

# **Meso-Tetraarylporphyrins Bearing Nitro or Amino Groups: Synthetic Strategies and Reactivity Profiles**

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**Abstract** Porphyrins bearing nitro and amino substituents have been used as excellent synthons for further functionalization in order to obtain new compounds with adequate features for a wide range of applications. This chapter brings an update on the effort of several research groups to study the synthesis and reactivity features of *meso*-tetraarylporphyrins bearing those functionalities.

**Keywords** Aminoporphyrins · Nitration · Nitroporphyrins · Porphyrins

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## 1 Introduction

The extraordinary development observed in the porphyrin field after the structure elucidation of protoporphyrin IX by Fisher in 1929 [1] and the synthesis of chlorophyll *a* by Woodward in 1960 [2] shows that the scientific community has been having a great interest in the potentiality of these unique compounds. Today, it is accepted that porphyrin derivatives, besides their central role in respiration, photosynthesis, and other vital functions, have a promising future in several fields such as medicine [3], catalysis [4], and electronic materials [5]. Knowing that all those applications are strongly dependent on the structure of the macrocycle, there has been a considerable research directed towards the development of synthetic strategies to functionalize readily available porphyrins, especially *meso*-tetraarylporphyrins. Part of that work has been related to the functionalization of a primary group inserted in *meso*- or in  $\beta$ -pyrrolic positions of *meso*-tetraarylporphyrins. In this chapter, we highlight the most relevant and recent synthetic strategies concerning the functionalization of *meso*-tetraarylporphyrins through nitro or amino groups located at  $\beta$ -pyrrolic positions or in *meso*-phenyl groups. Occasionally, other porphyrin derivatives may also be discussed. The interest in nitro- and aminoporphyrins is mainly due to the very attractive reactivity and versatility of these two functional groups [6, 7].

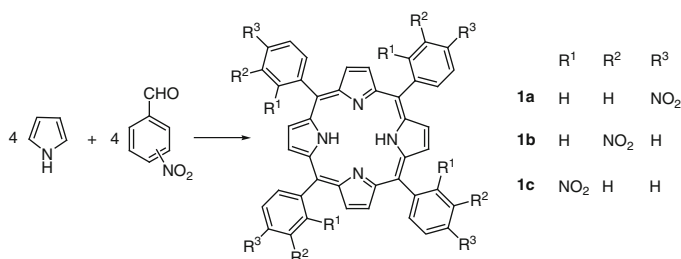
The nitro group can improve the ability of porphyrin systems to act as radiosensitizers [8] and their usefulness in porphyrin functionalization has been demonstrated and is well documented. Nitroporphyrins themselves are widely used as starting materials: they can undergo direct nucleophilic addition and substitution reactions with a wide range of nucleophiles and displacement of the nitro group. The reduction of the nitro group to the amino group is a very useful reaction that extends the porphyrin potentialities for further functionalization via the amino group. In fact, a wide range of porphyrin derivatives with improved properties have been prepared via amide linkage, *N*-alkylation, nucleophilic substitution, diazotization, cycloaddition, palladium-catalyzed reactions, etc.

Besides the clear differences in reactivity of the  $\beta$ - and *meso*-aryl positions, the selective nitration of such positions can be controlled by the choice of the nitrating agent and the metal ion coordinated with the porphyrin macrocycle. The following sections cover useful nitration procedures and the exploitation of the nitro group in further functionalization of the porphyrin macrocycle. In the last topic it is highlighted the recent synthetic strategies concerning the functionalization of *meso*-tetraarylporphyrins through amino groups.

## 2 Synthesis and Reactivity of Nitroporphyrins

### 2.1 Synthesis of *Meso*-(Nitrophenyl)porphyrins

*Meso*-(Nitrophenyl)porphyrins can be obtained by the condensation of pyrrole with nitrobenzaldehydes (Scheme 1) or by nitration of *meso*-tetraarylporphyrins.

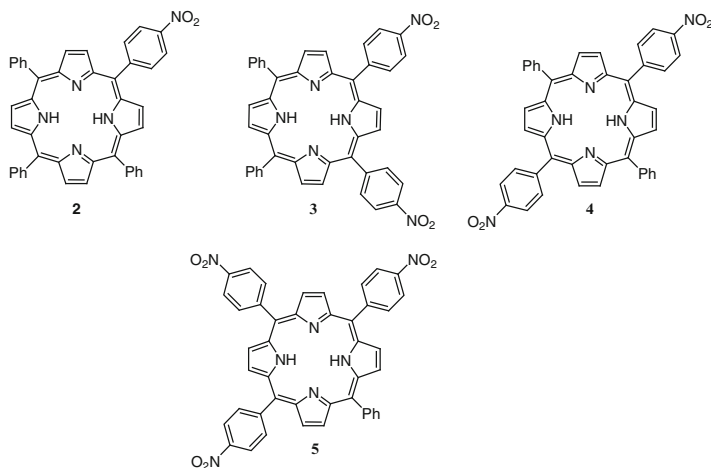


**Scheme 1** Synthesis of *meso*-(nitrophenyl)porphyrins

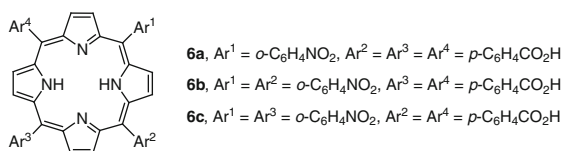
The first strategy was used by Martell and coworkers [9, 10] to synthesize *meso*-tetrakis(4-nitrophenyl)porphyrin (**1a**). This synthesis was based on the Rothmund's landmark conditions [11] to prepare *meso*-substituted porphyrins. The authors referred that the best yield (2.6%) was obtained when equimolar amounts of pyrrole and 4-nitrobenzaldehyde were heated at 120°C in a mixture of pyridine and methanol for 24 h. The synthetic improvements that appeared afterwards to obtain *meso*-tetraarylporphyrins were also considered in the synthesis of porphyrin **1a** and its isomers **1b** and **1c**, respectively, with the nitro groups at *para*, *meta*, or *ortho* positions of the phenyl substituents [12, 13]. Porphyrin **1a**, for instance, can be obtained in 19–22% by refluxing a solution of pyrrole and 4-nitrobenzaldehyde in propanoic acid containing acetic anhydride [14]. The same porphyrin can be obtained in 28% yield if the cyclocondensation is mediated by microwave irradiation in the presence of small amounts of propanoic acid [15]. Under the same microwave conditions, the cyclocondensation of equimolar amounts of pyrrole and 2-nitrobenzaldehyde afforded porphyrin **1c** in 25% after ca. 5 min of reaction [15]. Under classical heating, porphyrin **1c**, frequently used in the development of synthetic models for oxygen-binding hemoproteins, was obtained in 13% yield after refluxing pyrrole and 2-nitrobenzaldehyde in acetic acid for 20 min [16]. Much poor yields (4%) were reported for porphyrin **1b** when 3-nitrobenzaldehyde and pyrrole were heated at reflux in propanoic acid containing acetic anhydride [14].

The cyclocondensation of pyrrole with a mixture of two aldehydes gives access to a wide variety of multifunctional porphyrins. Although not being considered an efficient and elegant strategy, due to the low yields (<5%) and the purification procedures required to separate the products mixture, this mixed-aldehyde approach is expeditious and is being largely exploited for the preparation of porphyrins bearing one or more *meso*-nitrophenyl groups. For instance, Tsuchida and coworkers [17–19] used that strategy for the preparation of the mono-(4-nitrophenyl)porphyrin **2** (Fig. 1). Using a 3:1 ratio of benzaldehyde and 4-nitrobenzaldehyde the desired porphyrin **2** was obtained in 2.7% yield; the related bis- (**3** and **4**) and tris(4-nitrophenyl) (**5**) substituted porphyrins were also isolated.

The same strategy was considered by Collman [20] to obtain the mono-(2-nitrophenyl) analogue and by Martell and coworkers [21] to obtain unsymmetrical 3-nitrophenyl substituted porphyrins. Little has also reported the synthesis of unsymmetrical porphyrins containing a 2,6-dinitrophenyl group, or a hydroxynitrophenyl group, as potential intermediates in the synthesis of difunctional



**Fig. 1** Structures of *meso*-(4-nitrophenyl)porphyrins



**Fig. 2** Unsymmetrical porphyrins bearing *o*-nitrophenyl and *p*-carboxyphenyl groups

“tailed-porphyrins” [22]. The mixed-aldehyde approach was also followed to prepare unsymmetrical porphyrins bearing *o*-nitrophenyl and *p*-carboxyphenyl substituents (**6a–c**, Fig. 2) [23]. The authors were able to optimize the benzaldehyde derivatives molar ratio in order to obtain the desired porphyrins in high yields. Other examples of unsymmetrical porphyrins prepared by this approach can be found in a review by Lindsey [12].

As already mentioned, the direct nitration of *meso*-tetraarylporphyrins is another strategy to obtain porphyrins, mainly unsymmetrical ones, containing nitroaryl groups. This approach was considered for the first time by Kruper’s group in the nitration of *meso*-tetraarylporphyrins, namely TPP [24, 25]. The authors used an excess of red or yellow fuming nitric acid in different solvents (CHCl<sub>3</sub>, CH<sub>2</sub>Cl<sub>2</sub>, and AcOH) and referred higher yields for the mono-nitro derivative (ca 56%) in CHCl<sub>3</sub>; under these conditions the dinitro derivatives **3** and **4** (as a mixture of 2–3:1, respectively) were also isolated but the yields rarely exceed 5%. Better yields for the dinitro derivatives (28%) were obtained under conditions forcing the conversion of the mono-substituted derivative (use of 29 equivalents of red fuming nitric acid in CHCl<sub>3</sub>). The use of acetic acid as solvent allowed to obtain the tris(4-nitrophenyl) porphyrin **5** in 10% yield. The *para* regioselectivity was also observed in the nitration of porphyrins bearing 3-methyl- or 3-methoxyphenyl substituents.

Meng and coworkers [8] also studied the nitration of TPP but under slightly different conditions relatively to those reported by Kruper. The reactions were carried

out by using a mixture of nitric acid and acetic acid and the degree of nitration was controlled by the reaction time. The 5-(4-nitrophenyl)-10,15,20-triphenylporphyrin **2** was obtained in 74% yield after 1 h of reaction. Significant improvements were also reported for the dinitro derivatives **3** and **4** (70% yield after 5 h of reaction) and for the trinitro derivative **5** (30% yield after 2 days of reaction). Attempts to obtain the tetrakis(4-nitrophenyl)porphyrin **1a** via nitration of TPP failed and this was due to the degradation of the macrocycle during the time required for this lengthy reaction. Porphyrin **1a** was obtained as a by-product (2%) during the tri-nitration conditions. The same authors studied the nitration of unsymmetrical porphyrins bearing phenyl and pyridyl groups. The nitration of these porphyrins requires higher reaction times than those used for TPP due to the protonation of the pyridyl groups; in certain cases the use of a mixture of acetic and sulfuric acids was required.

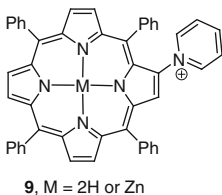
The selective nitration of TPP and other *meso*-tetraarylporphyrins at two neighboring aryl rings was described by Ostrowski and Lopuszynska [26]. Following a new protocol, which is based on the use of fuming yellow HNO<sub>3</sub> in CHCl<sub>3</sub>, accompanied by a careful control of the reaction temperature, nitration of TPP afforded compound **3** in 42% yield. *meso*-Tetraarylporphyrins bearing 3-chlorophenyl, 3-methoxyphenyl or 3-methylphenyl groups afforded the corresponding 5,10-bis(4-nitroaryl)porphyrins in 30%, 37%, and 83% yields, respectively. The same group reported that under exhaustive nitration conditions tri-substituted derivatives can also be obtained in reasonable yields [27]. For instance, nitration of TPP afforded derivative **5** in 35% yield.

Smith and coworkers reported the selective nitration of the phenyl groups of TPP with sodium nitrite and trifluoroacetic acid [28]. The authors found that the degree of nitration can be efficiently controlled just by varying the amount of NaNO<sub>2</sub>/TFA used and the reaction time. Compound **2** was obtained in excellent yield (80–90%) after 3 min of reaction at room temperature in the presence of 1.8 equivalents of NaNO<sub>2</sub> in TFA. The two isomeric bis(4-nitrophenyl)porphyrins **3** and **4** were obtained after 1.5 min of reaction in the presence of 8.1 equivalents of NaNO<sub>2</sub> in a total yield of 63%, while the tris(4-nitrophenyl)porphyrin **5** required 1 h of reaction and 36.7 equivalents of NaNO<sub>2</sub> to be isolated in 60% yield.

The nitration of the *meso*-phenyl groups of TPP with NO<sub>2</sub>BF<sub>4</sub> has been also reported [29]. The authors found that the mode of addition is the key step for the success of this methodology. Mono-, bis-, and tris(4-nitrophenyl) derivatives were obtained in excellent yields (>90%) by dropwise addition of a sulfolane solution of 1.0, 2.9, or 4.6 equivalents, respectively, of that nitrating agent to a dichloromethane solution of TPP at room temperature. The authors have also reported the selectivity of the dinitration procedure for the 5,10-bis(4-nitrophenyl) isomer.

## 2.2 Synthesis of $\beta$ -Nitro-Meso-Tetraarylporphyrins

Efficient nitrating procedures, based on electrophilic or radical conditions, are now well established for giving access to  $\beta$ -nitroporphyrins in excellent yields [30]. Most of the protocols are based on the use of metalloporphyrins. In fact, attempts to nitrate

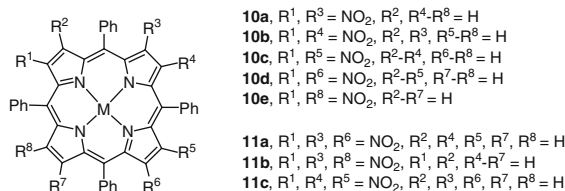


**Scheme 2** Synthesis of  $\beta$ -nitro-*meso*-tetraarylporphyrins **8** and pyridinium salt **9**

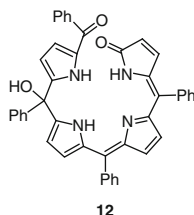
the free-base TPP using a mixture of nitric acid and sulfuric acid afforded only 2-nitro-*meso*-tetraphenylporphyrin **8a** (M = 2H, Scheme 2) in low yield; this is due to the conversion of the starting porphyrin into the unreactive dication [31, 32]. The nitration of TPP (**7a**, M = 2H) under essentially neutral conditions was considered by Jackson and coworkers. Using nitronium tetrafluoroborate in a mixture of pyridine/chloroform at 140°C, the  $\beta$ -nitroporphyrin **8a** (M = 2H) was isolated in 15% yield being accompanied by the pyridinium salt **9** (M = 2H) (18% yield). Attempted nitration of the zinc complex of TPP with nitronium tetrafluoroborate in pyridine afforded the pyridinium derivative **9** (M = Zn) in 80% yield [32].

In contrast with the previous results, nitration of the copper, nickel, and palladium complexes of TPP with  $\text{N}_2\text{O}_4$  occurs selectively at the  $\beta$ -pyrrolic positions, affording the corresponding complexes **8a** ( $\text{M} = \text{Cu}, \text{Ni}$  or  $\text{Pd}$ ) in quantitative yields [33]. The extension of this protocol to *meso*-tetraarylporphyrins **7b** and **7c**, ( $\text{M} = \text{Cu}$ ), afforded the corresponding derivatives **8b** and **8c** in high yields (>90%), thus confirming the generality of the process. The presence of extra substituents at the  $\beta$ -pyrrolic position does not affect the site of nitration. For instance, the nitration of the copper complex of  $\beta$ -nitroporphyrin afforded an isomeric mixture of  $\beta, \beta'$ -disubstituted derivatives **10a–e** (Fig. 3) in 85% total yield [34].

A procedure giving access to  $\beta$ -dinitro- and  $\beta$ -trinitro-*meso*-tetraphenylporphyrins using the controlled addition of fuming nitric acid to CuTPP was also reported [35]. The 2,12-dinitro- and 2,13-dinitro derivatives were obtained by the controlled addition of 0.7 mL of  $\text{HNO}_3$  to 100 mg of CuTPP in  $\text{CHCl}_3$  over a period of 1.2 min, while the 2,7-dinitro-, 2,8-dinitro-, and 2,18-dinitro derivatives were obtained by the addition of 1.0 mL of  $\text{HNO}_3$  during 1.0 min to the same amount of porphyrin. Yields of 20% for the pure products were reported. The trinitroporphyrins **11a–c** (2,7,13-, 2,7,18-, and 2,8,12-trinitro) were obtained



**Fig. 3** Structures of  $\beta$ -nitro-*meso*-tetraarylporphyrins

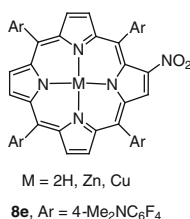


**Fig. 4** Structure of the bilinone obtained by nitration of MgTPP or ZnTPP by  $\text{N}_2\text{O}_4$

by increasing the amount of  $\text{HNO}_3$  up to 2.0 mL and maintaining the addition during the period of 1 min. The corresponding free-bases were obtained by demetallation with sulfuric acid. Electrochemical studies revealed that successive insertion of nitro groups at the  $\beta$ -positions shifts the one-electron ring oxidations anodically while the ring reduction occurs at a less cathodic potential relatively to the unsubstituted porphyrin free-bases.

Nitration of porphyrins coordinated with less electronegative metal ions, such as magnesium(II), zinc(II), chloroiron(III) and cobalt(II), and the  $\beta$ -nitro derivatives are accompanied by products resulting from reactions at the *meso*-position. In fact, the nitration of magnesium and zinc chelates of TPP by  $\text{N}_2\text{O}_4$  afforded the corresponding  $\beta$ -nitro derivatives in low yields (ca. 25%) giving mainly the ring-opened bilinone **12** (Fig. 4) [36] and other non-porphyrin products resulting from reactions at the *meso*-positions. This metal ion dependent selectivity was justified by considering that the metalloporphyrin  $\pi$ -cation radicals obtained via oxidation by  $\text{NO}_2\cdot$  have different electron spin distributions ( $a_{1u}$  or  $a_{2u}$ ) and, as a result, being the position of attack by further  $\text{NO}_2\cdot$  dependent on its spin density. The preferential attack at the *meso*-positions was also reported when the zinc complex of TPP was treated with thallium(III) nitrate or cerium(IV) ammonium nitrate followed by acid treatment [37]. Under these conditions the  $\beta$ -nitro derivative **8a** ( $M = 2\text{H}$ ) was isolated in low yields (15–28%) accompanied by porphodimethenes and the ring-opened bilinone **12**.

Callot and coworkers reported an excellent protocol to nitrate the copper complex of TPP based on the use of copper(I) nitrate in a mixture of chloroform, acetic acid, and acetic anhydride [38]. Using that nitrating mixture, Cavaleiro and coworkers prepared **8a** ( $M = \text{Cu}$ ) in 86% yield directly from TPP without the previous preparation of the copper complex [39]. The extension of this nitrating procedure

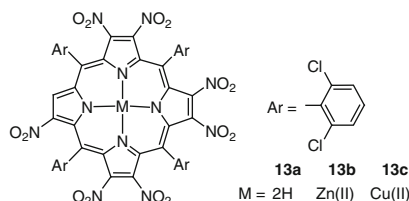


**Fig. 5** Structure of porphyrin **8e**

to *meso*-tetrakis(pentafluorophenyl)porphyrin (**7d**, M = 2H) has provided access to the mono-nitroporphyrin **8d** (M = 2H) and to a mixture of dinitro and trinitro isomers in quantitative yield [40]. Krishnan and coworkers also used copper(I) nitrate in chloroform to obtain the donor–acceptor porphyrins **8e** (Fig. 5) for studies concerning quadratic nonlinear optics [41]. Callot and coworkers reported a mild procedure for the nitration of the nickel or copper complexes of *meso*-tetraarylporphyrins using lithium nitrate in CHCl<sub>3</sub>/Ac<sub>2</sub>O/AcOH, for 1.5 h at 40–45°C, affording the 2-nitro derivatives in 90–95% yield (aryl = phenyl, *p*-tolyl, and 3,5-di-*tert*-butylphenyl) [42].

The selective  $\beta$ -mononitration of *meso*-tetraphenylporphyrin complexes can also be achieved using aqueous HNO<sub>3</sub>. Ostrowski et al. [43] found that several TPP complexes (**7a**, M = Zn, Cu, Ni, and Co) can be nitrated with adequate concentrations of HNO<sub>3</sub> (ca. 25%) to afford the corresponding complexes **8a** in very good yields (77% for M = Cu and 81% for M = Ni). A mixture of dinitro compounds (2–20%) is also detected in all cases. An extension of this work to other *meso*-tetraarylporphyrins (Ar = 3-NO<sub>2</sub>C<sub>6</sub>H<sub>4</sub>, 3-CH<sub>3</sub>C<sub>6</sub>H<sub>4</sub>, 3-ClC<sub>6</sub>H<sub>4</sub>, 2,6-Cl<sub>2</sub>C<sub>6</sub>H<sub>3</sub>, C<sub>6</sub>F<sub>5</sub>) afforded the corresponding mono- $\beta$ -nitrated products in yields ranging from 74% to 93% [44]. These results show that the type of *meso*-aryl substituent does not change the site of nitration; it only affects the reaction yield. In fact, the systems less prone to electrophilic substitution require slightly drastic conditions (higher concentration of nitric acid and longer reaction times) to ensure high yields. Again, some dinitro compounds were also formed.

The nitration of the free-base *meso*-tetrakis(2,6-dichlorophenyl)porphyrin with red fuming nitric acid, at room temperature, afforded a 1:9 mixture of  $\beta$ -pentanitro- and  $\beta$ -hexanitroporphyrins in 70% yield [45]. Nitration of *meso*-tetrakis(pentafluorophenyl)porphyrin under similar conditions led to a mixture of regioisomers containing one nitro group on each pyrrole ring (55% yield). All attempts to obtain *meso*-tetrakis(2,6-dichlorophenyl)porphyrin substituted by more than six  $\beta$ -nitro groups or *meso*-tetrakis(pentafluorophenyl)porphyrin substituted by more than four  $\beta$ -nitro groups by using more HNO<sub>3</sub>, higher temperatures or longer reaction times in reactions between HNO<sub>3</sub> and those porphyrins or their Zn(II) or Fe(III) complexes were unsuccessful [45]. Later, it was reported that the nitration of the zinc complex of *meso*-tetrakis(2,6-dichlorophenyl)porphyrin with red fuming nitric acid in the presence of nitromethane, acetic anhydride, and montmorillonite K-10, for 2 h at room temperature, affords the  $\beta$ -heptanitro derivative **13b** (Fig. 6) in 50%



**Fig. 6**  $\beta$ -Heptanitroporphyrin obtained by nitration of *meso*-tetrakis(2,6-dichlorophenyl)porphyrin with montmorillonite K10- $\text{HNO}_3$  under microwave irradiation

yield [46]. An expeditious  $\beta$ -polynitration of *meso*-tetrakis(2,6-dichlorophenyl)porphyrin with montmorillonite K10- $\text{HNO}_3$  using microwave irradiation has been described [47]. The microwave irradiation of that porphyrin with montmorillonite K10- $\text{HNO}_3$  for 1.5 min selectively gave  $\beta$ -heptanitro derivative **13a** in 72% yield. Similarly, the microwave irradiation of the Zn(II) and Cu(II) complexes with K10- $\text{HNO}_3$  gave the  $\beta$ -heptanitro derivatives **13b** and **13c** in 81% and 75% yield, respectively.

### 3 Functionalization of Porphyrins via Nitro Groups

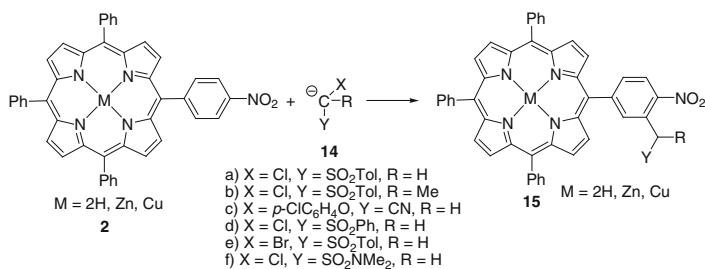
#### 3.1 Functionalization of Meso-(Nitrophenyl)porphyrins

The nucleophilic aromatic substitution methodology has been used to functionalize *meso*-(nitrophenyl)porphyrins. Ostrowski and coworkers [48], for instance, reported that the copper and the zinc complexes of the *meso*-(4-nitrophenyl)porphyrin **2** react with carbanions **14** affording the corresponding products **15** in yields ranging from 50% to 67% (Scheme 3). These vicarious nucleophilic substitutions take place selectively at the *ortho* position to  $\text{NO}_2$  group; bulky carbanions of lower nucleophilicity do not react. Further studies showed that these reactions can also be performed using free-base porphyrins, with improved yields, if low temperatures are considered [49].

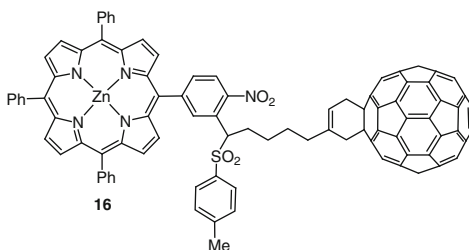
The potentiality of *meso*-(nitrophenyl)porphyrins for further functionalization was shown in the synthesis of the porphyrin-fullerene dyad **16** (Fig. 7), a new artificial photosynthetic model [50].

Ostrowski and coworkers also explored the activation of the nitro group towards the attack by nucleophiles to introduce the amino functionality in *meso*-tetraarylporphyrins bearing one or two nitrophenyl groups. For instance, the amino-functionalized porphyrins **17** (Fig. 8) were obtained from the reaction of the zinc, copper, and nickel complexes of porphyrin **2** with 1,1,1-trimethylhydrazinium iodide in the presence of KOH in DMSO [51, 52].

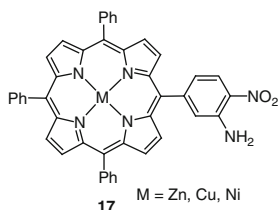
The reaction of 5-(4-nitrophenyl)-10,15,20-triphenylporphyrin (**2**) and the corresponding zinc and copper complexes with other nucleophiles was also studied [53]. The authors reported that in the reaction of **2** with NaCN the substitution



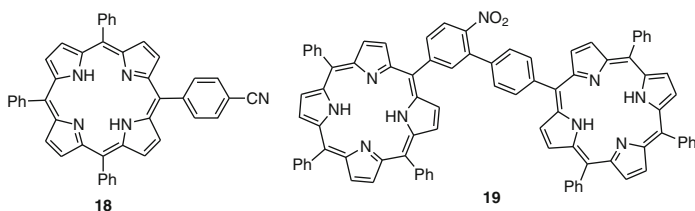
**Scheme 3** Vicarious nucleophilic substitution in *meso*-(4-nitrophenyl)porphyrins



**Fig. 7** Structure of a porphyrin-fullerene dyad



**Fig. 8** A porphyrin functionalized with a *meso*-(3-amino-4-nitrophenyl) group



**Fig. 9** Structures of porphyrins **18** and **19**

of the nitro group occurs and porphyrin **18** (Fig. 9) is obtained in reasonable yield. On the other hand, the reaction of **2** with phenoxides affords the diporphyrin derivative **19**, while under the same conditions, but using the metal complexes, the nitro group is reduced to the amino group. A similar reduction occurs in the reaction with thiolates [53].

### 3.2 Functionalization of $\beta$ -Nitroporphyrins

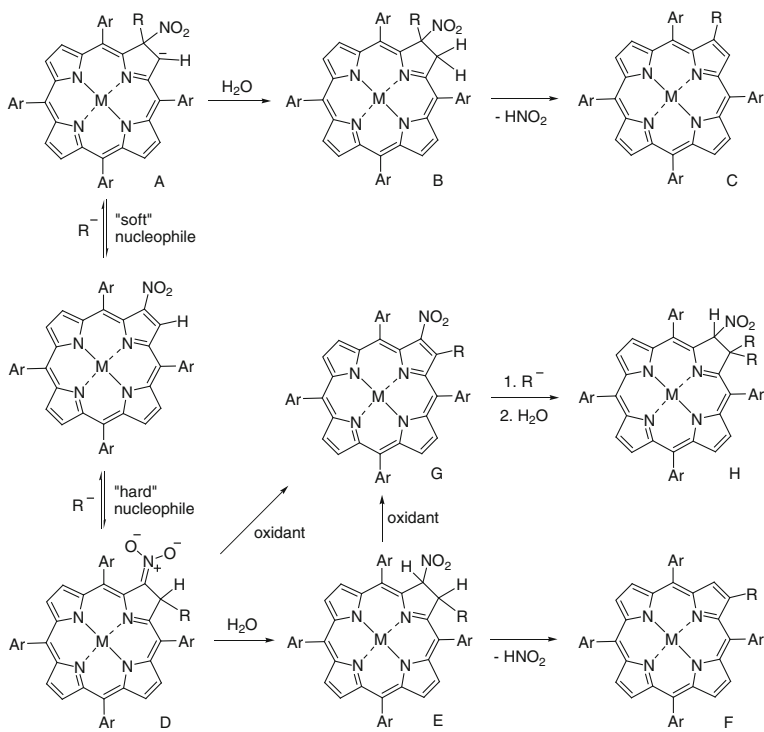
As already mentioned, nitroporphyrins are excellent starting materials to prepare new derivatives with improved features for specific applications. In fact, a nitro group is particularly useful to activate the pyrrole unit where it is inserted towards the attack by nucleophiles, dienes or 1,3-dipoles and also to direct electrophilic substitutions to the antipodal pyrrole ring. The alkene-type reactivity of  $\beta$ -nitro-*meso*-tetraarylporphyrins can be justified by the preferential localization of the double bond adjacent to the electron-withdrawing group; that double bond is not involved in the major aromatic delocalization pathway.

The possibility of using  $\beta$ -nitro-*meso*-tetraarylporphyrins for further functionalization at the  $\beta$ -pyrrolic positions was firstly considered by Crossley and coworkers [54, 55] who found that  $\beta$ -nitro-*meso*-tetraphenylporphyrin (**8a**, M = 2H) reacts with benzenethiolate and ethanethiolate to afford the corresponding  $\beta$ -thioethers. This pioneering work was followed by other publications exploring the reaction of  $\beta$ -nitro-*meso*-tetraarylporphyrins with nucleophiles to insert a variety of substituents at the  $\beta$ -pyrrolic positions. This topic has been comprehensively reviewed by Jaquinod [30].

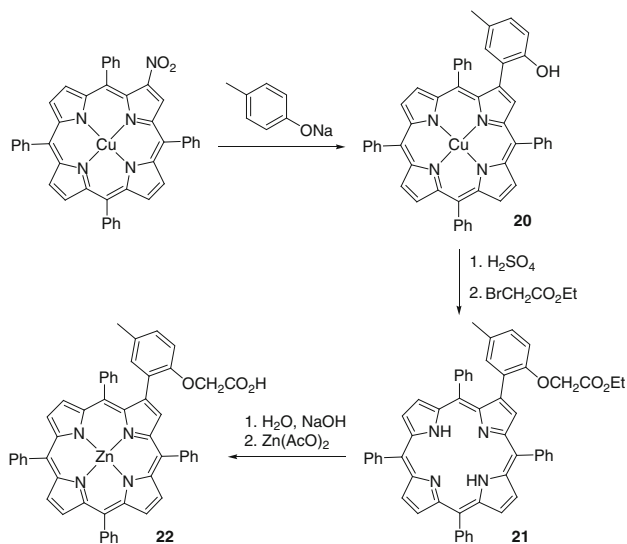
The attack by nucleophiles to a  $\beta$ -nitro-*meso*-tetraarylporphyrin can occur either at the carbon atom containing the nitro substituent (ipso-attack) or at the adjacent  $\beta$ -position ( $\alpha$ -attack) (Scheme 4). In fact, based on deuterium labeling experiments, Crossley and coworkers found that “soft” nucleophiles such as thiolates and the anion of benzaldoxime lead to products of type **C**, resulting from an ipso-attack [54, 56]. They also found that, in general, “hard” nucleophiles such as oxyanions [57], hydride [58], acylamide ions [59], Grignard and organolithium reagents [60] attack the  $\beta$ -pyrrolic position next to the nitro group. The outcome of these reactions is dependent on the nucleophile, coordinated metal ion, and temperature.

The direct displacement of the nitro group was also observed when phenoxide ion and other phenols were used in reactions with the free-base 2-NO<sub>2</sub>TPP and with the corresponding Cu(II) and Ni(II) complexes [61, 62]. It was found that the type of product (2-aryloxy- or 2-hydroxyaryl-) can be controlled by the choice of solvent. This methodology was recently explored to build the ditopic chemosensor **22** (Scheme 5) [63]. This compound interacts selectively with histamine when compared with L-histidine and nicotine. Following the same protocol, Chen et al. [64] found that **8a** and its Ni(II), Cu(II), and Zn(II) complexes react with 2-naphthoxide in protic solvents (2-naphthol, diglycol, and diglycol monomethyl ether), at 150°C, to afford only the C-coupling products **23** with yields varying from 50% to 81% (Scheme 6). In aprotic solvents (DMF or DMSO), at 150°C, the O-coupling products **24** are also obtained but at room temperature only compounds **23** are formed.

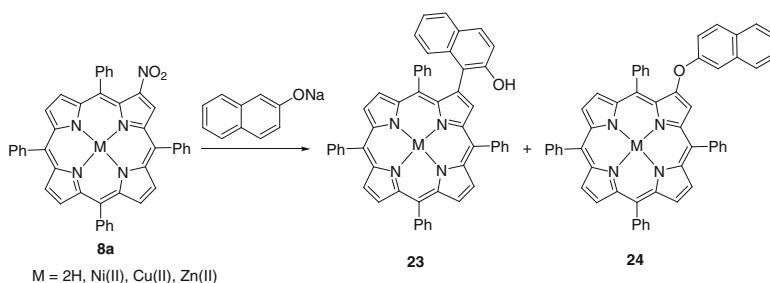
Following a synthetic methodology similar to the one developed by Crossley, Pan and coworkers [65] reported the synthesis of the  $\beta$ -(2,5-dihydroxyphenyl) porphyrins **25** (Scheme 7). The preliminary biological activity studies showed that



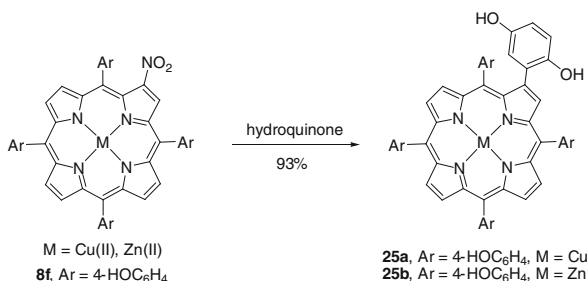
**Scheme 4** Representative reactivity of  $\beta$ -nitro-*meso*-tetraarylporphyrins with nucleophiles



**Scheme 5** Reaction of 2- $NO_2$ TPP with phenoxides



**Scheme 6** Reaction of 2-NO<sub>2</sub>TPP with 2-naphthoxide



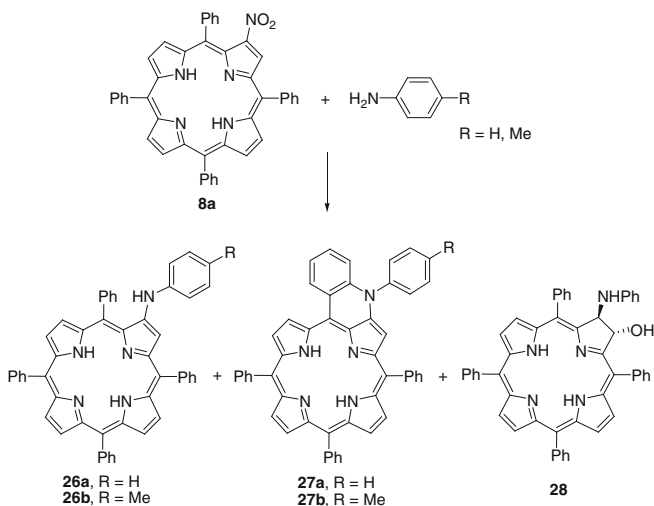
**Scheme 7** Reaction of  $\beta$ -nitroporphyrins with hydroquinone

the zinc(II) derivative has photo-toxicity on human chronic myelogenous leukemia cell and is able to cleave supercoiled DNA (pBR 322 DNA) while the copper(II) complex has lower biological activity.

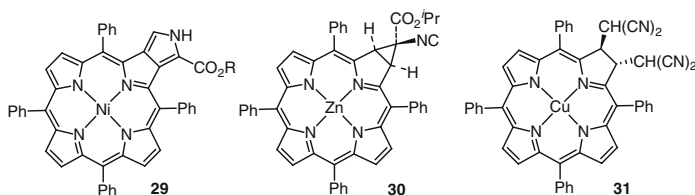
The use of anilines as nucleophiles in the reaction with  $\beta$ -nitro-*meso*-tetraarylporphyrins was considered by Cavaleiro and coworkers [66]. For instance, the reaction of **8a** with aniline, at reflux temperature, gives the 2-(phenylamino) porphyrin **26a** as the major product (53% yield), but the novel *N*-phenylquinolino [2,3,4-*at*]porphyrin **27a** (6% yield) and the chlorin **28** are also formed (Scheme 8). When this reaction is performed in refluxing *o*-dichlorobenzene, porphyrin **27a** is the main product (26% yield). This solvent was also adequate to obtain derivative **27b** when *p*-toluidine was selected as the nucleophile. The oxidative cyclization of 2-arylamino porphyrins **26** to the corresponding *N*-arylquinolino[2,3,4-*at*] porphyrins **27** can be done in excellent yields in nitrobenzene. This synthetic strategy is not efficient with anilines with electron-withdrawing substituents.

Smith and coworkers explored the nitroalkene character of  $\beta$ -nitro-*meso*-tetraarylporphyrins to prepare  $\beta$ -fused pyrroloporphyrins **29** (Fig. 10) via the Barton–Zard condensation of the nickel complex of 2-NO<sub>2</sub>TPP with  $\alpha$ -isocyanoacetic esters in the presence of DBU [67]. Interestingly, when the zinc complex of 2-NO<sub>2</sub>TPP was used, the cyclopropyl-annulated chlorin **30** was obtained.

Based on the conjugate addition of active methylene compounds, such as malonates or malononitrile, to  $\beta$ -nitro-*meso*-tetraarylporphyrins in the presence of a



**Scheme 8** Reaction of 2-NO<sub>2</sub>TPP with anilines

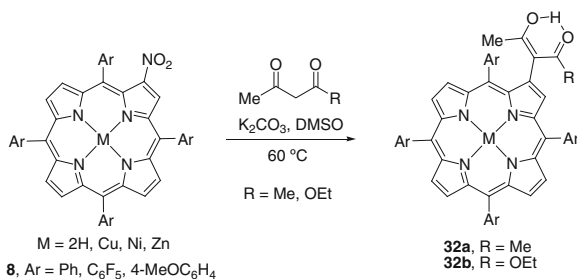


**Fig. 10** Structures of porphyrins 29–31

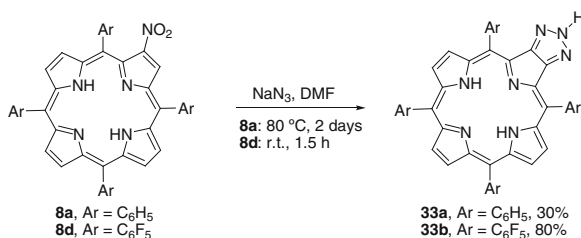
base, the same group was able to prepare a wide range of reduced porphyrins such as *trans*-nitrochlorins, cyclopropachlorins, or disubstituted *trans*-chlorins such as **31** [68, 69]. The product distribution can be controlled by the size of the carbanion, reaction time, and/or temperature as well as the use of free-bases or chelates.

Cavaleiro and coworkers reported that 1,3-diketones and 3-ketoesters such as acetylacetone and ethyl acetoacetate can act as efficient nucleophiles in Michael additions with  $\beta$ -nitro-*meso*-tetraarylporphyrins affording the corresponding derivatives **32** as the only products (Scheme 9) [70]. The central metal ion or the *meso*-aryl-substituents do not affect significantly the reactivity of the system, nor in terms of yields (72–88%) nor in terms of reaction times (40–50 min). The 1,3-dicarbonyl derivatives **32a,b** showed to be excellent C3 synthons for the synthesis of porphyrins bearing an heteroaromatic group at the  $\beta$ -position [70].

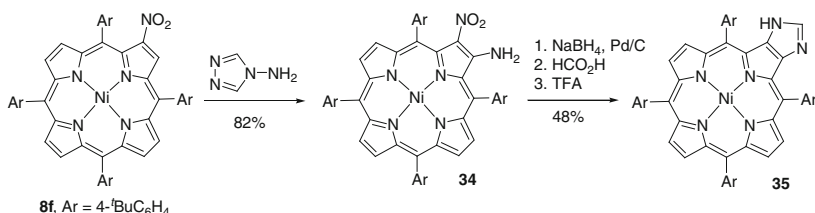
Cavaleiro and coworkers also considered the use of  $\beta$ -nitro-*meso*-tetraarylporphyrins as precursors to the novel [1,2,3]triazolo[4,5-*b*]porphyrins **33** (Scheme 10) [71]. Knowing that *N*-unsubstituted 1*H*-1,2,3-triazoles can be obtained from the reaction of sodium azide with alkenes bearing strongly electron-withdrawing, it was anticipated that the reaction  $\beta$ -nitroporphyrins with sodium azide could afford



**Scheme 9** Reaction of  $\beta$ -nitro-*meso*-tetraarylporphyrins with 1,3-diketones and 3-ketoesters



**Scheme 10** Synthesis of [1,2,3]triazolo[4,5-*b*]porphyrins

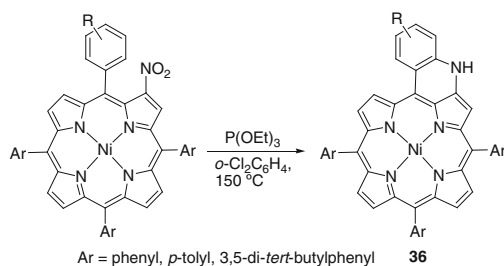


**Scheme 11** Synthesis of imidazo[4,5-*b*]porphyrins

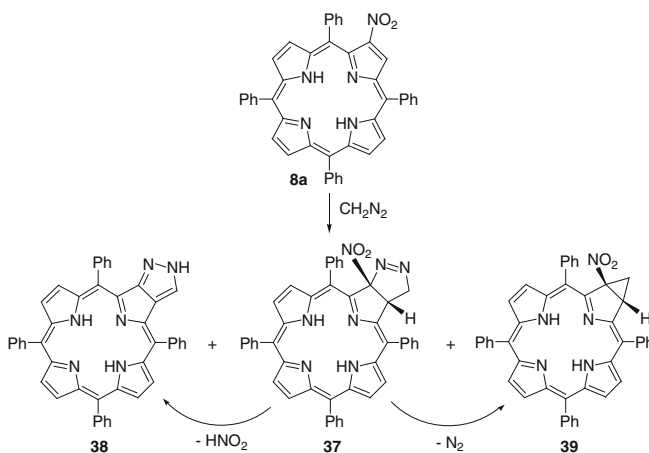
such type of compounds. As expected, the best yield (80%) was obtained with the porphyrin bearing electron-withdrawing groups at the *meso* positions.

A  $\beta$ -nitro-*meso*-tetraarylporphyrin was also used by Richeter et al. [72] to synthesize a porphyrin with an additional imidazole ring fused to a  $\beta,\beta'$ -pyrrolic bond (Scheme 11). The powerful amination reagent 4-amino-4*H*-1,2,4-triazole described by Callot and coworkers [73] was used to prepare intermediate **34** which, after reduction of the nitro group followed by reaction with formic acid and cyclization with trifluoroacetic acid, afforded the imidazo[4,5-*b*]porphyrin **35**. The same authors found that compound **35** can be obtained in better yield (70%) if trimethyl orthoformate is used as an alternative to formic acid [74].

Treatment of 2-nitro-*meso*-tetraarylporphyrins with excess triethyl phosphite at 155°C in 1,2-dichlorobenzene affords the corresponding cyclic enamines **36** in 70–75% yield (Scheme 12) [42].



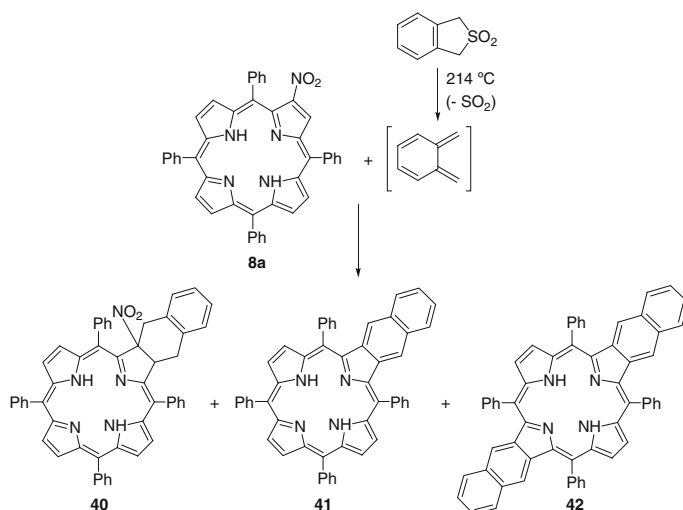
**Scheme 12** Reaction of 2-nitro-*meso*-tetraarylporphyrins with triethyl phosphite



**Scheme 13** Reaction of 2-NO<sub>2</sub>TPP with diazomethane

Cavaleiro and coworkers demonstrated that *meso*-tetraarylporphyrins can participate as dienophiles in Diels–Alder reactions affording adducts with important biological significance [75]. The same group found that they also participate as dipolarophiles in 1,3-dipolar cycloaddition reactions [76, 77]. As observed in other types of reactions, the presence of a  $\beta$ -nitro group also activates the porphyrin macrocycle towards cycloaddition reactions. This effect is evident in the reaction of  $\beta$ -NO<sub>2</sub>TPP **8a** with diazomethane (Scheme 13) [78]. In fact, the cycloaddition occurs selectively at the substituted pyrrolic unit affording the pyrazoline-fused chlorin **37** (in 41% yield) accompanied by two minor compounds (**38** and **39**). It was shown that chlorin **37** is the precursor of the two minor products.

The benefit of NO<sub>2</sub> as a substituent to activate the  $\beta,\beta'$ -double bond where it is inserted was also considered in Diels–Alder reactions. Ostrowski et al. [79] revisited the reaction of porphyrins with the highly reactive diene *ortho*-benzoquinodimethane but now using  $\beta$ -NO<sub>2</sub>TPP as the dienophile (Scheme 14). The expected chlorin **40** was isolated as the main product in 54% yield accompanied by the naphthoporphyrin **41** and the dinaphthoporphyrin **42**. When the non-functionalized TPP was used the expected chlorin was isolated in only 26% yield [75].



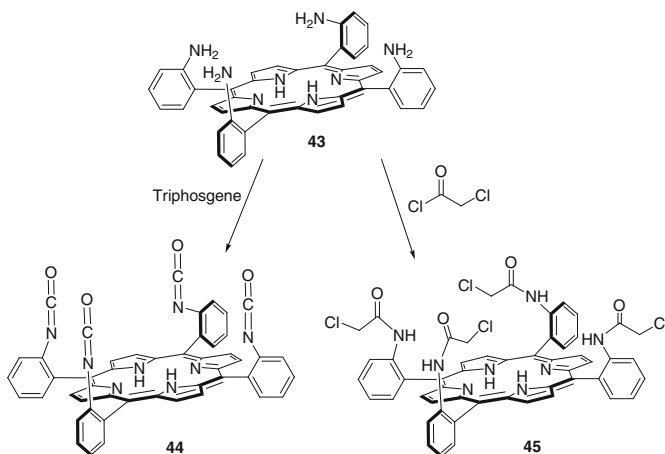
**Scheme 14** Diels-Alder reaction of 2-NO<sub>2</sub>TPP with *ortho*-benzoquinodimethane

## 4 Synthesis of Aminoporphyrins

In the last thirty years, porphyrins functionalized with amino groups have become popular starting materials for further functionalization. The possibility of using these versatile intermediates has been facilitated by their easy access in multigram scale from *meso*-tetraarylporphyrins, namely through well-known reduction procedures starting from adequate nitroporphyrins. Most of the protocols are based on the use of Sn/HCl or Sn/HCl /ultrasound [39], SnCl<sub>2</sub>/HCl [34, 80], NaBH<sub>4</sub>-Pd/C [54], HCOONH<sub>4</sub>-Pd/C [39], HCOONH<sub>4</sub>-Zn [81], or H<sub>2</sub>-Pd/C [82]. Other strategies consider the acid hydrolysis of adequate acetamidoporphyrins, prepared by condensation of pyrrole with acetamidobenzaldehydes under acidic conditions [83].

Nitrogen nucleophiles bearing a potential leaving group such as hydroxylamine, hydrazine, tosylhydrazine, and hydroxylamine *O*-sulfonic acid, 4-amino-4*H*-1,2,4-triazole are also being used to introduce the amino functionality directly in electrophilic centers of the porphyrinic core according to Callot procedures [73]. This approach was already mentioned for the amination of porphyrins bearing nitro groups and it is an important alternative to a previous approach involving also the reaction of 2-nitroporphyrins but with acylamide ions at the 3-position followed by hydrolysis of the amide bond [59].

The nucleophilic aromatic substitution of the *para*-F atoms of 5,10,15,20-tetrakis(pentafluorophenyl)porphyrin (TF<sub>5</sub>PP) by amines, discovered by Kadish in 1990 [84], is also considered an efficient strategy to introduce different amino functionalities on that versatile platform. A comprehensive mini-review dedicated to this topic was recently published [85].



**Scheme 15** Synthesis of “picket-fence” precursors

## 5 Functionalization of Aminoporphyrins

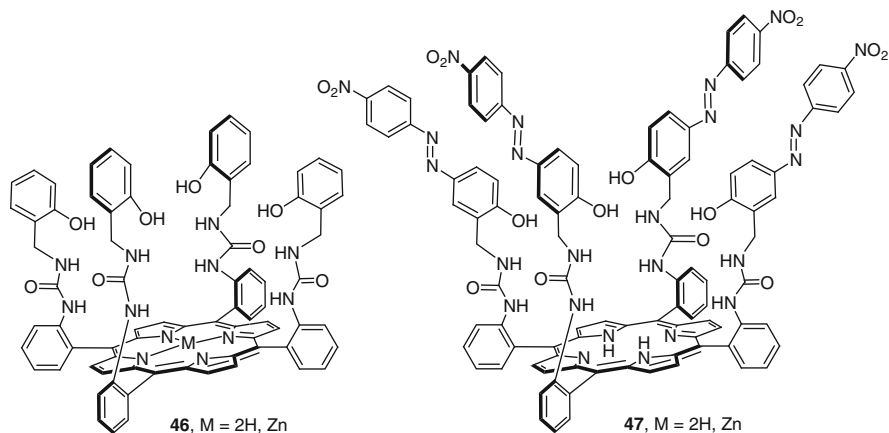
A wide range of porphyrin derivatives with improved properties have been prepared by functionalization of amino porphyrins, namely via amide linkage, alkylation, nucleophilic substitution, diazotization, cycloaddition reactions, and palladium-catalyzed transformations.

### 5.1 Via Amide Bonds

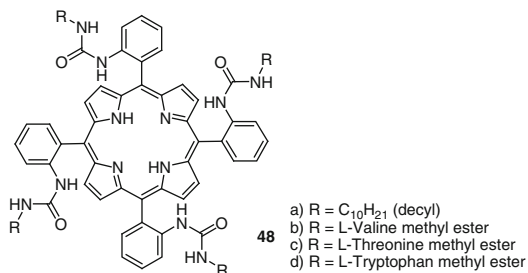
In the 1970 decade, *meso*-tetraarylporphyrins bearing aminophenyl groups, especially *ortho*-aminophenyl groups, were largely explored as excellent synthons in the construction of biomimetic models of heme proteins. The original work described by Collman in 1973 [86] was followed by the synthesis of a series of porphyrins named with fancy names such as “picket-fence”, “strapped”, or “pocket” porphyrins. Most of these compounds were constructed via amide bonds, and this topic has been the subject of exhaustive reviews [30, 87, 88].

The  $\alpha,\alpha,\alpha,\alpha$ -isomer of 5,10,15,20-tetrakis(*o*-aminophenyl)porphyrin **43** (Scheme 15) considered by Collman, also became very popular for the development of chiral catalysts and receptors for specific binding [89]. Most of the synthetic strategies reported on the development of receptors are based on the structural modification of porphyrin **43** using standard strategies or via its previous conversion into synthons **44** and **45** [90, 91].

Porphyrins **46–54** described below are examples of picket-fence porphyrin-type receptors prepared from the  $\alpha,\alpha,\alpha,\alpha$ -isomer **43** [92]. The  $\alpha,\alpha,\alpha,\alpha$ -tetrakis(*o*-isocyanatophenyl)porphyrin **44** was considered in the synthesis of the anion



**Fig. 11** “Picket-fence” porphyrins

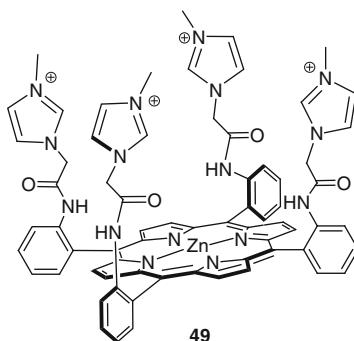


**Fig. 12** “Picket-fence” porphyrins bearing amino acid residues

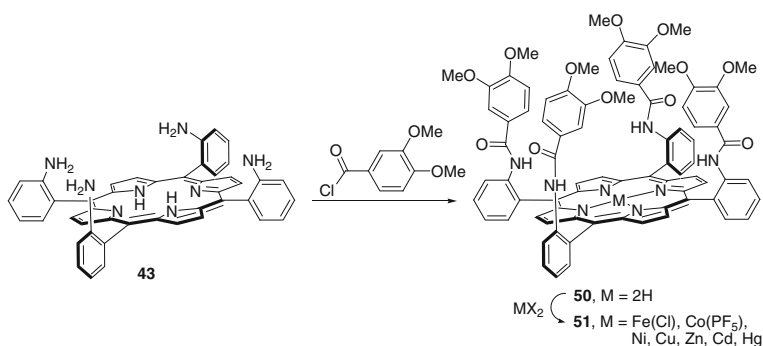
sensors **46** and **47** using the adequate 2-(aminomethyl)phenol derivatives (Fig. 11) [93]. Compounds **46** were described as exhibiting good selectivity for  $\text{AcO}^-$  and  $\text{H}_2\text{PO}_4^-$  while the *p*-nitrophenylazo derivatives **47** showed a selective coloration for  $\text{F}^-$ ,  $\text{H}_2\text{PO}_4^-$  and  $\text{AcO}^-$ . Porphyrin derivatives **48** (Fig. 12), bearing different amino acid residues, were prepared by a similar approach [94]. These compounds showed promising features in sugar recognition.

The reaction of  $\alpha,\alpha,\alpha,\alpha$ -tetrakis(*o*-chloroacetamidophenyl)porphyrin **45** with sodium imidazolate afforded porphyrin **49** (Fig. 13) containing imidazolium subunits [95]. UV/visible spectroscopic studies revealed that this receptor is selective for sulfate anions. Cyclic and square wave voltammetry studies demonstrate the receptor's ability of compounds **45** and **49** to sense a variety of anions electrochemically via significant cathodic perturbations of the respective porphyrin's first oxidation wave.

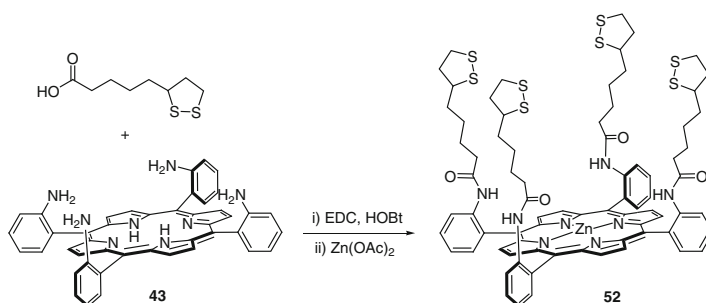
The reaction of **43** with 3,4-dimethoxybenzoyl chloride afforded the picket-fence porphyrin **50** and the corresponding complexes **51** were prepared using standard literature methods (Scheme 16). The anion binding ability of these compounds was



**Fig. 13** “Picket-fence” porphyrins containing imidazolium subunits



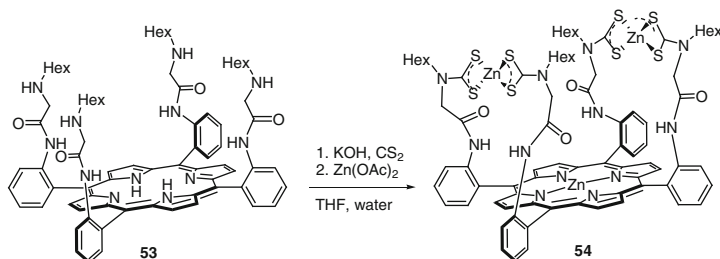
**Scheme 16** Synthesis of “picket-fence” porphyrin **50** and complexes **51**



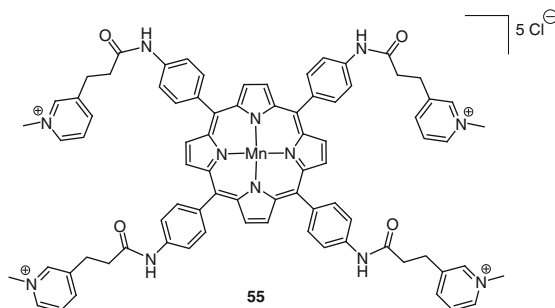
**Scheme 17** Synthesis of a “picket-fence” porphyrin bearing disulfide groups

evaluated and the best results were obtained with the cadmium and mercury complexes that showed to bind anions strongly in highly competitive solvent mixtures [96].

The disulfide and dithiocarbamate functionalized porphyrins **52** (Scheme 17) and **54** (Scheme 18) were considered in the synthesis of gold nanoparticles. The nanoparticles show to be more efficient to recognize anions than the free receptors



**Scheme 18** Synthesis of a “picket-fence” porphyrin bearing dithiocarbamate groups

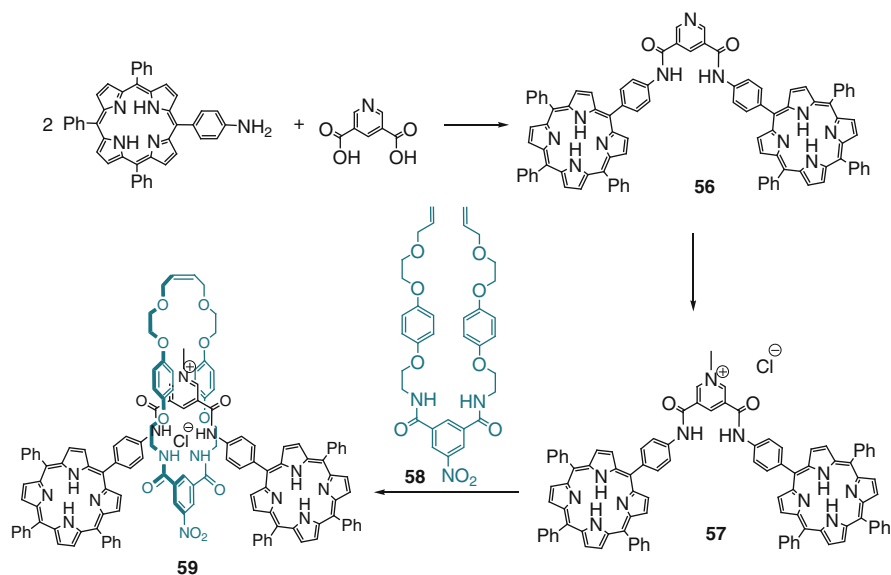


**Fig. 14** Structure of the tetracationic porphyrin **55**

in solution. The tetraamide **52** was prepared by reaction of **43** with thiocetic acid, in the presence of EDC and HOBt (1-hydroxybenzotriazole), followed by the addition of  $\text{Zn}(\text{AcO})_2$  (Scheme 17). The synthesis of the dithiocarbamateporphyrin **54** involved the reaction of synthon **45** with hexylamine, followed by reaction with carbon disulfide and  $\text{Zn}(\text{AcO})_2$  (Scheme 18) [97, 98].

*meso*-Tetraarylporphyrins bearing amino groups in *para* positions of the phenyl substituents were also considered in the design of receptors via amide bond. The cationic porphyrin **55** (Fig. 14), obtained by reacting 5,10,15,20-tetrakis (*p*-aminophenyl)porphyrin with 3-(pyridin-3-yl)propanoic acid in the presence of HOBt and HBTU (*O*-benzotriazol-1-yl-*N,N,N'*-tetramethyluronium hexafluorophosphate) followed by quaternization of the pyridyl nitrogens with methyl iodide and metallation with manganese(III), was described as showing a much higher preference for G-quadruplexes as opposed to duplex DNA [99].

The asymmetric 5-(4-aminophenyl)-10,15,20-triphenylporphyrin was used to prepare the porphyrin-functionalized [2]rotaxane host molecule **59** (Scheme 19). The synthesis involved the condensation of two equivalents of the aminoporphyrin with pyridine-3,5-dicarboxylic acid using adequate coupling agents, followed by cationization with methyl iodide. Then, a ring-closing metathesis mediated cyclization of the adequate bis-vinyl-functionalized benzene-1,3-dicarboxamide **58** in the presence of Grubbs 2nd generation catalyst afforded **59**. This rotaxane exhibits a high binding affinity and general selectivity for chloride anions [100].



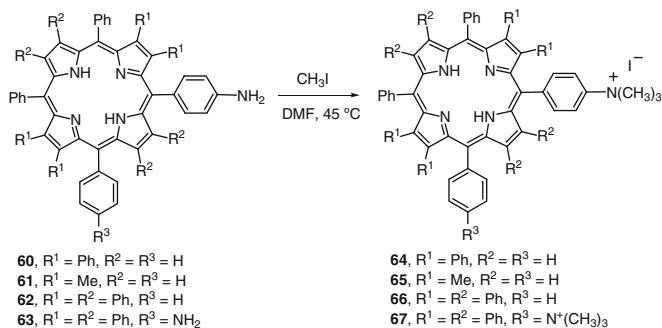
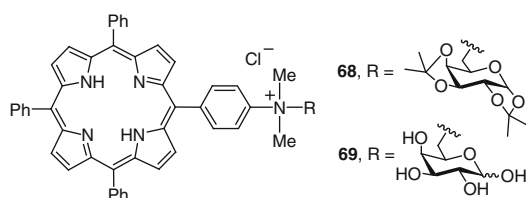
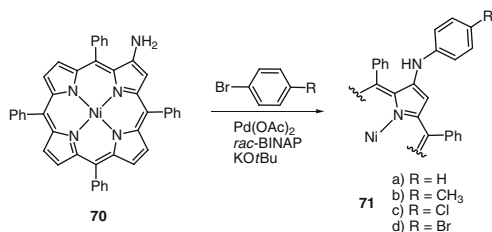
**Scheme 19** Synthesis of a porphyrin-functionalized [2]rotaxane

*meso*-Tetraarylporphyrins bearing aminophenyl groups have been used in the preparation of porphyrin derivatives conjugated to other bioactive compounds via amide bonds. A recent review covering this type of covalent attachment of porphyrins to peptides and proteins was recently published [101].

## 5.2 Via Alkylation of the Amino Group

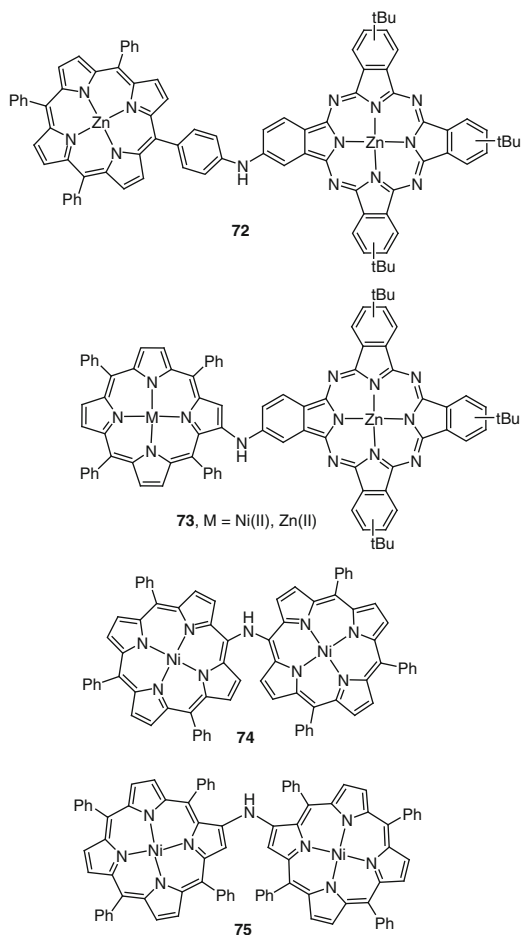
The cationization of the amino groups was explored by several research groups to improve porphyrin DNA binding, photodynamic effect, solubility in physiological fluids, and selectivity to cancer cells. For instance, the cationic  $\beta$ -tetra- and  $\beta$ -octasubstituted porphyrins **64–67** were prepared by cationization of the corresponding aminoporphyrins **60–63** (Scheme 20) [102]. The synthetic approach to  $\beta$ -tetrasubstituted porphyrins **60** and **61** involved the mononitration of the 2,3,12,13-tetrabromoTPP with fuming HNO<sub>3</sub>, followed by Suzuki coupling with the adequate boronic acids and then reduction of the nitro group with SnCl<sub>2</sub>. A similar strategy was used to obtain the octasubstituted porphyrins **62** and **63** although the nitration of the phenyl groups preceded the bromination step.

Alkylation of 5-(4-aminophenyl)-10,15,20-triphenylporphyrin with 6-iodo-1,2:3,4-di-*O*-isopropylidene- $\alpha$ -D-galactopyranose, followed by methylation with methyl iodide, afforded the cationic glycoporphyrin derivative **68** (Fig. 15) [103]. Removal of the isopropylidene groups from **68** by acid treatment afforded glycoporphyrin **69**.

**Scheme 20** Cationization of *meso*-(4-aminophenyl)porphyrins**Fig. 15** Cationic glycoporphyrins**Scheme 21** Synthesis of (2-arylamino)porphyrins via Buchwald–Hartwig amination

### 5.3 Via Transition Metal Catalysis

Modification of amino groups mediated by transition metal complexes, such as palladium(0), is an interesting alternative to bromoporphyrins for carbon–nitrogen bond formation [13]. Van Lier and coworkers reported for the first time, but without experimental details, that 2-aminoporphyrins react with aryl halides affording 2-(arylamino)porphyrins [104]. Based on that methodology, usually known as Buchwald–Hartwig amination, Cavaleiro and coworkers were able to synthesize 2-arylamino porphyrins **71** in excellent yields by reacting 2-NH<sub>2</sub>-NiTPP (**70**) with bromobenzene derivatives, even with electron-withdrawing substituents (Scheme 21) [66].

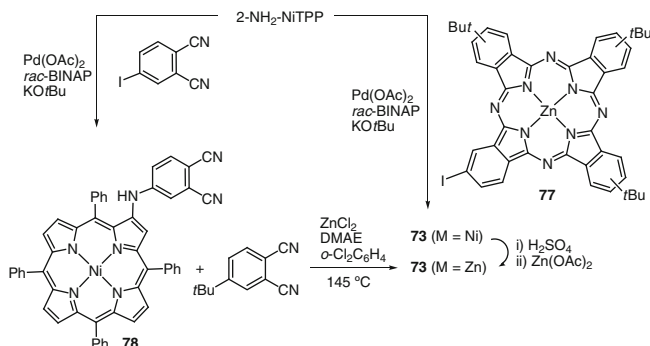


**Fig. 16** Structures of porphyrin-phthalocyanine dyads and porphyrin dyads obtained using Buchwald-Hartwig amination reactions

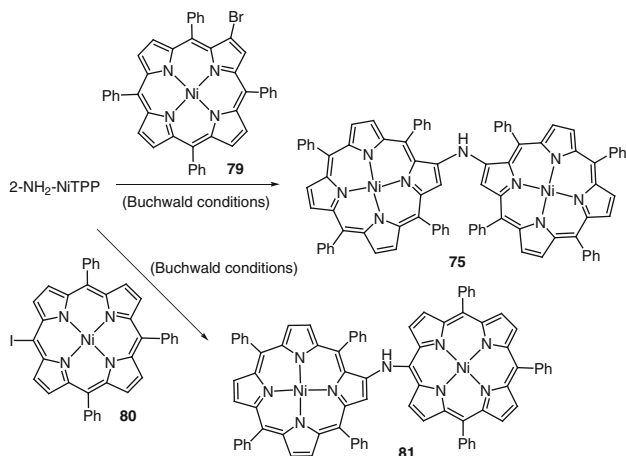
Cavaleiro and coworkers also used the Buchwald–Hartwig amination conditions to synthesize the porphyrin–phthalocyanine dyads **72** and **73** [105] and the porphyrin–porphyrin dyads **74** and **75** [106] (Fig. 16) where the two chromophores are linked by a nitrogen atom.

Dyad **73** was prepared by two complementary routes (Scheme 22). One of them involved the direct coupling of 2-NH<sub>2</sub>-NiTPP and the iodophthalocyanine **77** in the presence of Pd(OAc)<sub>2</sub>, *rac*-BINAP and KO<sup>t</sup>Bu. The other approach involved the statistical cross-condensation of porphyrin-2-ylaminophthalonitrile **78** with 4-*t*-butylphthalonitrile. Phthalonitrile **78** was obtained from 2-aminoTPP and 4-iodophthalonitrile, using the same coupling conditions [Pd(OAc)<sub>2</sub>, *rac*-BINAP and KO<sup>t</sup>Bu].

Similar catalytical conditions were used to couple 2-NH<sub>2</sub>-NiTPP with 2-Br-NiTPP (**79**) and 5-I-NiTPP (**80**) (Scheme 23). The electronic spectra of the dimers **75** and



**Scheme 22** Synthetic routes to a porphyrin-phthalocyanine dyad



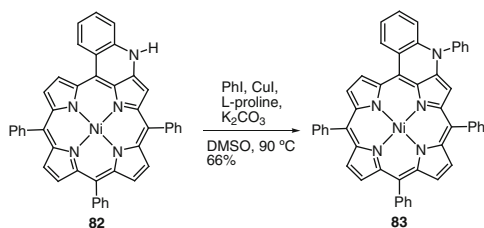
**Scheme 23** Synthesis of porphyrin dyads

**81** are typical of highly delocalized systems and electrochemistry studies have shown that the first oxidation step occurs on the connecting amine function.

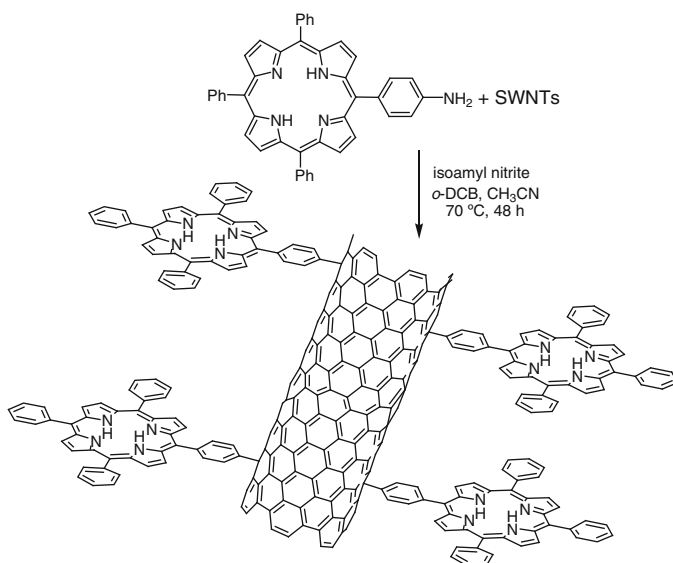
The cyclic enamine **82** [42] (structurally related to 2-NH<sub>2</sub>-NiTPP) reacts with iodobenzene under Ullmann amination conditions (copper iodide, L-proline, potassium carbonate) to give access to the *N*-phenylquinolino[2,3,4-*at*]porphyrin **83** in good yield (Scheme 24) [107]. Electrochemical studies with the free-base and the corresponding Ni, Cu, and Pd complexes have shown that the presence of the *N*-phenyl group is responsible for the formation of stable radical cations.

## 5.4 Via Diazonium Salts

The synthetic value of diazonium salts was considered in several synthetic approaches for further functionalization of the porphyrin core. These important synthons



**Scheme 24** *N*-Arylation of a quinolino[2,3,4-*at*]porphyrin

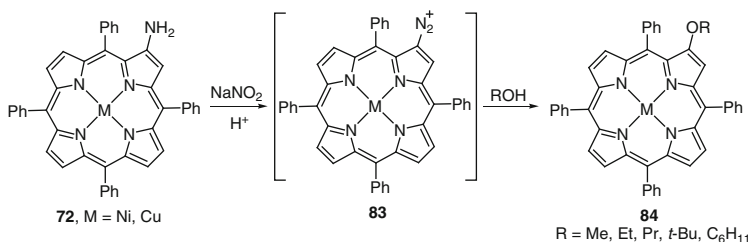


**Scheme 25** Synthesis of porphyrin-SWNT nanohybrids

can be accessible from adequate aminoporphyrins using different diazotization conditions such as sodium nitrite and tetrafluoroboric acid at  $-5^{\circ}\text{C}$  [108], sodium nitrite, and sulfuric acid [39] or with isoamyl nitrite [109].

The in situ decomposition of the diazonium salt obtained from 5-(4-aminophenyl)-10,15,20-triphenylporphyrin with isoamyl nitrite in the presence of single-walled carbon nanotubes (SWNTs) was considered in the synthesis of nanohybrids where the porphyrin was covalently attached to the nanotube (Scheme 25) [109]. The new materials showed better solubility and dispersion stability in organic solvents and superior optical limiting effects than SWNTs and  $\text{C}_{60}$ .

The diazonium salt of the nickel complex of 5-(4-aminophenyl)-10,15,20-triphenylporphyrin was used to graft the corresponding complex to glassy carbon and gold and indium tin oxide surfaces via reduction of the diazonium moiety. Nitrosium tetrafluoroborate ( $\text{NOBF}_4$ ) was selected as the diazotizing agent. The characterization of the resulting materials confirms that the metallated



**Scheme 26** Synthesis of  $\beta$ -alkyloxy substituted porphyrins via diazonium salts

porphyrin is intact, stably attached to the surface but with highly solvent-dependent electrochemistry [110].

The diazonium salts of the nickel or copper complexes of 2-amino-*meso*-tetraphenylporphyrin **72** are efficient intermediates to new 2-substituted porphyrins. Several  $\beta$ -alkyloxy substituted porphyrins **84** were obtained from the reaction of the in situ generated diazonium salt **83** (M = Cu) with alcohols or alkoxides (Scheme 26) [39, 111].

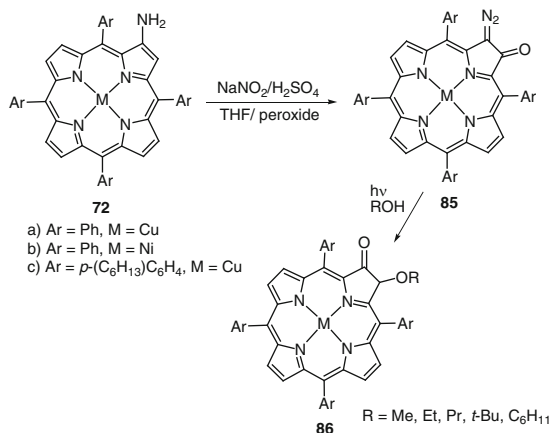
The diazotization of the 2-aminoporphyrins **72a–c** with NaNO<sub>2</sub> and sulfuric acid in tetrahydrofuran containing hydroperoxide gave rise to 2-diazo-3-oxo-tetraphenylchlorins **85** (Scheme 27) [112]. The photochemical induced dediazotization of metallo 2-diazo-3-oxo-tetraphenylchlorins **85** in the presence of alcohols afforded the corresponding 2-alkyloxy derivatives **86** and other compounds that were justified by the existence of different reaction pathways after the formation of ketocarbenes by dediazotiation [112].

The reaction of porphyrin diazonium salts with sodium azide afforded porphyrins bearing azido substituents in excellent yields (ex: **87** and **88**, Fig. 17). These compounds are important synthons for click chemistry [113–115].

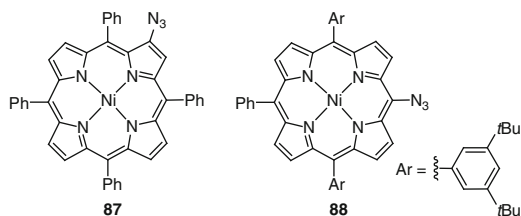
The porphyrin diazonium salt **83** (M = Ni) was also used as a pseudo-halide in Heck reactions [116]. The reactions were performed in the presence of methyl acrylate, propenal, and methyl vinyl ketone and afforded the expected unsaturated 2-substituted porphyrins **89a–c** (Fig. 18). Depending on the  $\alpha,\beta$ -unsaturated carbonyl compound used, the minor products **89d–f** were also obtained. The formation of pyridoporphyrins **90** was justified by the reaction of the unchanged 2-aminoporphyrin with the  $\alpha,\beta$ -unsaturated carbonyl compounds [117].

The extension of the previous studies to 3-sulfolene gave access, after isomerization and thermal extrusion of sulfur dioxide, to porphyrin **92** bearing a buta-1,3-dien-2-yl group in the  $\beta$ -pyrrolic position (Scheme 28) [118].

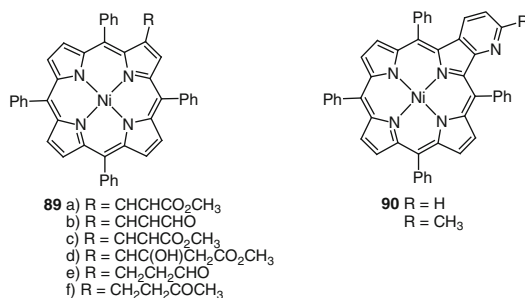
The  $\beta$ -butadienyl porphyrin **92** showed to be an efficient diene in Diels–Alder reactions with a wide range of dienophiles such as [60]fullerene, *N*-phenylmaleimide, 1,4-benzoquinone and 1,4-naphthoquinone and fumaronitrile affording the expected adducts and/or the dehydrogenated ones in good yields. The adduct obtained from the reaction of **92** with fumaronitrile was used as precursor to a porphyrin–phthalonitrile that gave access to a series of novel porphyrin–phthalocyanine dyads bearing a rigid arrangement of the two units in close proximity [119].



**Scheme 27** Synthesis of 2-diazo-3-oxo-tetraphenylchlorins

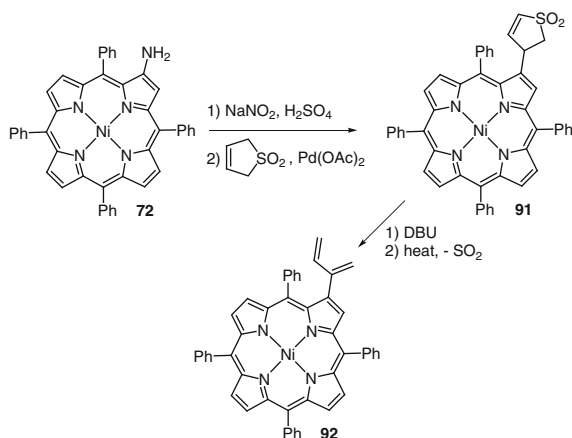


**Fig. 17** Structures of  $\beta$ - and *meso*-azidoporphyrins



**Fig. 18** Structures of porphyrins 89–90

Using the principles of the diazotization reaction, Igarashi's group [120] developed a highly sensitive porphyrin-based spectrophotometric method for the determination of nitrite ion. This methodology uses the ability of the amino group of 5,10,15,20-tetrakis(4-aminophenyl)porphyrin to form a diazo group in the presence of nitrite ion in acidic conditions. The formation of a quinoid structure is responsible for a significant decrease in the absorbance relatively to the initial porphyrin. Latter,



**Scheme 28** Synthesis of  $\beta$ -butadienyl porphyrin **92**

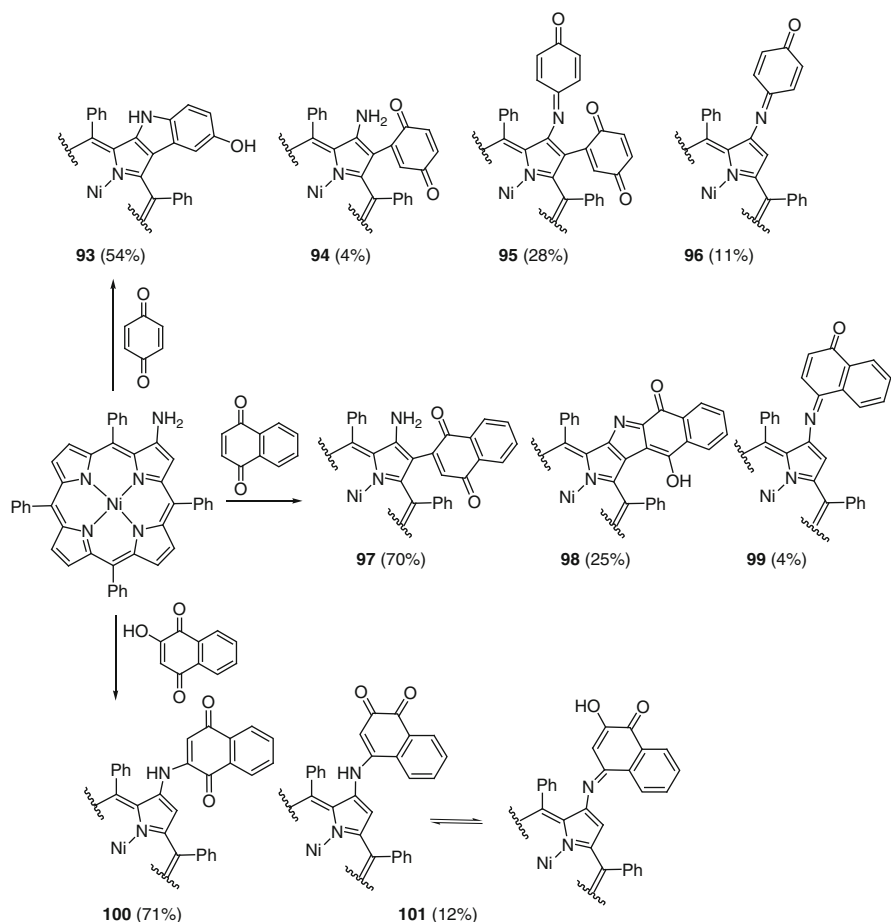
the same group used a porphyrin with only one amino group, the [5-(4-aminophenyl)-10,15,20-tris(4-pyridyl)porphyrin, in this sensing methodology [121].

## 5.5 The Dual Behavior of Aminoporphyrins

The dual behavior of 2-aminoporphyrins to act as an aromatic amine or as enamine gave access to an interesting number of new derivatives namely heterocyclic-fused porphyrins.

In 1997 Cavaleiro and coworkers reported that the reaction of the nickel(II) complex of 2-aminoTPP **81** with propenal and methyl vinyl ketone afforded, in the presence of  $\text{H}_2\text{SO}_4$  and  $\text{Pd}(\text{AcO})_2$ , the fused pyridoporphyrins **90** [117]. The authors referred that a Michael addition, imine formation, and a dehydrogenation took place in products formation. The extension of those studies by the same group to other  $\alpha,\beta$ -unsaturated carbonyl compounds such as 1,4-benzoquinone, 1,4-naphthoquinone and 2-hydroxy-1,4-naphthoquinone in the presence of catalytic amount of sulfuric acid, gave access to a plethora of new porphyrin–quinone dyads and  $\pi$ -extended heterocycle-fused porphyrin derivatives **93–98** (Scheme 29). The type of products obtained was dependent on the quinone used and was justified based on of dual behavior of the aminoporphyrin **81**. The aromatic character can explain the formation of products **94**, **99–101** while the others (**93**, **95–98**) can be justified by its enamine character. The adaptation of the Nenitzescu reaction allowed the authors to elucidate the formation of the  $\pi$ -extended heterocyclic fused porphyrin derivatives **93** and **98**.

The products obtained from the reaction of 2-amino-*meso*-tetraphenylporphyrin with acryloyl chloride, also reflects the dual behavior of 2-aminoporphyrins [122]. While the amide **102** was the result of *N*-acylation, the formation of the dihydro-2-pyridone fused porphyrin **103** was justified through the aza-annulation reaction

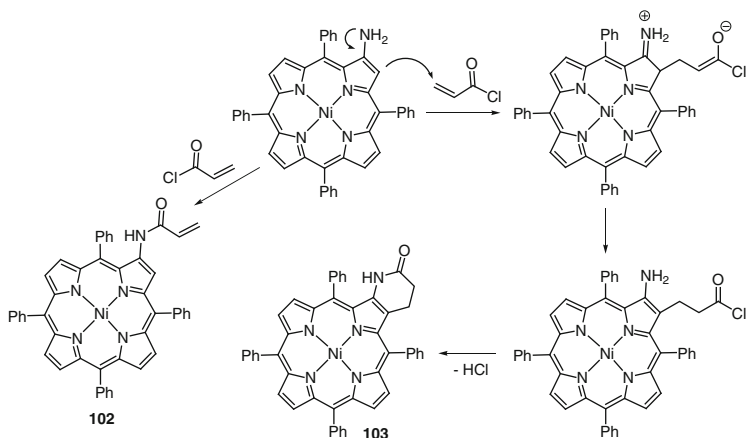
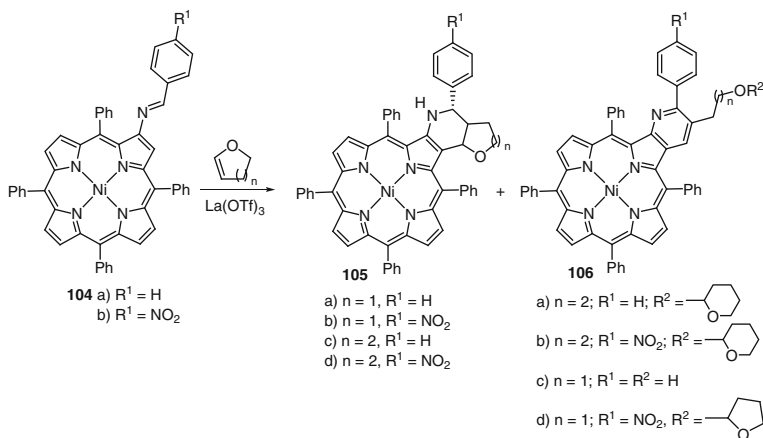


**Scheme 29** Reaction of 2-aminoTPP with quinones

initiated by the Michael addition of the enamine followed by an intramolecular *N*-acylation (Scheme 30). Compound **103** is easily oxidized with DDQ to the corresponding 2-pyridone. The failure to obtain the dihydro-2-pyridone from the reaction with cinnamoyl chloride was explained by considering steric or electronic effects due to the phenyl group present on the  $\beta$ -carbon of the acyl chloride.

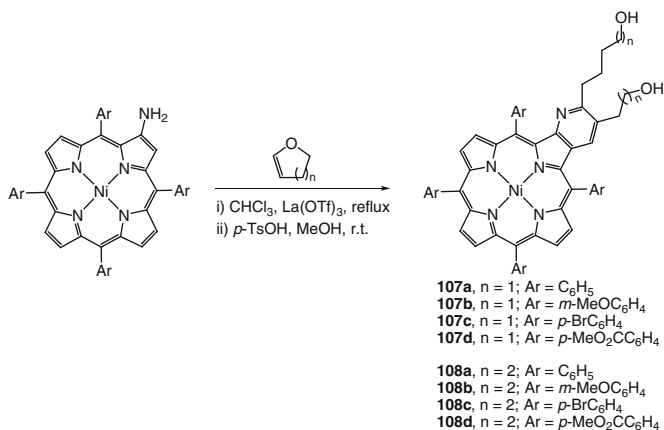
## 5.6 $\beta$ -Iminoporphyrins as Heterodienes

The possibility of using the  $\beta$ -iminoporphyrins **104** as heterodienes in hetero-Diels–Alder reactions was reported by Cavaleiro and coworkers [123, 124]. A three component reaction involving  $\beta$ -aminoTPP, an aromatic aldehyde and an

**Scheme 30** Reaction of 2-aminoTPP with acryloyl chloride**Scheme 31** Reaction of  $\beta$ -iminoporphyrin **104** with cyclic enol ethers

electron-rich dienophile (3,4-dihydro-2*H*-pyran or 2,3-dihydrofuran) catalyzed by lanthanum triflate leads to the expected tetrahydropyridine-fused derivatives **105** accompanied by the corresponding pyrido[2,3-*b*]porphyrins **106** (Scheme 31). A probable pathway to compounds **106** involves the aromatization of the pyridine ring, with the opening of the pyran ring, followed by the addition of another molecule of the enol ether. In the presence of  $La(OTf)_3$  and the enol ether, compounds **105** are converted into the corresponding pyrido[2,3-*b*]porphyrins **106**.

Pyrido[2,3-*b*]porphyrins bearing two vicinal hydroxyalkyl groups (**107** and **108**) were prepared through a two component domino reaction where an enol ether was used to generate the iminic heterodiene and also to act as the dienophile



**Scheme 32** Synthesis of pyrido[2,3-*b*]porphyrins **107–108**

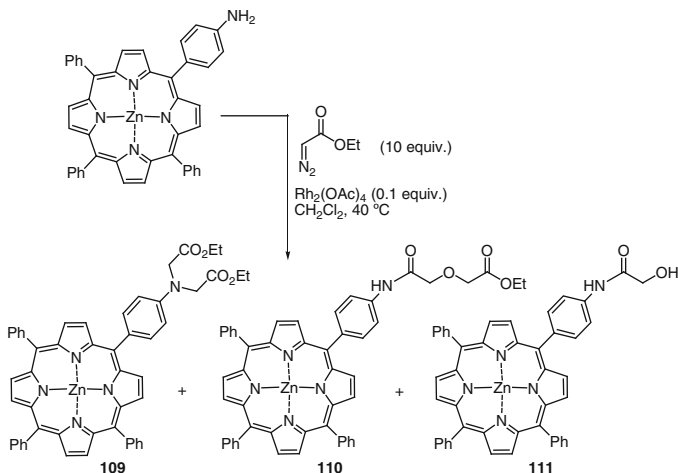
(Scheme 32) [125]. Treatment of the crude reaction mixture with a methanolic solution of *p*-toluenesulfonic acid is a key step in order to improve the yield of the desired products and to facilitate the purification process. The esterification of hydroxyalkyl groups in template **107a** with succinic anhydride and dodecanoyl chloride afforded the corresponding esters in almost quantitative yields. The crystal structure of the most hydrophobic one showed that these porphyrin derivatives form one-dimensional supramolecular structure in the solid state.

## 5.7 Aminoporphyrins as Carbene Acceptors

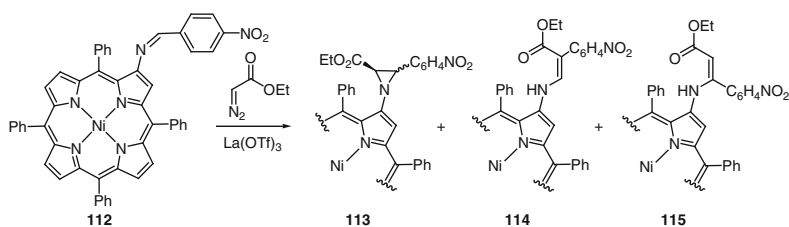
The catalytic insertion of ethyl diazoacetate into the amino group of 5-(4-aminophenyl)-10,15,20-triphenylporphyrin in the presence of an Rh-based catalyst was recently investigated [126]. Besides the formation of one compound resulting from the insertion of two carbene units, two other unexpected amides were isolated (Scheme 33). The formation of these amides was also observed when the 2-(4-aminophenyl)porphyrin was reacted with ethyl glycolate in the presence of the same catalyst. Derivative **110** crystallizes in an unusual chiral supramolecular metalloporphyrin chain, forming a right-handed helix arrangement.

The  $\beta$ -iminoporphyrin **112** reacts with carbenes generated from ethyl diazoacetate in the presence of catalytic amounts of lanthanum triflate (Scheme 34) [127]. The *cis*- and *trans*-aziridine **113** were obtained as the main products and the  $\beta$ -amino- $\alpha,\beta$ -unsaturated esters **114** and **115** as minor products (Scheme 35).

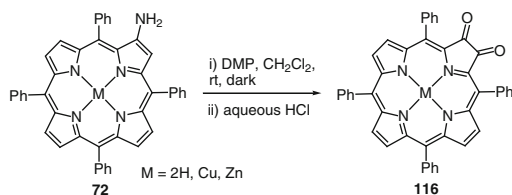
Porphyrin-2,3-diones **116** are another example of porphyrin derivatives that can be obtained from 2-aminoporphyrins. Traditionally, the route to porphyrin-2,3-diones is the photo-oxidation of a 2-aminoporphyrin followed by hydrolysis of the resulting keto-imino chlorin [128], or the oxidation of 2-hydroxyporphyrins



**Scheme 33** Reaction of 5-(4-aminophenyl)-10,15,20-triphenylporphyrin with carbenes



**Scheme 34** Reaction of  $\beta$ -iminoporphyrin **112** with carbenes



**Scheme 35** Synthesis of porphyrin-2,3-diones

with the Dess–Martin periodinane (DMP) [129]. Burn reported that DMP is also efficient for the oxidation of 2-aminoporphyrins to porphyrin-2,3-diones **116** (Scheme 35) [130]. This method allows the reaction to be carried out on a large scale and it is easier than the classic photo-oxidation procedure. The porphyrin-2,3-diones are commonly used as building blocks for conjugated porphyrin arrays in the development of organic materials and molecular wires [131].

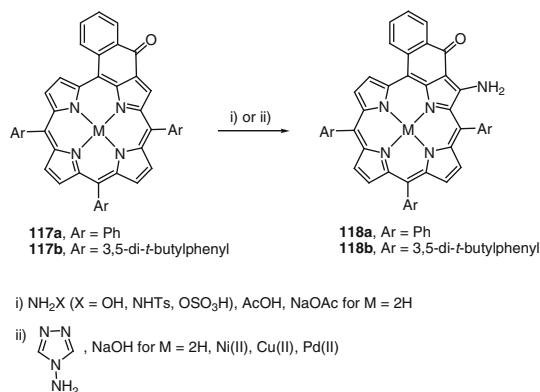
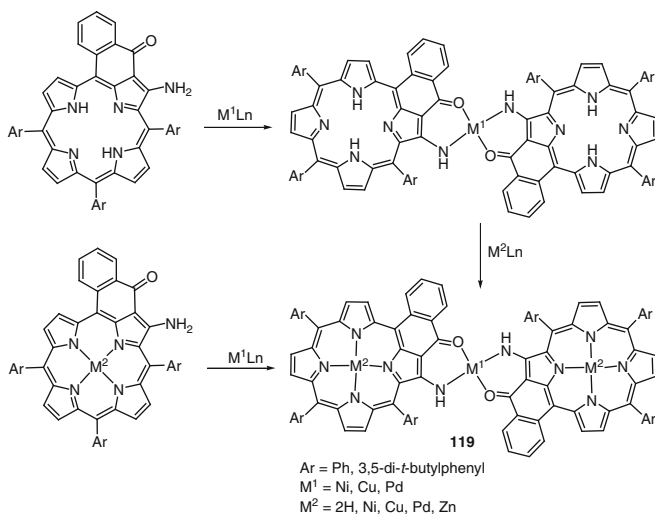
## 5.8 Aminoporphyrins in the Construction of New Assemblies

The design of molecular assemblies based on porphyrins self-association or aggregation is considered a simple method to afford supramolecular systems with a wide range of applications from models of enzyme active sites with relevance in catalysis to light-energy conversion and nanostructured components of electronic and optoelectronic devices.

In 1995 Gautam et al. [132] were able to conclude, from the coordination behavior of 5,10,15,20-tetrakis(3-aminophenyl)porphyrin and of the corresponding nitro precursor towards several metal(II) ions, such as Mg(II), Co(II), Zn(II) and Ag(II), that the amino derivatives are more prone to form aggregates than the nitro derivatives. These conclusions were based on the significant red shifts observed for the absorption and emission bands of the metallated amino derivatives when compared with the ones of the corresponding nitro derivatives. Similar red shifts were obtained for the nitro derivatives in the presence of dimethylaminopyridine supporting the existence of aggregated species in which metal ions are axially coordinated with the peripheral amino groups. Based on the model studies, possible structures were proposed and the authors refer that the amino group in the *meta* position is a key feature for the adequate binding of this group to the metal ion in the adjacent porphyrin.

The coordination ability of porphyrin derivatives bearing an amino group in conjugation with a keto group had also a great success in the construction of new assemblies connected by metal ions. The first studies [133, 134] involved the use of the enaminoketone porphyrins **118** obtained from the reaction of the corresponding ketone derivatives **117** with nitrogen nucleophiles bearing a potential leaving group (hydroxylamine, hydrazine, tosylhydrazine, and hydroxylamine *O*-sulfonic acid or 4-amino-4*H*-1,2,4-triazole) (Scheme 36). An alternative to the previous route used for obtaining ketone **117a** that involves the formylation of a metalloporphyrin under Vilsmeier–Haack conditions followed by acid-catalyzed cyclization of the aldehyde and demetallation of the porphyrin [135–137] was suggested for derivative **117b**. The new synthetic strategy is based on the hydrolysis of the ester group of the nickel complex of a porphyrin bearing a *o*-methoxycarbonylphenyl group and three 3,5-di-*tert*-butylphenyl groups, followed by acid chloride formation and an intramolecular Friedel–Crafts reaction. The authors refer the superiority of 4-amino-4*H*-1,2,4-triazole in the amination process when compared with the other nitrogen nucleophiles, since it can be used in the amination of free-bases and also of nickel, palladium, and copper complexes.

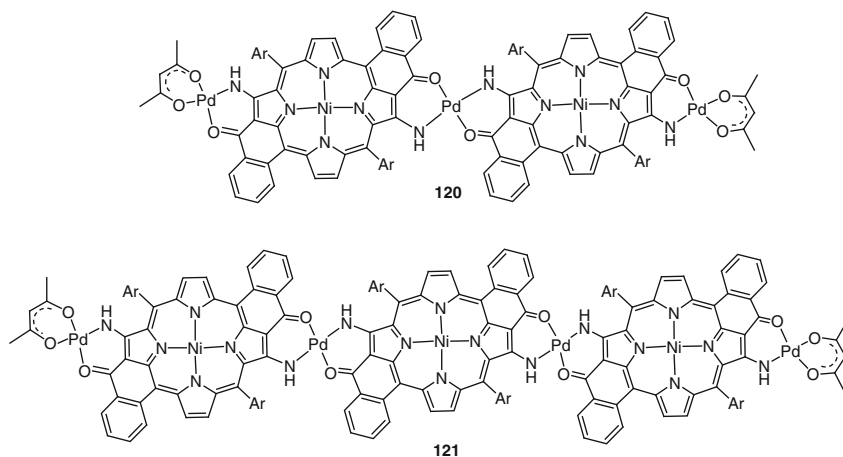
Porphyrin dimers **119** were assembled by several routes namely by the selective coordination of a metal ion to the external sites of two enaminoketone free-bases, followed by metallation of the internal sites or by coordination of two molecules of the metalloenaminoketone on a selected metal ion (Scheme 37). In general, this last approach showed to be more adequate due to the instability of the initial dimer obtained from the free-bases. The *trans* arrangement around the metal was confirmed by NMR experiments and the electronic spectra (intensified red-shifted Q bands) and electrochemical behavior (oxidation potentials split into two redox

**Scheme 36** Synthesis of enaminoketone porphyrins**Scheme 37** Synthesis of porphyrin dimers by coordination of a metal ion to the external sites of two enaminoketones

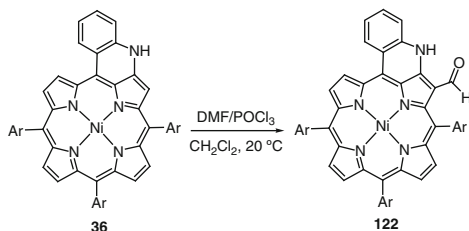
steps substantially lowered when compared with the monomeric units) of the dimers were indicative of a strong interaction between the two units introduced through the connecting metal; the coplanar coordination to the porphyrin ring is indicated by the authors as the main reason for the large interactions displayed in the ground state.

The extension of the previous studies to bis-enaminoketones allowed a step-wise preparation of polymetallic oligomers of type **120** and **121** (Fig. 19) connected by metal centers [73, 138].

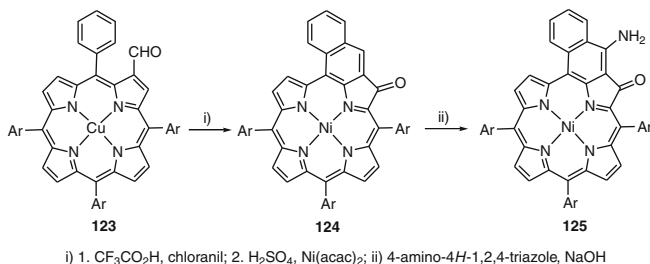
These studies were extended to the synthesis of a series of nickel bis-enaminoketone isomers and by thionation of these derivatives to bis-enaminothioketone analogues [139]. The authors refer that by controlling the amount of the Lawesson's reagent



**Fig. 19** Polymetallic porphyrin oligomers



**Scheme 38** Synthesis of enaminoaldehyde functionalized porphyrins



**Scheme 39** Synthesis of enaminketone porphyrins

used in the thionation process it was possible to isolate the monothionated analogues affording derivatives with mixed external chelating groups (NO/NS). The electrochemistry behavior of the new derivatives was also studied and it is in good agreement with the recorded electronic spectra.

Porphyrins bearing other peripheral chelating groups fully conjugated with the porphyrin core, such as the enaminoaldehydes **122** (Scheme 38) and the enaminketones **125** (Scheme 39), were also developed by the same group and were used in the preparation of porphyrin dimers linked by metal ions [42].

The enaminketone ligands **125** were obtained from 2-formyl-*meso*-tetraarylporphyrins **79** according to Ishkov conditions [140] followed by amination with 4-amino-4*H*-1,2,4-triazole. All ligands, namely the corresponding thioanalogues obtained by thionation with Lawesson's reagent, were metallated with palladium affording the corresponding dimers. From the structural characterization the authors were able to conclude that in the enamino aldehyde and thioaldehyde series the *cis* isomer is thermodynamically favored and strong porphyrin–porphyrin interactions were also detected in this new series of ligands.

## 6 Conclusions

This chapter brings an update to the synthesis and reactivity features of nitro- and aminoderivatives of *meso*-tetraarylporphyrins. Such derivatives can be obtained by well-established synthetic and derivatization methodologies. The nitro and the amino substituents play a key role in the functionalization of the corresponding porphyrin macrocycles into a variety of other ones which have already demonstrated significant applications.

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