Nonionic Superbase-Promoted Synthesis of Oxazoles and Pyrroles: Facile Synthesis of Porphyrins and α-*C*-Acyl Amino Acid Esters

Jiansheng Tang and John G. Verkade*

Gilman Hall, Department of Chemistry, Iowa State University, Ames, Iowa 50011

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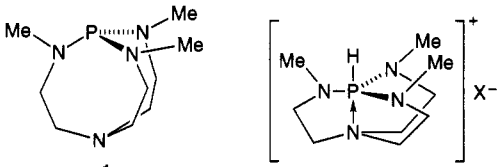
The reaction of acyl chlorides or acid anhydrides with isocyanoacetates in the presence of the superior strong nonionic base $P(MeNCH_2CH_2)_3N$ (**1**) gave oxazoles in 98–99% yield. Treatment of the oxazoles with HCl–MeOH gave α-*C*-acyl amino acid esters in 81–82% yield. The reaction of β-acetoxy-α-nitroalkanes or nitroalkenes with isocyanoacetates in the presence of **1** gave pyrroles in 100% yield. The conjugate acid of **1** can be treated with KO-*t*-Bu to regenerate **1**. Treatment of the pyrroles with $LiAlH_4$, followed by PTSA–$CH_2(OMe)_2$ and oxidation gave porphyrins in 65–69% yield. LiCl, which functions both as a strong nucleophile in the S_N2 demethylation of the 5,5′-bis(methoxycarbonyl)-3,3′,4,4′-tetramethyldipyrromethane **22a** and as a Lewis acid in the electrophilic substitution cyclization of paraformaldehyde at dipyrromethane, facilitates the combination of four reactions into a one-pot synthesis of octaethylporphyrin in 67% yield from **22a**.

Introduction

We have found that the bridgehead P–N transannulation in **2**[1,2] and partial transannulation in adducts **3**–**7**[3] and reaction intermediate **8**[4] greatly enhances their thermal stability. This effect renders **1** a very useful



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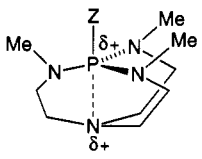
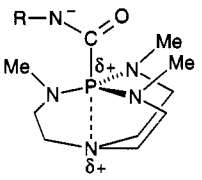


3, CS_2
4, $MeS(S)C^+$
5, S
6, $PhN{=}CSMe^+$
7, $NPhH^+$



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synthetic reagent as, for example, an extremely strong nonionic base[5,6] and as a superior catalyst for the conversion of isocyanates to isocyanurates in which evidence for intermediate **4** has been put forth.[4]

In connection with the potentially wide utility of **1** in organic synthesis, we were attracted to the powerful deprotonation capability of **1** whose basicity is about 10^{17} times stronger than DBU. While the latter base has been widely used in organic synthesis[7] because of its advantages over ionic bases, it is often inefficient or fails in reactions involving deprotonation. In the present paper, we report the application of **1** as a much stronger deprotonation agent than DBU in the improved synthesis of oxazoles and pyrroles which are utilized in the syntheses of α-*C*-acyl amino acid esters and porphyrins, respectively. We also report the importance of LiX in the facile synthesis of porphyrins from pyrroles.

Results and Discussion

Synthesis of Oxazoles and α-*C*-Acyl Amino Acid Esters. Oxazoles are intermediates to pharmaceutically interesting α-*C*-acyl amino acids which in turn are useful intermediates in the synthesis of β-hydroxy amino acids, especially β-aryl serines and amino alcohols including sympathomimetic agents such as ephedrine and epinephrine.[7] To obtain reasonable yields of oxazoles, reactions of isocyanoacetates with acyl chlorides or acid anhydrides in the presence of a large excess of triethylamine or DBU are quite lengthy (typically 48 h).[8ab] We repeated the reaction of **9a** with **10a** in Scheme 1 in the presence of 1 equiv of DBU and found that the reaction mixture obtained after 2 h of stirring at room temperature gave a very complicated ^1H NMR spectrum, and the GC of this mixture showed that only about 8% of **11a** had formed. On the other hand, in the presence of 1 equiv of **1**, the same reaction conditions gave ^1H NMR spectroscopically pure product **11a** and **2**(Cl) in 99 and 98% yields, respectively, within $^1/_2$ h. Similarly, the reaction of **9b** and **10a** in the presence of 1 equiv of **1** (Scheme 1) also went to completion within $^1/_2$ h, giving ^1H NMR spectroscopically pure products **11b** and **2**($PhCO_2$) in 100 and

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(3) (a) Tang, J. S.; Verkade, J. G. *J. Am. Chem. Soc.* **1993**, *115*, 5015. (b) Tang, J. S.; Laramay, M. A. H.; Young, V.; Ringrose, S.; Jacobson, R. A.; Verkade, J. G. *J. Am. Chem. Soc.* **1992**, *114*, 3129.
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(7) (a) Vediger, H.; Möller, F.; Eiter, K. *Synthesis* **1972**, 591. (b) Snider, B. B.; Buckman, B. O. *J. Org. Chem.* **1992**, *57*, 4883. (c) Magnus, P.; Giles, M.; Bonnert, R.; Kim, C. S.; McQuire, L.; Merrit, A.; Vicker, N. *J. Am. Chem. Soc.* **1992**, *114*, 4403. (d) Roush, W. R.; Murphy, M. *J. Org. Chem.* **1992**, *57*, 6022. (e) Warmas, J. S.; Dilley, G. J.; Meyers, A. I. *J. Org. Chem.* **1993**, *58*, 270.
(8) (a) Suzuki, M.; Iwasaki, T.; Matsumoto, K.; Okumura, K. *Synth. Commun.* **1972**, *2*, 237. (b) Suzuki, M.; Iwasaki, T.; Miyoshi, M.; Okumura, K.; Matsumoto, K. *J. Org. Chem.* **1973**, *38*, 3571 and references cited therein. (c) Wagner, I.; Musso, H. *Angew. Chem., Int. Ed. Engl.* **1983**, *22*, 816.

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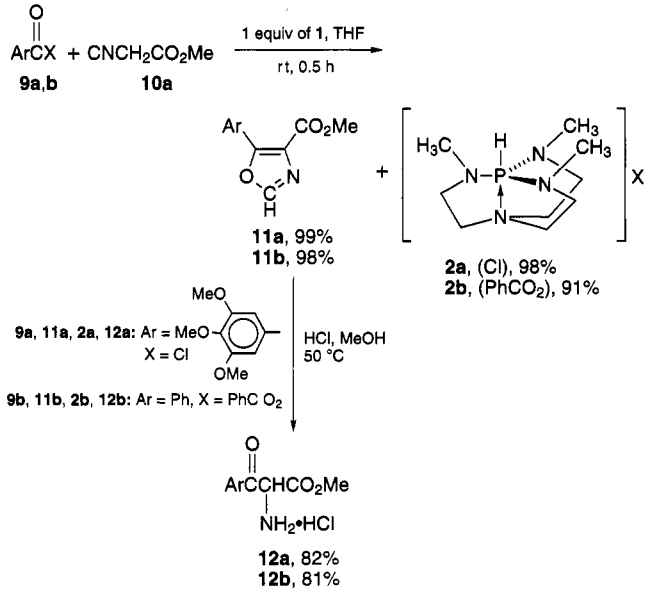
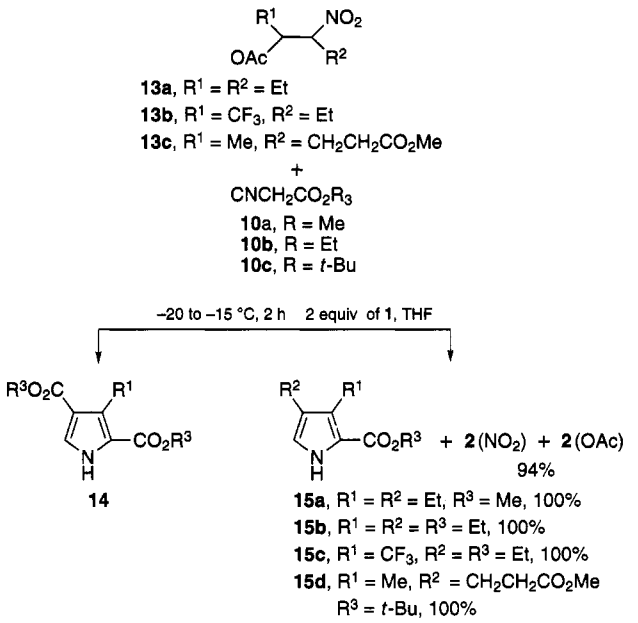
Scheme 1



91% yields, respectively. Products **11a** and **11b** were sufficiently pure that losses from recrystallization or chromatography could be avoided, allowing them to be directly reacted with HCl–MeOH to give pure **12a** and **12b** in 82 and 81% yields, respectively, after recrystallization. Another advantage of **1** over DBU is that crystalline **2**(Cl) and **2**($PhCO_2$) can be easily separated from **11a** or **11b** in high yield simply by filtration, since these salts are quite insoluble in nonpolar or weakly polar solvents. This also allows **1** to be regenerated by treating **2** with KO-*t*-Bu.[9]

Synthesis of α-(Alkoxycarbonyl) Pyrrole and Dipyrromethane Derivatives. Pyrrole derivatives are important intermediates in the synthesis of bioactive porphyrins. Octaethylporphyrin (OEP), for example, is widely used for biological modeling studies because of its high symmetry, relatively good solubility, and stability. Pyrrole derivatives are also important intermediates for the synthesis of bile pigments, drugs, and agrochemicals.[10,11] Most methods[12] for the synthesis of OEP begin from 2-(ethoxycarbonyl)-3,4-diethyl-5-methylpyrrole, prepared by the Knorr reaction of ethyl propionylacetate with 2,4-pentanedione. These methods are inconvenient owing to difficulties in preparing the starting materials and in appropriately transforming the 5-methyl group in the pyrrole ring system for further reaction. The methods developed recently by Barton et al.,[13] Ono et al.,[14] and Sessler et al.[15] for the synthesis of 3,4-disubstituted pyrrole-2-esters as key intermediates to porphyrins (starting from β-acetoxy-α-nitroalkenes (or α-nitroalkenes) and isocyanoacetates in the presence of a nonionic base such as DBU or guanidine) is very

Scheme 2



advantagious in view of its brevity, its use of easily accessible starting materials, and its flexibility for the synthesis of variously functionalized porphyrins, compared with the traditional Knorr approach. However, the preparation of OEP and other porphyrins is still problematic, particularly whenever more than 1 g is desired, because of the accompanying formation of undesired 2,4-bis(alkoxycarbonyl)pyrrole **14**[14b] in Scheme 2, which lowers the yield of the desired α-(alkoxycarbonyl) pyrrole **15**, thus requiring the latter to be isolated chromatographically on a small scale.

We tried to suppress the side reaction leading to **14** by reducing the reaction temperature. But at −20 to −15 °C, DBU failed to promote the formation of either **14** or **15** at an appreciable rate. For example, treatment of β-acetoxy-α-nitrohexane **13a** and ethyl isocyanoacetate **10b** in THF with 2 equiv of DBU at −20 to −15 °C for 2 h produced nearly undetectable amounts of **15** and no detectable quantity of **14** by ^1H NMR spectroscopy. On the other hand, treatment of **13** and **10** in THF with 2 equiv of **1** at −20 to −15 °C for 2 h afforded ^1H NMR spectroscopically pure pyrroles **15a–d** in quantitative yield with no detectable byproduct **14** (Scheme 2). Moreover, the protonated base was separated from **15** as a mixture of **2**(NO_2) and **2**(OAc) in high yield and purity by filtration. The high yield and purity of the crude products **15a–d** permitted the avoidance of chromatographic purification processes and the accompanying product losses, allowing these compounds to be directly used in the synthesis of porphyrins.

Superbase **1** has good solubility both in nonpolar solvents (e.g., benzene, pentane, hexane) and in polar solvents (e.g., THF, diethyl ether, acetonitrile, pyridine, and DMF). The corresponding crystalline protonated superbase salts **2**(NO_2) and **2**(OAc) are virtually insoluble in nonpolar and weakly polar solvents such as pentane, hexane, diethyl ether, ethyl acetate, and DMF but are very soluble in water. On the other hand, the pyrrole derivatives **15a–d** are very soluble in nonpolar and weakly polar solvents such as hexane, diethyl ether, and THF. The large difference in solubility between the salts **2**(NO_2) or **2**(OAc) and **15** allows the former to be removed by filtration, while **15** remains in solution. The salts can

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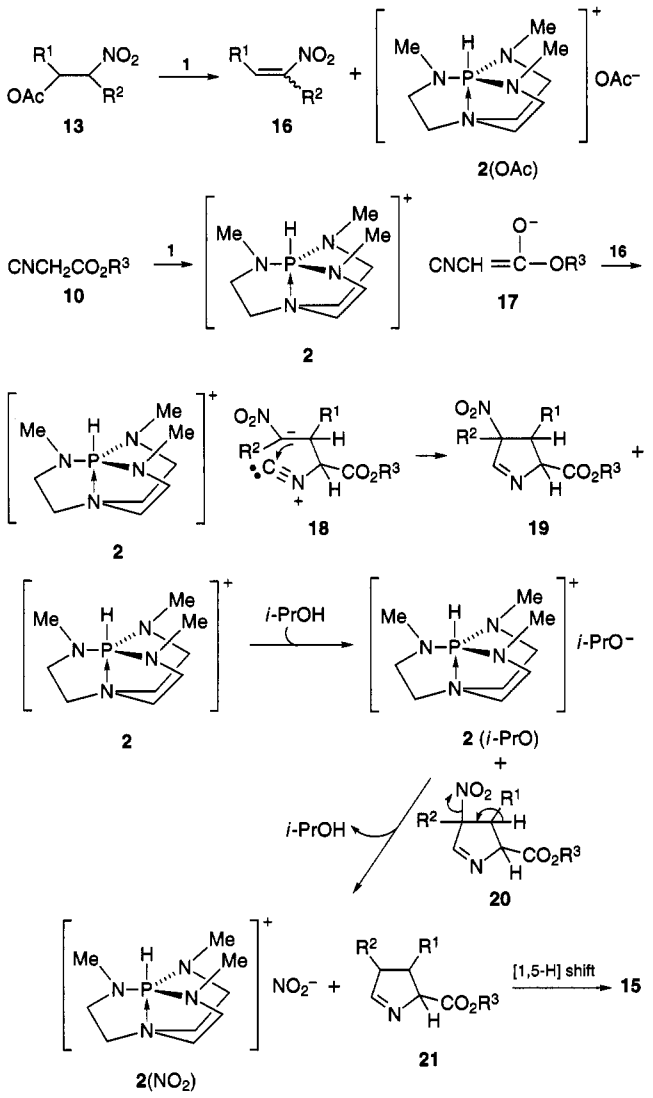
(15) Sessler, J. L.; Mozattari, A.; Johnson, M. *Org. Synth.* **1991**, *10*, 68.

Scheme 3

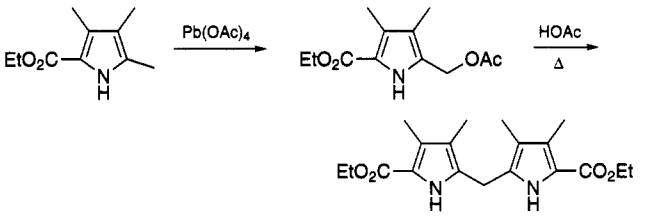


be subsequently deprotonated with *t*-BuOK in high yield, allowing **1** to be recycled for greater economy. To our knowledge, no isolation process of protonated DBU or any other protonated nonionic base followed by regeneration of the nonionic base has been established, mainly because protonated DBU, for example, is quite soluble both in nonpolar and polar solvents, making its recycling difficult.

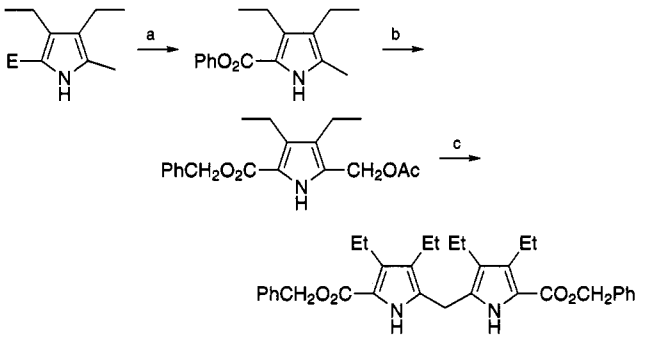
According to the reaction pathway in Scheme 3, which is similar to that proposed by Barton and co-workers,[13] it is believed that the strong basicity of **1** allows the rapid and complete elimination of HOAc from **13** to give **16**, and the rapid conversion of **10** to **17**. This is followed by Michael addition of the isocyanoacetate anion **17** to α-nitroolefin, even at low temperature. It has been reported[16] that the carbanions obtained by deprotonation of substrates with P_4-*t*-Bu are more nucleophilic than when obtained with lithium diisopropylamide. Anion **17** obtained by the action of **1** may also be more nucleophilic compared with similar anions obtained by deprotonation of isocyanoacetate with ionic bases or nonionic bases such as DBU and guanidine. In our process, cation **2** is charge-delocalized from the bridgehead P atom to three equatorial N atoms and to the transannulated bridgehead N atom which is located on the opposite end of the cage.

(16) Pietzonka, T.; Seebach, D. *Chem. Ber.* **1991**, *124*, 1837.

Scheme 4



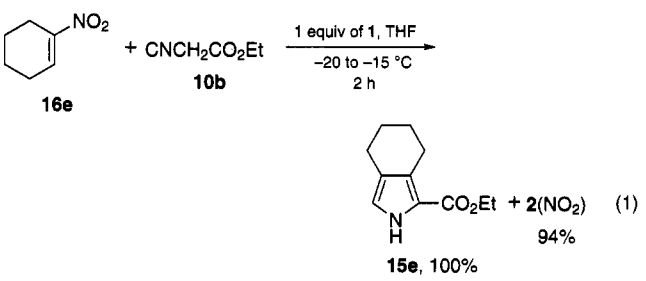
Scheme 5



(a) $PhCH_2OH$; (b) $Pb(OAc)_4$; (c) EtOH/HCl, Δ

This large cation may be only weakly attracted to anion **17**, allowing **17** to be relatively unencumbered by the cation and hence more nucleophilic. Thus, the stronger basicity of **1** and the enhanced nucleophilicity of **17** allow the reaction to proceed at low temperature to afford compound **15** as the only pyrrole product.

Similarly, treatment of commercially available α-nitrocyclohexene and ethyl isocyanoacetate in THF at −20 to −15 °C with 1 equiv of the superbase **1** rapidly affords 2-(ethoxycarbonyl)-3,4-tetramethylenepyrrole (**15e**) in quantitative yield (reaction 1).

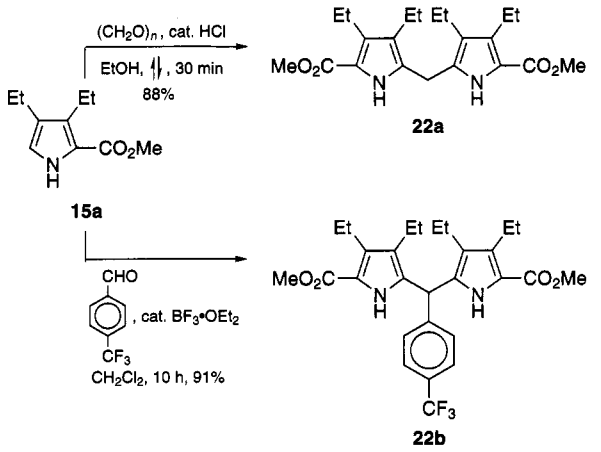


(1)

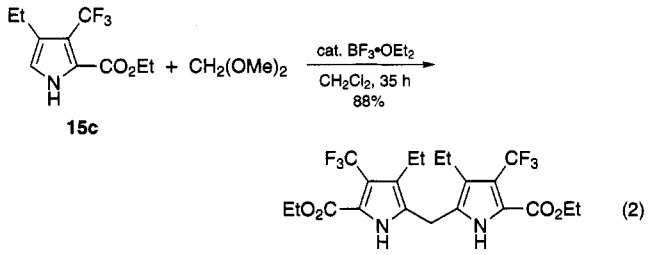
Dipyrromethane derivatives are precursors to important types of sterically blocked *meso*-diarylporphyrin compounds. Precursors such as 5,5′-bis(ethoxycarbonyl)-3,3′,4,4′-tetramethyldipyrromethane[17] and 5,5′-bis(ethoxycarbonyl)-3,3′-diethyl-4,4′-dimethyldipyrromethane[18] have been synthesized using comparatively tedious procedures. A more recent revised procedure[19] for 5,5′-bis(ethoxycarbonyl)-3,3′,4,4′-tetramethyldipyrromethane consists of a two-step reaction sequence from 2-(ethoxycarbonyl)-3,4,5-trimethylpyrrole shown in Scheme 4. A similar synthesis was described for 5,5′-bis(benzyloxycarbonyl)-3,3′,4,4′-tetraethyldipyrromethane[20] (Scheme 5).

(17) Gunter, M. J.; Mander, L. N. *J. Org. Chem.* **1981**, *46*, 4793.
(18) Young, R.; Chang, C. J. *J. Am. Chem. Soc.* **1985**, *107*, 898.
(19) Semeikin, A. S.; Kuz'min, N. G.; Koifman, O. I. *Izv. Vyssh. Uchbn. Zaved. Khim. Tekhnol.* **1988**, *31*, 39; *Chem. Abstr.* **1989**, *111*, 23264p.
(20) Paine, J. B., III; Woodward, R. B. *J. Org. Chem.* **1976**, *41*, 2826.

Scheme 6



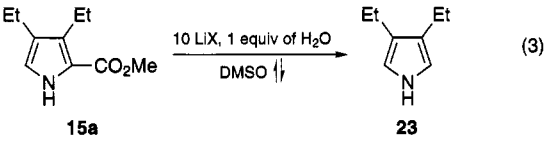
In the present work, 5,5′-bis(methoxycarbonyl)-3,3′,4,4′-tetraethyldipyrromethane (**22a**) was synthesized in one step in 88% yield directly from **15a** as shown in Scheme 6. The reaction was complete in about 30 min in refluxing ethanol in the presence of a catalytic amount of hydrochloric acid. Compound **22a** changes from colorless to red upon exposure to air, but it is stable under N_2 or in the refrigerator for at least 6 months. Ono and coworkers reported that electron-deficient trifluoromethyl-substituted pyrroles reacted with $CH_2(OMe)_2$ in the presence of the catalyst PTSA very slowly, taking 7 days for completion of the reaction. This is also true for pyrrole **15c**. Thus, PTSA-catalyzed electrophilic substitution of the pyrrole **15c** with $CH_2(OMe)_2$ took 10 days for completion as monitored by TLC. Hydrochloric acid is not a suitable catalyst because no apparent product **22c** (see reaction 2) was formed (as monitored by TLC)



when **15c** and $(CH_2O)_n$ in EtOH in the presence of a catalytic amount of hydrochloric acid was refluxed for 40 min. The proton of PTSA or HCl may be hydrogen-bound to either the F or the pyrrole ring nitrogen, rendering the pyrrole ring more electron-deficient, and thus decreasing electrophilic substitution. However, when BF_3•OEt_2 was used as a Lewis acid catalyst (reaction 2), the conversion of **15c** with $CH_2(OMe)_2$ to **22c** was complete within 35 h at room temperature. Similarly, the conversion of **15a** and 4-(trifluoromethyl)benzaldehyde to the dipyrromethane derivative **22b** (Scheme 6) was complete within 10 h at room temperature using the same catalyst. Products **22b** and **22c** were isolated by flash chromatography in 91 and 88% yields, respectively.

Preparation of α-Unsubstituted Pyrrole Derivative 23. The cleavage of esters to furnish a carboxylic acid is a common organic transformation that is usually carried out in a routine manner by acidic or basic hydrolysis. However, pyrrole derivatives are sensitive to acidic conditions and so the α-ester group is generally removed by saponification and subsequent thermal decarboxylation. Although this method provides a means of preparing 3,4-dialkylated pyrroles, the yield is very low (38–40%) and the product is not pure, thus requiring purification by subsequent vacuum distillation.[15]

A new method reported here for removing the α-ester group in pyrrole rings involves an S_N2 demethylation with lithium halides and subsequent thermal decarboxylation in DMSO (reaction 3). The advantages of this



approach are the following: (1) The S_N2 dealkylation with LiX in DMSO is very fast and 100% complete in 1.5–3.0 h at reflux temperature. The intermediate α-lithium carboxylate is quickly decarboxylated to 3,4-diethylpyrrole (**23**) without isolation, in contrast to the traditional saponification and subsequent decarboxylation which is completed in less than 50% yield in 6–10 h.[22] The reaction rates for lithium halides in our process decrease in the order LiCl (1–5 h) > LiBr (2.0 h) > LiI (3.0 h), with the commercially least expensive halide being the fastest in reaction 3. When **15a** in DMSO was refluxed with 10 equiv of NaCl, no product **23** was detected by TLC after 3 h. Apparently Li^+ is a better carboxy-oxygen complexing metal than Na^+, making the carboxy group a better S_N2 leaving group when Cl^- attacks the methyl of the ester group in an S_N2 fashion. (2) The decarboxylation produces α-unsubstituted pyrroles in high yield in a one-pot reaction, thus saving labor and energy. (3) The demethylation and subsequent decarboxylation process can potentially be carried out on a large scale. (4) One of the great values of pyrrole ester cleavage by S_N2 dealkylation is that the reaction can be selective. Biomolecular nucleophilic substitutions are well known to be quite sterically sensitive, and thus only the esters of unhindered alcohols undergo cleavage (methyl works best) if there are two or more different ester groups in the same pyrrole ring.

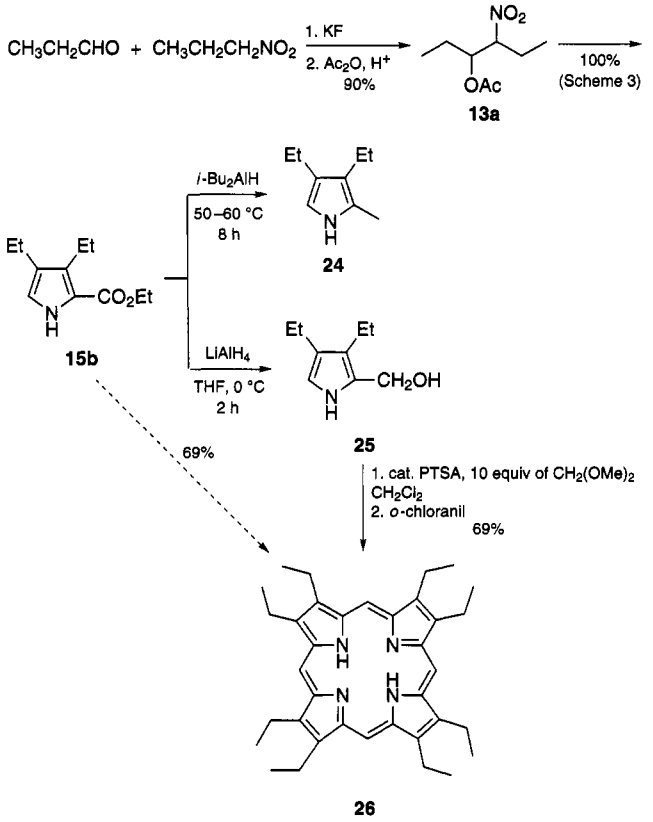
Synthesis of Porphyrins. It is well known that *i*-Bu_2AlH is a milder and more selective reducing agent than $LiAlH_4$, normally reducing esters to alcohols when 2 equiv are used.[23] However, when a solution of **15a** and 2 equiv of *i*-Bu_2AlH was stirred at room temperature for 1 h and at 50–65 °C for 2.6 h, no reduction occurred. On the other hand, at 50–60 °C for 8 h, **15b** was reduced to a compound containing no OH group, which is probably **24** in Scheme 7. Ono et al.[14] reported that under controlled reaction conditions, $LiAlH_4$ selectively reduced **15b** to α-(hydroxymethyl)-3,4-diethylpyrrole (**25**), which was converted to OEP **26** in two steps in trace to 55% yield under various conditions. These authors proposed that the catalyst PTSA first converted α-(hydroxymethyl)-3,4-diethylpyrrole to formaldehyde and 3,4-diethylpyrrole, which was subsequently cyclized to OEP **26**. They also found that $CH_2(OMe)_2$ as an additional source of formaldehyde increased the yield of OEP **26** from 23 to 55%.

(21) Ono, N.; Kawamura, H.; Maruyama, K. *Bull. Chem. Soc. Jpn.* **1989**, *62*, 3386.

(22) John, A. W.; Kay, I. T.; Markham, E.; Price, R.; Shaw, K. B. *J. Chem. Soc.* **1959**, 3416.

(23) Link, H.; Bernauer, K. *Helv. Chem. Acta* **1972**, *4*, 1054.

Scheme 7



Scheme 8

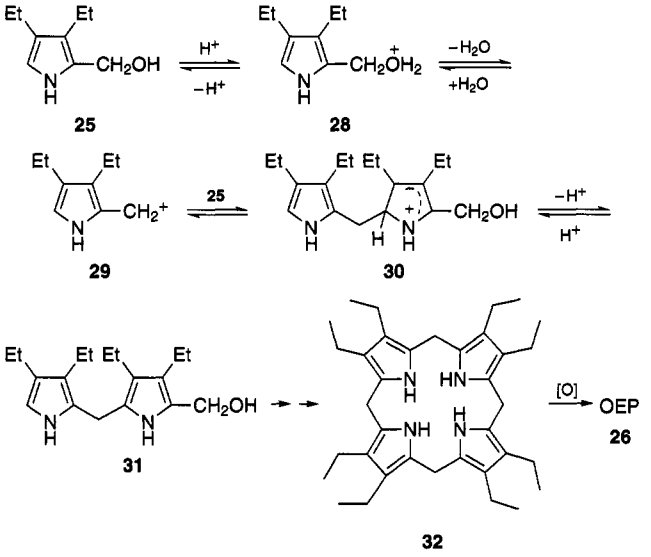
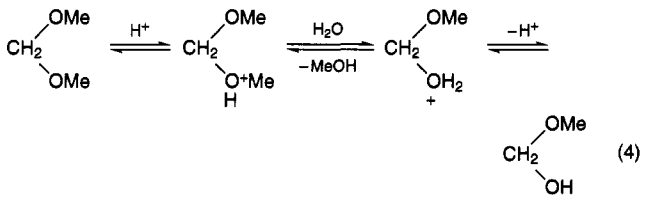


Table 1. Preparation of OEP 26 from 15b

expt	treatment of crude **25**	condensation reaction conditions	yield of OEP **26** (%)
1	not dried but immediately used	CH_2Cl_2, PTSA·H_2O $CH_2(OMe)_2$ (10 equiv)	69
2	dried with $MgSO_4$ for 12 h	CH_2Cl_2, PTSA·H_2O $CH_2(OMe)_2$ (10 equiv)	21
3	not dried but immediately used	CH_2Cl_2, PTSA·H_2O	53
4	not dried but immediately used	CH_2Cl_2, PTSA·H_2O $(CH_2O)_n$ (10 equiv)	23

[a] In all four experiments, *o*-chloranil was used as the oxidant, basic aluminum oxide was used as the chromatography packing material, and CH_2Cl_2 was employed as the eluting solvent.

In this report, the crude product **15b** prepared in 100% yield as mentioned earlier, was reduced to α-(hydroxymethyl)-3,4-diethylpyrrole (**25**) (Scheme 7) which was then converted to OEP **26** in various yields under different conditions (see Table 1 in the Experimental Section). In summary we found that **25** was not stable and changed its color from nearly colorless to red even upon storage in a refrigerator. If the crude product was stored or dried with anhydrous $MgSO_4$ overnight, the yield of OEP was only 21%. If the crude product **25** was not stored or dried but immediately reacted in the presence of the catalyst PTSA in CH_2Cl_2, the OEP yield increased to 53%. If the crude product was immediately reacted in the presence of the catalyst PTSA and 10 equiv of $CH_2(OMe)_2$ as a dehydrating agent, the OEP yield was increased to 69% (Scheme 7). However, the OEP yield was decreased to 23% when 10 equiv of $(CH_2O)_n$ replaced $CH_2(OMe)_2$. From these observations, we propose the possible reaction pathway shown in Scheme 8. Under acid conditions, α-(hydroxymethyl)-3,4-diethylpyrrole (**25**) reversibly eliminates a molecule of H_2O and generates 3,4-diethylpyrrole-α-methyl cation **29**, which then electrophilically reacts with another molecule of α-(hydroxymethyl)-3,4-diethylpyrrole (**25**) to afford the intermediate **30**. Species **30** eliminates H^+ to give the intermediate **31**. This process is repeated, finally affording octaethylporphyrinogen **32** which is subsequently oxidized to OEP. Since elimination and addition of H_2O is reversible, removal of H_2O would shift the equilibrium toward porphyrinogen **32**, thus increasing the yield of OEP. $CH_2(OMe)_2$ may be similar to $(CH_3)_2C(OMe)_2$, which is also a dehydrating agent,[24] converting H_2O to hemiacetal in the presence of an acid catalyst (reaction 4). Addition of $(CH_2O)_n$ decreases the OEP yield because $(CH_2O)_n$ competitively attacks the 5-position of the pyrrole ring **25** to form 2,5-bis(hydroxymethyl)-3,4-diethylpyrrole, consequently interrupting the tetramerization leading to the porphyrinogen **32**. Here the yield of OEP was increased to 69% from **15b** and the overall yield of OEP was as high as 62% on the basis of the commercially available starting materials CH_3CH_2CHO or $CH_3CH_2CH_2NO_2$.



(4)

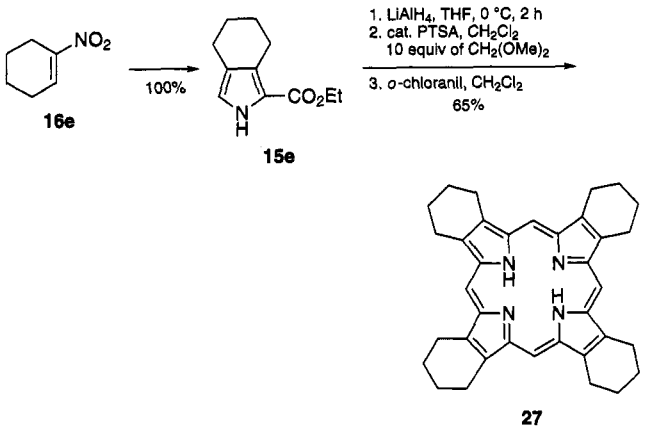
In a similar manner, porphyrin **27** was synthesized in 65% overall yield on the basis of the commercially available starting material α-nitrocyclohexene when 10 equiv of the dehydrating agent $CH_2(OMe)_2$ was used (Scheme 9).

As reported earlier by others,[14] we also find that the PTSA-catalyzed condensation cyclization of pyrrole **23** with formaldehyde followed by oxidation gives a very low yield (16%) of OEP **26**. This may be a consequence of the instability of the pyrrole **23**, or because of entropy-favored linear polymerization of the pyrrole **23** with formaldehyde. We therefore designed a one-pot reaction procedure involving four reactions (Scheme 10) in which

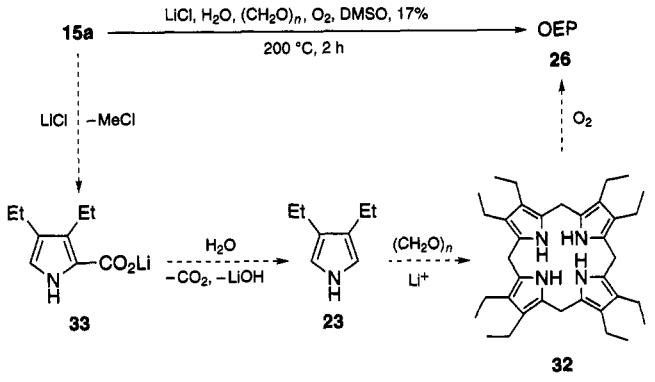
(24) (a) Sakamoto, M.; Kajiyama, K. I.; Tonami, H. *J. Chromatotogr.* **1974**, *95*, 189. (b) Muller, L. L.; Jacks, T. J. *J. Histochem. Cytochem.* **1975**, *23*, 107.

(25) Schwesinger, R.; Schlemper, H. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 1167.

Scheme 9



Scheme 10

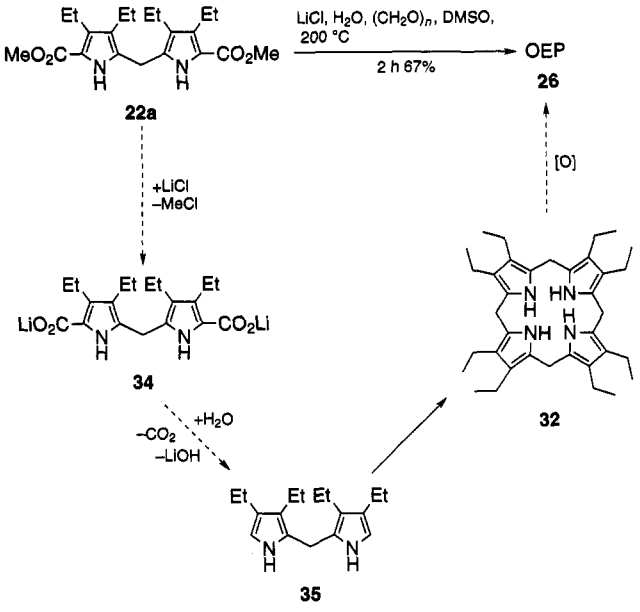


the pyrrole **23**, generated *in situ* by fast demethylation with LiCl and subsequent thermal decarboxylation, cyclized with paraformaldehyde by the catalysis of the Lewis acidic Li^+ cation to give the porphyrinogen **32** which was quickly oxidized by O_2 to afford OEP **26** in 17% overall yield. Here we find that LiCl functions both as a strong nucleophile (Cl^- anion) in the demethylation of **15a** and as a Lewis acid (Li^+) in the cyclization of **23** with paraformaldehyde. This experiment essentially restricted the instability effect of **23** on the low yield of OEP since **23** was generated *in situ*. The linear polymerization or oligomerization of **23** with formaldehyde could account for the low yield of OEP, and thus the preformation of the dipyrromethane **35** (Scheme 11) at least partially circumvents the entropy-unfavored tetramerization in Scheme 10. Indeed, as shown in Scheme 11, OEP was isolated in 67% yield in a one-pot synthesis from **22a**, which was prepared by the HCl-catalyzed electrophilic substitution of $(CH_2O)_n$ at **15a** and isolated in 88% yield.

Bases of type **1** are potentially useful as stoichiometric deprotonating agents in a variety of synthetic applications wherein weaker bases such as DBU are inadequate. Sterically hindered **1** and its analogues may also be useful in generating enolates under kinetic conditions, in catalyzing acylation and anionic polymerization reactions, and in serving as an electronically flexible ligand in palladium-catalyzed syntheses. Investigations of these and other applications of compound of type **1** are currently underway.

Conclusions. Compound **1** is a highly effacacious nonionic deprotonating agent for the high yield syntheses of α-*C*-acyl amino acid esters from oxazoles and porphyrins from pyrroles or dipyrromethanes. Because of the extremely strong basicity and nucleophilicity of **1**, deprotonations are more complete and faster than with typical nonionic bases such as Et_3N, DBU, or Proton Sponge. Other advantages of **1** demonstrated here are that deprotonations with this compound can be carried out at relatively low temperatures (thus minimizing side reactions), its protonated product **2**(X) can be easily separated from the reaction mixture by filtration, and **1** can be recovered in one step from **2**(X) for recycling. Halogenated solvents such as CH_2Cl_2, $CHCl_3$, and CCl_4 should be avoided, however, owing to their interesting reactivities with **1** to be reported later. Other useful synthetic improvements in the syntheses described here are (1) the use of $BF_3{\cdot}OEt_2$ as a better catalyst than a protic acid for the electrophilic substitution of fluoro-substituted pyrroles with $CH_2(OMe)_2$, (2) the utilization of $CH_2(OMe)_2$ as a dehydrating agent to improve the OEP yield, and (3) our discovery of the effectiveness of LiCl as both a nucleophile for dealkylation of the dicarboxylate **34** and as a Lewis acid catalyst in the electrophilic cyclization of dipyrromethane **35** with $(CH_2O)_n$ to give porphyrinogen **32** in our one-pot synthesis of OEP in 67% overall yield.

Scheme 11



Experimental Section

General. THF, toluene, and pentane were refluxed with sodium in the presence of benzophenone and freshly distilled. Benzene and acetonitrile were refluxed with CaH_2 and freshly distilled. Compound **1** was prepared as described previously.[1,2a] NMR spectrometers employed included a Nicolet NT-300 or a Varian VXR-300 for ^1H spectra, a Bruker WM-200 for ^{31}P spectra, and a Varian VXR-300 for ^{13}C spectra. Standards for the NMR spectra were TMS (^1H, internal), 85% H_3PO_4 (^{31}P, external), and the δ 118.20 peak of the solvent CD_3CN or the δ 77.0 peak of the solvent $CDCl_3$ (^{13}C, internal). Infrared spectra were recorded with a Bruker IFS-113V spectrometer. UV spectra were recorded with an HP8452A spectrophotometer. HRMS and fast atom bombardment (FAB) mass spectra were recorded with a KRATOS MS-50 spectrometer. The solvent and the matrix employed were CH_3CN and 3-nitrobenzyl alcohol, respectively, for FAB mass spectra of **12a** and **12b**. Elemental analyses were performed by Desert Analytics.

4-(Methoxycarbonyl)-5-(3,4,5-trimethoxyphenyl)-oxazole (11a)[8a,b] (Ar = 3,4,5-Trimethoxyphenyl)[8a,b] Using the Superbase 1. To a magnetically stirred solution of the superbase (0.47 g, 2.1 mmol) in dry THF (5 mL) at 5 °C was

added in one portion methyl isocyanoacetate (**10a**) (0.23 g, 2.1 mmol, 95%). The solution was stirred for 15 min. To this stirred solution was added dropwise a solution of 3,4,5-trimethoxybenzoyl chloride (**9a**) (0.50 g, 2.1 mmol, 98%) in THF (5 mL) at 5 °C. The reaction mixture was then stirred at room temperature for 30 min to form a solid–liquid biphasic system lacking an isocyanoacetate odor when the flask was opened. The biphasic mixture was diluted with ethyl acetate (40 mL) and filtered in vacuo. The solid was washed with ethyl acetate (2 × 10 mL) within the filter and dried in vacuo to give ^{31}P NMR and ^{1}H NMR spectroscopically pure **2**(Cl) (0.52 g, 98%). ^{31}P NMR (CD_3CN): −9.40. ^{1}H NMR (CD_3CN): 2.60 (d, 9 H, J_{PH} = 17.4 Hz), 2.98 (dt, 6 H, J_{PH} = 11.1 Hz, J_{HH} = 6.0 Hz), 3.12 (dt, 6 H, J_{PH} = 5.7 Hz, J_{HH} = 6.0 Hz), 5.28 (d, 1 H, J_{PH} = 493.8 Hz). The combined filtrate and washings were washed with water (5 mL). The organic phase was separated, and the aqueous phase was extracted with ethyl acetate (15 mL). The combined organic phases were dried over anhydrous $MgSO_4$ and rotary-evaporated to give ^{1}H NMR spectroscopically pure **11a** (0.61 g, 99%). ^{1}H NMR (CD_3CN): 3.78 (s, 3 H), 3.84 (s, 3 H), 3.85 (s, 6 H), 7.37 (s, 2 H), 8.06 (s, 1 H). HRMS: calcd 293.08994 for $C_{14}H_{15}NO_6$, measd 293.08940.

4-(Methoxycarbonyl)-5-(3,4,5-trimethoxyphenyl)-oxazole (11a) (Ar = 3,4,5-Trimethoxyphenyl)[8a,b] Using DBU. To a stirred solution of methyl isocyanoacetate (**10a**) (0.44 g, 4.2 mmol, 95%) in dry THF (5 mL) at 5 °C was added DBU (0.63 g, 4.2 mmol). After the solution was stirred for 45 min, a solution of 3,4,5-trimethoxybenzoyl chloride (0.99 g, 4.2 mmol) in THF (10 mL) was added dropwise at 5 °C. The mixture was then further stirred at room temperature for 2 h to give a brown solution with a heavy isocyanoacetate odor when the flask was opened. The solution was rotary evaporated, washed with water (10 mL), and extracted with ethyl acetate (2 × 35 mL). The combined organic extracts were rotary evaporated in vacuo to give a brown oil (0.68 g). The ^{1}H NMR spectrum showed that this brown oil contained mainly unreacted methyl isocyanoacetate and trimethoxybenzoic acid arising from the aqueous workup, with a small amount of the desired 4-(methoxycarbonyl)-5-(3,4,5-trimethoxyphenyl)oxazole (**11a**). Gas chromatography of this mixture showed that only ~8% of **11a** had formed.

4-(Methoxycarbonyl)-5-phenyloxazole (11b) (Ar = Ph)[8a,b] Using the Superbase 1. To a solution of the base **1** (0.91 g, 4.2 mmol) in dry THF (5 mL) at 5 °C was added by syringe methyl isocyanoacetate (**10a**) (0.44 g, 4.2 mmol, 95%). After the solution was stirred at 5 °C for 15 min, a solution of benzoic anhydride (0.97 g, 4.2 mmol) in dry THF (5 mL) was added at 5 °C. The mixture was then stirred at room temperature for 30 min to form a solid–liquid biphasic system without the odor of the isocyanoacetate when the flask was opened. The biphasic mixture was rotary-evaporated in vacuo, and the residue was treated with diethyl ether (30 mL) followed by filtration in vacuo. The solid was washed within the filter with ether (3 × 10 mL) and dried in vacuo to give **2**($PhCO_2$) (1.30 g, 91%). ^{31}P NMR (CD_3CN): −9.52. ^{1}H NMR (CD_3CN): 2.58 (d, 9 H, J_{PH} = 17.4 Hz), 2.96 (dt, 6 H, J_{PH} = 11.4 Hz, J_{HH} = 6.0 Hz), 3.10 (dt, 6 H, J_{PH} = 7.2 Hz, J_{HH} = 6.0 Hz), 5.28 (d, 1 H, J_{PH} = 493.8 Hz), 7.23 and 7.89 (two m, 5 H). The filtrate and the washings were combined and washed with water (10 mL). The organic phase was separated, and the aqueous phase was extracted with ethyl acetate (20 mL). The combined organic phases were rotary-evaporated in vacuo to give ^{1}H NMR spectroscopically pure **11b** (0.85 g, 100%). ^{1}H NMR (CD_3CN): 3.83 (s, 3 H), 7.49 and 7.96 (two m, 5 H), 8.03 (s, 1 H). HRMS: calcd 203.05824 for $C_{11}H_{19}NO_3$, measd 203.05833.

α-(3,4,5-Trimethoxyphenyl)acyl Amino Acid Methyl Ester Hydrochloride 12a (Ar = 3,4,5-Trimethoxyphenyl).[8a,b] The crude oxazole prepared using **1** (0.61 g, 2.1 mmol) was dissolved in a mixture of methanol (15 mL) and concentrated hydrochloric acid (5 mL). The solution was stirred at 50 °C for 6 h. The literature workup[8b] gave pure **12a** (0.55 g, 82%, lit.[8b] 80%), mp 175–176 °C (lit.[8b] mp 174–175 °C). ^{1}H NMR (DMSO-d_6): 3.71 (s, 3 H), 3.79 (s, 3 H), 3.87 (s, 6 H), 6.34 (s, 1 H), 7.47 (s, 2 H), 9.11 (br, 3 H). Mass spectrum (FAB): 284 $(M - Cl)^+$, required for $(M - Cl)^+$ 284.

α-Phenylacyl Amino Acid Methyl Ester Hydrochloride 12b (Ar = Ph).[8a,b] Crude 4-(methoxycarbonyl)-5-phenyloxazole (**11b**) (0.83 g, 4.1 mmol) prepared above using **1** was dissolved in a mixture of methanol (6 mL) and concentrated hydrochloric acid (2.5 mL) which was stirred at 50 °C for 6 h. The workup[8b] used for **12a** gave pure **12b** (0.76 g, 81%, lit.[8b] 84%), mp 186–187 °C (lit.[8b] mp 185–186 °C). ^{1}H NMR (DMSO-d_6): 3.88 (s, 3 H), 6.25 (s, 1 H), 7.61 (m, 2 H), 7.76 (m, 1 H), and 8.15 (d, 2 H, J_{HH} = 7.5 Hz), 9.20 (br, 3 H). Mass spectrum (FAB): 194 $(M - Cl)^+$, required for $(M - Cl)^+$ 194.

2-(Ethoxycarbonyl)-3,4-diethylpyrrole (15b)[14a] Using the Superbase 1. To a magnetically stirred solution of 4-acetoxy-3-nitrohexane (**13a**) (0.68 g, 3.6 mmol), ethyl isocyanoacetate (**10b**) (0.43 g, 3.6 mmol, 95%), and 2-propanol (0.8 mL) in dry THF (5 mL) at −20 °C was added dropwise a solution of **1** (1.6 g, 7.2 mmol) in dry THF (5 mL). The addition funnel was rinsed with 2 mL of dry THF, and the rinsing solution was added dropwise to the reaction mixture. The mixture was stirred at −20 °C to −15 °C for 2 h to form a solid **2**(Y)/liquid biphasic system which gave no isocyanoacetate odor when the flask was opened. The solvent was rotary-evaporated in vacuo, and the residue was extracted with hexane (20 mL). The precipitate was filtered in vacuo, washed within the filter with diethyl ether (2 × 10 mL), and dried in vacuo to give ^{31}P and ^{1}H NMR spectroscopically pure solid product **2**(Y) (Y = OAc, NO_2, mixture, 1.86 g, 96%). ^{31}P NMR (CD_3CN): −9.27 (Y = NO_2) and −9.47 (Y = AcO). ^{1}H NMR spectrum ($CDCl_3$) of the mixture of **2**(NO_2) and **2**(OAc): 1.98 (s, 3 H), 2.60 (d, 9 H, J_{PH} = 17.4 Hz), 2.98 (dt, 6 H, J_{PH} = 11.1 Hz, J_{HH} = 6.3 Hz), 3.11 (dt, 6 H, J_{PH} = 10.8 Hz, J_{HH} = 6.0 Hz), 5.27 (d, 1 H, J_{PH} = 494.1 Hz). The combined filtrate and washings were washed with water (15 mL). The organic phase was separated, and the aqueous phase was extracted with ethyl acetate (2 × 25 mL). The combined organic phases were dried with anhydrous $MgSO_4$ and rotary-evaporated in vacuo to give **15b** as a ^{1}H NMR spectroscopically pure orange oil (0.70 g, 100%). ^{1}H NMR ($CDCl_3$): 1.14 (t, 3 H, J_{HH} = 7.5 Hz), 1.17 (t, partially overlapped with the peak at 1.14, 3 H, J_{HH} = 7.5 Hz), 1.35 (t, 3 H, J_{HH} = 7.5 Hz), 2.45 (q, 2 H, J_{HH} = 7.5 Hz), 2.75 (2 H, J_{HH} = 7.5 Hz), 4.31 (q, 2 H, J_{HH} = 7.5 Hz), 6.67 (d, 1 H, J_{HH} = 2.7 Hz), 8.76 (br, 1 H, NH). HRMS: calcd 195.12593 for $C_{11}H_{17}NO_2$, measured 195.12556.

Salt **2**(Y) can be washed away with water if recovery of **1** is not desired. Thus, the solid–liquid biphasic mixture obtained in the aforementioned procedure was rotary-evaporated in vacuo. The residue was mixed with water (15 mL) and the mixture extracted with ethyl acetate (3 × 25 mL). The extract was dried with anhydrous $MgSO_4$ and rotary-evaporated in vacuo to give **15b** as a ^{1}H NMR spectroscopically pure orange oil (0.70 g, 100%).

Recycling Superbase 1. To a magnetically stirred suspension of potassium *tert*-butoxide (1.2 g, 0.011 mol) in dry CH_3CN (20 mL) was added dropwise a solution of **2**(Y) (Y = NO_2, OAc, a mixture, separated as aforementioned, 1.85 g, 6.9 mmol) in dry CH_3CN (20 mL) by syringe. The mixture was stirred at room temperature for 1 h and evaporated in vacuo (oil pump). By cannula, 200 mL of dry pentane was added to the residue which was then stirred overnight. The pentane solution was transferred by cannula to another dry flask (500 mL), from whence it was evaporated in vacuo to give a white solid which was sublimed at 50 °C/0.02 Torr to give pure **1** (1.22 g, 82%).

2-(Ethoxycarbonyl)-3,4-diethylpyrrole (15b)[14a] Using DBU. Method A. To a magnetically stirred solution of 4-acetoxy-3-nitrohexane (**13a**) (0.68 g, 3.6 mmol), ethyl isocyanoacetate (**10b**) (0.43 g, 3.6 mmol, 95%), and 2-propanol (0.8 mL) in dry THF (5 mL) was added dropwise a solution of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU, 1.12 g, 7.37 mmol) in dry THF (5 mL) at 0–35 °C. The addition funnel was rinsed with THF (2 mL), and the rinsing solution was added to the reaction mixture. After being stirred at room temperature for 15 h, the mixture was poured into water (15 mL), extracted with ethyl acetate (2 × 25 mL), and dried with anhydrous $MgSO_4$. The solvent was removed in vacuo to give a mixture of **15b** and **14b** (0.65 g) in a 9:1 ratio (as shown by ^{1}H NMR integration for the C(5)H peak assignment (see supplementary

material)). ^{1}H NMR ($CDCl_3$) of **14b**: 7.43 (d, $^2J_{HH}$ = 2.6 Hz), other peaks were overlapped with the peaks of **15b**. HRMS of the mixture of **14b** and **15b**: **15b** calcd 195.12593 for $C_{11}H_{17}NO_2$, measd 195.12546; **14b** calcd 239.13270 for $C_{12}H_{17}NO_4$, measd 239.13213. **Method B.** The same reaction was conducted at −20 to −15 °C for 2 h. The reaction mixture was then poured into water (15 mL) and rotary-evaporated in vacuo to remove THF. The residue was diluted with water (5 mL) and extracted with ethyl acetate (2 × 25 mL). The extracts were dried with anhydrous $MgSO_4$ overnight and rotary-evaporated in vacuo to give 0.68 g of a brown liquid with a heavy isocyanoacetate odor. The brown oil displayed a complicated ^{1}H NMR spectrum consistent with the presence of mainly starting material **13a** and **10b** with nearly no detectable **15b**.

2-(Methoxycarbonyl)-3,4-diethylpyrrole (15a) Using the Superbase 1. To a magnetically stirred solution of 4-acetoxy-3-nitrohexane (**13a**) (4.80 g, 25.0 mmol), methyl isocyanoacetate (**10a**) (2.64 g, 25.0 mmol, 95%) and 2-propanol (6.5 mL) in dry THF (15 mL) at −20 °C was added dropwise a solution of **1** (10.95 g, 50.69 mmol) in dry THF (15 mL). The mixture was stirred at −20 to −15 °C for 2 h to form a solid−liquid biphasic system which was rotary evaporated to dryness. The residue was stirred with hexane (80 mL) for 30 min. The precipitate was filtered in vacuo, washed with ether (2 × 30 mL), and dried in vacuo to give ^{31}P and ^{1}H NMR spectroscopically pure **2**(Y) (Y = NO_2, OAc mixture, 12.8 g, 95%). The combined filtrate and washings were washed with water (20 mL), and the organic layer was separated. The aqueous layer was extracted with ethyl acetate (2 × 50 mL), and the combined organic phases were dried with anhydrous $MgSO_4$ and rotary-evaporated in vacuo to give **15a** as a ^{1}H NMR spectroscopically pure orange oil (4.57 g, 100%) which solidified upon standing. ^{1}H NMR ($CDCl_3$): 1.13 (t, 3 H, J_{HH} = 7.5 Hz), 1.89 (t, 3 H, J_{HH} = 7.5 Hz), 2.46 (q, 2 H, J_{HH} = 7.4 Hz), 2.75 (q, 2 H, J_{HH} = 7.5 Hz), 3.84 (s, 3 H), 6.67 (d, 1 H, J_{HH} = 2.7 Hz), 8.77 (br, 1 H). For elemental analysis, a small amount of sample was recrystallized from hexane in a freezer. The supernatant was removed by syringe to give light yellowish crystals which were dried in vacuo. IR (KBr pellet): 601, 737, 776, 812, 929, 975, 993, 1089, 1140, 1277, 1399, 1438, 1508, 1568, 1676, 2872, 2967, 3027, 3316 cm^{-1}. HRMS: calcd 181.11028 for $C_{10}H_{15}NO_2$, measd 181.11008. Anal. Calcd: C, 66.26; H, 8.35; N, 7.33. Found: C, 66.03; H, 8.25; N, 7.98.

2-(Ethoxycarbonyl)-3,4-tetramethylenepyrrole (15e)[14a] Using the Superbase 1. To a solution of 1-nitrocyclohexene (**16e**) (0.66 g, 5.2 mmol) and ethyl isocyanoacetate (**10b**) (0.62 g, 5.2 mmol, 95%) in dry THF (5 mL) at −20 °C was added dropwise a solution of **1** (1.12 g, 5.23 mmol) in THF (5 mL). The addition funnel was rinsed with 2 mL of dry THF which was then added dropwise to the reaction mixture. The mixture was stirred at −20 to −15 °C for 2 h and evaporated in vacuo to dryness. The residue was stirred with hexane (25 mL) for 30 min and filtered in vacuo. The solid was washed with ether (2 × 10 mL) and dried in vacuo to give **2**(NO_2) (1.28 g, 94%). ^{31}P NMR (CD_3CN) of **2**(NO_2): −9.27. The combined filtrate and washings were washed with water (10 mL), and then the organic layer was separated. The aqueous layer was extracted with ethyl acetate (2 × 30 mL), and the combined organic layers were then dried with anhydrous $MgSO_4$ overnight and evaporated in vacuo to give **15e** (1.0 g, 100%) as a ^{1}H NMR spectroscopically pure solid. ^{1}H NMR ($CDCl_3$): 1.32 (t, 3 H, J_{HH} = 6.9 Hz), 1.72 (m, 4 H), 2.52 (t, 2 H, J_{HH} = 5.7 Hz), 2.79 (t, 2 H, J_{HH} = 4.2 Hz), 4.27 (q, 2 H, J_{HH} = 6.9 Hz), 6.62 (d, 1 H, J_{HH} = 2.4 Hz), 8.87 (br, 1 H, NH). HRMS: calcd 193.11028 for $C_{11}H_{15}NO_2$, measd 193.11045.

2-(Ethoxycarbonyl)-3-(trifluoromethyl)-4-ethylpyrrole (15c)[21] Using the Superbase 1. To a magnetically stirred solution of 2-acetoxy-3-nitro-1,1,1-trifluoropentane (**13b**) (1.99 g, 9.25 mmol), ethyl isocyanoacetate (**10b**) (1.10 g, 9.25 mmol, 95%), and 2-propanol (2.5 mL) in dry THF (5 mL) at −20 °C to −15 °C was added dropwise a solution of **1** (4.0 g, 18.5 mmol) in THF (5 mL). The addition funnel was rinsed with 2 mL of dry THF, and the rinsing solution was added to the reaction mixture. The mixture was stirred at −20 °C to −15 °C for 2 h to form a solid **2**(Y)/liquid biphasic system which gave no isocyanoacetate odor when the flask was opened. The solvent was removed, and the residue was mixed with water (20 mL) and extracted with hexane (3 × 50 mL). The combined extracts were dried with $MgSO_4$ and rotary-evaporated to give **15c** as a ^{1}H NMR spectroscopically pure oil (2.16 g, 100%). ^{1}H NMR ($CDCl_3$): 1.20 (s, 3 H, J_{HH} = 7.5 Hz), 1.36 (s, 3 H, J_{HH} = 7.5 Hz), 2.62 (q, 2 H, J_{HH} = 7.5 Hz), 4.38 (q, 2 H, J_{HH} = 7.5 Hz), 6.73 (d, 1 H, J_{HH} = 1.8 Hz), 9.51 (br, 1 H). HRMS: calcd 235.08201 for $C_{10}H_{12}F_3NO_2$, measd 235.08222.

2-*tert*-(Butoxycarbonyl)-4-(2-(methoxycarbonyl)ethyl)-3-methylpyrrole (15d)[13] Using Superbase 1. To a magnetically stirred solution of 5-acetoxy-4-nitrohexanoate (**13c**)[13] (0.83 g, 3.5 mmol), *tert*-butyl isocyanoacetate (0.53 g, 3.5 mmol, 95%), and 2-propanol (0.5 mL) in dry THF (5 mL) at −20 °C to −15 °C was added dropwise a solution of **1** (1.548 g, 7.167 mmol) in THF (5 mL). The addition funnel was rinsed, and the rinsing solution was added to the reaction mixture. The mixture was stirred at −20 °C to −15 °C for 2.0 h to form a solid **2**(Y)/liquid biphasic system which gave no isocyanoacetate odor when the flask was opened. The solvent was rotary evaporated in vacuo. The residue was mixed with water (20 mL) and extracted with hexane (3 × 50 mL). The extracts were dried with $MgSO_4$ and then rotary-evaporated to give a ^{1}H NMR spectroscopically pure oil (**15d**) (0.94 g, 100%). ^{1}H NMR ($CDCl_3$): 1.56 (s, 9 H), 2.26 (s, 3 H), 2.53 (t, 2 H, J_{HH} = 7.5 Hz), 2.75 (t, 2 H, J_{HH} = 7.5 Hz), 3.67 (s, 3 H), 6.65 (d, 1 H, J_{HH} = 3.4 Hz), 8.86 (br, 1 H). HRMS: calcd 267.16706 for $C_{14}H_{21}NO_4$, measd 267.16735.

5′,5′-Bis(methoxycarbonyl)-3,3′,4,4′-tetraethylpyrromethane (22a). A mixture of 2-(methoxycarbonyl)-3,4-diethylpyrrole (**15a**) (0.40 g, 2.2 mmol), paraformaldehyde (0.26 g, 8.6 mmol), ethanol (2.5 mL), and concentrated hydrochloric acid (0.05 mL) was refluxed for 30 min under argon, cooled to room temperature, and then kept in a freezer overnight at about −20 °C. The resulting crystals were filtered in vacuo to give a white solid (0.36 g, 87.5%), mp 130−131 °C. ^{1}H NMR ($CDCl_3$): 1.06 (t, 6 H, J_{HH} = 7.5 Hz), 1.15 (t, 6 H, J_{HH} = 7.5 Hz), 2.42 (q, 4 H, J_{HH} = 7.5 Hz), 2.72 (q, 4 H, J_{HH} = 7.5 Hz), 3.80 (s, 6 H), 3.87 (s, 2 H), 8.63 (br, 2 H). ^{13}C NMR (CD_3CN): 16.30, 17.56, 18.79, 23.40, 51.24, 117.33, 124.00, 134.46, 162.05. IR (KBr pellet): 723, 779, 1010, 1140, 1256, 1281, 1448, 1494, 1619, 1695, 2870, 2932, 2966, 3320, 3368. HRMS: calcd 374.22056 for $C_{21}H_{30}N_2O_4$, measd 374.22025. Anal. Calcd: C, 67.34; H, 8.08; N, 7.48. Found: C, 67.37; H, 8.00; N, 6.87.

5,5′-Bis(methoxycarbonyl)-3,3′,4,4′-tetraethylpyrro(4-(trifluoromethyl)phenyl)methane 22b. A solution of **15a** (1.0 g, 5.5 mmol) in CH_2Cl_2 (15 mL) was deaerated with argon for 5 min. 4-(Trifluoromethyl)benzaldehyde (1.1 g, 6.3 mmol) and BF_3·OEt_3 (0.31 g, 2.2 mmol) were added by syringe. After the mixture was stirred at room temperature for 10 h, TLC showed that **15a** disappeared and a new component (**22b**) appeared (R_f = 0.23, $CHCl_3$:hexane = 1:1). The volatiles were removed in vacuo at room temperature. The residue was dissolved in ethyl acetate (40 mL) and washed with sodium bicarbonate (50 mL, 5%). The organic layer was separated, and the aqueous layer was extracted with ethyl acetate (40 mL). The combined organic phases were concentrated in vacuo. Flash chromatography on silica gel (140 × 45 mm, $CHCl_3$:hexane = 1:1) gave the orange solid product **22b** (1.30 g, 90.9%). ^{1}H NMR ($CDCl_3$): 0.92 (t, 6 H, J_{HH} = 7.5 Hz), 1.14 (t, 6 H, J_{HH} = 7.5 Hz), 2.33 (q, 4 H, J_{HH} = 7.5 Hz), 2.71 (q, 4 H, J_{HH} = 7.5 Hz), 3.72 (s, 6 H), 5.63 (s, 1 H), 7.18 (d, 2 H, J_{HH} = 7.5 Hz), 7.76 (d, 2 H, J_{HH} = 8.1 Hz), 8.57 (b, 2 H). ^{13}C NMR ($CDCl_3$): 15.72, 15.78, 17.12, 18.32, 22.00, 51.05, 117.73, 124.23, 125.82 (q, J_{CF} = 3.1 Hz), 127.50 (q, J_{CF} = 266.8 Hz), 129.27 (q, J_{CF} = 32.3 Hz), 128.57, 130.73, 134.16, 144.09, 161.79 (C=O). IR (KBr pellet): 594, 778, 1013, 1067, 1091, 1258, 1327, 1410, 1463, 1499, 1654, 1711, 2872, 2933, 2966, 3339 (NH) cm^{-1}. HRMS: calcd 518.23924 for $C_{28}H_{33}F_3N_2O_4$, measd 518.23978. Anal. Calcd: C, 64.85; H, 6.41; N, 5.40. Found: C, 64.65; H, 6.20; N, 5.51.

5,5′-Bis(ethoxycarbonyl)-3,3′-(trifluoromethyl)-4,4′-diethylpyrromethane (22c). A solution of 2-(ethoxycarbonyl)-3-(trifluoromethyl)-4-ethylpyrrole (**15c**) (0.25 g, 1.1 mmol), $CH_2(OMe)_2$ (0.41 g, 5.4 mmol), and BF_3·OEt_2 (0.1 g, 0.7 mmol)

in dry CH_2Cl_2 (10 mL) under argon was stirred at room temperature for 35 h. TLC showed complete conversion of **15c** to **22c** (R_f = 0.31 for **22c** and R_f = 0.42 for **15c**, hexane:ethylacetate = 4:1). The solvent was removed under vacuum, and the residue was washed with 10% sodium bicarbonate (40 mL) and extracted with ethyl acetate (3 × 50 mL). The extracts were dried with sodium sulfate and rotary-evaporated to give a white solid which was purified by flash chromatography on silica gel using CH_2Cl_2 as the eluting solvent to give pure **22c** (0.23 g, 88.5%). ^1H ($CDCl_3$): 0.89 (t, 6 H, J_{HH} = 7.5 Hz), 1.29 (t, 3 H, J_{HH} = 7.5 Hz), 2.48 (q, 4 H, J_{HH} = 7.5 Hz), 4.25 (q, 4 H, J_{HH} = 7.5 Hz), 3.97 (s, 2 H), 10.23 (br, 2 H). ^{13}C NMR (CD_2Cl_2): 14.00 (s), 16.03 (s), 18.48 (q, J_{PC} = 2.1 Hz), 22.26 (s), 61.9 (s), 116.86 (q, J_{CF} = 38.1 Hz), 120.26 (q, J_{PC} = 3.8 Hz), 123.94 (q, J_{PC} = 268.9 Hz), 125.15 (q, cd, J_{PC} = 1.6 Hz), 129.05 (s), 160.44 (s). IR (KBr pellet): 779, 811, 1033, 1130, 1264, 1300, 1375, 1443, 1505, 1560, 1693, 1735, 2871, 2934, 2981, 3388 cm^{-1}. HRMS: 482.16403 calcd for $C_{21}H_{24}F_6N_2O_4$, measd 482.16389. Anal. Calcd: C, 52.26; H, 5.02; N, 5.81. Found: C, 52.22; H, 4.84; N, 5.82.

PTSA was also used as an acid catalyst but the reaction was much slower and needed 10 days to reach completion.

3,4-Diethylpyrrole (23)[15] Using LiX. A mixture of 2-(methoxycarbonyl)-3,4-diethylpyrrole (**15a**) (1.0 g, 55 mmol), lithium chloride (2.4 g, 0.055 mol), and water (0.1 g, 6 mmol) in DMSO (25 mL) was deaerated with argon for 10 min and then refluxed for 1.5 h. TLC (silica gel plate, hexane:diethyl ether = 5:1) showed that all of the starting material **15a** (R_f = 0.55) had disappeared and that a new composition (**23**) (R_f = 0.35) was formed. The mixture was poured into 100 g of ice–H_2O and extracted with diethyl ether (3 × 50 mL). The combined organic layers were washed with saturated sodium chloride (15 mL) and rotary-evaporated in vacuo to give **23** (0.68 g, 100%) as a ^1H NMR spectroscopically pure oil. ^1H NMR ($CDCl_3$): 1.20 (t, 6 H, J_{HH} = 7.5 Hz), 2.46 (q, 4 H, J_{HH} = 7.5 Hz), 6.52 (d, 2 H, J_{HH} = 2.4 Hz), 7.81 (br, 1 H). HRMS: calcd 122.10480 for $C_8H_{13}N$, measd 123.10483.

The same reaction was conducted with LiBr (10 equiv) and LiI (10 equiv). The time needed for complete conversion of **15a** into **23** was 2.0 h for LiBr and 3.0 h for LiI. The yield of **23** in both cases was 100%. When the reaction was conducted with NaCl, however, no product **23** was formed after 3 h of refluxing as shown by TLC.

Attempts To Make 3,4-Diethylpyrrole (23)[15] Using NaOH. Method A. To a solution of **15a** (1.0 g, 5.1 mmol) in 95% ethanol (5 mL) was added in one portion a sodium hydroxide (0.32 g, 8.2 mmol) solution in water (0.7 mL). The solution was deaerated with argon for 10 min and then refluxed for 2 h. Following this, 5 mL of ethanol was distilled out at an oil bath temperature of 110 °C. The residue was mixed with water (3.5 mL) and refluxed under argon for 6.5 h, cooled to rt, and extracted with diethyl ether (3 × 20 mL). The solvent was removed in vacuo to give a red-brown liquid (**23**) (0.31 g, 49%) which was contaminated with unreacted **15a** as shown by ^1H NMR spectroscopy. The aqueous layer was diluted with water (10 mL), neutralized with dilute hydrochloric acid, and extracted with ether (2 × 20 mL). The aqueous layer was washed with 10% $NaHCO_3$ solution (10 mL) and extracted again with diethyl ether (2 × 20 mL). Washing the combined ether phases with 10% $NaHCO_3$ (5 mL) followed by evaporation in vacuo gave no **23**, but 0.48 g of a grey solid whose ^1H NMR spectrum was consistent with the sodium salt of 3,4-diethylpyrrole-2-carboxylate. ^1H NMR ($CDCl_3$): 1.16 (t, 3 H, J_{HH} = 7.5 Hz), 1.20 (t, 3 H, J_{HH} = 7.5 Hz), 2.46 (t, 2 H, J_{HH} = 7.5 Hz), 2.78 (t, 2 H, J_{HH} = 7.5 Hz), 6.74 (d, 1 H, J_{HH} = 2.7 Hz), 8.92 (br, 1 H). **Method B.** To a solution of **15a** (1.0 g, 5.1 mmol) in 95% ethanol (5 mL) was added in one portion a sodium hydroxide (0.32 g, 8.2 mmol) solution in water (0.7 mL). The solution was deaerated with argon and then refluxed for 6.5 h. Ethanol was distilled out at an oil bath temperature of 110 °C. After being cooled to rt, the residue was dissolved in a mixture of ethanol (1 mL) and water (3.5 mL). The resulting solution was refluxed for 19 h under argon and extracted with diethyl ether (3 × 40 mL) to give 0.17 g of an unidentified solid.

Reduction of 15b with *i*-Bu_2AlH. A solution of **15b** (1.01 g, 5.18 mmol) in benzene (20 mL) was deaerated with dry argon. *i*-Bu_2AlH (3.7 mL, 2.9 g, 0.021 mol) was added by syringe over 10–15 min at 35–40 °C. The solution was heated at 50–60 °C for 8.0 h and then quenched with MeOH (15 mL) and H_2O (15 mL) at 20 °C. The solid was filtered off in vacuo and washed with boiling MeOH (3 × 25 mL). The combined filtrate and washings were concentrated in vacuo. The residue was mixed with hexane (30 mL) and filtered to remove solids. The filtrate was concentrated in vacuo to give 0.42 g of oil which upon distillation (43–50 °C/0.4 to 0.5 Torr) gave a light yellow liquid containing no desired **25** but which displayed spectroscopic properties consistent with those of **24**. ^1H NMR ($CDCl_3$): 1.08 (t, 3 H, J_{HH} = 7.0 Hz), 1.18 (t, 3 H, J_{HH} = 7.5 Hz), 2.16 (s, 3 H), 2.35–2.47 (m, 4 H), 6.38 (d, 1 H, J_{HH} = 1.2 Hz), 7.54 (br, 1 H). HRMS: 137.12045 calcd for $C_9H_{15}N$, measd 137.12054.

1,2,3,4,5,6,7,8-Octaethylporphyrin (26).[14,15] To a stirred suspension of $LiAlH_4$ (0.41 g, 0.011 mol) in dry THF (15 mL) at 0 °C to 3 °C was added dropwise a solution of crude **15b** (0.70 g, 3.6 mmol) in THF (15 mL). The addition funnel was rinsed with THF (2 mL), and the rinsing solution was added dropwise to the reaction mixture. The mixture was stirred at 0–3 °C for 2 h, and then 5 mL of ethyl acetate was added followed by 30 mL of saturated ammonium chloride to destroy excess $LiAlH_4$. The solid was filtered off and washed with ethyl acetate (40 mL). The organic phase was separated, and the aqueous phase was extracted with ethyl acetate (2 × 30 mL). The combined organic phases were rotary-evaporated in vacuo at room temperature (using ice–H_2O as a recycling coolant to accelerate evaporation of solvent) to give a light-yellow oil (**25**). To a solution of the crude, undried **25** and dimethoxymethane (2.7 g, 0.036 mol) in CH_2Cl_2 (15 mL, dried with P_4O_{10}) was added PTSA·H_2O (0.11 g, 0.59 mmol). The mixture, which was contained in an aluminum-foil-wrapped flask, was stirred at room temperature for 24 h. *o*-Chloranil (1.0 g, 4.1 mmol) in CH_2Cl_2 (10 mL) was added in one portion to the red reaction mixture, which was then stirred at room temperature for another 24 h. Finally, the mixture was washed with 1 N NaOH (50 mL) and extracted with $CHCl_3$ (3 × 100 mL). The combined organic phases were rotary-evaporated and chromatographed on aluminum oxide (basic, activated, Brochman I, 2.5 × 17 cm) using CH_2Cl_2 as eluent. After evaporation of the eluent, the product was recrystallized from $CHCl_3$–MeOH to give pure OEP **26** (0.33 g, 69%). ^1H NMR ($CDCl_3$): −3.75 (br, 2 H), 1.92 (t, 24 H, J_{HH} = 7.5 Hz), 4.10 (q, 16 H, J_{HH} = 7.5 Hz), 10.10 (s, 4 H). UV–vis ($CHCl_3$): λ_{max} 398, 498, 534, 566, 620 which was identical to that of an authentic sample from Aldrich. HRMS: calcd 534.37225 for $C_{36}H_{46}N_4$, measd 534.37072.

It was found (Table 1) that the combined organic phases containing crude 2-(hydroxymethyl)-3,4-diethylpyrrole (**25**) obtained from the $LiAlH_4$ reduction reaction should not be stored or dried if a high yield of OEP **26** was desired, because **25** is not stable. Dimethoxymethane used as a dehydration agent to remove water formed from the acid-catalyzed condensation reaction of **25** increases the yield of **26**.

Method B. A solution of 3,4-diethylpyrrole prepared from 2-(methoxycarbonyl)-3,4-diethylpyrrole (0.68 g, 5.4 mmol) and $(CH_2O)_n$ (0.165 g, 5.50 mmol) in benzene (200 mL) was deaerated with argon for 15 min. PTSA·H_2O (0.02 g, 0.1 mmol) was added, and the flask was wrapped with aluminum foil. The solution was heated at 55 °C for 15 h, and then it was allowed to cool to room temperature. Oxygen was bubbled through the solution with a fritted glass aerator until it was dry. The residue was dissolved in $CHCl_3$ (25 mL) and washed with a 1 N NaOH solution (25 mL) and water (2 × 20 mL). The organic layer was concentrated to 3–4 mL, layered with methanol (45 mL) for 24 h, and filtered to give a violet powder (0.12 g, 16%). ^1H NMR and UV spectra of the product **26** were identical with those of an authentic sample.

Method C. To a solution of 2-methoxy-3,4-diethylpyrrole (1.33 g, 7.52 mmol) in DMSO (35 mL) were added LiCl (9.7 g, 0.225 mol), $(CH_2O)_n$ (0.26 g, 7.5 mmol), and H_2O (0.13 g, 7.5 mmol). The mixture was heated at 190–200 °C for 4 h while O_2 was bubbled in, and then it was poured into ice–H_2O (200

mL). The solid was separated by filtration and purified by chromatography (aluminum oxide, basic, activated Brochman I, 45 × 15 mm, CH_2Cl_2) and finally recrystallized from $CHCl_3$–MeOH ($CHCl_3$, 3 mL; MeOH, 60 mL) to give the pure violet powdery product (0.17 g, 17%) which had ^1H NMR and UV spectra identical to those of an authentic sample of **26**.

Method D. A mixture of **22a** (1.05 g, 2.81 mmol) prepared from **15a** and $(CH_2O)_n$, LiCl (7.2 g, 0.17 mol), and water (0.10 g, 5.6 mmol) in DMSO (40 mL) was heated at 200–210 °C for 2 h with a small flow of air and then poured into ice-cooled phosphate buffer (100 mL). The solid was collected by filtration in vacuo. Residual solid adhering to the wall of the filter was collected by dissolving it in $CHCl_3$. The solid and $CHCl_3$ solution were combined and evaporated. The solid residue was chromatographed (Al_2O_3, basic, activated Brochman I, CH_2Cl_2) to give a violet powder which was recrystallized from $CHCl_3$ (3 mL) and methanol (70 mL) to give pure violet **26** (0.49 g, 67%) which possessed ^1H NMR and UV spectra identical to those of an authentic sample.

1,2:3,4:5,6:7,8-Tetrakis(tetramethylene)porphyrin 27.[14a] To a suspension of $LiAlH_4$ (0.65 g, 0.016 mmol) in dry THF (20 mL) was added dropwise at 0–3 °C to a solution of crude **15e** (1.0 g, 5.2 mmol) in dry THF (15 mL). The addition funnel was rinsed with dry THF (2 mL), and the rinsing solution was added dropwise to the reaction mixture. After the reaction mixture was stirred at 0–3 °C for 2 h, 5 mL of ethyl acetate and 40 mL of saturated ammonium chloride were added to destroy excess $LiAlH_4$. The solid was filtered off in vacuo and washed with ethyl acetate (50 mL). The organic phase was separated, and the aqueous phase was extracted with ethyl acetate (2 × 40 mL), washed with saturated sodium chloride, and rotary-evaporated in vacuo at room temperature (using ice–H_2O as a recycling coolant). To the residue were added dry CH_2Cl_2 (20 mL), dimethoxymethane (3.4 g, 0.052 mol), and PTSA·H_2O (0.21 g, 1.1 mmol). The mixture, which was contained in an aluminum-foil-wrapped flask, was stirred at room temperature for 24 h. *o*-Choranil (1.53 g, 6.22 mmol) in CH_2Cl_2 (10 mL) was added to the reaction mixture, which was then stirred for another 24 h. Finally, the reaction mixture was washed with a 1 N NaOH solution, extracted with $CHCl_3$ (3 × 100 mL), and chromatographed on aluminum oxide (basic, activated Brochman I, 2.5 × 15 cm, CH_2Cl_2). The product obtained upon evaporation was recrystallized from $CHCl_3$–MeOH to give pure **27** (0.44 g, 65%). ^1H NMR ($CDCl_3$): −3.84 (br, 2 H, NH), 2.49 (br, 16 H), 4.11 (br, 16 H), 9.88 (5, 4 H). UV–vis ($CHCl_3$): λ_{max} 398, 498, 534, 566, 618. HRMS: calcd 526.30966 for $C_{36}H_{38}N_4$, measd 526.30885.

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Supplementary Material Available: NMR data with peak assignments (3 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.