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A Scalable Synthesis of Meso-Substituted Dipyrromethanes

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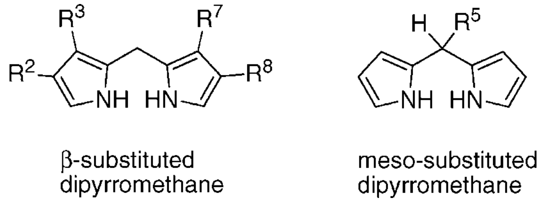
Abstract:

A one-flask synthesis of meso-substituted dipyrromethanes has been refined. The procedure entails reaction of an aldehyde in 100 equiv of pyrrole as the solvent containing a mild Lewis acid (e.g., $InCl_3$) at room temperature. Following removal and recovery of excess pyrrole, the dipyrromethane is obtained by crystallization. The procedure generates minimal waste and does not require aqueous/organic extraction, chromatography, or distillation. The procedure has been scaled linearly to obtain >100 g of 5-phenyldipyrromethane. The utility of various analytical methods for characterizing dipyrromethanes has been investigated.

Introduction

Dipyrromethanes occupy a central place in porphyrin chemistry. The dipyrromethane structures employed in the synthesis of naturally occurring porphyrins typically bear substituents at the β-positions and lack any substituent at the meso position (Chart 1). In the past decade, dipyrromethanes lacking β-substituents but substituted at the meso-position (i.e., the 5-position) have come to play a valuable role in the preparation of synthetic porphyrins and related compounds (dipyrrins, calixpyrroles, chlorins, corroles). A number of stepwise syntheses of dipyrromethanes lacking β-substituents have been developed,[1] while more direct routes have employed one-flask condensations of pyrrole and the desired aldehyde.[2−16]

Chart 1



The first report of a one-flask synthesis entailed reaction of 4-pyridinecarboxaldehyde with 2.1 mol equiv of pyrrole in methanol acidified with gaseous HCl, whereupon the corresponding 5-(4-pyridyl)dipyrromethane precipitated as the hydrochloride salt.[2] In most applications such precipitation is not possible, in which case an excess of pyrrole is employed to suppress the continued reaction leading to linear and cyclic oligomers. A number of reports in the early-mid 1990s described methods where the aldehyde (0.04−0.5 M) was treated with excess pyrrole (2.1−40 mol equiv) in an acidified organic solvent: $BF_3{\cdot}O(Et)_2/CH_2Cl_2$,[3] acetic acid/DMF[4] or THF,[5] $SnCl_4/CH_2Cl_2$,[6] *p*-toluenesulfonic acid/MeOH[7,8] or toluene,[9] or aqueous HCl/THF.[10] Workup typically entailed several steps including column chromatography, although Hammel et al. employed flash chromatography followed by Kugelrohr distillation.[3] In 1994, we reported a method that employed the reaction of the aldehyde (~0.3 M) dissolved in neat pyrrole (~14 M) with no other solvent, relying on column chromatography for purification ("1994 solventless synthesis").[11] Catalysis was achieved at room temperature with TFA or $BF_3{\cdot}O(Et)_2$ or, in some cases,[12] upon heating without added acid. The reaction proceeded in a few minutes at room temperature and afforded the dipyrromethane in yields of ~40−60%, but the use of chromatography for purification limited the scale.

Several groups have made modifications to the 1994 solventless synthesis. Both Boyle and we altered the workup protocol to facilitate preparative-scale synthesis. Boyle employed flash chromatography to remove higher oligomers, followed by Kugelrohr distillation, enabling isolation of as

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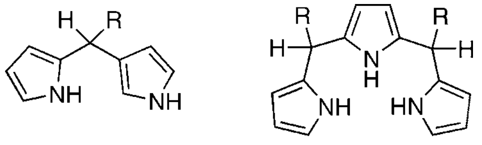
Chart 2



N-confused dipyrromethane

tripyrrane

much as ~9 g of product.[13−15] We examined the crude reaction mixture and found the dominant products to consist of the dipyrromethane, the α,β-linked "*N*-confused" dipyrromethane, and tripyrrane (Chart 2); other species were attributed to higher oligomers but not characterized.[16] We developed the following purification protocol: (1) aqueous base treatment and extraction with ethyl acetate; (2) removal of ethyl acetate and pyrrole; (3: an optional procedure that was done in cases where the crude product was especially darkened) filtration through a pad of silica to remove black material; (4) Kugelrohr distillation to give the dipyrromethane and *N*-confused dipyrromethane; and (5) recrystallization to remove the *N*-confused dipyrromethane. This multistep purification protocol was effective for many aldehydes in small-scale preparations. However, dipyrromethanes derived from aldehydes bearing large or sensitive substituents could not be distilled, in which case chromatography was typically employed for purification. A few reports have appeared of the direct crystallization of the dipyrromethane from the reaction mixture, but given the complexity of the reaction mixture, direct crystallization appears to be viable only for selected aldehydes.[17]

We sought to modify the conditions of the solventless synthesis such that the dipyrromethane could be isolated by crystallization from the crude reaction mixture. Our approach was guided by several observations. (1) Our prior analysis of the product distribution of the dipyrromethane-forming reaction employed GC and quantitated only the volatile products (dipyrromethane, *N*-confused dipyrromethane, and tripyrrane; ~80%, 2−3%, and 15% relative yields, respectively, with TFA catalysis) of the reaction.[16] However, TLC analysis of the crude reaction mixture showed the presence of black material at the origin. The isolated yield of dipyrromethane generally fell significantly below the 80% implied by the GC analysis, as expected if the black material is nonvolatile and not analyzed by GC. (2) We recently found that a wide variety of acid catalysts can be used in the pyrrole−aldehyde condensation leading to the porphyrinogen.[18,19] We also found that several mild Lewis acids [$InCl_3$, $Sc(OTf)_3$, $Dy(OTf)_3$, $Yb(OTf)_3$] provide superior results compared with TFA in porphyrin syntheses via dipyrromethane−carbinols.[20,21] Mild Lewis acids of this type have been found to have beneficial effects in diverse synthetic reactions.[22] (3) In a few cases examined, a larger pyrrole:aldehyde ratio (e.g., 400:1) gave dipyrromethanes in yields of 90−95%.[21,23] Accordingly, we began our studies by examining acids and pyrrole:aldehyde ratios that might afford less black material, which consumes starting material and complicates the purification procedure.

During the course of our work, two new methods were reported for carrying out the aldehyde−pyrrole condensation leading to dipyrromethanes: (1) the use of ion-exchange resins as acid catalysts[24] and (2) the use of refluxing aqueous acid as a solvent for the reaction from which the dipyrromethane is obtained as a crystalline solid.[25] The one-flask solventless synthesis approach also has found other applications, including (1) reaction of an aldehyde with excess furan or thiophene, affording the difurylmethane or dithienylmethane, respectively;[26] (2) reaction of a ketone with excess pyrrole, affording a 5,5-dialkyldipyrromethane;[27] and (3) reaction of an ortho ester with excess pyrrole, affording the corresponding tripyrromethane.[28] A free-radical reaction has been employed to obtain 5-trifluoromethyldipyrromethane.[29] Such reports illustrate the ongoing interest in efficient syntheses of dipyrromethanes and related compounds.

In this contribution we report our studies concerning the further refinement of the solventless synthesis. The studies include investigation of acid catalysts that are significantly milder than TFA or $BF_3{\cdot}O(Et)_2$, a survey of analytical methods to characterize reaction byproducts, and development of a simplified workup procedure. The resulting one-flask solventless synthesis employs exceptionally mild conditions, enables purification by crystallization, and can be scaled to give at least 100-g quantities of the dipyrromethane.

Results and Discussion

I. Analytical Methods. We first examined the applicability of various analytical techniques (TLC, NMR spectroscopy, GC, and elemental analysis) for identifying and quantifying the products of the pyrrole−aldehyde condensation. The model reaction of pyrrole + benzaldehyde was selected for these studies. The dominant products formed in this reaction are 5-phenyldipyrromethane (**1**), *N*-confused 5-phenyldipyrromethane (**2**), and 5,10-diphenyltripyrrane (**3**)

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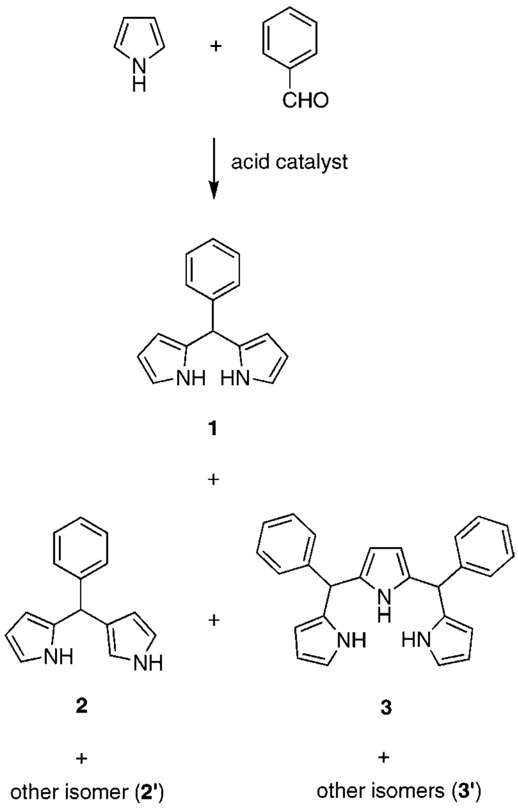
Scheme 1



(Scheme 1). We have used pure authentic samples of **1**,[16] **2**,[16] and **3**[30] for direct comparison during the analysis. The following results were obtained upon reaction of a 100:1 ratio of pyrrole:benzaldehyde at room temperature with catalysis by $InCl_3$ (identical results were obtained with TFA catalysis).

(a) TLC Analysis. Compounds **1**, **2**, and **3** possess similar R_f values on silica [hexanes/ethyl acetate (4/1)]: **1**, 0.53; **3**, 0.48; **2**, 0.38. The order of elution changed on alumina in the same solvent system: **1**, 0.52; **2**, 0.39; **3**, 0.32. Owing to the similar retention factors on either medium, careful chromatography is required to distinguish **1**, **2**, and **3** by TLC analysis (see Supporting Information). Benzaldehyde is readily distinguished on silica, however ($R_f = 0.64$). TLC can be used to quantitate the amount of unreacted benzaldehyde through the use of a series of standards of known concentration (see Experimental Section).[31] The limit of detection corresponds to 0.1% unreacted benzaldehyde for a reaction of pyrrole:benzaldehyde in a 100:1 ratio.

(b) Elemental Analysis. The synthesis of dipyrromethanes is such that a satisfactory elemental analysis (<0.4% deviation from calculated composition) for an isolated dipyrromethane may not necessarily imply the desired level of purity. Elemental analysis is obviously blind to the presence of an *N*-confused dipyrromethane, which is a dipyrromethane isomer. Perhaps less obvious is the lack of sensitivity to the presence of contamination by a tripyrrane. A tripyrrane is an oligomer of the dipyrromethane and has an elemental ratio similar to that of the dipyrromethane. For example, in the case of 5-phenyldipyrromethane (**1**), 5,10-diphenyltripyrrane (**3**) can be present as a contaminant at a level of up to 15.6%, yet the mixture will still fall within the 0.4% error limit upon elemental analysis. For other dipyrromethanes, the amount of contaminating tripyrromethane depends on the nature of the meso substituent as shown in Table 1 (also see Supporting Information). In short, an isolated dipyrromethane may give a satisfactory elemental analysis despite the presence of substantial amounts of *N*-confused dipyrromethane and tripyrrane contaminants.

Table 1. **Molecular formula and limitations of elemental analysis**

meso substituent	molecular formula: dipyrromethane	molecular formula: tripyrrane	maximum tripyrrane[a] (%)
phenyl[b]	$C_{15}H_{14}N_2$ $[C_{1.000}H_{0.933}N_{0.133}]$	$C_{26}H_{23}N_3$ $[C_{1.000}H_{0.885}N_{0.115}]$	15.6
H[c]	$C_9H_{10}N_2$ $[C_{1.000}H_{1.111}N_{0.222}]$	$C_{14}H_{15}N_3$ $[C_{1.000}H_{1.071}N_{0.214}]$	46.4
mesityl[d]	$C_{18}H_{20}N_2$ $[C_{1.000}H_{1.111}N_{0.111}]$	$C_{32}H_{35}N_3$ $[C_{1.000}H_{1.094}N_{0.094}]$	17.1

[a] Calculated maximum percentage of a tripyrrane contaminant in a dipyrromethane sample that gives a satisfactory elemental analysis (<0.4% deviation in any element). [b] 5-Phenyldipyrromethane and 5,10-diphenyltripyrrane. [c] Dipyrromethane and tripyrrane. [d] 5-Mesityldipyrromethane and 5,10-dimesityltripyrrane.

(c) NMR Spectroscopy. The ^1H NMR spectra of **1**, **2**, **3** are shown in Figure 1. Each peak was assigned by 2D-NMR (HH COSY and NOESY) measurements. The spectrum of a crude reaction mixture (following neutralization and removal of pyrrole) is also shown. While **1** is the dominant species, the presence of **2** and **3** can be readily detected by the characteristic (and nonoverlapping) peaks of the 5-phenyldipyrromethane meso-H^5 (~5.4 ppm), *N*-confused 5-phenyldipyrromethane H^7 (flanking the β-substituent, ~6.5 ppm), and the 5,10-diphenyltripyrrane H^7 (two protons at the β-positions of the central pyrrole ring, ~5.7 ppm). The relative amounts of the three species in the crude reaction mixture can be calculated by integration of these characteristic peaks, taking into account the 1:1:2 ratio of the number of hydrogens: **1**/**2**/**3** = 88:9:3. This method is satisfactory for identifying the presence of the *N*-confused 5-phenyldipyrromethane and 5,10-diphenyltripyrrane at the few percent level or greater.

(d) Gas Chromatography. We previously reported that the GC trace of the crude reaction mixture, obtained with TFA catalysis, shows three major peaks.[16] The GC trace of the crude reaction mixture obtained with 0.1 equiv of $InCl_3$ and a pyrrole:benzaldehyde ratio of 100:1 for 1 h also shows three major peaks (Figure 2A) that are assigned as **1** ($t_R = 16.4$ min), **2** ($t_R = 17.0$ min), and **3** ($t_R = 21.8$ min) on the basis of comparison with authentic samples. Closer scrutiny of the same GC trace upon amplification of the scale reveals a number of additional minor peaks (Figure 2B). The appearance and intensity of these minor peaks depend on the reaction conditions (catalyst, reaction time, and pyrrole:benzaldehyde ratio). For example, some of the minor peaks seen in $InCl_3$-catalyzed reactions are not observed in TFA-catalyzed reactions.

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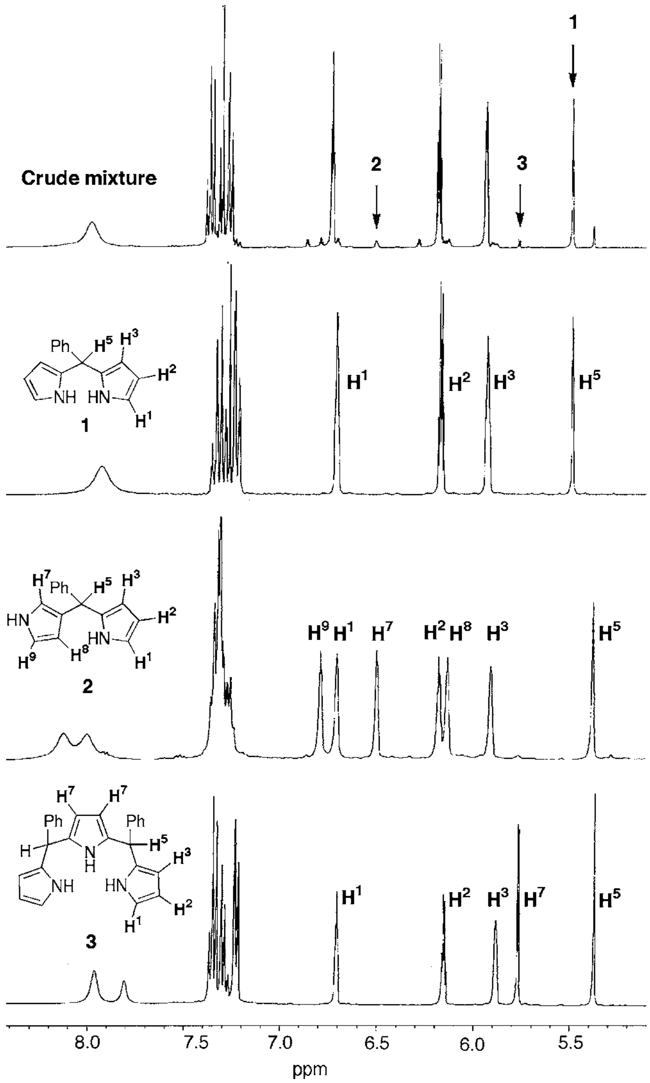


Figure 1. **^{1}H NMR spectra (in $CDCl_3$, 400 MHz) of 5-phenyldipyrromethane (1); *N*-confused 5-phenyldipyrromethane (2); 5,10-diphenyltripyrrane (3); and a sample from the crude reaction mixture (following neutralization and removal of pyrrole) obtained from the condensation of pyrrole and benzaldehyde (100:1) using 0.1 equiv of $InCl_3$.**

The region between 17 and 24 min was further expanded as shown in Figure 3. Some differences in the chromatogram are observed on the basis of the choice of detector [flame-ionization detector (FID) or electron capture (EC)]. We employed GC−MS to gain information concerning the identity of the various minor peaks. The peaks in the chromatograms of Figures 2 and 3 can be assigned as follows:

(i) The peak at t_R = 8.2 min stems from unreacted benzaldehyde, which was observed at early times but not after 1 h of reaction (not shown).

(ii) Broad, low-intensity peaks around 9−11 min were invariably observed, even upon injection of a sample of pyrrole alone and, to a lesser degree, upon injection of a sample of benzaldehyde alone. Such peaks are considered to be GC artifacts.

(iii) The peak at 12.9 min (denoted "A") shows m/z = 157 by GC−MS, which is consistent with a benzylpyrrole ($C_{11}H_{11}N$) structure.

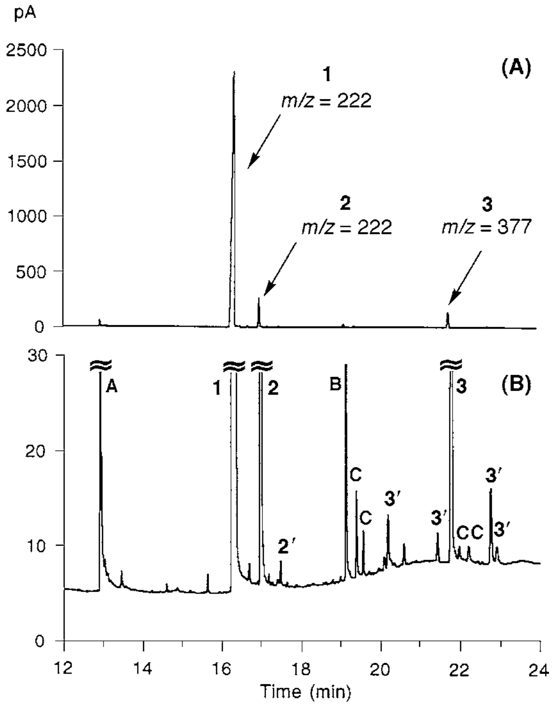


Figure 2. **Typical GC trace of the crude mixture (following neutralization) obtained from the condensation of pyrrole and benzaldehyde (100:1, 0.1 equiv of $InCl_3$, 3 h) using a GC (FID) with temperature gradient (temp 1, 35 °C (5 min); temp 2, 315 °C (12 min); rate 20 °C/min, total runtime 31 min). The peaks were confirmed with standard samples of 1, 2, and 3 or assigned in separate runs by GC−MS analysis. The peaks labeled as 2′ and 3′ are isomers of *N*-confused 5-phenyldipyrromethane (2) and 5,10-diphenyltripyrrane (3), respectively. The trace in (B) is an expansion of the trace in (A).**

(iv) The peaks due to **1** (t_R = 16.4 min), **2** (t_R = 17.0 min), and **3** (t_R = 21.8 min) were readily assigned on the basis of the use of authentic standards.

(v) GC−MS analysis showed the peak at 17.6 min to have m/z = 222, the same as **2**, implying this peak stems from an isomer of **2**. We label this peak **2′**.

(vi) The peak at 18.8 min (denoted "B") has m/z = 413, which is attributed to a chloro-substituted tripyrrane of unknown structure. Peak B virtually disappeared when the reaction was performed with TFA catalysis, suggesting $InCl_3$ as the source of the chloride.

(vii) Most of the remaining peaks fall into two categories, depending on the observed m/z. A number of the peaks have m/z = 377, the same as **3**, and are labeled **3′**, indicating they are isomers of **3**. Four such peaks are observed in the GC−FID trace (Figure 3A), while six such peaks are observed in the GC−MS trace (Figure 3B).

(viii) A number of other peaks have m/z = 310, consistent with benzyldipyrrin isomers or tautomers ($C_{22}H_{18}N_2$), and are labeled "C" (vide infra).

The apparent presence of additional isomers of the dipyrromethane and tripyrrane was at first surprising. However, there are three 5-phenyldipyrromethanes given the possibility of α or *β* substitution. Thus, **1** is the αα isomer, **2** is the α*β* isomer (which exists as a pair of enantiomers), and **2′** likely stems from the *ββ* isomer. There are 10 possible regioisomers of a 5,10-diphenyltripyrrane (**3** and **3′**), depend-

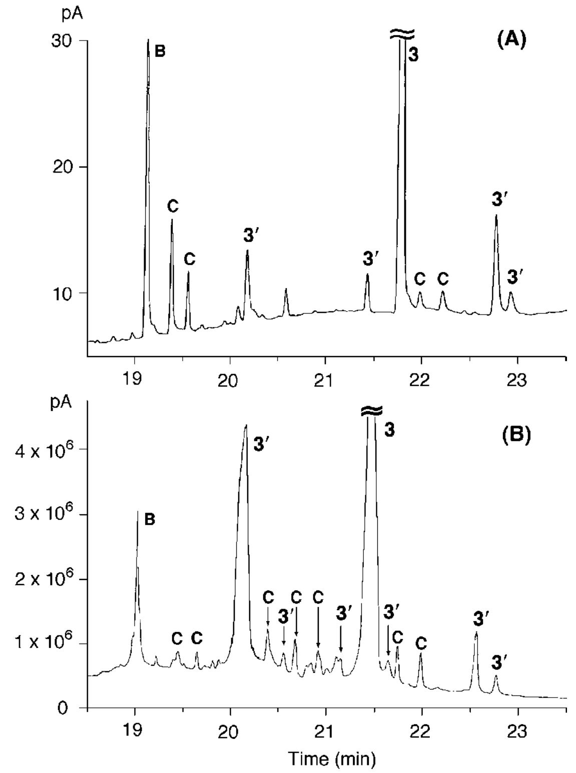


Figure 3. **Expanded region of the GC traces of the crude mixture (following neutralization) from the condensation of pyrrole and benzaldehyde (100:1, 0.1 equiv of $InCl_3$, 3 h). (A) Further expansion of the traces in Figure 2 (using FID). (B) The same reaction sample upon analysis by GC−MS with the same temperature gradient and a nearly identical column. Numerous peaks from t_R = 20.5 to 21.5 min are attributed to tripyrrane isomers (3′, *m*/*z* = 377) and unknown species “C” (*m*/*z* = 310, consistent with a benzyl dipyrrin).**

ing on whether the four substitutions occur at the α- or *β*-positions. Moreover, the two meso carbons in the tripyrrane are both chiral, leading to additional stereoisomers. The tripyrrane regioisomers are shown in Chart 3.

The structures of the components that give rise to peaks “C” are not known, but the observed *m*/*z* = 310 is consistent with benzyldipyrrin isomers or tautomers ($C_{22}H_{18}N_2$). An example of a benzyldipyrin is shown in Chart 4. Eight benzyldipyrrin isomers with various α/*β* substitution patterns are possible (and additional azafulvene tautomers are conceivable). It is noteworthy that a benzyldipyrrin analogous to **4** has been isolated as a side product in a porphyrin-forming reaction.[32] A mechanism for the formation of **4** in pyrrole−aldehyde condensations has been proposed.[33]

In the following studies, the relative yields of **1**, **2**, and **3** have been identified by GC analysis. The remaining peaks (except benzaldehyde and any known GC artifacts) in the 12−31 min region have been grouped as “other volatile components”. While the magnitude of the latter species are typically in the 1−5% range, these are components that must be removed during purification and which are not easily identified by ^{1}H NMR spectroscopy or elemental analysis. We have employed GC in conjunction with other analytical methods in the following survey to identify improved reaction conditions and workup procedures.

Chart 3. **Structures of possible tripyrromethane isomers (3′)**

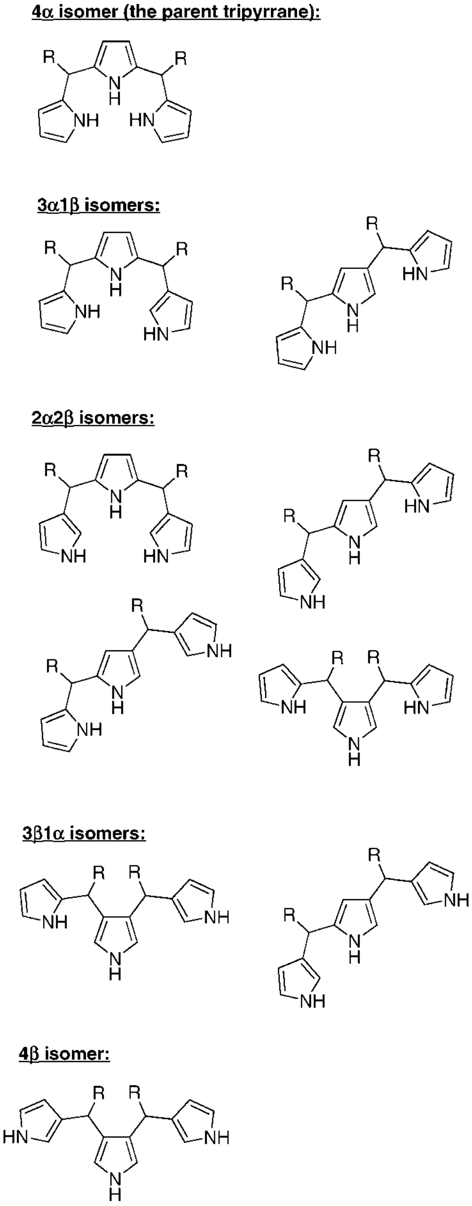
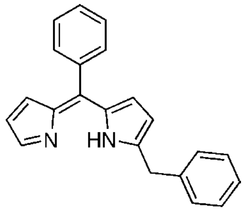


Chart 4



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None of the above analytical methods was applicable for assessing the amount of darkened material formed in the reactions. TLC analysis provided a means of separating black materials from the dipyrromethane and other mobile components, but was not reliable for gauging the extent of darkening of the reaction mixture. Accordingly, we employed visual inspection to gauge the extent of darkening in comparisons of the effects of different reaction conditions.

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(32) Hill, C. L.; Williamson, M. M. *J. Chem. Soc., Chem. Commun.* **1985**, 1228.
(33) Lindsey, J. S.; Wagner, R. W. *J. Org. Chem.* **1989**, *54*, 828.

Table 2. **Effects of different acids on the pyrrole−benzaldehyde condensation**[a]

acid (pK_a)	solubility[b]	darkness[c]	unreacted benzaldehyde[d] (%)	relative amounts (%) by GC[e]			
				1	**2**	**3**	other[f]
			Brønsted Acids				
trifluoroacetic (0.3)	soluble	++++	0.1−0.5	84.7	1.5	12.1	1.7
trichloroacetic (0.7)	soluble	+++	0.1−0.5	86.6	1.5	9.9	2.0
oxalic (1.2)	partially	+++	0.1−0.5	84.1	1.4	11.6	2.9
taurine (1.5)	insoluble	−	>50	<1	n.o.[g]	n.o.	2.8
malonic (2.8)	partially	+++	0.1−0.5	80.4	1.2	14.8	2.6
formic (3.8)	soluble	+	>50	13.1	n.o.	2.0	3.3
acetic (4.8)	soluble	−	>50	<2	n.o.	n.o.	n.o.
NH_4Cl (9.3)	insoluble	−	>50	<1	n.o.	n.o.	n.o.
			Lewis Acids				
$Yb(OTf)_3$	partially	+	0.1−0.5	75.4	20.1	1.1	3.4
$InCl_3$	insoluble	+	0.1−0.5	88.0	7.5	3.1	1.4
$Sc(OTf)_3$	insoluble	++	0.1−0.5	71.2	23.2	1.3	4.3
$MgBr_2$	insoluble	+	0.5−1	82.7	4.0	5.4	1.8
$CeCl_3$	insoluble	−	>50	<2	n.o.	n.o.	n.o.

[a] Condensations were performed with a 100:1 ratio of pyrrole and benzaldehyde at room temperature for 1 h. [b] Acid solubility was assessed visually. [c] Relative darkening of the reaction mixture: ++++, dark brown; +++, light brown; ++, yellow; +, pale yellow; −, colorless. [d] Unreacted benzaldehyde (%) was obtained from TLC using standards of known concentration (lower limit of detection is 0.1%; upper range is 50%). [e] Relative percentage obtained from GC analysis of the reaction mixture. The amount of benzaldehyde is omitted; hence the values may not sum to 100%. [f] Refers to "other nonvolatile components" as described in the text. [g] Not observed.

While hard to quantify, darkening of the reaction medium signals formation of materials that diminish the yield and complicate the purification.

II. Survey of Acids. *A. Effects of Acid.* A series of acids was examined in the one-flask synthesis of 5-phenyldipyrromethane. The acids include eight Brønsted acids with a range of pK_a values from ~0.3 (TFA) to 9.3 (NH_4Cl), and five Lewis acids [$Yb(OTf)_3$, $InCl_3$, $Sc(OTf)_3$, $MgBr_2$, and $CeCl_3$] that span a range of hard/soft acids. Each condensation was performed with a 50:1 or 100:1 ratio of pyrrole:benzaldehyde at room temperature for 30 min or 1 h. Samples were analyzed by TLC to quantitate the amount of unreacted benzaldehyde, by GC to assess the relative amount of **1**, **2**, **3**, and other species, and by visual inspection to gauge the amount of darkening of the reaction medium. The ideal acid would give negligible unreacted benzaldehyde, a high yield of **1**, and no darkening of the reaction medium.

The acids examined and the observations for the 100:1 reaction are listed in Table 2. Similar trends were obtained with the 50:1 pyrrole:benzaldehyde reaction, but the yield was lower, and isolation of the dipyrromethane by crystallization was more difficult (see Supporting Information). Several Brønsted acids (TFA, trichloroacetic acid, oxalic acid, and malonic acid) readily catalyzed formation of the dipyrromethane (>80% by GC) with near complete consumption of benzaldehyde. Weaker Brønsted acids showed lower reactivity as a catalyst. Brønsted acids that gave good yields of dipyrromethanes generally also gave a substantial amount (>10%) of tripyrrane **3**, negligible (<1.5%) *N*-confused dipyrromethane **2**, and darkened reaction mixtures. The direct crystallization of the dipyrromethane from darkened reaction mixtures was typically quite problematic.

On the other hand, the Lewis acids examined herein that gave good yields of dipyrromethanes generally gave little tripyrrane **3**, substantial amounts of *N*-confused dipyrromethane **2**, and little darkening of the reaction mixture. It is noteworthy that $Yb(OTf)_3$ and $Sc(OTf)_3$ give significant amounts of *N*-confused dipyrromethane **2**. The general trends observed in the Lewis or Brønsted acid-catalyzed reactions mirror those observed in our more limited studies with TFA and $BF_3 \cdot O(Et)_2$.[16]

Among all the acids examined, $InCl_3$ and $MgBr_2$ gave the best results, considering both the product distribution and relative absence of darkening of the reaction mixture. $MgBr_2$ gave fewer byproducts compared to other Lewis acids (although the reaction rate was slower than that of $InCl_3$), and unreacted benzaldehyde was observed by GC and TLC analysis. We decided to focus on the use of $InCl_3$ as a catalyst for the pyrrole−aldehyde condensation.

B. Concentration Effects on Reaction Rate and Product Distribution. We examined the effects of the pyrrole:benzaldehyde ratio (from 25:1 to 400:1) using $InCl_3$ as catalyst in reactions at room temperature. GC analysis was carried out to monitor the progress of the reaction and determine the relative yields of **1**, **2**, **3**, and other components.

Altering the ratio of pyrrole:benzaldehyde caused two effects: a change in product composition and a change in reaction rate. The effect of the pyrrole:benzaldehyde ratio on the product distribution is shown in the reaction time-courses in Figure 4A−D. The reaction with 25 equiv of pyrrole was complete within 10 min (not shown). The reaction with 50 equiv of pyrrole was complete within 30 min. With 200 equiv of pyrrole, the reaction required ~2 h to level off, while the reaction with 400 equiv of pyrrole was still proceeding at 3 h, and the benzaldehyde was completely consumed only after ~24 h. Thus, an increase in the excess of pyrrole caused a decrease in the reaction rate.

We attribute the decline in rate with increasing excess pyrrole to the dilution of the acid catalyst. The amount of $InCl_3$ was kept constant (0.1 equiv relative to the benzaldehyde) across the varying pyrrole:benzaldehyde ratios (Figure 4, A−D). Because pyrrole is the solvent, the acid concentration declined from 54 to 3.6 mM (and the benzaldehyde

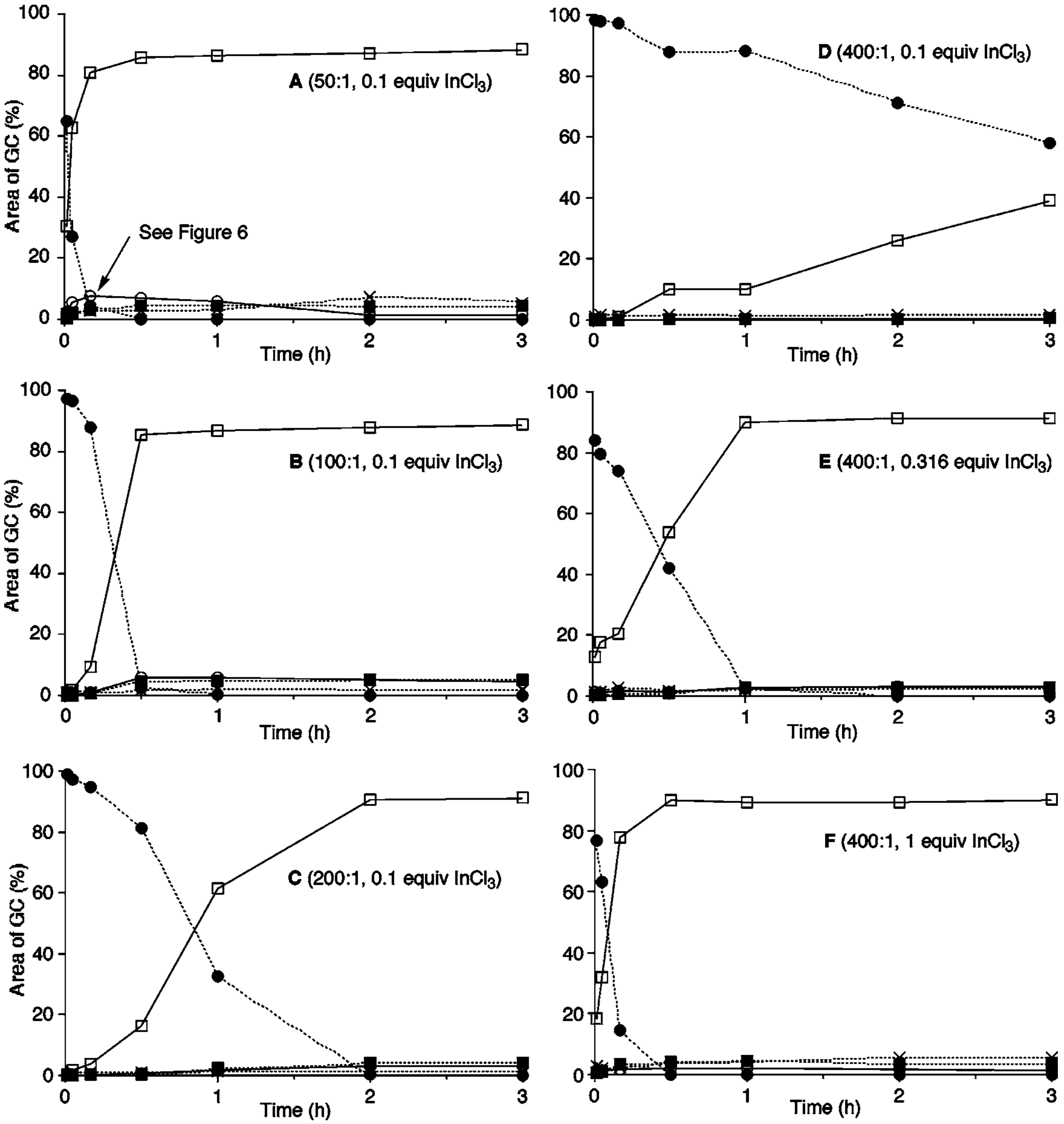

Figure 4. **Effect of pyrrole:benzaldehyde ratio on the reaction rate and product distribution. The data were obtained by GC analysis. The pyrrole:benzaldehyde ratios and the amount of $InCl_3$ are specified in panels A−F. The early timepoints were at 1, 3, and 10 min. Legend: 5-phenyldipyrromethane (1, □); *N*-confused 5-phenyldipyrromethane (2, ■); 5,10-diphenyltripyrrane (3, ○); benzaldehyde (●); and the sum of all other volatile components (×).**

concentration declined from 0.54 to 0.036 M) as the pyrrole:benzaldehyde ratio increased from 25:1 to 400:1.

Given the decreased rate of reaction with increasing pyrrole:benzaldehyde ratio, it became of interest to examine an increased amount of acid to compensate for the diminished reaction rate. Upon increasing the amount of the acid, the reaction time was shortened: with 0.316 or 1 equiv of $InCl_3$ and a 400:1 ratio of pyrrole:benzaldehyde, benzaldehyde was consumed within 2 h or 30 min, respectively (Figure 4, E and F). There was no significant change in the ultimate product distribution (for a given pyrrole:benzaldehyde ratio) (of **1**, **2**, and **3** with alteration of the acid concentration, thereby indicating that approximately the same final product distribution can be achieved at a desired rate by controlling the acid concentration.

The ultimate product distribution obtained as a function of pyrrole:benzaldehyde ratio and a fixed concentration of $InCl_3$ (0.1 equiv) is shown in Figure 5. Upon increasing the pyrrole from 25 to 400 equiv, the relative yield of **1** increased steadily from 82.5 to 92.9%, **3** decreased from 7.3 to 1.4%, and **2** declined from 5.6 to 1.9%.

The apparent clarity of the data masks underlying complexity. Close examination of the reaction timecourses obtained by GC analysis indicated that at least two species exhibit unusual dynamics. The data for tripyrrane **3** from Figure 4A are plotted at expanded scale in Figure 6, along with those for component A ($t_R = 12.9$ min, $m/z = 157$). The tripyrrane **3** appears in a burst and then declines during the course of the reaction, while component A forms initially and then increases late in the reaction.

While the mechanistic origins of the dynamics observed for **3** and component A are not known, interpretation of the changes in product distribution over time must take into consideration the changing reaction composition during the

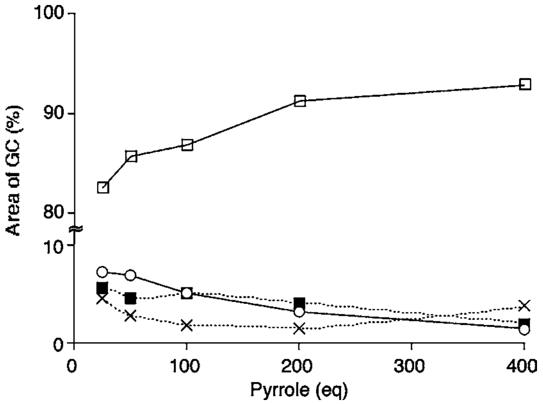

Figure 5. **Expanded display showing the effect of pyrrole: benzaldehyde ratio on the product distribution. The data were obtained by GC analysis for the condensation with $InCl_3$ (0.1 equiv) when the respective reactions leveled off: pyrrole: benzaldehyde = 25:1 or 50:1 (30 min); 100:1 (2 h); 200:1 (3 h); or 400:1 (24 h). Legend: 5-phenyldipyrromethane (1, □); *N*-confused 5-phenyldipyrromethane (2, ■); 5,10-diphenyltripyrrane (3, ○); and the sum of all other volatile components (×).**

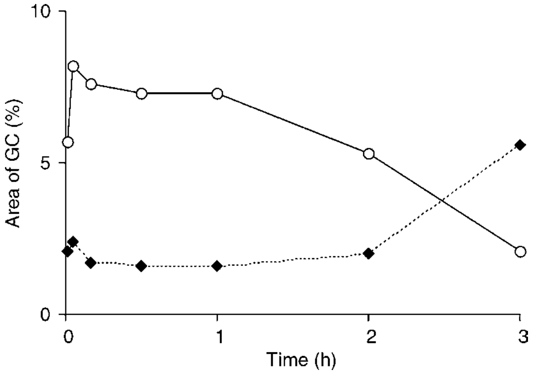

Figure 6. **Relative yield versus time for two byproducts (3, component "A"). The data were obtained by GC analysis from the condensation of pyrrole and benzaldehyde (50:1, 0.1 equiv of $InCl_3$). The early timepoints were at 1, 3, and 10 min. Legend; 5,10-diphenyltripyrrane (3, ○); unknown peak "A" at t_R = 12.9 min upon GC analysis (◆).**

course of the condensation. The reaction with a 100:1 ratio of pyrrole:aldehyde has initial concentrations of 0.14 M for the aldehyde, 14 M for pyrrole, and 0.014 M for the acid. At the end of the reaction the pyrrole concentration is essentially unchanged, while the concentration of water is equal to that of the initial aldehyde (0.14 M), assuming complete reaction. Thus, as the reaction progresses, the increasing concentration of water is likely to impact the nature of the acid catalysis. It has been shown that catalysis by lanthanides and related metals entails both Lewis acid catalysis and Brønsted acid catalysis, where the latter is derived by interaction of water with the Lewis acid.[21,34]

III. Workup Method and Purification. We developed a four-step workup procedure that is simple, scalable, and has minimal environmental impact. The four steps are as follows: (1) *Quench.* To terminate the condensation, excess powdered NaOH (or KOH, $LiOH{\cdot}H_2O$, or K_2CO_3) is added, and the mixture is stirred for 30 min. (2) *Filter.* Filtration affords recovery of most if not all of the acid catalyst and base. (3) *Remove pyrrole.* The filtrate is placed under vacuum, enabling removal and recovery of the excess pyrrole (bp 131 °C). The resulting crude dipyrromethane is often obtained as an oil. The latter is treated with a small volume of hexanes, and the hexanes/residual pyrrole mixture is removed under vacuum, which affords the solid dipyrromethane; this procedure may be repeated 2−3 times. (4) *Recrystallize.* Recrystallization (aqueous ethanol) affords the dipyrromethane as white crystals. This four-step procedure was applied in the subsequent studies described herein that employ Lewis acid catalysts. For reactions using a Brønsted acid, the same general procedure was employed, although quenching was performed by addition of TEA and the filtration step was omitted.

IV. Comparison of Catalysis by $InCl_3$ or TFA. The solventless synthesis has previously employed TFA as the reaction catalyst.[11,16] For comparison with catalysis by $InCl_3$, a number of studies that parallel those reported in Figures 4−6 for $InCl_3$ also were carried out with TFA. The data are provided in the Supporting Information, and the major results are summarized as follows. The TFA-catalyzed condensations were faster than those with $InCl_3$. All TFA-catalyzed reactions (0.1 equiv) gave complete consumption of benzaldehyde within 30 min, and the reaction composition remained unchanged thereafter. Regardless, the two dominant effects observed with $InCl_3$ also were observed with TFA catalysis: (1) An increase in the pyrrole:benzaldehyde ratio caused the reaction rate to decrease. (2) Upon increasing the pyrrole: benzaldehyde ratio from 25 to 400, the yield of **1** increased from 65 to 93%, the yield of **3** decreased, and the yield of **2** remained constant (∼2%).

One distinction between the two catalysts was observed in the purification process. The reaction mixture obtained upon TFA catalysis with a 200:1 or 400:1 ratio of pyrrole: benzaldehyde was worked up as described above. After neutralization of the acid and removal of the pyrrole, crystallization of the crude product gave a dark brown solid. The darkening of the product could not be remedied by repeated crystallization, requiring instead treatment with charcoal in hot ethanol (or, on a small scale, silica pad filtration) followed by recrystallization. By contrast, the reaction with $InCl_3$ typically gave the dipyrromethane as a colorless product.

V. Scope of Application. *General Method.* The refined synthesis conditions using $InCl_3$ were applied to the series of aldehydes shown in Scheme 2. We chose a pyrrole:aldehyde ratio of 100:1 as a compromise among three factors affected by an increasing pyrrole:aldehyde ratio (as observed for benzaldehyde): (i) the increased yield of dipyrromethane, (ii) the decreased rate of reaction, and (iii) the necessity to handle a large amount of pyrrole relative to the amount of product. Each reaction was performed at room temperature with 50 mmol of aldehyde and 0.1 equiv of $InCl_3$. The progress of the reactions was monitored by TLC and GC analysis. The four-step procedure outlined above was em-

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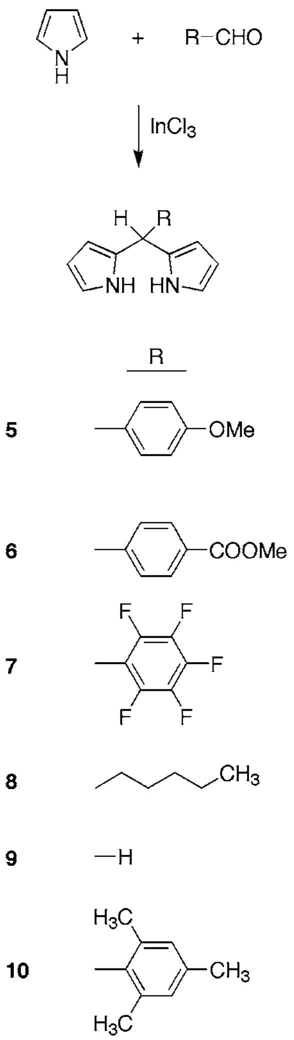
(34) Barrett, A. G. M.; Braddock, D. C.; Henschke, J. P.; Walker, E. R. *J. Chem. Soc., Perkin Trans. 1* **1999**, 873.

Scheme 2



ployed for purification. For comparison, the same reactions were carried out with 20 mmol of the aldehyde, and purification was carried out by column chromatography.

The results for dipyrromethanes **1** and **5**−**9** are summarized in Table 3. The general reaction conditions and workup procedure generally gave good results with each of the aldehydes. Each dipyrromethane gave a relative GC purity of >90%. Minor modifications were made for dipyrromethanes **6** and **8**. In the case of **6** a small amount (~7%) of transesterification product was obtained when aqueous ethanol was employed for recrystallization. Hence, aqueous methanol (10:1) was used for the recrystallization. Dipyrromethane **8**, an oil, was obtained by column chromatography. More extensive changes were made for the reactions with paraformaldehyde and mesitaldehyde.

Special Cases. *A. Paraformaldehyde.* Paraformaldehyde was relatively insoluble in neat pyrrole. The heterogeneous reaction mixture was heated at 50−55 °C for 2.5 h. Pyrrole was removed; dipyrromethane (**9**) was then extracted with hexanes/ethyl acetate (4:1). Evaporation of the solvent followed by crystallization [methanol/water (4:1)] afforded **9** in 45% yield (94.6% purity by GC).

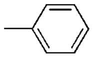
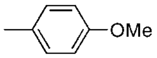
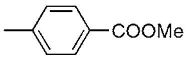
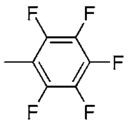
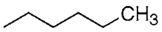
B. Mesitaldehyde. The reaction of mesitaldehyde with pyrrole in the presence of 0.1 equiv of $InCl_3$ proceeded very slowly. A survey of acid catalysts and acid concentration (0.1 to 1.0 equiv) was performed for the reaction with a 100:1 ratio of pyrrole:mesitaldehyde. The conditions that gave the best result for each acid are summarized in Table 4. The GC traces generally mirrored those obtained for benzaldehyde, including the appearance of 5-mesityldipyrromethane (**10**) and peaks assigned to *N*-confused 5-mesityldipyrromethane (**11**), 5,10-dimesityltripyrrane (**12**), and isomeric tripyrranes. The structures are shown in Chart 5. A representative GC trace and complete results of the acid survey are shown in the Supporting Information.

GC examination showed generally high relative yields of 5-mesityldipyrromethane (**10**) with each of the acids. However, the Brønsted acid catalysts gave dark brown−black reaction mixtures, while those with Lewis acid catalysts were only slightly darkened. In general, the extent of darkening of the reaction mixture—while difficult to quantify and stemming from products that are difficult to analyze—is the likely cause of the yield of isolated dipyrromethane falling short of that expected on the basis of GC analysis. A case in point is provided by the reaction obtained with TFA: the relative percentage of **10** is 77% (by GC analysis), while the isolated yield is 27%.[16] From these studies, we focused on the Lewis acid catalysts. The product distribution obtained with $Sc(OTf)_3$ contained a significant amount of the *N*-confused dipyrromethane **11**. The reaction with $InCl_3$ at 60 °C afforded a relatively good yield of the dipyrromethane **10**, but crystallization to high purity proved difficult. The best results overall were observed with $MgBr_2$, which also gave the least darkened reaction mixture. The isolated yield was 53% (93.0% purity), nearly double that obtained previously.

VI. Scale-up. A large-scale synthesis of 5-phenyldipyrromethane (**1**) was carried out using benzaldehyde (79.8 g) and 100 equiv of pyrrole (5.20 L), catalysis by $InCl_3$ (16.7 g), and mechanical stirring for 1.5 h at room temperature. The reaction mixture remained essentially at room temperature without application of external temperature control. The reaction was quenched by adding NaOH, and the mixture was filtered and washed with pyrrole (0.35 L). The mixture was concentrated, and pyrrole was recovered (5.30 L). The crude dipyrromethane solidified upon treatment with hexanes and was recrystallized from ethanol/water (4:1), affording four crops of crystals. The third and fourth crop were combined and recrystallized. The three samples each gave satisfactory elemental analyses, yet the GC analyses indicated purities of 94.8, 92.3, and 94.0%. The typical GC data (crop 2) indicated the relative amounts of 92.3% (**1**), 6.3% (**2**), 0.6% (**3**), and 0.8% (other volatile components). ^1H NMR analysis showed a corresponding ratio of **1**:**2**:**3**, while other components were not observed. Altogether, 115.5 g of **1** (69% yield, 94.2% purity) was obtained. Distillation of the recovered pyrrole afforded 4.92 L of pyrrole (90% final recovery).

VII. Material Recovery and Reuse. Filtration of the reaction mixture affords recovery of the indium employed

Table 3. Scope of application of the refined synthesis method[a]

Compound	Dipyrromethane meso substituent	Yield (Purity)[b]		
		Crystallization		Chromatography
		1st crystallization[c]	2nd crystallization	
1		71% (96.7%)		82% (>99%)
5		63% (92.0%)	43% (97.0%)	62% (>99%)
6		75% (97.0%)		75% (>99%)
7		79% (>99%)		80% (98.0%)
8[d]		n.a.[e]	n.a.	62% (94.3%)
9[f]	—H	45% (94.6%)		63% (>99%)

[a] Condensations were performed with a 100:1 ratio of pyrrole:aldehyde with 0.1 equiv of $InCl_3$ at room temperature for 1.5 h unless specified. [b] Relative purity (%) based on GC peak areas is shown in parentheses. The workup procedure involves quenching with powdered NaOH, filtration, removal of pyrrole, and entrainment with hexanes unless specified, followed by crystallization or chromatography. [c] May include a first and second crop of crystals. [d] Obtained as an oil. [e] Not applicable. [f] After reaction at 55 °C for 2.5 h, the reaction mixture was extracted with hexanes/ethyl acetate prior to crystallization.

Table 4. Refined acid catalysis conditions for the synthesis of 5-mesityldipyrromethane (10)[a]

catalyst	conditions	relative amounts (%) by GC					yield (purity) (%)[b]	
		MsCHO[c]	**10**	**11**	**12**	other[d]	crystallization	chromatography
TFA	0.1 equiv, rt, 1.5 h	0.2	77.1	2.1	12.5	8.1	25 (90.0)	27[e]
malonic acid	0.1 equiv, rt, 3 h	37.5	52.7	1.1	4.2	4.5	n.a.[f]	n.a.
$InCl_3$	0.3 equiv, 60 °C, 5 h	7.6	67.9	18.3	3.3	2.9	49 (85.7)[g]	56 (82.0)
$Sc(OTf)_3$	0.3 equiv, rt, 4 h	0.8	52.7	30.2	1.6	14.7	n.a.	n.a.
$MgBr_2$	0.5 equiv, rt, 1.5 h	0.9	82.9	3.5	4.8	7.9	53 (93.0)	65 (92.7)

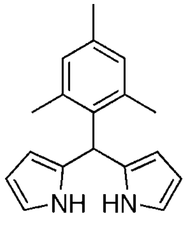
[a] Condensations were performed with a 100:1 ratio of pyrrole:mesitaldehyde. [b] Relative purity (%) based on GC peak areas is shown in parentheses. [c] Mesitaldehyde. [d] Refers to "other nonvolatile components" as described in the text. [e] Obtained by Kugelrohr distillation followed by crystallization using the reported method.[16] [f] Not applicable. [g] Yield of 32% (88.0%) in the first crop, 17% (81.2%) in the second crop.

as catalyst in conjunction with the excess base for neutralization. We have not attempted to regenerate the indium catalyst. However, the pyrrole has been recycled numerous times. One caveat is that an aldehyde (e.g., hexanal, bp 128 °C) may have a boiling point nearly identical with that of pyrrole (bp 131 °C). In such cases, the recovered pyrrole should be used exclusively for subsequent reaction with the same aldehyde to avoid any possibility of contamination by residual unreacted aldehyde.

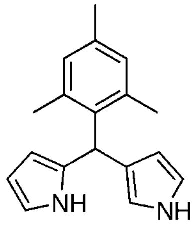
Conclusions

The one-flask solventless reaction of an aldehyde with excess pyrrole provides a simple means of preparing the corresponding dipyrromethane. Catalysis can be achieved with a wide variety of Brønsted or Lewis acids. The Brønsted acids that afford product also give a dark reaction mixture, while the Lewis acids give less darkening. Excellent results were obtained with $InCl_3$ (for benzaldehyde and other aryl aldehydes) and $MgBr_2$ (for mesitaldehyde). The workup procedure entails quenching with NaOH, filtration, removal of pyrrole, and crystallization. The simplicity of this procedure (no aqueous/organic extraction, distillation, or chromatography) minimizes waste and enables scalability. The absence of any reaction solvent other than pyrrole enables facile recovery of the excess pyrrole from the crude reaction mixture. The recovered pyrrole can be reused. Indeed, the reaction of 0.75 mol of benzaldehyde in 5.2 L of pyrrole gave 115.5 g of 5-phenyldipyrromethane and recovery of 90% of the excess pyrrole in a form suitable for reuse. Characterization of the purity of dipyrromethanes is best accomplished using a combination of analytical techniques, including gas chromatography. The *N*-confused dipyrromethane and the tripyrrane species are dominant byproducts of the reaction. Because the former is an isomer while

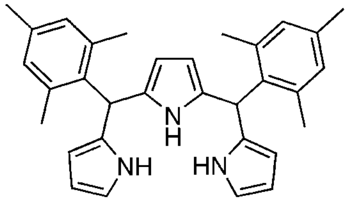
Chart 5



10



11



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the latter is an oligomer of the dipyrromethane, a satisfactory elemental analysis is a necessary but insufficient criterion of purity.

Experimental Section

General. ^{1}H NMR (400 MHz) spectra were recorded in $CDCl_3$ unless noted otherwise. CH_2Cl_2 (ACS grade), hexanes (ACS grade), ethyl acetate (ACS grade), and powdered NaOH (20−40 mesh beads) were used as received. The acids employed in this study were of the following grades (and were used in quantities without correction for less than 100% purity): trifluoroacetic acid (99%), trichloroacetic acid (98%), oxalic acid (97%), taurine (99%), malonic acid (99%), formic acid (98%), acetic acid (99.99%), NH_4Cl (99.5%), $MgBr_2$ (98.5%), $Yb(OTf)_3$ (99.99%), $InCl_3$ (98%), $Sc(OTf)_3$ (99%), and $CeCl_3$ (99.9%). All other chemicals including aldehydes were of reagent grade and were used as obtained. The first-reported characterization data for dipyrromethanes prepared by one-flask syntheses are as follows: **1**,[7] **5**,[16] **6**,[35] **7**,[16,36] **8**,[3] **9**,[37] and **10**.[11] Each compound prepared herein was characterized by GC, elemental analysis, mp, and ^{1}H NMR spectroscopy. All reported yields are based on the weight of the isolated dipyrromethane and are not corrected for the purity established by GC analysis.

Quality of Pyrrole. Pyrrole slowly darkens on standing. To determine how the purity of the dipyrromethane depends on the quality of the pyrrole employed, parallel reactions were performed using undistilled pyrrole or distilled pyrrole with a 100:1 ratio of pyrrole:benzaldehyde and $InCl_3$ at room temperature for 1 h. With undistilled pyrrole, the mixture was pale green, the GC yield was 89.8%, and the yield upon recrystallization was 61% (97.3% purity by GC). With distilled pyrrole, the reaction mixture was pale yellow, the GC yield was 91.0%, and the yield upon recrystallization was 68% (96.7% purity by GC). Given these differences, we employed distilled pyrrole throughout our experiments. Pyrrole (reagent grade) was distilled over calcium hydride before use.

Quantitative TLC. Unreacted benzaldehyde was examined by TLC analysis [silica, hexanes/ethyl acetate (4:1)] using known concentrations of benzaldehyde in ethyl acetate as standards, a method that enables quantitative analysis.[31] The standard samples corresponded to yields of unreacted benzaldehyde of 0.1−50%. Each TLC plate was spotted with a reaction sample and at least two standards for visual comparison. In this manner, the yield of benzaldehyde could be bracketed. The lower limit of detection of unreacted benzaldehyde is 0.1% for a reaction of 100:1 pyrrole: benzaldehyde. We made no effort to assess quantities in the range of 50−100% of unreacted benzaldehyde; such amounts are designated as >50% unreacted benzaldehyde.

Gas Chromatography. Gas chromatography was carried out using an HP 6890 gas chromatograph equipped with an FID detector and a fused silica capillary column HP-5 (30 m × 0.32 mm × 2.5 μm). All samples were examined under the following temperature gradient: temp 1, 35 °C (5 min); temp 2, 315 °C (12 min); rate 20 °C/min, total runtime 31 min. Relative yields were determined by direct integration of the peak areas of the gas chromatogram rather than by constructing calibration curves using standard solutions of each component. We demonstrated earlier that the detector had an approximately linear response to the amount of each component present.[16] GC−MS data were acquired using an HP 5890 GCD gas chromatograph using the same temperature gradient as described for GC analysis.

Variation in the workup process has little impact on the product distribution. Workup of the $InCl_3$-catalyzed condensation (100:1 ratio of pyrrole:benzaldehyde at room temperature for 1 h) by quenching with TEA or NaOH (or using ethyl acetate or CH_2Cl_2 as the GC injection solvent) gave nearly identical product distribution profiles. The only differences were the appearance of several minor peaks in the 19−24 min region. In general, the GC analyses were performed following neutralization of the reaction mixture (but without removal of excess pyrrole).

A control experiment where a sample of pyrrole and benzaldehyde (100:1) was injected into the GC instrument resulted in broad, low intensity peaks (9−11 min) as well as a peak due to 5-phenyldipyrromethane (at ~1% level). The former is a GC artifact as described earlier. The latter is not due to carryover from the prior sample. We have previously shown that benzaldehyde and pyrrole react, albeit slowly and in low yield, upon heating in the absence of an acid to give the dipyrromethane.[16] Thus, samples from reaction mixtures at room temperature where no reaction occurs can still give small amounts of the dipyrromethane as a GC artifact.

GC−MS data were obtained with high loading of samples to detect trace components. We were concerned that bleeding from earlier eluting species in a given run, especially those that were (1) present in an overloaded amount

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and (2) isomeric with later-eluting species could cause misleading assignment of the later-eluting species. Assignments were made by comparing the intensities of given mass spectral peaks as a function of time during which a component eluted to ensure that the observed spectral signature originated from the component rather than from earlier-eluting species.

Survey of Acid Catalysts. Analytical-scale reactions of benzaldehyde (1.50 mmol) and pyrrole (150 mmol) in the presence of each catalyst (0.15 mmol) were performed at room temperature. Reactions were quenched after 1 h. Quantitative TLC analysis was performed as described above. GC analysis was done by removing 200-μL aliquots of the reaction mixture after quenching and then diluting with 800 μL of CH_2Cl_2.

Effect of Pyrrole:Benzaldehyde Ratio and Concentration of Acids. Studies on the effect of the pyrrole:benzaldehyde ratio and the amount of added acid (TFA or $InCl_3$) on the product distribution were performed as illustrated for the following typical example (pyrrole:benzaldehyde 100:1): A mixture of pyrrole (26.8 g, 400 mmol) and benzaldehyde (424 mg, 4.00 mmol) was treated with 0.1 equiv of $InCl_3$. After 1, 2, 3, and 24 h, 250-μL aliquots from the reaction mixture were removed and immediately quenched by injection into a 500-μL solution of ethyl acetate/TEA (25:1) and then filtered (in the case of $InCl_3$). These samples were examined by GC analysis as described above.

General Procedure Illustrated for 5-phenyldipyrromethane (1). *A. Crystallization Method.* Pyrrole (347 mL, 5.00 mol) and benzaldehyde (5.31 g, 50.0 mmol) were added to a 500-mL single-neck round-bottomed flask containing a magnetic stir bar. The solution was degassed with a stream of argon for 10 min. $InCl_3$ (1.11 g, 5.00 mmol) was added, and the mixture was stirred under argon at room temperature for 1.5 h. The mixture turned yellow during the course of the reaction. NaOH (6.0 g, 0.15 mol, 20−40 mesh beads) was added to quench the reaction (see note i below). Stirring for 45 min afforded a pale yellow mixture. The mixture was filtered (Fisher brand qualitative filter paper) using a Buchner funnel. The contents of the flask and the filtered material were washed with a small amount of pyrrole. The filtrate was concentrated using a rotary evaporator under vacuum (0.2 mmHg); the evaporation flask was warmed at 40−50 °C, and the collection trap was cooled with a dry ice−acetone bath. The collected pyrrole was set aside. Traces of pyrrole were removed by entrainment with hexanes by performing the following procedure three times: the crude viscous residue in the evaporation flask was triturated with hexanes (50 mL), and the volatile components were evaporated (see note ii below). The resulting yellow solid was dissolved in 60 mL of ethanol/water (4:1) (see note iii below) with heating by a water bath. The resulting yellow solution containing a very small amount of white powder was filtered (Fisher brand qualitative filter paper), and the filtrate was set aside overnight at room temperature (see note iv below), affording a first crop of pale yellow crystals [7.22 g, 65% yield; mp 99−100 °C (lit.[7] mp 102−103 °C); 96.7% purity by GC; Anal. Calcd for $C_{15}H_{14}N_2$: C, 81.05; H, 6.35; N, 12.60. Found: C, 81.04; H, 6.41; N, 12.67]. The filtrate from the first crop was concentrated, yielding a second crop of pale brown crystals (1.22 g, 11% yield; 86.3% purity by GC). The latter was recrystallized [18 mL of ethanol/water (4:1)] affording yellow crystals (1.05 g, 10% yield; 92.0% purity by GC), which were recrystallized [16 mL, 2-propanol/water (15:1)], affording pale yellow crystals (0.66 g, 6% yield; mp 99−100 °C; 96.8% purity by GC; Anal. Calcd for $C_{15}H_{14}N_2$: C, 81.05; H, 6.35; N, 12.60. Found: C, 80.90; H, 6.36; N, 12.57). The first crop and the final crop were combined, affording pale yellow crystals (7.88 g, 71% yield; calcd 96.7% purity by GC).

Notes:

(i) It is essential to quench the reaction with a strong base (e.g., NaOH) and to stir the reaction mixture for a period thereafter (45 min). When the reaction mixture was quenched with an organic base (e.g., TEA) or not quenched at all, filtration still removed much of the indium material. However, the filtrate contained the crude dipyrromethane as well as a blue contaminant. The blue material proved very difficult to remove from the dipyrromethane by crystallization or charcoal but could be removed by flash chromatography.

(ii) It is essential that the crude dipyrromethane be obtained as a solid largely free of pyrrole prior to initiating crystallization.

(iii) Attempts to crystallize the crude product in other solvents [e.g., CH_2Cl_2/hexanes, ethyl acetate/hexanes, ether/hexanes, THF/water] were not successful.

(iv) Attempts to perform the crystallization at lower temperature gave less pure product.

B. Column Chromatography Method. Pyrrole (139 mL, 2.00 mol) and benzaldehyde (2.13 g, 20.1 mmol) were condensed in the presence of 0.1 equiv of $InCl_3$ in a manner similar to that described above. The crude product obtained after removal of pyrrole was purified by column chromatography [silica, 6 cm dia. × 14 cm, hexanes/CH_2Cl_2/ethyl acetate (7:2:1)]. The crude mixture was dissolved in CH_2Cl_2, silica gel was then added, and the mixture was evaporated to dryness. The resulting powder was loaded on the top of the column. Elution (400−1400 mL of eluant) followed by concentration of the eluted product gave a white solid (3.64 g, 82% yield; mp 100 °C; >99% purity by GC; Anal. Calcd for $C_{15}H_{14}N_2$: C, 81.05; H, 6.35; N, 12.60. Found: C, 80.94; H, 6.39; N, 12.55). Note that chromatographic purification of the crude product using common solvents such as CH_2Cl_2 or hexanes/CH_2Cl_2 (1:1) was unsuccessful. Even careful chromatography on silica with hexanes/ethyl acetate (4:1) gave mixtures of the three components although this solvent system happened to be a good solvent for TLC analysis.

Applications. *5-(4-Methoxyphenyl)dipyrromethane (**5**).* (A) The reaction of *p*-anisaldehyde (6.81 g, 50.0 mmol) with crystallization [ethanol/water (4:1)] afforded two crops of crystals: (crop 1) light brown crystals [5.17 g, 41% yield; mp 95−96 °C (lit.[16] mp 99 °C); 93.7% purity by GC; Anal. Calcd for $C_{16}H_{16}N_2O$: C, 76.16; H, 6.39; N, 11.10. Found: C, 75.75; H, 6.40; N, 10.98]; (crop 2) brown crystals (2.82 g, 22% yield; 91.0% purity by GC). Combination and recrystallization afforded light brown crystals (5.42 g, 43% yield; mp 98−99 °C; 97% purity by GC; Anal. Calcd for $C_{16}H_{16}N_2O$: C, 76.16; H, 6.39; N, 11.10. Found: C, 76.03; H, 6.36; N, 11.08).

(B) Reaction at the 20.0-mmol scale with chromatography [silica, hexanes/CH_2Cl_2/ethyl acetate (16:3:1)] afforded a yellow solid (3.12 g, 62% yield; mp 99 °C; >99% purity by GC; Anal. Calcd for $C_{16}H_{16}N_2O$: C, 76.16; H, 6.39; N, 11.10. Found: C, 76.06; H, 6.43; N, 10.99).

*5-(4-Carbomethoxyphenyl)dipyrromethane (**6**).* (A) The reaction of methyl 4-formylbenzoate (8.21 g, 50.0 mmol) with crystallization [methanol/water (10:1)] afforded two crops of crystals: (crop 1) pale yellow crystals [7.84 g, 56% yield; mp 162−163 °C (lit.[35] mp 158 °C); 97.2% purity by GC; Anal. Calcd for $C_{17}H_{16}N_2O_2$: C, 72.84; H, 5.75; N, 9.99. Found: C, 72.59; H, 5.75; N, 9.79]; (crop 2) pale yellow crystals (2.66 g, 19% yield; mp 161−162 °C; 96.5% purity by GC; Anal. Calcd for $C_{17}H_{16}N_2O_2$: C, 72.84; H, 5.75; N, 9.99. Found: C, 72.34; H, 5.83; N, 9.90). Altogether, 10.5 g (75% yield; calcd 97.0% purity by GC) was obtained.

(B) Reaction at the 20.0-mmol scale with chromatography [silica, hexanes/CH_2Cl_2/ethyl acetate (7:2:1)] afforded a white solid (4.20 g, 75% yield; mp 159−160 °C; >99% purity by GC; Anal. Calcd for $C_{17}H_{16}N_2O_2$: C, 72.84; H, 5.75; N, 9.99. Found: C, 72.48; H, 5.68; N, 9.74).

*5-(Pentafluorophenyl)dipyrromethane (**7**).* (A) The reaction of pentafluorobenzaldehyde (9.80 g, 50.0 mmol) with crystallization [ethanol/water (4:1)] afforded two crops of crystals: (crop 1) pale white crystals [8.27 g, 53% yield; mp 130−131 °C (lit.[16] mp 131−132 °C); >99% purity by GC; Anal. Calcd for $C_{15}H_9F_5N_2$: C, 57.70; H, 2.91; N, 8.97. Found: C, 57.92; H, 2.76; N, 9.04]; (crop 2) pale white crystals (4.05 g, 26% yield; mp 129−130 °C; >99% purity by GC; Anal. Calcd for $C_{15}H_9F_5N_2$: C, 57.70; H, 2.91; N, 8.97. Found: C, 57.66; H, 2.82; N, 8.84). Altogether, 12.3 g (79% yield; calcd >99% purity by GC) was obtained.

(B) Reaction at the 20.0-mmol scale with chromatography twice [silica, hexanes/CH_2Cl_2/ethyl acetate (10:2:1)] afforded a white solid (5.00 g, 80% yield; mp 131 °C; 98.0% GC purity; Anal. Calcd for $C_{15}H_9F_5N_2$: C, 57.70; H, 2.91; N, 8.97. Found: C, 57.64; H, 3.02; N, 8.95).

*5-(Pentyl)dipyrromethane (**8**).* The reaction of hexanal (5.01 g, 50.0 mmol) was performed in the standard way. The viscous liquid obtained upon removal of pyrrole was chromatographed twice [silica, hexanes/CH_2Cl_2/ethyl acetate (16:3:1); hexanes/ethyl acetate (9:1)], affording a yellow oil (6.70 g, 62% yield; 94.3% purity by GC; Anal. Calcd for $C_{14}H_{20}N_2$: C, 77.73; H, 9.32; N, 12.95. Found: C, 77.63; H, 9.48; N, 12.71).

*Dipyrromethane (**9**).* (A) A mixture of paraformaldehyde (1.50 g, 50.0 mmol) and pyrrole (347 mL, 5.00 mol) in a 500-mL flask was degassed with a stream of argon for 10 min at room temperature. The mixture was heated at 55 °C for about 10 min under argon to obtain a clear solution. $InCl_3$ (1.11 g, 5.00 mmol) was then added, and the mixture was stirred at 55 °C for 2.5 h. The heat source was removed, and NaOH (6.0 g, 0.15 mol) was added. The mixture was stirred for 1 h and then filtered. The filtrate was concentrated, and the pyrrole was recovered. The crude solid obtained after removing pyrrole was extracted with 20% ethyl acetate/hexanes (5 × 50 mL). The solvent was evaporated. Crystallization [methanol/water (4:1)] afforded pale white crystals [3.29 g, 45% yield; mp 70−71 °C (lit.[37] mp 74 °C); 94.6% purity by GC; Anal. Calcd for $C_9H_{10}N_2$: C, 73.94; H, 6.89; N, 19.16. Found: C, 74.00; H, 6.81; N, 19.15].

(B) The same procedure at the 20.0-mmol scale with chromatography [silica, hexanes/CH_2Cl_2/ethyl acetate (7:2:1)] afforded a white solid (1.84 g, 63% yield; mp 75 °C; >99% purity by GC; Anal. Calcd for $C_9H_{10}N_2$: C, 73.94; H, 6.89; N, 19.16. Found: C, 74.18; H, 6.92; N, 19.14).

*5-Mesityldipyrromethane (**10**).* (A) A mixture of mesitaldehyde (7.42 g, 50.0 mmol) and pyrrole (347 mL, 5.00 mol) in a 500-mL single-neck round-bottomed flask was degassed with a stream of argon for 10 min. $MgBr_2$ (4.60 g, 25.0 mmol) was added, and the mixture was stirred for 1.5 h at room temperature. The tan mixture was treated with powdered NaOH (10.0 g, 0.25 mol). The mixture was stirred for 1 h and then filtered. The filtrate was concentrated, and the pyrrole was recovered. The crude solid obtained upon removal of pyrrole was extracted with 20% ethyl acetate/hexanes (7 × 100 mL). The extract was gravity-filtered through a pad of silica (80 g). The eluted solution was concentrated to obtain a yellow solid. Crystallization [ethanol/water (4:1)] afforded pale yellow crystals [7.00 g, 53% yield; 93% purity by GC; mp 166−167 °C (lit.[11] mp 166−167 °C); Anal. Calcd for $C_{18}H_{20}N_2$: C, 81.78; H, 7.63; N, 10.60. Found: C, 81.16; H, 7.67; N, 10.19].

(B) The same procedure was performed at the 20.0-mmol scale. Following silica-pad filtration, chromatography [silica, toluene/CH_2Cl_2 (1:1)] afforded a yellow solid (3.43 g, 65% yield; mp 165−166 °C; 92.7% purity by GC; Anal. Calcd for $C_{18}H_{20}N_2$: C, 81.78; H, 7.63; N, 10.60. Found: C, 81.89; H, 7.66; N, 10.36).

*Large-Scale Synthesis of 5-Phenyldipyrromethane (**1**).* Pyrrole (5.20 L, 75.0 mol; recycled) and benzaldehyde (79.8 g, 0.752 mol) were added to a 12-L two-neck round-bottomed flask equipped with a mechanical stirrer. The solution was degassed with a stream of argon for 1 h. $InCl_3$ (16.7 g, 75.5 mmol) was added, and the mixture was stirred under argon at room temperature for 1.5 h. The mixture was yellow during the course of the reaction. The reaction was quenched by the addition of NaOH (90.1 g, 2.25 mol; 20−40 mesh beads). The mixture was stirred for 1.5 h. The stirrer was stopped, and the mixture was allowed to settle for 1 h. The mixture was filtered (Fisher brand qualitative filter paper) using a Büchner funnel. The flask and filtered material on the funnel was washed with pyrrole (350 mL). The filtered material after drying under vacuum with warming for 4 h constituted 118 g. The filtrate was concentrated using a rotary evaporator under vacuum (0.2 mmHg) at 40−60 °C (the trap was cooled in a dry ice−acetone bath). The amount of recovered pyrrole was 5.30 L. A crude viscous residue was left in the evaporation flask. The crude viscous residue was treated with hexanes to remove traces of pyrrole in the following manner four times: hexanes (450 mL) was added, and the volatile components were removed under vacuum. The crude product was obtained as a pale yellow solid (87.0% GC purity; containing 7.9% of *N*-confused dipyrromethane **2** and 1.0% of tripyrrane **3**). Recrystallization [ethanol/water (4:1), 1 L] afforded a first crop of pale yellow crystals [98.9 g; mp 100−101 °C (lit.[7] mp 102−103 °C); 94.8% purity by GC; Anal. Calcd for $C_{15}H_{14}N_2$: C, 81.05; H, 6.35; N, 12.60. Found: C, 80.84; H, 6.40; N, 12.62]. The filtrate from the first crop was concentrated to dryness. The residue was recrystallized, affording a second crop of yellow crystals (6.00 g; mp 98−99 °C; 92.3% purity by GC; Anal. Calcd for $C_{15}H_{14}N_2$: C, 81.05; H, 6.35; N, 12.60. Found: C, 80.84; H, 6.37; N, 12.57). The filtrate from the second crop was concentrated to dryness, and the residue was recrystallized, affording a third crop (14.1 g; 88.7% purity by GC). The filtrate from the third crop was concentrated to dryness, and the residue was recrystallized, affording a fourth crop (3.33 g; 83.1% purity by GC) of crystals. Crops three and four were combined and recrystallized [ethanol/water (4:1)], affording pale brown crystals (10.6 g; mp 99−100 °C; 94.0% purity by GC; Anal. Calcd for $C_{15}H_{14}N_2$: C, 81.05; H, 6.35; N, 12.60. Found: C, 80.88; H, 6.39; N, 12.63). Altogether, 115.5 g of the title compound was obtained (69% yield; calcd 94.2% purity by GC).

The filtered material (118 g) from the crude reaction mixture exceeds the mass of the $InCl_3$ (16.7 g) and NaOH (90.1 g); the difference is attributed to water of hydration (maximally ca. 13.5 g originating from the condensation). The recovered liquid (5.30 L), which contains predominantly pyrrole and residual water, was distilled. The recovered pyrrole (4.92 L, 90% recovery based on unreacted pyrrole) was suitable for reuse.

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Supporting Information Available

Description of analytical issues including TLC and elemental analysis; data for the pyrrole−mesitaldehyde reaction, and data for TFA catalysis. This material is available free of charge via the Internet at http://pubs.acs.org.

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