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Formyl group activation of a bromopyrrole ester in Suzuki cross-coupling reactions: application to a formal synthesis of Polycitone A and B and Polycitrin A

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ABSTRACT

A new pyrrole building block is described, which allows for the regiospecific synthesis of 2,3,5-trisubstituted pyrroles and 2,3,4,5-tetrasubstituted pyrroles. Optimization studies are presented for the preparation of the pyrrole building block along with the evaluation of various cross-coupling conditions and cross-coupling agents. A short, formal synthesis of the natural products Polycitone A, Polycitone B, and Polycitrin A from the pyrrole building block is also described.

1. Introduction

For some time now our research group has been interested in using vinylogous iminium salt derivatives[1] as key building blocks for the construction of highly functionalized pyrroles. These substances have proven to be important precursors for the synthesis of a variety of pyrrole-containing natural products such as the Polycitones[2] (**1a** and **1b**) as indicated in Fig. 1. The interest by a variety of international researchers to prepare such pyrrole-containing natural products is driven by their significant biological activities such as their inhibition of HIV-1 integrase, their cytotoxic activity against a variety of cancer cell lines, and their multi-drug resistance reversal activity. Consequently, a number of important reviews[3] have appeared, which discuss the synthesis and specific modes of action of many of these alkaloids along with their structure–activity relationships.

A partial example of our previously published[4] approach to the synthesis of the Polycitones is presented in Scheme 1 and involves the formation of a symmetrical vinamidinium salt (**4**), followed by the reaction of this salt with the appropriate α-aminocarbonyl compound (**5**) such that a 2,4-disubstituted pyrrole (**6**) is generated in good yield. This material (**6**) can be further functionalized to an intermediate (**7**) reported by Steglich[5] and co-workers in the first reported synthesis of the Polycitones.

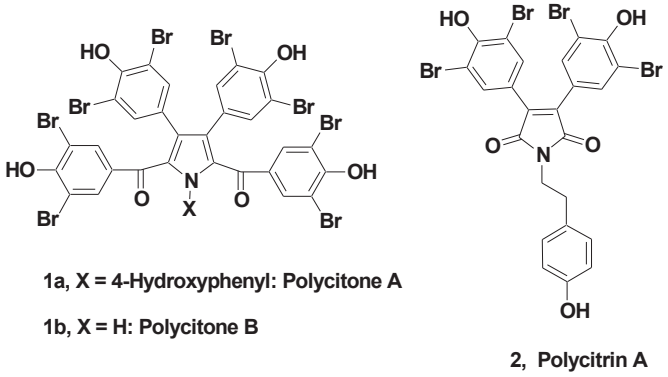

Fig. 1. Polycitone A (**1a**), Polycitone B (**1b**), and Polycitrin A (**2**).

Although our approach to such natural products has provided very effective transformations to the desired targets, the methodology is limited by not having a single key intermediate, which can be rapidly transformed into any of the desired pyrrole-containing natural products. Since the primary difference between many of

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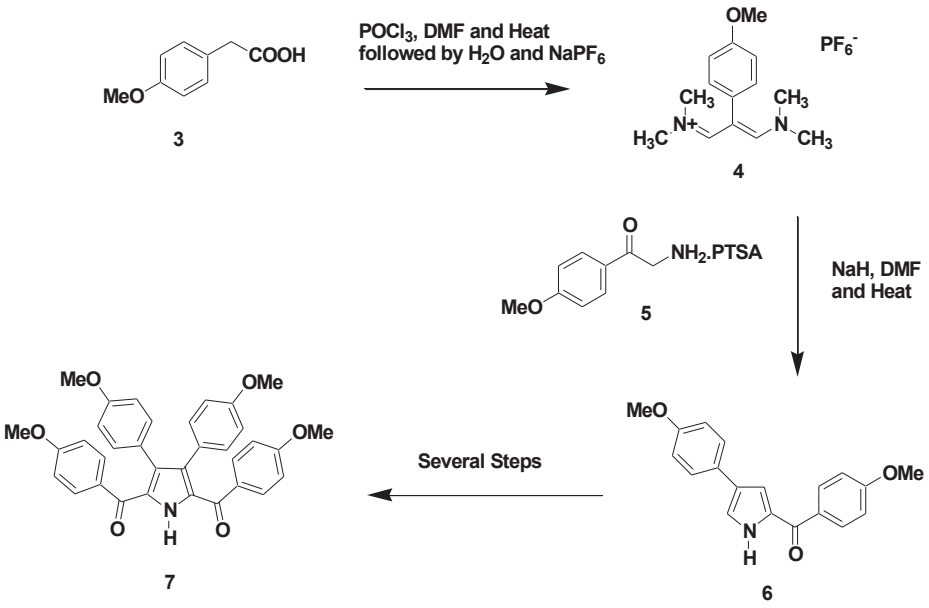


Scheme 1. Gupton group synthesis of key Polycitone precursor.

these targets involves the variation of the aromatic or heteroaromatic groups attached to the pyrrole core, an ideal strategy would involve a key pyrrole-containing compound, which could be rapidly functionalized with a variety of aromatic and heteroaromatic groups. We have previously employed[1] the Suzuki–Miyaura cross-coupling methodology in some of our steps to prepare pyrrole-containing natural products but have not utilized this reaction as the core strategy. Reports by Furstner,[6] Alvarez,[7] Banwell,[8] Handy,[9] Langer,[10] and Iwao[11] describe the use of such methodology but usually the pyrrole nitrogen is substituted when good yields are obtained. When the nitrogen has been unsubstituted, poor to modest yields are usually the result and the obvious implication is that such pyrrole based cross-coupling reactions work much better when nitrogen is substituted. In our previously mentioned Suzuki–Miyaura cross-coupling work, we have noticed that good yields are also obtained for nitrogen unsubstituted, brominated pyrroles, when the bromine is *ortho* to an ester group. When a typical substrate contains bromine, which is conjugated to a β-electron withdrawing group, the Suzuki–Miyaura cross-coupling reaction is normally facilitated. Consequently, it appears that the presence of an electron-withdrawing group *ortho* to the halogen is a more significant factor in the success of the cross-coupling reaction than having the pyrrole nitrogen protected in some manner. This also suggests that a variety of other electron-withdrawing groups attached to a pyrrole carbon and *ortho* to a bromine bearing carbon would produce a similar activating effect. On this basis we now describe a general methodology for rapid construction of a variety of nitrogen unsubstituted, aryl pyrroles from a single pyrrole building block that contains bromine at C-3 and a formyl group at C-2 of the pyrrole core. We also describe the application of this methodology to the formal synthesis of Polycitone A and B and Polycitrin A (Fig. 1).

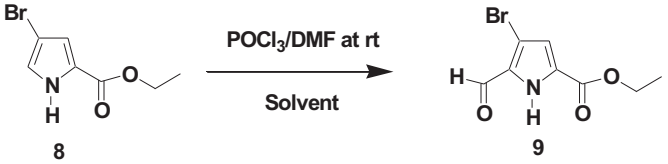
2. Results and discussions

Since many of the pyrrole-containing natural products possess carbonyl substitution at C-2 and/or C-5 of the pyrrole core, we decided to examine ethyl 3-bromo-2-formylpyrrole-5-carboxylate (**9**) as our 'potential pyrrole core building block'. The regiospecific preparation of ethyl 4-bromopyrrole-2-carboxylate (**8**) from 2-trichloroacetylpyrrole has been reported[12] in very good yield (90%) in two synthetic steps. Consequently, we have studied the formylation of ethyl 4-bromopyrrole-2-carboxylate (**8**) using Vilsmeier–Haack–Arnold conditions[13] and our results are summarized in Table 1 (Scheme 2). The results suggest that the reaction is very solvent-dependent and very good yields of ethyl 3-bromo-2-formylpyrrole-5-carboxylate (**9**) are obtained at room temperature, when conducted in chlorinated solvents. Interestingly, we could not detect any formylated product when the reaction was run in DMF. This three-step synthetic process can be easily scaled up such that multi-gram quantities of the ethyl 3-bromo-2-formylpyrrole-5-carboxylate (**9**) are easily accessed. It should be noted that the crude formylated product is usually very pure and can be employed in subsequent steps without any detrimental effect.

Table 1
Formylation of ethyl 4-bromopyrrole-2-carboxylate

Entry	Solvent	Ratio of $POCl_3$ to DMF	% Yield via HPLC	% Yield isolated
1	CH_2Cl_2	2.0:2.5	82	81
2	$CHCl_3$	2.0:2.5	79	80
3	CH_3CCl_3	2.0:2.5	67	56
4	DMF	2.0:2.5	0	NI
5	THF	2.0:2.5	0	NI
6	CH_2Cl_2	3.0:3.5	87	86

NI—not isolated; HPLC analyses were carried out on a Waters Alliance 2695 instrument with an Inertsil ODS-2 column using a 1:1 methanol/acetonitrile eluant at a flow rate of 0.25 mL per minute.



Scheme 2. Formylation of ethyl 4-bromopyrrole-2-carboxylate.

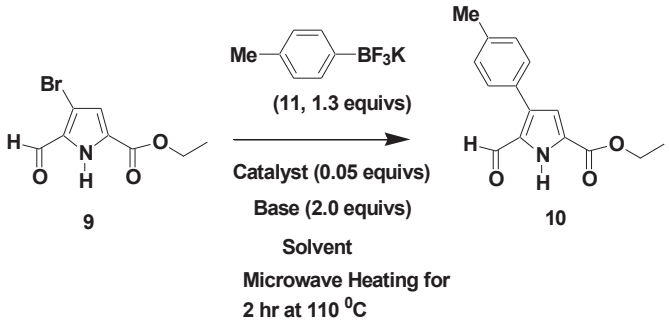
With substantial amounts of ethyl 3-bromo-2-formylpyrrole-5-carboxylate (**9**) in hand we next examined a variety of Suzuki–Miyaura cross-coupling reaction conditions. Potassium 4-methylphenyltrifluoroborate was utilized as the cross-coupling

partner in our initial studies and the results are reported in Table 2 (Scheme 3). Several different solvents were evaluated (entries 1–4, Table 2) and very little difference in product yield and purity was noted. As a result, we decided to stick with the toluene/ethanol mix, which we have utilized previously in other Suzuki–Miyaura cross-

Table 2
Evaluation of solvent, base, and catalyst in the Suzuki cross-coupling reaction of ethyl 3-bromo-2-formylpyrrole-5-carboxylate with potassium 4-methylphenyltrifluoroborate

Entry	Solvent	Base	Catalyst	% Yield via HPLC (isolated)
1	Toluene/EtOH	DIPEA	$Pd(PPh_3)_4$	86
2	THF	DIPEA	$Pd(PPh_3)_4$	86
3	CH_3CN	DIPEA	$Pd(PPh_3)_4$	86
4	EtOH	DIPEA	$Pd(PPh_3)_4$	86
5	Toluene/EtOH	Cs_2CO_3	$Pd(PPh_3)_4$	72
6	Toluene/EtOH	K_2CO_3	$Pd(PPh_3)_4$	73
7	Toluene/EtOH	Na_2CO_3	$Pd(PPh_3)_4$	83
8	Toluene/EtOH	DABCO	$Pd(PPh_3)_4$	91
9	Toluene/EtOH	DABCO	$Pd(OAc)_2$	84
10	Toluene/EtOH	DABCO	$PdCl_2$	98
11	Toluene/EtOH	DABCO	PdDBA	53 (42)
12	Toluene/EtOH	DABCO	$PdCl_2(PPh_3)_2$	100 (89)
13	Toluene/EtOH	DABCO	$PdDPPF(Cl)_2$	95 (99)

HPLC analyses were carried out on a Waters Alliance 2695 instrument with an Inertsil ODS-2 column using a 1:1 methanol/acetonitrile eluant at a flow rate of 0.25 mL per minute.



Scheme 3. Suzuki cross-coupling studies of ethyl 3-bromo-2-formylpyrrole-5-carboxylate with potassium 4-methylphenyltrifluoroborate.

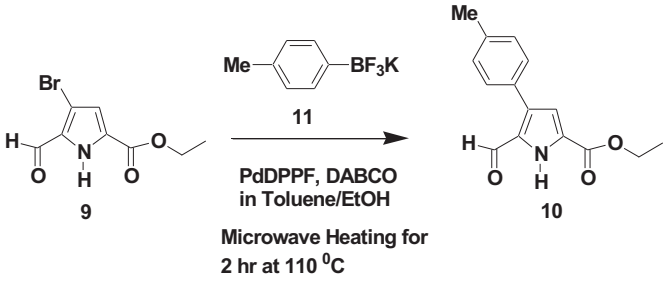
coupling reactions. We next examined the use of several different bases (entries 1 and 5–8, Table 2) and all the examples worked reasonably well but DABCO consistently gave better yields and cleaner cross-coupled products. Subsequently, a variety of palladium catalysts were evaluated (entries 8–13, Table 2) with dichloro [1,1′-bis-(diphenylphosphino)-ferrocene]palladium(II) dichloromethane adduct [$PdDPPF(Cl)_2$] giving the cleanest reaction products in very high yield. The dichloro-(bistriphenylphosphine) palladium(II) catalyst also proved quite effective. The rationale for the success of these particular catalysts is not obvious at this point. The last optimization parameter that we decided to look at was stoichiometry (Table 3 and Scheme 4). Various concentrations of catalysts were evaluated and no discernable differences in product yield or purity were observed. It was decided to utilize a 5 mol % concentration of the $PdDPPFCl_2$ for standard reaction conditions. When the quantities of base and boronic acid derivative were evaluated, the best yields and product purity were realized (entry 5, Table 3) when a slight excess of each reagent was used.

Following the completion of our optimization studies, we next turned our attention to examine the scope and limitation of our 'formyl group activation methodology' and several boronic acid derivatives were studied and the results are presented in Table 4.

Table 3
Optimization of Suzuki cross-coupling reaction stoichiometry of ethyl 3-bromo-2-formylpyrrole-5-carboxylate with potassium 4-methylphenyltrifluoroborate

Entry	Catalyst equivalents	DABCO equivalents	Trifluoroborate equivalents	% Yield via HPLC (isolated)
1	0.01	2.0	1.3	98
2	0.05	2.0	1.3	95 (99)
3	0.10	2.0	1.3	100
4	0.05	1.0	1.3	83
5	0.05	1.4	1.2	99 (99)
6	0.05	3.0	1.3	90
7	0.05	2.0	1.0	79
8	0.05	2.0	1.6	72
9	0.05	2.0	2.0	64

HPLC analyses were carried out on a Waters Alliance 2695 instrument with an Inertsil ODS-2 column using a 1:1 methanol/acetonitrile eluant at a flow rate of 0.25 mL per minute.



Scheme 4. Optimization of the stoichiometry for the Suzuki cross-coupling reaction of ethyl 3-bromo-2-formylpyrrole-5-carboxylate with potassium 4-methylphenyl trifluoroborate.

Oxygenated phenyl groups were examined (entries 2, 4, 5, 9, 11, and 12 Table 4), since this functionality is most often present in the various pyrrole-containing marine natural products.[3] These cross-coupling agents gave very good yields and product purities. In an overall sense, the variously substituted aryl groups produced very respectable yields and the lower yields in a couple of instances may have been due to physical losses during the purification process.

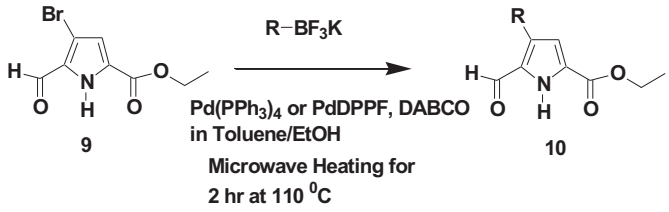
Table 4
Reactions of various aryl and heteroaryl boronic acid derivatives with ethyl 3-bromo-2-formylpyrrole-5-carboxylate under Suzuki cross-coupling conditions

Entry	Compound	Ar	% Yield isolated
1	10	4-MePh	99
2	12	4-MeOPh	86
3	13	4-ClPh	69
4	14	$3,4\text{-}(MeO)_2Ph$	70
5	15	$3,4,5\text{-}(MeO)_3Ph$	64
6	16	Ph	78
7	17	4-MeSPh	63
8	18	4-FPh	51 (69)[a]
9	19	Benzo(3,4)dioxolyl	99
10	20	$3,4\text{-}(Cl)_2Ph$	90[a]
11	21	4-HOPh	66[a]
12	22	$4\text{-}CF_3OPh$	96[a]
13	23	*N*-Phenylsulfonyl-3-indolyl	55

[a] These reactions utilized the corresponding boronic acids. All other reactions utilized the corresponding trifluoroborate.

The *N*-phenylsulfonyl-3-indolyl group (entry 13, Table 4) was chosen to study as a consequence of its presence[14] in several important, pyrrole-containing natural products (Scheme 5).

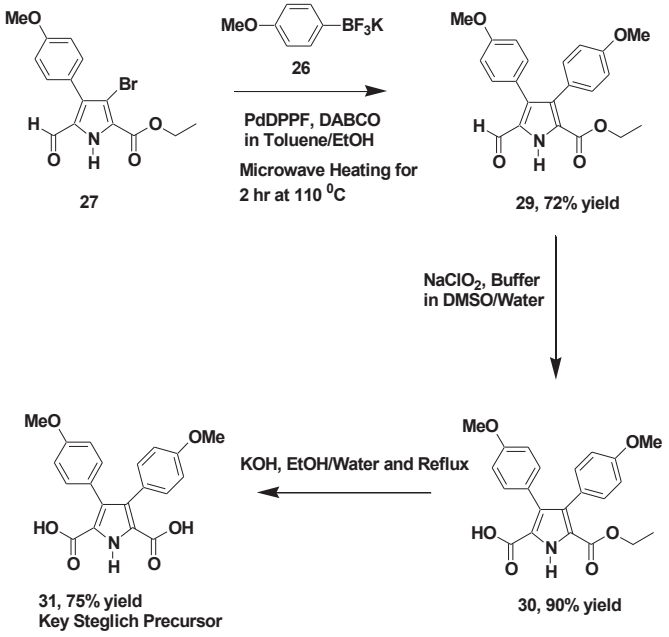
In addition to the studies that we have described, it was decided to demonstrate the flexibility of the methodology by preparing isomeric 3,4-diarylpyrroles. Since the actual pyrrole starting materials (**10** and **12**, Scheme 6) were derived from ethyl 3-bromo-2-formylpyrrole-5-carboxylate (**9**), the utility of the pyrrole building block is thereby extended. Bromination of both



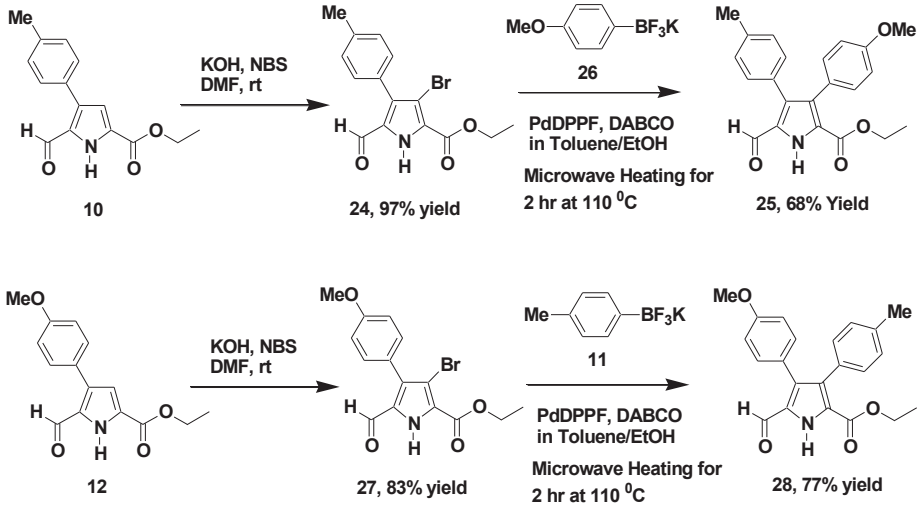
Scheme 5. Suzuki cross-coupling reactions of ethyl 3-bromo-2-formylpyrrole-5-carboxylate with various aryl and heteroaryl boronic acid derivatives.

pyrroles (**10** and **12**, Scheme 6) generated the corresponding 3-bromopyrroles (**24** and **27**, Scheme 6) in very good yields (97% and 83%). Subsequently, applying our optimized cross-coupling conditions to these brominated pyrroles produced the corresponding 3-aryl cross-coupled analogs (**25** and **28**, Scheme 6) in good yields (68% and 77%) as well.

The ultimate application of the 'formyl group activation' is to utilize the methodology for the construction of one of the pyrrole-containing marine natural products as suggested earlier. Polycitone A, Polycitone B, and Polycitrin A (Fig. 1) were chosen as the initial targets. Steglich[5,15] and co-workers have utilized a tetrasubstituted symmetrical pyrrole (**31**) as a key precursor to all three natural products (**1a**, **1b**, and **2**, Fig. 1) and therefore a synthesis (Scheme 7) of this material (**31**) would constitute a formal synthesis of Polycitone A, Polycitone B, and Polycitrin A.



Scheme 7. Formal synthesis of Polycitone A, Polycitone B, and Polycitrin A.



Scheme 6. Selective preparation of isomeric 3,4-diarylpyrroles via formyl group activation.

Cross-coupling of pyrrole **27** with potassium 4-methoxy trifluoroborate (**26**) under optimized conditions produced a tetrasubstituted pyrrole (**29**) in 72% yield. Oxidation of the cross-coupled product (**29**) with sodium chlorite in aqueous DMSO produced the pyrrole monoacid (**30**) in 90% yield and subsequent hydrolysis of this material under basic conditions gave the Steglich synthon[5,15] (**31**) in 75% yield. This sequence represents a five-step process from ethyl 3-bromo-2-formylpyrrole-5-carboxylate (**9**) in an overall yield of 42%.

3. Conclusions

In this article we have described the preparation of a very flexible pyrrole synthon [ethyl 3-bromo-2-formylpyrrole-5-carboxylate (**9**)], which can undergo Suzuki–Miyaura cross-coupling with a variety of boronic acid derivatives in good yield. This methodology allows for the convenient and efficient construction of various types of tetrasubstituted-3,4-diarylpyrroles including regioisomers. The completion of a short, formal synthesis of Polycitone A, Polycitone B, and Polycitrin A is also described. This methodology should prove very useful for the synthesis of libraries of highly functionalized pyrroles as a part of detailed SAR studies.

4. Experimental

4.1. General

All chemicals were used as received from the manufacturer (Aldrich Chemicals and Fisher Scientific). All solvents were dried over 4 Å molecular sieves prior to their use. NMR spectra were

obtained on either a Bruker 300 MHz spectrometer, or a Bruker 500 MHz spectrometer in either $CDCl_3$, DMSO-d_6, or acetone-d_6 solutions. IR spectra were recorded on a Nicolet Avatar 320 FT-IR spectrometer with an HATR attachment. High-resolution mass spectra were obtained on a Shimadzu IT-TOF mass spectrometer at the University of Richmond. Low-resolution GC–MS spectra were obtained on a Shimadzu QP 5050 instrument. Melting points and boiling points are uncorrected. Chromatographic purifications were carried out on a Biotage SP-1 instrument or a Biotage Isolera instrument (both equipped with a silica cartridge). Gradient elution with ethyl acetate/hexane was accomplished in both instances. The reaction products were normally eluted within the range of 4–8 column volumes of eluant with a gradient mixture of 60:40 ethyl acetate/hexane. TLC analyses were conducted on silica plates with hexane/ethyl acetate as the eluant. All purified reaction products gave TLC results, flash chromatograms, and ^{13}C NMR spectra consistent with a sample purity of >95%.

*4.1.1. Ethyl 3-bromo-2-formylpyrrole-5-carboxylate (**9**).* Into a 100 mL round bottom flask equipped with magnetic stirring and a rubber septum cap was placed 10 mL of anhydrous dichloromethane, 4.83 g (0.0661 mol) of dry DMF, 8.69 g (0.0566 mol) of phosphorus oxychloride, and the resulting mixture was stirred for 10 min. To this flask was then added 4.12 g (0.0189 mol) of ethyl 4-bromopyrrole-2-carboxylate in 15 mL of anhydrous dichloromethane and the resulting mixture was stirred overnight at room temperature. The reaction was worked up by the addition of 80 mL of water and separation of the two phases. The aqueous phase was extracted with additional dichloromethane (3×20 mL) and the combined dichloromethane phases were washed with brine (1×15 mL), dried over anhydrous sodium sulfate, and concentrated in vacuo to yield 4.01 g (86% yield) of a brown solid. This material was of sufficient purity to be used in subsequent experiments but an analytical sample was prepared by purification via flash chromatography on a Biotage Isolera system in which case a light colored solid was obtained, which exhibited the following physical properties: mp 91–92 °C; ^1H NMR ($CDCl_3$) δ 9.74 (s, 1H), 6.96 (d, J=1.2 Hz, 1H), 4.40 (q, J=7.2 Hz, 2H), and 1.39 (t, J=7.2 Hz, 3H); ^{13}C NMR (acetone-d_6) δ 179.0, 159.1, 131.0, 128.4, 117.5, 106.0, 61.1, and 13.6; IR (neat) 1711 and 1671 cm^{-1}; HRMS (ES, M+) *m/z* calcd for $C_8H_8BrNO_3$ 244.9688, found 244.9057.

*4.1.2. Ethyl 2-formyl-3-(4-methylphenylpyrrole)-5-carboxylate (**10**).* Into a 20 mL microwave reaction tube was placed a magnetic stir bar, ethyl 3-bromo-2-formylpyrrole-5-carboxylate (0.250 g, 1.02 mmol), potassium 4-methylphenyltrifluoroborate (0.255 g, 1.32 mmol), and DABCO (0.229 g, 2.04 mmol). A mixture of 3:1 toluene/ethanol (12 mL) was added to the microwave reaction tube along with 20 drops of water. After stirring for several minutes, dichloro[1,1′-bis-(diphenylphosphino)ferrocene]palladium(II) dichloromethane adduct (0.037 g, 0.051 mmol) was added to the reaction mixture and the tube was capped and sealed with a crimping tool. The reaction mixture was heated in a Biotage Initiator microwave system for 2 h at 110 °C. After cooling to room temperature, the reaction mixture was filtered through a short plug of silica gel and the silica was subsequently washed with 2×30 mL of ethyl acetate and the combined organic materials were concentrated in vacuo to give a dark solid (0.260 g, 99% yield). This material was quite pure by TLC and HPLC analysis but an analytical sample was prepared by flash chromatography on a Biotage Isolera system in which case a light colored solid was obtained. We have previously described[13] the synthesis of this substance by a different synthetic route and the spectral properties exhibited by this reaction product were identical to those reported earlier: ^1H NMR ($CDCl_3$) δ 9.78 (s, 1H), 7.40 (d, J=8.1 Hz, 2H), 7.29 (d, J=8.1 Hz, 2H), 7.02 (d, J=2.4 Hz, 1H), 4.41 (q, J=7.2 Hz, 2H), 2.43 (s, 3H), and 1.42 (t, J=7.2 Hz, 3H). It should be noted that a control experiment was run on 4-bromo-2-carbethoxypyrrole (the compound minus the 2-formyl group) under conditions as described above in which case a gross mixture of products was obtained.

*4.1.3. Ethyl 2-formyl-3-(4-methoxyphenylpyrrole)-5-carboxylate (**12**).* This material was prepared in a manner identical to the previous example with the exceptions that diisopropylethylamine (DIPEA) was used as the base instead of DABCO and tetrakis(-triphenylphosphine)palladium (0) was used as the catalyst and potassium 4-methoxyphenyltrifluoroborate was used as the coupling agent. Work up of the reaction mixture produced a dark solid, which was purified by flash chromatography on a Biotage Isolera system in which case a light colored solid was obtained (0.280 g, 72% yield). We have previously described[13] the synthesis of this substance by a different synthetic route and the spectral properties exhibited by this reaction product were identical to those reported earlier: ^1H NMR ($CDCl_3$) δ 9.76 (s, 1H), 7.43 (d, J=9.0 Hz, 2H), 7.00–7.02 (m, 3H), 4.41 (q, J=6.9 Hz, 2H), 3.88 (s, 3H), and 1.42 (t, J=6.9 Hz, 3H).

*4.1.4. Ethyl 2-formyl-3-(4-chlorophenylpyrrole)-5-carboxylate (**13**).* This material was prepared in a manner identical to the previous example with the exception that potassium 4-chlorophenyltrifluoroborate was used as the coupling agent. Work up of the reaction mixture produced a dark solid, which was purified by flash chromatography on a Biotage Isolera system in which case a light colored solid was obtained (0.116 g, 69% yield). We have previously described[13] the synthesis of this substance by a different synthetic route and the spectral properties exhibited by this reaction product were identical to those reported earlier: ^1H NMR ($CDCl_3$) δ 9.76 (s, 1H), 7.45 (d, J=8.5 Hz, 2H), 7.44 (d, J=8.5 Hz, 2H), 7.02 (d, J=2.9 Hz, 1H), 4.42 (q, J=7.2 Hz, 2H), and 1.42 (t, J=7.2 Hz, 3H).

*4.1.5. Ethyl 2-formyl-3-(3,4-dimethoxyphenylpyrrole)-5-carboxylate (**14**).* This material was prepared in a manner identical to the previous example with the exception that potassium 3,4-dimethoxyphenyltrifluoroborate was used as the coupling agent. Work up of the reaction mixture produced a dark solid, which was purified by flash chromatography on a Biotage Isolera system in which case a light colored solid was obtained (0.300 g, 70% yield). We have previously described[13] the synthesis of this substance by a different synthetic route and the spectral properties exhibited by this reaction product were identical to those reported earlier: ^1H NMR ($CDCl_3$) δ 9.79 (s, 1H), 7.04 (dd, J=2.0, 8.5 Hz, 1H). 7.00–7.02 (m, 3H), 4.42 (q, J=7.2 Hz, 2H), 3.95 (s, 6H), and 1.42 (t, J=7.2 Hz, 3H).

*4.1.6. Ethyl 2-formyl-3-(3,4,5-trimethoxyphenylpyrrole)-5-carboxylate (**15**).* This material was prepared in a manner identical to the previous example with the exception that potassium 3,4,5-trimethoxyphenyltrifluoroborate was used as the coupling agent. Work up of the reaction mixture produced a dark solid, which was purified by flash chromatography on a Biotage Isolera system in which case a light colored solid was obtained (0.110 g, 64% yield). We have previously described[13] the synthesis of this substance by a different synthetic route and the spectral properties exhibited by this reaction product were identical to those reported earlier: ^1H NMR ($CDCl_3$) δ 9.82 (s, 1H), 7.28 (d, J=2.4 Hz, 1H), 6.68 (s, 2H), 4.40 (q, J=6.9 Hz, 2H), 3.91 (s, 6H), 3.90 (s, 3H), and 1.41 (t, J=6.9 Hz, 3H).

*4.1.7. Ethyl 2-formyl-3-phenylpyrrole-5-carboxylate (**16**).* This material was prepared in a manner identical to the previous example with the exception that potassium phenyltrifluoroborate was used as the coupling agent. Work up of the reaction mixture produced

a dark solid, which was purified by flash chromatography on a Biotage Isolera system in which case a light colored solid was obtained (0.256 g, 78% yield). We have previously described[13] the synthesis of this substance by a different synthetic route and the spectral properties exhibited by this reaction product were identical to those reported earlier: ^{1}H NMR (acetone-d_6) δ 9.83 (s, 1H), 7.63 (d, J=7.5 Hz, 2H), 7.49 (t, J=7.5 Hz, 2H), 7.42 (t, J=7.5 Hz, 1H), 7.07 (s, 1H), 4.38 (q, J=7.5 Hz, 2H), and 1.38 (t, J=7.5 Hz, 3H).

*4.1.8. Ethyl 2-formyl-3-(4-methylthiophenylpyrrole)-5-carboxylate (**17**).* This material was prepared in a manner identical to the previous example with the exception that DABCO was used as the base, dichloro[1,1′-bis-(diphenylphosphino)ferrocene]palladium(II) dichloromethane adduct was used as the catalyst, and potassium 4-methylthiophenyltrifluoroborate was used as the coupling agent. Work up of the reaction mixture produced a dark solid, which was purified by flash chromatography on a Biotage Isolera system in which case a light colored solid was obtained (0.184 g, 63% yield), which exhibited the following physical properties: mp 123–124 °C; ^{1}H NMR ($CDCl_3$) δ 9.78 (s, 1H), 7.42 (d, J=8.4 Hz, 2H), 7.35 (d, J=8.4 Hz, 2H), 7.02 (d, J=2.7 Hz, 1H), 4.42 (q, J=7.2 Hz, 2H), 2.55 (s, 3H), and 1.42 (t, J=7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 180.7, 160.3, 139.1, 135.5, 130.2, 129.4, 129.2, 127.8, 126.6, 115.2, 61.5, 15.6, and 14.3; IR (neat) 1701 and 1685 cm^{-1}; HRMS (ES, M+H) m/z calcd for $C_{15}H_{16}NO_3S$ 290.0851, found 290.0837.

*4.1.9. Ethyl 2-formyl-3-(4-fluorophenylpyrrole)-5-carboxylate (**18**).* This material was prepared in a manner identical to the previous example with the exception that 4-fluorophenylboronic acid was used as the coupling agent. Work up of the reaction mixture produced a dark solid, which was purified by flash chromatography on a Biotage Isolera system in which case a light colored solid was obtained (0.219 g, 69% yield), which exhibited the following physical properties: mp 95–96 °C; ^{1}H NMR ($CDCl_3$) δ 9.75 (s, 1H), 7.47 (dd, J=5.4, 8.7 Hz, 2H), 7.17 (t, J=8.7 Hz, 2H), 7.01 (d, J=2.4 Hz, 1H), 4.42 (q, J=7.2 Hz, 2H), and 1.42 (t, J=7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 180.4, 162.9 (d, J=248.4 Hz), 160.2, 134.9, 130.7 (d, J=8.0 Hz), 103.2, 128.7 (d, J=3.5 Hz), 127.7, 115.9 (d, J=82.3 Hz), 115.3, 61.5, and 14.3; IR (neat) 1686 and 1655 cm^{-1}; HRMS (ES, M+H) m/z calcd for $C_{14}H_{13}FNO_3$ 262.0879, found 262.0868.

*4.1.10. Ethyl 2-formyl-3-[benzo(3,4)dioxolylpyrrole]-5-carboxylate (**19**).* This material was prepared in a manner identical to the previous example with the exception that potassium benzo[1,3]dioxolyltrifluorofluoroborate was used as the coupling agent. Work up of the reaction mixture produced a dark solid (0.300 g, 99% yield). This material was quite pure by TLC and HPLC and was not purified further. This material exhibited the following physical properties: mp 140–141 °C; ^{1}H NMR (acetone-d_6) δ 9.81 (s, 1H), 7.15 (d, J=1.5 Hz, 1H), 7.10 (dd, J=1.5, 8.0 Hz, 1H), 7.01 (s, 1H), 6.95 (d, J=8.0 Hz, 1H), 6.08 (s, 2H), 4.36 (q, J=7.0 Hz, 2H), and 1.37 (t, J=7.0 Hz, 3H); ^{13}C NMR (acetone-d_6) δ 180.1, 159.9, 148.2, 147.7, 134.6, 130.6, 127.7, 127.0, 123.0, 115.0, 109.3, 108.4, 101.4, 60.7, and 13.6; IR (neat) 1704 and 1644 cm^{-1}; HRMS (ES, M+H) m/z calcd for $C_{15}H_{14}NO_5$ 288.0872, found 288.0873.

*4.1.11. Ethyl 2-formyl-3-(3,4-dichlorophenylpyrrole)-5-carboxylate (**20**).* This material was prepared in a manner identical to the previous example with the exception that 3,4-dichlorophenylboronic acid was used as the coupling agent. Work up of the reaction mixture produced a dark solid, which was purified by flash chromatography on a Biotage Isolera system in which case a light colored solid was obtained (0.340 g, 90% yield) and this material exhibited the following physical properties: mp 160–161 °C; ^{1}H NMR ($CDCl_3$) δ 9.77 (s, 1H), 7.60 (d, J=2.1 Hz, 1H), 7.55 (d, J=8.1 Hz, 1H), 7.33 (dd, J=2.1, 8.1 Hz, 1H), 7.02 (d, J=2.4 Hz, 1H), 4.42 (q, J=7.2 Hz, 2H), and 1.42 (t, J=7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 179.9, 159.9, 133.2, 133.0, 132.7, 132.6, 130.9, 130.7, 130.1, 128.2, 127.9, 115.2, 61.6, and 14.3; IR (neat) 1717 and 1668 cm^{-1}; HRMS (ES, M+H) m/z calcd for $C_{14}H_{12}Cl_2NO_3$ 312.0194, found 312.0182.

*4.1.12. Ethyl 2-formyl-3-(4-hydroxyphenylpyrrole)-5-carboxylate (**21**).* This material was prepared in a manner identical to the previous example with the exception that potassium 4-hydroxyphenylboronic acid was used as the coupling agent. Work up of the reaction mixture produced a dark solid, which was purified by flash chromatography on a Biotage Isolera system in which case a light colored solid was obtained (0.173 g, 66% yield) and this material exhibited the following physical properties: mp 158–159 °C; ^{1}H NMR ($CDCl_3$) δ 9.76 (s, 1H), 7.38 (d, J=8.7 Hz, 2H), 6.99 (d, J=2.7 Hz, 1H), 6.94 (d, J=8.7 Hz, 2H), 4.41 (q, J=7.2 Hz, 2H), and 1.42 (t, J=7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 180.7, 160.3, 155.9, 135.8, 130.5, 130.1, 127.7, 125.3, 115.9, 115.1, 61.5, and 14.3; IR (neat) 3254, 1701, and 1634 cm^{-1}; HRMS (ES, M+H) m/z calcd for $C_{14}H_{14}NO_4$ 260.0923, found 260.0908.

*4.1.13. Ethyl 2-formyl-3-(4-trifluoromethoxyphenylpyrrole)-5-carboxylate (**22**).* This material was prepared in a manner identical to the previous example with the exception that potassium 4-trifluoromethoxyphenylboronic acid was used as the coupling agent. Work up of the reaction mixture produced a dark solid (0.320 g, 96% yield), which did not require additional purification. This material exhibited the following physical properties: mp 52–54 °C; ^{1}H NMR ($CDCl_3$) δ 9.77 (s, 1H), 7.53 (d, J=8.0 Hz, 2H), 7.33 (d, J=8.0 Hz, 2H), 7.03 (d, J=2.5 Hz, 1H), 4.42 (q, J=7.0 Hz, 2H), and 1.43 (t, J=7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 180.3, 160.2, 149.3, 134.3, 131.4, 130.4, 130.2, 127.8, 121.4, 120.5 (q, J=251.6 Hz), 115.3, 61.9, and 14.3; IR (neat) 1718 and 1661 cm^{-1}; HRMS (ES, M+H) m/z calcd for $C_{15}H_{13}F_3NO_4$ 328.0797, found 328.0796.

*4.1.14. Ethyl 3-(1-benzenesulfonyl-1H-indol-3-yl)-2-formylpyrrole-5-carboxylate (**23**).* This material was prepared in a manner identical to the previous example with the exceptions that diisopropylethylamine (DIPEA) was used as the base instead of DABCO and potassium 1-benzenesulfonyl-1*H*-indol-3-trifluoroborate was used as the coupling agent. Work up of the reaction mixture produced a dark orange solid, which was purified by flash chromatography on a Biotage Isolera system in which case a bright orange solid was obtained (0.470 g, 55% yield) and this material exhibited the following physical properties: mp 164–166 °C; ^{1}H NMR ($CDCl_3$) δ 9.94 (s, 1H), 8.10 (d, J=8.0 Hz, 1H), 7.97 (d, J=8.5 Hz, 2H), 7.70 (s, 1H), 7.65 (d, J=8.0 Hz, 1H), 7.60 (t, J=8.5 Hz, 1H), 7.51 (t, J=8.5 Hz, 2H), 7.44 (t, J=8.5 Hz, 1H), 7.36 (t, J=8.5 Hz, 1H), 7.13 (d, J=3.0 Hz, 1H), 4.43 (q, J=7.0 Hz, 2H), and 1.43 (t, J=7.0 Hz, 3H); ^{13}C NMR (acetone-d_6) δ 179.8, 159.8, 137.9, 135.1, 134.5, 131.7, 130.0, 129.7, 128.3, 127.0, 125.6, 125.3, 124.2, 124.0, 120.3, 115.6, 115.0, 113.7, 60.8, and 13.7; IR (neat) 1714 and 1659 cm^{-1}; HRMS (ES, M+H) m/z calcd for $C_{22}H_{18}N_2O_5S$ 423.1009, found 423.1003.

*4.1.15. Ethyl 4-bromo-2-formyl-3-(4-methoxyphenylpyrrole)-5-carboxylate (**27**).* Into a 100 mL round bottom flask equipped with magnetic stirring was placed ethyl 2-formyl-3-(4-methoxyphenylpyrrole)-5-carboxylate (0.140 g, 0.513 mmol), potassium hydroxide (0.0575 g, 1.03 mmol) and 15 mL of DMF. The mixture was stirred for 15 min and *N*-bromosuccinimide (0.0913 g, 0.513 mmol) was added to the reaction flask and the resulting reaction mixture was allowed to stir overnight at room temperature. The reaction mixture was subsequently quenched with 45 mL of water and extracted with ethyl acetate (3×20 mL). The combined organic phases were washed with a saturated, aqueous solution of lithium chloride and this was followed by drying the organic phase

over anhydrous sodium sulfate. The drying agent was removed by filtration and the filtrate was concentrated in vacuo to give a solid product. This material was subjected to flash chromatography on a Biotage Isolera system with a hexane/ethyl acetate gradient in which case a tan solid (0.150 g, 83% yield) was obtained, which exhibited the following physical properties: mp 132–134 °C; ^{1}H NMR ($CDCl_3$) δ 9.55 (s, 1H), 7.41 (d, J=6.9 Hz, 2H), 7.03 (d, J=6.9 Hz, 2H), 4.45 (q, J=7.0 Hz, 2H), 3.89 (s, 3H), and 1.45 (t, J=7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 180.6, 160.1, 159.3, 135.5, 131.8, 129.8, 124.7, 122.2, 114.1, 104.3, 61.8, 55.3, and 14.3; IR (neat) 1690 and 1664 cm^{-1}; HRMS (ES, M+H) *m/z* calcd for $C_{15}H_{15}BrNO_4$ 352.0184, found 352.0195.

*4.1.16. Ethyl 4-bromo-2-formyl-3-(4-methylphenylpyrrole)-5-carboxylate (**24**).* This material was prepared in a manner identical to the previous example with the exception that 2-formyl-3-(4-methylphenylpyrrole)-5-carboxylate was used as the starting material for the reaction. The solid product (0.441 g, 97% yield) was sufficiently pure to be used in a subsequent reaction but an analytical sample was prepared by flash chromatography on a Biotage Isolera system with a hexane/ethyl acetate gradient. The resulting purified solid exhibited the following physical properties: mp 125–127 °C; ^{1}H NMR ($CDCl_3$) δ 9.55 (s, 1H), 7.37 (d, J=8.1 Hz, 2H), 7.31 (d, J=8.1 Hz, 2H), 4.46 (q, J=7.2 Hz, 2H), 2.45 (s, 3H), and 1.45 (t, J=7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 180.7, 162.6, 159.4, 135.7, 130.5, 129.8, 129.3, 127.1, 124.8, 104.2, 61.8, 21.3, and 14.3: IR (neat) 1690 and 1659 cm^{-1}; HRMS (ES, M+Na) *m/z* calcd for $C_{15}H_{14}BrNNaO_3$ 358.0055, found 358.0057.

*4.1.17. Ethyl 2-formyl-4-(4-methoxyphenyl)-3-(4-methylphenyl)pyrrole-5-carboxylate (**25**).* Into a 20 mL microwave reaction tube equipped with a magnetic stir bar was placed ethyl 4-bromo-2-formyl-3-(4-methylphenylpyrrole)-5-carboxylate (0.150 g, 0.446 mmol), potassium 4-methoxyphenyltrifluoroborate (0.124 g, 0.580 mmol), and DABCO (0.100 g, 0.892 mmol). A mixture (12 mL) of 3:1 of toluene/ethanol was added to the reaction tube along with 20 drops of water followed by dichloro[1,1′-bis-(diphenylphosphino)ferrocene]palladium(II) dichloromethane adduct (0.016 g, 0.022 mmol). The reaction tube was capped and sealed with a crimping tool and the reaction mixture was heated in a Biotage Initiator microwave system for 2 h at 110 °C. After cooling to room temperature, the reaction mixture was filtered through a short plug of silica gel and the silica was subsequently washed with 2×30 mL of ethyl acetate and the combined organic materials were concentrated in vacuo to give a dark solid. This material was subjected to flash chromatography on a Biotage Isolera system with a hexane/ethyl acetate gradient in which case a tan solid (0.162 g, 68% yield) was obtained and exhibited the following physical properties: mp 116–118 °C; ^{1}H NMR ($CDCl_3$) δ 9.62 (s, 1H), 7.12 (br d, J=8.7 Hz, 4H), 7.05 (d, J=8.4 Hz, 2H), 6.82 (d, J=9.0 Hz, 2H), 4.28 (q, J=7.2 Hz, 2H), 3.81 (s, 3H), 2.35 (s, 3H), and 1.26 (t, J=7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 181.4, 160.3, 158.8, 137.5, 135.1, 131.9, 130.5, 130.4, 129.9, 129.1, 128.4, 124.6. 123.8, 113.1, 61.2, 55.1, 21.1, and 14.1: IR (neat) 1690 and 1664 cm^{-1}; HRMS (ES, M+Na) *m/z* calcd for $C_{22}H_{21}NNaO_4$ 386.1368, found 386.1372.

*4.1.18. Ethyl 2-formyl-3-(4-methoxyphenyl)-4-(4-methylphenyl)pyrrole-5-carboxylate (**28**).* This material was prepared in a manner identical to the previous example with the exception that ethyl 4-bromo-2-formyl-3-(4-methoxyphenylpyrrole)-5-carboxylate was used as the starting material and potassium 4-methyl phenyltrifluoroborate was employed as the cross-coupling agent. After the standard work up and purification a tan solid (0.150 g, 77% yield) was obtained, which exhibited the following physical properties: mp 130–131 °C; ^{1}H NMR ($CDCl_3$) δ 9.62 (s, 1H), 7.09–7.11 (m, 6H), 6.83 (d, J=9.0 Hz, 2H), 4.27 (q, J=7.2 Hz, 2H), 3.81 (s, 3H), 2.35 (s, 3H), and 1.25 (t, J=7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 181.3, 160.2, 159.3, 136.9, 134.8, 131.8, 130.6, 129.8, 129.3, 128.3, 123.9, 123.6, 113.8, 61.1, 56.2, 21.6, and 14.0; IR (neat) 1704 and 1659 cm^{-1}; HRMS (ES, M+Na) *m/z* calcd for $C_{22}H_{21}NNaO_4$ 386.1368, found 386.1382.

*4.1.19. Ethyl 2-formyl-3,4-bis-(4-methoxyphenyl)pyrrole-5-carboxylate (**29**).* This material was prepared in a manner identical to the previous example with the exception that potassium 4-methoxyphenyltrifluoroborate was employed as the cross-coupling agent. After the standard work up and purification a tan solid (0.232 g, 72% yield) was obtained, which exhibited the following physical properties: mp 130–132 °C; ^{1}H NMR ($CDCl_3$) δ 9.62 (s, 1H), 7.08–7.14 (m, 4H), 6.84 (d, J=5.7 Hz, 2H), 6.82 (d, J=5.7 Hz, 2H), 4.28 (q, J=7.2 Hz, 2H), 3.82 (s, 6H), and 1.26 (t, J=7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 181.5, 160.3, 159.3, 158.8, 134.8, 131.9, 131.8, 130.4, 129.9, 124.6, 123.8, 123.6, 113.9, 113.1, 61.1, 55.2, 55.1, and 14.1; IR (neat) 1704 and 1655 cm^{-1}; HRMS (ES, M+Na) *m/z* calcd for $C_{22}H_{21}NNaO_5$ 402.1317, found 402.1320.

*4.1.20. 3,4-Bis-(4-methoxyphenyl)pyrrole-2,5-dicarboxylic acid monoethyl ester (**30**).* Into a 20 mL microwave reaction tube equipped with a magnetic stir bar was placed ethyl 2-formyl-3,4-bis-(4-methoxyphenyl)pyrrole-5-carboxylate (0.100 g, 0.264 mmol), DMSO (10 mL), 0.050 M aqueous sodium dihydrogen phosphate (3 mL), and sodium chlorite monohydrate (0.143 g, 1.58 mmol). The reaction tube was capped and sealed with a crimping tool and the reaction mixture was heated in a Biotage Initiator microwave system for 2 h at 60 °C. The reaction mixture was cooled to room temperature, acidified with 6 M hydrochloric acid, diluted with 300 mL of water, and extracted with ethyl acetate (3×30 mL). The combined organic layers were washed with water, dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo to leave a tan solid (0.0940 g, 90% yield). This material was sufficiently pure to be used in the next step and exhibited the following physical properties: mp 259–260 °C; ^{1}H NMR (DMSO-d_6) δ 6.97 (d, J=8.5 Hz, 2H), 6.95 (d, J=8.5 Hz, 2H), 6.74 (d, J=8.5 Hz, 4H), 4.10 (q, J=7.2 Hz, 2H), 3.71 (s, 6H), and 1.13 (t, J=7.2 Hz, 3H); ^{13}C NMR (DMSO-d_6) δ 162.0, 160.4, 158.3, 158.2, 132.3, 132.2, 130.6, 130.1, 126.4, 126.3, 123.1, 121.9, 113.1, 60.4, 55.4, 55.3, and 14.3; IR (neat) 1699 and 1659 cm^{-1}; HRMS (ES, M+Na) *m/z* calcd for $C_{22}H_{21}NNaO_6$ 418.1267, found 418.1252.

*4.1.21. 3,4-Bis-(4-methoxyphenyl)pyrrole-2,5-dicarboxylic acid (**31**).* Into a 100 mL round bottom flask equipped with magnetic stirring and a reflux condenser was placed 3,4-bis-(4-methoxy phenyl)-pyrrole-2,5-dicarboxylic acid monoethyl ester (0.100 g, 0.253 mmol), potassium hydroxide (0.142 g, 2.53 mmol), and 30 mL of a 1:1 mixture of ethanol/water. The reaction mixture was refluxed overnight, cooled to room temperature, and acidified to pH 2 with 6 M hydrochloric acid. The mixture was diluted with 100 mL of water, extracted with ethyl acetate (3×30 mL), and the combined organic phases were washed with brine and dried over anhydrous sodium sulfate. The drying agent was removed by filtration and the filtrate was concentrated in vacuo to yield a solid (0.070 g, 75% yield). This material exhibited spectral properties identical to those reported by Steglich[15] and co-workers: mp 254–256 °C (lit. 268–270 °C); ^{1}H NMR (DMSO-d_6) δ 6.96 (d, J=8.5 Hz, 4H), 6.73 (d, J=8.5 Hz, 4H), and 3.71 (s, 6H); ^{13}C NMR (DMSO-d_6) δ 161.9, 158.2, 132.2, 130.2, 126.5, 122.6, 113.1, and 55.3; IR (neat) 1659 cm^{-1}; HRMS (ES, M+Na) *m/z* calcd for $C_{20}H_{17}NNaO_6$ 390.0954, found 390.0947.

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