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Nearly Chromatography-Free Synthesis of the A_3B-Porphyrin 5-(4-Hydroxymethylphenyl)-10,15,20-tri-*p*-tolylporphinatozinc(II)

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Abstract:

Rational routes to synthetic porphyrins bearing distinct meso-substituents have typically been implemented at modest scale (<1 g quantities). The A_3B-porphyrin 5-(4-hydroxymethylphenyl)-10,15,20-tri-*p*-tolylporphinatozinc(II) (Zn-1) is required in multigram quantities for possible commercial use in information storage applications. The synthesis of Zn-1 has been carried out by reaction of 5-(4-hydroxymethylphenyl)dipyrromethane and the dicarbinol derived from 1,9-di-*p*-toluoyl-5-*p*-tolyldipyrromethane. Four improvements have been made to the steps leading to the dipyrromethane and dipyrromethane−dicarbinol: (i) use of 50 equiv of pyrrole in the condensation of an aldehyde to give the dipyrromethane (versus 100 equiv previously), (ii) 1,9-diacylation of a dipyrromethane using the hindered Grignard reagent 2,6-dimethylphenylmagnesium bromide and *p*-toluoyl chloride to give the 1,9-diacyl versus 1-acyl products in >10:1 ratio (versus 4:1 using EtMgBr), (iii) isolation of the dibutyltin complex of the 1,9-diacyldipyrromethane from the crude reaction mixture by direct crystallization using methanol/methyl *tert*-butyl ether (MTBE) (versus silica chromatography), and (iv) reduction of the dibutyltin complex of the 1,9-diacyldipyrromethane (250 mM) with ∼10−15 mol equiv of $NaBH_4$ (versus 25 mM and 40 mol equiv). The procedures have been carried out with no chromatography at large scale, affording the dipyrromethane (31, 59, or 79 g), the dibutyltin complex of a 1,9-diacyldipyrromethane (361 g), and reduction of the latter (45 g). The porphyrin-forming reaction has been performed (25 mM reactants at 50-mmol scale, or 10 mM at 64-mmol scale) in a two-step process of condensation and oxidation to give the free base porphyrin 1 in 3.7- or 5.8-g quantities. Metalation with zinc acetate afforded Zn-1, which was isolated by direct crystallization. Taken together, the various improvements facilitate synthesis of the target porphyrin Zn-1 and may have broad applicability.

Introduction

The growing importance of porphyrins in fundamental studies as well as possible commercial applications places a premium on synthetic methods that afford substantial quantities of pure compounds in a straightforward manner. Porphyrins bearing four identical meso-substituents have been available commercially in gram quantities for some time. The current methods of synthesis for such A_4-porphyrins, which entail one-flask reaction of an aldehyde and pyrrole, should support large-scale synthesis where the substituents are rather simple.[1,2] For many applications, a distinct pattern of up to four different meso-substituents is desired, which generally requires a rational, stepwise synthesis.

A new commercial application of porphyrins may reside in next-generation memory devices, such as dynamic random access memory (DRAM) chips.[3−5] In this information storage application, the porphyrin serves as a charge-storage element in a hybrid molecular semiconductor chip. The porphyrin is attached to an electroactive surface, and hence must bear one surface attachment group. Other groups may be incorporated to alter the electrochemical potentials, provide steric bulk, or provide a site for derivatization with other components to complete the memory cell. Meso-substituted porphyrins that satisfy these architectural requirements are of the A_3B-, AB_2C-, or ABCD-type. For a monolayer of porphyrin in a memory device, a 1-cm^2 chip would incorporate ∼0.3 μg of porphyrin (assuming a 50 $Å^2$ molecular footprint and a molecular weight of 1000 Da). Although the amount of porphyrin per chip is tiny, the market for DRAM chips is vast. Moreover, the attachment procedures for incorporating porphyrins into chips are quite inefficient at present.[6,7] Accordingly, the development of streamlined procedures for the preparation of large quantities of porphyrins bearing multiple distinct meso substituents is of considerable importance.

A current candidate for incorporation in DRAM cells is a zinc porphyrin that bears three *p*-tolyl groups and one *p*-hydroxymethylphenyl moiety (Chart 1). This A_3B-porphyrin has been used in several applications as the zinc chelate (**Zn-1**) or as the free base form (**1**), including the preparation

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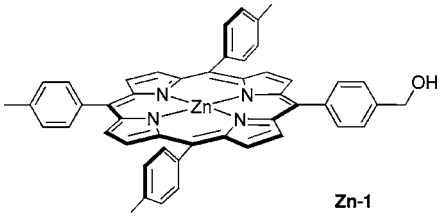
Chart 1



Zn-1

of porphyrin dyads,[8,9] attachment to silicon surfaces for studies of electron-transfer reactions,[10] and as one ligand in a lanthanide triple-decker sandwich coordination compound.[11] The applications have motivated several syntheses. An early synthesis employed statistical condensation of 4-carbomethoxybenzaldehyde (or the acetal thereof) and *p*-tolualdehyde under Adler conditions[9,12] or at room temperature[13] to give 5-(4-methoxycarbonylphenyl)-10,15,20-tri-*p*-tolylporphyrin (**2**). Reduction of porphyrin−ester **2** gave the free base porphyrin−alcohol **1**.[8,9] In general, the simplicity of statistical syntheses is offset by diminished yield and the complexity of the chromatography required to separate the desired product. Few exceptions to this rule are observed in porphyrin chemistry.

The most recent synthesis of **Zn-1**, via a rational approach, is shown in Scheme 1.[14] Condensation of *p*-tolualdehyde with excess pyrrole in the presence of TFA followed by bulb-to-bulb distillation afforded 5-*p*-tolyldipyrromethane (**3**). Acylation of the dipyrromethane was achieved upon treatment with 5 mol equiv each of EtMgBr and *p*-toluoyl chloride, affording the 1,9-diacyldipyrromethane **4**. Reduction of the latter with $NaBH_4$ in THF/methanol gave the corresponding dipyrromethane−dicarbinol **4-diol**. The critical porphyrin-forming step was carried out by the condensation of ester-dipyrromethane **5** (prepared in a manner similar to that of **3**) and **4-diol** in acetonitrile containing TFA at room temperature. The resulting porphyrinogen was oxidized to give the free base porphyrin **2**. These conditions support reaction without detectable acidolysis, thereby affording the porphyrin with the desired pattern of meso substituents. Subsequent metalation with zinc acetate gave the zinc porphyrin−ester **Zn-2**, which upon reduction with $LiAlH_4$ gave the target zinc porphyrin−alcohol **Zn-1**. Although this approach afforded the desired porphyrin **Zn-1**, each step in the synthesis typically required chromatographic separation procedures.

Over the past few years we have devoted a great deal of effort to refine the rational synthesis of meso-substituted porphyrins.[15−17] The pertinent improvements include the following:

(i) Dipyrromethane formation: the prior solventless synthesis[18] was modified to include use of a larger excess of pyrrole (100 equiv) relative to the amount of aldehyde, use of a mild Lewis acid (e.g., $InCl_3$) for catalysis, and workup by removal of the catalyst and pyrrole followed by direct crystallization of the dipyrromethane. In this manner, the dipyrromethane could be obtained in 100-g quantities without aqueous−organic extraction, distillation, or chromatography.[19]

(ii) Synthesis and isolation of a 1,9-diacyldipyrromethane: the prior method for diacylation of a dipyrromethane[20] was modified to use a ratio of dipyrromethane/EtMgBr/acid chloride of 1:5:2.2[17] or 1:5:2.5.[21] Regardless, the attempted diacylation of a dipyrromethane typically affords a mixture of the dipyrromethane, 1-acyldipyrromethane, 1,9-diacyldipyrromethane, and diacyldipyrromethane isomers.[17,20] Acyldipyrromethanes typically afford amorphous foams upon crystallization (or exist as oils), requiring resort to chromatography, where extensive streaking results in excessive consumption of solvents, chromatographic media, and the experimentalist's time. An incisive method of isolation entails treatment of the crude reaction mixture with Bu_2SnCl_2 and TEA, which selectively affords the dibutyltin complex of the 1,9-diacyldipyrromethane. The complex is nonpolar, easily purified, and has been obtained at the 20-g scale in procedures with only limited reliance on chromatography.[21] (Note that dibutyltin compounds are generally nontoxic, unlike their trialkyl or tetraalkyl cousins; for a more thorough discussion and entry into the literature on this topic, see ref 21.)

(iii) Acid catalysis for porphyrin formation: the use of TFA in CH_3CN with 2.5 mM reactants[17] has been supplanted by two advances. One advance entailed the use of a mild Lewis acid in CH_2Cl_2 at room temperature, which afforded condensation without detectable scrambling and also facilitated chromatographic isolation of the porphyrin.[22] A second advance identified conditions that supported condensation at 10-fold higher concentration (25 versus 2.5 mM). The refined acid catalysis conditions were employed in the condensation of a dipyrromethane and a dipyrromethane−dicarbinol (18-mmol scale with catalysis by $Sc(OTf)_3$), affording 2.88 g (22.8% yield) of an ABCD-porphyrin.[23]

We sought to apply these improvements to the synthesis of **Zn-1**. Two approaches to **Zn-1** are outlined in Scheme 2. Both routes employ the dibutyltin complex of 1,9-diacyl-

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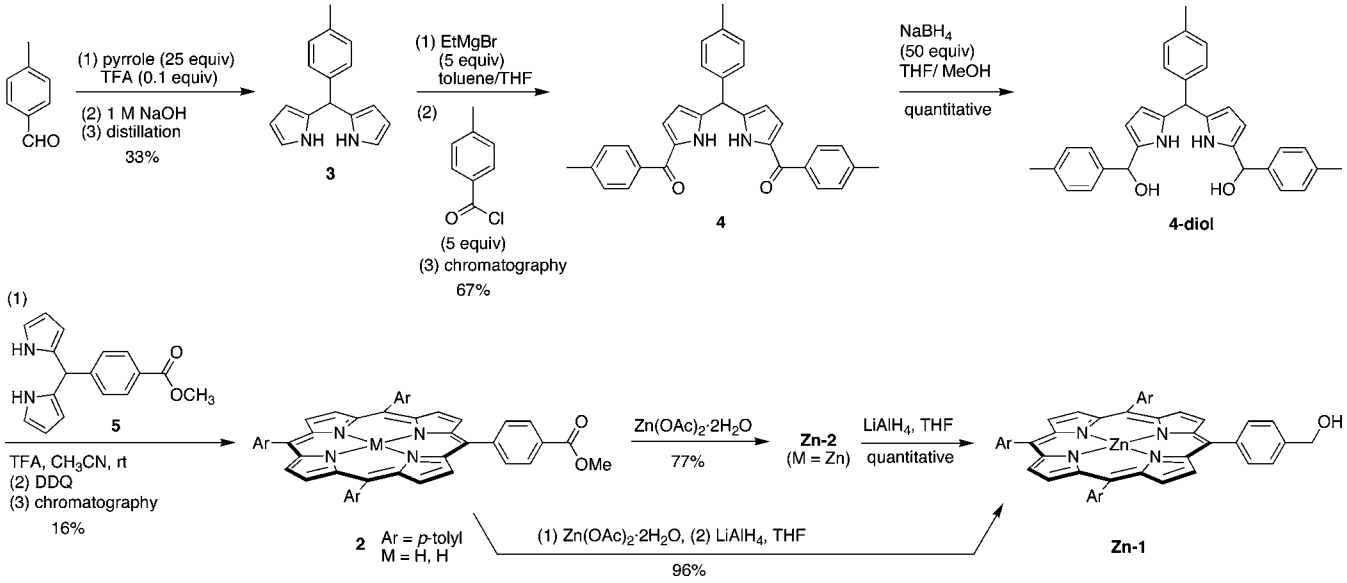
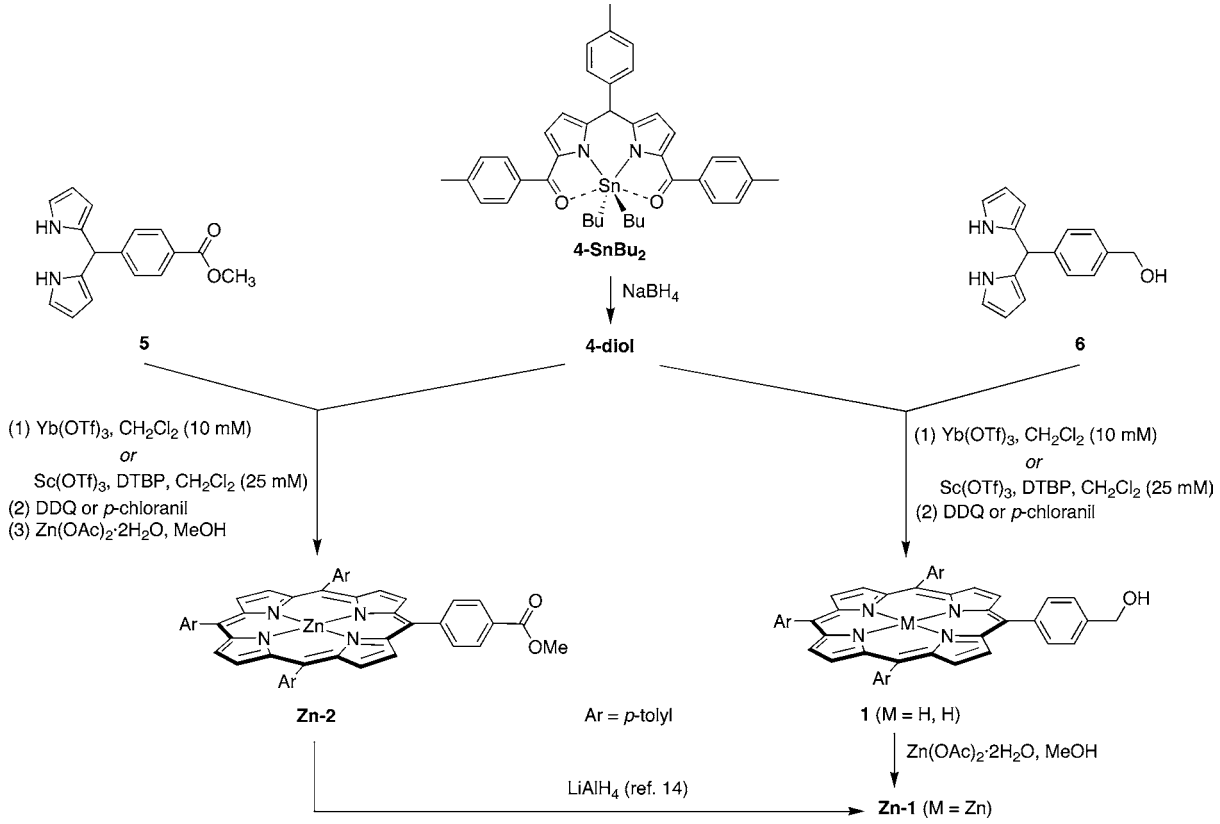
Scheme 1



Scheme 2



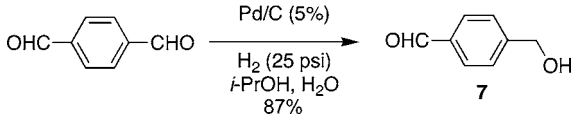
dipyrromethane **4** (**4-SnBu**$_2$) as a starting material, owing to its ready isolation. The corresponding dipyrromethane−dicarbinol is condensed with either dipyrromethane **6** or **5** to give the free base porphyrin **1** or **2**, respectively. Complexation affords the zinc chelate **Zn-1** or **Zn-2**. Porphyrin **Zn-2** can be reduced with $LiAlH_4$ to give **Zn-1**.

In attempting to carry out syntheses of **Zn-1** in multigram quantities, we developed additional refinements to the methods for preparing the porphyrin precursors. The refinements, which are reported herein, include dipyrromethane formation, 1,9-diacyldipyrromethane formation, isolation of the 1,9-diacyldipyrromethane−dibutyltin complex, and dipyrromethane−1,9-dicarbinol formation. The two approaches shown in Scheme 2 are employed to prepare the A_3B-porphyrin **Zn-1** in multigram quantities with limited reliance on chromatography.

Results and Discussion

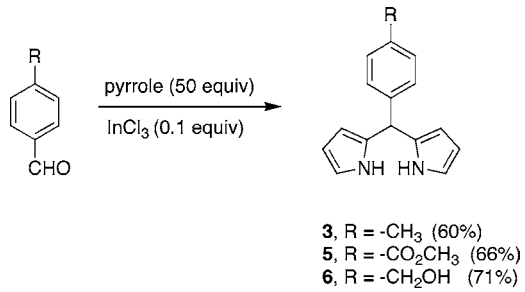
I. Preparation of Porphyrin Precursors. *I. A. 4-Hydroxymethylbenzaldehyde (7).* 4-Hydroxymethylbenzaldehyde (**7**) is not commercially available in large quantities. Compound **7** has been prepared in the literature via statistical

reduction of terephthalaldehyde using either $NaBH_4$ or $LiAlH_4$, followed by chromatographic workup,[24,25] or via catalytic hydrogenation using Pd/C catalysis.[26] Slight modifications to the latter procedure (use of *i*-PrOH instead of EtOH, 25 versus 45 psi of hydrogen pressure) afforded **7** in 87% yield after crystallization from a mixture of methyl *tert*-butyl ether (MTBE)/hexanes (1:1, v/v) (eq 1). Only minor amounts of 1,4-bis(hydroxymethyl)benzene (<5%) were formed after complete consumption of terephthalaldehyde. The use of MeOH or EtOH as solvent was found to produce sizable amounts of the corresponding monoacetal and diacetal byproducts. The use of *i*-PrOH as solvent diminished the acetal byproducts to <1% levels (as detected by GC−MS).



I. B. Preparation of Dipyrromethanes. The dipyrromethanes were prepared using a solventless reaction of an aldehyde with excess pyrrole in the presence of a mild Lewis acid (e.g., $InCl_3$) at room temperature.[19] An excess of pyrrole is essential to suppress the continued reaction that leads to linear or cyclic oligomers. The reaction is quenched by addition of powdered NaOH. Filtration removes insoluble organic material including inactivated catalyst and yields the crude dipyrromethane and excess pyrrole in the filtrate. Removal and recovery of excess pyrrole from the filtrate affords the crude dipyrromethane, which typically can be obtained by crystallization. The procedure generates little waste and does not require aqueous/organic extraction, distillation, or often, chromatography.

The dipyrromethanes employed in this work are shown in eq 2.



One modification to the prior procedure[19] was that 50 mol equiv of pyrrole was used instead of 100 mol equiv. The resulting reduction in the amount of pyrrole is advantageous on a large scale as it diminishes the raw material cost and shortens the time needed to remove the excess pyrrole via rotary evaporation. For the preparation of dipyrromethane **3**, no significant differences were observed in the reaction using 50 vs 100 equiv of pyrrole (as determined by GC−MS of the crude reaction mixtures). Accordingly, all subsequent dipyrromethane reactions were employed with a 50:1 pyrrole/aldehyde ratio. The reactions were readily monitored by GC or TLC. After 90 min, no aldehyde starting material was detected in each of the three cases examined. The reaction was quenched by the addition of solid NaOH.

A second modification to the standard procedure was introduced in the workup procedure. Upon removal of pyrrole under reduced pressure, the crude dipyrromethane (obtained as an oil, gum, or solid) typically contains residual pyrrole that is difficult to remove. The addition of a small amount of toluene followed by an evaporative co-strip of pyrrole and toluene afforded a cleaner dipyrromethane product.

Application of the two modifications (50:1 pyrrole/aldehyde ratio, toluene co-strip during workup) to the standard procedure[19] afforded dipyrromethane **3**[23] or **5**[19] in 60% (0.42 mol scale) or 66% (0.17 mol scale) yield upon recrystallization, respectively. No chromatography was required. For dipyrromethane−benzyl alcohol **6**, the crude product could not be obtained as a solid despite the use of the toluene co-strip. Hence, the resulting oil was passed through a silica column (7.6 × 20 cm) using an eluent of $CHCl_3$/MeOH (98:2 v/v). This step removed the tripyrrane and higher-molecular weight oligomers but did not separate the dipyrromethane and *N*-confused dipyrromethane. The product-containing fractions were concentrated to give a solid, which was recrystallized from toluene/EtOH (10:1 v/v) to afford **6** in 71% yield. The purity as determined by GC analysis was found to be >96%, with 3% of *N*-confused dipyrromethane as the sole identified byproduct after purification.

I. B.1. Pyrrole Purity. During the course of this work, we examined the purity of the pyrrole employed in the dipyrromethane synthesis. Significant variation was observed in the quality of commercial samples of pyrrole. Some commercial samples contained ∼1% of methylated pyrrole impurities, which severely hamper the purification step in the dipyrromethane synthesis. GC traces of two commercial samples of pyrrole are shown in Figure 1. The pyrrole obtained from Detrex, Inc. was found to have the highest quality among the suppliers examined and was used in all studies reported herein.

*I. C. Diacyldipyrromethane **4** and Tin Complex **4**-**SnBu**$_2$.* Diacylation of dipyrromethane **3** with *p*-toluoyl chloride leads to formation of the corresponding 1,9-diacyldipyrromethane intermediate (**4**), which is subsequently converted to the highly crystalline tin complex **4**-**SnBu**$_2$ (Scheme 3). Following the published method[21] using EtMgBr as Grignard reagent, the yield was not reproducible during preliminary development experiments. In addition, the exotherm of the reaction was difficult to control.

A chief challenge in this reaction is the requirement for 2 mol equiv of Grignard reagent to give the dipyrromethane bis(Grignard reagent) analogous to the pyrrole Grignard reagent. Upon each α-acylation process, 1 equiv of HCl is liberated. Accordingly, 2 equiv of base is required to neutralize the HCl liberated upon diacylation. The general approach has been to include 2 additional mol equiv of Grignard reagent (giving 4 mol equiv total) to provide the

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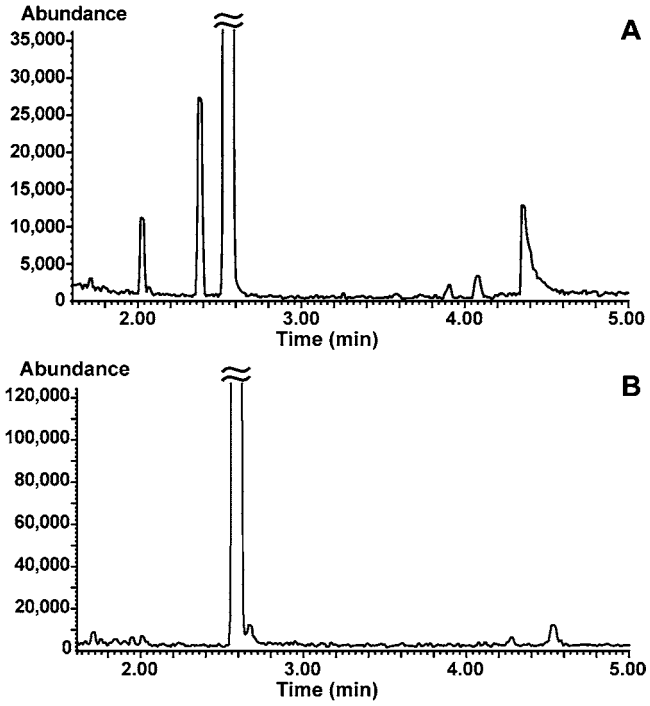

Figure 1. **GC traces of commercial samples of pyrrole. (A) Pyrrole obtained from a large commercial supplier (purity 98.2%). (B) Pyrrole obtained from Detrex, Inc. (purity >99.9%).**

necessary base. Not surprisingly, the use of EtMgBr results in reaction with *p*-toluoyl chloride to produce the corresponding ketone and alcohol (as determined by HPLC). In other studies we found that 9-acylation of a 1-acyldipyrromethane could be improved by use of hindered Grignard reagents or with bases other than EtMgBr to neutralize the liberated HCl.[27] On the other hand, a preliminary study (1-mmol scale) did not show improved 1,9-diacylation with use of hindered Grignard reagents (see Supporting Information of ref 27).[27]

The 1,9-diacylation of dipyrromethane **3** was examined using several commercially available Grignard reagents. The key issues are the ratio of the diacyldipyrromethane to the monoacyldipyrromethane, and the isolated yield of 1,9-diacyldipyrromethane. The diacyl/monoacyl ratio was assessed by HPLC analysis. The progress of the acylation also was examined by TLC. Using the solvent system hexanes/CH_2Cl_2/ethyl acetate (3:6:1) on silica, the dipyrromethane, 1-acyldipyrromethane, and 1,9-diacyldipyrromethane were readily separated with no streaking on TLC. The yield of 1,9-diacyldipyrromethane was assessed upon isolation as the dibutyltin complex (vide infra). With these analytical procedures in hand, the data in Table 1 were obtained for the 1,9-diacylation of **3** (8.46-mmol scale). The benchmark reaction with EtMgBr affords a diacyl/monoacyl ratio of ~4:1 and a yield of ~50% (entry 1). The use of hindered Grignard reagents afforded better ratios and higher yields (entries 2−4), reaching >10:1 and 70% in the case of 2,4,6-trimethylphenylmagnesium bromide (entry 2). The use of *p*-tolylmagnesium bromide (entry 5) gave results comparable to that of EtMgBr, indicating the essential role of steric hindrance in the improved results rather than an effect of aryl versus alkyl Grignard reagents. The amount of reagent also was optimized, wherein only 2.1 mol equiv of *p*-toluoyl chloride and 4.2 mol equiv of Grignard reagent (versus 2.5 and 5 mol equiv, respectively[21]) were utilized. Owing to price considerations, we chose 2,6-dimethylphenylmagnesium bromide versus mesitylmagnesium bromide as the Grignard reagent of choice for the diacylation process.

Scheme 3

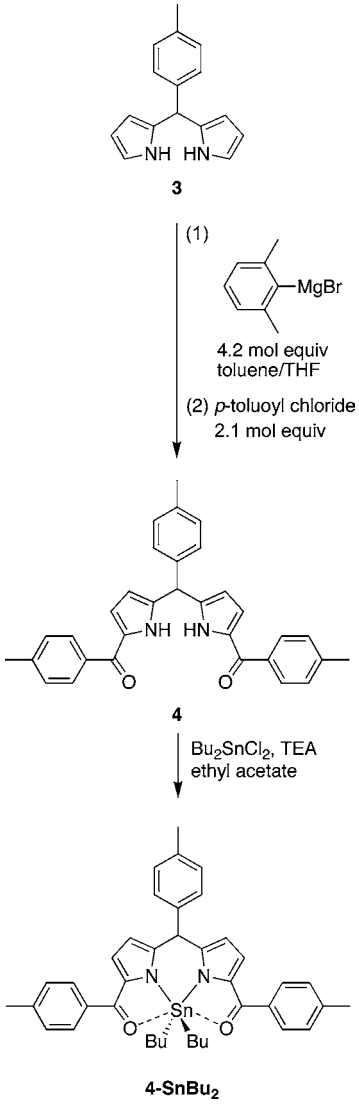

Table 1. **Effect of various Grignard reagents on the 1,9-diacylation reaction of 3[a]**

entry	Grignard	diacyl/mono[b]	yield (%)[c]
1	EtMgBr[d]	4:1	45−50
2	mesitylMgBr	>10:1	70
3	2,6-Me_2PhMgBr	>10:1	69
4	*o*-tolylMgCl	>10:1	64
5	*p*-tolylMgBr	3:1	not isolated

[a] All reactions were carried out with 8.46 mmol of **3** in toluene, 4.2 mol equiv of Grignard reagent (in THF) and 2.1 mol equiv of *p*-toluoyl chloride unless noted otherwise. [b] Ratio of 1,9-diacyldipyrromethane/1-acyldipyrromethane was assessed by HPLC analysis with absorption spectral detection at 220 nm (raw data without any correction for molar absorption coefficients). [c] Isolated yield of **4-SnBu$_2$** upon crystallization. [d] 5.0 mol equiv of Grignard reagent and 2.5 mol equiv of *p*-toluoyl chloride were employed.

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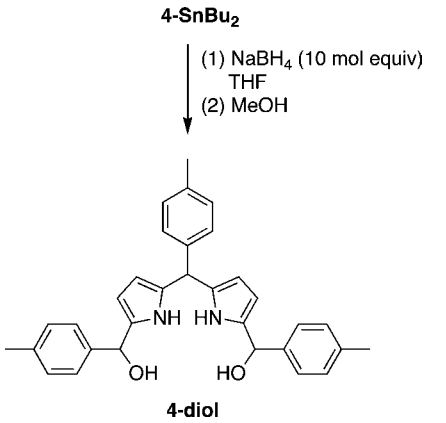
It is assumed that the hindered Grignard reagents are sufficiently reactive to form the pyrrole Grignard species but participate slowly in the side reaction with *p*-toluoyl chloride to produce the corresponding ketone and/or tertiary alcohol. By comparison with the prior diacylation study with mesitylmagnesium bromide (reported in the Supporting Information of ref 27),[27] the present conditions are characterized by a dipyrromethane concentration of 0.5 M and a final solvent composition of toluene/THF of ~1:2. The prior conditions (1-mmol scale) entailed 1 M dipyrromethane with THF as the sole solvent.[27] The specific origin of the improved diacylation results must await a more comprehensive study. Regardless, the present conditions with sterically hindered Grignard reagents afford better reproducibility, improved purity of the crude product, and higher yields versus that achieved previously.

The 1,9-diacylation of **3** was carried out at large scale (0.19 mol, 45 g of **3**) using 2,6-dimethylphenylmagnesium bromide and *p*-toluoyl chloride. The crude reaction mixture (containing 1,9-diacyldipyrromethane **4**) was treated with Bu_2SnCl_2 and triethylamine (TEA) in ethyl acetate to yield the corresponding tin complex, **4-SnBu$_2$**, a known compound[7] (Scheme 3). The tin-complexation method affords a nonpolar complex and is selective for the 1,9-diacyldipyrromethane.[21] Ethyl acetate was chosen versus CH_2Cl_2[7,21] as the solvent for tin complexation owing to environmental considerations. The reaction mixture was washed with water. This set of changes eliminated the need for filtration on silica gel.[7,21] The product was obtained by direct crystallization from a mixture of MeOH/MTBE (3:1 v/v). MTBE was chosen for recrystallization as a safer alternative to diethyl ether,[7,21] although MTBE is not without limitations given its environmental persistence. This new method was reproducible and has been implemented successfully at the 1-mol scale (50% yield, 361 g).

*I. D. Reduction of **4-SnBu$_2$** to **4-Diol**.* Equation 3 shows the reduction of **4-SnBu$_2$** to **4-diol** using $NaBH_4$ in THF/MeOH.



In prior reports,[17,21] this reduction was carried out via portionwise addition of $NaBH_4$ to a ~25 mM solution of the diacyldipyrromethane in THF/MeOH (10:1 or 3:1). In addition, 20−40 mol equiv of $NaBH_4$ was employed to achieve complete reduction to the dipyrromethane−dicarbinol. While suitable for small to modest scales, the preparation of dipyrromethane−dicarbinols on a large scale required modification. The specific changes made for the preparation of **4-diol** are as follows: (1) The reduction of **4-SnBu$_2$** to **4-diol** was carried out at 10-fold higher concentration (250 mM vs 20−30 mM) to diminish the amount of solvent required. (2) The order of addition was changed wherein methanol was added to a suspension of $NaBH_4$ in the THF/**4-SnBu$_2$** mixture, thereby limiting handling of $NaBH_4$ powder on a large scale. (3) By changing the order of addition, a lesser amount of $NaBH_4$ (10 mol equiv) was required to achieve full reduction of **4-SnBu$_2$** to **4-diol**. The lesser amount of unspent borohydride after the reduction also provided for safer workup. (4) The solvent system hexanes/ethyl acetate/methanol (4:1:1) was found to be an excellent TLC solvent (on silica) for monitoring the reduction to the dipyrromethane−dicarbinol. The diacyldipyrromethane, partially reduced intermediate (the monocarbinol), and dipyrromethane−dicarbinol were readily separated without streaking. (5) Workup of the dipyrromethane−dicarbinol species was achieved with a single wash with saturated aqueous NH_4Cl, rather than multiple water/brine washings. The pH of the organic layer was checked using pH paper and was found to be ~7. (6) Given that dipyrromethane−dicarbinols such as **4-diol** are typically rather reactive, the dried organic extract was simply diluted with CH_2Cl_2 to achieve the requisite 10 mM (or 25 mM, vide infra) concentration for subsequent porphyrin formation rather than concentrating the solution containing **4-diol** to the dry product. For large-scale reactions, the rotary evaporation step could require >1 h, thereby potentially compromising the integrity of the dicarbinol species. A summary of the modifications made to the diacyldipyrromethane reduction is given in Table 2.

Table 2. **Conditions for the diacyldipyrromethane reduction (4-SnBu$_2$ to 4-diol)**

reaction parameters	literature conditions[a]	refined conditions
reaction concentration (mM)	20−30	250
amount of $NaBH_4$ (mol equiv)	40	10
reaction time	2−4 h	<1 h
isolation of crude product	rotary evaporate to dry product	dilute with CH_2Cl_2 for porphyrin formation

[a] Reference 21.

Other reducing agents were explored to convert **4-SnBu$_2$** to **4-diol**. Sodium bis(2-methoxyethoxy)aluminum hydride (Red-Al) gave poor conversion to the dicarbinol, and removal of the spent aluminum salts proved tedious. Sodium trimethoxyborohydride showed no reactivity with **4-SnBu$_2$** even at 40 °C. The use of sodium borohydride at 0.3 M in a caustic solution (an alternate safe way to handle $NaBH_4$) was examined, but no reduction product(s) were detected, which we attribute to the nonreactive biphasic mixture formed under these conditions.

II. Synthesis of the porphyrins. The prior rational synthesis of **Zn-1** (Scheme 1) provided small quantities of

Table 3. **Summary of the porphyrin-forming reactions to prepare 1 and Zn-2**[a]

reaction parameters	porphyrin				
	2[b]	**1**		**Zn-2**	
reactants	**5 + 4-diol**	**6 + 4-diol**		**5 + 4-diol**	
[reactant],[c] mM	2.5	10	25	10	25
acid	TFA	$Yb(OTf)_3$[d]	$Sc(OTf)_3$	$Yb(OTf)_3$	$Sc(OTf)_3$
[acid], mM[e]	30	3.0	3.2	3.2	3.2
DTBP	−	−	32 mM	−	32 mM
solvent	CH_3CN	CH_2Cl_2	CH_2Cl_2	CH_2Cl_2	CH_2Cl_2
in situ Zn(II) complexation	No	No	No	Yes	Yes
reaction scale (mmol)	7.0	64	50	7.1	15
isolated yield	16%	13%	11%	23%	22%
isolated amount	0.798 g	5.87 g	3.78 g	1.27 g	2.64 g

[a] All reactions were performed at room temperature. [b] Literature data from ref 14. [c] The dipyrromethane and dipyrromethane−dicarbinol were used in equal concentrations. [d] Used as the hydrate (degree of hydration = 1−2). [e] The Lewis acids may not be entirely soluble but the amount employed is indicated in molar quantities for clarity.

porphyrin but was not well suited for larger-scale implementation.[14] The limitations were as follows: (i) the condensation was carried out at 2.5 mM in acetonitrile to give the porphyrin−ester **2**, (ii) at least one (usually two) chromatographic procedures were required to obtain the free base porphyrin **2**, and (iii) reduction and metalation were required to obtain the desired **Zn-1**.

Two subsequent studies of the porphyrin-forming reaction identified improved acid catalysis conditions that also afford condensation with little or no detectable scrambling. The avoidance of scrambling, which results in formation of unwanted mixtures of porphyrins, is of utmost importance given the difficulty of separating mixtures of porphyrins. The improvements entail use of a mild Lewis acid (e.g., $Yb(OTf)_3$, $Sc(OTf)_3$, $Dy(OTf)_3$, $InCl_3$) for catalysis in CH_2Cl_2 at 2.5 mM reactants[22] or at higher concentrations (10 or 25 mM versus 2.5 mM).[23] In some cases, the hindered base 2,6-di-*tert*-butylpyridine is included,[23,28] which serves as a Brønsted acid scavenger without significant interference with the Lewis acid. The new catalysis conditions were applied herein as described below.

The routes shown in Scheme 2 were followed for the preparation of the desired porphyrin−alcohol **Zn-1** and the porphyrin−ester **Zn-2**. Four porphyrin-forming reactions were carried out, two for each porphyrin under different condensation conditions. One set of conditions employed 10 mM reactants with catalysis by $Yb(OTf)_3$ (3.2 mM) in CH_2Cl_2. A second set of conditions employed 25 mM reactants with $Sc(OTf)_3$ (3.2 mM) and 2,6-di-*tert*-butylpyridine (32 mM) in CH_2Cl_2 at room temperature.

The results are summarized in Table 3. The synthesis of **Zn-2** was carried out in a three-step one-flask reaction of ester−dipyrromethane **5** and the dipyrromethane−dicarbinol **4-diol**. The three steps include condensation, oxidation, and in situ zinc insertion. The synthesis with 10 or 25 mM reactants afforded porphyrin−ester **Zn-2** in 23 or 22% yield, respectively. In each case the crude reaction mixture exhibited no detectable scrambling, and the porphyrin was isolated by a single chromatography procedure.

The synthesis of **Zn-1** was attempted via the three-step one-flask reaction of hydroxymethyl-dipyrromethane **6** and the dipyrromethane−dicarbinol **4-diol**. However, the zinc porphyrin proved difficult to purify from residual black materials. The purification may be hindered by self-association owing to coordination of the hydroxy group on one porphyrin with the apical site on the central zinc atom of another porphyrin. Regardless, the synthesis was carried out by a two-step one-flask reaction of **6** and **4-diol** to give free base porphyrin **1**. The synthesis with 10 or 25 mM reactants proceeded well without detectable scrambling, and porphyrin **1** was isolated by a single chromatographic procedure in 13 or 11% yield. The free base porphyrin **1** was metalated with zinc acetate, affording **Zn-1** in pure form without chromatography in 95% yield. In the synthesis of both **Zn-2** and **1**, an aerobic oxidation process[29] was examined wherein catalytic quantities (2.5 mol %) of an iron−phthalocyanine species and DDQ are combined with a stream of air (or O_2), but in both cases the yield of porphyrin was only ∼2−3%. The origins of the low yields in the aerobic process are not known.

Summary

The following improvements have been made in the synthesis of **Zn-1**:

(i) Three dipyrromethanes were prepared using a literature procedure[19] with slight modification (50 equiv of pyrrole instead of 100 equiv; use of a toluene co-strip upon workup). Use of pyrrole of high purity was essential. A diminished amount of pyrrole becomes a significant advantage in large-scale reactions.

(ii) The diacylation of the dipyrromethane was carried out using a hindered Grignard reagent (e.g., 2,6-dimethylphenylmagnesium bromide) instead of EtMgBr,[17] affording a diacyl/monoacyl ratio of >10:1 versus 4:1.

(iii) Complexation of the 1,9-diacyldipyrromethane with dibutyltin dichloride was carried out with the crude acylation mixture in the standard manner. On account of the relative

(28) Speckbacher, M.; Yu, L.; Lindsey, J. S. *Inorg. Chem.* **2003**, *42*, 4322−4337.

(29) (a) Ravikanth, M.; Achim, C.; Tyhonas, J. S.; Münck, E.; Lindsey, J. S. *J. Porphyrins Phthalocyanines* **1997**, *1*, 385−394. (b) Lindsey, J. S.; MacCrum, K. A.; Tyhonas, J. S.; Chuang, Y.-Y. *J. Org. Chem.* **1994**, *59*, 579−587.

cleanliness of the diacylation process, a water wash, and use of more appropriate solvents for crystallization (MTBE/MeOH), the dibutyltin complex of the diacyldipyrromethane was isolated from the crude reaction mixture by crystallization rather than silica pad filtration as used previously.[21] The new route was carried out to give 79 or 361 g of **4-SnBu$_2$** (versus 8.54 g previously[7]).

(iv) The reduction of the dibutyltin complex of the diacyldipyrromethane (**4-SnBu$_2$**) to give the dipyrromethane−dicarbinol **4-diol** was carried out at 250 mM reactant concentration with ∼10−15 mol equiv of $NaBH_4$ over the course of 1−2 h, to be compared with 20−30 mM reaction concentration and 40 mol equiv of $NaBH_4$ over 2−4 h.[17,21] The new route was carried out with 45 g (64 mmol) of **4-SnBu$_2$**.

(v) The prior synthesis of porphyrin−alcohol **1** entailed reduction of porphyrin−ester **2**, which in turn was prepared by condensation of ester−dipyrromethane **5** and **4-diol** (2.5 mM reactant concentration, 0.17−7.00 mmol scale) followed by oxidation.[14] The new synthesis of **1** was carried out by the condensation of hydroxymethyl-dipyrromethane **6** and **4-diol** at 4−10-fold higher concentration (10 or 25 mM) followed by oxidation, affording 5.87 g (10 mmol, 64-mmol scale) or 3.78 g (25 mM, 50-mmol scale) of **1**.

(vi) The metalation of **1** with zinc acetate was carried out without chromatography or aqueous−organic extraction, affording 10.0 g of **Zn-1**.

In summary, the advances described herein provide ready access to gram quantities of the A_3B-porphyrin **Zn-1**. The refined procedures for dipyrromethane formation, dipyrromethane diacylation, isolation of the dibutyltin complex of the diacyldipyrromethane, and reduction of the latter may prove useful for a broad set of substrates. The sole impediment to an entirely chromatography-free synthesis resides in the porphyrin-forming reaction. Fundamentally new approaches are required to overcome this obstacle. In the interim, this work provides the foundation for the synthesis of porphyrins at a scale suitable for consideration of commercial applications.

Experimental Section

General. ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were obtained in $CDCl_3$ unless noted otherwise. Absorption spectra were collected in toluene at room temperature. Silica gel (40 μm average particle size) was used for column chromatography. Pyrrole (Detrex, Inc.), Pd/C (Johnson and Matthey, lot #C-6757), 2,6-di-*tert*-butylpyridine (DTBP, Aldrich, 97%), $Sc(OTf)_3$ (Aldrich, 99%), $Yb(OTf)_3{\cdot}xH_2O$ (Aldrich, degree of hydration 1−2), $Yb(OTf)_3$ (Aldrich, 99.99%), $InCl_3$ (Aldrich, 98%), NaOH beads (20−40 mesh, Aldrich, 97%), $NaBH_4$ (Aldrich, 98%), *p*-toluoyl chloride (Aldrich, 98%), Bu_2SnCl_2 (Alfa Aesar, 95+%), and $Zn(OAc)_2{\cdot}2H_2O$ (Alfa Aesar, 98−101%), THF (HPLC grade or reagent-grade), CH_2Cl_2 (anhydrous or reagent-grade) and methanol (anhydrous or reagent-grade) were used as received from commercial sources.

The progress of the porphyrin-forming reactions was monitored by absorption spectroscopy. The extent of scrambling in the crude reaction mixture was determined by laser desorption ionization mass spectrometry (LD-MS) without a matrix as described previously.[30]

HPLC Analysis. HPLC analysis was carried out with a HP 1050 instrument using a Hypersil column (125 mm × 4 mm) with detection wavelengths of 220 and 325 nm. The solvent was acetonitrile/water (flow rate = 1 mL/min). The gradient program proceeded from 45% acetonitrile to 90% acetonitrile over 25 min with a hold at 90% acetonitrile for 3 min.

GC Analysis. All GC traces were recorded with a HP 6890 instrument equipped with a HP-5MS column (length = 30 m; diameter = 0.25 mm; film thickness = 0.25 μ) and a HP-5973 mass selective detector. The method was as follows: initial temperature 45 °C (hold 5 min); ramp at 15 °C per min until 270 °C is reached. The inlet temperature was 250 °C.

Representative procedure for diacylation studies: Compound **3** (2.00 g, 8.46 mmol) was dissolved in toluene (17 mL) and the solution was cooled to 0 °C. The Grignard reagent (4.2 mol equiv) was added dropwise. After 30 min, *p*-toluoyl chloride (2.1 mol equiv) was added dropwise at 0 °C. After stirring for 1 h, the mixture was poured over a mixture (1:1) of half-saturated aqueous NH_4Cl and ethyl acetate. The organic layer was washed with brine. The organic layer was dried ($MgSO_4$) and filtered. The filtrate was concentrated to an oil. An aliquot was taken for HPLC analysis. The oil was dissolved in ethyl acetate (40 mL), whereupon TEA (2.1 mL) was added. A sample of Bu_2SnCl_2 was added, keeping the temperature below 25 °C. After 1 h, the reaction was quenched by addition of water. The layers were separated. The organic layer was washed with brine, dried ($MgSO_4$), and filtered. The filtrate was concentrated to an oil. Crystallization from a mixture of MTBE/MeOH (1:3, v/v) afforded **4-SnBu$_2$**.

5-[4-(Hydroxymethyl)phenyl]-10,15,20-tri-*p*-tolylporphyrin (1) (10 mM reactants). A sample of **4-SnBu$_2$** (45.0 g, 64.0 mmol) was placed in a 1-L, three-necked round-bottomed flask equipped with a condenser, a pressure-equalizing addition funnel, a thermometer, and a mechanical overhead stirrer. Samples of $NaBH_4$ (24.3 g, 0.64 mol) and THF (270 mL) were added under an inert atmosphere, followed by the slow addition of MeOH (117 mL). The reaction temperature rose and was kept between 35 and 45 °C during the addition of methanol. After the addition was complete, the reaction was allowed to cool to room temperature with stirring. When starting material was no longer detected by TLC analysis (∼2 h), the reaction mixture was diluted with CH_2Cl_2 (250 mL). The resulting mixture was poured slowly into a mixture of CH_2Cl_2/saturated aqueous NH_4Cl (1:2 v/v, 3 L). The biphasic mixture was stirred for 30 min. The layers were separated. The organic layer was washed with water, dried (Na_2SO_4), and filtered. The filtrate was diluted with CH_2Cl_2 (total volume = 6.4 L). The resulting **4-diol** solution was added to a 12-L round-bottomed flask equipped with an overhead stirrer. Dipyrromethane **6** (16.2 g, 64.0 mmol) was added, and the mixture was stirred for 10 min. A sample

(30) Srinivasan, N.; Haney, C. A.; Lindsey, J. S.; Zhang, W.; Chait, B. T. *J. Porphyrins Phthalocyanines* **1999**, *3*, 283−291.

of $Yb(OTf)_3 \cdot xH_2O$ (11.9 g, 19.0 mmol) was added. After 15 min, a sample of DDQ (43.6 g, 192 mmol) was added in one portion. The resulting black mixture was stirred for 1 h. TEA (36 mL) was then added. The reaction mixture was poured over silica gel (1 kg) and purified by flash column chromatography using CH_2Cl_2/ethyl acetate (97:3) as eluent. The product-containing fractions were combined and concentrated. A sample of *i*-PrOH (500 mL) was added, and the mixture was stirred at 25 °C for 30 min. The solid was collected by filtration and washed with MeOH until the washings were colorless, affording 5.87 g (13.4%) of a purple solid: ^{1}H NMR δ −2.76 (s, 2H), 2.69 (s, 9H), 5.05 (d, J = 5.2 Hz, 2H). 7.53−7.55 (m, 6H), 7.74 (d, J = 8.0 Hz, 2H), 8.07−8.09 (m, 6H), 8.19 (d, J = 8.0 Hz, 2H), 8.82−8.87 (m, 8H); LD-MS obsd 686.4; FAB-MS obsd 686.3042, calcd 686.3046 ($C_{48}H_{38}N_4O$); λ_{abs} 421, 516, 551, 594, 650 nm.

5-[4-(Hydroxymethyl)phenyl]-10,15,20-tri-*p*-tolylporphyrin (1) (25 mM reactants). A sample of **4-SnBu$_2$** (35.2 g, 50.0 mmol) was added to a 1-L, three-necked round-bottomed flask equipped with a condenser, a pressure-equalizing addition funnel, and a thermometer. Reagent grade THF (200 mL) and $NaBH_4$ (18.9 g, 0.500 mol) were added under an inert atmosphere, followed by slow addition of reagent grade MeOH (100 mL). The reaction temperature rose and was kept between 35 and 45 °C during the addition of methanol; a water-cooled bath was used to maintain the temperature. After the addition was complete, the reaction mixture was stirred and allowed to cool to room temperature. The mixture was checked by TLC analysis (∼1.5 h) and found to contain small amounts of starting material and the partially reduced, 1-acyldipyrromethane−9-monocarbinol. Therefore, more $NaBH_4$ (9.47 g, 0.250 mol) was added followed by slow addition of MeOH (50 mL). After 0.5 h, at which point no starting material was detected by TLC analysis, the reaction mixture was diluted with CH_2Cl_2 (250 mL). The resulting mixture was poured slowly into a mixture of CH_2Cl_2/saturated aqueous NH_4Cl (1:1.5 v/v, 2.5 L). The biphasic mixture was stirred for 15 min. The layers were separated. The organic layer was washed with water, dried (Na_2SO_4), and filtered. The filtrate was diluted with reagent grade CH_2Cl_2 (total volume = 2.0 L). The resulting **4-diol** solution was added to a 3-L round-bottomed flask. Dipyrromethane **6** (12.6 g, 50.0 mmol) was added, and the mixture was stirred for 5 min. A sample of 2,6-di-*tert*-butylpyridine (DTBP; 14.7 mL, 65.0 mmol) was added followed by addition of $Sc(OTf)_3$ (3.20 g, 6.50 mmol). After 15 min, a sample of *p*-chloranil (36.9 g, 150 mmol) was added in one portion. The resulting black mixture was stirred for 30 min. The reaction mixture was poured over a short column of silica (500 g, 8 cm dia × 20 cm) with CH_2Cl_2/ethyl acetate (97:3) as eluent containing 0.1% TEA. The product-containing fractions were combined and concentrated. A sample of *i*-PrOH (500 mL) was added, and the suspension was stirred at room temperature for 30 min. The solid was collected by filtration and washed with MeOH until the washings were colorless, affording a purple solid (3.78 g, 11%): ^{1}H NMR δ −2.76 (s, 2H), 2.71 (s, 9H), 5.08 (d, J = 5.2 Hz, 2H). 7.55−7.57 (m, 6H), 7.76 (d, J = 8.0 Hz, 2H), 8.09−8.11 (m, 6H), 8.22 (d, J = 8.0 Hz, 2H), 8.82−8.87 (m, 8H); LD-MS obsd 686.8; FAB-MS obsd 686.3066, calcd 686.3046 ($C_{48}H_{38}N_4O$); λ_{abs} 420, 516, 551, 592, 648 nm.

Zn(II)-5-[4-(Hydroxymethyl)phenyl]-10,15,20-tri-*p*-tolylporphyrin (Zn-1). A sample of **1** (9.68 g, 14.0 mmol) was added to a 2-L, three-necked round-bottomed flask equipped with a heating mantle, a condenser, a thermometer, and a mechanical overhead stirrer. A sample of $Zn(OAc)_2 \cdot 2H_2O$ (3.71 g, 17.0 mmol) was added followed by THF (500 mL). The mixture was heated to reflux and stirred for 2 h. The mixture was checked by LD-MS and found to contain small amounts of free base porphyrin (**1**). Therefore, more $Zn(OAc)_2 \cdot 2H_2O$ (3.71 g) was added. After 2 h, the reaction mixture was filtered at 40 °C. The filtrate was concentrated to a purple solid. MeOH (300 mL) was added to the solid, and the resulting suspension was stirred at 25 °C for 2 h. The solid was collected and washed with MeOH until the washings were colorless. The solid was dried in vacuo, yielding 10.0 g (95%) of the title compound as a purple solid. The characterization data (^{1}H NMR, LDMS, FAB-MS, UV−vis spectra) were consistent with the reported values.[14]

Zn(II)-5-(4-Methoxycarbonylphenyl)-10,15,20-tri-*p*-tolylporphyrin (Zn-2) (10 mM reactants). A solution of **4-SnBu$_2$** (5.00 g, 7.11 mmol) in THF (28 mL, 250 mM) was treated with a sample of $NaBH_4$ (1.34 g, 35.5 mmol). A sample of methanol (12 mL) was then added dropwise by syringe over 5 min. Gas evolution began during the addition and was quite intense after the addition. After 30 min, TLC [alumina, CH_2Cl_2/ethyl acetate (95:5)] showed the reduction to the dipyrromethane−dicarbinol to be complete. After 1 h, the reaction mixture was poured into a stirred mixture of CH_2Cl_2/saturated aqueous NH_4Cl (150:200 mL), and stirred for 15 min. The organic layer was collected using a separatory funnel. The organic layer was dried (Na_2SO_4) and filtered. The filtrate was concentrated to give the dipyrromethane−diol **4-diol** as a yellow foam. A sample of dipyrromethane **5** (1.99 g, 7.11 mmol) was added to the flask containing **4-diol** followed by CH_2Cl_2 (711 mL). After a clear solution was obtained, a sample of $Yb(OTf)_3$ (1.41 g, 2.30 mmol, 3.2 mM) was added. After 15 min, a sample of DDQ (4.84 g, 21.3 mmol) was added. After 30 min, a solution of $Zn(OAc)_2 \cdot 2H_2O$ (1.56 g, 7.11 mmol) in methanol (30 mL) was added. The reaction mixture was then stirred at room temperature under air for 2 h. Analysis by TLC and fluorescence excitation spectroscopy indicated complete metalation. The reaction mixture was concentrated. The crude solid was treated with methanol (250 mL). The suspension was sonicated for 30 s. The mixture was filtered. The resulting dull purple precipitate was washed with methanol (50 mL). The solid was found to contain significant amounts of dark impurities. Several attempts to precipitate the title porphyrin resulted in improvements in purity, but complete removal of the dark impurities was not successful. Therefore, column chromatography [silica, $CHCl_3$/THF (10:1)] was used to afford the pure title compound in 23% yield (1.27 g). The characterization data (^{1}H NMR, LD-MS, FAB-MS, UV−Vis) were found to be in agreement with those from the product of a previous synthesis.[14]

Zn(II)-5-(4-Methoxycarbonylphenyl)-10,15,20-tri-*p*-tolylporphyrin (Zn-2) (25 mM reactants). A sample of **4-SnBu$_2$** (10.5 g, 15.0 mmol) was added to a three-necked, 1-L round-bottomed flask equipped with a condenser, a pressure-equalizing addition funnel, and a thermometer. Reagent grade THF (60 mL) and $NaBH_4$ (5.68 g, 150 mmol) were added under an inert atmosphere, followed by the slow addition of reagent grade MeOH (30 mL) over a period of 10 min. The reaction temperature rose during the addition of methanol and was kept between 35 and 45 °C through the use of a water-cooling bath. After the addition was complete, the reaction mixture was stirred and allowed to cool to room temperature. The mixture was checked by TLC analysis [alumina, CH_2Cl_2/methanol (97:3)] after ~1 h and found to contain small amounts of starting material and the intermediate reduction product, the 1-acyldipyrromethane−9-carbinol. Therefore, an additional quantity of $NaBH_4$ (2.84 g, 75.0 mmol) was added, followed by the slow addition of MeOH (15 mL). After 0.5 h, at which point no starting material was detected by TLC analysis, the reaction mixture was diluted with CH_2Cl_2 (100 mL). The resulting mixture was poured slowly into a mixture of CH_2Cl_2/saturated aqueous NH_4Cl (1:1.5 v/v, 1.25 L). The biphasic mixture was stirred for 15 min. The layers were separated. The organic layer was washed with water, dried (Na_2SO_4), and filtered. The filtrate was concentrated to give the dipyrromethane−dicarbinol **4-diol** as a yellow foam. The flask containing **4-diol** was treated with reagent grade CH_2Cl_2 (600 mL) and dipyrromethane **5** (4.20 g, 15.0 mmol). The mixture was stirred for ~5 min to give a clear solution. A sample of 2,6-di-*tert*-butylpyridine (DTBP; 4.40 mL, 19.5 mmol) was added followed by addition of $Sc(OTf)_3$ (0.960 g, 1.95 mmol). After 10 min, a sample of *p*-chloranil (11.1 g, 45.0 mmol) was added in one portion. After 30 min, a solution of $Zn(OAc)_2 \cdot 2H_2O$ (9.87 g, 45.0 mmol) in methanol (180 mL) was added. The reaction mixture was then stirred at room temperature under air for 1 h. Analysis by TLC and fluorescence excitation spectroscopy indicated complete metalation. The reaction mixture was washed with water (1 L). The organic layer was separated, dried (Na_2SO_4), and concentrated to a volume of ~20 mL. The resulting mixture was passed over a silica column [250 g; 7.0 cm i.d. × 14 cm, $CH_2Cl_2 \rightarrow CH_2Cl_2$/THF (10:1)]. The porphyrin-containing eluant was concentrated to give a purple solid. Methanol was added to the solid. The resulting suspension was sonicated (benchtop sonication bath) for 5 min. The suspension was filtered through a filter paper secured in a fritted glass filter holder. The filtered material was washed (first with methanol and second with hexanes) and then dried in vacuo at room temperature, affording a purple solid (2.64 g, 22%): The characterization data (^{1}H NMR, LD-MS, FAB-MS, UV−vis) were in agreement with those from the product of a previous synthesis.[14]

5-*p*-Tolyldipyrromethane (3). Compound **3** was prepared in 60% yield (0.42 mol scale) following the literature procedure[19] but at a 50:1 pyrrole:aldehyde ratio and with a toluene co-strip during workup (as described for **6**). The characterization data (^{1}H NMR, ^{13}C NMR, mp, FAB-MS) were in agreement with those from the product of a previous synthesis.[23] The elemental analysis data are as follows: Anal. Calcd for $C_{16}H_{16}N_2$: C, 81.32; H, 6.82; N, 11.85. Found: C, 81.07; H, 6.80; N, 11.78.

Dibutyl(5,10-dihydro-1,9-di-*p*-toluoyl-5-*p*-tolyldipyrrinato)tin(IV) (4-SnBu$_2$). Samples of **3** (45.0 g, 190 mmol) and toluene (385 mL) were placed in a 2-L three-necked round-bottomed flask equipped with a pressure-equalizing addition funnel and a mechanical overhead stirrer. The mixture was cooled to 0 °C, whereupon 2,6-dimethylphenylmagnesium bromide (800 mL, 0.8 mol, 1 M solution in THF) was added dropwise, keeping the temperature of the mixture below 15 °C. At the end of the addition, the mixture was stirred for 30 min and cooled to 0 °C. A sample of *p*-toluoyl chloride (53 mL, 400 mmol) was added dropwise, keeping the temperature below 25 °C. The mixture was stirred for 1 h after the addition. The solvent system hexanes/CH_2Cl_2/ethyl acetate (3:6:1) was found to be an excellent TLC solvent (on silica) for monitoring the progress of diacylation reaction. The reaction was quenched by addition of a mixture of saturated aqueous NH_4Cl/ethyl acetate (1:1 v/v, 1 L). After 15 min, the layers were separated. The organic layer was washed with saturated aqueous NH_4Cl and brine. The organic layer was dried ($MgSO_4$), filtered, and concentrated to a red oil. The oil was dissolved in ethyl acetate (1.4 L) and added to a 2-L three-necked round-bottomed flask equipped with an overhead stirrer. The mixture was cooled to 15 °C, whereupon TEA (66 mL) was added followed by Bu_2SnCl_2 (69.3 g, 230 mmol). After TLC analysis showed the disappearance of **7** (about 1 h), the reaction was quenched by addition of water. The layers were separated. The organic layer was washed with brine, dried ($MgSO_4$), and filtered through a short pad of Celite. The filtrate was concentrated to a dark oil and co-stripped with MTBE. Crystallization of the residue from a mixture of MTBE/MeOH (1:3, v/v) yielded the tin complex as a brown powder (93 g, 70% yield, >97% pure). Recrystallization from a mixture of MTBE/MeOH (1:2 v/v) yielded the title compound as a tan powder (79 g, 60%). Characterization data (^{1}H NMR, ^{13}C NMR, mp, elemental analysis) were consistent with the literature.[7] This reaction also was successfully implemented on a 1 mol scale to yield 361 g (50%) of the title compound.

5-(4-Methoxycarbonylphenyl)dipyrromethane (5). Compound **5** was prepared in 66% yield (0.17 mol scale) following the literature procedure[19] but at a 50:1 pyrrole/aldehyde ratio and with a toluene co-strip during workup (as described for **6**). The characterization data were in agreement with those from the product of previous syntheses.[19,31] Characterization data are as follows: mp 160−162 °C; ^{1}H NMR δ 3.90 (s, 3H), 5.51 (s, 1H), 5.89−5.90 (m, 2H), 6.15−6.18 (m, 2H), 6.71−6.72 (m, 2H), 7.27−7.29 (m, 2H), 7.94−7.99 (m, 4H); ^{13}C NMR δ 44.1, 52.3, 107.7, 108.8, 117.7, 128.6, 129.0, 130.1, 131.7, 147.5, 167.1; FABMS obsd 280.1209, calcd 280.1212 ($C_{17}H_{16}N_2O_2$). Anal. Calcd for $C_{17}H_{16}N_2O_2$: C, 72.84; H, 5.75; N, 9.99. Found: C, 72.58; H, 5.78; N, 9.97.

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5-[4-(Hydroxymethyl)phenyl]dipyrromethane (6). Following a standard procedure but using 50 mol equiv of pyrrole,[19] aldehyde **7** (60.0 g, 0.44 mol) and pyrrole (1.5 L, 22 mol) were added to a 3-L, three-neck round-bottomed flask equipped with a mechanical overhead stirrer. The mixture was stirred under Ar. When a clear solution was obtained, $InCl_3$ (8.9 g, 40 mmol) was added, and the mixture was stirred for 1.5 h. The reaction was quenched by addition of NaOH beads (53 g, 1.3 mol). The mixture was stirred for 1.5 h. The reaction mixture was allowed to settle over 20 min. The reaction mixture was filtered through Celite. The filtrate was concentrated under vacuum to give an oil, recovering the majority of excess pyrrole. The remaining traces of pyrrole were removed via three toluene costrips (3 × 100 mL). A viscous oil remained. Attempts to obtain a solid from the crude mixture were not successful; therefore, the mixture was diluted with MeOH and passed through a silica gel column [$CHCl_3$/MeOH (98:2); (7.6 cm × 20 cm)]. The product-containing fractions were concentrated to afford a bright yellow solid. Recrystallization of the latter from a mixture of toluene/EtOH (10:1 v/v) yielded a light-brown solid (79 g, 71%): mp 103−104 °C; ^{1}H NMR δ 4.67 (s, 2H), 5.47 (s, 1H), 5.89 (s, 2H), 6.14 (q, J = 2.9 Hz, 2H), 6.69 (m, 2H), 7.19−7.32 (m, 4H), 7.91 (br, 2H);^{13}C NMR δ 43.8, 65.2, 107.3, 108.5, 117.4, 127.5, 128.7, 132.6, 139.6, 141.8; FABMS obsd 252.1249, calcd 252.1263 ($C_{16}H_{16}N_2O$). Anal. Calcd for $C_{16}H_{16}N_2O$: C, 76.16; H, 6.39; N, 11.10. Found: C, 76.18; H, 6.37; N, 11.07.

4-(Hydroxymethyl)benzaldehyde (7). Terephthalaldehyde (20.0 g, 150 mmol), *i*-PrOH (100 mL) and 5% Pd/C (0.15 g) were added to a 500-mL Parr hydrogenation bottle. The mixture was purged with hydrogen, and the slurry was shaken under hydrogen at 25 psi for 6 h at room temperature. The reaction was monitored by TLC analysis [silica, hexanes/ethyl acetate/acetic acid (20:10:1)]. When less than 2% of terephthalaldehyde was detected by TLC/GC analysis, the catalyst was removed by filtration through Celite. The filtrate was concentrated to an oil. The crude oil was crystallized with MTBE/hexanes (1:1 v/v), yielding a white solid (17.7 g, 87%). Characterization data for this sample were consistent with the literature data (^{1}H NMR,[24,25] ^{13}C NMR,[24] mp,[32] elemental analysis[25]) as well as the expected FAB-MS analysis.

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