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Masked Imidazolyl−Dipyrromethanes in the Synthesis of Imidazole-Substituted Porphyrins

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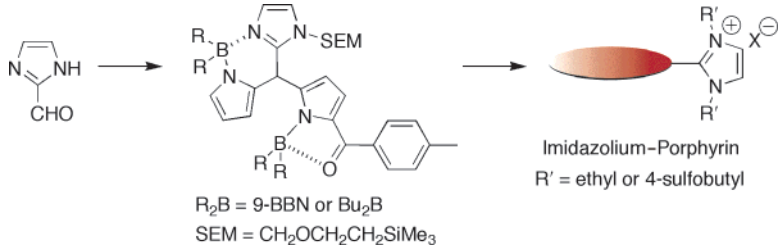

Imidazole-substituted metalloporphyrins are valuable for studies of self-assembly and for applications where water solubility is required. Rational syntheses of porphyrins bearing one or two imidazol-2-yl or imidazol-4-yl groups at the meso positions have been developed. The syntheses employ dipyrromethanes, 1-acyldipyrromethanes, and 1,9-diacyldipyrromethanes bearing an imidazole group at the 5-position. The polar, reactive imidazole unit was successfully masked by use of (1) the 2-(trimethylsilyl)ethoxymethyl (SEM) group at the imidazole pyrrolic nitrogen, and (2) a dialkylboron motif bound to the pyrrole of the dipyrromethane and coordinated to the imidazole imino nitrogen. The nonpolar nature of such doubly masked imidazolyl−dipyrromethanes facilitated handling. Selected masked dipyrromethanes were characterized by ^{11}B and ^{15}N NMR spectroscopy. Five distinct methods were examined to obtain *trans*-A_2B_2-, *trans*-AB_2C-, and *trans*-AB-porphyrins. Each porphyrin contained one or two SEM-protected imidazole units. The SEM group could be removed with TBAF or HCl. Two zinc(II) porphyrins and a palladium(II) porphyrin bearing a single imidazole moiety were prepared and subjected to alkylation (with ethyl iodide, 1,3-propane sultone, or 1,4-butane sultone) to give water-soluble imidazolium−porphyrins. This work establishes the foundation for the rational synthesis of a variety of porphyrins containing imidazole units.

Introduction

Imidazolyl−porphyrins are of widespread interest in materials chemistry and the life sciences. An early impetus for preparing imidazolyl−porphyrins stemmed from biomimicry studies of hemoglobin,[1] where an imidazole group occupies the apical site of an iron porphyrin. Since then, a large number of porphyrins have been prepared bearing imidazole units directly attached to the porphyrin macrocycle. In the latter cases, the imidazole group provides the basis for controlled self-assembly to give multimeric architectures for use in light-harvesting studies.[2] Alternatively, derivatization yields water-soluble imidazolium−porphyrins that have been investigated for superoxide dismutase behavior[3−5] and for DNA binding.[6] Despite these promising attributes, the methods for preparing imidazolyl porphyrins remain poorly developed.

Porphyrins bearing four *meso*-imidazolyl groups have been prepared by condensation of an imidazolecarboxaldehyde with pyrrole via the Adler method.[7,8] The similar reaction with

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inclusion of a second aldehyde has been used in a statistical synthesis of an A_3B-porphyrin bearing one imidazole group.[2,9] *trans*-AB-Porphyrins[10] and *trans*-AB_2C-porphyrins[11−18] have been prepared in a statistical approach by reaction of a dipyrromethane, an imidazolecarboxaldehyde, and a second aldehyde. The synthesis of *trans*-A_2B_2-porphyrins has been achieved in a rational manner by reaction of a dipyrromethane and an imidazolecarboxaldehyde.[19−22] However, the yields of *trans*-A_2B_2-porphyrins are typically quite low (in most cases ∼2%).[19,20]

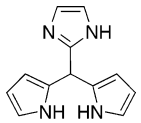
Several years ago we began studies aimed at the rational synthesis of porphyrins bearing one nitrogen heterocyclic group at the meso position. A given heterocyclic aldehyde (2-, 3-, 4-pyridinecarboxaldehyde, quinoline-3-carboxaldehyde, imidazole-2-carboxaldehyde, or uracil-5-carboxaldehyde) was condensed with pyrrole to afford the corresponding dipyrromethane, which upon reaction with a dipyrromethane−dicarbinol gave the respective A_3B-porphyrin bearing a single heterocyclic group. The yield of the imidazolyl−porphyrin was unacceptably low (1.5%), whereas the other porphyrins (e.g., pyridyl, quinolyl, uracil) were obtained in yields of 5−20%.[23] Similarly, the reaction of an imidazolyl−dipyrromethane and an aldehyde to give a *trans*-A_2B_2-porphyrin also proceeded in low yield (3%).[24]

The incorporation of the imidazole unit in porphyrins presents the following challenges: (1) imidazole-containing compounds are polar and streak upon chromatography, and (2) the imidazole nitrogens provide sites that function as a weak acid (pyrrolic nitrogen) and weak base or nucleophile (imino nitrogen). Indeed, the imidazole group in a dipyrromethane interferes with 1-acylation, thereby preventing access to dipyrromethane-1-carbinols (which are valuable precursors to *trans*-A_2B_2-porphyrins).[25,26] More generally, imidazolyl−dipyrromethanes afford low yields of porphyrin upon reaction with a dipyrromethane-1,9-dicarbinol. We considered that these problems might be mitigated by use of protecting groups for the imidazole nitrogens. In one of the earliest studies of the synthesis of imidazole-substituted A_4-porphyrins, Milgrom investigated benzyl or *p*-methoxybenzyl protecting groups for the imidazole pyrrolic nitrogen.[7] While promising, some difficulties were encountered in deprotecting the corresponding porphyrins. Despite the well-developed use of imidazole protecting groups in protein chemistry (to protect the imidazole moiety of histidine),[27] the use of imidazole protecting groups has not been further investigated in porphyrin chemistry.

In this paper, we report our studies aimed at developing improved methods for manipulating imidazolyl−dipyrromethanes. The SEM group has been examined to protect the imidazole pyrrolic nitrogen, whereas dialkylboron complexes of imidazolyl−dipyrromethanes were investigated for masking the imino nitrogen atom. The resulting masked dipyrromethanes and 1-acyldipyrromethanes have been used in five distinct routes to porphyrins. Taken together, this work provides a substantial improvement in methods for preparing porphyrins bearing one or two imidazole units.

Results and Discussion

1. Development of Masked Imidazol-2-yl Compounds for Use in Porphyrin Synthesis. A. Protecting the Imidazole Pyrrolic Nitrogen. 5-(Imidazol-2-yl)dipyrromethane (**1**) has been prepared by the solventless condensation of imidazole-2-carboxaldehyde in pyrrole under reflux.[23] However, the yield was low (14%), and **1** was incompatible with subsequent Grignard-mediated acylation of the dipyrromethane. The difficulties presented by the synthesis and derivatization of **1** prompted investigation of a variety of protecting group strategies.



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The imidazole protecting groups employed in peptide chemistry and related fields include trityl,[28] 2,4-dimethylpent-3-yloxycarbonyl,[29] 2-adamantyloxymethyl,[27] *p*-tosyl,[30] and SEM[31] groups. We considered the following in selecting a protecting group: (1) methods of introduction and removal, (2) compatibility with conditions employed in dipyrromethane preparation and derivatization, (3) compatibility with conditions employed in porphyrin formation, and (4) ease of purification via crystallization or chromatography. The *p*-tosyl group appeared attractive, but exploratory work indicated the *p*-tosyl-protected imidazole-2-carboxaldehyde required extensive chromatography for purification. Eventually we settled on use of the SEM group.

To mask the imidazole pyrrolic nitrogen with the SEM group,[31] we treated imidazole-2-carboxaldehyde with NaH followed by SEMCl, which afforded the SEM-protected aldehyde **2** in 82% yield (Scheme 1). The condensation of aldehyde **2** with excess pyrrole at room temperature in the presence of

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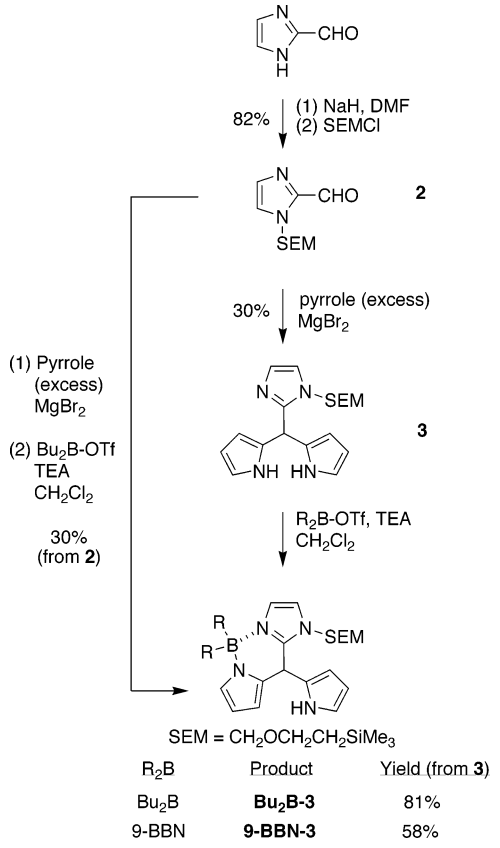
SCHEME 1



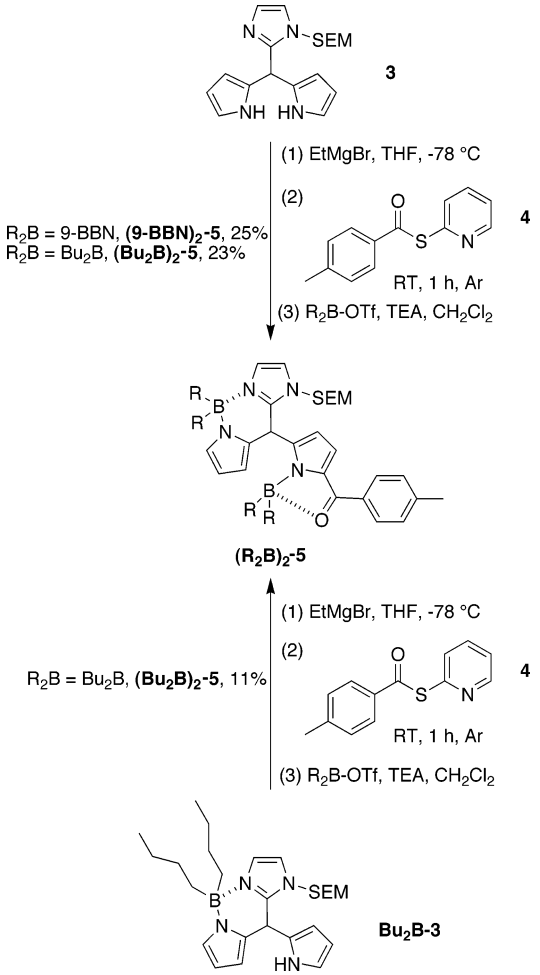
R_2B	Product	Yield (from **3**)
Bu_2B	**Bu_2B-3**	81%
9-BBN	**9-BBN-3**	58%

$MgBr_2$ (0.5 equiv)[32] afforded the protected imidazolyl−dipyrromethane **3** as a sticky solid in 30% yield following chromatography. The catalyst $InCl_3$ (0.3 equiv) also could be employed, but $MgBr_2$ afforded a cleaner reaction mixture.

B. Masking the Imidazole Imino Nitrogen by Dialkylboron Complexation. The imidazolyl−dipyrromethane **3** streaks upon chromatographic purification. Earlier we found that 1-acyldipyrromethanes, which also streak on chromatographic media, react with dialkylboron triflates to form dialkylboron complexes that are hydrophobic and are readily handled.[33] With the same objective of achieving a hydrophobic complex, we treated dipyrromethane **3** with excess Bu_2B-OTf, which afforded the dibutylboron complex **Bu_2B-3** as a viscous oil in 81% yield (Scheme 1). Similarly, treatment of **3** with 9-BBN-OTf afforded **9-BBN-3** as a dark red solid in 58% yield. In these complexes, the boron is presumably bonded to the pyrrole and coordinated to the imidazole imino nitrogen. Owing to both the dialkylboron complex and the SEM group, the two imidazole nitrogens are fully masked. As expected, **Bu_2B-3** and **9-BBN-3** proved to be of low polarity and chromatographed without streaking near the solvent front.

We also investigated dialkylboron complexation as a means of purifying the crude reaction mixture upon dipyrromethane formation. After the reaction of **2** and pyrrole in the presence of $MgBr_2$ (0.5 equiv), the crude reaction mixture was freed of pyrrole and then treated with TEA and Bu_2B-OTf (3 equiv), affording **Bu_2B-3** in 30% overall yield. The similar use of 9-BBN-OTf was unsuccessful. The streamlined synthesis provides ready access to **Bu_2B-3**.

SCHEME 2



The standard method for 1-acylation entails treatment of a dipyrromethane with EtMgBr followed by reaction with a 2-pyridyl thioester (Mukaiyama reagent). Application of this approach with dipyrromethane **3** and Mukaiyama reagent **4**[34] afforded a crude mixture of the 1-acyldipyrromethane. However, the resulting 1-acyldipyrromethane (**5**) was very polar and streaked extensively upon attempted chromatography. Treatment of the crude mixture with 9-BBN-OTf (2 equiv) afforded **(9-BBN)$_2$-5** as a nonpolar, crystalline solid in 25% yield (Scheme 2).

A similar synthesis using Bu_2B-OTf gave the dibutylboron complex **(Bu_2B)$_2$-5** in 23% yield, which also was nonpolar and readily isolated. An alternative route to **(Bu_2B)$_2$-5** from **3** entailed reversal of the order of acylation and dialkylboron complexation. Thus, a sample of the dibutylboron complex of **Bu_2B-3** was treated with EtMgBr (2 equiv) and Mukaiyama reagent **4** followed by TEA and Bu_2B-OTf (2 equiv). The desired bis(dibutylboron) complex **(Bu_2B)$_2$-5** was obtained in 11% yield (Scheme 2).

The dibutylboron complex **(9-BBN)$_2$-5** was characterized in detail. According to ^{1}H NMR spectroscopy, FAB-MS, and elemental analysis, the product contains two 9-BBN moieties. Confirmation of the structure was achieved by X-ray structural

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analysis (see Supporting Information). One 9-BBN unit is bound to the pyrrolic nitrogen atom and coordinated to the α-carbonyl moiety, forming a cyclic coplanar array of five atoms. The second 9-BBN unit is bound to the other pyrrolic nitrogen atom and coordinated to the pyridyl nitrogen of the imidazole unit, forming a cyclic array of six atoms. The C−O bond (1.302 Å) is longer than that in 2-benzoylpyrrole (1.234 Å),[35] suggesting some enolate character, whereas the C−C bond between the carbonyl carbon and the α-carbon of the acylpyrrole (1.404 Å) is significantly shorter than that in 2-benzoylpyrrole (1.446 Å),[35] suggesting partial multiple bond character. The B−N coordinate bond length (1.640 Å) is longer than the B−O coordinate bond length (1.557 Å). The presence of the three protecting groups effectively masks all polar and/or hydrogen-bonding sites and thereby renders the imidazolyl−dipyrromethane a rather hydrophobic complex.

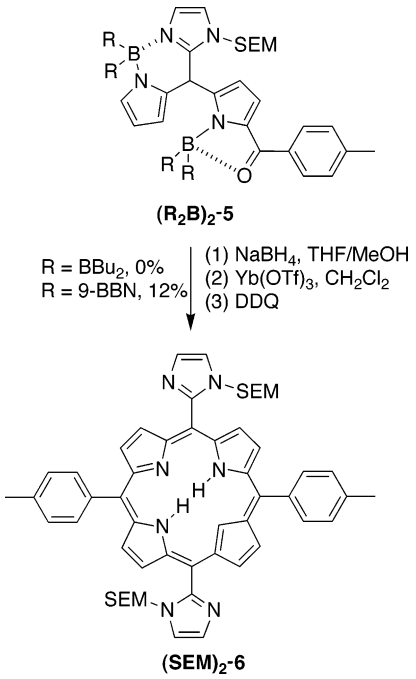
2. Synthesis of Imidazol-2-yl Porphyrins. A. *trans*-A_2B_2-Porphyrin Containing Two Imidazole Groups. Our goal was to employ the boron complex of 1-acyldipyrromethane **$(R_2B)_2$-5** in the synthesis of *trans*-A_2B_2 imidazolyl−porphyrin **$(SEM)_2$-6**. The established methods[33] for working with dialkylboron complexes of acyldipyrromethanes entail (1) decomplexation in refluxing 1-pentanol to give the acyldipyrromethane, which is then reduced with $NaBH_4$ to give the corresponding dipyrromethanecarbinol, or (2) direct reduction of the acyldipyrromethane−dialkylboron complex with $NaBH_4$, whereupon decomplexation occurs in situ yielding the dipyrromethanecarbinol.

Attempts to reduce dibutylboron-complex **$(Bu_2B)_2$-5** with $NaBH_4$, even with 100 equiv for ∼5 h, were not successful. Alternatively, **$(Bu_2B)_2$-5** was subjected to refluxing 1-pentanol for 7 h followed by reduction with $NaBH_4$, and the crude mixture was employed under conditions for porphyrin formation, but porphyrin **$(SEM)_2$-6** was not observed. However, reduction of **$(9\text{-BBN})_2$-5** with excess $NaBH_4$ (50 equiv) afforded the corresponding carbinol. The carbinol was then treated with Yb$(OTf)_3$ (3.2 mM) to carry out the self-condensation. Subsequent oxidation with DDQ afforded **$(SEM)_2$-6** in 12% yield (Scheme 3). Laser desorption mass spectrometry (LD-MS) analysis of the crude reaction mixture did not show any porphyrins derived from scrambling processes. TLC analysis of the product **$(SEM)_2$-6** showed two porphyrin components, as expected for the two atropisomers. After column chromatography, only the more polar atropisomer was isolated in pure form. In accord with the literature,[19] the more polar atropisomer was assigned the *cis*-configuration, where both SEM groups are positioned on the same plane of the porphyrin.

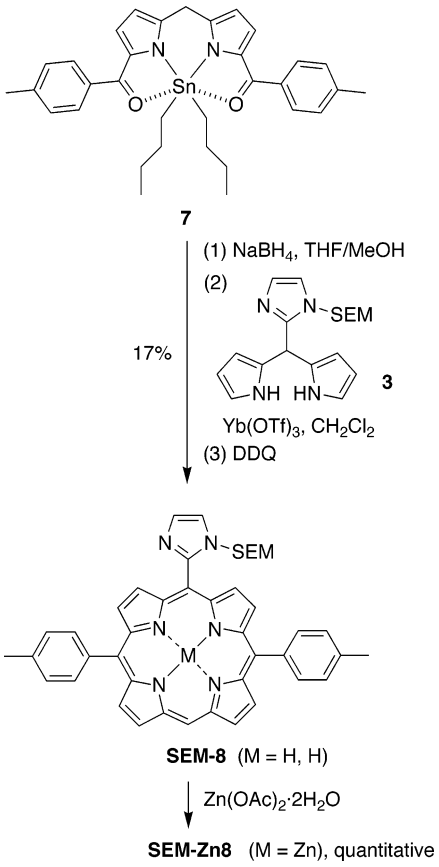
B. *trans*-AB_2C-Porphyrin Containing One Imidazole Group. A *trans*-AB_2C-porphyrin bearing one imidazole group was prepared as shown in Scheme 4. The tin complex of a 1,9-diacyldipyrromethane (**7**)[36] was reduced using $NaBH_4$ to give the corresponding dicarbinol, which was condensed with imidazol-2-yl dipyrromethane **3** in the presence of Yb$(OTf)_3$. The progress of the reaction was monitored by absorption spectroscopy. After 1 h, DDQ was added to give porphyrin **SEM-8** in 17% yield.

C. *trans*-AB-Porphyrins Containing One Imidazole Group. *trans*-AB-Porphyrins are valuable for life sciences applications owing to their compact size.[37] Two *trans*-AB-porphyrins were sought, one bearing an imidazole unit and a bioconjugatable handle, and a benchmark compound bearing an imidazole unit and a phenyl substituent. A new synthetic route to *trans*-AB-

SCHEME 3



SCHEME 4



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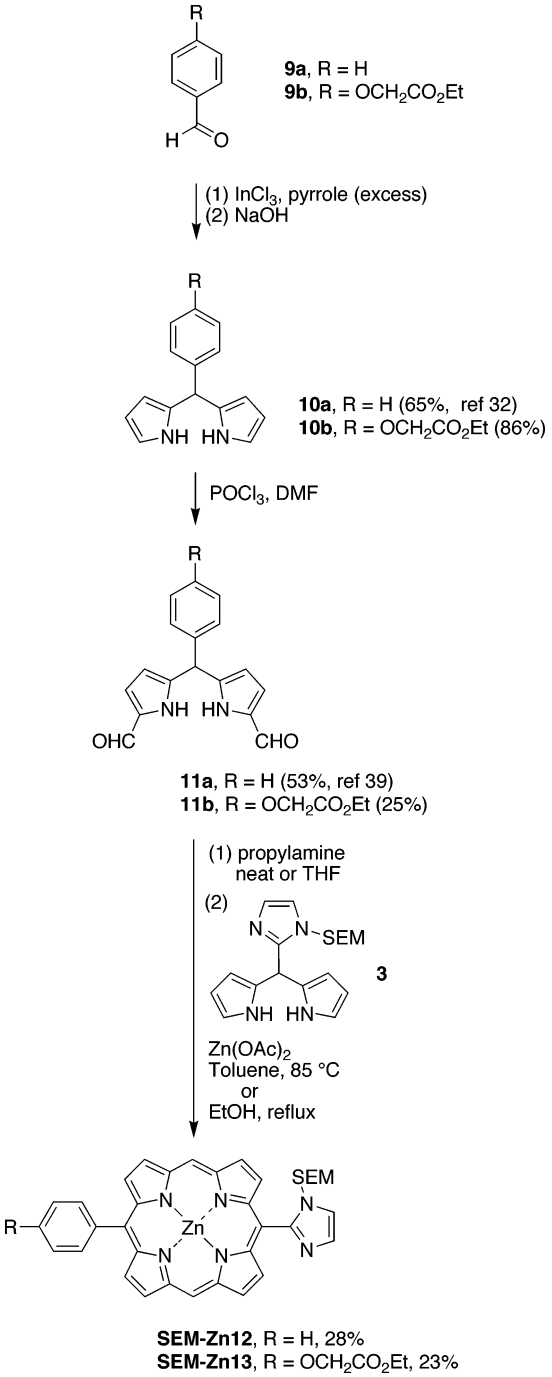
porphyrins relies on access to 1,9-diformyldipyrromethanes.[38] The required dipyrromethane **10a**[32] or **10b** (a known compound[39] with limited characterization data) was prepared by reaction of excess pyrrole with the respective aldehyde **9a** or **9b** (a known compound[39] with limited characterization data; see Supporting Information for a new preparation). Vilsmeier formylation of the dipyrromethanes gave **11a**[40] and **11b**. The reaction of 1,9-diformyldipyrromethane **11a** with *n*-propylamine in THF gave the corresponding bis(iminomethyl)dipyrromethane. The latter was combined with imidazolyl−dipyrromethane **3** in ethanol containing $Zn(OAc)_2$, which upon refluxing in the presence of air for 13 h afforded a mixture of porphyrin and chlorin species. Treatment of the mixture with DDQ (1.5 equiv) at room temperature converted chlorin to porphyrin, affording **SEM-Zn12** in 28% overall yield (Scheme 5). Similar treatment of 1,9-diformyldipyrromethane **11b** and **3** in hot toluene (85 °C) rather than refluxing ethanol gave porphyrin **SEM-Zn13** in 23% yield.

D. Palladium Porphyrin (*trans*-AB) Containing One Imidazole Group. Palladium porphyrins are valuable as phosphorescent markers[41] and for photodynamic therapy applications.[42] Following a new route to palladium porphyrins,[43] a mixture of 1,9-diformyldipyrromethane **11a**, dipyrromethane **3**, KOH, and $Pd(CH_3CN)_2Cl_2$ in EtOH was heated at reflux exposed to air for 2 h. Removal of the solvent followed by chromatography afforded the compact *trans*-AB palladium porphyrin **SEM-Pd12** in 32% yield (Scheme 6).

3. Development and Application of Masked Imidazol-4-yl Compounds in the Synthesis of Imidazol-4-yl Porphyrins. Treatment of 4(5)-imidazolecarboxaldehyde with NaH followed by SEMCl afforded a mixture of two isomers (1:1 ratio by ^{1}H NMR analysis) of the SEM-protected imidazolecarboxaldehyde **14** (**14a** and **14b**) in 88% overall yield (Scheme 7). The mixture of isomers of **14** was reacted with excess pyrrole in the presence of $InCl_3$. With 0.1 equiv of $InCl_3$, a mixture of a dipyrromethane and an unreacted aldehyde (by TLC and ^{1}H NMR analysis) was obtained, which was difficult to separate. In the presence of 1.0 equiv of $InCl_3$, a mixture of two isomers of the protected imidazolyl−dipyrromethane (**15a**, **15b**) was obtained. Two approaches were investigated to handle this mixture. (1) Chromatography afforded the less polar isomer (**15a**) in 16% yield upon small-scale reaction (on the basis of the 1:1 mixture of **14a**:**14b**), or 8% yield at larger scale. The chromatography was difficult because **15a** and **15b** each streaked and exhibited similar chromatographic retention factors. The more polar regioisomer was not isolated in pure form. (2) Alternatively, the mixture of **15a** and **15b** (from the dipyrromethane synthesis without purification) was treated with dibutylboron triflate in the presence of TEA. The dibutylboron complex **Bu_2B-15a** was obtained in 5% yield from aldehyde **14a** (two steps: dipyrromethane synthesis and boron complexation), whereas attempts to use 9-BBN-OTf resulted in decomposition of the corresponding 9-BBN complex upon chromatography.

SCHEME 5



Dipyrromethane **15a** was treated with EtMgBr followed by Mukaiyama reagent **4** in the standard approach for 1-acylation. The crude mixture was treated directly with TEA and 9-BBN-OTf[33] to give **(9-BBN)$_2$-16** in 34% yield (Scheme 8). Reduction of **(9-BBN)$_2$-16** with $NaBH_4$ gave the corresponding carbinol, which underwent self-condensation upon exposure to $Yb(OTf)_3$. Subsequent oxidation with DDQ afforded **(SEM)$_2$-17** in 15% yield. LD-MS analysis of the crude reaction mixture did not show the presence of any scrambled porphyrins. Alternatively, **Bu_2B-15a** was condensed with *p*-tolualdehyde in the presence of TFA to yield the bis(SEM-imidazolyl)porphyrin **(SEM)$_2$-17**, which requires in situ decomplexation of the dibutylboron

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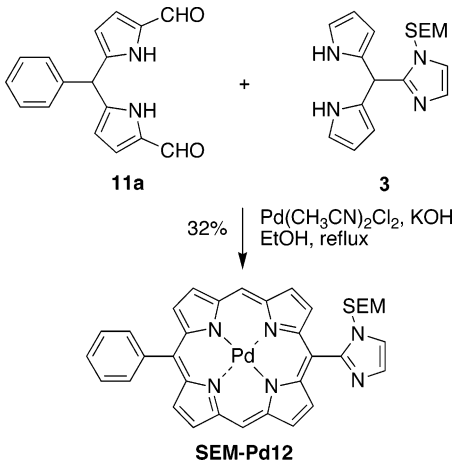
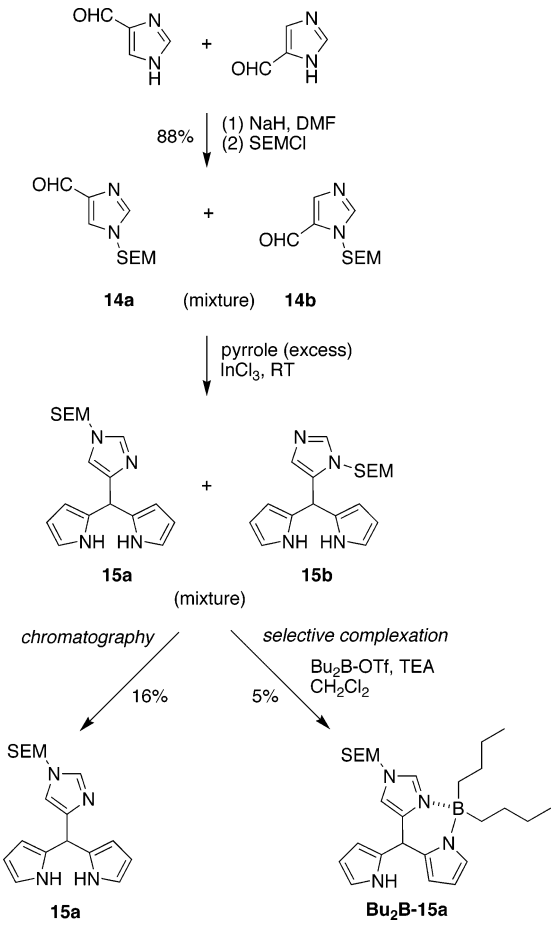
SCHEME 6



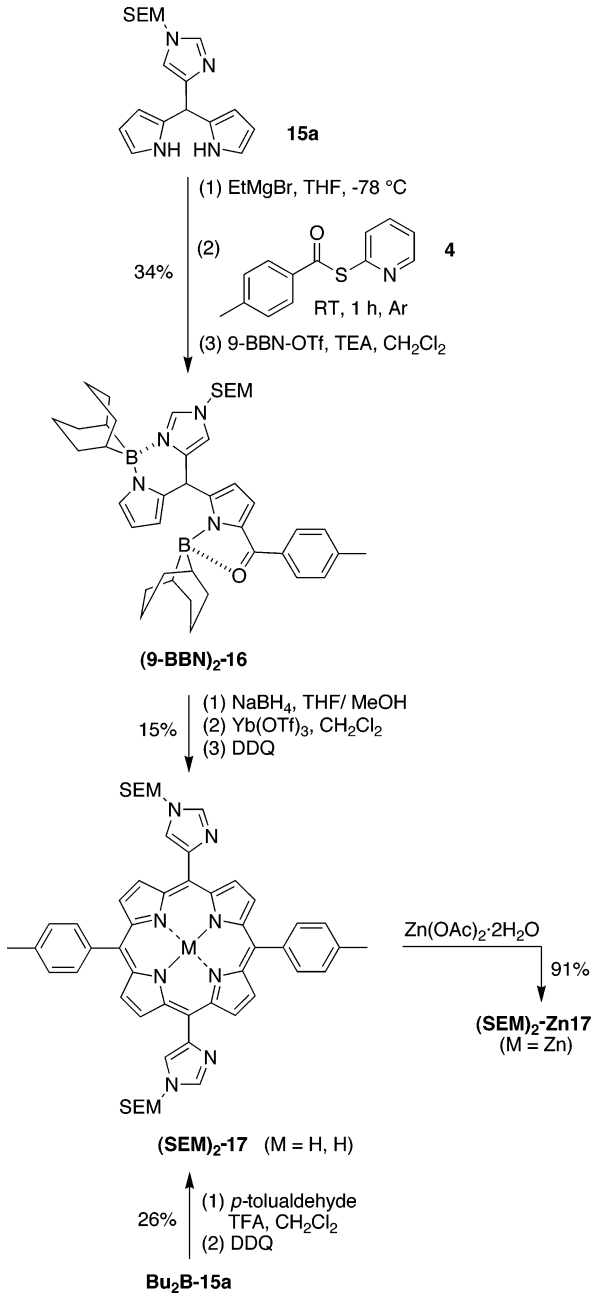
SCHEME 7



motif. A small amount of scrambling (Level 1)[44] was observed upon examination of the crude reaction mixture. The pure *trans*-A_2B_2-porphyrin **(SEM)$_2$-17** was isolated by chromatography in 26% yield.

4. ^{15}N NMR and ^{11}B NMR Spectroscopic Studies. Thompson and co-workers recently described the use of ^{15}N NMR spectroscopy for the identification of dipyrromethane compounds.[45] We utilized this powerful method to characterize the imidazolyl and pyrrolic nitrogen atoms in the various dipyrromethanes prepared herein. The results are summarized in Table 1. The assignments are summarized in the Supporting Information.

SCHEME 8



Proton-coupled gHMBC (gradient heteronuclear multiple bond correlation) analysis for SEM-protected imidazole-2-carboxaldehyde **2** showed two peaks (−84.3 and −195.0 ppm) corresponding to the imidazole imino nitrogen and SEM-protected imidazole pyrrolic nitrogen, respectively. Upon proton-coupled gHSQC (gradient heteronuclear single quantum coherence) analysis, dipyrromethane **3** showed a single peak at −227.7 ppm corresponding to the two identical pyrrolic nitrogens. Proton-coupled gHMBC analysis for dipyrromethane **3** showed peaks at −119.2, −205.3, and −227.7 ppm, attributed

(44) Littler, B. J.; Ciringh, Y.; Lindsey, J. S. *J. Org. Chem.* **1999**, *64*, 2864−2872.

(45) Wood, T. E.; Berno, B.; Beshara, C. S.; Thompson, A. *J. Org. Chem.* **2006**, *71*, 2964−2971.

TABLE 1. ^{15}N NMR Spectroscopic Data for Imidazole-Containing Compounds[a]

compound	δ ^{15}N NMR Resonances (ppm)[b] gHSQC	gHMBC
2	*c*	−84.3, −195.0
3	−227.7	−119.2, −205.3, −227.7
9-BBN-3[d]	−226.4	−162.1, −193.0, −199.4, −226.4
Bu_2B-3	−227.7	−167.9, −198.5, −202.5, −227.7
$(9\text{-BBN})_2$-5[d]	*c*	−146.8, −160.5, −193.7, −199.5
$(Bu_2B)_2$-5	*c*	−154.0, −167.2, −200.3, −202.3
Bu_2B-15a[e]	−228.4	−165.1, −197.2, −228.5
$(9\text{-BBN})_2$-16	*c*	−146.1, −160.5, −194.9, −198.5

[a] ^{15}N NMR spectroscopic data were collected with 0.2 M samples in THF-d_8 at room temperature. [b] Chemical shifts were standardized with respect to 1.0 M $MeNO_2$ (δ 0.0 ppm). [c] Not applicable. [d] A 0.1 M sample was used. [e] The resonance from the boron-complexed pyrrolic nitrogen was not observed.

to the imidazole imino nitrogen, SEM-protected imidazole pyrrolic nitrogen, and the pyrrole nitrogen, respectively.[46]

The dialkylboron-complexed imidazolyl−dipyrromethane **Bu_2B-3**, **Bu_2B-15a**, or **9-BBN-3** also showed only one peak in the gHSQC experiment, owing to the single NH in each molecule. The dialkylboron-complexed dipyrromethanes **9-BBN-3** and **Bu_2B-3** each showed four peaks upon gHMBC analysis. (Compound **Bu_2B-15a** exhibited only three peaks as the resonance from the boron-complexed pyrrole nitrogen was not observed.) For example, **9-BBN-3** revealed four resonances at distinct chemical shifts (−162.1, −193.0, −199.4, −226.4 ppm) as expected owing to the distinct environment of the imidazole imino nitrogen, the boron-complexed pyrrole nitrogen, the SEM-protected imidazole pyrrolic nitrogen, and the free pyrrole nitrogen, respectively. In general, dialkylboron complexation of the imidazole imino nitrogen caused an upfield chemical shift ($\Delta\delta$ = −43 ppm for 9-BBN; −49 ppm for Bu_2B) with respect to dipyrromethane **3** (−119.2 ppm). On the other hand, dialkylborylation of the pyrrole nitrogen caused deshielding ($\Delta\delta$ = 35 ppm for 9-BBN; 29 ppm for Bu_2B) compared to the free pyrrole nitrogen in **3** (−227.7 ppm).

The bis(dialkylboron) complexes of 1-acyl-5-imidazolyl−dipyrromethanes [**$(9\text{-BBN})_2$-5**, **$(Bu_2B)_2$-5**, and **$(9\text{-BBN})_2$-16**] typically exhibited four distinct resonances. Examination of the spectra indicate a downfield chemical shift ($\Delta\delta$ = 74−82 ppm) for the pyrrole nitrogen complexed by an oxygen-coordinated boron moiety versus that of dipyrromethane **3** (−227.7 ppm), which can be attributed to the combined electron-withdrawing effect of the alkylboron moiety and the acyl group. In summary, ^{15}N NMR chemical shift values were quite useful for structural comparison of compounds with multiple nitrogen atoms.

We also carried out ^{11}B NMR studies of selected dialkylboron complexes of the dipyrromethanes. ^{11}B NMR spectroscopy of **$(9\text{-BBN})_2$-5** showed two peaks (δ 12.65 and −0.04 ppm) for the two boron moieties relative to the ^{11}B standard (BF_3·$O(Et)_2$ at 0 ppm). The two peaks are consistent with coordination of one boron atom to the carbonyl oxygen and the other boron atom to the imidazole imino nitrogen, respectively. By comparison, **Bu_2B-3** gave only one peak (1.94 ppm), to be compared with *N*-(9-borabicyclo[3.3.1]non-9-yl)pyrrole, which lacks intramolecular coordination and resonates downfield at 59.9 ppm.[47] The results of the ^{11}B NMR studies are summarized in Table 2. In general, imidazole coordination results in an upfield resonance near that of the standard BF_3·$O(Et)_2$, whereas acyl oxygen coordination results in a slight downfield shift near 12−13 ppm.

TABLE 2. ^{11}B NMR Spectroscopic Data for Boron Complexes of Dipyrromethanes[a]

compound	δ ^{11}B NMR Resonances (ppm) N-BR_2	O-BR_2
Bu_2B-3	1.94	
9-BBN-3	1.93	
$(9\text{-BBN})_2$-5	−0.04	12.65
$(Bu_2B)_2$-5	1.08	13.24
$(9\text{-BBN})_2$-16[b]	1.44	12.06

[a] ^{11}B NMR spectroscopy was performed in THF-d_8 at 50 °C. [b] Data were obtained at room temperature.

5. Metalation of Imidazole-Substituted Porphyrins. We examined the synthesis of chelates of imidazolyl−porphyrins containing magnesium(II), zinc(II), palladium(II), and indium(III), all of which are of potential interest for photodynamic therapeutic applications. In addition, imidazolyl−porphyrins are known to form diverse assemblies upon chelation of metals that accept a fifth ligand (e.g., zinc, magnesium).[48] The chelates were formed either by metalation of a free base imidazolyl−porphyrin or by formation of the metalloporphyrin in the porphyrin-forming process. Regardless of method, each imidazole unit was masked with an SEM group. Zinc insertion was achieved by treatment of an SEM-protected imidazolyl−porphyrin with zinc acetate (Schemes 4 and 8).[49] Metalation as part of the porphyrin-forming process was achieved in refluxing ethanol with zinc acetate (Scheme 5) or $PdCl_2(CH_3CN)_2$ (Scheme 6). Metalation with magnesium (MgI_2/*N*,*N*-diisopropylethylamine)[50] or indium ($InCl_3$) was carried out at the microscale level with selected porphyrins, affording metalloporphyrins for exploratory studies (Supporting Information).

In our studies, each zinc chelate gave an aggregated sample in a nonpolar solvent, such as CH_2Cl_2 [*trans*-A_2B_2-porphyrin **$(SEM)_2$-Zn17**; *trans*-AB_2C-porphyrin **SEM-Zn8**; and *trans*-AB-porphyrins **SEM-Zn12** and **SEM-Zn13**]. The hallmark of aggregation in each case was the presence of a split Soret band (415 ± 5, 434 ± 5 nm). Each such zinc porphyrin gave a single sharp Soret band (∼425 nm) in a polar solvent, such as methanol. By contrast, palladium porphyrin **SEM-Pd12** showed a sharp Soret band regardless of solvent polarity, as expected due to the lack of interaction between the tetracoordinated palladium and imidazole species.

6. Synthesis of Water-Soluble *trans*-AB Imidazolium−Porphyrins. Dialkylation of an imidazole unit forms a charged species, which provides an attractive means for imparting water solubility to imidazolyl−porphyrins for life sciences applications. Conditions for the dialkylation were surveyed using porphyrins bearing a single imidazole motif. The porphyrins examined were **Zn12**, **Pd12**, and **13**, prepared from **SEM-Pd12**, **SEM-Zn12**, and **SEM-Zn13**, respectively, upon treatment with

(46) Berger, S.; Braun, S.; Kalinowski, H.-O. *NMR Spectroscopy of the Non-Metallic Elements*; John Wiley & Sons Ltd.: Toronto, 1997; pp 111−318.

(47) Wrackmeyer, B.; Schwarze, B. *J. Organomet. Chem.* **1997**, *534*, 207−211.

(48) (a) Satake, A.; Kobuke, Y. *Tetrahedron* **2005**, *61*, 13−41. (b) Kobuke, Y.; Ogawa, K. *Bull. Chem. Soc. Jpn.* **2003**, *76*, 689−708.

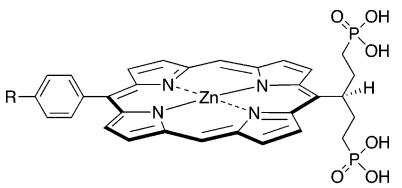
(49) Carcel, C. M.; Laha, J. K.; Loewe, R. S.; Thamyongkit, P.; Schweikart, K.-H.; Misra, V.; Bocian, D. F.; Lindsey, J. S. *J. Org. Chem.* **2004**, *69*, 6739−6750.

(50) O'Shea, D. F.; Miller, M. A.; Matsueda, H.; Lindsey, J. S. *Inorg. Chem.* **1996**, *35*, 7325−7338.

TBAF in refluxing THF or concentrated HCl in refluxing EtOH. Porphyrin **13** containing a carboxylate ester was metalated affording **Zn13**. Derivatives of **Zn12** and **Pd12** can serve as benchmark molecules to determine the hydrophilicity imparted upon the core porphyrin by dialkylation and as models for the optimization of the alkylation conditions. **Zn13** can also be utilized in the synthesis of water-soluble derivatives and, upon hydrolysis of the carboxylate ester group, attached to biomolecules for life sciences applications.

Conditions for the alkylation were surveyed by scanning various alkylating agents (ethyl iodide, 1,3-propane sultone, 1,4-butane sultone), bases (NaOMe, NaH), solvents (methanol, DMF, acetone, neat), reaction temperatures (ambient, ≥80 °C, microwave), and reaction times (5 min to 3 days). Key results of the alkylation optimization study are provided below, and additional information is provided in the Supporting Information.

Alkylations carried out with ethyl iodide on **Zn12**, **Pd12**, or **Zn13** in each case resulted in good yields of the dialkylated product **Zn12-Et$_2$**, **Pd12-Et$_2$**, or **Zn13-Et$_2$**, which was easily purified upon silica column chromatography. The identity of the pure material was validated by mass spectrometry (LD-MS, FAB-MS), ^{1}H NMR spectroscopy, and absorption spectroscopy. Alkylation of **Zn12** with 1,4-butane sultone gave a mixture of mono- and dialkylated products (**Zn12-S** and **Zn12-S$_2$**, respectively), along with large amounts of the sultone reagent. Conventional aqueous−organic workup (water/ethyl acetate) yielded the monoalkylated **Zn12-S** in the organic layer (as shown by ^{1}H NMR spectroscopy, ESI-MS, and reversed-phase HPLC). Concentration of the aqueous layer and purification of the residue with preparative reversed-phase chromatography yielded the dialkylated porphyrin **Zn12-S$_2$** devoid of 1,4-butane sultone reagent. Porphyrin **Zn12-S$_2$** was unstable in aqueous solution and rapidly dealkylated to give **Zn12-S** as shown by reversed-phase HPLC and ESI-MS. The instability is presumably caused by intramolecular nucleophilic attack of the sulfonate on the methylene unit attached to the imidazolium−nitrogen (an analogous process has been reported with free nucleophiles and alkylimidazoles[51]). The instability of the alkylsulfonates is easily rationalized, but nonetheless was somewhat surprising, given that *N*-sulfobutyl imidazolium species have been prepared for studies as ionic liquids.[52] The motivation for preparing the alkylsulfonic acid derivatives came from our prior studies of swallowtail porphyrins (e.g., **Zn18**) wherein the termini of the swallowtail motif bear ionizable groups.[37] Such porphyrins have high solubility in water.



Zn18a: R = Br
Zn18b: R = OCH_2CO_2H

The solubility of the dialkylated imidazolium−porphyrins was assessed in water (Table 3) and in four organic solvents (see Supporting Information). Porphyrin **Zn12-Et$_2$** was only weakly soluble in water (10^{-4} M), whereas **Zn12-S$_2$** displayed excellent water solubility (∼5 mM). It is noteworthy that both **Zn12-Et$_2$** and **Zn12-S$_2$** were soluble and gave sharp absorption bands in CH_2Cl_2, a solvent where the presence of a free imidazole nitrogen results in aggregation of the zinc porphyrin. The aqueous solubility of **Zn12-S$_2$** is only slightly lower than that of **Zn18a** or **Zn18b** (∼10 to 20 mM).[37] Replacement of the alkylsulfonate units with more stable analogues (e.g., quaternary amines) may result in the retention of the aqueous solubility while eliminating the problem caused by the hydrolysis of the alkylsulfonate moiety, thus giving porphyrins that are potentially useful for life sciences applications.

Outlook

Imidazolyl−porphyrins containing one or two imidazole units have been prepared by employing two masking agents for the imidazole nitrogens. The SEM group blocks the imidazole pyrrolic nitrogen, whereas the dialkylboron group blocks the imidazole imino nitrogen, thereby affording nonpolar imidazole species that are readily handled. The use of masked imidazole species (versus the unprotected imidazole unit) enables the rational synthesis of imidazolyl−porphyrins with yields more comparable to those where simple aryl substituents are employed. Five distinct routes have been successfully employed for forming imidazolyl−porphyrins. The zinc(II) and palladium(II) chelates of imidazolium−porphyrins may facilitate comparative studies of efficacy in photodynamic therapy. Taken together, facile access to imidazolyl porphyrins and imidazolium porphyrins should facilitate the design of porphyrin-based molecular architectures for various applications in supramolecular chemistry and the life sciences.

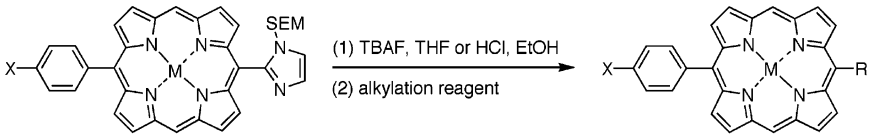
Experimental Section

Synthesis of an SEM-Protected Imidazolecarboxaldehyde: 1-[2-(Trimethylsilyl)ethoxymethyl]imidazole-2-carboxaldehyde (2).[31] Following a general procedure,[31] a sample of NaH (60% dispersion in mineral oil, 0.800 g, 20 mmol) was washed with hexanes (2 × 25 mL) under argon. The flask was charged with dry DMF (30 mL), and 2-imidazolecarboxaldehyde (1.92 g, 20.0 mmol) was added in small portions. After stirring at room temperature for 1.5 h, the reaction mixture was treated dropwise with SEMCl (3.53 g, 21.2 mmol). The reaction mixture became slightly warm upon addition of SEMCl. After stirring for 2.5 h, the reaction mixture was quenched with water and extracted with ethyl acetate. The organic extract was washed, dried (Na_2SO_4), and concentrated to give a yellow oil (3.7 g, 82%): ^{1}H NMR (300 MHz) δ −0.12 (s, 9H), 0.83 (t, J = 8.4 Hz, 2H), 3.48 (t, J = 8.4 Hz, 2H), 5.70 (s, 2H), 7.26−7.28 (m, 1H), 7.32−7.34 (m, 1H), 9.75 (s, 1H); ^{13}C NMR δ −1.4, 17.8, 66.9, 75.7, 125.5, 132.0, 143.5, 182.3; ^{15}N NMR δ −84.3, −195.0 (gHMBC); FAB-MS obsd 227.1221, calcd 227.1216 [(M + H)$^+$, M = $C_{10}H_{18}N_2O_2Si$].

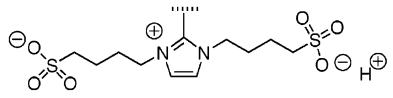
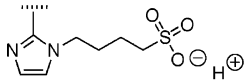
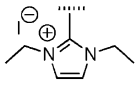
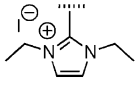
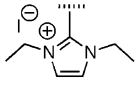
Synthesis of an SEM-Protected Imidazolyl−Dipyrromethane: 5-[1-(2-(Trimethylsilyl)ethoxymethyl)imidazol-2-yl]dipyrromethane (3). Following a general procedure[32] with modification, a mixture of pyrrole (104 mL, 1.50 mol) and aldehyde **2** (3.39 g, 15.0 mmol) was stirred and degassed with argon for 10 min. A sample of $MgBr_2$ (1.38 g, 7.50 mmol) was added, and the mixture was stirred under argon at room temperature for 1.5 h. The resulting dark yellow mixture was treated with NaOH (3.00 g, 75.0 mmol, 20−40 mesh beads). After stirring for 45 min, the resulting light brown mixture was filtered. The filtrate was concentrated under

(51) Glenn, A. G.; Jones, P. B. *Tetrahedron Lett.* **2004**, *45*, 6967−6969.
(52) (a) Yoshizawa, M.; Ohno, H. *Ionics* **2002**, *8*, 267−271. (b) Cole, A. C.; Jensen, J. L.; Ntai, I.; Tran, K. L. T.; Weaver, K. J.; Forbes, D. C.; Davis, J. H., Jr. *J. Am. Chem. Soc.* **2002**, *124*, 5962−5963. (c) Yoshizawa, M.; Hirao, M.; Ito-Akita, K.; Ohno, H. *J. Mater. Chem.* **2001**, *11*, 1057−1062.

TABLE 3. Dialkylation of Imidazolyl Porphyrins



SEM-M12 (X = H, M = Zn or Pd)
SEM-M13 (X = OCH_2CO_2Et, M = Zn)

entry	conditions	alkylation reagent	R	product	water solubility
1	(1) NaOMe/THF (2) DMF, 60 °C			**Zn12-S_2**	5 x 10^{-3} M
				**Zn12-S**	*a*
2	DMF, 60 °C			**Zn12-Et_2**	10^{-4} M
3	THF, reflux			**Pd12-Et_2**	10^{-6} M
4	THF, reflux			**Zn13-Et_2**	10^{-5} M

[a] The sample exhibited a split Soret band indicative of aggregation.

vacuum (0.2 mmHg). Traces of pyrrole were removed by thrice treatment of the crude viscous residue in the evaporation flask with hexanes (50 mL) followed by removal of the volatile components. The resulting light brown viscous liquid was purified by column chromatography [silica, CH_2Cl_2 → CH_2Cl_2/ethyl acetate (4:1)] to afford a brown viscous liquid (1.55 g, 30.2%): ^{1}H NMR δ −0.03 (s, 9H), 0.89 (t, J = 8.0 Hz, 2H), 3.45 (t, J = 8.0 Hz, 2H), 5.27 (s, 2H), 5.73 (s, 1H), 5.96−6.00 (m, 2H), 6.09−6.11 (m, 2H), 6.66−6.70 (m, 2H), 6.92−6.98 (m, 1H), 7.03−7.05 (m, 1H), 9.14−9.24 (br, 2H); ^{13}C NMR δ −1.4, 17.9, 35.4, 66.5, 75.1. 106.2, 108.2, 117.7, 119.9, 127.6, 129.9, 148.0; ^{15}N NMR δ −227.7 (gHSQC); −119.2, −205.3, −227.7 (gHMBC); FAB-MS obsd 343.1960, calcd 343.1954 [$(M + H)^+$, M = $C_{18}H_{26}N_4OSi$].

Boron Complexation of an Imidazolyl−Dipyrromethane: 10-(Dibutylboryl)-5-[1-(2-(trimethylsilyl)ethoxymethyl)imidazol-2-yl]dipyrromethane (Bu_2B-3). A solution of **3** (0.22 g, 0.64 mmol) in CH_2Cl_2 (1.3 mL) was treated with TEA (0.22 mL, 1.6 mmol) and Bu_2B-OTf (1.3 mL, 1.3 mmol, 1.0 M in CH_2Cl_2). After stirring for 1 h at room temperature, the mixture was poured onto a pad of silica, which was eluted with CH_2Cl_2. The product eluted as a fast moving red band, which upon concentration afforded a dark red viscous liquid (0.24 g, 81%): ^{1}H NMR δ −0.03 (s, 9H), 0.41−0.52 (m, 4H), 0.71−0.76 (m, 16H), 3.41−3.50 (m, 2H), 5.21 (d, J = 10.0 Hz, 1H), 5.45 (d, J = 10.0 Hz, 1H), 5.79 (s, 1H), 5.94−5.98 (m, 1H), 6.01−6.03 (m, 1H), 6.07−6.09 (m, 1H), 6.23−6.25 (m, 1H), 6.61−6.63 (m, 1H), 6.76−6.78 (m, 1H), 7.11−7.13 (m, 2H), 7.94−8.10 (br, 1H); ^{13}C NMR δ −1.1, 14.3, 18.0, 26.45, 26.60, 27.4, 28.7, 33.9, 67.4, 76.3, 104.6, 106.3, 107.9, 108.6, 118.4, 120.3, 121.2, 121.7, 144.9, resonances were not observed from two of the quaternary carbons in the pyrrolic rings and two of the carbon atoms adjacent to the boron atoms; ^{11}B NMR δ 1.94; ^{15}N NMR δ −227.7 (gHSQC); δ −167.9, −198.5, −202.5, −227.7 (gHMBC); FAB-MS obsd 467.3377, calcd 467.3372 [$(M + H)^+$, M = $C_{26}H_{43}BN_4OSi$].

Boron Complexation as a Purification Aid for Imidazolyl−Dipyrromethanes: Direct Conversion of 2 → Bu_2B-3. Following general procedures[32,33] with modification, a degassed mixture of pyrrole (10.5 mL, 0.151 mol) and aldehyde **2** (0.34 g, 1.5 mmol) was treated with $MgBr_2$ (0.14 g, 0.76 mmol). The mixture was stirred under argon at room temperature for 1.5 h. NaOH (0.30 g, 7.5 mmol, 20−40 mesh beads) was added to quench the reaction. Stirring for 1 h afforded a light brown mixture. The mixture was filtered. The filtrate was concentrated. Traces of pyrrole were removed by thrice treatment of the crude viscous residue in the evaporation flask with hexanes (50 mL) followed by removal of the volatile components. The resulting crude dipyrromethane was dissolved in CH_2Cl_2 (3.0 mL) and treated with TEA (0.76 mL, 5.4 mmol) and Bu_2B-OTf (4.5 mL, 4.5 mmol, 1.0 M in CH_2Cl_2). The mixture was stirred at room temperature. After 1 h, the mixture was poured onto a pad of silica, which was eluted with CH_2Cl_2. The product eluted as a fast moving red band, which upon concentration afforded a dark red viscous solid (0.21 g, 30%). Characterization data (^{1}H NMR, ^{13}C NMR, UV−vis) were consistent with the values reported above.

Boron Complexation of a 1-Acyl-5-imidazolyl−dipyrromethane: 10,11-Bis(9-borabicyclo[3.3.1]non-9-yl)-1-(4-methylbenzoyl)-5-[1-(2-(trimethylsilyl)ethoxymethyl)imidazol-2-yl]-dipyrromethane [(9-BBN)$_2$-5]. Following a general procedure[33] with slight modification, a solution of EtMgBr (9.50 mL, 9.5 mmol, 1.0 M in THF) was added slowly to a solution of **3** (1.63 g, 4.75 mmol) in THF (4.8 mL) under argon. The resulting mixture was stirred at room temperature for 10 min and then cooled to −78 °C.

A solution of **4** (1.09 g, 4.75 mmol) in THF (4.8 mL) was added. The reaction mixture was stirred at −78 °C for 10 min and then allowed to warm to room temperature over the course of 1.5 h. The reaction was quenched by addition of saturated aqueous NH_4Cl (20 mL). The mixture was extracted with ethyl acetate. The organic layer was washed (water and brine), dried (Na_2SO_4), and filtered. The filtrate was concentrated. The crude product (a reddish orange oil) thus obtained was dissolved in CH_2Cl_2 (9.5 mL) and treated with TEA (1.59 mL, 11.4 mmol) and 9-BBN-OTf (19 mL, 10 mmol, 0.5 M in hexanes) with stirring at room temperature. After 1 h, the mixture was poured onto a pad of silica (3 × 15 cm), which was eluted with CH_2Cl_2. The fast moving yellow band was concentrated. Further chromatography [silica, hexanes/CH_2Cl_2 (1:1)] afforded a yellow solid (846 mg, 25%): mp 170−172 °C; ^{1}H NMR δ −0.07 (s, 9H), 0.74−0.93 (m, 6H), 1.50−2.43 (m, 24H), 2.52 (s, 3H), 3.16−3.27 (m, 2H), 4.35 (d, J = 10.0 Hz, 1H), 4.62 (d, J = 10.0 Hz, 1H), 5.57 (s, 1H), 6.01−6.04 (m, 1H), 6.21−6.26 (m, 1H), 6.52−6.55 (m, 1H), 7.01−7.06 (m, 1H), 7.34−7.37 (m, 1H), 7.41−7.43 (m, 3H), 7.66−7.69 (m, 1H), 8.19 (d, J = 8.4 Hz, 2H); ^{13}C NMR δ −1.5, 18.1, 21.5, 22.1, 23.47, 23.63, 23.8, 25.0, 25.7, 26.2, 30.1, 31.01, 31.05, 31.7, 34.2, 34.41, 34.44, 34.8, 39.8, 67.2, 77.2 (overlapped with $CHCl_3$), 105.8, 107.4, 117.3, 118.1, 121.3, 124.3, 124.5, 127.7, 129.95, 130.09, 130.13, 134.7, 145.9, 146.4, 147.4, 175.7, resonances from the two of the bridgehead carbons in the 9-BBN rings were not observed; ^{11}B NMR δ −0.04, 12.65; ^{15}N NMR δ −146.8, −160.5, −193.7, −199.5 (gHMBC). Anal. Calcd for $C_{42}H_{58}B_2N_4O_2Si$: C, 72.00; H 8.34; N, 8.00. Found: C, 71.97; H, 8.32; N, 7.90; FAB-MS obsd 700.4572, calcd 700.4515 ($C_{42}H_{58}B_2N_4O_2Si$); λ_{abs} (THF) 297, 369 nm.

1-Acylation of an Imidazolyl−Dipyrromethane Boron Complex: Bu_2B-3 → $(Bu_2B)_2$5. Following a general procedure,[33] a solution of EtMgBr (1.40 mL, 1.40 mmol, 1.0 M in THF) was added slowly to a solution of **Bu_2B-3** (0.25 g, 0.54 mmol) in THF (0.60 mL) under argon. The resulting mixture was stirred at room temperature for 10 min and then cooled to −78 °C. A solution of **4** (0.15 g, 0.65 mmol) in THF (0.60 mL) was added. The reaction mixture was stirred at −78 °C for 10 min and then allowed to warm to room temperature with stirring for 3 h. The reaction mixture was treated with half-saturated aqueous NH_4Cl and ethyl acetate. The organic extract was washed (saturated aqueous $NaHCO_3$ and brine), dried (Na_2SO_4), and filtered. The filtrate was concentrated. The crude product thus obtained was dissolved in CH_2Cl_2 (1.1 mL) and treated with TEA (0.18 mL, 1.3 mmol) and Bu_2B-OTf (1.1 mL, 1.1 mmol, 1.0 M in CH_2Cl_2) with stirring at room temperature. After 1 h, the mixture was concentrated and chromatographed [silica, hexanes/CH_2Cl_2 (1:1) → CH_2Cl_2] affording a reddish orange viscous liquid (42 mg, 11%). Characterization data (^{1}H NMR, ^{13}C NMR) were consistent with the values reported in the Supporting Information.

Synthesis of a *trans*-A_2B_2-Porphyrin (Two Imidazole Groups): 5,15-Bis(4-methylphenyl)-10,20-bis[1-(2-(trimethylsilyl)ethoxymethyl)imidazol-2-yl]porphyrin [$(SEM)_2$-6]. Following general procedures[25,33] for the self-condensation of a dipyrromethane-1-carbinol with slight modification, a sample of $NaBH_4$ (0.95 g, 25 mmol, 50 molar equiv) was slowly added in small portions to a stirred solution of **$(9\text{-BBN})_2$-5** (0.35 g, 0.50 mmol) at 0 °C in THF/MeOH (3:1, 20 mL). The reaction was monitored by TLC analysis (silica, CH_2Cl_2). After 1.5 h, the reaction mixture was poured into a stirred solution of saturated aqueous NH_4Cl and ethyl acetate (1:1, 100 mL). The organic layer was washed with water, dried (Na_2SO_4), and concentrated to afford the carbinol as an orange oil. The carbinol (∼0.5 mmol) was immediately dissolved in CH_2Cl_2 (100 mL), and Yb(OTf)$_3$ (0.20 g, 0.32 mmol, 3.2 mM) was added. The mixture slowly darkened, and the reaction was monitored by absorption spectroscopy. After 4 h, the spectroscopic yield of porphyrin had essentially leveled off, whereupon DDQ (0.17 g, 0.75 mmol) was added. After stirring at room temperature for 1 h, TEA (89 μL, 0.64 mmol) was added. The entire reaction mixture was filtered through a pad of alumina [5 × 10 cm, CH_2Cl_2/MeOH (19:1 → 9:1)] until the eluent was no longer dark. Removal of solvent gave a dark solid, which upon column chromatography [silica, 3 × 20 cm, CH_2Cl_2/ethyl acetate (9:1 → 1:1)] gave a purple solid (24 mg, 12%): ^{1}H NMR (300 MHz) δ −2.86 to −2.78 (br, 2H), −0.42 (s, 9H), −0.38 (s, 9H), 0.35−0.45 (m, 4H), 2.72 (s, 6H), 2.84−2.96 (m, 4H), 5.40 (s, 2H), 5.11 (s, 2H), 7.58 (d, J = 8.1 Hz, 4H), 7.66−7.77 (m, 4H), 8.00−8.16 (m, 4H), 8.77−8.85 (m, 4H), 8.92 (d, J = 4.5 Hz, 4H); LD-MS obsd 883.0; FAB-MS obsd 883.4335, calcd 883.4300 [(M + H)$^+$, M = $C_{52}H_{58}N_8O_2Si_2$]; λ_{abs} 419, 516, 552, 589 nm; λ_{em} 655, 720 nm.

Synthesis of a *trans*-AB_2C-Porphyrin (One Imidazole Group): 5,15-Bis(4-methylphenyl)-10-[1-(2-(trimethylsilyl)-ethoxymethyl)imidazol-2-yl]porphyrin (SEM-8). Following general procedures[25] for the condensation of a dipyrromethane and a dipyrromethane-1,9-dicarbinol with slight modification, a sample of $NaBH_4$ (0.568 g, 15.0 mmol, 50 molar equiv) was slowly added in small portions to a stirred solution of **7** (0.184 g, 0.300 mmol) in THF/MeOH (5:1, 12 mL). The reaction was monitored by TLC analysis (silica, CH_2Cl_2). After 4.5 h, the reaction was quenched by slow addition of saturated aqueous NH_4Cl (60 mL). The reaction mixture was extracted with CH_2Cl_2, and the organic layer was dried (K_2CO_3) and concentrated to afford the dicarbinol. The dicarbinol (∼0.3 mmol) was immediately dissolved in CH_2Cl_2 (120 mL), then **3** (103 mg, 0.300 mmol) and Yb(OTf)$_3$ (0.242 g, 0.390 mmol, 3.2 mM) were added. The mixture slowly darkened. After 1 h, the spectroscopic yield of porphyrin had essentially leveled off, whereupon DDQ (0.204 g, 0.900 mmol) was added. The mixture was stirred at room temperature for 1 h. TEA (0.11 mL, 0.78 mmol) was added, and the entire reaction mixture was concentrated. The residue was chromatographed [silica, 3 × 18 cm, CH_2Cl_2/ethyl acetate (1:1) containing 1% TEA] to give a purple solid (35 mg, 17%): ^{1}H NMR δ −3.01 to −2.99 (br, 2H), −0.41 (s, 9H), −0.39 (t, J = 8.0 Hz, 2H), 2.72 (s, 6H), 2.86 (t, J = 8.0 Hz, 2H), 5.04 (s, 2H), 7.59 (d, J = 8.0 Hz, 4H), 7.68−7.69 (m, 1H), 7.72−7.73 (m, 1H), 8.08−8.15 (m, 4H), 8.81 (d, J = 8.0 Hz, 2H), 8.97 (d, J = 4.8 Hz, 2H), 9.05 (d, J = 4.8 Hz, 2H), 9.35 (d, J = 4.8 Hz, 2H), 10.28 (s, 1H); LD-MS obsd 686.8; FAB-MS obsd 687.3288, calcd 687.3268 [(M + H)$^+$, M = $C_{43}H_{42}N_6OSi$]; λ_{abs} 414, 510, 582 nm; λ_{em} 645, 710 nm.

Synthesis of a Zinc(II)-*trans*-AB-Porphyrin (One Imidazole Group): Zn(II)-5-Phenyl-10-[1-(2-(trimethylsilyl)ethoxymethyl)-imidazol-2-yl]porphyrin (SEM-Zn12). Following a general procedure[38] with slight modification, a solution of 1,9-diformyldipyrromethane **11a** (56 mg, 0.20 mmol) and *n*-propylamine (0.04 mL, 0.5 mmol) in THF (1 mL) was stirred at room temperature for 1 h. After removal of the excess *n*-propylamine and THF under vacuum, the residue and dipyrromethane **3** (69 mg, 0.20 mmol) were dissolved in ethanol (20 mL). The mixture was then treated with $Zn(OAc)_2$ (0.367 g, 2.00 mmol) and refluxed open to the air for 13 h. After removing the solvent, the residue was chromatographed [silica, CH_2Cl_2 → CH_2Cl_2/ethyl acetate (4:1)] to afford a dark purple solid (24 mg, 19%): ^{1}H NMR (300 MHz, CD_2Cl_2) δ −0.81 (s, 9H), −0.40 (t, J = 7.8 Hz, 2H), 1.55−1.61 (m, 2H), 1.91 (s, 1H), 3.16 (s, 2H), 5.54 (d, J = 3.9 Hz, 2H), 5.76 (s, 1H), 7.86−8.02 (m, 3H), 8.27 (d, J = 6.9 Hz, 1H), 8.77 (d, J = 6.9 Hz, 1H), 8.83 (d, J = 3.9 Hz, 2H), 9.24 (d, J = 3.9 Hz, 2H), 9.51 (d, J = 3.9 Hz, 2H), 10.23 (s, 2H); ^{13}C NMR (CD_2Cl_2, 300 MHz) δ −2.3, 16.8, 65.8, 74.7, 106.3, 116.3, 121.9, 126.7, 126.9, 127.6, 131.4, 132.5, 132.9 (a resonance from one of the β-carbons was overlapped), 135.1, 135.3, 143.7, 145.5, 149.2, 149.6, 149.9. 150.3; LD-MS obsd 644.3; FAB-MS obsd 644.1725, calcd 644.1698 ($C_{35}H_{32}N_6OSiZn$); λ_{abs} 402, 422, 551 nm; λ_{em} 595, 645 nm.

Synthesis of a Palladium(II)-*trans*-AB-Porphyrin (One Imidazole Group): Pd(II)-5-Phenyl-10-[1-(2-(trimethylsilyl)ethoxymethyl)imidazol-2-yl]porphyrin (SEM-Pd12). Following a general procedure,[43] samples of 1,9-diformyldipyrromethane **11a** (14 mg, 0.050 mmol), dipyrromethane **3** (17 mg, 0.049 mmol), KOH

(14 mg, 0.25 mmol), and $Pd(CH_3CN)_2Cl_2$ (8.0 mg, 0.031 mmol) were placed in a flask fitted with a condenser exposed to air. Ethanol (0.5 mL) was added, and the mixture was stirred and heated to reflux for 2 h. The solvent was evaporated. The residue was chromatographed [silica, toluene/THF (1:1)] to afford an orange solid (11 mg, 32%): ^{1}H NMR (CD_2Cl_2, 300 MHz) δ −0.38 (s, 9H), 0.40 (t, J = 8.1 Hz, 2H), 2.99 (t, J = 8.1 Hz, 2H), 5.10 (s, 2H), 7.70−7.74 (m, 2H), 7.76−7.85 (m, 3H), 8.10−8.23 (m, 2H), 8.93 (d, J = 4.8 Hz, 2H), 9.00 (d, J = 4.8 Hz, 2H), 9.31 (d, J = 4.8 Hz, 2H), 9.36 (d, J = 4.8 Hz, 2H), 10.32 (s, 2H); LD-MS obsd 686.0; FAB-MS obsd 686.1476, calcd 686.1442 ($C_{35}H_{32}N_6OSiPd$); λ_{abs} (toluene) 405, 515, 547 nm; λ_{em} (toluene) 550, 600 nm.

Dialkylation of an Imidazolyl−Metalloporphyrin: Zn(II)-5-(1,3-Diethylimidazol-2-ium)-10-phenylporphyrin (Zn12-Et$_2$). Following a general procedure,[31] porphyrin **SEM-Zn12** (26 mg, 0.040 mmol) was treated with TBAF (1.0 mL, 1.0 mmol, 1.0 M in THF), and the reaction mixture was heated to reflux for 26 h. Porphyrin **Zn12** had poor solubility in organic solvents (e.g., CH_2Cl_2, ethyl acetate, THF, and DMF). The porphyrin residue showed a single component by TLC and the expected molecule ion peak by LD-MS analysis, but did not afford a satisfactory ^{1}H NMR spectrum (CD_3OD, DMF-d_7). The sample was washed repeatedly with water to remove excess TBAF and then used directly in derivatization reactions. The entire sample of **Zn12** (∼0.04 mmol) was treated with EtI (0.100 mL, 1.25 mmol) in DMF (0.4 mL), and the reaction mixture was heated at 60 °C for 2 days. Because LD-MS of the crude sample showed the formation of the demetalated species along with the desired product **Zn12-Et$_2$**, the crude material was treated with $Zn(OAc)_2 \cdot 2H_2O$ (0.22 g, 1.0 mmol). The resulting mixture was heated at 60 °C for 12 h. After removal of DMF under high vacuum, the crude mixture was purified by column chromatography [silica, CH_2Cl_2/MeOH (99:1 → 3:1)] to afford a purple solid (10 mg, 36%, assuming an iodide counterion): ^{1}H NMR (300 MHz, CD_3OD) δ 0.90 (t, J = 6.6 Hz, 6H), 3.96−4.01 (m, 4H), 7.71−7.73 (m, 3H), 8.12 (d, J = 6.6 Hz, 2H), 8.26−8.30 (m, 2H), 8.72 (d, J = 4.5 Hz, 2H), 8.94 (d, J = 4.5 Hz, 2H), 9.35 (d, J = 4.5 Hz, 2H), 9.52 (d, J = 4.5 Hz, 2H), 10.33 (s, 2H); LD-MS obsd 571.0; FAB-MS obsd 571.1609, calcd 571.1589 ($C_{33}H_{27}N_6Zn$, lacking counterion); λ_{abs} (MeOH) 413, 544, 578 nm; λ_{abs} (water at pH 8) 408, 540, 574 nm; λ_{em} (MeOH) 540, 640 nm.

Zinc Metalation of an Imidazolyl−Porphyrin: Zn(II)-5,15-Bis(4-methylphenyl)-10,20-bis[1-(2-(trimethylsilyl)ethoxymethyl)imidazol-4-yl]porphyrin [(SEM)$_2$-Zn17]. Following a general procedure,[49] a solution of porphyrin **(SEM)$_2$-17** (12 mg, 14 μmol) in $CHCl_3$/MeOH (4 mL, 3:1) was treated with $Zn(OAc)_2 \cdot 2H_2O$ (77 mg, 0.35 mmol, 25 equiv). The reaction mixture was stirred at room temperature for 12 h. The reaction was quenched with water and extracted with ethyl acetate. The organic layer was dried (Na_2SO_4), concentrated, and chromatographed [silica, CH_2Cl_2 → CH_2Cl_2/ethyl acetate (1:1)] to afford a greenish purple solid (12 mg, 91%): ^{1}H NMR (300 MHz) δ −0.13 (s, 9H), 0.17 (s, 9H), 0.56 (t, J = 7.8 Hz, 2H), 1.17 (t, J = 7.8 Hz, 2H), 2.49 (s, 1H), 2.64 (t, J = 7.8 Hz, 2H), 2.85 (s, 6H), 3.93 (t, J = 7.8 Hz, 2H), 4.27 (s, 2H), 5.67 (s, 1H), 5.72 (s, 2H), 5.91 (d, J = 4.2 Hz, 2H), 7.55 (d, J = 6.9 Hz, 2H), 7.71 (d, J = 6.9 Hz, 2H), 7.88 (s, 1H), 7.99 (d, J = 6.9 Hz, 2H), 8.22 (s, 1H), 8.30 (d, J = 4.2 Hz, 2H), 8.57 (d, J = 6.9 Hz, 2H), 9.02 (d, J = 4.2 Hz, 2H), 9.22−9.34 (d, J = 4.2 Hz, 2H); LD-MS obsd 945.2; FAB-MS obsd 944.3358, calcd 944.3356 ($C_{52}H_{56}N_8O_2Si_2Zn$); λ_{abs} (THF) 417, 433, 572 nm; λ_{em} (CH_2Cl_2) 620, 675 nm.

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Supporting Information Available: Survey of conditions for dialkylation of imidazole-substituted porphyrins; solubility test for imidazolium−porphyrins; experimental section; description of NMR studies; X-ray data for **(9-BBN)$_2$-5**; and spectral data for selected compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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