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Synthesis of Unsymmetrically meso-Substituted Porphyrins

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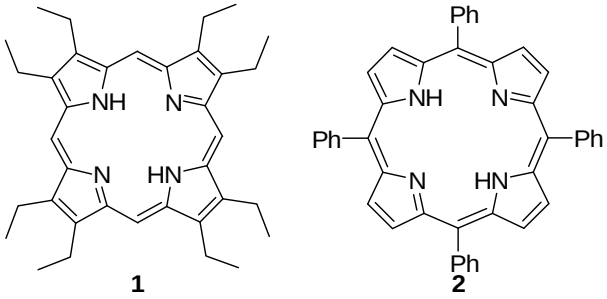
The continued development of new medicinal and industrial uses of highly substituted porphyrins, especially in the fields of photodynamic therapy, nonlinear optics and electron transfer systems, has led to a resurgent interest in developing new methodologies for porphyrin synthesis. The porphyrins in question, so called ABCD-type porphyrins, have mixed *meso* substituents, making them highly unsymmetric and thus not synthetically available through classical condensation routes. Synthetic strategies towards the formation of *meso* substituted porphyrins have been extensively researched over the last decade with various routes now available. While methods using mixed condensations are still preferred for systems with high symmetry, the number of possible products makes it an unviable route for the synthesis of the more useful non symmetric porphyrins. To this end novel syntheses of ABCD-type porphyrins have been developed using synthetic manipulations of pre-formed porphyrin scaffolds with various organolithium reagents and Pd catalysed metal couplings.

Introduction

The area of porphyrin research is perhaps one of the most widely studied in chemistry with almost 10,000 papers published within the last five years alone. This is due to the multitude of possible applications for tetrapyrroles in the fields of photodynamic therapy, non linear optics and electron transfer due to their unique photophysical and conformational properties. All of these applications only become possible, however, when reliable and efficient synthetic strategies exist. (1)

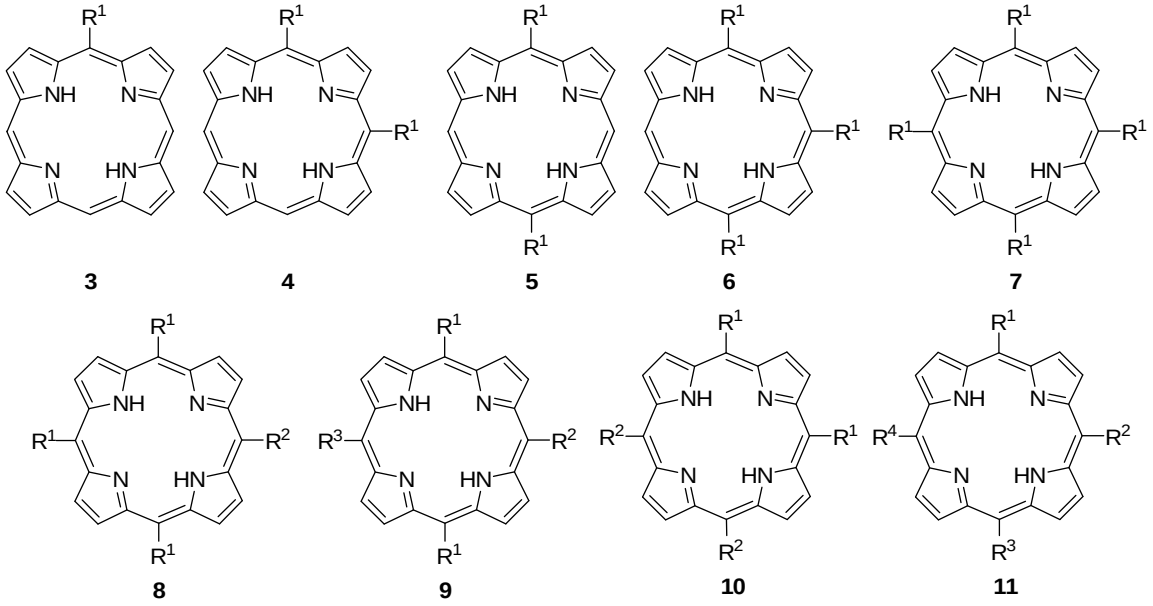
Traditionally the most widely used porphyrins for synthetic transformations have been β-substituted proto- and etioporphyrins or octaethylporphyrin (OEP) **1** but interest in these has waned in recent years due to their reasonably complicated synthetic availability. Nowadays the much more readily accessible meso substituted porphyrins such as tetraphenylporphyrin (TPP) **2** have become the workhorses of porphyrin chemistry. These meso aryl compounds are highly stable, easily prepared in high yielding, one pot, reactions and can be synthesized on multi gram scales. Continuous advances in their synthesis, majorly so by the group of Lindsey (2) have made the synthesis of symmetrical meso-substituted porphyrins very straightforward.



1 **2**

Figure 1: OEP and TPP

Modern applications, however, tend to require the availability of more unsymmetric porphyrins. Most applications in optics, material science and photomedicine require unsymmetrically substituted derivatives, e.g. amphiphilic systems for use as photosensitizers, donor-acceptor systems for applications in solar energy conversion, supramolecular chemistry and nonlinear optics, or suitably functionalized chiral systems as enantioselective catalysts (3). Interest has therefore shifted towards more unsymmetric systems with mixed types of meso substituents. Generally speaking, the target compounds are members of the A_x- and ABCD-type series (Figure 2), colloquially termed the porphyrin alphabet soup. Ideally, unsymmetrical systems with both meso alkyl (4) and aryl residues are required.



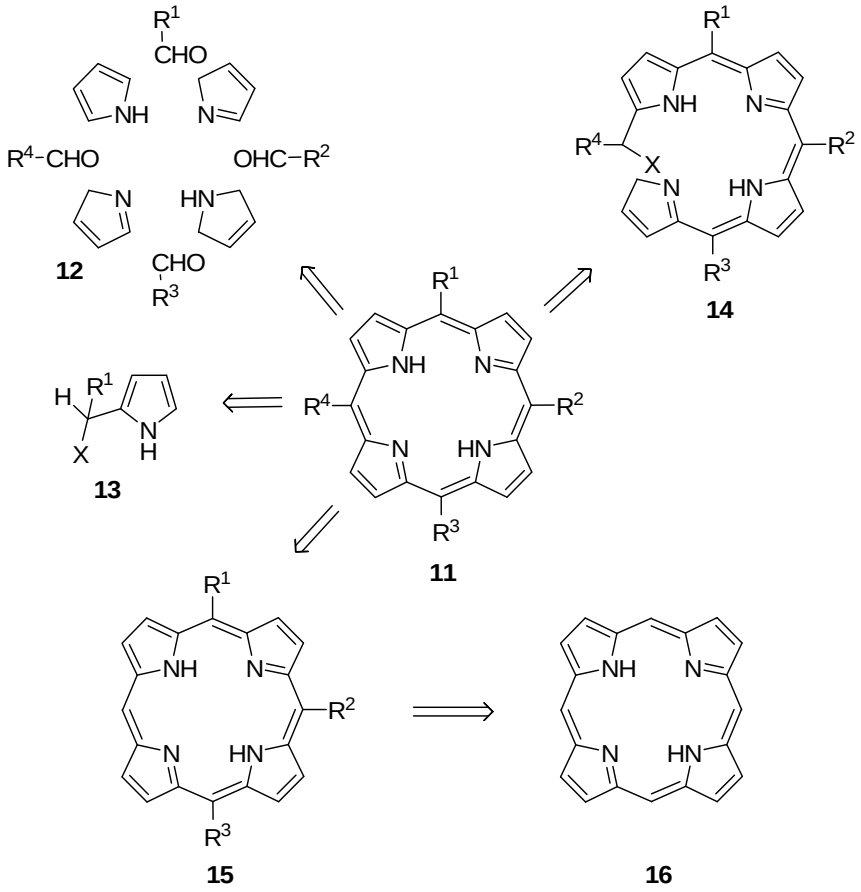
3 **4** **5** **6** **7**

8 **9** **10** **11**

Figure 2: Selected A_x- and ABCD-type members of the porphyrin alphabet soup of meso substituted porphyrins.

Synthetic Strategies

In practice there are three different synthetic routes to make meso substituted ABCD-type porphyrins **11**, namely: 1) mixed condensation, 2) total synthesis and 3) functionalisation of preformed systems (Scheme 1).



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

While on paper the straightforward mixed condensation reaction seems the most straightforward this is by far the least synthetically useful when a specific unsymmetric porphyrin is targeted. This is because this method tends to give a mix of all possible isomers which require lengthy chromatography to separate, if possible at all (2b). While kinetic control can give desired isomers in high yield in some circumstances this is not a generally applicable method for ABCD-type porphyrin synthesis, particularly where acid labile functional groups are desired. Use of stericaly hindered groups also presents a problem as the formation of porphodimethenes can become quantitative under certain conditions (5). The use of reactive pyrrole systems such as **13** improves selectivity somewhat but doesn't really overcome the main problems of this approach (6). This is not to write off the utility of condensation reactions wholesale, however, as major improvements have been made. Lindsey's group in particular have developed several condensation methods involving dipyrromethane derivatives, (2+2 additions), and tripyrromethane derivatives, (3+1 additions), which allow for the large scale preparation of 5,15-AB- and A_2B_2-type porphyrins (7).

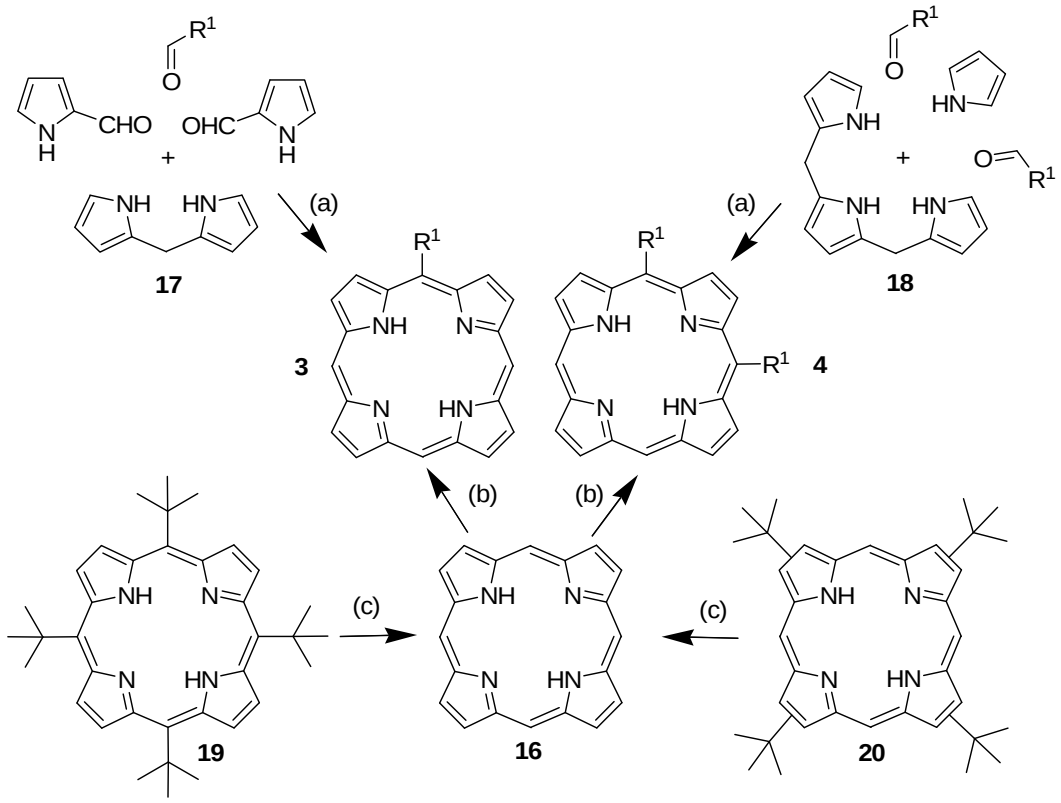
The most obvious alternative route is a direct total synthesis. The synthesis of a bilane precursor **14** from the desired pyrrole and aldehyde subunits allows precise positioning of all four meso substituents. This can then be easily cyclised and oxidized to the desired porphyrin (8). This is a very powerful method but as it is a total synthesis suffers somewhat from the amount of synthetic steps and manipulations required. Furthermore, acid induced scrambling of the final product presents a major problem but newer methods for selected residues has helped overcome this (7,8,9).

Our approach has focused on the third possibility, namely the stepwise introduction of desired functionalities to preformed systems. Initially our work was carried out on highly substituted porphyrins already bearing eight β residues (e.g. OEP). This gave access to dodecasubstituted ABCD-type porphyrins (10). Progress in this area then implied that the β-unsubstituted porphyrins may be similarly accessible (11). This method relies on the very high reactivity of the meso position towards strong nucleophiles in electrophilic addition oxidation reactions. The reaction **15** → **11** is reasonably straightforward but it does rely heavily on the availability of appropriate starting materials. Ultimately, what is required for this route to be fully complete is the synthetic availability of unsubstituted porphyrin (porphine). Historically this has been a significant issue as porphine suffers dramatically from low solubility. However, recent advances in porphine synthesis have overcome this problem to a large degree and the preparation and functionalisation of porphine, while still tricky, is at least now possible (12).

Synthesis of A_x- type Porphyrins

The Ax-type series of porphyrins have been widely used in research, mainly due to the ready availability of the A_4- **7** and 5,15-A_2-type **5** systems through classic condensation reactions and 2+2 additions (13). The breadth of research performed on these compounds left a gap somewhat with relation to the less synthetically available members of the group. Recent advances by us have helped to bridge this gap. To prepare the meso mono substituted porphyrins we initially attempted a 2+1+1 addition using pyrrole aldehyde, dipyrromethane **17** and an appropriate aldehyde. While this reaction does give some of the desired mono substituted product (2-12%) (14a), acid scrambling is a major problem in the reaction and makes the 5,15-A_2-type **5** porphyrin as a side product. The A_1 product is the sole soluble product when specific residues like 4-nitrophenyl, ^{t}Bu or 4-methoxyphenyl are used and so this method is applicable for large scale synthesis of very specific systems. A similar approach using tripyrromethane **18**, pyrrole and two equivalents of aldehyde can be used in a 3+1 addition to give 5,10-A_2-type systems (4-12%) (14b). The primary drawback of this method is the reasonably difficult synthesis and purification of tripyrromethane.

A more direct route into the A_x series is through successive functionalisation of porphine. This followed from our work with the addition of organolithium reagents to β-substituted porphyrins (11, 15). As discussed earlier this route only really became viable following Funasaki and Neya's success with the thermal dealkylation of tetra(*tert*-butyl)porphyrins, **19** or **20**, to give porphine in high yield (>70%) and excellent purity as well as already being in solution (4a, 16). With porphine in hand, careful selection of the amount of RLi used can give monosubstituted **3** (<1.5 equivalents, 40-70%) or disubstituted **4** (3-4 equivalents, 50-70%) porphyrins (14). All of this work allowed for the expansion in the amount of readily available A_x porphyrins which serve not only as useful starting blocks for other porphyrins but are also quite interesting compounds with relation to structural and electronic effect studies on the porphyrin macrocycle.



Scheme 2: Synthesis of A- and 5,10-A2-type porphyrins. (a) 1: TFA, CH2Cl2 2: DDQ; (b) 1: R1Li 2: H2O, DDQ; (c) H+, Δ.

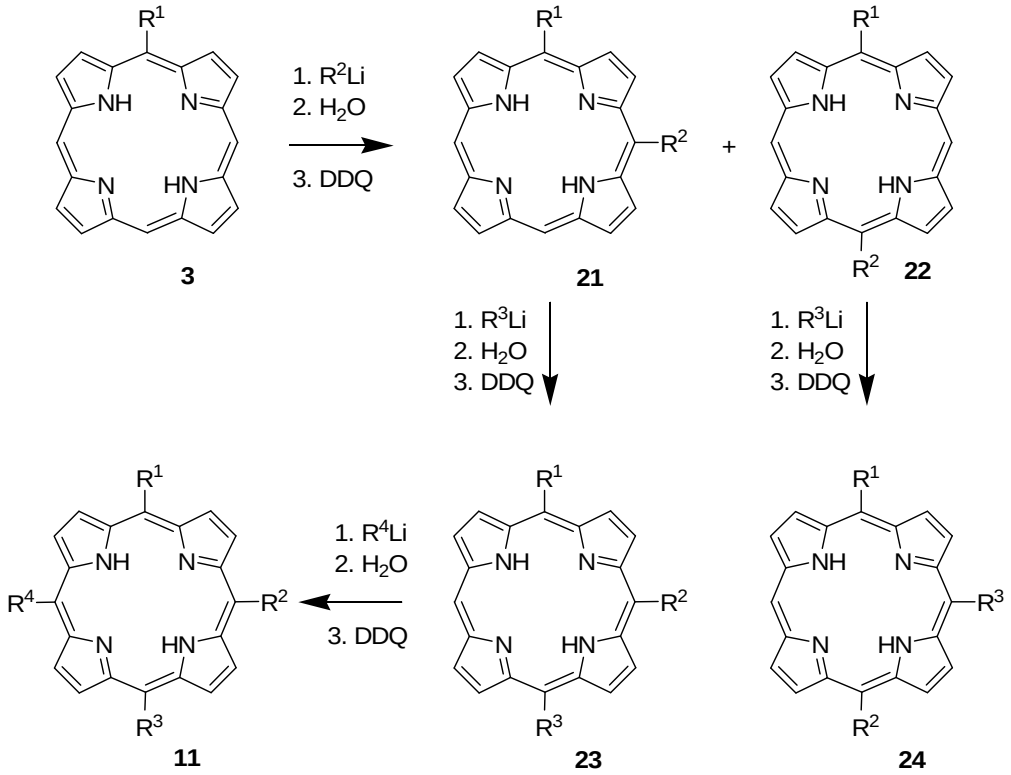
Synthesis of ABCD-type Porphyrins

The challenge in making ABCD-type porphyrins is to use the whole repertoire of available porphyrin scaffolds and possible functionalisation reactions to develop the most efficient route to any unsymmetrical target (17). This relies heavily on the pre-existing synthetic methods discussed earlier, i.e. if an A_2BC-type porphyrin is required it is probably much more sensible to start with a 5,15-A_2-type porphyrin from a 2+2 condensation rather than successive reactions on, slightly less attainable, porphine. Theoretically all ABCD-type porphyrins are accessible through consecutive functionalisation of porphine with organolithium reagents but oftentimes this is far from the most practical route. Overall the synthetic strategies employed by us fall into three main categories: 1) monosubstitution using organolithium reagents; 2) disubstitution using R^1Li and R^2X in a one pot reaction and 3) the use of transition metal catalyzed C-C coupling reactions.

1) Monosubstitution using organolithium reagents

As already discussed this method relies on the reactivity of the porphyrin meso position towards strong nucleophiles (11). In a very straightforward addition oxidation procedure virtually any alkyl or aryl residue can be installed onto a preformed porphyrin scaffold. This method makes great use of the range of porphyrins available from classical routes and is a very powerful modification technique. It involves the formation of RLi reagents which can then be reacted with either metallo or free base porphyrins. In general,

Nickel porphyrin complexes work better when installing alkyl residues while free bases are preferential when aryl residues are desired. That being said the method is highly robust and supports almost all combinations. The major drawback, apart from the availability of certain organolithiums, is that when working with stericaly hindered alkyl lithium reagents (e.g., ^{t}BuLi) multiple alkylation or β-alkylation products can be observed (18,19). Also the use with highly ruffled systems is not recommended due to the formation of porphodimethene products (20).



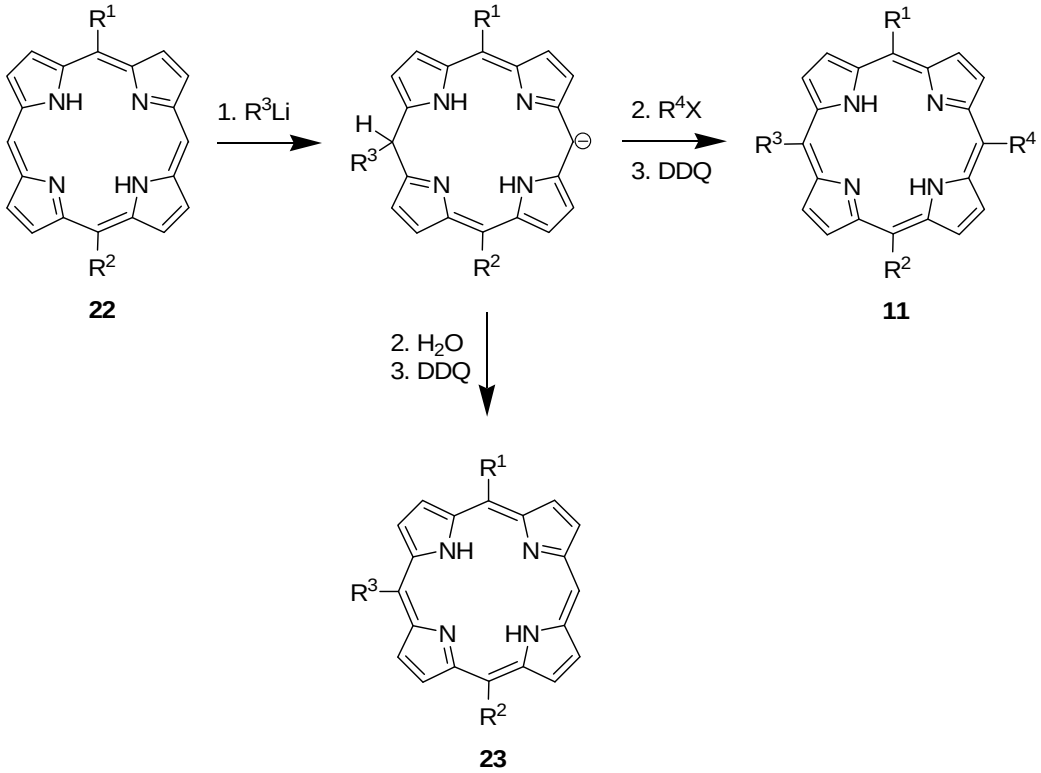
Scheme 3: Synthesis of ABCD-type porphyrins via monosubstitution with organolithium reagents

Scheme 3 shows the synthetic route to ABCD-type porphyrins, starting with an A-type porphyrin. By varying this chosen starting material or stopping at any point along the sequence almost any combination of meso substituents pattern is accessible via this route. When dealing with fully meso substituted porphyrins reaction with RLi allows for the formation of phlorins, porphodimethenes or chlorins depending on the initial substituent pattern. By adjusting reaction conditions between thermodynamic and kinetic control oxidation resistant calixphyrins and prophodimethenes can be predictably synthesised as can meso-meso linked bisporphyrins through radical dimerization immediately after oxidation (18b, 20a).

2) Disubstitution using R^1Li and R^2X

This method follows closely from method 1) and works on the fact that the porphyrin "anion" generated upon addition of a strong nucleophile may be trapped by an *in situ* electrophile. Instead of hydrolysis of the intermediate anion to a porphodimethene as used above, an organic electrophile is added which gives a disubstituted product where one residue has come from the organolithium reagent and the other from the organic

electrophile. This route was initially only applicable to the Ni(II) porphyrins but has since been optimized for free base systems. The main products of this procedure (24-28%) tend to be monosubstituted products **23**, formed by substitution with R^n from the organolithium reagent only. However, the desired compounds **11** are also formed as minor products (18-21%). The strength of this method lies in its ability to convert an AB-type porphyrin into an ABCD-type porphyrin in one step. Even with the low to moderate yields the method can still favorable in some circumstances over other synthetic alternatives available i.e. mixed condensations or multistep syntheses (21).



Scheme 4: Disubstitution using R^3Li/R^4X

3) Transition metal catalyzed C-C coupling reactions

The use of transition metal catalysis is perhaps the most widely investigated method for the functionalisation of porphyrins and was the first generally applicable method for the modification of the meso positions. All of the classic TM catalysts have been used to some extent but unsurprisingly palladium coupled reactions tend to be the most utilised. All of the benchmark Pd-catalyzed reactions like Stille, Heck, Sonagashira and Suzuki have been applied to the tetrapyrrole macrocycles with great success in most cases (22, 23).

These reactions all require initial halogenation (bromination or iodination) of the porphyrin. Electrophilic addition of bromine to a porphyrin with one free meso position is an incredibly facile reaction with near quantitative yields available (24, 25). Selective bromination of porphyrins with more than one free meso is slightly trickier and involves some tedious chromatography but careful control of the amount of NBS used tends to give high yielding targeted substitutions (26). Figure 3 shows some of the many possible bromoporphyrins synthetically available this way.

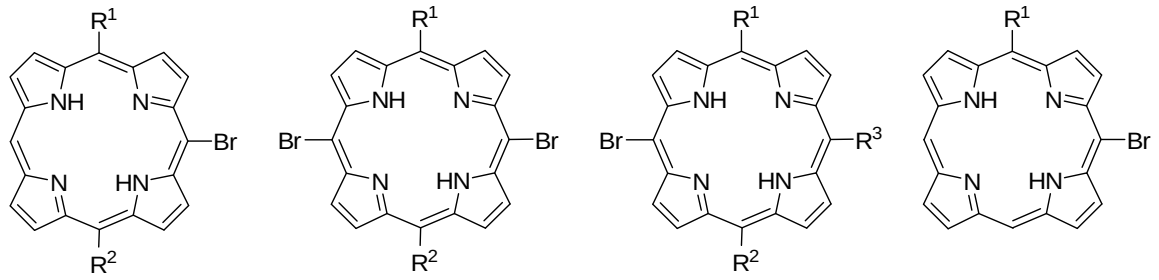
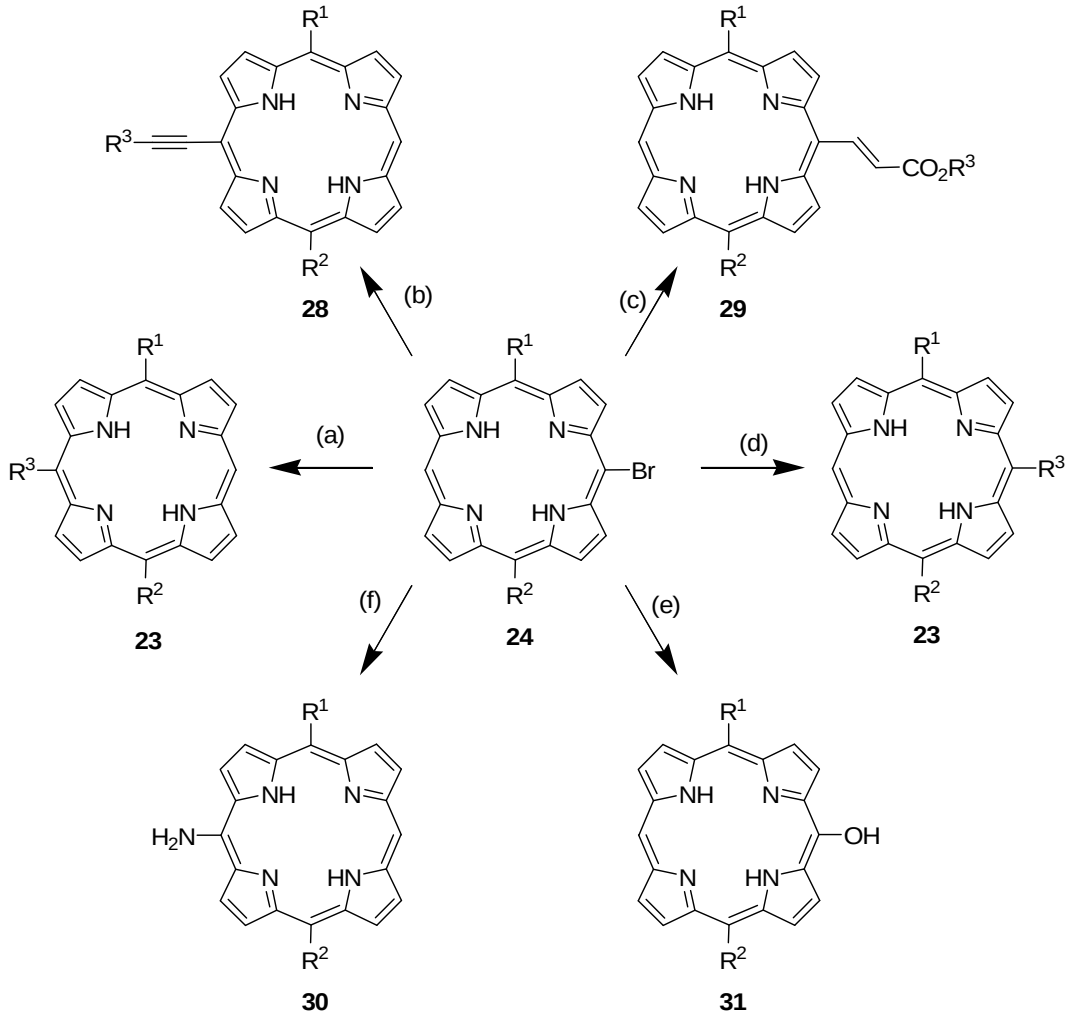


Figure 3: Selected examples of mono- and dibromoporphyrins

The range of possible additions to these bromo porphyrins is truly vast and many interesting and useful functional groups can be installed that aren't possible with any other method (i.e. labile groups) (23). This means that while TM-catalysed reactions are very powerful at installing simple alkyl and aryl residues (usually very high yielding) they can also be used to install specific functional groups which allow for further synthetic manipulations around the tetrapyrrole core. Some of these are illustrated in scheme 5 (27, 28).



Scheme 5: Selected Pd-catalyzed porphyrin reactions; (a) [Suzuki]$R^3B(OH)_2$, $Pd(PPh_3)_4$, K_3PO_4, THF; (b) Sonagashira; (c) Heck; (d) R^3BF_3K, $Pd(dppf)Cl_2$, $CsCO_3$, THF/H_2O, 80 ^oC; (e) Pd cat. THF, 68 ^oC, 4.5d; (f) hydrazine sulfate, Pd cat., THF, 68 ^oC, 16h

Conclusions

While none of the methods outlined here are perfect stand alone methods for optimum preparation of A_x- or ABCD-type porphyrins they are all very useful tools in the synthetic porphyrin chemist's belt. In reality there is no generally applicable method that works perfectly for all porphyrins. The key is always in choosing the right conditions and reagents based on the desired functionalities and tailoring a synthesis to best capitalise on the available methods.

In our experience condensation methods are still the best way to synthesise the 5,15-A_2 and -AB starting materials while the isomeric 5,10- systems are much more readily available through organolithium reactions. The use of A-porphyrins is still not optimised due to the formation of regioisomers and multiple alkylation products whereas using AB-systems provides a very suitable route to ABC- porphyrins. Further functionalisations on ABC- porphyrins are probably best performed through bromination and Pd-catalysed reactions as reactions of ABC-porphyrins with organolithiums tend to be somewhat lower yielding. Obtaining the ABCD- porphyrins via disubstitution of AB-systems offers the major advantages of a one pot synthesis but unfortunately suffers from poor yields. Use of Pd- catalysts with a dibromo compound is probably preferred although the RLi method is better for attaching alkyl residues. Overall a use of any one or combination of methods and/or the methods developed by Lindsey (7) can allow for every step in the reaction sequence A → AB → ABC → ABCD for almost any desired ABCD-type porphyrin.

Acknowledgments

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