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Novel transformation of α,β-unsaturated aldehydes and ketones towards γ-amino alcohols or 1,3-oxazines in a 4/5 step, one-pot multisequence.

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1. General experimental

All reagents were used as received from the supplier without further purification, unless stated. All solvents were used as received from the supplier, except THF (freshly distilled) and methanol (stored over molecular sieves). Molecular sieves, 3Å 1-2mm beads, were supplied from Alfa Aesar, and stored at 150 °C. Reactions were monitored by TLC analysis using POLTFRAM® SIL G/UV_{254} (40 x 80 mm) TLC plates. Flash column chromatography was carried out using Silica gel as supplied from Sigma-Aldrich (230-400 mesh, 40-63 µm, 60 Å) and monitored using TLC analysis.

^{1}H NMR spectra were recorded on a Varian-Mercury 500 MHz spectrometer, operating at ambient probe temperature unless specified elsewhere. ^{13}C NMR spectra were recorded on a Varian Mercury 500 MHz instrument, operating at 101 MHz, unless specified elsewhere. Deuterated chloroform $CDCl_3$ was used as solvent for all NMR spectra, unless specified elsewhere. NMR peaks are reported as singlet (s), doublet (d), triplet (t), quartet (q), broad (br), combinations thereof, or as a multiplet (m).

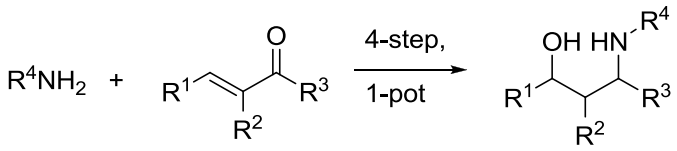
Mass spectra for liquid chromatography mass spectrometry (LCMS) were obtained using a Waters (UK) TQD mass spectrometer (low resolution ESI+, electrospray in positive ion mode, ES+), Waters (UK) Xevo QTOF mass spectrometer (low and high resolution ASAP+) and a Waters (UK) LCT premier XE (high resolution ESI+, electrospray in positive ion mode, ES+) unless stated elsewhere.

All *in situ* IR spectroscopy experiments (ReactIR) were carried out on the following instrument: ReactIR 4000 with MCT detector; ConcIRT window = 1900-900 cm^{-1}. Advance setting: Laser WN = 7901-415 cm^{-1}; Apodization = Happ General. Probe: Prob A DiComp (Diamond) connected *via* K6 Conduit (16 mm prob); Sampling 4000-6500 at 8 cm^{-1} resolution; Scan option: auto select, gain 2X.

2. General Procedures

These following procedures were employed in the preparation of the following species, unless specified elsewhere.

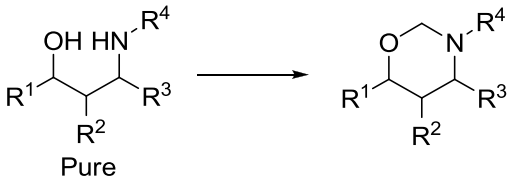
γ-Amino alcohol synthesis



THF (7 mL), 3Å molecular sieve pellets (2.5 g) were stirred under argon. Benzylamine (1.4 mmol) and α,β-unsaturated aldehyde/ketone (1.4 mmol) were added and stirred for 0-7 h. In a separate vessel, THF (4 mL), CuCl (0.07 mmol), PPh_3 (0.14 mmol) and NaO*t*-Bu (0.21 mmol) were stirred for 30 min. After 30 min, B_2pin_2 (1.54 mmol) was added and stirred in the CuCl solution for 10 min. Both solutions were combined and stirred for a further 30 min, after which methanol was added (2.80 mmol) and stirred for 18 h. $NaBH_4$ (4.20 mmol was added and the solution stirred. Methanol (3 mL) was added drop-wise over 10 min. After 3 h, all solvent was removed under reduced pressure. THF (10 mL), NaOH (0.60 mL, 20% w/v solution, 4 mmol), H_2O_2 (0.25 mL, 35% w/v solution, *ca.* 4 x 10^{-3} mol) was added to the resulting mass and refluxed for 1 h. The resulting solution was cooled and filtered through Celite, further EtOAc was passed through the Celite pad. The resulting solution was partitioned between EtOAc and brine. The aqueous layer was extracted further with EtOAc (3 x EtOAc). The organic phase was separated and dried over $MgSO_4$. After filtration the organic phase was removed under reduced pressure to yield a crude yellow oil. Purification was achieved by silica gel chromatography (hexane:EtOAc, 1:1 and 1% v/v Et_3N).

Oxazine synthesis

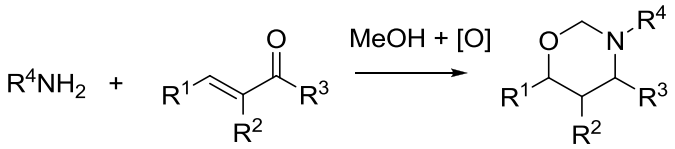
Route A – from the analogous γ-amino alcohol



γ-Amino alcohol (0.86 mmol) and formaldehyde solution (75 μL, 37% w/v solution, 1.00 mmol) was stirred in THF (6 mL) for 4.5 h. After 4.5 h, $MgSO_4$ was added, and the organic

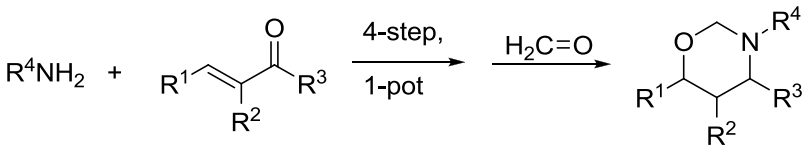
phase was filtered and removed under reduced pressure to leave a crude oil. Purification was achieved by silica gel chromatography (hexane:EtOAc, 2:1 as eluent).

Route B – MeOH present during oxidation step



THF (7 mL), 3Å molecular sieve pellets (2.5 g) were stirred under argon. Benzylamine (1.4 mmol) and α,β-unsaturated aldehyde/ketone (1.4 mmol) were added and stirred for 3 h. In a separate vessel, THF (4 mL), CuCl (60.07 mmol), PPh_3 (0.14 mmol) and NaO*t*-Bu (0.21 mmol) were stirred for 30 min. After 30 min, B_2pin_2 (1.54 mmol) was added and stirred in the CuCl solution for 10 min. Both solutions were combined and stirred for a further 30 min, after which methanol was added (2.80 mmol) and stirred for 18 h. $NaBH_4$ (4.20 mmol was added and the solution stirred. Methanol (15 mL) was added drop-wise over 10 min. After 3 h, NaOH (4.8 mL, 20% w/v solution, 4 mmol), H_2O_2 (2.0 mL, 35% w/v solution, *ca.* 4 x 10^{-3} mol) was added drop-wise to the resulting mass and refluxed for 4 h. The resulting solution was cooled and filtered through Celite, further EtOAc was passed through the Celite pad. The resulting solution was partitioned between EtOAc and brine. The aqueous layer was extracted further with EtOAc (3 x EtOAc). The organic phase was separated and dried over $MgSO_4$. After filtration the organic phase was removed under reduced pressure. Purification was achieved by silica gel chromatography (hexane:EtOAc, 5:1 as eluent).

Route C – MeOH removed before oxidation step



THF (7 mL), 3Å molecular sieve pellets (2.5 g) were stirred under argon. Benzylamine (1.4 mmol) and α,β-unsaturated aldehyde/ketone (1.4 mmol) were added and stirred for 3 h. In a separate vessel, THF (4 mL), CuCl (0.07 mmol), PPh_3 (0.14 mmol) and NaO*t*-Bu (0.21 mmol) were stirred for 30 min. After 30 min, B_2pin_2 (1.54 mmol) was added and stirred in the CuCl solution for 10 min. Both solutions were combined and stirred for a further 30 min, after which methanol was added (2.80 mmol) and stirred for 18 h. $NaBH_4$ (4.20 mmol was added and the solution stirred. Methanol (3 mL) was added drop-wise over 10 min. After 3 h,

all solvent was removed under reduced pressure. THF (10 mL), NaOH (0.60 mL, 20% w/v solution, 4 mmol), H_2O_2 (0.25 mL, 35% w/v solution, *ca.* 4 x 10^{-3} mol) was added to the resulting mass and refluxed for 1 h. The resulting solution was cooled and filtered through Celite, further EtOAc was passed through the Celite pad. The resulting solution was partitioned between EtOAc and brine. The aqueous layer was extracted further with EtOAc (3 x EtOAc). The organic phase was separated and dried over $MgSO_4$. After filtration the organic phase was removed under reduced pressure to yield the crude sample. Toluene (2 x 20 mL) was added to the crude sample and removed under pressure (this was repeated twice). After the toluene had been removed, THF (10 mL) and formaldehyde solution (0.12 mL, 37% w/v solution, 1.00 mmol) were sequentially added to the sample and the solution was stirred under argon overnight (15 h). $MgSO_4$ was added to the reaction, and the solution was filtered. The organics were removed under vacuum to yield a crude sample. Purification was achieved by silica gel chromatography (hexane:EtOAc, 5:1 as eluent).

ReactIR

All ReactIR experiments were carried out using ReactIR 4000 with MCT detector (see Fig. 12).

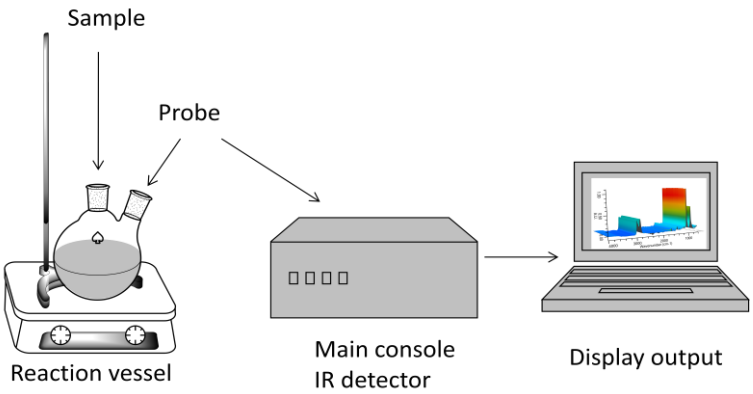
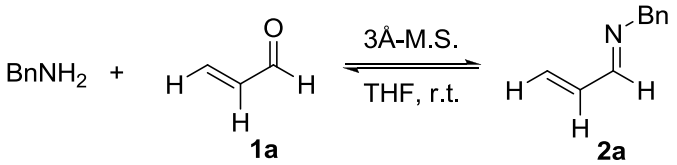


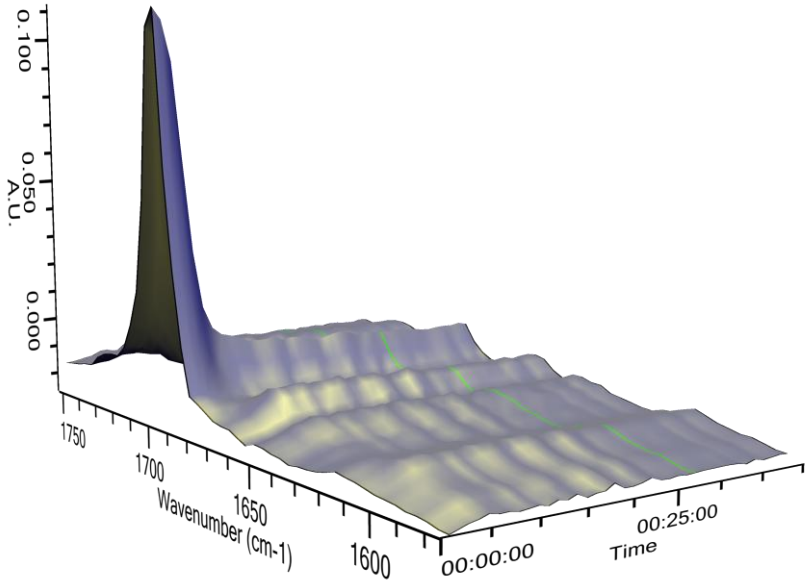
Figure 1. General reaction set-up.

The console (see Fig. 1) was cooled with liquid nitrogen (20 min), and the detector was fitted with a two-neck flask. At this point a background scan was taken. THF (7 mL) and 3Å molecular sieve pellets (2.5 g) were added to the flask, and stirred for 3 min. At this point a scan of the solvent was taken as reference. After this, the α,β-unsaturated carbonyl (2.8 mmol) species was added and the reaction was run for 3 min (128 scan min^{-1}) and the amine was subsequently added (2.8 mmol). Data processing: background correction using Pearson's correction. Solvent background removed (from reference scan).

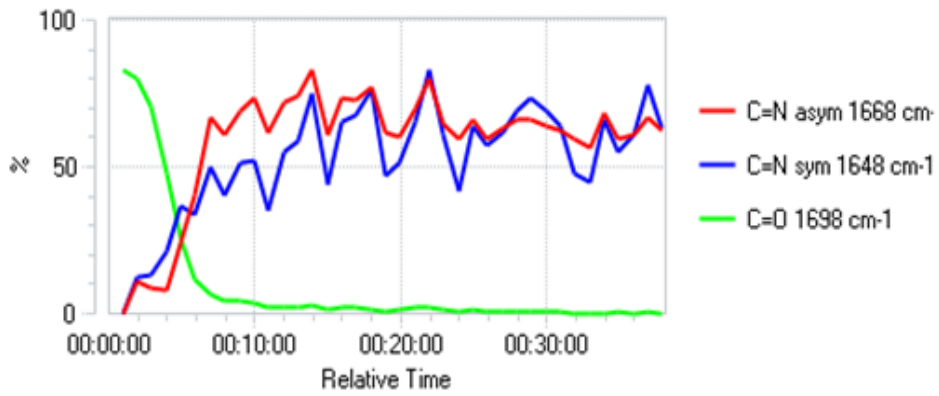
3. ReactIR

See general experimental section for experimental conditions. IR data for the compounds **1** are reported in the literature.[1]



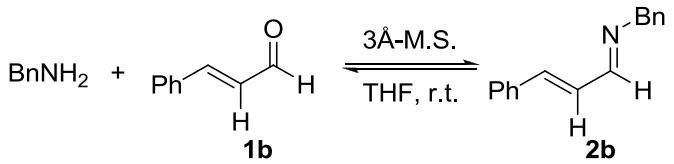


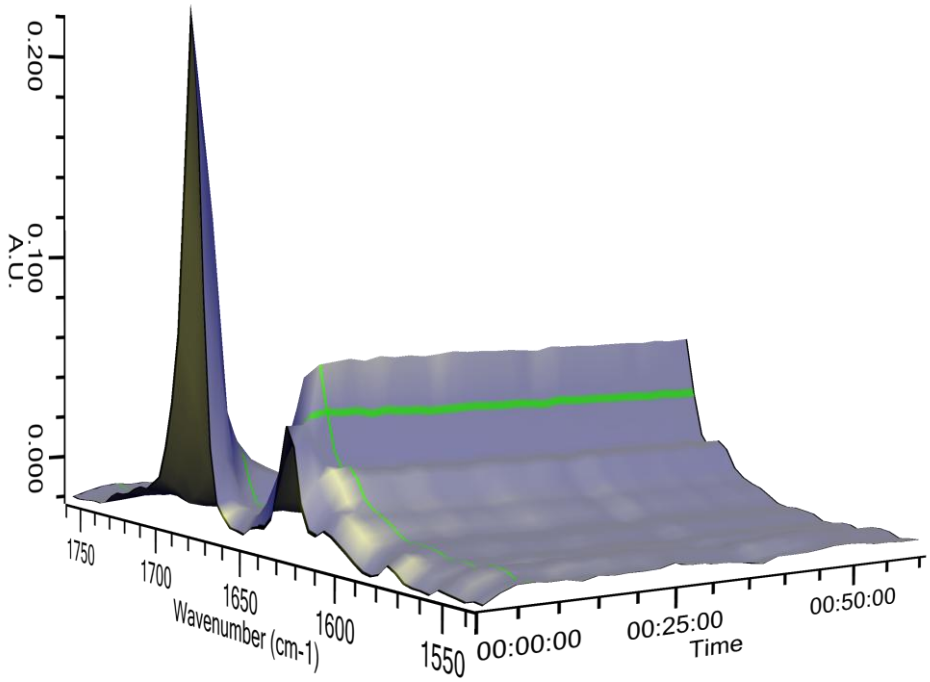
a



b

Figure 2. *In situ* IR spectroscopy showing the formation of α,β-unsaturated imine **2a** *via* 1,2-addition of benzylamine to acrolein **1a**, r.t., THF, 3Å-M.S. **a)** graphical output. **b)** absorption intensity (100%, C=O & C=N) *vs*. time.





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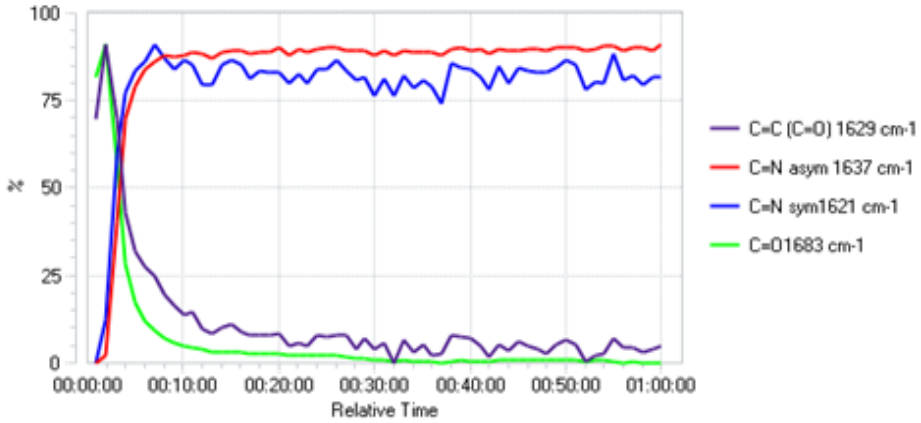
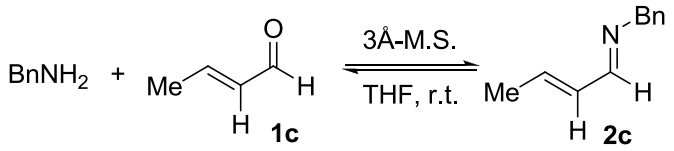
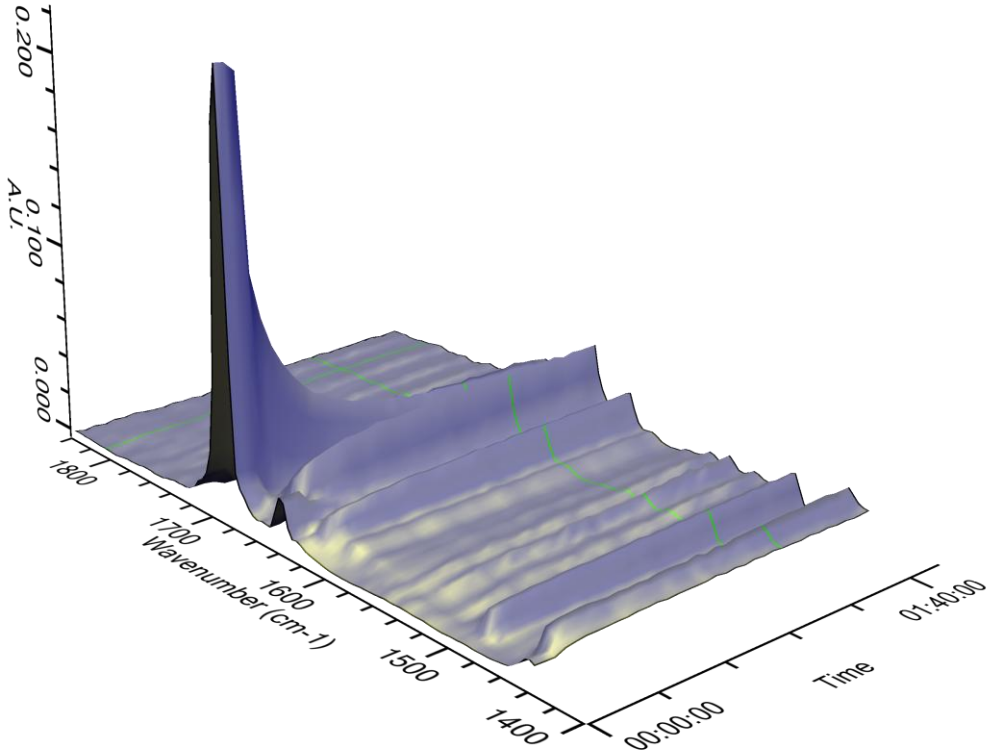


b

Figure 3. *In situ* IR spectroscopy showing the formation of α,β-unsaturated imine **2b** *via* 1,2-addition of benzylamine to cinnamaldehyde **1b**, r.t., THF, 3Å-M.S. **a)** graphical output. **b)** absorption intensity (100%, C=O & C=N) vs. time.





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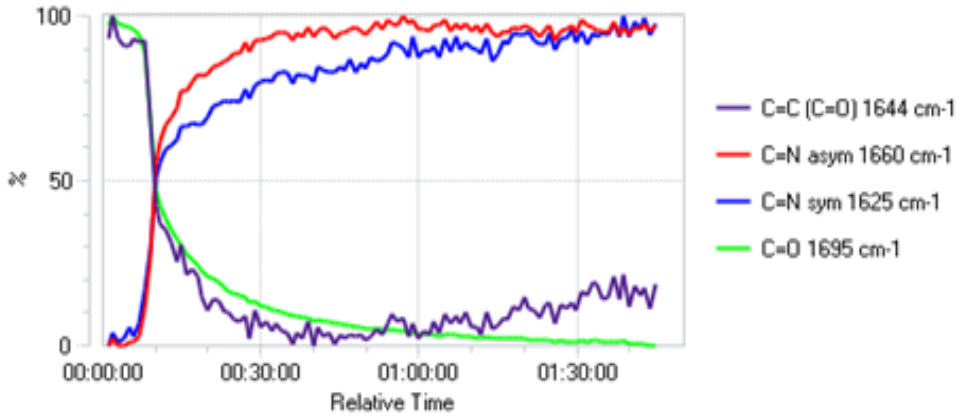
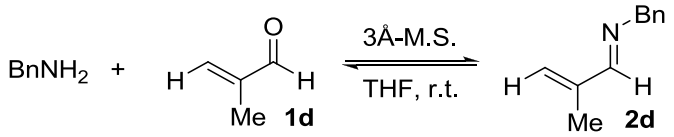
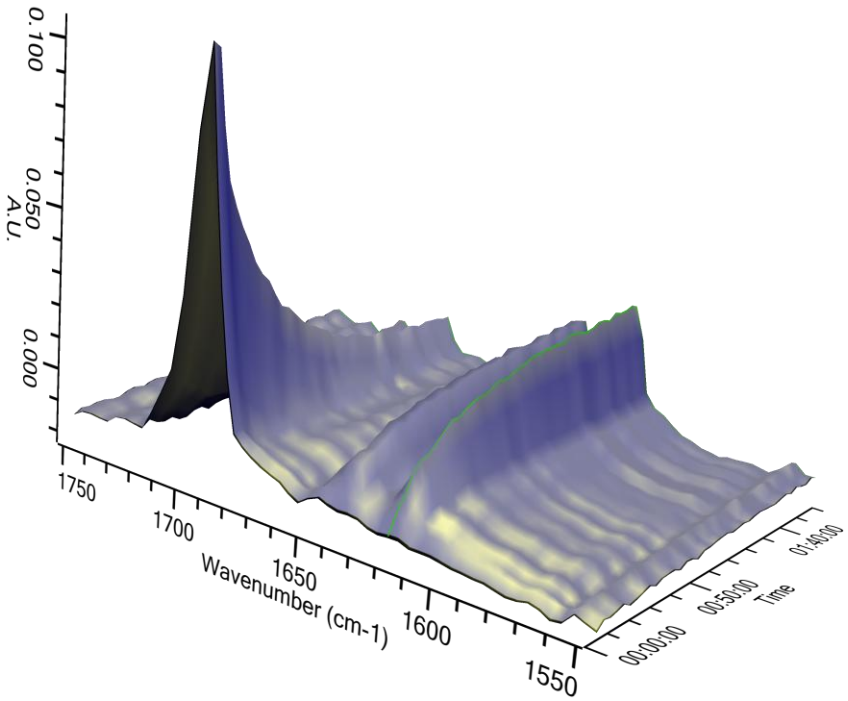


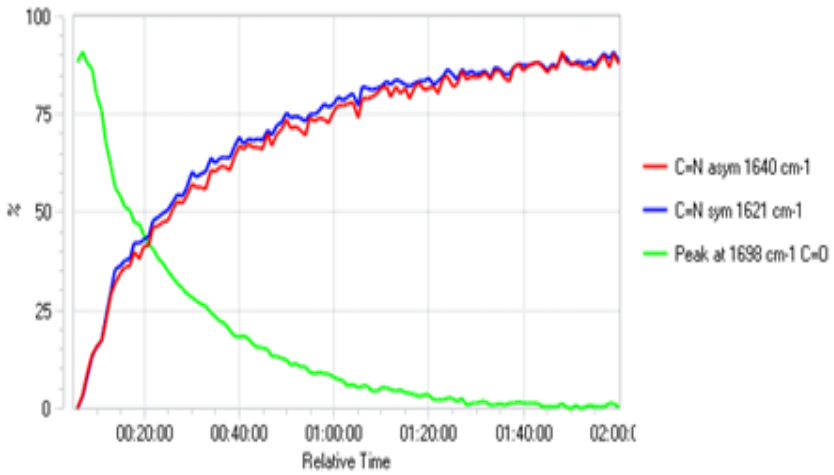
b

Figure 4. *In situ* IR spectroscopy showing the formation of α,β-unsaturated imine **2c** *via* 1,2-addition of benzylamine to crotonaldehyde **1c**, r.t., THF, 3Å-M.S. **a)** graphical output. **b)** absorption intensity (100%, C=O & C=N) vs. time.



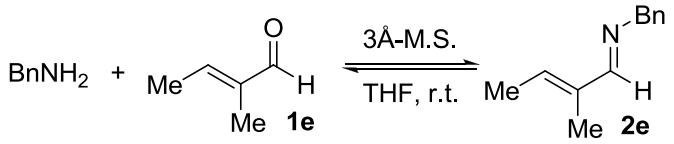


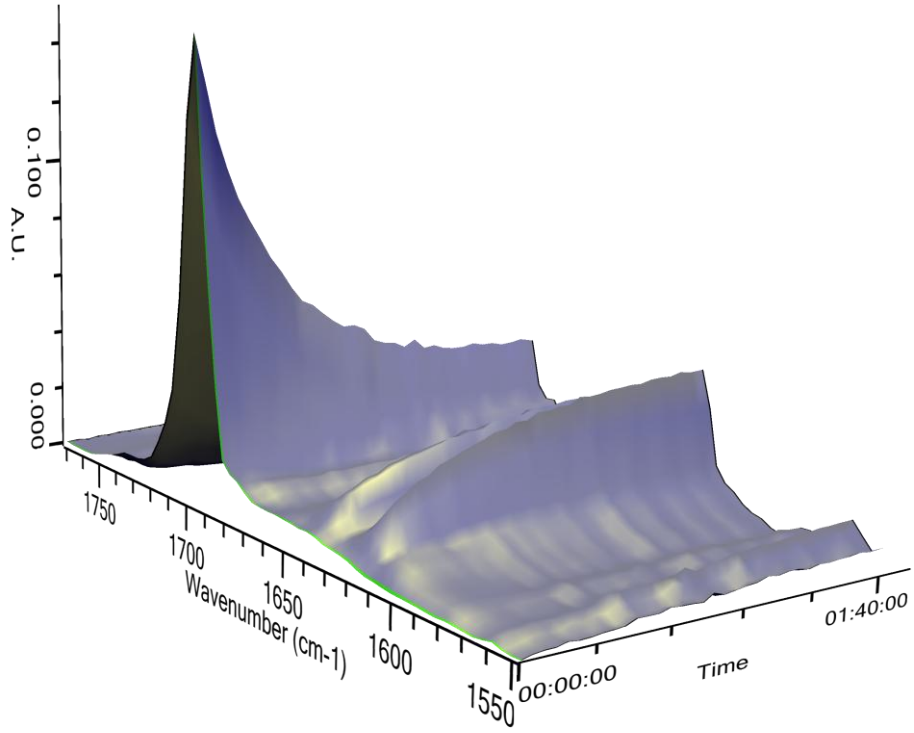
a



b

Figure 5. *In situ* IR spectroscopy showing the formation of α,β-unsaturated imine **2d** *via* 1,2-addition of benzylamine to methacrolein **1d**, r.t., THF, 3Å-M.S. **a)** graphical output. **b)** absorption intensity (100%, C=O & C=N) vs. time**.**





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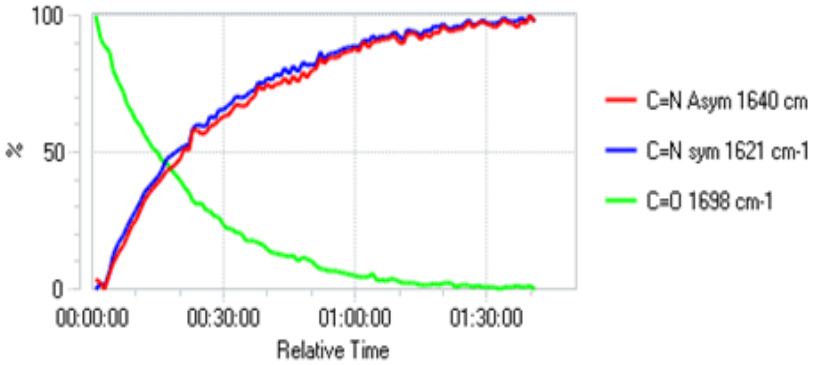
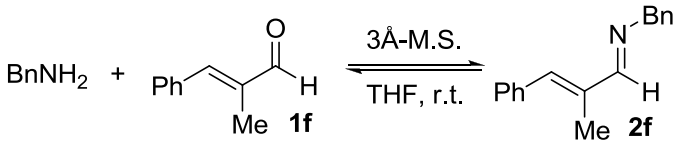
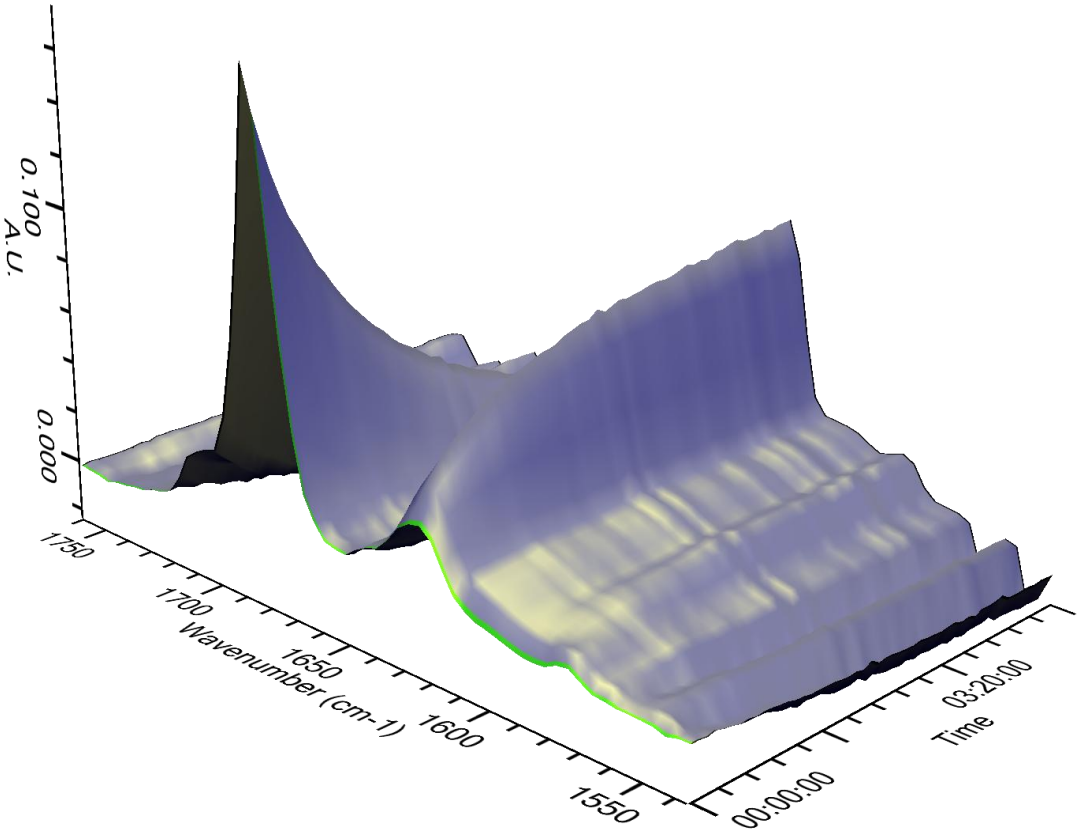


b

Figure 6. *In situ* IR spectroscopy showing the formation of α,β-unsaturated imine **2e** *via* 1,2-addition of benzylamine to tiglic aldehyde **1e**, r.t., THF, 3Å-M.S. **a)** graphical output. **b)** absorption intensity (100%, C=O & C=N) vs. time.





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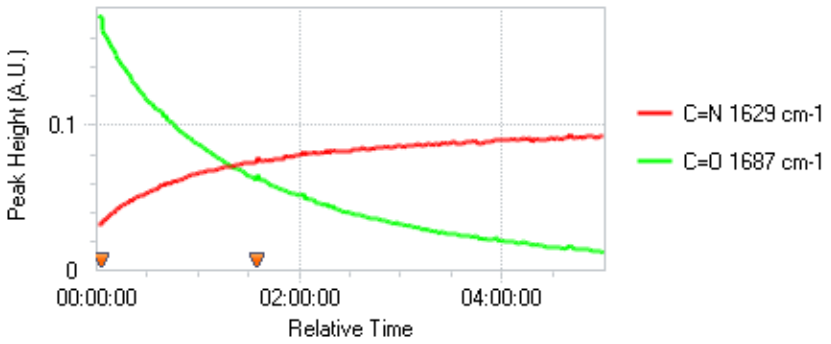
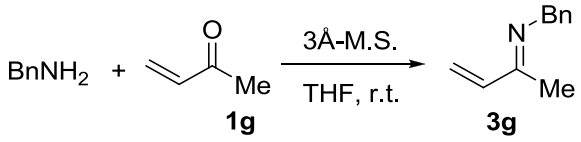
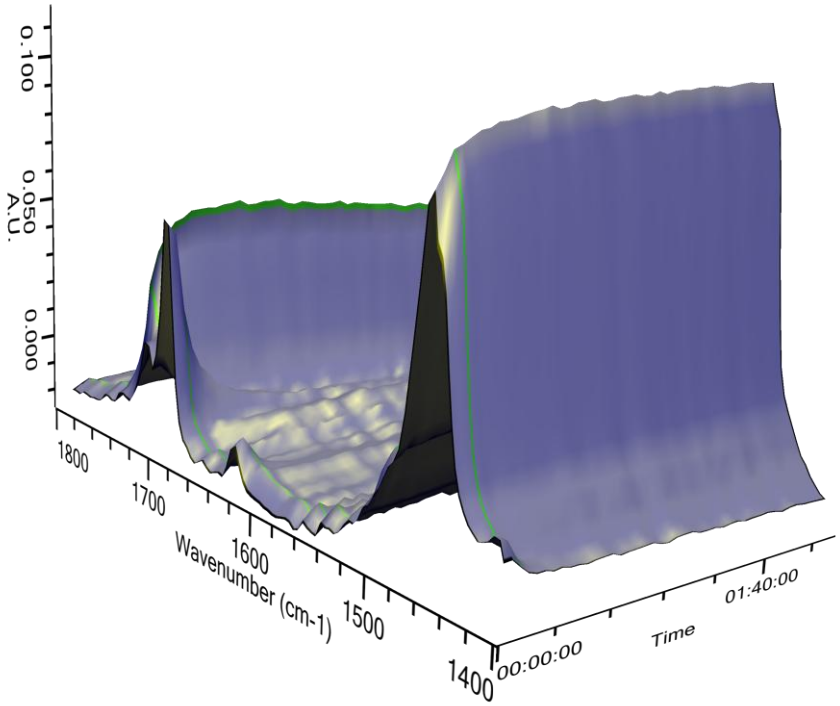


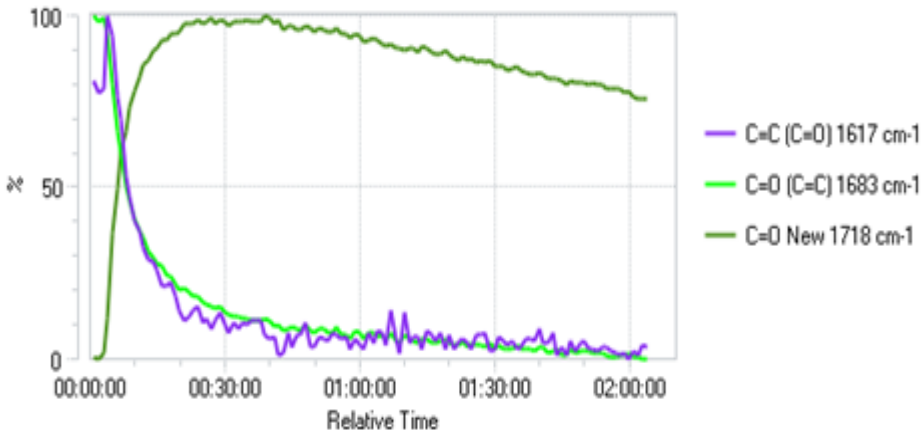
b

Figure 7. *In situ* IR spectroscopy showing the formation of α,β-unsaturated imine **2f** *via* 1,2-addition of benzylamine to alpha-methylcinnamaldehyde **1f**, r.t., THF, 3Å-M.S. **a)** graphical output. **b)** absorption intensity (100%, C=O & C=N) vs. time**.**





a

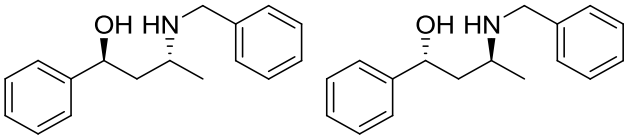


b

Figure 8. *In situ* IR spectroscopy showing the formation of showing 1,4 addition of benzylamine to **1g**, r.t., THF, 3Å-M.S. **a)** graphical output. **b)** absorption intensity (100%, C=O + C=O$_{new}$ & C=N) vs. time.

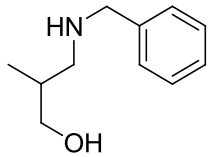
4. γ-Amino alcohols

3-(Benzylamine)-1-phenylbutan-1-ol (*rac*)-(*anti*)-**5h**



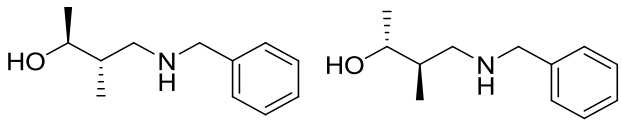
THF (10 mL), 3Å molecular sieve pellets (2.5 g) were stirred under argon. Benzylamine (0.15 mL, 1.4 mmol) and (3*E*)-4-phenylbut-3-en-2-one (0.20g, 1.4 mmol) were added and stirred for 6 h. In a separate vessel, THF (5 mL), CuCl (6.93 mg, 0.07 mmol), P*n*Bu$_3$ (34.5 μL, 0.14 mmol) and NaO*t*-Bu (24.0 mg, 0.25 mmol) were stirred for 30 min. After 30 min, B$_2$pin$_2$ (0.39g, 1.54 mmol) was added and stirred in the CuCl solution for 10 min. Both solutions were combined and stirred for a further 30 min, after which methanol was added (0.16 mL, 2.80 mmol) and stirred for 18 h. NaBH$_4$ (0.16 g, 4.20 mmol was added and the solution stirred. Methanol (3 mL) was added drop-wise over 10 min. After 3 h, all solvent was removed under reduced pressure. THF (10 mL), NaOH (0.60 mL, 20% w/v solution, 4 mmol), H$_2$O$_2$ (0.25 mL, 35% w/v solution, *ca.* 4 x 10^{-3} mol) was added to the resulting mass and refluxed for 1 h. The resulting solution was cooled and filtered through Celite, further EtOAc was passed through the Celite pad. The resulting solution was partitioned between EtOAc and brine. The aqueous layer was extracted further with EtOAc (3 x EtOAc). The organic phase was separated and dried over MgSO$_4$. After filtration the organic phase was removed under reduced pressure to yield a crude dark yellow oil. Purification by silica gel chromatography (hexane : EtOAc, 1% v/v Et$_3$N in eluent and silica, 4:1 eluent) gave the product as a cloudy colourless oil (0.32 g, 90%). IR (neat): 3336, 3027, 2971, 2925, 1494, 1448, 1367, 1300, 1142, 1059, 966, 942, 825, 747, 692 cm^{-1}. ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.33- 7.13 (m, 10H), 4.84 (dd, *J* = 10.6, 2.0 Hz, 1H), 3.92 (d, *J* = 12.5 Hz, 1H), 3.71 (d, *J* = 12.5, 1H), 3.09 - 2.95 (m, 1H), 1.68 (dt, *J* = 14.4, 2.3 Hz, 1H) 1.52 (dt, *J* = 14.4, 10.8 Hz, 1H) 1.14 (d, *J* = 6.3, 3H). ^{13}C NMR (101 MHz, CDCl$_3$): δ 145.3, 139.3, 128.6, 128.4, 128.2, 1271.3, 127.0, 125.6, 75.4, 54.3, 50.9, 46.1, 21.1. LRMS (ASAP+) 256.2 (28%) [M+H$^+$], 134.1.0 (100%). HRMS (TOF ASAP+) calculated [C$_{17}$H$_{21}$NO+H$^+$] 256.1701, found 256.1684.

3-(Benzylamine)-2-methylpropan-1-ol (*rac*)-***5d***



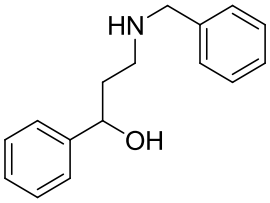
THF (7 mL), 3Å molecular sieve pellets (2.5 g) were stirred under argon. Benzylamine (0.15 mL, 1.4 mmol) and methacrolein (0.12 mL, 1.4 mmol) were added and stirred for 3 h. In a separate vessel, THF (4 mL), CuCl (6.93 mg, 0.07 mmol), PPh_3 (36.72 mg, 0.14 mmol) and NaO*t*-Bu (20.2 mg, 0.21 mmol) were stirred for 30 min. After 30 min, B_2pin_2 (0.39g, 1.54 mmol) was added and stirred in the CuCl solution for 10 min. Both solutions were combined and stirred for a further 30 min, after which methanol was added (0.11 mL, 2.80 mmol) and stirred for 18 h. $NaBH_4$ (0.16 g, 4.20 mmol was added and the solution stirred. Methanol (3 mL) was added drop-wise over 10 min. After 3 h, all solvent was removed under reduced pressure. THF (10 mL), NaOH (0.60 mL, 20% w/v solution, 4 mmol), H_2O_2 (0.25 mL, 35% w/v solution, *ca.* 4 x 10^{-3} mol) was added to the resulting mass and refluxed for 1 h. The resulting solution was cooled and filtered through Celite, further EtOAc was passed through the Celite pad. The resulting solution was partitioned between EtOAc and brine. The aqueous layer was extracted further with EtOAc (3 x EtOAc). The organic phase was separated and dried over $MgSO_4$. After filtration the organic phase was removed under reduced pressure to yield a crude yellow oil. Purification by silica gel chromatography (EtOAc, 1% v/v Et_3N in eluent and silica) gave the product as a cloudy colourless oil (0.19 g, 64% - **≥90% purity**). IR (neat): 3302, 2871, 2163, 1495, 1453, 1384, 1104, 1028, 953, 734, 697 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.35 - 7.15 (m, 5H), 3.80 (bs, 1H), 3.75 (d, *J* = 13.1 Hz, 1H), 3.65 (d, *J* = 13.2 Hz, 1H), 6.63 (ddd, *J* = 11.8, 3.3, 2.1 Hz, 1H), 3.48 (dd, 11.8, 10.2 Hz, 1H), 3.00 - 2.60 (bs, 1H), 2.83 (ddd, *J* = 11.8, 3.3, 2.1 Hz, 1H,), 2.50 (dd, 11.8, 10.2 Hz, 1H), 1.95 – 1.83 (m, 1H), 0.73 (d, *J* = 6.9 Hz). ^{13}C NMR (101 MHz, $CDCl_3$): δ 138.3, 127.6, 127.5, 127.2, 69.9, 55.9, 53.1, 33.3, 14.0 LRMS (ASAP+) 180.1 (54%) [$M+H^+$], 162.1 (40%), 120.1 (9%). HRMS (TOF ASAP+) calculated [$C_{11}H_{18}NO+H^+$] 180.1388, found 180.1358.

4-(Benzylamine)-3-methylbutan-2-ol (rac)-(anti)-**5e**



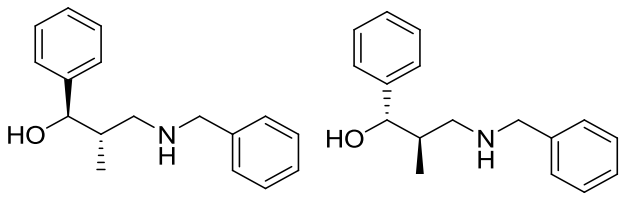
THF (7 mL), 3Å molecular sieve pellets (2.5 g) were stirred under argon. Benzyl amine (0.15 mL, 1.4 mmol) and tiglic aldehyde, (0.14 mL, 1.4 mmol) were added and stirred for 3 h. In a separate vessel, THF (4 mL), CuCl (6.93 mg, 0.07 mmol), P*n*Bu_3 (34.5 µL, 0.14 mmol) and NaO*t*-Bu (20.2 mg, 0.21 mmol) were stirred for 30 min. After 30 min, B_2pin_2 (0.39g, 1.54 mmol) was added and stirred in the CuCl solution for 10 min. Both solutions were combined and stirred for a further 30 min, after which methanol was added (0.11 mL, 2.80 mmol) and stirred for 18 h. $NaBH_4$ (0.16 g, 4.20 mmol was added and the solution stirred. Methanol (3 mL) was added drop-wise over 10 min. After 3 h, all solvent was removed under reduced pressure. THF (10 mL), NaOH (0.60 mL, 20% w/v solution, 4 mmol), H_2O_2 (0.25 mL, 35% w/v solution, *ca.* 4 x 10^{-3} mol) was added to the resulting mass and refluxed for 1 h. The resulting solution was cooled and filtered through Celite, further EtOAc was passed through the Celite pad. The resulting solution was partitioned between EtOAc and brine. The aqueous layer was extracted further with EtOAc (3 x EtOAc). The organic phase was separated and dried over $MgSO_4$. After filtration the organic phase was removed under reduced pressure to yield a crude yellow oil. Purification by silica gel chromatography (hexane : EtOAc, 1% v/v Et_3N in eluent and silica, 1:1 eluent) gave the product as a colourless clear oil (0.32 g, 70%). IR (neat): 3444, 2966, 2971, 1452, 1377, 1111, 733 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.34- 7.07 (m, 5H), 3.88 (dq, *J* = 10.0, 2.8 Hz, 1H), 3.72 (ABq, *J* = 13.0, 12.7 Hz, 2H), 2.79 – 2.64 (m, 2H), 1.87 – 1.77 (m, 1H), 1.03 (d, *J* = 6.5Hz, 3H) 0.80 (d, *J* = 7.16 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 139.4, 129.0, 128.5, 127.2, 72.0, 54.3, 53.4, 37.5, 18.8, 12.7 LRMS (ESI+) 194.3 (80%) [$M+H^+$], 194.8 (100%). HRMS (ESI+) calculated [$C_{12}H_{19}NO+H^+$] 194.1545 found, 194.1534.

<u>3-(Benzylamine)-1-propan-1-ol</u> (rac)-**5b**



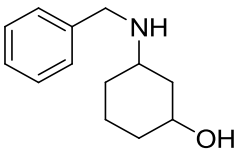
THF (7 mL), 3Å molecular sieve pellets (2.5 g) were stirred under argon. Benzylamine (0.15 mL, 1.4 mmol) and *trans* cinnamaldehyde (0.18 mL, 1.4 mmol) were added and stirred for 3 h. In a separate vessel, THF (4 mL), CuCl (6.93 mg, 0.07 mmol), PPh_3 (36.72 mg, 0.14 mmol) and NaO*t*-Bu (20.2 mg, 0.21 mmol) were stirred for 30 min. After 30 min, B_2pin_2 (0.39 g, 1.54 mmol) was added and stirred in the CuCl solution for 10 min. Both solutions were combined and stirred for a further 30 min, after which methanol was added (0.11 mL, 2.80 mmol) and stirred for 18 h. $NaBH_4$ (0.16 g, 4.20 mmol was added and the solution stirred. Methanol (3 mL) was added drop-wise over 10 min. After 3 h, all solvent was removed under reduced pressure. THF (10 mL), NaOH (0.60 mL, 20% w/v solution, 4 mmol), H_2O_2 (0.25 mL, 35% w/v solution, *ca.* 4 x 10^{-3} mol) was added to the resulting mass and refluxed for 1 h. The resulting solution was cooled and filtered through Celite, further EtOAc was passed through the Celite pad. The resulting solution was partitioned between EtOAc and brine. The aqueous layer was extracted further with EtOAc (3 x EtOAc). The organic phase was separated and dried over $MgSO_4$. After filtration the organic phase was removed under reduced pressure to yield a crude yellow oil. Purification by silica gel chromatography (hexane : EtOAc, 1% v/v Et_3N in eluent and silica, 2:1 eluent) gave the product as a cloudy colourless oil (0.20 g, 58%). IR (neat): 3250, 3026, 2836, 1603, 1493, 1451, 1438, 1180, 733, 696 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.41- 7.09 (m, 10H), 4.88 (dd, *J* = 8.6, 3.0 Hz, 1H), 3.74 (ABq, *J* = 13.0, 5.2 Hz, 2H), 2.94 - 2.80 (m, 2H), 1.88 – 1.67 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 145.0, 139.2, 132.2, 132.1, 131.9, 128.6, 128.4, 128.3, 75.6, 53.9, 47.8, 37.4. LRMS (ESI+) 242.6 (100%) [$M+H^+$], 120.4 (65%). HRMS (ESI+) calculated [$C_{16}H_{19}NO+H^+$] 242.1545, found 242.1550.

<u>3-(benzylamino)-2-methyl-1-phenylpropan-1-ol</u> (*rac*)-(*anti*)-**5f**



THF (6 mL), 3Å molecular sieve pellets (2.5 g) were stirred under argon. Benzylamine (101 μL, 1.0 mmol) and α-methylcinnamaldehyde (140 μL, 1.0 mmol) were added and stirred for 7 h. In a separate vessel, THF (3 mL), CuCl (4.95 mg, 0.05 mmol), P*n*Bu$_3$ (24.7 μL, 0.10 mmol) and NaO*t*-Bu (14.4 mg, 0.15 mmol) were stirred for 30 min. After 30 min, B$_2$pin$_2$ (0.28 g, 1.1 mmol) was added and stirred in the CuCl solution for 10 min. Both solutions were combined and stirred for a further 30 min, after which methanol was added (81.0 μL, 2.0 mmol) and stirred for 18 h. NaBH$_4$ (0.11 g, 3.0 mmol was added and the solution stirred. Methanol (2 mL) was added drop-wise over 10 min. After 3 h, all solvent was removed under reduced pressure. THF (10 mL), NaOH (0.43 mL, 20% w/v solution, 2.86 mmol), H$_2$O$_2$ (0.18 mL, 35% w/v solution, *ca.* 2.86 mmol) was added to the resulting mass and refluxed for 1 h. The resulting solution was cooled and filtered through Celite, further EtOAc was passed through the Celite pad. The resulting solution was partitioned between EtOAc and brine. The aqueous layer was extracted further with EtOAc (3 x EtOAc). The organic phase was separated and dried over MgSO$_4$. After filtration the organic phase was removed under reduced pressure to yield a yellow oil. Purification by silica gel chromatography (hexane : EtOAc, 1% v/v Et$_3$N in eluent and silica, 2:1 eluent) gave the product as a white solid (50 mg, 20%). IR (neat): 3320, 3062, 2912, 2841, 1602, 1493, 1453, 1040 cm^{-1}. ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.32-7.06 (m, 10H), 4.85 (d, *J* = 3.2 Hz, 1H), 3.74 (ABq, *J* = 13.0, 10.9 Hz, 2H), 2.76-2.64 (m, 2H), 2.12-2.04 (m, 1H), 0.67 (d, *J* = 7.2 Hz, 3H). ^{13}C NMR (101 MHz, CDCl$_3$): δ 141.7, 138.2, 127.8, 127.4, 127.0, 126.9, 126.4, 126.1, 79.7, 53.33, 52.33, 37.5, 11.68. LRMS (ESI+) 256.3 (100%) [M+H$^+$], 161.4 (27%). HRMS (ESI+) calculated [C$_{17}$H$_{21}$NO+H$^+$] 256.1701, found 256.1704.

<u>3-(Benzylamino)cyclohexan-1-ol</u> **5i** (*syn*/*anti* mixture)

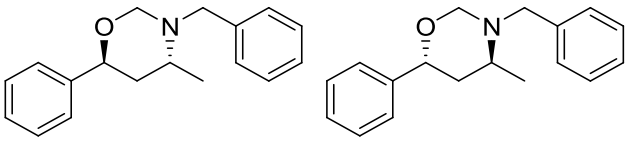


THF (12 mL), 3Å molecular sieve pellets (3.6 g), CuCl (9.9 mg, 0.1 mmol), P*n*Bu$_3$ (49.3 μL, 0.2 mmol) and NaO*t*-Bu (28.8 mg, 0.3 mmol) were stirred for 30 min under argon. After 30

min, B_2pin_2 (0.56 g, 1.1 mmol) was added and stirred for 10 min. Benzylamine (0.22 mL, 2.0 mmol) and cyclohexenone (0.19, 2.0 mmol) was added and stirred for 30 min, after which, methanol was added (0.16 mL, 4.0 mmol) and the resulting solution was stirred for 18 h. $NaBH_4$ (0.23 g, 6.0 mmol was added and the solution stirred. Methanol (4 mL) was added drop-wise over 10 min. After 3 h, all solvent was removed under reduced pressure. THF (15 mL), NaOH (0.86 mL, 20% w/v solution, 5.72 mmol), H_2O_2 (0.36 mL, 35% w/v solution, *ca.* 5.72 mmol) was added to the resulting mass and refluxed for 1 h. The resulting solution was cooled and filtered through Celite, further EtOAc was passed through the Celite pad. The resulting solution was partitioned between EtOAc and brine. The aqueous layer was extracted further with EtOAc (3 x EtOAc). The organic phase was separated and dried over $MgSO_4$. After filtration the organic phase was removed under reduced pressure to yield a dark yellow oil. Toluene (2 x 20 mL) was added to the crude oil and removed under pressure (this was repeated twice). After the toluene had been removed, purification by silica gel chromatography (EtOAc : MeOH, 1% v/v Et_3N in eluent and silica, 9:1 eluent) gave the product as a yellow oil (0.21 g, 51% - mixture diastereoisomers 7:3).[2] IR (neat): 3274, 2929, 2854, 1495, 1451, 1125, 1059 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.74-7.09 (m, 5H), 4.12-4.01 (m, 0.3H), 3.83-3.69 (m, 0.7H), 3.81-3.69 (ABq, *J* = 32.2, 12.8 Hz, 1.4H), 3.76-3.69 (ABq, *J* = 12.8, 4.2 Hz, 0.6H), 2.96-2.87 (m, 0.3H), 2.86-2.77 (m, 0.7H), 1.91-1.79 (m, 1H), 1.82-1.67 (m, 2H), 1.69-1.46 (m, 4H), 1.47-1.33 (m, 2H), 1.34-1.16 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 140.7, 140.0, 128.6, 128.2, 127.9, 127.1, 126.9, 126.8, 68.4, 66.8, 53.6, 51.6, 51.2, 39.9, 34.3, 33.7, 32.0, 31.6, 19.1 LRMS (ESI+) 206.2 (47%) $[M+H^+]$, 108.5 (15%). HRMS (ESI+) calculated $[C_{13}H_{19}NO+H^+]$ 206.1545, found 206.1533.

5. Oxazines

3-Benzyl-4-methyl-6-phenyl-1, 3-oxazinane (*rac*)-(*anti*)-**6h**



Route A

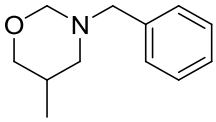
3-(Benzylamine)-1-phenylbutan-1-ol **5h** (0.22 g, 0.86 mmol) and formaldehyde solution (75 µL, 37% w/v solution, 1.00 mmol) was stirred in THF (6 mL) for 4.5 h. After 4.5 h, $MgSO_4$ was added, and the organic phase was filtered and removed under reduced pressure to leave a crude oil. Purification by silica gel chromatography (hexane : EtOAc, 2:1 eluent) gave a colourless clear oil (0.17 g, 74%).

Route B

THF (7 mL), 3Å molecular sieve pellets (2.5 g) were stirred under argon. Benzylamine (0.15 mL, 1.4 mmol) and (3E)-4-phenylbut-3-en-2-one (0.20g, 1.4 mmol) were added and stirred for 3 h. In a separate vessel, THF (4 mL), CuCl (6.93 mg, 0.07 mmol), PPh_3 (36.72 mg, 0.14 mmol) and NaO*t*-Bu (20.2 mg, 0.21 mmol) were stirred for 30 min. After 30 min, B_2pin_2 (0.39g, 1.54 mmol) was added and stirred in the CuCl solution for 10 min. Both solutions were combined and stirred for a further 30 min, after which methanol was added (0.11 mL, 2.80 mmol) and stirred for 18 h. $NaBH_4$ (0.16 g, 4.20 mmol was added and the solution stirred. Methanol (15 mL) was added drop-wise over 10 min. After 3 h, NaOH (4.8 mL, 20% w/v solution, 4 mmol), H_2O_2 (2.0 mL, 35% w/v solution, *ca.* 4 x 10^{-3} mol) was added drop-wise to the resulting mass and refluxed for 4 h. The resulting solution was cooled and filtered through Celite, further EtOAc was passed through the Celite pad. The resulting solution was partitioned between EtOAc and brine. The aqueous layer was extracted further with EtOAc (3 x EtOAc). The organic phase was separated and dried over $MgSO_4$. After filtration the organic phase was removed under reduced pressure to yield a crude yellow oil. Purification by silica gel chromatography (hexane : EtOAc, 3:1 eluent) gave the product as a colourless clear oil (0.18 g, 51%). IR (neat): 3027, 2996, 2859, 1602, 1494, 1452, 1363, 1207 (C-O), 988, 696 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.40 - 7.10 (m, 10H), 4.48 (d, *J* = 10.0 Hz, 1H), 4.48 (dd, *J* = 11.3, 2.8 Hz, 1H), 4.23 (d, *J* = 10 Hz, 1H), 3.93 (d, *J* = 13.6, 1H), 3.61 (d,

J = 13.6 Hz, 1H), 3.21 (m, 1H), 1.72 (dt, *J* = 13.4, 11.5 Hz, 1H), 1.57 (dt, *J* = 13.4, 2.8 Hz, 1H), 1.18 (d, *J* = 6.6 Hz, 3H) ^{13}C NMR (101 MHz, $CDCl_3$): δ 141.5, 138.3, 128.0, 127.6, 127.4, 127.3, 126.5, 125.9, 124.8, 82.7, 78.5, 54.3, 47.5, 36.4, 19.3 LRMS (ASAP+) 268.2 (14%) [M+H$^+$], 148.1 (100%), 134.1 (38%). HRMS (TOF ASAP+) calculated [$C_{18}H_{21}NO$+H$^+$] 268.1701, found 268.1708.

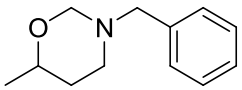
3-Benzyl-5-methyl-1,3-oxazinane (*rac*)-**6d**



THF (7 mL), 3Å molecular sieve pellets (2.5 g) were stirred under argon. Benzyl amine (0.15 mL, 1.4 mmol) and methacrolein (0.12 mL, 1.4 mmol) were added and stirred for 3 h. In a separate vessel, THF (4 mL), CuCl (6.93 mg, 0.07 mmol), PPh_3 (36.72 mg, 0.14 mmol) and NaO*t*-Bu (20.2 mg, 0.21 mmol) were stirred for 30 min. After 30 min, B_2pin_2 (0.39g, 1.54 mmol) was added and stirred in the CuCl solution for 10 min. Both solutions were combined and stirred for a further 30 min, after which methanol was added (0.11 mL, 2.80 mmol) and stirred for 18 h. $NaBH_4$ (0.16 g, 4.20 mmol was added and the solution stirred. Methanol (3 mL) was added drop-wise over 10 min. After 3 h, all solvent was removed under reduced pressure. THF (10 mL), NaOH (0.60 mL, 20% w/v solution, 4 mmol), H_2O_2 (0.25 mL, 35% w/v solution, *ca.* 4 x 10^{-3} mol) was added to the resulting mass and refluxed for 1 h. The resulting solution was cooled and filtered through Celite, further EtOAc was passed through the Celite pad. The resulting solution was partitioned between EtOAc and brine. The aqueous layer was extracted further with EtOAc (3 x EtOAc). The organic phase was separated and dried over $MgSO_4$. After filtration the organic phase was removed under reduced pressure to yield a yellow oil. Toluene (2 x 20 mL) was added to the crude oil and removed under pressure (this was repeated twice). After the toluene had been removed, THF (10 mL) and formaldehyde solution (0.12 mL, 37% w/v solution, 1.54 mmol) were sequentially added to the sample and the solution was stirred under argon overnight (15 h). $MgSO_4$ was added to the reaction, and the solution was filtered. The organics were removed under vacuum to yield a yellow oil. Purification by silica gel chromatography (hexane : EtOAc, 5:1 eluent) gave the product as a colourless oil (0.20g, 75%). IR (neat): 2953, 2850, 1453, 1017, 883, 698 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.34-7.13 (m, 5H), 4.35 (d, *J* = 9.6 Hz, 1H), 4.03 (d, *J* = 9.6 Hz, 1H), 3.92 (ddd, *J* = 10.9, 4.3, 1.7 Hz, 1H) 3.75 (ABq, *J* = 13.4, 5.7 Hz, 2H), 3.09 (t, *J* = 10.8 Hz, 1H) 2.89-2.80 (m, 1H), 2.29 (dd, *J* = 12.8, 11.2 Hz, 1H), 2.18-2.04 (m, 1H), 0.63 (d,

J = 6.6 Hz) ^{13}C NMR (101 MHz, $CDCl_3$): δ 138.6, 128.9, 128.3, 127.1, 84.2, 74.3, 57.2, 56.2, 25.9, 14.7 LRMS (ESI+) 192.5 (100%) [M+H$^+$], 180.5 (16%). HRMS (ESI+) calculated [$C_{12}H_{17}NO$+H$^+$] 192.1388, found 192.1368.

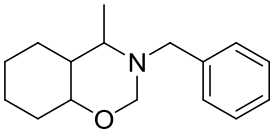
3-Benzyl-6-methyl-1,3-oxazinane (*rac*)-**6c**



THF (6 mL), 3Å molecular sieve pellets (1.8g) were stirred under argon. Benzylamine (0.11 mL, 1.0 mmol) and crotonaldehyde (83 μL, 1.0 mmol) were added and stirred for 3 h. In a separate vessel, THF (3 mL), CuCl (4.95 mg, 0.05 mmol), P*n*Bu_3 (24.7 μL, 0.10 mmol) and NaO*t*-Bu (14.4 mg, 0.15 mmol) were stirred for 30 min. After 30 min, B_2pin_2 (0.28 g, 1.1 mmol) was added and stirred in the CuCl solution for 10 min. Both solutions were combined and stirred for a further 30 min, after which methanol was added (81.0 μL, 2.0 mmol) and stirred for 18 h. $NaBH_4$ (0.11 g, 3.0 mmol was added and the solution stirred. Methanol (2 mL) was added drop-wise over 10 min. After 3 h, all solvent was removed under reduced pressure. THF (10 mL), NaOH (0.43 mL, 20% w/v solution, 2.86 mmol), H_2O_2 (0.18 mL, 35% w/v solution, *ca.* 2.86 mmol) was added to the resulting mass and refluxed for 1 h. The resulting solution was cooled and filtered through Celite, further EtOAc was passed through the Celite pad. The resulting solution was partitioned between EtOAc and brine. The aqueous layer was extracted further with EtOAc (3 x EtOAc). The organic phase was separated and dried over $MgSO_4$. After filtration the organic phase was removed under reduced pressure to yield a yellow oil. Toluene (2 x 20 mL) was added to the crude oil and removed under pressure (this was repeated twice). After the toluene had been removed, THF (8 mL) and formaldehyde solution (84 μL, 37% w/v solution, 1.1 mmol) were sequentially added to the sample and the solution was stirred under argon overnight (15 h). $MgSO_4$ was added to the reaction, and the solution was filtered. The organics were removed under vacuum to yield a yellow oil. Purification by silica gel chromatography (hexane : EtOAc, 5:1 eluent) gave the product as a colourless oil (0.10 g, 50%). IR (neat): 2967, 2931, 2853, 1495, 1453, 1082, 993, 735, 698 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35-7.10 (m, 5H), 4.40 (dd, *J* = 9.7, 2.1 Hz, 1H) 4.15 (d, *J* = 9.6 Hz, 1H) 3.71 (s, 2H), 3.58-3.47 (m, 1H), 2.93-2.85 (m, 1H), 2.70 (dd, *J* = 12.8, 3.2 Hz, 1H), 1.73-1.62 (m, 1H), 1.29-1.22 (m, 1H), 1.16 (d, *J* = 6.2 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 138.6, 129.0, 128.3, 127.1, 84.5, 73.6, 55.8, 49.5, 29.5, 21.9 LRMS

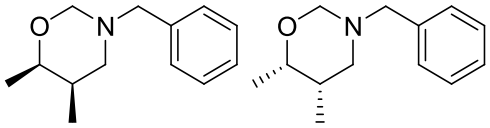
(ESI+) 192.5 (100%) [M+H$^+$], 134.4 (13%). HRMS (ESI+) calculated [$C_{12}H_{17}NO+H^+$] 192.1388, found 192.1400.

3-Benzyl-4-methyl-octahydro-2H-1,3-benzoxazine **6j**



THF (12 mL), 3Å molecular sieve pellets (3.6 g), CuCl (9.9 mg, 0.1 mmol), P*n*Bu$_3$ (49.3 µL, 0.2 mmol) and NaO*t*-Bu (28.8 mg, 0.3 mmol) were stirred for 30 min under argon. After 30 min, B_2pin_2 (0.56 g, 1.1 mmol) was added and stirred for 10 min. Benzylamine (0.22 mL, 2.0 mmol) and 1-Acetyl-1-cyclohexene (0.26, 2.0 mmol) was added and stirred for 30 min, after which, methanol was added (0.16 mL, 4.0 mmol) and the resulting solution was stirred for 18 h. $NaBH_4$ (0.23 g, 6.0 mmol was added and the solution stirred. Methanol (4 mL) was added drop-wise over 10 min. After 3 h, all solvent was removed under reduced pressure. THF (15 mL), NaOH (0.86 mL, 20% w/v solution, 5.72 mmol), H_2O_2 (0.36 mL, 35% w/v solution, *ca.* 5.72 mmol) was added to the resulting mass and refluxed for 1 h. The resulting solution was cooled and filtered through Celite, further EtOAc was passed through the Celite pad. The resulting solution was partitioned between EtOAc and brine. The aqueous layer was extracted further with EtOAc (3 x EtOAc). The organic phase was separated and dried over $MgSO_4$. After filtration the organic phase was removed under reduced pressure to yield a dark yellow oil. Toluene (2 x 20 mL) was added to the crude oil and removed under pressure (this was repeated twice). After the toluene had been removed, THF (15 mL) and formaldehyde solution (0.16, 37% w/v solution, 2.1 mmol) were sequentially added to the sample and the solution was stirred under argon overnight (15 h). $MgSO_4$ was added to the reaction, and the solution was filtered. The organics were removed under vacuum to yield a yellow oil. Purification by silica gel chromatography (hexane : EtOAc, 12:1 eluent) gave the product as a colourless oil (0.21 g, 42%). IR (neat): 2932, 2850, 1494, 1445, 1215, 1099 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.32-7.11 (m, 5H), 4.33 (d, *J* = 8.4 Hz, 1H), 3.84 (d, *J* = 14.3, 1H), 3.72 (d, *J* = 8.4, 1H), 3.52 (d, *J* = 2.5, 1H), 3.17 (d, *J* = 14.3, 1H), 2.63 (dq, *J* = 6.6, 4.0 Hz, 1H), 1.86-1.78 (m, 1H), 1.77-1.68 (m, 2H), 1.57-1.44 (m, 2H), 1.42-1.35 (m, 2H), 1.27-1.20 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 139.9, 128.4, 128.2, 126.7, 84.6, 59.2, 52.3, 41.7, 31.8, 25.8, 20.9, 20.8, 17.6 LRMS (ESI+) 247.6 (100%) [M+H$^+$], 102.4 (80%). HRMS (ESI+) calculated [$C_{16}H_{23}NO+H^+$] 246.1858, found 246.1852.

3-Benzyl-5,6-dimethyl-1,3-oxazine (*rac*)-(*anti*)-**6e**



THF (7 mL), 3Å molecular sieve pellets (2.5 g) were stirred under argon. Benzyl amine (0.15 mL, 1.4 mmol) and tiglic aldehde (0.14 mL, 1.4 mmol) were added and stirred for 3 h. In a separate vessel, THF (4 mL), CuCl (6.93 mg, 0.07 mmol), P*n*Bu$_3$ (34.5 µL, 0.14 mmol) and NaO*t*-Bu (20.2 mg, 0.21 mmol) were stirred for 30 min. After 30 min, B$_2$pin$_2$ (0.39g, 1.54 mmol) was added and stirred in the CuCl solution for 10 min. Both solutions were combined and stirred for a further 30 min, after which methanol was added (0.11 mL, 2.80 mmol) and stirred for 18 h. NaBH$_4$ (0.16 g, 4.20 mmol was added and the solution stirred. Methanol (3 mL) was added drop-wise over 10 min. After 3 h, all solvent was removed under reduced pressure. THF (10 mL), NaOH (0.60 mL, 20% w/v solution, 4 mmol), H$_2$O$_2$ (0.25 mL, 35% w/v solution, *ca.* 4 x 10^{-3} mol) was added to the resulting mass and refluxed for 1 h. The resulting solution was cooled and filtered through Celite, further EtOAc was passed through the Celite pad. The resulting solution was partitioned between EtOAc and brine. The aqueous layer was extracted further with EtOAc (3 x EtOAc). The organic phase was separated and dried over MgSO$_4$. After filtration the organic phase was removed under reduced pressure to yield a yellow oil. Toluene (2 x 20 mL) was added to the crude oil and removed under pressure (this was repeated twice). After the toluene had been removed, THF (10 mL) and formaldehyde solution (0.12 mL, 37% w/v solution, 1.54 mmol) were sequentially added to the sample and the solution was stirred under argon overnight (15 h). MgSO$_4$ was added to the reaction, and the solution was filtered. The organics were removed under vacuum to yield a yellow oil. Purification by silica gel chromatography (hexane : EtOAc, 6:1 eluent) gave the product as a colourless oil (0.80g, 28%). IR (neat): 2976, 1496, 1244, 1107, 742 cm^{-1}. ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.34-7.13 (m, 5H), 4.39 (dd, *J* = 8.3, 1.7 Hz, 1H), 3.77 (d, *J* = 8.3 Hz, 1H), 3.65 (dq, *J* = 6.6, 3.2 Hz, 1H), 3.56 (d, *J* = 13.5 Hz, 1H), 3.39 (d, *J* = 13.5 Hz, 1H), 2.71 (ddd, *J* = 11.8, 3.8, 1.7 Hz, 1H) 2.39 (dd, *J* = 11.8, 3.5 Hz, 1H), 1.66-1.56 (m, 1H), 1.1 (d, *J* = 6.6 Hz, 3H), 0.99 (d, *J* = 7.0 Hz, 3H). ^{13}C NMR (101 MHz, CDCl$_3$): δ 138.4, 128.6, 128.3, 127.0, 84.6, 75.3, 57.3, 57.2, 32.5, 17.3, 12.8 LRMS (ESI+) 206.5 (73%) [M+H$^+$], 194.1 (47%). HRMS (ESI+) calculated [C$_{13}$H$_{19}$NO+H$^+$] 206.1545, found 206.1549.

6. One-pot copper-catalyzed asymmetric β–boration *via* formation *in situ* of α,β-unsaturated imine 2h from benzyl amine

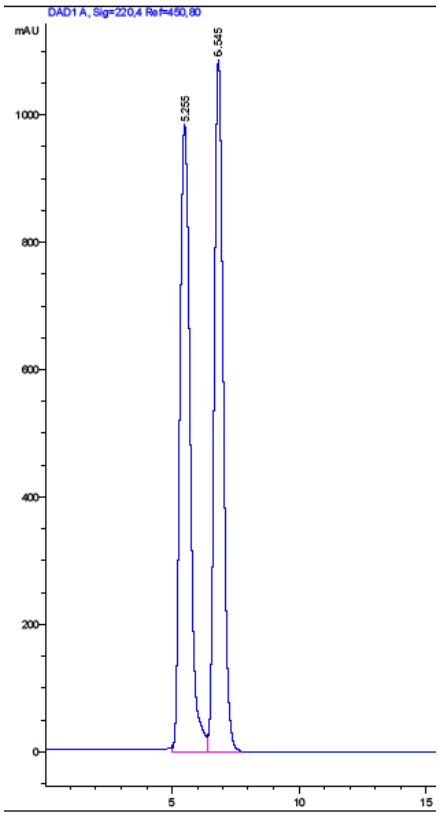
CuCl (0.01 mmol), chiral Josiphos-type diphosphine ligand **8** (0.01 mmol) and Na*t*OBu (0.03 mmol) were transferred into a Schlenck tube, and dissolved in THF (2.5 mL) under nitrogen. The suspension was stirred for 10 minutes and bis(pinacolato)diboron (140 mg, 0.55 mmol) was added. The suspension was stirred for 5 minutes, after which, the α,β-unsaturated ketone (0.5 mmol), benzylamine (0.5 mmol) and activated 3Å molecular sieve pellets (0.8 g) were then added. Finally, MeOH (40 µl, 2 eq.) was added, and the mixture was allowed to stir at room temperature for 6 h. Evaporation of the organic solvents yielded the crude product as a cloudy oils which was analyzed directly by ^{1}H NMR to calculate the conversion, and by HPLC-UV to determinate the enantioselectivity.

The enantioselective β-boration carried out from the isolated α,β-unsaturated imine **2h** from benzylamine using the same procedure to compare the enantiomeric excess, gave identical results.

6.1 Chiral HPLC analysis

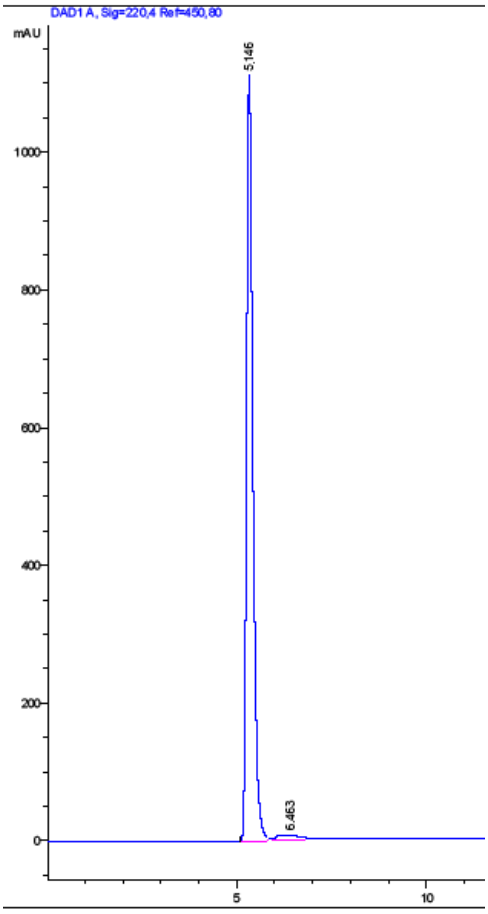
Monophosphine PCy_3 was used to obtain the racemic mixture and optimize the separation of the two enantiomers using chiral AD-H column (iPrOH-hexane, 95:5, 1mL/min, at 20ºC, tr = 5.25 and 6.54 min):

Racemic Mixture



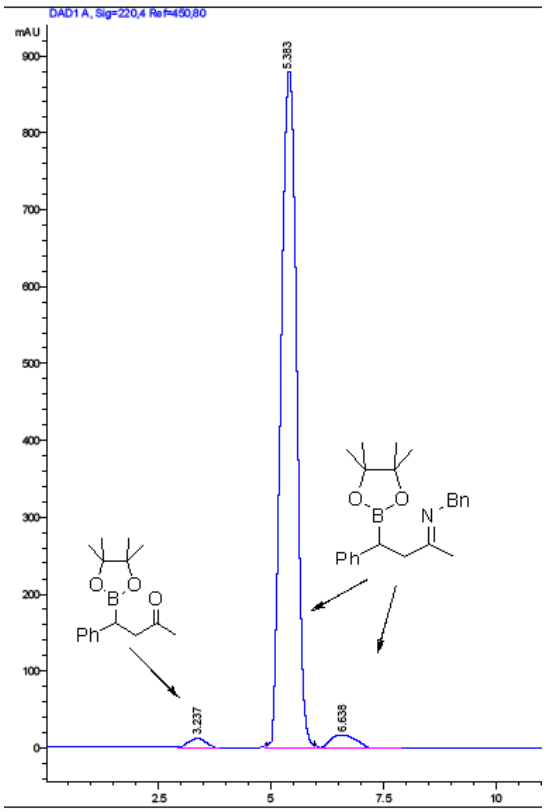
The (-)-99% *e.e.* was obtained by HPLC analysis using a chiral AD-H column (iPrOH-hexane, 95:5, 1 mL/min, at 20 ºC) when the isolated α,β–unsaturated imine **2h** from benzyl amine was the substrate of the copper-catalyzed β–boration:

Isolated α,β–unsaturated imine 2h



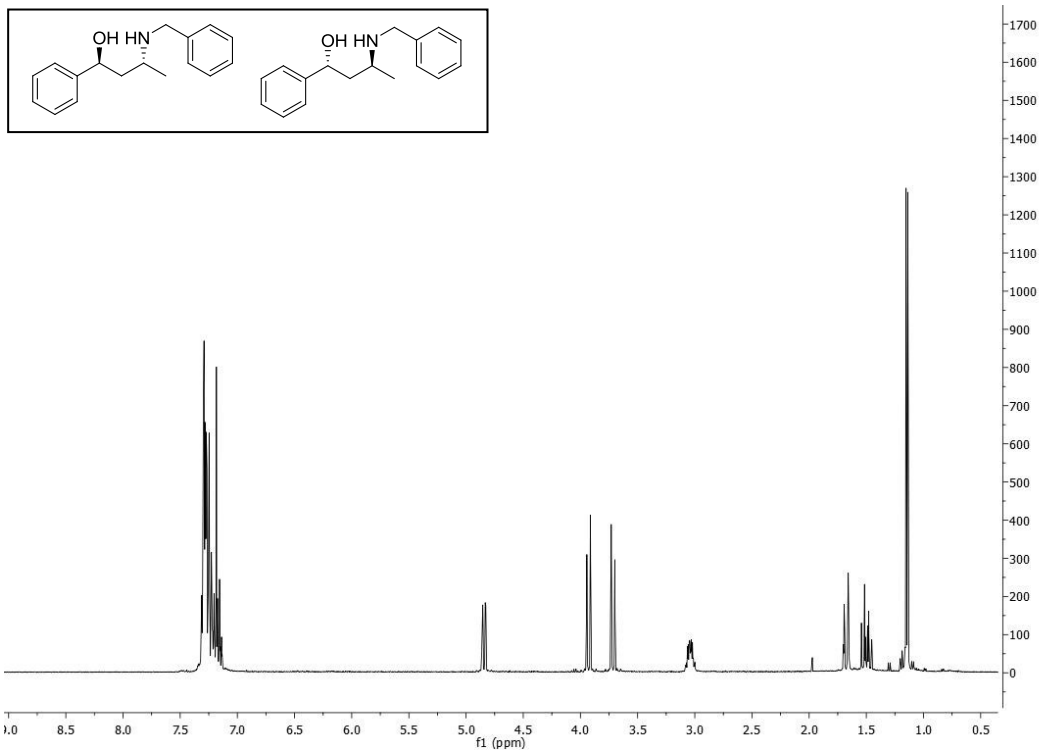
The enantiomeric excess was maintained [(-)-92 % *e.e.*] when the α,β–unsaturated imine from benzylamine was formated *in situ* following for the copper-catalyzed β–boration. A small amount of β–boryl ketone was observed during this process (only 4% of the total conversion):

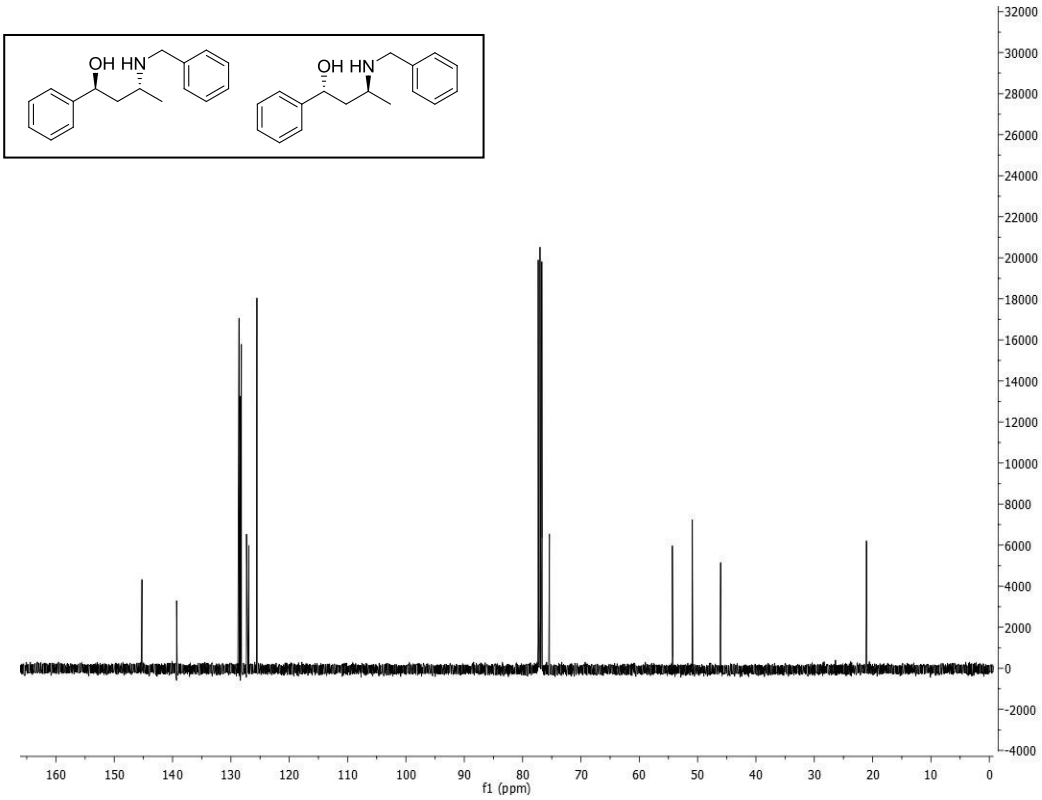
Formation *in situ* of α,β–unsaturated imine

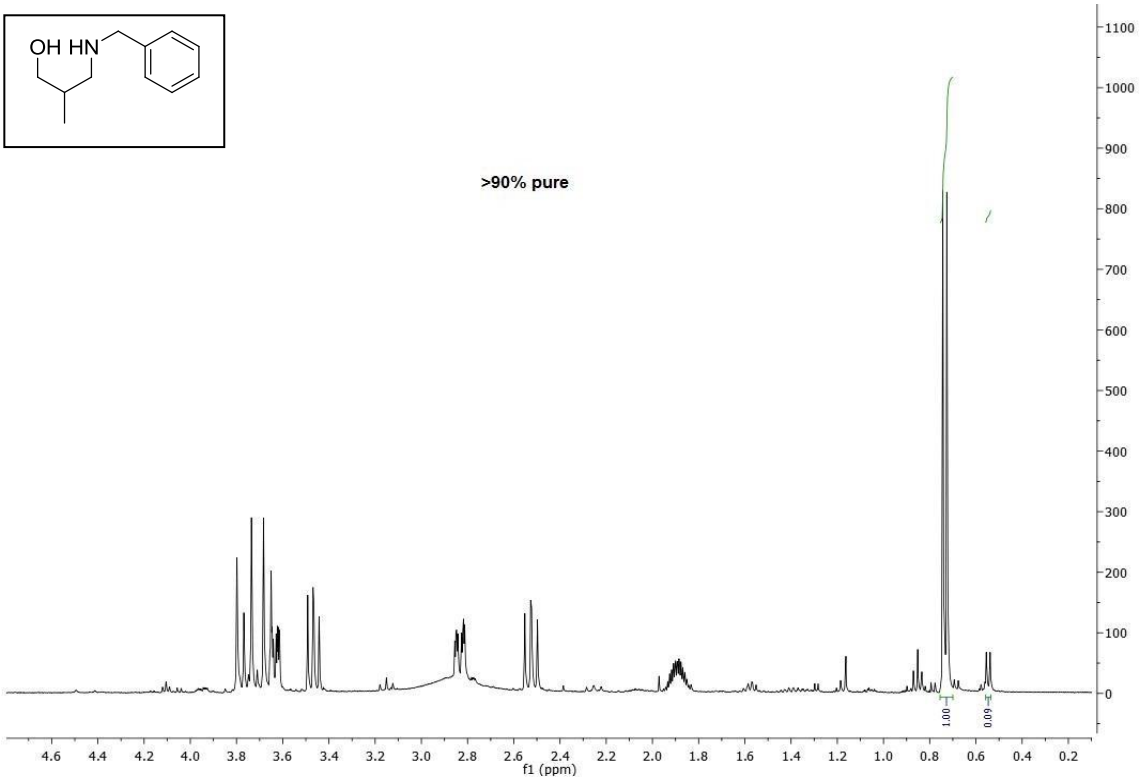


See previous work for characterization of **4h** and (-)-**7h**.[3,4]

7. ^{1}H & ^{13}C NMR – *d.e.* – *syn*/*anti* determination



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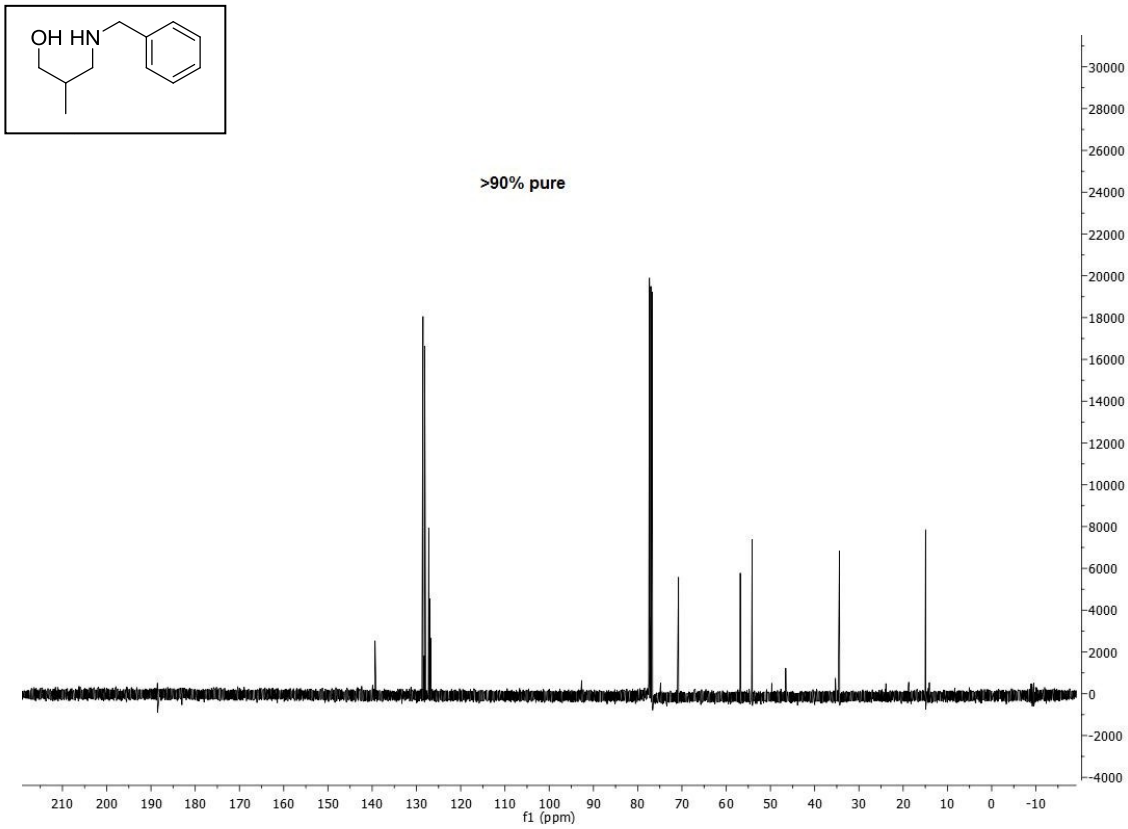
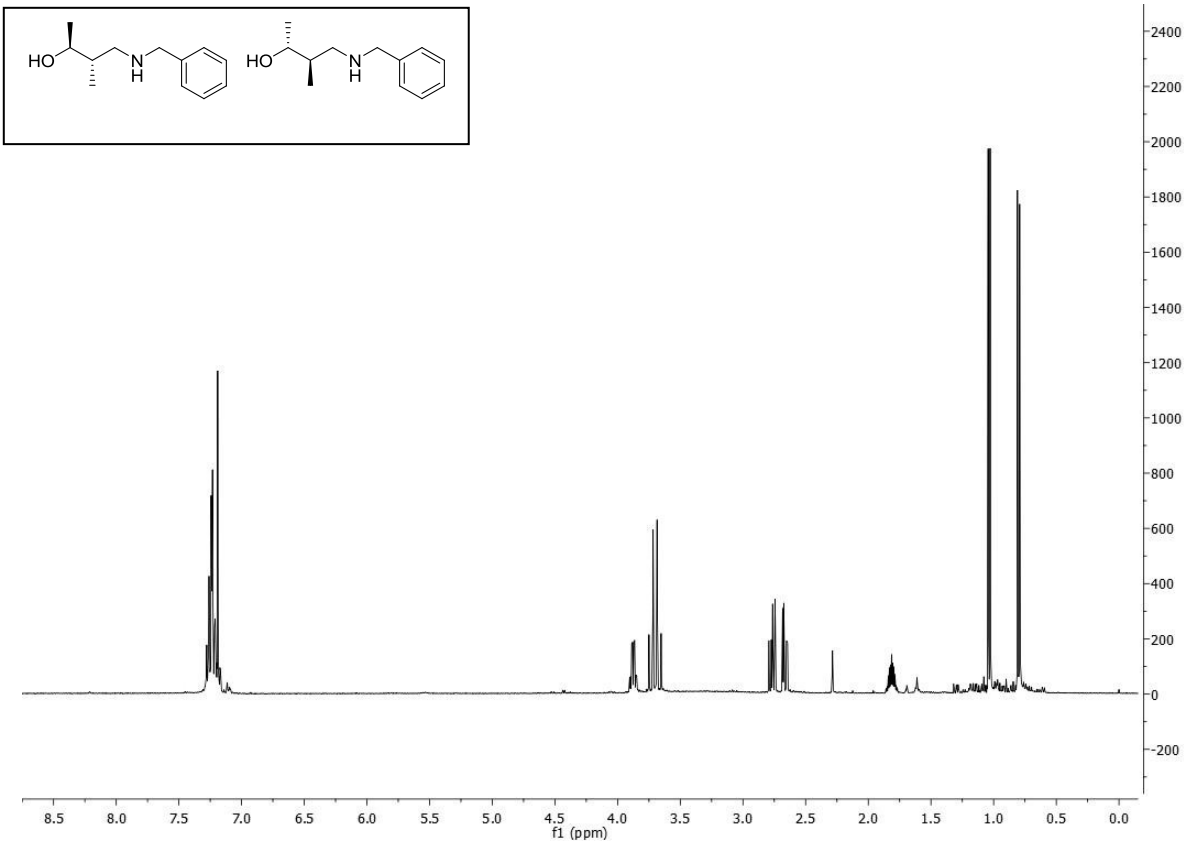
1.00
0.09
f1 (ppm)


OH HN
>90% pure
f1 (ppm)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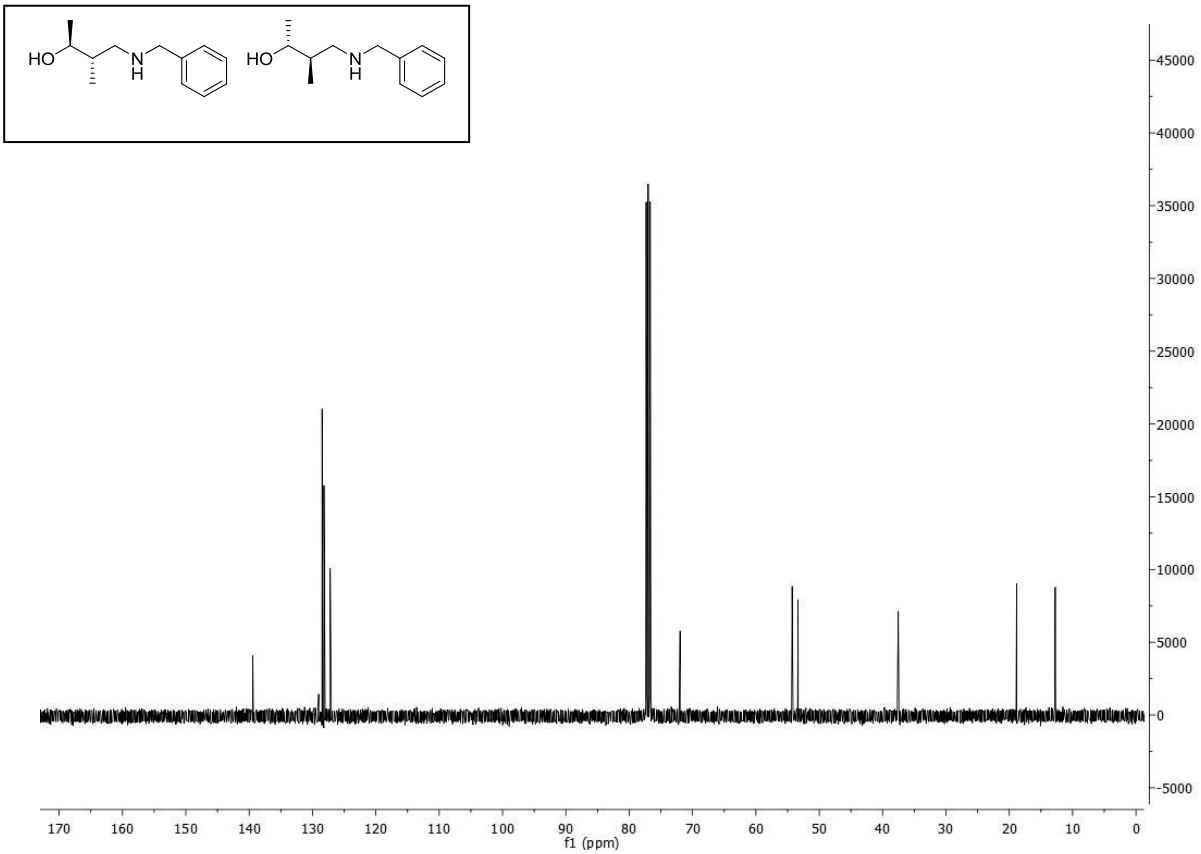
H
HO
N
H
f1 (ppm)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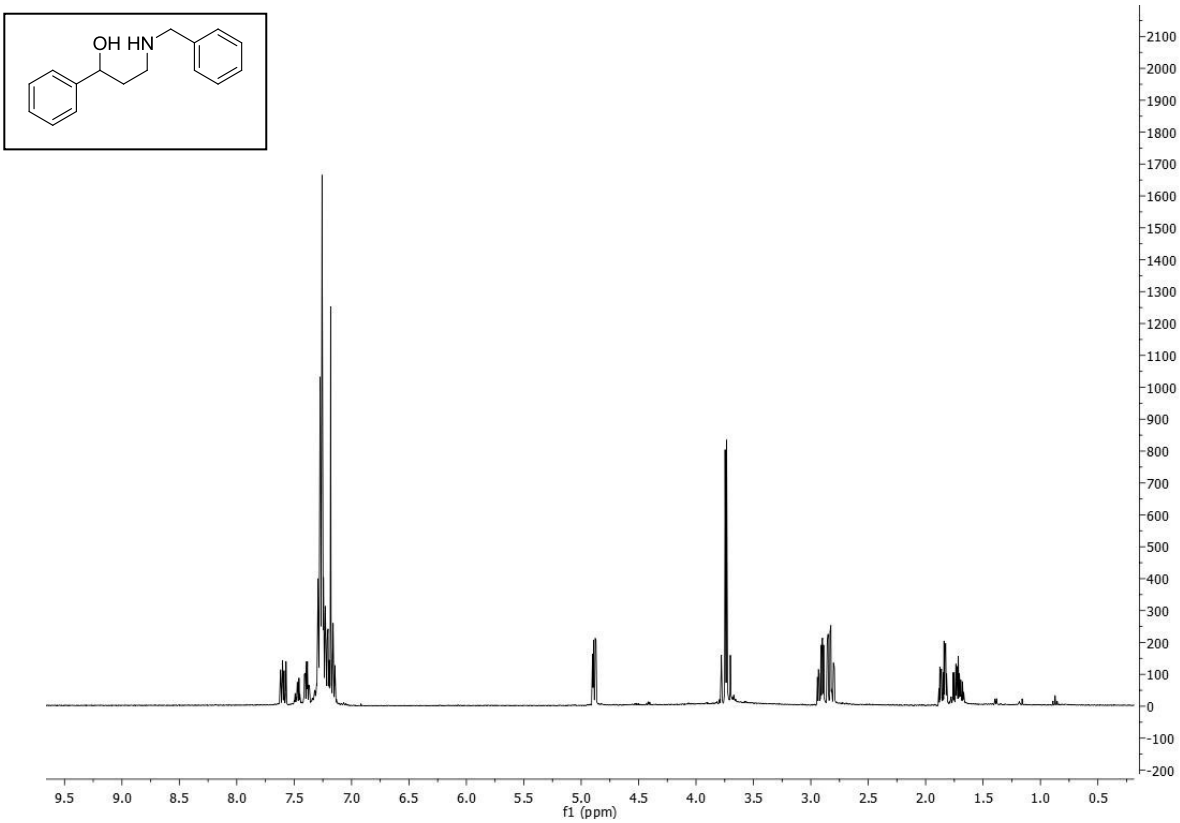
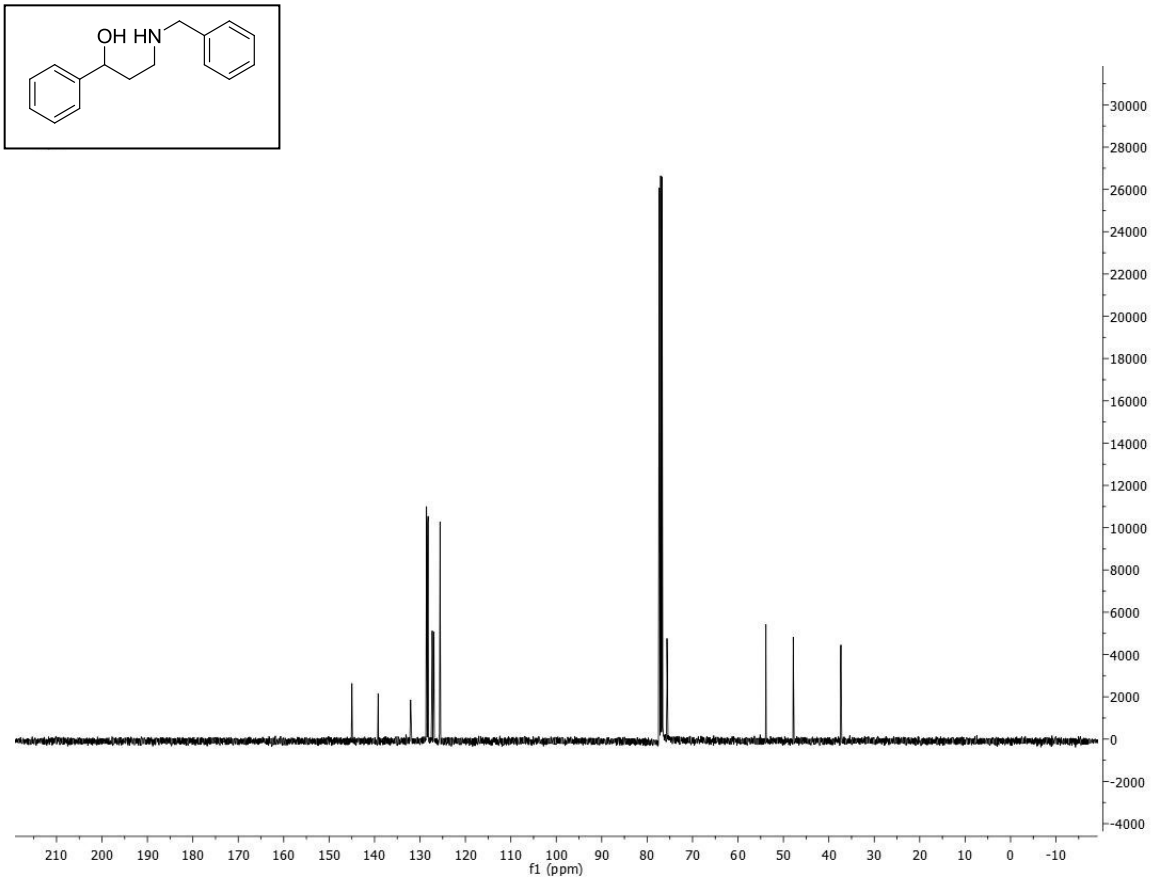
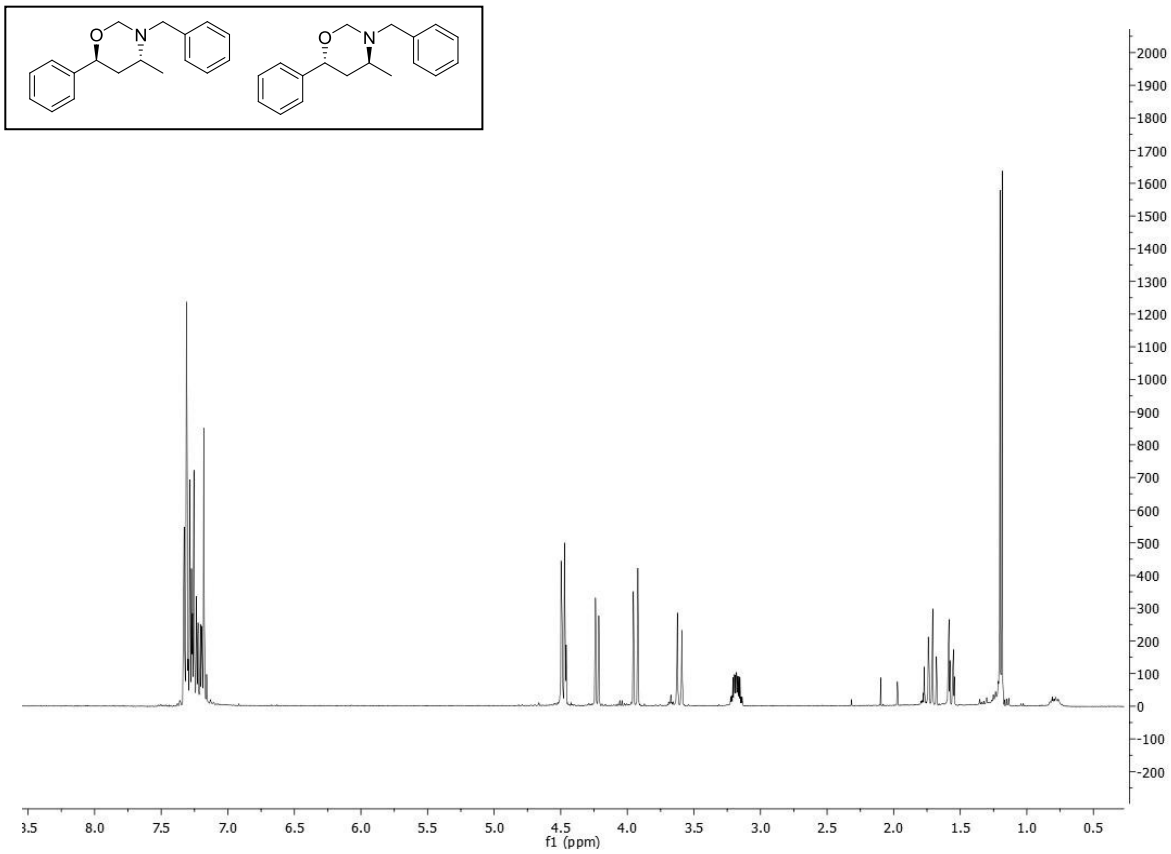
H
HO
N
H
f1 (ppm)


OH HN
f1 (ppm)


OH HN
f1 (ppm)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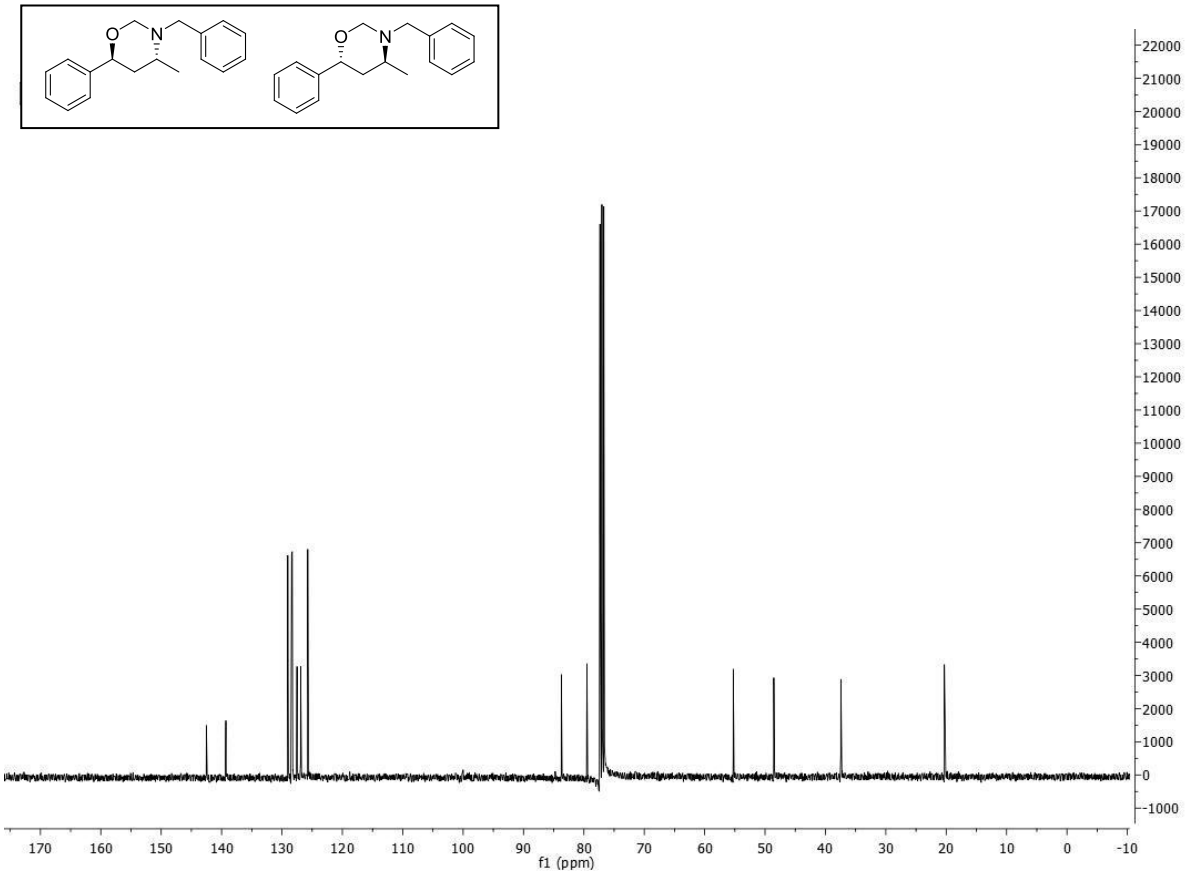
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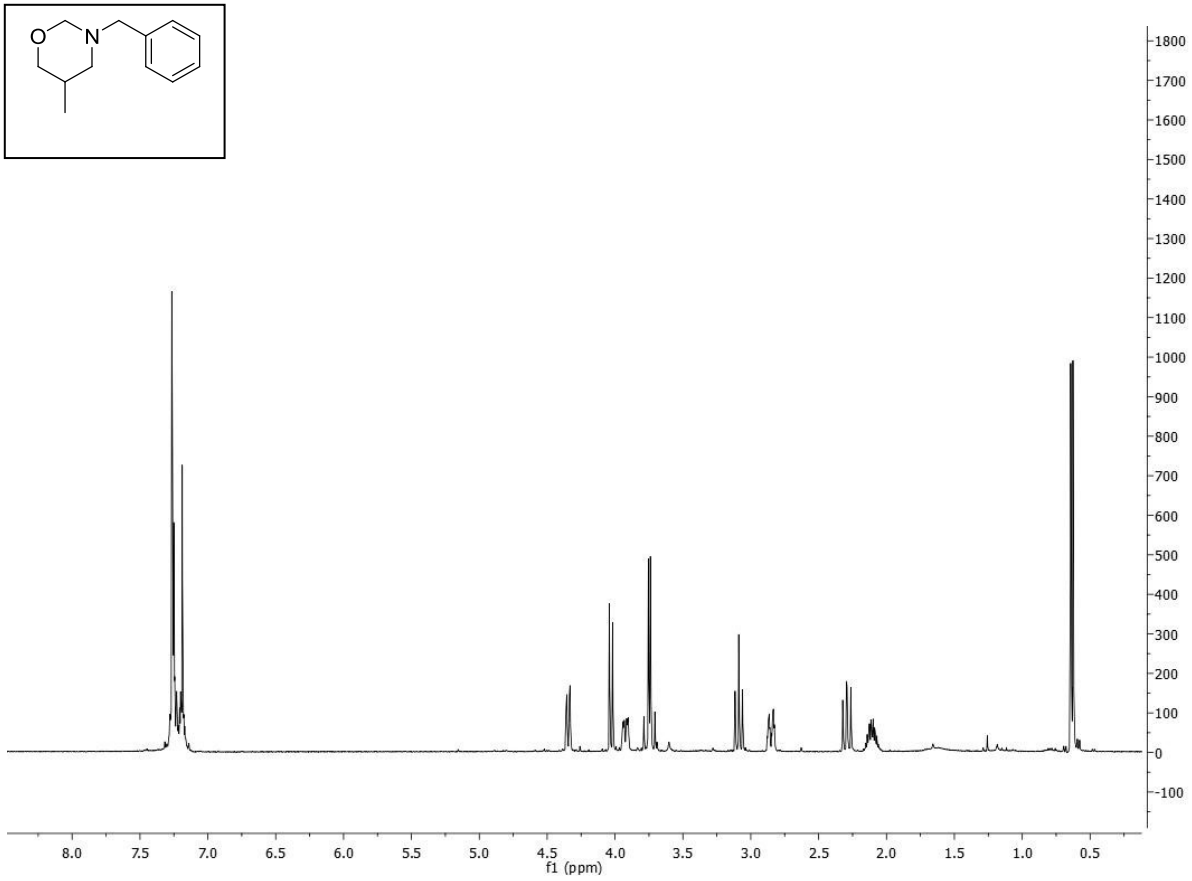
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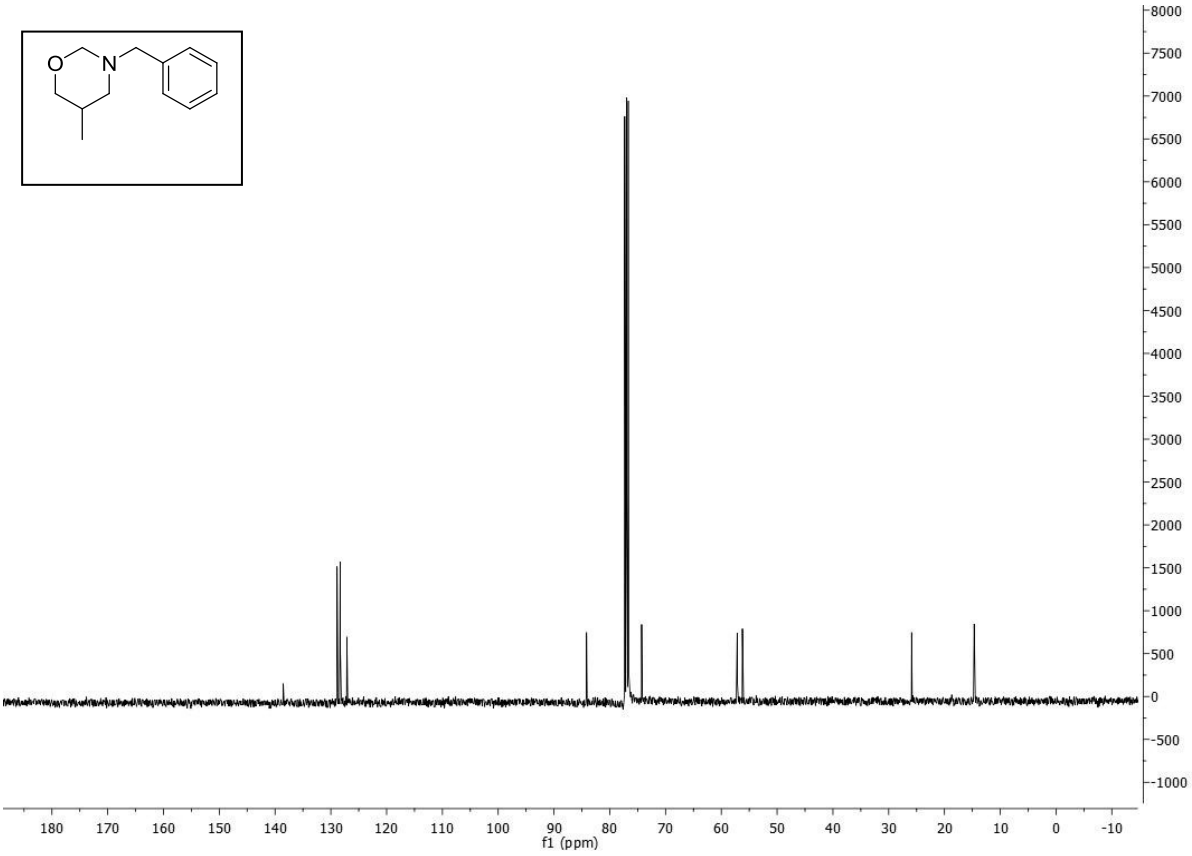
N
f1 (ppm)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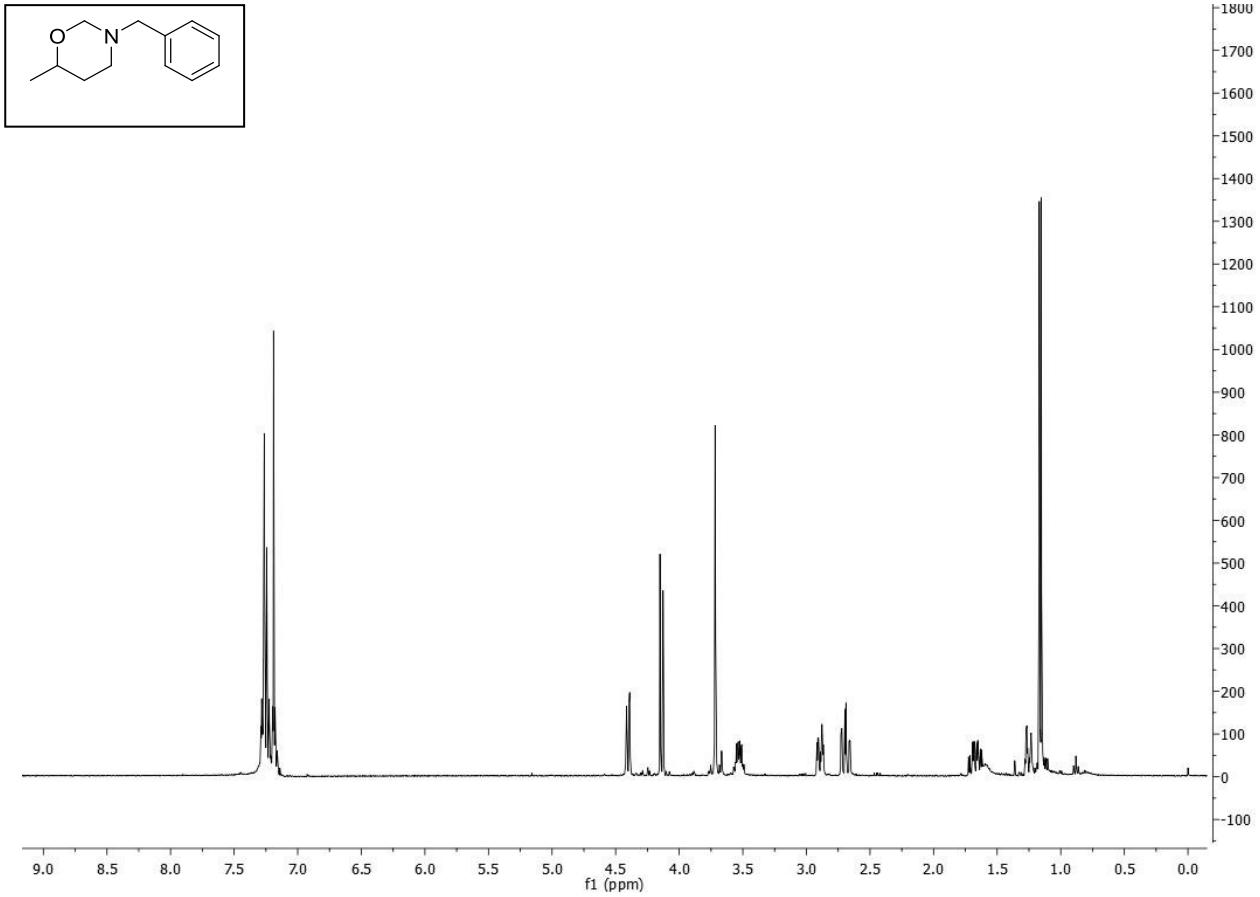
f1 (ppm)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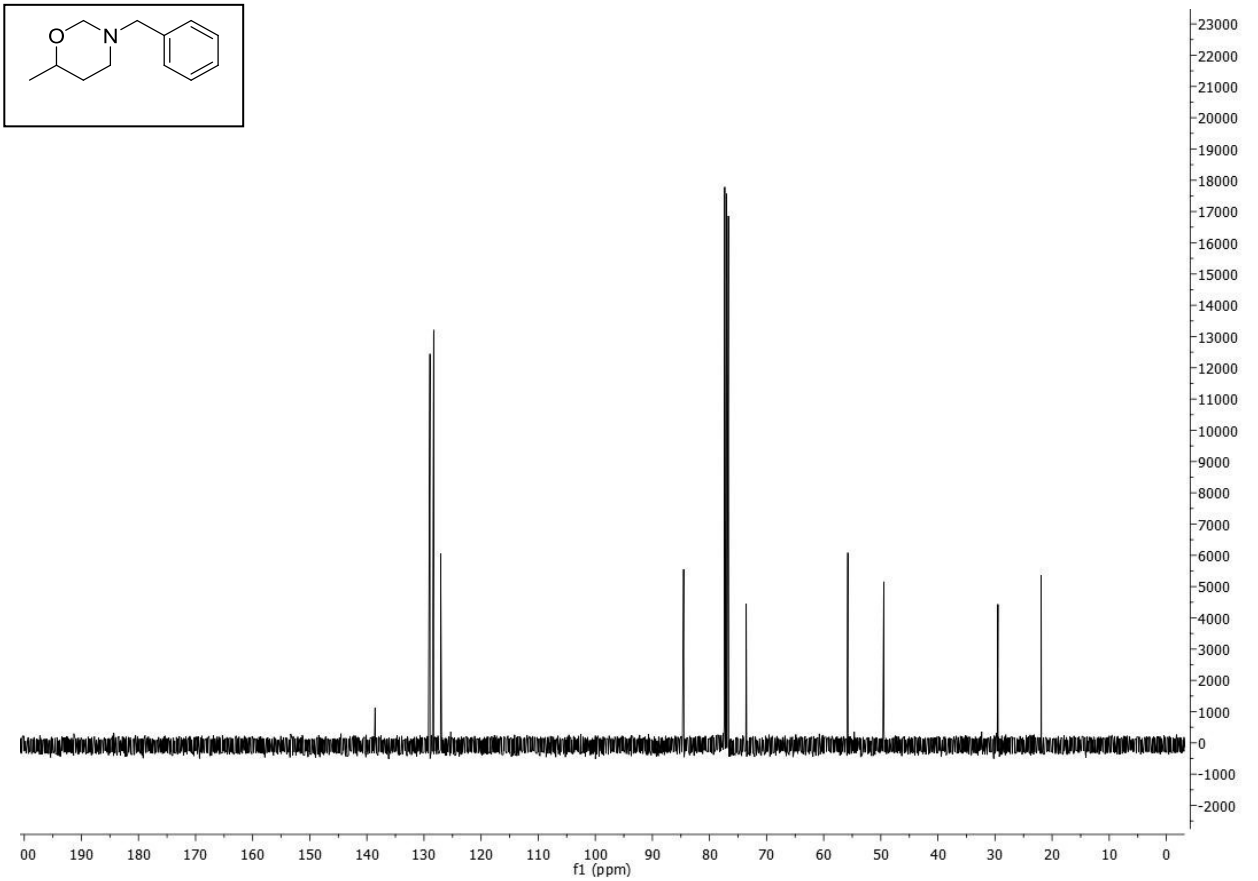
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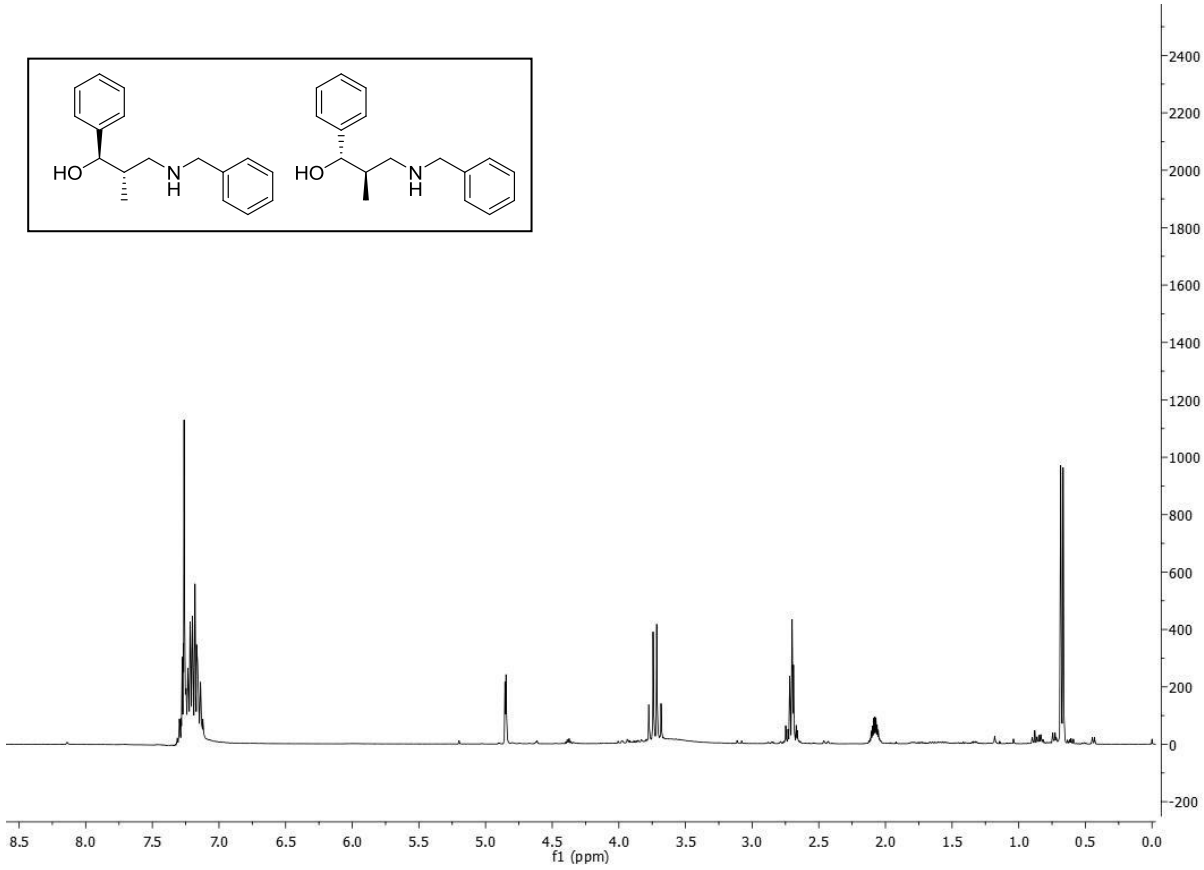
N
f1 (ppm)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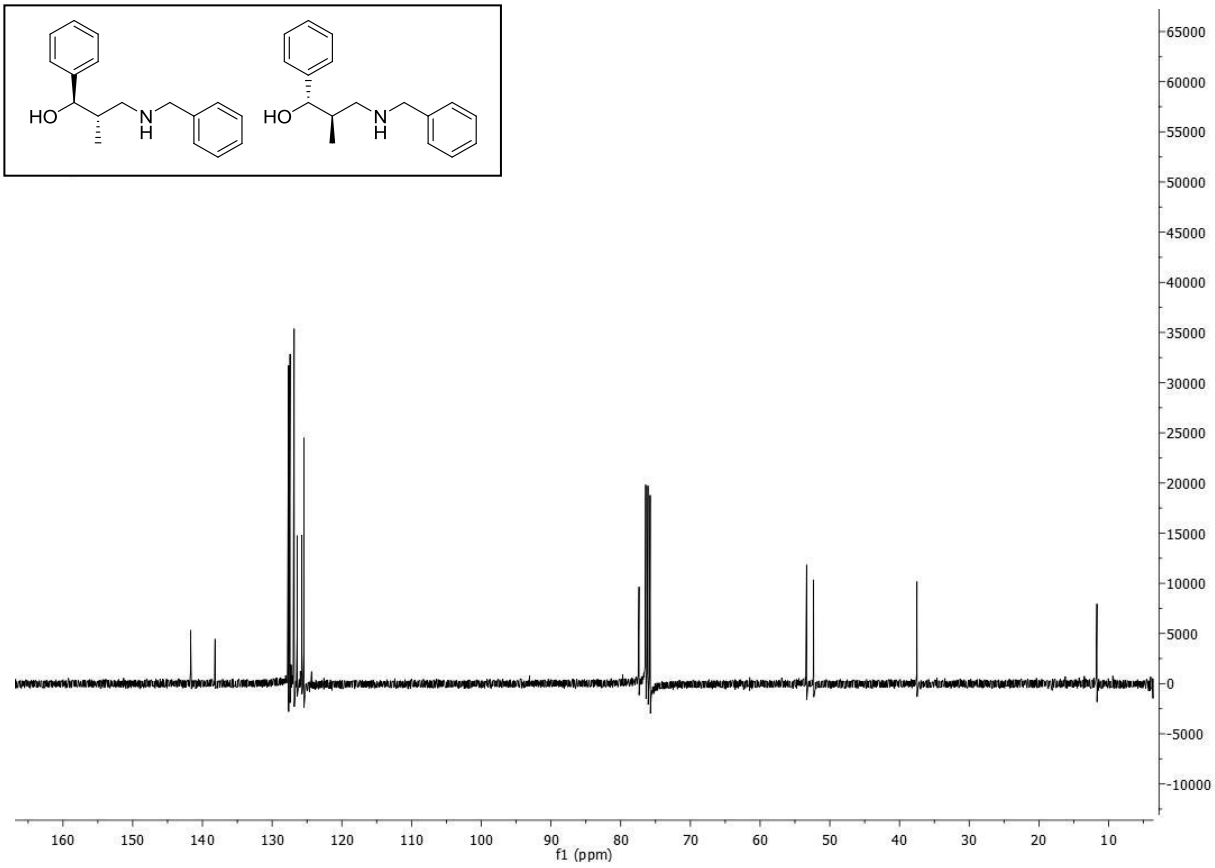
N
H
HO
N
H
f1 (ppm)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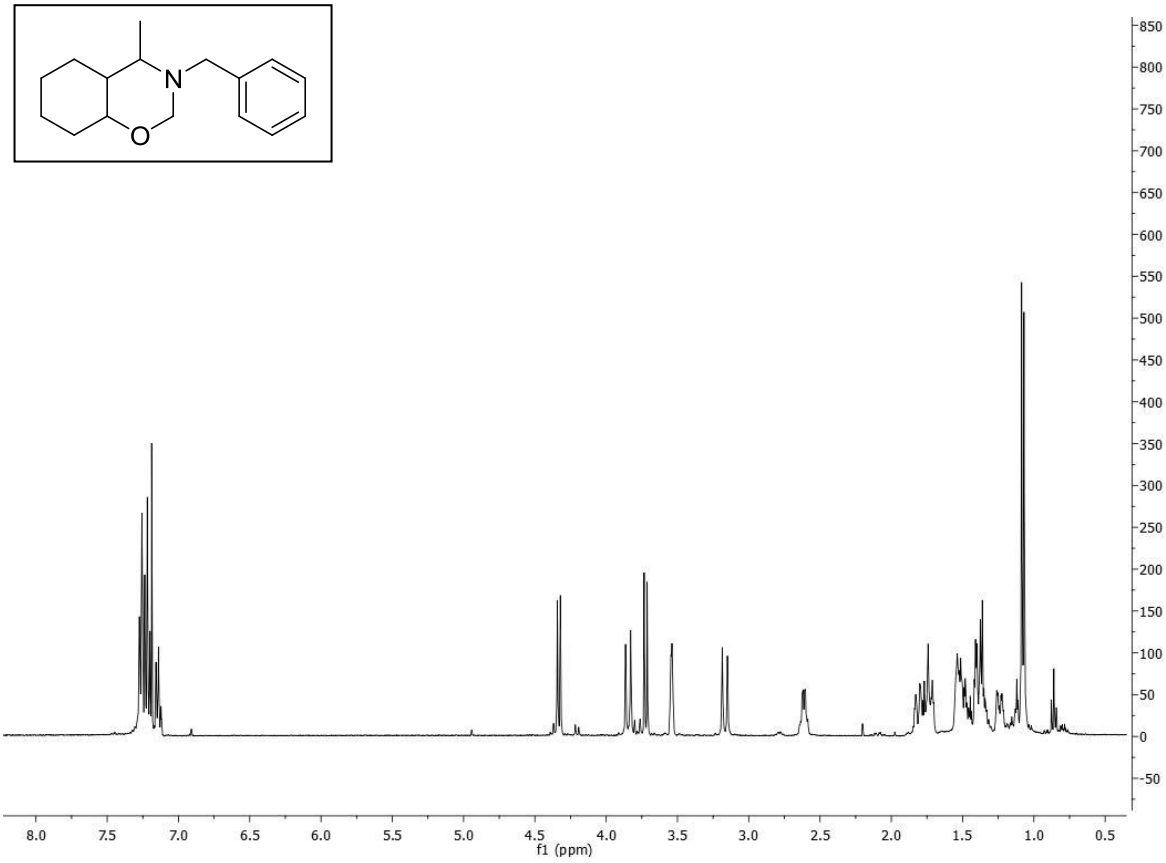
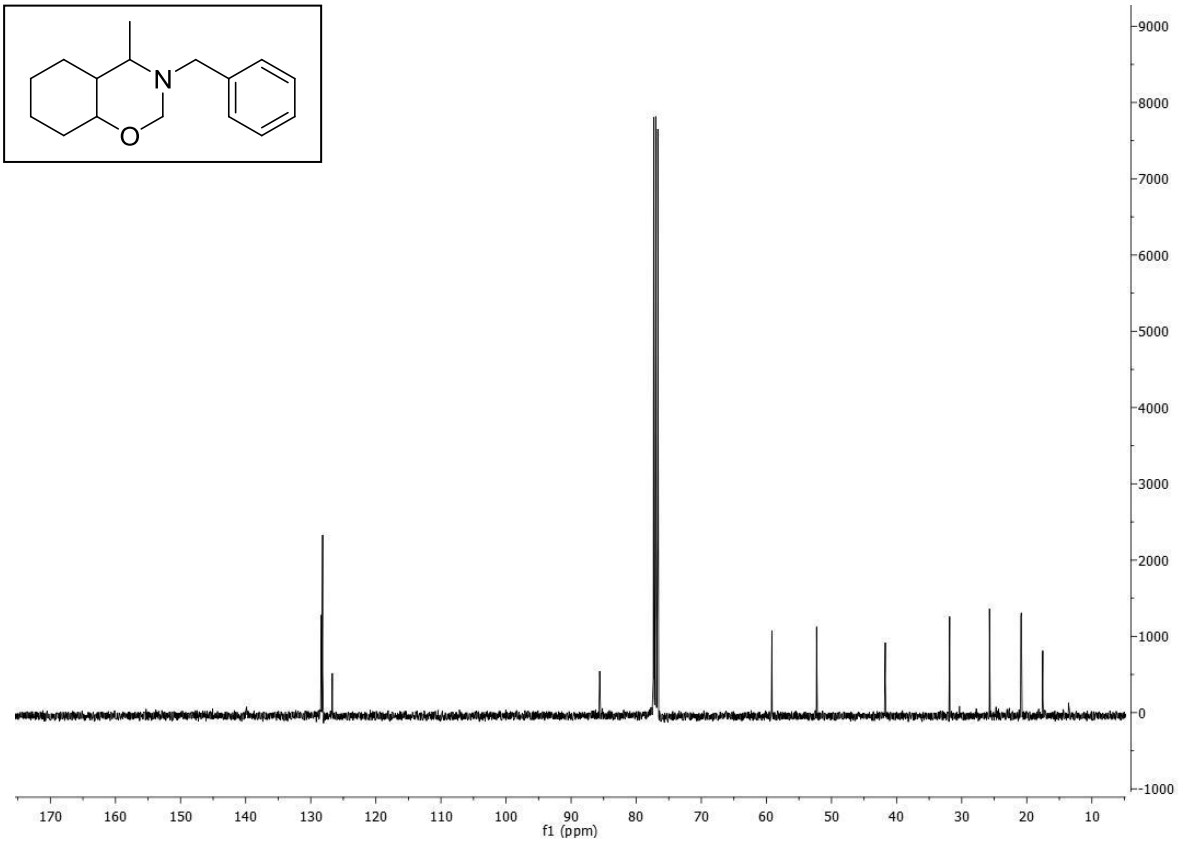
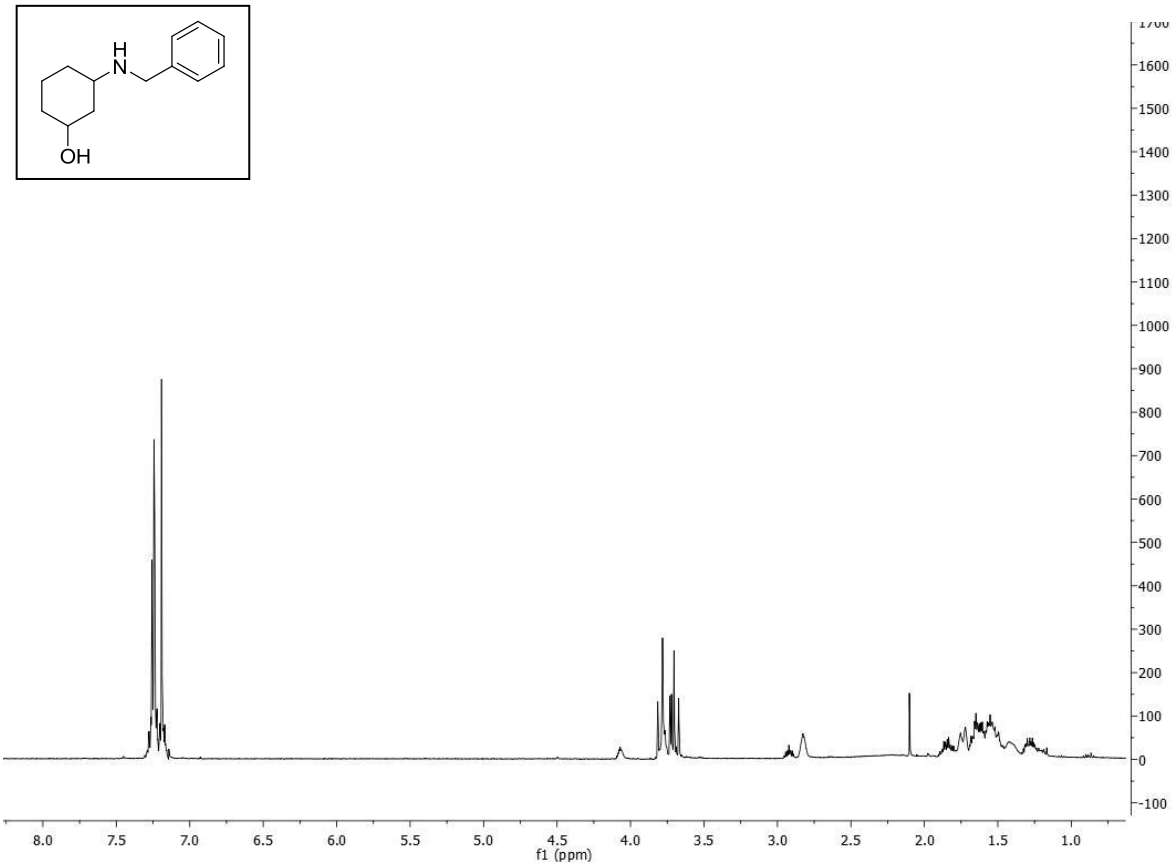
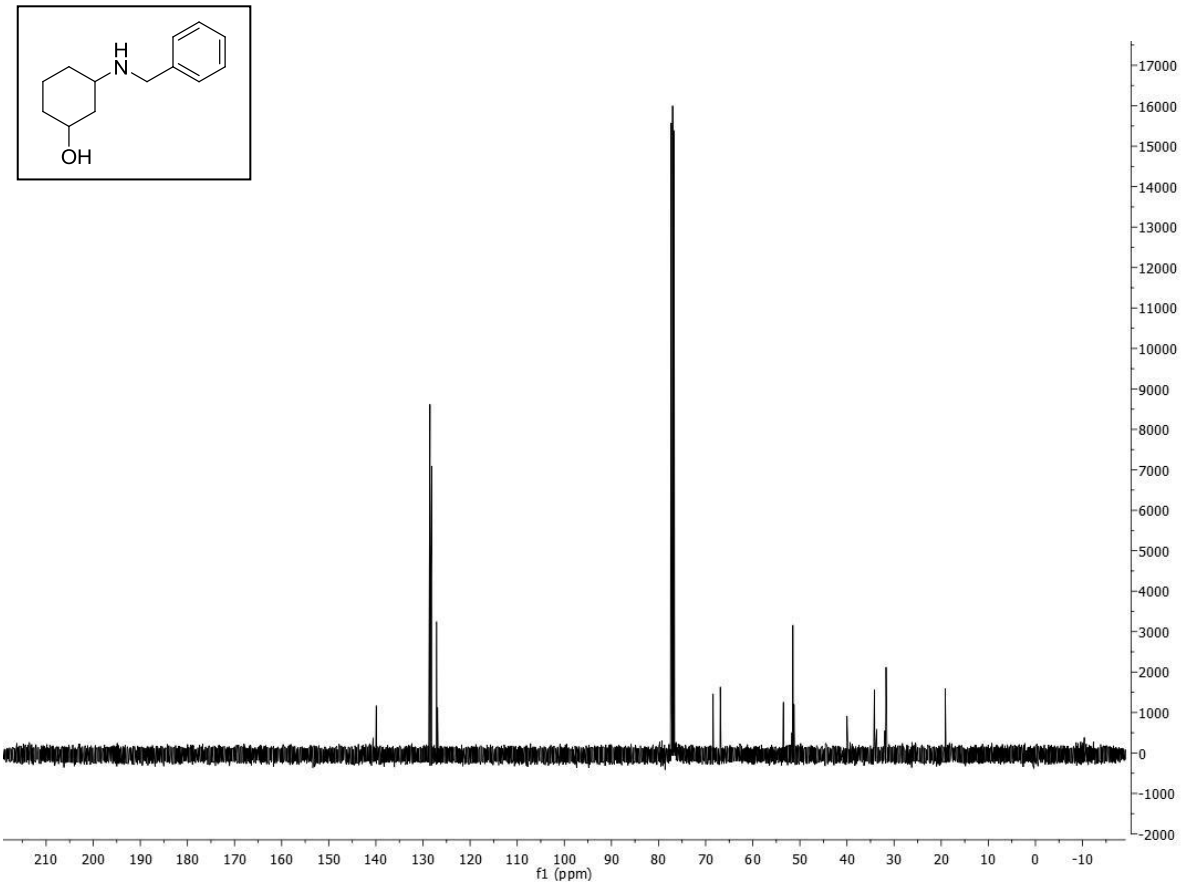
N
H
HO
N
H
f1 (ppm)

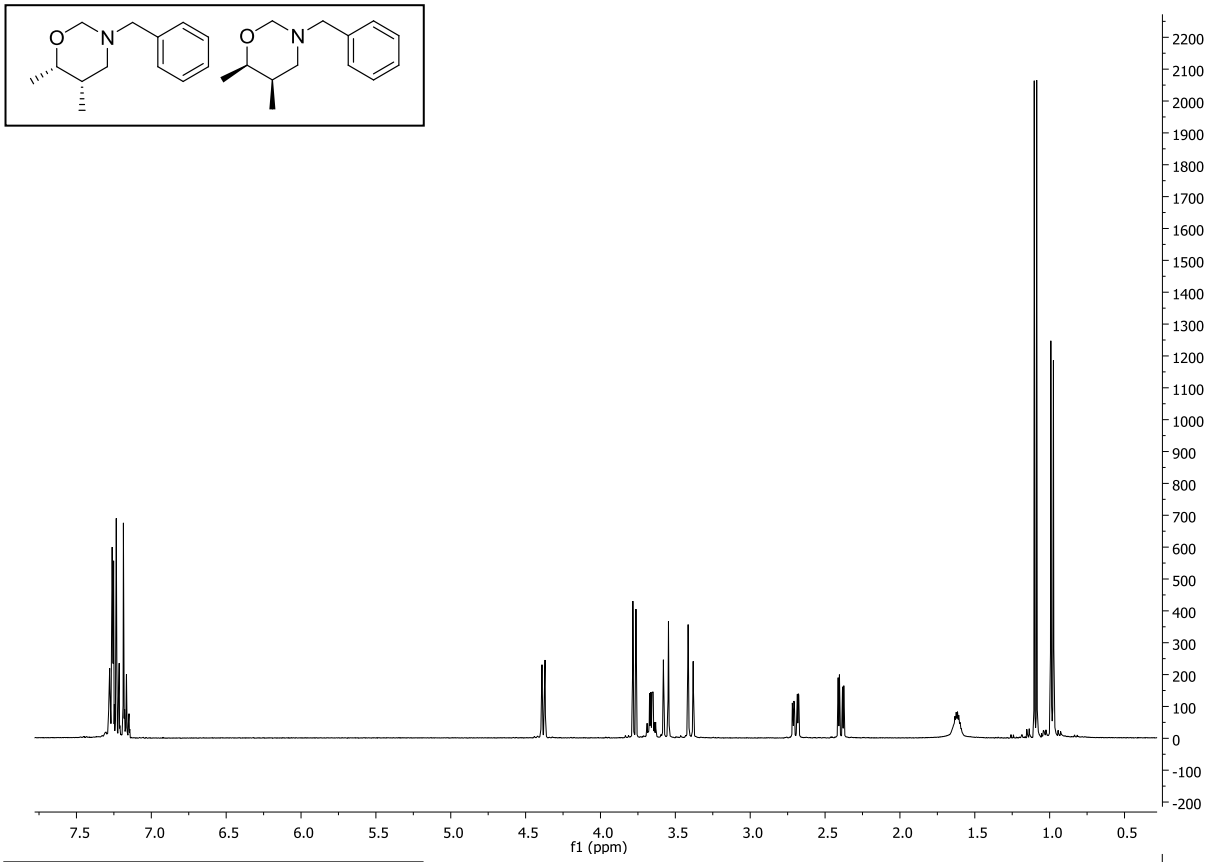

N
O
f1 (ppm)

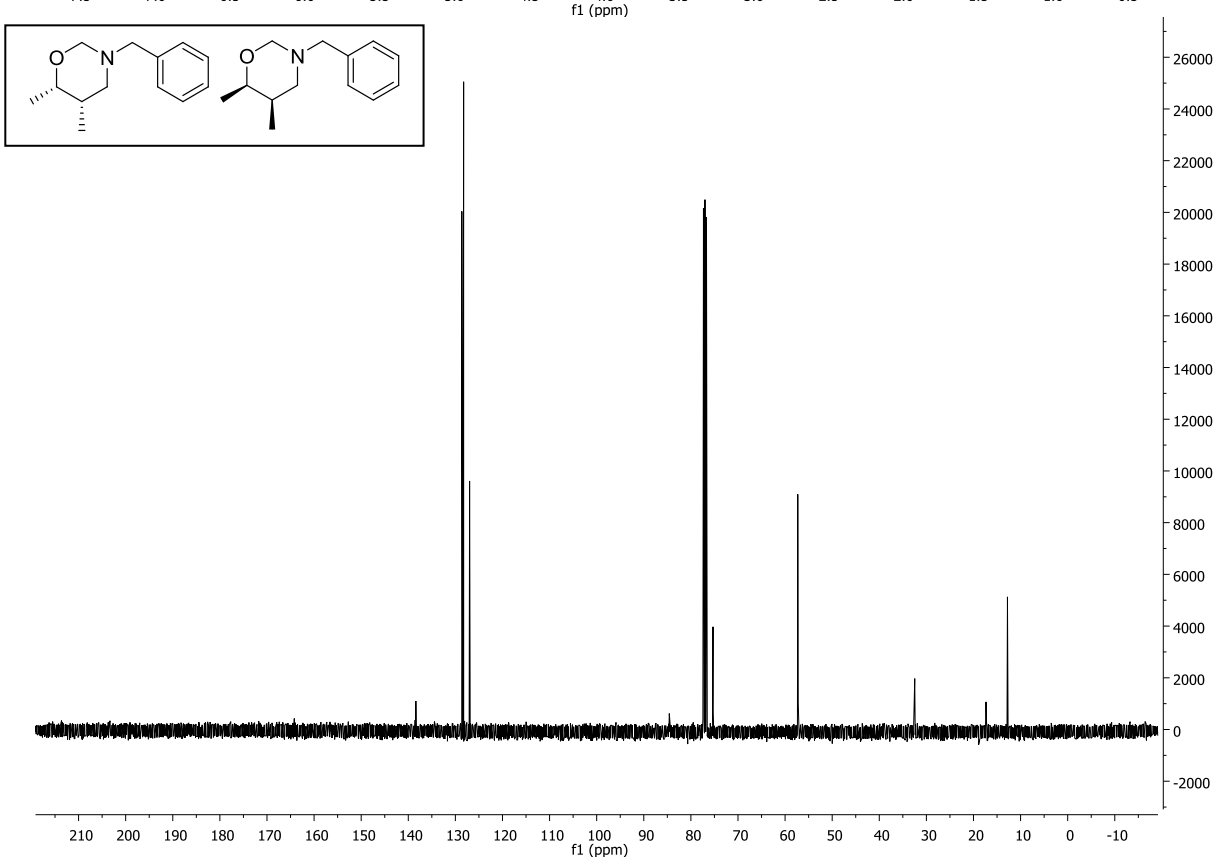

N
O
f1 (ppm)

Reported as a mixture of *syn* and *anti* diastereoisomers

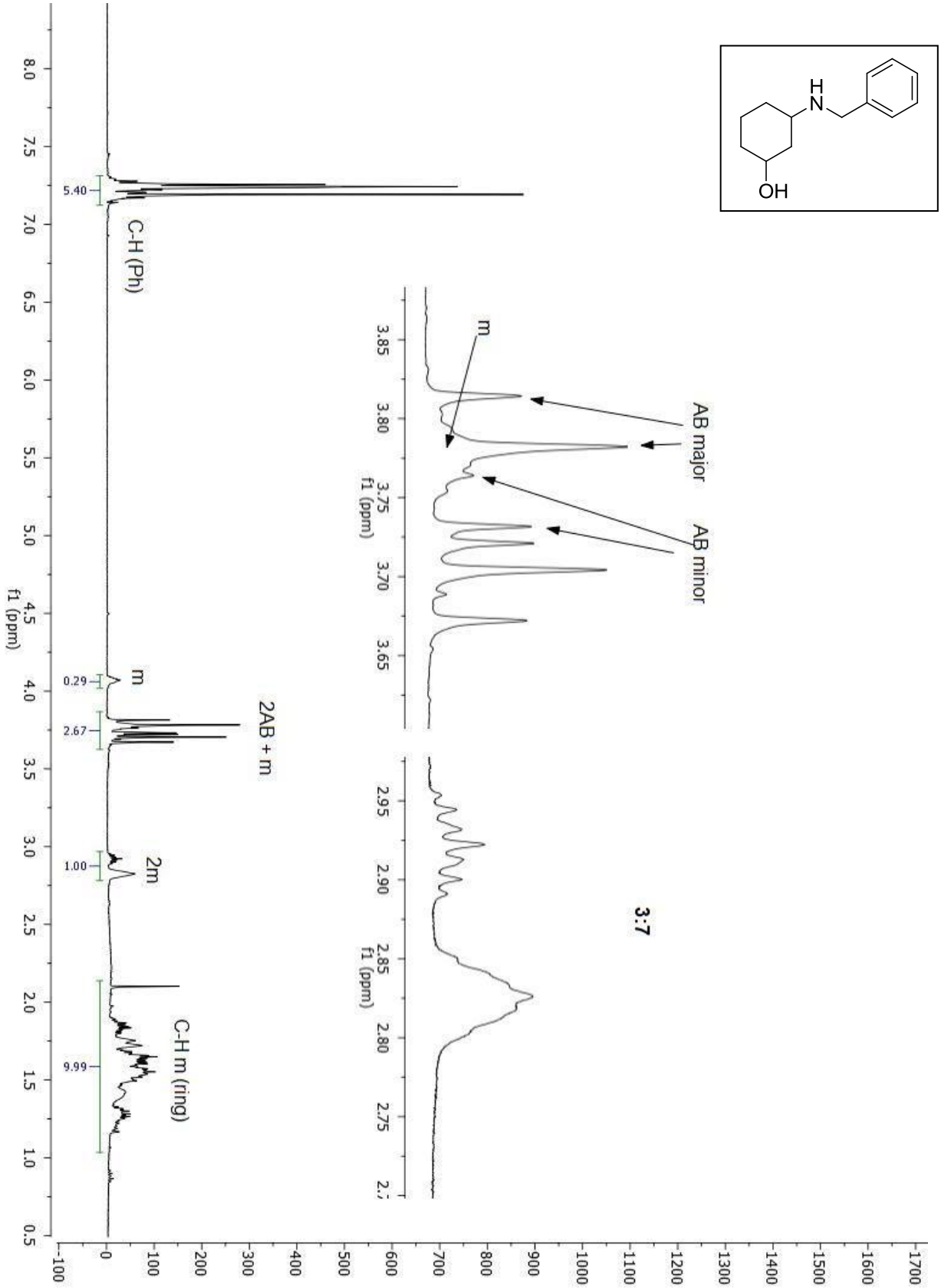





O
N
O
N
f1 (ppm)


O
N
O
N
f1 (ppm)

syn/*anti*


H
N
OH
3:7
AB major
AB minor
m
C-H (Ph)
2AB + m
2m
C-H m (ring)
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2.67
1.00
9.99
f1 (ppm)

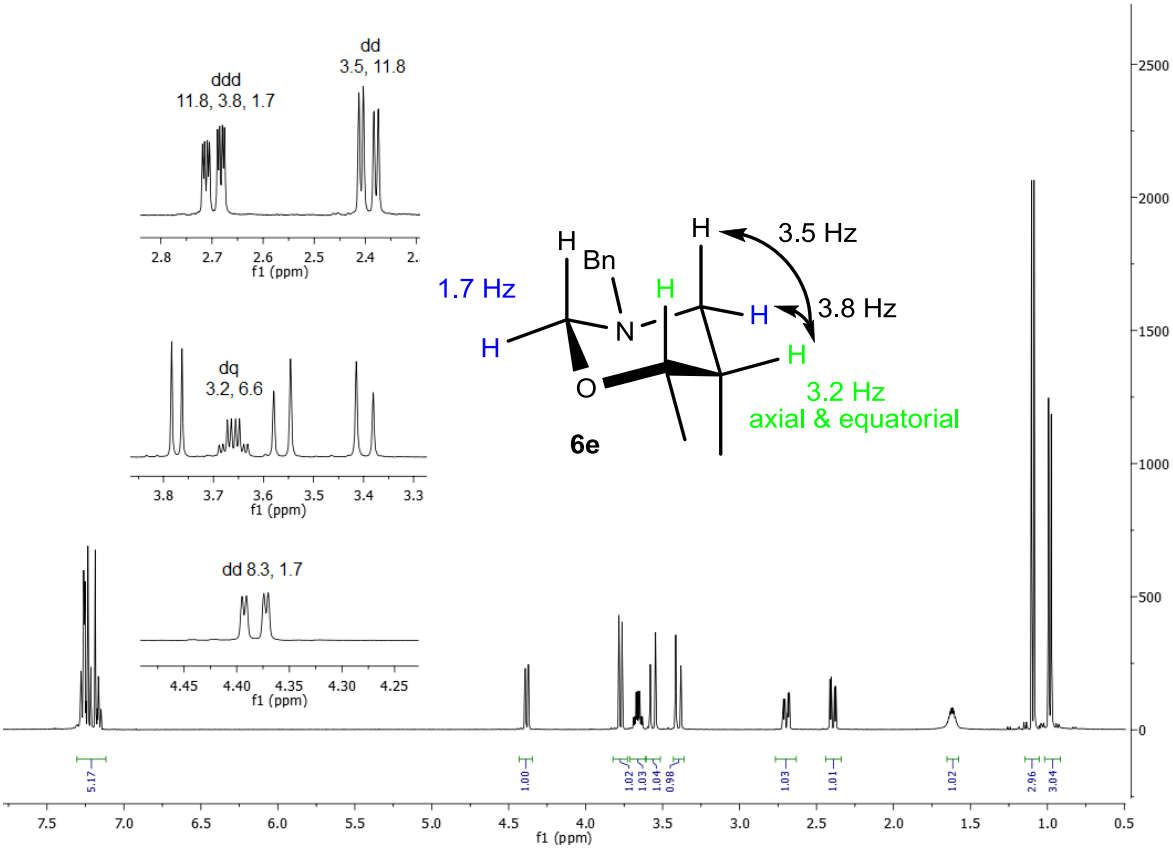

Fig. 9 ^{1}H NMR of (*rac*)-(*anti*)-**6e** in the determination of *syn*/*anti* diastereoisomerism.

5h and **6h** have been assigned in accordance with previous work by our groups.4[b]

5e, **6e** and **5f** are prepared from α,β-disubstituted α,β-unsaturated aldehydes which are prepared and isolated as a single diastereoisomer. The oxazine **6e** can be assigned as the racemic *anti*-diastereoisomer (R,R and S,S), whereby the two methyl groups are orientated in the axial and equatorial position (as determined from the ^{3}J of the Hs shown in green, see Fig. 9).

8. Reference

1. J. A. Ellman, T. Kochi, T. Tang, A. *J. Am. Chem. Soc.* **2002**, *124*, 6518-6519.

2. P. Bernardelli, M. Bladon, E. Lorthiois, A. C. Manage, F. Vergne, R. Wrigglesworthb, *Tetrahedron: Asymmetry*., 2004, **12**, 1451–1455.

3. E. Fernández, H. Gulyás, C. Solé, J. A. Mata, A. Tatla, A. Whiting, *Chem. Eur. J.*, 2011, **17**, 14248- 14257.

4. E. Fernández, C. Solé, *Chem. Asian J.*, 2009, **4**, 1790- 1793. (b) Solé, C.; Whiting,A.; Gulyás, H.; Fernández, E. *Adv. Synth. Catal.* **2011**, *353*, 376.