

Review

# Functionalization of Porphyrins Using Metal-Catalyzed C-H Activation

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**Abstract:** The review is devoted to the C–H functionalization of porphyrins. Porphyrins exhibit the properties of organic semiconductors, light energy converters, chemical and electrochemical catalysts, and photocatalysts. The review describes the iridium- and palladium-catalyzed direct functionalization of porphyrins, with more attention given to the results obtained in our laboratory. The development and improvement of synthetic methods that do not require preliminary modification of the substrate with various functional groups are extremely important for the preparation of new organic materials based on porphyrins. This makes it possible to simplify the synthetic procedure, to make the synthesis more economical, environmentally safe, and simple to perform.

**Keywords:** C–H functionalization; porphyrins; synthesis; direct functionalization; iridium-catalyzed functionalization; palladium-catalyzed functionalization; atom economy; green chemistry

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## 1. Introduction

Most of the substances used in the industry are carbon-based compounds. These are medicines, pesticides, herbicides, plastics, fibers, dyes, explosives, fire extinguishing agents, and materials with various properties [1]. For most of the listed organic substances, it is necessary to compose a synthetic route in such a way that, on the one hand, minimizes the amounts of the reagents, and, on the other hand, avoids dangerous and harmful compounds, if possible. This approach has found its development within the framework of atom economy and green chemistry [2]. Therefore, the development of new methods for the synthesis of organic compounds is an urgent task. One of the directions in organic synthesis is C–H functionalization.

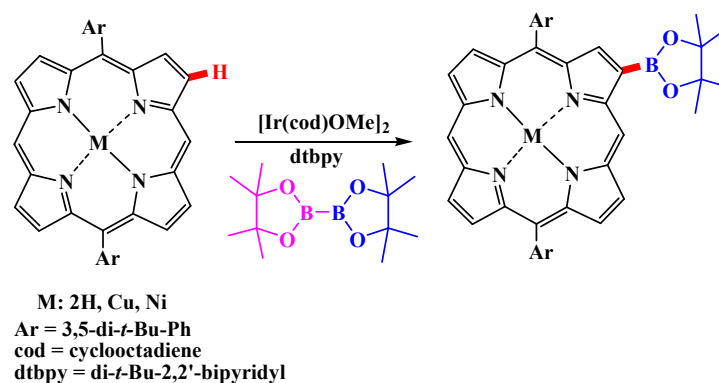
The possibility of introducing a new functional group into a molecule or the formation of a new C–C bond by C–H functionalization is a promising task due to the huge distribution of C–H bonds in organic compounds. The number of substrates is practically unlimited and includes: hydrocarbons, heterocyclic compounds, and synthetic and biological polymers, and the use of transition metals as reagents has opened up completely new opportunities in this field [3]. Methods of C–H functionalization require different reaction conditions and catalysts, including d- and f-metals in different oxidation states, and sometimes reactions take place only at high temperatures with specially selected bases and oxidizing agents. Despite the different conditions, these reactions are a development of the C–M/C–X cross-coupling method and therefore have significant advantages over the classical reaction. A large number of papers devoted to C–H functionalization have now been published. A wide variety of organic compounds have been modified [4–13]. C–H functionalization reactions are used, for example, for the synthesis of analogues of natural compounds, pharmaceuticals, organic materials of electronic components, etc. [14–24]. The modification of porphyrins

and their analogues, taking into account their attractive semiconductor, photophysical, electrochemical, and other properties, is of particular interest [25–40].

## 2. C-H-Functionalization on Porphyrins

A relatively small number of works have been devoted to the study of C-H functionalization in the field of porphyrin chemistry. This is due to the difficulties in detaching protons from the  $\beta$ - and meso-positions of porphyrins with the formation of a C-C and C-M bond without active groups. Currently, porphyrins containing such substituents as bromine, iodine, tosylate, and boron compounds are used for modification. In this regard, the development of new catalytic systems capable of activating hydrogen atoms in the  $\beta$ -, meso-positions of the porphyrin macrocycle, as well as in phenyl rings, followed by the formation of a new carbon-carbon and carbon-heteroatom bond, is an urgent task.

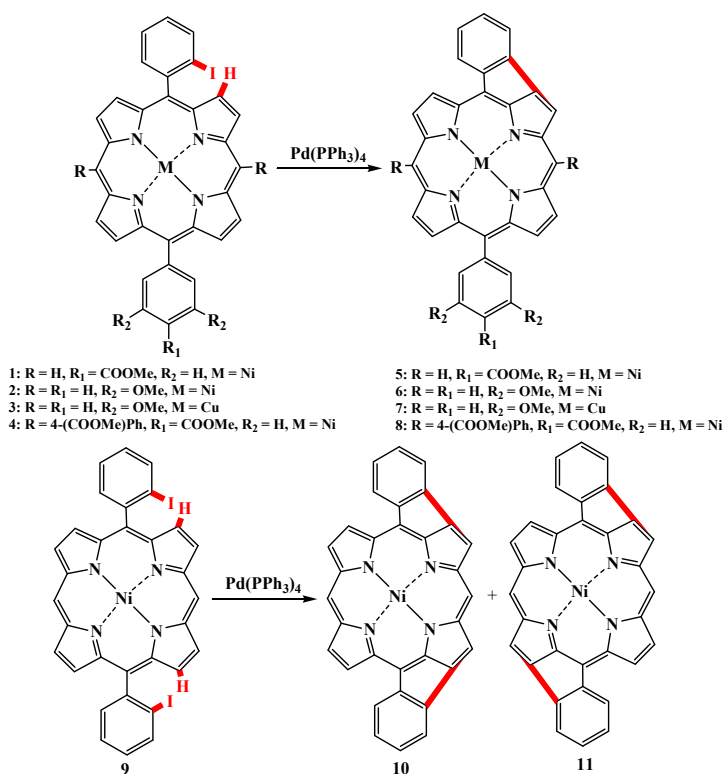
$\beta$ -Selective C-H functionalization was first carried out by the group of Professor Osuka [41]. Various unsubstituted diarylporphyrins were subjected to iridium-catalyzed borylation [41,42] (Scheme 1). In all cases, the borylation proceeded selectively at the  $\beta$ -positions located near the meso-carbon, with yields up to 47%, and was not observed at the meso-positions [41]. Diborylated triarylporphyrins and tetraborylated diarylporphyrins were obtained under similar conditions, and further substitution was observed only in the  $\beta$ -position adjacent to the vacant meso-carbon atom [41]. Osuka and co-workers demonstrated the usefulness of porphyrinylboronates as building blocks for multiporphyrin structures [43].



**Scheme 1.** Iridium-catalyzed borylation of diaryl porphyrins [41,42].

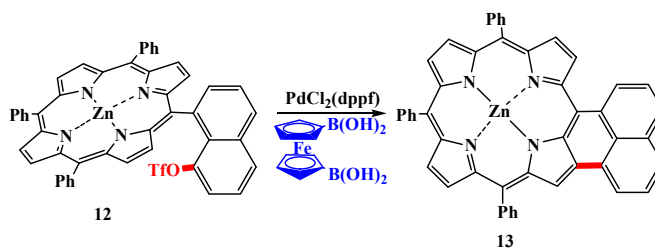
$\beta$ -borylation requires a catalytic amount of the iridium complex  $[\text{Ir}(\text{OMe})(\text{cod})]_2$  and the dtbpy ligand, as well as a stoichiometric amount of boron [44]. The study of the reaction mechanism showed that the introduction of iridium (III) at the C-H bond is the rate-determining step. The regioselectivity of  $\beta$ -borylation is explained only by the mutual steric hindrances that the reagent and substrate exert on each other [45,46].

The first example of a palladium-catalyzed reaction was the intramolecular cyclization of meso-phenyl porphyrins **1–4** orthoiodinated at the phenyl fragments by Boyle and Fox (Scheme 2) [47,48]. Both mono- (**5–8**, up to 44%) and doubly cyclized products (**10**, **11**, up to 36%) were obtained in acceptable yields, but the authors failed to separate isomers **10** and **11**. Similar reactions using ortho-bromophenylporphyrins could not be carried out.



**Scheme 2.** Palladium-catalyzed intramolecular cyclization of meso-phenyl porphyrins ortho-iodinated at the phenyl fragments [47,48].

An attempt to carry out the reaction of naphthyl triflate **12** with 1,1'-diborylferrocene under Suzuki reaction conditions did not lead to the expected double addition of porphyrin to ferrocene. As the only product in this reaction, naphthalene-condensed porphyrin **13** was isolated, which was formed due to intramolecular C–H arylation in 14% yield [49] (Scheme 3).



**Scheme 3.** Scheme for the synthesis of condensed porphyrin by intramolecular C–H-arylation [49].

Similarly, an attempt by Osuka and colleagues to perform a Suzuki coupling of borylporphyrin **14** with 1,2-diiodobenzene gave phenylene-fused porphyrin **15**, along with diporphyrin **16** (Scheme 4) [50]. It was found that the annulation involves the formation of meso-(o-iodophenyl)porphyrin and its subsequent intramolecular C–H arylation.

10 mol%  $[\text{Pd}_2(\text{dba})_3]$   
 80 mol% Tri(2-furyl)phosphine  
 10 eq.  $\text{Cs}_2\text{CO}_3$   
 10 eq.  $\text{CsF}$   
 THF:DMF:H<sub>2</sub>O  
 20:10:1  
 90 °C

Ar: 3,5-diethoxyphenyl

14

15

16

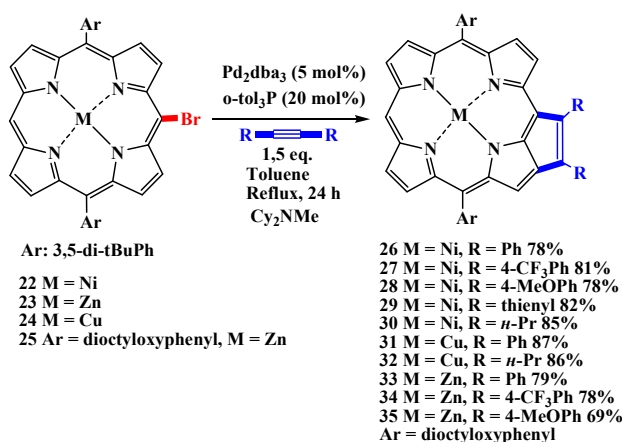
**Scheme 4.** Synthesis of phenylene-condensed porphyrin along with diporphyrin [50].

Matsuo synthesized thiophene-fused porphyrins **19** (47%) and **21** (79%) using a palladium-catalyzed intramolecular C-H/C-Cl or C-H/C-Br reaction of porphyrins **18** and **20** (Scheme 5) [51].

The reaction scheme illustrates the synthesis of nickel(II) phthalocyanine derivatives 17 through 21. The starting material 17 is a nickel(II) phthalocyanine with four aryl (Ar) substituents. The aryl group is defined as  $\text{Ar} = 3,5\text{-}t\text{Bu}_2\text{C}_6\text{H}_3$ . Compound 17 reacts with 2,5-dibromothiophene in the presence of  $\text{Pd}_2\text{dba}_3$ ,  $\text{PPh}_3$ , and  $\text{Cs}_2\text{CO}_3$  in toluene/DMF to form intermediate 18, which has a 2-bromothiophene substituent. Intermediate 18 then reacts with  $\text{Pd}(\text{OAc})_2$ ,  $\text{PCy}_3 \cdot \text{HBF}_4$ , and  $\text{K}_2\text{CO}_3$  in DMF to form product 19, which has a fused thiophene ring system. Similarly, compound 20, which has a 2-chlorothiophene substituent, reacts with  $\text{Pd}(\text{OAc})_2$ ,  $\text{PCy}_3 \cdot \text{HBF}_4$ , and  $\text{K}_2\text{CO}_3$  in DMF to form product 21, which also has a fused thiophene ring system.

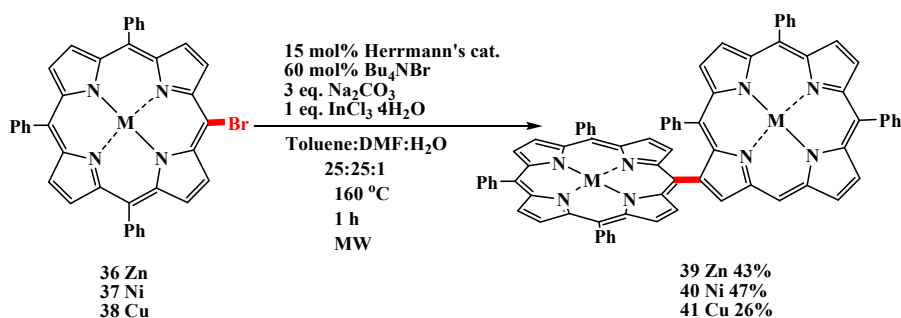
**Scheme 5.** Synthesis thiophene-fused porphyrins using a palladium-catalyzed intramolecular C-H/C-Cl or C-H/C-Br reaction [51].

Arnold's papers reported Heck-type coupling of nickel (II) meso-vinylporphyrinate with various meso-bromoporphyrins. In all cases, the only isolated product is the meso- $\beta$ -linked porphyrin dimer [52]. Osuka et al. reported the formation of various cyclopentadiene-condensed porphyrins **26–35** in palladium-catalyzed reactions of the corresponding bromoporphyrins **22–25** with symmetrical alkynes in high yields of 69–87% (Scheme 6) [53].



**Scheme 6.** Synthesis of cyclopentadiene-condensed porphyrins (26–35) in palladium-catalyzed reactions [53].

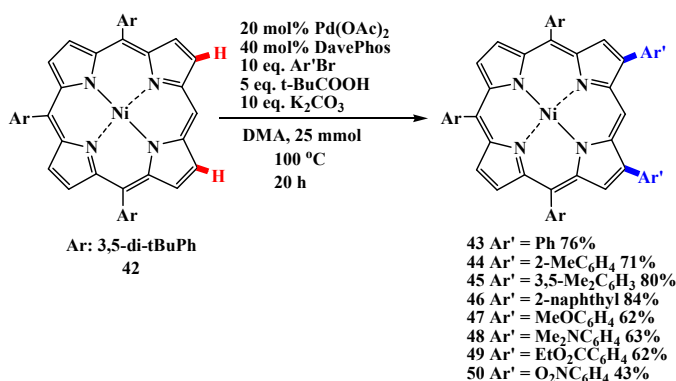
The first example of intermolecular CH-arylation of porphyrins is the palladium-catalyzed dimerization of meso-bromoporphyrins (Scheme 7) carried out by Osuka's group [54].



**Scheme 7.** Palladium-catalyzed dimerization of meso-bromoporphyrins [54].

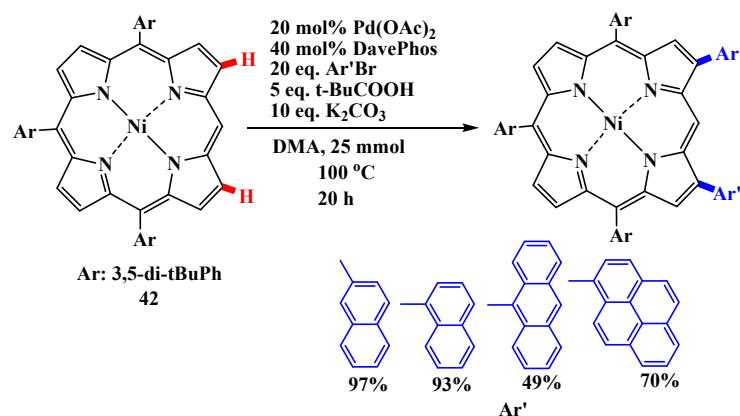
The palladium-catalyzed homocoupling reaction of meso-bromoporphyrins proceeds to form directly meso-β-linked diporphyrins in good yields and ideal regioselectivity. It should be noted that the C-H-functionalization of porphyrin proceeds to the most hindered β-position.

Osuka's group described intermolecular CH-arylation of the porphyrin periphery with aryl bromides as a general and efficient method of arylation [55]. Palladium-catalyzed C-H-arylation of arenes, proceeding with the participation of pivalic acid [56–60], was used for the β,β'-diarylation of meso-unsubstituted porphyrin **42** (Scheme 8) [61].



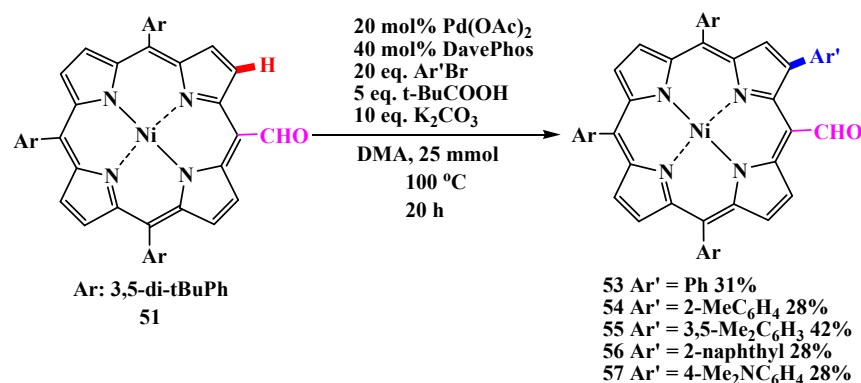
**Scheme 8.** Palladium-catalyzed C-H-arylation of arenes [61].

Its scope is quite wide, although the introduction of heteroatom-substituted aryl groups requires some changes in the reaction conditions. The reaction is efficient for the diarylation of 5,15-triarylporphyrin **42** (Scheme 9) [61].



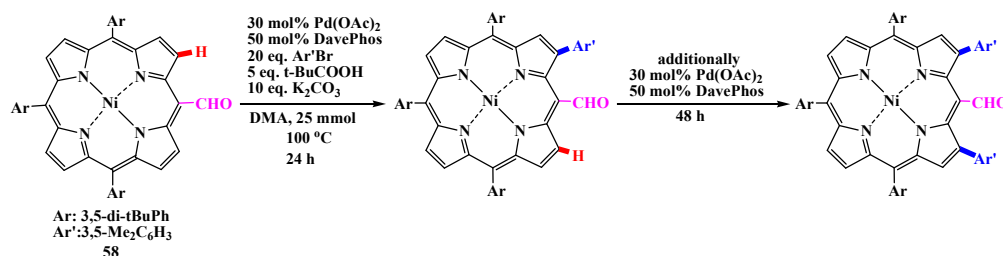
**Scheme 9.** Diarylation of 5,15-triarylporphyrin [61].

Direct arylation is so efficient that even formylporphyrin **51** could be arylated (Scheme 10).



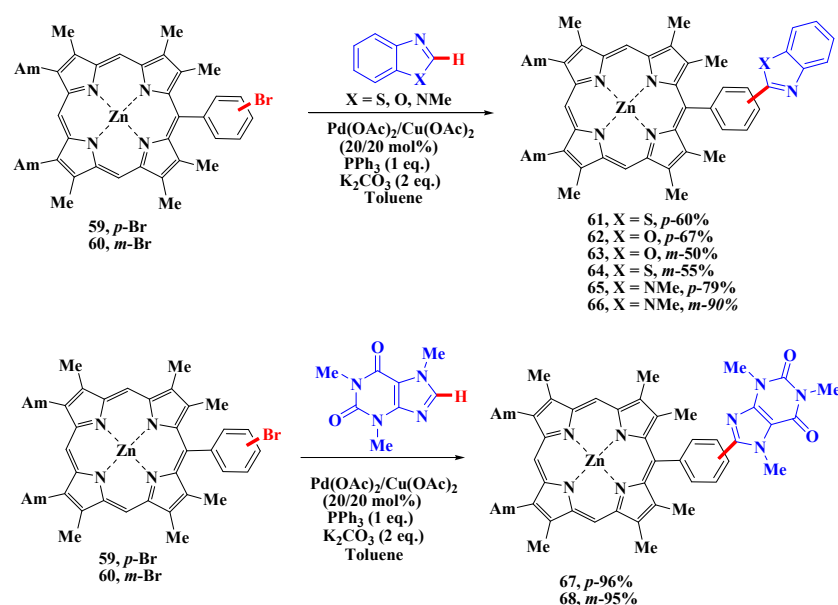
**Scheme 10.** Reaction of direct formylporphyrin arylation.

Due to the moderate steric hindrance of the formyl group, arylation proceeded much more slowly to the  $\beta$ -position adjacent to the formyl group, giving monoarylated products **53–57** under similar reaction conditions. Diarylation requires an additional amount of palladium catalyst (Scheme 11). The remaining formyl group can undergo further transformations, as evidenced by the McMurry coupling. It should be noted that an attempt at  $\beta$ -borylation of formylporphyrin **58** failed due to the transformation of the formyl group under the action of iridium catalysis [60].



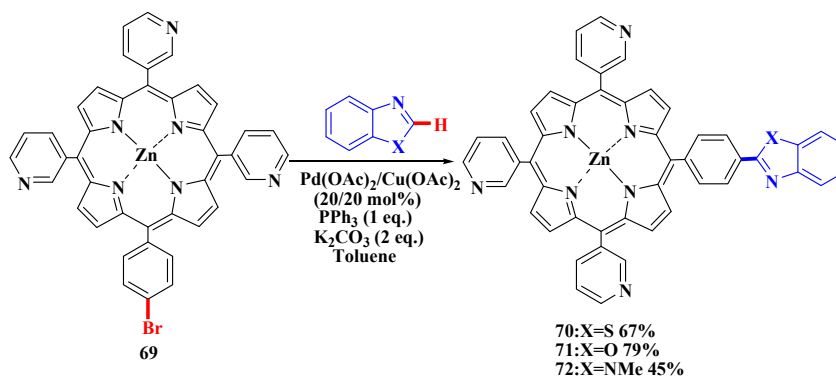
**Scheme 11.** Direct formylporphyrin diarylation [60].

Direct  $\beta$ -arylation has advantages over  $\beta$ -borylation and subsequent cross-coupling [24,62–75] because it does not involve the undesirable process of protodeborylation. An example of the introduction of heterocyclic fragments into a porphyrin molecule is the work carried out in our laboratory [76] where arylation by heteroarenes containing “acidic” C–H bonds, such as mono-, di- and tetra-meso-bromophenyl-substituted porphyrins, were exposed. The reactions were carried out in the presence of three alternative catalytic systems:  $\text{Pd}(\text{dba})_2/\text{DavePhos}/\text{Cs}_2\text{CO}_3$ ,  $\text{Pd}(\text{PPh}_3)_4/\text{PivOH}/\text{K}_2\text{CO}_3$ , and  $\text{Pd}(\text{OAc})_2/\text{Cu}(\text{OAc})_2/\text{PPh}_3/\text{K}_2\text{CO}_3$ . The first catalytic system turned out to be successful in the reaction with benzoxazole, while the second was less efficient. The third catalytic system turned out to be the most versatile and made it possible to obtain the corresponding mono-, di-, tri-, and even tetra-arylated porphyrin derivatives (Scheme 12) [76]. Porphyrins **59** and **60** were successfully heterylated. Despite the more “acidic” C–H bond in the benzoxazole molecule, the best result was obtained when carrying out the reaction with 1,3,7-trimethylxanthine (96%) **67** and (95%) **68**.



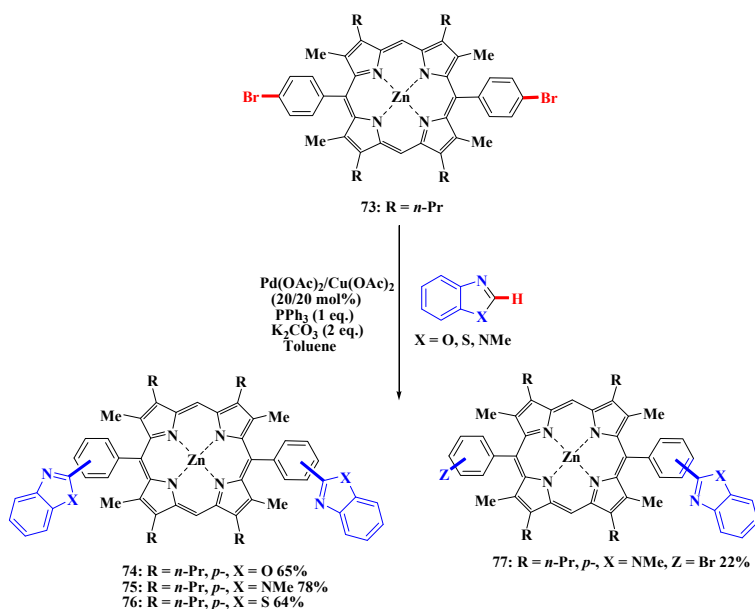
**Scheme 12.** Direct  $\beta$ -arylation of porphyrins with catalytic system containing  $\text{Pd}(\text{OAc})_2/\text{Cu}(\text{OAc})_2/\text{PPh}_3/\text{K}_2\text{CO}_3$  [76].

The C–H functionalization method allows targeted synthesis of porphyrin compounds that meet the requirements of biomedicine. For example, porphyrins **70–72** were constructed for high-affinity binding to pathogen DNA based on the results of molecular docking. These porphyrins form  $\pi$ – $\pi$  bonds with nitrogenous bases of one of the DNA strands in the helical stacking and H-bonds/ $\pi$ – $\pi$ -bonds with the nitrogenous bases of the second DNA strand outside the helical stacking. The desired porphyrins **70–72** were obtained by C–H functionalization of porphyrin **69** using the above catalytic system (Scheme 13). Compounds **70–72** were also capable of high-affinity binding to the receptor-binding domain of the SARS-CoV-2 S protein. The S-protein complex is not capable of binding to the human-angiotensin-converting enzyme with porphyrins **70–72** in vitro [77].



**Scheme 13.** Synthesis of hetaryl substituted porphyrins [77].

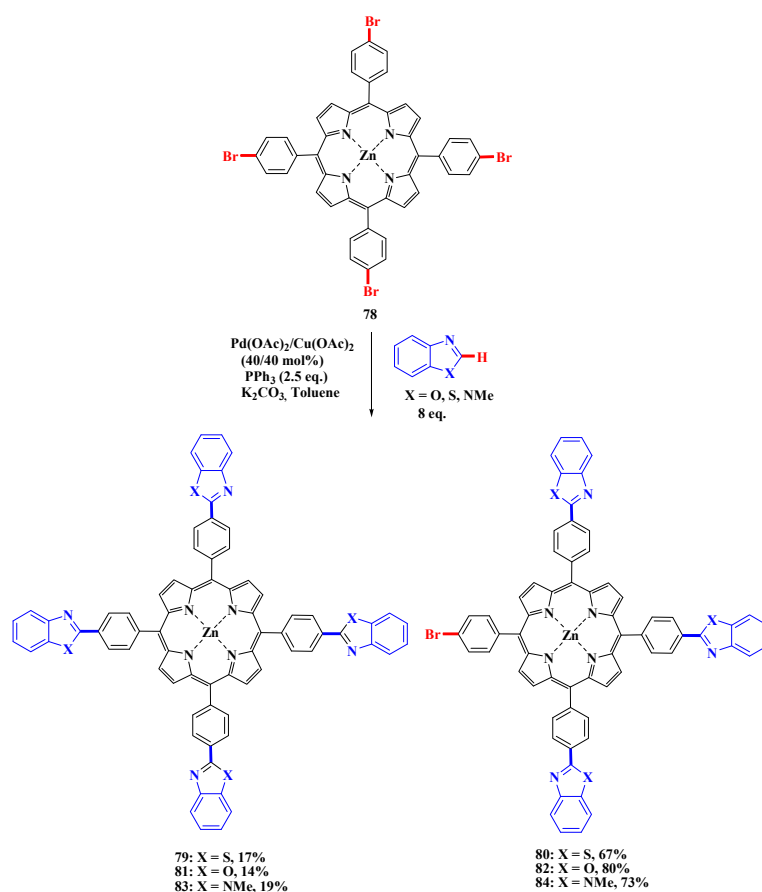
Porphyrin **73** was modified with the same heteroarenes. As a result, heterocycle-substituted porphyrins were obtained in good yields (Scheme 14).



**Scheme 14.** Scheme of porphyrins modification by heteroarenes.

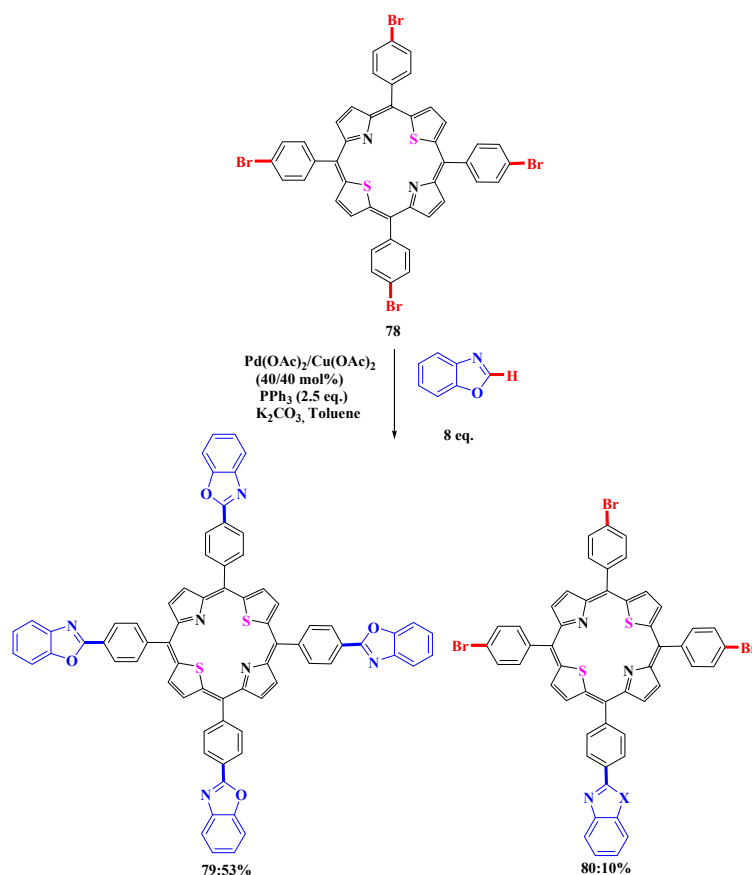
To study the possibilities and limitations of this approach, we carried out reactions with porphyrin **78** using 8 equivalent of corresponding heteroarenes, 40 mol%  $\text{Pd}(\text{OAc})_2/\text{Cu}(\text{OAc})_2$ , 2.5 equivalent  $\text{PPh}_3$  and 5 equivalent  $\text{K}_2\text{CO}_3$  (Scheme 15) [76].





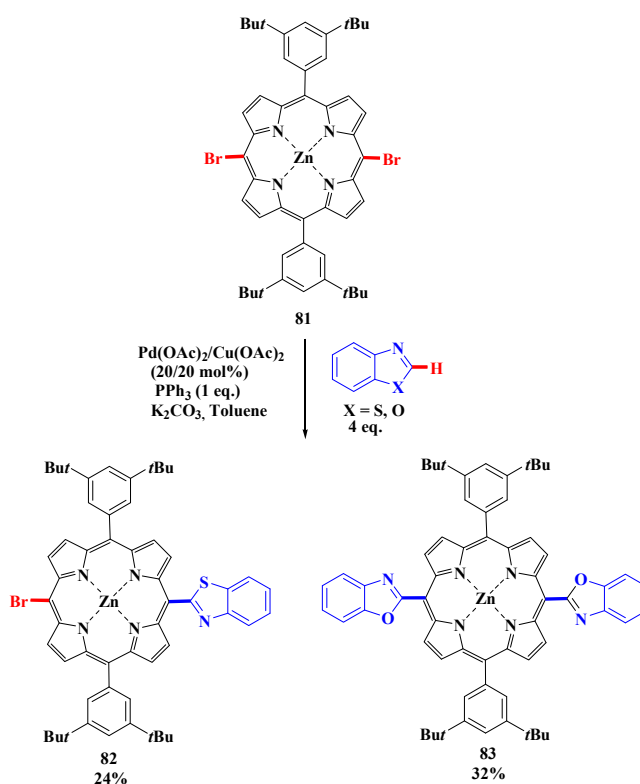
**Scheme 15.** Scheme of porphyrin modification by heteroarenes [76].

It was found that triarylation products **80**, **82**, **84** are the main ones in reactions with all heteroarenes. Tetrasubstituted derivatives **79**, **81**, **83** were obtained in low yields (17% for benzothiazole, 14% for benzoxazole, and 20% for N-methylbenzimidazole). It should be noted that no elimination of the bromine atom was observed in these reactions, although this process took place in almost all the reactions with monobromoporphyrins described above. We also carried out the modification of 5,10,15,20-tetrakis(4'-bromophenyl)-21,23-dithiopyrrole using the same conditions as in the case of tetrabromoporphyrins. It was found that, in contrast to 5,10,15,20-tetrakis(4'-bromophenyl)porphyrin, where triheteryl-substituted porphyrins are the main reaction product, their dithio analog gives a tetrasubstitution product (Scheme 16) [78].



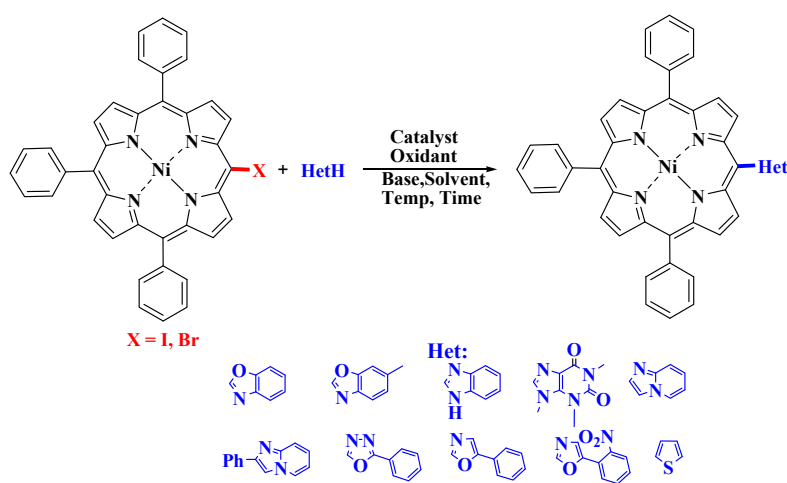
**Scheme 16.** Scheme of porphyrins modification by heteroarenes [78].

The possibility of introducing meso-bromoporphyrins in arylation reactions with heteroarenes opens up an approach to another family of heteroarylated porphyrins studied using meso-dibromoporphyrin **81** as an example (Scheme 17). Reactions with benzothiazole and benzoxazole were carried out using 4 eq of corresponding heteroarenes, 20 mol % catalyst, 1 eq  $\text{PPh}_3$  and 2 equivalent  $\text{K}_2\text{CO}_3$ . As a result of studying this process, it was also found that benzothiazole is less reactive than benzoxazole in these reactions. In the reaction with benzothiazole, only the monoarylated derivative **82** was obtained in 24% yield. In the case of the reaction with benzoxazole, diaryl-substituted porphyrin **83** was isolated in 32% yield [76].



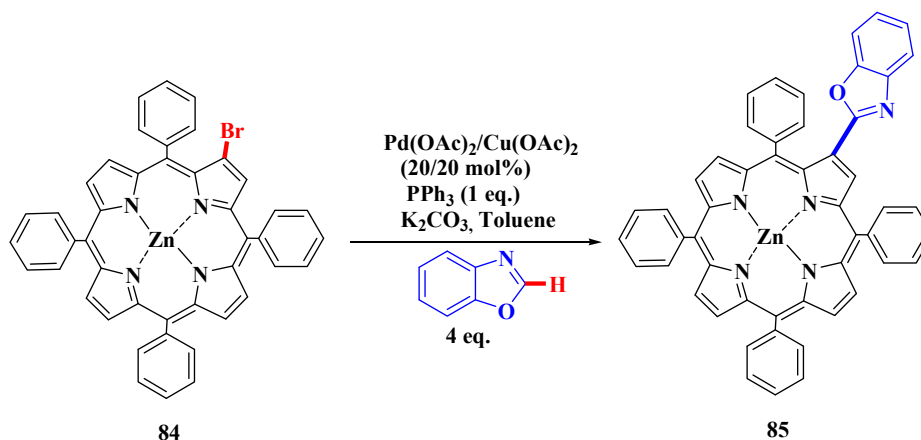
**Scheme 17.** Scheme of porphyrins modification by heteroarenes [76].

One of the main disadvantages of the metal-catalytic functionalization of the C-H bond is the duration of the reactions. A recent work by Kumar and co-workers developed an efficient method for carrying out these reactions using microwave radiation to obtain a variety of heteroaromatic substituted porphyrins [79]. Optimal conditions consisted of using Pd(OAc)<sub>2</sub> (10 mol.%), CuI (10 mol.%), and Cs<sub>2</sub>CO<sub>3</sub> (2 mol. equivalent) in DMF at 120 °C under microwave irradiation for 10 min. Using this technique, various meso-heteroaromatic substituted porphyrins were synthesized (Scheme 18). This is promising, as it can significantly reduce the reaction time.



**Scheme 18.** Scheme for the synthesis of heteroaromatic substituted porphyrins using microwave radiation [79].

We have studied the possibility of introducing heterocyclic residues into the  $\beta$ -position of the porphyrin core using a catalytic system based on  $\text{Pd}(\text{OAc})_2$  and  $\text{Cu}(\text{OAc})_2$  [76]. The reaction was carried out on a model porphyrin **84**. It turned out that the reaction proceeds only with benzoxazole with a 5% yield of product **85**. Almost quantitative elimination of the bromine atom is observed. Therefore, another catalytic system is required to modify the  $\beta$ -position (Scheme 19).



**Scheme 19.** Scheme for the synthesis of heteroaromatic substituted porphyrins [76].

### 3. Conclusions

Metal-catalyzed C-H functionalization in the chemistry of porphyrins opens up new possibilities for the design of porphyrin compounds of a given structure for various practical compounds. Despite the fact that metal-catalytic C-H functionalization of porphyrins is currently not a widely used method for the synthesis of porphyrins, this method is promising, since it allows the synthesis of a wide range of porphyrins from a small number of available precursors. This review makes it possible to single out the most promising directions in the development of the method of metal-catalytic C-H activation for the functionalization of porphyrins.

The basis for the successful modification of porphyrins was the work on the C-H functionalization of various arenes and heteroarenes, for example, those presented in reviews [8,80–82]. We found that when the bromine atom is in the phenyl ring of the macroheterocycle, the best catalytic system is the system reported by Z.-Z. Huang [83,84]. It is based on the use of Pd (II) and Cu (II) acetates. In the case of iridium-catalyzed direct borylation of porphyrins, the work of Smith, Hartwig, Ishiyama, and Miyaura [85–93] served as the basis. When a bromine atom or a hydrogen atom in the beta position of the porphyrin macrocycle undergoes modification, the system based on the work of Fagnou [56,94] serves as an excellent catalytic system. When it is necessary to introduce heterocyclic residues into the meso position of the porphyrin macrocycle, the system developed by Kumar [79] is the best.

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### Abbreviations

Am	amyl;
Ar	aryl;
Bu	butyl;
Cod	cyclooctadiene
DMF	N, N-dimethylformamide
Dtbp	di-t-Bu-2,2'-bipyridyl
DavePhos	2-Dicyclohexylphosphino-2'-(N, N-dimethylamino)biphenyl
Et	ethyl;
EtOH	ethanol
Herrmann's catalyst	(2-methanidylphenyl)-bis(2-methylphenyl) phosphane palladium (II) diacetate
Me	methyl;
MeOH	methanol
Mes	mesyl
Ph	phenyl
Ph <sub>3</sub> P	triphenylphosphine;
Pr	propyl
PCy <sub>3</sub>	tricyclohexylphosphine;
Py	pyridine
Pd(OAc) <sub>2</sub>	palladium (II) acetate
PdCl <sub>2</sub> (dppf)	[1,1'-bis(diphenylphosphino)ferrocene] palladium (II) dichloride
Pd <sub>2</sub> (dba) <sub>3</sub>	tris(dibenzylideneacetone) dipalladium (0)
THF	tetrahydrofuran
t-Bu	tert-butyl
t-BuCOOH	pivalic acid

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