Nucleophilic Aromatic Substitution (SNAr) and Related Reactions of Porphyrinoids: Mechanistic and Regiochemical Aspects

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Dedicated to Professor Hiroshi Shinokubo.

Abstract: The nucleophilic substitution of aromatic moieties (SNAr) has been known for over 150 years and found wide use for the functionalization of (hetero)aromatic systems. Currently, several “types” of SNAr reactions have been established and notably the area of porphyrinoid macrocycles has seen many uses thereof. Herein, we detail the SNAr reactions of seven types of porphyrinoids with differing number and type of pyrrole units: subporphyrins, norcorroles, corroles, porphyrins, azuliporphyrins, N-confused porphyrins, and phthalocyanines. For each we analyze the substitution dependent upon: a) the type of nucleophile and b) the site of substitution (α, β, or meso). Along with this we evaluate this route as a synthetic strategy for the generation of unsymmetrical porphyrinoids. Distinct trends can be identified for each type of porphyrinoid discussed, regardless of nucleophile. The use of nucleophilic substitution on porphyrinoids is found to often be a cost-effective procedure with the ability to yield complex substituent patterns, which can be conducted in non-anhydrous solvents with easily accessible simple porphyrinoids.

1. Introduction

The elegant stitching of pyrroles into a ring to yield porphyrins (Figure 1), is the cornerstone of nature’s production of respiratory and photosynthetic pigments, and also yields a cornucopia of catalytically active cofactors for a broad range of transformations.[1] In nature anabolic and catabolic processes involving porphyrins appear effortless and are something that occur, e.g., in our body millions of times a day without us realizing.[2] Humans have struggled to synthesize porphyrins in the laboratory by comparison. Historically, it was the unsymmetrical natural porphyrins that were synthesized first by Fischer in 1929,[3a] later culminating in the synthesis of chlorophyll a (Woodward, 1960)[3b] and vitamin B12 (Woodward, Eschenmoser, 1972).[3c,3d] Non-natural porphyrins became accessible with Rothemund’s synthesis of 5,10,15,20-tetraarylporphyrins in 1935,[4a,4b] which was built upon by Adler and Longo in the 1960’s,[4c] with the last leap in porphyrin synthesis coming from Lindsey in 1986, which facilitated broad-scale practical syntheses.[4d,4e]

Figure 1. a) The standard porphyrin system with labels for different types of positions upon the porphyrin macrocycle, and indication of the aromatic [18π] pathway (bold). b) Graphical depiction of the scope of this review.

Yet, despite this and allied advances,[5] the total synthesis of porphyrins is still a laborious task mostly handled by specialist research groups.[6] What we have become good at, instead, is the manipulation of preformed porphyrins; natural or synthetic.[7] The synthetic porphyrins used today resemble very little the natural porphyrins and most of the functionalization work is based on the desire to push the boundaries of the various properties of these porphyrins (electronic, electrochemical, photophysical, and structural).[8] The results have often been astounding, firmly keeping synthetic porphyrinoids center piece in heterocyclic chemistry and as test cases par excellence in all areas of chemistry, biomedicine, and the materials sciences.[9]
photochemical, and pericyclic. All of these are found with porphyrins and each has its own realm of uses. For example, addition or pericyclic reactions at the C_{trans}–C_{cis} double bonds not involved in the aromatic pathway form the standard entry into reduced species such as chlorins (Figure 1a). Being heteroaromatic compounds the vast majority of direct porphyrin functionalization reactions are aromatic substitution reactions (Scheme 1). Historically, electrophilic aromatic substitution (S_{Ar}) reactions such as nitration, halogenation or Friedel-Crafts reactions featured prominently in the development of porphyrin chemistry. Today they mainly serve to generate starting materials for transition metal-catalyzed coupling reactions. The latter field has been reviewed extensively, and thus we focus here on nucleophilic aromatic substitution (S_{Ar}N) reactions.

\[ \text{Nu}^+ \rightarrow \text{EDG} \rightarrow \text{EWG} \rightarrow \text{Nu}^- \rightarrow \text{LG} \]

Scheme 1. General schemes for addition-elimination type nucleophilic aromatic substitution (S_{Ar}N, top) and electrophilic aromatic substitution (S_{Ar}, bottom) on derivatives of benzene with canonical forms omitted for simplicity. EWG = electron withdrawing group, EDG = electron donating group, LG = leaving group, E = electrophile, Nu = nucleophile.

S_{Ar}N is one of the main two reactions that occurs on aromatic moieties (Scheme 1) and has been known for more than 150 years. Since then many types of and variations on the "traditional" two-step S_{Ar}N (addition-elimination) reaction have been named and studied in their own right; S_{Ar}N, S_{Ar}H, and vicarious nucleophilic substitutions; reactions occurring through benzyne intermediates; and the majority of cases involves the \( \beta \)-pyrrolic (C_{\beta}) and bridging meso-positions (C_{\eta}) and we have grouped the reactions accordingly. The contents of this review have been laid out in such a way that the compound types with reactivity more akin to porphyrins are discussed first. In the interest of ease of reading, the changes after each reaction step in the schemes presented in this review have been highlighted in blue (along with the various parts of the reagents responsible for the transformation) to make understanding of the syntheses easier for non-porphyrinoid specialists.

Lastly, throughout this review, and other manuscripts dealing with differing meso-substituted porphyrins, the "A", "B", "C", and "D" nomenclature system is used. In this, "A" represents a particular meso-substituent, "B" the next differing substituent and so on until an non-symmetrical ABCD-porphyrin is obtained, e.g., 5,10,15,20-tetraphenylporphyrin would be an \( \Lambda_2 \) porphyrin and 5,15-diphenylporphyrin would be a "trans"-\( \Lambda_2 \)-porphyrin. For clarity, various types of porphyrins with differing meso substitu-

Harry Sample graduated from the University of Hull, England, with a first-class M. Chem. (Hons) degree in July 2018. During this time at Hull, Harry undertook B.Sc., M.Chem., and an RSC funded undergraduate research project, all under the supervision of Prof. Ross W. Boyle. Harry's M. Chem. project concerned the synthesis of theranostic water-soluble porphyrin-amino acid conjugates utilizing photodynamic therapy (PDT) and single photon emission computed tomography (SPECT). In the following September, Harry started his Ph.D. program as an Early Stage Researcher in the Horizon2020 Marie Skłodowska-Curie actions “POLYTHEA” program. His work concerns the synthesis of unsymmetrical reduced porphyrinoids, their bioconjugation strategies, and efficacy as photosensitizers for PDT. His interests include the syntheses of heterocycles and reduced porphyrinoids, along with single-crystal X-ray crystallography and radiochemistry. Outside of the laboratory, Harry is a keen cyclist and home cook.

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2. SNAr Reactions of Porphyrins

2.1. Reactions with Organolithium Reagents

Organic chemists have several aims; to synthesize drug molecules, to isolate and synthesize natural products, and develop novel synthetic methodologies, amongst others. To put it another way – to devise synthetic routes to functional molecules. Next to C-X bonds this primarily requires the formation of C–C bonds. In the past, this was only possible with the addition of other heteroatoms and the C–C bond, e.g., the Henry reaction (nitro-alkene or β-hydroxy nitro group), Friedel-Crafts acylation (carbonyl group), and the Claisen condensation (α,α-diester), as examples. Along with this, another downfall was the lack of diversity in the functional groups that it these older reactions could implement.

In this review, we have already referred to how SNAr has been utilized since the mid-1800’s and the harsh conditions which were used initially. If the formation of C–C bonds could be done under milder conditions, and the moiety added could contain purely carbon and hydrogen atoms we could highly diversify the analogues we were capable of synthesizing. On the turn of the 20th century, that is exactly what happened.

Discovered in 1900 by Victor Grignard, the broad application and facile preparation of Grignard reagents made them highly attractive as organometallic reagents. Such was the extent of the applicability and success of these reagents that Grignard was awarded the Nobel Prize in Chemistry in 1912. What was unknown then, and arguably not truly understood now, is the number and nature of species present in a solution of a particular Grignard reagent. Whilst Grignard reagents still have an unequivocal place in organic synthesis (in some cases they were the favorites of the total synthesis groups) organolithium reagents have gone some way to surpassing them. It was Schlenk who, in 1917, first synthesized MeLi, EtLi, and PhLi. Discovered in 1900 by Victor Grignard, the broad applicability and facile preparation of Grignard reagents made them highly attractive as organometallic reagents. Such was the extent of the applicability and success of these reagents that Grignard was awarded the Nobel Prize in Chemistry in 1912. What was unknown then, and arguably not truly understood now, is the number and nature of species present in a solution of a particular Grignard reagent. Whilst Grignard reagents still have an unequivocal place in organic synthesis (in some cases they were the favorites of the total synthesis groups) organolithium reagents have gone some way to surpassing them. It was Schlenk who, in 1917, first synthesized MeLi, EtLi, and PhLi. Fourteen years later, Wittig and Gilman improved the syntheses of these organolithium reagents and with a simultaneous report shortly afterwards both groups had observed the halogen-lithium exchange with organobromides and phenyllithiums. With that, the modern use of organolithium reagents had been uncovered, and new synthetic methodologies made a possibility. Still, many decades passed until these reagents were investigated for their use in porphyrin functionalization reactions, but then with astounding success (Figure 3).

In 1980, Yoshida and co-workers reported the reaction of chloro(2,3,7,8,12,13,17,18-octaethylporphyrinato)rhodium(III) with a variety of organolithium reagents (4-methoxyphenyl- lithium, PhLi, and nBuLi). Whilst, to the best of our knowledge, this is the first published reaction of a porphyrinoid with an organolithium species – the product was formed through Rh-substitution and subsequent rearrangement, not a formal SNAr reaction. In 1984, Dolphin examined the reactivity of...
nitrated 2,3,7,8,12,13,17,18-octaethylporphyrins towards acetate, methoxide, chloride, and bromide nucleophiles. However, these were activated porphyrins. In 1992, Shimizu and co-workers managed to generate a phlorin from chloro(5,10,15,20-tetraphenylporphyrinato)gold(III) and tetrabutyl ammonium hydroxide. Although this was an SNAr reaction, the nucleophile was not carbon based but instead, the hydroxide anion. In 1994, Crossley and co-workers were the first to use an organolithium compound for reaction with a porphyrin in a more typical S$_2$Ar fashion, using the activated [2-nitro-5,10,15,20-tetraphenylporphyrinato]copper(II), in a work dominated by the use of Grignard reagents. Two years later, Smith and co-workers utilized Grignard reagents on meso-formyl octaethylporphyrins to meso-alkylate and generate "trans"-A$_2$-octaethylporphyrins.

Eventually, in 1998, the first reaction of organolithium reagents with non-activated porphyrins was described by us. We presented the transformation of various 2,3,7,8,12,13,17,18-octaethylporphyrins (M = 2H, Co, Ni, Cu) utilizing a variety of organolithium reagents (nBuLi, PhLi, 4-bromophenyllithium, 2,5-dimethoxyphenyllithium, and (3-(1,3-dioxan-2-yl)propyl)lithium). Amongst others, we and Callot have also studied the differing reactions of organolithium reagents with meso-tetraalkyl- vs. -tetraarylporphyrins.

The products of these reactions have been used to generate novel and modified photosensitizers for PDT,

$$\text{Scheme 2. Synthesis of A- and 5,10-A}_2\text{-substituted tetrabenzoporphyrins using organolithium reagents.}$$
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Scheme 3. Synthesis of 5-A and 5,10-A₂-substituted porphyrins using organolithium reagents (route C), or the (2+1+1) strategies (routes A and B).[53]

Scheme 4. Synthesis of 5-formyl-10,20-A₂-porphyrins by Takanami and co-workers using (2-pyridyldimethylsilyl)methylolithium 19.[56] The use of these milder conditions prevents and circumnavigates the issues of previous formylation procedures, i.e. the Vilsmeier formylation being limited to the Ni(II) and Cu(II) complexes, along with the absence of acid sensitive groups.[63,64] Earlier, we also developed a method suitable for this transformation, through the use of the 1,3-dithianyl moiety, albeit yields for the free base porphyrins were limited.[65] The reagent used by Takanami was chosen given the commercial availability of its precursor, and generation in almost quantitative yield.[66] Thus, Takanami trialed this reaction on ten different 5,15-A₂-porphyrins 14 with a wide variety of substituents; iBu, Ph, pTol, and various other aryl groups containing methoxy, trifluoromethyl, and (2-trisopropylsilyl)ethynylphenyl moieties with yields ranging from 61–91 %. The same conditions were applied to Ni(II), Cu(II) and, Zn(II) complexes of the diphenyl-, di(3-methoxyphenyl)- and, di(isobutyl)porphyrins. In all cases, yields varied from 67–87 %, with yields of the Zn(II) complexes being higher than that for free base porphyrins.

The first report of meso-hydroxymethyl porphyrins came from Smith, and these were generated through the reduction of the respective octaalkyl-meso-formylporphyrins.[67] However, Takanami reported the first direct meso-hydroxymethylation of the porphyrin core to yield 17.[58] Whilst initially the oxidation of the porphodimethene had been performed with DDQ, if O₂ (or even air) was used instead it was found that the meso-hydroxymethylporphyrin could be isolated in good yields with free base porphyrins being obtained in 55–76 % and metallo-porphyrins in 57–83 % yields. Interestingly, in this case no de-metallation of the Zn(II)porphyrins was observed. Along with
organolithium reagents, Takanami also examined the reactivity of Grignard reagents towards "trans"-A₂ systems using the Kumada coupling reaction.⁶⁸

C–B bonds can also be generated under RLi conditions thus introducing useful functional groups.⁶⁹ Notably, triaryl boranes exhibit high luminescence, anion-sensing, and nonlinear optical properties.⁷⁰–⁷² Fujimoto et al. had previously generated a porphyrinyl-Grignard reagent and examined its reactivity, and thus in a similar vein, with the aim of generating porphyrinylboranes the same authors set out to generate porphyrinyl-lithiums (Scheme 5).⁷³

As an initial proof of concept, analogous triaryl meso- and β-boron appended porphyrins through the generation of porphyrinylboranes. Ar = 3,5-di-tert-butylphenyl, Mes = 2,4,6-trimethylphenyl. For 20a,b

As an initial proof of concept, analogous triaryl meso- and β-iodo porphyrins 20a and 22, were treated with 1.5 equiv. nBuLi and quenched with excess D₂O. Both deuterated porphyrins were obtained in good yields (81 % for meso-deuteration and 82 % for β-deuteration). Subsequently, these porphyrins were then treated under the same conditions, but exposed to the respective boranes. Substitution was facile yielding analogous meso- and β-borylated products 21a and 23 in 52 % and 70 %, respectively. Notably, the bis(β-porphyrinyl)borane 24 was obtained in 25 % yield from 22 in one step. Identical conditions as for 24 were used with iodoporphyrin 20b but in this case formation of the bis(meso-porphyrinyl)borane was unsuccessful. The authors propose this is due to the highly crowded nature of the putative product. With regards to the desirable donor–acceptor (DA) type photo-physical properties that the use of boron can implement, porphyrin 21b did exhibit donor–acceptor properties with increased intramolecular charge transfer character in the S₁ state, and bis(porphyrinyl)borane 24 exhibited electronic communication between the two porphyrin moieties.

Likewise with organoboranes, organic radicals lend themselves to a variety of applications, e.g., spin labelling and use in polymer chemistry, amongst others.⁷⁴ Given the ability of large aromatic macrorcycles to hold and subsequently delocalize a charge over the macrocycle, porphyrins have shown themselves to be desirable hosts of organic radicals. However, until 2016,⁷⁵ only other porphyrinoid structures have been transformed into a radical structure. Examples include; [26]hexaphyrin(1.1.1.1.1.1) and keto-hexaphyrin derivatives⁷⁶,⁷⁷ meso-hydroxysubporphyrins,⁷⁸ corroles,⁷⁹ and meso-hydroxyboraporphyrins.⁸⁰,⁸¹ Hence, the generation of a stable porphyrin radical by Kato et al. was a historic development (Scheme 6).⁷⁵

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Scheme 5. Synthesis of meso- and β-boron appended porphyrins through the generation of porphyrinylboranes. Ar = 3,5-di-tert-butylphenyl, Mes = 2,4,6-trimethylphenyl. For 20a,b

Scheme 6. Synthesis of metallo- and free base-porphyrinyl radicals 27 and 28 through an SNAr strategy by Kato et al.⁷⁵ Ar = 3,5-di-tert-butylphenyl.

Treatment of trichloro-triarylporphyrin 25 with diphenylmethyl lithium cleanly yielded the diphenylmethane appended porphyrin 26 in 65 %. Subsequent dual intramolecular cyclization yielded 27 in 72 %. The product exhibited only a broad resonance in the 1H-NMR spectrum at δ = 1.55 ppm, corresponding to the tert-butyl groups, whilst the ESR spectrum yielded a signal at g = 2.0007. This aided in the assignment of the structure as porphyrinyl radical 27. This radical was stable enough to be entirely characterized, including by single-crystal X-ray diffraction, and to be demetalated. Subsequently, the free base counterpart 28 was obtained in 51 % yield, and also recrystallized. The structures produced were remarkably similar, with both porphyrins forming anti-parallel stacked dimers, remaining mostly planar excluding the diphenylmethane moiety which exhibited a "[4]helicene-like twist". Along with this, in both cases the central carbon atom was indicated to be of the C(sp²) hybridization state.

Thus far we have discussed the successes of S₄Ar using alkyl- and aryl-lithium reagents; but not alkynyllithium. Through
Shinokubo and co-workers' investigations of porphyrin-N,C,N-pincer complexes of Pt and Pd \cite{82,83}, it was found that the pyridyl-coordination of a moiety had a strong effect on the type of product observed. With this in mind, Anabuki et al. exposed [2,18-bis(2-pyridyl)-5,10,15-tris(3,5-di-tert-butylphenyl)porphynato]nickel(III), 29, to a range of alkynyllithium reagents and found meso-alkynyl-substitution in good to excellent yields (Scheme 7).\cite{84}

Scheme 7. Top: synthesis of meso-alkynylated porphyrin through double pyridyl coordination, \( r = \) reaction time = 12 h. Bottom: single crystal X-ray structure of 31d. Atoms represented as thermal ellipsoids at 50 % probability; meso-aryl groups, hydrogen atoms, and benzene solvate are omitted for clarity. Image generated from CCDC No. 872912.\cite{84} Ar = 3,5-di-tert-butylphenyl.

To evaluate the necessity for the double-pyridyl coordination, the same reaction was performed with phenylethynyllithium and the respective mono-pyridylporphyrin 32 under identical conditions. At \( t = 3 \) h, none of the respective product had formed. Stirring at r.t. for 12 h yielded 33 in 23 %; however, 12 h at 70 °C yielded a complex mixture of products. The same trends of yields could be observed when the respective porphyrin with no pyridyl units appended was used. This methodology was utilized to yield an ethynyl-porphyrin dimer, with one porphyrin unit containing the two 2-pyridyl moieties, in 60 % yield.

X-ray crystal structures of three of these meso-alkynylated porphyrins were obtained, and all exhibit similar features; the porphyrin core has become distorted into a saddle conformation, the aryl-ethynyl moiety deviates from the porphyrin mean plane through the steric hindrance of the 2-pyridyl moieties which have rotated away from the ethynyl group. One example, 31d, is presented (Scheme 7, inset).

2.2. Reactions with Other Nucleophiles: Meso Position

2.2.1. Dodecasubstituted Porphyrins. Dodecasubstituted porphyrins are an interesting class of compounds, mainly due to their often nonplanar macrocycles.\cite{8a,85} Nonplanar porphyrinoids are frequently found in nature and account in part for the functional variety of the pigments of life.\cite{86} Conformational distortion of porphyrins gives rise to significantly altered physico-chemical properties, atypical chemical reactivity and metal coordination, and allows access to the inner N–H/N units and use thereof in organocatalysis and sensing.\cite{8a,87} One of the oldest examples of these “highly substituted porphyrins”, \cite{88} is 2,3,7,8,12,13,17,18-octaethyl-5,10,15,20-tetranitroporphyrin, 34, which was prepared by Ogoshi and co-workers via tetranitration of 2,3,7,8,12,13,17,18-octaethylporphyrin (OEP).\cite{89} It has previously been reported that thiolates can displace the nitro group on porphyrins.\cite{35,90,91} Thus, following in Dolphin’s footsteps, our group utilized this knowledge to synthesize a family of highly substituted porphyrin thioethers under almost diametrically opposed conditions;\cite{92} base catalysis as opposed to acid catalysis and the use of sulfurous nucleophiles alone (Scheme 8).

Treatment of 34 with a variety of S-based nucleophiles in the presence of catalytic triethylamine yielded tri- and tetra-substituted thioether porphyrins in varied yields of between <5–86 %. The thiol used differed in steric hindrance (2,4,6-trimethylbenzenethiol 35e vs. 9-anthracenethiol 35k) and electronic properties (2,3,4,5,6-pentafluorobenzenethiol 35f vs. 4-methoxybenzenethiol 35h). Interestingly, when electron-rich nucleophiles were used (35b, 35e) only the trisubstituted product could be achieved; except for 35h where the product could only be isolated as a mixture of tri- and tetrasubstituted product. Given the use of thiols as nucleophiles, a prevalent side reaction is the denitration of the starting material 34 and generation of OEP along with the respective disulfide. This was examined with alkyl- and methyl-aryl thiols and found that complete denitration of 34 occurred smoothly over three days in 49 %.
Scheme 8. Synthesis of meso-porphyrin thioethers by Kielmann et al. \[92\]

$^a$ only trisubstituted product (5,10,15-trithioether) isolated, $^b$ 7.8 equiv. thiol used, $^c$ 8.8 equiv. thiol used. Single crystal X-ray structures of 34 (left), and the $\alpha_2\beta_2$-atropisomer of 2,3,7,8,12,13,17,18-octaethyl-5,10,15,20-tetakis(pyridin-2-ylthio)porphyrin, 36g (right). Atoms represented as thermal ellipsoids at 50 % probability. $\beta$-ethyl groups are omitted for clarity. Images generated from CCDC No. 1232025 and 1499411.\[89,92\]

2.2.2 5,15-$A_2$-porphyrins. "trans"-$A_2$- or 5,15-disubstituted porphyrins present an attractive target for porphyrin chemists. With two free meso-positions there are many potential uses. Aside from the generation of porphyrins of greater complexity (trans-$A_2B$, trans-$A_2B_2$ and, trans-$A_2BC$) their utility spans a wide variety of applications.\[54,93–95\] Synthesis of this type of porphyrins was first successfully accomplished by MacDonaldd.\[5b,96,97\]

In what to the best of our knowledge is the first examples of $S_A$Ar on the trans-$A_2$ scaffold Blake et al. synthesized a 5,15-dialkylideneporphyrin from the dibrominated precursor (Scheme 9).\[101\] Takahashi coupling of 37 with (dicyanomethyl)iodide (NaCH(CN)$_2$), followed by subsequent oxidation with oxygen and acetic acid yielded 38 in 53 % over the two steps.\[102\] This transformation was found to greatly increase the absorption of the tetrapyrole in the 600–650 nm region with an intensity almost equivalent to that of the Soret band of the parent porphyrin. Structurally, 38 was found to exhibit a structural profile akin to that of 5,15-dioxoporphyrins.\[103\] In 2016 Sugiuura’s group presented the synthesis of 40, the 5,10-analogue of 38.\[104\] The UV/Vis spectrum of the molecule was vastly different, with a bathochromic shift on the second band, up to 694 nm, and hypsochromic of the first, down to 437 nm, along with some IR absorption at 920 nm.

Scheme 9. Synthesis of dialkylideneporphyrin isomers 38 and 40 from the respective dibromoporphyrin precursors. Ar = 3,5-di-tert-butylphenyl.\[101,104\]

Birin et al. optimized the reaction of Ni(II), Zn(II) and 2H derivatives of 5,15-dibromo-10,20-diphenylporphyrin 41 to understand how the variation in conditions yielded the mono- and disubstituted porphyrins (Scheme 10).\[105\] The nucleophiles used were all O-based, and thus a wide variety of porphyrin-appended ethers were synthesized. Reactions were initially investigated with the nickel complex and an obvious steric effect was observed with 2,6-disubstituted phenols as ($X = H, Me, iPr, tBu$) the yields varied between 77 % ($X = Me$) and 0 % ($X = tBu$). Benzyl alcohol disubstituted successfully in 62 % yield, whilst n-hexanol did not yield the disubstituted product under a wide
variety of conditions. Whilst one set of conditions yielded the mono-substituted product cleanly, all others presented yielded mixtures of the starting material and mono-appended product. Reaction optimizations were continued with n-hexanol, and some interesting observations were noted; the Zn(II)porphyrins would only react at a higher temperature than the Ni(II) analogues, and with these higher temperatures came a large degree of hydrodebromination (42), Scheme 10, and considerable degradation of the porphyrins. However, it was possible to isolate the monosubstituted free base porphyrin in 64 % yield as the sole product.

Porphyrin ethers have also been utilized in the generation of strapped bisporphyrin systems; more specifically cofacial porphyrin dimers (Scheme 10). Yamashita et al., utilized various dihydroxyarenes and both mono- and trans-dibromo-A2 porphyrins to yield a variety of arylenedioxy-bridged porphyrin dimers. As noted by the authors, there have been limited reports regarding the preparation of “closely-stacked” porphyrin dimers, which require high dilution to be successful. Akin to the findings of Birin et al., debrominated by product was also yielded, mostly however with the use of mono-bromo-trans-A2 starting materials. Optimized conditions were applied to the dibromo-trans-A2 porphyrin with the respective resorcinol, and 2,7-dihydroxynaphthalene, to yield cofacial porphyrin dimers in very good yields, 61 % (45) and 69 % (46), respectively.

The Huisgen cycloaddition, referred to as the “premier example of a click reaction” is a 1,3-dipolar cycloaddition comprising of the reaction between an azide and an alkyne. Realized and devised by Huisgen, and built on by Sharpless, it has become one of the most widely used reactions in medicinal and bioorganic chemistry. Thus, given the use of porphyrins in medicinal chemistry, it is highly desirable to incorporate these moieties onto the porphyrin skeleton. Smith’s attempts to isolate a meso-azido porphyrin resulted in decomposition of the products upon work up and attempted isolation, and Pleux’s generation used diazotization fol-

Scheme 10. Synthesis of porphyrin appended ethers through S_NAr on a 5,15-dibromo-10,20-A2-porphyrin with various alcohols. M = 2H, Zn(II), Ni(II), Ar = Ph, Ar’ = 3,5-bis(3-methylbutoxy)phenyl. R^1, R^2 = alkyl, aryl.

Scheme 11. Synthesis of meso-azido porphyrins through S_NAr through the use of NaN_3 and 5,15-dibromo-10,20-A2-porphyrins. Ar = 3,5-bis(3-methylbutoxy)phenyl.
lowed by nucleophilic substitution, i.e. not direct substitution; however, in good yield (85 %).[116]

In 2012 Yamashita and Sugiura successfully generated meso-azido porphyrins from the respective meso-bromo porphyrins in one step (Scheme 11).[117] Treatment of the respective (5-bromo-10,15-diarylporphyrinato)nickel(II) (47a,b, Scheme 11) with sodium azide in DMF at 40 °C for 7 h yielded the meso-azido-diaryl porphyrin 49 in 93 %, and the meso-amino porphyrin in 1 %. Other reaction conditions were screened, and it was found that the meso-azido porphyrin could never be formed as a sole product. Interestingly, no reaction occurred in THF and, no reaction occurred with the Zn(II) porphyrin whereas the free base porphyrins were found to preferentially form the meso-amino product. The utility of the reaction was tested through reaction with the respective Ni(II)dibromoporphyrins and the yields of the diazido porphyrin were found to be excellent; 77 % for Ar = Ph, and 88 % for Ar = 3,5-bis(3-methylbutoxy)phenyl, 48, respectively. Lastly, the regiospecificity of the reaction was examined with (2-bromo-5,10,15,20-tetraphenylporphyrinato)nickel(II) 51 and under the same conditions no reaction was observed. Thus far, to the best of our knowledge, there has not been an analogous generation of a β-azido porphyrin.

In a dual SNAr strategy, Ermakova et al. successfully synthesized 5,15-diheteratom substituted porphyrins consisting of a diethoxyphosphoryl moiety on the 15-position, and a brominated 5-position (Scheme 12).[118] The parent porphyrin 54 was substituted with varying alcohols, thiols, and amines, utilizing a wide substrate scope over aliphatic and aryl compound types. Akin to the problems experienced by Kielmann et al.[92] dehydrodebromination was observed upon substitution with both benzenethiol and n-octanethiol. For O- and S-based nucleophiles Cs2CO3 was used as a base catalyst whereas with most N-nucleophiles used, Pd catalysis was necessary to obtain suitable yields. Interestingly, the use of piperazine successfully yielded the porphyrin dimer 56b in 10 % (as indicated by NMR analysis) along with the monosubstituted product 56a in 87 %. Substitution of 54 with morpholine yielded a 1D coordination polymer 57 chain in 2D layers in the solid state – bound through the P=O···Zn and morpholine-O···Zn. Interestingly, these results bear great similarities to earlier works surrounding 34 and other meso-nitro-2,3,7,8,12,13,17,18-octaethylporphyrins.[119]

### 2.2.3. A3- and trans-A2B-Porphyrins

A3- and trans-A2B-porphyrins present the simplest challenge with regards to SNAr on the meso-position of porphyrins as there is only one meso position free to substitute.

This was exactly the case for Chappaz-Gillot et al. in their synthesis of 5-amino-10,15,20-triphenylporphyrins 59a,b (Scheme 13, top).[120] Refluxing 5,10,15-triphenylporphyrin 58 with 200 equiv. of the respective nucleophile and THF as a co-solvent yielded 59a in 89 % for propylamine, and 59b in 85 % in the case of ethylene diamine. Interestingly, it appears that there was no formation of a propylamine linked dimer. Whereas, in the case of Devillers et al. synthesis of a di(porphyrinyl)-amines was an aim of theirs.[121] Given the apparent lack of SAr on meso-NO2 porphyrins with amine nucleophiles, they set out to examine this reaction for a variety of amines (Scheme 13, bottom). Initially, reaction with NaN3 occurred at ambient temperature, with no additives in 74 % (62f). However, for aryl/alkylamines – meso-NO2-porphyrin 60 was screened with p-methoxyaniline as a variety of conditions and eventually it was found that 10 equiv. of amine in DMF/KOH for 1 h at 150 °C was optimal and yielded the desired product 62c in 66 %. For other amines, more or less equiv. were used, e.g., for...
When the terminologies “A3” or “trans-A2B’” porphyrins are used, it is typically assumed that there are simple alkyl/aryl/alkynyl substituents on the meso positions, e.g., phenyl rings, or other (hetero)aromatic moieties. In one notable example, Osuka placed another porphyrin on the fourth meso position (Scheme 14).[122] This type of compound is known as a bisporphyrin, and there are multiple ways to synthesize them, e.g., our above mentioned synthesis of bisporphyrins through the use of nBuLi followed by DDQ with no aqueous quenching.[44a]

Osuka, however, initially undertook an oxidative coupling of [5-bromo-10,20-di(3,5-di-tert-butylphenyl)porphyrinato]nickel(II) (63) followed by tetraborylation, iodination, and chlorination yielding 64 in 13 % over four steps. Treatment of the hexahalo-meso-meso-dimer 64 with diphenylamine, or bis(4-methoxyphenyl)amine, in the presence of NaOtBu yielded the tetrafused-porphyrin dimers in 57 % (65a, R = H) and 66 % (65b, R = OMe). The same experiments were performed on the respective A3 parent porphyrin, [5,10,15-tri(3,5-(di-tert-butylphenyl)porphyrinato]nickel(III), with both amines and the yields were good with 81 % for R = H and 62 % for R = OMe, the converse trend when compared with the bisporphyrins. Bisporphyrins 65a, b were exposed to “Magic Blue” in attempt of fusing the two porphyrins, to form a triply fused porphyrin dimer. 65a formed the dicationic closed-shell quinoidal dimer whereas 65b formed only the meso-meso, [β-β] doubly-linked dimer.

Substitution with diamines is not uncommon, and we have discussed it multiple times previously in this review. However, the use of triaryl-diamines is certainly something noteworthy. Treatment of trichloro-triarylmetalloporphyrin 66, with N,N'-diarylated m- and p-phenylenediamines and NaOtBu in DMF yielded the bis(porphyrinyl)amines, m-67, in 62 % and p-67 in 16 %.[123,124] The main difference aside from the use of different

Scheme 13. Examination of the reactivities of amines with meso-free (58) and meso-NO2 (60) A2/trans-A2B’-porphyrins.[120,121]

Scheme 14. Synthesis of amine appended A3-porphyrins with amine nucleophiles through different halogenation strategies, by Osuka et al.[122–124] Ar = 3,5-di-tert-butylphenyl.
types of amines is the trihaloporphyrin precursor. In the case of 65a,b the initial reactions were performed using the 20-chloro-2,18-iodoporphyrin, however when the same reactions were attempted with 66, this yielded a complex inseparable mixture. The outcome was rationalized through the facile deiodination of the porphyrin given the electron rich nucleophile used.

However, it is not only the incorporation of nitrogenous moieties at the meso-position. Osaka utilized the tri-halo strategy his group has pioneered and exposed one such porphyrin to LiPPh2 (Scheme 15, top).\textsuperscript{125} Subsequent oxidation of P(III) to P(V) proceeded cleanly enabling the Pd-pivalic acid co-catalyzed fusion to yield 70 in 31 % over three steps. Transmetallation with Zn(II) proceeded smoothly in 77 %, and the crystal structures of both are displayed. Whilst both porphyrins display a meso-aryl (3,5-di(tert-butyl)phenyl) groups are omitted for clarity. Images generated from CCDC No.1509710, 1509712.\textsuperscript{125}

For most organic chemists, $S_{n}Ar$ would come in the form of mixing the reactants and applying either microwave radiation, cryogenic temperatures, or conventional heating. Less common is to consider the utilization of electrochemistry; however, it has been found to work on one occasion (Scheme 15, bottom). Dimé examined the electrochemical oxidation of Ni-porphyrin 72 in a selection of solvent systems (CH$_2$Cl$_2$/CH$_3$CN, CH$_2$Cl$_2$/DMF).\textsuperscript{126} It was found that treatment of 72 with 2,6-lutidine at $E_{app} = 0.95$ V/SCE in CH$_2$Cl$_2$/CH$_3$CN (4:1, v/v) and 0.1 M tetraethylammonium hexafluorophosphate yielded the respective meso-chlorinated porphyrin in 78 % yield. It is proposed that this reaction is $S_{n}Ar$H with Cl$^{-}$. Subsequently, addition of 20 equiv. PPh$_3$ to the reaction mixture, at $E_{app} = 1.00$ V/SCE, yielded the triphenylphosphonium appended porphyrin, 73, in 72 %, exhibiting the high reactivity of meso-Cl porphyrins (vide infra).

Ryan et al. investigated the reactions of porphyrin substituted thioethers (Scheme 16, top).\textsuperscript{127} Initially, porphyrins 74 were treated with 2-ethylhexyl-3-mercaptopropionate, 78, under Pd-catalyzed conditions, yielding porphyrins 75 in 63–85 %. Using methyl iodide, and $n$-bromohexane under base mediated conditions, it is possible to substitute at the thio-position in good yields (71–96 %). Again, use of base-mediated $S_{n}Ar$ conditions, the 2-ethylhexyl-3-mercaptopropionate side chain could be cleaved and exchanged for a $p$-C$_6$H$_4$Br group in 48 % (77a). Most interestingly, however, is the formation of bis[(porphyrinyl)thioethers. Treatment of porphyrins 75 with NaOEt induces a base-mediated cleavage of the thioether, and subsequent attack from one porphyrin thiolate on another thioether to yield a variety of bis[(porphyrinyl)thioethers in 55–72 % (76). When free base porphyrins were used in this transformation, the disulfide and bis[(porphyrinyl)thioether products formed in an inseparable mixture.

Berthelot et al. utilized both inter- and intramolecular $S_{n}Ar$ in their synthesis of novel $\pi$-extended porphyrins.\textsuperscript{128} It was demonstrated that formation of the porphyrin cation radical alone was not sufficient to induce C–C coupling, thus the need for a porphyrin dication. However, electrochemically these porphyrin dications can be further oxidized and degraded. Given this, the possibility of a fusing unit to hold a positive charge could stabilize the intermediate and prevent electrochemical degradation, hence 2-mercaptopypyridine was utilized. $S_{n}Ar$ between 79 and 2-mercaptopypyridine, followed by metalation, yielded 80 in 8 % over two steps.

Subsequent oxidation with PIFA, and hence subsequent intramolecular nucleophilic attack of pyridyl moiety, yielded the fused moiety 81 after anion exchange in 98 % The methodology was applied to an analogous trans-$\lambda_2$ dibromo porphyrin precursor, and the anti-diffused porphyrin system, anti-82, was yielded in 31 %. These oxidations were also performed electrochemically to yield 81 in 71 % and anti-82 in 23 %. Cyclic vol-

![Scheme 15. Incorporation of P-based motifs into the porphyrin skeleton via $S_{n}Ar$.\textsuperscript{123,126} $Ar = 3,5$-di-tert-butylphenyl, TEAPF$_6$ = tetraethylammonium hexafluorophosphate, SCE = Standard calomel electrode. Inset: single crystal X-ray structures of diphenyl phosphine oxide fused porphyrinoids, 70 (right) and Zn-70 (left). Atoms represented as thermal ellipsoids at 50 % probability. meso-aryl (3,5-di(tert-butyl)phenyl) groups are omitted for clarity. Images generated from CCDC No.1509710, 1509712.\textsuperscript{125}](image-url)
tammetric analyses were utilized to propose a mechanism for this transformation, in which there are three separate one electron oxidation steps. Given the formation of the anti-diffused moiety 82 and no formation of syn-82, it is apparent that this reaction occurs on the peripheral double bonds of the [18+4]π electron macrocycle.

Whilst the reactivity of meso-Cl-porphyrins is considerable, it is not supreme. Chen et al. examined the reactivity of [5-bromo-10,20-di(3,5-di-tert-butylphenyl)-15-phenylporphyrinato]nickel(II) with a wide variety of O-, S-, and C-based nucleophiles, with yields for O-based nucleophiles ranging from 23 % (benzyl alcohol) to 99 % (phenol), for S-based 71 % (2-naphthalenethiol) to 95 % (thiophenol and benzyl thiol), and for C-based 62 % (diethyl malonate) to 91 % (ethyl 2-cyanoacetate).[129] Along with examining S\textsubscript{N}Ar reactions on this scaffold over a large substrate scope, kinetic studies of the S\textsubscript{N}Ar reaction between phenol and 83a-d were undertaken (Scheme 17). We inadvertently prepared meso-phenoxy-porphyrins in 2001 through the treatment of 2,3,7,8,12,13,17,18-octaethyl-5,10,15-triphenylporphyrin with an “old” stock solution of PhLi.[130] Attempts to resynthesize this meso-phenoxy porphyrin with solutions of phenolate in the presence of H\textsubscript{2}O\textsubscript{2} and subsequent oxidation (DDQ) only returned starting material. At the time, we proposed that the steric hindrance of the porphyrin used were the major factor in the inability to resynthesize it. This assumption seems to hold true given the findings of Chen et al. At this experimental temperature (80 °C) the reaction of 83a (LG = F) “was too fast to measure”. However, for all other substituents, values for rate constants were obtained, with the substituents (relative constants) in the following order: F > Cl (4.95) > NO\textsubscript{2} (4.48) > Br (3.18) > I (1.0). This series exhibits the “element effect”, consistent with the classic S\textsubscript{N}Ar reaction (Figure 4).[131]

Scheme 16. Reactions of \( \text{A}_3\text{B} \)-porphyrins with sulfur-based nucleophiles. Ryan et al.[127] synthesis of bis(porphyrinyl)thioethers (top) and Berthelot et al.[128] first synthesis of C–N intramolecularly fused porphyrin through a dual S\textsubscript{N}Ar strategy (bottom). \( R^1 = \text{p-Tol}, \text{Ph}, 1\text{-ethylpropyl}, R^2 = \text{H}, \text{Ph}, \text{nBu} \).

**Figure 4.** Plot detailing the rate constants for the generation of 84 from various meso-halo-porphyrins towards S\textsubscript{N}Ar. Ar = 3,5-di-tert-butylphenyl.

Scheme 17. Transformation analyzed by Chen et al.[129] in order to understand the reactivity of various meso-halo-porphyrins towards S\textsubscript{N}Ar. Ar = 3,5-di-tert-butylphenyl.
2.3. Reactions with Other Nucleophiles: β-Position

2.3.1. 2-Nitro-A4-porphyrins. Both A4-type and meso-unsubstituted β-octasubstituted porphyrins are the simplest synthetic porphyrins, notably 5,10,15,20-tetraphenylporphyrin (TPP) and 2,3,7,8,12,13,17,18-octaethylporphyrin (OEP). TPP is a simple porphyrin to make, either under Adler-Longo,[4c] or Lindsey conditions.[4d] Particularly in the case of the Lindsey synthesis, it is possible to exchange benzaldehyde with other aldehydes (aryl or alkyl), contrasting with the Adler-Longo synthesis, in which only non-acid sensitive groups can be utilized. Aside from the difference in these syntheses, there are many possible reagents and conditions to yield the 2-nitro porphyrin. Thus, given these facile reactions – the amount of work considering them with respect to SNAr is considerable.

Amiri et al. were able to obtain a cyclopropane annulated chlorin via this method utilizing an arylacetonitrile (Scheme 18, A).[132] Utilizing KOH yielded a vastly differing set of products; an isoxazole KOH yielded a vastly differing set of products; an isoxazole yielded porphyrin 86, tricyclic system 87 and, hydroxyimino porphyrin 88, whereas K2CO3 yielded cycloprop-
ane-annulated chlorin, 89 (Scheme 18, B). Interestingly, 88 exhibited a very red-shifted UV/Vis spectrum for a porphin and it is arguably more akin to a chlorin in type, whereas 87 displayed one more akin to a π-expanded system. Likewise, Cavaleiro and co-workers found that refluxing 2-nitro-5,10,15,20-tetraphenylporphin (2-NO$_2$-TPP) in aniline yielded phenylamino porphin 92a (53 %), quinolino-fused porphin 93a (6 %) and trans-chlorin 94a (22 %) (Scheme 18, C).[133] Swapping aniline for p-toluidine yielded no product formation under the same conditions until the addition of o-dichlorobenzene as a cosolvent. Under these conditions, the analogous trans-chlorin did not form.

Noted by Crossley and King in 1996, premature quenching of the reaction mixture of metallo(2-nitro-TPPs) with RO-nucleophiles yielded the formation of 2,2-dinucleophile-3-nitro substituted porphins or chlorins.[134] However, the product distribution was found to be dependent upon the metal center used. Also in 1996, Smith presented the first synthesis of fused pyrrole derivatives.[135] The reaction of 2-NO$_2$-TPP with ethyl iso-cyanoacetate occurred in a Barton-Zard type fashion.[136] The fused pyrrole ring was found to undergo typical pyrrole type chemistry, and thus it was possible to form a porphin-fused dipyrromethane. Along with this, modification of the reaction conditions yielded cyclopropene anulated chlorins, 98, and in this particular case because of the use of the isocyanate group, the cyclopropyl substituent was found to coordinate to a Zn center in another chlorin (Figure 5).

![Figure 5. Crystal structure of cyclopropyl chlorin dimer 98. Atoms represented as spheres. meso-Phenyl substituents have been omitted for clarity. Image generated from CCDC No.: 1267053.](Image)

Chlorins (dihydroporphins) are not unexpected by-products from S$_n$Ar on 2-nitro-porphyrins. Smith and co-workers enabled the synthesis of both cyclopropane annulated chlorins and trans-chlorins from active-methylene C-nucleophiles.[137] Ni(II) 2-NO$_2$TPP was exposed to dimethyl malonate in the presence of NaOMe to yield the respective dimethyl ester cyclopropyl chlorin in 12 % yield. However, when Zn(II) 2-NO$_2$TPP was allowed to react with malonitrile in the presence of the non-nucleophilic base 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), the bis(malonitrile) trans-chlorin was obtained in 14 % yield.

Ostrowski and Grzyb synthesized a variety of metallo-A$_4$ porphyrins, with M = Zn(II) or Cu(II),[138] and subsequent treatment of these metalloporphyrins with 1,1,1-trimethylhydrazinium iodide ([IIH$_3$C]NNH$_3$) and KOH in dimethyl sulfoxide yielded the 2-amino-3-nitro porphyrins in good yields (90a-d, 64–89 %, Scheme 18 C). Interestingly, halogens (F, Cl) on the p-Ph positions did not undergo S$_n$Ar reactions, displaying the selectivity imparted by the nitro group. However, two years prior, Richetier’s group demonstrated the utility of the same reaction through the use of another nucleophilic amination reagent; 4-amino-4H-1,2,4-triazole.[139] The yields were higher through the use of this reagent, with 82 % when M = Ni(II), and 90 % when M = Cu(II), although there were only two examples presented.

Chen et al. examined the reaction of sodium-1-naphthoxide with multiple 2-nitro-TPPs.[140] In the majority of cases, regardless of solvent, temperature or inner core substituent (2H, Cu(II), Ni(III), or Zn(II)), 91a-d, Scheme 18, D), it was found that the main product was the respective 2-(2-hydroxynaphthyl)porphin. The reaction of these porphyrins was also examined with sodium phenoxide, and the rates of reaction were found to be significantly lower, and it was proposed that the reaction of these porphyrins with sodium-1-naphthoxide occurs via an SN1 type mechanism. As noted (vide supra)[133] Crossley demonstrated the reaction of Cu(II) 2-NO$_2$-TPP with $n$BuLi and found the product to be the respective 2-butylated porphin. The same type of reaction was analyzed with a variety of Grignard reagents MeMgI, iPrMgI, $n$BuMgI, tBuMgBr, and PhMgBr on a variety of metallo-2-NO$_2$-TPP’s [M = Cu(II), Ni(III), Zn(II)], with varying yields (10–80 % over 11 examples, 95a-k, Scheme 18, F). trans-Chlorins were formed to form but oxidized to the porphin upon purification via silica column chromatography.

In 1986 Jackson and co-workers analyzed the effects of nitronium tetrafluoroborate (NO$_2$BF$_4$) as a nitrating agent for porphyrins.[141] The reaction was performed in pyridine for both OEP and TPP, and whereas for OEP the product was found to be 5-nitro-OEP, for TPP the reaction yielded [2-pyridinium-5,10,15,20-tetraphenylporphin]chloride, 96a (Scheme 18, G), in 45 %. Other nitrogenous heterocycles were appended upon the macrocycle in a similar fashion, although under different conditions. In 2016, Liao et al.[142] synthesized a variety of piperidine appended porphyrins, 96b, and in 2017 followed it up with the same porphyrins having a morpholine ring appended in the same fashion, 96c.[143]

As discussed above, substitution of a NO$_2$ group with the azide anion is feasible in good yield.[121] However, for the β-NO$_2$ porphyrin Lacerda et al. obtained different products upon reaction of two A$_4$-porphyrins (TPP and TPPF$_{20}$) with Na$\text{N}_3$ in DMF (Scheme 18, H).[144] The yields product, in both cases, were [1,2,3]triazolo[4,5-b]porphyrins 97a,b, not β-azido. Unsurprisingly, the more electron deficient TPP$_{20}$ reacted far more readily (r.t., 1.5 h, 80 %) than its H-counterpart (80 °C, 48 h, 30 %).

2-Nitro-A$_4$ porphyrins then present unique mechanistic challenges. As detailed in Scheme 19, substitution can occur adjacent to the nitro group, leaving it intact, or ipso-substitution can occur with NO$_2$ acting as a leaving group. Further complication arises when the electronic properties of the nitro group are considered. The nitro group is an electron withdrawing group, promoting S$_n$Ar in positions ortho- and para- to itself on a phenyl ring, and ipso or alpha to itself on a porphin. Route 1 in Scheme 19 would be the typical addition-elimination type S$_n$Ar reaction, yielding the Meisenheimer complex 100[14c] and negative charge assisted loss of the NO$_2$ anion to yield 101.
Route 2 depicts attack at the $\alpha$-carbon and yields canonical forms 103 and 104. These can interconvert through the allylic-type resonance of the nitro group. Removal of a proton from intermediate 103 yields the 2-nitro-3-substituted porphyrin 105, whereas a proton shift between intermediates 104 and 106 yields an intermediate which proceeds via negative charge assisted loss of the NO$_2^-$ anion (106), yielding the 3-substituted porphyrin 101; however, due to the symmetry and subsequent nomenclature rules for porphyrins,

[145] it is inherently the 2-nitro product. Crossley et al. briefly discussed this previously and propose that the differences in the products formed (101 vs. 105) is entirely dependent on whether the nucleophile used is “hard” or “soft”.

2.3.2. $\beta$-Bromo- and $\beta$-Formylporphyrins. Akin to 2-nitroporphyrins, just like their meso-counterparts, 2-formylporphyrins are useful synthetic building blocks. In 2001 Callot and co-workers studied the reactivity of a carbonyl group on a porphyrin, albeit on a fused system, with the take home lesson being that nucleophilic attack would always occur adjacent to the carbonyl group. 

[147] Van der Salm utilized this knowledge in a dual-sequential $\text{S}_{\text{NR}}$ synthesis to examine the effect of unsaturated $\beta$-substituents on the photophysical properties of porphyrins (Scheme 20).

[148,149] Thus, starting from 2-formylporphyrins, subsequent $\text{S}_{\text{NR}}$ yielded the 2-cyano-3-formylporphyrins, 108, in moderate to good yields (17–66 %). However, further substitution reactions were only carried out on one of these A$_4$ porphyrins, where Ar = 3,5-di-tert-butylphenyl. Substitution at the formyl-groups indicated stark differences between the two works, namely that in the latter case the carbonyl group remained reactive, whereas Callot’s ketone was inert.

[147] Eventually, a series of 2-cyano-3-(4-(2-aryl(ethynyl))- and ($E$)-2-cyano-3-(2-aryl(ethenyl))-porphyrins were synthesized (109c–e and 110a–c respectively), through the use of phosphorus based reagents 112c–e and 111a–c.

As shown bromide is a very good leaving group and the efficacy of cyanide as a nucleophile has been demonstrated on 2-cyano-3-alkenyl/alkynyl porphyrins. [146] Ar = 3,5-di-tert-butylphenyl.
a variety of macrocycles, vide supra. The first report of β-cyano porphyrins came from Callot in 1973,[150] and eventually, through an understanding of the [18+4]-π-system within the porphyrin, i.e. the presence of two double bonds not involved in the aromatic system, it was possible to selectively tetra-brominate the porphyrin on the antipodal pyrrolenic positions (7, 8, 17, 18 positions, Figure 2).[151]

Sankar et al.,[152] successfully synthesized the complete series of porphyrins CuTPPBrn(CN)4−n (n = 0–4) and each was subject to UV-Visible spectroscopic and electrochemical analysis. However, attempts to separate the isomers of CuTPPBr2CN2 were unsuccessful. The effect of the electron-withdrawing cyano groups is clear to see (Figure 6), with red-shifting of the last Q-band and decreasing intensity of the Soret band.[153] Electrochemically, an anodic shift in both the first reduction and oxidation potentials of the porphyrins was observed.

2.4. SNAr Reactions on Azuliporphyrins and N-Confused Porphyrins (NCPs)

2.4.1. SNAr Reactions of Azuliporphyrins. Porphyrins have been continually modified in their core structure, and two of the most prevalent examples are azuliporphyrins and N-confused porphyrins. We have chosen to include these sections here because whilst they each exhibit distinct reactivities according to their structure type, they are macrocycle and core-modified porphyrins.

The replacement of the pyrrolic moiety in a porphyrin ring with another heterocycle, or carbocycle, is not always a simple endeavor. Despite this, it is an avenue that has been continually explored.[154,155] Azuliporphyrins are macrocycles in which one of the pyrrole rings has been replaced with an azulene. First synthesized in 1997 by Lash,[156] through a “3+1” style condensation of 1,3-azulinedialdehyde and a tripyrrane,[157–159] the resultant azuliporphyrin was described as exhibiting “borderline porphyrinoid aromaticity”. Interestingly, it was these conditions that prevailed, as Breitmaier and co-workers had reported less than a year previously how their conditions [i) HBr/AcOH/CH2Cl2/THF ii) NEt3, DDQ whereas Lash utilized i) TFA/CH2Cl2 ii) NEt3, DDQ] yielded carba-benzoporphyrins.[160] Of course, it is possible to build the macrocycle “the other way”, i.e. using the azulene to form the pseudo-tripyrane, and then condense with a pyrrole-2,5-carboxaldehyde.[161] In the last option, regarding their synthesis, it’s possible to perform a Lindsey style condensation utilizing a 1,3-unsubstituted azulene and pyrrole, with the respective aryl aldehyde to yield tetra-aryl-azuliporphyrins.[162–164]

Regardless, however, of meso substitution or a lack thereof – the electronics of the azulene direct nucleophilic attack to one position alone, the 6-position on the azulene/the 23-position on the macrocycle (Scheme 21). The susceptibility of this position to undergo nucleophilic attack was first displayed in 1998,[165] when addition of pyrrolidine to 113/113′ transformed a green solution to a brown one, producing 116 in quantitative yield (Scheme 22). Resulting 1H-NMR spectra indicated significant changes to the meso-proton signals, which were shifted upfield to ca. δ = 10 ppm, as well as those within the core, from δ = 1.5 ppm up to 7 ppm.

With the desire of synthesizing a fused tropone system Lash reacted 114 with a variety of oxidizing reagents, e.g., NaOCl, and alkaline solutions of H2O2. These attempts were all either unsuccessful or yielded complex mixtures of products. Eventually, however, tropone fused carbaporphyrins were successfully synthesized, although not through an SNAr methodology.[166]
However, reactions of 114 with tBuOOH yielded interesting results; reaction with tBuOOH in KOH/MeOH and CH₂Cl₂ at r.t. gave the respective benzocarbaporphyrin in 30 % yield, whereas reaction with tBuOOH in CH₂Cl₂ yielded the 3²-formyl benzocarbaporphyrin 115 in 40 % yield.[167]

Inherently, the next question is what happens when the 2¹-position is blocked? The synthesis of modified azulenes, necessary for this functionalization, is facile from the respectively substituted pyridine.[168] Thus, the respective 6-tert-butyl and 6-phenylazulenes were synthesized and incorporated into azuliporphyrins. In both cases, attack of the pyrrolidine occurred adjacent to the new group, i.e. at the 2²-position.[161] Likewise, subsequent analogous ring contractions to yield the benzocarbaporphyrins also occurred.

2.4.2. SₙAr Reactions of N-Confused Porphyrins. N-Confused Porphyrins (NCPs), 2-aza-21-carbaporphyrins to give them their proper name, are a peculiar class of core modified porphyrins.[169] With one of the pyrrole rings inverted, i.e. bonding through one of the pyrrolic α and one of the β positions, they exhibit properties that are far different to more typical porphyrinoids; vastly red-shifted UV-Visible spectra,[170] the ability for intramolecular fusion,[177] differing metal coordination properties,[8c,172] and an exterior N that can be functionalized,[173] along with heightened reactivity at the C₃-position, compared to porphyrins, which will be discussed vide infra. This core-modified porphyrin was first reported by the groups of Furuta,[174] and Latos-Grażyński.[175] Since their initial generation, cis-A₂B₂ and A₃B derivatives have been synthesized,[176] along with improvements to their synthesis.[177] More recently, this class of compounds has found a new purpose as anion sensors.[178]

Since their inception, much attention has been paid to modifying the core of this macrocycle.[179] In the present context it is necessary to focus on the SₙAr at the C₃- and C₂¹-positions. The differing reactivities of these two positions is evident; noted from early on was the carbene character of the C₂¹-position,[180] and hence along with this come intriguing coordination properties,[181] particularly of larger metals in unusual oxidation states. Where the C₂¹-position is carbene type in character, the C₃-position is imine-type in character.

The electrophilicity of the C₃-position was exhibited in studies by Li et al. and Liu et al. in which a wide variety of active-methylene compounds (Scheme 23, 120a–h, 122a–e) were examined with regards to their reactivity towards NCPs.[182,183] For cyclic compounds 121a–e, no catalyst was required due to the basicity of the NCP and yields of 79–90 % were obtained. There was found to be an electronic effect of the aryl group, however small, notably with the use of 121d. The reaction was also tested on an N-methyl NCP using 121a, where the inverted pyrrole nitrogen could not act as a base. Instead, the authors propose protonation of the inner NCP core, but the reaction proceeds otherwise identically, with the yield for the transfor-
mation of the N-methyl NCP, 82 %, entirely comparable to the others presented, and upon the use of non-cyclic nucleophiles a catalyst was utilized (L-proline) but even so the reactions proceeded in lower yields across the entire substrate scope, even with vastly increased reaction times (3–11 h).

The expansion of the porphyrin macrocycle is something we have already described previously herein, and further to this trend, the NCP core has also been expanded. Notable is the work of Yamamoto et al., in which a variety of peripherally π-extended NCPs were synthesized through rhenium-mediated ring fusions (Scheme 24).\[185\] Initially, treatment of 123 with Re(CO)5Br and 2,6-lutidine yielded 124a (R = H) in 2 %, along with an intramolecularly fused NCP Re(CO)3 complex in 6 % yield. Applying the same conditions post N-methylation successfully yielded 124b (R = Me) in 45 %, and subsequently insertion of a Re(CO)3 unit into the core enabled a yield of 75 % for 124b in the subsequent transformation. The authors present a proposed mechanism in the manuscript in which a (pyridine-2-ylmethyl)rhenium reagent is generated in situ.

NCPs have been utilized at catalysts for a variety of transformations since the early 2000s.\[186\] Miyazaki et al. utilized a bio-inspired approach in their catalyst design; a penta-coordinate pyridyl-NCP metal complex (Scheme 25).\[187,188\] The SNAr of the respective 2-substituted pyridine attacking the C21-position varied between the pyridines used; for 2-mercaptopyridine the thiol was the nucleophile, whereas for 2-amino and 2-hydroxy-pyridine, the pyridyl nitrogen was the “head” of the nucleophile. Interestingly, this was the case for both ruthenium (130–132) and cobalt (128). These results were confirmed through single-crystal X-ray crystallography (Scheme 25, inset). The systems 130–132 were evaluated as catalysts for the oxidation of styrene and all three were found to be more effective than the respective rhenium porphyrin, and ruthenium N-confused porphyrin with no tethered axial ligand. The cobalt complex 128 was also catalytically evaluated; however, instead for the cyclopropanation of styrene with ethyl diazoacetate. Once it had been reduced, it was found to again be more effective than the respective porphyrins.

3. SNAr Reactions of Subporphyrins

3.1. Reactions at the meso-Position

Tripyrrolic macrocycles, akin to tetrapyrroles, have multiple sites that can be modified in different ways – the β and the meso. Ever since the first syntheses of meso-aryl subporphyrins by Kobayashi and co-workers,\[189\] and the subsequent modifications of Osuka et al.\[190\] subporphyrins have presented themselves as a desirable target for functionalization. Through the synthetic methods developed, it quickly became possible to synthesize A2-, A2B-, ABC-, A2-, and AB-type subporphyrins,\[191\] along with only hexaβ-two- and hexaβ-two-tri-meso-substituted subporphyrins. Bromination of A2 subporphyrins was presented in 2012,\[191\] along with typical Pd-catalyzed reactions for brominated aromatic moieties; Negishi,\[192\] Heck,\[193\] Sonogashira and,\[194\] Glaser couplings.\[195\]

It was only two years later when the first example of an SnAr style reaction was reported. Shimizu et al. utilized methoxo-[5-halo-10,15-diphenylsubporphyrinato]boron(III) (where halo = chloro or bromo) and exposed these to a variety of diarylamines and N-heteroarenes.\[196\] In all cases where the bromo-derivative failed to react, the chloro-derivative did so, and yields of between 6–84 % were obtained. Following this success, attention was turned towards other heteroatom-based nucleophiles, i.e. oxygen and sulfur. These palladium-catalyzed SnAr
reactions yielded a variety of aliphatic and aryl ethers and thioethers, along with one phosphonate.\[197\] Likewise, the synthesis of fused subporphyrins became possible (Scheme 26).\[198\]

Treatment of trihalo-subporphyrin 133 with diphenylamine yielded meso-substitution in 25 % yield (Scheme 26). Treatment of 134a with NaOtBu at 100 °C for 10 min formed 135a in 21 %, 5 % over two steps. However, repeating the substitution at a higher temperature was found to be all that was necessary to form the triply-fused subporphyrin, 135a, in 12 %. Using di(p-dimethylaminophenyl)amine increased the yield to 28 % for 135b. The fused subporphyrins (135a,b) were found to have differing quantum yields of fluorescence (Φ_F) with a decrease for 135a (R = H) but an increase for 135b (R = N(CH3)2), when compared with their precursors. Along with this, the already domed subporphyrin scaffold exhibited a deepening of the bowl upon fusion (depth of 1.63 Å for 135a, and 1.61 Å for 135b) when compared with what is typically observed (ca. 1.3–1.5 Å). Oxidation of 135a yielded an isolatable cationic radical which could be observed by electron spin resonance (ESR) spectroscopy (g = 2.0030 in toluene).

Similarly, lithium–halogen exchange reactions were employed with subporphyrins. meso-Diarylsubporphyrins were treated with nBuLi at –98 °C and quenched with a variety of electrophiles (Scheme 27).\[199\] Through this method, a variety of useful functional groups were successfully introduced, e.g., formyl, carboxylic acid, TMS, and fluoro (137a–f). Other electrophiles also yielded interesting results; treatment of lithiosubporphyrin with 1,2-dichlorotetramethyldisilane yielded a disilyl-bridged subporphyrin dimer 138 in 18 % and treatment with dimethyl carbonate gave the carbonyl dimer 139 in 59 %.

Whilst our group has reported the synthesis of meso-meso linked porphyrin dimers utilizing this methodology,\[44a\] this approach has not yet been utilized for subporphyrins. Instead, Kitano and co-workers undertook a reductive coupling of the meso-monobromo-subporphyrin to yield a meso-meso-subporphyrin dimer in 31 %.\[200\]

3.2. Reactions at the \( \beta \)-Position

Less is known about reactions at the \( \beta \)-positions of subporphyrins. Initially, Yoshida and Osuka treated methoxo[5,10,15-triphenylsubporphyrinato]boron(III) with \( N \)-chlorosuccinimide and obtained the monochlorinated product 140 in 48 % (Scheme 28).\[201\] Subsequent SAr with 4-methoxybenzenethiol and bromination yielded the thioether-appended subporphyrin 141 in 77 % over two steps (Scheme 28). The use of 10 equiv. of \( N \)-chlorosuccinimide however, opposed to 1.1 equiv. previously, yielded the hexachlorinated subporphyrin in 95 %; it undergoes SNAr in identical fashion – with a variety of S-aryl and S-alkyl nucleophiles in very good yields (8–91 % over four examples.)

Treatment of 141 with m-CPBA delivered the respective sulfone in 35 % and 21 % (for the two diastereomers), and when the axial boron substituent was changed from OMe to Ph the yields increased to 52 % and 39 %.\[202\] The conversion to the
Transformation to the 2,3-dithiol occurred in two steps; S_NAr of the 2-bromo moiety of 142 with 146 followed by base-mediated thiol-deprotection and reduction yielded 143 in 92 %. As a result of these conditions however, the axial boron substituent was transformed from OMe to OH. S_NAr of 143 with 147, catalyzed by cesium carbonate, followed by treatment with 147 to reinstate an aryl axial-boron substituent, eventually produced the dithiine fused subporphyrin dimer. The syn-diastereomer, 144-syn, was obtained in 33 % and 144-anti in 23 %. The structure of 144-syn was unambiguously assigned through single-crystal X-ray diffraction experiments, clearly displaying the dithiine ring, along with the syn-structure resulting from the subporphyrin’s domed macrocycle (inset, Scheme 28).

4. S_NAr Reactions of Phthalocyanines

Unknowingly, the parent compound phthalocyanine (Pc) was reported in 1907,[203] and in 1927 upon the attempted conversion of o-dibromobenzene to phthalonitrile, de Diesbach and von der Weid yielded various CuPc’s, with a comment on their excellent stability but no characterization.[204] Despite these early scientific events, Linstead (the person responsible for a full analysis of Pc’s)[205,206] attributes the first discovery of Pc’s to Scottish Dyes, Ltd of Grangemouth.[205]

Although this class of compounds is known as “phthalocyanines”, which is the name attributed to them by IUPAC, their systematic name “tetrabenzof[b,g,l,q]-5,10,15,20-tetraazaporphyrin” gives a greater understanding to their structure. The misconception is that Pc’s cannot be substituted on the meso position, subsequently the syntheses of analogous 5,10,15-tri-aza-porphyrins and 5,10-diazasubporphyrins has been undertaken to yield meso-substituted macrocycles that were akin to meso-substituted Pc’s.[207a,207b] Whilst aza-N bridges have been modified on the tetra-azaporphyrin scaffold,[207c] we are aware of only one report on Pc’s.[207d] Kong et al. exposed CuPc (148) to 1,4-dibromobutane and observed a meso-N-alkylation to yield 149 in 85 %. 149 was further treated with modified pyridyl-linkers to yield ionic liquid crystals (Scheme 29).

Scheme 28. Top: synthesis of 141 and 142 from mono-β-chlorinated subporphyrin, 140 and subsequent synthesis of 1,4-dithiine-fused-subporphyrin dimers anti-144 and syn-144. Inset right: single crystal structure of syn-144 with thermal ellipsoids are shown at 50 %. Subporphyrin meso-phenyl groups and, solvent molecules have all been omitted for clarity. Image generated from CCDC No.: 1456523.[201,202]

Scheme 29. S_NAr of a Pc meso-aza-bridge, with 1,4-dibromobutane.[207d]

This leaves the fused phenyl rings as the point of attack. Pc substitution can occur at two types of position (Scheme 30); the “α” and the “β”. Given the syntheses of Pc’s – tetramerization of a single aromatic compound (phthalonitrile or phthalimide amongst others) with no need for an aldehyde to provide a meso-position – there are two methods for substituted Pc synthesis: 1) modify the starting material 150 then tetramerize to form the Pc, or 2) form the Pc 151 then substitute accordingly.
Unsurprisingly the majority of Pc starting materials, upon increasing complexity, are not commercially available and hence the substitution of starting material is often utilized preferentially.\(^\text{[208]}\) The use of mass spectrometry to identify the number of substituents is commonplace in this area of chemistry, and sometimes the only way to truly determine success of these S\(_\text{N}\)Ar reactions. For synthesis of substituted Pcs through route 1) as described prior, readers are directed to the appropriate reference.\(^\text{[209]}\)

Scheme 30. Scheme depicting two routes for the synthesis of substituted Pcs through the modification of either a phthalonitrile, or the substitution of the parent Pc.

In the only example of S\(_\text{N}\)Ar of both the precursor, and subsequent Pc, Lin et al. generated tetra-thioether 157 (Scheme 31), through S\(_\text{N}\)Ar of tetra-bromo 156 with \(n\)-octane-thiol in the presence of sodium hydride.\(^\text{[210]}\) Despite the lack of NMR spectra in the manuscript, the differing solubility of the product, along with a red-shift in the UV-Visible spectrum and mass spectrometry justifies its formation. Aside from the two aforementioned works, all other S\(_\text{N}\)Ar of Pcs concern only one specific Pc: \([\text{hexadecafluorophthalocyaninato}]\text{zinc(II)}\) 158, ZnPcF\(_\text{16}\). First synthesized by Birchall et al. in 1970,\(^\text{[211]}\) this singular molecule has been thoroughly examined with a variety of heteroatomic nucleophiles.

In 2004 Leznoff and Sosa-Sanchez started this adventure with examining the reaction of 158 with nucleophiles 159a, d, e, and f (Scheme 32). Under mild conditions, only the mono- or disubstituted Pcs were obtained; however, upon use of the amine as the solvent – mixtures of multiply-substituted Pcs were obtained.\(^\text{[213]}\) Along with this the reactions of a variety of diamines was examined; namely trans-1,2-diaminocyclohexane, 1,3-diaminopropane, 1,12-diaminododecane, and 1,11-diaminoundecane. Unsurprisingly, given the number of positions at which S\(_\text{N}\)Ar can take place, along with the multiply nucleophilic amines used, these reactions continually produced mixtures of a variety of Pcs. Mass spectrometry indicated both intramolecular S\(_\text{N}\)Ar (\(\alpha\)-\(\alpha\')', \(\alpha\)-\(\beta\'), \(\beta\)-\(\beta\') and intermolecular substitution (again varying to and from \(\alpha\) and \(\beta\) positions), essentially forming amine-linked Pcs.

Hence, the steric properties of the nucleophile heavily influence substitution pattern in the resultant product. This fact was exemplified by Drain and co-workers through the generation of a purely \(\beta\)-substituted Pc, which still contained the \(\alpha\)-fluorine substituents.\(^\text{[214]}\) 2,3,4,6-Tetra-O-acetyl-glucosylthioacetate 159k was utilized to generate a water-soluble, non-aggregating, and non-hydrolyzable Pc 160k that could be used as a PS in PDT. Disappearance of the 19F NMR resonance at \(\delta(19F) = -85\) ppm indicated the successful substitution of the \(\beta\)-positions, leaving the remaining signal at \(\delta(19F) = -109\) ppm, indicative of the \(\alpha\)-fluoro substitution. The sugar units were deprotected and the resultant Pc was analyzed via UV-Visible spectroscopy. As the polarity of the solvent increased from toluene to...
dimethyl sulfoxide, the aggregation was found to decrease, as observed through the increase of intensity of the Q-band. Despite the addition of eight sugar units, this molecule still aggregated in water.

Sugars derivatives are not the only thiol-nucleophiles that have been examined upon reaction with 158. In 2010, Varotto et al. generated Pc’s with varying degrees of thio-alkane (C_{12}H_{25}SH, 159i) substitution, which were analyzed regarding their photochemical properties.[215] It was found that as substitution increased, the wavelength of the Q band increased, and the optical band gap decreased. Leznoff and Sosa-Sanchez initially reported the substitution of 158 with 159j in 2004 and yielded the hexadeca-substituted product in 41 % yield.[212]

Farley et al. also successfully reacted 158 with 159j to yield the hexadecasubstituted product, 160j, in 44 % yield, along with synthesizing and analyzing every compound in the series ZnF_{16–x}(SR)_xPc, where R = C_{8}H_{17} [216] Where yields were provided, they ranged from 17 % (ZnF_{9}(SR)_7Pc) up to 44 % (Zn(SR)_{16}Pc), however excluding the hexadecasubstituted the highest yield observed was 26 % (ZnF_{11}(SR)_5Pc).[217] The use of 159j was because of the desire to increase the solubility of the synthesized Pc’s, without the possibility of these molecules exhibiting liquid crystal type properties. The photophysical properties of the Pc series were analyzed with the general trends being observed: 1) absorbance and fluorescence λ_{max} increased with the no. of -SC_{8}H_{17} substituents (672 nm for x = 0 to 777 nm for x = 16), 2) Φ_{f} decreased with increasing -SC_{8}H_{17} substitution, and 3) the Stokes shift also increased with -SC_{8}H_{17} substitution (6 nm for x = 0 to 25 nm for x = 16) (Figure 7).

5. S_NAr Reactions of Corroles

Corroles are non-natural porphyrinoids, but one related natural compound is that of cobalamin (vitamin B_{12}), a corrin.[218] The synthesis of corroles was first reported by the groups of Gross and Paolesse.[219,220] Following this, subsequent improvements by Gryko’s laboratory opened the door to large scale corrole synthesis.[221,222]

The nitration of porphyrins has been a staple reaction in synthetic porphyrin chemistry for a number of years – with methods having been developed for β-,[90] meso-,[223] and, β-Ph
nitrations.\textsuperscript{[224]} Whilst these nitrations are electrophilic, the opposite is true for corroles. As shown by Stefanelli et al. in 2007 the nitration proceeds through nucleophilic attack of NO\textsubscript{2}– on a silver-corrole π-cationic radical.\textsuperscript{[225]} AgNO\textsubscript{2} was used to avoid the harsh conditions sometimes used in the nitration of other aromatics, i.e. HNO\textsubscript{3}/H\textsubscript{2}SO\textsubscript{4}, given the susceptibility of the corrole macrocycle towards oxidizing conditions. The use of a free base corrole under these nitrating conditions typically yields the Ag-corrole, whereas metalation with Cu halts this (Scheme 33). In 2011 this reaction was revisited and the yield of 3-nitrocorrole was increased from 33 % to 75 % \textsuperscript{(162)}, along with the generation of the 3,17-dinitrocorrole in 15 % \textsuperscript{(163)}.\textsuperscript{[226]}

![Scheme 33. Top: synthesis of nitro-corroles 162 and 163 and their transformations to nitro-aminocorroles, and other 2,3-difunctionalized corroles, bottom: nitration of a meso free corrole. Ar = p-C\textsubscript{6}H\textsubscript{4}Bu\textsuperscript{[225–227]}.](image)

The dinitration of these macrocycles was also examined; the use of Cu-161 and AgNO\textsubscript{2} in a 1:50 ratio yielded 163 in 52 %; however, use of Cu-161, AgNO\textsubscript{2} and, NaNO\textsubscript{2} in a 1:2:8 ratio yielded 163 in 51 % yield (Scheme 33, top). Despite the lack of difference in yields, both methods were an improvement on that reported previously. With the desire to further functionalize these macrocycles, the reactivity of these nitrocorroles towards nucleophilic amination with 4-amino-4\textsubscript{H}-1,2,4-triazole was investigated. This reagent generates the amide anion and under base-catalyzed conditions this selectively substituted adjacent to the nitro group in both mono- and disubstitution, albeit in low yields (18 % 164, and 30 % 165, respectively). Akin to porphyrins, the nitration of a β-heptasubstituted corrole yielded the respective meso-nitrated silver(III) complex 169 in moderate yield (49 %) (Scheme 33, bottom).

The electrophilicity of the C\textsubscript{2}-position has also been examined with C-based active methylene nucleophiles.\textsuperscript{[227]} Treatment of 162 with diethyl malonate and NaOH yielded the diester appended corrole 166 in 34 %. Reaction of 162 with diethyl chloromalonate gave a mixture of compounds, but only yielded 166 in 28 %. Lastly, reaction of 162 with diethyl malonate, followed by addition of DDQ yielded methyl-hydroxy corrole 167 in 32 %.

The corrole macrocycle has also been extensively halogenated (Scheme 34). Selective tri- or tetraiodination\textsuperscript{[228]} and tetra-\textsuperscript{[229]} or octabromination\textsuperscript{[229,230]} was performed on 170a,b prior to S\textsubscript{N}Ar with FSO\textsubscript{2}CF\textsubscript{2}CO\textsubscript{2}Me, a source of the trifluoro-

![Scheme 34. Synthesis of a variety of halogenated corroles, and subsequent S\textsubscript{N}Ar to yield the trifluoromethyl-substituted corroles 173, 175, and 177. a = FSO\textsubscript{2}CF\textsubscript{2}CO\textsubscript{2}Me/Cu; Ar′ = p-C\textsubscript{6}H\textsubscript{4}F (170b).\textsuperscript{[229–231]}](image)
methyl anion.\textsuperscript{[231]} This approach selectively yielded tri-, tetra-, and octafluoromethylated gold corroles.\textsuperscript{[232,233]} The yields for iodine substitution were higher than those for bromine substitution across all examples. Ghosh and co-workers generated \textsuperscript{173}, and Cu\textsuperscript{-173} and analyzed them via single-crystal X-ray diffraction and found an 85° difference in saddling between the two, with \textsuperscript{173} being planar.\textsuperscript{[232]}

When Gross’s group generated their corroles\textsuperscript{[233]} they were analyzed through a variety of methods with the aim of understanding how the CF\textsubscript{3} substituents affected the corroles with regards to their photophysical and redox properties, and ability to participate in catalytic processes. along with their solid-state structures. Comparison between \textsuperscript{170a}, \textsuperscript{176} and \textsuperscript{177} showed significantly different UV/Vis spectra for \textsuperscript{170a} and \textsuperscript{176}, with a bathochromic shift of ca. 50 nm, and a doubling in the intensity of the band; however, upon trifluoromethylation there is very minimal change. Electrochemically, addition of CF\textsubscript{3} groups decreased both the oxidation and reduction potentials of the macrocycles.

Halogen substitution can also occur on the meso-position of corroles (Scheme 35, top). A rarity, due to low yielding syntheses, meso-free corroles present a small population of the corroles present in the literature despite multiple improvements.\textsuperscript{[234]} Recently however, Ueta et al. exploited the utility of meso-free corrole exclusively in S\textsubscript{N}Ar reactions.\textsuperscript{[235]} 5,15-Di-(pentfluorophenyl)corrole \textsuperscript{178} was initially modified by refluxing with excess NaOMe, as to remove the para-fluorophenyl substituents which themselves are susceptible to nucleophilic substitution. Thus, 5,15-bis(2,3,5,6-tetrafluoro-4-methoxyphenyl)corrole was chlorinated using Pala'\textsuperscript{ch}lor to yield the 10-chloro-corrole in 60 % yield. Subsequent metallation with AgOAc yielded the (corrolato)silver complex \textsuperscript{179} in 90 % yield (44 % over three steps). Both the 3H and Ag-corrolato complexes were exposed to S\textsubscript{N}Ar conditions. In the case of the 3H complex only a trace amount of an adduct was isolated. It was proposed that one of the inner-NH units became deprotonated and this prevented the reaction from occurring. Hence, with \textsuperscript{179}, the reaction proceeded smoothly and an meso-diphenylamino appended corrole \textsuperscript{180a} was formed in 54 %.

However, under strongly basic conditions extending the reaction time from 4 h to 20 h yielded the meso-diphenylamine appended free base corrole \textsuperscript{180b} in 54 % yield. The (corrolato)silver complex was also exposed to carbazole under identical conditions giving \textsuperscript{180c} in 54 % yield. With the aim of performing a ring fusion from the diphenylamino moiety to the macrocycle, Ueta et al. utilized DDQ and isolated a brown band post column-chromatography. This was identified by HR-APCI-TOF-MS and single-crystal X-ray analysis to be the 10,10-diethoxyisocorrole \textsuperscript{181}.

Nardis et al. also investigated the formation of isocorroles (Scheme 35, bottom).\textsuperscript{[236]} Treatment of 5,10,15-tris(p-tolyl)corrole \textsuperscript{182} with EtMgBr yielded four products: 10-ethylisocorrole (\textsuperscript{183a}, 25 %), 5-ethylisocorrole (\textsuperscript{183b}, 13 %), 2-bromocorrole (\textsuperscript{184a}, 30 %) and, 3-bromocorrole (\textsuperscript{184b}, 10 %). The\textsuperscript{9} isocorrole products bear some resemblance to the respective porphodimethines prepared with RLi reagents.\textsuperscript{[40b,41,237]} However, nBuLi is reported not to have reacted with \textsuperscript{182}, in stark contrast to analogous porphyrins.\textsuperscript{[236]} Caroleo et al. recently commented on the reactivity of corroles towards organolithium reagents, and indicate the lack of success is due to the electron-rich nature of the macrocycle.\textsuperscript{[238]} The closest example to a corrole reacting with an organolithium reagent, that we are aware of, was reported in 2002, when a 5,10-diphenyl-22-oxacorrole was treated with nBuLi to yield 15-butyl-5,10-diphenyl-22-oxacorrole in 10 %.\textsuperscript{[239]}

An intriguing example of S\textsubscript{N}Ar on the corrole scaffold was found with biscorroles.\textsuperscript{[240,241]} Very different synthetic strategies have been utilized to yield biscorroles; Barata et al. used rather forcing oxidative dimerization conditions (200 °C, 1,2,4-tri
chlorobenzene, 6 h, N₂ atm.) yielding the 2,3’-dimer in 7 %, the 3,3’-dimer in 2 % and the 2,2’,18,18’-doubly-linked dimer in 11 % yield. In contrast, Hiroto et al. began with 2-pinacolboryl-corrole and under Pd⁰-catalyzed coupling conditions selectively formed the 2,2’-dimer in excellent yield. Oxidation of this dimer with DDQ yielded doubly-linked system and addition of NaBH₄ subsequently gave the reduced form 186. This reduced form be readily and reversibly transformed into 185 through the use of DDQ (Scheme 36). These dimers were regioselectively pyridinated with multiple 4-substituted pyridines, along with pyridine itself.[242] The crystal structure of dipyridinated bistorrole 187a is shown in Scheme 36 (inset) indicating the regioselectivity of this substitution.

6. Nucleophilic Substitution Reactions of Norcorroles

Norcorroles are the smallest N₄-core tetrapyrroles and thus they have inherently been a target for synthetic chemists. Observed serendipitously by Bröring in 2008 as the homo-dimer,[243] the synthesis of this type of macrocycle was performed on gram scale by Shinokubo’s group.[244] One intriguing aspect of norcorroles is their antiaromatic macrocycle (hence we are not talking about SₗAr reactions here).[245,246] The synthesis of norcorroles involves the reductive coupling of two α,α’-dibromo dipyrrins, often resulting in symmetric systems with substituents on the 5- and 14- positions of the macrocycle. An exception is the use of mixed dipyrrinato complexes yielding the nonsymmetric norcorroles (15–45 %) (Scheme 37).[247] Unexpectedly, the symmetric norcorroles, regardless of electronic affect (electron donating or electron withdrawing), were unstable and hence non-isolable.

Despite their antiaromatic character norcorrole has been shown to undergo a range of nucleophilic substitution reactions, pioneered by Shinokubo’s laboratory.[248] They examined substitution reactions of the norcorrole macrocycle with C-, S- and O-based nucleophiles (Scheme 38). Monocyanation with 20 equiv. KCN in CH₃CN/THF yielded 192a in 56 %, with the dicyanated variants (3,7- and 3,12-disubstituted) being isolated as an inseparable mixture in 4 % yield. Likewise, nucleophilic attack by thiophenol and phenol gave 192d in 53 % and 192e in 25 %, respectively. Substitution with thiophenol was eventually pushed to tetrasubstitution to yield 193 in 37 %. Two years

Scheme 36. Top: Synthesis of mono- and di-pyridyl-substituted bistorroles through SₗAr. Bottom: single crystal X-ray structure of di-pyridinated doubly linked bis-corrole 187a. Atoms represented as thermal ellipsoids at 50 % probability. Image generated from CCDC No.: 710218.[242]

Scheme 37. Synthesis of norcorroles through reductive coupling of two α,α’-dibromo dipyrrins.[244,247]
later, Yoshida et al. again analyzed the reactions of 190, this time using amine nucleophiles. Treatment of 190 with the respective amine, with no catalyst in the majority of cases yielded the mono- and diaminated norcorroles in suitable yields.

\[ \text{Scheme 38. Nucleophilic substitution reactions with a variety of hetero-} \]
\[ \text{aromatic, and active methylene nucleophiles on the norcorrole backbone.} \]
\[ \text{Yields presented are given only for the 3-substituted product. Di- and trisubstituted products have been omitted for clarity. a = reaction time of 0.5h, b = reaction time of 2 h. For nucleophiles used previously, product is displayed in parentheses.} \]

Further to this was the work of Ren et al., who thoroughly examined the reactivity of norcorroles towards active methylene nucleophiles, in a similar manner to work from the same group on N-confused porphyrins (Scheme 23). Initial investigation of the reaction between 190 and 119a eventually yielded optimized conditions, generating 192h in 81 %, utilizing Cs2CO3 in THF at room temperature. Whilst the yields presented for the reactions of these active methylene compounds with 190 are good (53–81 %, 192h–p), it is evident that the greater number of electron-withdrawing groups, and their greater strength of electron withdrawal, play a crucial role in the yield of the desired product. UV-Visible spectroscopy indi-

\[ \text{Scheme 39. Amination of the norcorrole backbone, displaying all four prod-} \]
\[ \text{ucts of three different macrocycle types by Liu et al.} \]
cated that the 16π-electron system of the norcorrole remained undisturbed by the 3-substitution in all cases, this is despite the generation of keto-enol tautomeric systems appended on the 3-position.

Interestingly, reaction of 190 with nitromethane and acetone yielded no product formation even after prolonged reaction time (10 h). It is this that distinguishes the differing reactivity of the norcorrole macrocycle from the N-confused porphyrin.

Amination was also possible as shown by Liu et al. who successfully generated a free base amine on the norcorrole backbone in 2016 through the treatment of 190 with 4-amino-4H-1,2,4-triazole (Scheme 39). Four different products of three different macrocycle types were obtained; the desired 3-aminonorcute (194, 28 %), 10-azacorrole (195, 3 %), and the product of highest yield — a di-ring expanded norcorrole homodimer (196, 32 %). Interestingly, this dimer was not conjugated due to the C3(sp3) on both macrocycles; however, it did exist in a singlet-triplet equilibrium.

Whilst it has been demonstrated throughout that the norcorrole moiety possesses a strong susceptibility for nucleophilic attack, it may be surprising to find the norcorrole then itself becoming the nucleophile, without external influence. In the hope of reaching the “norcorrin”, Liu et al. aimed to reduce 190, and inadvertently synthesized a non-symmetric norcorrole homodimer (199, Scheme 40). The proposed mechanism indicates that upon oxidation of 198 with p-chloranil, the 2-position becomes electrophilic, and the 3-position becomes nucleophilic. Thus a 2,3′-dimer is generated, and interestingly they do not interact electronically, as determined by UV-Visible spectroscopy.

Whilst not directly-linked dimers, pyridine-fused-norcute dimers also demonstrate this property (Scheme 41). Nitration of the norcorrole macrocycle with amyl nitrite and subsequent reduction with SnCl2 yielded the 3-aminated norcorrole 194 on suitable scale. Addition of an aryl-aldehyde gave dipyrromethane type products 200a–e, and subsequent oxidation with p-chloranil induced a deaminative cyclization in quantitative yield in all cases. The 3-amine attacks the (δ+)C3 of the opposing norcorrole and yields a dihydropyridine intermediate, and subsequent oxidation yielded the respective pyridine.
The result was highly unexpected but has been confirmed unequivocally by single-crystal X-ray analysis (Scheme 41, inset). Carbenes and silylenes have also been used to modify norcorroles (Scheme 42). For example, Fukuoka et al. initially exposed 5,15-bis(2,4,6-trimethylphenyl)porphyrin to dialkylsilylene 207 and observed no reaction.[254] In stark contrast to this, 190 reacted with 207 in under 3 minutes to yield the mono-expanded norcorrole system 203 in 97%, containing a dihydro-1,4-azasiline ring. Upon use of excess 207, a tetra-adduct is observed, in which two rings have been expanded and two have been transformed into the respective silirane (202, 52%). Despite the "outlandish" structure of 202, the structure was successfully elucidated by X-ray crystallography.

Similarly, ring expansions were observed in reactions of norcorroles with carbenes by Liu et al.[255] Exposing 190 to dichlorocarbene 209 or N-heterocyclic carbene (NHC) 208 yielded multiple products. First, treatment of 190 with 208 gave the diazafulvene-substituted macrocycle 204 in 46%, with the nucleophile attacking in the expected place for this macrocyclic skeleton (vide infra). However, treatment of 190 with 209 produced three distinct products; [5,15-dichloro-10,20-dimesitylporphyrinato]nickel(II) 205 in 2%, and two (dichloroisoporylcorrolato)nickel(II) complexes 206a and 206b, in a combined yield of 14%. These products are atypical of nucleophilic substitution of the norcorrole. The authors attribute these products to a Cianian-Dennstedt reaction,[256] and the proposed mechanism for the formation of these products indicates initial formation of a mono-(meso)chloro-corrolato]nickel(II) cation, and again subsequent Cianian-Dennstedt reaction to yield the products. In each case, however, the initial carbene nucleophilic attack is at the 1-position of the norcorrole macrocycle. As the authors note; however, the mechanism of this process is elusive and here in particular, a radio-labelling experiment is of the utmost interest.

7. Conclusions and Outlook

From the literature we have presented herein, it is possible to analyze the substitution on each of the porphyrinoids discussed. In general terms, porphyrins appear to be better substrates for SNAr reactions than simple aromatics. This has its origin in the electron density of the aromatic systems and how the intermediary charge can be delocalized. A simple introductory organic chemistry textbook analogy is the comparison of aniline, benzene, and nitrobenzene (or for that matter benzene vs. pyridine). Following an addition-elimination type SNAr reaction, which proceeds via the generation of a Meisenheimer complex,[14c] aniline is simply too electron-rich to participate in SNAr reaction. Instead, as we have shown many times previously in this review, aniline is far better placed to be the nucleophile than the electrophile (Scheme 43).

Whilst benzene has been shown to undergo SNAr, it usually requires very harsh conditions and gives low yields. Recently, SNAr on benzene was shown to occur through the use of a β-diketiminate strontium hydride complex, resulting in the production of C6D5-C2H5.[257] Arguably, the main reason SNAr does not readily occur on benzene is the lack of electronic stabilization. This is indicated by the comparison with nitrobenzene which undergoes substitution on the ortho and/or para positions, and this is a direct consequence of the generation of Meisenheimer complexes. As can be seen through drawing of canonical forms and in Scheme 43, the electronics of the nucleophile in question are less relevant as the nucleophile remains electronically isolated from the aromatic ring in question through the generation of a C(sp3) center. The resonance of the charge around the phenyl ring is what is observed for SNAr, and it is this delocalization of charge that lowers the energy of the
transition state and enables the reaction to proceed with greater ease. Addition of the nitro group to the phenyl ring enables the charge to be resonated over a larger area, and subsequently there is a further decrease in transition state energy, making it even easier for the reaction to proceed. It is this stabilization over a large area, that enables the generation of a low energy transition state, and subsequently the reaction to proceed with relative ease. With this understanding one can also rationalize the observations for the porphyrinoids presented herein (Scheme 44).[258]

Unmodified porphyrins, along with subporphyrins and corroles, will preferentially react at a free meso position over a free β-position. Modified porphyrins we have discussed present differing reactivities: 2-nitro-A4-porphyrins react differently depending upon the nucleophile used - either directly attacking the C2-position (ipsos-) or adjacent to the nitro group at C3 (alpha-), likewise with β-formylporphyrins which direct S_{Ar} adjacent to the formyl group, whereas in the case of β-bromo-porphyrins, the bromine itself is substituted. Azuliporphyrins appear to substitute exclusively at the 23-position, however, the range of studies is still limited for this macrocycle. NCPs exhibit distinct reactivities across the two positions we have examined, whereas the C3-position has shown vast susceptibility to active-methylene nucleophiles, the C21-position has shown greater reactivity towards softer nucleophiles. Pc’s have been shown to substitute both the α- and β-positions dependent upon the steric properties of the nucleophile used. Lastly, norcorroles appear to substitute exclusively at the 3-position; however, further

Scheme 43. S_{Ar} reactions on (top to bottom); nitrobenzene, benzene and aniline.

Scheme 44. Schemes depicting the S_{Ar}/nucleophilic substitution of the different macrocycles discussed in this review, displaying the simplified electron delocalization pathway upon substitution and what we propose to be the most stable canonical form in each case. Nucleophile is assumed to possess negative charge. Substitution is shown to occur at preferred positions for each macrocycle. S_{Ar} at the C21-position of N-confused porphyrins, S_{Ar} of phthalocyanines, and S_{Ar} of subporphyrins are not presented, see text.
investigation is required in the case of compounds 205, 206a and 206b. This being said, the overall synthetic utility of \( S_{n}Ar \) is particularly reliant on prior electrophilic reactions; i.e. the introduction of halogens or nitro groups to be substituted. For example, this is how the A- and D-rings of the corrole macrocycle were substituted to such an extent. In the same vein, some of the schemes we have presented herein alternate between electrophilic and nucleophilic substitutions in order to obtain the desired products. We can explain these reactivities conveniently by grouping certain classes of compounds.

Porphyrins and subporphyrins can be grouped first. The key to their reactivity is the meso-positions. These systems succeed in resonating, and subsequently distributing the additional charge from nucleophilic attack, over the entire macrocycle thus creating a highly stable transition state/intermediate Meisenheimer complex.\(^{14b,15} \) This negative charge can be resonated onto the inner core nitrogen atoms of free base porphyrins, or onto the metal center in metalloporphyrin. Similarly, the charge can be resonated onto the central boron atom in subporphyrins.

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Equation 1. Determination of the number of permutations of a given number of substituents. The equation is:

\[ m_{Pc} = \frac{16!}{n!(16-n)!} \]  

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[258] This simplified explanation does not take into account the possibility for concerted reaction mechanisms or concerted reactions with long-lived transition states, which are dominant for many benzene derivatives. While in many porphyrin cases a “stable” Meisenheimer complex could be trapped with electrophiles or oxidized, detailed mechanistic studies are still lacking for many other members of the porphyrinoid family.

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