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Synthetic Routes to *meso*-Patterned Porphyrins

JONATHAN S. LINDSEY*
Department of Chemistry, North Carolina State University, Raleigh, North Carolina 27695-8204

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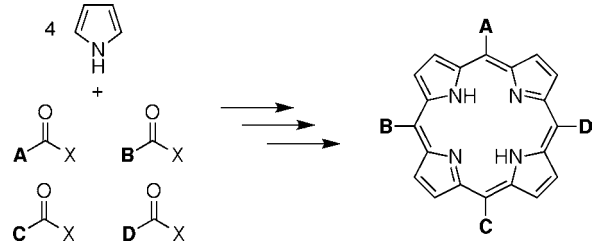

Synthetic *meso*-substituted porphyrins offer significant attractions compared with naturally occurring β-substituted porphyrins. The attractions include the rectilinear arrangement of the four *meso* substituents and potential synthetic amenability from pyrrole and simple acyl reactants, thereby avoiding the cumbersome syntheses of β-substituted pyrroles. In practice, however, the classical methods for the synthesis of *meso*-substituted porphyrins were characterized by high-temperature reactions, limited scope of substituents, and statistical mixtures accompanied by laborious chromatography if porphyrins bearing two different types of substituents were sought. Such methods left unrealized the tremendous utility of *meso*-substituted porphyrins across the enormously broad field of porphyrin science, which touches pure chemistry; energy, life and materials sciences; and medicine.

This Account surveys a set of strategies, developed over a generation, that provide rational access to porphyrins bearing up to four distinct *meso* substituents. A "2 + 2" route employs a dipyrromethane-1,9-dicarbinol and a dipyrromethane (bearing ABC- and D-substituents, respectively) in a two-step, one-flask process of acid-catalyzed condensation followed by oxidation at room temperature to form the free base "ABCD-porphyrin." A "bilane" route relies on the acid-catalyzed reaction of a 1-acyldipyrromethane (CD substituents) and a 9-bromodipyrromethane-1-carbinol (AB substituents) to form the corresponding 19-acyl-1-bromobilane. Reaction of the latter compound in the presence of $MgBr_2$, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), and toluene at reflux exposed to air affords the corresponding magnesium(II) porphyrin. The two routes are complementary, both in scope and in implementation. A suite of methods also affords *trans*-A_2B_2-porphyrins by reaction of a dipyrromethane and an aldehyde, self-condensation of a dipyrromethane-1-carbinol, or self-condensation of a 1-acyldipyrromethane. These new routes are also useful for preparing sparsely substituted porphyrins, which bear fewer than four *meso* substituents (e.g., *trans*-AB-porphyrins, A-porphyrins). Because of their compact size and the ability to incorporate hydrophilic or amphipathic groups, such molecules are ideal for biological applications.

The success of these new synthetic strategies has relied on a number of advances including (1) the development of simple yet efficient routes to dipyrromethanes, acyldipyrromethanes, and dipyrromethane-carbinols, (2) the identification of acid catalysts and reaction conditions for condensations of pyrromethane species without accompanying acidolysis (which underlies scrambling and formation of a mixture of porphyrin products), (3) the development of analytical methods to rapidly screen for scrambling and to characterize the distribution of oligopyrromethanes and macrocycles, (4) selection and refinement of synthetic methods to increase yields and to limit or avoid use of chromatography, thereby achieving scalability to multigram levels, and (5) exploitation of discoveries concerning the fundamental chemistry of pyrrolic species. With these developments, the prior era of porphyrin synthesis has been supplanted with rational routes that proceed under very mild conditions and afford a single porphyrin bearing up to four distinct *meso* substituents. The *meso* substituents encompass a very wide range of molecular complexity. The resulting porphyrins can serve as building blocks in the construction of model systems, as components of molecular materials, and as surrogates for naturally occurring tetrapyrrole macrocycles.

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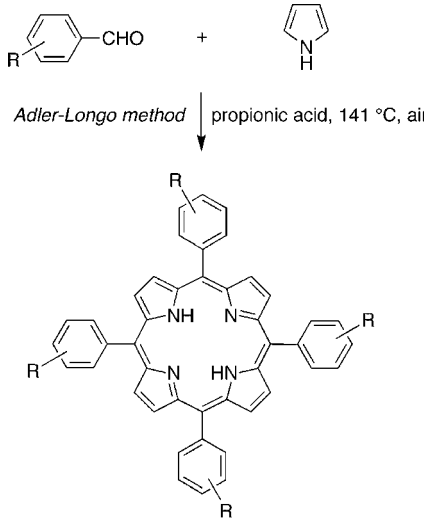
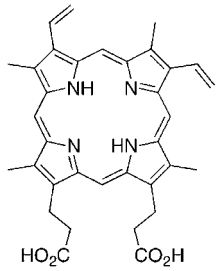
Introduction

I made my first porphyrin, a *meso*-substituted porphyrin, in 1979. Unlike the elaborate methods for synthesis of naturally occurring porphyrins, which bear substituents at most if not all of the β-pyrrole substituents, the method of synthesis was quite simple and definitely suitable for a young graduate student: reaction of pyrrole and an aryl aldehyde in refluxing propionic acid (bp 141 °C) in an open beaker for 30 min (Scheme 1). After slight cooling, filtration of the deep dark mixture yielded the porphyrin as glittering purple crystals. This one-flask synthetic method of Adler and Longo was developed in the 1960s, which in turn was a practical version of the even higher temperature, sealed-bomb method of Rothemund from the 1940s.[1,2] Of course, such a one-flask reaction could only afford a highly symmetric porphyrin, in this case containing an aryl substituent (derived from the aldehyde unit) at each of the four *meso* positions. Extension of the method to make porphyrins that bear two types of substituents relied on an early and widely practiced form of combinatorial chemistry, where condensation of two aldehydes (A-CHO and B-CHO) and pyrrole afforded a statistical mixture of six porphyrins (bearing substituents A_4, A_3B, *cis*-A_2B_2, *trans*-A_2B_2, AB_3, and B_4). The ease of carrying out the reaction was offset by the laborious chromatography often required to purify one of the target porphyrins from the mixture.

SCHEME 1. A Synthetic Porphyrin with Four Identical meso Substituents (Top) Compared with a Naturally Occurring β-Substituted Porphyrin (Bottom)



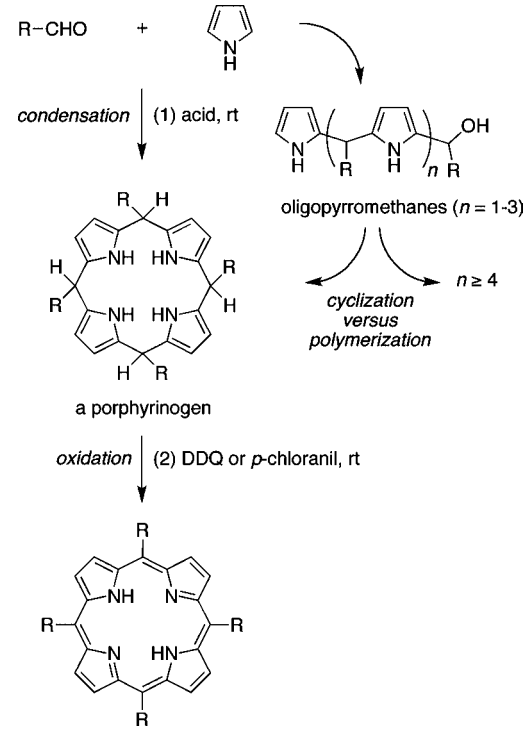
a meso-substituted porphyrin



protoporphyrin IX
(precursor to heme)

a β-substituted porphyrin

SCHEME 2. Two-Step, One-Flask Room-Temperature Synthesis of Porphyrins



The Adler–Longo method thus presented two significant limitations: (1) harsh reaction conditions limiting the scope of substituents (and often the yields) and (2) lack of any rational access to porphyrins bearing two to four distinct *meso* substituents. Such methods were insufficient to unlock the tremendous promise of *meso*-substituted porphyrins for use as building blocks in materials chemistry and as tailorable surrogates for naturally occurring porphyrins.

In the early 1980s, we developed a two-step, one-flask reaction strategy to overcome the first limitation (forcing conditions) of the prior methods. The approach entailed (1) acid-catalyzed condensation of an aldehyde and pyrrole to form a porphyrinogen and (2) addition of an oxidant to carry out the $6e^-/6H^+$ oxidative dehydrogenation of the porphyrinogen and thereby form the porphyrin (Scheme 2).[1,2] Mild conditions identified for the entire process included reaction at room temperature in a chlorinated solvent containing an acid such as trifluoroacetic acid (TFA) or $BF_3 \cdot O(Et)_2$, use of an organic-soluble oxidant such as *p*-chloranil or 2,3-dichloro-5,6-dicyano-

1,4-benzoquinone (DDQ), and somewhat dilute concentrations of aldehyde and pyrrole (0.01 M each) to appropriately balance the competition between oligomerization of pyrromethanes and cyclization to give a porphyrinogen. Studies of this reaction over the ensuing 20 years examined the interplay of acid catalysts, reaction conditions, reactant concentrations, and aldehyde structure on the course of the reaction, particularly the nature of the oligomer composition (identified by mass spectrometry) and the reversibility of macrocycle formation.[3−6]

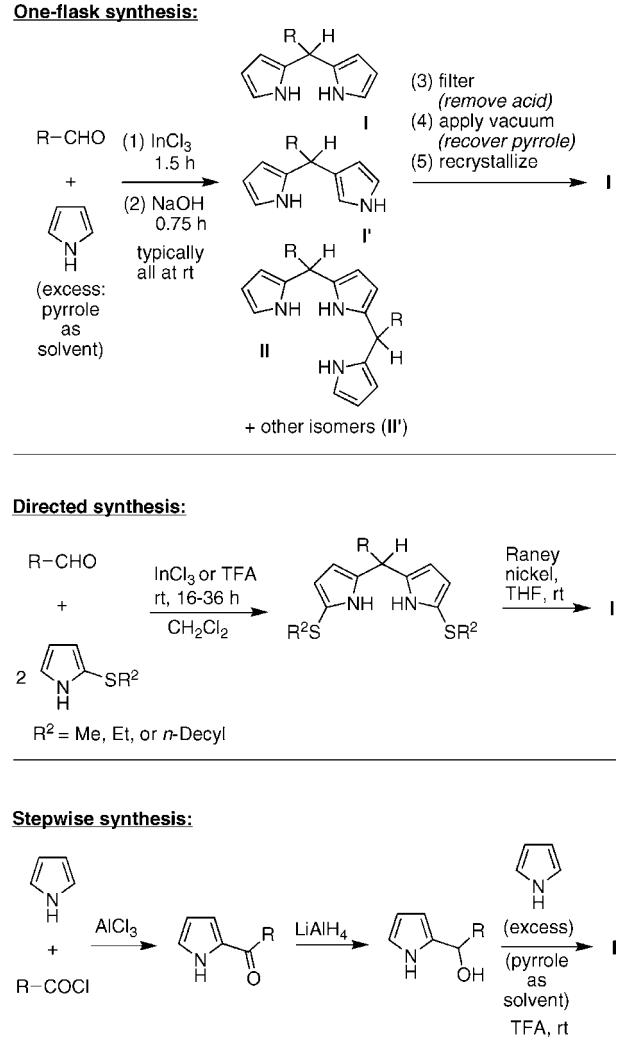
In the late 1980s, we embarked on a program to overcome the second limitation, namely, the inability to readily prepare unsymmetrically *meso*-substituted porphyrins. Our initial goals focused on rational routes (i.e., obtain the desired target without reliance on statistical reactions), use of mild conditions, and broad scope. Over time, our objectives grew to encompass processes that could be implemented with limited or no chromatography. The development of these directed routes was supported by the insights and methods that emerged from ongoing studies of the aldehyde plus pyrrole condensation. An overview of these routes for constructing porphyrin macrocycles bearing up to four distinct *meso* substituents constitutes the focus of this Account.

Dipyrromethanes

Directed routes for constructing porphyrins with distinct patterns of *meso* substituents typically begin with dipyrromethanes. As of 1990, almost all known dipyrromethanes contained β-pyrrole substituents and lacked *meso* substituents, which wrongly fueled our suspicion that β-unsubstituted, *meso*-substituted dipyrromethanes might be rather labile, despite their expected intermediacy in the pyrrole plus aldehyde condensation. In this regard, the challenge to obtaining a dipyrromethane in isolable quantities from the reaction of an aldehyde and pyrrole lies in stopping oligomerization at the dipyrromethane stage.

The method that we developed is quite simple.[7−9] A one-flask synthesis is carried out with pyrrole as the solvent, to which acid (TFA or $BF_3 \cdot O(Et)_2$ or $InCl_3$) is added at room temperature. The high pyrrole/aldehyde ratio (25:1 to 100:1) suppresses oligomerization beyond the dipyrromethane stage. The dipyrromethane can be purified by chromatography (small-scale),[7] by sublimation (gram quantities),[8] or by a process that is scalable to >100 g.[9] In the latter process, the acid ($InCl_3$) is precipitated and removed by filtration, the pyrrole is removed by vacuum, and the resulting crude solid is recrystallized (Scheme 3). The dipyrromethanes proved to be quite

SCHEME 3. Routes to *meso*-Substituted Dipyrromethanes



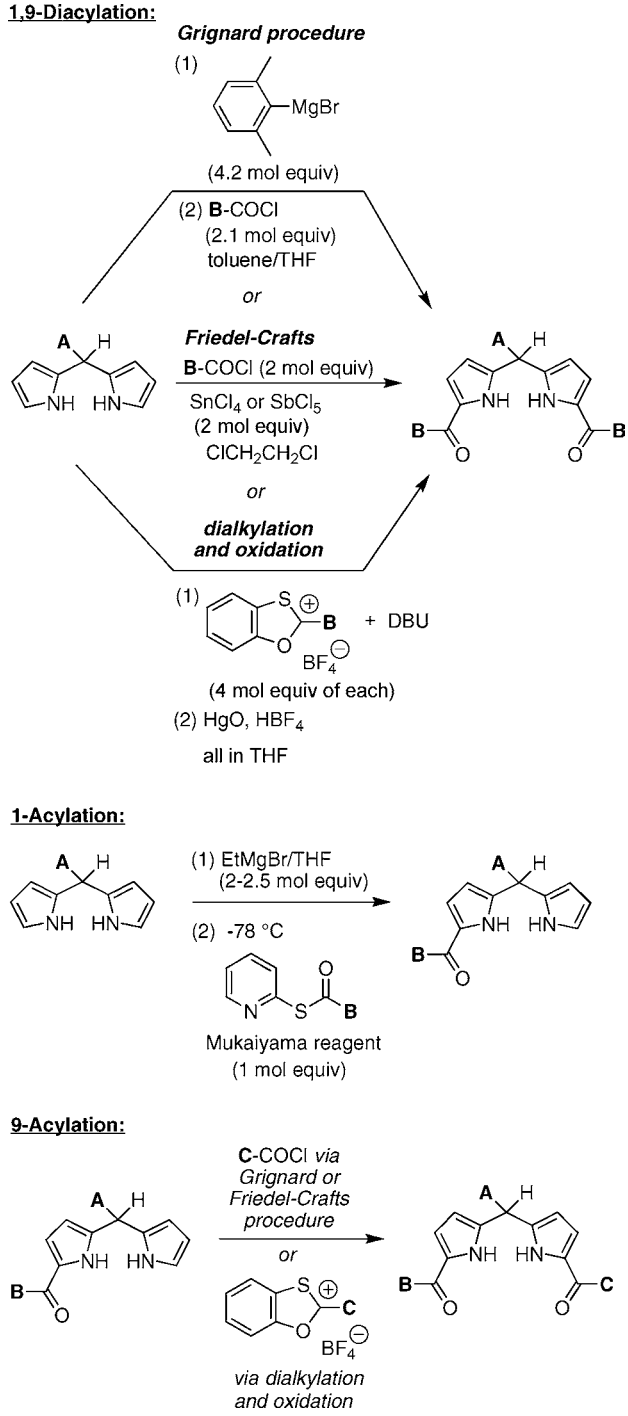
stable compounds, and hundreds have since been prepared from diverse aldehydes.

Alternative routes to dipyrromethanes are shown in Scheme 3. A directed synthesis employs reaction of a stoichiometric amount of an α-alkylthiopyrrole with an aldehyde.[10] The α-alkylthio group directs reaction to the α′-position, blocks further oligomerization, and can be removed by Raney nickel. The α-alkylthiopyrrole is obtained from acyclic precursors, which enables isotopic labeling of specific sites in the pyrrole.[11] A stepwise synthesis begins with an α-acylpyrrole, which upon reduction is treated with excess pyrrole.[7,12] This route enables use of substituted pyrroles. For most applications, the one-flask method is far preferred owing to its expediency and scalability.

Acylation of Dipyrromethanes

The selective introduction of acyl groups at the α-pyrrolic positions of dipyrromethanes is essential for the rational synthe-

SCHEME 4. Methods for Acylation of Dipyrromethanes at the 1- And 9-Positions



sis of porphyrins bearing distinct *meso* substituents. While numerous methods are available for α-acylation of pyrroles, dipyrromethanes present challenges owing to susceptibility to acidolysis as well as the equivalent, independent reactivity of the two α-pyrrolic positions. The reactions that we developed are shown in Scheme 4. A key theme is use of the dipyrromethane analogue of the pyrrole-Grignard reagent:

(1) 1,9-Diacylation. Treatment of a dipyrromethane with 4−5 mol equiv of RMgBr (e.g., R = Et[13] or *ortho*-hindered aryl[14]) followed by an acid chloride afforded the corresponding 1,9-diacyldipyrromethane (a B_2A unit).[12−16] Alternative methods entailed Friedel−Crafts acylation with an acid chloride and a Lewis acid, and alkylation with a benzoxathiolium tetrafluoroborate reagent [prepared from 2-mercaptophenol, an acid chloride bearing the substituent of interest, and $HBF_4 \cdot O(Et)_2$] in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) followed by oxidative hydrolysis.[13,17] Such alternatives may circumvent some limitations in scope imposed by use of Grignard reagents.

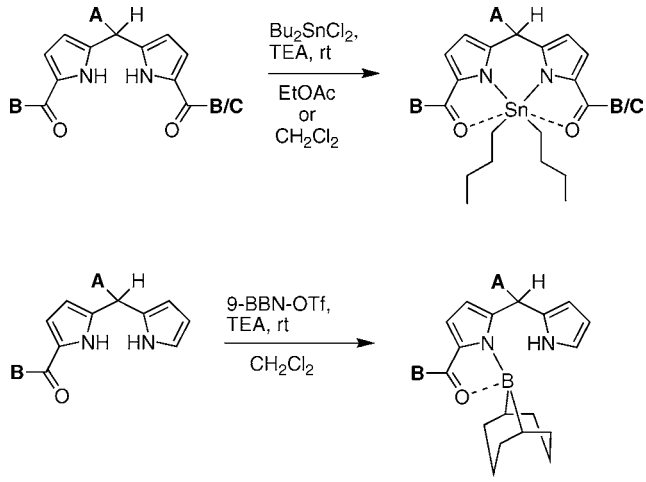
(2) 1-Acylation. Treatment of a dipyrromethane with EtMgBr (2−2.5 mol equiv) followed by a Mukaiyama reagent (obtained from 2-mercaptopyridine and an acid chloride)[16,18] at low temperature gave the 1-acyldipyrromethane (a BA unit). The reaction is relatively selective for monoacylation perhaps because acylation of the first basic pyrrole liberates an equivalent of HX, which is consumed by the second basic pyrrole.[16,18]

(3) 9-Acylation. The 1-acyldipyrromethane could be reacted via all the methods identified for 1,9-diacylation to give the 1-acyl-9-acyldipyrromethane (a BAC unit). The Grignard route has been used most extensively (albeit with excess EtMgBr and acid chloride) and affords yields of 60−70%.[15,16]

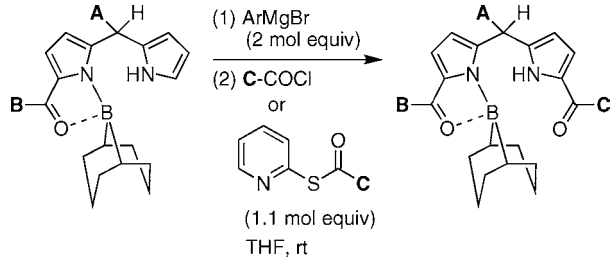
The utility of these methods was offset by two factors. First, none of the acylations proceeded quantitatively, requiring separation of dipyrromethane and mono/diacyldipyrromethane mixtures. Second, purification was cumbersome because the acyldipyrromethanes were typically obtained as solid foams unamenable to crystallization, and on chromatography, the acyldipyrromethanes typically streaked the length of the column. Hence we turned to complexation aides to facilitate isolation.

Treatment of the crude diacylation mixture with dibutyltin dichloride selectively gives the 1,9-diacyldipyrromethane−dibutyltin complex (a previously known structure wherein the tin is coordinated by both acyl oxygen atoms); by contrast, neither the 1-acyldipyrromethane nor the dipyrromethane forms a stable complex. The 1,9-diacyldipyrromethane−dibutyltin complex is relatively nonpolar and hence readily isolated.[13,14] Buoyed by this success, we screened a variety of possible complexation aides for the 1-acyldipyrromethane. Eventually we found that dialkylboron complexes served quite well, with either dibutylboron triflate or 9-borabicyclo[3.3.1]-nonyl (9-BBN) triflate yielding a crystalline complex.[19] Even

SCHEME 5. Complexation Aides for Acyldipyrromethanes



SCHEME 6. Dialkylboron Protective Group during 9-Acylation



when not crystalline, the dialkylboron or dibutyltin complex was relatively nonpolar and readily isolable via short column chromatography (Scheme 5).

A further advantage of the 1-acyldipyrromethane–dialkylboron complex is its amenability to 9-acylation.[16] The dialkylboron unit protects the acylpyrrole motif, and treatment with a stoichiometric amount of a bulky Grignard reagent (e.g., mesitylmagnesium bromide) followed by an acid chloride or Mukaiyama reagent gives the dialkylboron-protected 1,9-diacyldipyrromethane in 70–90% yield. All of the complexes shown in Schemes 5 and 6 could be decomplexed (via acid or alcohol) or used directly in reactions leading to porphyrins.[13,16,19]

"2 + 2" Route to ABCD-Porphyrins

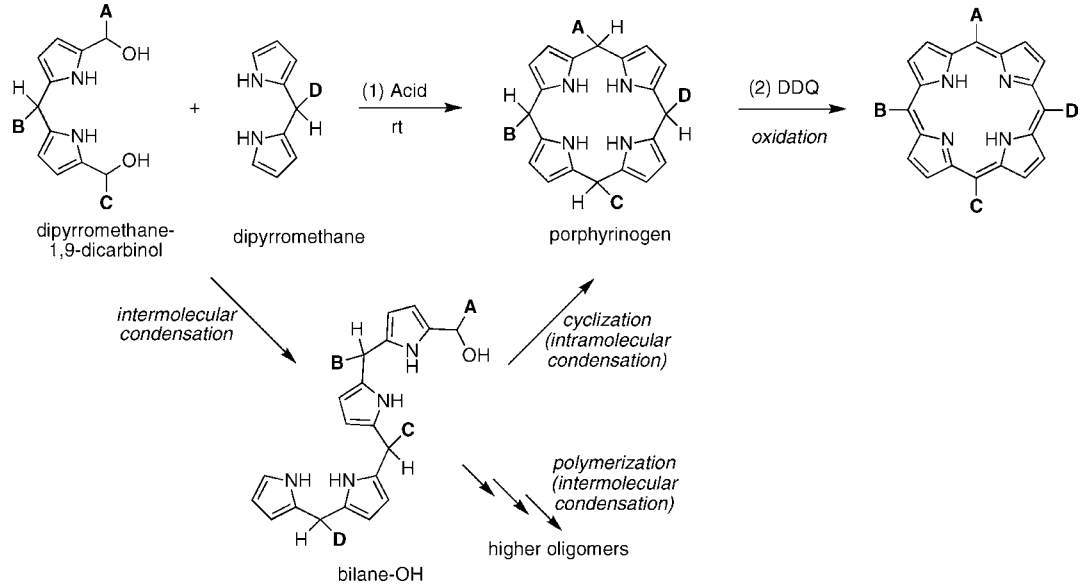
With 1,9-diacyldipyrromethanes in hand, the synthesis of an ABCD-porphyrin was achieved by reduction (with $NaBH_4$ in tetrahydrofuran (THF)/methanol)[14,15,17] to the highly reactive dipyrromethane-dicarbinol followed by condensation with a dipyrromethane and subsequent oxidation (Scheme 7). Our earliest attempts at such a condensation, using TFA or $BF_3 \cdot O(Et)_2$ in CH_2Cl_2, the standard conditions of the aldehyde plus pyrrole condensation, resulted in considerable scrambling of the position and type of substituents about the porphyrin core.[17] While such catalysis conditions may afford a desirable degree of reversibility of pyrromethane assembly/disassembly in the aldehyde plus pyrrole reaction, irreversible reaction is required with dipyrromethanes to avoid scrambling. The mechanism for reversible reaction (and hence scrambling) entails protonation of the α-position of pyrrole in a pyrromethane or porphyrinogen species, displacement of the adjacent pyrrole-α-methyl carbenium ion, and (undesired) recombination of the resulting fragments.[20] Scrambling in porphyrin syntheses must be assiduously avoided given the practical difficulty of separating the resulting mixtures.[15]

The first successful nonscrambling conditions emerged from a systematic study and entailed TFA (30 mM) in acetonitrile at room temperature, which enabled the synthesis of a wide variety of ABCD-porphyrins.[15] We subsequently observed that condensations with dipyrromethane-carbinols can be successfully catalyzed by Lewis acids that are ineffective in the more demanding aldehyde plus pyrrole/dipyrromethane condensations. A survey identified a handful of mild Lewis acids [$Yb(OTf)_3$, $Dy(OTf)_3$, $Sc(OTf)_3$, $InCl_3$] that provide reaction in CH_2Cl_2 with acceptable yields and no detectable scrambling.[21] Further studies found that inclusion of 2,6-di-*tert*-butylpyridine as a proton scavenger was effective for very acid-labile substrates.[22] The combination of a mild Lewis acid and a Brønsted acid scavenger has become a mainstay for condensations with dipyrromethane-carbinols.[23]

Two further improvements were made to facilitate larger scale syntheses. First, acid catalysis conditions were identified for carrying out the reaction at 25 mM (e.g., 3.2 mM $Sc(OTf)_3$ and 32 mM 2,6-di-*tert*-butylpyridine in CH_2Cl_2 for 15 min), with only slight decline in yield from the most effective concentration (2.5 mM reactants).[23] A challenge to use of higher reactant concentrations stems from the well-known concentration dependence of the competition of cyclization versus polymerization at the bilane juncture (Scheme 7),[24] which resembles that of the pyrrole plus aldehyde condensation (Scheme 2).[3,4] Perhaps less appreciated is that higher concentrations typically require an increased concentration of acid, whereupon the risk of acid-induced scrambling also is increased. Second, a streamlined implementation of a three-step, one-flask transformation entailed (i) condensation, (ii) aerobic oxidation using an iron(III) phthalocyanine and air at room temperature, and (iii) metal insertion (with Mg, Ni, Cu, Zn, Pd) whereupon the metalloporphyrin was isolated.[23] Typical yields are 15–20%. In summary, the entire synthesis can be carried out with little or no chromatography to give ~1 g quantities of the target ABCD-porphyrin.

A tactical consideration concerns the order of introduction of substituents.[15] For the "2 + 2" condensation of a dipyr-

SCHEME 7. Final Step (A One-Flask Transformation) in the "2 + 2" Route to ABCD-Porphyrins



romethane-dicarbinol (bearing A, B, and C substituents) and a dipyrromethane (bearing the D substituent), the D substituent only encounters conditions for mild acid catalysis (for dipyrromethane formation and porphyrin formation) and mild oxidation (porphyrin formation), whereas each of the ABC substituents also encounters the conditions for acylation and ketone reduction. The acylation typically entails formation of the pyrrole-Grignard species (via EtMgBr or MesMgBr) whereas the reduction entails vigorous reaction upon addition of $NaBH_4$ to THF/methanol. Thus, a very broad range of substituents can be incorporated at the D site versus a more limited range at sites A–C. A representative set of D substituents (drawn from our own work) includes **1**,[14] **2**,[15,25–27] **3**,[28] **4**–**7**,[15] **8**,[29] **9**,[30] **10**,[25] **11**,[15] **12**,[31] **13**,[15] **14**,[15] **15**,[32] **16**,[33] **17**,[33] **18**,[27,31,34] **19**,[35] **20**,[36] **21**,[15,30,31] **22**,[37] **23**,[38] **24**,[38] **25**,[27] **26**–**28**,[22] **29**,[39,40] **30**,[39] **31**,[28] **32**,[28] **33**–**35**,[33] **36**,[41] **37**,[32] **38**,[42] **39**,[43] **40**,[31] **41**,[15] **42**,[44] **43**,[31] **44**,[45] and **45**[29,33,46] (Scheme 8). The reaction also could be extended to the use of core-modified substrates (where N is replaced with O, S, etc.).[12] On the other hand, the use of alkyl or no substituent at the carbinol sites typically results in low levels of scrambling,[24] basic heterocycles at any site tend to interfere with acid catalysis resulting in low yields or scrambling,[24,47] and bulky acyl substituents resist reduction to the carbinol.[15]

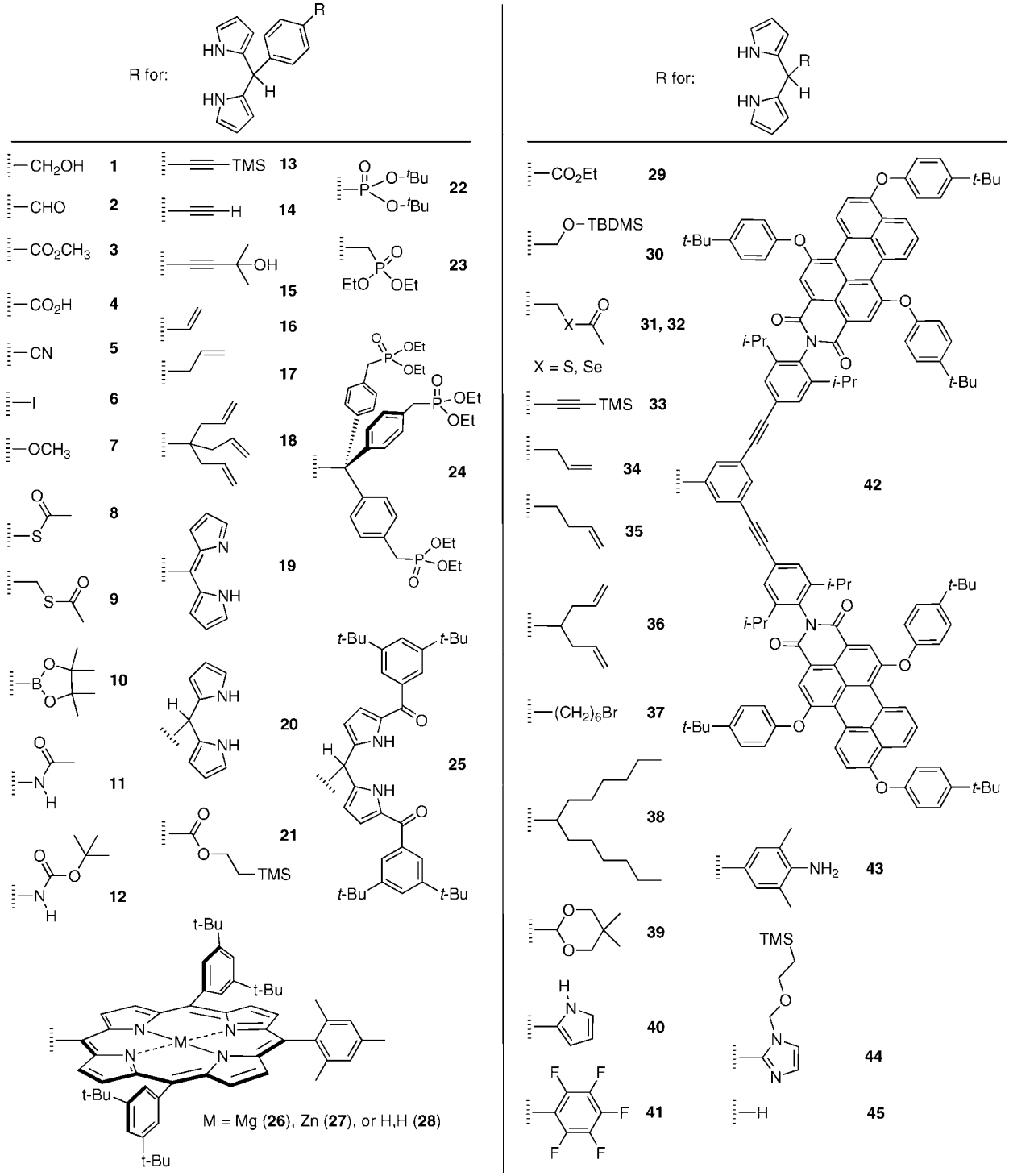
Routes to *trans*-Substituted Porphyrins

For many applications, the target porphyrin contains substituents at *trans*-positions. A handful of routes has been devised to fulfill this objective (Scheme 9).

(I) The reaction of a dipyrromethane with an aldehyde provides the simplest route to *trans*-A_2B_2-porphyrins, at least in principle, and this route predates the development of the "2 + 2" route to ABCD-porphyrins.[1,2] In practice, the acid-catalysis conditions required for the condensation introduce the possibility of scrambling. The susceptibility to scrambling depends largely on the nature of the *meso* substituent in the dipyrromethane.[48,49] An *ortho*-aryl-substituted *meso* group (e.g., A = mesityl or C_6F_5) gives the *trans*-A_2B_2-porphyrin with hardly any scrambling under reaction conditions similar to those of the aldehyde plus pyrrole reaction (17.8 mM TFA in CH_2Cl_2). When A = H, the same conditions cleanly give the *trans*-B_2-porphyrin. On the other hand, when A is nonbulky aryl (e.g., phenyl) or alkyl, a mixture of porphyrins inevitably forms (despite an extensive search for nonscrambling acid catalysis conditions).[48] Given that scrambling readily occurs when A = phenyl and B = mesityl, the diminished scrambling in the case of A = mesityl and B = phenyl must stem from a kinetic rather than thermodynamic impediment in acidolysis of the pyrromethane species.[49] The lack of generality of this method prompted invention of alternative methods, particularly the ability to preinstall one or both B-substituents at the α-positions of an A-dipyrromethane prior to condensation (as in route II below and the "2 + 2" route above).

(II) The self-condensation of an AB-substituted dipyrromethane-monocarbinol (derived from the 1-acyldipyrromethane by reduction) under the same conditions developed for the "2 + 2" route affords the corresponding *trans*-A_2B_2-porphyrin.[18] The chief attraction of this method versus the condensation of a dipyrromethane and

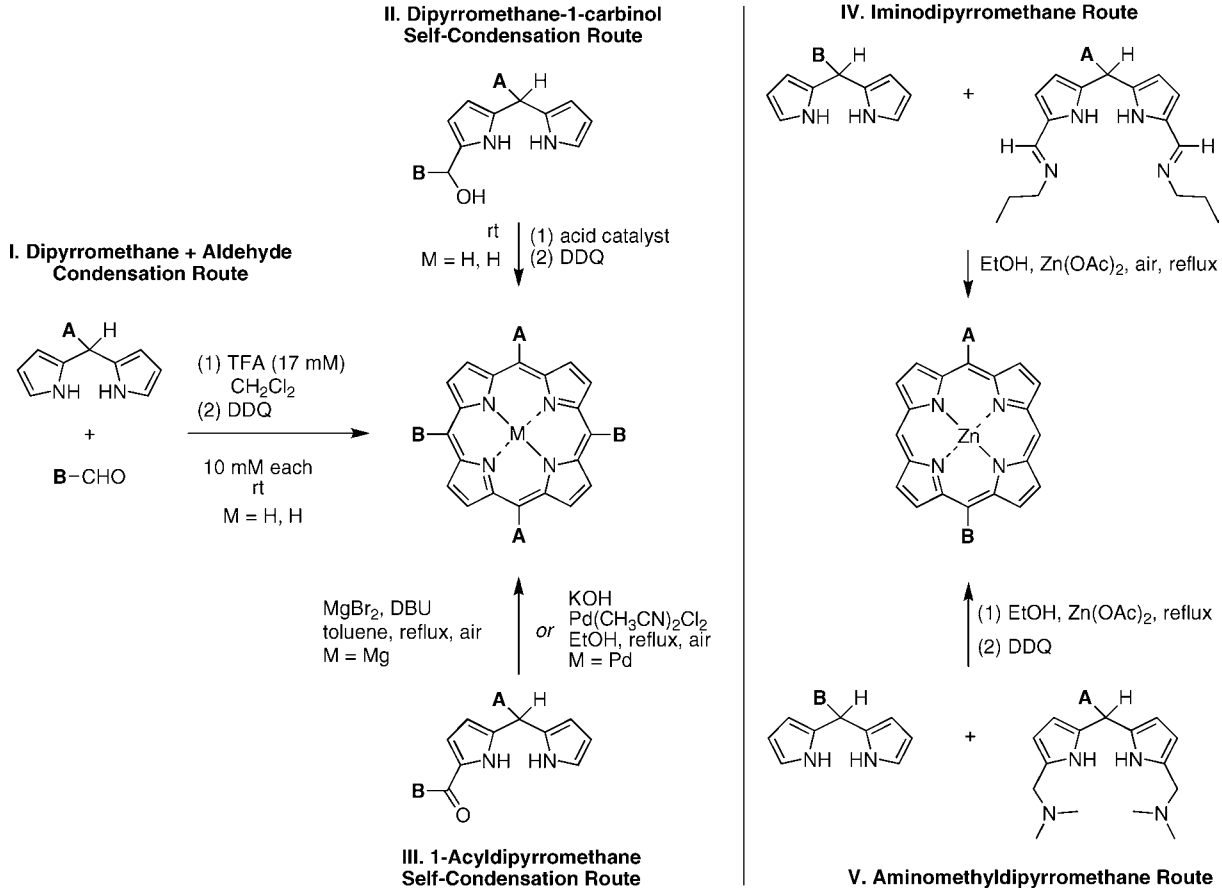
SCHEME 8. Representative "D Substituents" Incorporated via the "2 + 2" Route



an aldehyde is the ability to use milder acid catalysis, which is accompanied by a lack of scrambling for a wide variety of substituents. However, the limitations characteristic of reactions of dipyrromethane-carbinols, as observed in the "2 + 2" route, still remain.

(III) During our search for complexation aides for 1-acyldipyrromethanes, we examined various palladium reagents. To our surprise, the treatment of a 1-acyldipyrromethane with PdX_2 in hot basic ethanol did not stop at the complex but proceeded to give the palladium(II) porphyrin in yields near 50%.[50] This synthesis was concise but limited given that (i) only copper and nickel could be used in place of palladium and (ii) such metals could be removed from the porphyrin only with great difficulty. Eventually, we turned

SCHEME 9. Complementary Routes to *trans*-Substituted Porphyrins



to noncoordinating reaction conditions analogous to those employed for magnesiation of free-base porphyrins.[51] Thus, replacing KOH, ethanol, and PdX_2 with DBU, toluene, and $MgBr_2$ readily yielded the magnesium(II) *trans*-A_2B_2-porphyrin in ~60% yield.[52]

The self-condensation under $MgBr_2$/DBU/toluene has several attractive features: (1) Magnesium(II) porphyrins are readily demetalated by treatment with mild acid whereupon other metalloporphyrins can be prepared. (2) The reaction is compatible with either A or B = basic heterocycles (e.g., pyridyl), which often cause failure or scrambling in acid-catalyzed condensations. (3) *trans*-B_2-porphyrins are readily prepared when A = H. (4) The reaction of 1-formyldipyrromethane (A = B = H) directly affords magnesium(II) porphine in 40% yield.[53] Access to multigram quantities of magnesium(II) porphine opens the door to derivatization of this core motif,[54] which provides a valuable complement to the processes described here where the *meso* substituents are built into the dipyrromethane precursors. (5) The reaction simplicity and modularity of the reactants makes it well suited for combinatorial chemistry applications.

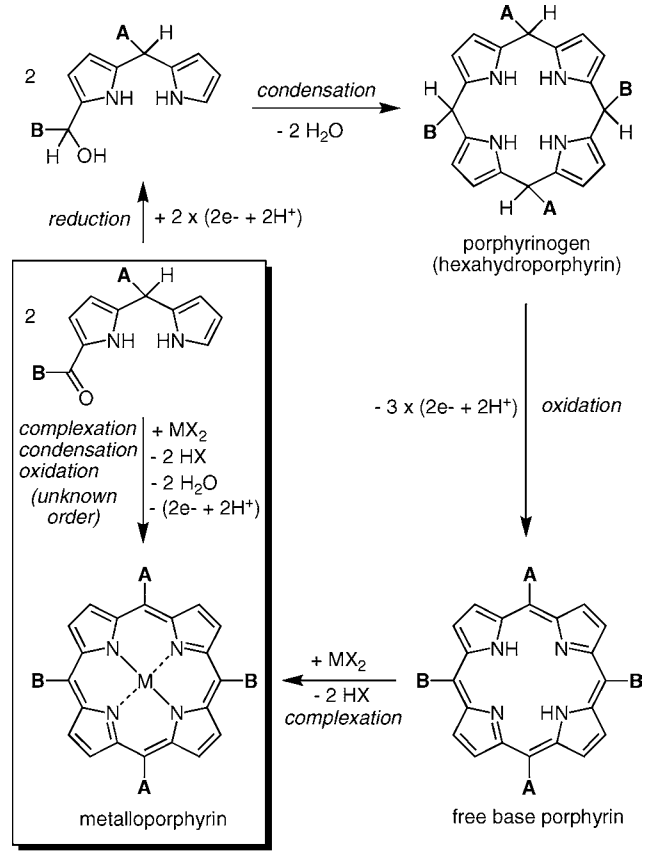
(IV) The ability to prepare sparsely substituted porphyrins, that is, those with fewer than four *meso* substituents, is attractive for a number of applications given the compact size of the resulting architecture. Porphyrins bearing only two *meso* substituents (*trans*-A_2-porphyrins or *trans*-B_2-porphyrins) are available via each of the routes I–III as well as the "2 + 2" route (by placement of the substituents at the carbinol sites), yet only the latter enables the synthesis of *trans*-AB-porphyrins. One new route to *trans*-AB-porphyrins entails formylation of a dipyrromethane, imination with propylamine, and reaction with a second dipyrromethane in refluxing ethanol containing zinc acetate. The reaction is compatible with aryl/aryl, aryl/alkyl, and aryl/H (i.e., A-porphyrins) substituents and proceeds in 30% yield without detectable scrambling.[55]

(V) A second route to *trans*-AB-porphyrins entails treatment of a dipyrromethane with Eschenmoser's reagent (*N,N*-dimethylmethyleneiminium iodide) at room temperature to give the 1,9-bis(*N,N*-dimethylaminomethyl)dipyrromethane. Condensation of the latter with a second dipyrromethane followed by oxidation with DDQ gives the

zinc(II) porphyrin. The reaction is compatible with substituent combinations such as alkyl/alkyl, aryl/alkyl, and alkyl/H (i.e., A-porphyrins), and proceeds in 5−20% yield without detectable scrambling.[56] Both routes IV and V have been exploited to prepare porphyrins bearing hydrophilic groups for use in aqueous media.[39,45,57−59]

The most surprising reaction among those shown in Scheme 9 is the self-condensation of a 1-acyldipyrromethane.[50,52,53] The conditions in some regard resemble the original Rothemund condensation of an aldehyde and pyrrole, which employed a basic solvent and metal acetate (e.g., collidine and zinc acetate),[2] albeit here the temperature is lower (78 or 110 versus >200 °C), the concentration is lower (0.1 versus >1 M), the yields are higher (up to 60% versus <5%), and the scope is profoundly broader. Little is known about the nature and order of specific steps; however, the efficiency of the reaction is thrown into sharp relief by comparison[50] with the route to *trans*-A_2B_2-porphyrins via a dipyrromethane-1-monocarbinol.[18] The direct reaction obviates the following separate steps of the dipyrromethane-1-carbinol process: (1) reduction of the acyldipyrromethane, (2) acid-catalyzed condensation, (3) oxidation of the porphyrinogen with an added quinone, and (4) metal insertion (Scheme 10). Regardless of mechanistic knowledge, the discovery of conditions wherein an α-acyldipyrromethane reacts to give the porphyrin provided a key pillar for the development of a fundamentally new route to porphyrins via α-acylbilanes.

SCHEME 10. The Self-Condensation of a 1-Acyldipyrromethane (In Box) Achieves in a One-Flask Process What Requires Four Distinct Steps via a Dipyrromethane-1-carbinol



Bilane Route to ABCD-Porphyrins

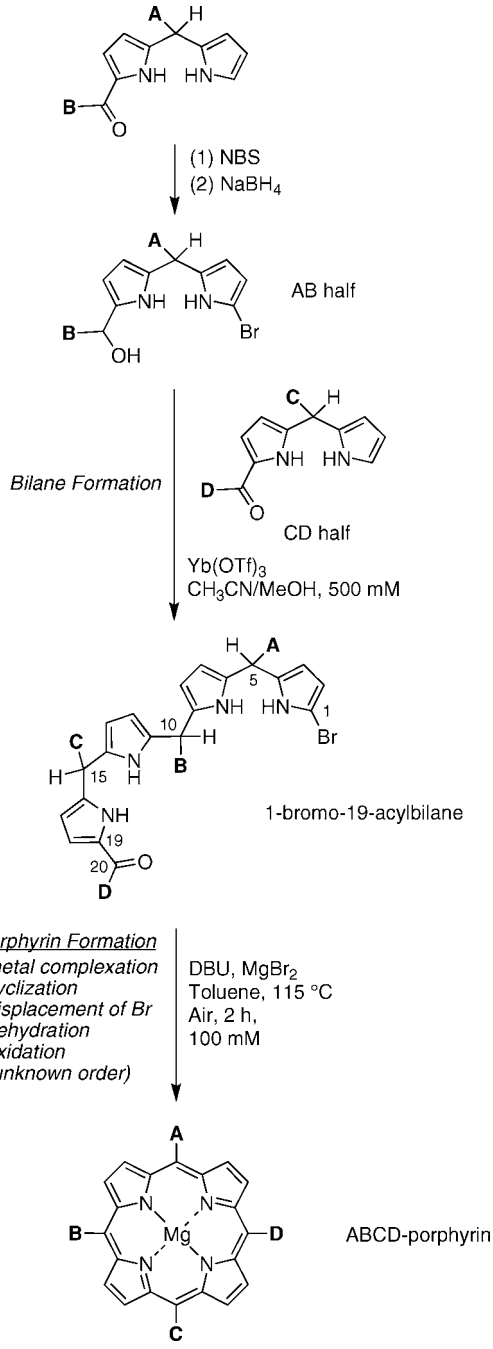
The "2 + 2" route to ABCD-porphyrins (Scheme 7) is quite versatile yet has a number of limitations, all of which stem from the macrocycle-forming step: (1) condensation in dilute solution (2.5−25 mM reactants), (2) yield of ≤20−30%, (3) acid catalysis affording scrambling with certain types of substituents (e.g., alkyl, heterocyclic, no substituent), and (4) an added chemical oxidant (DDQ) being employed for conversion of the porphyrinogen to the porphyrin. A new strategy for preparing ABCD-porphyrins was developed to overcome these limitations (Scheme 11). The route relies on two key reactions: (1) condensation of a 1-acyldipyrromethane (CD half) and a 9-protected dipyrromethane-1-carbinol (AB half, derived from a 9-protected 1-acyldipyrromethane) to give a 1-protected 19-acylbilane and (2) one-flask transformation of the 1-protected 19-acylbilane to give the corresponding metalloporphyrin.[60]

Identification of the α-pyrrole protecting group was essential, because this group must be easily introduced, block reaction of the dipyrromethane-1-carbinol during bilane formation, and be easily removed prior to or during cyclization of the bilane. Of several groups examined, a bromine atom proved most effective. Bromination of the 1-acyldipyrromethane is readily achieved, the 1-bromo-19-acylbilane is stable, and the bromine atom is replaced during the course of cyclization to give the porphyrin. The cyclization conditions entailed the 1-bromo-19-acylbilane at 100 mM in toluene containing DBU (10 mol equiv) and $MgBr_2$ (3 mol equiv) at 115 °C exposed to air for 2 h, which afforded the magnesium(II) porphyrin in 65% yield.

The bilane route to ABCD-porphyrins retains the desirable features of the "2 + 2" route yet has significant advantages: (i) high concentration (500 mM) for bilane formation in yields of up to 87%, (ii) 100 mM concentration under mildly basic conditions for the macrocycle-forming step in up to 60% yield, (iii) no added chemical oxidant (other than air, which apparently serves well in the 115 °C reaction), and (iv) magnesium(II) porphyrins as the products. In particular, the basic conditions provide complementary scope versus that of the "2 + 2" synthesis.

Exploration of the scope to date has focused on the nature of the 10- and 20-substituents, which are the sites of reac-

SCHEME 11. ABCD-Porphyrins via ABCD-Bilanes



tion during bilane and porphyrin formation, respectively.[61] Although bulky groups (e.g., mesityl) cannot be introduced at the 10- and 20-positions, the reaction otherwise appears to have broad scope, including compatibility with up to four alkyl groups and four aryl heterocyclic substituents (*o*-, *m*-, *p*-pyridyl). Such porphyrins are not available by the "2 + 2" route. Because the bilane route requires formation of two 1-acyldipyrromethanes, each A−D substituent must survive pyrrole-Grignard-mediated formation of the 1-acyldipyrromethane, the AB substituents must survive ketone reduction ($NaBH_4$ in THF/methanol) and electrophilic bromination, and all substituents must survive the final ring closure ($MgBr_2$ and DBU in toluene at 115 °C). By contrast, the "2 + 2" route enables introduction of a single sensitive "D" substituent but is less compatible with heterocycles and alkyl groups. An alternative to both the "2 + 2" and "bilane" routes relies on nucleophilic attack of (typically *meso*-unsubstituted) porphyrins followed by oxidation.[54]

The $MgBr_2$/DBU-mediated bilane cyclization and the related 1-acyldipyrromethane self-condensation were only developed recently, hence deeper insight concerning scope must await further studies. In both reactions, microwave irradiation provided superior yields with a number of reactants containing alkyl or heterocyclic substituents.[52,61] Much about the mechanism of macrocycle formation remains unknown, including the nature of the reactive end groups (acylpyrrole, bromopyrrole) upon cyclization, the possible role of metal templating (facilitating cyclization at reasonably high concentration), the course of oxidation prior to or following macrocycle formation, and in the bilane route, the relative reactivity of the different (up to eight) stereoisomeric forms of the acyclic 1-bromo-19-acylbilane. Gaining a deeper understanding of such mechanistic aspects may lead to milder reaction conditions and thereby further enlarge the scope of application. The accompanying synthetic entrée to *meso*-substituted bilanes, which have hardly been explored, may prove to be of comparable value.

Outlook

The research advances described herein largely conclude a program to develop workhorse methods for preparing synthetic porphyrins. The research, which has spanned 30 years and three universities, has been frequently painstaking, often surprising, and ultimately gratifying. The prior era of porphyrin synthesis, characterized by hammer-and-tong conditions, unwieldy statistical mixtures, laborious chromatography, and limited control over substituents and patterns, has now been supplanted with mild reaction conditions, rational routes that afford a single porphyrin, limited chromatography, and broad scope. The *meso*-substituted dipyrromethanes, acyldipyrromethanes, and dipyrromethane-carbinols also have found applications apart from use solely as precursors to porphyrins. Yet our goal "to achieve a scope of availability limited solely by imagination" may always remain elusive. Much remains to be done, particularly to redress the modest yields characteristic of porphyrin chemistry, to create direct routes to hydrophilic porphyrins without reliance on protecting groups, to understand the distinct reactivity (if any) of individual

stereoisomers in porphyrinogen formation, and to achieve increased simplicity of synthesis for pursuit of increased complexity of molecular architectures. Such advances likely will require invention of fundamentally new approaches as well as refinement of existing routes.

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Note Added after ASAP. This paper was posted to the web on October 28, 2009 with production errors concerning two citations. The revised version was published on November 2, 2009.

BIOGRAPHICAL INFORMATION

Jonathan S. Lindsey (b. 1956) grew up in Rockport, Indiana. He received a B.S. in Chemistry from Indiana University (1978) and a Ph.D. from Rockefeller University (1983), where he also did postdoctoral research. After 12 years at Carnegie Mellon University, he joined North Carolina State University (1996) as Glaxo Distinguished University Professor of Chemistry.

FOOTNOTES

*E-mail: jlindsey@ncsu.edu.

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