Investigation of Conditions Giving Minimal Scrambling in the Synthesis of *trans*-Porphyrins from Dipyrromethanes and Aldehydes

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A diverse range of reaction conditions for the MacDonald-type 2 + 2 condensation of a 5-substituted dipyrromethane and an aldehyde has been studied with the goal of eliminating acid-catalyzed polypyrrolic rearrangement reactions in the synthesis of *trans*-porphyrins. A rapid screening method based on laser desorption mass spectrometry has enabled the degree of rearrangement to be examined as a function of the acid catalyst, reagent concentration, reagent stoichiometry, solvent, salts, and temperature. For condensations involving 5-mesityldipyrromethane, we identified reaction at 10 mM concentration in CH_2Cl_2 with 17.8 mM TFA as optimal conditions for suppression of the rearrangement reaction. A synthetic procedure based on these conditions allowed the expedient synthesis of multigram batches of eight *trans*-porphyrins in 48−14% yield from 5-mesityldipyrromethane, with minimal chromatography. The same conditions were also effective for the synthesis of two *trans*-porphyrins derived from 5-(2,6-dichlorophenyl)dipyrromethane. Application of the same conditions to condensations involving 5-phenyldipyrromethane showed extensive rearrangement. Examination of a wide range of conditions showed that slow reactions are associated with less rearrangement. Two sets of conditions were identified that gave little or no scrambling: (1) condensation at 10 mM in MeCN at 0 °C with $BF_3 \cdot Et_2O$ catalysis in the presence of NH_4Cl followed by DDQ oxidation and (2) condensation at 0.1 M in DMSO at 100 °C in the presence of NH_4Cl (with no added acid catalyst) with air oxidation. Although yields are typically less than 10%, the elimination of the need to perform tedious chromatography improves the methodology available for the preparation of *trans*-porphyrins, derived from sterically unhindered dipyrromethanes.

Introduction

meso-Substituted *trans*-porphyrins are key structural components found in a wide range of model systems in biomimetic and materials chemistry. A *trans*-porphyrin provides a linear substitution pattern that can be used for the construction of porphyrin-based architectures with a well-defined structure. Recent applications of *trans*-porphyrins in model systems include charge separation devices that mimic photosynthesis,[1] enzyme models,[2] materials with nonlinear optical properties,[3] chiral catalysts,[4] chiral sensors,[5] synthetic receptors for small molecules,[6] optoelectronic devices,[7] potential sensitizers for photodynamic cancer therapy,[8] bilayer lipid membrane spanning arrays,[9] and liquid crystals.[10] Good synthetic methods for preparing *trans*-porphyrins are essential for the construction of such materials and devices.

As part of our research program in porphyrin chemistry, we have been developing methods for the synthesis of versatile porphyrin building blocks bearing a wide range of functionality.[11] We recently developed a convenient preparation of analytically pure multigram batches of 5-substituted dipyrromethanes by the acid-catalyzed condensation of an aldehyde with excess pyrrole in solvent-free conditions.[12] Condensation of a dipyrromethane with an aldehyde in a MacDonald-type 2 + 2 condensation,[13] as illustrated in Scheme 1, has been used to prepare a wide range of *meso*-substituted *trans*-porphyrins.[14]

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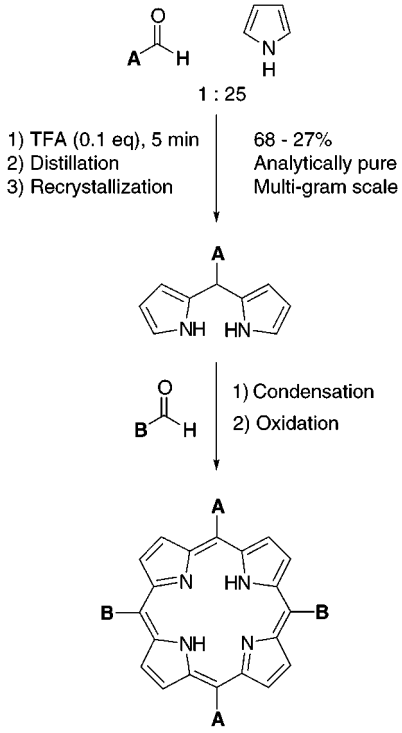
Scheme 1



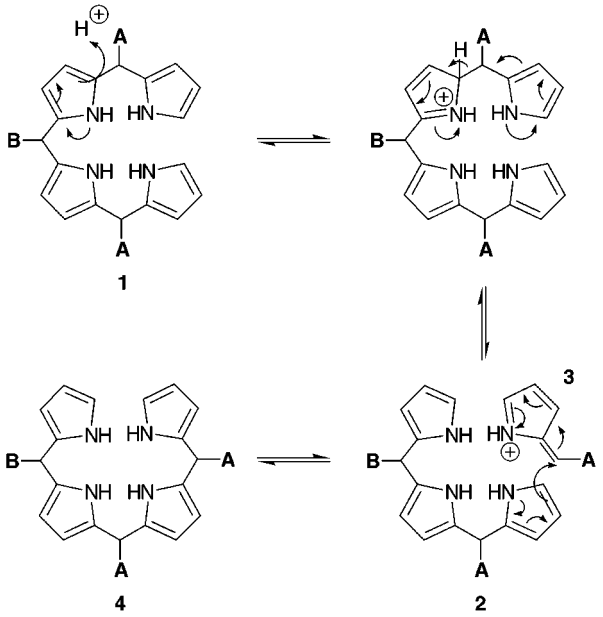
At present, this methodology suffers from three major limitations: (1) The condensation is performed in dilute solution (10 mM). (2) Isolated yields of porphyrin are modest (10−30%). (3) The product of a dipyrromethane−aldehyde condensation is frequently not just the desired *trans*-A_2B_2-porphyrin but a mixture of porphyrins that can be extremely difficult to separate (especially the *trans*-A_2B_2 and *cis*-A_2B_2 isomers). As a result, pure *trans*-porphyrins have been typically available only in limited quantities.

The exchange process frequently observed in polypyrrane condensations is proposed to occur by the acid-catalyzed fragmentation of a polypyrrane **1** into pyrrolic **2** and azafulvene **3** components.[15] As illustrated in Scheme 2, recombination of **2** and **3** can form a new polypyrrane **4** that cannot be formed by direct condensation of the dipyrromethane and aldehyde. Ultimately this process leads to the production of a scrambled mixture of porphyrins. The factors that promote the scrambling process in MacDonald-type 2 + 2 condensations are poorly understood, but suppression of scrambling is essential for preparing large quantities of pure *trans*-porphyrins. In this paper we describe a study of a wide range of reaction conditions for the 2 + 2 condensation that has led to refined synthetic procedures for the preparation of *trans*-porphyrins.

Results and Discussion

Screening Strategy. We adopted an empirical approach for reaction optimization, which required the ability to rapidly screen a large number of experiments. The reactions were performed on a small scale, and the

Scheme 2



overall porphyrin yield during the course of the condensation was monitored using UV−vis spectroscopy, by removing small aliquots that were then oxidized by DDQ.[16] The porphyrin distribution in the aliquots was then examined by time-of-flight laser desorption mass spectrometry (LD-MS).[17] The high sensitivity of mass spectrometry enabled detection of trace amounts of undesired porphyrin byproducts in aliquots removed from the small-scale reactions (vide infra). The data produced by mass spectrometry are semiquantitative; therefore we have chosen to categorize the extent of scrambling on the basis of the observed spectra (Figure 1):

Level 0	No scrambled products observed. Single envelope corresponding to $(M^{\bullet})^+$ of the expected A_2B_2-porphyrin.[18]
Level 1	Low levels of scrambled porphyrin.
Level 2	Significant levels of scrambled porphyrin.
Level 3	Peak intensities close to those anticipated from a statistical mixture formed from the combination of two aldehydes and pyrrole ($A_4 = B_4 = 6.25\%$, $A_3B = AB_3 = 25\%$, *cis*- and *trans*-$A_2B_2 = 37.5\%$).
Level 4	Skewed scrambling, such that the A_2B_2-porphyrin is no longer the major component.

1. Condensations with Sterically Hindered Dipyrromethanes. Previous studies have shown that 5-mesityldipyrromethane and an aldehyde can be condensed to give pure *trans*-A_2B_2-porphyrins in 50−100 mg batches after column chromatography.[19,20] We sought to optimize reaction conditions for the preparation of gram quantities of sterically hindered *trans*-porphyrins with minimal

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(17) LD-MS of porphyrins gives almost exclusively the porphyrin radical cation $(M^{\bullet})^+$ rather than the protonated species $(M + H)^+$. See: Srinivasan, N.; Haney, C. A.; Lindsey, J. S.; Zhang, W.; Chait, B. T. *J. Porphyrins Phthalocyanines*, in press.

(18) The mass spectrum provides no distinction among *cis*- and *trans*-A_2B_2-porphyrins. However, scrambling during the dipyrromethane−aldehyde condensation would not be expected to give exclusively the *cis*-A_2B_2-porphyrin. Regardless, ^{1}H NMR spectral examination of the isolated *trans*-A_2B_2-porphyrin in each case examined showed no contaminating *cis*-A_2B_2-porphyrin.

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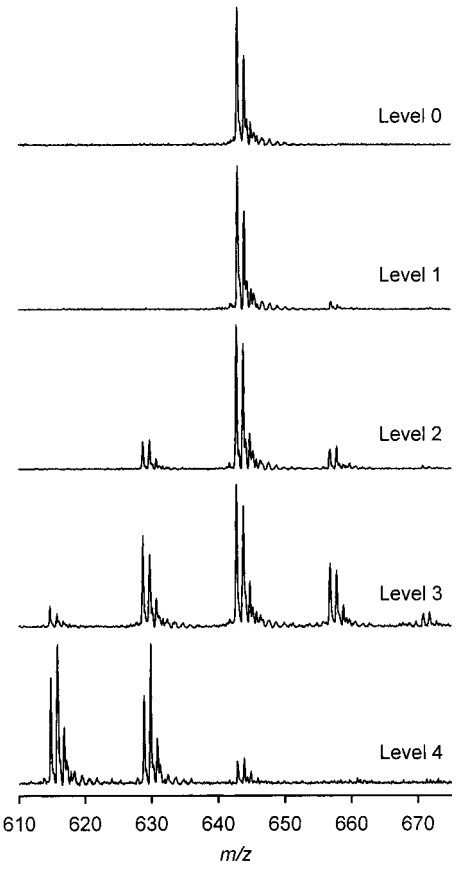


Figure 1. Illustrative LD-MS data of scrambling levels observed for the condensation of 5-phenyldipyrromethane and *p*-tolualdehyde.

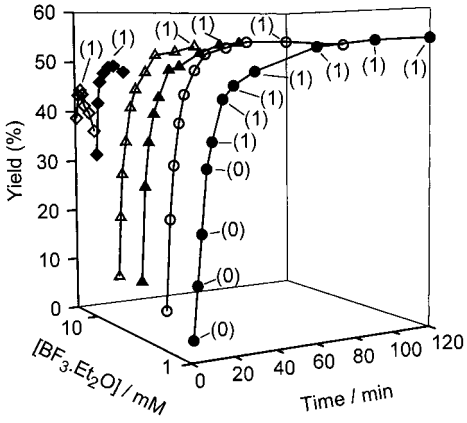
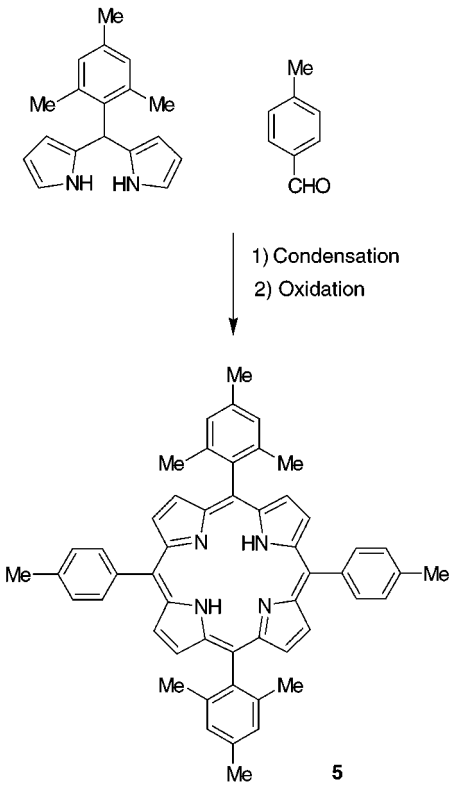


Figure 2. Dependence of the spectroscopic yield on $BF_3 \cdot Et_2O$ concentration (● 1.00, ○ 1.78, ▲ 3.16, △ 5.62, ◆ 10.0, and ◇ 17.8 mM) for the condensation of 5-mesityldipyrromethane and *p*-tolualdehyde (10 mM) in $CHCl_3$. Scrambling levels are shown in parentheses.

chromatography. The condensation of 5-mesityldipyrromethane[21] and *p*-tolualdehyde to form porphyrin **5** was chosen as our initial model system (Scheme 3).

We reinvestigated the standard reaction conditions for MacDonald-type 2 + 2 condensations; 5-mesityldipyrromethane (10 mM), *p*-tolualdehyde (10 mM) in $CHCl_3$ catalyzed by $BF_3 \cdot Et_2O$, followed by oxidation with

Scheme 3



DDQ.[19,20] Figure 2 shows the spectroscopic yields for a series of reactions run over a range of $BF_3 \cdot Et_2O$ concentration (1.00−17.8 mM). LD-MS examination of the aliquots removed at the time of maximum yield showed Level 1 scrambling in all cases. Therefore the purity of the final porphyrin product depends on removal of the trace byproducts by chromatography.

Examination of the porphyrin distribution over time for the reaction catalyzed by 1.00 mM $BF_3 \cdot Et_2O$ showed that scrambling increased from Level 0 to Level 1. This observation is consistent with a study on a 2 + 2 condensation involving 5-phenyldipyrromethane where scrambling was reduced by a short reaction time and low $BF_3 \cdot Et_2O$ concentration.[22] The data in Figure 2 show that such an approach is undesirable from a synthetic standpoint, because this would diminish the porphyrin yield. Also, the degree of scrambling is not easily monitored while the reaction is in progress, so determination of the optimal time to add the oxidant would be difficult.

To find reaction conditions that gave no scrambling at the time of maximum porphyrin yield, we screened reactions for spectroscopic yield and scrambling as a function of the acid catalyst, reaction solvent, reagent concentration, reaction temperature, presence of catalytic salts,[23] and reagent ratio. A complete description of these studies is included in the Supporting Information. The key findings were as follows:

1. Reactions catalyzed by TFA gave Level 0 scrambling for all aliquots examined regardless of the acid catalyst concentration, reaction solvent, reagent concentration, reaction temperature, presence of catalytic salts, or reagent ratio.

(21) During this study we found that use of analytically pure dipyrromethanes, prepared as described in ref 12, was imperative to achieve both the highest yields and the minimum scrambling.

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2. $CHCl_3$, CH_2Cl_2, and toluene were assessed as reaction solvents. CH_2Cl_2 was preferred because reaction in $CHCl_3$ required a higher TFA concentration and condensation in toluene gave lower yields. In CH_2Cl_2, 17.8 mM TFA gave the highest spectroscopic yield and optimal kinetics (40% in 30 min).

3. Identical yields and kinetics were observed for reactions performed in CH_2Cl_2 freshly distilled from CaH_2 and commercially supplied CH_2Cl_2 (Fisher, A.C.S. grade). Drying and distillation of the solvent prior to reaction is therefore unnecessary.

4. Use of a dipyrromethane and aldehyde concentration greater than 10 mM led to an unacceptable decrease in the porphyrin yield.

5. With TFA catalysis, cooling the reaction led to a slower reaction rate and lower yields.

6. For TFA catalysis, addition of simple inorganic salts had negligible catalytic effect.

7. A 1:1 dipyrromethane:aldehyde ratio gave the highest yield of porphyrin.

8. The optimal conditions that emerged from this survey are 5-mesityldipyrromethane (10 mM) and *p*-tolualdehyde (10 mM) in undistilled CH_2Cl_2 with TFA (17.8 mM) at room temperature, followed by oxidation with DDQ.[24]

The optimum conditions were used to develop a preparative procedure. The reaction was monitored spectroscopically, and DDQ was added when the spectroscopic yield had stopped increasing (typically 30 min). After stirring at room temperature for a further 1 h, the reaction mixture was filtered through a pad of alumina to separate porphyrin **5** from any unreacted oxidant, acid catalyst, and polypyrrolic byproducts. No scrambled byproducts were detected by LD-MS, ^{1}H NMR spectroscopy, or TLC, but close examination of the ^{1}H NMR and UV−vis spectra showed that a low level of chlorin impurity was present.[25] Attempts to prevent formation of chlorin in the oxidation step by adding an excess of DDQ (2 mol of DDQ per 1 mol of dipyrromethane), heating under reflux in CH_2Cl_2, or using distilled and degassed solvent were unsuccessful. However, reoxidation with fresh DDQ in toluene at reflux[26] removed the chlorin and gave porphyrin **5** with excellent purity.

Due to the suppression of the scrambling process this method was readily applied to gram-scale synthesis. For example, condensation of 10 mmol of 5-mesityldipyrromethane and 10 mmol of *p*-tolualdehyde gave 1.78 g (48% yield) of pure **5** within 6 h, requiring no chromatography except for filtration through alumina after the DDQ oxidation steps.

The scope of this procedure for preparing gram batches of *trans*-porphyrins from 5-mesityldipyrromethane was examined by condensation with the eight aldehydes shown in Table 1. No scrambling was observed in the syntheses with aryl aldehydes, so this procedure offers a general and simple gram-scale preparation of 5,15-dimesityl-10,20-diarylporphyrins. The only modification to the procedure was required for the reaction with pentafluorobenzaldehyde because the porphyrin was contaminated with non-porphyrin pigments, but these were readily removed by triturating with hexanes. Such pigments were also observed in the condensation with *n*-hexanal and were also easily removed by trituration with hexanes, however LD-MS showed a peak consistent with Level 1 scrambling in this condensation. Whether trace scrambling is a general occurrence for alkyl aldehydes was not pursued further in this study.

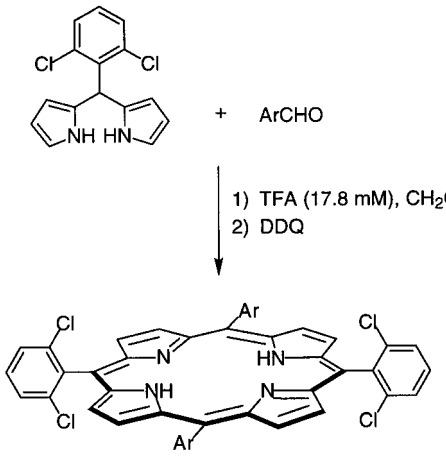
We also examined whether the conditions optimized for 5-mesityldipyrromethane could be applied to other 5-(2,6-disubstituted-aryl)dipyrromethanes. Two condensations performed with 5-(2,6-dichlorophenyl)dipyrromethane are shown in Table 2. No scrambling was observed, and the only differences due to the change in the dipyrromethane were (1) an increase in the time required for the porphyrin yield to reach a maximum (typically 60−90 min) and (2) that a low solubility of porphyrins **13** and **14** required that CH_2Cl_2 was added to the toluene solution after reoxidation to prevent

Table 1. Isolated Yield of Porphyrins Formed by Condensation of 5-Mesityldipyrromethane with Various Aldehydes[a]

aldehyde	porphyrin	yield (%)	scrambling level
p-tolualdehyde	**5**	48	0
benzaldehyde	**6**	38	0
o-tolualdehyde	**7**	35	0
4-iodobezaldehyde	**8**	35	0
3-iodobenzaldehyde	**9**	31	0
p-anisaldehyde	**10**	44	0
pentafluorobenzaldehyde	**11**	28	0
n-hexanal	**12**	14	1

[a] Reactions were performed with 5-mesityldipyrromethane (10 mM) and the aldehyde (10 mM) in CH_2Cl_2 with TFA (17.8 mM) followed by oxidation with DDQ. All reactions were performed with 0.01 mol of dipyrromethane and aldehyde.

Table 2. Isolated Yield of Porphyrins Formed by Condensation of Two Aldehydes with 5-(2,6-Dichlorophenyl)dipyrromethane[a]



aldehyde	porphyrin	yield (%)	scrambling level
benzaldehyde	**13**	35	0
4-iodobenzaldehyde	**14**	26	0

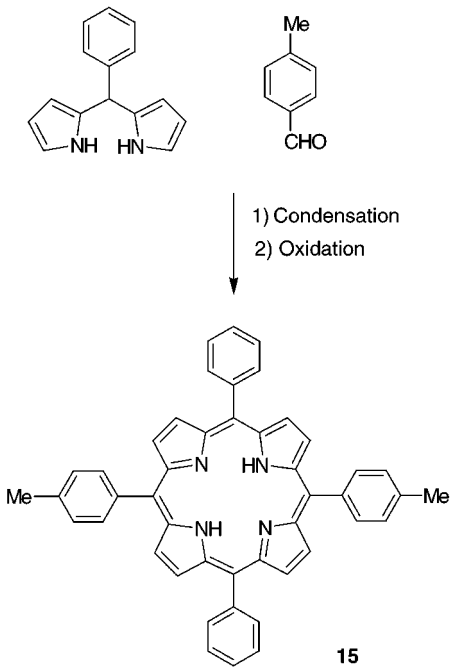
[a] Reactions performed with 5-(2,6-dichlorophenyl)dipyrromethane (10 mM) and the aldehyde (10 mM) in CH_2Cl_2 with TFA (17.8 mM) followed by oxidation with DDQ.

(24) The stoichiometry of the dipyrromethane−aldehyde condensation requires 1.5 mol of DDQ per 1 mol of dipyrromethane (giving 3 mol of DDQ per 1 mol of porphyrinogen). We have found that the oxidation can often be performed with less than the stoichiometric amount (1 mol of DDQ per 1 mol of dipyrromethane) without a decrease in the porphyrin yield or change in chlorin content. With 0.5 mol of DDQ per 1 mol of dipyrromethane, the yield did decline and the amount of chlorin increased.

(25) Crossley, M. J.; King, L. G. *J. Org. Chem.* **1993**, *58*, 4370−4375.

(26) Barnett, G. H.; Hudson, M. F.; Smith, K. M. *Tetrahedron Lett.* **1973**, 2887−2888. Rousseau, K.; Dolphin, D. *Tetrahedron Lett.* **1974**, 4251−4254. Barnett, G. H.; Hudson, M. F.; Smith, K. M. *J. Chem. Soc., Perkin Trans. 1* **1975**, 1401−1403.

Scheme 4



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precipitation of the porphyrin during the filtration through alumina.

2. Condensations with Unhindered Dipyrromethanes. Syntheses of *trans*-porphyrins not bearing sterically demanding groups in the 5-position have resulted in more extensive scrambling, and isolation of the pure porphyrin is often difficult, even after careful column chromatography.[27] Condensation of 5-phenyldipyrromethane and *p*-tolualdehyde was chosen as the model system for studying a 5-aryldipyrromethane that is not sterically hindered at the 2- and 6-positions of the aryl group (Scheme 4). This combination provides a small steric and electronic difference between the two components but allows resolution of the potential porphyrin products by LD-MS.[18]

(A) Use of Reaction Conditions Optimized for Sterically Hindered Dipyrromethanes. The procedure developed for condensation of sterically hindered dipyrromethanes was applied to a condensation of 5-phenyldipyrromethane and *p*-tolualdehyde (10 mM in CH_2Cl_2 containing 17.8 mM TFA for 1 h followed by DDQ oxidation). Porphyrin products were isolated in 31% yield. TLC showed a single porphyrin spot, and ^{1}H NMR spectroscopy (300 MHz) showed no signals characteristic of scrambling, but LD-MS showed Level 3 scrambling.[28] An identical condensation catalyzed by $BF_3{\cdot}Et_2O$ (1.0 mM) produced Level 4 scrambling, with 5,10,15-triphenyl-20-(4-methylphenyl)porphyrin formed as the major product.

The aliquot removed after 5 min (9% spectroscopic yield) from the TFA-catalyzed reaction showed Level 3 scrambling, demonstrating that scrambling occurs much more rapidly than porphyrinogen formation under the conditions that were suitable for reactions of sterically hindered dipyrromethanes. We therefore screened a wide range of reaction conditions with the aim of suppressing scrambling.

(B) Scope of Studies. Approximately 250 experiments were performed in a search to suppress scrambling in the condensation of 5-phenyldipyrromethane and *p*-tolualdehyde. A complete description of all studies performed is included in the Supporting Information, with the results of principal synthetic and mechanistic interest described below:

1. Montmorillonite K-10, a mesoporous clay that suppresses scrambling of porphyrinogens,[29] gave 10−25% yields and Level 2 scrambling in CH_2Cl_2. Reaction in diethyl ether, acetonitrile, hexanes, ethyl acetate, and THF gave slow reactions and less than 10% yields but reduced scrambling to Level 0 or Level 1.

2. Studies with other solid Lewis acids ($MgBr_2{\cdot}Et_2O$, $FeCl_3$, $ZnCl_2$, and Lewis acids supported on clays) gave Level 2 and Level 3 scrambling with yields between 3% and 40%. In general, fast reactions gave more scrambling than slow reactions.

3. Model condensations performed with $BF_3{\cdot}Et_2O$ and TFA as representative homogeneous acid catalysts were studied as a function of acid concentration, reaction solvent (CH_2Cl_2, toluene, acetonitrile), and reaction temperature (rt to −40 °C) and in the presence of 10 different catalytic salts.[23] Reaction in CH_2Cl_2 or toluene gave rapid porphyrin formation with good to excellent yield (25−65%) but Level 3 or Level 4 scrambling. In contrast, reaction in acetonitrile proceeded more slowly in lower yield, with less scrambling.[30] Cooling the acetonitrile reaction mixture with certain inorganic salts reduced scrambling to Level 0 or Level 1, but in all cases low scrambling was accompanied by a slow reaction rate and a porphyrin yield less than 10%.

4. Hombrecher reported that addition of 2,6-di-*tert*-butylpyridine, a non-nucleophilic base, to a particular MacDonald-type condensation dramatically suppressed scrambling.[31] For our model system, addition of 2,6-di-*tert*-butylpyridine gave Level 0 scrambling but reduced the porphyrin yield to 3% or less under all conditions examined.

5. Condensation in propionic acid at 70 °C gave a slow reaction and a low yield (4% at 6 h) with Level 1 scrambling.[32] Attempts to improve the yield by increasing the reaction temperature or adding inorganic salts gave a faster reaction rate, higher porphyrin yields, and Level 3 or 4 scrambling.

6. Heating 5-phenyldipyrromethane in neat excess *p*-tolualdehyde led to porphyrin formation with Level 0 scrambling, but in less than 10% yield. Screening studies on a thermal 2 + 2 condensation identified DMSO as a

(27) For examples see: (a) Wallace, D. M.; Leung, S. H.; Senge, M. O.; Smith, K. M. *J. Org. Chem.* **1993**, *58*, 7245−7257. (b) Gaud, O.; Granet, R.; Kaouadji, M.; Krausz, P.; Blais, J. C.; Bolbach, G. *Can. J. Chem.* **1996**, *74*, 481−499. (c) Setsune, J.; Hashimoto, M.; Shiozawa, K.; Hayakawa, J.; Ochi, T.; Masuda, R. *Tetrahedron* **1998**, *54*, 1407−1424. (d) Gerasimchuk, N. N.; Mokhir, A. A.; Rodgers, K. R. *Inorg. Chem.* **1998**, *37*, 5641−5650.

(28) This example illustrates that mass spectrometry is a more reliable method for determination of the presence or absence of scrambling.

(29) Onaka, M.; Shinoda, T.; Izumi, Y.; Nolen, E. *Chem. Lett.* **1993**, 117−120. Onaka, M.; Shinoda, T.; Izumi, Y.; Nolen, E. *Tetrahedron Lett.* **1993**, *34*, 2625−2628. Shinoda, T.; Onaka, M.; Izumi, Y. *Chem. Lett.* **1995**, 493−494. Shinoda, T.; Onaka, M.; Izumi, Y. *Chem. Lett.* **1995**, 495−496.

(30) Acetonitrile has previously been reported as a solvent for performing the 2 + 2 condensation of β-substituted dipyrromethanes under mild conditions. See: Osuka, A.; Nagata, T.; Kobayashi, F.; Maruyama, K. *J. Heterocycl. Chem.* **1990**, *27*, 1657−1659.

(31) Hombrecher, H. K.; Horter, G.; Arp, C. *Tetrahedron* **1992**, *48*, 9451−9460.

(32) For examples of MacDonald-type condensations performed in propionic acid see refs 27a, 27c, and 27d.

suitable reaction solvent that allowed the use of a 1:1 dipyrromethane:aldehyde ratio. At reflux in DMSO, Level 4 scrambling occurred, but lowering the reaction temperature to 90 °C and performing the reaction in the presence of NH_4Cl gave Level 1 scrambling and 5% yield.

Despite the wide range of factors examined, the most significant finding was that the scrambling process was extremely difficult to suppress. However, a clear correlation was observed over all of the diverse reaction conditions examined: *the slower the rate of reaction, the lower the level of scrambling*.

(C) Low-Scrambling Reaction Conditions. From the screening study of the model condensation, two sets of reaction conditions were identified that gave the highest yield of porphyrin with Level 0 or Level 1 scrambling:

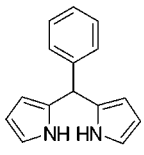
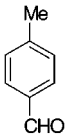
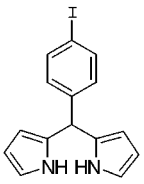
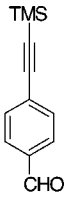
1. 5-Phenyldipyrromethane (10 mM) and *p*-tolualdehyde (10 mM) in MeCN at 0 °C, catalyzed by $BF_3{\cdot}Et_2O$ (1.0 mM) with NH_4Cl (100 mmol/L) added to the reaction mixture, although certain other inorganic chloride salts such as NaCl behave very similarly. The reaction was performed under an inert atmosphere, monitored by UV−vis spectroscopy, and then DDQ was added (typically after 4 h), with subsequent oxidation with DDQ in toluene at reflux to remove any chlorin, followed by column chromatography to isolate the porphyrin from non-porphyrin materials (9% yield, Level 1).

2. 5-Phenyldipyrromethane (100 mM) and *p*-tolualdehyde (100 mM) with NH_4Cl (316 mmol/L) in DMSO at 90 °C for 24 h. The reaction was performed without $BF_3{\cdot}Et_2O$ or TFA and is open to air to achieve oxidation of the porphyrinogen to the porphyrin by atmospheric oxygen. In the cases we examined, the porphyrin was insoluble in the DMSO reaction medium and was easily isolated by filtration, affording pure porphyrin without detectable chlorin byproduct (5% yield, Level 1). A wide range of salts was examined, but the catalytic effect was found to be highly specific, with only NH_4Cl leading to porphyrin formation.

The scope of these procedures for preparing *trans*-porphyrins was examined as shown in Table 3. Comparison of the two sets of reaction conditions demonstrates that the principal advantage of reaction in MeCN is higher yields, whereas reaction in DMSO benefits from an extremely simple workup procedure. The yields of porphyrin obtained are low in both cases, but the scrambling process is suppressed, eliminating the need for separation of a porphyrin mixture by chromatography. Analytically pure 5-substituted dipyrromethanes are now readily available in multigram quantities,[12] so greater than 100 mg of porphyrin can be easily isolated from a reaction performed with 10 mmol of reactants with minimal scrambling. Synthesis of 5,15-bis[4-(2-trimethylsilylethynyl)phenyl]-10,20-bis(4-iodophenyl)porphyrin **(16)** illustrates that despite the low yield these novel methods can be very useful and are anticipated to provide an expedient route to many *trans*-porphyrins.

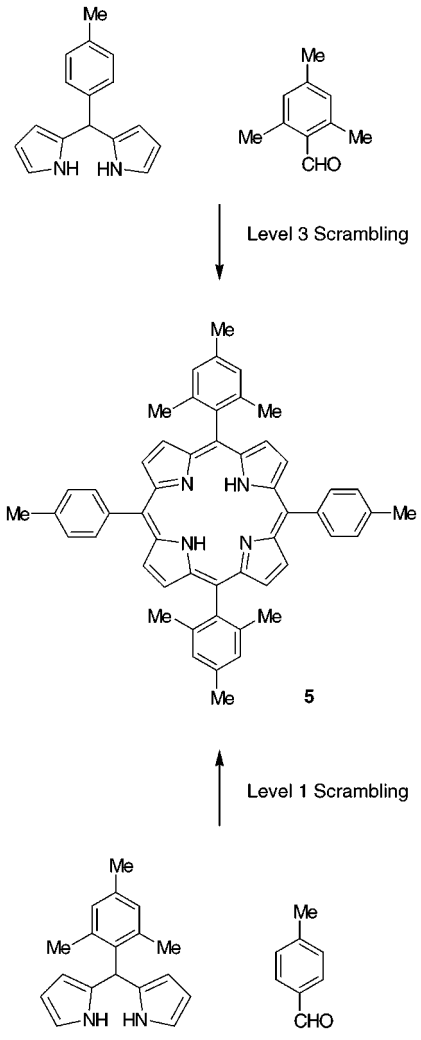
3. Synthetic Strategy in MacDonald-Type 2 + 2 Condensations. The symmetry of a *trans*-A_2B_2-porphyrin means that it can be synthesized by two alternative but complementary condensations. We therefore examined condensation of 5-(4-methylphenyl)dipyrromethane[12] with mesitaldehyde to compare the degree of scrambling obtained with that produced by condensation of 5-mesityldipyrromethane and *p*-tolualdehyde (Scheme 5).

Table 3. Isolated Yield of Porphyrins Obtained by Condensation of Dipyrromethanes and Aldehydes under Optimized Low-Scrambling Reaction Conditions

Dipyrromethane	Aldehyde	Porphyrin	Method	Yield (%)	Scrambling Level
		**15**	MeCN[a]	9	1
		15	DMSO[b]	5	1
		**16**	MeCN[a]	8	0
		16	DMSO[b]	5	0

[a] Reactions performed with 10 mM dipyrromethane and aldehyde in MeCN at 0 °C, catalyzed by $BF_3{\cdot}Et_2O$ (1.0 mM) with NH_4Cl (100 mmol/L). [b] Reactions performed with 100 mM dipyrromethane and aldehyde with NH_4Cl (316 mmol/L) in DMSO open to the air at 90 °C for 24 h.

Scheme 5[a]



Condensation of 5-(4-methylphenyl)dipyrromethane and mesitaldehyde (10 mM) by 17.8 mM TFA in $CHCl_3$ (containing 0.75% EtOH) at room temperature gave no

porphyrin formation. In contrast, $BF_3{\cdot}Et_2O$ catalysis under identical conditions gave a 44% spectroscopic porphyrin yield. Conditions suitable for condensation of a dipyrromethane with a sterically hindered aldehyde are therefore analogous to the condensation of pyrrole and mesitaldehyde for the formation of tetramesitylporphyrin: i.e., 2,6-dimethyl-substituted benzaldehydes require $BF_3{\cdot}Et_2O$/EtOH cocatalysis to react with pyrrolic species.[33] Reaction of 5-(4-methylphenyl)dipyrromethane and mesitaldehyde (10 mM) in $CHCl_3$ under $BF_3{\cdot}Et_2O$ catalysis produced Level 3 scrambling. In contrast, Level 1 scrambling was observed for the condensation of 5-mesityldipyrromethane and *p*-tolualdehyde under identical conditions. This result demonstrates that choosing the best disconnection of the *trans*-porphyrin into dipyrromethane and aldehyde components can be crucial to the success of the 2 + 2 strategy. In particular, a sterically hindered aryl group should be incorporated into the dipyrromethane rather than the aldehyde.

4. Mechanistic Implications. The results obtained in this study provide insight into two important mechanistic features of the acid-catalyzed condensation between an aldehyde and a 5-substituted dipyrromethane:

1. Scrambling is very difficult to suppress but is reduced at lower reaction temperatures. Therefore, the nonscrambling reaction leading to *trans*-porphyrins must have an activation energy that is only slightly lower than that of the scrambling process.

2. Complementary condensations should form the same porphyrinogen, but in the example we studied there were very different levels of scrambling. This demonstrates that most scrambling must occur prior to porphyrinogen formation.

Conclusions

Our detailed study into the 2 + 2 condensation between a dipyrromethane and an aldehyde for the preparation of pure *trans*-porphyrins has led to the following conclusions. (1) A rapid screening method based on spectroscopic yield detection and LD-MS allows a wide range of reaction conditions to be rapidly surveyed. Although we have not studied other systems, we anticipate that this screening method will be applicable to optimizing other oligopyrromethane-based syntheses where scrambling is a possibility: for example, 3 + 1 approaches to porphyrins,[34] synthesis of heteroatom-substituted porphyrins,[35] and preparation of expanded porphyrin analogues.[36] (2) For condensations involving sterically hindered dipyrromethanes we have identified reaction conditions that cause no scrambling and have developed a preparative procedure that gives pure *trans*-porphyrins in multigram batches. (3) Scrambling in MacDonald-type condensations with sterically unhindered dipyrromethanes is very difficult to suppress. Two sets of conditions were identified that reduced scrambling to the limit of detection by LD-MS. Although both sets of conditions gave the pure *trans*-porphyrin in less than 10% yield, they eliminate the need to perform lengthy chromatography. (4) In the retrosynthetic disconnection of the porphyrin into the dipyrromethane and aldehyde components, the sterically hindered group should be incorporated in the dipyrromethane where possible.

Experimental Section

All chemicals were obtained commercially and used as received unless otherwise noted. Montmorillonite K-10 (Fluka) was used as received or activated by heating to 100 °C at 0.03 Torr for 4 h.[29] Solvents (A.C.S. grade) were obtained from Fisher, except for DMSO, propionitrile, and butyronitrile (Aldrich). All inorganic salts were ground into a fine powder with a mortar and pestle prior to use. Pyrrole, CH_2Cl_2, acetonitrile, propionitrile, butyronitrile, and toluene were distilled from CaH_2, and $CHCl_3$ was distilled from K_2CO_3. Column chromatography was performed on silica (Baker, 200−400 mesh) or alumina (Fisher, 80−200 mesh). Reaction sampling was performed with syringes equipped with Teflon-tipped plungers. All reported NMR results were obtained at 300 MHz in $CDCl_3$. UV−vis absorption spectra were recorded in CH_2Cl_2/ethanol (3:1). Mass spectra of porphyrin mixtures were obtained by laser desorption mass spectrometry (LD-MS) without a matrix.[17]

General Procedure for the Investigation of Rreaction Conditions. The progress of the reaction was monitored by periodic removal of aliquots from the reaction mixture via syringe, followed by oxidization with DDQ and absorption spectroscopy. In particular, for 10.0, 31.6, and 100 mM reactions, 25, 10, and 5 μL aliquots, respectively, were removed from the reaction vessel and injected into 300 μL of a 10 mM DDQ solution in toluene. Then 25 μL of this oxidized solution was diluted in 3.0 mL of CH_2Cl_2/ethanol (3:1) and the visible absorption spectrum recorded. The yield of porphyrin was determined by the intensity of the Soret band (420 nm, ϵ = 500 000 M^{-1} cm^{-1}) measured from the apex to the base of the red edge of the band. This eliminated the contribution of the polypyrromethene and quinone components that exhibit a broad absorption in the 400−500 nm region. To obtain samples for LD-MS examination of the porphyrin distribution, the spectroscopic aliquots were filtered through a pad of silica (6 mm diameter × 50 mm) in a standard glass Pasteur pipet. The column was eluted with CH_2Cl_2 and one fraction collected to prevent chromatographic separation of the porphyrin mixture; the porphyrin mixture elutes close to the solvent front, while the highly colored byproducts of the oxidation remain bound to the top half of the pad.

5,15-Dimesityl-10,20-bis(4-methylphenyl)porphyrin (5). Samples of 5-mesityldipyrromethane (2.64 g, 10.0 mmol) and *p*-tolualdehyde (1.17 mL, 10.0 mmol) were dissolved in CH_2Cl_2 (1000 mL, Fisher A.C.S grade, undistilled) in a 2 L round-bottomed flask, and then TFA (1.37 mL, 17.8 mmol) was added slowly over 30 s. The reaction was stirred at room temperature with the progress of the reaction monitored by UV−vis spectroscopy. After 30 min, DDQ (2.27 g, 10.0 mmol)[24] was added, and the reaction mixture was stirred at room temperature for a further 1 h. The complete reaction mixture was poured onto a pad of alumina (75 mm maximum diameter × 100 mm in a 2000 mL separatory funnel) and eluted with CH_2Cl_2 until the eluting solution was pale brown (total solvent volume ca. 1500 mL). (Note: the reaction mixture should not be concentrated prior to filtration through the alumina pad because the porphyrin was often difficult to fully redissolve and/or precipitated during the filtration.) The solvent was removed under vacuum to give a black solid which was dissolved in toluene (200 mL) and heated under reflux for 1 h in the presence of DDQ (2.27 g, 10.0 mmol) to oxidize any remaining chlorin.[26] After cooling to room temperature, the entire reaction mixture was passed through a pad of alumina (65 mm maximum diameter × 80 mm in a 500 mL separatory funnel) and eluted with CH_2Cl_2 until the purple material had completely eluted (total solvent volume ca. 600 mL). Removal

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(35) Heo, P.-Y.; Shin, K.; Lee, C.-H. *Tetrahedron Lett.* **1996**, *37*, 197−200. Cho, W.-S.; Lee, C.-H. *Bull. Korean Chem. Soc.* **1998**, *19*, 314−319. Srinivasan, A.; Sridevi, B.; Reddy, V. R. R.; Narayanan, J.; Chandrashekar, T. K. *Tetrahedron Lett.* **1997**, *38*, 4149−4152.

(36) Brückner, C.; Sternberg, E. D.; Boyle, R. W.; Dolphin, D. *J. Chem. Soc., Chem. Commun.* **1997**, 1689−1690. Lash, T. D.; Richter, D. T. *J. Am. Chem. Soc.* **1998**, *120*, 9965−9966.

of the solvent under vacuum gave a purple solid (1.73 g, 48%): ^{1}H NMR δ −2.61 (br s, 2 H), 1.84 (s, 12 H), 2.62 (s, 6 H), 2.68 (s, 6 H), 7.27 (s, 4 H), 7.53 (d, J = 8.0 Hz, 4 H), 8.09 (d, J = 8.0 Hz, 4 H), 8.67 (d, J = 4.8 Hz, 4 H), 8.81 (d, J = 4.8 Hz, 4 H); λ_{abs} 418, 514, 550, 590, 645 nm; $C_{52}H_{46}N_4$ calcd mass 726.4, obsd 726.2 (LD-MS); calcd exact mass 726.3722, obsd 726.3722 (FAB-MS).

5,15-Dimesityl-10,20-diphenylporphyrin (6). Condensation of 5-mesityldipyrromethane (2.64 g, 10.0 mmol) and benzaldehyde (1.02 mL, 10.0 mmol) in CH_2Cl_2 (1000 mL) with TFA (1.37 mL, 17.8 mmol) following the procedure described for **5** gave a purple solid (1.34 g, 38%): ^{1}H NMR δ −2.62 (br s, 2 H), 1.84 (s, 12 H), 2.63 (s, 6 H), 7.28 (s, 4 H), 7.70−7.79 (m, 6 H), 8.20−8.24 (m, 4 H), 8.68 (d, J = 4.8 Hz, 4 H), 8.78 (d, J = 4.8 Hz, 4 H); λ_{abs} 417, 514, 548, 589, 645 nm; $C_{50}H_{42}N_4$ calcd mass 698.4, obsd 698.0 (LD-MS); calcd exact mass 698.3409, obsd 698.3414 (FAB-MS).

5,15-Dimesityl-10,20-bis(2-methylphenyl)porphyrin (7). Condensation of 5-mesityldipyrromethane (2.64 g, 10.0 mmol) and *o*-tolualdehyde (1.16 mL, 10.0 mmol) in CH_2Cl_2 (1000 mL) with TFA (1.37 mL, 17.8 mmol) following the procedure described for **5** gave a purple solid (1.27 g, 35%) as a 1:1 mixture of two atropisomers: ^{1}H NMR δ −2.58 (br s, 2 H), 1.82 (s, 3 H), 1.85 (s, 6 H), 1.88 (s, 3 H), 2.03 (s, 3 H), 2.07 (s, 3 H), 2.62 (s, 6 H), 7.27 (s, 4 H), 7.49−7.61 (m, 4 H), 7.67 (m, 2 H), 7.98 (d, J = 7.3 Hz, 1 H), 8.04 (d, J = 7.3 Hz, 1 H), 8.64 (m, 8 H); λ_{abs} 417, 513, 545, 589, 645 nm; $C_{52}H_{46}N_4$ calcd mass 726.4, obsd 726.2 (LD-MS); calcd exact mass 726.3722, obsd 726.3721 (FAB-MS).

5,15-Dimesityl-10,20-bis(4-iodophenyl)porphyrin (8). Condensation of 5-mesityldipyrromethane (2.64 g, 10.0 mmol) and 4-iodobenzaldehyde (2.32 g, 10.0 mmol) in CH_2Cl_2 (1000 mL) with TFA (1.37 mL, 17.8 mmol) following the procedure described for **5** gave a purple solid (1.67 g, 35%). Spectroscopic data were identical to those previously reported.[19]

5,15-Dimesityl-10,20-bis(3-iodophenyl)porphyrin (9). Condensation of 5-mesityldipyrromethane (2.64 g, 10.0 mmol) and 3-iodobenzaldehyde (2.32 g, 10.0 mmol) in CH_2Cl_2 (1000 mL) with TFA (1.37 mL, 17.8 mmol) following the procedure described for **5** gave a purple solid (1.46 g, 31%). Spectroscopic data were identical to those previously reported.[20]

5,15-Dimesityl-10,20-bis(4-methoxyphenyl)porphyrin (10). Condensation of 5-mesityldipyrromethane (2.64 g, 10.0 mmol) and *p*-anisaldehyde (1.36 g, 10.0 mmol) in CH_2Cl_2 (1000 mL) with TFA (1.37 mL, 17.8 mmol) following the procedure described for **5** gave a purple solid (1.66 g, 44%): ^{1}H NMR δ −2.60 (br s, 2 H), 1.84 (s, 12 H), 2.62 (s, 6 H), 4.08 (s, 6 H), 7.23−7.28 (m, 8 H), 8.12 (m, 4 H), 8.67 (d, J = 4.8 Hz, 4 H), 8.81 (d, J = 4.8 Hz, 4 H); λ_{abs} 420, 516, 552, 592, 647 nm; $C_{52}H_{46}N_4O_2$ calcd mass 758.4, obsd 758.1 (LD-MS); calcd exact mass 758.3621, obsd 758.3639 (FAB-MS).

5,15-Dimesityl-10,20-bis(pentafluorophenyl)porphyrin (11). Condensation of 5-mesityldipyrromethane (2.64 g, 10.0 mmol) and pentafluorobenzaldehyde (1.96 g, 10.0 mmol) in CH_2Cl_2 (1000 mL) with TFA (1.37 mL, 17.8 mmol) following the procedure described for **5** gave a dark solid (2.30 g). Trituration with hexanes removed undesired pigments and gave a purple solid (1.22 g, 28%): ^{1}H NMR δ −2.68 (br s, 2 H), 1.84 (s, 12 H), 2.64 (s, 6 H), 7.30 (s, 4 H), 8.76 (m, 8 H); λ_{abs} 414, 510, 542, 586, 642 nm; $C_{50}H_{32}F_{10}N_4$ calcd mass 878.2, obsd 878.4 (LD-MS); calcd exact mass 878.2467, obsd 878.2490 (FAB-MS).

5,15-Dimesityl-10,20-bis(*n*-pentyl)porphyrin (12). Condensation of 5-mesityldipyrromethane (2.64 g, 10.0 mmol) and *n*-hexanal (1.00 g, 10.0 mmol) in CH_2Cl_2 (1000 mL) with TFA (1.37 mL, 17.8 mmol) following the procedure described for **5** gave a dark solid (0.66 g). Trituration with hexanes removed undesired pigments and gave a purple solid (0.49 g, 14%): ^{1}H NMR δ −2.49 (br s, 2 H), 0.97 (t, J = 7.3 Hz, 6 H), 1.55 (m, 4 H), 1.79 (m, 4 H), 1.83 (s, 12 H), 2.52 (m, 4 H), 2.65 (s, 6 H), 4.91 (m, 4 H), 7.29 (s, 4 H), 8.70 (d, J = 4.8 Hz, 4 H), 9.35 (d, J = 4.8 Hz, 4 H); λ_{abs} 417, 517, 551, 595, 652 nm; $C_{48}H_{54}N_4$ calcd mass 686.4, obsd 686.2 (M^+, 100%), 629.1 [$(M^\bullet - C_4H_9)^+$, 55%], 734.2 [5,10,15-trimesityl-20-(*n*-pentyl)porphyrin, 3%] (LD-MS); calcd exact mass 686.4348, obsd 686.4346 (FAB-MS).

5,15-Bis(2,6-dichlorophenyl)-10,20-diphenylporphyrin (13). Utilizing the procedure developed for condensations performed with 5-mesitydipyrromethane, 5-(2,6-dichlorophenyl)dipyrromethane (2.91 g, 10.0 mmol) and benzaldehyde (1.02 g, 10.0 mmol) were condensed in CH_2Cl_2 (1000 mL) with TFA (1.37 mL, 17.8 mmol) following the procedure described for **5** with only one modification. To prevent precipitation of the porphyrin during filtration through the second alumina pad, CH_2Cl_2 (500 mL) was added to the solution of porphyrin in toluene after heating at reflux for 1 h and cooling to room temperature. After filtration through the alumina pad, removal of the solvent under vacuum gave a purple solid (1.32 g, 35%): ^{1}H NMR δ −2.63 (br s, 2 H), 7.68−7.82 (m, 12 H), 8.23 (m, 4 H), 8.66 (d, J = 4.9 Hz, 4 H), 8.87 (d, J = 4.9 Hz, 4 H); λ_{abs} 417, 513, 546, 589, 646 nm; $C_{44}H_{26}Cl_4N_4$ calcd mass 750.1, obsd 751.0 (LD-MS); calcd exact mass 750.0912, obsd 750.0926 (FAB-MS).

5,15-Bis(2,6-dichlorophenyl)-10,20-bis(4-iodophenyl)-porphyrin (14). Condensation of 5-(2,6-dichorophenyl)dipyrromethane (2.23 g, 7.67 mmol) and 4-iodobenzaldehyde (1.78 g, 7.67 mmol) in CH_2Cl_2 (770 mL) with TFA (1.06 mL, 13.7 mmol, 17.8 mM) following the procedure described for **13** gave a purple solid (1.01 g, 26%): ^{1}H NMR δ −2.68 (br s, 2 H), 7.72 (m, 2 H), 7.81 (m, 4 H), 7.96 (d, J = 8.2 Hz, 4 H), 8.09 (d, J = 8.2 Hz, 4 H), 8.68 (d, J = 4.8 Hz, 4 H), 8.84 (d, J = 4.8 Hz, 4 H); λ_{abs} 418, 514, 550, 587 nm; $C_{44}H_{24}Cl_4I_2N_4$ calcd mass 1001.9, obsd 999.6 (LD-MS); calcd exact mass 1001.8845, obsd 1001.8861 (FAB-MS).

5,15-Bis(4-methylphenyl)-10,20-diphenylporphyrin (15).[27a] **DMSO Method.** In a two-neck round-bottomed flask equipped with an air condenser and a digital thermocouple, samples of 5-phenyldipyrromethane (2.22 g, 10.0 mmol) and *p*-tolualdehyde (1.18 mL, 10.0 mmol) were dissolved in DMSO (100 mL) containing NH_4Cl (1.69 g, 31.6 mmol). The mixture was heated at 90 °C open to air for 24 h and then allowed to cool slowly to room temperature over 3 h. Filtration of the crude reaction mixture under suction gave a dark solid. Washing with diethyl ether gave a purple solid (142 mg, 5%). TLC analysis and ^{1}H NMR spectroscopy showed no clear evidence of scrambling, but Level 1 scrambling was observed via the LD-MS assay: ^{1}H NMR δ −2.78 (br s, 2 H), 2.70 (s, 6 H), 7.55 (d, J = 7.8 Hz, 4 H), 7.71−7.81 (m, 6 H), 8.10 (d, J = 7.8 Hz, 4 H), 8.21 (m, 4 H), 8.85 (m, 8 H); $C_{46}H_{34}N_4$ calcd mass 642.3, obsd 642.2 ($M^{\bullet+}$, 100%) and 657.2 [5,10,15-tris(4-methylphenyl)-20-phenylporphyrin, 6%] (LD-MS).

MeCN Method. A 2000 mL round-bottomed flask, equipped with a magnetic stirrer bar, was flushed with Ar. Then MeCN (1000 mL, Fisher A.C.S. grade, undistilled) was added and degassed with a stream of Ar for 10 min. Freshly ground NH_4Cl (5.35 g, 100 mmol) was added, and the flask placed in an ice bath and cooled under Ar. Samples of 5-phenyldipyrromethane (2.22 g, 10.0 mmol) and *p*-tolualdehyde (1.18 mL, 10 mmol) were added, followed by $BF_3{\cdot}Et_2O$ (126 μL, 1.00 mmol), and the mixture was stirred at 0 °C under Ar. The progress of the reaction was monitored by UV−vis spectroscopy, and after 4.5 h DDQ (2.27 g, 10.0 mmol) was added. The ice bath was removed, and the mixture was stirred at room temperature for 1 h and then filtered through a pad of alumina eluted with CH_2Cl_2. The solvent was removed to give a dark solid that was dissolved in toluene (250 mL); then DDQ was added (2.27 g, 10.0 mmol) and the mixture heated at reflux for 1 h. The mixture was allowed to cool to room temperature and then filtered through a pad of alumina eluted with CH_2Cl_2. Removal of the solvent gave a mixture of a purple solid and a black solid (357 mg). Trituration of the crude product with hexanes followed by filtration gave a purple solid (303 mg, 9%). TLC analysis and ^{1}H NMR spectroscopy showed no clear evidence of scrambling, but Level 1 scrambling was observed via the LD-MS assay: $C_{46}H_{34}N_4$ calcd mass 642.3, obsd 642.2 ($M^{\bullet+}$, 100%), 656.2 [5,10,15-tris(4-methylphenyl)-20-phenylporphyrin, 7%], 628.1 [5,10,15-triphenyl-20-(4-methylphenyl)porphyrin, 1%] (LD-MS).

5,15-Bis[4-(2-trimethylsilylethynyl)phenyl]-10,20-bis-(4-iodophenyl)porphyrin (16). A mixture of 5-(4-iodophenyl)dipyrromethane (1.78 g, 5.12 mmol), 4-(2-trimethylsilyl-

ethynyl)benzaldehyde (1.04 g, 5.12 mmol), and NH_4Cl (0.87 g, 16.2 mmol) in DMSO (51.2 mL) was heated at 90 °C for 24 h following the procedure described for **15** to give a purple solid (146 mg, 5%): ^{1}H NMR δ −2.87 (br s, 2 H), 0.38 (s, 18 H), 7.87 (d, J = 8.1 Hz, 4 H), 7.93 (d, J = 8.2 Hz, 4 H), 8.09 (d, J = 8.2 Hz, 4 H), 8.14 (d, J = 8.1 Hz, 4 H), 8.83 (m, 8 H); λ_{abs} 421, 517, 552, 591, 646 nm; $C_{54}H_{44}I_2N_4Si_2$ calcd mass 1058.1, obsd 1059.1 (LD-MS); calcd exact mass 1058.1194, obsd 1058.1199 (FAB-MS).

5,15-Bis[4-(2-trimethylsilylethynyl)phenyl]-10,20-bis-(4-iodophenyl)porphyrin (16). A mixture of 5-(4-iodophenyl)dipyrromethane (1.78 g, 5.12 mmol), 4-(2-trimethylsilylethynyl)benzaldehyde (1.04 g, 5.12 mmol), and NH_4Cl (2.74 g, 51.2 mmol) in ice-cold MeCN (512 mL) under Ar was treated with $BF_3 \cdot Et_2O$ (64.5 μL, 0.512 mmol, 1 mM) following the procedure described for **15**. The reaction mixture was stirred for 3.5 h; then DDQ (2.00 g, 8.81 mmol) was added and stirring was continued at room temperature for 1 h. The reaction mixture was filtered through an alumina pad eluted with CH_2Cl_2 (ca. 2000 mL, due to low solubility of the porphyrin). The solvent was removed to give a dark solid that was dissolved in toluene (300 mL), DDQ (2.00 g) was added, and the mixture heated at reflux for 1 h. The mixture was cooled to room temperature and filtered through an alumina pad eluted with CH_2Cl_2. Removal of the solvent gave a dark solid that TLC and ^{1}H NMR analysis showed to be a mixture of the desired porphyrin and undefined pigments. Flash column chromatography (silica, CH_2Cl_2) gave a purple solid (222 mg, 8%) despite low solubility of the porphyrin in CH_2Cl_2 leading to very slow elution of the desired compound. Spectral properties were identical to those of the sample prepared above.

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Supporting Information Available: A full description of the screening studies performed on the reaction of 5-mesityldipyrromethane and *p*-tolualdehyde and the reaction of 5-phenyldipyrromethane and *p*-tolualdehyde; ^{1}H NMR spectra of porphyrins **5**−**16**; LD-MS spectra of porphyrins **5**, **12**, **15**, **16**. This material is available free of charge via the Internet at http://pubs.acs.org.

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