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Boron-containing tetrapyrroles

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Abstract: The recent advances in the synthesis of carborane and boronic ester-substituted tetrapyrroles (porphyrins, porphyrazines, and phthalocyanines) are reviewed together with their possible utilization as agents for photodynamic therapy (PDT) and boron neutron capture therapy of cancer (BNCT) as well as dual PDT/BNCT sensitizers.

Key words: Porphyrins, porphyrazines, phthalocyanines, polyhedral boranes, carborane, boronic acid, boron neutron capture therapy, photodynamic therapy

1. Introduction

The basic tetrapyrrole skeleton of porphyrin, found in many natural pigments, is probably one of the oldest bioorganic structures known to man.[1] Porphyrazines, structural analogs of natural porphyrins, are small-ring tetrapyrrolic macrocycles in which the meso positions contain nitrogen atoms instead of CH groups. They largely retain the flexibility of the porphyrin's core and show intense to very intense absorbance in the 'therapeutic window'.[2]

Apart from their uses as dyes or pigments, phthalocyanines receive great interest due to their special properties. They show exceptional thermal and chemical stability. The conjugated π system, containing 18 electrons, leads to very intense absorption bands in the ultraviolet region at around 300–350 nm and in the visible region at around 700 nm with high extinction coefficients.[3] In addition, their properties can be altered through the addition of substituents to the periphery of the macrocycle or binding of axial ligands to central metal ion.

On the basis of their photophysical properties, both naturally occurring and synthetic tetrapyrrole derivatives have recently found specific biomedical applications, particularly in the field of photodynamic therapy (PDT).[4]

PDT is a minimally invasive treatment that destroys target cells in the presence of oxygen when light irradiates a photosensitizer, generating highly reactive singlet oxygen. Singlet oxygen then attacks cellular targets, causing destruction through direct cellular damage, vascular shutdown, and activation of an immune response against targeted cells.[5] PDT requires 3 elements to generate singlet oxygen: a photosensitizer, appropriate light, and oxygen. The wavelengths of the light that are typically used for PDT are in the red or near infrared spectral range as these wavelengths exhibit a greater penetration depth into most human tissues and are not absorbed by normal tissue constituents.[6]

For many decades, interest in medical application of boron chemistry has centered primarily on the boron

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neutron capture therapy (BNCT) approach to cancer treatment.[7] BNCT is based on the nuclear capture and fission reactions that occur when boron-10 (^{10}B), which is a nonradioactive constituent of the natural elemental boron, is irradiated with low energy thermal neutrons to yield high linear energy transfer alpha particles (^{4}He) and recoiling lithium-7 (^{7}Li) nuclei.[8] The short travel range (5–9 Å) of the fragments combined with the local accumulation of B permits the destruction of selected tissue areas.[8−11]

The success of boron neutron therapy application depends on the properties of the boron delivery agents. An efficacious boron delivery agent should display the following characteristics: 1) low systemic toxicity and normal tissue uptake with high tumor uptake and concomitantly high tumor/brain and tumor/ blood concentration ratios (above 3–4:1); 2) a minimum concentration of 20–35 μg of ^{10}B nuclei per gram of tumor; 3) rapid clearance from blood and normal tissues and persistence in the tumor during BNCT.[8,12]

The major challenges in compound development for BNCT have been the requirements for selective tumor targeting and the delivery of therapeutic boron concentrations to tumors with minimal normal tissue toxicity.[12,13] The polyhedral borane anions and many of the various carboranes appear to meet the requirement of possessing high boron percentages, and, for this reason, there has been significant effort in the area of compound development directed toward the incorporation of such entities into organic structures.[10]

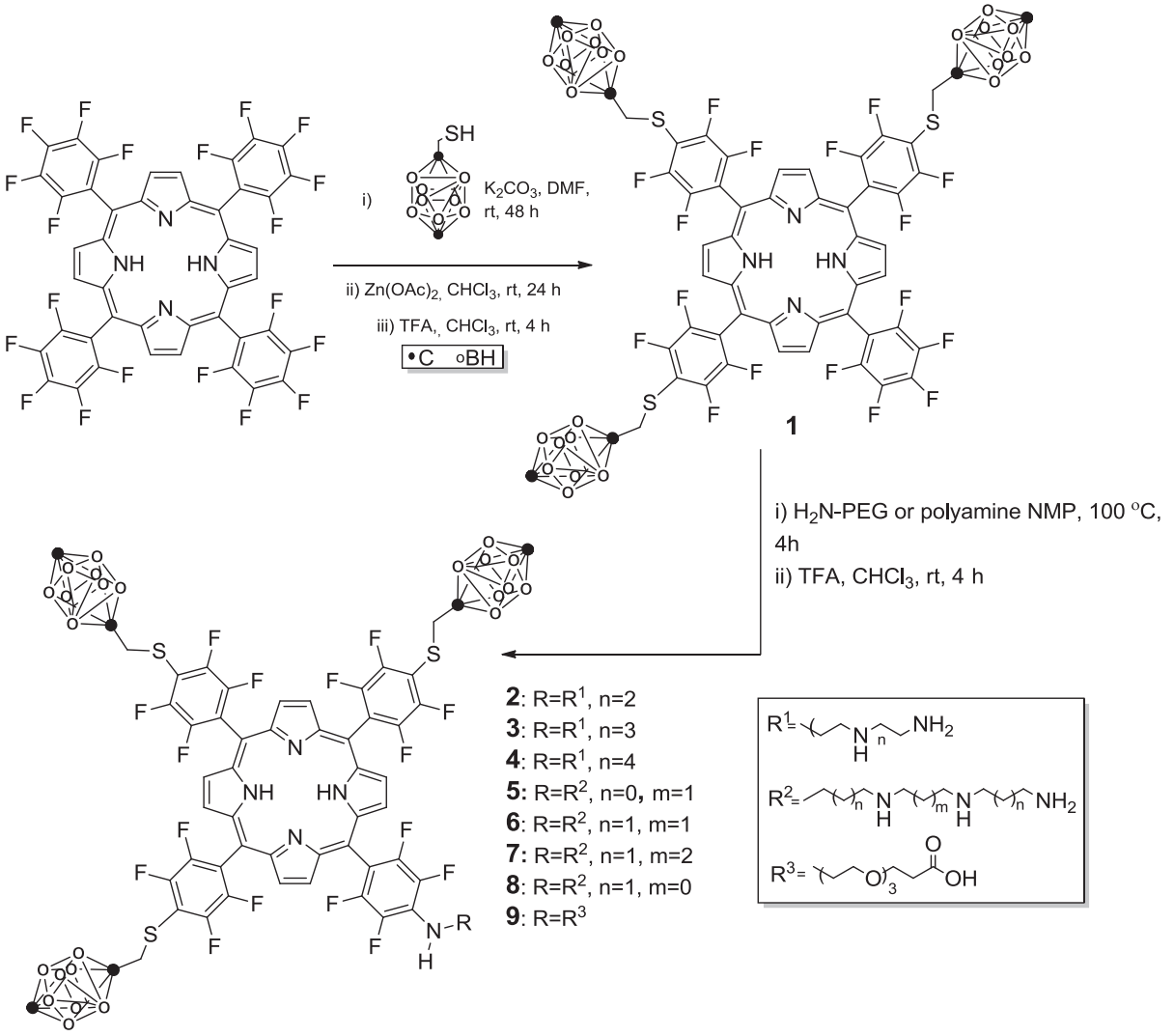
The majority of known carboranes resemble regular icosahedron C_2B_{10} cages. A special attribute of icosahedral C_2B_{10} cages is their nearly spherical shape with a spatial requirement only slightly larger than that of a rotating phenyl ring, allowing replacement of aryl rings with carboranyl units in biologically active molecules while substantially retaining their general properties. Moreover, one can fine-tune the behavior of such species by varying the type of carborane system and by introducing one or more metal centers, either as part of a metallacarborane cage or as exopolyhedral substituents. Another very important property of C_2B_{10} clusters is their previously noted hydrophobicity, which increases in the order of $o- > m- > p$-carborane (with decreasing dipole moment).[7]

Many new types of compounds containing both tetrapyrrole macrocycles and polyhedral boron units in a single molecule have been prepared over the past 20 years[2,10,12,14,15] as this class of compounds shows several advantages for use as BNCT delivery vehicles, including: 1) their demonstrated tumor selectivity and long retention times in tumors; 2) low dark toxicities; 3) their ability for sensitizing the production of cytotoxic oxygen species on light activation, which constitutes the basis for their use in PDT[4,12,16] of tumors; 4) their ability for DNA and RNA binding and for inducing cell apoptosis upon brief exposure to light; 5) their fluorescent properties, which facilitate the detection of tissue-localized boron and treatment planning; 6) their ability to form stable in vivo complexes with a variety of metal ions while retaining their biodistribution and pharmacokinetic properties.[16−18]

2. Carborane-substituted porphyrins

The potential for medical application of porphyrin-like compounds is of interest for several reasons in addition to the cytotoxicity toward tumor cells: they accumulate in cells via binding of their planar aromatic systems to DNA; they can form stable complexes with a variety of metal ions; and their fluorescence makes them ideal for spectroscopic detection and imaging. Furthermore, appending polyhedral boron cages to porphyrins adds even greater versatility, opening up possible applications in BNCT.[8,14,19,20] The pharmacological properties of carboranyl porphyrins and the utilization of compounds of this type in BNCT and PDT have been already documented in reviews.[12,14]

Polyamines are known to be essential for cell growth and differentiation, and due to an upregulated polyamine transport system they accumulate in high concentrations in tumor cells. Thus, conjugation of polyamines to a boron-containing porphyrin could potentially increase boron uptake into tumor cells, favoring DNA binding and overall BNCT efficiency. More recently, synthesis of several polyamine conjugates of a tri(p-carboranylmethylthio)tetra- fluorophenylporphyrin (**1**–**9**) has been reported (Scheme 1). [21]



Scheme 1. Synthesis of compounds **1**–**9**.

These polyamine conjugates showed low dark cytotoxicity and low phototoxicity. All polyamine conjugates, with one exception, showed higher uptake into human glioma T98G cells (up to 12-fold) than the PEG conjugate, and they localized preferentially in the cell endoplasmic reticulum, Golgi, and lysosomes. [21]

Three carboranyltetraphenylporphyrins containing 40 or 80 boron atoms were synthesized and evaluated for their biodistribution and toxicity in EMT-6 tumor-bearing mice. Copper(II) meso-5,10,15,20-tetrakis[3-methoxy-4-(o-carboranylmethoxy)phenyl] porphyrin (**10**) and copper(II) meso-5,10,15,20-tetrakis[3-hydroxy-4-(o-carboranylmethoxy)phenyl]porphyrin (**11**) are B_{40} congeners with different lipophilicities, each less than their

B_{80} congener, copper(II) meso-5,10,15,20-tetrakis[m-(3,5-di-o-carboranylmethoxybenzyloxy)phenyl]porphyrin (**12**) (Figure 1). It was demonstrated that porphyrin **10** may rank among the most clinically promising carboranyl porphyrins ever made to deliver ^{10}B to tumors for BNCT that has also been tested for its toxicity in vivo.[22]

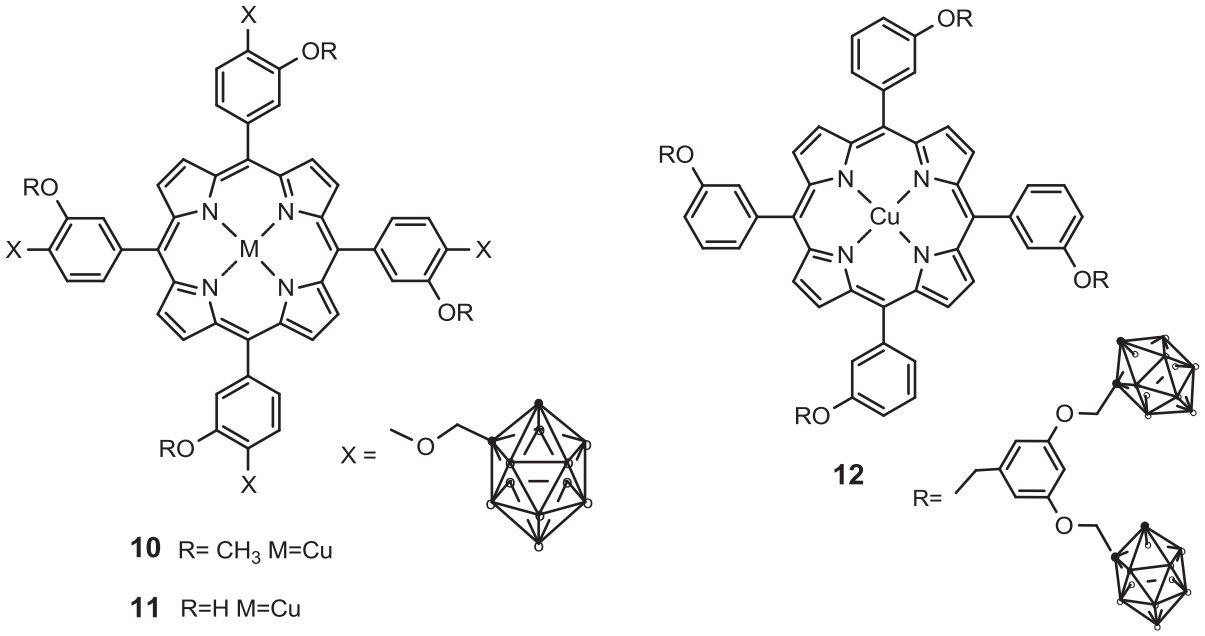


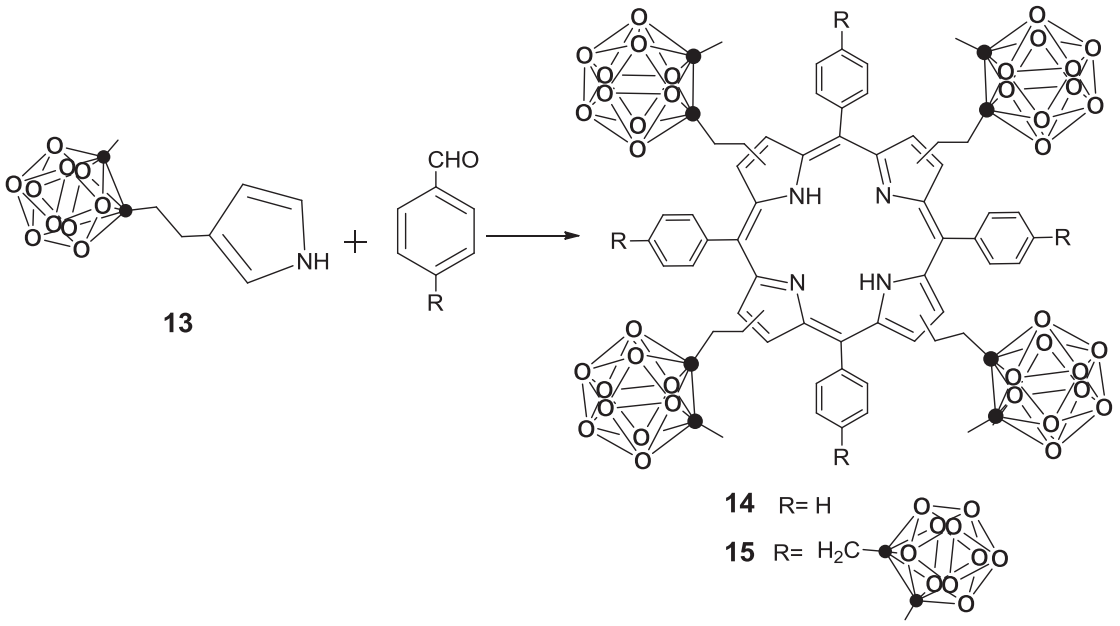
Figure 1. Structures of compounds **10**–**12**.

In most of the porphyrins, carborane cages are linked to the porphyrin macrocycle via the meso-phenyl groups. The study by Vicente and colleagues[23] showed for the first time that multiple boron clusters can be readily incorporated into the same porphyrin macrocycle, linked to both the β-pyrrolic positions and the meso-phenyl rings. These β- carboranylporphyrins of high boron content (32%–43%) (**14,15**) were prepared by the condensation reaction of novel carboranylpyrrole **13** with benzaldehyde under Lindsey conditions (Scheme 2).

Since high amounts of boron are needed for effective BNCT, porphyrins of high boron content are potentially promising delivery vehicles for this therapy. Porphyrins **16**–**19**, containing 8 carborane cages linked via carbon–carbon bonds to the meso-phenyl groups of the porphyrin ring, were synthesized in moderate yields (Figure 2). While the closo-carboranylporphyrins **16** and **17** are highly hydrophobic and completely insoluble in water, the octa-anionic nido analogs **18** and **19** show good solubility in polar solvents (e.g., water, methanol, DMSO) due to their amphiphilic nature.[24]

The results of that study indicated, for the first time, that a porphyrin derivative bearing 8 nido-carborane groups linked to the porphyrin platform via carbon–carbon bonds can still accumulate intracellularly and shows similar low dark toxicity to that found for related carboranylporphyrins of lower boron content, and therefore might have promise for application in BNCT.[24]

Tetrabenzoporphyrins, as the name indicates, contain 4 β,β-fused benzene rings on a porphyrin macrocycle, and thus belong to the family of π-extended porphyrins. Tetrabenzoporphyrins have an advantage over porphyrins as PDT sensitizers in that they typically absorb strongly in the red region of the optical spectrum. The first water-soluble carboranyl-tetrabenzoporphyrin (**23**) was prepared in 43% overall yield as shown in Scheme 3. Condensation of butanopyrrole (**20**) and carboranyl-benzaldehyde (**21**) under Lindsey-type conditions gave



Scheme 2. Synthesis of compounds **14** and **15**.

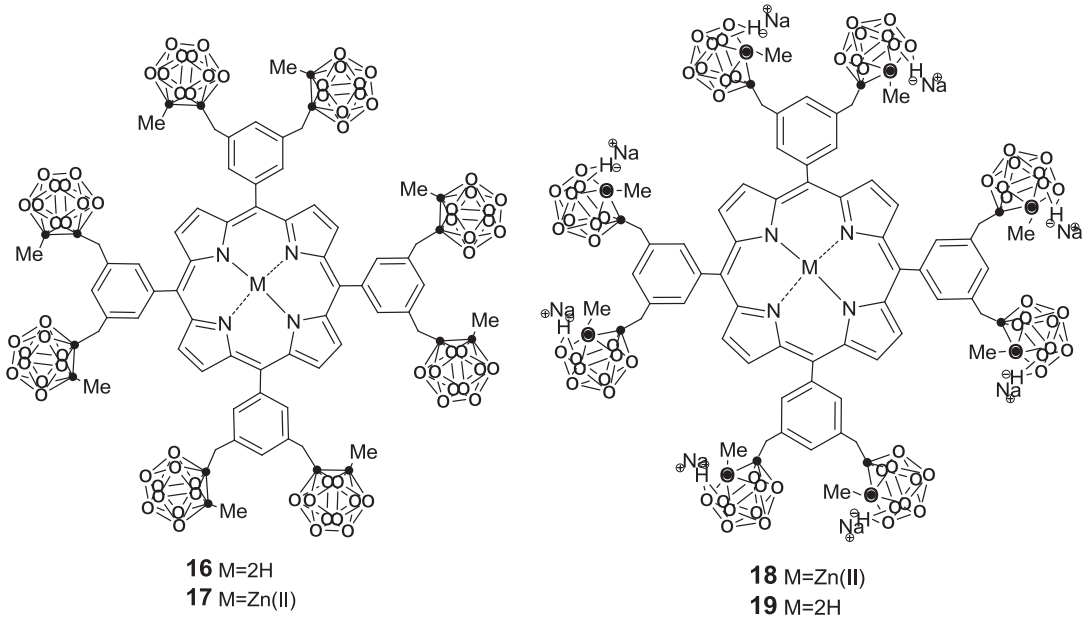
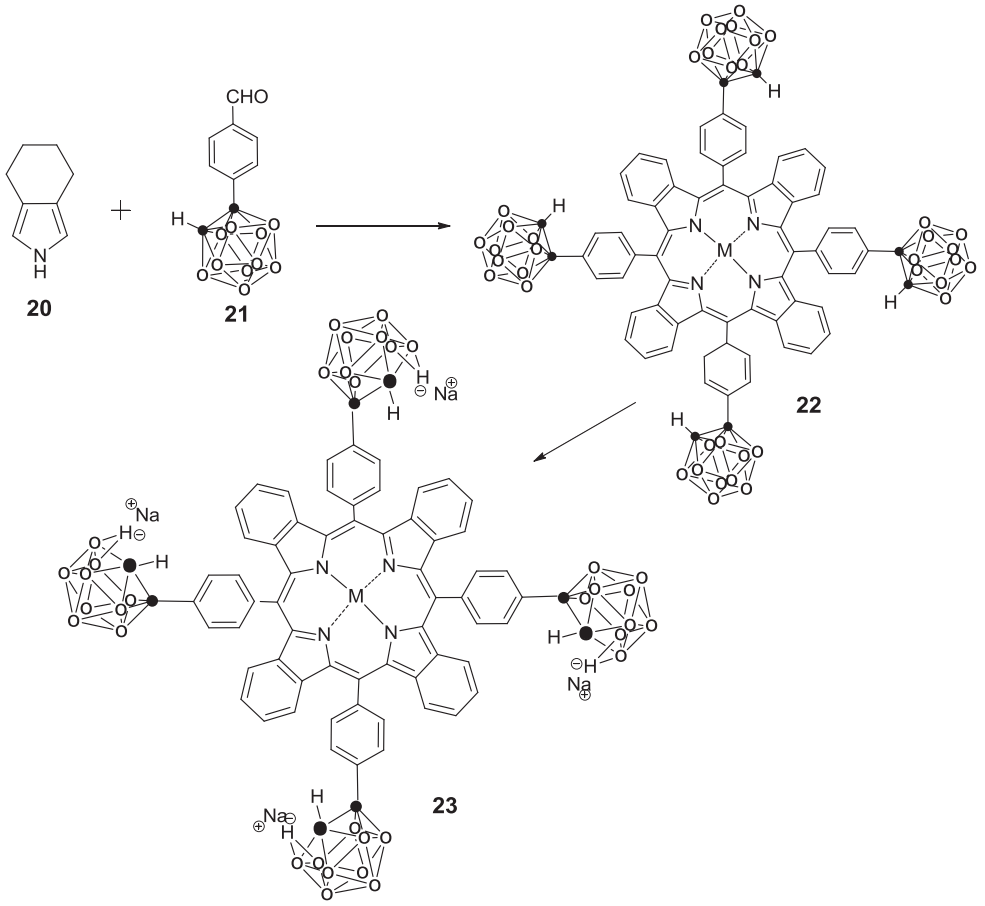


Figure 2. Structures of compounds **16**–**19**.

the corresponding carboranylporphyrin. Insertion of Cu(II) was achieved quantitatively with copper(II) chloride in refluxing toluene for 4 h. Oxidation of the Cu(II)–porphyrin to tetrabenzoporphyrin **22** was accomplished in 75% yield using 8 equiv. of DDQ in refluxing toluene. Demetalation of Cu(II)–tetrabenzoporphyrin **22** occurred upon treatment with concentrated H_2SO_4 at room temperature. The metal-free tetrabenzoporphyrin was converted into the water-soluble nido-carboranyl derivative **23** in 95% overall yield by deboronation of the carborane cages in the presence of tetra-butylammonium fluoride, followed by ion exchange using a Dowex 50WX2-100 resin in the sodium form.[25]



Scheme 3. Synthesis of compounds **22** and **23**.

It was revealed that this tetrabenzoporphyrin compound accumulated within human glioblastoma T98G cells to a significantly higher extent than a structurally related nido-carboranylporphyrin and localized preferentially in the cell lysosomes. The data of animal toxicity studies showed that both compounds are nontoxic even at a dose of 160 mg/kg, administered intraperitoneally as a single injection at a concentration of 4 mg/mL.[26]

Recently, metallacarboranes, and in particular the cobaltabisdicarbollide anion, have received much interest[27] because these complexes contain a larger number of boron atoms than the carboranes and the closo-dodecaborate anions and are water-soluble in the form of sodium or potassium salts while still maintaining the hydrophobic character needed for crossing cellular membranes. Furthermore, they show remarkable stability in the presence of acids, moderate bases, radiation, and high temperature.

Several porphyrincobaltacarborane conjugates (**24**–**28**) that contained 4 to 16 carborane clusters per porphyrin macrocycle were prepared in excellent yields (90%–97%) by means of a ring-opening reaction of the zwitterionic cobaltacarborane [3,3'-Co(8-$C_4H_8O_2$–1,2-$C_2B_9H_{10}$)(1',2'-$C_2B_9H_{11}$)] (Figure 3).[28] It was demonstrated that the cellular uptake of this series of conjugates depends on the number of cobaltacarborane moieties at the porphyrin periphery and their distribution, amphiphilic character, and aggregation properties. Conjugates **25** and **27**, bearing 2 adjacent and three 3,5-dicobaltacarboranephenyl groups, respectively, accumulated the most within HEp_2 cells, showed very low dark toxicity and phototoxicity, and are, therefore, the most promising BNCT agents.[28]

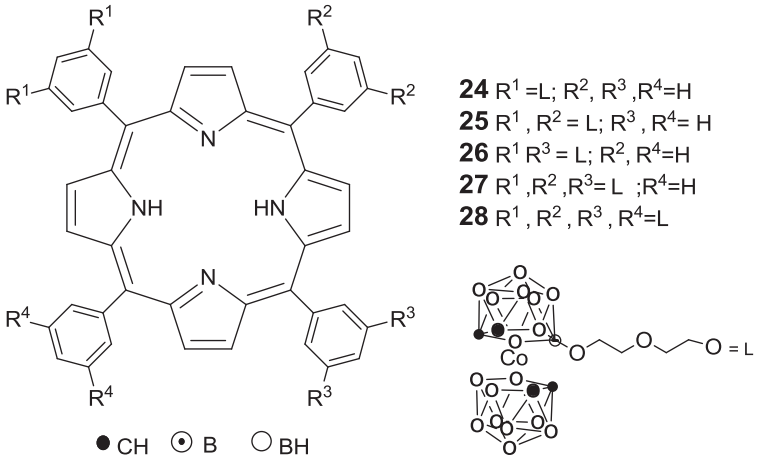
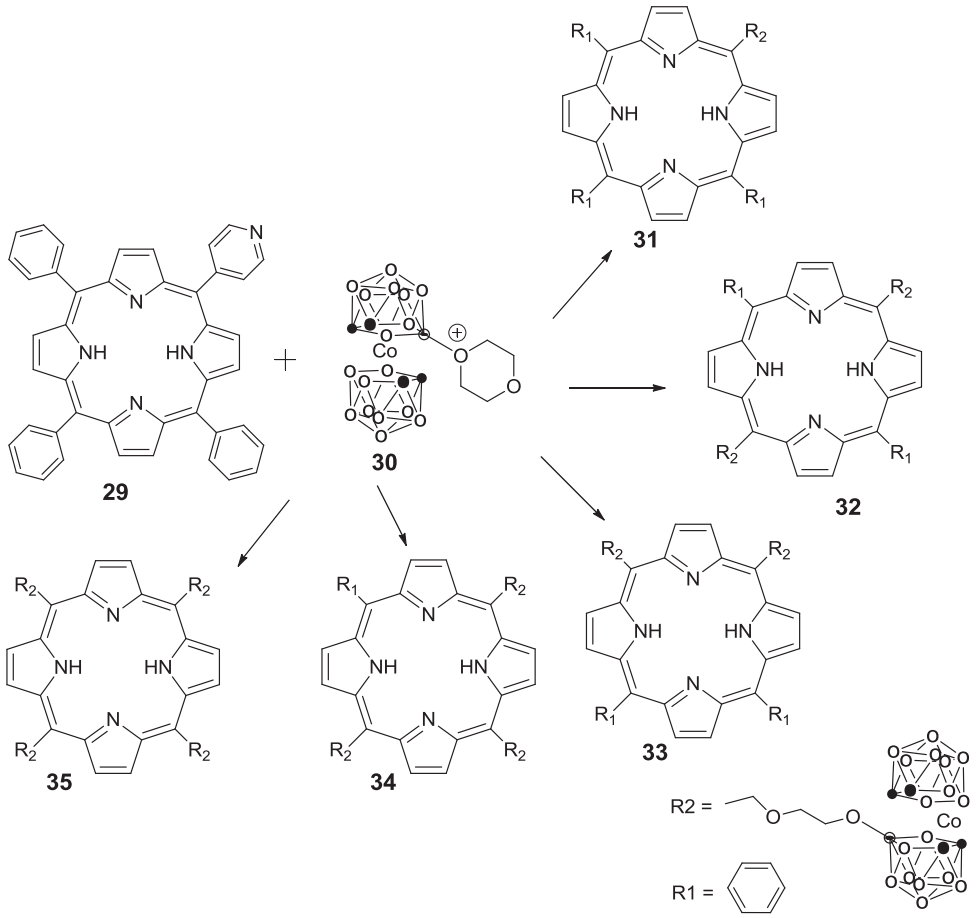


Figure 3. Structures of compounds **24**–**28.**

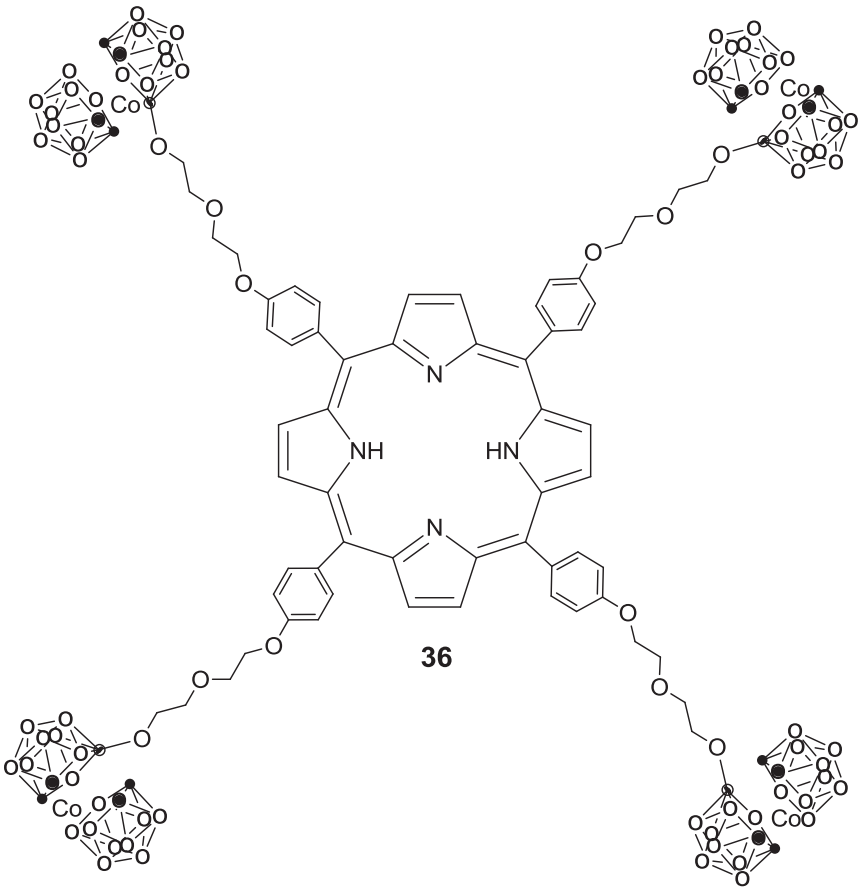
The total syntheses of 5 new porphyrin-cobaltacarborane conjugates (**31**–**35**) have been achieved in 88%–98% yields in a single-step ring-opening reaction between a nucleophilic meso-pyridyl-containing porphyrin (**29**) and zwitterionic cobaltacarborane [3,3'-Co(8-$C_4H_8O_2$-1,2-$C_2B_9H_{10}$)(1',2'-$C_2B_9H_{11}$)] (**30**) (Scheme 4). These unique zwitterionic compounds have 1 to 4 cobaltabisdicarbollide anions conjugated to the porphyrin



Scheme 4. Synthesis of compounds **31**–**35**.

macrocycle via $(CH_2CH_2O)_2$ chains. The cellular uptake, cytotoxicity, and subcellular localization of cobaltacarborane-porphyrins **31**–**35** were investigated in human HEp_2 cells. It was found that the number and distribution of cobaltacarborane residues linked to the porphyrin macrocycle has a significant effect on the cellular uptake of the conjugates.[29]

It was discovered that this easy, efficient, high yielding reaction also proceeds with phenol-substituted porphyrins as the nucleophilic species. The conjugation of 5,10,15,20-tetra(4-hydroxyphenyl)-porphyrin with cobaltacarborane was achieved in 85% yield upon activation of the porphyrin hydroxyl groups with either cesium carbonate or potassium carbonate in anhydrous acetone, thus affording conjugate **36** as cesium or potassium salts (Figure 4).[30]



36

Figure 4. Structure of compound **36**.

The second strategy for preparing the boronated porphyrin derivatives is the direct functionalization of a preformed macrocycle (protoporphyrin-type or meso-tetraphenylporphyrin-type). Protoporphyrin IX [i.e. bis(α-methyl-β-pentylethylether) protoporphyrin IX (**37**) and bis(α-methyl-β-dodecanylethylether)-protoporphyrin IX] bearing polyhedral borane anions ($B_{12}H_{11}SH^{-2}$ or $B_{12}H_{11}OH^{-2}$) (**38**–**41**) was synthesized with reasonable yields (Figure 5). Modification of the protoporphyrin IX structure was achieved by variation of the lengths of the alkyl chains (pentyl and dodecanyl) attached through ether linkages to the former vinyl groups. The goal of this modification was to develop boronated porphyrins with chemical and physical properties that differed from those of protoporphyrin IX. Importantly, these new structurally varied boronated

porphyrins displayed a wide spectrum of water solubilities and surprising spectroscopic properties with extremely stable and nontoxic closo-borane anions. Furthermore, it was found that the boronated porphyrins exhibited low cytotoxicities and high levels of accumulation and induced potent PDT effects with a variety of cancer cell lines.[31]

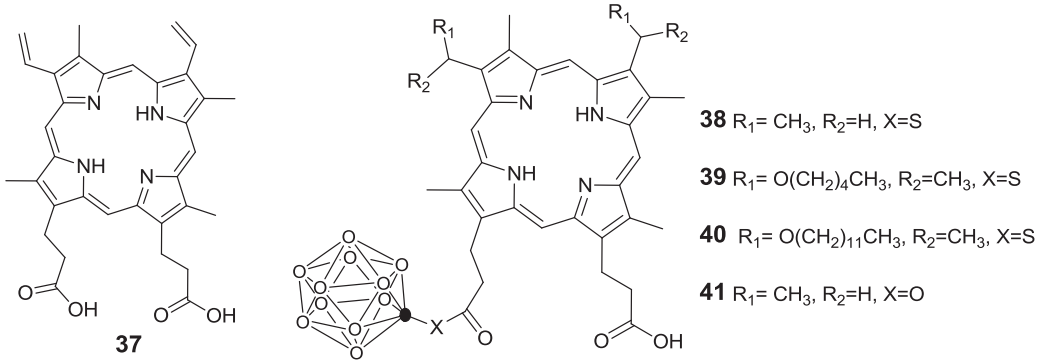


Figure 5. Structures of compounds **37**–**41**.

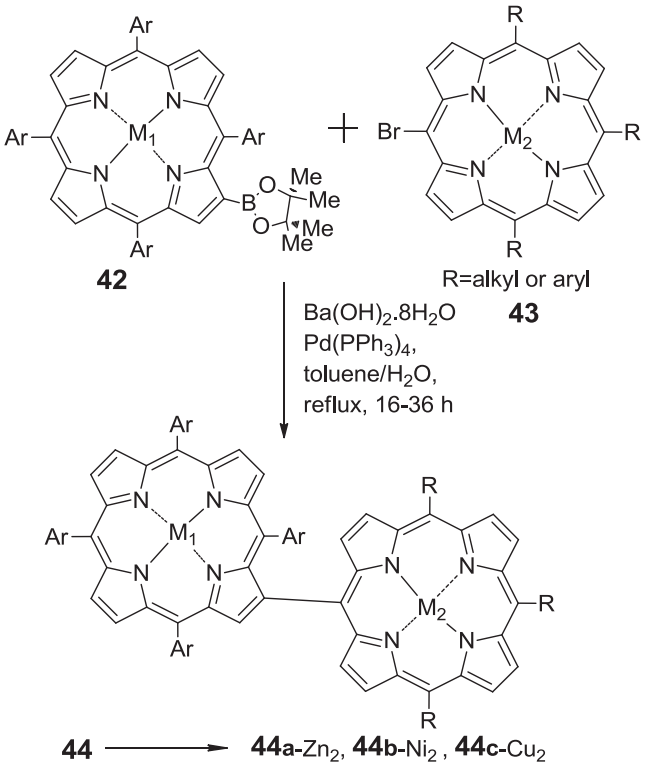
3. Porphyrins with boronic ester groups

The synthesized porphyrinyl boronic acid esters have proven to be valuable coupling partners in Suzuki couplings, leading to the synthesis of a broad variety of intrinsically axially chiral β,β'-linked bisporphyrins.[32,33] A recent paper described a variable, straightforward synthetic procedure for the construction of β,meso-linked porphyrin multichromophores in good to excellent yields.[34] In a Suzuki-type coupling reaction β-borylated 5,10,15,20-tetraarylporphyrins (TAPs) served as versatile building blocks for the preparation of a plethora of directly linked, unsymmetrically substituted di- and triporphyrins. Besides their interesting photophysical properties, the trimeric porphyrin arrays show particularly exciting stereochemical features. The established protocols thus opened a convenient entry into the synthesis of achiral and chiral unsymmetrically substituted β,meso-linked oligoporphyrins, e.g., for applications in biomedicine or nonlinear optics.[34]

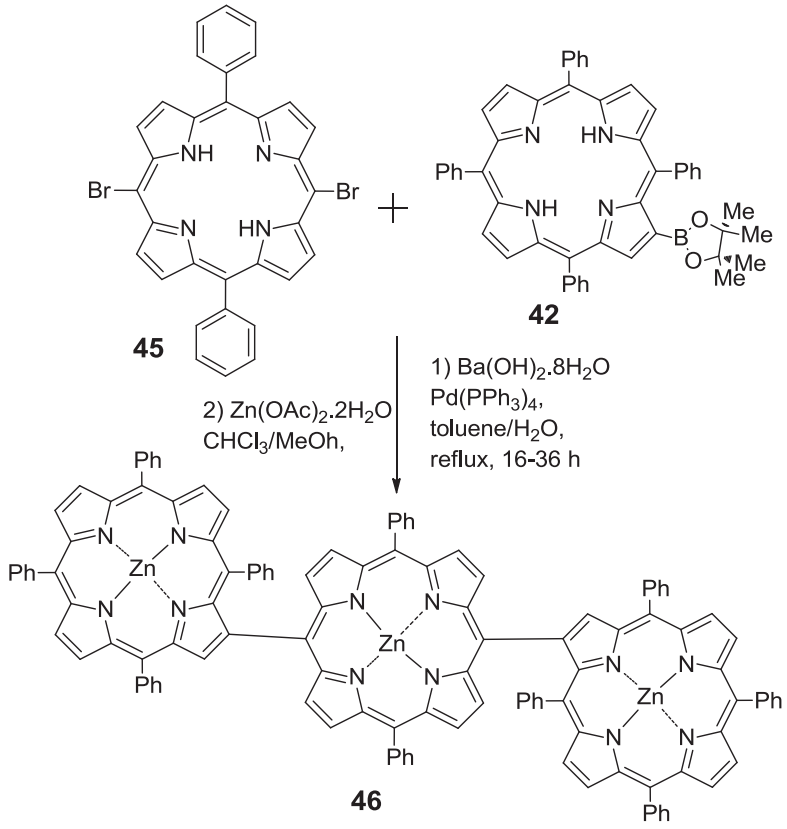
Starting with 5,10,15-homosubstituted precursors (**43**) and porphyrin boronic acid esters (**42**) as the coupling partners, the simple Cs-symmetric A3-βTAP-type bisporphyrins **44a**–**44c** bearing 3 identical aryl or alkyl substituents in the meso-linked moiety were generated in good yields (Scheme 5). Full metalation of the dimers **44** to give the respective zinc(II), nickel(II), or copper(II) complexes **44a**–**44c** was easily achieved in yields higher than 92%.[34]

The established strategy also offers an easy entry into the design of trimeric porphyrins featuring 2 direct porphyrin–porphyrin axes: starting from dibrominated 5,15-diphenylporphyrin (**45**), the βTAP-5,15-A2-βTAP trimer (**46**) was synthesized, in which 2 identical TAPs were β-linked to the central porphyrin macrocycle in a linear array (Scheme 6).[34]

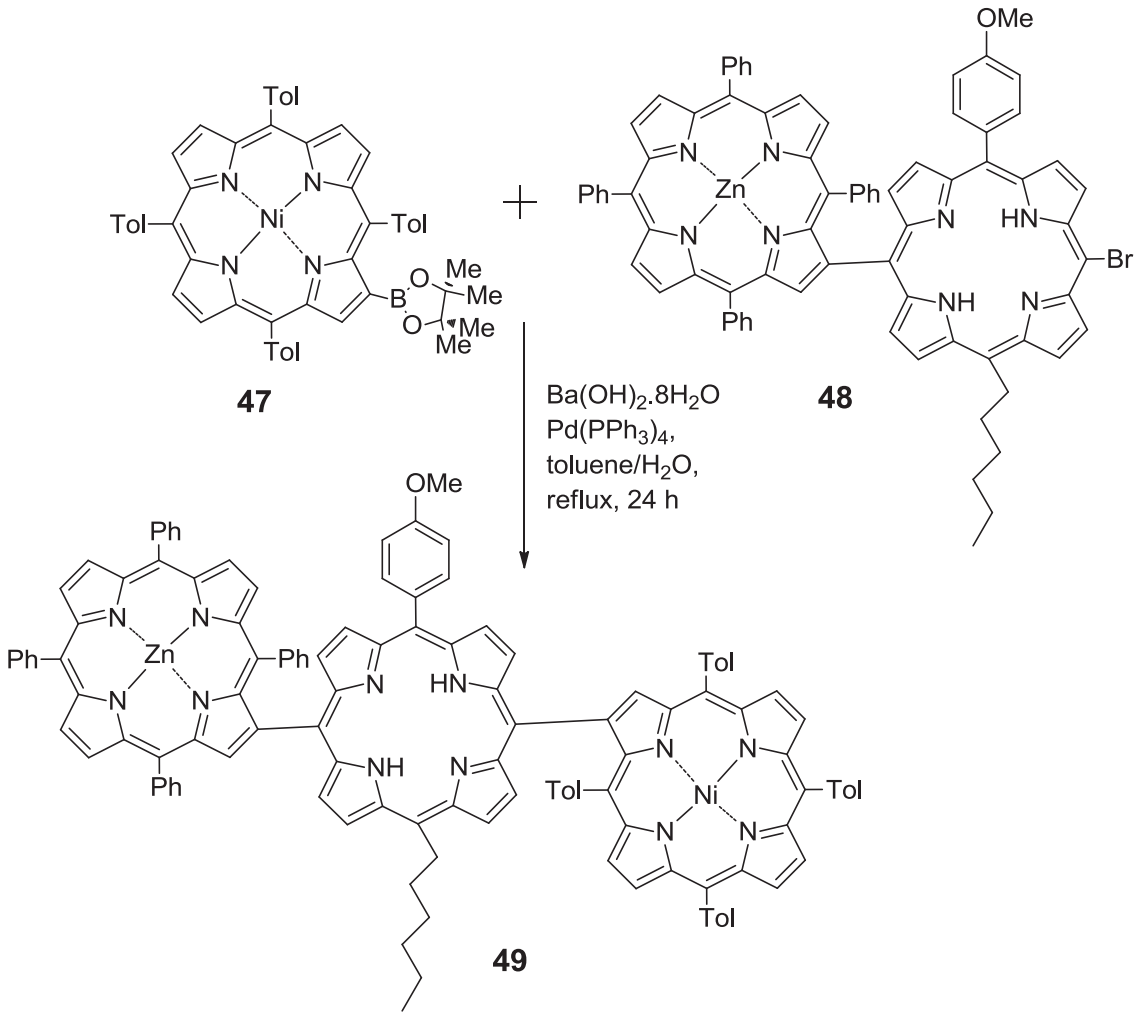
As expected, the functionalized dimers were proved to be versatile precursors for the construction of highly complex porphyrin trimers (Scheme 7).[34]



Scheme 5. Synthesis of compound **44**.



Scheme 6. Synthesis of compound **46**.



Scheme 7. Synthesis of compound **49**.

4. Carborane-substituted porphyrazines

Porphyrazines, with chemical and physical properties not easily accessible to porphyrins, are readily synthesized through template cyclotetramerization of an appropriate dinitrile derivative. As, in principle, boron-containing porphyrazines may conjugate the photosensitizing properties of the macrocycle with the BNCT sensitizing capability of the boronated substituents, they have potential in multiple approaches for anticancer therapy.[35]

An effective strategy to synthesize a new family of boronated porphyrazines to be delivered through the membrane of cancerous tissues as such or with the help of liposomes was developed recently. The synthesis and the basic physicochemical properties of neutral octa-closo-carboranyl-alkylthio-porphyrazine as well as of their water-soluble counterpart (**50**) were obtained by mild deboronation of the closo-polyedra (Figure 6).[35]

5. Porphyrazines with boronic ester groups

Formation of boronic ester from difunctional boronic acid with diols has been used for the construction of discrete cycles and cages.[36,37] Although the presence of 2 oxygen donor atoms is generally sufficient to complete boronic ester formation, an additional N donor has also been effectively used to form a further B–N bond.[38] Studies

showed that, in such a case, the boron atom is tetra-coordinated and forms a dative bond with the nitrogen atom.[39]

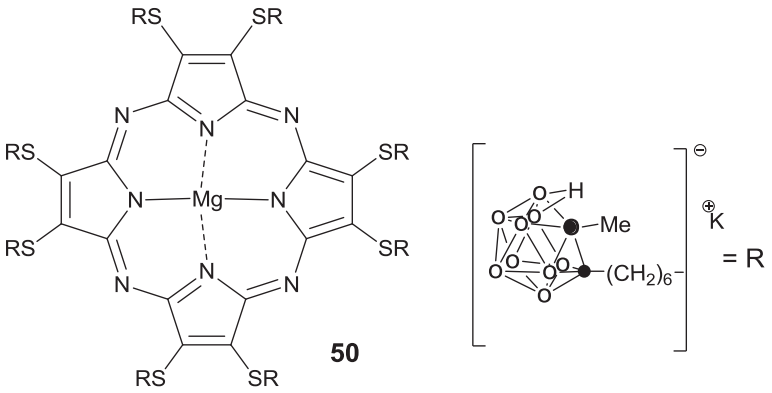


Figure 6. Structure of compound **50**.

Phenylboronic acid esters of an unsaturated precursor 1,2-dicyano-1,2-bis(2-hydroxyethylthio) ethylene and the magnesium porphyrazine derived from it (**51b**) have been prepared either by refluxing a mixture of the reagents in chloroform in the presence of a molecular sieve or by solvent-free heating in an oven under reduced pressure. The critical point is whether meso-N-atoms of the porphyrazine core will take part in binding to the boron group, as shown in Figure 7a, or if only O-donors will form the ester structure, as in Figure 7b.[39]

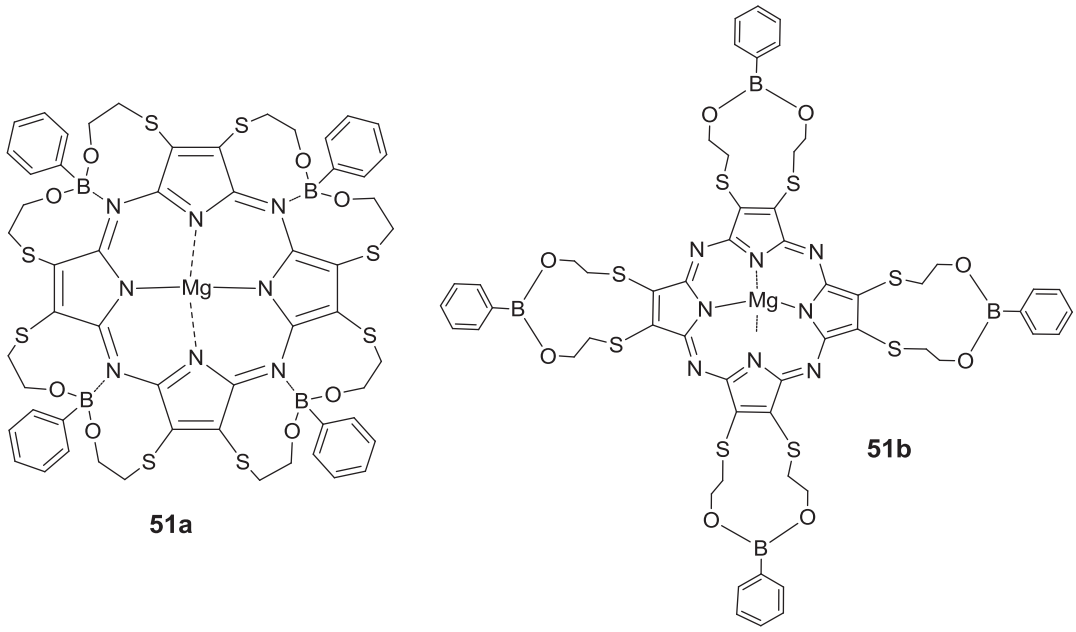


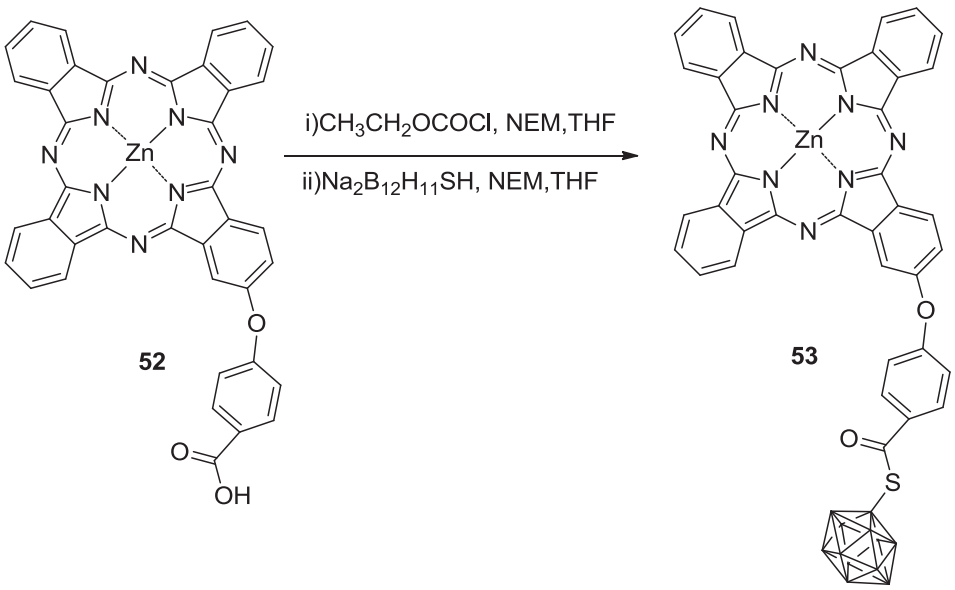
Figure 7. Two possible bonding patterns for the boronic ester of Mg-porphyrazine: tetracoordinated boron (**51a**) and tricoordinated boron (**51b**).

The ^{11}B NMR spectrum is extremely useful in deciding on the coordination number of boron atoms. It is a general rule that 4-coordinate boron compounds give a signal around 10 ppm, while in the case of 3-coordinate compounds it comes out around 30 ppm.[40–42]

^{11}B NMR of porphyrazine molecules is illustrative and simple with a single chemical shift at 28.18 ppm as a consequence of the tricoordinated boron atom present in the structure. These data provide the critical proof to decide on the structure where boron atoms are esterified with 2 hydroxyethylthio units without any interaction with the aza functionalities of the porphyrazine core.[39]

6. Carborane-substituted phthalocyanines

Research involving boron-containing phthalocyanines is at a much more elementary stage of development, both as chemical entities and certainly in terms of their biological evaluation.[10] Only a few boron-containing phthalocyanines have been reported to date and it may be due to their difficult syntheses and purification procedures. In order to investigate the possible utilization of boronated phthalocyanines as photo-/radiotherapeutic agents in a combined PDT+BNCT approach to tumor treatment, Fabris et al.[43] prepared a Zn-phthalocyanine peripherally substituted with a dodecaborane (**53**) through the reaction of borocaptate disodium salt with an asymmetric anhydride of 2-(4-carboxyphenoxy) phthalocyaninato Zn(II) (**52**). The reaction was carried out in anhydrous tetrahydrofuran and the yield was 71% (Scheme 8).[43]

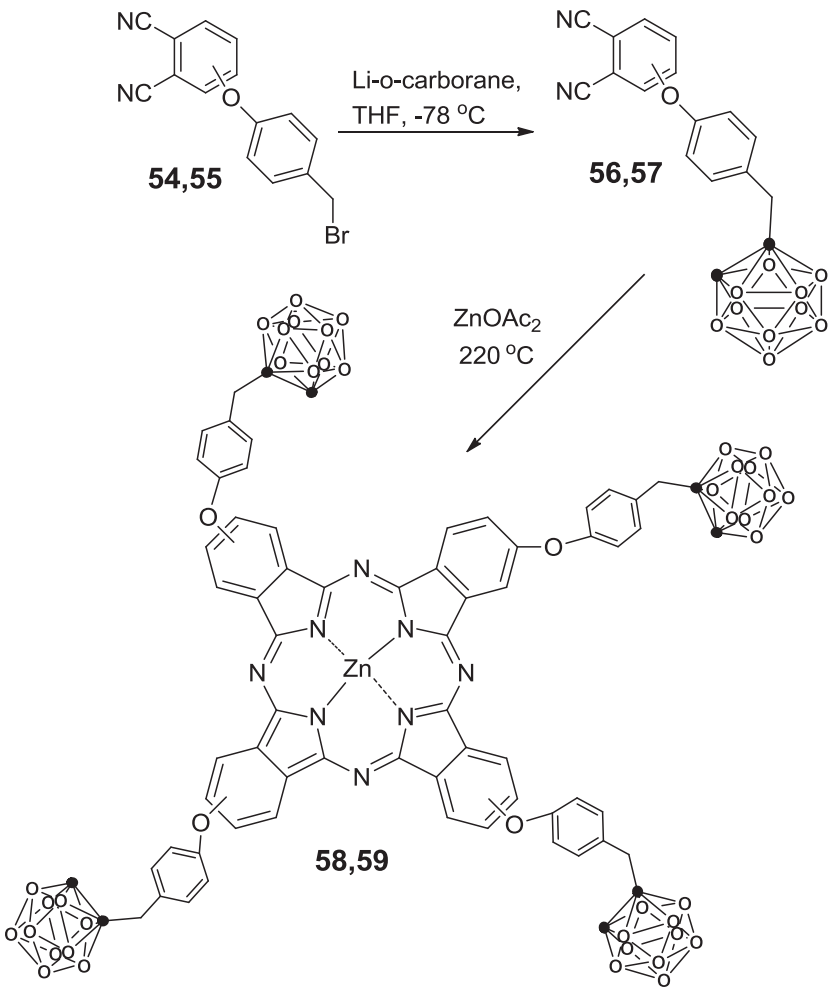


Scheme 8. Synthesis of compound **53**.

The boronated phthalocyanines appear to be efficient photodynamic sensitizers as no significant variations can be detected in the quantum yields for the generation of singlet oxygen and in the efficiency of photooxidative modification of tryptophan.[43]

1,8(11),15(18),22(25)- and 2,9(10),16(17),23(24)-tetrasubstituted zinc(II)-phthalocyanines carrying 4 carbon–carbon linked *o*-carboranyl units (40 boron atoms, 27.5% boron by weight) were prepared by the tetramerization of the carborane cage containing phthalocyanine precursors.[44] Phthalonitriles **56** and **57** were synthesized in satisfactory yields (55% and 48%, respectively) by reaction of the lithium salt of *o*-carborane with benzyl bromide (**54** and **55**) in anhydrous THF. The conversion of the phthalonitriles **56** and **57** to the corresponding Zn(II)-phthalocyanines **58** and **59** was carried out by heating a finely ground mixture of **56** or **57** and zinc acetate at 220 °C for several hours (Scheme 9). Any attempt to obtain phthalocyanines **58** and **59** by different

methods failed because of the extensive decomposition of the precursors due to the low stability of the carborane cage towards strong basic conditions.[44]



Scheme 9. Synthesis of compounds **56**–**59**.

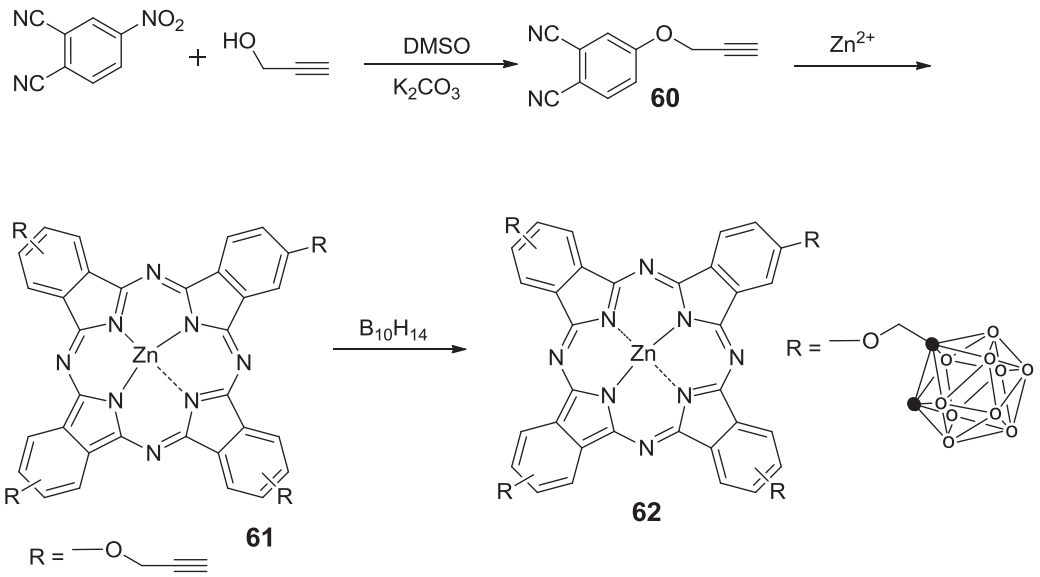
The investigations focused on a more detailed characterization of the photosensitization pathways involved in cell inactivation and an exploratory test of its PDT and BNCT activity in mice bearing a tumor known to be poorly responsive to conventional PDT, such as malignant melanotic melanoma.[45]

It was found that the ether bonds connecting the 4 carborane cages to the main tetraazaisoindole macrocycle were very stable in a variety of biologically relevant media, as well as in cells. The photophysical and photokinetic properties of carboranyl-carrying phthalocyanine were found to be similar to those typical of other photodynamically active porphyrin-type photosensitizers, including a singlet oxygen quantum yield of 0.67, which means that a high fraction of the absorbed photons promote a chemical reaction, namely an oxidative attack on a variety of cell/tissue constituents, including unsaturated lipids, aromatic and sulfur-containing amino acid residues, and guanosine bases.[45] In spite of the steric hindrance caused by the bulky *p*-(methyl-carboranyl)phenoxy moieties, ZnB_4Pc is taken up with a high efficiency by melanotic melanoma cells enough to induce a statistically significant tumor growth delay upon BNCT treatment.[45]

Two strategies are then obvious for the preparation of a boronated phthalocyanine: 1) attach the boron at an early stage by placing the boron moiety on the phthalonitrile-"phthalonitrile route", or 2) add the boron group to a reactive functional group on a suitably preformed phthalocyanine derivative-"phthalocyanine route".[46]

For the following carborane-substituted phthalocyanines, the "phthalocyanine route" is preferable to the "phthalonitrile route" because only partial substitution occurs.

o-Carboranyl-substituted phthalocyanine zinc(II) complexes with good solubility in organic solvents were successfully prepared in good yields from the reaction of substituted phthalocyanine zinc(II) complexes with polyhedral boron compounds.[47] For the synthesis of the phthalocyanine **62** with an oxymethylene unit between the phthalocyanine and *o*-carboranyl groups, 4-nitrophthalonitrile was reacted first with propargyl alcohol to give the propynyloxy-substituted derivative **60** with 97% yield. The cyclotetramerization of phthalonitrile **60** in n-pentanol with zinc(II) acetate yielded tetrapropynyloxy-substituted phthalocyanine **61** (Scheme 10). The last step was the reaction of **61** and decaborane in a mixture of acetonitrile and toluene to give the tetra-*o*-carboranyl-substituted phthalocyanine **62** in 33% yield (Scheme 10).[47]



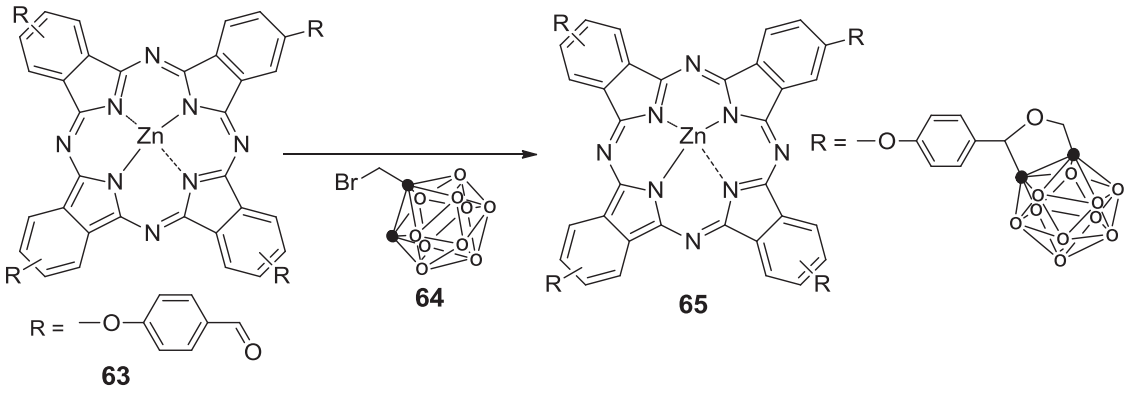
Scheme 10. Synthesis of compounds **60**–**62**.

The tetra-*o*-carboranyl-substituted phthalocyanine (**65**) was prepared by the reaction of the tetraformylphenoxy-substituted phthalocyanine (**63**) and 1-bromomethyl-2-lithium-*o*-carborane (**64**) generated in situ by the metalation of bromomethylcarborane with lithium diisoproylamide (Scheme 11).[47]

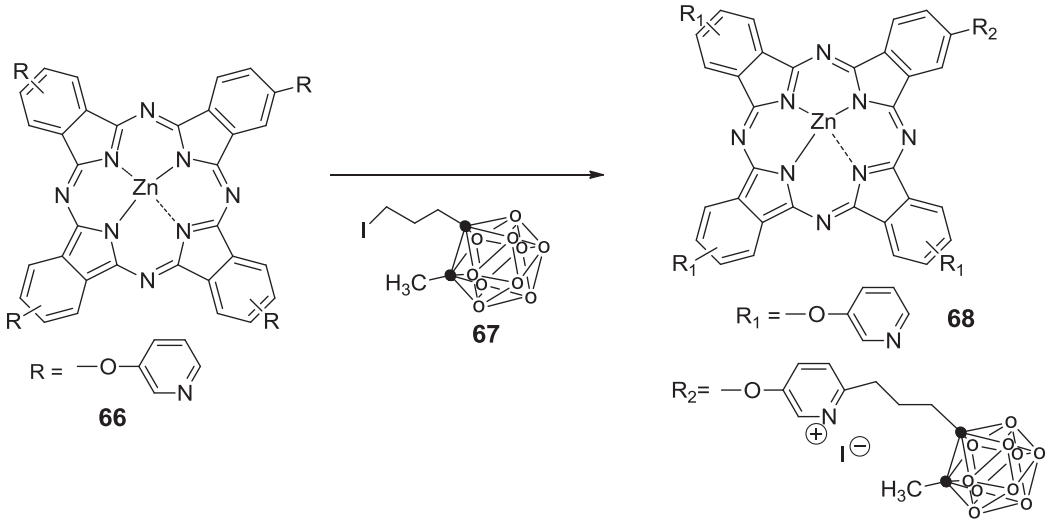
The phthalocyanine derivative **68** with a propylene unit between the positively charged phthalocyanine and the *o*-carboranyl groups was obtained in a yield of 34% through N-alkylation of 2,9,16,23-tetra-(3-pyridyloxy)-phthalocyanine zinc(II) (**66**)[48] with 1-iodopropyl-2-methylcarborane (**67**) (Scheme 12).[49] Although an excess of **67** was used, only mono-alkylation could be achieved. The reason may be a side reaction by attack of the N-atom of the pyridyl group as a nucleophile at the carborane derivative.[47]

o-Carboranyl-substituted phthalocyanines **71** and **74** with an ester or an amide unit between the phthalocyanine and the carboranyl groups had been obtained before from the reaction of 2,9,16,23-tetra-(4-hydroxyphenoxy)-phthalocyanine zinc(II) (**69**) with *o*-C-carboranyl acetyl chloride (**70**) or 2,9,16,23-tetra-(4-

aminophenoxy)-phthalocyanine zinc(II) (**72**) with C-methyl-CO-chlorocarbonyl-o-carborane (**73**) in 53% and 65% yields, respectively (Scheme 13).[50]



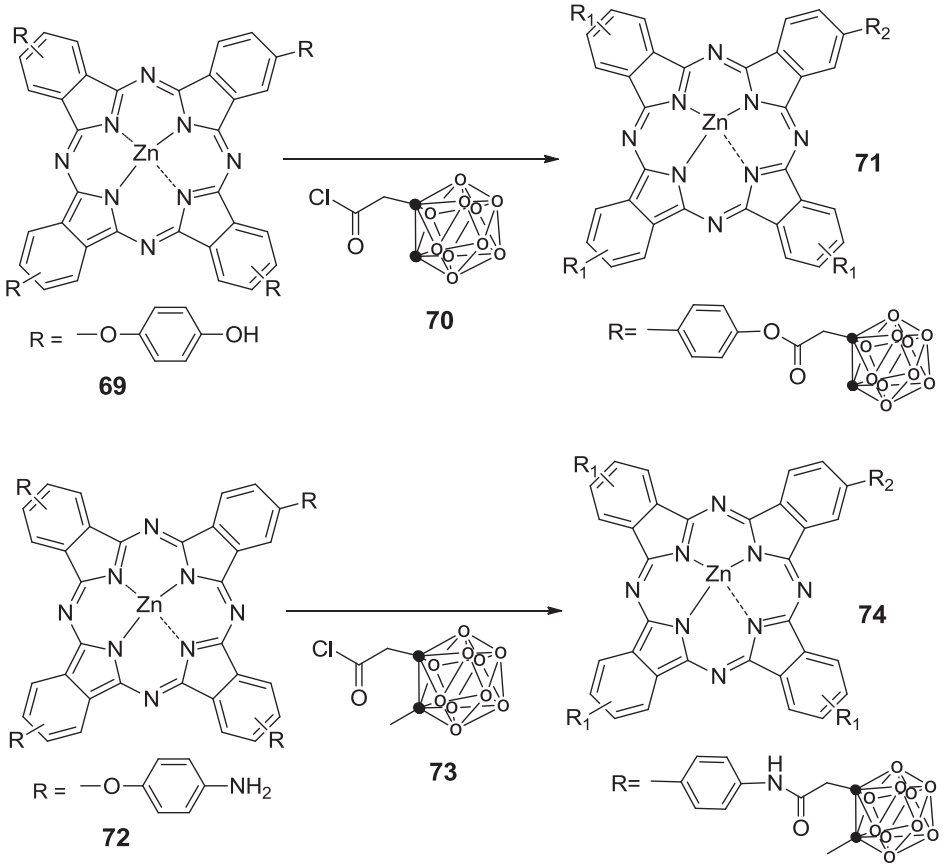
Scheme 11. Synthesis of compound **65**.



Scheme 12. Synthesis of compound **68**.

These *o*-carboranyl substituted phthalocyanine zinc(II) complexes exhibit improved singlet oxygen quantum yields, photooxidative stabilities, and photocatalytic activities compared to phthalocyanine zinc(II) complexes without *o*-carboranyl groups. Therefore these *o*-carboranyl complexes are of interest for use in cancer therapy.[47]

The closo-dodecaborate anion has low toxicity and large amounts of boron atoms, and it can be easily produced from ^{10}B-enriched commercial materials. These advantages make it a good candidate for design of BNCT agents. A new Zn(II)-phthalocyanine with 8 closo-dodecaborane units (96 boron atoms) (**75**) was prepared through a multistep reaction sequence starting with cyclotetramerization of 4-(3,5-dimethoxyphenoxy)phthalonitrile in the presence of zinc(II) acetate (Figure 8). The conjugate was constructed to estimate its potential as a boron delivery agent for anticancer boron neutron capture therapy. The boronated phthalocyanine was found to accumulate in A549 human lung adenocarcinoma.[51]



Scheme 13. Synthesis of compounds **71** and **74**.

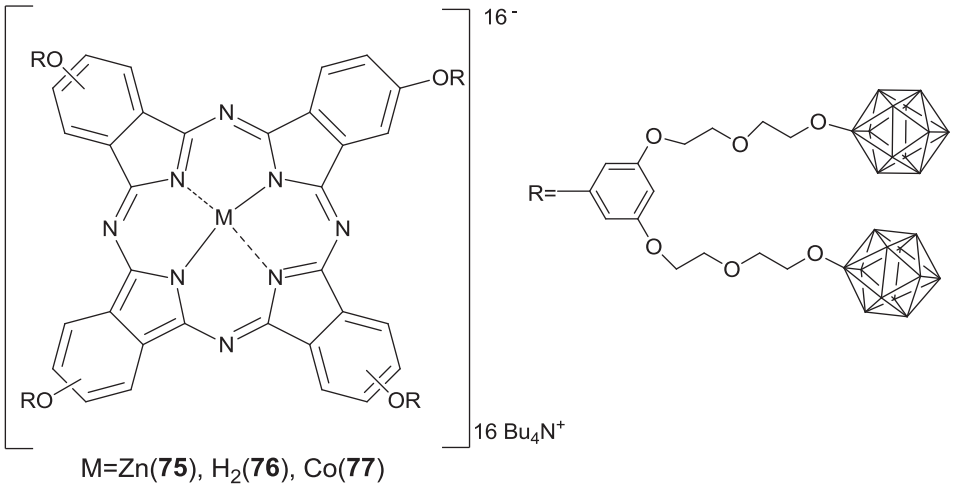


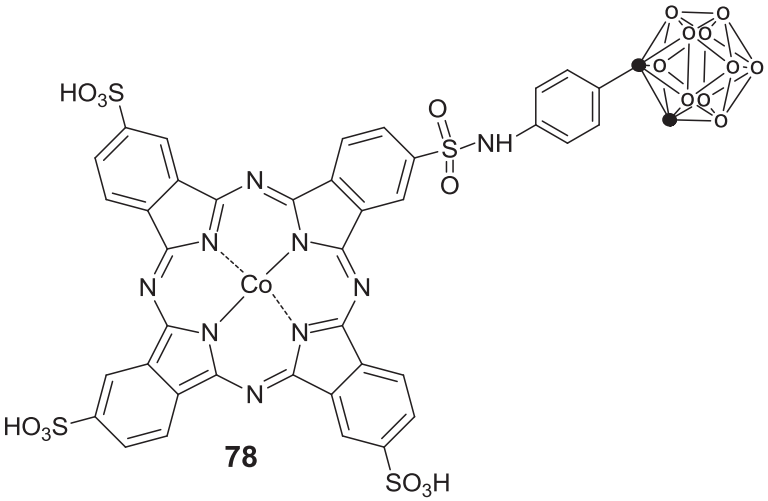
Figure 8. Structures of compounds **75**–**77**.

The electrochemical and spectroelectrochemical properties of metal-free (**76**) and Co(II) (**77**)-derivative of phthalocyanine **75** were also investigated.[52]

Water solubility is a goal for many chemists in various fields, as several of the current applications of phthalocyanines are of biological interest and/or require environmental friendliness, necessitating water solubility

in various ranges of concentrations, pH levels, etc. This is the case of biological and medical applications such as photodynamic therapy.

The first water-soluble boronated phthalocyanine, bearing only one closo-carborane cage, was synthesized by Soloway and colleagues.[53] However, no detailed information on its purification and characterization was reported (Figure 9).



78

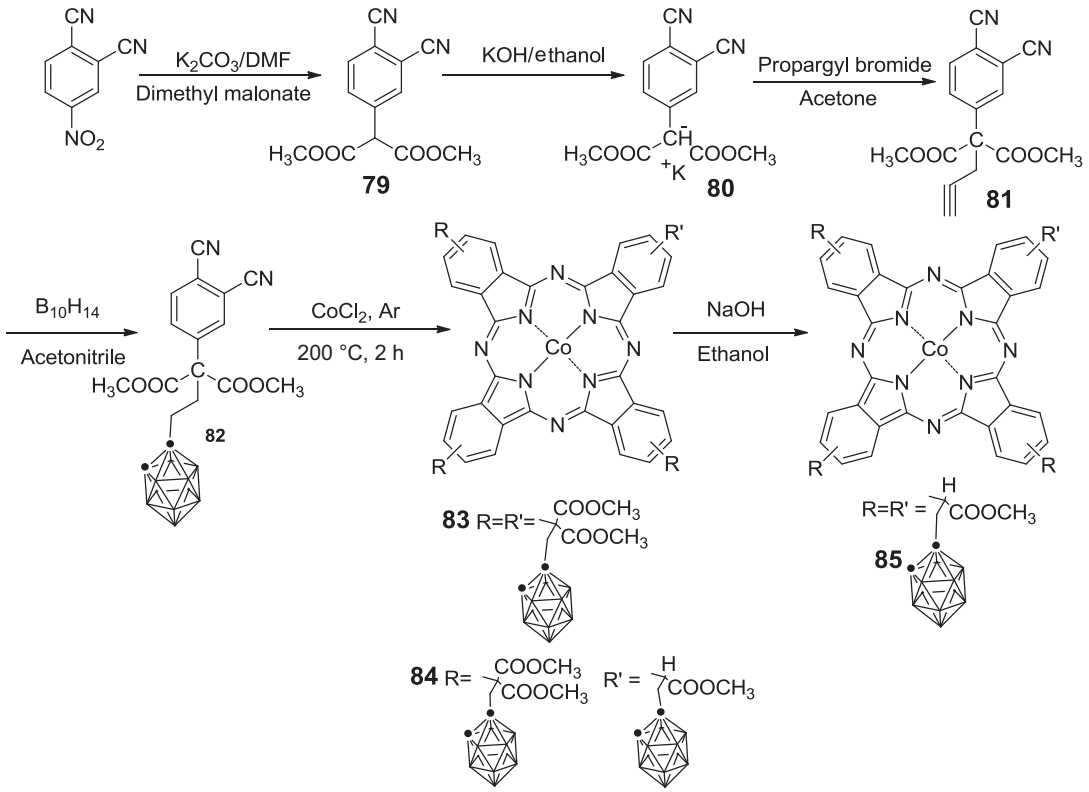
Figure 9. Structure of compound **78**.

The phthalonitrile route is preferable for the preparation of soluble phthalocyanines containing carborane units, since it appeared possible to incorporate a protected solubilizing group, the methyl esters, into the phthalonitrile and then deprotect in a later step.

A study in 1996 reported the synthesis and characterization of the first boronated metallophthalocyanine in which 4 closo-carborane cages are covalently linked to the periphery of the phthalocyanine ring.[46] Reaction of 4-nitrophthalonitrile with dimethyl malonate in the presence of a base yielded dimethyl(3,4-dicyanophenyl)malonate, which was converted into dimethyl(3,4-dicyanophenyl)propargylmalonate (**81**) by sequential treatment with potassium hydroxide and propargyl bromide. Formation of the *o*-carborane cage was accomplished by reaction of the alkyne with decaborane ($B_{10}H_{14}$) in acetonitrile at reflux. High-temperature solid-state condensation of the resulting *o*−carboranylphthalonitrile with cobalt(II) chloride followed by ester deprotection and cation exchange to the sodium salt provided the water-soluble closo-carboranylphthalocyanine product (**85**) (Scheme 14).[46]

Boron hydride compounds have very different solubility in water: closo-carboranes have exceptionally hydrophobic characters, whereas nido-carboranes and closo-dodecaborate, due to their anionic nature, are very soluble as sodium salts. The possible transformation of closo-carborane into nido- provides the possibility to increase the water solubility of the designed compounds.[14]

The first phthalocyanine bearing 8 nido-carborane units, the octaanionic 2,3,9,10,16,17,23,24-octakis (7-methyl-7,8-dicarba-nido-undecaboran-8-yl)hexylthio-6,13,20,27-(29H,31H)phthalocyanine (**86**) in the form of potassium salt, was synthesized through direct cyclization of the corresponding dicyano derivative in the presence of DBU in a 1:7 molar ratio. DBU is a sufficiently weak nucleophile to limit deboronation to the closo–nido conversion (Figure 10).[54]



Scheme 14. Synthesis of compounds **79**–**85**.

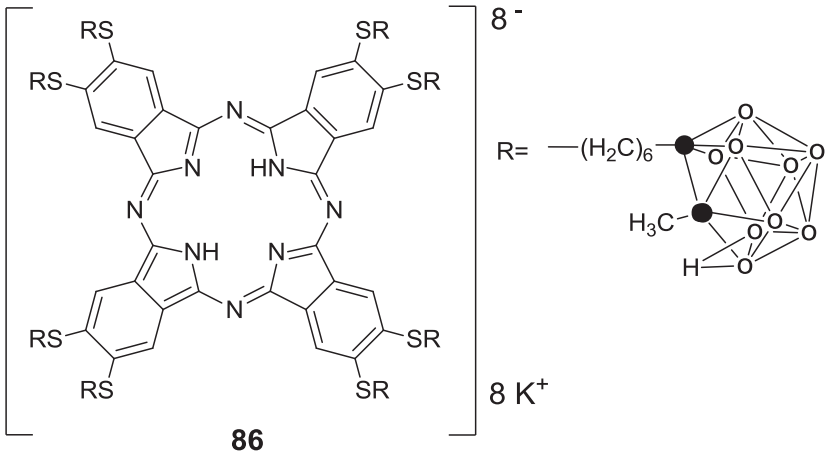
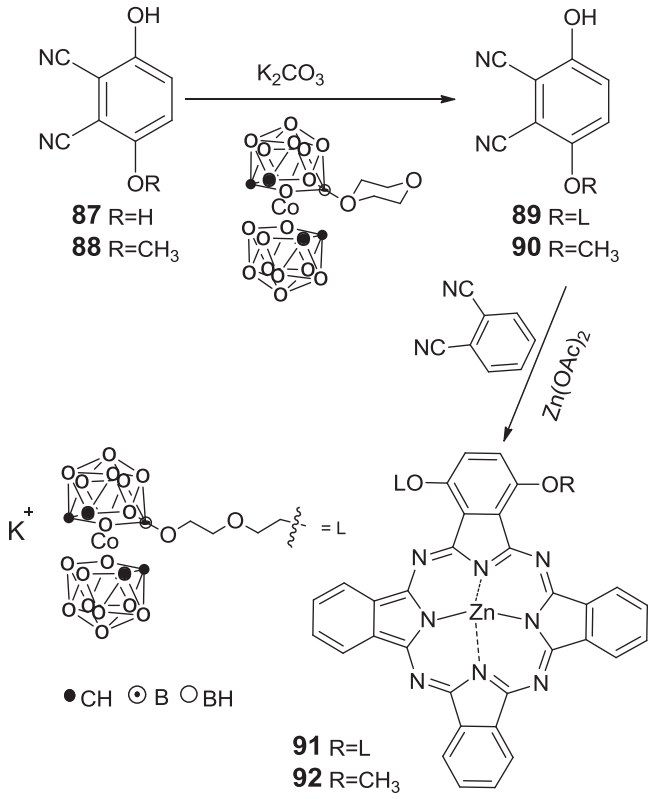
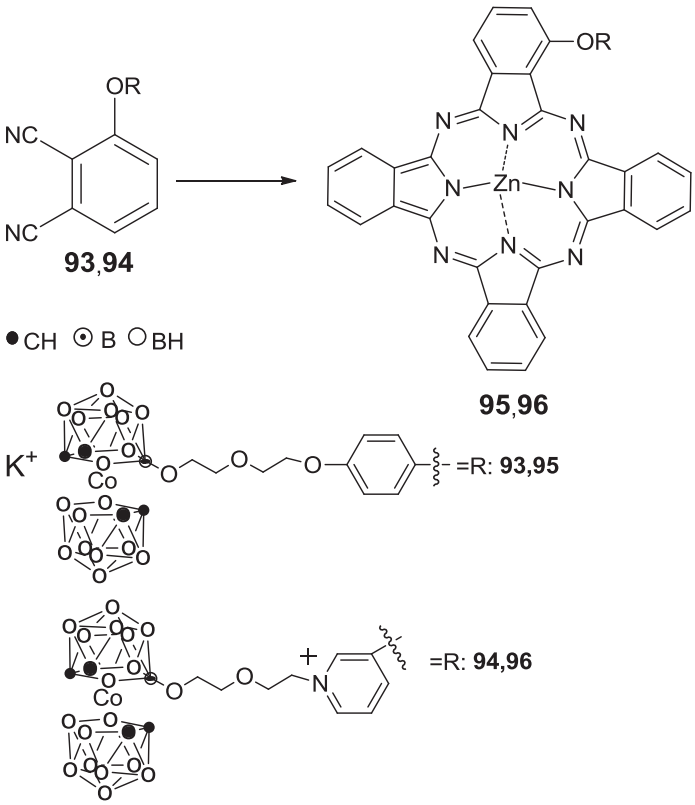


Figure 10. Structure of compound **86**.

The first A_3B-type cobaltacarborane-containing Zn(II)-Pcs (**91** and **92**) was prepared by cyclotetramerization of phthalonitriles **89** and **90** in the presence of an excess of zwitterionic 3,30-Co(8-$C_4H_8O_2$-1,2-$C_2B_9H_{10}$)(10,20-$C_2B_9H_{10}$) and anhydrous potassium carbonate in either acetone (in the case of **87**) or in a mixture of acetone/ chloroform 5:1 (in the case of **88**). The optimized reaction conditions use a 40-fold excess of phthalonitrile over a carboranyl-functionalized phthalonitrile (**89** or **90**) and take advantage of the easy separation of the target A_3B-type Pcs from the insoluble (unsubstituted) A_4-type Pc (Scheme 15).[55]



Scheme 15. Synthesis of compounds **89**–**92**.

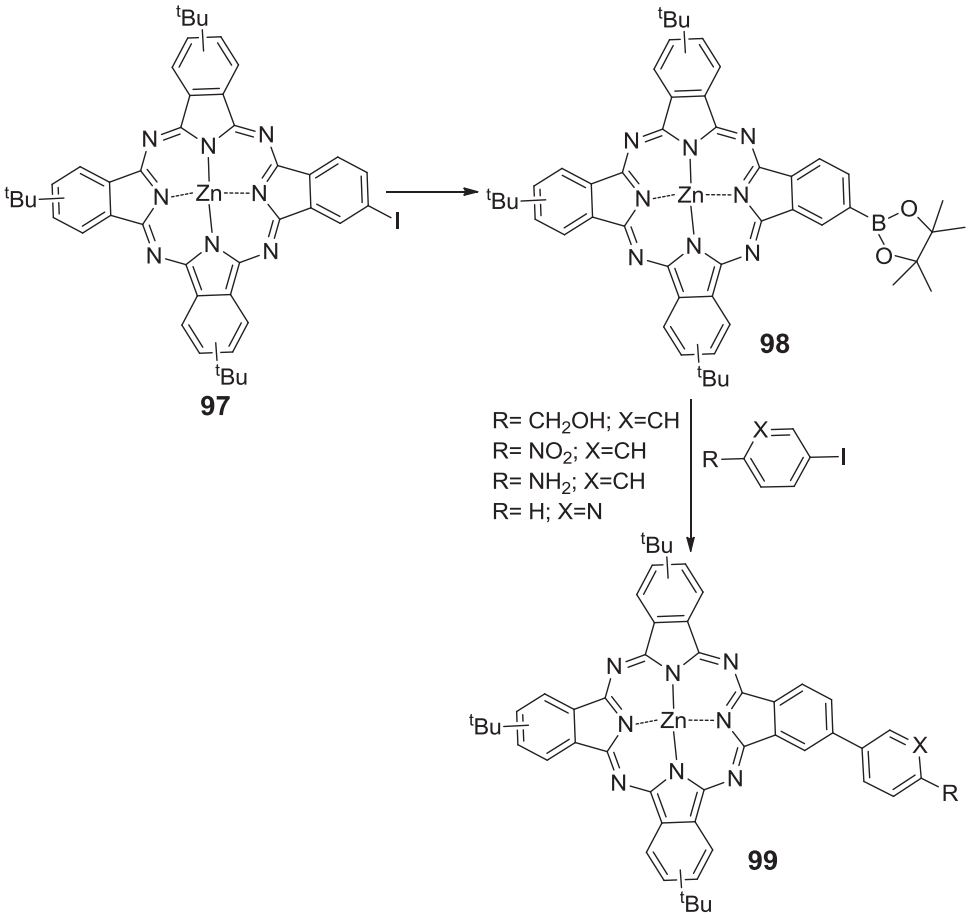


Scheme 16. Synthesis of compounds **95** and **96**.

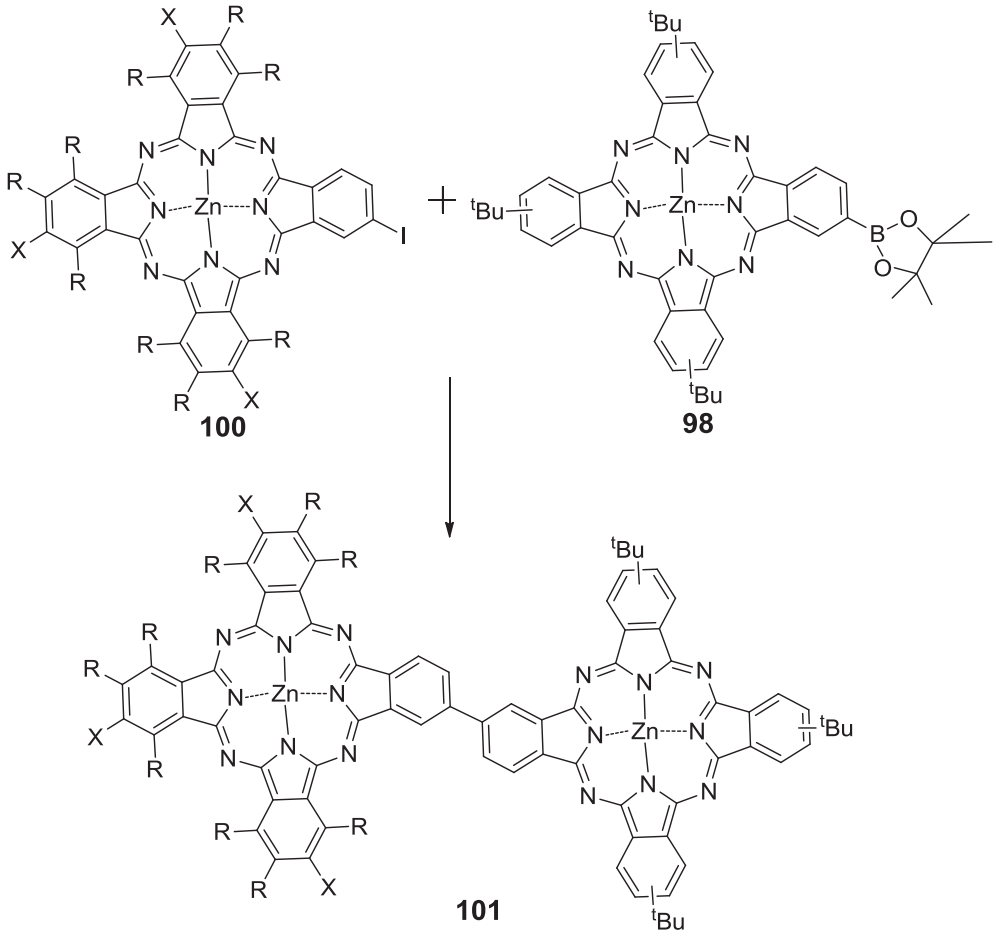
Syntheses of 2 new cobaltacarborane–phthalocyanine conjugates, 1 anionic (**95**) and 1 zwitterionic (**96**), were accomplished via cyclotetramerization of the corresponding cobaltacarborane-substituted phthalonitriles (**93** or **94**) with excess phthalonitrile and zinc acetate in quinoline (Scheme 16).[56] The anionic conjugate **95** exists mainly as a monomer in polar organic solvents and has fluorescence quantum yields in the region of 0.2–0.3. The zwitterionic conjugate **96** aggregates in solution and displays lower quantum yields of about 0.1 in organic solvents.[56]

7. Phthalocyanines with boronic ester groups

Carbon–carbon bond forming reactions are key steps in the preparation of complex bioactive molecules. One of the most important carbon–carbon bond-forming methodology is the cross-coupling reaction of organoboron compounds (Suzuki synthons) with organic electrophiles catalyzed by a palladium (Pd) complex.[57] Pd-catalyzed coupling reactions of Pc using halogenated Pc templates provide an interesting route to synthesize new families of unusually elaborated Pc macrocycles. Ali and van Lier[57] reported the synthesis of Pc-boronate and evaluated its use as a synthon for the Suzuki coupling reaction with various arylhalides for the first time (Scheme 17). The procedure allows for the synthesis of novel unsymmetrical Pc–Pc heterodimers and a Pc-based branched triad, that is, Pc–$(Pc)_2$ (Schemes 18 and 19).[57]



Scheme 17. Synthesis of phthalocyanine-borane synthon (**98**) and its reaction with aryl halides.

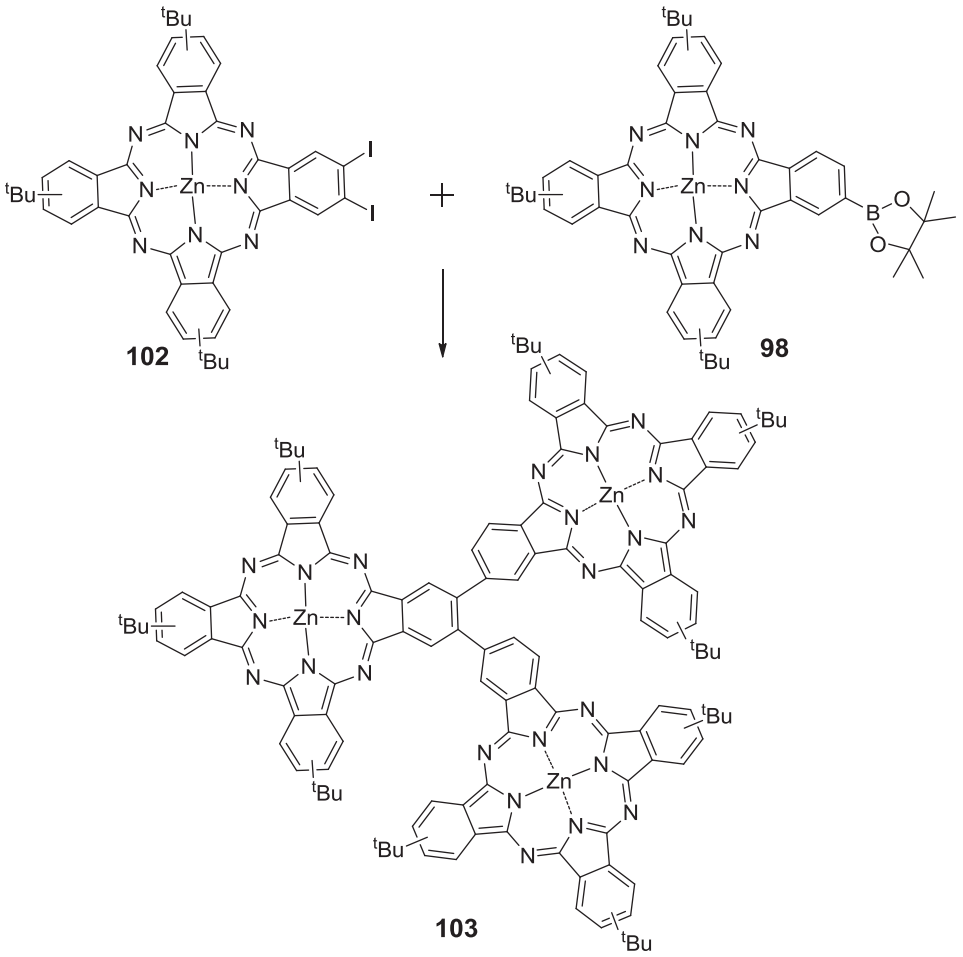


Scheme 18. Synthesis of phthalocyanine-phthalocyanine hetero-dimer (**101**).

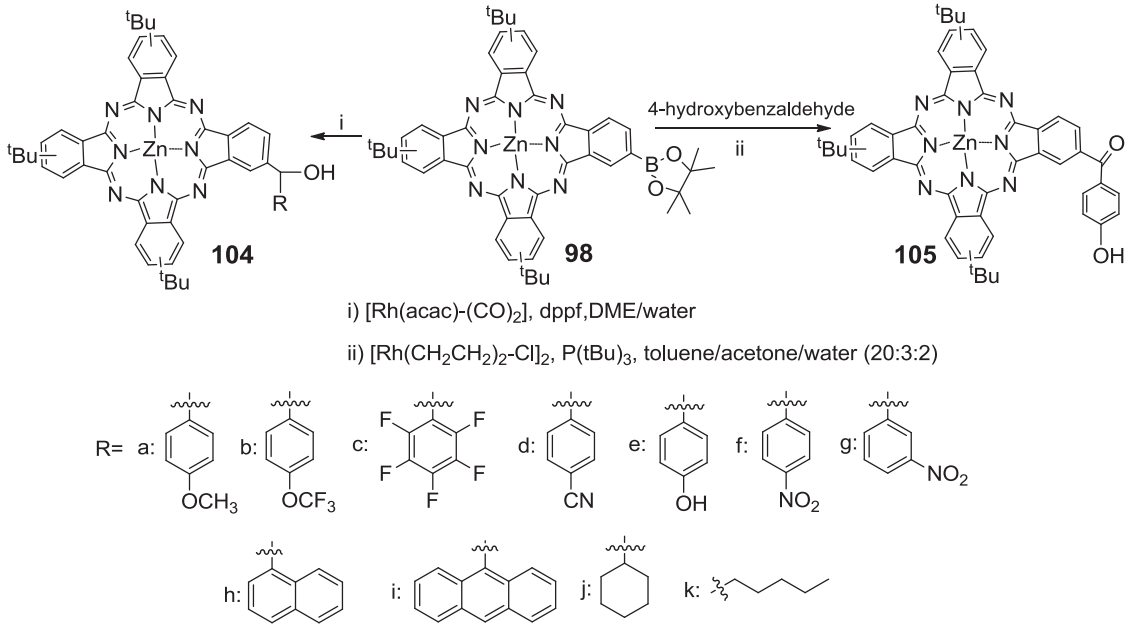
The rhodium-catalyzed carbon–carbon bond forming reaction using phthalocyanine-boronate ester is a powerful tool for further derivatization of Pc. In 2013, Ali and van Lier[58] reported the use of Rh-catalyzed transformations for the synthesis of Pc derivatives for the first time (Scheme 20).

A new covalent organic framework (PBBA COF) (**108**) featuring a square lattice composed of phthalocyanine macrocycles joined by phenylene bis(boronic acid) linkers was prepared by combining phthalocyanine **106**, 1,4-phenylenebis(boronic acid) (PBBA) (**107**), and $BF_3.OEt_2$ (0.015 mL) in a 1:1 mixture of mesitylene and 1,2-dichloroethane in a flame-sealed glass reaction vessel placed in a 120 °C oven for 6 days (Scheme 21). The material's broad absorbance over the solar spectrum, potential for efficient charge transport through the stacked phthalocyanines, good thermal stability, and modular nature of COF synthesis showed strong promise for applications in organic photovoltaic devices.[59]

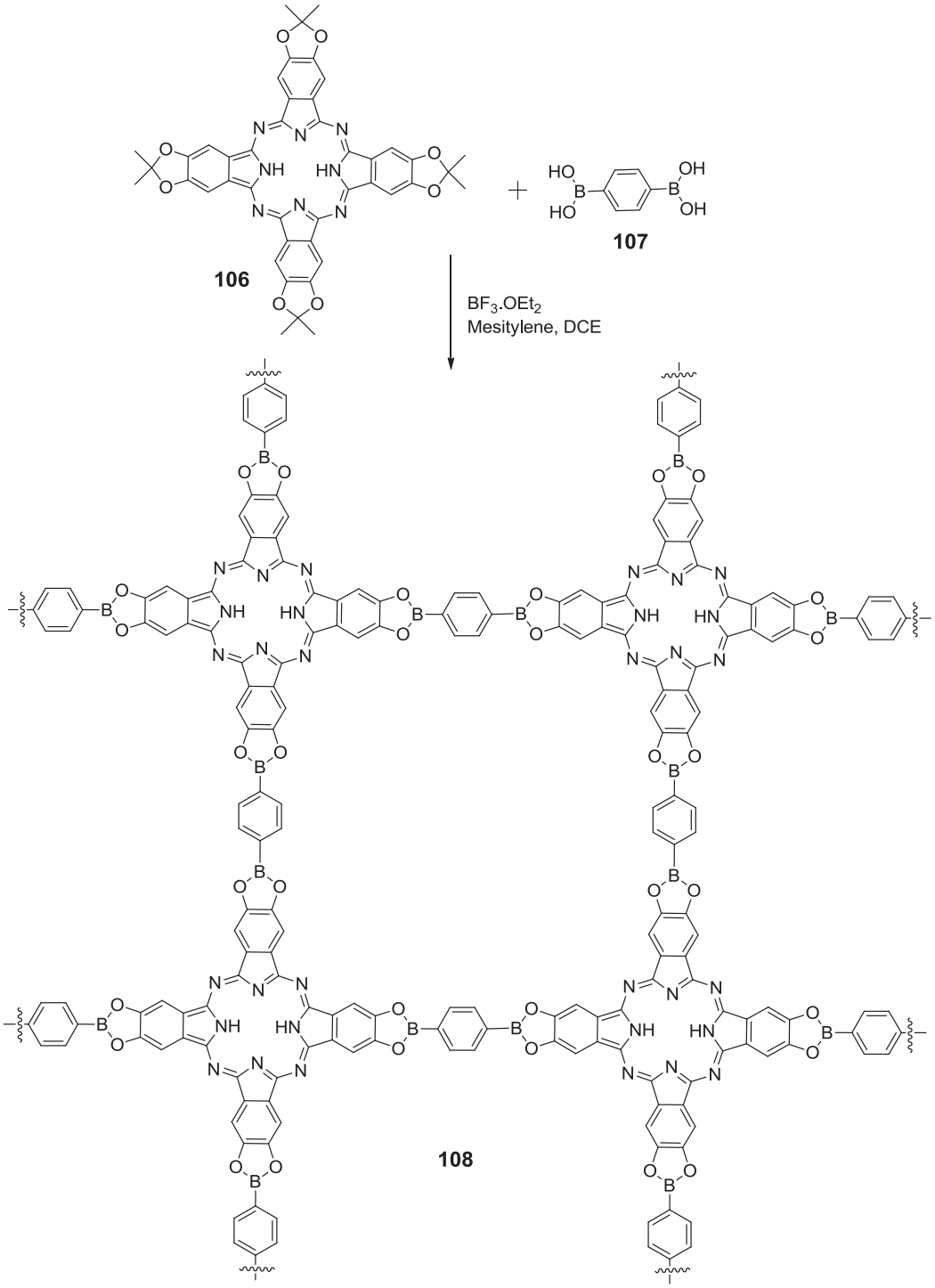
Nickel phthalocyanine-based COF (NiPc COF) (**110**) was synthesized by the boronate esterification reaction of (2,3,9,10,16,17,23,24-octahydroxyphthalocyaninato)-nickel(II), $[(OH)_8PcNi]$ (**109**), and 1,4-benzenediboronic acid (**107**) in dimethylacetamide (DMAc)/*o*-dichlorobenzene under solvothermal conditions (Scheme 22). These 2D COFs provide preorganized conduction paths based on precise ordering of the phthalocyanine stack and are ideal for charge carrier transport.[60]



Scheme 19. Synthesis of phthalocyanine-(phthalocyanine)$_2$ homo-triad (**103**).



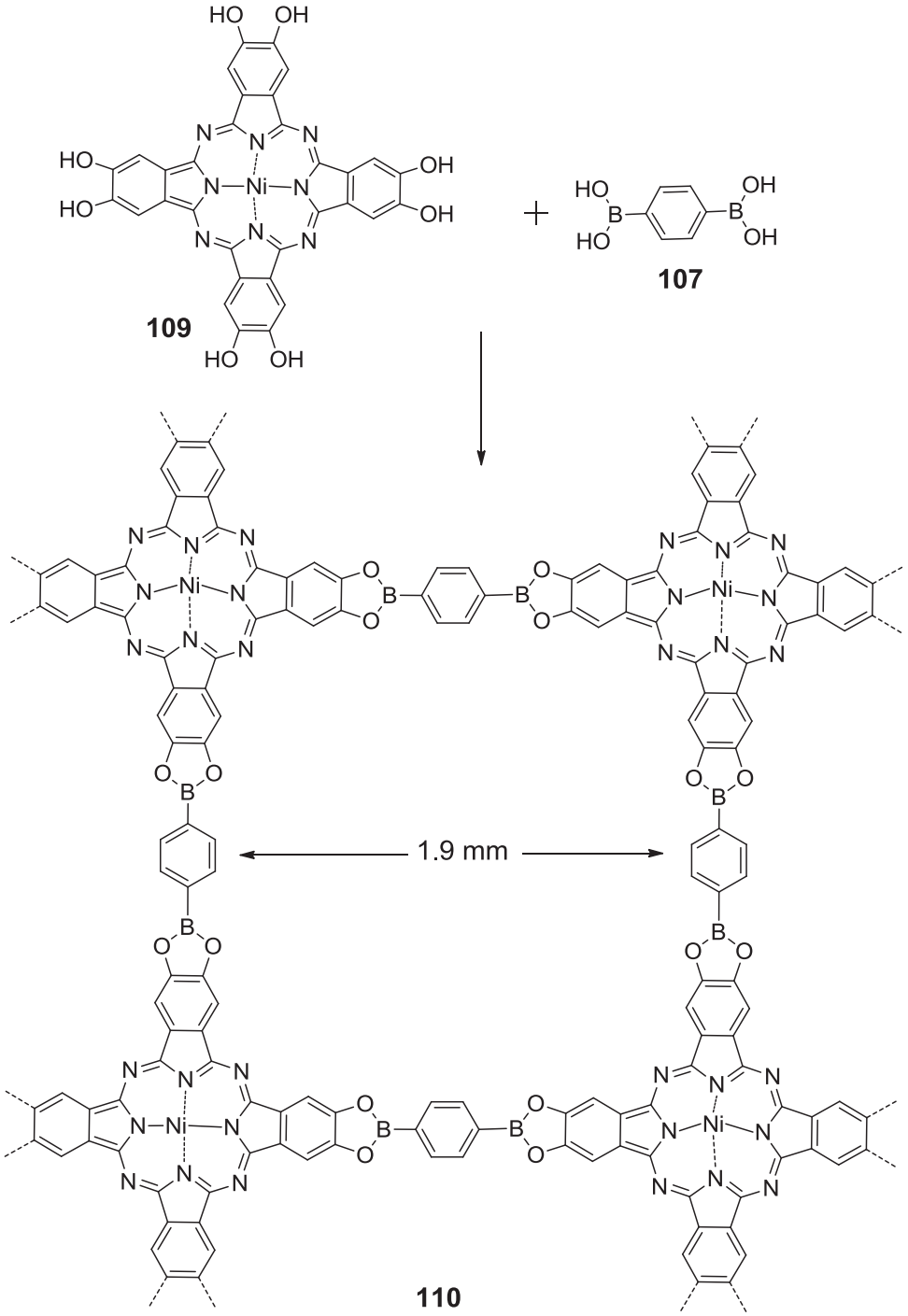
Scheme 20. Synthesis of compounds **104** and **105**.



Scheme 21. Synthesis of compound **108**.

Farfán and colleagues[61] investigated the imino Diels Alder reactions with organoboron esters prepared by the condensation of the salicylaldimines with phenylboronic acid ($PhB(OH)_2$) or diphenylborinic acid (Ph_2BOH) and discovered that related systems are potential candidates for third-order nonlinear optical studies.[61] 4-(4-Formyl-3-hydroxyphenoxy)phthalonitrile and its condensation product with 2-aminophenol have

been synthesized to reach 4-(3-hydroxy-4-(((2-hydroxyphenyl)imino)-methyl)phenoxy)phthalonitrile (**111**), a tridentate ligand possessing ONO binding sites. Subsequent condensation of phenylboronic acid with **111** afforded a novel boronic ester of a Schiff base with a phthalonitrile group (**112**) (Figure 11). Boronate **112** displays high stability and can be handled in air due to the presence of coordinative B-N and covalent B-O bonds in its structure.[62]



Scheme 22. Synthesis of compound **110**.

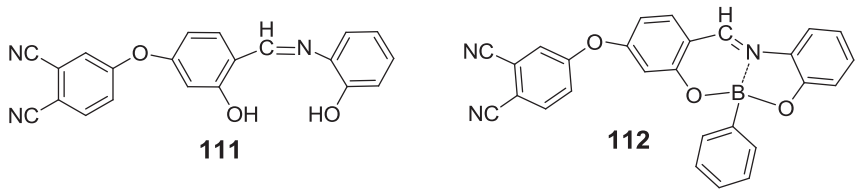
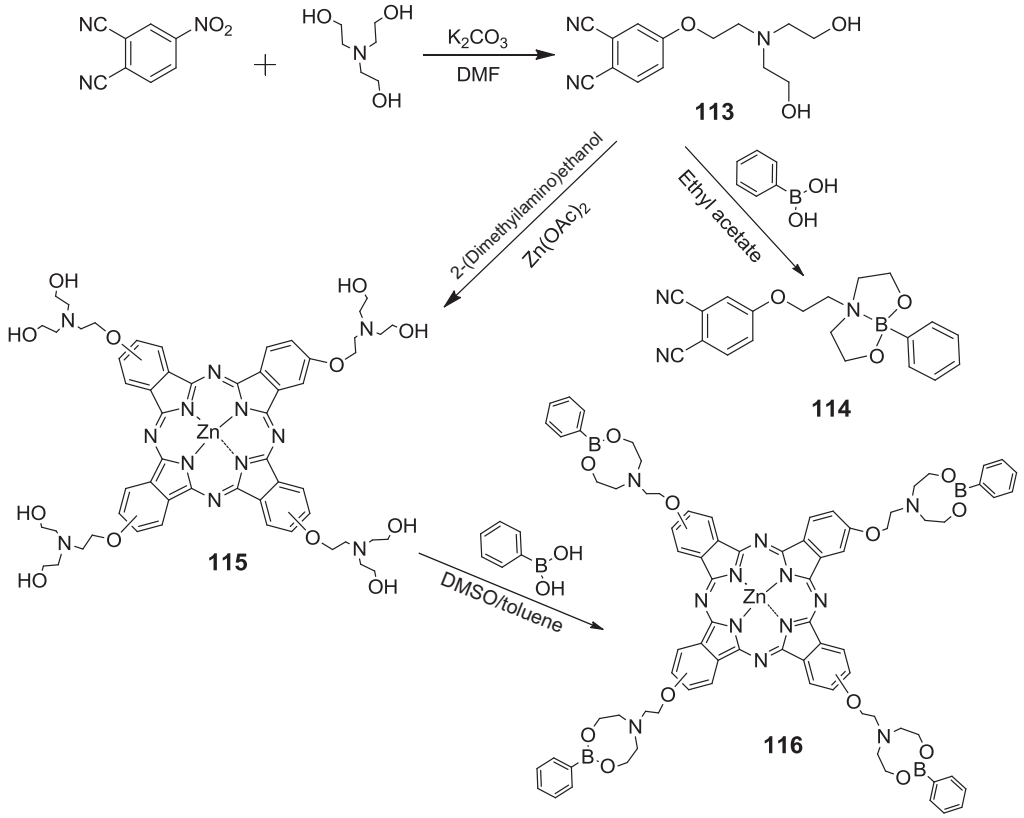


Figure 11. Structure of compounds **111** and **112**.

The first Zn phthalocyanine bearing 4 phenylboronic azaester substituents at peripheral positions (**116**) and the phenylboronic azaester of its precursor, namely 4-(2-(2-phenyl-1,3,6,2-dioxazaborocan-6-yl)ethoxy)phthalonitrile (**114**), were synthesized as seen in Scheme 23.

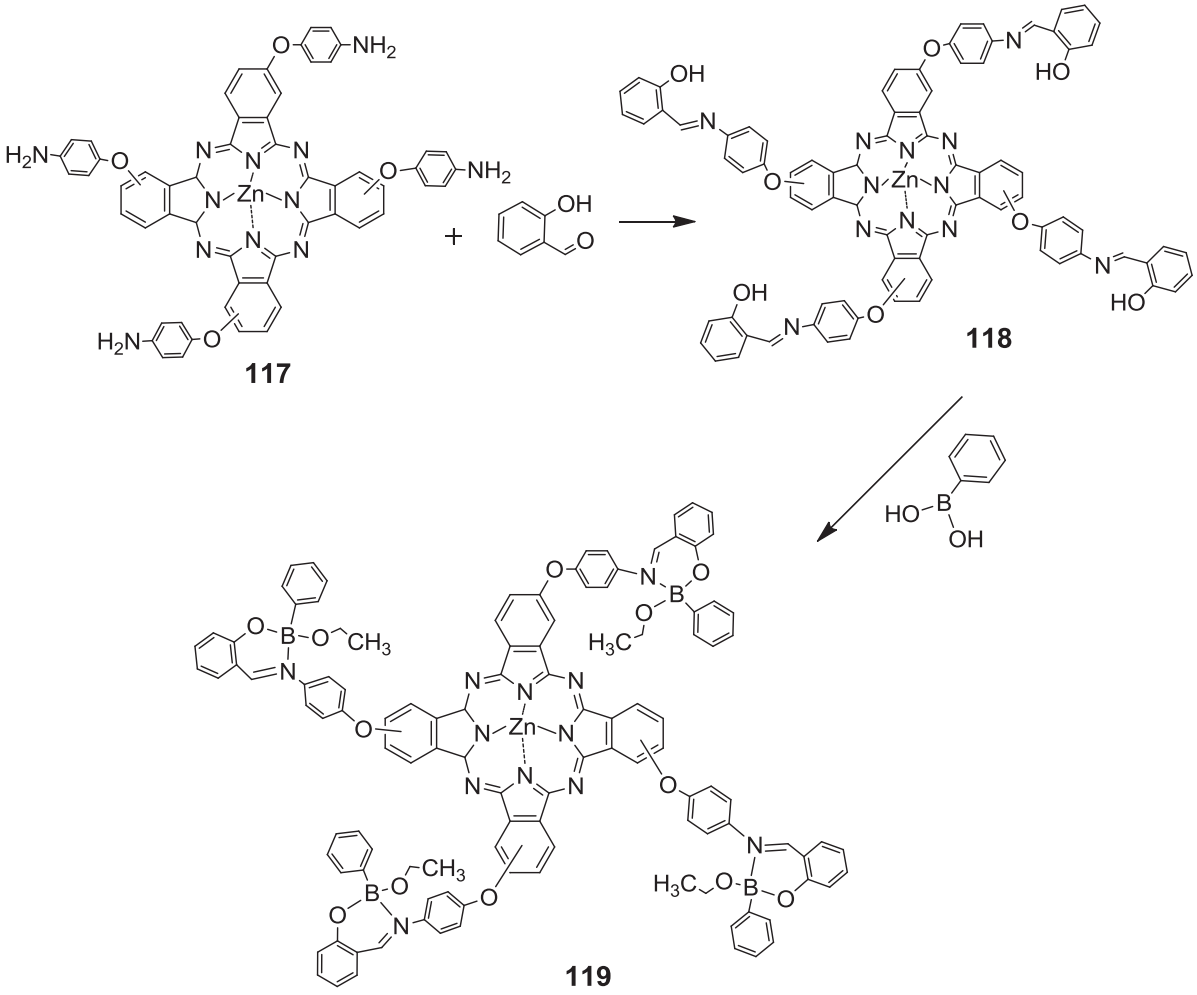


Scheme 23. Synthesis of compounds **113**–**116**.

4-[2-(bis(2-Hydroxyethyl)amino)ethoxy]phthalonitrile (**113**) was synthesized by the aromatic nucleophilic substitution reaction of 4-nitrophthalonitrile with triethanolamine. 2,9(10),16(17),23(24)-Tetrakis[2-(bis(hydroxyethyl)amino)ethoxy]phthalocyaninato-zinc(II) **(115)** was prepared from the cyclotetramerization of dinitrile **113** in the presence of anhydrous zinc(II) acetate by microwave irradiation. Treatment of phthalocyanine **115** with phenylboronic acid in a mixture of DMSO/toluene (20/1, v/v) afforded the desired phthalocyanine **116**. The complexation reaction of precursor **113** and phenylboronic acid in ethyl acetate under reflux conditions yielded the desired dioxazaborocane **114**. It was demonstrated that the boron atom of phthalonitrile **114** is in the tetracoordinated state with the formation of a coordinative N-B bond (closed form), while in the case of phthalocyanine **116**, the open conformer possessing a tricoordinated boron atom is favored.[63]

Esters of boronic acids are notoriously unstable to hydrolysis.[64] However, organoboran compounds with a boroxazolidine ring in their structure exhibited high hydrolytic stability. This notable increase in hydrolytic stability is ascribed to the formation of a B-N coordinative bond.[65] Furthermore, compounds containing B-N bonds have been shown to possess biological activity. In this respect synthesis of zinc phthalocyanine substituted with boronic acid ester of Schiff base groups was reported for the first time.[66]

As the first step, the Schiff base product (**118**) was obtained from the reaction of salicylaldehyde with 2,9(10),16(17),23(24)-tetra-(4-[4-aminophenoxy])-phthtalocyaninatozinc(II) (**117**) in THF under argon atmosphere. The Schiff base structure obtained from the reaction of salicylaldehyde with amine groups of compound **117** presents 2 active sites to the boron reagent: the OH group, which can form boron esters, and the nitrogen, which can give N-B coordination compounds.[67] Treatment of compound **118** with benzeneboronic acid in ethanol/toluene mixture at reflux temperature afforded the phthalocyanine **119** substituted peripherally with 4 benzeneboronic acid esters of Schiff base groups in high yield (Scheme 24). Spectrophotometric data indicated that the boron atom in the boronate groups is in the tetracoordinated state with formation of a coordinative N-B bond.[66]



Scheme 24. Synthesis of compounds **118** and **119**.

Addition of boron-containing moieties including carboranes, dodecaboranes, and boronic esters to tetrapyrrole derivatives provides a rich group of chemicals applicable to PDT, BNCT, coupling reactions, etc.

In conclusion, we have tried to summarize recent works on new interesting materials composed of phthalocyanine, porphyrin, or porphyrazine moieties on one side and boron-containing substituents (e.g., carborane, decaborane, boronic ester, borinic ester) on the other. These combinations are applicable to products exceptionally useful in a variety of fields, from medical applications such as BNCT or PDT to organic photovoltaic devices. As Turkey is a country rich in boron minerals, practical advice to qualified synthetic chemists on phthalocyanines can be to combine advanced materials properties of tetrapyrrole derivatives with boron-containing groups.

Acknowledgments

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