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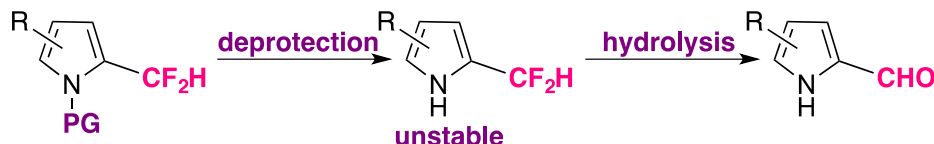
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Probing the Hydrolytic Reactivity of 2-Difluoromethyl Pyrroles

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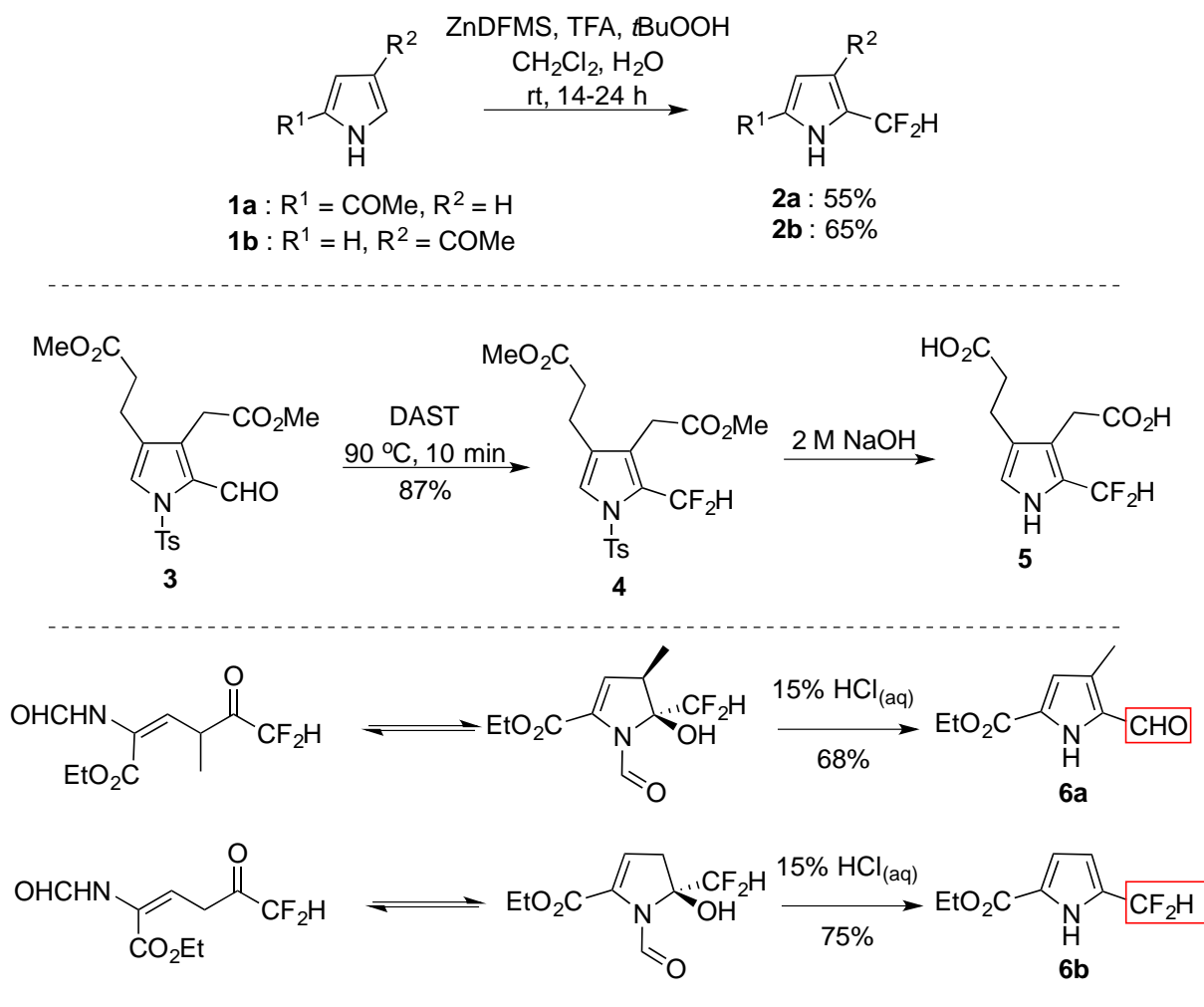


Abstract: α -Difluoromethyl pyrroles were found to be stable while *N*-protected with an electron-withdrawing group. Due to the propensity of pyrroles to access azafulvenium-like intermediates, the C–F bonds of an α -difluoromethyl substituent are labile under hydrolytic conditions. The presence of certain electron-withdrawing substituents about the pyrrolic ring can accelerate this process, as determined through a kinetic comparison of the deprotection and subsequent hydrolysis reactions of *N*-protected β -aryl α -difluoromethyl pyrroles.

Introduction

Porphyrinogens have been intensely studied, particularly as regards to chemical and biological relevance of the corresponding porphyrins.^{1–4} Although spontaneous oxidation of porphyrinogens to porphyrins can render the isolation of these precursors rather challenging,⁵ calix[4]pyrroles⁶ bear eight alkyl or aryl groups at the *meso* positions of the tetrapyrrolic skeleton and thus resist oxidation.^{7–14} The presence of a *meso* sp³ carbon confers to the structure a significant conformational freedom,⁵ enabling potential binding of these macrocycles for a wide range of applications.^{7–14} As part of an ongoing effort to develop functionalised dipyrrolic structures, we began to investigate the synthesis of pyrroles featuring a –CF₂– moiety at the α -position, contrasting with the –CR₂– unit (R = alkyl or aryl) used as precursors to calix[4]pyrroles. The strength of the C–F bond,¹⁵ alongside its ability to sterically mimic

the C–H unit, has driven growing interest in the use of fluorine as an isostere of hydrogen, a common strategy in agrochemical¹⁶ and pharmaceutical industries.^{17,18} In tandem, the development of more efficient and diverse methods through which to incorporate this functional moiety, either directly¹⁹⁻²² or via the fluorination of existing functionality,²³ renders this group even more suitable for incorporation into a wide variety of frameworks. However, there are few reports describing pyrroles bearing a difluoromethyl substituent directly appended to the heterocyclic core. Baran and co-workers developed a fluorinating reagent for the installation of a difluoromethyl group on nitrogen-containing heteroaromatic compounds *via* a radical mechanism (Scheme 1, top):¹⁹ *N*-unsubstituted 2- and 3-acyl pyrroles **1a-b** were shown to react promptly with ZnDFMS in the presence of *t*BuOOH and gave the α -difluoromethyl-substituted analogues **2a-b** in moderate yield. Note that **2a** and **2b** both feature conjugated electron-withdrawing acyl groups that serve to stabilise the heterocyclic core.



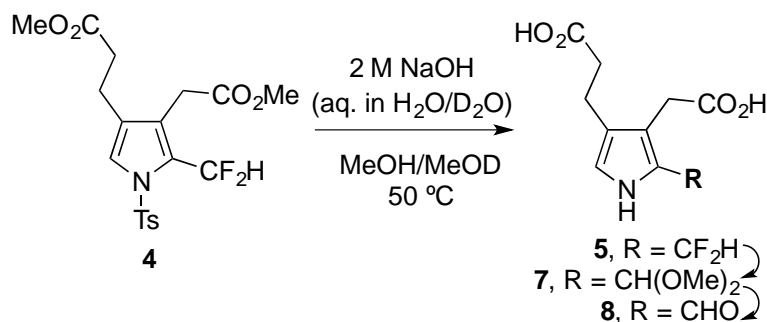
Scheme 1. Examples of α -difluoromethyl-substituted pyrroles.

In 1995 Scott reported the fluorination of several 2-formyl pyrroles using DAST, with the goal of synthesising an inhibitor of the uroporphyrinogen III cosynthase.²⁴ Pyrrole **3**, which features a substitution pattern matching that of the enzyme substrate, uroporphomethene, reacted with DAST to render **4** in high yield (87%, Scheme 1, middle). Subsequent deprotection of **4** under standard hydrolysis conditions was reported to give the desired α -difluoromethyl pyrrole **5** apparently without loss of fluorine. However, experimental conditions or isolated yields for this step are not described, nor does the report include any evidence for the stated maintenance of fluoro substituents. As reported by Haufe (Scheme 1, bottom),²⁵ upon exposure to acid the stability of the difluoromethyl group is strongly

influenced by the electronic nature of ring substitution. Indeed, in the presence of the electron-donating methyl group the difluoromethyl group was hydrolysed to the corresponding 2-formyl pyrrole **6a**, while, under the same reaction conditions, pyrrole **6b** was reported to be stable (Scheme 1). With the backdrop of these limited reports, we report herein upon the reactivity of α -difluoromethyl pyrroles under hydrolytic conditions,²⁴ as well as an approach for the preparation of β -aryl- α -difluoromethyl pyrroles. Furthermore, the influence of the pyrrolic ring substitution pattern upon the reactivity of the α -difluoromethyl functional group is discussed.

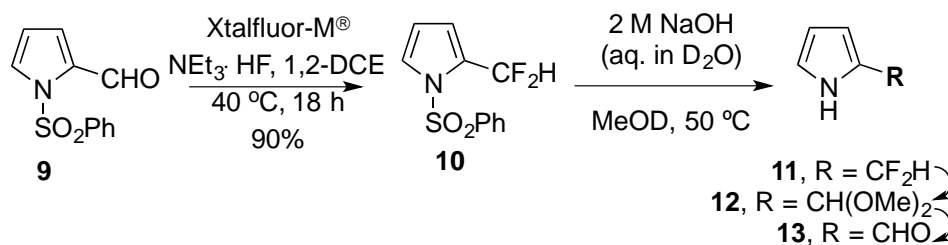
Results and discussion

The procedure for the synthesis of pyrrole **5** was repeated according to Scott's method (Scheme 1, middle).²⁴ However, upon N-deprotection of **4** the isolated product corresponded to the *N*-unprotected aldehyde **8** (75%, Scheme 2), with the two pendant esters of course hydrolysed to the corresponding carboxylic acids. As this result clearly contradicts the literature report,²⁴ the reaction was repeated in deuterated solvents and progress was followed via ^1H and ^{19}F NMR spectroscopic analysis. The initial *N*-deprotection of the α -difluoromethyl pyrrole **4** was determined to occur immediately upon addition of 2 M NaOH. The *N*-deprotected product **5** is unstable under these reaction conditions, forming first the α -dimethylacetal pyrrole **7** which then hydrolyses to the α -formyl pyrrole **8** (Scheme 2 and Figure 1 in the Supplementary Information).



Scheme 2. *N*-deprotection and hydrolysis of pyrrole bearing a 2-difluoromethyl group.

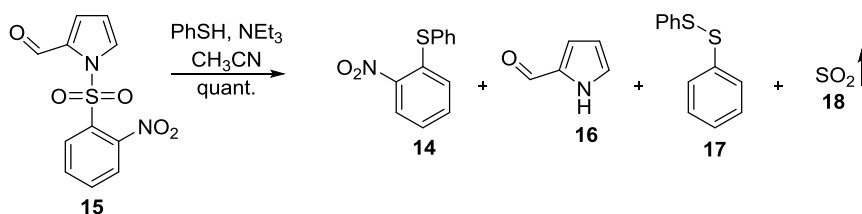
In order to exclude the possibility that the two alkanoate moieties influence the hydrolytic reactivity of the α -difluoromethyl group, the unsubstituted variant **10** was exposed to the same conditions.²⁶ Xtalfluor-M[®] was used to fluorinate the 2-formyl pyrrole **9**, giving the α -difluoromethyl pyrrole **10** in high yield (90%, Scheme 3). The use of a stabilising *N*-protecting group proved essential for the fluorination reaction to be successful. To study the *N*-deprotection, aliquots from the reaction of **10** with 2 M aqueous NaOH in MeOD at 50 °C were analysed using ¹H and ¹⁹F NMR spectroscopy. As observed previously for **4**, the rapid appearance of the *N*-unprotected material **11** was followed by methoxide displacement of the fluoro substituents, to give the acetal **12**, which hydrolysed to the aldehyde **13** (Scheme 3 and Figure 2 in Supporting Information).



Scheme 3: Formation and hydrolysis of α -difluoromethyl pyrrole **11.**

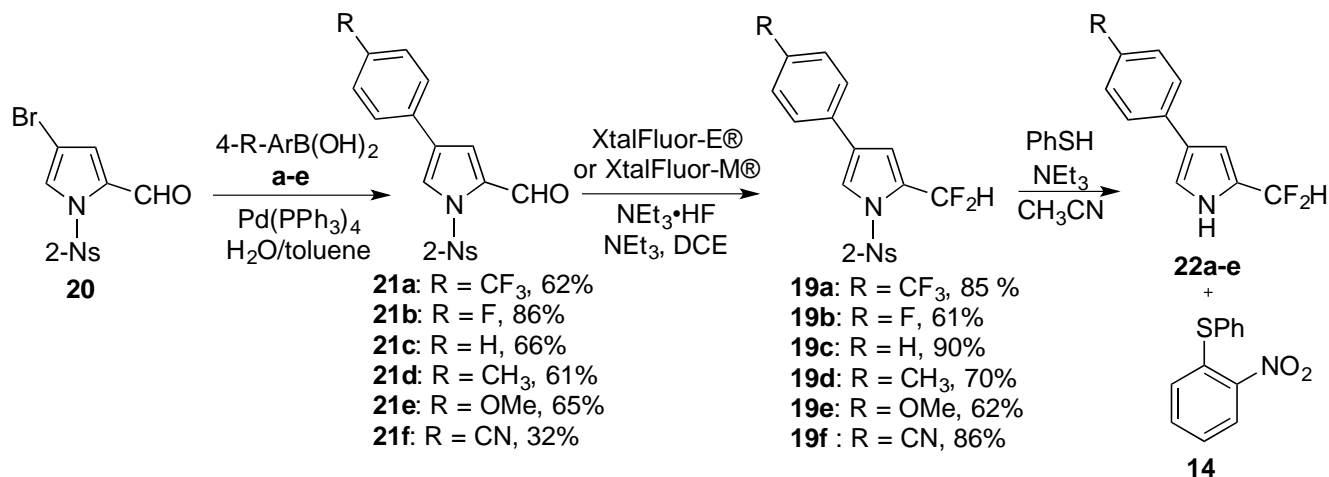
Although some *N*-unprotected α -difluoromethyl pyrroles featuring electron-withdrawing substituents on the heterocycle are stable (Scheme 1),¹⁹ such systems are clearly different to pyrroles such as **5** and **11**, whereupon hydrolysis to result in loss of fluorine is facile. In order to investigate the influence of the electronic properties of substituents about the pyrrolic ring upon the deprotection and hydrolysis reactions, a series of *N*-(2-nosyl)- β -aryl-substituted pyrroles were synthesised. Moving away from the tosyl and -SO₂Ph protecting groups, the 2-nosyl group was selected thus enabling the *N*-deprotection to be monitored *via* release of 2-nitrophenyl phenyl sulfide (**14**, Scheme 4).^{27,28} Moreover, *N*-deprotection of the 2-nosyl group would be achieved under anhydrous conditions. However, despite 2,4-dinitrophenol (2,4-DNP) being commonly used as a reporter for measuring reaction rates, we were unable to find reports of monitoring reaction rates through detection of yellow 2-nitrophenyl, 4-

nitrophenyl or 2,4-dinitrophenyl phenyl sulfides. Furthermore, although 2-nitrophenyl phenyl sulfide is known,²⁹⁻³¹ full characterisation proved elusive in the literature. Compound **14** was, therefore, prepared *via* deprotection of **15** using PhSH and NEt₃. The ejected sulfide **14** was isolated in quantitative yield (Scheme 4), thereby demonstrating that this anhydrous method is viable for the needed *N*-deprotection of *N*-(2-nosyl) pyrroles.^{27,28,32} The absorption maximum of **14** occurs at 368 nm (CH₃CN), with an extinction coefficient of 4000 L mol⁻¹ cm⁻¹.



Scheme 4. Synthesis of 2-nitrophenyl phenyl sulfide 14.

α -Difluoromethyl pyrroles **19a-f** featuring various aryl groups at the β -position of the ring were synthesised according to Scheme 5. Suzuki coupling between *N*-(2-nosyl)-3-bromo-2-formyl pyrrole **20** and boronic acids **a-f** gave the corresponding β -aryl pyrroles **21a-f**. Subsequent fluorination yielded the desired α -difluoromethyl pyrroles **19a-f** (Scheme 5).



Scheme 5: Synthesis of 22a-f.

Upon *N*-deprotection of pyrroles **19a-e** with PhSH and NEt₃ under anhydrous conditions, the resulting pyrroles (**22a-e**) proved to be stable providing the material remained under an inert and anhydrous environment (Scheme 5). As such, the deprotection and subsequent hydrolysis reaction could be studied separately. The first step was studied using UV-Vis spectroscopy under pseudo-first order conditions using 400 equivalents of PhSH and 560 equivalents of NEt₃ in CH₃CN at 0 °C under an inert atmosphere. Despite maintaining a steady flow of nitrogen gas in the sample chamber of the spectrophotometer, the presence of phenyl disulfide (**17** in Scheme 4) was noted upon careful inspection of the reaction mixture arising from the *N*-deprotection of **19a-e**. Several pathways to **17** may be at play during the reaction, *e.g.* thiophenol affords disulfide in the presence of an oxidising agent and a base;^{33,34} the reaction by-product sulfur dioxide **18** acts as an oxidising agent. As the disulfide **17** also absorbs at 368 nm, the absorbance reading at this³⁵ wavelength is representative of both products. Since the interference from **17** is constant across the sample set, the relative production of **14** (Table 1, in Supporting Information) represents a qualitative estimation of the *N*-deprotection rate (Table 1). The starting materials provide no interference at the monitoring wavelength. The production of **14** was monitored *via* its absorbance at 368 nm (Table 1 in Supporting Information), and the relative rate constants of deprotection were thus calculated:

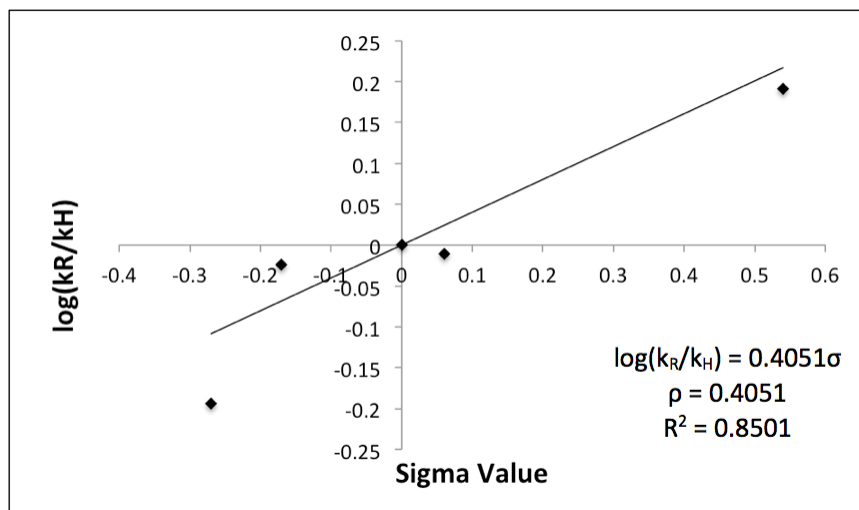
$$\log\left(\frac{K_R}{K_H}\right) = \rho \sigma$$

As shown in Table 1, the presence of electron-withdrawing character in the aryl substituent causes an increase in the rate of *N*-deprotection (**19a**, R = CF₃). In contrast, electron-donating character (**19e**, R = OCH₃) impedes the reaction rate. Fig. 1 shows a Hammett reaction constant (ρ) of 0.4, suggesting an increase of negative charge in the reaction intermediates.

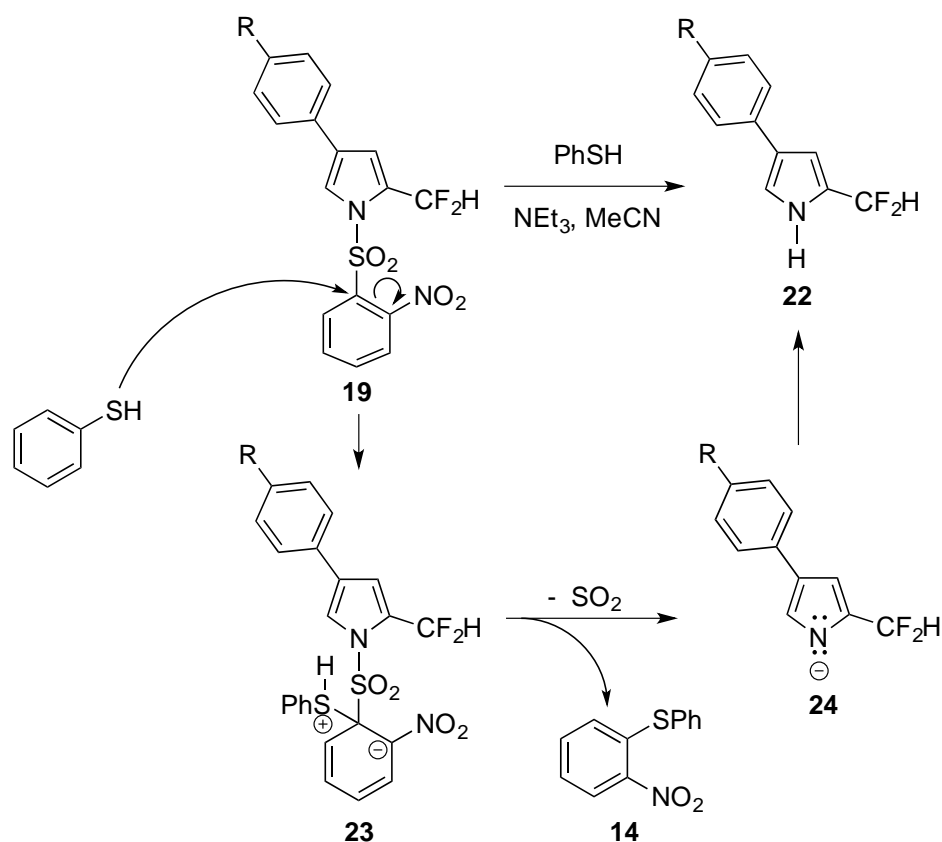
Table 1. Relative rate constants and Hammett parameters for the deprotection of 19a-e.

Compound	Substituent (R)	[Starting Material] (M)	Rate Constants (s ⁻¹) ^a	Hammett Substituent Constants (σ^b)	$\log\left(\frac{k_R}{k_H}\right)$
19a	CF ₃	4.03×10 ⁻⁴	(1.96 ± 0.01) × 10 ⁻²	0.54	0.19
19b	F	4.11×10 ⁻⁴	(1.23 ± 0.04) × 10 ⁻²	0.06	-0.01
19c	H	4.08×10 ⁻⁴	(1.24 ± 0.08) × 10 ⁻²	0	0.000
19d	CH ₃	4.15×10 ⁻⁴	(1.19 ± 0.03) × 10 ⁻²	-0.17	-0.02
19e	OCH ₃	3.57×10 ⁻⁴	(0.81 ± 0.02) × 10 ⁻²	-0.27	-0.19

^a rate constants calculated on two replicates of each substrate using Kaleidagraph v 4.1.3 and error on replicates calculated using XLSTAT v 2015.4.01.21576; ^b as reported³⁶

**Fig. 1 Hammett plot for N-deprotection of 19a-e.**

These features support the reaction mechanism proposed in Scheme 6. After nucleophilic attack by PhSH,^{37,38} the Meisenheimer-type intermediate **23** presumably collapses to give the reaction intermediate **24** and the development of anionic character in the orthogonal p-orbital of the pyrrolide nitrogen atom.²⁷ The ability of the substituent (R) within the aryl group to stabilise the transition state leading to **24** thus plays an important role in the rate of deprotection. Indeed, electron-withdrawing groups serve to stabilize the forming pyrrolide anion, thereby enhancing the reaction rate, yet electron-withdrawing groups serve to destabilise the transition state en route to **24**. As the electron-donating and electron-withdrawing R substituents are somewhat distant from the developing anionic nitrogen atom, their effects in stabilising the transition state are small and thus the ρ value (Fig. 1) is small.



Scheme 6: Proposed mechanism for the N-deprotection of 19.

Having determined successful N-deprotection conditions, attention was turned to the hydrolysis of the α -difluoromethyl group. Hydrolysis was monitored using ¹⁹F NMR spectroscopy under pseudo first-order conditions. Pyrroles **19** were first N-deprotected in an NMR tube using 1.8 equivalents of PhSH and 2.5 equivalents of NEt₃, dissolved in CD₃CN. Subsequently, hydrolysis was initiated through the injection of 1000 equivalents of water at 40 °C. As the hydrolysis reaction progressed, the decreasing intensity of the ¹⁹F doublet arising from the –CF₂H group, with respect to the inert internal standard (hexafluorobenzene, 0.5 equiv., 0.4 M solution in CD₃CN), was measured and the rates of hydrolysis calculated (Table 2). The disappearance of the –CF₂H group signal in each case was accompanied by the expected appearance of the HF singlet, which derives from hydrolysis of the –CF₂H group (Figure 3-7 in the Supporting Information).

Table 2. Rates and Hammett parameters for the hydrolysis of 22a-f.

Compound	Substituent (R)	[Starting Material] M	Rate Constant (s ⁻¹) ^a	Hammett Substituent Constants (σ ^b)	log ($\frac{K_R}{K_H}$)
22a	CF ₃	1.400×10 ⁻²	(1.712 ± 0.092) ×10 ⁻³	0.54	0.27
22b	F	1.408×10 ⁻²	(0.966 ± 0.108) ×10 ⁻³	0.06	0.02
22c	H	1.501×10 ⁻²	(0.914 ± 0.094) ×10 ⁻³	0.00	0.00
22d	CH ₃	1.422×10 ⁻²	(1.021 ± 0.013) ×10 ⁻³	-0.17	0.05
22e	OCH ₃	1.450×10 ⁻²	(1.195 ± 0.025) ×10 ⁻³	-0.27	0.12
22f	CN	1.488×10 ⁻²	(1.749 ± 0.040) ×10 ⁻³	0.66	0.28

^a rate constants calculated using Kaleidagraph v 4.1.3 and error is calculated using XLSTAT v 2015.4.01.21576; ^b as reported³⁶

Although the variation in the rates of hydrolysis are subtle, the Hammett plot (Fig 2) resembles a concave up parabola with a minimum at R = H (**22c**). To confirm the concave up parabola, we synthesized and analysed **22f** (R = CN), following the same protocols as previously, and were delighted to observe an excellent fit with the data generated from **22a-22e**. The non-linear relationship^{39,40} revealed on the Hammett plot points to the influence of the electronic features of the substituents on the aryl ring of pyrroles **22**. The ρ value for electron-donating groups was found to be -0.4, suggesting a build-up of positive charge (or neutralisation of negative charge, negative slope, Fig 2). In contrast, the ρ value for electron-withdrawing groups was found to be 0.4, suggesting an increase of the negative charge character in the transition state of the rate-determining step (positive slope, Fig 2).

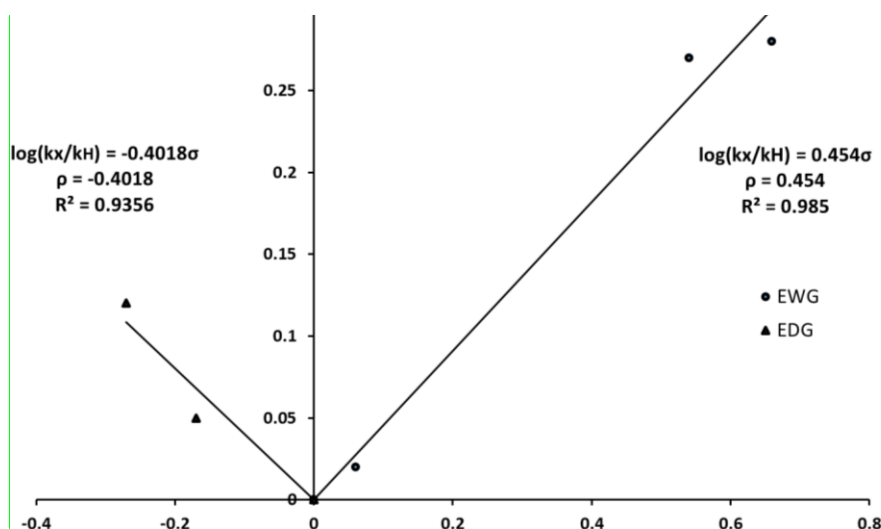
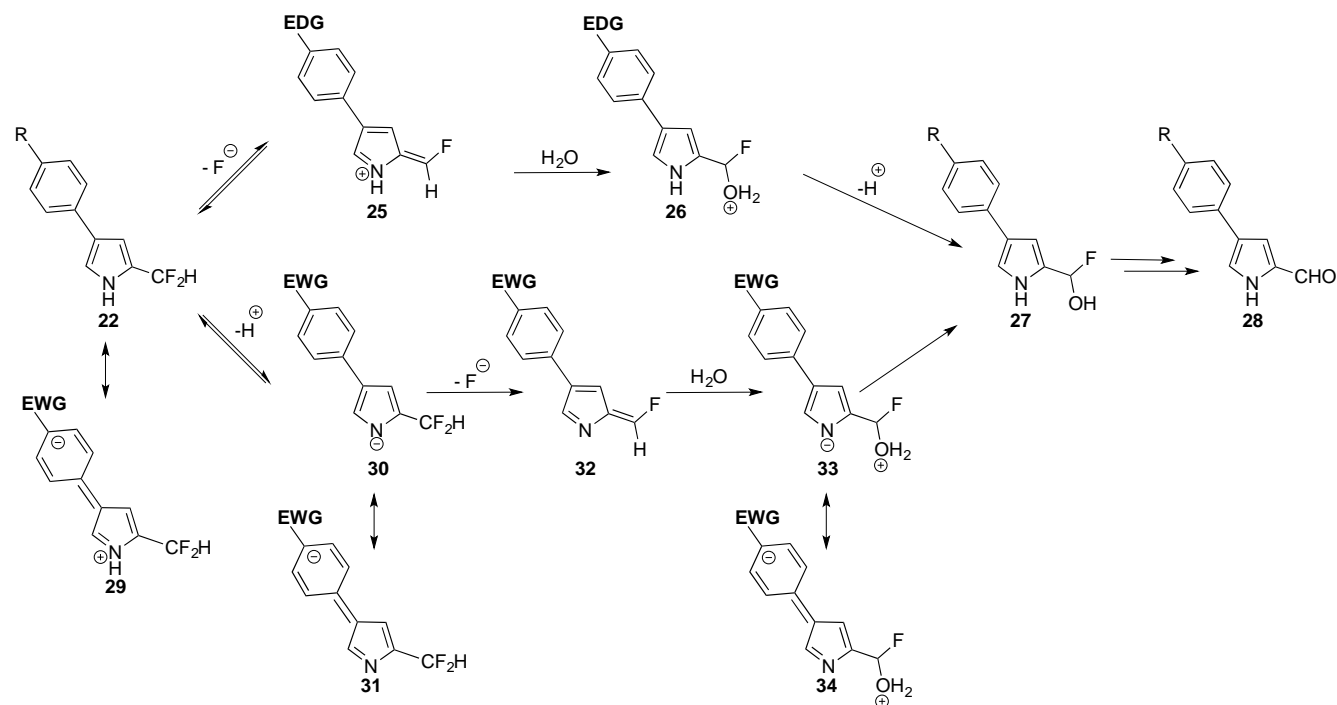


Fig 2 Hammett plot for the hydrolysis of 19a-f following *N*-deprotection.

Based on these results, and the concave up parabola of the Hammett plot, two competing reaction pathways are proposed for the hydrolysis of **22** (Scheme 7). In the case of R being an electron-donating group (R = CH₃ and OCH₃), the rate-determining step is considered to be the loss of fluoride and formation of the positively charged azafulvenium intermediate **25**, whose methylene carbon atom is activated towards the fast addition of water and the return of aromaticity to the pyrrole ring in **26**.⁴¹⁻⁴⁴ After proton loss the intermediate **27** would collapse into the isolated aldehyde **29**, again through loss of fluoride via azafulvenium formation. In the case of R being an electron-withdrawing group (R = CF₃, F and CN) the generation of **25** would be slow, as appreciated upon consideration of the resonance contributor **29**. In this case, loss of a proton, to form negatively charged pyrrolide **30**, is proposed as the rate-determining step. The transition state en route to **30** would be stabilised by electron-withdrawing substituents on the aryl ring. Loss of fluoride would then generate the azafulvene **32**, followed by addition of water to give **33**. Proton exchange would provide **27**, which would collapse into the isolated aldehyde **29**, presumably again via initial pyrrolide formation and subsequent generation of the corresponding azafulvene. Akin to the *N*-deprotection step, as the electron-donating and electron-withdrawing substituents (R) are somewhat distant from the developing azafulvenium and pyrrolide

cores, their effects in stabilising the transition states are small and consistent with the small ρ values (Fig. 1) for the two constituent slopes of the concave up parabola.



Scheme 7. Proposed mechanisms for the hydrolysis of 22.

To summarise, the tendency for α -difluoromethyl pyrroles to react with water is significant, particularly in the absence of significant electron-withdrawing *N*-protection. As such, the electronic nature of substituents about α -difluoromethyl pyrroles influences the reactivity, and hence the stability, of the α -difluoromethyl group. Driven by azafulvenium formation, the loss of fluoride is facile,⁴¹ yet a significant electron-donating character on the pyrrolic ring serves to make azafulvenium character (*via* loss of fluoride) less favourable. In these cases, hydrolysis is proposed to rely upon *N*-deprotonation, followed by azafulvene formation *via* loss of fluoride. Therefore, the design of air-stable difluoromethyl pyrroles must consider the incorporation and **positioning?** of units with significant pyrrole stabilising ability,⁴²⁻⁴⁴ and/or electron-withdrawing capacity *via* *N*-protection, in order to avoid hydrolysis.

Experimental

General information

All ^1H and ^{13}C NMR spectra were obtained using a 500 MHz NMR spectrometer (operating at 500 MHz and 125 MHz, respectively) and CDCl_3 as solvent. Chemical shifts were recorded in parts per million (ppm) with internal reference to CDCl_3 (^1H NMR at 7.26 ppm, ^{13}C NMR at 77.16 ppm) and to $(\text{CD}_3)_2\text{CO}$ (^1H NMR at 2.05 ppm, ^{13}C NMR at 29.84 and 206.26 ppm). ^{19}F NMR spectra were obtained using a 500 MHz NMR instrument (operating at 470 MHz) using trifluoroacetic acid (TFA, ^{19}F NMR at -76.55 ppm vs. CFCl_3). Splitting patterns are indicated as follows: a, apparent, br, broad; s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet. Coupling constants (J) are reported in units of Hertz (Hz). High and low resolution ESI+ mass spectra were recorded using ion trap instruments. Column chromatography was performed using 230-400 mesh ultrapure silica. TLC was performed using silica gel or neutral aluminum oxide plates and were visualised using UV light (254 nm) and/or developed with vanillin stain. UV analysis was carried out with the baseline manually corrected for the solvent used. Moisture-sensitive reactions were performed in flame-dried glassware under a positive pressure of nitrogen. Solutions of air- and moisture-sensitive compounds were introduced via syringe or cannula through a rubber septum. Compounds **4**,⁴⁵ **9**,⁴⁶ and **15**⁴⁷ were prepared according to literature procedures.

3-(4-(Carboxymethyl)-5-formyl-1*H*-pyrrol-3-yl)propanoic acid (**8**)

Compound **4**⁴⁵ (0.050 g, 0.120 mmol) was added to a solution of 1M NaOH in 1:1 $\text{H}_2\text{O}/\text{MeOH}$ (1 mL). The reaction mixture was heated to 50 °C until TLC analysis showed complete consumption of the starting material. The reaction mixture was diluted with H_2O (50 mL) and acidified to pH 4 by use of 2M aq. HCl at 0 °C. The reaction mixture was then extracted with CH_2Cl_2 (3 x 50 mL), and the combined organic fractions were washed with brine, dried over anhydrous Na_2SO_4 , concentrated *in*

vacuo and purified *via* column chromatography (50% EtOAc/hexanes). The title compound was isolated as a white solid (0.012 g, 27% yield). ^1H (300 MHz, $\text{C}(\text{O})(\text{CD}_3)_2$): δ 10.81 (br s, 1H), 9.70 (s, 1H), 7.07 (as, 1H), 3.85 (s, 2H), 2.78 (t, $J = 8.0$ Hz, expected 2H but overlaps with water peak), 2.59 (t, $J = 8.0$ Hz, 2H) ppm; HRMS-ESI (m/z): $[\text{M} + \text{Na}]^+$ Calcd 248.0529 for $\text{C}_{10}\text{H}_{11}\text{NNaO}_5$; found 248.0528. ^{13}C NMR is not reported because of the instability of **8** in CDCl_3 , $\text{C}(\text{O})(\text{CD}_3)_2$, and CD_3OD for prolonged periods of time and its insolubility in $\text{THF-}d_8$ and CD_3CN .

General Procedure (GP1) for Fluorination using XtalFluor[®]

XtalFluor-E[®] (3 equiv) or XtalFluor-M[®] (3 equiv) was added, as indicated, to a solution of $\text{NEt}_3 \cdot 3\text{HF}$ (4 equiv) and NEt_3 (2 equiv) in 1,2-DCE [0.3 M], with stirring at room temperature under N_2 atmosphere at 70 °C. The 2-formylpyrrole substrate (1 equiv) was then added in one portion and the reaction mixture was stirred under N_2 at room temperature overnight, before quenching with sat. aqueous NaHCO_3 (10 mL) and then stirring for 15 minutes. The reaction mixture was then diluted with CH_2Cl_2 (30 mL) and washed with H_2O (30 mL) and brine (30 mL). The organic phase was dried over anhydrous Na_2SO_4 , concentrated *in vacuo* and purified *via* column chromatography.

2-(Difluoromethyl)-1-(phenylsulfonyl)-pyrrole (10)

Using GP1 and XtalFluor-M[®] with gentle heating (35 °C) in CH_2Cl_2 , the title compound was synthesised from 1-(phenylsulfonyl)-pyrrole-2-carbaldehyde (**9**)⁴⁶ (0.13 g, 0.57 mmol). The title compound was isolated as a white solid (0.13 g, 92% yield) after column chromatography (10% Et_2O /hexanes). M.p.: 64-66 °C; ^1H NMR (CDCl_3 , 500 MHz): δ 7.89 (d, 2H, $J = 8.0$ Hz), 7.63 (t, 1H, $J = 8.0$ Hz), 7.53 (t, 2H, $J = 8.0$ Hz), 7.32 (br s, 1H), 7.12 (t, 1H, $J_{\text{HF}} = 55$ Hz, CF_2H), 6.66 (br s, 1H), 6.31 (at, 1H, $J = 1.8$ Hz) ppm; ^{19}F NMR (CDCl_3 , 470 MHz) δ -110.8 (d, $J_{\text{FH}} = 55.0$ Hz, CF_2H) ppm; $^{13}\text{C}\{^1\text{H}\}$ NMR (CDCl_3 , 125 MHz): δ 138.6, 134.5, 129.6, 127.9, 127.4, 125.1 (t, $J_{\text{CF}} = 3.0$ Hz), 115.6

(t, $J_{CF} = 5.0$ Hz), 112.2, 108.9 (t, $J_{CF} = 233$ Hz, CF_2H) ppm; HRMS-ESI (m/z): $[\text{M} + \text{Na}]^+$ calcd 280.0214 for $\text{C}_{11}\text{H}_9\text{F}_2\text{NNaO}_2\text{S}$; found 280.0201.

(2-Nitrophenyl)(phenyl) sulfide (14)

A solution of PhSH (0.30 mL, 3.21 mmol) and 1-(2-nitrophenylsulfonyl)-1*H*-pyrrole-2-carbaldehyde (**15**)⁴⁷ (0.50 g, 1.78 mmol) in anhydrous CH_3CN (89 mL) was bubbled with N_2 for 10 minutes, after which anhydrous NEt_3 (0.62 mL, 4.46 mmol) was added under N_2 . The reaction mixture was stirred for 30 minutes before the solvent was removed *in vacuo*. The crude residue was then dissolved in CH_2Cl_2 (200 mL) and washed with brine (200 mL). The organic layer was dried over Na_2SO_4 , concentrated *in vacuo* and purified *via* column chromatography (0→5% EtOAc/ CH_2Cl_2). The title compound was isolated as a yellow solid (0.41 g, quant.). M.p.: 69-70 °C; ^1H (500 MHz, CDCl_3): δ 8.21 (d, 1H, $J = 8.0$ Hz), 7.59-7.51 (m, 2H), 7.50-7.46 (m, 3H), 7.33 (t, 1H, $J = 8.0$ Hz), 7.21 (t, 1H, $J = 8.0$ Hz), 6.87 (d, 1H, $J = 8.0$ Hz), comparable to previously reported data;⁴⁸ $^{13}\text{C}\{^1\text{H}\}$: NMR (CDCl_3 , 125 MHz): δ 145.2, 139.5, 136.0, 133.5, 131.2, 130.2, 130.1, 128.5, 125.8, 125.1 ppm; HRMS-ESI (m/z): $[\text{M} + \text{Na}]^+$ calcd 254.0246 for $\text{C}_{12}\text{H}_9\text{NNaO}_2\text{S}$; found 254.0239; $\epsilon_{368\text{ nm}} = 4000\text{ L mol}^{-1}\text{cm}^{-1}$ in CH_3CN .

2-(Difluoromethyl)-1-(2-nitrophenylsulfonyl)-4-(4-(trifluoromethyl)phenyl)-pyrrole (19a)

Using GP1 and XtalFluor-M[®], the title compound was synthesised from **21a** (0.32 g, 0.75 mmol). The title compound was isolated as a beige solid (0.29 g, 85% yield) after column chromatography (50% CH_2Cl_2 /hexanes). M.p.: 80-81 °C; ^1H NMR (CDCl_3 , 500 MHz): δ 7.88 (ad, 1H), 7.80-7.84 (m, 1H), 7.71-7.76 (m, 3H), 7.64-7.67 (m, 4H), 7.09 (s, 1H), 7.08 (t, 1H, $J_{HF} = 55$ Hz, CF_2H) ppm; ^{19}F NMR (CDCl_3 , 470 MHz) δ -63.7 (s), -113.1 (d, $J_{FH} = 55$ Hz, CF_2H) ppm; $^{13}\text{C}\{^1\text{H}\}$ NMR (CDCl_3 , 125 MHz): δ 147.9, 135.8, 135.6, 133.1, 132.5, 130.3, 129.8 (q, $J_{CF} = 27$ Hz), 126.3 (q, $J_{CF} = 256$ Hz, CF_3), 126.2 (aq, $J_{CF} = 3.0$ Hz), 126.1, 125.5, 122.6, 114.3 (t, $J_{CF} = 5.0$ Hz), 108.7 (t, $J_{CF} = 235$ Hz, CF_2H) ppm, two

carbon signals missing; HRMS-ESI (m/z): $[M + Na]^+$ calcd 469.0257 for $C_{18}H_{11}F_5N_2NaO_4S$; found 469.0241.

2-(Difluoromethyl)-4-(4-fluorophenyl)-1-(2-nitrophenylsulfonyl)-pyrrole (19b)

Using GP1 and Xtalfluor-E[®], the title compound was synthesised from **21b** (0.29 g, 0.78 mmol). The title compound was isolated as a beige solid (0.19 g, 61% yield) after column chromatography (50% CH_2Cl_2 /hexanes). M.p.: 86-88 °C; 1H NMR ($CDCl_3$, 500 MHz): δ 7.88 (d, 1H, $J = 8.0$ Hz), 7.80 (t, 1H, $J = 8.0$ Hz), 7.71 (t, 1H, $J = 8.0$ Hz), 7.63 (d, 1H, $J = 8.0$ Hz), 7.59 (d, 1H, $J = 1.8$ Hz), 7.49-7.52 (m, 2H), 7.09 (t, 2H, $J = 9.0$ Hz), 7.06 (t, 1H, $J_{HF} = 55$ Hz, CF_2H), 7.02 (s, 1H) ppm; ^{19}F NMR ($CDCl_3$, 470 MHz) δ -113.0 (d, $J_{FH} = 55$ Hz, CF_2H), -(115.0-115.1) (m) ppm; $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz): δ 162.6 (d, $J_{CF} = 248$ Hz, CF), 147.8, 135.4, 133.1, 132.8, 130.0, 129.4, 128.3 (d, $J_{CF} = 3.0$ Hz), 127.6 (d, $J_{CF} = 8.0$ Hz), 126.8, 125.4, 121.4, 116.1 (d, $J_{CF} = 22$ Hz), 114.6 (t, $J_{CF} = 5.0$ Hz), 108.8 (t, $J_{CF} = 235$ Hz, CF_2H) ppm; HRMS-ESI (m/z): $[M + Na]^+$ calcd 419.0289 for $C_{17}H_{11}F_3N_2NaO_4S$; found 419.0287.

2-(Difluoromethyl)-1-(2-nitrophenylsulfonyl)-4-phenyl-1H-pyrrole (19c)

Using GP1 and Xtalfluor-E[®], the title compound was synthesised from **21c** (0.23 g, 0.65 mmol). The title compound was isolated as a beige solid (0.22 g, 90% yield) after column chromatography (50% CH_2Cl_2 /hexanes). M.p.: 100-103 °C; 1H NMR ($CDCl_3$, 500 MHz): δ 7.89 (d, 1H, $J = 8.0$ Hz), 7.79 (t, 1H, $J = 8.0$ Hz), 7.70 (t, 1H, $J = 8.0$ Hz), 7.65 (as, 1H), 7.54-7.57 (m, 3H), 7.41 (t, 2H, $J = 8.0$ Hz), 7.32 (t, 1H, $J = 7.0$ Hz), 7.09 (s, 1H), 7.07 (t, 1H, $J_{HF} = 55$ Hz, CF_2H) ppm; ^{19}F NMR ($CDCl_3$, 470 MHz) δ -113.0 (d, $J_{FH} = 55$ Hz, CF_2H) ppm; $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz): δ 135.3, 133.1, 133.0, 129.8, 129.4, 129.2, 128.0, 127.7, 125.9, 125.4, 121.6, 114.7 (t, $J_{CF} = 5.0$ Hz), 108.8 (t, $J_{CF} = 235$ Hz, CF_2H) ppm 2 C missing; HRMS-ESI (m/z): $[M + H]^+$ calcd 379.0564 for $C_{17}H_{13}F_2N_2O_4S$; found 379.0544.

2-(Difluoromethyl)-1-(2-nitrophenylsulfonyl)-4-*p*-tolyl-1*H*-pyrrole (19d)

Using GP1 and Xtalfluor-E[®], the title compound was synthesised from **21d** (0.24 g, 0.65 mmol). The title compound was isolated as a beige solid (0.18 g, 70% yield) after column chromatography (50% CH₂Cl₂/hexanes). M.p.: 114-115 °C; ¹H NMR (CDCl₃, 500 MHz): δ 7.88 (d, 1H, *J* = 8.0 Hz), 7.78 (t, 1H, *J* = 8.0 Hz), 7.69 (t, 1H, *J* = 8.0 Hz), 7.61 (d, 1H, *J* = 1.8 Hz), 7.53 (d, 1H, *J* = 8.0 Hz), 7.43 (d, 2H, *J* = 8.0 Hz), 7.21 (d, 2H, *J* = 8.0 Hz), 7.06 (s, 1H), 7.06 (t, 1H, *J*_{HF} = 55 Hz, CF₂H), 2.37 (s, 3H) ppm; ¹⁹F NMR (CDCl₃, 470 MHz) δ -113.0 (d, *J*_{FH} = 55 Hz, CF₂H) ppm; ¹³C{¹H} NMR (CDCl₃, 125 MHz): δ 137.9, 135.2, 133.1, 129.8, 129.7, 129.3, 129.2, 127.8, 125.8, 125.4, 121.3, 114.7 (t, *J*_{CF} = 5.0 Hz), 108.8 (t, *J*_{CF} = 235 Hz, CF₂H), 21.3 ppm, two carbon signals missing; HRMS-ESI (*m/z*): [M + Na]⁺ calcd 415.0540 for C₁₈H₁₄F₂N₂NaO₄S; found 415.0522.

2-(Difluoromethyl)-4-(4-methoxyphenyl)-1-(2-nitrophenylsulfonyl)-1*H*-pyrrole (19e)

Using GP1 and Xtalfluor-E[®], the title compound was synthesised from **21e** (0.30 g, 0.78 mmol). The title compound was isolated as a beige solid (0.20 g, 62% yield) after column chromatography (50% CH₂Cl₂/hexanes). M.p.: 145-148 °C; ¹H NMR (CDCl₃, 500 MHz): δ 7.88 (d, 1H *J* = 8.0 Hz), 7.78 (t, 1H, *J* = 8.0 Hz), 7.69 (t, 1H, *J* = 8.0 Hz), 7.56 (d, 1H, *J* = 1.8 Hz), 7.53 (d, 1H, *J* = 8.0 Hz), 7.46 (d, 2H, *J* = 9.0 Hz), 7.07 (t, 1H, *J*_{HF} = 55 Hz, CF₂H), 7.03 (s, 1H), 6.94 (d, 2H, *J* = 9.0 Hz), 3.84 (s, 3H) ppm; ¹⁹F NMR (CDCl₃, 470 MHz) δ -113.0 (d, *J*_{FH} = 55 Hz, CF₂H) ppm; ¹³C{¹H}: NMR (CDCl₃, 125 MHz): δ 159.6, 147.7, 135.2, 133.1, 129.6, 129.3, 129.1, 127.5, 127.1, 125.4, 124.7, 120.7, 114.7 (t, *J*_{CF} = 5.0 Hz), 114.6, 108.8 (t, *J*_{CF} = 235 Hz, CF₂H), 55.5 ppm; HRMS-ESI (*m/z*): [M + Na]⁺ calcd 431.0489 for C₁₈H₁₄F₂N₂NaO₅S; found 431.0491.

2-(Difluoromethyl)-4-(4-cyanophenyl)-1-(2-nitrophenylsulfonyl)-1*H*-pyrrole (19f)

Using GP1 and Xtalfluor-E[®], the title compound was synthesised from **21f** (0.13 g, 0.33 mmol). The title compound was isolated as a beige solid (0.12 g, 86% yield) after column chromatography (90%

CH₂Cl₂/hexanes). M.p.: 171-173 °C; ¹H NMR (CDCl₃, 500 MHz): δ 7.88 (d, 1H *J* = 8.0 Hz), 7.81-7.85 (m, 1H), 7.74-7.80 (m, 3H), 7.69 (d, 1H, *J* = 8.3 Hz), 7.64 (d, 2H, *J* = 8.3 Hz), 7.07 (t, 1H, *J*_{HF} = 55 Hz, CF₂H), 7.07 (s, 1H) ppm; ¹⁹F NMR (CDCl₃, 470 MHz) δ -112.0 (d, *J*_{FH} = 55 Hz, CF₂H) ppm; ¹³C{¹H}: NMR (CDCl₃, 125 MHz): δ 147.9, 136.8, 135.8, 133.1, 133.0, 132.2, 130.6, 129.7 (t, *J*_{CF} = 31.5 Hz), 126.3, 125.6, 125.5, 123.1, 118.8, 114.1 (t, *J*_{CF} = 5.0 Hz), 111.4, 108.6 (t, *J*_{CF} = 235 Hz, CF₂H) ppm; HRMS-ESI (*m/z*): [M + Na]⁺ calcd 426.0331 for C₁₈H₁₁F₂N₃NaO₄S; found 426.0341.

4-Bromo-1-(2-nitrophenylsulfonyl)-pyrrole-2-carbaldehyde (20)

4-Bromo-2-formyl pyrrole⁴⁹ (2.72 g, 15.6 mmol), 2-nitrobenzenesulfonylchloride (3.15 g, 14.2 mmol) and NEt₃ (2.97 mL, 21.3 mmol) were dissolved in CH₂Cl₂ (55 mL). Dimethylaminopyridine (0.17 g, 1.42 mmol) was added to the stirring reaction mixture, and the solution was stirred overnight. The reaction mixture was washed with H₂O (60 mL) and brine (60 mL). The organic layer was dried over Na₂SO₄, concentrated *in vacuo* and purified *via* column chromatography (50% CH₂Cl₂/hexanes). The title compound was isolated as an off-white solid (4.17 g, 82% yield). M.p.: 143-145 °C; ¹H NMR (CDCl₃, 500 MHz): δ 9.57 (s, 1H), 8.47-8.49 (m, 1H), 7.83-7.85 (m, 3H), 7.71 (s, 1H), 7.16 (s, 1H) ppm; ¹³C{¹H} NMR (CDCl₃, 125 MHz): δ 176.9, 148.2, 136.0, 133.8, 133.5, 132.7, 131.1, 130.7, 129.5, 125.3, 100.9 ppm; HRMS-ESI (*m/z*): [M + H]⁺ calcd 358.9337 for C₁₁H₈BrN₂O₅S; found 358.9325.

General Procedure (GP2) for the Suzuki Cross-Coupling of 4-Bromopyrroles

4-Bromo-1-(2-nitrophenylsulfonyl)-pyrrole-2-carbaldehyde (**20**) (1 equiv) was dissolved in toluene [0.1 M], along with a boronic acid **a-e** (1.2 equiv) and Pd(PPh₃)₄ (0.1 equiv) under N₂ atmosphere with stirring. K₂CO₃ (4 equiv) was prepared as an aqueous solution [1.1 M], and then purged with N₂ for 15 minutes. The K₂CO₃ aqueous solution was then added to the stirring reaction mixture, which was subsequently heated with stirring at 90 °C overnight. The reaction mixture was then partitioned and the

aqueous layer was extracted with CH₂Cl₂ (equivalent volume to aqueous layer x 3). The combined organic layers were dried over Na₂SO₄, filtered, concentrated *in vacuo* and then purified *via* column chromatography.

1-(2-Nitrophenylsulfonyl)-4-(4-(trifluoromethyl)phenyl)-pyrrole-2-carbaldehyde (21a)

Using GP2 and 4-(trifluoromethyl)phenylboronic acid, the title compound was synthesised from **20** (0.50 g, 1.39 mmol). The title compound was isolated as an off-white solid (0.36 g, 62% yield) after column chromatography (CH₂Cl₂). M.p.: 187-189 °C; ¹H NMR (CDCl₃, 500 MHz): δ 9.70 (s, 1H), 8.56-8.60 (m, 1H), 8.03 (s, 1H), 7.85-7.88 (m, 3H), 7.68-7.72 (m, 4H), 7.49 (d, 1H, *J* = 2.0 Hz) ppm; ¹⁹F NMR (CDCl₃, 470 MHz) δ -62.6 (s) ppm; ¹³C{¹H} NMR (CDCl₃, 125 MHz): δ 177.3, 176.9, 148.3, 135.9, 135.4, 134.2, 133.9, 132.6, 131.2, 130.1 (q, *J*_{CF} = 33 Hz), 128.3, 126.3 (q, *J*_{CF} = 270 Hz, CF₃), 126.2 (ad *J*_{CF} = 3.5 Hz), 126.2, 125.8, 125.3 ppm; HRMS-ESI (*m/z*): [M + Na]⁺ calcd 447.0238 for C₁₈H₁₁F₃N₂NaO₅S; found 447.0235.

4-(4-Fluorophenyl)-1-(2-nitrophenylsulfonyl)-pyrrole-2-carbaldehyde (21b)

Using GP2 and 4-fluorophenylboronic acid, the title compound was synthesised from **20** (0.50 g, 1.39 mmol). The title compound was isolated as an off-white solid (0.45 g, 86% yield) after column chromatography (CH₂Cl₂). M.p.: 172-175 °C; ¹H NMR (CDCl₃, 500 MHz): δ 9.68 (s, 1H), 8.51-8.53 (m, 1H), 7.90 (s, 1H), 7.83-7.85 (m, 3H), 7.53-7.55 (m, 2H), 7.42 (d, 1H, *J* = 2.0 Hz), 7.12 (t, 2H, *J* = 9.0 Hz) ppm; ¹⁹F NMR (CDCl₃, 470 MHz) δ -(113.6-113.7) (m) ppm; ¹³C{¹H} NMR (CDCl₃, 125 MHz): δ 177.6, 162.8 (d, *J*_{CF} = 248 Hz, CF), 135.7, 134.1, 133.7, 132.6, 131.4, 129.6, 128.0 (d, *J*_{CF} = 3.0 Hz), 127.7 (d, *J*_{CF} = 8.0 Hz), 127.5, 126.8, 126.0, 125.2, 116.3 (d, *J*_{CF} = 22 Hz); HRMS-ESI (*m/z*): [M + Na]⁺ Calcd 397.0270 for C₁₇H₁₁FN₂NaO₅S; found 397.0271.

1-(2-Nitrophenylsulfonyl)-4-phenyl-pyrrole-2-carbaldehyde (21c)

Using GP2 and phenylboronic acid, the title compound was synthesised from **20** (0.87 g, 2.78 mmol). The title compound was isolated as an off-white solid (0.65 g, 66% yield) after column chromatography (CH₂Cl₂). M.p.: 177-178 °C; ¹H NMR (CDCl₃, 500 MHz): δ 9.69 (s, 1H), 8.48-8.50 (m, 1H), 7.96 (s, 1H), 7.83 (ad, 3H), 7.58 (d, 2H, *J* = 8.0 Hz), 7.49 (s, 1H), 7.43 (t, 2H, *J* = 8.0 Hz), 7.34 (t, 1H, *J* = 7.0 Hz) ppm; ¹³C{¹H} NMR (CDCl₃, 125 MHz): δ 177.7, 135.7, 134.1, 133.5, 132.6, 131.7, 131.5, 129.3, 128.2, 127.7 (×2C), 126.2, 126.0, 125.2 ppm, one carbon signal missing; HRMS-ESI (*m/z*): [M + H]⁺ calcd 357.0540 for C₁₇H₁₂N₂NaO₅S; found 357.0553.

1-(2-Nitrophenylsulfonyl)-4-*p*-tolyl-pyrrole-2-carbaldehyde (21d)

Using GP2 and 4-tolueneboronic acid, the title compound was synthesised from **20** (0.50 g, 1.39 mmol). The title compound was isolated as an off-white solid (0.315 g, 61% yield) after column chromatography (CH₂Cl₂). M.p.: 171-172 °C; ¹H NMR (CDCl₃, 500 MHz): δ 9.68 (s, 1H), 8.44-8.46 (m, 1H), 7.92 (d, 1H, *J* = 1.0 Hz), 7.81-7.82 (m, 3H), 7.47 (d, 2H, *J* = 8.0 Hz), 7.46 (s, 1H), 7.23 (d, 2H, *J* = 8.0 Hz), 2.38 (s, 3H) ppm; ¹³C{¹H} NMR (CDCl₃, 125 MHz): δ 177.7, 148.2, 138.1, 135.6, 134.0, 133.4, 132.6, 131.6, 129.9, 128.8, 127.8, 127.3, 126.1, 125.9, 125.2, 21.3 ppm; HRMS-ESI (*m/z*): [M + Na]⁺ calcd 393.0521 for C₁₈H₁₄N₂NaO₅S; found 393.0508.

4-(4-Methoxyphenyl)-1-(2-nitrophenylsulfonyl)-pyrrole-2-carbaldehyde (21e)

Using GP2 and 4-methoxyphenylboronic acid, the title compound was synthesised from **20** (0.50 g, 1.39 mmol). The title compound was isolated as an off-white solid (0.35 g, 65% yield) after column chromatography (CH₂Cl₂). M.p.: 165-166 °C; ¹H NMR (CDCl₃, 500 MHz): δ 9.68 (s, 1H), 8.43-8.45 (m, 1H), 7.87 (s, 1H), 7.80-7.82 (m, 3H), 7.49 (d, 2H, *J* = 9.0 Hz), 7.43 (d, 1H, *J* = 2.0 Hz), 6.96 (d, 2H, *J* = 9.0 Hz), 3.84 (s, 3H) ppm; ¹³C{¹H} NMR (CDCl₃, 125 MHz): δ 177.7, 159.7, 148.2, 135.6,

134.0, 133.3, 132.6, 131.6, 127.6, 127.2, 126.8, 126.0, 125.1, 124.3, 114.7, 55.5 ppm; HRMS-ESI (m/z): $[M + Na]^+$ calcd 409.0470 for $C_{18}H_{14}N_2NaO_6S$; found 409.0464.

4-(4-Cyanophenyl)-1-(2-nitrophenylsulfonyl)-pyrrole-2-carbaldehyde (21f)

Using GP2 and 4-cyanophenylboronic acid, the title compound was synthesised from **20** (0.25 g, 0.70 mmol). The title compound was isolated as an off-white solid (0.085 g, 32% yield) after column chromatography (CH_2Cl_2). M.p.: 195-197 °C with decomp.; 1H NMR ($CDCl_3$, 500 MHz): δ 9.69 (s, 1H), 8.60-8.61 (m, 1H), 8.04 (d, 1H, $J = 1.4$ Hz), 7.85-7.88 (m, 3H), 7.73 (d, 2H, $J = 8.3$ Hz), 7.68 (d, 2H, $J = 8.3$ Hz), 7.48 (d, 1H, $J = 1.4$ Hz) ppm; $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz): δ 177.5, 148.3, 136.4, 136.0, 134.3, 134.1, 133.1, 132.7, 132.0, 128.7, 126.4, 125.6, 125.5, 125.3, 118.7, 111.7 ppm; HRMS-ESI (m/z): $[M + Na]^+$ calcd 404.0312 for $C_{18}H_{11}N_3NaO_5S$; found 404.0305.

Electronic Supplementary Information

Data regarding rates of reaction; copies of NMR spectra. See DOI: XXX

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