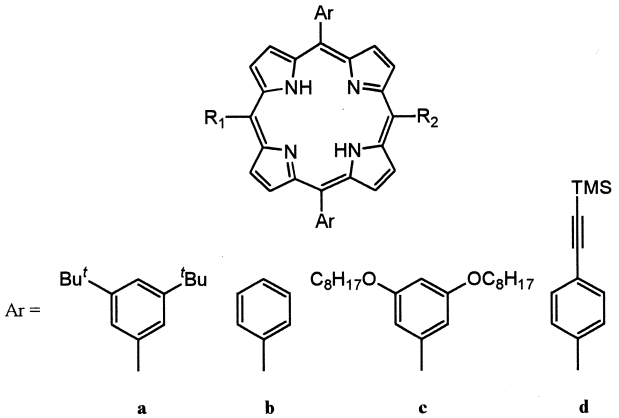


Scheme 17.

the nitrating reagent was prepared in situ and reacted with OEP nickel complex to give the nitrated derivative in 75% yield.

Halogenation of porphyrins at the *meso*-position is another reaction, which can give access to synthetically useful precursors. Chlorination of OEP nickel complex with phenylselenyl chloride gives a product bearing one to four *meso*-chloro substituents as shown by van Lier et al.[104] Although *meso*-chlorinated porphyrins are of little use for further synthetic modification, the corresponding bromo- and iodoporphyrins have been used in palladium mediated coupling reactions. Therien et al.[105] have used *N*-bromosuccinimide (NBS) to effect the *meso*-dibromination of 5,15-diphenylporphyrin, and it was reported that the halogenation[106] took place cleanly without substitution at the β-positions (Scheme 17). More recently, Anderson et al.[107] have *meso*-dibrominated a phenyl-substituted metallated diphenylporphyrin, using a similar method and in the same yield.

Table 1. *Meso*-iodinated porphyrins



Ar	R_1	R_2	Yield (%) after demetallation
a	I	H	59
b	I	H	35
c	I	H	51
d	I	H	31
c	I	I	61
a	I	a	75
c	I	Br	71

Iodination has proved more difficult, probably due to the larger steric bulk of the iodinium cation. Mono-iodination of 5,15-diphenylporphyrin has been accomplished by Dolphin et al.[108] using bis(trifluoroacetoxy)iodobenzene and iodine in 70% isolated yield. Bis-iodination also occurred, with the second iodine being introduced non-regiospecifically at one of the β-carbons. Recently Osuka et al.[109] have reported regioselective *meso*-iodination of diphenylporphyrins; this method used $AgPF_6$ and iodine to effect the mono and diiodination of zinc 5,15-diphenylporphyrins in good yield (Table 1).

Using this protocol, no β-iodinated products were detected, provided that sterically bulky substituents were present on the phenyl rings; this finding is in accord with an earlier report by Boyle et al.[110] using Dolphin's conditions. Interestingly, triaryl and *meso*-brominated diphenylporphyrins are also iodinated efficiently at the final available *meso*-position.[109] Differentially *meso*-halogenated porphyrins have been prepared by Boyle et al.[110] who *meso*-brominated 5,15-diphenylporphyrin and then iodinated the remaining *meso*-position using bis(trifluoroacetoxy)iodobenzene and iodine in quantitative yield. It was also reported that the regioselectivity of this iodinating agent was dependent on the nature of the phenyl substituent on the 5,15-diphenylporphyrin.[110] *Meso*-iodotriarylporphyrin has also been prepared by Shultz et al.[111] and subsequently used in the construction of butadiyne-linked porphyrin dimers.[111]

Attack of nucleophiles at the *meso*-position is also known.[112–116] An example of this is the addition of *tert*-butyllithium to TPP to give a phlorin (Fig. 2). This molecule was the first fully characterised 5,10-dihydroporphyrin, the relative stereochemistry of the two *tert*-butyl groups being defined by X-ray crystallography.[117]

3.2. Reactions at the β-position

The Vilsmeier formylation reaction can also be carried out at the β-pyrrolic position on a suitable porphyrin substrate. The nickel, copper and cobalt complexes of TPP were selectively mono β-formylated by Ponomarev et al.[118] It was reported that the intermediate 'phosphorus complex' could be isolated and the formylated porphyrin could be prepared in 65% yield. Nitration of *meso*-tetraarylporphyrins at the β-position is found to be dependent on the metal which is coordinated at the porphyrin core. Copper(II), nickel(II) and palladium(II) metalloporphyrins were found to undergo exclusive mono β-nitration, as shown by Crossley et al.[119] The thiocyanate group can also be introduced at a β-position using ammonium thiocyanate. Callot et al.[120] used copper

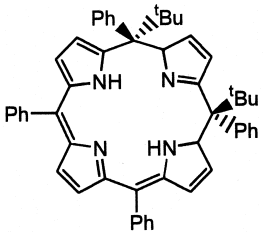
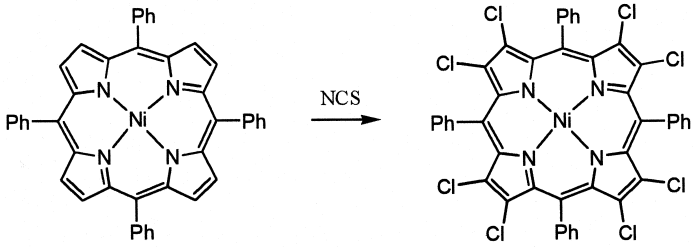
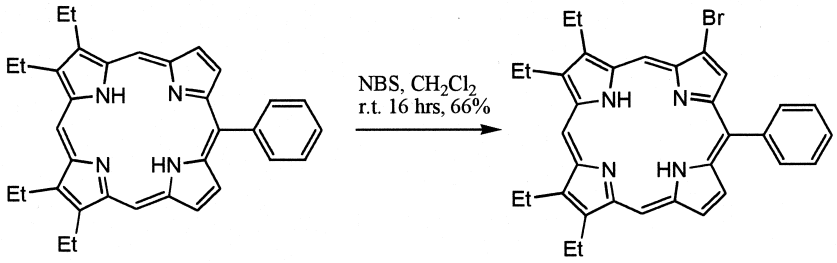


Figure 2. 5,10-Dihydroporphyrin.



Scheme 18.

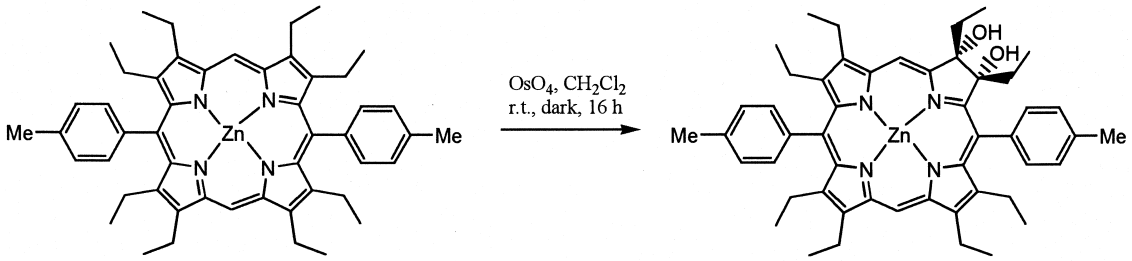


Scheme 19.

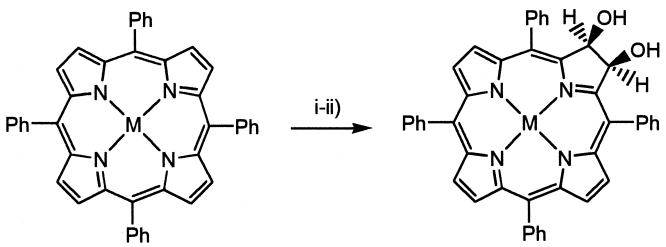
TPP as the substrate and formed copper (II) 2-thiocyanato-tetraphenylporphyrin. The halogenation of porphyrin β-positions has also been studied. van Lier et al.[104] treated the nickel complex of TPP with PhSeCl to produce a mixture of di-, tri- and polychlorinated products. Using three-fold molar excess of PhSeBr and the same porphyrin, they found that 80–90% of the porphyrin was brominated and the major product (90–95%) was the mono β-brominated compound. The fully β-chlorinated nickel (II) TPP has been prepared by Dolphin et al.[121] by treatment of the metallated TPP with *N*-chlorosuccinimide (NCS) (Scheme 18).

The completely brominated copper complex of TPP has been prepared using bromine and a mixture of $CHCl_3$ and CCl_4.[121,122] Sterically hindered tetramesitylporphyrin has also been β-perbrominated as the zinc complex.[123,124] Mono β-bromination of porphyrins bearing both β- and *meso*-substituents is also known (Scheme 19).[125]

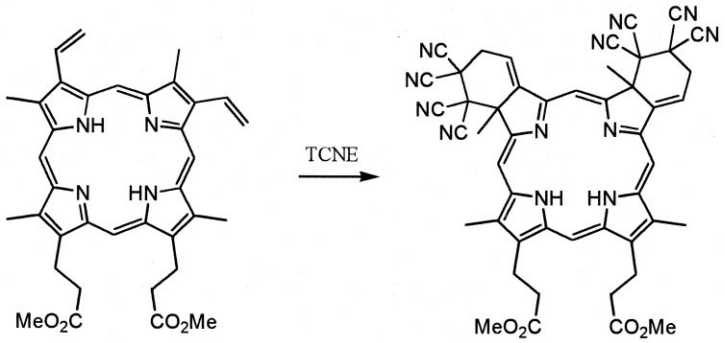
The 'exocyclic' double bonds of porphyrins will undergo addition reactions, providing another method for the introduction of groups at β-positions. Classically, the diimide reduction method has been used to selectively *syn*-hydrogenate porphyrins to the corresponding chlorins.[126] The



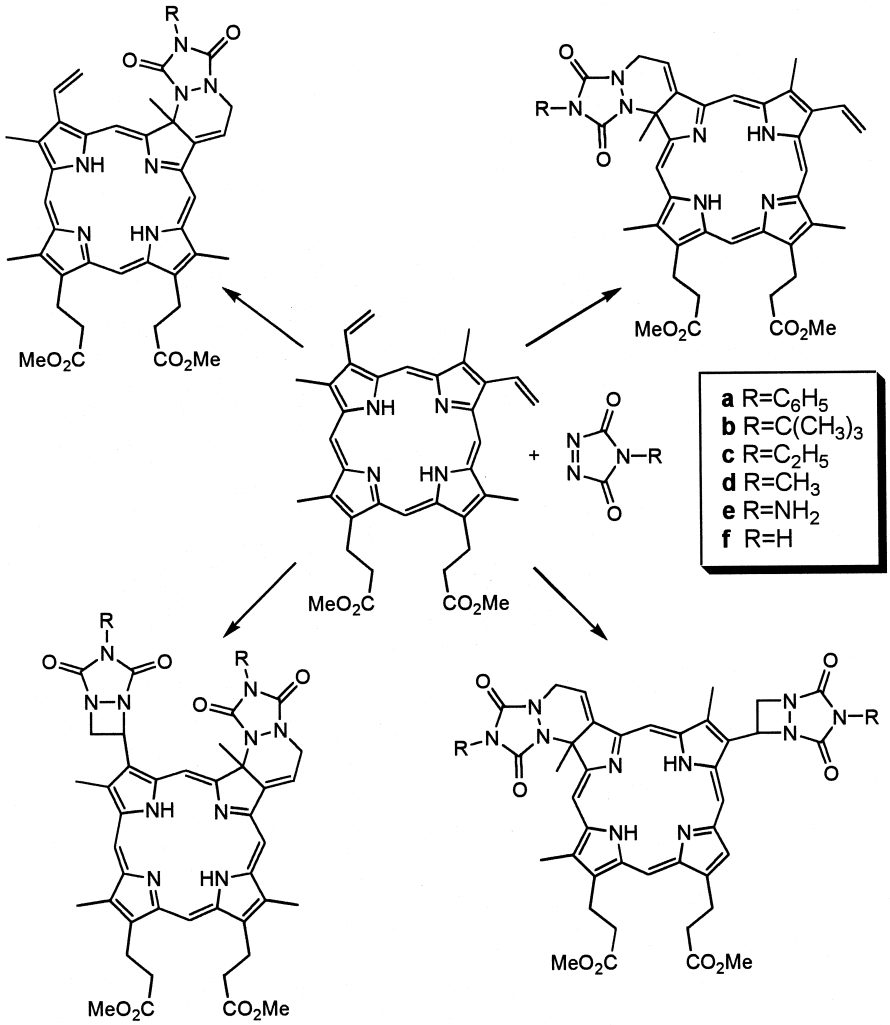
Scheme 20. Zn(II) Dihydroxychlorin.



Scheme 21. (i) 1.2 equiv. OsO_4, 2.5% pyr./$CHCl_3$, r.t., 7 days. (ii) H_2S bubble, 5 min, filtration.

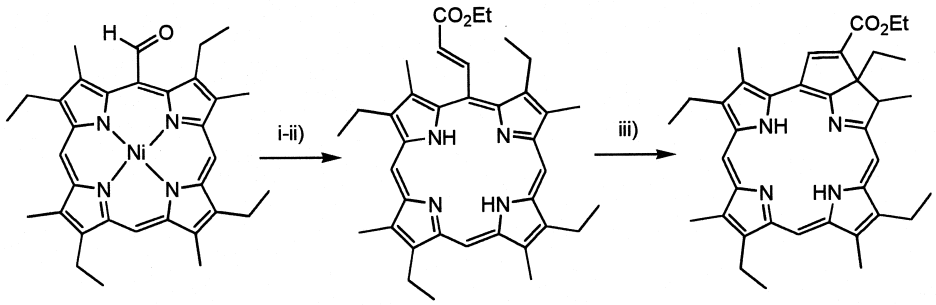


Scheme 22. Reaction of protoporphyrin IX dimethyl ester with TCNE.



	a	b	c	d	e	f
% [4+2]	10	50	63	48	33	12
%[4+2]/[2+2]	3	17	2	8	-	-

Scheme 23.



Scheme 24. (i) $Ph_3P{=}CHCO_2Et$. (ii) H_2SO_4. (iii) AcOH, N_2. Yields for all steps were over 90%.

hydrogenation of porphyrin derivatives is well covered in the review by Flitsch.[127]

Oxidation at the β-position can lead to 1,2-diols and can be carried out by the osmium mediated dihydroxylation reaction. Examples of this include the dihydroxylation of 5,15-diaryloctaethylporphyrin as shown by Osuka et al. (Scheme 20).[128]

The osmium tetroxide mediated oxidation of *meso*-tetraarylporphyrins and their metallated counterparts has also been carried out to produce 2,3-*vic*-dihydroxy-*meso*-tetraphenylchlorins and metallochlorins[129] (Scheme 21).

The oxidation was carried out using a stoichiometric quantity of osmium tetroxide/pyridine complex and the resulting osmate ester was reduced with H_2S. It was also reported that the same reaction was successfully performed on a number of substrates including Cu(II), Zn(II) and Fe(III) metallated TPPs and TPP derivatives where the phenyl rings were sustituted with groups including chloro-, nitro-, hydroxy-, sulfonato- and carbomethoxy-. Although the reaction was slow (up to one week), yields of 50% were recorded. Dolphin et al.[130] have also osmylated tetraphenylchlorin and dihydroxytetraphenylchlorin by the same method to produce the corresponding bacteriochlorin analogues.

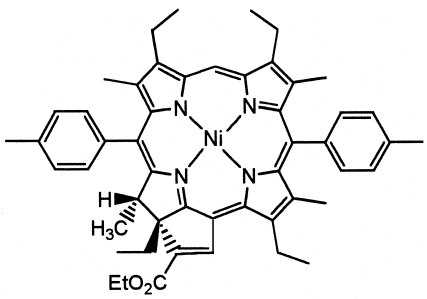
Depending on the functionality available at the β- or *meso*-positions of the porphyrin, further reactions can take place; these include intramolecular cyclisation, functional group interconversions and functionalisation of the phenyl groups on arylporphyrins.

3.3. Cyclisation reactions

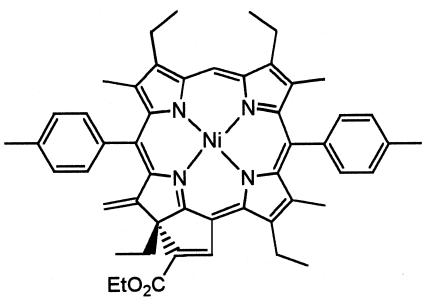
3.3.1. Diels–Alder reactions. Protoporphyrin IX dimethyl ester reacts on the A and/or B pyrrolic rings, with electron deficient acetylenes and alkenes in a [4+2] cycloaddition reaction. When this porphyrin is reacted with tetracyanoethylene (TCNE) for example[131,132] an isobacteriochlorin is formed which can be used as a model for sirohydrochlorin (Scheme 22).[133] Reaction of protoporphyrin IX dimethyl ester with dimethyl acetylenedicarboxylate (DMAD) produces benzoporphyrin derivative (BPD), which is a second generation photosensitizer for use in photodynamic therapy.[132]

More recently, Kohli et al.[134] have reacted protoporphyrin IX dimethyl ester with urazines (azo dienophiles) to give the corresponding [4+2] adduct. It was also found that [2+2] adducts could be detected in addition to the [4+2] products (Scheme 23). Other work in this area includes the use of tetraarylporphyrins as dienophiles in reactions with *o*-benzoquinodimethane, to give naphtho[2,3-*b*]porphyrins amongst other products.[135] Naphthoporphyrins have also been prepared by Callot et al.[136] from the copper complex of 2-formyl TPP under acid catalysis. Using TFA as the acid source, the copper metallated naphthoporphyrin could be formed in 45% yield; it was also found that substituted α-styrylcobalt(III) TPP can rearrange to give the same naphthoporphyrin skeleton.

3.3.2. Purpurin analogues. Purpurins are formed by cyclisation of an appropiate side chain attached to a *meso*-position, to an adjacent β-pyrrolic carbon, resulting in the formation of a fused five membered ring. They have gained importance as potential new sensitizers for photodynamic

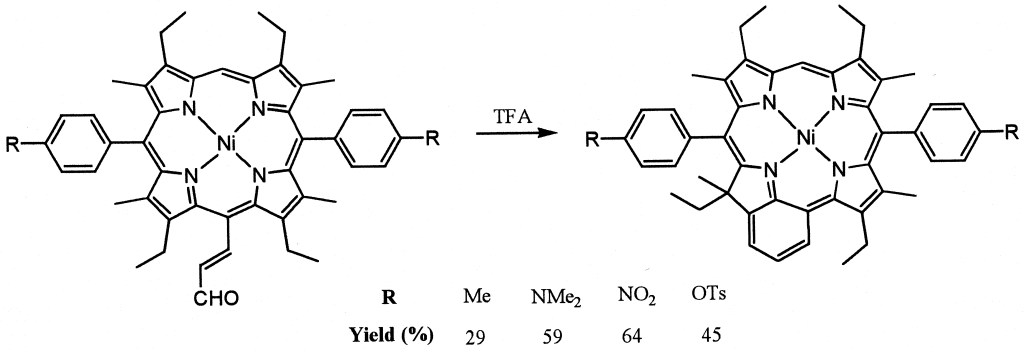


Type A purpurin

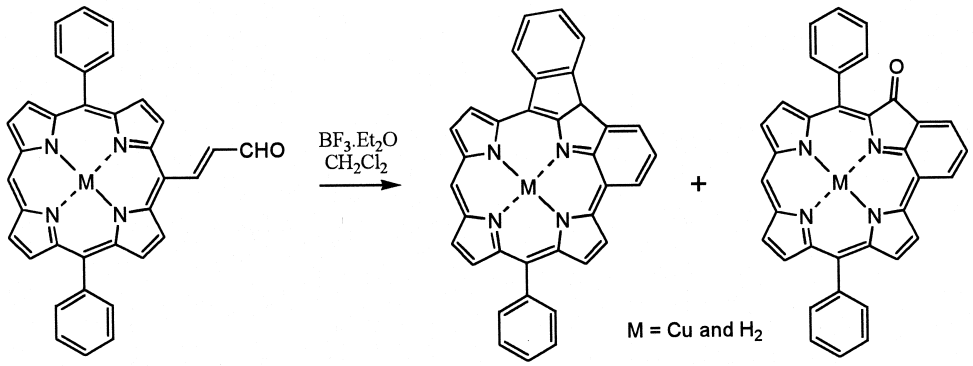


Type B purpurin

Figure 3.



Scheme 25. Preparation of substituted benzochlorins.

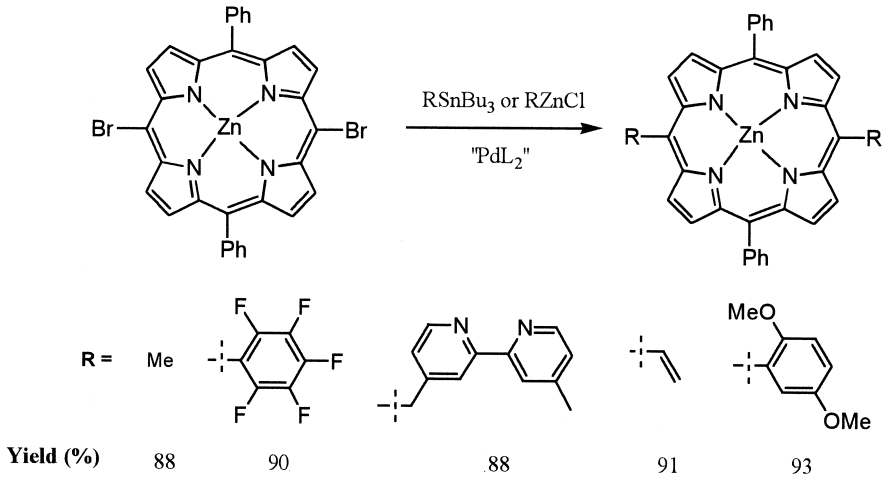


Scheme 26.

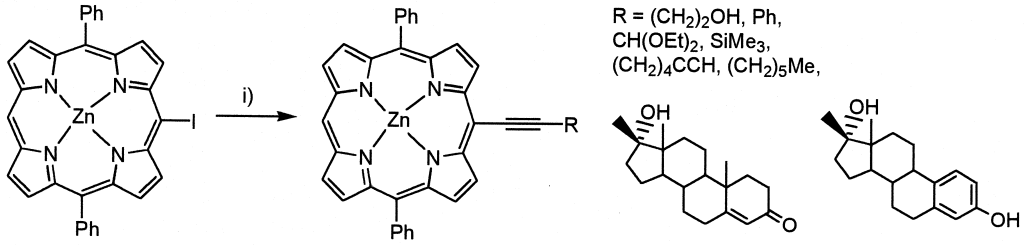
therapy,[137] due to their enhanced absorption in the red region of the visible spectrum. Morgan et al.[137] have shown that *meso*-formylated nickel etioporphyrin I can be converted to a purpurin in high yield (Scheme 24). After initial Wittig reaction to introduce an unsaturated ester and removal of the nickel, acid mediated cyclisation in an inert atmosphere produced the single purpurin shown.

Gunter et al.[138] have shown that both type A and type B purpurins with *meso*-phenyl substituents can be prepared (Fig. 3). It was found that the yield of each purpurin was dependent on the temperature at which the reaction was conducted, purpurin B being formed at higher temperatures. More recently, Morgan et al.[139] have prepared benzopurpurins, isobacteriobenzopurpurins and bacteriobenzopurpurins.

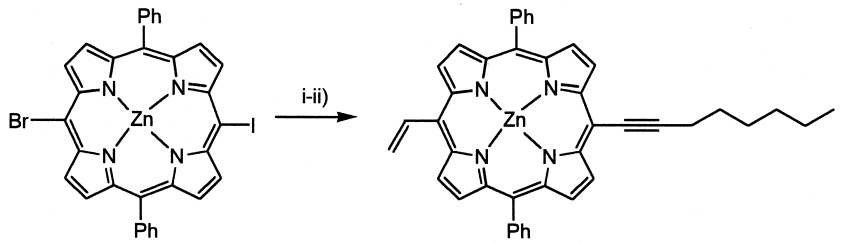
3.3.3. Benzoporphyrins. This class of compound can be synthesised by acid mediated cyclisation[102,140] of the corresponding *meso*-(2-formylvinyl)porphyrin. Gunter et al.[141] have prepared a range of 5,15-diaryl substituted



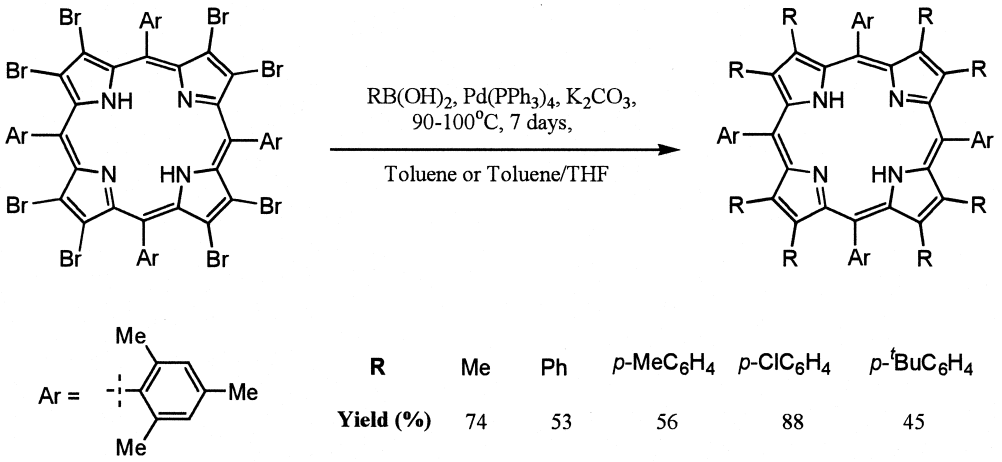
Scheme 27.



Scheme 28. Reaction conditions: (i) R–C≡C–H, $Pd(PPh_3)_2Cl_2$, CuI, Et_3N, THF, r.t. 2 h, 50–90%.



Scheme 29. Reaction conditions: (i) Octyne, $Pd(PPh_3)_2Cl_2$, CuI, Et_3N, THF, r.t., overnight, 78%; (ii) Vinyltributyltin, $Pd(PPh_3)_4$, THF, reflux, 45 h, 52%.



R	Me	Ph	*p*-MeC_6H_4	*p*-ClC_6H_4	*p*-$^tBuC_6H_4$
Yield (%)	74	53	56	88	45

Scheme 30. Suzuki coupling of H_2TMPBr_8.

benzochlorins using similar precursors to those used for the synthesis of type A and B purpurins. The cyclisations were carried out at room temperature, under a nitrogen atmosphere, using trifluoroacetic acid (Scheme 25). Substituted chlorins and benzochlorins have been synthesised by Morgan et al.[142]

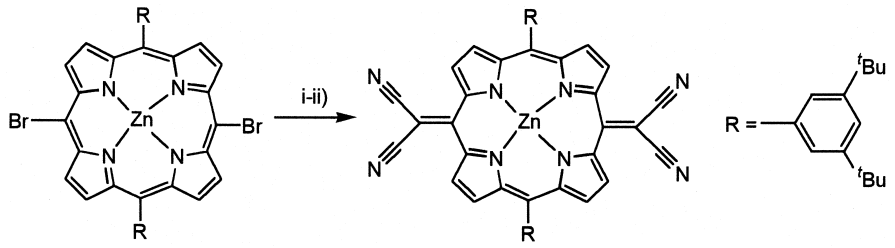
5,15-Diphenyloxobenzochlorins with unsubstituted β-positions have been prepared by Dolphin et al.[143] The authors also report the isolation of a multiple fused ring benzochlorin as an unexpected side product (Scheme 26).

3.4. Functional group interconversions on the porphyrin macrocycle

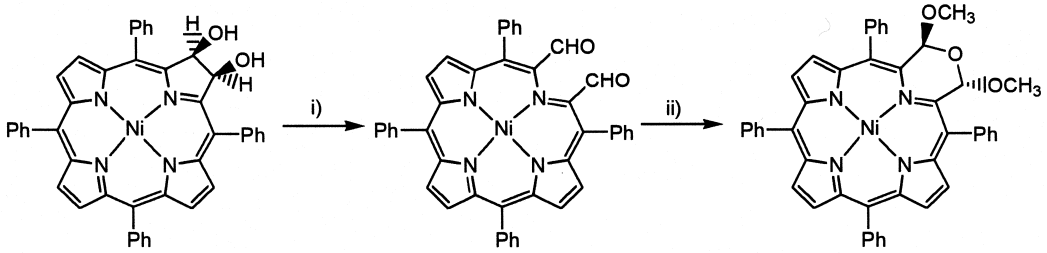
Synthetic routes based around palladium catalysed coupling reactions have recently become very widely used in porphyrin chemistry. This is possibly due to the relative ease of preparation of the required halogenated porphyrin precursors and the vast number of substrates that can be used as coupling partners. Therien and co-workers[105] have used zinc metallated *meso*-dibrominated 5,15-diphenylporphyrin to prepare a range of substituted porphyrins (Scheme 27).

The aryl and vinyl groups were introduced using either an organostannane or organozinc reagent and the palladium catalyst used was either $Pd(PPh_3)_4$ or $Pd(dppf)Cl_2$ (Scheme 27). Coupling reactions were also carried out at a brominated β-position. Dolphin et al.[108] have also used 5,15-diphenylporphyrin in palladium coupling reactions. 5-Iodo-10,20-diphenylporphyrin was used in Heck alkynylation reactions to produce unsymmetrically *meso*-substituted porphyrins as shown in Scheme 28.

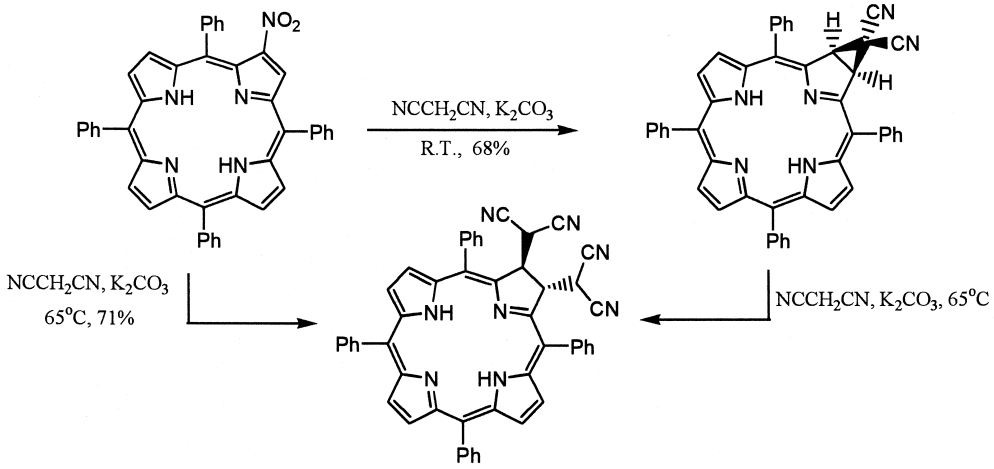
This methodology has recently been extended by Boyle et al.[110] to produce differentially substituted *meso*-diphenylporphyrins. Using the differing reactivity of the bromo



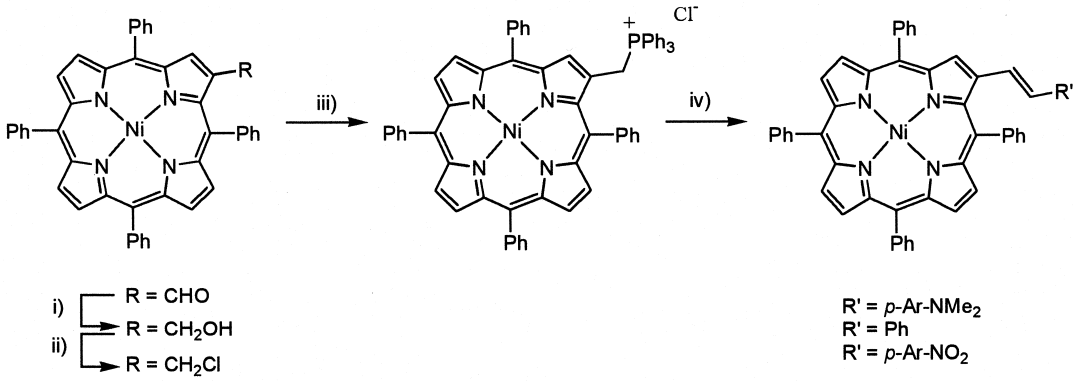
Scheme 31. Reaction conditions: (i) $NaCH(CN)_2$, $Pd(dba)_3$, CuI, PPh_3; (ii) AcOH, O_2; 53% overall yield.



Scheme 32. Reaction conditions: (i) $Pb(OAc)_4$, 80%; (ii) MeOH, H^+, 90%.



Scheme 33. Formation of cyclopropylchlorins and disubstituted *trans*-chlorins.



Scheme 34. Reaction conditions: (i) $NaBH_4$, THF, H_2O, 15 min; (ii) $SOCl_2$, pyridine, Et_2O, 15 min; (iii) PPh_3, $CHCl_3$, reflux, 8 h; (iv) R(CHO, NaOH, CH_2Cl_2.

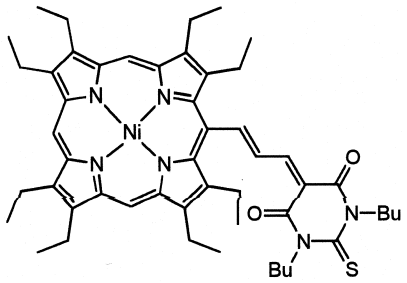


Figure 4. Thiobarbituric acid functionalised porphyrins.

and iodo group; the more reactive iodo group was subjected to Heck alkynylation, the bromo group was then used in a cross coupling with vinyltributyltin under Stille conditions (Scheme 29).

Porphyrins are also known to take part in Suzuki cross couplings.[123,144] Octa β-brominated tetramesitylporphyrin (H_2TMPBr_8) has been coupled with aryl and alkyl boronic acids as shown by Chan et al.[145] (Scheme 30).

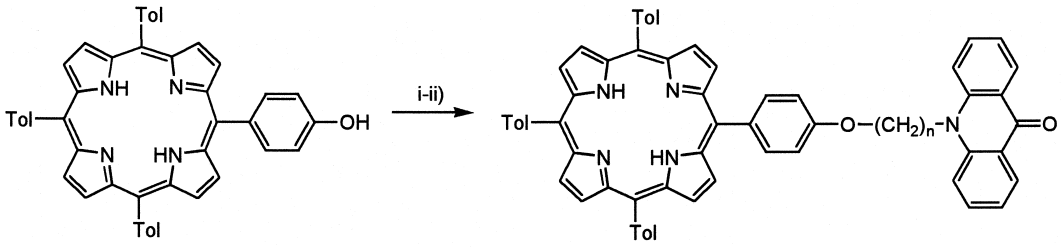
Related procedures have been used including modified Sonogashira protocols to form bisporphyrins connected by linkers.[111] Takahashi coupling with the malonitrile anion has been employed by Anderson et al.[107] to form dialkylidene porphyrin (Scheme 31).

Further functionalisation at the β-position is also well known. Dolphin et al.[146] have prepared a *meso*-tetraphenylsecochlorin and a homoporphyrin, starting from dihydroxylated tetraphenylchlorin (Scheme 32).

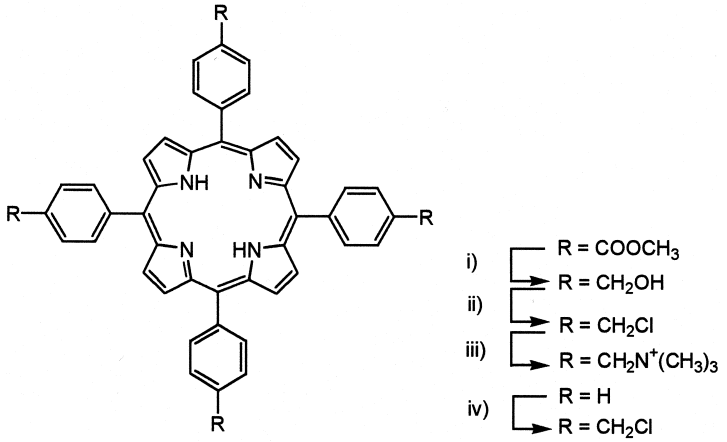
Mono β-nitrated porphyrins are useful intermediates for the preparation of functionalised porphyrins. These species readily expel HNO_2 to give substituted porphyrin derivatives. Crossley et al.[147] have used Grignard reagents and organolithiums with 2-nitro TPP to produce 2-alkyl TPPs. Copper(II) 2-nitro TPP also reacts with sodium methoxide to form 2-methoxy derivatives.[148] Recently, Smith et al.[149] have reported the use of 2-nitro-5,10,15,20-tetraphenylporphyrin for the formation of a range of cyclopropylchlorins, *trans*-nitrochlorins and functionalised *trans*-chlorins. They found that using small methylene containing compounds such as malononitrile gave cyclopropylchlorins and disubstituted *trans*-chlorins, depending on the temperature (Scheme 33). Using bulkier methylene compounds such as dimethyl malonate, nitrochlorins and cyclopropylchlorins were prepared but no disubstituted *trans*-chlorins were formed.

Amino substituted porphyrins are also useful for forming modified heterocyclic systems. Crossley et al.[150] have used 2-amino TPP to form a ring expanded morpholine derivative.

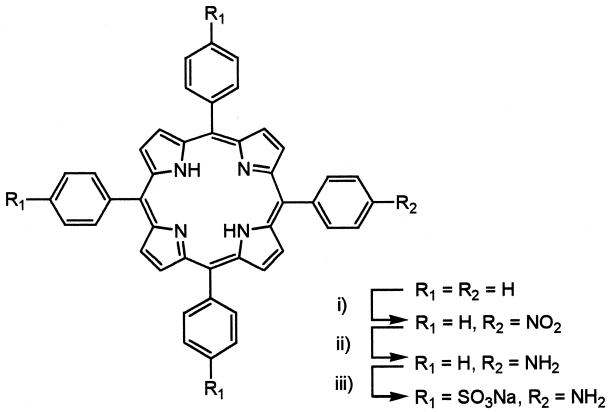
Further functionalisation at the β-position has lead to the formation of styryltetraphenylporphyrins, as shown by Officer et al.[151] A phosphonium salt of the porphyrin was formed and subjected to Wittig reactions with aryl aldehydes (Scheme 34). Aryl dialdehydes have been attached



Scheme 35. Reaction conditions: (i) $Br(CH_2)_nBr$, K_2CO_3, DMF, 90%; (ii) acridone, KOH–toluene, TEBACl, 45–70%.



Scheme 36. Reaction conditions: (i) $LiAlH_4$, THF, reflux, 2 h, 60%; (ii) $SOCl_2$, r.t.,10 h, 100%; (iii) Me_3N, H_2O, $CHCl_3$, r.t., 15 h, 90%; (iv) $ClSO_3H$, NaCl, HCHO, 0°C, 10 min, 50%.



Scheme 37. Reaction conditions: (i) Fuming HNO_3, $CHCl_3$, 0–5°C, 55%; (ii) $SnCl_2$, conc. HCl, 65°C, 75%; (iii) conc. H_2SO_4, 70°C, 92%.

to the phosphonium salt to produce a linker for the preparation of porphyrin dimers.[152]

More exotic molecules have also been synthesised by manipulation of functionalised porphyrins. For example, Morgan et al.[153] have reported the synthesis of barbituric acid functionalised porphyrins and chlorins, for use in photodynamic therapy. Compounds of the type shown in Fig. 4, have been prepared.

Further examples of functional group interconversion include various reactions carried out at the *meso*-positions of 5,15-diphenylporphyrins by Ng et al.[154] Smith et al.[155] have functionalised alkyl substituents in octaalkylporphyrins. Morgan et al.[156,157] have synthesised carboranylporphyrins[156] from haematoporphyrin and also reacted organolithiums with octaethylporphyrinone.[157]

3.5. Phenyl ring transformations of arylporphyrins

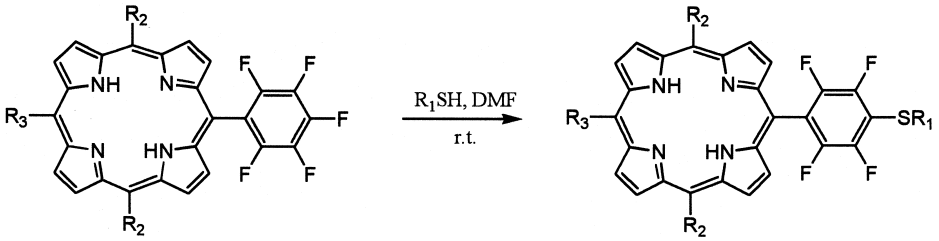
Changing or introducing functionality at the phenyl rings of a *meso*-tetraarylporphyrin or diarylporphyrin is one of the most common ways to modify porphyrins; this is primarily due to the fact that tetraarylporphyrins are particularly readily prepared. Milgrom has prepared some novel tetraarylporphyrins from tetrahydroxyphenylporphyrin using this general strategy.[158] The intermediate phenoxide anion was treated with various halogenated compounds to produce aryl ethers. This approach has been used to prepare porphyrin–acridone hybrids to study photoinitiated nuclease activity. Mehta et al.[159] linked a monohydroxy TPP to an acridone with the aid of triethylbenzylammonium chloride (TEBACl), the latter reagent acting as a phase transfer reagent (Scheme 35). Similar reactions of the phenoxy group have been reported by Maillard et al.,[160] in the glycoconjugation of a benzochlorin with 1-bromoethoxy-per-acetylmaltose.[160]

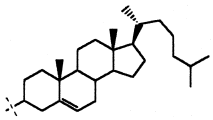
Cationic porphyrins have been synthesised from *meso*-tetrakis(4-(carboxymethyl)phenyl)porphyrin and their interaction with DNA analysed[161] (Scheme 36).

Regiospecific aryl nitration of TPP[162] has been carried out to produce monoamino TPP, which was then sulfonated to produce a bifunctional porphyrin (Scheme 37). Kruper et al.[162] also showed that the nitration could be carried out on substituted phenylporphyrins.

The monoamino TPP produced by the method mentioned above has also been used in the synthesis of electrophilic and nucleophilic porphyrins which were subsequently attached to peptides, as shown by Threadgill et al.[163] Carbamate and more reactive amino functionalised porphyrins were prepared and coupled to the peptides to give urea

Table 2.



R^1	R^2	R^3	% Yield	Time (h)
p-HOC_6H_4	*p*-$MeOC_6H_4$	*p*-$MeOC_6H_4$	89	12
p-$H_2NC_6H_4$	*p*-$MeOC_6H_4$	*p*-$MeOC_6H_4$	73	12
Ph	*p*-$MeOC_6H_4$	*p*-$MeOC_6H_4$	94	12
Benzyl	*p*-$MeOC_6H_4$	*p*-$MeOC_6H_4$	72	12
CH_2CH_2OH	*p*-$MeOC_6H_4$	*p*-$MeOC_6H_4$	80	12
$CH_3(CH_2)_{17}$	*p*-$MeOC_6H_4$	*p*-$MeOC_6H_4$	82	36
p-Pyridyl	*p*-$MeOC_6H_4$	*p*-$MeOC_6H_4$	71	48
	*p*-$MeOC_6H_4$	*p*-$MeOC_6H_4$	70	168
p-HOC_6H_4	H	*p*-$MeOC_6H_4$	84	12
p-HOC_6H_4	H	3,4,5-$(MeO)_3C_6H_2$	89	12
p-HOC_6H_4	H	*p*-$MeO_2CC_6H_4$	77	
$CH_3(CH_2)_{17}$	H	*p*-$MeO_2CC_6H_4$	91	12

and amide linkages. The isocyanate group on the phenyl ring of the porphyrin has also recently been prepared by Collman et al.[164] who used triphosgene and a tetraaminoporphyrin to form the tetraisocyanatoporphyrin in 87% yield. This substrate was used to form various urea functionalised porphyrins.

Pentafluorinated phenyl groups are a useful way of introducing functionality to the porphyrin. Mansuy et al.[165] have treated tetra(pentafluorophenyl)porphyrin with various nucleophiles such as amines, alkoxides and thiols to produce compounds in which the *p*-fluorine has been transformed *via* a nucleophilic aromatic substitution. Boyle et al.[166] have prepared mono(pentafluorophenyl)porphyrins and reacted them with a variety of thiols under mild conditions to produce porphyrin thioethers (Table 2). Both tetraaryl and diarylporphyrins were used and high yields were obtained. It was, however, found that highly hindered thiols and thioesters were not compatible with the reaction conditions. Porphyrin thiols have been synthesised by Woo et al.[167] from monoamino TPP and bis-thiols from β-substituted amino-containing diphenylporphyrins. The route involved reaction of a protected thiol-containing acid chloride with the amino group, followed by removal of the protecting group. Other examples include the alkyl- and arylporphyrin thiols synthesised by Collman et al.[168] for the study of the active site of cytochrome P-450, using amino-functionalised porphyrins as the precursor. It was reported that these porphyrins were highly air sensitive. Carotene–porphyrin dyads have been synthesised by Gust et al.[169] and their singlet and triplet energy transfer has been studied.

Phenyl ring substituents can be used to link porphyrins together and form dimers or trimers. Examples include the reaction of a dibromoalkane with a phenoxyporphyrin, in the presence of base followed by further reaction with another porphyrin as shown by Little.[170] Cofacial bisporphyrins[171] have been prepared in which the two porphyrins have four phenyl ring based linkages between them (Fig. 5).[171,172] Recently, Lindsey et al.[173] have synthesised a molecular square consisting of four mutually coplanar porphyrins.

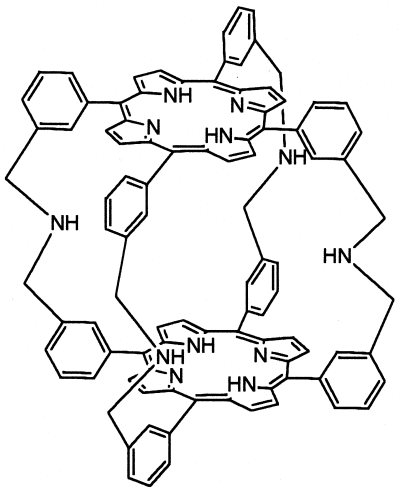


Figure 5.

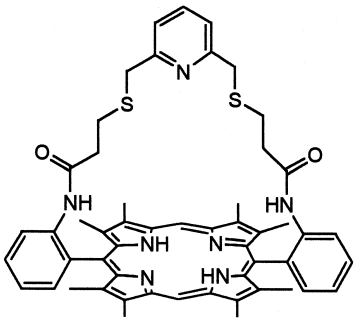


Figure 6.

The acetylene functionality has been used to produce cyclic porphyrin trimers by Sanders et al.[174] In this molecule, three octaethyl-substituted porphyrins were linked by butadiyne groups.

The phenyl groups on *meso*-arylporphyrins can be linked together to form sterically constrained compounds of which there are many examples. The most common of these modified tetraphenylporphyrins are the 'tailed,'[168,175–177] 'strapped,'[37,178–184] 'pocket,'[185] and 'capped'[186–188] porphyrins. Gunter et al.[189] used the amino groups of a β-substituted diphenylporphyrin to form amide bonds and thus form a 'capped' porphyrin as shown in Fig. 6. Collman et al.[190] have also made several hindered porphyrins which were used as biomimetic heme analogues. The synthesis involved the use of several Michael additions to appropriate substrates.

4. Conclusions

It can be seen from the material covered in this review that the field of synthetic porphyrin chemistry is a vibrant and rapidly changing area of research. Many reactions only recently applied to porphyrins, such as the palladium catalysed cross-couplings of Heck, Stille and Suzuki, have opened up new possibilities for erecting even more elaborate molecular frameworks around porphyrin building blocks. It must be assumed that many other reactions and synthetic chemical techniques, only now being developed, will also be applied to porphyrins in the future. Perhaps then the synthetic porphyrin chemist may aspire to construct molecular devices, which rival the elegance of natural systems such as haemoglobin, the cytochromes and the photosynthetic reaction centre.

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