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Nucleophilic Substitution as a Tool for the Synthesis of Unsymmetrical Porphyrins

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ABSTRACT

Porphyrins readily undergo S_NAr reactions with organolithium reagents, preferentially at the *meso*-positions. The reaction is highly versatile as it is accomplished with both metal complexes and free-base porphyrins in good yields and high regioselectivity. It can be used in sequence for the introduction of up to four different *meso*-substituents and is the first general method for the direct introduction of functional groups into unactivated porphyrins, including porphine. Depending on the porphyrin, the structure of the anionic intermediate, or the reaction conditions, this method also allows trapping of the intermediary anion with electrophiles, transformation into *meso*−*meso*-linked bisporphyrins, synthesis of phlorins or porphodimethenes, and β-addition to yield hydroporphyrins.

Introduction

Porphyrins are a unique class of compounds that are ubiquitous in nature and function in a wide variety of roles ranging from oxygen transport, electron transfer, and oxidation catalysts to photosynthesis. They are among the most widely distributed and important cofactors found in nature and are crucial regulatory effectors in many biochemical processes. Thus, disruption of their biosynthesis results in significant health problems, and tetrapyrroles play a central role in disparate areas such as photodynamic therapy, malaria, porphyrias, and unsolved medical problems such as drug-induced neuropsychiatric disorders. On a chemical basis, these effects are related to their chemical properties, namely, their photochemical (energy and exciton transfer), redox (electron transfer, catalysis), and coordination (metal and axial ligand binding) properties, and their conformational flexibility (functional control). By virtue of these properties they are some of the most important fine chemicals in industry and are utilized in an ever-expanding array of applications ranging from use as pigments and oxidation catalysts to use in emerging areas such as cancer therapy, artificial photosynthesis, sensors, nonlinear optics, and nanomaterials.

In this context porphyrin chemistry has undergone quite a renaissance, and a recent comprehensive work on porphyrins required 20 volumes to give an overview of the state of the art of this area.[1] But, as disparate as the topics listed above might appear, they have a common denominator founded in the underlying chemistry of these compounds. Most of the current applications require the synthesis of unsymmetrically substituted porphyrins, i.e., systems with different substituents in a regiochemically defined manner. Typical examples are the so-called ABCD-porphyrins **5**, where four different *meso*-substituents are present.[2] Depending on the type and arrangement of these substituents, different applications are possible: Different residues with functional groups suitable for small-molecule binding may be used for catalysis, a mixture of polar and nonpolar residues yields amphiphilic porphyrins suitable for photodynamic therapy, and a mix of electron-donating and -withdrawing groups will give push−pull porphyrins for applications in nonlinear optics, to name only a few possibilities.

However, future progress in this area is hampered by the limited synthetic accessibility of porphyrins. There is still a notable absence of practical and general methods for the synthesis of unsymmetrically substituted porphyrins, the keyword being "practical". Since the work of Willstätter, Fischer, Woodward, and Eschenmoser, almost any desired β-substituted porphyrins can be synthesized on paper and methods for their preparation are continuously evolving.[3] However, total syntheses are very cumbersome and often involve so many steps to be practically irrelevant, while for *meso*-substituted porphyrins no reliable method existed until recently. Thus, there is a pressing need to develop porphyrin syntheses that can yield unsymmetrically substituted macrocycles in few synthetic steps.

meso-Substituted Porphyrins

Due to their symmetry and simple preparation, most of the applications currently under study use 5,10,15,20-tetraarylporphyrins **4**, and a significant body of methods has been developed for the modification of the β-positions in such systems.[4] Thus, porphyrins with different *meso*-substituents (e.g., **5**) would offer a versatile class of compounds both for direct use in applications and for subsequent chemical transformations.

In principle, there are three ways to access such compounds (Scheme 1). The most logical would be the disconnection into a bilane **2** or any combination of pyrrole building blocks **3** that can be used in [2+2] or [3+1] condensation reactions (B or C). The latter approach is very involved but possible for certain substituents.[5] Theoretically possible is also a mixed condensation using pyrrole **1** and various aldehydes (path A). Obviously, this will work only for systems of lower symmetry. Otherwise the number of regioisomers formed is too large, and the

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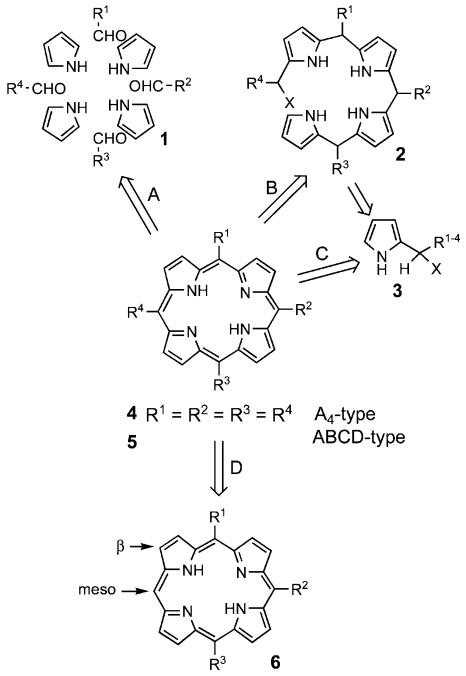
Scheme 1. Retrosynthetic Analysis of *meso*-Substituted Porphyrins



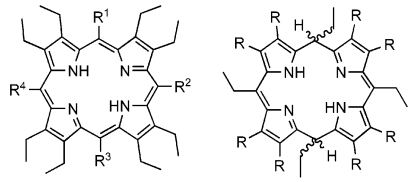
necessary purification and separation workup is too cumbersome if possible at all. In addition, all these reactions involve acid-catalyzed condensation reactions, often resulting in significant scrambling of the pyrrole units and limiting the types of substituents that can be used. Thus, it would be much more logical to introduce different substituents directly at the *meso*-positions (path D), for example, by transformation of a trisubstituted ABC-porphyrin (**6**) to porphyrin **5**.

Existing Methods and Limitations

Contrary to transformations involving the β-positions, much fewer methods involve modifications of the *meso*-positions. Although these positions should be the most reactive for both electrophilic and nucleophilic substitutions, the reality is quite different.[6] Porphyrins have proven to be resilient toward many reactions such as Friedel–Crafts or Grignard reactions that the unsuspecting person would believe to occur easily. Most of the useful methods are S_E reactions, e.g., reactions with carbenes, rearrangements, reductive methylation,[7] nitration, thiocyanation, halogenation, and Vilsmeier formylation.[8] The latter two are the most widely employed reactions and have been used as entry reactions for many derivatives. However, formylation deactivates the macrocycle toward additional formylations, and both reactions are difficult to control in a regioselective manner. Nevertheless, *meso*-halogenated porphyrins are of considerable importance as the prerequisite for subsequent C–C coupling reactions and transition-metal-catalyzed reactions and have found widespread use in recent years.[6,8,9]

Applications of S_N reactions are even more limited and either exclusively involve special cases or require activated porphyrin systems.[8] While porphyrins are easily reduced by electrons to the respective phlorins or chlorins, their

Chart 1



7

11

8 $R^1 = R^2 = R^3 = R^4 = Ph$
9 $R^1 = R^2 = R^3 = R^4 = H$
10 $R^1 = R^2 = R^3 = R^4 = Et$

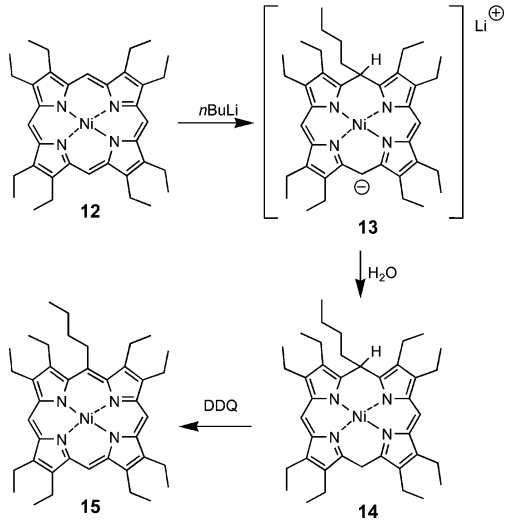
reactivity toward nucleophiles has only been studied infrequently on the basis of the assumption that such attempts would be futile.[6] For example, metalloporphyrin cation radicals and dications have been shown to react with nucleophiles, while activation toward nucleophiles could be achieved via electron-withdrawing substituents, appropriate central metals,[10] or steric effects.[11,12] All these reactions required modification of the porphyrin, were limited with regard to the type and number of substituents that can be introduced, proceeded under irreversible formation of nonaromatic systems, or gave low yields.

Nucleophilic Substitution of Octaethylporphyrin

While many of these reactions proved useful, none could be used for the *direct meso*-substitution of unactivated porphyrins with alkyl or aryl residues or for the introduction of more than two *meso*-substituents.[10] In the mid-1990s we were involved in studies on the biological relevance of the conformational flexibility of porphyrins, where highly substituted porphyrins such as **8** (Chart 1) exhibit quite distorted macrocycles.[13,14] However, symmetric porphyrins exhibit symmetric distortion modes, and unsymmetrical ones such as **7** were needed to mimic natural pigments in vivo. Nevertheless, ABCD-type derivatives **7** of 2,3,7,8,12,13,17,18-octaethylporphyrin (OEP, **9**) were inaccessible with existing methods, and even simple looking porphyrins such as the dodecaalkylporphyrin **10** could not be prepared via condensation reactions, invariably yielding oxidation-resistant porphodimethenes of type **11**.[15] To access such compounds based on the OEP framework, we undertook a comprehensive investigation of the reactivity of the porphyrin system toward organometallic reagents. While attempting to prepare porphyrin Grignard reagents from bromo-OEP, we also tried a halogen–metal exchange with *n*BuLi and noted the formation of lightly colored intermediates which upon exposure to air turned red to give more apolar products.[16]

More detailed studies using Ni^{II}(OEP) (**12**) showed that the porphyrin had undergone a *meso*-alkylation reaction (Scheme 2).[16] On the basis of the reaction conditions and color changes involved, we surmised a reaction mechanism akin to the Ziegler alkylation, i.e., intermediary formation of a Meisenheimer-type complex (**13**), which is hydrolyzed to a porphodimethene (**14**) and that in turn is oxidized to the product porphyrin **15**. Thus, overall the reaction followed an addition–oxidation mechanism. Surprisingly, this reaction was easily achieved in quantitative yield with *n*BuLi. Comparative investigations with

Scheme 2. Initial Reaction: Ni^{II}(OEP) + *n*BuLi

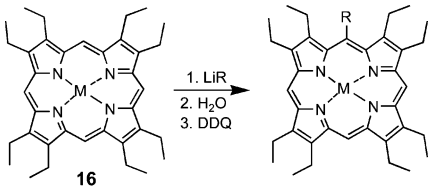


other metal complexes showed that the reaction could also be performed with zinc, copper, and cobalt porphyrins in yields ranging from 40% to 90%, while iron porphyrins underwent degradation. More importantly, LiR reacted smoothly with free-base porphyrins, indicating that this might be a versatile reaction for unactivated porphyrin systems. The reaction was easily extended to a variety of different organolithium reagents including those yielding porphyrins suitable for subsequent chemical transformations and C−C coupling reactions (Scheme 3).[17] With the exception of the sterically hindered *t*BuLi, all LiR reagents gave good to excellent yields, especially when compared to the <5% yields of mixed condensations.[2] While for a given porphyrin differences in the reactivity of the organolithium reagent were reflected in the yields, the lower yields observed for reaction of **12** with aryllithium reagents were counterbalanced by the observation that their reactivity with the free-base porphyrin was often higher. Thus, alkyllithium compounds typically give higher yields with metalloporphyrins, while aryllithium reagents often give better yields with free-base porphyrins.

Multiple Alkylations and Regioselectivity for β-Substituted Porphyrins

Successful introduction of one *meso*-substituent prompted investigations into whether a stepwise substitution of all four *meso*-positions would be possible. Indeed, this could be achieved as shown in Scheme 4 for the example of *meso*-butylations.[16,17] As expected, gradual introduction of *meso*-butyl residues led to a bathochromic shift of the absorption bands, indicating increasing macrocycle distortion.[13,18] Using this approach, dodecasubstituted OEP derivatives with various combinations of *meso*-aryl and -alkyl residues, i.e., ABCD-type derivatives **7**, could be synthesized with overall yields of 20−40%.[19] Subsequent substitution reactions were regioselective with a clear preference (about 7−20:1) for the 5,10-pattern; i.e., the new substituent is introduced in the *meso*-position neighboring the one already carrying a substituent (Scheme 5). This directing effect is more pronounced for *meso*-aryl

Scheme 3. Reaction of OEP with Various RLi Compounds



	R	**a** M = Ni	**b** M = 2H
17		>95 %	50 %
18		82 %	
19		no react.	
20		>95 %	
21	OPh	60 %	
22		70 %	
23		75 %	48 %
24		65 %	>95 %
25	Br	40 %	56 %
26	OMe, MeO	65 %	40 %
27	NH_2		72 %
28			48 %

substituents than *meso*-alkyl residues. For example, 5,10-diarylporphyrins such as **36** did not react with RLi at all as the typical mesomeric stabilization of the benzylic anion **38** is not possible due to steric constraints in **39**.

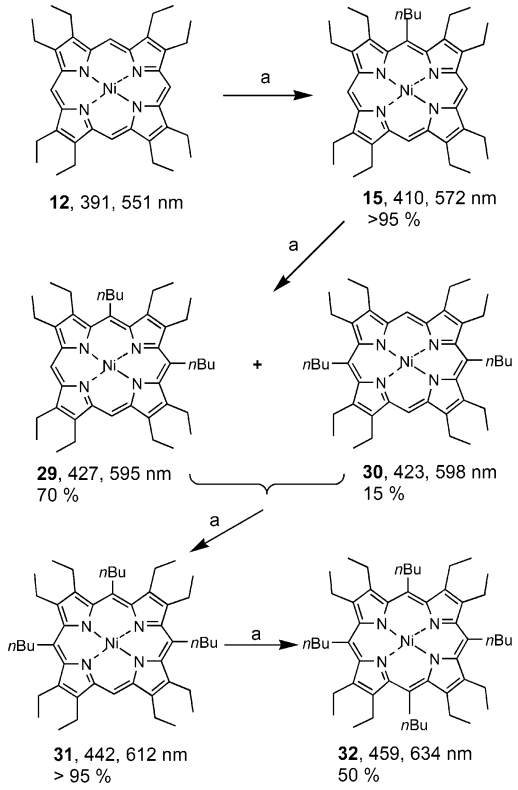
Regioselectivity for β-Unsubstituted Porphyrins with Free *meso*-Positions

During our initial studies Krattinger and Callot had reported on the reaction of tetraphenylporphyrin (TPP, **92**) with *n*BuLi and *t*BuLi and described both *meso*- and β-alkylations (see below).[11] Using 5,15-disubstituted porphyrins such as **40** as a test bed, linear alkyl- and aryllithium reagents showed complete regioselectivity for the *meso*-position and resulted in the formation of the respective A_2B-type porphyrins **41** in good to excellent yields (Scheme 6).[20] In the latter case, yields were slightly lower than for the aryl porphyrins. With increasing steric bulk of the attacking anion, an increasing number of colored byproducts were formed, indicating β- and *meso*-addition reactions to yield phlorins, chlorins, and ring-opened products.[21]

Reaction Mechanism

During the reaction of porphyrins with organolithium reagents, the deep red porphyrin solution turns brown immediately after addition of LiR. Upon hydrolysis with

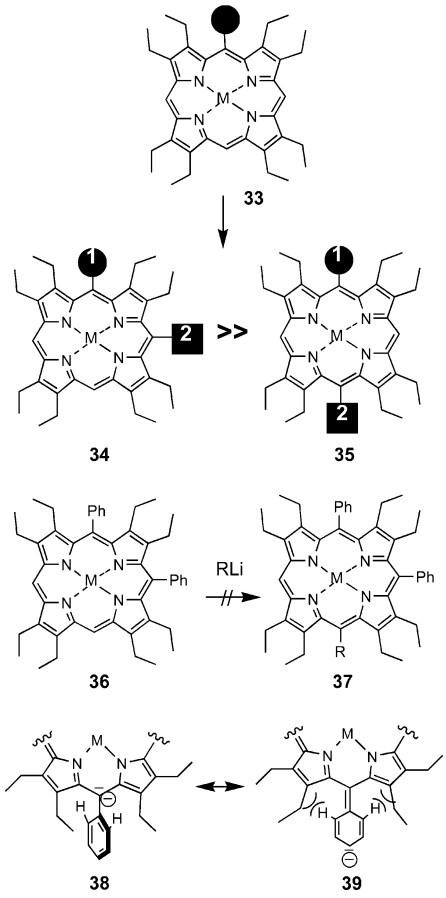
Scheme 4. Successive Butylation of Ni^{II}(OEP)[a]



[a] The numbers give the main absorption bands and yields. Reagents and conditions: (a) (1) *n*BuLi, THF, −70 °C, (2) H_2O, (3) DDQ.

water, the color remains unchanged in experiments with nickel(II) complexes while for free-base porphyrins an additional color change from brown to blue-green occurs. As shown in Figure 1, the different absorption spectra for the two intermediates after addition of water are indicative of a porphodimethene (for metalloporphyrins) and a phlorin (for free bases). Thus, different intermediates have to be postulated for S_NAr reactions of free-base porphyrins versus metalloporphyrins. Using porphyrins of both the OEP series and **40**, detailed mechanistic studies indeed revealed different reaction pathways.[22] For example, the nickel(II) porphyrin **58** was deuterated at the *meso*-position opposite the attacking butyl residue by dilute DCl (**60**) but not by D_2O. In contrast, the free-base porphyrin **59** showed no incorporation of deuterium with D_2O or dilute DCl (Scheme 7). Only with concentrated DCl did deuteration to **57** occur. The pH-dependent differences indicate that deuteration of the free base proceeds through a H/D exchange of a phlorin, while for the nickel(II) complex deuteration of the intermediary carbanion is assumed. Thus, the carbanion of the nickel(II) complex **64** takes a central place in the reaction mechanism (Scheme 8). As the basic structural framework is that of a porphodimethene, a roof-type conformation of the intermediary anion can be presumed (see the inset in Scheme 8). In contrast, the phlorin-type intermediate of the free-base reaction will have a much more planar conformation. Together with its stability toward hydrolysis, this makes **64**/**65** a prime candidate for use as a reactive nucleophile in further transformations.

Scheme 5. Regioselectivity of *meso*-Substitution of OEP Derivatives

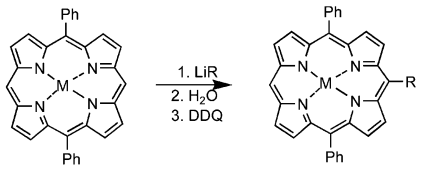


Synthetic Variations

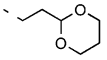
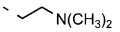
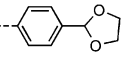
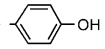
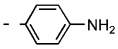
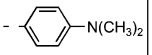
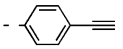
On the basis of the mechanistic studies, several possibilities for variation of the reaction conditions exist. Using nickel(II) porphyrins such as **58** as starting materials, the in situ formed anion **64**/**65** could indeed be used as a nucleophile for the trapping of organic electrophiles. For example, when the porphyrin **58** or **67** was treated with *n*BuLi or PhLi followed by hydrolysis of excess RLi and addition of alkyliodides, the A_2BC-type porphyrins **68**−**76** were obtained in good to excellent yields.[23] Thus, a simple two-step one-pot reaction suitable for the introduction of base-stable functional groups could be developed (Scheme 9).

Similarly useful synthetic variations were also possible with free-base porphyrins. One such example is the preparation of directly *meso*−*meso*-linked bisporphyrins (Scheme 10). Using the free-base porphyrin **77** or **59**, the bisporphyrins **78**−**80** were accessible in good yields simply by performing reactions similar to those described above, but omitting the hydrolysis step.[24] The mechanism of dimerization presumably proceeds via oxidation of the initial intermediate to a π-stabilized radical followed by radical dimerization. This reaction also yielded minor amounts of 5,10,15-tri- and 5,10,15,20-tetrasubstituted porphyrins. Thus, an alternative pathway to oxidation of the radical is hydride abstraction to the neutral trisubstituted porphyrins, which can react with a second molecule (RLi). Use of the respective nickel(II) complex **58** or **67**

Scheme 6. Reaction of 5,15-Diphenylporphyrins with Various RLi Compounds



40 **41**

R	**a** M = Ni	**b** M = 2H
42	>95 %	94 %
43 	52 % + byproducts	30 % + byproducts
44 	65 % + byproducts	15 % + byproducts
45 	53 % + byproducts	> 20 diff. products
46 	73 %	n.d.
47 	n.d.	75 %
48 	92 %	89 %
49 	n.d.	86 %
50 	n.d.	80 %
51 	n.d.	30 %
52 	n.d.	78 %
53 	n.d.	83 %
54 	n.d.	82 %
55 	n.d.	78 %
56 	n.d.	85 %

only gave substitution products; no dimer formation was observed.[21] This method gives convenient access to bisporphyrins with mixed *meso*-substituents while using simple starting materials and complements the Ag(I)-promoted coupling of zinc(II) porphyrins, which is a facile method for unsubstituted bis- and oligoporphyrins.[25]

Thermodynamic versus Kinetic Control

The overall reaction mechanism of most reactions described here is that of an addition−oxidation reaction. Thus, like the biosynthesis of natural tetrapyrroles, most reactions proceed through some kind of intermediary hydroporphyrin stage, and the possibility exists to use this for the targeted synthesis of hydroporphyrins with an interrupted aromatic system. Typically, the organolithium reactions described were performed at low temperatures, depending on the starting material and reagent, between −100 and −40 °C. Thus, these reactions were generally

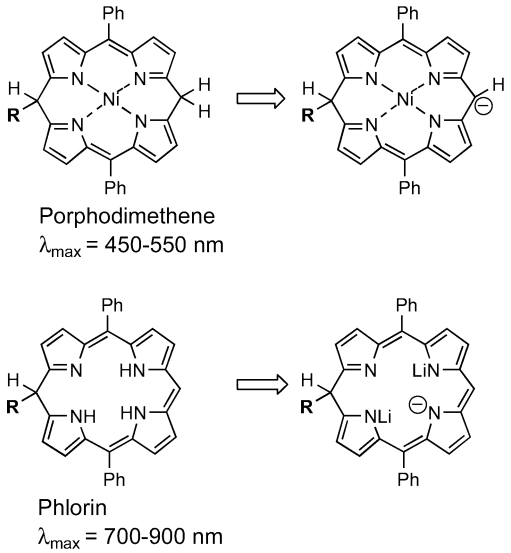
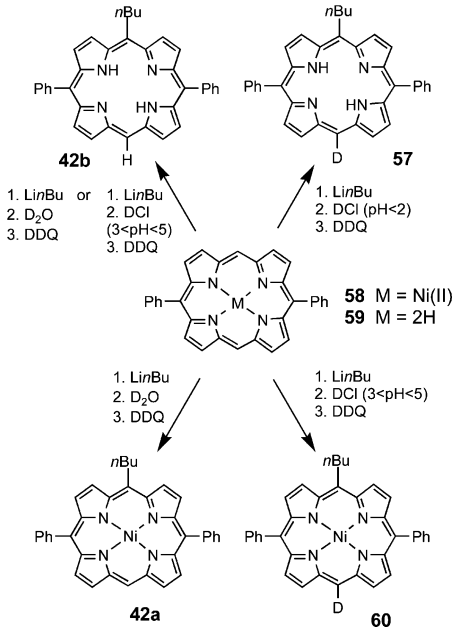


FIGURE 1. Putative intermediates during the reaction of free-base porphyrins and metalloporphyrins with RLi.

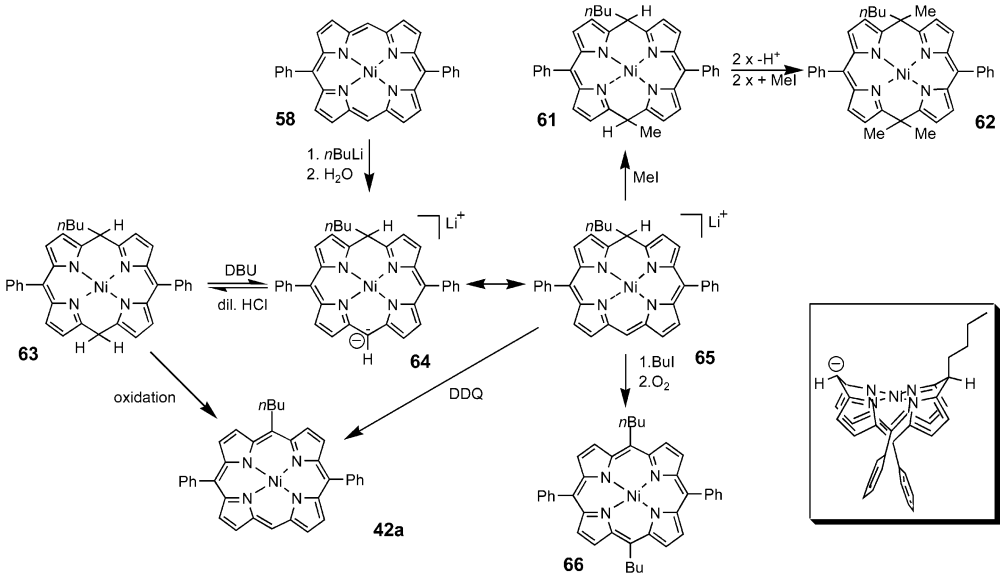
Scheme 7. Deuteration Studies with Free-Base and Nickel(II) Porphyrins



kinetically controlled and gave fully conjugated porphyrins with various substituent patterns. However, the methodology presented here also offers an entry toward porphodimethenes **81** when switching to thermodynamic control. Nowadays often called calixphyrrins, porphodimethenes are important biosynthetic intermediates of tetrapyrroles and have been developed by Sessler as anion sensors.[26] Synthetically they can be prepared via condensation reactions,[26] reductive alkylations,[7] or dealkylation of *meso*-substituted porphyrinogens.[27]

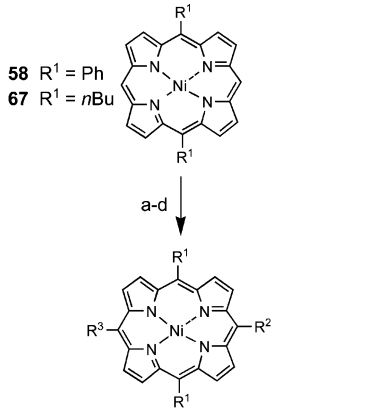
During the synthesis of highly substituted porphyrins we noted that introduction of the first three *meso*-substituents into OEP generally proceeds with almost quantitative yields while introduction of the fourth substituent at best gave 50−60% yield.[17] The remainder of the starting material was converted into a porphodimethene;

Scheme 8. Detailed Reaction Mechanism for the Nickel(II) Porphyrin 58[a]



[a] The inset shows the putative structure of the intermediary porphodimethene carbanion.

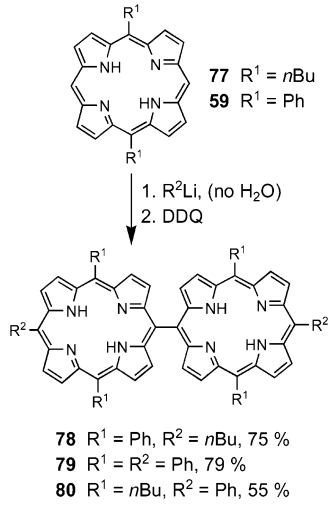
Scheme 9. One-Pot Two-Step Reaction of 5,15-Disubstituted Nickel(II) Porphyrins with R^2Li/R^3I[a]



	R^1	R^2	R^3	yield (%)
68	Ph	*n*Bu	*n*Bu	92
69	Ph	Ph	*n*Bu	90
70	Ph	Bu	$CH_2CH_2CH_2CH_2I$	79
71	Ph	Ph	$CH_2CH_2CH_2CH_2I$	71
72	Ph	Bu	$CH_2CH_2CH_2CH_2OH$	48
73	Ph	Ph	$CH_2CH_2CH_2COOEt$	52
74	Ph	Ph	$CH_2CH_2CH_2CN$	80
75	*n*Bu	Ph	$CH_2CH_2CH_2CN$	62
76	Ph	Ph	$CH_2CH_2CH_2CH_2Br$	24

[a] Reagents and conditions: (a) LiR^2, THF, −70 °C; (b) H_2O; (c) R^3I, 60 min, room temperature (rt); (d) air.

Scheme 10. Syntheses of Directly *meso*−*meso*-Linked Bisporphyrins in the Absence of Water



e.g., **83** was obtained in 40% yield during reaction of **31** with *n*BuLi to give **32.** This porphodimethene was isolated although the standard workup included oxidation with DDQ and was also resistant toward oxidation with other oxidants. Likewise, reaction of **30** with *n*BuLi under standard low-temperature conditions exclusively gave the trisubstituted porphyrin **31**. However, upon raising the reaction temperature above −80 °C, formation of the porphodimethene **82** occurred and became quantitative at temperatures above −30 °C.[17] Again, this compound was stable against common oxidants. A crystal structure analysis of **82** (see Figure 2) showed a *syn-axial* configuration of the *meso*-hydrogen atoms that was also found for other nonoxidizable porphodimethenes.[28] Thus, upon performing the reaction under thermodynamic conditions, the intermediate is locked in a configuration that is more difficult to oxidize than the one (probably *anti* configurated) that is the normal intermediate of standard porphyrin formation reactions. The tendency of the intermediate to lock into the nonoxidizable form increases with the degree of conformational distortion (i.e., the degree of overall substitution) already present in the parent porphyrin.

These observations indicated a simple way to design a synthesis for porphodimethenes using OEP as starting material (Scheme 11).[28] When **12** was reacted under standard conditions with RLi/RI combinations as given in Scheme 9, the monosubstituted porphyrin **87** was the sole product. Direct oxidation of the intermediate after addition of LiR and/or using an excess of LiR resulted in the formation of mixtures of monosubstituted (**87**) and

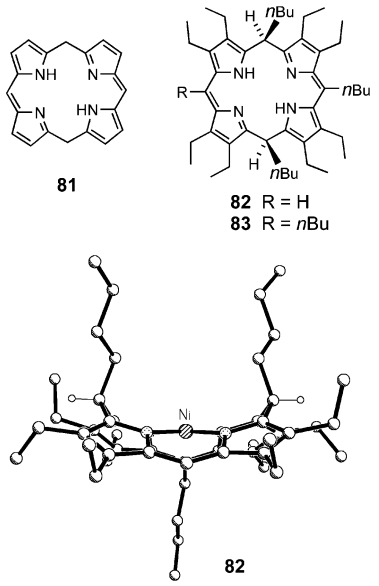
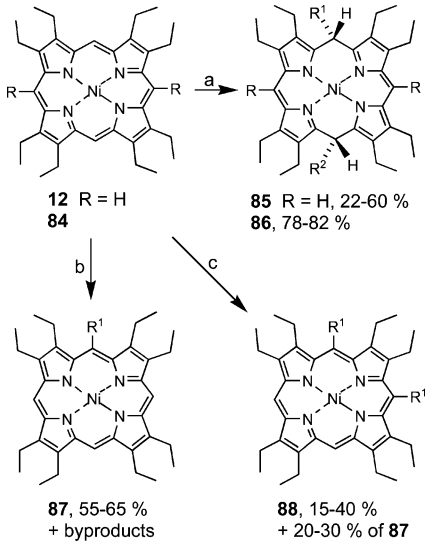


FIGURE 2. 5,15-Dihydroporphyrins (porphodimethenes) and side view of the molecular structure of the porphodimethene **82** in the crystal.

Scheme 11. Kinetic versus Thermodynamic Control in the Reaction of Ni^{II}(OEP) with R^1Li/R^2I[a]

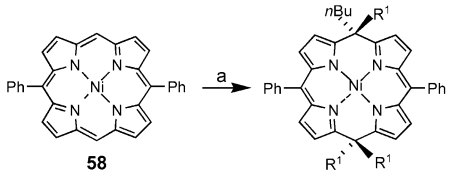


[a] Reagents and conditions: (a) (1) R^1Li, $T \ll$ rt, (2) R^2I, $T >$ rt, 5−12 h; (b) (1) R^1Li, $T \ll$ rt, (2) R^2I, $T <$ rt, (3) DDQ; (c) (1) large excess of R^1Li, $T \ll$ rt, (2) DDQ.

disubstituted (**88**) porphyrins. However, when trapping of the alkyliodides was attempted at higher temperatures and with longer reaction times, the decasubstituted porphodimethenes **85** were obtained in low to moderate yields. Use of decasubstituted porphyrins **84** as starting materials gave the dodecasubstituted porphodimethenes **86** in good to excellent yields, indicating the influence of steric effects in the formation of the porphodimethenes under thermodynamic control. Again, all these porphodimethenes showed a *syn-diaxial* configuration and were resistant toward oxidation.[28]

Use of LiR and RI for the preparation of porphodimethenes is not restricted to β-substituted porphyrin starting materials. As shown in Scheme 9, 5,15-disubstituted porphyrins such as **58** do react under conditions similar to those just described to functionalized *meso*-substituted porphyrins. However, when the substituent R^2 of the alkyl iodides employed was relatively small, novel reaction products such as **62** were obtained in about 80% yield (Scheme 12). These products are stable porphodimethenes that had undergone multiple substitutions at the C-10 and C-20 positions. To some extent this reaction can be enforced with larger residues using a large excess of RI (e.g., R = 3-cyanopropyl, 40−50 equiv) and higher temperature (50−60 °C). The mechanism for the formation of such porphodimethenes might involve a repeated deprotonation of positions 10 and 20 after formation of the monoanionic intermediate followed by trapping with electrophiles (see **61** and **62** in Scheme 8). This reaction was limited to porphyrin intermediates resulting from addition of alkyllithium reagents.

Scheme 12. Multiple Alkylation of the Disubstituted Porphyrin 58[a]



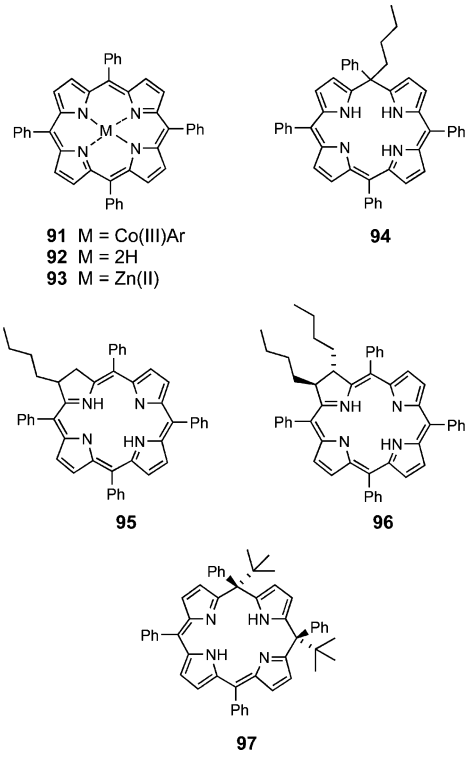
[a] Reagents and conditions: (a) (1) *n*BuLi, THF, −70 °C, (2) H_2O, (3) R^1I, 60 min, rt.

Reactions of Tetra-*meso*-Substituted Porphyrins

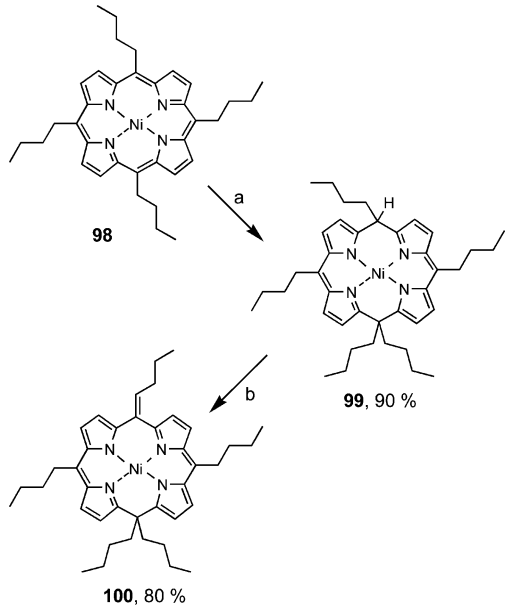
So what happens when all *meso*-positions are already occupied by substituents? Callot reported the first such study in 1996.[29] During reactions with **91** (Chart 2) aimed at exchanging the axial ligand, he noted the formation of numerous compounds when reactions with *n*BuLi were performed at 0 °C. Some of these were identified as small amounts (<3%) of mono-, di-, and tri-β-butylated porphyrins and chlorins (e.g., such as **95** or **96**).[12] Reaction of the free-base TPP **92** with *n*BuLi gave 28% of the phlorin **94** and 18% of the chlorin **95**,[11,12] while similar reactions with the zinc(II) complex **93** gave a monobutylated (**95**, 7%) and a dibutylated (**96**, 18%) chlorin.[16,17] *s*BuLi gave similar chlorins among other products.[12,30] Use of the more hindered *t*BuLi again gave a mixture of β-alkylated chlorins akin to **93** and **94** and the 5,10-di-*tert*-butylated porphodimethene **95**, albeit in yields of <5%.[8b,26] Thus, TPP and presumably other tetraarylporphyrins can undergo both *meso*- and β-addition reactions. Note that two of the $\beta-\beta$ bonds in porphyrins are not part of the aromatic system und thus easily undergo addition reactions.

In contrast to arylporphyrins such as TPP, the 5,10,-15,20-tetraalkylporphyrin counterparts are only now beginning to attract attention. However, depending on the steric bulk of the *meso*-substituents, their macrocycle conformation can vary from planar to highly ruffled,

Chart 2. Alkylation Products of TPP



Scheme 13. Reaction of (5,10,15,20-Tetra-*n*-butylporphyrinato)nickel(II) with *n*BuLi[a]



[a] Reagents and conditions: (a) (1) *n*BuLi, THF, −40 °C, (2) H_2O; (b) DDQ.

depending on the steric demand of the *meso*-alkyl group.[31] Thus, we reacted the nickel(II) porphyrin **98** with *n*BuLi and found almost quantitative conversion to the porphodimethene **99** (Scheme 13).[16,17] This compound in turn could be oxidized at the *meso*- and *ipso*-positions to yield a novel type of 5,5[1]-didehydroporphodimethenes **100** with an exocyclic double bond. Similar results were obtained with porphyrins bearing *iso*-butyl, 1-ethylpropyl, or *tert*-butyl residues; naturally no oxidation was possible in the

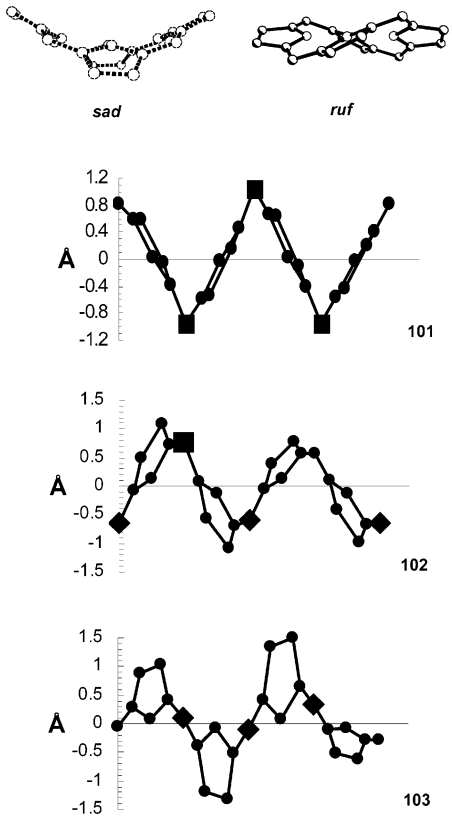


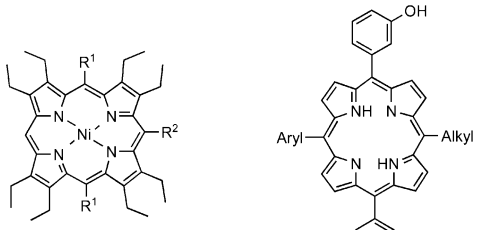
FIGURE 3. View of *sad*- and *ruf*-distorted tetrapyrrole ring systems and skeletal deviation plots for porphyrins **101**−**103**. ■ denotes a *meso*-*n*Bu substituent, ◆ a *meso*-Ph substituent.

latter case. Thus, *meso*-alkylporphyrins react with sterically unhindered organolithium reagents exclusively at the *meso*-positions. This is a further indication of the higher reactivity of the *meso*-positions toward nucleophilic attack. The selectivity might be a result of the larger degree of macrocycle ruffling in the nickel(II) tetraalkylporphyrins compared to free-base or Zn^{II}(TPP), which makes the *meso*-carbon atoms more accessible.[31]

Synthetic Applications

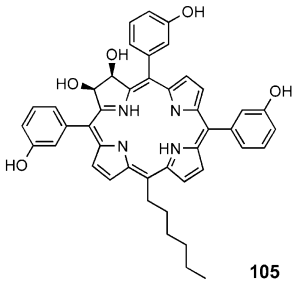
The methods described offer simple access to almost all classes of *meso*-substituted porphyrins, and we have used them in the past few years for some applied projects.[32] For example, two prominent distortion modes of nonplanar porphyrins are the *sad* and *ruf* distortions, resulting in quite different electrochemical and photophysical properties.[13−15] While porphyrins with one type of substituents exhibit predominantly one type of distortion (**101** and **103** in Figure 3), a mix of substituents (**102**) results in a mixing of distortion modes. Such compounds are suitable model compounds for biological cofactors and aid in understanding the structural and conformational parameters that govern pigment−protein interactions and help to elucidate the interrelationship among macrocycle conformation, physicochemical properties, and biological function.[19] Likewise, amphiphilic porphyrins could be rapidly generated with this method for use in photodynamic cancer therapy.[33] Optimum photosensitizers for cancer treatment require improved photophysical proper-

Chart 3

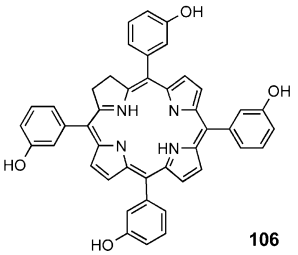


101 $R^1 = R^2 = n$Bu
102 R^1 = Ph, $R^2 = n$Bu
103 $R^1 = R^2$ = Ph

104



105

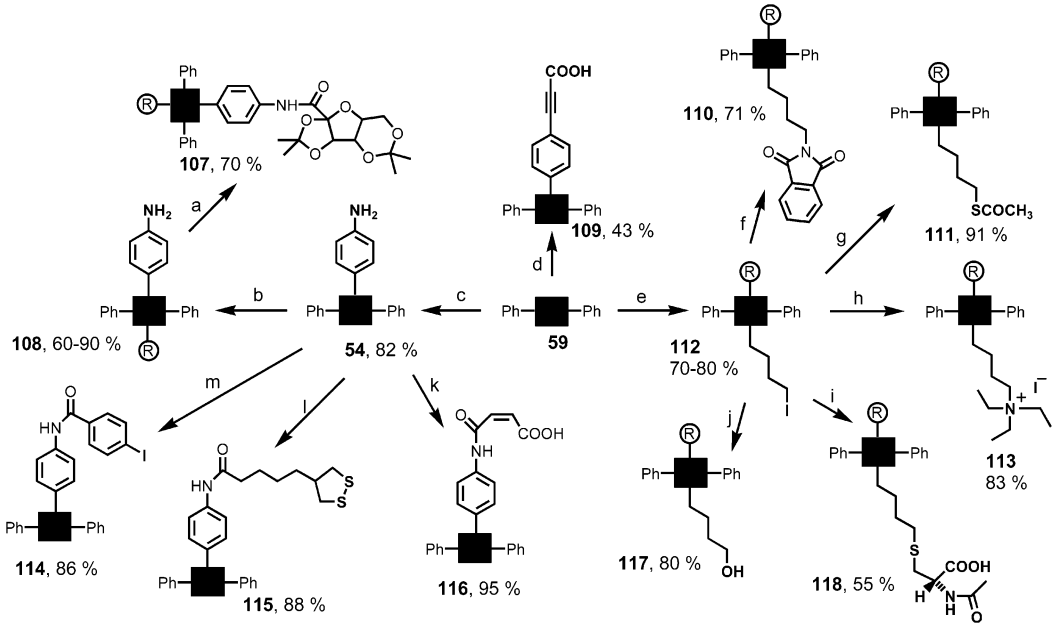


106

ties and a possibility to control the localization of the sensitizer within the tumor cell. Initial studies showed that amphiphilic derivatives such as **104** or **105** are superior candidates for new clinical studies compared to more symmetric compounds (e.g., Foscan, **106**) that are currently in clinical use (Chart 3).

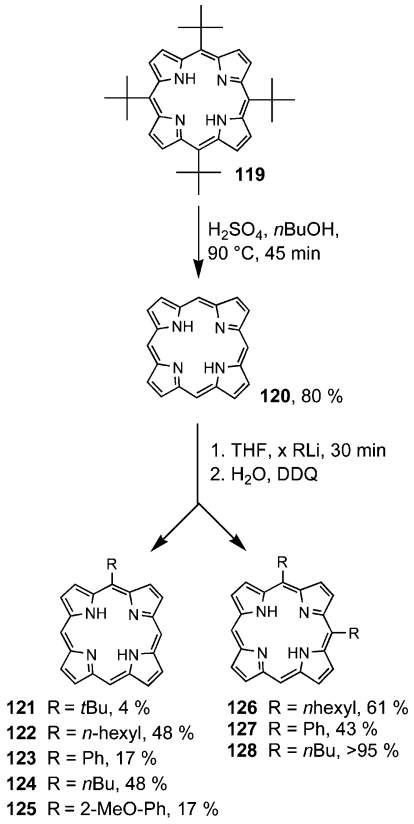
We believe that two aspects will be featured prominently in the future use of these methods. First, this method significantly shortens complex syntheses by not requiring prior activation steps (e.g., halogenations for transition-metal-catalyzed coupling reactions or metalation), circumvents the harsh reaction conditions of other methods (e.g., formylations, halogenations, nitrations) with their low tolerance for functional groups, and gives regioselective access to porphyrins that otherwise at best are accessible via mixed condensations or complex total syntheses in low yields. Scheme 14 exemplifies this by focusing on some simple transformations of an aminophenylporphyrin (**54**) and iodoalkylporphyrin **112**. As shown, porphyrins with useful chemical and physical properties such as amphiphilicity, water solubility, and electrochemical redox activity and some with biologically relevant functional groups were prepared in one or two steps in good to excellent yields starting with the easily accessible porphyrin **59**.[21] Second, this method offers a rational approach toward ABCD-type porphyrins **4** without having to resort to total syntheses. In analogy to Scheme 4, this requires stepwise introduction of substituents into the parent porphyrin (porphine, **120**). With the recent development of a convenient preparation of **120** via dealkylation of **119**,[34] this has become possible. Scheme 15 outlines syntheses of mono-*meso*-substituted (**121**−**125**) and 5,10-di-*meso*-substituted (**126**−**128**) porphyrins without β-substituents based on this approach.[35,36] We also developed condensation methods for these two classes of porphyrins, which hitherto had been almost unknown.[35−37] Here, generation of porphine, followed by in situ reaction with RLi, allowed the synthesis of either

Scheme 14. Synthesis of Porphyrins with Functional Groups[a]



[a] Reagents and conditions: (a) (−)-2,3:4,6-di-*O*-isopropylidene-L-*gulo*-hex-2-ulofuranosonic acid, DCC; (b) (1) RLi, (2) H_2O, (3) DDQ; (c) (1) *p*-aminophenyllithium, (2) H_2O, (3) DDQ; (d) (1) 4-(lithioethynyl)phenyllithium, (2) CO_2, (3) H_2O, (4) DDQ; (e) (1) RLi, (2) H_2O, (3) 1,4-diiodobutane, (4) DDQ; (f) potassium phthalimide; (g) $KSCOCH_3$; (h) NEt_3; (i) *N*-acetyl-L-cysteine, DBU; (j) KOH, 60 °C; (k) maleic anhydride; (l) DL-α-lipoic chloride; (m) 4-iodobenzoyl chloride.

Scheme 15. Reaction of Unsubstituted Porphyrin with RLi

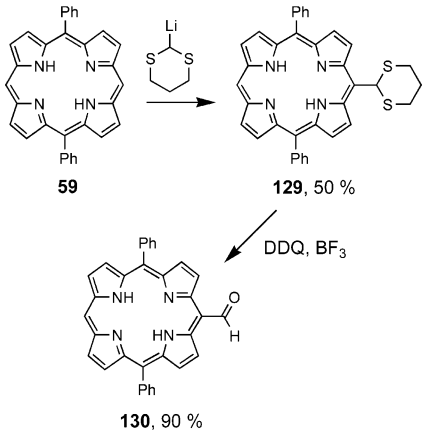


5-monosubstituted (**121**−**125**) or 5,10-disubstituted (**126**−**128**) porphyrins in low to excellent yields depending on the number of equivalents of RLi used in the reaction. In the meantime we have prepared a few 5,10- and 5,15-AB-, 5,10-A_2B_2-, 5,10-A_2BC-, and ABCD-type porphyrins using these compounds as starting material (unpublished results). Thus, it appears likely that with appropriate planning of the sequence in which the substituents are introduced all of the various alphabet combinations and structural isomers of the "porphyrin alphabet soup" are accessible.

Conclusion and Outlook

The present results clearly show that porphyrins react readily and often quantitatively with organolithium reagents, preferably at the *meso*-positions. Organolithium reagents can be used to introduce a broad range of substituents with functional groups that hitherto either were inaccessible or required multistep syntheses or mixed condensation reactions with laborious chromatographic workup. The *meso*-substitution reaction proceeds via an addition−oxidation mechanism where the intermediates derived from free-base porphyrins and metallo complexes have different electron distributions and conformations. These anionic intermediates are believed to possess phlorin- or porphodimethene-like structures, and the nickel(II) intermediates are stable against hydrolysis and exhibit a high degree of nucleophilic reactivity at the *meso*-position opposite the position of the nucleophilic attack of the organolithium reagent. The exact reaction pathway depends primarily on steric aspects and the

Scheme 16. Synthesis of *meso*-Formylporphyrins under Basic Conditions



macrocycle conformation of the reacting porphyrin and only secondarily on the steric bulk of the organolithium reagent. The methodology developed can be used to prepare mono-, di-, tri-, and tetra-*meso*-functionalized porphyrins, as well as bisporphyrins, phlorins, calixphyrrins, and chlorins. It opens a simple entry into ABCD-type porphyrins, allows the synthesis of highly substituted porphyrins with a mixed substituent pattern, and finally opens a practical way to use unsubstituted porphyrin (porphine) in syntheses. Nevertheless, some limitations remain. Organolithium reagents are not tolerated by reactive functional groups, and the synthesis of more complex RLi reagents often is cumbersome. Thus, more complex syntheses will require a combination of different C−C coupling methods.

Several aspects of this chemistry remain to be explored, notably an extension to other tetrapyrrolic systems and the use of other reactive nucleophiles.[38] In the context of studies described here, the chemistry of the tetra-*meso*-alkylporphyrins deserves more attention and detailed investigations on the regioselectivity of reactions toward ABCD-type porphyrins are necessary. Related chemistry can also be used to circumvent synthetic limitations in other methods currently used in tetrapyrrole chemistry. For example, we are currently utilizing the dithianyl anion as a synthon for the generation of formylporphyrins **130** under basic conditions (Scheme 16).[39] Similarly, we have indications that the two-step method using RLi/RI combinations for introduction of two different residues in a one-pot reaction, which so far has been optimized only for nickel(II) porphyrins, can be extended to free-base porphyrins as well by modification of the reaction conditions. Likewise, sterically very hindered residues (e.g., *t*Bu) can now be introduced by using appropriate cocatalysts. This will further improve the applicability of the methodology described here for complex tetrapyrrole syntheses.

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