Stirring the porphyrin alphabet soup – Functionalization reactions for porphyrins

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Advances in the synthesis of unsymmetrically meso substituted porphyrins are based on the development of new total syntheses and porphyrin functionalization methods. These methods have replaced earlier mixed condensation reactions and give synthetic access to almost any desired meso-substituted porphyrin. They include the complete series of porphyrin homologues and regioisomers of the A_x-series with either alkyl or aryl residues, and numerous examples of ABCD-type chromophores. The syntheses are based on a combination of classic functionalization reactions, the use of organolithium reagents in S_NAr reactions, and organometallic reactions with Pd, Ni, Cr, Ru, B, and Sn catalysis. This feature article gives an account of our work in the past decade to develop synthetic methods for the A_x- and ABCD-type porphyrins and their use as optical materials and photosensitizers.

Introduction

Research on porphyrins continues at an almost frantic pace and porphyrins are perhaps the most widely investigated compounds in chemistry. The latest attempt to summarize the current state of the art in porphyrin research is currently in publication and will encompass 15 volumes, after another 20 volumes published a mere decade ago.^{1,2} Almost 10,000 papers on porphyrins were published in the last five years alone. This is not too surprising as their stability, optical and photophysical properties, conformational flexibility, and chemical versatility together with their biological relevance in photosynthesis, respiration, medicine and as ubiquitous cofactors in biochemistry make them research objects par excellence. However, none of this would be possible without synthetic access to these fascinating molecules.

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Mathias O. Senge, born in Silbach, Germany (1961), studied chemistry and biochemistry in Freiburg, Amherst, Marburg, and Lincoln and graduated as Diplom-Chemiker from the Philipps Universität Marburg in 1986. After a Ph.D. thesis in plant biochemistry with Prof. Horst Senger in Marburg (1989) and a postdoctoral fellowship with Prof. Kevin M. Smith at UC Davis, he moved to the Freie Universität Berlin and received his habilitation in Organic Chemistry in 1996. From 1996 on he was a Heisenberg fellow at the Freie Universität Berlin and UC Davis and held visiting professorships at Greifswald and Potsdam. In 2002 he was appointed Professor of Organic Chemistry at the Universität Potsdam and since 2005 holds the Chair of Organic Chemistry at Trinity College Dublin. He was the recipient of fellowships from the Studienstiftung des Deutschen Volkes and the Deutsche Forschungsgemeinschaft; from 2005-2009 he was a Science Foundation Ireland Research Professor. His main interests are the synthetic organic chemistry, chemistry and biochemistry of tetrapyrroles, photobiology and photomedicine, crystallography and structural chemistry, and medicinal and bioorganic chemistry.

Historically, the initial studies by Willstätter, Stoll, Küster and Fischer exclusively focused on the structure elucidation of the naturally occurring chlorophylls and hemes. This was then followed by Fischer's development of total syntheses of related β-substituted porphyrins and later by total syntheses of chlorophyll and vitamin B₁₂ derivatives. Practical use of compounds such as the proto- and etioporphyrins or octaethylporphyrin (OEP) **1** has declined in recent years, mostly a result of the synthetic efforts required in their preparation and the decline in the number and funding of large organic chemistry groups focusing on synthetic porphyrin chemistry. Instead, most practical applications utilize the more easily accessible meso substituted porphyrins.

Fig. 1 Selected A_x- and ABCD-type members of the porphyrin alphabet soup of meso substituted porphyrins.

The classic example of a symmetric, meso substituted porphyrin is 5,10,15,20-tetraphenylporphyrin **2** and was first prepared by Rothmund in 1935.³ The meso-aryl compounds are very stable, easily prepared in high yield one-pot reactions and can be synthesized on a multi-gram scale. Since then, continuous advances, significantly so by the group of Lindsey,⁴ have turned the symmetric systems into the workhorses of many porphyrin applications. However, advances in the various application areas today mandate the use of more unsymmetric porphyrins. Most applications in optics, material science and photomedicine require unsymmetrically substituted derivatives, e.g. amphiphilic systems for use as photosensitizers,^{5a} donor-acceptor systems for applications in solar energy conversion,^{5b,c} supramolecular chemistry^{5c} and nonlinear optics,^{5d} or suitably functionalized chiral systems as enantioselective catalysts.^{5e} Thus, interest has shifted towards the use of meso substituted porphyrins with mixed types of substituents and to less symmetric systems. Generally speaking, the target compounds are members of the A_x- and ABCD-type series (Fig. 1), colloquially termed the porphyrin alphabet soup. Ideally, unsymmetrical systems with both meso alkyl^{3b,6} and aryl residues are required.

Our entry into this field was in the late nineties and was prompted by our interest in highly substituted, nonplanar porphyrins, a story told here a few years ago.⁷ Many groups have been involved in this research during the past decade⁸ and it is impossible to give justice to all significant contributions here and the reader is referred to the various chapters of the Handbook of Porphyrin Science.^{1,2} In the following we give a personal account of our contributions in this area and describe selected examples for the application of these novel synthetic methods.

Synthetic approach

In principle there are three different synthetic approaches for the synthesis of meso substituted ABCD-type porphyrins **11**: a) mixed condensation, b) total synthesis, and c) functionalization of preformed systems (Scheme 1).

The title of this article alludes to the old-fashioned way to prepare porphyrins with different or functionalized meso substituents and is indeed akin to stirring a soup. It involves mixed condensations of two or more different aldehydes with pyrrole **13** to yield a mixture of the various isomers.^{4b} In some instances selective formation of target compounds may be achieved through kinetic control but in general this requires tedious chromatographic work-up and often fails for selected target compounds such as acid labile groups. Likewise use of sterically hindered residues is problematic and can result in formation of porphodimethenes.⁹

The use of reactive pyrrole species such as **15** in condensation reactions is possible, but does not really alleviate the underlying problems of this approach.¹⁰ However, by now various improvements have been made for condensations reactions. Notably, Lindsey's group has developed a range of 2+2 and 3+1 condensation methods that can be performed on a large scale and are especially suited for the preparation of 5,15-AB- and A₂B₂-type porphyrins.¹¹

The most logical route is obviously a total synthesis, i.e. construction of an appropriate bilane precursor **14** followed by cyclization and oxidation to the desired porphyrin. Depending on the type of bilane many different approaches are possible.¹²

Scheme 1 Retrosynthetic analysis for the synthesis of A_x- and ABCD-type porphyrins.

Nevertheless, such a total synthesis of a porphyrin requires a significant number of synthetic steps. Acid-catalyzed scrambling in the final step has been an ongoing problem.¹³ For selected residues this has been overcome by newer developments, esp. the MgBr₂/DBU cyclization method.^{11,12b}

Our approach has focused on the third possibility, the functionalization of preformed systems. With respect to meso substituted systems this requires the step-wise introduction of the desired **16** residues. It relies on the intrinsic reactivity of the porphyrin meso position for electrophilic reactions and towards strong nucleophiles. While a reaction such as **16** → **11** on paper and in practice is easily accomplished it requires access to the respective precursors. Ultimately, unsubstituted porphyrin (porphine) **17** is required for a sequential introduction of the meso substituents. This was highly problematic as its preparation and functionalization was almost impossible due to its low solubility until recently.¹⁴

While this problem has now been overcome it was by no means obvious when we started this research. Indeed, initially our focus was not on the systems outlined herein but on highly substituted porphyrins, i.e. dodecasubstituted ABCD-type porphyrins with eight β substituents.¹⁵ Progress made in that area of research¹⁶ then made it clear that access to the β-unsubstituted porphyrins might be in reach as well. Thus, while the synthetic story is told here in the retrosynthetically logical way, its historical development was by no means straightforward.

Synthesis of A_x-type Porphyrins

Substituted porphyrins with one type of meso residues have been used widely. However, this has almost exclusively focused on the symmetric A₄- **7** and 5,15-A₂-type **5** systems. The latter are easily

Scheme 2 Synthesis of A- and 5,10-A₂-type porphyrins..

accessible through appropriate dipyrromethane 2+2
condensations.¹⁷ Except for a few cases prepared through mixed
condensations in low yield, the other members of the A_x series, esp.
the A- **3** and 5,10-A₂-type **4** systems remained inaccessible.

Initially we developed simple condensation methods for meso
monosubstituted porphyrins (A-type **3**) to get some measure on
their properties (Scheme 2). Using a 2+1+1 approach with pyrrole
aldehyde **18**, dipyrromethane **19** and a suitable aldehyde this
method gave access to the target compounds in 2-12 % yield.^{18a}
Obviously, scrambling may occur under these conditions and the
5,15-disubstituted compound **5** is formed under these conditions as
well. However, this product is easily removed via column
chromatography and this method gives a reasonably practical route
to these systems. For some residues (e.g., 4-nitrophenyl, ^tBu, 4-
methoxyphenyl) the monosubstituted product is the sole soluble
product and thus the method can be used for large scale synthesis.
Likewise, the 5,10-A₂-type systems **4** became accessible through a
protocol based on a 3+1 condensation of tripyrrane **20** with
aldehyde (in 4-12 % yield).^{18b} Here, the monosubstituted porphyrin
3 is formed as well, but can also easily be separated by
chromatography.

~A more logical approach was based on our earlier success in
using nucleophilic aromatic substitution with organolithium
reagents for the meso functionalization of OEP derivatives and
other β-substituted porphyrins.^{16,19} The reaction of porphyrins with
RLi reagents followed an addition oxidation mechanism and
resulted in high yields of meso substituted porphyrins.^{19c}
Preparation of **3** from **17** obviously requires access to the
unsubstituted porphyrin. While working on a similar approach
this became possible through Funasaki and Neya's porphine
synthesis through the acid-catalyzed thermal dealkylation of
tetra(*tert*-butyl)porphyrins **21**^{6a} or **22**.²⁰

The dealkylation provides porphine in high yield (>70 %),
excellent purity and in solution. Thus it can be reacted *in situ* with
organolithium reagents. Depending on the number of equivalent
RLi used this gave excellent access to the meso mono- **3** (40-70 %)
or disubstituted **4** porphyrins (50-70%).¹⁸ Residues successfully
tested so far included alkyl, aryl, methoxyphenyls, haloaryls, and
dithianyl, amongst others.²¹ Besides being suitable starting
materials for the other members of the A_x and ABCD series these
systems are interesting compounds in their own right. They allow
an investigation of the structural and electronic influence of

Fig. 2 View of a) the nonplanar molecular structure of {5-(*tert*-butyl)porphyrinato}copper(II) in the crystal²² and b) the clathrate crystal structure of (5,10-diphenylporphyrinato)copper(II) hexane solvate.²²

individual substituents on the tetrapyrrole macrocycle and present
interesting synthons for crystal engineering (Fig. 2).^{7,18,22}

Synthesis of ABCD-type Porphyrins

Having the necessary starting materials in hand it became now
possible to start a logical sequence of conversion of A- → AB- →
ABC- → ABCD-type porphyrins. In principle it is possible to

Scheme 3 Schematic overview of transformations involving A_x - and ABCD-type porphyrins. Strategic starting materials in green boxes, target compounds in blue boxes. RLi = monosubstitution with organolithium reagents; RLi/RX = one-pot disubstitution via anion trapping; NBS = bromination; TM = transition metal catalyzed reactions.

perform these conversions via three consecutive reactions with RLi reagents ($3 \rightarrow 23/24 \rightarrow 16 \rightarrow 11$). An example for such a sequence is given in Scheme 3. However, in practical terms it is more convenient to use the whole repertoire of available meso functionalization methods for these conversions.²³ Scheme 3 gives an overview of the possible interconversions.

Overall the synthetic sequences developed by us for the A_x and ABCD porphyrins employ three key reactions. These are a) the monosubstitution using organolithium reagents, b) the disubstitution using RLi and R²X in a one-pot reaction, and c) the use of transition metal catalyzed C-C coupling reactions.

Method a) employs the standard S_NAr reactions developed by us before.¹⁶ It involves preparation of RLi reagents which then are reacted with either metallo or free base porphyrins. Roughly speaking, alkyl lithium reagents react better with nickel(II) porphyrins while aryl lithium reagents give higher yields with free base porphyrins. Next to availability of the organolithium reagents, the only limitations are the use of sterically hindered alkyl lithium reagents (e.g., ^tBuLi), which can result in multiple alkylation and/or β -alkylation reactions (e.g., formation of chlorins).^{24,25}

With fully meso substituted porphyrins reaction with LiR can be used for either the preparation of phlorins, porphodimethenes (5,15-dihydroporphyrins, including 5¹-5²-didehydroporphyrins) or chlorins (2,3-dihydroporphyrins) depending on the substituent type in the educt porphyrins.^{16,19,25,26} Further variations are achieved through thermodynamic versus kinetic control giving access to

oxidation resistant calixphyrins and porphodimethenes,^{26b} or through oxidation of the anionic intermediate followed by radical dimerization to yield directly meso-meso linked bisporphyrins.^{24b,26a,27}

Method b) is derived from method a) and involves the trapping of the *in situ* generated "anion" derived from the attack of the nucleophile. Instead of hydrolysis of the intermediate to a porphodimethene the presence of an organic electrophile allows capture of the intermediate to yield a disubstituted product where one residue (A) is derived from the organolithium reagent and the other (B) from the organic electrophile.²⁸ Initially, this method was only applicable to nickel(II) porphyrins but we could now extend it to free base porphyrins as well.^{28b} Thus, it is possible to convert an AB porphyrin in one step into an ABCD porphyrin.

Method c) encompasses a whole range of Pd-catalyzed reactions.²⁹ Since the first reports on such reactions with porphyrins most of the standard Pd-catalyzed reactions (esp. Heck, Suzuki, Sonogashira, and Stille) have been applied to tetrapyrroles.³⁰ These reactions require first bromination or iodination, easily achieved in often quantitative yield for one free meso position, followed by the transition metal catalyzed coupling reaction. Yields are good to excellent in most cases. These methods are continuously developed further³¹ for use with porphyrins (*vide supra*) and surveys of new advances have been provided.^{8,9,29} Limitations still exist with regard to the introduction of alkyl residues or heteroatom linked groups. Another problem is the halogenation of porphyrins with

more than one free meso position. Here two or more products are formed which require chromatographic separation.³² The bromoporphyrins can also be used to access the respective Grignard species.³³

Another possibility is the bromination of A-porphyrins to yield the bromoporphyrins **25-29**. Although this reaction is not very selective and results in mixtures, it can be controlled to some extent by the number of equivalents of NBS used.³⁴ The bromoporphyrins can then be used for analogous sequences to yield the A_x or ABCD porphyrins. Obviously, any other meso functionalization reaction (e.g., formylation, nitration, etc.) can be employed at each step. Some examples for this are outlined below. Likewise, more interconversions than shown in Scheme 3 are possible. For example, the 5,10-disubstituted porphyrins **24** can be monohalogenated and converted into **16**. Naturally, derivatives of 5,15-A₂ porphyrins **5** are accessible through the same sequences as outlined above with **A** = **B**. As these compounds are widely employed in applications they have been included in Scheme 3 as a separate pathway.

None of the outlined three strategic methods alone is a *conditio sine qua non* for optimum preparation of A_x or ABCD porphyrins. In reality there is no generally applicable sequence that works well for all porphyrins. Each of the individual reaction types has some limitations (*vide infra*). The synthetic route chosen always depends on the desired target compounds and substituents involved. For some substituents a mixed condensation gives only one product and thus is superior to functionalization reactions. In our experience synthesis of the 5,15-A₂ and -AB starting materials is still best accomplished via condensation methods, while the 5,10-AB species are more easily accessible through RLi reactions. Due to the formation of regioisomers and multiply alkylation products use of A-porphyrins is still somewhat problematic. The AB-porphyrins are suitable starting materials for ABC-type systems through nucleophilic substitution and the reactions give good yield. Subsequent steps are perhaps better performed with Pd-catalyzed reactions of appropriately brominated systems. The ABC porphyrins can be transformed with RLi reagents to the respective ABCD-type systems but the yields can be low. As shown, AB-systems can be converted via RLi/RI to ABCD-porphyrins, again with low yields. Here use of Pd-catalyzed reactions is preferred although the RLi method gives easier access to alkyl substituted systems. Monobromination of ABC-porphyrins proceeds well and the subsequent coupling reactions give acceptable yields. However, a use of either method for the individual steps in the sequence A → AB → ABC → ABCD porphyrins and/or the methods developed by Lindsey¹¹ can give almost any desired ABCD porphyrins.

Classic Functionalization Reactions

Despite the success made in developing a strategic approach to the A_x and ABCD porphyrins it became quickly clear that this is not the end of porphyrin chemistry but just the opening of a new avenue. Established methods need further improvements and new methods are necessary as well to develop the full potential of this approach. Thus we have taken another look at some well known reactive porphyrins and begun a program to develop new transition metal catalyzed reactions for porphyrins. An example for the former are the formylporphyrins.

Scheme 4 Syntheses and transformations of formylporphyrins. a) DMF, POCl₃; b) 1. PyMe₂SiCH₂Li, THF, -78 °C → rt, 2. HCl, 0 °C, 3. DDQ, 65 °C; c) 1. 1,3-dithiane, BuLi, TMEDA, 2. H₂O, DDQ; d) DDQ, BF₃·OEt₂; e) Grignard reaction; f) Wittig reaction; g) PyMe₂SiCH₂Li, THF, -78 °C → rt, 2. HCl, 0 °C, 3. O₂; h) PyMe₂SiCH₂Li, THF, -78 °C → rt, 2. RCOCl, -78 °C → rt, 3. HCl 0 °C, 3. DDQ, 65 °C; i) 3-(dimethylamino)acrolein, POCl₃.

Formylporphyrins

Sometimes "old-fashioned" methods are still the best. One of the most versatile derivatives of porphyrins are formylporphyrins.³⁵ Initially used mostly for OEP derivatives, they are easily accessible through Vilsmeier formylation in the meso or β position. For example, reaction with A₂-porphyrins gives the mono- **40** and/or diformylporphyrins **41** in good yields (Scheme 4). However, the reaction may yield mixtures and requires the use of metalloporphyrins (Cu or Ni). In order to overcome these drawbacks and to allow a synthesis under nucleophilic instead of electrophilic conditions we developed an alternative protocol based on the dithianyl synthon **43**.³⁶ This can be used in condensation reactions or used as a nucleophile with free base and metalloporphyrins to yield the dithianylporphyrins **44**^{36c} and give the formylporphyrins after deprotection.

A complementary method utilizes reaction with (2-pyridyldimethylsilyl)methyl lithium **42** to give the formylporphyrins in high to excellent yield.^{37a} This reagent can also be used to access the carbinols **45**^{37b} or to generate acylformylporphyrins **46**.^{37c} Another method is the Pd-mediated coupling of a bromo derivative with a one-carbon synthon (hydroxymethyl tributyltin or CO) which has been used for the preparation of formylchlorins.^{37d}

The porphyrins discussed here can also undergo a vinylogous Vilsmeier reaction to yield the acroleinylporphyrins **47**.^{35c,38,39} The formylporphyrins easily undergo Grignard reactions to yield **48** or Wittig reactions to give **49**.^{36b} They are versatile precursors for

many other reactions, e.g., McMurry⁴⁰ or Peterson olefination^{35e} and are often used as precursors for the preparation of multiporphyrin arrays.^{35d,40,41}

Transition Metal Catalyzed Reactions

Transition metal catalyzed reactions present the most widely investigated methods for the functionalization of porphyrins. They were the first method to allow the direct modification of the meso carbons in a general fashion.^{8,29-31} Prior to that, only "simple" reactions such as halogenation, nitration, or formylations were possible and most "functionalization reactions" involved functionalization of peripheral residues such as meso aryl groups. The advent of TM reactions for tetrapyrroles initiated a shift away from mixed condensations or total syntheses and jump started synthetic applications of porphyrins, notably in the use of conjugated dimers and porphyrin arrays. By now many such reactions are known, both for the meso and β positions. Most are based on Pd-catalyzed reactions and in the following we give a brief account of our recent endeavors in this area. Needless to say, this field is ever expanding and actively investigated by other groups as well.^{8,29-31}

Palladium

The archetypical Pd-catalyzed reaction is the Heck reaction.^{30a,42} It and the Suzuki reaction^{30d,f,g} are the most widely used TM-catalyzed reactions for porphyrins.

Our first foray into this involved a β functionalization reaction and was an extension of our work with RLi reagents (Scheme 5). Reaction of fully meso substituted porphyrins **50** with RLi typically gives phlorins or chlorins (through β - β addition) in low yield.^{19a,25} However, reaction of alkyl lithium reagents in conjunction with Pd catalysts significantly increased the yield of the chlorins **52**.⁴³ Depending on the type of **50**, the steric bulk of the RLi reagent and the catalyst [$\text{Pd}(\text{PPh}_3)_4$ or $\text{Pd}_3(\text{dba})_2 \cdot \text{CHCl}_3$] the reaction could be

Scheme 5 Synthesis of 5,10-porphodimethenes and/or β -substituted chlorins.

Fig. 3 View of the molecular structure of 5,5,10,10,15,20-hexaphenylporphyrin in the crystal (**52** with $\text{R}^1 = \text{R}^2 = \text{Ph}$). Hydrogen atoms have been omitted for clarity.^{43c}

directed to give predominantly either the chlorin **52** or, surprisingly, the 5,10-porphodimethene **51**. The latter are a new class of calixporphyrins⁴⁴ and exhibit very nonplanar cavities suitable for anion binding (Fig. 3).^{43c,44b}

More typical C–C coupling reactions are based on the conversion of halenoporphyrins (Scheme 6).³² Arnold's group reported a number of interesting reactions of bromo- and iodoporphyrins.^{29c,45} On one hand reaction the monobromo derivatives **53** could be converted into the useful monoiodo compounds **55** via halogen exchange reactions through the η^1 -palladioporphyrin intermediate **54**.^{45a} Pd-catalyzed phosphination of the iodo compounds with $(\text{MeCN})_2\text{PdCl}_2$ gave meso porphyrinylphosine oxides **59**.^{45a,b} Similar reactions were possible for the respective halovinyl compounds giving another entry into ethenyl linked bisporphyrins.^{42,45a} On the other hand, the nickel(II) complexes of **53** could be converted into the primary **56** and secondary **57** amines with hydrazine under Pd catalysis or to the hydroxyporphyrins **58**.^{45c} A metal free amination of bromoporphyrins has been reported as well.⁴⁶ For an excellent

Scheme 6 Selected transformations of monobromoporphyrins. a) $\text{Pd}_2(\text{dba})_3$, dppe; b) I_2 ; c) $(\text{MeCN})_2\text{PdCl}_2$; d) 1 equiv. hydrazine sulfate, Pd cat., THF, 68 °C, 16 h; e) excess amine, Δ , neat, or μw ; f) **53**, Pd cat., dioxane, 100 °C, 3 d; g) 0.5 equiv. hydrazine sulfate, Pd cat., THF, 68 °C, 15 h; h) Pd cat., THF, 68 °C, 4.5 d.

Scheme 7 Syntheses and transformations of acrylic acid porphyrins.

analysis of the use of **53** for the preparation of meso vinyl- and allenylporphyrins **49** via Stille and Heck reactions see Ref. 42.

We were interested in introducing carbon based functional groups amenable for further transformations. Since porphyrin carboxylic acids are frequently used in bioconjugate chemistry we investigated the chemistry of acrylic acid derivatives of porphyrins in some detail (Scheme 7 and 10).⁴⁷ Porphyrins with one or two acroleinyl groups were prepared from **60** via Heck reactions in with methyl acrylate in 80-95 % yield. These can saponified in high yield to the acids **62** and then to the acyl chlorides **63**. The latter need not be isolated but can be used *in situ* for the preparation of activated esters **64** (60-95 %) or dimeric porphyrins. The acyl chlorides can also easily be coupled with porphyrin alcohols to give dimers in good yield.

Next we investigated the chemistry of the unknown porphyrin β-keto esters.⁴⁷ Our approach utilized the reaction of **63** with ethyl diazoacetate in the presence of PPh₃.^{48a} This yields the phosphazine **65** (70 %). In CDCl₃ this slowly undergoes partial hydrolysis to **67**. Likewise it is unstable in methylene chloride and autotransforms into the stable β-keto ester **66** in 78 % yield. This one-step method significantly improves on the synthesis of β-keto esters^{48b} which typically require the hydrolysis of the phosphazines formed in the reaction of non-acrylic acid chlorides with diazoacetate and further elimination of an NNH₂-group. Reactions of homologous compounds are described below.

More reactive (or labile) groups can be introduced as well using Pd-catalyzed reactions. We had been interested for some time in the chemistry of allenyl compounds and spend considerable effort on developing access to allenylporphyrins using the classic Wittig-Wadsworth-Emmons approach (Scheme 8).⁴⁹ However, while

preparation of the phosphonates **69** was achieved easily from the formyl- or bromoporphyrin precursors, this proved to be a dead end. Attempts to promote the second olefination step failed. When using RCHO in conjunction with LDA and nickel(II) porphyrins the result was the unexpected substitution of diisopropylamine from the base onto the alkenephosphonate to give porphyrin **70**. Use of the non-nucleophilic base, ^tBuOK, only resulted in partial dehydrophosphonation to the alkynylporphyrin **71**, while the free base of **69** did not react at all. Thus, we turned our attention to a Suzuki approach using the allenylboronic acid pinacol ester.⁵⁰ Indeed, this was successful and the nickel(II)porphyrin **73** could be obtained in 50 % yield. However, the reaction requires very exacting conditions as only small changes lead to other products.⁴⁹ Thus, depending on the base and metalloporphyrin used either the 1-propynyl- **72**, allenyl- **73**, or 2-propynylporphyrin **74** could be prepared (Scheme 8).⁵⁰

Scheme 8 Synthetic attempts to prepare allenylporphyrins. a) H₂C[OP(OR)₂]₂, NaH, THF, 0 °C, M = Ni(II), 88 %; b) Heck, H₂C=CHPO(OR)₂, M = 2H, 68 %; c) LDA, THF, -78 °C, PhCHO, M = Ni(II), 77 %; d) ^tBuOK, PhCHO, THF, -78 °C, M = Ni(II), 31 %; e) PdCl₂(dppe), Cs₂CO₃, THF, 80 °C, M = Ni(II), 61 %; f) PdCl₂(dppe), K₂CO₃, THF, 80 °C, M = Ni(II), 50 %; g) PdCl₂(dppe), K₂CO₃, THF, 80 °C, M = Zn(II), 46 %; h) MeLi, MeI, THF, -30 °C, M = Zn(II), 88 %.

Although Suzuki-Miyaura couplings are frequently used in porphyrin chemistry^{51a} there are still some limitations. Almost exclusively aryl boronic acids are used as coupling partners probably due to the fact that cross-coupling reactions using alkylmetallic compounds have proven problematic due to β-hydride elimination of the organopalladium intermediates.^{51b} Nevertheless, as outlined in the ABCD-porphyrin section, alkylsubstituted porphyrins are desirable target compounds and the RLi method developed by us, as any other, has some limitations. Thus, we decided to expand the utility of the Suzuki reaction in porphyrin chemistry to the respective alkyl derivatives. A possible approach to circumvent the β-hydride elimination is the use of potassium organotrifluoroborates instead of boronic acids or

esters.^{51b} They offer higher air stability and a number of potassium organotrifluoroborates are commercially available that cannot be obtained as the boronic acid or ester analogues due to their instability.

Scheme 9 Reaction of potassium organotrifluoroborates with bromoporphyrins.

Again, we used the A₃- or A₂-bromoporphyrins as starting materials and first optimized the conditions developed by Molander *et al.*^{52a} for the Suzuki coupling of porphyrins.^{52b} Gratifyingly, 5,10,15-tris(4-methylphenyl)-20-vinylporphyrin **75** could be obtained from 5-bromo-10,15,20-tris(4-methylphenyl)porphyrin in 61% yield. Thus encouraged we employed various potassium organotrifluoroborates for similar reactions (Scheme 9).⁵³

Although not yet optimized for the individual compounds the reaction give acceptable to good yields. Note, that the potassium organotrifluoroborates used for the synthesis of compounds **78-82** are not commercially available as their boronic acid or ester analogues and thus this approach offers significant advantages. The reaction can be applied equally well to the β -position, e.g. to give **83** from 2-bromo-5,10,15,20-tetraphenylporphyrin in good yield. Surprisingly, reaction of the more reactive iodo derivative **55** with potassium bromomethyltrifluoroborate gave the meso-meso directly linked dimer **84** in low yield.

Ruthenium

The standard Ru catalyzed reaction is the metathesis reaction with Grubbs catalysts.⁵⁴ It has been used for the conversion of

Scheme 10 Reactions of allylporphyrins and porphyrin acrylic esters. a) Grubbs II, 39 °C; b) TFA, CH₂Cl₂; c) KOH, MeOH/EtOH; d) vinyl boronic ester pinacol ester, Grubbs I, Δ ; e) (pinacolato)diboron [(Me₄C₂O₂)B-B(O₂CMe₄)], CuCl, KOAc, DMF, 55 °C; f) Grubbs II, acrylic acid, g) 1. SOCl₂, THF, 35 °C, 2. RX, CH₂Cl₂; h) EDC, DMAP, HC $\equiv$ CCH₂OH, rt, CH₂Cl₂; i) **64c**, Grubbs I $\rightarrow$ **95** (95 %, *E/Z* = 3/2), for free base; j) **64c**, Grubbs II $\rightarrow$ **95** (55 %, *E/Z* = 2/1) + **96** (31 %, *Z*) for free base.

vinylporphyrins, the synthesis of benzochlorins and various bioconjugates.^{54b} It is generally easy to perform and gives high yields. We investigated two aspects of this reaction. First we were interested in gaining access to the homologues of the acrylic porphyrins described in Scheme 7, i.e., those bearing an additional CH₂ group next to the double bond of the α,β -unsaturated fragment.⁴⁷

As outlined in Scheme 10 esters of type **86** could be obtained in very good yield from the allylporphyrin **85** via metathesis with Grubbs II catalyst. The allylporphyrins are easily accessible through Suzuki reactions and have proven versatile precursors for our investigations. The esters derived from these could be

hydrolyzed to the acid **87** with TFA. Attempts to hydrolyze the methyl ester of **86** in KOH-EtOH resulted in formation of a very polar compound, which upon treatment with HCl gave **64**. An alternative approach for the synthesis of a porphyrin acrylic acid would be reaction of the allylporphyrin **85** and the acrylic acid in the presence of Grubbs II catalyst. However, such reactions gave the acroleinylporphyrin **90** (for a similar transformation see Scheme 12).⁴⁷

The acrylic esters also proved to be good precursors for versatile boron containing porphyrin synthons.⁵⁵ Cross-metathesis with Grubbs I catalysts gave porphyrins with mono and disubstituted unsaturated boron residues **88** in good yields and complete *E*-stereoselectivity. In addition, formal cross-metathesis products with α,β -unsaturated chains smoothly underwent 1,4-addition with bis(pinacolato)diboron to the corresponding saturated boron compounds **89**.⁵⁵

Further studies showed that **87** can undergo rearrangement reactions via vinylketenes to yield both regioisomers. Reaction of the acyl chloride generated from **87** yielded compounds **91** or **92** while reactions with propargyl alcohol in the presence of a bulky soft base (DMAP) gave regioselective access to either a rearrangement product **94** or the product of esterification reactions **93** depending on the reaction conditions. Enyne metathesis of these propargyl esters with allyl porphyrins provided an easy access to 1,3-disubstituted butadienes **95** or **96**. Here, the stereochemistry and competing reactions depend on the type of Grubbs catalyst used.⁴⁷

Scheme 11 Pauson-Khand reactions of porphyrins. a) $\text{Co}_2(\text{CO})_8$, THF, Δ , 12h.

Cobalt

The first example for a cobalt catalyzed transformation of a porphyrin was given through use of the Pauson-Khand reaction.⁵⁶ The reaction is a very flexible and atom economical method for the synthesis of five-membered rings. It involves the reaction of an alkene, an alkyne and a carbon monoxide molecule in a transition-metal mediated coupling to form a cyclopentenone system.

Initially we attempted the reaction of allylporphyrins **85** with phenylacetylene (Scheme 11).⁵⁷ While the reaction gave the target compounds **97** and **98**, the yields were moderate. Thus, we changed the type of reaction partners. Reaction of the alkynylporphyrin **99** with, e.g., norbornene gave the desired adducts **100** in acceptable to good yield. In the case of norbornene this compound could then be reaction with **99** to yield the two regioisomers of the dimeric porphyrin **101** in almost quantitative yield. This method presents a simple entry into multicomponent systems.

Nickel

The allylporphyrins **85** also lead us to the identification of a new nickel-mediated reaction.⁵⁸ During the course of our investigations on metathesis reactions we prepared the diallylporphyrins **102** through Suzuki coupling of the respective dibromo precursor **38**. However, initially no reaction was observed upon treatment of compound **102** (A = 4-methylphenyl) with Grubbs I catalyst. Thus, we intended to use related metal complexes and attempted the

Scheme 12 Nickel(II) mediated reactions of allylporphyrins. a) allylboronic ester, K_3PO_4 , $\text{Pd}(\text{dppf})\text{Cl}_2$, THF, Δ ; b) $\text{Ni}(\text{OAc})_2$, DMF, Δ ; c) $\text{Ni}(\text{OAc})_2$, AcOH, DMF, 20-70%.

insertion of nickel(II). This is one of the easiest and simplest reactions in porphyrin chemistry and treatment of a free base with nickel acetate or $\text{Ni}(\text{II})(\text{acac})_2$ will normally give the metalloporphyrin quickly and in quantitative yield. But not here.

Surprisingly, in addition to the expected red nickel(II) derivative **102** two additional green fractions were obtained and identified as compounds **104** and **105**. More detailed mechanistic investigations showed that no other transition(II) salts, e.g., $\text{Pd}(\text{OAc})_2$, $\text{Zn}(\text{OAc})_2$, NiCl_2 , ZnCl_2 resulted in the formation of mono- or diacroleinyl- or the monoacroleinyl-monoformylporphyrins and indicated that nickel(II) as well as the acetate play a significant role in the reaction mechanism. Further optimization showed that the reactions

requires three equivalents of Ni(II) and can be enhanced by acetic acid⁵⁹ and then leads only to the formation of diacroleinyl porphyrins **104** in up to 70 % yield.⁵⁸

Tin

Last but not least an example for advances in the use of tin organic reagents for porphyrins. The Stille reaction^{60a} has been applied to porphyrins a few times, mainly involving C–C bond formations starting from porphyrin bromides and the non-porphyrin tin-counterparts.^{60b} We wanted to improve access to specific stannyl synthons **106** and thus undertook a study of various Stille couplings⁶¹ for porphyrins.

Reaction of standard precursor bromoporphyrins under copper free Stille conditions gave the stannyl porphyrins **107–109** in up to 60 % yield (Scheme 13). Note, these reactions use free bases and

Scheme 13 Stille reactions of porphyrins. a) tin reagent, Pd(PPh₃)₄, toluene, Δ; b) 1. LiC₆H₄Br, 2. Stille = a); c) silica gel.

no palladium insertion was observed. The reactions exclusively gave tin products, when two (for mono-substitution) or four (for disubstitution) equivalents of the tin compounds were used. No dimer formation was detected. This method can also be used for modification of the β-positions (**110**) or to yield meso disubstituted derivatives (**111**). Related stannyl porphyrins (**112,113**) can also be prepared for the OEP **1** series. The methodology is easily applicable to the preparation of various bisporphyrins, e.g. **114** and **115**.

Synthetic Applications

The question is, what can we do with all these reactions? As outlined above there is considerable interest to apply the various synthetic methods for specific application purposes. Most of these are related to optics, biomedicine, electron transfer and materials science. The following gives a brief description of our endeavors in these areas in the past years.

Nonplanar porphyrins

Continuing our interest in highly substituted, nonplanar porphyrins⁶² we have expanded on the development of the RLi reactions with OEP derivative.¹⁹ Using a sequence of lithium organic substitution reactions the synthesis of novel free base 5,10-A₂- and 5,10-AB-2,3,7,8,12,13,17,18-octaethylporphyrins bearing donating groups such as -OMe and -NMe₂ on the aryl-substituent was achieved.^{19c} Larger aromatic residues could be introduced into the macrocycle system as well, and these systems were used for the preparation of highly substituted ABCD-type porphyrins with a mixed substituent pattern **116**. For example, the complete series of meso phenanthrenyl substituted OEPs was prepared. Structural studies clearly showed the influence of individual substituents on the conformation of the tetrapyrrole macrocycle and conformational analyses revealed the variation of the underlying distortion modes depending on the type and arrangement of the meso substituents (Fig. 4).

Fig. 4 View of the molecular structure of (5-butyl-10-phenyl-2,3,7,8,12,13,17,18-octaethylporphyrinato)palladium(II). Hydrogen atoms have been omitted for clarity.⁶³

Photosensitizers

Since our move to Trinity in 2005 we have increasingly become involved in studies on photomedicine. With regard to porphyrins photodynamic therapy (PDT) is clearly the most prominent photomedical use of these chromophores. This method uses the combination of a dye (the photosensitizer) and light to generate reactive oxygen species, most prominently singlet oxygen, to damage unwanted tissue or cells.^{64a} Originally applied for the

575 treatment of tumors, PDT has gained an increasing number of potential applications, e. g., antiviral and antibacterial PDT, for the treatment of psoriasis or for age-related macular degeneration.⁶⁴ Numerous substances have been tested for their suitability as photosensitizers but until today only a few photosensitizers have

580 gained approval of the legal authorities.

One fundamental requirement for a good photosensitizer is an amphiphilic structure.^{64b} Amphiphilicity facilitates localization in membrane structures of the cells and thus, when developing new photosensitizers for PDT, the target should be a series of compounds differing in the extent of hydrophilic/hydrophobic substitution but related to a common lead structure to allow QSAR studies. From a synthetic viewpoint the search for new photosensitizers requires the synthesis of unsymmetrically substituted tetrapyrrolic systems with mixed

590 hydrophilic/hydrophobic substitution pattern.

This should sound familiar as it clearly related to the synthetic strategies outlined in Scheme 3. Utilization of "ABCD-approach" should allow the rapid generation of libraries for screening. Indeed, using the strategies described above, we were able to quickly

595 synthesize several hundred compounds based on the A_x, A₂BC and ABCD systems as potential photosensitizers and as probes for assessing membrane affinity.^{23,39} Most of the syntheses are still unpublished and these compounds are currently undergoing high content analysis. Our initial focus here is on the treatment of

600 oesophageal cancer and Barretts metaplasia (Fig. 5).⁶⁶

Fig. 5 Localization of one of the photosensitizers (red fluorescence) near the nucleus (blue) in OE21 (human oesophageal squamous carcinoma cell line) cells. Left: untreated cells; right: cells with photosensitizer.

Obviously, a simple mix of hydrophobic/hydrophilic residues is not enough but must be accompanied by a fine-tuning of the photophysical properties through electronic and/or conformational chromophore modulation⁶⁷ in order to optimize the singlet oxygen

605 generation and the absorption properties (e.g., long absorption in the red/far-red region of the spectrum to enhance tissue penetration of the exciting light) of the dyes. Thus, the methods described for the unsymmetrical porphyrins must (and have been to some extent) be accompanied and combined with methods for the preparation of

610 hypodiporphyrins, fused and π -extended systems. In turn, the synthesis of a basic chromophore type must be combined with methods to optimize the delivery and targeting of the active photosensitizer. This can be achieved through nanomedicinal strategies,⁶⁸ bioconjugation and dual modality systems.

Scheme 14 Some reactions involving *o*-nitrobenzyl appended porphyrins. a) 1. 4-methoxycarbonylphenyl boronic acid, K₃PO₄, Pd(PPh)₃, 2. NaOH, EtOH; b) *o*-nitrobenzyl alcohol, DCC, DMAP, $\rightarrow$ **118** (40-70 %) + **119** (30-40 %); c) *o*-nitrobenzyl alcohol, EDAC, DMAP, $\rightarrow$ **119** (73-90 %); d) EDAC, DMAP; e) TFA; f) ethylene glycol, Δ .

615 The latter is often a chemical problem as it requires the synthesis of appropriately functionalized photosensitizers. We have undertaken two such studies in recent years. The first involved our attempts to cross-link porphyrins to a biological target receptors via photocleavable linker groups, where a controlled released of the

620 porphyrin can be monitored upon irradiation.⁶⁹ Our goal here is to deliver the photosensitizer to the target via selective bioconjugate groups and then releasing it through a photochemical prodrug $\rightarrow$ drug conversion step (Fig. 6). One such cross-linker is the *o*-nitrobenzyl group, which is compatible with a variety of

625 functional groups, easily synthesized, stable under ambient light, and gives clean cleavage and fast fragmentation upon photoirradiation.⁷⁰

Fig. 6 Schematic illustration of a photocleavable photosensitizer target adduct.

Our synthetic pathways involved esterification of a porphyrin-carboxylic acid and a unit containing the *o*-nitrobenzyl alcohol moiety and the bioconjugate (Scheme 14).⁶⁹ Reactions model porphyrins and *o*-nitrobenzyl alcohol using the carbonyl activating DCC gave a stable *N*-acyl urea porphyrin **118**, whereas use of EDAC (1-ethyl-3-(3-dimethyl aminopropyl)carbodiimide hydrochloride) gave the desired compounds **119**. The synthesis of nitrobenzyl analogues containing an active phenolic group for connection to the bioconjugate group started required some protecting group chemistry (we used the MEM group) to prepare **118**. This could then be employed to give **119**. Deprotection under neutral conditions with ethylene glycol could be used to prepare **121** which allows a quick entry into multiporphyrin systems such as **122**. Similar reactions could be employed for β substituted systems.

In terms of suitable bioconjugate groups we have focused our attention on glycoporphyrins.^{24a,69} Our target here are tumor specific lectins displayed on the surface of cancer cells. The weak lectin-carbohydrate interactions require access to a photosensitizer displaying more than one carbohydrate unit; ideally ones that display more than one kind of carbohydrate.⁷¹ In order to overcome the limitation of the usual condensation reactions employed for glycoporphyrins before, and to open the field to the rational synthesis of lectin specific polycarbohydrate containing porphyrins we have applied the Cu(I)-catalyzed 1,3-dipolar Huisgen cycloaddition "click" reaction.⁷²

As shown in Scheme 15 the "click" reaction of **123** under microwave heating conditions provides a general and robust methodology for the synthesis of mono- **124** (and di-, tri- and tetramodified glycoporphyrins).⁷³ A sequential "double-click" method was employed to access a new class of bis-modified 5,10-

Scheme 15 Synthesis of carbohydrate appended porphyrins via "click" reaction. a) Glc(OAc), THF/H₂O (4:1), μ w, 80 °C, 40 min; b) Man(OAc), THF/H₂O (4:1), μ w, 80 °C, 40 min.

diglycoporphyrins **126** displaying heterogeneous carbohydrates towards one side of the porphyrin edge. This method has been optimized to allow functionalization of the tetrapyrrole core with both protected and fully deprotected carbohydrates. In a sense the sequential modification of the carbohydrate units is akin to the ABC approach described above for direct porphyrin modifications.

Optical limiters

Probably the most active field with regard to a combination of applications and the development of new porphyrin chemistry is optics, esp. the area of nonlinear optics.^{5d,74} There are too many different uses to discuss them here and our efforts in this area have focused on reversal saturable absorption^{74c} and nonlinear optical materials. Our entry into this area was prompted by the development of the syntheses of the 5,10-A₂-type porphyrins **4** described above (Scheme 2).¹⁸

One design principle for optimized NLO materials is the presence of a strong intramolecular dipole moment as is realized in so-called *push-pull* porphyrins. Typical and well studied examples are unsymmetrically substituted A₂BC porphyrins **127** where the polarizability of the porphyrin system is modulated by appropriate donor and acceptor groups along a meso-meso carbon vector. A conceptually related class of compounds that offer the potential to construct systems with stronger intramolecular dipole moment would be the 5,10-A₂B₂-type porphyrins **10**. Here, two donor and acceptor groups can be attached to the π -system giving rise to a system with a dipole moment across a pyrrole-pyrrole vector **128**. Synthetically this is a problem similar to that encountered in the last section for amphiphilic porphyrin. Simple "exchange" of the hydrophobic/hydrophilic residues for electron donating/withdrawing will give the target compounds.

We showed that such compounds can be quickly prepared in 2-3 steps from the 5,10-A₂-porphyrins **4** (Scheme 16). Subsequent introduction of the electron withdrawing substituents (B) was achieved *via* bromination to **129** followed by Heck or Suzuki couplings or LiR chemistry. The bromination proceeded smoothly in 74-95 % yield and was followed by the introduction of an electron withdrawing group (e.g., 4-cyanophenyl, 3-nitrophenyl, 4-nitrophenyl, 4-methoxycarbonylphenyl, 40-60 %).⁷⁵ All these compounds and other 5,15-A₂BC dyes prepared by us show promise as nonlinear optical materials.⁷⁶

Our Z-scan experiments have revealed interesting features of

Fig. 7 Open aperture Z-scan data for {5,10-di(4-methylphenyl)-15,20-bis(3-nitrostyrenyl)porphyrinato}zinc(II) in DMF at laser intensities of I_0 . $I_0 = -0.07$ G.W.cm⁻¹, $I_0 = -0.2$ G.W.cm⁻¹ and $I_0 = -0.5$ G.W.cm⁻¹ with indication of the tight focal regime.⁷⁵

nonlinear absorption properties for the series of A_2B_2 -type porphyrins (Fig. 7). At 532 nm the nonlinear processes were studied under ns irradiation, a non resonant absorption. Reverse saturable absorption was observed at low fluence intensities and at higher intensities saturable absorption followed by reverse saturable absorption again. This tight focal switch regime was shown to occur at high intensities symmetrically. Hence, porphyrins of this type offer significant degree of design flexibility and thus potential to fabricate practical optical materials.

Scheme 16 Synthesis of 5,10- A_2B_2 -type porphyrins.

710 Porphyrin arrays and electron transfer systems

Another means to optimize the properties of dye for optical applications is through the use of conjugated multiporphyrin systems, an approach spearheaded by the groups of Anderson and Osuka.^{26b,29a,74b} Next to use as optical materials porphyrin dimers, trimers and arrays are of interest as biomimetic compounds for electron-transfer studies and for applications in solar energy.^{5b,c}

Most electron transfer studies are aimed at the synthesis and investigation of donor-acceptor complexes that mimic the natural processes. In very simple terms, this involves the construction of systems consisting of donor(s), a covalent or noncovalent bridging unit, and acceptor(s). Increasingly porphyrin arrays are used as one of the components to mimic the antenna systems and di-, tri- and oligomeric porphyrin systems have been synthesized.^{30f,77} However, only a few methodological studies have targeted unsymmetrical multiporphyrin systems.^{77b} Thus we have undertaken a program aimed at using the strategies outlined for the monomeric ABCD-systems above for the construction of unsymmetric porphyrin arrays. We were especially interested in facilitating methods that would allow further modification of these systems through follow-up chemistry and a more detailed modulation of the electronic and structural properties through mixing of the substituent types on the individual porphyrin subunits.³⁴

The chemistry applied was similar to the one shown in Schemes 3 and 9 but obviously focused more on the use of synthons suitable for further transformations.³⁴ Scheme 17 gives a few selected examples of the building blocks developed and synthetic sequences for the preparation of di- and trimeric porphyrin systems with unsymmetrical substituent patterns and linker groups. Due to their utility in nonlinear optical porphyrins,^{5d,76} we initially concentrated

Scheme 17 Selected examples for the synthesis of porphyrin dimers and trimers. a) 4-nitrophenylboronic acid pinacol ester, K_3PO_4 , $Pd(PPh_3)_4$; b) NBS; c) ethynyltrimethylsilane, CuI, $Pd(PPh_3)_2Cl_2$; d) TBAF; e) $AsPh_3$, $Pd_2(dba)_3$, THF, TEA, 65 °C.

on alkynyl-linked systems.^{30a,78} These are conveniently prepared via Pd-catalyzed coupling reactions and require the appropriate unsymmetrical bromo precursors which were available from our earlier studies on the ABCD systems. As can be shown various systems can be prepared quickly although the yields need to be improved further.

Similar sequences can also be applied to the preparation of meso- β linked systems.^{41a,79} Together with Bringmann's group we have developed variable and straightforward synthetic routes for the preparation of unsymmetrical meso- β -linked porphyrin multichromophores in good to excellent yields. Here, β -borylated tetraarylporphyrins served as one of the building blocks in Suzuki-type coupling reactions and esp. the trimeric porphyrin arrays **140** show intriguing stereochemical features (Fig. 8).⁸⁰

The last example illustrates the use of novel linker groups for larger porphyrin arrays. Larger antenna systems are increasingly used for light harvesting models, these require either rational self-organized construction or rigid linker groups with defined geometry.^{30f} In the past we had utilized triptycene quinones as acceptor systems in ET studies.⁸¹ Based on this experience we decided that the rigid triptycene system might make a suitable core group for dendritic porphyrin systems.

Fig. 8 Illustration of a chiral meso-β-linked porphyrin trimer.

Indeed, 2,6,14-triiodotriptycene **142** was generated in a three-step synthesis from commercially available triptycene and could be coupled with borylated porphyrins **141** under Suzuki cross-coupling conditions to the desired porphyrin trimers **143**. Likewise, reaction of ethynylporphyrins **99** under Sonogashira conditions gave the target compounds **144** (Scheme 18). These synthetic pathways provide a straightforward approach for the design of rigid porphyrin trimers with a three-pronged 120° orientations with either meso or β-linkages and opened up access to a new class of porphyrin arrays.⁸²

Scheme 18 Synthesis of triptycene-linked porphyrin trimers. a) Suzuki conditions; b) Sonogashira conditions.⁸²

Nanotechnology

Porphyrin chemistry is always expanding in other areas and nanotechnology is no exception. Current attention is given to the formation of surface nanostructures and self-assembled ordered template structures.⁸³ Akin to the situation for crystal engineering this necessitates the appropriate synthons. For example, even the

Fig. 9 a) Model for the (porphyrinato)nickel(II) molecular overlayer on a Ag/Si(111) surface;^{84a} b) nanolines formed by the same molecule on a Ag(111) surface at rt;^{84b} c) self-assembled rows of a nickel(II) porphyrin dimer (**84** with Ph instead of tolyl) on a Ag(111) surface.^{84c}

most simple systems such as (porphyrinato)nickel(II) show fascinating surface chemistry. On a Ag/Si(111) surface it arranges in a hexagonal monolayer while on a Ag(111) surface it forms nanolines at rt (Fig. 9).⁸⁴

Practical Aspects – Scale and Costs

The referees asked me to comment on scale, purification and costs. As everyone involved in porphyrin chemistry knows, a main problem is the low solubility of porphyrins. Reactions are typically carried out with mM concentrations and exploratory reactions are carried out on, at most, a 50-100 mg scale. Add in the costs for necessary organometallic reagents, chromatographic materials and solvents and porphyrin chemistry is "expensive". Thus, while any of the reactions described here is suitable for the generation of lead compounds, upscaling of the reactions requires more planning.

Generally speaking any condensation reaction with pyrroles, dipyrromethanes, etc. can easily be performed on a 20-50 g scale. Similarly, "simple" functionalization reactions such as brominations or formylations are possible at a 5-10 g scale without modifications. Many of these reactions can be purified via recrystallization or simple filtration through silica gel. In the case of the 5,10- and 5,15-disubstituted porphyrins often one of the two components formed is highly insoluble, which aids purification. A scale up of the RLi reactions above 500 mg results in significantly lower yields. The Pd-catalyzed reactions described can be performed on a g scale. However, large scale use of many of the boronate salts or boronic acid derivatives in Pd-catalyzed reactions becomes prohibitively expensive. However, yields and purity of reactions are improving, esp. through use of microwave conditions. For industrial use it will always be necessary to go back to the drawing board after identification of an interesting lead and, for example, utilize or modify Lindsey's dipyrromethane methods¹¹ for

810 upscaling or to revert to simple side chain modification reactions.

An aspect often neglected by us chemists is formulation of the target materials. While it is possible to synthesize almost anything, it might not be necessary for many applications. For example, there is a strong interest in water soluble porphyrins for medical applications, which contrasts with the "organic" chemistry possible for modification. Here optimization of the basic photophysical properties of the chromophore through synthetic chemistry to yield a water insoluble lead might be enough. The material can then be incorporated into, e.g., liposomes to make it water soluble and biocompatible. Thus, many synthetic steps can be omitted and give a better cost-benefit return then preparing a highly optimized, but unaffordable material that fulfills all criteria.

The question of the potential development costs for devices is more difficult to address. This depends on the added value and the possible sales market. For use as simple dyes porphyrins will never be able to compete with the industrial processes already in place for phthalocyanines. Although stable compounds, porphyrins can undergo significant photooxidation with time. However, high value products such as photosensitizers, sensors, catalysts for fine chemicals and optical limiters can be prepared at competitive rates and in kg scale and several of these have reached the market place.

Outlook

What can happen in the near future? Advances in synthesis are always difficult to predict. Despite all logical planning serendipity plays a major role in methods development. Surely the main application areas solar energy conversion, optical materials, photosensitizers, chiral sensors,^{85a} and catalysis will continue to drive the field forward. Many of the methods described here and elsewhere for porphyrins are now applied to the functionalization of related contracted, expanded and isomeric tetrapyrrole systems. Many more surprises can be expected from this area of research which now has begun to enter the stage of synthetic transformations.^{85b}

For standard porphyrins, another look at the meso functionalization of β substituted porphyrins appears worthwhile. This will require better access to, e.g., a meso monosubstituted OEP suitable for subsequent functionalization. For the meso tetrasubstituted systems described here there is still room for improvement of β -functionalization methods. Only few of these have been used for regiochemical problems. Likewise, enantioselective reactions have only rarely been applied to porphyrins. Peripherally metalated^{29c} and organometallic π -complexes of porphyrins are still in their infancy^{85c} and only the former have been used for synthetic reactions. More surprisingly, despite their character as chromophores par excellence only a handful synthetic photochemical reactions have been described for porphyrins.^{85d} Most likely synthetic efforts will focus more on the preparation of multifunctional and multimodality systems, e.g., bioconjugates and our own efforts currently go into this area.

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GRAPHICAL ABSTRACT:

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Unsymmetrically substituted porphyrins are not that difficult to make!
Advances made in recent years allow the synthesis of almost any
desired meso substituted A_x- or ABCD-type porphyrin.

Picture of author for biography:

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