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Two-Step, One-Flask Synthesis of a Meso-Substituted Phlorin

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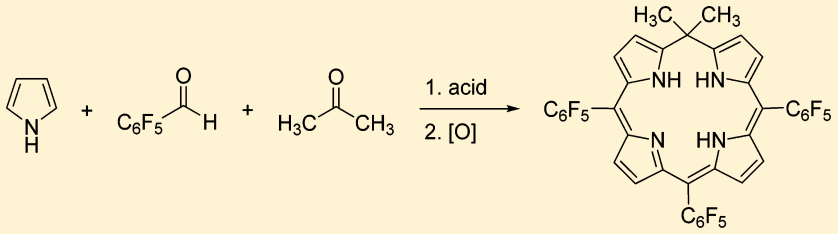
Supporting Information



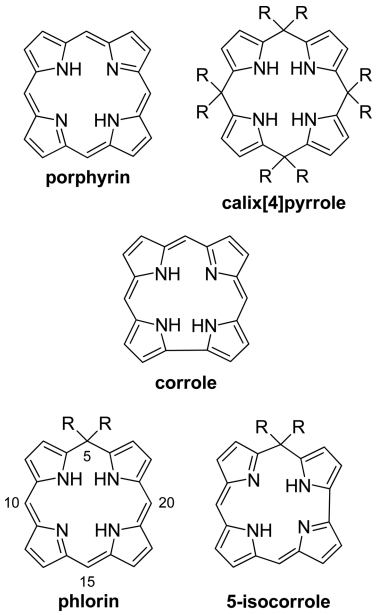
ABSTRACT: A two-step, one-flask reaction of pyrrole with pentafluorobenzaldehyde and acetone was investigated to determine the potential for a streamlined synthesis of a phlorin and/or 5-isocorrole as an alternative to stepwise, dipyrromethanecarbinol routes. Analytical-scale reactions were performed examining the effect of reactant concentration, reactant ratio, acid catalyst (TFA or $BF_3{\cdot}OEt_2$), concentration of acid catalyst, oxidant quantity, and reaction time on the distribution of phlorin and 5-isocorrole as well as three additional porphyrinoids (porphodimethene, porphyrin, and corrole). Phlorin was observed ubiquitously in yields up to 20−26%, whereas 5-isocorrole was not detected. Promising reaction conditions for the one-flask synthesis of the phlorin were performed on a preparative scale. The best reaction condition afforded the phlorin in an isolated yield of 20−21% (249−268 mg). Preliminary attempts to extend the methodology to the preparation of phlorins derived from other ketones resulted in a low yield of phlorin from acetophenone (5%) and no detectable phlorin from benzophenone. The discovery of reaction conditions for the two-step, one-flask synthesis of a phlorin provides easier access to this interesting compound, and provides encouragement for the further study of reactions of pyrrole with an aldehyde and a ketone.

INTRODUCTION

The calix[4]phyrin family of porphyrinoids, of which phlorin is a member, have structures intermediate to porphyrin and calix[4]pyrrole (porphyrinogen).[1,2] Calix[4]phyrins contain a combination of sp^2- and sp^3-hybridized carbon atoms at the four meso-positions, whereas porphyrins have entirely sp^2-hybridized meso-carbon atoms and calix[4]pyrroles have only sp^3-hybridized meso-carbon atoms. Many calixphyrins have been prepared and studied, including species with expanded, contracted, N-confused, and/or heteroatom modified core structures.[1,2]

Two members of the broader calixphyrin family have been of particular interest to us—phlorin[3−5] and 5-isocorrole.[6] We were initially interested in phlorin and 5-isocorrole due to their intriguing structural relationship to the better known porphyrin and corrole macrocycles. Phlorin possesses four bridging meso-carbons (like porphyrin), but it has three internal N−H groups (like corrole). In a complementary fashion, 5-isocorrole has three bridging meso-carbon atoms and a direct bipyrrole linkage (like corrole), but it has two internal N−H groups (like porphyrin). Phlorin and 5-isocorrole also have the structural distinction of a single sp^3-hybridized meso-carbon atom, interrupting the macrocycle conjugation found in porphyrin and corrole.

In the course of our prior studies of phlorin and 5-isocorrole, we developed stepwise syntheses for both compounds[4,6] by adapting dipyrromethanecarbinol routes initially developed for the rational synthesis of porphyrins bearing different meso-



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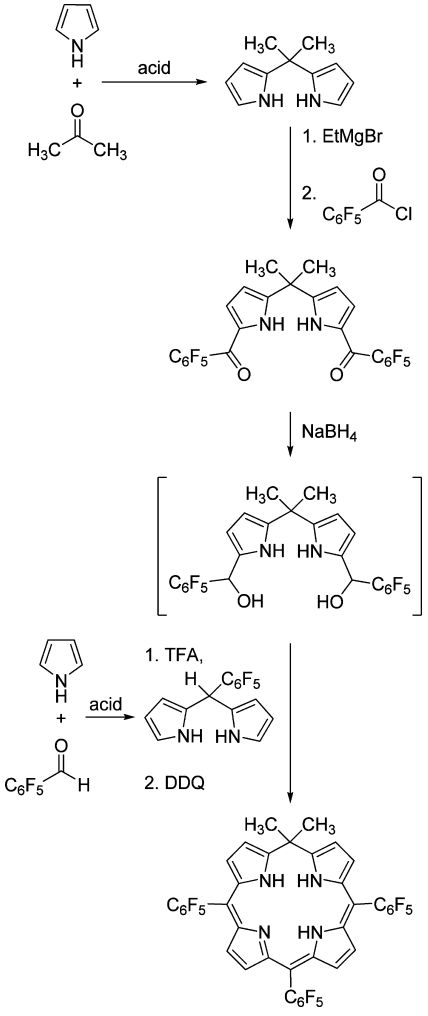
substituents in defined positions.[7−9] Our published syntheses of a phlorin and a 5-isocorrole are adequate for the preparation of 100−200 mg quantities—sufficient for spectroscopic characterization, X-ray structure determination, and studies of stability toward light and air (many phlorins have poor stability toward light and air[3−5,10]). Additionally, in collaboration with Ziegler and co-workers, a small number of metal complexes of a 5-isocorrole have been prepared and characterized.[11] We have also applied our stepwise synthesis of phlorin to the preparation of phlorins bearing different substituents at the sp^3-hybridized meso-position.[5] The stepwise methodology has been recently utilized by Rosenthal and co-workers in their independent studies of phlorin spectroscopy, structure, electrochemistry, and anion binding.[12−15]

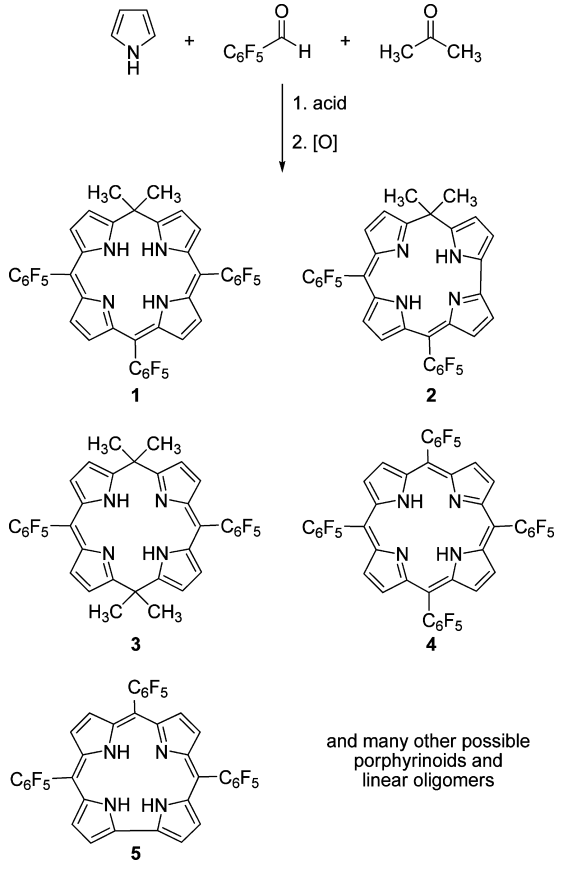
Despite the utility of stepwise syntheses of phlorin and 5-isocorrole, these routes have important limitations as illustrated by the stepwise synthesis of a phlorin (Scheme 1).[4] While the synthesis is reasonably concise, the preparation of dipyrromethane and acyldipyrromethane building block molecules is required, which adds time to the synthesis, places limits on the scale of the synthesis, and increases the degree of required synthetic expertise. A one-flask approach could address these limitations, and potentially increase the relevance of phlorin and 5-isocorrole. It is not surprising that many of the most widely studied porphyrinoids can be obtained by straightforward, one-flask syntheses. Examples include meso-substituted porphyrin,[16−18] N-confused porphyrin,[19−21] and corrole.[22,23]

Scheme 1. Stepwise Synthesis of a Meso-Substituted Phlorin



Unfortunately, calixphyrins such as phlorin and 5-isocorrole are not obvious candidates for a one-flask approach. The presence of both sp^2- and sp^3-hybridized meso-positions lowers the symmetry of calixphyrins relative to the porphyrins commonly prepared from the one-flask reaction of pyrrole with an aldehyde. The synthesis of calixphyrins is more analogous to the preparation of porphyrins bearing two different meso-substituents. While such porphyrins have been prepared by the one-flask reaction of pyrrole with two different aldehydes, the reaction inevitably produces a mixture of up to six porphyrins bearing different combinations of meso-substituents.[24] The product mixture lowers yield and complicates purification. A one-flask synthesis of phlorin and/or 5-isocorrole via the reaction of pyrrole with an aldehyde and a ketone would be expected to produce a complicated mixture of porphyrinoids and linear oligomers (Scheme 2). Note that only a subset of the possible products are shown in the scheme.

Scheme 2. Reaction of Pyrrole, Pentafluorobenzaldehyde, and Acetone Leading to a Number of Possible Porphyrinoids and Linear Oligomers



Given the complicated reaction mixture expected from the reaction of pyrrole with an aldehyde and a ketone, it is not surprising that there are few reported examples. Furuta, Osuka, Ishikawa, and co-workers isolated an N-confused calix[4]phyrin species in a yield of 3% from the reaction of pyrrole with *p*-tolualdehyde and acetone.[25] Hu and co-workers have investigated the reaction of pyrrole with arylaldehydes and acenapthenequinone (a 1,2-diketone) with the stated goal of obtaining a phlorin.[26] Instead, depending on the reaction

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Table 1. Comparison of Porphyrinoid Yields from Preliminary Analytical-Scale Experiments[a,b]

entry	[pyrrole], mM	[aldehyde], mM	[acetone], mM	acid	[acid], mM	% yield of porphyrin[c]	% yield of corrole[c]	% yield of phlorin[c]
1a	10	10	–	TFA	215	20	2	–[d]
2a	10	7.5	–	TFA	215	22	7	–[d]
3a	10	7.5	2.5	TFA	215	19	6	5
4a	10	5.0	2.5	TFA	215	12	9	5
5a	10	5.0	5.0	TFA	215	11	7	12
1b	10	10	–	$BF_3{\cdot}OET_2$	10	32	0	–[d]
2b	10	7.5	–	$BF_3{\cdot}OET_2$	10	50	1	–[d]
3b	10	7.5	2.5	$BF_3{\cdot}OET_2$	10	43	1	3
4b	10	5.0	2.5	$BF_3{\cdot}OET_2$	10	25	4	3
5b	10	5.0	5.0	$BF_3{\cdot}OET_2$	10	21	3	4

[a]The reactions were performed in CH_2Cl_2 with the indicated reactants on a 10 mL scale at room temperature. The reactions were monitored at 15 min, 1 h, and 4 h upon oxidation of an aliquot (1.2 mL) with DDQ (2.0 mg). [b]5-Isocorrole **2** and porphodimethene **3** were not detected. [c]The highest yield (HPLC) of any of the three time points is reported. [d]Phlorin **1** could not be obtained from this reaction as acetone was not present.

condition, they isolated 5-(8-ethoxycabonyl-1-naphthyl)-10,15,20-triarylporphyrins in yields of 1−11%,[26,27] a β,β'-linked porphyrin-chlorin heterodimer and a π-extended porphyrin in yields of 3−4% and 7−8% respectively,[28] or 5,10- and 5,15-porphodimethenes in yields of 4−7%.[29] Overall, these reports show that it is possible to obtain lower symmetry porphyrinoids from mixed reactions of pyrrole with an aldehyde and a ketone, albeit in generally modest yield.

Herein, we report an investigation of a two-step (acid catalyzed condensation followed by oxidation), one-flask reaction of pyrrole with pentafluorobenzaldehyde and acetone (Scheme 2). The objectives of the present work were to explore the interplay of reaction conditions on the yields of a variety of potential porphyrinoid products, and to determine whether a one-flask reaction could afford phlorin **1**, 5-isocorrole **2**, and/or other calixphyrins (e.g., porphodimethene **3**) in a meaningful yield with straightforward purification. Pentafluorobenzaldehyde was employed as the aldehyde as the electron-withdrawing pentafluorophenyl substituent is known to stabilize phlorin[4] and corrole[30] toward degradation upon exposure to light and air. Acetone was employed as the ketone for consistency with the geminal dimethyl groups present in our prior stepwise syntheses of phlorin[4] and 5-isocorrole.[6]

Key to this work was the development of an HPLC method that allowed monitoring crude, reaction mixtures for the yield of phlorin **1**, 5-isocorrole **2**, porphodimethene **3**, porphyrin **4**, and corrole **5**. Other potential porphyrinoid products (e.g., 10-isocorrole) were not included due to the absence of authentic compounds required for HPLC method development and calibration of detector response. A small number of initial analytical-scale reactions were carried out to determine the scope of reaction conditions to explore. Further analytical-scale reactions were then performed to systematically investigate the effect of reactant concentration, reactant ratio, aldehyde concentration, acid catalyst, acid catalyst concentration, oxidant quantity, and reaction time. Promising reaction conditions were repeated on a preparative scale. Refined reaction conditions were applied to reactions with two other ketones (acetophenone and benzophenone).

RESULTS AND DISCUSSION

Reaction Monitoring. The reaction of pyrrole with pentafluorobenzaldehyde and acetone could produce a number of possible products (Scheme 2). We sought to monitor analytical-scale reactions for as many of these products as possible. From prior studies,[4,6,30] we had authentic phlorin **1**, 5-isocorrole **2**, porphodimethene **3**, porphyrin **4**, and corrole **5** from which an HPLC method could be developed. The five compounds are also a representative sampling of possible products of the reaction. The HPLC method was adapted from prior studies in which we monitored crude reaction mixtures for yields of phlorin **1**,[4] 5-isocorrole **2** and porphodimethene **3**,[6] or 5-isocorrole **2** and porphyrin **4**[6] (see the Supporting Information for an expanded discussion of HPLC method development). Reactions were also monitored by TLC to detect other colored compounds in addition to the five porphyrinoids assessed by HPLC.

Preliminary Analytical-Scale Experiments. Ten reaction conditions were selected as the starting point for the study (Table 1). The reaction conditions were modeled after refined two-step, one-flask conditions for the preparation of porphyrin **4**,[31] with varying ratios of pyrrole, pentafluorobenzaldehyde, and acetone consistent with the stoichiometric requirements for porphyrinoids **1**−**5**. Entries 1a,b and 2a,b afforded good levels of porphyrin **4**, a low yield of corrole **5**, and no detectable phlorin **1**, 5-isocorrole **2**, or porphodimethene **3**, consistent with the absence of acetone in these reactions. The yield of corrole **5** was higher for entries 2a,b given the more favorable ratio of pyrrole to aldehyde for corrole synthesis. Reactions carried out in the presence of acetone (entries 3−5) afforded lower yields of porphyrin **4**, similar yields of corrole **5**, and low to modest yields of phlorin **1**. 5-Isocorrole **2** and porphodimethene **3** were not detected. The consistent presence of phlorin **1** in all reactions containing acetone was encouraging, especially the observation of a yield of phlorin **1** of 12% (entry 5a).

Survey of Acetone Concentration. Encouraged by the results of the preliminary experiments, a systematic survey of reaction conditions was performed targeting a one-flask synthesis of phlorin **1**. As calixphyrins, such as phlorin **1**, possess defined ratios of sp^2- and sp^3-hybridized meso-positions, the concentration of acetone relative to pyrrole and pentafluorobenzaldehyde was expected to be an important parameter. Thus, a survey of acetone concentration was carried out for reactions utilizing pyrrole (10 mM) and pentafluorobenzaldehyde (2.5, 5.0, or 7.5 mM) with catalysis by TFA (215 mM) or $BF_3{\cdot}OEt_2$ (10 mM).

A representative plot of the yield of phlorin **1** as a function of acetone concentration for reactions with pyrrole, pentafluorobenzaldehyde (5.0 mM), and TFA is provided in Figure 1, panel A1. Panel A2 provides a summary of the highest yield of phlorin **1**, porphyrin **4**, and corrole **5** observed at any of the

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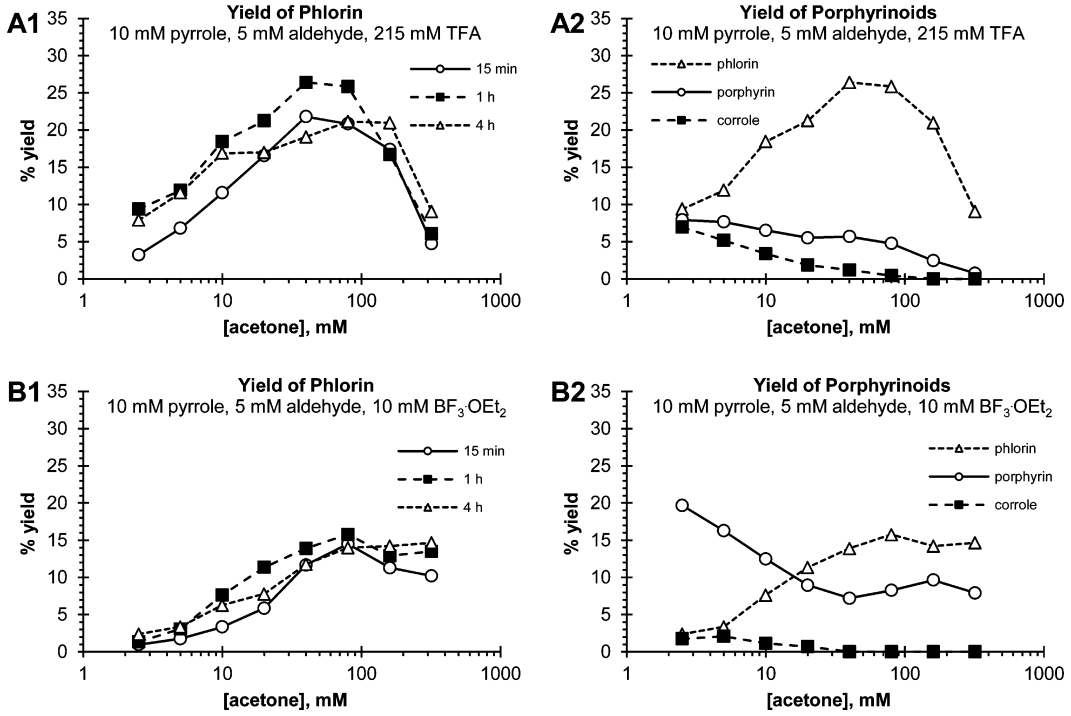

Figure 1. Yields of porphyrinoids from the reactions of pyrrole (10 mM), pentafluorobenzaldehyde (5.0 mM), and acetone as a function of acetone concentration. (A) Reactions with TFA (215 mM). Panel A1 provides the yield of phlorin **1** at condensation reaction times of 15 min, 1 h, and 4 h, and panel A2 provides the highest yield of phlorin **1**, porphyrin **4**, and corrole **5** observed from the three time points. (B) Reactions with $BF_3{\cdot}OEt_2$ (10 mM). Panel B1 provides the yield of phlorin **1** at condensation reaction times of 15 min, 1 h, and 4 h, and panel B2 provides the highest yield of phlorin **1**, porphyrin **4**, and corrole **5** observed from the three time points. The reactions were performed in CH_2Cl_2 at room temperature, and were monitored by HPLC. Porphodimethene **3** was observed in low yields (0−2%), and 5-isocorrole **2** was not detected.

three time points. (Note: 5-isocorrole **2** and porphodimethene **3** are not included in this or other plots as 5-isocorrole was not detected and the yield of porphodimethene was generally very low.) The highest yield of phlorin **1** (26%) was obtained at acetone concentrations of 40−80 mM. However, detectable phlorin **1** was observed from all acetone concentrations surveyed (2.5−320 mM). The yields of porphyrin **4** and corrole **5** declined with increasing acetone concentration as would be expected from increased incorporation of ketone units into oligomer precursors. Porphodimethene **3** was observed in low yield (<2%) in reactions with ≥20 mM acetone. TLC analyses of crude, oxidized aliquots revealed a number of colored compounds of varying polarity in addition to the five porphyrinoids assessed by HPLC. However, none of the additional pigments were of sufficient prevalence or intensity to merit further investigation. On the basis of the results of HPLC monitoring, an acetone concentration of 80 mM was found to provide the best balance of the yield of phlorin **1** (26%) while minimizing the yield of other porphyrinoids, in particular porphyrin **4** (4%). Analogous reactions utilizing $BF_3{\cdot}OEt_2$ (10 mM) provided similar trends, albeit with lower maximum yields of phlorin **1** (16%) and higher yields of porphyrin **4** (Figure 1, panels B1 and B2). Porphodimethene **3** was observed in low yield (<1%) in reactions with ≥20 mM acetone. An acetone concentration of 80 mM was again judged to be the best condition.

Experiments utilizing 2.5 mM or 7.5 mM pentafluorobenzaldehyde provided similar trends, though differing maximum yields (see the Supporting Information for a complete set of plots). The highest yields of phlorin **1** for reactions with 2.5 mM aldehyde were 20% (TFA) and 10% ($BF_3{\cdot}OEt_2$). With 7.5 mM aldehyde, the highest yields of phlorin **1** were 17% (TFA) and 14% ($BF_3{\cdot}OEt_2$). Phlorin **1** was a fairly ubiquitous product, with at least low levels detected from almost every reaction. In the reactions with 2.5 mM aldehyde, porphodimethene **3** was observed in low yield (<3%) in reactions with ≥20 mM acetone. In the reactions with 7.5 mM aldehyde, porphodimethene **3** was observed only at the highest acetone concentration in a yield of ∼3%. For reactions utilizing 2.5 mM or 7.5 mM pentafluorobenzaldehyde with either TFA or $BF_3{\cdot}OEt_2$ catalysis, an acetone concentration of 80 mM was again found to strike a good balance between the yield of phlorin and the yields of other porphyrinoids.

Survey of Acid Catalysis Conditions. The concentration of acid catalyst is known to impact the trajectory and maximum yield of two-step, one-flask syntheses of porphyrinoids.[24,32] Thus, a survey of TFA and $BF_3{\cdot}OEt_2$ concentration was carried out for reactions utilizing pyrrole (10 mM), pentafluorobenzaldehyde (2.5, 5.0, or 7.5 mM), and acetone (80 mM).

A representative plot of the yield of phlorin **1** as a function of TFA concentration for reactions with pyrrole, pentafluorobenzaldehyde (5.0 mM), and acetone is provided in Figure 2, panel A1. Panel A2 provides a summary of the highest yield of phlorin **1**, porphyrin **4**, and corrole **5** observed at any of the three time points. The highest yield of phlorin **1** (24%) was obtained at TFA concentrations of 215−290 mM. The range of TFA concentrations providing the best yield of phlorin **1** was in agreement with the initial choice of 215 mM. Detectable phlorin **1** was observed with TFA concentrations of 55−500 mM—a nearly 10-fold range. Porphodimethene **3** was observed in low yield (<2%) from reactions with ≥160 mM TFA. Analogous reactions surveying the concentration of $BF_3{\cdot}OEt_2$

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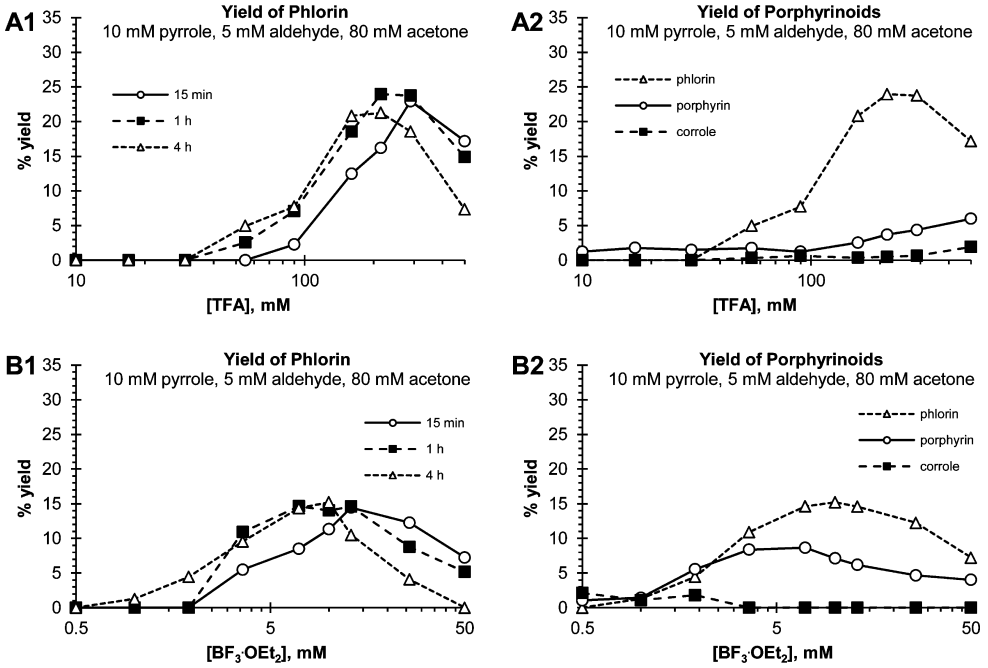

Figure 2. Yields of porphyrinoids from the reactions of pyrrole (10 mM), pentafluorobenzaldehyde (5.0 mM), and acetone (80 mM) as a function of acid concentration. (A) Reactions with TFA. Panel A1 provides the yield of phlorin **1** at condensation reaction times of 15 min, 1 h, and 4 h, and panel A2 provides the highest yield of phlorin **1**, porphyrin **4**, and corrole **5** observed from the three time points. (B) Reactions with $BF_3{\cdot}OEt_2$. Panel B1 provides the yield of phlorin **1** at condensation reaction times of 15 min, 1 h, and 4 h, and panel B2 provides the highest yield of phlorin **1**, porphyrin **4**, and corrole **5** observed from the three time points. The reactions were performed in CH_2Cl_2 at room temperature, and were monitored by HPLC. Porphodimethene **3** was generally observed in low yields (0−2%) with the exception of the lowest concentrations of $BF_3{\cdot}OEt_2$ (0.5−1.0 mM) which afforded **3** in yields of 8−9%. 5-Isocorrole **2** was not detected.

provided generally similar trends, albeit with lower maximum yields of phlorin **1** (15%) and higher yields of porphyrin **4** (Figure 2, panels B1 and B2). The highest yields of phlorin **1** were obtained with $BF_3{\cdot}OEt_2$ concentrations of 7.0−13 mM. The range of $BF_3{\cdot}OEt_2$ concentrations providing the best yield of phlorin was again in agreement with the initial choice of 10 mM.

Experiments utilizing 2.5 mM or 7.5 mM pentafluorobenzaldehyde afforded similar trends, though differing maximum yields (see the Supporting Information for a complete set of plots). TFA was generally a better catalyst than $BF_3{\cdot}OEt_2$ for the synthesis of phlorin **1**. The highest yields of phlorin **1** from reactions with 2.5 mM aldehyde were 19% (TFA, 215 mM) and 14% ($BF_3{\cdot}OEt_2$, 10 mM). At 7.5 mM aldehyde, the highest yields of phlorin **1** were 20% (TFA, 160−290 mM) and 18% ($BF_3{\cdot}OEt_2$, 10−26 mM). In the reactions with 2.5 mM aldehyde, porphodimethene **3** was observed in modest yield (4%) in reactions with the lowest concentrations of $BF_3{\cdot}OEt_2$ (0.5−1.0 mM). For reactions utilizing 2.5 mM or 7.5 mM aldehyde, the initial selections of 215 mM TFA and 10 mM $BF_3{\cdot}OEt_2$ were found to be appropriate.

Investigation of Oxidation Conditions. In two-step, one-flask syntheses of porphyrins, it is common to employ a stoichiometric quantity of oxidant (e.g., DDQ) in the oxidation step (assuming quantitative formation of the porphyrinogen precursor). However, we have found that syntheses of corrole,[30] phlorin,[4] and 5-isocorrole[6] from stepwise dipyrromethanecarbinol routes are sensitive to the quantity of oxidant, and that the optimal amount of oxidant is not always in accordance with the calculated stoichiometric quantity. Thus, we examined oxidant quantity at the beginning of the study, and again after the surveys of acetone and acid catalyst concentrations.

At the beginning of the study, oxidation of aliquots (1.2 mL) from a handful of trial reactions was done with both 1.0 and 2.0 mg of DDQ. These quantities of DDQ were selected based on amounts we had previously found to be effective in stepwise syntheses of phlorin **1**,[4] 5-isocorrole **2**,[6] and corrole **5**[30] carried out at similar reactant concentrations. From comparison of the two DDQ quantities, we found that higher yields of all porphyrinoids detected were generally obtained from 2.0 mg of DDQ. Thus, the preliminary analytical-scale experiments summarized in Table 1 utilized 2.0 mg of DDQ. Upon completion of these experiments, DDQ quantity (0.25−16 mg) was investigated further before proceeding with the systematic survey of reaction conditions. The examination of DDQ quantity supported continued oxidation of reaction aliquots with 2.0 mg of DDQ.

After conducting systematic surveys of the concentration of acetone and acid catalyst, DDQ quantity was again investigated. Representative plots of the yield of phlorin **1**, porphyrin **4**, and corrole **5** as a function DDQ quantity used in the oxidation of aliquots (1.2 mL) are provided in Figure 3. Under catalysis by TFA, the maximum yield of phlorin **1** (22%) was obtained with 2.0 mg of DDQ. At lower and higher DDQ quantities, the yield of phlorin **1** declined sharply. The highest yields of porphyrin **4** and corrole **5** were obtained with 3.0 mg of DDQ, and there was no decline in yield with higher quantities of DDQ. The analogous reaction mediated by $BF_3{\cdot}OEt_2$ afforded similar results, with the maximum yield of phlorin (18%) obtained from 1.0 to 2.0 mg of DDQ. Experiments utilizing 2.5 mM or 7.5 mM pentafluorobenzaldehyde provided similar results (see the Supporting Information for a complete set of plots).

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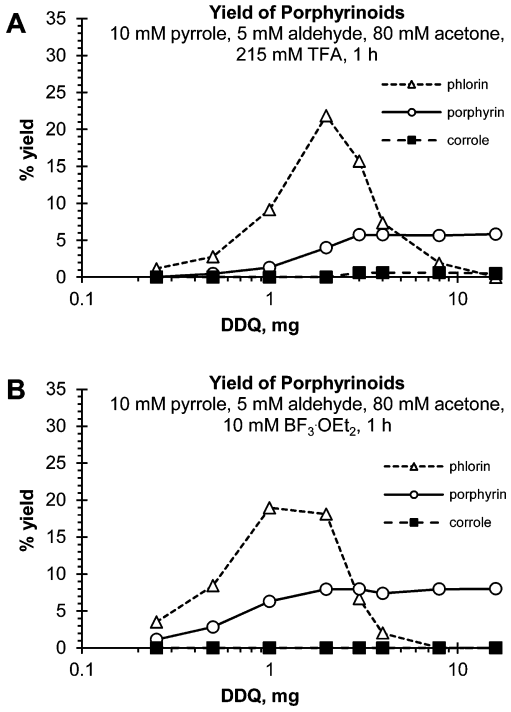

Figure 3. Yields of porphyrinoids from the reaction of pyrrole (10 mM), pentafluorobenzaldehyde (5.0 mM), and acetone (80 mM) at a reaction time of 1 h as a function of DDQ quantity used to oxidize reaction aliquots (1.2 mL). (A) TFA (215 mM). (B) $BF_3{\cdot}OEt_2$ (10 mM). The reaction was performed in CH_2Cl_2 at room temperature, and the oxidized aliquots were assessed by HPLC. A consistent, low yield porphodimethene **3** (1−2%) was observed with DDQ quantities ≥2.0 mg. 5-isocorrole **2** was not detected.

Overall, oxidation of aliquots of reaction mixtures required a fairly exacting quantity of DDQ, with 2.0 mg providing maximal or near maximal yields for all porphyrinoids detected from each of the reaction conditions investigated.

It is interesting that a 3-fold difference in the concentration of pentafluorobenzaldehyde had a negligible effect on the optimal quantity of DDQ. For each porphyrinoid detected, the aldehyde was generally the limiting reagent. Thus, the stoichiometric quantity of DDQ required for the preparation of each porphyrinoid from their reduced precursor declines with decreasing aldehyde concentration. For example, the stoichiometric quantities of DDQ required for the preparation of phlorin **1** (assuming quantitative formation of its reduced precursor during the condensation step) are 1.4, 0.91, and 0.45 mg for aliquots (1.2 mL) from reactions performed with aldehyde concentrations of 7.5, 5.0, and 2.5 mM, respectively. Nonetheless, the composition of the overall, complex reaction mixture appears to be such that a consistent amount of DDQ is required over the range of aldehyde concentration investigated. In practical terms, the quantity of oxidant did not need be adjusted for analytical-scale reactions performed with different concentrations of the limiting reagent.

Reaction Time-Course Experiments. The survey of reaction parameters provided promising conditions in terms of the yield of phlorin **1** and level of porphyrinoid byproducts. Seven conditions were selected for reaction monitoring from 1 min to 24 h. Six reactions utilized pyrrole (10 mM) and acetone (80 mM), along with pentafluorobenzaldehyde (2.5, 5.0, or 7.5 mM) and TFA (215 mM) or $BF_3{\cdot}OEt_2$ (10 mM). The seventh reaction was performed with pyrrole (10 mM), pentafluorobenzaldehyde (7.5 mM), and acetone (160 mM) mediated by TFA (215 mM) in an attempt to further suppress porphyrin **4** formation.

A representative plot of the yields of phlorin **1**, porphyrin **4**, and corrole **5** as a function of time for the reaction with pyrrole (10 mM), pentafluorobenzaldehyde (5.0 mM), and TFA (215 mM) is provided in Figure 4A. A near maximum yield of

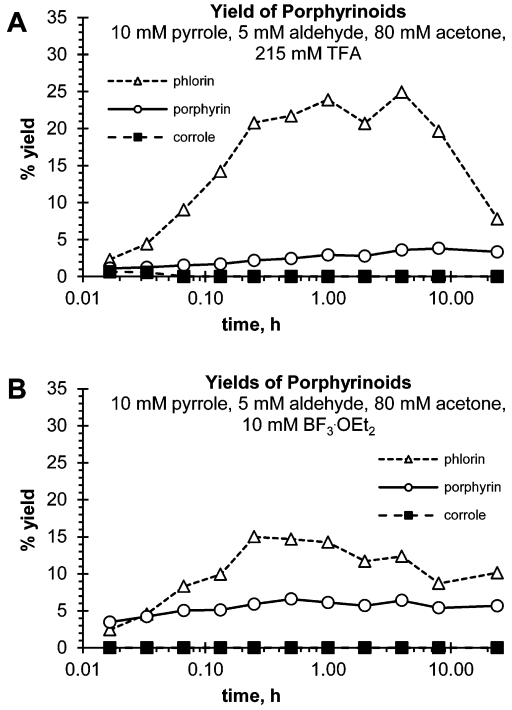

Figure 4. Yields of porphyrinoids from the reaction of pyrrole (10 mM), pentafluorobenzaldehyde (5.0 mM), and acetone (80 mM) as a function of condensation reaction time (1 min to 24 h). (A) TFA (215 mM). (B) $BF_3{\cdot}OEt_2$ (10 mM). The reactions were performed in CH_2Cl_2 at room temperature, and monitored by HPLC. Porphodimethene **3** was observed in low yields (0−2%), and 5-isocorrole **2** was not detected. Note the logarithmic scale for time.

phlorin **1** (21%) was obtained by a reaction time of 15 min, and remained fairly constant from 4 to 8 h. The observation of a consistent yield of phlorin **1** over an extended period of time is of practical significance as the precise timing of the oxidation should not impact reproducibility of preparative-scale syntheses. Porphyrin **4** (2−3% yield) was observed from 4 min to 24 h, and a very low level of corrole **5** (<1%) was detected from 1 to 2 min. Porphodimethene **3** (<2% yield) was observed from 15 min to 24 h. The analogous reaction with $BF_3{\cdot}OEt_2$ afforded similar results (Figure 4B). The maximum yield of phlorin **1** (15%) was obtained from 15 min to 1 h, with only modest decline in yield by 4 h. The yield of porphyrin **4** was fairly constant (5−6%) from 4 min to 24 h. Porphodimethene **3** (<1%) was observed from 30 min to 8 h.

The yield trajectories from the other reactions were similar (see the Supporting Information for the complete set of plots). Reactions utilizing TFA generally provided higher yields of phlorin **1** (20−25%) than reactions with $BF_3{\cdot}OEt_2$ (13−15%). Reactions mediated by $BF_3{\cdot}OEt_2$ also provided higher levels of porphyrin **4** relative to analogous reactions with TFA. Reactions performed with a higher concentration of pentafluorobenzaldehyde resulted in higher levels of porphyrin **4**.

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Preparative-Scale Phlorin Syntheses. To confirm results of analytical-scale experiments, three reaction conditions were performed on a preparative scale: (1) pyrrole (10 mM), pentafluorobenzaldehyde (5.0 mM), acetone (80 mM), and TFA (215 mM); (2) pyrrole (10 mM), pentafluorobenzaldehyde (7.5 mM), acetone (160 mM), and TFA (215 mM); and (3) pyrrole (10 mM), pentafluorobenzaldehyde (2.5 mM), acetone (80 mM), and TFA (215 mM). The reaction conditions were selected based on the yield of phlorin **1** and other porphyrinoids observed in the analytical-scale reactions. Each condition afforded similarly good yields of phlorin **1**, but differing quantities of porphyrin **4**. We sought to determine the extent to which the porphyrin (along with the very low levels of porphodimethene **3** and corrole **5**) would complicate purification of phlorin **1**. We found in our analytical-scale experiments that the level of porphyrin **4** can be suppressed without a significant decline in the yield of phlorin **1** by decreasing the concentration of aldehyde. However, doing so increases the volume of solvent required to prepare a given quantity of phlorin **1**. Thus, it was important to determine the level of porphyrin **4** and other porphyrinoids that can be tolerated.

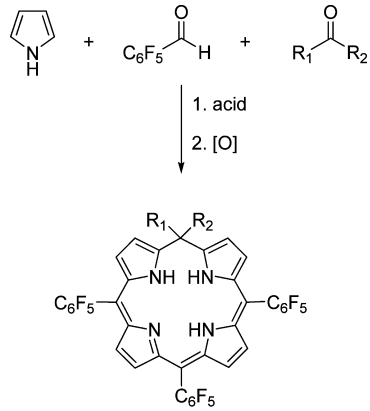
The reaction utilizing a pentafluorobenzaldehyde concentration of 5.0 mM was performed first. On the basis of observations from the analytical-scale reactions, we suspected that this condition would provide the best balance between the yield of phlorin **1**, suppression of other porphyrinoid products, and concentration of the limiting reagent thereby minimizing solvent volume. Preoxidation monitoring of the reaction by HPLC provided the following yield estimates: phlorin **1** (21%), isocorrole **2** (not detected), porphodimethene **3** (1%), porphyrin **4** (4%), and corrole **5** (0.4%). These values were similar to yields obtained from HPLC monitoring of the analogous analytical-scale reaction: phlorin **1** (22−26%), isocorrole **2** (not detected), porphodimethene **3** (1%), porphyrin **4** (3−4%), and corrole **5** (trace levels). Monitoring of the reaction mixture by HPLC after bulk oxidation with DDQ afforded similar estimates of the yield of phlorin **1** (22%), isocorrole **2** (not detected), porphodimethene **3** (1%), porphyrin **4** (4%), and corrole **5** (0.4%). The reaction mixture was purified by filtration through a pad of silica gel, followed by silica gel column chromatography. Isolated quantities of porphodimethene **3**, porphyrin **4**, and corrole **5** corresponded to yields of 1%, 4%, and 0.5%, respectively. Fractions containing phlorin **1** were further purified by neutral alumina chromatography affording phlorin **1** in good purity (297 mg, 24% yield). Crystallization afforded 266 mg of phlorin (21% yield), in agreement with HPLC monitoring and with results on the analytical-scale. This condition was performed two additional times, with similar results. Isolated yields for each porphyrinoid from the two additional trials were: phlorin **1** (postalumina column, 24%, 22%), phlorin **1** (postcrystallization, 21%, 20%) porphodimethene **3** (1%, 1%), porphyrin **4** (5%, 5%) and corrole **5** (0.6%, 0.5%).

The reaction performed at higher pentafluorobenzaldehyde concentration (7.5 mM) proceeded similarly well with the exception of a low level of residual impurity present in the phlorin isolated from neutral alumina chromatography which was removed by crystallization. Isolated yields for each porphyrinoid were phlorin **1** (postcrystallization, 17%) porphodimethene **3** (0.7%), and porphyrin **4** (6%). 5-Isocorrole **2** and corrole **5** were not detected. The isolated yields are similar to yields obtained from HPLC monitoring of the analogous analytical-scale reaction: phlorin **1** (21%) porphodimethene **3** (1%), porphyrin **4** (6%), and corrole **5** (not detected).

The reaction performed at lower pentafluorobenzaldehyde concentration (2.5 mM) proceeded well overall, but the larger solvent volume was inconvenient and allowed a higher level of impurity to pass through the initial silica pad. Nonetheless, further purification of the phlorin was not overly impacted. Isolated yields for each porphyrinoid were phlorin **1** (postalumina column, 22%), phlorin **1** (postcrystallization, 18%) porphodimethene **3** (2%), and porphyrin **4** (1%). 5-Isocorrole **2** and corrole **5** were not detected. These yields were in good agreement with yields obtained from HPLC monitoring of the analogous analytical-scale reaction: phlorin **1** (19−22%) porphodimethene **3** (2%), porphyrin **4** (2%), and corrole **5** (not detected). Given that the yield of phlorin was similar for the three reaction conditions and that the presence of porphodimethene **3**, porphyrin **4** and corrole **5** were found to not adversely complicate purification of phlorin under any of the conditions investigated, it is not necessary to perform the reaction at the lowest concentration of pentafluorobenzaldehyde.

Attempted Reactions with Benzophenone and Acetophenone. Although the reaction of pyrrole with pentafluorobenzaldehyde and acetone was the focus of the present work, we were interested in the extension of the findings to other ketones. Previously, we found that the presence of different substituents at the sp^3-hybridized meso-position of phlorin can impact structure, spectroscopic properties, and stability.[5] While a comprehensive examination of additional ketones was beyond the scope of the present work, we attempted reactions using acetophenone and benzophenone (Scheme 3). These ketones were selected due to their different electronic and steric aspects relative to acetone, and we had previously prepared phlorins **6** and **7** via stepwise, dipyrromethanecarbinol routes.[5] Each ketone was subjected to a reaction condition found to work well for the preparation of phlorin **1**: pyrrole (10 mM), pentafluorobenzaldehyde (5.0 mM), ketone (80 mM), and

Scheme 3. Attempted Two-Step, One-Flask Syntheses of Phlorins Bearing Different Substituents at the sp^3-Hybridized Meso-Position



	R_1	R_2
6	$-CH_3$	-Ph
7	-Ph	-Ph

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TFA (215 mM) in CH_2Cl_2 at room temperature for 1 h followed by oxidation with DDQ.

Both reactions were challenging. The level of phlorin in the crude reaction mixtures appeared to be low (acetophenone reaction) or absent (benzophenone reaction) as qualitatively judged by TLC analysis. In addition, residual, excess ketone was more difficult to remove from the crude reaction mixtures due to the lower volatility of acetophenone and especially benzophenone which could not be removed by evaporation. Purification of phlorin **6** (derived from acetophenone) was hampered by a more complicated reaction mixture, by the more similar chromatographic retention of phlorin **6** to corrole **5**, and by the lower yield of phlorin **6**. After chromatography on silica gel, neutral alumina, and silica gel again, phlorin **6** of modest purity was isolated (64 mg, 5% yield). The reaction also afforded porphyrin **4** (6% yield) and corrole **5** (4% yield). Although phlorin **7** did not appear to be present in the reaction involving benzophenone, the reaction mixture was subjected to silica gel chromatography from which porphyrin **4** and corrole **5** were isolated in yields of 8% and 7%, respectively. No phlorin **7** was detected. The chromatographic purification of porphyrin **4** and corrole **5** was complicated by the presence of the excess benzophenone. The excess benzophenone streaked down the column negatively impacting the separation of porphyrin **4** and corrole **5**, and contaminating fractions with a low level of benzophenone. A second silica column was required to separate the porphyrin **4** and corrole **5** from each other and from the remaining benzophenone.

It is not surprising that conditions identified for the preparation of phlorin **1** from acetone did not provide similarly good yields of phlorins **6** and **7** given sharp difference in ketones. Two-step, one-flask syntheses of porphyrins can require substantial refinement of reaction conditions based on the nature of the aldehyde.[31] Nonetheless, it is encouraging that the reaction with acetophenone afforded some phlorin **6**.

CONCLUSION

The two-step, one-flask reaction of pyrrole with pentafluorobenzaldehyde and acetone was investigated with the goal of achieving a streamlined synthesis of calixphyrins such as phlorin. Phlorin **1** was found to be a fairly ubiquitous product of the reaction, with yields reaching 20−26% in analytical-scale reactions monitored by HPLC. An isolated yield of phlorin **1** of 20−21% (249−268 mg) was obtained from three trials of the reaction of pyrrole (10 mM), pentafluorobenzaldehyde (5.0 mM), and acetone (80 mM) mediated by TFA (215 mM). The preparation of a phlorin in good yield from a two-step, one-flask approach shows that it is possible to obtain meaningful quantities of a calixphyrin in a streamlined fashion. This observation provides encouragement for further studies of two-step, one-flask reactions of pyrrole with an aldehyde and a ketone. The scope of phlorins that can be directly prepared from the methodology, the extent to which conditions can be further refined to afford phlorins that are not prepared in good yield (or at all) from the present conditions, and the potential to obtain other calixphyrins (e.g., 5-isocorrole) in good yield from a wider survey of reaction conditions could be further investigated. In the meantime, improved access to phlorin **1** will facilitate studies of phlorin properties, reactivity, and metal chemistry.

EXPERIMENTAL SECTION

General Experimental Methods. ^{1}H NMR (400 MHz), ^{13}C NMR (100 MHz), and absorption spectra were collected routinely. Column chromatography was performed on silica (Sorbent Technologies, standard grade, 230−400 mesh, 60 Å) or neutral alumina (Fisher, 80−200 mesh). CH_2Cl_2 used in analytical-scale reactions was distilled from K_2CO_3 and stored over 4-Å Linde molecular sieves. CH_2Cl_2 used in sample preparation for HPLC determination of yield of porphyrinoids **1**−**5** was passed through a pad of basic alumina prior to use. Pyrrole was distilled from CaH_2 and stored at −15 °C. The distilled pyrrole was used prior to the appearance of any discoloration. All other chemicals are reagent grade and were used as received. Authentic phlorin **1**,[4] 5-isocorrole **2**,[6] porphodimethene **3**,[6,33,34] and corrole **5**[35] used as standards for HPLC method development and detector response calibration were prepared as described in the literature. Porphyrin **4** was available commercially.

HPLC Determination of Yields of Porphyrinoids 1−5. Analytical-scale reactions of pyrrole with pentafluorobenzaldehyde and acetone were monitored for the yield of phlorin **1**, 5-isocorrole **2**, porphodimethene **3**, porphyrin **4**, and corrole **5** by adaptation of a literature method for the analysis of phlorin **1**[4] and 5-isocorrole **2**[6] in crude reaction mixtures. An aliquot (1.2 mL) of a condensation reaction mixture was transferred by adjustable pipet to a 1.8 mL microcentrifuge tube containing DDQ (2.00 mg, 0.00881 mmol), the mixture was vortex mixed for ∼5 s, and centrifuged for ∼5 s. [Microfuge tubes containing DDQ were prepared by dispensing 220 μL of a DDQ solution (40 mM in toluene) in each microfuge tube, and evaporating the solvent under a vacuum at room temperature.] Triethylamine (2 equiv relative to acid) was added, the mixture was vortex mixed for ∼5 s, and centrifuged for ∼5 s. A portion of the oxidized reaction mixture (0.70 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 dispensed from a solvent pump, and solvent was driven off the silica pad with a hand-held pipet tool. The eluent was transferred to an autosampler vial. HPLC analysis was performed with an injection volume of 1 μL, a normal phase silica column (Alltech, Altima, 5 μ, 4.6 mm × 250 mm), using an isocratic solvent mixture of 95.5% hexanes and 4.5% acetone. The hexanes solvent was 50% water saturated by mixing equal portions of hexanes and hexanes stored over water. The solvent flow rate was controlled as follows: T = 0−6 min, 1 mL/min; T = 6−7 min, linear increase to 2 mL/min; T = 7−14 min, 2 mL/min; T = 14−15 min, linear decrease to 1 mL/min. The phlorin **1**, 5-isocorrole **2**, porphodimethene **3**, porphyrin **4**, and corrole **5** eluted at 8.3, 7.3, 7.5, 8.0, and 8.7 min, respectively. Detection was performed at 434 nm (phlorin **1**), 418 nm (5-isocorrole **2**), 420 nm (porphodimethene **3**), 410 nm (porphyrin **4**), and 406 nm (corrole **5**). The yields of porphyrinoids **1**−**5** were determined from the peak area by application of a detector response factor determined from the calibration of the detector response for each compound. Representative chromatograms and further details on the HPLC method development, control and reproducibility experiments, detector response calibration, and the calculation of porphyrinoid yields from HPLC peak areas may be found in the Supporting Information.

General Procedure for Analytical-Scale Reactions, Exemplified by the Reaction of Pyrrole (10 mM), Pentafluorobenzaldehyde (5.0 mM), and Acetone (80 mM) with Catalysis by TFA (215 mM). The reaction was performed at room temperature in a tightly capped 20 mL vial, and stirred with a micro stir bar. CH_2Cl_2 (10 mL) was dispensed into the vial, followed by pyrrole (50 μL, 0.10 mmol, 2.0 M solution in CH_2Cl_2), pentafluorobenzaldehyde (25 μL, 0.050 mmol, 2.0 M solution in CH_2Cl_2), and acetone (59 μL, 0.80 mmol). After stirring briefly, TFA (165 μL, 2.15 mmol) was added. The reactions were monitored by HPLC at 0.25, 1, and 4 h as described above. TLC was performed on the crude, oxidized mixtures [silica, CH_2Cl_2/hexanes (1:1)].

Survey of Acetone Concentration. Reactions were performed as described in the general procedure, with an acetone concentration of 2.5, 5.0, 10, 20, 40, 80, 160, or 320 mM. Reactions with a low

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concentration of acetone (≤20 mM) utilized a 1.0 M solution of acetone in CH_2Cl_2.

Survey of Acid Catalysis Conditions. Reactions were performed as described in the general procedure, with a TFA concentration of 10, 17, 30, 55, 90, 160, 215, 290, or 500 mM; or a $BF_3{\cdot}OEt_2$ concentration of 0.5, 1.0, 1.9, 3.6, 7.0, 10, 13, 26, or 50 mM. Reactions with a low concentration of TFA (≤17 mM) utilized a 2.0 M solution of TFA in CH_2Cl_2. Reactions with a low concentration of $BF_3{\cdot}OEt_2$ (≤1.9 mM and 3.6−13 mM) utilized a 0.25 or 1.0 M solution of $BF_3{\cdot}OEt_2$ in CH_2Cl_2, respectively.

Survey of Oxidation Conditions Exemplified by the Reaction of Pyrrole (10 mM), Pentafluorobenzaldehyde (5.0 mM), and Acetone (80 mM) with Catalysis by TFA (215 mM). The reaction was performed at room temperature in tightly capped 20 mL vial, and stirred with a micro stir bar. CH_2Cl_2 (15 mL) was dispensed into the vial, followed by pyrrole (75 μL, 0.15 mmol, 2.0 M solution in CH_2Cl_2), pentafluorobenzaldehyde (38 μL, 0.075 mmol, 2.0 M solution in CH_2Cl_2), and acetone (88 μL, 1.2 mmol). After stirring briefly, TFA (247 μL, 3.23 mmol) was added. At 1 h, aliquots (1.2 mL) of the reaction were transferred to microfuge tubes containing 0.25, 0.5, 1.0, 2.0, 3.0, 4.0, 8.0, or 16 mg of DDQ. The oxidized mixtures were prepared for HPLC analysis and analyzed as described above. TLC was performed on the crude, oxidized mixtures [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 general procedure with the exception of using a 20 mL reaction volume in a tightly capped, 50 mL pear shaped flask. The reactions were monitored by HPLC as described above at 1 min, 2 min, 4 min, 8 min, 15 min, 30 min, 1, 2, 4, 8, and 24 h. TLC was performed on the crude, oxidized mixtures [silica, CH_2Cl_2/hexanes (1:1)].

5,5-Dimethyl-10,15,20-tris(pentafluorophenyl)phlorin 1, [Reaction of Pyrrole (10 mM), Pentafluorobenzaldehyde (5.0 mM), and Acetone (80 mM) with Catalysis by TFA (215 mM)]. To a 2-L round-bottom flask containing a stir bar were added CH_2Cl_2 (900 mL), pyrrole (0.624 mL, 9.00 mmol), pentafluorobenzaldehyde (0.556 mL, 4.50 mmol), and acetone (5.29 mL, 72.0 mmol). After stirring briefly, the reaction was initiated by the addition of TFA (14.8 mL, 194 mmol). The flask was tightly capped, and the reaction was stirred at room temperature. At reaction times of 30 min and 1 h, the reaction was monitored by HPLC as described above, and the yield of phlorin **1** was found to be satisfactory. At a reaction time of 1 h, the reaction mixture was oxidized by the addition of DDQ (1.50 g, 6.61 mmol) at room temperature. After ∼1 min, triethylamine (29.7 mL, 213 mmol, 1.1 equiv relative to the acid) was added and the mixture was stirred at room temperature. At oxidation reaction times of 30 min and 1 h an aliquot (1.2 mL) of the reaction mixture was removed for HPLC analysis. At 1 h, the reaction mixture was filtered through a pad of silica gel and eluted with CH_2Cl_2 (∼400 mL) until the eluant was no longer green. The filtrate was concentrated to a dark, viscous liquid. The impure phlorin was diluted with CH_2Cl_2 (50 mL), adsorbed onto silica gel (40 g), evaporated to dryness, and subjected to chromatography [silica, CH_2Cl_2/hexanes (1:5), (1:3), (1:2), (1:1)]. With a solvent composition of CH_2Cl_2/hexanes (1:3), fractions containing a mixture of porphodimethene **3** and porphyrin **4** eluted, followed closely by fractions containing a mixture of largely porphyrin **4** and corrole **5**. The quantity of porphodimethene **3** (20 mg, 1.3%), porphyrin **4** (48 mg, 4.4%), and corrole **5** (7 mg, 0.6%) were estimated based on the dry mass of the collected fractions and the integrated peak areas of the ^{1}H NMR spectra of the fractions (see the Supporting Information). Upon increasing the polarity of the solvent to CH_2Cl_2/hexanes (1:2), fractions containing phlorin **1** were collected, and evaporated to dryness affording 354−377 mg of impure phlorin. The impure phlorin was redissolved in CH_2Cl_2 (25 mL), adsorbed onto neutral alumina (15 g), evaporated to dryness, and subjected to chromatography [neutral alumina, CH_2Cl_2/hexanes (1:4)]. After elution of a bright red band of unknown structure, a dark green band containing phlorin **1** was collected, and evaporated to dryness affording phlorin (274−297 mg) of good purity (see the Supporting Information for the HPLC chromatogram, UV−vis spectrum, and ^{1}H NMR spectrum). Crystallization from CH_2Cl_2/hexanes with gradual evaporation of the CH_2Cl_2 (50−60 °C) gave fine, needle crystals that were stored overnight at −15 °C. The crystals were collected by vacuum filtration aided by rinsing with pentane, affording dark purple crystals of phlorin **1** (249−268 mg, 20−21%). ^{1}H NMR ($CDCl_3$ and DMSO-d_6), UV−vis (CH_2Cl_2), and LD-MS analyses were consistent with published values.[4]

5,5-Dimethyl-10,15,20-tris(pentafluorophenyl)phlorin 1 [Reaction of Pyrrole (10 mM), Pentafluorobenzaldehyde (7.5 mM), and Acetone (160 mM) with Catalysis by TFA (215 mM)]. To a 2-L round-bottom flask containing a stir bar were added CH_2Cl_2 (600 mL), pyrrole (0.416 mL, 6.00 mmol), pentafluorobenzaldehyde (0.556 mL, 4.50 mmol), and acetone (7.05 mL, 96.0 mmol). After stirring briefly, the reaction was initiated by the addition of TFA (9.88 mL, 129 mmol). The flask was tightly capped, and the reaction was stirred at room temperature. At a reaction time of 30 min the reaction was monitored by HPLC as described above, and the yield of phlorin **1** was found to be satisfactory. At a reaction time of 30 min, the reaction mixture was oxidized by the addition of DDQ (1.00 g, 4.41 mmol) at room temperature. After ∼1 min, triethylamine (19.8 mL, 142 mmol, 1.1 equiv relative to the acid) was added and the mixture was stirred at room temperature. At oxidation reaction times of 30 min and 1 h, an aliquot (1.2 mL) of the reaction mixture was removed for HPLC analysis. At 1 h, the reaction mixture was filtered through a pad of silica gel and eluted with CH_2Cl_2 (∼400 mL) until the eluant was no longer green. Further purification of the impure product was carried out by silica gel chromatography as described above. Fractions containing a mixture of porphodimethene **3** (12 mg, 0.7%) and porphyrin **4** (65 mg, 5.9%) were collected and analyzed as described above. The fractions containing phlorin (355 mg) were purified further by chromatography on neutral alumina as described above, affording phlorin (285 mg) in good purity (see the Supporting Information for the HPLC chromatogram, UV−vis spectrum, and ^{1}H NMR spectrum). Crystallization from CH_2Cl_2/hexanes gave dark purple crystals of phlorin **1** (212 mg, 17%). ^{1}H NMR ($CDCl_3$ and DMSO-d_6), UV−vis (CH_2Cl_2), and LD-MS analyses were consistent with published values.[4]

5,5-Dimethyl-10,15,20-tris(pentafluorophenyl)phlorin 1 [Reaction of Pyrrole (10 mM), Pentafluorobenzaldehyde (2.5 mM), and Acetone (80 mM) with Catalysis by TFA (215 mM)]. To a 2-L round-bottom flask containing a stir bar were added CH_2Cl_2 (1.8 L), pyrrole (1.25 mL, 18.0 mmol), pentafluorobenzaldehyde (0.556 mL, 4.50 mmol), and acetone (10.6 mL, 144 mmol). After stirring briefly, the reaction was initiated by the addition of TFA (29.6 mL, 387 mmol). The flask was tightly capped, and the reaction was stirred at room temperature. At reaction times of 30 min and 1 h the reaction was monitored by HPLC as described above, and the yield of phlorin **1** was found to be satisfactory. At a reaction time of 1 h, the reaction mixture was oxidized by the addition of DDQ (3.00 g, 13.2 mmol) at room temperature. After ∼1 min, triethylamine (59.4 mL, 426 mmol, 1.1 equiv relative to the acid) was added and the mixture was stirred at room temperature. At oxidation reaction times of 30 min and 1 h an aliquot (1.2 mL) of the reaction mixture was removed for HPLC analysis. At 1 h, the reaction mixture was filtered through a pad of silica gel and eluted with CH_2Cl_2 (∼400 mL) until the eluant was no longer green. Further purification of the impure product was carried out by silica gel chromatography as described above. Fractions containing a mixture of porphodimethene **3** (34 mg, 2.2%) and porphyrin **4** (14 mg, 1.3%) were collected and analyzed as described above. The fractions containing phlorin (624 mg) were purified further by chromatography on neutral alumina as described above, affording phlorin (276 mg) in good purity (see the Supporting Information for the HPLC chromatogram, UV−vis spectrum, and ^{1}H NMR spectrum). Crystallization from CH_2Cl_2/hexanes gave dark purple crystals of phlorin **1** (230 mg, 18%). ^{1}H NMR ($CDCl_3$ and DMSO-d_6), UV−vis (CH_2Cl_2), and LD-MS analyses were consistent with published values.[4]

5-Methyl-5-phenyl-10,15,20-tris(pentafluorophenyl)phlorin 6. To a 2-L round-bottom flask containing a stir bar were added CH_2Cl_2 (900 mL), pyrrole (0.624 mL, 9.00 mmol), pentafluoro-

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benzaldehyde (0.556 mL, 4.50 mmol), and acetophenone (8.40 mL, 72.0 mmol). After stirring briefly, the reaction was initiated by the addition of TFA (14.8 mL, 194 mmol). The flask was tightly capped, and the reaction was stirred at room temperature. At a reaction time of 1 h, the reaction mixture was oxidized by the addition of DDQ (1.50 g, 6.61 mmol) at room temperature. After ∼1 min, triethylamine (29.7 mL, 213 mmol, 1.1 equiv relative to the acid) was added and the mixture was stirred at room temperature. At an oxidation reaction time of 1 h, the reaction mixture was filtered through a pad of silica gel and eluted with CH_2Cl_2 (∼450 mL) until the eluant was no longer green. The filtrate was concentrated to a dark, viscous liquid. The sample was placed under a vacuum at 60 °C to remove as much of the excess acetophenone as possible. The impure phlorin was diluted with CH_2Cl_2 (50 mL), adsorbed onto silica gel (40 g), evaporated to dryness, and subjected to chromatography [silica, CH_2Cl_2/hexanes (1:5), (1:3), (1:2), (1:1)]. With a solvent mixture of CH_2Cl_2/hexanes (1:3), fractions containing porphyrin **4** (64 mg, 5.8%) eluted, followed closely by fractions containing an impure mixture of corrole **5** and phlorin **6**. The impure mixture of corrole and phlorin was redissolved in CH_2Cl_2 (25 mL), adsorbed onto neutral alumina (15 g), evaporated to dryness, and subjected to chromatography [neutral alumina, CH_2Cl_2/hexanes (1:5), (1:4), CH_2Cl_2, and CH_2Cl_2/MeOH (20:1)]. A dark green band containing phlorin **6** eluted rapidly. The band was collected and evaporated to dryness affording phlorin (85 mg) of modest purity. Corrole **5** was retained strongly by the neutral alumina, requiring elution with CH_2Cl_2 and CH_2Cl_2/MeOH (20:1). Fractions containing corrole were collected and evaporated to dryness affording corrole (47 mg, 4.0%) with good purity (see the Supporting Information for UV−vis and ^{1}H NMR spectra). Due to the low quantity of phlorin, crystallization from CH_2Cl_2/hexanes was not successful. Instead, the phlorin was further purified by silica gel chromatography. The impure phlorin was dissolved with a minimal volume of CH_2Cl_2/hexanes (1:5), and passed through a silica gel column, eluting with CH_2Cl_2/hexanes (1:3). Upon evaporation of solvent, phlorin **6** (64 mg, 4.7%) contaminated with a low level of impurities was isolated (see the Supporting Information for UV−vis and ^{1}H NMR spectra). ^{1}H NMR ($CDCl_3$), UV−vis (CH_2Cl_2), and LD-MS analyses were consistent with published values.[5]

Attempted Synthesis of 5,5-Diphenyl-10,15,20-tris-(pentafluorophenyl)phlorin 7. To a 2-L round-bottom flask containing a stir bar were added CH_2Cl_2 (900 mL), pyrrole (0.624 mL, 9.00 mmol), pentafluorobenzaldehyde (0.556 mL, 4.50 mmol), and benzophenone (13.1 g, 72.0 mmol). After stirring briefly, the reaction was initiated by the addition of TFA (14.8 mL, 194 mmol). The flask was tightly capped, and the reaction was stirred at room temperature. At a reaction time of 1 h, the reaction mixture was oxidized by the addition of DDQ (1.50 g, 6.61 mmol) at room temperature. After ∼1 min, triethylamine (29.7 mL, 213 mmol, 1.1 equiv relative to the acid) was added and the mixture was stirred at room temperature. TLC analysis [silica, CH_2Cl_2/hexanes (1:1)] revealed the presence of porphyrin **4** and corrole **5**, but not phlorin **7**. At an oxidation reaction time of 1 h, the reaction mixture was filtered through a pad of silica gel and eluted with CH_2Cl_2 (∼500 mL). The filtrate was concentrated to a dark, viscous liquid. The sample was diluted with CH_2Cl_2 (50 mL), adsorbed onto silica gel (40 g), evaporated to dryness, and subjected to chromatography [silica, CH_2Cl_2/hexanes (1:5), (1:3), (1:2)]. With a solvent mixture of CH_2Cl_2/hexanes (1:3), fractions containing a mixture of porphyrin **4** and corrole **5** contaminated with benzophenone eluted quickly. No phlorin **7** was observed upon further elution of the column. To determine the yield of porphyrin **4** and corrole **5**, the mixture of porphyrin **4** and corrole **5** contaminated with benzophenone was subjected to a second silica gel column, again eluting with CH_2Cl_2/hexanes (1:5), (1:3), (1:2). With a lower initial level of impurity, the porphyrin (87 mg, 8.0%) cleanly eluted first followed by the corrole (88 mg, 7.3%) with no contamination from benzophenone. ^{1}H NMR ($CDCl_3$), UV−vis (CH_2Cl_2), and LD-MS analyses were consistent with published values.[22]

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b00571.

Discussion of HPLC method development; control and reproducibility experiments, and detector response calibration; calculation of porphyrinoid yield from HPLC peak area; plots of porphyrinoid yields from analytical-scale reactions; summary of conditions affording porphodimethene **3** in yields exceeding 2%; HPLC chromatograms, UV−vis spectra, and ^{1}H NMR spectra of phlorin **1** isolated from preparative-scale reactions; estimation of the yield of porphodimethene **3**, porphyrin **4**, and corrole **5** from preparative-scale reactions; and UV−vis spectra and ^{1}H NMR spectra of 5-methyl-5-phenylphlorin **6** and corrole **5** from the reaction of pyrrole, pentafluorobenzaldehyde, and acetophenone mediated by TFA. (PDF)

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Notes

The authors declare no competing financial interest.

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