Flexible synthesis of polyfunctionalised 3-fluoropyrroles†

Thomas J. Cogswell,a Craig S. Donaldb and Rodolfo Marquez*a,c

An efficient and selective approach for the synthesis of polyfunctionalised 3-fluoropyrroles has been developed starting from commercial aldehydes. The methodology is concise, efficient and allows for the modular and systematic assembly of polysubstituted 3-fluoropyrroles. This synthesis provides an alternative and highly convergent strategy for the generation of these chemically and biologically important units.

Introduction

Polyfunctionalised pyrroles are an integral part of medicinal chemistry, forming the core unit of a number of biologically active compounds.1–4 Fluorinated polyfunctionalised pyrroles are particularly interesting due to their useful biological, metabolic, physical and pharmacokinetic properties. Key fluorinated pyrroles include compounds such as 1 and 2 which have been developed as anti-inflammatory and anti-hypertension agents respectively (Fig. 1).5,6

Thus, it is not surprising that a significant amount of interest has been devoted to the synthesis of fluorinated pyrroles in recent years.7–9 As such, new flexible and efficient methods for their syntheses are desired.

Fluorinated α,β-unsaturated lactams were first synthesised via a ring-closing metathesis approach by Haufe and co-workers.10 The work was extended by the groups of Rutjes and Marquez to produce a number of novel fluorinated compounds (Scheme 1). To date, most work has been centred on the synthesis of 5 and 6-membered lactams with various degrees of functionalisation.11,12 We feel fluorinated α,β-unsaturated γ-lactams would be the ideal building block to provide access to polyfunctionalised fluorinated pyrroles.

Herein, we would like to report a quick, flexible and modular synthesis of polyfunctionalised fluorinated pyrroles. The methodology allows for the systematic introduction of substituents to produce novel polyfunctionalised fluorinated building blocks (Scheme 1).

Results and discussion

Our initial approach to the synthesis of the pyrrole core began with the condensation of benzaldehyde 3 with t-butyldimethylsilylamine to generate the corresponding imine, which upon vinylamination with vinylmagnesium bromide afforded the desired allylic amine 4 in excellent yield.13 Reductive amination of amine 4...
with p-anisaldehyde then produced the PMB protected amine 5 in high yield (Scheme 2).

Coupling of amine 5 with 2-fluoroacrylic acid 6 then proceeded to produce the desired amide unit 7 in reasonable yield. Subsequent treatment of diene 7 with Grubbs 2nd gen. catalyst then afforded the expected α,β-unsaturated lactam 8 in good yield.12

Rewardingly, alkylation of fluorolactam 8 with methyl-lithium proceeded cleanly to generate the desired pyrrole unit 9 in excellent yield (Scheme 3).14 Mechanistically, we believe that this aromatisation process takes place through hemiaminal formation followed by elimination of water and double bond isomerisation.15

The alkylation-aromatisation methodology was then expanded by including an array of nucleophiles so as to allow for the selective introduction of substituents at the C2 position of the C3 fluorinated-pyrrole ring. Thus, a collection of organometallic reagents including DIBAL-H, n-butyllithium, phenyl-lithium and allylmagnesium bromide were used to generate the desired substituted pyroles 10–13 in high yields

<table>
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<tr>
<th>RM</th>
<th>Yield</th>
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<tr>
<td>DIBAL-H</td>
<td>78%</td>
</tr>
<tr>
<td>PhLi</td>
<td>93%</td>
</tr>
<tr>
<td>nBuLi</td>
<td>78%</td>
</tr>
<tr>
<td>AllylMgBr</td>
<td>75%</td>
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Table 1 Introduction of different nucleophiles (RM) in the synthesis of tetrasubstituted pyroles (9–13)

- Having demonstrated the ability to incorporate substituents at the pyrrole C2 position through an alkylation-aromatisation process, it was decided to explore the ability of our methodology to incorporate substituents in the other pyrrole positions.
- Thus, it was decided to showcase the methodology by generating a number of C3 fluorinated pyrrole analogues with different N-substituents. Synthetically, the generation of the new analogues was envisioned as originating through the incorporation of different aldehyde units during the reductive amination step.

Following this approach, different aromatic substitution patterns were initially explored with the benzyl and 4-bromo-benzyl derivatives 14a and 14b being cleanly converted to the RCM precursors 15a and 15b in high yields (Table 2).

<table>
<thead>
<tr>
<th>R</th>
<th>Yield</th>
<th>Yield</th>
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<tbody>
<tr>
<td>Ph</td>
<td>74%</td>
<td>14a</td>
</tr>
<tr>
<td>Br</td>
<td>81%</td>
<td>14b</td>
</tr>
<tr>
<td>Me</td>
<td>82%</td>
<td>14c</td>
</tr>
<tr>
<td>N</td>
<td>71%</td>
<td>14d</td>
</tr>
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</table>

Table 2 Synthesis of fluorinated diene-amides 15a–d

The non-aromatic derivative 15c, bearing a cyclohexylmethyl group, worked well with yields upwards of 80% for both steps. N-Methylpyrrole-2-carboxaldehyde was also cleanly incorporated, yielding the desired diene 15d in good yield over the sequence.

Ring-closing metathesis was then successfully carried out in all cases, with isolated yields higher than 80%.17
Gratifyingly, treatment of pyrrolidone compounds 16a–d with methyllithium under our alkylation-aromatisation methodology afforded the desired N-substituted pyrrole derivatives 17a–d in excellent isolated yields (Table 3). At this point, it was decided to now focus on exploring the nature and effect of the starting aldehyde on our pyrrole forming sequence. By changing the identity of the starting aldehyde, a range of functional groups could be efficiently installed at the C5 position (Table 4). Electron donating and withdrawing aromatic analogues were investigated, resulting in good yields of the allylic amine intermediates 18a–c. Aliphatic aldehydes could also be converted to the corresponding primary amines 18d–e in reasonable yields. Treatment of the crude allylic amines 18a–e under reductive amination conditions afforded the secondary amines 19a–e which upon coupling with 2-fluoroacrylic acid 6 generated the desired fluorinated amides 20a–20e in good yields.

Ring-closing metathesis in all cases proceeded in high yields (Table 5). However, examples with electron withdrawing substituents required extended reaction times and higher catalyst loadings (15 mol%) to achieve high yields. Gratifyingly, treatment of all the pyrrolidone intermediates (21a–21e) under the methyllithium promoted alkylation-aromatisation conditions yielded the desired fluorinated tetrasubstituted pyrroles 22a–e in good to excellent yield.

### Conclusion

In conclusion, we have developed an efficient and selective approach for the synthesis of polyfunctionalised 3-fluorinated pyrroles. The methodology is concise and allows for the modular synthesis of chemically and biologically important units.

### Experimental

All reactions were performed in oven-dried glassware under an inert argon atmosphere unless otherwise stated. Tetrahydrofuran (THF), diethyl ether, toluene and dichloromethane (DCM) were purified through a solvent purification system. Petroleum ether refers to the fraction boiling between 40–60 °C. All reagents were used as received, unless otherwise stated. Solvents were evaporated under reduced pressure at 40 °C unless otherwise stated. IR spectra were recorded as thin films on NaCl plates using a Fourier Transform spectrometer. Only significant absorptions (\(\nu_{\max}\)) are reported in wavenumbers (cm\(^{-1}\)). Proton magnetic resonance spectra (\(^1\)H NMR) were recorded at either 400 or 500 MHz. Fluorine magnetic
resonance spectra (19F NMR) were recorded at either 377 or 470 MHz. Carbon magnetic resonance spectra (13C NMR) were recorded at either 100 or 125 MHz. Chemical shifts (δ) are reported in parts per million (ppm) and are referenced to the residual solvent peak. The order of citation in parentheses is (1) number of equivalent nuclei (by integration), (2) multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, quint = quintet, sext = sextet, sept = septet, m = multiplet, b = broad), (3) and coupling constant (J) quoted in Hertz to the nearest 0.1 Hz. High resolution mass spectra were obtained by electrospray (EI) chemical ionisation (CI) mass spectrometry operating at a resolution of 15 000 full widths at half height. Flash chromatography was performed using silica gel (40–63 micron) as the stationary phase. TLC was performed on aluminium sheets pre-coated with silica (Silica Gel 60 F254) unless otherwise stated. The plates were visualised by the quenching of UV fluorescence (λmax 254 nm) and/or by staining with either anisaldehyde, potassium permanganate, iodine or cerium ammonium molybdate followed by heating.

General procedure I
A solution of the diene (1 eq.) in toluene (0.005 g ml−1) and was heated to 100 °C. Grubbs 2nd generation catalyst was added in portions and the reaction was stirred until completion as indicated by TLC analysis. The reaction was cooled down to room temperature, the solvent was removed under reduced pressure and the crude material was purified by flash column chromatography.

General procedure II
α,β-Unsaturated lactam (1 eq.) was dissolved in diethyl ether (5 mL) and cooled to 0 °C. Methylthionium (1 eq.) was added dropwise and the mixture was stirred for 1 h. Following this time, the reaction was quenched with H2O (10 mL), extracted with diethyl ether (3 × 10 mL), dried (Na2SO4) and evaporated in vacuo. The crude residue was purified by flash column chromatography.

3-Fluoro-1-[(4'-methoxyphenyl)methyl]-2-methyl-5-phenyl-1H-pyrrole, 9. α,β-Unsaturated lactam 8 (36 mg, 0.12 mmol) was reacted with methyl lithium (83 µL, 0.13 mmol, 1.6 M in diethyl ether) following General procedure II. The product was purified by flash column chromatography (0–2.5% diethyl ether in petroleum ether) to yield the pyrrole 9 (30 mg, 0.1 mmol, 86%) as a white solid. 1H NMR (CDCl3, 400 MHz) δ: 7.35–7.13 (5H, m), 6.78–6.76 (4H, m), 5.96 (1H, s), 4.93 (2H, s), 3.72 (3H, s), 1.98 (3H, d, JF = 1.6 Hz). 19F NMR (CDCl3, 470 MHz) δ: −169.4. 13C NMR (CDCl3, 125 MHz) δ: 158.7, 149.2 (d, JF = 235.6 Hz), 132.9, 130.6, 130.1 (d, JF = 6.9 Hz), 128.8 (2C), 128.5 (2C), 127.1, 126.7 (2C), 114.2 (2C), 112.5 (d, JF = 24.3 Hz), 96.4 (d, JF = 16.4 Hz), 55.3, 47.2, 8.2. m/z [EI (+ve)] 295.2 [M]+, HRMS found [M]+ 295.1373. C19H18FNO requires 295.1372. IR (thin film) νmax = 2928, 2359, 1614, 1599, 1512, 1532, 1249, 1174 cm−1. m.p. 73–75 °C.

4-Fluoro-1-[(4'-methoxyphenyl)methyl]-2-phenyl-1H-pyrrole, 10. α,β-Unsaturated lactam 8 (40 mg, 0.13 mmol) was dissolved in CH2Cl2 (4 mL) and cooled to −78 °C. Diisobutylaluminium hydride (0.41 mL, 0.41 mmol, 1 M in hexanes) was added dropwise and the mixture was stirred for 16 h. Following this time, the reaction was quenched with H2O (10 mL), extracted with diethyl ether (3 × 10 mL), dried (Na2SO4) and evaporated in vacuo. The crude residue was purified by flash column chromatography (0–2.5% diethyl ether in petroleum ether) to yield the pyrrole 10 (30 mg, 0.11 mmol, 85%) as a yellow oil. 1H NMR (CDCl3, 400 MHz) δ: 7.40–7.32 (5H, m), 6.98 (2H, d, JH = 8.7 Hz), 6.86 (2H, d, JH = 8.7 Hz), 6.46 (1H, dd, JF = 3.2 Hz, JH = 2.0 Hz), 6.04 (1H, d, JF = 2.4 Hz), 4.99 (2H, s), 3.82 (3H, s). 19F NMR (CDCl3, 470 MHz) δ: −165.4. 13C NMR (CDCl3, 125 MHz) δ: 159.0, 152.0 (d, JF = 239.1 Hz), 132.5 (d, JF = 1.6 Hz), 131.8 (d, JF = 6.4 Hz), 130.2, 129.0 (2C), 128.5 (2C), 127.9 (2C), 127.5, 114.1 (2C) 105.5 (d, JF = 27.3 Hz), 97.1 (d, JF = 16.4 Hz), 55.3, 50.2. m/z [EI (+ve)] 281.1 [M]+, HRMS found [M]+ 281.1215. C18H16FNO requires 281.1216. IR (thin film) νmax = 2956, 2837, 1701, 1612, 1512, 1247, 1176 cm−1.

3-Fluoro-1-[(4'-methoxyphenyl)methyl]-2,5-diphenyl-1H-pyrrole, 11. α,β-Unsaturated lactam 8 (45 mg, 0.15 mmol) was dissolved in diethyl ether (5 mL) and cooled to 0 °C. Phenylthionium (87 µL, 0.16 mmol, 1.9 M in di-n-butyl ether) was added dropwise and the mixture was stirred for 1 h. Following this time, the reaction was quenched with H2O (10 mL), extracted with diethyl ether (3 × 10 mL), dried (Na2SO4) and evaporated in vacuo. The crude residue was purified by flash column chromatography (0–2.5% diethyl ether in petroleum ether) to yield the pyrrole 11 (50 mg, 0.14 mmol, 93%) as a white solid. 1H NMR (CDCl3, 400 MHz) δ: 7.39–7.36 (7H, m), 7.35–7.37 (3H, m), 6.66 (2H, d, JF = 8.8 Hz), 6.55 (2H, d, JF = 8.8 Hz), 6.17 (1H, br s), 5.10 (2H, s), 3.74 (3H, s). 19F NMR (CDCl3, 470 MHz) δ: −163.5. 13C NMR (CDCl3, 125 MHz) δ: 156.0 (d, JF = 45.8 Hz), 151.9, 136.0 (d, JF = 279.6 Hz), 133.9 (d, JF = 2.1 Hz), 129.8 (2C), 129.3 (2C), 129.2, 128.6, 127.6 (2C), 118.4 (d, JF = 4.4 Hz), 114.2 (2C), 59.1 (d, JF = 5.7 Hz), 55.3, 43.5. m/z [EI (+ve)] 297.2 [M]+, HRMS found [M]+ 297.1164, C18H14FNO requires 297.1165. IR (thin film) νmax = 2355, 1710, 1666, 1514, 1247 cm−1.
The reaction was quenched with H2O (10 mL), extracted with diethyl ether (3 × 10 mL), dried (Na2SO4) and evaporated in vacuo. The crude residue was purified by flash column chromatography (0–5% EtOAc in petroleum ether) to yield the pyrrole 12 (34 mg, 0.10 mmol, 78%) as a white solid.

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1-Benzyl-3-fluoro-2-methyl-5-phenyl-1H-pyrole, 17a. α,β-Unsaturated lactam 16a (33 mg, 0.13 mmol) was reacted with methyllithium (100 µL, 0.14 mmol, 1.4 M in diethyl ether) following General procedure II. The product was purified by flash column chromatography (0.2-5% diethyl ether in petroleum ether) to yield the pyrrole 17a (29 mg, 0.11 mmol, 86%) as a white solid. 1H NMR (CDCl3, 400 MHz) δ: 7.30-7.09 (8H, m), 6.87-6.84 (2H, m), 5.98 (1H, s), 4.99 (2H, s), 1.97 (3H, d, J = 1.6 Hz). 13C NMR (CDCl3, 125 MHz) δ: -169.3. 19F NMR (CDCl3, 470 MHz) δ: -196.5. 15N NMR (CDCl3, 125 MHz) δ: 149.2 (d, J = 235.6 Hz), 136.8, 132.6, 130.2 (d, J = 3.3 Hz), 128.8 (2C), 128.8 (2C), 128.5 (2C), 127.2, 127.1, 125.6 (2C), 112.6 (d, J = 24.4 Hz), 96.5 (d, J = 16.5 Hz), 47.8, 8.2. m/z [EI (+ve)] 265.1 [M]+. HRMS found [M]+ 265.1269. C18H14FN requires 265.1267. IR (thin film) νmax = 2924, 1622, 1594, 1452, 1318 cm⁻¹. m.p. 92-94 °C.

1-(1-Benzyl-3-fluoro-5-methyl-1H-pyrrole)-2,5-dihydro-1H-pyrrolo-2-one, 21a. Dialkene 20a (100 mg, 0.31 mmol) was treated with 7.5 mol% Grubbs 2nd generation catalyst as described in General procedure I. The crude product was purified by flash column chromatography (0-10% EtOAc in petroleum ether) to yield the desired α,β-un saturated lactam 21a (70 mg, 0.22 mmol, 71%) as a white solid. 1H NMR (CDCl3, 400 MHz) δ: 7.35-7.29 (3H, m), 7.14-7.13 (2H, m), 7.03 (2H, d, J = 8.7 Hz), 6.93 (2H, d, J = 8.7 Hz), 6.25 (1H, d, J = 1.6 Hz), 5.15 (1H, d, J = 15.0 Hz), 4.75 (1H, dd, J = 5.8 Hz, J = 21.2 Hz), 3.85 (3H, s), 3.61 (1H, d, J = 15.0 Hz). 19F NMR (CDCl3, 470 MHz) δ: -138.7. 13C NMR (CDCl3, 125 MHz) δ: 162.9 (d, J = 31.3 Hz), 160.3, 152.3 (d, J = 279.3 Hz), 136.7, 128.9 (2C), 128.8 (2C), 128.4 (2C), 127.8, 125.4 (d, J = 2.1 Hz), 118.5 (d, J = 4.0 Hz), 114.6 (2C), 58.7 (d, J = 5.8 Hz, 55.4, 43.9. m/z [EI (+ve)] 297.1 [M]+, HRMS found [M]+ 297.1163. IR (thin film) νmax = 2933, 1707, 1666, 1512, 1247, 1174, 1030 cm⁻¹. m.p. 101–103 °C.

1-Benzyl-3-fluoro-5-(4′-trifluoromethyl)phenyl-2,5-dihydro-1H-pyrrolo-2-one, 21b. Dialkene 20b (80 mg, 0.22 mmol) was treated with 15 mol% Grubbs 2nd generation catalyst as described in General procedure I. The crude product was purified by flash column chromatography (0-10% EtOAc in petroleum ether) to yield the desired α,β-un saturated lactam 21b (70 mg, 0.20 mmol, 88%) as a pale yellow oil. 1H NMR (CDCl3, 400 MHz) δ: 7.58 (2H, d, J = 8.1 Hz), 7.26-7.21 (3H, m), 7.16 (2H, d, J = 8.1 Hz), 7.03-7.01 (2H, m), 6.19 (1H, d, J = 1.2 Hz), 5.09 (1H, d, J = 15.0 Hz), 4.77 (1H, dd, J = 4.8 Hz, J = 2.0 Hz), 3.57 (1H, d, J = 15.0 Hz), 2.17 (3H, d, J = 1.6 Hz). 13C NMR (CDCl3, 125 MHz) δ: -168.8. 15N NMR (CDCl3, 125 MHz) δ: 149.3 (d, J = 236.2 Hz), 137.7, 132.6, 131.9 (2C), 130.2 (d, J = 6.8 Hz), 128.8 (2C), 128.6 (2C), 127.3 (2C), 127.1, 121.0, 112.4 (d, J = 24.4 Hz), 96.8 (d, J = 16.5 Hz), 47.2, 8.1 (d, J = 2.1 Hz). m/z [EI (+ve)] 343.1 [M]+, HRMS found [M]+ 343.0367. C18H12F4NO requires 343.0372. IR (thin film) νmax = 2924, 1680, 1599, 1489, 1363, 1072, 1010 cm⁻¹. m.p. 98–100 °C.
(2H, d, $J_H = 8.4$ Hz), 7.36–7.30 (3H, m), 7.13–7.10 (2H, m), 7.00 (2H, d, $J_H = 8.4$ Hz), 6.26 (1H, $d_J = 1.6$ Hz), 5.17 (1H, $d_J = 15.0$ Hz), 4.76 (1H, $d_J = 5.8$ Hz, $J_H = 2.2$ Hz), 3.62 (1H, $d_J = 15.0$ Hz).$^{19}$F NMR (CDCl$_3$, 470 MHz) $\delta$: $-137.7$. $^{13}$C NMR (CDCl$_3$, 125 MHz) $\delta$: 162.9 (2H, $d_J = 31.2$ Hz), 152.5 (2H, $d_J = 31.2$ Hz), 136.3, 132.9 (2H, $d_J = 123.5$ Hz), 129.2 (2C), 128.9 (2C), 128.4 (2C), 128.0, 123.2, 118.1 (d, $J_F = 4.7$ Hz), 58.6 (d, $d_J = 5.7$ Hz), 44.2. m/z [EI (+ve)] 345.1 $M^+$. HRMS found $M^+ 345.0165$. IR (thin film) $\nu_{max} = 3404, 2926, 1616$ cm$^{-1}$. m.p. 74–76 °C.

1-Benzyl-3-fluoro-2-methyl-1-(4′-trifluoromethylphenyl)-1H-pyrrole, 22b. $\alpha,\beta$-Unsaturated lactam 21b (22 mg, 0.06 mmol) was reacted with methyllithium (51 μL, 0.07 mmol, 1.4 M in diethyl ether) following General procedure II. The product was purified by flash column chromatography (0–2.5% diethyl ether in petroleum ether) to yield the pyrrole 22b (16 mg, 0.05 mmol, 73%) as a yellow solid. $^1$H NMR (CDCl$_3$, 400 MHz) $\delta$: 7.46 (2H, d, $J_H = 8.7$ Hz), 7.32–7.17 (5H, m), 6.87–6.85 (2H, m), 6.05 (1H, s), 5.01 (2H, s), 2.00 (3H, $d_J = 1.6$ Hz).$^{19}$F NMR (CDCl$_3$, 470 MHz) $\delta$: $-62.5$, $-168.5$. $^{13}$C NMR (CDCl$_3$, 125 MHz) $\delta$: 149.3 (d, $d_J = 236.4$ Hz), 138.1, 136.3, 129.0, 128.9 (2C), 128.6 (d, $d_J = 7.2$ Hz), 128.5 (2C), 127.4, 126.0 (d, $d_J = 3.8$ Hz), 125.5, 125.4 (2C), 114.1 (d, $d_J = 24.4$ Hz), 96.7 (d, $d_J = 16.5$ Hz), 47.9, 8.2 (d, $d_J = 2.0$ Hz), m/z [EI (+ve)] 333.2 $M^+$. HRMS found $M^+ 333.139$, C$_{19}$H$_{18}$F$_4$N requires 333.141. IR (thin film) $\nu_{max} = 2926, 1606, 1325, 1166, 1124$ cm$^{-1}$. m.p. 75–77 °C.

1-Benzyl-5-(4′-bromophenyl)-3-fluoro-2-methyl-1H-pyrrole, 22c. $\alpha,\beta$-Unsaturated lactam 21c (43 mg, 0.13 mmol) was reacted with methyllithium (98 μL, 0.14 mmol, 1.4 M in diethyl ether) following General procedure II. The product was purified by flash column chromatography (0–2.5% diethyl ether in petroleum ether) to yield the pyrrole 22c (34 mg, 0.10 mmol, 78%) as a brown solid. $^1$H NMR (CDCl$_3$, 400 MHz) $\delta$: 7.37 (2H, d, $d_J = 8.6$ Hz), 7.29–7.16 (3H, m), 7.04 (2H, $d_J = 8.6$ Hz), 6.85–6.83 (2H, m), 5.97 (1H, s), 4.96 (2H, s), 1.98 (3H, $d_J = 1.6$ Hz).$^{19}$F NMR (CDCl$_3$, 470 MHz) $\delta$: $-168.9$. $^{13}$C NMR (CDCl$_3$, 125 MHz) $\delta$: 149.2 (d, $d_J = 236.1$ Hz), 138.3, 131.7 (d, $d_J = 1.8$ Hz), 131.6 (2C), 130.2 (2C), 128.9 (2C), 128.8, 127.3, 125.5 (2C), 121.2, 113.3 (d, $d_J = 24.3$ Hz), 96.9 (d, $d_J = 16.5$ Hz), 47.7, 8.2 (d, $d_J = 2.0$ Hz), m/z [EI (+ve)] 343.1 $M^+$. HRMS found $M^+ 343.0368$. C$_{19}$H$_{18}$BrF$_4$N requires 343.0372. IR (thin film) $\nu_{max} = 2922, 1683, 1612, 1471, 1352$ cm$^{-1}$. m.p. 98–100 °C.

1-Benzyl-5-(2′-phenylethyl)-2,5-dihydro-1H-pyrrole-2-one, 21b. Dialkene 20d (100 mg, 0.34 mmol) was treated with 7.5 mol% Grubbs 2nd generation catalyst as described in General procedure I. The crude product was purified by flash column chromatography (0–5% EtOAc in petroleum ether) to yield the desired $\alpha,\beta$-unsaturated lactam 21d (90 mg, 0.32 mmol, 95%) as a white solid. $^1$H NMR (CDCl$_3$, 400 MHz) $\delta$: 7.28–7.16 (5H, m), 6.12 (1H, $d_J = 2.1$ Hz), 5.03 (1H, $d_J = 15.2$ Hz), 4.01 (1H, $d_J = 15.2$ Hz), 3.72–3.70 (1H, m), 1.83–1.69 (2H, m), 1.66–1.54 (3H, m), 1.31–1.18 (2H, m), 1.05–0.97 (3H, m), 0.87–0.77 (1H, m). $^{19}$F NMR (CDCl$_3$, 470 MHz) $\delta$: $-136.9$. $^{13}$C NMR (CDCl$_3$, 125 MHz) $\delta$: 163.4 (d, $d_J = 31.5$ Hz), 152.8 (d, $d_J = 277.4$ Hz), 136.7, 128.3 (2C), 128.0 (2C), 127.7, 115.6 (d, $d_J = 4.2$ Hz), 60.1 (d, $d_J = 4.4$ Hz), 44.2, 37.8, 30.1, 36.5, 26.3, 25.7, 25.5. m/z [EI (+ve)] 273.2 $M^+$. HRMS found $M^+ 273.1527$, C$_{17}$H$_{13}$BrFNO requires 273.1529. IR (thin film) $\nu_{max} = 3030, 1708, 1489, 1408, 1220, 1078, 1010$ cm$^{-1}$.
1-Benzyl-3-fluoro-2-methyl-5-(2′-phenylethyl)-1H-pyrrole, 22e. α,β-Unsaturated lactam 21e (34 mg, 0.11 mmol) was reacted with methyllithium (91 µL, 0.12 mmol, 1.4 M in diethyl ether) following General procedure II. The product was purified by flash column chromatography (0–2.5% diethyl ether in petroleum ether) to yield the pyrrole 22e (24 mg, 0.08 mmol, 74%) as a yellow oil. 1H NMR (CDCl3, 400 MHz) δ: 7.24–7.08 (6H, m), 7.04–7.00 (2H, m), 6.80–6.76 (2H, m), 5.71 (1H, s), 4.83 (2H, s), 2.76–2.71 (2H, m), 2.64–2.60 (2H, m), 1.97 (3H, br s). 13F NMR (CDCl3, 470 MHz) δ: –170.5. 13C NMR (CDCl3, 125 MHz) δ: 148.3 (d, JF = 234.1 Hz), 141.4, 138.2, 128.8 (2C), 128.4 (2C), 127.9 (d, JF = 6.3 Hz), 127.2, 126.1, 125.5 (2C), 110.0 (d, JF = 24.6 Hz), 94.1 (d, JF = 16.8 Hz), 46.5, 35.4, 28.4, 7.9 (d, JF = 2.1 Hz). m/z [EI (+ve)] 293.1 [M]+, HRMS found [M]+ 293.1581, C20H20FN requires 293.1580. IR (thin film) νmax = 2923, 1614, 1496, 1454, 1417, 1363, 1114 cm⁻¹.

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References