Porphyrinoids
Порфириноиды

Макрогетероциклы

http://macroheterocycles.isuct.ru

Review
Обзор

Functionalized 2,2′−Bipyrroles: Building Blocks for Pyrrolic Macrocycles

Gonzalo Anguera,[a,b] James T. Brewster II,[a] David Sánchez-García,[b] and Jonathan L. Sessler[a@]

[a]Department of Chemistry, the University of Texas at Austin, A5300 Austin, 78712-1224 Texas, United States
[b]Grup d'Enginyeria de Materials (GEMAT), Institut Químic de Sarrià, Universitat Ramon Llull, 08017 Barcelona, Spain
[@]Corresponding author E-mail: sessler@cm.utexas.edu

Functionalized N-unsubstituted 2,2'-bipyrroles are basic building blocks for the preparation of pyrrolic macrocycles and natural products, such as prodigiosines. The aim of this review is to provide a description of the most important methodologies used to prepare 2,2'-bipyrroles and their central role as building blocks for the synthesis of porphyrinoids and property-defining structural elements therein.

Keywords: 2,2'-Bipyrroles, macrocycles, expanded porphyrins, oligopyrroles.

Функционализированные 2,2′−бипирролы: строительные блоки для пиррольных макроциклов

Г. Ангуера,[a,b] Д. Т. Брюстер II,[a] Д. Санчез-Гарсиа,[b] Д. Л. Сесслер[a@]

[a]Техасский университет, A5300 Остин, 78712-1224 Техас, США
[b]Химический институт Сарриа, Университет Рамона Льюлла, 08017 Барселона, Испания
[@]E-mail: sessler@cm.utexas.edu

Функционализированные N-незамещенные 2,2'-бипирролы являются основными строительными блоками для синтеза пиррол-содержащих макроциклов и таких природных соединений, как продигиозины. В обзоре представлены наиболее важные методики синтеза и функционализации 2,2'-бипирролов, а также наиболее важных порфириноидов и расширенных порфиринов на их основе.

Ключевые слова: 2,2'-Бипирролы, макроциклы, расширенные порфирины, олигопирролы.

Introduction

Heterocycles represent a privileged class of compounds that have seen utility across a wide range of application areas and which play essential roles in the chemical and medicinal sciences.[1] Of the known heterocycles, pyrrole is one of the simplest. This five-membered heteroaromatic ring compound is characterized by its reactivity; indeed, it is more prone towards electrophilic attack than its related furan or thiophene congeners. It also possesses three sites for potential functionalization (the α- and β-pyrrolic positions and the proton-bearing N).[2–4] Since its discovery in 1834 as a component of coal tar,[5] pyrrole and its derivatives have been found as an integral functionality in numerous natural products (Scheme 1).[6] Not surprisingly, the preparation and modification of pyrrole has been the focus of many research programs with concomitant attention devoted to the synthesis of pyrrole-incorporated therapeutics,[7] supramolecular constructs,[8] and functional materials.[9]

Acyclic synthetic and natural compounds containing pyrrole typically comprise a modified pyrrole-core integrated within more complex structural motifs, such as 2,2'-bipyrrole. Systems incorporating 2,2'-bipyrrole-based building blocks are now found extensively in the literature (Scheme 2).[70] However, practical applications of these systems rely on compound availability. This, in turn, requires the development of appropriate synthetic methods that furnish the requisite functionalized starting materials, particularly

those with suitable physical properties, such as solubility, controlled light absorption, and stability, among other desirable characteristics. There are a number of reviews focused on the preparation of pyrrole[11,12] and pyrrole-based building blocks.[13,14] Some that encompass the preparation of 2,2'-bipyrroles, as well as other functional precursors, such as naphthobipyrroles,[15,16] benzobipyrroles,[17] or Bröring's conformationally restricted 2,2'-bipyrrole,[18] have appeared in recent years.[19–24] Furthermore, in 2017 Setsune published a review highlighting recent advances in 2,2'-bipyrrole-based porphyrinoids with a section devoted to preparative methods.[20] Nevertheless, a dedicated overview of the synthetic literature regarding bipyrroles with an update on recent applications is viewed as something that could complement prior reviews while stimulating further research progress in the area of oligopyrrolic materials.[16–18,25] Our goal is to provide such a survey. In providing this overview, we also review the chemistry of synthetic macrocycles wherein bipyrrole is used as a key synthetic building block. Not covered are systems, such as corroles and corrins, that contain bipyrroles (or bipyrrole derivatives) but whose mode of preparation does not pass through a bipyrrolic intermediate. We view the discussion provided in the present summary as being complementary to that provided by Setsune.[20]
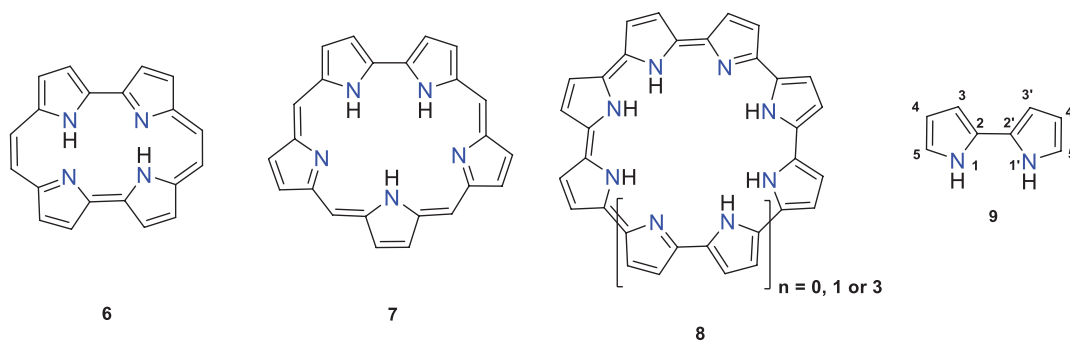
Synthesis of 2,2'-Bipyrroles

First synthesis of a 2,2'-bipyrrole

The first method detailing a purported synthesis of 2,2'-bipyrrole reported by Grabowski and Marchlewski and involved out combining so-called hämopyrrol (**10**) and 4-methylbenzenediazonium chloride (**11**) *"und längere zeit stehen gelassen"* (and leaving to stand for some time) to yield **12** as blue crystals, as determined by elemental analysis (Scheme 3).[26] Reanalysis of this work by Webb and Threlkeld led to the proposal that the blue crystals obtained by Grabowski and Marchlewski were in fact 2-pyrryl-2-pyrrolenine salts.[27,28]
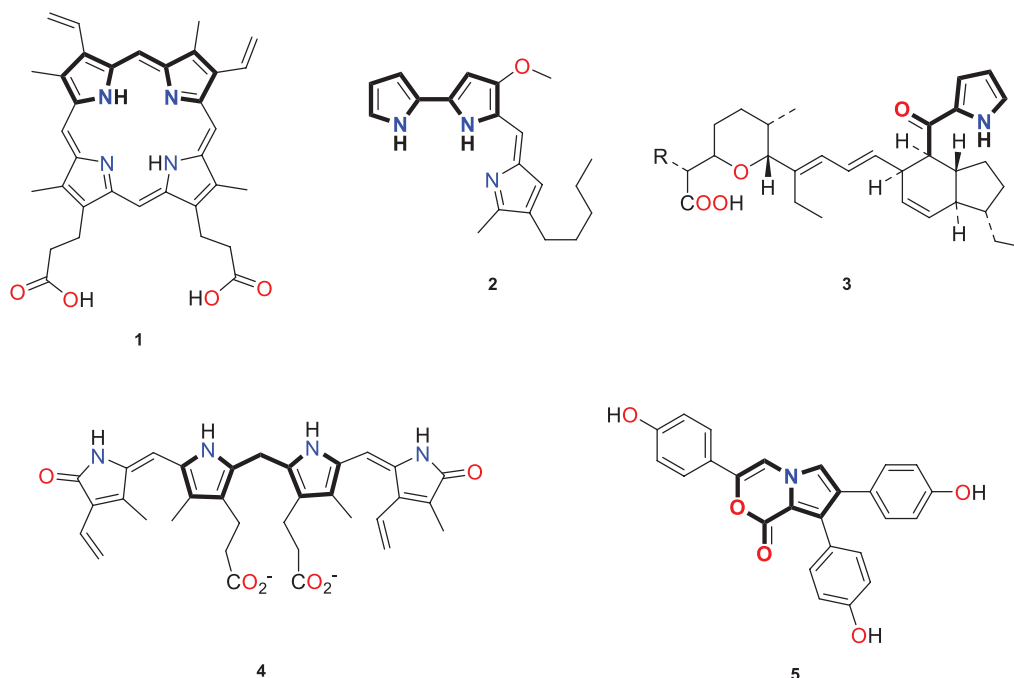
Scheme 1. Selected natural products containing pyrrole: Protoporphyrin IX (**1**), prodigiosin (**2**), indanomicine (**3**), bilirubin (**4**), and lukianol (**5**).

Scheme 2. Synthetic porphyrinoids containing one or more 2,2'-bipyrrole (**9**) motifs: porphycene (**6**), sapphyrin (**7**) and cyclo[n]pyrroles (**8**).
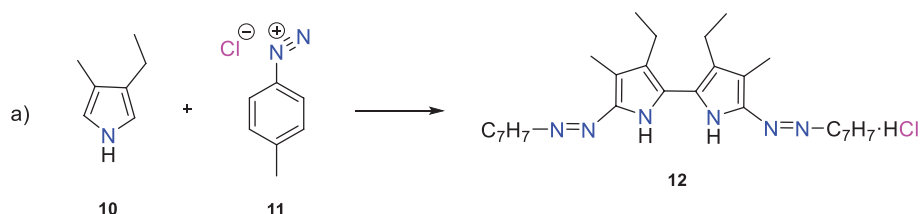
Scheme 3. Preparation of the first 2,2'-bipyrrole by Grabowski and Marchlewski.[26]

Syntheses using the Vilsmeier-Haack reaction

Inspired by the fact that the 2,2'-bipyrrole motif is a key structural component of prodigiosin (**2**), Rapoport and co-workers sought to develop new routes amenable to the preparation of asymmetric 2,2'-bipyrroles.[29] Utilizing methods developed by Fuhlhage and Van der Werf wherein pyrrole was condensed with 1-pyrroline to yield 2-(pyrrolidin-2-yl)pyrrole (**15**, Scheme 4a),[30] Rapoport and co-workers were able to obtain an asymmetric 2-(pyrrolidin-2-yl)pyrrole (**17**).[31] The presence of an ester group on the α-position of the starting pyrrole was shown to deactivate the pyrrole and prevent formation of the 2,2'-pyrrolidinylpyrrole. The introduction of a β-methoxy group was able to counteract this latter deactivation effect, allowing for the preparation of intermediate **17** (Scheme 4b). The desired 2,2'-bipyrrole was obtained in a 40 % yield *via* dehydrogenation of **17** using Pd/C at elevated temperature (Scheme 4b). The synthesis was later modified by way of a Vilsmeier-Haack reaction between 2-pyrrolidinone and pyrrole yielding 5-(pyrrol-2-yl)-3,4-dihydro-2*H*-pyrrole in improved yields (Scheme 4c).[32] The so-called Rapoport bipyrrole synthesis would later include various pyrrole and 2-pyrrolidinone analogues, thus expanding the substrate scope and allowing access to various asymmetric species.[33] In a continuation of these efforts, Rapoport and Bordner would also develop a route yielding asymmetric 2,2'-bipyrroles directly from 1,5-dihydropyrrol-2-ones of general structure **23** and pyrrole (Scheme 4d).[33]

In pursuit of new methods for the facile construction of prodigiosin-type natural products, Hao and co-workers described a one-pot synthesis of pyrrolyldipyrromethenes from 5-halogenated-2-formylpyrrole (Scheme 5).[34] This synthesis relies on the use of POCl$_3$ to generate an intermediate 9-halodipyrromethene **25**, which readily undergoes nucleophilic aromatic substitution to yield the target pyrrolyldipyrromethenes **26** in 41–79 % yield. Mechanistic studies supported the intermediacy of a 9-halodipyrromethene **25** that undergoes a subsequent S$_N$Ar reacton with pyrrole to yield the corresponding pyrrolyldipyrromethenes in 51–90 % yield.
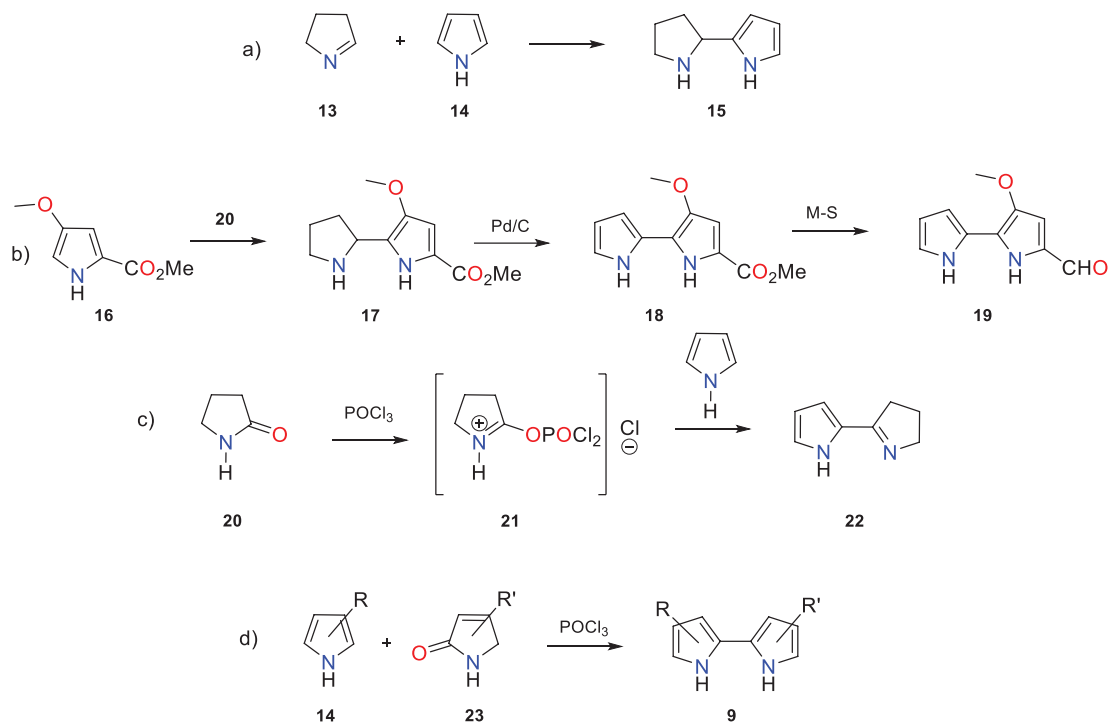

Scheme 4. Dehydrogenation of 2,2'-pyrrolidinylpyrrole **15** (a). Preparation of 2,2'-bipyrrole **17**, used as a building block for the synthesis of prodigiosin (b). Synthesis of 2,2'-(1-pyrrolyl)pyrrole **22** by means of a Vilsmeier-Haack reaction (c). Synthesis of 2,2'-bipyrrole **9** (d).
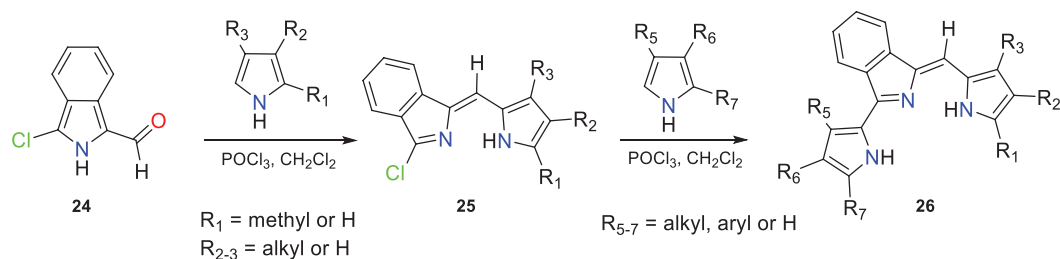
Scheme 5. Synthesis of pyrrolyldipyrromethenes **26** from 5-halogenated 2-acylpyrroles as detailed by Hao, *et al.*[34]

Syntheses using the Paal-Knorr reaction

With a view to preparing natural products containing 1,2'-, 1,3'-, and 2,2'-bipyrrole subunits, Gribble and co-workers described the preparation of 2,2'-bipyrroles in a three-steps sequence involving the Paal-Knorr reaction (Scheme 6).[35] Treatment of pyrrole ketoaldehyde (**28**) with benzylamine and acetic acid in methanol led to a series of *N*-substituted-2,2'-bipyrroles (**29**) in 30–96 % yield. The resulting bipyrroles could be readily halogenated to give polyhalogenated bipyrrolyl natural products.
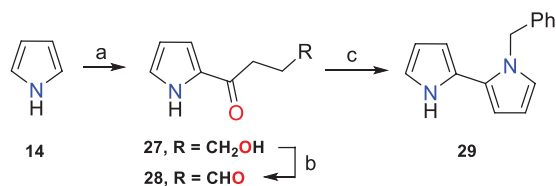

Scheme 6. Synthesis of 2,2'-bipyrrole **29** as described by Gribble *et al.*[35] a) Butyrolactone, MeMgI, toluene, 89 %. b) PCC, NaOAc, CH$_2$Cl$_2$, 92 %. c) PhCH$_2$NH$_2$, AcOH, MeOH, 81 %.

Synthesis using the Ullmann coupling

Initial attempts to synthesize *N,N*'-disubstituted and *N,N*'-unsubstituted-2,2'-bipyrroles were focused on the Ullmann coupling using a mixture of copper powder and 2-halopyrrole without solvent at high temperature (160–200 °C), as reported by Webb and Threlkeld (Scheme 7a,b).[27,28] Interestingly, introduction of ethoxycarbonyl groups attenuated the reactivity of the pyrrole and allowed for preparation of *N*-substituted iodopyrrole with subsequent coupling furnishing 2,2'-bipyrrole in 58.6 % yield. In the context of *N*-unsubstituted pyrrole, the authors found that upon switching from a 2-iodo- to 2-bromopyrrole, bipyrrole could be readily prepared in 54 % yield (Scheme 7b). Although limited in terms of substrate scope, Webb and Threlkeld had demonstrated the ability to control pyrrole reactivity while detailing a facile preparation of symmetric 2,2'-bipyrroles.

In pursuit of new methods allowing for the preparation of 5,5'-unsubstituted-2,2'-bipyrroles en route to modified porphyrin rings, Grigg and co-workers optimized the Webb and Threlkeld procedure. The judicious placement of ethoxycarbonyl groups in the α-position permitted the preparation
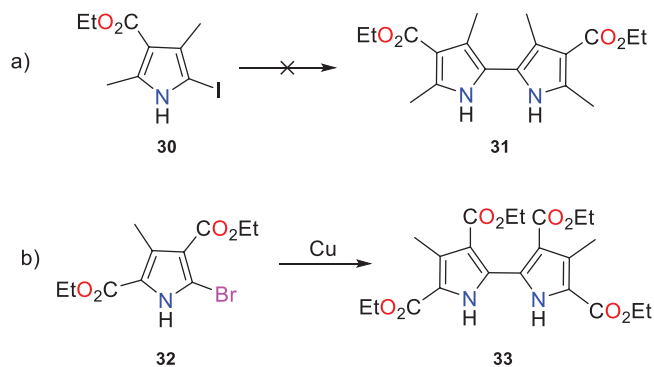

Scheme 7. Preparation of 2,2'-bipyrroles by means of an Ullman coupling. Attempted synthesis of **31** (a). Ullmann coupling as used in the synthesis of **33** (b).[27,28]

and use of 2-iodopyrroles in the Ullmann coupling protocol. Furthermore, by carrying out the coupling in *N,N*-dimethylformamide the temperature could be reduced to 100 °C. In some instances, the reaction could even be completed at room temperature (Scheme 8).[12] The ethoxycarbonyl groups also served as a functional handle allowing for saponification and decarboxylation to yield 5,5'-unsubstituted-2,2'-bipyrrole **36** (Scheme 8). Various substitution patterns were explored in the β-position with the authors noting that alkyl-2,2'-bipyrroles are unstable to air, acid, and turn first green and then blue in a few hours after exposure to air. Upon revisiting this route, Sessler and co-workers demonstrated that BOC-protection of the pyrrole nitrogen improved the yield of the bipyrrole by 20–30 %.[36]

In celebrated chemistry associated with efforts to prepare the corrin core of vitamin B$_{12}$, Woodward and co-workers sought to cyclize a tetrapyrrolic precursor using formic acid and HBr followed by oxidation with iodine. In pursuing this chemistry, the Harvard group serendipitously isolated a deep blue solid that they named sapphyrin (**39**). This penta-aza macrocycle may be considered as being a "heterocycle-inserted" expanded porphyrin that contains both 2,2'-bipyrrole and a tripyrrane moieties. In an attempt to study further extensions of the π-system, as well as the coordination chemistry, an optimized synthesis was developed; it involved a 3+2 coupling of 5,5'-diformylated-2,2'-bipyrrole **37** with tripyrrane dicarboxylate **38** (Scheme 8).[22]

The Harvard group also reported a new route towards 2,2'-bipyrroles by way of cyanoacrylate protected aldehydes (**41**, Scheme 9). Here, a copper catalyzed Ullmann
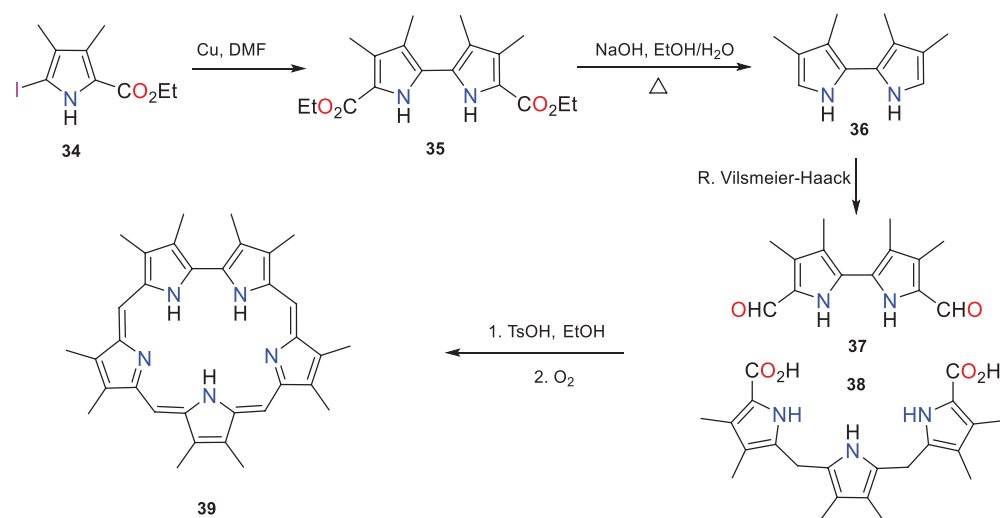
Scheme 8. Synthesis of sapphyrin **39**.[22]
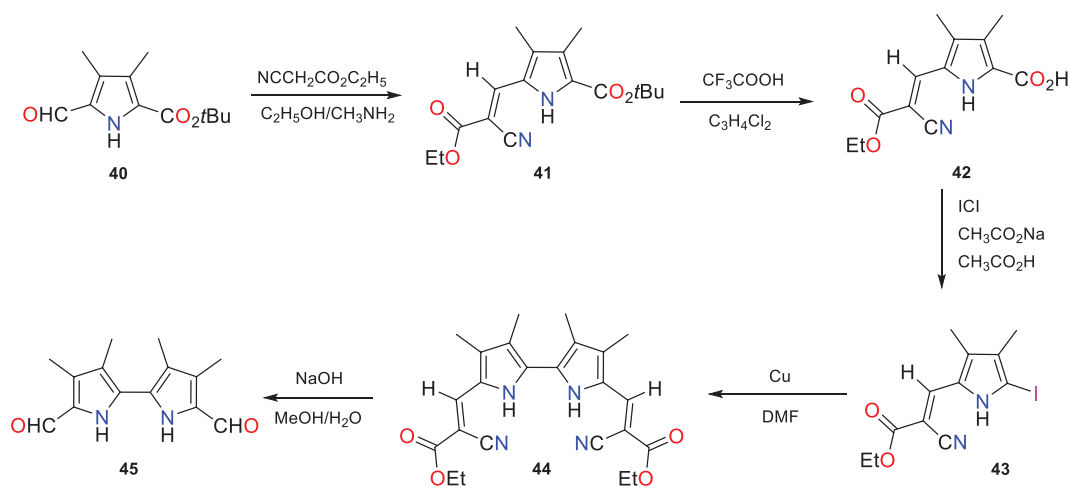
**Scheme 9**. Production of a diformylated 2,2'-bipyrrole by means of an Ullmann coupling-based strategy.[37]

coupling between the cyanoacrylate of the iodopyrrole **43** furnished bipyrrole **44** in about 35 % yield.[37] Although the yield was lower than that afford by the Ullman coupling of the monoester as described separately by Grigg,[22] this newer route afforded the bipyrrole dialdehyde (**45**) after retro-Knoevenagel reaction of the cyanoacrylate **44**. This

modification obviated the need for hydrolysis of the ethyl ester and follow-up decarboxylation and formylation.

As part of their respective efforts to prepare porphyrinoids incorporating 2,2'-bipyrrole subunits, the groups of Vogel and Nonell modified the common approach involving decarboxylation of the 5,5'-carboxylate-2,2'-
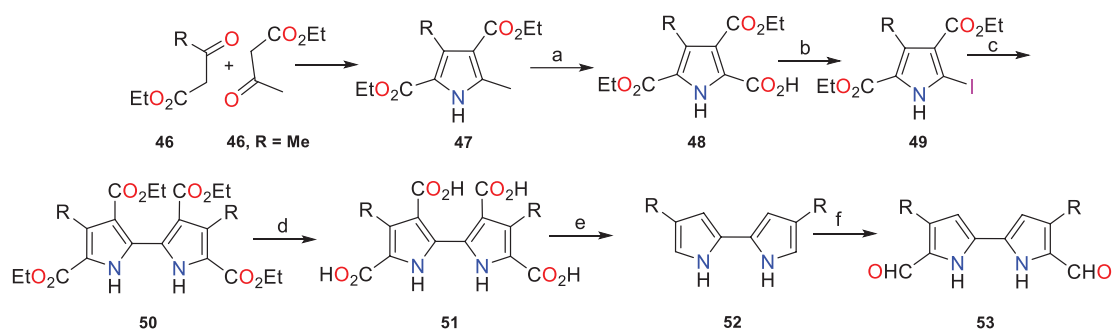
Scheme 10. Synthesis of bipyrrole **53** as a precursor in the preparation of porphycene. a) Br_2, SO_2Cl_2, AcOH/HCOOH, 0 °C, 4 h (50–58 %). b) KI/I_2, EtOH/H$_2$O, 75 °C (75–77 %). c) Cu, DMF, 20 °C, 17 h (61–71 %). d) NaOH, EtOH/H$_2$O, 15 h, reflux (96 %). e) Sublimation 230 °C, 0.2 torr (89 %). f) POCl$_3$/DMF, NaOAc/H$_2$O (86 %).[21,38]
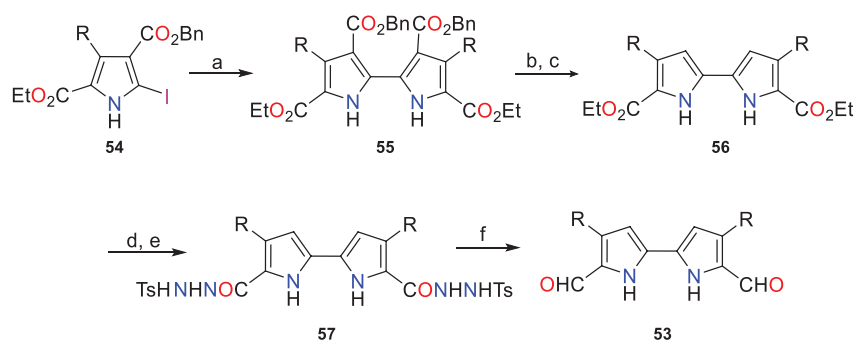
Scheme 11. Non-decarboxylative synthesis of diformyl-2,2'-bipyrroles. Reaction conditions: a) Cu, DMF, 23 °C.
b) Pd/C, HCOOH/HCOONH$_4$, reflux, 4 h (100 %). c) EG, 170 °C, 5 h (93 %). d) NH$_2$-NH$_2$, EtOH, reflux, 48 h (93 %).
e) TsCl, pyridine, 23 °C, 1 h (96 %). f) ethylene glycol, Na$_2$CO$_3$, 170 °C (92 %).[39]
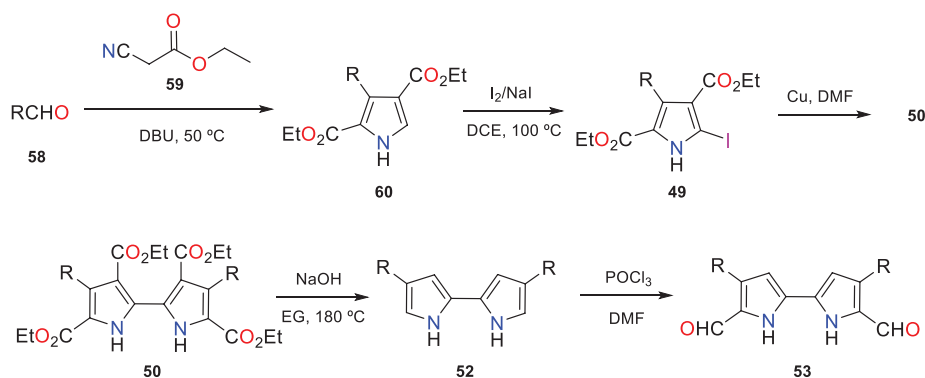
**Scheme 12.** Synthesis of pyrroles from aldehydes and subsequent Ullman coupling to 2,2'-bipyroles.[40]

bipyrrole (**51**) (Scheme 10).[21,38] Vogel and co-workers switched to a sublimation step to enact decarboxylation, while the Nonell group used sodium hydroxide in ethylene glycol at high temperature. Through these latter modifications, Nonell, *et al.* were able to carry gram scale quantities of 5,5'-carboxylate-2,2'-bipyrrole through the subsequent decarboxylation and formylation steps to give 5,5'-formyl-2,2'-bipyrrole in approximately 30 % yield over two steps.

It was also reported by Stockert and co-workers that the unstable α-free bipyrrole could be bypassed by utilizing bipyrrole-2,2'-dicarbonyl tosylhydrazide (**57**) (Scheme 11).[39] These efforts allowed for improved yields in terms of preparing α-formyl substituted 2,2'-bipyrroles, albeit at the cost of an increased step count.

As a way to expand further the array of substituents that could be incorporated into bipyrroles, Sessler and co-workers implemented a Schollkopf-Magnus-Barton-Zard approach utilizing simple aldehydes and alkyl isocyanoacetates to furnish pyrrole **60** in 50–70 % yield.[40,41] The simple preparation of a dialkyl pyrrole-2,4-carboxylate allowed subsequent iodination and Ullmann coupling to give 4,4'-disubstituted-2,2'-bipyrrole (**50**) in only three steps (Scheme 12). The authors noted that the iodopyrrole must contain electron-withdrawing groups for the coupling to proceed in moderate to good yields.

As a culmination of previous efforts involving protecting or adding an α-formyl group at a relatively late step, Jiao and co-workers described a modification of the Ullmann

reaction that allowed for the preparation of 5,5-diformyl-2,2'-bipyrrole (**62**).[42] These researchers exploited a reductive cross coupling using Pd/C and zinc metal in a biphasic mixture; this allowed highly substituted 2,2'-bipyrroles to be prepared in 26–54 % yield (Scheme 13).
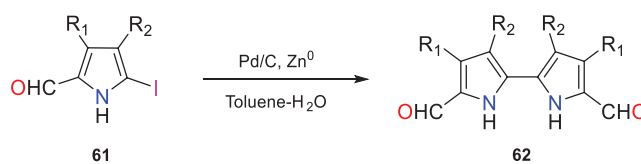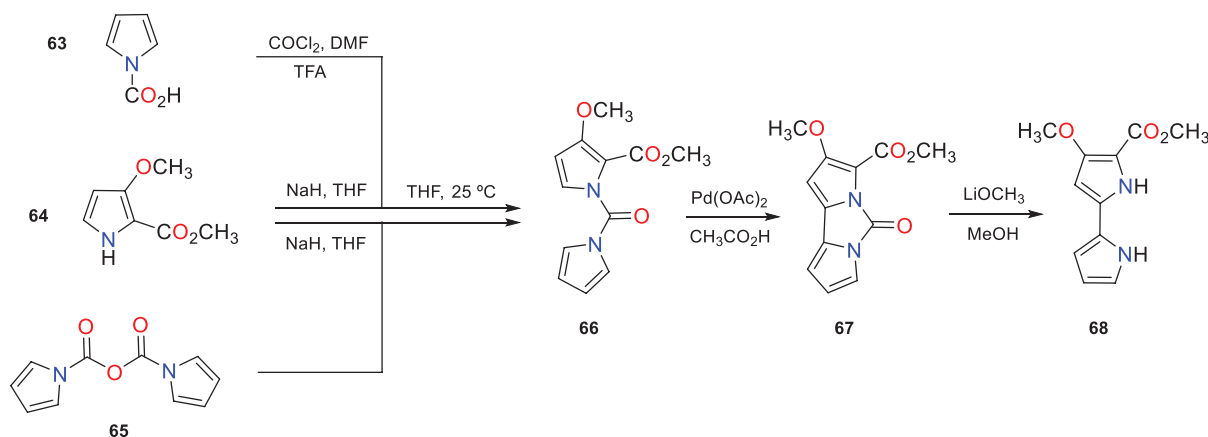

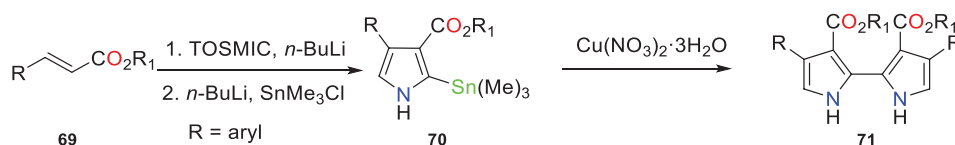**Scheme 13.** Synthesis of 2,2'-bipyrrole **62** by Jiao *et al.*[42]

Syntheses by means of oxidative couplings

The Ullmann coupling of iodopyrrole has remained a mainstay in the preparation of symmetric 2,2'-bipyrroles. However, routes toward asymmetric constructs have predominately relied on the Rapaport bipyrrole synthesis that proceeds *via* 2,2'-pyrrolidinylpyrroles. In order to simplify the latter procedure, Patel and co-workers developed a Pd(OAc)$_2$-based oxidative coupling (Scheme 14). This procedure relies on the preparation of 1,1'-carbonyldipyrrole **66**, obtained by the coupling of a pyrrole-1-carboxylic acid **63** with the sodium salt of the corresponding pyrrole (**64**) or the anhydride of the pyrrole-1-carboxylic acid (**65**).[43]

Scheme 14. Synthesis of asymmetric 2,2'-bipyrroles by Patel *et al.*[43]

Scheme 15. Synthesis of 2,2'-bipyrroles *via* a stannylated pyrrole derivative as reported by Sánchez-García *et al.*[45]

Treatment of the corresponding 1,1'-carbonyldipyrrole (**66**) with Pd(OAc)$_2$ in acetic acid, followed by hydrolysis, gives the asymmetric 2,2'-bipyrrole (**68**) in four steps and in 30 % yield (Scheme 14).

Recent efforts to prepare bipyrroles *via* cross-coupling approaches have served to optimize previously reported strategies. In fact, by modifying the original preparation of α-stannyl pyrrole developed by Van Leussen and co-workers,[44] the Sánchez-García group developed a one-pot synthesis of 2,2'-bipyrroles of general structure **71** from easily prepared or commercially available cinnamates (**69**) (Scheme 15).[45] This method allows the gram-scale synthesis of dialkyl 4,4'-biaryl-2,2'-bipyrrole-3,3'-carboxylates (**71**) in up to 50 % yield. The authors made note of what was a short and rapid aqueous extraction for the purification of the stannyl pyrrole crude product before it was subject to Cu-coupling; this generally improves the yield.

Synthetic procedures giving *N*-unsubstituted bipyrroles directly are limited. Advances in hypervalent iodine chemistry, however, have been applied recently to pyrrole precursors and have provided a new route towards 2,2'-bipyrroles.[46,47] One of the first demonstrations of a hypervalent iodine-based bipyrrole synthesis was reported by Kita and co-workers. Here, phenyliodine bis(trifluoroacetate) (PIFA) in the presence of a Lewis acid (*e.g.*, TMSBr or BF$_3$-OEt$_2$) was used to effect the oxidative coupling of pyrrole.[48] This new method furnished a range of 3,3',4,4'-tetrasubstituted, 3,3'-disubstituted, and unsubstituted bipyrroles. Interestingly, this approach proved amenable to electron-rich pyrroles and, upon *N*-protection, could furnish 2,3'-bipyrroles as well. Moreover, when there is only one substituent in the pyrrolic β-position, the reaction can afford a mixture of 3,4'- or 3,3'-substituted 2,2'-bipyrroles. The groups of Waluk, as well as of Panda,

used this generalized strategy to prepare 2,2'-bipyrroles that were carried on to yield *meso*-substituted porphycenes and a β-octamethoxyporphycene (**74a**), respectively (Scheme 16a).[49,50] A similar oxidative coupling protocol was developed by Stępień and co-workers as part of efforts to develop the chemistry of bis(phenanthropyrroles) (**76**).[46] Interestingly, when added to FeCl$_3$, the α-free-β-diaryl-monopyrrole (**75**) was observed to undergo intramolecular ring closure of the β-aryl substituents, as well as an inter-molecular α-α coupling of two pyrrole subunits *via* a Scholl reaction. Unlike the PIFA method, the authors were required to protect the α-position to prevent formation of oligomeric and polymerized by-products (Scheme 16b).

Synthesis via Suzuki-Miyaura coupling

In pursuit of methods that would allow access to natural products such as prodigiosine and tambjamine, Reynolds and co-workers developed Suzuki cross-coupling protocols involving pyrrole-2-boronic acids and bromopyrroles (Scheme 17).[51] Here, the authors used 1,3-dibromo-5,5-dimethylhydantoin (DBDMH) as a mild bromination reagent to access a series of bromopyrrole derivatives.

Miscellaneous methods

New methodologies devoted to the synthesis of 5-membered heterocycles have allowed for the preparation of 2,2'-bipyrrolic species. Within this context, Pagenkopf and co-workers described a trimethylsilyl trifluoromethanesulfonate (TMSOTf)-mediated reaction between donor-acceptor cyclopropanes (**83**) with 2-cyanopyrroles and 2-cyanothiophene (**84**) as a means of preparing 2,2'-bipyrroles and 2,2'-thienylpyrroles (**85**, Scheme 18).[52,53]
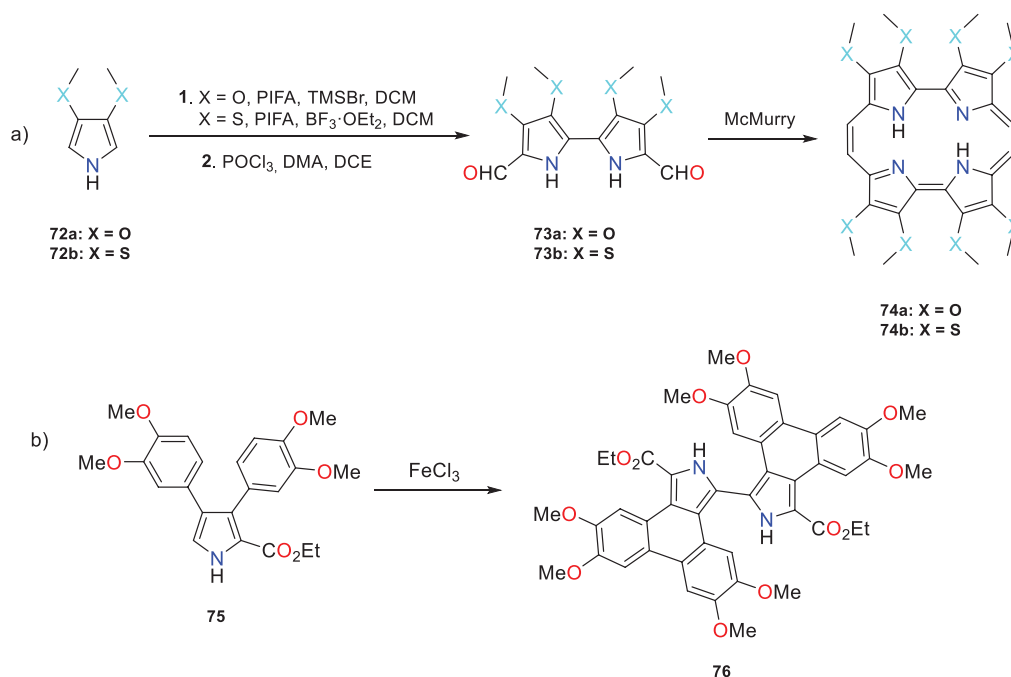
Scheme 16. Synthesis of *meso*-substituted porphycenes (a) and synthesis of β-octamethoxyporphycene **74a** and β-octakis(methylthio) porphycene **74b** (b) and synthesis of bis(phenanthropyrroles) **76** *via* a tandem Scholl reaction (b).
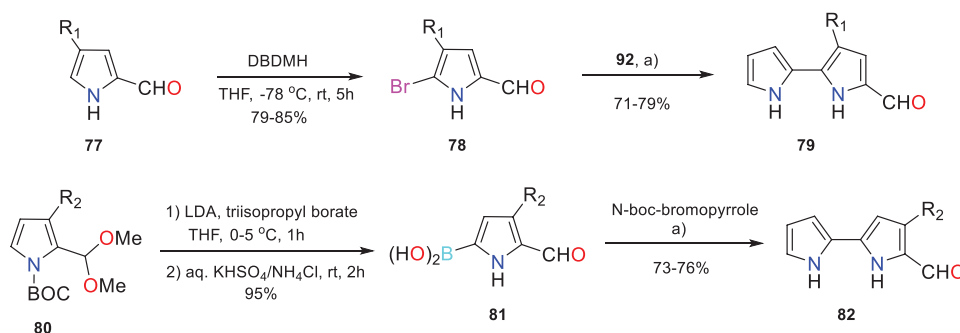
Scheme 17. Synthesis of 2,2'-bipyrroles **79** and **82** *via* the Suzuki reaction as reported by Reynolds *et al.*[51] a) i. Pd(PPh₃)₄, dioxane/H₂O, Na₂CO₃, 100 °C, 3 h, ii. LiOH, THF-MeOH, rt, 30 min.
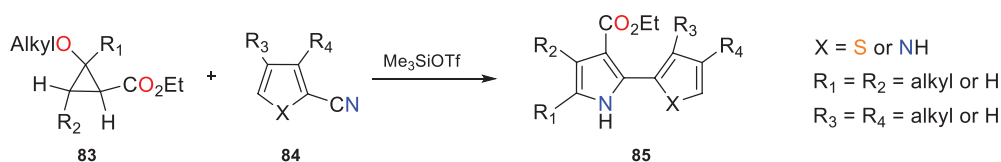
Scheme 18. Syntheses of unsymmetrical bipyrroles and thienylpyrroles **85** as reported by Pagenkopf *et al.*[52,53]

The Pagenkopf bipyrrole synthesis allowed for complete regiocontrol, as well as for the preparation of new asymmetric bipyrroles and thienylpyrroles **85**. As a general rule, these products could not otherwise be accessed or, if so, only through tedious synthetic means.

Motivated by a desire to prepare bicyclic pyrrole-containing structures, Opatz and co-workers reported a cyclization procedure that allowed for the preparation of 5,6,7,8-tet-

rahydroindolizines, 2,3-dihydro-1*H*-pyrrolizines, 2,2'-bipyrroles **88**, 6,7,8,9-tetrahydro-5*H*-pyrrolo[1,2-*a*]azepines **89**, and 5,5'-bis(5-cyano-1-pyrrolines) **90**.[54] Starting from readily available 3,4-dihydro-2*H*-pyrrole-2-carbonitriles **87**, this method furnished 2,2'-bipyrroles with α,α'-aryl substituents (Scheme 19).[55]

Trofimov and co-workers reported an elegant example of rearrangement chemistry applied to the preparation
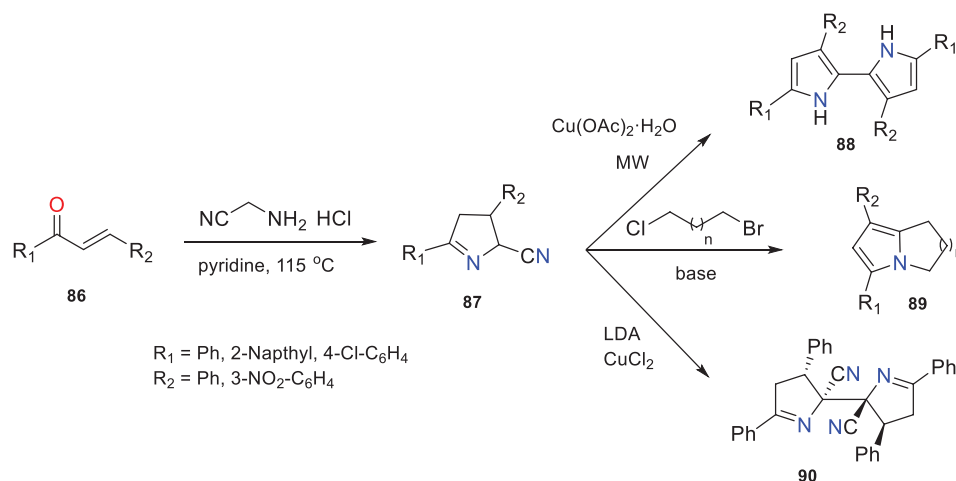
Scheme 19. Synthesis of 2,2'-bipyrroles *via* a two-step route from commercial available substrates as reported by Opatz, *et al.*[55]

of pyrrolo-bicyclic 1-amino-3-iminopyrrolizines (**94**). The route involved carbodithioation of 2,3-disubstituted pyrrole **91** followed by synthesis of the cyano-substituted pyrrolizine ring (**93**). Benzoylation of the methylated amine followed by pyrrolizine ring opening and an intramolecular cyclization cascade gave 2,2'-bipyrrole **95**. This route provided access to purine pyrrole analogues, as well as cyano-substituted bipyrroles. However, it is limited in its application as it requires α-substituents and protection of the pyrrole nitrogen atom (Scheme 20).[56] In a similar vein, Würthwein and co-workers described the preparation of several pyrrole derivatives, among them 2,2-bipyrroles, *via* the Aza-Nazarov reaction of 1-aza-1,4-pentadien-3-ones. Unfortunately, in this case the complex preparation of the starting materials and the substitution pattern of the product reduced the applications-related utility of the method.[57]

**Functionalization of 2,2'-bipyrroles**

Most synthetic methods for functionalization of 2,2'-bipyrroles rely on electrophilic substitution reactions, such as acylations, notably the Vilsmeier-Haack reaction and halogenations. Other approaches preinstall in the starting materials the functional groups that will

appear in the β-positions of the desired β-substituted-2,2'-bipyrrole. Examples of the latter approach include Ullman couplings involving a β-substituted iodo-pyrrole or the copper coupling of a stannyl derivative prepared from the correspondent cinnamate. All these methodologies have in common the fact that the β-substituted groups must be installed from the beginning of the synthesis, and in some cases the preparation of such derivatives can be long and tedious. Borrell and co-workers circumvented what were previously considered to be canonical preparative limitations by means of desulfurization of thienodipyrroles **101** using Raney nickel. This strategy allowed for the modification of the typical 2,2'-bipyrrole substitution pattern as demonstrated by bromination and use of Suzuki cross-coupling procedures to give 4,4'-diaryl-2,2'-thienodipyrroles (**101**) (Scheme 21).[58]

For the most part preparations of diformyl 2,2'-bipyrroles have relied on the use of the Vilsmeier-Haack reaction and related electrophilic aromatic substitution procedures. However, recently Sánchez-García and co-workers described the preparation of the first 5,5'-dibrominated-2,2'-bipyrrole (Scheme 22).[59] They studied the reactivity of dibrominated bipyrrole **103** under Suzuki and Stille coupling conditions and found they could produce several new oligopyrroles, such as quater pyrrole or 5,5'-bis(2-thienyl)-2,2'-bipyrrole (**104**, G=pyrrole or thiophene).[60]
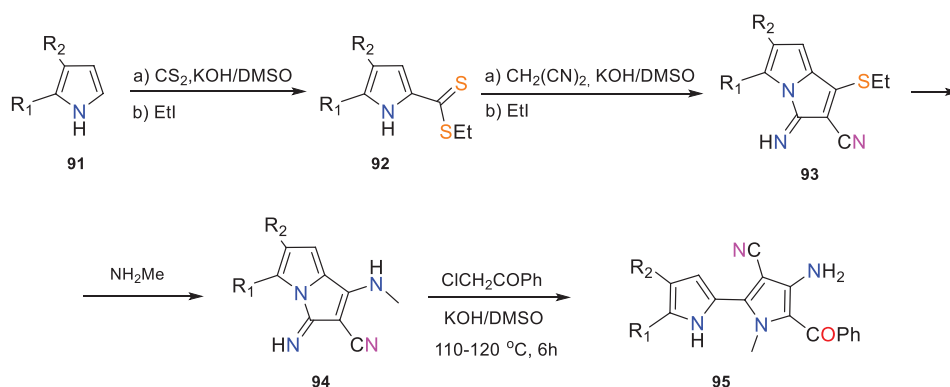
Scheme 20. Trofimov's synthesis of 2,2'-bipyrroles **95**.[56]
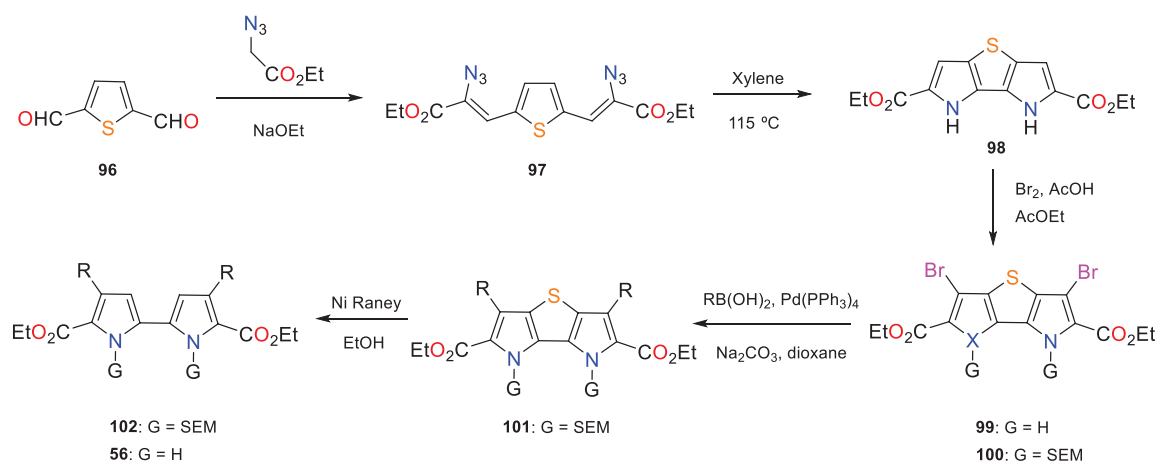
Scheme 21. Synthesis of 2,2'-bipyrroles from thienodipyrroles as reported by Borell, *et al.*[58]
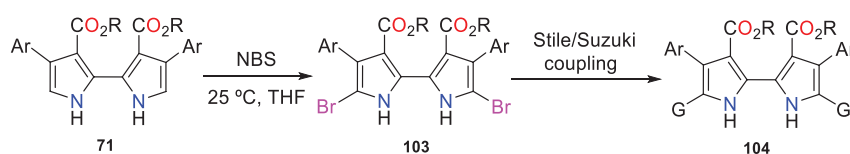
**Scheme 22**. Synthesis of α-substituted 2,2'-bipyrroles by Sánchez-García *et al.*[59,60]

2,2'-Bipyrroles as versatile building blocks for the preparation of pyrrolyl macrocycles

Tetrapyrrolic porphyrinoids

Pyrrolic macrocycles represent some of the most important prosthetic groups found in nature. Indeed, tetrapyrrolic macrocycles play key roles in many of the biochemical pathways essential for life. This has led to intense study of classic synthetic and semi-synthetic tetrapyrrolic macrocycles, including porphyrin, corrole,[61] and porphycene.[21] These systems have remained a focal point of interest within innumerable research groups and have attracted attention across a wide swath of the chemical and medical communi-

ties. Corroles are related to porphyrins but distinct in terms of lacking a *meso*-bridge. Formally, they contain a 2,2'-bipyrrole incorporated within a macrocyclic structure. Corrole was first synthesized by Kay and Johnson. Initial efforts by Johnson and co-workers utilized an oxidative cyclization of *a,c*-biladienes to yield the corrole core.[61] The synthesis of corrole has since been modified to allow for a one pot procedure furnishing gram scale quantities of the desired system (Scheme 23a).[62–64] The mainstay of corrole chemistry continues to rely on the oxidative cyclization to prepare the 2,2'-bipyrrole and yield the macrocyclic core.

Porphycenes (**6**) were arguably the first reported structural isomers of porphyrin. These systems replace the dipyrromethene subunit with 2,2'-bipyrrole, a substitution that endows the resultant porphyrinoid with new character-
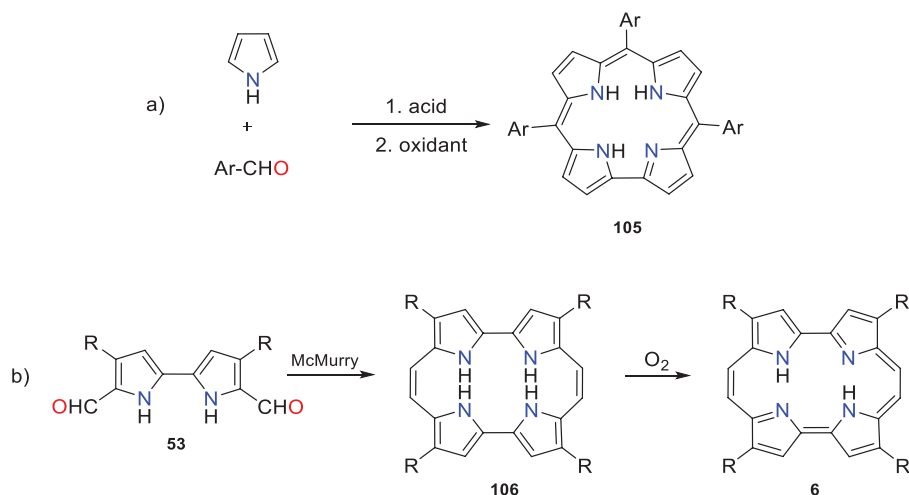
Scheme 23. Synthesis of corrole **105** (a) and porphycene **6** (b).

istics. The original synthesis described by Vogel and co-workers implemented a modified synthetic route towards 5,5'-diformyl-2,2'-bipyrrole (**53**), followed by cyclization *via* McMurry coupling and oxidation (Scheme 23b).[21] The authors reported yields ranging from 2–50 % with a correlation between yield and solubility of the 2,2'-bipyrrole. Advances in the synthesis of various substituted 2,2'-bipyrroles has resulted in improved yields of the porphycene core as well as tunable absorption profiles giving way to new photosensitizers with potential therapeutic applications.[65–72]
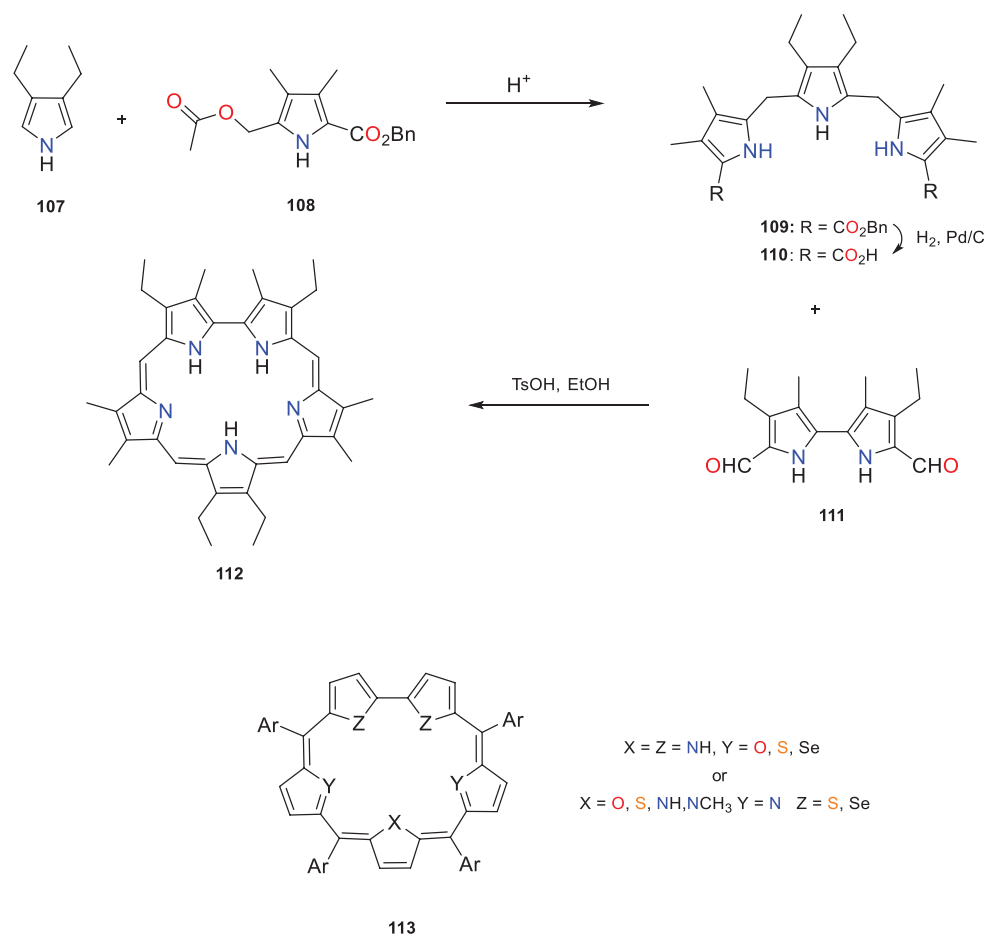
Pentaphyrins: sapphyrin

Sapphyrin (**39** or **112**) is regarded as the first reported expanded porphyrin and is recognized by its penta-aza-heterocyclic core containing tripyrrane and 2,2'-bipyrrole building blocks.[22] Following the initial report by Woodward, the groups of Johnson and Gibbs would explore modification of the heterocyclic constituents through the synthesis of oxa- and thiasapphyrins (Scheme 24).[73] In a continuation of the efforts, the groups of Sessler and Ibers developed an optimized synthesis of sapphyrin.[74] This new method improved yields and, most notably, implemented the Schollkopf-Magnus-Barton-Zard pyrrole synthesis allowing for multigram quantities of the ethyl 3,4-dialkyl pyrrole ester to be synthesized. The bipyrrole was prepared using standard copper mediated cross cou-

pling (Scheme 24).[75,76] The synthesis of a new expanded porphyrin initiated an entire field of porphyrinoid chemistry while demonstrating the importance of 2,2'-bipyrrole as a central motif in these pyrrolyl macrocycles.[77–84]
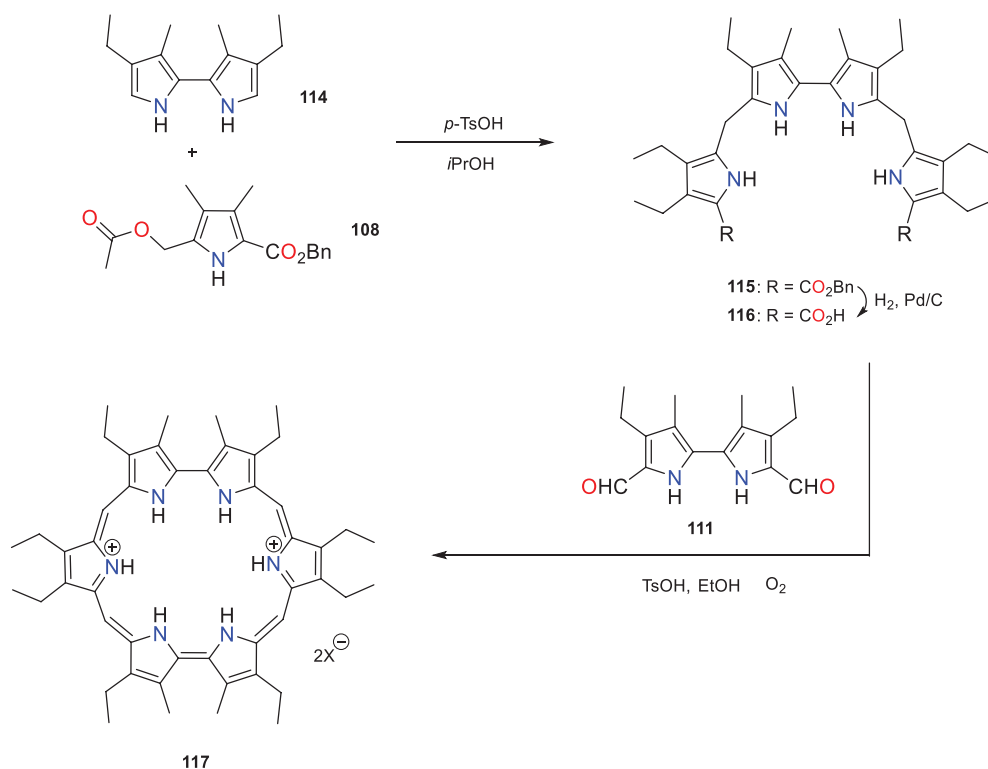
Hexaphyrins

Sessler and co-workers continued their initial efforts to expand the chemistry of pyrrolic macrocycles by reporting the synthesis of rubyrin (**117**).[85] Rubyrin is a hexa-azaporphyrinoid containing two 2,2'-bipyrrole subunits bridged by a central pyrrole. The final compound was prepared utilizing a MacDonald coupling between intermediate tetrapyrrole **116** and bipyrrole **111** (Scheme 25). The first rubyrin to be reported (**117**) shows physicochemical properties similar to those of sapphyrin (**112**). In analogy to earlier efforts with sapphyrin, various heterorubyrins (**119**) were also prepared.[86,87] Several showed promise in terms of biomedical and anion sensor and recognition applications (Scheme 26).[75,86,88,89]

Sessler and co-workers prepared the next relative within the hexaphyrin family, so-called isoamethyrin (**121**). In analogy to what was true in the case of corroles, the 2,2'-bipyrrole subunit of this expanded porphyrin was prepared *via* oxidative cyclization of a linear intermediate (**120**) (Scheme 27).[90] The development of this new oxidative coupling methodology was further applied to the synthesis

Scheme 24. Synthesis of sapphyrin **112** and heterosapphyrins **113**.

Functionalized 2,2'-Bipyrroles

Scheme 25. Synthesis of rubyrin **117**.
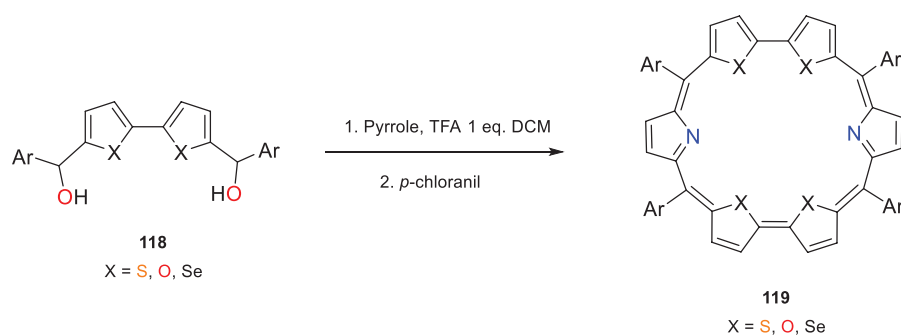
Scheme 26. Synthesis of heterorubyrins **119**.

Scheme 27. Synthesis of hexaphyrin **121**.

Scheme 28. Synthesis of cyclo[6]pyrrole **123** (a) and synthesis of uranyl complex of cylco[6]pyrrole **126** (b).

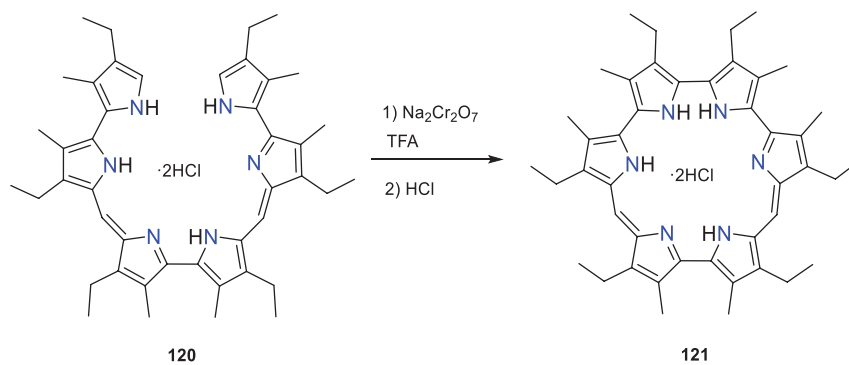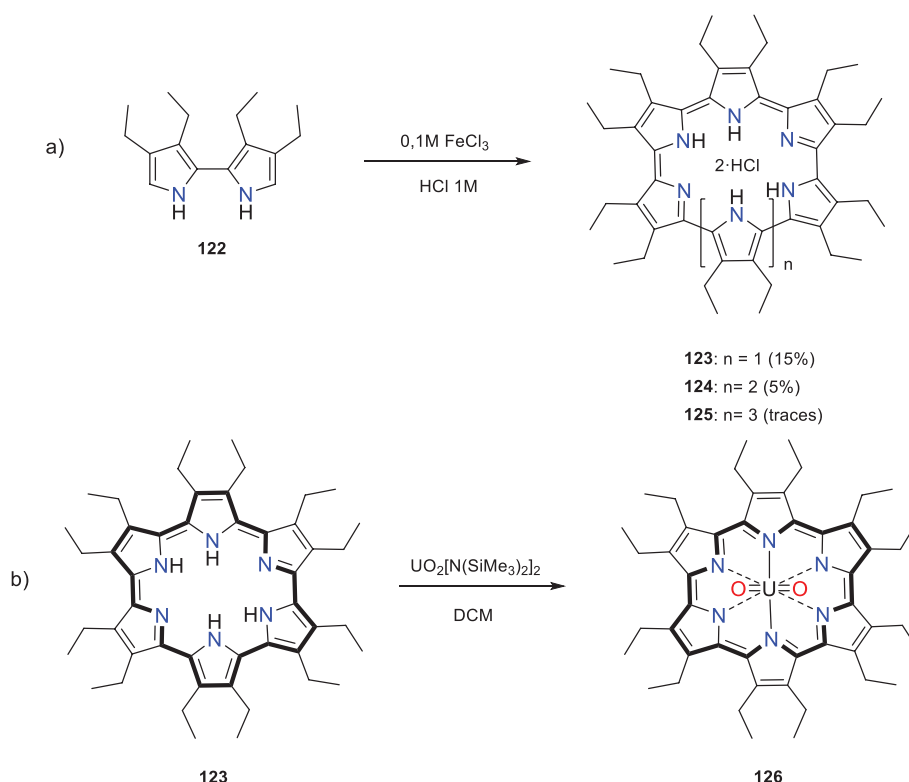of a new class of hybrid expanded porphyrins, the so-called cyclo[n]pyrroles.[23,24,91] Cyclo[6]pyrrole (**123**) was obtained by oxidative coupling of 2,2'-bipyrrole in a CH_2Cl_2:HCl (1 M) biphasic system with $FeCl_3$ (Scheme 28a).[23] Interestingly, the acid counteranion was also found to have a templating effect and could be modified to vary the ratio of cyclo[6]pyrrole (**123**), cyclo[7]pyrrole (**124**), and cyclo[8] pyrrole (**125**). It was found that several of the cyclo[n]pyrroles could be useful in the realm of anion sensing; others, particularly cyclo[6]pyrrole showed promise in the area of uranyl cation coordination chemistry (Scheme 28b).[92]

The development of new methodologies for the synthesis of 2,2'-bipyrrole have provided the starting point for recent efforts by the groups of Sánchez-García and Sessler that led to a convergent approach for the construction of isoamethyrin (**130**)[93] and naphthoisoamethyrin (**131**),[94,95] respectively (Scheme 29).
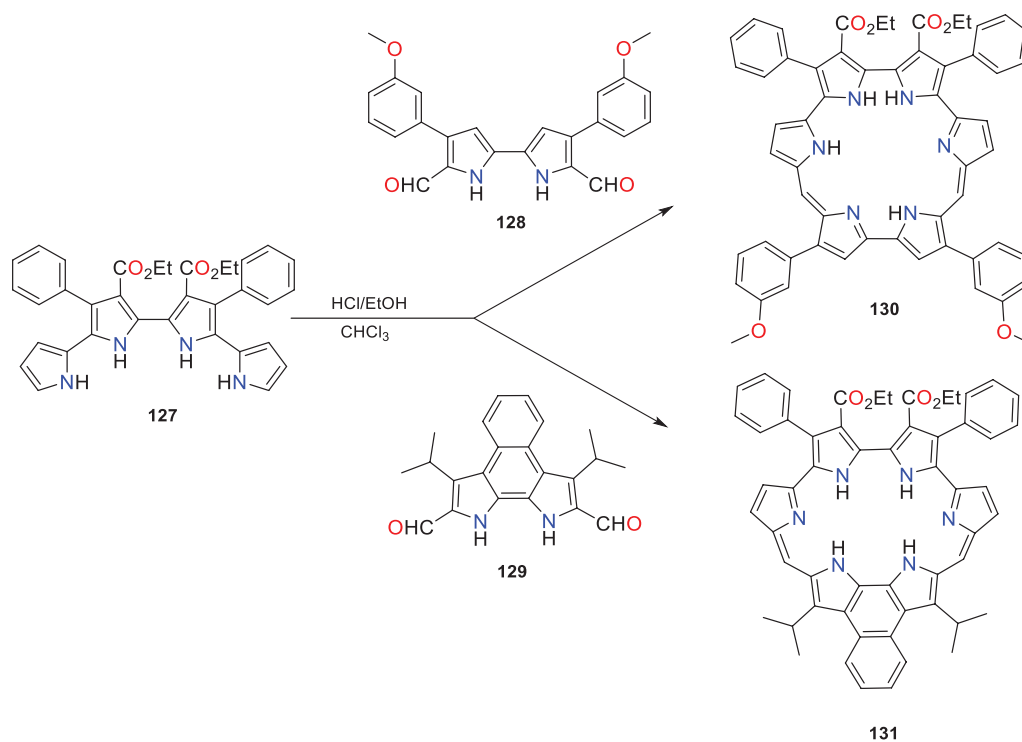
Heptaphyrins

Heptaphyrins, as the name implies, are the next congener within the expanded porphyrin series after hexaphyrins. Building on their previous efforts, Sessler and co-workers used 2,2'-bipyrrole derivatives as building blocks for the synthesis of such compounds.[96,97] Heptaphyrin **134** was prepared in a two-step sequence from 2,2'-bipyrrole **36** and terpyrrole **132** by way of condensation followed by oxidative cyclization of linear precursor **133** (Scheme 30).[97] Osuka and co-workers have also disclosed the preparation of two heptaphyrins,[98] namely **135** and **136**; they were prepared by a one pot reaction between pentafluorobenzaldehyde, pyrrole, dodecyl sulfate, and $Sc(OTf)_3$ under aqueous

conditions. These two heptaphyrins contain a 2,2'-bipyrrole, which results from the *in situ* formation of the linear precursor followed by oxidative cyclization.
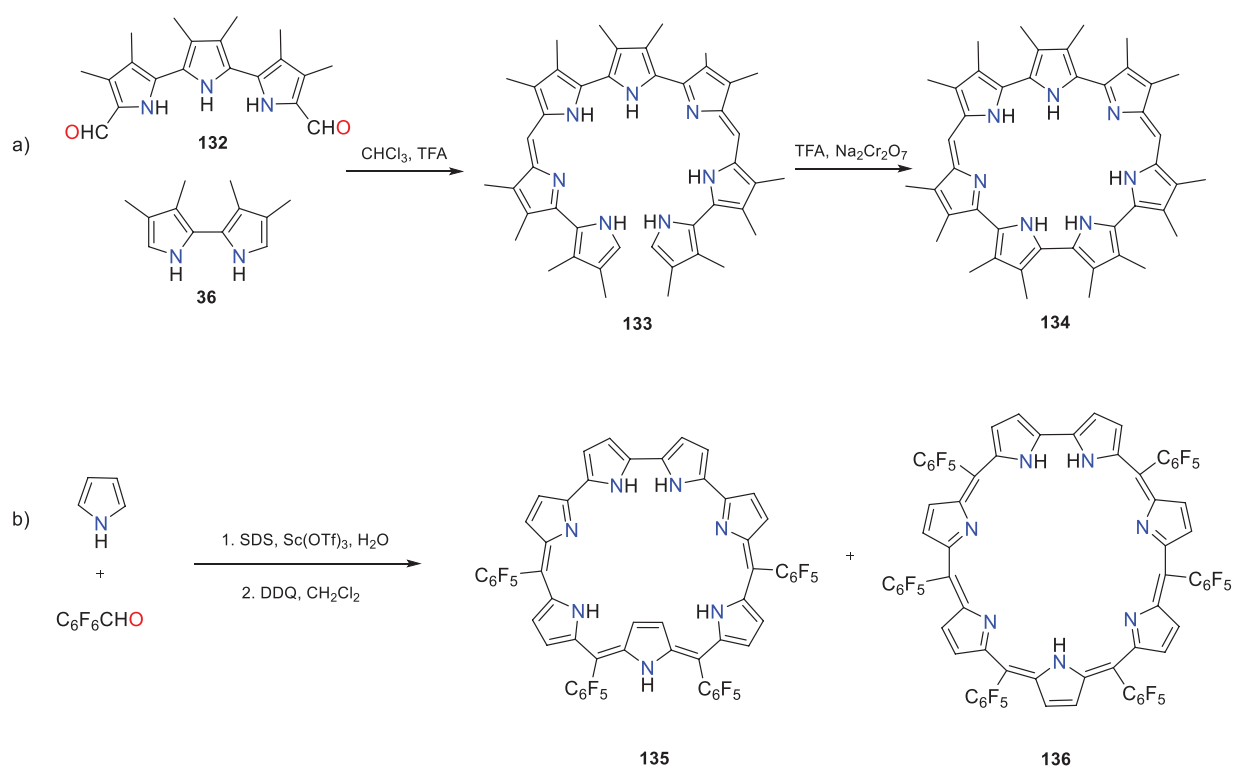
Octaphyrins

Octaphyrins containing two 2,2'-bipyrrole moieties linked through two dipyrromethane subunits can be considered as 2x expanded corroles. The first octaphyrin system of this type was reported by Houk and co-workers and its synthesis relied on an acid mediated condensation between 2,2'-bipyrrole dialdehyde (**53**) and a dipyrrylmethane dicarboxylic acid (**137**) (Scheme 31a).[99,100] More recently, Geier and co-workers have synthesized octaphyrin by coupling a dipyrromethanedicarbinol (**140**) with an α-unsubstituted 2,2'-bipyrrol **9** or an α-free dipyrromethane with a 2,2'-bypyrroledicarbinol.[101,102] Houk and co-workers also reported the synthesis of octaphyrins (**142–143**) achieved through condensation of the 2,2'-bipyrrole **122** with the diformyl 2,2'-bipyrrole **141** (Scheme 31b).[99] Recent endeavors by Shinokubo and co-workers have also prepared octaphyrins (**142** and **143**) *via* Ni-templated intermolecular homocouplings of an α,α'-dibromodipyrrin **144** to yield nickel norcorrole with subsequent ring expansion effected through addition of an aryl Grignard.[103]

Sessler and co-workers have also described a route toward octaphyrins (*e.g.*, **146**) containing only two *meso*-bridges (Scheme 32). This synthesis relied on the acid catalyzed condensation of two 2,2'-bipyrrole subunits, which gives tetrapyrrolic precursor **145**, a species that readily undergoes a tandem oxidative coupling and cyclization to give octaphyrin **146**.[97]
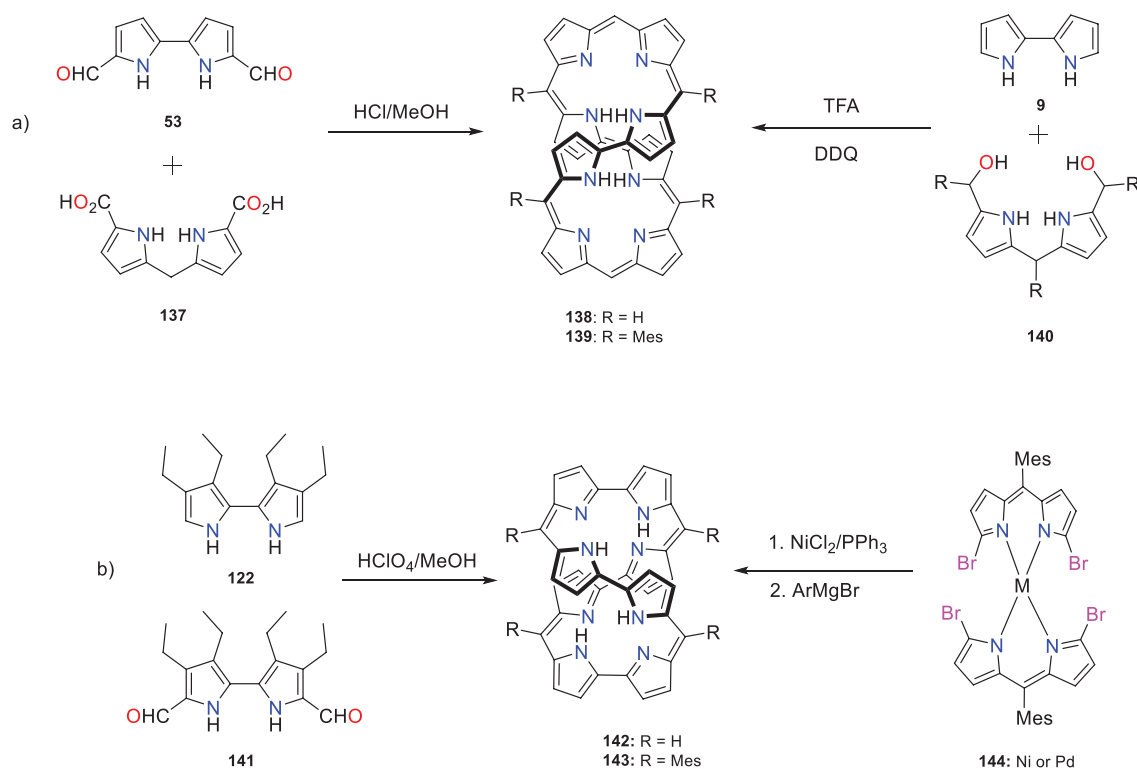
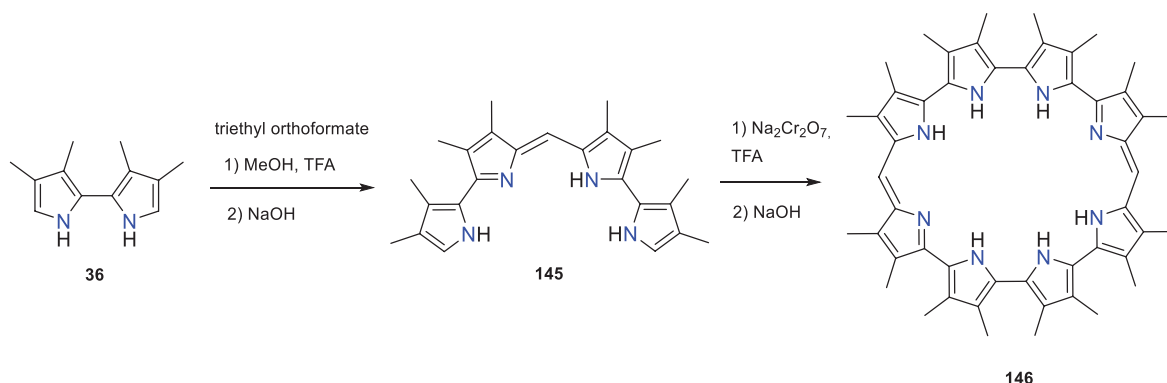**Scheme 29.** Synthesis of isoamethyrin **130** and naphthoisoamethyrin **131**.

Scheme 30. Synthesis of heptaphyrin **134** (a), **135** and **136** (b).

Scheme 31. Synthesis of octaphyrins **138-139** (a) and **142-143** (b). Note: β-ethyl chains omitted for clarity in **143**.

Scheme 32. Synthesis of octaphyrin **146** (a).

Utilizing methods they developed for the preparation of 2,2'-bipyrrole, Sánchez-García and co-workers have also prepared the octaphyrin **149** *via* a MacDonald condensation of quaterpyrrole **127** with the diformylated quaterpyrrole **148** in 33 % yield, and the cyclo[8]pyrrole **147** *via* oxidative coupling of quaterpyrrole **127** (Scheme 33).[59]

Expanded porphyrins containing more than eight pyrroles

The controlled synthesis of expanded porphyrins with more than eight pyrrolic constituents remains a challenge.[104–106] Sessler and co-workers are among the first to describe such a compound in the preparation of turcasarin (**151**) (Scheme 34).[89,104] This porphyrinoid contains ten pyrrole units and exists in a dynamic equilibrium between two figure-eight conformations under normal laboratory condi-

tions, such as room temperature. Setsune and co-workers would continue to expand the porphyrin core by preparing a dodecaphyrin (**153**) and a hexadecaphyrin (**154**). Both targets were obtained *via* the reaction between 2,2'-bipyr-role **122** and benzaldehyde **152** (Scheme 35).[106] Modification of this protocol and using the 2,2'-bis(azafulvene) **155**, derived from 2,2'-bipyrrole **156**, with 2,2'-bipyrrole afforded the same compounds.[107,108]

Kobayashi and co-workers have also synthesized a cyclo[10]pyrrole (**158**) derived only from 2,2'-bipyrrole **157** by using an oxidative cyclization with croconic acid as a template (Scheme 36).[109] This remains the largest cyclo[n] pyrrole prepared to date.

Recent efforts devoted to expansion of the porphyrin core have led Sessler and co-workers to prepare one of the largest expanded porphyrin yet reported, namely hexadecaphyrin (**160**) (Scheme 37).[110] This compound
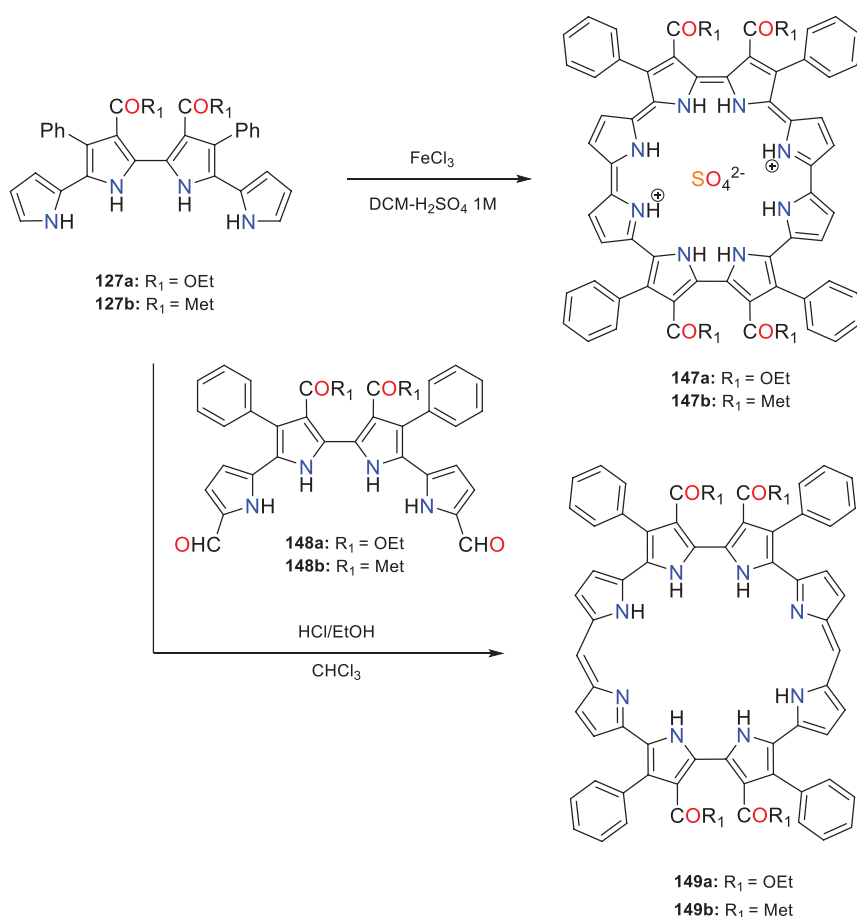
Scheme 33. Synthesis of cyclo[8]pyrrole **147** and octaphyrin **149** from quaterpyrrole **127**.
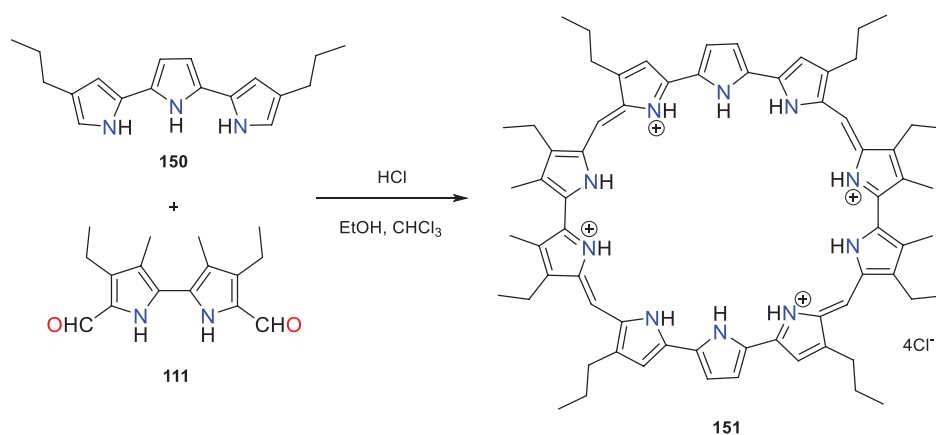
Scheme 34. Synthesis of turcasarin **151**.

contains eight direct α-pyrrole-to-α-pyrrole linkages and was obtained *via* the condensation 2,2'-bipyrrole dialdehyde **141** with the hexapyrrolic derivative **159**. This expanded porphyrin was shown to support the formation of different metal complexes that interconvert between different conformations as temperature is applied to the solution. The conformational changes produce color differences that may be observed by the naked eye.

Conclusion

The chemistry described in this review is a glimpse into the synthetic efforts devoted to the construction of both 2,2'-bipyrroles and systems containing this subunit within conjugated macrocyclic cores. As the synthetic protocols continue to improve and access to new precursors with varying substitution patterns emerge, the preparation
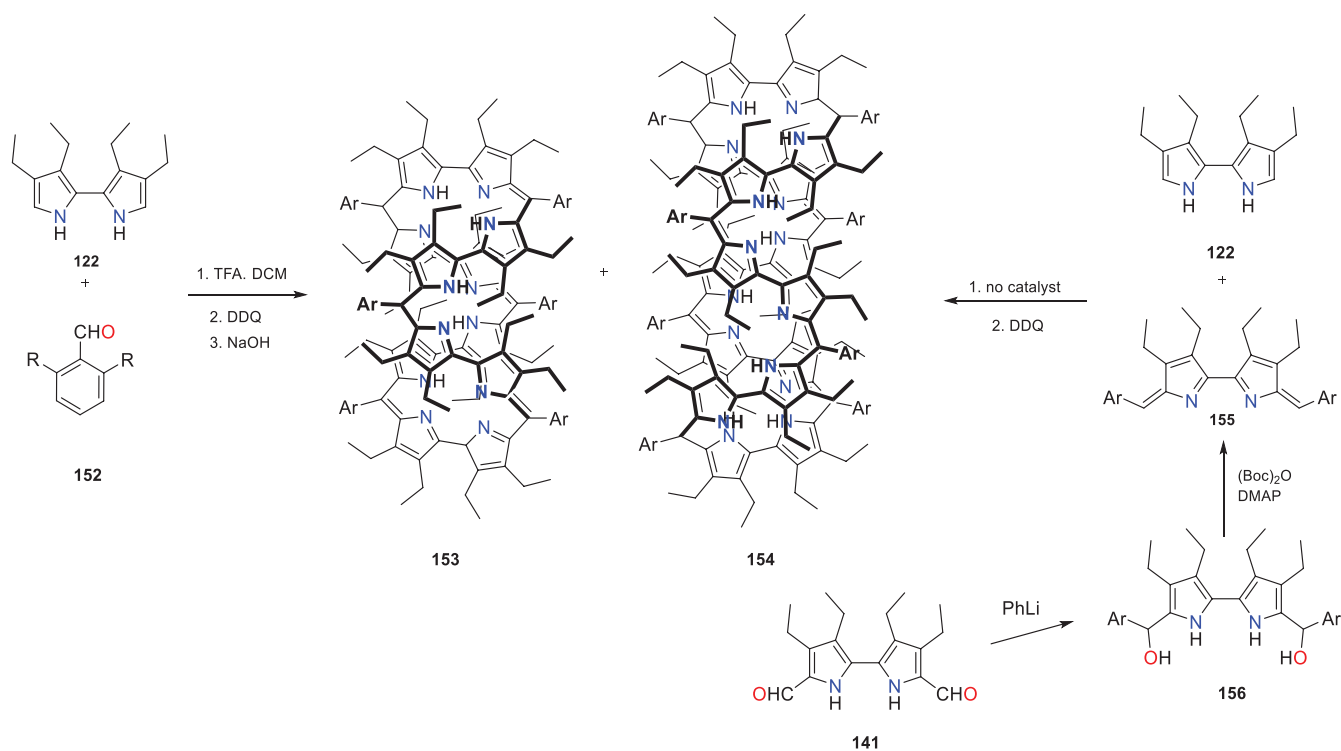
Scheme 35. Synthesis of dodecaphyrin **153** and hexadecaphyrin **154**.
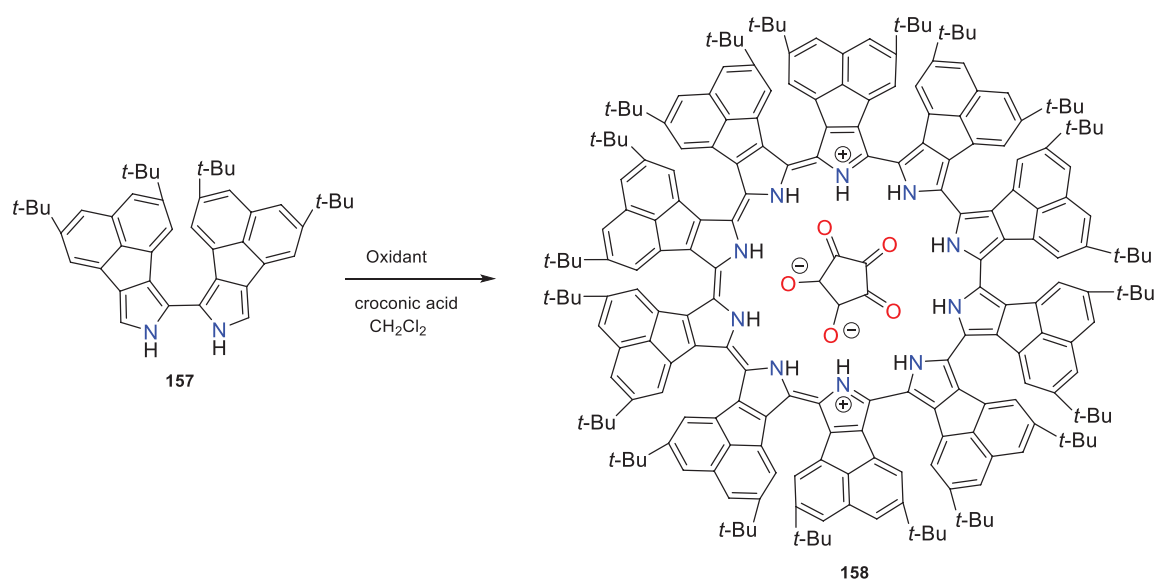
Scheme 36. Synthesis of cyclo[10]pyrrole **158**.
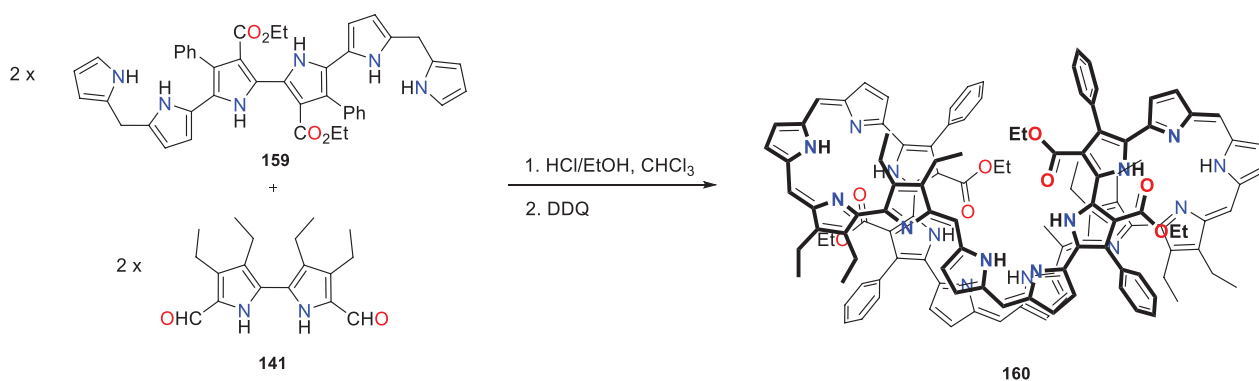
Scheme 37. Synthesis of hexadecaphyrin **160** *via* the condensation of **159** and **141**.

of even more complex targets becomes enabled, as gives access to systems of potential real world utility. Indeed, several decades of optimization have already yielded scalable procedures for therapeutically active porphycenes and 2,2'-bipyrrole-derived oligopyrrolic functional materials. We thus expect that 2,2'-bipyrrole will remain a keystone in the construction of new and interesting pyrrole-containing macrocyclic species.

References

1. John A., Joule K.M. *Heterocyclic Chemistry*, 5th Edition, John Wiley & Sons, Ltd, **2010**.
2. Trofimov B.A., Mikhaleva A.I., Schmidt E.Yu., Sobenina L.N. *Chemistry of Pyrroles.* CRC press, **2016**.
3. Baltazzi E., Krimen L.I. *Chem. Rev.* **1963**, *63*(5), 511–556.
4. Anderson L.R., Liu K.-C. In: *Kirk-Othmer Encyclopedia of Chemical Technology.* John Wiley & Sons, Inc.: Hoboken, NJ, USA, **2000**.
5. Groenendaal L. *The Chemistry of Oligopyrroles: Design, Synthesis and Characterization of Well-Defined and Functional alpha,alpha-Linked Oligomers.* Eindhoven: Technische Universiteit Eindhoven, **1996**.
6. Young I.S., Thornton P.D., Thompson A. *Nat. Prod. Rep.* **2010**, *27*, 1801–1839.
7. Bhardwaj V., Gumber D., Abbot V., Dhiman S., Sharma P. *RSC Adv.* **2015**, *5*(20), 15233–15266.
8. Maeda H. In: *Anion Recognition in Supramolecular Chemistry* (Gale P.A., Dehaen W., Eds.) Springer, **2010**. p. 103–144.
9. Maeda H. In: *Handbook of Porphyrin Science: With Applications to Chemistry, Physics, Materials Science, Engineering, Biology and Medicine* (Kadish K.M., Ed.) World Scientific, **2010**. p. 166–228.
10. Cragg P.J. *Supramolecular Chemistry.* Netherlands: Dordrecht, Springer, **2010**.
11. Estévez V., Villacampa M., Menéndez J.C. *Chem. Soc. Rev.* **2010**, *39*(11), 4402.
12. Estévez V., Villacampa M., Menéndez J.C. *Chem. Soc. Rev.* **2014**, *43*(13), 4633–4657.
13. Sharma A., Piplani P. *J. Heterocycl. Chem.* **2017**, *54*(1), 27–34.
14. Mohamed M., Abd El-Hameed R., Sayed A. *J. Adv. Pharm. Res.* **2017**, *1*(1), 1–24.
15. Roznyatovskiy V., Lynch V., Sessler J.L. *Org. Lett.* **2010**, *12*(19), 4424–4427.
16. Sarma T., Panda P.K., Anusha P.T., Rao S.V. *Org. Lett.* **2011**, *13*(2), 188–191.
17. Vogel E. *Pure Appl. Chem.* **1993**, *65*(1), 143–152.
18. Bröring M., Link S. *Synthesis (Stuttg)* **2004**, *2002*(1), 67–70.
19. Korostova S.E., Mikhaleva A.I., Trofimov B.A. *Russ. Chem. Rev.* **1999**, *68*(6), 459–482.
20. Setsune J. *Chem. Rev.* **2017**, *117*(4), 3044–3101.
21. Vogel E., Köcher M., Schmickler H., Lex J. *Angew. Chem. Int. Ed.* **1986**, *25*(3), 257–259.
22. Bauer V.J., Clive D.L.J., Dolphin D., Paine J.B., Harris F.L., King M.M., Loder J., Wang S.W.C., Woodward R.B. *J. Am. Chem. Soc.* **1983**, *105*(1), 6429–6436.
23. Köhler T., Seidel D., Lynch V., Arp F.O., Ou Z., Kadish K.M., Sessler J.L. *J. Am. Chem. Soc.* **2003**, *125*(23), 6872–6873.
24. Seidel D., Lynch V., Sessler J.L. *Angew. Chem. Int. Ed.* **2002**, *41*(8), 1422–1425.
25. Roznyatovskiy V.V., Roznyatovskaya N.V., Weyrauch H., Pinkwart K., Tübke J., Sessler J.L. *J. Org. Chem.* **2010**, *75*(5), 8355–8362.
26. Grabowski J., Marchlewski L. *Ber. Dtsch. Chem. Ges.* **1914**, *47*, 2159–2161.
27. Webb J.L.A.J. *J. Org. Chem.* **1953**, *18*(10), 1413–1417.
28. Webb J.L.A., Threlkeld R.R. *J. Org. Chem.* **1953**, *18*(10), 1406–1412.
29. Wasserman H.H., McKeon J.E., Smith L., Forgione P. *J. Am. Chem. Soc.* **1960**, *82*(2), 506–507.
30. Fuhlhage D.W., VanderWerf C.A. *J. Am. Chem. Soc.* **1958**, *80*(23), 6249–6254.
31. Rapoport H., Holden K.G. *J. Am. Chem. Soc.* **1960**, *82*(20), 5510–5511.
32. Rapoport H., Castagnoli N. *J. Am. Chem. Soc.* **1962**, *84*(1939), 2178–2181.
33. Bordner J., Rapoport H. *J. Org. Chem.* **1965**, *30*(11), 3824–3828.
34. Yu C., Jiao L., Tan X., Wang J., Xu Y., Wu Y., Yang G., Wang Z., Hao E. *Angew. Chem. Int. Ed.* **2012**, *51*(31), 7688–7691.
35. Fu L., Gribble G.W. *Tetrahedron Lett.* **2008**, *49*(52), 7352–7354.
36. Sessler J.L., Hoehner M.C. *Synlett.* **1994**, *1994*(3), 211–212.
37. Paine J.B., Woodward R.B., Dolphin D. *J. Org. Chem.* **1976**, *41*(26), 2826–2835.
38. Nonell S., Bou N., Borrell J., Teixidó J., Villanueva A., Juarranz A., Cañete M. *Tetrahedron Lett.* **1995**, *36*(19), 3405–3408.
39. Gavalda A., Borrell J.I., Teixido J., Nonell S., Arad O., Grau R., CaÑete M., Juarranz A., Villanueva A., Stockert J.C. *J. Porphyrins Phthalocyanines* **2001**, *5*(12), 846–852.
40. Sanchez-Garcia D., Sessler J.L. In: *ICPP-4.* **2006**.
41. Suzuki M., Miyoshi M., Matsumoto K. *J. Org. Chem.* **1974**, *39*(13), 1980.
42. Jiao L., Hao E., Grac M., Vicente H., Smith K.M. *J. Org. Chem.* **2007**, *72*(21), 8119–8122.
43. Boger D., Patel M. *J. Org. Chem.* **1988**, *66*(4), 1405–1415.
44. Dijkstra H.P., Ten Have R., Van Leusen A.M. *J. Org. Chem.* **1998**, *63*(16), 5332–5338.
45. Sánchez-García D., Borrell J.I., Nonell S. *Org. Lett.* **2009**, *11*(1), 77–79.
46. Gońka E., Myśliwiec D., Lis T., Chmielewski P.J., Stępień M. *J. Org. Chem.* **2013**, *78*(3), 1260–1265.
47. Dohi T., Ito M., Yamaoka N., Morimoto K., Fujioka H., Kita Y. *Tetrahedron* **2009**, *65*(52), 10797–10815.
48. Dohi T., Morimoto K., Ito M., Kita Y. *Synthesis (Stuttg)* **2007**, *2007*(18), 2913–2919.
49. Rana A., Panda P.K. *Org. Lett.* **2014**, *16*(1), 78–81.
50. Rana A., Lee S., Kim D., Panda P.K. *Chem. Commun.* **2015**, *51*(36), 7705–7708.
51. Kancharla P., Reynolds K.A. *Tetrahedron* **2013**, *69*(39), 8375–8385.
52. Yu M., Pantos G.D., Sessler J.L., Pagenkopf B.L. *Org. Lett.* **2004**, *6*(6), 1057–1059.
53. Yu M., Pagenkopf B.L. *Org. Lett.* **2003**, *5*(26), 5099–5101.
54. Nebe M.M., Kucukdisli M., Opatz T. *J. Org. Chem.* **2016**, *81*(10), 4112–4121.
55. Opatz T., Kucukdisli M., Nebe M.M., Bartelt M.S. *Heterocycles* **2016**, *93*(1).
56. Petrova O.V., Sagitova E.F., Sobenina L.N., Ushakov I.A., Borodina T.N., Smirnov V.I., Trofimov B.A. *Tetrahedron Lett.* **2016**, *57*(32), 3652–3656.

57. Dieker J., Fröhlich R., Würthwein E.-U. *Eur. J. Org. Chem.* **2006**, *2006*(23), 5339–5356.

58. Arad O., Morros J., Batllori X., Teixidó J., Nonell S., Borrell J.I. *Org. Lett.* **2006**, *8*(5), 847–850.

59. Anguera G., Kauffmann B., Borrell J.I., Borrós S., Sánchez-García D. *Org. Lett.* **2015**, *17*(9), 2194–2197.

60. Anguera G., Kauffmann B., Borrell J.I., Borrós S., Sánchez-García D. *J. Org. Chem.* **2017**, *82*(13), 6904–6912.

61. Johnson A.W., Kay I.T. *J. Chem. Soc.* **1965**, *1620*, 1620.

62. Gross Z., Galili N., Saltsman I. *Angew. Chem. Int. Ed. Engl.* **1999**, *38*(10), 1427–1429.

63. Paolesse R., Mini S., Sagone F., Boschi T., Jaquinod L., Nurco D.J., Smith K.M. *Chem. Commun.* **1999**, *64*(14), 1307–1308.

64. Orowski R., Gryko D., Gryko D.T. *Chem. Rev.* **2017**, *117*(4), 3102–3137.

65. Stockert J.C., Cañete M., Juarranz A., Villanueva A., Horobin R.W., Borrell J.I., Teixidó J., Nonell S. *Curr. Med. Chem.* **2007**, *14*(9), 997–1026.

66. García-Díaz M., Sánchez-García D., Soriano J., Sagristà M.L., Mora M., Villanueva A., Stockert J.C., Cañete M., Nonell S. *MedChemComm* **2011**, *2*(7), 616.

67. Sánchez-García D., Sessler J.L. *Chem. Soc. Rev.* **2008**, *37*(1), 215–232.

68. Dosselli R., Tampieri C., Ruiz-González R., De Munari S., Ragàs X., Sánchez-García D., Agut M., Nonell S., Reddi E., Gobbo M. *J. Med. Chem.* **2013**, *56*(3), 1052–1063.

69. Rosàs E., Santomá P., Duran-Frigola M., Hernandez B., Llinàs M.C., Ruiz-González R., Nonell S., Sánchez-García D., Edelman E.R., Balcells M. *Langmuir* **2013**, *29*(31), 9734–9743.

70. Ragàs X., Sánchez-García D., Ruiz-González R., Dai T., Agut M., Hamblin M.R., Nonell S. *J. Med. Chem.* **2010**, *53*, 7796–7803.

71. Anguera G., Llinàs M.C., Batllori X., Sánchez-García D. *J. Porphyrins Phthalocyanines* **2011**, *15*(09n10), 865.

72. Arnbjerg J., Jiménez-Banzo A., Paterson M.J., Nonell S., Borrell J.I., Christiansen O., Ogilby P.R. *J. Am. Chem. Soc.* **2007**, *129*(16), 5188–5199.

73. Hooker J.D., Nguyen V.H., Taylor V.M., Cedeño D.L., Lash T.D., Jones M.A., Robledo S.M., Vélez I.D. *Photochem. Photobiol.* **2012**, *88*(1), 194–200.

74. Sessler J.L., Cyr M.J., Lynch V., McGhee E., Ibers J.A. *J. Am. Chem. Soc.* **1990**, *112*(2), 2810–2813.

75. Sessler J.L., Seidel D. *Angew. Chem. Int. Ed.* **2003**, *42*(42), 5134–5175.

76. Broadhurst M.J., Grigg R., Johnson A.W. *J. Chem. Soc., Perkin Trans. 1* **1972**, 2111–2116.

77. Judy M.M., Matthews J.L., Newman J.T., Skiles H.L., Boriack R.L., Sessler J.L., Cyr M., Maiya B.G., Nichol S.T. *Photochem. Photobiol.* **1991**, *53*(1), 101–107.

78. Parmeswaran D., Pushpan S.K., Srinivasan A., Ravi Kumar M., Chandrashekar T.K., Ganesan S. *Photochem. Photobiol.* **2003**, *78*(5), 487–495.

79. Král V., Davis J., Andrievsky A., Kralová J., Synytsya A., Poučková P., Sessler J.L. *J. Med. Chem.* **2002**, *45*(5), 1073–1078.

80. Naumovski L., Ramos J., Sirisawad M., Chen J., Thiemann P., Lecane P., Magda D., Wang Z., Cortez C., Boswell G., Gyu Cho D., Sessler J., Miller R. *Mol. Cancer Ther.* **2005**, *4*(6), 968–976.

81. Umezawa K., Tohda K., Lin X.M., Sessler J.L., Umezawa Y. *Anal. Chim. Acta* **2001**, *426*(1), 19–32.

82. Tabata M., Kaneko K., Murakami Y., Hisaeda Y., Mimura H. *Microchem. J.* **1994**, *49*(2-3), 136–144.

83. Nishimoto J., Yamada T., Tabata M. *Anal. Chim. Acta* **2001**, *428*(2), 201–208.

84. Allen W.E., Sessler J.L. *ChemTech* **1999**, *29*, 16.

85. Sessler J.L., Morishima T., Lynch V. *Angew. Chem. Int. Ed. Engl.* **1991**, *30*(8), 977–980.

86. Srinivasan A., Reddy V.M., Narayanan S.J., Sridevi B., Pushpan S.K. Ravikumar M., Chandrashekar T.K. *Angew. Chem. Int. Ed. Engl.* **1997**, *36*(23), 2598–2601.

87. Kumar R., Misra R., Chandrashekar T.K., Nag A., Goswami D., Suresh E., Suresh C.H. *Eur. J. Org. Chem.* **2007**, 4552–4562.

88. Srinivasan A., Pushpan S.K., Ravikumar M., Chandrashekar T.K., Raja R. *Tetrahedron* **1999**, *55*(21), 6671–6680.

89. Saito S., Osuka A. *Angew. Chem. Int. Ed.* **2011**, *50*(19), 4342–4373.

90. Sessler J.L., Seidel D., Vivian A.E., Lynch V., Scott B.L., Keogh D.W. *Angew. Chem. Int. Ed.* **2001**, *40*(3), 591–594.

91. Sessler J.L., Seidel D., Bolze F.R., Koehler T. *Method for the preparation of cyclo[n]pyrroles via an oxidative coupling procedure.* U.S. Patent No. 6,984,734, **2006**.

92. Melfi P.J., Kim S.K., Lee J.T., Bolze F., Seidel D., Lynch V.M., Veauthier J.M., Gaunt A.J., Neu M.P., Ou Z., Kadish K.M., Fukuzumi S., Ohkubo K., Sessler J.L. *Inorg. Chem.* **2007**, *46*(13), 5143–5145.

93. Anguera G., Borrós S., Borrell J.I., Sánchez-García D. *J. Porphyrins Phthalocyanines* **2016**, *20*(08n11), 1055–1059.

94. Anguera G., Brewster J.T., Moore M.D., Lee J., Vargas-Zúñiga G.I., Zafar H., Lynch V.M., Sessler J.L. *Inorg. Chem.* **2017**, *56*(16), 9409–9412.

95. Brewster J.T., Anguera G., Moore M.D., Dolinar B.S., Zafar H., Thiabaud G.D., Lynch V.M., Humphrey S.M., Sessler J.L. *Inorg. Chem.* **2017**, *56*(21), 12665–12669.

96. Bucher C., Seidel D., Lynch V., Sessler J.L. *Chem. Commun.* **2002**, 328–329.

97. Sessler J.L., Seidel D., Lynch V. *J. Am. Chem. Soc.* **1999**, *121*(48), 11257–11258.

98. Hiroto S., Shinokubo H., Osuka A. *J. Am. Chem. Soc.* **2006**, *128*(20), 6568–6569.

99. Vogel E., Bröring M., Fink J., Rosen D., Schmickler H., Lex J., Chan K.W.K., Wu Y.-D., Plattner D.A., Nendel M., Houk K.N. *Angew. Chem. Int. Ed. Engl.* **1995**, *34*(22), 2511–2514.

100. Bröring M., Jendrny J., Zander L., Schmickler H., Lex J., Wu Y., Nendel M., Chen J., Plattner D., Houk K.N., Vogel E. *Angew. Chem. Int. Ed. Engl.* **1995**, *34*(22), 2515–2517.

101. Geier G.R., Grindrod S.C. *J. Org. Chem.* **2004**, *69*(19), 6404–6412.

102. Braaten K.C., Gordon D.G., Aphibal M.M., Geier G.R. *Tetrahedron* **2008**, *64*(42), 9828–9836.

103. Kido H., Shin J.-Y.Y., Shinokubo H. *Angew. Chem. Int. Ed.* **2013**, *52*(51), 13727–13730.

104. Sessler J.L., Weghorn S.J., Lynch V., Johnson M.R. *Angew. Chem. Int. Ed. Engl.* **1994**, *33*(14), 1509–1512.

105. Shimizu S., Cho W.S., Sessler J.L., Shinokubo H., Osuka A. *Chem. Eur. J.* **2008**, *14*(9), 2668–2678.

106. Setsune J., Katakami Y., Iizuna N. *J. Am. Chem. Soc.* **1999**, *121*(38), 8957–8958.

107. Setsune J., Maeda S. *J. Am. Chem. Soc.* **2000**, *122*(49), 12405–12406.

108. Setsune J., Tanabe A., Watanabe J., Maeda S. *Org. Biomol. Chem.* **2006**, *4*(11), 2247.

109. Okujima T., Ando C., Agrawal S., Matsumoto H., Mori S., Ohara K., Hisaki I., Nakae T., Takase M., Uno H., Kobayashi N. *J. Am. Chem. Soc.* **2016**, *138*(24), 7540–7543.

110. Anguera G., Cha W.-Y., Moore M.D., Lee J., Guo S., Lynch V.M., Kim D., Sessler J.L. *J. Am. Chem. Soc.* **2018**, *140*(11), 4028–4034.