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Synthesis of Chlorin-Sensitized Near Infrared-Emitting Lanthanide Complexes

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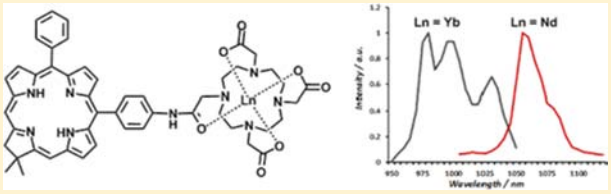
Supporting Information

ABSTRACT: Lanthanide (Yb^{3+}, Nd^{3+}) complexes equipped with red-absorbing hydroporphyrin (chlorin) antennae were synthesized and characterized. The syntheses are scalable, highly modular, and enable the introduction of different chlorins functionalized with a single reactive group (COOH or NH_2). Absorption maxima were dependent on chlorin substitution pattern (monomeso aryl or dimeso aryl) and metalation state (free base or zinc chelate). The complexes benefit from dual chlorin (610−639 nm) and lanthanide (980 or 1065 nm for Yb- or Nd-complexes, respectively) emission in the biologically relevant red and near IR region of the spectrum.



INTRODUCTION

The power of fluorescence spectroscopy to investigate biological phenomena is amply documented. Biomolecule synthesis[1] and interactions,[2] enzymatic activity,[3] and communication networks[4] are readily tracked with the help of fluorescent reporters. However, challenges remain, and additional ones emerge with the increasing complexity of the systems studied. Therefore, efforts toward the development of fluorescent and luminescent compounds with improved photophysical properties and biological applicability continue.

Chlorins are porphyrin-type tetrapyrroles, with one of the pyrrolic double bonds reduced (Figure 1A). This apparently small change impacts the photophysical properties profoundly. Unlike porphyrins, which are only poorly absorbing in the red, chlorins have pronounced, narrow Q-bands (fwhm ≤ 20 nm, λ_{abs} ∼ 590−670 nm, $\varepsilon \sim 10^4$ cm^{-1} M^{-1}) the position of which is adjustable by judicious choice of substitution pattern and metalation state.[5,6,7a] Despite their appreciable fluorescence quantum yields (typically $\Phi \sim 0.1-0.3$), the application of chlorins as fluorescent labels is hampered by the dearth of methods to access fluorophores equipped with a single reactive group that would enable straightforward attachment to biomolecules. Additionally, due to the small chlorin Stoke's shifts (∼50 cm^{-1}), selective detection of fluorescence without interference from scattered excitation light is challenging.[6,7a] Incorporation of chlorins into FRET-pairs with bacteriochlorin acceptors can increase the apparent Stoke's shifts to ∼1600 cm^{-1}.[7] However, for imaging applications, chlorin−bacteriochlorin dyads have a number of drawbacks including nontrivial synthesis, hydrophobicity, and short (∼5 ns) emission lifetimes.

We envisioned that instead of a bacteriochlorin, a near IR-emitting luminescent lanthanide (Ln; Yb or Nd) could also accept the energy harvested by the chlorin (the so-called antenna effect[8]). Such an architecture would combine the chlorin absorption in the red with the unique lanthanide luminescence (emission in the biologically most relevant 800−1100 nm region, microsecond to millisecond lifetime, ∼20 nm fwhm emission bands[8]). Biological tissue is transparent in the 800−1300 nm region, which has been an important motivation for the development of near IR-emitting lanthanide complexes

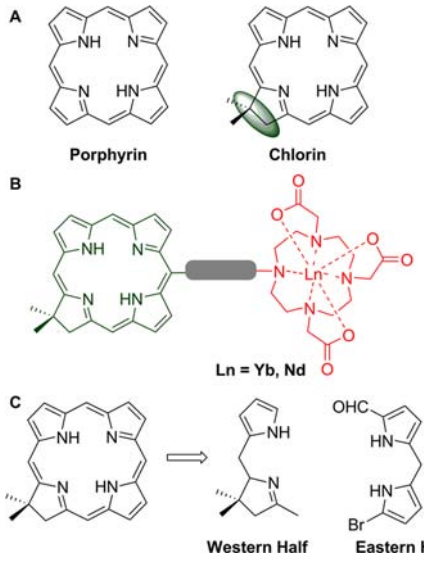


Figure 1. (a) Porphyrin and chlorin core structures. (b) General target structures. (c) Retrosynthesis of sparsely substituted chlorins.

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for imaging.[9] However, in addition to the emitted signal, the excitation light should also be as low-energy as possible to minimize damage to cells, reduce sample autofluorescence, and enhance tissue penetration. To this end, visible-absorbing organic[10] and transition metal-based[11] antennae for Nd and Yb sensitization have been developed.

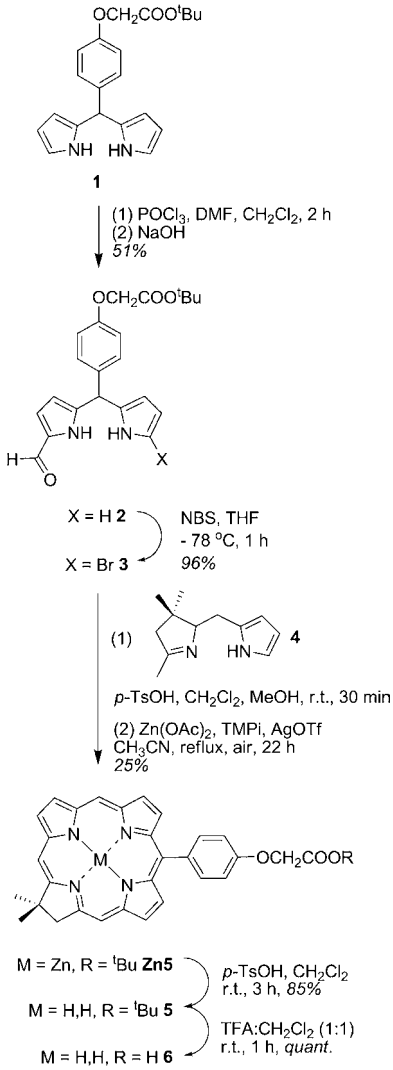
The pioneering work by Gouterman has established porphyrins as suitable sensitizers for Yb;[12] since then, both luminescent Ln−porphyrin[13] and Ln−*N*-confused porphyrin[14] complexes have been reported. However, to the best of our knowledge, chlorin-sensitized near IR-emitting Ln complexes have not been prepared. The energies (11550−12800 cm^{-1}) and quantum yields ($\Phi_T \sim 0.5-0.9$) of free base and zinc chlorin triplet excited states suggested that chlorins could serve as sensitizers for Nd and Yb.[5,15,16] In principle, given the narrow absorption and emission bands, and the tunability of the former, a series of compounds with nonoverlapping excitations and/or emissions could be obtained. Such compounds are much sought after in the biomedical community to address problems involving multicolor imaging.[7a] Here, we report the synthesis and characterization of emissive Nd and Yb complexes sensitized by free base and zinc chlorin antennae.

RESULTS AND DISCUSSION

Molecular Design. Our target structure for chlorin-sensitized near IR-emitting Ln complexes is shown in Figure 1B. The lanthanide ion is held by a multidentate cyclen (1,4,7,10-tetraazacyclododecane)-based framework, which provides kinetic and thermodynamic stability. The Ln-metal binding site is attached to the chlorin antenna by an amine or carboxylic acid terminated linker. The limitations of chlorin synthesis methodology required careful design of the target tetrapyrroles with complementary (COOH or NH_2) functionality. The choice of chlorin structure, and thus, the synthesis route was decided based on the following considerations. Naturally occurring chlorins suffer from poor synthetic malleability, as they often carry a full complement of peripheral substituents, which render functionalization difficult. Reduction or derivatization of synthetic porphyrins is practical only in the cases where regioisomer formation is not an issue.[17] De novo synthesized chlorins, unlike their naturally occurring counterparts, afford considerable flexibility in terms of substitution pattern. In this regard, two potentially general methods have been reported. Jacobi's elegant 2 + 2 synthesis affords chlorins with 0−1 meso and a full complement of β-substituents.[18] The method of Battersby,[19] which has recently been modified and extended by Lindsey[15] affords chlorins bearing 0−2 peripheral (meso) substituents; there is a possibility to introduce additional (meso and/or β) substituents. Chlorin photophysical properties are strongly correlated with the number, nature, and position of β-substituents. Therefore, with an eye to future photophysical fine-tuning by late-stage modification of the macrocycle periphery, we have decided to adapt this method to our needs.

Synthesis. Antenna syntheses are shown in Schemes 1 and 2. The key step in the Lindsey chlorin synthesis entails acid-catalyzed condensation between a 1-bromo-9-acyldipyrromethane (Eastern half) and a tetrahydrodipyrrin (Western half, **4**), followed by intramolecular cyclization (Figure 1C). Chlorin **Zn5** was synthesized from 1-bromo-9-formyldipyrromethane **3** and **4**.[20] The zinc chelate was isolated in 25% yield after silica column chromatography. Compound **3** in turn was available from dipyrromethane **1**[21] by monoformylation under

Scheme 1



Vilsmeier conditions, and then selective α-bromination with NBS. The modest (51%) yield of the monoformylation is predominantly due to loss of the ester protecting group; the formation of diformylated species accounted for <10% of the mass balance. Demetalation of **Zn5** with *p*-TsOH, followed by TFA-mediated cleavage of the *tert*-butyl group afforded carboxylate-functionalized chlorin **6** in 85% yield over two steps.

Commonly used amine protecting groups were expected to be labile to Eastern half synthesis and/or macrocycle formation conditions. Therefore, we have opted to introduce a masked amine in the form of a nitro group, which could be reduced to the amine after the chlorin has been assembled. Amine-equipped chlorin **11** was prepared starting from 5-phenyldipyrromethane **7**[22] (Scheme 2). Acylation with *p*-nitrophenylbenzoyl chloride afforded monoacyl-dipyrromethane in 58% yield as a pale yellow solid after chromatographic purification. Bromination was more sluggish than for **2** → **3**, presumably due to the strongly electron-withdrawing *p*-nitrobenzoyl substituent. Reaction of **9** with **4** gave zinc chlorin **Zn10** in 10% yield, which was subsequently demetalated with TFA.

It is worth commenting on the lower yield of **Zn10** than **Zn5**, attributed to the decreased stability of acylated *p*-

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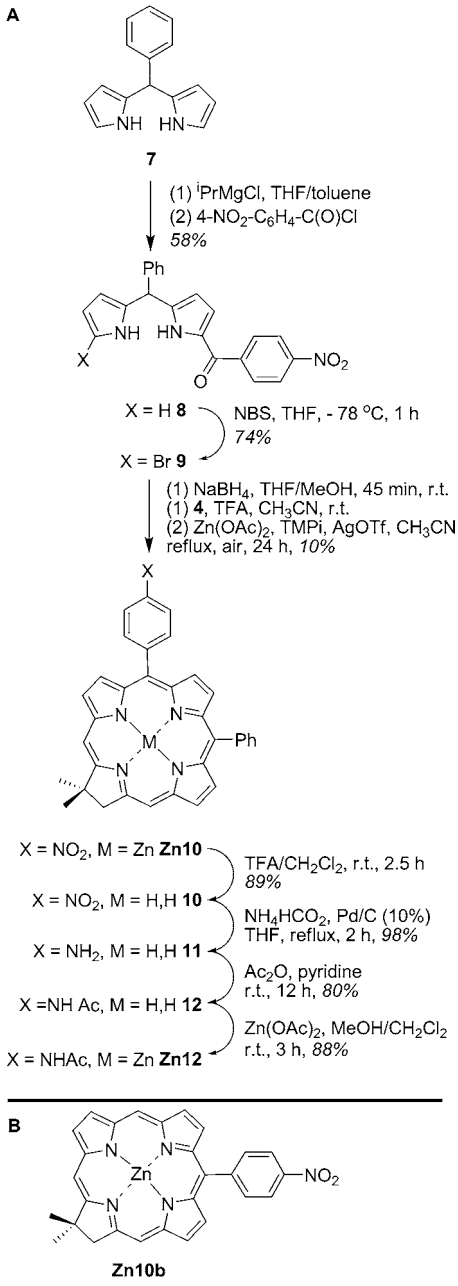
Scheme 2

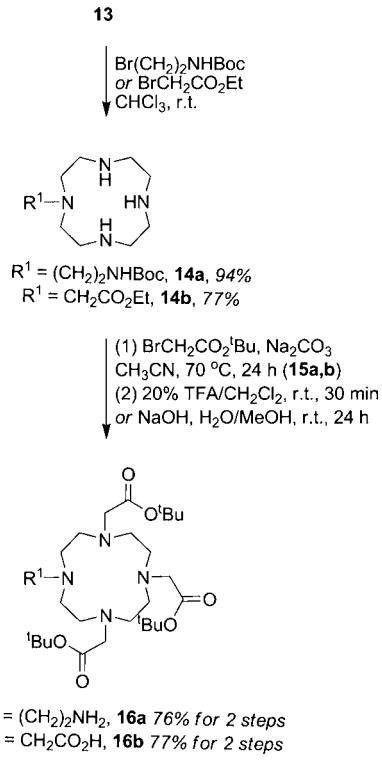


nitrophenyl dipyrromethanes compared to their non-nitrated counterparts. In fact, standard mono-[23] or diformylation[24] of 5-*p*-nitrophenyl dipyrromethane results in complete decomposition of the starting material (c.f. 80% yield of 1,9-diformyl-5-*p*-bromophenyl dipyrromethane under identical conditions[21]). Additionally, we have attempted the synthesis of chlorin **Zn10b**, a simpler analogue of **Zn10**. While we were able to obtain **Zn10b** in a disappointing 3.8% yield, the synthesis was not amenable to scale-up, and our efforts to optimize the chlorin formation reaction were met with frustration. Despite these initial setbacks, with the improved design, several hundreds of milligrams of *p*-nitrophenylchlorin **Zn10** could be obtained in a single batch.

Transfer hydrogenation of **10** with NH_4HCO_2/Pd(C) produced aminochlorin **11** (98% isolated yield) after removal of the catalyst by filtration, and aqueous−organic workup. Reference compound **12**, in which the amine is capped by an acetyl group instead of a lanthanide complex was isolated after acetylation of **11** with Ac_2O/pyridine. The zinc chelate **Zn12** was prepared in 88% yield by treatment of **12** with $Zn(OAc)_2$ in CH_2Cl_2/MeOH.

Known **16a**[25] and **16b**[26] were prepared in three steps from cyclen (**13**) (Scheme 3); our procedure (see the Supporting

Scheme 3



Information (SI) for details) enables the synthesis of multigram quantities of these compounds. Monoalkylation in $CHCl_3$ without added base[27] with *N*-Boc bromoethylamine or ethyl bromoacetate furnished **14a,b** in excellent (94% and 77%, respectively) yield. Only 1.5 equiv of **13** was required as opposed to the 4 equiv typically employed in similar reactions.[28] Monoalkylated cyclen derivatives are key intermediates en route to cyclens with 1 + 3 *N*-substituents, and cyclens regioselectively *N*-substituted with up to three different groups.[29] Alkylation of the three remaining secondary nitrogens with *tert*-butyl bromoacetate afforded **15a,b**. Removal of the Boc protecting group in **15a** proceeded smoothly in CH_2Cl_2 with 20% TFA, providing **16a** analytically pure (as determined by ^1H and ^{13}C NMR and HR-ESI-MS analysis) in 90% yield after extraction from aqueous KOH. The high yield and purity suggest that unproductive *tert*-butyl ester cleavage is negligible. Treatment of **15b** with NaOH in MeOH/H_2O gave **16b** in quantitative yield.

At this point we were ready to join the chlorin antennae with the cyclen frameworks (Scheme 4). Initial attempts to forge the amide bond between the carboxylic acid of **6** and the primary amine in **16a** using (1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide) (EDCI) coupling agent were disappointing. Yields varied widely (0−30%), and the purification of the product was tedious. With (2-(7-aza-1*H*-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate) (HATU) in the presence of (diisopropylethylamine) (DIPEA), yields were

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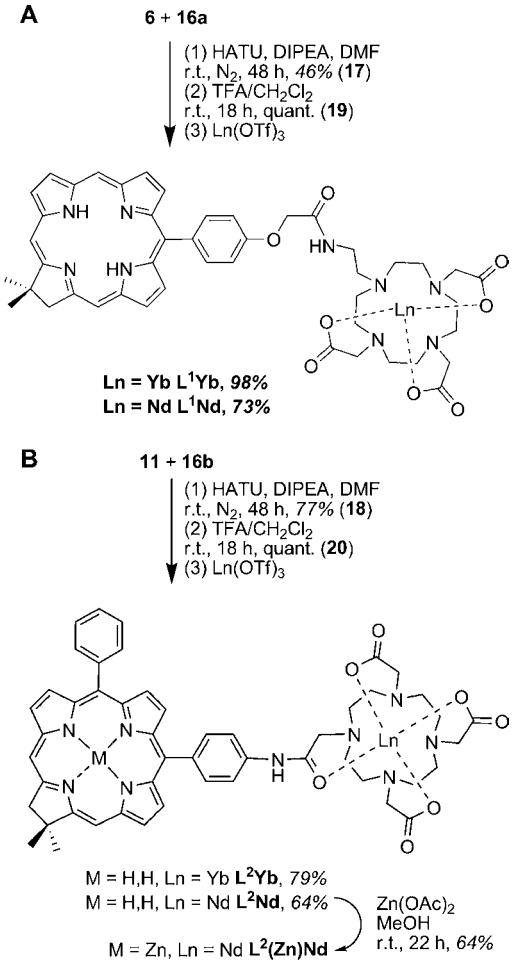
Scheme 4



consistently good (46% and 76% for **17** and **18**, respectively), and chromatography was very straightforward, having been reduced to the isolation of a single dark green (**17**) or red colored (**18**) band. Quantitative cleavage of the *tert*-butyl esters in TFA:CH_2Cl_2 (1:1, 18 h) and exposure of the deprotected ligands to the appropriate lanthanide triflates afforded the target complexes **L¹Yb,Nd** and **L²Yb,Nd** in 64−98% yield. Zinc chelate **L²(Zn)Nd** was prepared by treatment of the free base analogue **L²Nd** with $Zn(OAc)_2$.

All new diamagnetic compounds were fully characterized by ^1H and ^{13}C NMR spectroscopy and HR-ESI-MS, and the data obtained were in agreement with the expected structures. The ^1H and ^{13}C NMR spectra of cyclen derivatives were complex, indicative of the presence of multiple conformations in solution. Paramagnetic Ln-complexes were characterized by UV−vis absorption spectroscopy, fluorescence and near IR-luminescence spectroscopy (vide infra), and HR-ESI-MS. For all complexes, the molecule ions were observed with the expected isotope distribution pattern.

Photophysical Characterization. Photophysical investigations of Ln-complexes **L¹Yb,Nd**, **L²Yb,Nd**, and **L²(Zn)Nd**, and chlorin reference compounds **6**, **12**, and **Zn12** were carried out in methanolic solutions. Chlorin absorption and emission spectra, and fluorescence lifetimes were in line with data reported for sparsely substituted chlorins (Table 1).[6] Characteristic features include a short-wavelength absorption (B) band and a long-wavelength absorption band (Q_y). The I^B/I^Q ratio,

Table 1. Photophysical Properties of Chlorins and Lanthanide Complexes[a]

	λ_{max} (nm)[b] (I^B/I^Q)	λ_{em} (nm)	$\tau_{chlorin}$ (ns)	τ_{Ln} (ns)	$\Phi_{complex}/\Phi_{reference}$[c]
6	634 (4.8)	636	7.2		
12	639 (6.4)	639	7.8		
Zn12	608 (10.2)	610, 637	1.5		
L¹Yb	634 (4.8)	635	7.2	2900[d]	0.99
L¹Nd	633 (4.5)	635	6.7	144[e]	0.78
L²Yb	637 (5.3)	639	7.8	734[d]	1.10
L²Nd	637 (5.8)	639	7.8	220[e]	1.18
L²(Zn)Nd	607 (6.8)	610, 639	1.5, 8.8[f]	122[e]	1.20

[a]Measured at room temperature in MeOH. [b]Measured at the Q_y band. [c]**L¹Yb** and **L¹Nd** referenced to **6**, **L²Yb** and **L²Nd** referenced to **12**, **L²(Zn)Nd** referenced to **Zn12**. [d]Measured at 980 nm. [e]Measured at 1065 nm. [f]Attributed to trace amount of free base chlorin, measured at 640 nm.

which is a more accurate descriptor[30] of chlorin absorption properties than ε varied between 4.5 and 10.1. The B bands of all compounds were in the 402−410 nm region. The free base chlorins and Ln−chlorin complexes had Q_y bands at 634−639 nm. The Q_y bands of the Zn compounds were blue-shifted to 607 nm. There were no significant differences between the absorption and fluorescence emission spectra of the lanthanide complexes and their corresponding model compounds (c.f. **6** and **L¹Nd**, **12** and **L²Nd**, and **Zn12** and **L²(Zn)Nd** spectra in Figure 2 and Supporting Information Figure S1). Chlorin

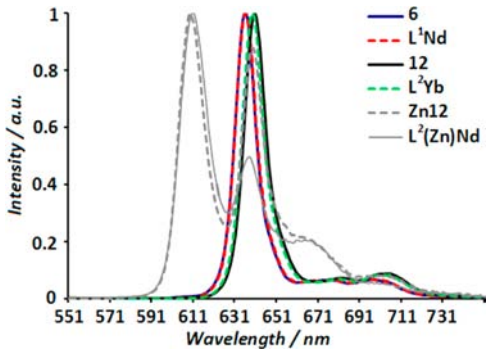


Figure 2. Fluorescence emission spectra of chlorin-equipped lanthanide complexes and their respective model compounds. Spectra were recorded at ambient temperature in MeOH with excitation at the chlorin Q-bands.

Stoke's shifts were small, ~ 50 cm^{-1}, for both the complexes and model compounds. The chlorin fluorescence quantum yields were not significantly affected by the presence of the lanthanide, with $\Phi_{complex}/\Phi_{reference}$ in the 0.78−1.20 range. Free base chlorin-equipped Ln complexes displayed fluorescence lifetimes in the 6.7−7.8 ns range, which is similar to that observed for model compounds **6** and **12** (7.2 and 7.8 ns, respectively). Zinc chelate-equipped complex **L²(Zn)Nd** had a chlorin fluorescence lifetime of 1.5 ns, which is identical within experimental error to that of its model compound **Zn12**. A longer-lived component (8.8 ns) was also observed for **L²(Zn)Nd**, which we attribute to a small amount of residual free base chlorin.

Upon excitation of the chlorin antenna, near IR Ln-emission was observed. The relevant regions of the emission spectra of **L²Yb** and **L²Nd** with the characteristic Yb (980 nm) and Nd

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(1065 nm) emission bands are shown in Figure 3. Lanthanide luminescence lifetimes were measured at 980 nm for Yb and 1065 nm for Nd complexes and were up to 2.9 μs long (**L^{1}Yb**, Table 1).

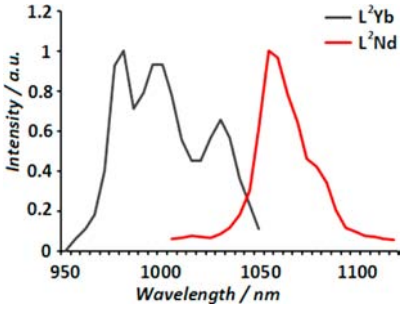

Figure 3. Time-resolved near IR emission spectra of **L^{2}Yb** and **L^{2}Nd** upon excitation at 337 nm at ambient temperature in MeOH.

The lack of changes in the chlorin fluorescence lifetimes and quantum yields upon the introduction of the lanthanide chelate suggest that Ln excited states are populated from the chlorin triplet states. Additional evidence was obtained by monitoring the singlet oxygen phosphorescence in solutions of **L^{2}Yb** and **L^{2}Nd**, and that of the reference chlorin antenna **12** in CD_3OD. Excitation of **12** at 337 nm yielded robust $^1O_2$ phosphorescence at 1270 nm with a lifetime of 50 μs (SI Figure S2). No signals attributable to $^1O_2$ were observed upon excitation of **L^{2}Yb**, in accordance with rapid energy transfer from the antenna triplet state to Yb. Irradiation of **L^{2}Nd** resulted in dual lanthanide and $^1O_2$ luminescence at 1065 and 1270 nm, respectively (Figure 3 and SI Figure S2). The lifetime of the latter was 190 μs. The Nd excited state at 11 200 cm^{-1} is close enough (<2000 cm^{-1} below[31]) to the chlorin triplet state (11 550−12 800 cm^{-1})[16] to enable thermal repopulation of the antenna T_1 level. This renders **L^{2}Nd** susceptible to quenching by atmospheric O_2, which produces $^1O_2$. The Yb excited state, located at 10 300 cm^{-1} is too low for energy back transfer to the chlorin to occur, explaining the lack of $^1O_2$ phosphorescence.

CONCLUSIONS

We have developed robust synthetic routes to access lanthanide complexes equipped with red-absorbing chlorin antennae. Two ligand designs were explored bearing chlorins of different substitution patterns and metalation states, and thus possessing different absorption maxima. Complexation with Yb and Nd afforded near IR-emissive lanthanide complexes. This work adds chlorins to a growing list of long wavelength-absorbing antennae for Nd and Yb. Current work focuses on the investigation of the chlorin-Ln energy transfer, and improving the sensitization efficiency by optimization of antenna triplet state lifetime and quantum yield. We are further working toward chlorin-sensitized luminescent Ln complex-based responsive probes.

EXPERIMENTAL SECTION

General Procedures. ^{1}H NMR (400 or 500 MHz) and ^{13}C NMR (100 or 125 MHz) spectra were recorded on a Varian or a Bruker 400 MHz, or a Bruker 500 MHz instrument, respectively. Chemical shifts were referenced to residual solvent peaks and are given as follows: chemical shift (δ, ppm), multiplicity (s, singlet; br, broad; d, doublet, t, triplet; q, quartet; m, multiplet), coupling constant (Hz), integration. HR-ESI-MS analyses were performed on a Bruker MicroTOF ESI mass spectrometer. All compounds displayed the expected isotope distribution pattern. Anhydrous CH_2Cl_2 was obtained by distillation from CaH_2 under an Ar atmosphere. Anhydrous THF was available from a VAC solvent purifier. Compounds **1**,[21] **4**,[20] **7**,[22] and *N*-Boc bromoethylamine[32] were synthesized following literature methods. For the synthesis of **14a**,[33] **15a**,[34] **15b**,[26] and **16a**,[25b] see the Supporting Information. All other chemicals were from commercial sources and used as received.

Chromatography. Preparative chromatography was carried out on silica gel [Davisil chromatographic silica media (35−70 μm)]. Thin layer chromatography was performed on silica-coated glass plates. Samples were visualized by UV-light (254 nm), staining with $KMnO_4$/NaOH, or exposure to Br_2-vapor.

Spectroscopy. UV−vis absorption spectroscopy was performed on a Varian Cary 300 instrument at room temperature in the solvents indicated. Fluorescence spectra were recorded on a Jobin Yvon Fluorolog instrument. Emission intensities and luminescent lifetimes of the Nd and Yb complexes were determined in methanol at ambient temperature either analogously to a reported method[35] or as follows. Samples were dissolved in CD_3OD (Aldrich) and diluted with the same solvent to give an absorbance of ca. 0.05 at 337 nm in a 1 cm path length cuvette. The emission lifetimes and time-resolved emission spectra were recorded using a dedicated NIR fluorimeter. The samples were excited at 337 nm using the output of a nitrogen laser operating at 10 Hz, and providing a pulse energy of ca. 10 μJ at the sample with a duration of ca. 5 ns. The emission was collected at 90° and focused onto the entrance slit of the monochromator (Bentham TM300V) equipped with a grating optimized for the NIR (600 g/mm, 1 μm blaze). The selected wavelength was detected using a NIR photomultiplier (Hamamatsu H10330-A-45) operating in photon counting mode. The arrival times of detected photons were determined using a 100 Ms/s digital oscilloscope (NI-6133) and the data from many laser shots used to construct a histogram of frequency vs arrival time. Data was fitted to an exponential function of the form $I(t) = A_0 + A_1\exp(-t/\tau)$ using a nonlinear least-squares method. The quality of fit was judged by the value of the reduced chi-squared ($\chi^2 < 1.3$) and the randomness of the weighted residuals. The time-resolved spectrum was recorded by acquiring the luminescence decays obtained from a constant number of laser shots as a function of emission wavelength. Integration of the decay over a fixed time window allowed the construction of the spectra.

Singlet oxygen emission was recorded using the same spectrometer to observe the $^1\Delta_g \rightarrow {}^3\Sigma_g^-$ phosphorescence at 1270 nm. In order to increase the s/n of the observed decays, the data was binned in the time domain to give a total of ca. 500 time channels and the data fitted as above.

The fluorescence lifetimes were measured using time correlated single photon counting (TCSPC) using a 396 nm pulsed laser diode. The fluorescence emission was collected at right angles to the excitation source with the emission wavelength selected using a monochromator and detected by a single photon counting photomultiplier (IBH TXB-04). The instrument response function was measured using a dilute LUDOX suspension as the scattering sample, setting the monochromator at the emission wavelength of the laser, giving an instrument response function (IRF) of 200 ps. The resulting intensity decay is a convolution of the fluorescence decay with the IRF, and iterative reconvolution of the IRF with a decay function and nonlinear least-squares analysis was used to analyze the convoluted data.[36]

2. $POCl_3$ (680 μL, 7.37 mmol) was added to 6 mL DMF at 0 °C under nitrogen. The solution was stirred for 10 min to form the Vilsmeier reagent. A solution of **1**[21] (2.59 g, 7.37 mmol) in 30 mL CH_2Cl_2 was treated with the Vilsmeier reagent at 0 °C under nitrogen. The mixture was stirred for 2 h. The reaction was quenched by the addition of 100 mL aqueous NaOH solution (10%) at 0 °C. The phases were separated, and the water phase was extracted three times with CH_2Cl_2. The organic phase was dried over Na_2SO_4 and concentrated. Column chromatography [silica, pentane/EtOAc (2:1)] afforded a light brown oil (1.44 g, 51%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.49 (s, 9H), 4.50 (s, 2H), 5.46 (s, 1H), 5.93−5.95

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(m, 1H), 6.06−6.09 (m, 1H), 6.15−6.18 (m, 1H), 6.71−6.73 (m, 1H), 6.86 (d, J = 8.8, 2H), 6.89−6.91 (m, 1H), 7.10 (d, J = 8.8, 2H), 7.80−7.95 (br, 1H), 8.90−9.05 (br, 1H), 9.41 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 28.1, 43.3, 65.7, 82.5, 107.7, 108.3, 110.9, 114.8, 118.0, 122.9, 129.5, 131.1, 132.3, 133.9, 143.8, 157.0, 168.1, 178.8. ESI-MS obsd 403.1661, calcd 403.1628 [$(M + Na)^+$, M = $C_{22}H_{24}N_2O_4$].

3. A sample of **2** (1.44 g, 3.79 mmol) was dissolved in 30 mL THF and cooled to −78 °C. NBS (674 mg, 3.79 mmol) was added in one portion. The mixture was stirred at −78 °C for 1 h. Water and EtOAc were added, the phases were separated, and the organic phase was washed with water. The organic phase was dried over Na_2SO_4 and concentrated without heating. Column chromatography [silica, pentane/EtOAc (3:1)] gave a light brown oil, which was used shortly after isolation to avoid decomposition (1.67 g, 96%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.49 (s, 9H), 4.49 (s, 2H), 5.41 (s, 1H), 5.85−5.86 (m, 1H), 6.05−6.07 (m, 1H), 6.09−6.10 (m, 1H), 6.81 (d, J = 8.7 Hz, 2H), 6.90−6.91 (m, 1H), 7.06 (d, J = 8.7 Hz, 2H), 7.89 (br, 1H), 9.06 (br, 1H), 9.40 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.1, 43.4, 65.8, 82.6, 97.9, 109.7, 110.6, 111.0, 115.0, 122.5, 129.4, 132.3, 132.5, 132.8, 142.3, 157.4, 168.0, 178.8. ESI-MS obsd 481.0760, calcd 481.1733 [$(M + Na)^+$, M = $C_{22}H_{23}BrN_2O_4$].

Zn5. Following a standard procedure for chlorin formation,[37] a solution of **4**[20] (376 mg, 2.0 mmol) and **3** (918 mg, 2.0 mmol) in dry CH_2Cl_2 (16 mL) under nitrogen was treated dropwise with a solution of p-TsOH·H_2O in anhydrous methanol (4 mL). The mixture was stirred at room temperature (rt) for 30 min. TMPi (3.3 mL, 20 mmol) was added, and the mixture was stirred for 5 min and concentrated under reduced pressure without heating. The resulting yellow/brown solid was dissolved in CH_3CN and treated with 2,2,6,6-tetramethylpiperidine (TMPi) (8.3 mL, 50.0 mmol), $Zn(OAc)_2$ (5.49 g, 30.0 mmol), and AgOTf (1.54 g, 6.0 mmol). The reaction mixture was refluxed for 22 h open to the air. The mixture was concentrated. Column chromatography [silica, pentane/CH_2Cl_2 (1:1), then CH_2Cl_2] yielded a blue/green solid (303 mg, 25%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.58 (s, 9H), 2.04 (s, 6H), 4.52 (s, 2H), 4.71 (s, 2H), 7.19 (d, J = 8.6 Hz, 2H), 7.99 (d, J = 8.6 Hz, 2H), 8.52 (d, J = 4.3 Hz, 1H), 8.60 (s, 1H), 8.63 (d, J = 4.4 Hz, 1H), 8.68 (s, 1H), 8.70 (d, J = 4.4 Hz, 1H), 8.77 (d, J = 4.4 Hz, 1H), 8.86 (d, J = 4.3 Hz, 1H), 9.08 (d, J = 4.4 Hz, 1H), 9.60 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.2, 31.0, 45.4, 50.3, 50.5, 66.0, 82.6, 94.1, 96.8, 109.4, 112.9, 123.2, 126.6, 127.3, 128.0, 129.1, 132.9, 133.1, 134.7, 135.8, 146.0, 146.1, 146.5, 147.6, 153.1, 154.0, 157.6, 159.1, 168.3, 171.0. ESI-MS obsd 608.1759, calcd 608.1760 (M^+, $C_{34}H_{32}N_4O_3Zn$). λ_{abs} (CH_2Cl_2) 405, 560, 500, 605 nm.

5. A sample of **Zn5** (330 mg, 0.54 mmol) was dissolved in CH_2Cl_2/MeOH (8 mL, 3:1). p-TsOH·H_2O (205 mg, 1.08 mmol) was added, and the mixture was stirred at rt for 3 h. The reaction was quenched with aq. sat. $NaHCO_3$, and the aqueous phase was extracted with CH_2Cl_2. The organic phase was dried over Na_2SO_4 and concentrated. Purification by column chromatography (silica, CH_2Cl_2) gave a dark green solid (252 mg, 85%): ^{1}H NMR (400 MHz, $CDCl_3$) δ (−2.34)−(−2.30) (br, 1H), (−1.96)−(−1.90) (br, 1H), 1.62 (s, 1H), 2.07 (s, 6H), 4.65 (s, 2H), 4.80 (s, 2H), 7.27 (d, J = 8.6 Hz, 2H), 8.07 (d, J = 8.6 Hz, 2H), 8.66 (d, J = 4.3, 1H) 8.83 (s, 2H), 8.91 (s, 1H), 8.95 (d, J = 4.5 Hz, 1H), 8.97 (d, J = 4.3 Hz, 1H), 9.04 (s, 1H), 9.24 (d, J = 4.5 Hz, 1H), 9.86 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.2, 30.9, 31.2, 46.5, 52.0, 66.1, 82.6, 94.1, 96.8, 107.2, 113.1, 121.1, 123.2, 123.5, 128.3, 132.1, 132.3, 134.1, 135.0, 135.1, 135.5, 139.5, 141.0, 150.8, 152.8, 157.8, 162.8, 168.2, 175.3, 207.0. ESI-MS obsd 547.2685, calcd 547.2704 [$(M + H)^+$, M = $C_{34}H_{34}N_4O_3$]. λ_{abs} (CH_2Cl_2) 395, 410, 500, 585, 635 nm.

6. A sample of **5** (100 mg, 0.18 mmol) was dissolved in a mixture of CH_2Cl_2 (2 mL) and TFA (2 mL). The reaction mixture was stirred at rt for 1 h. The mixture was concentrated to yield a blue/green solid that was used without further purification (quant): ^{1}H NMR (400 MHz, CD_3OD) δ 2.16 (s, 6H), 4.80 (s, 2H), 5.05 (s, 2H), 7.55 (d, J = 8.7 Hz, 2H), 8.32 (d, J = 8.7 Hz, 2H), 8.67 (d, J = 4.4 Hz, 1H), 9.01 (d, J = 4.8 Hz, 1H), 9.12 (d, J = 4.8 Hz, 1H), 9.21 (d, J = 4.4 Hz, 1H), 9.32 (d, J = 4.8 Hz, 1H), 9.39 (s, 1H), 9.50 (s, 1H), 9.61 (d, J = 4.8 Hz, 1H), 10.38 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 29.8, 46.4, 47.7, 64.8, 92.0, 95.5, 110.5, 112.8, 114.6, 115.6, 124.2, 125.7, 126.7, 127.5, 128.4, 132.0, 132.6, 138.5, 138.7, 139.7, 139.9, 142.1, 148.6, 151.2, 154.7, 159.9, 169.2, 172.5. ESI-MS obsd 491.2099, calcd 491.2078 [$(M + H)^+$, M = $C_{30}H_{26}N_4O_3$]. λ_{abs} (MeOH) 403, 498, 583, 634 nm.

8. Following a standard procedure for dipyrromethane monoacylation,[38] dipyrromethane **7**[22] (1.53 g, 6.90 mmol) was dissolved in anhydrous toluene (28 mL) under N_2. The solution was cooled in an ice−water bath and was treated dropwise with ^{i}PrMgBr (6.9 mL of 2.0 M solution in THF, 13.8 mmol). Stirring was continued for 20 min, after which the reaction mixture was cooled to −78 °C. 4-Nitrobenzoylchloride (1.92 g, 10.34 mmol) was added portionwise. Stirring was continued with cooling for 20 min and at room temperature for 40 min. The reaction mixture was carefully diluted with water and EtOAc. The aqueous layer was extracted three times with EtOAc. The combined organic phase was washed with water and brine, and dried ($MgSO_4$). Column chromatography [silica, pentane/EtOAc (4:1 → 2:1)] afforded a pale brown solid (1.42 g, 58%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.56 (s, 1H), 6.00−6.01 (m, 1H), 6.12−6.13 (m, 1H), 6.18−6.20 (m, 2H), 6.72−6.73 (m, 1H), 6.77−6.78 (m, 1H), 7.22−7.24 (m, 2H), 7.29−7.37 (m, 3H), 7.93−7.97 (m, 2H), 7.99 (br, 1H), 8.30−8.33 (m, 2H), 9.51 (br, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 44.3, 108.0, 108.9, 111.3, 118.0, 121.3, 123.6, 127.7, 128.4, 129.1, 129.7, 130.1, 130.4, 140.3, 142.8, 143.8, 149.6, 182.0. ESI-MS obsd 370.1181, calcd 370.1197 [$(M - H)^-$, M = $C_{22}H_{17}N_3O_3$].

9. Monoacyldipyrromethane **8** (291 mg, 0.82 mmol) was dissolved in THF (5 mL), and the solution was cooled to −78 °C. NBS (157 mg, 0.90 mmol) was added in one portion. After 1 h, dilute aqueous $NaHCO_3$ and EtOAc were added, and the mixture was allowed to warm to room temperature. The aqueous layer was extracted twice with EtOAc. The combined organic phase was washed with water and dried ($MgSO_4$). Column chromatography (silica, pentane/EtOAc 4:1 → 2:1) afforded a pale brown solid which was used shortly after isolation to avoid decomposition (265 mg, 74%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.54 (s, 1H), 5.93−5.94 (m, 1H), 6.06−6.07 (m, 1H), 6.17−6.18 (m, 1H), 6.78−6.79 (m, 1H), 7.17−7.19 (m, 1H), 7.28−7.33 (m, 3H), 7.83−7.86 (m, 2H), 8.28−8.31 (m, 2H), 8.46 (br, 1H), 10.27 (br, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 44.2, 98.1, 110.0, 110.6, 111.8, 122.2, 123.6, 127.8, 128.2, 128.3, 129.1, 129.8, 129.9, 130.4, 132.0, 139.8, 142.8, 143.6, 149.6, 182.3. ESI-MS obsd 448.0311, calcd 448.0302 [$(M - H)^-$, M = $C_{22}H_{15}BrN_3O_3$].

Zn10. Monobromo, monoacyldipyrromethane **9** (265 mg, 0.611 mmol) was dissolved in a mixture of THF and MeOH (4:1, 12.2 mL), and the solution was cooled in an ice−water bath. $NaBH_4$ (226 mg, 6.11 mmol) was added portionwise. TLC analysis after 45 min indicated the consumption of the starting material. The mixture was diluted with water and EtOAc. The aqueous layer was extracted with EtOAc twice. The combined organic phase was washed with water, dried ($MgSO_4$), filtered, and the filtrate was concentrated. The solid residue was dissolved in CH_3CN (6.1 mL), and a sample of **4** (115 mg, 0.612 mmol) was added. The flask was covered with aluminum foil. The mixture was treated with TFA (47 μL, 0.61 mmol). After 30 min the reaction mixture was diluted with CH_3CN (37 mL). 2,2,6,6-Tetramethylpiperidine (TMPi) 1.54 mL, 9.05 mmol), $Zn(OAc)_2$ (843 mg, 4.59 mmol), and AgOTf (235 mg, 0.91 mmol) were added consecutively. The flask was placed in an oil bath preheated to 85 °C. Stirring was continued with heating, with the reaction mixture open to the air. After 24 h the mixture was cooled to room temperature, the volatile components were evaporated, and the residue was purified by column chromatography [silica, pentane/CH_2Cl_2 (1:1) → 100% CH_2Cl_2] to afford a dark green solid (38.5 mg, 10%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.06 (s, 6H), 4.53 (s, 2H), 7.69−7.73 (m, 3H), 8.06−8.08 (m, 2H), 8.24−8.26 (m, 2H), 8.29 (d, J = 4.4 Hz, 1H), 8.44 (d, J = 4.4 Hz, 1H), 8.54−8.57 (m, 3H), 8.63 (d, J = 4.5 Hz, 1H), 8.65 (s, 1H), 8.68 (d, J = 4.5 Hz, 1H), 8.70 (s, 1H), 8.73 (d, J = 4.5 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 31.0, 45.4, 50.3, 95.1, 97.5, 121.1, 121.8, 124.4, 126.8, 127.4, 127.6, 127.8, 127.9, 129.1, 132.4, 133.6, 133.7, 134.2, 142.3, 145.1, 146.1, 146.5, 147.5, 147.8, 149.7, 153.8, 154.3, 160.0, 171.7. ESI-MS obsd 599.1374, calcd 599.1300 [M^+, M = $C_{34}H_{25}N_5O_2Zn$]. λ_{abs} (CH_2Cl_2) 408, 508, 568, 610 nm.

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10. A sample of **Zn10** (38.5 mg, 0.064 mmol) was dissolved in CH_2Cl_2 (3 mL). TFA (1 mL) was added, and the reaction mixture was stirred at room temperature for 2.5 h. The volatile components were removed by rotary evaporation. The residue was dissolved in a mixture of CH_2Cl_2 and dilute aqueous $NaHCO_3$. The aqueous phase was extracted once with CH_2Cl_2. The combined organic layer was dried ($MgSO_4$), filtered, and the filtrate was concentrated. The residue was purified by silica column chromatography [pentane/CH_2Cl_2 (1:1) → CH_2Cl_2] affording a dark green solid (30.7 mg, 89%): ^{1}H NMR (500 MHz, $CDCl_3$) δ −1.94 (br 2H), 2.08 (s, 6H), 4.64 (s, 2H), 7.72−7.75 (m, 3H), 8.12−8.14 (m, 2H), 8.28−8.30 (m, 2H), 8.37 (d, J = 4.5 Hz, 1H), 8.53 (d, J = 4.5 Hz, 1H), 8.57−8.59 (m, 2H), 8.67 (d, J = 4.7 Hz, 1H), 8.79−8.83 (m, 2H), 8.90 (d, J = 4.6 Hz, 1H), 8.94 (s, 1H), 9.03 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 31.1, 31.2, 46.6, 51.8, 95.2, 97.4, 118.9, 121.9, 122.0, 122.4, 123.8, 124.0, 126.8, 127.0, 127.7, 127.8, 129.2, 131.1, 132.5, 133.89, 133.92, 134.0, 134.57, 134.61, 135.4, 140.4, 141.0, 141.9, 147.7, 149.3, 150.7, 152.4, 163.9, 175.6. ESI-MS obsd 538.2191, calcd 538.2243 [$(M + H)^+$, M = $C_{34}H_{27}N_5O_2$]. λ_{abs} (CH_2Cl_2) 413, 507, 589, 641.

11. A sample of **10** (44.9 mg, 0.0836 mmol) was dissolved in THF (5.9 mL). NH_4HCO_2 (53 mg, 0.84 mmol) and Pd/C (10%, 53 mg) were added, and the mixture was heated at reflux for 2 h. The reaction mixture was cooled to room temperature, filtered, and the filtrate was diluted with CH_2Cl_2 and water. The aqueous layer was extracted once with CH_2Cl_2. The combined organic phase was dried ($MgSO_4$). The sample was >95% pure (as shown by ^{1}H NMR and HR-ESI-MS analysis) and could be used without further purification. Alternatively, column chromatography [silica, CH_2Cl_2/MeOH (100:0 → 9:1)] afforded a deep red solid (42 mg, 98%): ^{1}H NMR (500 MHz, $CDCl_3$) δ −1.75 (br, 2H), 2.07 (s, 6H), 4.59 (s, 2H), 6.83−6.85 (m, 2H), 7.73−7.75 (m, 3H), 7.88−7.90 (m, 2H), 8.16−8.18 (m, 2H), 8.52 (d, J = 4.4 Hz, 1H), 8.60 (d, J = 4.4 Hz, 1H), 8.78 (s, 1H), 8.85−8.88 (m, 3H), 8.92 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 31.2, 46.4, 51.8, 94.6, 96.5, 113.6, 122.0, 123.0, 123.1, 123.2, 126.8, 127.6, 128.7, 128.9, 131.7, 132.2, 132.6, 134.1, 135.0, 135.04, 135.3, 140.3, 140.9, 142.3, 145.5, 152.2, 152.6, 163.5, 174.9. ESI-MS obsd 508.2495, calcd 508.2496 [$(M + H)^+$, M = $C_{34}H_{29}N_5$]. λ_{abs} (CH_2Cl_2) 415, 508, 538, 586, 638 nm.

12. A sample of **11** (18 mg, 0.036 mmol) was dissolved in pyridine (2.5 mL). Ac_2O (2.5 mL) was added to the solution. Stirring was continued at room temperature for 12 h. The reaction mixture was diluted with CH_2Cl_2 and saturated aqueous $NaHCO_3$. The aqueous layer was extracted twice with CH_2Cl_2. The combined organic phase was washed with multiple portions of $NaHCO_3$ (sat. aq.), dried ($MgSO_4$), filtered, and the volatiles were evaporated. The solid residue was purified by column chromatography (silica, CH_2Cl_2/MeOH, 0 → 10%) affording a deep red solid (17.9 mg, 80%, one molecule of pyridine retained after extensive drying): ^{1}H NMR (500 MHz, $CDCl_3$) δ −1.87 (br, 2H), 2.05 (s, 6H), 2.21 (s, 3H), 4.60 (s, 2H), 4.69 (br, 1H), 7.31−7.34 (m, 1H), 7.66 (br, 1H), 7.68−7.75 (m, 4H), 7.76−7.78 (m, 2H), 8.06 (d, J = 8.4 Hz, 2H), 8.09 (br, 1H), 8.12−8.14 (m, 2H), 8.47−8.50 (m, 2H), 8.61 (d, J = 4.0 Hz, 1H), 8.77−8.83 (m, 4H), 8.86 (s, 1H), 8.96 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 24.7, 31.2, 46.5, 51.8, 94.9, 96.9, 118.1, 121.8, 122.0, 123.4, 124.1, 126.8, 127.7, 128.8, 129.0, 129.8, 131.7, 134.1, 134.6, 135.0, 135.1, 136.9, 137.7, 137.9, 140.4, 141.1, 142.0, 149.0, 151.6, 163.8, 165.5 (x 2), 168.7, 175.3. ESI-MS obsd 550.2640, calcd 550.2601 [$(M + H)^+$, M = $C_{36}H_{31}N_5O$]. λ_{abs} (CH_2Cl_2) 416, 509, 535, 587, 639 nm.

Zn12. A solution of **12** (10.9 mg, 0.0198 mmol) in CH_2Cl_2/MeOH [4 mL (3:1)] was treated with $Zn(OAc)_2$ (18.2 mg, 0.099 mmol, 1.5 equiv.). When UV−vis absorption spectroscopy indicated the consumption of the starting material (λ_{max} = 639 nm) and the formation of a single metalated chlorin (λ_{max} = 608 nm; approximately 3 h), the reaction mixture was diluted with CH_2Cl_2 and water. The aqueous layer was extracted with CH_2Cl_2. The combined organic phase was dried ($MgSO_4$), filtered, and concentrated. The solid residue was purified by column chromatography (silica, CH_2Cl_2/MeOH, 0 → 10%) affording an iridescent blue-green solid (10.6 mg, 88%): ^{1}H NMR (500 MHz, $CDCl_3$/CD_3OD) δ 1.99 (s, 6H), 2.24 (s, 3H), 4.47 (s, 2H), 7.62−7.65 (m, 3H), 7.79−7.80 (m, 2H), 7.96−7.97 (m, 2H), 8.01−8.04 (m, 2H), 8.28, 8.31 (ABq, J_{AB} = 4.3 Hz, 2H), 8.46 (s, 1H), 8.52−8.55 (m, 3H), 8.57−5.59 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$/CD_3OD) δ 23.9, 29.7, 30.9, 45.2, 50.4, 93.9, 96.1, 117.9, 123.2, 123.4, 126.4, 126.8, 127.1, 128.0, 128.1, 129.7, 132.7, 132.8, 133.7, 134.1, 137.5, 139.0, 143.1, 146.0, 146.1, 147.1, 147.2, 153.4, 153.8, 159.3, 170.1, 170.7. ESI-MS obsd 612.1714, calcd 612.1736 [$(M + H)^+$, M = $C_{36}H_{39}N_5OZn$]. λ_{abs} (CH_2Cl_2) 409, 504, 562, 608 nm.

17. A sample of **16a** (109 mg, 0.196 mmol) and **6** (89 mg, 0.182 mmol) were dissolved in DMF (1.5 mL) under an N_2 atmosphere. DIPEA (62 μL, 0.364 mmol) was added, and the solution was stirred under nitrogen for 3 min at rt before being cooled to 0 °C. HATU (75 mg, 0.182 mmol) was added, and stirring was continued with cooling for 10 min and at rt for 48 h. EtOAc was added, and the solution was washed 3 times with water and, then, once with saturated aqueous solution of $NaHCO_3$. The organic phase was dried (Na_2SO_4) and concentrated. Column chromatography, [silica, CH_2Cl_2/MeOH (0 → 5%)] gave a green solid (92 mg, 46%): ^{1}H NMR (multiple isomers detected, data reported for all, 500 MHz, $CDCl_3$) δ −2.37 (br, 1H), −1.97 (br, 1H), 1.27−1.50 (m, 33H), 2.05 (s, 6H), 2.52−3.72 (m, 19H), 4.60 (2*s*, 2H), 4.65−4.77 (2*s*, 2H), 7.12 (t, J = 6.1 Hz, 0.62H), 7.30 (d, J = 8.6 Hz, 1.63H), 7.72 (t, J = 3.3 Hz, 0.25H), 8.02−8.08 (m, 2H), 8.63, 8.67 (2*d*, J = 4.3 Hz, 1H), 8.81−8.85 (m, 2H), 8.93−9.02 (m, 4H), 9.22−9.24 (m, 1H), 9.83−9.86 (m, 1H). ^{13}C NMR (multiple isomers detected, data reported for all, 125 MHz, $CDCl_3$) δ 27.6, 27.71, 27.74, 27.8, 27.9, 27.97, 28.0, 28.1, 29.3, 29.6, 31.1, 31.2, 31.3, 33.3, 35.2, 36.4, 38.6, 46.37, 46.38, 48.0, 49.2, 49.9, 50.8, 51.8, 52.3, 52.5, 53.4, 54.0, 55.2, 56.1, 56.8, 67.3, 81.96, 82.04, 82.1, 82.5, 94.2, 86.9, 107.2, 113.3, 113.4, 120.9, 121.0, 123.3, 123.4, 123.7, 128.2, 128.37, 128.44, 132.0, 132.1, 132.4, 133.99, 134.04, 134.92, 134.94, 135.19, 135.24, 135.27, 135.33, 135.35, 139.4, 140.8, 140.9, 150.8, 152.6, 152.7, 157.2, 162.5, 162.86, 162.94, 168.8, 169.4, 170.1, 172.4, 173.0, 175.4, 175.5. ESI-MS obsd 1030.6163, calcd 1030.6124 [$(M + H)^+$, M = $C_{58}H_{80}N_9O_8$] obsd 515.8131, calcd 515.8099 $(M + 2H)^{2+}$. λ_{abs} (CH_2Cl_2) 406, 500, 584, 635 nm.

18. A sample of **16b** (109 mg, 0.196 mmol) and **11** (70 mg, 0.138 mmol) were dissolved in DMF (2.5 mL). DIPEA (63 μL, 0.37 mmol) was added, and the solution was stirred under nitrogen for 3 min at rt before being cooled to 0 °C. HATU (62 mg, 0.15 mmol) was added, and the mixture was stirred at 0 °C for 10 min and, then, at rt under nitrogen for 48 h. Water and EtOAc were added. The aqueous layer was extracted three times with EtOAc. The combined organic phase was washed 3 times with water and once with saturated aqueous solution of $NaHCO_3$. The organic phase was dried ($MgSO_4$) and concentrated. Column chromatography, [silica, CH_2Cl_2/MeOH (0 → 10%)] gave a brown-red solid (114.6 mg, 77%): ^{1}H NMR (500 MHz, $CDCl_3$) δ −1.89 (br, 2H), 1.41−1.45 (m, 27H), 2.06 (s, 6H), 2.32−3.75 (m, 24H), 4.61 (s, 2H), 7.70−7.74 (m, 3.3H), 7.95−7.96 (m, 2.2H), 8.10−8.12 (m, 3.2H), 8.45−8.56 (m, 2.4H), 8.71−8.87 (m, 5H), 8.95, 8.97 (2 × br, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 27.90, 27.92, 31.2, 31.5, 36.59, 36.63, 46.5, 48.1, 51.8, 51.9, 52.5, 54.5, 54.7, 55.4, 55.5, 55.6, 55.7, 55.8, 56.5, 81.9, 82.01, 82.04, 82.1, 82.2, 94.7, 96.8, 113.6, 118.5, 118.8, 122.0, 122.3, 123.2, 123.4, 126.8, 127.7, 128.8, 131.7, 132.0, 134.0, 134.1, 134.5, 135.0, 137.3, 138.0, 140.2, 140.9, 142.1, 152.1, 162.7, 163.6, 171.3, 172.4, 172.7, 172.8, 172.9, 173.0. ESI-MS obsd 1084.6016, calcd 1084.5995 [$(M + Na)^+$, M = $C_{62}H_{79}N_9O_7$]. λ_{abs} (CH_2Cl_2) 413, 639 nm. The sample retained DMF even after extensive drying.

19. The ^{t}Bu-protected ligand **17** (114.6 mg, 0.106 mmol) was dissolved in CH_2Cl_2 (5 mL), and TFA (5 mL) was added. The mixture was stirred at rt overnight. The mixture was concentrated to give a dark green solid that was used without further purification (quant): ^{1}H NMR (400 MHz, CD_3OD) δ 2.14 (s, 6H), 2.80 (s, 1H), 3.06−3.12 (m, 7H), 3.45−3.95 (m, 22H), 4.13−4.16 (m, 3 H), 4.79 (s, 2H), 4.94 (s, 2H), 7.61 (d, J = 8.8 Hz, 2H), 8.35 (d, J = 8.8 Hz, 2H), 8.64 (d, J = 4.4 Hz, 1H), 8.98 (d, J = 4.8 Hz, 2H), 9.11 (d, J = 4.8 Hz, 1H), 9.21 (d, J = 4.4 Hz, 1H), 9.31 (d, J = 4.8 Hz, 1H), 9.38 (s, 1H), 9.50 (s, 1H), 9.60 (d, J = 4.8 Hz, 1H), 10.39 (s, 1H). ^{13}C NMR (125 MHz, CD_3OD) δ 32.0, 36.4, 39.7, 50.7−56.5 (br m), 69.3, 99.2, 102.3, 105.6, 116.6, 117.4, 119.7, 122.2, 127.7, 127.8, 128.0, 129.0, 132.2, 134.2, 135.5, 138.6, 139.4, 139.5, 141.7, 143.1, 146.2, 147.6, 161.3, 170.3,

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172.8, 175.4, 183.7. ESI-MS obsd 862.4295, calcd 862.4246 ($C_{46}H_{56}N_9O_8$) obsd (M+2H) 431.7166, calcd (431.7160) ($C_{46}H_{57}N_9O_8$); λ_{abs} (MeOH) 404, 499, 565, 613, 634 nm.

20. The ^{t}Bu-protected ligand **18** (114.6 mg, 0.106 mmol) was dissolved in CH_2Cl_2 (5 mL), and TFA (5 mL) was added. The mixture was stirred at rt overnight. The mixture was concentrated to give a dark green solid that was used without further purification (quant): ^{1}H NMR (500 MHz, CD_3OD, 2 isomers detected, data reported for the major isomer) δ 2.14 (s, 6H), 3.18−4.26 (m, 24H), 4.74 (s, 2H), 7.92−7.96 (m, 3H), 8.19−8.20 (m, 2H), 8.29−8.40 (m, 6H), 8.94−8.96 (m, 2H), 9.08−9.09 (m, 1H), 9.14−9.15 (m, 1H), 9.36−9.37 (m, 2H). ^{13}C NMR (125 MH, CD_3OD, data reported for all isomers) δ 29.4, 29.8, 35.6, 37.5, 50.8−53.2 (br m), 97.7, 97.8, 99.3, 113.0, 115.3, 117.6, 118.1, 118.8, 119.1, 119.5, 119.6, 119.8, 119.9, 120.2, 124.7, 124.76, 124.83, 124.9, 125.7, 126.0, 126.1, 126.39, 126.43, 127.8, 129.1, 129.2, 130.3, 130.4, 130.6, 130.7, 135.65, 135.71, 136.0, 136.4, 136.5, 136.86, 136.93, 137.0, 137.5, 139.3, 140.0, 141.06, 141.12, 141.2, 144.6, 169.55, 169.61, 180.1, 180.5. ESI-MS obsd 916.4194, calcd 916.4117 [$(M + Na)^+$, M = $C_{50}H_{55}N_9O_7$]. λ_{abs} (MeOH) 410, 506, 535, 585, 637 nm.

L^1Yb. The ligand **19** was dissolved in a minimum amount (<0.5 mL) of MeCN. Yb(OTf)$_3$ (3 equiv) was added, and the mixture was stirred at 70 °C for 48 h. The mixture was concentrated, and the residue was crystallized from MeCN/Et_2O. The solid obtained was suspended in acetonitrile (∼ 10 mL), and stirred at room temperature for 1 h. The solid was collected by centrifugation and suspended in MeOH (∼3 mL). Aqueous HCl (1 M) was added dropwise until a homogeneous solution was obtained. The volatiles were removed under reduced pressure. The residue was dissolved in a minimum amount of water, filtered through a plug of cotton wool, and the filtrate was freeze-dried to afford a voluminous dark green solid (44 mg, 98%): ESI-MS obsd 1033.3410, calcd 1033.3406 [$(M + H)^+$, M = $C_{46}H_{52}N_9O_8Yb$]. λ_{abs} (MeOH) 405, 498, 565, 613, 634 nm; (H_2O) 403, 503, 637.

L^1Nd. The ligand **19** was dissolved in a minimum amount (<0.5 mL) of MeCN. Nd(OTf)$_3$ (3 equiv) was added, and the mixture was stirred at 70 °C for 48 h. The mixture was concentrated and crystallized from MeCN/Et_2O. The solid obtained was suspended in acetonitrile (∼10 mL) and stirred at room temperature for 1 h. The solid was collected by centrifugation and suspended in MeOH (∼ 3 mL). Aqueous HCl (1 M) was added dropwise until a homogeneous solution was obtained. The volatiles were removed under reduced pressure. The residue was dissolved in a minimum amount of water and filtered through a plug of cotton wool, and the filtrate was freeze-dried to afford a voluminous dark green solid (30 mg, 73%): ESI-MS obsd 1003.3134, calcd 1003.3122 [$(M + H)^+$, M = $C_{46}H_{52}N_9O_8Nd$]. λ_{abs} (CH_3OH) 405, 499, 564, 613, 633 nm; (H_2O) 403, 501, 635 nm.

L^2Yb. The ligand (**20**, as the TFA-salt, 36 mg, ∼0.043 mmol) and $YbCl_3$ (13.1 mg, 0.047 mmol) were dissolved in a mixture of MeOH and water (3 mL, 2:1). The pH was adjusted to 7 with 0.1 M aqueous NaOH (approximately 200 μL). The reaction mixture was heated to 55 °C for 18 h. The mixture was concentrated, and the residue was suspended in acetonitrile (∼10 mL) and stirred at room temperature for 1 h. The solid was collected by centrifugation and suspended in water and MeOH (∼ 3 mL, 1:1). Aqueous HCl (1 M) was added dropwise until a homogeneous solution was obtained. The volatiles were removed under reduced pressure. The residue was dissolved in a minimum amount of MeOH and triturated with diethyl ether to afford a dark green solid (35.7 mg, 79%): ESI-MS calcd 1063.3300, obsd 1063.3321 [$(M - H)^-$, M = $C_{50}H_{52}N_9O_7Yb$]. λ_{abs} 410, 503, 585, 637 (MeOH); 417, 641 (H_2O); 400, 415, 591, 639 (pH 7 buffer).

L^2Nd. The ligand (**20**, as the TFA-salt, 23.4 mg, ∼0.027 mmol) and Nd(OTf)$_3$ (17.3 mg, 0.029 mmol) were dissolved in a mixture of MeOH and ^{i}PrOH (4 mL, 1:1). Et_3N (50 μL) was added, resulting in the formation of a dark green precipitate. The reaction mixture was heated to 65 °C for 18 h. The mixture was concentrated, and the residue was suspended in acetonitrile (∼10 mL) and stirred at room temperature for 1 h. The solid was collected by centrifugation and suspended in water and MeOH (∼3 mL, 1:1). Aqueous HCl (1 M) was added dropwise until a homogeneous solution was obtained. The volatiles were removed under reduced pressure. The residue was dissolved in a minimum amount of MeOH, and triturated with diethyl ether to afford a dark green solid (17.4 mg, 64%): ESI-MS calcd 1031.2989, obsd 1031.2962 [$(M - H)^-$, M = $C_{50}H_{52}N_9O_7Nd$]. λ_{abs} 412, 573, 637 (MeOH), 419, 512, 593, 642 (H_2O), 409, 417, 513, 591, 641 (pH 7 buffer).

L^2(Zn)Nd. The free-base chlorin-equipped complex (**L^2Nd**, 0.039 mmol) was dissolved in MeOH (2 mL). Diisopropylethylamine (50 μL) was added, followed by a single portion of $Zn(OAc)_2$ (11 mg, 0.059 mmol). The reaction mixture was stirred at room temperature, and the progress of the reaction was monitored by UV−vis absorption spectroscopy. After ∼22 h a single metalated chlorin species was detected (λ_{max} = 607 nm). The reaction mixture was diluted with a large volume of diethyl ether, resulting in the formation of a dark green precipitate, which was further purified by a second round of trituration from MeOH with Et_2O. A bluish-green solid was obtained (24.8 mg, 64%): ESI-MS calcd 1093.2129, obsd 1093.2225 [$(M - H)^-$, M = $C_{50}H_{50}N_9NdO_7Zn$]. λ_{abs} 411, 607 (MeOH).

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Additional synthetic procedures and spectral characterization, and copies of ^{1}H and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Author Contributions

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Notes

The authors declare no competing financial interest.

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