DOI: 10/1070/RCR4565

# Synthesis of chlorins, bacteriochlorins and their tetraaza analogues

**Semyon V. Dudkin,[a, b] Elena A. Makarova,[a] Evgeny A. Lukyanets [a]**

[a] *State Scientific Center 'Organic Intermediates and Dyes Institute' (NIOPIK) ul. Bolshaya Sadovaya 1, kor. 4, 123995 Moscow, Russian Federation*

[b] *National Research Tomsk Polytechnic University prosp. Lenina 30, 634050 Tomsk, Russian Federation*

The currently known methods for the synthesis of hydrogenated derivatives of synthetic porphyrins — chlorins, bacteriochlorins, isobacteriochlorins and their tetraaza analogues — are considered. Reactions involving quasi-isolated double bonds including reduction, oxidative addition and cycloaddition are presented. Examples of direct synthesis of these macroheterocycles are given.
The bibliography includes 168 references.

## Contents

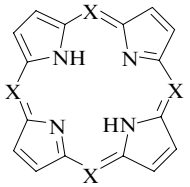
I. Introduction 700
II. Reduction of quasi-isolated double bonds of porphyrins and tetraazaporphyrins 701
III. Oxidative addition at the quasi-isolated double bonds of porphyrins and tetraazaporphyrins 704
IV. Cycloaddition reactions of porphyrins and tetraazaporphyrins 706
V. Direct synthesis of chlorins, bacteriochlorins and their tetraaza analogues 721
VI. Conclusion 728

## I. Introduction

Porphyrins and their isoelectronic analogues — tetraazaporphyrins (TAPs), or porphyrazines — belong to the abundant class of tetrapyrrole macroheterocyclic systems, which find extensive practical application in various fields of science and technology.[1, 2]

The porphine (**1**) and porphyrazine (**2**) molecules are 16-membered macrocycles consisting of two pyrrole and two pyrrolenine moieties that are connected by methine bridges in the former case and by nitrogen atoms in the latter case and form a common conjugated system.

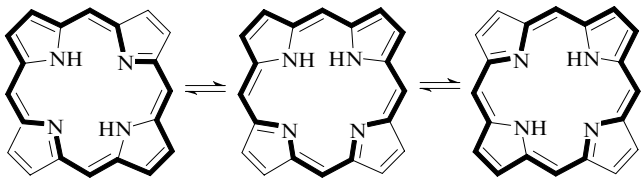
**Structures 1, 2**



**1**, **2** X = CH (**1**), N (**2**)

The system of conjugation of the porphine and TAP molecules is multicontour; its inner chromophore contains 18 π-electrons. Two peripheral C(β)═C(β) double bonds are quasi-isolated (Scheme 1, the bold line shows the system of conjugation); therefore, hydrogenation of these bonds does not break the major macrocyclic aromatic π-system.[3 – 6]

**Scheme 1**



In the case of porphine (**1**), hydrogenation of the double bond in the pyrroline moiety affords 2,3-dihydroporphyrin (chlorin, **I**), hydrogenation of two opposite double bonds

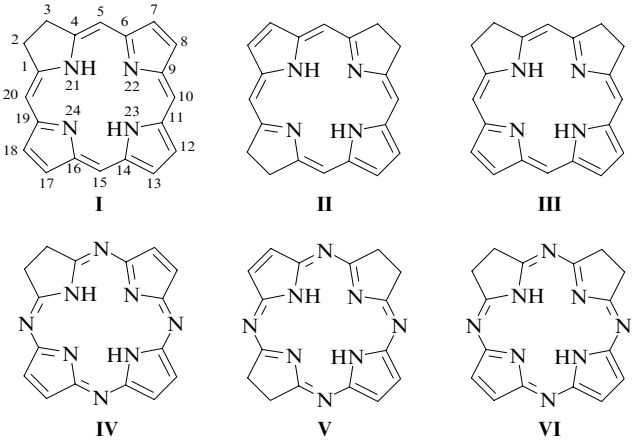
**S.V.Dudkin**. Candidate of Chemical Sciences, Dissertator at the SSC NIOPIK (2012), Research Engineer (PostDoc) at the Department of Technology of Organic and Polymeric Materials, Institute of Natural Resources, NRTPU (since 2014).
Telephon: +7(3822)606 – 119, e-mail: semdudkin@gmail.com
**Current research interests**: synthesis and spectral properties of tetrapyrrole macroheterocyclic compounds; synthesis of photosensitizers for photodynamic therapy.
**E.A.Makarova**. Candidate of Chemical Sciences, Leading Researcher at the Department of Functional Dyes, SSC NIOPIK.
Telephone: +7(495)408 – 7390, e-mail: ea_makarova22@yahoo.com
**E.A.Lukyanets**. Doctor of Chemical Sciences, Professor, Head of the same Laboratory.
Telephone: +7(499)254 – 9547, e-mail: rmeluk@niopik.ru
**Current research interests of the authors**: synthesis and properties of tetrapyrrole macroheterocyclic compounds as functional dyes, catalysts and photocatalysts for medical applications.

Received 6 April 2015
Translation: Z.P.Svitanko

© 2016 Russian Academy of Sciences and Turpion Ltd.

gives 7,8,17,18-tetrahydroporphyrin (bacteriochlorin, BC, **II**), while hydrogenation of two adjacent moieties results in the formation of 2,3,7,8-tetrahydroporphyrin (isobacteriochlorin, iBC, **III**).[7] Similarly, hydrogenation of one or two double bonds of the pyrrole rings of porphyrazine (**2**) furnishes 2,3-dihydrotetraazaporphyrin (tetraazachlorin, TAC, **IV** ), 7,8,17,18-tetrahydrotetraazaporphyrin (tetraazabacteriochlorin, TABC, **V**) and 2,3,7,8-tetrahydrotetraazaporphyrin (tetraazaisobacteriochlorin, TAiBC, **VI**), respectively.

**Structures I – VI**



Owing to the intense absorption and luminescence in the red and near-IR regions, chlorins and bacteriochlorins have been widely studied in recent years as second-generation photosensitizers for the photodynamic therapy (PDT) of cancer and skin diseases.[8 – 18]

Tetraaza analogues of chlorin and bacteriochlorin also exhibit intense absorption in the red and near-IR spectral regions, which makes them promising compounds to be used as a new class of functional dyes, in particular, as photosensitizers for PDT with absorption in the therapeutic window (650 – 900 nm).[19 – 22] However, until recently, these compounds, unlike chlorins and bacteriochlorins, have been very little investigated because of the lack of methods for their synthesis. The effective methods for the preparation of hydrogenated TAP derivatives developed in the last two decades stimulated the progress of chemistry of this new class of tetrapyrrole macrocycles.[23, 24]

The research into the synthesis of hydrogenated porphyrins is pursued along two lines. The first one comprises chemical modification of compounds obtained from natural feedstocks (chlorophyll, bacteriochlorophyll and their derivatives). This topic has been comprehensively surveyed by A.F.Mironov and co-workers (Russia),[11, 25 – 27] Pandey and co-workers (USA),[12, 15] Senge and co-workers (Ireland)[28] and Scherz and co-workers (Israel)[29, 30] and is not addressed in the present review. The second line of research aimed at the preparation of hydrogenated porphyrin derivatives comprises the development of methods for the synthesis of only synthetic chlorins and bacteriochlorins.[31 – 33]

The reviews on this subject published to date concern particular branches of the chemistry of hydrogenated porphyrin and tetraazaporphyrin derivatives. For instance, Cavaleiro's group (Portugal)[31, 34 – 36] studied in detail the cycloaddition reactions in the series of *meso*-tetraarylporphyrins. The works of Lindsey and co-workers (USA)[32] and Brückner and co-workers (USA)[33] are devoted to the preparation of only BC and iBC derivatives. Our review[23, 24] and a review of Fukuda and Kobayashi (Japan)[37] consider the chemistry and spectroscopy of hydrogenated TAP derivatives. However, survey publications that would compare methods for the synthesis of chlorins, bacteriochlorins and their tetraaza analogues are lacking in both Russian and foreign scientific literature.

The goal of this review is to describe systematically and analyze the data, both published in the literature and obtained by the authors, on the synthesis of hydrogenated derivatives of porphyrins and their tetraaza analogues and to elucidate the general patterns of the formation of these macrocycles.

Methods of synthesis of (tetraaza)chlorins and (tetraaza)bacteriochlorins can be divided into two major groups:

— substitution reactions in the prepared macrocycle — porphyrin or TAP;

— transformations involving cyclization of intermediates to give the hydrogenated macrocycle.

The material is arranged in sections that deal with reduction, oxidative addition, cycloaddition and direct synthesis as approaches to the preparation of the title compounds.

## II. Reduction of quasi-isolated double bonds of porphyrins and tetraazaporphyrins

The reduction of porphyrins to the corresponding chlorins and bacteriochlorins is a traditional and the simplest method for their synthesis. The first attempts to reduce porphyrins were made by Fischer and co-workers[38, 39] in the early 1930s. These publications report on the synthesis of etiochlorin I by the reduction of the Fe complex of etioporphyrin I with sodium metal in isoamyl alcohol ($Am^iOH$). In a later study, the reduction of iron etioporphyrin II afforded a mixture of etiochlorin II and etioporphyrin II in a total yield of 79%.[40]

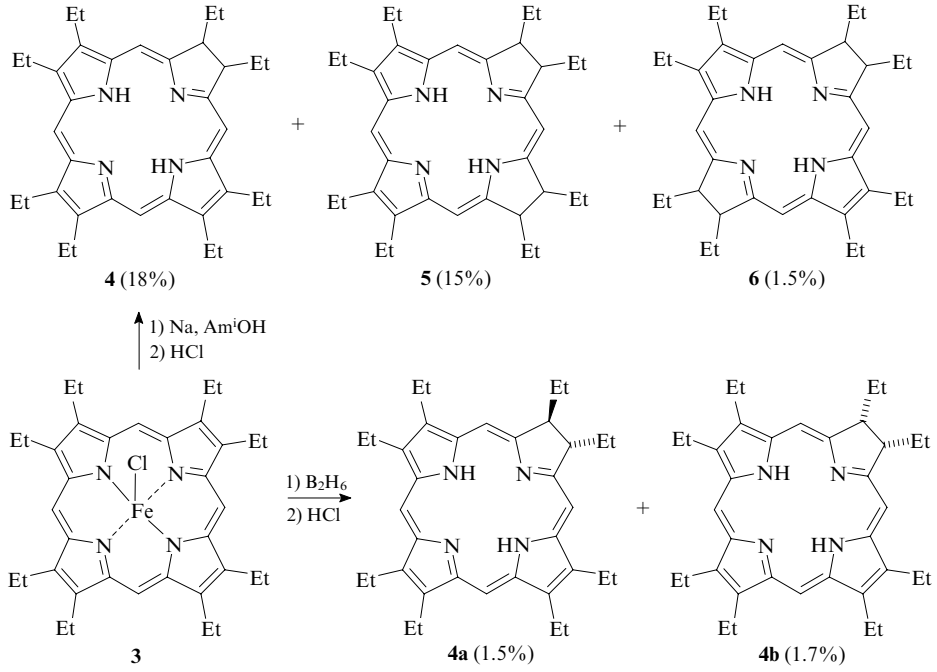
Iron octaethylporphyrin **3** is reduced under similar conditions; the subsequent demetallation on treatment with hydrochloric acid affords a mixture of octaethylchlorin (**4**) and the corresponding derivatives of isobacteriochlorin (**5**) and bacteriochlorin (**6**) (Scheme 2); the products were separated by chromatography, and the structure of each of them was established by $^1$H NMR spectroscopy.[41, 42]

On treatment of porphyrin **3** with diborane at room temperature, a mixture of isomeric *cis*- and *trans*-octaethylchlorins **4a**,**b** is formed in a moderate yield (see Scheme 2),[42] while the reduction of *meso*-tetrakis[3,5-di(*tert*-butyl)phenyl]porphyrin with the same reagent affords the corresponding chlorin in a high yield (91%), which is indicative of a dependence of the efficiency of this reaction on the structure of the starting porphyrin.[43]

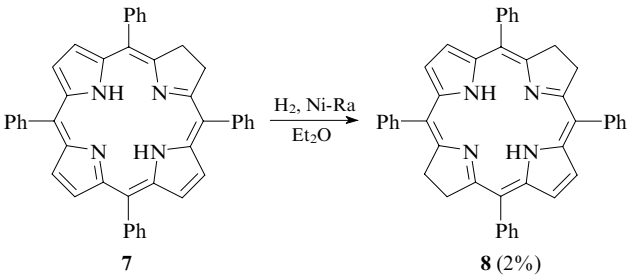
Dorough and Miller[44] described the catalytic hydrogenation of porphyrins. Upon hydrogenation of *meso*-tetraphenylchlorin **7** with hydrogen in the presence of Raney nickel (Ni-Ra), *meso*-tetraphenylbacteriochlorin **8** was isolated in moderate yield (Scheme 3).

Catalytic hydrogenation of substituted TAPs was investigated by Linstead and co-workers[45] in 1958. The hydrogenation of magnesium tetramethyl- (**9a**), octamethyl- (**9b**) and tetra(cyclohexeno)tetraazaporphyrins (**9c**) with hydrogen catalyzed by palladium black in pyridine (PyH) followed by demetallation of the reduction products on

**Scheme 2**

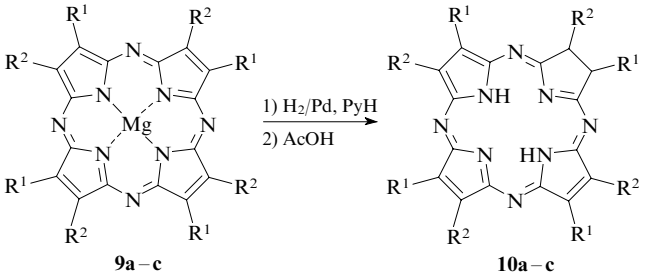



**Scheme 3**




treatment with acetic acid furnished substituted TACs **10a – c** (Scheme 4).

**Scheme 4**



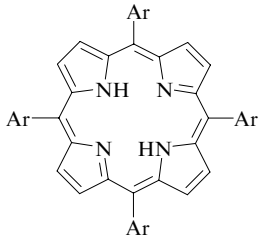

$R^1$ = Me: $R^2$ = H (**a**, 43% yield), Me (**b**, 84%);
$R^1 – R^2$ = $(CH_2)_4$ (**c**, 76%)

The attempts to reduce TAP free bases under similar conditions were unsuccessful because of the limited solubility of these compounds in pyridine and substantial destruction.

In 1969, Whitlock and co-workers [46] proposed the use of the diimide generated *in situ* from *p*-toluenesulfonyl hydrazide (tosyl hydrazide, $TsNHNH_2$) in the presence of potassium carbonate in pyridine for the synthesis of hydrogenated porphyrins. The structure and the ratio of reaction products depended on the porphyrin : $TsNHNH_2$ molar ratio. For example, the reduction of *meso*-tetraphenylporphyrin **11** on treatment with $TsNHNH_2$ in the presence of potassium carbonate in pyridine at 1 : 6 ratio of the reactants gave chlorin **7** in a high yield, while the same reaction at 1 : 17 ratio of the reactants gave bacteriochlorin **8**. The authors also demonstrated that porphyrin (chlorin) free bases and metal complexes behave in considerably different ways when reduced with the diimide (Scheme 5). Indeed, porphyrin **11** is reduced to chlorin **7** and then to bacteriochlorin **8** with a 2% – 4% impurity of the corresponding iBC. Zinc *meso*-tetraphenylporphyrin **12** is first reduced to the corresponding Zn chlorin complex **13**, which, unlike free base **11**, is further reduced to give zinc isobacteriochlorin **14** (see Scheme 5).[46] In the authors' opinion, this selectivity is related to higher stability of the Zn complexes compared with the free bases under the reaction conditions.

Subsequently, the simple and facile process proposed by Whitlock and co-workers was used by several research group [43, 47 – 57] to convert porphyrins **11**, **15 – 41** to substituted chlorins **7**, **42 – 54** and bacteriochlorins **8**, **55 – 79** (Table 1).

**Structures 15 – 41**




In some cases, minor modifications of the procedure were made. For example, for the reduction of halo-substituted porphyrins **24 – 26**, the required diimide was generated from $TsNHNH_2$ either in the presence or in the absence of

**Scheme 5**

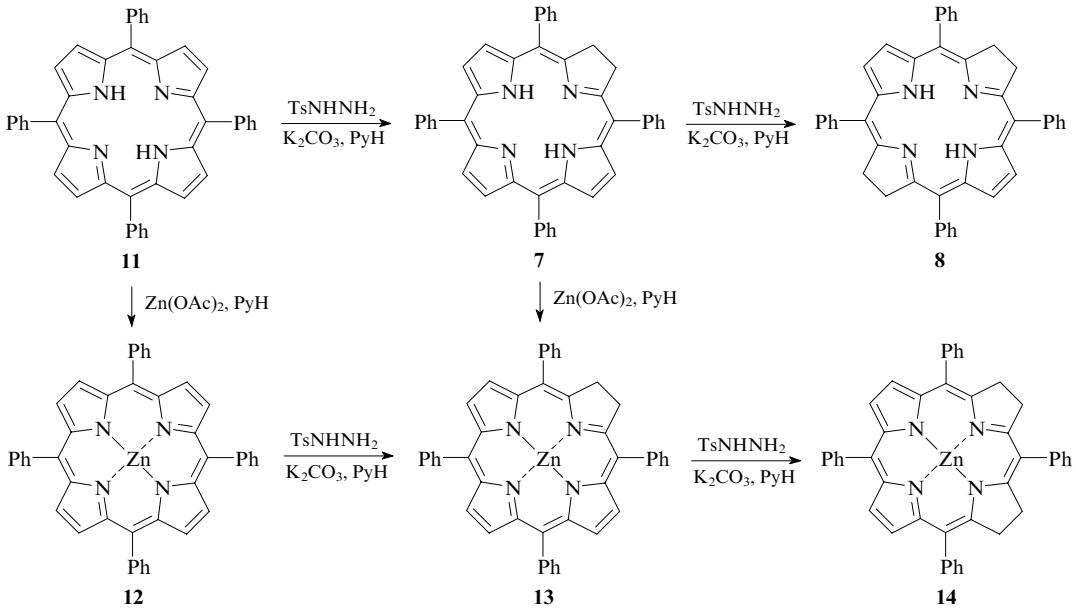



**Table 1**. Synthesis of *meso*-substituted chlorins and bacteriochlorins from porphyrins **11**, **15** – **41**.

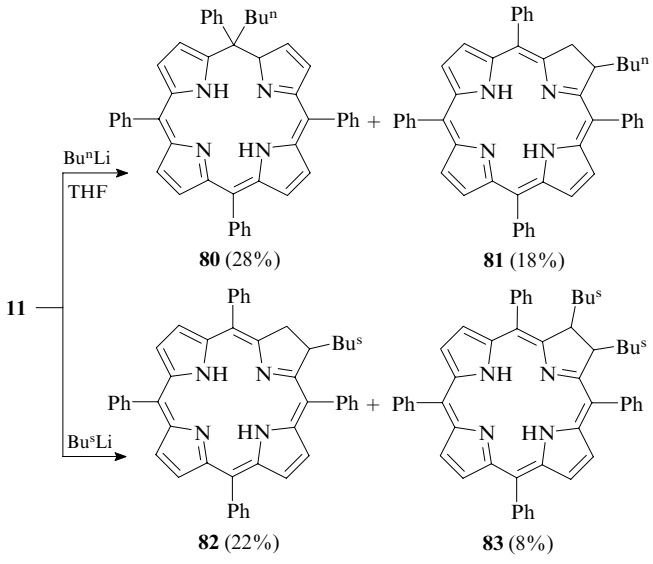
| Porphyrin | Ar | Chlorins | Yield (%) | Bacterio-chlorins | Yield (%) | Ref. |
|---|---|---|---|---|---|---|
| **11** | Ph | **7** | 72 | **8** | 50 | 46 |
| **11** | Ph | **7** | 25 (80) [a] | **8** | 75 | 55 |
| **15** | 2-$HOC_6H_4$ | **42** | 64 | – | – | 47 |
| **16** | 3-$HOC_6H_4$ | **43** | 37 | **55** | 26 | 47 |
| **16** | 3-$HOC_6H_4$ | **43** | 20 (65) [a] | **55** | 80 | 55 |
| **17** | 4-$HOC_6H_4$ | **44** | 47 | – | – | 47 |
| **18** | 4-$MeC_6H_4$ | **45** | 80 | **56** | 10 | 48 |
| **19** | 3,5-$Bu^t_2C_6H_3$ | – | – | **57** | 65 | 43 |
| **20** | 3-Py | – | – | **58** | 40 | 49 |
| **21** | 4-Py | – | – | **59** | 5 | 50 |
| **22** | 4-$Br(CH_2)_4OC_6H_4$ | – | – | **60** | 12 | 51 |
| **23** | 4-$EtO_2CCH_2OC_6H_4$ | – | – | **61** | 16 | 51 |
| **24** | 2-$ClC_6H_4$ | – | – | **62** | 66 (71) [b] | 52 |
| **25** | 2,6-$Cl_2C_6H_3$ | – | – | **63** | 51 (63) [b] | 52 |
| **25** | 2,6-$Cl_2C_6H_3$ | **46** | 15 (75) [a] | **63** | 85 | 55 |
| **26** | 2,6-$F_2C_6H_3$ | – | – | **64** | 55 (57) [b] | 52 |
| **26** | 2,6-$F_2C_6H_3$ | – | – | **64** | 60 | 57 |
| **27** | 2,6-$Cl_2$-3-$HO_3SC_6H_2$ | **47** | 80 | **65** | 77 | 53, 54, 56 |
| **28** | 2,6-$Cl_2$-3-$EtNHO_2SC_6H_2$ | **48** | 63 | **66** | 85 | 53, 54, 56, 57 |
| **29** | 2,6-$Cl_2$-3-(n-$C_7H_{15}$)$NHO_2SC_6H_2$ | **49** | See [c] | **67** | 85 | 53, 54, 56, 57 |
| **30** | 3-$MeOC_6H_4$ | **50** | 15 (90) [a] | **68** | 85 | 55 |
| **31** | 4-$MeOC_6H_4$ | **51** | 35 (90) [a] | **69** | 65 | 55 |
| **32** | 4-$BrC_6H_4$ | **52** | 35 (85) [a] | **70** | 65 | 55 |
| **33** | 4-$Bu^tC_6H_4$ | **53** | 30 (70) [a] | **71** | 45 | 55 |
| **34** | 2-Cl-5-$HO_3SC_6H_3$ | – | – | **72** | 70 | 56 |
| **35** | 2-Cl-5-$EtNHO_2SC_6H_3$ | – | – | **73** | 75 | 56 |
| **36** | 2,6-$F_2$-3-$HO_3SC_6H_2$ | – | – | **74** | 85 | 56 |
| **37** | 2-F-5-$MeNHO_2SC_6H_3$ | **54** | 46 | **75** | 83 | 56, 57 |
| **38** | 2-F-5-$Me_2NO_2SC_6H_3$ | – | – | **76** | 71 | 56 |
| **39** | 2,6-$F_2$-3-$F_3CCFHCF_2CH_2O_3SC_6H_2$ | – | – | **77** | 84 | 57 |
| **40** | 2,6-$F_2$-3-$HOCH_2CMe_2NHO_2SC_6H_2$ | – | – | **78** | 87 | 57 |
| **41** | 2,6-$F_2$-3-$Bu^i(MeO_2C)CHNHO_2SC_6H_2$ | – | – | **79** | 80 | 57 |

**Note**. The dash means that the compound has not been isolated. [a] The values in parentheses are the product yields in the presence of $MnO_2$; [b] the yield upon thermal decomposition of tosyl hydrazide; that in the presence of potassium carbonate is in parentheses; [c] the yield is not indicated in the original publication.

potassium carbonate.[52] Upon thermal decomposition of tosyl hydrazide, the yields of the target products **62**–**64** proved to be somewhat lower.[52] 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU) and 1,4-diazabicyclo[2.2.2]octane (DABCO) were also proposed as bases for the preparation of chlorins **47**–**49** and bacteriochlorins **65**–**67**.[53, 54, 57]

Recent publications report on the preparation of *meso*-aryl-substituted BCs using microwave irradiation[55] and melting of the starting reactants (solvent-free approach).[56, 57] Heating of porphyrins **11**, **16**, **25** and **30**–**33** with tosyl hydrazide and potassium carbonate in a unit with microwave exposure at 100 W affords bacteriochlorins **8**, **55**, **63** and **68**–**71** in higher yields than the conventional thermal reaction (see Table 1).[55] In the same study, manganese(IV) dioxide is shown to be suitable as a mild oxidant for converting bacteriochlorins to chlorins; these conditions were used to prepare compounds **7**, **43** , **46** and **50**–**53**. An advantage of the microwave-assisted reaction is considerable shortening of the reaction time, from 6.5–48 h to 25 min. Melting of porphyrins **27**–**29**, **34**–**41** with tosyl hydrazide in a sealed tube yielded chlorin **54** and bacteriochlorins **65**–**67** and **72**–**79** (see Table 1).[56, 57] The benefits of this method are the absence of a solvent and the possibility of scaling-up the synthesis of *meso*-arylbacteriochlorins to preparative quantities.

**Scheme 6**




The synthesis of hydrogenated derivatives by treatment of porphyrins and TAPs with n-butyl- (Bu$^n$Li) or *sec*-butyllithium (Bu$^s$Li) has been reported.[58–61] The reaction of porphyrin **11** with Bu$^n$Li (3 equiv.) resulted in the isolation of a mixture of butyl-substituted phlorin **80** and chlorin **81**. Meanwhile, in the case of Bu$^s$Li, no phlorin **80** was detected, but a mixture of mono- (**82**) and bis-alkylated chlorins **83** was isolated (Scheme 6).

Vagin *et al.*[61] reported that the treatment of 2,3,7,8,12,13,17,18-octakis(3-trifluoromethylphenyl)tetraazaporphyrin or its Mg complex with Bu$^n$Li gives adducts, which were identified as TAC derivatives considering the data of electronic absorption spectra and mass spectra.

## III. Oxidative addition at the quasi-isolated double bonds of porphyrins and tetraazaporphyrins

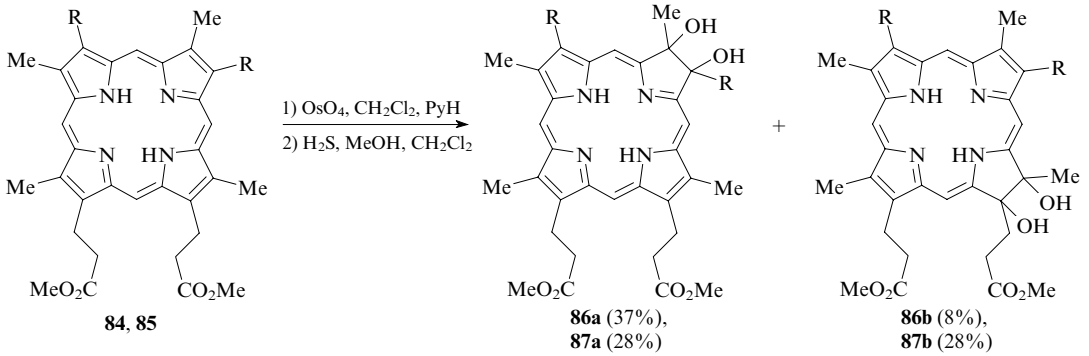
Hydroxylation of the quasi-isolated double bonds of porphyrins with osmium tetroxide ($OsO_4$) in the presence of pyridine followed by treatment of the intermediate ester of osmic acid (osmate) with hydrogen sulfide can serve as a method for the synthesis of vicinal hydroxylated hydrogenated porphyrins.

The application of $OsO_4$ for the synthesis of hydrogenated derivatives of natural porphyrins was described for the first time by Fischer and co-workers [62, 63] in the 1940s. In these early papers, they reported the preparation of hydroxylated chlorins by reduction of the corresponding osmates with sodium sulfite. A publication of 1985 described the synthesis of chlorins from dimethyl esters of 2,4-dimethyldeuteroporphyrin IX (**84**) and its ethyl analogue **85** in which hydrogen sulfide was used for the reduction of the intermediate osmates.[64] Porphyrins **84** and **85** were made to react with a small excess of $OsO_4$ (1.2 equiv.) in the presence of pyridine, and then hydrogen sulfide was passed into the reaction mixture to give isomeric *vic*-hydroxylated chlorins **86a**,**b** and **87a**,**b**, respectively (Scheme 7).

Later, Brückner and Dolphin[65] demonstrated that treatment of porphyrin **11** with osmium tetroxide in the presence of pyridine gives complex **88** similar to that formed from simple alkenes; treatment of complex **88** with hydrogen sulfide afforded vicinal hydroxylated chlorin. Subsequently, complex **89** of a similar structure was also isolated in the case of zinc isobacteriochlorin.[33]

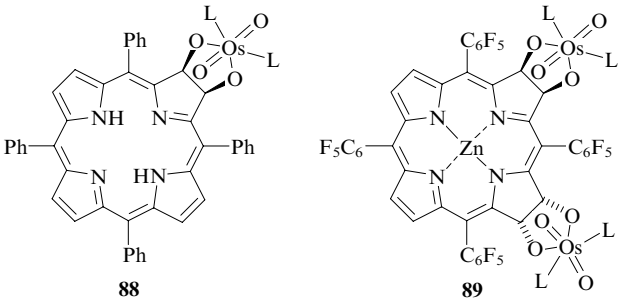
The hydroxylation of metal-free porphyrins results in the formation of mainly chlorins and, in some cases, bacteriochlorins. For example, the reaction of porphyrins

**Scheme 7**




R = Me (**84**, **86**), Et (**85**, **87**)

**Structure 88, 89**



**88** **89**

L = PyH

**11**, **33**, **90** or **91** with a stoichiometric amount of $OsO_4$ at room temperature followed by passing hydrogen sulfide resulted in the synthesis of a number of substituted chlorins **92** – **95** (~80% yield) and bacteriochlorins **96** – **99** (~80% yield) containing electron-donating groups in the *meso*-phenyl moieties (Scheme 8).[65, 66] Dolphin and co-workers[67] utilized this procedure to prepare a series of *meso*-tetraarylchlorins with various electron-donating and electron-withdrawing substituents in the benzene rings. A chlorin and bacteriochlorin mixture was also obtained in a study of Bonnett and co-workers[68, 69] by treatment of octaethylporphyrin with a slight excess of $OsO_4$ (1.6 equiv.).

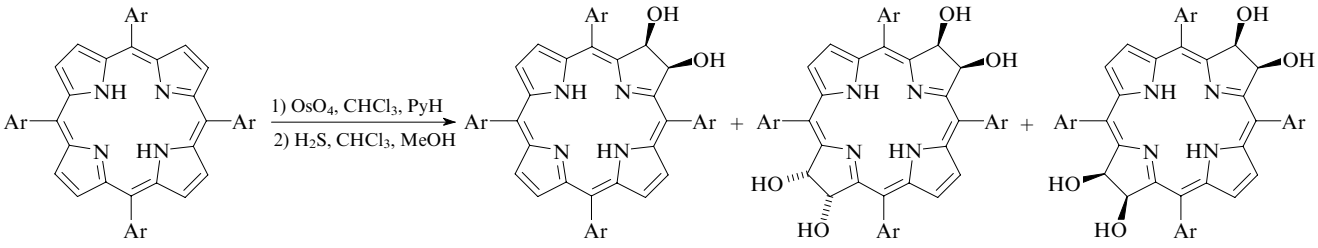
The behaviour of chlorins and their metal complexes in the $OsO_4$ mediated dihydroxylation is similar to the behaviour in the diimide reduction, namely, hydroxylation of chlorin free bases yields bacteriochlorins, whereas metal complexes are converted, under the same conditions, to metal complexes of isobacteriochlorins.[70 – 72] For instance, hydroxylation of *vic*-dihydroxychlorin **92** and its Zn complex **100** with $OsO_4$ furnished BC (**96a**,**b**) and iBC (**101a** ,**b**) isomers, respectively (Scheme 9).[72]

5,15-Diphenylporphyrins **102** – **112** containing various electron-donating and electron-withdrawing substituents in the *meso*-aryl moieties are converted on treatment with $OsO_4$ (2.5 equiv.) to the corresponding chlorins **113** – **123**, while the use of a larger excess of the reagent (5 equiv.) leads to bacteriochlorins **124** – **134** (Scheme 10).[73, 74]

A similar result was obtained in the reaction of $OsO_4$ with unsymmetrical porphyrin containing glucose and glutaric acid moieties.[75] The synthesis of hydroxylated chlorins and bacteriochlorins by treating *meso*-tetrakis(*p*-tolyl)dithiaporphyrin with $OsO_4$ has also been reported.[76, 77]

Brückner and Dolphin[72] proposed a combined procedure for the preparation of BC and iBC derivatives in which they used both the diimide reduction and hydroxylation. The reaction of chlorin **7** or its Zn complex **13** with a stoichiometric amount of $OsO_4$ at room temperature and the subsequent treatment with hydrogen sulfide results in *vic*-dihydroxybacteriochlorin **135** or zinc *vic*-dihydroxyisobacteriochlorin **136**. Compounds **135** and **136** were also prepared by reduction of *vic*-dihydroxytetraphenylchlorin **92** or its Zn complex **100** with diimide in pyridine (Scheme 11).[72]

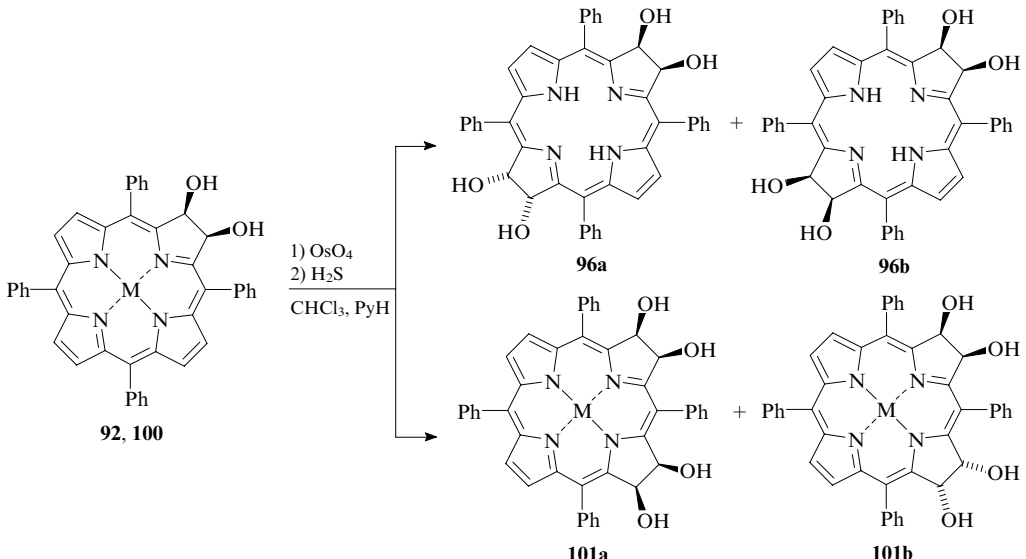
**Scheme 8**



**11**, **33**, **90**, **91** **92** – **95** **96a** – **99a** **96b** – **99b**

Ar = Ph (**11**, **92**, **96**), 4-Bu$^t$C$_6$H$_4$ (**33**, **93**, **97**), 4-Pr$^i$C$_6$H$_4$ (**90**, **94**, **98**), 3,4,5-(MeO)$_3$C$_6$H$_2$ (**91**, **95**, **99**)

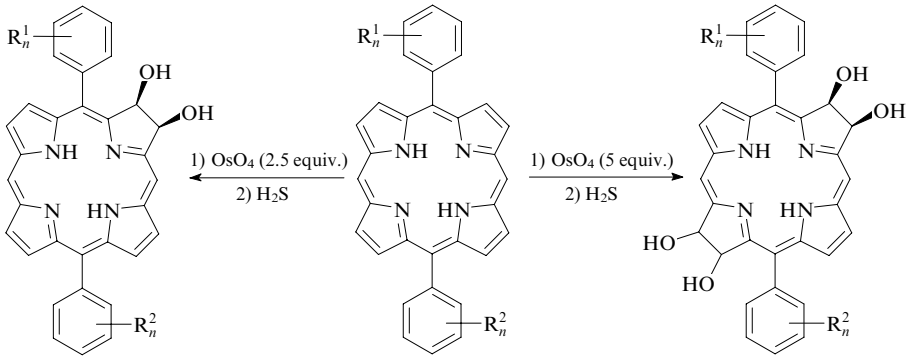
**Scheme 9**



**92**, **100** **96a** **96b** **101a** **101b**

M = 2 H (**92**, **96**), Zn (**100**, **101**)

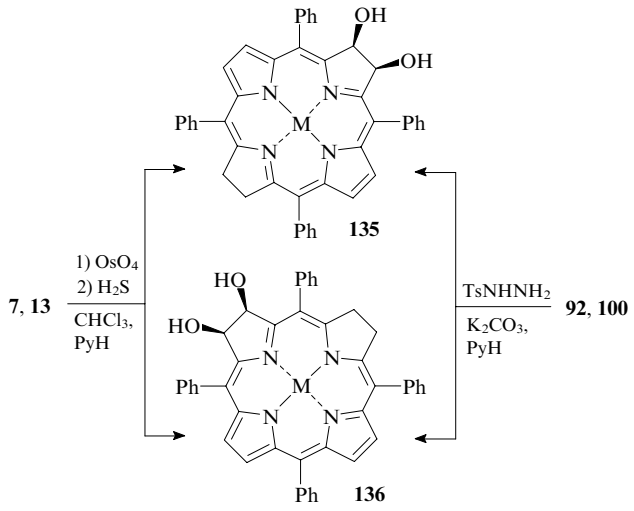
**Scheme 10**




**113** – **123** (34% – 57%) **102** – **112** **124** – **134** (27% – 72%)

$R_n^1 = R_n^2$ = H (**102**, **113**, **124**),
4-Me (**103**, **114**, **125**), 4-Br (**104**, **115**, **126**),
4-$CO_2$Me (**105**, **116**, **127**),
3,4,5-$(OMe)_3$ (**106**, **117**, **128**);
$R_n^1$ = 4-OMe: $R_n^2$ = 4-$NH_2$ (**107**, **118**, **129**),
4-$CO_2$Me (**108**, **119**, **130**);
$R_n^2$ = 4-Me: $R_n^1$ = 3,4,5-$(OMe)_3$
(**109**, **120**, **131**), 4-CN (**110**, **121**, **132**);
$R_n^1$ = 4-$CO_2$Me: $R_n^2$ = 4-CN (**111**, **122**, **133**),
4-Br (**112**, **123**, **134**)

**Scheme 11**




**7**, **13** **92**, **100**

**135** **136**

M = 2 H (**7**, **92**, **135**), Zn (**13**, **100**, **136**)

To our knowledge, the use of $OsO_4$ for the preparation of hydrogenated TAP derivatives is described in only one paper.[78] By treatment of 2,3,12,13,17,18-hexakis(4-*tert*-butylphenyl)tetraazaporphyrin or its Ni complex with $OsO_4$, the authors isolated the corresponding TAC derivative (69% yield) or its Ni complex (65% yield).

Despite the fact that hydroxylation with $OsO_4$ can selectively furnish chlorins, this method has drawbacks, particularly, high toxicity and high cost of the reagents, which restricts the applicability of this synthetic approach.

## IV. Cycloaddition reactions of porphyrins and tetraazaporphyrins

### IV.1. [4 + 2]-Cycloaddition reactions

As noted above, two double bonds of porphyrins and tetraazaporphyrins are partially isolated from the macrocycle [3 – 6] and can behave in chemical reactions as the double bonds of alkenes. This enables the use of cycloaddition for the synthesis of hydrogenated porphyrin and TAP derivatives.[23, 24, 31, 34 – 37] The major products formed in these reactions both from porphyrins and TAP derivatives are monoadducts, *i.e.*, substituted chlorins or tetraazachlorins, but in some cases, bis-adducts of different structure — bacterio- and isobacteriochlorin derivatives or their tetraaza analogues — can also be isolated.

#### IV.1.a. Porphyrins as dienophiles in [4 + 2]-cycloaddition

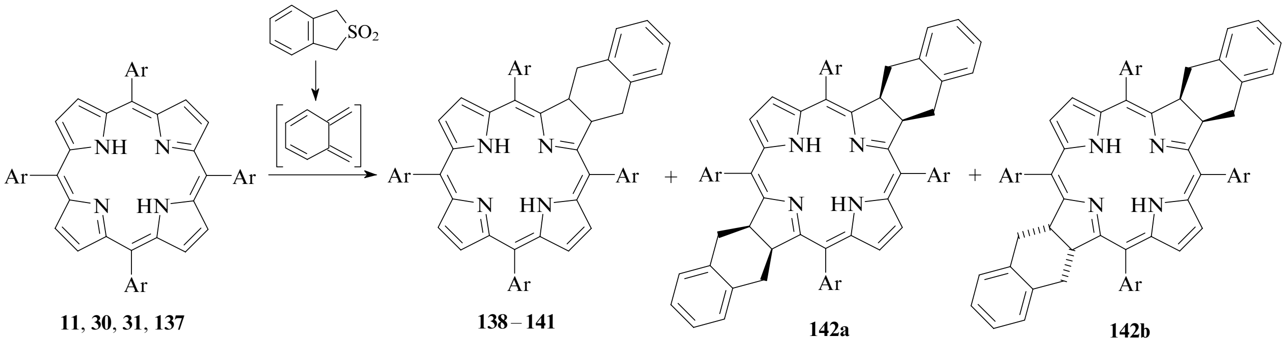
In [4 + 2]-cycloaddition reactions, porphyrins and their tetraaza analogues can function as both dienophiles [79 – 87] and dienes.[88 – 98] (It is noteworthy that the use of TAPs as dienes is so far unknown.)

In 1997, Cavaleiro and co-workers [79] demonstrated for the first time that *meso*-tetraaryl-substituted porphyrins can participate in the Diels – Alder reactions as dienophiles. The authors investigated the behaviour of porphyrins **11**, **30**, **31** and **137** towards carbo- and heterocyclic *o*-quinodimethane dienes, which were obtained *in situ* upon thermal decomposition of sulfones.[79 – 81] It was shown that porphyrins with electron-donating substituents in the *meso*-aryl groups form mainly chlorins, whereas porphyrins with electron-withdrawing substituents form also bacteriochlorins, together with chlorins. Thus refluxing of porphyrins **11**, **30** and **31** with *o*-benzoquinodimethane in 1,2,4-trichlorobenzene afforded chlorins **138** – **140** (the yield of the former was 26%) (Scheme 12).[79] When 5,15-bis(4-methoxyphenyl)porphyrin is introduced in the same reaction as a dienophile, chlorin is also formed as the major product, while the reaction of *meso*-tetrakis(pentafluorophenyl)porphyrin **137** gives not only chlorin **141** but also diastereomeric bacteriochlorins **142a**,**b**, which are separated by preparative thin layer chromatography (see Scheme 12).[79]

Porphyrins **11** and **137** behave in a similar way when react with *o*-quinodimethane prepared *in situ* from substituted pyrrolosulfolene. When porphyrin **11** reacts with a large excess of this diene in 1,2,4-trichlorobenzene at reflux in the presence of 4 Å molecular sieves, a mixture of enantiomers of chlorin **143** is formed (Scheme 13).[80] Apart from chlorin, pyrroloporphyrin and a minor quantity of isoindoloporphyrin were also isolated from the reaction mixture, and the formation of bis(pyrrolo)bacteriochlorin was spectrally detected.[80] The use of porphyrin **137** as the dienophile in this reaction gave rise to chlorin **144** and bacteriochlorin **145** (see Scheme 13).[80] The authors note that zinc and nickel *meso*-tetraphenylporphyrins showed lower reactivities than the free base **11**.[80]

For increasing the oxidative stability of the resulting hydrogenated derivatives, β,β-disubstituted porphyrins — octaethylporphyrin and its Fe complex **3** — were tested as dienophiles in the reaction with pyrrolosulfolene. However, both porphyrins showed low reactivity, possibly, because of steric hindrance and the electron-donating nature of substituents; as a result, only the expected chlorin and its Fe complex were isolated in low yields (2% – 6%).[80]

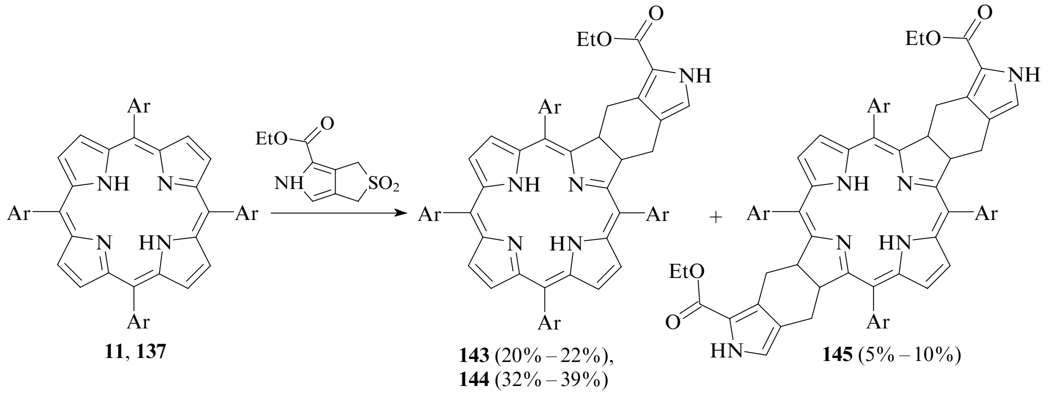
**Scheme 12**



**11**, **30**, **31**, **137** **138** – **141** **142a** **142b**

Ar = Ph (**11**, **138**), 3-MeO$C_6H_4$ (**30**, **139**), 4-MeO$C_6H_4$ (**31**, **140**), $C_6F_5$ (**137**, **141**, **142**)

**Scheme 13**



**11**, **137** **143** (20% – 22%), **144** (32% – 39%) **145** (5% – 10%)

Ar = Ph (**11**, **143**), $C_6F_5$ (**137**, **144**, **145**)

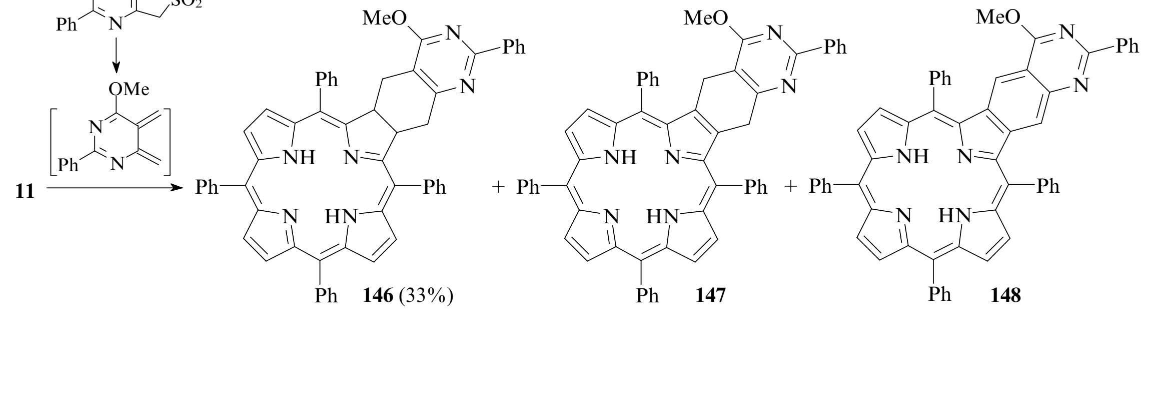
An attempt has been reported to prepare chlorins and bacteriochlorins by the reaction of porphyrins **11**, **25** and **137** with *o*-pyrazinoquinodimethane generated *in situ* from 5,6-bis(bromomethyl)-2,3-dicyanopyrazine. However, the hydrogenated derivatives that formed were readily oxidized under the reaction conditions to related porphyrins containing one or two dicyanoquinoxaline moieties.[81]

The reaction of porphyrin **11** with substituted pyrimidinosulfolene led to isolation of a mixture of tetrahydroquinazolinochlorin **146**, dihydroquinazolinoporphyrin **147** and quinazolinoporphyrin **148**, most likely, a product of partial oxidation of chlorin **146** (Scheme 14).[36] No experimental details or spectral characteristics of chlorin **146** are reported in the paper cited.

In order to solve the problem of oxidation of hydrogenated derivatives in the reaction with *o*-benzoquinodimethane, Ostrowski and Wyrebek[82] used 2-nitro-*meso*-tetraphenylporphyrin **149** and its Zn complex **150** as dienophiles. The electron-withdrawing behaviour of the nitro group enhances the reactivity of the quasi-isolated double bond; as a result, porphyrin **149** reacts with *o*-benzoquinodimethane on refluxing in 1,2,4-trichlorobenzene to give chlorin **151**. However, under rigorous conditions, aromatization of the products takes place (*via* nitrous acid elimination and oxidation), giving rise to naphtho- (**152**) and dinaphthoporphyrins (**153**) (Scheme 15).[82] When complex **150** reacts with *o*-benzoquinodimethane under similar conditions, this gives a mixture of products comprising chlorin **154**, naphthoporphyrins **155** – **157** and bacteriochlorin **158** and the recovered starting porphyrin **150** (see Scheme 15).[82]

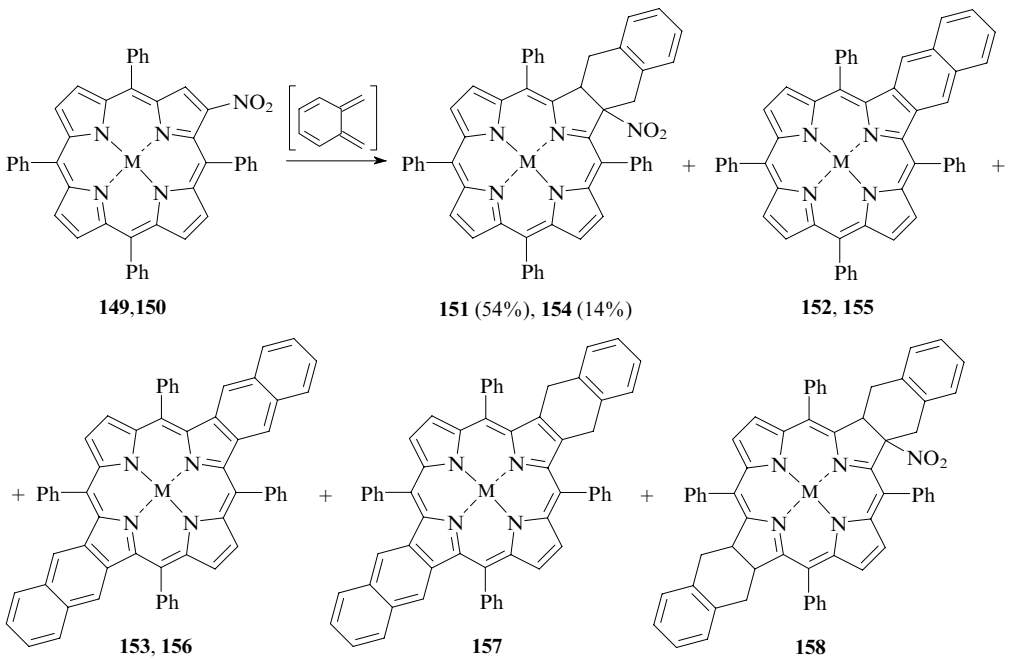
Apart from the *o*-benzoquinodimethane derivatives, aromatic polycyclic hydrocarbons were also introduced as

**Scheme 14**



**11** **146** (33%) **147** **148**

**Scheme 15**

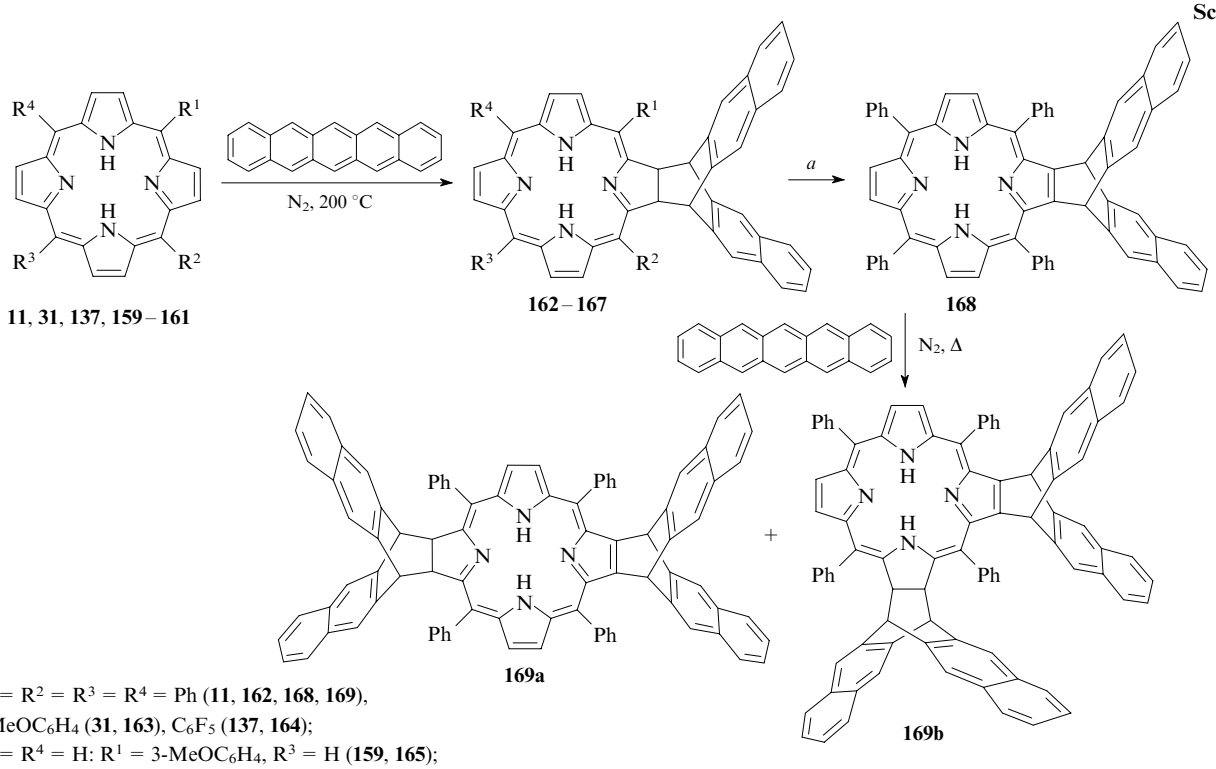



M = 2 H (**149**, **151** – **153**), Zn (**150**, **154** – **158**)

dienes into [4 + 2]-cycloaddition with *meso*-aryl-substituted porphyrins. Symmetrical (**11**, **31**, **137**) and unsymmetrical (**159** – **161**) porphyrins react with pentacene in 1,2,4-trichlorobenzene yielding chlorins **162** – **167** (Scheme 16).[83] The oxidation of chlorin **162** on treatment with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) affords dinaphthobarrelenoporphyrin **168**, which reacts with pentacene to give a mixture of isomeric chlorins **169a**,**b** in a minor yield (see Scheme 16).[83]

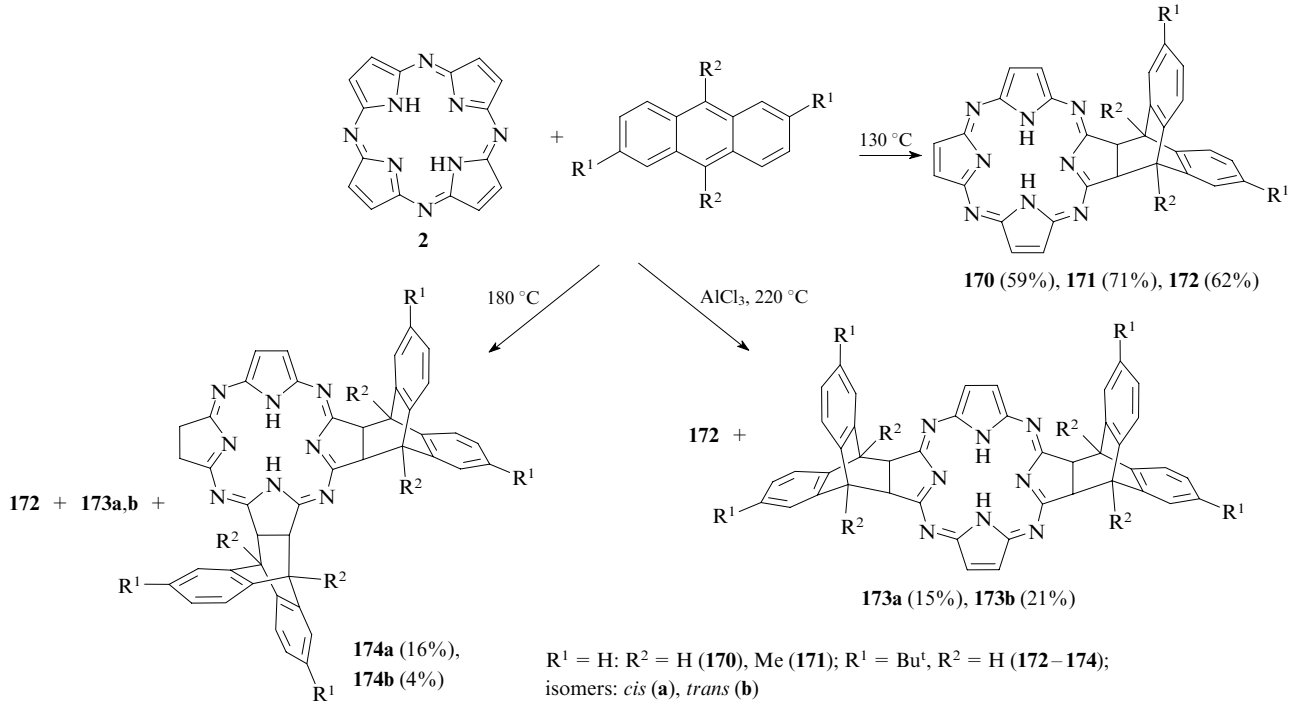
With the use of microwave radiation, the Diels – Alder reaction involving polycyclic hydrocarbons was effected under less rigorous conditions. Indeed, microwave heating of porphyrin **137** with pentacene in *o*-dichlorobenzene at 200 °C afforded chlorin **164** (83% yield),[84] which was less reactive as a dienophile than porphyrin **137**. The reaction of chlorin **164** with pentacene under similar conditions resulted in BC and iBC derivatives in a total yield of 7%. Apart from bis-adducts, the starting chlorin **164** (65% yield) and porphyrin **137** (16% yield), which is formed upon

**Scheme 16**




$R^1 = R^2 = R^3 = R^4$ = Ph (**11**, **162**, **168**, **169**),
4-$MeOC_6H_4$ (**31**, **163**), $C_6F_5$ (**137**, **164**);
$R^2 = R^4$ = H: $R^1$ = 3-$MeOC_6H_4$, $R^3$ = H (**159**, **165**);
$R^1 = R^3$ = 4-$MeOC_6H_4$ (**160**, **166**), 3-$MeOC_6H_4$ (**161**, **167**); (*a*) DDQ ($R^1 = R^2 = R^3 = R^4$ = Ph)

**Scheme 17**




retrodiene decomposition, were isolated after this reaction. The reaction of porphyrin **137** with tetracene in *o*-dichlorobenzene gave a mixture of chlorin isomers in a total yield of 23%. The low yield of bis-adducts was attributed [84] to retro-Diels – Alder reaction under the reaction conditions.

**IV.1.b. Tetraazaporphyrins as dienophiles in [4 + 2]-cycloaddition**

The possibility of participation of TAP derivatives as dienophiles in the Diels – Alder reaction was first demonstrated for the reaction of TAP (**2**) with anthracene type dienes. The condensation of compound **2** with anthracene, 9,10-dimethylanthracene and 2,6-di(*tert*-butyl)anthracene in refluxing chlorobenzene furnished a number of dibenzobarrelenotetraazachlorins **170** – **172** (Scheme 17).[85] The use of aluminium chloride as a catalyst in the reaction of TAPs with 2,6-di(*tert*-butyl)anthracene provided *cis*- and *trans*-dibenzobarrelenotetraazabacteriochlorins **173a**,**b**.[85] Subsequently, it was shown that the reaction of compound **2** with 2,6-di(*tert*-butyl)anthracene in refluxing *o*-dichlorobenzene yields *cis*- and *trans*-dibenzobarrelenotetraazaisobacteriochlorins **174a**,**b** along with the expected TAC (**172**) and TABC (**173**) derivatives (see Scheme 17).[86]

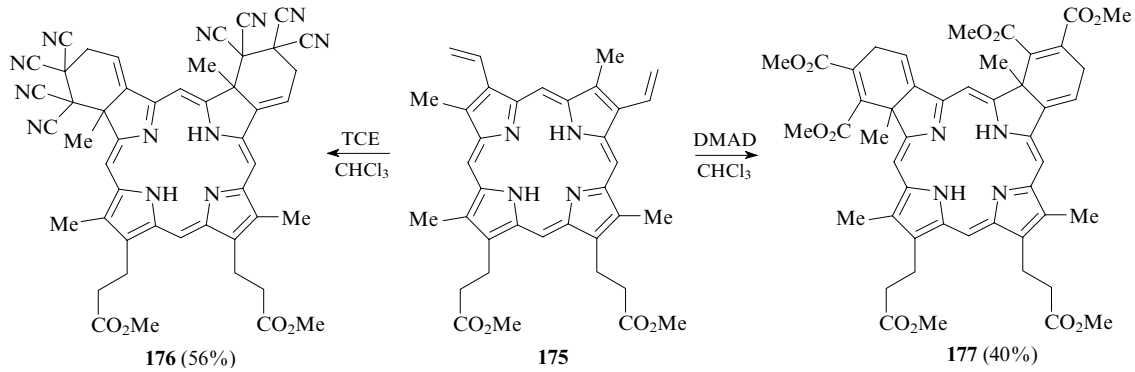
When TAP (**2**) reacts with a more reactive diene, tetracene, bis-adducts are also formed without a catalyst. When the reaction is conducted at 140°C, naphtho[*b*]benzobarrelenotetraazachlorin is formed as the major product with a minor impurity of the corresponding TABC derivative, whereas the same reaction at 220°C produces a mixture of four compounds — *cis*- and *trans*-isomers of TABC and TAiBC derivatives.[85]

Similar patterns were also observed in the [4 + 2]-cycloaddition reaction of TAP (**2**) with cyclopentadienes — unsubstituted cyclopentadiene, 1,2,3,4,5,5-hexachloro- and 5,5-dimethyl-1,2,3,4-tetrachlorocyclopentadienes.[87] Depending on the diene reactivity, the molar ratio of the reactants and the temperature, the reaction gives either norbornenotetraazachlorin or a mixture of the tetraazachlorin and TABC and TAiBC bis-norbornene derivatives.

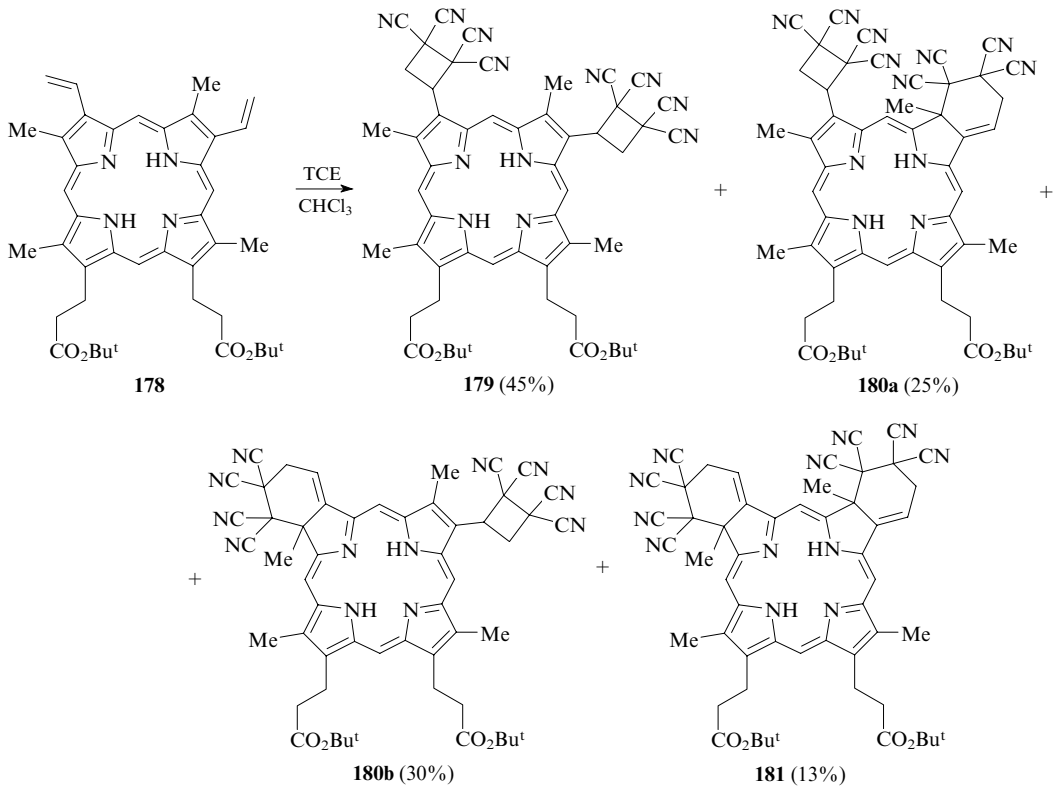
**IV.1.c. Porphyrins as dienes in the Diels – Alder reaction**

Using porphyrins containing one or two vinyl groups in the adjacent or opposite pyrrole groups as dienes in the Diels – Alder reaction gave hydrogenated derivatives of porphyrins stable against oxidation.[88 – 98]

**Scheme 18**



**Scheme 19**




The first study[88] devoted to the use of porphyrins as dienes was published in 1973. Protoporphyrin IX dimethyl ester (**175**) was made to react with tetracyanoethylene (TCE) and with dimethyl acetylenedicarboxylate (DMAD) in chloroform at room temperature for 48 h, the reaction yielding fused bacteriochlorins **176** and **177**, respectively (Scheme 18).[88, 89]

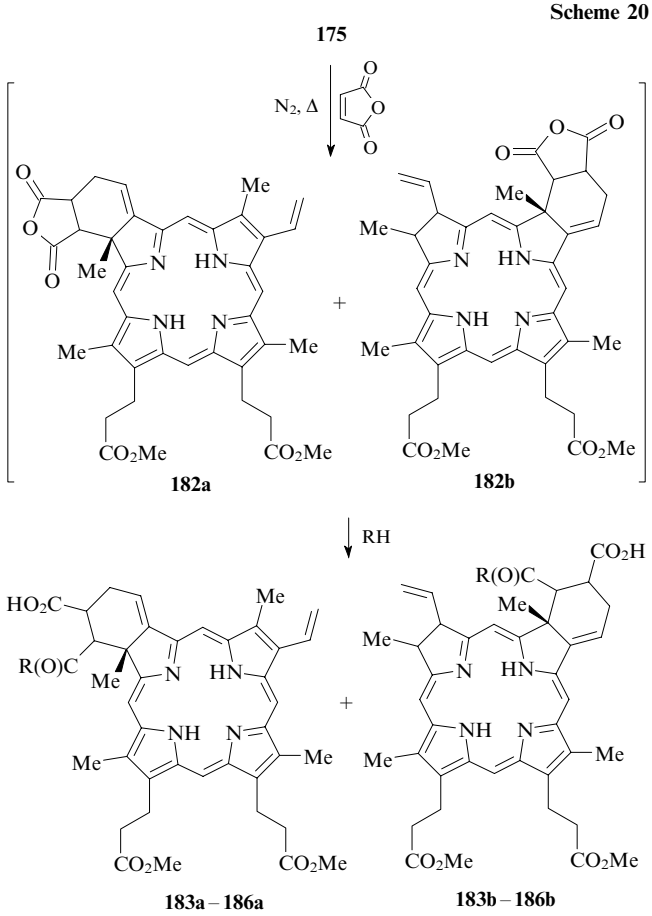
Depending on the conditions (molar ratio of the reactants and reaction temperature and duration), protoporphyrin IX di-*tert*-butyl ester (**178**) reacts with TCE to give either chlorins and isobacteriochlorins ([4 + 2]-cycloaddition products) or porphyrins containing tetracyanocyclobutane moieties in the β-positions ([2 + 2]-cycloaddition products).[90] Refluxing of porphyrin **178** with excess TCE (5 equiv.) in chloroform for 2 – 4 h resulted in the isolation of porphyrin **179** with two tetracyanocyclobutane groups, isomeric chlorins **180a**,**b** and iBC derivative **181** (Scheme 19).[90]

On short-term heating of porphyrin **178** with 2 equiv. of TCE, porphyrin **179** is formed as the major product, while increase in the reaction time leads to the formation of thermodynamically more stable chlorins **180a**,**b**. In the opinion of the researchers cited,[90] the formation of iBC derivative **181** competes with elimination of TCE from the cyclobutane groups of chlorins **180**.

The Diels – Alder reaction of porphyrin **175** with maleic anhydride as a dienophile affords amphiphilic chlorins **182a**,**b**, which were converted to fused chlorins **183** – **186** upon treatment with methanol, triethylene glycol monomethyl ether, triethylene glycol or ethanolamine (Scheme 20).[91]

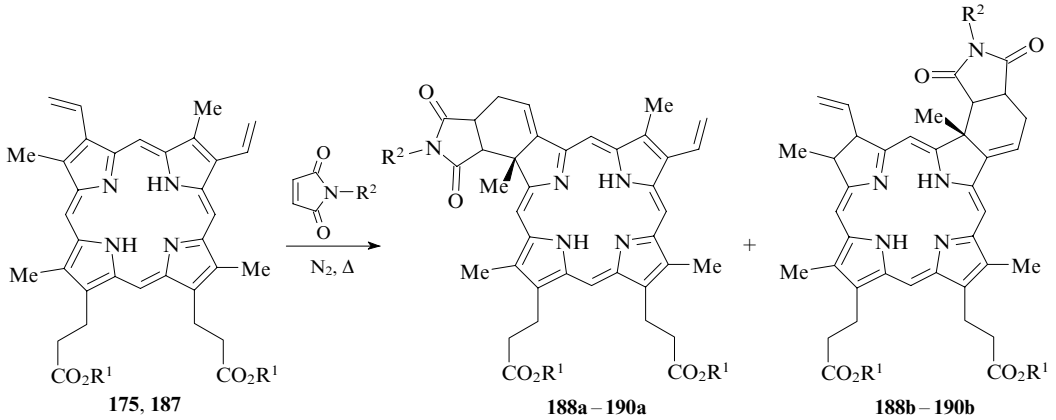
When N-substituted maleimides are employed as dienophiles in the reactions with porphyrin **175** or protoporphyrin IX diethyl ester (**187**), analogous chlorins **188** – **190** are formed, *endo*-adducts being major products (Scheme 21).[92]

**Scheme 20**




R = OMe (**183**, 70% yield), $O(CH_2CH_2O)_3Me$ (**184**, 53%), $O(CH_2CH_2O)_3H$ (**185**, 45%), $NH(CH_2)_2OH$ (**186**, 62%)

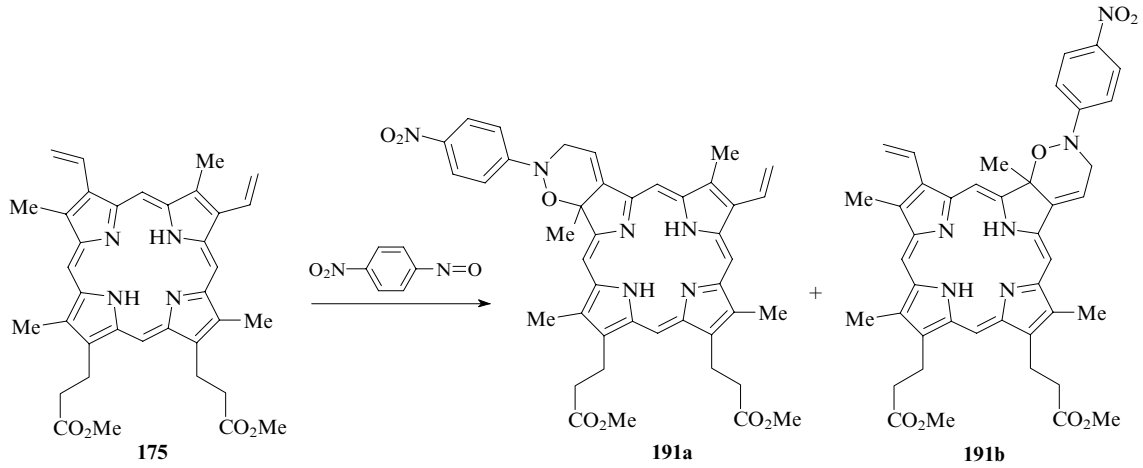
**Scheme 21**



**175**, **187** **188a – 190a** **188b – 190b**

$R^1$ = Me (**175**, **188**, **189**), Et (**187**, **190**); $R^2$ = Ph (**188**, 72% yield), n-$C_8H_{17}$ (**189**, 58%), 4-$O_2NC_6H_4$ (**190**, 66%)

**Scheme 22**

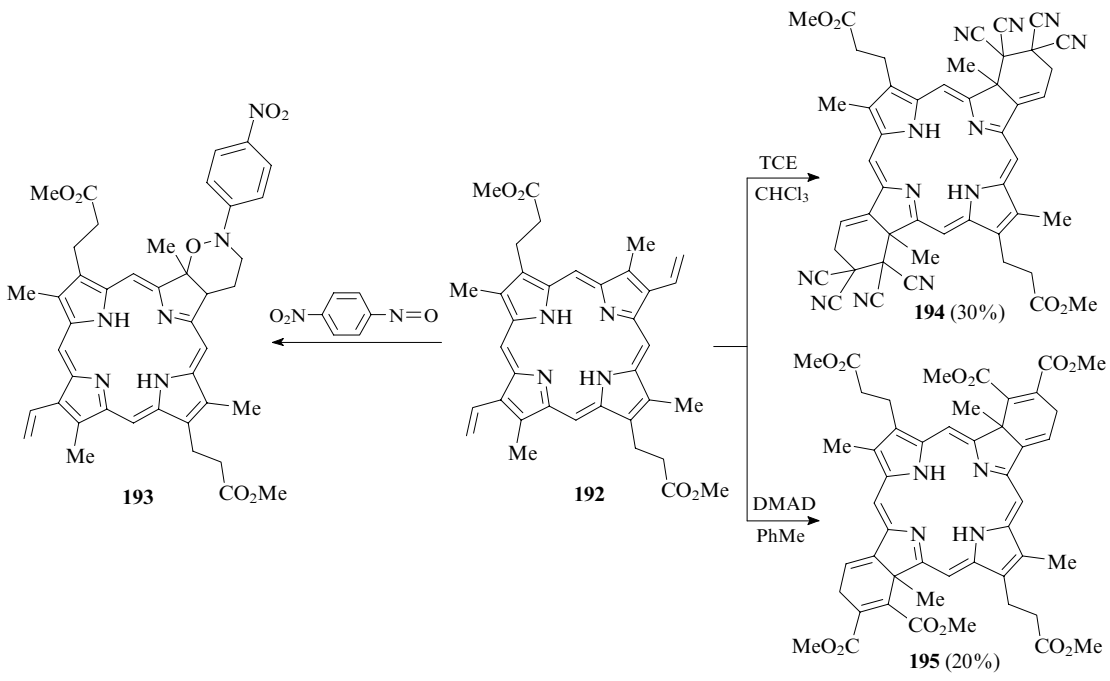


**175** **191a** **191b**

The reaction of porphyrin **175** with *p*-nitrosonitrobenzene taken as a dienophile affords chlorin isomers **191a**,**b** (Scheme 22).[93]

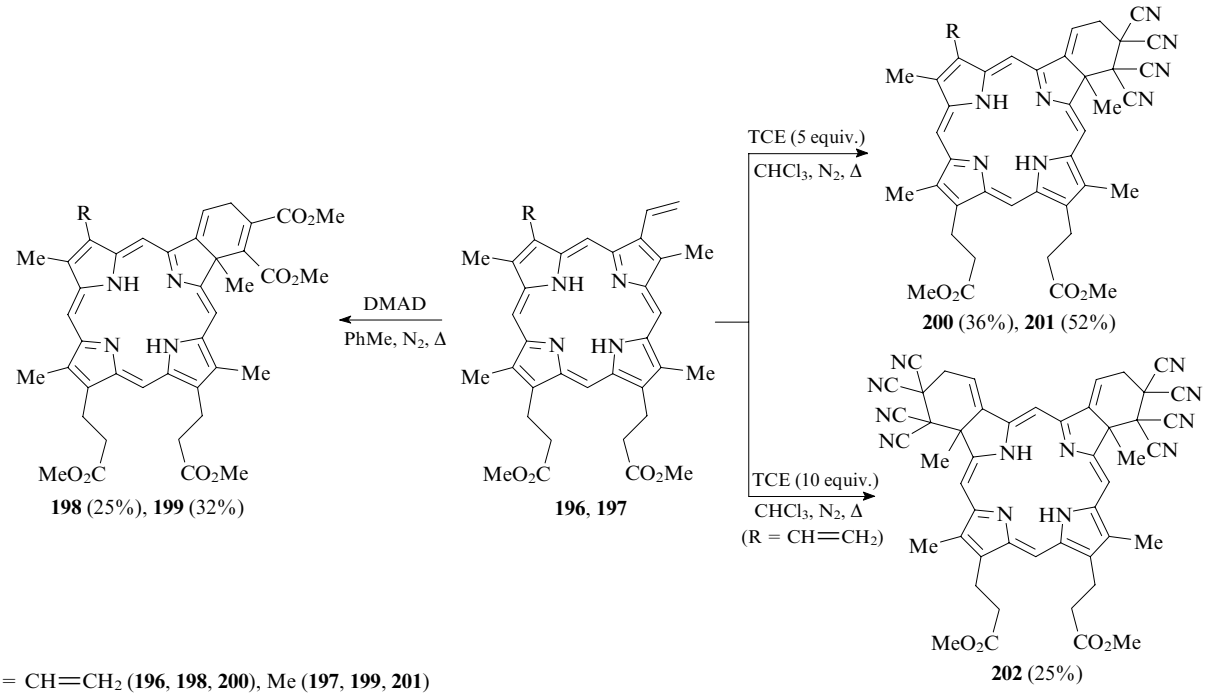
It was also shown that the protoporphyrin II dimethyl ester (**192**) reacts as a diene with *p*-nitrosonitrobenzene under mild conditions to give chlorin **193** (Scheme 23).

**Scheme 23**



**193** **192** **194** (30%) **195** (20%)

**Scheme 24**




R = CH=CH$_2$ (**196**, **198**, **200**), Me (**197**, **199**, **201**)

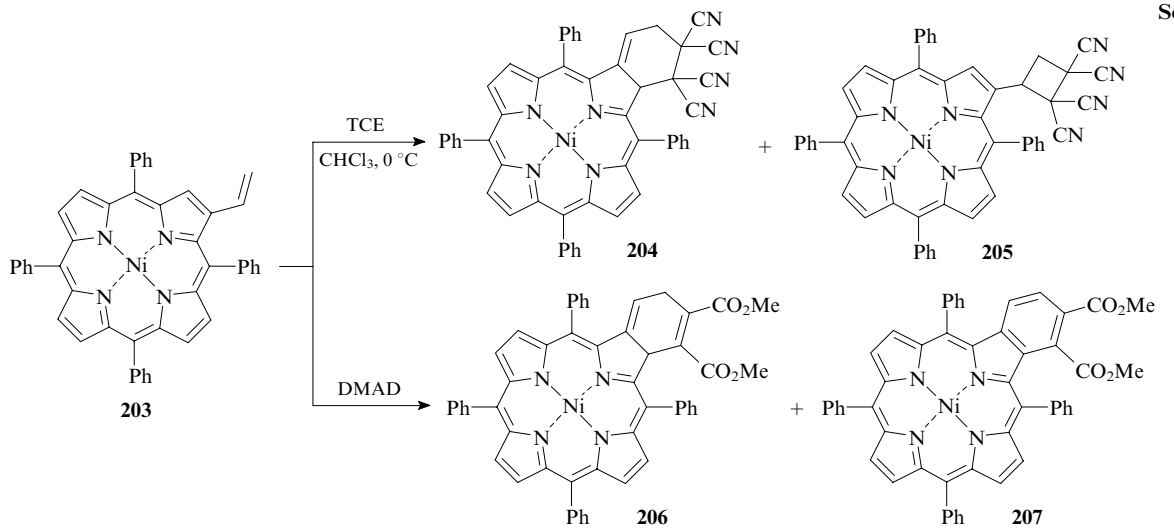
Porphyrin **192** reacts with dienophiles such as TCE or DMAD to afford BC derivatives **194** or **195** (see Scheme 23).[94] However, it is noteworthy that the electronic absorption spectra of these bacteriochlorins attest to the presence of a considerable content of the corresponding chlorins in the products.

The same researchers investigated the Diels – Alder reaction of TCE and DMAD with divinylporphyrin —protoporphyrin III dimethyl ester (**196**) — and monovinylporphyrin **197**. After their reaction with DMAD in toluene in an inert atmosphere for 5 days, chlorins **198** and **199** were isolated (Scheme 24).[94] Refluxing of these porphyrins with excess TCE (5 equiv.) in chloroform affords chlorins **200** and **201**.[92] When porphyrin **196** is refluxed with a large excess of TCE (10 equiv.) in chloroform, iBC **202** is formed (see Scheme 24).[92]

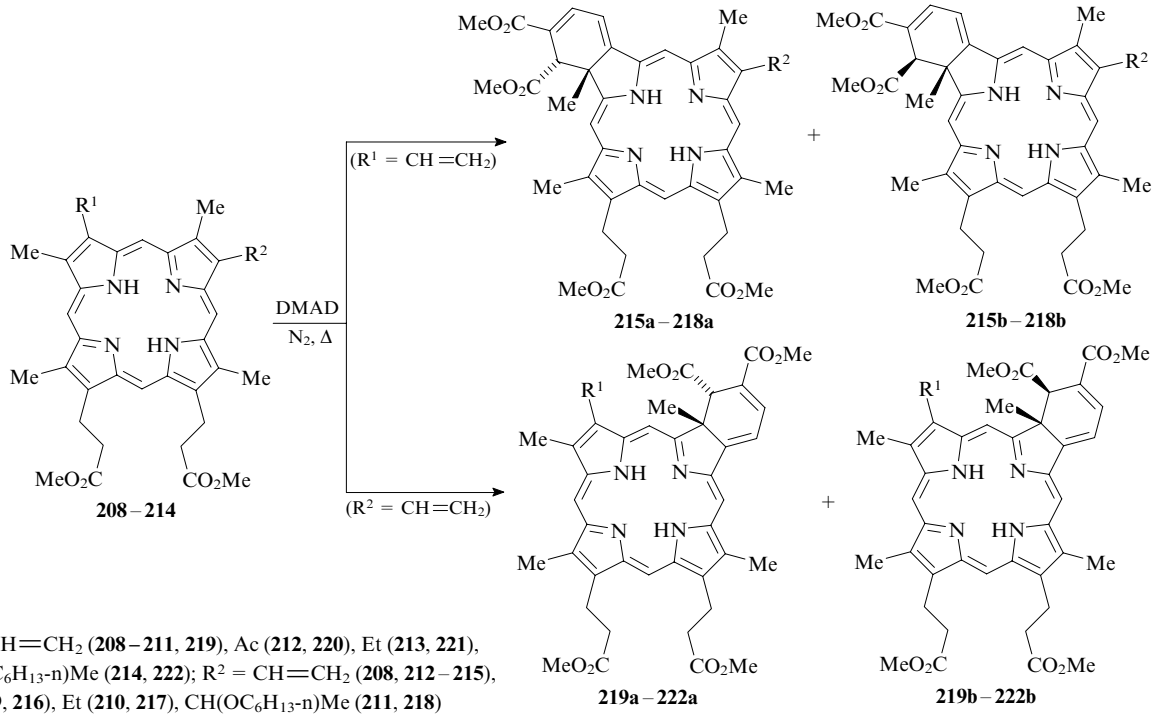
Apart from porphyrin **175** as a free base, its iron and nickel complexes were also investigated as dienes in the reactions with TCE and DMAD; however, no hydrogenated derivatives were formed.[88] When nickel 2-vinyl-*meso*-tetraphenylporphyrin **203** was made to react with TCE in chloroform at 0 °C, nickel tetracyanotetrahydrobenzochlorin **204** and nickel cyclobutylporphyrin **205** were isolated (Scheme 25).[95] Upon the reaction with DMAD, complex **203** was converted to nickel chlorin **206** as a mixture with nickel monobenzoporphyrin **207**.[96]

Mounier *et al.*[97] described the Diels – Alder reaction of divinyl- (**208**) and vinyl-substituted porphyrins (**209** – **214**) with DMAD carried out in toluene in an inert atmosphere for 5 days; the authors isolated *cis*- and *trans*-dihydrobenzochlorins **215a**,**b** – **222a**,**b** in good yields (42% – 93%) (Scheme 26).

**Scheme 25**

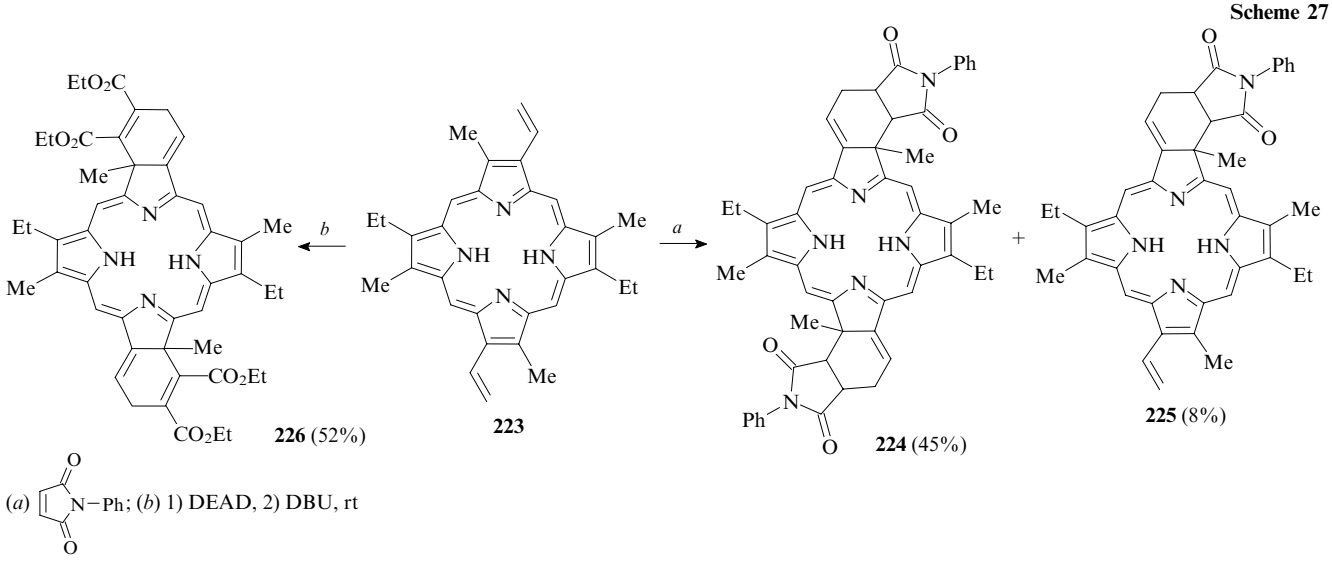


**Scheme 26**




$R^1$ = CH=$CH_2$ (**208 – 211**, **219**), Ac (**212**, **220**), Et (**213**, **221**), $CH(OC_6H_{13}$-n)Me (**214**, **222**); $R^2$ = CH=$CH_2$ (**208**, **212 – 215**), Ac (**209**, **216**), Et (**210**, **217**), $CH(OC_6H_{13}$-n)Me (**211**, **218**)

**Scheme 27**




Divinylporphyrin **223** reacts with *N*-phenylmaleimide on refluxing in toluene for 72 h to form bis(*N*-phenyltetrahydrophthalimido)bacteriochlorin **224** in a high yield as a mixture with chlorin **225** (Scheme 27).[98] The reaction of the same porphyrin with diethyl acetylenedicarboxylate (DEAD) followed by treatment with a base (DBU) yielded bacteriochlorin **226** (see Scheme 27).[98]

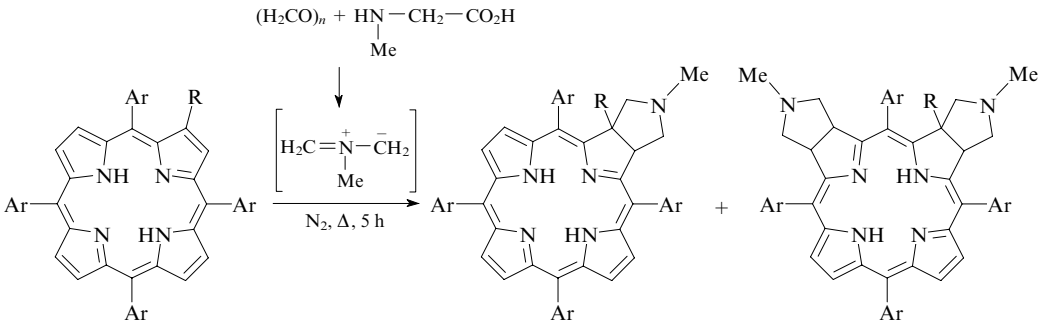
## IV.2. [3 + 2]-cycloaddition reactions of porphyrins and tetraazaporphyrins

### IV.2.a. Porphyrins in [3 + 2]-cycloaddition

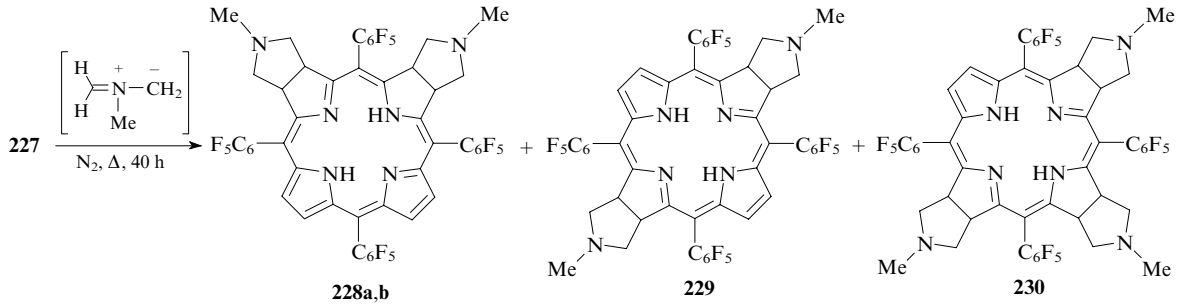
The [3 + 2]-cycloaddition reaction involving porphyrins and TAPs as dipolarophiles with various 1,3-dipoles is a convenient method for the synthesis of hydrogenated porphyrin and TAP derivatives with fused five-membered heterocycles. For porphyrins, there have been reported reactions with azomethine ylides,[99 – 108] nitrones,[36, 108, 109] silyl nitronates,[110] carbonyl ylide,[111] nitrile oxides,[112 – 116] nitrile imines[117, 118] and diazomethane.[119, 120] The [3 + 2]-cycloaddition of TAPs has yet been studied less comprehensively and is reported only in several papers.[20, 50, 121 – 124] As in the case of [4 + 2]-cycloaddition, the major [3 + 2]-cycloaddition products for both porphyrins and TAPs are monoadducts but, in some cases, bis-adducts of various structure could also be isolated.

The first study[99] devoted to the addition of 1,3-dipoles to porphyrins was published in 1999. The authors described the reaction of azomethine ylide, generated *in situ* from sarcosine and paraformaldehyde, with porphyrin **137** in refluxing toluene for 5 h giving a mixture of pyrrolidinochlorin **227** and bis(pyrrolidino)isobacteriochlorin **228**

**Scheme 28**




**Scheme 29**




(Scheme 28). The unreacted starting porphyrin **137** was also recovered from the reaction mixture.

The further reaction of chlorin **227** with sarcosine and paraformaldehyde in 1 : 2 : 5 molar ratio conducted by refluxing in toluene for 40 h in an inert atmosphere gave *trans*- (**228a**, 37% yield) and *cis*-isomers (**228b**, 5% yield) of the pyrrolidine-fused isobacteriochlorin derivative and traces of bis(pyrrolidino)bacteriochlorin **229** and tris-adduct **230** (Scheme 29).[100]

The [3 + 2]-cycloaddition of azomethine ylide with porphyrins **11**, **25** and **31** containing aryl substituents in the *meso*-positions and with porphyrin **149** with a nitro group in the β-position of the macrocycle was described[100] (see Scheme 28 and Table 2). It was noted that chlorins **231** – **234** are the major products of cycloaddition, while bis-adduct **235** is formed only from porphyrin **25**. As the temperature was raised from 110 to 180 °C, the yields of chlorins **231** – **234** increased almost twofold.

The reaction of azomethine ylide with Pt and Pd complexes of porphyrin **137** was also known. In both cases, metal chlorins are formed in moderate yields.[101]

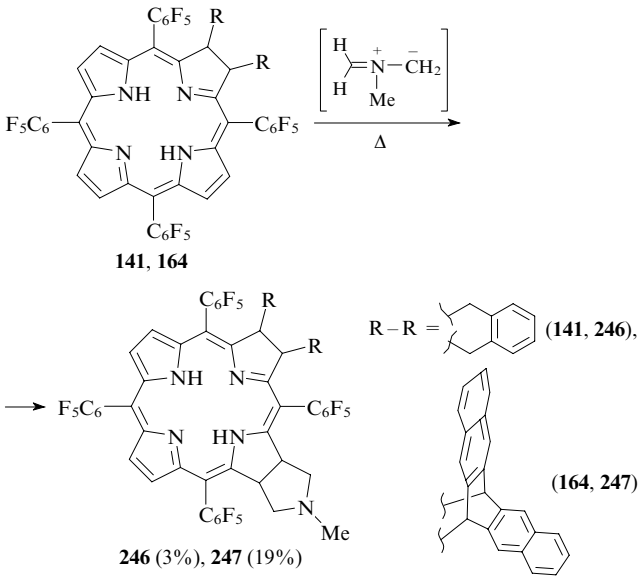
Gryko and Galezowski[102, 103] prepared *N*-methylpyrrolidinochlorins **236** – **245** by [3 + 2]-cycloaddition of azomethine ylide with 5,10-substituted porphyrins containing two alkoxycarbonyl groups in the β-positions of one of the pyrrole rings.

Isobacteriochlorin derivatives are also prepared by combined cycloaddition.[100] First, the Diels – Alder reaction is carried out to give chlorins **141** (see Ref. 79) and **164**,[83] which are then treated with azomethine ylide to give isobacteriochlorins **246** and **247**, respectively (Scheme 30).

**Table 2**. [3 + 3]-Cycloaddition of azomethine ylide to *meso*-arylporphyrins (see Scheme 28).

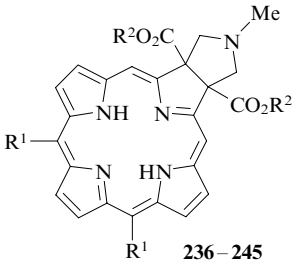
| Porphyrin | Ar | R | Chlorin | Yield (%) | Isobacteriochlorin | Yield (%) |
|---|---|---|---|---|---|---|
| **11** | Ph | H | **231** | 12 | – | – |
| **25** | 2,6-$Cl_2C_6H_3$ | H | **232** | 26 | **235** | 6 |
| **31** | 4-$MeOC_6H_4$ | H | **233** | 3 | – | – |
| **137** | $C_6F_5$ | H | **227** | 61 | **228** | 11 |
| **149** | Ph | $NO_2$ | **234** | 27 | – | – |

**Scheme 30**




The reaction of unsymmetrical *meso*-tris(pentafluorophenyl)(4-pyridyl)porphyrin with sarcosine and paraformaldehyde in an inert atmosphere in toluene for 10 h produced a mixture of isomeric chlorins, which was sepa-

**Structures 236 – 245**



**236 – 245**

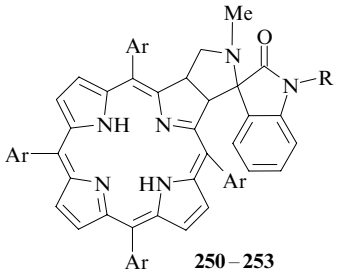
| Chlorin | $R^1$ | $R^2$ | Yield (%) |
|---|---|---|---|
| **236** | 3,4,5-$(MeO)_3C_6H_2$ | Et | 42 |
| **237** | 4-$MeOC_6H_4$ | Et | 47 |
| **238** | 2,4,5-$(MeO)_3C_6H_2$ | Et | 57 |
| **239** | Ph | Et | 21 |
| **240** | 3-Py | Et | 42 |
| **241** | 4-$NCC_6H_4$ | Me | 35 |
| **242** | 4-$NCC_6H_4$ | Et | 43 |
| **243** | 4-$NCC_6H_4$ | $Bu^t$ | 47 |
| **244** | $C_6F_5$ | Et | 30 |
| **245** | $CF_3$ | Et | 10 |

rated by chromatography.[104] The reaction of β-octakis(2-carboxyethyl)porphyrin with benzylazomethine ylide gave *N*-benzylpyrrolidinochlorin (18% yield) and then the corresponding BC derivative.[105]

The condensation of porphyrin **137** with azomethine ylides containing a protected galactose moiety produces C- and N-glycosyl-substituted pyrrolidinochlorins.[106] It was noted that the reactivity of monosaccharide-substituted azomethine ylides depends on the substituent position. For instance, the cycloaddition of *C*-glycosylazomethine ylide to porphyrin **137** in toluene in the presence of molecular sieves gives rise to a mixture of chlorin isomers **248a**,**b** (51% yield), while the cycloaddition of *N*-glycosylazomethine ylide affords chlorin **249** (19%) (Scheme 31).[106]

The synthesis of chlorins containing a spiro(oxindole-3′,2-pyrrolidine) moiety has been reported. Chlorins **250 – 253** were obtained by condensation of porphyrin **11** or *meso*-tetrakis(4-chlorophenyl)porphyrin with a sarcosine and isatin or *N*-benzylisatin mixture in refluxing toluene.[107]

**Structures 250 – 253**



**250 – 253**

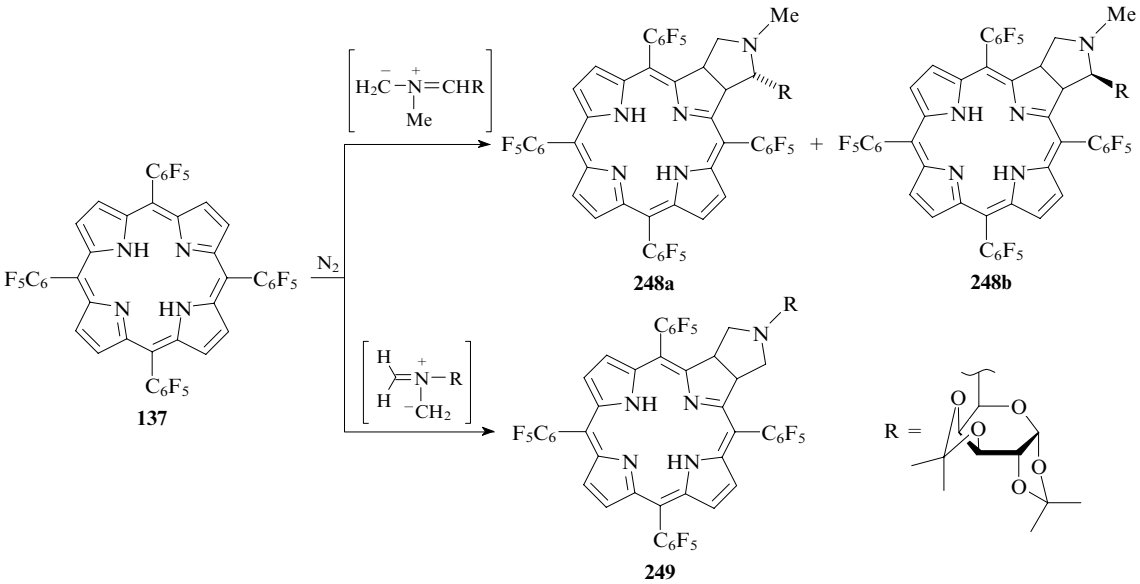
Ar = Ph: R = H (**250**, 45% yield), Bn (**252**, 48%);
Ar = 4-$ClC_6H_4$: R = H (**251**, 55%), Bn (**253**, 59%)

By using nitrones as 1,3-dipoles for the addition to porphyrins, isoxazolidine-fused adducts were formed. For example, porphyrin **137** reacts with *N*-benzylnitrone containing a protected galactosyl moiety in toluene in an inert atmosphere furnishing *N*-benzylisoxazolidinochlorin **254** and two bis(*N*-benzylisoxazolidino)bacteriochlorin isomers **255a**,**b** (Scheme 32), each of which can exist as two diastereomers.[108] The reaction of porphyrin **137** with *N*-methylnitrone results in the formation of similar products.[36]

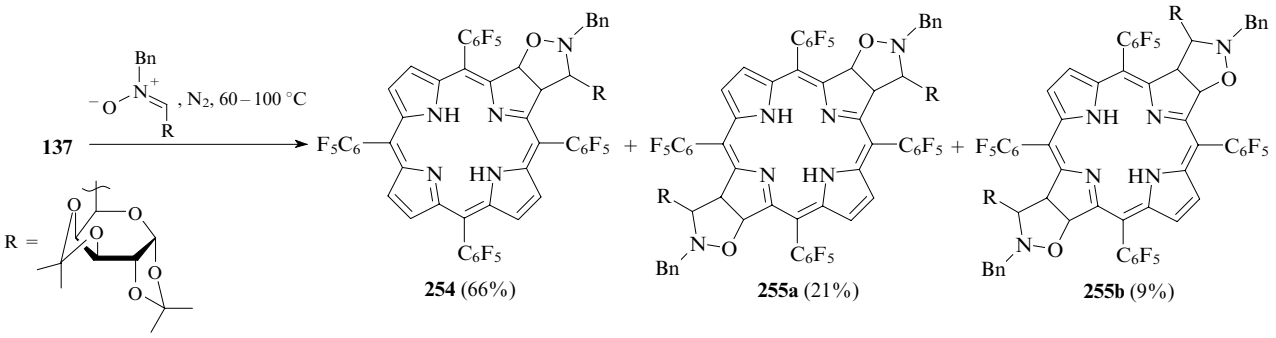
The preparation of isoxazolinochlorins **256 – 258** by cycloaddition of substituted silylnitrones to porphyrin **137** in toluene at 85 °C over a period of 5 days has been reported (Scheme 33).[109]

In order to explain the selectivity of 1,3-dipolar cycloaddition of porphyrins to azomethine ylides and nitrones, Jimenez-Oses *et al.*[110] carried out DFT quantum chemical calculations of the thermodynamic stability of the compounds formed. According to the results of these calculations, in the cycloaddition of azomethine ylide to porphyrin, the step of chlorin formation is irreversible and the reaction is kinetically controlled. In the case of nitrone, the step of chlorin formation is reversible and the reaction is thermodynamically controlled. It was also reported that BC deriv-

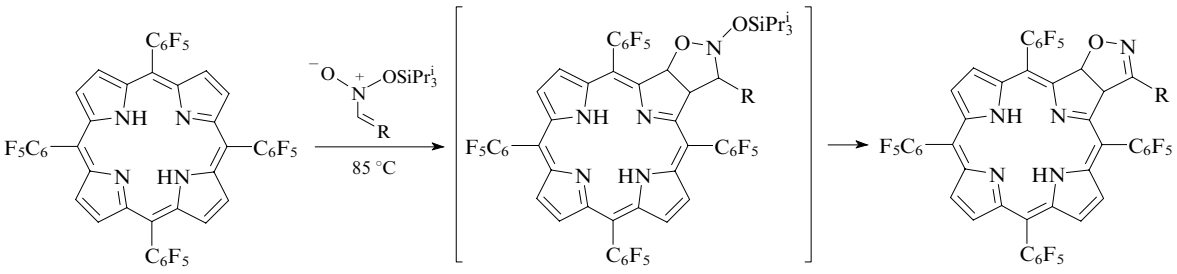
**Scheme 31**



**Scheme 32**

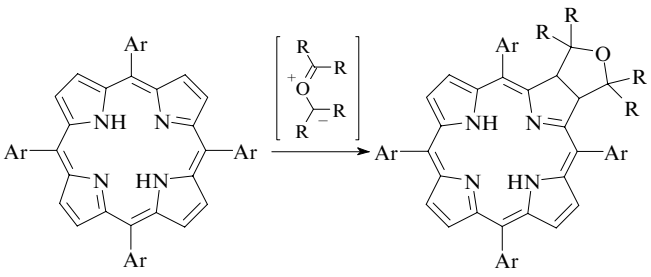


**Scheme 33**



R = Pr$^n$ (**256**, 16% yield), n-$C_5H_{11}$ (**257**, 18%), $CO_2Me$ (**258**, 34%)

**Scheme 34**



Ar = Ph (**11**, **259**), $C_6F_5$ (**137**, **260**); R = CN (**259**), H (**260**)

atives are more stable and more aromatic than iBC analogues.[110]

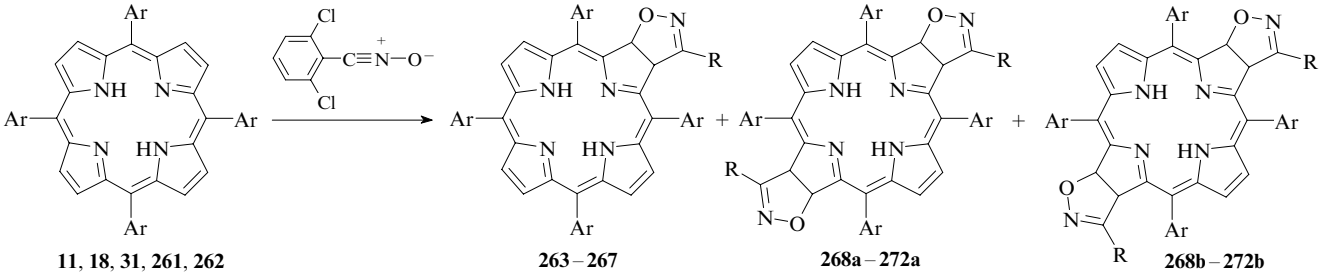
The reactions of porphyrins with carbonyl ylides afford chlorins containing a tetrahydrofuran ring. For example, chlorin **259** was obtained in 20% yield by refluxing porphyrin **11** and tetracyanoethylene oxide in toluene in an inert atmosphere for 1 h (Scheme 34).[111] When porphyrin **137**, as a dipolarophile, was made to react with bis(chloromethyl) ether, chlorin **260** was synthesized in 38% yield.[111]

[3 + 2]-Cycloaddition of 2,6-dichlorobenzonitrile oxide to substituted porphyrins **11**, **18**, **31**, **261** and **262** results in isoxazolinochlorins **263** – **267** (21% – 51% yields) and isomeric bis(isoxazolino)bacteriochlorins **268a**,**b** – **272a**,**b** (4% – 26% yields) (Scheme 35).[112 – 114]

Li *et al.*[112] showed that metal porphyrins are less reactive in this reaction than free bases. For example, zinc *meso*-tetrakis(4-chlorophenyl)porphyrin undergoes 1,3-cycloaddition with 2,6-dichlorobenzonitrile oxide to be converted only to chlorin.[112]

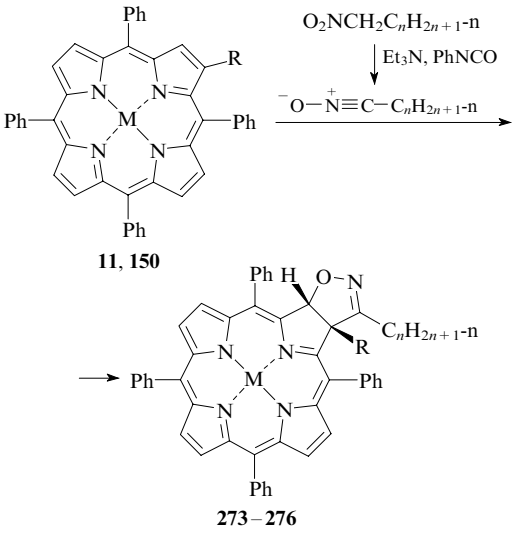
Isoxazolinochlorins containing an alkyl substituent in the isoxazoline ring were obtained by using alkyl-substituted nitrile oxides as 1,3-dipoles. Thus, the reaction of porphyrins **11** and **150** with nitrile oxides, formed *in situ* from nitroalkanes on treatment with phenyl isocyanate in the presence of triethylamine, affords lipophilic chlorins **273** – **276** (Scheme 36).[115, 116]

**Scheme 35**



Ar = Ph (**11**, **263**, **268**), 4-$MeC_6H_4$ (**18**, **264**, **269**), 4-$MeOC_6H_4$ (**31**, **265**, **270**), 4-$MeO_2CC_6H_4$ (**261**, **266**, **271**), 4-$ClC_6H_4$ (**262**, **267**, **272**);
R = 2,6-$Cl_2C_6H_3$

**Scheme 36**

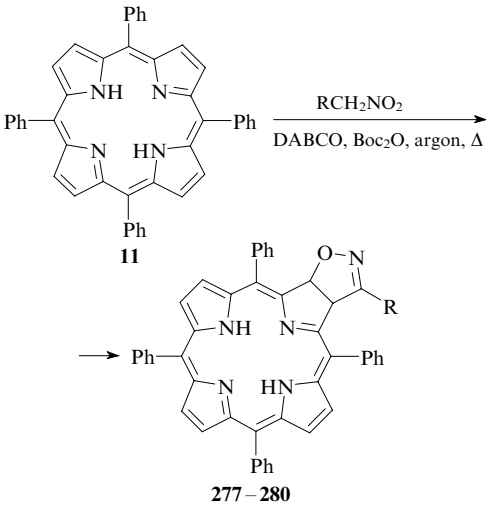



**11**, **150**

**273** – **276**

M = 2 H, R = H (**11**, **273** – **275**); M = Zn, R = $NO_2$ (**150**, **276**);
*n* = 2 (**273**, 16% yield), 4 (**274**, 10%; **276**, 37%), 5 (**275**, 30%)

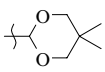
**Scheme 37**

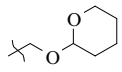



**11**

**277** – **280**

R = $CO_2Et$ (**277**, 31% yield), $CH_2OBu^t$ (**278**, 24%),

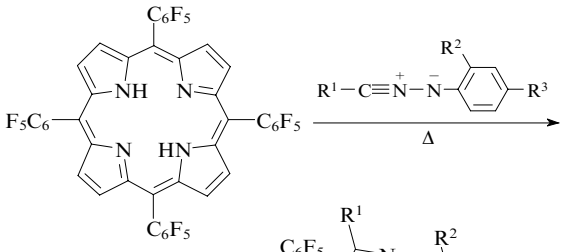

(**279**, 40%),


(**280**, 63%)

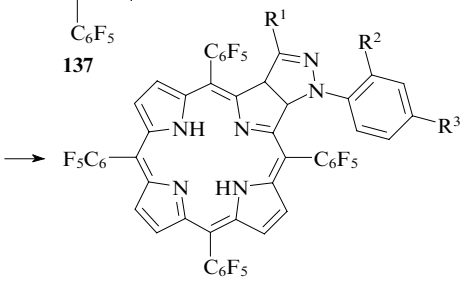
Subsequently the same authors proposed a modified method for the synthesis of isoxazolinochlorins. Porphyrin **11** was made to react with substituted nitrile oxides formed *in situ* from nitroalkanes in the presence of DABCO and di(*tert*-butyl) dicarbonate ($Boc_2O$), which led to isoxalinochlorins **277** – **280** (Scheme 37).[116]

[3 + 2]-Cycloaddition of porphyrin **137** to nitrilimines generated *in situ* from ethyl hydrazono-α-bromoglyoxylates and α-chloroalkylidene arylhydrazine derivatives in the presence of bases gives pyrazolinochlorins **281** – **288** (Scheme 38).[117, 118] The product yields depend on the reaction conditions and, in some cases, vary over a broad range.

**Scheme 38**




**137**

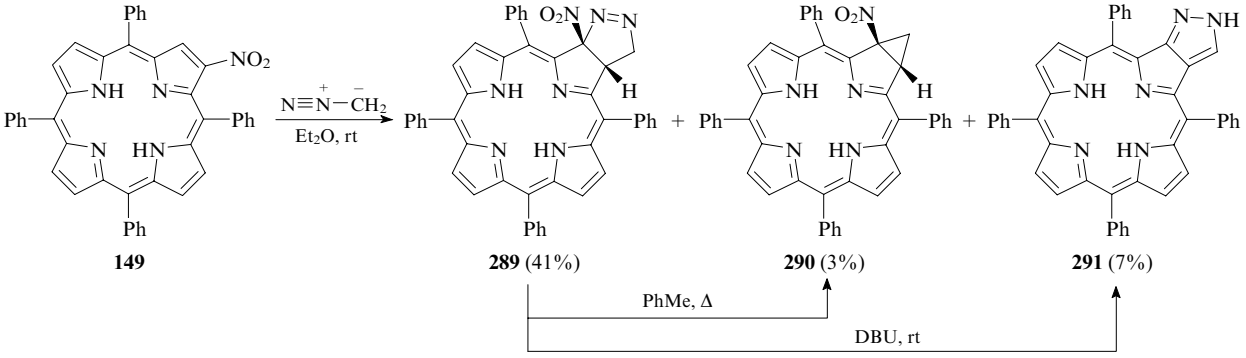



**281** – **288**

| Chlorin | $R^1$ | $R^2$ | $R^3$ | Yields (%) |
|---|---|---|---|---|
| **281** | $CO_2Et$ | H | Me | 4 – 37 |
| **282** | $CO_2Et$ | H | OMe | 6 – 40 |
| **283** | $CO_2Et$ | H | Cl | 17 – 22 |
| **284** | Ph | H | H | 23 – 29 |
| **285** | $C_6H_4Me$-4 | H | H | 23 – 32 |
| **286** | $C_6H_4OMe$-4 | H | H | 19 |
| **287** | $C_6H_4Me$-4 | Et | H | 7 |
| **288** | $C_6H_4OMe$-4 | Et | H | 3 |

The [3 + 2]-cycloaddition reaction of diazomethane with *meso*-tetraarylporphyrins follows an unusual pathway.[119, 120] Porphyrin **149** reacts with diazomethane in diethyl ether at room temperature for 15 days to afford a mixture of pyrazolinochlorin **289**, cyclopropanochlorin **290** and pyrazoloporphyrin **291** (Scheme 39).[119] In the same

**Scheme 39**




**149**

**289** (41%)

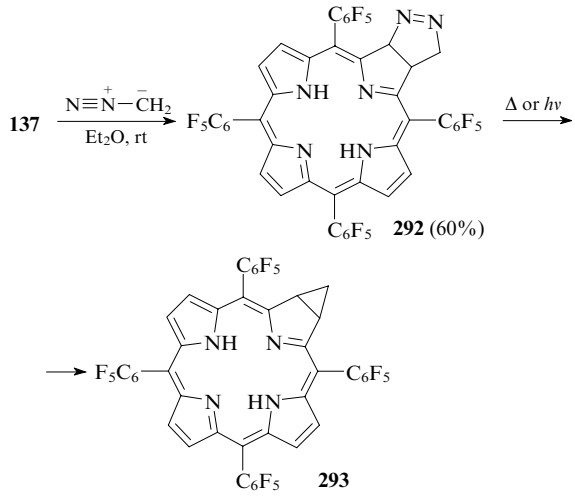
**290** (3%)

**291** (7%)

paper, it is shown that in the presence of a strong base (DBU), chlorin **289** is converted to porphyrin **291** (72% yield) and upon refluxing in toluene, it is converted to cyclopropanochlorin **290** (24% yield) *via* thermal extrusion of $N_2$.[119]

The reaction of porphyrin **137** with diazomethane carried out under similar conditions gave pyrazolinochlorin **292**, which splits off a nitrogen molecule under the action of heat or light to be converted to chlorin **293** in a quantitative yield (Scheme 40).[120]

**Scheme 40**



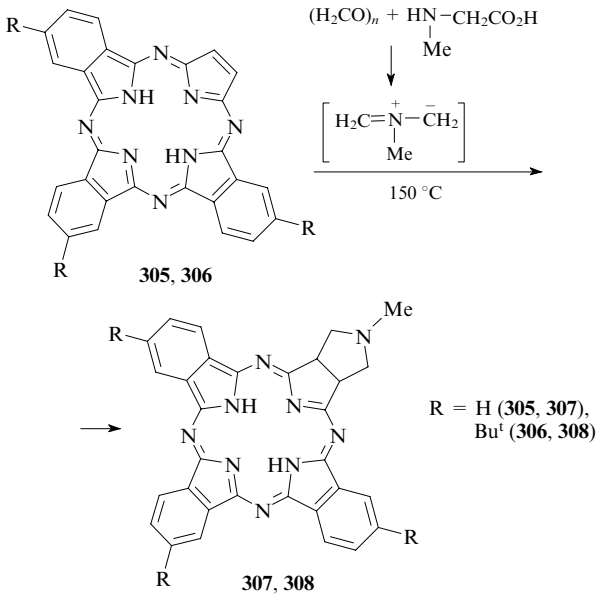

**IV.2.b. Tetraazaporphyrins in the [3 + 2]-cycloaddition**

When tetraazaporphyrin (**2**) or tetra- (**294**) and octasubstituted TAPs (**295**, **296**) react with azomethine ylide, either pyrrolidine TAC derivatives (**297** – **300**) or mixtures of these derivatives and bis-pyrrolidine TAiBC derivatives (**301** – **304**) are formed, depending on the temperature and the ratio of reactants (Scheme 41).[20, 50, 121 – 123]

The [3 + 2]-cycloaddition of octasubstituted TAPs **295**, **296** with azomethine ylide was found to proceed under more rigorous conditions than that of TAP (**2**) and its derivative **294**; this is likely to be due to the steric effect of substituents.[50, 121, 122]

It was shown [123] that the double bond of tribenzotetraazaporphyrins is also active towards [3 + 2]-cycloaddition

**Scheme 42**

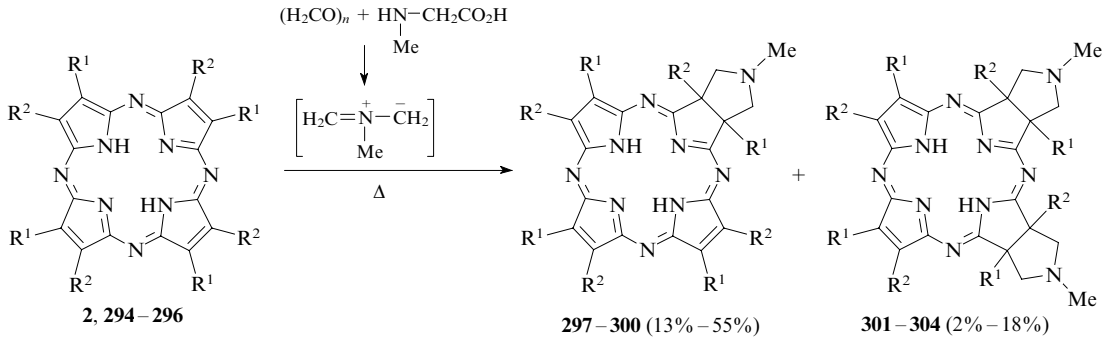



with azomethine ylide. Tribenzo- (**305**) and tris(4-*tert*-butylbenzo)-TAP derivatives (**306**) react with sarcosine and paraformaldehyde in 1 : 2 : 5 molar ratio in an inert atmosphere to afford *N*-methylpyrrolidinotribenzo-fused TAC derivatives **307** and **308** in 10% – 20% yields (Scheme 42). An extension of the π-electron system of the macrocycle results in a decrease in the stability of the products against oxidation to related tribenzo-TAP derivatives as compared with non-fused analogues.

The 1,3-cycloaddition with TAP as a dipolarophile and *N*-(2-porphinylmethyl)glycine **309** as a 1,3-dipole in *o*-dichlorobenzene led to TAC dimer **310**.[124] The starting porphyrin **309**, which served as the precursor of azomethine ylide, was synthesized from nickel β-formyl-*meso*-tetraphenylporphyrin **311** in three steps (Scheme 43).

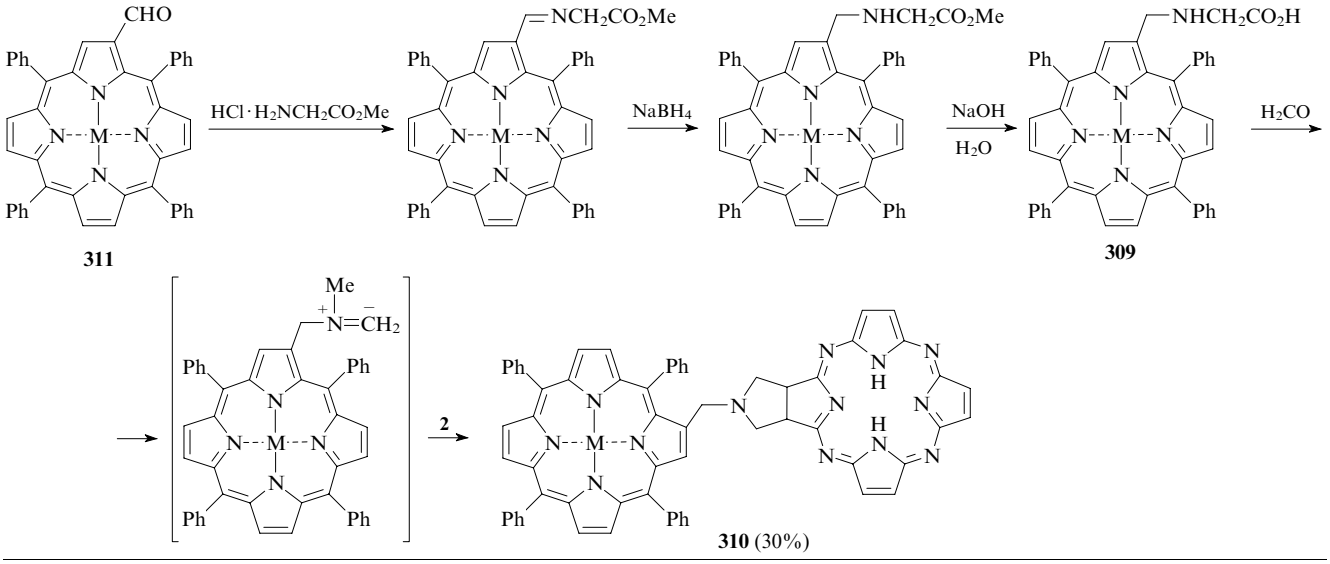
Isoxazolidine TAC derivatives **312** (51% yield) and **313** were synthesized by the reaction of compound **2** with nitrones generated from *N*-methyl- or *N*-benzylhydroxylamine and paraformaldehyde in the presence of dry potassium carbonate (molar ratio TAP : nitrone = 1 : 5) (Scheme 44).[23, 123] As the molar ratio increased to 1 : 10, bis-isoxazolidine TABC analogues **314** (7% yield) and **315** were formed together with TAC derivatives.

**Scheme 41**

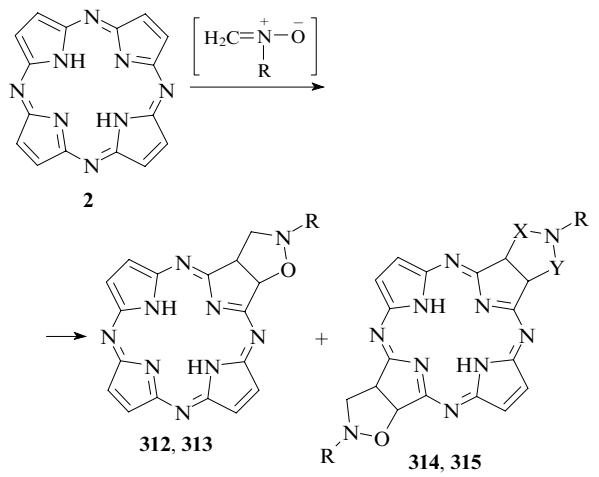



$R^2$ = H: $R^1$ = H (**2**, **297**, **301**), Ph (**294**, **298**, **302**); $R^1$ = $R^2$ = SMe (**295**, **299**, **303**), Ph (**296**, **300**, **304**)

**Scheme 43**




**Scheme 44**



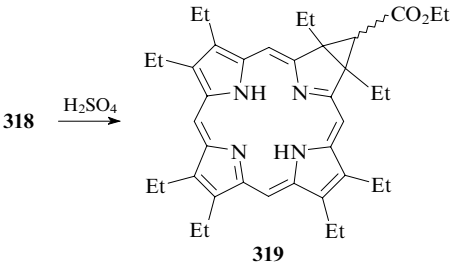

R = Me (**312**, **314**), Bn (**313**, **315**);
X = O, Y = $CH_2$ (**314**); X = $CH_2$, Y = O (**315**)

## IV.3. Porphyrins and tetraazaporphyrins in [1 + 2]- and [1,7]-cycloaddition

The [1 + 2]-cycloaddition (cyclopropanation) of porphyrins and TAPs can serve as a method for the synthesis of hydrogenated porphyrin analogues containing one or two cyclopropane moieties.[50, 122, 125 – 128]

The first paper describing the addition of carbene to porphyrin was published by Callot and Johnson [125] in 1969. They carried out the copper(I) iodide-catalyzed reaction of cobalt octaethylporphyrin **316** with ethyl diazoacetate (EDA) in benzene and obtained copper complexes of octaethylporphyrin **317** and substituted octaethylchlorin **318**, the latter existing as two epimers with different configurations of the ester group (Scheme 45). Demetallation of chlorins **318** with concentrated sulfuric acid resulted in a mixture of chlorin free bases **319** (Scheme 46).

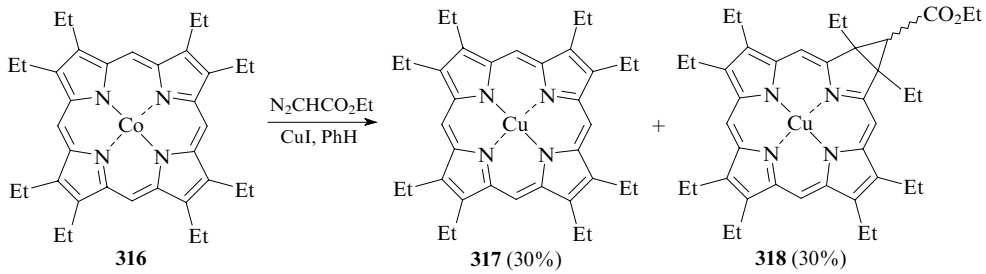
**Scheme 46**



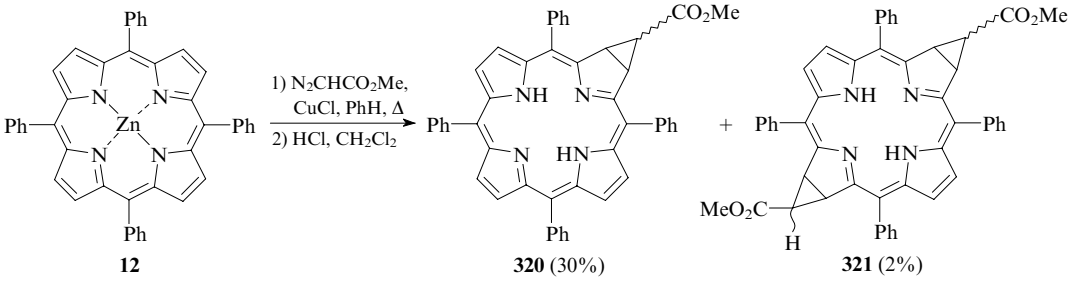

The reaction of zinc *meso*-tetraphenylporphyrin **12** with methyl diazoacetate in refluxing benzene in the presence of CuCl followed by demetallation with hydrochloric acid yielded cyclopropanochlorin **320** and bis-cyclopropane BC derivative **321** (as a mixture of diastereomers) (Scheme 47).[126]

Zinc complexes **12**, **322** and **323** react with EDA in dichloromethane in the presence of various catalysts [Cat = CuCl, $Cu(OTf)_2$, $Pd(OAc)_2$, $Rh_2(OAc)_4$, Cu(OTf)(PhH), iron *meso*-tetrakis(2,6-dichlorophenyl)porphyrin] to give zinc chlorin complexes **324a**,**b** – **326a**,**b** (as

**Scheme 45**



**Scheme 47**




**12** **320** (30%) **321** (2%)

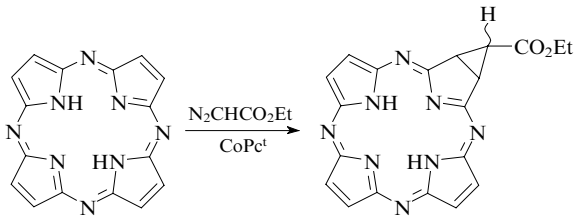
mixtures of *trans*- and *cis*-isomers), BC derivatives (**327** – **329**) and iBC derivative **330** (from **323**) (Scheme 48).[127] By testing a series of catalysts for EDA decomposition, the authors ascertained that copper compounds are the catalysts of choice, providing the formation of mainly *trans*-chlorins. Indeed, the $Rh_2(OAc)_4$-catalyzed reaction gave *trans*- (**324a**) and *cis*-chlorins (**324b**) in approximately equal yields (21% and 18%), while with CuCl catalyst, the yield of *trans*-chlorin **324a** increased to 28%, and the yield of *cis*-chlorin **324b** decreased to 5%. Bacteriochlorins **327** – **329** were isolated in minor yields (< 3%) only when CuCl was used as the catalyst, and the yield of compound **330** with copper or palladium catalysts ranged from 1% to 40%.

Gomes *et al.*[128] reported on the preparation of zinc chlorin complexes (24% – 33% yields) containing glycosyl-substituted cyclopropane moieties by reactions of porphyrin **323** with glycosylated diazoacetic acid derivatives in dichloromethane in the presence of CuCl. The major products were *trans*-chlorins, while BC and iBC derivatives were isolated in only trace amounts. An exception is galactopyranosyl-substituted diazoacetate, which is converted to an iBC derivative (9%) and traces of the corresponding BC. It was also shown that zinc chlorins containing glycosylated cyclopropane moieties are readily demetallated with trifluoroacetic acid at room temperature.[128]

We studied the [1 + 2]-cycloaddition of ethoxycarbonylcarbene with unsubstituted TAP.[50, 122] Upon the reaction of compound **2** with excess EDA in the presence of cobalt tetrakis(4-*tert*-butyl)phthalocyanine ($CoPc^t$) in *o*-dichlorobenzene at 80 – 85 °C in an inert atmosphere, we obtained cyclopropane TAC derivative **331** (Scheme 49). Variation of the reaction conditions led to only minor changes in the product yield, and no bis-adducts were formed.

When the zinc complex of unsubstituted TAP was introduced in the reaction under the same conditions, no TAC derivatives were detected even by spectroscopy. In the reaction of tetraazaporphyrin **294**, no formation of cyclopropanotetraazachlorins was observed either.[50, 122]

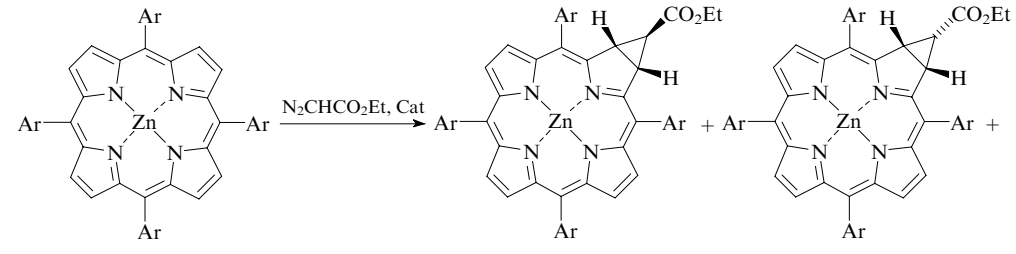
**Scheme 49**



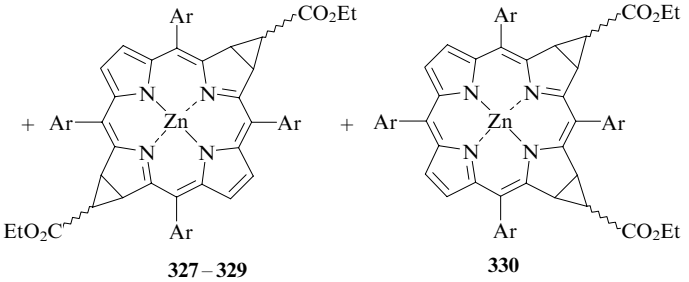

**2** **331** (4%)

The preparation of hydrogenated *meso*-arylporphyrins upon cycloaddition of diazafulvenium methide generated *in situ* upon thermal elimination of sulfur dioxide from pyrazolosulfolane has been reported.[129, 130] A short-term (10 – 20 min) microwave irradiation of *meso*-tetraaryl- (**11**, **18**, **25**, **30**, **31**, **137**, **262**) or 5,15-diarylporphyrins (**102**, **103**, **332**) with diazafulvenium methide in 1,2,4-trichlorobenzene leads to the formation of chlorins **333** – **342** in yields of

**Scheme 48**



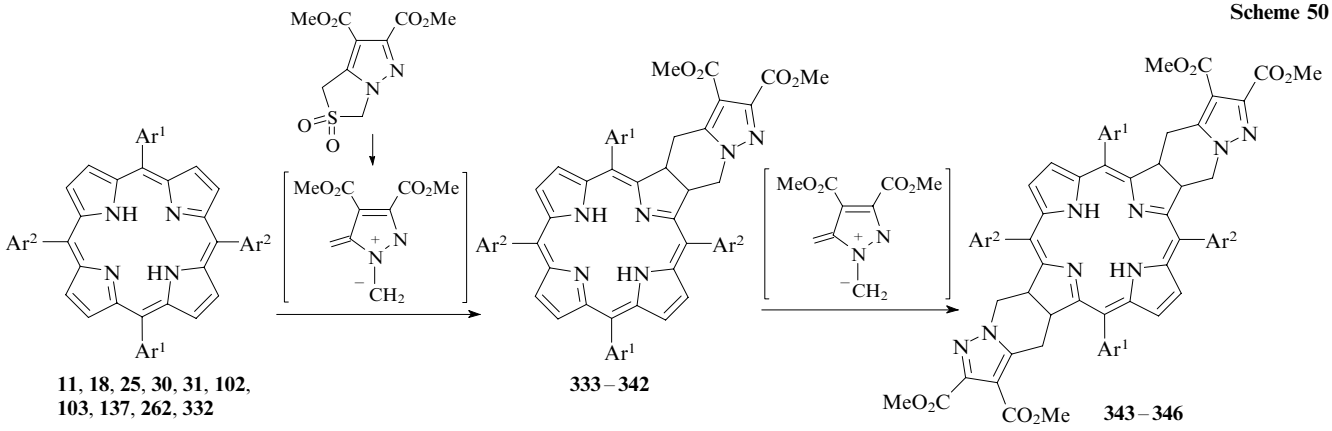

**12**, **322**, **323** **324a** – **326a** **324b** – **326b**




**327** – **329** **330**

| Porphyrin | Ar | Cyclopropanation products [yield (%)] |
|---|---|---|
| **12** | Ph | **324a** (20 – 28), **324b** (1 – 18), **327** (2.3) |
| **322** | 3-$MeC_6H_4$ | **325a** (11 – 26), **325b** (1 – 22), **328** (1.1) |
| **323** | $C_6F_5$ | **326a** (11 – 85), **326b** (1 – 2), **329** (< 1.0), **330** (1 – 40) |

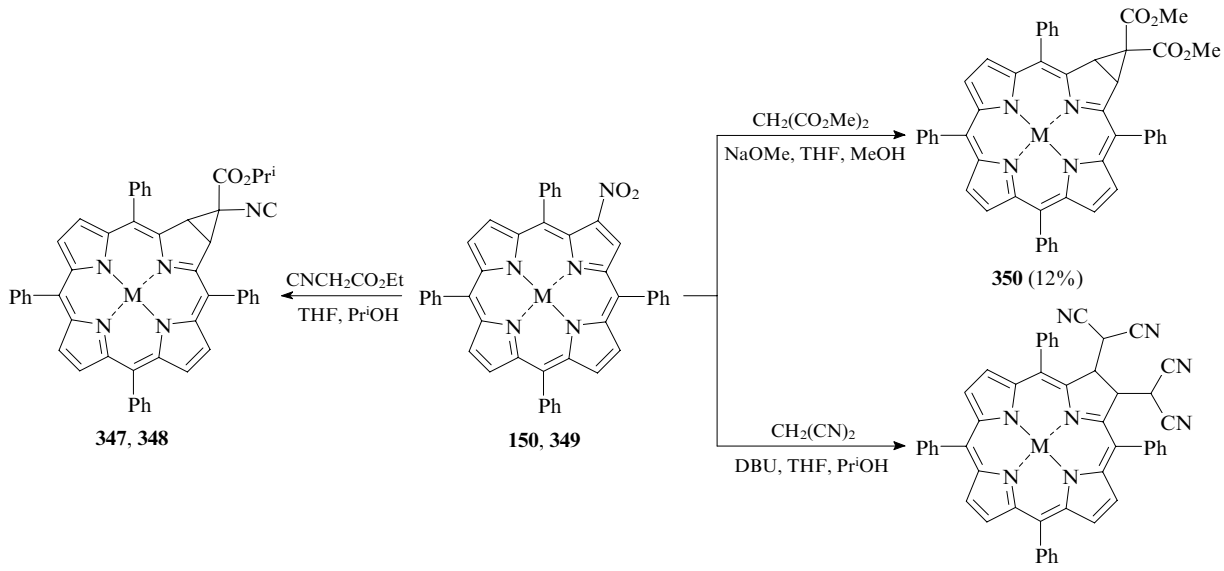
**Scheme 50**



**11**, **18**, **25**, **30**, **31**, **102**, **103**, **137**, **262**, **332** → **333** – **342** → **343** – **346**

$Ar^1 = Ar^2 = Ph$ (**11**, **333**, **343**), 4-$MeC_6H_4$ (**18**, **334**, **344**), 2,6-$Cl_2C_6H_3$ (**25**, **335**), 3-$MeOC_6H_4$ (**30**, **336**), 4-$MeOC_6H_4$ (**31**, **337**, **345**), $C_6F_5$ (**137**, **338**), 4-$ClC_6H_4$ (**262**, **339**, **346**); $Ar^1 = H$, $Ar^2 = Ph$ or $Ar^1 = Ph$, $Ar^2 = H$ (**102**, **340**); $Ar^1 = H$, $Ar^2 = 4\text{-}MeC_6H_4$ or $Ar^1 = 4\text{-}MeC_6H_4$, $Ar^2 = H$ (**103**, **341**); $Ar^1 = H$, $Ar^2 = 4\text{-}ClC_6H_4$ or $Ar^1 = 4\text{-}ClC_6H_4$, $Ar^2 = H$ (**332**, **342**)

**Scheme 51**



**347**, **348** ← **150**, **349** → **350** (12%), **351** (14%)

M = Zn (**150**, **347**, **351**), 2 H (**348**), Ni (**349**, **350**)

8% – 31% (Scheme 50).[129] Diarylchlorins **340** – **342** were formed as mixtures of two regioisomers.[130]

It was also demonstrated [129, 130] that chlorins **333**, **334**, **337** and **339** enter into 1,7-cycloaddition with diazafulvenium methide to give bacteriochlorins **343** – **346**, respectively (16% – 36% yields) (see Scheme 50), with the yield of product **346** being higher upon conventional heating for 4 h (36%) than upon microwave irradiation for 20 min (8%).[129]

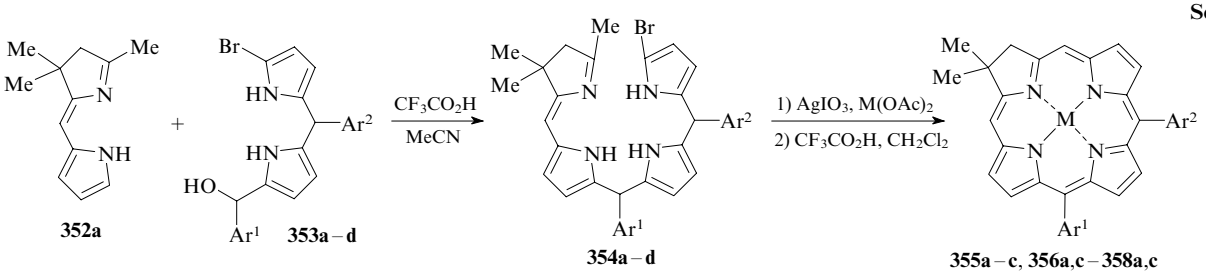
Apart from [1 + 2]-cycloaddition with carbenes [125 – 128] and [3 + 2]-cycloaddition with diazomethane,[119, 120] the Barton – Zard reaction is also suitable for the preparation of hydrogenated porphyrin derivatives containing a cyclopropane moiety.[131, 132] For example, zinc chlorin complex **347** was synthesized by refluxing porphyrin **150** and ethyl α-isocyanoacetate in a THF – isopropyl alcohol mixture (10 : 1) (Scheme 51).[131] The free base **348** was isolated upon treatment of chlorin **347** with a 1% solution of trifluoroacetic acid in dichloromethane.[131]

Refluxing of nickel porphyrin **349** and dimethyl malonate in the presence of sodium methoxide affords cyclopropanochlorin **350** (see Scheme 51).[132] The structures of chlorins **347** and **350** were established by X-ray diffraction analysis.[131, 132] The reaction of porphyrin **150** with malononitrile in the presence of DBU gives chlorin **351** instead of the expected cyclopropanochlorin.[132]

## V. Direct synthesis of chlorins, bacteriochlorins and their tetraaza analogues

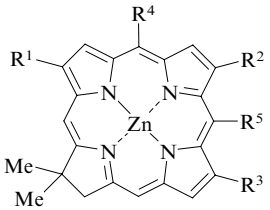
The first paper [133] describing the direct synthesis of chlorin was published in 1955. Chlorin (0.85% yield) was formed upon refluxing of 2-(*N*,*N*-dimethylaminomethyl)pyrrole and ethylmagnesium bromide in xylene. In 2000, Lindsey and co-workers [134, 135] proposed a method for the preparation of stable 5-*meso*-aryl- and 5,10-*meso*-diarylchlorins containing, in the pyrroline moiety, a quaternary carbon atom with methyl groups arranged outside the plane of the molecule. The condensation of 3,3-dimethyl-2,3-dihydrodi-

**Scheme 52**




$Ar^2$ = 4-$MeC_6H_4$: $Ar^1$ = 2,4,5-$Me_3C_6H_2$ (**353a**, **354a**, **355**), 4-$IC_6H_4$ (**353b**, **354b**, **356**), 4-$Me_3SiC{\equiv}CC_6H_4$ (**353c**, **354c**, **357**); $Ar^1$ = $Ar^2$ = $C_6F_5$ (**353a**, **354a**, **358**); **355** – **358**: M = Zn (**a**), 2 H (**c**); M = Cu (**355b**)

**Structures 359 – 364**

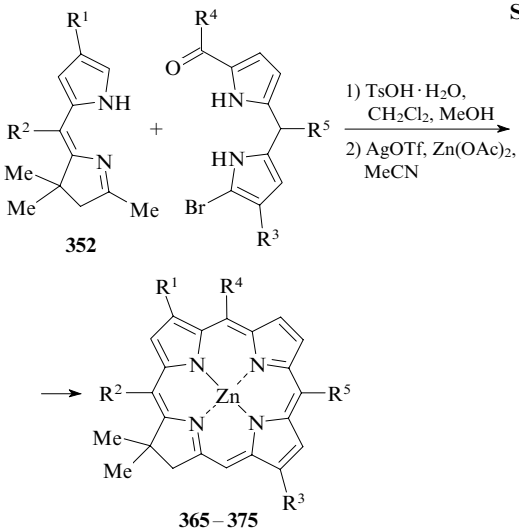



**359** – **364**

| Chlorin | $R^1$ | $R^2$ | $R^3$ | $R^4$ | $R^5$ | Yield (%) |
|---|---|---|---|---|---|---|
| **359** | H | H | 4-$IC_6H_4$ | 4-$MeC_6H_4$ | H | 18 |
| **360** | H | H | 4-$Me_3SiC{\equiv}CC_6H_4$ | 4-$MeC_6H_4$ | H | 22 |
| **361** | H | 4-$IC_6H_4$ | H | 4-$MeC_6H_4$ | H | 24 |
| **362** | 4-$IC_6H_4$ | H | 4-$Me_3SiC{\equiv}CC_6H_4$ | 4-$MeC_6H_4$ | H | 24 |
| **363** | 4-$IC_6H_4$ | H | 4-$Me_3SiC{\equiv}CC_6H_4$ | 3,5-$Bu^t_2C_6H_3$ | H | 8 |
| **364** | H | H | H | 4-$MeC_6H_4$ | 4-$MeOC_6H_4$ | 36 |

pyrrin (**352a**) with aryl-substituted bromodipyrromethane **353a** at 0 °C in acetonitrile in the presence of trifluoroacetic acid yielded dihydrobilene *a* (**354a**); oxidative cyclization of this product in the presence of silver iodate, piperidine and zinc or copper salts gave oxidatively stable metal 5,10-*meso*-diarylchlorins **355a**,**b** (4% – 10% yields) (Scheme 52).[134] Zinc complexes **356a** – **358a** were prepared in a similar way. Treatment of these complexes with trifluoroacetic acid at room temperature afforded chlorin free bases **355c** – **358c** in quantitative yields.[134]

**Scheme 53**



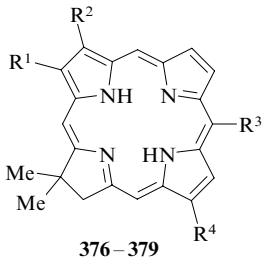

**365** – **375**

| Chlorin | $R^1$ | $R^2$ | $R^3$ | $R^4$ | $R^5$ | Yield (%) |
|---|---|---|---|---|---|---|
| **365** | H | Ph | H | H | H | 5 |
| **366** | H | H | H | Ph | H | 16 |
| **367** | H | Ph | H | 4-$MeC_6H_4$ | 2,4,5-$Me_3C_6H_2$ | 11 |
| **368** | H | H | H | H | 2,4,5-$Me_3C_6H_2$ | 42 |
| **369** | Br | H | H | H | 2,4,5-$Me_3C_6H_2$ | 37 |
| **370** | H | H | Br | H | 2,4,5-$Me_3C_6H_2$ | 26 |
| **371** | Br | H | Br | H | 2,4,5-$Me_3C_6H_2$ | 30 |
| **372** | $Pr^i_3SiC{\equiv}C$ | H | Br | H | 2,4,5-$Me_3C_6H_2$ | 11 |
| **373** | H | H | H | H | H | 16 |
| **374** | Br | H | Br | H | H | 26 |
| **375** | $Pr^i_3SiC{\equiv}C$ | H | H | Br | H | 7 |

The approach proposed by Lindsey and co-workers[134, 135] was used to prepare zinc complexes of some unsymmetrical chlorins. For instance, the reaction of β,β-dimethyl-substituted dihydrodipyrrins **352** with bromo-substituted dipyrromethanes at room temperature in the presence of *p*-toluenesulfonic acid in an inert atmosphere followed by treatment with silver trifluoromethanesulfonate and zinc acetate afforded zinc chlorins **365** – **375** in up to 42% yields (Scheme 53).[137, 138]

The same approach and the subsequent demetallation by treatment with trifluoroacetic acid resulted in the formation of bromo-substituted chlorin free bases **376** – **379**.[139, 140]

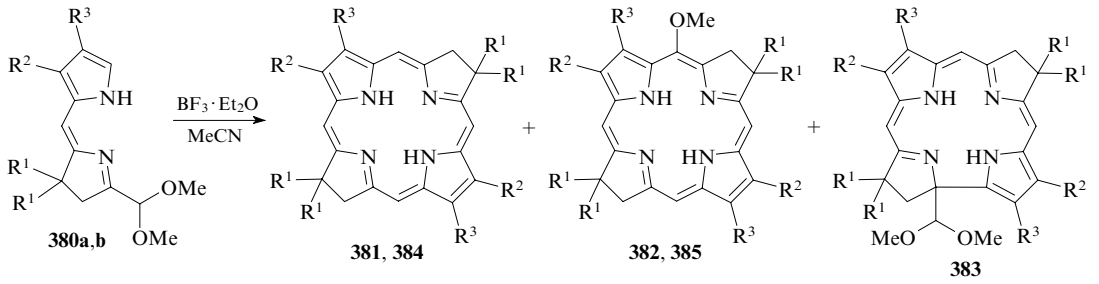
**Structures 376 – 379**




**376** – **379**

| Chlorin | $R^1$ | $R^2$ | $R^3$ | $R^4$ | Yield (%) |
|---|---|---|---|---|---|
| **376** | H | H | 2,4,5-$Me_3C_6H_2$ | Br | 38 |
| **377** | H | Br | 2,4,5-$Me_3C_6H_2$ | Br | 25 |
| **378** | Br | H | H | H | 5 |
| **379** | H | Br | H | H | 14 |

**Scheme 54**



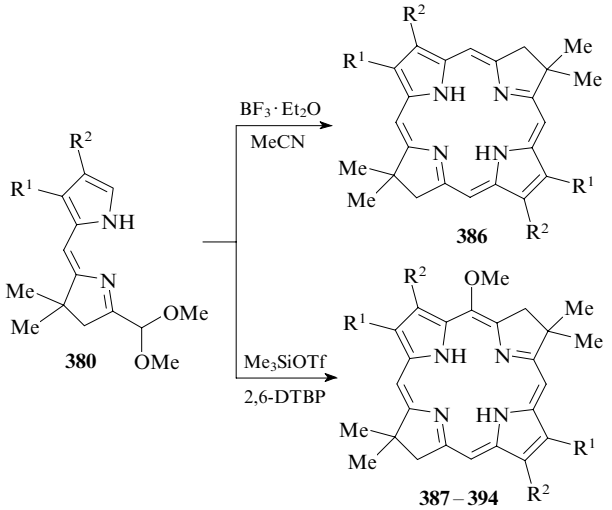
$R^1$ = Me, $R^2$ = 4-$MeC_6H_4$, $R^3$ = H (**380a**, **381** – **383**); $R^1$ – $R^1$ = $(CH_2)_2NH(CH_2)_2$, $R^2$ = Et, $R^3$ = $CO_2Et$ (**380b**, **384**, **385**)

While developing his method, Lindsey and co-workers [141, 142] proposed a synthetic route to stable BC derivatives involving the condensation of two dihydrodipyrrin moieties in the presence of Lewis or Brønsted acids. For example, the condensation of *p*-tolyl-substituted dihydrodipyrrin acetal **380a** in acetonitrile in the presence of boron trifluoride etherate at room temperature furnished bacteriochlorin **381** (49% yield). Depending on the acid concentration, apart from product **381**, the formation of 5-methoxy derivative **382** and tetrahydrocorrin **383** is also possible (Scheme 54).[141]

3,13- Dibromo-substituted bacteriochlorin was synthesized under similar conditions (15% yield).[142] Reddy *et al.*[143] used a fairly effective method for stabilizing single bonds in dihydrodipyrrin and pyrroline moieties of bacteriochlorin (see Scheme 54). Instead of two geminal methyl groups, a spiro-piperidine unit was integrated into each pyrroline ring (compound **380b**). This simultaneously solved two problems: provided stable product **384** (44% yield) and increased the water solubility of the target molecule for subsequent quaternization of the piperidine nitrogen atom. In the synthesis of compound **384** , as in the case of its analogue **381**, the formation of 5-methoxybacteriochlorin **385** was observed (7% yield).[143]

Lindsey and co-workers [144] carried out an extensive study on optimization of conditions for the synthesis of stable BC derivatives in high yields. They elucidated the influence of conditions of condensation of dihydrodipyrrin acetal and some its derivatives (**380**) containing electron-donating or electron-withdrawing substituents on the yield of the resulting substituted BCs **386** – **394**. More than twenty Lewis and Brønsted acids were tested and a systematic study of the effects of the starting dihydrodipyrrin acetal concentration and the nature of the acid on the yields of products was performed. It was found that the trimethylsilyl triflate – 2,6-di(*tert*-butyl)pyridine (2,6-DTBP) system is the

**Scheme 55**

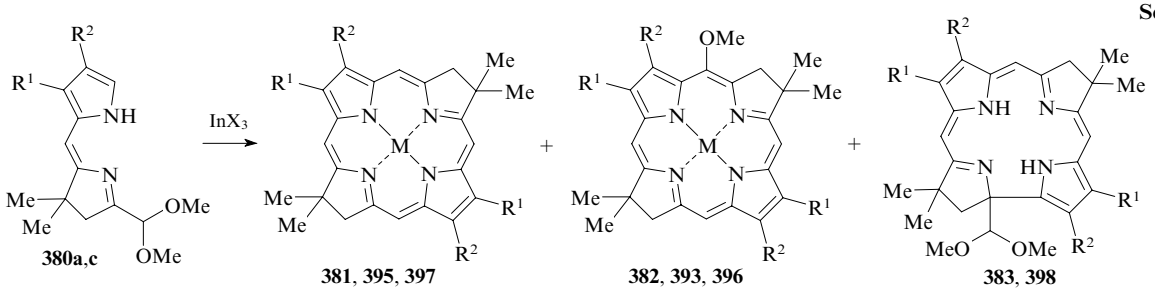


$R^1$ = H: $R^2$ = Br (**387**), H (**388**); $R^2$ = $CO_2Et$: $R^1$ = Et (**386**, **389**), $CO_2Et$ (**390**), H (**391**), 4-$MeC_6H_4$ (**392**), Me (**393**), 4-$IC_6H_4$ (**394**)

catalyst of choice for the preparation of substituted 5-methoxy-BC derivatives **387** – **394**: the product yields reached 63%; in the case of product **386**, boron trifluoride etherate was a good catalyst (41% yield) (Scheme 55).

Krayer *et al.*[145] investigated the condensation of β-aryl- or β-alkyl-substituted dihydrodipyrrin acetals **380** in the presence of indium(III) salts. The composition and the yields of reaction products were found to depend on the catalyst and the solvent. For example, condensation of *p*-tolyl-substituted dihydrodipyrrin acetal **380a** in the presence of indium triflate (X = OTf) in dichloromethane resulted in the synthesis of bacteriochlorin **381** (9% yield), 5-methoxy-BC derivative **382** (11% yield) and tetrahydro-

**Scheme 56**



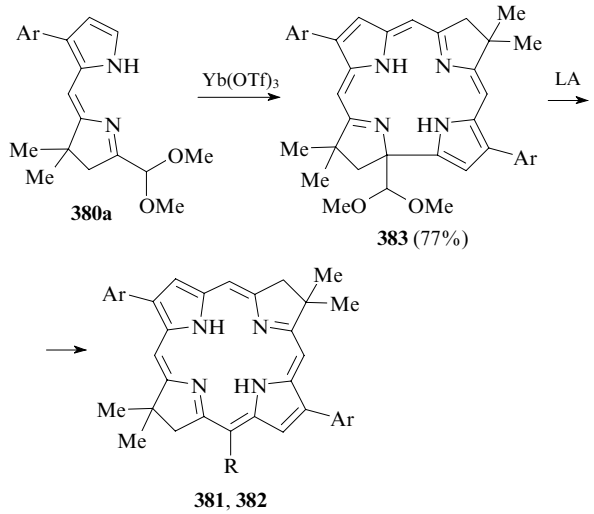
$R^1$ = 4-$MeC_6H_4$, $R^2$ = H (**380a**): M = 2 H (**381** – **383**); $R^1$ = Me, $R^2$ = $CO_2Et$ (**380c**): M = InBr (**395**, **396**), 2 H (**393**, **397**, **398**); X = OTf, Br

corrin **383** in a trace amount; when acetonitrile serves as the solvent under the same conditions, only product **382** was formed (14% yield). The condensation of β-alkyl-substituted dihydrodipyrrin acetal **380c** ($R^1$ = Me, $R^2$ = $CO_2Et$) in the presence of indium(III) bromide (X = Br) in acetonitrile gave a mixture consisting of indium complexes of tetrasubstituted BCs **395** and **396** and the corresponding free bases **393** and **397** (1% – 2% yields),while the major product was tetrasubstituted tetrahydrocorrin **398** (11% yield) (Scheme 56).

The condensation of β-(*p*-tolyl)-substituted dihydrodipyrrin acetal **380a** in the presence of ytterbium triflate in dichloromethane furnishes tetrahydrocorrin **383**, which is converted to a mixture of 5-unsubstituted (**381**) and 5-methoxybacteriochlorin (**382**) derivatives under the action of Lewis acids (LA) (Scheme 57). The yields and the structures of the reaction products depend on the nature of the Lewis acid and the solvent. For example, if trimethylsilyl triflate in dichloromethane is used as the Lewis acid, compounds **381** (4% yield) and **382** (56% yield) are formed, whereas in the case of boron trifluoride etherate in the same solvent, the reaction gives only **381** (20% yield) with a minor tetrahydrocorrin impurity.[146]

The Lindsey method considered above is suitable for the preparation of oxidatively stable hydrogenated porphyrins and also for the selective synthesis of chlorins or bacteriochlorins (without isobacteriochlorin impurity). However, the syntheses of the starting dihydrodipyrrins and dipyrromethanes are complicated multistep processes, which hampers the preparative use of the method. The starting dipyrromethanes are formed in four steps from pyrroles and aromatic aldehydes, and dihydrodipyrrins are prepared in nine steps. As a consequence, the final yield of hydrogenated porphyrins synthesized by this method does not exceed 5%.

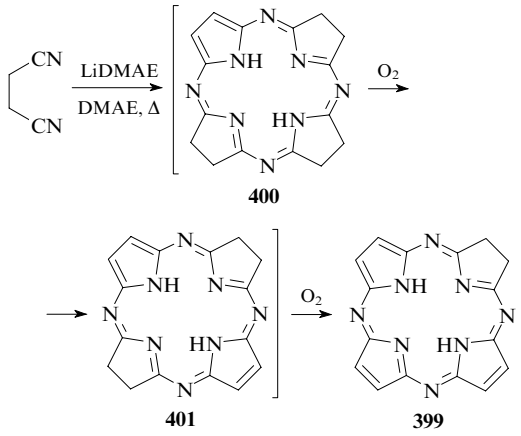
**Scheme 57**




Ar = 4-$MeC_6H_4$ (**380a**, **383**): R = H (**381**), MeO (**382**)

There are two methods for the direct preparation of hydrogenated TAPs, namely, tetramerization of succinonitrile or mixed condensation of phthalogens with different hydrogenation levels. The preparation of TAC derivatives by tetramerization of succinonitrile is considered in only one study where succinonitrile condensation is carried out in the presence of lithium dimethylaminoethoxide (LiDMAE) in refluxing dimethylaminoethanol (DMAE) either in an inert atmosphere or in air. Unsubstituted TAC **399** was prepared for the first time in 16% yield by tetramerization of succinonitrile carried out in the presence of LiDMAE in an argon flow for 30 min (Scheme 58).[147]

**Scheme 58**

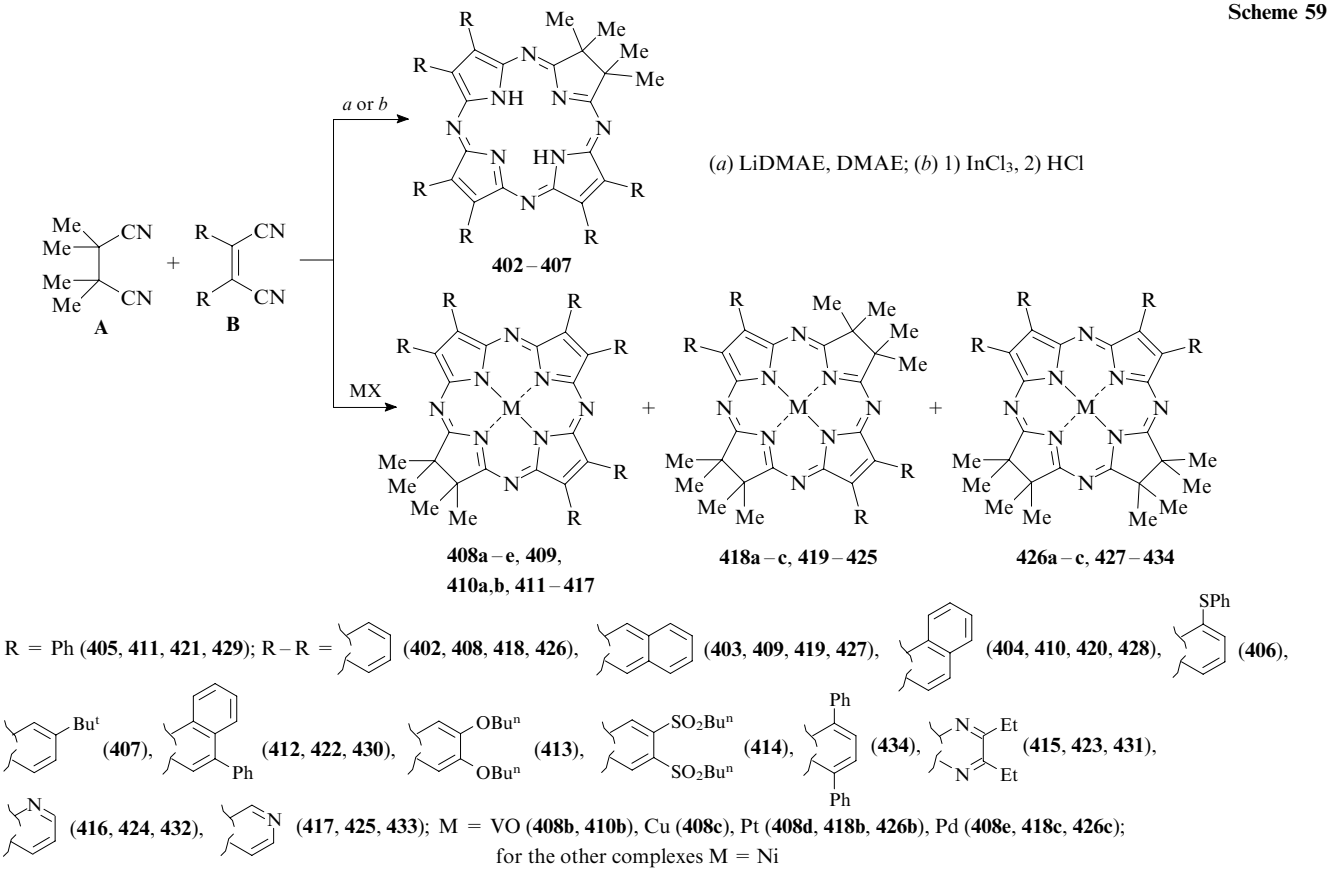



Compound **399** was shown to be stable against oxidation in air in the solid state or in neutral organic solvents; meanwhile, heating of its solution in acetic acid at 80 °C for 30 min leads to quantitative oxidation to TAP (**2**). When this reaction is carried out under aerobic conditions for 1.5 h, compound **2** is formed in a moderate yield (15%).[147] Apparently, the reaction involves the intermediate formation of hexahydro- (**400**) and tetrahydrotetraazaporphyrins (**401**) (see Scheme 58). Indeed, the electronic absorption spectrum of the reaction mixture recorded several minutes after the onset of the reaction exhibited absorption bands at 602 and 794 nm, which were assignable to intermediates **400** and **401**; however, the researchers were unable to isolate the intermediates in the pure state.[147]

The mixed condensation strategy of two or more starting compounds is a key method for the preparation of unsymmetrical TAPs.[148, 149] The first attempt to condense a mixture of phthalogens with different hydrogenation levels was made by Linstead and Elvidge[150] in 1955. Subsequently, tribenzotetraazaporphyrin (32% yield) mixed with phthalocyanine (Pc) was obtained by the reaction of succinimidine with diiminoisoindoline in 1 : 3 molar ratio in refluxing n-butyl alcohol.[151] When the molar ratio of reactants was 1 : 1, a small amount of tribenzotetraazachlorin with a long-wavelength absorption at 752 nm was formed; however, the attempted isolation of this compound failed.[151] The condensation of succinonitrile with phthalonitrile in the presence of LiDMAE gives rise to a mixture of di- and tribenzo TAP and Pc derivatives.[147] This and other unsuccessful attempts at the synthesis of tribenzotetraazachlorin reported by Linstead and Elvidge[150] and Kopranenkov *et al.*[151] are attributable to its lower oxidative stability compared with unsubstituted TAC, which is apparently a consequence of the extension of the π-system of the macrocycle.

We developed two processes of condensing a mixture of saturated (**A**) and unsaturated (**B**) phthalogens for the preparation of tetraazachlorin free bases. The first process comprises conducting the reaction under the action of LiDMAE in DMAE (Scheme 59, conditions *a*),[19, 152] and according to the other one, the reaction proceeds in the

**Scheme 59**




presence of indium(III) chloride in quinoline, and the resulting indium complexes are demetallated (conditions *b*).[153, 154]

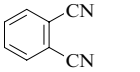
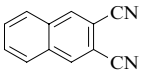
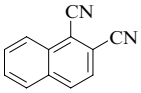
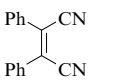
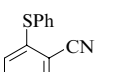
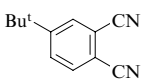
The compounds used as the saturated phthalogens **A** include: tetramethylsuccinonitrile (TMSN),[19, 152 – 161] 1,2-dicyanofullerene,[161 – 165] some succinic acid derivatives with substituents at one of the saturated carbon atoms,[166] 5,5-dimethyl-1,3-oxazolidine-2,4-dione [167] and 5,5-diphenylhydantoin.[168] The unsaturated phthalogen **B** was represented by anhydrides, imides and nitriles of *o*-phthalic,[19, 152 – 155, 159 – 168] naphthalene-1,2-dicarboxylic,[19, 152 – 154, 156, 167] naphthalene-2,3-dicarboxylic [19, 152, 155, 167] and heteroaromatic 1,2-dicarboxylic acids [158] and diphenylfumaronitrile.[153, 154, 157]

Mixed condensation of TMSN with some unsaturated phthalogens (phthalodinitrile, 1,2- and 2,3-dicyanonaphthalenes, diphenylfumaronitrile) induced by LiDMAE in refluxing DMAE afforded small yields of TAC derivatives **402 – 405** mixed with the tetramerization products of unsaturated phthalogen **B** (see Scheme 59, Table 3).[19, 152, 155 – 157]

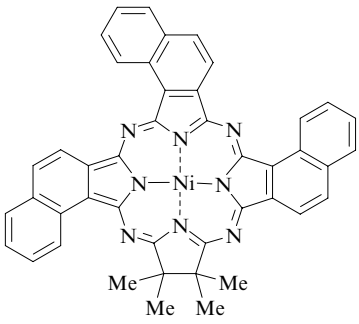
We found a convenient method for the synthesis of TACs **402 – 405** by template condensation of TMSN mixtures with unsaturated phthalogens in 3 : 1 molar ratio in the presence of indium(III) chloride and ammonium molybdate (MOA) in quinoline at 230 – 235 °C followed by demetallation of the intermediate indium complexes with hydrochloric acid at room temperature.[153, 154] This method not only ensured substantially higher yields of known TAC derivatives **402 – 405** (see Table 3) but also permitted the preparation of tris(3-phenylsulfanylbenzo)- (**406**) and tris(4-*tert*-butylbenzo)tetraazachlorins (**407**) inaccessible by other methods.

An extensive series of metal complexes **408 – 434** were synthesized by mixed condensation of a mixture of TMSN and phthalogens in refluxing quinoline with

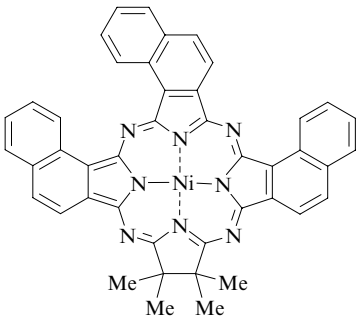
**Table 3**. Conditions of synthesis and yields of tetraazachlorins **402 – 407**.

| Tetra-aza-chlorin | Phthalogen **B** | Molar ratio **A** : **B** | Reaction condi-tions | Yield (%) | Ref. |
|---|---|---|---|---|---|
| **402** |  | 1 : 1 | *a* | 1.6 | 19, 149, 152 |
| | | 1 : 1 | *b* | 14 | 150, 151 |
| | | 3 : 1 | *b* | 40 | 150, 151 |
| **403** |  | 1 : 1 | *a* | 1.5 | 152 |
| **404** |  | 1 : 1 | *a* | 2.1 | 153 |
| | | 3 : 1 | *b* | 28 | 150, 151 |
| **405** |  | 1 : 1 | *a* | 4 | 154 |
| | | 3 : 1 | *b* | 38 | 150, 151 |
| **406** |  | 3 : 1 | *b* | 12 | 150, 151 |
| **407** |  | 3 : 1 | *b* | 18 | 150, 151 |

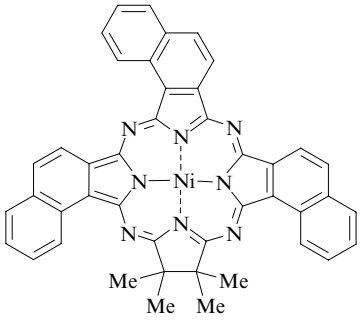
**Structures 410a, 420, 428**



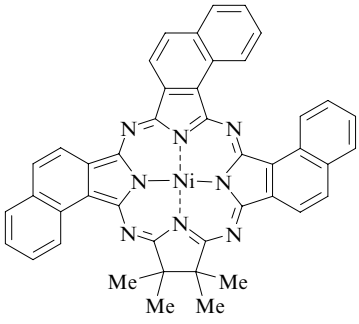

**410aa**



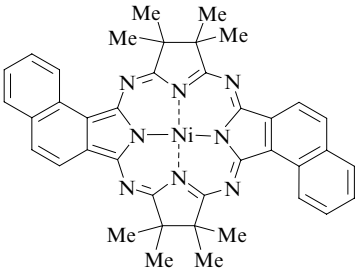

**410ab**



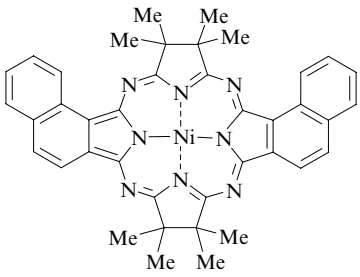

**410ac**



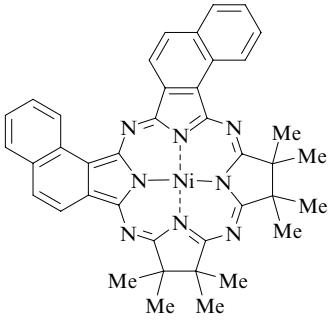

**410ad**



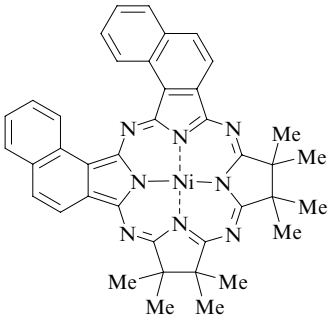

**420a**



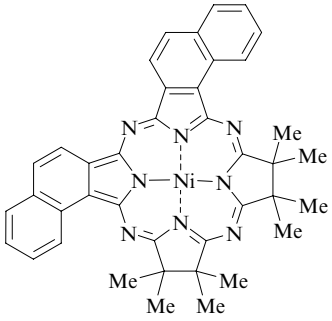

**420b**




**428a**




**428b**




**428c**

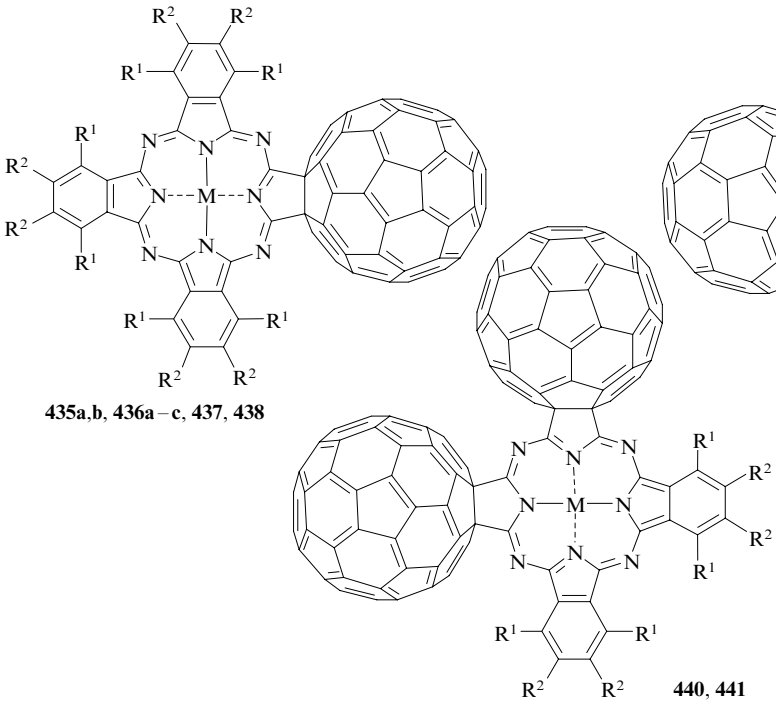
metal salts in the presence of a catalytic amount of MOA. The authors not only succeeded in the isolation of a variety of metal tribenzotetraazachlorins **408** – **414** (in up to 25% yields) but also were able to prepare for the first time nickel, vanadyl, copper, palladium and platinum tribenzotetraazabacterio- (**418** – **422**) and -isobacteriochlorins (**426** – **430**, **434**) in 1% – 4% yields (see Scheme 59).[19, 152, 155 – 160] The strategy of mixed condensation of phthalogens with different hydrogenation levels served to synthesize nickel complexes of the aza analogues of hydrogenated TAP derivatives, **415** – **417** (1% – 18% yields), **423** – **425** (1% – 14%) and **431** – **433** (1% – 11%) containing fused pyrazine or pyridine rings.[158]

By using 1,2-dicyanofullerene as the saturated phthalogen, various hydrogenated metal (Ni, Co, Fe, VO) TAPs **435** – **441** containing one or two fused fullerene moieties have been prepared in 1% – 13% yields.[158 – 162]

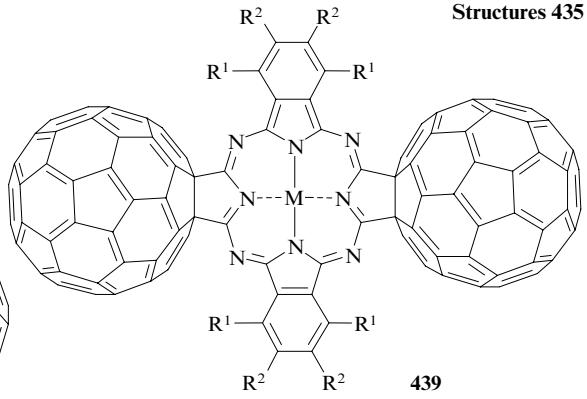
It is noteworthy that 1,2-naphtho- (**410**, **420**, **428**), 2,3-pyridino- (**416**, **424**, **432**) and 3,4-pyridino-fused (**417**, **425**, **433** ) TACs, TABCs and TAiBCs are formed, unlike the corresponding 2,3-naphtho (**409**, **419**, **427**) and pyrazino derivatives (**415**, **423**, **431**), as mixtures of various randomers.[156, 158] Indeed, unsymmetrical TACs can exist as mixtures of four isomers, TABCs have two isomers and analogous TAiBCs can exist as three isomers. Complete separation and identification of hydrogenated TAP isomers was first carried out in 2005.[156] Two TABC isomers **420** and three TAiBC isomers **428** were separated by thin layer chromatography on silica gel. The TAC isomers **410a** were separated by high performance liquid chromatography.[156] For pyridino-fused compounds **416**, **417**, **424**, **425**, **432** and **433**, all possible isomers were isolated by preparative thin layer chromatography on silica gel.[158]

Apart from TMSN, other succinic acid derivatives have also been tested as the saturated components in the co-condensation of phthalogens; examples are 2,2-pentamethylenosuccinonitrile and 2,2-diphenyl- and 2,2-dimethylsuccinonitriles containing two substituents at one saturated carbon atom.[166] These compounds were made to react with phthalonitrile in the presence of nickel chloride in refluxing quinoline to be converted to nickel tribenzo-TACs **442** – **444** (9% – 15% yields) (Scheme 60).

**Structures 435 – 441**



**435a**,**b**, **436a – c**, **437**, **438**



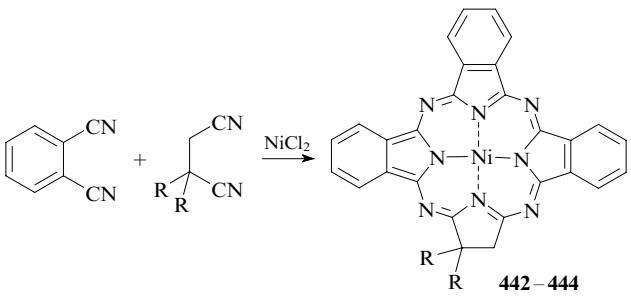
**439**



**440**, **441**

$R^1$ = H, $R^2$ = $OBu^n$: M = Ni (**435a**, **440**), VO (**435b**); $R^1$ = H, $R^2$ = $SO_2Bu^n$: M = Ni (**436a**, **439**, **441**), Fe (**436b**), Co (**436c**); $R^1$ = $OBu^n$, $R^2$ = H, M = Ni (**437**); $R^1$ = H, $R^2 – R^2$ = $O(CH_2CH_2O)_4$, M = Ni (**438**)

**Scheme 60**

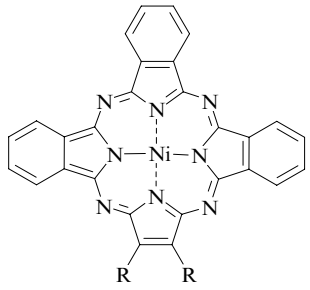


**442 – 444**

R – R = $(CH_2)_5$ (**442**); R = Ph (**443**), Me (**444**)

Compounds **443** and **444** were noted to be less stable than tetramethyl-substituted analogue **408a**. During chromatographic purification on silica gel or alumina, these TAC derivatives were converted to nickel β,β-diphenyl- (**445**) or β,β-dimethyl tribenzo-TAPs (**446**) *via* dehydrogenation and intramolecular rearrangement with migration of one phenyl or methyl group to the neighbouring β-pyrrole carbon atom.[166]

**Structures 445, 446**

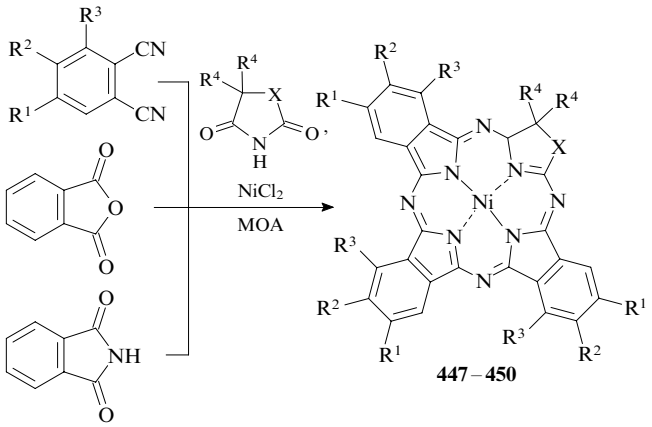


**445**, **446**

R = Ph (**445**), Me (**446**)

The problem of the lack of stability of β,β-disubstituted tribenzotetraazachlorins was solved by introducing a heteroatom into the β-position of the hydrogenated pyrrole moiety. The preparation of stable nickel complexes **447 – 450** containing an oxygen or nitrogen atom in the β-position of the macrocycle pyrrole moiety has been reported.[167, 168] Nickel oxatetraazachlorins **447 – 449** (4% – 8% yields) are formed upon condensation of a mixture of 5,5-dimethyl-1,3-oxazolidine-2,4-dione with phthalic and naphthalene-1,2- and -2,3-dicarboxylic acid derivatives in the presence of urea, nickel(II) chloride and MOA in quinoline at 250 °C (Scheme 61).[167]

**Scheme 61**



**447 – 450**

X = O, $R^4$ = Me: $R^1$ = $R^2$ = $R^3$ = H (**447**); $R^3$ = H, $R^1 – R^2$ is benzo (**448**); $R^1$ = H, $R^2 – R^3$ is benzo (**449**); X = NH: $R^1$ = $R^2$ = $R^3$ = H, $R^4$ = Ph (**450**)

The mixed condensation of phthalimide and 5,5-diphenylhydantoin in refluxing sulfolane afforded nickel 5,7,10,15,20-pentaazachlorin **450** (5% yield) (see Scheme 61).[168] The replacement of the quaternary carbon atom bearing two geminal methyl groups in the β-position of the hydrogenated pyrrole moiety by a heteroatom decreases the solubility of these tetraazachlorins in organic solvents.

## VI. Conclusion

This review integrates the data on the synthesis of hydrogenated porphyrins and their tetraaza analogues published since 1930 up to present day. Considering the published data, the synthetic methods are divided into four groups, namely, reduction, oxidative addition, cycloaddition and direct synthesis of (tetraaza)chlorins and (tetraaza)bacteriochlorins. Each method has its own benefits and drawbacks. For instance, the diimide reduction of porphyrins mainly serves for the preparation of BC derivatives; the oxidative addition method opens up the way to the selective preparation of chlorins; cycloaddition reactions may yield either dihydro derivatives (chlorins) or mixtures of chlorins and tetrahydro derivatives (bacterio- and isobacteriochlorins). Furthermore, bacteriochlorins can be synthesized by mixed procedures combining the described approaches. The direct *de novo* synthesis of hydrogenated porphyrins developed by Lindsey is suitable for the selective preparation of oxidatively stable chlorins or bacteriochlorins. A new facile approach to the synthesis of metal-free TAC derivatives by the condensation of various phthalogens with tetramethylsuccinonitrile in the presence of indium(III) chloride made it possible to isolate new representatives of this class of tetrapyrrole macroheterocycles.

The development of new and upgrading of known methods for the preparation of hydrogenated porphyrin derivatives and their tetraaza analogues is topical because the yields of the target compounds, especially bacterio- and tetraazabacteriochlorins, are still modest, while the scope of applicability of these compounds in science and technology is extending.

This review was prepared with the financial support of the Russian Foundation for Basic Research (Project No. 15-04-04363) and Ministry of Education and Science of the Russian Federation (Project 'Science' No. 4.2569.2014/K).

## References

1. *The Porphyrin Handbook* Vol. 6 (Eds K M Kadish, K M Smith, R Guilard) (San Diego, CA: Academic Press, 2000)
2. *Handbook of Porphyrin Science with Applications to Chemistry, Physics, Materials Science, Engineering, Biology and Medicine* Vol. 12 (Eds K M Kadish, K M Smith, R Guilard) (Singapore: World Scientific, 2011)
3. M Gouterman, in *The Porphyrins* (Ed. D Dolphin) (New York: Academic Press, 1978) p. 1
4. J Juselius, D Sundholm *Phys. Chem. Chem. Phys.* **2** 2145 (2000)
5. N Otero, S Fias, S Rodenković, P Bultinck, A M Grana, M Mandado *Chem. – Eur. J.* **17** 3274 (2011)
6. H Fliegel, D Sundholm *J. Org. Chem.* **77** 3408 (2012)
7. G P Moss *Pure Appl. Chem.* **59** 779 (1987)
8. E D Sternberg, D Dolphin, C Brückner *Tetrahedron* **54** 4151 (1998)
9. R K Pandey, G Zheng, in *The Porphyrin Handbook* Vol. 6 (Eds K M Kadish, K M Smith, R Guilard) (San Diego, CA: Academic Press, 1999) p. 157
10. R Bonnett, in *Chemical Aspects of Photodynamic Therapy* (Amsterdam: Gordon and Breach, 2000) p. 177
11. A F Mironov, in *Uspekhi Khimii Porfirinov* (Progress in Porphyrin Chemistry) (St Petersburg: Research Institute of Chemistry, SPbSU, 2004) Vol. 4, p. 271
12. Y Chen, G Li, R K Pandey *Curr. Org. Chem.* **8** 1105 (2004)
13. Chan Tkhi Khai Ien, G V Ramenskaya, N A Oborotova *Ros. Bioterapevt. Zh.* **8** (4) 99 (2009)
14. H Ali, J E van Lier, in *Handbook of Porphyrin Science with Applications to Chemistry, Physics, Materials Science, Engineering, Biology and Medicine* Vol. 4 (Eds K M Kadish, K M Smith, R Guilard) (Singapore: World Scientific, 2010) p. 1
15. M Ethirajan, N J Patel, R K Pandey, in *Handbook of Porphyrin Science with Applications to Chemistry, Physics, Materials Science, Engineering, Biology and Medicine* Vol. 4 (Eds K M Kadish, K M Smith, R Guilard) (Singapore: World Scientific, 2010) p. 249
16. M Senge, J C Brandt *Photochem. Photobiol.* **87** 1240 (2011)
17. E A Lukyanets *Fotodinamich. Terap. Fotodiagnostika* **2** (3) 3 (2013)
18. T G S Denis, Y-Y Huang, M R Hamblin, in *Handbook of Porphyrin Science with Applications to Chemistry, Physics, Materials Science, Engineering, Biology and Medicine* Vol. 27 (Eds K M Kadish, K M Smith, R Guilard) (Singapore: World Scientific, 2013) p. 255
19. E A Makarova, G V Koroleva, E A Lukyanets *Russ. J. Gen. Chem.* **71** 821 (2001) [*Zh. Obshch. Khim.* **71** 874 (2001)]
20. Patent RF 2278119 (2006); *Chem. Abstr.* **145** 78843 (2006)
21. V I Ivanova-Radkevich, L V Umnova, S V Barkanova, E A Makarova, E A Lukyanets *Ros. Bioterapevt. Zh.* **7** (3) 39 (2008)
22. V I Ivanova-Radkevich, V M Negrimovskii, S V Barkanova, E A Makarova, V F Donyagina, T V Pleteneva *Pharm. Chem. J.* **43** 239 (2009) [*Khim.-Farm. Zh.* **43** (5) 7 (2009)]
23. E A Makarova, E A Lukyanets, in *Uspekhi Khimii Porfirinov* (Advances in Porphyrin Chemistry) (St Petersburg: Research Institute of Chemistry, SPbSU, 2007) Vol. 5, p. 28
24. E A Makarova, E A Lukyanets *J. Porphyrins Phthalocyanines* **13** 188 (2009)
25. A F Mironov *Ros. Khim. Zh.* **42** (5) 23 (1998); *Chem. Abstr.* **132** 64076 (2000)
26. M A Grin, A F Mironov, in *Chemical Processes with Participation of Biological and Related Compounds* (Eds T N Lomova, G E Zaikov) (Leiden: Brill, 2008) p. 5
27. M A Grin, A F Mironov, A A Shtil *Anticancer Agents Med. Chem.* **8** 683 (2008)
28. M O Senge, A Wiehe, C Ryppa, in *Advances in Photosynthesis and Respiration* Vol. 25 (Eds B Grimm, R J Porra, W Rüdiger, H Scheer) (Dordrecht; Springer, 2006) p. 27
29. A S Brandis, Y Salomon, A Scherz, in *Advances in Photosynthesis and Respiration* Vol. 25 (Eds B Grimm, R J Porra, W Rüdiger, H Scheer) (Dordrecht; Springer, 2006) p. 461
30. A S Brandis, Y Salomon, A Scherz, in *Advances in Photosynthesis and Respiration* Vol. 25 (Eds B Grimm, R J Porra, W Rüdiger, H Scheer) (Dordrecht; Springer, 2006) p. 485
31. J A S Cavaleiro, A C Tome, M G P M S Neves, in *Handbook of Porphyrin Science with Applications to Chemistry, Physics, Materials Science, Engineering, Biology and Medicine* Vol. 2 (Eds K M Kadish, K M Smith, R Guilard) (Singapore: World Scientific, 2010) p. 193
32. J S Lindsey, O Mass, C-Y Chen *New J. Chem.* **35** 511 (2011)
33. C Brückner, L Samankumara, J Ogikubo, in *Handbook of Porphyrin Science with Applications to Chemistry, Physics, Materials Science, Engineering, Biology and Medicine* Vol. 17 (Eds K M Kadish, K M Smith, R Guilard) (Singapore: World Scientific, 2012) p. 1
34. J A S Cavaleiro, M G P M S Neves, A C Tome *ARKIVOC* (xiv) 107 (2003)
35. A C Tome, M G P M S Neves, J A S Cavaleiro *J. Porphyrins Phthalocyanines* **13** 408 (2009)
36. A C Tome, P S S Lacerda, A M G Silva, M G P M S Neves, J A S Cavaleiro *J. Porphyrins Phthalocyanines* **4** 532 (2000)
37. T Fukuda, N Kobayashi *Dalton Trans.* 4685 (2008)
38. H Fischer, K Platz, H Helberger, H Niemer *Ann. Chem.* **479** 26 (1930)

39. H Fischer, P Rothemund *Ber. Dtsch. Chem. Ges.* **64** 201 (1931)
40. W Schlesinger, A H Corwin, L J Sargent *J. Am. Chem. Soc.* **72** 2867 (1950)
41. H H Inhoffen, J W Buchler, R Thomas *Tetrahedron Lett.* **10** 1141 (1969)
42. H H Inhoffen, J W Buchler, R Thomas *Tetrahedron Lett.* **10** 1145 (1969)
43. M W Wicks, P L Burn *J. Porphyrins Phthalocyanines* **9** 444 (2005)
44. G D Dorough, J R Miller *J. Am. Chem. Soc.* **74** 6106 (1952)
45. G E Ficken, R P Linstead, E Stephen, M Whalley *J. Chem. Soc.* 3879 (1958)
46. H W Whitlock Jr, R Hanauer, M Y Oester, B K Bower *J. Am. Chem. Soc.* **91** 7485 (1969)
47. R Bonnett, R D White, U J Winfield, M C Berenbaum *Biochem. J.* **261** 277 (1989)
48. A M Stolzenberg, S W Simerly, B D Steffey, G S Haymond *J. Am. Chem. Soc.* **119** 11843 (1997)
49. Patent RF 2479585 (2013); *Chem. Abstr.* **158** 585515 (2013)
50. S V Dudkin, Candidate Thesis in Chemical Science, SSC NIOPIK, Moscow, 2012
51. R I Yakubovskaya, N B Morozova, A D Plutinskaya, V I Chissov, E A Lukyanets, G N Vorozhtsov, E A Makarova, S V Dudkin, A P Shchukina, in *Book of Abstracts of Deutsch – Russisches Onkologie Symposium, Munich, 2010* p. 21
52. M Pineiro, A M d'A Rocha Gonsalves, M M Pereira, S J Formosinho, L G Arnaut *J. Phys. Chem. A* **106** 3787 (2002)
53. Patent FR 2877943 (2006); *Chem. Abstr.* **144** 445349 (2006)
54. M M Pereira, C J P Monteiro, A V C Simões, S M A Pinto, L G Arnaut, G F F Sá, E F F Silva, L B Rocha, S Simões, S J Formosinho *J. Porphyrins Phthalocyanines* **13** 567 (2009)
55. B F O Nascimento, M d'A Rocha Gonsalves, M Pineiro *Inorg. Chem. Commun.* **13** 395 (2010)
56. M M Pereira, C J P Monteiro, A V C Simões, S M A Pinto, A R Abreu, G F F Sá, E F F Silva, L B Rocha, J M Dabrowski, S J Formosinho, S Simões, L G Arnaut *Tetrahedron* **66** 9545 (2010)
57. M M Pereira, A R Abreu, N P F Gonsalves, M J F Calvete, A V C Simoões, C J P Monteiro, L G Arnaut, M E Eusébio, J Canotilho *Green Chem.* **14** 1666 (2012)
58. B Krattinger, H J Callot *Tetrahedron Lett.* **39** 1165 (1998)
59. B Krattinger, H J Callot *Eur. J. Org. Chem.* 1857 (1999)
60. M O Senge, W W Kalisch, I Bischoff *Chem. – Eur. J.* **6** 2721 (2000)
61. S Vagin, M Hanack, B Kammerer, A Frickenschmidt *Eur. J. Org. Chem.* 4245 (2004)
62. H Fischer, H Eckoldt *Liebigs Ann. Chem.* **544** 138 (1940)
63. H Fischer, H Pfeiffer *Liebigs Ann. Chem.* **556** 131 (1944)
64. C K Chang, C Sotiriou *J. Org. Chem.* **50** 4989 (1985)
65. C Brückner, D Dolphin *Tetrahedron Lett.* **36** 3295 (1995)
66. L P Samankumara, M Zeller, J A Krause, C Brückner *Org. Biomol. Chem.* **8** 1951 (2010)
67. J K MacAlpine, R Boch, D Dolphin *J. Porphyrins Phthalocyanines* **6** 146 (2002)
68. R Bonnett, A N Nizhnik, M C Berenbaum *J. Chem. Soc., Chem. Commun.* 1822 (1989)
69. K R Adams, M C Berenbaum, R Bonnett, A N Nizhnik, A Salgado M A Valles *J. Chem. Soc., Perkin Trans. 1* 1465 (1992)
70. M A Hyland, M D Morton, C Brückner *J. Org. Chem.* **77** 3038 (2012)
71. C K Chang, C Sotiriou, W Wu *J. Chem. Soc., Chem. Commun.* 1213 (1986)
72. C Brückner, D Dolphin *Tetrahedron Lett.* **36** 9425 (1995)
73. J M Sutton, N Fernandez, R W Boyle *J. Porphyrins Phthalocyanines* **4** 655 (2000)
74. J M Sutton, O J Clarke, N Fernandez, R W Boyle *Bioconjug. Chem.* **13** 249 (2002)
75. J R McCarthy, J Bhaumik, N Merbouh, R Weissleder *Org. Biomol. Chem.***7** 3430 (2009)
76. K K Lara, C R Rinaldo, C Brückner *Tetrahedron Lett.* **44** 7793 (2003)
77. K K Lara, C R Rinaldo, C Brückner *Tetrahedron* **61** 2529 (2005)
78. H Nie, C Stern, A G Barrett, B M Hoffman *Chem. Commun.* 703 (1999)
79. A C Tome, P S S Laserda, M G P M S Neves, J A S Cavaleiro *Chem. Commun.* 1199 (1997)
80. M G H Vicente, M T Cancilla, C B Lebrilla, K M Smith *Chem. Commun.* 2355 (1998)
81. S Zhao, M G P M S Neves, A C Tome, A M S Silva, J A S Cavaleiro, M R M Domingues, A J F Correira *Tetrahedron Lett.* **46** 2189 (2005)
82. S Ostrowski, P Wyrebek *Tetrahedron Lett.* **47** 8437 (2006)
83. A M G Silva, A C Tome, M G P M S Neves, J A S Cavaleiro *Tetrahedron Lett.* **41** 3065 (2000)
84. A M G Silva, A C Tome, M G P M S Neves, J A S Cavaleiro, C O Kappe *Tetrahedron Lett.* **46** 4723 (2005)
85. E A Makarova, G V Korolyova, O L Tok, E A Lukyanets *J. Porphyrins Phthalocyanines* **4** 525 (2000)
86. H Miwa, E A Makarova, K Ishii, E A Lukyanets, N Kobayashi *Chem. – Eur. J.* **8** 1082 (2002)
87. S V Dudkin, E A Makarova, E A Lukyanets *Russ. J. Gen. Chem.* **78** 1441 (2008) [*Zh. Obshch. Khim.* **78** 1208 (2008)]
88. H J Callott, A W Johnson, A Sweeney *J. Chem. Soc., Perkin Trans. 1* 1424 (1973)
89. A R Morgan, V S Pangka, D Dolphin *J. Chem. Soc., Chem. Commun.* 1047 (1984)
90. R K DiNello, D Dolphin *J. Org. Chem.* **45** 5196 (1980)
91. K T de Oliveira, A M S Silva, A C Tome, M G P M S Neves, C R Neri, V S Garcia, O A Serra, Y Iamamoto, J A S Cavaleiro *Tetrahedron* **64** 8709 (2008)
92. A F Uchoa, K T de Oliveira, M S Baptista, A J Bortoluzzi, Y Iamamoto, O S Serra *J. Org. Chem.* **76** 8824 (2011)
93. J A S Cavaleiro, A H Jackson, M G P M S Neves, K R N Rao *J. Chem. Soc., Chem. Commun.* 776 (1985)
94. R K Pandey, F-Y Shiau, K Ramachndran, T J Dougerty, K M Smith *J. Chem. Soc., Perkin Trans. 1* 1377 (1992)
95. M A F Faustino, M G P M S Neves, M G H Vicente, A M S Silva, J A S Cavaleiro *Tetrahedron Lett.* **37** 3569 (1996)
96. M A F Faustino, M G P M S Neves, A M S Silva, J A S Cavaleiro *Chimia* **51** 472 (1997)
97. I Mounier, R K Pandey, M O Senge, T J Dougherty, K M Smith *J. Chem. Soc., Perkin Trans. 1* 961 (1994)
98. P Yon-Hin, T P Wijesekera, D Dolphin *Tetrahedron Lett.* **32** 2875 (1991)
99. A M G Silva, A C Tome, M G P M S Neves, A M S Silva, J A S Cavaleiro *Chem. Commun.* 1767 (1999)
100. A M G Silva, A C Tome, M G P M S Neves, A M S Silva, J A S Cavaleiro *J. Org. Chem.* **70** 2306 (2005)
101. M Obata, S Hirohara, R Tanaka, S Kinoshita, K Ohkubo, S Fukuzumi, M Tanihara, Y Yano *J. Med. Chem.* **52** 2747 (2009)
102. D T Gryko, M Galezowski *Org. Lett.* **7** 1749 (2005)
103. M Galezowski, D T Gryko *J. Org. Chem.* **71** 5942 (2006)
104. A P J Maestrin, A O Ribeiro, A C Tedesco, C R Neri, F S Vinhado, O A Serra, P R Martins, Y Iamamoto, A M G Silva, A C Tome, M G P M S Neves, J A S Cavaleiro *J. Braz. Chem. Soc.* **15** 923 (2004)
105. F F de Assis, J M de Souza, B H K Assis, T J Brocksom, K T de Oliveira *Dyes Pigm.* **98** 153 (2013)
106. A M G Silva, A C Tome, M G P M S Neves, J A S Cavaleiro, D Perrone, A Dondoni *Synlett* 857 (2005)
107. P Saravan, A R Suresh Babu, R Raghunathan *Synt. Commun.* **40** 2329 (2010)

108. A M G Silva, A C Tome, M G P M S Neves, A M S Silva, J A S Cavaleiro, D Perrone, A Dondoni *Tetrahedron Lett*. **43** 603 (2002)
109. M M Ebrahim, M Moreau, M O Senge *Heterocycles* **83** 627 (2011)
110. G Jimenez-Oses, J I Garcia, A M G Silva, A R N Santos, A C Tome, M G P M S Neves, J A S Cavaleiro *Tetrahedron* **64** 7937 (2008)
111. J Flemming, D Dolphin *Tetrahedron Lett*. **43** 7281 (2002)
112. X Li, J Zhuang, Y Li, H Liu, S Wang, D Zhu *Tetrahedron Lett*. **46** 1555 (2005)
113. X Liu, Y Feng, X Chen, F Li, X Li *Synlett* 1030 (2005)
114. X Liu, Y Feng, X Hu, X Li *Synthesis* 3632 (2005)
115. S Ostrowski, P Wyrebek, A Mikus *Heterocycles* **68** 885 (2006)
116. P Wyrebek, A Mikus, S Ostrowski *Heterocycles* **85** 57 (2012)
117. N M M Moura, F Guintini, M A F Faustino, M G P M S Neves, A C Tome, A M S Silva, E M Rakib, A Hannioni, S Abouricha, B Roder, J A S Cavaleiro *ARKIVOC* (v) 24 (2010)
118. P Wyrebek, S Ostrowski *Bull. Chem. Soc. Jpn*. **85** 1167 (2012)
119. A M G Silva, A C Tome, M G P M S Neves, J A S Cavaleiro *Synlett* 1155 (2002)
120. A Desjardins, J Flemming, E D Sternberg, D Dolphin *Chem. Commun*. 2622 (2002)
121. E A Makarova, E A Lukyanets, in *Book of Abstracts of 20th International Congress of Heterocyclic Chemistry, Palermo, 2005* p. 503
122. S V Dudkin, E A Makarova, E A Lukyanets, in *Tezisy Dokladov 11-i Mezhdunarodnoi Konferentsii po Fizicheskoi i Koordinatsionnoi Khimii Porfirinov i Ikh Analogov (ICPC-11)* [Book of Abstracts of the 11th International Conference on Physical and Coordination Chemistry of Porphyrins and Their Analogues (ICPC-11), Odessa 2011] p. 51
123. E A Makarova, E A Lukyanets *J. Porphyrins Phthalocyanines* **8** 760 (2004)
124. A M G Silva, P S S Lacerda, A C Tome, M G P M S Neves, A M S Silva, J A S Cavaleiro, E A Makarova, E A Lukyanets *J. Org. Chem*. **71** 8352 (2006)
125. H J Callot, A W Johnson *J. Chem. Soc., Chem. Commun*. 749 (1969)
126. H J Callot *Tetrahedron Lett*. 1011 (1972)
127. A T P C Gomes, R A C Leao, C M A Alonso, M G P M S Neves, M A F Faustino, A C Tome, A M S Silva, S Pinheiro, M C B V de Souza, V F Ferreira, J A S Cavaleiro *Helv. Chim. Acta* **91** 2270 (2008)
128. A T P C Gomes, R A C Leao, F C da Silva, M G P M S Neves, M A F Faustino, A C Tome, A M S Silva, S Pinheiro, M C B V de Souza, V F Ferreira, J A S Cavaleiro *J. Porphyrins Phthalocyanines* **13** 247 (2009)
129. N A M Pereira, A C Serra, T M V D Pinho e Melo *Eur. J. Org. Chem*. 6539 (2010)
130. N A M Pereira, S M Fonseca, A C Serra, T M V D Pinho e Melo, H D Burrows *Eur. J. Org. Chem*. 3970 (2011)
131. L Jaquinod, C Gros, M M Olmstead, M Antolovich, K M Smith *J. Chem. Soc., Chem. Commun*. 1475 (1996)
132. L Jaquinod, S Gros, R G Khoury, K M Smith *J. Chem. Soc., Chem. Commun*. 2581 (1996)
133. U Eisner, R P Linstead *J. Chem. Soc*. 3742 (1955)
134. J-P Strachan, D F O'Shea, T Balasubramanian, J S Lindsey *J. Org. Chem*. **65** 3160 (2000)
135. T Balasubramanian, J-P Strachan, P D Boyle, J S Lindsey *J. Org. Chem*. **65** 7919 (2000)
136. D Ra, K A Gauger, K Muthukumaran, T Balasubramanian, V Chandrashaker, M Taniguchi, Z Yu, D C Talley, M Ehudin, M Ptaszek, J S Lindsey *J. Porphyrins Phthalocyanines* **19** 547 (2015)
137. J K Laha, C Muthiah, M Taniguchi, B E McDowell, M Ptaszek, J S Lindsey *J. Org. Chem*. **71** 4092 (2006)
138. K Aravindu, H-J Kim, M Taniguchi, P L Dilbeck, J R Dier, D F Bocian, D Holten, J S Lindsey *Photochem. Photobiol. Sci*. **12** 2089 (2013)
139. M Ptaszek, D Lahaye, M Krayer, C Muthiah, J S Lindsey *J. Org. Chem*. **75** 1659 (2010)
140. M Liu, M Ptaszek, O Mass, D J Minkler, R D Sommer, J Bhaumik, J S Lindsey *New J. Chem*. **38** 1717 (2014)
141. H-J Kim, J S Lindsey *J. Org. Chem*. **70** 5475 (2005)
142. M Taniguchi, D L Cramer, A D Bhise, H L Kee, D F Bocian, D Holten, J S Lindsey *New J. Chem*. **32** 947 (2008)
143. K R Reddy, E Lubian, M P Pavan, H-Y Kim, E Yang, D Holten, J S Lindsey *New J. Chem*. **37** 1157 (2013)
144. M Krayer, M Plaszek, H-J Kim, K R Meneely, D Fan, K Secor, J S Lindsey *J. Org. Chem*. **75** 1016 (2010)
145. M Krayer, E Yang, H-J Kim, H L Kee, R M Deans, C E Sluder, J R Diers, C Kirmaier, D F Bocian, D Holten, J S Lindsey *Inorg. Chem*. **50** 4607 (2011)
146. K Aravindu, M Krayer, H-J Kim, J S Lindsey *New J. Chem*. **35** 1376 (2011)
147. E A Makarova, G V Koroleva, E A Lukyanets *Russ. J. Gen. Chem*. **69** 1306 (1999) [*Zh. Obshch. Khim*. **69** 1356 (1999)]
148. V N Kopranenkov, E A Lukyanets *Russ. Chem. Bull*. **44** 2216 (1995) [*Izv. Akad. Nauk, Ser. Khim*. 2320 (1995)]
149. N Kobayashi, in *The Porphyrin Handbook* Vol. 2 (Eds K M Kadish, K M Smith, R Guilard) (San Diego, CA: Academic Press, 1999) p. 301
150. J A Elvidge, R P Linstead *J. Chem. Soc*. 3536 (1955)
151. V N Kopranenkov, A M Tsygankova, E A Lukyanets *Anilinokrasochnaya Prom-st'* (5) 1 (1979)
152. Patent RF 2188200 (2002); *Chem. Abstr*. **138** 368675 (2003)
153. E A Makarova, S V Dudkin, E A Lukyanets *J. Porphyrins Phthalocyanines* **17** 785 (2013)
154. Patent RF 2479586 (2013); *Chem. Abstr*. **158** 534643 (2013)
155. T Fukuda, E A Makarova, E A Lukyanets, N Kobayashi *Chem. – Eur. J*. **10** 117 (2004)
156. E A Makarova, T Fukuda, E A Lukyanets, N Kobayashi *Chem. – Eur. J*. **11** 1235 (2005)
157. E A Makarova, E V Dzyuina, E A Lukyanets *Russ. J. Gen. Chem*. **76** 1165 (2006) [*Zh. Obshch. Khim*. **76** 1213 (2006)]
158. E A Makarova, E V Dzyuina, T Fukuda, H Kaneko, N Hashimoto, Y Kikukawa, N Kobayashi, E A Lukyanets *Inorg. Chem*. **48** 164 (2009)
159. T Fukuda, Y Ogi, N Kobayashi *Chem. Commun*. 159 (2006)
160. P P Pershukevich, V A Galievsky, A S Stasheuski, E A Makarova, E A Lukyanets, K N Solovyov *J. Appl. Spectrosc*. **77** 790 (2011) [*Zh. Prikl. Spektrosk*. **77** 852 (2011)]
161. T Fukuda, S Masuda, N Kobayashi *J. Am. Chem Soc*. **129** 5472 (2007)
162. T Fukuda, S Masuda, N Hashimoto, N Kobayashi *Inorg. Chem*. **47** 2576 (2008)
163. T Fukuda, H Kaneko, N Kobayashi *J. Porphyrins Phthalocyanines* **13** 999 (2009)
164. T Fukuda, I Sugita, N Kobayashi *Chem. Commun*. 3449 (2009)
165. K I Ozoemena, S A Mamuru, T Fukuda, N Kobayashi, T Nyokong *Electrochem. Commun*. **11** 1221 (2009)
166. E A Makarova, T Fukuda, N Kobayashi, E A Lukyanets, in *Trudy 9-i Mezhdunarodnoi Konferentsii po Khimii Porfirinov i Ikh Analogov* (Proceedings of the 9th International Conference on the Chemistry of Porphyrins and Their Analogues, Suzdal', 2003) p. 23
167. S V Dudkin, E A Makarova, T Fukuda, N Kobayashi, E A Lukyanets *Tetrahedron Lett*. **52** 2994 (2011)
168. E A Makarova, E A Lukyanets, in *Book of Abstracts of the 6th International Conference on Porphyrins and Phthalocyanines, New Mexico, 2010* p. 379