

Synthesis of indaphyrins: *meso*-tetraarylsecochlorin-based porphyrinoids containing direct *o*-phenyl-to- β -linkages

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The synthesis of indaphyrins, novel *meso*-tetraarylsecochlorin-derived chromophores incorporating *o*-phenyl-to- β -linkages, is described. Oxidative diol cleavage of *meso*-tetraaryl-2,3-dihydroxy-2,3-chlorins results in the formation of a secochlorin bisaldehyde. Depending on the reaction conditions during the ring cleavage reaction, one or two of the aldehyde groups react with the adjacent *o*-phenyl positions, leading to an intramolecular electrophilic aromatic substitution of the *o*-phenyl proton, and the establishment of a direct *o*-phenyl-to- β -linkage. The initially formed carbinol is spontaneously oxidized to the corresponding ketone. This modification forces the aryl groups into co-planarity with the macrocycle, allowing for interactions between the π -electrons of the aryl groups, the ketone linkage, and those of the chromophore, resulting in a significant electronic modulation of the porphyrinic π -system. The UV-vis spectroscopic properties of the free base, Cu^{II}, Ni^{II}, and Zn^{II} indaphyrins are discussed.

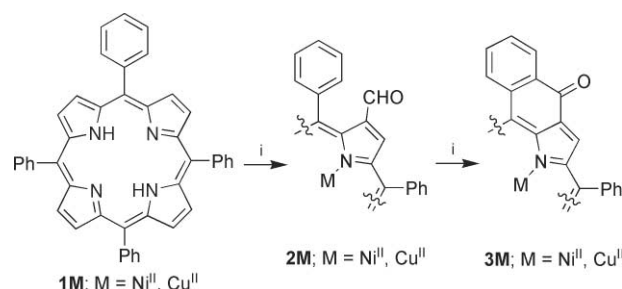
Introduction

One of the main driving forces behind current synthetic porphyrin chemistry is the synthesis of chromophores with designed optical properties. The maximum wavelength of absorption for porphyrins and many chlorins (β, β' -dihydroporphyrins) is about 650 nm. However, porphyrinoid chromophores absorbing and emitting in the red to infra-red region of the electromagnetic spectrum are of potential use in photodynamic therapy (PDT),¹ as well as in cell imaging and tagging applications.² This is due to the so called 'spectroscopic window' of biological systems, the range of light that is able to penetrate tissue. Red and near-infra-red wavelengths penetrate tissue the best.¹ Light scattering in opaque biological media is also wavelength dependent – longer wavelengths scatter less than shorter ones.³ Chromophores with a broad absorption over the entire visible range may also aid in the design of synthetic light harvesting assemblies.⁴

Much of the research toward the goal of synthesizing red-absorbing porphyrinoids has focused on the synthesis of expanded and isomeric porphyrins,⁵ heteroporphyrins and porphyrin-analogs containing non-pyrrolic heterocycles.⁶ The majority of these chromophores were made from monopyrrolic starting materials using a step-by-step approach.

An alternative synthesis of porphyrinoids relies upon the modification of porphyrins.^{7–10} This method has a number of advantages, especially when utilizing *meso*-tetraarylporphyrin **1** as the starting material: firstly, porphyrin **1** is readily available with a wide range of *meso*-aryl substituents, allowing the adjustment of the solubility and biodistribution properties of *meso*-arylporphyrin-derived chromophores.¹¹ Secondly, the *meso*-aryl groups themselves can potentially be utilized in the modulation of the porphyrinic chromophore. The aryl groups in **1** are arranged essentially orthogonal to the plane of the porphyrin. Hence, aryl-substituents have only a minor effect on the optical properties of **1**. However, the establishment of a covalent linkage between the *o*-phenyl position and the β -position of a porphyrin forces the aryl group into (idealized) co-planarity with the macrocycle. As a result, the π -system of the aryl group can interact with the porphyrinic π -system, leading to a significant modulation of the electronic properties of the chromophore.

The validity of this approach was firstly demonstrated by Henrick *et al.* using a serendipitously discovered reaction (Scheme 1).¹² *Meso*-Tetraarylporphyrin **1**, as its Ni^{II} or Cu^{II}



Scheme 1 Synthesis of naphthoporphyrins **3M** from *meso*-tetraarylporphyrins **1**. Reaction conditions: i. 1. POCl₃/DMF, 2. H₂O; ii. TFA.

complex, was β -formylated under Vilsmeier–Haak conditions. An attempt to demetallate the resulting β -formyl porphyrins **2M** with TFA resulted in an intramolecular ring closure reaction and formation of naphthoporphyrin **3M**. The overall result of the direct *o*-phenyl-to- β -linkages is a benzocyclohexenone unit fused into the porphyrin macrocycle. The photophysical consequences of this ring closure are exemplified by a 32 nm bathochromically shifted Soret band for **3Cu** ($\lambda_{\text{Soret}} = 465$ nm), as compared to that of **2Cu** ($\lambda_{\text{Soret}} = 432$ nm), and a 75% reduction of the extinction coefficient. The longest wavelength of absorption is even 100 nm bathochromically shifted ($\lambda_{\text{max}} = 594$ nm for **2Cu** as compared to 694 nm for **3Cu**). The utility of this reaction was further explored by the groups of Callot and Dolphin.^{13,14} Derivatives of **3** were designed to chelate to transition metals and were used in the construction of metal-linked porphyrin-oligomers.¹⁵

If the general reaction depicted in Scheme 1 is performed on the methoxyphenyl-substituted porphyrin **1M**, the resulting product is identified as the doubly-cyclized naphthoporphyrin **4H₂** (Fig. 1).¹⁴ Besides the naphthoporphyrin linkage, a direct *o*-phenyl-to- β -position linkage was established. This chromophore is one example of a *meso*-arylporphyrin-derived chromophore containing a five-membered ring between the aryl group and the porphyrin ring. Most recently, Fox and Boyle introduced the Pd(0)-catalyzed *o*-to- β -ring closure of *o*-iodinated *meso*-arylporphyrins to establish such a fused five-membered ring.¹⁵

A small number of other chromophores with *o*-phenyl-to- β -linkages are known. For instance, acid-catalyzed ring-closure of 2-vinylporphyrin generates naphthochlorin **5aM**, which has a λ_{max} of 670 nm (for M = Ni).¹⁶ The mechanism of formation of

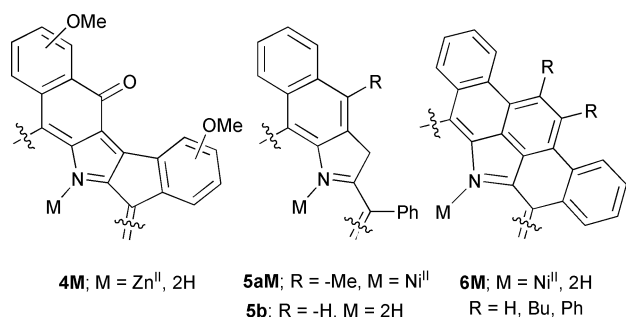


Fig. 1 Structures of precedent porphyrinoid chromophores containing *o*-phenyl-to- β -linkages.^{14,16,17}

this chlorin-like chromophore is reminiscent of the formation of naphthoporphyrins **3M**. A fundamentally different fashion of generating chromophores with co-planar *meso*-aryl groups was described by Smith and co-workers. Bergman cyclization of *meso*-tetraphenyl-2,3-dialkynylporphyrins afforded **6M**, a chromophore containing a [5]phenacene unit fused to the porphyrin macrocycle.¹⁷ Again, the optical properties of **6M** are much altered as compared to those of porphyrins, with a much bathochromically shifted λ_{\max} of 629 nm for **6Ni** and of 684 nm for the corresponding free base chromophore.

We have reported the utility of *meso*-tetraaryl-2,3-dihydroxychlorins **7**, made by OsO₄-mediated dihydroxylations of the corresponding porphyrins **1**,^{8,18} in the synthesis of porphyrinoid chromophores in which one of the pyrrolic units of a porphyrin was formally replaced by a non-pyrrolic heterocycle.^{8,19,20} For

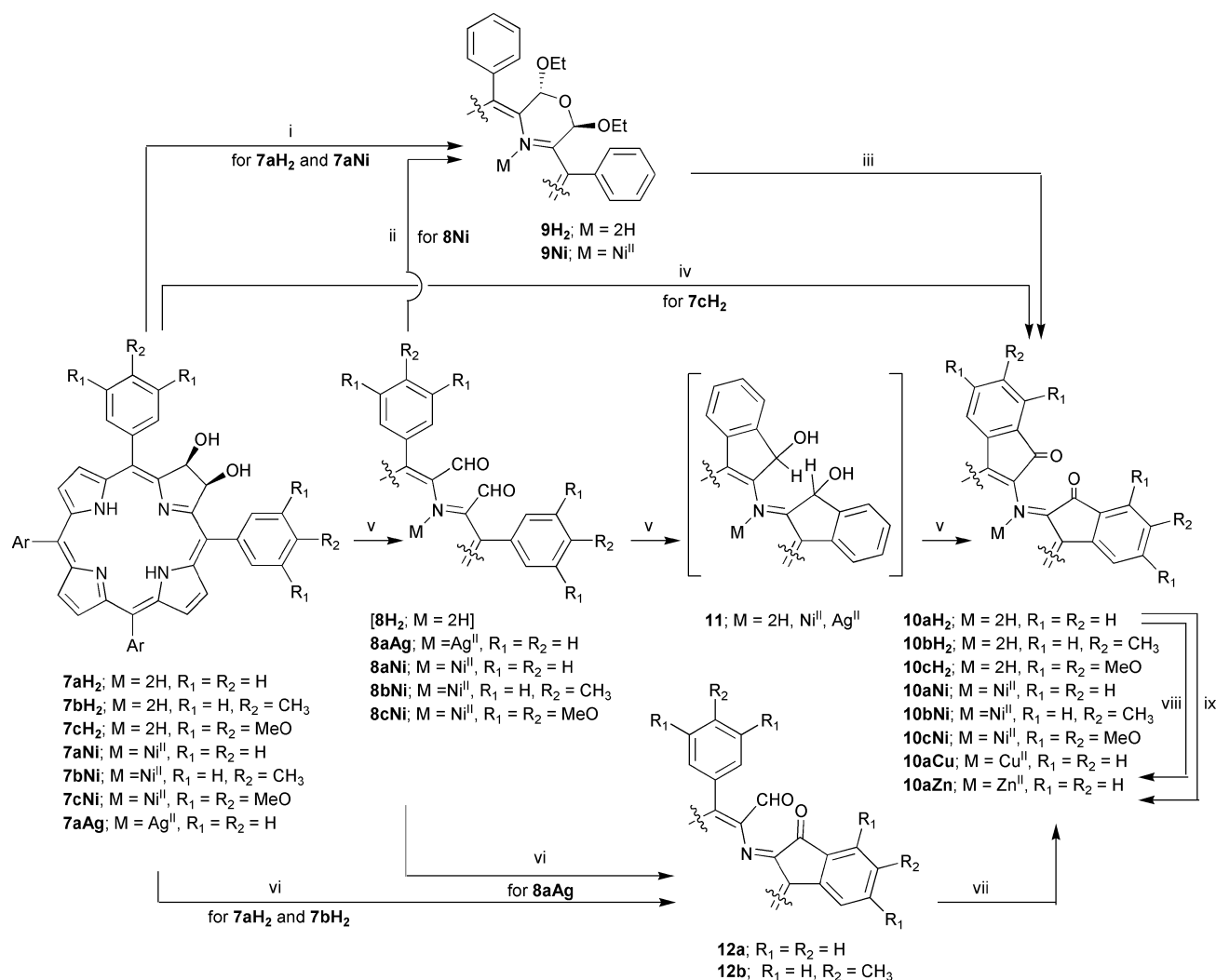
instance, reaction of **7aH₂** under diol cleavage conditions (NaIO₄-silica gel) in the presence of EtOH produced morpholinochlorin **9aH₂** incorporating a morpholine building block (Scheme 2).²⁰ The key intermediate in these syntheses was the *in situ* reacted unstable secochlorin bisaldehyde intermediate **8H₂**. As its Ni^{II} complex **8Ni**, the secochlorin can be isolated.^{8,9}

Following up on our recent communication, we report here on the use of **7**, **8**, and **9** in the synthesis of diphenylindaphyrins **10**, novel secochlorin-based chromophores incorporating *o*-phenyl-to- β -position linkages.¹⁰ We will describe different routes toward the synthesis of these macrocycles as their free base, Cu^{II}, Ni^{II}, and Zn^{II} complexes. The optical properties of these chromophores will be discussed. In so doing, we further expand the class of *meso*-aryl-based porphyrinoid chromophores containing *o*-phenyl-to- β -linkages, and introduce a novel class of secochlorin-based chromophores with extremely red-shifted optical spectra.

Results and discussion

Synthesis and characterization of indaphyrins

The nucleophile-induced intramolecular ring-closure reaction of bisaldehyde **8Ni** to form morpholinochlorin **9Ni** is acid-catalyzed using only traces of acid (Scheme 2).^{8,19,20} However, when **8aNi** was reacted with EtOH in the presence of too high a concentration of acid or for an extended period of time, one non-polar, deep green degradation product formed at the expense of morpholinochlorin **9aNi**. The high resolution mass spectrum of this product indicated its composition to be



Scheme 2 Reaction conditions: i. NaIO₄/silica gel, EtOH; ii. EtOH, TFA; iii. 10% TFA/CH₂Cl₂; iv. [O]; v. NaIO₄/silica gel or Pb^{IV}(OAc)₄; vi. TFA vapors; vii. 2% TFA/CH₂Cl₂; viii. Zn^{II}(OAc)₂, 10% MeOH/CHCl₃, Δ ; ix. Cu^{II}(OAc)₂, DMF, Δ .

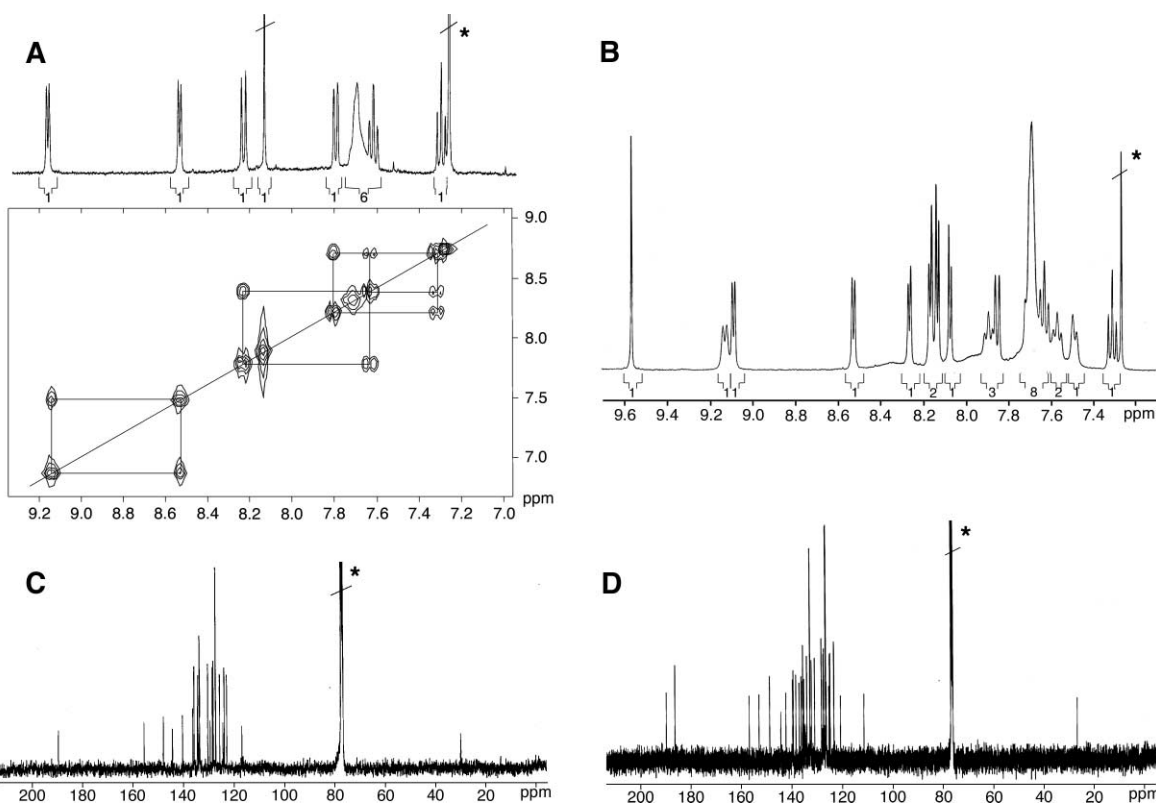


Fig. 2 A: Partial $^1\text{H},^1\text{H}$ COSY (CDCl_3 , 400 MHz, r.t.) spectrum of 10aH_2 ; B: Partial ^1H NMR (CDCl_3 , 400 MHz, r.t.) spectrum of 12aH_2 ; C: Full ^{13}C NMR (CDCl_3 , 100 MHz, r.t.) spectrum of 10aH_2 ; D: Full ^{13}C NMR (CDCl_3 , 100 MHz, r.t.) spectrum of 12aH_2 .

$\text{C}_{44}\text{H}_{24}\text{N}_4\text{NiO}_2$ ($m/z = 698.1262$, M^+ , FAB+), *i.e.* formally derived from 8aNi by loss of four hydrogens. This suggested that EtOH was not involved in the transformation. Indeed, the identical product was obtained as the major product when 8aNi was reacted with TFA in the absence of an alcohol (80% yield, 5×10^{-5} mol scale). The UV-vis absorption spectrum of 10aNi resembles that of a bathochromically shifted Ni^{II} chlorin, indicating the presence of a porphyrinoid macrocycle, and excluding the presence of a linear oligopyrrolic product (see Fig. 3; for a detailed discussion of the optical properties of this chromophore, see below). The ^1H and ^{13}C NMR spectra of this compound are well resolved and indicate a porphyrinic chromophore of two-fold symmetry. A carbonyl stretch at 1599 cm^{-1} is present in its IR spectrum. However, 10aNi is unstable and decomposes in solution within 12 hours, providing a red pigment with a spectroscopic signature suggesting a ring-opened, linear oligopyrrolic structure.²¹

Fortunately, free base morpholinochlorin 9H_2 proved to be susceptible to an equivalent acid-induced reaction, producing 10aH_2 in 30% isolated yield as a stable, non-polar, deep red chromophore of the composition $\text{C}_{44}\text{H}_{27}\text{N}_4\text{O}_2$ ($m/z = 643.2145$, MH^+ , FAB+). Again, the pigment is formally derived from secochlorin bisaldehyde 8H_2 by loss of four hydrogens. The ^1H NMR spectrum of this product (10aH_2) is shown in Fig. 2A. This spectrum has features generally observed in two-fold symmetric pyrrole-modified porphyrins such as **7**, **8**, and **9**.^{8,19,20} The β -protons appear as two doublets (centred at 8.54 and 9.15 ppm, with the small 3J of 4.9 Hz characteristic of β -protons) and a singlet (8.15 ppm) in a 1 : 1 : 1 intensity ratio. The phenyl region of the ^1H NMR spectrum is, however, unusual. The signals are split into two distinct sets (Fig. 2A). One broad peak corresponds to the ten hydrogens of two phenyl groups. This unresolved signal is similar to that observed for the phenyl groups in many *meso*-phenylporphyrin derivatives. The second set are four well resolved signals, corresponding to 2H each (two doublet-of-doublets centred at 7.32 and 7.64 ppm, and two doublets centred at 7.81 and 8.24 ppm, all with a coupling constant of 7.7 Hz). The H,H-COSY spectrum of the aromatic

region shows the correlation between the four signals, which corresponds to a non-symmetrically 1,2-disubstituted phenyl group. For reactions involving the *meso*-tolyl- or *meso*-(3,4,5-trimethoxyphenyl)-substituted secochlorin bisaldehydes **8b** and **8c**, the proton signals in the phenyl region were correspondingly simplified (**10c**, for instance, displays only two singlets in a 1 : 2 ratio in the phenyl region). Additional signals for the methyl- and methoxy-groups were observed for these derivatives, respectively.

This spectroscopic evidence suggests the presence of an *o*-phenyl-to- β -position linkage. What, however, is its nature? The mass spectrum suggests the presence of two carbonyl groups.²³ This implication is confirmed by the observation of a $\nu_{\text{C=O}}$ at 1699 cm^{-1} in the IR spectrum of 10aH_2 . The ^{13}C NMR spectrum of 10aH_2 also provides clear evidence for the presence of a carbonyl carbon (189.5 ppm, Fig. 2C). Thus, chromophore **10** was assigned the structure shown in Scheme 2. In this macrocycle, a ketone functionality joins the *o*-phenyl position with the α -position of a secochlorin chromophore, fusing indanone moieties to a secochlorin backbone. Thus, we suggest the trivial name 'indaphyrin' for this chromophore.

The inner NH protons in 10aH_2 resonate in the ^1H NMR at 1.49 ppm. The down-field shift (*cf.* to the corresponding signals at -0.84 ppm for 7aH_2) may indicate an unusual π -resonance pattern which reduces the diatropic ring current of the porphyrinoid chromophore. Alternatively, this shift may indicate a significant non-planarity of the chromophore. However, models do not suggest an unusually large deviation from planarity for 10aH_2 (see below). The extinction coefficient for the diphenylindaphyrin is also reduced as compared to diol chlorin 7aH_2 , further supporting the notion of a perturbed aromatic system. The unusual UV-vis properties of indaphyrins are discussed below.

The mechanism of formation of indaphyrin **10** from secochlorin **8** can be rationalized by an acid-catalyzed intramolecular electrophilic attack of the formyl groups onto the adjacent *o*-phenyl positions, forming carbinol **11**, which then oxidizes spontaneously to the final product (Scheme 2). The

sensitivity of carbinols of this type towards air oxidation was previously shown by Barloy and co-workers.¹⁴ In the decomposition reactions of morpholinochlorins **9**, the double acetal group functions as a masked bisaldehyde which is liberated under the acidic reaction conditions, and which reacts *in situ*.

This mechanism suggests a rational synthesis of the free base chromophore **10H₂**, *i.e.* a synthesis not involving the initial formation of morpholinochlorin **9H₂**. We have earlier shown that bisaldehyde **8H₂** is unstable but can be formed and reacted *in situ*.²⁰ Correspondingly, reaction of free base diol chlorins **7aH₂** or **7bH₂** under diol cleavage conditions (NaIO₄/silica gel) in the presence of acid (2% TFA/CH₂Cl₂) produces indaphyrin **10H₂** in 44% isolated yield. This synthesis constitutes a greatly improved procedure over the originally reported one.¹⁰ If, however, this reaction is performed using **7aH₂** in a solvent containing only traces of TFA, a low polarity orange compound **12aH₂** is isolated as the main product, and no indaphyrin **10** is formed. The mass spectrum of **12aH₂** specifies a composition of C₄₄H₂₉N₄O₂ (*m/z* = 645.2334, MH⁺, FAB⁺), *i.e.* formally derived from secochlorin bisaldehyde **8aH₂** by loss of only two hydrogens. The ¹H NMR spectrum of this compound is shown in Fig. 2B. Clearly, the two-fold symmetry of the starting material is lost (see *e.g.* the 6 doublets in the β-region, 8.0–9.1 ppm, 1H each). The phenyl region is convoluted, but the coupling pattern corresponding to one 1,2-disubstituted phenyl group can be distinguished: two doublets centred at 7.86 and 9.13 (*J* = 7.2 Hz) and two doublet-of-doublets centred at 7.32 and 7.66 ppm (*J* = 7.6 Hz). A singlet at 9.57 ppm suggests the presence of an aldehyde moiety. Furthermore, the ¹³C NMR and IR spectra indicate the presence of two different carbonyls (187.3 and 190.7 ppm, Fig. 2D, and ν_{C=O} = 1655 and 1710 cm⁻¹). Thus, we assign it the structure of the *meso*-triphenyl-1-formylindaphyrin **12aH₂**. This compound can be smoothly converted to *meso*-diphenylindaphyrin **10aH₂** by treatment with 2% TFA in CH₂Cl₂.

In reactions using the trimethoxyphenyl-derived diols **7cH₂** or bisaldehyde **8cNi**, the ring-forming reaction proceeded much faster (within minutes instead of hours) and using lower acid concentrations (TFA vapours instead of the 2% TFA/CH₂Cl₂ used in the synthesis of **10aH₂**). This reflects the increased susceptibility of the trimethoxyphenyl group toward electrophilic aromatic substitution and, most likely, the subsequent oxidation of the benzylic carbinol.

We have recently demonstrated that Ag^{II} can serve as a removable metal template in the diol cleavage reaction of diol chlorins, and that the Ag^{II} secochlorin bisaldehyde **8aAg** is isolable, albeit in low yields.²² When [diolchlorinato]Ag^{II} **7aAg** is subjected to the diol cleavage conditions (NaIO₄/silica gel), followed by addition of acid upon consumption of the starting material, free base formyl indaphyrin **10aH₂** is isolated in up to 20% yield. Thus, the use of templating metal to stabilize the secochlorin bisaldehyde intermediate **8aAg** provides here no advantage over the use of the free base diol chlorin. Further, the presence of this templating metal does not seem to affect the course of the reaction as compared to the reactivity of the free base diol chlorin.

Preliminary studies on the reactivity of indaphyrins have been undertaken. We have previously demonstrated the hydrodecarbonylation of secochlorin bisaldehyde **8aNi** to the corresponding chlorophin.⁹ However, reaction of formyl indaphyrin **12aH₂** under the same decarbonylation conditions (Wilkinson's catalyst, PhCN, reflux for several h) leads only to the formation of indaphyrin **10aH₂**. Evidently, the thermally induced ring closure reaction is faster than decarbonylation. The ketone moieties of **10aH₂** are not susceptible to reduction by NaBH₄, likely owing to their stabilization through conjugation. Bonnett and co-workers reported a similarly unreactive conjugated carbonyl group incorporated into a porphyrinoid chromophore.²⁴

The susceptibility of the indaphyrins toward metallation reactions was tested. Insertion of zinc(II) or copper(II) using

standard conditions (M(OAc)₂, 10% MeOH/CHCl₃ for M = Zn^{II} or DMF for M = Cu^{II}) proceeds smoothly. The deep red color of the free base indaphyrin **10aH₂** changes upon formation of the Cu^{II} complex **10aCu** to red–orange whereas the red color of the Zn^{II} complex **10aZn** is very similar to that of the free base. Insertion of nickel(II) using Ni(OAc)₂ in hot pyridine or DMF did not take place, instead, the free base indaphyrin was recovered quantitatively. This finding is very unusual for porphyrinoid macrocycles. In line with this finding, however, the Ni^{II} diphenylindaphyrin **10aNi** is also relatively unstable. This may indicate that the insertion of Ni^{II} into indaphyrins requires a significant conformational change. Molecular modelling studies (see below) provide some confirmation of this assumption. The optical properties of the metalloindaphyrins are discussed below.

UV-vis properties of indaphyrins

The combination of the steric and electronic effects caused by the formation of indaphyrins is expected to have a profound impact on the photophysical properties of these chromophores. The formation of an *o*-aryl-to-β-position ketone linkage in indaphyrins **10** and **12** forces one or two phenyl groups into idealized co-planarity, and thus, conjugation with the macrocycle, expanding the porphyrinic π-system. Carbonyl functionalities are also known to greatly influence the optical properties of porphyrins.^{8,25,26} In indaphyrin **10**, ketone bridges link both the phenyl and chromophore π-systems, while in **12**, one aldehyde functionality and one linking ketone functionality are in conjugation with the porphyrinic chromophore. The *o*-aryl-to-β-position linkage may also distort the secochlorin chromophore from planarity. Any distortion of a porphyrinoid chromophore from planarity has pronounced effects on its electronic structure, although the exact reasons for this effect are currently being debated.²⁷

Fig. 3 shows the UV-vis absorption spectrum of [indaphyrinato]Ni^{II} **10aNi** in comparison to that of a number of related [chlorinato]Ni^{II} complexes. The spectrum of **10aNi** is metallochlorin-like, albeit significantly bathochromically shifted (λ_{Soret} = 446 nm, λ_{max} = 635 nm) as compared to, for instance, the spectrum of [diolchlorinato]Ni^{II} **7aNi** (λ_{Soret} = 416 nm, λ_{max} = 612 nm)⁸. A comparison of the UV-vis spectra of **10aNi** with those of the largely planar [2,3-dioxochlorinato]Ni^{II} **13Ni**²⁵ and the non-planar [diformylsecochlorinato]Ni^{II} **8aNi**^{8,9} allows some delineation of the steric and electronic influences operating in these chromophores. The two conjugated carbonyl groups in **13Ni** render its UV-vis spectrum broadened, and one band emerges next to the Soret band. However, the position of the Soret band of **13Ni** is comparable to that of planar [diolchlorinato]Ni^{II} **7aNi**. The spectrum of the extremely ruffled [diformylsecochlorinato]Ni^{II} **8aNi**, a chromophore also containing two carbonyl groups at the β-positions, is also some-

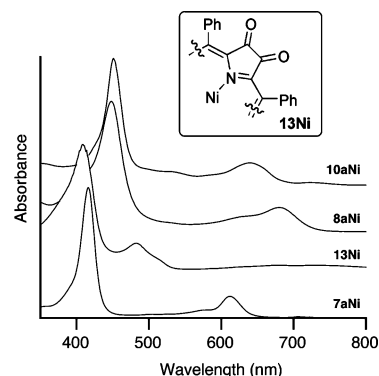


Fig. 3 Comparison of the normalized UV-vis absorption spectra of [diolchlorinato]Ni^{II} **7aNi**, [2,3-dioxochlorinato]Ni^{II} **13Ni** (structure of this chromophore is shown above), [diformylsecochlorinato]Ni^{II} **8aNi**, and [diphenylindaphyrinato]Ni^{II} **10aNi** (all in CH₂Cl₂).

what broadened but, most significantly, much bathochromically shifted as compared to that of dioxochlorin **13Ni**. In that respect, the spectra of **13Ni** and **10aNi** are, however, similar, likely indicating that the [indaphyrinato]Ni^{II} complex is also non-planar.

The fact that the co-planar aryl groups are in conjugation with the porphyrinic π -system can be ascertained by comparing the UV-vis spectra of the phenyl-, tolyl- and trimethoxyphenyl-substituted derivatives. For instance, λ_{max} of the free base indaphyrins shifts from 810 nm for the phenyl derivative **10aH₂**, to 812 nm for the tolyl-derivative **10bH₂**, and to 818 nm in the trimethoxyphenyl-derivative **10cH₂**. This shift, albeit modest in absolute terms, is an unusually large phenyl-substituent effect for *meso*-tetraarylporphyrins.

Interestingly, the UV-vis spectra of naphtho-porphyrins and -chlorins, as their Ni^{II} complexes, show characteristics similar to that of the spectrum of [indaphyrinato]Ni^{II} **10aNi**.^{12–14,16} Bonnett and coworkers have synthesized a [dioxosecochlorinato]Ni^{II} complex with ketone moieties at its β -positions.²⁴ The UV-vis absorption spectrum of this macrocycle is very similar to that of **10aNi** ($\lambda_{\text{Soret}} = 444$ nm, $\lambda_{\text{max}} = 648$ nm), which illustrates the general combined effect of the carbonyl moiety and inferred non-planarity on the photophysical properties of [secochlorinato]Ni^{II} chromophores.

The unusual UV-vis spectrum of free base diphenyl-indaphyrin **10aH₂** is shown in Fig. 4. It is dissimilar to a regular chlorin spectrum. It features a broad “double-Soret” band ($\lambda_{\text{Soret}} = 419, 554$ nm), and an absorption into the NIR region of the spectrum ($\lambda_{\text{max}} = 812$ nm). As well, the extinction coefficients for **10aH₂** are reduced by ~75%, as compared to those measured for diol chlorin **7aH₂**.

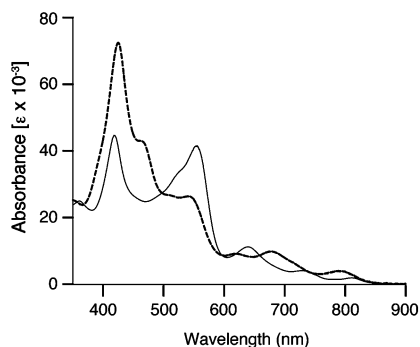


Fig. 4 UV-vis absorption spectra of **10aH₂** (—), and **12aH₂** (·····).

In contrast, the UV-vis absorption spectrum of the formyl indaphyrin **12aH₂** features a single Soret band, ($\lambda_{\text{Soret}} = 425$ nm, Fig. 4) but its absorption also ranges almost up to 800 nm ($\lambda_{\text{max}} = 792$ nm). The differences between the spectra of **10aH₂** and **12aH₂** illustrate the effect of the conversion of one formyl group into an indaphyrin-type linkage, and the concomitant electronic and conformational changes this modification causes.

The UV-vis absorption spectra of the Cu^{II} and Zn^{II} complexes of **10aH₂** are presented in Fig. 5. Similar to the spectrum of **10aH₂**, the spectrum of the Zn^{II} diphenylindaphyrin **10aZn** features a broad “double-Soret” band. The most intense absorption band was at 566 nm ($\log \epsilon = 4.70$). The Soret band of the Cu^{II} derivative **10aCu** is very broad. It seems likely that the two bands of the “double-Soret” feature of the free base chromophore overlap. As expected, all metalloindaphyrin spectra show a reduced number of side bands as compared to the spectrum of the free base. Remarkably, the [indaphyrinato]Ni^{II} spectrum is unlike that of the Cu^{II} complex. We interpret this as further indication that the Ni^{II} complexes possess different conformations.

The Ni^{II} ion is relatively small (the effective ionic radius of Ni^{II} in a square planar complex is 0.63 Å) whereas the ionic

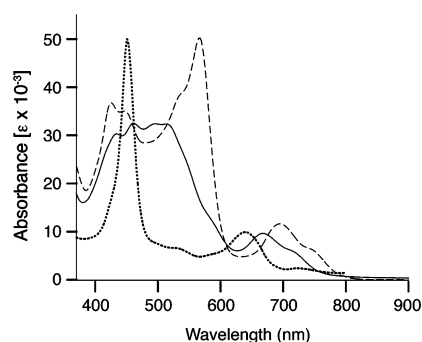


Fig. 5 UV-vis absorption spectra of **10aCu** (—), **10aNi** (·····), and **10aZn** (---). **10aNi** normalized to $\epsilon = 50\,000$ M⁻¹cm⁻¹.

radii of Cu^{II} and Zn^{II} are significantly larger (0.71 Å and 0.74 Å, respectively).²⁸ The central cavity of porphyrins is a little too large to perfectly fit Ni^{II}. Thus, the central metal pulls the coordinating nitrogens inward, leading to a ruffling of the porphyrin ring, whereby the structural rigidity of the macrocycle limits the degree of ruffling. This effect of Ni^{II} on the conformation of porphyrins is well described.^{9,29–31} Secochlorins, by virtue of their ring cleavage and inherent compromised structural stability, are particularly susceptible to a Ni^{II}-induced ruffling.⁹ The ruffling leads to a contraction of the central core and the achievement of ideal Ni–N bond distances. We, therefore, also assume the [indaphyrinato]Ni^{II} complexes to be significantly ruffled. On the other hand, the larger ions, Cu^{II} and Zn^{II}, do not induce any ruffling of porphyrins and, by analogy, in the indaphyrins described here.

Molecular modelling of indaphyrins

We did not succeed in growing crystals suitable for single crystal X-ray diffractometry studies for any of the indaphyrins. None of the derivatives have shown a propensity to form well-defined crystals. In fact, indaphyrins are remarkably well soluble in a wide range of solvents.

In the absence of X-ray diffractometry results, we had to rely upon molecular modelling studies to ascertain the possible conformations of the indaphyrins.³² Fig. 6 shows energy-minimized models of the chromophores **10aH₂**, **12aH₂**, and **10aNi**. The two free base chromophores are expected to be slightly ruffled (root mean square deviation from planarity (rms) of C₂₀N₄ core

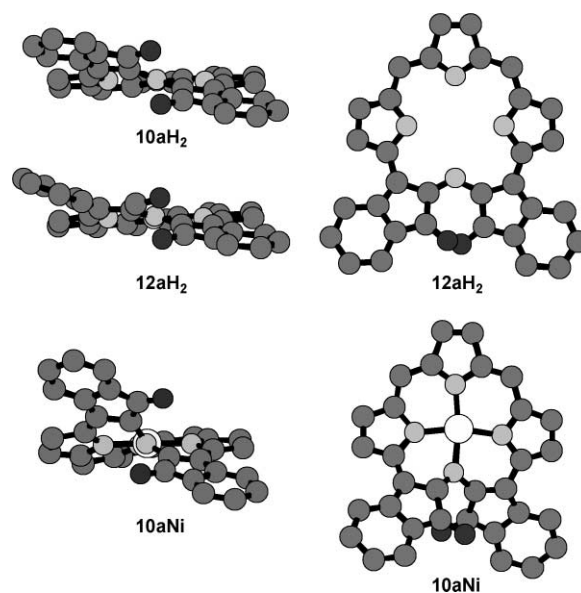


Fig. 6 Molecular models of 1-formyl indaphyrin **12aH₂** and diphenyl-indaphyrins **10aH₂** and **10aNi**. Non-participating phenyl groups included in the calculations but here removed for clarity. MM3 basis set, Ni–N bond distances locked to 1.9 Å, the inferred ‘ideal’ bond distance for square planar Ni^{II}–N bonds of this type.⁹

of **10aH₂**: 0.36 Å, and of **12aH₂**: 0.39 Å). The ruffling appears to be mainly caused by the steric interaction between the two carbonyl functionalities (O–O distance 2.58 Å). The indaphyrin linkage itself appears to cause only a minor distortion of the macrocycle, if any, while the interactions between the *o*'-phenyl proton with the protons of the β-pyrrolic units adjacent to the cleaved pyrrole are likely the origins of non-planarity. The molecular modelling studies of **4H₂**, performed by Barloy *et al.* also show a chromophore which has a deviation from planarity comparable to that of **10aH₂**.¹⁴ The main difference between the two models is that they have different deformation modes (due to the presence, or lack of, a β,β'-bond). As predicted based on the optical properties of the Ni^{II}-complexes of indaphyrins, the ruffling of the free bases is dramatically enhanced in the presence of the central metal Ni^{II} (rms of C₂₀N₄ core of **10aNi**: 0.63 Å). This observation is analogous to observations in other [secochlorinato]Ni^{II}-derived complexes, in particular when comparing the conformation of free base morpholinochlorin **9H₂** (rms of C₂₀N₄ core 0.03 Å)²⁰ and its Ni^{II} complex **9Ni** (rms of C₂₀N₄ core 0.55 Å)⁹. The extreme distortion of the C₂₀N₄ core highlights the response of the ring-fused indaphyrin macrocycle toward a ruffling distortion and likely contributes to the unusual instability of this complex. The degree of distortion may be the upper limit at which [secochlorinato]Ni^{II}-derivatives can be distorted from planarity.

The indaphyrins were computed to be ruffled, *i.e.* they are of idealized C₂-symmetry, they are chiral. We can, at this point, not reliably estimate the barrier of inversion of the two free base enantiomers of **10** but estimate **10aNi** to be conformationally rigid. Thus, racemic resolution of this macrocycle may be possible, as was shown for [morpholinochlorinato]Ni^{II} complexes.³³

Conclusions

In conclusion, we have demonstrated the synthesis of a novel class of secochlorin-based chromophores containing direct *o*-phenyl-to-β-linkages, establishing an indanone unit fused into the porphyrin macrocycle. The indaphyrins are, due to their long-wavelength absorption properties, potentially useful in photomedicine.

Experimental

General

All solvents and reagents used were reagent grade or better and were used as received. The analytical TLC plates were Silicycle ultra pure silica gel 60 (aluminum backed, 250 μm); preparative TLC plates (500 μm silica gel on glass) and the flash column silica gel (standard grade, 60 Å, 32–63 μm) used were provided by Sorbent Technologies, Atlanta, GA. ¹H and ¹³C NMR spectra were recorded on a Bruker DRX400 at ambient temperatures and were referenced to residual solvent peaks. UV-vis spectra were recorded on a Cary 50 spectrophotometer and IR spectra on a Perkin-Elmer Model 834 FT-IR spectrometer. ESI mass spectra were recorded on a Micromass Quattro II. High resolution FAB mass spectra were provided by the Mass Spectrometry Facility, Department of Chemistry and Biochemistry, University of Notre-Dame (Bill Boggess). Elemental analyses were provided by Numega Resonance Labs Inc., San Diego, CA. Compounds **7aH₂**, **7bH₂**, and **7cH₂** were prepared according to the literature procedures.^{8,34}

Preparation of silica gel-supported NaIO₄³⁵. NaIO₄ (2.57 g, 12 mmol) was dissolved in hot water (5 mL, ~70 °C) in a 25 mL round-bottom flask. To the hot solution was added silica gel (10 grams, 40 μ flash grade) under vigorous swirling and shaking. The resulting product was dried in an open vessel at 50 °C for 12 h, resulting in a free flowing powder.

meso-Diphenylindaphyrin (10aH₂). **Method A.** NaIO₄ heterogenized on silica gel (1.0 g) and **7aH₂** (126 mg, 1.94 × 10⁻¹ mmol) are combined in a flask. To this was added 2% TFA/CH₂Cl₂ (40 mL). The solution was stirred for 10 h, after which time Et₃N (5 mL) was slowly added. The solution was filtered to remove the silica gel, and the filter cake washed with CH₂Cl₂ until the filtrate was colorless. The filtrate was washed twice with aq. NaHCO₃, and once with H₂O. The solution was dried (anhydr MgSO₄), filtered, and evaporated to dryness *in vacuo*. **10aH₂** was purified by flash chromatography (CH₂Cl₂ : pet. ether 30–60, 2 : 1, silica gel), and recovered as a microcrystalline powder by slow solvent exchange with MeOH (yield: 44%, 55 mg).

Method B. A slurry of acidified silica gel (silica gel wetted with conc. HCl and air dried, ~500 mg) in CHCl₃ (10 mL amylene-stabilized) containing morpholinochlorin **9H₂** (125 mg) was allowed to react for 12 h. The filtered solution was subjected to preparative TLC chromatography to provide **10aH₂** in 30% yield (33 mg).

Method C. Under an atmosphere of N₂, silica gel-heterogenized NaIO₄ (2.0 g) was added to a stirring solution of **7aAg** (84 mg, 1.1 × 10⁻¹ mmol) in CH₂Cl₂ (15 mL). The reaction proceeded until the starting material was consumed (~15 min), at which point TFA (0.5 mL) was added to the reaction mixture, which then was allowed to stir for an additional 10 min. The solution was filtered to remove the silica gel. The volume of the solution was reduced to ~5 mL and loaded onto a flash chromatography column (CH₂Cl₂/pet ether 30–60, 2 : 1). **10aH₂** was isolated in 20% yield (14 mg). *R_f* (silica–CH₂Cl₂): 0.67; UV-vis (CH₂Cl₂) λ_{max} (log ε): 419 (4.65), 554 (4.61), 639 (4.05), 730 (3.62), 812 (3.29) nm; ¹H NMR (400 MHz, CDCl₃, δ): 1.49 (br s, 1H, exchangeable with D₂O), 7.32 (t, *J* = 7.6 Hz, 1H), 7.64 (t, *J* = 7.7 Hz, 1H), 7.71 (br s, 5H), 7.81 (d, *J* = 7.7 Hz, 1H), 8.14 (s, 1H), 8.24 (d, *J* = 7.7 Hz, 1H), 8.54 (d, *J* = 4.9 Hz, 1H), 9.15 (d, *J* = 4.9 Hz, 1H) ppm; ¹³C NMR (100 MHz, CDCl₃, δ): 116.7, 122.7, 123.7, 124.2, 125.5, 127.1, 128.1, 128.5, 129.4, 130.3, 133.6, 134.1, 134.4, 135.7, 136.2, 140.3, 144.3, 147.9, 155.6, 189.5 ppm; IR (KBr) ν = 1699 cm⁻¹ (C=O); +ESI-MS (70 V, CH₃CN) *m/z* = 643 (MH⁺); HR-MS (FAB⁺ of MH⁺, PEG) calcd for C₄₄H₂₇O₂N₄: 643.2134, found: 643.2145.

[meso-Diphenylindaphyrinato]Ni(II) (10aNi). A solution of **8aNi** (29 mg, 4.1 × 10⁻² mmol) in CHCl₃ (10 mL amylene-stabilized) was treated with TFA vapours obtained from the headspace of a bottle of 10% TFA/CH₂Cl₂, and administered by pipette. After all the starting material was consumed (~15 min, TLC control), the reaction mixture was filtered through a plug of basic alumina. The resulting mixture was separated by preparative TLC chromatography to provide **10aNi** in 80% yield (23 mg). UV-vis (CH₂Cl₂) λ_{max} (rel. intensity): 446 (1.00), 635 (0.20) nm; ¹H NMR (400 MHz, CDCl₃, δ): 7.36–7.39 (t, *J* = 7.3 Hz, 1H), 7.52–7.56 (t, 7.24 Hz, 1H), 7.65 (br s, 3H), 7.84 (d, *J* = 7.3 Hz, 1H), 8.20 (d, *J* = 7.6 Hz, 1H), 8.09 (s, 1H), 8.21 (d, *J* = 7.64 Hz, 1H), 8.50 (d, *J* = 4.84 Hz, 1H), 8.9 (d, *J* = 4.9 Hz, 1H) ppm; ¹³C NMR (100 MHz, CDCl₃, δ): 110.7, 122.6, 124.9, 125.1, 125.3, 126.7, 127.9, 129.8, 130.2, 132.9, 134.9, 139.2, 139.8, 141.5, 141.8, 142.9, 148.5, 206.9 ppm; IR (KBr) ν: 1599 cm⁻¹ (C=O); HR-MS (FAB⁺ of M⁺, PEG) *m/z*: calcd for C₄₄H₂₄N₄NiO₂: 698.1253, found: 698.1262.

[meso-Diphenylindaphyrinato]Cu(II) (10aCu). To a solution of **10aH₂** (20.5 mg, 3.19 × 10⁻² mmol) in DMF was added Cu(OAc)₂·H₂O (9.5 mg, 1.5 eq). The solution was heated to reflux and the reaction progress monitored by TLC. Upon consumption of the starting material, the solution was evaporated to dryness *in vacuo*. The residue was re-dissolved in CH₂Cl₂, and crystallized by slow solvent exchange with MeOH to yield **10aCu** as a black microcrystalline powder in quantitative yield.

(20 mg). R_f (silica- CH_2Cl_2): 0.59; UV-vis (CH_2Cl_2) λ_{max} (log ϵ): 433 (4.48), 462 (4.51), 496 (4.51), 513 (4.51), 667 (3.98), 716 (sh) nm; IR (KBr) ν : 1709 cm^{-1} (C=O); +ESI-MS (70 V, CH_3CN) m/z = 703 (M^+); HR-MS (FAB+ of M^+ , PEG) calcd for $\text{C}_{44}\text{H}_{24}\text{N}_4\text{O}_2\text{Cu}$: 704.1274, found: 704.1296.

[meso-Diphenylindaphyrinato]Zn(II) (10aZn). To a solution of **10aH₂** (26.2 mg, 4.0×10^{-2} mmol) in 10% MeOH- CHCl_3 was added $\text{Zn}(\text{OAc})_2$ (13.3 mg, 6.07×10^{-2} mmol, 1.5 eq). The reaction solution was heated to reflux for ~30 min. Progress of the reaction was monitored by UV-vis. Upon consumption of the starting material, the solution was evaporated to dryness *in vacuo*, the residue re-dissolved in CH_2Cl_2 , and crystallized by slow solvent exchange with ligroine to yield **10aZn** as a black precipitate in quantitative yields (26 mg). R_f (silica- CH_2Cl_2 /1% MeOH): 0.38; UV-vis (DMF) λ_{max} (log ϵ): 425 (4.57), 446 (4.55), 535 (sh), 566 (4.70), 695 (4.07), 747 (sh) nm; ^1H NMR (400 MHz, DMF- d_7 , δ): 7.35 (m, 2H), 7.74 (m, 12H), 8.16 (s, 2H), 8.50 (d, J = 4.6 Hz, 2H), 8.54 (d, J = 7.8 Hz, 2H), 9.37 (d, J = 4.6 Hz, 2H) ppm; ^{13}C NMR (100 MHz, DMF- d_7 , δ): 125.1, 125.1, 126.6, 126.9, 127.7, 128.4, 128.6, 131.6, 131.8, 134.1, 135.8, 136.8, 142.1, 147.6, 149.2, 151.1, 190.3 ppm; IR (KBr) ν : 1702 cm^{-1} (C=O); +ESI-MS (60 V, CH_3CN) m/z = 704 (M^+); HR-MS (FAB+ of M^+ , PEG) calcd for $\text{C}_{44}\text{H}_{24}\text{N}_4\text{O}_2\text{Zn}$: 705.1269, found: 705.1295.

meso-Triphenyl-1-formylindaphyrin (12aH₂). To a stirring solution of **7aH₂** (107 mg, 1.65×10^{-1} mmol) in CH_2Cl_2 (50 mL) were added NaIO_4 heterogenized on silica gel (1 g), followed by TFA vapors administered by pipette from the headspace of a bottle of 10% TFA/ CH_2Cl_2 . The reaction was allowed to proceed until the starting material had been consumed (tlc control, ~20 min), at which point Et_3N (1 mL) was added. The resulting solution was filtered to remove the silica gel, washed twice with conc NaHCO_3 , once with H_2O , dried (anhydr MgSO_4), and evaporated to dryness *in vacuo*. **12aH₂** was purified by flash chromatography (silica gel, CHCl_3). The main fraction was evaporated to dryness, re-dissolved in CH_2Cl_2 , and crystallized by slow solvent exchange with MeOH. Yield 60% yield (64 mg). R_f (silica- CH_2Cl_2): 0.69; UV-vis (CH_2Cl_2) λ_{max} (log ϵ): 425 (4.86), 468 (sh), 541 (sh), 618 (3.95), 678 (3.98), 792 (3.59) nm; ^1H NMR (400 MHz, CDCl_3 , δ): 1.90 (br s, 2H), 7.32 (t, J = 7.3 Hz, 1H), 7.50 (d, J = 7.2 Hz, 1H), 7.58 (t, J = 7.1 Hz, 2H), 7.66 (t, J = 7.6 Hz, 1H), 7.73 (br s, 7H), 7.86 (d, J = 7.2 Hz, 1H), 7.90 (t, J = 7.4 Hz, 2H), 8.08 (d, J = 4.6 Hz, 1H), 8.16 (m, 3H), 8.27 (d, J = 4.6 Hz, 1H), 8.53 (d, J = 5.0 Hz, 1H), 9.09 (d, J = 5.0 Hz, 1H), 9.13 (d, J = 7.2 Hz, 1H), 9.57 (s, 1H) ppm; ^{13}C NMR (100 MHz, CDCl_3 , δ): 112.2, 124.2, 124.2, 125.7, 125.9, 127.4, 127.6, 128.3, 128.4, 128.4, 129.2, 131.9, 133.2, 133.8, 135.0, 136.6, 137.2, 139.3, 140.3, 143.2, 149.6, 153.9, 157.7, 187.3, 190.7 ppm; IR (KBr) ν : 1655 (C=O), 1710 cm^{-1} (C=O); LR-ESI-MS (30 V, CH_3CN) m/z = 645 (MH^+); HR-MS (FAB+ of MH^+ , PEG) calcd for $\text{C}_{44}\text{H}_{29}\text{N}_4\text{O}_2$: 645.2291, found: 645.2334.

[meso-Di(3,4,5-trimethoxyphenyl)-3',4',5'-methoxyindaphyrinato]Ni(II) (10cNi). Prepared in 85% yield (36 mg, 3.5×10^{-2} mmol) according to the procedure for **10aNi**, using **8cNi** (43 mg, 4.1×10^{-2} mmol scale) as starting material. R_f (silica-5% MeOH/ CH_2Cl_2): 0.83; UV-vis (CHCl_3) λ_{max} (rel. intensity): 460 (1.00), 651 (0.35) nm; ^1H NMR (400 MHz, CDCl_3 , δ): 3.84-4.23 (m, 36H), 6.7 (br s), 7.54 (s, 2H), 8.17 (s, 2H), 8.57 (br s), 8.60 (d, J = 8.0 Hz, 2H), 8.85 (d, J = 8.0 Hz, 2H) ppm.

meso-Di(3,4,5-trimethoxyphenyl)-3',4',5'-methoxyindaphyrin (10cH₂). To a stirring solution of *meso*-tetra(3,4,5-trimethoxyphenyl)-2,3-dihydrochlorin **7cH₂** (25 mg, 2.5×10^{-2} mmol) in CH_2Cl_2 (10 mL) were added, by pipette, TFA vapours from the headspace of a bottle containing 10%TFA/ CH_2Cl_2 . To this was added NaIO_4 heterogenized on silica gel (0.25 g). Upon

consumption of the starting material (~20 min), the solution was neutralized with Et_3N (1.0 mL), washed twice with conc NaHCO_3 , once with H_2O , and dried (anhydr MgSO_4). The solution was evaporated to dryness *in vacuo*. **10cH₂** was purified by flash chromatography (1% MeOH/ CH_2Cl_2) and crystallized by slow solvent exchange into MeOH to yield of **10cH₂** in 60% yield (12 mg, 1.1×10^{-2} mmol). R_f (silica-2.5% MeOH/ CH_2Cl_2): 0.24; UV-vis (CH_2Cl_2) λ_{max} (log ϵ): 424 (4.58), 529 (sh), 560 (4.48), 641 (4.00), 692 (sh), 736 (sh), 810 (3.46) nm; ^1H NMR (400 MHz, CDCl_3 , δ): 1.44 (s, 2H), 3.75-4.40 (m, 36H), 7.52 (s, 2H), 8.23 (s, 2H), 8.59 (d, J = 4.8 Hz, 2H), 8.99 (d, J = 4.6 Hz, 2H) ppm; ^{13}C NMR (100 MHz, CDCl_3 , δ): 45.5, 56.3, 56.6, 61.2, 61.6, 62.5, 104.5, 111.6, 113.1, 115.5, 122.4, 123.8, 130.0, 133.6, 133.9, 135.7, 135.9, 138.0, 141.9, 145.0, 145.7, 151.8, 154.7, 155.1, 159.7, 186.6 ppm; IR (KBr) ν : 1696 cm^{-1} (C=O); LR-ESI-MS (30 V, CH_3CN) m/z = 1003 (MH^+); HR-MS (FAB+ of MH^+ , PEG) calcd for $\text{C}_{56}\text{H}_{51}\text{N}_4\text{O}_{14}$: 1003.3402, found: 1003.3401.

meso-Ditolyl-4'-methylindaphyrin (10bH₂). Prepared in 40% yield (8 mg, 1.2×10^{-2} mmol) according to the procedure for **10aH₂**, using **7bH₂** (21 mg, 3.0×10^{-2} mmol scale). R_f (silica- CH_2Cl_2): 0.78; UV-vis (CH_2Cl_2) λ_{max} (log ϵ): 364 (4.52), 420 (4.66), 498 (sh), 524 (sh), 560 (4.58), 644 (4.09), 741 (sh), 818 (3.31) nm; ^1H NMR (400 MHz, CDCl_3 , δ): 1.43 (br s, 2H), 2.43 (s, 6H), 2.64 (s, 6H), 7.41 (d, J = 7.6 Hz, 2H), 7.48 (br s, 4H), 7.61 (s, 2H), 8.11 (d, J = 7.8 Hz, 2H), 8.14 (s, 2H), 8.52 (d, J = 4.8 Hz, 2H), 9.10 (d, J = 5.0 Hz, 2H) ppm; ^{13}C NMR (100 MHz, CDCl_3 , δ): 21.2, 21.4, 122.6, 123.5, 123.8, 126.1, 127.9, 129.8, 130.0, 133.6, 134.0, 134.1, 136.2, 136.4, 137.5, 137.8, 138.6, 144.8, 145.4, 155.8, 189.8 ppm; IR (KBr) ν : 1703 cm^{-1} (C=O); LR-ESI-MS (30 V, CH_3CN) m/z = 699 (MH^+); HR-MS (FAB+ of MH^+ , PEG) calcd for $\text{C}_{48}\text{H}_{35}\text{N}_4\text{O}_2$: 699.2760, found: 699.2786.

[meso-Ditolyl-4'-methylindaphyrinato]Ni^{II} (10bNi). Prepared in 80% yield (43 mg, 5.7×10^{-2} mmol) according to the procedure for **10aNi** using **8bNi** (54 mg, 7.1×10^{-2} mmol scale) as starting material. R_f (silica- CH_2Cl_2 /0.5% MeOH): 0.88; UV-vis (CHCl_3) λ_{max} (rel. intensity): 431 (1.00), 640 (0.20) nm; ^1H NMR (400 MHz, CDCl_3 , δ): 7.36 (d, J = 7.2 Hz, 2H), 7.52 (br s, 6H), 7.67 (s, 2H), 8.12 (s, 2H), 8.13 (d, with overlapping signal, 2H), 8.51 (d, J = 4.6 Hz, 2H), 8.92 (d, J = 4.9 Hz, 2H) ppm; HR-MS (FAB+ of M^+ , PEG) calcd for $\text{C}_{48}\text{H}_{32}\text{N}_4\text{NiO}_2$: 754.19, found: 772.94 (M^+ + H_2O).

meso-Tritolyl-1-formyl-(4'-methyl)indaphyrin (12bH₂). Prepared in 50% yield (8 mg, 1.1×10^{-2} mmol) according to the procedure for **12aH₂**, using **7bH₂** (17 mg, 2.4×10^{-2} mmol scale) as starting material. R_f (silica- CH_2Cl_2): 0.70; UV-vis (CH_2Cl_2) λ_{max} (log ϵ): 427 (4.71), 470 (sh), 550 (sh), 626 (3.83), 682 (3.91), 795 (3.42) nm; ^1H NMR (400 MHz, CDCl_3 , δ): 1.96 (br s, 2H), 2.43 (s, 3H), 2.62 (m, 9H), 7.45 (m, 8H), 7.68 (m, 2H), 7.82 (br s, 2H), 8.02 (d, J = 7.8, 1H), 8.08 (d, J = 4.6, 1H), 8.14 (d, J = 4.6, 1H), 8.17 (d, J = 4.6, 1H), 8.26 (d, J = 4.6, 1H), 8.51 (d, J = 5.0, 1H), 8.99 (d, J = 7.4, 1H), 9.03 (d, J = 5.0, 1H), 9.51 (s, 1H) ppm; ^{13}C NMR (100 MHz, CDCl_3 , δ): 21.6, 21.9, 22.0, 30.2, 112.5, 124.2, 124.3, 125.8, 126.6, 127.3, 127.3, 128.3, 128.4, 131.8, 133.2, 133.9, 135.1, 136.0, 137.4, 138.1, 138.4, 138.6, 139.4, 143.6, 147.4, 154.1, 158.1, 187.6, 191.0 ppm; IR (KBr) ν : 1711 (C=O), 1662 cm^{-1} (C=O); LR-ESI-MS (30 V, CH_3CN) m/z = 701 (MH^+); HR-MS (FAB+ of MH^+ , PEG) calcd for $\text{C}_{48}\text{H}_{37}\text{N}_4\text{O}_2$: 701.2917, found: 701.2878.

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