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A New Route for Installing the Isocyclic Ring on Chlorins Yielding 13[1]-Oxophorbines

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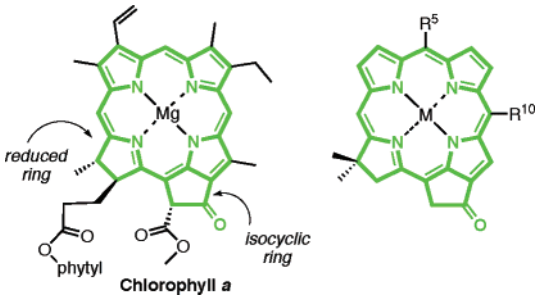


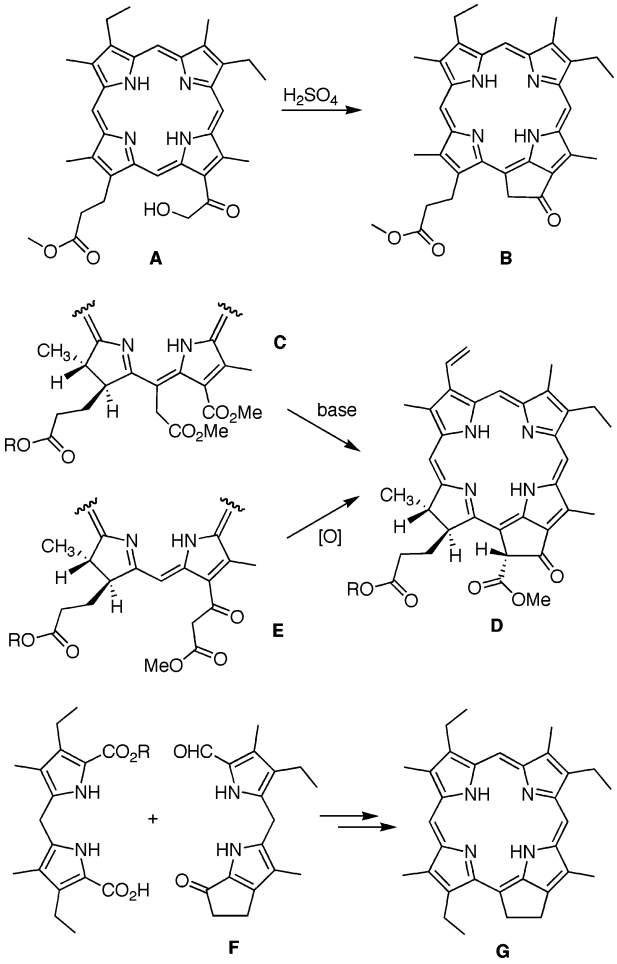
A new route to 13[1]-oxophorbines, the parent macrocycle of chlorophylls, begins with the synthesis of a 13-bromochlorin. Pd-mediated coupling of the latter with tributyl(1-ethoxyvinyl)tin and subsequent acidic hydrolysis afforded the 13-acetylchlorin (**1**). Treatment of **1** with NBS afforded the 15-bromo analogue in 70% yield. Pd-mediated α-arylation closed the isocyclic ring to give the 13[1]-oxophorbine (**2**) in 85% yield. Facile access to 13[1]-oxophorbines should enable a variety of spectroscopic studies and diverse applications.

Introduction

The fundamental skeleton of chlorophylls is a phorbine, which differs from porphyrins in containing one reduced pyrrole ring and a five-membered exocyclic ring. The exocyclic ring (known as the isocyclic ring) is ortho-perifused across the 13- and 15-positions and contains a 13[1]-oxo group.[1] Chlorophyll *a* absorbs strongly in the blue (B band, ~430 nm) and the red (Q_y band, ~660 nm) regions of the visible spectrum. The 13-keto group, which is conjugated with the π-electrons of the macrocycle, causes a significant red-shift and intensification of the Q_y band compared to synthetic chlorins lacking a 13-keto substituent.[2] Intense absorption in the red region is attractive for applications encompassing solar cells,[3] medical imaging,[4] and photodynamic therapy.[5] Moreover, the 13-keto substituent is an essential motif for self-assembly of certain chlorophyll species.[6]

Surprisingly few routes are known for the construction of the isocyclic ring (Scheme 1).[7] Fischer reported the dehydration of a (hydroxymethylcarbonyl)porphyrin using concentrated H_2SO_4 to give the "pheoporphyrin" bearing the isocyclic ring (**A** → **B**),[8] and Dieckmann cyclization to convert chlorin e_6 trimethyl ester to methyl pheophorbide *a* (**C** → **D**).[9,10] The Dieckmann cyclization has been carried out using KOH/pyridine,[9] sodium methoxide in methanol/acetone,[10] potassium *tert*-butoxide/pyridine,[11] sodium bis(trimethylsilylamide),[12] or potassium *tert*-butoxide/collidine.[13] Kenner employed oxidative cyclization with a porphyrin bearing a β-ketoester to give the pheoporphyrin,[14] a route extended by Smith for conversion of a chlorin to the methyl pheophorbide *a* (**E** → **D**).[15] Finally, a

SCHEME 1



† Equal contributions by both authors.

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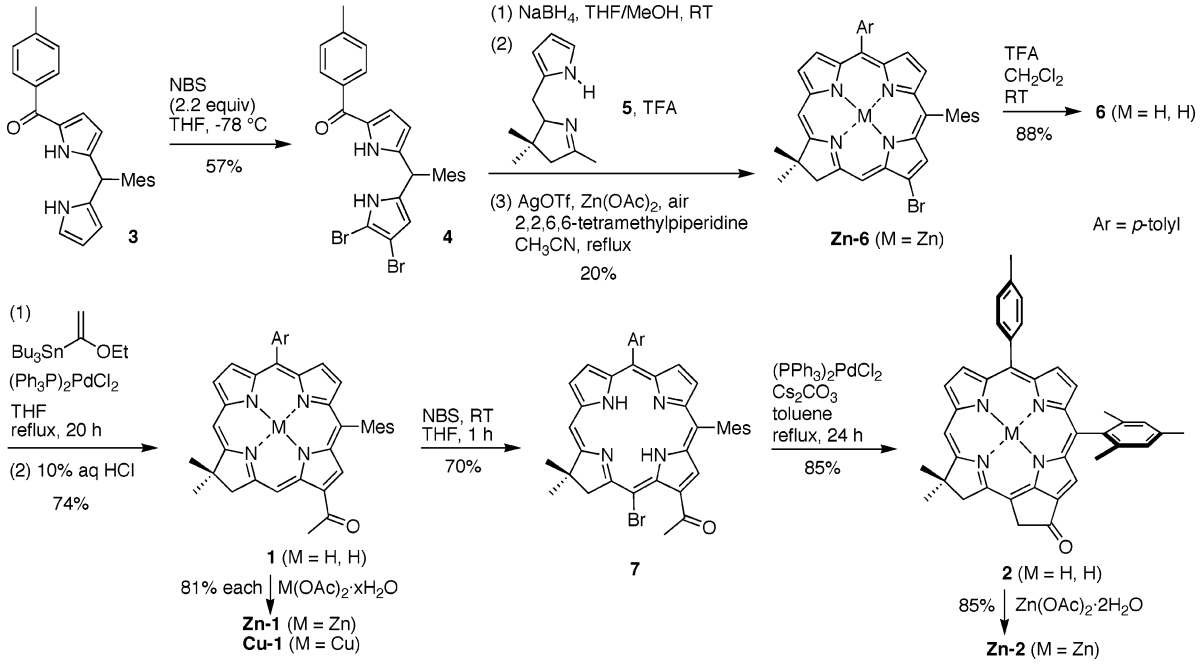
SCHEME 2



dipyrromethane bearing an annulated oxocyclopentanyl ring (**F**) provided an intriguing route to deoxophylloerythroetioporphyrin (**G**), although this macrocycle is a porphyrin and lacks the desired 13-keto functionality.[16] Lash has employed annulated dipyrromethanes in the synthesis of **G** and related porphyrin analogues.[17] Each of these routes has certain attractions; however, none appeared compatible with our existing synthetic route to chlorins.

We have developed synthetic methods for preparing chlorins wherein each chlorin incorporates a geminal dimethyl moiety in the reduced, pyrroline ring to block adventitious dehydrogenation.[18,19] We recently exploited this route to gain access to chlorins bearing substituents that afford enhanced red absorption spectral features, including 3-acetyl, 3-ethynyl, 3-vinyl, 13-acetyl, and 13-ethynyl groups.[20] Here, we describe extension of the route for preparing 13-acetylchlorins to install the isocyclic ring under mild reaction conditions.

Results and Discussion

A. Chlorin Precursors. Treatment of 5-mesityldipyrromethane[21] with 3.0 molar equiv of EtMgBr at room temperature followed by *S*-2-pyridyl 4-methylbenzothioate[22] at −78 °C gave 1-acyldipyrromethane **3** in 73% yield, to be compared with 37% achieved previously upon acylation with *p*-toluoyl chloride.[18] Treatment of **3** with 2.2 molar equiv of NBS at −78 °C gave the 8,9-dibromo-product **4** along with several side products (Scheme 2). Although somewhat labile, compound **4** could be handled effectively by workup without heating and by avoiding adverse solvents (ethyl acetate, chlorinated hydrocarbons; see Supporting Information) and was obtained following column chromatography in 57% yield. The 8,9-dibromo-substitution pattern in **4** was established by NMR spectroscopy (^{1}H−^{1}H 2D-COSY and NOESY experiments).

B. Chlorin Formation. Reduction of **4** with $NaBH_4$ at room temperature for 3 h gave the corresponding dipyrromethane-1-carbinol (Eastern half), which was condensed with Western half **5**[23] under the standard conditions[19] of TFA catalysis. The putative tetrahydrobilene-*a* formed in situ was subjected to metal-catalyzed oxidative cyclization (2,2,6,6-tetramethylpiperidine, $Zn(OAc)_2$, and AgOTf) in refluxing acetonitrile in the presence of air for 18 h, affording the zinc chelate of the 13-bromochlorin (**Zn**−**6**) in 20% yield (from **4**).

The conversion of the 13-bromochlorin to the 13-acetylchlorin was carried out by Pd-mediated coupling using tributyl(1-ethoxyvinyl)tin[24] followed by acidic hydrolysis of the resulting enol ether. Use of the zinc chlorin **Zn**−**6** gave limited conversion upon reaction in refluxing toluene (7% yield) or THF (∼29% yield). The synthesis of **1** was improved by carrying out the palladium coupling using free base chlorin **6**, which was obtained in 88% yield by demetalation of **Zn**−**6** with TFA in CH_2Cl_2 at room temperature. The coupling of **6** (20 mM)

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TABLE 1. Spectral Properties of Chlorins and 13[1]-Oxophorbines[a]

compound	λ_B (fwhm) in nm	logϵ_B	λ_{Qy} (fwhm) in nm	logϵ_{Qy}	$\Delta\nu_{Qy}$ (cm^{-1})[b]	I_B/I_Q[c]	λ_{em} (nm)[d]	$\Delta\nu$(cm^{-1})[e]	Φ_f[f]
Zn−8	412 (13)[g]	5.27	608 (11)	4.64	0	4.9	611	80	0.062
Zn−1	424 (17)[h]	5.30	635 (14)	4.85	700	2.8	639	100	0.25
Zn−2	431 (16)[i]	5.15	643 (11)	4.84	900	2.1	646	70	0.28
8	414 (34)[j]	4.95	641 (9)	4.45	0	3.3	643	50	0.23
1	423 (36)	5.14	661 (13)	4.72	470	2.6	665	90	0.25
2	417 (49)[k]	5.00	660 (11)	4.71	450	2.0	663	70	0.37
Zn−Pheo *a*[l,m]	423 (38)	5.09	653 (18)	4.96	−	1.4	657	90[n]	0.23[n]
Pheo *a*[o,p]	410 (63[q])	4.97	667 (21[q])	4.65	−	2.1	675[q]	180[q]	0.28[r]
Chl *a*[s,t]	433 (39[q])	5.01	666 (19[q])	4.89	−	1.3	671[q]	110[q]	0.325[u]

[a] In toluene at room temperature unless noted otherwise. [b] The redshift of the Q_y band relative to that of the parent chlorin (**8** or **Zn−8**). [c] Ratio of the intensities of the B and Q_y bands. [d] Excitation was performed at the λ_{max} of the B band. [e] Stokes shift. [f] Determined with λ_{exc} at the B band maximum using chlorophyll *a* as a standard ($\Phi_f = 0.322$) unless noted otherwise (see Supporting Information). [g] Shoulder at 391 nm. [h] Shoulder at 402 nm. [i] Shoulder at 409 nm (log $\epsilon = 4.73$). [j] Shoulder at 398 nm. [k] Shoulder at 431 nm (log $\epsilon = 4.97$). [l] In diethyl ether. [m] Absorption data from ref 30. The absorption spectrum is essentially identical in $CHCl_3$.[29] [n] Reference 32. The Φ_f value was calculated using data from ref 32 with chlorophyll *a* as standard. A value of $\Phi_f = 0.17$ in diethyl ether/petroleum ether has been reported.[31] [o] In ethanol. [p] Absorption and emission data from ref 33. [q] This work. [r] In ethanol. The Φ_f in toluene was found to be as follows: Pheophorbide *a* (0.26), pyropheophorbide *a* (0.29), pyropheophorbide *a* methyl ester (0.30). [s] In benzene. [t] Absorption data from ref 28. [u] Reference 27.

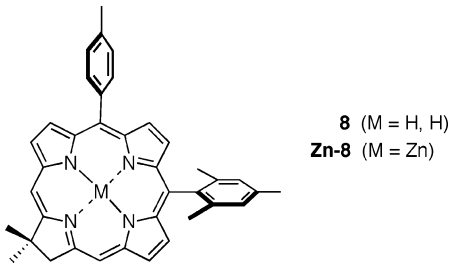
and tributyl(1-ethoxyvinyl)tin (40 mM) in the presence of 15 mol % of $(PPh_3)_2PdCl_2$ in THF for 20 h followed by hydrolysis with 10% aqueous HCl gave 13-acetylchlorin **1** in 74% yield. A streamlined procedure including demetalation, Pd-coupling, and acidic workup gave **1** in 68% yield starting from **Zn−6**. The free-base 13-acetylchlorin **1** was metalated with $Zn(OAc)_2 \cdot 2H_2O$ or $Cu(OAc)_2 \cdot H_2O$ to obtain **Zn−1** or **Cu−1**, respectively. The chlorins were characterized by mass spectrometry (LD-MS, FAB-MS) and absorption, fluorescence, and ^{1}H NMR spectroscopy. The X-ray structure of **Cu−1** confirmed the presence of the acetyl group at the 13-position of the chlorin macrocycle (Supporting Information).

C. Isocyclic Ring Installation. The α-arylation of aliphatic ketones has been carried out on a wide variety of aryl substrates, including aryl bromides under Pd-mediated coupling conditions.[25] Treatment of **1** to conditions for 15-bromination (1 equiv of NBS at room temperature for 1 h)[26] gave the 15-bromochlorin **7** in 70% yield. The reaction of **7** under conditions for α-arylation [$(PPh_3)_2PdCl_2$ in the presence of Cs_2CO_3 in toluene at reflux][25] for 24 h gave oxophorbine **2** in 85% yield. A combined procedure of bromination and Pd-mediated ring closure gave oxophorbine **2** in 44% yield from **1**. Treatment of **2** with $Zn(OAc)_2 \cdot 2H_2O$ at room temperature gave **Zn−2** in 85% yield. Oxophorbines **2** and **Zn−2** were characterized by mass spectrometry (LD-MS, FAB-MS) and absorption, fluorescence, IR and ^{1}H NMR spectroscopy.

D. Spectral Properties. The spectral properties of the 13-acetylchlorins and 13[1]-oxophorbines are listed in Table 1, accompanied by those of chlorophyll *a* (**Chl *a***),[27,28] the zinc (**Zn−Pheo *a***)[29−32] and free base (**Pheo *a***)[33,34] analogues of chlorophyll *a*, as well as benchmark zinc or free base chlorins (**Zn−8**, **8**)[18] lacking a 13-substituent (Chart 1). The absorption spectra of the synthetic oxophorbines and chlorins are shown in Figure 1. The major observations are as follows:

(1) Absorption spectral effects of the 13-acetyl substituent: The presence of the 13-acetyl substituent in the zinc complex (**Zn−1** vs. **Zn−8**) red-shifts both the B band (12 nm) and the Q_y band (27 nm), increases the intensity of the Q_y band (1.6-fold), and alters the I_B/I_{Q_y} ratio from 4.9 to 2.8. Similar trends are observed in the free base chlorins.

CHART 1



(2) Absorption spectral effects of the isocyclic ring: The presence of the isocyclic ring in the zinc complex (**Zn−2** vs **Zn−8**) red-shifts the Q_y band by 35 nm and increases the intensity of the Q_y band (1.5-fold). A similar trend was observed for the free base oxophorbine **2**, although the magnitude was less pronounced than for the zinc complexes given that the Q_y band of free base chlorin **8** appears at 641 nm. The absorption spectrum of the free base oxophorbine **2** closely resembles that of pheophorbide *a* (667 nm),[33,34] a free base analogue of chlorophyll *a* (see Supporting Information for overlaid spectra).

(3) Fluorescence yields: The fluorescence quantum yield (Φ_f) increases by >4-fold in going from the benchmark zinc chlorin (**Zn−8**, $\Phi_f = 0.062$) to the zinc 13-acetylchlorin **Zn−1** or zinc oxophorbine **Zn−2**. The yields are comparable to that of the chlorophyll derivative **Zn−Pheo *a*** (0.23). The effect of introducing a keto substituent in the free base compounds is less pronounced, where the parent chlorin **8** is already rather emissive ($\Phi_f = 0.23$).

(4) IR properties: 13-Acetylchlorin **1** exhibits a carbonyl stretch (ν_{max}) at 1728 cm^{-1}, whereas that of oxophorbine **2** appears at 1701 cm^{-1}. The latter matches well with that of

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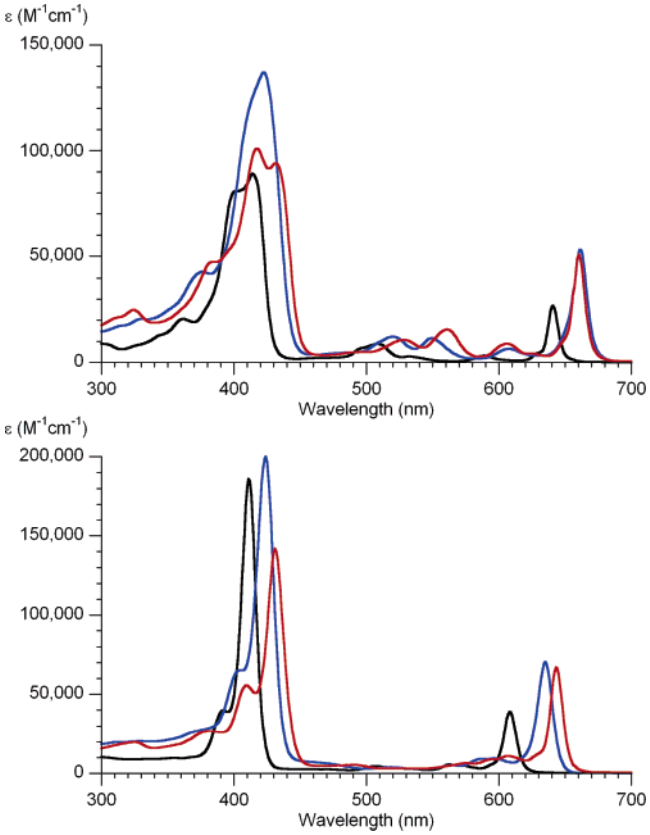

FIGURE 1. Absorption spectra in toluene at room temperature. Upper panel: free base compounds (color in graph; Q_y band position) include **8** (black, 641 nm); **1** (blue, 661 nm); **2** (red, 660 nm). Lower panel: zinc chelates include **Zn**−**8** (black, 608 nm); **Zn**−**1** (blue, 635 nm); **Zn**−**2** (red, 643 nm).

pheophytin *a* (1705 cm^{-1}),[35] methyl pheophorbide *a* (1703 cm^{-1}),[35] and methyl pyropheophorbide *a* (1695 cm^{-1}).[35]

In summary, a new route has been developed for installing the isocyclic ring on tetrapyrrole macrocycles. The route entails preparation of a 13-acetylchlorin, which undergoes bromination at the 15-position followed by a Pd-mediated α-arylation procedure to close the ortho-perifused ring. The presence of a keto group at the 13-position significantly red-shifts the absorption maximum and increases the intensity of the Q_y band. The ability to install the isocyclic ring opens a number of possible applications ranging from artificial photosynthesis to photomedicine.

Experimental Section

13-Acetylation: 13-Acetyl-17,18-dihydro-10-mesityl-18,18-dimethyl-5-*p*-tolylporphyrin (1). Following a procedure for Stille coupling on aromatic compounds,[24] a mixture of **6** (19.8 mg, 0.0315 mmol), tributyl(1-ethoxyvinyl)tin (21.3 μL, 0.0630 mmol), and $(PPh_3)_2PdCl_2$ (3.40 mg, 0.00472 mmol) was refluxed in THF (1.5 mL) for 20 h in a Schlenk line. The reaction mixture was treated with 10% aqueous HCl (1 mL) at room temperature for 2 h. CH_2Cl_2 was added, and the organic layer was separated. The organic layer was washed with saturated aqueous $NaHCO_3$, water, and brine. The organic layer was dried (Na_2SO_4), concentrated, and chromatographed [silica, hexanes then CH_2Cl_2/hexanes (1:1)], affording a purple solid (13.7 mg, 74%): IR 1728 cm^{-1}; ^1H NMR δ −0.98 (br, 2H), 1.86 (s, 6H), 2.02 (s, 6H), 2.61 (s, 3H), 2.66 (s, 3H), 3.05 (s, 3H), 4.56 (s, 2H), 7.24 (s, 2H), 7.50 (d, J = 7.8 Hz, 2H), 7.96 (d, J = 7.8 Hz, 2H), 8.23 (d, J = 4.4 Hz, 1H), 8.31 (d, J = 4.4 Hz, 1H), 8.68 (d, J = 4.4 Hz, 1H), 8.69 (s, 1H), 8.70 (d, J = 4.4 Hz, 1H), 8.86 (s, 1H), 9.98 (s, 1H); LD-MS obsd 590.6; FAB-MS obsd 590.3052, calcd 590.3046 ($C_{40}H_{38}N_4O$); λ_{abs} 423 (log ϵ = 5.14), 661 (4.72) nm; λ_{em} 665 (Φ_f = 0.25).

15-Bromination: 13-Acetyl-15-bromo-17,18-dihydro-10-mesityl-18,18-dimethyl-5-*p*-tolylporphyrin (7). Following a reported procedure,[26] a solution of **1** (26.4 mg, 0.0447 mmol) in THF (22 mL) was treated with NBS (7.95 mg, 0.0447 mmol) at room temperature for 1 h. CH_2Cl_2 was added. The mixture was washed with aqueous $NaHCO_3$. The organic layer was dried (Na_2SO_4), concentrated, and chromatographed [silica, hexanes then CH_2Cl_2/hexanes (3:1)], affording a purple solid (20.8 mg, 70.%): ^1H NMR δ −1.30 to −1.40 (br, 1H), −0.98 to −1.02 (br, 1H), 1.86 (s, 6H), 2.04 (s, 6H), 2.60 (s, 3H), 2.66 (s, 3H), 3.06 (s, 3H), 4.55 (s, 2H), 7.21 (s, 2H), 7.51 (d, J = 7.8 Hz, 2H), 7.96 (d, J = 7.8 Hz, 2H), 8.26 (d, J = 4.4 Hz, 1H), 8.34 (d, J = 4.4 Hz, 1H), 8.45 (s, 1H), 8.70−8.76 (m, 3H); LD-MS obsd 668.4; FAB-MS obsd 668.2145, calcd 668.2150 ($C_{40}H_{37}BrN_4O$); λ_{abs} 418, 652 nm.

Installation of the Isocyclic Ring: 18,18-Dimethyl-10-mesityl-13^1-oxo-5-*p*-tolylphorbine (2). A mixture of **7** (20.2 mg, 0.0301 mmol), Cs_2CO_3 (49.0 mg, 0.150 mmol), and $(PPh_3)_2PdCl_2$ (4.22 mg, 0.0125 mmol) was refluxed in toluene (3.0 mL) for 24 h in a Schlenk line. CH_2Cl_2 was added. The reaction mixture was washed with water and brine. The organic layer was dried (Na_2SO_4), concentrated, and chromatographed [silica, hexanes then hexanes/Et_2O (1:1)], affording a purple solid (15.1 mg, 85%): IR 1701 cm^{-1}; ^1H NMR δ −1.25 (br, 1H), 0.73 (br, 1H), 1.88 (s, 6H), 2.02 (s, 6H), 2.57 (s, 3H), 2.65 (s, 3H), 4.27 (s, 2H), 5.12 (s, 2H), 7.20 (s, 2H), 7.49 (d, J = 7.8 Hz, 2H), 7.93 (d, J = 7.8 Hz, 2H), 8.22 (d, J = 4.4 Hz, 1H), 8.28 (d, J = 4.4 Hz, 1H), 8.53 (s, 1H), 8.58 (s, 1H), 8.62 (d, J = 4.4 Hz, 1H), 8.70 (d, J = 4.4 Hz, 1H); LD-MS obsd 589.2; FAB-MS obsd 589.2971, calcd 589.2967 [$(M+H)^+$, M = $C_{40}H_{36}N_4O$]; λ_{abs} 417 (log ϵ = 5.00), 431 (sh, 4.97), 660 (4.71) nm; λ_{em} 663 (Φ_f = 0.37).

Zinc Insertion: Zn(II)-10-Mesityl-18,18-dimethyl-13^1-oxo-5-*p*-tolylphorbine (Zn−**2).** A solution of $Zn(OAc)_2 \cdot 2H_2O$ (106 mg, 0.484 mmol) in methanol (1.4 mL) was added to a solution of **2** (19.0 mg, 0.0323 mmol) in $CHCl_3$ (5.6 mL) with stirring at room temperature. After 16 h, the reaction mixture was concentrated, and CH_2Cl_2 was added. The organic layer was washed (saturated aqueous $NaHCO_3$, H_2O), dried (Na_2SO_4), and filtered. The filtrate was concentrated to dryness. The resulting solid was washed with hexanes several times. The solid was dissolved in a minimum amount of methanol, and then hexanes was added (∼2:1 ratio of hexanes/methanol), affording a green solid (18.0 mg, 85%): ^1H NMR (THF-d_8) δ 1.88 (s, 6H), 2.03 (s, 6H), 2.56 (s, 3H), 2.63 (s, 3H), 4.30 (s, 2H), 5.00 (s, 2H), 7.22 (s, 2H), 7.47 (d, J = 7.6 Hz, 2H), 7.88 (d, J = 7.6 Hz, 2H), 8.15 (d, J = 4.4 Hz, 1H), 8.18 (d, J = 4.4 Hz, 1H), 8.33 (s, 1H), 8.48 (s, 1H), 8.50 (d, J = 4.4 Hz, 1H), 8.62 (d, J = 4.4 Hz, 1H); LD-MS obsd 650.2; FAB-MS obsd 650.2031, calcd 650.2024 ($C_{40}H_{34}N_4OZn$); λ_{abs} 409 (sh, log ϵ = 4.73), 431 (5.15), 643 (4.84) nm; λ_{em} 646 (Φ_f = 0.28).

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Supporting Information Available: Complete experimental procedures; description of phorbine nomenclature; crystallographic data for **Cu**−**1**. This material is available free of charge via the Internet at http://pubs.acs.org.

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