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Syntheses and Functionalizations of Porphyrin Macrocycles

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Abstract

Porphyrin macrocycles have been the subject of intense study in the last century because they are widely distributed in nature, usually as metal complexes of either iron or magnesium. As such, they serve as the prosthetic groups in a wide variety of primary metabolites, such as hemoglobins, myoglobins, cytochromes, catalases, peroxidases, chlorophylls, and bacteriochlorophylls; these compounds have multiple applications in materials science, biology and medicine. This article describes current methodology for preparation of simple, symmetrical model porphyrins, as well as more complex protocols for preparation of unsymmetrically substituted porphyrin macrocycles similar to those found in nature. The basic chemical reactivity of porphyrins and metalloporphyrin is also described, including electrophilic and nucleophilic reactions, oxidations, reductions, and metal-mediated cross-coupling reactions. Using the synthetic approaches and reactivity profiles presented, eventually almost any substituted porphyrin system can be prepared for applications in a variety of areas, including in catalysis, electron transport, model biological systems and therapeutics.

Keywords

Aromaticity; porphyrin; pyrrole; reactivity; substitutions; synthesis

1. INTRODUCTION

In this article we review the widely-used methodology which has been utilized to synthesize tetrapyrrole macrocycles in the porphyrin series from monopyrrole precursors; we also review selected porphyrin reactivity profiles.

1.1. Monographs

The porphyrin area has been honored, over time, with a significant number of Nobel prizes for its heroes, and is thus a research field that is rich in its history. Between 1934 and 1940 Hans Fischer and the Munich porphyrin group published three volumes that became a

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roadmap for synthesis of porphyrin compounds [1-3]; in particular, these three volumes of *Die Chemie des Pyrrols* contained a compendium of laboratory methods. The tradition of laboratory methods within porphyrin monographs was continued in 1964 when Falk's book "Porphyrins and Metalloporphyrins" was published [4]; this contained a fairly detailed laboratory methods section but also attempted, for the first time, to apply modern principles of chemistry and electronic theory to the porphyrin field. This was followed in 1974 by a new version of "Porphyrins and Metalloporphyrins" (edited by one of us), which also contained a laboratory methods section, and then by Dolphin's more traditional series called "The Porphyrins" (1978-80). An authoritative and highly detailed description of the synthetic art of porphyrin chemistry and of reactivity profiles in the "octa-alkyl" and "tetra-aryl" porphyrin series can be found in "The Porphyrin Handbook", which consists of two ten-volume sets containing no less than 122 chapters [5]. Since then, the follow-on series (30 volumes to date) by the same editors entitled "The Handbook of Porphyrin Science" has featured no less than six complete volumes with the word "synthesis" in their titles [6-11]. By and large, however, these more recent volumes [6-11] have dealt with syntheses of porphyrins with specific arrays of substituent for use in commercial applications, rather than on the development of new ways to synthesize the porphyrin core. A very thorough book dealing with syntheses and properties of porphyrin isomers, as well as contracted and expanded systems (outside the purview of this review) has also appeared [12].

1.2. Nomenclature

The Fischer system for nomenclature of porphyrins is shown in structure **1**. Along with this simple numbering system, Fischer also created a host of trivial names for porphyrins [*e.g.* protoporphyrin (the "first" porphyrin), deuteroporphyrin (the "second" porphyrin), etioporphyrin] and for chlorophyll derivatives (chlorin-e_6, rhoding$_7$, etc.). Fischer also created a "type" isomer system of nomenclature (see later for the etioporphyrin examples) which was used to define the nature of the substituent array in certain porphyrins. For example, a porphyrin made from tetramerization of a monopyrrole containing one methyl and one ethyl group can have four isomers - types I-IV. Enumeration of isomers of substituted porphyrins, and the construction of combinatorial libraries, has been authoritatively reviewed by Taniguchi and Lindsey [13]. The Fischer system for porphyrin nomenclature (structure **1**) provides a link back to the rich history of porphyrin chemistry. As biosynthetic studies of vitamin B_{12} and porphyrins began to assume a dominant position in organic and biological chemistry, and as unique radiochemical and stable isotope labeling became the norm in these studies, it became necessary to identify every carbon atom in the porphyrin ring uniquely, but the Fischer system (**1**) leaves several carbon atoms unassigned; to be sure, these unassigned carbons never carry a substituent in a porphyrin, but they assumed importance as the biological origin of every carbon in porphyrins and vitamin B_{12} was investigated. The IUPAC subsequently adopted a system of nomenclature (structure **2**); this is the officially adopted nomenclature system, and is used in this article (Fig. **1**).

2. PORPHYRIN SYNTHESES

A full description of all currently available routes to porphyrins is outside the scope of this brief article. Such a treatment can be found elsewhere [14]. Instead, with increasing complexity, three of the most typical synthetic approaches will be described.

The choice of which synthetic route to use to synthesize any particular porphyrin depends upon the symmetry features of the product itself. Syntheses of porphyrins by simple polymerization of monopyrroles will be discussed first; typical examples of porphyrins which can be made from this approach are octaethylporphyrin **3** and 5,10,15,20-tetraphenylporphyrin **4** (Fig. **1**). Next we shall progress to the so-called MacDonald route using two dipyrromethanes (the [2+2] approach) and one of its variants (the [3+1] method); porphyrins **5** and **6** are typical examples that can be approached synthetically in this way (Fig. **1**). Finally, we shall finish the synthetic part of the article with porphyrin synthesis through cyclization of an open-chain tetrapyrrole (the so-called a,c-biladienes); this approach yields porphyrins such as **7**, and is truly general because it possesses no symmetry restrictions.

A multitude of preparative routes to monopyrroles exist; reviews of this literature have been published [1, 15-17]. Methods for elaboration of monopyrroles into dipyrromethane, tripyrrane, and a,c-biladiene compounds will be discussed in the sections related to the porphyrins in which they are used as essential intermediates.

Porphyrin syntheses from monopyrroles are best described with reference to two classical porphyrins - octaethylporphyrin (**3**; OEP) and tetraphenylporphyrin (**4**; TPP). Simply based on the symmetry properties of these two porphyrins, the most economical approach must involve some kind of monopyrrole tetramerization, either using monopyrroles bearing a 2-substituent which can provide the four interpyrrolic carbons in the product, or using a 2,5-di-unsubstituted monopyrrole with a separate reagent which will furnish the one-carbon bridging atoms. Attempting to synthesize OEP **3** by laborious multi-step construction of an open-chain tetrapyrrolic intermediate would be wasteful in time and resources.

2.1. Porphyrins *via* Monopyrrole Tetramerization

Everyone in the porphyrin field agrees that the easiest porphyrin to synthesize is TPP, **4**. One simply needs to react pyrrole **8** with benzaldehyde under acidic conditions. The route was first reported by Rothemund [18, 19], who preferred to carry out the reaction in sealed glass tubes at high temperature. Roald Hoffmann has related to one of us that explosion of such a sealed glass tube converted him into a theoretician, and subsequently, a 1981 Nobel Laureate in Chemistry. A modification by Adler, Longo and their colleagues (involving use of refluxing propionic acid instead of sealed tube chemistry) [20], reproducibly affords a 20-25% yield of TPP from these simple shelf chemicals). This trivial procedure involves addition of equimolar amounts of pyrrole **8** and benzaldehyde to refluxing propionic acid (Scheme **1**); after heating for about one half hour, the mixture is allowed to cool and the TPP is filtered off. The reaction also works with a limited number of substituted benzaldehydes that are able to survive refluxing propionic acid. The synthesis was finally optimized by Lindsey's group [21, 22], which showed that excellent yields of a wide variety of

tetraarylporphyrins can be obtained using a high dilution two step reaction between arylaldehydes and pyrrole, in presence of a Lewis acid catalyst (usually BF_3-etherate). In the second step of the reaction, the initial product (a colorless porphyrinogen, **9**) is oxidized to porphyrin **4** using a quinone such as 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ). Material isolated from the Rothemund and Adler/Longo approaches is highly crystalline but is nonetheless contaminated [23] with about 5% or less of 5,10,15,20-tetraphenylchlorin **10**. Brief treatment [24] of the product with DDQ (which is the final step in the more recent Lindsey procedure) accomplishes transformation of **10** into **4**; the *separation* of these two components by chromatography is much more demanding than is *transformation* of **10** into **4**.

A majority of naturally occurring porphyrins (*i.e.* those not derived by degradation of chlorophylls or bacteriochlorophylls) do not contain *meso*-substituents, and there are certainly none that possess four such substituents. This has led many to question the utility of TPP as a "natural" mimic. Thus, over the years, OEP has been favored as a model for natural porphyrins more than has TPP. Synthetic approaches to porphyrins such OEP are a more complex because of the increased difficulty of preparing the 3,4-disubstituted pyrrole starting materials; pyrrole **8** can, of course simply be purchased and only needs to be distilled.

In the synthesis of TPP, the interpyrrolic carbons are provided by the aldehyde group of the corresponding arylaldehyde. In the case of octaalkylporphyrins (such as **3**), the future *meso*-(*i.e.* interpyrrolic) carbons can either be added separately by being not attached to the pyrrole (as for TPP) or can be already present in the form of a 2-substituent on the pyrrole. It is important to note that monopyrrole tetramerizations can only produce a structurally unique product if the 3- and 4-substituents in the monopyrrole are identical (Scheme **2**).

There are two major routes to OEP **3**. Firstly, tetramerization of 2,5-di-unsubstituted pyrroles in the presence of reagents which can provide the four *meso* methine carbons of the product can be used. Thus, cyclization of 3,4-diethylpyrrole **11** with formaldehyde affords 55-75% yields of OEP (**3**) (Scheme **2**) [25]. Secondly, but in an approach which was chronologically developed first, tetramerization of pyrroles bearing 2-CH_2R substituents gives acceptable yields of porphyrin; the "R" group on the "benzylic" methylene must be a good leaving group because the methylene carbon will eventually be the source of the interpyrrolic carbons of the product after a nucleophilic attack upon it. Once the condensation reaction has taken place, an oxidation step is necessary in order to afford good yields of symmetrical porphyrin from an intermediate porphyrinogen. The required CH_2R groups can be attached to pyrrolic intermediates by used of the Mannich reaction of pyrrole **11** with formaldehyde and dimethylamine [or with commercially available (*N*,*N*-dimethylmethylene)ammonium iodide (Eschenmoser's reagent [26, 27])] to give the 2-(*N*,*N*-dimethylaminomethyl)pyrrole **12**; heating of **12** in acetic acid affords about a 50% yield of **3** (Scheme **2**) [28, 29]. Alternatively, pyrrole **13** can be cyclotetramerized to give a similar yield of **3** by heating in acetic acid containing potassium ferricyanide [30, 31]. The Barton-Zard pyrrole synthesis [32] has afforded a very efficient access to monopyrroles of the type **14**, which can be reduced (to the carbinol **15**) and then tetramerized under acidic conditions to give **3** in high yield [33, 34].

Surprise is often expressed when relatively good yields of porphyrins are obtained from monopyrrole polymerizations - would not infinite linear polymers be preferred? If one constructs molecular models of the open-chain tetrapyrrole seco-porphyrinogen, one can see that once one has achieved an open-chain tetrapyrrole polymer (**16**) the head of the polymer is virtually biting the tail (Scheme **3**).

This is particularly true if the monopyrrole precursor has fairly large 3- and 4-substituents because these enforce a helical geometry upon the elongating molecule. For this reason too, attempts to prepare the unsubstituted porphyrin **17** from pyrrole and formaldehyde usually gives a very low yield, probably due to a preference for infinite elongation due to the small 3- and 4-substituents in **8** (Scheme **4**) and due to solubility problems of the product **17**. However, several groups have synthesized substituted porphyrins and can be desubstituted and this simplifies the problems associated with the low solubility in almost all solvents, of **17**. An example is the synthesis of the soluble tetra-*tert*-butylporphyrin **18** from the Mannich pyrrole **19**, followed by removal of the four *tert*-butyl groups using aqueous sulfuric acid to give **17** in 64% yield (Scheme **5**) [35].

Monopyrrole tetramerization works best for pyrroles with identical 3- and 4-substituents. If the 3- and 4-substituents on the monopyrrole reactant are not identical, mixtures will usually result due to acid-catalyzed pyrrole ring scrambling reactions [13, 36]. As an example, and as mentioned earlier in this article, acid-catalyzed tetramerization of pyrrole **20** will result in a mixture of the four so-called etioporphyrin type isomers (**21**-**24**) (Scheme **6**). With appropriate care to avoid acidic conditions, etioporphyrin I **21** can be obtained by tetramerization of a monopyrrole; pyrrole **25** has a leaving group which is labile even under neutral conditions [37, 38], and when reacted in methanol containing potassium ferricyanide gives a good yield of pure etioporphyrin I **21** (Scheme **7**).

2.2. The MacDonald [2+2] Porphyrin Synthesis

The development of the so-called MacDonald synthesis was a game-changer for porphyrin synthesis [39]. At about the same time, Woodward and coworkers reported their landmark synthesis of chlorophyll-a that also employed a similar [2+2] approach in the fabrication of the initial porphyrin macrocycle [40].

Dipyrromethanes are the key intermediates in the MacDonald approach.

2.2.1. Syntheses of Dipyrromethanes—Dipyrromethanes can be synthesized using fairly straightforward methods. These important intermediates for porphyrin syntheses are categorized as either symmetrical or unsymmetrical about the interpyrrolic 5-carbon. Symmetrically substituted dipyrromethanes such as **26** can be prepared in one step by self-condensation of bromomethylpyrroles such as **27** in hot methanol [41], or by heating 2-acetoxymethylpyrroles such as **28** in methanol/hydrochloric acid [42]. The pyrrole **28** is obtained from the corresponding methylpyrrole **29** by oxidation of the 2-methyl with lead tetra-acetate. Catalytic hydrogenation cleaves the terminal benzyl esters to afford the corresponding 1,9-dicarboxylic acid **30** which can be formylated using the Vilsmeier reagent (dimethylformamide with either phosphoryl chloride or benzoyl chloride) to give **31** (Scheme **8**).

These two formyl groups provide the bridging carbons in the MacDonald [2+2] porphyrin macrocyclization (see later). Unsymmetrically substituted dipyrromethanes such as **32**, are obtained by condensation of 2-acetoxymethylpyrroles, *e.g.* **33**, with 2-unsubstituted pyrroles **34** in acetic acid and a catalytic amount of *p*-toluenesulfonic acid (Scheme **9**) [43]. Montmorillonite K-10 clay has also been shown to be a very useful acid catalyst in dipyrromethane syntheses [44, 45].

Condensation of two unsymmetrical dipyrromethanes **35** and **36** with appropriate bridging carbons will result in two porphyrin products (**37** and **38**) because the dipyrromethanes can react in either of two orientations related by a 180° rotation of one of the dipyrromethanes (Scheme **10**).

These symmetry complications in a porphyrin synthesis involving an A-B and a C-D dipyrromethane can be avoided if the A-B or C-D dipyrromethane unit (only one of them!) is symmetrical about its interpyrrolic (5-) carbon atom. Thus, MacDonald and coworkers generically showed [39] that a symmetrical 1,9-diformyldipyrromethane such as **31**, can be reacted with a 1,9-di-unsubstituted dipyrromethane **39** (obtained from **32**), or the corresponding 1,9-dicarboxylic acid **40**, in the presence of an hydriodic acid catalyst to give pure porphyrin, such as **41**, in very high yields (Scheme **11**). The method can be modified such that a monoformyldipyrromethane such as **42** is self-condensed to give centrosymmetrical porphyrins (*e.g.* **43**) (Scheme **12**). The initially formed intermediate is a porphodimethene salt **44**; conversion to porphyrin requires an oxidation step that is usually provided by adventitious aerial oxygen; chemical oxidants such as *o*-chloranil or DDQ can also be used. Since MacDonald's report [39], others have shown that *p*-toluenesulfonic acid is a much better choice as the catalyst [46, 47].

A modification of the MacDonald [2+2] approach that avoids the final oxidation step has been published [48, 49]. Treatment of the 1,9-di-iododipyrromethane **45** with the known 1,9-diformyldipyrromethane **31** in acetic acid and acetic anhydride containing trifluoromethylsulfonic acid gave a 76% yield of the diacetylporphyrin **46**. Porphyrin **46** was then further transformed into hematoporphyrin-IX dimethyl ester **47** (by double reduction) and protoporphyrin-IX dimethyl ester **48** (by double dehydration of **47**) (Scheme **13**).

The [2+2] route using dipyrromethanes is probably the most widely used pathway to synthetic porphyrins.

2.3. From Tripyrrolic Intermediates: The [3+1] Route

The so-called [3+1] route to porphyrins employs the fundamental chemistry developed in the MacDonald approach. However, instead of condensing two dipyrromethanes (hence [2+2]), a tripyrrane **49** is reacted with a monopyrrole **50** bearing the two "bridging" carbon atoms. This macrocyclization of a 2,5-difunctionalized monopyrrole unit with an open-chain tripyrrole to produce a porphyrin **51** has a number of useful applications (Scheme **14**).

It is often the case that the purpose of a particular porphyrin synthesis is to attach or conjugate the porphyrin to another species *via* unique functionality on the porphyrin. Thus, access to a uniquely functionalized point on the porphyrin will enable the application. Using

the [3+1] protocol permits efficient synthesis of a porphyrin in which the required functional handle group is situated on the monopyrrole component to be inserted at the final stage. This kind of chemistry has been facilitated by Sessler's recent advance in tripyrrane syntheses [50]. In its simplest form Sessler's route only yields symmetrically substituted tripyrranes, but the ease with which tripyrranes can be made using this method far outweighs the symmetry limitation. Thus, reaction of two equivalents of pyrrole **52** with pyrrole **53** affords the dibenzyl tripyrrane-1,14-dicarboxylate **54** in excellent yield. Catalytic debenzylation then affords the required tripyrrane-1,14-dicarboxylic acid **55** (Scheme **15**).

The [3+1] approach has symmetry limitations because the terminal rings of the tripyrrane are usually identical. Removal of this limitation will require an advance in tripyrrane synthesis.

The first example of the [3+1] approach to porphyrins was reported by Boudif and Momenteau. A 2,5-diformylpyrrole and a tripyrrane were used [51]. Though the approach clearly has general applicability, Boudif and Momenteau targeted only bis-acrylic or bis-propionic porphyrins, *e.g.* **56**, from tripyrrane **57** and diformylpyrrole **58** (Scheme **16**). Lash's group expanded the generality of the approach in their syntheses of porphyrins such as **59** (Fig. **2**) [52]. Sessler and his group also showed the applicability of the approach and also reported syntheses of porphyrins such as **60** (Fig. **2**) [53].

Our own group developed a [3+1] procedure which does not need acid catalysis, and which guarantees the integrity of the tripyrrane reactant against pyrrole ring-scrambling reactions [54]; treatment of tripyrrane **61**, with the 2,5-bis(*N*,*N*-dimethylaminomethyl)pyrrole **62** in methanol containing ferricyanide gave the porphyrin **63**, in good yield (Scheme **17**).

2.4. From a,c-Biladiene Salts

The synthesis of a porphyrin (*e.g.* **7**) with a completely unsymmetrical array of substituents must progress through open-chain tetrapyrrolic intermediates. Though a number of open-chain tetrapyrroles have been investigated and utilized with success [14] over the years, the most used open-chain precursors of choice have been shown to be 1,19-dimethyl-a,c-biladiene salts such as **64**.

Symmetrical 1,19-dimethyl-a,c-biladienes, *e.g.* **64**, can be synthesized by condensation of dipyrromethane-1,9-dicarboxylic acids **30** with two equivalents of a 2-formyl-5-methylpyrrole **65**. The method of choice in earlier studies for cyclization of the a,c-biladiene to give porphyrin, always as its copper(II) complex **66**, has involved use of copper(II) chloride or acetate in hot dimethylformamide. Demetalation with H_2SO_4/ TFA then affords, for example, the metal free porphyrin **67** [55, 56] (Scheme **18**). Other cyclization protocols have been studied [57-65] including other metal salts or even electrochemical oxidation. The mechanism of this cyclization, which involves loss of (at least) one of the terminal methyl groups of the a,c-biladiene is not immediately obvious, and a full review of the evidence and conclusions has been published [56]. A breakthrough in the mechanistic investigation of a,c-biladiene cyclizations was achieved when it was shown [56, 60, 61] that electrochemical oxidation of, for example, a,c-biladiene dihydrobromide **68** proceeds to give metal free porphyrin **69** *via* the cyclic dihydroporphyrin intermediate **70** (Scheme **19**) which then

eliminates the quaternary methyl group (presumably by an S_N2 attack that involves the newly aromatized porphyrin as the leaving group) after macrocyclization.

The electrochemical cyclization [60, 61] has the advantage that it gives the metal free porphyrin (*e.g.* **69**) as the product, thereby eliminating the need to treat the copper(II) complex [from the copper(II) chloride route] with concentrated sulfuric and trifluoroacetic acids. Also, the reaction progress can be monitored using ^{1}H-NMR spectroscopy in the absence of the paramagentic copper(II) ion. But scaling-up of electrochemical reactions to preparative quantities is not easy. However, it has been found that use of chromium(III) for the oxidative cyclization results in the production of the metal-free porphyrin product [66]. Many researchers had assumed that the metal salts used in these cyclization provided template around which the a,c-biladiene, or some subsequent intermediate on the pathway to porphyrin, could assemble. Recent results however show [65] that the primary function of the metal ion is oxidation, and not templation, and this is also confirmed by the success of the electrochemical approach that uses no transition metal salts at all. Several mechanistic studies [57-59], and experiments involving oxidation with different metal ions have been published, and these have been reviewed and analyzed [56].

Symmetry limitations associated with the earlier a,c-biladiene syntheses were removed by development of routes to unsymmetrically substituted a,c-biladienes [14, 67, 68]. There now exists two complementary methods, which involve “clockwise” or “counterclockwise” elongation of the developing a,c-biladiene (Scheme **20**). The counterclockwise route was developed first [67] and involves catalytic hydrogenation of a benzyl tert-butyl dipyrromethane-1,9-dicarboxylate **32** to give a monocarboxylic acid **71** which reacts under mild conditions with a 2-formyl-5-methylpyrrole **65** to afford a high yield of a so-called tripyrrene salt **72**. Treatment with TFA (which serves to cleave the tert-butyl ester) and a second, different 2-formylpyrrole **73**, gives a high yield of 1,19-dimethyl-a,c-biladiene salt **74** with a completely unsymmetrical array of substituents; cyclization using, for example, the copper(II) method, followed by demetalation with concentrated sulfuric acid in trifluoroacetic acid gives the porphyrin **75**. Any other method for cyclization, *e.g.* the chromium(III) method [54, 66], or electrochemical methods [60, 61] which give directly the metal free porphyrin can be used.

The second, so-called clockwise approach (Scheme **20**), involves [68] treatment of the dipyrromethane mixed ester **32** with TFA to give the dipyrromethane **76**; treatment with formylpyrrole **73** affords the tripyrrene salt **77**. Catalytic hydrogenation cannot be used for cleavage of the benzyl ester because this would also saturate the tripyrrene double bond. Thus, sulfuric acid/HBr is used, and this is followed by addition of formylpyrrole **65** to give the a,c-biladiene salt **74**, identical with that obtained using the other tripyrrene route. a,c-Biladiene cyclization proceeds as earlier to give porphyrin. There is an advantage to having two different routes to the same a,c-biladiene and porphyrin, particularly when very valuable monopyrroles are being used (*e.g.* carbon-13 or carbon-14 labeled) and good synthetic strategy requires that this precious pyrrole be added in the last possible step.

1,19-Dimethyl-a,c-biladienes are highly effective intermediates for porphyrin synthesis; good yields of porphyrin are obtained and there are no obvious symmetry or substituent

difficulties. The use of a,c-biladienes bearing 1- and 19-substituents other than methyls [62-65] has been investigated, and these reactions yield the predictable *meso*-substituted porphyrins, along with a host of macrocycles in which either the 1- or the 19-substituent in the original a,c-biladiene has migrated around the macrocycle. These results are also discussed in detail elsewhere [56, 62-65].

3. PORPHYRIN FUNCTIONALIZATION

The porphyrin macrocycle contains 22 conjugated π-electrons, but only 18 of these are required for its conjugated aromatic network. As a consequence, porphyrins can undergo additions and substitution reactions without loss of their aromaticity, as well as cross-couplings, oxidations and reductions, to produce a variety of functionalized macrocycles and linear tetrapyrroles, that continue to find multiple applications in biology, medicine and materials science.

The most electronically reactive positions at the porphyrin periphery are the *meso*-positions, and generally the preferential sites for electrophilic aromatic substitutions, additions and radical reactions. On the other hand, the β-pyrrolic positions are the most sterically accessible and can also undergo the same type of reactions. Substitution, cross-couplings and radical reactions have been used to produce a variety of functionalized porphyrins, whereas additions to β-β' peripheral double bonds lead to the formation of chlorins, bacteriochlorins, or isobacteriochlorins, and to the *meso* positions produce phlorins, porphodimethenes, and expanded tetrapyrrolic macrocycles. The inner pyrrolenine nitrogen atoms of porphyrins can be protonated to give the corresponding mono- or di-cations, and the NH groups can be deprotonated to produce di-anions. Porphyrins can also be readily metalated with a wide variety of metal ions and all the naturally occurring porphyrins are metal complexes. The metal ions have an important inductive effect on the π-electron system and strongly influence the chemical reactivity, photophysical properties and biological functions of porphyrin macrocycles. Closed-shell configuration metals incapable of dπ-pπ back-bonding, such as Zn(II) and Cd(II), induce the highest negative charge onto the porphyrin periphery, conferring them the lowest one-electron oxidation potentials. On the other hand, metals capable of π-back-bonding decrease the electron density on the macrocycle, for example Cu(II) and Ni(II) with d^6-d^9 configurations, and in particular metals with d^1-d^5 configurations, such as Sn(IV) and Fe(III), strongly reduce the electron density at the porphyrin periphery.

3.1. Halogenation and Pd(0)-Catalyzed Coupling Reactions

Electron-rich porphyrins normally undergo electrophilic reactions at unsubstituted peripheral positions, when the inner pyrrolenine nitrogens are "protected" by metalalation. Fluorination reagents include *N*-fluoropyridinium triflates [69], cesium fluoroxysulfate [70], and fluorides of cobalt or silver [71]. *N*-Chlorosuccinimide (NCS) [72-77] or chlorine [64, 65] are normally used for chlorination, although HCl/H_2O_2 [78] and $PhSeCl_3$ [79] have also been reported. Similarly, *N*-bromosuccinimide (NBS) [63, 64, 67, 80-84], bromine [64, 73, 85, 86], HBr/H_2O_2 [66, 71], copper(II) bromide [85] and $PhSeBr_3$ [69] have been used for bromination of porphyrin macrocycles. Polybromination can lead to mixtures of regioisomers when unsubstituted β- and *meso*-positions are available at the macrocycle

periphery. Nevertheless, in the case of *meso*-tetraarylporphyrins, such as TPP **4**, tetra-bromination can be achieved regioselectively using a slight excess of NBS in refluxing $CHCl_3$, leading to the corresponding 2,3,12,13-tetrabromoporphyrins, such as **78** in about 80% yield (Scheme **21**) [88].

This regioselectivity is only observed in metal-free porphyrins, where bond fixation occurs after the first substitution, therefore promoting bromination on antipodal pyrrolic units. β-Octabromination can also be obtained using an excess NBS in refluxing *o*-dichlorobenzene or bromine in chloroform/carbon tetrachloride; in this case the best yields are obtained with the metal complexes of porphyrins (usually Cu, which can be demetalated under acid conditions) due to their higher stability under the reaction conditions, to produce *e.g.* **79** [89]. Mono- and di-iodination have been accomplished with bis(trifluoroacetoxy)-iodobenzene-iodine in chloroform/pyridine [90, 91]. Using *meso*-5,15-diphenylporphyrin **80**, the first iodination occurs selectively at one of the free *meso*-positions while the second substitution occurs at one of the β positions leading to a mixture of diiodo regioisomers. However, the *meso*-dibrominated porphyrin **81** can be obtained in high yield (96%) and regioselectively, by reacting **80** with NBS in chloroform and pyridine at 0 °C for one hour (Scheme **22**) [92]. Two different halogens can also be inserted into porphyrin **80** by performing consecutive bromination and iodination reactions (in this order), giving porphyrin **82** in 66% yield [80]. Regioselective di-iodination was also accomplished when bulky *meso*-aryl groups are present, such as in 5,15-di(3',4',5'-trimethoxyphenyl)porphyrin **83**, the *meso*-diiodo porphyrin **84** is obtained regioselectively (Scheme **23**).

Side reactions of brominations and iodinations have been reported, *via* the formation of porphyrin π-cation radicals, which can react in multiple ways. For example, OEP **3** reacted with NBS in the presence of 2,2'-azobis(2-methylpropionitrile) (AIBN) to produce *trans*-(2-bromovinyl)porphyrin **85** (Scheme **24**) by way of a (1-bromoethyl) intermediate, which can be trapped as the ether derivative in the presence of alcohols [66, 93].

The nucleophilic substitution of halogen substituents has also been reported, by for example cyanide [76, 94, 95], nitrite [96], and thiolate ions [88]. The main use of bromo- and iodo-porphyrins is as starting materials for cross-coupling reactions, *via* palladium(0)-catalyzed Suzuki, Sonogashira, Heck and Stille type reactions to produce various aryl, ethynyl and alkenyl-functionalized porphyrin systems; dimeric and oligomeric porphyrin systems have also been prepared using these methodologies [97-108]. For example, dodecaarylporphyrins **86** were prepared in 14-65% yields using a Suzuki coupling reaction of metal-free **79** with arylboronic acids (Scheme **25**) [109-111].

This methodology has been used to produce a variety of functionalized porphyrins, for example carborane-containing porphyrin **87** in 78% from bromoporphyrin **78** (Scheme **26**) [112] and carboxylate-functionalized **88** from **80** (Scheme **27**) [70, 81].

Metalloporphyrins are often used in palladium(0)-catalyzed coupling reactions to avoid macrocycle metalation by palladium and/or copper, sometimes used as co-catalyst. Allenylboronate has also been used to produce allenyl and alkynyl-functionalized porphyrins from the corresponding bromoporphyrins [113]. Both *meso*- and β-

bromoporphyrins have been functionalized by palladium(0)-catalyzed couplings with amines, amides, alcohols, sulfides, carbazates, hydrazones and phosphines [114-123]. Examples are the synthesis of porphyrins **89** [88] and **90** [102] from **81** or its zinc(II) complex (Scheme **27**).

Brominated porphyrins have also been coupled with iodo-alkyl fluorides in the presence of tris(dibenzylideneacetone)dipalladium(0), triphenylarsine and copper(0) in DMSO to produce *meso*- and β-perfluoroalkylated porphyrins in 40-85% yields [124], and with potassium organotrifluoroborates in the presence of $Pd(dppf)Cl_2$ and Cs_2CO_3 to produce a variety of functionalized porphyrins [125].

Suzuki-type couplings have also been performed on borylated porphyrins, which can be prepared from palladium-catalyzed reactions of bromoporphyrins with pinacol borane or bispinacol borane. Borylated porphyrins undergo a variety of palladium-catalyzed coupling reactions with aryl halides [126-132]. One example is the borylation of the zinc(II) complex of *meso*-diphenylporphyrin **80**, followed by palladium(0)-catalyzed coupling to *N*-Boc protected 4-iodo-phenylalanine to give porphyrin **91** (Scheme **28**) [112].

Sonogashira coupling reactions are used for the preparation of a variety of ethynyl-substituted porphyrins, usually by reaction of a *meso*- or β-halogenated porphyrin with acetylene compounds [117, 133-138]. Using this methodology, the zinc(II) complex of di-iodoporphyrin **84** was converted into ethynylporphyrins **92** in 25-72% yields (Scheme **29**) [81], and nickel(II)-porphyrin **81** gave **93** in 66% yield upon coupling with ferrocenylethyne (Scheme **30**) [119].

Different functionalizations can be introduced onto a porphyrin by performing successive halogenation-coupling-halogenation-coupling reactions or by taking advantage of the different reactivity of two halogens (*e.g.* Br and I) that are first introduced into the macrocycle, followed by two coupling reactions. For example, porphyrins **94** were prepared from zinc(II) porphyrin **82** by consecutive Sonogashira and Stille coupling reactions (Scheme **31**) [81]. An interesting cross-annulative coupling reaction has also reported between *meso*-diarylporphyrin **95** and various acetylenes in the presence of $Pd_2(dba)_3$, tris(*o*-tolyl)phosphine and dicyclohexylmethylamine in refluxing toluene, to give porphyrins **96** in 78-87% yields (Scheme **32**) [139].

Heck and Stille coupling reactions are used to prepare alkenyl and aryl-substituted porphyrins [140-144]. Stille-type reactions were first used in porphyrin functionalization for the preparation of protoporphyrin IX dimethyl ester **98** from dibromo-deuteroporphyrin IX dimethyl ester **97** in 85% yield (Scheme **33**) [87].

Mono-substituted alkenes under Heck conditions tend to produce the corresponding *trans*-alkenylporphyrins, particularly for large, sterically demanding substituents. For example, bromoporphyrins **99** gave the corresponding *trans*-alkenylporphyrins **100** in >65% yields (the *cis*-isomer was also observed when R = CN) under Heck conditions [123] and zinc(II)-porphyrin **101** was produced in 86% yield under Stille conditions (Scheme **34**) [125]. Mono- di- and tetra-benzoporphyrins have been prepared *via* vicinal Heck couplings of di-, tetra-,

and octa-bromoporphyrins followed by *in situ* 6π-electrocyclization and aromatization [145-147].

For example, dibenzoporphyrins **103** were prepared from tetrabromoporphyrins **102** in a single step, in 48-60% yields (Scheme **35**) [130]. Using a Stille cross-coupling reaction, porphyrin **104** was prepared in 60% yield from porphyrin **78** (Scheme **36**) [129].

Silylmethyl-substituted porphyrins, such as **105**, are prepared by palladium(0)-catalyzed Kumada cross-coupling reactions of both *meso*- and β-bromoporphyrins with silylmethyl Grignard reagents [148]. For example, **105** was obtained from porphyrin **81** in 82% yield (Scheme **37**). The silylmethylporphyrins can be converted into a variety of functional groups, including CHO, CH_2OH, and CH_2F.

3.2. Nitration and Reactions of Nitroporphyrins

The nitration of porphyrins can be achieved with nitric acid [149-153], nitrate salts (usually of copper, zinc or silver) [154], or with N_2O_4 [155-158] or nitrite ion [159-161] *via* the corresponding porphyrin π-cation radicals. The peripheral nitro substituents of porphyrins can be reduced to the corresponding amino derivatives using $SnCl_2$/HCl [162], or with $NaBH_4$ and 10% Pd/C in methanol [163], and β-aminoporphyrins have been shown to undergo acylation, diazotization and various reactions with carbonyl compounds [164-167].

Meso- and β-nitroporphyrins undergo *ipso* substitution of the nitro group to produce a variety of functionalized porphyrin macrocycles [106,168-172]. In addition, β-nitroporphyrins also undergo nucleophilic Michael-type additions at the adjacent β-position [92, 105, 116, 158, 173-178] to produce functionalized porphyrins and chlorins. For example, β-nitroporphyrin **106** reacted with alkylmagnesium bromides or organolithium reagents to give alkylated porphyrins **107** [156] and with sodium methoxide or benzaldoxime to produce the corresponding 2-methoxy- or 2-hydroxy-porphyrin, respectively, *via* chlorin intermediates (Scheme **38**). Several functionalized macrocycles have been obtained using this methodology, including 2-and 2,3-substituted porphyrins and chlorins. For example, *trans*-chlorins **109** were produced by reaction with active methylene compounds in the presence of base, *via* a fused cyclopropane chlorin [163]. β-Fused pyrroloporphyrins, such as **108**, were also obtained from metallo-2-nitro-5,10,15,20-tetraphenylporphyrin by reaction with α-isocyanoacetic esters in the presence of a base [179, 180]. On the other hand, 5-nitro-octaethylporphyrin **110** reacted by *ipso*-substitution of the nitro group in the presence of soft nucleophiles to produce porphyrins **111**, whereas hard nucleophiles, such as methylmagnesium bromide and benzyl oxide gave the corresponding 15-substituted porphyrins (Scheme **39**) [157], due to the higher stability of the intermediate, conferred by the 5-nitro group.

A β-nitro substituent on a porphyrin macrocycle, such as **106**, directs electrophilic substitutions to the antipodal pyrrole ring, and this strategy has been used to regioselectively prepare 2,3-dibromo-*meso*-tetrarylporphyrins after reductive denitration [181].

3.3. Formylation and Acylation Reactions

The Vilsmeier formylation of porphyrins using DMF/$POCl_3$ followed by treatment with aqueous base introduces a formyl group at the *meso*- or the β-position of porphyrin macrocycles [182-185]. The use of a sterically hindered Vilsmeier reagent, such as that prepared from *N*,*N*-diisobutylformamide/$POCl_3$ favors substitution at the β-positions [186] whereas *N*,*N*-(dimethylamino)acrolein (3-DMA)/$POCl_3$ produces 2-formylvinylporphyrins in good yields [187, 188].

Other regioselective formylation methods use trimethyl orthoformate in TFA [189, 190], and *via* oxidation of 1,3-dithianylporphyrins [191, 192] or (2-pyridyldimethylsilyl)methylporphyrins [193].

Formyl groups at the periphery of porphyrins can undergo a variety of reactions, including reductions, oxidations and nucleophilic additions, leading to a variety of functionalized macrocycles [194-206]. *meso*-Hydroxymethylporphyrins undergo dimerization under acidic conditions, producing dimers which upon dehydrogenation in acetic acid are transformed into *trans*-ethylene porphyrin dimers [207-210]. 1,2-Ethylene porphyrin dimers (*cis*- and *trans*-isomers), such as **113**, are obtained directly by reductive coupling of metalloformylporphyrins (*e.g.* **112**) using low-valent titanium complexes *via* a McMurry coupling reaction (Scheme **40**) [89, 139, 140, 211-214]. Formyl-porphyrins also undergo Grignard and Wittig reactions [215-221] to produce a variety of *cis*- and *trans*-(2-substituted-vinyl)porphyrins, which can be further functionalized (see also section below). The electrophilic acylation of metalloporphyrins can be achieved with acetic anhydride in the presence of Lewis acid catalysts, such as $SnCl_4$, and occurs preferentially at the β-positions due to steric factors [222, 223]. The acetyl substituents of porphyrins can be reduced to vinyl groups with $NaBH_4$ followed by dehydration using *p*-toluenesulfonic acid in 1,2-dichlorobenzene or alternatively by use of benzoyl chloride/DMF [224]. Alternatively, the enantioselective reduction of mono- and diacetyldeuteroporphyrin IX dimethyl ester can be accomplished with borane dimethyl sulfide in the presence of methyloxazaborolidine as the homochiral catalyst [225-227]. Acetylporphyrins also react under Vilsmeier conditions to produce 1-chloro-2-(formyl)vinyl derivatives, which can be converted to ethynyl-functionalized porphyrins by treatment with base [228, 229]. Under Wittig conditions zinc(II) acetylporphyrins react to produce isopropenylporphyrins [230, 231].

3.4. Reactions with Nucleophiles

Porphyrin macrocycles react with strong nucleophiles, such as Grignard and organolithium reagents preferentially at the *meso*-positions, with formation of *meso*-functionalized porphyrins as well as phlorins and porphodimethenes, or at the β-positions with formation of chlorins. The best known nucleophilic addition reactions occur on the π-cation radicals of metalloporphyrins, which can be obtained by chemical or electrochemical oxidation. The Mg(II) and Zn(II) complexes of porphyrins are usually employed since these display the lowest oxidation potentials and I_2 (usually in the presence of $AgClO_4$ or $AgPF_6$), tris(*p*-bromophenyl)ammoniumyl hexachloroantimonate (TBAH) or *N*-chorobenzotriazole (CBT) are the oxidizing agents of choice. Although relatively stable in methanol, the π-cation

radicals of metalloporphyrins react with a variety of soft nucleophiles to produce the corresponding *meso*- and β-substituted metalloporphyrins. For example, *meso*-nitroporphyrins are obtained by treatment of metalloporphyrins with thallium(III) nitrate or cerium(IV) ammonium nitrate [232]. Pyridinium porphyrin salts are produced from the reaction of π-cation radicals with various pyridines [233-237]. Other nucleophiles (CN^-, SCN^-, Cl^-, CH_3CO^{2-}, imidazole, PPh_3) were also shown to react with the π-cation radicals of porphyrins [202, 238]; dimeric and higher oligomeric porphyrin systems have been obtained from bidentate nucleophiles, such as bipyridine [239-241]. Chemical and electrochemical oxidative couplings of Zn(II) 5,15-diarylporphyrins lead to the formation of *meso*-*meso* and *meso*-β linked porphyrin arrays, *via* nucleophilic attack of the π-cation radicals by neutral porphyrins [161, 242, 243]. Treatment of Zn(II) 5,15-diarylporphyrins with $AgPF_6$ and I_2 in the presence of pyridine led to regioselective *meso*-iodination [244]. The more electrophilic π-dications of porphyrins are formed under stronger oxidation conditions and react with, for example, methanol, preferentially at the *meso*-positions, leading to isoporphyrin derivatives [245, 246].

Reactions of organometallic reagents with both free-base and metalloporphyrins at unsubstituted *meso*-positions leads to the formation of intermediate phlorins and porphodimethenes, which are oxidized to the corresponding *meso*-substituted porphyrins [247, 248]. For example OEP **3** and several of its metal complexes produced the corresponding *meso*-functionalized porphyrins **115** in 40-90% yields (Scheme **41**). Di-, tri-, and tetra-*meso*-alkylated porphyrins can also be obtained *via* this methodology in overall yields of 20-40%, by successive one equivalent additions of alkyllithium at low temperature, followed by hydrolysis and oxidation with DDQ [249]. Alkyl- and aryl-lithium agents showed *meso*-regioselectivity when 5,15-disubstituted porphyrins, such as **80** were used, producing the corresponding porphyrins **116** in 56-94% yields (Scheme **42**) [250-252].

meso-Tetrasubstituted porphyrins react with alkyllithiums to produce porphodimethenes, phlorins or chlorins [253]. Regioselective 15-*meso*-alkylation of zinc(II) 5-formyloctaethylporphyrin **112** was accomplished by addition of methyl or ethyl magnesium bromide to give porphyrins **114**, *via* a phlorin intermediate (Scheme **40**) [254]; under the same conditions the free-base and Ni(II) derivatives react preferentially at the *meso*-formyl group with formation of the 1-hydroxylalkyl derivatives. Nucleophilic addition of hydroxide ion to Au(III) 5,10,15,20-tetraphenylporphyrin also occurs at a *meso*-position with formation of the corresponding hydroxyphlorin, whereas the Cu(II), Pd(II), Cd(II) and Mn(III) complexes of TPP were unreactive under the same conditions [255]. Reactions of organometallic reagents with iron(III) porphyrins occur preferentially at the metal center with formation of σ-bonded species [256, 257]; migration of the σ-bonded groups (alkyl, vinyl, aryl) from the metal ion to the nitrogen atom is induced by oxidation or by acid treatment [258-264].

3.5. Oxidations and Reductions

Porphyrins and metalloporphyrins (usually zinc complexes) can be oxidized to oxophlorins and oxochlorins, or to ring-opened products such as formyl- and benzoyl-biliverdins. 5-Oxophlorins (such as **117**) are formed by hydrolysis of *meso*-trifluoroacetoxyporphyrins,

obtained from reaction of Zn(II) and Mg(II) β-substituted porphyrins with thallium(III) trifluoroacetate (TTFA) (Scheme **43**) [265, 266].

Hydrogen peroxide in concentrated sulfuric acid [267, 268] and benzoyl peroxide can also be used for *meso*-oxidation [269, 270]. Reactions at the periphery of 5-oxophlorins occur preferentially at the electron-rich position-15 [271]. Neutral π-radicals of 5-oxophlorins are easily formed under mild conditions, and were shown to be stabilized by bulky 15-substituents [272, 273]. Extensive *meso*-oxidation can lead to formation of di-, tri-, and tetraoxoporphyrins (the so-called xanthoporphyrinogens). Osmium tetroxide reacts selectively at the β-β' double bonds of porphyrins to produce the corresponding *cis*-dihydroxychlorins; for example **118** is obtained from reaction of OEP **3** (Scheme **43**) [274-277]. The β-substituted *cis*-dihydroxychlorins undergo pinacol-pinacolone rearrangement in perchloric acid or fuming sulfuric acid to give β-oxochlorins (for example **119** from **118**). The regioselectively of the osmylation reaction and the migratory aptitudes of different peripheral substituents in the pinacol-pinacolone rearrangement have been investigated [278-282]. Metal-free oxochlorins such as **119** react further with osmium tetroxide regioselectively at the opposite pyrrole ring, whereas metal derivatives react preferentially at the adjacent β-β' double bond producing the corresponding *vic*-dihydroxy- and oxo-bacteriochlorins and isobacteriochlorins [283-287]. *meso*-Tetraarylporphyrins such as TPP react with benzoyl peroxide producing β-benzoyloxyporphyrins, which are converted into β-hydroxyporphyrins such as **120** by metalation, basic hydrolysis and demetalation (Scheme **44**). Compound **120** can also be obtained from 2-nitro-*meso*-tetraphenylporphyrin by nucleophilic displacement of the nitro group with the sodium salt of *E*-benzaldoxime [156, 157]. Oxidation of **120** to the 2,3-dioneporphyrin **121** can be accomplished under a variety of conditions, including CrO_3/acetic acid [288], photooxidation [157], and SeO_2/dioxane [157]; dioneporphyrin **121** reacts with aromatic *o*-diamines and with aromatic aldehydes in the presence of NH_4OAc/AcOH in $CHCl_3$, producing a variety of pyrazino- and imidazole-porphyrin monomers and oligomeric systems [151, 289-292].

Open-chain oxygenated tetrapyrroles are obtained under several conditions, including O_2 in the presence of ascorbic acid or hydrazine (the so-called coupled oxidation of iron porphyrins) [293, 294], using thallium(III) or cerium(IV) trifluoroacetate salts [232, 295], N_2O_4 or sodium nitrate and trifluoroacetic acid [296, 297], hydrogen peroxide [298], or *meta*-chloroperoxybenzoic acid (mCPBA) in pyridine [299], by reactions of metalloporphyrin π-cation radicals with nucleophiles [236], or from photo-oxidation by singlet oxygen, in the presence of light and molecular oxygen to give bilitrienones [300-308]. Porphyrins can also be reduced to dihydro- (chlorins, phlorins, porphodimethenes), tetrahydro- (isobacteriochlorins, bacteriochlorins, porphomethenes), and hexahydro-porphyrins (porphyrinogens). Reduction to *cis*-chlorins is normally accomplished with diimide (obtained from *p*-toluenesulfonylhydrazine) and potassium carbonate [309-312]. On the other hand, *trans*-chlorins can be obtained from the reduction of Fe(III) β-substituted porphyrins with sodium metal in isopentyl alcohol [313, 314]. Porphyrins can also be photo-reduced by light in the presence of amines, ascorbic acid, and other compounds [315-320]. Regioselective photoreductions to *cis*-chlorins are achieved with ascorbic acid in the presence of diazabicyclo[2.2.2]octane (DABCO) as catalyst.

Tetrahydroporphyrins are obtained by further reduction of chlorins under the conditions above. Metalloporphyrins often give isobacteriochlorins, whereas metal-free porphyrins preferentially give bacteriochlorins. Reduction to porphyrinogen can be accomplished by catalytic hydrogenation and this methodology has been used to prepare unsymmetrical macrocycles from symmetric porphyrins [321]. Metalloporphyrins can be reduced to π-anion radicals and π-dianions with, for example, sodium in THF or with sodium anthracenide [322-326]. Protonation and alkylation of porphyrin π-anions occurs preferentially at the *meso*-positions with formation of phlorins and porphodimethenes, which can rearrange to chlorins and be oxidized to porphyrins.

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LIST OF ABBREVIATIONS

TPP	*meso*-tetraphenylporphyrin
OEP	octaethylporphyrin
DDQ	2,3-dichloro-5,6-dicyanobenzoquinone
TFA	trifluoroacetic acid
TTFA	thallium(III) trifluoroacetate
NBS	*N*-bromosuccinimide
NCS	*N*-chlorosuccinimide
dppf	bis(diphenylphosphino)ferrocene
dba	dibenzylideneacetone
DPEphos	(oxydi-2,1-phenylene)bis (diphenylphosphine)
DMSO	dimethylsulfoxide
DMF	dimethylformamide
DME	dimethoxyethane
AIBN	2,2’-azobis(2-methylpropionitrile)
Boc	*tert*-butoxycarbonyl
THF	tetrahydrofuran
BHT	butylated hydroxytoluene
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
TBAH	tris(*p*-bromophenyl)ammoniumyl hexachloroantimonate
CBT	*N*-chorobenzotriazole
DABCO	diazabicyclo[2.2.2]octane

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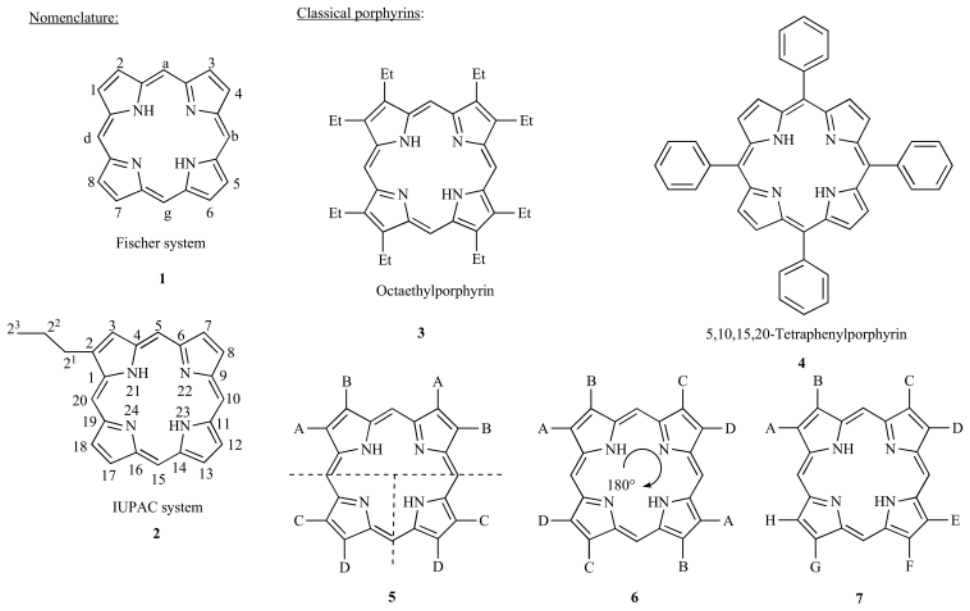
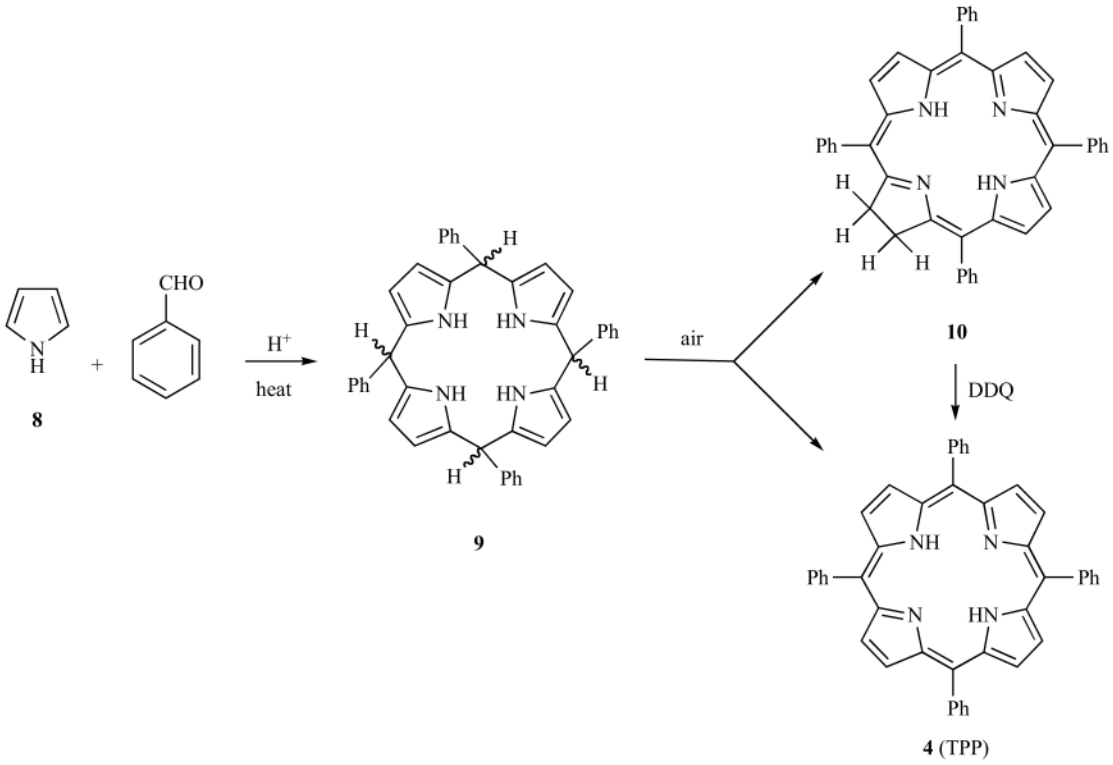
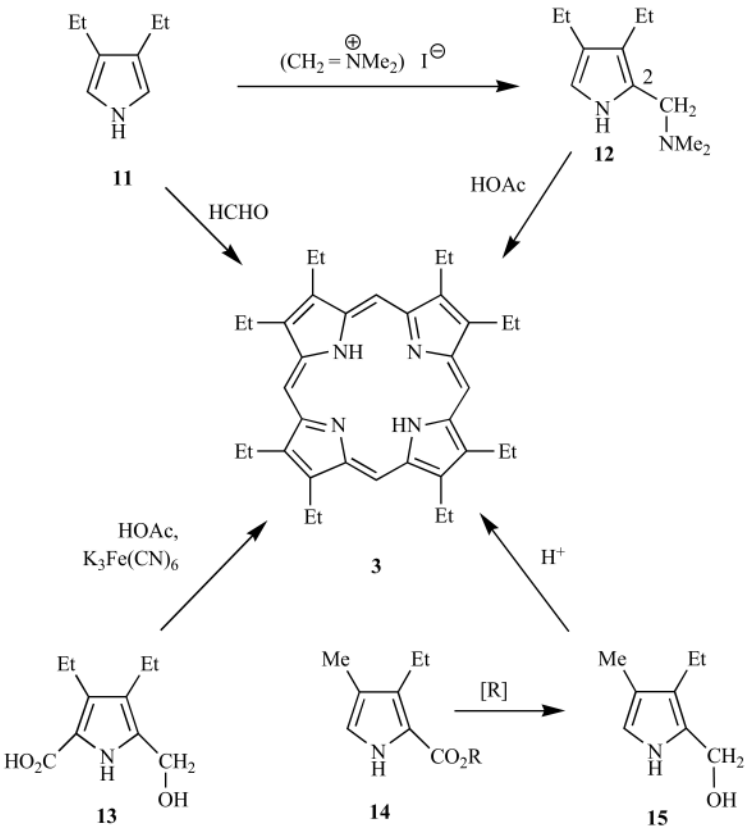


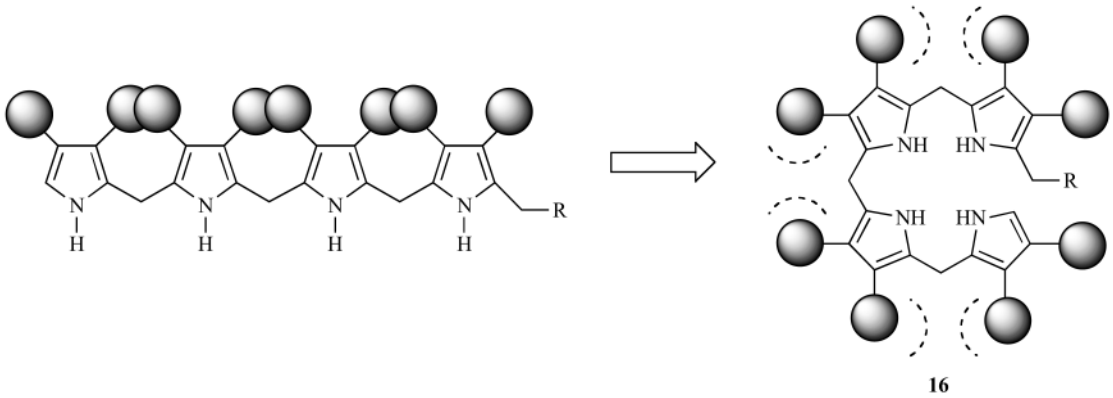
Fig. (1).
Porphyrin nomenclature.



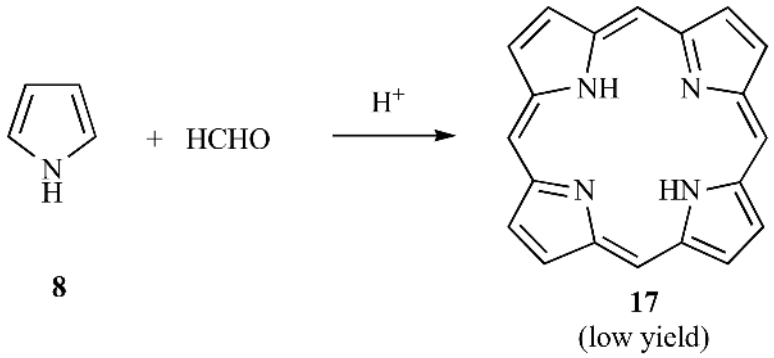
Scheme 1.



Scheme 2.

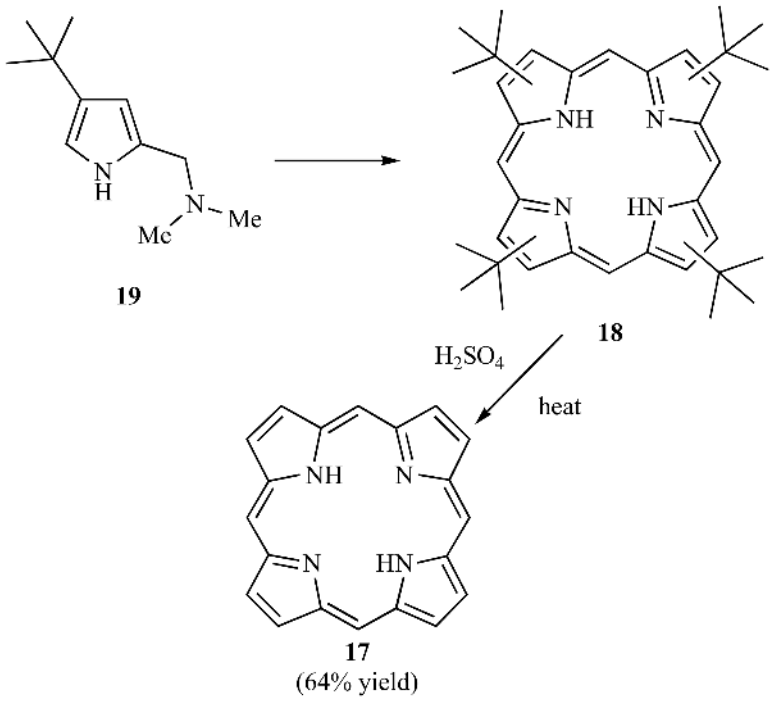


Scheme 3.

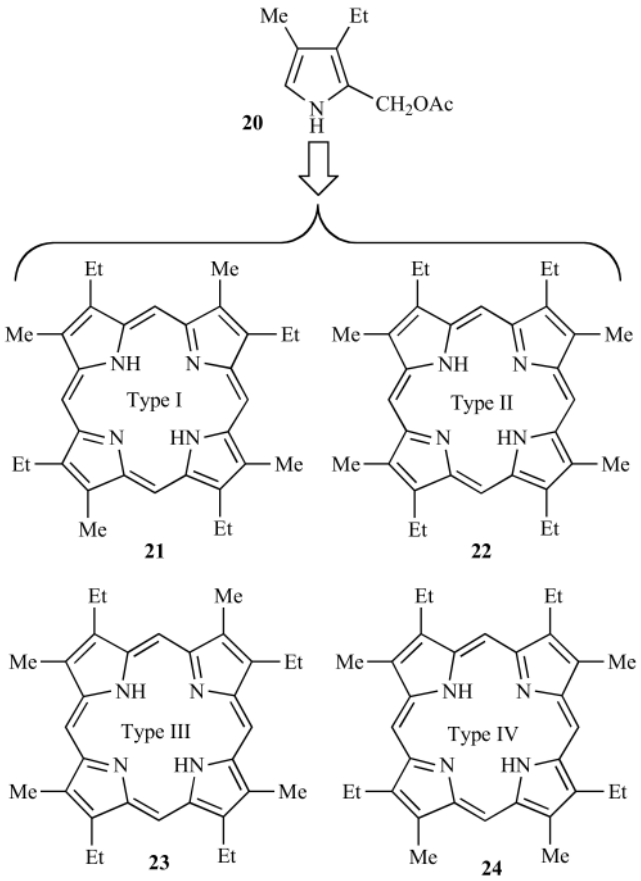


8 **17** (low yield)

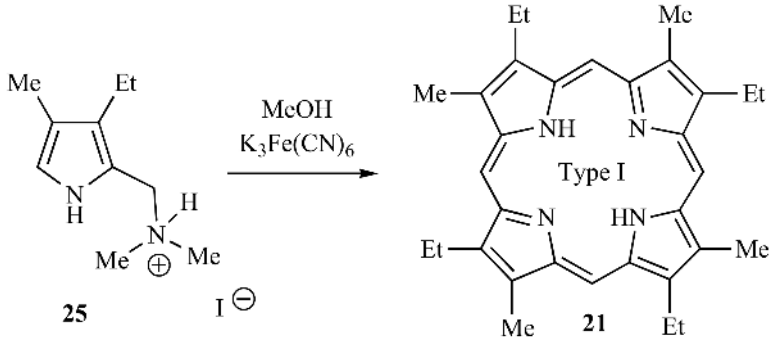
Scheme 4.



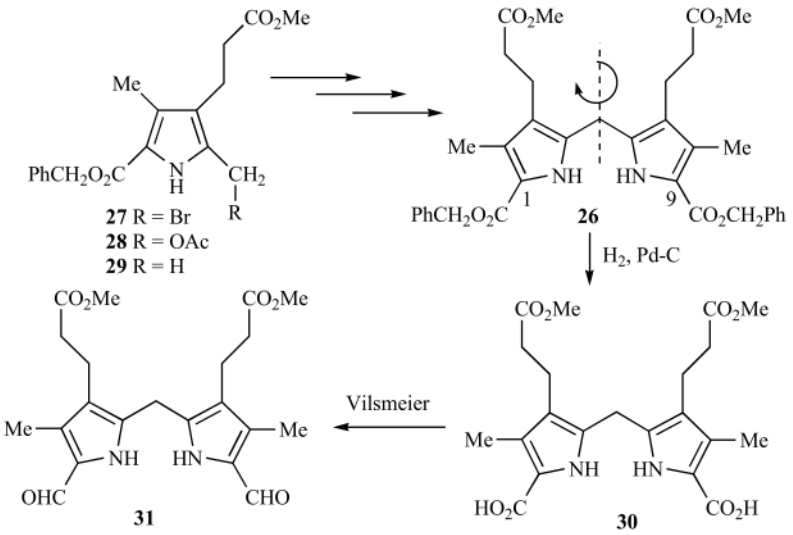
Scheme 5.



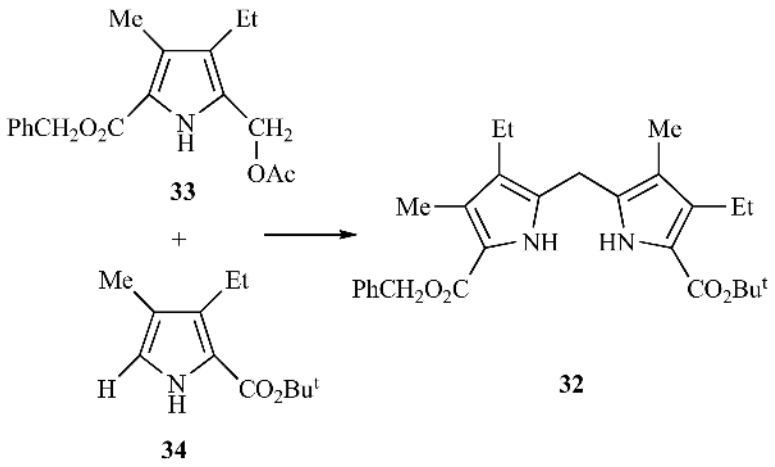
Scheme 6.



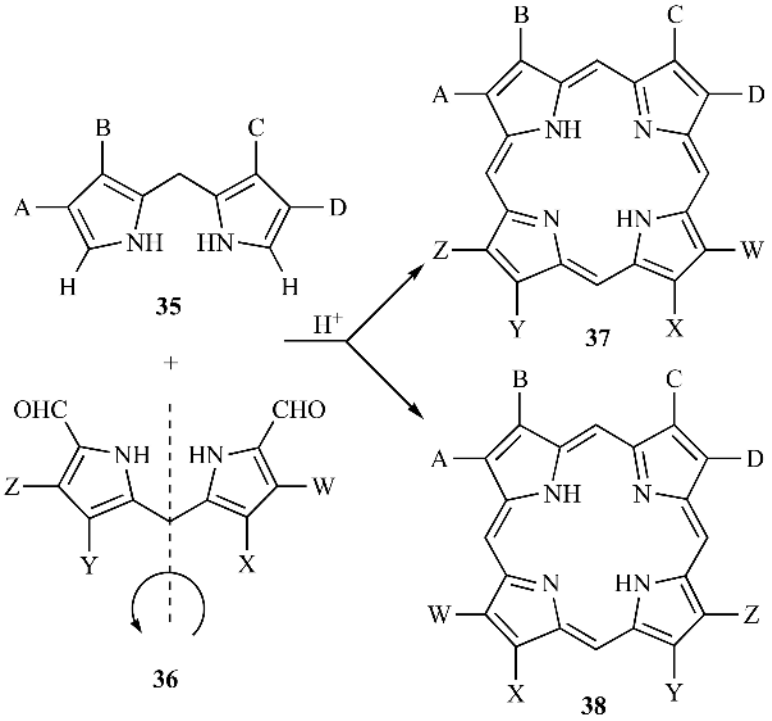
Scheme 7.



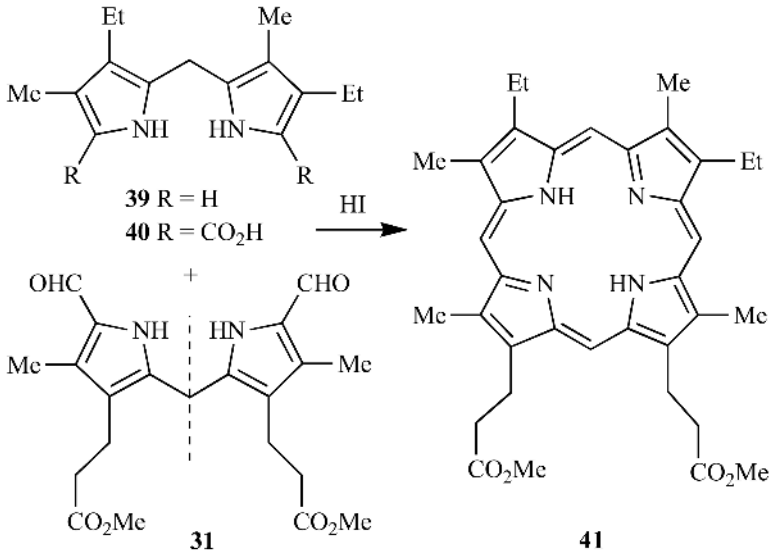
Scheme 8.



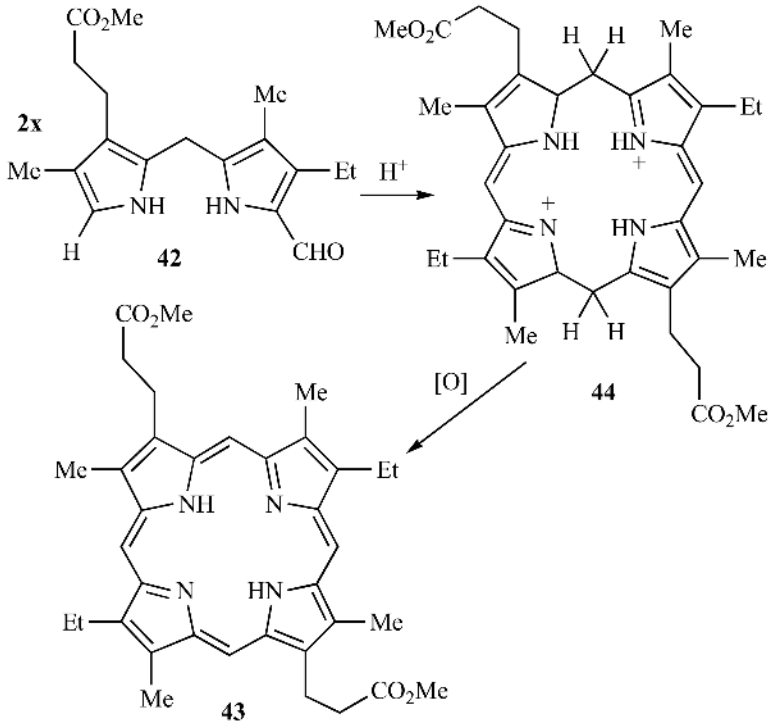
Scheme 9.



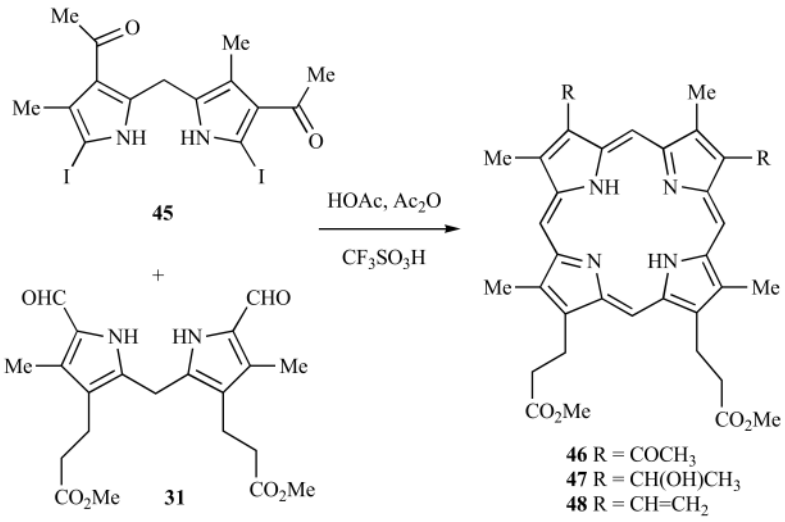
Scheme 10.



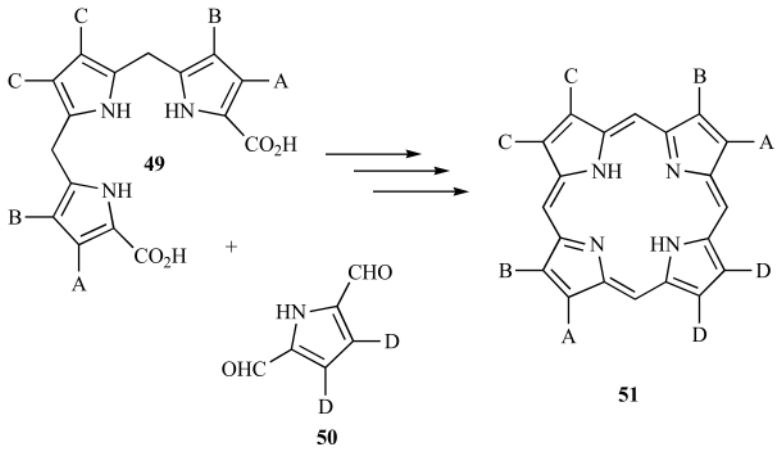
Scheme 11.



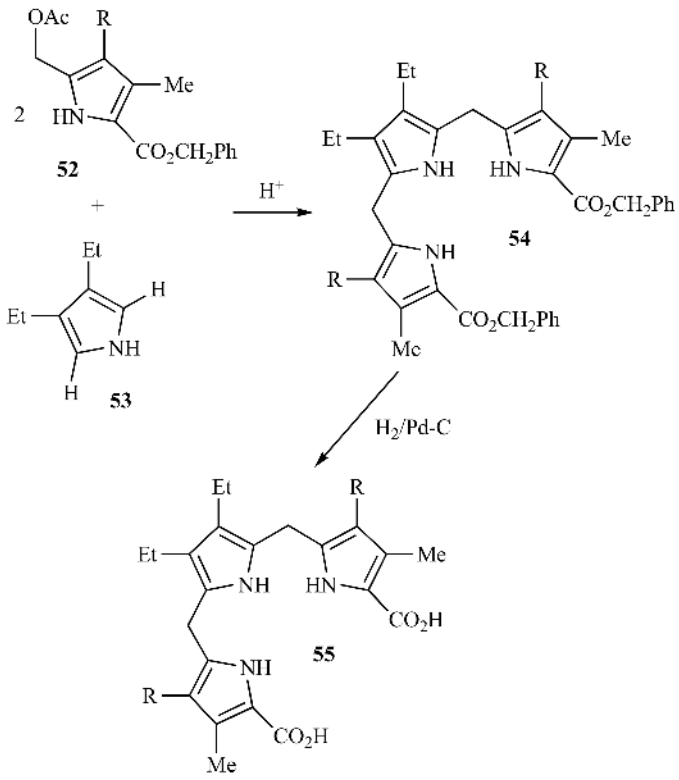
Scheme 12.



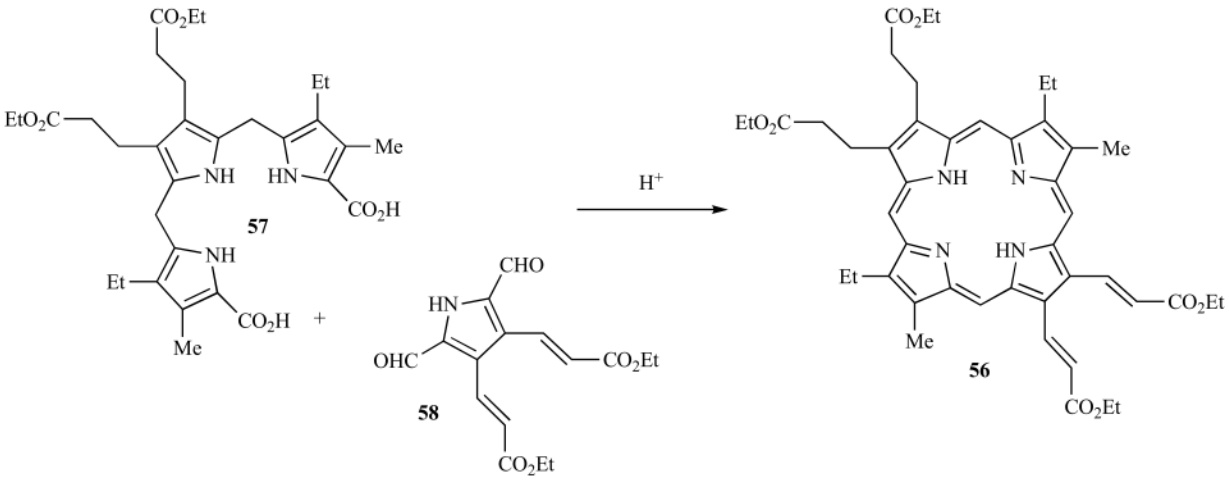
Scheme 13.



Scheme 14.



Scheme 15.



Scheme 16.

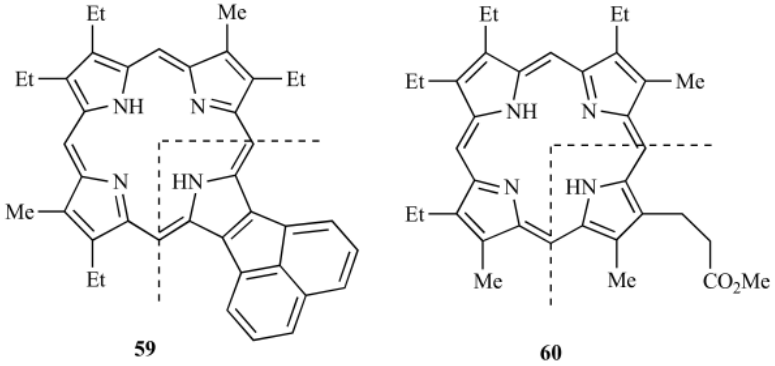
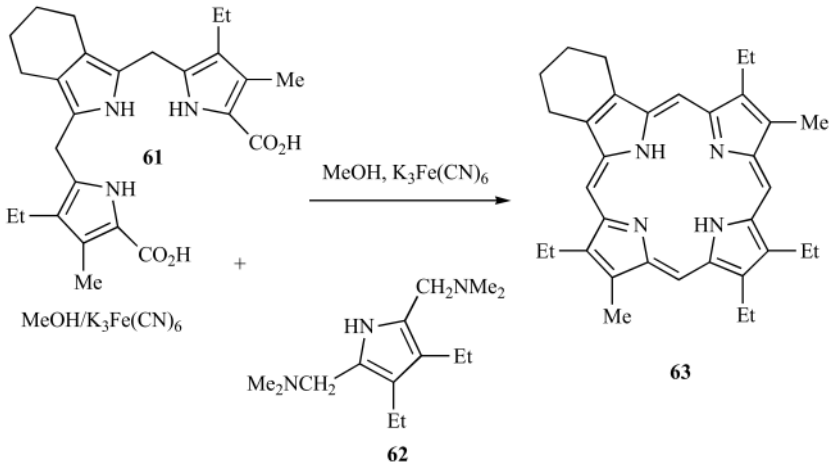
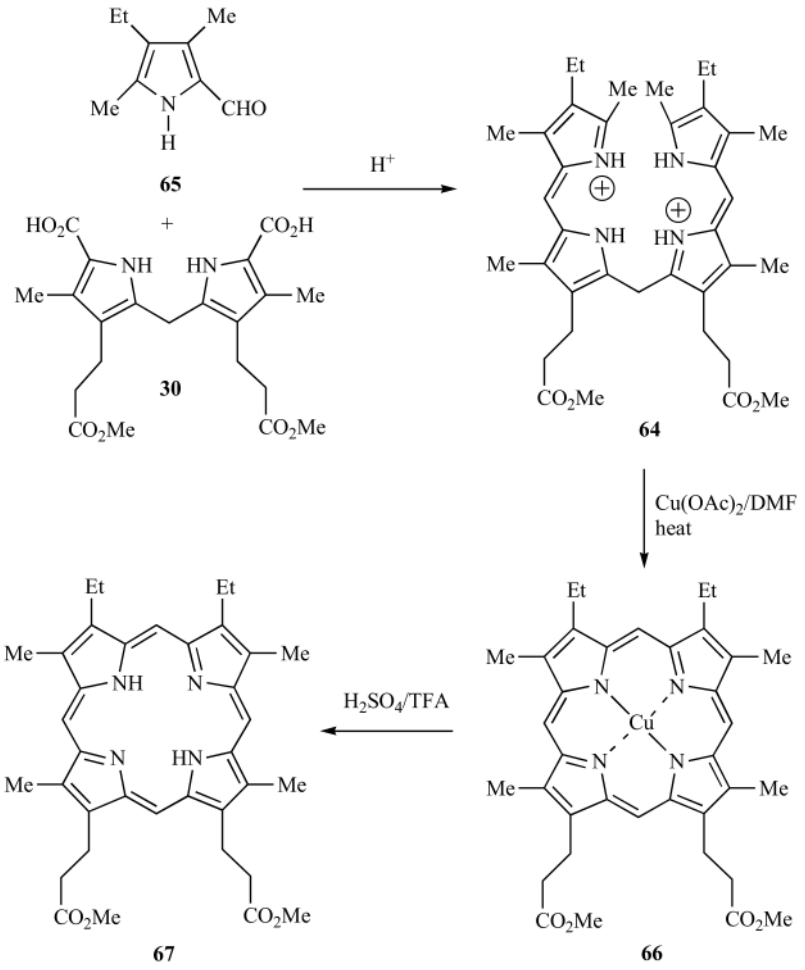


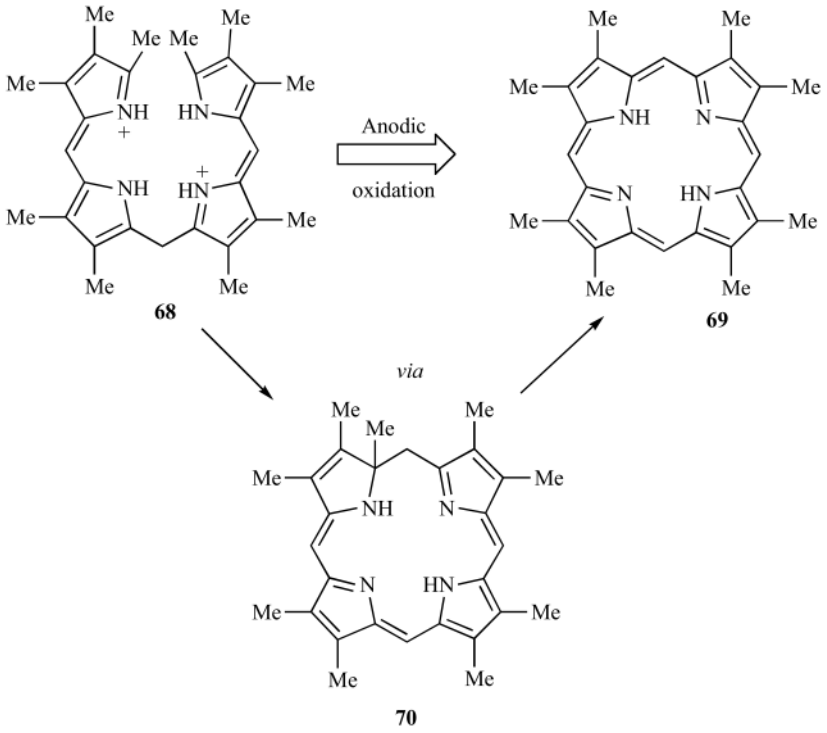
Fig. (2).
Lash's 3+1 products.



Scheme 17.



Scheme 18.



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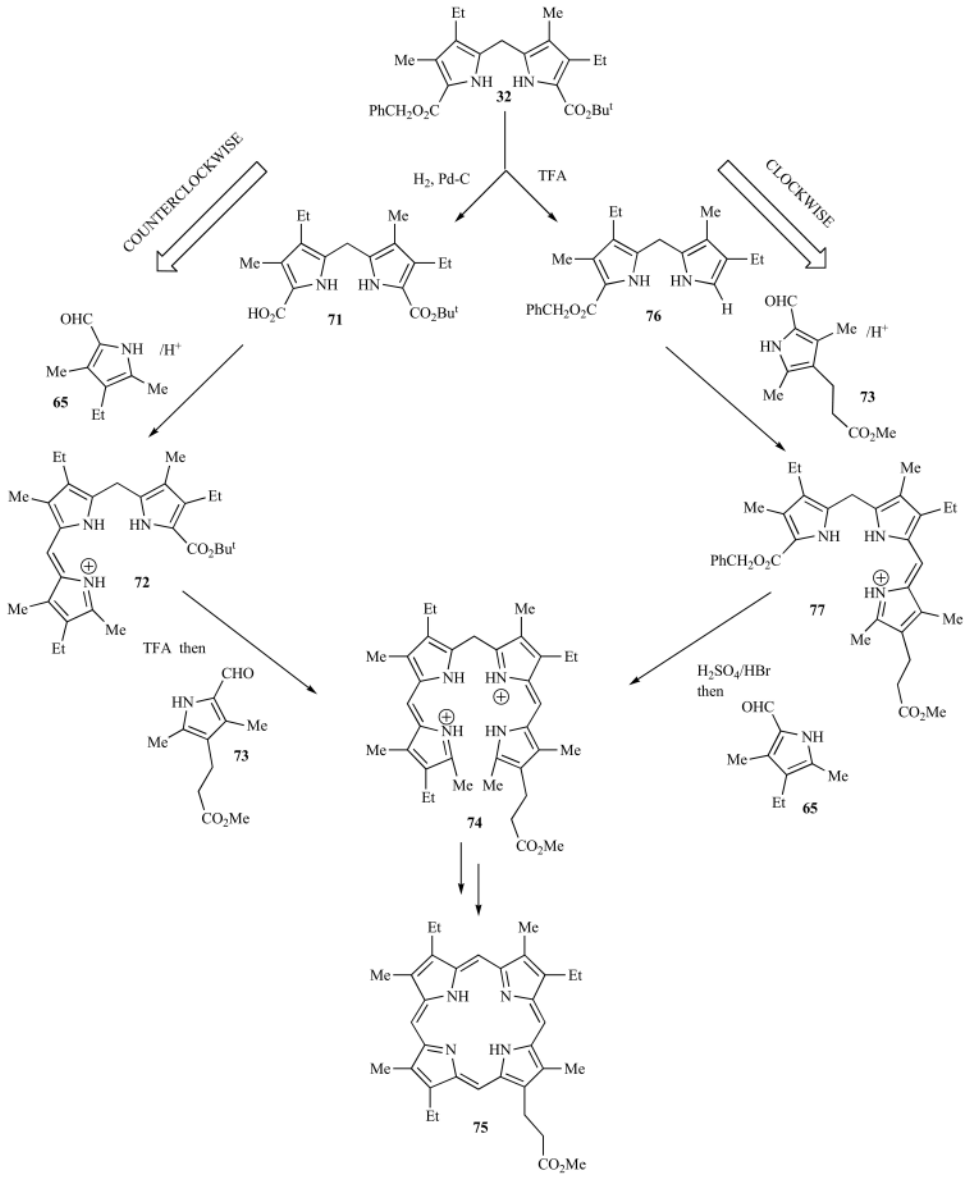

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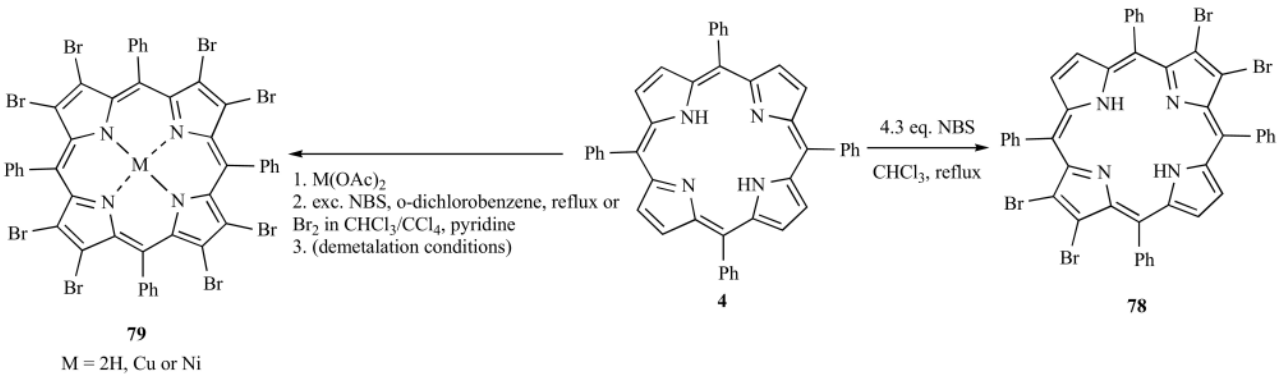
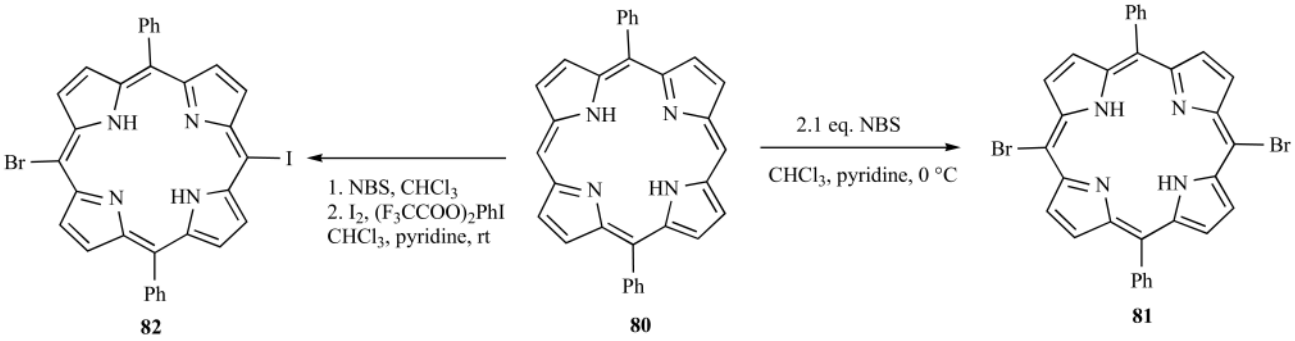


Scheme 21.



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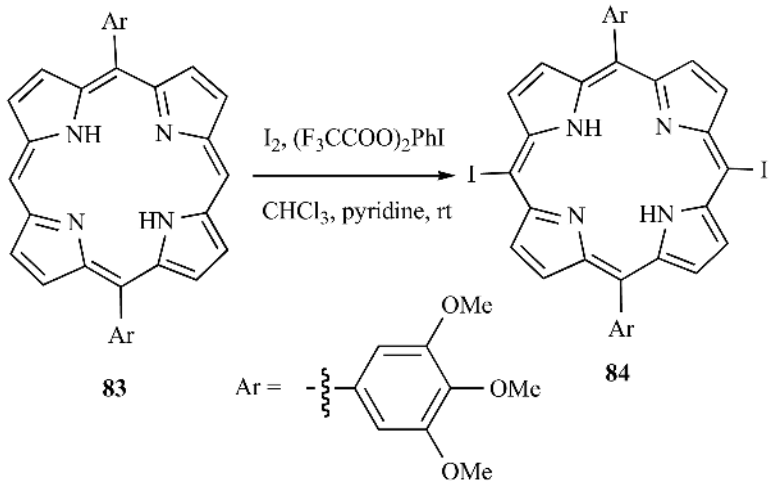

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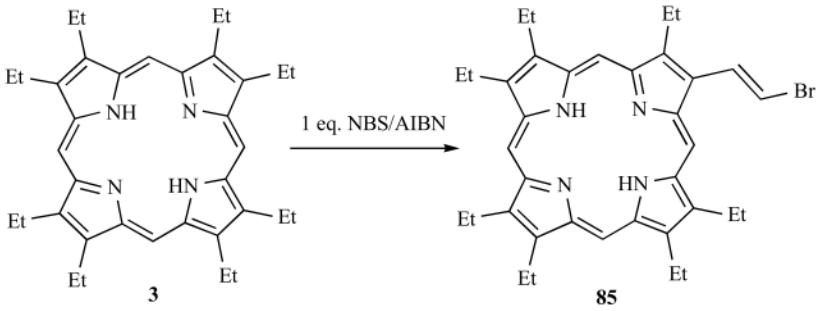

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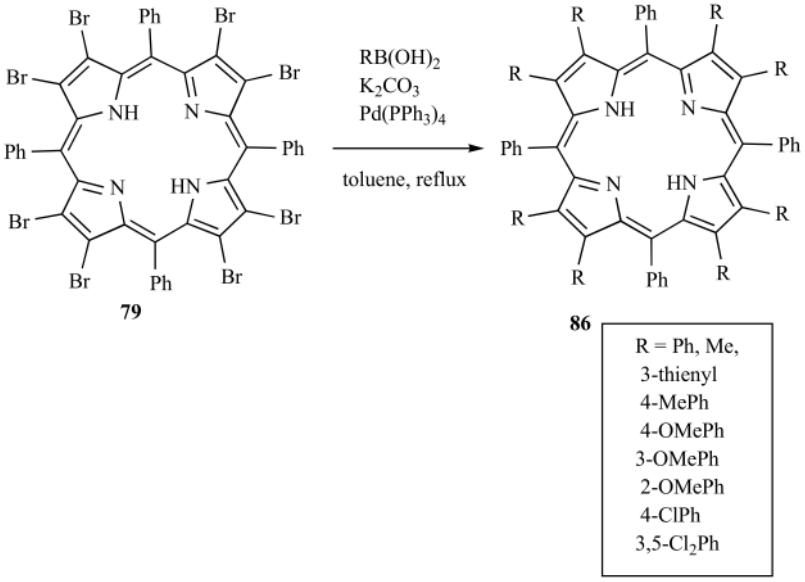

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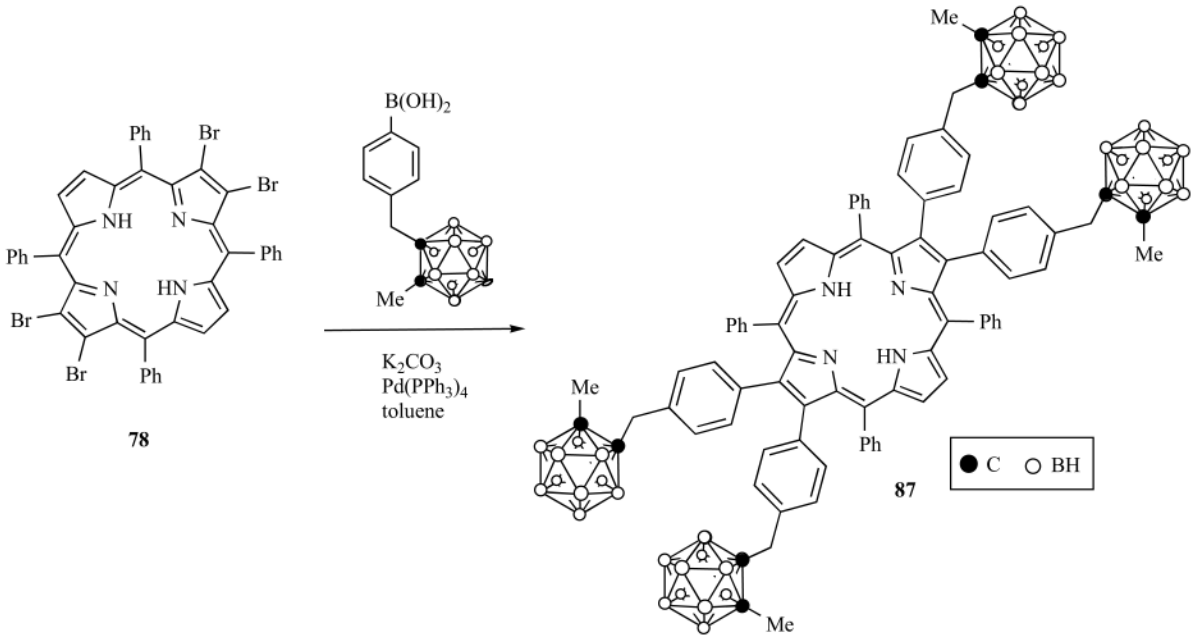
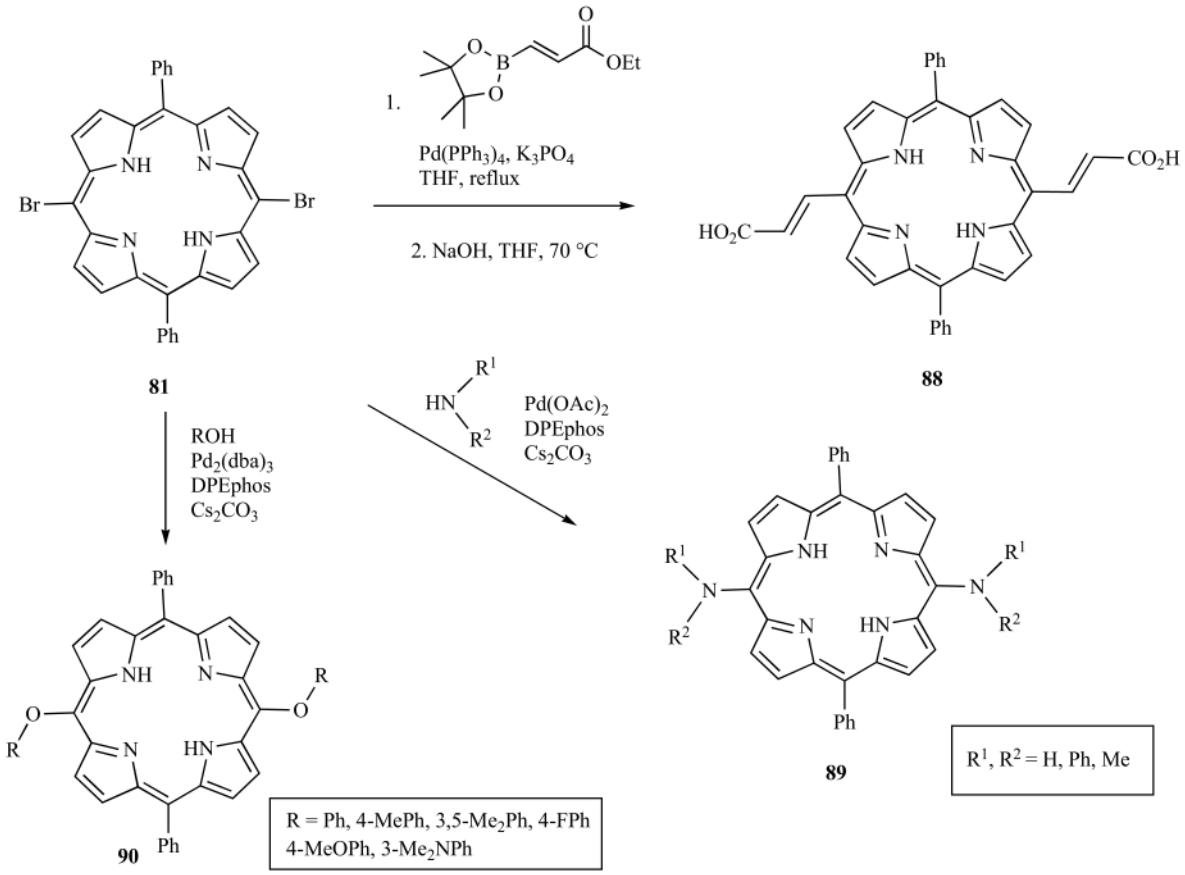
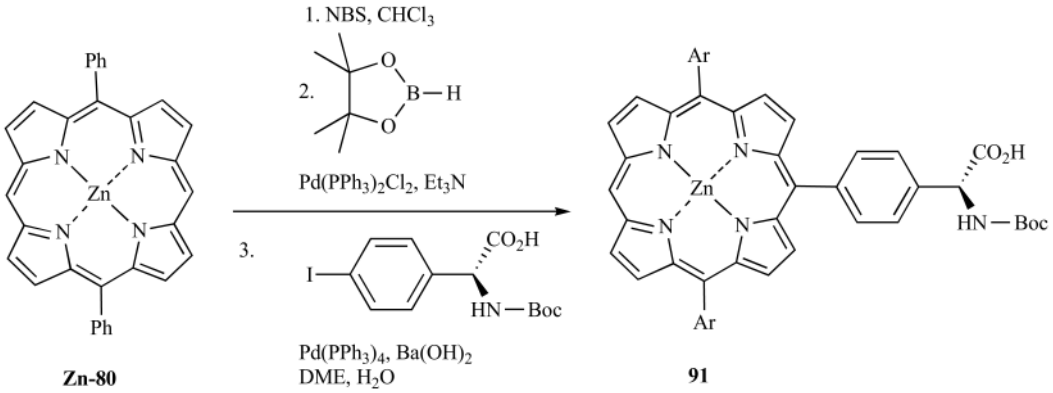


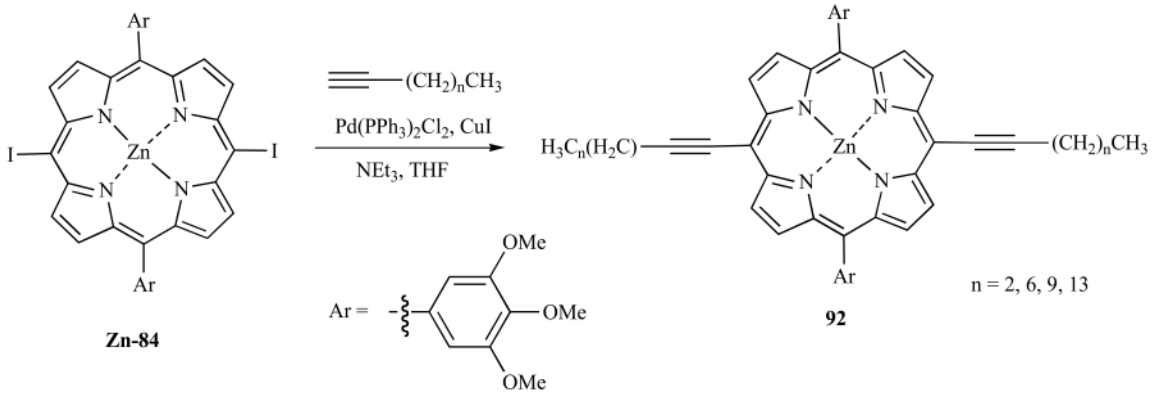
Scheme 26.



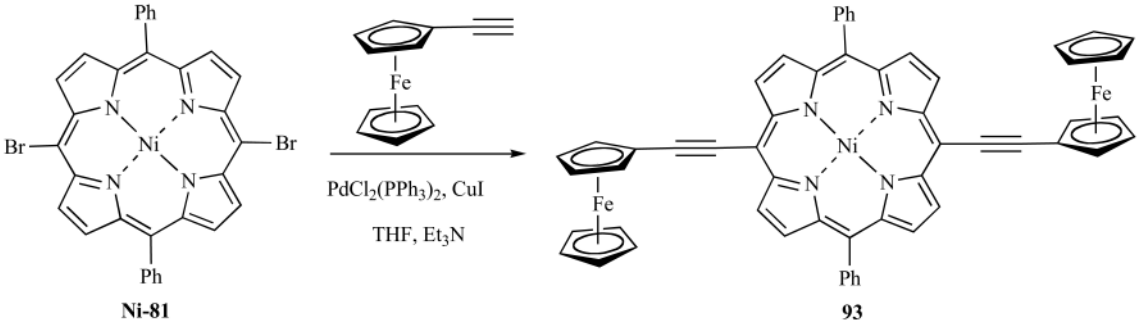
Scheme 27.



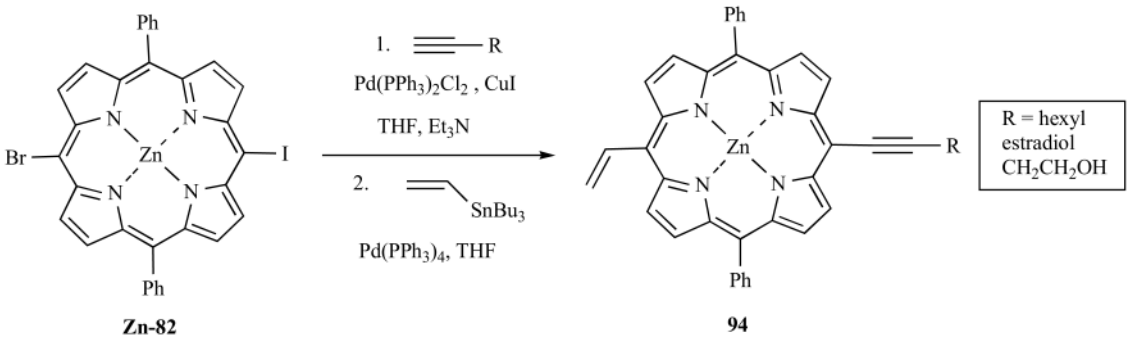
Scheme 28.



Scheme 29.

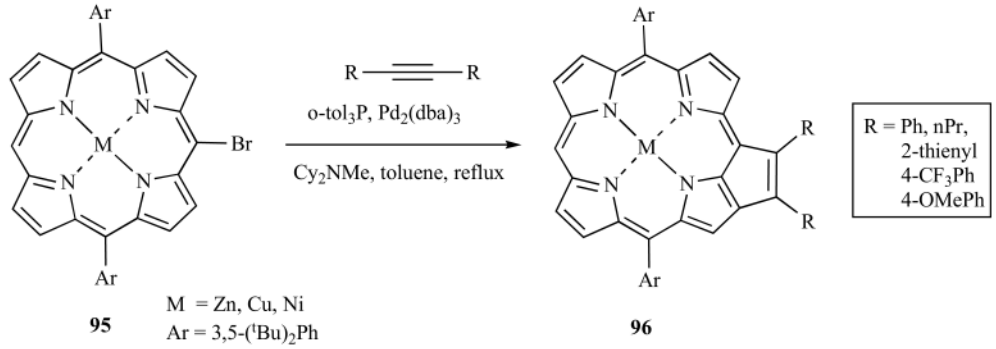


Scheme 30.

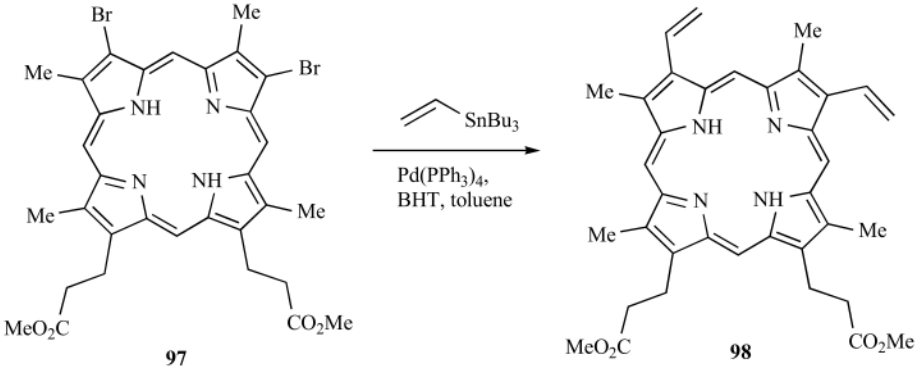


Zn-82 **94**

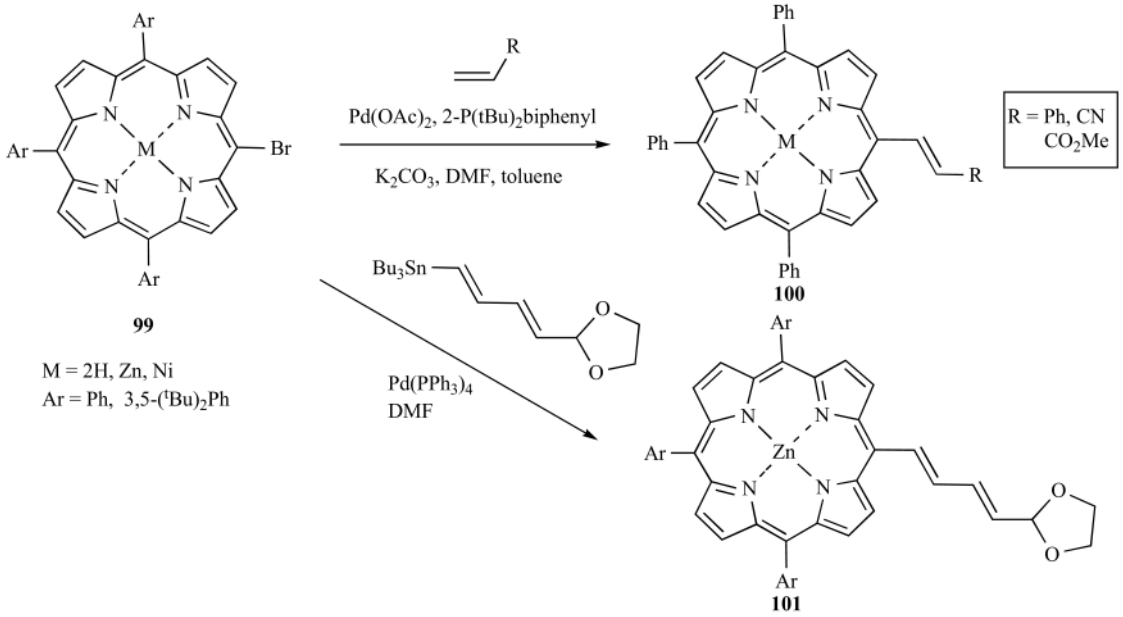
Scheme 31.



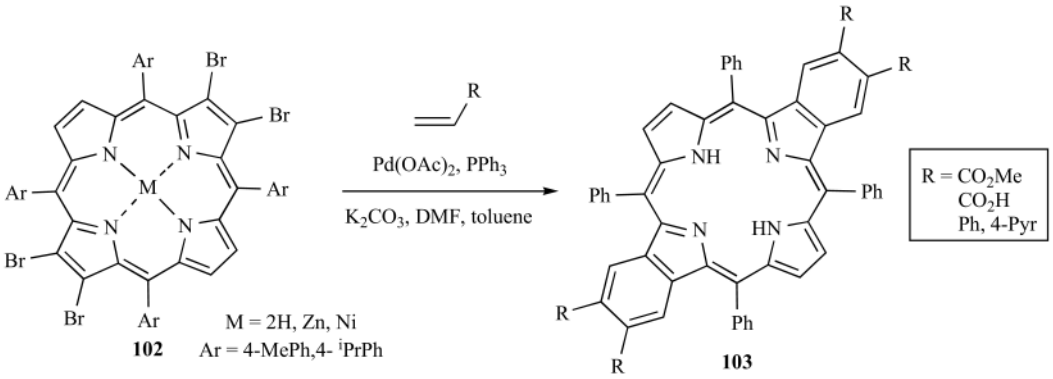
Scheme 32.



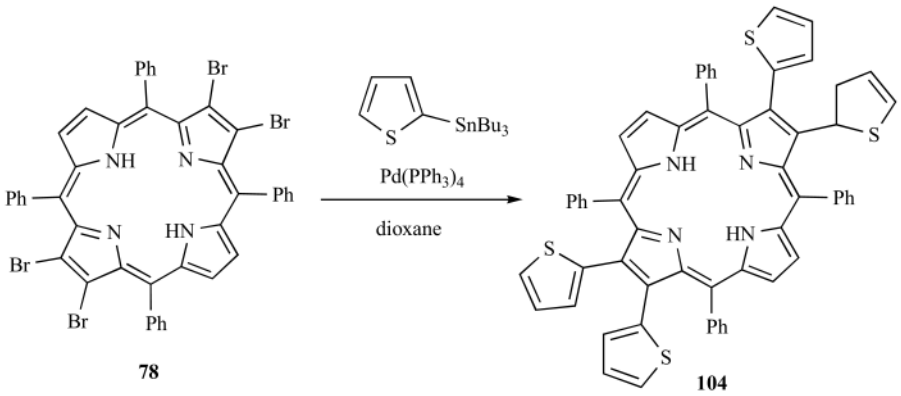
Scheme 33.



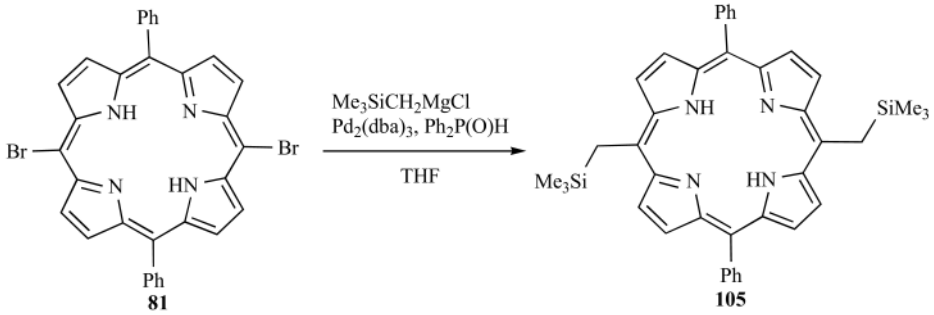
Scheme 34.



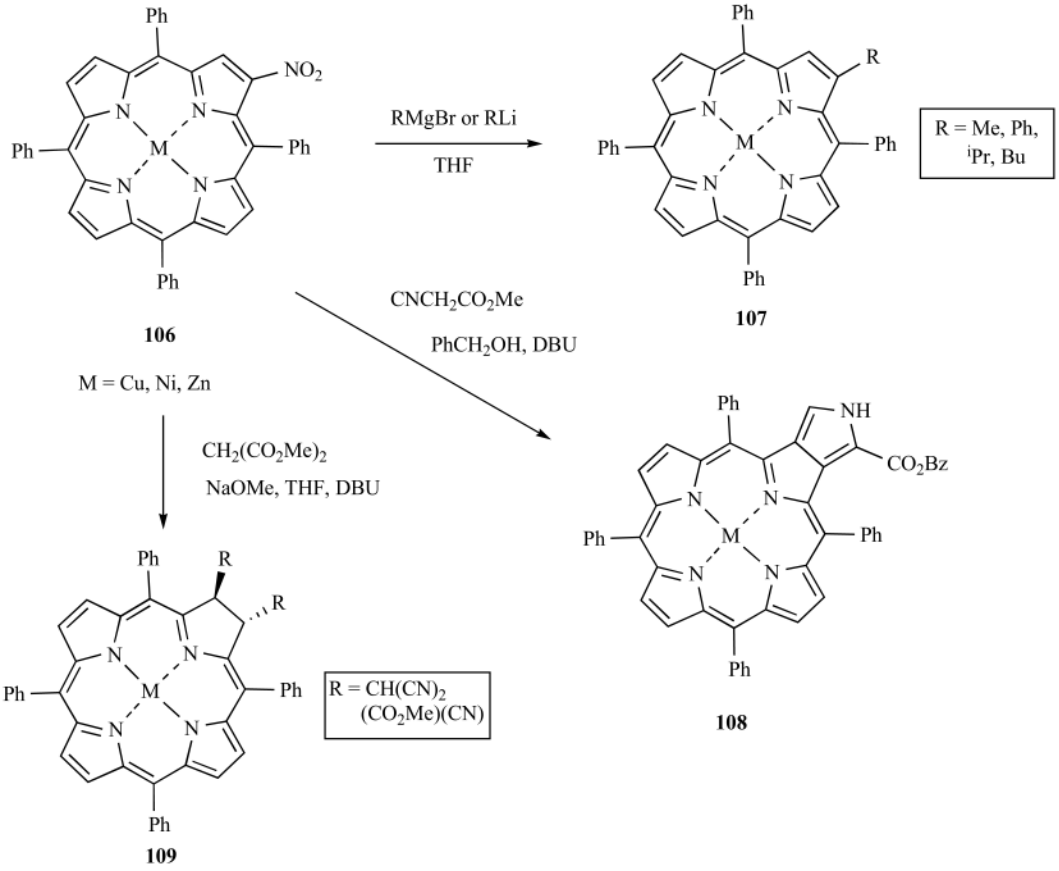
Scheme 35.



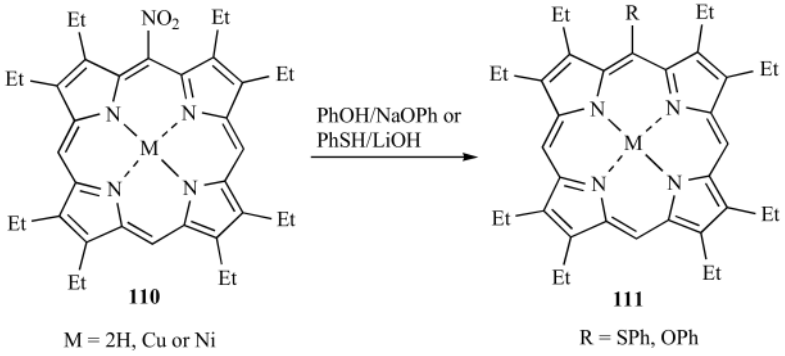
Scheme 36.



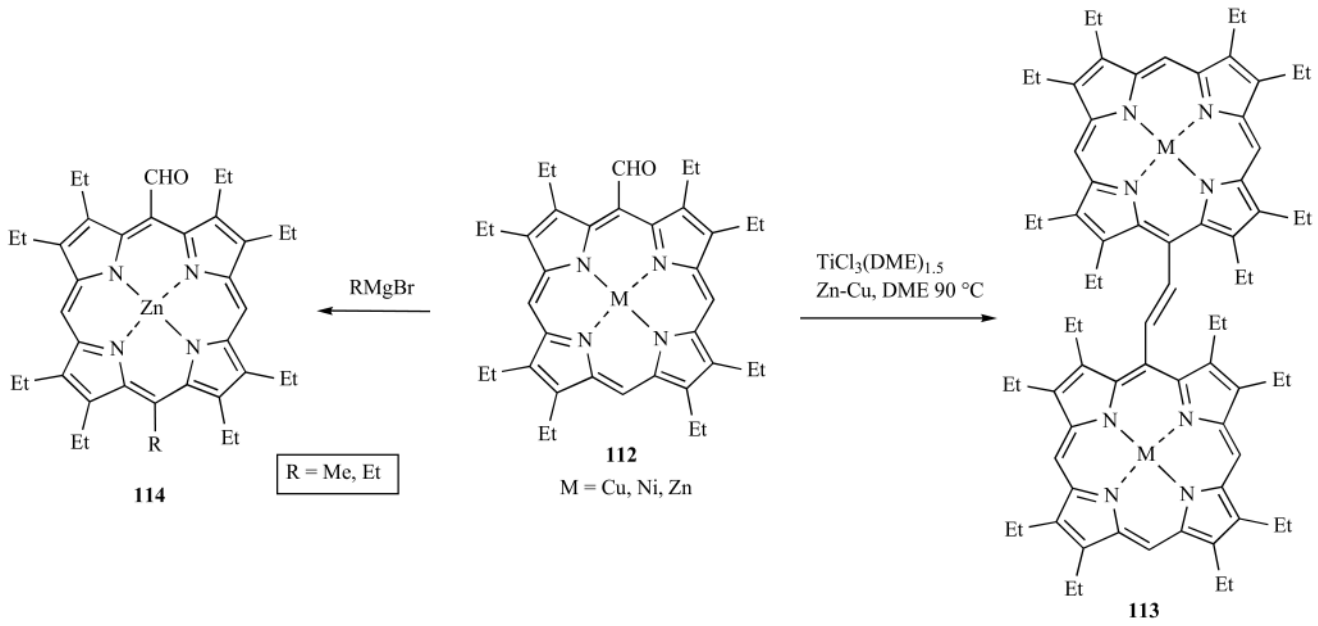
Scheme 37.



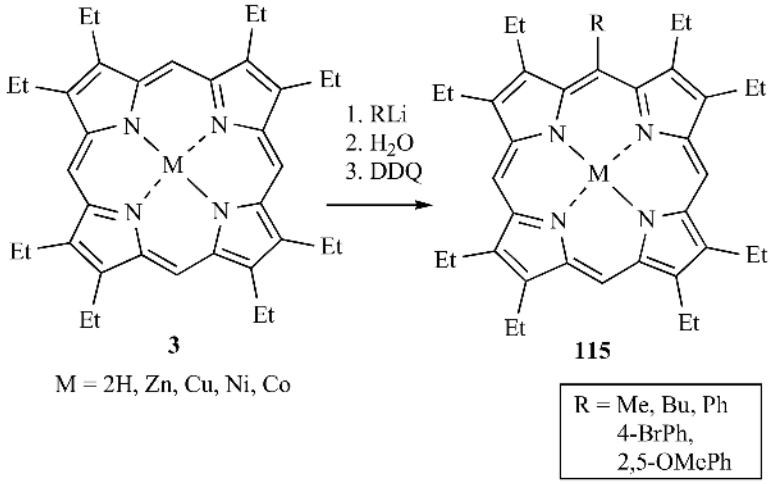
Scheme 38.



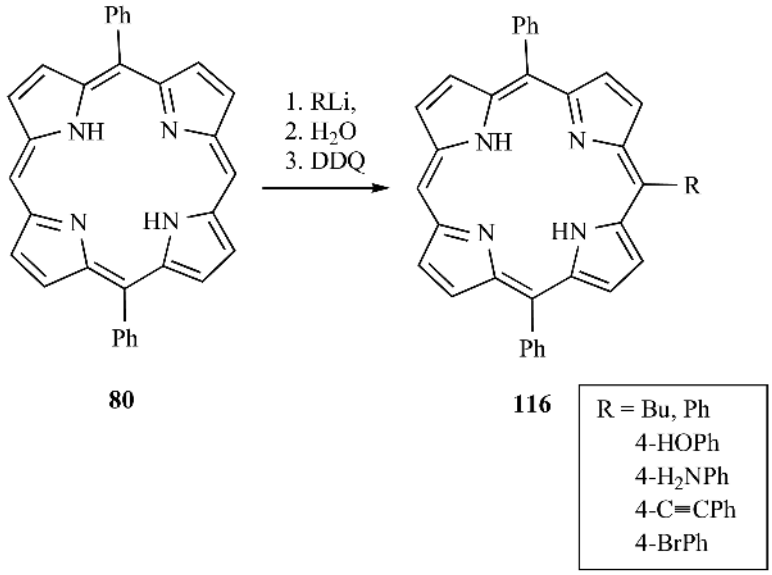
Scheme 39.



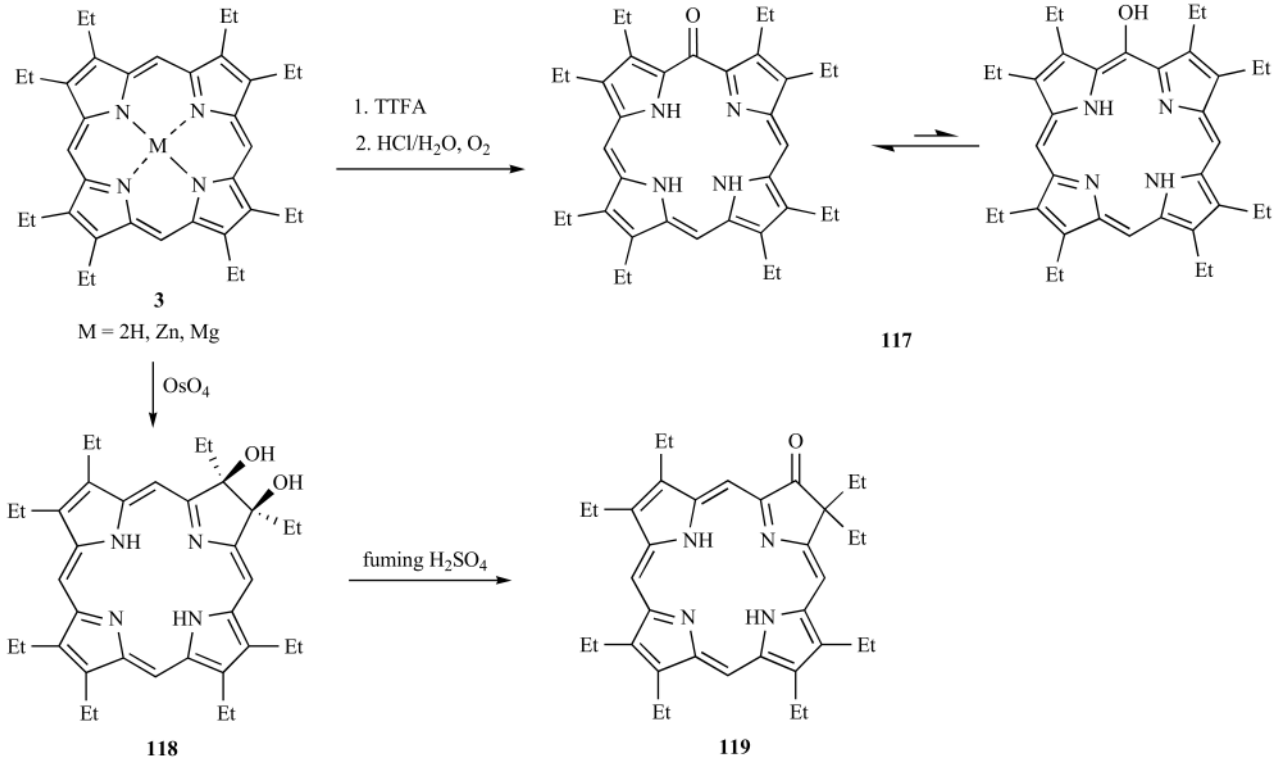
Scheme 40.



Scheme 41.



Scheme 42.



3

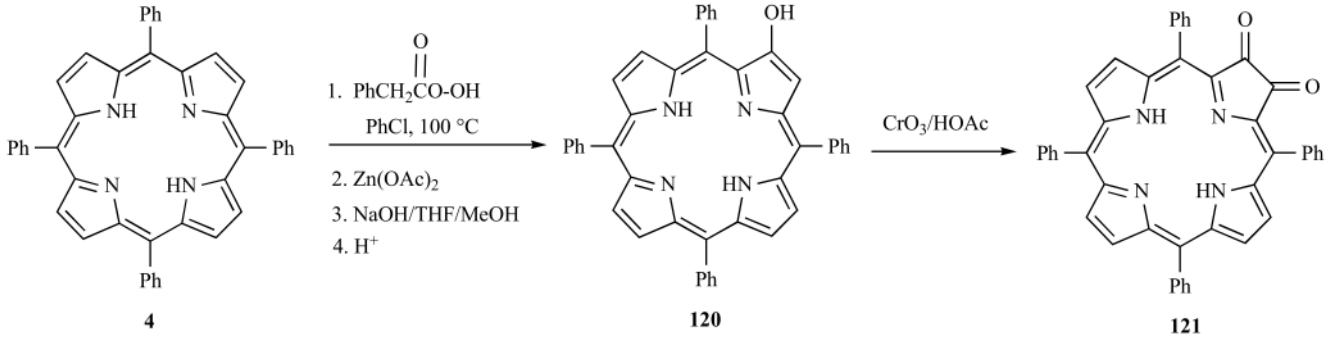
M = 2H, Zn, Mg

117

118

119

Scheme 43.



Scheme 44.