Supporting Information

for

Synthesis of enones, pyrazolines and pyrrolines with gem-difluoroalkyl side chains

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Note: all compounds 2 and 4–12 are prepared in racemic form only.
General Methods

All reagents were obtained commercially and used without further purification. All reactions were carried out under a nitrogen atmosphere and dry conditions. The solvents used were freshly distilled under anhydrous conditions, unless otherwise specified. The reaction mixtures were magnetically stirred with Teflon stirring bars, and the temperatures were measured externally. Reactions that required anhydrous conditions were carried out by using oven dried (120 °C, 24 h) glassware. Yields refer to chromatographically and spectroscopically (1H, 13C, and 19F NMR) homogeneous materials. Reactions were monitored by 19F NMR and by thin-layer chromatography (TLC), carried out on 0.25 mm Merck silica gel plates (60 F254) with detection by UV light or staining with p-anisaldehyde. The eluents used were mixtures of pentane (Pent) and ether (Et2O). Acros silica gel (60, particle size 0.040–0.063 mm) was used for column chromatography. Nuclear magnetic resonance (NMR) spectra have been recorded with Bruker Avance 500, 400 and 300 spectrometers. 1H NMR spectra: δ (H) are given in ppm relative to tetramethylsilane (TMS), using [δ (CHCl3) = 7.26 ppm] as internal reference. 13C NMR spectra: δ (C) are given in ppm relative to TMS, using [δ (CDCl3) = 77.0 ppm] as internal reference. 19F NMR spectra: δ (F) are given in ppm relative to CFCl3 = 0.0 ppm as external reference. Multiplicities were designated as singlet (s), doublet (d), triplet (t), quartet (q), quintet (qt), multiplet (m) or br (broad). Mass spectral analyses have been performed at the Centre Régional de Mesures Physiques de l’Ouest (CRMPO) in Rennes (France).

1. General procedure for the synthesis of difluoropropargylic alcohols (2)

To a solution of propargylic gem-difluoro intermediate 1 (1 equiv) in anhydrous THF (2 ml per mmol) cooled at −78 °C, was added, dropwise under nitrogen, a solution of n-BuLi in hexanes (1.2 equiv). The mixture was stirred for 1 h at T ≤ −40 °C. Then the aldehyde (1.2 equiv) in anhydrous THF (1 ml per mmol) was added at −78 °C and the resulting solution was allowed to warm to room temperature over 2 h. The mixture was treated with saturated ammonium chloride solution and extracted with ether (3 x 10 ml). The combined organic phases were washed with water, dried over MgSO4 and concentrated in vacuo. The crude product is purified by chromatography on silica gel, using a mixture of ether/pentane as eluent.
1.1. Synthesis of 4,4-difluoro-1-phenyl-tridec-2-yn-1-ol (±)-2a

The reaction was performed with 1 (990 mg, 4.90 mmol) and benzaldehyde (0.6 ml, 9.8 mmol), according to the general procedure. After purification by chromatography on silica gel, propargylic alcohol 2a was obtained as a yellow oil (1.30 g, 82% yield). \( R_f = 0.38 \) (Et\(_2\)O/pentane 1/9). \(^1\)H NMR (CDCl\(_3\), 300 MHz), \( \delta \) ppm: 7.54-7.41 (m, 2H); 7.38-7.27 (m, 3H); 5.47 (t, 1H, \( J_{HF} = 3.9 \) Hz); 2.19 (bs, 1H); 2.13-1.97 (m, 2H); 1.60-1.52 (m, 2H); 1.30-1.27 (m, 12H); 0.89 (t, 3H, \( J = 6.7 \) Hz). \(^{13}\)C NMR (CDCl\(_3\), 75 MHz), \( \delta \) ppm: 139.0 (t, \( J_{CF} = 1.4 \) Hz); 128.9 (2C); 126.6 (2C); 114.9 (t, \( J_{CF} = 232.8 \) Hz); 86.3 (t, \( J_{CF} = 6.7 \) Hz); 79.7 (t, \( J_{CF} = 41.2 \) Hz); 64.3 (t, \( J_{CF} = 1.9 \) Hz); 39.5 (t, \( J_{CF} = 25.7 \) Hz); 31.9; 29.4; 29.32; 29.26; 28.9; 22.7 (t, \( J_{CF} = 3.5 \) Hz); 22.7; 14.1. \(^{19}\)F NMR (CDCl\(_3\), 282 MHz), \( \delta \) ppm: -83.10 (td, \( J_{FH} = 15.0 \) Hz, 3.9 Hz). HRMS (ESI) caleld for C\(_{19}\)H\(_{26}\)F\(_2\)O\(^79\)BrNa: [M +Na]\(^+\) : m/z 331.19518. Found: m/z 331.1953 (1ppm).

1.2. Synthesis of 4,4-difluoro-1-(pyridine-3-y1)-tridec-2-yn-1-ol (±)-2b

The reaction was performed with 1 (400 mg, 1.29 mmol) and 3-pyridinecarboxaldehyde (0.22 ml, 2.38 mmol), according to the general procedure. After purification by chromatography on silica gel, propargylic alcohol 2b was obtained as a yellow oil (472 mg, 78% yield). \( R_f = 0.29 \) (Et\(_2\)O/pentane 7/3). \(^1\)H NMR (CDCl\(_3\), 300 MHz), \( \delta \) ppm: 8.66 (s, 1H); 8.54 (d, 1H, \( J = 4.4 \) Hz); 7.92 (d, 1H, \( J = 7.4 \) Hz); 7.38 (dd, 1H, \( J = 7.4 \) Hz, \( J = 4.4 \) Hz); 5.62 (t, 1H, \( J_{HF} = 3.8 \) Hz); 3.80 (bs, 1H); 2.13-1.92 (m, 2H); 1.61-1.43 (m, 2H); 1.16-1.45 (m, 12H); 0.88 (t, H\(_1\), \( J = 6.6 \) Hz). \(^{13}\)C NMR (CDCl\(_3\), 75 MHz), \( \delta \) ppm: 148.6; 147.3; 136.3; 135.2; 123.9; 114.8 (t, \( J_{CF} = 232.9 \) Hz); 86.1 (t, \( J_{CF} = 6.8 \) Hz); 79.6 (t, \( J_{CF} = 41.2 \) Hz); 61.3; 39.1 (t, \( J_{CF} = 25.7 \) Hz); 31.8; 29.4; 29.3; 29.2; 28.9; 22.7 (t, \( J_{CF} = 3.4 \) Hz); 22.7; 14.1. \(^{19}\)F NMR (CDCl\(_3\), 282 MHz), \( \delta \) ppm: -83.23 (td, \( J_{FH} = 15.3 \) Hz, 3.8 Hz). HRMS (ESI) caleld for C\(_{22}\)H\(_{32}\)NO\(_2\)F\(_2\)\(^79\)BrNa: [M +Na]\(^+\) : m/z 332.18019. Found: m/z 332.1812 (3 ppm).

1.3. Synthesis of 4,4-difluoro-1-(furane-2-y1)-tridec-2-yn-1-ol (±)-2c

The reaction was performed with 1 (400 mg, 1.29 mmol) and furane-2-carbaldehyde (0.2 ml, 2.38 mmol), according to the general procedure. After purification by chromatography on silica gel, propargylic alcohol 2c was obtained as a yellow oil (463 mg, 79% yield). \( R_f = 0.46 \) (Et\(_2\)O/pentane 2/8). \(^1\)H NMR (CDCl\(_3\), 300 MHz), \( \delta \) ppm: 7.44 (dd, 1H, \( J = 1.8 \) Hz, \( J = 0.8 \) Hz).
Hz); 6.47 (dt, 1H, J = 3.3 Hz, J = 0.7 Hz); 6.38 (dd, 1H, J = 3.3 Hz, J = 1.8 Hz); 5.54 (t, 1H, $^5J_{HF} = 3.8$ Hz); 2.47 (bs, 1H); 2.19-1.98 (m, 2H); 1.61-1.42 (m, 2H); 1.15-1.34 (m, 12H); 0.88 (t, H$_t$, J = 6.3 Hz). $^{13}$C NMR (CDCl$_3$, 75 MHz), δ ppm: 151.4 (t, $^3J_{CF} = 2.0$ Hz); 143.4; 114.8 (t, $^1J_{CF} = 233.1$ Hz); 110.6; 108.4; 83.9 (t, $^3J_{CF} = 6.7$ Hz); 78.8 (t, $^2J_{CF} = 41.4$ Hz); 57.8 (t, $^4J_{CF} = 1.8$ Hz); 39.1 (t, $^2J_{CF} = 25.6$ Hz); 31.8; 29.4; 29.30; 29.2; 28.9; 22.7 (t, $^3J_{CF} = 3.5$ Hz); 22.7; 14.1. $^{19}$F NMR (CDCl$_3$, 282 MHz), δ ppm: -83.51 (td, $J_{FH} = 15.2$ Hz, 3.8 Hz). HRMS (ESI) calcd for C$_{17}$H$_{24}$OF$_2$S$^{79}$BrNa: [M + Na]$^+$ : m/z 321.16421. Found: m/z 321.1641 (0 ppm).

1.4. Synthesis of 4,4-difluoro-1-(thiophene-2-yl)-tridec-2-yn-1-ol ((±)-2d)

The reaction was performed with 1 (877 mg, 4.34 mmol) and thiophene-2-carbaldehyde (0.47 ml, 5.21 mmol), according to the general procedure. After purification by chromatography on silica gel, propargylic alcohol 2d was obtained as a yellow oil (966 mg, 71% yield). R$_f$ = 0.43 (Et$_2$O/pentane 2/8). $^1$H NMR (CDCl$_3$, 300 MHz), δ ppm: 7.24 (dd, 1H, J = 5.1 Hz, J = 1.2 Hz); 7.18 (dt, 1H, J = 3.4 Hz, 0.9 Hz); 6.38 (dd, 1H, J = 5.1 Hz, J = 3.4 Hz); 5.62 (bs, 1H); 2.72 (bs, 1H); 2.18-1.84 (m, 2H); 1.61-1.42 (m, 2H); 1.37-1.17 (m, 12H); 0.83 (t, H$_t$, J = 6.7 Hz). $^{13}$C NMR (CDCl$_3$, 75 MHz), δ ppm: 142.7 (t, $^5J_{CF} = 1.7$ Hz); 126.9; 126.6; 126.1; 114.9 (t, $^1J_{CF} = 233.2$ Hz); 85.6 (t, $^3J_{CF} = 6.7$ Hz); 79.1 (t, $^2J_{CF} = 41.4$ Hz); 59.9 (t, $^4J_{CF} = 1.8$ Hz); 39.1 (t, $^2J_{CF} = 25.6$ Hz); 31.9; 29.4; 29.33; 29.27; 29.0; 22.7 (t, $^3J_{CF} = 3.8$ Hz); 22.7; 14.1. $^{19}$F NMR (CDCl$_3$, 282 MHz), δ ppm: -83.45 (td, $J_{FH} = 15.0$ Hz, 3.8 Hz). HRMS (ESI) calcd for C$_{17}$H$_{24}$OF$_2$S$^{79}$BrNa: [M + Na]$^+$ : m/z 377.14136. Found: m/z 337.1416 (1 ppm).

1.5. Synthesis of 1-(4-bromophenyl)-4,4-difluoro-tridec-2-yn-1-ol ((±)-2e)

The reaction was performed with 1 (400 mg, 1.98 mmol) and 4-bromobenzaldehyde (0.44 mg, 2.376 mmol), according to the general procedure. After purification by chromatography on silica gel, propargylic alcohol 2e was obtained as a yellow oil (614 mg, 81% yield). R$_f$ = 0.34 (Et$_2$O/pentane 1/9). $^1$H NMR (CDCl$_3$, 300 MHz), δ ppm: 7.41-7.32 (m, 2H); 7.25-7.16 (m, 2H); 5.28 (t, 1H, $^5J_{HF} = 3.7$ Hz); 2.46 (bs, 1H); 2.02-1.88 (m, 2H); 1.50-1.35 (m, 2H); 1.29-1.11 (m, 12H); 0.80 (t, H$_t$, J = 6.4 Hz). $^{13}$C NMR (CDCl$_3$, 75 MHz), δ ppm: 138.0; 131.9; 128.3; 122.9; 114.8 (t, $^1J_{CF} = 233.0$ Hz); 85.8 (t, $^3J_{CF} = 6.7$ Hz); 79.9 (t, $^2J_{CF} = 41.3$ Hz); 63.4 (t, $^4J_{CF} = 1.8$ Hz); 39.1 (t, $^2J_{CF} = 25.7$ Hz); 32.0; 29.43; 29.35; 29.30; 28.9; 22.7 (t, $^3J_{CF} = 3.5$ Hz); 22.7; 14.1. $^{19}$F NMR (CDCl$_3$, 282 MHz), δ ppm: -83.25 (td, $J_{FH} = 15.1$ Hz, 3.7

2. General procedure for the synthesis of gem-difluoroenones (3)

The difluoropropargylic alcohol 2 (1 equiv) was dissolved in THF (2 ml per mmol), then DBU (1.5 equiv) was added, and stirred at 35 °C for the appropriate time (monitored by $^{19}$F NMR). After completion of the reaction, the mixture was neutralized with a saturated solution of NH$_4$Cl. After extraction with diethyl ether, the organic phases were washed with water, dried (MgSO$_4$) and concentrated in vacuo. The crude product was purified by chromatography on silica gel, using ether/pentane as eluent.

2.1. Synthesis of 4,4-difluoro-1-phenyl-tridec-2-en-1-one (3a)

The reaction was performed with 2a (920 mg, 2.99 mmol) according to the general procedure. After 6 h, $^{19}$F NMR showed 100% conversion, and there were two enones, cis and trans (1/100). After purification by flash chromatography on silica gel, the enone 3a was isolated as a yellow oil (570 mg, 62%). $\text{R}_f$ = 0.30 (Et$_2$O/pentane 2/98). $^1$H NMR (CDCl$_3$, 400 MHz), $\delta$ ppm: 8.02-7.94 (m, 2H); 7.66-7.57 (m, 1H); 7.55-7.46 (m, 2H); 7.31 (dt, 1H, $J$ = 15.6 Hz, $^4$J$_{HF}$ = 2.3 Hz ); 6.85 (dt, 1H, $J$ = 15.6 Hz, $^3$J$_{HF}$ = 11.6 Hz); 2.08-1.91 (m, 2H); 1.51-1.43 (m, 2H); 1.41-1.17 (m, 12H); 0.88 (t, 3H, $J$ = 6.7 Hz). $^{13}$C NMR (CDCl$_3$, 100 MHz), $\delta$ ppm: 189.3; 138.9 (t, $^2$J$_{CF}$ = 27.3 Hz); 133.6; 136.9; 128.8 (2C); 128.7 (2C); 127.40 (t, $^3$J$_{CF}$ = 7.5 Hz); 121.3 (t, $^1$J$_{CF}$ = 239.9 Hz); 37.3 (t, $^2$J$_{CF}$ = 25.7 Hz); 31.8; 29.4; 29.3; 29.2 (2C); 22.7; 22.2 (t, $^3$J$_{CF}$ = 4.1 Hz); 14.1. $^{19}$F NMR (CDCl$_3$, 282 MHz), $\delta$ ppm: -98.36 (tdd, $J_{HF}$ = 16.0 Hz, 11.6 Hz, 2.3Hz ). HRMS (ESI) calcd for C$_{19}$H$_{26}$F$_2$O$_{79}$BrNa: [M +Na]$^+$: m/z 331.19518. Found: m/z 331.1952 (0ppm).

2.2. Synthesis of 4,4-difluoro-1-(pyridine-3-yl)-tridec-1-en-1-one (3b)

The reaction was performed with 2b (386 mg, 1.25 mmol) according to the general procedure. After 30 min, $^{19}$F NMR showed 100% conversion, and that a single product is formed. After purification by flash chromatography on silica gel, the enone 3b was isolated as a sticky syrup (225 mg, 62%). $\text{R}_f$ = 0.26 (Et$_2$O/pentane 3/7). $^1$H NMR (CDCl$_3$, 300 MHz), $\delta$ ppm: 9.16 (dd, 1H, $J$ = 2.1 Hz, $J$ = 0.5 Hz); 8.80 (dd, 1H, $J$ = 4.8 Hz, $J$ = 1.6 Hz); 8.23 (ddd,
1H, J = 7.9 Hz, J = 2.1 Hz, J = 1.6 Hz); 7.44 (dd, 1H, J = 7.9 Hz, J = 4.8 Hz, J = 0.5 Hz); 7.26 (dt, 1H, J = 15.5 Hz, 4J\textsubscript{HF} = 2.3 Hz); 6.88 (dt, 1H, J = 15.5 Hz, 3J\textsubscript{HF} = 11.9 Hz); 2.06-1.90 (m, 2H); 1.51-1.40 (m, 2H); 1.39-1.12 (m, 12H); 0.85 (t, 3H, J = 6.7 Hz). \textsuperscript{13}C NMR (CDCl\textsubscript{3}, 75 MHz), δ ppm: 188.0; 153.8; 149.9; 140.0 (t, 2J\textsubscript{CF} = 27.5 Hz); 135.9; 132.1; 126.6 (t, 3J\textsubscript{CF} = 7.5 Hz); 123.7; 121.0 (t, 1J\textsubscript{CF} = 239.9 Hz); 37.1 (t, 2J\textsubscript{CF} = 25.6 Hz); 31.8; 29.3; 29.2; 29.1 (2C); 22.6; 22.1 (t, 3J\textsubscript{CF} = 4.1 Hz); 14.0. \textsuperscript{19}F NMR (CDCl\textsubscript{3}, 282 MHz), δ ppm: -98.63 (td, J\textsubscript{FH} = 15.4 Hz, 11.9 Hz). HRMS (ESI) calcd for C\textsubscript{18}H\textsubscript{25}NO\textsubscript{2}F\textsuperscript{19}BrNa: [M +Na]+: m/z 332.18019 Found: m/z 332.1814 (4 ppm).

2.3. Synthesis of 4,4-difluoro-1-(furane-2-yl)-tridec-2-en-1-one (3c)

The reaction was performed with 2c (386 mg, 1.25 mmol) according to the general procedure. After 40 min, \textsuperscript{19}F NMR showed 100% conversion, and there were two enones, cis and trans (1/100). After purification by flash chromatography on silica gel, the enone 3c was isolated as yellow oil (138 mg, 63%). RF = 0.31 (Et\textsubscript{2}O/pentane 5/95). \textsuperscript{1}H NMR (CDCl\textsubscript{3}, 300 MHz), δ ppm: 7.67 (dd, 1H, J = 1.7 Hz, J = 0.7 Hz); 7.33 (dd, 1H, J = 3.7 Hz, J = 0.7 Hz); 7.18 (dt, 1H, J = 15.6 Hz, 4J\textsubscript{HF} = 2.2 Hz); 6.92 (dt, 1H, J = 15.6 Hz, 3J\textsubscript{HF} = 11.5 Hz); 6.59 (dd, 1H, J = 3.6 Hz, J = 1.7 Hz); 2.08-1.85 (m, 2H); 1.55-1.39 (m, 2H); 1.35-1.14 (m, 12H); 0.85 (t, 3H, J = 6.7 Hz). \textsuperscript{13}C NMR (CDCl\textsubscript{3}, 75 MHz), δ ppm: 176.7; 152.9; 147.4; 138.4 (t, 2J\textsubscript{CF} = 27.5 Hz); 126.7 (t, 3J\textsubscript{CF} = 7.6 Hz); 121.2 (t, 1J\textsubscript{CF} = 239.7 Hz); 119.0; 112.8; 37.24 (t, 2J\textsubscript{CF} = 25.7 Hz); 31.82; 29.37; 29.3; 29.2 (2C); 22.6; 22.1 (t, C\textsubscript{8}, 3J\textsubscript{CF} = 4.1 Hz); 14.1. \textsuperscript{19}F NMR (CDCl\textsubscript{3}, 282 MHz), δ ppm: -98.48 (td, J\textsubscript{FH} = 16.1 Hz, 11.5 Hz, 2.1 Hz). HRMS (ESI) calcd for C\textsubscript{17}H\textsubscript{24}O\textsubscript{2}F\textsubscript{2}\textsuperscript{19}BrNa: [M +Na]+: m/z 321.16421 Found: m/z 321.1640 (1 ppm).

2.4. Synthesis of 4,4-difluoro-1-(thiophene-2-yl)-tridec-2-en-1-one (3d)

The reaction was performed with 2d (730 mg, 2.32 mmol) according to the general procedure. After 1 h, \textsuperscript{19}F NMR showed 100% conversion, and there were two enones, cis and trans (1/100). After purification by flash chromatography on silica gel, the enone 3c was isolated as a yellow oil (437 mg, 60%). RF = 0.24 (Et\textsubscript{2}O/pentane 2/98). \textsuperscript{1}H NMR (CDCl\textsubscript{3}, 300 MHz), δ ppm: 7.83 (dd, 1H, J = 3.9 Hz, J = 1.1 Hz); 7.73 (dd, 1H, J = 5.0 Hz, J = 1.1 Hz); 7.19 (dt, 1H, J = 15.4 Hz, 4J\textsubscript{HF} = 2.3 Hz); 7.18 (dd, 1H, J = 5.0 Hz, J = 3.9 Hz); 6.89 (dt, 1H, J = 15.4 Hz, 3J\textsubscript{HF} = 11.6 Hz); 2.09-1.90 (m, 2H); 1.52-1.43 (m, 2H); 1.38-1.18 (m, 12H); 0.87...
(t, 3H, J = 6.2 Hz). $^{13}$C NMR (CDCl$_3$, 75 MHz), δ ppm: 181.0; 144.4; 138.4 (t, $^2$J$_{CF}$ = 27.2 Hz); 135.2; 133.0; 128.5; 127.1 (t, $^3$J$_{CF}$ = 7.5 Hz); 121.2 (t, $^4$J$_{HF}$ = 239.7 Hz); 37.3 (t, $^2$J$_{CF}$ = 25.7 Hz); 31.8; 29.4; 29.3; 29.2 (2C); 22.7; 22.1 (t, $^3$J$_{CF}$ = 4.1 Hz); 14.1. $^{19}$F NMR (CDCl$_3$, 282 MHz), δ ppm: -98.45 (td, $J_{FH}$ = 16.1 Hz, 11.6 Hz, 2.3 Hz). HRMS (ESI) calcd for C$_{17}$H$_{24}$OF$_2$S$^{79}$BrNa: [M +Na]$^+$ : m/z 377.14136. Found: m/z 337.1418 (1 ppm).

2.5. Synthesis of 1-(4-bromophenyl)-4,4-difluoro-tridec-2-en-1-one (3e)

The reaction was performed with 2e (332 mg, 1.07 mmol) according to the general procedure. After 1 h, $^{19}$F NMR showed 100% conversion, and there were two enones, cis and trans (1/100). After purification by flash chromatography on silica gel, the enone 3c was isolated as a sticky syrup (203 mg, 61%). $^1$H NMR (CDCl$_3$, 300 MHz), δ ppm: 7.86-7.62 (m, 4H); 7.26 (dt, 1H, $J$ = 15.5 Hz, $^4$J$_{HF}$ = 2.3 Hz); 6.86 (dt, 1H, J = 15.5 Hz, $^3$J$_{HF}$ = 11.5 Hz); 2.07-1.89 (m, 2H); 1.53-1.41 (m, 2H, H$_8$); 1.40-1.2 (m, 12H); 0.87 (t, 3H, J = 6.7 Hz). $^{13}$C NMR (CDCl$_3$, 75 MHz), δ ppm: 188.2; 139.5 (t, $^2$J$_{CF}$ = 27.3 Hz); 135.60; 132.2 (2C); 130.2 (2C); 128.9; 126.8 (t, $^3$J$_{CF}$ = 7.5 Hz); 121.1 (t, $^4$J$_{HF}$ = 239.8 Hz); 37.3 (t, $^2$J$_{CF}$ = 25.7 Hz); 31.9; 29.4; 29.3; 29.2 (2C); 22.7; 22.2 (t, $^3$J$_{CF}$ = 4.1 Hz); 14.1. $^{19}$F NMR (CDCl$_3$, 282 MHz), δ ppm: -98.47 (td, $J_{FH}$ = 16.1 Hz, 11.5 Hz, 2.3 Hz). HRMS (ESI) calcd for C$_{19}$H$_{25}$OF$_2$Br$^{79}$BrNa: [M +Na]$^+$ : m/z 409.09545. Found: m/z 409.0952 (1 ppm).

3. General procedure for the synthesis of pyrazolines (4)

The enone 3 (1 equiv) was dissolved in ethanol (2 ml per 1 mmol), then methylhydrazine (4 equiv) was added. The reaction mixture was stirred at 40 °C for the appropriate time (monitored by $^{19}$F NMR). After evaporation of ethanol, the crude product was crystallized and the pyrazoline 4 was purified by chromatography on silica gel, using ether/pentane as eluent.

3.1. Synthesis of 5-(1,1-difluorodecyl)-1-methyl-3-phenyl-4,5-dihydro-1H-pyrazole ((±)-4a)

The reaction was performed with 3a (100 mg, 0.33 mmol) according to the general procedure. After 11.5 h, $^{19}$F NMR monitoring showed the absence of starting material. After purification by flash chromatography on silica gel, the pyrazoline 4a was isolated as a sticky syrup (90 mg, 85%). $R_f$ = 0.47 ((Et$_2$O/pentane 1/9). $^1$H NMR (CDCl$_3$, 400 MHz), δ ppm: 7.72-7.62 (m, 2H); 7.34-7.33 (m, 3H); 3.54 (ddddd, 1H, $^3$J$_{HF}$ = 11.7 Hz, J = 11.6 Hz, J = 11.6
Hz, $^3J_{HF} = 7.4$ Hz); 3.36 (dd, 1H, $J = 16.8$ Hz, $J = 11.6$ Hz); 3.07 (dd, 1H, $J = 16.8$ Hz, $J = 11.6$ Hz); 2.99 (s, 3H); 2.05-1.82 (m, 2H); 1.62-1.54 (m, 2H); 1.38-1.22 (m, 12H); 0.89 (t, 3H, $J = 6.7$ Hz). $^{13}$C NMR (CDCl$_3$, 100 MHz); δ ppm: 149.3; 132.1; 128.9; 128.8 (2C); 127.1 (2C); 124.7 (t, $^3J_{CF} = 251.9$ Hz); 71.19 (dd, $^2J_{CF} = 27.5$ Hz, $^2J_{CF} = 26.6$ Hz); 43.9; 35.8 (dd, $^3J_{CF} = 5.3$ Hz, $^3J_{CF} = 2.0$ Hz); 33.0 (t, $^2J_{CF} = 24.2$ Hz); 31.9; 29.43; 29.40; 29.3; 22.7; 22.2 (t, $^3J_{CF} = 4.2$ Hz); 14.1. $^{19}$F NMR (CDCl$_3$, 282 MHz), δ ppm: -102.11 (dddd, $J_{FF} = 250.6$ Hz, $J_{FH} = 20.8$ Hz, 15.6 Hz, 11.7 Hz); -104.33 (ddddd, $J_{FF} = 250.6$ Hz, $J_{FH} = 22.1$ Hz, 16.5 Hz, 7.4 Hz). HRMS (ESI) calcd for C$_{20}$H$_{30}$F$_2$N$_5^{79}$BrNa: [M +Na]$^+$ : m/z 359.22747. Found: m/z 359.2274 (0 ppm).

3.2. Synthesis 3-[5-(1,1-difluorodecyl)-1-methyl-4,5-dihydro-1H-pyrazole-3-yl]-pyridine ((±)-4b)

The reaction was performed with 3b (100 mg, 0.29 mmol) according to the general procedure. After 2.5 h, $^{19}$F NMR monitoring showed the absence of starting material. After purification by flash chromatography on silica gel, the pyrazoline 4b was isolated as yellow crystals (88 mg, 79%). Mp: 51-53 °C. R$_f$ = 0.44 (Et$_2$O/pentane 5/5). $^1$H NMR (CDCl$_3$, 300 MHz), δ ppm: 8.72 (s, 1H); 8.50 (d, 1H, $J = 3.8$ Hz); 7.93 (dt, 1H, $J = 8.0$ Hz, $J = 1.6$ Hz); 7.23 (dd, 1H, $J = 8.0$ Hz, $J = 3.8$ Hz); 3.51 (dddd, 1H, $J = 11.9$ Hz, $J = 11.7$ Hz, $^3J_{HF} = 11.7$ Hz, $^2J_{HF} = 6.6$ Hz); 3.26 (dd, 1H, $J = 16.9$ Hz, $J = 11.7$ Hz); 2.94 (dd, 1H, $J = 16.9$ Hz, $J = 11.9$ Hz); 2.93 (s, 3H); 2.03-1.66 (m, 2H); 1.56-1.41 (m, 2H); 1.34-1.09 (m, 12H); 0.80 (t, 3H, $J = 6.7$ Hz). $^{13}$C NMR (CDCl$_3$, 75 MHz), δ ppm: 149.6; 147.1; 146.1; 132.8; 128.2; 124.36 (t, C$_{10}$, $^1J_{CF} = 242.8$ Hz); 123.4; 71.1 (dd, $^2J_{CF} = 27.9$ Hz, $^2J_{CF} = 27.2$ Hz); 43.67 (t, $J = 1.5$ Hz); 35.2 (dd, $^3J_{CF} = 5.1$ Hz, $^3J_{CF} = 2.6$ Hz); 32.90 (t, $^2J_{CF} = 24.3$ Hz); 31.2; 29.39 (2C); 29.36; 29.2; 22.6; 21.1 (t, $^3J_{CF} = 4.0$ Hz); 14.1. $^{19}$F NMR (CDCl$_3$, 282 MHz), δ ppm: -102.55 (ddt, $J_{FF} = 250.7$ Hz, $J_{FH} = 26.5$ Hz, 11.7 Hz); -104.54 (ddddd, $J_{FF} = 250.7$ Hz, $J_{FH} = 26.3$ Hz, 10.4 Hz, 6.6 Hz). HRMS (ESI) calcd for C$_{19}$H$_{29}$F$_2$N$_3^{79}$BrNa: [M +H]$^+$ : m/z 338.24078. Found: m/z 338.2408 (0 ppm).

3.3. Synthesis of 5-(1,1-difluorodecyl)-3-furan-2-yl-1-methyl-4,5-dihydro-1H-pyrazole ((±)-4c)

The reaction was performed with 3c (58 mg, 0.17 mmol) according to the general procedure. After 2 h 35 min, $^{19}$F NMR monitoring showed the absence of starting material. After purification by flash chromatography on silica gel, the pyrazoline 4c was isolated as white
crystals (54 mg, 81%). Mp: 68-70 °C. \( R_f = 0.31 \) (Et₂O/pentane 1/9). \(^1\)H NMR (CDCl₃, 300 MHz), δ ppm: 7.44 (dd, 1H, \( J = 1.8 \) Hz, 0.7 Hz); 6.52 (dd, 1H, \( J = 3.4 \) Hz, \( J = 0.7 \) Hz); 6.43 (dd, 1H, \( J = 3.4 \) Hz, \( J = 1.8 \) Hz); 3.50 (ddd, 1H, \( J = 11.9 \) Hz, \( 3J_{HF} = 11.9 \) Hz, \( J = 11.8 \) Hz, \( 3J_{HF} = 6.2 \) Hz); 3.24 (dd, 1H, \( J = 16.9 \) Hz, \( J = 11.9 \) Hz); 3.00 (dd, 1H, \( J = 16.9 \) Hz, \( J = 12.1 \) Hz); 2.87 (s, 3H); 2.02-1.77 (m, 2H); 1.61-1.49 (m, 2H); 1.39-1.19 (m, 12H); 0.85 (t, 3H, \( J = 6.7 \) Hz). \(^{13}\)C NMR (CDCl₃, 125 MHz), δ ppm: 147.5; 143.5; 141.3; 124.5 (t, \( 3J_{CF} = 242.8 \) Hz); 111.5; 109.8; 123.4; 71.9 (dd, \( 2J_{CF} = 28.5 \) Hz, \( 2J_{CF} = 27.5 \) Hz); 43.9; 35.7 (dd, \( 3J_{CF} = 5.4 \) Hz, \( 3J_{CF} = 2.1 \) Hz); 32.9 (t, \( 2J_{CF} = 24.3 \) Hz); 31.9; 29.43 (2C); 29.39; 29.2; 22.7; 21.1 (t, \( 3J_{CF} = 4.0 \) Hz); 14.1. \(^{19}\)F NMR (CDCl₃, 282 MHz), δ ppm: -102.05 (ddt, \( J_{FF} = 251.6 \) Hz, \( J_{FH} = 27.3 \) Hz, 11.9 Hz); -104.17 (ddddd, \( J_{FF} = 251.6 \) Hz, \( J_{FH} = 25.8 \) Hz, 11.6 Hz, 6.2 Hz). HRMS (ESI) calcd for C₁₉H₂₈F₂N₂O⁷⁹BrNa: \([\text{M} + \text{Na}]^+\) : m/z 349.20674. Found: m/z 349.2067 (0 ppm).

3.4. Synthesis of 5-(1,1-difluorodecyl)-1-methyl-3-(thiophen-2-yl)-4,5-dihydro-1H-pyrazole ((±)-4d)

The reaction was performed with 3d (155 mg, 0.45 mmol) according to the general procedure. After 4 h 35 min, \(^{19}\)F NMR monitoring showed the absence of starting material. After purification by flash chromatography on silica gel, the pyrazoline 4d was isolated as white crystals (137 mg, 82%). Mp: 67-69 °C. \( R_f = 0.29 \) (Et₂O/pentane 5/95). \(^1\)H NMR (CDCl₃, 300 MHz), δ ppm: 7.28 (dd, 1H, \( J = 5.0 \) Hz, 1.2 Hz); 7.06 (dd, 1H, \( J = 3.6 \) Hz, \( J = 1.2 \) Hz); 7.00 (dd, 1H, \( J = 5.0 \) Hz, \( J = 3.6 \) Hz); 3.52 (ddddd, 1H, \( J = 11.9 \) Hz, \( J = 11.5 \) Hz, \( 3J_{HF} = 11.5 \) Hz, \( 3J_{HF} = 6.7 \) Hz); 3.31 (dd, 1H, \( J = 16.7 \) Hz, \( J = 11.5 \) Hz); 3.05 (dd, 1H, \( J = 16.7 \) Hz, \( J = 11.9 \) Hz); 2.89 (s, 3H); 2.09-1.76 (m, 2H); 1.65-1.49 (m, 2H); 1.43-1.23 (m, 12H); 0.88 (t, 3H, \( J = 6.7 \) Hz). \(^{13}\)C NMR (CDCl₃, 75 MHz), δ ppm: 145.1; 135.8; 127.2; 126.8; 126.3; 124.5 (t, \( 1J_{CF} = 242.6 \) Hz); 71.6 (dd, \( 2J_{CF} = 28.5 \) Hz, \( 2J_{CF} = 27.6 \) Hz); 43.8 (t, \( 3J = 1.4 \) Hz); 36.5 (dd, \( 3J_{CF} = 5.4 \) Hz, \( 3J_{CF} = 2.4 \) Hz); 32.8 (t, \( 2J_{CF} = 24.2 \) Hz); 31.2; 29.37 (2C); 29.34; 29.2; 22.6; 21.0 (t, \( 3J_{CF} = 4.0 \) Hz); 14.0. \(^{19}\)F NMR (CDCl₃, 282 MHz), δ ppm: -101.92 (ddt, \( J_{FF} = 250.9 \) Hz, \( J_{FH} = 27.9 \) Hz, 11.5 Hz); -104.21 (ddddd, \( J_{FF} = 250.9 \) Hz, \( J_{FH} = 27.5 \) Hz, 11.2 Hz, 6.7 Hz). HRMS (ESI) calcd for C₁₉H₂₈F₂N₂O⁷⁹BrNa: \([\text{M} + \text{Na}]^+\) : m/z 365.18390. Found: m/z 365.1849 (3 ppm).
3.5. Synthesis of 3-(4-bromophenyl)-5-(1,1-difluorodecyl)-1-methyl-4,5-dihydro-1H-pyrazole (±)-4e

The reaction was performed with 3e (75 mg, 0.18 mmol) according to the general procedure. After 2.5 h, $^{19}$F NMR monitoring showed the absence of starting material. After purification by flash chromatography on silica gel, the pyrazoline 4e was isolated as a sticky syrup (74 mg, 86%). $R_f$ = 0.43 (Et$_2$O/pentane 5/95). $^1$H NMR (CDCl$_3$, 300 MHz), $\delta$ ppm: 7.47 (s, 4H); 3.55 (dddd, 1H, $J_{HF} = 12.0$ Hz, $^3J_{HF} = 11.8$ Hz, $^3J_{HF} = 6.6$ Hz); 3.29 (dd, 1H, $J = 16.9$ Hz, $J = 11.8$ Hz); 3.00 (dd, 1H, $J = 16.9$ Hz, $J = 12.0$ Hz); 2.99 (s, 3H); 2.08-1.75 (m, 2H); 1.64-1.49 (m, 2H); 1.43-1.18 (m, 12H); 0.88 (t, 3H, $J = 6.7$ Hz). $^{13}$C NMR (CDCl$_3$, 75 MHz), $\delta$ ppm: 148.0; 131.7 (2C); 131.1; 127.7 (2C); 124.5 (t, $^1J_{CF} = 242.6$ Hz); 123.0; 71.3 (dd, $^2J_{CF} = 28.5$ Hz, $^2J_{CF} = 27.5$ Hz); 43.8 (t, 1.4 Hz); 35.6 (dd, $^3J_{CF} = 5.1$ Hz, $^3J_{CF} = 2.5$ Hz); 33.1 (t, $^2J_{CF} = 24.3$ Hz); 31.9; 29.5 (2C); 29.4; 29.3; 22.7; 21.1 (t, $^3J_{CF} = 3.9$ Hz); 14.1. $^{19}$F NMR (CDCl$_3$, 282 MHz), $\delta$ ppm: -102.23 (ddt, $J_{FF} = 250.8$ Hz, $J_{FH} = 26.9$ Hz, 11.8 Hz); -104.38 (dddt, $J_{FF} = 250.8$ Hz, $J_{FH} = 27.3$ Hz, 11.5 Hz, 6.6 Hz). HRMS (ESI) calcd for C$_{20}$H$_{29}$F$_2$N$_2$Br$^{79}$BrNa: [M +Na]$^+$ : m/z 437.13799. Found: m/z 437.1382 (0 ppm).
4. General procedure for the synthesis of pyrrolines (6)

To a solution of *gem*-difluoroenone 3 (1 equiv) and Schiff base 5 (1 equiv) in CH₂Cl₂ (1.5 ml per mmol) cooled to 5 °C was added DBU (0.5 equiv). After stirring at 25 °C for the appropriate time (monitored by ¹⁹F NMR), HCl (12 N, 1.5 equiv) was added and the mixture was stirred at 25 °C for the time *t* (monitored by ¹⁹F NMR). Then water was added and the mixture was extracted with CH₂Cl₂. The organic layers were combined, dried over MgSO₄, filtered and concentrated in vacuo. The crude residue was then purified by flash chromatography over silica gel.

4.1. Synthesis of 3-(1,1-difluorodecyl)-5-phenyl-3,4-dihydro-2H-pyrrole-2-carboxylic acid ethyl ester ((±)-6a)

The reaction was performed from 3a (400 mg, 1.29 mmol) according to the general procedure. After purification by chromatography on silica gel, pyrrole 6a was obtained as beige crystals (378 mg, 74% yield). Mp: 66-68 °C. Rₛ = 0.31 (Et₂O/pentane 2/8). ¹H NMR (CD₆D₆, 300 MHz), δ ppm: 7.85-7.75 (dd, 2H, J = 7.7 Hz, J = 1.4 Hz); 7.11-7.03 (m, 3H); 5.23 (dt, 1H, J = 6.5 Hz, ⁴J_HF = 1.7 Hz); 4.41-3.94 (m, 2H); 3.51-3.29 (m, 1H); 2.92 (dd, 1H, J = 17.4 Hz, J = 7.2 Hz, ⁴J_HF = 1.7 Hz); 2.82 (ddd, 1H, J = 17.4 Hz, J = 10.0 Hz, ⁴J_HF = 2.3 Hz); 1.73-1.62 (m, 2H); 1.56-1.43 (m, 2H); 1.33-1.12 (m, 12H); 0.96 (t, 3H, J = 7.1 Hz), 0.91 (t, 3H, J = 6.6 Hz). ¹³C NMR (CDCl₃, 75 MHz), δ ppm: 174.1; 171.8; 133.2; 131.2; 128.4 (2C); 128.0 (2C); 124.4 (t, ¹J_CF = 243.1 Hz); 75.5 (dd, ³J_CF = 4.0 Hz, ³J_CF = 2.7 Hz); 61.6; 46.1 (t, ²J_CF = 25.1 Hz); 36.7 (dd, ³J_CF = 5.0 Hz, ³J_CF = 2.7 Hz); 35.3 (t, ²J_CF = 25.1 Hz); 31.8; 29.4; 29.32; 29.27; 29.2; 22.6; 21.8 (t, ³J_CF = 4.3 Hz); 14.11; 14.05. ¹⁹F NMR (CD₆D₆, 282 MHz), δ ppm: -103.05 (dq, 1F, J_FF = 244.1 Hz, J_FH = 16.5 Hz); -104.8 (dq, 1F, J_FF = 244.1 Hz, J_FH = 16.2 Hz). HRMS (ESI) calcd for C₂₃H₃₃F₂NO₂²⁹BrNa: [M +Na]⁺: m/z 416.23771. Found: m/z 416.2370 (2 ppm).

4.2. Synthesis of 3-(1,1-Difluorodecyl)-5-(pyridin-3-yl)-3,4-dihydro-2H-pyrrole-2-carboxylic acid ethyl ester ((±)-6b)

The reaction was performed from 3b (205 mg, 0.66 mmol) according to the general procedure. After purification by chromatography on silica gel, pyrrole 6b was obtained as
white crystals (191 mg, 73% yield). Mp: 43-45 °C. \( R_f = 0.32 \) (Et₂O/pentane 7/3). \(^1\)H NMR (\( \text{CD}_6\), 300 MHz), \( \delta \) ppm: 8.91 (d, 1H, \( J = 1.2 \) Hz); 8.46 (dd, 1H, \( J = 4.6 \) Hz, \( J = 1.2 \) Hz); 7.94 (dt, 1H, \( J = 8.0 \) Hz, \( J = 1.8 \) Hz); 6.61 (ddd, 1H, \( J = 8.0 \) Hz, \( J = 4.6 \) Hz, \( J = 0.6 \) Hz); 5.19 (dt, 1H, \( J = 6.5 \) Hz, \( 4 J_{HF} = 1.7 \) Hz); 4.10-3.94 (m, 2H); 3.45-3.21 (m, 1H); 2.74 (ddd, 1H, \( J = 17.5 \) Hz, \( J = 7.2 \) Hz, \( 4 J_{HF} = 1.7 \) Hz); 2.63 (ddd, 1H, \( J = 17.5 \) Hz, \( J = 10.0 \) Hz, \( 4 J_{HF} = 2.4 \) Hz); 1.75-1.59 (m, 2H); 1.54-1.45 (m, 2H); 1.28-1.13 (m, 12H); 0.96 (t, 3H, \( J = 7.1 \) Hz), 0.92 (t, 3H, \( J = 7.0 \) Hz). \(^{13}\)C NMR (\( \text{CDCl}_3\), 75 MHz), \( \delta \) ppm: 171.9; 171.5; 152.0; 149.3; 135.1; 129.0; 127.5; 124.3 (t, \( 1 J_{CF} = 243.3 \) Hz); 123.5; 75.6 (dd, \( 3 J_{CF} = 4.2 \) Hz, \( 3 J_{CF} = 2.8 \) Hz); 61.8; 46.1 (t, \( 2 J_{CF} = 25.3 \) Hz); 36.6 (dd, \( 3 J_{CF} = 5.2 \) Hz, \( 3 J_{CF} = 2.7 \) Hz); 35.7 (t, \( 2 J_{CF} = 24.8 \) Hz); 31.8; 29.4; 29.34; 29.30; 29.2; 22.6; 21.8 (t, \( 3 J_{CF} = 3.9 \) Hz); 14.1; 14.0. \(^{19}\)F NMR (\( \text{CDCl}_3\), 282 MHz), \( \delta \) ppm: -103.55 (dq, 1F, \( J_{FF} = 244.4 \) Hz, \( J_{FH} = 17.8 \) Hz); -105.86 (dq, 1F, \( J_{FF} = 244.5 \) Hz, \( J_{FH} = 15.5 \) Hz). HRMS (ESI) calcld for C\(_{22}\)H\(_{32}\)F\(_2\)N\(_2\)O\(_2\)-\(^{79}\)BrNa: [M +Na]\(^+\) : \( m/z \) 417.23295. Found: \( m/z \) 417.2328 (0 ppm).

4.3. Synthesis of 3-(1,1-difluorodecyl)-5-(furan-2-yl)-3,4-dihydro-2H-pyrrole-2-carboxylic acid ethyl ester ((±)-6c)

The reaction was performed from 3c (236 mg, 0.79 mmol) according to the general procedure. After purification by chromatography on silica gel, pyrroline 6c was obtained as beige crystals (227 mg, 75% yield). Mp: 64-66 °C. \( R_f = 0.28 \) (Et₂O/pentane 3/7). \(^1\)H NMR (\( \text{CD}_6\), 300 MHz), \( \delta \) ppm: 6.96 (d, 1H, \( J = 1.5 \) Hz); 6.74 (d, 1H, \( J = 3.5 \) Hz); 5.94 (dd, 1H, \( J = 3.5 \) Hz, \( J = 1.5 \) Hz); 5.21 (dt, 1H, \( J = 6.3 \) Hz, \( 4 J_{HF} = 1.9 \) Hz); 4.07-3.91 (m, 2H); 3.43-3.21 (m, 1H); 2.95 (ddd, 1H, \( J = 17.7 \) Hz, \( J = 7.4 \) Hz, \( 4 J_{HF} = 1.8 \) Hz); 2.86 (ddd, 1H, \( J = 17.7 \) Hz, \( J = 9.9 \) Hz, \( 4 J_{HF} = 2.1 \) Hz); 1.74-1.56 (m, 2H); 1.52-1.38 (m, 2H); 1.34-1.08 (m, 12H); 0.94 (t, 3H, \( J = 7.2 \) Hz), 0.91 (t, 3H, \( J = 6.9 \) Hz). \(^{13}\)C NMR (\( \text{CD}_6\), 75 MHz), \( \delta \) ppm: 171.7; 164.4; 150.0; 144.5; 124.8 (t, \( 1 J_{CF} = 243.0 \) Hz); 113.3; 111.8; 76.3 (dd, \( 3 J_{CF} = 3.7 \) Hz, \( 3 J_{CF} = 2.9 \) Hz); 61.3; 46.2 (t, \( 2 J_{CF} = 25.3 \) Hz); 36.9 (dd, \( 3 J_{CF} = 4.9 \) Hz, \( 3 J_{CF} = 3.0 \) Hz); 35.9 (t, \( 2 J_{CF} = 25.1 \) Hz); 32.1; 29.7; 29.6; 29.5; 29.4; 22.9; 22.1 (t, \( 3 J_{CF} = 4.2 \) Hz); 14.2; 13.9. \(^{19}\)F NMR (\( \text{CD}_6\), 282 MHz), \( \delta \) ppm: -103.43 (dq, 1F, \( J_{FF} = 244.3 \) Hz, \( J_{FH} = 16.4 \) Hz); -104.57 (dq, 1F, \( J_{FF} = 244.3 \) Hz, \( J_{FH} = 15.9 \) Hz). HRMS (ESI) calcld for C\(_{23}\)H\(_{31}\)F\(_2\)NO\(_3\)-\(^{79}\)BrNa: [M +Na]\(^+\) : \( m/z \) 406.21697. Found: \( m/z \) 406.2168 (0 ppm).
4.4. Synthesis of 3-(1,1-difluorodecyl)-5-(thiophen-2-yl)-3,4-dihydro-2H-pyrrole-2-carboxylic acid ethyl ester ((±)-6d)

The reaction was performed from 3d (250 mg, 0.79 mmol) according to the general procedure. After purification by chromatography on silica gel, pyrrole 6d was obtained as white crystals (235 mg, 74% yield). Mp: 67-69 °C. Rf = 0.24 (Et2O/pentane 2/8). 1H NMR (CD6, 400 MHz), δ ppm: 6.87 (dd, 1H, J = 3.6 Hz, J = 0.8 Hz); 6.81 (dd, 1H, J = 4.9 Hz, J = 0.8 Hz); 6.59 (dd, 1H, J = 4.9 Hz, J = 3.6 Hz); 5.14 (dt, 1H, J = 6.4 Hz, 4JHF = 1.4 Hz); 4.08-3.92 (m, 2H); 3.49-3.29 (m, 1H); 2.91 (ddd, 1H, J = 17.2 Hz, J = 7.1 Hz, 4JHF = 1.5 Hz); 2.80 (ddd, 1H , J = 17.2 Hz, J = 10.1 Hz, 4JHF = 2.2 Hz); 1.73-1.61 (m, 2H); 1.55-1.42 (m, 2H); 1.32-1.09 (m, 12H); 0.93 (t, 3H, J = 7.2 Hz), 0.88 (t, 3H, J = 6.8 Hz). 13C NMR (CD6, 75 MHz), δ ppm: 171.8; 168.2; 150.0; 138.7; 130.4; 130.3; 127.3; 124.9 (t, 1JCF = 243.0 Hz); 76.0 (dd, 3JCF = 4.2 Hz, 3JCF = 1.2 Hz); 61.5; 47.0 (t, 2JCF = 25.3 Hz); 37.4 (dd, 3JCF = 4.9 Hz, 3JCF = 1.9 Hz); 36.0 (t, 2JCF = 25.1 Hz); 32.2; 29.8; 29.71; 29.66; 29.59; 23.1; 22.2 (t, 3JCF = 4.2 Hz); 14.3; 14.0. 19F NMR (CD6, 282 MHz), δ ppm: -102.73 (dq, 1F, JFF = 244.3 Hz, JFH = 16.8 Hz); -104.8 (dq, 1F, JFF = 244.3 Hz, JFH = 16.1 Hz). HRMS (ESI) calcd for C21H31F2NO2S79BrNa: [M+Na]+ : m/z 422.19413. Found: m/z 422.1927 (3 ppm).

4.5. Synthesis of 5-(4-bromophenyl)-3-(1,1-difluorodecyl)-3,4-dihydro-2H-pyrrole-2-carboxylic acid ethyl ester ((±)-6e)

The reaction was performed from 3e (380 mg, 0.98 mmol) according to the general procedure. After purification by chromatography on silica gel, pyrrole 6e was obtained as white crystals (363 mg, 78% yield). Mp: 45-47 °C. Rf = 0.29 (Et2O/pentane 1/9). 1H NMR (CD6, 400 MHz), δ ppm: 7.40 (d, 1H, J = 8.6 Hz, J = 1.9 Hz); 7.17 (dd, 1H, J = 8.6 Hz, J = 1.6 Hz); 5.16 (dt, 1H, J = 6.5 Hz, 4JHF = 1.7 Hz); 4.09-3.95 (m, 2H); 3.48-3.21 (m, 1H); 2.78 (ddd, 1H, J = 17.4 Hz, J = 7.3 Hz, 4JHF = 1.5 Hz); 2.65 (ddd, 1H , J = 17.4 Hz, J = 10.1 Hz, 4JHF = 2.3 Hz); 1.76-1.64 (m, 2H); 1.57-1.45 (m, 2H); 1.34-1.14 (m, 12H); 0.91 (t, 3H, J = 7.1 Hz), 0.86 (t, 3H, J = 6.5 Hz). 13C NMR (CDCl3, 75 MHz), δ ppm: 173.2; 171.7; 132.1; 131.8 (2C); 129.6 (2C); 125.9; 124.4 (t, 1JCF = 243.2 Hz); 75.6 (dd, 3JCF = 4.1 Hz, 3JCF = 2.6 Hz); 61.8; 46.2 (t, 2JCF = 25.2 Hz); 36.7 (dd, 3JCF = 5.1 Hz, 3JCF = 2.6 Hz); 35.7 (t, 2JCF = 24.9 Hz); 31.9; 29.4; 29.39; 29.34; 29.28; 22.7; 21.9 (t, 3JCF = 4.1 Hz); 14.2; 14.1. 19F NMR (CDCl3, 282 MHz), δ ppm: -103.48 (dq, 1F, JFF = 244.5 Hz , JFH = 13.6 Hz); -105.73 (dq, 1F, JFF = 244.5 Hz, JFH = 15.6 Hz). HRMS (ESI) calcd for C23H32F2NO2Br79BrNa: [M+Na]+ : m/z 494.14822. Found: m/z 494.1483 (0 ppm).
5. General procedure for the Suzuki–Miyaura reaction

A solution of brominated derivates 4e or 6e (1 equiv), phenylboronic acid (2 equiv), palladium dichlorobistriphenylphosphine (5 mol %) and potassium carbonate (2 equiv) in a 5/1 mixture of dioxane and water (1 ml per 0.1 mmol) was stirred at 90 °C for 24 h. After addition of MgSO₄ and filtration, the residues were washed with ether and the solution concentrated in vacuo. The crude residue was then purified by flash chromatography on silica gel.

5.1. Synthesis of 3-biphenyl-4-yl-5(1,1-difluorodecyl)-1-methyl-4,5-dihydro-1H-pyrazole ((±)-7e)

The reaction was performed from 4e (78 mg, 0.19 mmol) according to the general procedure. After purification by chromatography on silica gel, the product 7e was isolated as a sticky syrup (64 mg, 82% yield). Rf = 0.31 (Et₂O/pentane 5/95). ¹H NMR (CDCl₃, 300 MHz), δ ppm: 7.72-7.67 (m, 2H); 7.64-7.57 (m, 4H); 7.49-7.34 (m, 3H); 3.54 (dddd, 1H, J = 12.0 Hz, J = 11.7 Hz, ³J_HF = 11.7 Hz, ³J_HF = 6.6 Hz); 3.29 (dd, 1H, J = 16.9 Hz, J = 11.7 Hz); 3.02 (dd, 1H, J = 16.9 Hz, J = 12.0 Hz); 3.00 (s, 3H); 2.09-1.74 (m, 2H); 1.63-1.51 (m, 2H); 1.43-1.18 (m, 12H); 0.87 (t, 3H, J = 6.7 Hz). ¹³C NMR (CDCl₃, 75 MHz), δ ppm: 149.3; 141.7; 140.3; 130.8; 128.82 (2C); 127.6; 127.2 (2C); 127.0 (2C); 126.4 (2C); 124.5 (t, ¹J_CF = 242.8 Hz); 71.1 (dd, ²J_CF = 28.4 Hz, ²J_CF = 27.4 Hz); 44.0; 35.8 (dd, ³J_CF = 5.1 Hz, ³J_CF = 2.1 Hz); 33.0 (t, ²J_CF = 24.4 Hz); 31.8; 29.43 (2C); 29.40; 29.3; 22.7; 21.1 (t, ³J_CF = 4.1 Hz); 14.1. ¹⁹F NMR (CDCl₃, 282 MHz), δ ppm: -102.13 (ddt, J_FF = 250.5 Hz, J_FH = 26.8 Hz, 11.7 Hz); -104.33 (dddd, J_FF = 250.5 Hz, J_FH = 27.2 Hz, 11.5 Hz, 6.6 Hz). HRMS (ESI) calcd for C₂₆H₃₄F₂N₂⁺BrNa: [M +Na]⁺: 435.25878. m/z Found: 435.2584 (1 ppm).

5.2. Synthesis of 5-biphenyl-4-yl-3-(1,1-difluorodecyl)-3,4-dihydro-2H-pyrrole-2-carboxylic acid ethyl ester (±)-10e

The reaction was performed from 6e (67 mg, 0.14 mmol) according to the general procedure. After purification by chromatography on silica gel, the product 10e was isolated as a sticky syrup (52 mg, 78% yield). Rf = 0.35 (Et₂O/pentane 2/8). ¹H NMR (C₆D₆, 300 MHz), δ ppm: 7.88-7.79 (m, 2H); 7.43-7.34 (m, 4H); 7.24-7.16 (m, 3H); 5.28 (dt, 1H, J = 6.4 Hz, ⁴J_HF = 1.5 Hz); 4.06-3.92 (m, 2H); 3.55-3.32 (m, 1H); 3.01 (ddd, 1H, J = 17.4 Hz, J = 7.3 Hz, ⁴J_HF = 1.6 Hz).
Hz; 2.88 (ddd, 1H, J = 17.4 Hz, J = 10.1 Hz, \(^4J_{HF} = 2.3\) Hz); 1.84-1.63 (m, 2H); 1.61-1.48 (m, 2H); 1.36-1.12 (m, 12H); 0.99 (t, 3H, J = 7.1 Hz), 0.92 (t, 3H, J = 7.0 Hz). \(^{13}\text{C}\) NMR (CD\(_2\)OD, 75 MHz), \(\delta\) ppm: 173.3; 172.1; 144.0; 140.7; 132.9; 129.2 (2C); 129.1(2C); 127.3 (2C); 127.2 (2C); 125.1 (t, \(^1J_{CF} = 242.9\) Hz); 76.4 (dd, \(^3J_{CF} = 3.7\) Hz, \(^3J_{CF} = 2.7\) Hz); 61.5; 46.8 (t, \(^2J_{CF} = 24.8\) Hz); 36.9 (dd, \(^3J = 4.6\) Hz, \(^3J_{CF} = 2.7\) Hz); 35.1 (t, \(^2J_{CF} = 25.1\) Hz); 32.2; 29.84; 29.75; 29.68; 29.65; 23.1; 22.3 (t, \(^3J_{CF} = 4.3\) Hz); 14.3; 14.1. \(^{19}\text{F}\) NMR (CD\(_2\)OD, 282 MHz), \(\delta\) ppm: -102.9 (dq, 1F, \(J_{FF} = 243.8\) Hz, \(J_{FH} = 16.7\) Hz); -104.8 (dq, 1F, \(J_{FF} = 243.8\) Hz, \(J_{FH} = 16.2\) Hz). HRMS (ESI) calcd for C\(_{20}\)H\(_{37}\)F\(_2\)NO\(_2\)\(^{39}\)BrNa: [M +Na]\(^+\) : m/z 492.26901. Found: m/z 492.2682 (2 ppm).

6. General procedure for the Heck reaction

Et\(_3\)N (1 ml per 0.1 mmol) was first degassed by bubbling argon for 10 min. Then were added successively: bromo-compound 4e or 6e (1 equiv), palladium acetate (10 mol %), tri-o-tolylphosphine (0.2 equiv) and methyl acrylate (3.2 equiv). The reaction mixture was stirred under argon at 100 °C for 12 h. After addition of ether, the reaction mixture was washed with water and the aqueous phase was extracted with ether. The combined organic phases were dried (MgSO\(_4\)), filtered and concentrated in vacuo. The crude residue was then purified by flash chromatography on silica gel.

6.1. Synthesis of 3-(4-[5-(1,1-difluorodecyl)-1-methyl-4,5-dihydro-1H-pyrazol-3-yl]-phenyl)-acrylic acid methyl ester ((\pm\)-8e)

The reaction was performed from 4e (111 mg, 0.27 mmol) according to the general procedure. After purification by chromatography on silica gel, the product 8e was isolated as a sticky syrup (81 mg, 72% yield). \(R_f = 0.30\) (Et\(_2\)O/pentane 1/9). \(^1\text{H}\) NMR (CDCl\(_3\), 300 MHz), \(\delta\) ppm: 7.67 (d, 1H, \(J = 16.1\) Hz); 7.61 (d, 2H, \(J = 8.4\) Hz ); 7.50 (d, 2H, \(J = 8.4\) Hz); 6.45 (d, 1H, \(J = 16.1\) Hz); 3.80 (s, 3H); 3.58 (dddd, 1H, \(J = 12.0\) Hz, \(^3J_{HF} = 11.9\) Hz, \(J = 11.7\) Hz, \(^3J_{HF} = 6.5\) Hz); 3.33 (dd, 1H, \(J = 16.8\) Hz, \(J = 11.7\) Hz); 3.02 (dd, 1H, \(J = 16.8\) Hz, \(J = 12.0\) Hz); 3.01 (s, 3H); 2.08-1.76 (m, 2H); 1.63-1.50 (m, 2H); 1.39-1.17 (m, 12H); 0.88 (t, 3H, \(J = 6.7\) Hz). \(^{13}\text{C}\) NMR (CDCl\(_3\), 75 MHz), \(\delta\) ppm: 167.3; 148.1; 144.0; 134.6; 133.9; 128.2 (2C); 126.2 (2C); 124.5 (t, \(^1J_{CF} = 242.6\) Hz); 118.0; 71.2 (t, \(^2J_{CF} = 28.8\) Hz); 51.7; 43.7; 35.5 (dd, \(^3J_{CF} = 5.0\) Hz, \(^3J_{CF} = 2.3\) Hz); 33.0 (t, \(^2J_{CF} = 24.3\) Hz); 31.8; 29.41 (2C); 29.37; 29.2; 22.6; 21.1 (t, \(^3J_{CF} = 4.0\) Hz); 14.1. \(^{19}\text{F}\) NMR (CDCl\(_3\), 282 MHz), \(\delta\) ppm: -102.22 (ddt, \(J_{FF} = 250.5\) Hz, \(J_{FH} =
27.0 Hz, 11.9 Hz); -104.34 (dddd, \( J_{FF} = 250.9 \) Hz, \( J_{FH} = 26.7 \) Hz, 12.2 Hz, 6.5 Hz). HRMS (ESI) calcd for C\(_{24}\)H\(_{33}\)F\(_{2}\)N\(_{2}\)O\(_{2}\)Na: [M + Na]\(^+\) : m/z 443.24860. Found: m/z 443.2787 (0 ppm).

6.2. Synthesis of 3-(1,1-difluorodecyl)-5-[4-(2-methoxycarbonyl-vinyl)-phenyl]-3,4-dihydro-2H-pyrrole-2-carboxylic acid ethyl ester ((\(\pm\))-11e)

The reaction was performed from 6e (124 mg, 0.26 mmol) according to the general procedure. After purification by chromatography on silica gel, the product 11e was isolated as a sticky syrup (80 mg, 64% yield). \( \text{Rf} = 0.14 \) (Et\(_2\)O/pentane 2/8). \(^1\)H NMR (C\(_6\)D\(_6\), 300 MHz), \( \delta \) ppm: 7.70 (d, 1H, \( J = 16.1 \) Hz); 7.62 (d, 2H, \( J = 8.3 \) Hz); 7.00 (d, 2H, \( J = 8.3 \) Hz); 6.37 (d, 1H, \( J = 16.1 \) Hz); 5.23 (dt, 1H, \( J = 6.4 \) Hz, \( 4J_{HF} = 1.8 \) Hz); 4.12-3.94 (m, 2H); 3.48 (s, H); 3.47-3.29 (m, 1H); 2.83 (ddd, 1H, \( J = 17.4 \) Hz, \( J = 7.3 \) Hz, \( 4J_{HF} = 1.6 \) Hz); 2.65 (ddd, 1H, \( J = 17.4 \) Hz, \( J = 10.1 \) Hz, \( 4J_{HF} = 2.3 \) Hz); 1.80-1.62 (m, 2H); 1.60-1.45 (m, 2H); 1.31-1.13 (m, 12H); 0.98 (t, 3H, \( J = 7.1 \) Hz), 0.92 (t, 3H, \( J = 6.5 \) Hz). \(^{13}\)C NMR (C\(_6\)D\(_6\), 75 MHz), \( \delta \) ppm: 173.0; 171.9; 166.7; 143.8; 137.1; 135.1; 128.8 (2C); 128.2; 124.4 (t, \( 1J_{CF} = 242.7 \) Hz); 119.6; 75.4 (dd, \( 3J_{CF} = 4.2 \) Hz, \( 3J_{CF} = 2.7 \) Hz); 61.6; 51.3; 46.7 (t, \( 2J_{CF} = 25.4 \) Hz); 36.8 (dd, \( 3J_{CF} = 5.0 \) Hz, \( 3J_{CF} = 2.7 \) Hz); 36.1 (t, \( 2J_{CF} = 25.0 \) Hz); 32.2; 29.8; 29.73; 29.67; 29.6; 23.1; 22.3 (t, \( 3J_{CF} = 4.0 \) Hz); 14.3; 14.1. \(^{19}\)F NMR (C\(_6\)D\(_6\), 282 MHz), \( \delta \) ppm: -102.90 (dq, 1F, \( J_{FF} = 244.3 \) Hz, \( J_{FH} = 16.2 \) Hz); -105.0 (dq, 1F, \( J_{FF} = 244.3 \) Hz, \( J_{FH} = 16.8 \) Hz). HRMS (ESI) calcd for C\(_{27}\)H\(_{37}\)F\(_{2}\)NO\(_{4}\)Na: [M + Na]\(^+\) : m/z 500.25883. Found: m/z 500.2590 (0 ppm).

7. General procedure for the Sonogashira reaction

Dioxane (1 ml per 0.1 mmol) was first degassed by bubbling argon. Then were added successively: bromo-compound (4e or 6e) (1 equiv), palladium dichlorobistriphenylphosphine (5 mol %), copper iodide (2.5 mol %), potassium carbonate (2 equiv) and ethynylbenzene (1 equiv). The reaction mixture was stirred under argon at 90 °C for 2 d. After addition of ether the reaction mixture was washed with water, the aqueous phase was extracted with ether. The combined organic phases were dried (MgSO\(_4\)), filtered and concentrated in vacuo. The crude residue was then purified by flash chromatography on silica gel.

7.1. Synthesis of 5-(1,1-difluorodecyl)-1-methyl-3-(4-phenylethynyl-phenyl)-4,5-dihydro-1H-pyrazole ((\(\pm\))-9e)

The reaction was performed from 4e (100 mg, 0.26 mmol) according to the general procedure. After purification by chromatography on silica gel, the product 9e was isolated as
a sticky syrup (78 mg, 74% yield). $R_f = 0.29$ (Et$_2$O/pentane 5/95). $^1$H NMR (CDCl$_3$, 300 MHz), δ ppm: 7.67-7.53 (m, 6H); 7.42-7.36 (m, 3H); 3.61 (dddd, 1H, $J = 12.0$ Hz, $^3J_{HF} = 11.8$ Hz; $J = 11.7$ Hz, $^3J_{HF} = 6.4$ Hz); 3.29 (dd, 1H, $J = 16.8$ Hz, $J = 11.7$ Hz); 3.00 (dd, 1H, $J = 16.8$ Hz, $J = 12.0$ Hz); 3.04 (s, 3H); 2.15-1.81 (m, 2H); 1.63-1.58 (m, 2H); 1.41-1.24 (m, 12H); 0.91 (t, 3H, $J = 6.5$ Hz). $^{13}$C NMR (CDCl$_3$, 75 MHz), δ ppm: 148.4; 131.9; 131.7 (2C); 131.6 (2C); 128.4 (2C); 125.9 (2C); 125.3; 124.6 (t, $^1J_{CF} = 242.7$ Hz); 123.6; 123.1; 90.9; 89.3; 71.3 (dd, $^2J_{CF} = 28.6$ Hz, $J_{CF} = 27.4$ Hz); 43.8; 35.5 (dd, $^3J_{CF} = 5.1$ Hz, $J_{CF} = 2.3$ Hz); 33.0 (t, $^2J_{CF} = 24.5$ Hz); 31.9; 29.43 (2C); 29.40; 29.3; 22.7; 21.1 (t, $^3J_{CF} = 4.1$ Hz); 14.1. $^{19}$F NMR (CDCl$_3$, 282 MHz), δ ppm: -102.23 (ddt, $J_{FF} = 250.8$ Hz, $J_{FH} = 26.9$ Hz, 11.8 Hz); -104.38 (dddd, $J_{FF} = 250.8$ Hz, $J_{FH} = 27.3$ Hz, 11.5 Hz, 6.4 Hz). HRMS (ESI) calcd for C$_{28}$H$_{34}$F$_2$N$_2$BrNa: [M + Na]$^+$ : m/z 459.2583. Found: m/z 459.2587 (0 ppm).

7.2. Synthesis of 3-(1,1-difluorodecyl)-5-(4-phenylethynyl-phenyl)-3,4-dihydro-2H-pyrrole-2-carboxylic acid ethyl ester ((±)-12e)

The reaction was performed from 6e (100 mg, 0.21 mmol) according to the general procedure. After purification by chromatography on silica gel, the product 12e was isolated as a sticky syrup (73 mg, 70% yield). $R_f = 0.21$ (Et$_2$O/pentane 1/9). $^1$H NMR (C$_6$D$_6$, 400 MHz), δ ppm: 7.69-7.61 (m, 2H); 7.55-7.49 (m, 2H); 7.46-7.40 (2H); 7.1-6.8 (3H); 5.22 (dt, 1H, $J = 6.5$ Hz, $^4J_{HF} = 1.6$ Hz); 4.13-3.97 (m, 2H); 3.49-3.32 (m, 1H); 2.85 (ddd, 1H, $J = 17.4$ Hz, $J = 7.4$ Hz, $^4J_{HF} = 1.6$ Hz); 2.71 (ddd, 1H , $J = 17.4$ Hz, $J = 10.2$ Hz, $^4J_{HF} = 2.3$ Hz); 1.77-1.64 (m, 2H); 1.57-1.47 (m, 2H); 1.29-1.15 (m, 12H); 0.99 (t, 3H, $J = 7.1$ Hz), 0.92 (t, 3H, $J = 6.9$ Hz). $^{13}$C NMR (CDCl$_3$, 75 MHz), δ ppm: 172.7; 171.6; 133.3; 131.7 (2C); 131.6 (2C); 128.4 (2C); 128.3 (2C); 126.1; 124.7 (t, $^1J_{CF} = 242.9$ Hz); 92.0; 89.6; 76.1; 61.3; 46.2 (t, $^2J_{CF} = 25.1$ Hz); 36.5 (dd, $^3J = 5.0$ Hz, $^3J_{CF} = 2.0$ Hz); 35.9 (t, $^2J_{CF} = 25.1$ Hz); 32.0; 29.6; 29.5; 29.4; 22.8; 21.0 (t, $^3J_{CF} = 3.9$ Hz); 14.1; 13.8. $^{19}$F NMR (C$_6$D$_6$, 282 MHz), δ ppm: -102.91 (dq, 1F, $J_{FF} = 243.9$ Hz, $J_{FH} = 16.5$ Hz); -104.75 (dq, 1F, $J_{FF} = 243.9$ Hz, $J_{FH} = 16.1$ Hz). HRMS (ESI) calcd for C$_{51}$H$_{77}$F$_2$NO$_2$BrNa: [M + Na]$^+$ : m/z 516.26901. Found: m/z 516.2689 (0 ppm).
8. Analysis of $^{19}$F/$^1$H HOESY 2D-NMR spectrum of (±)-6a

Figure S-1: Pulse gradient $^{19}$F/$^1$H HOESY 2D-NMR spectrum of (±)-6a in C$_6$D$_6$ recorded at 300 K and 9.4 T (Bruker avance I NMR spectrometer equipped with a QXO probe, ($^v$(^{19}F) = 376.5 MHz/$^v$(^1^H) = 400.1 MHz) and 300 K. The map was recorded using a 2D matrix of 4096($t_1$) x 256($t_2$) data points, and then zero-filled to 4096($t_1$) x 1024($t_2$) data points. The mixing time was set up at 800 ms. 16 scans were added per $t_1$ increment. Exponential filtering (LB = 5 Hz) was applied in both spectral dimensions. The $F_1$ and $F_2$ projections displayed correspond to $^{19}$F-$^1$H} and $^1$H 1D spectra, respectively.
9. Library of $^1$H, $^{13}$C-{$^1$H}, $^{19}$F-{$^1$H} and $^{19}$F 1D-NMR spectra
CDCl₃, 202 MHz

CDCl₃, 202 MHz