The catalytic Mannich reaction of 1,1-difluoro-2-trialkyl(aryl)silyl-2-trimethylsilyloxyethenes:

Preparation of β -amino acid derivatives

*Woo Jin Chung, Masaaki Omote and John T. Welch**

Department of Chemistry, University at Albany, State University of New York, 1400 Washington Ave.,

Albany, NY 12222, USA

jwelch@uamail.albany.edu

Table of Contents

Synthesis of 1,1-difluoro-2-trialkyl(aryl)silyl-2-trimethylsilyloxyethenes (3)	S2
General procedure for the formation of 7	S4
	S10
General procedure for the formation of 8	S13
General procedure for the formation of 9	S14
Synthesis of <i>N</i> -Ethyl-2,2-difluoro-3-amino-3-phenylpropionamide (10)	S15

Experimental section

All reactions were carried out under inert atmosphere. Reagents were purchased from commercial sources and used without further purification. THF was purified by standard methods and freshly distilled under argon from sodium/benzophenone ketyl. Dichloromethane was distilled immediately prior to use from calcium hydride. ^1H (300 MHz), ^{13}C (75 MHz), and ^{19}F (282 MHz) NMR spectra were measured in CDCl_3 unless notified. ^{19}F chemical shifts are referenced to CFCl_3 as an external standard.

Synthesis of 1,1-difluoro-2-trialkyl(aryl)silyl-2-trimethylsilyloxyethenes (3)

To a round bottom flask (flame-dried, 3-neck with a septum cap, 250-mL), THF (100 mL), and *i*- Pr_2NH (24.7 mL, 175 mmol, 3.5 eq.) were put under argon and chilled on an ice-salt bath. *n*-BuLi (70.0 mL, 175 mmol, 3.5 eq., 2.5 M in hexane) was slowly added and stirred for 30 min to ensure the generation of LDA. To another round bottom flask (flame-dried, 3-neck with a septum cap, 500-mL), THF (50 mL), trifluoroethanol (5.00g, 50 mmol), a chlorotrialkylsilane (50 mmol) were added and chilled on dry ice bath. The LDA solution was added dropwise and the resulting solution was stirred at an elevated temperature for a certain time. Chlorotrimethylsilane (8.15 g, 75 mmol) was added and resulting mixture was stirred at room temperature for overnight. Hexane and H_2O were added to the resulting solution and then the organic layer was separated, washed with two portions of H_2O , and dried over anhydrous Na_2SO_4 . After the removal of the drying reagent, the solvent was evaporated *in vacuo* and the residue was subjected to distillation or silica gel column chromatography to afford the product.

1,1-Difluoro-2-trimethylsilyl-2-trimethylsilyloxyethene (3a)

Yield = 62 %, colorless oil, bp = 64-69 °C/40 mmHg: ^1H NMR δ 0.16 (s, 9H), 0.15 (s, 9H); ^{13}C NMR δ 159.8 (dd, $^1J_{\text{C-F}} = 278.2, 278.1$ Hz), 112.9 (dd, $^2J_{\text{C-F}} = 56.9, 56.7$ Hz), 0.16, -2.3; ^{19}F NMR δ -86.4 (d, $J_{\text{F-F}} = 68.5$ Hz, 1F), -112.6 (d, $J_{\text{F-F}} = 68.5$ Hz, 1F); Anal. Calcd for $\text{C}_8\text{H}_{18}\text{F}_2\text{OSi}_2$: C, 42.82; H, 8.09. Found: C, 43.00; H, 8.17.

1,1-Difluoro-2-triethylsilyl-2-trimethylsilyloxyethene (3b)

Yield = 80 %, colorless oil, bp = 97-100 °C/20 mmHg: ^1H NMR δ 0.95 (t, $J = 8.0$ Hz, 9H), 0.64 (q, $J = 8.0$ Hz, 6H), 0.15 (s, 9H); ^{13}C NMR δ 160.1 (dd, $^1J_{\text{C-F}} = 277.3, 277.3$ Hz), 111.1 (dd, $^2J_{\text{C-F}} = 58.4, 57.9$ Hz), 7.1, 2.4, 0.21; ^{19}F NMR δ -85.8 (d, $J_{\text{F-F}} = 70.2$ Hz, 1F), -113.5 (d, $J_{\text{F-F}} = 69.8$ Hz, 1F); Anal. Calcd for $\text{C}_{11}\text{H}_{24}\text{F}_2\text{OSi}_2$: C, 49.58; H, 9.08. Found: C, 49.75; H, 8.96.

1-(*tert*-Butyldimethylsilyl)-2,2-difluoro-1-trimethylsilyloxyethene (3c)

Yield = 65 %, colorless oil, bp = 87-89 °C/0.3 mmHg: ^1H NMR δ 0.91 (s, 9H), 0.16 (s, 9H), 0.09 (s, 6H); ^{13}C NMR δ 160.2 (dd, $^1J_{\text{C-F}} = 278.5, 278.4$ Hz), 112.1 (dd, $^2J_{\text{C-F}} = 56.1, 55.3$ Hz), 26.5, 17.3, 0.35, -6.6; ^{19}F NMR δ -85.9 (d, $J_{\text{F-F}} = 70.4$ Hz, 1F), -112.2 (d, $J_{\text{F-F}} = 70.2$ Hz, 1F); Anal. Calcd for $\text{C}_{11}\text{H}_{24}\text{F}_2\text{OSi}_2$: C, 49.58; H, 9.08. Found: C, 49.66; H, 8.89.

2-(*tert*-Butyldiphenylsilyl)-1,1-Difluoro-2-trimethylsilyloxyethene (3d)

Yield = 71 %, yellow oil: ^1H NMR δ 7.62-7.31 (m, 10H), 1.12 (s, 9H), 0.05 (s, 9H); ^{13}C NMR δ 160.3 (dd, $^1J_{\text{C-F}} = 282.5, 282.2$ Hz), 136.1, 132.8, 129.5, 127.6, 110.5 (dd, $^2J_{\text{C-F}} = 52.6, 52.3$ Hz), 28.1,

18.8, 0.41; ^{19}F NMR δ -84.3 (d, $J_{\text{F-F}} = 62.6$ Hz, 1F), -105.7 (d, $J_{\text{F-F}} = 62.1$ Hz, 1F); Anal. Calcd for $\text{C}_{21}\text{H}_{28}\text{F}_2\text{OSi}_2$: C, 64.57; H, 7.23. Found: C, 64.59; H, 7.25.

1,1-Difluoro-2-triphenylsilyl-2-trimethylsilyloxyethene (3e)

Yield = 67 %, yellow solid, mp = 73-74 °C: ^1H NMR δ 7.58-7.34 (m, 15H), -0.06 (s, 9H); ^{13}C NMR δ 160.8 (dd, $^1J_{\text{C-F}} = 283.8, 283.1$ Hz), 136.2, 132.1, 129.9, 127.9, 110.4 (dd, $^2J_{\text{C-F}} = 52.0, 51.9$ Hz), 0.13; ^{19}F NMR δ -83.2 (d, $J_{\text{F-F}} = 56.7$ Hz, 1F), -105.5 (d, $J_{\text{F-F}} = 57.3$ Hz, 1F); Anal. Calcd for $\text{C}_{23}\text{H}_{24}\text{F}_2\text{OSi}_2$: C, 67.28; H, 5.89. Found: C, 67.26; H, 5.96.

1,1-Difluoro-2-triisopropylsilyl-2-trimethylsilyloxyethene (3f)

Yield = 69 %, colorless oil, bp = 120-123 °C/10 mmHg: ^1H NMR δ 1.18 (m, 3H), 1.06 (d, $J = 6.8$ Hz, 18H), 0.17 (s, 9H); ^{13}C NMR δ 160.0 (dd, $^1J_{\text{C-F}} = 277.0, 276.8$ Hz), 110.7 (dd, $^2J_{\text{C-F}} = 58.5, 58.3$ Hz), 18.5, 10.8, 0.53; ^{19}F NMR δ -86.4 (d, $J_{\text{F-F}} = 74.8$ Hz, 1F), -113.7 (d, $J_{\text{F-F}} = 74.4$ Hz, 1F); Anal. Calcd for $\text{C}_{14}\text{H}_{30}\text{F}_2\text{OSi}_2$: C, 54.50; H, 9.80. Found: C, 54.46; H, 10.00.

General procedure for the formation of 7: To a mixture of sulfonylimine (**6**, 0.8 mmol) and trimethylsilyl trifluoromethanesulfonate (18 mg, 0.08 mmol) in 3 mL of dichloromethane was added a solution of **3** (1 mmol) in 2 mL of dichloromethane at 0 °C and resulting mixture was stirred at room temperature for 24 hours. Reaction was quenched with 10 mL of saturated sodium bicarbonate solution

and extracted with dichloromethane (2 × 20 mL). Organic layer was dried over anhydrous MgSO₄, filtered, and concentrated. Recrystallization in hexane provided compound **7** as solid.

***N*-(2,2-Difluoro-3-oxo-1-phenyl-3-trimethylsilylpropyl)-benzenesulfonamide (7a)**

Yield = 76 %, white solid, mp = 114-115 °C: ¹H NMR δ 7.66 (d, *J* = 7.8 Hz, 2H), 7.39 (t, *J* = 7.0, 1H), 7.27 (t, *J* = 7.8 Hz, 2H), 7.16-7.05 (m, 5H), 6.00 (d, *J* = 9.6 Hz, 1H), 4.95 (td, *J* = 13.1, 9.6 Hz, 1H), 0.04 (s, 9H); ¹³C NMR δ 236.3 (t, ²*J*_{C-F} = 35.9 Hz), 140.1, 132.5, 132.4, 128.7, 128.6, 128.5, 128.4, 127.0, 115.3 (t, ¹*J*_{C-F} = 259.0 Hz), 57.9 (t, ²*J*_{C-F} = 24.7 Hz), -3.6; ¹⁹F NMR δ -111.2 (dd, *J* = 276.2, 12.2 Hz, 1F), -112.8 (dd, *J* = 276.2, 13.7 Hz, 1F); Anal. Calcd for C₁₈H₂₁F₂NO₃SSi (%): C, 53.39; H, 5.32. Found (%): C, 54.51; H, 5.49.

***N*-(2,2-Difluoro-3-oxo-1-phenyl-3-triethylsilylpropyl)-benzenesulfonamide (7b)**

Yield = 85 %, white solid, mp = 124-126 °C: ¹H NMR δ 7.64 (d, *J* = 8.0 Hz, 2H), 7.39 (t, *J* = 7.1, 1H), 7.27 (t, *J* = 8.2 Hz, 2H), 7.15-7.05 (m, 5H), 5.67 (d, *J* = 9.5 Hz, 1H), 4.97 (td, *J* = 12.7, 9.5 Hz, 1H), 0.78 (t, *J* = 7.5 Hz, 9H), 0.60 (q, *J* = 7.5 Hz, 6H); ¹³C NMR δ 236.4 (t, ²*J*_{C-F} = 37.8 Hz), 140.1, 132.4, 128.6, 128.5, 128.3, 126.9, 114.6 (t, ¹*J*_{C-F} = 258.4 Hz), 57.8 (t, ²*J*_{C-F} = 24.3 Hz), 6.6, 1.69; ¹⁹F NMR -111.8 (dd, *J* = 281.2, 13.2 Hz, 1F), -112.8 (dd, *J* = 281.5, 13.3 Hz, 1F); Anal. Calcd for C₂₁H₂₇F₂NO₃SSi (%): C, 57.38; H, 6.19. Found (%): C, 57.50; H, 6.37.

***N*-[3-(*tert*-Butyldimethylsilyl)-2,2-difluoro-3-oxo-1-phenylpropyl]-benzenesulfonamide (7c)**

Yield = 74 %, white solid, mp = 109-111 °C: ^1H NMR δ 7.65 (d, J = 7.5 Hz, 2H), 7.41 (t, J = 7.1, 1H), 7.29 (t, J = 8.2 Hz, 2H), 7.17-7.06 (m, 5H), 5.61 (d, J = 9.5 Hz, 1H), 4.95 (td, J = 12.7, 9.5 Hz, 1H), 0.77 (s, 9H), 0.01 (s, 6H); ^{13}C NMR δ 236.5 (t, $^2J_{\text{C-F}}$ = 36.6 Hz), 140.1, 132.4, 128.6, 128.5, 128.4, 126.9, 114.6 (t, $^1J_{\text{C-F}}$ = 259.4 Hz), 58.0 (t, $^2J_{\text{C-F}}$ = 24.7 Hz), 26.1, 16.9, -7.3; ^{19}F NMR -110.8 (dd, J = 278.9, 9.1 Hz, 1F), -112.2 (dd, J = 278.9, 13.1 Hz, 1F); Anal. Calcd for $\text{C}_{21}\text{H}_{27}\text{F}_2\text{NO}_3\text{SSi}$ (%): C, 57.38; H, 6.19. Found (%): C, 57.11; H, 6.20.

***N*-[3-(*tert*-Butyldiphenylsilyl)-2,2-difluoro-3-oxo-1-phenylpropyl]-benzenesulfonamide (7d)**

Yield = 84 %, white solid, mp = 141-143 °C: ^1H NMR δ 7.65-6.59 (m, 20H), 5.13 (d, J = 9.6 Hz, 1H), 4.79 (ddd, J = 17.0, 9.6, 9.3 Hz, 1H), 1.05 (s, 9H); ^{13}C NMR δ 231.8 (t, $^2J_{\text{C-F}}$ = 34.9 Hz), 140.0, 136.4, 136.3, 132.3, 131.9, 130.1, 129.9, 129.8, 128, 5, 128.4, 128.2, 127.0, 127.8, 126.8, 114.6 (dd, $^1J_{\text{C-F}}$ = 259.1, 259.0 Hz), 57.7 (dd, $^2J_{\text{C-F}}$ = 23.2, 23.0 Hz), 27.4, 18.9; ^{19}F NMR δ -107.3 (dd, J = 278.4, 9.3 Hz, 1F), -113.8 (dd, J = 278.5, 16.8 Hz, 1F); Anal. Calcd for $\text{C}_{31}\text{H}_{31}\text{F}_2\text{NO}_3\text{SSi}$ (%): C, 66.05; H, 5.54. Found (%): C, 66.21; H, 5.68.

***N*-(2,2-Difluoro-3-oxo-1-phenyl-3-triphenylsilylpropyl)-benzenesulfonamide (7e)**

Yield = 88 %, white solid, mp = 159-161 °C: ^1H NMR δ 7.58-6.80 (m, 25H), 5.36 (d, J = 10.0 Hz, 1H), 4.86 (ddd, J = 16.4, 9.9, 9.8 Hz, 1H); ^{13}C NMR δ 230.0 (t, $^2J_{\text{C-F}}$ = 35.5 Hz), 139.9, 136.3, 132.4, 132.0, 130.6, 128.6, 128.5, 128.4, 128.3, 128.1, 126.9, 115.4 (dd, $^1J_{\text{C-F}}$ = 258.5, 258.1 Hz), 57.8 (dd,

$^2J_{\text{C-F}} = 23.3, 23.3 \text{ Hz}$); ^{19}F NMR δ -107.5 (dd, $J = 276.8, 9.5 \text{ Hz}$, 1F), -112.9 (dd, $J = 276.9, 16.5 \text{ Hz}$, 1F); Anal. Calcd for $\text{C}_{33}\text{H}_{27}\text{F}_2\text{NO}_3\text{SSi}$ (%): C, 67.90; H, 4.66. Found (%): C, 68.15; H, 4.54.

***N*-(2,2-Difluoro-3-oxo-1-phenyl-3-triisopropylsilylpropyl)-benzenesulfonamide (7f)**

Yield = 68 %, white solid, mp = 143-144 °C: ^1H NMR δ 7.64 (d, $J = 7.5 \text{ Hz}$, 2H), 7.39 (t, $J = 7.2$, 1H), 7.26 (t, $J = 7.0 \text{ Hz}$, 2H), 7.14-7.09 (m, 5H), 5.71 (d, $J = 8.2 \text{ Hz}$, 1H), 4.97 (td, $J_{\text{H-F}} = 12.5, 9.8 \text{ Hz}$, 1H), 1.30-1.16 (m, 3H), 0.90 (d, $J = 7.5 \text{ Hz}$, 18H); ^{13}C NMR δ 236.2 (t, $^2J_{\text{C-F}} = 39.7 \text{ Hz}$), 140.2, 132.6, 132, 4, 128.7, 128.6, 128.5, 128.3, 127.0, 113.9 (t, $^1J_{\text{C-F}} = 258.4 \text{ Hz}$), 57.8 (t, $^2J_{\text{C-F}} = 24.6 \text{ Hz}$), 18.1, 11.0; ^{19}F NMR δ -110.4 (dd, $J = 291.2, 11.8 \text{ Hz}$, 1F), -111.7 (dd, $J = 291.2, 12.5 \text{ Hz}$, 1F); Anal. Calcd for $\text{C}_{24}\text{H}_{33}\text{F}_2\text{NO}_3\text{SSi}$ (%): C, 59.85; H, 6.91. Found (%): C, 60.00; H, 7.08.

***N*-(2,2-Difluoro-3-oxo-1-phenyl-3-trimethylsilylpropyl)-4-methoxybenzenesulfonamide (7g)**

Yield = 75 %, white solid, mp = 123-124 °C: ^1H NMR δ 7.56 (d, $J = 8.9 \text{ Hz}$, 2H), 7.19-7.06 (m, 5H), 6.75 (d, $J = 8.9 \text{ Hz}$, 2H), 5.49 (d, $J = 9.0 \text{ Hz}$, 1H), 4.89 (m, 1H), 3.78 (s, 3H), 0.06 (s, 9H); ^{13}C NMR δ 236.2 (t, $^2J_{\text{C-F}} = 37.1 \text{ Hz}$), 162.7, 132.5, 131.6, 129.1, 128.5, 128.4, 128.3, 115.4 (t, $^1J_{\text{C-F}} = 260.0 \text{ Hz}$), 113.8, 57.9 (t, $^2J_{\text{C-F}} = 25.1 \text{ Hz}$), 55.4, -3.6; ^{19}F NMR δ -110.6 (dd, $J = 276.0, 12.5 \text{ Hz}$, 1F), -113.0 (dd, $J = 276.3, 14.1 \text{ Hz}$, 1F); Anal. Calcd for $\text{C}_{19}\text{H}_{23}\text{F}_2\text{NO}_4\text{SSi}$ (%): C, 53.38; H, 5.42. Found (%): C, 53.18; H, 5.34.

***N*-(2,2-Difluoro-3-oxo-1-phenyl-3-trimethylsilylpropyl)-4-methylbenzenesulfonamide (7h)**

Yield = 79 %, white solid, mp = 164-166 °C: ^1H NMR δ 7.52 (d, J = 8.4 Hz, 2H), 7.22-7.13 (m, 3H), 7.12-7.04 (m, 4H), 5.47 (d, J = 9.4 Hz, 1H), 4.90 (ddd, J = 13.7, 12.0, 9.4 Hz, 1H), 2.32 (s, 3H), 0.06 (s, 9H); ^{13}C NMR δ 236.4 (t, $^2J_{\text{C-F}}$ = 36.3 Hz), 143.3, 137.1, 132.6, 129.3, 128.6, 128.5, 128.4, 127.0, 115.3 (t, $^1J_{\text{C-F}}$ = 259.1 Hz), 58.0 (t, $^2J_{\text{C-F}}$ = 25.1 Hz), 21.4, -3.6; ^{19}F NMR δ -110.5 (dd, J = 276.5, 11.9 Hz, 1F), -112.9 (dd, J = 276.5, 13.7 Hz, 1F); Anal. Calcd for $\text{C}_{19}\text{H}_{23}\text{F}_2\text{NO}_3\text{SSi}$ (%): C, 55.45; H, 5.63. Found (%): C, 55.30; H, 5.59.

***N*-(2,2-Difluoro-3-oxo-1-phenyl-3-trimethylsilylpropyl)-4-nitrobenzenesulfonamide (7i).** **7i** was obtained according to general procedure using 2 equivalents of **3a** and $\text{Cu}(\text{OTf})_2$.

Yield = 85 %, pale yellow solid, mp = 127-129 °C: ^1H NMR δ 8.13 (d, J = 9.0 Hz, 2H), 7.81 (d, J = 8.9 Hz, 2H) 7.21-7.05 (m 5H), 5.81 (d, J = 9.4 Hz, 1H), 5.01 (td, J = 12.4, 9.4 Hz, 1H), 0.03 (s, 9H); ^{13}C NMR δ 236.4 (t, $^2J_{\text{C-F}}$ = 36.5 Hz), 149.8, 145.8, 131.8, 129.0, 128.6, 128, 5, 128.2, 123.9, 115.0 (t, $^1J_{\text{C-F}}$ = 259.4 Hz), 58.3 (t, $^2J_{\text{C-F}}$ = 24.9 Hz), -3.7; ^{19}F NMR δ -110.7 (dd, J = 278.4, 12.5 Hz, 1F), -112.6 (dd, J = 278.3, 13.3 Hz, 1F); Anal. Calcd for $\text{C}_{18}\text{H}_{20}\text{F}_2\text{N}_2\text{O}_5\text{SSi}$ (%): C, 48.86; H, 4.56. Found (%): C, 48.76; H, 4.76.

***N*-[1-(4-Chlorophenyl)-2,2-difluoro-3-oxo-3-trimethylsilylpropyl]-benzenesulfonamide (7j)**

Yield = 72 %, white solid, mp = 149-151 °C: ^1H NMR δ 7.64 (d, J = 7.1 Hz, 2H), 7.46 (t, J = 7.3, 1H), 7.33 (t, J = 7.3 Hz, 2H), 7.14 (d, J = 8.5 Hz, 2H), 7.03 (d, J = 8.5 Hz, 2H), 5.59 (d, J = 9.1 Hz, 1H), 4.95 (ddd, J = 14.0, 11.3, 9.2 Hz, 1H), 0.09 (s, 9H); ^{13}C NMR δ 235.8 (t, $^2J_{\text{C-F}}$ = 36.7 Hz), 139.9, 134.8, 132.7, 131.2, 129.9, 128.8, 128.6, 127.0, 115.0 (t, $^1J_{\text{C-F}}$ = 259.8 Hz), 57.3 (t, $^2J_{\text{C-F}}$ = 24.2 Hz), -3.6; ^{19}F NMR δ -109.7 (dd, J = 282.1, 11.2 Hz, 1F), -113.3 (dd, J = 282.6, 14.1 Hz, 1F); Anal. Calcd for $\text{C}_{18}\text{H}_{20}\text{ClF}_2\text{NO}_3\text{SSi}$ (%): C, 50.05; H, 4.67. Found (%): C, 50.21; H, 4.82.

***N*-(2,2-Difluoro-3-oxo-1-*p*-tolyl-3-trimethylsilylpropyl)-benzenesulfonamide (7k)**

Yield = 71 %, white solid, mp = 138-140 °C: ^1H NMR δ 7.65 (d, J = 7.9 Hz, 2H), 7.42 (t, J = 7.7, 1H), 7.30 (t, J = 7.9 Hz, 2H), 6.96 (s, 4H), 5.56 (d, J = 9.5 Hz, 1H), 4.89 (ddd, J = 13.8, 12.1, 9.4 Hz, 1H), 2.24 (s, 3H), 0.06 (s, 9H); ^{13}C NMR δ 236.4 (t, $^2J_{\text{C-F}}$ = 36.5 Hz), 140.1, 138.5, 132.4, 129.5, 129.1, 128.6, 128.3, 127.0, 115.4 (t, $^1J_{\text{C-F}}$ = 259.1 Hz), 57.7 (t, $^2J_{\text{C-F}}$ = 25.4 Hz), 20.9, -3.6; ^{19}F NMR δ -110.6 (dd, J = 276.8, 11.7 Hz, 1F), -113.0 (dd, J = 276.5, 13.8 Hz, 1F); Anal. Calcd for $\text{C}_{19}\text{H}_{23}\text{F}_2\text{NO}_3\text{SSi}$ (%): C, 55.45; H, 5.63. Found (%): C, 55.38; H, 5.64.

***N*-[2,2-Difluoro-1-(4-nitrophenyl)3-oxo-3-trimethylsilylpropyl]-benzenesulfonamide (7l)**

Yield = 51 %, white solid, mp = 106-108 °C: ^1H NMR δ 8.05 (d, J = 8.8 Hz, 2H), 7.47 (d, J = 7.1, 2H), 7.47 (t, J = 7.4 Hz, 1H), 7.37-7.32 (m, 4H), 5.77 (d, J = 9.0 Hz, 1H), 5.07 (ddd, J = 14.1, 9.8, 9.4 Hz, 1H), 2.24 (s, 3H), 0.07 (s, 9H); ^{13}C NMR δ 234.9 (dd, $^2J_{\text{C-F}}$ = 37.9, 37.8 Hz), 147.9, 139.9, 139.7,

133.0, 129.6, 128.9, 127.0, 123.4, 114.8 (t, $^1J_{\text{C-F}} = 259.7$ Hz), 57.2 (dd, $^2J_{\text{C-F}} = 24.1, 23.9$ Hz), -3.6 ^{19}F NMR δ -108.0 (dd, $J = 288.6, 10.4$ Hz, 1F), -113.9 (dd, $J = 288.7, 14.4$ Hz, 1F); Anal. Calcd for $\text{C}_{18}\text{H}_{20}\text{F}_2\text{N}_2\text{O}_5\text{SSi}$ (%): C, 48.86; H, 4.56. Found (%): C, 49.00; H, 4.69.

***N*-[2,2-Difluoro-1-(4-methoxyphenyl)-3-oxo-3-trimethylsilylpropyl]-benzenesulfonamide (7m)**

Yield = 56 %, white solid, mp = 144-146 °C: ^1H NMR δ 7.65 (d, $J = 7.6$ Hz, 2H), 7.43 (t, $J = 7.4$, 1H), 7.31 (t, $J = 7.9$ Hz, 2H), 6.98 (d, $J = 8.6$ Hz, 2H), 6.67 (d, $J = 8.7$ Hz, 2H), 5.61 (d, $J = 9.1$ Hz, 1H), 4.88 (td, $J = 13.1, 9.4$ Hz, 1H), 3.72 (s, 3H), 0.07 (s, 9H); ^{13}C NMR δ 236.5 (t, $^2J_{\text{C-F}} = 36.2$ Hz), 159.7, 140.2, 132.5, 129.8, 128.7, 127.0, 124.5, 115.4 (t, $^1J_{\text{C-F}} = 258.7$ Hz), 113.9, 57.5 (t, $^2J_{\text{C-F}} = 25.2$ Hz), 55.2, -3.6; ^{19}F NMR δ -111.0 (dd, $J = 276.9, 12.2$ Hz, 1F), -112.7 (dd, $J = 276.6, 13.7$ Hz, 1F); Anal. Calcd for $\text{C}_{19}\text{H}_{23}\text{F}_2\text{NO}_4\text{SSi}$ (%): C, 53.38; H, 5.42. Found (%): C, 53.31; H, 5.50.

***N*-(2,2-Difluoro-3-oxo-1-*o*-tolyl-3-trimethylsilylpropyl)-benzenesulfonamide (7n)**

Yield = 49 %, white solid, mp = 136-137 °C: ^1H NMR δ 7.59 (d, $J = 7.4$ Hz, 2H), 7.39 (t, $J = 7.5$, 1H), 7.26 (t, $J = 7.6$ Hz, 2H), 7.01-6.98 (m, 4H), 5.54 (d, $J = 9.4$ Hz, 1H), 5.26 (ddd, $J = 16.2, 9.8, 9.4$ Hz, 1H), 2.24 (s, 3H), 0.09 (s, 9H); ^{13}C NMR δ 236.3 (t, $^2J_{\text{C-F}} = 36.7$ Hz), 140.0, 137.0, 132.5, 131.1, 130.6, 129.1, 128.7, 127.6, 126.9, 126.3, 115.9 (t, $^1J_{\text{C-F}} = 258.7$ Hz), 53.2 (dd, $^2J_{\text{C-F}} = 24.3, 24.0$ Hz), 19.4, -3.5; ^{19}F NMR δ -109.4 (dd, $J = 279.2, 8.8$ Hz, 1F), -114.1 (dd, $J = 276.3, 15.4$ Hz, 1F); Anal. Calcd for $\text{C}_{19}\text{H}_{23}\text{F}_2\text{NO}_3\text{SSi}$ (%): C, 55.45; H, 5.63. Found (%): C, 55.32; H, 5.61.

To a mixture of *N*-alkylidene-4-methylbenzenesulfonamide **6j-m** (0.8 mmol) and trimethylsilyl trifluoromethanesulfonate (18 mg, 0.08 mmol) in 3 mL of dichloromethane was added a solution of **3a** (1 mmol) in 2 mL of dichloromethane at -78 °C, then resulting mixture was stirred at this temperature for 6 hours and over night at room temperature. Reaction was quenched with 10 mL of saturated sodium bicarbonate solution and then extracted with dichloromethane (2 x 20 mL). Organic layer was dried over anhydrous MgSO₄, filtered and concentrated. Compound **7** was purified by silica gel column chromatography using a mixture of hexane and ethyl acetate (25 : 1 = v:v), then recrystallization in hexane.

***N*-(1-Cyclohexyl-2,2-difluoro-3-oxo-3-trimethylsilylpropyl)-4-methylbenzenesulfonamide (7o)**

Yield = 63 %, white solid; mp = 107-109 °C: ¹H NMR δ 7.67 (d, *J* = 7.7 Hz, 2H), 7.24 (d, *J* = 7.5 Hz, 2H), 4.84 (d, *J* = 9.9 Hz, 1H), 3.83 (tdd, *J* = 14.0, 10.2, 3.7 Hz, 1H), 2.38 (s, 3H), 1.68-1.42 (m, 6H), 1.21-0.93 (m, 5H), 0.17 (s, 9H); ¹³C NMR δ 235.3 (t, ²*J*_{C-F} = 38.1 Hz), 143.2, 138.2, 129.3, 127.0, 116.9 (t, ¹*J*_{C-F} = 257.2 Hz), 58.1 (t, ²*J*_{C-F} = 23.0 Hz), 37.8, 30.7, 27.6, 26.2, 25.9, 25.7, 21.4, -3.3; ¹⁹F NMR δ -108.6 (dd, *J* = 286.4, 13.6 Hz, 1F), -109.7 (dd, *J* = 287.0, 14.2 Hz, 1F); Anal. Calcd for C₁₉H₂₉F₂NO₃SSi (%): C, 54.65; H, 7.00. Found (%): C, 54.72; H, 6.80.

***N*-(2,2-Difluoro-1-isopropyl-3-oxo-3-trimethylsilylpropyl)-4-methylbenzenesulfonamide (7p)**

Yield = 49 %, white solid, mp = 105-107 °C: ¹H NMR: δ 7.68 (d, *J* = 8.1 Hz, 2H), 7.24 (d, *J* = 8.1 Hz, 2H), 4.84 (d, *J* = 10.0 Hz, 1H), 3.87 (tdd, *J* = 13.8, 10.3, 3.5 Hz, 1H), 2.38 (s, 3H), 1.95-1.85 (m,

1H), 0.86 (d, $J = 5.7$ Hz, 3H), 0.85 (d, $J = 6.9$ Hz, 3H), 0.18 (s, 9H); ^{13}C NMR δ 235.1 (dd, $^2J_{\text{C-F}} = 35.9, 35.8$ Hz), 143.2, 138.2, 129.4, 127.0, 116.9 (t, $^1J_{\text{C-F}} = 256.9$ Hz), 57.9 (t, $^2J_{\text{C-F}} = 24.6$ Hz), 27.8, 21.4, 20.5, 17.0, -3.3; ^{19}F NMR δ -109.3 (dd, $J = 287.2, 13.1$ Hz, 1F), -110.6 (dd, $J = 287.3, 14.6$ Hz, 1F); Anal. Calcd for $\text{C}_{16}\text{H}_{25}\text{F}_2\text{NO}_3\text{SSi}$ (%): C, 50.90; H, 6.67. Found (%): C, 51.12; H, 6.65.

***N*-[1-(1,1-Difluoro-2-oxo-2-trimethylsilyl)-3-methylbutyl]-4-methylbenzenesulfonamide (7q)**

Yield = 51 %, white solid, mp = 119-121 °C: ^1H NMR δ 7.68 (d, $J = 8.4$ Hz, 2H), 7.25 (d, $J = 6.5$ Hz, 2H), 4.58 (d, $J = 10.0$ Hz, 1H), 4.03-3.88 (m, 1H), 2.39 (s, 3H), 1.70-1.63 (m, 1H), 1.36-1.16 (m, 2H), 0.85 (d, $J = 6.7$ Hz, 3H), 0.82 (d, $J = 6.5$ Hz, 3H), 0.18 (s, 9H); ^{13}C NMR δ 235.7 (dd, $^2J_{\text{C-F}} = 37.6, 37.5$ Hz), 143.2, 138.1, 129.4, 127.0, 116.1 (t, $^1J_{\text{C-F}} = 255.9$ Hz), 52.9 (t, $^2J_{\text{C-F}} = 23.7$ Hz), 38.6, 23.7, 23.4, 21.4, 20.9, -3.3; ^{19}F NMR δ -111.6 (d, $J = 10.9$ Hz, 1F), -111.8 (d, $J = 10.7$ Hz, 1F); Anal. Calcd for $\text{C}_{17}\text{H}_{27}\text{F}_2\text{NO}_3\text{SSi}$ (%): C, 52.15; H, 6.95. Found (%): C, 52.34; H, 7.07.

***N*-(1-(1,1-Difluoro-2-oxo-2-trimethylsilylethyl)-pentyl)-4-methylbenzenesulfonamide (7r)**

Yield = 54 %, white solid, mp = 66-68 °C: ^1H NMR: δ 7.68 (d, $J = 8.3$ Hz, 2H), 7.25 (d, $J = 7.6$ Hz, 2H), 4.66 (d, $J = 9.5$ Hz, 1H), 3.91-3.77 (m, 1H), 2.39 (s, 3H), 1.39-1.03 (m, 6H), 0.78 (t, $J = 6.5$ Hz, 3H), 0.19 (s, 9H); ^{13}C NMR δ 235.8 (t, $^2J_{\text{C-F}} = 39.2$ Hz), 143.3, 138.1, 129.4, 127.0, 116.1 (t, $^1J_{\text{C-F}} = 256.4$ Hz), 54.4 (t, $^2J_{\text{C-F}} = 24.6$ Hz), 29.0, 27.3, 22.1, 21.4, 13.6, -3.4; ^{19}F NMR δ -111.1 (dd, $J = 288.2, 12.8$ Hz, 1F), -113.0 (dd, $J = 288.4, 11.4$ Hz, 1F); Anal. Calcd for $\text{C}_{17}\text{H}_{27}\text{F}_2\text{NO}_3\text{SSi}$ (%): C, 52.15; H, 6.95. Found (%): C, 52.32; H, 7.08.

General procedure for the formation of 8

To a mixture of **7g** or **7i** (0.2 mmol) and H₂O₂ (1 mL) in THF (2 mL) was added TBAF (0.3 mmol, 0.3 mL of 1 M solution in THF) and resulting mixture was stirred at room temperature for 10 min. Reaction was quenched with water (10 mL) and extracted with ethyl acetate (20 mL x 2). Combined organic phase was dried over anhydrous MgSO₄, filtered and concentrated. Crude product was subjected to esterification with chlorotrimethylsilane (65 mg, 0.6 mmol) in ethanol under reflux for 5 hrs. Reaction was quenched with water (10 mL) and extracted with ethyl acetate (20 mL x 2). Combined organic phase was dried over anhydrous MgSO₄, filtered and concentrated. Product was purified by silica gel column chromatography using a mixture of hexane and ethyl acetate (4 : 1 = v:v).

2,2-Difluoro-3-(4-methoxybenzenesulfonylamino)-3-phenylpropionic acid ethyl ester (**8a**)

Yield = 88 %, white solid, mp = 94-96 °C: ¹H NMR δ 7.55 (d, *J* = 8.9 Hz, 2H), 7.22-7.09 (m, 5H), 6.74 (d, *J* = 8.9 Hz, 2H), 5.32 (d, *J* = 10.0 Hz, 1H), 4.99 (ddd, *J* = 16.4, 9.8, 9.7 Hz, 1H), 4.21 (q, *J* = 7.3 Hz, 2H), 3.78 (s, 3H), 1.24 (t, *J* = 7.5 Hz, 3H); ¹³C NMR δ 162.9, 162.5 (dd, ²*J*_{C-F} = 32.1, 30.7 Hz), 131.9, 131.7, 129.2, 129.0, 128.6, 128.2, 113.9, 113.7 (dd, ¹*J*_{C-F} = 257.2, 257.0 Hz), 63.4, 59.7 (dd, ²*J*_{C-F} = 23.8, 23.6 Hz), 55.5, 13.7; ¹⁹F NMR δ -111.6 (dd, *J* = 258.2, 9.7 Hz, 1F), -115.7 (dd, *J* = 258.1, 16.6 Hz, 1F); Anal. Calcd for C₁₈H₁₉F₂NO₅S (%): C, 54.13; H, 4.79. Found (%): C, 54.09; H, 4.99.

2,2-Difluoro-3-(4-nitrobenzenesulfonylamino)-3-phenylpropionic acid ethyl ester (**8b**)

Yield = 92 %, white solid, mp = 138-140 °C: ^1H NMR δ 8.07 (d, J = 8.6 Hz, 2H), 7.80 (d, J = 8.9 Hz), 7.70-7.09 (m, 5H), 6.42 (d, J = 10.1 Hz, 1H), 5.10 (ddd, J = 15.4, 10.8, 10.5 Hz, 1H), 4.24 (q, J = 7.1 Hz, 2H), 1.23 (t, J = 7.1 Hz, 3H); ^{13}C NMR δ 162.4 (t, $^2J_{\text{C-F}}$ = 31.8 Hz), 149.8, 145.7, 131.0, 129.4, 128.7, 128.2, 123.9, 113.4 (t, $^1J_{\text{C-F}}$ = 258.6 Hz), 63.7, 60.0 (t, $^2J_{\text{C-F}}$ = 26.1 Hz), 13.7; ^{19}F NMR δ -112.4 (dd, J = 259.0, 10.7 Hz, 1F), -114.4 (dd, J = 258.9, 14.9 Hz, 1F); Anal. Calcd for $\text{C}_{17}\text{H}_{16}\text{F}_2\text{N}_2\text{O}_6\text{S}$ (%): C, 49.27; H, 3.89. Found (%): C, 49.22; H, 4.08.

General procedure for the formation of 9

To a solution of **8a** or **8b** (0.25 mmol) in 3 mL of THF was added a solution of ethylamine (22.5 mg, 4 mmol) in 2 mL of THF at 0 °C and resulting mixture was stirred at room temperature for 24 hrs. Reaction was quenched with water (10 mL) and extracted with diethyl ether (20 mL x 2). Organic layer was dried over anhydrous MgSO_4 , filtered and concentrated. Product was purified by recrystallization in hexane.

N-Ethyl-2,2-difluoro-3-(4-methoxybenzenesulfonylamino)-3-phenylpropionamide (**9a**)

Yield = 90 %, white solid, mp = 192-193 °C: ^1H NMR (DMSO- d_6) δ 8.77 (d, J = 10.6 Hz, 1H), 8.60 (br, 1H), 7.46 (d, J = 8.9 Hz, 2H), 7.24-7.06 (m, 5H), 6.80 (d, J = 8.8 Hz, 2H), 5.12-4.94 (m, 1H), 3.71 (s, 3H), 3.07-2.90 (m, 2H), 0.82 (t, J = 7.2 Hz, 3H); ^{13}C NMR (DMSO- d_6) δ 161.8, 161.6 (t, $^2J_{\text{C-F}}$ = 27.7 Hz), 132.9, 128.6, 128.4, 128.0, 127.8, 115.4 (t, $^1J_{\text{C-F}}$ = 258.9 Hz), 113.7, 58.8 (t, $^2J_{\text{C-F}}$ = 24.2 Hz), 55.5, 33.6, 13.9; ^{19}F NMR (DMSO- d_6) δ -107.8 (dd, J = 246.2, 15.2 Hz, 1F), -109.8 (dd, J = 248.7, 15.5 Hz, 1F); Anal. Calcd for $\text{C}_{18}\text{H}_{20}\text{F}_2\text{N}_2\text{O}_4\text{S}$ (%): C, 54.26; H, 5.06. Found (%): C, 54.44; H, 5.18.

***N*-Ethyl-2,2-difluoro-3-(4-nitrobenzenesulfonylamino)-3-phenylpropionamide (9b)**

Yield = 96 %, white solid, mp = 216-218 °C: ^1H NMR (DMSO- d_6) δ 9.36 (br, 1H), 8.66 (br, 1H), 8.12 (d, J = 8.8 Hz, 2H), 7.79 (d, J = 8.9 Hz, 2H), 7.16-7.09 (m, 5H), 5.20-5.01 (m, 1H), 2.97 (q, J = 6.5 Hz, 2H), 0.82 (t, J = 7.1 Hz, 3H); ^{13}C NMR (DMSO- d_6) δ 161.4 (t, $^2J_{\text{C-F}}$ = 27.5 Hz), 149.1, 146.5, 132.4, 128.6, 128.3, 128.0, 123.9, 115.2 (t, $^1J_{\text{C-F}}$ = 258.8 Hz), 59.0 (t, $^2J_{\text{C-F}}$ = 24.8 Hz), 33.6, 13.9; ^{19}F NMR (DMSO- d_6) δ -107.6 (dd, J = 247.5, 14.1 Hz, 1F), -109.7 (dd, J = 247.4, 14.1 Hz, 1F); Anal. Calcd for $\text{C}_{17}\text{H}_{17}\text{F}_2\text{N}_3\text{O}_5\text{S}$ (%): C, 49.39; H, 4.14. Found (%): C, 49.15; H, 4.12.

Synthesis of *N*-Ethyl-2,2-difluoro-3-amino-3-phenylpropionamide (10)

A solution of **9b** (0.2 mmol) and K_2CO_3 (83 mg, 0.6 mmol) in 1 mL of DMF was deoxygenated by evacuating and purging with argon three times. Thiophenol (33 mg, 0.3 mmol) was added and the reaction mixture was stirred for 6 h at room temperature. Reaction was quenched with saturated sodium bicarbonate solution (10 mL) and extracted with ethyl acetate (20 mL x 2). Organic layer was

dried over anhydrous MgSO_4 , filtered and concentrated. Product was purified by silica gel column chromatography using a mixture of chloroform and methanol (9.5 : 0.5 = v:v).

Yield = 91 %, white solid, mp = 65-67 °C: ^1H NMR δ 7.40-7.30 (m, 5H), 6.37 (br, 1H), 4.58 (m, 1H), 3.23 (qd, J = 11.1, 6.7 Hz, 1H), 3.19 (qd, J = 11.1, 6.7 Hz, 1H), 2.50-2.23 (br, 2H), 0.99 (t, J = 6.7 Hz, 3H); ^{13}C NMR ($\text{CDCl}_3 + \text{CD}_3\text{OD}$) δ 163.5 (t, $^2J_{\text{C-F}}$ = 28.1 Hz), 143.7, 128.7, 128.5, 128.0 116.1 (t, $^1J_{\text{C-F}}$ = 256.7 Hz), 57.4 (t, $^2J_{\text{C-F}}$ = 24.8 Hz), 35.4, 14.6; ^{19}F NMR δ -115.7 (dd, J = 251.4, 12.2 Hz, 1F), -117.2 (dd, J = 251.4, 12.2 Hz, 1F); Anal. Calcd for $\text{C}_{11}\text{H}_{14}\text{F}_2\text{N}_2\text{O}$ (%): C, 57.89; H, 6.18. Found (%): C, 57.99; H, 5.97.