Supporting Information

RCM-Mediated Synthesis of Trifluoromethyl-Containing Nitrogen Heterocycles

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Experimental Section

General Information: All reactions were carried out under an atmosphere of dry nitrogen. Solvents were distilled from the appropriate drying agents immediately prior to use. Infrared (IR) spectra were recorded on a FTIR spectrometer and absorptions are reported in cm^{-1} . NMR spectra were recorded using a 300 or 400 MHz spectrometer from CDCl_3 solutions using TMS as internal standard. ^{13}C NMR spectra were calibrated at $\delta = 77.16$ ppm, unless mentioned otherwise. Flash chromatography was performed with silica gel (0.035–0.070 nm). The microwave reactions were carried out in a commercial monomode microwave oven (CEM Discover) with continuous monitoring of internal pressure and infrared temperature control.

2-Trifluoromethylbicyclo[2.2.1]hept-5-ene-2-carboxylic acid (10**):**¹ Cyclopentadiene (30 mL, 42.8 mmol) was added dropwise in 30 min to a solution of 2-(trifluoromethyl)acrylic acid (5.01 g, 35.7 mmol) in CH_2Cl_2 (20 mL) at 0–5 °C. The mixture was stirred overnight at rt; then CH_2Cl_2 and the excess of cyclopentadiene were removed under reduced pressure to give **10** (7.13 g, 97%) after recrystallization (CHCl_3 /heptane 15:6) in a 2:1 mixture of *endo/exo*-diastereoisomers as a white solid. Mp: 84.4–85.4 °C; IR (neat, cm^{-1}): 3155, 2890, 2922, 2904, 1707, 1407, 1282, 1246, 1155, 1120, 1070; ^1H NMR (300 MHz, CDCl_3 , both diastereoisomers) $\delta = 11.1$ (br s, 1H), 6.34–6.29 (m, 1H), 6.11–6.03 (m, 1H), 3.48 + 3.38 (br s, 1H), 2.98 (br s, 1H), 2.04 (br s, 2H), 1.77 (d, $J = 9.3$ Hz, 1H), 1.52–1.54 (m, 1H); ^{13}C NMR (100 MHz, CDCl_3 , two diastereoisomers) $\delta = 176.4 + 175.1$, 140.7 + 140.2, 134.9 + 132.3, 126.3 + 125.7 (both q, $J = 285$ Hz), 60.3 (q, $J = 33.0$ Hz), 49.8 + 48.6, 47.8 + 47.7, 42.7 + 41.9, 32.3 + 32.2; HRMS (EI) calcd for $\text{C}_9\text{H}_9\text{O}_2\text{F}_3$ (M^+) 206.0555, found 206.0554.

^1H NMR (400 MHz)

2-Trifluoromethylbicyclo[2.2.1]hept-5-ene-2-carboxylic acid methyl ester (11):² A solution of **10** (646 mg, 3.13 mmol) in dry acetone (5 mL), dimethyl sulfate (0.38 mL, 4 mmol) and K₂CO₃ (554 mg, 4 mmol) was refluxed for 5 h. The solution was then decanted and the acetone layer was evaporated to give the crude product **11** (685 mg, 99%, 2:1 mixture of *endo/exo*-isomers) as a light brown oil. IR (neat, cm⁻¹): 2902, 2848, 1741, 1265, 1149, 1047, 1101; ¹H NMR (300 MHz, CDCl₃, both diastereoisomers) δ = 6.31–6.25 (m, 1H), 6.04–5.97 (m, 1H), 3.69 (s, 3H), 3.44 + 3.36 (br s, 1H), 2.96 (s, 1H), 2.04–2.08 (m, 2H), 1.77 + 1.74 (br s, 1H), 1.47 + 1.45 (br s, 1H); ¹³C NMR (75 MHz, CDCl₃, both diastereoisomers) δ = 170.1 + 169.5, 140.2 + 134.5, 139.8 + 132.1, 126.3 + 125.8 (both q, *J* = 279.7 Hz), 59.8 (q, *J* = 21.8 Hz), 58.7, 53.4 + 52.9, 48.6 + 47.8 (both q, *J* = 1.5 Hz), 42.7 + 42.0, 32.8 + 32.6; HRMS (EI) calcd for C₁₀H₁₁F₃O₂ (M⁺) 220.0711, found 220.0711.

¹H NMR (300 MHz)

¹³C NMR (75 MHz)

2-Trifluoromethylbicyclo[2.2.1]hept-5-ene-2-methanol (12):³ A solution of **11** (776 mg, 3.52 mmol) in anhydrous Et₂O (6 mL) was added to a suspension of LiAlH₄ (134 mg, 3.52 mmol) in anhydrous Et₂O (6 mL) over 30 min at rt and the reaction was stirred for 5 h. EtOAc (8 mL) was added slowly, followed by saturated aqueous Na₂SO₄ (a few drops) and solid Na₂SO₄. After stirring for a few min, the mixture was filtrated. The solvent was evaporated and the crude product **12** (554 mg, 82%) was obtained as a white solid (2:1 mixture of *endo/exo*-isomers). Mp = 52.7 °C; IR (neat, cm⁻¹): 3261, 2979, 2892, 1379, 1246, 1197, 1032, 1144; ¹H NMR (300 MHz, CDCl₃, both diastereoisomers) δ = 6.25–6.02 (m, 2H), 3.99–3.92 + 3.83–3.77 (m, 2H), 3.32–3.24 + 3.20–3.11 (m, 1H), 3.07–3.03 + 2.94–2.88 (m, 1H), 1.88–1.77 (m, 2H), 1.48–1.36 (m, 2H); ¹³C NMR (75 MHz, CDCl₃, both diastereoisomers, the quaternary carbons were not visible) δ = 138.4 + 138.1, 135.5 + 133.5, 130.1 (q, *J* = 280.3 Hz), 66.9 + 66.0 (q, *J* = 1.5 Hz), 47.9 + 45.7 (q, *J* = 1.4 Hz), 42.7 + 41.9, 32.1 + 31.3, 30.0; HRMS (EI) calcd for C₉H₁₁F₃O (M⁺) 192.0762, found 192.0766.

¹H NMR

¹³C NMR

Toluene-4-sulfonic acid 2-trifluoromethylbicyclo[2.2.1]hept-5-en-2-ylmethyl ester (13):⁴ A solution of **12** (127 mg, 0.66 mmol) and *p*-toluenesulfonyl chloride (136 mg, 0.71 mmol) in dry pyridine (0.63 mL) was kept at room temperature for 24 h. The reaction mixture was poured into chilled hydrochloric acid (2 mL) and extracted with ether (3 × 5 mL). The extract was washed with dilute hydrochloric acid (5 mL), aqueous sodium bicarbonate (5 mL), saturated aqueous sodium chloride (5 mL) and dried with MgSO₄. After removal of the solvent, the crude product **13** (210 mg, 92%) was obtained as a white solid. Mp = 50.8 °C; IR (neat, cm⁻¹): 3066, 2985, 1365, 1176, 980, 831, 725; ¹H NMR (300 MHz, CDCl₃, both diastereoisomers) δ = 7.78-7.72 (m, 2H), 7.34-7.31 (m, 2H), 6.23-6.19 (m, 1H), 6.09-6.06 + 6.01-5.98 (m, 1H), 4.28, 4.12 (AB system of one isomer, *J* = 12.0 Hz), 4.09, 4.01 (AB system of other isomer, *J* = 12.0 Hz), 3.14 + 3.10 (br s, 1H), 2.91 (br s, 1H), 2.44 (s, 3H), 1.93-1.75 (m, 2H), 1.49-1.43 (m, 2H); ¹³C NMR (75 MHz, CDCl₃, both diastereoisomers) δ = 144.9 + 144.8, 138.8 + 138.6, 134.9 + 133.0, 132.5 + 130.2, 129.8, 127.9, 127.4 (q, *J* = 280.3 Hz), 71.6 + 71.2 (q, *J* = 1.5 Hz), 52.0-51.5 (m), 47.8 + 47.5, 46.0 + 45.9, 42.7 + 42.1, 32.7, 31.6, 22.0; HRMS (EI) calcd for C₁₆H₁₇ F₃O₃S (M⁺) 346.0851, found 346.0849.

¹H NMR

¹³C NMR

Toluene-4-sulfonic acid 2-trifluoromethylallyl ester (8) using a microwave: A mixture of ester **13** (1.01 g, 2.89 mmol) and 1-butyl-3-methylimidazolium hexafluorophosphate (six drops) in Ph₂O (25

mL) was heated in a resealable vial in a microwave for 50 min at 240 °C and 182 W. The Ph₂O was then removed using column chromatography (heptane) and the product was separated from impurities (heptane/EtOAc 10:1 to 3:1) to give **8** (687 mg, 85%) as a colorless oil.

¹H NMR

¹³C NMR

Benzylbut-3-enyl-(2-trifluoromethylallyl)amine (14): Compound **8** (137.2 mg, 0.49 mmol) was added dropwise to a solution of *N*-benzylbut-3-en-1-amine⁵ (80 mg, 0.49 mmol) and Et₃N (68 μ L, 0.49 mmol) in Et₂O (1 mL). The reaction mixture was stirred at room temperature overnight, filtrated and concentrated to give product **13** (59 mg, 47%) as a yellow oil. The crude product was used for the RCM reaction without further purification. ¹H NMR (300 MHz) δ = 7.29-7.23 (m, 5H, ArH), 5.78-5.67 (m, 3 H, H₂C=CH, CF₃C=CH₂), 5.02-5.96 (m, 2H, H₂C=CH), 3.58 (s, 2H, CH₂Ph), 3.16 (s, 2H, NCH₂CCF₃), 2.51-2.48 (m, 2H, NCH₂), 2.25-2.22 (m, 2H, NCH₂CH₂).

***N*-Allyl-*N*-(2-trifluoromethylallyl)benzamide (15):** To a suspension of NaH (26 mg, 1.06 mmol) in DMF (2 mL) was added at rt *N*-allylbenzamide⁶ (86 mg, 0.53 mmol). After stirring for 15 min, compound **8** (150 mg, 0.53 mmol) was added dropwise. The reaction was stirred for 12 h, quenched with water (2 mL) and extracted with Et₂O (3 $\times$ 2 mL). The ether layers were dried (MgSO₄), evaporated and the residue was purified using column chromatography (heptane/EtOAc 10:1) to give **15** (48 mg, 34%) as a colorless oil. IR (neat, cm⁻¹): 3040, 2963, 2902, 1731, 1630, 1412, 1264, 1091, 1027, 802, 620; ¹H NMR (300 MHz) δ = 7.45-7.24 (s, 5H), 5.89 (s, 1H), 5.78-5.58 (m, 1H), 5.53 (s, 1H), 5.26-5.15 (m, 2H), 4.32-3.85 (m, 4H); ¹³C NMR (75 MHz, CDCl₃, the quaternary carbons are not visible due to rotamers) δ = 171.9, 135.4, 132.3 (br s), 129.9, 128.4, 126.4, 118.4, 99.2, 51.4, 42.9; HRMS (EI) calcd for C₁₄H₁₄F₃NO (M⁺) 269.1028, found 269.1022.

¹H NMR

***N*-Allyl-*N*-(2-trifluoromethylallyl)carbamic acid *tert*-butyl ester (**16**):** To a suspension of NaH (56 mg, 2.32 mmol) in DMF (4 mL) was added at rt *N*-Boc-allylamide⁷ (182 mg, 1.16 mmol). After stirring for 15 min, compound **8** (326 mg, 1.16 mmol) was added dropwise. The reaction was stirred for 12 h, quenched with water (4 mL) and extracted with Et₂O (3 × 4 mL). The ether layers were dried (MgSO₄), evaporated and the residue was purified using column chromatography (heptane/EtOAc 10:1) to give **16** (193 mg, 63%) as a colorless oil. IR (neat, cm⁻¹): 2976, 2928, 1705, 1549, 1459, 1407, 1368, 1325, 1251, 1174, 1126, 927, 871, 772; ¹H NMR (300 MHz) δ = 5.82-5.68 (m, 1H), 5.76 (s, 1H), 5.37 (s, 1H), 5.19-5.08 (m, 2H), 4.07-3.77 (m, 4H), 1.44 (s, 9H); ¹³C NMR (75 MHz, CDCl₃, some signals appear as rotamers) δ = 154.9, 124.9, 123.1 (q, *J* = 270 Hz), 121.3, 118.4-116.8 (m), 80.5, 49.6 + 49.1, 45.0, 28.5; HRMS (EI) calcd for C₁₁H₁₅F₃NO₂ (*M* – Me)⁺ 250.1055, found 250.1057.

¹H NMR

¹³C NMR

General procedure for the RCM reactions

To a 0.01 M solution of the diolefin in dry toluene under an inert atmosphere, catalyst **5** was added at the indicated temperature. Stirring was continued until the reaction was complete (indicated by TLC or GC), followed by concentration of the reaction mixture and subsequent purification with column chromatography.

N-Benzoyl-3-trifluoromethyl-2,5-dihydropyrrole (**17**):

^1H NMR (300 MHz)

^{13}C NMR (75 MHz)

3-Trifluoromethyl-2,5-dihydropyrrole-1-carboxylic acid *tert*-butyl ester (18**):** To a solution of ester **16** (100 mg, 0.377 mmol) in dry toluene (40 mL) catalyst **5** (10 mol %) was added at 100 °C in small portions. The reaction was complete in 2 h. The mixture was evaporated and the product was purified using column chromatography (heptane/EtOAc 10:1) to give **18** (87 mg, 97%) as a brown oil. IR (neat, cm^{-1}): 3058, 2919, 2867, 1713, 1632, 1385, 1303, 1269, 1165, 1122, 1043, 789, 694, 672; ^1H NMR (300 MHz, CDCl_3 , some signals appear as rotamers) δ = 6.32 + 6.27 (br s, 1H), 4.26 (br s, 4H), 1.47 (s, 9H); ^{13}C NMR (75 MHz, CDCl_3 , some signals appear as rotamers) δ = 153.7, 130.1-129.7 (m), 129.3 (q, J = 35.1 Hz), 122.8 (q, J = 263.9 Hz), 80.5 + 80.4, 53.4 + 53.2, 50.8 + 50.6, 28.6; HRMS (EI) calcd for $\text{C}_{10}\text{H}_{14}\text{F}_3\text{NO}_2$ (M^+) 237.0977, found, 237.0978.

^1H NMR

^{13}C NMR

1-(4-Fluorophenyl)but-3-enyl-(2-trifluoromethylallyl)carbamic acid *tert*-butyl ester (26): To a solution of *tert*-butyl carbamate **19** (392 mg, 2.97 mmol) in CH₂Cl₂ (6 mL) were added at 0 °C 4-fluorobenzaldehyde (0.32 mL, 2.97 mmol), BF₃·OEt₂ (0.38 mL, 2.97 mmol) and allyltrimethylsilane (0.47 mL, 2.97 mmol). The mixture was reacted for 3 h at rt, then CH₂Cl₂ was removed under reduced pressure and the product purified with column chromatography (heptane/EtOAc 6:1) to give ***tert*-butyl 1-(4-fluorophenyl)but-3-enylcarbamate (21)**, 172 mg, 22%) as a white solid. Mp: 89-91 °C; IR (neat, cm⁻¹): 3425, 3352, 3071, 3002, 2976, 2928, 1697, 1511, 1359, 1251, 1225, 1165, 1014, 919, 828; ¹H NMR (300 MHz, CDCl₃): δ = 7.20 (dd, 2H, *J* = 6.0, 9.3 Hz), 6.98 (dd, 2H, *J* = 8.7, 8.7 Hz), 5.70-5.67 (m, 1H), 5.10 (d, 1H, *J* = 17.1 Hz), 5.08 (d, 1H, *J* = 9.3 Hz), 4.79 (br s, 1H), 4.67 (br s, 1H), 2.47 (br dd, 2H, *J* = 6.3, 6.6, Hz), 1.39 (s, 9H); ¹³C NMR (75 MHz, CDCl₃): δ = 162.0 (d, *J* = 243.5 Hz), 155.3, 138.6, 133.8, 127.9, 127.8, 118.6, 115.6 (2 × CH), 115.3 (2 × CH), 53.5, 41.4, 28.5; HRMS (EI) calcd for C₁₅H₂₁FNO₂ (M + H)⁺ 266.1556, found 266.1555.

¹H NMR (21)

¹³C NMR (21)

¹³C-Spectrum calibrated at 77.0 ppm.

To a suspension of NaH (31 mg, 1.3 mmol) in DMF (2 mL) was added at room temperature product **21** (172 mg, 0.65 mmol). After stirring for 15 min, compound **8** (182 mg, 0.65 mmol) was added dropwise. The reaction was stirred for 12 h, quenched with water (2 mL) and extracted with Et₂O (3 × 4 mL). The ether layers were dried (MgSO₄), evaporated and the residue was purified using column chromatography (heptane/EtOAc 10:1) to give **26** (150 mg, 62%) as colorless oil. IR (neat, cm⁻¹): 3071, 2976, 2933, 1697, 1601, 1506, 1398, 1316, 1234, 1161, 1122, 919, 836, 772; ¹H NMR (300 MHz, CDCl₃): δ = 7.27 (dd, 2H, *J* = 5.7, 8.4 Hz), 6.97 (dd, 2H, *J* = 8.7, 8.7 Hz), 5.79-5.66 (m, 1H), 5.51 (s, 1H), 5.47 (br s, 1H), 5.14-5.02 (m, 3H), 3.76 (br s, 2H), 2.66 (dd, 2H, *J* = 7.2, 7.2 Hz), 1.44 (s, 9H); ¹³C NMR (75 MHz, CDCl₃, some signals appear as rotamers): δ = 162.0 (d, *J* = 244.1 Hz), 155.3, 135.0, 134.4, 129.7 + 129.6, 123.1 (q, *J* = 271.1 Hz), 119.6 (q, *J* = 5.5 Hz), 117.7, 117.0 (br s), 115.3 (d, *J* = 21.3 Hz), 80.7, 57.6, 41.8, 35.9, 28.5; HRMS (EI) calcd for C₁₉H₂₃F₄NO₂ (M⁺) 373.1665, found 373.1669.

¹H NMR

¹³C NMR

1-(4-Fluorophenyl)but-3-enyl-(2-trifluoromethylallyl)carbamic acid methyl ester (27):⁸ To a solution of methyl carbamate **20** (1.01 g, 13.3 mmol) in CH₂Cl₂ (27 mL) were added at 0 °C 4-fluorobenzaldehyde (1.43 mL, 13.3 mmol), BF₃·OEt₂ (1.68 mL, 13.32 mmol) and allyltrimethylsilane (1.68 mL, 13.32 mmol). The mixture was reacted for 3 h at room temperature, then CH₂Cl₂ was removed under reduced pressure and the product purified with column chromatography (heptane/EtOAc 6:1) to give **methyl 1-(4-fluorophenyl)but-3-enylcarbamate (22**, 1.48 g, 50%) as a yellow solid. Mp: 39-41 °C; IR (neat, cm⁻¹): 3438, 3321, 3070, 2997, 2954, 2846, 1692, 1511, 1437, 1217, 1040, 914, 828, 772; ¹H NMR (300 MHz, CDCl₃): δ = 7.20 (dd, 2H, *J* = 6.0, 9.3 Hz), 6.98 (dd, 2H, *J* = 8.7, 8.7 Hz), 5.71-5.57 (m, 1 H), 5.53 (s, 1 H), 5.10 (d, 1H, *J* = 17.1 Hz), 5.08 (d, 1H, *J* = 9.3 Hz), 5.01 (br s, 1H), 4.73 (br s, 1H), 3.63 (s, 3H), 2.50 (dd, 2H, *J* = 6.6 Hz); ¹³C NMR (75 MHz, CDCl₃): δ = 162.0 (d, *J* = 243.5 Hz), 156.4, 138.11, 133.7, 127.9, 127.8, 118.6, 115.5, 115.3, 54.0, 52.2, 41.1; HRMS (EI) calcd for C₁₂H₁₅FNO₂ (M + H)⁺ 224.1087, found 224.1087.

¹H NMR (22)

¹³C NMR (22)

To a suspension of NaH (31 mg, 1.3 mmol) in DMF (2 mL) was added at rt product **22** (156 mg, 0.71 mmol). After stirring for 15 min, compound **8** (196 mg, 0.71 mmol) was added dropwise. The reaction was stirred for 12 h, quenched with water (2 mL) and extracted with Et₂O (3 × 4 mL). The ether layers were dried (MgSO₄), evaporated and the residue was purified using column chromatography (heptane/EtOAc 10:1) to give **27** (128 mg, 56%) as yellow oil. IR (neat, cm⁻¹): 3084, 2950, 2933, 1705, 1610, 1511, 1394, 1321, 1230, 1161, 1113, 914, 836, 763; ¹H NMR (300 MHz, CDCl₃): δ = 7.30 (dd, 2H, *J* = 6.0, 9.3 Hz), 6.97 (dd, 2H, *J* = 8.7, 8.7 Hz), 5.77-5.64 (m, 1H), 5.53 (s, 1H), 5.42 (br s, 1H), 5.10 (d, 1H, *J* = 17.1 Hz), 5.09 (br s, 1H), 5.08 (d, 1H, *J* = 9.3 Hz), 3.87-3.79 (m, 2H), 3.73 (s, 3H), 2.69 (dd, 2H, *J* = 6.6, 6.6 Hz); ¹³C NMR (75 MHz, CDCl₃, some signals appear as rotamers):[‡] δ = 161.9 (d, *J* = 244.4 Hz), 156.7, 134.4 + 134.3, 133.9, 129.8 + 129.7, 122.9 (q, *J* = 271.1 Hz), 123.3 (q, *J* = 5.2 Hz), 117.8, 117.5 (br s), 115.3 (d, *J* = 21.3 Hz), 58.6, 53.1, 41.7, 35.7; HRMS (EI) calcd for C₁₆H₁₇F₄NO₂ (M⁺) 331.1195, found 331.1196.

¹H NMR

¹³C NMR

[‡] ¹³C spectrum calibrated at 77.0 ppm.

1-(2,4-Dichlorophenyl)but-3-enyl-(2-trifluoromethylallyl)carbamic acid methyl ester (28): To a solution of methyl carbamate **19** (360 mg, 4.8 mmol) in CH₂Cl₂ (10 mL) were added at 0 °C 2,4-dichlorobenzaldehyde (839 mg, 4.81 mmol), BF₃·OEt₂ (0.61 mL, 4.8 mmol) and allyltrimethylsilane (0.76 mL, 4.8 mmol). The mixture was reacted for 3 h at room temperature, then CH₂Cl₂ was removed under reduced pressure and the product purified with column chromatography (heptane/EtOAc 10:1 to 6:1) to give **methyl 1-(2,4-dichlorophenyl)but-3-enylcarbamate (23)**, 813 mg, 68%) as a white solid. Mp: 100-104 °C; IR (neat, cm⁻¹): 3425, 3313, 3067, 2980, 2950, 1692, 1532, 1467, 1264, 1100, 1040, 914, 819; ¹H NMR (300 MHz, CDCl₃): δ = 7.34 (s, 1H), 7.19 (br s, 2H), 5.71-5.57 (m, 1H), 5.15-5.10 (m, 4H), 3.62 (s, 3H), 2.58-2.44 (m, 2H); ¹³C NMR (75 MHz, CDCl₃): δ = 156.2, 135.0, 133.6, 133.2, 129.8, 128.4, 127.4, 119.3, 52.4, 51.7, 39.2; HRMS (EI) calcd for C₁₂H₁₄Cl₂NO₂ (M + H)⁺ 274.0402, found 274.0389.

¹H NMR (23)

¹³C NMR (23)

To a suspension of NaH (31 mg, 1.3 mmol) in DMF (2 mL) was added at room temperature product **23** (174 mg, 0.7 mmol). After stirring for 15 min, compound **8** (196 mg, 0.7 mmol) was added dropwise. The reaction was stirred for 12 h, quenched with water (2 mL) and extracted with Et₂O (3 × 4 mL). The ether layers were dried (MgSO₄), evaporated and the residue was purified using column chromatography (heptane/EtOAc 10:1) to give **28** (158 mg, 60%) as colorless oil. IR (neat, cm⁻¹): 3079, 2954, 1705, 1588, 1472, 1398, 1316, 1165, 1117, 953, 914, 819, 767; ¹H NMR (300 MHz, CDCl₃): δ = 7.36-7.20 (m, 3H), 5.77-5.61 (m, 2H), 5.50 (s, 1H), 5.22-5.03 (m, 3H), 3.94 (d, *J*=17.7 Hz, 1H), 3.73 (s, 3H), 3.7(d, *J*=18.0 Hz, 1H), 2.81-2.63 (m, 2H); ¹³C NMR (75 MHz, CDCl₃, some signals appear as rotamers, signals of the CCF₃ carbon are not visible): δ = 156.6, 135.9, 134.4 + 134.2, 133.5 + 133.3, 129.7, 129.5, 127.0 + 126.9, 122.8 (q, *J* = 271.1 Hz), 118.5 + 118.3, 117.5-117.3 (m), 53.5, 42.3, 36.1, 32.1; HRMS (EI) calcd for C₁₆H₁₆Cl₂F₃NO₂ (M⁺) 381.051, found 381.0511.

¹H NMR

¹³C NMR

1-(3,5-Dichlorophenyl)but-3-enyl-(2-trifluoromethylallyl)carbamic acid methyl ester (29): To a solution of methyl carbamate **19** (360 mg, 4.80 mmol), in CH₂Cl₂ (10 mL) were added at 0 °C 3,5-dichlorobenzaldehyde (839 mg, 4.8 mmol), BF₃·OEt₂ (0.61 mL, 4.8 mmol) and allyltrimethylsilane (0.76 mL, 4.8 mmol). The mixture was reacted for 3 h at rt, then CH₂Cl₂ was removed under reduced pressure and the product purified with column chromatography (heptane/EtOAc 10:1 to 6:1) to give **methyl 1-(3,5-dichlorophenyl)but-3-enylcarbamate (24, 602 mg, 51%)** as a white solid. Mp: 108-110 °C; IR (neat, cm⁻¹): 3291, 3062, 2976, 2950, 2924, 1684, 1528, 1264, 1191, 1053, 923, 858, 793, 685; ¹H NMR (300 MHz, CDCl₃): δ = 7.23 (s, 1H), 7.14 (s, 2H), 5.70-5.57 (m, 1H), 5.17-5.11 (m, 2H) 5.02 (br s, 1H), 4.7 (br s, 1H), 3.66 (s, 3H), 2.57-2.40 (m, 2H); ¹³C NMR (75 MHz, CDCl₃): δ = 156.3, 136.9, 135.3, 132.8, 127.7, 124.9, 119.6, 53.8, 52.5, 40.9; ; HRMS (EI) calcd for C₁₂H₁₄Cl₂NO₂ (M + H)⁺ 274.0402, found 274.0405.

¹H NMR (24)

¹³C NMR (24)

To a suspension of NaH (31 mg, 1.31 mmol) in DMF (2 mL) was added at room temperature product **24** (174 mg, 0.7 mmol). After stirring for 15 min, compound **8** (196 mg, 0.71 mmol) was added dropwise. The reaction was stirred for 12 h, quenched with water (2 mL) and extracted with Et₂O (3 × 4 mL). The ether layers were dried (MgSO₄), evaporated and the residue was purified using column chromatography (heptane/EtOAc 10:1) to give **29** (186 mg, 70%) as light-yellow oil. IR (neat, cm⁻¹): 3079, 2958, 1701, 1571, 1398, 1321, 1264, 1165, 1122, 919, 862, 798, 607; ¹H NMR (300 MHz, CDCl₃): δ = 7.25 (s, 1H), 7.19 (s, 2H), 5.76-5.61 (m, 2H), 5.32 (br s, 1H), 5.15-5.06 (m, 3H), 3.84 (d, *J* = 5.4 Hz, 2H), 3.74 (s, 3H), 2.70-2.65 (m, 2H); ¹³C NMR (75 MHz, CDCl₃): δ = 156.6, 142.3, 135.0, 133.2, 128.0, 126.6, 122.9 (q, *J* = 271.1 Hz), 119.8 (q, *J* = 5.5 Hz), 118.4, 118.0 (br s), 58.7, 53.3, 42.3, 35.5; HRMS (EI) calcd for C₁₆H₁₆Cl₂F₃NO₂ (M⁺) 381.051, found 381.0511.

¹H NMR

¹³C NMR

[1-(4-Methoxyphenyl)but-3-enyl]-(2-trifluoromethylallyl)carbamic acid methyl ester (30): To a solution of methyl carbamate **19** (721 mg, 9.6 mmol), in CH₂Cl₂ (20 mL) were added at 0 °C 4-methoxybenzaldehyde (1.16 mL, 9.6 mmol), BF₃·OEt₂ (1.22 mL, 9.6 mmol) and allyltrimethylsilane (1.53 mL, 9.6 mmol). The mixture was reacted for 3 h at rt, then CH₂Cl₂ was removed under reduced pressure and the product purified with column chromatography (heptane/EtOAc 6:1) to give **methyl 1-(4-methoxyphenyl)but-3-enylcarbamate (25, 667 mg, 30%)** as a yellow solid. Mp: 82-85 °C; IR (neat, cm⁻¹): 3326, 3075, 3002, 2945, 2902, 2829, 1697, 1506, 1455, 1243, 1174, 1031, 914, 828; ¹H NMR (300 MHz, CDCl₃): δ = 7.15 (d, *J* = 8.4 Hz, 2H), 6.81 (d, *J* = 8.7 Hz, 2H), 5.72-5.58 (m, 1H), 5.24 (br s, 1H), 5.09-5.02 (m, 2H), 4.70 (br s, 1H), 3.74 (s, 3H), 3.60 (s, 3H), 2.51-2.46 (m, 2H); ¹³C NMR (75 MHz, CDCl₃): δ = 158.9, 156.4, 134.3, 134.1, 127.5, 118.4, 114.1, 55.4, 54.1, 52.2, 41.2; HRMS (EI) calcd for C₁₅H₂₁FNO₃ (M + H)⁺ 236.1287, found 236.1284.

¹H NMR (25)

¹³C NMR (25)

To a suspension of NaH (31 mg, 1.3 mmol) in DMF (2 mL) was added at room temperature product **25** (174.3 mg, 0.7 mmol). After stirring for 15 min, compound **8** (196 mg, 0.71 mmol) was added dropwise. The reaction was stirred for 12 h, quenched with water (2 mL) and extracted with Et₂O (3 × 4 mL). The ether layers were dried (MgSO₄), evaporated and the residue was purified using column chromatography (heptane/EtOAc 10:1) to give **30** (186 mg, 46%) as light-yellow oil. IR (neat, cm⁻¹): 3075, 3002, 2950, 2833, 1701, 1614, 1515, 1459, 1321, 1251, 1161, 1113, 1035, 919, 828, 771; ¹H NMR (300 MHz, CDCl₃): δ = 7.21 (d, *J* = 10.8 Hz, 2H), 6.80 (d, *J* = 10.8 Hz, 2H), 5.78-5.65 (m, 1H), 5.52 (s, 1H), 5.50 (br s, 1H), 5.12-5.05 (m, 3H), 3.78 (s, 6H), 3.72 (br s, 2H), 2.67-2.65 (m, 2H); ¹³C NMR (75 MHz, CDCl₃, the signals of the CCF₃ carbon are not visible): δ = 159.0, 134.5, 130.6, 129.3, 127.7, 123.1 (q, *J* = 271.1 Hz), 117.6, 117.4, 113.8, 58.8, 55.4, 53.1, 41.6, 35.9; HRMS (EI) calcd for C₁₇H₂₀F₃NO₃ (M⁺) 343.1395, found 343.1394.

¹H NMR

¹³C NMR

2-(4-Fluorophenyl)-5-trifluoromethyl-3,6-dihydro-2H-pyridine-1-carboxylic acid *tert*-butyl ester (31):

¹H NMR

¹³C NMR

2-(4-Fluorophenyl)-5-trifluoromethyl-3,6-dihydro-2H-pyridine-1-carboxylic acid methyl ester (32):

^1H NMR

^{13}C NMR

2-(3,4-Dichlorophenyl)-5-trifluoromethyl-3,6-dihydro-2H-pyridine-1-carboxylic acid methyl ester (33): To a solution of **28** (142 mg, 0.37 mmol) in dry toluene (40 mL, 0.02 M solution) in a resealable vial was added catalyst **5** (4.3 mg, 1 mol%). The mixture was heated at 80 °C in a microwave open system for 10 min at 300 W. The reaction was followed by GC and new portions of catalyst were added, followed by heating until the reaction was complete (at total of 3 mol% of catalyst, 30 min heating). The mixture was evaporated and the residue was purified using column chromatography (heptane/EtOAc 10:1) to give **33** (106 mg, 63%) as a colorless oil. IR (neat, cm^{-1}): 3071, 2958, 2898, 1709, 1585, 1446, 1346, 1308, 1165, 1113, 1022, 966, 854, 772; ^1H NMR (200 MHz, CDCl_3): δ = 7.37 (s, 1H), 7.16 (d, J = 8.4 Hz, 1H), 6.98 (d, J = 8.4 Hz, 1H), 6.47 (br s, 1H), 5.74 (br s, 1H), 4.42 (d, J = 18.0 Hz, 1H), 3.77 (d, J = 18.3 Hz, 1H), 3.73 (s, 3H), 2.87-2.75 (m, 1H), 2.64-2.56 (m, 1H); ^{13}C NMR (75 MHz, CDCl_3): δ = 155.4, 137.0, 134.0, 129.9, 127.8, 127.4 (br s), 127.0, 126.4 (q, J = 32 Hz), 122.5 (q, J = 269.1 Hz), 53.4, 49.0, 39.2, 32.2; HRMS (EI) calcd for $\text{C}_{14}\text{H}_{12}\text{F}_3\text{Cl}_2\text{NO}_2$ (M^+) 353.0197, found 353.0197.

^1H NMR

^{13}C NMR

2-(3,5-Dichlorophenyl)-5-trifluoromethyl-3,6-dihydro-2H-pyridine-1-carboxylic acid methyl ester (34): To a solution of **29** (183 mg, 0.48 mmol) in dry toluene (50 mL, 0.02 M solution) in a resealable vial was added catalyst **5** (6 mg, 1 mol %). The mixture was heated at 80 °C in a microwave open system for 10 min at 300 W. The reaction was followed by GC and new portions of catalyst were added, followed by heating until the reaction was complete (at total of 3 mol % of catalyst, 30 min heating). The mixture was evaporated and the residue was purified using column chromatography (heptane/EtOAc 10:1) to give **34** (134 mg, 79%) as a colorless oil. IR (neat, cm^{-1}): 3075, 2954, 2859, 1709, 1572, 1446, 1321, 1251, 1113, 1031, 966, 798, 768; ^1H NMR (200 MHz, CDCl_3): δ = 7.28-7.26 (m, 1H), 7.10 (s, 2H), 6.57 (br s, 1H), 5.61 (br s, 1H), 4.49 (d, J = 18.1 Hz, 1H), 3.81 (s, 3H), 3.47 (d, J = 18.3 Hz, 1H), 2.77-2.71 (m, 2H); ^{13}C NMR (75 MHz, CDCl_3): δ = 155.6, 142.6, 135.3, 127.9 (br s), 126.4 (q, J = 32 Hz), 125.2, 122.3 (q, J = 269.1 Hz), 53.5, 49.9, 37.7, 27.0; HRMS (EI) calcd for $\text{C}_{14}\text{H}_{12}\text{NCl}_2\text{F}_3\text{O}_2$ (M^+) 353.0197, found 353.0197.

^1H NMR

^{13}C NMR

2-(4-Methoxyphenyl)-5-trifluoromethyl-3,6-dihydro-2H-pyridine-1-carboxylic acid methyl ester (35): To a solution of **30** (100 mg, 0.29 mmol) in dry toluene (40 mL) in a resealable vial was added catalyst **5** (2 mg, 0.6 mol%). The mixture was heated at 80 °C in a microwave open system for 10 min at 300 W. The reaction was followed by GC and new portions of catalyst were added, followed by heating until the reaction was complete (at total of 5 mol% of catalyst, 40 min heating). The mixture was evaporated and the residue was purified using column chromatography (heptane/EtOAc 10:1) to give **35** (73 mg, 80%) as a colorless oil. IR (neat, cm^{-1}): 3002, 2954, 2902, 2837, 1701, 1610, 1515, 1446, 1316, 1247, 1109, 1035, 966, 832, 767; ^1H NMR (300 MHz, CDCl_3): δ = 7.13 (d, J = 8.4 Hz, 2H), 6.81 (d, J = 9.0 Hz, 2H), 6.55 (br s, 1H), 5.59 (br s, 1H), 4.42 (d, J = 18.0 Hz, 1H), 3.77 (s, 6H), 3.35 (d, J = 18.9 Hz, 1H), 2.80-2.63 (m, 2H); ^{13}C NMR (75 MHz, CDCl_3): δ = 158.8, 155.7, 131.0, 127.9, 127.8 (br s), 126.1 (q, J = 31 Hz), 122.6 (q, J = 269.1 Hz), 113.9, 55.4, 53.2, 49.9, 37.3, 27.3; HRMS (EI) calcd for $\text{C}_{15}\text{H}_{16}\text{F}_3\text{NO}_3$ (M^+) 315.1082, found 315.1082.

^1H NMR

^{13}C NMR

2-[*tert*-Butoxycarbonyl-(2-trifluoromethylallyl)amino]pent-4-enoic acid methyl ester (38**):** To a suspension of NaH (34 mg, 1.42 mmol) in DMF (3 mL) was added Boc-protected allylglycine methyl ester **37** (164 mg, 0.71 mmol) at room temperature. After stirring for 15 min, compound **8** (200 mg, 0.71 mmol) was added. The reaction was stirred for 12 h, quenched with water (7 mL) and extracted with Et₂O (3 × 10 mL). The ether layer was dried (MgSO₄), the solvent evaporated and the residue purified using column chromatography (heptane/EtOAc 10:1) to give **38** (146 mg, 61%) as a colorless oil. IR (neat, cm⁻¹): 3079, 2980, 1744, 1705, 1459, 1368, 1321, 1251, 1169, 1117, 1001, 919, 858, 772; ¹H NMR (400 MHz, CDCl₃): δ 5.79-5.61 (m, 3H), 5.15-5.08 (m, 2H), 4.55 (s, 1H), 4.28-3.99 (m, 2H), 3.72 (s, 3H), 2.78-2.58 (m, 1H), 2.56-2.46 (m, 1H), 1.42 (s, 9H); ¹³C NMR (75 MHz, CDCl₃, some signals appear as rotamers, signals of the CCF₃ are not visible): δ = 171.1, 155.0, 133.7, 123.1 (q, *J* = 271.1 Hz), 118.93, 118.9-118.2 (m), 81.5 + 81.2, 59.3, 52.3, 46.6-45.3 (m), 35.1 + 34.3, 28.4; HRMS (ESI) calcd for C₁₅H₂₂F₃NNaO₄ (M + Na)⁺ 360.1398, found 360.1416.

¹H NMR

¹³C NMR

5-Trifluoromethyl-3,6-dihydro-2*H*-pyridine-1,2-dicarboxylic acid 1-*tert*-butyl ester 2-methyl ester (39):

¹H NMR

¹³C NMR

2-[(5-Chloro-2-methoxyphenyl)sulfonyl]amino)pent-4-enoic acid (40): To a suspension of allylglycine (**36**, 2.00 g, 17.4 mmol) in CH₂Cl₂ (35 mL) was added Me₃SiCl (2.2 mL, 17.4 mmol). The mixture was heated at reflux for 2 h, Et₃N (4.87 mL, 34.8 mmol) was added, followed by a solution of 5-chloro-2-methoxybenzenesulfonyl chloride (4.20 g, 17.4 mmol) in CH₂Cl₂ (17.5 mL). The resulting mixture was vigorously stirred for 1 h at rt, MeOH (2.78 mL, 20.0 mmol) was added and the mixture was evaporated. The residue was dissolved in water and brought to pH 8 using aqueous K₂CO₃. The aqueous layer was washed with Et₂O (3 × 10 mL), acidified to pH 1 using 1 N hydrochloric acid (1 N) and extracted with EtOAc (3 × 20 mL). The combined organic layers were dried (MgSO₄) and the solvent was evaporated to afford crude **40** (4.41 g, 80%) as a yellow solid. The crude acid was used without further purification in the next reactions.

2-[[5-Chloro-2-methoxyphenyl)sulfonyl]-2-(trifluoromethylallyl)amino}-N-(2-methoxybenzyl)pent-4-enamide (45): A solution of crude acid **37** (500 mg, 1.6 mmol) in CH₂Cl₂ (33 mL) was stirred for 1 h at rt with HOBt (233 mg, 1.73 mmol) and EDCI (331 mg, 1.73 mmol). 2-Methoxybenzylamine (0.3 mL, 2.0 mmol) was added, the mixture was stirred for 12 h and the solvent was evaporated. The residue was dissolved in EtOAc (20 mL), washed with brine (10 mL) and aqueous NaHCO₃ (10 mL). The combined water phases were reextracted with EtOAc (3 × 10 mL), and the combined organic layers were dried (MgSO₄) and evaporated. The residue was crystallized (heptane/EtOAc 2:1) to give **2-[(5-chloro-2-methoxyphenyl)sulfonyl]amino}-N-(2-methoxybenzyl)pent-4-enamide (41**, 520 mg, 76%) as a white solid. Mp = 105–108 °C; IR (neat, cm⁻¹): 3404, 3157, 3066, 2967, 2932, 2902, 2833, 1653, 1601, 1489, 1463, 1325, 1234, 1156, 1014, 914, 828; ¹H NMR (400 MHz, CDCl₃): δ = 7.82 (d, *J* = 2.4 Hz, 1H), 7.41–7.38 (m, 1H), 7.30–7.25 (m, 1H), 7.17–7.14 (m, 1H), 6.92–6.81 (m, 3H), 6.68 (br s, 1H), 5.61–5.51 (m, 2H), 5.08–5.02 (m, 2H), 4.31–4.29 (m, 2H), 3.89 (s, 3H), 3.84 (s, 3H), 3.71–3.68 (m, 1H), 2.58–2.51 (m, 1H), 2.33–2.26 (m, 1H); ¹³C NMR (75 MHz, CDCl₃): δ = 169.6, 154.8, 134.4, 133.9, 133.6, 132.3, 131.8, 129.4, 129.3, 128.8, 128.1, 127.4, 125.5, 120.4, 113.4, 56.6, 56.4, 55.2, 39.4, 37.5; HRMS (EI) calcd for C₂₀H₂₃ClN₂O₅S (M⁺) 438.1016, found 438.1013.

¹H NMR (41)

¹³C NMR (41)

To a suspension of NaH (34 mg, 1.43 mmol) in DMF (3 mL) was added at rt **41** (304 mg, 0.71 mmol). After stirring for 15 min, compound **8** (200 mg, 0.71 mmol) was added dropwise. The reaction was stirred for 12 h, quenched with water (3 mL) and extracted with Et₂O (3 × 6 mL). The ether layers were dried (MgSO₄), evaporated and the residue was purified using column chromatography (heptane/EtOAc 6:1 to 1:1) to give **45** (170 mg, 45%) as a yellow oil. IR (neat, cm⁻¹): 3384, 3324, 3076, 2945, 2840, 1679, 1588, 1522, 1481, 1437, 1388, 1338, 1319, 1273, 1245, 1157, 1116, 1067, 1017, 949, 910, 812, 754, 644, 592; ¹H NMR (400 MHz, CDCl₃): δ = 7.87 (d, *J* = 2.4 Hz, 1H), 7.41-7.38 (m, 1H), 7.30-7.25 (m, 1H), 7.18-7.16 (m, 1H), 6.91-6.82 (m, 3H), 6.71 (br s, 1H), 5.57 (d, *J* = 6.9 Hz, 2H), 5.41-5.32 (m, 1H), 4.96-4.86 (m, 2H), 4.52 (d, *J* = 18.4 Hz, 1H), 4.31-4.21 (m, 2H), 4.13-4.10 (m, 2H), 3.87 (s, 6H), 2.68-2.61 (m, 1H), 2.22-2.15 (m, 1H); ¹³C NMR (100 MHz, CDCl₃): δ = 167.8, 157.6, 155.3, 134.5 (q, *J* = 29.1 Hz), 133.0, 130.8, 129.9, 129.0, 128.6, 125.3, 122.9 (q, *J* = 272.3 Hz), 120.4, 120.2 (q, *J* = 5.5 Hz), 118.3, 113.5, 110.2, 59.1, 56.3, 55.2, 43.2, 39.6, 33.1; HRMS (EI) calcd for C₂₄H₂₇ClF₃N₂O₅S (M + H)⁺ 547.1174, found 547.1281.

¹H NMR

¹³C NMR

¹³C spectrum calibrated at 77.0 ppm.

2-[(5-Chloro-2-methoxyphenyl)sulfonyl]-[2-(trifluoromethyl)allyl]amino}-N-(4-chloro-3-trifluoromethylbenzyl)pent-4-enamide (46): A solution of crude acid **37** (500 mg, 1.6 mmol) in CH₂Cl₂ (33 mL) was stirred for 1 h at rt with HOBt (233 mg, 1.73 mmol) and EDCI (331 mg, 1.73 mmol). 4-Chloro-3-trifluoromethylbenzylamine (418 mg, 2.0 mmol) was added, the mixture was stirred for 12 h and the solvent was evaporated. The residue was dissolved in EtOAc (20 mL), washed with brine (10 mL) and aqueous NaHCO₃ (10 mL). The combined water phases were reextracted with EtOAc (3 × 10 mL), and the combined organic layers were dried (MgSO₄) and evaporated. The residue was crystallized (heptane/EtOAc 2:1) to give **2-[(5-chloro-2-methoxyphenyl)sulfonyl]amino}-N-(4-chloro-3-trifluoromethylbenzyl)pent-4-enamide (42**, 808 mg, 99%) as a white solid. Mp = 140-143 °C; IR (neat, cm⁻¹): 3300, 3257, 3079, 2945, 2852, 1649, 1554, 1472, 1316, 1161, 1122, 1022, 897, 810, 646; ¹H NMR (400 MHz, CDCl₃): δ = 7.85 (d, *J* = 3.6 Hz), 7.57-7.46 (m, 3H), 7.38-7.35 (m, 1H), 6.98-6.94 (m, 2H), 5.58-5.43 (m, 2H), 5.15-5.06 (m, 2H), 4.49-4.34 (m, 2H), 3.96 (s, 3H), 3.77-3.71 (m, 1H), 2.64-2.55 (m, 1H), 2.33-2.24 (m, 1H); ¹³C NMR (75 MHz, CDCl₃): δ = 170.4, 154.9, 137.2, 134.9, 132.0, 131.9, 131.8, 131.3 (q, *J* = 2.01 Hz), 130.0, 128.5 (q, *J* = 31.3 Hz), 127.9, 126.7 (q, *J* = 5.2 Hz), 126.0, 122.8 (q, *J* = 271.7 Hz), 120.2, 113.7, 56.7, 56.6, 42.6, 36.9; HRMS (EI) calcd for C₂₀H₁₉Cl₂F₃N₂O₄S (M⁺) 510.0395, found 510.0399.

¹H NMR (42)

¹³C NMR (42)

To a suspension of NaH (34 mg, 1.43 mmol) in DMF (3 mL) was added at room temperature **42** (364 mg, 0.71 mmol). After stirring for 15 min, compound **8** (200 mg, 0.71 mmol) was added dropwise at rt. The reaction was stirred for 12 h, quenched with water (3 mL) and extracted with Et₂O (3 × 6 mL). The ether layers were dried (MgSO₄), evaporated and the residue was purified using column chromatography (heptane/EtOAc 6:1 to 1:1) to give **46** (190 mg, 44%) as a colorless oil. IR (neat, cm⁻¹): 3373, 3076, 2945, 2852, 1687, 1588, 1528, 1478, 1437, 1388, 1319, 1275, 1171, 1130, 1067, 1037, 1015, 946, 908, 842, 817, 740, 647, 589, 524; ¹H NMR (400 MHz, CDCl₃): δ = 7.85 (d, *J* = 2.8 Hz, 1H), 7.57-7.43 (m, 3H), 7.37-7.34 (m, 1H), 6.95 (d, *J* = 8.8 Hz, 1H), 6.88 (br s, 1H), 5.73 (s, 1H), 5.61 (s, 1H), 5.42-5.31 (m, 1H), 4.99-4.91 (m, 2H), 4.54-4.40 (m, 2H), 4.27-4.08 (m, 3H), 3.92 (s, 3H), 2.74-2.67 (m, 1H), 2.26-2.19 (m, 1H); ¹³C NMR (100 MHz, CDCl₃): δ = 168.8, 155.4, 136.9, 134.8, 134.2 (q, *J* = 29.1 Hz), 132.6, 132.2, 131.6, 131.2, 130.7, 128.5, 128.4 (q, *J* = 30.5 Hz), 126.9 (q, *J* = 4.5 Hz), 125.5, 122.8 (q, *J* = 274.6 Hz), 122.6 (q, *J* = 271.5 Hz), 121.5 (q, *J* = 6.1 Hz), 118.6, 113.6, 59.0, 56.4, 43.4, 42.5, 32.7; HRMS (EI) calcd for C₂₄H₂₃Cl₂F₆N₂O₄S (M+H)⁺ 619.0660, found 619.0616.

¹H NMR

¹³C NMR

¹³C spectrum calibrated at 77.0 ppm.

2-[[5-(5-Chloro-2-methoxyphenyl)sulfonyl]-[2-(trifluoromethyl)allyl]amino}-N-(3,4-difluorobenzyl)pent-4-enamide (47): A solution of crude acid **37** (1.00 g, 3.13 mmol) in CH₂Cl₂ (65 mL) was stirred for 1 h at with HOBt (466 mg, 3.45 mmol) and EDCI (662 mg, 3.45 mmol). 3,4-Difluorobenzylamine (1.1 mL, 9.39 mmol) was added, the mixture was stirred for 12 h and the solvent was evaporated. The residue was dissolved in EtOAc (20 mL), washed with brine (10 mL) and aqueous NaHCO₃ (10 mL). The combined water phases were reextracted with EtOAc (3 × 10 mL), and the combined organic layers were dried (MgSO₄) and evaporated. The residue was crystallized (heptane/Et₂O 3:1) to give **2-[[5-(5-chloro-2-methoxyphenyl)sulfonyl]amino}-N-(3,4-difluorobenzyl)pent-4-enamide (43**, 1.21 g, 87%) as a white solid. Mp = 115–118 °C; IR (neat, cm⁻¹): 3309, 3261, 3097, 3075, 2980, 2894, 1653, 1515, 1437, 1329, 1282, 1156, 1113, 1070, 1014, 897, 815, 646; ¹H NMR (400 MHz, CDCl₃): δ = 7.85 (d, *J* = 3.2 Hz, 1H), 7.55-7.52 (m, 1H), 7.15-6.92 (m, 4H), 6.85 (br s, 1H), 5.57-5.44 (m, 2H), 5.15-5.05 (m, 2H), 4.39-4.25 (m, 2H), 3.95 (s, 3H), 3.74 (t, *J* = 8.0 Hz, 1H), 2.61-2.53 (m, 1H), 2.34-2.24 (m, 1H); ¹³C NMR (75 MHz, CDCl₃) δ = 170.3, 154.9, 150.1 (dd, *J* = 47.1, 247.0 Hz), 149.9 (dd, *J* = 47.1, 247.0 Hz), 135.0-134.9 (m), 134.8, 132.0, 129.8, 127.8, 125.8, 123.6-123.4 (m), 119.9, 117.0 (dd, *J* = 17.2, 61.7 Hz), 116.9 (dd, *J* = 17.2, 61.7 Hz), 113.6, 56.6, 56.5, 42.5, 37.1; HRMS (EI) calcd for C₁₉H₁₉ClF₂N₂O₄S (M⁺) 444.0722, found 444.0718.

¹H NMR (43)

¹³C NMR (43)

To a suspension of NaH (27 mg, 1.10 mmol) in DMF (2 mL) was added at rt **43** (250 mg, 0.56 mmol). After stirring for 15 min, compound **8** (156 mg, 0.56 mmol) was added dropwise at rt. The reaction was stirred for 12 h, quenched with water (2 mL) and extracted with Et₂O (3 × 4 mL). The ether layers were dried (MgSO₄), evaporated and the residue was purified using column chromatography (heptane/EtOAc 6:1 to 1:1) to give **47** (185 mg, 60%) as a colorless oil. IR (neat, cm⁻¹): 3373, 3082, 2978, 2939, 2846, 1890, 1684, 1610, 1588, 1517, 1481, 1388, 1322, 1278, 1155, 1113, 1067, 952, 817, 740, 642, 589; ¹H NMR (400 MHz, CDCl₃): δ = 7.72 (d, *J* = 3.5 Hz, 1H), 7.38-7.34 (m, 1H), 7.00-6.88 (m, 2H), 6.81-6.79 (m, 2H), 6.59 (br s, 1H), 5.59 (s, 1H), 5.47 (s, 1H), 5.28-5.15 (m, 1H), 4.86-4.76 (m, 2H), 4.38 (d, *J* = 24 Hz, 1H), 4.26-4.19 (m, 1H), 4.11-4.06 (m, 1H), 3.98-3.91 (m, 2H), 3.77 (s, 3H), 2.61-2.51 (m, 1H), 2.13-2.04 (m, 1H); ¹³C NMR (100 MHz, CDCl₃): δ = 168.7, 155.4, 151.2 (dd, *J* = 12.8, 53.9 Hz), 148.7 (dd, *J* = 12.4, 52.4 Hz), 134.8, 134.7 (q, *J* = 5.3 Hz), 134.2 (q, *J* = 29.0 Hz), 132.8, 130.9, 128.6, 125.7, 125.6 (q, *J* = 272.3 Hz), 124.2, 123.9-123.7 (m), 121.5 (q, *J* = 4.4 Hz), 117.3 (d, *J* = 16.3 Hz), 116.9 (d, *J* = 17.3 Hz), 113.7, 59.1, 56.5, 43.5, 42.7, 32.8; HRMS (EI) calcd for C₂₃H₂₃ClF₅N₂O₄S (M + H)⁺ 553.0987, found 553.0972.

¹H NMR

¹³C NMR

¹³C spectrum calibrated at 77.0 ppm.

2-{[(5-Chloro-2-methoxyphenyl)sulfonyl]-[2-(trifluoromethyl)allyl]amino}-N-(2-chlorobenzyl)pent-4-enamide (48): A solution of crude acid **37** in CH₂Cl₂ (35 mL) was stirred for 1 h with HOBt (233 mg, 1.75 mmol) and EDCI (331 mg, 1.75 mmol). 2-Chlorobenzylamine (250 μ L, 1.75 mmol) was added, the mixture was stirred for 12 h and the solvent was evaporated. The residue was dissolved in EtOAc (20 mL), washed with brine (10 mL) and aqueous NaHCO₃ (10 mL). The water layer was reextracted with EtOAc (3 $\times$ 10 mL), and the combined organic layers were dried (MgSO₄) and evaporated. The residue was crystallized (heptane/Et₂O 3:1) to give the **2-{[(5-chloro-2-methoxyphenyl)sulfonyl]amino}-N-(2-chlorobenzyl)pent-4-enamide (44**, 700 mg, 99%) as a white solid. Mp = 97-100 $^{\circ}$ C; IR (neat, cm⁻¹): 3404, 3114, 3075, 2967, 2933, 2846, 1653, 1528, 1480, 1437, 1325, 1277, 1156, 1018, 914, 750; ¹H NMR (400 MHz, CDCl₃): δ = 7.85 (d, *J* = 2.4 Hz, 1H), 7.49-7.46 (m, 1H), 7.38-7.35 (m, 1H), 7.30-7.23(m, 3H), 6.90 (d, *J* = 8.8 Hz, 1H), 6.66 (br s, 1H), 5.58-5.48 (m, 2H), 5.11-5.04 (m, 2H), 4.48-4.37 (m, 2H), 3.93 (s, 3H), 3.77-3.73 (m, 1H), 2.61-2.54 (m, 1H), 2.33-2.26 (m, 1H); ¹³C NMR (75 MHz, CDCl₃): δ = 170.1, 154.9, 134.9, 134.6, 133.6, 133.4, 132.1, 129.7, 129.6, 129.5, 128.9, 127.9, 127.1, 125.7, 119.7, 113.5, 56.6, 56.5, 41.5, 37.4; HRMS (EI) calcd for C₁₉H₂₀Cl₂N₂O₄S (M⁺) 442.0521, found 442.0514.

¹H NMR (44)

¹³C NMR (44)

1-(5-Chloro-2-methoxybenzenesulfonyl)-5-trifluoromethyl-1,2,3,6-tetrahydropyridine-2-carboxylic acid 2-methoxybenzylamide (49): To a solution of **45** (158 mg, 0.29 mmol) in dry toluene (60 mL) catalyst **5** (10 mol %) was added at 100 °C in small portions. The reaction was complete in 60 min. The solvent was evaporated and the residue purified using column chromatography (heptane/EtOAc 3:1 to 1:1) to give **49** (105 mg, 70%) as a white solid. Mp = 120-123 °C; IR (neat, cm⁻¹): 3384, 3313, 3076, 2923, 2846, 1679, 1591, 1519, 1489, 1478, 1437, 1390, 1341, 1305, 1273, 1245, 1163, 1116, 1078, 1017, 965, 899, 839, 814, 754, 735, 644, 589; ¹H NMR (400 MHz, CDCl₃): δ = 7.91 (d, *J* = 2.4 Hz, 1H), 7.50-7.47 (m, 1H), 7.30-7.18 (m, 3H), 6.92-6.87 (m, 3H), 6.38 (br s, 1H), 4.51-4.35 (m, 4H), 3.86 (s, 3H), 3.76 (s, 3H), 3.70 (s, 1H), 2.95-2.89 (m, 1H), 1.87-1.80 (m, 1H); ¹³C NMR (100 MHz, CDCl₃): δ = 167.5, 157.5, 155.1, 134.9, 134.3, 131.0, 129.6, 129.1, 127.9 (q, *J* = 5.3 Hz), 127.8, 125.7, 125.5, 124.5, 124.1 (q, *J* = 30.5 Hz), 122.4 (q, *J* = 270.9 Hz), 120.5, 113.5, 110.6, 56.3, 55.2, 52.7, 40.4, 38.9, 29.6, 22.5; HRMS(EI) calcd for C₂₂H₂₁ClF₃N₂O₅S (M-H)⁺ 517.0812, found 517.0823.

¹H NMR

¹³C NMR

¹³C spectrum calibrated at 77.0 ppm.

1-(5-Chloro-2-methoxybenzenesulfonyl)-5-trifluoro-1,2,3,6-tetrahydropyridine-2-carboxylic acid 4-chloro-3-trifluoromethylbenzylamide (50): To a solution of **46** (180 mg, 0.29 mmol) in dry toluene (68 mL) catalyst **5** (10 mol %) was added at 100 °C in small portions. The reaction was complete in 60 min. The solvent was evaporated and the residue purified using column chromatography (heptane/EtOAc 3:1 to 1:1) to give **50** (167 mg, 98%) as a white solid. Mp = 203-205 °C; IR (neat, cm⁻¹): 3390, 3087, 2956, 2928, 2851, 1670, 1585, 1522, 1478, 1440, 1396, 1341, 1316, 1305, 1270, 1160, 1113, 1075, 1031, 1012, 960, 894, 836, 814, 735, 642; ¹H NMR (400 MHz, CDCl₃): δ = 7.93 (d, *J* = 2.8 Hz, 1H), 7.57-7.45 (m, 3H), 7.37-7.34 (m, 1H), 7.19 (br s, 1H), 6.95 (d, *J* = 8.8 Hz, 1H), 6.45-6.44 (m, 1H), 4.59-4.40 (m, 4H), 3.84 (s, 3H), 3.78 (s, 1H), 2.95-2.84 (m, 1H), 1.87-1.81 (m, 1H); ¹³C NMR (100 MHz, CDCl₃): δ = 168.4, 155.2, 137.1, 135.2, 134.2 (q, *J* = 29.1 Hz), 131.8, 131.7, 131.5, 131.2, 129.8, 128.8 (q, *J* = 31.2 Hz), 127.8 (q, *J* = 5.6 Hz), 127.4, 126.6 (q, *J* = 5.3 Hz), 126.0, 124.6, 124.2, 122.6 (q, *J* = 274.6 Hz), 122.4 (q, *J* = 269.9 Hz), 113.7, 52.6, 42.9, 39.3, 22.5; HRMS (EI) calcd for C₂₂H₁₉Cl₂F₆N₂O₄S (M+H)⁺ 591.0347, found 591.0402.

¹H NMR

¹³C NMR

¹³C spectrum calibrated at 77.0 ppm.

1-(5-Chloro-2-methoxybenzenesulfonyl)-5-trifluoro-1,2,3,6-tetrahydropyridine-2-carboxylic acid 3,4-difluorobenzylamide (51): To a solution of **47** (110 mg, 0.20 mmol) in dry toluene (40 mL) catalyst **5** (10 mol %) was added at 100 °C in small portions. The reaction was complete in 60 min. The solvent was evaporated and the residue purified using column chromatography (heptane/EtOAc 3:1 to 1:1) to give **51** (73 mg, 70%) as a white solid. Mp = 148-149 °C; IR (neat, cm⁻¹): 3302, 3098, 3054, 2939, 2846, 1657, 1607, 1519, 1481, 1434, 1388, 1338, 1303, 1273, 1209, 1160, 1111, 1070, 1015, 954, 899, 812, 729, 647, 584, 521; ¹H NMR (400 MHz, CDCl₃): δ = 7.92 (d, *J* = 2.8 Hz, 1H), 7.52-7.51 (m, 1H), 7.13-6.94 (m, 5H), 6.43-6.42 (m, 1H), 4.58-4.33 (m, 4H), 3.83 (s, 3H), 3.78 (s, 1H), 2.95-2.90 (m, 1H), 1.87-1.81 (m, 1H); ¹³C NMR (100 MHz, CDCl₃): δ = 168.2, 155.2, 151.3 (dd, *J* = 12.6, 59.1 Hz), 148.8 (dd, *J* = 12.8, 58.1 Hz), 135.2, 134.9 (q, *J* = 1.2 Hz), 131.1, 127.9 (q, *J* = 5.5 Hz), 127.5, 125.9, 124.5 (q, *J* = 31.1 Hz), 123.3 (q, *J* = 2.7 Hz), 122.4 (q, *J* = 270.3 Hz), 117.5 (d, *J* = 17.2 Hz), 116.5 (d, *J* = 17.5 Hz), 113.7, 56.4, 52.6, 42.9, 39.2, 22.6; HRMS (EI) calcd for C₂₁H₁₉ClF₅N₂O₄S (M+H)⁺ 525.0674, found 525.0678.

¹H NMR

¹³C NMR

¹³C spectrum calibrated at 77.0 ppm.

1-(5-Chloro-2-methoxy-benzenesulfonyl)-5-trifluoromethyl-1,2,3,6-tetrahydropyridine-2-carboxylic acid 2-chlorobenzylamide (52):[‡]

¹H NMR

¹³C NMR

[‡] ¹³C Spectrum calibrated at 77.0 ppm.

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