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Nucleophilic Aromatic Substitution | *Very Important Paper* |

Nucleophilic Aromatic Substitution (S_NAr) 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 (S_NAr) has been known for over 150 years and found wide use for the functionalization of (hetero)aromatic systems. Currently, several "types" of S_NAr reactions have been established and notably the area of porphyrinoid macrocycles has seen many uses thereof. Herein, we detail the S_NAr 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 B_{12} (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]

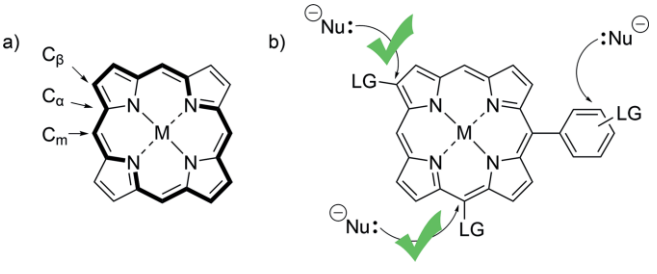

Figure 1. a) The standard porphyrin system with labels for different types of positions upon the porphyrin macrocycle, and indication of the aromatic [18π] pathway (bold). b) Graphical depiction of the scope of this review.

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]

Porphyrins may not be on every chemist's radar but all of us are aware of the main types of organic reactions: ionic, radical,

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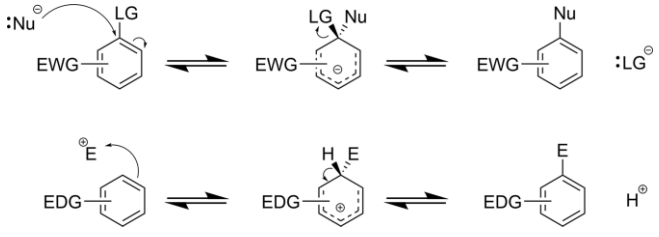
photochemical, and pericyclic. All of these are found with porphyrins and each has their own realm of uses. For example, addition or pericyclic reactions at the C_β–C_β double bonds not involved in the aromatic pathway form the standard entry into reduced species such as chlorins (Figure 1a).[10] Being heteroaromatic compounds the vast majority of direct porphyrin functionalization reactions are aromatic substitution reactions (Scheme 1). Historically, electrophilic aromatic substitution (S_EAr) reactions such as nitration, halogenation or Friedel-Crafts reactions featured prominently in the development of porphyrin chemistry.[11] Today they mainly serve to generate starting materials for transition metal-catalyzed coupling reactions. The latter field has been reviewed extensively;[7,12] and thus we focus here on nucleophilic aromatic substitution (S_NAr) reactions.



Scheme 1. General schemes for addition-elimination type nucleophilic aromatic substitution (S_NAr, top) and electrophilic aromatic substitution (S_EAr, 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_NAr is one of the main two reactions that occurs on aromatic moieties (Scheme 1) and has been known for more than 150 years.[13] Since then many types of and variations on the "traditional" two-step S_NAr (addition-elimination) reaction have been named and studied in their own right; S_NAr,[14] S_NArH, and vicarious nucleophilic substitutions,[15] reactions occurring through benzyne intermediates,[16] $S_{RN}1$,[17] S_N1 type S_NAr typical of diazo-compounds,[18] and more recently concerted nucleophilic aromatic substitution, cS_NAr.[19]

This review aims to highlight the use of S_NAr as a synthetic tool for the modification and generation of novel porphyrinoids. The literature for some of the members of the "porphyrin family" (e.g., for the parent porphyrins) has been catalogued up until 2006, and these sections are duly noted.[20] Rather, we present the literature for a wide variety of porphyrinoids, ranging in size from subporphyrin all the way to phthalocyanine, identifying the uses and viability of the respective transformations along with comparisons between compounds of the same type or analogous symmetries (Figure 2).

This review aims to encompass the literature regarding S_NAr reactions on the porphyrinoid skeleton. While there is no discrimination regarding the number of pyrrolic rings, nor the number of "meso-positions"/methene/aza bridges, the focus is on substitution of the macrocyclic positions (Figure 1b). Thus, we are not considering modification of motifs attached to the macrocyclic skeleton, i.e. SF_5 substitution or C_6F_5 substitution.[21] Likewise, the "breaking and mending" methodology developed by Brückner will not be considered due to greater modifications of the macrocyclic skeleton, along with it being covered gracefully elsewhere.[10,22] Reactions to be deemed as Pd-catalyzed S_NAr vs. Pd-catalyzed cross-coupling reactions have been evaluated on a case by case basis. This issue is particularly prevalent with Buchwald-Hartwig aminations,[23] and reviews regarding this subject have been published.[24] While nucleophilic attack can occur at each type of position [M, N, C_α, C_β, C_m] the majority of cases involves the β-pyrrolic (C_β) and bridging meso-positions (C_m) 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_x" nomenclature system is used.[4e,7a] 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 A_4 porphyrin and 5,15-diphenylporphyrin would be a "*trans*"-A_2-porphyrin. For clarity, various types of porphyrins with differing meso substitu-

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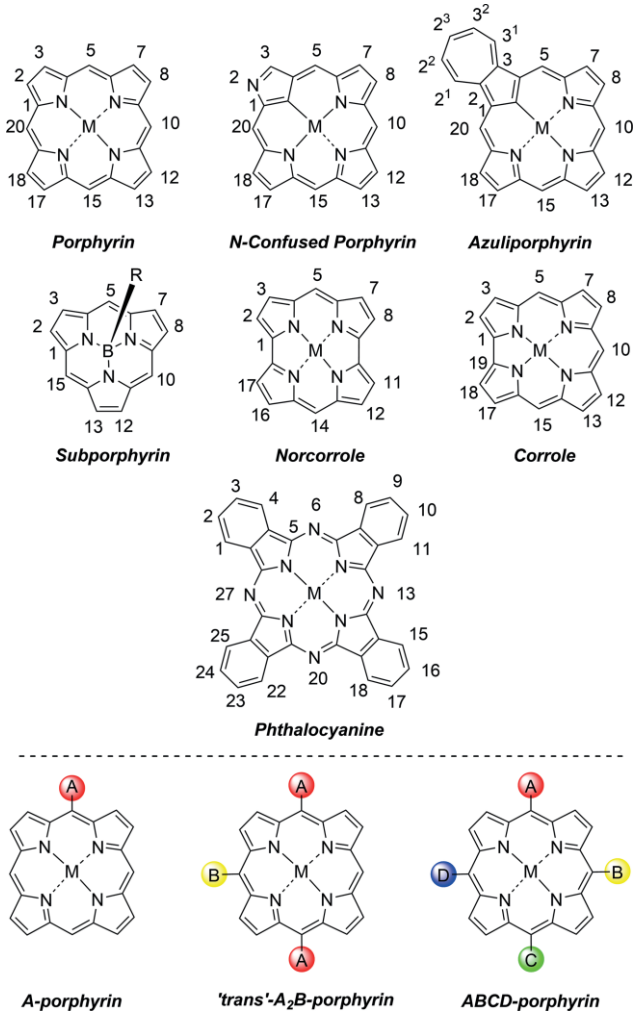


Figure 2. Top: structures of the main classes of porphyrinoids discussed herein and respective numbering systems used. Bottom: pictorial representation of the A_x-nomenclature for the porphyrin scaffold.

ents are depicted in Figure 2 (bottom). We have also adapted this nomenclature system to apply it to the other porphyrinoids discussed throughout, where applicable.

2. S_NAr 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),[25a] Friedel-Crafts acylation (carbonyl group),[25b] and the Claisen condensation (α,α-diester),[25c] 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 S_NAr has been utilized since the mid-1800's and the harsh conditions which were used initially.[13] 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,[26] 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.[27] 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.[28] 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.[29] Fourteen years later, Wittig and Gilman improved the syntheses of these organolithium reagents,[30,31] and with a simultaneous report shortly afterwards – both groups had observed the halogen-lithium exchange with organobromides and phenyllithiums.[32,33] 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).

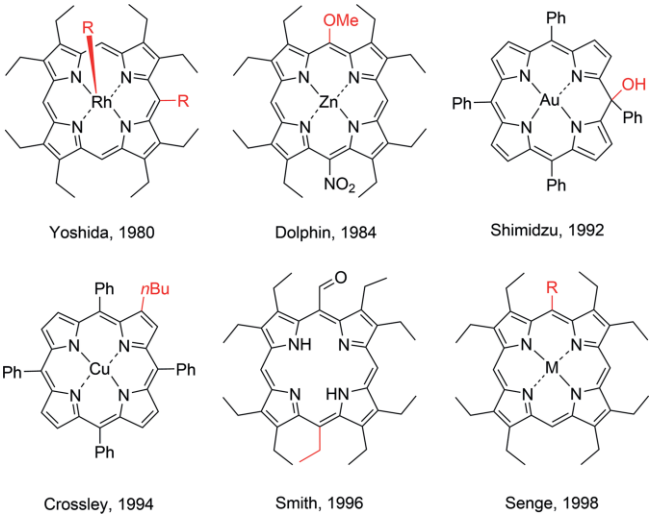


Figure 3. Key historical compounds prepared by S_NAr of porphyrins with a variety of nucleophiles.[34–39a]

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-methoxyphenyllithium, PhLi, and *n*BuLi).[34] 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 S_NAr reaction. In 1984, Dolphin examined the reactivity of

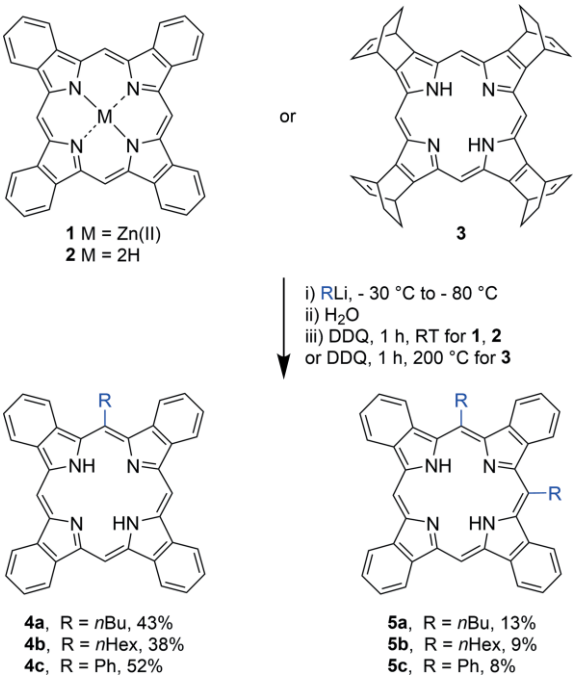
nitrated 2,3,7,8,12,13,17,18-octaethylporphyrins towards acetate, methoxide, chloride, and bromide nucleophiles.[35] However, these were activated porphyrins. In 1992, Shimidzu and co-workers managed to generate a phlorin from chloro(5,10,15,20-tetraphenylporphyrinato)gold(III) and tetrabutyl ammonium hydroxide.[36] Although this was an S_NAr 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_NAr fashion, using the activated [2-nitro-5,10,15,20-tetraphenylporphyrinato]copper(II), in a work dominated by the use of Grignard reagents.[37] Two years later, Smith and co-workers utilized Grignard reagents on meso-formyl octaethylporphyrins to meso-alkylate and generate "*trans*"-A_2-octaethylporphyrins.[38]

Eventually, in 1998, the first reaction of organolithium reagents with non-activated porphyrins was described by us.[39] 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 (*n*BuLi, 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.[40]

The products of these reactions have been used to; generate novel and modified photosensitizers for PDT,[41,42] examine the differences in Pd-catalyzed and non-catalyzed approaches along with specific synthesis of 5,10-porphodimethenes,[43] generate facile synthetic methods to yield meso-meso-linked bisporphyrins, unsymmetrical porphyrin dimers and trimers,[44,45] and facile stepwise synthesis of ABCD-type porphyrins,[46] with structural analyses throughout.[47] It will come as no surprise to the reader that we have covered this topic at length previously.[7a,8a] With that in mind, this section focuses on more recent and notable synthetic advances in the reactions of porphyrins with organolithium reagents.

Tetrabenzoporphyrins are a lesser represented tetrapyrrolic macrocycle, which were recently rejuvenated by the Jux laboratory.[48] Most prior functionalizations to this scaffold either focused on appending all four meso-positions with one specific residue,[49] or modification of the annulated rings.[50] Instead, with the aim of increasing regiospecificity of substitution, we examined the reaction of common organolithium reagents on (*b*,*g*,*l*,*q*-tetrabenzoporphyrinato)zinc(II) (**1**) (Scheme 2), free base tetrabenzoporphyrin (**2**),[51] and the tetrabenzoporphyrin precursor (**3**).[52]

Initial treatment of (tetrabenzoporphyrinato)zinc(II) **1** with *n*BuLi yielded two demetalated products; mono-butylated product **4a** (43 %), and the 5,10-dibutylated product **5a** (13 %), as well as recovering starting material **2** (10 %). Likewise, reaction with *n*HexLi produced a similar product distribution: **4b** (38 %), **5b** (9 %), and **2** (3 %). Attempts to increase the yields of **5b** through raising the number of equivalents of *n*HexLi from 3 equiv. to 8 equiv. were fruitless. Despite the addition of meso groups, the solubility of the benzoporphyrins only became suitable for analysis upon disubstitution (whereas the mono-substituted products were analyzed as diprotonated dications). The

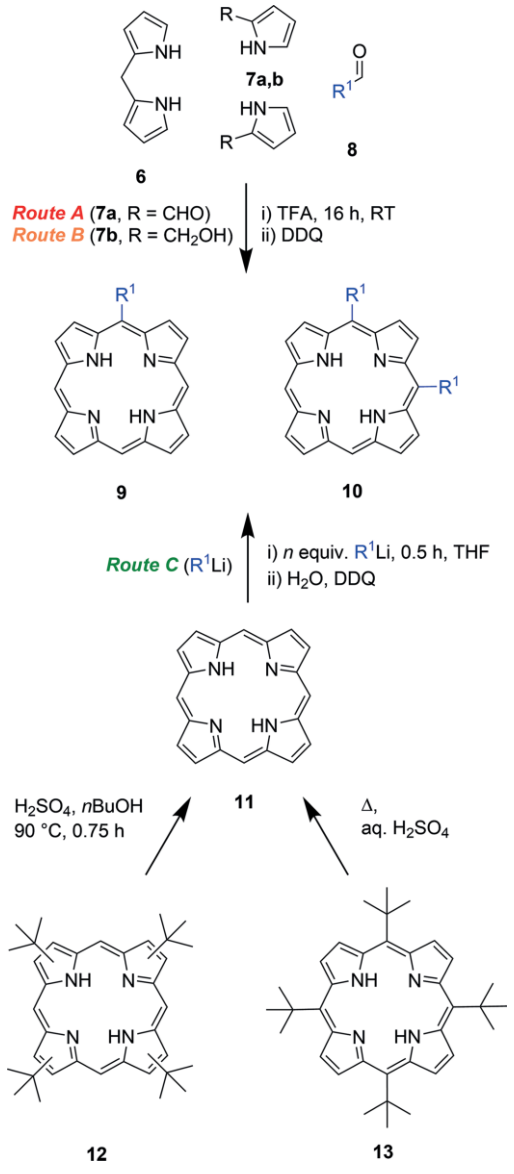


Scheme 2. Synthesis of A- and 5,10-A_2-substituted tetrabenzoporphyrins using organolithium reagents.[51,52]

reaction was also examined on tetrabenzoporphyrin precursor **3**, given its heightened solubility. Reaction of **3** with *n*BuLi yielded the monosubstituted **4a** as the main product, with smaller amounts of **5a** – but in this reduced stage they were inseparable. Thus, the retro-Diels-Alder was performed and **4a** was obtained in 43 % yield, and **5a** in 7 % yield. Whilst **1** was unable to react with PhLi, **3** did so to yield the mono- and disubstituted products **4c** and **5c** in 52 % and 8 %, respectively.

In the same vein, we compared the synthesis of A- and 5,10-A_2-porphyrins through the respective [2+1+1] strategies and the S_NAr techniques we have pioneered (Scheme 3).[53] Regarding routes A and B, we observed differences between the use of **7a** and **7b**, with the yields from **7a** being twice as high as those for **7b** in the majority of cases. However, using this [2+1+1] strategy, no yield of **9** or **10** exceeded 15 %. Much higher yields are observed when organolithium reagents are used (Route C), excluding *t*BuLi. We found that the reactivity of the organolithium reagent has vast influence on the product distribution and thus the equivalents of R^1Li must be tailored accordingly, e.g., using 1.2–1.5 equiv. of *n*HexLi or *n*BuLi yields the respective monosubstituted porphyrins in 48 % each, but when using PhLi, 3 equiv. only yields the respective monosubstituted product in 17 % yield, and to produce 5-(2-methoxyphenyl)porphyrin in 17 % yield, 8 equiv. of the respective organolithium were used. In 2011, we again utilized this methodology to modify a variety of "*trans*"-A_2 porphyrins, appending them with a variety of donor and acceptor groups with the aim of generating photosensitizers for PDT which exhibit non-linear optical properties, and subsequently generating a library of 5,15-A_2B_2, -A_2BC porphyrins,[54a] and bisporphyrins.[54b]

The controlled, regioselective addition of an aldehyde to the C_m positions of the porphyrin macrocycle via Vilsmeier formyl-

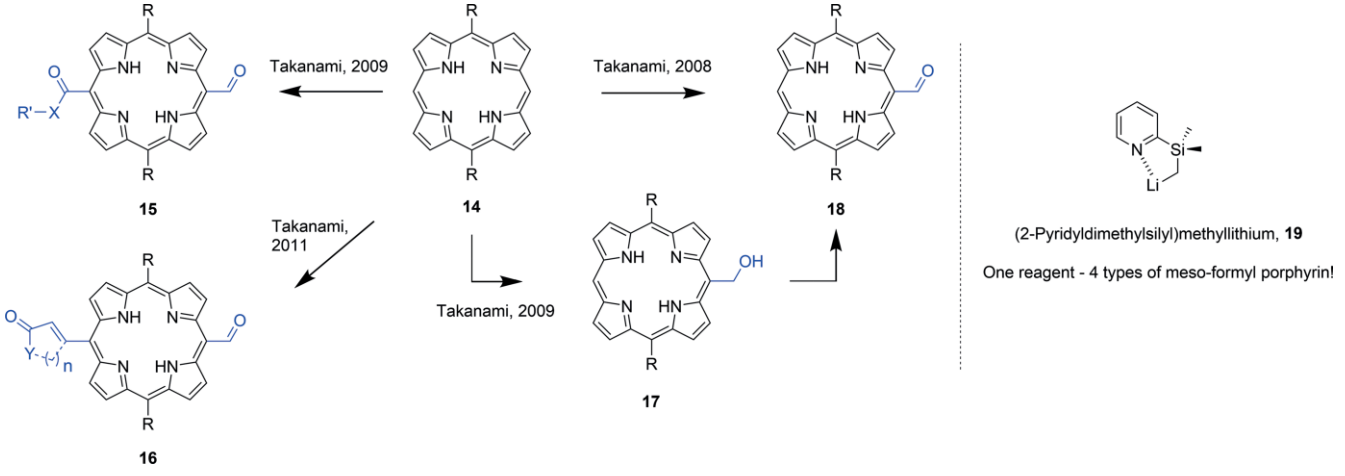


Scheme 3. Synthesis of 5-A and 5,10-A_2-substituted porphyrins using organolithium reagents (route C), or the [2+1+1] strategies (routes A and B).[53]

ation is a challenge but also presents one of the first classic porphyrin functionalization reactions.[55] Here, Takanami et al. exploited the reactivity of the meso-positions of 5,15-A_2-porphyrins in the syntheses of a variety of meso-formyl-porphyrins (Scheme 4).[56–59] Given the prominent featuring of the aldehyde functionality in the synthesis of porphyrins and pyrrins,[60,61] such compounds can be envisaged as the building blocks of multiporphyrin arrays.[62]

In 2008, Takanami presented a facile one-pot procedure for the conversion of 5,15-A_2-porphyrins **14** into 5-formyl-10,20-A_2 porphyrins, **18**, using (2-pyridyldimethylsilyl)methyllithium **19** (Scheme 4).[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-A_2-porphyrins (**14**) with a wide variety of substituents; *i*Bu, Ph, *p*Tol, and various other aryl groups containing methoxy, trifluoromethyl, and (2-triisopropylsilyl)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.

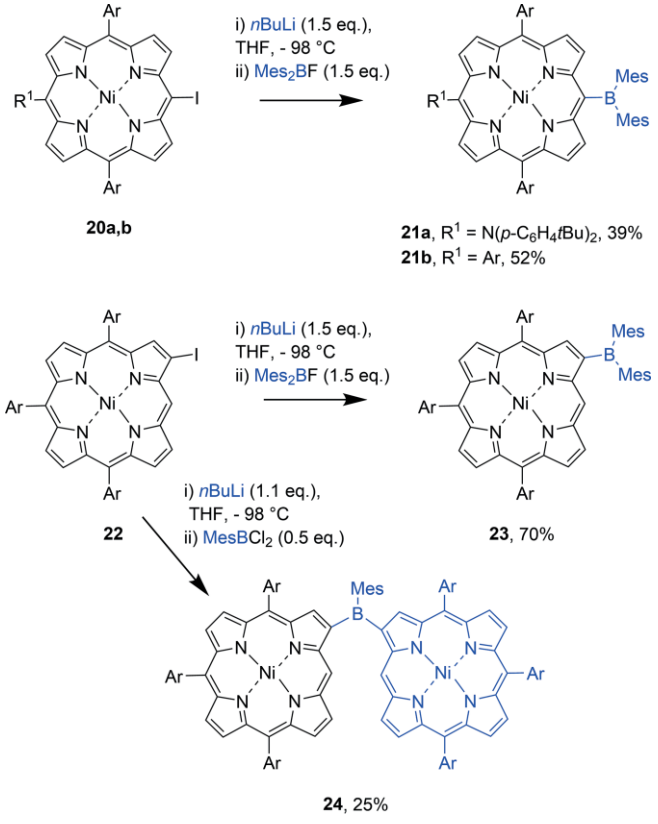
The first report of meso-hydroxylmethyl porphyrins came from Smith, and these were generated through the reduction of the respective octaalkyl-meso-formylporphyrins.[67] However, Takanami reported the first direct meso-hydroxylmethylation of the porphyrin core to yield **17**.[58] Whilst initially the oxidation of the porphodimethene had been performed with DDQ, if O_2 (or even air) was used instead it was found that the meso-hydroxylmethylporphyrin could be isolated in good yields with free base porphyrins being obtained in 55–76 % and metalloporphyrins in 57–83 % yields. Interestingly, in this case no demetallation of the Zn(II)porphyrins was observed. Along with



Scheme 4. Synthesis of 5-formyl-10,20-A_2-porphyrins by Takanami and co-workers using **19**. R, R′ = alkyl, aryl, X = NH, O, C. Y = O when $n \neq 0$, Me when $n = 0$, OMe when $n = 0$, $0 \leq n \leq 2$.[56–59]

organolithium reagents, Takanami also examined the reactivity of Grignard reagents towards "*trans*"-A_2 systems using the Kumada coupling reaction.[68]

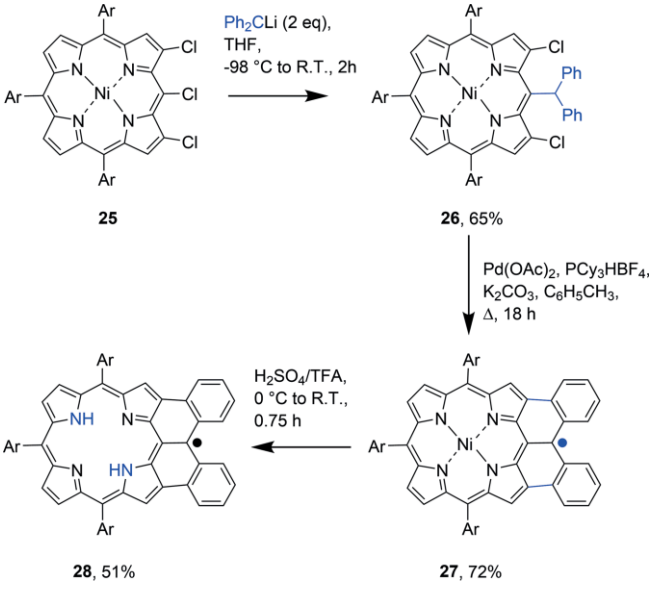
C–B bonds can also be generated under RLi conditions thus introducing useful functional groups.[69] Notably, triaryl boranes exhibit high luminescence, anion-sensing, and nonlinear optical properties.[70–72] Fujimoto et al. had previously generated a porphyrinyl-Grignard reagent and examined its reactivity,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



Scheme 5. Synthesis of meso- and β-boron appended porphyrins through the generation of porphyrinyllithiums. Ar = 3,5-di-*tert*-butylphenyl, Mes = 2,4,6-trimethylphenyl. For **20**,**21a**: R^1 = N(*p*-C_6H_4*t*Bu)$_2$, **20**,**21b** R^1 = Ar.[73]

As an initial proof of concept, analogous triaryl meso- and β-iodo porphyrins **20a** and **22**, were treated with 1.5 equiv. *n*BuLi and quenched with excess D_2O. 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 desired 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 photophysical properties that the use of boron can implement, porphyrin **21b** did exhibit donor–acceptor properties with increased intramolecular charge transfer character in the S_1 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 macrocycles 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 derivatives,[76,77] meso-hydroxysubporphyrins,[78] corroles,[79] and meso-hydroxyporphyrins.[80,81] Hence, the generation of a stable porphyrin radical by Kato et al. was a historic development (Scheme 6).[75]

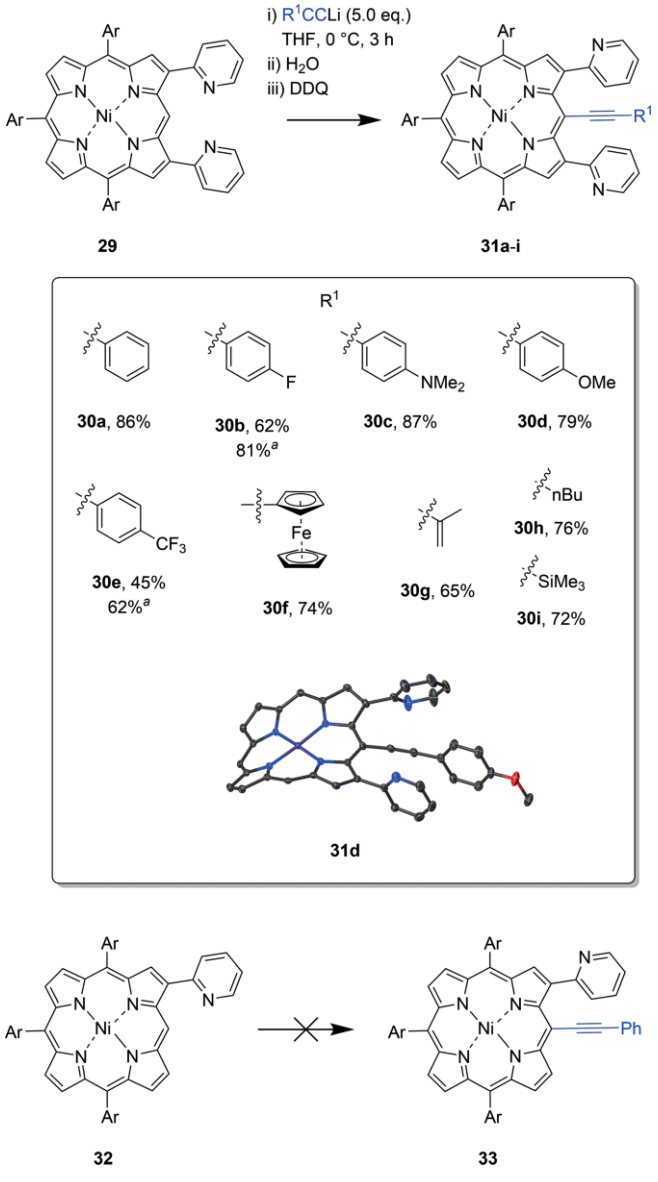


Scheme 6. Synthesis of metallo- and free base-porphyrinyl radicals **27** and **28** through an S_NAr strategy by Kato et al.[75] Ar = 3,5-di-*tert*-butylphenyl.

Treatment of trichloro-triarylporphyrin **25** with diphenylmethyllithium 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 ^{1}H-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(sp^2) hybridization state.

Thus far we have discussed the successes of S_NAr 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,[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)porphyinato]nickel(II), **29**, to a range of alkynyllithium reagents and found meso-alkynyl-substitution in good to excellent yields (Scheme 7).[84]



Scheme 7. Top: synthesis of meso-alkynylated porphyrin through double pyridyl coordination, [a] = 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.[84] Ar = 3,5-di-*tert*-butylphenyl.

Trends can be drawn from the variety of aryl reagents, namely that the electron withdrawn reagents (yielding **30b** and **e**) gave lower yields, and reaction times must be lengthened to produce comparable yields, whereas electron donating groups (yielding **30c** and **d**) appear to have no drastic effect on yield.

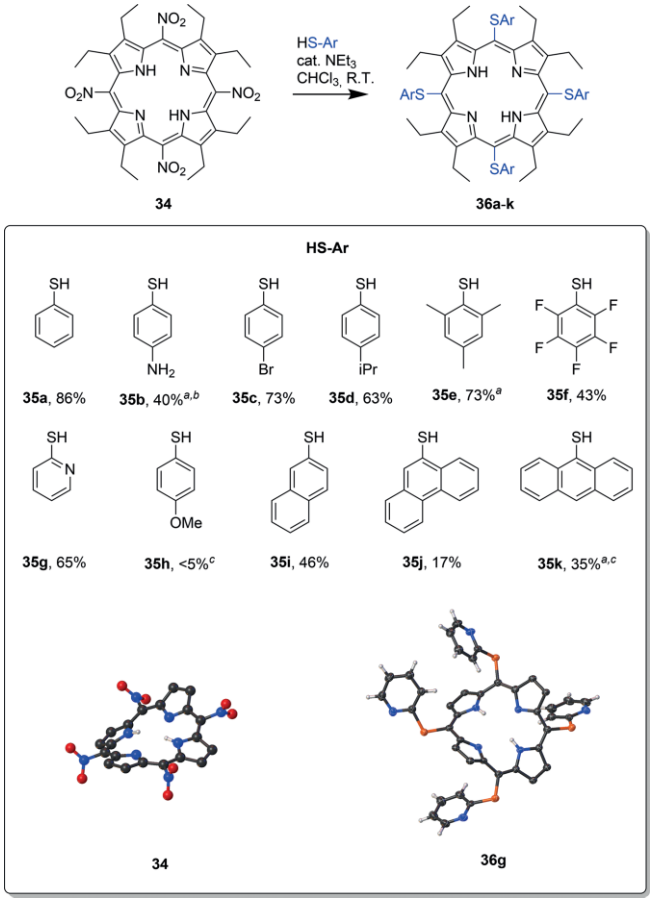
To evaluate the necessity for the double-pyridyl coordination, the same reaction was performed with phenylethynyllithium and the respective mono-pyridylporphyrin **32** under identical conditions. At t = 3 h, none of the respective product had formed. Stirring at r.t. for 12 h yielded **33** in 23 %; 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.[8a,85] Nonplanar porphyrinoids are frequently found in nature and account in part for the functional variety of the pigments of life.[86] Conformational distortion of porphyrins gives rise to significantly altered physicochemical properties, atypical chemical reactivity and metal coordination, and allows access to the inner N–H/N units and use thereof in organocatalysis and sensing.[8a,87] One of the oldest examples of these "highly substituted porphyrins",[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).[89] It has previously been reported that thiolates can displace the nitro group on porphyrins.[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;[35] base catalysis as opposed to acid catalysis and the use of sulfurous nucleophiles alone (Scheme 8).[92]

Treatment of **34** with a variety of S-based nucleophiles in the presence of catalytic triethylamine yielded tri- and tetrasubstituted thioether porphyrins in varied yields of between <5–86 %. The thiols 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 %.

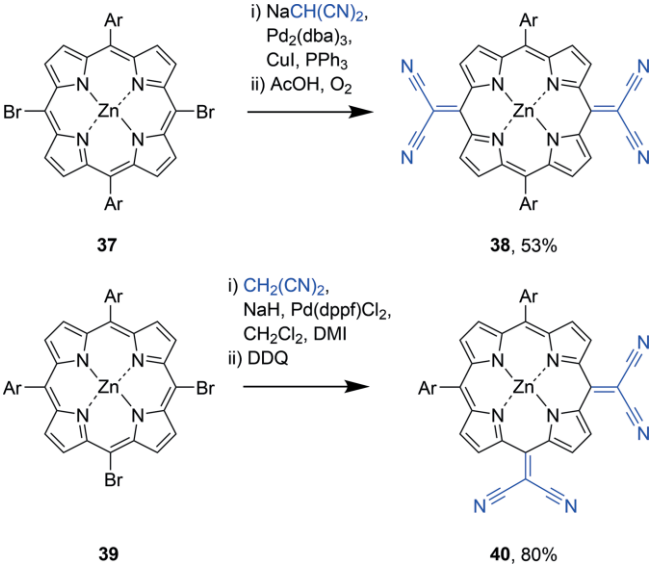


Scheme 8. Synthesis of meso-porphyrin thioethers by Kielmann et al.[92] [a] = only trisubstituted product (5,10,15-trithioether) isolated, [b] = 7.8 equiv. thiol used, [c] = 8.8 equiv. thiol used. Single crystal X-ray structures of **34** (left), and the $\alpha_2\beta_2$-atropisomer of 2,3,7,8,12,13,17,18-octaethyl-5,10,15,20-tetrakis(pyridin-2-ylthio)porphyrin, **36g** (right). Atoms represented as thermal ellipsoids at 50 % probability. β-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 MacDonald.[5b,96,97]

In what to the best of our knowledge is the first examples of a meso-bromoporphyrin S_NAr utilizing an amine nucleophile, Balaban et al., demonstrated the susceptibility of the meso-bromo substituted porphyrins towards S_NAr.[98,99] Utilizing a 5,15-dibromo-porphyrin, a dicarboxyl-porphyrin was yielded over two steps, through a 5,15-dicyanoporphyrin intermediate, in 59 % yield. Further in this initial work was the generation of a small library of 5-di(substituted)amino-15-cyano-10,20-di(3,5-di-*tert*-butylphenyl)porphyrins, as to generate a donor-acceptor (D–A) system. Later, a more thorough screening of this reaction took place on 5-bromo-10,20-diarylporphyrins. The main result of this study was the efficacy of microwave irradiation and how this varies between types of nucleophiles. With mono-substitution over a range of amines (*n*-propylamine, *n*-butylamine, benzylamine, 4-methoxybenzylamine, and 4-fluorobenzylamine) the yields were found to increase from 3 % to 77 % upon microwave irradiation. Disubstitution with *n*-propylamine occurred in 52 % yield, with 50 % for *n*-butylamine. However, disubstitution with ethylenediamine and 2-hydroxyethanolamine was less successful under microwave irradiation and a decrease in yield was observed in both cases.

5,15-Dialkylideneporphyrins have been shown to exhibit interesting non-linear optical properties,[100] and thus in the first example of S_NAr 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)sodium ($NaCH(CN)_2$), 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 tetrapyrrole 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 Sugiura'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.



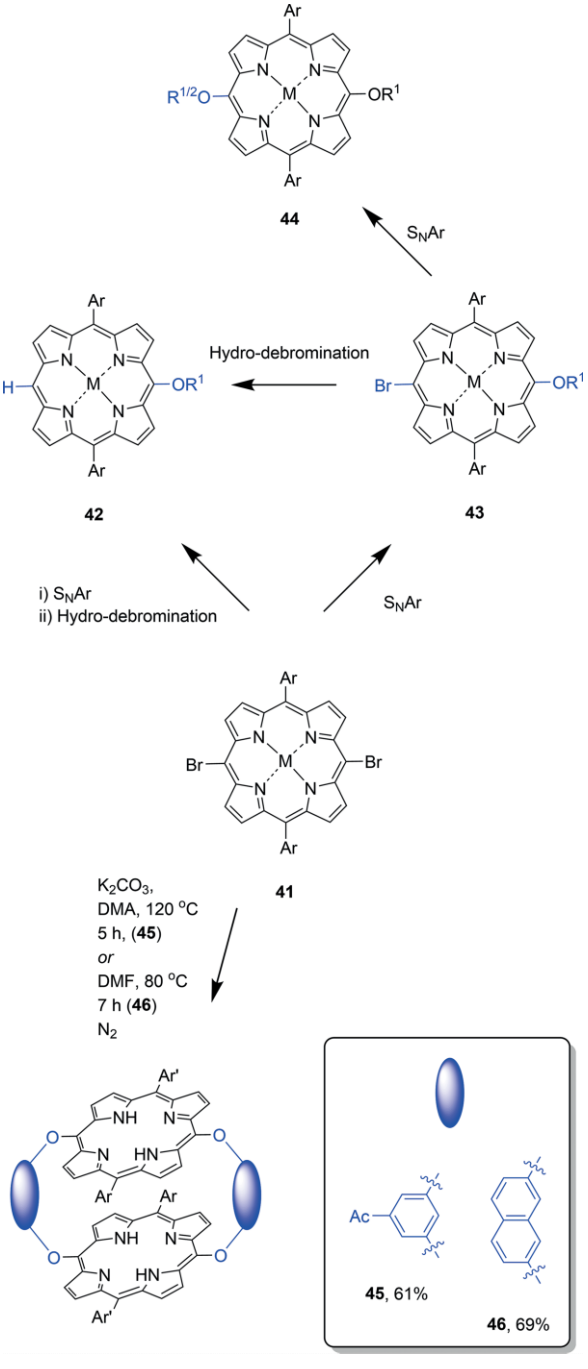
Scheme 9. Synthesis of dialkylideneporphyrin isomers **38** and **40** from the respective dibromoporphyrin precursors. Ar = 3,5-di-*tert*-butylphenyl.[101,104]

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, *i*Pr, *t*Bu) the yields varied between 77 % (X = Me) and 0 % (X = *t*Bu). Benzyl alcohol disubstituted successfully in 62 % yield, whilst *n*-hexanol did not yield the disubstituted product under a wide

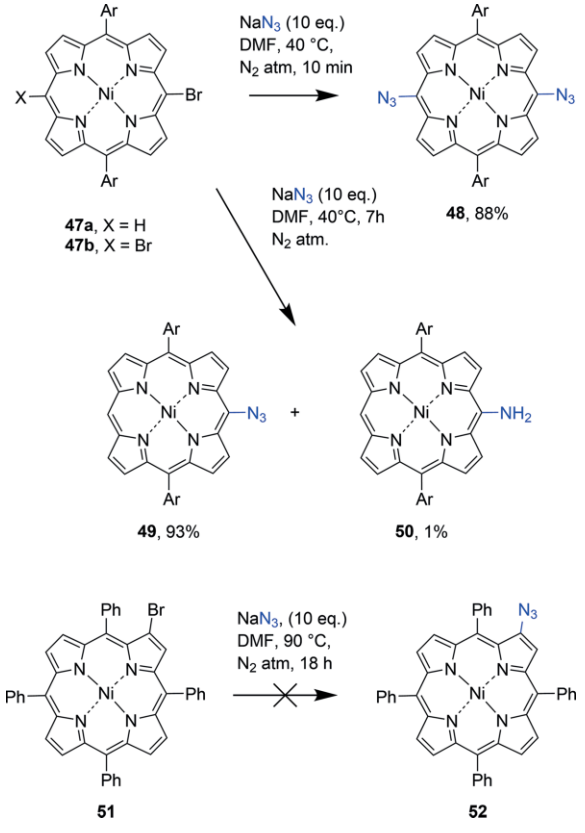
variety of conditions. Whilst one set of conditions yielded the mono-substituted product cleanly, all others presented yielded mixtures of the starting material and mono-appended product. Reaction optimizations were continued with *n*-hexanol, and some interesting observations where noted; the Zn(II)porphyrins 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.,[106] utilized various dihydroxyarenes and both mono- and *trans*-dibromo-A_2 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.,[105] debrominated by product was also yielded, mostly however with the use of mono-bromo-*trans*-A_2 starting materials. Optimized conditions were applied to the dibromo-*trans*-A_2 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,[107] referred to as the "premier example of a click reaction"[108] is a 1,3-dipolar cycloaddition comprising of the reaction between an azide and an alkyne. Realized and devised by Huisgen,[109] and built on by Sharpless,[110] it has become one of the most widely used reactions in medicinal and bioorganic chemistry.[111–113] Thus, given the use of porphyrins in medicinal chemistry,[114] 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,[115] and Pleux's generation used diazotization fol-



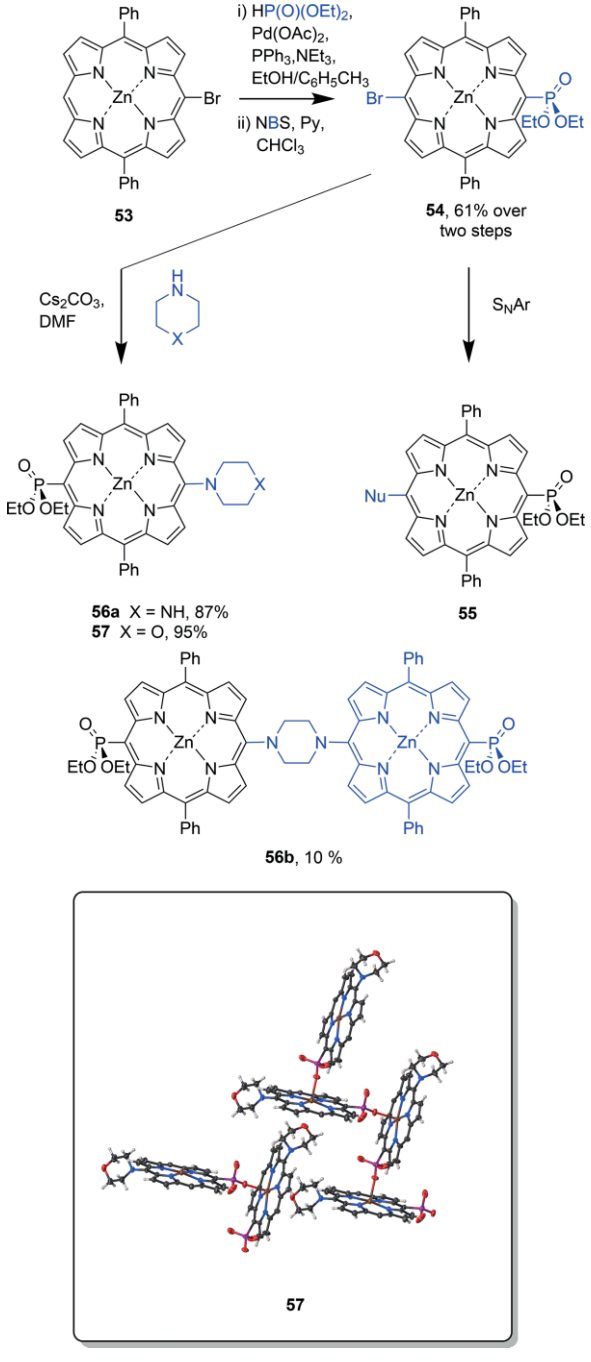
Scheme 10. Synthesis of porphyrin appended ethers through S_NAr on a 5,15-dibromo-10,20-A_2-porphyrin with various alcohols. M = 2H, Zn(II), Ni(II), Ar = Ph, Ar′ = 3,5-bis(3-methylbutoxy)phenyl. R^1, $R^{1/2}$ = alkyl, aryl.[105,106]



Scheme 11. Synthesis of meso-azido porphyrins through S_NAr through the use of NaN_3 and 5,15-dibromo-10,20-A_2-porphyrins.[117] 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.

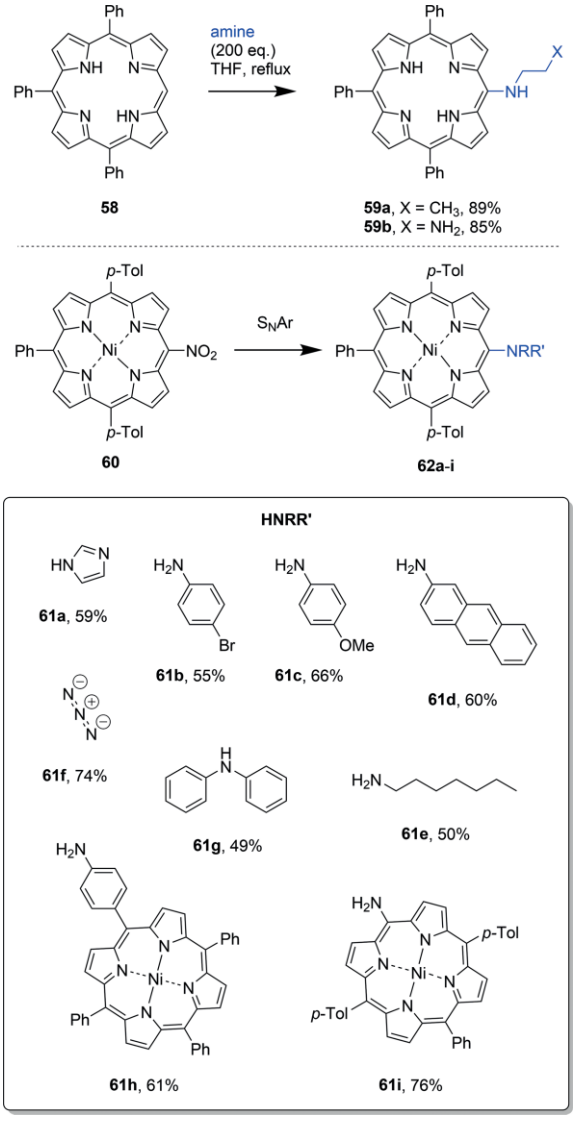


Scheme 12. Synthesis of di(ethoxy)phosphoryl appended porphyrins through a dual-sequential S_NAr synthesis, along with the piperazine appended porphyrin **56a** and piperazine linked porphyrin dimer **56b**. Nu = OR, SR, NR^1R^2 or $NR^1{}_2$, and single crystal X-ray structure of **57** (inset). Atoms represented as thermal ellipsoids at 50 % probability. Phosphoryl ethyl and meso-phenyl groups are omitted for clarity. Images generated from CCDC No. 1893716.[118]

In a dual S_NAr 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 Cs_2CO_3 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. A_3- and *trans*-A_2B-Porphyrins. A_3/*trans*-A_2B porphyrins present the simplest challenge with regards to S_NAr 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 S_NAr on meso-NO_2 porphyrins with amine nucleophiles, they set out to examine this reaction for a variety of amines (Scheme 13, bottom). Initially, reaction with NaN_3 occurred at ambient temperature, with no additives in 74 % (**62f**). However, for aryl/alkylamines – meso-NO_2-porphyrin **60** was screened with *p*-methoxyaniline over 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



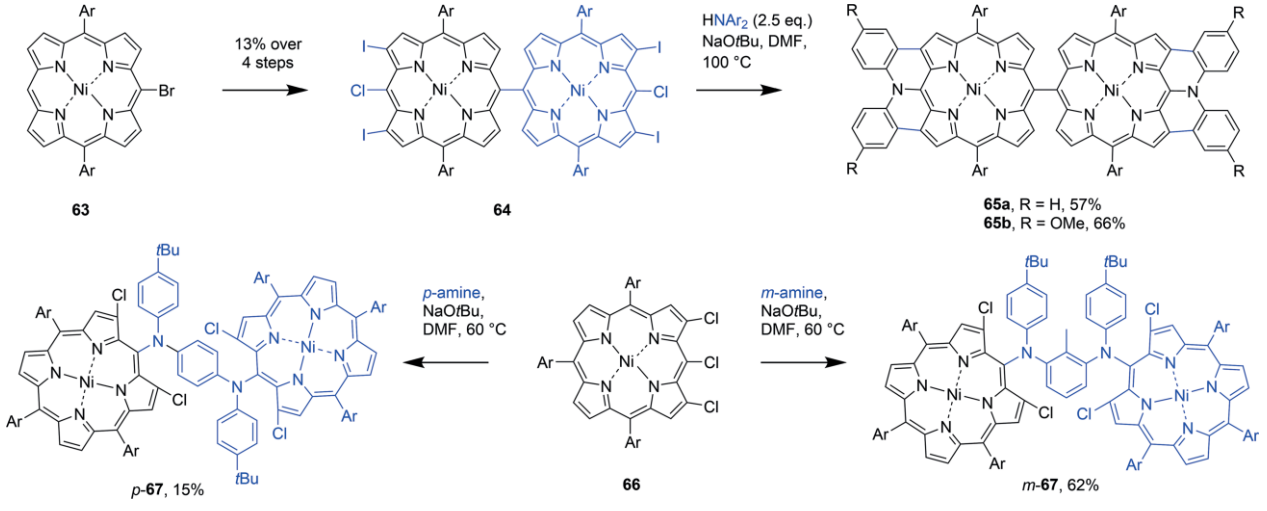
Scheme 13. Examination of the reactivities of amines with meso-free (**58**) and meso-NO_2 (**60**) A_3/*trans*-A_2B-porphyrins.[120,121]

62i only 1 equiv. of amine was used and 1.5 eq for **62h**. Interestingly when Zn-**60** was used under the same conditions, the yield for substitution with *p*-bromoaniline dropped from 55 % to 6 %, demonstrating the large effect the central metal ion on the electronics of the system, and hence substitution of the system.

When the terminologies "A_3" or "*trans*"-A_2B' 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 *n*BuLi 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 NaO*t*Bu yielded the tetrafused-porphyrin dimers in 57 % (**65a**, R = H) and 66 % (**65b**, R = OMe). The same experiments were performed on the respective A_3 parent porphyrin, [5,10,15-tri(3,5-(di-*tert*-butylphenyl)porphyrinato]nickel(II), 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.

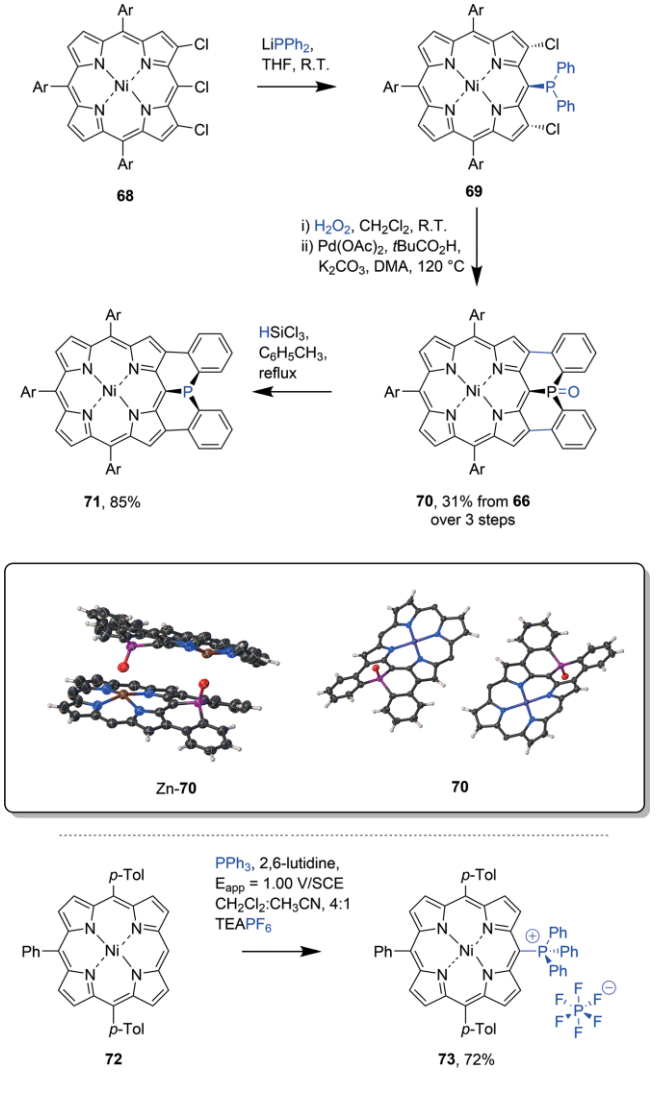
Substitution with diamines is not uncommon, and we have discussed it multiple times previously in this review. However, the use of triaryl-diamines is certainly something noteworthy. Treatment of trichloro-triaylmetalloporphyrin **66**, with N,N'-diarylated *m*- and *p*-phenylenediamines and NaO*t*Bu 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 14. Synthesis of amine appended A_3-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. Osuka utilized the tri-halo strategy his group has pioneered and exposed one such porphyrin to $LiPPh_2$ (Scheme 15, top).[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 waved structure, the distinct difference in the oxophilicity of



Scheme 15. Incorporation of P-based motifs into the porphyrin skeleton via S_NAr.[125,126] 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.[125]

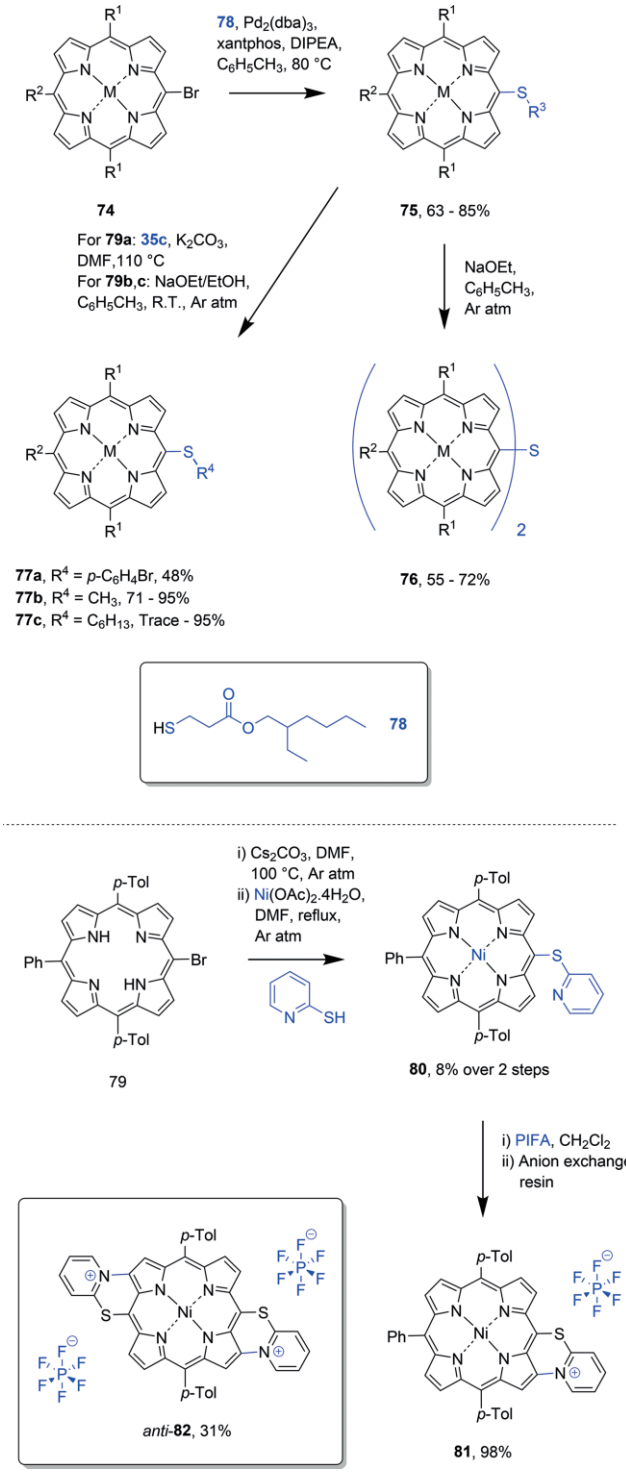
the metal centers results in the vast difference observed. In the case of **70**, the Ni–Ni distance is 10.961 Å with no interaction whereas for Zn-**70** it is 6.374 Å with strong Zn–O interactions of lengths 2.064 and 2.070 Å. Reduction of the phosphine oxide to the phosphine with $HSiCl_3$ in toluene yielded the Ni(II) phosphine fused porphyrin, **71**, in 85 %.

For most organic chemists, S_NAr 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_2Cl_2/CH_3CN, CH_2Cl_2, DMF).[126] It was found that treatment of **72** with 2,6-lutidine at E_{app} = 0.95 V/SCE in CH_2Cl_2/CH_3CN (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_NArH 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).[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_NAr conditions, the 2-ethylhexyl-3-mercaptopropionate side chain could be cleaved and exchanged for a *p*-C_6H_4Br 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_NAr in their synthesis of novel π-extended porphyrins.[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-mercaptopyridine was utilized. S_NAr between **79** and 2-mercaptopyridine, followed by metalation, yielded **80** in 8 % over two steps.

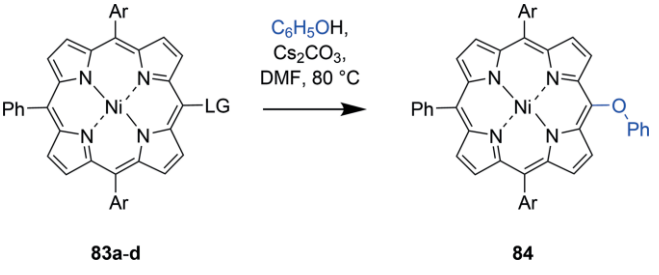
Subsequent oxidation with PIFA, and hence subsequent intramolecular nucleophilic attack of pyridyl moiety, yielded the fused moiety **81** after anion exchange in 98 % The methodology was applied to an analogous *trans*-A_2 dibromo porphyrin precursor, and the anti-diffused porphyrin system, *anti*-**82**, was yielded in 31 %. These oxidations were also performed electrochemically to yield **81** in 71 % and *anti*-**82** in 23 %. Cyclic vol-



Scheme 16. Reactions of A_3B-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_NAr strategy (bottom). R^1 = *p*Tol, Ph, 1-ethylpropyl, R^2 = H, Ph, *n*Bu.

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_NAr reactions on this scaffold over a large substrate scope, kinetic studies of the S_NAr reaction between phenol and **83a-d** were undertaken (Scheme 17). We inadvertently prepared meso-phenoxyporphyrins 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_2O_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_2 (4.48) > Br (3.18) > I (1.0). This series exhibits the "element effect", consistent with the classic S_NAr reaction (Figure 4).[131]



Scheme 17. Transformation analyzed by Chen et al.[129] in order to understand the reactivity of various meso-halo-porphyrins towards S_NAr. Ar = 3,5-di-*tert*-butylphenyl.

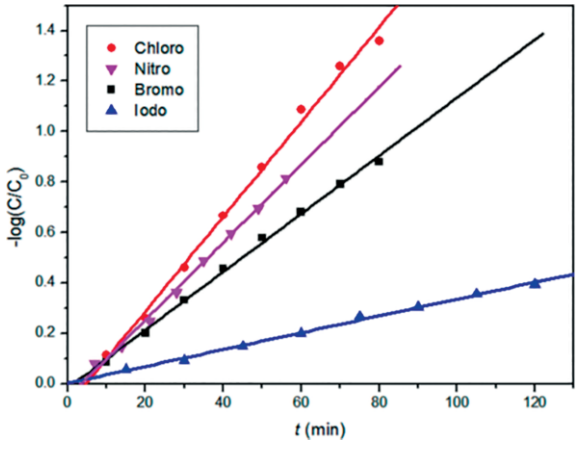
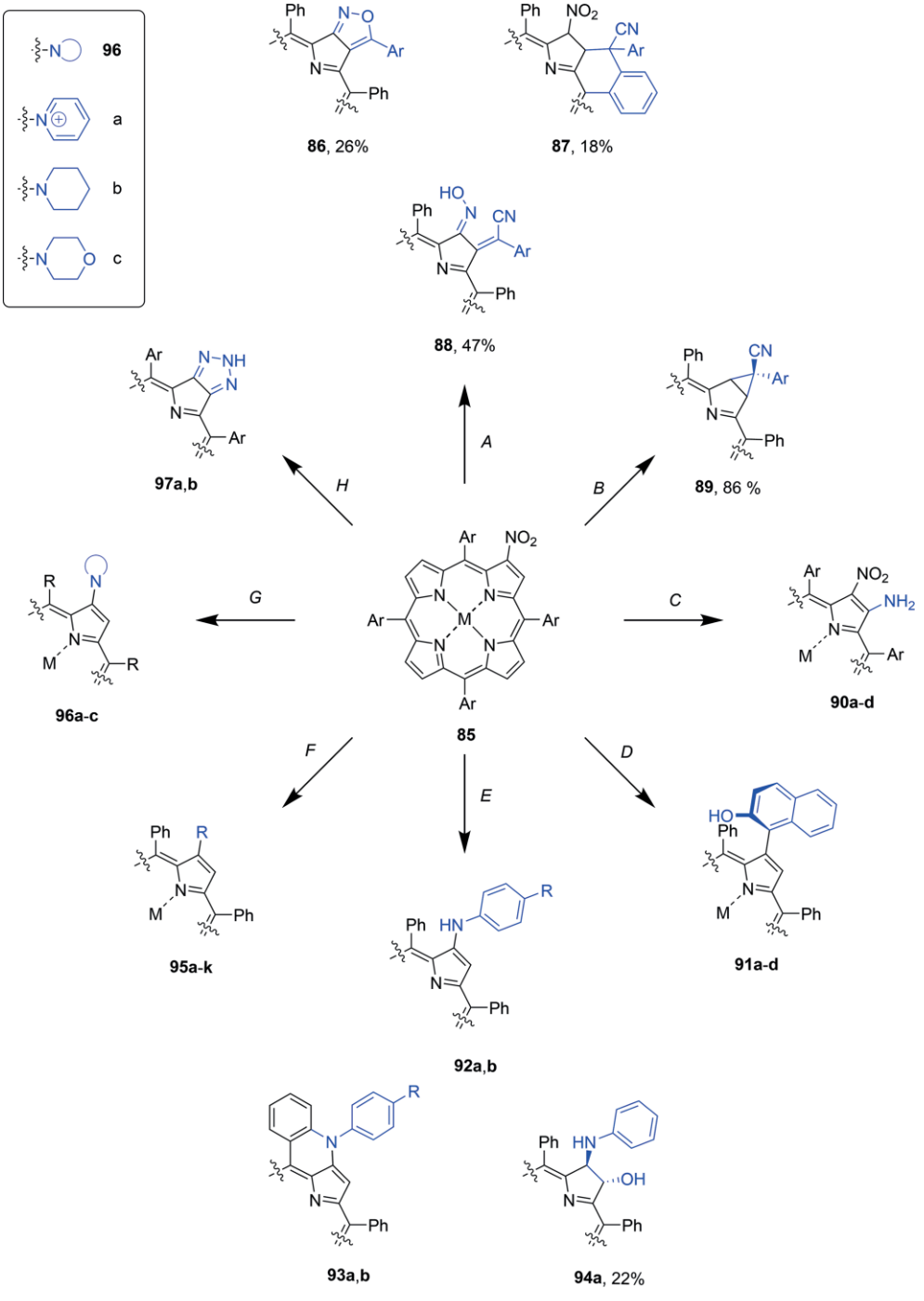


Figure 4. Plot detailing the rate constants for the generation of **84** from various meso-halo-porphyrins **83a-d**. Reproduced from ref.[129] Copyright (2014) American Chemical Society.[129]

2.3. Reactions with Other Nucleophiles: β-Position

2.3.1. 2-Nitro-A_4-porphyrins. Both A_4-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 S_NAr is considerable.

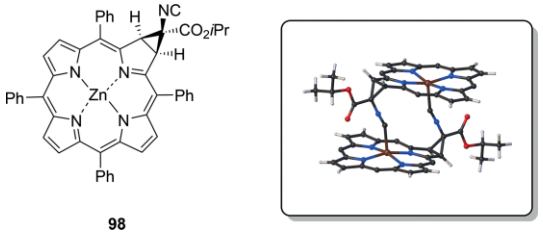
Amiri et al. were able to obtain a cyclopropane annulated chlorin via this method utilizing an arylacetonitrile (Scheme 18, *A*).[132] Utilizing KOH yielded a vastly differing set of products; an isoxazole appended porphyrin **86**, tricyclic system **87** and, hydroxyimino porphyrin **88**, whereas K_2CO_3 yielded cycloprop-



Scheme 18. Reactions of 2-nitro-A_4-porphyrins with a variety of nucleophiles.[33,132–144]

ane-annulated chlorin, **89** (Scheme 18, *B*). Interestingly, **88** exhibited a very red-shifted UV/Vis spectrum for a porphyrin 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-tetraphenylporphyrin (2-NO_2-TPP) in aniline yielded phenylamino porphyrin **92a** (53 %), quinolino-fused porphyrin **93a** (6 %) and *trans*-chlorin **94a** (22 %) (Scheme 18, *E*).[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 porphyrins 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 pyrroloporphyrins.[135] The reaction of 2-NO_2-TPP with ethyl isocyanoacetate 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 porphyrin-fused dipyrromethane. Along with this, modification of the reaction conditions yielded cyclopropane annulated chlorins, **98**, and in this particular case because of the use of the isocyanate ester,[137] the cyclopropyl substituent was found to coordinate to a Zn center in another chlorin (Figure 5).



98

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.[135]

Chlorins (dihydroporphyrins) are not unexpected by-products from S_NAr 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_2TPP 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_2TPP 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.

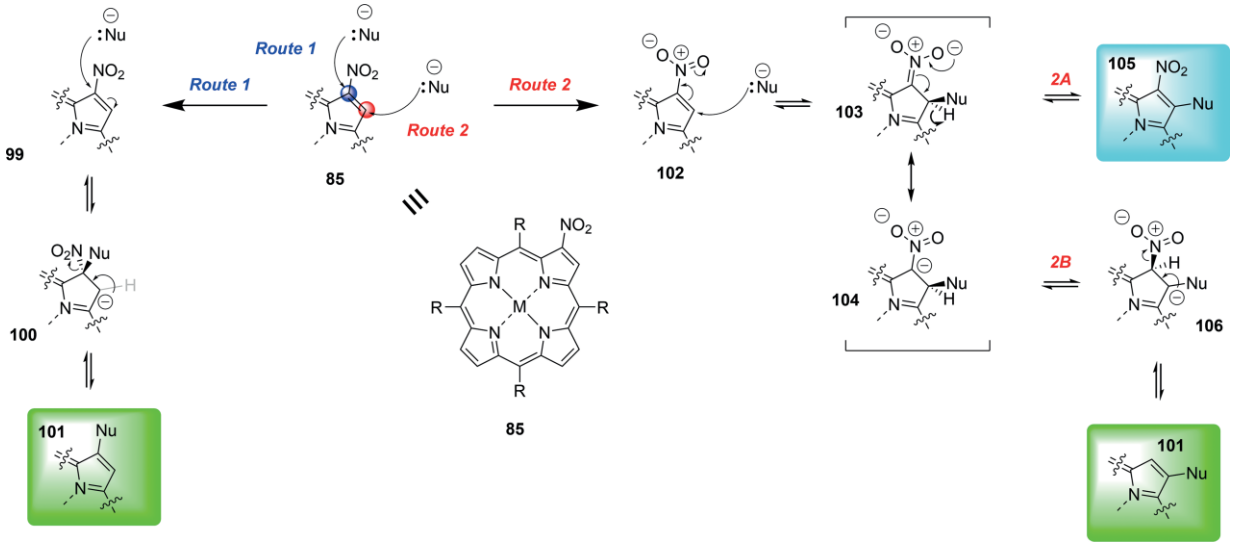
Ostrowski and Grzyb synthesized a variety of metallo-A_4 porphyrins, with M = Zn(II) or Cu(II),[138] and subsequent treatment of these metalloporphyrins with 1,1,1-trimethylhydrazinium iodide ($I(H_3C)_3NNH_2$) and KOH in dimethyl sulfoxide yielded the 2-amino-3-nitro porphyrins in good yields (**90a-d**, 64–89 %, Scheme 18 *C*). Interestingly, halogens (F, Cl) on the *p*-Ph positions did not undergo S_NAr reactions, displaying the selectivity imparted by the nitro group. However, two years prior, Richeter's group demonstrated the utility of the same reaction through the use of another nucleophilic amination reagent; 4-amino-4*H*-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(II), or Zn(II); **91a-d**, Scheme 18, *D*), it was found that the main product was the respective 2-(2-hydroxynaphthyl)porphyrin. 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 $S_{RN}1$ type mechanism. As noted (vide supra)[33] Crossley demonstrated the reaction of Cu(II) 2-NO_2-TPP with *n*BuLi and found the product to be the respective 2-butylated porphyrin. The same type of reaction was analyzed with a variety of Grignard reagents MeMgI, *i*PrMgI, *n*BuMgI, *t*BuMgBr, and PhMgBr on a variety of metallo-2-NO_2-TPP's [M = Cu(II), Ni(II), Zn(II)], with varying yields (10–80 % over 11 examples, **95a-k**, Scheme 18, F). *trans*-Chlorins were found to form but oxidized to the porphyrin upon purification via silica column chromatography.

In 1986 Jackson and co-workers analyzed the effects of nitronium tetrafluoroborate (NO_2BF_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-tetraphenylporphyrin]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 NaN_3 in DMF (Scheme 18, *H*).[144] The yielded products, in both cases, were [1,2,3]triazolo[4,5-*b*]porphyrins **97a,b**, not β-azido. Unsurprisingly, the more electron deficient $TPPF_{20}$ 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_NAr in positions *ortho*- and *para*- to itself on a phenyl ring, and *ipso* or *alpha* to itself on a porphyrin. ***Route 1*** in Scheme 19 would be the typical addition-elimination type S_NAr reaction, yielding the Meisenheimer complex **100**,[14c] and negative charge assisted loss of the NO_2^- anion to yield **101**.

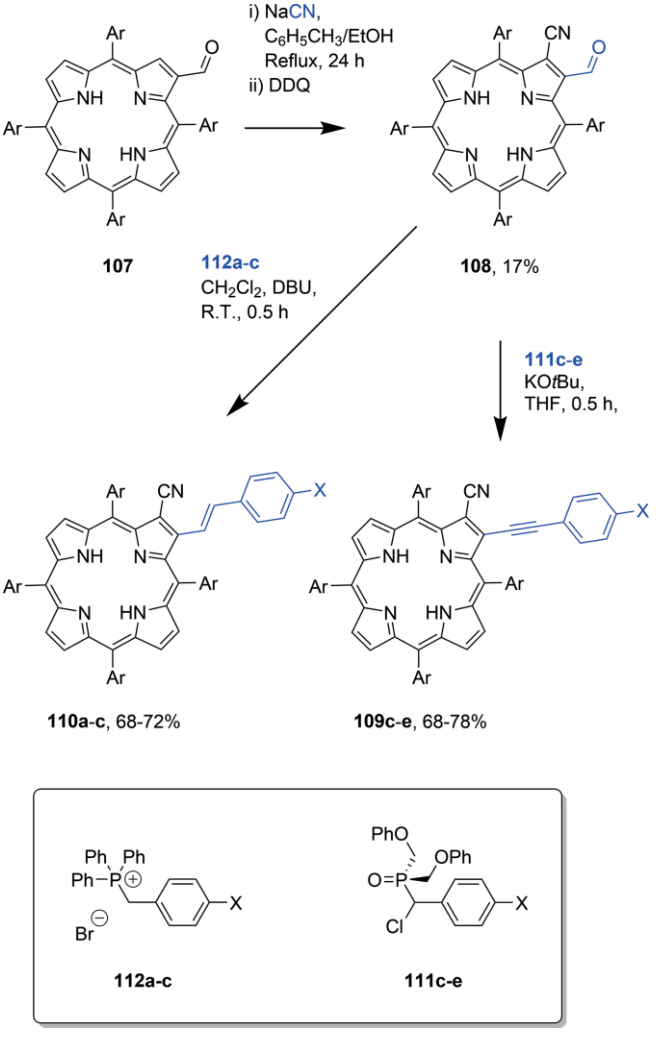


Scheme 19. Mechanistic considerations into the product formations in non-radical S_NAr type reactions on 2-NO_2-A_4 porphyrins. Stereochemistry shown for clarity. In cases where it is presented, the other enantiomer may also be generated. B = base, Nu = nucleophile, M = 2H, M(II).

Route 2 depicts attack at the α-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".[91]

2.3.2. β-Bromo- and β-Formylporphyrins. Akin to 2-nitroporphyrins, just like their meso-counterparts, 2-formylporphyrins are useful synthetic building blocks.[146] 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 S_NAr synthesis to examine the effect of unsaturated β-substituents on the photophysical properties of porphyrins (Scheme 20).[148,149] Thus, starting from 2-formylporphyrins, subsequent S_NAr 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



Scheme 20. Synthesis of 2-cyano-3-alkenyl/alkynyl porphyrins.[148] 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 tetrabrominate 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 $CuTPPBr_n(CN)_{4-n}$ (n = 0–4) and each was subject to UV-Visible spectroscopic and electrochemical analysis. However, attempts to separate the isomers of $CuTPPBr_2CN_2$ 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.

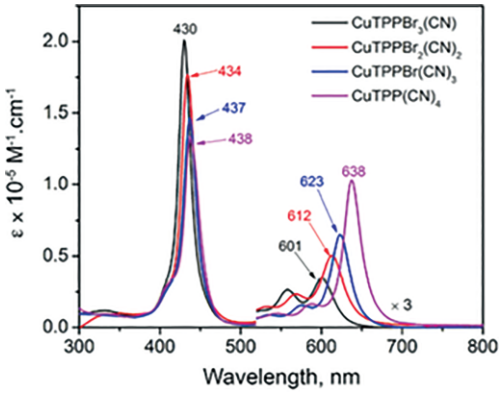


Figure 6. UV-Visible spectra of $CuTPPBr_n(CN)_{4-n}$ (n = 0–4) generated by Sankar et al. Reproduced from ref.[152] Copyright (2016) World Scientific Publishing.[152]

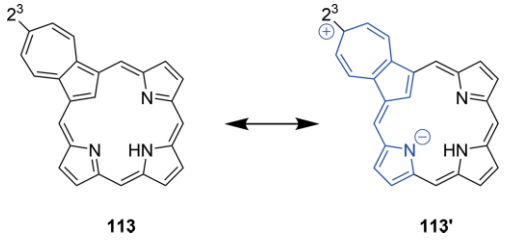
2.4. S_NAr Reactions on Azuliporphyrins and *N*-Confused Porphyrins (NCPs)

2.4.1. S_NAr 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.

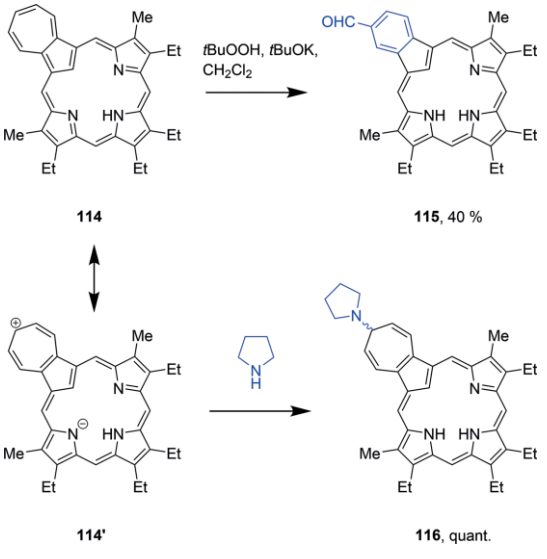
First synthesized in 1997 by Lash,[156] through a "3+1" style condensation of 1,3-azulinedialdehyde and a tripyrrane,[157–159] the resultant azuliporphyrin was described as exhibiting "borderline porphyrinoid aromaticity". Interestingly, it was these conditions that prevailed, as Breitmaier and co-workers had reported less than a year previously how their conditions [i) HBr/AcOH/CH_2Cl_2/THF ii) NEt_3, DDQ whereas Lash utilized i) TFA/CH_2Cl_2 ii) NEt_3, 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-tripyrrane, 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-azulipophyrins.[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 2^3-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 ^{1}H-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.



113 **113'**

Scheme 21. Canonical forms of unsubstituted azuliporphyrin, with the electrophilic 2^3-position labelled.



Scheme 22. Generation of 2^3-substituted azuliporphyrin, **116**, and benzocarbaporphyrin **115** through the reaction of **114**/**114′** with different nucleophiles.[165,167]

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 H_2O_2. These attempts were all either unsuccessful or yielded complex mixtures of products. Eventually, however, tropone fused carbaporphyrins were successfully synthesized, although not through an S_NAr methodology.[166]

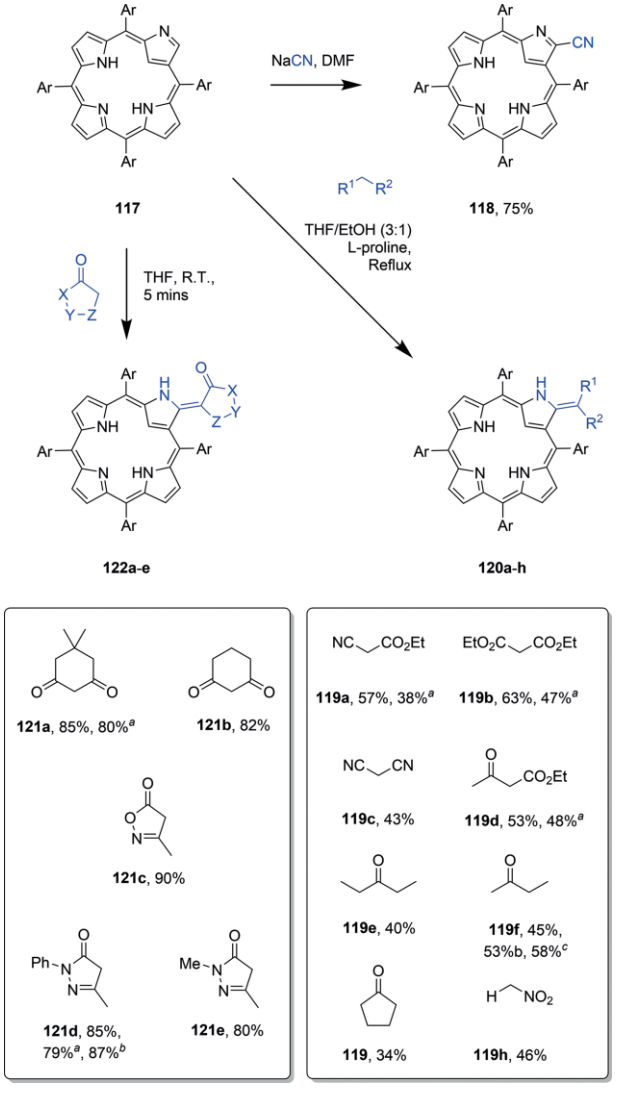
However, reactions of **114** with *t*BuOOH yielded interesting results; reaction with *t*BuOOH in KOH/MeOH and CH_2Cl_2 at r.t. gave the respective benzocarbaporphyrin in 30 % yield, whereas reaction with tBuOOH with *t*BuOK in CH_2Cl_2 yielded the 3^2-formyl benzocarbaporphyrin **115** in 40 % yield.[167]

Inherently, the next question is what happens when the 2^3-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 2^2-position.[161] Likewise, subsequent analogous ring contractions to yield the benzocarbaporphyrins also occurred.

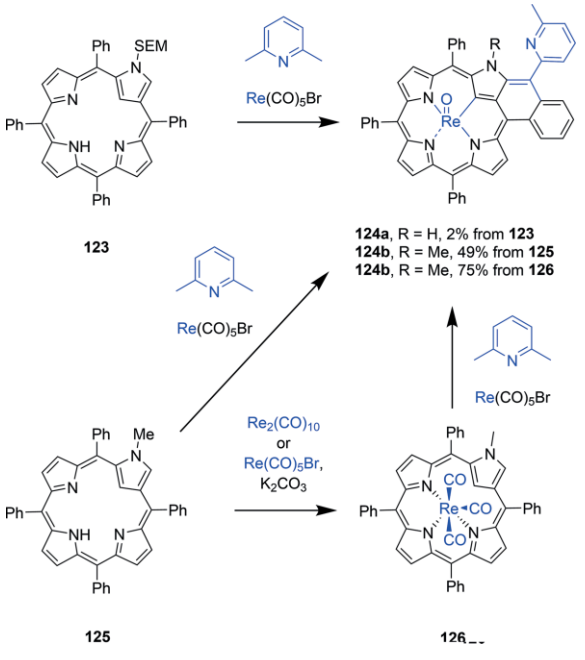
2.4.2. S_NAr Reactions of *N*-Confused Porphyrins. *N*-Confused Porphyrins (NCPs), 2-aza-21-carbaporphyrins to give them their proper name, are a peculiar class of core modified porphyrins.[169] With one of the pyrrole rings inverted, i.e. bonding through one of the pyrrolic α and one of the β positions, they exhibit properties that are far different to more typical porphyrinoids; vastly red-shifted UV-Visible spectra,[170] the ability for intramolecular fusion,[171] differing metal coordination properties,[8c,172] and an exterior N that can be functionalized,[173] along with heightened reactivity at the C^3-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*-A_2B_2 and A_3B 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 S_NAr at the C^3- and C^{21}-positions. The differing reactivates of these two positions is evident; noted from early on was the carbene character of the C^{21}-position,[180] and hence along with this come intriguing coordination properties,[181] particularly of larger metals in unusual oxidation states. Where the C^{21}-position is carbene type in character, the C^3-position is imine-type in character.

The electrophilicity of the C^3-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-



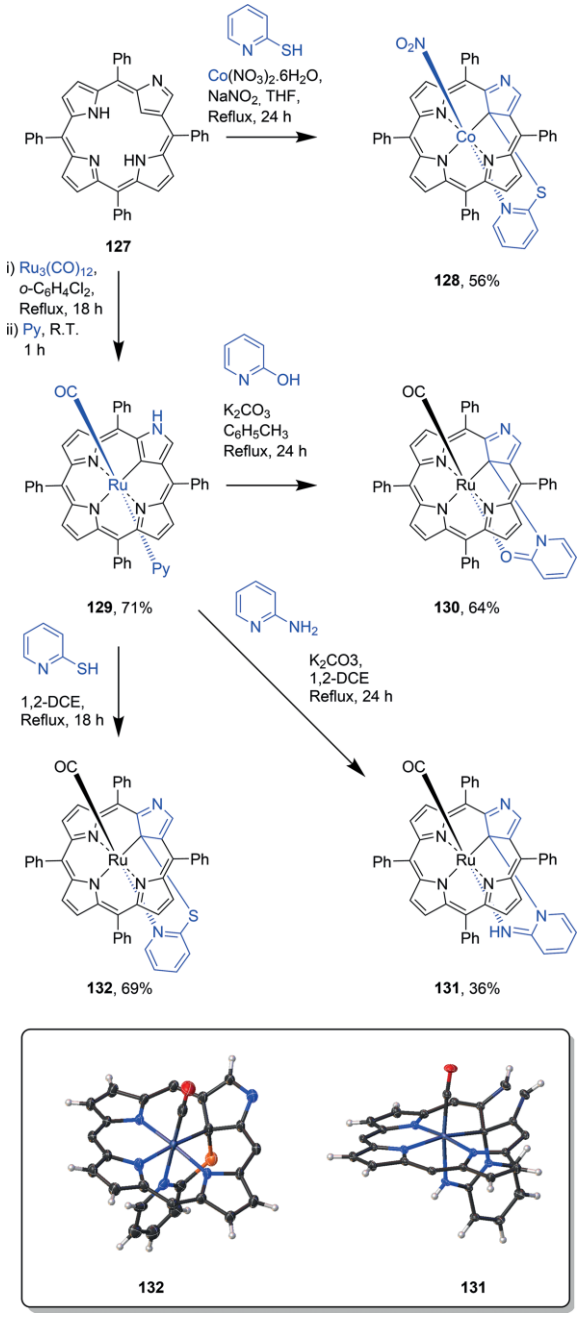
Scheme 23. S_NAr reaction of *N*-confused porphyrins with various active-methylene compounds. Unless stated otherwise, Ar = *p*Tol, [a] = Ph, [b] = *m*-$C_6H_4OCH_3$, [c] = 3,4,5-$C_6H_2(OCH_3)_3$, [d] = *p*-$C_6H_4CO_2CH_3$.[182–184]



Scheme 24. Synthesis of peripherally π-extended NCPs (**124a**,**b**) through rhenium-mediated ring fusions.[185] SEM = 2-(trimethylsilyl)ethoxymethyl.

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.



Scheme 25. Top: Synthesis of catalytically active penta-coordinate metallo-NCPs through S_NAr of 2-substituted pyridines. 1,2-DCE = 1,2-dichloroethane, Py = pyridine. Bottom: single crystal X-ray structures of **132** (left) and **131** (right) showing the difference in binding between the tethering ligands. Chlorobenzene solvates and meso-phenyl groups have been omitted for clarity. Atoms represented as thermal ellipsoids at 30 % probability. Images generated from CCDC No.: 1579797, 1881756.[187,188]

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 S_NAr of the respective 2-substituted pyridine attacking the C^{21}-position varied between the pyridines used; for 2-mercaptopyridine the thiol was the nucleophile, whereas for 2-amino and 2-hydroxypyridine, 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 ruthenium 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.

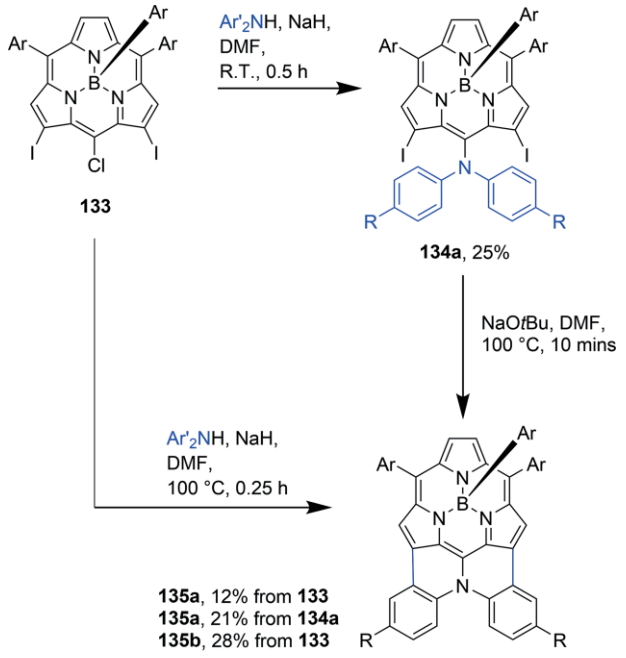
3. S_NAr Reactions of Subporphyrins

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 A_3-, A_2B-, ABC-, A_2-, and AB-type subporphyrins,[191] along with only hexa-β- and hexa-β-tri-meso-substituted subporphyrins. Bromination of A_2 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 S_NAr 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 S_NAr

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]

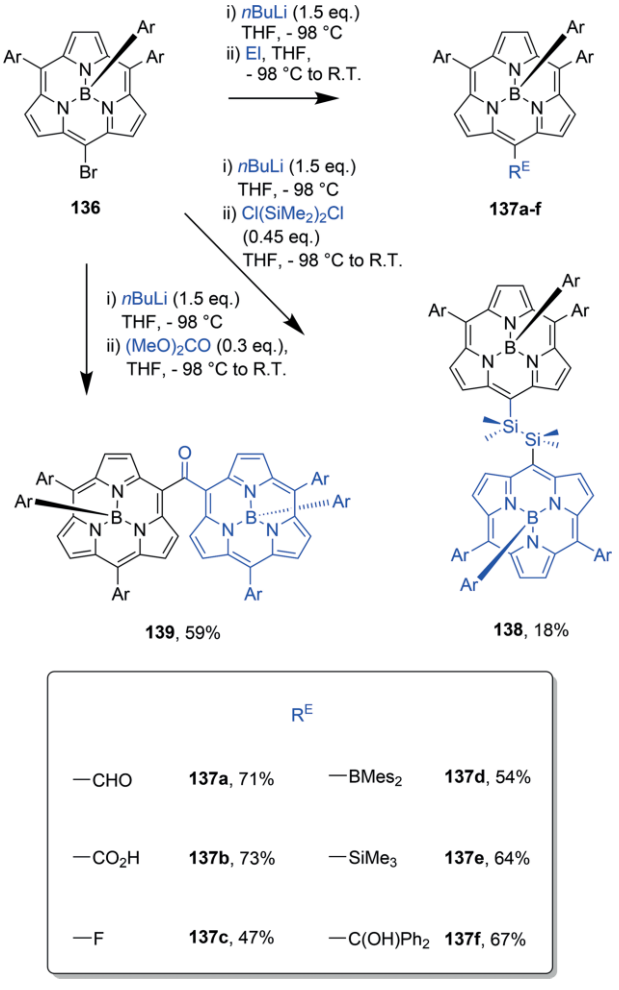


Scheme 26. Kise et al. synthesis of di-fused subporphyrins **135a**,**b** from tri-halogenated starting materials. Ar = *p*Tol, for a, R = H, and for b, R = $N(CH_3)_2$.[198]

Treatment of trihalo-subporphyrin **133** with diphenylamine yielded meso-substitution in 25 % yield (Scheme 26). Treatment of **134a** with NaO*t*Bu 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 = $N(CH_3)_2$), 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 *n*BuLi 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



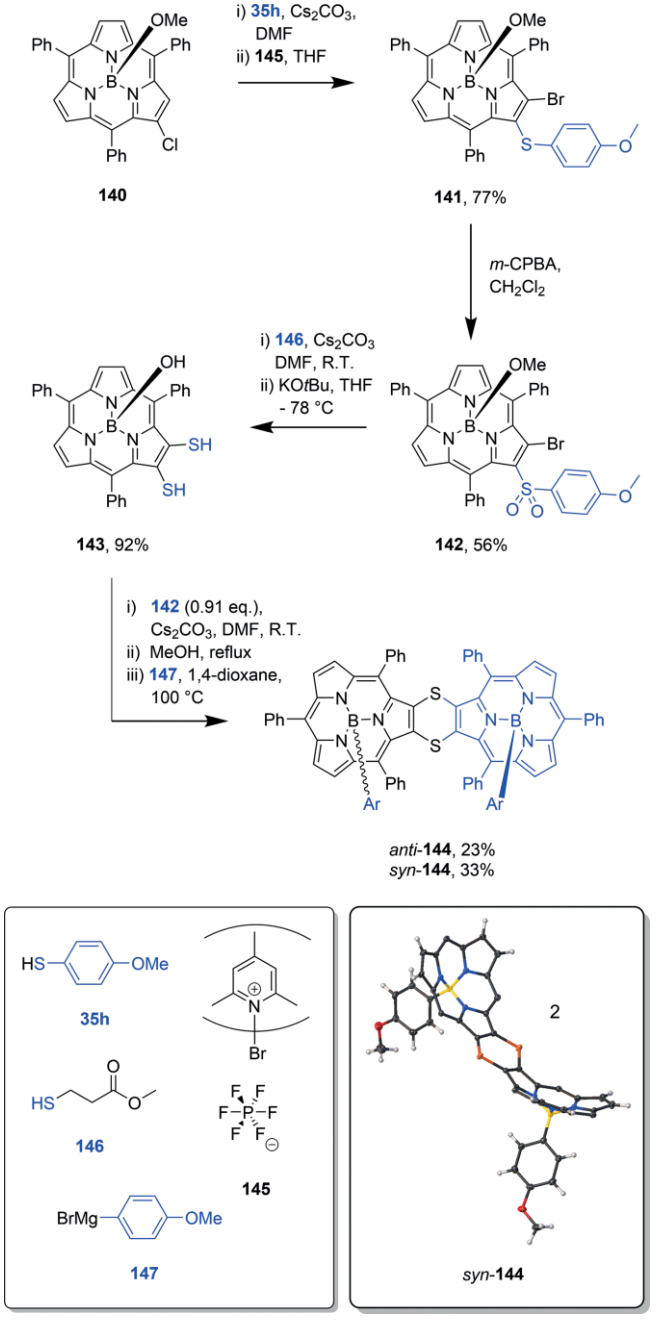
Scheme 27. Generation of meso-substituted subporphyrins through the generation of subporphyrinyllithiums. Ar = *p*Tol.[199]

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 β-Position

Less is known about reactions at the β-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 S_NAr 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 S_NAr 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 sulfoxide 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



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]

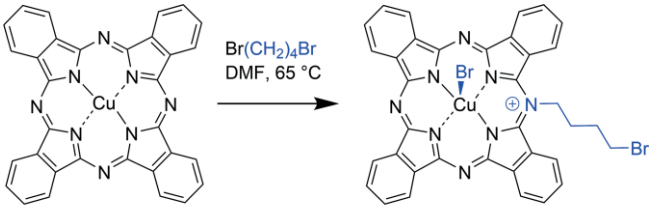
sulfoxide enables the separation and isolation of the two diastereomers of the subporphyrin. These two diastereomers exhibited different ^{1}H NMR spectra, immediately noticeable through the -OCH_3 signal and the adjacent aryl protons. Interestingly, **142** did interconvert in [D_4]methanol and [D_6]ethanol, but not in other solvents listed ([D_5]pyridine, [D_3]acetonitrile, [D]chloroform and, [D_6]benzene). In contrast, (BPh)-**142** was not found to interconvert even after exposing to harsh conditions (140 °C, 24 h).

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]

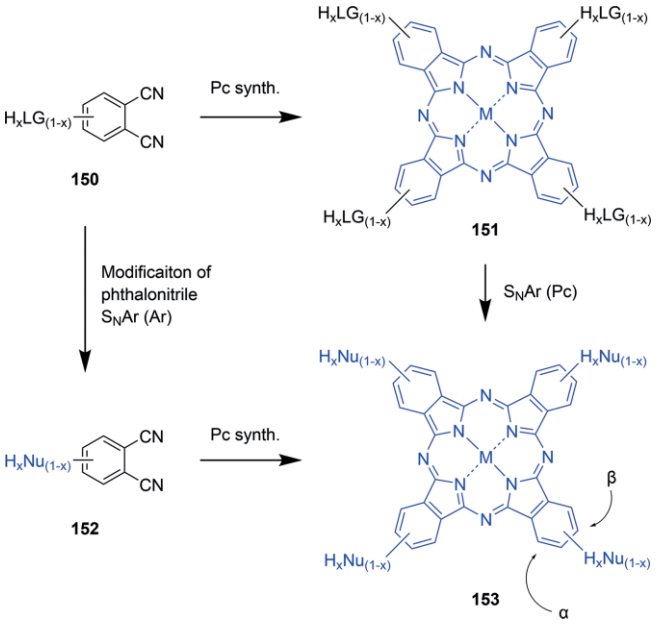
Although this class of compounds is known as "phthalocyanines", which is the name attributed to them by IUPAC, their systematic name "tetrabenzo[*b*,*g*,*l*,*q*]-5,10,15,20-tetraazaporphyrin" gives a greater understanding to their structure. The misconception is that Pc's cannot be substituted on the meso position, subsequently the syntheses of analogous 5,10,15-triaza-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 Pcs.[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 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.

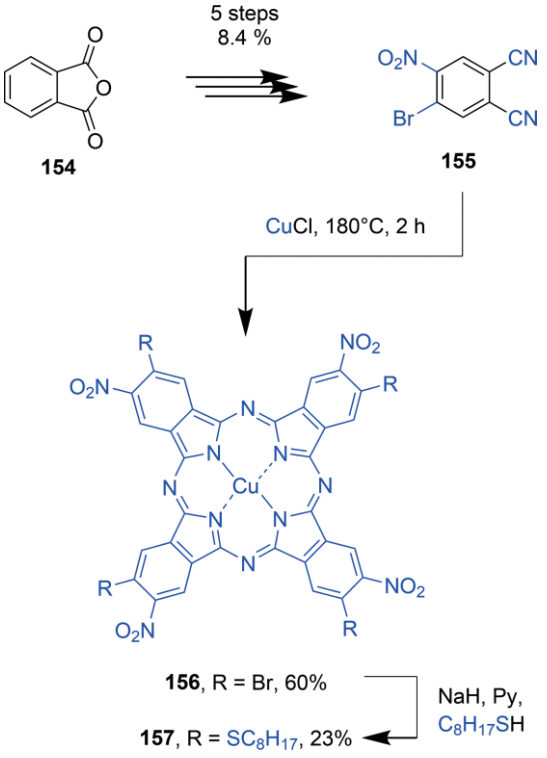
Unsurprisingly the majority of Pc starting materials, upon increasing complexity, are not commercially available and hence the substitution of starting material is often utilized preferentially.[208] The use of mass spectrometry to identify the number of substituents is common place in this area of chemistry, and sometimes the only way to truly determine success of these S_NAr reactions. For synthesis of substituted Pc's through route 1) as described prior, readers are directed to the appropriate reference.[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_NAr of both the precursor, and subsequent Pc, Lin et al. generated tetra-thioether **157** (Scheme 31), through S_NAr of tetra-bromo **156** with *n*-octanethiol in the presence of sodium hydride.[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_NAr of Pcs concern only one specific Pc: [hexadecafluorophthalocyaninato]zinc(II) **158**, $ZnPcF_{16}$. First synthesized by Birchall et al. in 1970,[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 **159b**, **g**, **h**, **j**, and **l**.[212] Only two of the nucleophiles achieved full hexadecasubstitution, **159j** yielding **160j** in 41 % and **159l** yielding **160l** in 6 %, probably due to the low steric demand of these nucleophiles. The low yield from the use of potassium cyanide (**159l**) is despite the use of 18-crown-6 to trap the potassium ions and generate the cyanide anion exclusively in situ. Use of **159h** yielded the dodecasubstituted **160h** in 53 %, although which isomer was not specified. In the case of **160b**, the crude product was found to exhibit a mass spectrum indica-

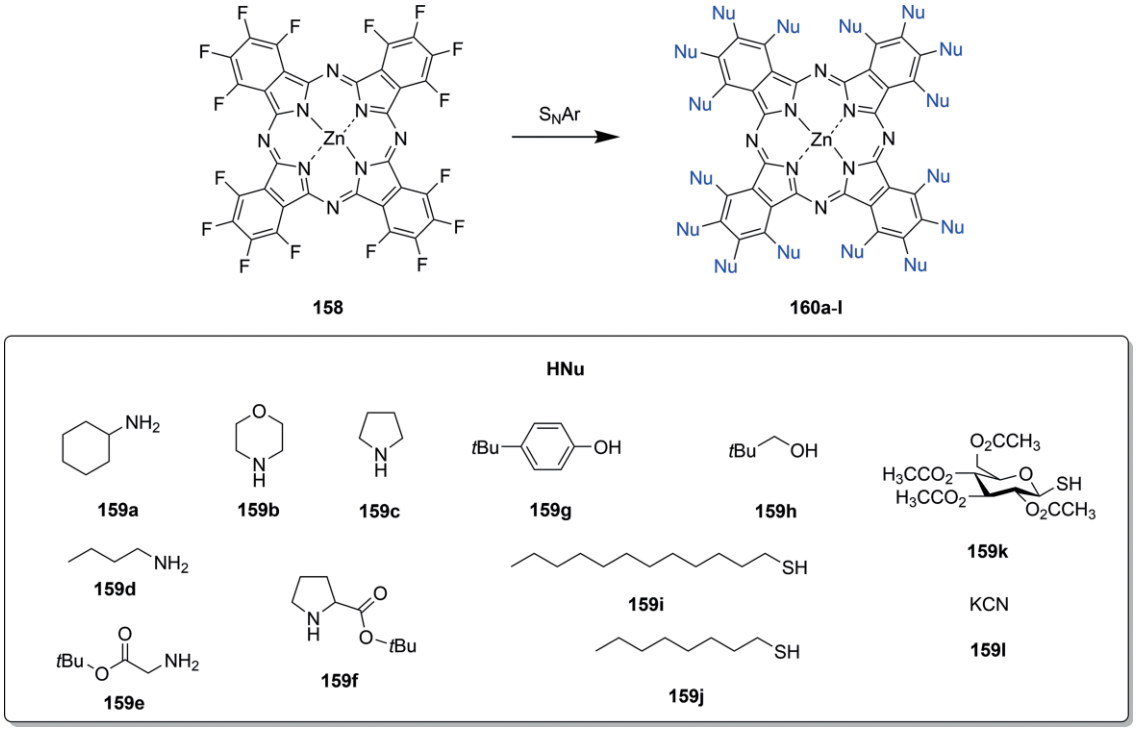


Scheme 31. Synthesis of tetra-bromo-tetra-nitro-Pc, **156** and subsequent S_NAr to yield the tetra-thioether Pc **157**. Only one regioisomer of **157** is shown, out of the four possible.[210]

tive of between seven to ten morpholino groups substituted upon the Pc backbone.

Leznoff also examined the reaction of a wide variety of amines with **158** using **159a**, **c**, **d**, **e**, and **f** (Scheme 32). Under mild conditions, only the mono- or disubstituted Pc's were obtained; however, upon use of the amine as the solvent – mixtures of multiply-substituted Pcs were obtained.[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_NAr can take place, along with the multiply nucleophilic amines used, these reactions continually produced mixtures of a variety of Pc's. Mass spectrometry indicated both intramolecular S_NAr (α-α′, α-β, β-β′) and intermolecular substitution (again varying to and from α and β positions), essentially forming amine-linked Pc's.

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 β-substituted Pc, which still contained the α-fluorine substituents.[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 ^{19}F NMR resonance at $\delta(^{19}F)$ = –85 ppm indicated the successful substitution of the β-positions, leaving the remaining signal at $\delta(^{19}F)$ = –109 ppm, indicative of the α-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



Scheme 32. Reaction of $ZnPcF_{16}$ **158** with a variety of heteroatomic mono-nucleophiles, **159a-l**.[212–216]

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

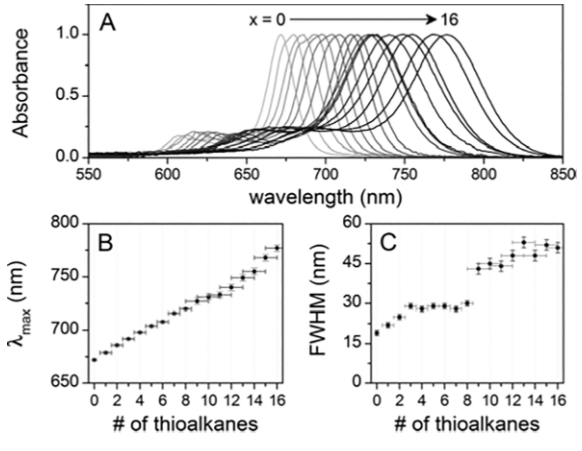


Figure 7. Photophysical analysis of the series of Pc's with general formula $ZnF_{16-x}(SR)_xPc$. (A) Normalized absorbance spectra of compounds $ZnF_{16-x}(SR)_xPc$ (x = 0–16). (B) Wavelength of maximum absorbance (λ_{max}) as a function of the number of thioalkane substituents. (C) Peak widths as a function of the number of thioalkane substituents, as measured by the full-width at half-maximum (fwhm). Reproduced from ref.[216] Copyright (2016) American Chemical Society.

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]

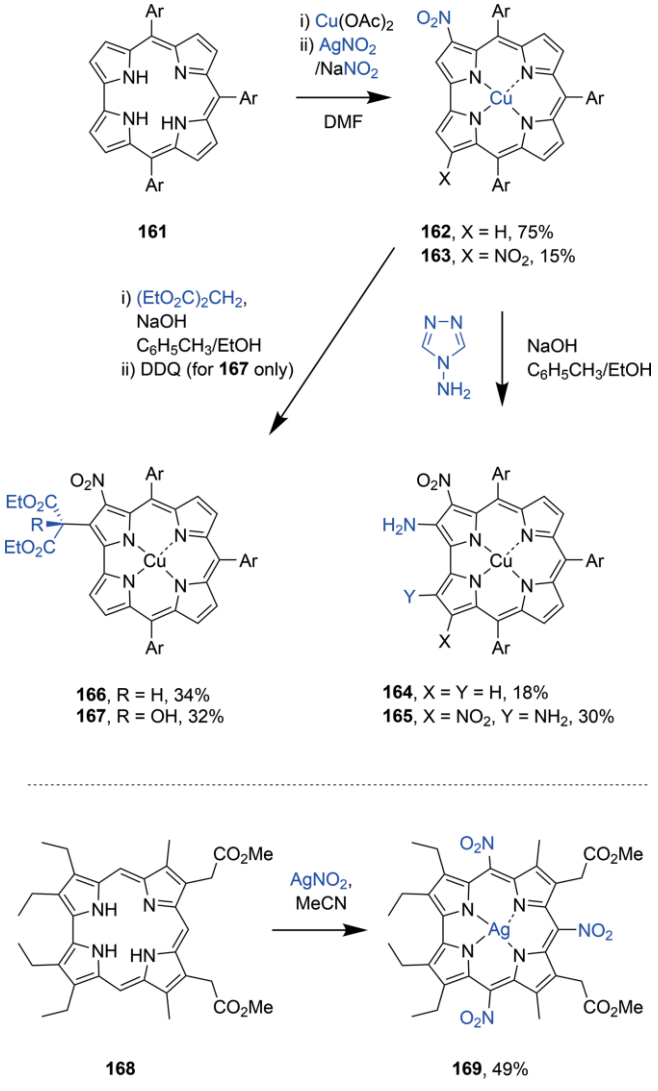
Farley et al. also successfully reacted **158** with **159j** to yield the hexadecasubstituted product, **160j**, in 44 % yield, along with synthesizing and analyzing every compound in the series $ZnF_{16-x}(SR)_xPc$, where R = C_8H_{17}.[216] Where yields were provided, they ranged from 17 % ($ZnF_9(SR)_7Pc$) 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_8H_{17} substituents (672 nm for x = 0 to 777 nm for x = 16), 2) Φ_F decreased with increasing -SC_8H_{17} substitution, and 3) the Stokes shift also increased with -SC_8H_{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, *p*-Ph

nitration.[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_2^- on a silver-corrole π-cationic radical.[225] $AgNO_2$ was used to avoid the harsh conditions sometimes used in the nitration of other aromatics, i.e. HNO_3/H_2SO_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 % (**162**), along with the generation of the 3,17-dinitrocorrole in 15 % (**163**).[226]

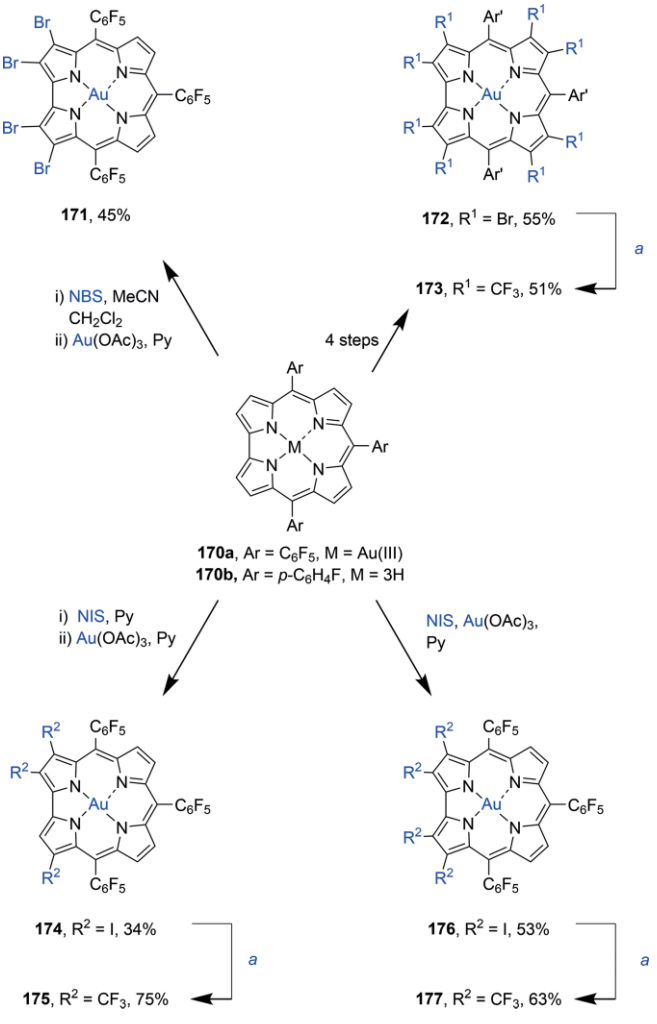


Scheme 33. Top: synthesis of nitro-corroles **162** and **163** and their transformations to nitro-aminocorroles, and other 2,3-difunctionalized corroles, bottom: nitration of a meso free corrole. Ar = *p*-C_6H_4tBu.[225–227]

The dinitration of these macrocycles was also examined; the use of Cu-**161** and $AgNO_2$ in a 1:50 ratio yielded **163** in 52 %; however, use of Cu-**161**, $AgNO_2$ and, $NaNO_2$ 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*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 ^{2}-position has also been examined with C-based active methylene nucleophiles.[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,[228] and tetra-[229] or octabromination[229,230] was performed on **170a**,**b** prior to S_NAr with $FSO_2CF_2CO_2Me$, a source of the trifluoro-



Scheme 34. Synthesis of a variety of halogenated corroles, and subsequent S_NAr to yield the trifluoromethyl-substituted corroles **173**, **175**, and **177**. *a* = $FSO_2CF_2CO_2Me$/CuI, Ar′ = *p*-C_6H_4F (**170b**).[228–233]

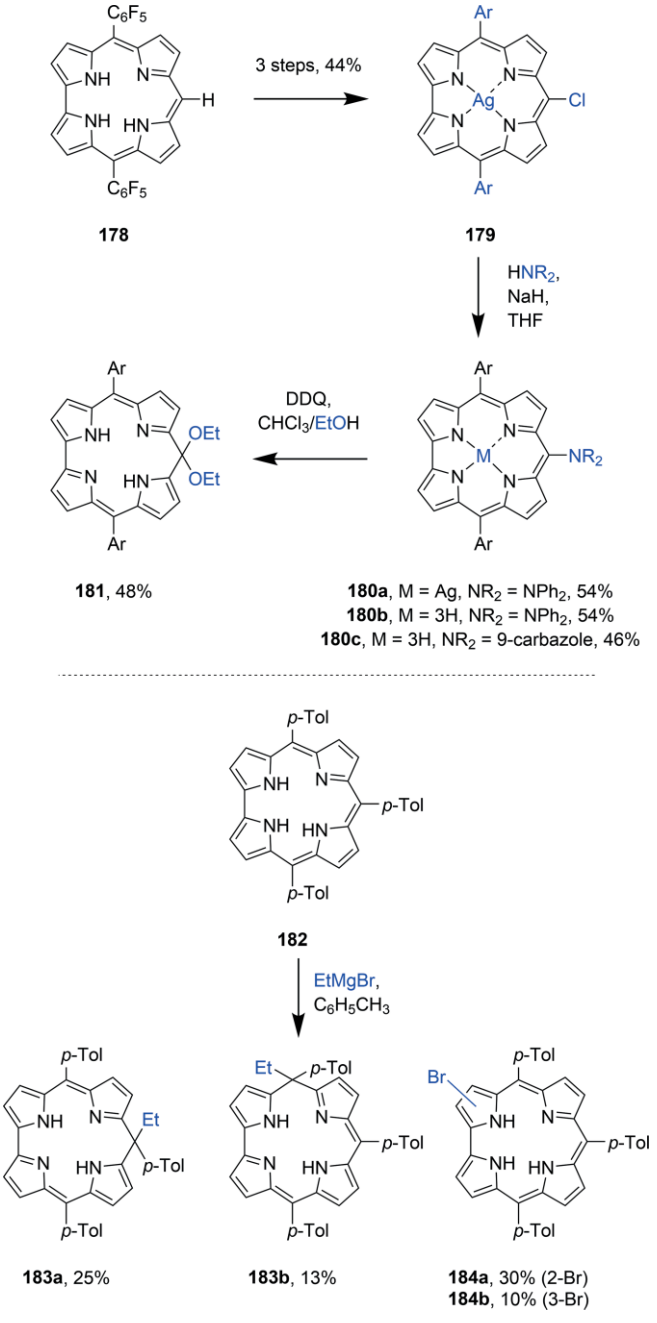
methyl anion.[231] This approach selectively yielded tri-, tetra-, and octarifluoromethylated gold corroles,[232,233] The yields for iodine substitution were higher than those for bromine substitution across all examples. Ghosh and co-workers generated **173**, and Cu-**173** and analyzed them via single-crystal X-ray diffraction and found an 85° difference in saddling between the two, with **173** being planar.[232]

When Gross's group generated their corroles,[233] they were analyzed through a variety of methods with the aim of understanding how the CF_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 **170a**, **176** and **177** showed significantly different UV/Vis spectra for **170a** and **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_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.[234] Recently however, Ueta et al. exploited the utility of meso-free corrole exclusively in S_NAr reactions.[235] 5,15-Di-(pentafluorophenyl)corrole **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 Palau'chlor to yield the 10-chloro-corrole in 60 % yield. Subsequent metallation with AgOAc yielded the (corrolato)silver complex **179** in 90 % yield (44 % over three steps). Both the 3H and Ag-corrolato complexes were exposed to S_NAr 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 **179**, the reaction proceeded smoothly and an meso-diphenylamino appended corrole **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 **180b** in 54 % yield. The (corrolato)silver complex was also exposed to carbazole under identical conditions giving **180c** in 46 % 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 **181**.

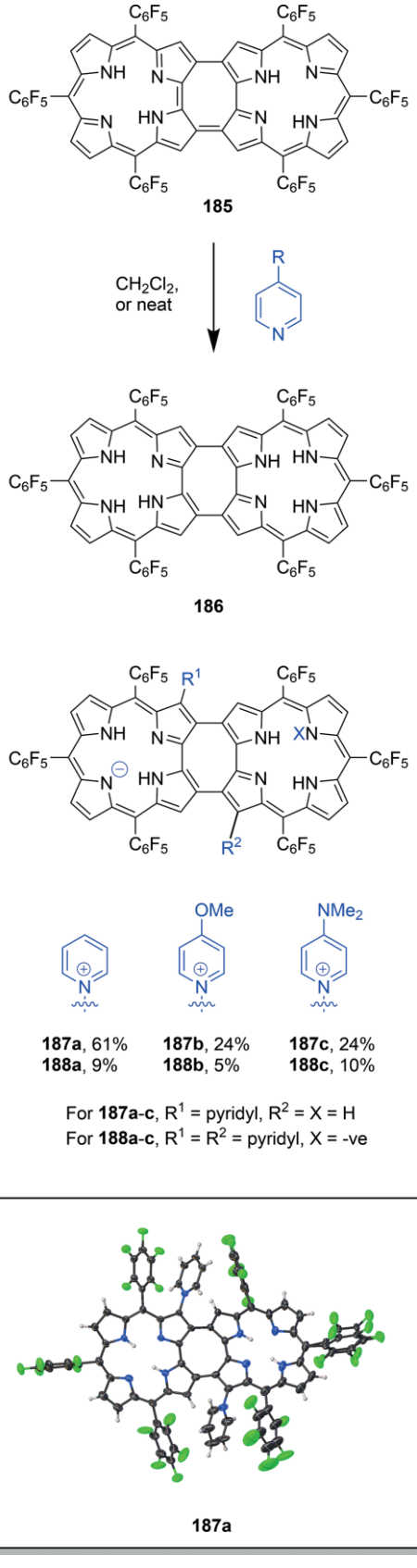
Nardis et al. also investigated the formation of isocorroles (Scheme 35, bottom).[236] Treatment of 5,10,15-tris(*p*-tolyl)corrole **182** with EtMgBr yielded four products: 10-ethylisocorrole (**183a**, 25 %), 5-ethylisocorrole (**183b**, 13 %), 2-bromocorrole (**184a**, 30 %) and, 3-bromocorrole (**184b**, 10 %). Thes9] isocorrole products bear some resemblance to the respective porphodimethenes prepared with RLi reagents.[40b,41,237] However, *n*BuLi is reported not to have reacted with **182**, in stark contrast to analo-



Scheme 35. Top: meso-S_NAr on the corrole backbone with amine nucleophiles, bottom: meso-S_NAr on the corrole backbone with EtMgBr. Ar = 2,3,5,6-tetrafluoro-4-methoxyphenyl.[235,236]

gous porphyrins.[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.[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 *n*BuLi to yield 15-butyl-5,10-diphenyl-22-oxacorrole in 10 %.[239]

An intriguing example of S_NAr on the corrole scaffold was found with biscorroles.[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-

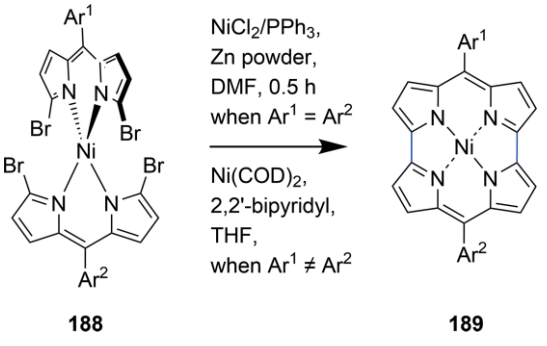


Scheme 36. Top: Synthesis of mono- and di-pyridyl-substituted biscorroles through S_NAr. Bottom: single crystal X-ray structure of di-pyridinated doubly linked bis-corrole **187a**. Atoms represented as thermal ellipsoids at 50 % probability. Image generated from CCDC No.: 710218.[242]

chlorobenzene, 6 h, N_2 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 Pd^0-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 $NaBH_4$ 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 biscorrole **187a** is shown in Scheme 36 (inset) indicating the regioselectivity of this substitution.

6. Nucleophilic Substitution Reactions of Norcorroles

Norcorroles are the smallest N_4-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 S_NAr 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.

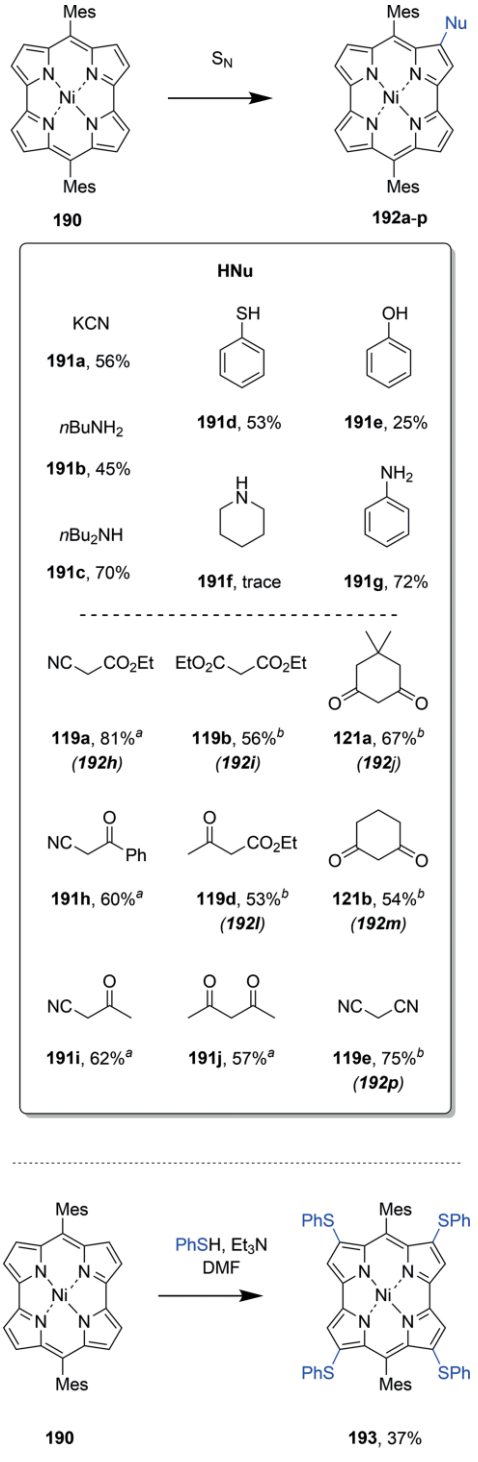


Scheme 37. Synthesis of norcorroles through reductive coupling of two α,α′-dibromo dipyrrins.[244,247]

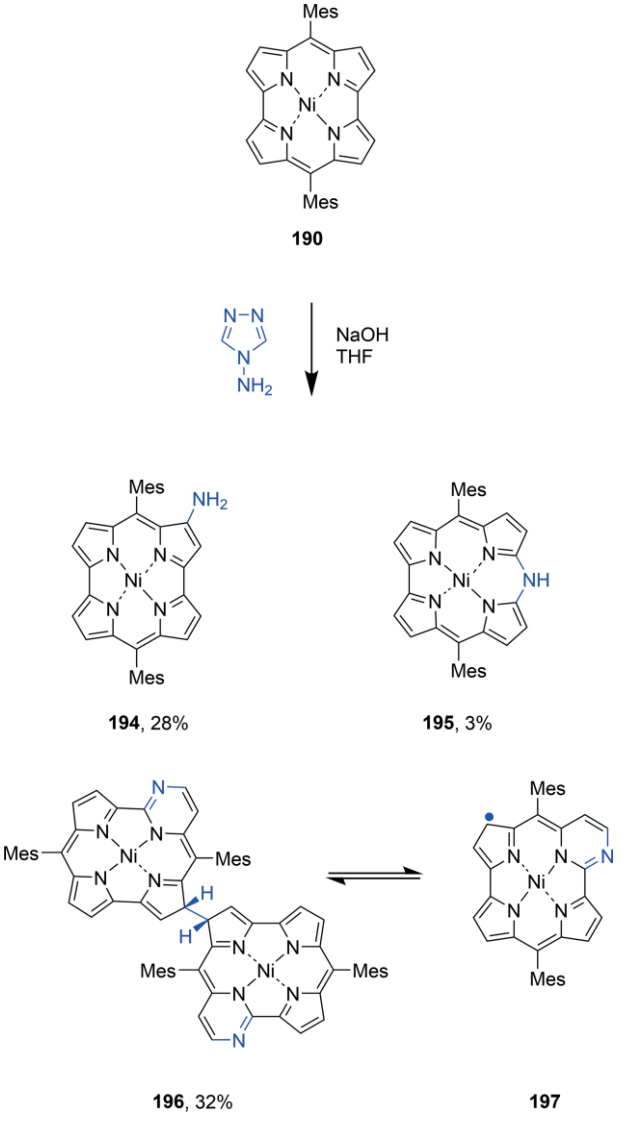
Despite their antiaromatic character norcorrole has been shown to undergo a range of nucleophilic substitution reactions, pioneered by Shinokubo's laboratory.[248] They examined substitution reactions of the norcorrole macrocycle with C-, S- and O-based nucleophiles (Scheme 38). Monocyanation with 20 equiv. KCN in CH_3CN/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

later, Yoshida et al. again analyzed the reactions of **190**, this time using amine nucleophiles.[249] Treatment of **190** with the respective amine, with no catalyst in the majority of cases yielded the mono- and diaminated norcorroles in suitable yields (Trace–82 %) utilizing several amines (*n*-butylamine, di(*n*-butylamine), piperidine and, aniline). Computational analysis by Yoshida was in agreement with a nucleophilic substitution reaction, given the disruption of the LUMO's when modelled with density functional theory (DFT) at the B3LYP/6-31G(d)+SDD level.

Further to this was the work of Ren et al.,[250] 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).[182,183] Initial investigation of the reaction between **190** and **119a** eventually yielded optimized conditions, generating **192h** in 81 %, utilizing Cs_2CO_3 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-



Scheme 38. Nucleophilic substitution reactions with a variety of heteroaromatic, and active methylene nucleophiles on the norcorrole backbone.[248–250] 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.



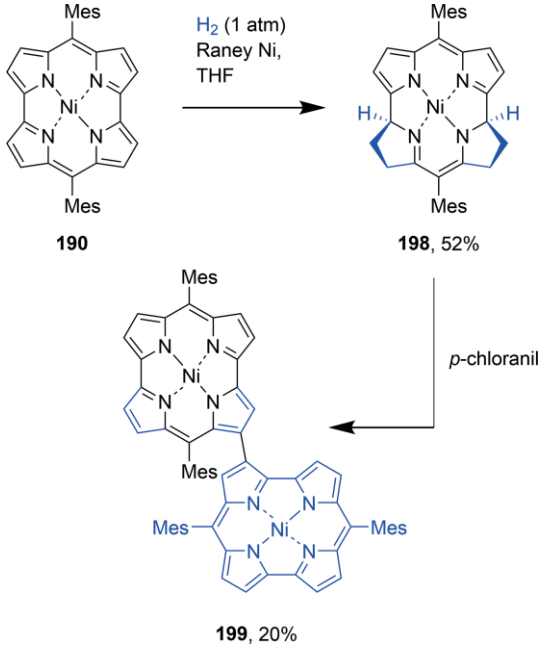
Scheme 39. Amination of the norcorrole backbone, displaying all four products of three different macrocycle types by Liu et al.[251]

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.

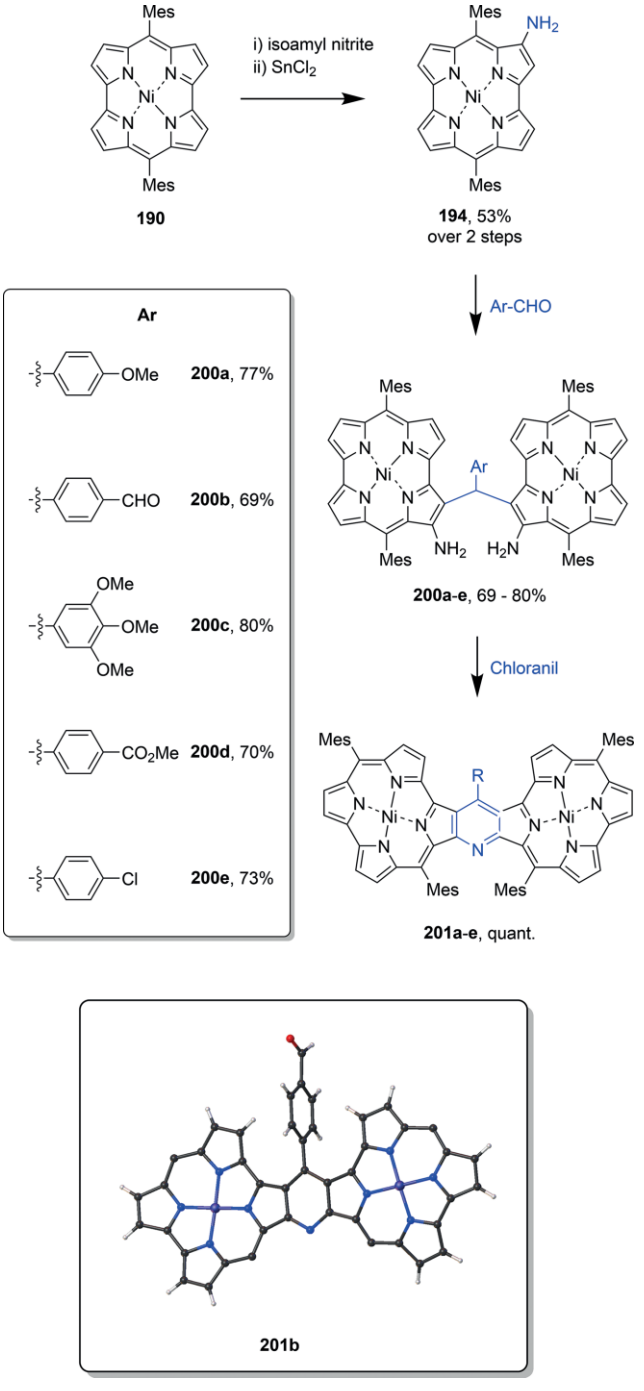
Amination was also possible as shown by Liu et al. who successfully generated a free base amine on the norcorrole backbone in 2016 through the treatment of **190** with 4-amino-4*H*-1,2,4-triazole (Scheme 39).[251] Four different products of three different macrocycle types were obtained; the desired 3-amino-norcorrole (**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 $C^3(sp^3)$ 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).[252] 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.



Scheme 40. Reduction of **190** and generation of a non-symmetrical norcorrole homodimer, **199**, through a nucleophilic dimerization by Liu et al.[252]

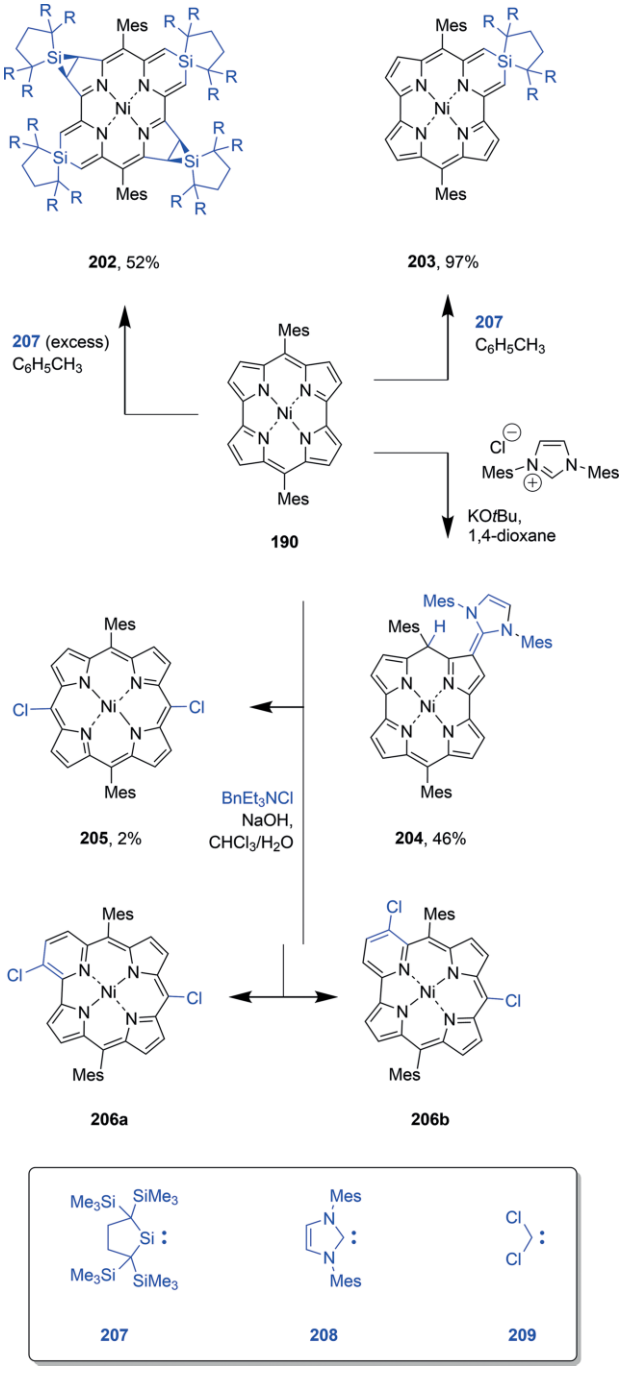
Whilst not directly-linked dimers, pyridine-fused-norcorrole dimers also demonstrate this property (Scheme 41).[253] Nitration of the norcorrole macrocycle with amyl nitrite and subsequent reduction with $SnCl_2$ yielded the 3-aminated norcorrole **194** on suitable scale. Addition of an aryl-aldehyde 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 $(\delta^+)C^3$ of the opposing norcorrole and yields a dihydropyridine intermediate, and subsequent oxidation yielded the respective pyridine.



Scheme 41. Top: synthesis of pyridine-fused bisnorcorroles through aminated norcorrole **194** followed by a deaminative intramolecular nucleophilic cyclization. Bottom: single crystal X-ray structure of **201b**. 5,14-Mesityl substituents have been omitted for clarity. Atoms represented as spheres. Image generated from CCDC No.: 1553620.[253]

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.



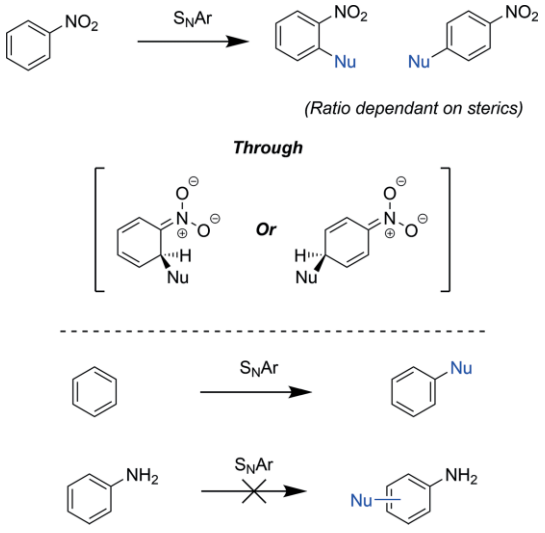
Scheme 42. Reactions of norcorroles with carbenes and silylenes to yield expanded norcorroles, and other macrocycles.[254,255]

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 (dichloroisopyriocorrolato)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 Ciamician-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 Ciamician-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 S_NAr 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 S_NAr reaction, which proceeds via the generation of a Meisenheimer complex,[14c] aniline is simply too electron-rich to participate in S_NAr 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).

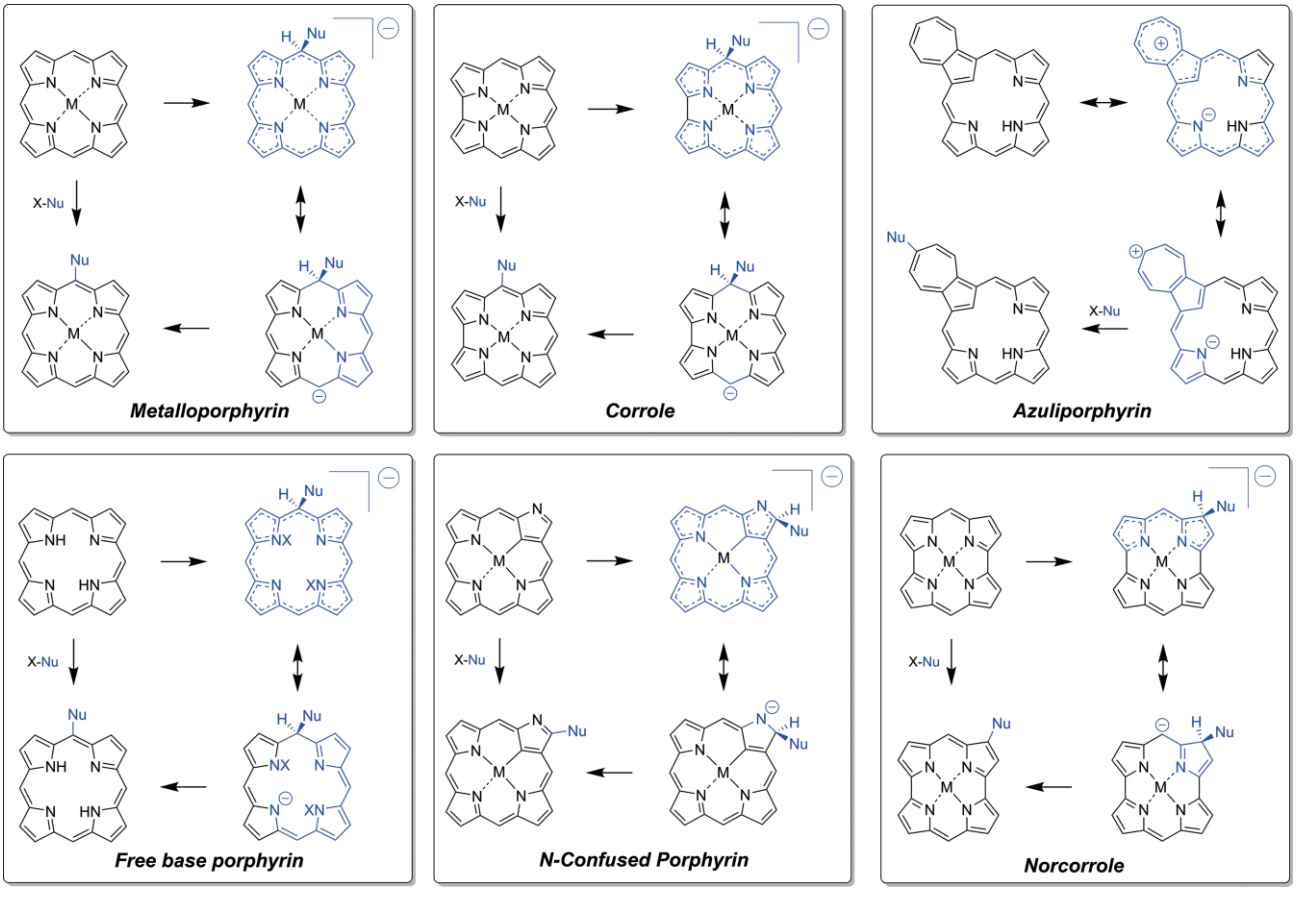
Whilst benzene has been shown to undergo S_NAr, it usually requires very harsh conditions and gives low yields. Recently, S_NAr on benzene was shown to occur through the use of a β-diketiminate strontium hydride complex, resulting in the production of C_6D_5-C_2H_5.[257] Arguably, the main reason S_NAr 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(sp^3) center. The resonance of the charge around the phenyl ring is what is observed for S_NAr, and it is this delocalization of charge that lowers the energy of the



Scheme 43. S_NAr reactions on (top to bottom); nitrobenzene, benzene and aniline.

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-A_4-porphyrins react differently depending upon the nucleophile used - either directly attacking the C^2-position (*ipso*-) or adjacent to the nitro group at C^3 (*alpha*-), likewise with β-formylporphyrins which direct S_NAr adjacent to the formyl group, whereas in the case of β-bromoporphyrins, the bromine itself is substituted. Azuliporphyrins appear to substitute exclusively at the 2^3-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 C^3-position has shown vast susceptibility to active-methylene nucleophiles, the C^{21}-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 44. Schemes depicting the S_NAr/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_NAr at the C^{21}-position of *N*-confused porphyrins, S_NAr of phthalocyanines, and S_NAr 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_NAr 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.[14c] 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.

Pc's are very large aromatic systems with the ability to distribute the additional charge over an even larger area. Their reactivity tends to be more dependent on the steric properties of the nucleophile than the position of attack. Given the ruling out of the meso-positions, the only two left are the α- and β-positions. Regardless of which of these is substituted, it is possible to resonate the negative charge into the macrocyclic core, thus creating a stable intermediate and hence, successful S_NAr.

NCPs present a significant challenge. Whilst one can rationalize substitution at the C^3-position of the macrocycle using resonance arguments (Scheme 44) the situation is less clear for C^{21}-subsitution. For norcorroles, their ability to undergo nucleophilic substitution can in part be explained by looking at structure **204**. The LUMO's of the norcorrole macrocycle as calculated by Yoshida et al.,[249] and Woller et al.,[259] exhibit fourfold symmetry and reside partly on the 3-, 7-, 12-, and 16-positions. Thus, through the substitution at any one of these positions the norcorrole resonance structures can be envisaged with the greatest charge localization on the meso-position.

Herein we have presented a survey of the newer literature regarding the nucleophilic (aromatic) substitution (S_NAr) of seven different porphyrinoids; porphyrins, azuliporphyrins, *N*-confused porphyrins, subporphyrins, corroles, phthalocyanines and, norcorroles. Clearly, there has been a vast acceleration in the understanding, and utility of S_NAr with a wide variety of structure types. Still, there is more potential with regards to S_N reactions of porphyrinoids, notably as we extend out towards the more atypical systems (subporphyrins, norcorroles, and N-confused porphyrins). The well-known capability for the formation of C–C bonds on porphyrins utilizing this methodology has now been extended to other porphyrinoids.[7a,20] Most promising is the vast expanse of heteroatom-based reactions on all of the porphyrinoid scaffolds presented, which further diversifies the structure types one can synthesize and utilize. S_NAr can be performed with compounds which are synthetic cornerstones in their respective classes and facile to synthesize; key molecules such as OEP, 2-NO_2-TPP, **158**, and **190** are cases in point. Often, these reactions can be performed with bulk reagents in non-anhydrous solvents. Clearly, S_NAr and related reactions are a viable and promising methodology to synthesize unsymmetrical porphyrinoids of all types. The now widespread use of these reactions to construct modified porphyrinoids for myriad applications, and recent breakthroughs with the more atypical porphyrinoids, indicate a very bright future for this field.

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Keywords: Porphyrinoids · Nucleophilic Aromatic Substitution · Aromaticity

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$$^{m}Pc = \frac{16!}{n!(16-n)!} \qquad (1)$$

Equation 1. Determination of the number of permutations of a given number of substituents around the 16 possible positions upon the **158** macrocycle,[214] where ^{m}Pc = no. of permutations, *n* = no. of non-fluoro substituents.
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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.[14c] 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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