Synthesis of 3-fluoroazetidines

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I. General methods

^1H NMR spectra were recorded at 270 or 300 MHz with CDCl_3 as solvent and tetramethylsilane as internal standard. ^{13}C NMR spectra were recorded at 68 or 75 MHz with CDCl_3 as solvent. Mass spectra were obtained with a mass spectrometer (70 eV) using a GC-MS coupling (20 m glass capillary column, i.d. 0.53 mm, He carrier gas), LC-MS coupling or were recorded using a direct inlet system (70 eV).

II. Synthetic procedures and spectroscopic data

1. Synthesis of *N*-(alkylidene- or 1-arylmethylidene)-2-propenylamines **2a-f**

To a suspension of 0.1 mol of aldehyde **1** in dry dichloromethane was added 0.15 mol of MgSO_4 and 0.1 mol of 2-methyl or 2-phenyl-2-propenylamine **2**. If the amine is used as a hydrochloride salt, 0.1 mol of triethylamine was added. After 30 minutes of reflux or 1 hour at room temperature (see Scheme 1) the resulting mixture was filtered and the solvent was evaporated, affording *N*-allylimines **2a-f** (if no triethylamine is used). If triethylamine was used, the reaction mixture was dissolved in dry diethyl ether and triethylamine hydrochloride was filtered off. After evaporation of the solvent, *N*-allylimines **2a-f** were obtained, sufficiently pure (>95%) for further use in the next step. These imines may also be distilled under vacuum. For spectral data see also reference (29).

N-(4-Methoxybenzylidene)-2-methyl-2-propenylamine **2c**

Yield: 86%, Bp: 80-83°C/ 0.02 mmHg. ^1H NMR (270 MHz, CDCl_3): δ 1.80 (3H, s), 3.82 (3H, s), 4.11 (2H, s), 4.86-4.90 (2H, m), 6.92 and 7.71 (4H, 2 $\times$ d, J = 8.9 Hz), 8.19 (1H, s). ^{13}C NMR (68 MHz, CDCl_3): δ 21.1, 55.3, 67.0, 111.3, 113.9, 129.7, 129.2, 143.8, 161.2, 161.6.

IR (NaCl, cm^{-1}): 1645, 1610, 1510. **MS** (ES+) m/z (%): 190 ($M^+ + 1$, 100). Anal. Calcd for $\text{C}_{12}\text{H}_{15}\text{NO}$: C 76.16; H 7.99; N 7.40. Found: C 76.29; H 7.86; N 7.59.

***N*-(2,2-Dimethyl-1-propylidene)-2-methyl-2-propenylamine 2e**

Yield: 89%, Bp: 52-56°C/ 41mmHg. **^1H NMR** (270 MHz, CDCl_3): δ 1.09 (9H, s) 1.73 (3H, s), 3.90 (2H, s), 4.81 (2H, s), 7.52 (1H, s). **^{13}C NMR** (68 MHz, CDCl_3): δ 21.0, 27.0, 36.2, 66.5, 110.8, 143.6, 173.2. **IR** (NaCl, cm^{-1}): $\nu_{\text{C}=\text{N}}$ = 1678. **MS** (70 eV) m/z (%): 139(M^+ , 0.8); 125(1); 124(10); 97(3); 84(11); 82(38); 57(17); 56(12); 53(4); 52(4); 41(17). Anal. Calcd for $\text{C}_9\text{H}_{17}\text{N}$: C 77.63; H 12.31; N 10.06. Found: C 77.76; H 12.19; N 10.01.

2. Bromofluorination of *N*-(allyl)imines 2a-f

For the experimental procedure and spectroscopic data of compound **3a** is referred to the manuscript text.

***N*-(4-Methylbenzylidene)-3-bromo-2-fluoro-2-methylpropylamine 3b**

Yield: 78%. **^1H NMR** (270 MHz, CDCl_3): δ 1.54 (3H, d, $J = 21.5$ Hz), 2.34 (3H, s), 3.60 (1H, d×d, $J = 16.8$ Hz, $J = 11.1$ Hz), 3.62 (1H, d×d, $J = 16.8$ Hz, $J = 11.1$ Hz), 3.73-3.96 (2H, m), 7.18 and 7.62 (2×2H, 2×d, $J = 8.1$ Hz), 8.21 (1H, s). **^{13}C NMR** (68 MHz, CDCl_3): δ 21.5, 22.5 (d, $J = 22.0$ Hz), 37.3 (d, $J = 26.8$ Hz), 66.27 (d, $J = 24.5$ Hz), 94.18 (d, $J = 175.8$ Hz), 128.2, 129.3, 133.2, 141.2, 163.5. **IR** (NaCl, cm^{-1}): 1640. **MS** (70 eV) m/z (%): 271/3 (M^+ , 3); 192 ($M^+ - \text{Br}$, 3); 172(3); 163(3); 134(3); 133(30); 132(100); 131(6); 130(6); 118(12); 117(9); 116(5); 105(99); 104(5); 103(10); 91(11); 90(6); 89(6); 79(8); 77(16); 66(5); 65(12); 63(7); 59(10); 53(7); 52(6); 51(14); 49(5); 44(6). Anal. Calcd for $\text{C}_{12}\text{H}_{15}\text{BrFN}$: C 52.96; H 5.56; N 5.15. Found: C 53.15; H 5.43; N 5.30.

***N*-(4-Methoxybenzylidene)-3-bromo-2-fluoro-2-methylpropylamine 3c**

Yield: 71%. Boiling point: 135°C/ 0.01 mm Hg. ¹H NMR (270 MHz, CDCl₃): δ 1.58 (3H, d, *J* = 21.8 Hz), 3.60-3.70 (2H, m), 3.84 (3H, s), 3.89 (2H, s), 6.93 and 7.72 (2×2H, 2×d, *J* = 8.9 Hz), 8.24 (1H, s). ¹³C NMR (68 MHz, CDCl₃): δ 22.6 (d, *J* = 22.0 Hz), 37.27 (d, *J* = 26.8 Hz), 55.4, 66.1 (d, *J* = 24.5 Hz), 94.30 (d, *J* = 203.8 Hz), 114.1, 130.1, 128.6, 162.1, 163.3. IR (NaCl, cm⁻¹): 1606, 1310, 1265, 1525, 1170, 1035. MS (ES+) *m/z* (%): 288/90 (*M*⁺+1, 100). Anal. Calcd for C₁₂H₁₅BrFNO: C 50.02; H 5.25; N 4.86. Found: C 50.23; H 5.39; N 4.78.

***N*-(2-Ethylbutyl)-3-bromo-2-fluoro-2-methylpropylamine 3d**

Yield: 68%. Boiling point: 70-75°C/ 0.3 mm Hg. ¹H NMR (270 MHz, CDCl₃): δ 0.89 (6H, t, *J* = 7.6 Hz), 1.43-1.54 (4H, m), 1.54 (3H, d, *J* = 21.5 Hz), 2.01-2.19 (1H, m), 3.51-3.60 (1H, m), 3.62-3.72 (2H, m), 7.47 (1H, d×t, *J* = 6.6 Hz, *J* = 1.1 Hz). ¹³C NMR (68 MHz, CDCl₃): δ 11.6, 22.5 (d, *J* = 23.2 Hz), 24.9, 37.0 (d, *J* = 28.1 Hz), 48.48, 66.5 (d, *J* = 23.2 Hz), 94.1 (d, *J* = 175.8 Hz), 172.9. IR (NaCl, cm⁻¹): 2975, 2939, 2882, 1671, 1463, 1387. MS (ES+) *m/z* (%): 252/4 (*M*⁺+1, 100). Anal. Calcd for C₁₀H₁₉BrFN: C 47.63; H 7.59; N 5.55. Found: C 47.53; H 7.48; N 5.68.

***N*-(2,2-Dimethyl-1-propylidene)-3-bromo-2-fluoro-2-methylpropylamine 3e**

Yield: 73%. ¹H NMR (270 MHz, CDCl₃): δ 1.07 (9H, s), 1.50 (3H, d, *J* = 21.5 Hz), 3.51-3.73 (4H, m), 7.58 (1H, d×d, *J* = 1.0 Hz, *J* = 1.3 Hz). ¹³C NMR (68 MHz, CDCl₃): δ 22.5 (d, *J* = 23.2 Hz), 26.7, 36.4, 36.9 (d, *J* = 28.0 Hz), 66.1 (d, *J* = 24.5 Hz), 94.1 (d, *J* = 175.8 Hz), 175.4. IR (NaCl, cm⁻¹): 1671. MS (ES+) *m/z* (%): 237/9 (*M*⁺; 1), 222/4 (1), 180/2(16), 153/5(19), 133/5(5), 98(100), 84(5), 82(7), 73(42), 69(21), 59(8), 57(13), 56(12), 55(13),

53(13), 47(10), 42(18), 41(48). Anal. Calcd for C₉H₁₇BrFN: C 45.39; H 7.20; N 5.88. Found: C 45.31; H 7.34; N 5.95.

***N*-Benzylidene-3-bromo-2-fluoro-2-phenylpropylamine 3f**

Yield: 77%. ¹H NMR (270 MHz, CDCl₃): δ 3.96 (1H, d×d, *J* = 20.4 Hz, *J* = 11.4 Hz), 4.09 (1H, d×d, *J* = 20.4 Hz, *J* = 11.4 Hz), 4.13-4.20 (2H, m), 7.26-7.87 (10H, m), 8.26 (1H, s). ¹³C NMR (68 MHz, CDCl₃): δ 37.3 (d, *J* = 25.6 Hz), 67.3 (d, *J* = 26.8 Hz), 96.2 (d, *J* = 176.4 Hz), 124.9, 125.0, 128.3, 128.3, 128.6, 131.1, 135.2, 139.3 (d, *J* = 201.6 Hz), 164.4. IR (NaCl, cm⁻¹): 1643. MS (ES+) *m/z* (%): decomposition of the product occurred during direct inlet or GC-MS. Anal. Calcd for C₁₆H₁₅BrFN: C 60.02; H 4.72; N 4.37. Found: C 60.19; H 4.66; N 4.19.

3. Synthesis of 3-fluoroazetidines 4a-f

For the experimental procedure and spectroscopic data of compound **4a** is referred to the manuscript text.

3-Fluoro-3-methyl-1-(4-methylbenzyl)azetidine 4b

Yield: 61%. ¹H NMR (270 MHz, CDCl₃): δ 1.55 (3H, d, *J* = 22.1 Hz), 2.30 (3H, s), 3.20 (2H, d×d, *J* = 22.1 Hz, *J* = 8.3 Hz), 3.29 (2H, d×d×d, *J* = 13.8 Hz, *J* = 8.3 Hz, *J* = 2.0 Hz), 3.58 (2H, s), 7.07-7.19 (4H, m). ¹³C NMR (68 MHz, CDCl₃): δ 21.0, 23.0 (d, *J* = 25.6 Hz), 63.2, 65.1 (d, *J* = 21.9 Hz), 89.7 (d, *J* = 203.9 Hz), 128.4, 129.0, 134.6, 136.7. IR (NaCl, cm⁻¹): 1517, 1381, 1361, 1327, 1230, 1212. MS (70 eV) *m/z* (%): 193 (M⁺, 1); 192(7); 191(3); 178(1); 149(1); 132(7); 112(17); 106(17); 105(100); 104(3); 103(5); 102(3); 91(3); 79(8); 78(5); 77(13); 44(20); 43(1); 42(3); 41(7). Anal. Calcd for C₁₂H₁₆FN: C 74.58; H 8.34; N 7.25. Found: C 74.76; H 8.45; N 7.12.

3-Fluoro-3-methyl-1-(4-methoxybenzyl)azetidine 4c

Yield: 65%. $^1\text{H NMR}$ (270 MHz, CDCl_3): δ 1.59 (3H, d, $J = 22.4$ Hz), 3.17-3.38 (4H, m), 3.61 (2H, s), 3.80 (3H, s), 6.85 and 7.20 (4H, 2 $\times$ d, $J = 9.2$ Hz). $^{13}\text{C NMR}$ (68 MHz, CDCl_3): δ 23.2 (d, $J = 25.6$ Hz), 55.2, 62.2, 65.1 (d, $J = 21.9$ Hz), 89.9 (d, $J = 203.8$ Hz), 113.8, 129.7, 129.9, 158.8. **IR** (NaCl, cm^{-1}): 1511, 1304, 1259, 1248, 1180, 1037. **MS** (ES+) m/z (%): 211 ($M^+ + 2$, 100). Anal. Calcd for $\text{C}_{12}\text{H}_{16}\text{FNO}$: C 68.88; H 7.71; N 6.69. Found: C 68.62; H 7.56; N 6.79.

3-Fluoro-3-methyl-1-(2-ethylbutyl)azetidine 4d

Yield: 61%. $^1\text{H NMR}$ (300 MHz, CDCl_3): δ 0.84 (6H, t, $J = 7.3$ Hz), 1.15-1.39 (5H, m), 1.58 (3H, d, $J = 22.3$ Hz), 2.36 (2H, d, $J = 6.3$ Hz), 3.08 (2H, m), 3.32 (2H, d $\times$ d $\times$ d, $J = 13.2$ Hz, $J = 7.0$ Hz, $J = 2.1$ Hz). $^{13}\text{C NMR}$ (68 MHz, CDCl_3): δ 10.9, 23.2 (d, $J = 25.4$ Hz), 24.0, 39.6, 63.9, 66.1 (d, $J = 20.8$ Hz), 89.9 (d, $J = 203.1$ Hz). **IR** (NaCl, cm^{-1}): 1455, 1380, 1054. **MS** (ES+) m/z (%): 175 ($M^+ + 2$, 100). Anal. Calcd for $\text{C}_{10}\text{H}_{20}\text{FN}$: C 69.32; H 11.63; N 8.08. Found: C 69.45; H 11.78; N 7.95.

3-Fluoro-3-methyl-1-(2,2-dimethylpropyl)azetidine 4e

Yield: 59%. $^1\text{H NMR}$ (270 MHz, CDCl_3): δ 0.86 (9H, s), 1.58 (3H, d, $J = 22.4$ Hz), 2.26 (2H, s), 3.19-3.43 (4H, m). $^{13}\text{C NMR}$ (68 MHz, CDCl_3): δ 20.1, 23.7 (d, $J = 25.6$ Hz), 32.4, 68.1 (d, $J = 20.7$ Hz), 73.2, 90.3 (d, $J = 202.6$ Hz). **IR** (NaCl, cm^{-1}): 1378, 1358, 1322, 1229, 1205, 1067. **MS** (70 eV) m/z (%): 159 (M^+ ; 3); 144(6); 102(100); 82(6); 73(4); 57(7); 55(8); 43(21); 42(37); 41(12). Anal. Calcd for $\text{C}_9\text{H}_{18}\text{FN}$: C 67.88; H 11.39; N 8.80. Found: C 67.76; H 11.55; N 8.85.

1-Benzyl-3-fluoro-3-phenylazetidine 4f

Yield: 60%. **¹H NMR** (270 MHz, CDCl₃): δ 3.60-3.79 (4H, m), 3.82 (2H, s), 7.29-7.61 (10H, m). **¹³C NMR** (68 MHz, CDCl₃): δ 63.3, 66.2 (d, *J* = 23.2 Hz), 91.7 (d, *J* = 206.2 Hz), 124.2, 124.4, 127.4, 128.2, 128.4, 140.1, 138.9 (d, *J* = 199.0 Hz). **IR** (NaCl, cm⁻¹): 1488, 1445, 1292, 1210, 1050, 1023. **MS** (70 eV) *m/z* (%): 241 (*M*⁺; 7); 220(2); 199(2); 130(2); 122(47); 119(4); 118(9); 96(4); 92(10); 91(100); 77(3); 65(6); 51(4); 42(4); 41(5). Anal. Calcd for C₁₆H₁₆FN: C 79.64; H 6.68; N 5.80. Found: C 79.75; H 6.60; N 5.86.

1-Benzhydryl-2-(fluoromethyl)aziridine 10

Yield: 17%. **¹H NMR** (270 MHz, CDCl₃): δ 1.64 (1H, d×d, *J* = 6.6 Hz, *J* = 2.3 Hz), 1.88 (1H, d×d, *J* = 3.3 Hz, *J* = 1.0 Hz), 1.94-2.03 (1H, m), 3.58 (1H, s), 4.23-4.33 and 4.41-4.51 (2H, m), 7.20-7.49 (10H, m). **¹³C NMR** (68 MHz, CDCl₃): δ 31.67 (d, *J* = 6.1 Hz), 38.18 (d, *J* = 26.8 Hz), 77.7, 85.04 (d, *J* = 168.5 Hz), 127.2, 127.2, 127.3, 127.5, 128.4, 128.4. **IR** (NaCl, cm⁻¹): 1492; 1451; 1078; 1055; 1028; 1000. **MS** (70 eV) *m/z* (%): 241 (*M*⁺; 3); 168 (15); 167 (100). Anal. Calcd for C₁₆H₁₆FN: C 79.64; H 6.68; N 5.80. Found: C 79.71; H 6.63; N 5.76.