SUPPORTING INFORMATION

Synthesis of organocatalysts using non-covalent chemistry; understanding the reactivity of ProNap, an enamine-type organocatalyst that can self assemble with complementary co-catalysts.

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Contents.

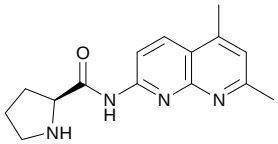
1. Experimental.

Dry ethylene chloride was obtained from an Innovative Technologies Puresolve 400 solvent still. Other solvents were bought and used as received without further purification. All manipulations were carried out under an atmosphere of nitrogen unless otherwise stated. Solvents were removed by rotary evaporation on a Heidolph labrota 4000. Flash column chromatography was performed on Davisil silica gel Fluorochem 60 Å, particle size 35-70 μm. HPLC analysis was determined on a Varian Prostar operated by Galaxie workstation software. NMR spectra were recorded on Bruker Avance 300 and 400 instruments. Proton chemical shifts are referenced to internal residual solvent protons. Proton signal

multiplicities are given as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), br (broad) or a combination of the above. When appropriate, coupling constants (*J*) are quoted in Hz and are reported to the nearest 0.1 Hz. All spectra were recorded at room temperature unless otherwise stated and the solvent for a particular spectrum is given in parentheses. Carbon chemical shifts are referenced to the carbon signal of the deuterated solvents. Enamine studies were performed in a Bruker Avance 500 equiped with a 5 mm inverse probe. Infrared spectra were recorded on a Perkin Elmer Paragon 1000 Spectrum GX FT-IR system. Chemical ionisation mass spectroscopy and electron ionisation mass spectroscopy were performed on a Micromass GCT spectrometer. Electrospray mass spectroscopy was performed on a Micromass LCT spectrometer. All were operated by Mrs Caroline Horsburgh at St Andrews University, or at the ESPSRC National Mass Spectrometry Service Centre, Swansea University, using Waters ZQ4000, Thermofisher LTQ Orbitrap XL and Finnigan MAT 900 XLT Instruments. Only major peaks are reported, and intensities are quoted as percentages of the base peaks. Optical rotations were measured on a Perkin elmer 341 polarimeter using a 1 ml cell with a 1 dm path length at 20 ºC using the sodium D-line. Microanalysis for carbon, hydrogen and nitrogen were performed by Mr Stephen Boyer at the London Metropolitan University.

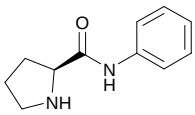
2. Synthesis of organocatalysts.

(*S*)-*N*-(2,4-dimethyl-1,8-naphthyridin-7-yl)pyrrolidine-2-carboxamide, ProNap 1.



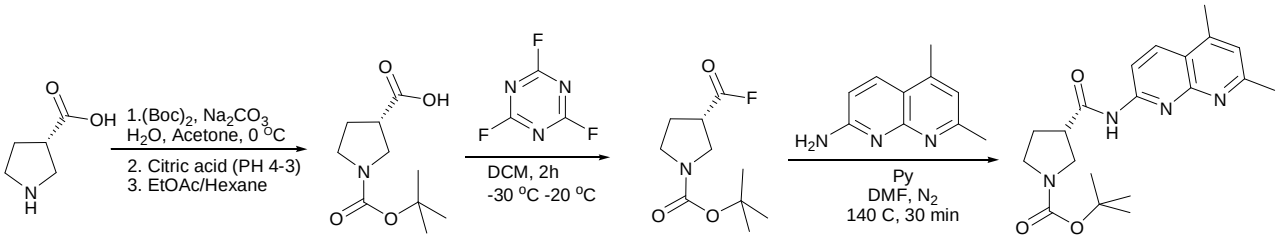
Prepared as previously described.[2] Mp 150-151 ºC; $[\alpha]_D^{rt}$ +35.0 (*c* 0.600, $CHCl_3$); IR (KBr**,** cm^{-1}) 3269, 2959, 2882, 1701, 1599, 1510, 1434, 1398, 1310 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ= 10.59 (1H, br s), 8.43 (1H, d, *J* 9.0 Hz), 8.23 (1H, d, *J* 9.0 Hz), 7.03 (1H, s), 3.87 (1H, dd, *J* 9.3, 5.0 Hz), 2.93-3.07 (2H, m), 2.63 (3H, s), 2.57 (3H, s), 1.95-2.24 (2H, m , 1H brs), 1.66-1.77 (2H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ= 175.5, 163.1, 155.2, 153.1, 145.6, 135.7, 122.5, 118.9, 113.7, 61.5, 47.7, 31.4, 26.6, 25.9, 18.4; MS (TOF ES) m/z: 293.2 (MNa^+, 5%), 271.2 (MH^+, 100); Found (TOF ES) 271.1555 (MH^+), $C_{15}H_{19}N_4O$ requires 271.1559. Elem. Anal. Found: C, 66.67; H, 6.80; N, 20.75. Calcd. for $C_{15}H_{18}N_4O$: C, 66.64; H, 6.71; N, 20.73.

(*S*)-N-phenylpyrrolidine-2-carboxamide, 17.



Prepared as previously described.[3] ^{1}H NMR (360 MHz, $CDCl_3$) δ= 9.76 (1H, br s), 7.61 (2H, d, *J* 7.7 Hz), 7.35-7.29 (2H, m), 7.11-7.06 (1H, m), 3.83 (1H, dd, *J* 9.1, 5.2 Hz), 3.10-2.93 (2H, m), 2.27 (1H, br s), 2.23-1.99 (2H, m), 1.78-1.69 (2H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ= 174.0, 138.3, 129.3, 124.3, 119.7, 61.4, 47.8, 31.2, 26.8; MS (TOF ES) m/z: 191.2 (MH^+, 100%).

Synthesis of (*S*)-tert-butyl 3-(2,4-dimethyl-1,8-naphthyridin-7-ylcarbamoyl)pyrrolidine-1-carboxylate, Boc-β-ProNap.

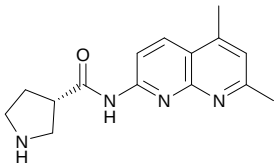


A mixture of (*S*)-β-proline (0.5g, 4.34 mmol), di-*tert*-butyl dicarbonate (1.14g, 5.2 mmol) and sodium carbonate (0.2 g, 1.9 mmol) was dissolved in water (5 mL) and diluted with acetone (15 mL). The flask was placed in an ice bath and the reaction mixture stirred for 3 hours. After this time, acetone was evaporated at reduced pressure, and the mixture was treated with citric acid until a pH 3-4 was reached. The mixture was extracted three times with EtOAc (20 ml) and the collected organic layers were dried over $MgSO_4$. The solvent was reduced under vacuum till ca 5 mL of solvent were left and following addition of hexane (30 mL) *N*-Boc-(*S*)-β-proline was obtained as a white solid (0.63 g, 2.9 mmol, 67%) and was used without further purification in the next step.[1]

To a stirred suspension of the *N*- Boc-(*S*)-β-proline (0.215 g, 1 mmol) in dry DCM (6 mL) and pyridine (0.082 ml, 1 mmol) under a N_2 atmosphere was added cyanuric fluoride (0.11 ml, 1.2 mmol) at –30 °C. A white precipitate formed and gradually increased in amount. After stirring at -30 to -20 °C for 2 h, crushed ice with cold water (5 mL) was added along with 10 ml of additional DCM. The organic layer was separated and the aqueous layer extracted with DCM (1 x 10 ml). The combined organic layers were washed with 10 ml of water, dried over anhydrous $MgSO_4$ and the solvent was removed with a rotary evaporator at room temperature to give the corresponding *N*-Boc-(*S*)-β-proline acid fluoride as colourless oil which was used straightforward in the next step.

N-Boc-(*S*)-β-proline acid fluoride obtained from the previous step (0.217 g, 1.0 mmol) was dissolved in dry DMF (3 mL) and added under a nitrogen atmosphere to a 5 ml microwave process vial containing 5,7-dimethyl-1,8-naphthyridin-2-amine (208 mg, 1.2 mmol). Anhydrous pyridine (0.14 ml, 1.73 mmol) was added and the reaction mixture was heated by microwave irradiation at 140 °C for 30 min. After being cooled to ambient temperature the mixture was diluted with DCM (20 mL) and washed with water 2 x 15 (mL). The organic layer was dried over anhydrous $MgSO_4$ and the solvent was removed with a rotary evaporator. The crude product was purified by chromatography on a SiO_2 column using EtOAc/MeOH 10:1 as eluent to give Boc-β-ProNap (261 mg, 0.71 mmol, 71%) as a yellow solid. Mp 210-212 ºC; $[\alpha]_D^{20}$ +12.6 (*c* 1.0, $CHCl_3$); IR (KBr, cm^{-1}) 3140, 3183, 2973, 2892, 1701, 1599, 1509, 1401, 1278 and 1146cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ= 9.51 (1H, brs, NH), 8.45 (1H, d, *J* 9.0 Hz, Ar*H*), 8.33 (1H, d, *J* 9.0 Hz, Ar*H*), 7.11 (1H, s, Ar*H*), 3.75-3.46 (3H, m, NHCH_2C*H*), 3.38-3.21 (2H, m, CH_2CH_2NH), 2.67 (3H, s, CH_3*Nap*), 2.64 (3H, d, *J* 0.5 Hz, CH_3*Nap*), 2.13-2.20 (2H, m, CH_2CH_2CH), 1.44 (9H, s, (CH_3)$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ= 172.0 (N*C*=O), 163.0 (Ar*C*), 154.5 (O*C*=O), 154.2 (Ar*C*), 153.1 (Ar*C*), 145.3 (Ar*C*), 135.7 (Ar*C*H), 122.5 (Ar*C*H), 118.7 (Ar*C*), 114.0 (Ar*C*H), 79.4 (*C*(CH$_3$)$_3$), 48.4 (N*C*H$_2$CH), 45.7 (*C*H), 45.3 (N*C*H$_2$CH$_2$), 28.8 (CH$_2$*C*H$_2$CH), 28.5 (C(*C*H$_3$)$_3$), 25.4 (CH$_3$), 18.0 (CH$_3$); MS (TOF ES) *m/z*: 393.1 ([MNa]$^+$, 100%), 371.1 ([MH]$^+$, 42); Found (TOF ES) 393.1901 ([MNa]$^+$), $C_{20}H_{26}N_4O_3Na$ requires 393.1903. Elem. Anal. Found: C, 64.91; H, 7.12; N, 15.12. Calcd. for $C_{20}H_{26}N_4O_3$: C, 64.84; H, 7.07; N, 15.12.

(*S*)-*N*-(2,4-dimethyl-1,8-naphthyridin-7-yl)pyrrolidine-3-carboxamide, β-ProNap 18.

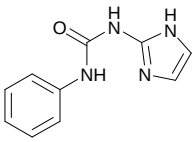


Boc-β-ProNap (261 mg, 0.71 mmol) was dissolved in a mixture of methylene chloride (8 mL) and trifluoroacetic acid (3 mL) and stirred at room temperature for 2 hours. The resulting reaction mixture was concentrated under reduced pressure and saturated aqueous sodium bicarbonate was added slowly to the reaction residue to make weakly alkaline. The reaction mixture thus obtained was extracted with a mixture of chloroform/2-propanol 3:1 (2 x 10 mL). The combined organic extract was dried over anhydrous $MgSO_4$ and the solvent was removed with a rotary evaporator to afford β-ProNap **18** as a pale yellow solid (179 mg, 0.66 mmol, 93%). Mp 204-206 ºC; $[\alpha]_D^{20}$ +20.8 (*c* 0.125, H_2O); IR (KBr, cm^{-1}) 3182, 3030, 2811, 1687, 1613, 1580, 1532, 1512, 1408, 1312, 1199, 1169 and 1130 cm^{-1}; ^{1}H NMR (300 MHz, MeOD) δ= 8.48 (1H, d, *J* 9.0 Hz, Ar*H*), 8.36 (1H, d, *J* 9.0 Hz, Ar*H*), 7.27 (1H, s, Ar*H*), 3.70-3.34

(5H, m, C*H*$_2$NHC*H*$_2$C*H*), 2.68 (6H, s, 2xC*H*$_3$), 2.51-2.39 (1H, m, CH$_2$C*H*$_2$CH), 2.36-2.25 (1H, m, CH$_2$C*H*$_2$CH); ^{13}C NMR (75 MHz, MeOD) δ= 173.9 (*C*=O), 164.0 (Ar*C*), 155.5 (Ar*C*), 154.9 (Ar*C*), 148.5 (Ar*C*), 137.1 (Ar*C*H), 123.6 (Ar*C*H), 120.0 (Ar*C*), 115.2 (Ar*C*H), 49.0 (N*C*H$_2$CH), 46.8 (N*C*H$_2$CH$_2$), 45.4 (*C*H), 30.5 (CH$_2$*C*H$_2$CH), 25.0 (CH$_3$), 18.1 (CH$_3$); MS (TOF ES) *m/z*: 271.1 ([MH]$^+$, 100%); Found (TOF ES) 271.1557 ([MH]$^+$), $C_{15}H_{19}N_4O$ requires 271.1559.

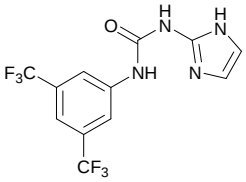
3. Synthesis of ureidoimidazoles.

1-(1H-imidazol-2-yl)-3-phenylurea, 10.



Ureidoimidazole **10** was prepared as described by Wilson *et al.*[4] ^{1}H NMR (300 MHz, DMSO-d$_6$) δ= 10.51 (2H, brs, NH), 9.60 (1H, brs, NH), 7.48 (2H, d, *J* 7.8 Hz, ArC*H*), 7.29 (2H, t, *J* 7.9 Hz, ArC*H*), 6.99 (1H, t, *J* 7.4 Hz, ArC*H*), 6.70 (2H, s, *im*C*H*); ^{13}C NMR (75 MHz, DMSO-d$_6$) δ= 152.5, 143.6, 139.2, 128.8, 122.2, 118.4, 114.0; MS (ES) *m/z*: 203.1 ([MH]$^+$, 100%).

1-(3,5-bis(trifluoromethyl)phenyl)-3-(1H-imidazol-2-yl)urea, 11.

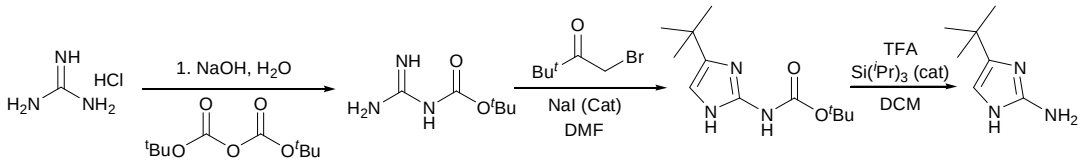


To a stirred solution of 2-aminoimidazole sulphate (1.15 g, 4.35 mmol) in water (5.0 mL) was added sodium carbonate (0.461 g, 4.35 mmol). The reaction mixture was stirred for one hour and was then concentrated to leave a brown viscous solid. Ethanol (30 mL) was added and the resulting mixture was stirred for one hour and then filtered through a pad of celite, concentrated and dried under vacuum. The resultant free amine was placed under a N_2 atmosphere and anhydrous THF (60 mL) and triethylamine (1.84 mL, 13.1 mmol) were added. 3,5-Bis(trifluoromethyl-phenyl)isocyanate (0.5 mL, 2.91 mmol) was then added dropwise in THF (25 mL) over a period of 20 minutes. The solution was stirred overnight and was then concentrated to 4 mL and diluted with dichloromethane (40 mL). The resulting white precipitate was filtered and dried thoroughly to give the product (0.427 g, 1.26 mmol, 43%) as a white solid, Mp 194-196 ºC; IR (KBr, cm^{-1}) 3424, 3403, 3271, 3012, 1708, 1577, 1474, 1390, 1334, 1135 and 1057 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d$_6$) δ= 11.71 (2H, brs, NH), 9.78 (1H, brs, NH), 8.28 (2H, s,

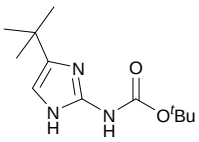
ArC*H*), 7.50 (1H, s, ArC*H*), 6.72 (2H, s, *im*C*H*); ^{13}C NMR (100 MHz, DMSO-d_6) δ= 157.6, 147.0, 143.1, 130.4 (q, *J* 32.3), 123.4, (q, *J* 272.7), 117.3, 114.3, 113.0; ^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$) δ= –62.19; MS (TOF CI) *m/z*: 339.1 ($[MH]^+$, 90%), 319.1 (96), 230.1 (17), 210.0 (27), 110.0 (100), 84.1 (22); Found (TOF CI) 339.0685 ($[MH]^+$), $C_{12}H_9N_4OF_6$ requires 339.0681. Elem. Anal. Found: C, 42.72; H, 2.22; N, 16.49. Calcd. for $C_{12}H_8F_6N_4O$: C, 42.62; H, 2.38; N, 16.57.

Synthesis of ureido-4-*tert*-butyl-imidazoles.

Ureidoimidazole **12** was prepared as described by Wilson *et al.*[4]

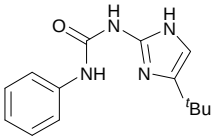


2-*tert*-Butoxyamido-4-*tert*-butylimidazole.[4]



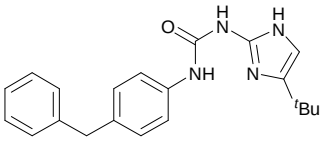
^{1}H NMR (400 MHz, $CDCl_3$) δ= 6.43 (1H, s, *im*C*H*), 6.02 (2H, brs, NH), 1.57 (9H, s, (CH_3)$_3$), 1.19 (9H, s, *im*(CH_3)$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ= 150.1, 149.6, 148.5, 103.9, 84.4, 31.4, 29.3, 28.0; MS (TOF ES) *m/z*: 240.1 ($[MH]^+$, 100%).

1-(4-tert-butyl-1H-imidazol-2-yl)-3-phenylurea, 12.[4]



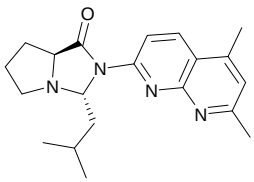
^{1}H NMR (400 MHz, $CDCl_3$) δ= 10.34 (2H, brs, NH), 9.03 (1H, brs, NH), 7.34 (2H, d, *J* 7.8 Hz, ArC*H*), 7.25 (2H, t, *J* 7.8 Hz, ArC*H*), 7.03 (1H, *J* 7.3 Hz, ArC*H*), 6.24 (2H, s, *im*C*H*), 1.23 (9H, s, (CH_3)$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ= 154.1, 143.6, 138.2, 128.9, 123.4, 119.8, 30.6, 29.7; MS (TOF ES) *m/z*: 259.0 ($[MH]^+$, 100%).

1-(4-*tert*-butyl-1H-imidazol-2-yl)-3-(4-benzylphenyl)urea, 13.



2-*tert*-Butoxyamido-4-*tert*-butylimidazole (0.450 g, 2.32 mmol) was dissolved in a mixture of methylene chloride (14 mL), trifluoroacetic acid (7 mL) and triisopropylsilane (3 drops, cat.) and the mixture was stirred at room temperature for 3 hours. The resulting reaction mixture was concentrated under reduced pressure and dried under vacuum. The resulted deprotected amine was dissolved in dry THF (20 mL) and triethyl amine (1.55 mL, 11.0 mL) and heated to reflux under N_2. 4-Benzylphenylisocyanate (0.41 mL, 2.20 mmol) in dry THF (15 mL) was added dropwise, using an addition funnel, over 30 minutes and the reaction stirred at reflux for 15 hours. After cooling at room temperature the solvent was removed under reduce pressure and the reaction mixture partitioned between methylene chloride and 1M HCl. The layers were separated and the aqueous phase extracted with DCM (2 x 15 mL). The combined organic layers were washed with a saturated solution of sodium bicarbonate (15 mL) and brine (15 mL), dried over anhydrous $MgSO_4$ and the solvent was removed with a rotary evaporator. The crude product was purified by chromatography on a SiO_2 column using 5% MeOH/DCM as eluent to give the desired ureidoimidazole **13** (0.520 g, 1.49 mmol, 68%) as an off-white solid. Mp 74-76 ºC; IR (KBr, cm^{-1}) 3272, 3027, 2966, 1654, 1548, 1513, 1494, 1414, 1317, 1202 and 1139 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ= 11.18 (2H, brs, NH), 9.14 (1H, vbrs, NH), 7.20-6.90 (9H, m, ArC*H*), 6.19 (1H, s, *im*C*H*), 3.80 (2H, s, CH_2), 1.16 (9H, s, (CH_3)$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ= 153.2, 142.3, 141.0, 136.8, 135.5, 129.3, 128.8, 128.4, 126.0, 120.7, 123.4, 119.8, 108.9 (brs, *im*CH), 41.2 (*C*H_2), 30.5 *C*(CH_3)$_3$, 29.4 (*C*H_3)$_3$; MS (TOF ES) *m/z*: 349.1 ([MH]$^+$, 100%); Found (TOF ES) 349.2031 ([MH]$^+$), $C_{21}H_{25}N_4O$ requires 349.2028.

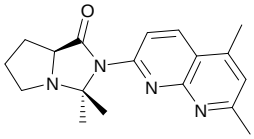
(3R,7aS)-hexahydro-3-isobutyl-2-(2,4-dimethyl-1,8-naphthyridin-7-yl)pyrrolo[1,2-e]imidazol-1-one, 16b.



Mp 103-104 ºC; $[\alpha]_D^{20}$ +49.4 (*c* 1.6, $CHCl_3$); IR ($CDCl_3$, cm^{-1}) 2958, 2927, 2871, 1707, 1598, 1509, 1406, 1368, 1314, 1181 and 1145 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ= 8.58 (1H, d, *J* 9.0 Hz, Ar*H*), 8.29 (1H, d, *J* 9.0 Hz, Ar*H*), 7.12 (1H, d, *J* 0.7 Hz, Ar*H*), 5.84 (1H, dd, *J* 9.6, 3.1 Hz, N-C*H*-N), 4.09

(1H, dd, *J* 9.2, 4.1, Hz, C*H*-C=O), 3.28-3.22 (1H, m, CH_2N), 2.72 (3H, s, CH_3*Nap*), 2.68-2.62 (1H, m, CH_2N), 2.64 (3H, d, *J* 0.7 Hz, CH_3*Nap*), 2.30-1.73 (6H, m, CH_2CH_2, CH_2C*H*-(CH_3)$_2$), 1.54 (1H, ddd, *J* 13.3, 9.6, 4.9 Hz, CH_2CH-(CH_3)$_2$), 1.09 (3H, d, *J* 6.6 Hz CH_3), 0.94 (3H, d, *J* 6.7 Hz CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ= 176.5 (*C*=O), 162.8 (Ar*C*), 154.8 (Ar*C*), 152.4 (Ar*C*), 145.1 (Ar*C*), 134.8 (Ar*C*H), 122.5 (Ar*C*H), 118.4 (Ar*C*), 113.9 (Ar*C*H), 79.2 (N-*C*H-N), 65.6 (*C*H-C=O), 55.1 (*C*H_2N), 42.9 (*C*H_2CH-(CH_3)$_2$), 27.3 (*C*H_2), 25.5 (*C*H_3*Nap*), 25.1 (*C*H(CH_3)$_2$), 24.8 (*C*H_2), 23.5 (*C*H_3), 22.2 (*C*H_3), 18.0 (*C*H_3*Nap*); MS (NSI) *m/z*: 339.2 ([MH]$^+$, 100%), 271.2 (52); Found (NSI) 339.2179 ([MH]$^+$), $C_{20}H_{27}N_4O$ requires 339.2179.

(*S*)-hexahydro-3,3-dimethyl-2-(2,4-dimethyl-1,8-naphthyridin-7-yl)pyrrolo[1,2-e]imidazol-1-one, 16a.



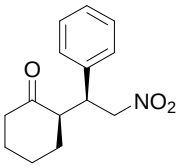
(*S*)-ProNap **1** (35 mg, 0.13 mmol) was dissolved in acetone (2 mL) and anhydrous K_2CO_3 (0.36 g) was added. The mixture was stirred at room temperature under N_2 for 24 h and the filtered *via* cannula into a Sclenck tube. Acetone was then removed under vacuum and the resulting crude mixture was dissolved in benzene-d6 under N_2 and analysed by ^{1}H-NMR. The desired product **16a** was obtained as a 4:1 mixture with ProNap **1**. The same experiment carried out with normal work up in air and $CDCl_3$ as solvent afforded **15a** as a 1:2.5 mixture with ProNap **1**. ^{1}H NMR (400 MHz, C_6D_6) δ= 8.60 (1H, d, *J* 9.0 Hz, Ar*H*), 7.72 (1H, d, *J* 9.0 Hz, Ar*H*), 6.50 (1H, d, *J* 0.9 Hz, Ar*H*), 3.81 (1H, dd, *J* 9.7, 4.3, Hz, C*H*-C=O), 2.65-2.68 (1H, m, CH_2N), 2.53 (3H, s, CH_3*Nap*), 2.14-2.25 (2H, m, CH_2), 2.04 (3H, s, CH_3), 1.98 (3H, d, *J* 0.9 Hz, CH_3*Nap*), 1.92-1.97 (1H, m, CH_2), 1.89 (3H, s, CH_3) 1.38-1.61 (2H, m, CH_2); ^{13}C NMR (100 MHz, C_6D_6) δ= 177.5 (*C*=O), 162.2 (Ar*C*), 155.2 (Ar*C*), 153.9 (Ar*C*), 144.5 (Ar*C*), 134.4 (Ar*C*H), 122.1 (Ar*C*H), 118.3 (Ar*C*), 116.2 (Ar*C*H), 82.9 (N-*C*-N), 63.9 (*C*H-C=O), 48.3 (*C*H_2N), 27.8 (*C*H_3*Nap*), 26.4 (*C*H_2), 25.0 (*C*H_3), 25.1 (*C*H_2), 23.5 (*C*H_3), 17.5 (*C*H_3*Nap*); MS (ES$^+$) *m/z*: 311.1 ([MH]$^+$, 100%); Found (ES$^+$) 311.1872 ([MH]$^+$), $C_{18}H_{23}N_4O$ requires 311.1872.

4. General procedure for the conjugate addition of a ketone (aldehyde) to a nitroolefin.

Catalyst (10 mol%) and additive (10 mol%) were stirred in $CHCl_3$ (2 ml) for 30 minutes. The relevant ketone (1.2 mmol) and nitroolefin (0.25 mmol) were added to the catalyst suspension. The resulting mixture was stirred for the time and temperature required. The reaction was quenched with 1 ml of HCl

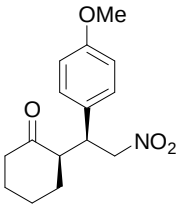
1M, diluted with DCM (1ml) and H_2O (1 ml) and the aqueous phase extracted with DCM (3 x 5 ml). The combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography to give the Michael products. The ee of the product was determined by chiral HPLC analysis. Relative (*syn*) and absolute configuration of the product was determined by comparison with the known ^{1}H NMR data and optical rotation values.

(*R*)-2-((*S*)-2-nitro-1-phenylethyl)cyclohexanone, 9a (obtained using (*R*)-ProNap, **1**).[5]



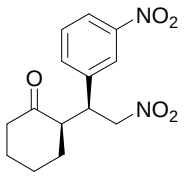
^{1}H NMR (360 MHz, $CDCl_3$) δ= 1.10-1.23 (1H, m), 1.43-1.73 (4H, m), 1.97-2.05 (1H, m), 2.26-2.45 (2H, m), 2.57-2.66 (1H, m), 3.65-3.73 (1H, m), 4.56 (1H, dd, *J* 12.5, 9.9 Hz), 4.87 (1H, dd, *J* 12.5, 4.5 Hz), 7.07-7.28 (5H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ= 25.0, 28.5, 33.2, 42.8, 44.0, 52.5, 78.9, 127.8, 128.2, 129.0, 137.8, 212.0. The enantiomeric excess was determined by chiral HPLC with a Chiralpack AD-H column at 210 nm (hexane:2-propanol 90:10), 1.0 ml/min; t_r= 11.6 min (major), 14.8 min (minor). Absolute configuration: *R*, *S* by comparison with sign of optical rotation with literature values.[5(c)]

(*R*)-2-((*S*)-1-(4-methoxyphenyl)-2-nitroethyl)cyclohexanone, 9b (obtained using (*R*)-ProNap, **1**).[5(b)]



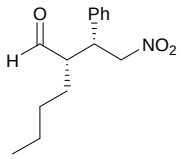
^{1}H NMR (360 MHz, $CDCl_3$) δ= 1.10-1.23 (1H, m), 1.44-1.74 (4H, m), 1.98-2.04 (1H, m), 2.26-2.43 (2H, m), 2.53-2.62 (1H, m), 3.60-3.68 (1H, m), 3.71 (3H, s), 4.51 (1H, dd, *J* 12.3, 9.9 Hz), 4.84 (1H, dd, *J* 12.3, 4.6 Hz), 6.78 (2H, d, *J* 8.7 Hz), 7.01 (2H, d, *J* 8.7 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ= 25.0, 28.5, 33.2, 42.7, 43.2, 52.7, 55.2, 79.1, 114.3, 129.2, 129.5, 159.0, 212.1. The enantiomeric excess was determined by chiral HPLC with a Chiralpack AD column at 254 nm (hexane:2-propanol 95:5), 1 ml/min; t_r= 21.6 min (major), 27.3 min (minor). Absolute configuration: *R*, *S* by comparison with sign of optical rotation with literature values. [5(b)]

(*R*)-2-((*S*)-2-nitro-1-(3-nitrophenyl)ethyl)cyclohexanone, 9c (obtained using (*R*)-ProNap, **1**).[6]



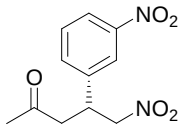
^{1}H NMR (360 MHz, $CDCl_3$) δ= 1.14-1.28 (1H, m), 1.51-1.79 (4H, m), 2.02-2.10 (1H, m), 2.28-2.45 (2H, m), 2.63-2.72 (1H, m), 3.83-3.91 (1H, m), 4.63 (1H, dd, *J* 13.0, 10.1 Hz), 4.94 (1H, dd, *J* 13.0, 4.5 Hz), 7.43-7.52 (2H, m), 8.01-8.10 (2H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ= 25.1, 28.3, 33.2, 42.8, 43.7, 52.3, 78.1, 122.9, 123.0, 130.0, 134.9, 140.2, 148.6, 210.9. The enantiomeric excess was determined by chiral HPLC with a Chiralpack AD-H column at 210 nm (hexane:2-propanol 90:10), 0.5 ml/min; t_r= 52 min (major), 62 min (minor). Absolute configuration: *R, S* by comparison with sign of optical rotation with literature values.[5(c)]

(*S*)-2-((*R*)-2-nitro-1-phenylethyl)hexanal, 9d (obtained using (*S*)-ProNap, **1**).[7]



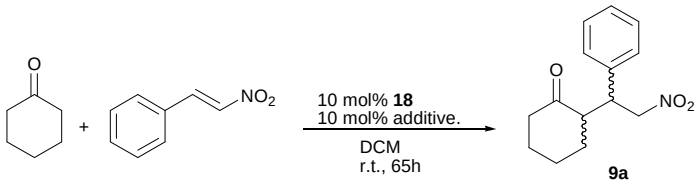
^{1}H NMR (360 MHz, $CDCl_3$) δ= 9.70 (1H, d, *J* 2.8 Hz), 7.37-7.26 (3H, m), 7.19-7.15 (2H, m), 4.71 (1H, dd, *J* 12.8, 5.5 Hz), 4.63 (1H, dd, *J* 12.8, 9.4 Hz), 3.81-3.73 (1H, m), 2.73-2.65 (1H, m), 1.52-1.07 (6H, m), 0.78 (3H, t, *J* 6.9 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ= 203.3, 136.8, 129.0, 128.1, 128.0, 78.5, 53.9, 43.1, 28.4, 27.1, 22.5. 13.5. The enantiomeric excess was determined by chiral HPLC with a Chiralcel OD-H column at 210 nm (hexane:2-propanol 80:20), 1.0 ml/min; t_r= 12.8 min (major), 13.8 min (minor).

5-nitro-4-(3-nitrophenyl)pentan-2-one, **9e** (obtained using (*S*)-ProNap, **1**).[6]



^{1}H NMR (360 MHz, $CDCl_3$) δ= 2.99 (3H, s), 2.85-2.99 (2H, m), 4.04-4.13 (1H, m), 4.59 (1H, dd, *J* 12.8, 8.2 Hz), 4.70 (1H, dd, *J* 12.8, 6.3 Hz), 7.44-7.57 (2H, m), 8.04-8.10 (2H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ= 30.3, 38.5, 45,7, 78.7, 122.2, 123.0, 130.1, 134.3, 141.1, 148.6, 204.5. The enantiomeric excess was determined by chiral HPLC with a Chiralpack AD-H column at 254 nm (hexane:2-propanol 90:10), 1 ml/min; t_r[(–)]= 25.8 min (minor), t_r[(+)]= 28.5 min (major).

Table 1. E.S.I. Nitro-Michael reaction using β-ProNap **18**.



Entry[a]	Addit.	C[%][b]	d.r.[c]	ee[%][d]
1	none	14	26:1	1
2	**5**	49	37:1	2
3	**10**	99	25:1	3
4	**11**	99	18:1	6
5	**12**	99	22:1	5
6	**13**	27	n.d.	1

[a]Reactions carried out at r.t. in 2 ml of dry DCM pre-stirring additive and pre-catalyst for 30 min and using 4.8 eq of ketone; [b]Michael products/(Michael products+nitroalkene)x100 determined by ^{1}H-NMR integration; [c]Ratio determined by ^{1}H-NMR integration after work-up; [d]Determined by chiral HPLC.

5. References.

1. G Cardillo, L. Gentilucci, A. Tolomelli, M. Calienni, A. R. Qasem and S. Spampinato, *Org. Biomol.Chem.*, 2003, 1, 1498.

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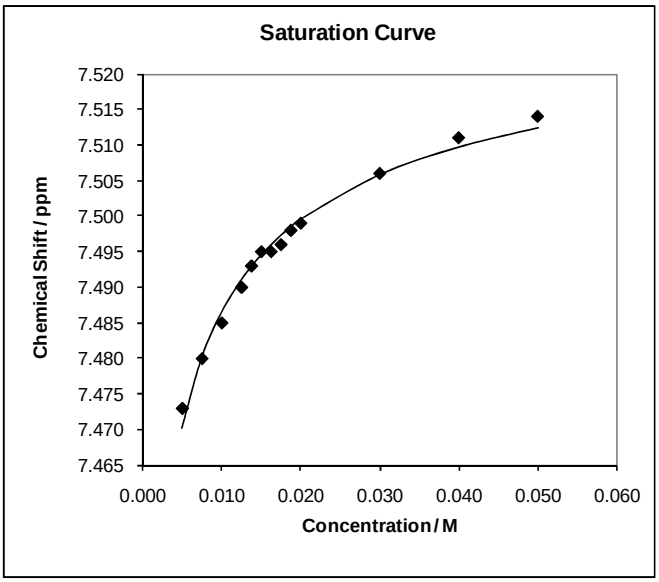
7. M. Wiesner, M. Neuburger and H. Wennemers, *Chem. Eur. J.* 2009, **15**, 10103.

6. Binding constant determination for ProNap 1 and Additive 12.

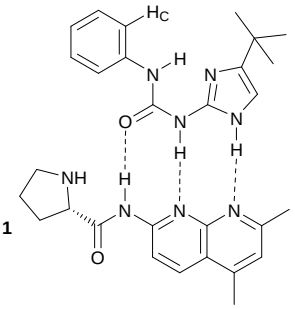
The binding constant value (Ka) was calculated from ^{1}H NMR dilution (1:1 model) data. Experiments were carried out in $CDCl_3$ at 273K.



Host:Guest pair

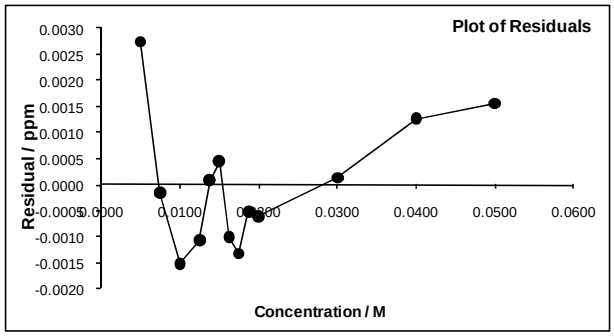
12

(*R*)-ProNap 1



Optimised Value of K_a	ΔG / kcalmol^{-1}
840	-3.79

Conc / M	dobs	dcalc	Residual	SR
0.0050	7.4730	7.4703	0.0027	7.51E-06
0.0075	7.4800	7.4801	-0.0001	2.19E-08
0.0100	7.4850	7.4865	-0.0015	2.29E-06
0.0125	7.4900	7.4911	-0.0011	1.14E-06
0.0138	7.4930	7.4929	0.0001	7.30E-09
0.0150	7.4950	7.4945	0.0005	2.05E-07
0.0163	7.4950	7.4960	-0.0010	1.01E-06
0.0175	7.4960	7.4973	-0.0013	1.74E-06
0.0188	7.4980	7.4985	-0.0005	2.63E-07
0.0200	7.4990	7.4996	-0.0006	3.61E-07
0.0300	7.5060	7.5059	0.0001	1.95E-08
0.0400	7.5110	7.5097	0.0013	1.60E-06
0.0500	7.5140	7.5124	0.0016	2.43E-06
			SSR	1.861E-05



7. NMR spectra of enamine, hemiacetal and pyrroloimidazolidone mixtures.

Figure 1 E.S.I. ^{1}H-NMR spectra (expansion) in $CDCl_3$ of the reaction mixture of *iso*butyraldehyde and ProNap **1** showing the characteristic resonances for the naphthyridine protons.

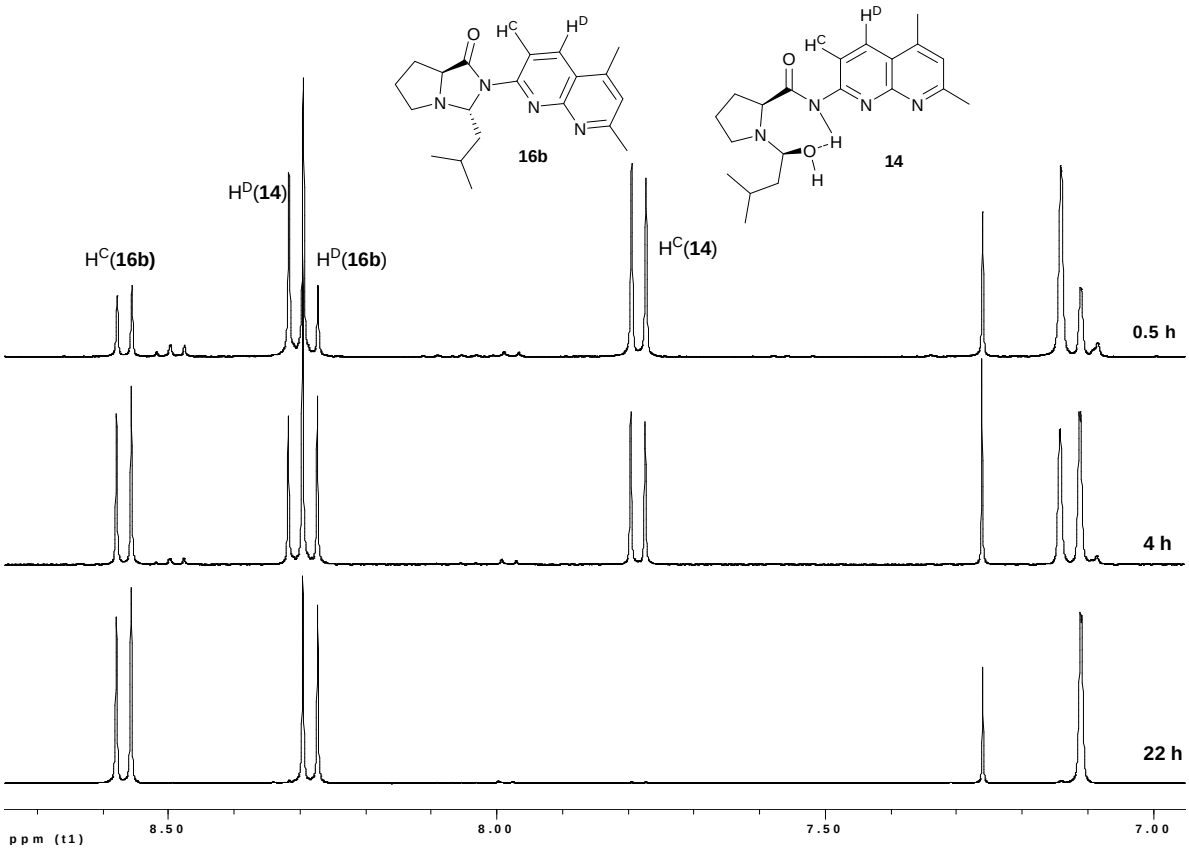
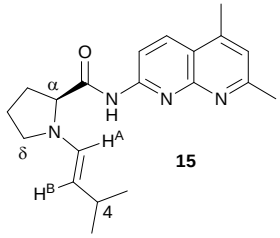


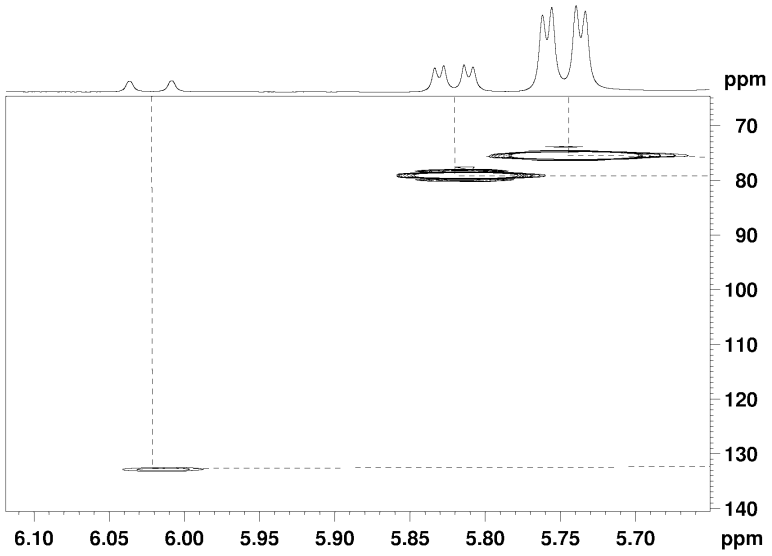
Figure 2 E.S.I. NMR spectroscopy characterisation of enamine **15**: a) Enamine **15**, nomenclature; b) Expansion of $^{1}H,^{13}C$ HSQC spectrum of reaction mixture containing compounds **14**, **15** and **16b** recorded shortly after mixing reagents in a NMR tube at room temperature; c) ^{1}H, ^{13}C HMBC showing long range correlations from H^{A} to Cα, Cδ, C^{B} and C4.

a)



15

b)



c)

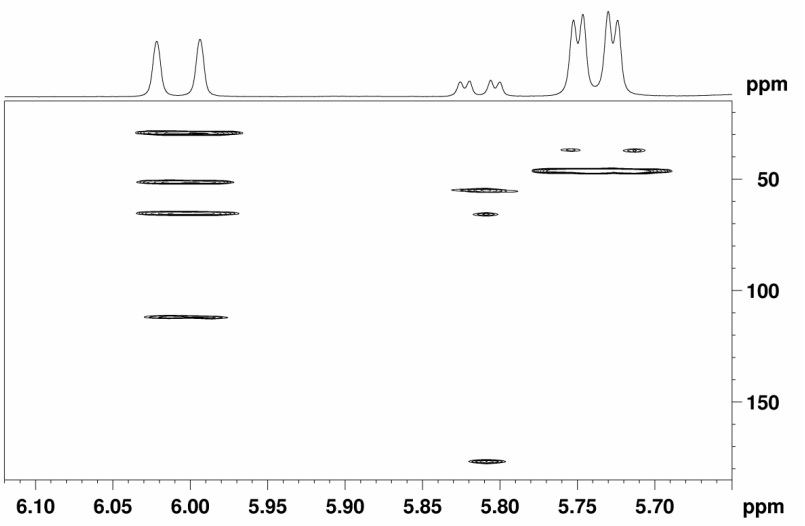


Figure 3 E.S.I.

a) Conventional ^{1}H NMR of **16b** in $CDCl_3$. **b)** 1D gs-NOESY of **16b** in $CDCl_3$ recorded with mixing time 800 ms. The doublet of doublet resonance at 4.09 ppm shows only weak NOE for CH resonance at 5.84 ppm but much stronger NOE for one of diastereotopic protons of the adjacent methylene group (m, 1.54 ppm) which implies *S*, *R*-stereochemistry.

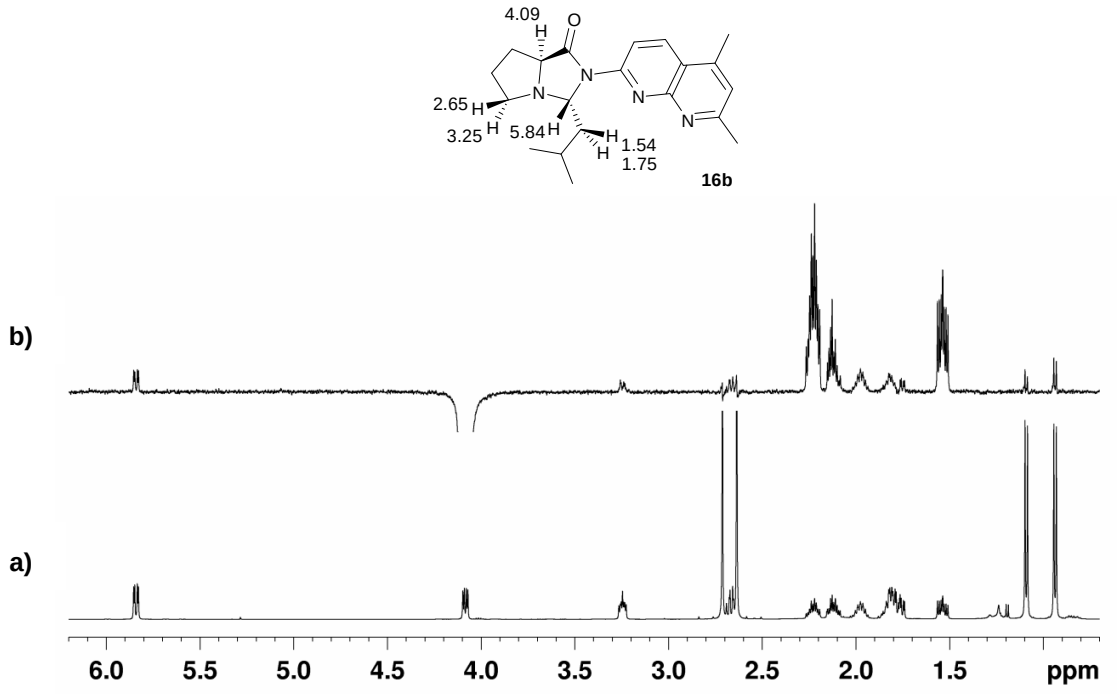


Figure 4 E.S.I. ^{1}H-NMR spectra in $CDCl_3$ of the reaction mixture of *iso*butyraldehyde (1.2 eq) and ProNap **1** (1eq, 0.077 mM) showing the characteristic resonances for pyrroloimidazolidone **16b**, *N-O*-hemiacetal **14** and enamine **15** intermediates and the downfield shift observed for the enamine in the presence of additive **12** (1 eq).

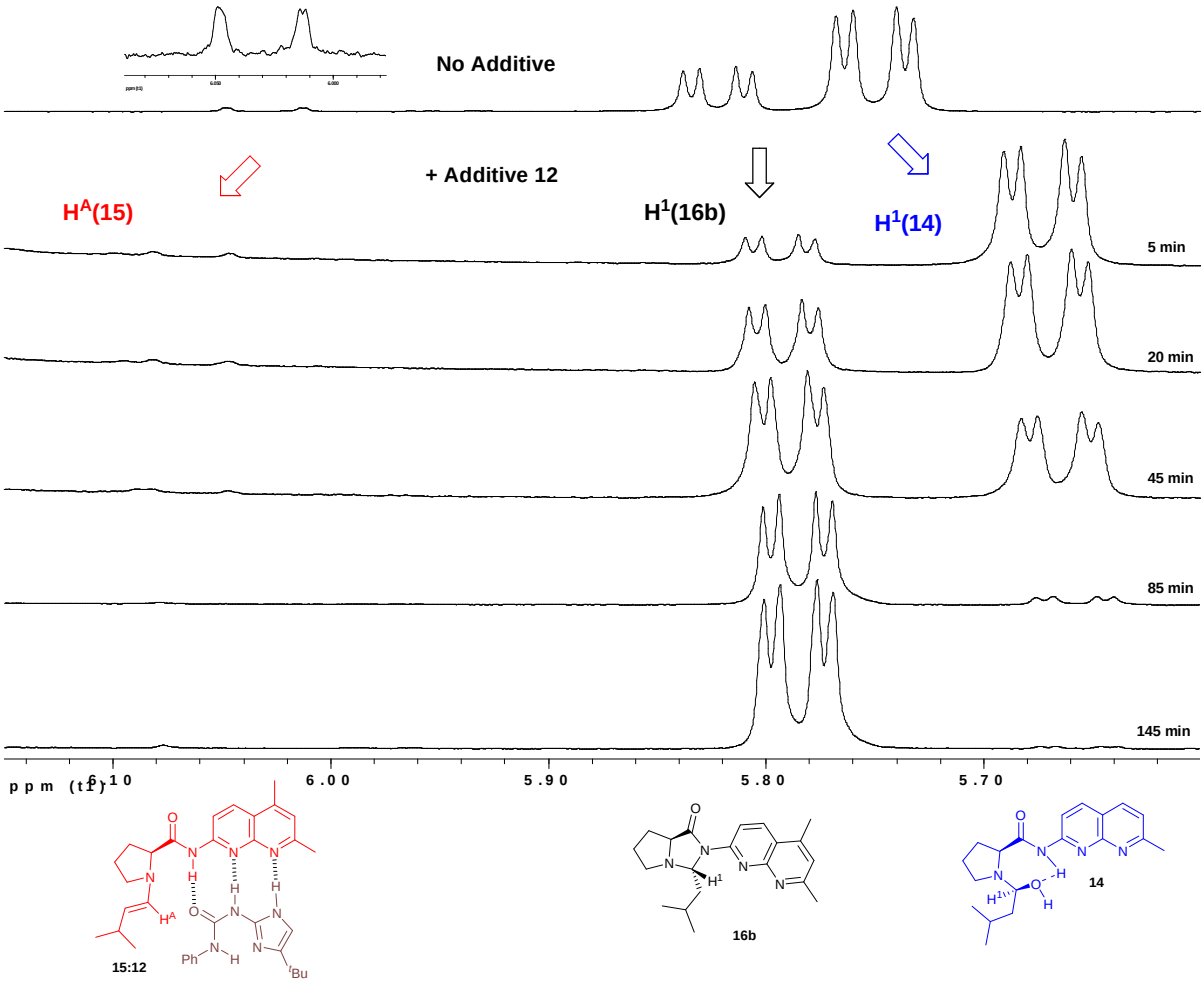
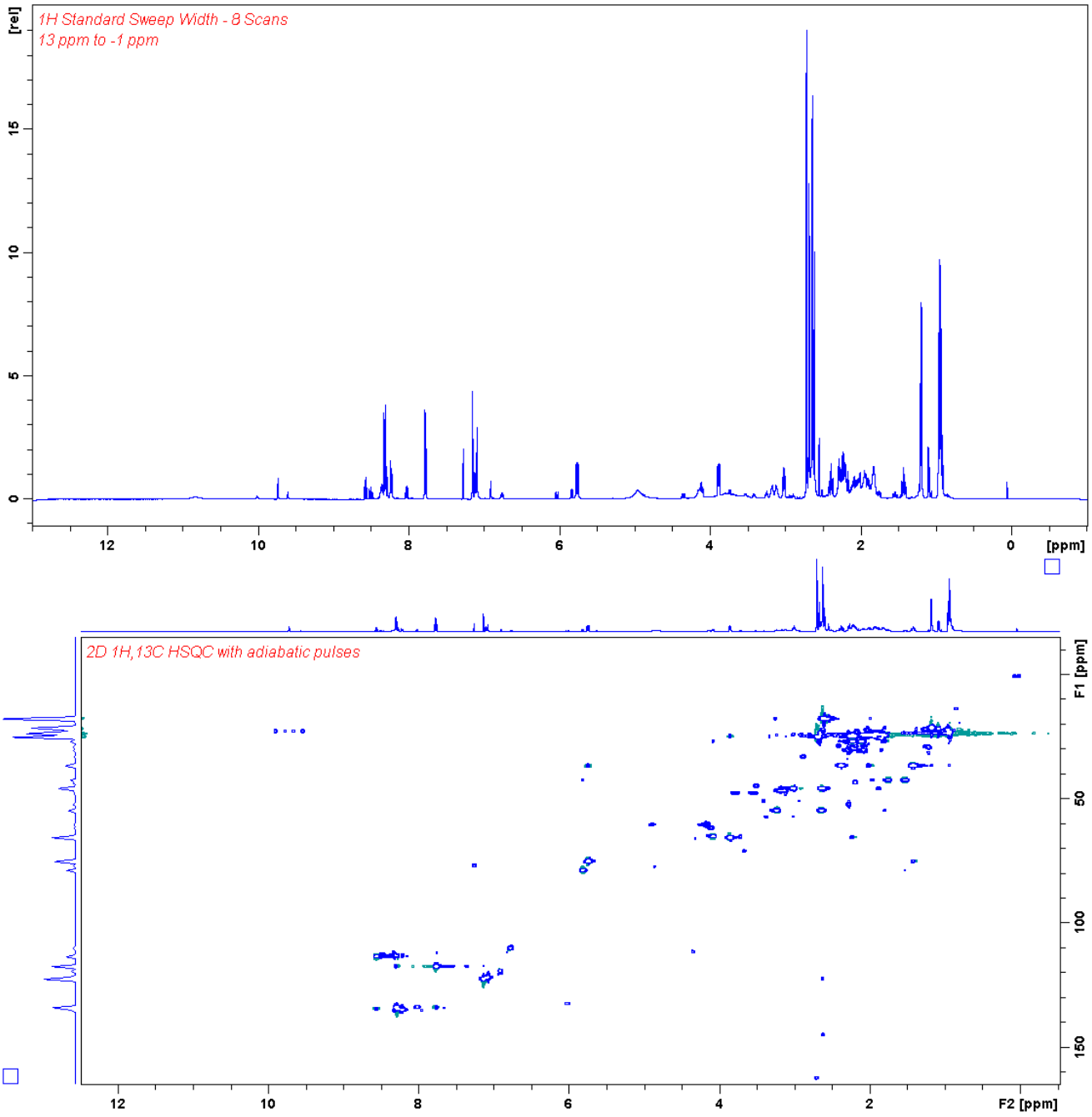


Figure 5 E.S.I.

a) $^{1}H,^{13}C$ HSQC spectrum of reaction mixture containing compounds **14**, **15** and **16b** in $CDCl_3$ recorded shortly after mixing reagents in a NMR tube at room temperature.



b) ^{1}H, ^{13}C HMBC spectrum of reaction mixture containing **14**, **15** and **16b** in $CDCl_3$recorded shortly after mixing reagents in a NMR tube at 273 K in order to obtain higher concentration of intermediate **15**.

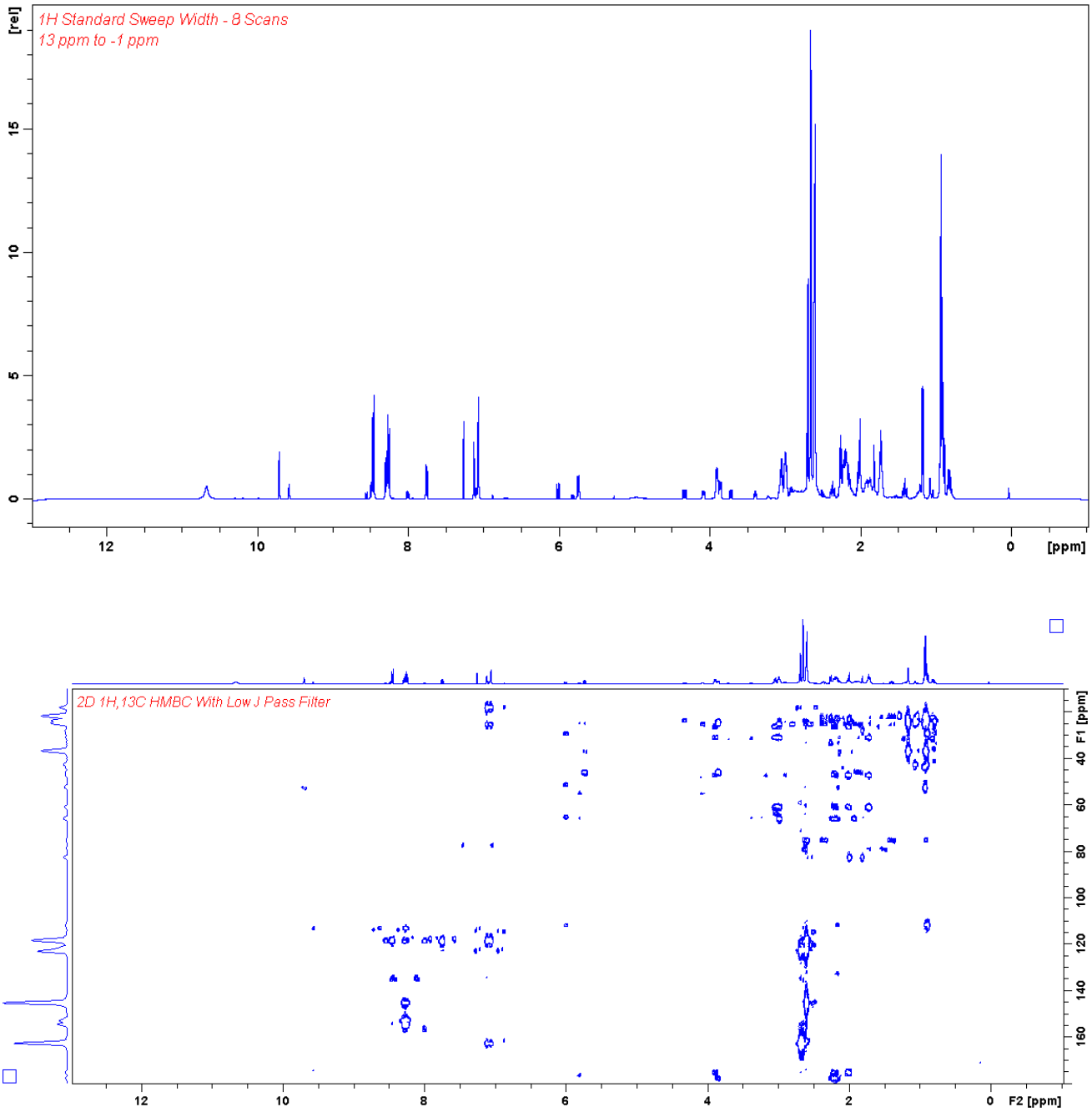
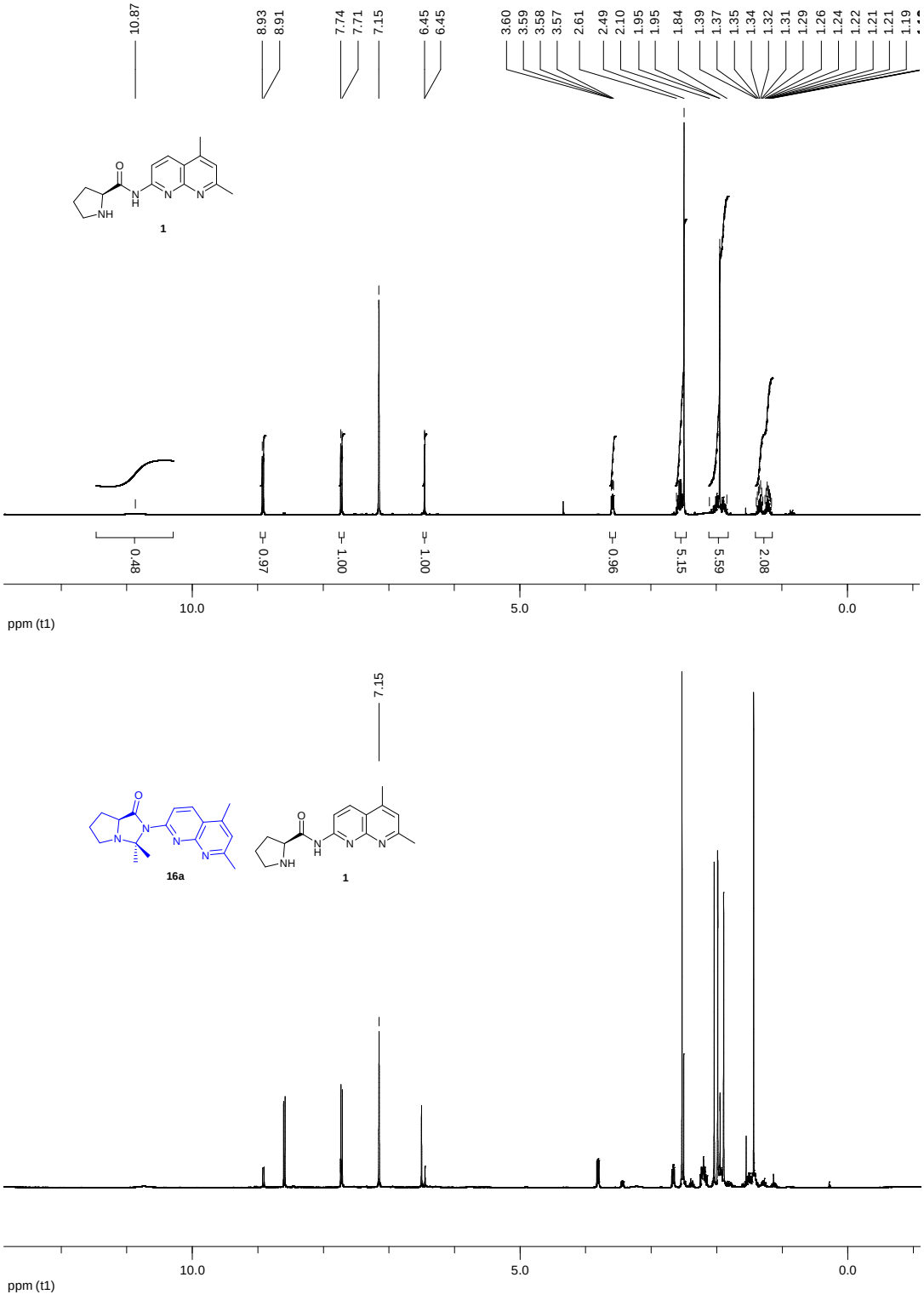
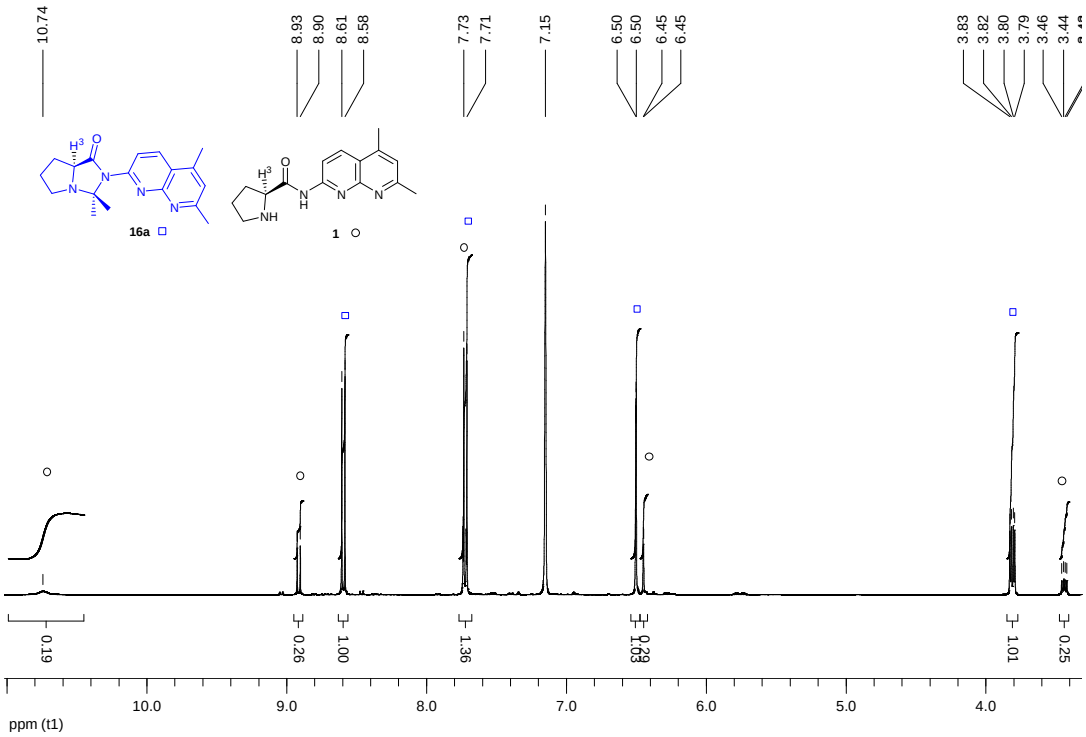


Figure 6 E.S.I.

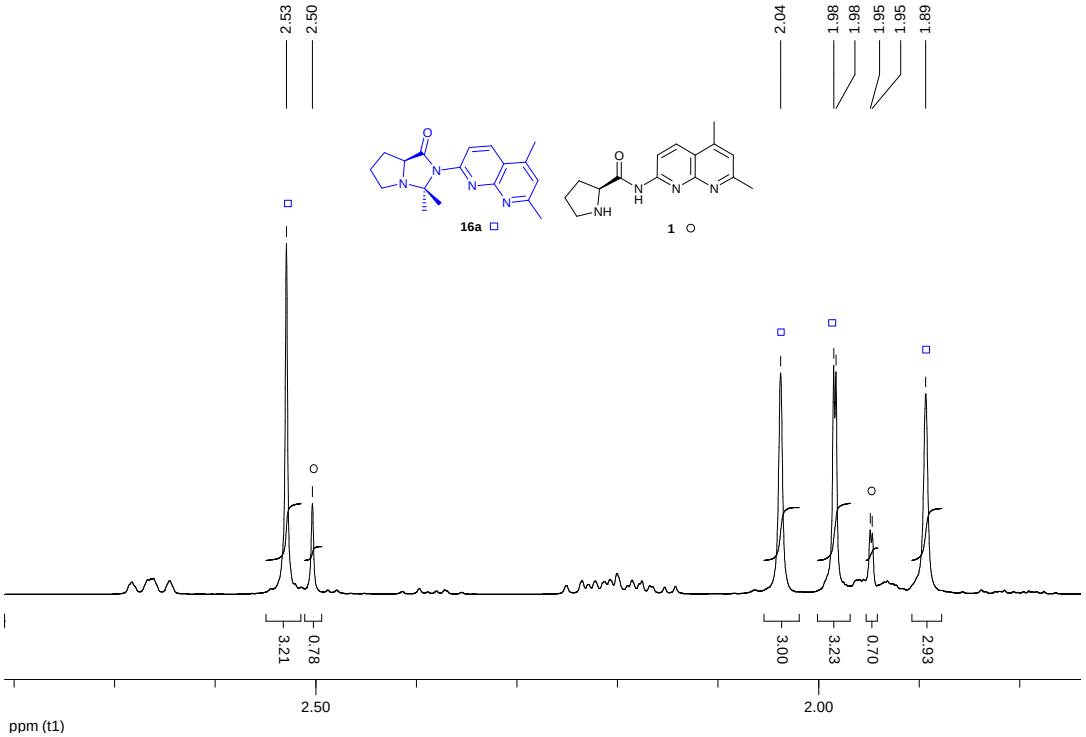
a) ^{1}H NMR spectrum of ProNap **1** and reaction mixture containing compounds **1** and **16a** in C_6D_6.



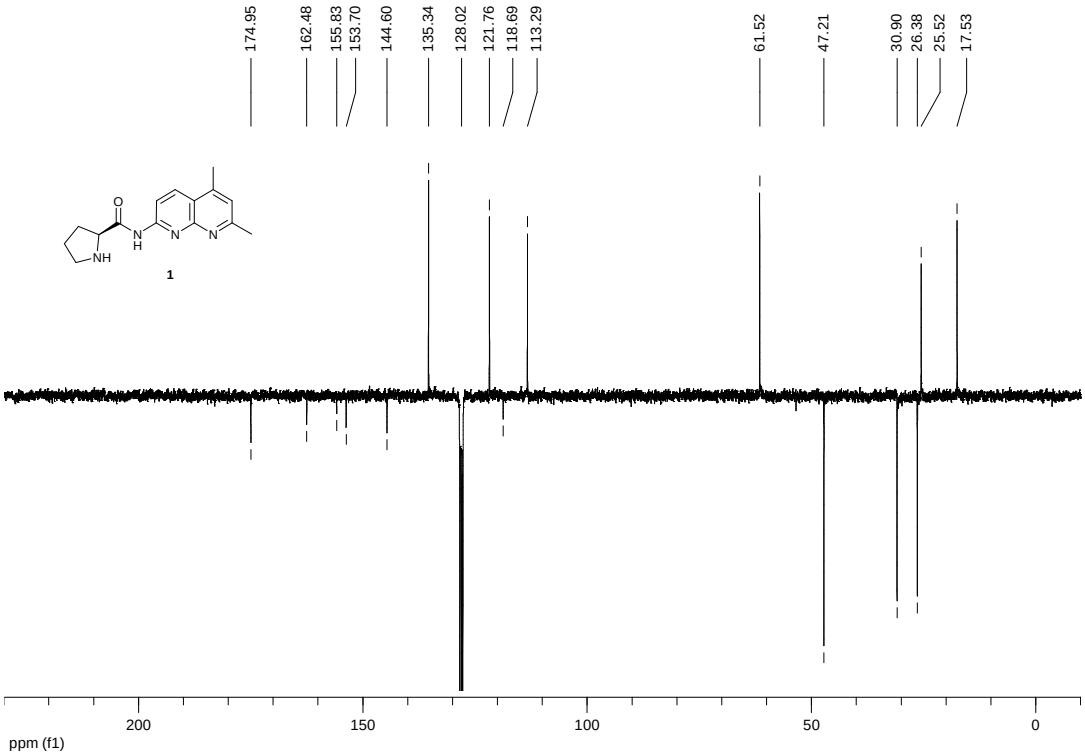
b) ^{1}H NMR expansion of the reaction mixture containing compounds **1** and **16a** in C_6D_6 showing the aromatic region and the characteristic H^3.

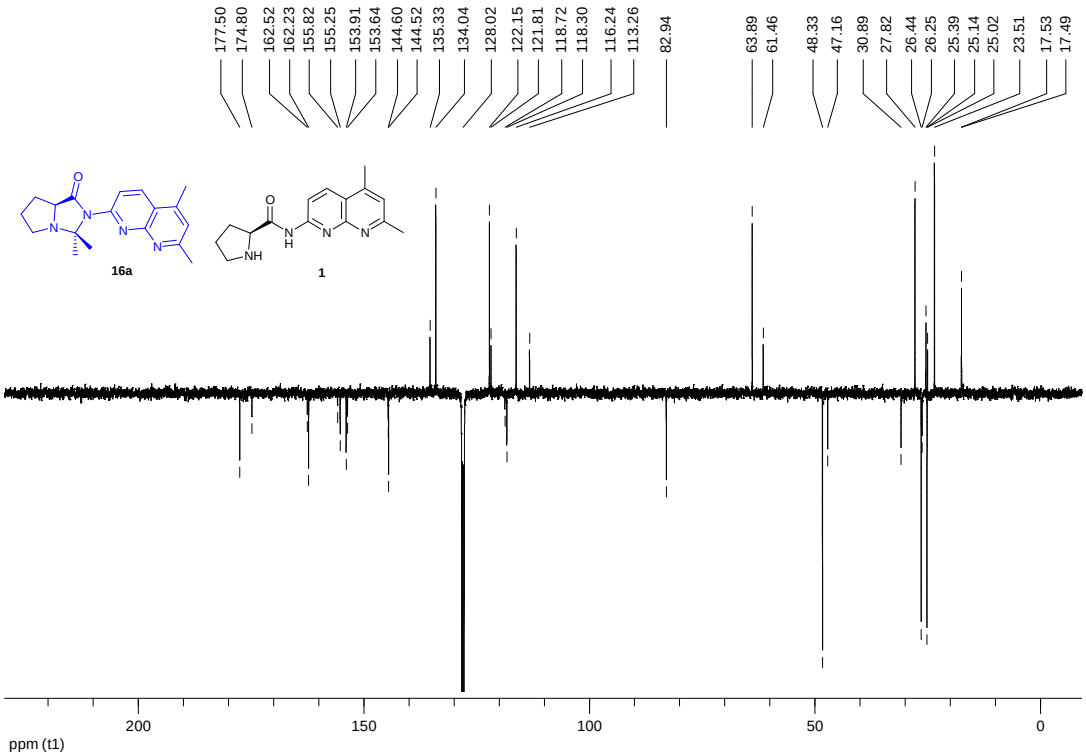


c) ^{1}H NMR expansion of the reaction mixture containing compounds **1** and **16a** in C_6D_6 showing the methyl region.

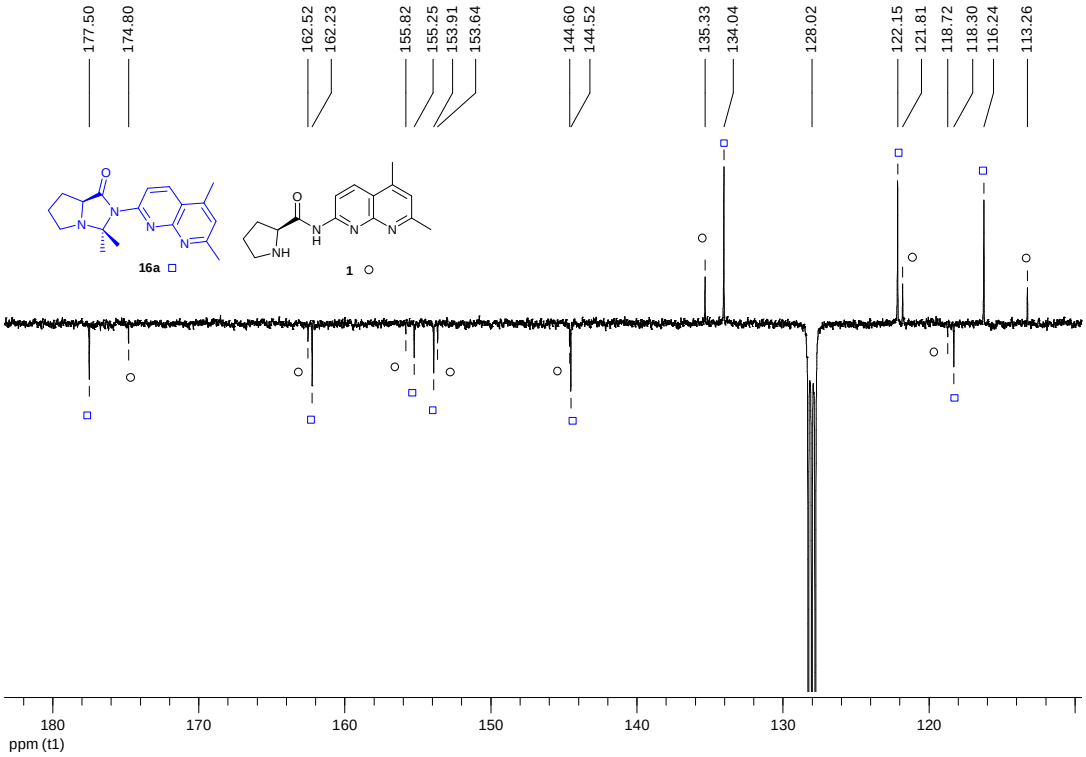


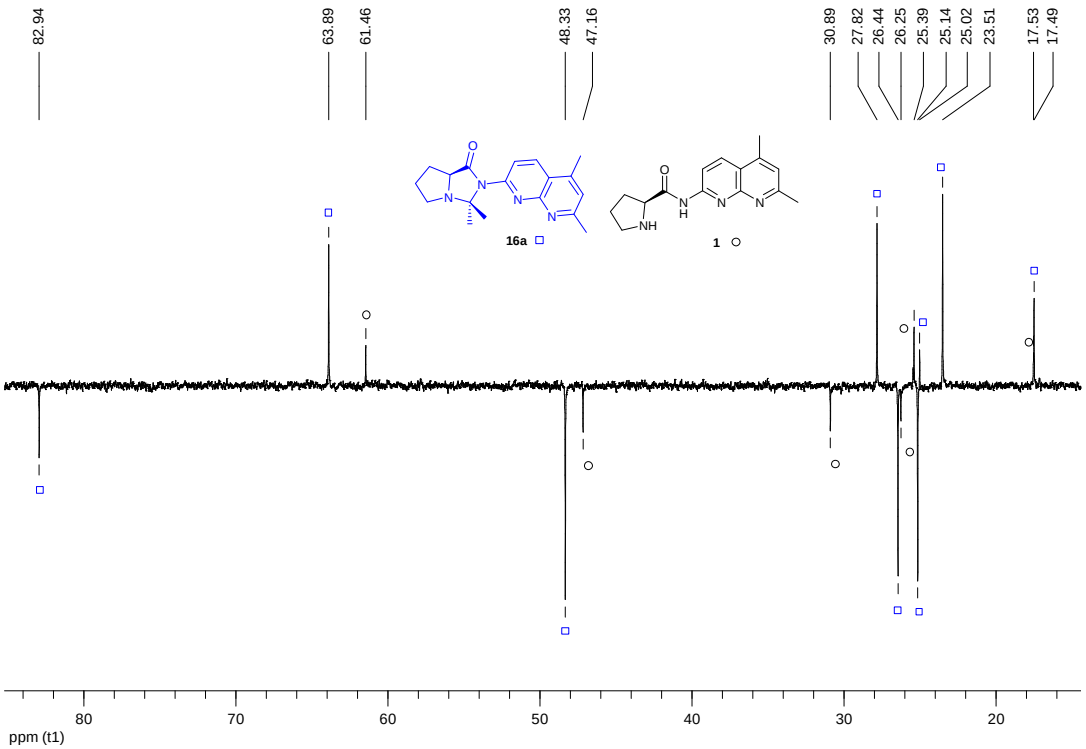
d) ^{13}C NMR spectrum of ProNap **1** and reaction mixture containing compounds **1** and **16a** in C_6D_6.





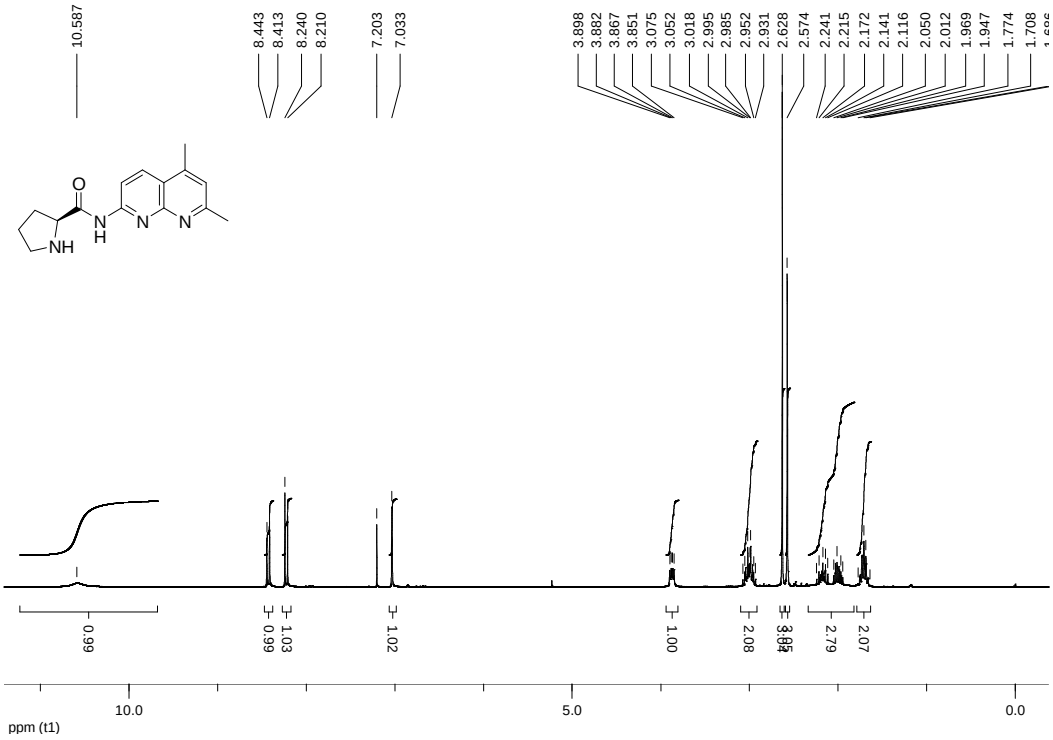
e) ^{13}C NMR expansions of the reaction mixture containing compounds **1** and **16a** in C_6D_6.

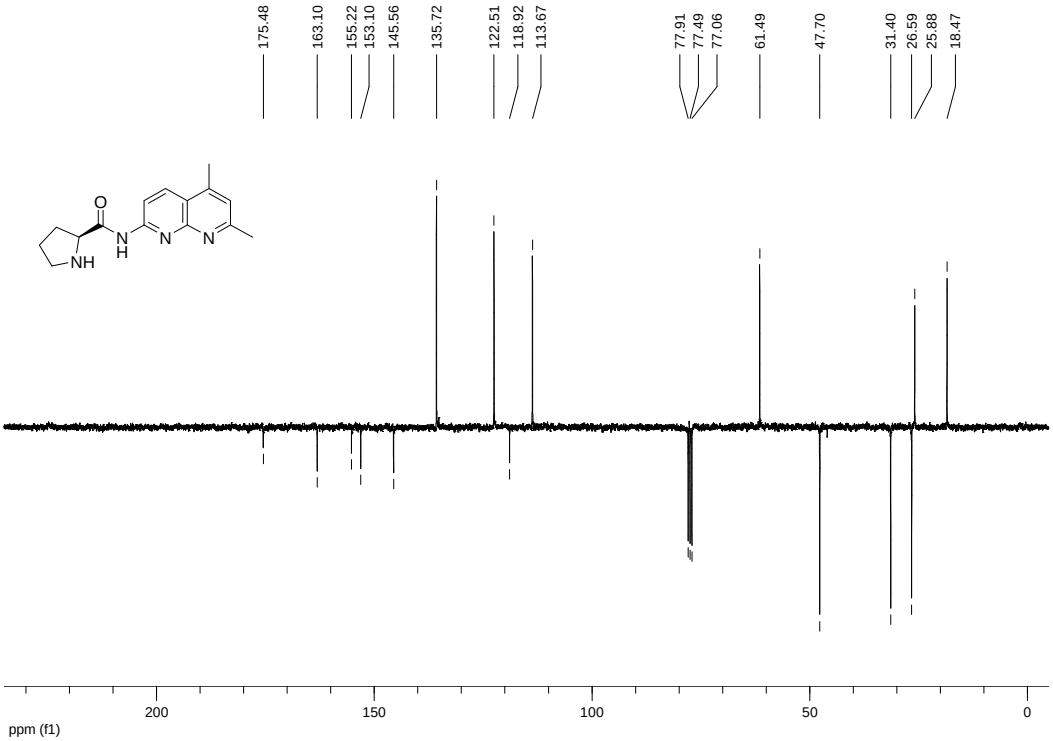




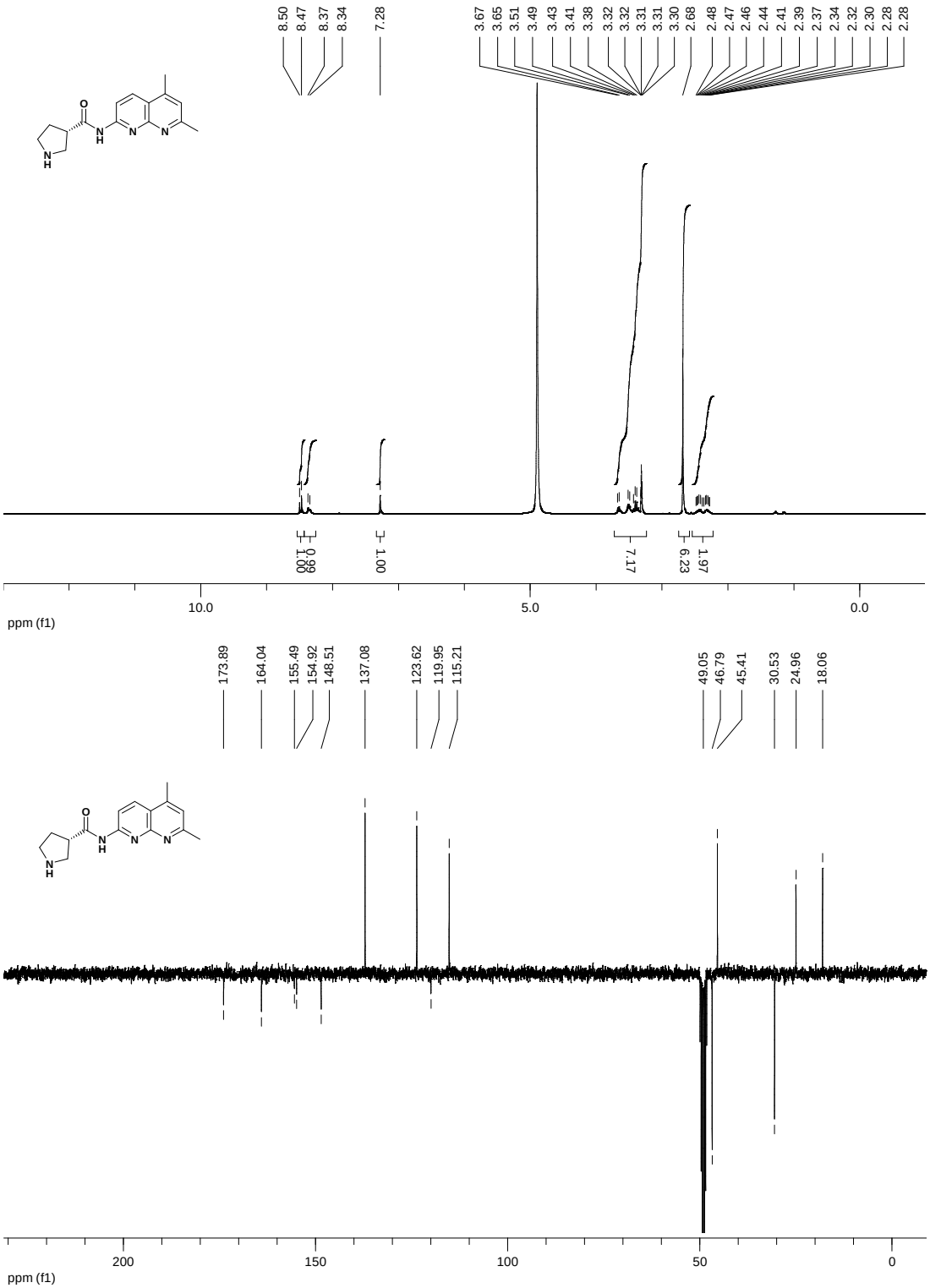
8. NMR spectra of selected compounds.

(*S*)-*N*-(2,4-dimethyl-1,8-naphthyridin-7-yl)pyrrolidine-2-carboxamide, ProNap 1.

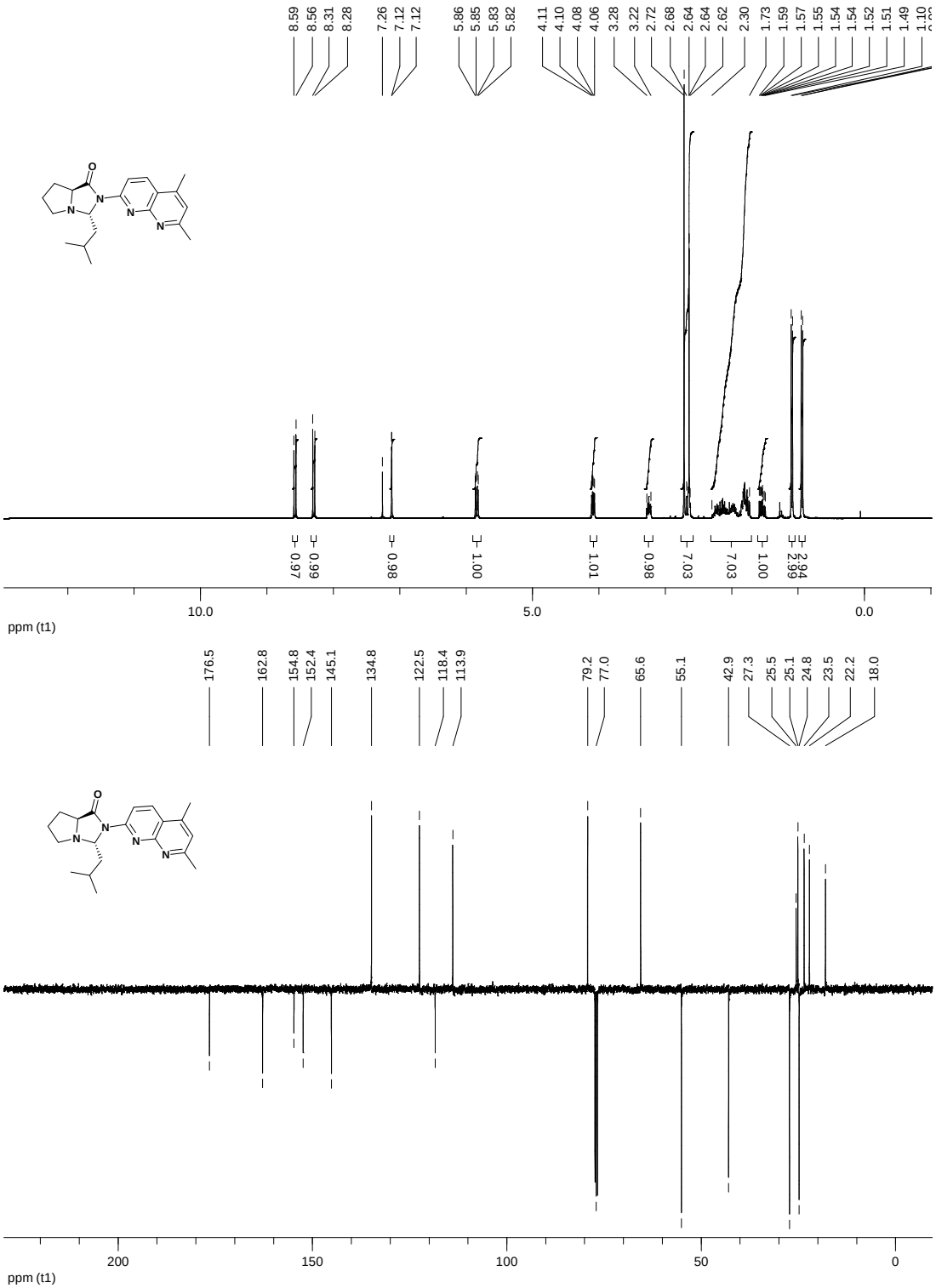




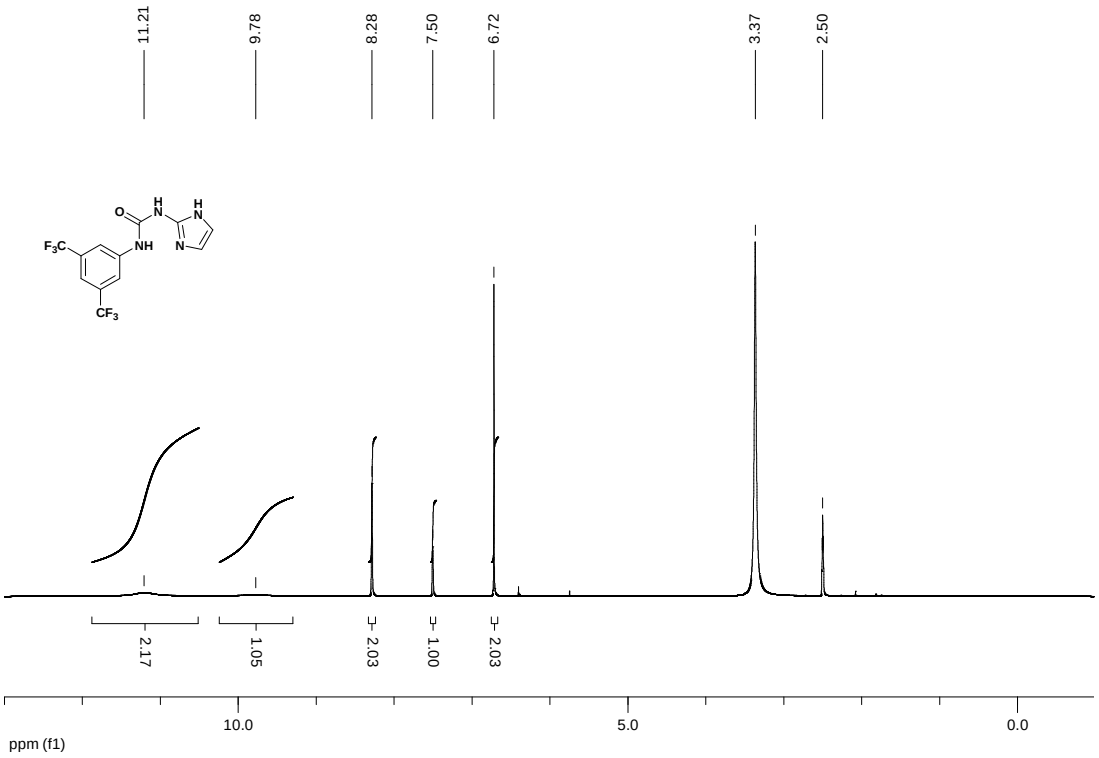
(*S*)-*N*-(2,4-dimethyl-1,8-naphthyridin-7-yl)pyrrolidine-3-carboxamide, β-ProNap 18.

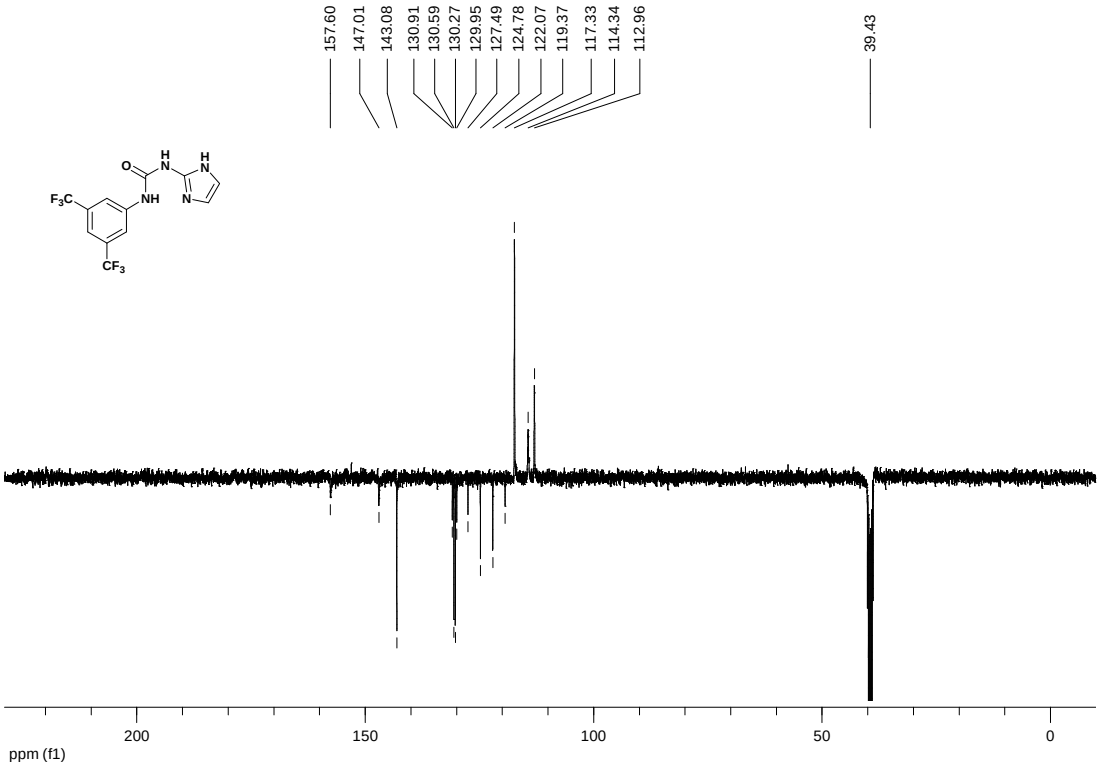


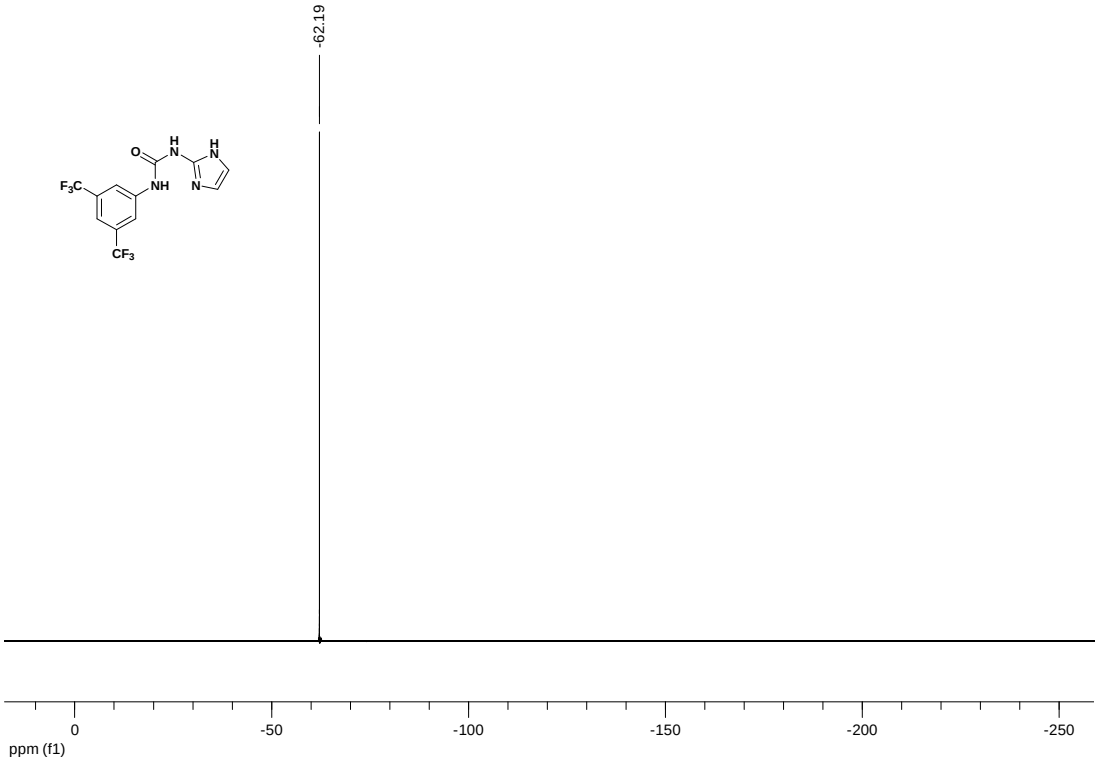
(3R,7aS)-hexahydro-3-isobutyl-2-(2,4-dimethyl-1,8-naphthyridin-7-yl)pyrrolo[1,2-e]imidazol-1-one, 16b.



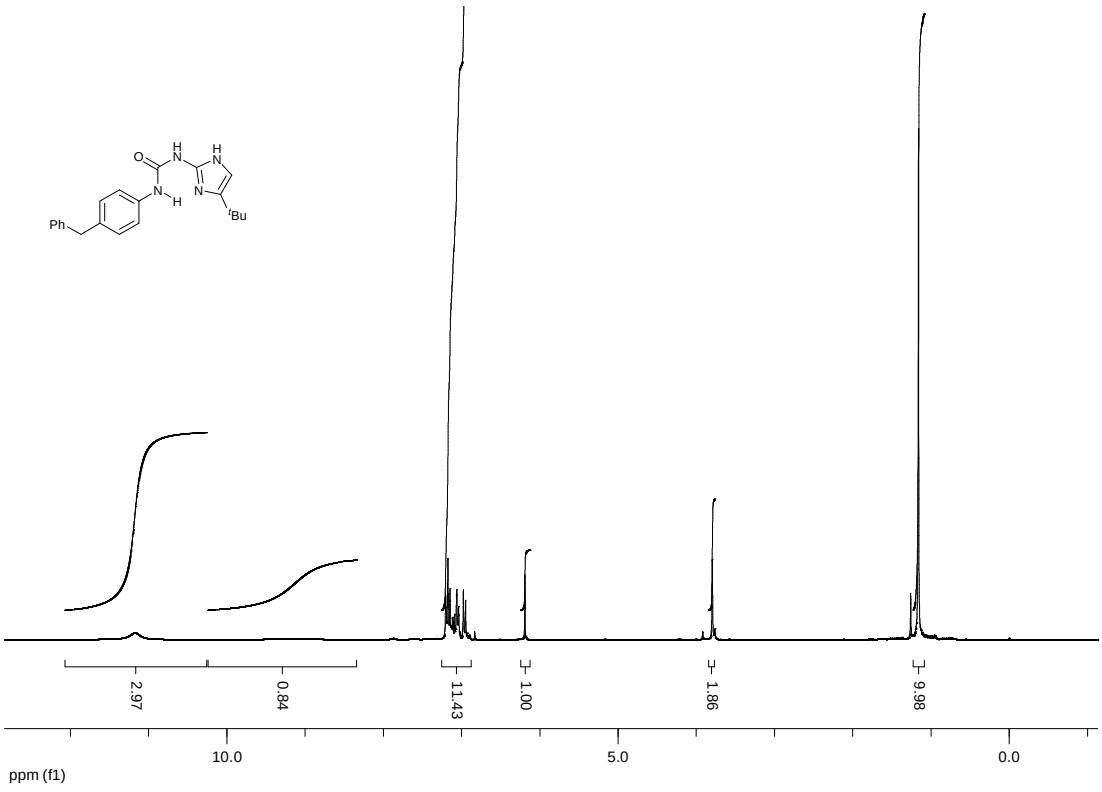
1-(3,5-bis(trifluoromethyl)phenyl)-3-(1H-imidazol-2-yl)urea 11.

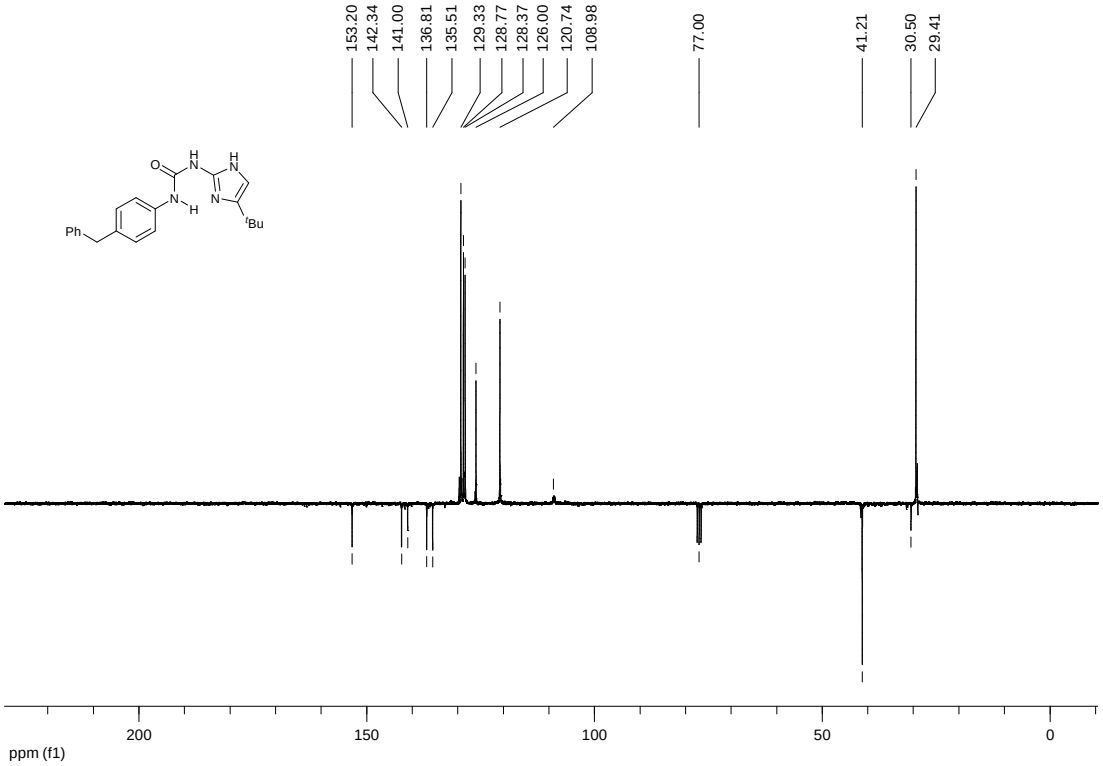




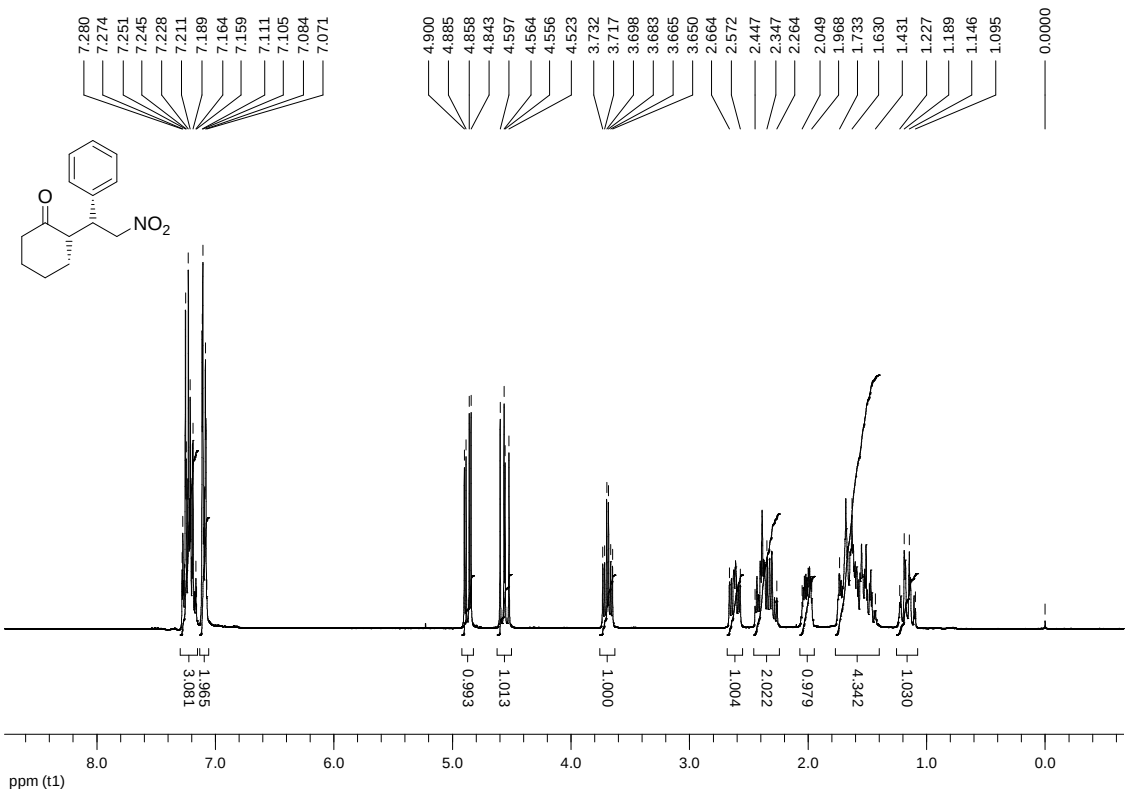


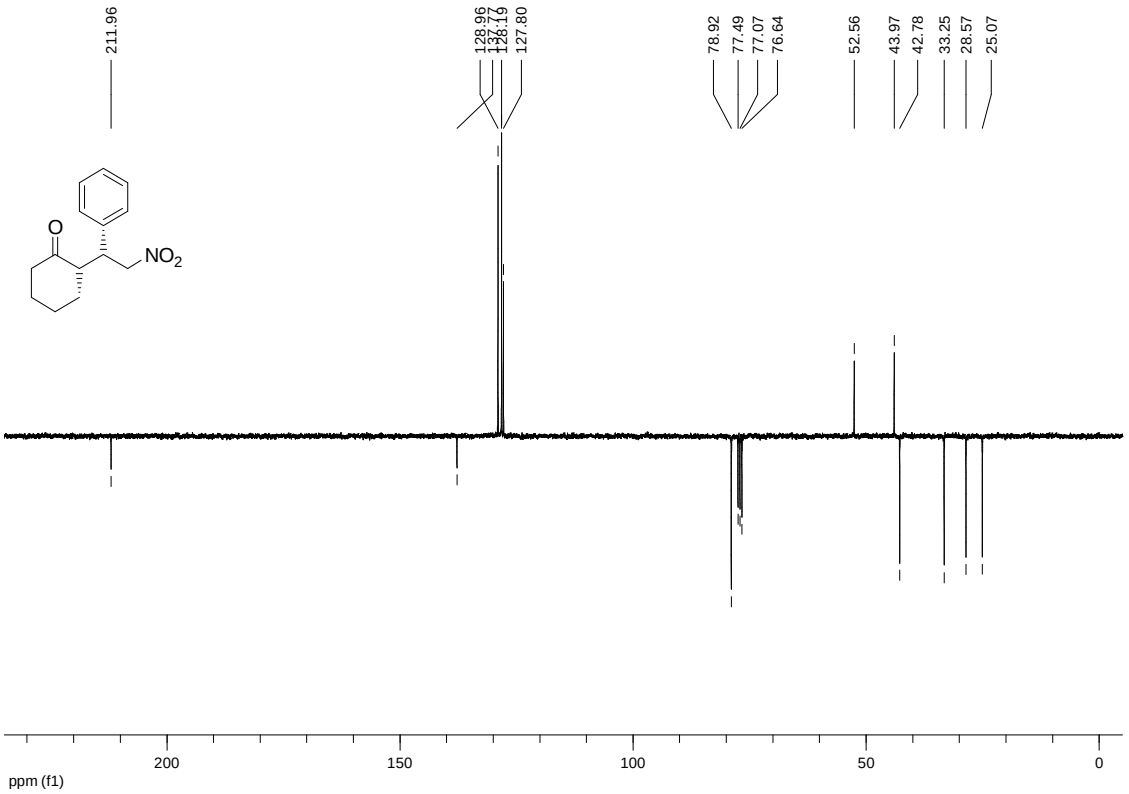
1-(4-*tert*-butyl-1H-imidazol-2-yl)-3-(4-benzylphenyl)urea, 13.



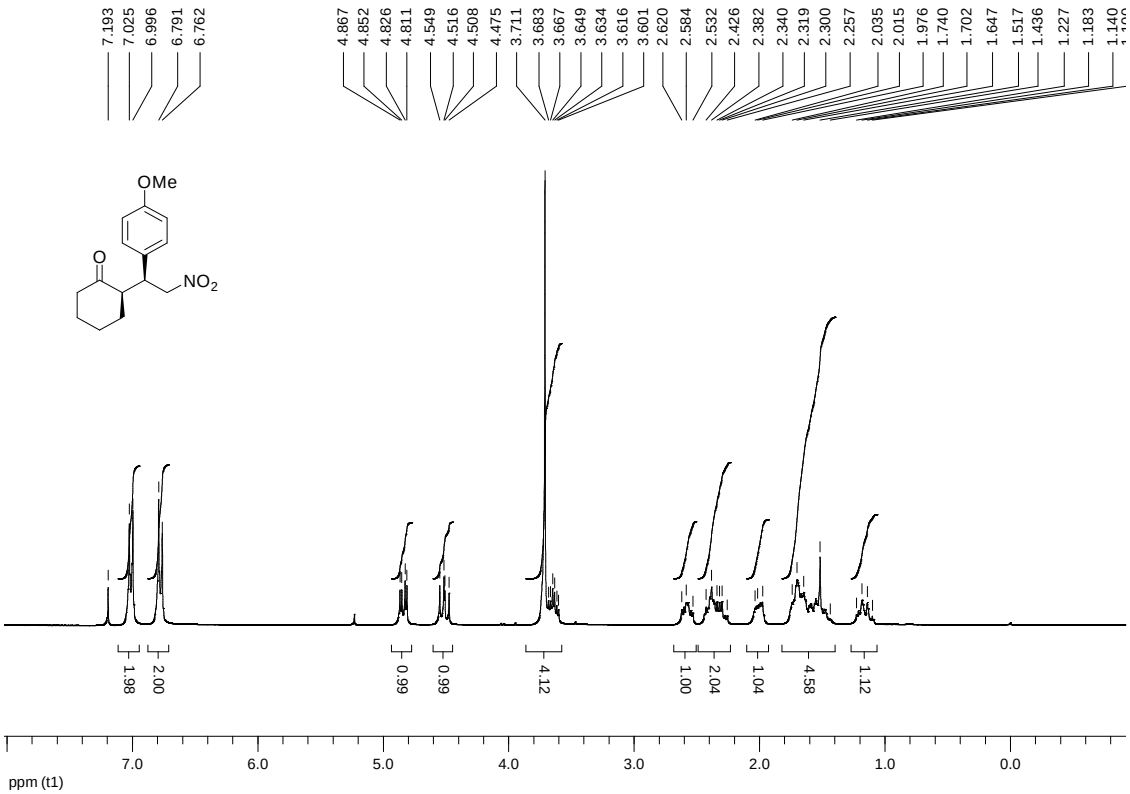


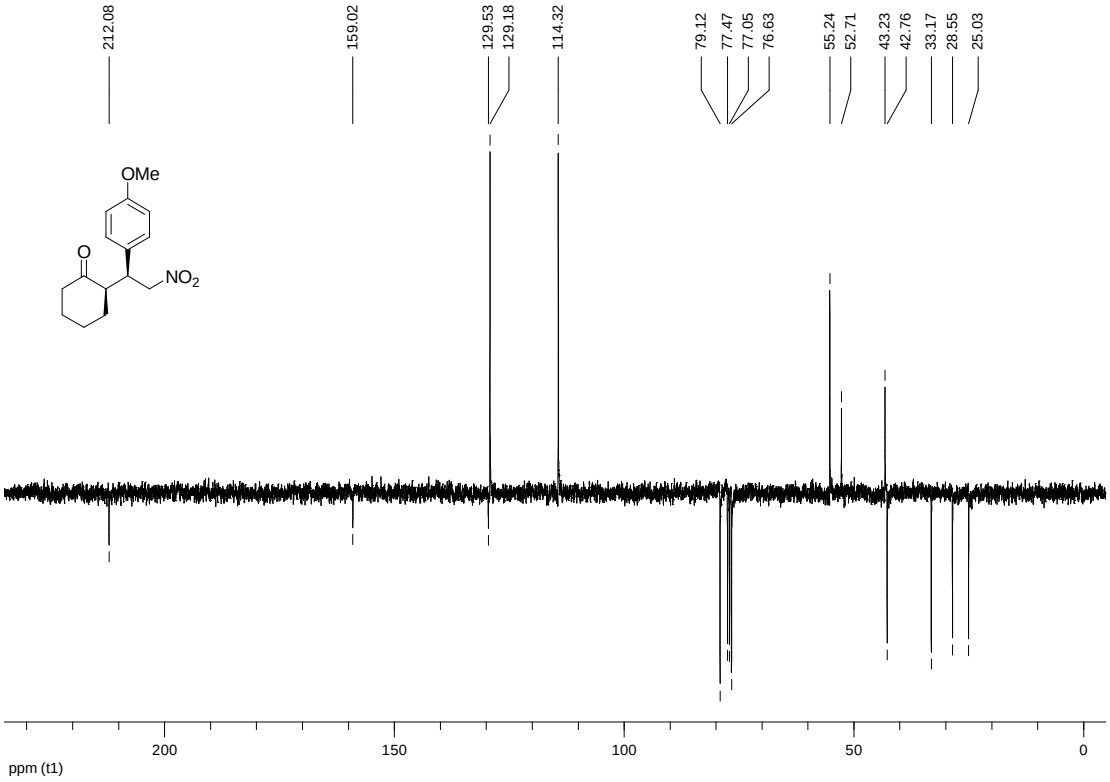
(*S*)-2-((*R*)-2-nitro-1-phenylethyl)cyclohexanone, 9a.



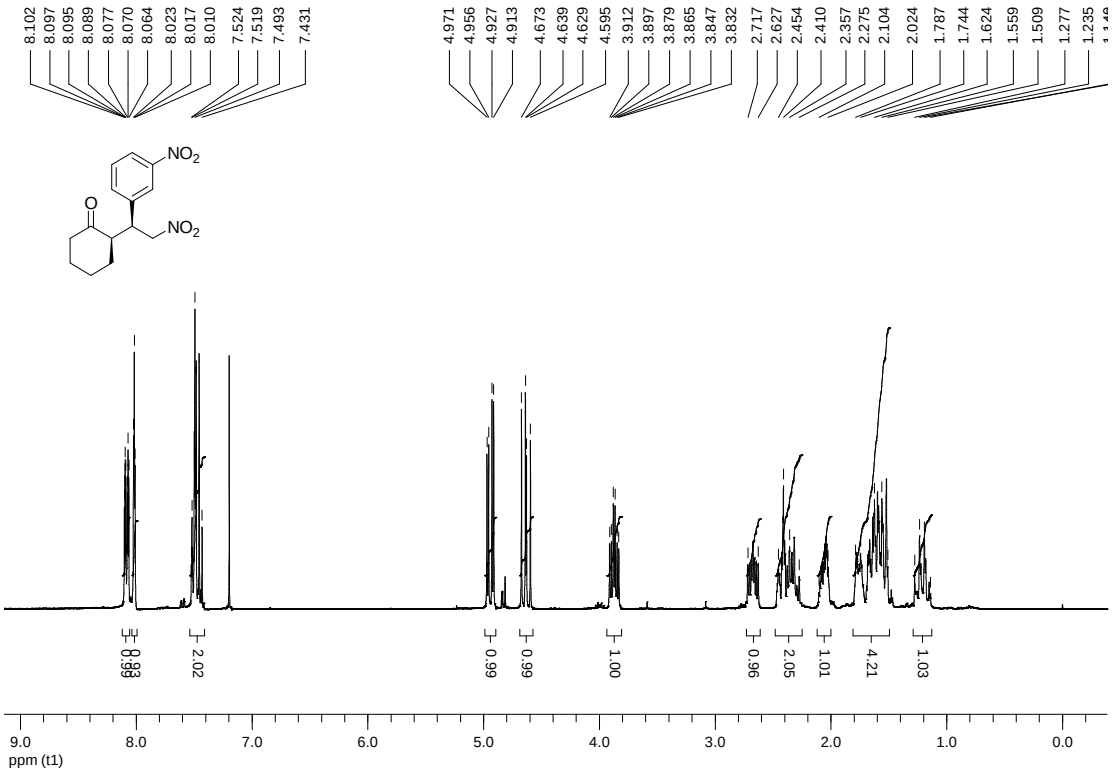


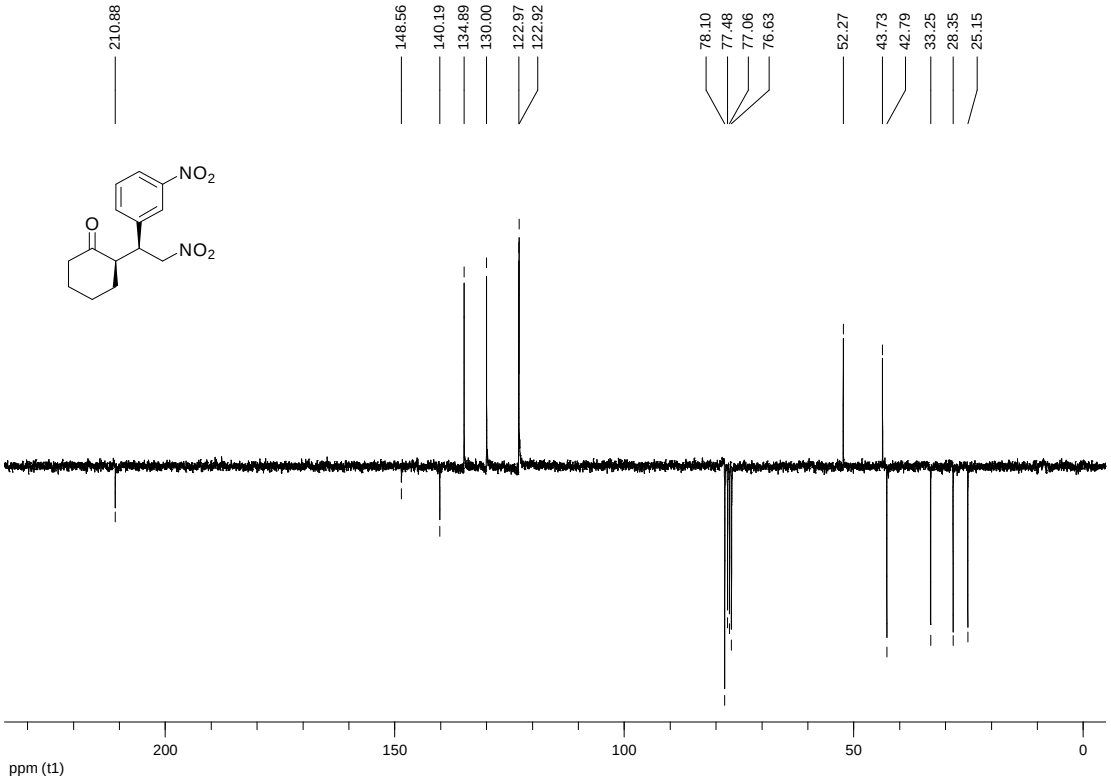
(*R*)-2-((*S*)-1-(4-methoxyphenyl)-2-nitroethyl)cyclohexanone, 9b.



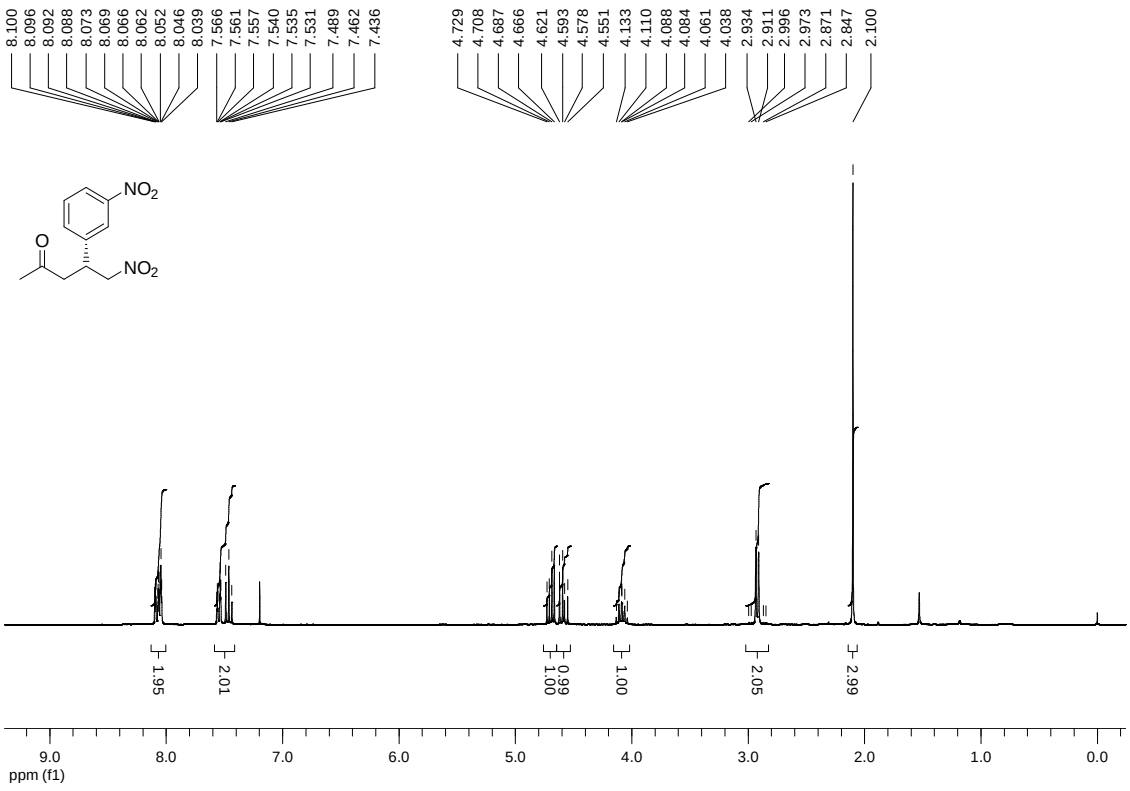


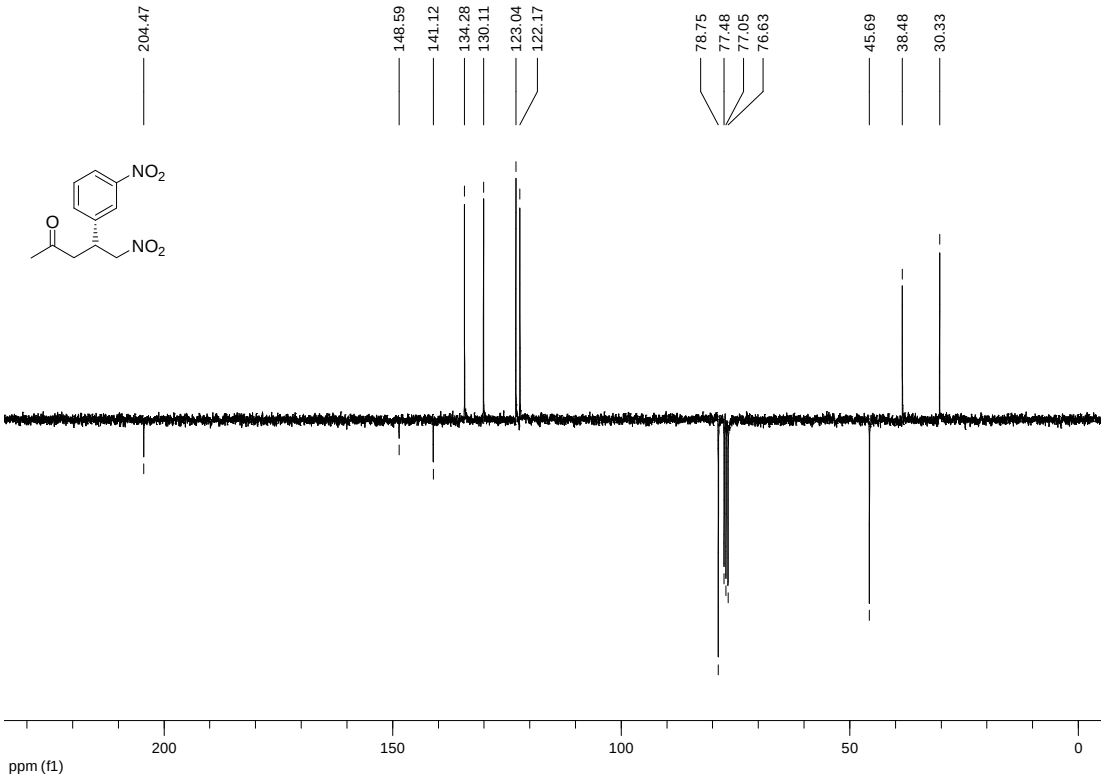
(*R*)-2-((*S*)-2-nitro-1-(3-nitrophenyl)ethyl)cyclohexanone, 9c.



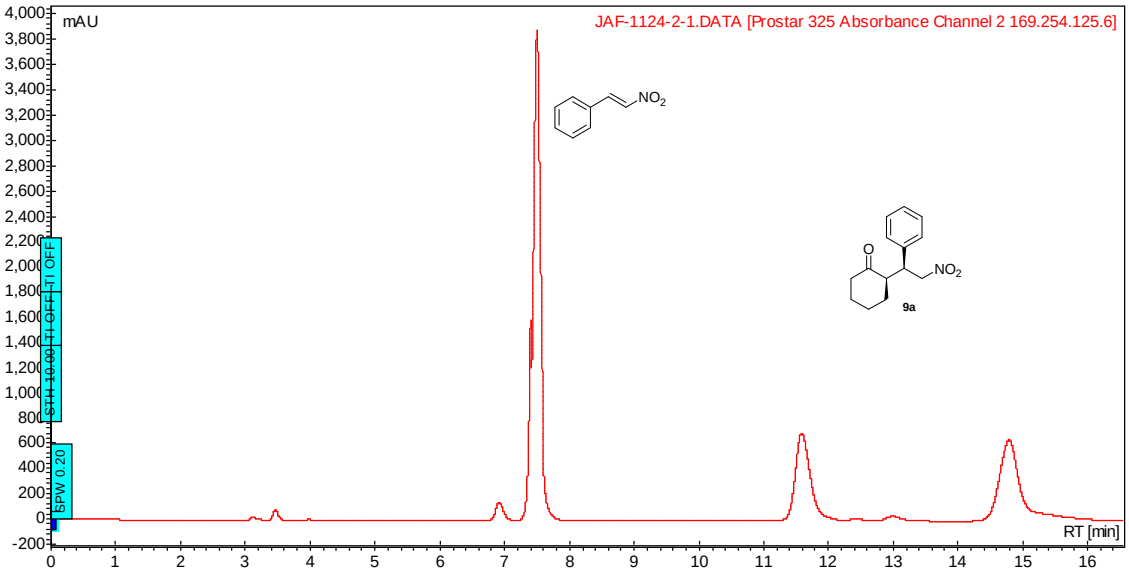


5-nitro-4-(3-nitrophenyl)pentan-2-one, 9e.

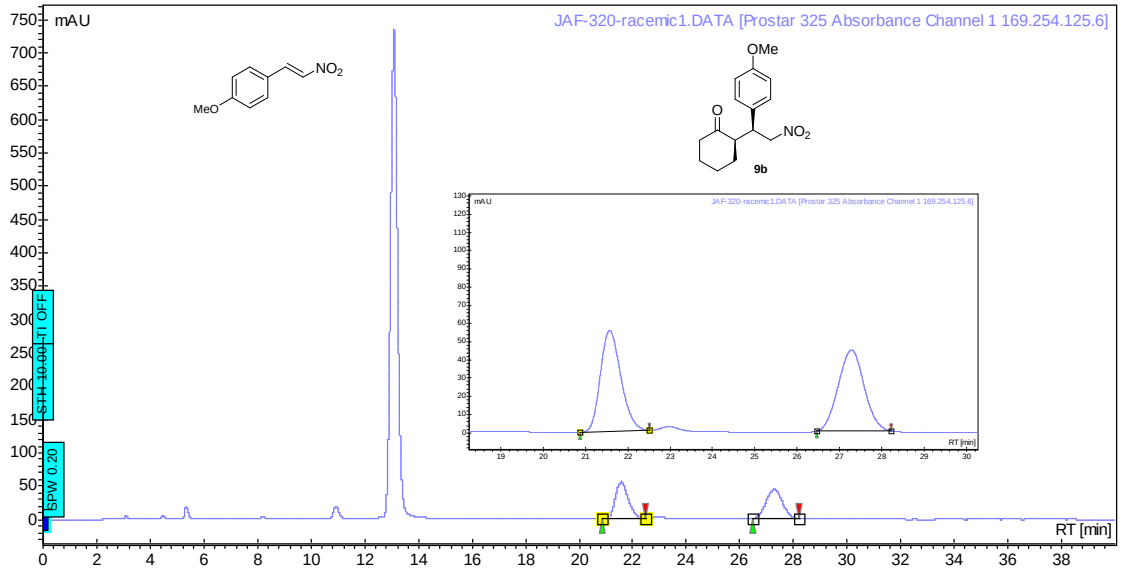




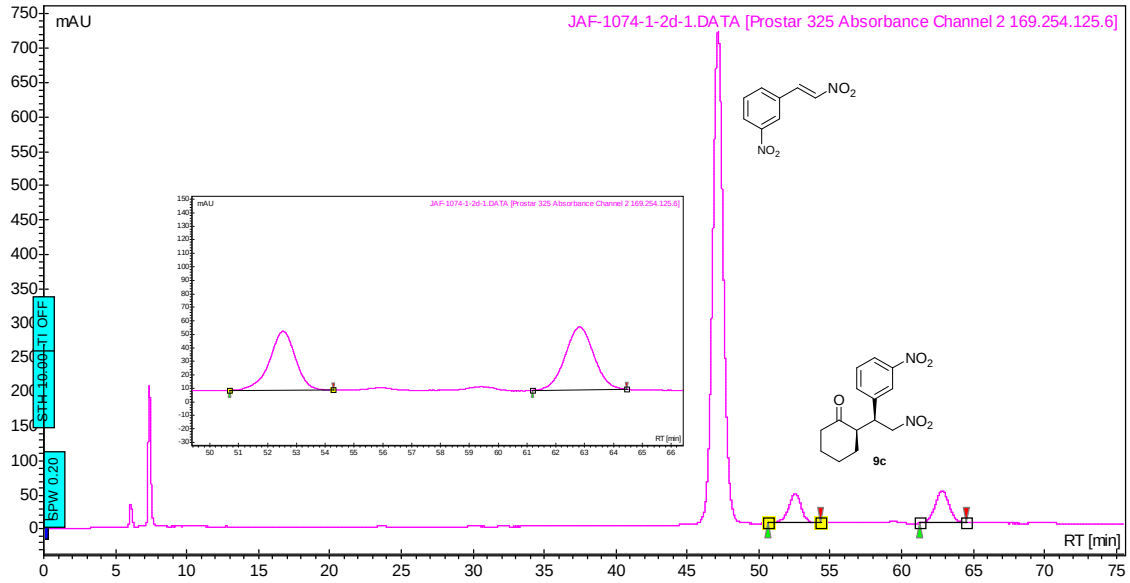
9. HPLC chromatograms for racemic Michael compounds 9a-e.



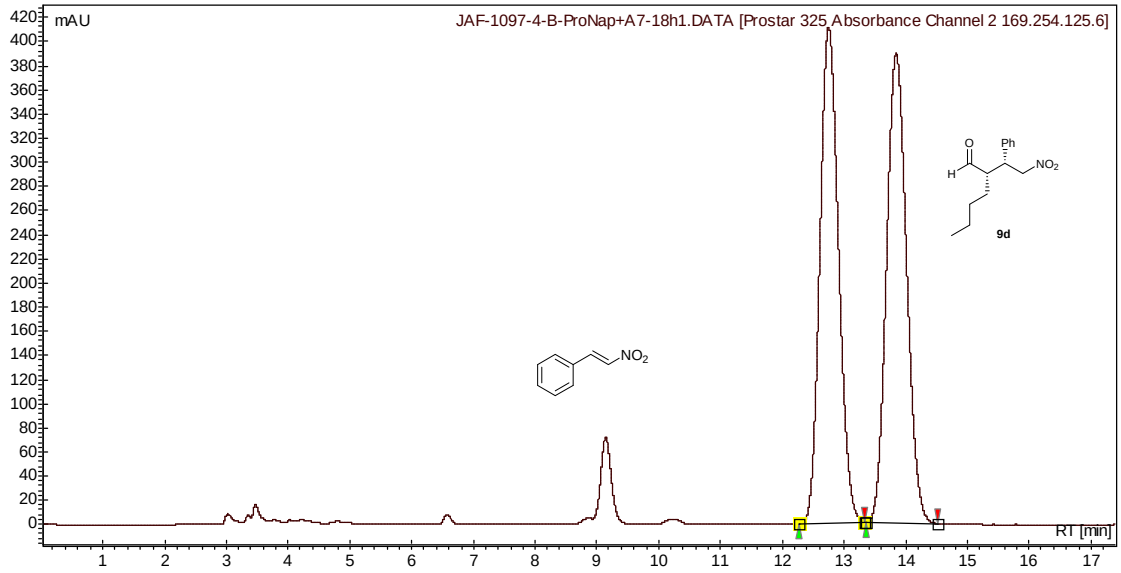
#	Name	Time [Min]	Quantity [% Area]		Height [mAU]	Area [mAU.Min]	Area % [%]
1	UNKNOWN	11.59	49.55	693.3	186.3	49.551	
2	UNKNOWN	14.79	50.45	602.2	189.7	50.449	
Total			100.00	1295.5	376.0	100.000	



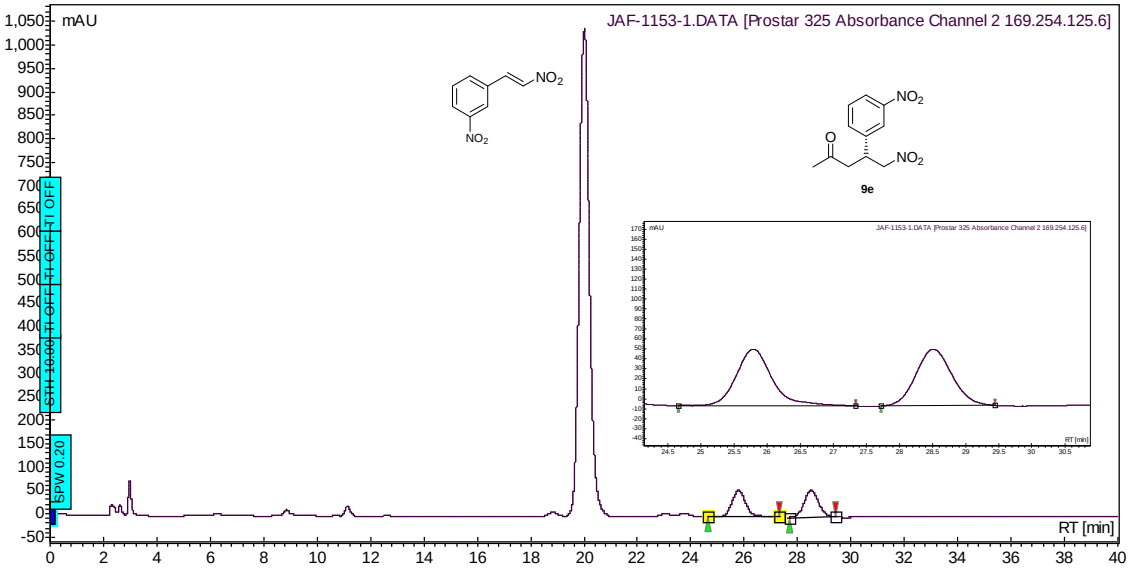
#	Name	Time [Min]	Quantity [% Area]		Height [mAU]	Area [mAU.Min]	Area % [%]
1	UNKNOWN	21.56	49.62	55.4	31.1	49.623	
2	UNKNOWN	27.29	50.38	44.5	31.6	50.377	
Total			100.00	99.9	62.7	100.000	



#	Name	Time [Min]	Quantity [% Area]		Height [mAU]	Area [mAU.Min]	Area % [%]
1	UNKNOWN	52.52	49.98	18.9	20.0	49.984	
2	UNKNOWN	62.81	51.02	19.2	20.8	51.016	
Total			100.00	38.1	40.8	100.000	



#	Name	Time [Min]	Quantity [% Area]		Height [mAU]	Area [mAU.Min]	Area % [%]
1	UNKNOWN	12.75	49.53	410.8	143.6	49.528	
2	UNKNOWN	13.84	50.47	389.1	146.3	50.472	
Total			100.00	799.9	289.9	100.000	



#	Name	Time [Min]	Quantity [% Area]		Height [mAU]	Area [mAU.Min]	Area % [%]
1	UNKNOWN	25.79	49.79	56.9	35.7	49.788	
2	UNKNOWN	28.51	50.21	56.9	36.0	50.212	
Total			100.00	113.8	71.6	100.000	

10. Variation of the concentration of nitroalkene tables.

ProNap **1** (3.4 mg 0.0125 mmol) and co-catalyst **12** (3.2 mg, 0.0125 mmol) were placed in 3 NMR tubes and dissolved in $CDCl_3$ (1 mL). The mixture was left to stand for 30 min and then cyclohexanone (0.389 mL, 3.75 mmol) and the corresponding amount of β,3-dinitrostyrene were added to each tube: A (24.3 mg, 0.125 mmol, 90 mM), B (12.1 mg, 0.0625 mmol, 45 mM), C (6.1 mg, 0.03125 mmol, 22.5 mM). The reaction mixture was then analysed by ^{1}H-NMR.

A, 90 mM	
t (h)	**C (%)**
1.37	1.2
2.75	5.8
3.72	8.0
5.08	10.4
7.0	16.8
9.25	20.8
15.12	31.3
22.83	42.4

B, 45 mM	
t (h)	**C (%)**
1.33	1.4
2.70	8.8
3.67	11.4
5.0	18
6.93	24.3
9.22	36
15.0	54

C, 22.5 mM	
t (h)	**C (%)**
1.20	4.9
2.58	10
3.53	19
4.90	33
6.82	47