Fluorination of pyrrole derivatives by Selectfluor™
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Abstract: Fluorination of a range of pyrrole substrates bearing various electron donating and withdrawing substituents at the 1-, 2- and 3-positons using Selectfluor™ has been assessed in order to develop effective methodology for the synthesis of corresponding fluoropyrrole derivatives. The synthesis of some novel fluorinated pyrrole derivatives were achieved in reasonable quantities although many pyrrole substrates were oxidatively polymerised by the fluorinating reagent, reducing the scope of a selective fluorination approach for the preparation of fluoropyrrole products.

Keywords: fluoroheterocycle, selective fluorination, fluoropyrrole, electrophilic fluorination, Selectfluor™

1. Introduction

Since the discovery of the bioactivity of 9α-fluorocortisoid derivatives by Fried and Sabo in 1954,¹ fluorine and fluorinated groups have been used extensively in drug design for many reasons including changing lipophilicity, enhancing metabolic stability and controlling pH profiles.²–⁶ Consequently, fluorine-containing drugs are now prevalent within the life science industries and a considerable number of blockbuster pharmaceuticals and agrochemicals now contain at least one fluorine atom.⁷–⁹

In particular, fluorinated azaheterocycles are very important subunits within life science products and a growing number of pharmaceuticals that contain fluoroheteroaromatic motifs such as Voriconazole (antifungal, Pfizer), Capecitabine (anticancer, Roche) and Diclosulam (herbicide, Dow) have now reached the commercial market¹⁰–¹² with many others in clinical trials such as Abemaciclib (anticancer, Eli Lilly), Riociguat (heart failure, Bayer) and Verubecestat (Alzheimers,
Notably, these pharmaceuticals all contain a fluorinated six-membered azaheterocycle, such as fluoro-pyridine or -pyrimidine structural sub-unit, and effective synthetic procedures at both discovery and manufacturing scales are well reported in the literature. In contrast, it is particularly striking that pharmaceuticals bearing related five-membered azaheterocycles, such as fluorinated pyroles, furans and thiophenes, are very rarely found in life science products and this is, in part, due to the lack of available, efficient and regioselective methodology for the synthesis of, for example, appropriate fluoropyrrole derivatives both for medicinal chemistry programmes and large scale synthesis.

Of relevance to this study, the few reported methods for the synthesis of fluorinated pyroles that have been published involve the use of fluorinated building blocks in cyclisation reactions such as the cyclocondensation of α,α-difluoro-γ-iododicarbonyl compounds with ammonia and various primary amines, related cyclisation reactions of α,α-difluoro-γ-iodotrimethylsilyl ketones, rhodium catalysed intramolecular N-H insertion of 5-amino-4,4-difluoro-2-diao-3-ketoesters, silver catalysed aminofluorination of activated allenes, 1,3-dipolar cycloaddition of DMAD with azomethine ylides formed by reaction of imines and difluorocarbene, the reaction of gem-difluorocyclopropyl ketones with nitriles in the presence of trifluoromethanesulfonylic acid and ring closing metathesis of fluoroamidoalkene derivatives followed by alkylation-aromatisation. All cyclisation methods provide access to fluoropyrrole products but the range of systems possible are limited by the structural complexity of the fluorinated building blocks and so corresponding synthesis of libraries of functional fluoro-pyrroles for drug screening programs are therefore limited. Other approaches that require prefunctionalisation of pyrrole derivatives and reaction with a suitable fluorinating agent include a photochemical modification of the Balz-Schiemann reaction, fluorodecarboxylation of highly substituted derivatives using Selectfluor™ and also the reaction of Grignard or lithiated intermediates with NFSI, formed from corresponding brominated pyrrole precursors. These methods rely on multi-step access to appropriately functionalised pyrroles which may be difficult to prepare efficiently and, consequently, have not been developed to any great extent.

The most direct method for the synthesis of fluoropyrroles is the transformation of C-H to C-F bonds by reaction of the parent pyrrole with an electrophilic fluorinating agent. Electrophilic bromination and chlorination reactions of pyroles are very well established where NBS, NCS, Br₂ or Cl₂, give simple access to a variety of halogenated pyrrole scaffolds. However, related fluorination processes for the preparation of fluoropyrroles are very rare with only two reports published in
which electrophilic fluorinating agents $\text{XeF}_2^{38,39}$ and, for a limited number of ester derivatives, Selectfluor$^\text{TM}$ are employed.$^{40}$ Similarly, fluorination of pyrrole substrates utilising a nucleophilic source of fluorine is also very limited with only one example in which Et$_3$N.2HF is used in anodic fluorination reactions but these generally result in low yields and significant amounts of polyfluorinated by-products.$^{41}$ This is despite the obvious potential utility of late stage fluorination of pyrroles for incorporation into drug discovery programmes.

In this paper, we describe our attempts to develop general selective fluorination strategies for the synthesis of functionalised fluoropyrrole derivatives for use in life-science discovery laboratories. For this purpose, Selectfluor$^\text{TM}$, a shelf stable, commercially available fluorinating agent of the N-F class was used.$^{42}$ We aimed to assess a model range of pyrrole substrates, bearing electron-donating and -withdrawing substituents and protecting groups attached to the pyrrole ring nitrogen (Scheme 1), that could be efficiently and regioselectively fluorinated using Selectfluor$^\text{TM}$, with a view to establishing the regioselectivity of electrophilic fluorination processes and providing access to a range of polyfunctional fluoropyrroles for incorporation into pharmaceutical screening libraries (Scheme 1).

![Scheme 1 Proposed synthesis of fluoropyrrole derivatives.](image)

2. Results and Discussion

We began our investigations by attempting the fluorination of pyrrole and N-methylpyrrole using Selectfluor$^\text{TM}$ by reaction in acetonitrile but all attempts utilising various conditions gave an insoluble black solid which we attribute to the formation of appropriate poly(pyrrole) derivatives. Pyrrole and related systems are readily polymerised when in contact with oxidising systems such as $\text{H}_2\text{O}_2$, $m\text{CPBA}$, $\text{O}_3$, $\text{AgNO}_3$, and $\text{FeCl}_3$, and it appears that Selectfluor$^\text{TM}$ is sufficiently oxidising to allow the formation of polymer
products to occur. Selectfluor™ has been reported to oxidise benzyl alcohols to corresponding aldehydes,\textsuperscript{45} consistent with these observations (Scheme 2).

In light of this, we switched our focus to the fluorination of pyrrole derivatives bearing an electron withdrawing substituent to lower the oxidation potential of the pyrrole substrate in order to limit competing oxidation reactions. Reaction of pyrrole-2-carboxylate 1 was attempted using microwave irradiation which resulted in the formation of a number of fluorinated products and some insoluble polymeric material with an appreciable amount of starting material remaining. From the crude product mixture, however, it was possible to isolate monofluorinated pyrrole derivative (2) in 23 % yield (Scheme 3) by purification using column chromatography.

DFT computations\textsuperscript{46} were performed to predict the $^{19}\text{F}$ chemical shifts of the three possible fluorinated pyrrole isomers and, therefore, determine the regioselectivity of the fluorination reaction. The calculations (Scheme 3) show that the predicted shift for fluorine attached to the carbon atom adjacent to the ring nitrogen (-130.6 ppm) is in excellent agreement with the measured value (-130.73 ppm). In addition, the $^{19}\text{F}$ chemical shifts of the three possible difluorinated isomers were also calculated, confirming that the 4,5-difluorinated derivative is the minor product formed.

**Scheme 2** Attempted synthesis of fluoropyrrole derivatives using Selectfluor™.
Scheme 3 Synthesis of ethyl 5-fluoropyrrole-2-carboxylate 2 and DFT predicted $^{19}$F chemical shifts of fluoropyrrole isomers.

Subsequently, N-methyl protected pyrrole-2-carboxylate derivative (3) was employed as the substrate but, under the same conditions as above, gave a much more complex mixture of fluorinated products due to the increased nucleophilicity of the substrate. Nevertheless, it was possible to isolate the monofluorinated pyrrole derivative (4), in 16 % yield (Scheme 4). The lower yield was attributed to a combination of loss of material during solvent removal due to the high volatility of the product and the greater number of by-products observed by $^{19}$F NMR spectroscopy. The reaction was also performed at room temperature and using conventional heating in an attempt to decrease the formation of by-products but, unfortunately, many fluorinated products were observed at reasonable conversion.

In attempts to improve the regioselectivity of these processes, fluorination of pyrrole-2-carboxylate derivative (1) was screened using a range of Lewis acid catalysts (Table 1). However, the addition of all Lewis acids screened lowered the observed yields of fluoropyrrole product, when either Selectfluor™ or related electrophilic fluorinating agent N-fluoro-benzene sulfonimide (NFSI) were used.

Scheme 4 Synthesis of methyl 1-methyl-5-fluoropyrrole-2-carboxylate.

Table 1 Reaction of 1 with electrophilic fluorinating agent in the presence of a Lewis acid under microwave conditions

| Entry | Fluorinating Agent | Lewis Acid | NMR Yield / %
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Selectfluor™</td>
<td>-</td>
<td>21</td>
</tr>
<tr>
<td>2</td>
<td>Selectfluor™</td>
<td>ZrCl$_4$</td>
<td>8</td>
</tr>
</tbody>
</table>
Consequently, due to the highly nucleophilic nature of pyrrole derivatives and the oxidising ability of Selectfluor\textsuperscript{TM}, we chose to assess fluorination reactions of pyrrole-2-carboxylates bearing electron withdrawing protecting groups attached to ring nitrogen, in an attempt to improve the regioselectivity and yield of fluoropyrrole product. Therefore, the synthesis of a 4-nitrobenzyl protected pyrrole derivative (5) was carried out by reaction of nitro-benzyl bromide and pyrrole 1 and the product successfully isolated in 51 % yield. Fluorination of nitrobenzyl pyrrole 5 was assessed and a range of reaction conditions were screened (Table 2). From the initial starting point (entry 1), the time of reaction was increased but no improvement in yield was observed despite significant quantities of starting material remaining. Hence, the reaction time was lowered (entry 4) but, again, no improvement in yield was observed. The reaction temperature was varied but neither an increase or decrease in temperature, over a range of reaction times, gave increased yields of fluoropyrrole product and, in all cases, the yield of 5-fluoropyrrole product remained low (~ 20 %). Despite this, the desired product (6) could be isolated by column chromatography in 15 % yield.

We next studied reaction of a pyrrole derivative bearing a nitrile substituent which could be transformed to a number of substrates of synthetic versatility post fluorination. Initially, the unprotected pyrrole-2-carbonitrile derivative (7) was used as substrate for a similar screen of fluorination conditions (Table 3) and in this case, conditions shown in entry 1 gave a much-improved yield of 62 %.

Table 2 Reaction of 5 with Selectfluor\textsuperscript{TM} under microwave conditions\textsuperscript{a}

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reagent</th>
<th>Lewis acid</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>Selectfluor\textsuperscript{TM}</td>
<td>AgNO\textsubscript{3}</td>
<td>2</td>
</tr>
<tr>
<td>4</td>
<td>Selectfluor\textsuperscript{TM}</td>
<td>Ga(OTf)\textsubscript{3}</td>
<td>10</td>
</tr>
<tr>
<td>5</td>
<td>Selectfluor\textsuperscript{TM}</td>
<td>BF\textsubscript{3}.Et\textsubscript{2}O</td>
<td>6</td>
</tr>
<tr>
<td>6</td>
<td>Selectfluor\textsuperscript{TM}</td>
<td>HfCl\textsubscript{4}</td>
<td>9</td>
</tr>
<tr>
<td>7</td>
<td>Selectfluor\textsuperscript{TM}</td>
<td>InCl\textsubscript{3}</td>
<td>12</td>
</tr>
<tr>
<td>8</td>
<td>NFSI</td>
<td>-</td>
<td>4</td>
</tr>
<tr>
<td>9</td>
<td>NFSI</td>
<td>ZrCl\textsubscript{4}</td>
<td>&lt; 1</td>
</tr>
</tbody>
</table>

\textsuperscript{a} Conditions: 1 (1.5 mmol), ‘F’ reagent (1 eq.), Lewis acid (0.5 eq.), MeCN (15 mL), 70 °C, 5 min. \textsuperscript{b} NMR yield determined using an \textit{α,α,α-trifluorotoluene} reference.
<table>
<thead>
<tr>
<th>Entry</th>
<th>Temp / °C</th>
<th>Time / min</th>
<th>Yield / %&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>70</td>
<td>5</td>
<td>27 (15)</td>
</tr>
<tr>
<td>2</td>
<td>70</td>
<td>10</td>
<td>21</td>
</tr>
<tr>
<td>3</td>
<td>70</td>
<td>15</td>
<td>20</td>
</tr>
<tr>
<td>4</td>
<td>70</td>
<td>2</td>
<td>23</td>
</tr>
<tr>
<td>5</td>
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<td>5</td>
<td>22</td>
</tr>
<tr>
<td>6</td>
<td>100</td>
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<td>20</td>
</tr>
<tr>
<td>7</td>
<td>100</td>
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</tr>
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<td>5</td>
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<td>60</td>
<td>10</td>
<td>25</td>
</tr>
<tr>
<td>10</td>
<td>60</td>
<td>15</td>
<td>25</td>
</tr>
</tbody>
</table>

<sup>a</sup> Conditions: 5 (0.5-0.6 mmol.), Selectfluor<sup>TM</sup> (1 eq.), MeCN (15 mL).  
<sup>b</sup> NMR yield determined using an α,α,α-trifluorotoluene reference, isolated yield in parentheses.

However, variations in the reaction time and temperature (entries 2 and 3) resulted in reduced yields. The desired product (8) could however, be purified by column chromatography and was isolated in a 30 % yield. Similarly, the 4-nitrobenzyl substituted pyrrole-2-carbonitrile derivative was again synthesised but subsequent related fluorination reactions gave no improvement in yield.

Due to the limited success observed when employing the 4-nitrobenzyl group, the tosyl group was selected as ring nitrogen protecting group due to its strong electron-withdrawing ability, stability to oxidising conditions and ease of introduction and removal. Both tosyl protected pyrroles 9 and 10 were synthesised and subsequent fluorination conditions were screened (Table 4).

**Table 3** Reaction of 7 with Selectfluor<sup>TM</sup> under microwave conditions<sup>a</sup>

![Reaction diagram]

---

*7*
<table>
<thead>
<tr>
<th>Entry</th>
<th>Temp / °C</th>
<th>Time / min</th>
<th>Yield / %$^b$</th>
</tr>
</thead>
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<tr>
<td>1</td>
<td>70</td>
<td>5</td>
<td>62 (30)</td>
</tr>
<tr>
<td>2</td>
<td>70</td>
<td>10</td>
<td>46</td>
</tr>
<tr>
<td>3</td>
<td>70</td>
<td>2</td>
<td>38</td>
</tr>
<tr>
<td>4</td>
<td>60</td>
<td>5</td>
<td>40</td>
</tr>
<tr>
<td>5</td>
<td>60</td>
<td>10</td>
<td>53</td>
</tr>
<tr>
<td>6</td>
<td>60</td>
<td>15</td>
<td>45</td>
</tr>
<tr>
<td>7</td>
<td>100</td>
<td>2</td>
<td>45</td>
</tr>
<tr>
<td>8</td>
<td>100</td>
<td>5</td>
<td>47</td>
</tr>
</tbody>
</table>

$^a$ Conditions: 7 (2-10 mmol), Selectfluor$^{TM}$ (1 eq.), MeCN (15-25 mL). $^b$ NMR yield determined using an $\alpha,\alpha,\alpha$-trifluorotoluene reference, isolated yield in parentheses.

Table 4 Reaction of 9 with Selectfluor$^{TM}$ under microwave conditions$^a$

![Reaction Diagram]

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>Temp / °C</th>
<th>Time / min</th>
<th>Yield / %$^b$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CO$_2$Et</td>
<td>70</td>
<td>5</td>
<td>&lt; 1</td>
</tr>
<tr>
<td>2</td>
<td>CO$_2$Et</td>
<td>70</td>
<td>60</td>
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<td>CO$_2$Et</td>
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<td>60</td>
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<td>4</td>
<td>CN</td>
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<td>0</td>
</tr>
<tr>
<td>5</td>
<td>CN</td>
<td>100</td>
<td>15</td>
<td>&lt; 1</td>
</tr>
<tr>
<td>6</td>
<td>CN</td>
<td>150</td>
<td>15</td>
<td>11</td>
</tr>
<tr>
<td>7</td>
<td>CN</td>
<td>100</td>
<td>60</td>
<td>6</td>
</tr>
<tr>
<td>8</td>
<td>CN</td>
<td>100</td>
<td>180</td>
<td>10</td>
</tr>
</tbody>
</table>

$^a$ Conditions: 9 or 10 (1 mmol), Selectfluor$^{TM}$ (1 eq.), MeCN (15 mL). $^b$ NMR yield determined using an $\alpha,\alpha,\alpha$-trifluorotoluene reference.
Initial fluorination reactions of 9 and 10 demonstrated the ability of the tosyl substituent to reduce the nucleophilicity of the pyrrole ring compared to substrates attempted previously but, in these cases, negligible conversion to fluorinated products was observed (entries 1 and 4). Unfortunately, upon increasing the reaction time and temperature of the fluorination reactions, the major product observed was an unwanted fluorosulfonyl derivative (12) (Fig. 1), which was identified by $^{19}$F NMR and GC-MS of the crude reaction mixture. The formation of this species presumably occurs via nucleophilic attack of fluoride at the sulfur atom of the tosyl group and we suspect that the fluoride ion originates from the tetrafluoroborate counterion of the Selectfluor™ reagent, due to prolonged exposure to high temperatures under microwave conditions.

An additional substituent present on the pyrrole ring will prevent the formation of any 4,5-difluorinated by-product which can be difficult to separate and could provide useful functionality for subsequent synthetic transformations. Consequently, the synthesis of 13 was carried out, as a bromine substituent allows a range of possible synthetic transformations, particularly palladium catalysed cross coupling chemistry. 4-Bromopyrrole-2-carboxaldehyde (13) was obtained in good yield and optimised fluorination conditions (Table 5) provided the desired product in 29 % yield. Furthermore, the structure of 14 was confirmed by X-ray crystallography (Fig. 2) and the regiochemistry of the fluorination reaction was consistent with DFT predicted $^{19}$F NMR data.

![Figure 1 Possible reaction mechanism resulting in the formation of fluorinated by-product 12.](image)

**Table 5.** Reaction of 13 with Selectfluor™ under microwave conditions

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reaction Conditions</th>
<th>Yields (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><strong>Selectfluor™</strong>, 40 °C</td>
<td>12%</td>
</tr>
<tr>
<td>2</td>
<td><strong>Selectfluor™</strong>, 60 °C</td>
<td>29%</td>
</tr>
<tr>
<td>3</td>
<td><strong>Selectfluor™</strong>, 80 °C</td>
<td>5%</td>
</tr>
</tbody>
</table>

*Data from the research paper.*
\[
\begin{array}{ccc}
\text{Entry} & \text{Time / min} & \text{Yield / %} \\
1 & 5 & 29 \\
2 & 10 & 31 \\
3 & 15 & 12 \\
4 & 7.5 & 34 (29)
\end{array}
\]

\textsuperscript{a} Conditions: 5 (1-6 mmol), Selectfluor\textsuperscript{TM} (1 eq.), MeCN (15-25 mL). \textsuperscript{b} NMR yield determined using an \(\alpha,\alpha,\alpha\)-trifluorotoluene reference, isolated yield in parentheses.

Figure 2 Molecular structure of 14.

The reactivity of 3-substituted pyrrole derivatives bearing an electron withdrawing substituent, such as methyl pyrrole-3-carboxylate (15), was also investigated (Table 6). Based on steric and electronic factors, the major product predicted was the 5-fluoro product 16 and the initial conditions applied gave a promising yield of around 10 % as measured by \(^{19}\text{F}\) NMR spectroscopy since the other major component in the crude reaction mixture was unreacted starting material. However, upon increasing the reaction time, a larger quantity of insoluble polymer product was observed alongside a slight decrease in yield. Therefore, a shorter reaction time was employed both with the temperature unchanged and at an elevated temperature of 100 °C but, in both cases, comparable yields were obtained. Finally, two equivalents of Selectfluor\textsuperscript{TM} were used in an attempt to increase conversion but a large amount of polymeric product was obtained and a negligible yield of the 5-fluorinated product observed by NMR.
Finally, the reactivity of a 2,5-disubstituted pyrrole derivative was assessed as it was envisaged that two electron withdrawing substituents would help to prevent competing oxidation reactions. Methyl 5-formylpyrrole-2-carboxylate (17) was employed and early investigations of reactions conducted at 70 °C (Table 7) did not give rise to any polymeric product. However, even after a period of 2.5 h at this temperature (entry 3), the yield of fluorinated product was disappointingly low and hence the reaction temperature was increased. The results obtained at a reaction temperature of 100 °C were somewhat similar to that seen at lower temperatures and again a low yield of 17 % was obtained even after 2.5 h although a large proportion of starting material still remained. Further increases in reaction temperature, however, showed no significant benefit in terms of obtained yield, but appreciable amounts of polymer by-product began to form.

**Table 6** Reaction of 15 with Selectfluor™ under microwave conditions

| Entry | Temp / °C | Time / min | Yield / %
<table>
<thead>
<tr>
<th></th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>70</td>
<td>5</td>
<td>10</td>
</tr>
<tr>
<td>2</td>
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<td>10</td>
<td>9</td>
</tr>
<tr>
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<td>5</td>
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<td>2</td>
<td>9</td>
</tr>
<tr>
<td>6b</td>
<td>70</td>
<td>5</td>
<td>-</td>
</tr>
</tbody>
</table>

*a Conditions: 15 (2 mmol), Selectfluor™ (1 eq.), MeCN (15 mL). b Selectfluor (2 eq.). c NMR yield determined using an α,α,α-trifluorotoluene reference.*

**Table 7** Reaction of 17 with Selectfluor™ under microwave conditions
<table>
<thead>
<tr>
<th>Entry</th>
<th>Temp / °C</th>
<th>Time / min</th>
<th>Yield / %&lt;sup&gt;b&lt;/sup&gt;</th>
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<tr>
<td>1</td>
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<tr>
<td>2</td>
<td>70</td>
<td>30</td>
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<td>3</td>
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<tr>
<td>10</td>
<td>150</td>
<td>10</td>
<td>18</td>
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<sup>a</sup> Conditions: 17 (1 mmol), Selectfluor<sup>TM</sup> (1 eq.), MeCN (15 mL). <sup>b</sup>NMR yield determined using an α,α,α-trifluorotoluene reference.

### 3. Conclusions

In conclusion, the effect of various substituents on the fluorination of pyrrole substrates using Selectfluor<sup>TM</sup> has been assessed but, unfortunately, general methodology for the ready synthesis of fluoropyrroles could not be achieved despite assessment of a range of pyrrole derivatives in electrophilic fluorination reactions. In general, competing oxidation and subsequent polymerisation of the pyrrole substrates by Selectfluor<sup>TM</sup>, which is established as a reasonably strong oxidising agent as well as a fluorinating agent, was a recurring problem for all substrates encountered. However, the synthesis of fluorinated pyrrole derivatives (2, 4, 6, 8 and 14), which possess suitable functionality for further synthetic transformations to produce structures relevant for application in the life science industries, was achieved in synthetically useful reactions.
4. Experimental

4.1 General

Chemicals were purchased from Alfa Aesar, Apollo Scientific, Fluorochem or Sigma Aldrich and, unless otherwise stated, were used without any further purification. Dry solvents were obtained using an Innovative Technology Inc. Solvent Purification System. All column chromatography was carried out using Silicagel LC60A (40–63 micron) purchased from Fluorochem. Microwave reactions were performed in a Biotage Initiator microwave synthesiser (0-400 W) in a sealed vessel. Proton, carbon and fluorine nuclear magnetic resonance spectra (¹H NMR, ¹³C NMR and ¹⁹F NMR) were recorded on a Bruker 400 Ultrashield (¹H NMR at 400 MHz; ¹³C NMR at 101 MHz; ¹⁹F NMR at 376 MHz) spectrometer or a Varian VNMR-700 (¹H NMR at 700 MHz; ¹³C NMR at 176 MHz) with residual solvent peaks as the internal standard. ¹H, ¹³C and ¹⁹F spectroscopic data are reported as follows: chemical shift (ppm), integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constant (Hz). Accurate mass analysis was achieved with a QtoF Premier mass spectrometer (Waters Ltd, UK) or an LCT Premier XE mass spectrometer (Waters Ltd, UK) equipped with an accurate solids analysis probe (ASAP). Infra-red (IR) spectra were recorded on a Perkin Elmer FTIR Spectrum Two™ fitted with an ATR probe. Melting points were measured with a Gallenkamp apparatus at atmospheric pressure and are uncorrected.

4.2 Fluorination of pyrroles. General procedures

4.2.1 Reaction of ethyl pyrrole-2-carboxylate (1) with electrophilic fluorinating agent in the presence of a Lewis acid under microwave conditions (Table 1): To a solution of 1 (0.21 g, 1.5 mmol) and Selectfluor™ (0.53 g, 1.5 mmol) in dry MeCN (15 mL) was added Lewis Acid (50 mol%) before heating with microwave irradiation at 70 °C for 5 min. The reaction was quenched by the addition of H₂O (30 mL) and CHCl₃ (30 mL) was subsequently added. The layers were separated and the aqueous phase extracted with CHCl₃ (3 x 30 mL) before the solvent was removed in vacuo; analysis by ¹⁹F NMR relative to an α,α,α-trifluorotoluene reference gave the yield of 5-fluorinated product.
4.2.2 Reaction of Ethyl N-(4-nitrobenzyl)-pyrrole-2-carboxylate (5) with Selectfluor\textsuperscript{TM} under microwave conditions (Table 2): A solution of 5 (0.15 g, 0.55 mmol) and Selectfluor\textsuperscript{TM} (0.20 g, 0.55 mmol) in MeCN (15 mL) was heated with microwave irradiation. The reaction was quenched by the addition of H\textsubscript{2}O (30 mL) and CHCl\textsubscript{3} (30 mL) was subsequently added. The layers were separated and the aqueous phase extracted with CHCl\textsubscript{3} (3 x 30 mL) before the solvent was removed in vacuo; analysis by \textsuperscript{19}F NMR relative to an $\alpha,\alpha,\alpha$-trifluorotoluene reference gave the yield of 5-fluorinated product.

4.2.3 Reaction of pyrrole-2-carbonitrile (7) with Selectfluor\textsuperscript{TM} under microwave conditions (Table 3): A solution of 7 (0.18 g, 2 mmol) and Selectfluor\textsuperscript{TM} (0.71 g, 2 mmol) in MeCN (15 mL) was heated with microwave irradiation. The reaction was quenched by the addition of H\textsubscript{2}O (30 mL) and CHCl\textsubscript{3} (30 mL) was subsequently added. The layers were separated and the aqueous phase extracted with CHCl\textsubscript{3} (3 x 30 mL) before the solvent was removed in vacuo; analysis by \textsuperscript{19}F NMR relative to an $\alpha,\alpha,\alpha$-trifluorotoluene reference gave the yield of 5-fluorinated product.

4.2.4 Reaction of Ethyl N-tosyl-pyrrole-2-carboxylate (9) with Selectfluor\textsuperscript{TM} under microwave conditions (Table 4): A solution 9 or 10 (1 mmol) and Selectfluor\textsuperscript{TM} (0.35 g, 1 mmol) in MeCN (15 mL) was heated with microwave irradiation. The reaction was quenched by the addition of H\textsubscript{2}O (30 mL) and CHCl\textsubscript{3} (30 mL) was subsequently added. The layers were separated and the aqueous phase extracted with CHCl\textsubscript{3} (3 x 30 mL) before the solvent was removed in vacuo; analysis by \textsuperscript{19}F NMR relative to an $\alpha,\alpha,\alpha$-trifluorotoluene reference gave the yield of 5-fluorinated product. The presence of fluorinated by-product 12 was confirmed by a combination of \textsuperscript{19}F NMR and GC-MS analysis. \textsuperscript{19}F NMR (376 MHz, Chloroform-d) $\delta$ 66.31 (1 F, s, SF). GC-MS (EI) m/z 174.0.

4.2.5 Reaction of 4-Bromopyrrole-2-carboxaldehyde (13) with Selectfluor\textsuperscript{TM} under microwave conditions (Table 5): A solution of 13 (0.17 g, 1 mmol) and Selectfluor\textsuperscript{TM} (0.35 g, 1 mmol) in MeCN (15 mL) was heated with microwave irradiation at 70 °C. The reaction was quenched by the addition of H\textsubscript{2}O (30 mL) and CHCl\textsubscript{3} (30 mL) was subsequently added. The layers were separated and the aqueous phase extracted with CHCl\textsubscript{3} (3 x 30 mL) before the solvent was removed in vacuo; analysis by \textsuperscript{19}F NMR relative to an $\alpha,\alpha,\alpha$-trifluorotoluene reference gave the yield of 5-fluorinated product.
4.2.6 Reaction of methyl pyrrole-3-carboxylate (15) with Selectfluor™ under microwave conditions (Table 6): A solution of 15 (0.25 g, 2 mmol) and Selectfluor™ (0.71 g, 2 mmol) in MeCN (15 mL) was heated with microwave irradiation. The reaction was quenched by the addition of H₂O (30 mL) and CHCl₃ (30 mL) was subsequently added. The layers were separated and the aqueous phase extracted with CHCl₃ (3 x 30 mL) before the solvent was removed in vacuo; analysis by ¹⁹F NMR relative to an α,α,α-trifluorotoluene reference gave the yield of 5-fluorinated product.

4.2.7 Reaction of Methyl 5-formylpyrrole-2-carboxylate (17) with Selectfluor™ under microwave conditions (Table 7): A solution of 17 (0.15 g, 1 mmol) and Selectfluor™ (0.35 g, 1 mmol) in MeCN (15 mL) was heated with microwave irradiation. The reaction was quenched by the addition of H₂O (30 mL) and CHCl₃ (30 mL) was subsequently added. The layers were separated and the aqueous phase extracted with CHCl₃ (3 x 30 mL) before the solvent was removed in vacuo; analysis by ¹⁹F NMR relative to an α,α,α-trifluorotoluene reference gave the yield of 5-fluorinated product.

4.3 Synthesis of pyrrole substrates

4.3.1 Ethyl N-(4-nitrobenzyl)-pyrrole-2-carboxylate (5)

To a solution of ethyl pyrrole-2-carboxylate 1 (2.09 g, 15 mmol) in dry DMF (25 mL) at 0 °C, sodium hydride (0.54 g, 23 mmol) was added. The reaction mixture was stirred for 20 min, before the dropwise addition of 4-nitrobenzyl bromide (4.80 g, 23 mmol) in dry DMF (10 mL). After a further 25 min, any excess hydride was decomposed by the addition of ethanol (15 mL) and the reaction mixture poured into distilled water (50 mL). The aqueous solution was extracted with DCM (4 x 50 mL) and washed with distilled water (9 x 100 mL) and brine (100 mL) before being dried (Na₂SO₄) and concentrated in vacuo. The crude product was purified by column chromatography on silica gel using a gradient of hexane/ethyl acetate (0-20 % ethyl acetate) as the eluent to give ethyl N-(4-nitrobenzyl)-pyrrole-2-carboxylate 5 (2.10 g, 51 %) as a yellow solid; Mp 92-94 °C. ¹H NMR (400 MHz, Chloroform-d) δ 8.21 – 8.11 (2 H, m, C₃'H), 7.21 – 7.13 (2 H, m, C₂'H), 7.05 (1 H, dd, ³JHH 4.0, ⁴JHH 1.8, C5H), 6.93 (1 H, dd, ³JHH 2.6, ⁴JHH 1.8, C3H), 6.25 (1 H, dd, ³JHH 4.0, ³JHH 2.6, C4H), 5.65 (2 H, s, ArCH₂), 4.19 (2 H, q,
$^3J_{HH} 7.1, CH_2CH_3$), 1.28 (3 H, t, $^3J_{HH} 7.1, CH_2CH_3$). $^{13}$C NMR (176 MHz, Chloroform-$d$) $\delta$ 161.1 (s, C=O), 147.4 (s, C4'), 146.1 (s, C1'), 129.2 (s, C3), 127.2 (s, C2') , 124.0 (s, C3'), 122.4 (s, C2), 118.9 (s, C5), 109.2 (s, C4), 60.2 (s, CH_2CH_3), 51.8 (s, ArCH_2), 14.5 (s, C2H_2).

HRMS (ESI) m/z calculated for [M+H]$^+$ C_{14}H_{15}N_2O_4 275.1032; found 275.1043.

4.3.2 N-(4-Nitrobenzyl)-pyrrole-2-carbonitrile

The same procedure as for the synthesis of 5 was employed with pyrrole-2-carbonitrile 7 (0.36 g, 4 mmol), sodium hydride (0.14 g, 6 mmol) and 4-nitrobenzyl bromide (1.28 g, 6 mmol). The crude product obtained was purified by column chromatography on silica gel using a gradient of hexane/ethyl acetate (0-10% ethyl acetate) as the eluent to yield N-(4-Nitrobenzyl)-pyrrole-2-carbonitrile (0.22 g, 24%) as a yellow solid; Mp 97-99 °C. IR (neat, cm$^{-1}$) 3142, 3127, 3077, 2212, 1507, 1340, 1072, 734. $^1$H NMR (700 MHz, Chloroform-$d$) $\delta$ 8.22 – 8.19 (2 H, m, C3'H), 7.30 – 7.27 (2 H, m, C2'H), 6.91 (1 H, dd, $^3J_{HH}$ 2.7, $^4J_{HH}$ 1.6, C5H), 6.88 (1 H, dd, $^3J_{HH}$ 4.0, $^4J_{HH}$ 1.6, C3H), 6.28 (1 H, dd, $^3J_{HH}$ 4.0, $^3J_{HH}$ 1.6, C4H), 5.33 (2 H, s, ArCH2). $^{13}$C NMR (176 MHz, Chloroform-$d$) $\delta$ 148.0 (s, C1'), 143.2 (s, C4'), 127.9 (s, C2'), 127.1 (s, C5), 124.4 (s, C3'), 121.1 (s, C3), 113.5 (s, CN), 110.8 (s, C4), 104.5 (s, C2), 51.7 (s, ArCH2). HRMS (ASAP) m/z calculated for [M]$^+$ C_{12}H_9N_3O 227.0693; found 227.0695.

4.3.3 Ethyl N-tosyl-pyrrole-2-carboxylate (9)

Sodium hydride (0.43 g, 18 mmol) was suspended in anhydrous DMF (10 mL) and cooled to 0 °C before a solution of ethyl pyrrole-2-carboxylate 1 (2.09 g, 15 mmol) in anhydrous DMF (15 mL) was added over a period of 20 min. The reaction mixture was then allowed to return to room temperature and stirred for 1 h before the addition of tosyl chloride (3.43 g, 18 mmol) in anhydrous DMF (10 mL). After 17 h the reaction mixture was poured into distilled water (100 mL) and the aqueous solution extracted with ethyl acetate (3 x 50 mL). The combined organic extracts were washed with distilled water (4 x 100 mL) and brine (100 mL) before being dried (Na$_2$SO$_4$) and concentrated in vacuo. The crude product was filtered through a silica plug using ethyl acetate as the eluent and the solvent removed in vacuo to yield 9 (3.27 g, 88%) as a pale yellow solid; Mp 43-45 °C. IR (neat, cm$^{-1}$) 2993, 2980, 1725, 1705, 1681, 1543, 1359, 1258, 1171. $^1$H NMR (700 MHz, Chloroform-$d$) $\delta$ 7.90 – 7.84 (2 H, m, C2'H), 7.70 (1 H, dd, $^3J_{HH}$ 3.2, $^4J_{HH}$ 1.9, C5H), 7.35 – 7.28 (2 H, m, C3'H), 7.04 (1 H, dd, $^3J_{HH}$ 3.7,
$^{4}\text{J}_{\text{HH}}$ 1.9, C3H), 6.30 (1 H, t, $^{3}\text{J}_{\text{HH}}$ 3.4, C4H), 4.19 (2 H, q, $^{3}\text{J}_{\text{HH}}$ 7.1, CH$_2$CH$_3$), 2.42 (3 H, s, ArCH$_3$), 1.26 (3 H, t, $^{3}\text{J}_{\text{HH}}$ 7.1, CH$_2$CH$_3$). $^{13}\text{C}$ NMR (176 MHz, Chloroform-d) $\delta$ 158.9 (s, C=O), 145.0 (s, C4'), 136.1 (s, C1'), 129.6 (s, C3'), 129.2 (s, C5), 128.3 (s, C2'), 125.4 (s, C2), 123.2 (s, C3), 110.4 (s, C4), 60.9 (s, CH$_2$CH$_3$), 21.8 (s, ArCH$_3$), 14.3 (s, ArCH$_3$). HRMS (ESI) m/z calculated for [M-H]$^-$ C$_{14}$H$_{14}$NO$_4$S 292.0644; found 292.0640.

4.3.4 N-Tosyl-pyrrole-2-carbonitrile (10)

The same procedure as for the synthesis of 9 was employed with pyrrole-2-carbonitrile 7 (1.38 g, 15 mmol), sodium hydride (0.43 g, 18 mmol) and tosyl chloride (3.43 g, 18 mmol). The crude product was recrystallized from hexane/ethyl acetate to give N-tosyl-pyrrole-2-carbonitrile 10 (3.02 g, 82 %) as a pale yellow solid; Mp 110–112 °C (lit 114–115 °C). IR (neat, cm$^{-1}$) 2989, 1726, 1705, 1681, 1582, 1354, 1283, 1134. $^{1}$H NMR (400 MHz, Chloroform-d) $\delta$ 8.01 – 7.85 (2 H, m, C2'H), 7.47 (1 H, dd, $^{3}\text{J}_{\text{HH}}$ 3.2, $^{4}\text{J}_{\text{HH}}$ 1.6, C5H), 7.40 – 7.34 (2 H, m, C3'H), 6.95 (1 H, dd, $^{3}\text{J}_{\text{HH}}$ 3.7, $^{4}\text{J}_{\text{HH}}$ 1.6, C3H), 6.32 (1 H, t, $^{3}\text{J}_{\text{HH}}$ 3.5, C4H), 2.44 (3 H, s, ArCH$_3$). $^{13}$C NMR (176 MHz, Chloroform-d) $\delta$ 146.7 (s, C4'), 134.3 (s, C1'), 130.5 (s, C3'), 128.0 (s, C2'), 126.7 (s, C5), 126.7 (s, C3), 112.4 (s, C4), 111.8 (s, CN), 103.9 (s, C2), 21.9 (s, ArCH3). HRMS (ESI) m/z calculated for [M+H]$^+$ C$_{12}$H$_{11}$NO$_2$S 247.0541; found 247.0547.

4.3.5 4-Bromopyrrole-2-carboxaldehyde (13)

A solution of pyrrole-2-carboxaldehyde 12 (3.80 g, 40 mmol) in dry THF (40 mL) was cooled to 0 °C under Argon. NBS (7.12 g, 40 mmol) was added and the reaction mixture stirred for 15 min before the solvent was removed in vacuo. The crude product was dried under high vacuum for 30 min before the addition of distilled water (20 mL) and the resulting suspension filtered. The resulting solid was dissolved in a minimum amount of hot ethanol/water solution (9:1) before the addition of activated charcoal and filtration through a celite plug. Upon cooling, the product recrystallised to give 4-bromopyrrole-2-carboxaldehyde 13 (3.54 g, 51 %) as an off white solid; Mp 119-122 °C. IR (neat, cm$^{-1}$) 3204, 3108, 3982, 2861, 1653, 1378, 1354, 918, 769. $^{1}$H NMR (400 MHz, Acetone-d$_6$) $\delta$ 11.39 (1 H, s, NH), 9.52 (1 H, d, $^{4}\text{J}_{\text{HH}}$ 1.0, CHO), 7.34 – 7.31 (1 H, m, C5H), 7.09 – 7.05 (1 H, m, C3H). $^{13}$C NMR (101 MHz, Acetone-d$_6$) $\delta$ 179.4 (s, C=O), 134.3 (s, C2), 126.8 (s, C5), 121.5 (s, C3), 98.4 (s, C4). HRMS (ESI) m/z calculated for [M+H]$^+$ C$_{12}$H$_{11}$BrNO 173.9554; found 173.9553.
4.4 Preparative scale fluorination of pyrrole derivatives

4.4.1 Ethyl 5-fluoropyrrole-2-carboxylate (2)

A solution of ethyl pyrrole-2-carboxylate 1 (0.56 g, 4 mmol) and Selectfluor™ (1.42 g, 4 mmol) in MeCN (25 mL) was heated by microwave irradiation at 70 °C for 5 min. The reaction was quenched by the addition of H₂O (50 mL) and CHCl₃ (50 mL) was subsequently added. The layers were separated and the aqueous phase extracted with CHCl₃ (3 x 25 mL). The combined organic phases were dried (Na₂SO₄) and concentrated in vacuo. The crude product was purified by column chromatography on silica gel using hexane/diethyl ether (5:1) as the eluent to give ethyl 5-fluoropyrrole-2-carboxylate 2 (0.15 g, 23 %) as a yellow solid; Rₕ (3:1, hexane:Et₂O) 0.40. IR (neat, cm⁻¹) 3218, 2984, 1676, 1586, 1237. ¹H NMR (400 MHz, Chloroform-d) δ 9.85 (1 H, s, NH), 6.75 (1 H, ddd, 4JHF 4.7, 3JHH 4.0, 4JHH 2.9, C3H), 5.58 (1 H, ddd, 3JHF 4.0, 3JHH 4.0, 4JHH 2.7, C4H), 4.31 (2 H, q, 3JHH 7.1, CH₂CH₃), 1.34 (3 H, t, 3JHH 7.2, CH₂CH₃). ¹⁹F NMR (376 MHz, Chloroform-d) δ -130.64 (1 F, ddd, 4JHF 4.7, 3JHF 4.0, 3JHF 2.5). ¹³C NMR (176 MHz, Chloroform-d) δ 161.0 (s, C=O), 149.4 (d, 1JCF 267.4, CF), 115.2 (s, C3), 114.2 (s, C2), 89.2 (d, 2JCF 11.4, C4), 60.6 (s, CH₂CH₃), 14.6 (s, CH₂CH₃). HRMS (ESI) m/z calculated for [M+H]+ C₇H₉FNO₂ 158.0617; found 158.0598.

4.4.2 Methyl 1-methyl-5-fluoropyrrole-2-carboxylate (4)

A solution of methyl 1-methyl-pyrrole-2-carboxylate 3 (0.56 g, 4 mmol) and Selectfluor™ (1.42 g, 4 mmol) in MeCN (25 mL) was heated by microwave irradiation at 70 °C for 5 min. The reaction was quenched by the addition of H₂O (50 mL) and CHCl₃ (50 mL) was subsequently added. The layers were separated and the aqueous phase extracted with CHCl₃ (3 x 25 mL). The combined organic phases were dried (Na₂SO₄) and concentrated in vacuo. The crude product was purified by column chromatography on silica gel using hexane/diethyl ether (5:1) as the eluent to yield methyl 1-methyl-5-fluoropyrrole-2-carboxylate 4 (0.10 g, 16 %) as a colourless oil; Rₕ (3:1, hexane:Et₂O) 0.42. IR (neat, cm⁻¹) 2955, 1704, 1565, 1472, 1252, 1103. ¹H NMR (400 MHz, chloroform-d) δ 6.81 (1 H, dd, 4JHF 6.3, 3JHH 4.3, C3H), 5.56 (1 H, dd, 3JHH 4.3, 3JHF 4.3, C4H), 3.79 (3 H, s, CO₂CH₃), 3.76 (3 H, d, 4JHF 1.2, NCH₃). ¹⁹F NMR (376 MHz, Chloroform-d) δ -131.89 (1 F, ddq, 4JHF 6.3, 3JHF 4.2, 4JHF 4.2, JCF 267.4, CF), 115.2 (s, C3), 114.2 (s, C2), 89.2 (d, 2JCF 11.4, C4), 60.6 (s, CH₂CH₃), 14.6 (s, CH₂CH₃). HRMS (ESI) m/z calculated for [M+H]+ C₇H₉FNO₂ 158.0617; found 158.0598.
1.2). $^{13}$C NMR (101 MHz, Chloroform-$d$) $\delta$ 161.4 (d, $^4J_{CF}$ 2.2, C=O), 150.5 (d, $^1J_{CF}$ 267.1, CF), 116.0 (d, $^3J_{CF}$ 4.3, C3), 114.5 (s, C2), 87.6 (d, $^2J_{CF}$ 12.2, C4), 51.1 (s, OCH3), 30.6 (d, $^3J_{CF}$ 2.8, NCH3). HRMS (ESI) m/z calculated for [M+H]$^+$ C7H9FNO2 158.0617; found 158.0615.

4.4.3 Ethyl N-(4-nitrobenzyl)-5-fluoropyrrole-2-carboxylate (6)

A solution of ethyl N-(4-nitrobenzyl)-pyrrole-2-carboxylate 5 (0.15 g, 0.55 mmol) and Selectfluor$^\text{TM}$ (0.20 g, 0.55 mmol) in MeCN (15 mL) was heated with microwave irradiation at 70 °C for 5 min. The reaction was quenched by the addition of H2O (30 mL) and CHCl3 (30 mL) was subsequently added. The layers were separated and the aqueous phase extracted with CHCl3 (3 x 30 mL). The combined organic extracts were dried (Na2SO4) and concentrated in vacuo. The crude product was purified by column chromatography on silica gel using a gradient of hexane/diethyl ether (0-10 % diethyl ether) as the eluent to give ethyl N-(4-nitrobenzyl)-5-fluoropyrrole-2-carboxylate 6 (25 mg, 15 %) as a pale yellow solid; Mp 52-54 °C. $R_f$ (3:1, hexane:Et2O) 0.26. IR (neat, cm$^{-1}$) 3217, 2932, 1751, 1667, 1523, 1344, 1256. $^1$H NMR (400 MHz, Chloroform-$d$) $\delta$ 8.21 – 8.12 (2 H, m, C3'H), 7.31 – 7.27 (2 H, m, C2'H), 6.93 (1 H, dd, $^4J_{HF}$ 6.2, $^3J_{HH}$ 4.2, C3H), 5.69 (1 H, dd, $^3J_{HH}$ 4.2, $^3J_{HF}$ 4.2, C4H), 5.59 (2 H, s, ArCH2), 4.21 (2 H, q, $^3J_{HH}$ 7.1, CH2CH3), 1.29 (3 H, t, $^3J_{HH}$ 7.1, CH2CH3). $^{19}$F NMR (376 MHz, Chloroform-$d$) $\delta$ -131.65 (1 F, dd, $^4J_{HF}$ 6.2, $^4J_{HF}$ 4.2). $^{13}$C NMR (176 MHz, Chloroform-$d$) $\delta$ 160.8 (d, $^4J_{CF}$ 2.1, C=O), 150.3 (d, $^1J_{CF}$ 268.7, CF), 147.5 (s, C4'), 144.7 (s, C1'), 127.7 (s, C2'), 124.1 (s, C3'), 117.0 (d, $^3J_{CF}$ 4.0, C3), 114.3 (s, C2), 88.3 (d, $^2J_{CF}$ 11.6, C4), 60.2 (s, CH2CH3), 46.2 (d, $^3J_{CF}$ 2.0, ArCH2), 14.5 (s, CH2CH3). HRMS (ESI) m/z calculated for [M+H]$^+$ C14H13FNO2 293.0938; found 293.0944.

4.4.4 5-Fluoropyrrole-2-carbonitrile (8)

A solution of pyrrole-2-carbonitrile 7 (0.90 g, 10 mmol) and Selectfluor$^\text{TM}$ (3.55 g, 10 mmol) in MeCN (25 mL) was heated with microwave irradiation at 70 °C for 5 min. The reaction was quenched by the addition of H2O (100 mL) and CHCl3 (50 mL) was subsequently added. The layers were separated and the aqueous phase extracted with CHCl3 (3 x 30 mL). The combined organic extracts were dried (MgSO4) and concentrated in vacuo. The crude product was purified by column chromatography on silica gel using a gradient of hexane/diethyl ether (0-10 % diethyl ether) as the eluent to give 5-fluoropyrrole-2-
carbonitrile 8 (0.33 g, 30 %) as a white solid; Mp 55-57 °C. R_f (3:1, hexane:Et_2O) 0.25. IR (neat, cm⁻¹) 3196, 3152, 2227, 1588, 1007. ¹H NMR (400 MHz, Chloroform-d) δ 8.67 (1 H, s, NH), 6.72 (1 H, ddd, ⁴J_HF 4.5, ³J_HH 4.3, ⁴J_HH 3.0, C3H), 5.64 (1 H, ddd, ³J_HH 4.1, ³J_HH 3.6, ⁴J_HH 2.7, C4H). ¹⁹F NMR (376 MHz, Chloroform-d) δ -128.90 (1 F, ddd, ⁴J_HF 4.5, ³J_HH 3.6, ⁴J_HH 2.5). ¹³C NMR (176 MHz, Chloroform-d) δ 148.7 (d, ¹J_CF 268.1, CF), 120.7 (d, ³J_CF 2.7, C3), 114.1 (s, CN), 92.8 (d, ³J_CF 5.2, C2), 89.3 (d, ²J_CF 11.0, C4). HRMS (ESI) m/z calculated for [M-H]⁻ C₅H₅FNO 221.0196; found 221.0196.

4.4.5 4-Bromo-5-fluoropyrrole-2-carboxaldehyde (14)

A solution of 4-bromopyrrole-2-carboxaldehyde 13 (1.04 g, 6 mmol) and Selectfluor™ (2.13 g, 6 mmol) in MeCN (25 mL) was heated with microwave irradiation at 70 °C for 7.5 min. The reaction was quenched by the addition of H₂O (50 mL) and CHCl₃ (50 mL) was subsequently added. The layers were separated and the aqueous phase extracted with CHCl₃ (3 x 30 mL). The combined organic extracts were dried (Na₂SO₄) and concentrated in vacuo. The crude product was purified by column chromatography on silica gel using a gradient of hexane/diethyl ether (0-20 % diethyl ether) as the eluent to give 4-bromo-5-fluoropyrrole-2-carboxaldehyde 14 (0.33 g, 29 %) as off white crystals. Mp 148-150 °C (with degradation). R_f (3:1, hexane:Et_2O) 0.20. IR (neat, cm⁻¹) 3115, 2950, 2783, 2676, 2553, 1627, 1576, 1409, 1143, 668. ¹H NMR (400 MHz, Acetone-d₆) δ 9.40 (1 H, d, ⁴J_HH 3.5, CHO), 7.05 (1 H, d, ⁴J_HF 4.5, C3H). ¹⁹F NMR (376 MHz, Acetone-d₆) δ -132.72 (1 F, m). ¹³C NMR (151 MHz, Acetone-d₆) δ 178.2 (d, ⁴J_CF 2.7, C=O), 149.3 (d, ¹J_CF 268.0, CF), 124.3 (s, C2), 120.9 (s, C3), 76.1 (d, ²J_CF 15.1, C4). HRMS (ESI) m/z calculated for [M+H]⁺ C₅H₅BrNOF 191.9460; found 191.9463.

Crystal data for 14: C₅H₅BrFNO, M = 191.99, orthorhombic, space group P bca, a = 7.1484(3), b = 8.5392(4), c = 19.5396(9) Å, U = 1192.73(9) Å³, F(000) = 736.0, Z = 8, D_c = 2.138 mg m⁻³, μ = 6.817 mm⁻¹ ( Mo-Kα, λ = 0.71073 Å), T = 120(1)K. 15683 reflections were collected on a Bruker D8 Venture diffractometer (Photon100 CMOS detector, IμS-microsource, focusing mirrors) yielding 1582 unique data (R_{merge} = 0.0669). The structure was solved by direct method and refined by full-matrix least squares on F² for all data using SHELXTL and OLEX2 software. All non-hydrogen atoms were refined with anisotropic displacement parameters, H-atoms were placed in calculated positions and refined in riding mode. Final wR₂(F²) = 0.0934 for all data (82 refined parameters), conventional R₁ (F) =
0.0399 for 1201 reflections with I ≥ 2σ, GOF = 1.111. Crystallographic data for the structure have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication CCDC-14449050.

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6. Notes and references

46. All ab initio computations were carried out with the Gaussian09 package. Geometries were optimized at the B3LYP/6-31G* level of theory. Frequency calculations were computed on these optimized geometries at B3LYP/6-31G* and showed no imaginary frequencies. Calculated NMR shifts at GIAO-B3LYP/6-31G* were obtained from the optimized geometries, with $^{19}$F chemical shifts converted to the CFCl$_3$ scale; $\delta$ ($^{19}$F) = 179.0 - 0.97$\sigma$ ($^{19}$F).