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Flexible synthesis of polyfunctionalised 3-fluoropyrroles†

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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).

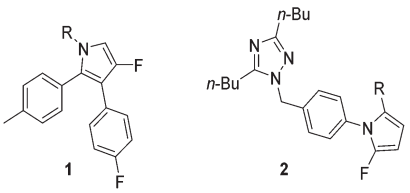
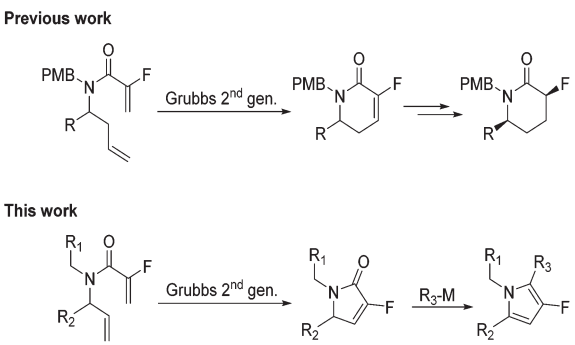


Fig. 1 Biologically active fluorinated pyrrole examples. Pyrrole **1** has anti-inflammatory activity, while pyrrole **2** is used to alleviate hypertension.[1,2]



Scheme 1 Previous work to generate fluorinated δ-lactams *via* RCM approach.

Results and discussion

Our initial approach to the synthesis of the pyrrole core began with the condensation of benzaldehyde **3** with *t*-butylsulfinamide to generate the corresponding imine, which upon vinylation with vinylmagnesium bromide afforded the desired allylic amine **4** in excellent yield.[13] Reductive amination of amine **4**

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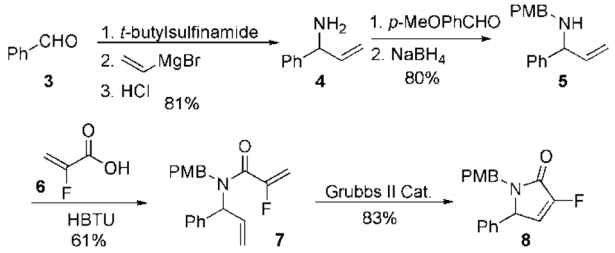
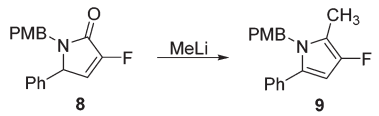


Scheme 2 Synthesis of fluorinated α,β-unsaturated lactam **8**.



Scheme 3 Synthesis of fluorinated polysubstituted pyrrole **9**.

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 methyllithium proceeded cleanly to generate the desired pyrrole unit **9** in excellent yield (Scheme 3).[14,15] Mechanistically, we believe that this aromatisation process takes place through hemiaminal formation followed by elimination of water and double bond isomerisation.[15,16]

The alkylation–aromatisation methodology was then expanded by including an array of nucleophiles 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, phenyllithium and allylmagnesium bromide were used to generate the desired substituted pyrroles **10–13** in high yields (Table 1).[14–16]

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-bromobenzyl derivatives **14a** and **14b** being cleanly converted to the RCM precursors **15a** and **15b** in high yields (Table 2).

Table 1 Introduction of different nucleophiles (RM) in the synthesis of tetrasubstituted pyrroles (**9–13**)

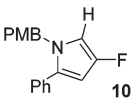
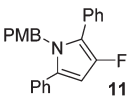
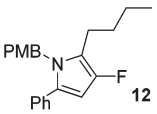
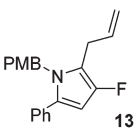
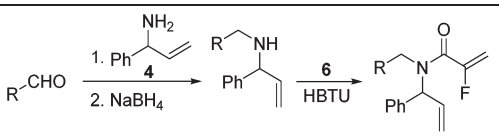
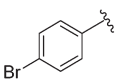
RM	Yield	
DIBAL-H	78%	 **10**
PhLi	93%	 **11**
*n*BuLi	78%	 **12**
AllylMgBr	75%	 **13**

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

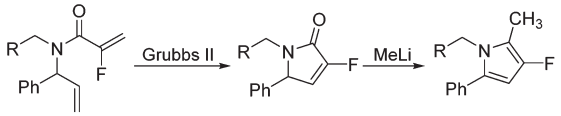


R	Yield		Yield	
	74%	**14a**	74%	**15a**
	81%	**14b**	71%	**15b**
	82%	**14c**	86%	**15c**
	71%	**14d**	58%	**15d**

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]

Table 3 Synthesis of fluorinated pyrroles **17a–d**



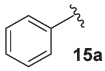
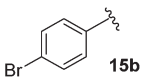
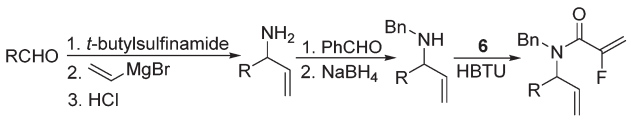
R	Yield		Yield	
 **15a**	98%	**16a**	86%	**17a**
 **15b**	96%	**16b**	83%	**17b**
 **15c**	92%	**16c**	84%	**17c**
 **15d**	81%	**16d**	75%	**17d**

Table 4 Synthesis of fluorinated amides **20a–e**



R	Yield		Yield		Yield	
4-$MeOC_6H_4$	71%	**18a**	79%	**19a**	60%	**20a**
4-$CF_3C_6H_4$	61%	**18b**	80%	**19b**	45%	**20b**
4-BrC_6H_4	75%	**18c**	84%	**19c**	62%	**20c**
Cyclohexyl	50%	**18d**	70%	**19d**	76%	**20d**
$PhCH_2CH_2$	58%	**18e**	88%	**19e**	75%	**20e**

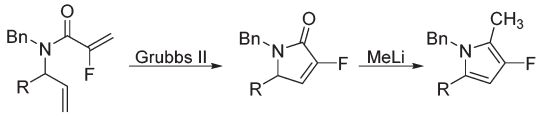
Gratifyingly, treatment of pyrrolidone compounds **16a–d** with methyllithium under our alkylation–aromatisation methodology afforded the desired *N*-substituted pyrrole derivatives **17a–d** in excellent isolated yields (Table 3).

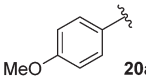
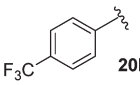
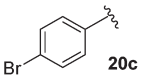
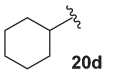
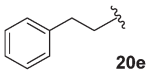
At this point, it was decided to now focus on exploring the nature and effect of the starting aldehyde on our pyrrole forming sequence. By changing the identity of the starting aldehyde, a range of functional groups could be efficiently installed at the C5 position (Table 4).

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.[18] 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

Table 5 Synthesis of fluorinated pyrroles **22a–d**



R	Yield		Yield	
 **20a**	71%	**21a**	88%	**22a**
 **20b**	88%	**21b**	73%	**22b**
 **20c**	94%	**21c**	78%	**22c**
 **20d**	95%	**21d**	92%	**22d**
 **20e**	96%	**21e**	74%	**22e**

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 (ν^{max}) are reported in wavenumbers (cm^{-1}). Proton magnetic resonance spectra (^1H NMR) were recorded at either 400 or 500 MHz. Fluorine magnetic

resonance spectra (^{19}F NMR) were recorded at either 377 or 470 MHz. Carbon magnetic resonance spectra (^{13}C 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 spectrometery 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 (λ_{max} 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. Methyllithium (1.1 eq.) was added dropwise and the mixture was stirred for 1 h. Following this time, the reaction was quenched with H_2O (10 mL), extracted with diethyl ether (3 × 10 mL), dried (Na_2SO_4) and evaporated *in vacuo*. The crude residue was purified by flash column chromatography.

3-Fluoro-1-[(4′-methoxyphenyl)methyl]-5-phenyl-2,5-dihydro-1*H*-pyrrol-2-one, 8. Dialkene **7** (270 mg, 0.84 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 (0–15% EtOAc in petroleum ether) to yield the desired α,β-unsaturated lactam **8** (210 mg, 0.71 mmol, 83%) as a pale yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.50–7.33 (3H, m), 7.20–7.09 (2H, m), 7.06 (2H, J_H = 8.6 Hz), 6.85 (2H, d, J_H = 8.6 Hz), 6.26 (1H, d, J_H = 1.6 Hz), 5.12 (1H, d, J_H = 14.8 Hz), 4.78 (1H, dd, J_F = 6.0 Hz, J_H = 2.4 Hz), 3.82 (3H, m), 3.58 (1H, J_H = 14.8 Hz). ^{19}F NMR ($CDCl_3$, 470 MHz) δ: −138.5. ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 163.0 (d, J_F = 31.2 Hz), 159.2, 152.3 (d, J_F = 279.6 Hz), 133.9 (d, J_F = 2.1 Hz), 129.8 (2C), 129.3 (2C), 129.2, 128.6, 127.6 (2C), 118.4 (d, J_F = 4.4 Hz), 114.2 (2C), 59.1 (d, J_F = 5.7 Hz), 55.3, 43.5. *m*/*z* [EI (+ve)] 297.2 [M]$^+$, HRMS found [M]$^+$ 297.1164, $C_{18}H_{16}FNO_2$ requires 297.1165. IR (thin film) ν_{max} = 2355, 1710, 1666, 1514, 1247 cm^{-1}.

3-Fluoro-1-[(4′-methoxyphenyl)methyl]-2-methyl-5-phenyl-1*H*-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. ^{1}H NMR ($CDCl_3$, 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, J_F = 1.6 Hz). ^{19}F NMR ($CDCl_3$, 470 MHz) δ: −169.4. ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 158.7, 149.2 (d, J_F = 235.6 Hz), 132.9, 130.6, 130.1 (d, J_F = 6.9 Hz), 128.8 (2C), 128.5 (2C), 127.1, 126.7 (2C), 114.2 (2C), 112.5 (d, J_F = 24.3 Hz), 96.4 (d, J_F = 16.4 Hz), 55.3, 47.2, 8.2. *m*/*z* [EI (+ve)] 295.2 [M]$^+$, HRMS found [M]$^+$ 295.1373 $C_{19}H_{18}FNO$ requires 295.1372. IR (thin film) ν_{max} = 2928, 2359, 1614, 1599, 1512, 1352, 1249, 1174 cm^{-1}. m.p. 73–75 °C.

4-Fluoro-1-[(4′-methoxyphenyl)methyl]-2-phenyl-1*H*-pyrrole, 10. α,β-Unsaturated lactam **8** (40 mg, 0.13 mmol) was dissolved in CH_2Cl_2 (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 H_2O (10 mL), extracted with diethyl ether (3 × 10 mL), dried (Na_2SO_4) and evaporated *in vacuo*. The crude residue was purified be 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. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.40–7.32 (5H, m), 6.98 (2H, d, J_H = 8.7 Hz), 6.86 (2H, d, J_H = 8.7 Hz), 6.46 (1H, dd, J_F = 3.2 Hz, J_H = 2.0 Hz), 6.04 (1H, d, J_F = 2.4 Hz), 4.99 (2H, s), 3.82 (3H, s). ^{19}F NMR ($CDCl_3$, 470 MHz) δ: −165.4. ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 159.0, 152.0 (d, J_F = 239.1 Hz), 132.5 (d, J_F = 1.6 Hz), 131.8 (d, J_F = 6.4 Hz), 130.2, 129.0 (2C), 128.5 (2C), 127.9 (2C), 127.5, 114.1 (2C) 105.5 (d, J_F = 27.3 Hz), 97.1 (d, J_F = 16.4 Hz), 55.3, 50.2. *m*/*z* [EI (+ve)] 281.1 [M]$^+$, HRMS found [M]$^+$ 281.1215, $C_{18}H_{16}FNO$ requires 281.1216. IR (thin film) ν_{max} = 2956, 2837, 1701, 1612, 1512, 1247, 1176 cm^{-1}.

3-Fluoro-1-[(4′-methoxyphenyl)methyl]-2,5-diphenyl-1*H*-pyrrole, 11. α,β-Unsaturated lactam **8** (45 mg, 0.15 mmol) was dissolved in diethyl ether (5 mL) and cooled to 0 °C. Phenyllithium (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 H_2O (10 mL), extracted with diethyl ether (3 × 10 mL), dried (Na_2SO_4) and evaporated *in vacuo*. The crude residue was purified be 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. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.39–7.36 (7H, m), 7.35–7.37 (3H, m), 6.66 (2H, d, J_H = 8.8 Hz), 6.55 (2H, d, J_H = 8.8 Hz), 6.17 (1H, br s), 5.10 (2H, s), 3.74 (3H, s). ^{19}F NMR ($CDCl_3$, 470 MHz) δ: −165.3. ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 158.5, 149.6 (d, J_F = 242.5 Hz), 133.0 (d, J_F = 7.1 Hz), 132.9 (d, J_F = 1.8 Hz), 130.8, 129.9 (d, J_F = 3.3 Hz), 129.5, 129.1 (2C), 128.5 (2C), 128.5 (2C), 127.5, 127.3 (2C), 127.2, 119.1 (d, J_F = 21.0 Hz), 113.7 (2C), 98.4 (d, J_F = 16.6 Hz), 55.2, 48.3. *m*/*z* [EI (+ve)] 357.0 [M]$^+$, HRMS found [M]$^+$ 357.1531, $C_{24}H_{20}FNO$ requires 357.1529. IR (thin film) ν_{max} = 3063,

2955, 2835, 1610, 1512, 1492, 1435, 1247, 1176 cm^{-1}. m.p. 84–86 °C.

2-Butyl-3-fluoro-1-[(4′-methoxyphenyl)methyl]-5-phenyl-1*H*-pyrrole, 12. α,β-Unsaturated lactam **8** (38 mg, 0.13 mmol) was dissolved in diethyl ether (5 mL) and cooled to 0 °C. *n*-Butyllithium (54 μL, 0.13 mmol, 2.5 M in hexanes) was added dropwise and the mixture was stirred for 1 h. Following this time, the reaction was quenched with H_2O (10 mL), extracted with diethyl ether (3 × 10 mL), dried (Na_2SO_4) 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 **12** (34 mg, 0.10 mmol, 78%) as a white solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.22–7.14 (5H, m), 6.74 (4H, m), 5.95 (1H, s), 4.94 (2H, s), 3.71 (3H, s), 2.37 (2H, t, J_H = 7.6 Hz), 1.43–1.34 (2H, m), 1.25–1.18 (2H, m), 0.78 (3H, t, J_H = 7.3 Hz). ^{19}F NMR ($CDCl_3$, 470 MHz) δ: −168.0. ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 158.7, 149.5 (d, J_F = 236.1 Hz), 133.0, 131.0, 130.0 (d, J_F = 7.0 Hz), 128.9 (2C), 128.4 (2C), 127.1, 126.7 (2C), 117.0 (d, J_F = 23.5 Hz), 114.1 (2C), 96.7 (d, J_F = 16.6 Hz), 55.3, 47.1, 31.3 (d, J_F = 2.0 Hz), 23.1 (d, J_F = 2.6 Hz), 22.4, 13.8. *m*/*z* [EI (+ve)] 337.2 $[M]^+$, HRMS found $[M]^+$ 337.1840, $C_{22}H_{24}FNO$ requires 337.1842. IR (thin film) ν_{max} = 2956, 2929, 2858, 1612, 1595, 1512, 1464, 1249 cm^{-1}. m.p. 32–34 °C.

3-Fluoro-1-[(4″-methoxyphenyl)methyl]-5-phenyl-2-(prop-2′-en-1′-yl)-1*H*-pyrrole, 13. α,β-Unsaturated lactam **8** (41 mg, 0.14 mmol) was dissolved in diethyl ether (5 mL) and cooled to 0 °C. Allylmagnesium bromide (0.21 mL, 0.21 mmol, 1 M in Et_2O) was added dropwise and the mixture was stirred for 1.5 h. Following this time, the reaction was quenched with H_2O (10 mL), extracted with diethyl ether (3 × 10 mL), dried (Na_2SO_4) and evaporated *in vacuo*. The crude residue was purified be flash column chromatography (0–2.5% diethyl ether in petroleum ether) to yield the pyrrole **13** (34 mg, 0.11 mmol, 75%) as a white solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.30–7.12 (5H, m), 6.75 (4H, m), 5.98 (1H, s), 5.76 (1H, ddt, J_H = 16.1, 10.1, 6.0 Hz), 5.00–4.84 (4H, m), 3.71 (3H, s, O*CH*$_3$), 3.12 (2H, dd, J_H = 5.9, 0.8 Hz). ^{19}F NMR ($CDCl_3$, 470 MHz) δ: −168.0. ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 158.7, 149.5 (d, J_F = 237.3 Hz), 135.3, 132.8, 130.8, 130.7, 128.9 (2C), 128.5 (2C), 127.2, 126.7 (2C), 115.4, 114.2 (2C), 113.9 (d, J_F = 23.5 Hz), 96.6 (d, J_F = 16.3 Hz), 55.3, 47.1, 27.5 (d, J_F = 2.1 Hz). *m*/*z* [EI (+ve)] 321.1 $[M]^+$, HRMS found $[M]^+$ 321.1526, $C_{21}H_{20}FNO$ requires 321.1529. IR (thin film) ν_{max} = 2931, 1612, 1595, 1512, 1354, 1247, 1174 cm^{-1}. m.p. 30–32 °C.

1-Benzyl-3-fluoro-5-phenyl-2,5-dihydro-1*H*-pyrrol-2-one, 16a. Dialkene **15a** (110 mg, 0.36 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-unsaturated lactam **16a** (100 mg, 0.35 mmol, 98%) as a pale yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.35–7.29 (3H, m), 7.26–7.20 (3H, m), 7.05–7.01 (4H, m), 6.19 (1H, d, J_H = 1.9 Hz), 5.08 (1H, d, J_H = 15.0 Hz), 4.70 (1H, dd, J_F = 5.8 Hz, J_H = 2.3 Hz), 3.53 (1H, d, J_H = 15.0 Hz). ^{19}F NMR ($CDCl_3$, 470 MHz) δ: −138.6. ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 163.0 (d, J_F = 31.3 Hz), 152.4 (d, J_F = 279.5 Hz), 136.5, 133.8, 129.3 (2C), 129.2, 128.8 (2C), 128.4 (2C), 127.8, 127.6 (2C), 118.5 (d, J_F = 4.4 Hz), 59.3 (d, J_F = 5.7 Hz), 44.1. *m*/*z* [ESI (+ve)] 290.1 [M + Na]$^+$, HRMS found [M + Na]$^+$ 290.0943, $C_{17}H_{14}FNONa$ requires 290.0940. IR (thin film) ν_{max} = 3063, 1710, 1666, 1456, 1220, 1186 cm^{-1}.

3-Fluoro-1-[(4′-bromophenyl)methyl]-5-phenyl-2,5-dihydro-1*H*-pyrrol-2-one, 16b. Dialkene **15b** (120 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 (0–5% EtOAc in petroleum ether) to yield the desired α,β-unsaturated lactam **16b** (100 mg, 0.29 mmol, 96%) as a pale yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.36 (2H, d, J_H = 8.3 Hz), 7.34–7.28 (3H, m), 7.03–7.00 (2H, m), 6.91 (2H, d, J_H = 8.3 Hz), 6.21 (1H, d, J_H = 2.0 Hz), 4.98 (1H, J_H = 15.0 Hz), 4.69 (1H, dd, J_F = 5.8 Hz, J_H = 2.2 Hz), 3.54 (1H, J_H = 15.0 Hz). ^{19}F NMR ($CDCl_3$, 470 MHz) δ: −138.5. ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 163.0 (d, J_F = 31.3 Hz), 152.3 (d, J_F = 279.8 Hz), 135.5, 133.6 (d, J_F = 2.2 Hz), 132.0 (2C), 130.1 (2C), 129.4 (2C), 129.3, 127.5 (2C), 121.9, 118.6 (d, J_F = 4.4 Hz), 59.4 (d, J_F = 5.6 Hz), 43.6. *m*/*z* [EI (+ve)] 344.9 $[M]^+$, HRMS found $[M]^+$ 345.0167, $C_{17}H_{13}BrFNO$ requires 345.0165. IR (thin film) ν_{max} = 2960, 1708, 1666, 1489, 1404, 1220, 1012 cm^{-1}.

3-Fluoro-1-(cyclohexylmethyl)-5-phenyl-2,5-dihydro-1*H*-pyrrol-2-one, 16c. Dialkene **15c** (150 mg, 0.5 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 (0–7.5% EtOAc in petroleum ether) to yield the desired α,β-unsaturated lactam **16c** (130 mg, 0.46 mmol, 92%) as a pale yellow oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 7.37–7.22 (3H, m), 7.09–7.07 (2H, m), 6.20 (1H, d, J_H = 1.5 Hz), 4.90 (1H, dd, J_F = 5.5 Hz, J_H = 2.0 Hz), 3.48 (1H, dd, J_H = 14.0, 8.7 Hz), 2.46 (1H, dd, J_H = 14.0, 6.0 Hz), 1.63–1.58 (2H, m), 1.40–1.43 (3H, m), 1.09–1.04 (3H, m), 0.87–0.79 (3H, m). ^{19}F NMR ($CDCl_3$, 470 MHz) δ: −138.4. ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 163.3 (d, J_F = 31.0 Hz), 152.6 (d, J_F = 279.3 Hz), 134.2, 129.3 (2C), 129.1, 127.4 (2C), 117.9 (d, J_F = 4.4 Hz), 60.7 (d, J_F = 5.9 Hz), 46.6, 37.0, 30.9, 30.4, 26.3, 25.7, 25.6. *m*/*z* [EI (+ve)] 273.2 $[M]^+$, HRMS found $[M]^+$ 273.1528, $C_{17}H_{20}FNO$ requires 273.1529. IR (thin film) ν_{max} = 2922, 2852, 1703, 1666, 1448, 1220, 1116 cm^{-1}.

3-Fluoro-1-[(1′-methyl-1*H*-pyrrol-2′-yl)methyl]-5-phenyl-2,5-dihydro-1*H*-pyrrol-2-one, 16d. Dialkene **15d** (80 mg, 0.27 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 α,β-unsaturated lactam **16d** (60 mg, 0.22 mmol, 81%) as a pale yellow solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.45–7.27 (3H, m), 7.09–7.06 (2H, m), 6.51 (1H, appt t, J_H = 2.4 Hz), 6.18 (1H, d, J_H = 2.0 Hz), 5.95 (1H, dd, J_H = 3.6, 2.8 Hz), 5.78 (1H, dd, J_H = 3.6, 2.0 Hz), 4.99 (1H, d, J_H = 15.5 Hz), 4.74 (1H, dd, J_F = 5.9 Hz, J_H = 2.3 Hz), 3.60 (1H, d, J_H = 15.5 Hz), 3.48 (3H, s). ^{19}F NMR ($CDCl_3$, 470 MHz) δ: −138.7. ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 162.4 (d, J_F = 31.3 Hz), 151.9 (d, J_F = 279.8 Hz), 133.7, 129.3 (2C), 129.1, 127.6 (2C), 126.8, 123.3, 118.8 (d, J_F = 4.2 Hz), 110.3, 106.9,

58.9 (d, J_F = 5.5 Hz), 35.4, 34.1. *m/z* [EI (+ve)] 270.1 $[M]^+$, HRMS found $[M]^+$ 270.1170, $C_{16}H_{15}FN_2O$ requires 270.1168. IR (thin film) ν_{max} = 2960, 2359, 1716, 1666, 1417, 1217 cm^{-1}. m.p. 92–94 °C.

1-Benzyl-3-fluoro-2-methyl-5-phenyl-1*H*-pyrrole, 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. ^{1}H NMR ($CDCl_3$, 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_F = 1.6 Hz). ^{19}F NMR ($CDCl_3$, 470 MHz) *δ*: −169.3. ^{13}C NMR ($CDCl_3$, 125 MHz) *δ*: 149.2 (d, J_F = 235.6 Hz), 138.6, 132.8, 130.2 (d, J_F = 3.3 Hz), 128.8 (2C), 128.8 (2C), 128.5 (2C), 127.2, 127.1, 125.6 (2C), 112.6 (d, J_F = 24.4 Hz), 96.5 (d, J_F = 16.5 Hz), 47.8, 8.2. *m/z* [EI (+ve)] 265.1 $[M]^+$, HRMS found $[M]^+$ 265.1269, $C_{18}H_{16}FN$ requires 265.1267. IR (thin film) ν_{max} = 2924, 1662, 1599, 1452, 1352, 1118 cm^{-1}. m.p. 44–46 °C.

1-[(4′-Bromophenyl)methyl]-3-fluoro-2-methyl-5-phenyl-1*H*-pyrrole, 17b. α,β-Unsaturated lactam **16b** (38 mg, 0.11 mmol) was reacted with methyllithium (74 μL, 0.12 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 **17b** (31 mg, 0.09 mmol, 83%) as a white solid. ^{1}H NMR ($CDCl_3$, 400 MHz) *δ*: 7.36 (2H, d, J_H = 8.6 Hz), 7.27–7.14 (5H, m), 6.72 (2H, d, J_H = 8.6 Hz), 5.98 (1H, s), 4.93 (2H, s), 1.97 (3H, d, J_F = 1.6 Hz). ^{19}F NMR ($CDCl_3$, 470 MHz) *δ*: −168.8. ^{13}C NMR ($CDCl_3$, 125 MHz) *δ*: 149.3 (d, J_F = 236.2 Hz), 137.7, 132.6, 131.9 (2C), 130.2 (d, J_F = 6.8 Hz), 128.8 (2C), 128.6 (2C), 127.3 (2C), 127.3, 121.0, 112.4 (d, J_F = 24.4 Hz), 96.8 (d, J_F = 16.5 Hz), 47.2, 8.1 (d, J_F = 2.1 Hz). *m/z* [EI (+ve)] 343.1 $[M]^+$, HRMS found $[M]^+$ 343.0367, $C_{18}H_{15}FNBr$ requires 343.0372. IR (thin film) ν_{max} = 2924, 1680, 1599, 1489, 1363, 1072, 1010 cm^{-1}. m.p. 98–100 °C.

1-(Cyclohexylmethyl)-3-fluoro-2-methyl-5-phenyl-1*H*-pyrrole, 17c. α,β-Unsaturated lactam **16c** (36 mg, 0.13 mmol) was reacted with methyllithium (91 μL, 0.15 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 **17c** (29 mg, 0.11 mmol, 84%) as a white solid. ^{1}H NMR ($CDCl_3$, 500 MHz) *δ*: 7.31–7.28 (2H, m), 7.25–7.20 (3H, m), 5.81 (1H, s), 3.66 (2H, d, J_H = 7.0 Hz), 2.17 (3H, d, J_F = 1.6 Hz), 1.50–1.45 (3H, m), 1.28–1.23 (3H, m), 0.98–0.88 (3H, m), 0.56–0.49 (2H, m). ^{19}F NMR ($CDCl_3$, 470 MHz) *δ*: −170.1. ^{13}C NMR ($CDCl_3$, 125 MHz) *δ*: 149.1 (d, J_F = 235.0 Hz), 133.9, 130.0 (d, J_F = 7.2 Hz), 128.3 (2C), 128.3 (2C), 126.8, 112.2 (d, J_F = 23.8 Hz), 96.3 (d, J_F = 16.3 Hz), 50.2, 39.2, 30.4 (2C), 26.2, 25.7 (2C), 8.5 (d, J_F = 1.9 Hz). *m/z* [EI (+ve)] 271.1 $[M]^+$, HRMS found $[M]^+$ 271.1733, $C_{18}H_{22}FN$ requires 271.1736. IR (thin film) ν_{max} = 2926, 2852, 1597, 1450, 1348, 1112 cm^{-1}. m.p. 73–75 °C.

3-Fluoro-2-methyl-1-[(1′-methyl-1*H*-pyrrole-2′-yl)methyl]-5-phenyl-1*H*-pyrrole, 17d. α,β-Unsaturated lactam **16d** (31 mg, 0.12 mmol) was reacted with methyllithium (79 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 **17d** (23 mg, 0.09 mmol, 75%) as a white solid. ^{1}H NMR ($CDCl_3$, 400 MHz) *δ*: 7.28–7.23 (2H, m), 7.23–7.19 (3H, m), 6.46 (1H, appt t, J_H = 2.5 Hz), 5.95 (1H, appt t, J_H = 3.5 Hz), 5.92 (1H, s), 5.70–5.69 (1H, m), 4.88 (2H, s), 3.26 (3H, s), 2.03 (3H, d, J_F = 1.6 Hz). ^{19}F NMR ($CDCl_3$, 470 MHz) *δ*: −169.5. ^{13}C NMR ($CDCl_3$, 125 MHz) *δ*: 149.2 (d, J_F = 235.4 Hz), 133.0, 129.9 (d, J_F = 6.9 Hz), 128.8 (3C), 128.5 (2C), 127.1, 122.3, 112.9 (d, J_F = 24.6 Hz), 107.9, 107.1, 96.4 (d, J_F = 16.5 Hz), 41.6, 33.7, 8.2. *m/z* [EI (+ve)] 268.1 $[M]^+$, HRMS found $[M]^+$ 268.1380, $C_{17}H_{17}FN_2$ requires 268.1376. IR (thin film) ν_{max} = 2922, 1705, 1599, 1469, 1361, 1301, 1089 cm^{-1}. m.p. 69–71 °C.

1-Benzyl-3-fluoro-5-(4′-methoxyphenyl)-2,5-dihydro-1*H*-pyrrol-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-unsaturated lactam **21a** (70 mg, 0.22 mmol, 71%) as a white solid. ^{1}H NMR ($CDCl_3$, 400 MHz) *δ*: 7.35–7.29 (3H, m), 7.14–7.13 (2H, m), 7.03 (2H, d, J_H = 8.7 Hz), 6.93 (2H, d, J_H = 8.7 Hz), 6.25 (1H, d, J_H = 1.6 Hz), 5.15 (1H, d, J_H = 15.0 Hz), 4.75 (1H, dd, J_F = 5.8 Hz, J_H = 2.1 Hz), 3.85 (3H, s), 3.61 (1H, d, J_H = 15.0 Hz). ^{19}F NMR ($CDCl_3$, 470 MHz) *δ*: −138.7. ^{13}C NMR ($CDCl_3$, 125 MHz) *δ*: 162.9 (d, J_F = 31.3 Hz), 160.3, 152.3 (d, J_F = 279.3 Hz), 136.7, 128.9 (2C), 128.8 (2C), 128.4 (2C), 127.8, 125.4 (d, J_F = 2.1 Hz), 118.5 (d, J_F = 4.0 Hz), 114.6 (2C), 58.7 (d, J_F = 5.8 Hz), 55.4, 43.9. *m/z* [EI (+ve)] 297.1 $[M]^+$, HRMS found $[M]^+$ 297.1169, $C_{18}H_{16}FNO_2$ requires 297.1165. IR (thin film) ν_{max} = 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-1*H*-pyrrol-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 (0–15% EtOAc in petroleum ether) to yield the desired α,β-unsaturated lactam **21b** (70 mg, 0.20 mmol, 88%) as a pale yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) *δ*: 7.58 (2H, d, J_H = 8.1 Hz), 7.26–7.21 (3H, m), 7.16 (2H, d, J_H = 8.1 Hz), 7.03–7.01 (2H, m), 6.19 (1H, d, J_H = 1.2 Hz), 5.09 (1H, d, J_H = 15.0 Hz), 4.77 (1H, dd, J_F = 4.8 Hz, J_H = 2.0 Hz), 3.57 (1H, d, J_H = 15.0 Hz). ^{19}F NMR ($CDCl_3$, 470 MHz) *δ*: −62.9, −137.2. ^{13}C NMR ($CDCl_3$, 125 MHz) *δ*: 162.9 (d, J_F = 31.2 Hz), 152.7 (d, J_F = 280.9 Hz), 138.1, 136.1, 131.7, 131.4, 129.0 (2C), 128.4 (2C),128.1, 128.0 (2C), 126.3 (2C, q, J_F = 3.7 Hz), 118.0 (d, J_F = 5.0 Hz), 58.7 (d, J_F = 5.7 Hz), 44.4. *m/z* [EI (+ve)] 335.0 $[M]^+$, HRMS found $[M]^+$ 335.0932, $C_{18}H_{13}F_4NO$ requires 335.0933. IR (thin film) ν_{max} = 2362, 2332, 1718, 1670, 1421, 1325, 1166, 1126, 1066 cm^{-1}.

1-Benzyl-3-fluoro-5-(4′-bromophenyl)-2,5-dihydro-1*H*-pyrrol-2-one, 21c. Dialkene **20c** (100 mg, 0.3 mmol) was treated with 10 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-unsaturated lactam **21c** (90 mg, 0.3 mmol, 94%) as a pale yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) *δ*: 7.54

(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_H = 1.6 Hz), 5.17 (1H, d, J_H = 15.0 Hz), 4.76 (1H, dd, J_F = 5.8 Hz, J_H = 2.2 Hz), 3.62 (1H, d, J_H = 15.0 Hz). ^{19}F NMR ($CDCl_3$, 470 MHz) δ: −137.7. ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 162.9 (d, J_F = 31.2 Hz), 152.5 (d, J_F = 280.5 Hz), 136.3, 132.9 (d, J_F = 2.2 Hz), 132.5 (2C), 129.2 (2C), 128.9 (2C), 128.4 (2C), 128.0, 123.2, 118.1 (d, J_F = 4.7 Hz), 58.6 (d, J_F = 5.7 Hz), 44.2. *m/z* [EI (+ve)] 345.1 $[M]^+$, HRMS found $[M]^+$ 345.0165, $C_{17}H_{13}BrFNO$ requires 345.0165. IR (thin film) ν_{max} = 3030, 1708, 1666, 1489, 1408, 1220, 1078, 1010 cm^{-1}.

1-Benzyl-3-fluoro-5-cyclohexyl-2,5-dihydro-1*H*-pyrrol-2-one, 21d. 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 α,β-unsaturated lactam **21d** (90 mg, 0.32 mmol, 95%) as a white solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.28–7.16 (5H, m), 6.12 (1H, d, J_H = 2.1 Hz), 5.03 (1H, d, J_H = 15.2 Hz), 4.01 (1H, d, J_H = 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) δ: −136.9. ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 163.4 (d, J_F = 31.5 Hz), 152.8 (d, J_F = 277.4 Hz), 136.7, 128.3 (2C), 128.0 (2C), 127.7, 115.6 (d, J_F = 4.2 Hz), 60.1 (d, J_F = 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, $C_{17}H_{20}FNO$ requires 273.1529. IR (thin film) ν_{max} = 2928, 2854, 1703, 1666, 1450, 1421, 1240, 1145 cm^{-1}. m.p. 53–55 °C.

1-Benzyl-3-fluoro-5-(2′-phenylethyl)-2,5-dihydro-1*H*-pyrrol-2-one, 21e. Dialkene **20e** (120 mg, 0.38 mmol) was treated with 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-unsaturated lactam **21e** (110 mg, 0.36 mmol, 96%) as a white solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.26–7.11 (8H, m), 6.97–6.96 (2H, m), 6.17 (1H, d, J_H = 1.6 Hz), 5.00 (1H, d, J_H = 15.2 Hz), 4.06 (1H, d, J_H = 15.2 Hz), 3.88–3.85 (1H, m), 2.49–2.31 (2H, m), 2.11–2.04 (1H, m), 1.86–1.75 (1H, m). ^{19}F NMR ($CDCl_3$, 470 MHz) δ: −137.0. ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 163.1 (d, J_F = 31.3 Hz), 152.7 (d, J_F = 278.2 Hz), 140.4, 136.5, 128.9 (2C), 128.7 (2C), 128.2 (2C), 128.1 (2C), 127.9, 126.4, 117.2 (d, J_F = 4.2 Hz), 55.0 (d, J_F = 5.0 Hz), 44.3, 31.7 (d, J_F = 2.0 Hz), 30.0. *m/z* [EI (+ve)] 295.2 $[M]^+$, HRMS found $[M]^+$ 295.1373, $C_{19}H_{18}FNO$ requires 295.1372. IR (thin film) ν_{max} = 2935, 2364, 1707, 1666, 1454, 1226 cm^{-1}. m.p. 62–65 °C.

1-Benzyl-3-fluoro-5-(4′-methoxyphenyl)-2-methyl-1*H*-pyrrole, 22a. α,β-Unsaturated lactam **21a** (32 mg, 0.11 mmol) was reacted with methyllithium (83 μL, 1.2 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 **22a** (28 mg, 0.09 mmol, 88%) as a white solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.25–7.16 (3H, m), 7.10 (2H, d, J_H = 8.9 Hz), 6.86–6.84 (2H, m), 6.76 (2H, d, J_H = 8.9 Hz), 5.91 (1H, s), 4.95 (2H, s), 3.71 (3H, s), 1.97 (3H, d, J_F = 1.6 Hz). ^{19}F NMR ($CDCl_3$, 470 MHz) δ: −169.6. ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 158.9, 149.1 (d, J_F = 235.4 Hz), 138.7, 130.2 (2C), 129.9 (d, J_F = 3.3 Hz), 128.8 (2C), 127.1, 125.6 (2C), 125.4 (d, J_F = 1.6 Hz), 113.9 (2C), 111.8 (d, J_F = 24.4 Hz), 96.0 (d, J_F = 16.4 Hz), 55.3, 47.6, 8.1 (d, J_F = 2.0 Hz). *m/z* [EI (+ve)] 295.2 $[M]^+$, HRMS found $[M]^+$ 295.1373, $C_{19}H_{18}FNO$ requires 295.1372. IR (thin film) ν_{max} = 2929, 1653, 1603, 1454, 1249, 1176 cm^{-1}. m.p. 74–76 °C.

1-Benzyl-3-fluoro-2-methyl-5-[(4′-trifluoromethyl)phenyl]-1*H*-pyrrole, 22b. α,β-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) δ: 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_F = 1.6 Hz). ^{19}F NMR ($CDCl_3$, 470 MHz) δ: −62.5, −168.5. ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 149.3 (d, J_F = 236.4 Hz), 138.1, 136.3, 129.0, 128.9 (2C), 128.6 (d, J_F = 7.2 Hz), 128.5 (2C), 127.4, 126.0 (d, J_F = 3.8 Hz), 125.5, 125.4 (2C), 114.1 (d, J_F = 24.4 Hz), 96.7 (d, J_F = 16.5 Hz), 47.9, 8.2 (d, J_F = 2.0 Hz). *m/z* [EI (+ve)] 333.2 $[M]^+$, HRMS found $[M]^+$ 333.1139, $C_{19}H_{15}F_4N$ requires 333.1141. IR (thin film) ν_{max} = 2926, 1606, 1325, 1166, 1124 cm^{-1}. m.p. 75–77 °C.

1-Benzyl-5-(4′-bromophenyl)-3-fluoro-2-methyl-1*H*-pyrrole, 22c. α,β-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) δ: 7.37 (2H, d, J_H = 8.6 Hz), 7.29–7.16 (3H, m), 7.04 (2H, d, J_H = 8.6 Hz), 6.85–6.83 (2H, m), 5.97 (1H, s), 4.96 (2H, s), 1.98 (3H, d, J_F = 1.6 Hz). ^{19}F NMR ($CDCl_3$, 470 MHz) δ: −168.9. ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 149.2 (d, J_F = 236.1 Hz), 138.3, 131.7 (d, J_F = 1.8 Hz), 131.6 (2C), 130.2 (2C), 128.9 (2C), 128.8, 127.3, 125.5 (2C), 121.2, 113.2 (d, J_F = 24.3 Hz), 96.9 (d, J_F = 16.5 Hz), 47.7, 8.2 (d, J_F = 2.0 Hz). *m/z* [EI (+ve)] 343.1 $[M]^+$, HRMS found $[M]^+$ 343.0368, $C_{18}H_{15}BrFN$ requires 343.0372. IR (thin film) ν_{max} = 2922, 1683, 1612, 1471, 1352 cm^{-1}. m.p. 98–100 °C.

1-Benzyl-5-cyclohexyl-3-fluoro-2-methyl-1*H*-pyrrole, 22d. α,β-Unsaturated lactam **21d** (32 mg, 0.12 mmol) was reacted with methyllithium (92 μL, 0.13 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 **22d** (29 mg, 0.11 mmol, 92%) as a white solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.25–7.13 (3H, m), 6.80–6.76 (2H, m), 5.64 (1H, s), 4.90 (2H, s), 2.33–2.24 (1H, m), 1.91 (3H, d, J_F = 1.6 Hz), 1.74–1.63 (4H, m), 1.26–1.08 (6H, m). ^{19}F NMR ($CDCl_3$, 470 MHz) δ: −170.6. ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 148.6 (d, J_F = 233.9 Hz), 138.7, 134.8 (d, J_F = 5.7 Hz), 128.7 (2C), 127.1, 125.5 (2C), 109.3 (d, J_F = 24.7 Hz), 91.8 (d, J_F = 16.8 Hz), 46.4, 35.6, 34.1 (2C), 26.6 (2C), 26.0, 7.8 (d, J_F = 2.1 Hz). *m/z* [EI (+ve)] 271.1 $[M]^+$, HRMS found $[M]^+$ 271.1737, $C_{18}H_{22}FN$ requires 271.1736. IR (thin film) ν_{max} = 2926, 2852, 1616, 1446, 1365, 1348, 1112 cm^{-1}. m.p. 55–57 °C.

1-Benzyl-3-fluoro-2-methyl-5-(2′-phenylethyl)-1*H*-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. ^{1}H NMR ($CDCl_3$, 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). ^{19}F NMR ($CDCl_3$, 470 MHz) δ: −170.5. ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 148.3 (d, J_F = 234.1 Hz), 141.4, 138.2, 128.8 (2C), 128.4 (2C), 128.3 (2C), 127.9 (d, J_F = 6.3 Hz), 127.2, 126.1, 125.5 (2C), 110.0 (d, J_F = 24.6 Hz), 94.1 (d, J_F = 16.8 Hz), 46.5, 35.4, 28.4, 7.9 (d, J_F = 2.1 Hz). *m*/*z* [EI (+ve)] 293.1 $[M]^+$, HRMS found $[M]^+$ 293.1581, $C_{20}H_{20}FN$ requires 293.1580. IR (thin film) ν_{max} = 2922, 1614, 1496, 1454, 1417, 1363, 1114 cm^{-1}.

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