JOC*Article*

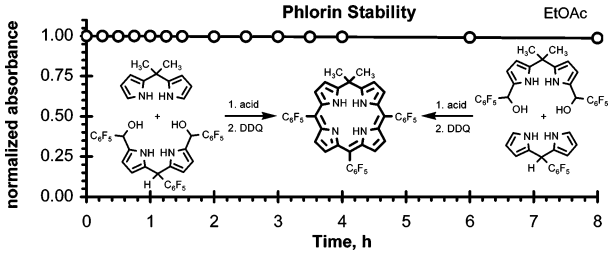
Dipyrromethane + Dipyrromethanedicarbinol Routes to an Electron Deficient meso-Substituted Phlorin with Enhanced Stability

Anna Y. O'Brien, John P. McGann, and G. Richard Geier, III*

Department of Chemistry, Colgate University, 13 Oak Drive, Hamilton, New York 13346

ggeier@mail.colgate.edu

Received February 1, 2007



Two dipyrromethane + dipyrromethanedicarbinol routes to a meso-substituted phlorin bearing electron-withdrawing pentafluorophenyl substituents (TpFPPhl) were investigated in an attempt to obtain a phlorin with enhanced stability toward light and air and to explore the application of dipyrromethanecarbinol chemistry to the preparation of phlorins. For each route, a systematic survey of reaction parameters for the two-step, one-flask reaction leading to TpFPPhl was performed. The analytical-scale reactions were monitored for yield of TpFPPhl by HPLC. Sharp differences were observed in the yield of TpFPPhl afforded by the two synthetic routes. The most promising reaction condition (TFA catalysis, 100 mM) was performed on a preparative scale providing TpFPPhl in a yield of 45% (189 mg). The stability of the electron-deficient phlorin in dilute solution upon exposure to light and air was probed in a number of solvents, and decomposition was monitored by UV−vis spectroscopy and HPLC. Many of the solutions of TpFPPhl were found to be quite stable for periods of ~8 h, with decomposition requiring exposure periods of several days. Taken together, this work contributes an efficient synthesis of a meso-substituted phlorin of practical stability and provides further insights toward the adaptation of dipyrromethanecarbinol chemistry to the preparation of diverse porphyrinoids.

Introduction

Phlorins are porphyrinic macrocycles that differ from porphyrins by the presence of an sp^3-hybridized carbon atom at one of the four meso-positions.[1] Phlorins were first reported in the course of Woodward's landmark studies of macrocycles related to chlorophyll a.[2] Phlorins were later identified as intermediates in syntheses of porphyrins,[3] in studies of reductions of porphyrins,[4] and in reactions of porphyrins with nucleophiles.[5] A phlorin structure has been implicated in the catalytic cycle of heme P460 of hydroxylamine oxidoreductase,[6] and phlorins have been relevant in model studies of coenzyme F430.[7] The equilibrium between phlorin and chlorin tautomers has been investigated.[8] More recently, phlorins have garnered interest for their anion binding properties.[9] Phlorins have been detected as side products in reactions intended to prepare other porphyrinoids,[9,10] N-confused phlorins have been reported,[11] and

(1) Sessler, J. L.; Zimmerman, R. S.; Bucher, C.; Kral, V.; Andrioletti, B. *Pure Appl. Chem.* **2001**, *73*, 1041−1057.

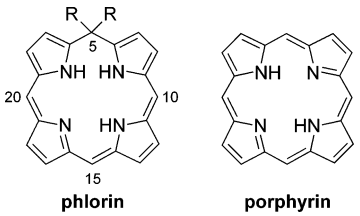
(2) Woodward, R. B. *Ind. Chim Belg.* **1962**, *27*, 1293−1308.

(3) (a) Rocha Gonsalves, A. M. d'A.; Pereira, M. M. *J. Heterocycl. Chem.* **1985**, *22*, 931−933. (b) Lash, T. D. *J. Porphyrins Phthalocyanines* **1997**, *1*, 29−44. (c) Lash, T. D.; Gandhi, V. *J. Org. Chem.* **2000**, *65*, 8020−8026.

(4) (a) Mauzerall, D. *J. Am. Chem. Soc.* **1962**, *84*, 2437−2445. (b) Closs, G. L.; Closs, L. E. *J. Am. Chem. Soc.* **1963**, *85*, 818−819. (c) Fuhrhop, J.-H.; Mauzerall, D. *J. Am. Chem. Soc.* **1968**, *90*, 3875−3876. (d) Lanese, J. G.; Wilson, G. S. *J. Electrochem. Soc.* **1972**, *119*, 1039−1043. (e) Harel, Y.; Meyerstein, D. *J. Am. Chem. Soc.* **1974**, *96*, 2720−2727. (f) Langhus, D. L.; Wilson, G. S. *Anal. Chem.* **1979**, *51*, 1139−1144. (g) Marrese, C. A.; Carrano, C. J. *Inorg. Chem.* **1983**, *22*, 1858−1862. (h) Marrese, C. A.; Carrano, C. J. *Inorg. Chem.* **1984**, *23*, 3961−3968. (i) Baral, S.; Hambright, P.; Neta, P. *J. Phys. Chem.* **1984**, *88*, 1595−1600. (j) Harriman, A. *J. Photochem.* **1985**, *29*, 139−150. (k) Abou-Gamra, Z.; Harriman, A.; Neta, P. *J. Chem. Soc., Faraday Trans. 2* **1986**, *82*, 2337−2350. (l) Sutter, T. P. G.; Rahimi, R.; Hambright, P.; Bommer, J. C.; Kumar, M.; Neta, P. *J. Chem. Soc., Faraday Trans.* **1993**, *89*, 495−502.

10.1021/jo070216k CCC: $37.00
Published on Web 04/27/2007

there has been interest in syntheses of phlorins from building block precursors in analogy to stepwise syntheses of meso-substituted porphyrins.[12,13]



The presence of an sp^3-hybridized meso-carbon atom has a profound effect on the structure and properties of phlorins. The sp^3-hybridized carbon atom disrupts the conjugation of the macrocycle, and it renders the ring nonplanar. Additionally, the inner core of the phlorin macrocycle contains three N−H-type nitrogen atoms compared to the two found in porphyrins. Thus, the phlorin ligand upon deprotonation and metal insertion is trianionic compared to the dianionic nature of porphyrins. Finally, phlorins are generally unstable toward ambient light and air. Phlorins bearing a hydrogen atom at the sp^3-hybridized position readily undergo oxidation to the corresponding aromatic porphyrins. Phlorins for which this pathway is blocked by substituents at the sp^3-hybridized carbon atom are still subject to oxidation, leading to ring-opened biladienone species.[14] The poor stability of phlorins complicates their preparation and study.

The handful of phlorins sufficiently stable for isolation and characterization have generally possessed either an electronegative central metal ion[15] or structurally distorting substituents/tethers on one or more of the core nitrogen atoms.[16,17] Until recently (vide infra), the use of peripheral substituents to improve the stability of phlorins had only been demonstrated in Woodward's work involving a phlorin stabilized by the steric bulk of β-pyrrole substituents adjacent to the sp^3-hybridized carbon atom.[2] The use of peripheral substituents to enhance phlorin stability is attractive as such substituents are less perturbing than metal insertion or N-substituents to the macrocycle structure and to the central core. Our earlier observations on the effect of meso-substituents on corrole stability[18] inspired our attempts to obtain stable phlorins via the judicious selection of meso-substituents. Sterically bulky substituents (e.g., mesityl) were expected to shield the meso-positions from oxidation, and electron-withdrawing substituents (e.g., pentafluorophenyl) were expected to render the macrocycle electron deficient and therefore less prone to oxidation.

Our initial efforts to explore the effect of peripheral meso-substituents on the stability of phlorins considered the effect of sterically bulky mesityl substituents, as the methodology of Krattinger and Callot for the preparation of phlorins via alkylation of a porphyrin precursor[19] provided an attractive route for the preparation of meso-mesityl substituted phlorins. Encouragingly, we found that phlorin stability could be enhanced by the incorporation of mesityl substituents at the three sp^2-hybridized meso-positions, increasing the half-life of dilute solutions of phlorin exposed to light and air from <15 to >90 min.[20] Importantly, we found that steric protection was required at all three sp^2-hybridized meso-positions, not just the two positions adjacent to the sp^3-hybridized carbon atom (positions 10 and 20). The favorable outcome of this study provided motivation for the investigation of electron-withdrawing substituents, and the recent report of stable phlorin−dipyrrin conjugates possessing sterically bulky and electron-withdrawing meso-substituents provided further encouragement.[10] Our efforts to prepare a phlorin bearing pentafluorophenyl substituents and studies of its stability are described herein. The targeted phlorin species, 5,5-dimethyl-10,15,20-tris(pentafluorophenyl)phlorin **3** (TpFPPhl), was selected as the two methyl groups prevent oxidation of the sp^3-hybridized meso-carbon atom and the pentafluorophenyl groups would render the sp^2-hybridized meso-positions electron deficient.

The preparation of TpFPPhl required an approach different from alkylation of the corresponding porphyrin as the pentafluorophenyl groups are reactive toward strong nucleophiles. Thus, we elected to explore dipyrromethanecarbinol chemistry initially reported for the preparation of meso-substituted porphyrins[21,22] and later extended to the preparation of other porphyrinoids such as heteroatom modified porphyrins,[23] chlorin,[24]

(5) (a) Setsune, J.; Yazawa, T.; Ogoshi, H.; Yoshida, Z. *J. Chem. Soc., Perkin Trans. I* **1980**, 1641−1645. (b) Pandian, R. P.; Chandrashekar, T. K.; Chandrasekhar, V. *Ind. J. Chem.* **1991**, *30A*, 579−583. (c) Segawa, H.; Azumi, R.; Shimidzu, T. *J. Am. Chem. Soc.* **1992**, *114*, 7564−7565. (d) Jiang, X; Nurco, D. J.; Smith, K. M. *Chem. Commun.* **1996**, 1759−1760. (e) Collman, J. P.; Boulatov, R. *J. Am. Chem. Soc.* **2000**, *122*, 11812−11821. (f) Senge, M. O.; Kalisch, W. W.; Bischoff, I. *Chem.—Eur. J.* **2000**, *6*, 2721−2738. (g) Feng, X.; Bischoff, I.; Senge, M. O. *J. Org. Chem.* **2001**, *66*, 8693−8700.

(6) Arciero, D. M.; Hooper, A. B. *Biochem. Soc. Trans.* **1998**, *26*, 385−389.

(7) (a) Stolzenberg, A. M.; Stershic, M. T. *Inorg. Chem.* **1987**, *26*, 3082−3083. (b) Stolzenberg, A. M.; Stershic, M. T. *J. Am. Chem. Soc.* **1988**, *110*, 6391−6402.

(8) Whitlock, H. W.; Oester, M. Y. *J. Am. Chem. Soc.* **1973**, *95*, 5738−5741.

(9) Ka, J. W.: Lee, C. H. *Tetrahedron Lett.* **2001**, *42*, 4527−4529.

(10) Gryko, D. T.; Koszarna, B. *Eur. J. Org. Chem.* **2005**, 3314−3318.

(11) (a) Li, X.; Chmielewski, P. J.; Xiang, J.; Xu, J.; Li, Y.; Liu, H.; Zhu, D. *Org. Lett.* **2006**, *8*, 1137−1140. (b) Li, X.; Chmielewski, P. J.; Xiang, J.; Xu, J.; Jiang, L.; Li, Y.; Liu, H.; Zhu, D. *J. Org. Chem.* **2006**, *71*, 9739−9742.

(12) Bucher, C.; Seidel, D.; Lynch, V.; Kral, V.; Sessler, J. L. *Org. Lett.* **2000**, *2*, 3103−3106.

(13) Hong, S. J.; Ka, J. W.; Won, D. H.; Lee, C. H. *Bull. Korean Chem. Soc.* **2003**, *24*, 661−663.

(14) Jeandon, C.; Krattinger, B.; Ruppert, R.; Callot, H. J. *Inorg. Chem.* **2001**, *40*, 3149−3153.

(15) Sugimoto, H. *J. Chem. Soc., Dalton. Trans.* **1982**, 1169−1171.

(16) (a) Setsune, J.-i.; Ikeda, M.; Iida, T.; Kitao, T. *J. Am. Chem. Soc.* **1988**, *110*, 6572−6574. (b) Setsune, J.-i.; Ishimaru, Y.; Kitao, T. *Chem. Lett.* **1990**, 1351−1354. (c) Setsune, J.-i.; Yamaji, H.; Kitao, T. *Tetrahedron Lett.* **1990**, *31*, 5057−5060. (d) Setsune, J.-i.; Wada, K.-i.; Higashino, H. *Chem. Lett.* **1994**, 213−216. (e) Setsune, J.-i.; Kashihara, K.; Wada, K.-i. *Chem. Lett.* **2001**, 608−609.

(17) (a) Krattinger, B.; Callot, H. J. *Chem. Commun.* **1996**, 1341−1342. (b) Ruppert, R.; Jeandon, C.; Sgambati, A.; Callot, H. J. *Chem. Commun.* **1999**, 2123−2124. (c) Ishimaru, Y.; Sumida, S.; Iida, T. *Tetrahedron Lett.* **2001**, *42*, 419−421.

(18) Geier, G. R., III; Chick, J. F. B.; Callinan, J. B.; Reid, C. G.; Auguscinski, W. P. *J. Org. Chem.* **2004**, *69*, 4159−4169.

(19) (a) Krattinger, B.; Callot, H. J. *Tetrahedron Lett.* **1996**, *37*, 7699−7702. (b) Krattinger, B.; Callot, H. J. *Eur. J. Chem.* **1999**, 1857−1867.

(20) LeSaulnier, T. D.; Graham, B. W.; Geier, G. R., III. *Tetrahedron Lett.* **2005**, *46*, 5633−5637.

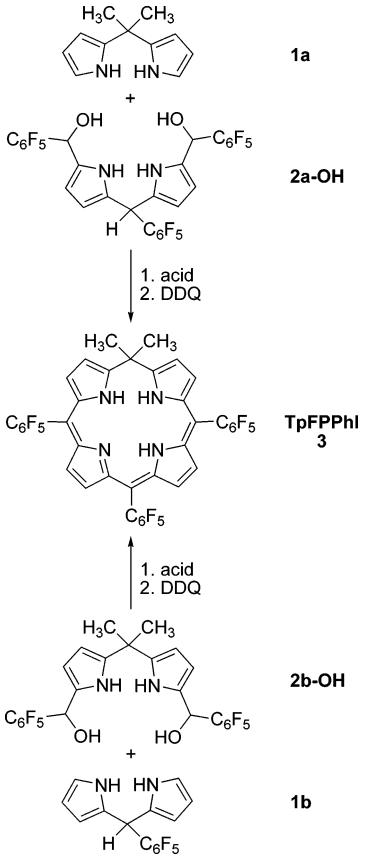
(21) (a) Lee, C. H.; Li, F.; Iwamoto, K.; Dadok, J.; Bothner-By, A. A.; Lindsey, J. S. *Tetrahedron* **1995**, *51*, 11645−11672. (b) Rao, P. D.; Dhanalekshmi, S.; Littler, B. J.; Lindsey, J. S. *J. Org. Chem.* **2000**, *65*, 7323−7344. (c) Geier, G. R., III; Callinan, J. B.; Rao, D. P.; Lindsey, J. S. *J. Porphyrins Phthalocyanines* **2001**, *5*, 810−823.

(22) Wallace, D. M.; Leung, S. H.; Senge, M. O.; Smith, K. M. *J. Org. Chem.* **1993**, *58*, 7245−7257.

(23) Cho, W. S.; Kim, H. J.; Littler, B. J.; Miller, M. A.; Lee, C. H.; Lindsey, J. S. *J. Org. Chem.* **1999**, *64*, 7890−7901.

(24) (a) Strachan, J. P.; O'Shea, D. F.; Balasubramanian, T.; Lindsey, J. S. *J. Org. Chem.* **2000**, *65*, 3160−3172. (b) Balasubramanian, T.; Strachan, J. P.; Boyle, P. D.; Lindsey, J. S. *J. Org. Chem.* **2000**, *65*, 7919−7929.

SCHEME 1. Complementary Dipyrromethane + Dipyrromethanedicarbinol Routes for the Preparation of a Phlorin Bearing Electron-Withdrawing Pentafluorophenyl Substituents



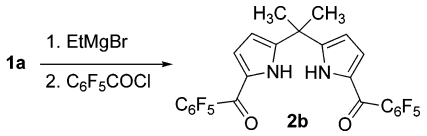
corrole,[18,25] and an octaphyrin.[26] We are aware of only one other attempt to prepare meso-substituted phlorins via a dipyrromethanecarbinol approach.[13] In this work of Lee and co-workers, a pair of reactions were explored with one providing a phenyl-substituted phlorin in a yield of 2% and the other failing to provide phlorin. It was not clear whether these results were due to fundamental problems with the overall approach, the selection of reaction conditions, or poor stability of the targeted phlorins. Thus, we felt that a further investigation of a dipyrromethanecarbinol route might add clarity to the feasibility of preparing phlorins in this fashion while also providing further insights toward the general application of dipyrromethanecarbinol species to syntheses of diverse porphyrinoids.

Toward that end, two dipyrromethane + dipyrromethanedicarbinol routes leading to TpFPPhl were explored (Scheme 1). The route involving the condensation of dipyrromethane **1a** with dipyrromethanedicarbinol **2a-OH** was attractive as both precursors are known in the literature, although the diacyl dipyrromethane precursor **2a** to **2a-OH** is challenging to obtain in high yield.[21b] The route involving the condensation of **1b** and **2b-OH** was of interest as the selection of the dipyrromethane and dipyrromethanedicarbinol partners may have an effect on the reaction outcome, and the as yet unknown diacyl dipyrromethane precursor **2b** to **2b-OH** might be obtained more efficiently than **2a**.

To explore the preparation of TpFPPhl, the required precursors were prepared and a systematic survey of key reaction parameters (acid catalyst, acid concentration, reaction time, and oxidant quantity) was performed for each route. The yield of TpFPPhl in these analytical-scale reactions was assessed by HPLC. Preparative-scale reactions were performed using the best condition identified from the analytical-scale reactions, and TpFPPhl was isolated and characterized. The stability of TpFPPhl in dilute solution toward light and air was examined in a number of solvents by monitoring changes in UV−vis spectra and HPLC chromatograms as a function of time.

Results and Discussion

Preparation of Dipyrromethanes, Diacyl Dipyrromethanes, and Dipyrromethanedicarbinols. Dipyrromethanes **1a,b**[27] and the diacyl dipyrromethane **2a**[21b] (precursor to **2a-OH**) were prepared according to the literature. Diacyl dipyrromethane **2b** (precursor to **2b-OH**) was a new compound, and it was prepared from dipyrromethane **1a** (eq 1) in accordance with typical conditions for the preparation of other diacyl dipyrromethanes[21b]—with one notable exception. We found that **2b** could be isolated and purified by multiple precipitations from CH_2Cl_2/hexanes rather than requiring chromatography. In this fashion, **2b** was obtained in yields ranging from 13−29% (370−830 mg). This compares favorably with our preparations of **2a** in yields of 5−13%. Dipyrromethanedicarbinol species **2a-OH** and **2b-OH** were prepared immediately before use by $NaBH_4$ reduction of the appropriate diacyl dipyrromethane and were used without purification as reported in the literature.[21b]



(1)

Survey of Reaction Conditions in Two-Step, One-Flask Reactions of a Dipyrromethane and a Dipyrromethanedicarbinol Leading to TpFPPhl. Studies of the two reaction routes leading to TpFPPhl involved the isolation of authentic TpFPPhl, the development of an analytical method for monitoring the production of TpFPPhl in analytical-scale reactions, a survey of acid catalysis conditions, an investigation of oxidation conditions, and reaction time course experiments.

1. Isolation of TpFPPhl. As the preparation of the target phlorin had not been previously reported, reactions of **1a** and **2a-OH** and reactions of **1b** and **2b-OH** were performed using $Dy(OTf)_3$ (10 mM) as the acid catalyst so as to obtain a small quantity of TpFPPhl for preliminary characterization and for use in the development of an HPLC method for monitoring the production of TpFPPhl in analytical-scale reactions. The distinctive green appearance and the characteristic UV−vis spectrum of phlorins helped to guide the search for TpFPPhl. Further analysis of promising pigments by laser desorption mass spectrometry (LD-MS) led to the provisional identification of TpFPPhl. Additional characterization was performed on

(25) (a) Guilard, R.; Gryko, D. T.; Canard, G.; Barbe, J.-M.; Koszarna, B.; Brandes, S.; Tasior, M. *Org. Lett.* **2002**, *4*, 4491−4494. (b) Gryko, D. T.; Tasior, M.; Koszarna, B. *J. Porphyrins Phthalocyanines* **2003**, *7*, 239−248. (c) Decreau, R. A.; Collman, J. P. *Tetrahedron Lett.* **2003**, *44*, 3323−3327.

(26) Geier, G. R., III; Grindrod, S. C. *J. Org. Chem.* **2004**, *69*, 6404−6412.

(27) (a) Littler, B. J.; Miller, M. A.; Hung, C.-H.; Wagner, R. W.; O'Shea, D. F.; Boyle, P. D.; Lindsey, J. S. *J. Org. Chem.* **1999**, *64*, 1391−1396. (b) Laha, J. K.; Dhanalekshmi, S.; Taniguchi, M.; Ambroise, A.; Lindsey, J. S. *Org. Process Res. Dev.* **2003**, *7*, 799−812.

TpFPPhl prepared later in the study after methods for its synthesis and purification were further refined.

2. HPLC Method for Monitoring the Production of TpFPPhl in Analytical-Scale Reactions. To perform a large number of analytical-scale reactions in parallel, methodology for the efficient monitoring of the yield of TpFPPhl was required. UV−vis spectroscopy is often employed to monitor reactions leading to porphyrinoids due to the strong absorbance of these species.[28] Unfortunately, the absorbance of phlorins is much weaker; thus, we found it difficult to detect TpFPPhl by UV−vis spectroscopy in the presence of other pigments. Passing an aliquot of the crude reaction mixture through a silica pad to remove polar pigments as performed in our earlier studies of corrole[18] and an octaphyrin[26] was still not sufficient to allow accurate spectrophotometric detection of TpFPPhl in the presence of remaining byproducts. As a result, an HPLC method originally developed for the quantitation of porphyrin, N-confused porphyrin, and sapphyrin[29] was adapted to this study (see the Supporting Information for a discussion of the HPLC method development, control experiments, reproducibility, calibration, and representative chromatograms). In short, the adapted method entailed the oxidation of an aliquot of the condensation reaction mixture with DDQ, basification by the addition of triethylamine, filtration of the oxidized reaction mixture through a silica pad to remove insoluble and strongly polar species, and analysis by HPLC.

3. Survey of Acid Catalysis Conditions. Two-step, one-flask syntheses of porphyrinoids involve an acid-mediated condensation step, where starting materials are converted to various linear and cyclic oligomers, and a subsequent oxidation step, where appropriate oligomers are converted to the oxidized porphyrinoid species. It is well-established that key reaction parameters in the condensation step (e.g., the choice of acid catalyst, acid concentration, and reaction time) can have a profound effect on the outcome of the reaction.[28,30] In this study, five acid catalysts [TFA, $InCl_3$, $Sc(OTf)_3$, $Yb(OTf)_3$, and $Dy(OTf)_3$] at five concentrations (0.32, 1.0, 3.2, 10, and 32 mM—and in some cases 100 and 320 mM)[31] were investigated. Each reaction was monitored for the yield of TpFPPhl at 0.25, 1, and 4 h. TFA is a benchmark acid for condensations leading to porphyrinoids,[28] and the four mild Lewis acids have been found to be well-suited for dipyrromethanecarbinol routes to porphyrin[21c] and other porphyrinoids.[18,26]

The conditions providing the highest yield of TpFPPhl for each acid catalyst in reactions of **1a** with **2a-OH** or **1b** with **2b-OH** are summarized in Table 1. Representative plots of the yield of TpFPPhl as a function of acid catalyst concentration for the reaction of **1b** with **2b-OH** are provided in Figure 1 (see the Supporting Information for a complete set of plots).

The highest yields of TpFPPhl (40−44%) were obtained from the reaction of **1b** with **2b-OH** using TFA (100 mM) or $Sc(OTf)_3$ (100 mM) catalysis (Table 1, entries 6 and 8). These maximal yields of TpFPPhl are within the range of yields typically obtained in porphyrinoid syntheses from dipyrromethanedicarbinols. Other key observations are as follows. (1) The reaction of **1a** with **2a-OH** provided markedly lower yields of TpFPPhl than the complementary reaction of **1b** with **2b-OH**. The difference in yield of TpFPPhl between the two routes is most pronounced with the mildest acid catalysts (e.g., Table 1, entries 4 and 9). While it is not clear why the reaction of **1b** with **2b-OH** provides a higher yield of TpFPPhl, it is clear that the positioning of substituents on the dipyrromethane and dipyrromethanedicarbinol precursors can significantly impact the outcome of the reaction. (2) The lowest concentration of acid catalyst affording the maximal yield of TpFPPhl was quite similar for the two reaction routes in the case of TFA, $InCl_3$, and $Sc(OTf)_3$ catalysis (e.g., Table 1, entries 1 and 6 for TFA) and quite different in the case of $Yb(OTf)_3$ and $Dy(OTf)_3$ (e.g., Table 1, entries 4 and 9). $Yb(OTf)_3$ and $Dy(OTf)_3$ are

TABLE 1. Reaction Conditions Providing the Highest Yield of TpFPPhl for Each Acid Catalyst[a]

entry	reactants	acid	[acid], mM[b]	% yield of TpFPPhl[c]
1	**1a** + **2a-OH**	TFA	100	19
2	**1a** + **2a-OH**	$InCl_3$	3.2	17
3	**1a** + **2a-OH**	$Sc(OTf)_3$	32	15
4	**1a** + **2a-OH**	$Yb(OTf)_3$	10	4
5	**1a** + **2a-OH**	$Dy(OTf)_3$	32	4
6	**1b** + **2b-OH**	TFA	100	44
7	**1b** + **2b-OH**	$InCl_3$	3.2	32
8	**1b** + **2b-OH**	$Sc(OTf)_3$	100	40
9	**1b** + **2b-OH**	$Yb(OTf)_3$	0.32	19
10	**1b** + **2b-OH**	$Dy(OTf)_3$	0.32	20

[a] The reactions were performed with the indicated reactants (2.5 mM each) on a 5−10 mL scale in CH_2Cl_2 at room temperature. The reactions were monitored at 0.25, 1, and 4 h. [b] The lowest acid concentration that provided a near-maximum yield of TpFPPhl. Higher quantities of some acids provided yields of TpFPPhl similar to those reported here. [c] The highest yield (HPLC) of the three time points is reported.

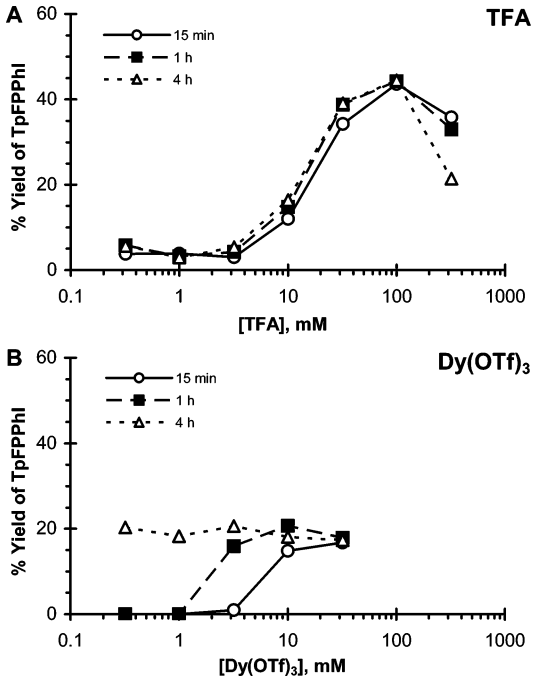


FIGURE 1. Yield of TpFPPhl as a function of (A) [TFA] and (B) [$Dy(OTf)_3$] for reactions of **1b** and **2b-OH** (2.5 mM each) at room temperature. The reactions were monitored by HPLC.

(28) Lindsey, J. S.; Schreiman, I. C.; Hsu, H. C.; Kearney, P. C.; Marguerettaz, A. M. *J. Org. Chem.* **1987**, *52*, 827−836.

(29) Geier, G. R., III; Lindsey, J. S. *J. Org. Chem.* **1999**, *64*, 1596−1603.

(30) (a) Geier, G. R., III; Lindsey, J. S. *J. Chem. Soc., Perkin Trans. 2* **2001**, 677−686. (b) Geier, G. R., III; Lindsey, J. S. *J. Chem. Soc., Perkin Trans. 2* **2001**, 687−700. (c) Geier, G. R., III; Lindsey, J. S. *J. Porphyrins Phthalocyanines* **2002**, *6*, 159−185.

(31) The quantity of acid is reported in concentration units of molarity for convenience of comparison of reaction conditions; however, $InCl_3$, $Sc(OTf)_3$, $Yb(OTf)_3$, and $Dy(OTf)_3$ are poorly soluble in CH_2Cl_2, and the reaction mixtures were heterogeneous as reported previously.[21c]

reasonable catalysts for the reaction of **1b** with **2b-OH** but poor catalysts for the other route. (3) The acid concentration providing the highest yield of TpFPPhl is generally quite high (with the exceptions found in Table 1, entries 9 and 10). This observation is consistent with a previous study of reactions of pyrrole with pentafluorobenzaldehyde leading to the corresponding meso-substituted porphyrin that found that a 10-fold higher concentration of acid was required compared to reactions not involving an electron-deficient aldehyde.[32] (4) The effect of acid concentration on the yield of TpFPPhl is similar to that which we have observed previously in the synthesis of other porphyrinoids.[18,26] Stronger acids (e.g., TFA) require more exacting conditions, whereas the milder acids provided a similar yield of TpFPPhl regardless of the acid concentration (Figure 1). The concentration of the milder acids had more of an impact on the rate of obtainment of the maximal yield of TpFPPhl than on the value of the maximal yield. (5) The effect of acid concentration on the yield of TpFPPhl is similar between the two reaction routes, despite the overall lower yield of TpFPPhl obtained from the reaction of **1a** with **2a-OH**. (6) Reaction reversibility was probed by HPLC and TLC monitoring of the crude reaction mixtures for the presence of pentafluorophenylporphyrin. The presence of porphyrin could only come about through reversible processes (i.e., scrambling). Both reaction routes were found to be resistant toward reversible processes as only reactions employing high concentrations of the stronger acids [e.g., TFA (320 mM), $InCl_3$ (32 mM), $Sc(OTf)_3$ (32 and 100 mM)] afforded trace levels of porphyrin. This finding is consistent with previous studies of reversibility in porphyrin synthesis which found that oligomers possessing electron-withdrawing substituents are resistant to reversible processes.[32] There was little difference between the two reaction routes in regards to the detection of porphyrin byproduct. The catalysis conditions noted in Table 1 generally provided TpFPPhl devoid of porphyrin byproduct (exceptions are entries 3 and 8). In summary, the survey of acid catalysts revealed conditions affording TpFPPhl in good yield, found that the reaction route involving **1b** and **2b-OH** is superior, and showed that in many respects the reaction of a dipyrromethane and dipyrromethanedicarbinol leading to TpFPPhl is similar to analogous reactions leading to other porphyrinoids.

4. Investigation of Oxidation Conditions. While the two-step, one-flask syntheses of some porphyrinoids are quite tolerant of a wide range of oxidation conditions (e.g., meso-aryl substituted porphyrins), others require more exacting conditions (e.g., meso-aryl substituted corroles[18]). Thus, to appropriately monitor reactions leading to TpFPPhl in the survey of acid catalysis conditions and in subsequent experiments, we investigated conditions for the oxidation of reaction aliquots—the effect of the quantity of DDQ oxidant and its application as a neat, solid or in solution (10 mM in toluene). We initially explored oxidation conditions prior to performing the survey of acid catalyst conditions. The reactions of **1a** with **2a-OH** and **1b** with **2b-OH** mediated by $Dy(OTf)_3$ (10 mM) were performed, and aliquots (1.2 mL) of the reaction mixture were transferred to quantities of DDQ (0.5, 1.0, 2.0, 4.0, 8.0, 16, or 32 mg) or to quantities of DDQ in solution (equivalent to 0.25, 0.5, and 1.0 mg of DDQ). The oxidized reaction mixtures were assessed by HPLC and TLC. Later, once the reaction of **1b** with **2b-OH** mediated by TFA (100 mM) was found to provide the highest yield of TpFPPhl, a condensation reaction of **1b** with **2b-OH** under TFA catalysis was performed and aliquots (1.2 mL) were transferred to quantities of DDQ (0.25, 0.5, 1.0, 2.0, 4.0, 8.0, 16, and 32 mg).

For both reaction routes and under either condensation condition, the highest yield of TpFPPhl was obtained using 1.0 mg of solid DDQ. At both higher and lower quantities of DDQ, the yield of TpFPPhl decreased and the presence of other pigments increased. At DDQ quantities of $\geq$16 mg, only trace levels of TpFPPhl were observed. The use of DDQ in toluene solution afforded TpFPPhl yields about half that obtained from the use of an equivalent amount of solid DDQ (after adjusting for dilution due to the toluene). The stoichiometric quantity of DDQ for the 1.2 mL aliquot is 1.36 mg (2 equiv per reduced phlorin precursor).[33] Thus, the best oxidation conditions identified from these experiments utilized a little less than the stoichiometric quantity of DDQ (1.5 equiv). Care was taken in the survey of acid catalysis conditions and subsequent experiments to dispense 1.00 ± 0.05 mg of DDQ for oxidation of reaction aliquots prior to HPLC and TLC analysis.

5. Reaction Time Course Experiments. Promising reaction conditions identified from the survey of acid catalysis conditions[34] were performed for the reaction of **1a** with **2a-OH** and **1b** with **2b-OH** with monitoring by HPLC and TLC at time points ranging from 1 min to 24 h. A summary of reaction conditions investigated and the highest yield of TpFPPhl observed is provided in Table 2. Representative plots of the yield of TpFPPhl as a function of condensation time are provided in Figure 2 (see the Supporting Information for the complete set of plots).

As with the survey of acid catalysis conditions, the reaction of **1b** with **2b-OH** with TFA catalysis (100 mM) provided the highest yield of TpFPPhl (56%). In this reaction, the maximum yield of TpFPPhl was obtained quite quickly ($\sim$2 min), and it remained fairly steady throughout the duration of the experiment (Figure 2A). The steady yield of TpFPPhl as a function of time is of practical significance, as it suggests that this reaction need not be monitored closely to obtain a maximum yield of TpFPPhl. Other key observations are as follows. (1) The reaction of **1a** with **2a-OH** again provided much lower yields of TpFPPhl than the corresponding reactions of **1b** with **2b-OH**. (2) Despite the difference in yield of TpFPPhl between the two reaction routes, the yield trajectories were quite similar. TFA and $InCl_3$ catalysis afforded fairly rapid obtainment of the maximum yield of TpFPPhl, with only a slight decline in yield at long reaction times. $Sc(OTf)_3$ catalysis provided a more gradual increase in the yield of TpFPPhl followed by a sharp turnover after the maximum yield was obtained (Figure 2B). It is interesting that the two reaction routes had similar reaction yield trajectories, but ultimately provided very different yields of TpFPPhl. It is also interesting that the milder acid $Sc(OTf)_3$ provided a more pronounced turnover in yield than TFA catalysis involving a

(32) Geier, G. R., III; Lindsey, J. S. *Tetrahedron* **2004**, *60*, 11435–11444.

(33) This is the same as 2 equiv of DDQ relative to the dipyrromethane or dipyrromethanedicarbinol starting materials.

(34) The condensation reaction conditions selected from the acid survey experiments were chosen based on both the yield of TpFPPhl and the condensation reaction time required to obtain the highest yield of TpFPPhl. As a result, in some cases, a higher concentration of acid catalyst was employed in the time course experiments than the minimal concentration identified in Table 1. For example, reactions of **1b** with **2b-OH** mediated by $Dy(OTf)_3$ afforded a similar yield of TpFPPhl regardless of the acid concentration; however, reactions employing a higher concentration of the acid proceeded more quickly (Figure 1B). Thus, Table 1 reports 0.32 mM as the lowest concentration of $Dy(OTf)_3$ providing a near-maximal yield of TpFPPhl, whereas a concentration of 10 mM was employed in the time course experiment so that the reaction would be faster.

TABLE 2. Summary of Results from Reaction Time Course Experiments[a]

entry	reactants	acid	[acid], mM	time, h[b]	% yield of TpFPPhl[c]
1	**1a** + **2a-OH**	TFA	100	0.25	20
2	**1a** + **2a-OH**	$InCl_3$	10	0.5	14
3	**1a** + **2a-OH**	$Sc(OTf)_3$	32	1	18
4	**1b** + **2b-OH**	TFA	100	0.033	56
5	**1b** + **2b-OH**	$InCl_3$	10	0.5	45
6	**1b** + **2b-OH**	$Sc(OTf)_3$	32	0.5	41
7	**1b** + **2b-OH**	$Yb(OTf)_3$	3.2	0.25	23
8	**1b** + **2b-OH**	$Dy(OTf)_3$	10	0.25	21

[a] The reactions were performed with the indicated reactants (2.5 mM each) on a 15−18 mL scale in CH_2Cl_2 at room temperature. The reactions were monitored from 1 min to 24 h. [b] The reaction time that first provided the highest yield of TpFPPhl. [c] The highest yield of TpFPPhl (HPLC) is reported.

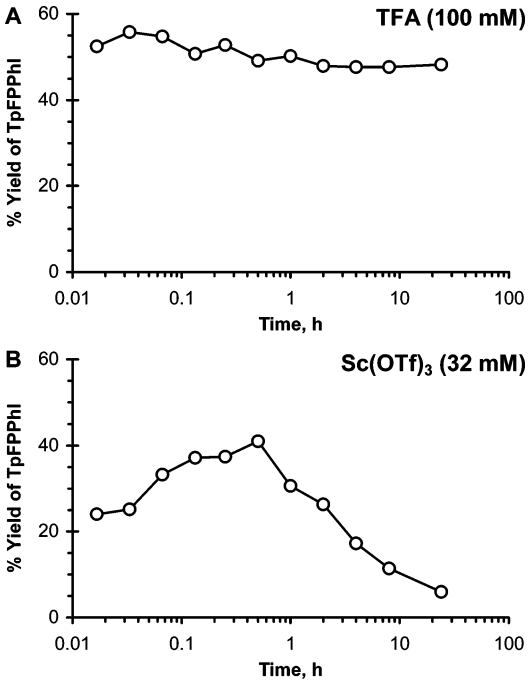


FIGURE 2. Yield of TpFPPhl as a function of condensation time for reaction of **1b** and **2b-OH** (2.5 mM each) in CH_2Cl_2 at room temperature under catalysis with (A) TFA (100 mM) or (B) $Sc(OTf)_3$ (32 mM). The reactions were monitored by HPLC. Note the log scale for time.

fairly high concentration of TFA (100 mM).[35] (3) The yield trajectories for the reaction of **1b** with **2b-OH** with $Yb(OTf)_3$ and $Dy(OTf)_3$ show a gradual increase in the yield of TpFPPhl with no turnover at long reaction times (Supporting Information). These trajectories are similar to those observed in dipyrromethanecarbinol routes to porphyrins[21c] and corroles.[18] (4) The yields of TpFPPhl observed in these experiments were generally similar to those obtained at equivalent time points in the survey of acid catalysis conditions. Thus, the reactions and HPLC monitoring were reproducible. (5) Reaction reversibility as indicated by the presence of porphyrin byproduct was only observed in a subset of the reactions. $InCl_3$ and $Sc(OTf)_3$ catalysis conditions (Table 2, entries 3, 5, and 6) provided trace levels of porphyrin. This observation is consistent with the results of the survey of acid catalysis conditions. The best condition in terms of yield of TpFPPhl (Table 2, entry 4) afforded TpFPPhl devoid of porphyrin.

Preparative-Scale Synthesis of TpFPPhl. To confirm findings of the analytical-scale experiments and to obtain a sufficient quantity of TpFPPhl for characterization and stability studies, preparative-scale reactions were performed. The best reaction route and condition identified from the analytical-scale reactions was utilized for the preparative-scale reactions [reaction of **1b** with **2b-OH** (2.5 mM each), TFA catalysis (100 mM), in CH_2Cl_2 at room temperature followed by oxidation with DDQ (1.5 equiv)[33]]. A discussion of an investigation of oxidation conditions for preparative-scale reactions may be found in the Supporting Information. Reaction of **1b** with **2b-OH** on a 0.500 mmol scale was carried out for 15 min prior to the addition of DDQ. Consistent with analytical-scale reactions, an HPLC yield of TpFPPhl of 55% was obtained from an aliquot of the condensation reaction mixture removed immediately prior to DDQ oxidation of the bulk reaction mixture. After DDQ addition, triethylamine (5 equiv relative to acid) was added and the mixture was allowed to stir for 30 min at room temperature. Analysis of an aliquot of the oxidized reaction mixture by HPLC provided a yield of TpFPPhl of 48%, indicating fairly effective oxidation of the bulk reaction mixture. TpFPPhl was isolated from polar and insoluble byproducts by passage through a silica pad, washing with CH_2Cl_2. TpFPPhl was further purified by a short silica gel column [CH_2Cl_2/hexanes (1:3) to CH_2Cl_2] followed by a short neutral alumina column [CH_2Cl_2/hexanes (1:4)] to afford 189 mg, 45% yield. The isolated yield of TpFPPhl was similar to the yield determined by HPLC after oxidation of the reaction mixture. The isolated yield of 45% compares favorably to syntheses of other porphyrinoids via dipyrromethanecarbinol routes as well as to the recent report of phlorin−dipyrrin conjugates.[10] To obtain TpFPPhl in a form more easily dispensed, attempts were made to crystallize the phlorin. This proved to be challenging as TpFPPhl displayed good solubility in solvents of a wide range of polarities. The best conditions identified utilized CH_2Cl_2 and pentane, affording TpFPPhl as dark green, needle-like crystals (110 mg).

Characterization of TpFPPhl. UV−vis spectra characteristic of phlorins were obtained from the isolated sample of TpFPPhl, and satisfactory LD-MS and high-resolution FAB-MS data were obtained. The ^{1}H NMR spectrum recorded in $CDCl_3$ was in accordance with expectations with four doublets in the region of 6.78−7.36 ppm corresponding to the four pairs of nonequivalent β-pyrrole protons, a sharp singlet at 1.47 ppm corresponding to the six equivalent methyl protons, and a very broad singlet centered at ∼2.7 ppm corresponding to the N−H protons (Supporting Information). The downfield location of the N−H signals relative to aromatic porphyrinoids is consistent with the absence of overall macrocycle aromaticity as would be expected for a phlorin. The ^{1}H NMR spectrum recorded in DMSO-d_6 again revealed signals for the pairs of nonequivalent β-pyrrole protons (6.73−7.61 ppm) and the six equivalent methyl protons (1.63 ppm) (Supporting Information). Interestingly, the signals for the N−H protons appeared as a pair of much sharper signals at 6.10 (1H) and 6.89 (2H) ppm, and the N−H protons at 6.89 ppm showed coupling in the ^{1}H NMR and COSY spectra to two of the pairs of nonequivalent β-pyrrole protons (Supporting

(35) The cause of the turnover in yield of TpFPPhl under catalysis by $Sc(OTf)_3$ is not clear. In two-step, one-flask reactions of pyrrole and benzaldehyde leading to tetraphenylporphyrin, it has been shown that a turnover in yield of porphyrin is accompanied by the formation of truncated oligomers.[30a] Whether similar shunt processes are involved in the $Sc(OTf)_3$-mediated condensation reaction leading to TpFPPhl is not presently clear.

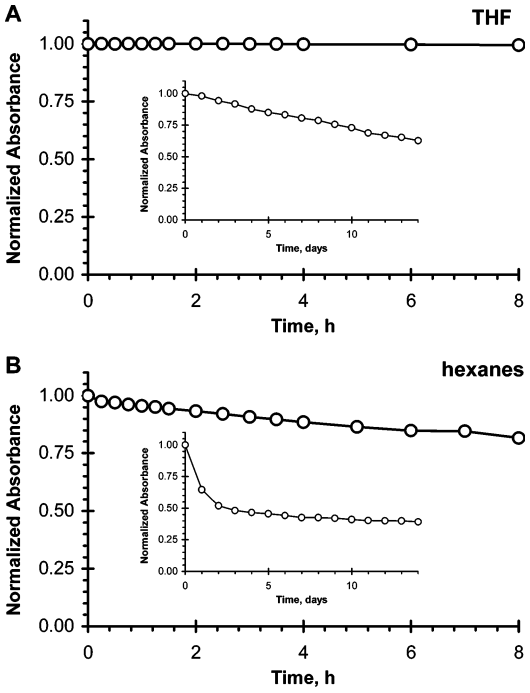


FIGURE 3. Plots of absorbance as a function of time of exposure to light for solutions of TpFPPhl in (A) THF (655 nm) and (B) hexanes (643 nm). Note the difference in time scale for the inset plots.

Information). The assignment of the N−H protons was supported by the absence of correlations to carbon atoms in the HMQC spectrum (Supporting Information). The presence of two distinct N−H signals and coupling with β-pyrrole protons suggests preference among the possible N−H tautomers of TpFPPhl when in DMSO solution.

Stability of TpFPPhl. The stability toward light and air of TpFPPhl in dilute solution was investigated. Similar to our previous studies of the stability of meso-substituted corroles,[18] octaphyrins,[26] and phlorins bearing mesityl substituents,[20] solutions of TpFPPhl in solvents of varying polarity (hexanes, toluene, CH_2Cl_2, THF, ethyl acetate, acetone, acetonitrile, and methanol) were prepared, and changes in UV−vis spectra were followed as a function of time of exposure to ambient room light (i.e., light from conventional overhead fluorescent lighting). The solutions were monitored closely for 8 h of exposure, followed by monitoring once a day for a period of 2 weeks. Plots of TpFPPhl absorbance (~650 nm) as a function of time for 8 h and 14 days are shown in Figure 3 for the most stable solution (THF) and the least stable solution (hexanes) (see Supporting Information for the complete set of plots). Plots of overlaid UV−vis spectra for the same solutions at 8 h and 14 days are shown in Figure 4 (see Supporting Information for the complete set of overlaid spectra).

As shown by the illustrative data, the dilute solutions of TpFPPhl are quite stable over 8 h of exposure to light and air. The most stable solution in THF provided better than 99% of its initial absorbance at 655 nm after 8 h, and even the least stable solution in hexanes provided 82% of its initial absorbance at 643 nm (Figure 3). When exposed to light continuously for longer periods of time, all solutions of TpFPPhl showed gradual decomposition. Decomposition was generally more rapid in solvents of lower polarity, though the correlation is not perfect. The changes observed in the UV−vis spectra of each solution of TpFPPhl during decomposition were similar but not identical.

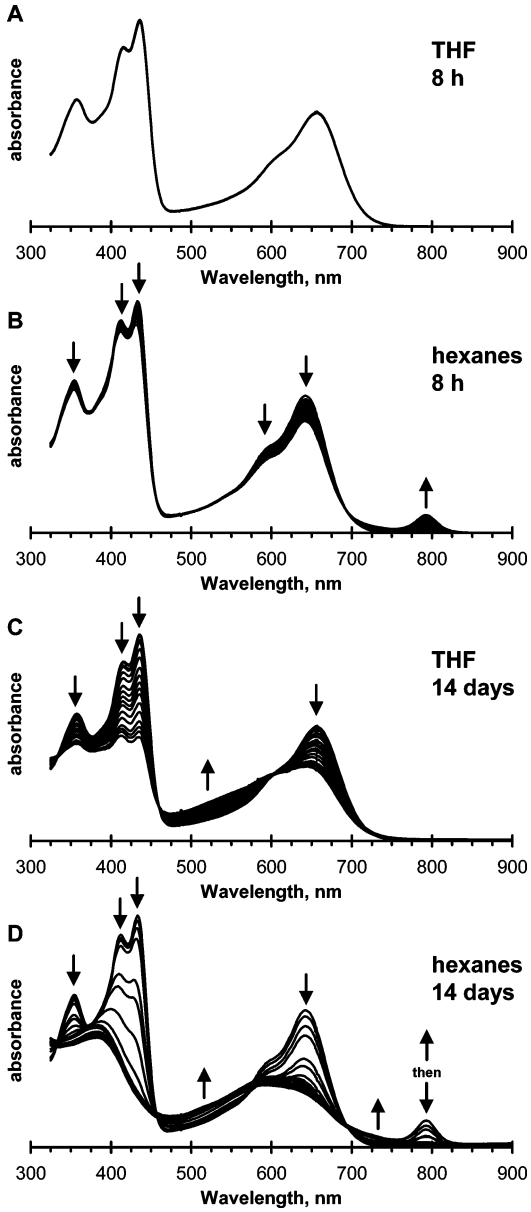


FIGURE 4. UV−vis spectra of solutions of TpFPPhl recorded after exposure to light and air in (A) THF, 0−8 h; (B) hexanes, 0−8 h; (C) THF, 0−14 days; and (D) hexanes, 0−14 days. The arrows indicate the direction of the change.

Generally, the overlaid spectra provided fairly clean isobestic points (e.g., Figure 4D) as was observed in our previous studies of phlorins bearing mesityl substituents. Light is required for the observed changes in the UV−vis spectra, as dilute solutions stored in the dark showed little change in their UV−vis spectra. In the course of these experiments, the absorbance at the wavelength selected for monitoring (~650 nm) did not fall to zero as degradation products also absorb in this region. Thus, in some cases, it was difficult to determine exactly when decomposition of TpFPPhl was complete. To confirm the results of UV−vis monitoring, fresh solutions were prepared in hexanes, CH_2Cl_2, or THF, exposed to light, and the disappearance of TpFPPhl was monitored by HPLC for a period of 2 weeks (see the Supporting Information for plots of peak area of TpFPPhl as a function of time of exposure to light). Consistent with the UV−vis monitoring, no change was observed in the THF or CH_2Cl_2 solutions in the first 8 h of

exposure to light and only a decrease in peak area of 6% was observed for the hexanes solution. At the end of 2 weeks, the THF solution contained ~80% of the original level of TpFPPhl, the CH_2Cl_2 solution contained ~25%, and the hexanes solution had no detectable TpFPPhl. The half-lives of the TpFPPhl in CH_2Cl_2 and hexanes in these experiments were ~5 and 2.5 days, respectively.

The stability of TpFPPhl compares exceptionally well to the phlorins prepared in our previous study probing the effects of meso-mesityl substituents.[20] The most stable phlorin in that study underwent noticeable decomposition in all solvents in less than 90 min, and in nonpolar solvents, its half-life was about 10 min. It is more difficult to compare the stability of TpFPPhl to other phlorins reported in the literature. In most instances, phlorins are simply described as being stable or unstable without elaboration. An investigation of the stability of phlorin−dipyrrin conjugates bearing sterically bulky and electron-withdrawing substituents was reported by Gryko and Koszarna.[10] However, decomposition was monitored qualitatively by TLC and ESI-MS analysis of solutions exposed to light for only up to 10 h. The solvents employed in their experiments were not specified. Thus, it is difficult to draw comparisons to TpFPPhl. Overall, the stability of TpFPPhl is quite good. Under conditions of normal handling, TpFPPhl is quite stable and no precautions to avoid exposure to light are required.

Conclusions

Two complementary dipyrromethane + dipyrromethanedicarbinol routes to a meso-substituted phlorin bearing electron-withdrawing pentafluorophenyl substituents were investigated. Although the reaction routes were similar in regards to the best conditions for acid catalysis and the reaction time course trajectories, they were quite different in terms of the maximum yield of TpFPPhl. The substantially different yields of TpFPPhl provided by the two routes demonstrate that the placement of substituents in the precursors can have a profound effect on the outcome of the reaction. Using the superior route of the reaction of **1b** with **2b-OH** under TFA catalysis (100 mM), TpFPPhl could be obtained relatively efficiently on a good scale. Dilute solutions of TpFPPhl were found to be quite resistant toward degradation upon exposure to light and air, with solutions in polar solvents being generally more stable than solutions in nonpolar solvents. The preparation of a phlorin of practical stability provides encouragement for further studies of the stabilization of phlorin via peripheral meso-substituents, and the efficient synthesis of TpFPPhl will facilitate the detailed study of additional properties and coordination chemistry of meso-substituted phlorins.

Experimental Section

5,5-Dimethyl-1,9-bis(pentafluorobenzoyl)dipyrromethane (2b). Following a general diacylation procedure from the literature,[21b] ethyl magnesiumbromide (25.0 mL, 250 mmol, 1 M in THF) was added dropwise over 15 min to a solution of 5,5-dimethyldipyrromethane **1a** (0.871 g, 5.00 mmol) in dry toluene (100 mL) under argon. The reaction mixture was stirred for 30 min at room temperature, and a solution of pentafluorobenzoylchloride (1.80 mL, 12.5 mmol) in dry toluene (12.5 mL) was added dropwise over 10 min. The reaction mixture was stirred for 30 min at room temperature. The reaction was quenched by addition of saturated aqueous NH_4Cl (75 mL). The organic layer was separated and washed with water (50 mL) and then brine (50 mL) followed by drying over Na_2SO_4. The crude product mixture was concentrated, yielding a reddish solid. Multiple precipitations (3−6 times) of the crude mixture from CH_2Cl_2/hexanes afforded purified **2b** as a white crystalline solid (13−29%, 370−830 mg). The range in isolated yield is largely related to the number of precipitations required for purification of **2b**: mp 225 °C decomp; ^{1}H NMR (DMSO-d_6) δ 12.24 (s, 2H), 6.81 (d, J = 4.0 Hz, 2H), 6.09 (d, J = 4.0 Hz, 2H), 1.76 (s, 6H); ^{13}C NMR (DMSO-d_6) δ 27.3, 36.4, 109.4, 114.3 (t, J = 22 Hz), 123.0, 131.3, 137.4 (d, J = 253 Hz), 141.6 (d, J = 245 Hz), 143.3 (d, J = 244 Hz), 150.1, 170.9; CI-MS obsd 563 (MH^+), calcd 563 (MH^+); ν_{max} (thin film)/cm^{-1} 1621. Anal. Calcd for $C_{25}F_{10}O_2H_{12}N_2$: C, 53.40; H, 2.15; N, 4.98. Found: C, 53.53; H, 2.09; N, 5.06.

HPLC Determination of the Yield of TpFPPhl. Analytical-scale reactions of **1a** with **2a-OH** and **1b** with **2b-OH** were monitored for the yield of TpFPPhl by adaptation of a literature method for the analysis of porphyrin, N-confused porphyrin, and sapphyrin in crude reaction mixtures.[29] An aliquot (1.2 mL) of a condensation reaction mixture was transferred by adjustable pipet to a 1.8 mL microcentrifuge tube containing DDQ (1.00 mg, 0.00441 mmol), and the mixture was vortex mixed for 2−5 s. Triethylamine (5 equiv relative to acid) was added. A portion of the oxidized reaction mixture (1.0 mL) was transferred via adjustable pipet to a Pasteur pipet filled two-thirds full with silica gel (~1.5 g). The sample was eluted with three 1 mL portions of CH_2Cl_2, and solvent was driven off the column with a handheld pipet tool. The eluant was transferred to an autosampler vial and capped. HPLC analysis was performed with an injection volume of 1 μL, a normal phase silica column (Alltech, Altima, 4.6 mm × 250 mm), using an isocratic solvent mixture of 92% hexanes and 8% acetone. The hexanes solvent was water saturated by storing over water prior to use. The solvent flow rate was controlled as follows: T = 0−8 min, 1 mL/min; T = 8−9 min, linear increase to 2 mL/min; T = 9−14 min, 2 mL/min; T = 14−15 min, linear decrease to 1 mL/min TpFPPhl eluted at 8.4 min. Detection was performed at 417 and 435 nm. The limit of detection at either wavelength was ~1% yield of TpFPPhl. The yield of TpFPPhl was determined from the peak area by calibration of the detector response to TpFPPhl. Representative chromatograms and further details on the analysis method development, control and reproducibility experiments, and HPLC calibration may be found in the Supporting Information.

Survey of Acid Catalysis Conditions. Immediately prior to the condensation reactions, the diacyl dipyrromethane [**2a** (175 mg, 0.250 mmol) or **2b** (141 mg, 0.250 mmol)] was reduced to the corresponding dipyrromethanedicarbinol (**2a-OH** or **2b-OH**) with $NaBH_4$ (0.475 g, 12.5 mmol) in THF/methanol (20 mL, 3:1) following a literature procedure.[21b] The reduction reactions were monitored by TLC [**2a**, alumina, EtOAc/hexanes (1:1); **2b** alumina, EtOAc/CH_2Cl_2 (1:1)]. After being dried under vacuum for 30 min, the dicarbinol was dissolved in CH_2Cl_2 and transferred to a 100 mL volumetric flask. Dipyrromethane **1a** (43.6 mg, 0.250 mmol) or **1b** (78.1 mg, 0.250 mmol) was added to the flask, and volume was brought to the mark by adding CH_2Cl_2. Reactions were performed at room temperature in tightly capped 20 mL vials that were stirred with a micro stir bar. Solid acids were weighed into all reaction vials prior to the beginning of the reaction sequence for the day, and each reaction was initiated by the addition of 5−10 mL of the reactant solution via volumetric pipet. Reactions involving TFA were initiated by the addition of TFA to reaction vials already containing 5 mL of the reactant solution. The reactions were monitored by HPLC at 0.25, 1, and 4 h as described above. TLC was performed on the crude, oxidized mixture [silica, CH_2Cl_2/hexanes (1:1)].

Reaction Time Course Experiments. Reaction monitoring as a function of time was performed as described above for the survey of acid catalysis conditions with the exception of using a 15−18 mL reaction volume. The reactions were monitored by HPLC as described above for yield of TpFPPhl at 1, 2, 4, 8, 15, and

30 min, and 1, 2, 4, 8, and 24 h. TLC was performed on the crude, oxidized mixture [silica, CH_2Cl_2/hexanes (1:1)].

5,5-Dimethyl-10,15,20-tris(pentafluorophenyl)phlorin, TpFPPhl (3). The reduction of **2b** (281 mg, 0.500 mmol) with $NaBH_4$ (946 mg, 25.0 mmol) in THF/methanol (40 mL, 3:1) afforded the corresponding dicarbinol **2b-OH** which was used without purification. The dicarbinol was dried under vacuum for 30 min and then immediately subjected to condensation with **1b** (156 mg, 0.500 mmol) in the presence of TFA (1.54 mL, 20.0 mmol) in CH_2Cl_2 (200 mL) for 15 min at room temperature. Immediately before oxidation, an aliquot (1.2 mL) of the condensation reaction was removed for HPLC analysis. Oxidation of the remainder of the reaction was carried out by the addition of DDQ (167 mg, 0.730 mmol) at room temperature. After 5 min, triethylamine (14 mL, 100 mmol) was added and the mixture was stirred at room temperature for a further 30 min. An aliquot (1.2 mL) of the oxidized reaction mixture was removed for HPLC analysis. The remaining reaction mixture was filtered through a pad of silica gel and eluted with CH_2Cl_2 until the eluant was no longer green. The filtrate was concentrated and adsorbed onto silica gel (10 g), concentrated to dryness, and purified by chromatography [silica, CH_2Cl_2/hexanes (1:3, 1:2, 1:1, 3:2, 2:1, and 3:1)]. To remove a low level of residual impurities, the sample was adsorbed onto alumina (15 g) and purified by chromatography [alumina, CH_2Cl_2/hexanes (4:1)] affording TpFPPhl, **3** (189 mg, 45%) that was subsequently crystallized from CH_2Cl_2/pentane providing dark green crystals (110 mg): λ_{abs} (toluene, $\epsilon \times 10^3$) 358 (33.3), 417 (46.2), 438 (52.7), 654 (30.4); ^{1}H NMR ($CDCl_3$) δ 1.47 (s, 6H), 2.70 (br s, 3H), 6.78 (d, $J = 3.9$ Hz, 2H), 6.95 (d, $J = 3.9$ Hz, 2H), 7.12 (d, $J = 5.0$ Hz, 2H), 7.36 (d, $J = 5.0$ Hz, 2H); (DMSO-d_6) δ 1.63 (s, 6H), 6.10 (s, 1H), 6.73 (dd, $J = 2.3$, 3.6 Hz, 2H), 6.89 (s, 2H), 7.09 (dd, $J = 2.0$, 3.4 Hz, 2H), 7.35 (d, $J = 5.0$ Hz, 2H), 7.61 (d, $J = 5.0$ Hz, 2H); LD-MS obsd 838.1 (M^+); HRMS (FAB) 838.1236 (M^+), calcd 838.1214 (M^+) ($C_{40}H_{17}F_{15}N_4$).

TpFPPhl Stability Experiments (UV−Vis).[20] In a darkened lab, solutions of TpFPPhl were prepared in hexanes, toluene, CH_2Cl_2, THF, ethyl acetate, acetone, acetonitrile, and methanol. The concentration of each solution was adjusted so that the maximum absorbance in the visible range (642−655 nm) was between 0.5 and 0.9. UV−vis spectra were recorded in the dark, and then the solutions were exposed to room lights (conventional overhead fluorescent lighting). Spectra were recorded at 15, 30, and 45 min, 1, 1.25, 1.5, 2, 2.5, 3, 3.5, 4, 6, and 8 h, and 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, and 14 days of continuous exposure to room lights. Decomposition of TpFPPhl was inferred from changes in the intensity of the visible band (642−655 nm). Data were normalized with respect to the maximum absorbance in the visible range prior to exposure to light. As a control, an analogous experiment was performed with solutions of TpFPPhl (CH_2Cl_2 and hexanes) maintained in the dark.

TpFPPhl Stability Experiments (HPLC). In a darkened lab, solutions of TpFPPhl were prepared in hexanes, CH_2Cl_2, and THF. The concentration of each solution was adjusted so that the initial peak area was between 150 and 300 area units. The samples were analyzed in the dark by HPLC using the same analysis parameters as described above for analysis of oxidized reaction mixtures, and then the solutions were exposed to light (conventional overhead fluorescent lighting). Chromatograms were recorded at 15 min, 1, 2, 4, 6, and 8 h, and 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 9, 12, 13, and 14 days of continuous exposure to room lights. Decomposition of TpFPPhl was inferred by a decline in the peak area.

Acknowledgment. Support for this work was provided by the National Science Foundation under Grant Nos. 0517882 and 0310521. Acknowledgment is made to the donors of The Petroleum Research Fund, administered by the American Chemical Society, for partial support of this research. We thank Tim LeSaulnier for performing preliminary experiments. High-resolution FAB mass spectra were obtained at the Mass Spectrometry Laboratory for Biotechnology at North Carolina State University. Partial funding for the facility was obtained from the North Carolina Biotechnology Center and the National Science Foundation.

Supporting Information Available: General experimental methods; discussion of the HPLC method development, control experiments, reproducibility, and calibration; representative chromatograms of reaction mixtures; plots of yield of TpFPPhl as a function of acid concentration; plots of yield of TpFPPhl as a function of condensation reaction time; investigation of oxidation conditions for preparative-scale syntheses of TpFPPhl; plots of absorbance of TpFPPhl as a function of exposure to light; overlaid UV−vis spectra recorded from solutions of TpFPPhl exposed to light, plots of HPLC peak area of TpFPPhl as a function of time of exposure to light; ^{1}H NMR spectrum of **2b**; and ^{1}H NMR, COSY, and HMQC spectra of TpFPPhl **3**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO070216K