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Metal catalyst-free amination of *meso*-bromoporphyrins: an entry to supramolecular porphyrinoid frameworks

Mihaela Carmen Balaban [a,b], Cyril Chappaz-Gillot [c], Gabriel Canard [c], Olaf Fuhr [a,b], Christian Roussel [c], Teodor Silviu Balaban [a,b,c,*]

[a] *Karlsruhe Institute of Technology, Forschungszentrum Karlsruhe, Institute for Nanotechnology, Postfach 3640, D-76021 Karlsruhe, Germany*
[b] *Center for Functional Nanostructures at the Universität Karlsruhe (TH), Germany*
[c] *Université Paul Cézanne Aix-Marseille III, UMR 6263 - ISM2-Chirosciences, Faculté des Sciences de Saint-Jérôme Case A 62, Avenue Escadrille Normandie-Niemen, F-13397 Marseille Cedex 20, France*

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ABSTRACT

meso-Bromoporphyrins can be conveniently substituted by primary and secondary amines in a metal catalyst-free reaction which gives access to a large variety of *meso*-*N*-substituted derivatives. In some cases, considerable acceleration of this amination can be effected under microwave irradiation. The amino anchor on the porphyrin skeleton is useful for constructing novel self-assembling porphyrinoids as demonstrated by a single crystal X-ray analysis as well as stationary absorption and fluorescence spectroscopies.

1. Introduction

The Buchwald–Hartwig palladium catalysed aminations have had an enormous impact on modern synthetic methodologies allowing the preparation in high yields of almost any secondary or sterically unhindered tertiary amines from aryl or hetaryl halogenides.[1,2] However for pharmaceutical applications, where amine functionalities abound, even at low catalyst loadings, a complete removal of the transition (or noble) metal catalysts still remains a challenge and drastically augments the costs, if large scale chromatographic separations have to be performed. Very recently, scavenging of palladium to 100 ppm was demonstrated by means of a simple sodium bisulfite wash at 60 °C,[3] however other functionalities in the final coupled molecules must resist this reductive treatment. Porphyrins can be easily reduced to chlorins or even bacteriochlorins under these conditions.[4] In the present article we report a catalyst-free direct amination of *meso*-bromo-substituted porphyrins. Porphyrinoids are currently an active field of research for third generation photodynamic therapy (PDT) agents[5] and due to their rich coordination chemistry, magnetic resonance imaging (MRI) contrast agents[6] can be relatively easily developed. Other potential applications relate to dye-sensitized solar cells.[7] We have been interested in self-assembling porphyrins, which are biomimetic light-harvesting systems.[8] Self-assembly is used by green photosynthetic bacteria to fabricate a peculiar antenna system, the so-called chlorosome (green sac), which agglomerates bacteriochlorophyll (BChl) *c*, *d*, or *e* molecules. We have been successful in engineering the same groups as in BChl's,[9] or other recognition groups,[10] onto desired positions of porphyrins and chlorins. As such, a preparatively useful method for directly linking a substituted amine onto a porphyrin skeleton, by circumventing the use of any transition metal catalyst and which can be easily upscaled for obtaining a pure active pharmaceutical ingredient (API), or other novel self-assembling porphyrins, is of timely interest.

2. Results and discussion

2.1. Syntheses

Scheme 1 presents the title reaction which we encountered serendipitously while trying to synthesize push–pull porphyrins substituted by 5-amino and 15-cyano groups.[11] In an experiment with 5-bromo-15-cyanoporphyrin, in order to test its stability towards weak bases and heating and to check for the formation of secondary products, we heated it to reflux in morpholine in the absence of any metal catalyst. We were surprised by the high yield of direct amination product and in subsequent trials we could definitely exclude that this reaction could be due to trace amounts of metal catalyst adsorbed on the walls of glass vessels. This metal-free nucleophilic substitution of an aromatic bromide by amines is not unprecedented as shown by Imahori and co-workers for

* Corresponding author. Tel.: +49 724 782 6415; fax: +49 724 782 9030.
E-mail addresses: silviu.balaban@int.fzk.de, ts.balaban@univ-cezanne.fr (T.S. Balaban).

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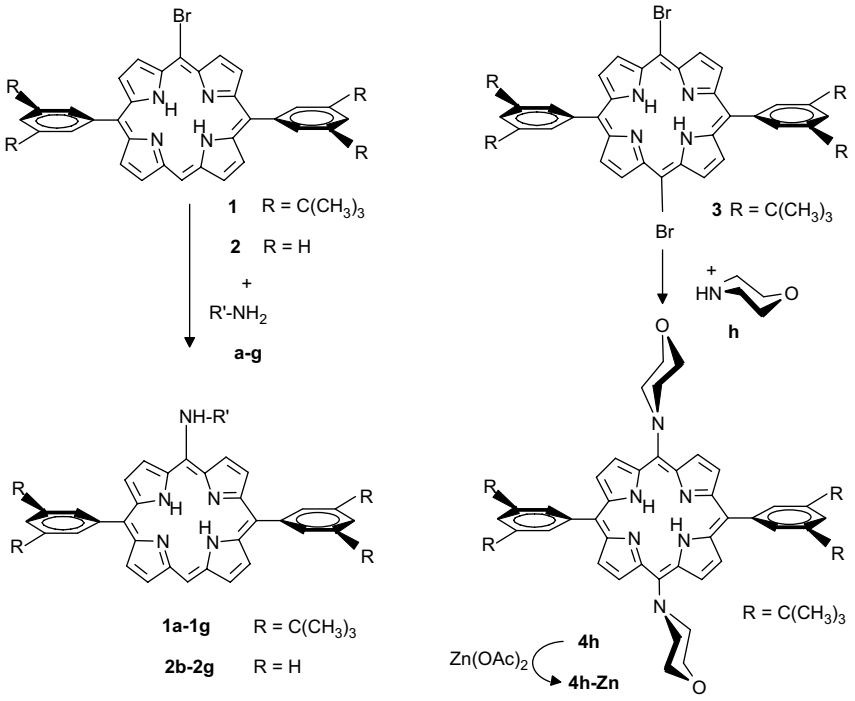

Scheme 1. See Table 1 for reaction conditions and yields.

a bromoperylene tetracarboxylic acid diimide.[12] Two other substitutions at sp^2 carbon atoms have been described recently.[13] Another earlier example includes the substitution of 2- and 4-chloronitrobenzene by piperidine.[14] The herein described bromine replacement is however novel to porphyrin chemistry allowing direct coupling of primary and secondary amines to the *meso*-positions. The bromine atoms substituting a β-pyrrolic position in *meso*-tetraphenylporphyrin do not react even upon prolonged heating or microwave irradiation. In the presence of palladium catalysts the β-bromine atoms can be substituted but may also lead to cyclized products onto the neighbouring *meso*-phenyl group.[15] Examples of amino-substituted porphyrins, which were obtained by Pd or Ni catalysis have been described before.[16] Senge has pioneered other nucleophilic substitutions at the *meso*-positions of porphyrins,[17] which in our case, do not require an oxidant for rearomatization of the intermediate phlorin.

Table 1 presents the herein explored direct aminations with reaction conditions and yields. It is advantageous if a liquid (or molten) amine is used in great excess as solvent that can be easily recovered at the end of the reaction by vacuum stripping, leaving a solid residue, which can be then conveniently purified by column chromatography. Alternatively, a solvent such as tetrahydrofuran can be used. Yields increase with reaction time and excess of amine on the order of 400 equiv. Primary alkyl amines generally gave

Table 1
Isolated yields and reaction times of *meso*-bromoporphyrins **1** and **2** at room temperature

Entry	Porphyrin	Amine	R′NH_2	Equiv of amine	Product	Time (min)	THF (mL/mmol)	Yield[a] (%)
1	**1**	**a**	$CH_3CH_2CH_2NH_2$	400	**1a**	1440	76	72*
1 MW	***1***	***a***		*200*	***1b***	*40*		*75*
2	**1**	**b**	$CH_3CH_2CH_2CH_2NH_2$	400	**1b**	120		91*
2 MW	***1***	***b***		*200*	***1b***	*40*		*95*
3	**1**	**c**	$C_6H_5CH_2NH_2$	400	**1c**	90		36**
3 MW	***1***	***c***		*200*	***1c***	*3*		*99*
4	**1**	**d**	(4-H_3CO-C_6H_4)-CH_2NH_2	400	**1d**	180		46**
4 MW	***1***	***d***		*200*	***1d***	*3*		*77*
5	**1**	**e**	(4-F-C_6H_4)-CH_2NH_2	400	**1e**	90		12**
5 MW	***1***	***e***		*200*	***1e***	*6*		*89*
6	**1**	**f**	$H_2NCH_2CH_2NH_2$	200	**1f**	1440	96	78**
7	**1**	**g**	$HOCH_2CH_2NH_2$	400	**1g**	1440	96	40*/30**
8	**1**	**h**	4-CH_3-C_6H_4-NH_2	130	**1h**	840		36**
9	**2**	**a**	$CH_3CH_2CH_2NH_2$	200	**2a**	1200	11	52**
10	**2**	**b**	$CH_3CH_2CH_2CH_2NH_2$	200	**2b**	120		50**
11	**2**	**c**	$C_6H_5CH_2NH_2$	200	**2c**	90		40**
11 MW	***2***	***c***		*200*	***2c***	*3*		*89*
12	**2**	**f**	$H_2NCH_2CH_2NH_2$	200	**2f**	300	11	53**
12 MW	***2***	***f***		*200*	***2f***	*13*		*47*
13	**2**	**g**	$HOCH_2CH_2NH_2$	200	**2g**	480	11	48**
13 MW	***2***	***g***		*200*	***2g***	*3*		*10*

[a] The yields denoted by ** are isolated yields after column chromatography and recrystallization; yields denoted by * are isolated yields after column chromatography. All other yields are based on ^{1}H NMR integrals from the crude reaction mixtures. Microwave experiments are italicized and details such as power and ramping settings can be found in Supplementary data.

higher yields than variously substituted benzyl amines while anilines reacted more sluggishly.

The *meso*-bromoporphyrins **1** and **2** also did not react directly with alcohols, alkoxides, or sulfides. The substitution reactions with ethylenediamine and ethanolamine provide synthons, which can be readily derivatized to various porphyrin conjugates.

It is interesting to note a considerable acceleration of the reaction in some cases by using microwaves. While benzylamine reacts quantitatively after 3 min, propylamine and butylamine, due to their low boiling points, needed longer microwave irradiation times under pressure (5–10 bar). On the contrary, even after prolonged irradiation and heating up to 180 °C, *p*-toluidine did not react at ambient pressure. Palladium catalysed aminations under microwave irradiation have been extensively studied by Maes and co-workers,[18] while microwave-assisted uncatalysed amination of (hetero)aryl halides or triflates have been recently described,[19] and reviewed.[20] Details of the microwave experiments are given in Supplementary data.

The advantage of a metal catalyst-free reaction, besides of considerably lowering the costs, resides mainly in the easier purification of the products. Especially Pd-catalysts although very versatile, lead to tailing in chromatographic separations, which thus often need to be repeated with different eluents and/or stationary phases.

In the case where the amine is solid or when the solubility of the porphyrins in the amine is low (for instance in the cases **a**, **f**, and **g**) use of a cosolvent such as THF is recommended. Table 2 (in the Experimental section) lists the solubilities of porphyrins **1** and **2** in the various amines employed here.

The potential for further functionalization of *N*-substituted porphyrins is illustrated by the 5,15-dimorpholinyl-porphyrin **4**, which was obtained from the corresponding 5,15-dibromoporphyrin (**3**) in 49% yield.[11] In a similar reaction of porphyrin **1** with morpholine (**h**) the monomorpholinyl-porphyrin **1h** (not depicted in Scheme 1) was obtained in 61% yield.[11] The free bases **1h** and **4h** could be easily metallated with zinc acetate to give the corresponding new compounds **1h-Zn** and **4h-Zn** in good yields.

2.2. Self-assembly in nonpolar solvents of 4h-Zn

In nonpolar solvents the dimorpholinyl zinc porphyrin **4h-Zn** self-assembles giving broad and redshifted peaks similar to other synthetic bacteriochlorophyll mimics.[8–10] Figure 1A presents the absorption spectra in dry *n*-heptane while Figure 1B shows the stationary fluorescence spectra upon excitation of the Soret band of the monomer (at 420 nm) or of the aggregated species (at ~455 nm). Upon methanol addition the aggregate bands disappear giving rise to the monomeric spectrum of the **4h-Zn**·**MeOH** adduct (dotted traces).

The fluorescence of the aggregates is self-quenched by a factor of ten in comparison to the monomers. However, the fact that it is not entirely quenched, as is the case with most chromophores in the solid state, speaks for an orderly arrangement within the self-assembled species.

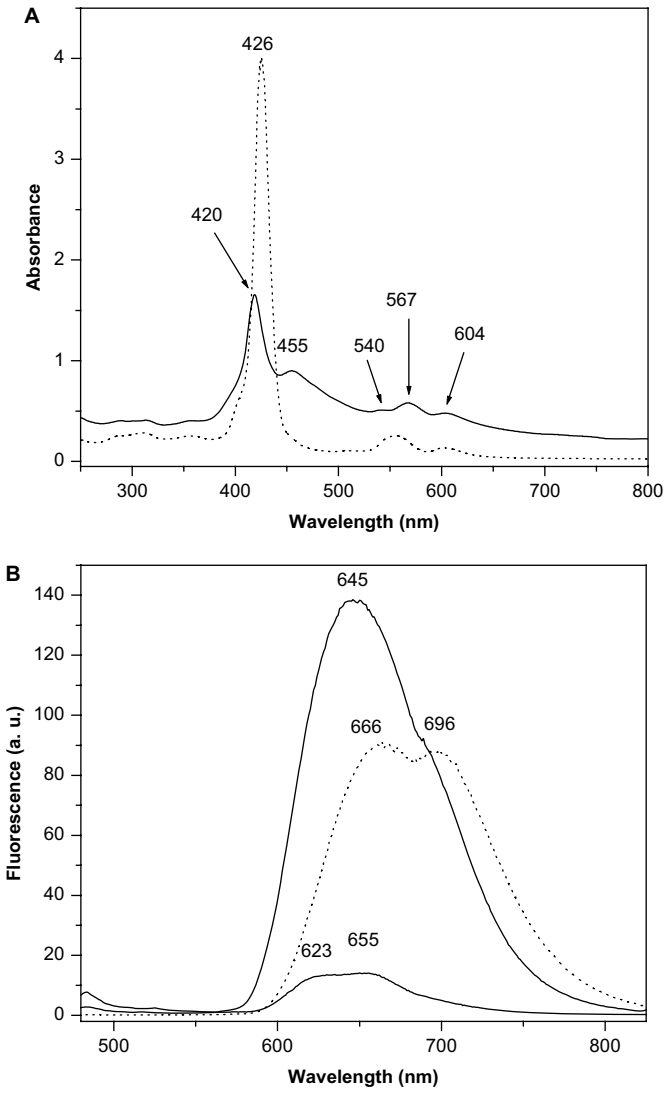

Figure 1. (A) Full trace: 50 μL of a 1.5 mM concentrated homogeneous dispersion (1.4 mg in 500 μL) of **4h-Zn** in dry methylene chloride is injected into 3 mL of dry *n*-heptane (to give a final concentration of 25 μM) and shaken vigorously. The baseline shift is due to light scattering by the greenish-red suspension. Dotted trace: absorption spectrum of the same cuvette after addition of 100 μL methanol, threefold dilution with *n*-heptane and 250 μL methylene chloride to ensure a homogeneous solution. (B) Corresponding fluorescence spectra: intense full trace upon 420 nm excitation; quenched full trace upon 458 nm excitation; dotted trace after methanol addition and dilution (426 nm excitation). Pathlength of the quartz cuvette was 1 cm and the fluorescence spectra are uncorrected.

Table 2
Solubilities of porphyrins **1** and **2** in different amines at 25 °C or upon heating under reflux of the amine or of THF, which can be added as a cosolvent[a]

Amine	R′NH_2	25 °C	Δ
a	$CH_3CH_2CH_2NH_2$	−	
b	$CH_3CH_2CH_2CH_2NH_2$	++	++
c	$C_6H_5CH_2NH_2$	+	++
d	(4-H_3CO-C_6H_4)-CH_2NH_2	+	++
e	(4-F-C_6H_4)-CH_2NH_2	+	++
f	$H_2NCH_2CH_2NH_2$	−	+
g	$HOCH_2CH_2NH_2$	−−	−

[a] ++ signifies complete solubility; + signifies good solubility; − signifies poor solubility; and −− signifies insoluble.

Self-assembly of **4h-Zn** occurs also in dry methylene chloride at high concentrations. Upon dilution the aggregate maxima (at 453 nm and 613 nm) gradually decrease (Fig. 2).

The monomorpholino compound **1h-Zn** stays under the same conditions monomeric as no changes in the absorption spectra either in dry dichloromethane or in *n*-heptane are encountered. In the MALDI-TOF mass spectra however a dimer peak cluster could be reproducibly observed.

2.3. Self-assembly in the crystal of 4h-Zn

Upon zinc metallation the metal core becomes a coordination center for morpholinyl oxygens of neighbouring porphyrins. This strong 2.20 Å Zn–O ligation in the crystal of **4h-Zn** leads to

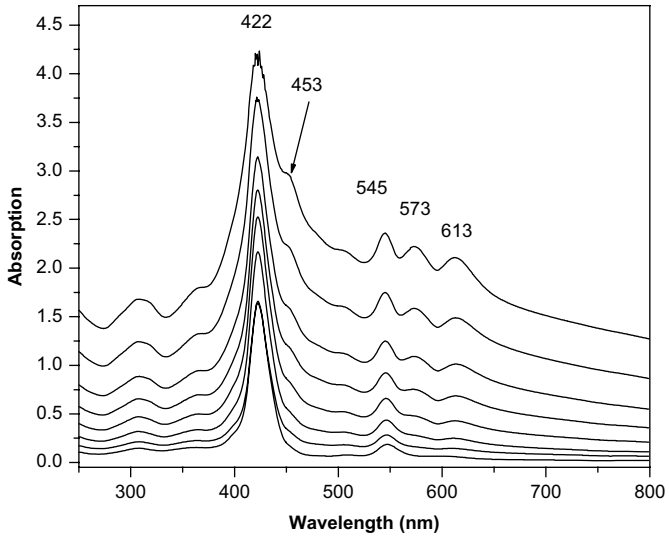

Figure 2. Dilution of a concentrated dispersion of **4h-Zn** in dry dichloromethane. The concentrations from the top trace to the bottom trace were (mM): 1.5, 1.0, 0.6, 0.48, 0.36, 0.3, 0.2, 0.15. The strongly light scattering suspension of the more concentrated dispersion lead to a baseline shift, which was not corrected in the spectra (raw data are presented). The topmost trace slightly saturates the detector at the Soret band (422 nm) of the monomeric form.

a framework of stacked porphyrins with an interesting nano-architecture. Figure 3 shows the monomeric unit as well as the supramolecular assembly where beside the Zn–O ligations, multiple hydrophobic interactions between the di-*tert*-butylphenyl groups assure a dense packing, which does not include the crystallization solvents chloroform and cyclohexane. The zinc atoms are 5-coordinate and only one morpholinyl oxygen in each porphyrin binds to a zinc atom in an adjacent porphyrin while again only one of its two morpholinyl groups ligates the next porphyrin in the stack. The spectator morpholinyl groups are more than 4.5 Å away from any bonding atom. It is indeed intriguing that only one morpholinyl group participates in the orchestration of the network. This could be due to the preference of the zinc atom for a fivefold coordination in spite of the extra free ligand, which could enable a sixfold coordinated zinc atom. At present it is still challenging to predict crystal structure packings, especially with porphyrins where several weak interactions abound. The stacking axes passing through the zinc atoms are parallel and the slightly domed porphyrin planes are inclined with 55° to these axes. The two porphyrin planes are inclined with 70° to each other.

The encountered stacking of the porphyrin macrocycles has a spacing, which is much increased in comparison with the usual 3.45 Å π–π stacking distance. As such the π–π interaction is

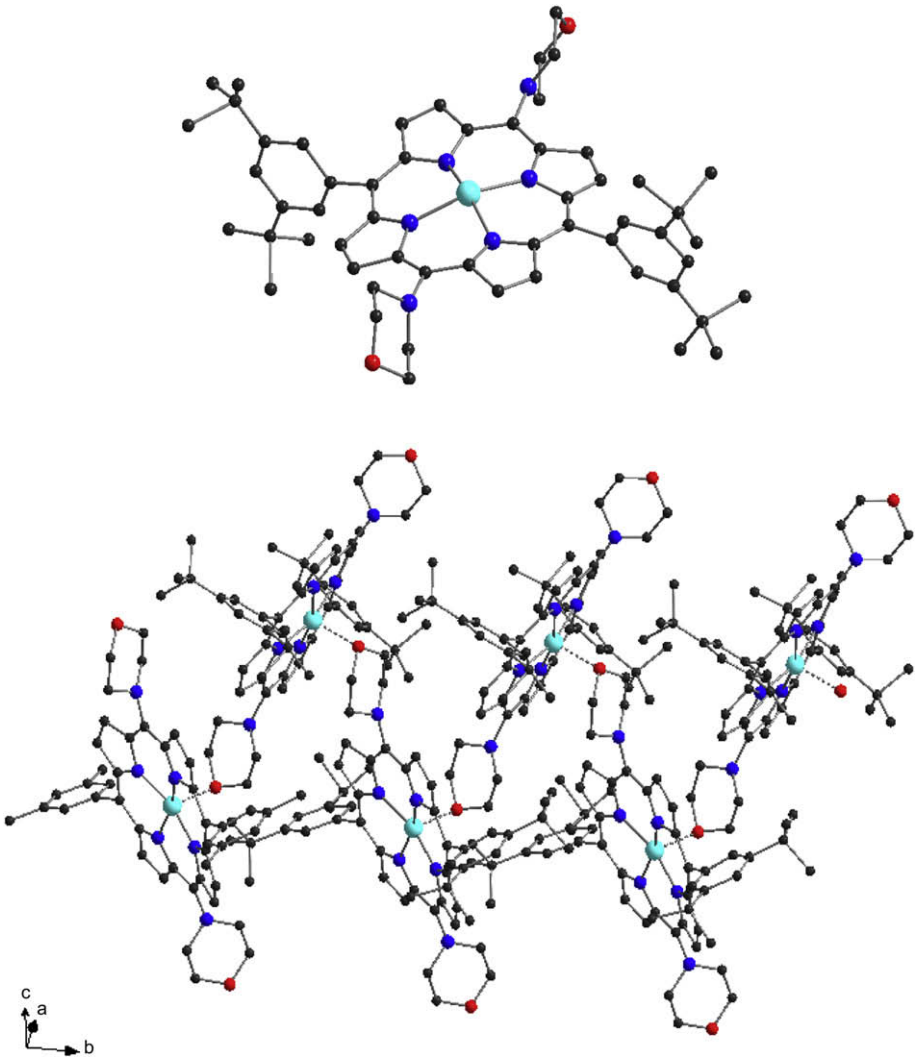

Figure 3. Top: monomeric **4h-Zn**. Bottom the porphyrinoid network assembled by Zn–O ligations. Colour coding: carbon-black, nitrogen-blue, hydrogen-red and zinc-cyan. Hydrogen atoms were omitted for clarity.

recessive the crystal structure being dominated by the strong Zn–O ligations. This weak coupling of the chromophore with a Zn–Zn distance of 10.0 Å within a stack and 9.19 Å in between adjacent stacks can lead to efficient exciton diffusion. Architectures of stacked bacteriochlorophylls are encountered in light-harvesting systems of green photosynthetic bacteria,[8–10,21] which we are trying to mimic with fully synthetic and more robust porphyrinoid pigments.

In conclusion we have developed a new and facile direct amination of *meso*-bromo-substituted porphyrins. With ethylenediamine or ethanolamine a second functionality can be easily introduced, which may be used for further coupling in porphyrinic conjugates. The Zn-metalated bis-morpholinyl porphyrin **4h-Zn** self-assembles both in nonpolar solvents and in the crystal.

3. Experimental part

3.1. General methods

^{1}H NMR (300 MHz or 200 MHz) spectra were recorded on Bruker Avance 300 or Avance 200 spectrometers and are referenced with respect to the residual solvent peaks, e.g., 7.26 ppm for the proton of $CHCl_3$. Mass spectra were routinely performed as MALDI-TOF on a Voyager, Applied Biosystems instrument using as the matrix 1,8,9-anthracenetriol (dithranol). High resolution mass spectra were recorded either as FAB on a Finnigan MAT 90 instrument with 3-nitrobenzyl alcohol as the matrix, or as electrospray on a QStar Elite spectrometer from Applied Biosystems SCIEX using in both cases PEG oligomers as internal standard. UV–vis spectra were measured either with a Shimadzu UV-2401 (PC) instrument or for the self-assembly experiments on a Varian Cary 500 equipped with a Peltier temperature controller. Stationary fluorescence spectra were recorded on a Varian Eclipse fluorimeter in 1×1 cm quartz cuvettes. Porphyrins **1** and **2** were synthesized and purified according to procedures in the literature.[22] Dichloromethane was distilled from calcium hydride while cyclohexane and *n*-heptane were freshly distilled from sodium metal. The other reagents and solvents were commercially bought and used as received. Reactions were monitored by thin layer chromatography (Merck, silica gel 60). Column flash chromatography was performed on silica gel (SDS, 35–70 μm). Microwave experiments were performed in 10 mL sealed tubes within the cavity of a professional focused *Discover* microwave oven from *CEM*. Colour changes or precipitation could be followed during the irradiation period with an external video camera connected via fiber optics.

3.2. General procedure for the amination of 5-bromo-10,20-bis(3,5-di-*tert*-butylphenyl)porphyrin

A solution of the porphyrin **1** (50 mg, 65 μmol, 1 equiv) in excess amine (400 equiv) and eventually tetrahydrofuran (90 mL/mmol of porphyrin) for the insoluble porphyrins (see Table 2) was heated at reflux under argon. The mixture was evaporated and the residue was deposited onto silica gel by vacuum evaporation. Column chromatography on silica gel eluted with the appropriate eluent affords the product, which was, if possible, recrystallized to get the pure product.

3.2.1. 5-Propylamino-10,20-bis(3,5-di-tert-butylphenyl) porphyrin (*1a*)

Following the general procedure with tetrahydrofuran, after 24 h of reflux (note that the boiling point of propylamine is 48 °C) and chromatography (dichloromethane, R_f=0.32), the porphyrin **1a** was obtained as a dark green solid (35 mg, 72% yield). ^{1}H NMR (200 MHz, $CDCl_3$; δ, ppm): 9.64 (H-*meso*, 1H, s), 9.26 (H-β, 2H, d, ^3J=4.7 Hz), 9.03 (H-β, 2H, d, ^3J=4.7 Hz), 8.83 (H-β, 2H, d, ^3J=4.7 Hz), 8.71 (H-β, 2H, d, ^3J=4.7 Hz), 8.06 (Ar–H, 4H, d, ^4J=1.8 Hz), 7.80 (Ar–H, 2H, t, ^4J=1.8 Hz), 4.37 (CH_2NH, 2H, t, ^3J=7.2 Hz), 2.08 (CH_2CH_3, 2H, m), 1.56 ($C(CH_3)_3$, 36H, s), 1.03 (CH_2CH_3, 3H, t, ^3J=7.4 Hz), −1.69 (NH, 2H, s). UV–vis [$CHCl_3$, λ_{max} (log ε_{max}), nm]: 423 (5.05), 459 (3.75), 524 (3.63), 574 (3.76), 669 (3.64).

3.2.2. 5-Butylamino-10,20-bis(3,5-di-tert-butylphenyl) porphyrin (*1b*)

Following the general solvent-free procedure, after 2 h of reflux and chromatography (dichloromethane, R_f=0.20), the porphyrin **1b** was obtained as a dark green solid (45 mg, 91% yield). ^{1}H NMR (200 MHz, $CDCl_3$; δ, ppm): 9.64 (H-*meso*, 1H, s), 9.25 (H-β, 2H, d, ^3J=4.6 Hz), 9.03 (H-β, 2H, d, ^3J=4.6 Hz), 8.83 (H-β, 2H, d, ^3J=4.6 Hz), 8.71 (H-β, 2H, d, ^3J=4.6 Hz), 8.05 (Ar–H, 4H, d, ^4J=1.8 Hz), 7.79 (Ar–H, 2H, t, ^4J=1.8 Hz), 4.40 (CH_2NH, 2H, t, ^3J=7.2 Hz), 2.05 ($CH_2CH_2CH_2$, 2H, m), 1.67 (CH_2CH_3, 2H, m), 1.56 ($C(CH_3)_3$, 36H, s), 1.03 (CH_2CH_3, 3H, t, ^3J=7.4 Hz), −1.69 (NH, 2H, s). UV–vis [$CHCl_3$, λ_{max} (log ε_{max}), nm]: 421 (5.00), 457 (3.95), 517 (3.65), 576 (3.65), 670 (3.52).

3.2.3. 5-Benzylamino-10,20-bis(3,5-di-tert-butylphenyl)-porphyrin (*1c*)

Following the general solvent-free procedure, after 1.5 h of reflux, chromatography (dichloromethane/hexane 7:3, R_f=0.30) and slow recrystallization from diethyl ether, porphyrin **1c** was obtained as a purple powder (19 mg, 36% yield). ^{1}H NMR (200 MHz, $CDCl_3$; δ, ppm): 9.73 (H-*meso*, 1H, s), 9.21 (H-β, 2H, d, ^3J=4.8 Hz), 9.09 (H-β, 2H, d, ^3J=4.7 Hz), 8.90 (H-β, 2H, d, ^3J=4.7 Hz), 8.74 (H-β, 2H, d, ^3J=4.8 Hz), 8.09 (Ar–H, 4H, d, ^4J=1.8 Hz), 7.82 (Ar–H, 2H, t, ^4J=1.8 Hz), 7.39–7.60 (Bz–H, 5H, m), 5.57 (CH_2, 2H, s), 1.57 ($C(CH_3)_3$, 36H, s), −1.81 (NH, 2H, s). HRMS-ESI ($[M+H]^+$): found 792.4999, calcd 792.5000 for $C_{55}H_{61}N_5$. UV–vis [$CHCl_3$, λ_{max} (log ε_{max}), nm]: 423 (5.29), 524 (3.77), 571 (3.89), 668 (3.76).

3.2.4. 5-(4-Methoxybenzylamino)-10,20-bis(3,5-di-tert-butylphenyl)porphyrin (*1d*)

Following the general solvent-free procedure, after 3 h of reflux, chromatography (dichloromethane, R_f=0.33) and recrystallization from ethanol, porphyrin **1d** was obtained as a dark purple powder (25 mg, 46% yield). ^{1}H NMR (300 MHz, $CDCl_3$; δ, ppm): 9.72 (H-*meso*, 1H, s), 9.20 (H-β, 2H, d, ^3J=4.5 Hz), 9.09 (H-β, 2H, d, ^3J=4.5 Hz), 8.92 (H-β, 2H, d, ^3J=4.8 Hz), 8.75 (H-β, 2H, d, ^3J=4.8 Hz), 8.11 (Ar–H, 4H, d, ^4J=1.8 Hz), 7.85 (Ar–H, 2H, t, ^4J=1.8 Hz), 7.46 (Bz–H, 2H, d, ^3J=8.6 Hz), 6.92 (Bz–H, 2H, d, ^3J=8.6 Hz), 5.52 (CH_2, 2H, s), 3.81 (CH_3, 3H, s), 1.56 ($C(CH_3)_3$, 36H, s), −1.78 (NH, 2H, s). HRMS-ESI ($[M+H]^+$): found 822.5102, calcd 822.5105 for $C_{56}H_{63}N_5O$. UV–vis [$CHCl_3$, λ_{max} (log ε_{max}), nm]: 423 (5.25), 525 (3.68), 573 (3.87), 670 (3.73).

3.2.5. 5-(4-Fluorobenzylamino)-10,20-bis(3,5-di-tert-butylphenyl)porphyrin (*1e*)

Following the general solvent-free procedure, after 1.5 h of reflux, chromatography (dichloromethane/hexane 7:3, R_f=0.49) and recrystallization from ethanol, porphyrin **1e** was obtained as a dark purple powder (6 mg, 12% yield). ^{1}H NMR (300 MHz, $CDCl_3$; δ, ppm): 9.76 (H-*meso*, 1H, s), 9.18 (H-β, 2H, d, ^3J=4.5 Hz), 9.10 (H-β, 2H, d, ^3J=4.6 Hz), 8.90 (H-β, 2H, d, ^3J=4.8 Hz), 8.75 (H-β, 2H, d, ^3J=4.5 Hz), 8.07 (Ar–H, 4H, d, ^4J=1.8 Hz), 7.81 (Ar–H, 2H, t, ^4J=1.8 Hz), 7.47–7.51 (Bz–H, 2H, m), 7.05 (Bz–H, 2H, t, ^3J=8.4 Hz), 5.50 (CH_2, 2H, s), 1.56 ($C(CH_3)_3$, 36H, s), −1.91 (NH, 2H, s). ^{19}F NMR (282 MHz, $CDCl_3$; δ, ppm): −115.1. HRMS-ESI ($[M+H]^+$): found 810.4901, calcd 810.4906 for $C_{55}H_{60}N_5F$. UV–vis [$CHCl_3$, λ_{max} (log ε_{max}), nm]: 421 (5.22), 522 (3.69), 569 (3.80), 667 (3.60).

3.2.6. 5-(2-Aminoethylamino)-10,20-bis(3,5-di-tert-butylphenyl)porphyrin (*1f*)

Following the general procedure with tetrahydrofuran, after 24 h of reflux, chromatography (dichloromethane/methanol 10:1, R_f=0.32) and recrystallization from diethyl ether, porphyrin **1f** was obtained as a dark purple powder (38 mg, 78% yield). ^{1}H NMR (200 MHz, $CDCl_3$; δ,

ppm): 9.65 (H-*meso*, 1H, s), 9.38 (H-β, 2H, d, ^3J=4.7 Hz), 9.03 (H-β, 2H, d, ^3J=4.7 Hz), 8.84 (H-β, 2H, d, ^3J=4.7 Hz), 8.71 (H-β, 2H, d, ^3J=4.7 Hz), 8.06 (Ar–H, 4H, d, ^4J=1.8 Hz), 7.80 (Ar–H, 2H, t, ^4J=1.8 Hz), 4.43 (CH_2NH, 2H, t, J=5.6 Hz), 3.29 (CH_2NH$_2$, 2H, t, J=5.6 Hz), 1.56 (C(CH_3)$_3$, 36H, s), −1.69 (NH, 2H, s). HRMS-ESI ([M+H]$^+$): found 745.4943, calcd 745.4952 for $C_{50}H_{60}N_6$. UV–vis [$CHCl_3$, λ_{max} (log ε_{max}), nm]: 422 (5.31), 523 (3.83), 572 (3.93), 668 (3.81).

3.2.7. 5-(2-Hydroxyethylamino)-10,20-bis(3,5-di-tert-butylphenyl)porphyrin (**1g**)

Following the general procedure with tetrahydrofuran, after 24 h of reflux and chromatography (dichloromethane/methanol 100:2.5, R_f=0.23), the porphyrin **1g** was obtained as a dark purple oil (15 mg, 30% yield). ^{1}H NMR (200 MHz, $CDCl_3$; δ, ppm): 9.76 (H-*meso*, 1H, s), 9.41 (H-β, 2H, d, ^3J=4.7 Hz), 9.09 (H-β, 2H, d, ^3J=4.7 Hz), 8.89 (H-β, 2H, d, ^3J=4.7 Hz), 8.78 (H-β, 2H, d, ^3J=4.7 Hz), 8.07 (Ar–H, 4H, d, ^4J=1.8 Hz), 7.80 (Ar–H, 2H, t, ^4J=1.8 Hz), 4.53 (CH_2NH, 2H, t, ^3J=5.2 Hz), 4.11 (CH_2OH, 2H, t, ^3J=5.2 Hz), 1.56 (C(CH_3)$_3$, 36H, s), −2.01 (NH, 2H, s). UV–vis [$CHCl_3$, λ_{max} (log ε_{max}), nm]: 421 (5.26), 523 (3.80), 567 (3.91), 664 (3.76).

3.2.8. 5-(4-Toluidin-1yl)-10,20-bis(3,5-di-tert-butylphenyl) porphyrin (**1h**)

5-Bromo-10,20-bis(3,5-di-*tert*-butylphenyl)21*H*,23*H*-porphine (**1**, 50 mg, 0.065 mmol) was heated overnight with 3.0 g *p*-toluidine at 140 °C under nitrogen. Then the reaction mixture was cooled at room temperature and extracted in the minimal quantity of dichloromethane. Column chromatography (L=25 cm, Φ=3 cm) after elution with dichloromethane gave a first intensely coloured fraction, which after evaporation of the solvent gave a brick red powder. Recrystallization from hot chloroform to which methanol was added until a cloudy suspension was formed, afforded after cooling to −20 °C, 18.7 mg of pure **1h** (36% yield).

R_f (CH_2Cl_2)=0.82. ^{1}H NMR (300 MHz, $CDCl_3$; δ, ppm): 10.10 (H-5, 1H, s), 9.35 (H-13 and H-17, 2H, d, ^3J=4.8 Hz), 9.27 (H-3 and H-7, 2H, d, ^3J=4.5 Hz), 9.01 (H-2 and H-8, 2H, d, ^3J=4.5 Hz), 8.86 (H-12 and H-18, 2H, d, ^3J=4.8 Hz), 8.09 (2″,6″-Ar–H, 4H, d, ^4J=1.8 Hz), 7.81 (4″-Ar–H, 2H, t, ^4J=1.8 Hz), 6.98 (3′,5′-$C_6H_4CH_3$, 2H, d, ^3J=8.4 Hz), 6.80 (2′,6′-$C_6H_4CH_3$, 2H, d, ^3J=8.4 Hz), 2.26 (–$C_6H_4CH_3$, 3H, s), 1.57, 1.55, 1.53 (C(CH_3)$_3$, 36H, three s with intensities 1:2:1), −2.60 (NH, 2H, s). Assignments are based on COSY and NOESY spectra. HRMS-FAB ([M+H]$^+$): found 792.5010, calcd 792.5005 for $C_{55}H_{62}N_5$. UV–vis [CH_2Cl_2, λ_{max} (log ε_{max}), nm]: 415.5 (5.20, FWHM=39 nm), 515 (4.06), 590 (3.70), 656 (3.50).

3.3. General procedure for the amination of 5-bromo-10,20-diphenylporphyrin (2)

A solution of the porphyrin **2** (50 mg, 92 μmol, 1 equiv) in excess amine (200 equiv) and eventually tetrahydrofuran (11 mL/mmol of porphyrin) for the insoluble porphyrins was heated at reflux under argon. The mixture was evaporated and the residue was deposited onto silica gel by vacuum evaporation. Column chromatography on silica gel eluted with the appropriate eluent affords the product, which was recrystallized from *n*-heptane to get the pure products **2b**–**2g**.

3.3.1. 5-Propylamino-10,20-diphenylporphyrin (**2a**)

Following the general procedure with tetrahydrofuran, after 20 h of reflux and chromatography (dichloromethane/hexane 7:3, R_f=0.10), the porphyrin **2a** was obtained as a dark green solid (25 mg, 52% yield). ^{1}H NMR (200 MHz, $CDCl_3$; δ, ppm): 9.61 (H-*meso*, 1H, s), 9.19 (H-β, 2H, d, ^3J=4.8 Hz), 9.00 (H-β, 2H, d, ^3J=4.8 Hz), 8.77 (H-β, 2H, d, ^3J=4.8 Hz), 8.62 (H-β, 2H, d, ^3J=4.8 Hz), 8.18 (Ph–H, 4H, m), 7.77 (Ph–H, 6H, m), 4.34 (CH_2NH, 2H, t, ^3J=7.2 Hz), 2.05 (CH_2CH_2CH_3, 2H, m), 1.00 (CH_2CH_3, 3H, t, ^3J=7.5 Hz), −1.72 (NH, 2H, s). HRMS-ESI ([M+H]$^+$): found 520.2508, calcd 520.2496 for $C_{35}H_{29}N_5$. UV–vis [$CHCl_3$, λ_{max} (log ε_{max}), nm]: 421 (5.23), 523 (3.73), 573 (3.84), 670 (3.70).

3.3.2. 5-Butylamino-10,20-diphenylporphyrin (**2b**)

Following the general solvent-free procedure, after 2 h of reflux, chromatography (dichloromethane, R_f=0.15) and recrystallization, porphyrin **2b** was obtained as a dark purple powder (25 mg, 50% yield). ^{1}H NMR (200 MHz, $CDCl_3$; δ, ppm): 9.61 (H-*meso*, 1H, s), 9.19 (H-β, 2H, d, ^3J=4.6 Hz), 9.00 (H-β, 2H, d, ^3J=4.6 Hz), 8.78 (H-β, 2H, d, ^3J=4.6 Hz), 8.64 (H-β, 2H, d, ^3J=4.6 Hz), 8.19 (Ph–H, 4H, m), 7.77 (Ph–H, 6H, m), 4.35 (CH_2NH, 2H, t, ^3J=7.1 Hz), 1.95–2.03 (CH_2CH_2CH$_2$, 2H, m), 1.57–1.64 (CH_2CH$_3$, 2H, m), 1.00 (CH$_2$CH_3, 3H, t, ^3J=7.3 Hz), −1.64 (NH, 2H, s). HRMS-ESI ([M+H]$^+$): found 534.2648, calcd 534.2652 for $C_{36}H_{31}N_5$. UV–vis [$CHCl_3$, λ_{max} (log ε_{max}), nm]: 421 (5.22), 523 (3.68), 574 (3.84), 670 (3.71).

3.3.3. 5-Benzylamino-10,20-diphenylporphyrin (**2c**)

Following the general solvent-free procedure, after 1.5 h of reflux, chromatography (dichloromethane/hexane 8:2, R_f=0.14) and recrystallization, porphyrin **2c** was obtained as a dark purple powder (21 mg, 40% yield). ^{1}H NMR (200 MHz, $CDCl_3$; δ, ppm): 9.70 (H-*meso*, 1H, s), 9.15 (H-β, 2H, d, ^3J=4.5 Hz), 9.05 (H-β, 2H, d, ^3J=4.8 Hz), 8.82 (H-β, 2H, d, ^3J=4.5 Hz), 8.65 (H-β, 2H, d, ^3J=4.8 Hz), 8.19 (Ph–H, 4H, m), 7.76 (Ph–H, 6H, m), 7.52 (Bz–H, 2H, m), 7.37 (Bz–H, 3H, m), 5.54 (CH$_2$, 2H, s), −1.82 (NH, 2H, s). HRMS-ESI ([M+H]$^+$): found 568.2493, calcd 568.2496 for $C_{39}H_{29}N_5$. UV–vis [$CHCl_3$, λ_{max} (log ε_{max}), nm]: 420 (5.28), 516 (3.82), 571 (3.84), 672 (3.76).

3.3.4. 5-(2-Aminoethylamino)-10,20-diphenylporphyrin (**2f**)

Following the general procedure with tetrahydrofuran, after 5 h of reflux, chromatography (dichloromethane/methanol 9:1, R_f=0.10) and recrystallization, porphyrin **2f** was obtained as a dark purple powder (49 mg, 53% yield). ^{1}H NMR (200 MHz, $CDCl_3$; δ, ppm): 9.61 (H-*meso*, 1H, s), 9.33 (H-β, 2H, d, ^3J=4.5 Hz), 9.00 (H-β, 2H, d, ^3J=4.8 Hz), 8.77 (H-β, 2H, d, ^3J=4.8 Hz), 8.63 (H-β, 2H, d, ^3J=4.5 Hz), 8.18 (Ph–H, 4H, m), 7.76 (Ph–*H*, 6H, m), 4.38 (CH_2NH, 2H, t, ^3J=5.6 Hz), 3.24 (CH_2NH$_2$, 2H, t, ^3J=5.6 Hz), −1.63 (N*H*, 2H, s). HRMS-ESI ([M+H]$^+$): found 521.2448, calcd 521.2448 for $C_{34}H_{28}N_6$. UV–vis [$CHCl_3$, λ_{max} (log ε_{max}), nm]: 420 (5.19), 517 (3.84), 572 (3.84), 668 (3.67).

3.3.5. 5-(2-Hydroxyethylamino)-10,20-diphenylporphyrin (**2g**)

Following the general procedure with tetrahydrofuran, after 8 h of reflux, chromatography (dichloromethane, R_f=0.47 in dichloromethane/methanol 100:8) and recrystallization, porphyrin **2g** was obtained as a dark purple powder (23 mg, 48% yield). ^{1}H NMR (200 MHz, $CDCl_3$; δ, ppm): 9.74 (H-*meso*, 1H, s), 9.36 (H-β, 2H, d, ^3J=4.7 Hz), 9.08 (H-β, 2H, d, ^3J=4.7 Hz), 8.82 (H-β, 2H, d, ^3J=4.7 Hz), 8.68 (H-β, 2H, d, ^3J=4.7 Hz), 8.19 (Ph–H, 4H, m), 7.77 (Ph–H, 6H, m), 4.48 (CH_2NH, 2H, t, ^3J=5.2 Hz), 4.03 (CH_2OH, 2H, t, ^3J=5.0 Hz), −2.00 (NH, 2H, s). HRMS-ESI ([M+H]$^+$): found 522.2284, calcd 522.2288 for $C_{34}H_{27}N_5O$. UV–vis [$CHCl_3$, λ_{max} (log ε_{max}), nm]: 420 (5.24), 520 (3.83), 566 (3.83), 664 (3.65).

3.3.6. 5,15-Dimorpholino-10,20-bis(3,5-di-tert-butylphenyl)-porphyrinato zinc(II) (**4h-Zn**)

To a solution of 5,15-dimorpholino-10,20-bis (3,5-di-*tert*-butylphenyl)porphyrin[11] (**4h**) (45 mg, 0.053 mmol) in chloroform (8 mL), zinc acetate (48 mg, 0.26 mmol) in methanol (1.6 mL) was added. The mixture was deaerated with nitrogen and then stirred for 1.5 h (monitoring by UV–vis) under nitrogen atmosphere. The reaction mixture was washed with distilled water (4×150 mL) until

neutral pH. The organic layer was concentrated by rotary evaporation. After column chromatography on silica gel, 33.1 mg of the reddish compound **4h-Zn** was obtained (68% yield). A $CDCl_3$ concentrated solution (~0.6 mL) was layered in a 20 cm tall glass tube with an internal diameter of 7 mm with an intermediate layer of a 1:1 (v/v) solution of nondeuterated chloroform and cyclohexane (~0.5 mL). Then cyclohexane was added until filling the tube, which was sealed by a rubber septum. After nine months microcrystals were formed, which in the same tube were grinded with dry nondeuterated chloroform, which was layered with dry, freshly distilled cyclohexane from sodium metal. After another six months a ruby-red needle like crystal was collected and mounted on a STOE IPDS II at the ANKA Synchrotron (λ=0.8 Å) at the Forschungszentrum Karlsruhe (beamline for small crystal diffraction) at 140 K. The structure solutions and full matrix least square refinements based on F^2 were performed with SHELX-97 program package.[23] Molecular diagrams were prepared using the program Diamond.[24] M_r=1004.7, monoclinic, space group $P2_1/n$ (No. 14), a=22.9743(7), b=10.0085(3), c=25.3334(8) Å, β=107.936(2)°, V=5542.0(3) Å^3, Z=4, D_c=1.204 g cm^{-3}, $\mu(\lambda$=0.8 Å)=0.772 mm^{-1} giving a final R_1 value of 0.0752 for 647 parameters and 6399 unique reflections with $I\geq 2\sigma(I)$ and wR_2 of 0.1895 for all 7195 reflections. A disorder has been modelled for two symmetry equivalent *tert*-butyl groups. CCDC 704397 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html [or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: (internat.) +44 1223 336 033; e-mail: deposit@ccdc.cam.ac.uk].

^{1}H NMR (300 MHz, $CDCl_3$; δ, ppm): 9.72 (H-β, 4H, d, ^3J=4.5 Hz), 8.99 (H-β, 4H, d, ^3J=4.8 Hz), 8.06 (Ar–H, 4H, d, ^4J=1.8 Hz), 7.82 (4′-Ar–H, 2H, d, ^4J=1.8 Hz), 4.28 and 4.25 (morpholinyl-H, 16H, two br s), 1.54 ($C(CH_3)_3$, 36H, s). In dioxane-d_8 a self-assembled species is present in equilibrium with the monomeric form. Upon increasing the temperature the equilibrium is shifted towards the monomer. HRMS-FAB ($[M+H]^+$): found 917.4453, calcd 917.4460 for $C_{56}H_{65}N_6O_2^{65}Zn$; ($[M+2H]^+$): found 918.4543, calcd 918.4539 for $C_{56}H_{66}N_6O_2^{65}Zn$. UV–vis [$CH_2Cl_2$, λ_{max} (log ε_{max}), nm]: 306 (4.06), 422.5 (5.22), 549 (4.1), 600 (3.1). For other UV–vis and fluorescence spectra see Figures 1 and 2.

3.3.7. 5-Morpholino-10,20-bis(3,5-di-tert-butylphenyl)-porphyrinato zinc(II) (**1h-Zn**)

Metallation with $Zn(OAc)_2$ of the free base **1h**[11] (28 mg, 0.036 mmol) was performed as described above for **4h** affording after column chromatography on silica gel eluted with CH_2Cl_2/*n*-hexane (1:1, v:v) **1h-Zn** as a violet-raspberry powder (20 mg, 66% yield). ^{1}H NMR (300 MHz, $CDCl_3$; δ, ppm): 10.19 (15-H, 1H, s), 9.69 (H-β, 2H, d, ^3J=4.5 Hz), 9.36 (H-β, 2H, d, ^3J=4.5 Hz), 9.10 (H-β, 2H, d, ^3J=4.5 Hz), 9.06 (H-β, 4H, d, ^3J=4.5 Hz), 8.10 (Ar–H, 4H, d, ^4J=1.8 Hz), 7.82 (4′-Ar–H, 2H, d, ^4J=1.8 Hz), 4.02 and 3.91 (morpholinyl-H, 8H, two br s), 1.55 ($C(CH_3)_3$, 36H, s). MALDI-TOF MS: 832.9 $[M+H]^+$ (100%), 1668.1 $[Dimer+H]^+$ (4%). UV–vis [*n*-heptane/CH_2Cl_2, 25:1, v/v, λ_{max} (relative intensity), nm]: 303 (0.14), 412.5 (3.5), 541 (0.2).

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Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2009.02.039.

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