Electronic Supporting Information

for

Highly chemoselective difluoromethylative homologation of iso(thio)cyanates: expeditious access to unprecedented α,α-difluoro(thio)amides

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Table of contents

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Materials and Methods 2</td>
</tr>
<tr>
<td>2.</td>
<td>General procedures for the preparation of α,α-difluoromethyl-(thio)amides 3</td>
</tr>
<tr>
<td>3.</td>
<td>Spectral and characterization data for α,α-difluoromethyl thioamides 4</td>
</tr>
<tr>
<td>4.</td>
<td>Spectral and characterization data for α,α-difluoromethyl oxoamides 22</td>
</tr>
<tr>
<td>5.</td>
<td>Synthetic manipulations of compounds (Scheme 4) 32</td>
</tr>
<tr>
<td>6.</td>
<td>$^1$H- and $^{13}$C-NMR spectra 35</td>
</tr>
<tr>
<td>7.</td>
<td>$^{19}$F-NMR spectra 79</td>
</tr>
<tr>
<td>8.</td>
<td>References 101</td>
</tr>
</tbody>
</table>
1. Materials and Methods

Melting Points were determined on a Reichert-Kofler hot-stage microscope and are uncorrected. Mass spectra were obtained on a Shimadzu QP 1000 instrument (EI, 70 eV) and on a Bruker maXis 4G instrument (ESI-TOF, HRMS). $^1$H, $^{13}$C, $^{15}$N and $^{19}$F NMR spectra were recorded on a Bruker Avance III 400 spectrometer (400 MHz for $^1$H, 100 MHz for $^{13}$C, 40 MHz for $^{15}$N, 376 MHz for $^{19}$F) at 297 K using a directly detecting broadband observe (BBFO) probe. The centre of the solvent signal was used as an internal standard which was related to TMS with δ 7.26 ppm ($^1$H in CDCl$_3$), δ 77.00 ppm ($^{13}$C in CDCl$_3$). $^{15}$N spectra (gsHMBC) were referenced against neat, external nitromethane, $^{19}$F NMR spectra by absolute referencing via $\Xi$ ratio. Spin-spin coupling constants ($J$) are given in Hz.

In nearly all cases, full and unambiguous assignment of all resonances was performed by combined application of standard NMR techniques, such as APT, HSQC, HMBC, COSY and NOESY experiments.

All the reactions were carried out under inert atmosphere of argon. THF was distilled over Na/benzophenone. Chemicals were purchased from Sigma-Aldrich, Acros, Alfa Aesar and TCI Europe. Solutions were evaporated under reduced pressure with a rotary evaporator.

TLC was carried out on aluminium sheets precoated with silica gel 60F254 (Merchery-Nagel, Merk); the spots were visualised under UV light ($\lambda$ = 254 nm).
2. General Procedures

2.1 General Procedure A for the synthesis of α,α-difluoromethyl thioamides.

Difluoromethyltrimethylsilane (1.5 equiv) was added under an inert atmosphere to a solution of isothiocyanate (1 equiv) in dry THF and the mixture was cooled down to 0 °C. Then potassium tert-amylate solution (0.9 M in THF, 1.2 equiv) was added dropwise over a period of 30 minutes. Then the mixture was stirred at 0°C for 1 hour and then quenched with aqueous NH₄Cl solution. The reaction mixture was then extracted with Et₂O (x 3), washed with brine, dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The resulting reaction crudes were purified through column chromatography as indicated.

2.2 General Procedure B for the synthesis of α,α-difluoromethyl amides.

Difluoromethyltrimethylsilane (1.5 equiv) was added under an inert atmosphere to a solution of isocyanate (1 equiv) in dry THF and the mixture was cooled down to 0 °C. Then potassium tert-amylate solution (0.9 M in THF, 1.2 equiv) was added dropwise over a period of 30 minutes. Then the mixture was stirred at 0°C for 1 hour and then quenched with aqueous NH₄Cl solution. The reaction mixture was then extracted with Et₂O (x 3), washed with brine, dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The resulting reaction crudes were purified through column chromatography as indicated.

ethyl 4-[(2,2-difluoroethanethioyl)amino]benzoate (2)

By following General Procedure A, starting from ethyl 4-isothiocyanatobenzoate (0.207 g, 1 mmol, 1.0 equiv) in dry THF (10 mL), CHF₂SiMe₃ (0.185 g, 1.5 mmol, 1.5 equiv) and potassium tert-amylate solution 0.9 M in THF (1.3 mL, 1.2 mmol, 1.2 equiv), compound 2 was obtained in 83% yield (0.215 g) as yellow solid (mp 71-74°C) after column chromatography on silica gel (n-hexane:ethyl acetate 9:1).

1H NMR (400 MHz, CDCl₃): δ 9.33 (br s, 1H, NH), 8.13 (m, 2H, Ph H-2,6), 7.99 (m, 2H, Ph H-3,5), 6.27 (t, 3JFH = 56.5 Hz, 1H, CHF₂), 4.39 (q, 3J =7.1 Hz, 2H, OCH₂), 1.41 (t, 3J = 7.1 Hz, 3H, CH₃).

13C NMR (100 MHz, CDCl₃): δ 165.5 (CO), 140.6 (Ph C-4), 130.8 (Ph C-2,6), 129.2 (Ph C-1), 121.7 (Ph C-3,5), 112.9 (t, 1JC,F = 258.3 Hz, CHF₂), 61.2 (OCH₂), 14.3 (CH₃).

15N NMR (40 MHz, CDCl₃): δ -291.0 (NH).

19F NMR (376 MHz, CDCl₃): δ -115.9 (dd, 2JHF = 56.5 Hz, 0JHF = 3.4 Hz, CHF₂).

HRMS (ESI), m/z: calcd. for C₁₁H₁₂F₂NO₂S⁺: 260.0551 [M+H]⁺; found: 260.0546.

ethyl 4-[[((2-methyl-2-butanyl)oxy)carbothioyl]amino]benzoate (2b)

1H NMR (400 MHz, CDCl₃): δ 7.97 (m, 2H, Ph H-2,6), 7.42 (m, 2H, Ph H-3,5), 6.69 (br s, 1H, NH), 4.35 (q, 3J =7.1 Hz, 2H, OCH₂), 1.84 (q, 3J =7.5 Hz, 2H, CH₂), 1.49 (s, 6H, CH₃), 1.38 (t, 3J = 7.1 Hz, 3H, OCH₂CH₃), 0.93 (t, 3J = 7.5 Hz, 3H, CH₃).

13C NMR (100 MHz, CDCl₃): δ 166.3 (CO), 152.1 (C=S), 142.6 (Ph C-4), 130.8 (Ph C-2,6), 124.7 (Ph C-1), 117.3 (Ph C-3,5), 83.7 (C(CH₃)₂), 60.7 (OCH₂), 33.6 (CH₂), 25.7 (2C, CH₃), 14.3 (OCH₂CH₃), 8.2 (CH₃).

HRMS (ESI), m/z: calcd. for C₁₅H₂₁NO₃S⁺: 296.1315 [M+H]⁺; found: 296.1319.
**N-(4-cyanophenyl)-2,2-difluoroethanethioamide (3)**

By following General Procedure A, starting from 4-isothiocyanatobenzonitrile (0.160 g, 1 mmol, 1.0 equiv) in dry THF (10 mL), CHF$_2$SiMe$_3$ (0.185 g, 1.5 mmol, 1.5 equiv) and potassium tert-amylate solution 0.9 M in THF (1.3 mL, 1.2 mmol, 1.2 equiv), compound 3 was obtained in 93% yield (0.197 g) as pale yellow solid (mp 155-158 °C) after column chromatography on silica gel (n-hexane:ethyl acetate 9:1).

$^1$H NMR (400 MHz, CDCl$_3$): δ 9.33 (br s, 1H, NH), 8.07 (m, 2H, Ph H-2,6), 7.74 (m, 2H, Ph H-3,5), 6.27 (t, $^2$J$_{H,F}$ = 56.4 Hz, 1H, CHF$_2$).

$^{13}$C NMR (100 MHz, CDCl$_3$): δ 187.4 (t, $^2$J$_{C,F}$ = 20.3 Hz, C=S), 140.6 (Ph C-1), 133.3 (Ph C-3,5), 122.4 (Ph C-2,6), 118.0 (CN), 112.8 (t, $^1$J$_{C,F}$ = 258.8 Hz, CHF$_2$), 110.7 (Ph C-4).

$^{15}$N NMR (40 MHz, CDCl$_3$): δ -292.4 (NH).

$^{19}$F NMR (376 MHz, CDCl$_3$): δ -115.9 (dd, $^2$J$_{H,F}$ = 56.4 Hz, $^3$J$_{H,F}$ = 3.4 Hz, CHF$_2$).


**N-(3-cyanophenyl)-2,2-difluoroethanethioamide (4)**

By following General Procedure A, starting from 3-isothiocyanatobenzonitrile (0.160 g, 1 mmol, 1.0 equiv) in dry THF (10 mL), CHF$_2$SiMe$_3$ (0.185 g, 1.5 mmol, 1.5 equiv) and potassium tert-amylate solution 0.9 M in THF (1.3 mL, 1.2 mmol, 1.2 equiv), compound 4 was obtained in 86% yield (0.182 g) as yellow solid (mp 112-115°C) after column chromatography on silica gel (n-hexane:ethyl acetate 8:2).
$^1$H NMR (400 MHz, CDCl$_3$): δ 9.34 (br s, 1H, NH), 8.31 (m, 1H, Ph H-2), 8.02 (m, 1H, Ph H-6), 7.62 (m, 1H, Ph H-4), 7.57 (m, 1H, Ph H-5), 6.28 (t, $^{2}$$J_{H,F}$ = 56.3 Hz, 1H, CHF$_2$).

$^{13}$C NMR (100 MHz, CDCl$_3$): δ 187.8 (t, $^{2}$$J_{C,F}$ = 20.8 Hz, C=S), 137.7 (Ph C-1), 130.9 (Ph C-4), 130.2 (Ph C-5), 126.9 (Ph C-6), 125.8 (Ph C-2), 117.7 (CN), 113.4 (Ph C-3), 112.7 (t, $^{1}$$J_{C,F}$ = 258.4 Hz, CHF$_2$).

$^{15}$N NMR (40 MHz, CDCl$_3$): δ -294.1 (NH).

$^{19}$F NMR (376 MHz, CDCl$_3$): δ -116.1 (dd, $^{2}$$J_{H,F}$ = 56.3 Hz, $^{2}$$J_{H,F}$ = 3.2 Hz, CHF$_2$).


2,2-difluoro-N-(4-nitrophenyl)ethanethioamide (5)

By following General Procedure A, starting from 1-isothiocyanato-4-nitrobenzene (0.180 g, 1 mmol, 1.0 equiv) in dry THF (10 mL), CHF$_2$SiMe$_3$ (0.185 g, 1.5 mmol, 1.5 equiv) and potassium tert-amylate solution 0.9 M in THF (1.3 mL, 1.2 mmol, 1.2 equiv), compound 5 was obtained in 85% yield (0.197 g) as brown solid (mp 60-63°C) after column chromatography on silica gel (n-hexane:ethyl acetate 7:3).

$^1$H NMR (400 MHz, CDCl$_3$): δ 9.41 (br s, 1H, NH), 8.33 (m, 2H, Ph H-3,5), 8.14 (m, 2H, Ph H-2,6), 6.29 (t, $^{2}$$J_{H,F}$ = 56.3 Hz, 1H, CHF$_2$).

$^{13}$C NMR (100 MHz, CDCl$_3$): δ 187.6 (t, $^{2}$$J_{C,F}$ = 20.6 Hz, C=S), 145.7 (Ph C-4), 142.2 (Ph C-1), 125.0 (Ph C-3,5), 122.2 (Ph C-2,6), 112.8 (t, $^{1}$$J_{C,F}$ = 258.8 Hz, CHF$_2$).

$^{15}$N NMR (40 MHz, CDCl$_3$): δ -293.0 (NH).

$^{19}$F NMR (376 MHz, CDCl$_3$): δ -115.9 (dd, $^{2}$$J_{H,F}$ = 56.3 Hz, $^{2}$$J_{H,F}$ = 3.2 Hz, CHF$_2$).

HRMS (ESI), m/z: calcld. for C$_8$H$_6$F$_2$N$_2$NaO$_2$: 255.0010 [M+Na]$^+$; found: 255.0009.

N-(4-azidophenyl)-2,2-difluoroethanethioamide (6)
By following General Procedure A, starting from 1-isothiocyanato-4-azidobenzene (0.176 g, 1 mmol, 1.0 equiv) in dry THF (10 mL), CHF$_2$SiMe$_3$ (0.185 g, 1.5 mmol, 1.5 equiv) and potassium tert-amylate solution 0.9 M in THF (1.3 mL, 1.2 mmol, 1.2 equiv), compound 6 was obtained in 88% yield (0.201 g) as yellow oil after column chromatography on silica gel (n-hexane:ethyl acetate 8:2).

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 9.25 (br s, 1H, NH), 7.84 (m, 2H, Ph C-2,6), 7.10 (m, 2H, Ph C-3,5), 6.28 (t, $^2$J$_{H,F}$ = 56.5 Hz, 1H, CHF$_2$).

$^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 186.6 (t, $^2$J$_{C,F}$ = 20.4 Hz, C=S), 133.6 (Ph C-1), 139.1 (Ph C-4), 124.2 (Ph C-2,6), 119.6 (Ph C-3,5), 112.8 (t, $^1$J$_{C,F}$ = 258.1 Hz, CHF$_2$).

$^{15}$N NMR (40 MHz, CDCl$_3$): $\delta$ -291.7 (NH).

$^{19}$F NMR (376 MHz, CDCl$_3$): $\delta$ -116.1 (dd, $^2$J$_{H,F}$ = 56.5 Hz, $^3$J$_{H,F}$ = 3.3 Hz, CHF$_2$).

HRMS (ESI), m/z: calcd. for C$_8$H$_7$F$_2$N$_4$S$: 229.0354 [M+H]$: found: 229.0342.

2,2-difluoro-N-{4-[(E)-phenyldiazenyl]phenyl}ethanethioamide (7)

By following General Procedure A, starting from 1-(4-isothiocyanatophenyl)-2-phenyldiazene (0.239 g, 1 mmol, 1.0 equiv) in dry THF (10 mL), CHF$_2$SiMe$_3$ (0.185 g, 1.5 mmol, 1.5 equiv), potassium tert-amylate solution 0.9 M in THF (1.3 mL, 1.2 mmol, 1.2 equiv), compound 7 was obtained in 90% yield (0.262 g) as orange solid (mp 83-86°C) after column chromatography on silica gel (n-hexane:diethyl ether 7:3).
\( ^1H \text{ NMR} \) (400 MHz, CDCl\(_3\)): \( \delta \) 9.37 (br s, 1H, NH), 8.08 (m, 2H, Ph1 H-2,6), 8.02 (m, 2H, Ph1 H-3,5), 7.93 (m, 2H, Ph2 H-2,6), 7.54 (m, 2H, Ph H-3,5), 7.51 (m, 1H, Ph2 H-4), 6.30 (t, \(^2J_{H,F} = 56.5\) Hz, 1H, CHF\(_2\)).

\( ^{13}C \text{ NMR} \) (100 MHz, CDCl\(_3\)): \( \delta \) 186.7 (C=S), 152.6 (Ph2 C-1), 151.0 (Ph1 C-4), 138.9 (Ph1 C-1), 131.4 (Ph2 C-4), 129.2 (Ph2 C-3,5), 123.9 (Ph1 C-3,5), 123.0 (Ph2 C-2,6), 122.7 (Ph1 C-2,6), 112.9 (t, \(^1J_{C,F} = 258.3\) Hz, CHF\(_2\)).

\( ^{15}N \text{ NMR} \) (40 MHz, CDCl\(_3\)): \( \delta \) -290.6 (NH).

\( ^{19}F \text{ NMR} \) (376 MHz, CDCl\(_3\)): \( \delta \) -115.9 (dd, \(^2J_{H,F} = 56.5\) Hz, \(^3J_{H,F} = 3.4\) Hz, CHF\(_2\)).

HRMS (ESI), \( m/z \): calcd. for C\(_{14}\)H\(_{12}\)F\(_3\)N\(_3\)S\(^+\): 292.0715 [M+H]\(^+\); found: 292.0706.
**N-(4-bromophenyl)-2,2-difluoroethanethioamide (8)**

By following General Procedure A, starting from 1-isothiocyanato-4-bromobenzene (0.214 g, 1 mmol, 1.0 equiv) in dry THF (10 mL), CHF$_2$SiMe$_3$ (0.185 g, 1.5 mmol, 1.5 equiv) and potassium tert-amylate solution 0.9 M in THF (1.3 mL, 1.2 mmol, 1.2 equiv), compound 8 was obtained in 91% yield (0.242 g) as yellow oil after column chromatography on silica gel (n-hexane:ethyl acetate 9:1).

**Reaction conducted on 10 mmol scale.** By following General Procedure A, starting from 1-isothiocyanato-4-bromobenzene (2.14 g, 10 mmol, 1.0 equiv) in dry THF (80 mL), CHF$_2$SiMe$_3$ (1.85 g, 15 mmol, 1.5 equiv) and potassium tert-amylate solution 0.9 M in THF (13 mL, 12 mmol, 1.2 equiv), compound 8 was obtained in 88% yield (2.34 g) as yellow oil after column chromatography on silica gel (n-hexane:ethyl acetate 9:1).

*Spectral and spectrometric data match with those reported for the compound obtained in the 1 mmol scale reaction.*

$^1$H NMR (400 MHz, CDCl$_3$): δ 9.20 (br s, 1H, NH), 7.75 (m, 2H, Ph H-2,6), 7.57 (m, 2H, Ph H-3,5), 6.27 (t, $^2J_{HF}$ = 56.5 Hz, 1H, CHF$_2$).

$^{13}$C NMR (100 MHz, CDCl$_3$): δ 186.9 (t, $^1J_{CF}$ = 20.3 Hz, C=S), 135.9 (Ph C-1), 132.3 (Ph C-3,5), 124.1 (Ph C-2,6), 120.6 (Ph C-4), 112.8 (t, $^1J_{CF}$ = 258.2 Hz, CHF$_2$).

$^{15}$N NMR (40 MHz, CDCl$_3$): δ -292.3 (NH).

$^{19}$F NMR (376 MHz, CDCl$_3$): δ -116.1 (dd, $^2J_{HF}$ = 56.5 Hz, $^2nJ_{HF}$ = 3.3 Hz, CHF$_2$).

HRMS (ESI), m/z: calcd. for C$_8$H$_7$BrF$_2$NS$^+$: 265.9445 [M+H]$^+$; found: 265.9438.
**N-(3-bromophenyl)-2,2-difluoroethanethioamide (9)**

![Chemical Structure](image)

By following General Procedure A, starting from 1-isothiocyanato-3-bromobenzene (0.213 g, 1 mmol, 1.0 equiv) in dry THF (10 mL), CHF$_2$SiMe$_3$ (0.185 g, 1.5 mmol, 1.5 equiv) and potassium tert-amylate solution 0.9 M in THF (1.3 mL, 1.2 mmol, 1.2 equiv), compound 9 was obtained in 87% (0.230 g) as yellow oil after column chromatography on silica gel (n-heptane:ethyl acetate 8:2).

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 9.21 (br s, 1H, NH), 8.10 (m, 1H, Ph H-2), 7.76 (m, 1H, Ph H-6), 7.47 (m, 1H, Ph H-4), 7.32 (m, 1H, Ph H-5), 6.27 (t, $^2$J$_{HF}$ = 56.5 Hz, 1H, CHF$_2$).

$^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 187.0 (C=S), 138.0 (Ph C-1), 130.6 (Ph C-4), 130.5 (Ph C-5), 125.5 (Ph C-2), 122.6 (Ph C-3), 121.3 (Ph C-6), 112.8 (t, $^1$J$_{CF}$ = 258.3 Hz, CHF$_2$).

$^{15}$N NMR (40 MHz, CDCl$_3$): $\delta$ -292.9 (NH).

$^{19}$F NMR (376 MHz, CDCl$_3$): $\delta$ -116.1 (dd, $^2$J$_{HF}$ = 56.5 Hz, $^3$J$_{HF}$ = 3.3 Hz, CHF$_2$).

HRMS (ESI), m/z: calcd. for C$_{8}$H$_{7}$BrF$_2$NS$^+$: 265.9445 [M+H$^+$]; found: 265.9421

**2,2-difluoro-N-(4-fluorophenyl)ethanethioamide (10)**

![Chemical Structure](image)

By following General Procedure A, starting from 1-isothiocyanato-4-fluorobenzene (0.153 g, 1 mmol, 1.0 equiv) in dry THF (10 mL), CHF$_2$SiMe$_3$ (0.185 g, 1.5 mmol, 1.5 equiv) and potassium tert-amylate solution 0.9 M in THF (1.3 mL, 1.2 mmol, 1.2 equiv), compound 10 was obtained in 95% yield (0.195 g) as yellow oil after column chromatography on silica gel (n-hexane:ethyl acetate 8:2).
**1H NMR** (400 MHz, CDCl₃): δ 9.26 (br s, 1H, NH), 7.79 (m, 2H, Ph H-2,6), 7.14 (m, 2H, Ph H-3,5), 6.28 (t, JHF = 56.5 Hz, 1H, CHF₂).

**13C NMR** (100 MHz, CDCl₃): δ 187.1 (t, JC,F = 20.4 Hz, C=S), 161.1 (d, JCF = 248.7 Hz, Ph C-4), 132.8 (d, JCF = 3.0 Hz, Ph C-1), 124.9 (d, JCF = 8.4 Hz, Ph C-2,6), 116.1 (d, JCF = 23.0 Hz, Ph C-3,5), 112.8 (t, JCF = 258.0 Hz, CHF₂).

**15N NMR** (40 MHz, CDCl₃): δ -308.6 (NH).

**19F NMR** (376 MHz, CDCl₃): δ -116.2 (dd, JHF = 56.4 Hz, JHF = 3.3 Hz, CHF₂), -112.4 (m, Ph-F).

**HRMS** (ESI), m/z: calcd. for C₈H₇F₂NS: 206.0246 [M+H]+; found: 206.0233.

**N-(3-chlorophenyl)-2,2-difluoroethanethioamide (11)**

By following General Procedure A, starting from 1-isothiocyanato-3-chlorobenzene (0.169 g, 1 mmol, 1.0 equiv) in dry THF (10 mL), CHF₂SiMe₃ (0.185 g, 1.5 mmol, 1.5 equiv) and potassium tert-amylate solution 0.9 M in THF (1.3 mL, 1.2 mmol, 1.2 equiv), compound 11 was obtained in 86% yield (0.190 g) as yellow oil after column chromatography on silica gel (n-hexane:ethyl acetate 8:2).

**1H NMR** (400 MHz, CDCl₃): δ 9.21 (br s, 1H, NH), 7.98 (m, 1H, Ph H-2), 7.69 (m, 1H, Ph H-6), 7.38 (m, 1H, Ph H-5), 7.31 (m, 1H, Ph H-4), 6.27 (t, JHF = 56.5 Hz, 1H, CHF₂).

**13C NMR** (100 MHz, CDCl₃): δ 187.1 (t, JC,F = 20.8 Hz, C=S), 137.9 (Ph C-1), 134.9 (Ph C-3), 130.2 (Ph C-5), 127.7 (Ph C-4), 122.7 (Ph C-2), 120.7 (Ph C-6), 112.8 (t, JCF = 258.4 Hz, CHF₂).

**15N NMR** (40 MHz, CDCl₃): δ -292.5 (NH).

**19F NMR** (376 MHz, CDCl₃): δ -116.1 (dd, JHF = 56.4 Hz, JHF = 3.3 Hz, CHF₂).

**N-(5-chloro-2-methoxyphenyl)-2,2-difluoroethanethioamide (12)**

![Chemical structure of compound 12]

By following General Procedure A, starting from ethyl 4-cloro-2-isothiocyanato-1-methoxybenzoate (0.199 g, 1 mmol, 1.0 equiv) in dry THF (10 mL), CHF$_2$SiMe$_3$ (0.185 g, 1.5 mmol, 1.5 equiv) and potassium tert-amylate solution 0.9 M in THF (1.3 mL, 1.2 mmol, 1.2 equiv), compound 12 was obtained in 83% yield (0.208 g) as brown solid (mp 70-72°C) after column chromatography on silica gel (n-hexane:ethyl acetate 7:3).

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 9.99 (br s, 1H, NH), 9.25 (d, $^3$J$_{H,H}$ = 2.5 Hz, 1H, Ph H-6), 7.22 (dd, $^3$J$_{H,H}$ = 8.8 Hz, $^4$J$_{H,H}$ = 2.5 Hz, 1H, Ph H-4), 6.90 (d, $^3$J$_{H,H}$ = 8.8 Hz, 1H, Ph H-3), 6.23 (t, $^2$J$_{H,F}$ = 56.6 Hz, 1H, CHF$_2$), 3.95 (s, 3H, OCH$_3$).

$^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 185.1 (t, $^2$J$_{C,F}$ = 20.4 Hz, C=S), 148.0 (Ph C-2), 127.6 (Ph C-1), 126.8 (Ph C-4), 125.6 (Ph C-5), 120.4 (Ph C-6), 113.0 (t, $^3$J$_{C,F}$ = 258.4 Hz, CHF$_2$), 111.2 (Ph C-3), 56.4 (OCH$_3$).

$^{15}$N NMR (40 MHz, CDCl$_3$): $\delta$ -299.5 (NH).

$^{19}$F NMR (376 MHz, CDCl$_3$): $\delta$ -115.8 (dd, $^2$J$_{H,F}$ = 56.6 Hz, $^2n$J$_{H,F}$ = 3.4 Hz, CHF$_2$).

HRMS (ESI), $m/z$: calcd. for C$_9$H$_9$ClF$_2$NOS$: 252.0056 [M+H]$^+$; found: 252.0050.

**N-(4-ethoxyphenyl)-2,2-difluoroethanethioamide (13)**

![Chemical structure of compound 13]

By following General Procedure A, starting from 1-isothiocyanato-4-ethoxybenzene (0.179 g, 1 mmol, 1.0 equiv) in dry THF (10 mL), CHF$_2$SiMe$_3$ (0.185 g, 1.5 mmol, 1.5 equiv) and potassium tert-amylate solution 0.9 M in THF (1.3 mL, 1.2 mmol, 1.2 equiv), compound 13 was obtained in 93% yield (0.214 g) as brown oil after column chromatography on silica gel (n-hexane:ethyl acetate 8:2).
\(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 9.20 (br s, 1H, NH), 7.72 (m, 2H, Ph H-2,6), 6.94 (m, 2H, Ph H-3,5), 6.28 (t, \(^2J_{H,F}\) = 56.6 Hz, 1H, CHF\(_2\)), 4.06 (q, \(^3J = 7.0\) Hz, 2H, OCH\(_2\)), 1.43 (t, \(^3J = 7.0\) Hz, 3H, CH\(_3\)).

\(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \(\delta\) 186.0 (t, \(^2J_{C,F} = 20.3\) Hz, C=S), 158.0 (Ph C-4), 129.6 (Ph C-1), 124.3 (Ph C-2,6), 114.8 (Ph C-3,5), 112.8 (t, \(^1J_{C,F} = 257.8\) Hz, CHF\(_2\)), 63.8 (OCH\(_2\)), 14.7 (CH\(_3\)).

\(^{15}\)N NMR (40 MHz, CDCl\(_3\)): \(\delta\) -290.5 (NH).

\(^{19}\)F NMR (376 MHz, CDCl\(_3\)): \(\delta\) -116.1 (dd, \(^2J_{H,F} = 56.5\) Hz, \(^nJ_{H,F} = 3.4\) Hz, CHF\(_2\)).

HRMS (ESI), \(m/z\): calcd. for C\(_{10}\)H\(_{11}\)F\(_2\)NNaOS: 254.0422 [M+Na]\(^+\); found: 224.0420.

2,2-difluoro-N-[4-(methylsulfanyl)phenyl]ethanethioamide (14)

![Diagram of the molecule](attachment:diagram.png)

By following General Procedure A, starting from 1-isothiocyanato-4-methylsulfanylbenzene (0.181 g, 1 mmol, 1.0 equiv) in dry THF (10 mL), CHF\(_2\)SiMe\(_3\) (0.185 g, 1.5 mmol, 1.5 equiv) and potassium tert-amylate solution 0.9 M in THF (1.3 mL, 1.2 mmol, 1.2 equiv), compound 14 was obtained in 88% yield (0.209 g) as yellow oil after column chromatography on silica gel (n-heptane:ethyl acetate 8:2).

\(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 9.22 (br s, 1H, NH), 7.77 (m, 2H, Ph H-2,6), 7.30 (m, 2H, Ph H-3,5), 6.27 (t, \(^2J_{H,F}\) = 56.5 Hz, 1H, CHF\(_2\)), 2.51 (s, 3H, SCH\(_3\)).

\(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \(\delta\) 186.1 (t, \(^2J_{C,F} = 20.5\) Hz, C=S), 138.4 (Ph C-4), 133.9 (Ph C-1), 126.7 (Ph C-2,6), 123.0 (Ph C-3,5), 112.8 (t, \(^1J_{C,F} = 258.1\) Hz, CHF\(_2\)), 15.7(SCH\(_3\)).

\(^{15}\)N NMR (40 MHz, CDCl\(_3\)): \(\delta\) -290.6 (NH).

\(^{19}\)F NMR (376 MHz, CDCl\(_3\)): \(\delta\) -116.0 (dd, \(^2J_{H,F} = 56.5\) Hz, \(^nJ_{H,F} = 3.5\) Hz, CHF\(_2\)).

HRMS (ESI), \(m/z\): calcd. for C\(_9\)H\(_{10}\)F\(_2\)NS\(_2\): 234.0217 [M+H]\(^+\); found: 234.0205.
2,2-difluoro-N-phenylethanethioamide (15)

![Structure of 2,2-difluoro-N-phenylethanethioamide (15)](image)

By following General Procedure A, starting from isothiocyanatobenzene (0.135 g, 1 mmol, 1.0 equiv) in dry THF (10 mL), CHF₂SiMe₃ (0.185 g, 1.5 mmol, 1.5 equiv) and potassium tert-amylate solution 0.9 M in THF (1.3 mL, 1.2 mmol, 1.2 equiv), compound 15 was obtained in 91% yield (0.170 g) as yellow oil after column chromatography on silica gel (n-hexane:ethyl acetate 85:15).

**¹H NMR** (400 MHz, CDCl₃): δ 9.26 (br s, 1H, NH), 7.83 (m, 2H, Ph H-2,6), 7.45 (m, 2H, Ph H-3,5), 7.33 (m, 1H, Ph H-4) 6.28 (t, J₃ˌ₅ = 56.5 Hz, 1H, CHF₂).

**¹³C NMR** (100 MHz, CDCl₃): δ 186.7 (t, JÕ₃ˌ₅ =20.5 Hz, C=S), 136.8 (Ph C-1), 129.2 (Ph C-3,5), 127.7 (Ph C-4), 122.6 (Ph C-2,6), 112.9 (t, J₁ˌ₅ = 258.2 Hz, CHF₂).

**¹⁵N NMR** (40 MHz, CDCl₃): δ -290.0 (NH).

**¹⁹F NMR** (376 MHz, CDCl₃): δ -116.1 (dd, J₂ˌ₅ =56.5 Hz, J₃ˌ₅ = 3.3 Hz, CHF₂).

**HRMS (ESI), m/z**: calcd. for C₈H₈F₂NS⁺: 188.0340 [M+H]⁺; found: 188.0342.

2,2-difluoro-N-(1-naphthyl)ethanethioamide (16)

![Structure of 2,2-difluoro-N-(1-naphthyl)ethanethioamide (16)](image)

By following General Procedure A, starting from 1-isothiocyanatonaphthalene (0.185 g, 1 mmol, 1.0 equiv) in dry THF (10 mL), CHF₂SiMe₃ (0.185 g, 1.5 mmol, 1.5 equiv) and potassium tert-amylate solution 0.9 M in THF (1.3 mL, 1.2 mmol, 1.2 equiv), compound 16 was obtained in 92% yield (0.218 g) as brown oil after column chromatography on silica gel (n-hexane:ethyl acetate 8:2).
$^1$H NMR (400 MHz, CDCl$_3$): δ 9.52 (br s, 1H, NH), 7.93 (m, 2H, H-4,5), 7.91 (m, 1H, H-2), 7.80 (m, 1H, H-8), 7.58 (m, 1H, H-7), 7.57 (m, 1H, H-6), 7.55 (m, 1H, H-3), 6.45 (t, $^2$J$_{H,F}$ = 56.3 Hz, 1H, CHF$_2$).

$^{13}$C NMR (100 MHz, CDCl$_3$): δ 189.6 (t, $^2$J$_{C,F}$ = 20.7 Hz, C=S), 134.3 (napht C-1), 131.9 (napht C-4a), 129.0 (napht C-5), 128.9 (napht C-4), 128.0 (Ph C-9), 127.3 (napht C-7), 126.7 (napht C-6), 125.3 (napht C-3), 123.7 (napht C-2), 120.8 (napht C-8), 113.0 (t, $^1$J$_{C,F}$ = 257.4 Hz, CHF$_2$).

$^{15}$N NMR (40 MHz, CDCl$_3$): δ -297.2 (NH).

$^{19}$F NMR (376 MHz, CDCl$_3$): δ -115.9 (dd, $^2$J$_{H,F}$ = 56.3 Hz, $^3$J$_{H,F}$ = 3.0 Hz, CHF$_2$).

HRMS (ESI), m/z: calcd. for C$_{12}$H$_9$F$_2$NNaS: 260.0316 [M+Na]$^+$; found: 260.0318.

2,2-difluoro-N-(4-methylphenyl)ethanethioamide (17)

By following General Procedure A, starting from 1-isothiocyanato-4-methylbenzene (0.149 g, 1 mmol, 1.0 equiv) in dry THF (10 mL), CHF$_2$SiMe$_3$ (0.185 g, 1.5 mmol, 1.5 equiv) and potassium tert-amylate solution 0.9 M in THF (1.3 mL, 1.2 mmol, 1.2 equiv), compound 17 was obtained in 90% yield (0.181 g) as brown oil after column chromatography on silica gel (n-hexane:ethyl acetate 9:1).

$^1$H NMR (400 MHz, CDCl$_3$): δ 9.22 (br s, 1H, NH), 7.69 (m, 2H, Ph H-2,6), 7.25 (m, 2H, Ph H-3,5), 6.28 (t, $^2$J$_{H,F}$ = 56.6 Hz, 1H, CHF$_2$), 2.38 (s, 3H, CH$_3$).

$^{13}$C NMR (100 MHz, CDCl$_3$): δ 186.4 (t, $^2$J$_{C,F}$ = 20.2 Hz, C=S), 137.8 (Ph C-4), 134.3 (Ph C-1), 129.7 (Ph C-3,5), 122.6 (Ph C-2,6), 112.8 (t, $^1$J$_{C,F}$ = 258.0 Hz, CHF$_2$), 21.2 (CH$_3$).

$^{15}$N NMR (40 MHz, CDCl$_3$): δ -289.9 (NH).

$^{19}$F NMR (376 MHz, CDCl$_3$): δ -116.1 (dd, $^2$J$_{H,F}$ = 56.6 Hz, $^3$J$_{H,F}$ = 3.4 Hz, CHF$_2$).

HRMS (ESI), m/z: calcd. for C$_9$H$_9$F$_2$NNaS: 224.0316 [M+Na]$^+$; found: 224.0310.
**N-(2,6-dimethylphenyl)-2,2-difluoroethanethioamide (18)**

By following General Procedure A, starting from 2-isothiocyanato-1,3-dimethylbenzene (0.163 g, 1 mmol, 1.0 equiv) in dry THF (10 mL), CHF$_2$SiMe$_3$ (0.185 g, 1.5 mmol, 1.5 equiv) and potassium tert-amylate solution 0.9 M in THF (1.3 mL, 1.2 mmol, 1.2 equiv), compound 18 was obtained in 90% yield (0.194 g) as brown oil after column chromatography on silica gel (n-hexane:ethyl acetate 9:1).

$^1$H NMR (400 MHz, CDCl$_3$): δ 8.93 (br s, 1H, NH), 7.24 (m, 1H, Ph H-4), 7.15 (d, $^3$J = 7.5 Hz, 2H, Ph H-3,5), 6.36 (t, $^2$J$_{H,F}$ = 56.2 Hz, 1H, CHF$_2$), 2.23 (s, 6H, CH$_3$).

$^{13}$C NMR (100 MHz, CDCl$_3$): δ 189.7 (t, $^2$J$_{C,F}$ = 20.9 Hz, C=S), 135.2 (Ph C-2,6), 133.6 (Ph C-1), 129.0 (Ph C-4), 128.6 (Ph C-3,5), 112.8 (t, $^1$J$_{C,F}$ = 256.8 Hz, CHF$_2$).

$^{15}$N NMR (40 MHz, CDCl$_3$): δ -295.8 (NH).

$^{19}$F NMR (376 MHz, CDCl$_3$): δ -116.1 (dd, $^2$J$_{H,F}$ = 56.2 Hz, $^3$J$_{H,F}$ = 2.7 Hz, CHF$_2$).

HRMS (ESI), m/z: calcd. for C$_{10}$H$_{11}$F$_2$NNaS: 238.0472 [M+Na]$^+$; found: 238.0475.

**2,2-difluoro-N-mesitylethanethioamide (19)**

By following General Procedure A, starting from 2-isothiocyanato-1,3,5-trimethylbenzene (0.177 g, 1 mmol, 1.0 equiv) in dry THF (10 mL), CHF$_2$SiMe$_3$ (0.185 g, 1.5 mmol, 1.5 equiv) and potassium tert-amylate solution 0.9 M in THF (1.3 mL, 1.2 mmol, 1.2 equiv), compound 19 was obtained in 88% yield (0.202 g) as brown oil after column chromatography on silica gel (n-heptane:ethyl acetate 9:1).
**N-(2,6-diisopropylphenyl)-2,2-difluoroethanethioamide (20)**

By following General Procedure A, starting from 1,3-diisopropyl-2-isothiocyanatobenzene (0.149 g, 1 mmol, 1.0 equiv) in dry THF (10 mL), CHF$_2$SiMe$_3$ (0.185 g, 1.5 mmol, 1.5 equiv) and potassium tert-amylate solution 0.9 M in THF (1.3 mL, 1.2 mmol, 1.2 equiv), compound 20 was obtained in 88% yield (0.238 g) as pale yellow solid (mp 96-99°C) after column chromatography on silica gel (n-hexane:DCM 8:2).

**1H NMR** (400 MHz, CDCl$_3$): δ 8.88 (br s, 1H, NH), 7.25 (d, $^3$J = 7.8 Hz, 2H, Ph H-3,5), 7.41 (t, $^3$J = 7.8 Hz, 1H, Ph H-4), 6.39 (t, $^3$J$_{HF} = 56.2$ Hz, 1H, CHF$_2$), 2.92 (sept., $^3$J = 6.85 Hz, 2H, CH(CH$_3_2$), 1.24 (d, $^3$J = 6.8 Hz, 6H, CH$_3$), 1.19 (d, $^3$J = 6.9 Hz, 6H, CH$_3$).

**13C NMR** (100 MHz, CDCl$_3$): δ 191.1 (t, $^2$J$_{CF} = 20.8$ Hz, C=S), 145.6 (Ph C-2,6), 129.8 (Ph C-4), 130.9 (Ph C-1), 124.1 (Ph C-3,5), 112.9 (t, $^1$J$_{CF} = 257.0$ Hz, CHF$_2$), 28.7 (CH(CH$_3_2$), 24.2 (CH$_3$), 23.2 (CH$_3$).

**15N NMR** (40 MHz, CDCl$_3$): δ -297.9 (NH).

**19F NMR** (376 MHz, CDCl$_3$): δ -116.2 (dd, $^2$J$_{HF} = 56.2$ Hz, $^3$J$_{HF} = 2.6$ Hz, CHF$_2$).

**HRMS** (ESI), m/z: calcd. for C$_{14}$H$_{19}$F$_2$NNaS: 294.1098 [M+Na]'; found: 294.1103.
**N-cyclohexyl-2,2-difluoroethanethioamide (21)**

By following General Procedure A, starting from isothiocyanatocyclohexane (0.141 g, 1 mmol, 1.0 equiv) in dry THF (10 mL), CHF₂SiMe₃ (0.185 g, 1.5 mmol, 1.5 equiv) and potassium tert-amylate solution 0.9 M in THF (1.3 mL, 1.2 mmol, 1.2 equiv), compound 21 was obtained in 85% yield (0.164 g) as brown oil after column chromatography on silica gel (n-hexane:ethyl acetate 9:1).

**¹H NMR** (400 MHz, CDCl₃): δ 7.68 (br s, 1H, NH), 6.15 (t, ²J₉,F = 56.4 Hz, 1H, CHF₂), 4.33 (m, 1H, H-1), 2.10 (m, 2H, H-2,6), 1.78 (m, 2H, H-3,5), 1.68 (m, 1H, H-4), 1.43 (m, 2H, H-3,5), 1.30 (m, 2H, H-2,6), 1.25 (m, 1H, H-4).

**¹³C NMR** (100 MHz, CDCl₃): δ 187.9 (t, ²J₉,F =20.9 Hz, C=S), 112.1 (t, ¹J₉,F = 255.9 Hz, CHF₂), 53.6 (C-1), 31.0 (C-2,6), 25.3 (C-4), 24.5 (C-3,5).

**¹⁵N NMR** (40 MHz, CDCl₃): δ -281.1 (NH).

**¹⁹F NMR** (376 MHz, CDCl₃): δ -117.5 (dd, ²J₉,F = 56.4 Hz, ²J₉,F = 2.5 Hz, CHF₂).

**HRMS** (ESI), m/z: calcd. for C₈H₁₃F₂NNaS: 216.0629 [M+Na]⁺; found: 216.0622.

**N-(cyclohexylmethyl)-2,2-difluoroethanethioamide (22)**

By following General Procedure A, starting from (isothiocyanatomethyl)cyclohexane (0.155 g, 1 mmol, 1.0 equiv) in dry THF (10 mL), CHF₂SiMe₃ (0.185 g, 1.5 mmol, 1.5 equiv) and potassium tert-amylate solution 0.9 M in THF (1.3 mL, 1.2 mmol, 1.2 equiv), compound 22 was obtained in 83% yield (0.172 g) as yellow oil after column chromatography on silica gel (n-hexane:ethyl acetate 9:1).
**1H NMR** (400 MHz, CDCl$_3$): $\delta$ 7.91 (br s, 1H, NH), 6.19 (t, $^{2}\text{J}_{\text{H,F}} = 56.4$ Hz, 1H, CHF$_2$), 3.55 (t, $^{3}\text{J} = 6.2$ Hz, NCH$_2$), 1.76 (m, 4H, H-2,3,5,6), 1.74 (m, 1H, H-1), 1.69 (m, 1H, H-4), 1.26 (m, 2H, H-3,5), 1.19 (m, 1H, H-4), 1.03 (m, 2H, H-2,6).

**13C NMR** (100 MHz, CDCl$_3$): $\delta$ 189.6 (t, $^{2}\text{J}_{\text{C,F}} = 21.0$ Hz, C=S), 112.1 (t, $^{1}\text{J}_{\text{C,F}} = 255.7$ Hz, CHF$_2$), 51.2 (NCH$_2$), 36.6 (C-1), 30.9 (C-2,6), 26.1 (C-4), 25.6 (C-3,5).

**15N NMR** (40 MHz, CDCl$_3$): $\delta$ -297.3 (NH).

**19F NMR** (376 MHz, CDCl$_3$): $\delta$ -117.2 (dd, $^{2}\text{J}_{\text{H,F}} = 56.4$ Hz, $^{n}\text{J}_{\text{H,F}} = 2.7$ Hz, CHF$_2$).

**HRMS** (ESI), $m/z$: calcd. for C$_9$H$_{15}$F$_2$NNaS: 230.0785 [M+Na]$^+$; found: 230.0778.

2,2-difluoro-N-(2-phenylethyl)ethanethioamide (23)

By following General Procedure A, starting from (2-isothiocyanatoethyl)benzene (0.163 g, 1 mmol, 1.0 equiv) in dry THF (10 mL), CHF$_3$SiMe$_3$ (0.185 g, 1.5 mmol, 1.5 equiv) and potassium tert-amylate solution 0.9 M in THF (1.3 mL, 1.2 mmol, 1.2 equiv), compound 23 was obtained in 84% yield (0.181 g) as orange oil after column chromatography on silica gel (n-hexane:ethyl acetate 9:1).

**1H NMR** (400 MHz, CDCl$_3$): $\delta$ 7.88 (br s, 1H, NH), 7.35 (m, 2H, Ph H-3,5), 7.28 (m, 1H, Ph H-4), 7.22 (m, 2H, Ph H-2,6), 6.15 (t, $^{2}\text{J}_{\text{H,F}} = 56.2$ Hz, 1H, CHF$_2$), 3.96 (m, 2H, C$_2$H$_2$NH), 3.01 (t, $^{3}\text{J} = 7.1$ Hz, CH$_2$Ph).

**13C NMR** (100 MHz, CDCl$_3$): $\delta$ 189.7 (t, $^{2}\text{J}_{\text{C,F}} = 21.0$ Hz, C=S), 137.4 (Ph C-1), 129.0 (Ph C-3,5), 128.6 (Ph C-2,6), 127.1 (Ph C-4), 112.0 (t, $^{1}\text{J}_{\text{C,F}} = 255.7$ Hz, CHF$_2$), 46.0 (CH$_2$NH), 33.4 (CH$_2$Ph).

**15N NMR** (40 MHz, CDCl$_3$): $\delta$ -297.5 (NH).

**19F NMR** (376 MHz, CDCl$_3$): $\delta$ -117.4 (dd, $^{2}\text{J}_{\text{H,F}} = 56.2$ Hz, $^{n}\text{J}_{\text{H,F}} = 2.7$ Hz, CHF$_2$).

**HRMS** (ESI), $m/z$: calcd. for C$_{10}$H$_{12}$F$_2$NS$^+$: 216.0653 [M+H]$^+$; found: 216.0650.
By following General Procedure A, starting from (2-isothiocyanatocyclopentyloxy)methylbenzene (0.233 g, 1 mmol, 1.0 equiv) in dry THF (10 mL), CHF$_2$SiMe$_3$ (0.185 g, 1.5 mmol, 1.5 equiv) and potassium tert-amylate solution 0.9 M in THF (1.3 mL, 1.2 mmol, 1.2 equiv), compound 24 was obtained in 90% yield (0.257 g) as yellow oil after column chromatography on silica gel (n-hexane:ethyl acetate 8:2).

$^1$H NMR (400 MHz, CDCl$_3$): δ 7.67 (br s, 1H, NH), 7.34 (m, 4H, Ph H-2,3,5,6), 7.29 (m, 1H, Ph H-4), 6.16 (t, $^2$J$_{H,F}$ = 56.4 Hz, 1H, CHF$_2$), 4.75 (m, 1H, H-1), 4.66 (A-part of an AB-system, $^2$J$_{AB}$= 12.2 Hz, 1H, OCH$_2$), 4.66 (B-part of an AB-system, $^2$J$_{AB}$= 12.2 Hz, 1H, OCH$_2$), 3.94 (m, 1H, H-2), 2.39 (m, 1H, H-5), 1.92 (m, 2H, H-4,3), 1.83 (m, 1H, H-3), 1.75 (m, 1H, H-4), 1.53 (m, 1H, H-5).

$^{13}$C NMR (100 MHz, CDCl$_3$): δ 188.9 (t, $^2$J$_{C,F}$=21.0 Hz, C-S), 138.2 (Ph C-1), 128.4 (Ph C-3,5), 127.69 (Ph C-4) 127.66 (Ph C-2,6), 112.1 (t, $^1$J$_{C,F}$ = 256.0 Hz, CHF$_2$), 83.4 (C-2), 71.3 (OCH$_2$), 60.9 (C-1), 30.7 (C-3), 29.5 (C-5), 21.7 (C-4).

$^{15}$N NMR (40 MHz, CDCl$_3$): δ -287.3 (NH).

$^{19}$F NMR (376 MHz, CDCl$_3$): δ -117.1 (d, $^2$J$_{H,F}$ = 56.4 Hz, CHF$_2$).

HRMS (ESI), m/z: calcd. for C$_{19}$H$_{17}$F$_2$NNaOS: 308.0891 [M+Na]$^+${; found: 308.0889.}

2,2-difluoro-N-(1-phenylethyl)ethanethioamide (25)
By following General Procedure A, starting from (1-isothiocyanatoethyl)benzene (0.163 g, 1 mmol, 1.0 equiv) in dry THF (10 mL), CHF₂SiMe₃ (0.185 g, 1.5 mmol, 1.5 equiv) and potassium tert-amylate solution 0.9 M in THF (1.3 mL, 1.2 mmol, 1.2 equiv), compound 25 was obtained in 91% yield (0.196 g) as pale yellow oil after column chromatography on silica gel (n-hexane:ethyl acetate 8:2).

¹H NMR (400 MHz, CDCl₃): δ 7.99 (br s, 1H, NH), 7.39 (m, 2H, Ph H-3,5), 7.34 (m, 2H, Ph H-2,6), 7.33 (m, 1H, Ph H-4), 6.18 (t, ²J₉,F = 56.3 Hz, 1H, CHF₂), 5.66 (m, 1H, NCH), 1.66 (d, ³J = 6.9 Hz, 3H, CH₃).

¹³C NMR (100 MHz, CDCl₃): δ 188.3 (t, ²J₉,F = 21.0 Hz, C=S), 140.1 (Ph C-1), 129.0 (Ph C-3,5), 128.3 (Ph C-4), 126.5 (Ph C-2,6), 112.1 (t, ¹J₉,C = 256.0 Hz, CHF₂), 54.0 (NCH), 19.8 (CH₃).

¹⁵N NMR (40 MHz, CDCl₃): δ -281.6 (NH).

¹⁹F NMR (376 MHz, CDCl₃): δ -117.2 (dd, ²J₉,F = 56.3 Hz, ³J₉,F = 2.4 Hz, CHF₂).

HRMS (ESI), m/z: calcd. for C₁₀H₁₁F₂NNaS: 238.0467 [M+Na]⁺; found: 238.0474.
4. Spectral and characterization data for α,α-difluoromethy-oxoamides

*N-(4-cyanophenyl)-2,2-difluoroacetamide (26)*

![Chemical Structure](image)

By following General Procedure B, starting from 4-isocyanatobenzonitrile (0.144 g, 1.0 mmol, 1.0 equiv) in dry THF (10 mL), CHF₂SiMe₃ (0.186 g, 1.5 mmol, 1.5 equiv) and potassium tert-amylate solution 0.9 M in THF (1.4 mL, 1.2 mmol, 1.2 equiv), compound 26 was obtained in 90% yield (0.176 g) as yellow solid (mp 125-127 °C) after column chromatography on silica gel (n-hexane:ethyl acetate 8:2).

**¹H NMR** (400 MHz, CDCl₃) δ: 8.10 (br s, 1H, NH), 7.74 (m, 2H, Ph H-2,6), 7.68 (m, 2H, Ph H-3,5), 6.04 (t, ²J_H,F = 54.1 Hz, 1H, CHF₂).

**¹³C NMR** (100 MHz, CDCl₃) δ: 160.6 (t, ²J_C,F =25.2 Hz, C=O), 139.7 (Ph C-1), 133.5 (Ph C-3,5), 120.3 (Ph C-2,6), 118.2 (CN), 109.1 (Ph C-4), 108.3 (t, ¹J_C,F = 254.6 Hz, CHF₂).

**¹⁵N NMR** (40 MHz, CDCl₃) δ: -258.6 (NH).

**¹⁹F NMR** (376 MHz, CDCl₃) δ: -125.5 (dd, ²J_H,F = 54.1 Hz, ³J_H,F = 1.9 Hz, CHF₂).


*N-(4-chlorophenyl)-2,2-difluoroacetamide (27)*

![Chemical Structure](image)

By following General Procedure B, starting from 1-chloro-4-isocyanatobenzene (0.153 g, 1.0 mmol, 1.0 equiv) in dry THF (10 mL), CHF₂SiMe₃ (0.186 g, 1.5 mmol, 1.5 equiv) and potassium tert-amylate solution 0.9 M in THF (1.4 mL, 1.2 mmol, 1.2 equiv), compound 27 was obtained in 86% yield (0.177 g) as yellow solid (mp 101-103 °C) after column chromatography on silica gel (n-hexane:ethyl acetate 8:2).
**H NMR** (400 MHz, CDCl$_3$) $\delta$: 7.91 (br s, 1H, NH), 7.53 (m, 2H, Ph H-2,6), 7.34 (m, 2H, Ph H-3,5), 6.01 (t, $^2J_{HF}$ = 54.3 Hz, 1H, CHF$_2$).

**$^{13}$C NMR** (100 MHz, CDCl$_3$) $\delta$: 160.3 (t, $^2J_{CF} = 24.6$ Hz, C=O), 134.2 (Ph C-1), 131.1 (Ph C-4), 129.4 (Ph C-3,5), 121.5 (Ph C-2,6), 108.4 (t, $^1J_{CF} = 254.3$ Hz, CHF$_2$).

**$^{15}$N NMR** (40 MHz, CDCl$_3$) $\delta$: -260.3 (NH).

**$^{19}$F NMR** (376 MHz, CDCl$_3$) $\delta$: -125.5 (dd, $^2J_{HF} = 54.3$ Hz, $^1J_{HF} = 2.4$ Hz, CHF$_2$).

**HRMS** (ESI), $m/z$: calcd. for C$_8$H$_6$ClF$_2$NNaO: 227.9999 [M+Na]^+; found: 227.9999.

**$N$-(4-bromophenyl)-2,2-difluoroacetamide (28)**

By following General Procedure B, starting from 1-bromo-4-isocyanatobenzene (0.198 g, 1.0 mmol, 1.0 equiv) in dry THF (10 mL), CHF$_2$SiMe$_3$ (0.186 g, 1.5 mmol, 1.5 equiv) and potassium tert-amylate solution 0.9 M in THF (1.4 mL, 1.2 mmol, 1.2 equiv), compound 28 was obtained in 91% yield (0.227 g) as brown solid (mp 114-116 °C) after column chromatography on silica gel (n-hexane:ethyl acetate 9:1).

**Reaction conducted on 10 mmol scale.** By following General Procedure B, starting from 1-bromo-4-isocyanatobenzene (1.98 g, 10 mmol, 1.0 equiv) in dry THF (80 mL), CHF$_2$SiMe$_3$ (1.86 g, 15 mmol, 1.5 equiv) and potassium tert-amylate solution 0.9 M in THF (14 mL, 12 mmol, 1.2 equiv), compound 28 was obtained in 86% yield (2.15 g) as brown solid after column chromatography on silica gel (n-hexane:ethyl acetate 9:1). **Spectral and spectroscopic data match with those ones obtained when the product was prepared in 1 mmol scale.**

**H NMR** (400 MHz, CDCl$_3$) $\delta$: 7.93 (br s, 1H, NH), 7.49 (‘s’, 4H, Ph H-2,3,5,6), 6.01 (t, $^2J_{HF}$ = 54.2 Hz, 1H, CHF$_2$).

**$^{13}$C NMR** (100 MHz, CDCl$_3$) $\delta$: 160.3 (t, $^2J_{CF} = 24.6$ Hz, C=O), 134.7 (Ph C-1), 132.3 (Ph C-3,5), 121.8 (Ph C-2,6), 118.7 (Ph C-4), 108.4 (t, $^1J_{CF} = 254.3$ Hz, CHF$_2$).

**$^{15}$N NMR** (40 MHz, CDCl$_3$) $\delta$: -260.0 (NH).
**19F NMR** (376 MHz, CDCl₃) δ: -125.6 (dd, 2J_{H,F} = 54.2 Hz, 3J_{H,F} = 1.2 Hz, CHF₂).

**HRMS** (ESI), m/z: calcd. for C₈H₆BrF₂NNaO: 271.9493 [M+Na]⁺; found: 271.9488.

2,2-difluoro-N-(4-fluorophenyl)acetamide (29)

![Diagram of 2,2-difluoro-N-(4-fluorophenyl)acetamide](image)

By following General Procedure B, starting from 1-fluoro-4-isocyanatobenzene (0.137 g, 1.0 mmol, 1.0 equiv) in dry THF (10 mL), CHF₂SiMe₃ (0.186 g, 1.5 mmol, 1.5 equiv) and potassium tert-amylate solution 0.9 M in THF (1.4 mL, 1.2 mmol, 1.2 equiv), compound 29 was obtained in 87% yield (0.164 g) as white crystals (mp 91-93 °C) after column chromatography on silica gel (n-hexane:ethyl acetate 8:2).

**1H NMR** (400 MHz, CDCl₃) δ: 7.86 (br s, 1H, NH), 7.55 (m, 2H, Ph H-2,6), 7.08 (m, 2H, Ph H-3,5), 6.02 (t, 2J_{H,F} = 54.3 Hz, 1H, CHF₂).

**13C NMR** (100 MHz, CDCl₃) δ: 160.3 (t, 2J_{C,F} = 24.4 Hz, C=O), 160.2 (d, 1J_{C,F} = 245.8 Hz, Ph C-4), 131.6 (d, 4J_{C,F} = 3.0 Hz, Ph C-1), 122.2 (d, 3J_{C,F} = 8.1 Hz, Ph C-2,6), 116.1 (2J_{C,F} = 22.8 Hz, Ph C-3,5), 108.5 (t, 1J_{C,F} = 254.3 Hz, CHF₂).

**15N NMR** (40 MHz, CDCl₃) δ: -261.1 (NH).

**19F NMR** (376 MHz, CDCl₃) δ: -125.5 (dd, 2J_{H,F} = 54.3 Hz, 3J_{H,F} = 2.3 Hz, CHF₂), -115.6 (m, Ph 4-F).

**HRMS** (ESI), m/z: calcd. for C₈H₆F₃NNaO: 212.0294 [M+Na]⁺; found: 212.0294.

2,2-difluoro-N-[4-trifluoromethoxy)phenyl]acetamide (30)

![Diagram of 2,2-difluoro-N-[4-trifluoromethoxy)phenyl]acetamide](image)
By following General Procedure B, starting from 1-isocyanato-4-(trifluoromethoxy)benzene (0.203 g, 1.0 mmol, 1.0 equiv) in dry THF (10 mL), CHF₂SiMe₃ (0.186 g, 1.5 mmol, 1.5 equiv) and potassium tert-amylate solution 0.9 M in THF (1.4 mL, 1.2 mmol, 1.2 equiv), compound 30 was obtained in 88% yield (0.224 g) as white needles (mp 105-107 °C) after column chromatography on silica gel (n-heptane:ethyl acetate 9:1).

¹H NMR (400 MHz, CDCl₃) δ: 7.93 (br s, 1H, NH), 7.62 (m, 2H, Ph H-2,6), 7.24 (m, 2H, Ph H-3,5), 6.03 (t, ²Jᵢ,F = 54.4 Hz, 1H, CH).

¹³C NMR (100 MHz, CDCl₃) δ: 160.3 (t, ²J₉,F = 24.6 Hz, C=O), 146.4 (Ph C-4), 134.2 (Ph C-1), 122.0 (Ph C-3,5), 121.6 (Ph C-2,6), 120.4 (q, ¹J₉,F = 257.5 Hz, CF₃), 108.4 (t, ¹J₉,F = 254.3 Hz, CHF₂).

¹⁵N NMR (40 MHz, CDCl₃) δ: -260.7 (NH).

¹⁹F NMR (376 MHz, CDCl₃) δ: -125.5 (dd, ²Jᵢ,F = 54.3 Hz, ³Jᵢ,F = 2.3 Hz, CHF₂), -58.1 (s, CF₃).

HRMS (ESI), m/z: calcd. for C₉H₆F₅NNa₂O₂⁺: 278.0211 [M+Na⁺]; found: 278.0205.

2,2-difluoro-N-(3-methoxyphenyl)acetamide (31)

By following General Procedure B, starting from 1-isocyanato-3-methoxybenzene (0.149 g, 1.0 mmol, 1.0 equiv) in dry THF (10 mL), CHF₂SiMe₃ (0.186 g, 1.5 mmol, 1.5 equiv) and potassium tert-amylate solution 0.9 M in THF (1.4 mL, 1.2 mmol, 1.2 equiv), compound 31 was obtained in 90% yield (0.181 g) as brown solid (mp 67-69 °C) after column chromatography on silica gel (n-heptane:ethyl acetate 7:3).

¹H NMR (400 MHz, CDCl₃) δ: 7.90 (br s, 1H, NH), 7.30 (m, 1H, Ph H-2), 7.27 (m, 1H, Ph H-5), 7.05 (m, 1H, Ph H-6), 6.76 (m, 1H, Ph H-4), 6.01 (t, ²Jᵢ,F = 54.4 Hz, 1H, CHF₂), 3.81 (s, 3H, OCH₃).

¹³C NMR (100 MHz, CDCl₃) δ: 160.3 (t, ²J₉,F = 24.5 Hz, C=O), 160.3 (Ph C-3), 136.8 (Ph C-1), 130.0 (Ph C-5), 112.4 (Ph C-6), 111.6 (Ph C-4), 108.5 (t, ¹J₉,F = 254.3 Hz, CHF₂), 55.4 (OCH₃).

¹⁵N NMR (40 MHz, CDCl₃) δ: -258.5 (NH).

¹⁹F NMR (376 MHz, CDCl₃) δ: -125.6 (dd, ²Jᵢ,F = 54.4 Hz, ³Jᵢ,F = 2.4 Hz, CHF₂).
**N-(4-ethoxyphenyl)-2,2-difluoroacetamide (32)**

By following General Procedure B, starting from 1-ethoxy-4-isocyanatobenzene (0.163 g, 1.0 mmol, 1.0 equiv) in dry THF (10 mL), CHF$_2$SiMe$_3$ (0.186 g, 1.5 mmol, 1.5 equiv) and potassium tert-amylate solution 0.9 M in THF (1.4 mL, 1.2 mmol, 1.2 equiv), compound 32 was obtained in 86% yield (0.185 g) as grey needles (mp 109-111 °C) after column chromatography on silica gel (n-hexane:ethyl acetate 9:1).

**$^1$H NMR** (400 MHz, CDCl$_3$) $\delta$: 7.83 (br s, 1H, NH), 7.46 (m, 2H, Ph H-2,6), 6.89 (m, 2H, Ph H-3,5), 6.00 (t, $^2$J$_{H,F}$ = 54.4 Hz, 1H, CHF$_2$), 4.02 (q, $^3$J = 7.0 Hz, 2H, OCH$_2$), 1.41 (t, $^3$J = 7.0 Hz, 3H, CH$_3$).

**$^{13}$C NMR** (100 MHz, CDCl$_3$) $\delta$: 160.1 (t, $^2$J$_{C,F}$ = 24.3 Hz, C=O), 156.8 (Ph C-4), 128.4 (Ph C-1), 122.0 (Ph C-2,6), 114.9 (Ph C-3,5), 108.6 (t, $^1$J$_{C,F}$ = 254.0 Hz, CHF$_2$), 63.7 (OCH$_2$), 14.8 (CH$_3$).

**$^{15}$N NMR** (40 MHz, CDCl$_3$) $\delta$: -260.5 (NH).

**$^{19}$F NMR** (376 MHz, CDCl$_3$) $\delta$: -125.5 (dd, $^2$J$_{H,F}$ = 54.4 Hz, $^3$J$_{H,F}$ = 2.4 Hz, CHF$_2$).

**HRMS (ESI), m/z**: calcd. for C$_{10}$H$_{11}$F$_2$NaO: 238.0650 [M+Na]$^+$; found: 238.0654.

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**2,2-difluoro-N-(4-phenoxyphenyl)acetamide (33)**

By following General Procedure B, starting from 1-isocyanato-4-phenoxybenzene (0.211 g, 1.0 mmol, 1.0 equiv) in dry THF (10 mL), CHF$_2$SiMe$_3$ (0.186 g, 1.5 mmol, 1.5 equiv) and potassium tert-amylate solution...
0.9 M in THF (1.4 mL, 1.2 mmol, 1.2 equiv), compound 33 was obtained in 90% yield (0.237 g) as white solid (mp 77-79 °C) after column chromatography on silica gel (n-heptane:ethyl acetate 8:2).

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$: 7.84 (br s, 1H, NH), 7.53 (m, 2H, Ph1 H-2,6), 7.35 (m, 2H, Ph2 H-3,5), 7.12 (m, 1H, Ph2 H-4), 7.02 (m, 2H, Ph1 H-3,5), 7.01 (m, 2H, Ph2 H-2,6), 6.02 (t, $^2$J$_{H,F}$ = 54.4 Hz, 1H, CHF$_2$).

$^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$: 160.2 (t, $^2$J$_{C,F}$ = 24.5 Hz, C=O), 157.0 (Ph2 C-1), 155.0 (Ph1 C-4), 130.8 (Ph1 C-1), 129.8 (Ph2 C-3,5), 123.5 (Ph2 C-4), 122.1 (Ph1 C-2,6), 119.5 (Ph1 C-3,5), 118.9 (Ph2 C-2,6), 108.6 (t, $^1$J$_{C,F}$ = 254.3 Hz, CHF$_2$).

$^{15}$N NMR (40 MHz, CDCl$_3$) $\delta$: -260.6 (NH).

$^{19}$F NMR (376 MHz, CDCl$_3$) $\delta$: -125.5 (dd, $^2$J$_{H,F}$ = 54.4 Hz, $^2$J$_{H,F}$ = 2.4 Hz, CHF$_2$).

HRMS (ESI), m/z: calcd. for C$_{14}$H$_{11}$F$_2$NaO$_2$: 286.0650 [M+Na]$^+$; found: 286.0654.

2,2-difluoro-N-[4-(methylsulfanyl)phenyl]acetamide (34)

By following General Procedure B, starting from 1-isocyanato-4-(methylsulfanyl)benzene (0.165 g, 1.0 mmol, 1.0 equiv) in dry THF (10 mL), CHF$_2$SiMe$_3$ (0.186 g, 1.5 mmol, 1.5 equiv) and potassium tert-amylate solution 0.9 M in THF (1.4 mL, 1.2 mmol, 1.2 equiv), compound 34 was obtained in 89% yield (0.193 g) as brown solid (mp 110-121 °C) after column chromatography on silica gel (n-hexane:ethyl acetate 8:2).

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$: 7.94 (br s, 1H, NH), 7.50 (m, 2H, Ph H-2,6), 7.25 (m, 2H, Ph H-3,5), 6.01 (t, $^2$J$_{H,F}$ = 54.3 Hz, 1H, CHF$_2$), 2.48 (s, 3H, CH$_3$).

$^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$: 160.2 (t, $^2$J$_{C,F}$ = 24.4 Hz, C=O), 135.8 (Ph2 C-4), 132.9 (Ph C-1), 127.5 (Ph C-3,5), 120.9 (Ph C-2,6), 108.5 (t, $^1$J$_{C,F}$ = 254.1 Hz, CHF$_2$), 16.1 (CH$_3$).

$^{15}$N NMR (40 MHz, CDCl$_3$) $\delta$: -259.4 (NH).

$^{19}$F NMR (376 MHz, CDCl$_3$) $\delta$: -125.5 (d, $^2$J$_{H,F}$ = 54.3Hz, CHF$_2$).

HRMS (ESI), m/z: calcd. for C$_9$H$_9$F$_2$NNaOS: 240.0265 [M+Na]$^+$; found: 240.0262.
2,2-difluoro-N-phenylacetamide (35)

By following General Procedure B, starting from isocyanatobenzene (0.119 g, 1.0 mmol, 1.0 equiv) in dry THF (10 mL), CHF₂SiMe₃ (0.186 g, 1.5 mmol, 1.5 equiv) and potassium tert-amylate solution 0.9 M in THF (1.4 mL, 1.2 mmol, 1.2 equiv), compound 35 was obtained in 85% yield (0.145 g) as brown solid (mp 62 °C, lit.¹ 65 °C) after column chromatography on silica gel (n-hexane:ethyl acetate 9:1).

¹H NMR (400 MHz, CDCl₃) δ: 7.94 (br s, 1H, NH), 7.58 (m, 2H, Ph H-2,6), 7.38 (m, 2H, Ph H-3,5), 7.21 (m, 1H, Ph H-4), 6.02 (t, 2J_H,F = 54.4 Hz, 1H, CHF₂).

¹³C NMR (100 MHz, CDCl₃) δ: 160.3 (t, 2J_C,F =24.5 Hz, C=O), 135.6 (Ph C-1), 129.3 (Ph C-3,5), 125.8 (Ph C-4), 120.3 (Ph C-2,6), 108.5 (t, 1J_C,F = 254.2 Hz, CHF₂).

¹⁵N NMR (40 MHz, CDCl₃) δ: -258.7 (NH).

¹⁹F NMR (376 MHz, CDCl₃) δ: -125.5 (dd, 2J_H,F = 54.4 Hz, 6J_H,F = 2.3 Hz, CHF₂).

HRMS (ESI), m/z: calcd. for C₈H₇F₂NNaO: 194.0388 [M+Na]+; found: 194.0386.

N-(2,6-dimethylphenyl)-2,2-difluoroacetamide (36)

By following General Procedure B, starting from 2-isocyanato-1,3-dimethylbenzene (0.147 g, 1.0 mmol, 1.0 equiv) in dry THF (10 mL), CHF₂SiMe₃ (0.186 g, 1.5 mmol, 1.5 equiv) and potassium tert-amylate solution 0.9 M in THF (1.4 mL, 1.2 mmol, 1.2 equiv), compound 36 was obtained in 84% yield (0.167 g) as white needles (mp 110-112 °C) after column chromatography on silica gel (n-hexane:ethyl acetate 9:1).
$^1$H NMR (400 MHz, CDCl$_3$) $\delta$: 7.56 (br s, 1H, NH), 7.16 (m, 1H, Ph H-4), 7.10 (m, 2H, Ph H-3,5), 6.06 (t, $^3$J$_{H,F}$ = 54.2 Hz, 1H, CHF$_2$), 2.22 (s, 6H, CH$_3$).

$^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$: 161.0 (t, $^2$J$_{C,F}$ =24.7 Hz, C=O), 135.3 (Ph C-2,6), 131.1 (Ph C-1), 128.4 (Ph C-3,5), 128.2 (Ph C-4), 108.9 (t, $^1$J$_{C,F}$ = 253.4 Hz, CHF$_2$), 18.1 (CH$_3$).

$^{15}$N NMR (40 MHz, CDCl$_3$) $\delta$: -266.8 (NH).

$^{19}$F NMR (376 MHz, CDCl$_3$) $\delta$: -124.8 (dd, $^2$J$_{H,F}$ = 54.2 Hz, $^3$J$_{H,F}$ = 1.8 Hz, CHF$_2$).

HRMS (ESI), m/z: calcd. for C$_{10}$H$_{11}$F$_2$NNaO: 222.0701 [M+Na]$^+$; found: 222.0703.

$N$-(2,6-dimethylphenyl)-2,2-difluoroacetamide (37)

By following General Procedure B, starting from 2-isocyanato-1,3-diisopropylbenzene (0.203 g, 1.0 mmol, 1.0 equiv) in dry THF (10 mL), CHF$_2$SiMe$_3$ (0.186 g, 1.5 mmol, 1.5 equiv) and potassium tert-amylate solution 0.9 M in THF (1.4 mL, 1.2 mmol, 1.2 equiv), compound 37 was obtained in 80% yield (0.204 g) as white solid (mp 137-140 °C) after column chromatography on silica gel (n-hexane:ethyl acetate 9:1).

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$: 7.54 (br s, 1H, NH), 7.35 (m, 1H, Ph H-4), 7.22 (d, $^3$J$_{H,H}$ = 7.7 Hz, 2H, Ph H-3,5), 6.08 (t, $^3$J$_{H,F}$ = 54.2 Hz, 1H, CHF$_2$), 3.01 (sept, $^3$J$_{H,H}$ = 6.9 Hz, 2H, CH), 1.21 (d, $^3$J$_{H,H}$ = 6.9 Hz, 12H, CH$_3$).

$^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$: 162.1 (t, $^2$J$_{C,F}$ = 24.6 Hz, C=O), 146.0 (Ph C-2,6), 129.2 (Ph C-4), 128.3 (Ph C-1), 123.8 (Ph C-3,5), 109.0 (t, $^1$J$_{C,F}$ = 253.6 Hz, CHF$_2$), 28.7 (CHMe$_2$), 23.5 (CH$_3$).

$^{15}$N NMR (40 MHz, CDCl$_3$) $\delta$: -270.1 (NH).

$^{19}$F NMR (376 MHz, CDCl$_3$) $\delta$: -124.7 (dd, $^2$J$_{H,F}$ = 54.2 Hz, $^3$J$_{H,F}$ = 2.1 Hz, CHF$_2$).

HRMS (ESI), m/z: calcd. for C$_{14}$H$_{19}$F$_2$NNaO: 278.1327 [M+Na]$^+$; found: 278.1330.
2,2-difluoro-N-[2-(3-isopropenylphenyl)-2-propanyl]acetamide (38)

By following General Procedure B, starting from 1-(2-isocyanato-2-propanyl)-3-isopropenylbenzene (0.201 g, 1.0 mmol, 1.0 equiv) in dry THF (10 mL), CHF$_2$SiMe$_3$ (0.186 g, 1.5 mmol, 1.5 equiv) and potassium tert-amylate solution 0.9 M in THF (1.4 mL, 1.2 mmol, 1.2 equiv), compound 38 was obtained in 81% yield (0.205 g) as pale yellow needles (mp 94-96 °C) after column chromatography on silica gel (n-hexane:ethyl acetate 9:1).

$^1$H NMR (400 MHz, CDCl$_3$) δ: 7.47 (m, 1H, Ph H-2), 7.37 (m, 1H, Ph H-4), 7.33 (m, 1H, Ph H-5), 7.30 (m, 1H, Ph H-6), 6.51 (br s, 1H, NH), 5.81 (t, $^2$J$_{H,F}$ = 54.5 Hz, 1H, CHF$_2$), 5.35 (s, 1H, H$_a$), 5.11 (m, 1H, H$_b$), 2.16 (s, 3H, alkene-CH$_3$), 1.79 (s, 6H, CH$_3$).

$^{13}$C NMR (100 MHz, CDCl$_3$) δ: 161.4 (t, $^2$J$_{C,F}$ = 24.0 Hz, C=O), 145.3 (Ph C-1), 143.3 (H$_2$C=CMe), 141.7 (Ph C-3), 128.5 (Ph C-5), 124.5 (Ph C-4), 123.7 (Ph C-6), 121.8 (Ph C-2), 112.8 (H$_2$C=CMe), 108.7 (t, $^1$J$_{C,F}$ = 254.0 Hz, CHF$_2$), 56.6 (1C, CMMe$_2$), 28.6 (NC-CH$_3$), 21.8 (H$_2$C=CCMe$_3$).

$^{15}$N NMR (40 MHz, CDCl$_3$) δ: -251.9 (NH).

$^{19}$F NMR (376 MHz, CDCl$_3$) δ: -125.0 (dd, $^2$J$_{H,F}$ = 54.5Hz, $^8$J$_{H,F}$ = 1.7 Hz, CHF$_2$).

HRMS (ESI), m/z: calcd. for C$_{14}$H$_{17}$F$_2$NNaO: 276.1170 [M+Na]$^+$; found: 276.1170.

N-cyclohexyl-2,2-difluoroacetamide (39)

By following General Procedure B, starting from isocyanatocyclohexane (0.125 g, 1.0 mmol, 1.0 equiv) in dry THF (10 mL), CHF$_2$SiMe$_3$ (0.186 g, 1.5 mmol, 1.5 equiv) and potassium tert-amylate solution 0.9 M in
THF (1.4 mL, 1.2 mmol, 1.2 equiv), compound 39\(^\circ\) was obtained in 83% yield (0.147 g) as volatile white solid (mp 65-67 °C) after column chromatography on silica gel (n-hexane:ethyl acetate 9:1).

\(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\): 6.14 (br s, 1H, NH), 5.86 (t, \(^2\)\(J_{HF}\) = 54.5 Hz, 1H, CHF\(_2\)), 3.80 (m, 1H, cyclohexyl H-1), 1.95 (m, 2H, cyclohexyl H-2,6 ), 1.74 (m, 2H, cyclohexyl H-3,5), 1.64 (m, 1H, cyclohexyl H-4), 1.38 (m, 2H, cyclohexyl H-3,5), 1.21 (m, 2H, cyclohexyl H-2,6), 1.19 (m, 2H, cyclohexyl H-4).

\(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\): 161.6 (t, \(^2\)\(J_{CF}\) = 24.3 Hz, C=O), 108.5 (t, \(^1\)\(J_{CF}\) = 252.7 Hz, CHF\(_2\)), 48.4 (cyclohexyl C-1), 32.6 (cyclohexyl C-2,6), 25.3 (cyclohexyl C-4), 24.6 (cyclohexyl C-3,5).

\(^{15}\)N NMR (40 MHz, CDCl\(_3\)) \(\delta\): -256.7 (NH).

\(^{19}\)F NMR (376 MHz, CDCl\(_3\)) \(\delta\): -126.2 (dd, \(^2\)\(J_{HF}\) = 54.5 Hz, \(^{10}\)\(J_{HF}\) = 2.0 Hz, CHF\(_2\)).

HRMS (ESI), \(m/z\): calcd. for C\(_8\)H\(_{13}\)F\(_2\)NNaO: 200.0857 [M+Na]\(^+\); found: 200.0858.

\(N\)-(adamantan-1-yl)-2,2-difluoroacetamide (40)

By following General Procedure B, starting from 1-isocyanatodamantane (0.177 g, 1.0 mmol, 1.0 equiv) in dry THF (10 mL), CHF\(_2\)SiMe\(_3\) (0.186 g, 1.5 mmol, 1.5 equiv) and potassium tert-amylate solution 0.9 M in THF (1.4 mL, 1.2 mmol, 1.2 equiv), compound 40 was obtained in 85% yield (0.195 g) as white solid (mp 89-91 °C) after column chromatography on silica gel (n-hexane:ethyl acetate 9:1).

\(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\): 5.89 (br s, 1H, NH), 5.75 (t, \(^2\)\(J_{HF}\) = 54.7 Hz, 1H, CHF\(_2\)), 2.11 (m, 3H, adamantyl H-3,5,7), 2.03 (m, 6H, adamantyl H-2,8,9 ), 1.70 (m, 6H, adamantyl H-4,6,10).

\(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\): 161.3 (t, \(^2\)\(J_{CF}\) =23.5 Hz, C=O), 108.5 (t, \(^1\)\(J_{CF}\) = 254.0 Hz, CHF\(_2\)), 52.6 (adamantyl C-1), 41.2 (adamantyl C-2,8,9), 36.1 (adamantyl C-4,6,10), 29.3 (adamantyl C-3,5,7).

\(^{15}\)N NMR (40 MHz, CDCl\(_3\)) \(\delta\): -249.7 (NH).

\(^{19}\)F NMR (376 MHz, CDCl\(_3\)) \(\delta\): -125.1 (dd, \(^2\)\(J_{HF}\) = 54.7 Hz, \(^{10}\)\(J_{HF}\) = 2.2 Hz, CHF\(_2\)).

HRMS (ESI), \(m/z\): calcd. for C\(_{12}\)H\(_{17}\)F\(_2\)NNaO: 252.1170 [M+Na]\(^+\); found: 252.1169.
5. Synthetic manipulation of compounds (Scheme 3)

\[N-(biphenyl-4-yl)-2,2\text{-difluoroacetamide (41)}\]

\[
\text{In a dry Schlenk flask Pd}_2\text{(dba)}_3 (4.6 mg, 0.005 mmol, 2.5 mol\%) and P(t-Bu)}_3 (0.4 mg, 0.002 mmol, 10 mol\%) were added to anhydrous toluene. Then, difluoroamide 8 (0.38 mmol, 101 mg) was added to the mixture at -20 °C. Phenyllithium [1.9 M in \(n\)-dibutyl ether, 1.14 mmol, 0.6 mL] was diluted with toluene to reach a concentration of 0.6 M and TMEDA (0.46 mmol, 0.068 mL) was added to it; this solution was slowly added over 2 h via a syringe pump. After the addition was completed, NaHCO}_3 (aq. 5\%) was added and the mixture was extracted 3 times with diethyl ether. The organic phases were collected and concentrated under reduced pressure. The desired product 41 was obtained in 65\% yield (65 mg) as pale yellow solid (mp 177-180°C) after column chromatography on silica gel (\(n\)-hexane:ethyl acetate 8:2).
\]

\[\textit{H NMR} \ (400 MHz, CDCl}_3): \delta 7.92 (br s, 1H, NH), 7.66 (m, 2H, Ph1 C-3,5), 7.62 (m, 2H, Ph1 C-2,6), 7.58 (m, 2H, Ph2 C-2,6), 7.45 (m, 2H, Ph2 C-3,5), 7.35 (m, 1H, Ph2 C-4), 6.05 (t, \_2J_{HF} = 54.4 \text{ Hz}, 1H, CHF}_2).\]

\[\textit{C NMR} \ (100 MHz, CDCl}_3): \delta 160.2 (m, C=O), 140.1 (Ph2 C-1), 138.8 (Ph1 C-1), 134.8 (Ph1 C-4), 127.9 (Ph1 C-2,6), 128.9 (Ph2 C-3,5), 127.5 (Ph2 C-4), 126.9 (Ph2 C-2,6), 120.6 (Ph1 C-3,5), 108.6 (t, \_2J_{CF} = 254.8 \text{ Hz}, \text{CHF}_2).\]

\[\textit{N NMR} \ (40 MHz, CDCl}_3): \delta -295.5 (NH).\]

\[\textit{F NMR} \ (376 MHz, CDCl}_3): \delta -125.4 (dd, \_2J_{HF} = 54.4 \text{ Hz}, \_4J_{HF} = 2.4 \text{ Hz}, \text{CHF}_2).\]

\[\textit{HRMS} \ (ESI), m/z: \text{calcd. for } \text{C}_{14}\text{H}_{11}\text{F}_{2}\text{NNaO: } 270.0701 \ [\text{M+Na}]^+; \text{found: } 270.0696.\]
Methyl (1Z)-N-(2,6-diisopropylphenyl)-2,2-difluoroethanimidothioate (42)

1,3-diisopropyl-2-isothiocyanatobenzene 20 (0.149 g, 0.55 mmol, 1.0 equiv) was dissolved in anhydrous acetone (5 mL) and, under argon, KOH (111 mg, 1.98 mmol, 3.6 equiv) and iodomethane (116 mg, 0.82 mmol, 1.5 equiv) were introduced. The resulting mixture was heated at 56 °C and the stirring was continued for 1 h. Upon completion of the reaction – as indicated by TLC analysis – the mixture was filtered on Celite. The corresponding filtrate – after evaporation of the solvent - was columned on silica gel (n-hexane:diethyl ether 9:1), giving compound 42 (115 mg, 73% yield) as a pale yellow oil.

\[^1{H}\ NMR\ (400\ MHz,\ CDCl_3):\ δ\ 7.13 (m, 3H, Ph H-3,4,5), 6.38 (br m-t, CHF_2), 2.70 (sept., \(^3J = 6.9\ Hz, 2H, CH(CH_3)_2), 1.20 (br d, \(^3J = 6.9\ Hz, 6H, CH_3)), 2.53 (s, 3H, SCH_3), 1.13 (d, \(^3J = 6.9\ Hz, 6H, CH_3)).\]

\[^{13}C\ NMR\ (100\ MHz,\ CDCl_3):\ δ\ 160.5\ (C=N), 143.7\ (Ph\ C-1), 136.0\ (Ph\ C-2,6), 125.0\ (Ph\ C-4), 123.2\ (Ph\ C-3,5), 28.1\ (CH(CH_3)_2), 23.4\ (CH_3), 23.0\ (CH_3), 12.7\ (SCH_3).\]

\[^{19}F\ NMR\ (376\ MHz,\ CDCl_3):\ δ\ -114.3\ (d, \(^2J_{HF} = 52\ Hz).\]

HRMS (ESI), m/z: calcd. for C_{15}H_{21}F_2NNaS: 308.1255 [M+Na]^+; found: 308.1259.
2,2-difluoro-N-(4-methylphenyl)acetamide (43)

Bromo-oxamide 28 (125 mg, 0.5 mmol, 1.0 equiv) was dissolved in anhydrous toluene (5 mL) and, under argon, Pd(PPh$_3$)$_4$ (57 mg, 0.05 mmol, 0.10 equiv) and methyl stannatrane (274 mg, 1.0 mmol, 2.0 equiv) were introduced. The resulting mixture was heated at 90 °C and the stirring was continued for 4 h. Upon completion of the reaction – as indicated by TLC analysis – the mixture was filtered on Celite washing with Et$_2$O (15 mL). The corresponding filtrate – after evaporation of the solvent - was columned on silica gel (n-hexane:ethyl acetate 9:1), giving compound 43 (76 mg, 82% yield) as a pale yellow solid (mp 106-108 °C).

$^1$H NMR (400 MHz, CDCl$_3$) δ: 7.83 (br s, 1H, NH), 7.45 (m, 2H, Ph H-2,6), 7.18 (m, 2H, Ph H-3,5), 6.01 (t, $^2$J$_{H,F}$ = 54.4 Hz, 1H, CHF$_2$), 2.34 (s, 3H, CH$_3$).

$^{13}$C NMR (100 MHz, CDCl$_3$) δ: 160.1 (C=O), 135.7 (Ph C-4), 133.0 (Ph C-1), 129.8 (Ph C-3,5), 120.3 (Ph C-2,6), 108.6 (t, $^1$J$_{C,F}$ = 254.2 Hz, CHF$_2$), 20.9 (CH$_3$).

$^{15}$N NMR (40 MHz, CDCl$_3$) δ: -259.4 (NH).

$^{19}$F NMR (376 MHz, CDCl$_3$) δ: -125.5 (dd, $^2$J$_{H,F}$ = 54.4 Hz, $^3$J$_{H,F}$ = 2.3 Hz, CHF$_2$).

HRMS (ESI), m/z: calcd. for C$_9$H$_9$F$_2$NNaO: 208.0544 [M+Na]$^+$; found: 208.0562.
6. $^{1}H$- and $^{13}C$-NMR spectra.
3b ($^1$H-NMR, 400 MHz, CDCl$_3$)

3b ($^{13}$C-NMR, 100 MHz, CDCl$_3$)
3 (\(^1\text{H-NMR, 400 MHz, CDCl}_3\))

3 (\(^{13}\text{C-NMR, 100 MHz, CDCl}_3\))
4 (¹H-NMR, 400 MHz, CDCl₃)

4 (¹³C-NMR, 100 MHz, CDCl₃)
8 (1H-NMR, 400 MHz, CDCl₃)

8 (13C-NMR, 100 MHz, CDCl₃)
9 (\textsuperscript{1}H-NMR, 400 MHz, CDCl\textsubscript{3})

9 (\textsuperscript{13}C-NMR, 100 MHz, CDCl\textsubscript{3})
11 (1H-NMR, 400 MHz, CDCl₃)

11 (13C-NMR, 100 MHz, CDCl₃)
12 (\textsuperscript{1}H-NMR, 400 MHz, CDCl$_3$)

12 (\textsuperscript{13}C-NMR, 100 MHz, CDCl$_3$)
15 ($^1$H-NMR, 400 MHz, CDCl$_3$)

15 ($^{13}$C-NMR, 100 MHz, CDCl$_3$)
18 \(^{(1}^H\text{-NMR, 400 MHz, CDCl}_3\))

18 \(^{(13}^C\text{-NMR, 100 MHz, CDCl}_3\))
20 (\textsuperscript{1}H-NMR, 400 MHz, CDCl\textsubscript{3})

20 (\textsuperscript{13}C-NMR, 100 MHz, CDCl\textsubscript{3})
21 (°H-NMR, 400 MHz, CDCl₃)

21 (°C-NMR, 100 MHz, CDCl₃)
22 ($^1$H-NMR, 400 MHz, CDCl$_3$)

22 ($^{13}$C-NMR, 100 MHz, CDCl$_3$)
23 (\(^1\)H-NMR, 400 MHz, CDCl\(_3\))

23 (\(^{13}\)C-NMR, 100 MHz, CDCl\(_3\))
24 ($^1$H-NMR, 400 MHz, CDCl$_3$)

24 ($^{13}$C-NMR, 100 MHz, CDCl$_3$)
25 ($^1$H-NMR, 400 MHz, CDCl$_3$)

25 ($^{13}$C-NMR, 100 MHz, CDCl$_3$)
27 ($^{13}$C-NMR, 100 MHz, CDCl$_3$)

27 ($^1$H-NMR, 400 MHz, CDCl$_3$)
28 (\(^1\)H-NMR, 400 MHz, CDCl\(_3\))

28 (\(^{13}\)C-NMR, 100 MHz, CDCl\(_3\))
29 (1H-NMR, 400 MHz, CDCl₃)

29 (13C-NMR, 100 MHz, CDCl₃)
30 (\(^1\)H-NMR, 400 MHz, CDCl\textsubscript{3})

30 (\(^{13}\)C-NMR, 100 MHz, CDCl\textsubscript{3})
31 $^{1}H$-NMR, 400 MHz, CDCl$_3$)

31 $^{13}C$-NMR, 100 MHz, CDCl$_3$)
34 ($^1$H-NMR, 400 MHz, CDCl$_3$)

34 ($^{13}$C-NMR, 100 MHz, CDCl$_3$)
35 ($^1$H-NMR, 400 MHz, CDCl$_3$)

35 ($^{13}$C-NMR, 100 MHz, CDCl$_3$)
37 (\(^1\)H-NMR, 400 MHz, CDCl\(_3\))

37 (\(^{13}\)C-NMR, 100 MHz, CDCl\(_3\))
$^{1}H$-NMR, 400 MHz, CDCl$_3$)

$^{13}C$-NMR, 100 MHz, CDCl$_3$)
39 (\textsuperscript{1}H-NMR, 400 MHz, CDCl\textsubscript{3})

39 (\textsuperscript{13}C-NMR, 100 MHz, CDCl\textsubscript{3})
40 ($^1$H-NMR, 400 MHz, CDCl$_3$)

40 ($^{13}$C-NMR, 100 MHz, CDCl$_3$)
42 ($^1$H-NMR, 400 MHz, CDCl$_3$)

42 ($^{13}$C-NMR, 100 MHz, CDCl$_3$)
$43 \left( ^1H-NMR, 400 \text{ MHz, CDCl}_3 \right)$

$43 \left( ^13C-NMR, 100 \text{ MHz, CDCl}_3 \right)$
7. $^{19}$F-NMR spectra.
$^{19}$F-NMR, 376 MHz, CDCl$_3$
10 (\(^{19}\text{F-NMR, 376 MHz, CDCl}_3\))

11 (\(^{19}\text{F-NMR, 376 MHz, CDCl}_3\))
12 ($^{19}$F-NMR, 376 MHz, CDCl$_3$)

13 ($^{19}$F-NMR, 376 MHz, CDCl$_3$)
14 ($^{19}$F-NMR, 376 MHz, CDCl$_3$)

15 ($^{19}$F-NMR, 376 MHz, CDCl$_3$)
16 ($^{19}$F-NMR, 376 MHz, CDCl$_3$)

17 ($^{19}$F-NMR, 376 MHz, CDCl$_3$)
20 ($^{19}$F-NMR, 376 MHz, CDCl$_3$)

21 ($^{19}$F-NMR, 376 MHz, CDCl$_3$)
24 ($^{19}$F-NMR, 376 MHz, CDCl$_3$)

25 ($^{19}$F-NMR, 376 MHz, CDCl$_3$)
26 ($^{19}$F-NMR, 376 MHz, CDCl$_3$)

27 ($^{19}$F-NMR, 376 MHz, CDCl$_3$)
28 ($^{19}$F-NMR, 376 MHz, CDCl$_3$)

29 ($^{19}$F-NMR, 376 MHz, CDCl$_3$)
$^{19}$F-NMR, 376 MHz, CDCl$_3$
34 (\(\text{\textsuperscript{19}F-NMR, 376 MHz, CDCl}_3\))

35 (\(\text{\textsuperscript{19}F-NMR, 376 MHz, CDCl}_3\))
36 (¹⁹F-NMR, 376 MHz, CDCl₃)

37 (¹⁹F-NMR, 376 MHz, CDCl₃)
38 (\(^{19}\text{F-NMR, 376 MHz, CDCl}_3\))

39 (\(^{19}\text{F-NMR, 376 MHz, CDCl}_3\))
40 ($^{19}$F-NMR, 376 MHz, CDCl$_3$)

41 ($^{19}$F-NMR, 376 MHz, CDCl$_3$)
43 ($^{19}$F-NMR, 376 MHz, CDCl₃)
8. References