

# Light-Enabled Enantiodivergence: Stereospecific Reduction of Activated Alkenes using a Single Organocatalyst Enantiomer

Theresa Hostmann, John J. Molloy, Kathrin Bussmann and Ryan Gilmour\*  
Organisch-Chemisches Institut, Westfälische Wilhelms-Universität Münster, Corrensstrasse 40, 48149 Münster, Germany

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## General information

All chemicals were purchased as reagent grade and used without further purification. Solvents for purification (extraction and column chromatography) were purchased as technical grade and distilled on the rotary evaporator prior to use. Solvents for analytical HPLC were purchased as HPLC grade (isopropanol), per analysis grade (*n*-hexane, methanol, ethanol, dibutylamine). As stationary phase for column chromatography SiO<sub>2</sub>-60 (230-400 mesh ASTM; *Fluka*) was used. Analytical thin layer chromatography (TLC) was performed on glass plates pre-coated with SiO<sub>2</sub>-60 F254 (*Merck*) and visualized with a UV-lamp (254 nm) and KMnO<sub>4</sub> solution or I<sub>2</sub> on silica gel. Concentration *in vacuo* was performed at ca. 10 mbar and 50 °C, drying at ca. 10<sup>-2</sup> mbar at room temperature. NMR spectra were measured by the NMR service of the Organisch-Chemisches Institut, Westfälische Wilhelms-Universität Münster on a *Bruker Avance II 300*, a *Bruker Avance II 400*, an *Agilent DD2 500* or an *Agilent DD2 600* spectrometer at room temperature. <sup>1</sup>H-NMR spectra are reported as follows: chemical shift  $\delta$  in ppm (multiplicity, coupling constant *J* in Hz, number of protons, assignment of proton). The deuterated solvent residual peak was used as internal reference: CHCl<sub>3</sub> ( $\delta_{\text{H}} = 7.26$  ppm). <sup>13</sup>C-NMR spectra are reported as follows: chemical shift  $\delta$  in ppm (multiplicity if different from singlet, coupling constant *J* in Hz, assignment of carbon). The solvent residual peak was used as internal reference: CDCl<sub>3</sub> ( $\delta_{\text{C}} = 77.16$  ppm). <sup>19</sup>F-NMR spectra are reported as follows: chemical shift  $\delta$  in ppm (multiplicity, coupling constant *J* in Hz, assignment of fluorine [if more than one fluorine present]). The resonance multiplicity is abbreviated as: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), sext (sextet) and br (broad). Assignments of unknown compounds are based on COSY (HH), HMBC, HSQC and NOESY spectra. Melting points were measured on a *Büchi B-545* melting-point apparatus in open capillaries and are uncorrected. IR spectra were recorded on a *Perkin-Elmer 100 FT-IR* spectrometer, selected adsorption bands are reported in wavenumbers  $\nu$  (cm<sup>-1</sup>) and intensities are reported as: w (weak), m (medium) and s (strong). Mass spectra (HR-ESI, GC-EI) were measured by the MS service of the Organisch-Chemisches Institut, Westfälische Wilhelms-Universität Münster on a *Bruker Daltonics MicrOTof ESI*, a *Thermo Fisher Scientific Orbitrap LTQ XL* or a *Thermo Fisher Scientific ISQ 7000 GC-MS*. Isomerization reactions at 402 nm were performed with a set-up of 4 *Winger WEPUV3-S2 UV Power LED Star (Schwarzlicht) 1.2 W* (emission spectrum see Figure 1) . The forward current per chip was set to 700 mA with a resulting forward voltage of 3.4 V and a radiant flux of 1200 mW. The distance between the reaction vessel and the UV-lamp was set to 1 cm (see Figure 2). Determination of the *Z:E*-ratio was done by integration of the <sup>1</sup>H-NMR signal of the methyl group  $\alpha$  to the aromatic ring. UV Absorption spectra were recorded on a *Agilent Cary 60 UV-Vis* Spectrophotometer. Optical rotations were identified with a *JASCO P-200* polarimeter. Enantiomeric ratios were determined by analytical HPLC using the following chiral columns: *Reprosil Chiral-OM* (5  $\mu\text{m}$ , 250x4.6 mm, *Dr. Maisch*), *Chiralcel® OJ-H* (5  $\mu\text{m}$ , 250x4.6 mm, *Daicel Chemical Industries, Ltd.*), *Reprosil Chiral-AM* (10  $\mu\text{m}$ , 250x4.6 mm, *Dr. Maisch*) or *Chiralpac® IA* (5  $\mu\text{m}$ , 250x4.6 mm, *Daicel Chemical Industries, Ltd.*).

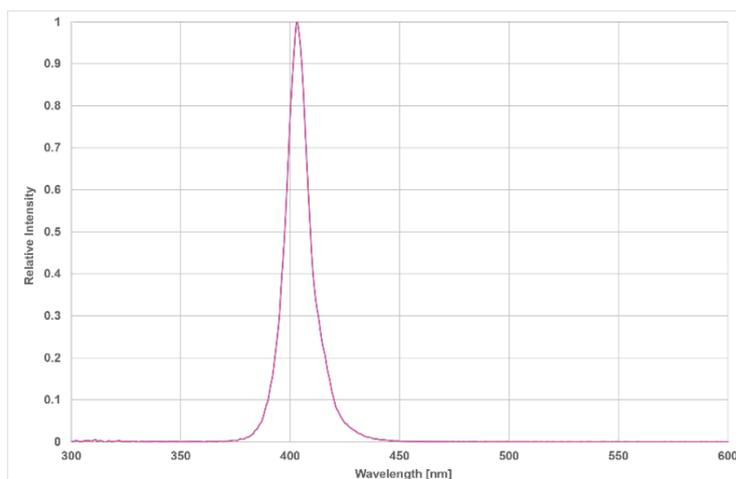


Figure 1: Emission spectrum of the utilized UV-lamp Winger WEPUV3-S2 UV Power LED Star (Schwarzlicht) 1.2 W.



Figure 2: Reaction set-up for the isomerization of *E*-nitrostyrenes to *Z*-nitrostyrenes.



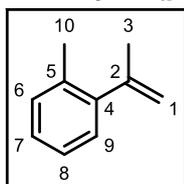
Figure 3: Reaction set up for the hydrogenation of nitrostyrenes to nitroalkanes.

## Synthesis of alkenes

### General procedure A for the preparation of terminal alkenes

Following a modified literature procedure,<sup>[1]</sup> PPh<sub>3</sub>MeBr (2 eq.) was suspended in dry Et<sub>2</sub>O (0.1 M) in a flame dried Schlenk flask under argon and cooled to 0 °C before KO<sup>t</sup>Bu (2 eq.) was added. The resulting yellow suspension was stirred at 0 °C for 1 h and the specified ketone (1 eq.) was added. While warming up to room temperature, the reaction mixture was monitored by TLC and upon conversion of the starting material or after stirring over night it was quenched with a sat. aq. NH<sub>4</sub>Cl solution. The separated organic layer was washed with water (3 x), dried over MgSO<sub>4</sub>, filtered and concentrated under reduced pressure in a cold rotavap bath (ca. 20 °C, >200 mbar) due to the volatility of most of the terminal alkenes. Purification by column chromatography (SiO<sub>2</sub>, *n*-pentane) afforded the terminal alkene.

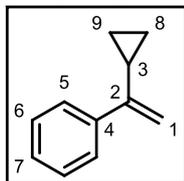
#### 1-Methyl-2-(prop-1-en-2-yl)benzene (S1)



Prepared according to general procedure **A**, 2'-methylacetophenone (2.6 mL, 20 mmol) was converted to **S1** in 4 h, yielding a colorless liquid (2.1 g, 11.8 mmol, 59%) after purification by column chromatography (SiO<sub>2</sub>, *n*-pentane).

$R_f = 0.79$  (*n*-pentane); <sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>):  $\delta = 7.21 - 7.09$  (m, 4H, H6, H7, H8, H9), 5.22 – 5.17 (m, 1H, H1-*cis*), 4.88 – 4.82 (m, 1H, H1-*trans*), 2.32 (s, 3H, H10), 2.07 – 2.02 (m, 3H, H3) ppm; <sup>13</sup>C{<sup>1</sup>H}-NMR (101 MHz, CDCl<sub>3</sub>):  $\delta = 146.0$  (C2), 144.0 (C4), 134.6 (C5), 130.2 (C6/7/8/9), 128.0 (C6/7/8/9), 126.9 (C6/7/8/9), 125.7 (C6/7/8/9), 114.8 (C1), 24.5 (C3), 19.9 (C10) ppm; IR (ATR):  $\tilde{\nu} = 3078$  (w), 3018 (w), 2967 (w), 1639 (w), 1489 (m), 1435 (m), 1371 (w), 1303 (w), 1095 (w), 1048 (w), 1005 (w), 897 (s), 763 (s), 729 (s) cm<sup>-1</sup>; GC-EI-MS:  $m/z$  [M]<sup>+</sup> calcd. for C<sub>10</sub>H<sub>12</sub><sup>+</sup>: 132.10; found: 132.14. The analytical data are in agreement with the literature.<sup>[2]</sup>

#### (1-Cyclopropylvinyl)benzene (S2)



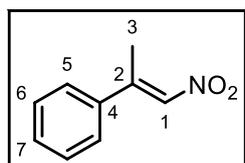
Prepared according to general procedure **A**, cyclopropyl(phenyl)methanone (4.2 mL, 30 mmol) was converted to **S2** over night, yielding a colorless liquid (3.96 g, 27.4 mmol, 92%) after purification by column chromatography (SiO<sub>2</sub>, *n*-pentane).

$R_f = 0.76$  (*n*-pentane); <sup>1</sup>H-NMR (600 MHz, CDCl<sub>3</sub>):  $\delta = 7.65 - 7.61$  (m, 2H, H5), 7.39 – 7.34 (m, 2H, H6), 7.33 – 7.28 (m, 1H, H7), 5.30 (m, 1H, H1-*trans*), 4.96 (m, 1H, H1-*cis*), 1.72 – 1.64 (m, 1H, H3), 0.89 – 0.84 (m, 2H, H8/9), 0.66 – 0.59 (m, 2H, H8/9) ppm; <sup>13</sup>C{<sup>1</sup>H}-NMR (151 MHz, CDCl<sub>3</sub>):  $\delta = 149.5$  (C2), 141.8 (C4), 128.3 (C6), 127.6 (C7), 126.3 (C5), 109.1 (C1), 15.8 (C3), 6.82 (C8, C9) ppm; IR (ATR):  $\tilde{\nu} = 3083$  (w), 3057 (w), 3004 (w), 2927 (w), 1624 (w), 1601 (w), 1574 (w), 1495 (m), 1445 (w), 1427 (w), 1382 (w), 1288 (w), 1261 (w), 1173 (w), 1072 (w), 1051 (w), 1021 (m), 939 (m), 889 (s), 837 (w), 820 (m), 773 (s), 700 (s) cm<sup>-1</sup>; GC-EI-MS:  $m/z$  [M]<sup>+</sup> calcd. for C<sub>11</sub>H<sub>12</sub><sup>+</sup>: 144.10; found: 144.13. The analytical data are in agreement with the literature.<sup>[3]</sup>

## Synthesis of *E*-nitrostyrenes

### General procedure B for the preparation of the (*E*)-nitrostyrenes

Following a modified literature procedure,<sup>[1]</sup> Ce(NH<sub>4</sub>)<sub>2</sub>(NO<sub>3</sub>)<sub>6</sub> (1 eq.) and NaNO<sub>2</sub> (10 eq.) were suspended in CHCl<sub>3</sub> (0.08 M). Subsequently the specified terminal alkene (1 eq.) and AcOH (12 eq.) were added. The flask was connected to a bubbler containing a sat. aq. NaHCO<sub>3</sub> solution and sonicated while the sonicator bath slowly heated itself up to ca. 50 °C. The reaction was monitored by TLC and upon conversion of the starting material the remaining solids were filtered off. The filtrate was quenched with a sat. aq. NaHCO<sub>3</sub> solution and washed two additional times with NaHCO<sub>3</sub> and brine. The separated organic layer was dried over MgSO<sub>4</sub>, filtered and concentrated *in vacuo*. Purification by column chromatography (SiO<sub>2</sub>, Et<sub>2</sub>O:*n*-pentane) afforded the (*E*)-nitrostyrene.

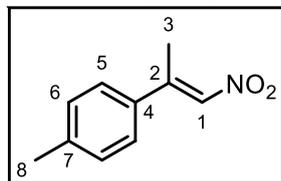


#### (*E*)-(1-Nitroprop-1-en-2-yl)benzene (**E-1**)

Prepared according to general procedure **B**,  $\alpha$ -methyl styrene (3.9 mL, 30 mmol) was converted to **E-1** in 5 h, yielding a yellow oil (3.2 g, 19.6 mmol, 65%) after purification by column chromatography (SiO<sub>2</sub>, Et<sub>2</sub>O:*n*-pentane, 5:95).

$R_f$  = 0.58 (Et<sub>2</sub>O:*n*-pentane, 5:95); <sup>1</sup>H-NMR (600 MHz, CDCl<sub>3</sub>):  $\delta$  = 7.47 – 7.43 (m, 5H, H5, H6, H7), 7.31 (q, <sup>4</sup>J<sub>HH</sub> = 1.4 Hz, 1H, H1), 2.65 (d, <sup>4</sup>J<sub>HH</sub> = 1.4 Hz, 3H, H3) ppm; <sup>13</sup>C{<sup>1</sup>H}-NMR (101 MHz, CDCl<sub>3</sub>):  $\delta$  = 150.1 (C2), 138.4 (C4), 136.5 (C1), 130.5 (C7), 129.2 (C5/6), 127.0 (C5/6), 18.7 (C3) ppm; IR (ATR):  $\tilde{\nu}$  = 3105 (w), 3060 (w), 2841 (w), 1622 (m), 1575 (w), 1508 (s), 1444 (m), 1374 (m), 1334 (s), 1255 (m), 1186 (w), 1160 (w), 1078 (w), 1028 (w), 1000 (w), 919 (m), 833 (m), 804 (w), 765 (s), 737 (s), 639 (s) cm<sup>-1</sup>; GC-EI-MS: *m/z* [M]<sup>+</sup> calcd. for C<sub>9</sub>H<sub>9</sub>NO<sub>2</sub><sup>+</sup>: 163.10; found: 163.11. The analytical data are in agreement with the literature.<sup>[1]</sup>

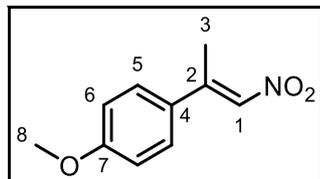
#### (*E*)-1-Methyl-4-(1-nitroprop-1-en-2-yl)benzene (**E-2**)



Prepared according to general procedure **B**, 1-methyl-4-(prop-1-en-2-yl)benzene (2.6 g, 20 mmol) was converted to **E-2** in 5 h, yielding a yellow oil (1.5 g, 8.5 mmol, 42%) after purification by column chromatography (SiO<sub>2</sub>, Et<sub>2</sub>O:*n*-pentane, 5:95).

$R_f$  = 0.82 (Et<sub>2</sub>O:*n*-pentane, 5:95); <sup>1</sup>H-NMR (600 MHz, CDCl<sub>3</sub>):  $\delta$  = 7.39 – 7.33 (m, 2H, H5), 7.32 (q, <sup>4</sup>J<sub>HH</sub> = 1.4 Hz, 1H, H1), 7.26 – 7.23 (m, 2H, H6), 2.64 (d, <sup>4</sup>J<sub>HH</sub> = 1.4 Hz, 3H, H3), 2.40 (s, 3H, H8) ppm; <sup>13</sup>C{<sup>1</sup>H}-NMR (151 MHz, CDCl<sub>3</sub>):  $\delta$  = 150.1 (C2), 141.0 (C7), 135.9 (C1), 135.5 (C4), 129.9 (C6), 126.9 (C5), 21.4 (C8), 18.6 (C3) ppm; IR (ATR):  $\tilde{\nu}$  = 3678 (w), 3107 (w), 2924 (w), 1618 (m), 1607 (m), 1568 (w), 1506 (s), 1441 (w), 1410 (w), 1374 (w), 1332 (s), 1258 (m), 1216 (w), 1190 (w), 1126 (w), 1077 (w), 1038 (w), 1018 (w), 920 (m), 836 (w), 811 (s), 709 (s) cm<sup>-1</sup>; GC-EI-MS: *m/z* [M]<sup>+</sup> calcd. for C<sub>10</sub>H<sub>11</sub>NO<sub>2</sub><sup>+</sup>: 177.10; found: 177.12. The analytical data are in agreement with the literature.<sup>[4]</sup>

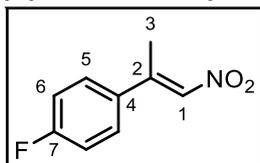
#### (*E*)-1-Methoxy-4-(1-nitroprop-1-en-2-yl)benzene (**E-3**)



Prepared according to general procedure **B**, 1-methoxy-4-(prop-1-en-2-yl)benzene (2.96 g, 20 mmol) was converted to **E-3** in 4 h, yielding a yellow solid (936 mg, 4.85 mmol, 24%) after purification by column chromatography (SiO<sub>2</sub>, Et<sub>2</sub>O:*n*-pentane, 5:95).

$R_f$  = 0.24 (Et<sub>2</sub>O:*n*-pentane, 5:95); <sup>1</sup>H-NMR (600 MHz, CDCl<sub>3</sub>):  $\delta$  = 7.45 – 7.42 (m, 2H, H5), 7.34 (q, <sup>4</sup>J<sub>HH</sub> = 1.4 Hz, 1H, H1), 6.97 – 6.93 (m, 2H, H6), 3.86 (s, 3H, H8), 2.64 (d, <sup>4</sup>J<sub>HH</sub> = 1.4 Hz, 3H, H3) ppm; <sup>13</sup>C{<sup>1</sup>H}-NMR (151 MHz, CDCl<sub>3</sub>):  $\delta$  = 161.8 (C2), 149.8 (C7), 135.3 (C1), 130.4 (C4), 128.6 (C5), 114.6 (C6), 55.6 (C8), 18.5 (C3) ppm; IR (ATR):  $\tilde{\nu}$  = 3105 (w), 3012 (w), 2937 (w), 2840 (w), 1598 (s), 1571 (w), 1556 (w), 1505 (s), 1462 (m), 1441 (w), 1418 (w), 1374 (w), 1328 (s), 1291 (s), 1245 (s), 1179 (s), 1121 (w), 1078 (w), 1026 (s), 920 (m), 823 (s), 784 (m), 734 (w), 710 (w) cm<sup>-1</sup>; GC-EI-MS: *m/z* [M]<sup>+</sup> calcd. for C<sub>10</sub>H<sub>11</sub>NO<sub>3</sub><sup>+</sup>: 193.07334; found: 193.07328; **m.p.**: 33-34 °C. The analytical data are in agreement with the literature.<sup>[4]</sup>

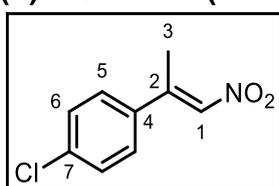
### (E)-1-Fluoro-4-(1-nitroprop-1-en-2-yl)benzene (E-4)



Prepared according to general procedure **B**, 1-fluoro-4-(prop-1-en-2-yl)benzene (3.23 g, 23.7 mmol) was converted to **E-4** in 4 h, yielding a yellow oil (2.49 g, 13.8 mmol, 58%) after purification by column chromatography (SiO<sub>2</sub>, Et<sub>2</sub>O:*n*-pentane, 5:95).

$R_f = 0.46$  (Et<sub>2</sub>O:*n*-pentane, 5:95); **<sup>1</sup>H-NMR** (600 MHz, CDCl<sub>3</sub>):  $\delta = 7.47 - 7.43$  (m, 2H, H5), 7.28 (q, <sup>4</sup>*J*<sub>HH</sub> = 1.4 Hz, 1H, H1), 7.15 – 7.11 (m, 2H, H6), 2.63 (d, <sup>4</sup>*J*<sub>HH</sub> = 1.4 Hz, 3H, H3) ppm; **<sup>13</sup>C{<sup>1</sup>H}-NMR** (151 MHz, CDCl<sub>3</sub>):  $\delta = 164.1$  (d, <sup>1</sup>*J*<sub>CF</sub> = 251.6 Hz, C7), 148.8 (C2), 136.4 (C1), 134.4 (d, <sup>4</sup>*J*<sub>CF</sub> = 3.4 Hz, C4), 129.0 (d, <sup>3</sup>*J*<sub>CF</sub> = 8.5 Hz, C5), 116.4 (d, <sup>2</sup>*J*<sub>CF</sub> = 21.9 Hz, C6), 18.73 (C3) ppm; **<sup>19</sup>F-NMR** (564 MHz): -109.8 (tt, <sup>3</sup>*J*<sub>FH</sub> = 8.3 Hz, <sup>4</sup>*J*<sub>FH</sub> = 5.1 Hz) ppm; **IR** (ATR):  $\tilde{\nu} = 3108$  (w), 2967 (w), 2849 (w), 1621 (m), 1601 (m), 1505 (s), 1437 (w), 1409 (w), 1375 (w), 1335 (s), 1283 (s), 1233 (s), 1163 (s), 1104 (w), 1077 (w), 1014 (w), 920 (m), 825 (s), 791 (m), 729 (w), 712 (w) cm<sup>-1</sup>; **GC-EI-MS**: *m/z* [M]<sup>+</sup> calcd. for C<sub>9</sub>H<sub>8</sub>FN<sub>2</sub><sup>+</sup>: 181.10; found: 181.10. The analytical data are in agreement with the literature.<sup>[4]</sup>

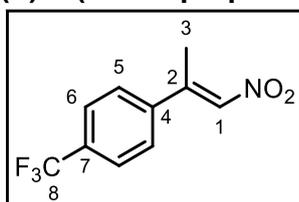
### (E)-1-Chloro-4-(1-nitroprop-1-en-2-yl)benzene (E-5)



Prepared according to general procedure **B**, 1-chloro-4-(prop-1-en-2-yl)benzene (3.05 g, 20 mmol) was converted to **E-5** in 4 h, yielding a yellow oil (1.88 g, 9.5 mmol, 48%) after purification by column chromatography (SiO<sub>2</sub>, Et<sub>2</sub>O:*n*-pentane, 5:95).

$R_f = 0.46$  (Et<sub>2</sub>O:*n*-pentane, 5:95); **<sup>1</sup>H-NMR** (600 MHz, CDCl<sub>3</sub>):  $\delta = 7.45 - 7.36$  (m, 4H, H5, H6), 7.28 (q, <sup>4</sup>*J*<sub>HH</sub> = 1.4 Hz, 1H, H1), 2.62 (d, <sup>4</sup>*J*<sub>HH</sub> = 1.4 Hz, 3H, H3) ppm; **<sup>13</sup>C{<sup>1</sup>H}-NMR** (151 MHz, CDCl<sub>3</sub>):  $\delta = 148.6$  (C2), 136.8 (C4, C7), 136.6 (C1), 129.7 (C5/6), 128.3 (C5/6), 18.6 (C3) ppm; **IR** (ATR):  $\tilde{\nu} = 3106$  (w), 1621 (m), 1591 (m), 1564 (w), 1510 (s), 1489 (m), 1436 (w), 1401 (m), 1374 (w), 1331 (s), 1254 (w), 1185 (w), 1095 (s), 1011 (s), 920 (w), 819 (s), 754 (s), 722 (w), 662 (w) cm<sup>-1</sup>; **GC-EI-MS**: *m/z* [M]<sup>+</sup> calcd. for C<sub>9</sub>H<sub>8</sub>ClNO<sub>2</sub><sup>+</sup>: 197.02; found: 197.08. The analytical data are in agreement with the literature.<sup>[4]</sup>

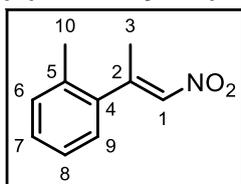
### (E)-1-(1-Nitroprop-1-en-2-yl)-4-(trifluoromethyl)benzene (E-6)



Prepared according to general procedure **B**, 1-(prop-1-en-2-yl)-4-(trifluoromethyl)benzene (2.95 g, 20 mmol) was converted to **E-6** in 5 h, yielding a yellow oil (1.34 g, 5.8 mmol, 37%) after purification by column chromatography (SiO<sub>2</sub>, Et<sub>2</sub>O:*n*-pentane, 5:95).

$R_f = 0.43$  (Et<sub>2</sub>O:*n*-pentane, 5:95); **<sup>1</sup>H-NMR** (600 MHz, CDCl<sub>3</sub>):  $\delta = 7.71$  (d, <sup>2</sup>*J*<sub>HH</sub> = 8.3 Hz, 2H, H6), 7.56 (d, <sup>2</sup>*J*<sub>HH</sub> = 8.3 Hz, 2H, H5), 7.29 (d, <sup>4</sup>*J*<sub>HH</sub> = 1.4 Hz, 1H, H1), 2.65 (d, <sup>4</sup>*J*<sub>HH</sub> = 1.5 Hz, 3H, H3) ppm; **<sup>13</sup>C{<sup>1</sup>H}-NMR** (151 MHz, CDCl<sub>3</sub>):  $\delta = 148.2$  (C2), 142.0 (d, <sup>5</sup>*J*<sub>CF</sub> = 1.3 Hz, C4), 137.4 (C1), 132.3 (d, <sup>2</sup>*J*<sub>CF</sub> = 33.0 Hz, C7), 127.4 (C5), 126.2 (q, <sup>3</sup>*J*<sub>CF</sub> = 3.7 Hz, C6), 123.8 (d, <sup>1</sup>*J*<sub>CF</sub> = 272.3 Hz, C8), 18.7 (C3) ppm; **<sup>19</sup>F-NMR** (470 MHz, CDCl<sub>3</sub>):  $\delta = -62.97$  (s) ppm; **IR** (ATR):  $\tilde{\nu} = 3107$  (w), 2961 (w), 1625 (w), 1574 (w), 1518 (m), 1437 (w), 1409 (w), 1377 (w), 1346 (m), 1319 (s), 1257 (w), 1167 (m), 1115 (s), 1082 (m), 1063 (s), 1015 (s), 959 (w), 919 (w), 829 (s), 777 (w), 727 (s) cm<sup>-1</sup>; **GC-EI-MS**: *m/z* [M-H]<sup>+</sup> calcd. for C<sub>10</sub>H<sub>7</sub>NO<sub>2</sub>F<sub>3</sub><sup>+</sup>: 230.04234; found: 230.04250. The analytical data are in agreement with the literature.<sup>[5]</sup>

### (E)-1-Methyl-2-(1-nitroprop-1-en-2-yl)benzene (E-7)

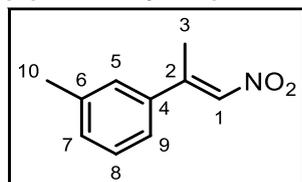


Prepared according to general procedure **B**, **S1** (2.0 g, 15.1 mmol) was converted to **E-7** in 4 h, yielding a yellow oil (557 mg, 3.14 mmol, 21%) after purification by column chromatography (SiO<sub>2</sub>, Et<sub>2</sub>O:*n*-pentane, 5:95).

$R_f = 0.53$  (Et<sub>2</sub>O:*n*-pentane, 5:95); **<sup>1</sup>H-NMR** (500 MHz, CDCl<sub>3</sub>):  $\delta = 7.30$  (td, <sup>3</sup>*J*<sub>HH</sub> = 7.4 Hz, <sup>4</sup>*J*<sub>HH</sub> = 1.4 Hz, 1H, H7), 7.26 – 7.20 (m, 2H, H8, H6), 7.10 (dd, <sup>3</sup>*J*<sub>HH</sub> = 7.6 Hz, <sup>4</sup>*J*<sub>HH</sub> = 1.4 Hz, 1H, H9), 7.00 (q, <sup>4</sup>*J*<sub>HH</sub> = 1.5 Hz, 1H, H1), 2.54 (d, <sup>4</sup>*J*<sub>HH</sub> = 1.5 Hz, 3H, H3), 2.32 (s, 3H, H10) ppm; **<sup>13</sup>C{<sup>1</sup>H}-NMR** (126 MHz, CDCl<sub>3</sub>):  $\delta = 151.8$  (C2), 139.1 (C4), 137.7 (C1), 134.5 (C5), 131.0 (C8), 129.1 (C7), 127.4 (C9), 126.2 (C6), 21.0 (C3), 19.8 (C10) ppm; **IR** (ATR):  $\tilde{\nu} = 3100$  (w), 2962 (w), 1627 (w), 1513 (s), 1486 (m), 1455 (w), 1371 (w), 1341 (s), 1288 (w), 1248 (w), 1161 (w), 1123 (w), 1072 (w), 1046 (w),

919 (w), 838 (m), 788 (w), 761 (s), 728 (s), 712 (m)  $\text{cm}^{-1}$ ; **GC-EI-MS**:  $m/z$ :  $[\text{M}-\text{H}]^+$  calcd. for  $\text{C}_{10}\text{H}_{10}\text{NO}_2^+$ : 173.07061; found: 176.07063. The analytical data are in agreement with the literature.<sup>[5]</sup>

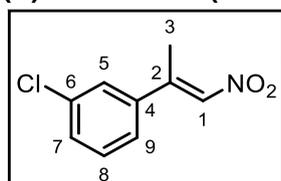
### (E)-1-Methyl-3-(1-nitroprop-1-en-2-yl)benzene (E-8)



Prepared according to general procedure **B**, 1-methyl-3-(prop-1-en-2-yl)benzene (4.0 g, 30.3 mmol) was converted to **E-8** in 4 h, yielding a yellow oil (2.52 g, 14.2 mmol, 47%) after purification by column chromatography ( $\text{SiO}_2$ ,  $\text{Et}_2\text{O}$ :*n*-pentane, 5:95).

$R_f = 0.45$  ( $\text{Et}_2\text{O}$ :*n*-pentane, 5:95);  **$^1\text{H-NMR}$**  (500 MHz,  $\text{CDCl}_3$ ):  $\delta = 7.35 - 7.31$  (m, 1H, H5), 7.31 (q,  $^4J_{\text{HH}} = 1.5$  Hz, 1H, H1), 7.28 - 7.24 (m, 3H, H7, H8, H9), 2.64 (d,  $^4J_{\text{HH}} = 1.5$  Hz, 3H, H3), 2.41 (s, 3H, H10) ppm;  **$^{13}\text{C}\{^1\text{H}\}\text{-NMR}$**  (126 MHz,  $\text{CDCl}_3$ ):  $\delta = 150.3$  (C2), 139.0 (C6), 138.5 (C4), 136.3 (C1), 131.3 (C7/8/9), 129.1 (C5), 127.6 (C7/8/9), 124.1 (C7/8/9), 21.5 (C10), 18.7 (C3) ppm; **IR** (ATR):  $\tilde{\nu} = 3107$  (w), 3026 (w), 2924 (w), 1619 (w), 1603 (w), 1582 (w), 1508 (s), 1442 (w), 1374 (w), 1334 (s), 1268 (m), 1192 (w), 1101 (w), 1040 (w), 999 (w), 938 (w), 882 (w), 860 (w), 833 (m), 784 (s), 715 (m), 694 (m)  $\text{cm}^{-1}$ ; **GC-EI-MS**:  $m/z$ :  $[\text{M}-\text{H}]^+$  calcd. for  $\text{C}_{10}\text{H}_{10}\text{NO}_2^+$ : 176.07061; found: 176.07066. The analytical data are in agreement with the literature.<sup>[6]</sup>

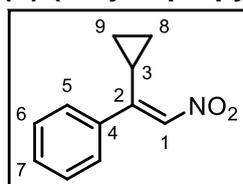
### (E)-1-Chloro-3-(1-nitroprop-1-en-2-yl)benzene (E-9)



Prepared according to general procedure **B**, 1-chloro-3-(prop-1-en-2-yl)benzene (3.0 g, 15.2 mmol) was converted to **E-9** in 5 h, yielding a yellow oil (2.07 g, 10.5 mmol, 69%) after purification by column chromatography ( $\text{SiO}_2$ ,  $\text{Et}_2\text{O}$ , *n*-pentane, 5:95).

$R_f = 0.39$  ( $\text{Et}_2\text{O}$ :*n*-pentane, 5:95);  **$^1\text{H-NMR}$**  (400 MHz,  $\text{CDCl}_3$ ):  $\delta = 7.47 - 7.40$  (m, 2H, H5, H7), 7.42 - 7.34 (m, 1H, H8), 7.33 (dt,  $^3J_{\text{HH}} = 7.6$  Hz,  $^4J_{\text{HH}} = 1.6$  Hz, 1H, H9), 7.28 (q,  $^4J_{\text{HH}} = 1.4$  Hz, 1H, H1), 2.62 (d,  $^4J_{\text{HH}} = 1.4$  Hz, 3H, H3) ppm;  **$^{13}\text{C}\{^1\text{H}\}\text{-NMR}$**  (101 MHz,  $\text{CDCl}_3$ ):  $\delta = 148.4$  (C2), 140.2 (C4), 137.0 (C1), 135.3 (C6), 130.5 (C7, C8), 127.2 (C5), 125.1 (C9), 18.6 (C3) ppm; **IR** (ATR):  $\tilde{\nu} = 3110$  (w), 3080 (w), 3060 (w), 1619 (w), 1563 (w), 1504 (m), 1473 (w), 1408 (w), 1377 (w), 1336 (s), 1267 (w), 1248 (m), 1171 (w), 1102 (w), 1082 (w), 1017 (w), 996 (w), 929 (w), 900 (w), 839 (m), 796 (s), 767 (w), 720 (w), 682 (s)  $\text{cm}^{-1}$ ; **GC-EI-MS**:  $m/z$ :  $[\text{M}]^+$  calcd. for  $\text{C}_9\text{H}_8\text{ClNO}_2^+$ : 197.02; found: 197.07. The analytical data are in agreement with the literature.<sup>[7]</sup>

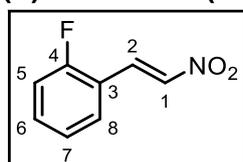
### (E)-(1-Cyclopropyl-2-nitrovinyl)benzene (E-10)



Prepared according to general procedure **B**, **S2** (2.0 g, 15.1 mmol) was converted to **E-10** in 5 h, yielding a yellow oil (557 mg, 3.14 mmol, 21%) after purification by column chromatography ( $\text{SiO}_2$ ,  $\text{Et}_2\text{O}$ :*n*-pentane, 5:95).

$R_f = 0.45$  ( $\text{Et}_2\text{O}$ :*n*-pentane, 5:95);  **$^1\text{H-NMR}$**  (400 MHz,  $\text{CDCl}_3$ ):  $\delta = 7.40 - 7.35$  (m, 3H, H6, H7), 7.20 - 7.16 (m, 2H, H5), 7.07 (d,  $^4J_{\text{HH}} = 0.8$  Hz, 1H, H1), 3.11 (tt,  $^3J_{\text{HH}} = 8.4, 5.3$  Hz,  $^4J_{\text{HH}} = 0.9$  Hz, 1H, H3), 1.09 - 1.04 (m, 2H, H8/9), 0.62 - 0.58 (m, 2H, H8/9) ppm;  **$^{13}\text{C}\{^1\text{H}\}\text{-NMR}$**  (101 MHz,  $\text{CDCl}_3$ ):  $\delta = 157.2$  (C2), 137.5 (C1), 134.3 (C4), 129.3 (C7), 128.5 (C5), 128.4 (C6), 13.5 (C3), 8.2 (C8, C9) ppm; **IR** (ATR):  $\tilde{\nu} = 3100$  (w), 3016 (w), 2928 (w), 2854 (w), 1597 (m), 1575 (w), 1552 (w), 1509 (s), 1489 (m), 1443 (m), 1427 (w), 1365 (m), 1335 (s), 1279 (w), 1258 (w), 1195 (w), 1178 (w), 1159 (w), 1123 (w), 1103 (w), 1075 (w), 1061 (w), 1032 (w), 1001 (w), 920 (m), 824 (m), 772 (s), 729 (s), 701 (s), 667 (m)  $\text{cm}^{-1}$ ; **GC-EI-MS**:  $m/z$ :  $[\text{M}-\text{H}]^+$  calcd. for  $\text{C}_{11}\text{H}_{11}\text{NO}_2^+$ : 189.0789; found: 188.07063.

### (E)-1-Fluoro-2-(2-nitrovinyl)benzene (E-12)



Following a modified literature procedure,<sup>[8]</sup> a solution of 2-fluorobenzaldehyde (1.24 g, 10 mmol, 1 eq.) in  $\text{MeNO}_2$  (0.65 mL, 12 mmol, 1.2 eq.) and  $\text{MeOH}$  (16 mL) was added at ca. 5 °C to a solution of  $\text{NaOH}$  (2.5 M in  $\text{H}_2\text{O}$ , 4.8 mL, 12 mmol, 1.2 eq.) and  $\text{MeOH}$  (4.8 mL) over 30 min. The reaction mixture was stirred for 30 min, before a solution of  $\text{ZnCl}_2$  (6.82 g, 50 mmol, 5 eq.), aq.  $\text{HCl}$  (12 M, 2.1 mL, 25 mmol, 2.5 eq.)

and H<sub>2</sub>O (2.7 mL) was added at ca. 5 °C over 30 min. While warming up to room temperature, stirring was continued for further 3 h. The light yellow precipitate was collected by filtration and washed with a solution of MeOH in H<sub>2</sub>O (40%, 3 x 5 mL) to yield **E-11** as a light yellow solid (763 mg, 4.56 mmol, 46%).

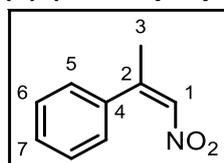
**<sup>1</sup>H-NMR** (500 MHz, CDCl<sub>3</sub>): δ = 8.06 (d, <sup>3</sup>J<sub>HH</sub> = 13.8 Hz, 1H, H1), 7.73 (d, <sup>3</sup>J<sub>HH</sub> = 13.8 Hz, 1H, H2), 7.54 – 7.46 (m, 2H, H8, H6), 7.27 – 7.16 (m, 2H, H7, H5) ppm; **<sup>13</sup>C{<sup>1</sup>H}-NMR** (126 MHz, CDCl<sub>3</sub>): δ = 162.0 (d, <sup>1</sup>J<sub>CF</sub> = 256.4 Hz, C4), 139.6 (d, <sup>3</sup>J<sub>CF</sub> = 11.5 Hz, C2), 133.8 (d, <sup>3</sup>J<sub>CF</sub> = 9.1 Hz, C6), 132.6 (d, <sup>4</sup>J<sub>CF</sub> = 0.7 Hz, C1), 131.5 (d, <sup>3</sup>J<sub>CF</sub> = 2.5 Hz, C8), 125.2 (d, <sup>4</sup>J<sub>CF</sub> = 3.6 Hz, C7), 118.6 (d, <sup>2</sup>J<sub>CF</sub> = 12.0 Hz, C3), 116.8 (d, <sup>2</sup>J<sub>CF</sub> = 21.7 Hz, C5) ppm; **<sup>19</sup>F-{<sup>1</sup>H}-NMR** (282 MHz, CDCl<sub>3</sub>): δ = -109.11 ppm; **IR** (ATR):  $\tilde{\nu}$  = 3163 (w), 3049 (w), 2841 (w), 1633 (w), 1611 (m), 1507 (s), 1493 (s), 1450 (m), 1381 (w), 1346 (s), 1305 (w), 1287 (w), 1262 (w), 1248 (w), 1234 (w), 1215 (m), 1203 (m), 1189 (w), 1160 (w), 1106 (w), 1037 (w), 967 (s), 889 (w), 865 (w), 842 (m), 809 (w), 780 (w), 755 (s), 732 (s) cm<sup>-1</sup>; **GC-EI-MS**: *m/z*: [M]<sup>+</sup> calcd. for C<sub>8</sub>H<sub>6</sub>FNO<sub>2</sub><sup>+</sup>: 167.04; found: 167.07; **m.p.** = 50 – 53 °C. The analytical data are in agreement with the literature.<sup>[9]</sup>

## Synthesis of *Z*-nitrostyrenes

### General procedure C for the preparation of the (*Z*)-nitrostyrenes

In a flame dried 10 mL round bottom flask, the (*E*)-nitrostyrene (0.5 mmol, 1 eq.) was dissolved in dry MeCN (0.5 mL, 1 M). The flask was sealed with a rubber septum and the mixture was degassed by bubbling argon through it with a needle for ca. 2 min. The flask was connected to a balloon filled with argon and placed in the shown irradiation set up (Figure 2). After irradiation at 402 nm for 7 h, the solvent was removed under reduced pressure and the residue was filtered over a plug of SiO<sub>2</sub>. Subsequent elution of the products with Et<sub>2</sub>O:*n*-pentane 1:9 and concentration *in vacuo* yielded the mixture of the (*Z*)- and (*E*)-isomer. The yield was determined by mass recovery based on NMR purity and the *Z*:*E*-ratio was determined by integration of the <sup>1</sup>H-NMR signal of the methyl group α to the aromatic ring (for **Z-1 – Z-9**), the CH-proton of the cyclopropyl (for **Z-10**) or the methanylyliden protons (for **Z-11** and **Z-12**). A second purification by column chromatography (SiO<sub>2</sub>, Et<sub>2</sub>O:*n*-pentane) yielded the pure (*Z*)-nitrostyrene. Reported yields and *Z*:*E* stereoselectivities are an average of two duplicate reactions.

#### (*Z*)-(1-Nitroprop-1-en-2-yl)benzene (**Z-1**)

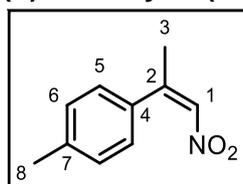


Prepared according to general procedure **C**, **E-1** (82 mg) was converted to **Z-1** yielding a yellow oil as a mixture of isomers (58.8 mg, 0.36 mmol, 72%, *Z*:*E* = 92:08).

**R<sub>f</sub>** = 0.42 (Et<sub>2</sub>O:*n*-pentane, 5:95); <sup>1</sup>H-NMR (600 MHz, CDCl<sub>3</sub>): δ = 7.43 – 7.35 (m, 3H, H6, H7), 7.20 (dd, <sup>3</sup>J<sub>HH</sub> = 7.7 Hz, <sup>4</sup>J<sub>HH</sub> = 1.8 Hz, 2H, H5), 7.06 (q, <sup>4</sup>J<sub>HH</sub> = 1.4 Hz, 1H, H1), 2.19 (d, <sup>4</sup>J<sub>HH</sub> = 1.4 Hz, 3H, H3) ppm;

<sup>13</sup>C{<sup>1</sup>H}-NMR (151 MHz, CDCl<sub>3</sub>): δ = 148.5 (C2), 137.3 (C4), 134.6 (C1), 129.0 (C7), 128.7 (C6), 126.4 (C5), 24.2 (C3) ppm; IR (ATR):  $\tilde{\nu}$  = 3099 (w), 2987 (w), 2916 (w), 1635 (w), 1600 (w), 1576 (w), 1515 (s), 1431 (m), 1395 (w), 1374 (w), 1337 (s), 1209 (w), 1182 (w), 1158 (w), 1077 (w), 1027 (w), 1001 (w), 956 (w), 916 (w), 823 (m), 774 (s), 752 (m), 696 (s) cm<sup>-1</sup>; GC-EI-MS: *m/z* [M-H]<sup>+</sup> calcd. for C<sub>9</sub>H<sub>8</sub>NO<sub>2</sub><sup>+</sup>: 162.05496; found: 162.05493. The analytical data are in agreement with the literature.<sup>[10]</sup>

#### (*Z*)-1-Methyl-4-(1-nitroprop-1-en-2-yl)benzene (**Z-2**)

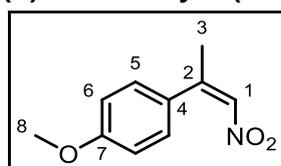


Prepared according to general procedure **C**, **E-2** (89 mg) was converted to **Z-2** yielding a yellow oil as a mixture of isomers (72.9 mg, 0.41 mmol, 82%, *Z*:*E* = 88:12).

**R<sub>f</sub>** = 0.45 (Et<sub>2</sub>O:*n*-pentane, 5:95); <sup>1</sup>H-NMR (600 MHz, CDCl<sub>3</sub>): δ = 7.22 – 7.19 (m, 2H, H6), 7.12 – 7.10 (m, 2H, H5), 7.05 (q, <sup>4</sup>J<sub>HH</sub> = 1.4 Hz, 1H, H1), 2.38 (s, 3H, H8), 2.17 (d, <sup>4</sup>J<sub>HH</sub> = 1.5 Hz, 3H, H3) ppm; <sup>13</sup>C{<sup>1</sup>H}-NMR (151

MHz, CDCl<sub>3</sub>): δ = 148.5 (C2), 139.2 (C7), 134.3 (C1), 134.2 (C4), 129.4 (C5/6), 126.5 (C5/6), 24.2 (C3), 21.5 (C8) ppm; IR (ATR):  $\tilde{\nu}$  = 3099 (w), 3029 (w), 2982 (w), 2922 (w), 1736 (w), 1687 (w), 1632 (m), 1556 (w), 1518 (s), 1432 (m), 1398 (w), 1374 (m), 1335 (s), 1216 (w), 1203 (w), 1187 (w), 1155 (w), 1085 (w), 1033 (m), 1020 (w), 955 (m), 817 (s), 764 (m), 711 (m) cm<sup>-1</sup>; GC-EI-MS: *m/z* [M-H]<sup>+</sup> calcd. for C<sub>10</sub>H<sub>10</sub>NO<sub>2</sub><sup>+</sup>: 176.07061; found: 176.07058.

#### (*Z*)-1-Methoxy-4-(1-nitroprop-1-en-2-yl)benzene (**Z-3**)

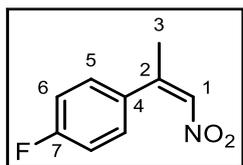


Prepared according to general procedure **C**, **E-3** (97 mg) was converted to **Z-3** yielding a yellow oil as a mixture of isomers (86.7 mg, 0.45 mmol, 90%, *Z*:*E* = 88:12).

**R<sub>f</sub>** = 0.16 (Et<sub>2</sub>O:*n*-pentane, 5:95); <sup>1</sup>H-NMR (500 MHz, CDCl<sub>3</sub>): δ = 7.20 – 7.16 (m, 2H, H5), 7.03 (d, <sup>4</sup>J<sub>HH</sub> = 1.4 Hz, 1H, H1), 6.93 – 6.90 (m, 2H, H6), 3.83 (s, 3H, H8), 2.17 (d, <sup>4</sup>J<sub>HH</sub> = 1.4 Hz, 3H, H3) ppm;

<sup>13</sup>C{<sup>1</sup>H}-NMR (126 MHz, CDCl<sub>3</sub>): δ = 160.4 (C7), 147.9 (C2), 134.0 (C1), 129.0 (C4), 128.5 (C5), 114.1 (C6), 55.5 (C8), 24.0 (C3) ppm; IR (ATR):  $\tilde{\nu}$  = 3098 (w), 2958 (w), 2840 (w), 1606 (m), 1575 (w), 1513 (s), 1463 (m), 1441 (w), 1417 (w), 1334 (s), 1292 (s), 1246 (s), 1178 (s), 1115 (w), 1085 (w), 1028 (s), 955 (w), 831 (s), 808 (s), 764 (m), 728 (w), 709 (w) cm<sup>-1</sup>; GC-EI-MS: *m/z* [M-H]<sup>+</sup> calcd. for C<sub>10</sub>H<sub>11</sub>NO<sub>3</sub><sup>+</sup>: 193.07334; found: 193.07329.

### (Z)-1-Fluoro-4-(1-nitroprop-1-en-2-yl)benzene (Z-4)

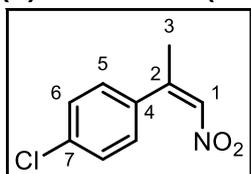


Prepared according to general procedure **C**, **E-4** (91 mg) was converted to **Z-4** yielding a yellow oil as a mixture of isomers (68.0 mg, 0.38 mmol, 75%, *Z:E* = 88:12).

$R_f$  = 0.22 (Et<sub>2</sub>O:*n*-pentane, 5:95); **<sup>1</sup>H-NMR** (500 MHz, CDCl<sub>3</sub>):  $\delta$  = 7.22 – 7.17 (m, 2H, H5), 7.12 – 7.07 (m, 2H, H6), 7.06 (q, <sup>4</sup>*J*<sub>HH</sub> = 1.4 Hz, 1H, H1), 2.18 (d, <sup>4</sup>*J*<sub>HH</sub> = 1.4 Hz, 3H, H3) ppm; **<sup>13</sup>C{<sup>1</sup>H}-NMR** (126 MHz, CDCl<sub>3</sub>):

$\delta$  = 163.0 (d, <sup>1</sup>*J*<sub>CF</sub> = 249.0 Hz, C7), 147.4 (C2), 134.8 (C1), 133.0 (d, <sup>4</sup>*J*<sub>CF</sub> = 3.6 Hz, C4), 128.6 (d, <sup>3</sup>*J*<sub>CF</sub> = 8.4 Hz, C5), 115.8 (d, <sup>2</sup>*J*<sub>CF</sub> = 21.9 Hz, C6), 24.2 (C3) ppm; **<sup>19</sup>F-NMR** (470 MHz, CDCl<sub>3</sub>):  $\delta$  = -112.06 (m) ppm; **IR** (ATR):  $\tilde{\nu}$  = 3105 (w), 2985 (w), 2866 (w), 1635 (w), 1603 (m), 1557 (w), 1516 (s), 1433 (w), 1405 (w), 1336 (s), 1302 (w), 1223 (s), 1160 (m), 1099 (w), 1032 (w), 1015 (w), 956 (w), 834 (s), 765 (m), 713 (m) cm<sup>-1</sup>; **GC-ESI-MS**: *m/z* [M-H]<sup>+</sup> calcd. for C<sub>9</sub>H<sub>8</sub>NO<sub>2</sub>F<sup>+</sup>: 181.05336; found: 181.05328.

### (Z)-1-Chloro-4-(1-nitroprop-1-en-2-yl)benzene (Z-5)

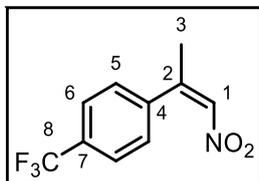


Prepared according to general procedure **C**, **E-5** (99 mg) was converted to **Z-5** yielding a yellow oil as a mixture of isomers (80.5 mg, 0.41 mmol, 82%, *Z:E* = 92:08).

$R_f$  = 0.22 (Et<sub>2</sub>O:*n*-pentane, 5:95); **<sup>1</sup>H-NMR** (600 MHz, CDCl<sub>3</sub>):  $\delta$  = 7.39 – 7.36 (m, 2H, H6), 7.16 – 7.13 (m, 2H, H5), 7.06 (q, <sup>4</sup>*J*<sub>HH</sub> = 1.5 Hz, 1H, H1), 2.17 (d, <sup>4</sup>*J*<sub>HH</sub> = 1.5 Hz, 3H, H3) ppm; **<sup>13</sup>C{<sup>1</sup>H}-NMR** (151 MHz, CDCl<sub>3</sub>):

$\delta$  = 147.3 (C2), 135.6 (C4), 135.1 (C7), 134.9 (C1), 129.0 (C6), 128.0 (C5), 24.1 (C3) ppm; **IR** (ATR):  $\tilde{\nu}$  = 3101 (w), 2984 (w), 1641 (w), 1595 (w), 1556 (w), 1516 (s), 1491 (m), 1432 (w), 1399 (w), 1372 (w), 1335 (s), 1209 (w), 1093 (m), 1078 (w), 1031 (w), 1013 (m), 956 (w), 827 (s), 772 (m), 763 (m), 718 (w) cm<sup>-1</sup>; **GC-ESI-MS**: *m/z* [M-H]<sup>+</sup> calcd. for C<sub>9</sub>H<sub>8</sub>NO<sub>2</sub>Cl<sup>+</sup>: 197.02381; found: 197.02384. The analytical data are in agreement with the literature.<sup>[11]</sup>

### (Z)-1-(1-Nitroprop-1-en-2-yl)-4-(trifluoromethyl)benzene (Z-6)

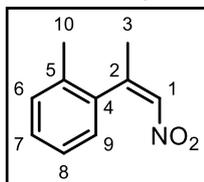


Prepared according to general procedure **C**, **E-6** (116 mg) was converted to **Z-6** yielding a yellow oil as a mixture of isomers (101.9 mg, 0.44 mmol, 88%, *Z:E* = 89:11).

$R_f$  = 0.14 (Et<sub>2</sub>O:*n*-pentane, 5:95); **<sup>1</sup>H-NMR** (500 MHz, CDCl<sub>3</sub>):  $\delta$  = 7.67 (d, <sup>3</sup>*J*<sub>HH</sub> = 8.0 Hz, 2H, H6), 7.31 (d, <sup>3</sup>*J*<sub>HH</sub> = 8.0 Hz, 2H, H5), 7.10 (q, <sup>4</sup>*J*<sub>HH</sub> = 1.4 Hz, 1H, H1), 2.20 (d, <sup>4</sup>*J*<sub>HH</sub> = 1.4 Hz, 3H, H3) ppm; **<sup>13</sup>C{<sup>1</sup>H}-NMR** (126

MHz, CDCl<sub>3</sub>):  $\delta$  = 147.2 (C2), 141.2 (q, <sup>5</sup>*J*<sub>CF</sub> = 1.2 Hz, C4), 135.3 (C1), 130.9 (q, <sup>2</sup>*J*<sub>CF</sub> = 32.7 Hz, C7), 126.8 (C5), 125.8 (q, <sup>3</sup>*J*<sub>CF</sub> = 3.8 Hz, C6), 122.9 (q, <sup>1</sup>*J*<sub>CF</sub> = 272.6 Hz, C8), 24.1 (C3) ppm; **<sup>19</sup>F-NMR** (470 MHz, CDCl<sub>3</sub>):  $\delta$  = -62.83 (s) ppm; **IR** (ATR):  $\tilde{\nu}$  = 3110 (w), 2987 (w), 2859 (w), 1647 (w), 1617 (w), 1525 (s), 1512 (m), 1434 (w), 1408 (w), 1352 (m), 1319 (s), 1208 (w), 1164 (m), 1110 (s), 1089 (m), 1062 (s), 1032 (w), 1016 (m), 956 (w), 840 (s), 767 (w), 730 (m); **GC-ESI-MS**: *m/z* [M-H]<sup>+</sup> calcd. for C<sub>10</sub>H<sub>7</sub>NO<sub>2</sub>F<sub>3</sub><sup>+</sup>: 230.04234; found: 230.04245.

### (Z)-1-Methyl-2-(1-nitroprop-1-en-2-yl)benzene (Z-7)

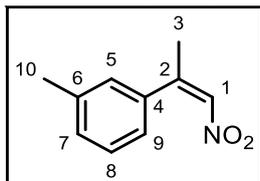


Prepared according to general procedure **C**, **E-7** (89 mg) was converted to **Z-7** yielding a yellow oil as a mixture of isomers (53.4 mg, 0.30 mmol, 60%, *Z:E* = 88:12). The *Z*-isomer could not be isolated cleanly and was not progressed for further hydrogenation analysis.

$R_f$  = 0.29 (Et<sub>2</sub>O:*n*-pentane, 5:95); **<sup>1</sup>H-NMR** (500 MHz, CDCl<sub>3</sub>):  $\delta$  = 7.27 – 7.18 (m, 3H, H6, H7, H8), 7.16 (q, <sup>4</sup>*J*<sub>HH</sub> = 1.5 Hz, 1H, H1), 6.97 (d, <sup>3</sup>*J*<sub>HH</sub> = 7.6 Hz,

1H, H9), 2.22 (s, 3H, H10), 2.14 (d, <sup>4</sup>*J*<sub>HH</sub> = 1.5 Hz, 3H, H3) ppm; **<sup>13</sup>C{<sup>1</sup>H}-NMR** (126 MHz, CDCl<sub>3</sub>):  $\delta$  = 149.6 (C2), 137.5 (C4), 135.6 (C1), 133.6 (C5), 130.4 (C6), 128.3 (C7), 126.2 (C8), 125.3 (C9), 24.1 (C3), 19.2 (C10) ppm; **IR** (ATR):  $\tilde{\nu}$  = 2925 (w), 1724 (w), 1642 (w), 1601 (w), 1556 (m), 1519 (s), 1488 (w), 1457 (w), 1429 (w), 1372 (w), 1348 (s), 1335 (m), 1195 (w), 1125 (w), 1075 (w), 1045 (w), 958 (w), 830 (w), 773 (m), 752 (m), 724 (m) cm<sup>-1</sup>; **GC-ESI-MS**: *m/z* [M-H]<sup>+</sup> calcd. for C<sub>10</sub>H<sub>10</sub>NO<sub>2</sub><sup>+</sup>: 176.07061; found: 176.07086.

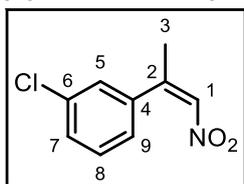
### (Z)-1-Methyl-3-(1-nitroprop-1-en-2-yl)benzene (Z-8)



Prepared according to general procedure **C**, **E-8** (89 mg) was converted to **Z-8** yielding a yellow oil as a mixture of isomers (77.3 mg, 0.44 mmol, 87%, *Z:E* = 95:05).

$R_f$  = 0.29 (Et<sub>2</sub>O:*n*-pentane, 5:95); <sup>1</sup>H-NMR (600 MHz, CDCl<sub>3</sub>): δ = 7.32 – 7.26 (m, 1H, H8), 7.20 – 7.18 (m, 1H, H5), 7.05 (q, <sup>4</sup>J<sub>HH</sub> = 1.4 Hz, 1H, H1), 7.01 – 6.99 (m, 2H, H7, H9), 2.37 (s, 3H, H10), 2.18 (d, <sup>4</sup>J<sub>HH</sub> = 1.4 Hz, 3H, H3) ppm; <sup>13</sup>C{<sup>1</sup>H}-NMR (151 MHz, CDCl<sub>3</sub>): δ = 148.8 (C2), 138.4 (C6), 137.3 (C4), 134.4 (C1), 129.8 (C5), 128.6 (C8), 126.9 (C7), 123.5 (C9), 24.3 (C3), 21.6 (C10) ppm; IR (ATR):  $\tilde{\nu}$  = 3099 (w), 2922 (w), 2864 (w), 1635 (w), 1603 (w), 1583 (w), 1556 (w), 1517 (s), 1431 (w), 1374 (w), 1337 (s), 1261 (w), 1236 (w), 1101 (w), 1084 (w), 1034 (w), 957 (w), 909 (w), 884 (w), 788 (s), 763 (w), 700 (m) cm<sup>-1</sup>; GC-EI-MS: *m/z* [M-H]<sup>+</sup> calcd. for C<sub>10</sub>H<sub>10</sub>NO<sub>2</sub><sup>+</sup>: 176.07061; found: 176.07054.

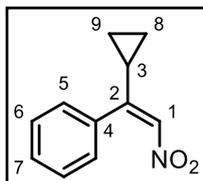
### (Z)-1-Chloro-3-(1-nitroprop-1-en-2-yl)benzene (Z-9)



Prepared according to general procedure **C**, **E-9** (99 mg) was converted to **Z-9** yielding a yellow oil as a mixture of isomers (80.4 mg, 0.41 mmol, 82%, *Z:E* = 93:07).

$R_f$  = 0.21 (Et<sub>2</sub>O:*n*-pentane, 5:95); <sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>): δ = 7.38 – 7.29 (m, 2H, H5, H7), 7.20 – 7.17 (m, 1H, H8), 7.07 – 7.05 (m, 2H, H9, H1), 2.18 (d, <sup>4</sup>J<sub>HH</sub> = 1.5 Hz, 3H, H3) ppm; <sup>13</sup>C{<sup>1</sup>H}-NMR (151 MHz, CDCl<sub>3</sub>): δ = 147.1 (C2), 139.1 (C4), 135.1 (C1), 130.1 (C6), 129.0 (C5), 126.5 (C7, C8), 124.6 (C9), 24.1 (C3) ppm; IR (ATR):  $\tilde{\nu}$  = 3102 (w), 2920 (w), 1642 (w), 1594 (w), 1556 (m), 1519 (s), 1473 (w), 1432 (w), 1415 (w), 1373 (w), 1345 (s), 1334 (s), 1301 (w), 1209 (w), 1168 (w), 1106 (w), 1077 (m), 1034 (w), 999 (w), 957 (w), 934 (w), 882 (m), 819 (m), 787 (s), 763 (m), 719 (w), 691 (s), 678 (m) cm<sup>-1</sup>; GC-EI-MS: *m/z* [M-H]<sup>+</sup> calcd. for C<sub>9</sub>H<sub>7</sub>NO<sub>2</sub>Cl<sup>+</sup>: 196.01598; found: 196.01592.

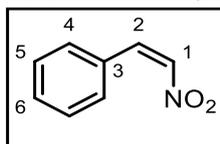
### (Z)-(1-Cyclopropyl-2-nitrovinyl)benzene (Z-10)



Prepared according to general procedure **C**, **E-10** (95 mg) was converted to **Z-10** yielding a yellow oil as a mixture of isomers (78.3 mg, 0.41 mmol, 83%, *Z:E* = 86:14).

$R_f$  = 0.18 (Et<sub>2</sub>O:*n*-pentane, 5:95); <sup>1</sup>H-NMR (500 MHz, CDCl<sub>3</sub>): δ = 7.41 – 7.36 (m, 3H, H6, H7), 7.13 (s, 1H, H1), 7.11 – 7.08 (m, 2H, H5), 1.76 – 1.70 (m, 1H, H3), 0.97 – 0.92 (m, 2H, H8/9), 0.69 – 0.62 (m, 2H, H8/9) ppm; <sup>13</sup>C{<sup>1</sup>H}-NMR (126 MHz, CDCl<sub>3</sub>): δ = 156.1 (C2), 134.0 (C4), 133.9 (C1), 128.6 (C7), 128.4 (C6), 127.1 (C5), 17.6 (C3), 7.3 (C8, C9) ppm; IR (ATR):  $\tilde{\nu}$  = 3092 (w), 3019 (w), 2972 (w), 2926 (w), 2856 (w), 1621 (w), 1597 (w), 1576 (w), 1514 (s), 1443 (w), 1424 (w), 1369 (w), 1335 (s), 1216 (m), 1176 (w), 1158 (w), 1115 (w), 1075 (w), 1060 (w), 1035 (w), 995 (m), 915 (w), 871 (m), 815 (m), 772 (m), 744 (m), 721 (m), 699 (s), 669 (w) cm<sup>-1</sup>; GC-EI-MS: *m/z* [M-O]<sup>+</sup> calcd. for C<sub>11</sub>H<sub>11</sub>NO<sup>+</sup>: 173.08352; found: 178.08346.

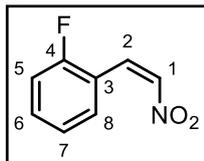
### (Z)-(2-Nitrovinyl)benzene (Z-11)



Prepared according to general procedure **C**, (*E*)-(2-nitrovinyl)benzene (75 mg) was converted to **Z-11** yielding a yellow oil as an inseparable mixture of isomers (49.9 mg, 0.33 mmol, 67%, *Z:E* = 46:54).

$R_f$  = 0.68 (Et<sub>2</sub>O:*n*-pentane, 5:95); <sup>1</sup>H-NMR (500 MHz, CDCl<sub>3</sub>): δ = 7.53 – 7.43 (m, 5H, H4, H5, H6), 6.97 (d, <sup>3</sup>J<sub>HH</sub> = 9.5 Hz, 1H, H1), 6.78 (d, <sup>3</sup>J<sub>HH</sub> = 9.5 Hz, 1H, H2) ppm; <sup>13</sup>C{<sup>1</sup>H}-NMR (126 MHz, CDCl<sub>3</sub>): δ = 135.9 (C1), 133.9 (C2), 130.8 (C3), 130.6 (C5), 130.0 (C4), 128.7 (C6) ppm; IR (ATR):  $\tilde{\nu}$  = 3110 (w), 3035 (w), 1634 (w), 1602 (w), 1577 (w), 1549 (w), 1516 (s), 1495 (m), 1449 (w), 1374 (w), 1339 (s), 1260 (w), 1201 (w), 1180 (w), 1072 (w), 1029 (w), 964 (m), 837 (w), 792 (w), 764 (m), 737 (w), 696 (s), 680 (m) cm<sup>-1</sup>; GC-EI-MS: *m/z* [M]<sup>+</sup> calcd. for C<sub>8</sub>H<sub>7</sub>NO<sub>2</sub><sup>+</sup>: 149.05; found: 149.08. The analytical data are in agreement with the literature.<sup>[12]</sup>

**(Z)-1-Fluoro-2-(2-nitrovinyl)benzene (E-12)**



Prepared according to general procedure **C**, **E-12** (84 mg) was converted to **Z-12** yielding a yellow oil as an inseparable mixture of isomers (23.1 mg, 0.14 mmol, 28%, *Z:E* = 67:33).

$R_f$  = 0.65 (Et<sub>2</sub>O:*n*-pentane, 5:95); <sup>1</sup>H-NMR (600 MHz, CDCl<sub>3</sub>): δ = 7.50 – 7.46 (m, 1H, H8), 7.44 – 7.39 (m, 1H, C6), 7.20 – 7.15 (m, 1H, C7), 7.15 – 7.09 (m, 1H, C5), 7.07 (d, <sup>3</sup>J<sub>HH</sub> = 9.2 Hz, 1H, C2), 6.89 (d, <sup>3</sup>J<sub>HH</sub> = 9.2 Hz, 1H, C1) ppm; <sup>13</sup>C{<sup>1</sup>H}-NMR (151 MHz, CDCl<sub>3</sub>): δ = 160.5 (d, <sup>1</sup>J<sub>CF</sub> = 251.8 Hz, C4), 138.0 (d, <sup>3</sup>J<sub>CF</sub> = 1.1 Hz, C2), 132.3 (d, <sup>3</sup>J<sub>CF</sub> = 8.8 Hz, C6), 130.6 (d, <sup>3</sup>J<sub>CF</sub> = 1.9 Hz, C8), 127.0 (d, <sup>4</sup>J<sub>CF</sub> = 3.6 Hz, C1), 124.3 (d, <sup>4</sup>J<sub>CF</sub> = 3.5 Hz, C7), 119.3 (d, <sup>2</sup>J<sub>CF</sub> = 13.5 Hz), 115.9 (d, <sup>2</sup>J<sub>CF</sub> = 21.6 Hz, C5) ppm; <sup>19</sup>F-<sup>1</sup>H-NMR (470 MHz, CDCl<sub>3</sub>): δ = -111.60 (s) ppm; IR (ATR):  $\tilde{\nu}$  = 3110 (w), 2925 (w), 2855 (w), 1637 (w), 1611 (w), 1579 (w), 1517 (s), 1486 (m), 1456 (m), 1372 (w), 1339 (s), 1283 (w), 1222 (w), 1155 (w), 1098 (w), 1033 (w), 964 (m), 890 (w), 865 (w), 833 (w), 820 (w), 809 (w), 755 (s), 732 (m) cm<sup>-1</sup>; GC-EI-MS: *m/z*: [M]<sup>+</sup> calcd. for C<sub>8</sub>H<sub>8</sub>FNO<sub>2</sub><sup>+</sup>: 167.04; found: 167.07.

## Synthesis of nitroalkanes

### General procedure D for the preparation of the racemic nitroalkanes

Following a modified literature procedure,<sup>[1]</sup> the *E*-nitroalkene **E-1-10** (1 eq.) was dissolved in THF:MeOH (10:1, 0.2 M) and NaBH<sub>4</sub> (1.5 eq.) was added portionwise (gas evolution). The reaction mixture was stirred at room temperature and monitored by TLC. Upon conversion of the starting material and cease of the gas evolution, the reaction was quenched with H<sub>2</sub>O. The aqueous layer was extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 x) and the combined organic layers were washed with brine, dried over MgSO<sub>4</sub>, filtered and concentrated *in vacuo*. No further purification was required.

### General procedure E for the preparation of the (*S*)-nitroalkanes

Following a modified literature procedure,<sup>[1]</sup> the *E*-nitroalkene (0.2 mmol, 1 eq.) was weighed into a 2 mL vial. The specified catalyst (**A**: 3.8 mg or **B**: 4.2 mg, 0.01 mmol, 0.05 eq.) and the Hantzsch ester (di-*tert*-butyl 2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate, HE) (68 mg, 0.22 mmol, 1.1 eq.) were added and the walls of the vial were rinsed with toluene (616  $\mu$ L, 0.32 M). A rubber septum and parafilm were used to seal the vial, which was then placed in a preheated metal heating block at 40 °C for 48 h (Figure 3). After that time, the crude reaction mixture was filtered through a plug of silica, which was rinsed with Et<sub>2</sub>O:*n*-pentane (2:98) to remove the catalyst and most of the oxidized Hantzsch ester. The filtrate was concentrated *in vacuo* and purified by column chromatography to yield the (*S*)-nitroalkane. **Reported yields and stereoselectivities are an average of two duplicate reactions.** The enantiomeric ratio was determined *via* chiral HPLC and a spectrum of a single reaction is shown.

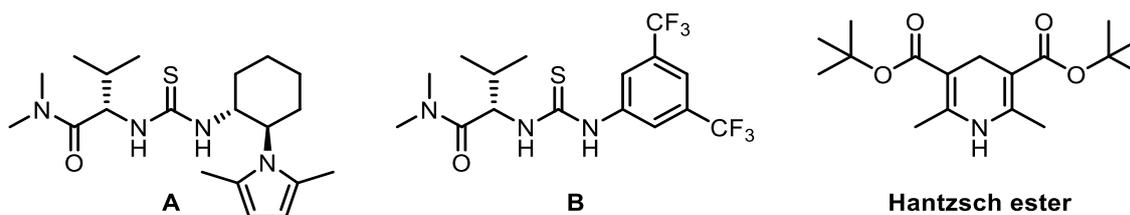


Figure 4: Structures of the used catalysts and Hantzsch ester.

### General procedure F for the preparation of the (*R*)-nitroalkanes

Following a modified literature procedure,<sup>[1]</sup> the *Z*-nitroalkene (0.2 mmol, 1 eq.) was weighed into a 2 mL vial. The specified catalyst (**A**: 3.8 mg or **B**: 4.2 mg, 0.01 mmol, 0.05 eq.) and the Hantzsch ester (di-*tert*-butyl 2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate, HE) (68 mg, 0.22 mmol, 1.1 eq.) were added and the walls of the vial were rinsed with toluene (616  $\mu$ L, 0.32 M). A rubber septum and parafilm was used to seal the vial which was then placed in a preheated metal heating block at 40 °C for 48 h (Figure 3). After that time, the crude reaction mixture was filtered through a plug of silica, which was rinsed with Et<sub>2</sub>O:*n*-pentane (2:98) to remove the catalyst and most of the oxidized Hantzsch ester. The filtrate was concentrated *in vacuo* and purified by column chromatography to yield the (*R*)-nitroalkane. **Reported yields and stereoselectivities are an average of two duplicate reactions.** The enantiomeric ratio was determined *via* chiral HPLC and a spectrum of a single reaction is shown.

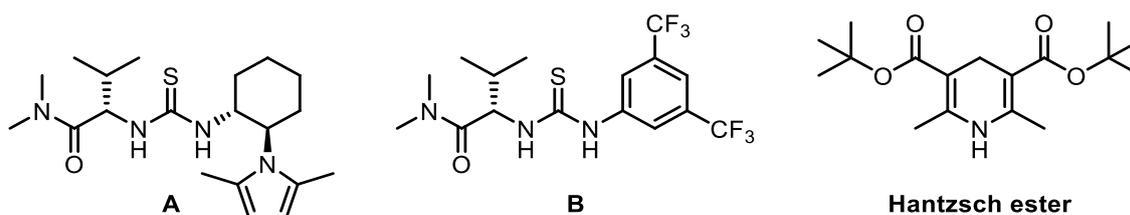
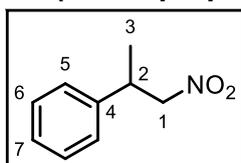


Figure 5: Structures of the used catalysts and Hantzsch ester.

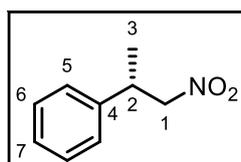
## Preparation and analytical data of the nitroalkanes

### *rac*-(1-Nitropropan-2-yl)benzene (*rac*-13)



Following general procedure **D**, **E-1** (33 mg, 0.2 mmol, 1 eq.) was treated with NaBH<sub>4</sub> (11 mg, 1.5 mmol, 1.5 eq.) in THF:MeOH (10:1, 1 mL) to obtain *rac*-**13** after 4 h as a colorless oil (19.0 mg, 0.12 mmol, 58%).

### (*S*)-(1-Nitropropan-2-yl)benzene (*S*-13)

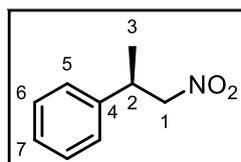


Prepared according to general procedure **E**, **E-1** (33 mg) was converted to (*S*)-**13**, a colorless oil, using the catalyst stated in Table 1. The outcome for the given catalyst is summarized in Table 1 with the enantiomeric ratio determined by chiral HPLC (Reprosil OM, *n*-hexane:*i*PrOH 97:3, 1.0 mL/min, λ = 210 nm).

Table 1: Reaction outcome for the hydrogenation of **E-1** to (*S*)-**13**.

| entry | catalyst | yield   |           | er  | t <sub>R</sub> (minor) | t <sub>R</sub> (major) |            |
|-------|----------|---------|-----------|-----|------------------------|------------------------|------------|
| 1     | <b>A</b> | 31.6 mg | 0.19 mmol | 96% | 04:96                  | 10.561 min             | 13.396 min |
| 2     | <b>B</b> | 28.5 mg | 0.17 mmol | 86% | 09:91                  | 10.511 min             | 13.350 min |

### (*R*)-(1-Nitropropan-2-yl)benzene (*R*-13)



Prepared according to general procedure **F**, **Z-1** (33 mg) was converted to (*R*)-**13**, a colorless oil, using the catalyst stated in Table 2. The outcome for the given catalyst is summarized in Table 2 with the enantiomeric ratio determined by chiral HPLC (Reprosil OM, *n*-hexane:*i*PrOH 97:3, 1.0 mL/min, λ = 210 nm).

Table 2: Reaction outcome for the hydrogenation of **Z-1** to (*R*)-**13**.

| entry | catalyst | yield   |           | er  | t <sub>R</sub> (major) | t <sub>R</sub> (minor) |            |
|-------|----------|---------|-----------|-----|------------------------|------------------------|------------|
| 1     | <b>A</b> | 29.0 mg | 0.18 mmol | 88% | 84:16                  | 10.544 min             | 13.454 min |
| 2     | <b>B</b> | 31.0 mg | 0.19 mmol | 94% | 93:07                  | 10.491 min             | 13.388 min |

(*S*)-**13** (er 04:96): [α]<sub>D</sub><sup>25</sup> = -46.7 (c = 0.5 in CHCl<sub>3</sub>); (*R*)-**13** (er 93:07): [α]<sub>D</sub><sup>25</sup> = +39.9 (c = 0.5 in CHCl<sub>3</sub>); *R<sub>f</sub>* = 0.53 (Et<sub>2</sub>O:*n*-pentane, 5:95); <sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>): δ = 7.39 – 7.30 (m, 2H, H6), 7.30 – 7.21 (m, 3H, H5, H7), 4.59 – 4.46 (m, 2H, H1), 3.64 (h, <sup>3</sup>J<sub>HH</sub> = 7.0 Hz, 1H, H2), 1.39 (d, <sup>3</sup>J<sub>HH</sub> = 7.0 Hz, 3H, H3) ppm; <sup>13</sup>C{<sup>1</sup>H}-NMR (101 MHz, CDCl<sub>3</sub>): δ = 141.0 (C4), 129.1 (C6), 127.7 (C7), 127.1 (C5), 82.0 (C1), 38.8 (C2), 18.9 (C3) ppm; IR (ATR):  $\tilde{\nu}$  = 3673 (w), 2972 (w), 1604 (w), 1546 (s), 1495 (w), 1454 (m), 1431 (w), 1377 (m), 1332 (w), 1310 (w), 1291 (w), 1226 (w), 1203 (w), 1120 (w), 1074 (w), 1022 (w), 900 (w), 796 (w), 765 (m), 697 (s) cm<sup>-1</sup>; GC-EI-MS: *m/z*: [M]<sup>+</sup> calcd. for C<sub>9</sub>H<sub>11</sub>NO<sub>2</sub><sup>+</sup>: 165.10; found: 165.16. The analytical data are in agreement with the literature.<sup>[11]</sup>

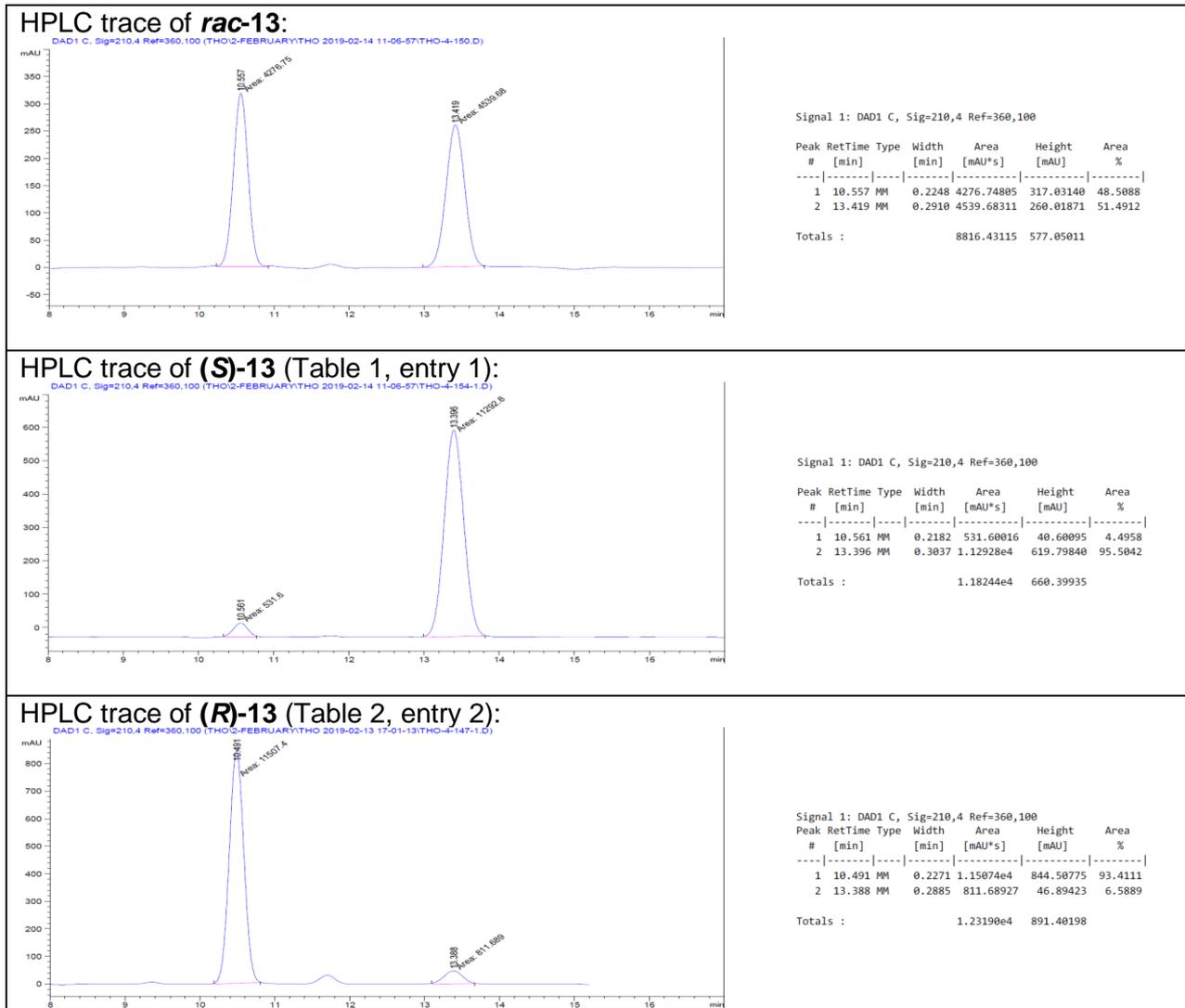
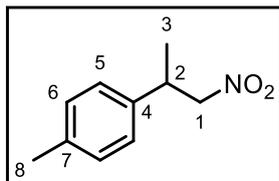


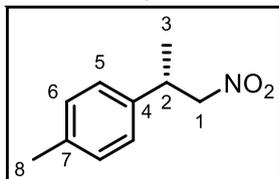
Figure 6: HPLC traces of 13; top: *rac*-13, middle: (*S*)-13 (Table 1, entry 1), bottom: (*R*)-13 (Table 2, entry 2).

### ***rac*-1-Methyl-4-(1-nitropropan-2-yl)benzene (*rac*-14)**



Following general procedure **D**, **E-2** (35 mg, 0.2 mmol, 1 eq.) was treated with NaBH<sub>4</sub> (11 mg, 0.3 mmol, 1.5 eq.) in THF:MeOH (10:1, 1.4 mL) to obtain **rac-14** after 4 h as a colorless oil (11.1 mg, 0.06 mmol, 31%).

### **(*S*)-1-Methyl-4-(1-nitropropan-2-yl)benzene ((*S*)-14)**

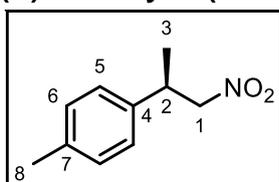


Prepared according to general procedure **E**, **E-2** (35 mg) was converted to **(S)-14**, a colorless oil, using the catalyst stated in Table 3. The outcome for the given catalyst is summarized in Table 3 with the enantiomeric ratio determined by chiral HPLC (Reprosil OM, *n*-hexane:*i*PrOH 99:1, 1.0 mL/min,  $\lambda$  = 210 nm).

Table 3: Reaction outcome for the hydrogenation of **E-2** to **(S)-14**.

| entry | catalyst | yield               | er         | t <sub>R</sub> (minor) | t <sub>R</sub> (major) |
|-------|----------|---------------------|------------|------------------------|------------------------|
| 1     | <b>A</b> | 31.2 mg, 0.17 mmol, | <b>87%</b> | 9.674 min              | 14.603 min             |
| 2     | <b>B</b> | 26.8 mg, 0.15 mmol, | 75%        | 9.727 min              | 14.660 min             |

### **(*R*)-1-Methyl-4-(1-nitropropan-2-yl)benzene ((*R*)-14)**



Prepared according to general procedure **F**, **Z-2** (35 mg) was converted to **(R)-14**, a colorless oil, using the catalyst stated in Table 4. The outcome for the given catalyst is summarized in Table 4 with the enantiomeric ratio determined by chiral HPLC (*n*-hexane:*i*PrOH 99:1, 1.0 mL/min,  $\lambda$  = 210 nm).

Table 4: Reaction outcome for the hydrogenation of **Z-2** to **(R)-14**.

| entry          | catalyst | yield               | er         | t <sub>R</sub> (major) | t <sub>R</sub> (minor) |
|----------------|----------|---------------------|------------|------------------------|------------------------|
| 1 <sup>a</sup> | <b>A</b> | 26.3 mg, 0.15 mmol, | 74%        | 11.975 min             | 20.508 min             |
| 2              | <b>B</b> | 33.8 mg, 0.19 mmol, | <b>94%</b> | 9.648 min              | 14.607 min             |

<sup>a</sup> measured on a different HPLC system; racemic: 12.252 min and 21.199 min

**(S)-14** (er 07:93):  $[\alpha]_{\text{D}}^{25} = -45.7$  ( $c = 0.5$  in CHCl<sub>3</sub>); **(R)-14** (er 88:12):  $[\alpha]_{\text{D}}^{25} = +41.2$  ( $c = 0.5$  in CHCl<sub>3</sub>);  $R_f = 0.55$  (Et<sub>2</sub>O:*n*-pentane, 5:95); <sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>):  $\delta = 7.17 - 7.09$  (m, 4H, H5, H6), 4.56 – 4.43 (m, 2H, H1), 3.60 (se, <sup>3</sup>J<sub>HH</sub> = 7.0 Hz, 1H, H2), 2.33 (s, 3H, H8), 1.36 (d, <sup>3</sup>J<sub>H</sub> = 7.0 Hz, 3H) ppm; <sup>13</sup>C{<sup>1</sup>H}-NMR (101 MHz, CDCl<sub>3</sub>):  $\delta = 138.0$  (C4), 137.4 (C7), 129.8 (C6), 126.9 (C5), 82.2 (C1), 38.5 (C2), 21.2 (C8), 18.9 (C3) ppm; IR (ATR):  $\tilde{\nu} = 2972$  (w), 2922 (w), 1546 (s), 1515 (m), 1455 (w), 1431 (w), 1377 (m), 1310 (w), 1199 (w), 1122 (w), 1032 (w), 1019 (w), 898 (w), 815 (s), 772 (w), 719 (w), 686 (w) cm<sup>-1</sup>; GC-EI-MS:  $m/z$ : ([M]<sup>+</sup> calcd. for C<sub>10</sub>H<sub>13</sub>NO<sub>2</sub><sup>+</sup>: 179.09; found: 179.12. The analytical data are in agreement with the literature.<sup>[13]</sup>

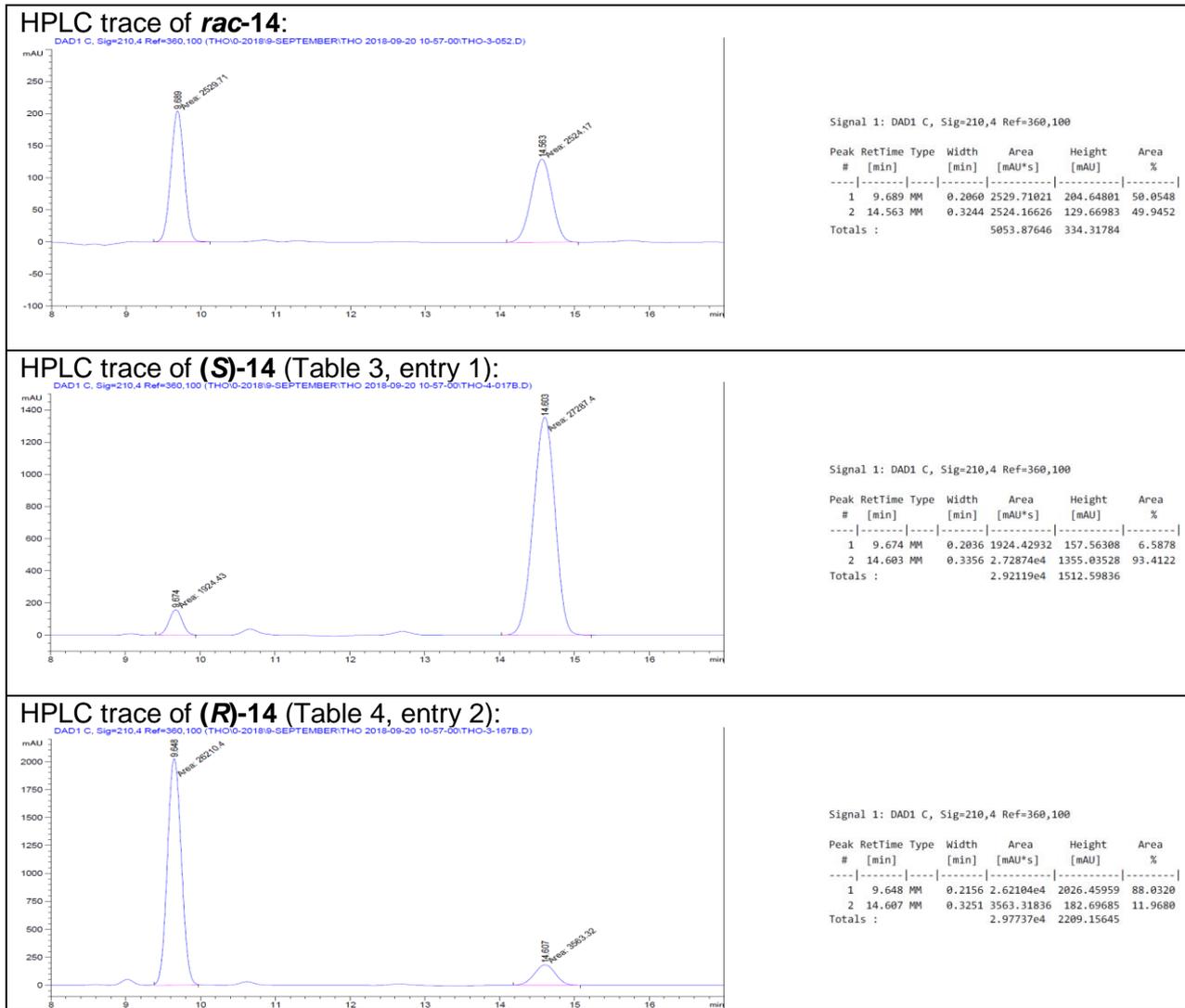
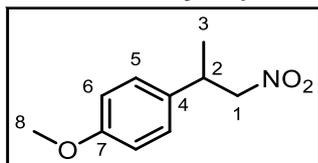
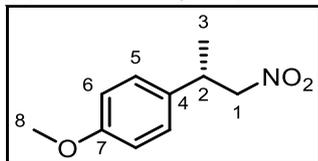


Figure 6: HPLC traces of **14**; top: *rac*-14, middle: (*S*)-14 (Table 3, entry 1), bottom: (*R*)-14 (Table 4, entry 2).

**rac-1-Methoxy-4-(1-nitropropan-2-yl)benzene (rac-15)**

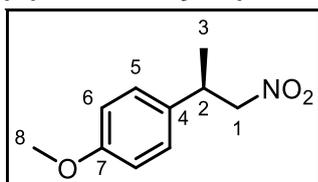
Following general procedure **D**, **E-3** (30 mg, 0.15 mmol, 1 eq.) was treated with NaBH<sub>4</sub> (9 mg, 0.23 mmol, 1.5 eq.) in THF:MeOH (10:1, 1 mL). After stirring for 4 h, a second portion of NaBH<sub>4</sub> (9 mg, 0.23 mmol, 1.5 eq.) was added and the reaction mixture was stirred for 1 h to yield **rac-15** as a colorless oil (18.6 mg, 0.10 mmol, 64%).

**(S)-1-Methoxy-4-(1-nitropropan-2-yl)benzene ((S)-15)**

Prepared according to general procedure **E**, **E-3** (40 mg) was converted to **(S)-15**, a colorless oil, using the catalyst stated in Table 5. The outcome for the given catalyst is summarized in Table 5 with the enantiomeric ratio determined by chiral HPLC (Chiralcel® OJ-H, *n*-hexane:*i*PrOH 98:2, 1.0 mL/min, λ = 210 nm).

Table 5: Reaction outcome for the hydrogenation of **E-3** to **(S)-15**.

| entry | catalyst | yield               | er               | t <sub>R</sub> (minor) | t <sub>R</sub> (major) |
|-------|----------|---------------------|------------------|------------------------|------------------------|
| 1     | <b>A</b> | 30.3 mg, 0.16 mmol, | <b>78% 06:94</b> | 30.029 min             | 35.123 min             |
| 2     | <b>B</b> | 32.2 mg, 0.16 mmol, | 82% 11:89        | 29.766 min             | 34.810 min             |

**(R)-1-Methoxy-4-(1-nitropropan-2-yl)benzene ((R)-15)**

Prepared according to general procedure **F**, **Z-3** (40 mg) was converted to **(R)-15**, a colorless oil, using the catalyst stated in Table 6. The outcome for the given catalyst is summarized in Table 6 with the enantiomeric ratio determined by chiral HPLC (Chiralcel® OJ-H, *n*-hexane:*i*PrOH 98:2, 1.0 mL/min, λ = 210 nm).

Table 6: Reaction outcome for the hydrogenation of **Z-3** to **(R)-15**.

| entry | catalyst | yield               | er               | t <sub>R</sub> (major) | t <sub>R</sub> (minor) |
|-------|----------|---------------------|------------------|------------------------|------------------------|
| 1     | <b>A</b> | 35.0 mg, 0.18 mmol, | <b>90% 85:15</b> | 29.381 min             | 34.895 min             |
| 2     | <b>B</b> | 31.7 mg, 0.16 mmol, | 81% 87:13        | 29:434 min             | 34:923 min             |

**(S)-15** (er 06:94): [α]<sub>D</sub><sup>25</sup> = -48.5 (c = 0.5 in CHCl<sub>3</sub>); **(R)-15** (er 90:10): [α]<sub>D</sub><sup>25</sup> = +42.9 (c = 0.5 in CHCl<sub>3</sub>); *R<sub>f</sub>* = 0.21 (Et<sub>2</sub>O:*n*-pentane, 5:95); <sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>): δ = 7.17 – 7.12 (m, 2H, H5), 6.89 – 6.85 (m, 2H, H6), 4.54 – 4.42 (m, 2H, H1), 3.79 (s, 3H, H8), 3.59 (h, <sup>3</sup>J<sub>HH</sub> = 7.1 Hz, 1H, H2), 1.36 (d, <sup>3</sup>J<sub>HH</sub> = 7.1 Hz, 3H, H3) ppm; <sup>13</sup>C{<sup>1</sup>H}-NMR (101 MHz, CDCl<sub>3</sub>): δ = 159.1 (C7), 133.0 (C4), 128.1 (C5), 114.5 (C6), 82.3 (C1), 55.4 (C8), 38.1 (C2), 19.0 (C3) ppm; IR (ATR):  $\tilde{\nu}$  = 2969 (w), 2936 (w), 2838 (w), 1612 (w), 1585 (w), 1550 (s), 1515 (s), 1459 (w), 1384 (w), 1300 (w), 1250 (m), 1181 (m), 1124 (w), 1038 (w), 1026 (w), 899 (w), 832 (m), 773 (w), 726 (w), 696 (w) cm<sup>-1</sup>; GC-ESI-MS: *m/z*: [M]<sup>+</sup> calcd. for C<sub>10</sub>H<sub>13</sub>NO<sub>3</sub><sup>+</sup>: 195.08899; found: 195.08889. The analytical data are in agreement with the literature.<sup>[13]</sup>

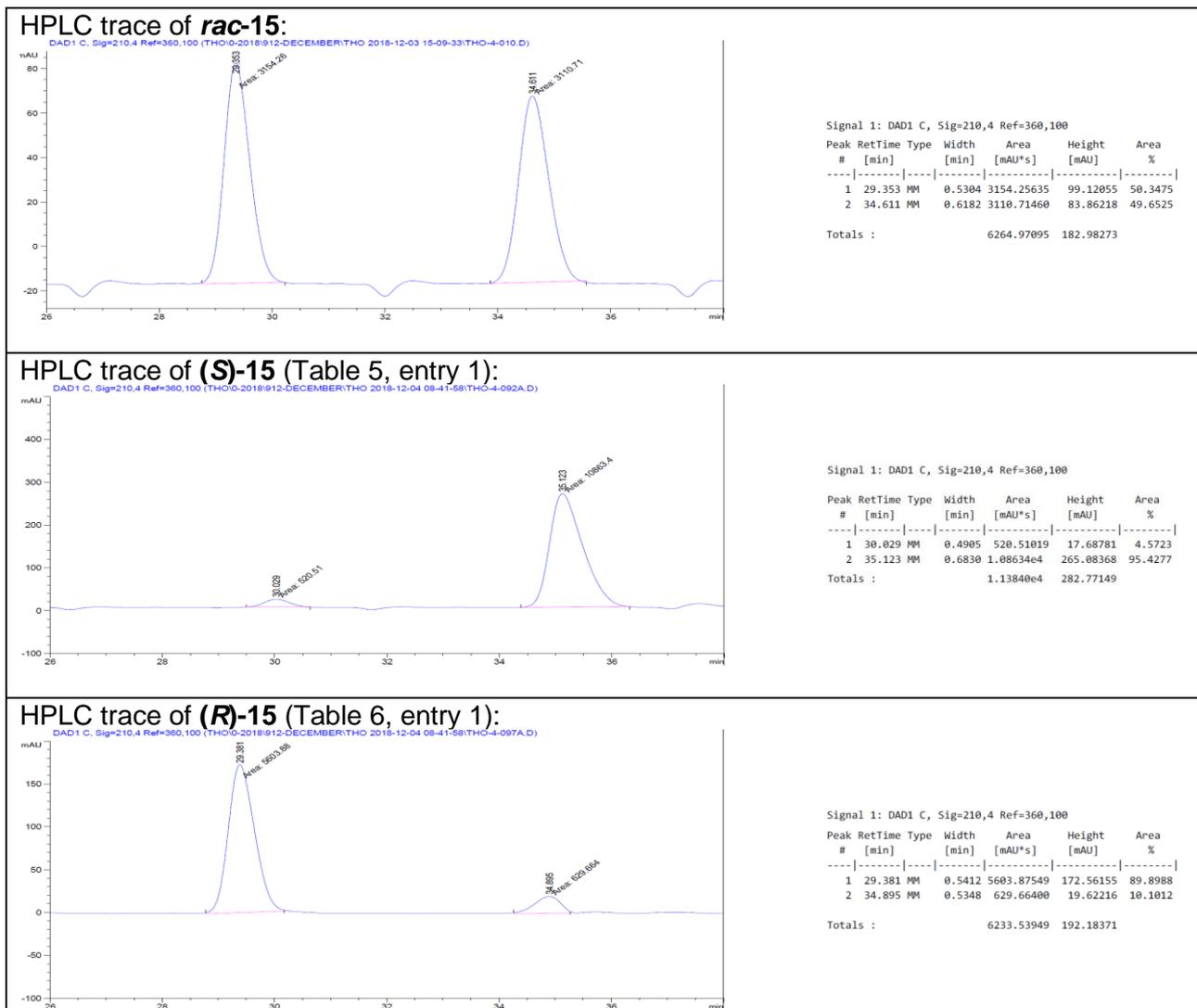
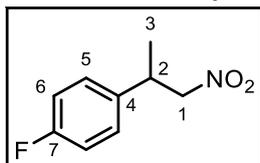
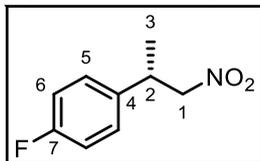


Figure 8: HPLC traces of **15**; top: *rac*-15, middle: (*S*)-15 (Table 5, entry 1); bottom: (*R*)-15 (Table 6, entry 1).

**rac-1-Fluoro-4-(1-nitropropan-2-yl)benzene (*rac*-16)**

Following general procedure **D**, **E-4** (62 mg, 0.34 mmol, 1 eq.) was treated with NaBH<sub>4</sub> (19 mg, 0.51 mmol, 1.5 eq.) in THF:MeOH (10:1, 2.4 mL) to obtain **rac-16** after 5 h as a colorless oil (14.4 mg, 0.08 mmol, 22%).

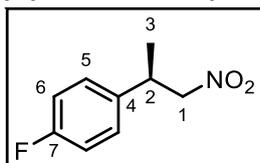
**(S)-1-Fluoro-4-(1-nitropropan-2-yl)benzene ((S)-16)**

Prepared according to general procedure **E**, **E-4** (36 mg) was converted to **(S)-16**, a colorless oil, using the catalyst stated in Table 7. The outcome for the given catalyst is summarized in Table 7 with the enantiomeric ratio determined by chiral HPLC (Reprosil Chiral-OM, *n*-hexane:PrOH 99.7:0.3, 1.0 mL/min, λ = 210 nm).

Table 7: Reaction outcome for the hydrogenation of **E-4** to **(S)-16**.

| entry          | catalyst | yield               | er                      | t <sub>R</sub> (minor) | t <sub>R</sub> (major) |
|----------------|----------|---------------------|-------------------------|------------------------|------------------------|
| 1              | <b>A</b> | 29.3 mg, 0.16 mmol, | <b>80%</b> <b>06:94</b> | 21.277 min             | 24.544 min             |
| 2 <sup>a</sup> | <b>B</b> | 33.0 mg, 0.18 mmol, | 90% 10:90               | 21.618 min             | 25.132 min             |

<sup>a</sup> measured on a different HPLC system; racemic: 20.508 min and 23.457 min

**(R)-1-Fluoro-4-(1-nitropropan-2-yl)benzene ((R)-16)**

Prepared according to general procedure **F**, **Z-4** (36 mg) was converted to **(R)-16**, a colorless oil, using the catalyst stated in Table 8. The outcome for the given catalyst is summarized in Table 8 with the enantiomeric ratio determined by chiral HPLC (Reprosil Chiral-OM, *n*-hexane:PrOH 99.7:0.3, 1.0 mL/min, λ = 210 nm).

Table 8: Reaction outcome for the hydrogenation of **Z-4** to **(R)-16**.

| entry | catalyst | yield               | er                      | t <sub>R</sub> (major) | t <sub>R</sub> (minor) |
|-------|----------|---------------------|-------------------------|------------------------|------------------------|
| 1     | <b>A</b> | 35.5 mg, 0.19 mmol, | 97% 65:35               | 21.159 min             | 24.852 min             |
| 2     | <b>B</b> | 32.7 mg, 0.18 mmol, | <b>89%</b> <b>85:15</b> | 21.489 min             | 25.252 min             |

**(S)-16** (er 07:93): [α]<sub>D</sub><sup>25</sup> = -44.5 (c = 0.5 in CHCl<sub>3</sub>); **(R)-16** (er 86:14): [α]<sub>D</sub><sup>25</sup> = +31.8 (c = 0.5 in CHCl<sub>3</sub>); R<sub>f</sub> = 0.30 (Et<sub>2</sub>O:*n*-pentane, 5:95); <sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>): δ = 7.25 – 7.15 (m, 2H, H5), 7.08 – 6.98 (m, 2H, H6), 4.55 – 4.44 (m, 2H, H1), 3.63 (h, <sup>3</sup>J<sub>HH</sub> = 7.1 Hz, 1H, H2), 1.37 (d, <sup>3</sup>J<sub>HH</sub> = 7.1 Hz, 3H, H3) ppm; <sup>13</sup>C{<sup>1</sup>H}-NMR (101 MHz, CDCl<sub>3</sub>): δ = 162.1 (d, <sup>1</sup>J<sub>CF</sub> = 267.1 Hz, C7), 136.7 (d, <sup>4</sup>J<sub>CF</sub> = 3.3 Hz, C4), 128.6 (d, <sup>3</sup>J<sub>CF</sub> = 8.1 Hz, C5), 116.0 (d, <sup>2</sup>J<sub>CF</sub> = 21.5 Hz, C6), 82.0 (C1), 38.1 (C2), 19.0 (C3) ppm; <sup>19</sup>F-{<sup>1</sup>H}-NMR (376 MHz, CDCl<sub>3</sub>): δ = -114.79 ppm; IR (ATR):  $\tilde{\nu}$  = 2971 (w), 2930 (w), 1605 (w), 1547 (s), 1510 (s), 1456 (w), 1432 (w), 1377 (m), 1343 (w), 1301 (w), 1223 (m), 1161 (m), 1118 (w), 1101 (w), 1028 (w), 1015 (w), 899 (w), 833 (s), 778 (w), 720 (w), 697 (w) cm<sup>-1</sup>; GC-EI-MS: *m/z* [M]<sup>+</sup> calcd. for C<sub>9</sub>H<sub>10</sub>FNO<sub>2</sub><sup>+</sup>: 183.06; found: 183.03. The analytical data are in agreement with the literature.<sup>[1]</sup>

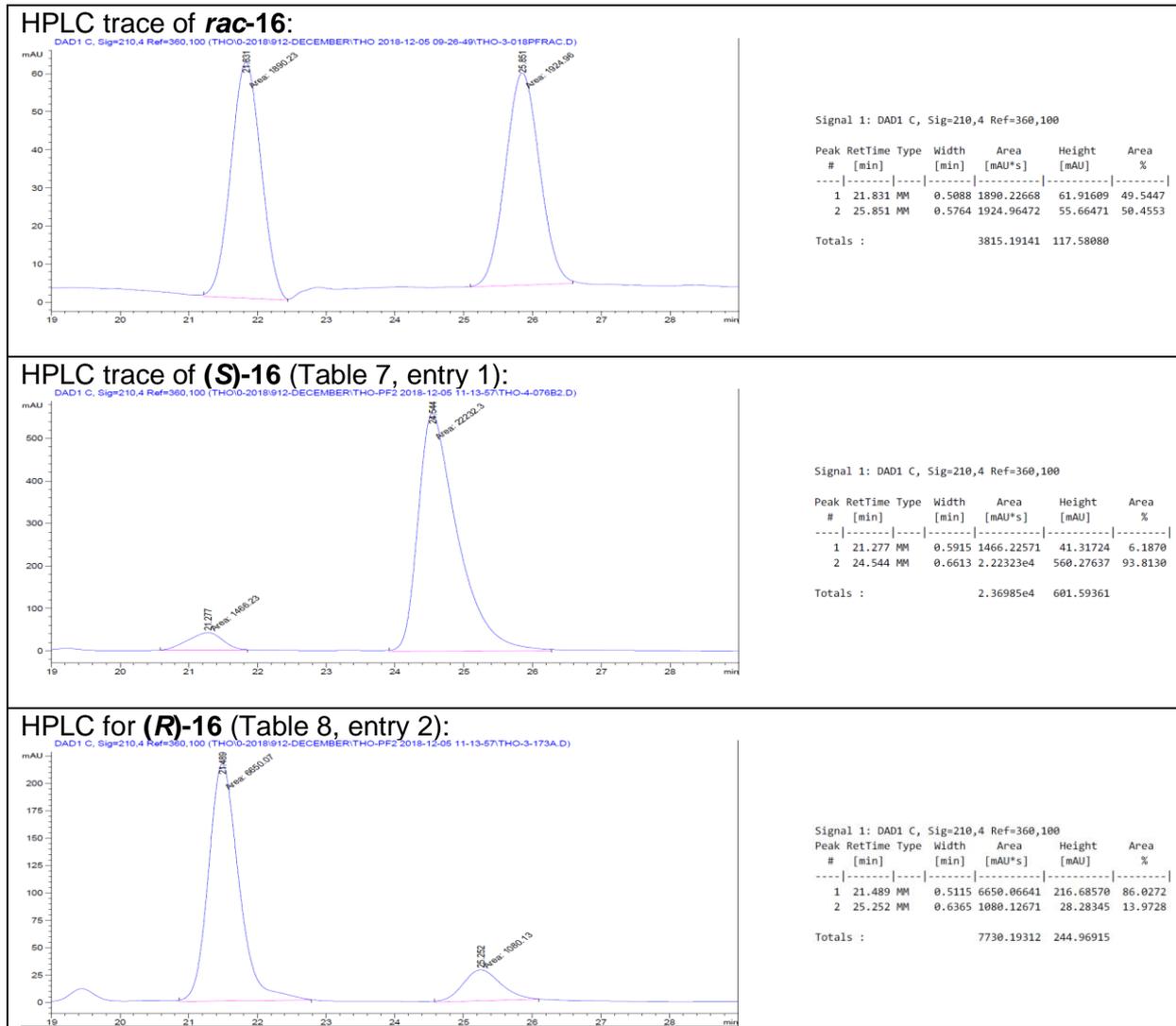
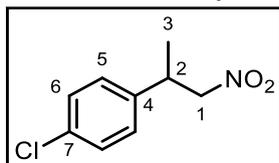
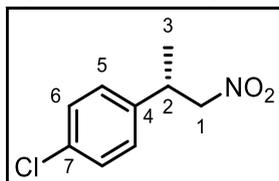


Figure 9: HPLC traces of **16**; top: *rac*-16, middle: (*S*)-16 (Table 7, entry 1); bottom: (*R*)-16 (Table 8, entry 2).

**rac-1-Chloro-4-(1-nitropropan-2-yl)benzene (*rac*-17)**

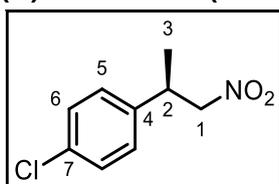
Following general procedure **D**, **E-5** (79 mg, 0.4 mmol, 1 eq.) was treated with NaBH<sub>4</sub> (18 mg, 0.48 mmol, 1.5 eq.) in THF:MeOH (10:1, 2.3 mL) to obtain **rac-17** after 4 h as a colorless oil (70.5 mg, 0.35 mmol, 88%).

**(S)-1-Chloro-4-(1-nitropropan-2-yl)benzene ((S)-17)**

Prepared according to general procedure **E**, **E-5** (40 mg) was converted to **(S)-17**, a colorless oil, using the catalyst stated in Table 9. The outcome for the given catalyst is summarized in Table 9 with the enantiomeric ratio determined by chiral HPLC (Reprosil Chiral-OM, *n*-hexane:*i*PrOH 99:1, 1.0 mL/min, λ = 210 nm).

Table 9: Reaction outcome for the hydrogenation of **E-5** to **(S)-17**.

| entry | catalyst | yield               | er         | t <sub>R</sub> (minor) | t <sub>R</sub> (major) |
|-------|----------|---------------------|------------|------------------------|------------------------|
| 1     | <b>A</b> | 38.8 mg, 0.19 mmol, | <b>97%</b> | 13.753 min             | 18.563 min             |
| 2     | <b>B</b> | 38.1 mg, 0.19 mmol, | 95%        | 13.910 min             | 18.787 min             |

**(R)-1-Chloro-4-(1-nitropropan-2-yl)benzene ((R)-17)**

Prepared according to general procedure **F**, **Z-5** (40 mg) was converted to **(R)-17**, a colorless oil, using the catalyst stated in Table 10. The outcome for the given catalyst is summarized in Table 10 with the enantiomeric ratio determined by chiral HPLC (Reprosil Chiral-OM, *n*-hexane:*i*PrOH 99:1, 1.0 mL/min, λ = 210 nm).

Table 10: Reaction outcome for the hydrogenation of **Z-5** to **(R)-17**.

| entry | catalyst | yield               | er         | t <sub>R</sub> (major) | t <sub>R</sub> (minor) |
|-------|----------|---------------------|------------|------------------------|------------------------|
| 1     | <b>A</b> | 36.4 mg, 0.18 mmol, | 91%        | 13.762 min             | 18.812 min             |
| 2     | <b>B</b> | 38.1 mg, 0.19 mmol, | <b>96%</b> | 13.871 min             | 18.921 min             |

**(S)-17** (er 05:95): [α]<sub>D</sub><sup>25</sup> = -37.5 (c = 0.5 in CHCl<sub>3</sub>); **(R)-17** (er 88:12): [α]<sub>D</sub><sup>25</sup> = +32.1 (c = 0.5 in CHCl<sub>3</sub>); *R<sub>f</sub>* = 0.27 (Et<sub>2</sub>O:*n*-pentane, 5:95); <sup>1</sup>H-NMR (600 MHz, CDCl<sub>3</sub>): δ = 7.35 – 7.27 (m, 2H, H<sub>6</sub>), 7.19 – 7.14 (m, 2H, H<sub>5</sub>), 4.55 – 4.43 (m, 2H, H<sub>1</sub>), 3.62 (h, <sup>3</sup>J<sub>HH</sub> = 7.1 Hz, 1H, H<sub>2</sub>), 1.36 (d, <sup>3</sup>J<sub>HH</sub> = 7.1 Hz, 3H, H<sub>3</sub>) ppm; <sup>13</sup>C{<sup>1</sup>H}-NMR (151 MHz, CDCl<sub>3</sub>): δ = 139.5 (C<sub>4</sub>), 133.5 (C<sub>7</sub>), 129.3 (C<sub>6</sub>), 128.4 (C<sub>5</sub>), 81.7 (C<sub>1</sub>), 38.2 (C<sub>2</sub>), 18.9 (C<sub>3</sub>) ppm; IR (ATR): ν̄ = 2974 (w), 2934 (w), 1548 (s), 1494 (m), 1456 (w), 1432 (w), 1413 (w), 1377 (m), 1343 (w), 1302 (w), 1226 (w), 1199 (w), 1120 (w), 1092 (m), 1013 (m), 900 (w), 826 (s), 774 (w), 738 (m), 717 (w) cm<sup>-1</sup>; HR-ESI-MS: *m/z* [M-H]<sup>+</sup> calcd. for C<sub>9</sub>H<sub>9</sub>ClNO<sub>2</sub><sup>+</sup>: 198.0322; found: 198.73782. The analytical data are in agreement with the literature.<sup>[13]</sup>

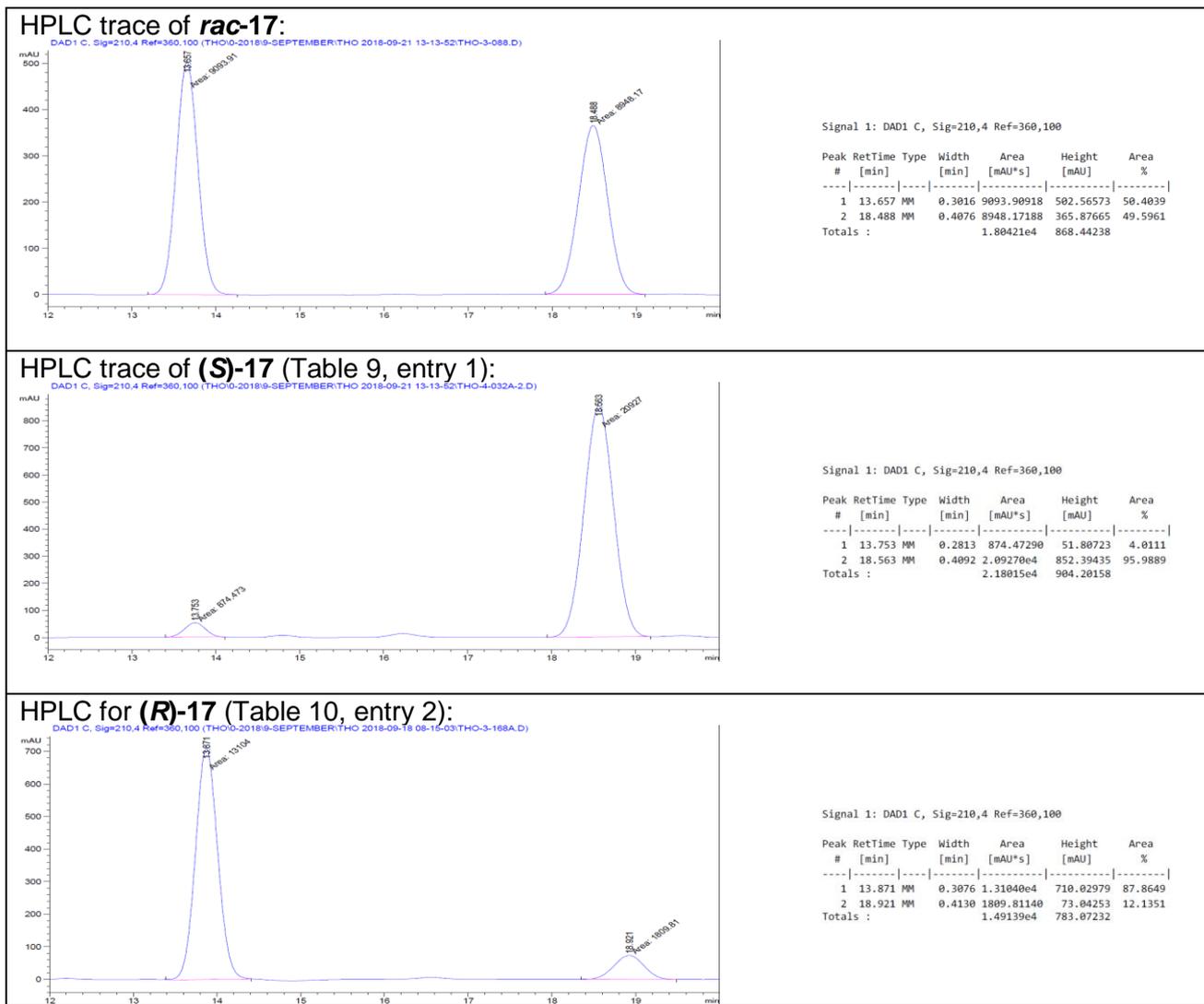
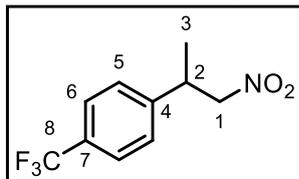
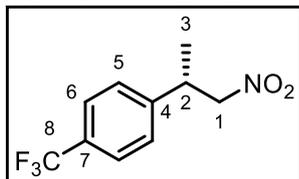


Figure 10: HPLC traces for 17; top: *rac*-17, middle: (*S*)-17 (Table 9, entry 1); bottom: (*R*)-17 (Table 10, entry 2).

**rac-1-(1-Nitropropan-2-yl)-4-(trifluoromethyl)benzene (rac-18)**

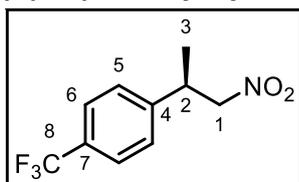
Following general procedure **D**, **E-6** (46 mg, 0.2 mmol, 1 eq.) was treated with NaBH<sub>4</sub> (11 mg, 0.3 mmol, 1.5 eq.) in THF:MeOH (10:1, 1.4 mL) to obtain **rac-18** after 4 h as a colorless oil (22.0 mg, 0.10 mmol, 47%).

**(S)-1-(1-Nitropropan-2-yl)-4-(trifluoromethyl)benzene ((S)-18)**

Prepared according to general procedure **E**, **E-6** (46 mg) was converted to **(S)-18**, a colorless oil, using the catalyst stated in Table 11. The outcome for the given catalyst is summarized in Table 11 with the enantiomeric ratio determined by chiral HPLC (Reprosil Chiral-OM, *n*-hexane:*i*PrOH 97:3, 1.0 mL/min, λ = 210 nm).

Table 11: Reaction outcome for the hydrogenation of **E-6** to **(S)-18**.

| entry | catalyst | yield                   | er           | t <sub>R</sub> (minor) | t <sub>R</sub> (major) |
|-------|----------|-------------------------|--------------|------------------------|------------------------|
| 1     | <b>A</b> | 35.7 mg, 0.15 mmol, 78% | <b>10:90</b> | 10.273 min             | 11.817 min             |
| 2     | <b>B</b> | 39.0 mg, 0.17 mmol, 84% | 12:88        | 10.423 min             | 12.006 min             |

**(R)-1-(1-Nitropropan-2-yl)-4-(trifluoromethyl)benzene ((R)-18)**

Prepared according to general procedure **F**, **Z-6** (46 mg) was converted to **(R)-18**, a colorless oil, using the catalyst stated in Table 12. The outcome for the given catalyst is summarized in Table 12 with the enantiomeric ratio determined by chiral HPLC (Reprosil Chiral-OM, *n*-hexane:*i*PrOH 97:3, 1.0 mL/min, λ = 210 nm).

Table 12: Reaction outcome for the hydrogenation of **Z-18** to **(R)-18**.

| entry | catalyst | yield                   | er           | t <sub>R</sub> (major) | t <sub>R</sub> (minor) |
|-------|----------|-------------------------|--------------|------------------------|------------------------|
| 1     | <b>A</b> | 39.9 mg, 0.17 mmol, 86% | 85:15        | 10.224 min             | 11.798 min             |
| 2     | <b>B</b> | 38.5 mg, 0.17 mmol, 83% | <b>89:11</b> | 10.247 min             | 11.830 min             |

**(S)-18** (er 10:90): [α]<sub>D</sub><sup>25</sup> = -25.1 (c = 0.5 in CHCl<sub>3</sub>); **(R)-18** (er 89:11): [α]<sub>D</sub><sup>25</sup> = +30.0 (c = 0.5 in CHCl<sub>3</sub>); **R<sub>f</sub>** = 0.19 (Et<sub>2</sub>O:*n*-pentane, 5:95); **<sup>1</sup>H-NMR** (600 MHz, CDCl<sub>3</sub>): δ = 7.61 (d, <sup>3</sup>J<sub>HH</sub> = 8.1 Hz, 2H, H6), 7.36 (d, <sup>3</sup>J<sub>HH</sub> = 8.1 Hz, 2H, H5), 4.61 – 4.48 (m, 2H, H1), 3.72 (sext, <sup>3</sup>J<sub>HH</sub> = 7.2 Hz, 1H, H2), 1.41 (d, <sup>3</sup>J<sub>HH</sub> = 7.2 Hz, 3H, H3) ppm; **<sup>13</sup>C{<sup>1</sup>H}-NMR** (101 MHz, CDCl<sub>3</sub>): δ = 145.1 (q, <sup>5</sup>J<sub>CF</sub> = 1.2 Hz, C4), 130.1 (q, <sup>2</sup>J<sub>CF</sub> = 32.6 Hz, C7), 127.5 (C5), 126.1 (q, <sup>3</sup>J<sub>CF</sub> = 3.8 Hz, C6), 124.1 (q, <sup>1</sup>J<sub>CF</sub> = 272.1 Hz, C8), 81.4 (C1), 38.6 (C2), 18.9 (C3) ppm; **<sup>19</sup>F-NMR** (376 MHz, CDCl<sub>3</sub>): δ = -62.63 (s) ppm; **IR** (ATR):  $\tilde{\nu}$  = 2976 (w), 2939 (w), 1621 (w), 1551 (s), 1459 (w), 1442 (w), 1378 (w), 1323 (s), 1164 (m), 1119 (s), 1068 (s), 1016 (m), 956 (w), 901 (w), 839 (w), 768 (w), 713 (w) cm<sup>-1</sup>; **HR-ESI-MS**: *m/z*: [M-NO<sub>2</sub>]<sup>+</sup> calcd. for C<sub>10</sub>H<sub>10</sub>F<sub>3</sub><sup>+</sup>: 187.07; found: 187.11. The analytical data are in agreement with the literature.<sup>[14]</sup>

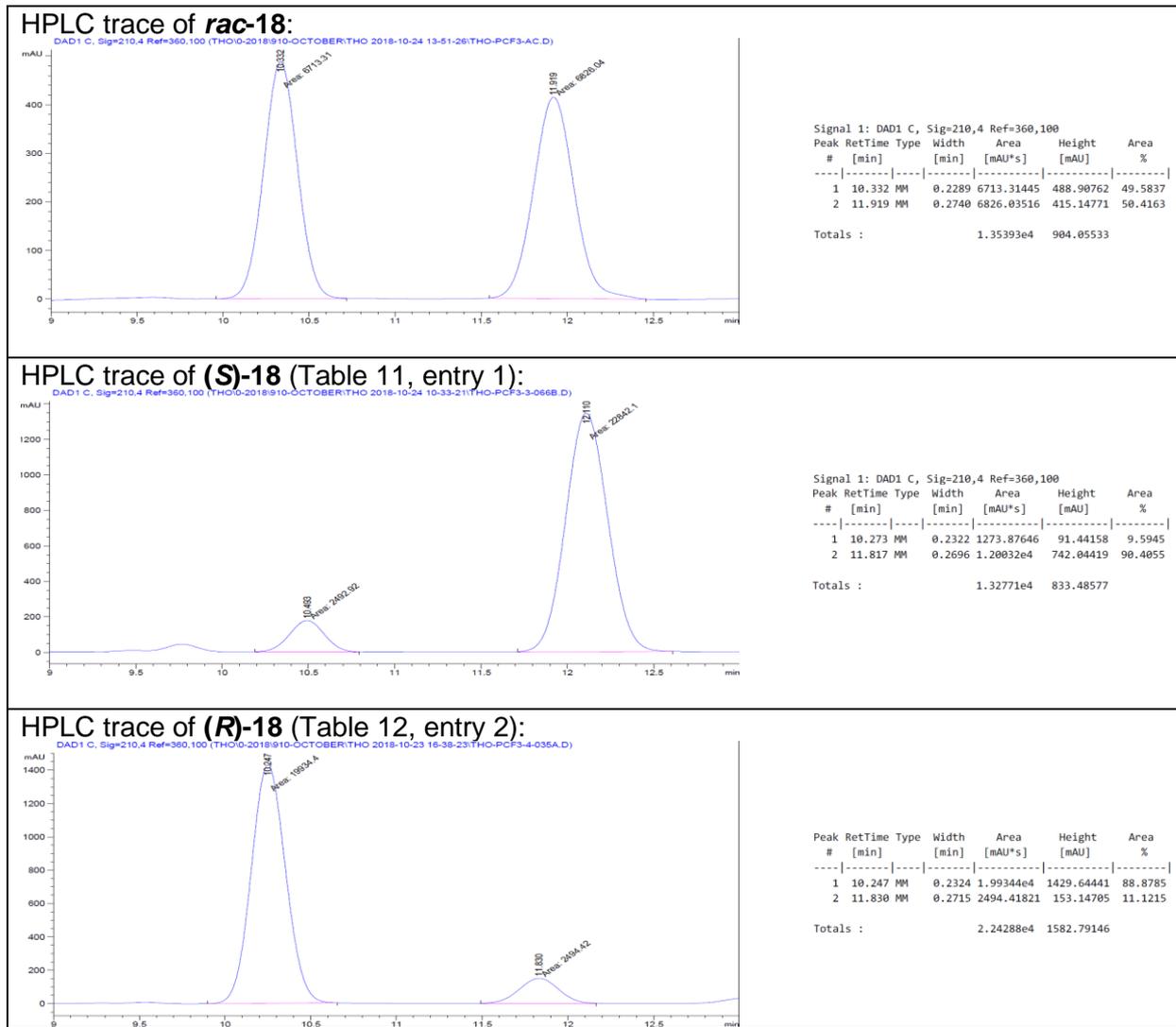
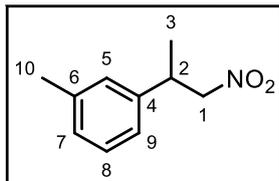
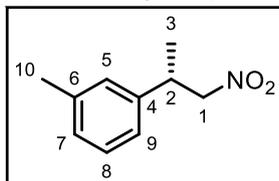


Figure 11: HPLC traces of **18**; top: *rac*-18, middle: (*S*)-18 (Table 11, entry 1); bottom: (*R*)-18 (Table 12, entry 2).

**rac-1-Methyl-3-(1-nitropropan-2-yl)benzene (rac-19)**

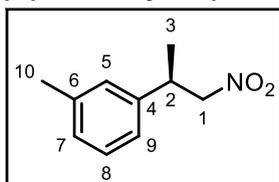
Following general procedure **D**, **E-8** (89 mg, 0.5 mmol, 1 eq.) was treated with NaBH<sub>4</sub> (28 mg, 0.75 mmol, 1.5 eq.) in THF:MeOH (10:1, 4 mL) to obtain **rac-19** after 4 h as a colorless oil (58.5 mg, 0.33 mmol, 65%).

**(S)-1-Methyl-3-(1-nitropropan-2-yl)benzene ((S)-19)**

Prepared according to general procedure **E**, **E-8** (35 mg) was converted to **(S)-19**, a colorless oil, using the catalyst stated in Table 13. The outcome for the given catalyst is summarized in Table 13 with the enantiomeric ratio determined by chiral HPLC (Reprosil Chiral-OM, *n*-hexane:*i*PrOH 97:3, 1.0 mL/min, λ = 210 nm).

Table 13: Reaction outcome for the hydrogenation of **E-8** to **(S)-19**.

| entry | catalyst | yield               | er         | t <sub>R</sub> (minor) | t <sub>R</sub> (major) |
|-------|----------|---------------------|------------|------------------------|------------------------|
| 1     | <b>A</b> | 33.3 mg, 0.19 mmol, | <b>93%</b> | <b>05:95</b>           | 7.708 min / 10.219 min |
| 2     | <b>B</b> | 31.8 mg, 0.18 mmol, | 89%        | 12:88                  | 7.699 min / 10.206 min |

**(R)-1-Methyl-3-(1-nitropropan-2-yl)benzene ((R)-19)**

Prepared according to general procedure **F**, **Z-8** (35 mg) was converted to **(R)-19**, a colorless oil, using the catalyst stated in Table 14. The outcome for the given catalyst is summarized in Table 14 with the enantiomeric ratio determined by chiral HPLC Reprosil Chiral-OM, *n*-hexane:*i*PrOH 97:3, 1.0 mL/min, λ = 210 nm).

Table 14: Reaction outcome for the hydrogenation of **Z-8** to **(R)-19**.

| entry | catalyst | yield               | er         | t <sub>R</sub> (major) | t <sub>R</sub> (minor) |
|-------|----------|---------------------|------------|------------------------|------------------------|
| 1     | <b>A</b> | 26.3 mg, 0.15 mmol, | 73%        | 87:13                  | 7.372 min / 10.129 min |
| 2     | <b>B</b> | 29.0 mg, 0.16 mmol, | <b>81%</b> | <b>91:09</b>           | 7.648 min / 10.087 min |

**(S)-19** (er 05:95): [α]<sub>D</sub><sup>25</sup> = -41.2 (c = 0.5 in CHCl<sub>3</sub>); **(R)-19** (er 91:09): [α]<sub>D</sub><sup>25</sup> = +36.6 (c = 0.5 in CHCl<sub>3</sub>); **R<sub>f</sub>** = (Et<sub>2</sub>O:*n*-pentane, 5:95); **<sup>1</sup>H-NMR** (600 MHz, CDCl<sub>3</sub>): δ = 7.49 – 7.42 (m, 1H, H8), 7.31 (d, <sup>3</sup>J<sub>HH</sub> = 7.8 Hz, 1H, H7), 7.27 – 7.23 (m, 2H, H5, H9), 4.81 – 4.66 (m, 2H, H1), 3.89 – 3.75 (m, 1H, H2), 2.57 (s, 3H, H10), 1.59 (d, <sup>3</sup>J<sub>HH</sub> = 7.0 Hz, 3H, H3) ppm; **<sup>13</sup>C{<sup>1</sup>H}-NMR** (151 MHz, CDCl<sub>3</sub>): δ = 141.0 (C4), 138.8 (C6), 129.0 (C8), 128.5 (C7), 127.8 (C5), 124.0 (C9), 82.1 (C1), 38.7 (C2), 21.6 (C10), 18.9 (C3) ppm; **IR** (ATR):  $\tilde{\nu}$  = 2973 (w), 2922 (w), 1608 (w), 1547 (s), 1491 (w), 1456 (w), 1431 (w), 1375 (m), 1212 (w), 1166 (w), 1119 (w), 1040 (w), 904 (w), 882 (w), 786 (m), 703 (s) cm<sup>-1</sup>; **GC-ESI-MS**: *m/z*: [M-H]<sup>+</sup> calcd. for C<sub>10</sub>H<sub>12</sub>NO<sub>2</sub><sup>+</sup>: 178.08626; found: 178.08632.

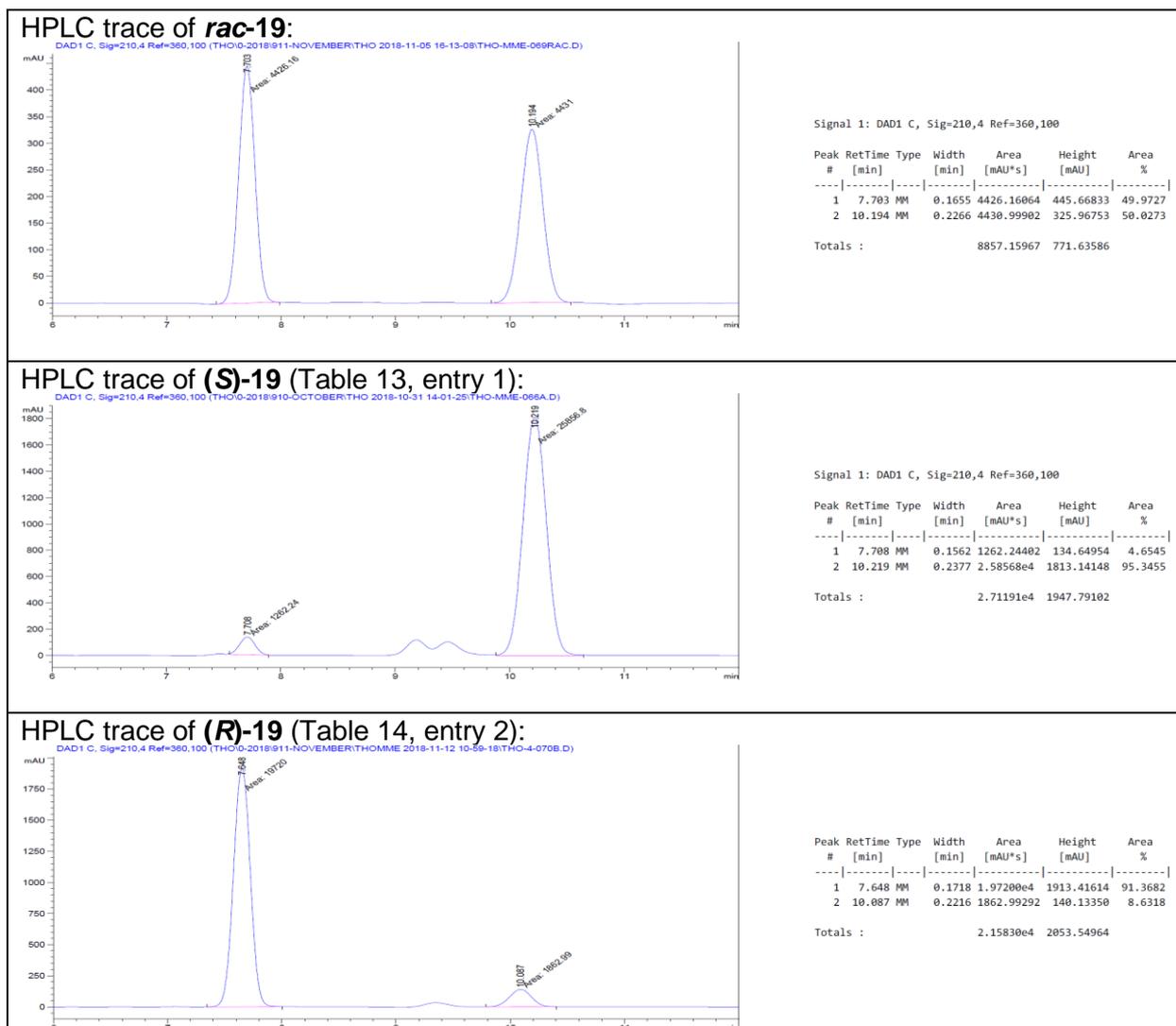
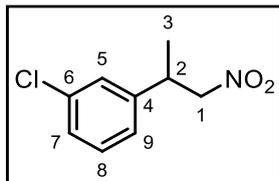
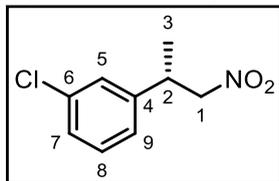


Figure 12: HPLC traces for **19**; top: *rac*-19, middle: (*S*)-19 (Table 13, entry 1); bottom: (*R*)-19 (Table 14, entry 2).

**rac-1-Chloro-3-(1-nitropropan-2-yl)benzene (rac-20)**

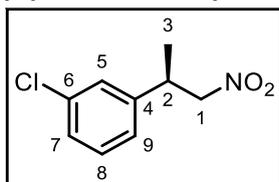
Following general procedure **D**, **E-9** (299 mg, 1.5 mmol, 1 eq.) was treated with NaBH<sub>4</sub> (85 mg, 2.3 mmol, 1.5 eq.) in THF:MeOH (10:1, 7.5 mL) to obtain **rac-20** after 4 h as a colorless oil (266.2 mg, 1.33 mmol, 89%).

**(S)-1-Chloro-3-(1-nitropropan-2-yl)benzene ((S)-20)**

Prepared according to general procedure **E**, **E-9** (40 mg) was converted to **(S)-20**, a colorless oil, using the catalyst stated in Table 15. The outcome for the given catalyst is summarized in Table 15 with the enantiomeric ratio determined by chiral HPLC (Reprosil Chiral-OM, *n*-hexane:*i*PrOH 97:3, 1.0 mL/min, λ = 210 nm).

Table 15: Reaction outcome for the hydrogenation of **E-9** to **(S)-20**.

| entry | catalyst | yield               | er         | t <sub>R</sub> (minor) | t <sub>R</sub> (major) |            |
|-------|----------|---------------------|------------|------------------------|------------------------|------------|
| 1     | <b>A</b> | 37.3 mg, 0.19 mmol, | <b>93%</b> | <b>05:95</b>           | 11.172 min             | 15.988 min |
| 2     | <b>B</b> | 34.2 mg, 0.17 mmol, | 86%        | 10:90                  | 11.451 min             | 16.564 min |

**(R)-1-Chloro-3-(1-nitropropan-2-yl)benzene ((R)-20)**

Prepared according to general procedure **F**, **Z-9** (40 mg) was converted to **(R)-20**, a colorless oil, using the catalyst stated in Table 16. The outcome for the given catalyst is summarized in Table 16 with the enantiomeric ratio determined by chiral HPLC (Reprosil Chiral-OM, *n*-hexane:*i*PrOH 97:3, 1.0 mL/min, λ = 210 nm).

Table 16: Reaction outcome for the hydrogenation of **Z-9** to **(R)-20**.

| entry | catalyst | yield               | er         | t <sub>R</sub> (major) | t <sub>R</sub> (minor) |            |
|-------|----------|---------------------|------------|------------------------|------------------------|------------|
| 1     | <b>A</b> | 28.5 mg, 0.14 mmol, | 71%        | 78:22                  | 11.532 min             | 16.756 min |
| 2     | <b>B</b> | 26.8 mg, 0.13 mmol, | <b>67%</b> | <b>93:07</b>           | 11.401 min             | 16.545 min |

**(S)-20** (er 04:96): [α]<sub>D</sub><sup>25</sup> = -36.4 (c = 0.5 in CHCl<sub>3</sub>); **(R)-20** (er 94:06): [α]<sub>D</sub><sup>25</sup> = +33.8 (c = 0.5 in CHCl<sub>3</sub>); R<sub>f</sub> = 0.33 (Et<sub>2</sub>O:*n*-pentane, 5:95); <sup>1</sup>H-NMR (600 MHz, CDCl<sub>3</sub>): δ = 7.31 – 7.23 (m, 2H, H7, H8), 7.23 – 7.21 (m, 1H, H5), 7.14 – 7.09 (m, 1H, H9), 4.57 – 4.44 (m, 2H, H1), 3.62 (h, <sup>3</sup>J<sub>HH</sub> = 7.2 Hz, 1H, H2), 1.37 (d, <sup>3</sup>J<sub>HH</sub> = 7.2 Hz, 3H, H3) ppm; <sup>13</sup>C{<sup>1</sup>H}-NMR (151 MHz, CDCl<sub>3</sub>): δ = 143.0 (C4), 134.9 (C6), 130.4 (C8), 128.0 (C7), 127.3 (C5), 125.3 (C9), 81.5 (C1), 38.5 (C2), 18.8 (C3) ppm; IR (ATR): ν̄ = 2974 (w), 2930 (w), 1598 (w), 1547 (s), 1479 (w), 1456 (m), 1432 (m), 1375 (m), 1346 (w), 1265 (w), 1120 (w), 1084 (m), 1039 (w), 999 (w), 881 (w), 815 (w), 786 (s), 738 (w), 694 (s), 677 (m) cm<sup>-1</sup>; HR-ESI-MS: m/z: [M-O]<sup>+</sup> calcd. for C<sub>9</sub>H<sub>10</sub>ClNO<sup>+</sup>: 183.04454; found: 183.04460. The analytical data are in agreement with the literature.<sup>[15]</sup>

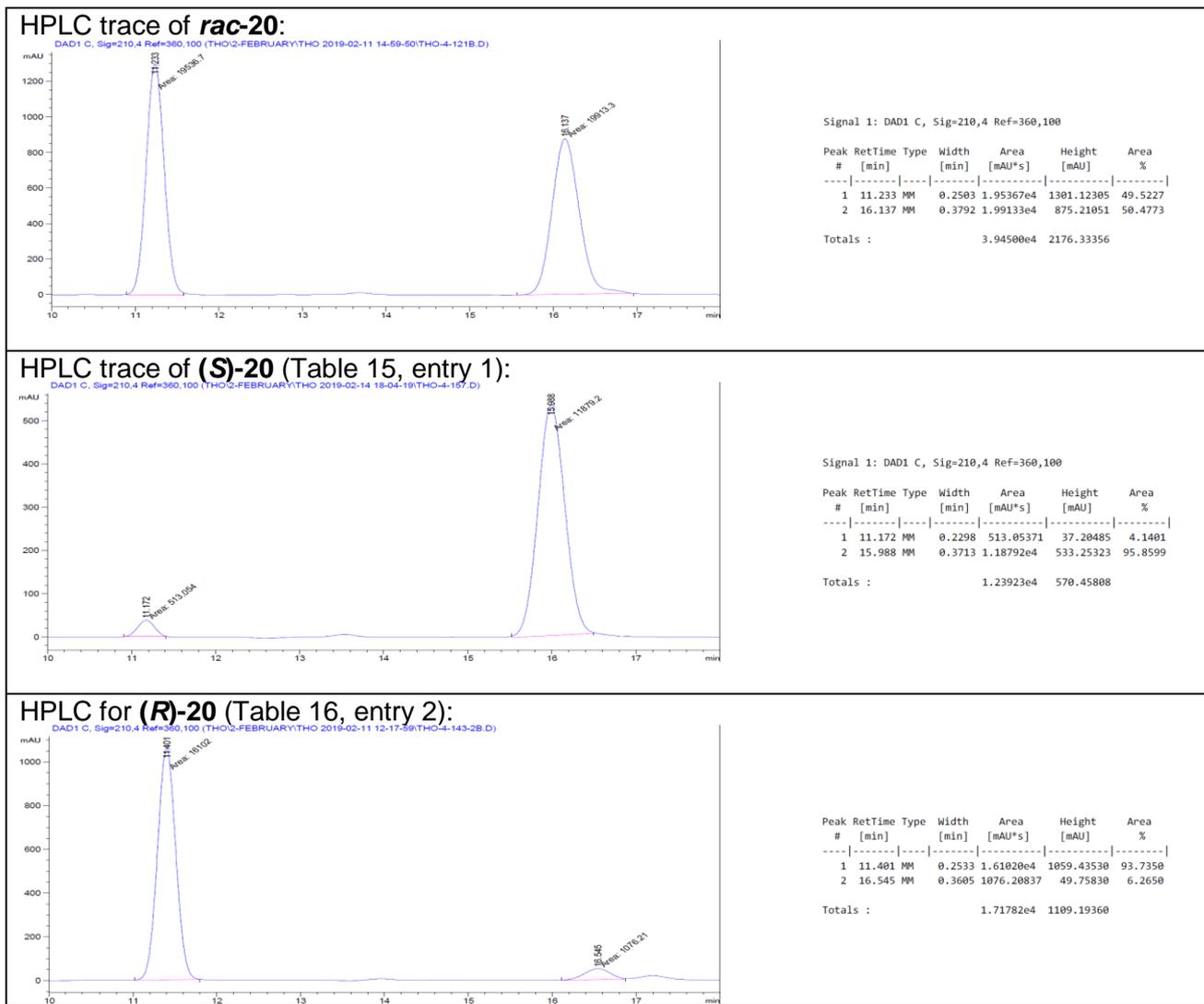
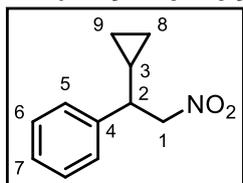


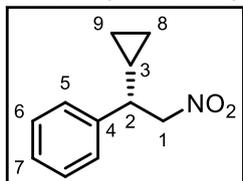
Figure 13: HPLC traces of **20**; top: *rac*-**20**, middle: (*S*)-**20** (Table 15, entry 1); bottom: (*R*)-**20** (Table 16, entry 2).

### *rac*-(1-Cyclopropyl-2-nitroethyl)benzene (*rac*-21)



Following general procedure **D**, **E-10** (34 mg, 0.18 mmol, 1 eq.) was treated with NaBH<sub>4</sub> (13 mg, 0.34 mmol, 1.5 eq.) in THF:MeOH (10:1, 2 mL) to obtain *rac*-21 after 5 h as a colorless oil (25.1 mg, 0.13 mmol, 73%).

### (*S*)-(1-Cyclopropyl-2-nitroethyl)benzene ((*S*)-21)

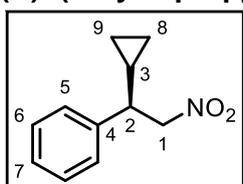


Prepared according to general procedure **E**, **E-10** (38 mg) was converted to (*S*)-21, a colorless oil, using the catalyst stated in Table 17. The outcome for the given catalyst is summarized in Table 17 with the enantiomeric ratio determined by chiral HPLC (Reprosil Chiral-OM, *n*-hexane:*i*PrOH 99:1, 1.0 mL/min,  $\lambda = 210$  nm).

Table 17: Reaction outcome for the hydrogenation of **E-20** to (*S*)-21.

| entry | catalyst | yield                   | er           | t <sub>R</sub> (minor) | t <sub>R</sub> (major) |
|-------|----------|-------------------------|--------------|------------------------|------------------------|
| 1     | <b>A</b> | 29.2 mg, 0.15 mmol, 76% | <b>03:97</b> | 16.587 min             | 21.148 min             |
| 2     | <b>B</b> | 28.3 mg, 0.15 mmol, 74% | 07:93        | 16.571 min             | 21.318 min             |

### (*R*)-(1-Cyclopropyl-2-nitroethyl)benzene ((*R*)-21)



Prepared according to general procedure **F**, **Z-20** (38 mg) was converted to (*R*)-21, a colorless oil, using the catalyst stated in Table 18. The outcome for the given catalyst is summarized in Table 18 with the enantiomeric ratio determined by chiral HPLC (Reprosil Chiral-OM, *n*-hexane:*i*PrOH 99:1, 1.0 mL/min,  $\lambda = 210$  nm).

Table 18: Reaction outcome for the hydrogenation of **Z-10** to (*R*)-21.

| entry | catalyst | yield                   | er           | t <sub>R</sub> (minor) | t <sub>R</sub> (major) |
|-------|----------|-------------------------|--------------|------------------------|------------------------|
| 1     | <b>A</b> | 25.7 mg, 0.13 mmol, 68% | 91:09        | 16.417 min             | 21.312 min             |
| 2     | <b>B</b> | 29.2 mg, 0.15 mmol, 76% | <b>93:07</b> | 16.412 min             | 21.314 min             |

(*S*)-21 (er 03:97):  $[\alpha]_{\text{D}}^{25} = +35.5$  ( $c = 0.5$  in CHCl<sub>3</sub>); (*R*)-21 (er 93:07):  $[\alpha]_{\text{D}}^{25} = -30.4$  ( $c = 0.5$  in CHCl<sub>3</sub>);  $R_f = 0.62$  (Et<sub>2</sub>O:*n*-pentane 5:95); <sup>1</sup>H-NMR (500 MHz, CDCl<sub>3</sub>):  $\delta = 7.37 - 7.32$  (m, 2H, H6), 7.30 - 7.22 (m, 3H, H5, H7), 4.77 - 4.55 (m, 2H, H1), 2.77 - 2.68 (m, 1H, H2), 1.14 - 1.05 (m, 1H, H3), 0.72 - 0.63 (m, 1H, H8/8'/9/9'), 0.55 - 0.46 (m, 1H, H8/8'/9/9'), 0.38 - 0.30 (m, 1H, H8/8'/9/9'), 0.24 - 0.15 (m, 1H, H8/8'/9/9') ppm; <sup>13</sup>C{<sup>1</sup>H}-NMR (126 MHz, CDCl<sub>3</sub>):  $\delta = 139.9$  (C4), 129.0 (C6), 127.7 (C7), 127.5 (C5), 81.0 (C1), 49.4 (C2), 14.6 (C3), 5.4 (C8/9), 3.6 (C8/9) ppm; IR (ATR):  $\tilde{\nu} = 3083$  (w), 3006 (w), 2917 (w), 1602 (w), 1547 (s), 1495 (w), 1455 (w), 1431 (w), 1377 (m), 1260 (w), 1194 (w), 1145 (w), 1078 (w), 1051 (w), 1022 (m), 987 (w), 946 (w), 925 (w), 861 (w), 824 (w), 771 (w), 753 (m), 698 (s) cm<sup>-1</sup>; GC-EI-MS:  $m/z$ : [M-NO<sub>2</sub>]<sup>+</sup> calcd. for C<sub>11</sub>H<sub>13</sub><sup>+</sup>: 145.10; found: 145.12.

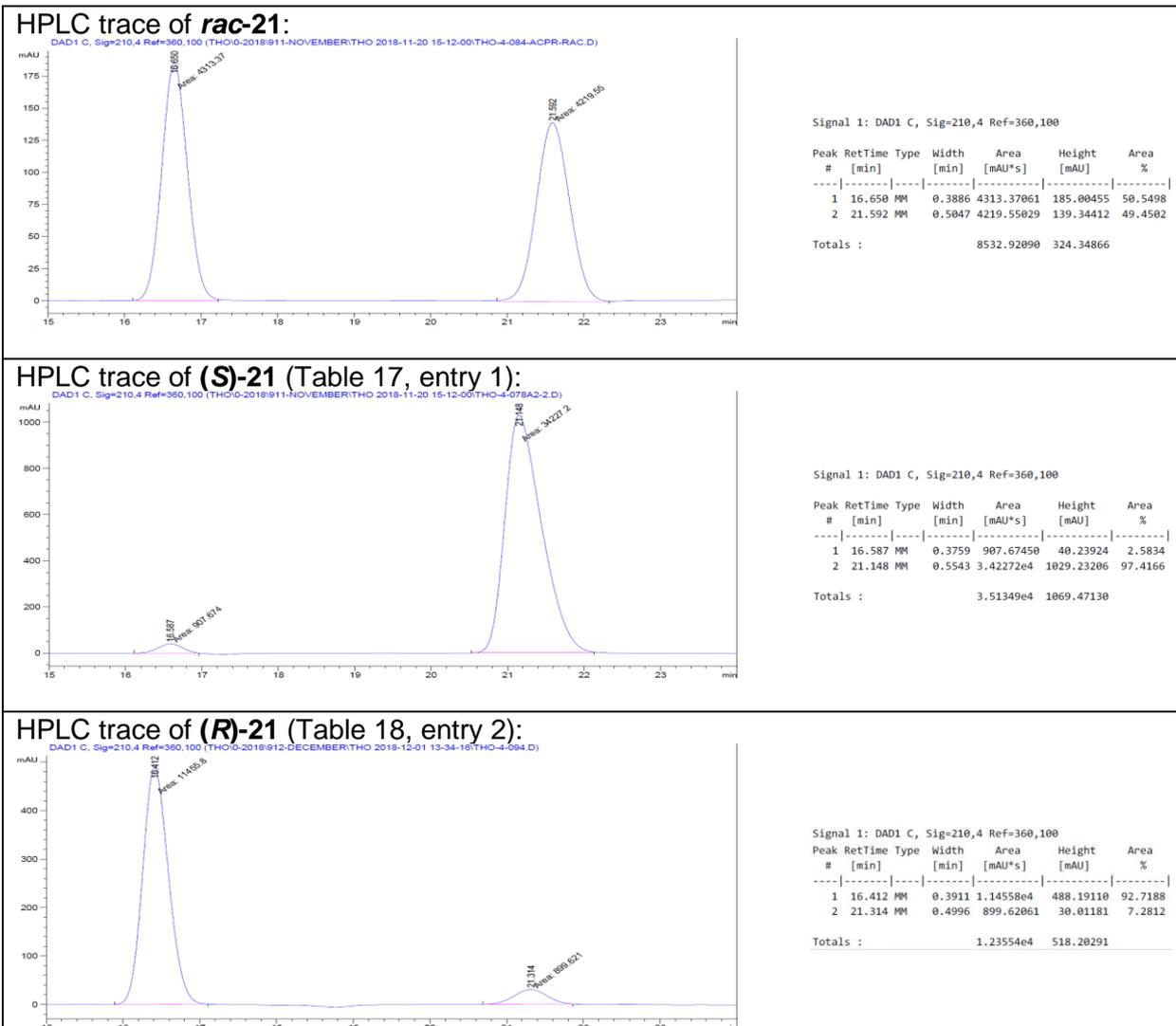
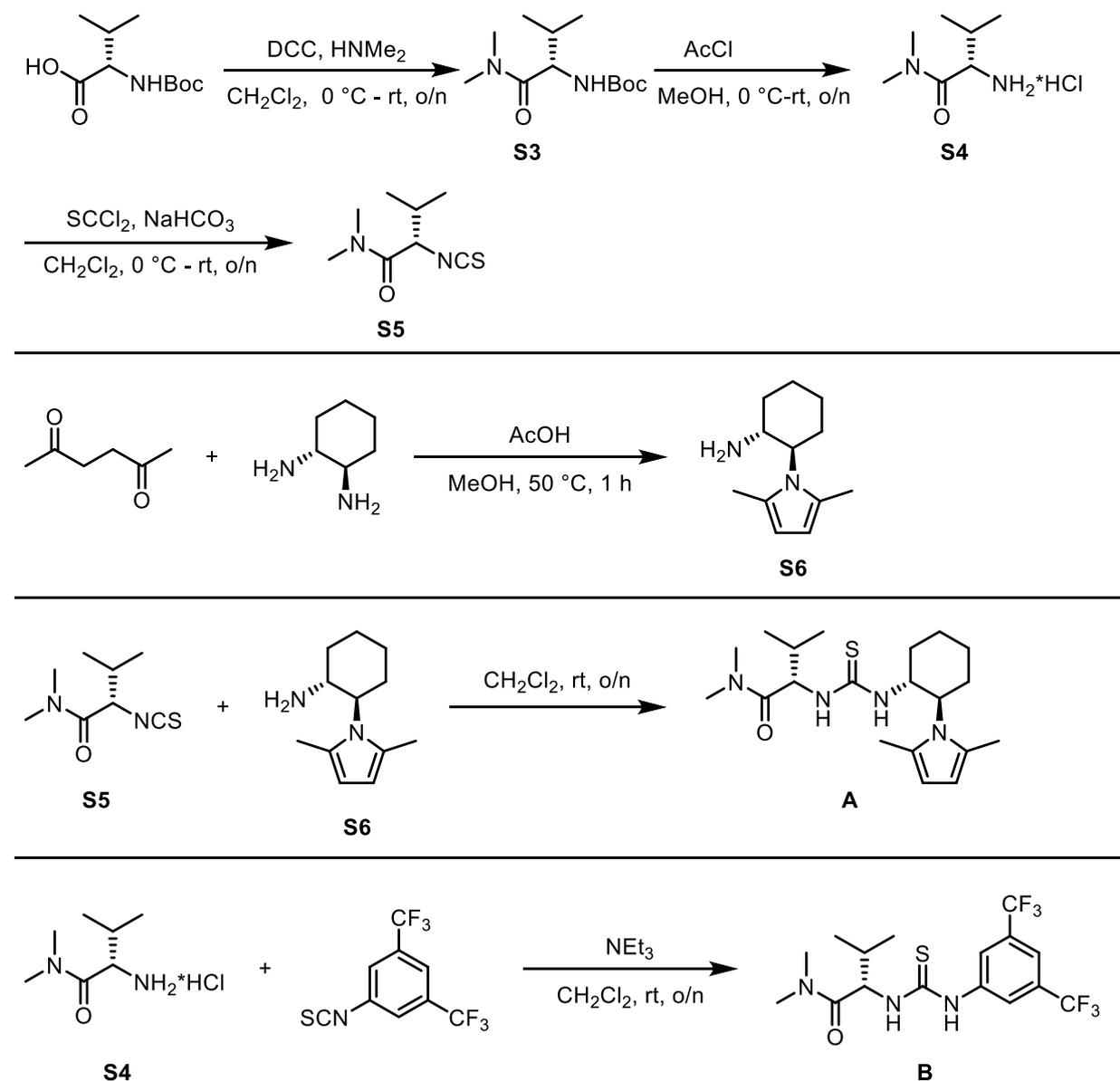


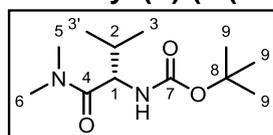
Figure 14: HPLC traces of **21**; top: *rac*-**21**, middle: (*S*)-**21** (Table 17, entry 1); bottom: (*R*)-**21** (Table 18, entry 2).

## Synthesis of thiourea catalysts



Scheme 1: Reaction Scheme for the preparation of the catalysts **A** and **B**.

### *tert*-Butyl (S)-(1-(dimethylamino)-3-methyl-1-oxobutan-2-yl)carbamate (**S3**)

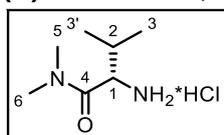


Following an adapted literature procedure,<sup>[16]</sup> *N*-Boc-L-Valine (4.26 g, 19.6 mmol, 1 eq.) was dissolved in dry CH<sub>2</sub>Cl<sub>2</sub> (20 mL) under an argon atmosphere and cooled to 0 °C before *N,N*-dicyclohexyl carbodiimide (4.65 g, 22.6 mmol, 1.15 eq.) was added portionwise. HNMe<sub>2</sub> (2 M in THF, 19.6 mL, 39.2 mmol, 2 eq.) was added at 0 °C and the reaction mixture was stirred over night while warming to room temperature. All volatiles were removed *in vacuo* and the crude product was purified by column chromatography (SiO<sub>2</sub>, Et<sub>2</sub>O:*n*-pentane 2:3) yielding **S3** as a viscous colorless oil (3.50 g, 14.3 mmol, 73%).

**[α]<sub>D</sub><sup>25</sup>** = -10.5 (c = 1.0 in MeOH); **R<sub>f</sub>** = 0.50 (Et<sub>2</sub>O:*n*-pentane 1:1); **<sup>1</sup>H-NMR** (400 MHz, CDCl<sub>3</sub>): δ = 5.29 (d, <sup>3</sup>J<sub>HH</sub> = 9.2 Hz, 1H, NH), 4.44 (dd, <sup>3</sup>J<sub>HH</sub> = 9.2, 5.9 Hz, 1H, H1), 3.07 (s, 3H, H5/6), 2.94 (s, 3H, H5/6), 1.97 – 1.84 (m, 1H, H2), 1.40 (s, 9H, H9), 0.93 (d, <sup>3</sup>J<sub>HH</sub> = 6.8 Hz, 3H, H3/3'), 0.87 (d, <sup>3</sup>J<sub>HH</sub> = 6.8 Hz, 3H, H3/3') ppm; **<sup>13</sup>C{<sup>1</sup>H}-NMR** (101 MHz, CDCl<sub>3</sub>): δ = 172.3 (C4), 156.0 (C7), 79.5 (C8), 55.0 (C1), 37.5 (C2), 35.7 (C5/6), 31.6 (C5/6), 28.5 (C9), 19.6 (C3/3'), 17.4 (C3/3') ppm; **IR** (ATR):  $\tilde{\nu}$  = 3304 (w), 2967 (w), 2933 (w), 1704 (m), 1638 (s), 1490 (m), 1415 (w), 1392 (m), 1365 (m), 1311 (w), 1245 (m), 1167 (s), 1086 (w), 1042 (w), 1015 (m), 979 (w), 933 (w), 880 (w), 845 (w), 779 (w), 745 (w), 698 (w) cm<sup>-1</sup>; **HR-ESI-MS**: *m/z*. [M+Na]<sup>+</sup> calcd. for

C<sub>12</sub>H<sub>24</sub>N<sub>2</sub>O<sub>3</sub>Na<sup>+</sup>: 267.1679; found: 267.1697. The analytical data are in agreement with the literature.<sup>[16]</sup>

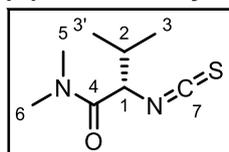
### (S)-2-Amino-N,N,3-trimethylbutanamide hydrochloric acid (S4)



**S3** (2.44 g, 10 mmol, 1 eq.) was dissolved in MeOH (100 mL) and cooled to 0 °C before AcCl (4.2 mL, 60 mmol, 6 eq.) was added slowly. The reaction mixture was stirred for 6 h while warming up to room temperature. Removing of the volatiles *in vacuo* yielded **S4** as a colorless hygroscopic solid (1.61 g, 8.90 mmol, 89%).

[ $\alpha$ ]<sub>D</sub><sup>25</sup> = +93.6 (c = 1.0 in MeOH); **<sup>1</sup>H-NMR** (400 MHz, (CD<sub>3</sub>)<sub>2</sub>SO):  $\delta$  = 8.21 (s, 2H, NH<sub>2</sub>), 4.21 – 4.13 (m, 1H, H1), 3.04 (s, 3H, H5), 2.89 (s, 3H, H6), 2.12 – 2.00 (m, 1H, H2), 0.97 (d, <sup>3</sup>J<sub>HH</sub> = 6.9 Hz, 3H, H3/3'), 0.91 (d, <sup>3</sup>J<sub>HH</sub> = 6.9 Hz, 3H, H3/3') ppm; **<sup>13</sup>C{<sup>1</sup>H}-NMR** (101 MHz, (CD<sub>3</sub>)<sub>2</sub>SO):  $\delta$  = 168.1 (C4), 53.9 (C1), 37.0 (C5), 35.3 (C6), 29.3 (C2), 18.5 (C3/3'), 17.2 (C3/3') ppm; **IR** (ATR):  $\tilde{\nu}$  = 2934 (m), 2851 (m), 2660 (w), 2618 (w), 1985 (w), 1640 (s), 1564 (s), 1504 (s), 1482 (s), 1394 (m), 1366 (s), 1279 (w), 1249 (w), 1193 (w), 1176 (w), 1148 (m), 1118 (m), 1099 (w), 1063 (m), 1022 (m), 932 (w), 893 (w), 819 (w), 796 (w), 717 (m), 698 (w) cm<sup>-1</sup>; **HR-ESI-MS**: *m/z*: [M-CI]<sup>+</sup> calcd. for C<sub>7</sub>H<sub>17</sub>N<sub>2</sub>O<sup>+</sup>: 145.1335; found: 145.1364; **m.p.** = 27 – 29 °C. The analytical data are in agreement with the literature.<sup>[16]</sup>

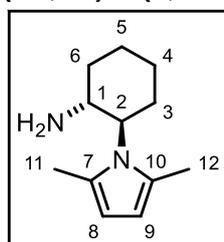
### (S)-2-Isothiocyanato-N,N,3-trimethylbutanamide (S5)



Following an adapted literature procedure,<sup>[17]</sup> **S4** (1.08 g, 6 mmol, 1 eq.) was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (30 mL) and a sat. aq. NaHCO<sub>3</sub> (30 mL) solution at 0 °C and stirred for 5 min at 0 °C before the stirring was stopped and SCl<sub>2</sub> (0.5 mL, 6.6 mmol, 1.1 eq.) was added to the organic layer. After stirring for 2 h at 0 °C, the organic layer was separated and the aqueous layer was extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 x 20 mL). The combined organic layers were dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and the solvent and remaining thiophosgene was removed by distillation (do not remove the solvent outside a vented fume hood; thiophosgene is highly toxic). Purification by column chromatography (SiO<sub>2</sub>, Et<sub>2</sub>O:*n*-pentane 3:2) yielded **S5** as a brown oil (974 mg, 5.23 mmol, 87%).

[ $\alpha$ ]<sub>D</sub><sup>25</sup> = +61.6 (c = 1.0 in MeOH); **R<sub>f</sub>** = 0.26 (Et<sub>2</sub>O:*n*-pentane 3:2); **<sup>1</sup>H-NMR** (500 MHz, CDCl<sub>3</sub>):  $\delta$  = 4.23 (d, <sup>3</sup>J<sub>HH</sub> = 6.1 Hz, 1H, H1), 3.05 (s, 3H, H5), 3.00 (s, 3H, H6), 2.28 – 2.21 (m, 1H, H2), 1.07 (d, <sup>3</sup>J<sub>HH</sub> = 6.7 Hz, 3H, H3/3'), 1.02 (d, <sup>3</sup>J<sub>HH</sub> = 6.7 Hz, 3H, H3/3') ppm; **<sup>13</sup>C{<sup>1</sup>H}-NMR** (126 MHz, CDCl<sub>3</sub>):  $\delta$  = 166.9 (C4), 136.7 (C7), 63.7 (C1), 37.4 (C5), 36.5 (C6), 32.2 (C2), 20.0 (C3/3'), 18.0 (C3/3') ppm; **IR** (ATR):  $\tilde{\nu}$  = 2967 (w), 2933 (w), 2875 (w), 2043 (s), 1652 (s), 1496 (w), 1464 (w), 1400 (m), 1371 (w), 1351 (m), 1319 (w), 1261 (w), 1166 (w), 1122 (m), 1100 (w), 1057 (w), 976 (w), 928 (w), 853 (m), 828 (w), 742 (m), 689 (w) cm<sup>-1</sup>; **HR-ESI-MS**: *m/z*: [M+Na]<sup>+</sup> calcd. for C<sub>8</sub>H<sub>14</sub>N<sub>2</sub>OSNa<sup>+</sup>: 209.0719; found: 209.0731.

### (1R,2R)-2-(2,5-Dimethyl-1H-pyrrol-1-yl)cyclohexan-1-amine (S6)



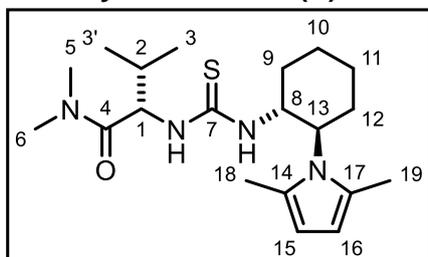
Following an adapted literature procedure,<sup>[18]</sup> (*R,R*)-diaminocyclohexane (1.14 g, 10 mmol, 1 eq.), 2,5-hexanedione (1.17 mL, 10 mmol, 1 eq.) and acetic acid (0.57 mL, 10 mmol, 1 eq.) were dissolved in MeOH (50 mL) and stirred at 50 °C for 1 h. The volatiles were removed under reduced pressure and the residue was redissolved in CH<sub>2</sub>Cl<sub>2</sub> (50 mL) and aq. NaOH solution (4 M, 50 mL). The separated aqueous layer was extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 x 30 mL) and the combined organic layers were dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated *in vacuo*. Purification by column chromatography

(SiO<sub>2</sub>, 1<sup>st</sup>: acetone:CH<sub>2</sub>Cl<sub>2</sub> 10:90 – 30:70; 2<sup>nd</sup>: MeOH:CH<sub>2</sub>Cl<sub>2</sub> 1:99 – 3:97) yielded **S6** as an orange oil (1.18 g, 6.13 mmol, 61%).

[ $\alpha$ ]<sub>D</sub><sup>25</sup> = -48.8 (c = 1.0 in CHCl<sub>3</sub>); **R<sub>f</sub>** = 0.10 (TFA:MeOH:CH<sub>2</sub>Cl<sub>2</sub> 1:4:95); **<sup>1</sup>H-NMR** (500 MHz, CDCl<sub>3</sub>):  $\delta$  = 5.78 (s, 1H, H8/9), 5.75 (s, 1H, H8/9), 3.60 (td, <sup>3</sup>J<sub>HH</sub> = 10.8, 4.7 Hz, 1H, H2), 3.26 (td, <sup>3</sup>J<sub>HH</sub> = 10.6, 4.0 Hz, 1H, H1), 2.36 (s, 3H; H11/12), 2.23 (s, 3H, H11/12), 2.10 – 2.01 (m, 1H, H6), 1.92 – 1.83 (m, 3H, H3, H3', H4), 1.83 – 1.76 (m, 1H, H5), 1.41 – 1.33 (m, 2H, H4', H5'), 1.28 – 1.15 (m, 1H, H6') ppm; **<sup>13</sup>C{<sup>1</sup>H}-NMR** (126 MHz, CDCl<sub>3</sub>):  $\delta$  = 130.0 (C7/10), 127.0

(C7/10), 108.0 (C8/9), 105.4 (C8/9), 63.9 (C2), 53.1 (C1), 35.6 (C6), 31.5 (C3), 26.4 (C4), 25.3 (C5), 15.4 (C11/12), 13.9 (C11/12) ppm; **IR** (ATR):  $\tilde{\nu}$  = 2934 (w), 2859 (w), 1659 (w), 1553 (w), 1518 (w), 1448 (w), 1395 (m), 1291 (m), 1215 (w), 1143 (w), 1024 (w), 979 (w), 952 (w), 870 (w), 850 (w), 745 (s), 664 (m)  $\text{cm}^{-1}$ ; **HR-ESI-MS**:  $m/z$ :  $[\text{M}+\text{H}]^+$  calcd. for  $\text{C}_{12}\text{H}_{20}\text{N}_2\text{H}^+$ : 193.1699; found: 193.1701. The analytical data are in agreement with the literature.<sup>[18]</sup>

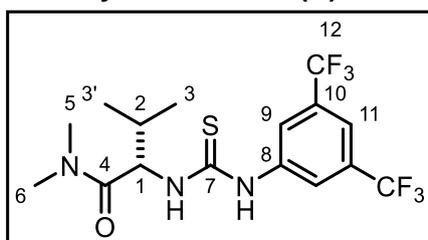
**(S)-2-(3-((1R,2R)-2-(2,5-Dimethyl-1H-pyrrol-1-yl)cyclohexyl)thioureido)-N,N,3-trimethylbutanamide (A)**



Following an adapted literature procedure,<sup>[18]</sup> **S5** (745 mg, 4 mmol, 1.0 eq.) and **S6** (846 mg, 4.4 mmol, 1.1 eq.) were dissolved in  $\text{CH}_2\text{Cl}_2$  (35 mL) and stirred at room temperature for 22 h. The solvent was removed and purification by column chromatography (1<sup>st</sup>:  $\text{MeOH}:\text{CH}_2\text{Cl}_2$  0:1 – 1.5:98.5; 2<sup>nd</sup>:  $\text{EtOAc}:\text{cyclohexane}$  3:7 – 1:1) yielded **A** (1.01 g, 2.68 mmol, 67%) as an orange solid.

$[\alpha]_{\text{D}}^{25} = +44.8$  ( $c = 0.5$  in  $\text{CHCl}_3$ );  $R_f = 0.14$  ( $\text{EtOAc}:\text{cyclohexane}$  2:3);  **$^1\text{H-NMR}$**  (500 MHz,  $\text{CDCl}_3$ ):  $\delta = 6.57$  (br s, 1 H,  $\text{NH}^{7-8}$ ), 6.21 (br s, 1 H,  $\text{NH}^{1-7}$ ), 5.70 (s, 2H, H15, H16), 5.27 (br s, 1H, H13), 4.38 (br s, 1H, H8), 3.83 – 3.73 (m, 1H, H1), 3.14 (s, 3H, H5), 2.94 (s, 3H, H6), 2.57 – 2.10 (m, 7H, H9, H18, H19), 2.10 – 1.68 (m, 5H, H2, H10, H11, H12, H12'), 1.45 – 1.13 (m, 3H, H9', H10, H11'), 0.87 (d,  $^3J_{\text{HH}} = 6.8$  Hz, 6H, H3) ppm;  **$^{13}\text{C}\{^1\text{H}\}\text{-NMR}$**  (151 MHz,  $\text{CDCl}_3$ ):  $\delta = 182.1$  (C7), 172.8 (C4), 129.1 (C14), 127.3 (C17), 108.7 (C15/16), 106.1 (C15/16), 59.9 (C1), 59.6 (C13), 56.1 (C8), 38.0 (C5), 35.8 (C6), 34.2 (C9), 32.3 (C2), 32.1 (C12), 26.0 (C10/11), 24.9 (C10/11), 19.1 (C3/3'), 18.8 (C3/3'), 15.6 (C18/19), 13.7 (C18/19) ppm; **IR** (ATR):  $\tilde{\nu} = 3247$  (w), 3048 (w), 2930 (w), 2859 (w), 2053 (w), 1632 (s), 1546 (s), 1520 (m), 1465 (w), 1447 (w), 1418 (w), 1396 (s), 1316 (w), 1291 (w), 1260 (w), 1230 (w), 1180 (w), 1130 (w), 1093 (w), 1069 (w), 1012 (w), 978 (w), 954 (w), 871 (w), 843 (w), 801 (w), 739 (w)  $\text{cm}^{-1}$ ; **HR-ESI-MS**:  $m/z$ :  $[\text{M}+\text{Na}]^+$  calcd. for  $\text{C}_{20}\text{H}_{34}\text{N}_4\text{OSNa}^+$ : 401.2346; found: 401.2347; **m.p.**: = 141-143  $^\circ\text{C}$ . The analytical data are in agreement with the literature.<sup>[18]</sup>

**(S)-2-(3-((1R,2R)-2-(2,5-Dimethyl-1H-pyrrol-1-yl)cyclohexyl)thioureido)-N,N,3-trimethylbutanamide (B)**



Following an adapted literature procedure,<sup>[18]</sup> **S4** was converted to the free amine by dissolving in  $\text{CH}_2\text{Cl}_2$  and washing with a sat. aq.  $\text{NaHCO}_3$  solution, drying over  $\text{Na}_2\text{SO}_4$ , filtering and concentration *in vacuo*. The free amine of **S4** (115 mg, 0.8 mmol, 1 eq.) was dissolved in  $\text{CH}_2\text{Cl}_2$  (5 mL) and  $\text{NEt}_3$  (0.11 mL, 0.8 mmol, 1 eq.) was slowly added. After stirring for 5 min at room temperature, 3,5-bis(trifluoromethyl)phenyl isothiocyanate (0.15 mL,

0.8 mmol, 1 eq.) was added and the reaction mixture was stirred at room temperature over night. The solvent was removed *in vacuo* and purification by column chromatography ( $\text{SiO}_2$ ,  $\text{EtOAc}:\text{cyclohexane}$  2:3) yielded **B** as an off-white solid (215 mg, 0.52 mmol, 65%).

$[\alpha]_{\text{D}}^{25} = -93.8$  ( $c = 0.5$  in  $\text{CHCl}_3$ );  $R_f = 0.13$  ( $\text{EtOAc}:\text{cyclohexane}$  2:3);  **$^1\text{H-NMR}$**  (600 MHz,  $\text{CDCl}_3$ ):  $\delta = 9.33$  (s, 1H,  $\text{NH}^{7-8}$ ), 8.37 (d,  $^3J_{\text{HH}} = 7.7$  Hz, 1H,  $\text{NH}^{1-7}$ ), 8.0 (s, 2H, H9), 7.48 (s, 1H, H11), 5.25 (t,  $^3J_{\text{HH}} = 8.0$  Hz, 1H, H1), 3.39 (s, 3H, H5/6), 3.05 (s, 3H, H5/6), 2.08 (m, 1H, H2), 1.13 (d,  $^3J_{\text{HH}} = 6.8$  Hz, 3H, H3/3'), 1.09 (d,  $^3J_{\text{HH}} = 6.8$  Hz, 3H, H3/3') ppm;  **$^{13}\text{C}\{^1\text{H}\}\text{-NMR}$**  (151 MHz,  $\text{CDCl}_3$ ):  $\delta = 181.6$  (C7), 174.9 (C4), 140.7 (C8), 131.4 (q,  $^2J_{\text{CF}} = 33.4$  Hz, C10), 123.3 (q,  $^1J_{\text{CF}} = 272.8$  Hz, C12), 122.7 (q,  $^3J_{\text{CF}} = 3.8$  Hz, C9), 117.5 (q,  $^3J_{\text{CF}} = 3.9$  Hz, C11), 59.7 (C1), 38.5 (C5/6), 36.4 (C5/6), 31.9 (C2), 19.4 (C3/3'), 19.2 (C3/3') ppm;  **$^{19}\text{F-NMR}$**  (564 MHz):  $\delta = -63.13$  ppm; **IR** (ATR):  $\tilde{\nu} = 3315$  (w), 3268 (w), 3099 (w), 3975 (w), 1645 (w), 1613 (w), 1597 (w), 1541 (m), 1474 (w), 1422 (w), 1407 (w), 1385 (m), 1271 (s), 1219 (w), 1170 (s), 1120 (s), 1108 (s), 1000 (w), 966 (m), 929 (w), 907 (w), 879 (m), 849 (w), 836 (w), 771 (w), 721 (m), 697 (w), 677 (m)  $\text{cm}^{-1}$ ; **HR-ESI-MS**:  $m/z$ :  $[\text{M}+\text{Na}]^+$  calcd. for  $\text{C}_{16}\text{H}_{19}\text{N}_3\text{OSF}_6\text{Na}^+$ : 438.1045; found: 438.1046; **m.p.**: = 142-144  $^\circ\text{C}$ . The analytical data are in agreement with the literature.<sup>[18]</sup>

## Reaction optimization

### Optimization and upscaling of the isomerization

Isomerization reactions were performed similar to general procedure **C** with differences shown in Table 19.

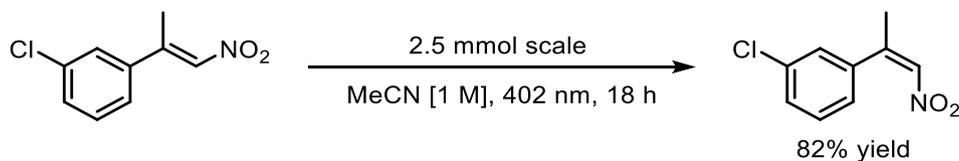
Table 19: Optimization of the isomerization of **E-1** to **Z-1**.

| entry           | scale [mmol] | molarity [M] | solvent                         | time | yield  | Z:E   |
|-----------------|--------------|--------------|---------------------------------|------|--------|-------|
| 1               | 0.2          | 0.1          | MeCN                            | 16 h | 33%    | 89:11 |
| 2               | 0.2          | 0.1          | 1,4-dioxane                     | 16 h | 25%    | 78:22 |
| 3               | 0.2          | 0.1          | toluene                         | 16 h | 29%    | 57:43 |
| 4               | 0.2          | 0.1          | THF                             | 16 h | 42%    | 78:22 |
| 5               | 0.2          | 0.1          | cyclohexane                     | 16 h | 38%    | 85:15 |
| 6               | 0.2          | 0.1          | CH <sub>2</sub> Cl <sub>2</sub> | 16 h | 52%    | 86:14 |
| 7 <sup>a</sup>  | 0.2          | 0.1          | MeCN                            | 14 h | 51%    | 90:10 |
| 8 <sup>b</sup>  | 0.2          | 0.1          | cyclohexane                     | 14 h | 44%    | 87:13 |
| 9               | 0.2          | 0.1          | MeCN                            | 4 h  | 60%    | 80:20 |
| 10              | 0.2          | 0.1          | MeCN                            | 6 h  | 43%    | 85:15 |
| 11              | 0.2          | 0.1          | MeCN                            | 24 h | 35%    | 91:09 |
| 12              | 0.2          | 0.2          | MeCN                            | 16 h | 34%    | 86:14 |
| 13              | 0.2          | 0.5          | MeCN                            | 16 h | 39%    | 90:10 |
| 14              | 0.2          | 1.0          | MeCN                            | 16 h | 47%    | 89:11 |
| 15              | 1.0          | 0.2          | MeCN                            | 16 h | 69%    | 90:10 |
| 16 <sup>c</sup> | 0.2          | 0.1          | MeCN                            | 16 h | quant. | <1:99 |
| 17 <sup>d</sup> | 0.2          | 0.1          | MeCN                            | 16 h | quant. | 99:<1 |
| 18 <sup>e</sup> | 0.5          | 1.0          | MeCN                            | 7 h  | 72%    | 92:08 |

<sup>a</sup> (-)-riboflavin (0.05 eq.) were added; <sup>b</sup> (-)-riboflavin tetraacetate (0.05 eq.) were added; <sup>c</sup> stirred in darkness; <sup>d</sup> stirred in darkness, starting from the Z-isomer; <sup>e</sup> average of two experiments

### Upscaling

Isomerization reaction was performed in a 25 mL round bottom flask according to general procedure **C** using a small LED (~ 402 nm). The reaction was run on a 2.5 mmol scale under irradiation for 18 h.

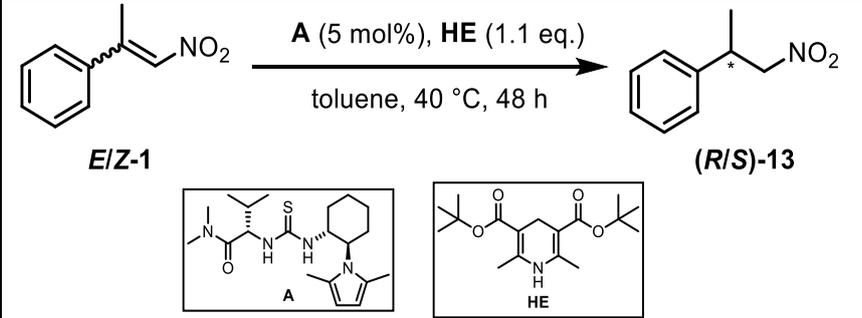


Scheme 2: Upscaling of the isomerization of **E-9** to **Z-9**.

## Optimization of the hydrogenation using catalyst A

Hydrogenations were performed similar to general procedure E with differences shown in Table 20.

Table 20: Optimization of hydrogenation of *E*-1 or *Z*-1 to (*S*)-13 or (*R*)-13.

|  |          |              |              |       |       |
|--|----------|--------------|--------------|-------|-------|
| entry  | isomer   | scale [mmol] | molarity [M] | yield | er    |
| 1  | <i>E</i> | 0.39         | 1.3          | 84%   | 05:95 |
| 2  | <i>Z</i> | 0.39         | 1.3          | 83%   | 87:13 |
| 3 <sup>a</sup>   | <i>E</i> | 0.20         | 0.33         | 96%   | 04:96 |
| 4 <sup>a</sup>   | <i>Z</i> | 0.20         | 0.33         | 88%   | 84:16 |
| <sup>a</sup> average of two experiments  |          |              |              |       |       |

## Optimization of the hydrogenation using the Z-isomer

Hydrogenations were performed similar to general procedure **F** with differences shown in Table 21.

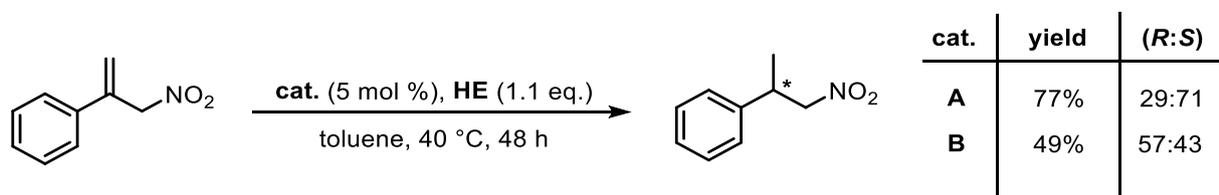
Table 21: Optimization of the hydrogenation of **Z-1** to **(R)-13** and control experiments.

| entry             | cat. | cat. loading | HE loading | yield            | er <sup>a</sup> |
|-------------------|------|--------------|------------|------------------|-----------------|
| 1 <sup>b</sup>    | A    | 5.0%         | 1.1 eq.    | 88%              | 84:16           |
| 2                 | A    | 10.0%        | 1.1 eq.    | 61%              | 65:35           |
| 3                 | A    | 20.0%        | 1.1 eq.    | 86%              | 55:45           |
| 4                 | A    | 1.0%         | 1.1 eq.    | 71%              | 61:39           |
| 5                 | A    | 2.5%         | 1.1 eq.    | 58%              | 76:24           |
| 6                 | A    | 5.0%         | 3.0 eq.    | 73%              | 78:22           |
| 7                 | A    | 5.0%         | 4.4 eq.    | 75%              | 77:23           |
| 8                 | A    | 5.0%         | 5.0 eq.    | 38%              | 75:25           |
| 9 <sup>b</sup>    | B    | 5.0%         | 1.1 eq.    | 94%              | 93:07           |
| 10 <sup>b,c</sup> | B    | 5.0%         | 1.1 eq.    | 86%              | 09:91           |
| 11                | -    | -            | 1.1 eq.    | 89% <sup>d</sup> | 50:50           |
| 12 <sup>c</sup>   | -    | -            | 1.1 eq.    | 95% <sup>e</sup> | 50:50           |
| 13                | A    | 5.0%         | -          | -                | -               |
| 14                | B    | 5.0%         | -          | -                | -               |
| 15 <sup>c</sup>   | A    | 5.0%         | -          | -                | -               |
| 16 <sup>c</sup>   | B    | 5.0%         | -          | -                | -               |

<sup>a</sup> where applicable; <sup>b</sup> average of two experiments; <sup>c</sup> starting from **E-1**; <sup>d</sup> combined yield (alkane:**Z**:**E**:regioisomer 40:11:35:14); <sup>e</sup> combined yield (alkane:**Z**:**E**:regioisomer 90:<1:8:2).

## Analysis of Regioisomer Hydrogenation

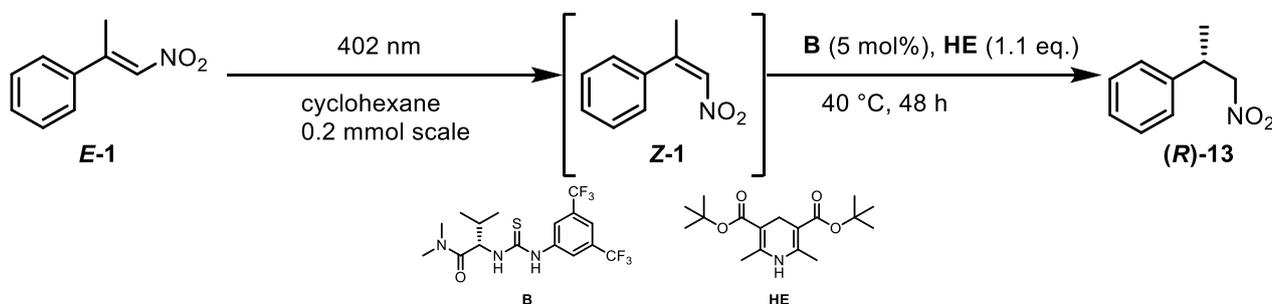
Throughout the isomerization scope small quantities of regioisomer could not be separated from the corresponding *Z*-isomer for a small number of substrates. However, during hydrogenation reactions the regioisomer was retained in similar quantities. Despite this, we looked to analyse the hydrogenation of the regioisomer to disclude any negative or cooperative effects it may have. Hydrogenations were performed similar to general procedure **F** with differences shown in Scheme 3.



Scheme 3: Hydrogenation of the regioisomer.

As observed hydrogenation did occur in much smaller quantities in comparison to *E*- and *Z*-isomers. This is presumably due to a preliminary, *in situ*, positional isomerization to reform the conjugated system followed by a subsequent hydrogenation. The data supports this hypothesis as enantioselectivity is scrambled demonstrating a mixture of *E*- and *Z*-isomer are formed and subsequently hydrogenated. Notably catalyst **A** prefers formation of the enantiomer derived from the *E*-isomer. As hydrogenation of the *Z*-isomer (in which small quantities of regioisomer persist) proceeded smoothly, this indicates that the presence of regioisomer has no effect on reaction output.

## One Pot Isomerization-Hydrogenation of *E*-1 to (*R*)-13

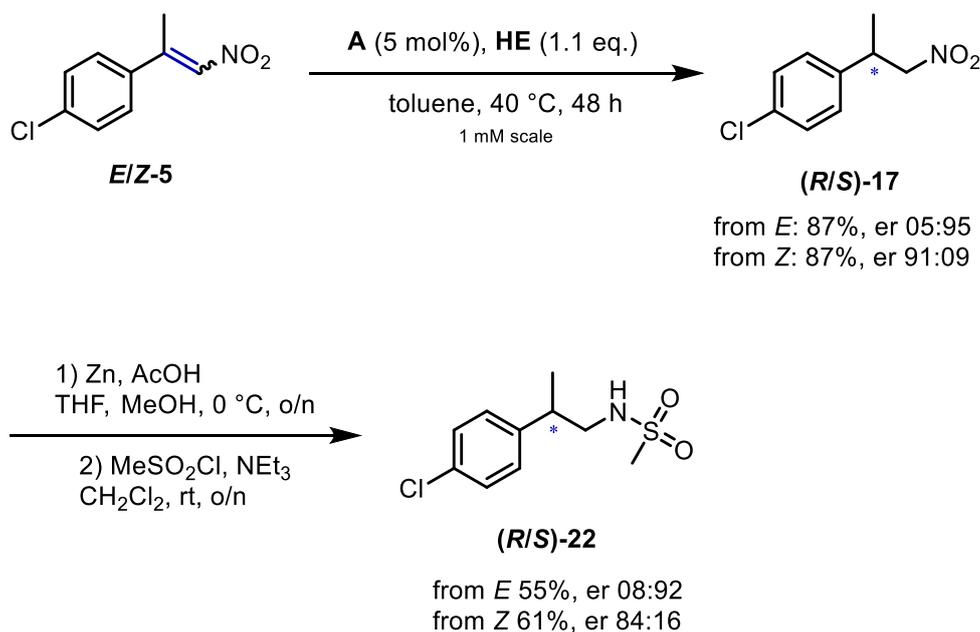


The one pot isomerization-hydrogenation was conducted as follows:

In a flame dried 2 mL vial, the (*E*)-nitrostyrene (0.2 mmol, 1 eq.) was dissolved in dry cyclohexane (616  $\mu$ L, 0.32 M). The vial was sealed with a rubber septum and parafilm and the mixture was degassed by bubbling argon through it with a needle for ca. 2 min. The vial was connected to a balloon filled with argon and placed over the LED in the shown irradiation set up (Figure 2). After irradiation at 402 nm for 7 h, catalyst **B** (4.2 mg, 0.01 mmol, 0.05 eq.) and the Hantzsch ester (di-*tert*-butyl 2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate) (68 mg, 0.22 mmol, 1.1 eq.) were added. A rubber septum and parafilm were used to seal the vial, which was then placed in a preheated metal heating block at 40 °C for 48 h (Figure 3). After that time, the crude reaction mixture was filtered through a plug of silica, which was rinsed with Et<sub>2</sub>O:*n*-pentane (2:98) to remove the catalyst and most of the oxidized Hantzsch ester. The filtrate was concentrated *in vacuo* and purified by column chromatography to yield the (*R*)-**13** as a colorless oil (26.7 mg, 0.16 mmol, 81%). The enantiomeric ratio was found to be 83:17, determined *via* chiral HPLC (Reprosil OM, *n*-hexane:*i*PrOH 97:3, 1.0 mL/min,  $\lambda$  = 210 nm).

## Synthesis of drug scaffolds

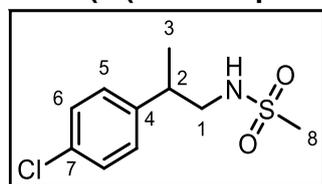
### General procedure G for the synthesis of sulfonamides



Scheme 4: Preparation of chiral sulfonamides.

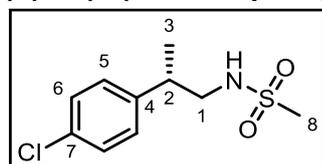
Following an adapted literature procedure,<sup>[7]</sup> **(R/S)-17** (1.0 eq.) was dissolved in THF:MeOH (10:1, 0.25 M) and cooled to 0 °C before Zn dust (5 eq.) and AcOH (30 eq.) were added. The ice bath was removed and the reaction mixture was stirred at room temperature for 24 h. Zn was removed by filtration and the residue was diluted with H<sub>2</sub>O. The pH of the filtrate was adjusted to pH 11 with NaOH (5 M) and organics were extracted with EtOAc (3 x). The combined organic layers were washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated *in vacuo* to yield the crude amine which was used for the next step without further analysis and purification. The amine from the previous step (1.0 eq.) was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (0.25 M), cooled to 0 °C before NEt<sub>3</sub> (5.74 eq.) and methanesulfonylchloride (1.50 eq.) were added dropwise. After one hour at 0 °C the reaction mixture was stirred at room temperature over night. Then the reaction mixture was diluted with Et<sub>2</sub>O and H<sub>2</sub>O was added. The separated organic layer was washed with HCl (0.2 M), sat. aq. NaHCO<sub>3</sub> and brine before being dried over MgSO<sub>4</sub>. After filtration and concentration *in vacuo*, the crude residue was purified by column chromatography (SiO<sub>2</sub>, EtOAc:cyclohexane) yielding the sulfonamide.

#### **rac-N-(2-(4-Chlorophenyl)propyl)methanesulfonamide (rac-22)**



Prepared according to general procedure **G**, **rac-17** (250 mg, 1.25 mmol, 1.0 eq.) in THF:MeOH (10:1, 5 mL) was reduced to the amine using Zn dust (409 mg, 6.25 mmol, 5 eq.) and AcOH (2.14 mL, 37.5 mmol, 30 eq.). The crude amine was treated with NEt<sub>3</sub> (1.0 mL, 7.17 mmol, 5.74 eq.) and methanesulfonyl chloride (145 μL, 1.88 mmol, 1.50 eq.) in CH<sub>2</sub>Cl<sub>2</sub> (5 mL) to yield **rac-22** as a colorless solid (212.0 mg, 0.86 mmol, 68%) after purification by column chromatography (SiO<sub>2</sub>, EtOAc: cyclohexane 15:85 – 30:70).

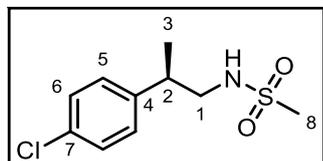
#### **(S)-N-(2-(4-Chlorophenyl)propyl)methanesulfonamide ((S)-22)**



Prepared according to general procedure **G**, **(S)-17** (er: 05:95, 50 mg, 0.25 mmol, 1.0 eq.) in THF:MeOH (10:1, 5 mL) was reduced to the amine using Zn dust (82 mg, 1.25 mmol, 5 eq.) and AcOH (0.43 mL, 7.5 mmol, 30 eq.). The crude amine was treated with NEt<sub>3</sub> (0.2 mL, 1.43 mmol, 5.74 eq.) and methanesulfonyl chloride (29 μL,

0.38 mmol, 1.50 eq.) in CH<sub>2</sub>Cl<sub>2</sub> (1 mL) to yield **(S)-22** as a colorless solid (34.0 mg, 0.14 mmol, 55%) after purification by column chromatography (SiO<sub>2</sub>, EtOAc: cyclohexane 15:85 – 30:70). The enantiomeric ratio was found to be 08:92 by chiral HPLC (Reprosil Chiral-AM, *n*-hexane:*i*PrOH 98:2, 1.0 mL/min, λ = 210 nm, t<sub>R</sub> (major): 37.839 min, t<sub>R</sub> (minor): 43.132 min).

**(R)-N-(2-(4-Chlorophenyl)propyl)methanesulfonamide ((R)-22)**



Prepared according to general procedure **G**, **(R)-17** (er: 91:09, 50 mg, 0.25 mmol, 1.0 eq.) in THF:MeOH (10:1, 5 mL) was reduced to the amine using Zn dust (82 mg, 1.25 mmol, 5 eq.) and AcOH (0.43 mL, 7.5 mmol, 30 eq.). The crude amine was treated with NEt<sub>3</sub> (0.2 mL, 1.43 mmol, 5.74 eq.) and methanesulfonyl chloride (29 μL, 0.38 mmol, 1.50 eq.) in CH<sub>2</sub>Cl<sub>2</sub> (1 mL) to yield **(R)-22** as a colorless solid (38.0 mg, 0.15 mmol, 61%) after purification by column chromatography (SiO<sub>2</sub>, EtOAc: cyclohexane 15:85 – 30:70). The enantiomeric ratio was found to be 84:16 by chiral HPLC Reprosil Chiral-AM, *n*-hexane:*i*PrOH 98:2, 1.0 mL/min, λ = 210 nm, t<sub>R</sub> (major): 37.161 min, t<sub>R</sub> (minor): 42.785 min).

**(S)-22** (er 92:08): [α]<sub>D</sub><sup>25</sup> = +29.3 (c = 0.5 in CHCl<sub>3</sub>); **(R)-22** (er 16:84): [α]<sub>D</sub><sup>25</sup> = -29.4 (c = 0.5 in CHCl<sub>3</sub>); *R<sub>f</sub>* = 0.33 (EtOAc:cyclohexane, 20:80); <sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>): δ = 7.34 – 7.29 (m, 2H, H6), 7.18 – 7.14 (m, 2H, H5), 4.13 – 3.94 (m, 1H, NH), 3.38 – 3.30 (m, 1H, H1), 3.25 – 3.15 (m, 1H, H1'), 3.02 – 2.92 (m, 1H, H2), 2.83 (s, 3H, H8), 1.30 (d, <sup>3</sup>J<sub>HH</sub> = 6.9 Hz, 3H, H3) ppm; <sup>13</sup>C{<sup>1</sup>H}-NMR (101 MHz, CDCl<sub>3</sub>): δ = 141.5 (C4), 133.1 (C7), 129.2 (C6), 128.8 (C5), 50.0 (C1), 40.7 (C8), 40.1 (C2), 19.1 (C3) ppm; IR (ATR):  $\tilde{\nu}$  = 3244 (w), 2915 (w), 1491 (w), 1452 (w), 1436 (w), 1411 (w), 1384 (w), 1345 (w), 1335 (w), 1311 (s), 1270 (w), 1196 (w), 1155 (m), 1125 (m), 1112 (w), 1090 (m), 1070 (s), 1023 (m), 1011 (m), 983 (m), 925 (w), 894 (w), 847 (m), 822 (s), 784 (m), 760 (s), 690 (w) cm<sup>-1</sup>; HR-ESI-MS: *m/z*: [M+Na]<sup>+</sup> calcd. for C<sub>10</sub>H<sub>14</sub>NO<sub>2</sub>SCINa<sup>+</sup>: 270.0326; found: 270.0320; m.p.: = 90 – 92 °C.

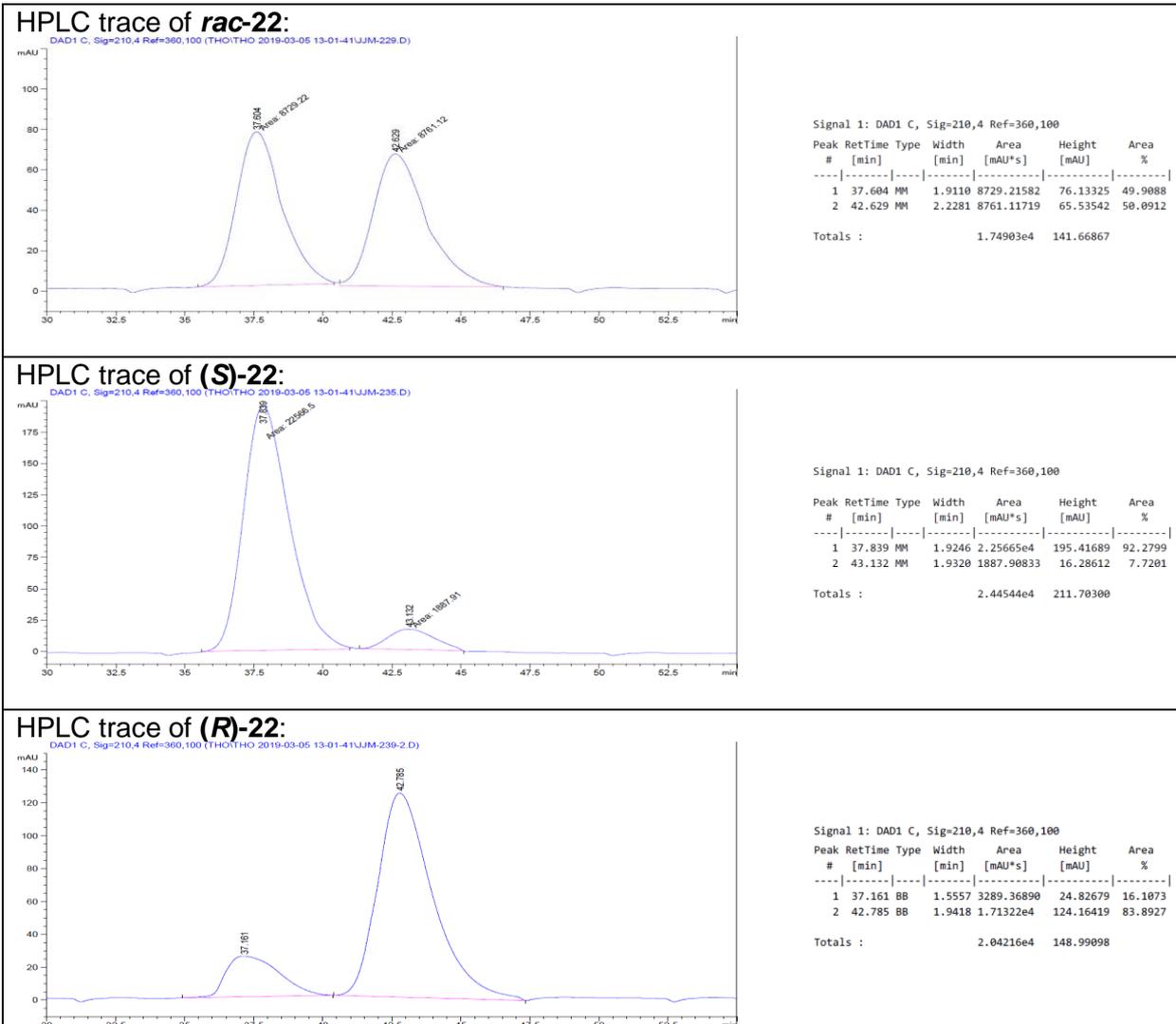
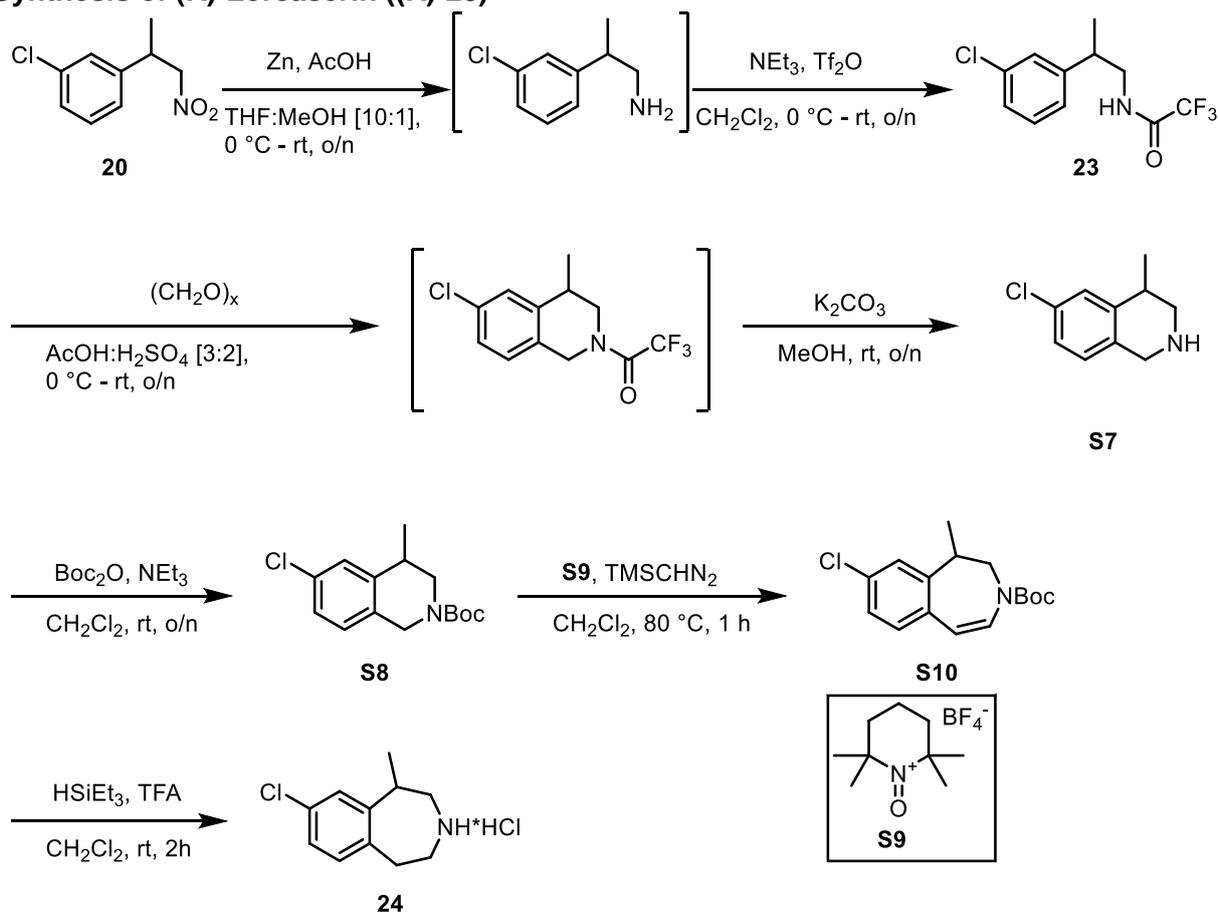


Figure 15: HPLC traces of **22**; top: *rac*-**22**; middle: (*S*)-**22** ; bottom: (*R*)-**22**.

### Synthesis of (*R*)-Lorcaserin ((*R*)-28)

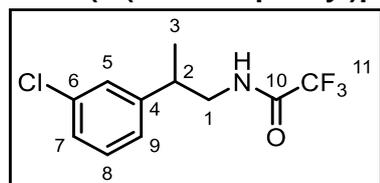


Scheme 5: Preparation of racemic and (*R*)-Lorcaserin ((*R*)-24).

### General procedure H for the synthesis of *N*-(2-(3-Chlorophenyl)propyl)-2,2,2-trifluoroacetamide (**23**)

Following an adapted literature procedure,<sup>[7]</sup> **20** (1.0 eq.) was dissolved in THF:MeOH (10:1, 0.25 M) and cooled to 0 °C before Zn dust (5 eq.) and AcOH (30 eq.) were added. The ice bath was removed and the reaction mixture was stirred at room temperature for 24 h. Zn was removed by filtration and the residue was diluted with H<sub>2</sub>O. The pH of the filtrate was adjusted to pH 11 with NaOH (5 M) and was extracted with EtOAc (3 x). The combined organic layers were washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated *in vacuo* to yield the crude amine which was used for the next step without further analysis and purification. The amine from the previous step (1.0 eq.) was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (0.12 M), cooled to 0 °C before NEt<sub>3</sub> (1.13 eq.) and trifluoroacetic anhydride (1.65 eq.) were added slowly. The reaction mixture was stirred over night while warming up to room temperature. After this time the reaction mixture was poured onto H<sub>2</sub>O and the separated aqueous layer was extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 x). The combined organic layers were dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated *in vacuo*. Purification by column chromatography (SiO<sub>2</sub>, EtOAc: cyclohexane) yielded the trifluoroacetamide.

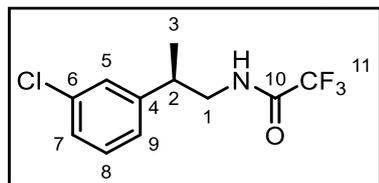
### *rac*-*N*-(2-(3-Chlorophenyl)propyl)-2,2,2-trifluoroacetamide (*rac*-23)



Prepared according to general procedure **H**, *rac*-**20** (405 mg, 2.03 mmol, 1 eq.) in THF:MeOH (10:1, 8.2 mL) was reduced to the amine (321.0 mg, 1.89 mmol, 93%) using Zn dust (663 mg, 10.14 mmol, 5 eq.) and AcOH (3.48 mL, 60.86 mmol, 30 eq.). The crude amine (236 mg, 1.39 mmol, 1.00 eq.) was treated with NEt<sub>3</sub> (0.22 mL, 1.57 mmol, 1.13 eq.) and trifluoroacetic anhydride (0.32 mL, 2.30 mmol, 1.65 eq.) in CH<sub>2</sub>Cl<sub>2</sub> (12 mL) to yield *rac*-**23** as a light yellow oil

(157.0 mg, 0.59 mmol, 43%) after purification by column chromatography (SiO<sub>2</sub>, EtOAc:cyclohexane, 5:95).

**(R)-N-(2-(3-Chlorophenyl)propyl)-2,2,2-trifluoroacetamide ((R)-23)**



Prepared according to general procedure H, (**R**)-**20** (er 95:05, 349 mg, 1.75 mmol, 1. eq.) in THF:MeOH (10:1, 7 mL) was reduced to the amine (288 mg, 1.70 mmol, 97%) using Zn dust (572 mg, 8.75 mmol, 5 eq.) and AcOH (3 mL, 52.5 mmol, 30 eq.). The crude amine (288 mg, 1.70 mmol, 1.00 eq.) was treated with NEt<sub>3</sub> (0.27 mL, 1.92 mmol, 1.13 eq.) and trifluoroacetic anhydride (0.39 mL, 2.81 mmol, 1.65 eq.) in CH<sub>2</sub>Cl<sub>2</sub> (8 mL) to yield (**R**)-**23** as a light yellow oil (372.9 mg, 1.40 mmol, 83%) after purification by column chromatography (SiO<sub>2</sub>, EtOAc:cyclohexane, 5:95). The enantiomeric ratio was found to be 95:05 by chiral HPLC (Reprosil Chiral-OM, *n*-hexane:*i*PrOH 97:03, 1.0 mL/min, λ = 210 nm, t<sub>R</sub> (major): 11.640 min, t<sub>R</sub> (minor): 14.254 min).

**(R)-23** (er 95:05): [α]<sub>D</sub><sup>25</sup> = +54.2 (c = 0.5 in CHCl<sub>3</sub>); R<sub>f</sub> = 0.21 (EtOAc:cyclohexane 5:95); <sup>1</sup>H-NMR (600 MHz, CDCl<sub>3</sub>): δ = 7.30 – 7.24 (m, 2H, H8, H7), 7.20 (t, <sup>4</sup>J<sub>HH</sub> = 1.9 Hz, 1H, H5), 7.09 – 7.07 (m, 1H, H9), 6.13 (s, 1H, NH), 3.69 – 3.63 (m, 1H, H1), 3.39 – 3.31 (m, 1H, H1'), 3.06 – 2.97 (m, 1H, H2), 1.31 (d, <sup>3</sup>J<sub>HH</sub> = 7.0 Hz, 3H, H3) ppm; <sup>13</sup>C{<sup>1</sup>H}-NMR (151 MHz, CDCl<sub>3</sub>): δ = 157.4 (q, <sup>2</sup>J<sub>CF</sub> = 36.5 Hz, C10), 145.0 (C4), 135.0 (C6), 130.4 (C8), 127.6 (C7), 127.3 (C5), 125.5 (C9), 115.9 (q, <sup>1</sup>J<sub>CF</sub> = 287.8 Hz, C11), 46.3 (C1), 39.3 (C2), 18.9 (C3) ppm; <sup>19</sup>F-{<sup>1</sup>H}-NMR (564 MHz, CDCl<sub>3</sub>): δ = -76.01 (s) ppm; IR (ATR): ν̄ = 3305 (w), 3105 (w), 2972 (w), 1702 (s), 1598 (w), 1558 (w), 1479 (w), 1457 (w), 1433 (w), 1384 (w), 1365 (w), 1338 (w), 1205 (m), 1154 (s), 1084 (w), 999 (w), 931 (w), 880 (w), 836 (w), 784 (m), 725 (m), 696 (s) cm<sup>-1</sup>; HR-ESI-MS: *m/z* [M+Na]<sup>+</sup> calcd. for C<sub>11</sub>H<sub>11</sub>NOCIF<sub>3</sub>Na<sup>+</sup>: 288.0378; found: 288.0380. The analytical data are in agreement with the literature.<sup>[7]</sup>

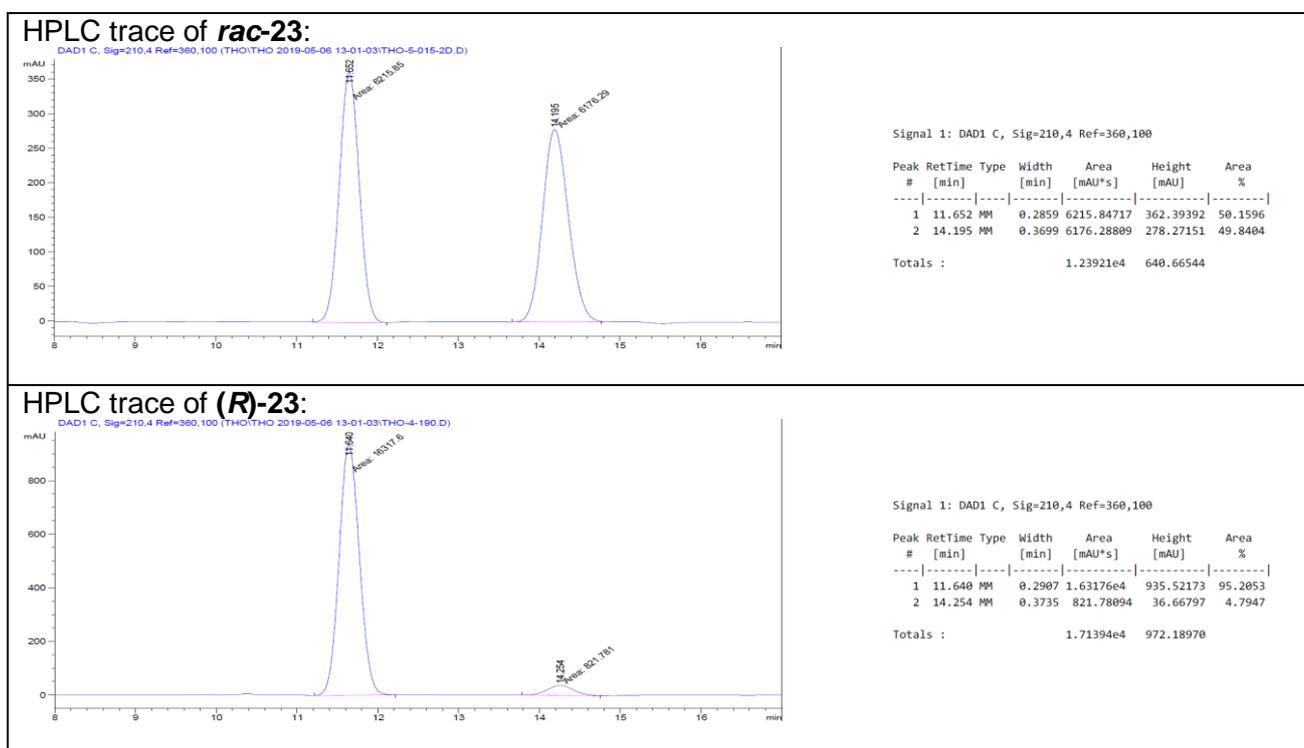
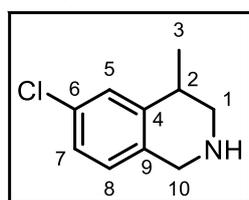


Figure 16: HPLC traces of **23**; top: *rac*-**23**; bottom: (**R**)-**23**.

### General procedure I for the synthesis of 6-chloro-4-methyl-1,2,3,4-tetrahydroisoquinoline (S7)

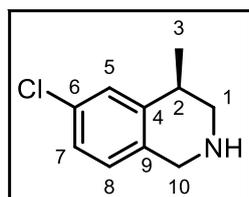
Following an adapted literature procedure,<sup>[7]</sup> AcOH (0.23 M) and H<sub>2</sub>SO<sub>4</sub> (0.35 M) were mixed at 0 °C before **23** (1 eq.) and paraformaldehyde (2 eq.) were added sequentially. The reaction mixture was stirred at room temperature over night and then poured onto H<sub>2</sub>O. After extraction with EtOAc (3 x), the combined organic layers were washed with a sat. aq. NaHCO<sub>3</sub> solution, H<sub>2</sub>O and brine, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated *in vacuo*. The crude trifluoroacetate protected tetrahydroisoquinoline was used without further analysis and purification for the next step. The crude trifluoroacetate protected tetrahydro-isoquinoline (1.0 eq.) from the previous step was dissolved in MeOH (0.1 M) and an aqueous K<sub>2</sub>CO<sub>3</sub> solution (0.44 M, 3 eq.) was added. The reaction mixture was stirred at room temperature overnight before being acidified to pH 8 with HCl (1 M). This mixture was extracted with EtOAc (3 x) and the combined organic layers were washed with H<sub>2</sub>O (2 x), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated *in vacuo*. Purification by column chromatography (SiO<sub>2</sub>, MeOH:EtOAc) yielded **S7**.

### *rac*-6-chloro-4-methyl-1,2,3,4-tetrahydroisoquinoline (*rac*-S7)



Prepared according to general procedure I, *rac*-**23** (133 mg, 0.50 mmol, 1 eq.) and paraformaldehyde (30 mg, 1.00 mmol, 2 eq.) were reacted in AcOH (2.2 mL) and H<sub>2</sub>SO<sub>4</sub> (1.4 mL) to the crude trifluoroacetate protected tetrahydroisoquinoline, a light yellow oil (94.1 mg, 0.34 mmol, 68%). This trifluoroacetate protected tetrahydroisoquinoline (77 mg, 0.28 mmol, 1 eq.) was deprotected using an aqueous K<sub>2</sub>CO<sub>3</sub> solution (0.44 M, 1.9 mL, 0.84 mmol, 3 eq.) and MeOH (3.3 mL). Purification by column chromatography (SiO<sub>2</sub>, MeOH:EtOAc 0:1 – 1:1) yielded *rac*-**24** as a yellow solid (16.0 mg, 0.09 mmol, 18%).

### (*R*)-6-chloro-4-methyl-1,2,3,4-tetrahydroisoquinoline ((*R*)-S7)



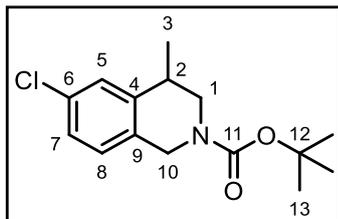
Prepared according to general procedure I, (*R*)-**23** (er 95:05, 310 mg, 1.17 mmol, 1 eq.) and paraformaldehyde (21 mg, 0.70 mmol, 2 eq.) were reacted in AcOH (1.5 mL) and H<sub>2</sub>SO<sub>4</sub> (1 mL) to the crude trifluoroacetate protected tetrahydroisoquinoline, a light yellow oil (320.7 mg, 1.15 mmol, 99%). This crude tetrafluoroacetate protected tetrahydroisoquinoline (320 mg, 1.15 mmol, 1 eq.) was deprotected using an aqueous K<sub>2</sub>CO<sub>3</sub> solution (0.44 M, 8 mL, 3.51 mmol, 3 eq.) and MeOH (14 mL). Purification by column chromatography (SiO<sub>2</sub>, MeOH:EtOAc 0:1 – 1:1) yielded (*R*)-**S7** as viscous yellow oil (90.1 mg, 0.50 mmol, 43%).

(*R*)-**23**: [ $\alpha$ ]<sub>D</sub><sup>25</sup> = +35.5 (c = 0.5 in CHCl<sub>3</sub>); R<sub>f</sub> = 0.27 (MeOH:EtOAc 20:80); <sup>1</sup>H-NMR (600 MHz, CDCl<sub>3</sub>):  $\delta$  = 7.22 (s, 1H, H5), 7.14 (d, <sup>3</sup>J<sub>HH</sub> = 8.1 Hz, 1H, H7), 6.98 (d, <sup>3</sup>J<sub>HH</sub> = 8.1 Hz, 1H, H8), 5.53 (br s, 1H, NH), 4.10 (s, 2H, H10), 3.33 (d, <sup>2</sup>J<sub>HH</sub> = 12.5 Hz, 1H, H1/1'), 3.11 – 3.03 (m, 1H, H2), 2.88 – 2.82 (m, 1H, H1/1'), 1.33 (d, <sup>3</sup>J<sub>HH</sub> = 7.2 Hz, 3H, H3) ppm; <sup>13</sup>C{<sup>1</sup>H}-NMR (151 MHz, CDCl<sub>3</sub>):  $\delta$  = 140.6 (C4), 133.0 (C6), 130.3 (C9), 127.9 (C8), 127.9 (C5), 126.8 (C7), 49.2 (C1), 46.4 (C10), 31.0 (C2), 19.7 (C3) ppm; IR (ATR):  $\tilde{\nu}$  = 2932 (w), 2862 (w), 2749 (w), 2670 (w), 2590 (w), 2470 (w), 2429 (w), 1679 (w), 1601 (w), 1573 (w), 1483 (m), 1448 (s), 1405 (w), 1383 (w), 1351 (w), 1332 (w), 1271 (w), 1222 (w), 1190 (w), 1132 (w), 1096 (w), 1082 (w), 1028 (w), 971 (w), 961 (w), 917 (w), 880 (w), 857 (w), 829 (s), 808 (w), 779 (w), 730 (w), 698 (w), 662 (m) cm<sup>-1</sup>; HR-ESI-MS: m/z. [M+H]<sup>+</sup> calcd. for C<sub>10</sub>H<sub>12</sub>NCIH<sup>+</sup>: 182.0731; found: 182.0739.

### General procedure J for the synthesis of *tert*-butyl-6-chloro-4-methyl-3,4-dihydroisoquinoline-2(1*H*)-carboxylate (S8)

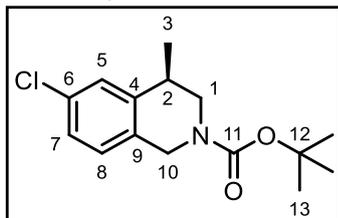
Following an adapted literature procedure,<sup>[7]</sup> **S7** (1.0 eq.) was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (0.03 M) and Boc<sub>2</sub>O (1.1 eq.) and NEt<sub>3</sub> (1.2 eq.) were added. The reaction mixture was stirred at room temperature over night, before H<sub>2</sub>O was added. The aqueous layer was extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 x) and the combined organic layers were washed with an aq. NaOH solution (1 M), brine, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated *in vacuo*. The carboxylate was used for the next step without further purification.

### *rac-tert*-Butyl-6-chloro-4-methyl-3,4-dihydroisoquinoline-2(1*H*)-carboxylate (*rac*-S8)



Prepared according to general procedure J, *rac*-S7 (15 mg, 0.08 mmol, 1.0 eq.) was Boc-protected using Boc<sub>2</sub>O (25 mg, 0.09 mmol, 1.1 eq.) and NEt<sub>3</sub> (3 drops) in CH<sub>2</sub>Cl<sub>2</sub> (3 mL). The carboxylate was obtained as a yellow oil (21.0 mg, 0.08 mmol, 93%) and used without further purification.

### *tert*-Butyl (*R*)-6-chloro-4-methyl-3,4-dihydroisoquinoline-2(1*H*)-carboxylate (*(R)*-S8)



Prepared according to general procedure J, (*R*)-S7 (70 mg, 0.38 mmol, 1.0 eq.) was Boc-protected using Boc<sub>2</sub>O (119 mg, 0.42 mmol, 1.1 eq.) and NEt<sub>3</sub> (0.06 mL, 0.46 mmol, 1.2 eq.) in CH<sub>2</sub>Cl<sub>2</sub> (15 mL). The carboxylate was obtained as a yellow oil (63.7 mg, 0.23 mmol, 59%) after purification by column chromatography (SiO<sub>2</sub>, EtOAc:cyclohexane 5:95). The enantiomeric ratio was found to be 95:05 by chiral HPLC (Reprosil

Chiral-OM, *n*-hexane:*i*PrOH 99.3:0.7, 1.0 mL/min, λ = 210 nm, t<sub>R</sub> (major): 7.022 min, t<sub>R</sub> (minor): 7.452 min).

(*R*)-25 (er 95:05): [α]<sub>D</sub><sup>25</sup> = -18 (c = 0.1 in CHCl<sub>3</sub>); R<sub>f</sub> = 0.34 (EtOAc:cyclohexane 5:95); <sup>1</sup>H-NMR (500 MHz, CDCl<sub>3</sub>): δ = 7.18 (s, 1H, H5), 7.16 – 7.13 (m, 1H, H7), 7.02 (d, <sup>3</sup>J<sub>HH</sub> = 8.1 Hz, 1H, H8), 4.69 (br s, 1H, H10), 4.48 – 4.31 (m, 1H, H10'), 3.52 (br s, 2H, H1), 3.00 – 2.86 (m, 1H, H2), 1.49 (s, 9H, H13), 1.26 (d, <sup>3</sup>J<sub>HH</sub> = 7.0 Hz, 3H, H3) ppm; <sup>13</sup>C{<sup>1</sup>H}-NMR (126 MHz, CDCl<sub>3</sub>): δ = 155.2 (C11), 142.0 (C4), 132.3 (C6), 131.7 (C9), 127.7 (C5), 127.6 (C8), 126.5 (C7), 80.1 (C12), 47.6 (C1), 45.5 (C10), 33.2 (C2), 28.6 (C13), 19.5 (C3) ppm; IR (ATR):  $\tilde{\nu}$  = 2978 (w), 2933 (w), 1807 (w), 1757 (w), 1694 (m), 1600 (w), 1573 (w), 1478 (w), 1458 (w), 1419 (w), 1369 (w), 1327 (w), 1307 (w), 1236 (w), 1211 (m), 1162 (m), 1114 (s), 1065 (s), 1012 (w), 940 (w), 914 (w), 874 (w), 844 (m), 818 (w), 774 (w), 706 (w) cm<sup>-1</sup>; HR-ESI-MS: *m/z*: [M+Na]<sup>+</sup> calcd. for C<sub>15</sub>H<sub>20</sub>NO<sub>2</sub>ClNa<sup>+</sup>: 304.1075; found: 304.1089. The analytical data are in agreement with the literature.<sup>[7]</sup>

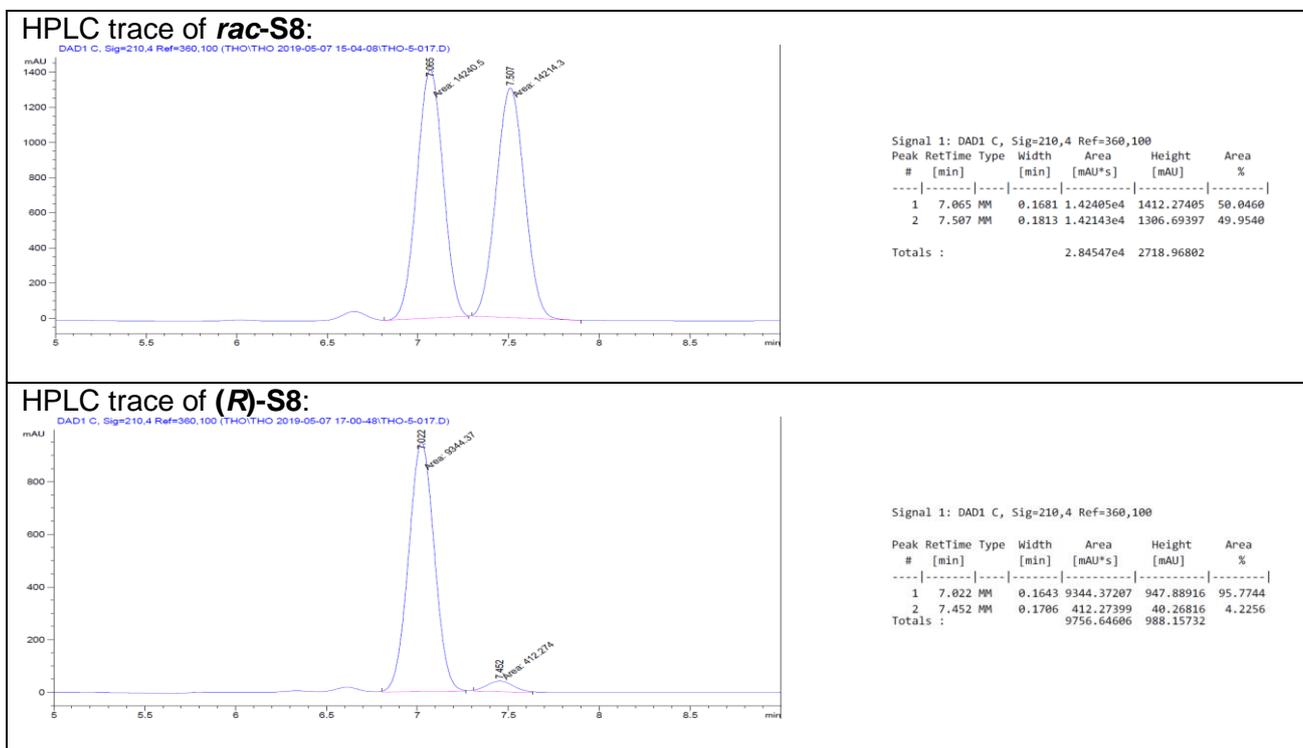
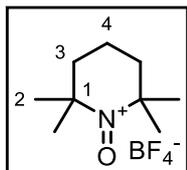


Figure 17: HPLC traces of S8; top: *rac*-S8; bottom: (*R*)-S8.

### 2,2,6,6-Tetramethylpiperidine-1-oxoammonium tetrafluoroborate (**S9**)



Following an adapted literature procedure,<sup>[19]</sup> TEMPO (1.78 g, 11.4 mmol, 1.0 eq.) was suspended in H<sub>2</sub>O (6 mL) and HBF<sub>4</sub> (48% in H<sub>2</sub>O, 1.75 mL, 13.1 mmol, 1.15 eq.) was added over 15 min *via* addition funnel. The mixture was stirred at room temperature for 30 min before being cooled to 0 °C. At that temperature NaOCl (11-15% in H<sub>2</sub>O, 3.9 mL, 5.7 mmol, 0.5 eq.) was added *via* an addition funnel over 30 min and the resulting mixture was stirred for further

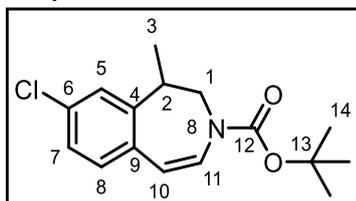
60 min. The resulting yellow suspension was filtered and the yellow solid was washed with ice cold H<sub>2</sub>O (4 x 5 mL) and CH<sub>2</sub>Cl<sub>2</sub> (3 x 5 mL). After drying at the lyophiliser over night **S9** was obtained as a yellow powder (1.31 g, 5.37 mmol, 47%).

<sup>1</sup>H-NMR (500 MHz, CD<sub>3</sub>CN): δ = 2.50 (br s, 4H, H3), 2.41 (br s, 2H, H4), 1.66 (s, 12H, H2) ppm; <sup>13</sup>C{<sup>1</sup>H}-NMR (126 MHz, CD<sub>3</sub>CN): no signals; <sup>19</sup>F{<sup>1</sup>H}-NMR (470 MHz, CD<sub>3</sub>CN): δ = -151.59 (s), -151.64 (s) ppm; <sup>11</sup>B-<sup>1</sup>H-NMR (96 MHz): δ = -1.21 ppm; IR (ATR):  $\tilde{\nu}$  = 2943 (w), 1627 (m), 1473 (w), 1400 (w), 1382 (w), 1290 (w), 1242 (w), 1212 (w), 1098 (m), 1062 (s), 975 (m), 899 (w), 878 (w), 858 (w), 765 (w), 705 (w) cm<sup>-1</sup>; HR-ESI-MS: *m/z*: [M-BF<sub>4</sub>]<sup>+</sup> calcd. for C<sub>9</sub>H<sub>18</sub>NO<sup>+</sup>: 156.13829; found: 156.13816; *m.p.*: = 147 – 148°C (decomposition). The analytical data are in agreement with the literature.<sup>[19]</sup>

### General procedure K for the synthesis of *tert*-butyl-8-chloro-1-methyl-1,2-dihydro-3*H*-benzo[d]azepine-3-carboxylate (**S10**)

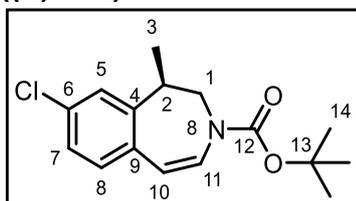
Following an adapted literature procedure,<sup>[7]</sup> **S8** (1 eq.) was dissolved in dry CH<sub>2</sub>Cl<sub>2</sub> (0.1 M) in a flame dried Schlenk pressure tube under an argon atmosphere. **S9** (1.5 eq.) was added followed by dropwise addition of TMSCHN<sub>2</sub> (2 M in Et<sub>2</sub>O, 2.4 eq.). The reaction mixture was stirred at 80 °C for 1 h. After removal of the solvent and purification by column chromatography (SiO<sub>2</sub>, Et<sub>2</sub>O:*n*-pentane) **S10** was obtained as a yellow oil.

### *rac*-*tert*-Butyl-8-chloro-1-methyl-1,2-dihydro-3*H*-benzo[d]azepine-3-carboxylate (*rac*-**S10**)



Prepared according to general procedure **K**, *rac*-**S8** (52 mg, 0.18 mmol, 1.0 eq.), **S9** (67 mg, 0.28 mmol, 1.5 eq.) and TMSCHN<sub>2</sub> (2 M in Et<sub>2</sub>O, 0.22 mL, 0.44 mmol, 2.4 eq.) were reacted in CH<sub>2</sub>Cl<sub>2</sub> (1.8 mL) to the crude benzo[d]azepine carboxylate. Purification by column chromatography (SiO<sub>2</sub>, Et<sub>2</sub>O:*n*-pentane 3:97) yielded *rac*-**S10** as a yellow oil (16.6 mg, 0.06 mmol, 31%).

### *tert*-Butyl (*R*)-8-chloro-1-methyl-1,2-dihydro-3*H*-benzo[d]azepine-3-carboxylate (*R*-**S10**)



Prepared according to general procedure **K**, (*R*)-**S8** (er 95:05, 56 mg, 0.20 mmol, 1 eq.), **S9** (78 mg, 0.30 mmol, 1.5 eq.) and TMSCHN<sub>2</sub> (2 M in Et<sub>2</sub>O, 0.24 mL, 0.48 mmol, 2.4 eq.) were reacted in CH<sub>2</sub>Cl<sub>2</sub> (2.0 mL) to the crude benzo[d]azepine carboxylate. Purification by column chromatography (SiO<sub>2</sub>, Et<sub>2</sub>O:*n*-pentane 1:99) yielded (*R*)-**S10** as a yellow oil (17.3 mg, 0.06 mmol, 33%).

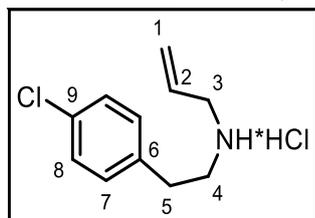
*R<sub>f</sub>* = 0.54 (Et<sub>2</sub>O:*n*-pentane, 3:97); <sup>1</sup>H-NMR (600 MHz, CDCl<sub>3</sub>): δ = 7.13 – 7.07 (m, 3H, H7, H8, H5), 6.92 (br s, 1H, H11), 5.58 (br s, 1H, H10), 4.59 (br s, 1H, H1/1'), 3.28 (p, <sup>3</sup>J<sub>HH</sub> = 7.1 Hz, 1H, H2), 3.11 (br s, 1H, H1/1'), 1.53 (s, 9H, H14), 1.10 (d, <sup>3</sup>J<sub>HH</sub> = 7.1 Hz, 3H, H3) ppm; <sup>13</sup>C{<sup>1</sup>H}-NMR (151 MHz, CDCl<sub>3</sub>): δ = 183.8 (C12), 145.9 (C4), 132.5 (C9), 132.4 (C5), 131.3 (C6), 128.5 (C8), 127.6 (C11), 126.5 (C7), 107.3 (C10), 81.9 (C13), 47.3 (C1), 40.9 (C2), 28.4 (C14), 16.6 (C3) ppm; IR (ATR):  $\tilde{\nu}$  = 2928 (w), 1811 (w), 1754 (w), 1711 (w), 1638 (w), 1595 (w), 1459 (w), 1434 (w), 1369 (m), 1354 (w), 1305 (w), 1244 (m), 1211 (w), 1154 (m), 1116 (s), 1067 (m), 1011 (w), 955 (w), 926 (w), 835 (s), 758 (w), 689 (w), 656 (w) cm<sup>-1</sup>; HR-ESI-MS: *m/z*: [M+Na]<sup>+</sup> calcd.

for  $C_{16}H_{20}NO_2ClNa^+$ : 316.1075; found: 316.1082. The analytical data are in agreement with the literature.<sup>[7]</sup>

### Synthesis of 8-chloro-1-methyl-2,3,4,5-tetrahydro-1H-benzo[d]azepine hydrochloric acid; Lorcaserin (24)

The racemic sample of racemic Lorcaserin was synthesized *via* the following different two step procedure.<sup>[20]</sup>

#### N-(4-Chlorophenethyl)prop-2-en-1-amine hydrochloric acid (S11)

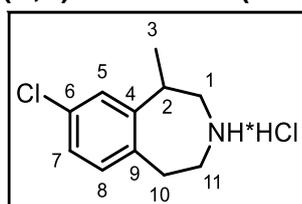


2-(4-Chlorophenyl)ethan-1-ol (5 mL, 36.9 mmol, 1.0 eq.) and powdered KOH (8.29 g, 147.8 mmol, 4.0 eq.) were dissolved in dry THF (65 mL) and cooled to 10 °C. 4-Toluenesulfonylchloride (9.16 g, 48.0 mmol, 1.3 eq.) was added and the reaction mixture was stirred over night while warming up to room temperature. Filtration over Celite® and concentration *in vacuo* yielded an orange oil which was dissolved in allylamine (11.1 mL, 147.8 mmol, 4.0 eq.) stirred at

50 °C over night. The volatiles were removed *in vacuo* and the residue was dissolved in toluene before an aq. NaOH solution (2 M) was added. The separated aqueous layer was extracted with toluene (2 x) and the combined organic layers were washed with HCl (1 M, 3 x). Extraction of the aqueous layer with  $CH_2Cl_2$  (3 x), drying over  $MgSO_4$ , filtration and concentration *in vacuo* yielded a the crude product as off-white solid. This crude product was suspended in *i*PrOH and stirred over night. Filtration yielded **S11** as a colorless solid (3.76 g, 16.17 mmol, 44%).

<sup>1</sup>H-NMR (600 MHz,  $CDCl_3$ ):  $\delta$  = 9.91 (s, 2H,  $NH_2$ ), 7.27 (d,  $^3J_{HH}$  = 8.4 Hz, 2H, H8), 7.17 (d,  $^3J_{HH}$  = 8.4 Hz, 2H, H7), 6.14 – 6.06 (m, 1H, H2), 5.50 (d,  $^3J_{HH}$  = 17.1 Hz, 1H, H1-*cis*), 5.46 (d,  $^3J_{HH}$  = 10.2 Hz, 1H, H1-*trans*), 3.63 (q,  $^3J_{HH}$  = 4.8 Hz, 2H, H3), 3.25 – 3.20 (m, 2H, H5), 3.15 – 3.08 (m, 3H, H4) ppm; <sup>13</sup>C{<sup>1</sup>H}-NMR (151 MHz,  $CDCl_3$ ):  $\delta$  = 135.0 (C6), 133.2 (C9), 130.2 (C7), 129.2 (C8), 127.7 (C2), 124.5 (C1), 49.8 (C3), 47.6 (C4), 31.7 (C5) ppm; IR (ATR):  $\tilde{\nu}$  = 2940 (w), 2761 (w), 2705 (w), 2642 (w), 2427 (w), 1894 (w), 1640 (w), 1598 (w), 1493 (m), 1475 (w), 1439 (m), 1424 (w), 1412 (w), 1385 (w), 1341 (w), 1286 (w), 1219 (m), 1164 (m), 1125 (w), 1112 (w), 1092 (m), 1036 (m), 1011 (m), 992 (m), 964 (w), 942 (s), 869 (w), 835 (m), 823 (m), 806 (s), 782 (w), 712 (w), 685 (m), 672 (s)  $cm^{-1}$ ; HR-ESI-MS: *m/z*: [M-Cl]<sup>+</sup> calcd. for  $C_{11}H_{15}NCl^+$ : 196.0888; found: 196.0902; m.p.: 172 – 173 °C (decomposition). The analytical data are in agreement with the literature.<sup>[20]</sup>

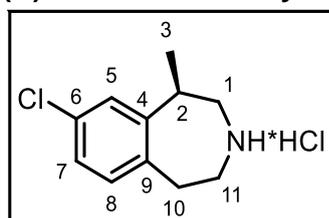
#### rac-8-Chloro-1-methyl-2,3,4,5-tetrahydro-1H-benzo[d]azepine hydrochloric acid; (R,S)-Lorcaserin (rac-24)



**S11** (1.00 g, 4.30 mmol, 1.0 eq.) and  $AlCl_3$  (1.00 g, 7.54 mmol, 1.75 eq.) were combined in a dry Schlenk pressure tube and stirred at 125 °C for 4 h. The hot, molten reaction mixture was poured into a -5 °C cooled brine solution and the reaction tube was rinsed with  $H_2O$  and  $CH_2Cl_2$  (cave: HCl gas evolution). This mixture was stirred overnight before being filtered over Celite®. The layers were separated and the aqueous layer was extracted with  $CH_2Cl_2$  (3 x).

The combined organic layers were dried over  $MgSO_4$ , filtered and concentrated *in vacuo*. The residue was suspended in acetone and stirred for 30 min at room temperature. The solid was filtrated and washed with acetone to yield **rac-24** as a colorless solid (426 mg, 1.84 mmol, 43%).

#### (R)-8-Chloro-1-methyl-2,3,4,5-tetrahydro-1H-benzo[d]azepine, (R)-Lorcaserin ((R)-24)



Following an adapted literature procedure,<sup>[7]</sup> (**R**)-**S10** (20 mg, 0.068 mmol, 1.0 eq.) was dissolved in dry  $CH_2Cl_2$  (662  $\mu$ L) in a flame dried Schlenk pressure tube under an argon atmosphere and  $HSiEt_3$  (22  $\mu$ L, 0.136 mmol, 2 eq.) and trifluoroacetic acid (49  $\mu$ L, 7% v/v) were added. The reaction mixture was stirred at room temperature for 2 h before a sat. aq. solution of  $NaHCO_3$  was added

slowly until gas evolution stopped. The pH was adjusted to pH 10 by addition of solid NaOH and the resulting mixture was vigorously stirred for 20 min. The mixture was extracted with EtOAc (3 x) and the combined organic layers were washed with H<sub>2</sub>O, brine, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated *in vacuo*. The crude product was dissolved in HCl (4 M in 1,4-dioxane, 0.5 mL, 2 mmol, 30 eq.) at 0 °C and stirred for 30 min at room temperature. The solvent was removed *in vacuo* and the remaining solid was washed with Et<sub>2</sub>O to yield (**R**)-**24** as colorless solid (1.2 mg, 0.005 mmol, 8%). The enantiomeric ratio was found to be 81:19 by chiral HPLC (Chiralpac® IA, *n*-hexane:EtOH:MeOH:diethylamine 95:2.5:2.5:0.1, 1.0 mL/min, λ = 220 nm, t<sub>R</sub> (major): 7.056 min, t<sub>R</sub> (minor): 8.436 min).

**R<sub>f</sub>** = (EtOAc:cyclohexane); **<sup>1</sup>H-NMR** (600 MHz, CDCl<sub>3</sub>): δ = 10.21 (br s, NH<sub>2</sub>), 9.93 (br s, NH<sub>2</sub>), 7.20 (d, <sup>4</sup>J<sub>HH</sub> = 2.1 Hz, 1H, H5), 7.18 (dd, <sup>3</sup>J<sub>HH</sub> = 8.1 Hz, <sup>4</sup>J<sub>HH</sub> = 2.1 Hz, 1H, H7), 7.09 (d, <sup>3</sup>J<sub>HH</sub> = 8.1 Hz, 1H, H8), 3.66 – 3.40 (m, 4H, H2, H1, H10, H11), 3.10 – 2.82 (m, 3H, H1', H10', H11'), 1.50 (d, <sup>3</sup>J<sub>HH</sub> = 7.1 Hz, H3) ppm; **<sup>13</sup>C{<sup>1</sup>H}-NMR** (126 MHz, CDCl<sub>3</sub>): δ = 144.5 (C4), 137.0 (C9), 133.6 (C6), 131.3 (C8), 127.4 (C7), 126.5 (C5), 51.6 (C1), 45.7 (C11), 35.0 (C2), 32.2 (C10), 18.1 (C3) ppm; **IR** (ATR):  $\tilde{\nu}$  = 2979 (w), 2685 (s), 2644 (s), 2600 (m), 2499 (m), 2430 (w), 1580 (s), 1485 (m), 1427 (w), 1403 (m), 1390 (m), 1377 (w), 1331 (w), 1316 (w), 1287 (w), 1263 (w), 1231 (w), 1185 (w), 1172 (w), 1127 (w), 1105 (w), 1081 (w), 1059 (w), 1024 (w), 1008 (w), 932 (s), 876 (m), 831 (m), 747 (w), 681 (w) cm<sup>-1</sup>; **HR-ESI-MS**: *m/z*: [M+H]<sup>+</sup> calcd. for C<sub>11</sub>H<sub>15</sub>NCl<sup>+</sup>: 196.0888; found: 196.0896; **m.p.**: 207 – 209 °C (decomposition). The analytical data are in agreement with the literature.<sup>[7,21]</sup>

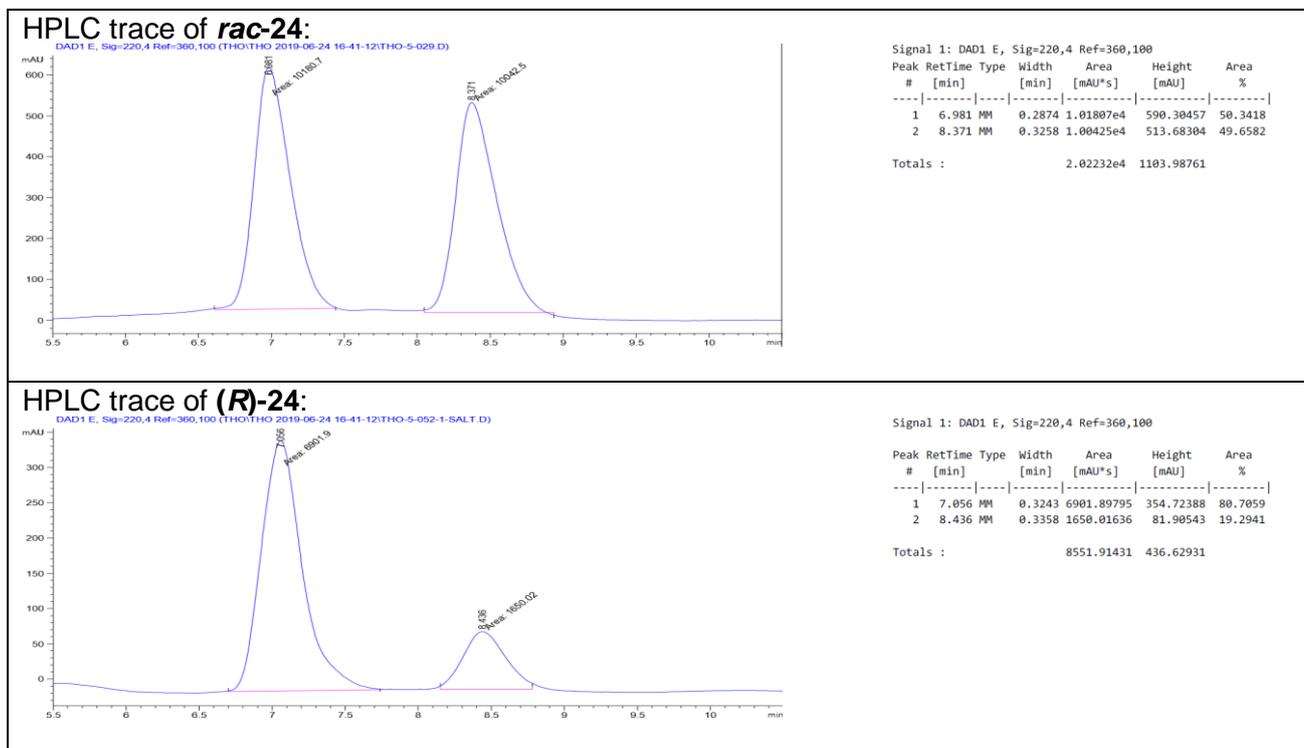


Figure 18: HPLC traces of **24**; top: *rac*-**24**; bottom: (**R**)-**24**.

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## UV/Vis Absorption spectra

Spectra was recorded on an Agilent Cary60 in acetonitrile at ambient temperature, with a pathlength of 1 cm.

Molar absorption coefficients for **E-1** and **Z-1** were calculated at 402 nm for concentrations of 1 mM and 10 mM. **E-1** =  $85 \text{ dm}^3 \text{ mol}^{-1} \text{ cm}^{-1}$ ; **Z-1** =  $42 \text{ dm}^3 \text{ mol}^{-1} \text{ cm}^{-1}$ .

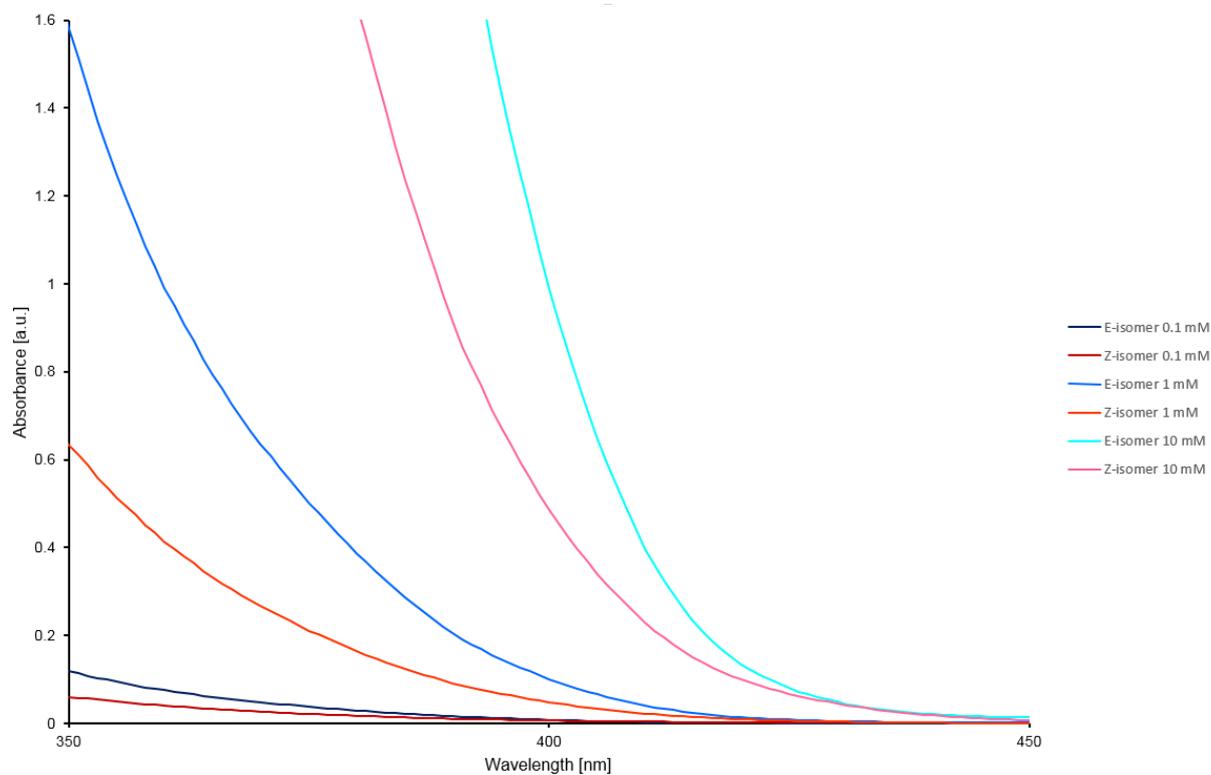
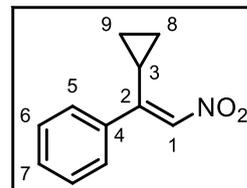


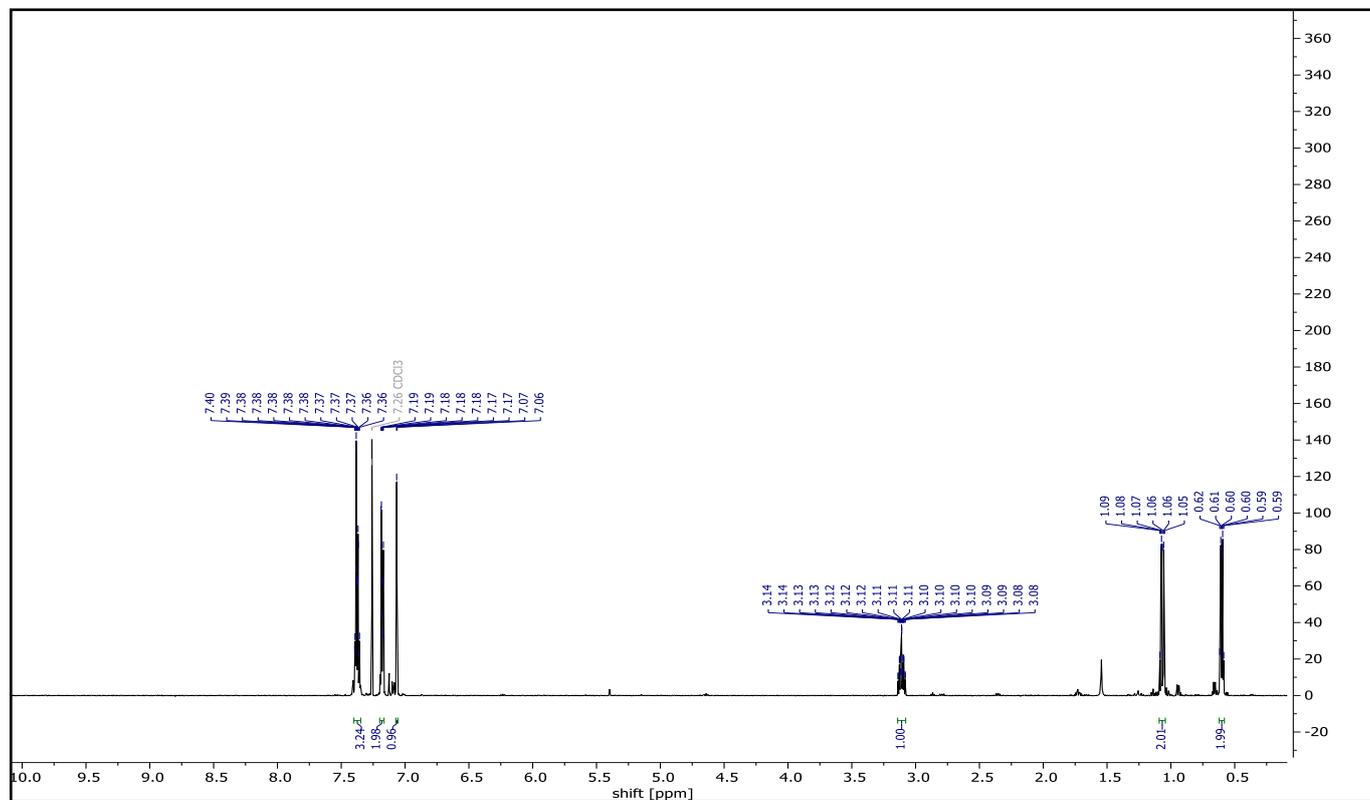
Figure 19: UV/Vis spectra (350-450 nm) of **E-1** and **Z-1** at varying concentrations.

# NMR spectra of key compounds

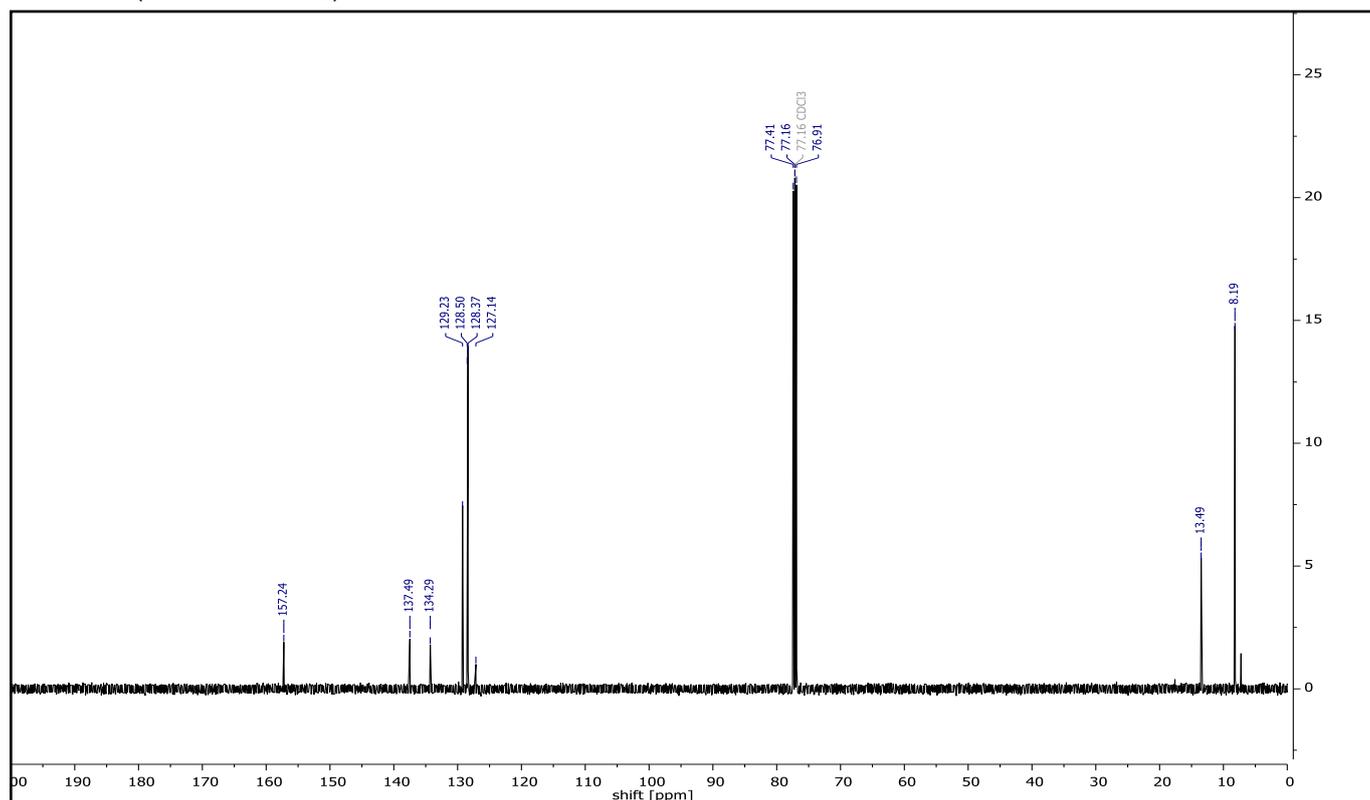
## (E)-1-(Cyclopropyl-2-nitrovinyl)benzene (E-10)



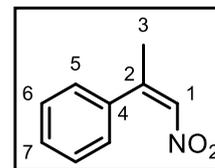
<sup>1</sup>H-NMR (500 MHz, CDCl<sub>3</sub>)



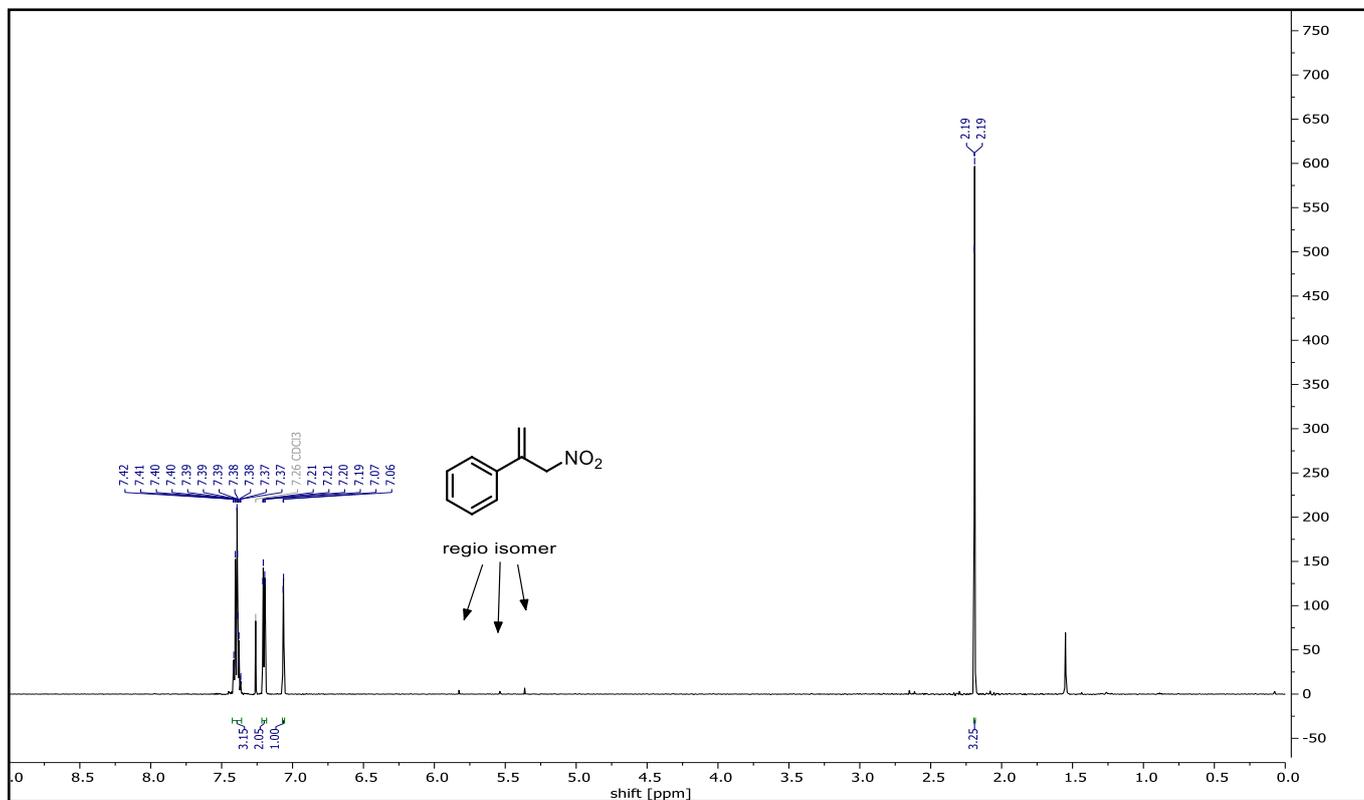
<sup>13</sup>C-NMR (126 MHz, CDCl<sub>3</sub>)



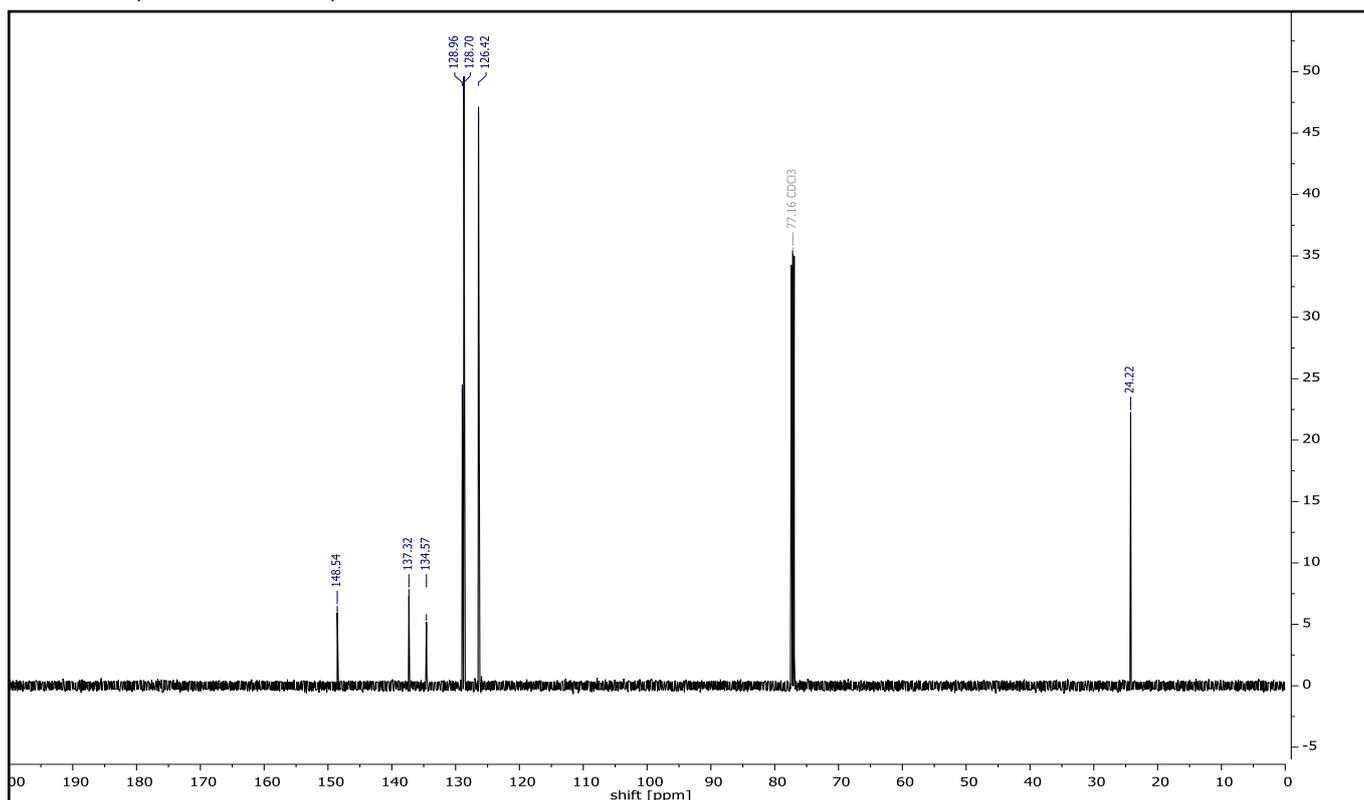
# (Z)-(1-Nitroprop-1-en-2-yl)benzene (Z-1)



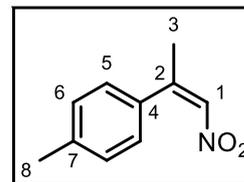
<sup>1</sup>H-NMR (600 MHz, CDCl<sub>3</sub>)



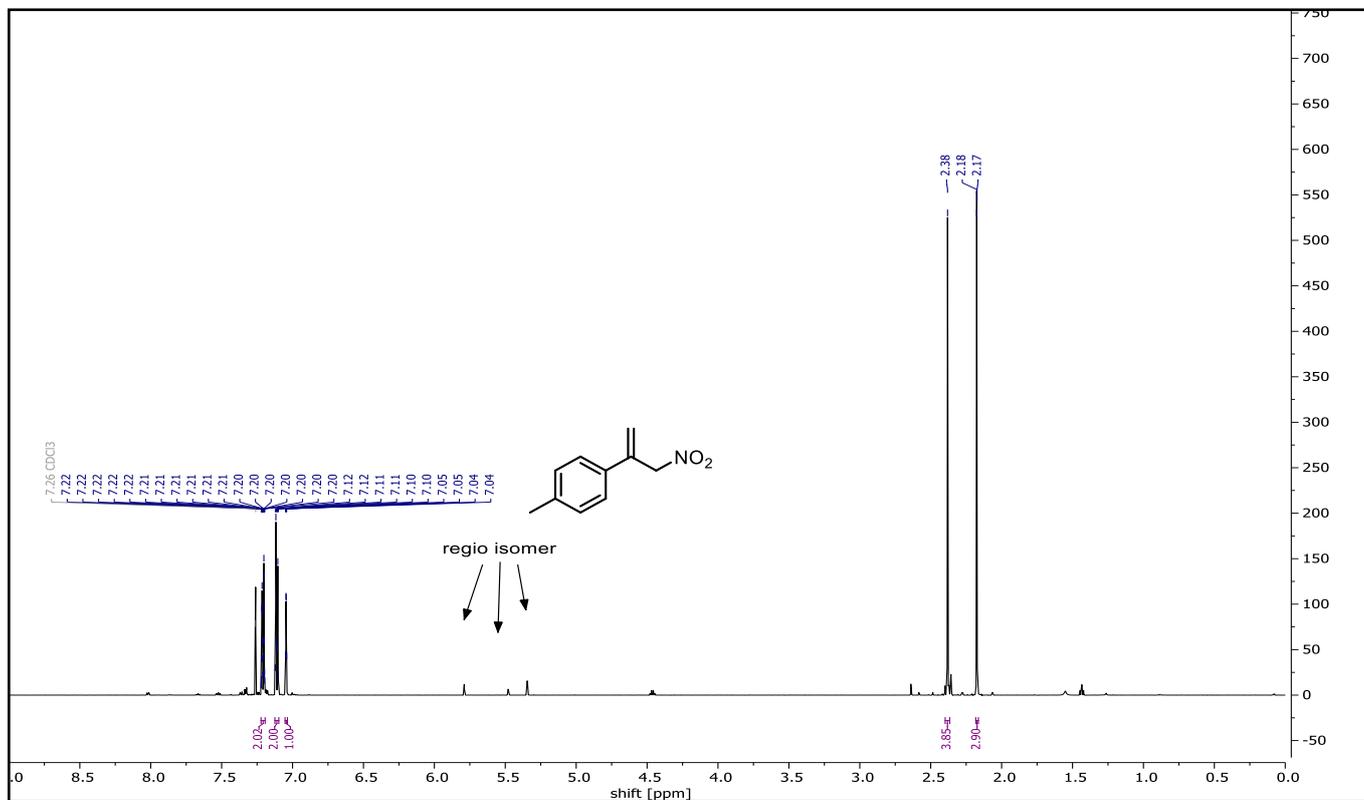
<sup>13</sup>C-NMR (151 MHz, CDCl<sub>3</sub>)



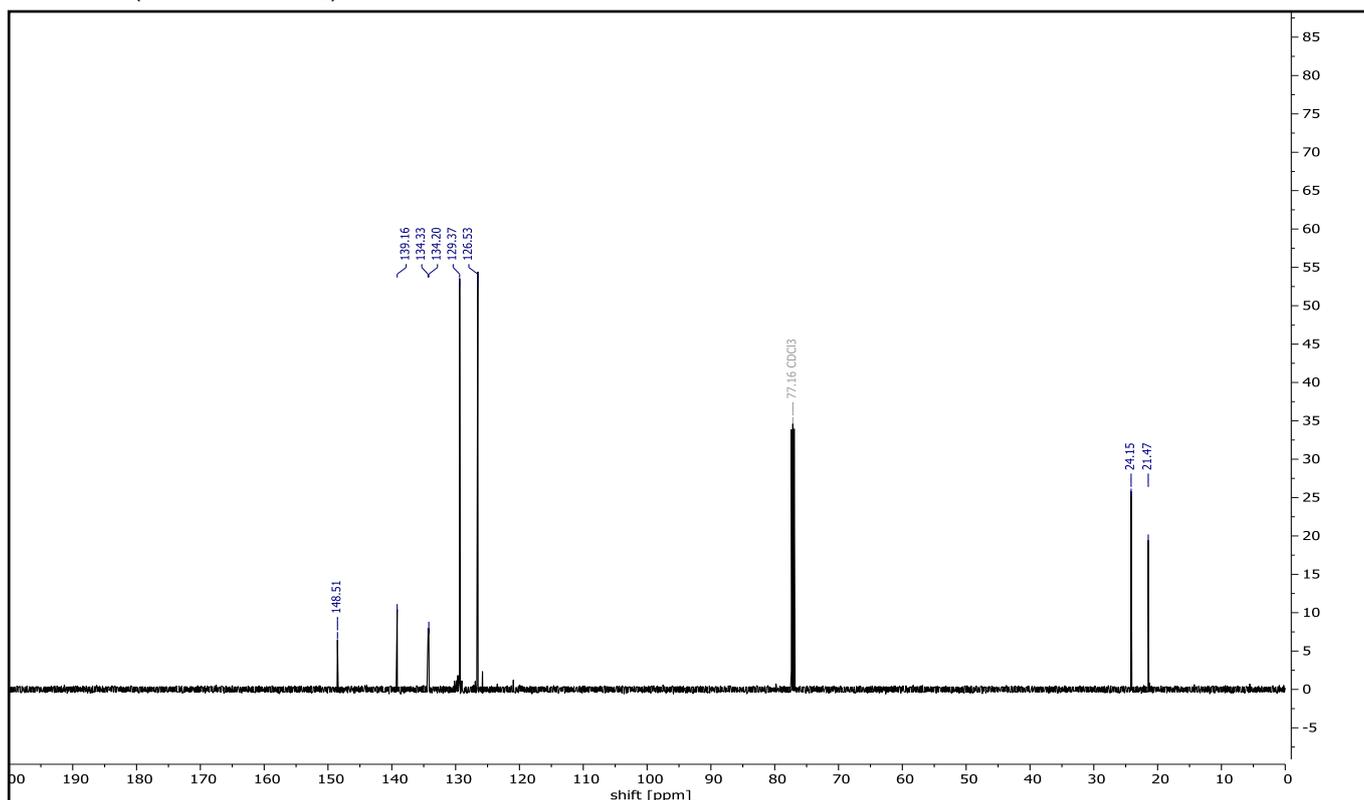
# (Z)-1-Methyl-4-(1-nitroprop-1-en-2-yl)benzene (Z-2)



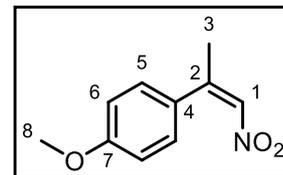
## <sup>1</sup>H-NMR (600 MHz, CDCl<sub>3</sub>)



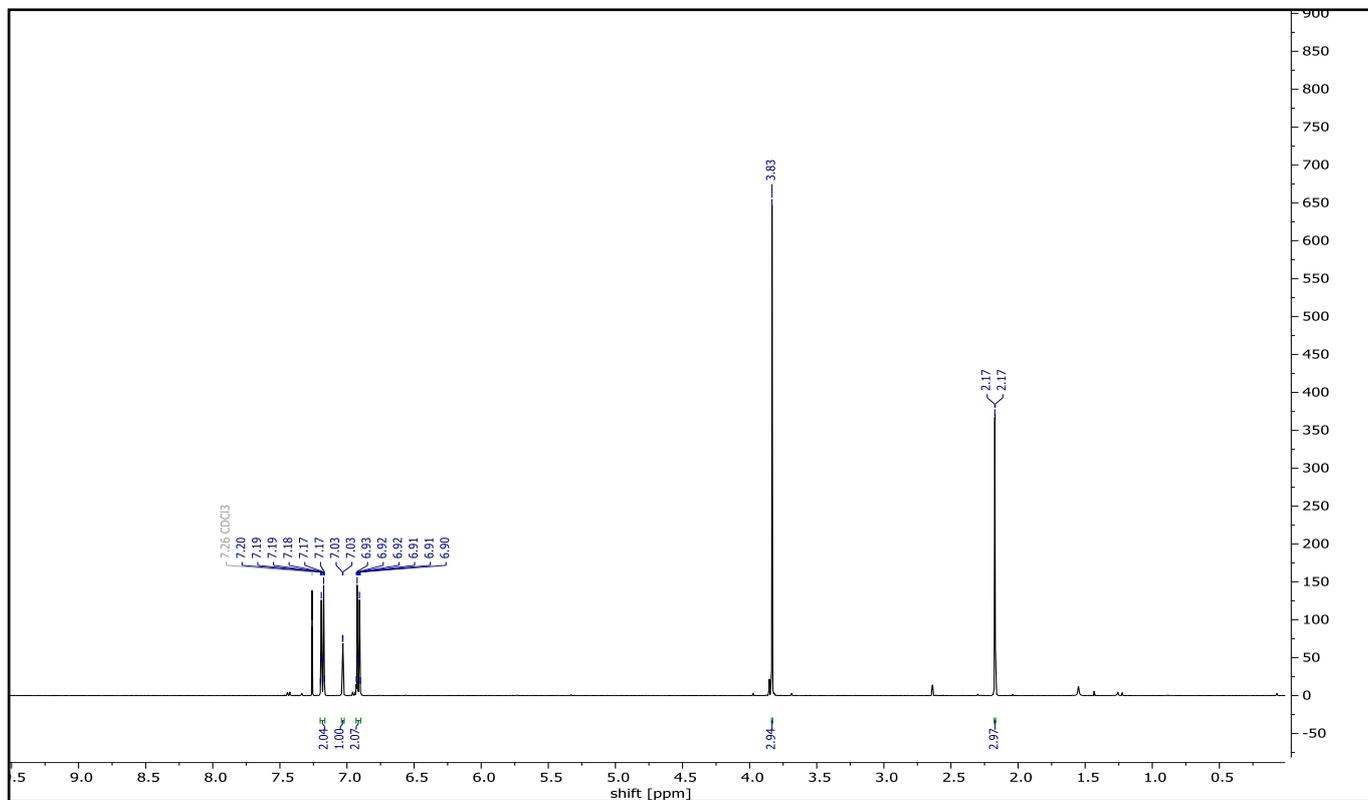
## <sup>13</sup>C-NMR (151 MHz, CDCl<sub>3</sub>)



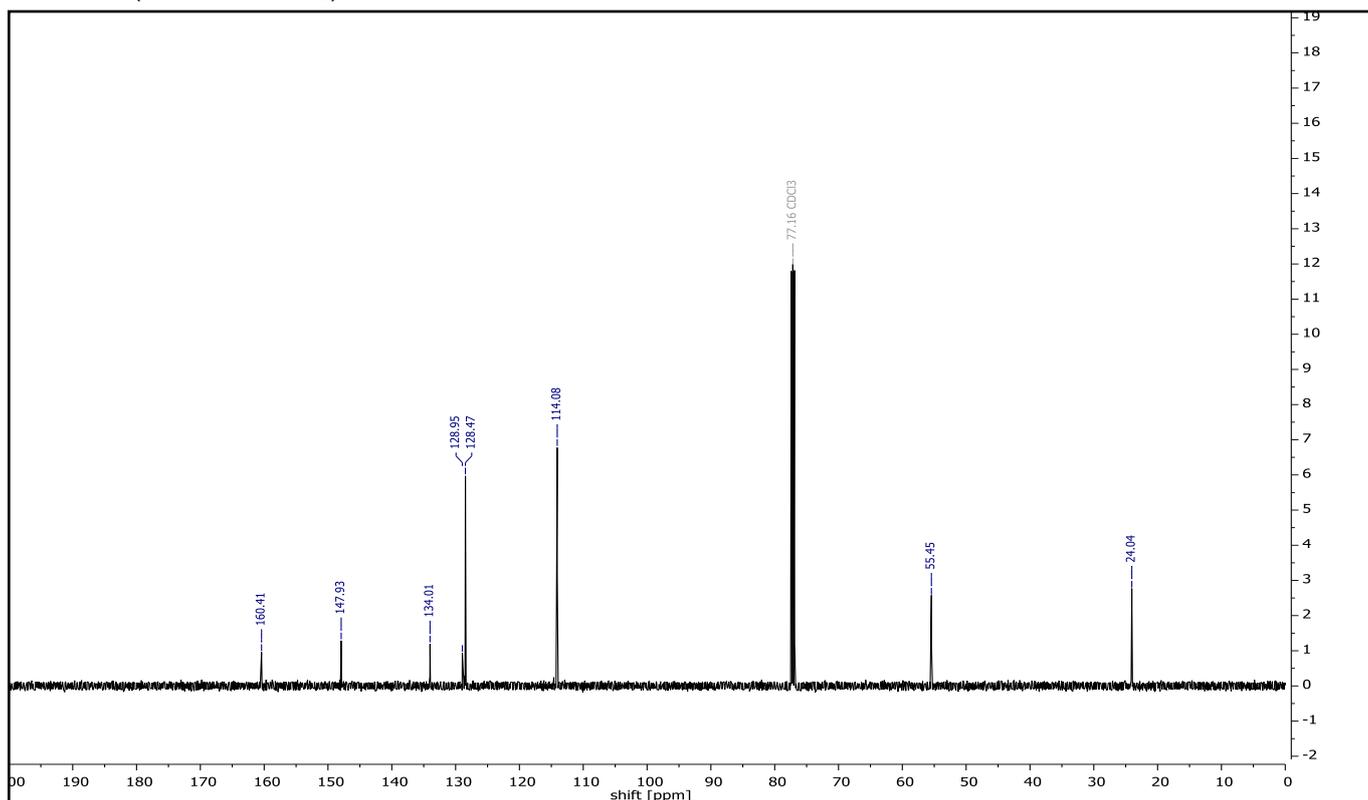
**(Z)-1-Methoxy-4-(1-nitroprop-1-en-2-yl)benzene (Z-3)**



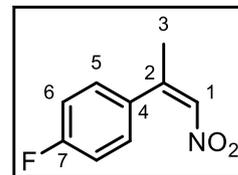
<sup>1</sup>H-NMR (500 MHz, CDCl<sub>3</sub>)



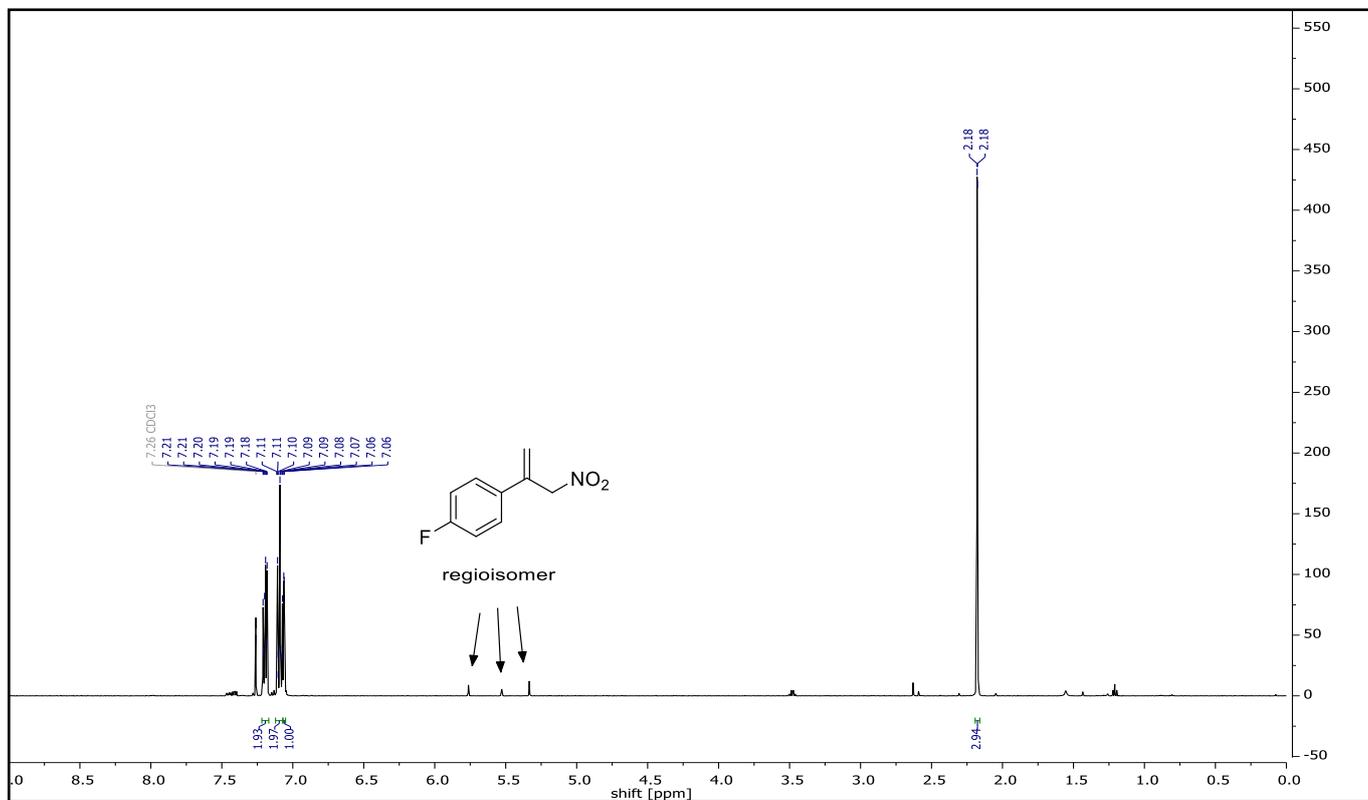
<sup>13</sup>C-NMR (126 MHz, CDCl<sub>3</sub>)



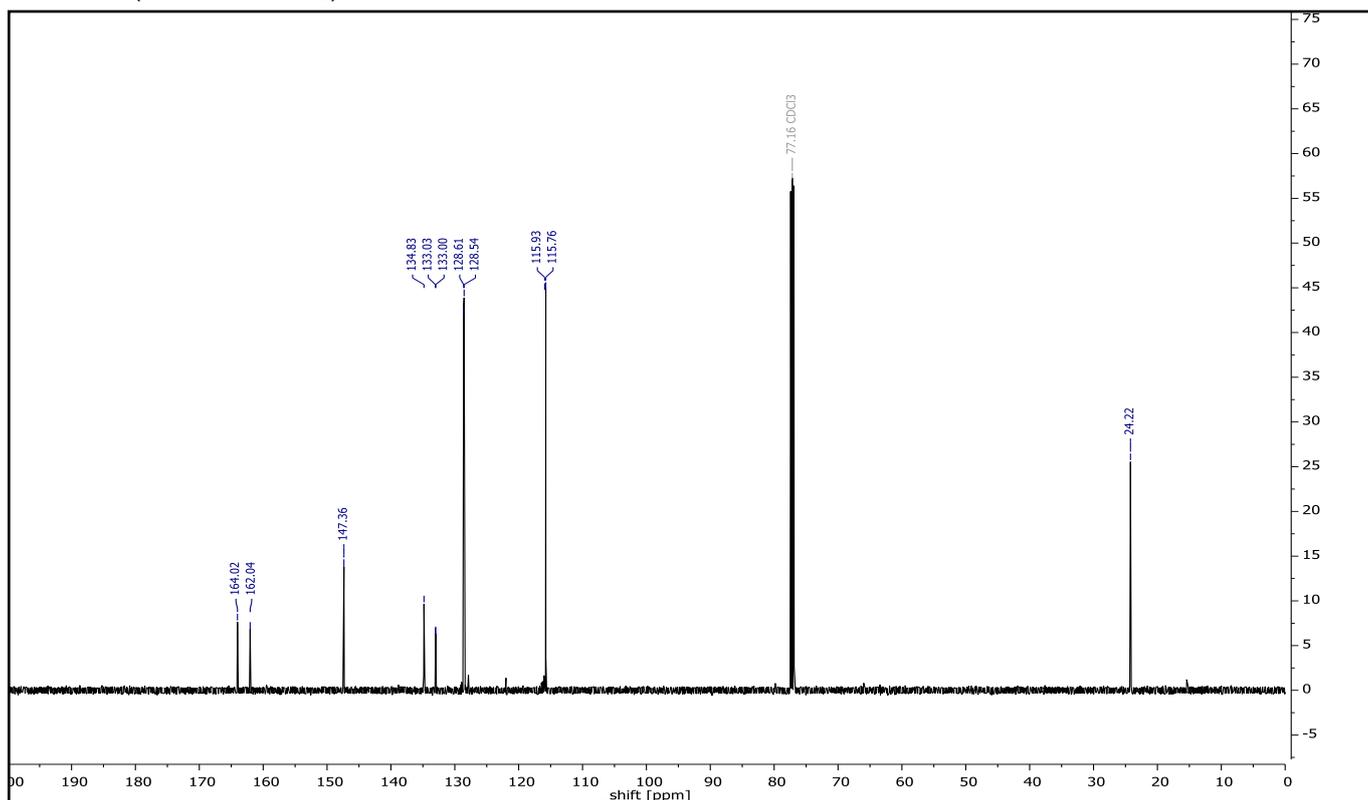
**(Z)-1-Fluoro-4-(1-nitroprop-1-en-2-yl)benzene (Z-4)**



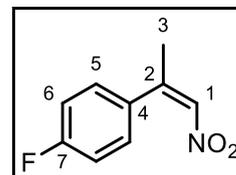
**<sup>1</sup>H-NMR (500 MHz, CDCl<sub>3</sub>)**



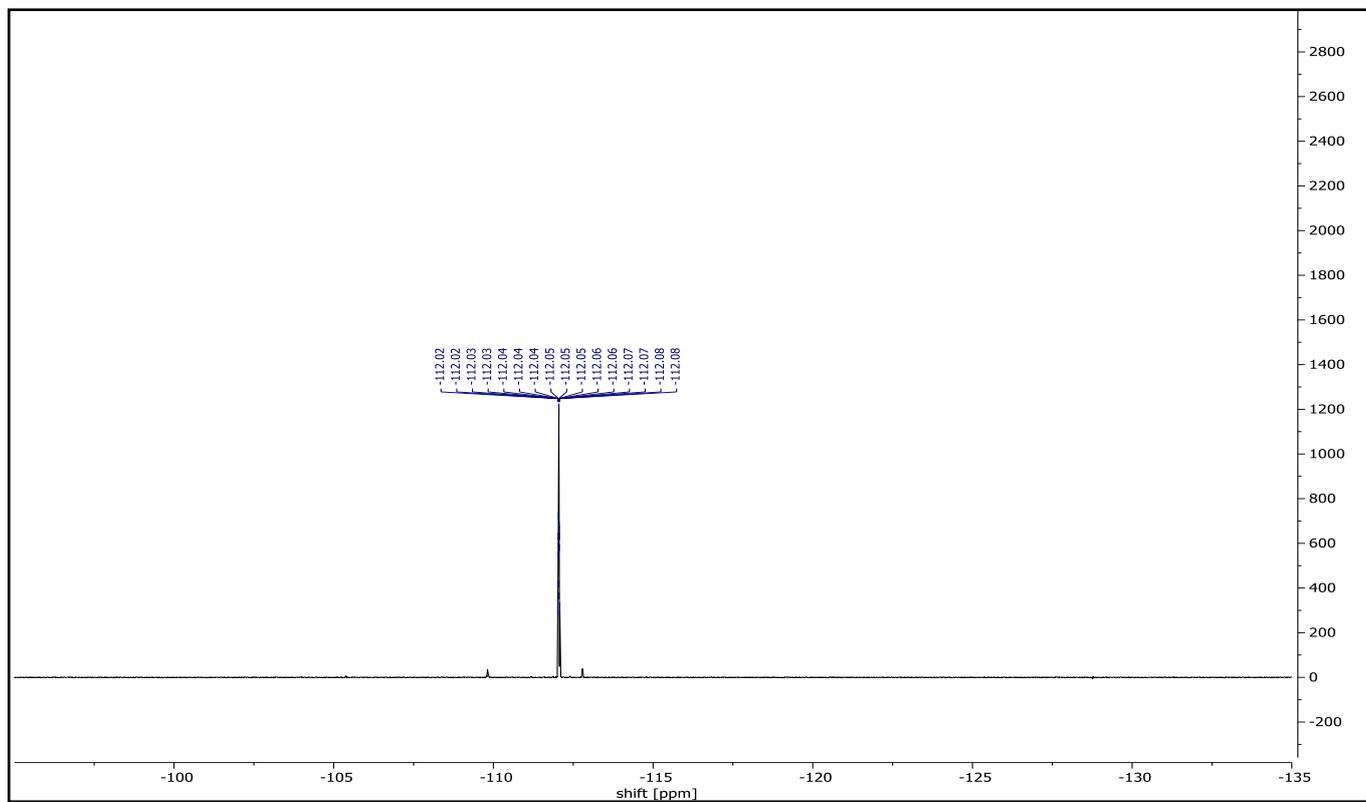
**<sup>13</sup>C-NMR (126 MHz, CDCl<sub>3</sub>)**



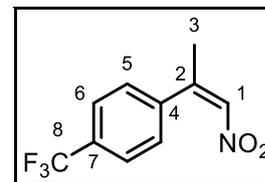
(Z)-1-Fluoro-4-(1-nitroprop-1-en-2-yl)benzene (Z-4)



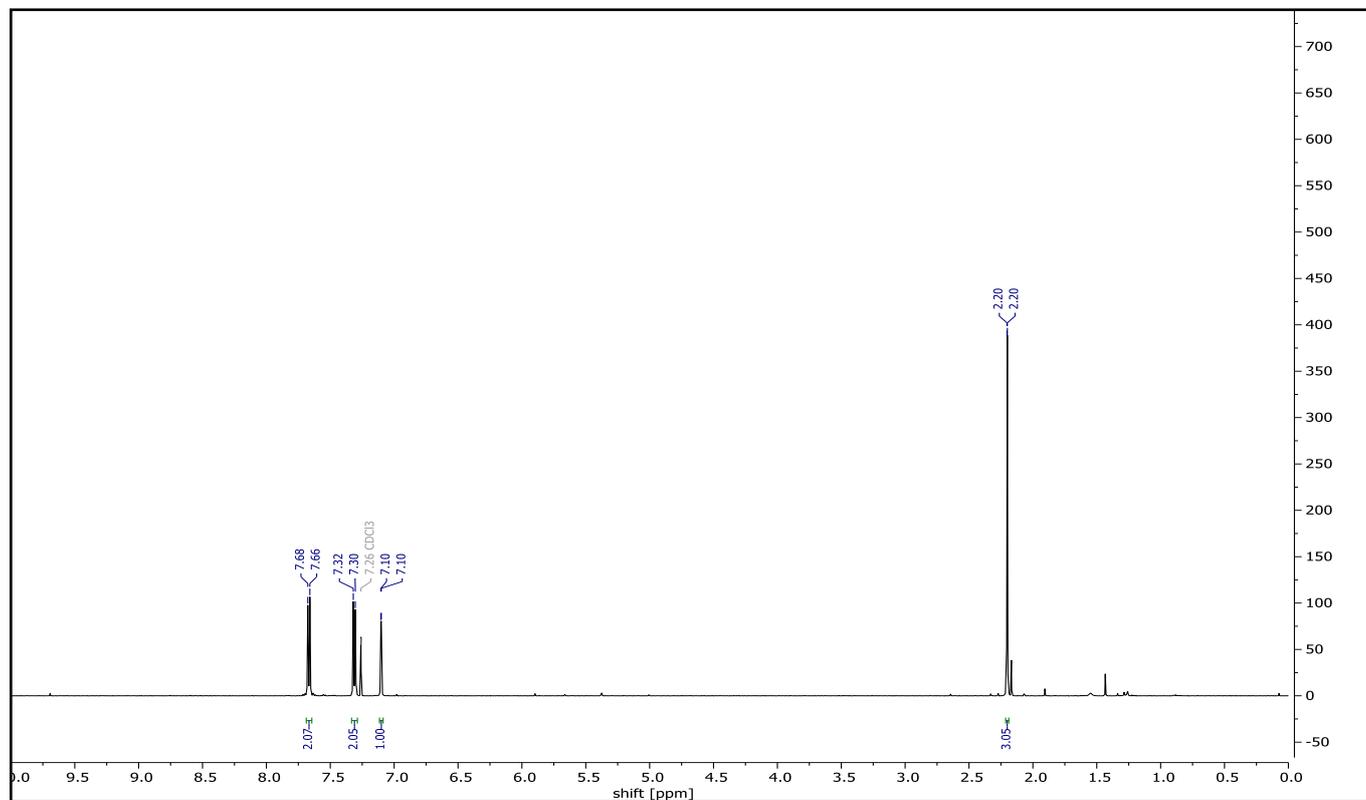
<sup>19</sup>F-NMR (470 MHz, CDCl<sub>3</sub>)



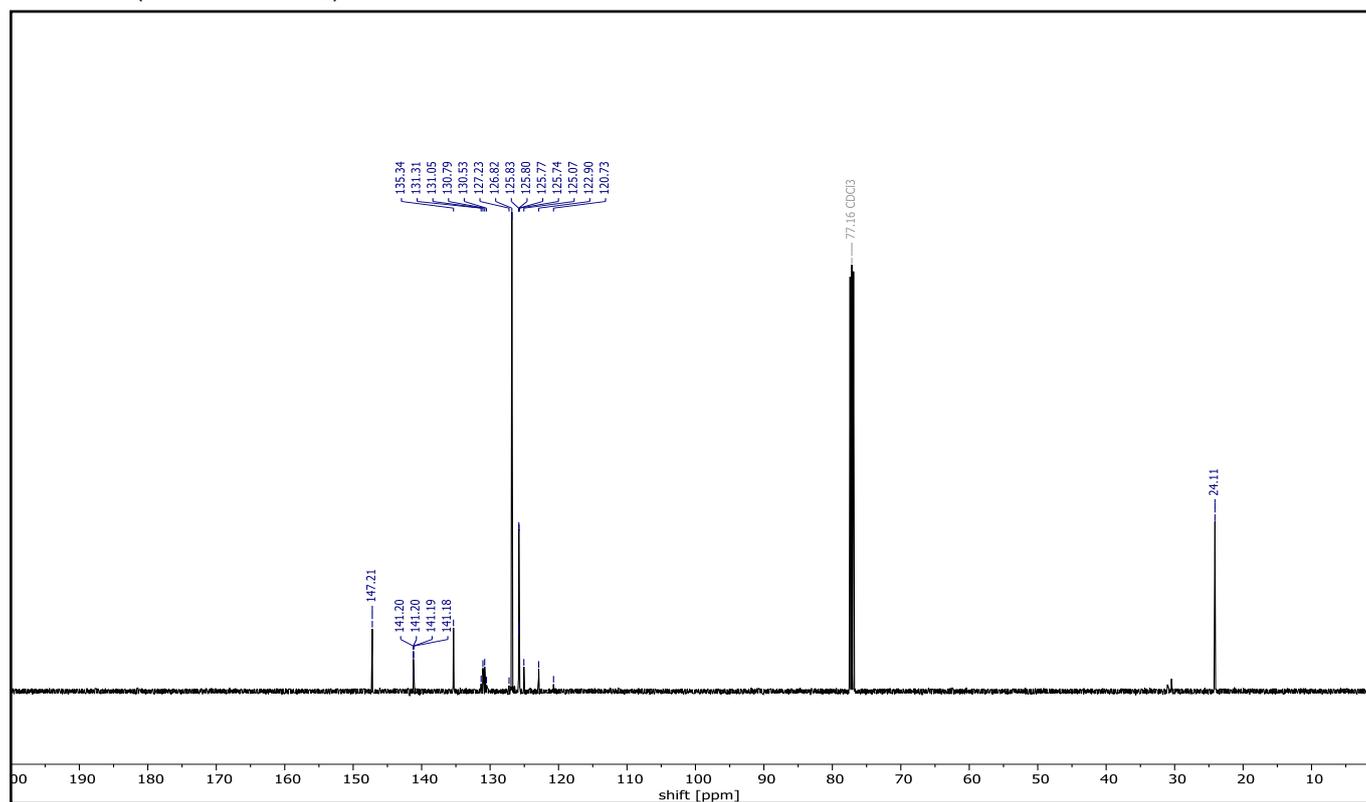
**(Z)-1-(1-nitroprop-1-en-2-yl)-4-trifluoromethylbenzene (Z-6)**



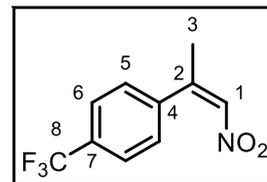
<sup>1</sup>H-NMR (500 MHz, CDCl<sub>3</sub>)



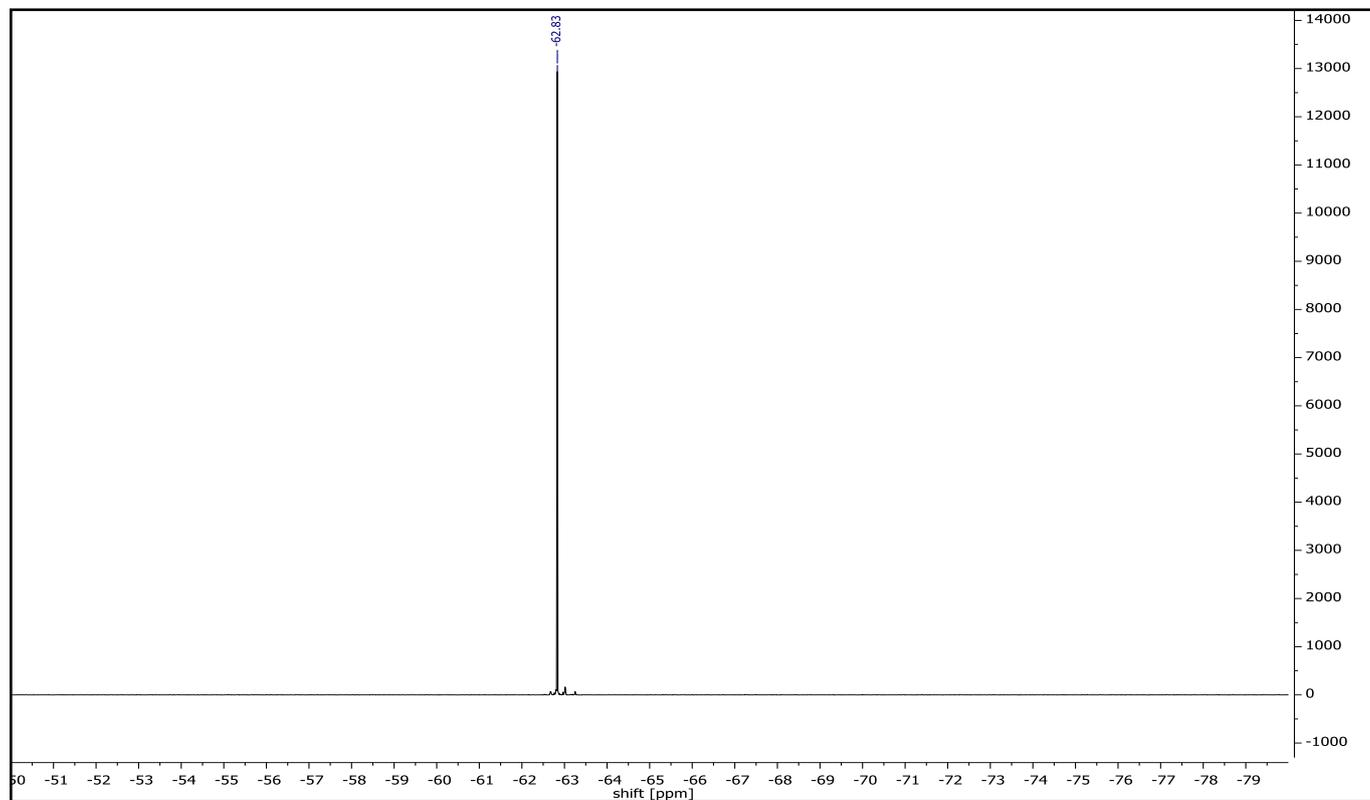
<sup>13</sup>C-NMR (126 MHz, CDCl<sub>3</sub>)



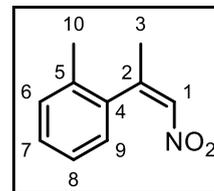
**(Z)-1-(1-nitroprop-1-en-2-yl)-4-trifluoromethylbenzene (Z-6)**



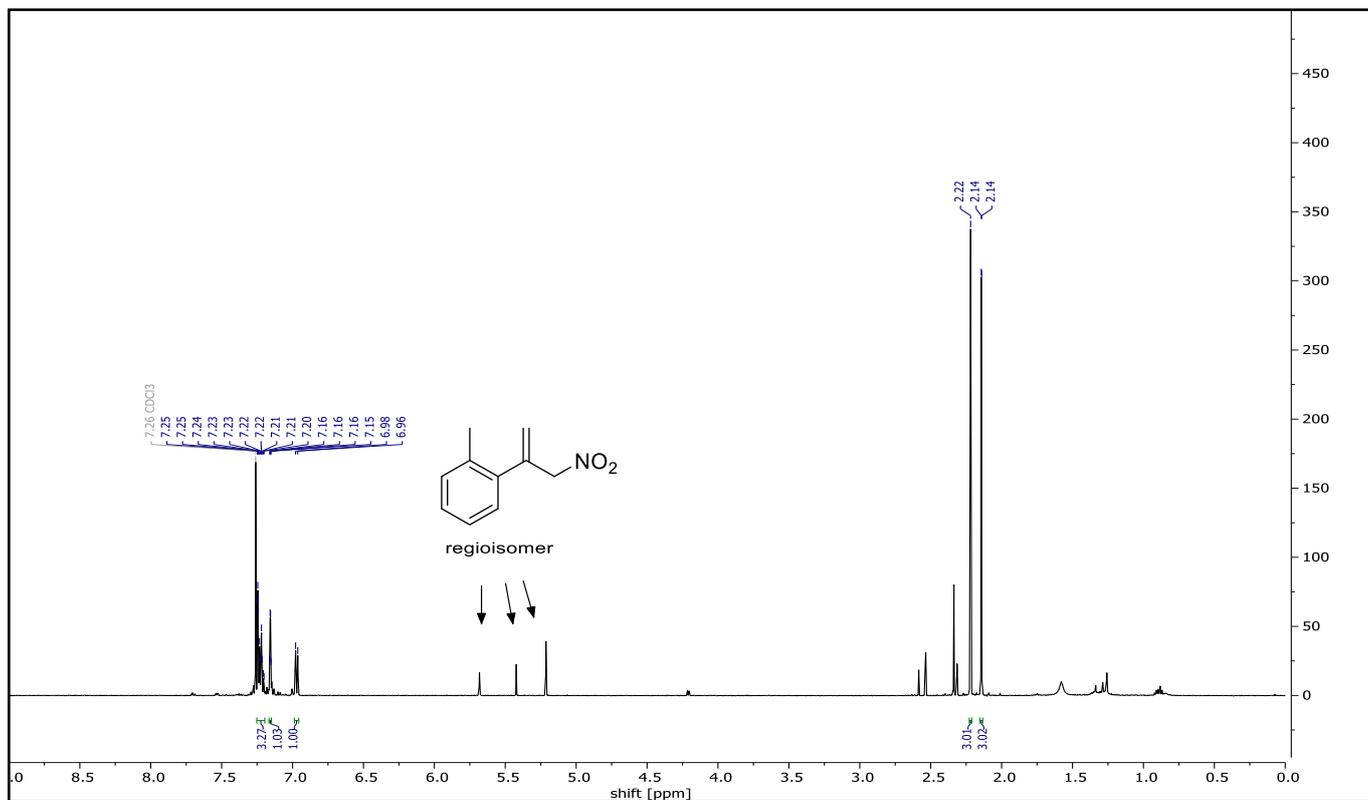
<sup>19</sup>F-NMR (470 MHz, CDCl<sub>3</sub>)



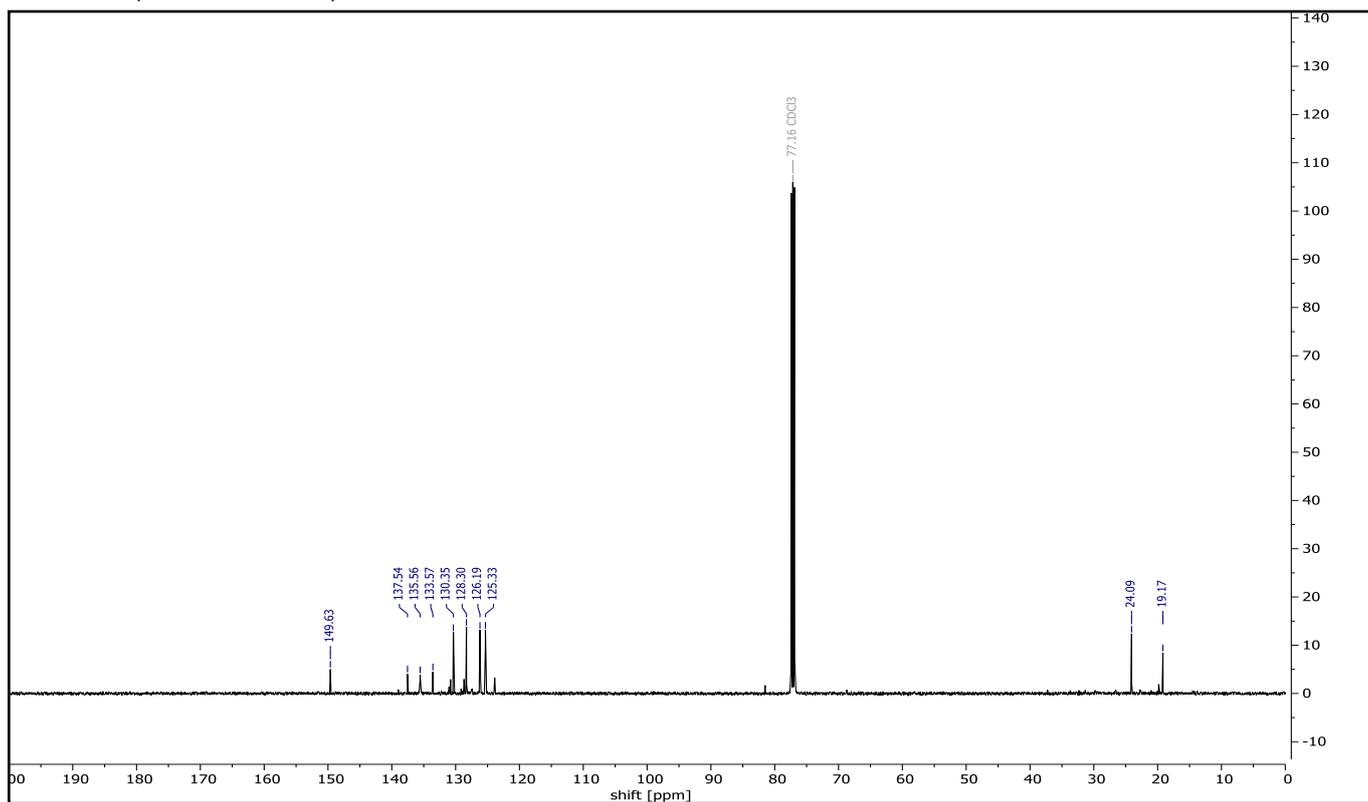
**(Z)-1-Methyl-2-(1-nitroprop-1-en-2-yl)benzene (Z-7)**



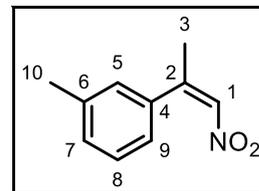
<sup>1</sup>H-NMR (500 MHz, CDCl<sub>3</sub>)



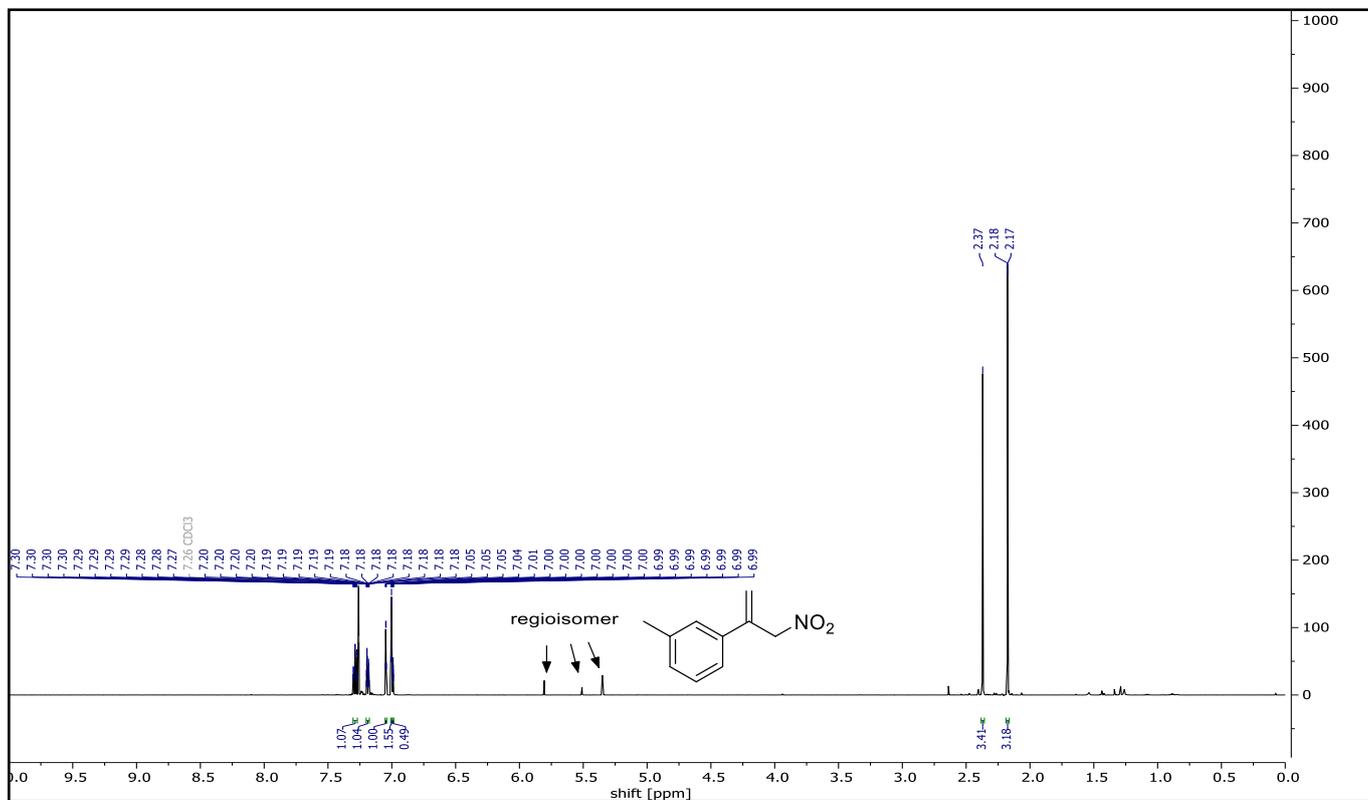
<sup>13</sup>C-NMR (126 MHz, CDCl<sub>3</sub>)



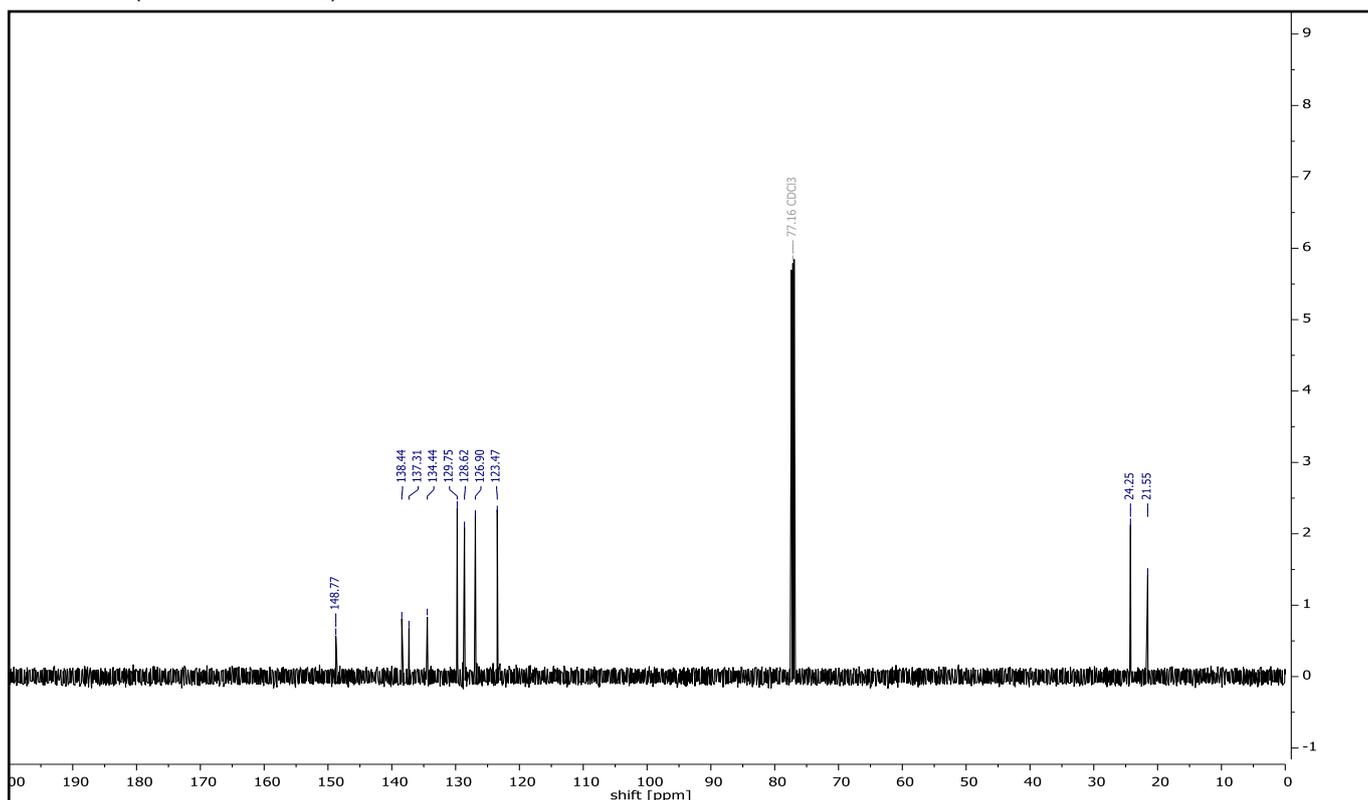
**(Z)-1-Methyl-3-(1-nitroprop-1-en-2-yl)benzene (Z-8)**



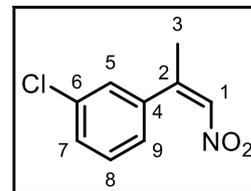
<sup>1</sup>H-NMR (600 MHz, CDCl<sub>3</sub>)



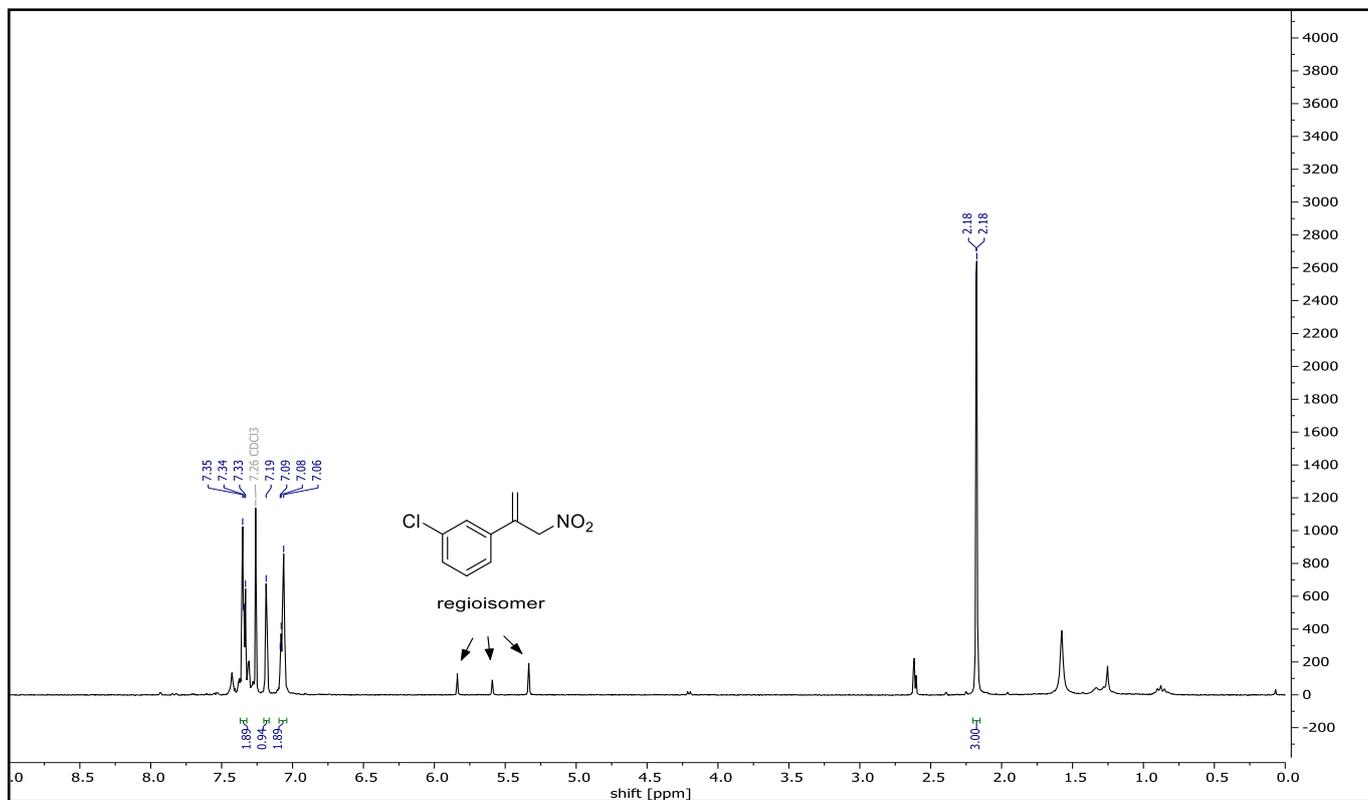
<sup>13</sup>C-NMR (151 MHz, CDCl<sub>3</sub>)



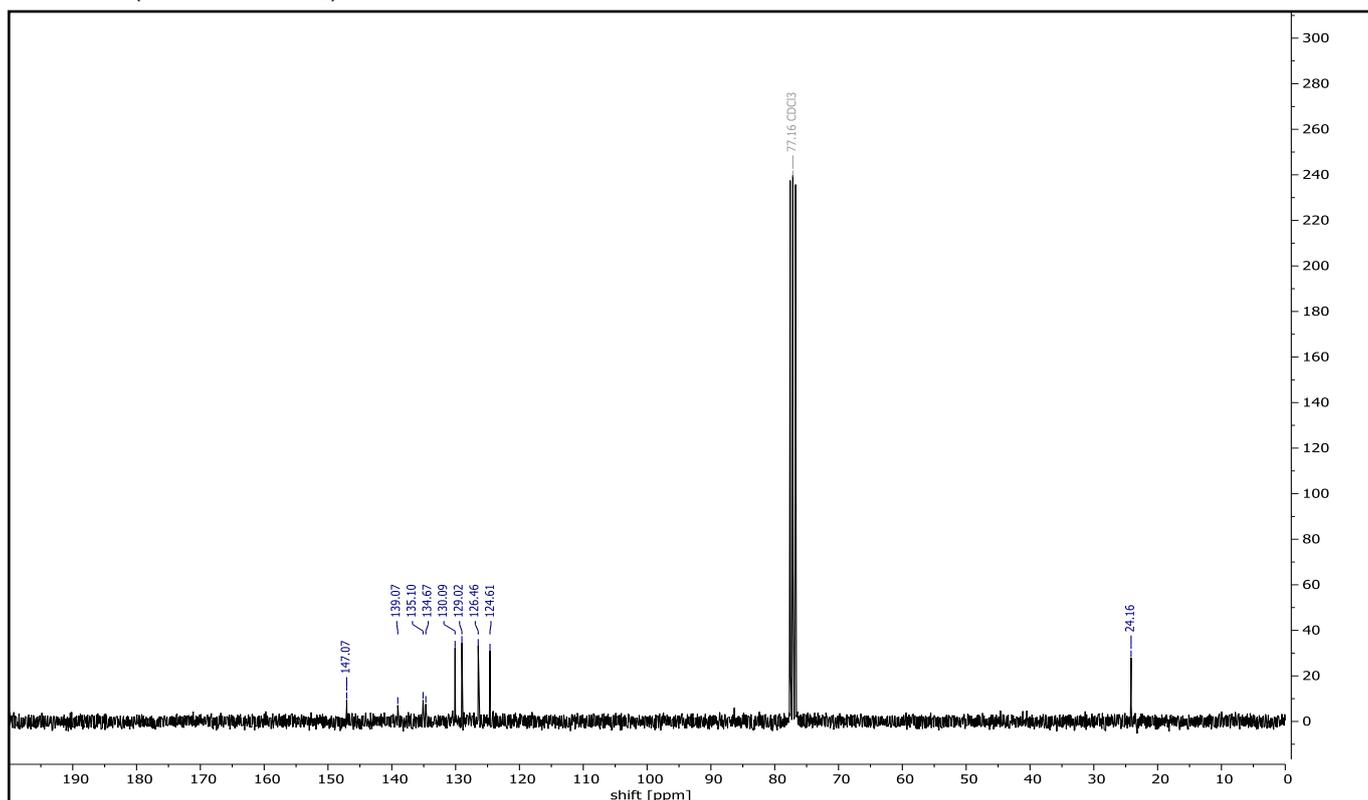
**(Z)-1-Chloro-3-(1-nitroprop-1-en-2-yl)benzene (Z-9)**



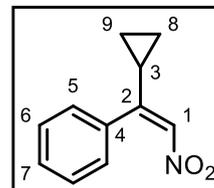
**<sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>)**



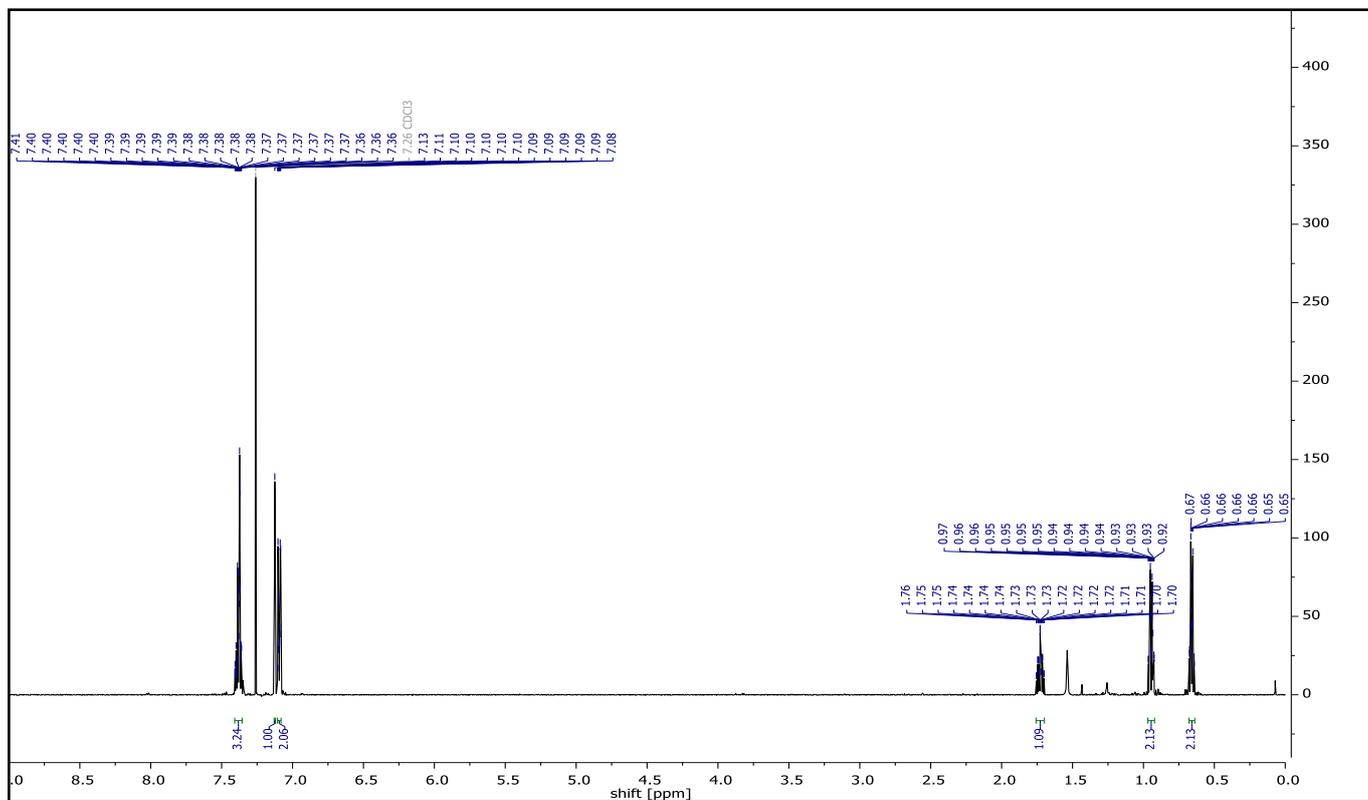
**<sup>13</sup>C-NMR (101 MHz, CDCl<sub>3</sub>)**



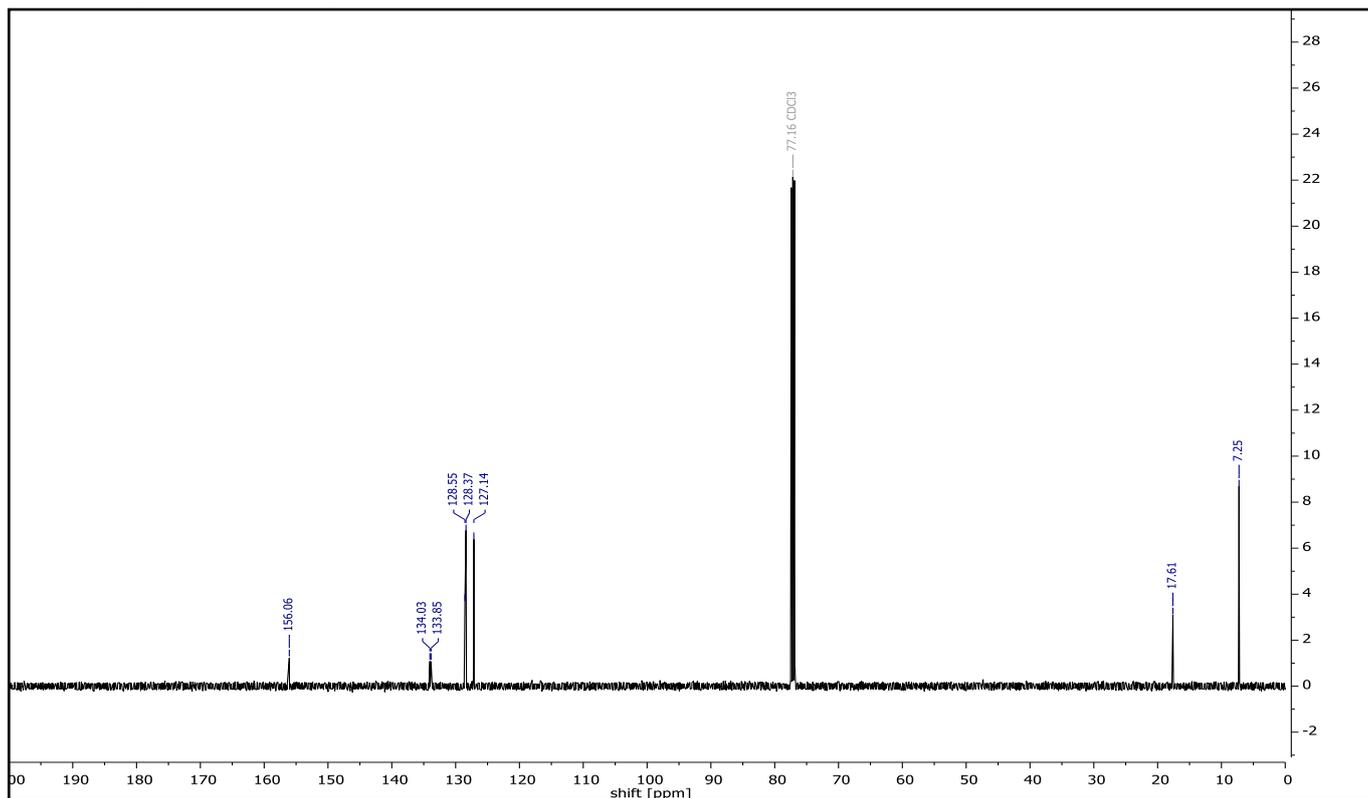
# (Z)-1-(Cyclopropyl-2-nitrovinyl)benzene (Z-10)



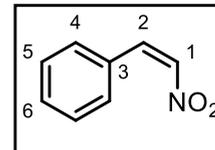
## <sup>1</sup>H-NMR (500 MHz, CDCl<sub>3</sub>)



## <sup>13</sup>C-NMR (101 MHz, CDCl<sub>3</sub>)

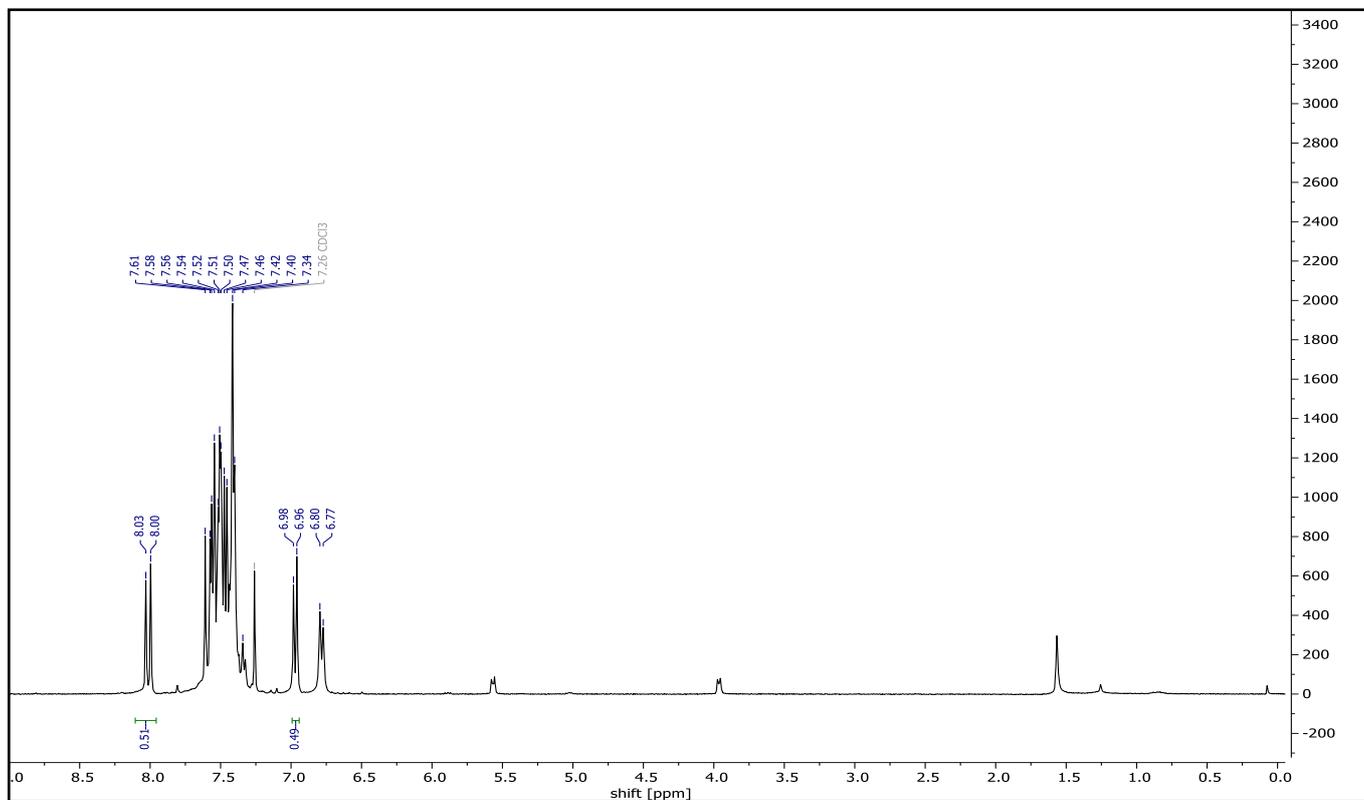


## (Z and E)-(2-Nitrovinyl)benzene (Z and E-11)

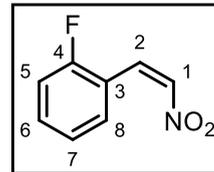


Isomerization led to an inseparable mixture of *Z* and *E* isomers after column chromatography as indicated by  $^1\text{H-NMR}$

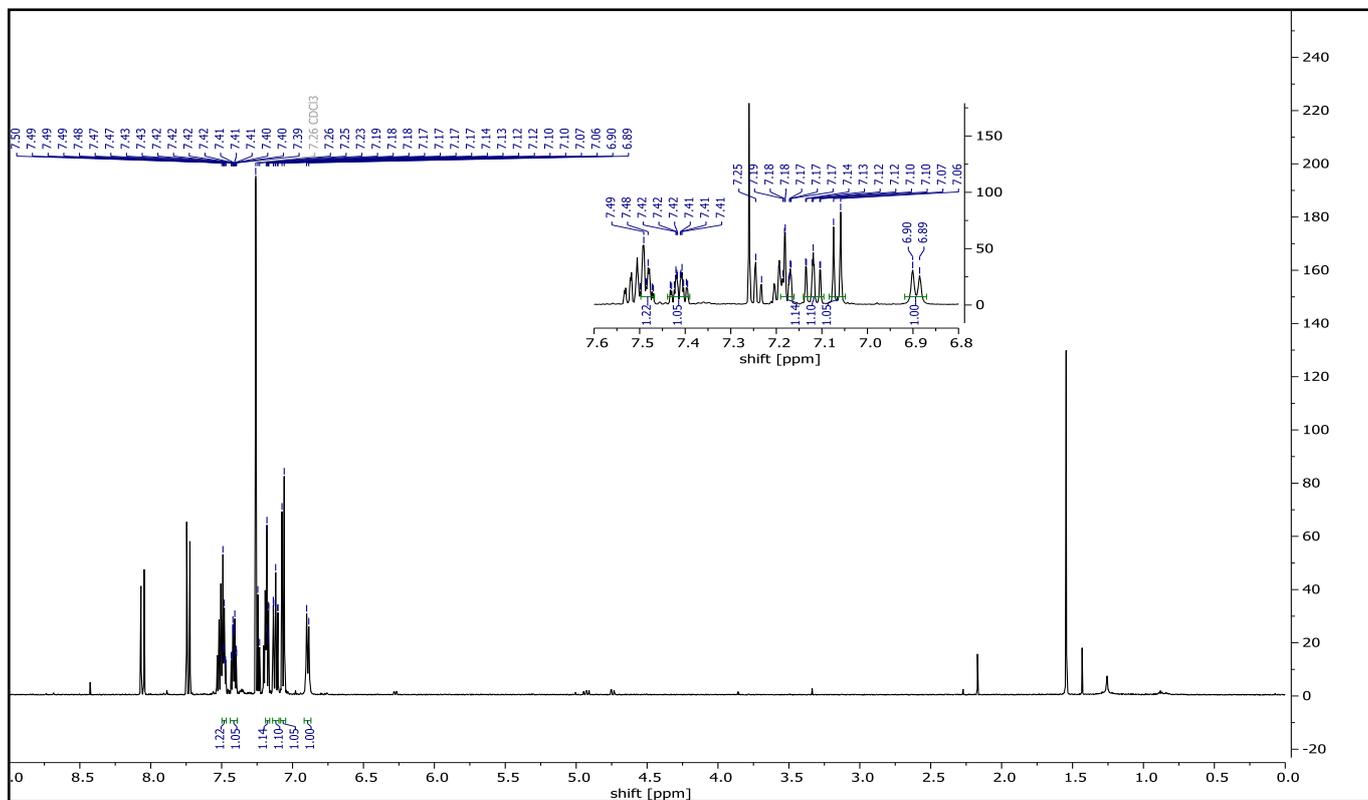
$^1\text{H-NMR}$  (400 MHz,  $\text{CDCl}_3$ )



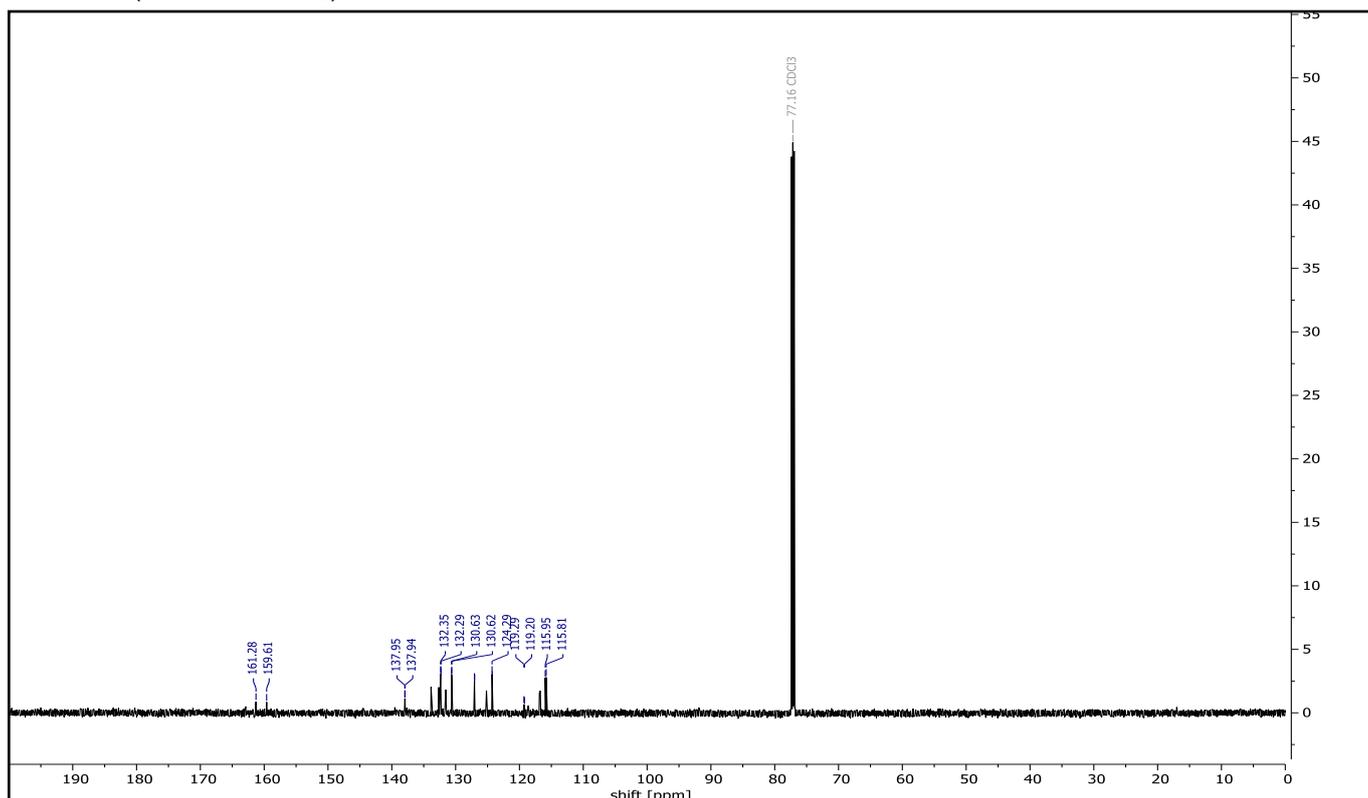
(Z and E)-1-Fluoro-2-(2-nitrovinyl)benzene (Z- and E-12)



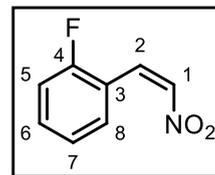
<sup>1</sup>H-NMR (600 MHz, CDCl<sub>3</sub>)



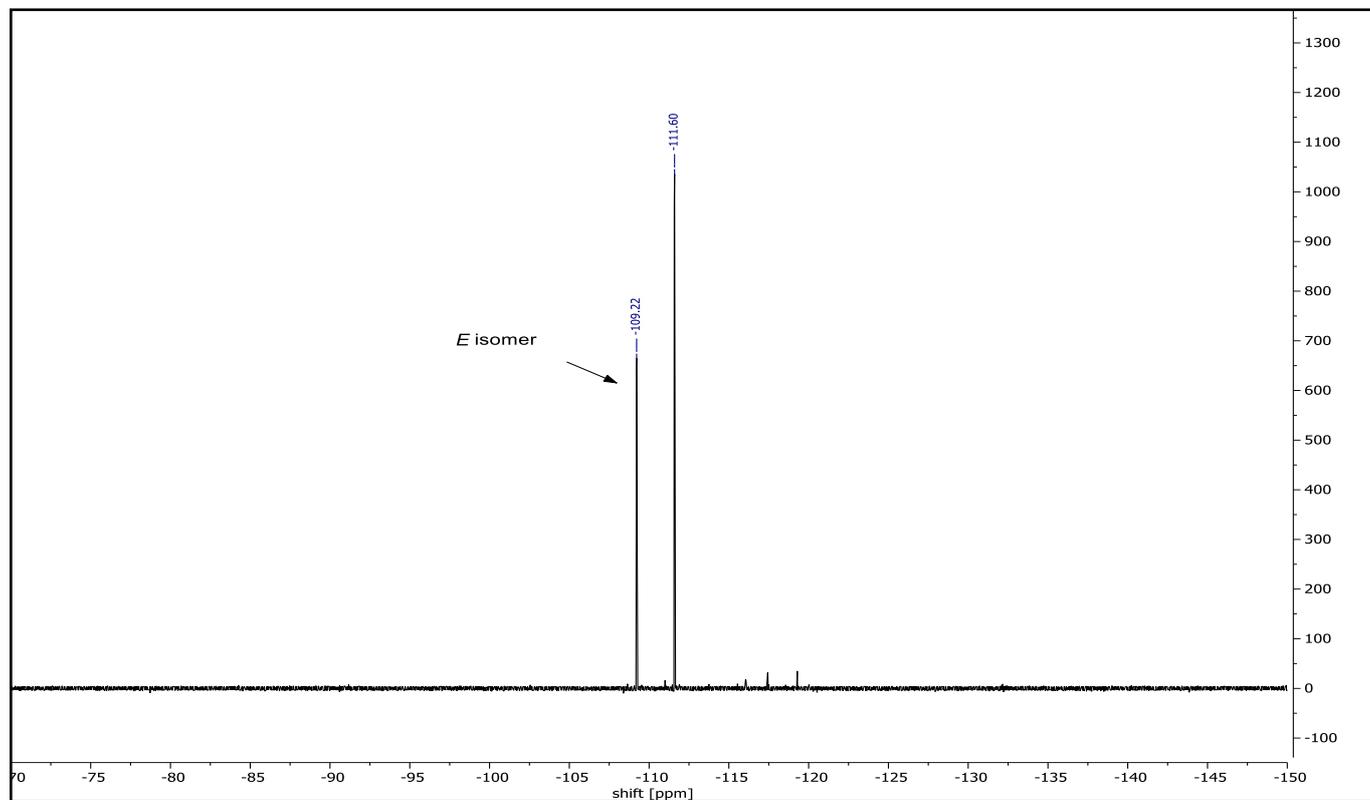
<sup>13</sup>C-NMR (151 MHz, CDCl<sub>3</sub>)



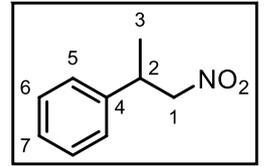
(Z and E)-1-Fluoro-2-(2-nitrovinyl)benzene (Z- and E-12)



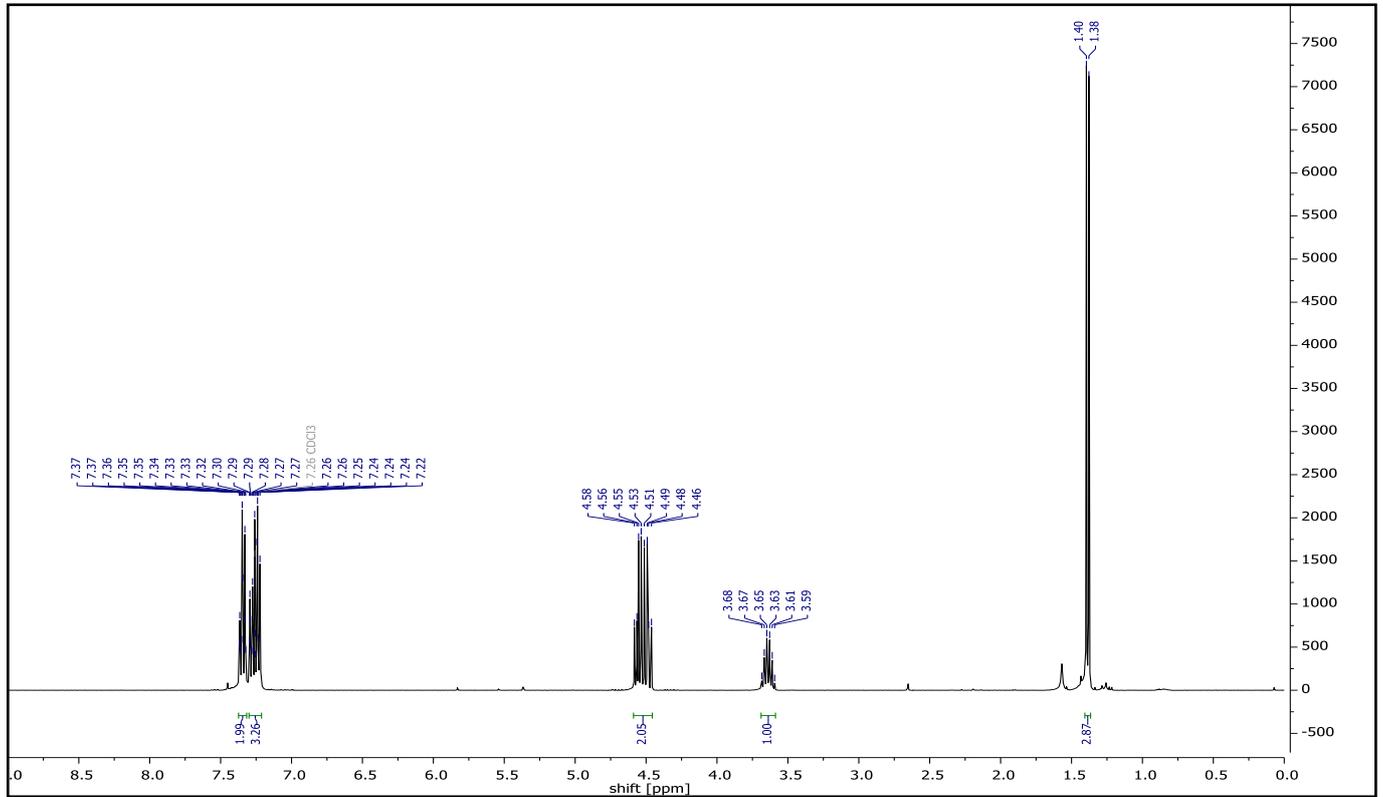
$^{19}\text{F}$ -NMR (564 MHz,  $\text{CDCl}_3$ )



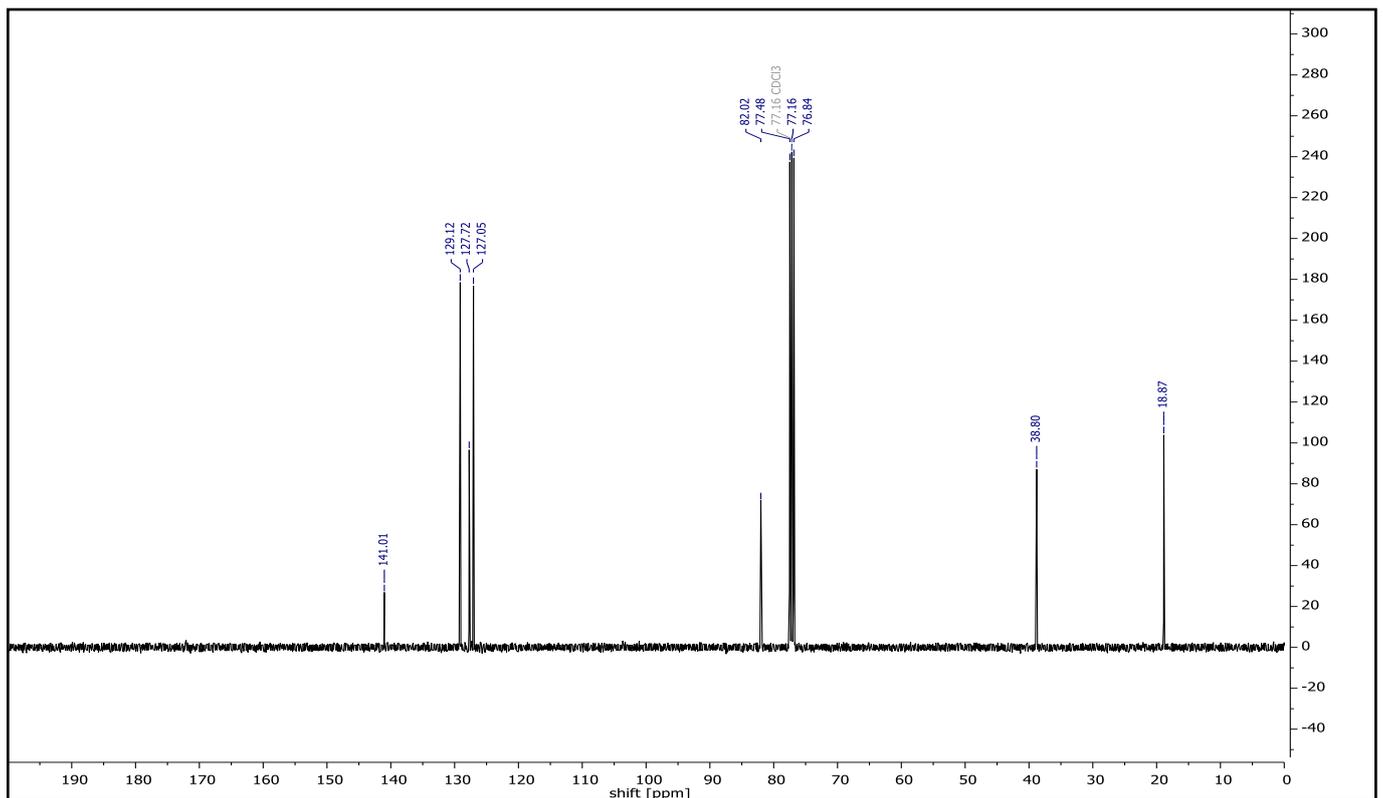
# (1-Nitropropan-2-yl)benzene (13)



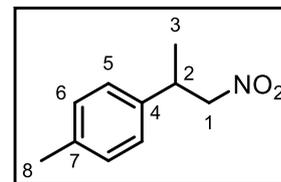
## <sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>)



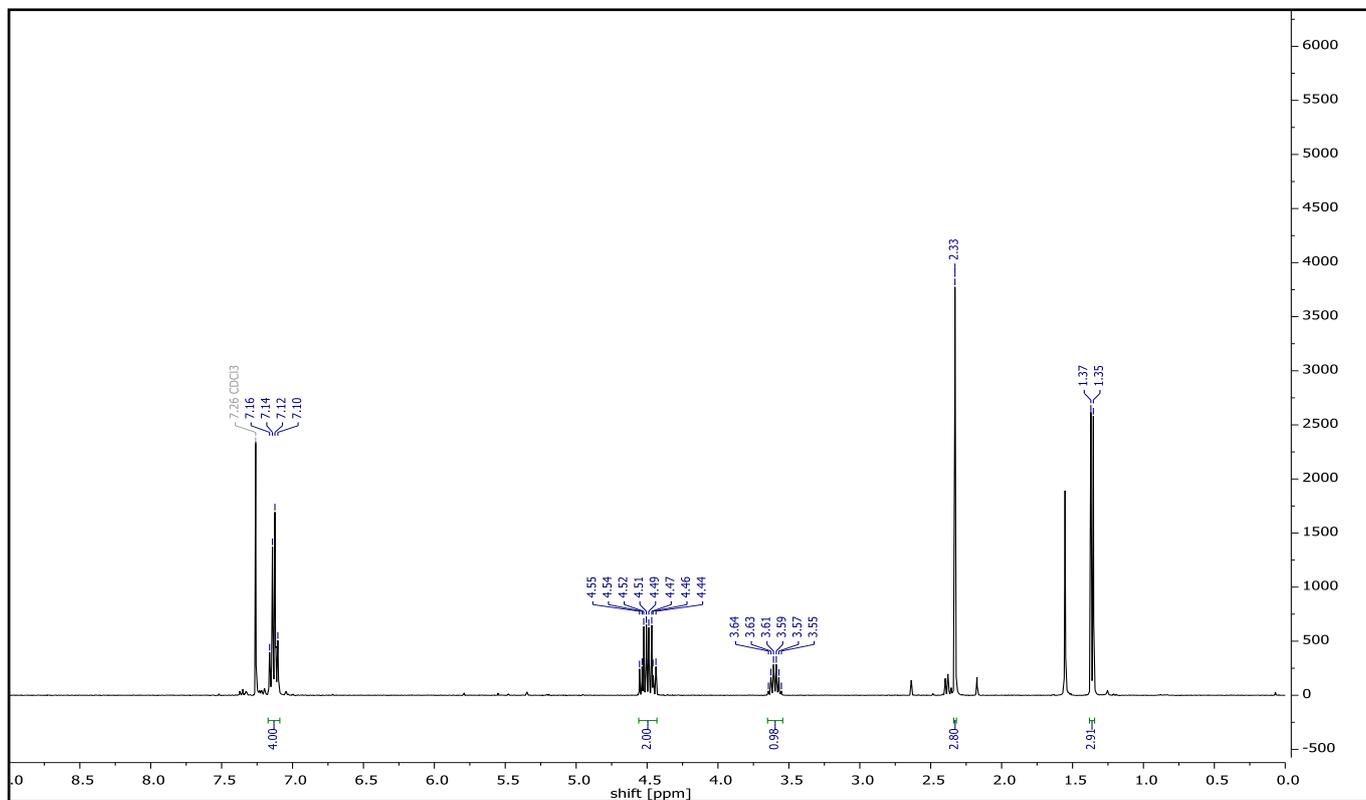
## <sup>13</sup>C-NMR (101 MHz, CDCl<sub>3</sub>)



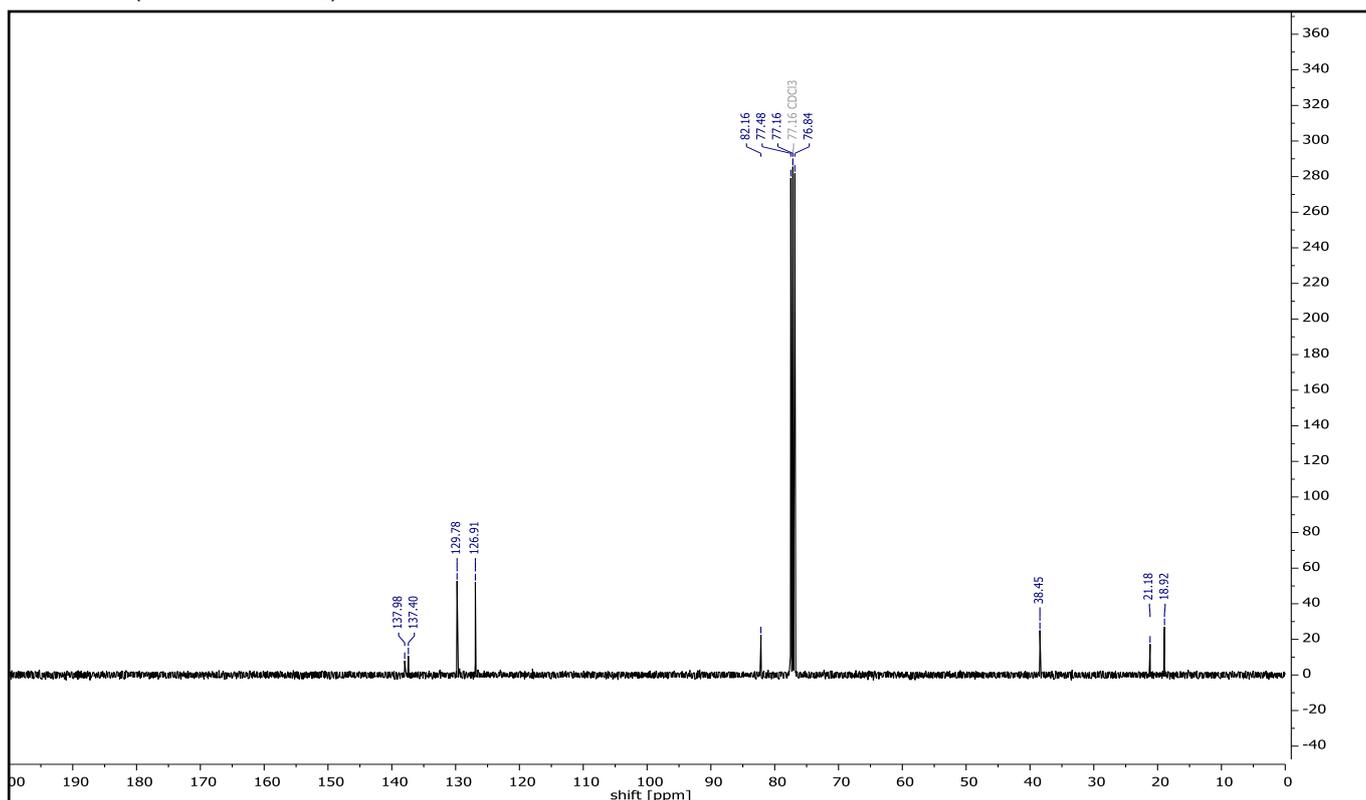
# 1-Methyl-4-(1-nitropropan-2-yl)benzene (14)



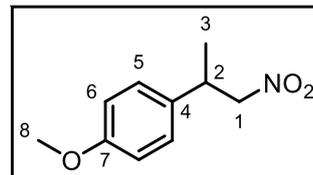
## <sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>)



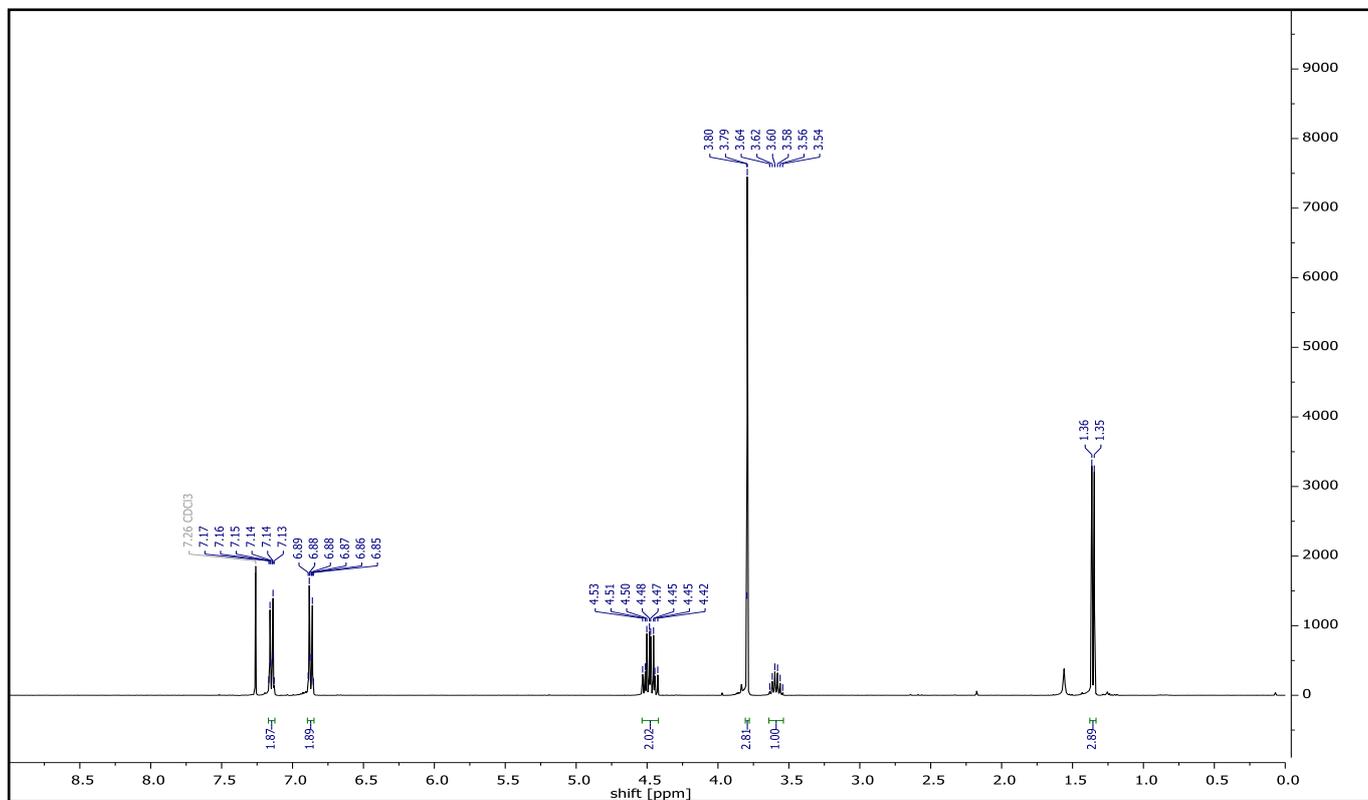
## <sup>13</sup>C-NMR (101 MHz, CDCl<sub>3</sub>)



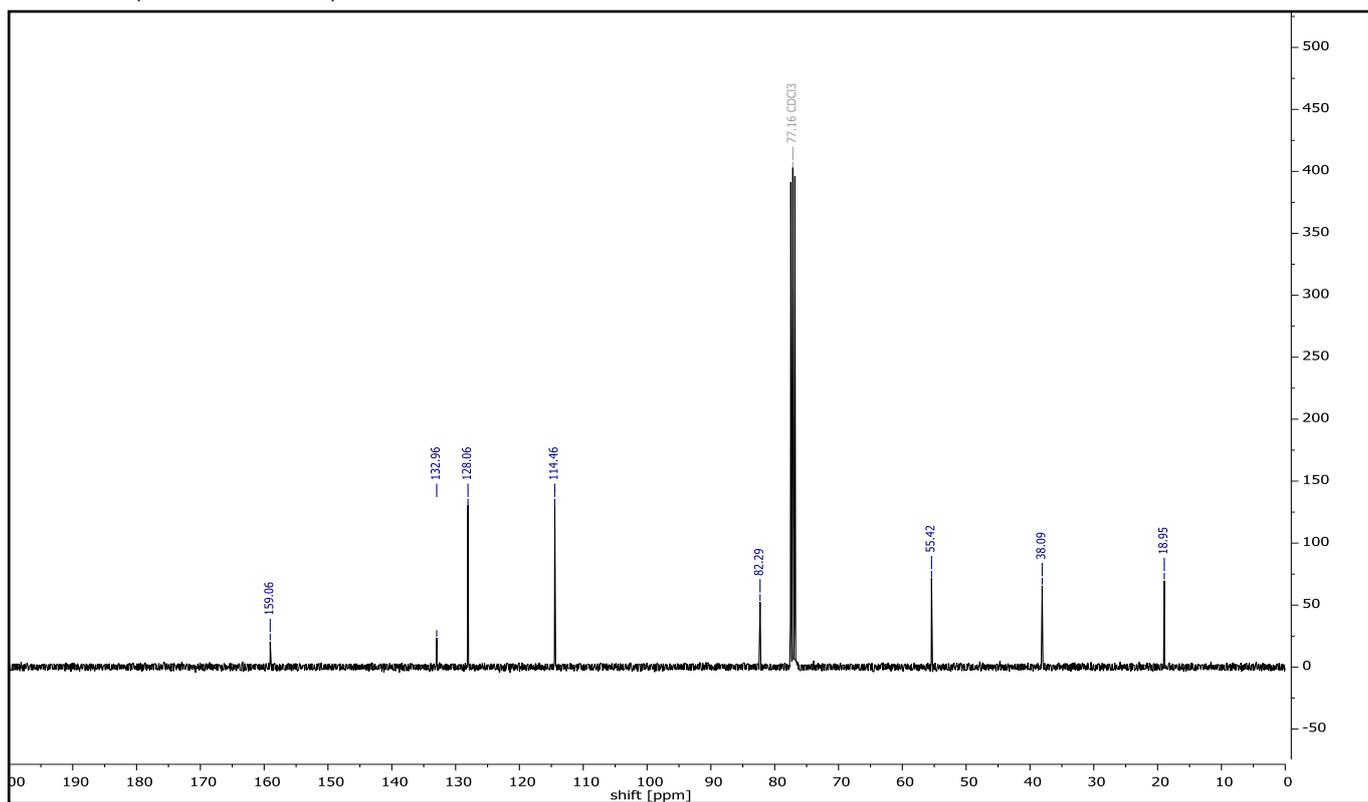
# 1-Methoxy-4-(1-nitropropan-2-yl)benzene (15)



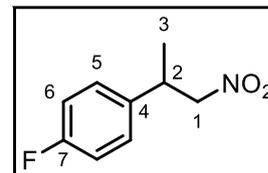
## <sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>)



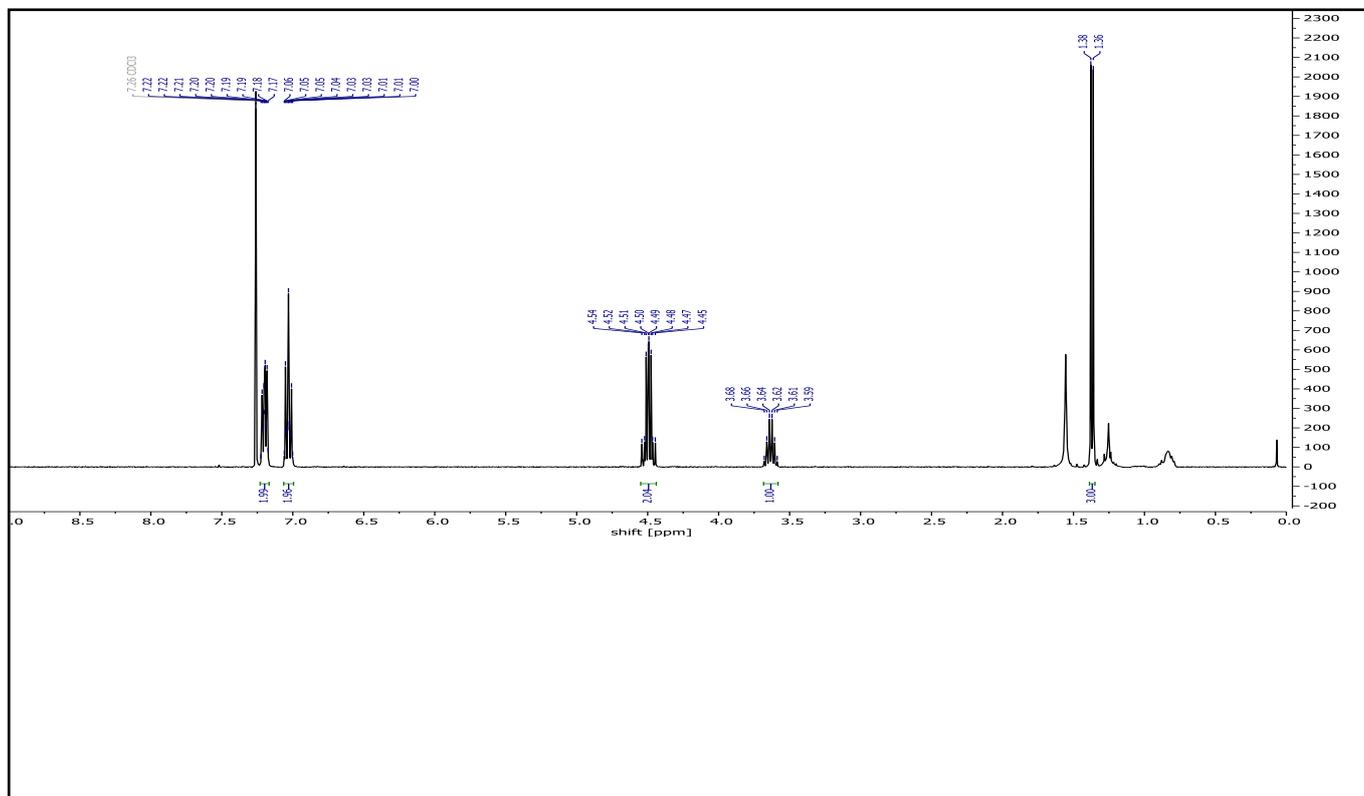
## <sup>13</sup>C-NMR (101 MHz, CDCl<sub>3</sub>)



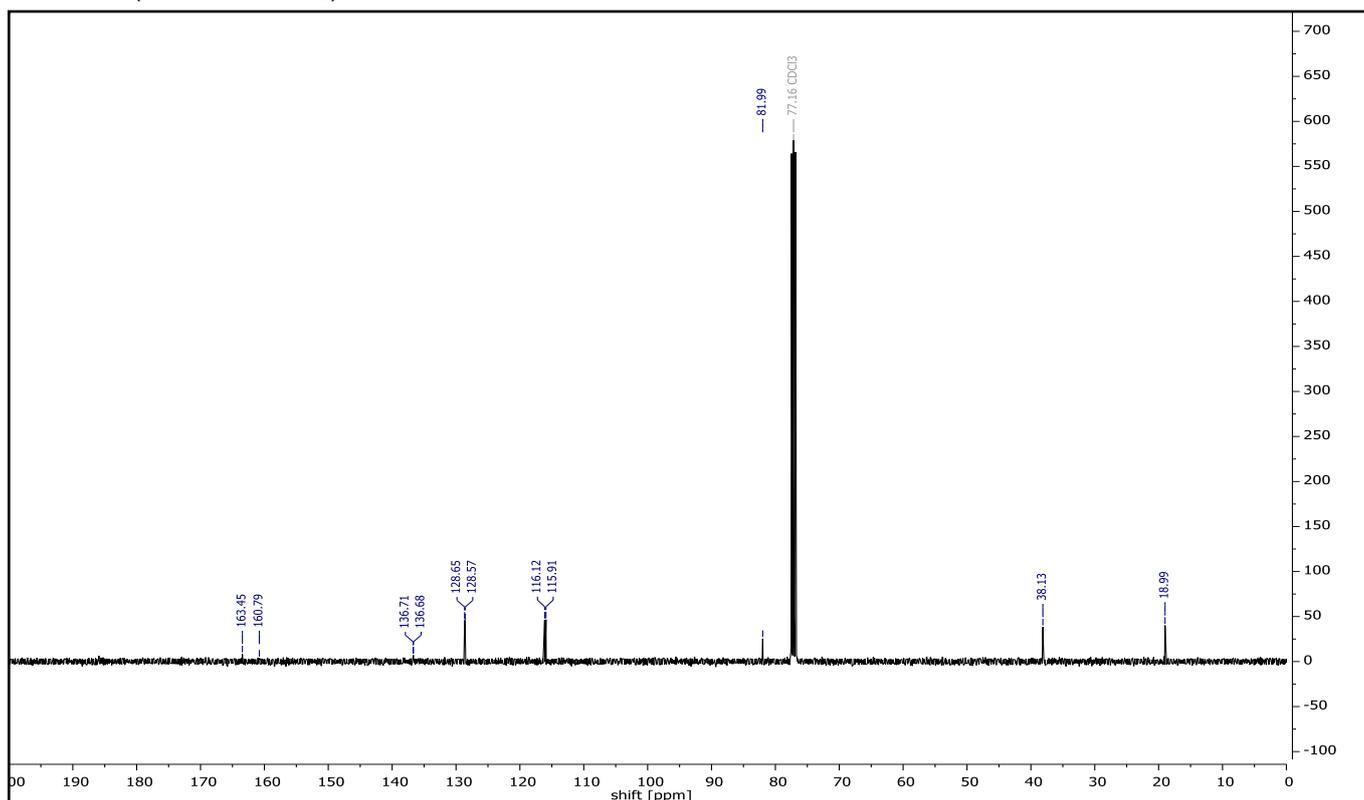
# 1-Fluoro-4-(1-nitropropan-2-yl)benzene (16)



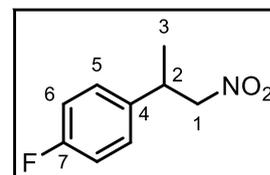
## $^1\text{H-NMR}$ (400 MHz, $\text{CDCl}_3$ )



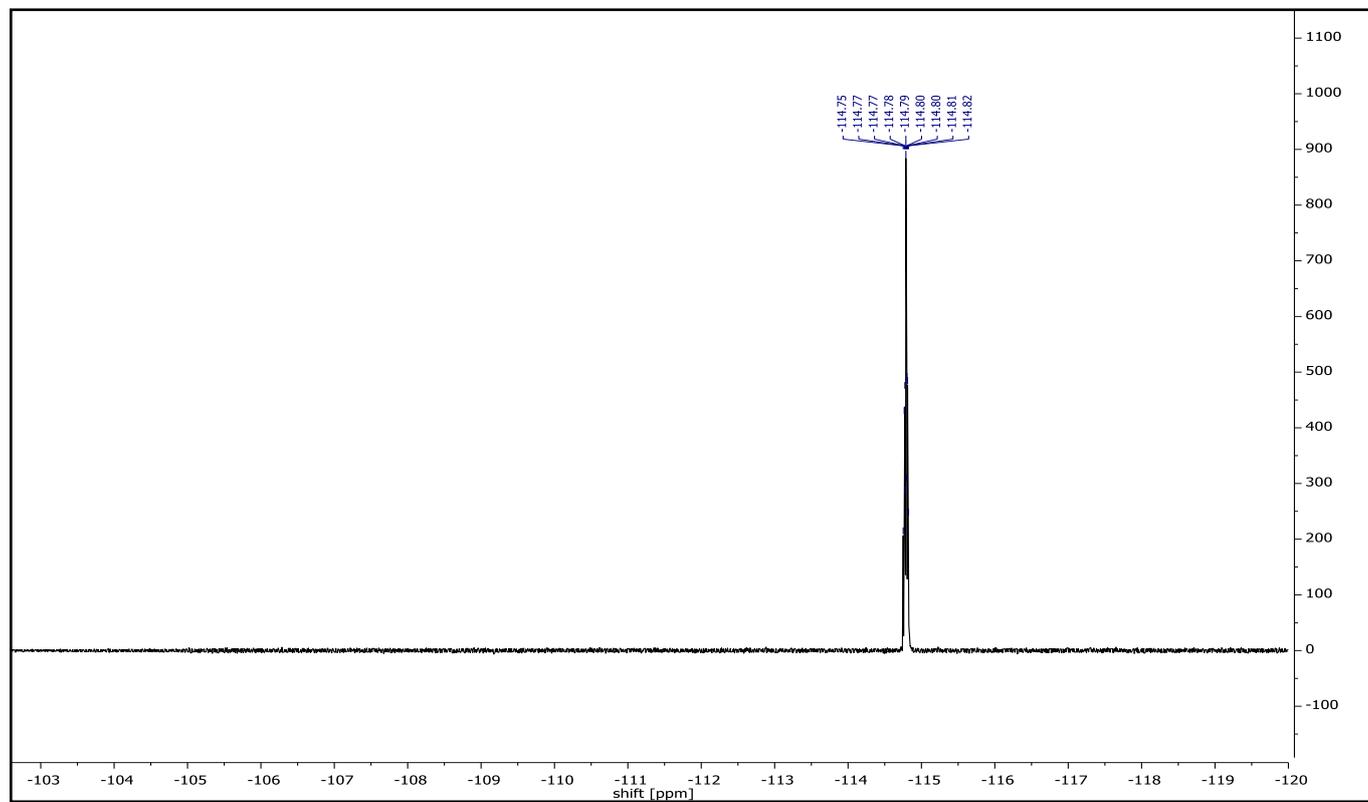
## $^{13}\text{C-NMR}$ (101 MHz, $\text{CDCl}_3$ )



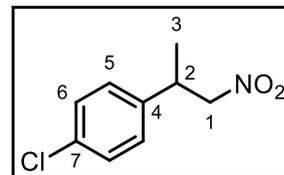
# 1-Fluoro-4-(1-nitropropan-2-yl)benzene (16)



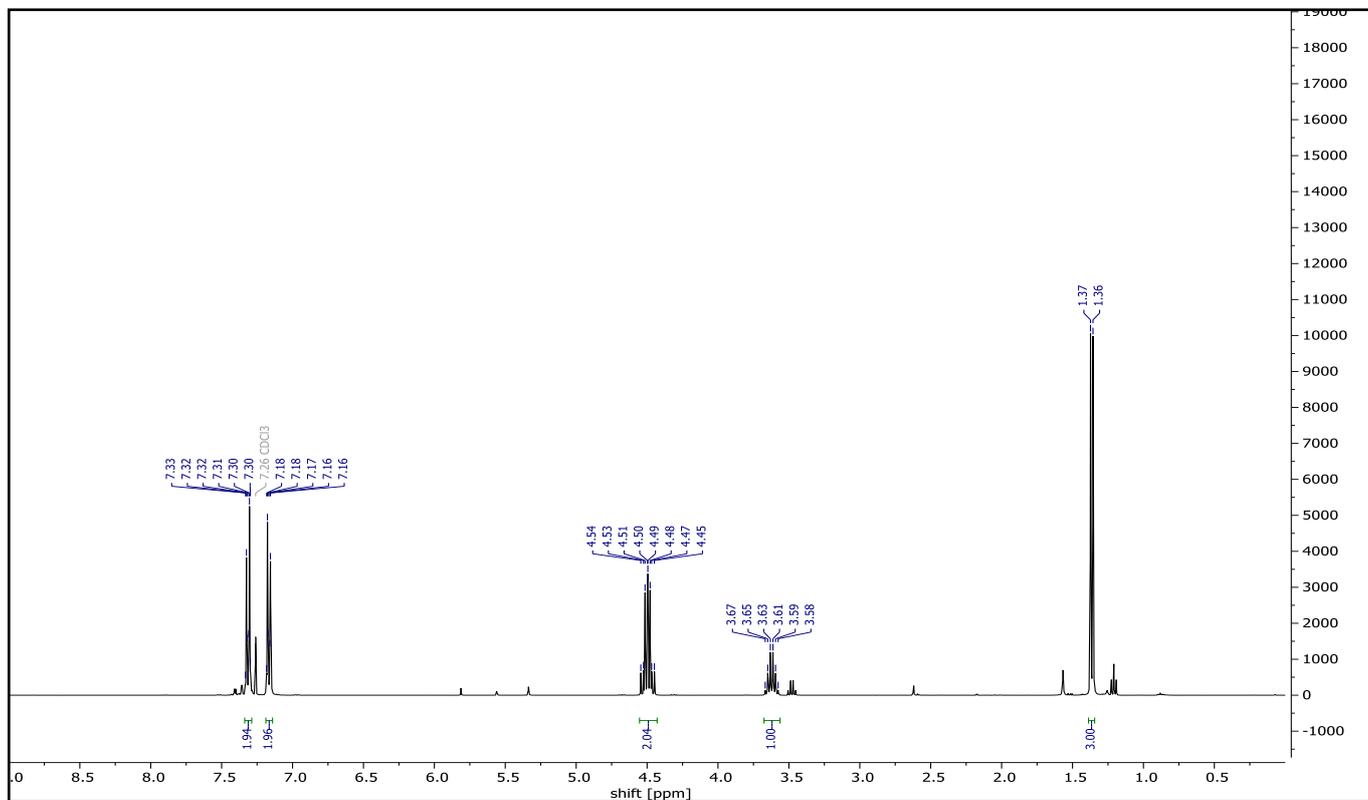
$^{19}\text{F}$ -NMR (376 MHz,  $\text{CDCl}_3$ )



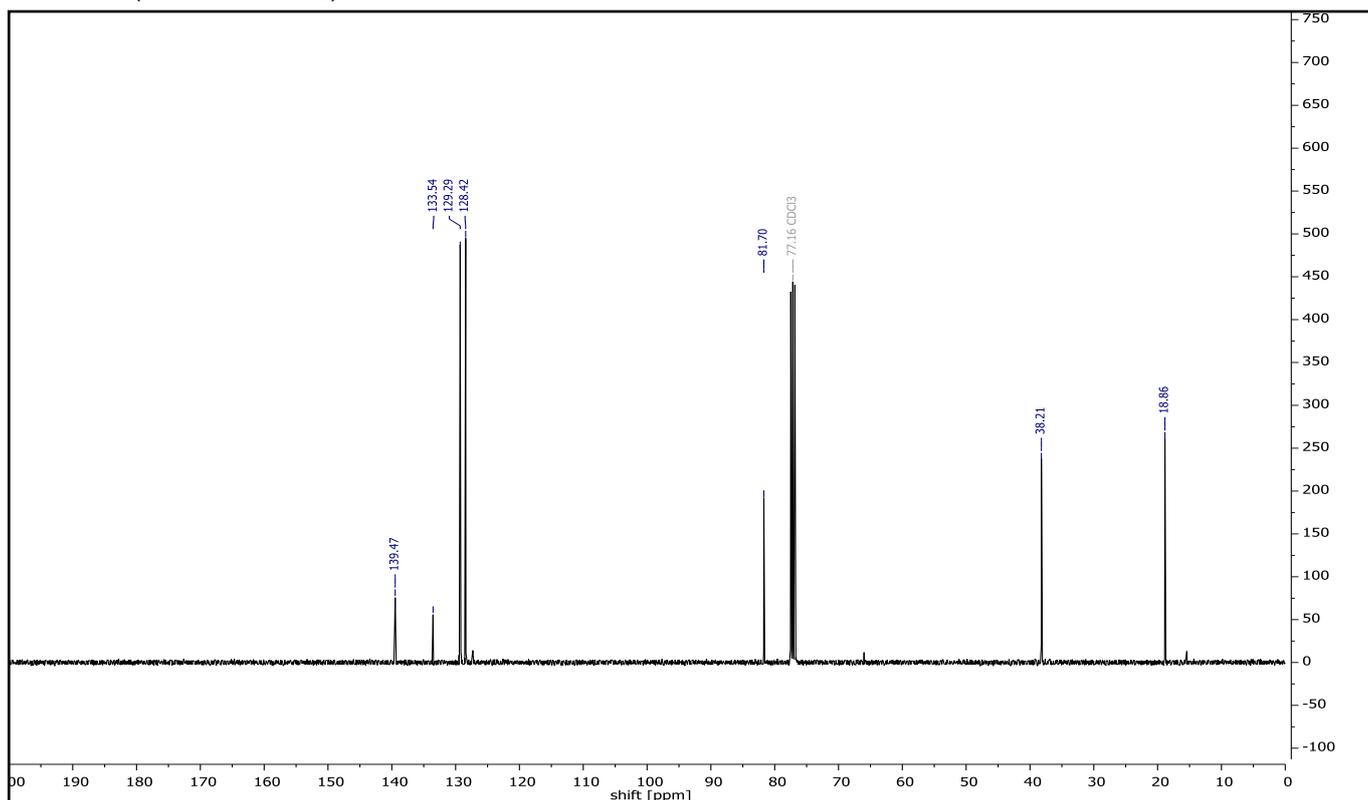
# 1-Chloro-4-(1-nitropropan-2-yl)benzene (17)



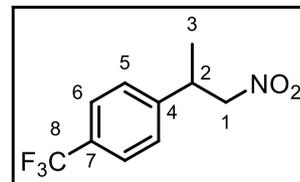
## $^1\text{H-NMR}$ (400 MHz, $\text{CDCl}_3$ )



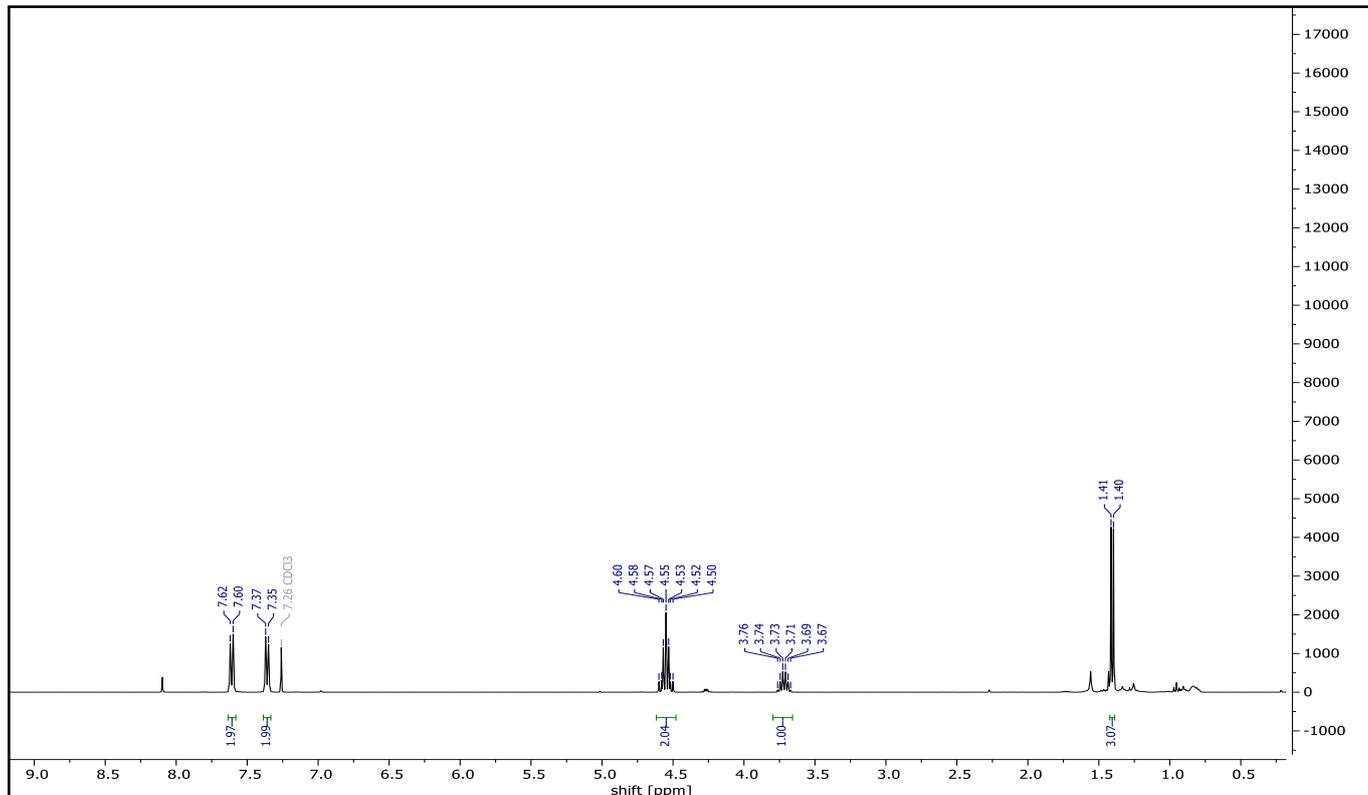
## $^{13}\text{C-NMR}$ (101 MHz, $\text{CDCl}_3$ )



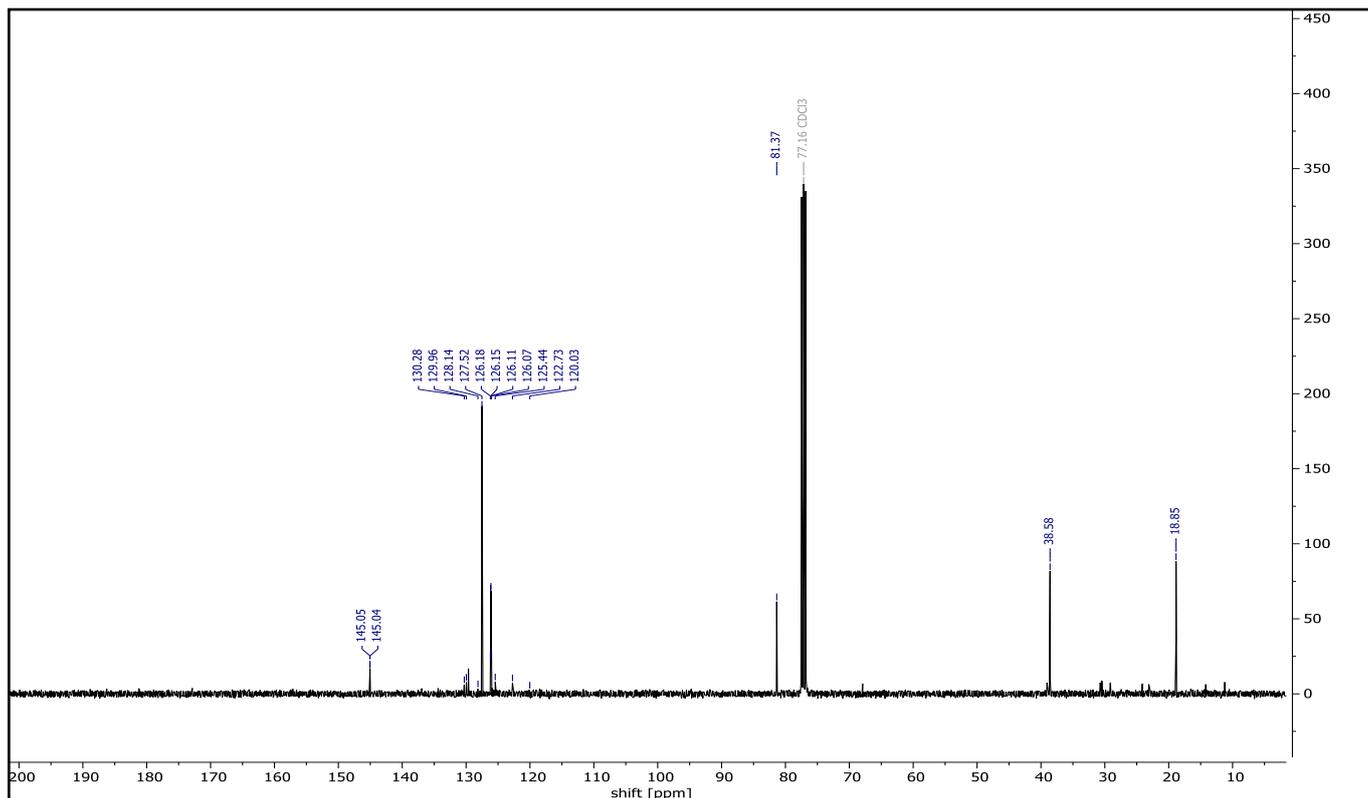
1-(1-Nitropropan-2-yl)-4-(trifluoromethyl)benzene (18)



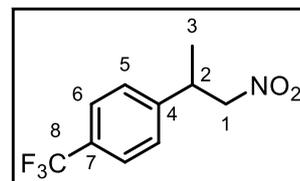
<sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>)



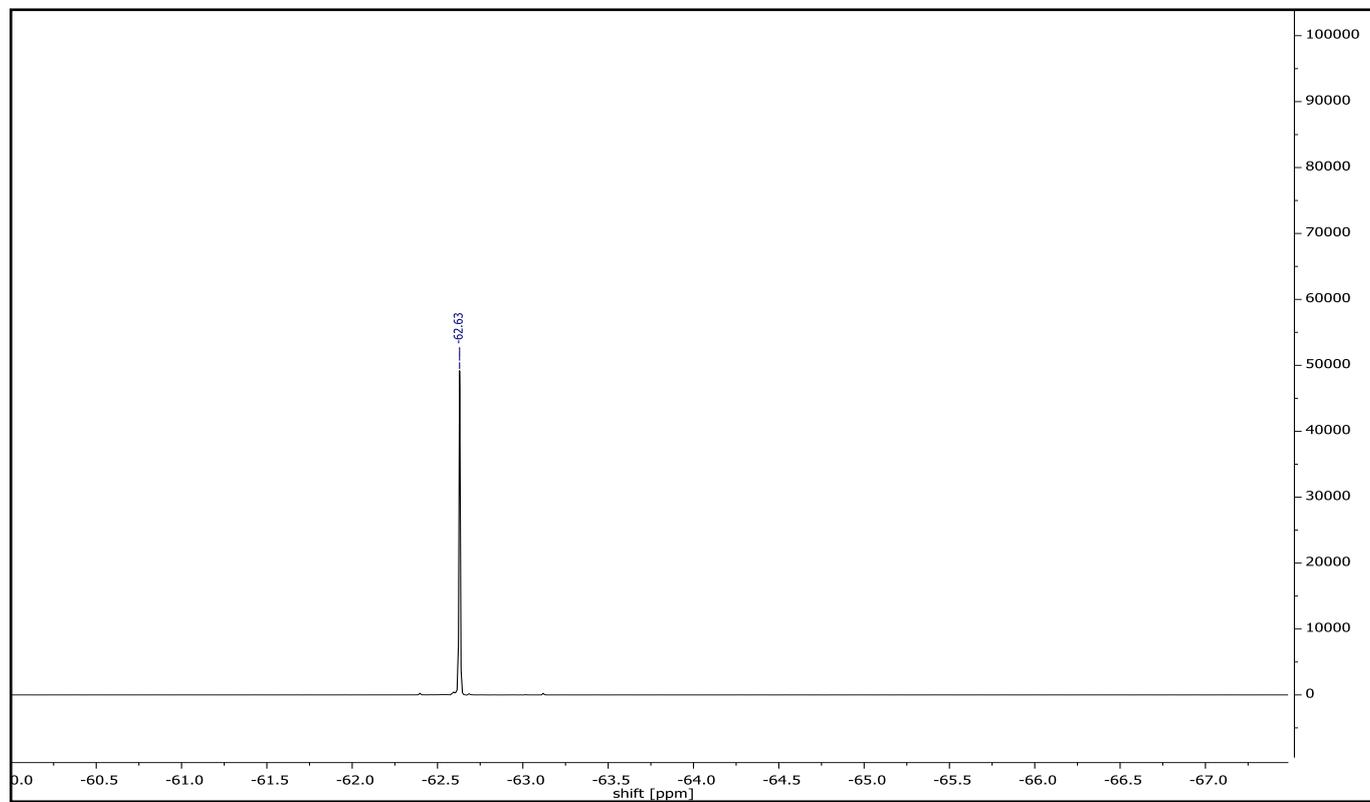
<sup>13</sup>C-NMR (101 MHz, CDCl<sub>3</sub>)



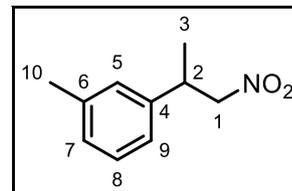
1-(1-Nitropropan-2-yl)-4-(trifluoromethyl)benzene (18)



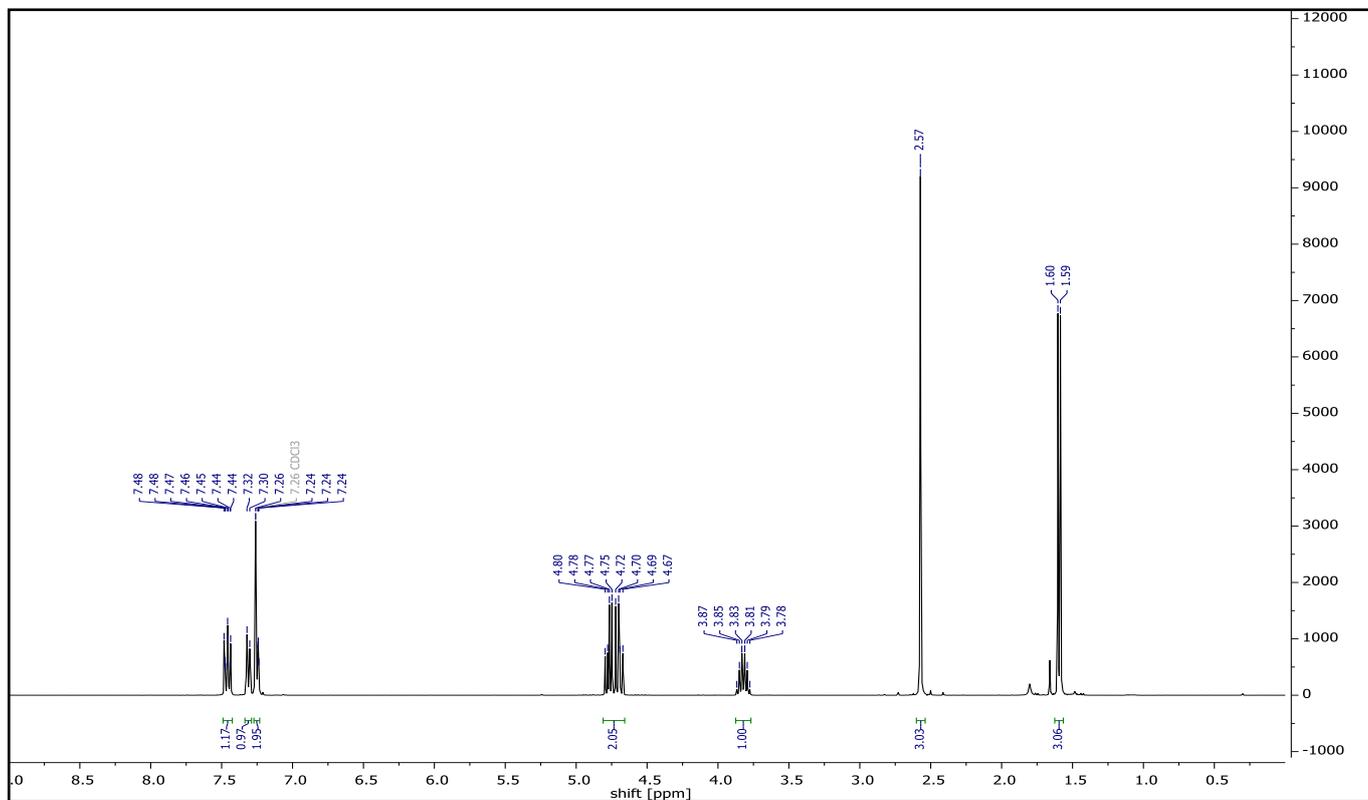
<sup>19</sup>F-NMR (376 MHz, CDCl<sub>3</sub>)



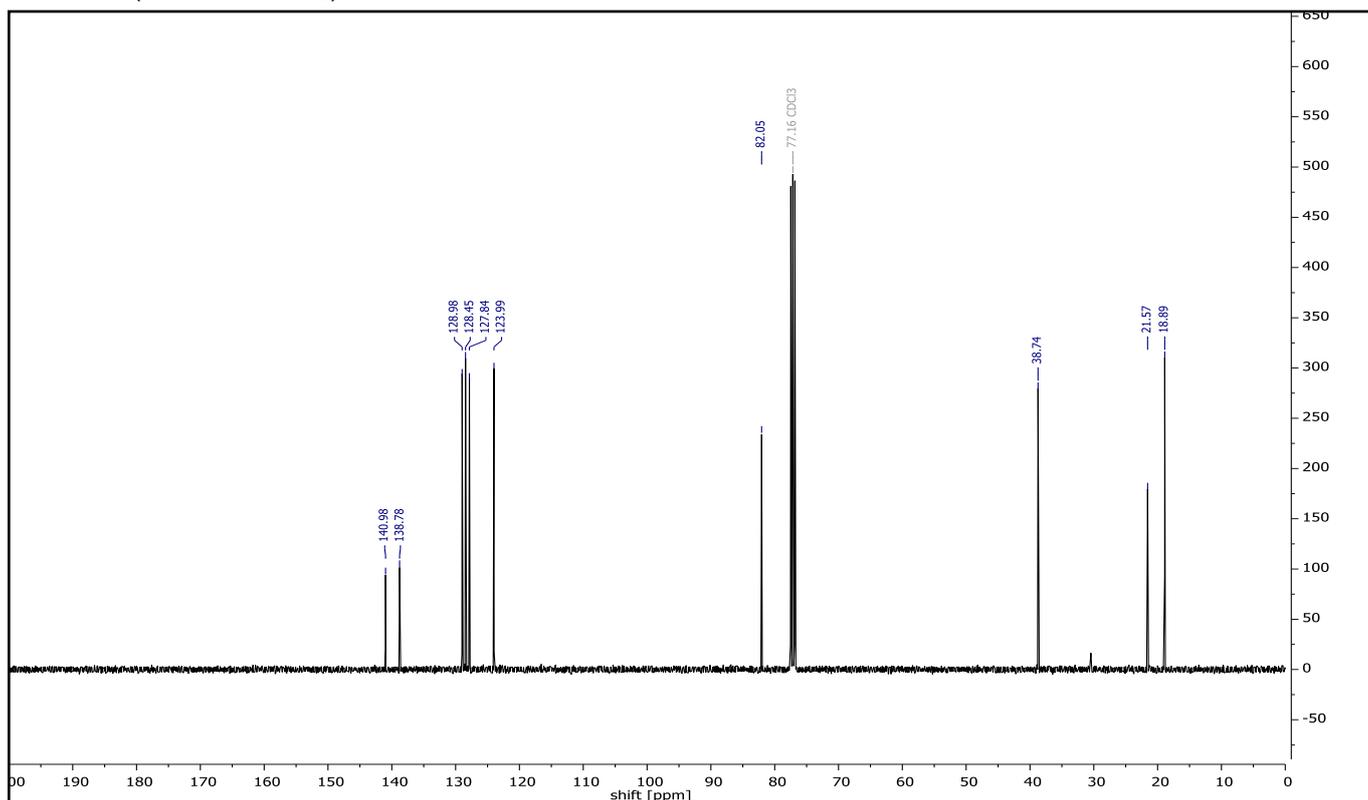
# 1-Methyl-3-(1-nitropropan-2-yl)benzene (19)



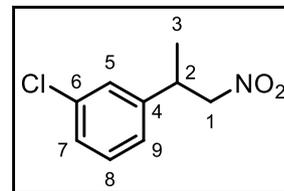
## $^1\text{H-NMR}$ (400 MHz, $\text{CDCl}_3$ )



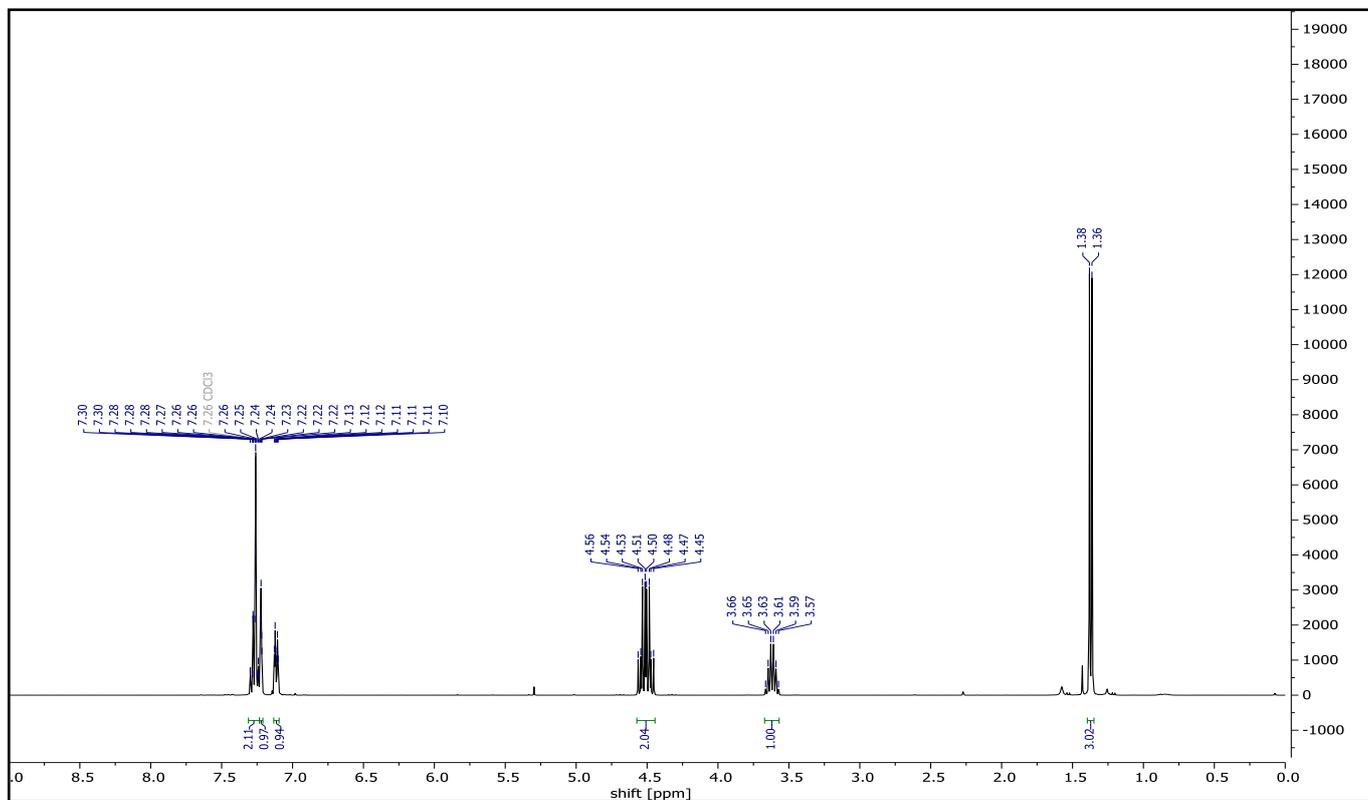
## $^{13}\text{C-NMR}$ (101 MHz, $\text{CDCl}_3$ )



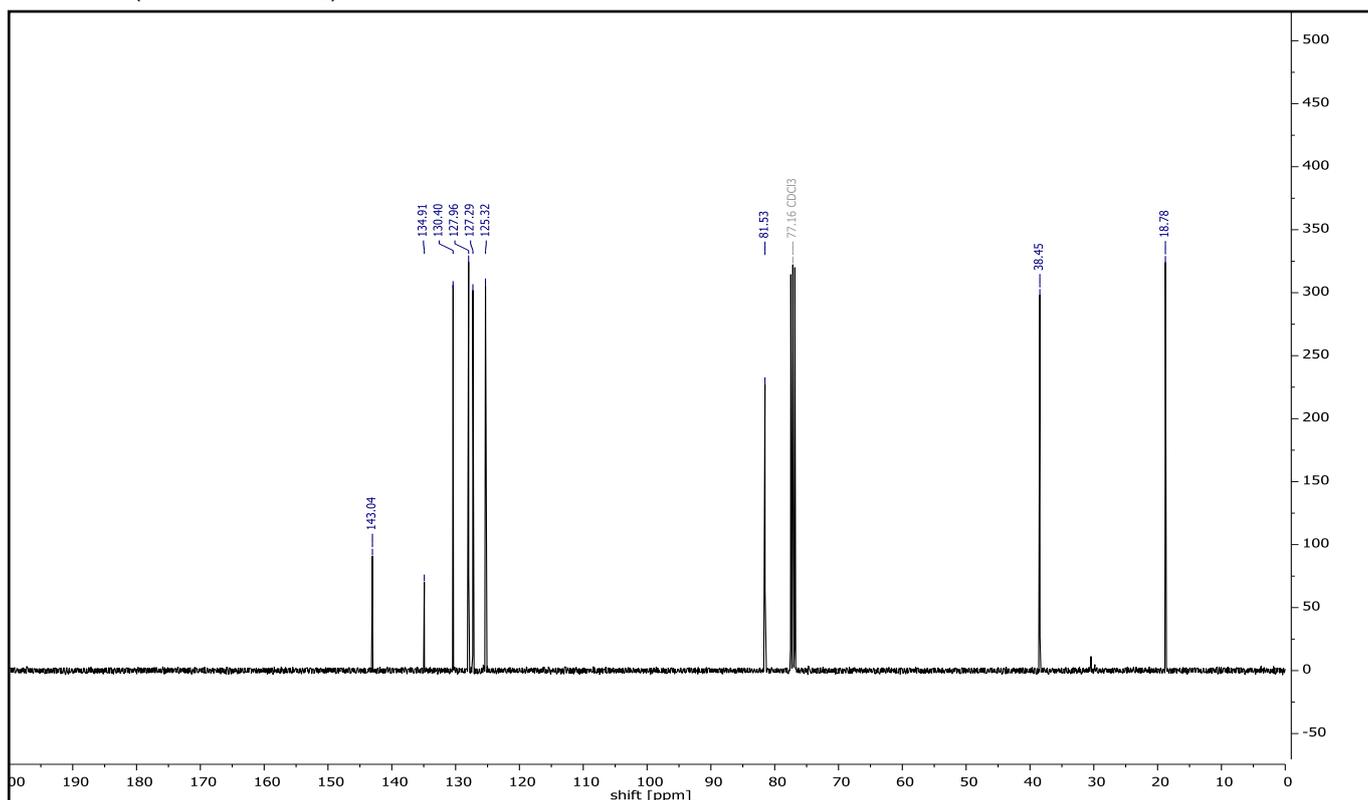
# 1-Chloro-3-(1-nitropropan-2-yl)benzene (20)



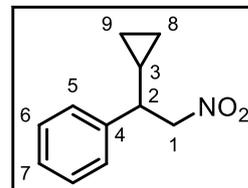
$^1\text{H-NMR}$  (400 MHz,  $\text{CDCl}_3$ )



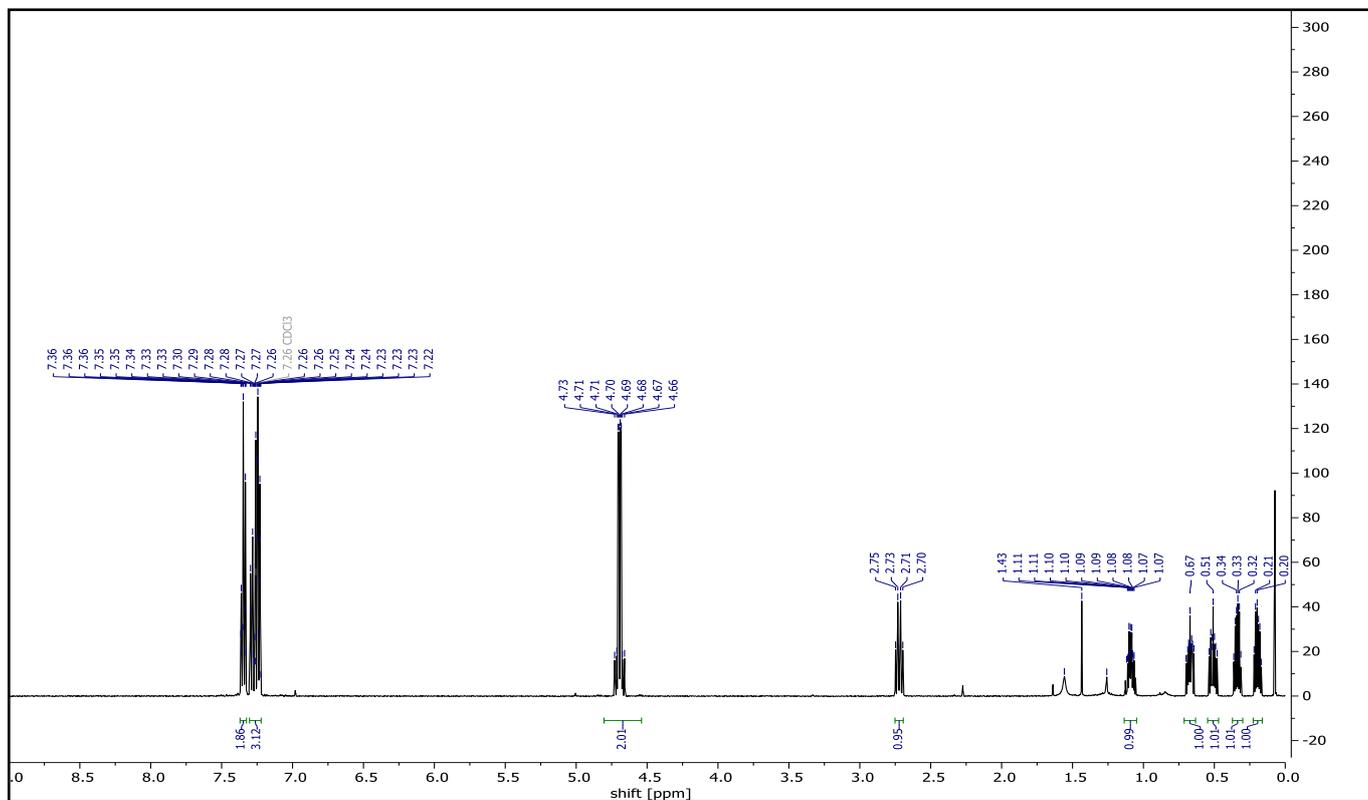
$^{13}\text{C-NMR}$  (101 MHz,  $\text{CDCl}_3$ )



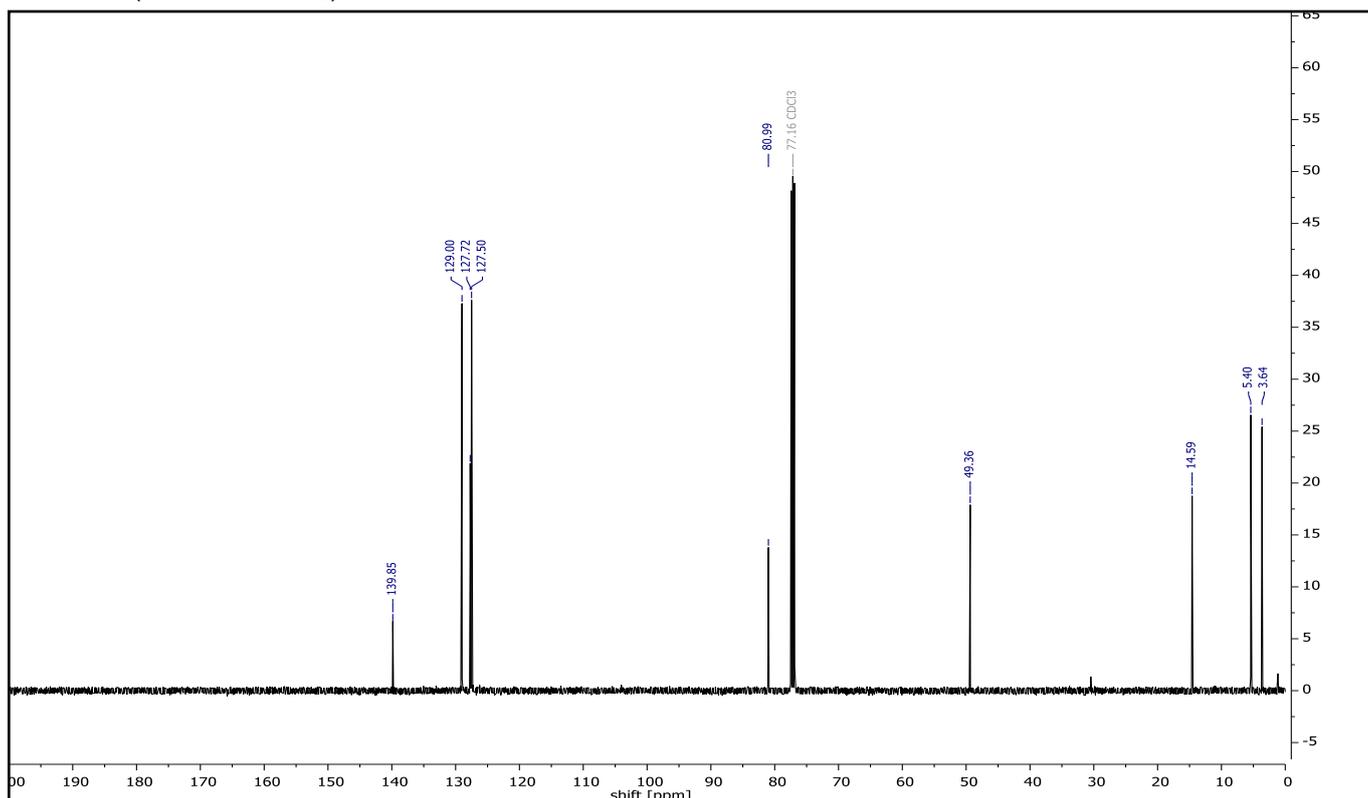
# (1-Cyclopropyl-2-nitroethyl)benzene (21)



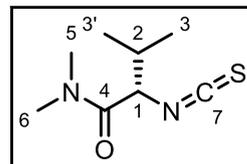
## <sup>1</sup>H-NMR (500 MHz, CDCl<sub>3</sub>)



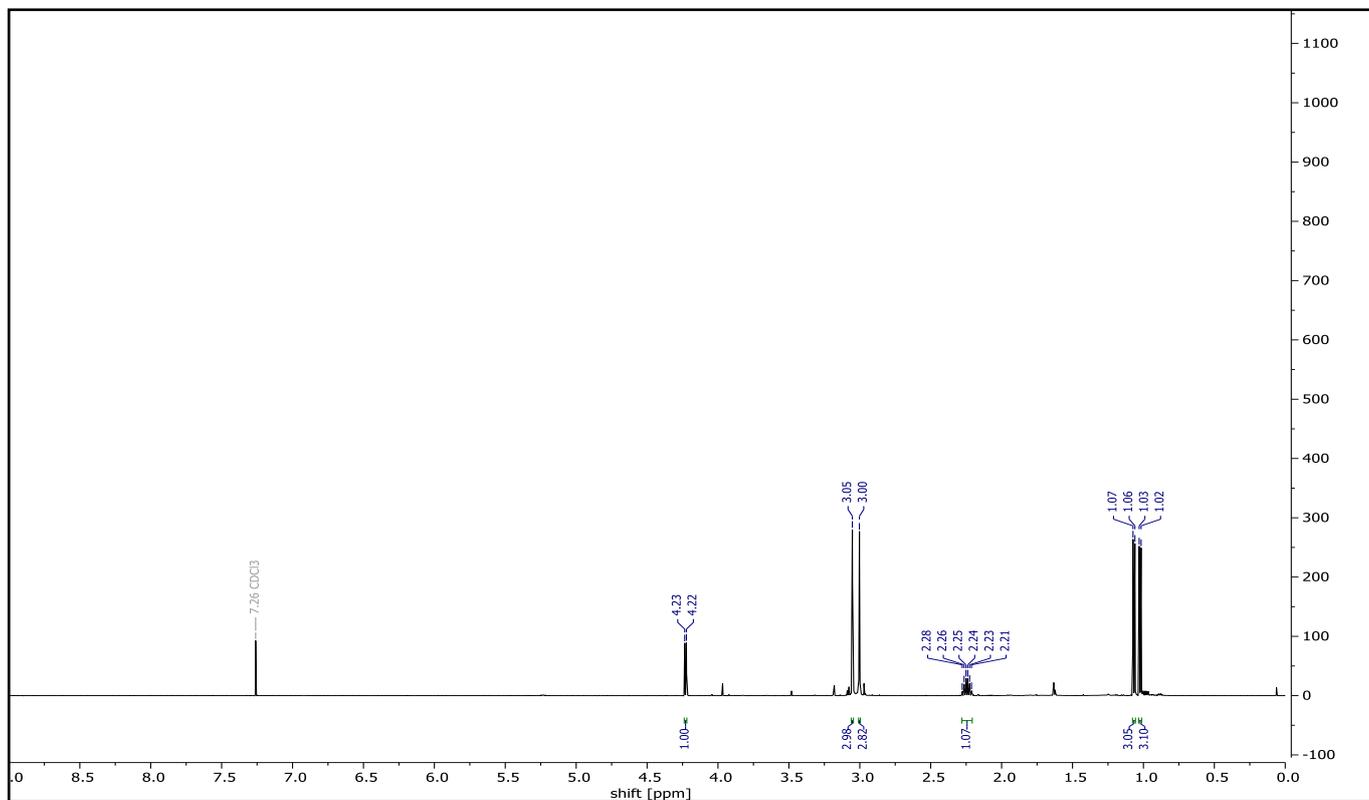
## <sup>13</sup>C-NMR (126 MHz, CDCl<sub>3</sub>)



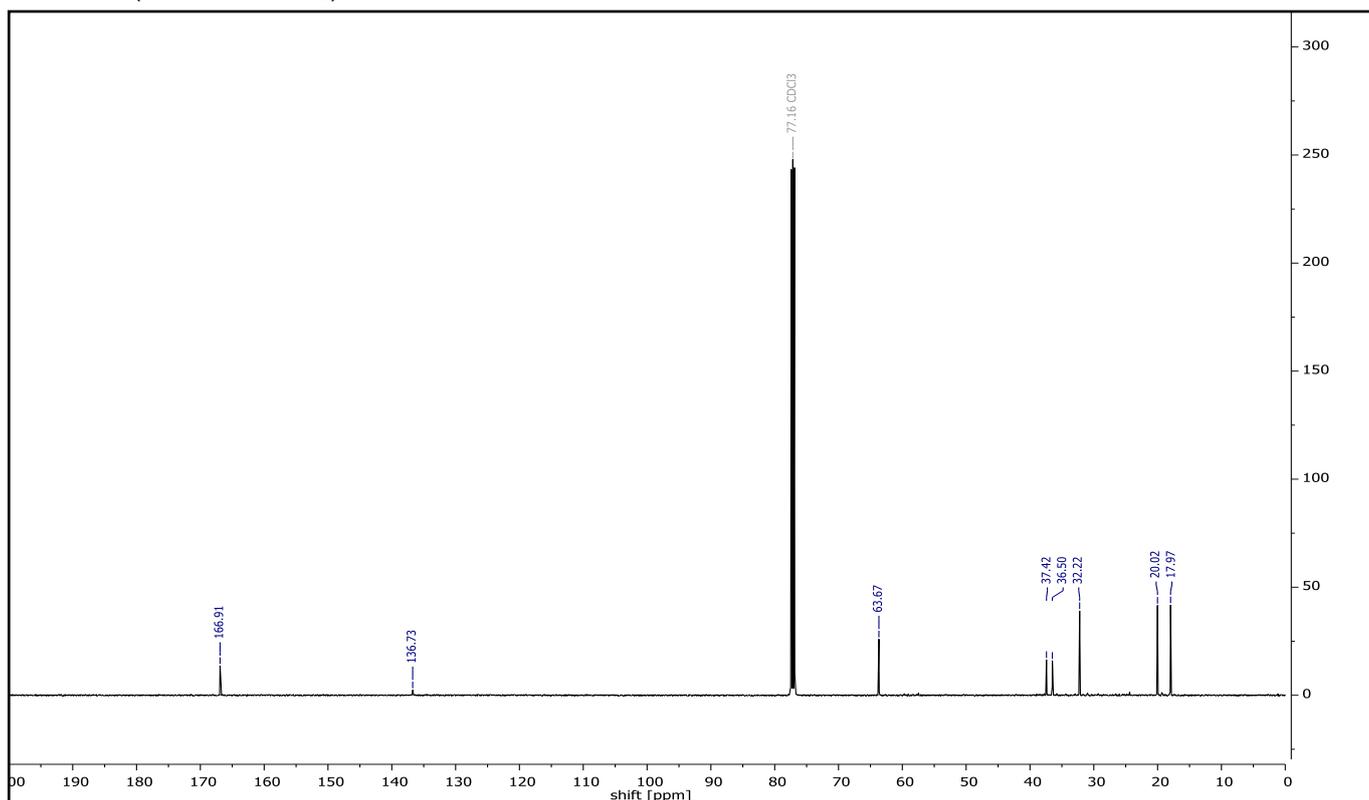
**(S)-2-Isothiocyanato-N,N,3-trimethylbutanamide (S5)**



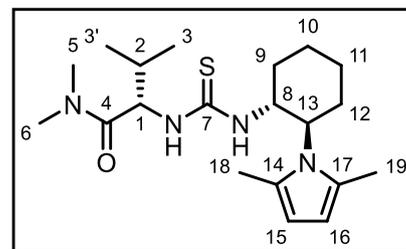
<sup>1</sup>H-NMR (500 MHz, CDCl<sub>3</sub>)



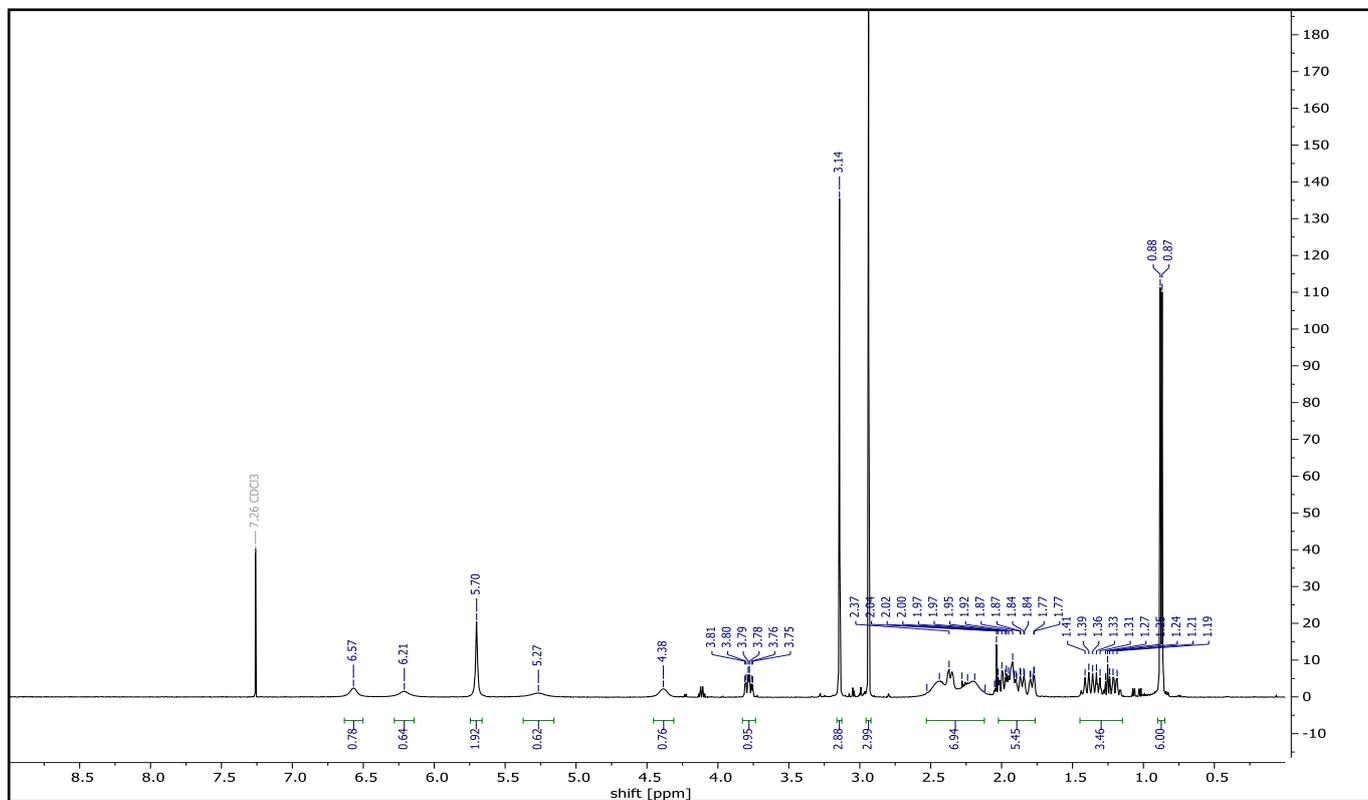
<sup>13</sup>C-NMR (300 MHz, CDCl<sub>3</sub>)



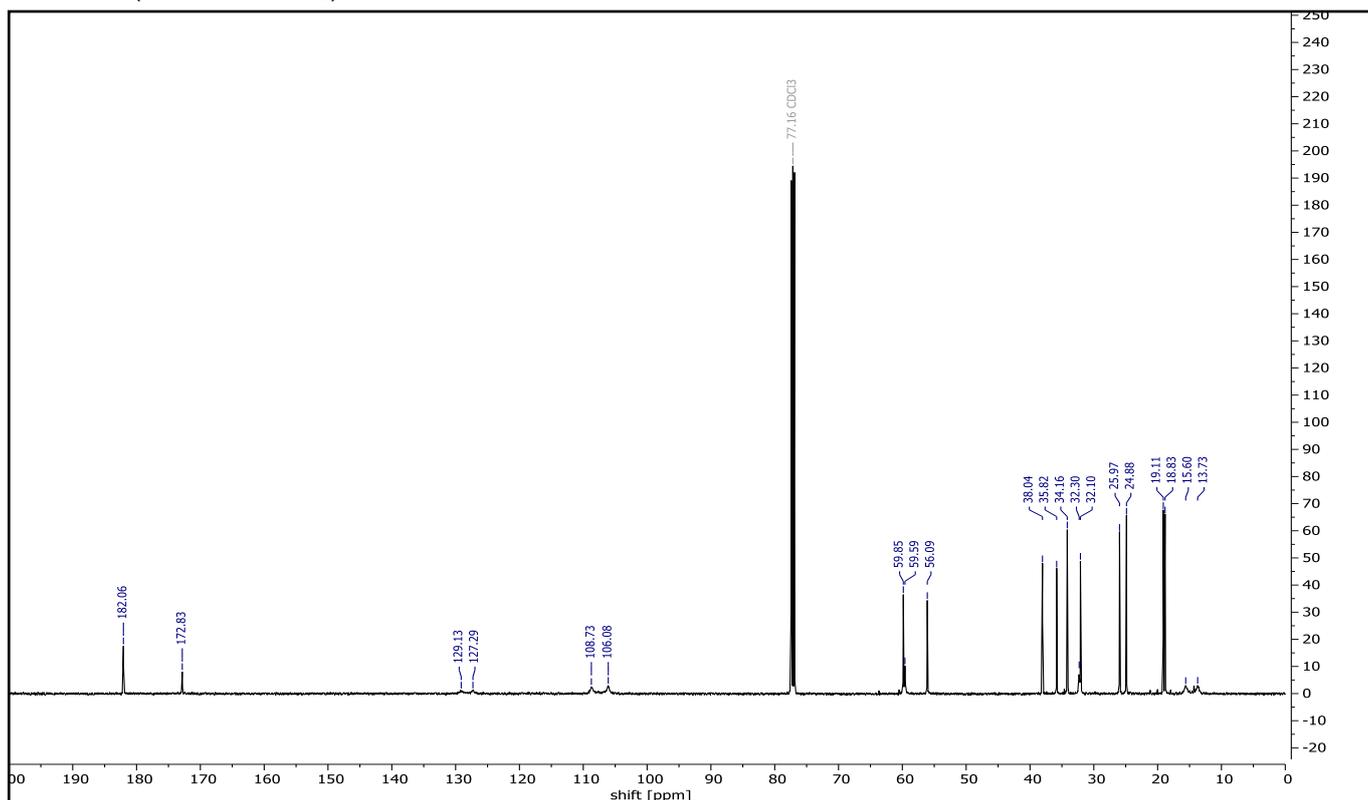
**(S)-2-(3-((1R,2R)-2-(2,5-Dimethyl-1H-pyrrol-1-yl)cyclohexyl)thioureido)-N,N,3-trimethylbutanamide (A)**



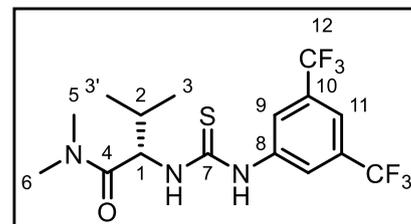
$^1\text{H-NMR}$  (500 MHz,  $\text{CDCl}_3$ )



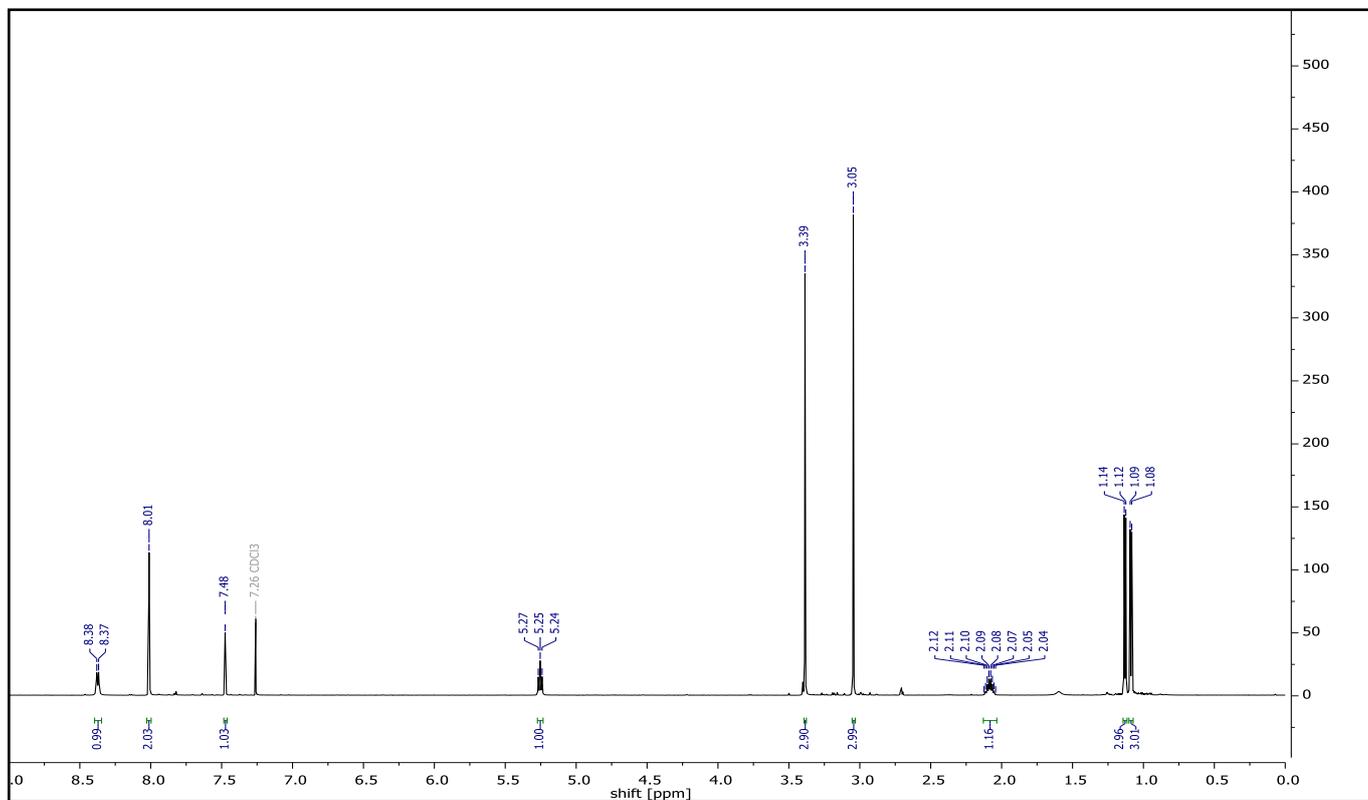
$^{13}\text{C-NMR}$  (126 MHz,  $\text{CDCl}_3$ )



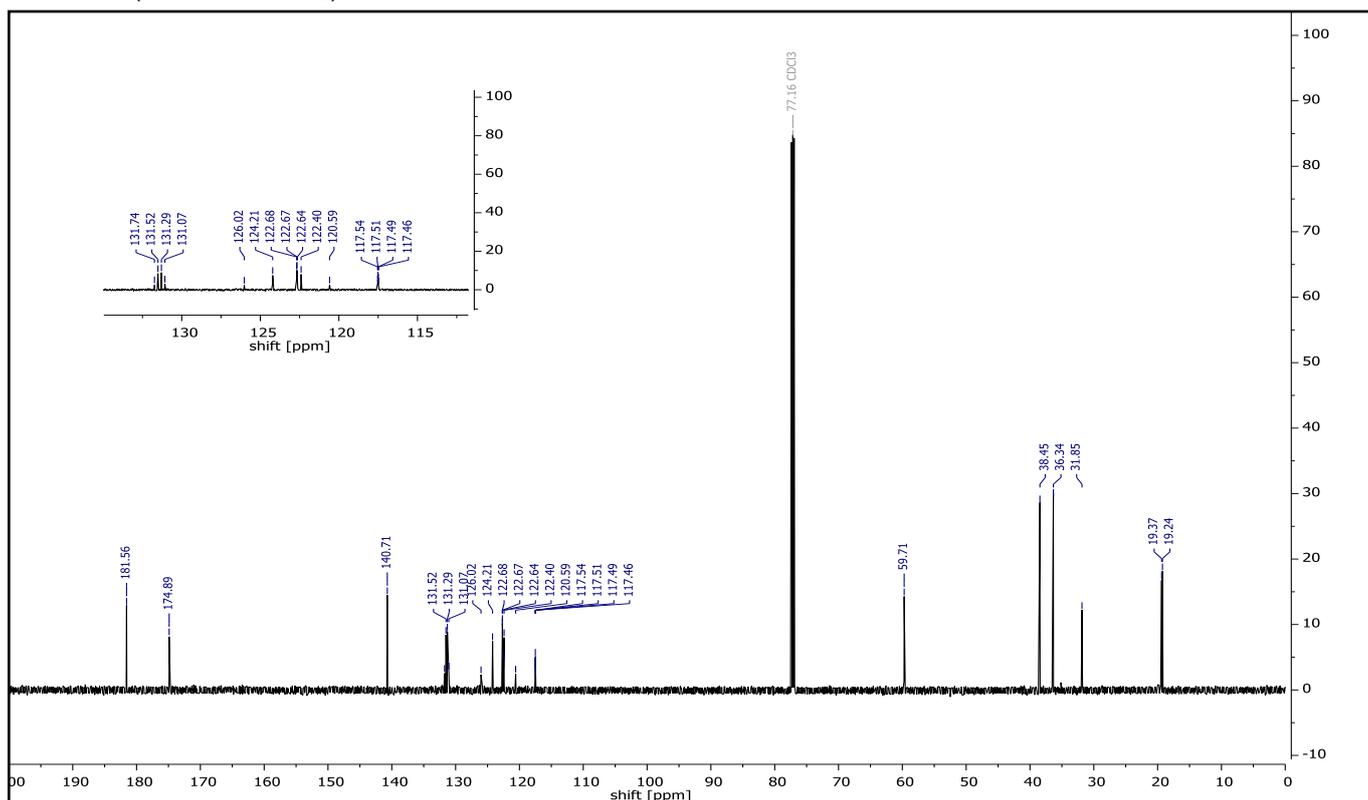
**(S)-2-(3-((1*R*,2*R*)-2-(2,5-Dimethyl-1*H*-pyrrol-1-yl)cyclohexyl)thioureido)-*N,N*,3-trimethylbutanamide (B)**



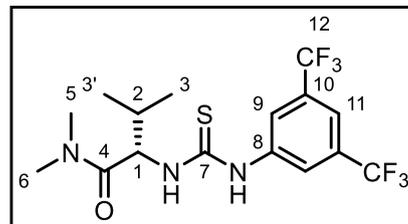
<sup>1</sup>H-NMR (600 MHz, CDCl<sub>3</sub>)



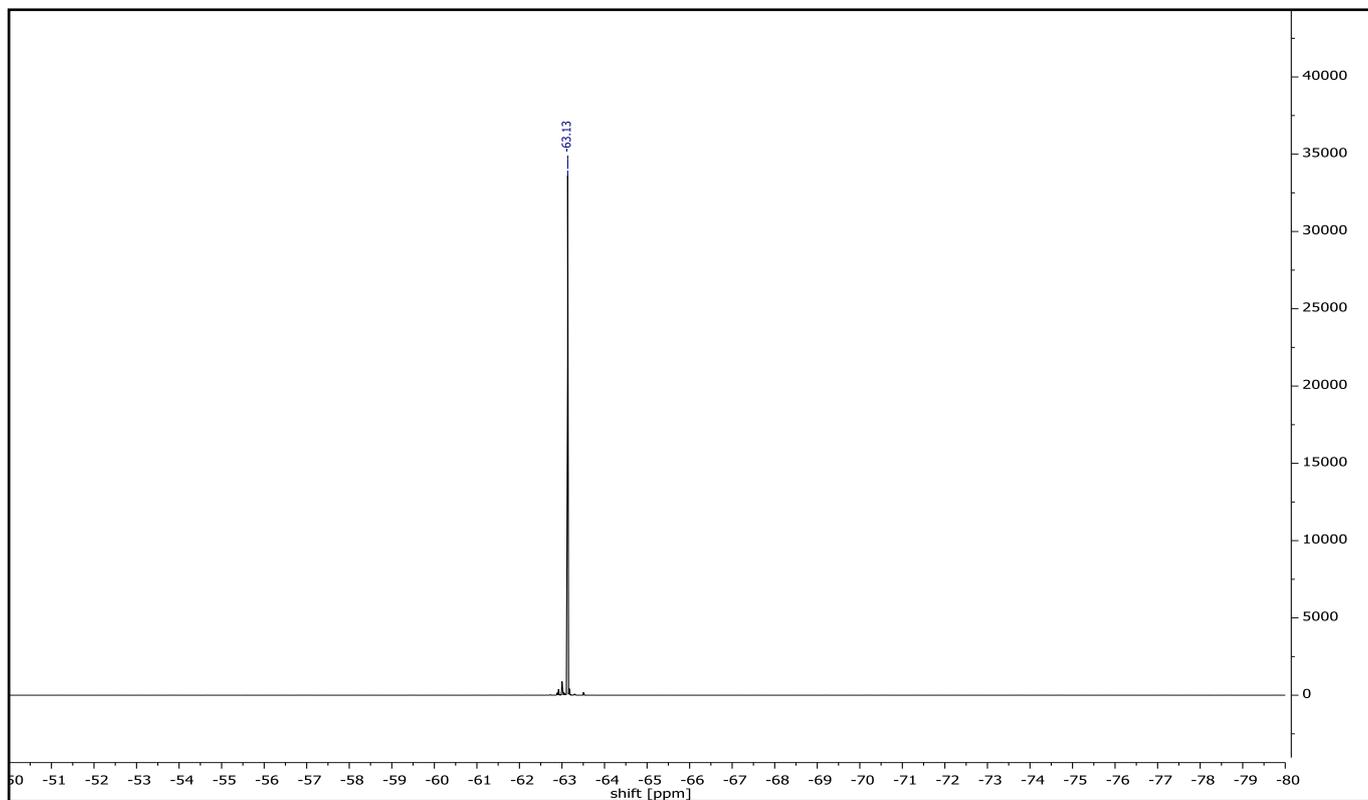
<sup>13</sup>C-NMR (151 MHz, CDCl<sub>3</sub>)



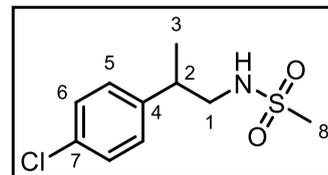
**(S)-2-(3-((1R,2R)-2-(2,5-Dimethyl-1H-pyrrol-1-yl) cyclohexyl)thioureido)-N,N,3-trimethylbutanamide (B)**



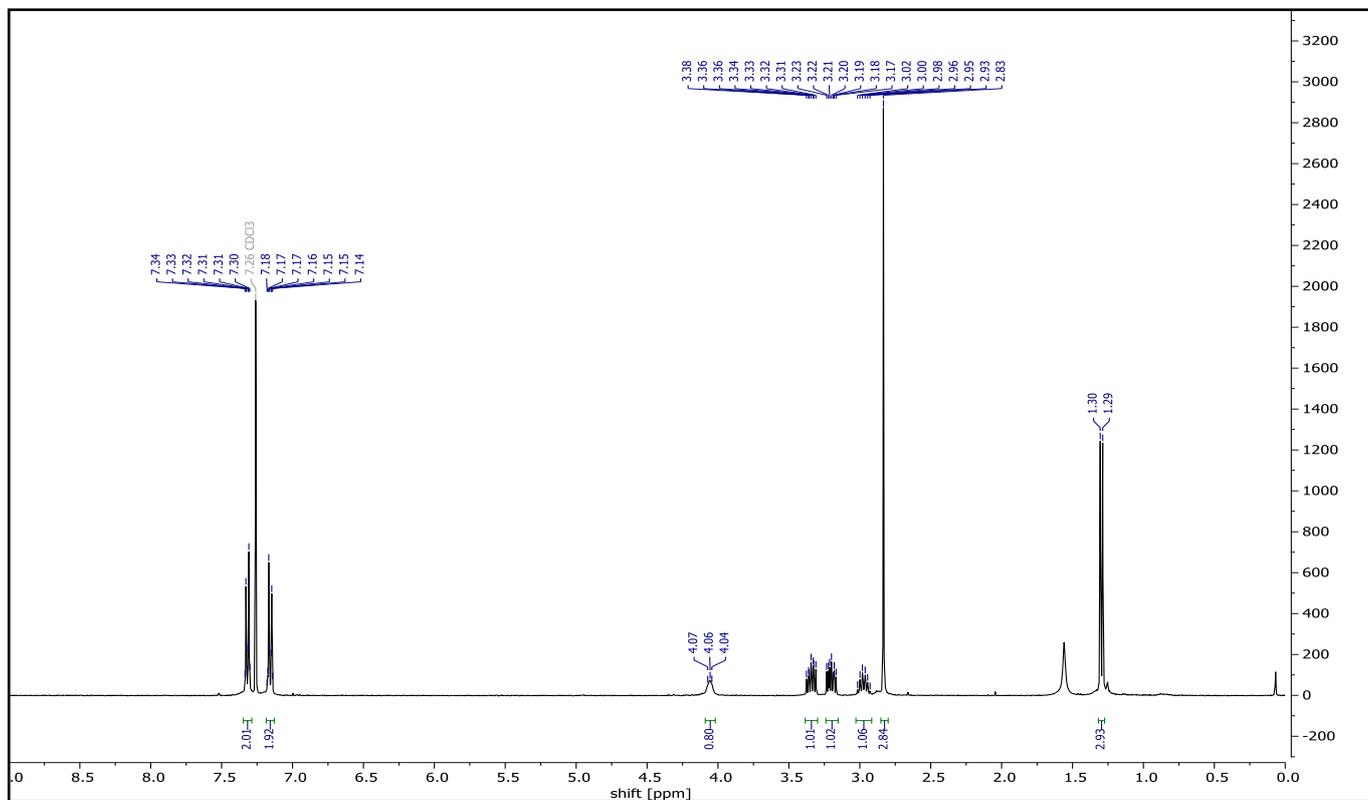
$^{19}\text{F}$ -NMR (564 MHz,  $\text{CDCl}_3$ )



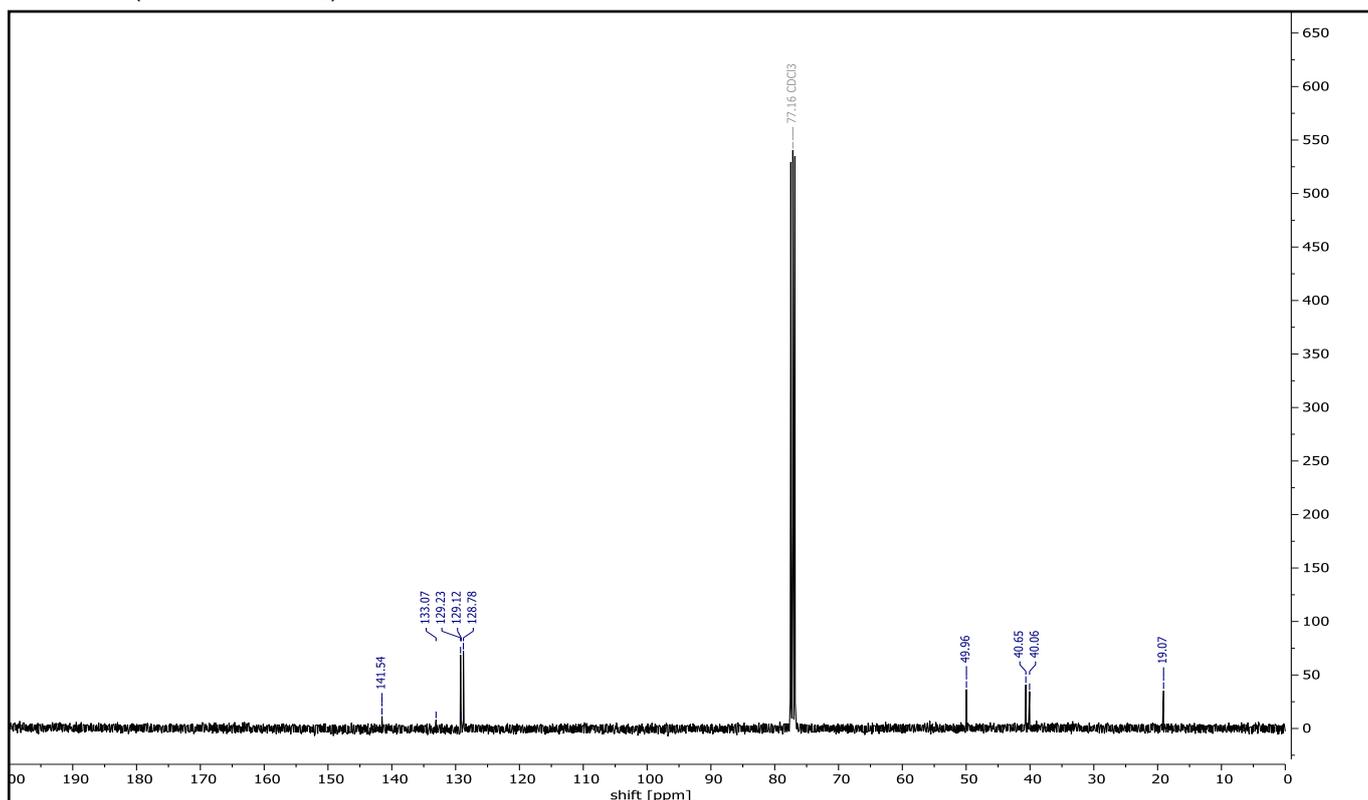
# N-(2-(4-Chlorophenyl)propyl)methanesulfonamide (22)



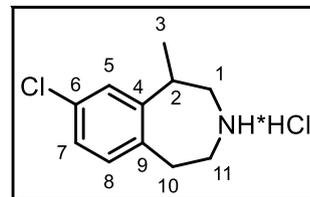
## <sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>)



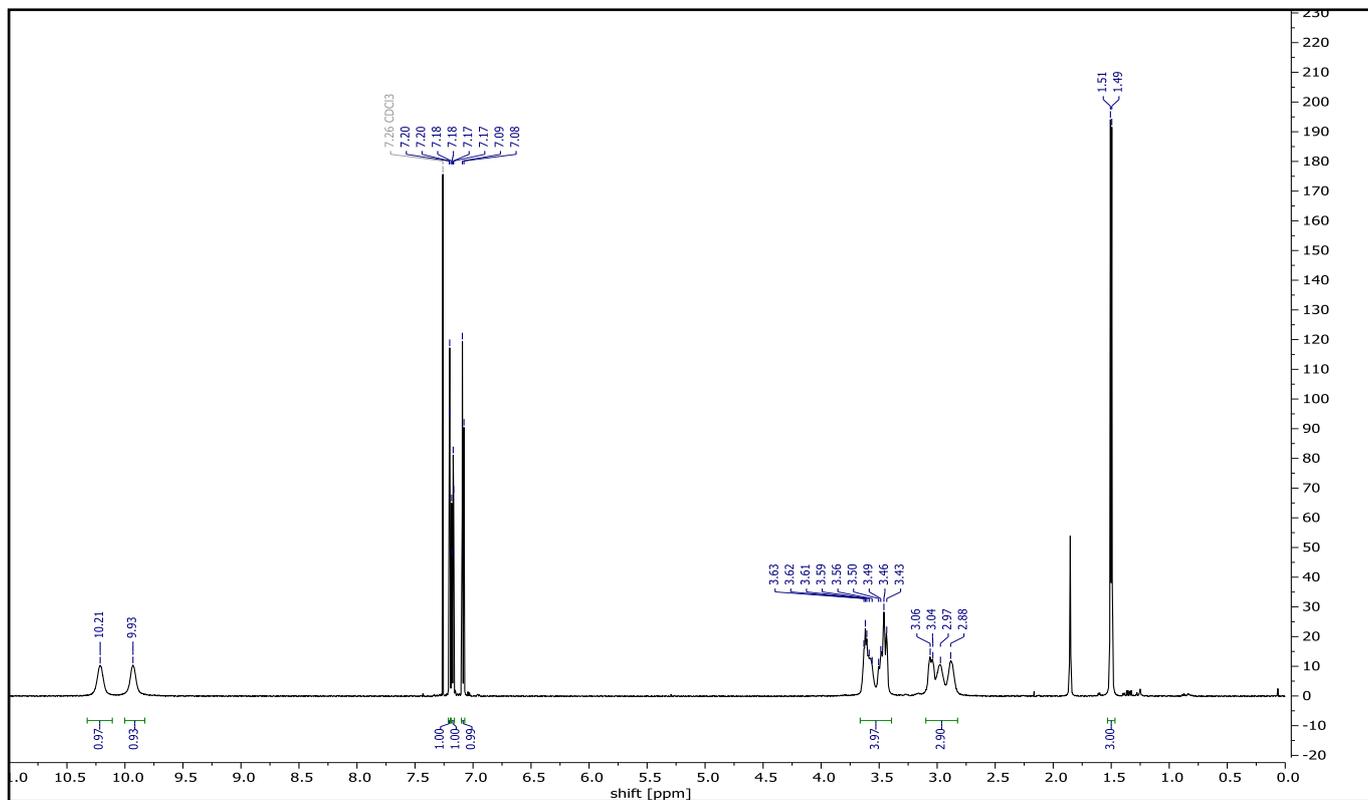
## <sup>13</sup>C-NMR (300 MHz, CDCl<sub>3</sub>)



**8-Chloro-1-methyl-2,3,4,5-tetrahydro-1H-benzo[d]azepine hydrochloric acid (24)**



$^1\text{H-NMR}$  (600 MHz,  $\text{CDCl}_3$ )



$^{13}\text{C-NMR}$  (151 MHz,  $\text{CDCl}_3$ )

