Supplementary Information

The enantioselective benzoin condensation promoted by chiral triazolium precatalysts: stereochemical control via hydrogen bonding

Sarah E. O'Toole and Stephen J. Connon*

Centre for Synthesis and Chemical Biology, School of Chemistry, University of Dublin, Trinity College, Dublin 2, Ireland.

Fax: +353 1 6712826; Tel: +353 1 8961306; E-mail: connons@tcd.ie

Table of Contents

1.0 General

Proton Nuclear Magnetic Resonance spectra were recorded on 400 MHz and 600 MHz spectrometers in $CDCl_3$ referenced relative to residual $CHCl_3$ (δ = 7.26 ppm), DMSO-d_6 referenced relative to residual DMSO (H) (δ = 2.51 ppm) and CD_3CN referenced relative to residual CH_3CN (δ = 1.96 ppm). Chemical shifts are reported in ppm and coupling constants in Hertz. Carbon NMR spectra were recorded on the same instruments (100 MHz and 150 MHz) with total proton decoupling. All melting points are uncorrected. Infrared spectra were obtained using neat samples on a Perkin Elmer Spectrum 100 FT-IR spectrometer equipped with a universal ATR sampling accessory. Flash chromatography was carried out using silica gel, particle size 0.04-0.063 mm. TLC analysis was performed on precoated $60F_{254}$ slides, and visualised by either UV irradiation or $KMnO_4$ staining. Optical rotation measurements were made on a Rudolph Research Analytical Autopol IV instrument, and are quoted in units of 10^{-1} deg cm^2 g^{-1}. Toluene, ether and THF were distilled from sodium. Methylene chloride and triethylamine were distilled from calcium hydride. Analytical CSP-HPLC was performed using Daicel CHIRALCEL AD (4.6 mm x 25 cm) and CHIRALCEL OD-H (4.6 mm x 25 cm) and CHIRALCEL OJ-H (4.6 mm x 25 cm) columns. Unless otherwise stated, all chemicals were obtained from commercial sources and used as received. All reactions were carried out in oven-dried glassware with magnetic stirrers under an atmosphere of argon, unless specified.

2.0 Reaction Condition Sets

Condition Set A - K_2CO_3/KOH as Base

To a 5 cm^3 round-bottomed flask, equipped with a magnetic stirring bar, were added K_2CO_3 (99.995%, anhydrous, 8.76 mg, 0.0634 mmol) and KOH (0.79 mg, 0.0141 mmol) that had both been finely ground using a mortar and pestle. The reaction vessel was put under a vacuum and heated with a heat gun for 4 one-minute intervals. When cooled to ambient temperature the appropriate catalyst (0.088 mmol) and (*E*)-stilbene (49.57 mg, 0.275 mmol) were added and the flask was fitted with a septum seal. The reaction was evacuated for 4 min and put under an atmosphere of Ar. The required aldehyde was washed in CH_2Cl_2 with aq. $NaHCO_3$. The lower organic layer was separated, dried over $MgSO_4$, filtered and solvent removed *in vacuo*. The aldehyde was distilled under vacuum and used directly. THF (1.78 cm^3) was charged to the reaction, followed by the aldehyde (2.200 mmol). The reaction was stirred at room temperature for 48 h after which CH_2Cl_2 (3.0 cm^3) and deionised H_2O (3.0 cm^3) were added. The lower organic layer was removed and the aqueous layer was washed with CH_2Cl_2 (4 x 3.0 cm^3). The organic layers were combined, dried ($MgSO_4$), filtered and the solvent removed under reduced pressure. The product was purified using column chromatography.

Condition Set B - KHMDS 'Normal' Addition

To a 5 cm^3 round-bottomed flask, equipped with a magnetic stirring bar, was added the appropriate catalyst (0.220 mmol), and the flask was fitted with a septum seal. The reaction was evacuated for 4 min and put under an atmosphere of Ar. The required aldehyde was washed in CH_2Cl_2 with aq. $NaHCO_3$. The lower organic layer was separated, dried over $MgSO_4$, filtered and solvent removed *in vacuo*. The aldehyde was distilled under vacuum and used directly. Toluene (1.34 cm^3) was charged to the reaction, followed by dropwise addition of the aldehyde (2.200 mmol). The reaction was stirred for 5 min and KHMDS (440 μL, 0.220 mmol, 0.5 M solution in toluene) was added *via* syringe over 15 min. The reaction was stirred at room temperature for the time indicated in Table 2. To quench the reaction EtOAc (6.0 cm^3) and deionised H_2O (3.0 cm^3) were added. The organic layer was removed and the aqueous layer was washed with EtOAc (4 x 6.0 cm^3). The organic layers were combined, dried ($MgSO_4$), filtered

and the solvent removed under reduced pressure. The product was purified using column chromatography. Note: The internal standard (*E*)-stilbene (49.57 mg, 0.275 mmol) was added to the reaction after the work-up (prior to removal of the solvent) due to poor solubility of the internal standard in toluene.

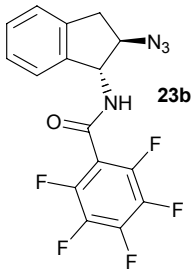
Condition Set C - KHMDS 'Inverse' Addition

To a 5 cm^3 round-bottomed flask, equipped with a magnetic stirring bar, was added the appropriate catalyst (0.110 mmol), and the flask was fitted with a septum seal. The reaction was evacuated for 4 min and put under an atmosphere of Ar. The required aldehyde was washed in CH_2Cl_2 with aq. $NaHCO_3$. The lower organic layer was separated, dried over $MgSO_4$, filtered and solvent removed *in vacuo*. The aldehyde was distilled under vacuum and used directly. Toluene (0.73 cm^3) was charged to the reaction, followed by addition *via* syringe of KHMDS (220 μL, 0.110 mmol, 0.5 M solution in toluene) over 7 min. The reaction was stirred for 15 min and the required aldehyde (1.100 mmol) was added dropwise to the reaction over 5 min. The reaction was stirred at room temperature for 16 h (unless otherwise indicated in Table 3). To quench the reaction EtOAc (6.0 cm^3) and deionised H_2O (3.0 cm^3) were added. The organic layer was removed and the aqueous layer was washed with EtOAc (4 x 6.0 cm^3). The organic layers were combined, dried ($MgSO_4$), filtered and the solvent removed under reduced pressure. The product was purified using column chromatography. Note: The internal standard (*E*)-stilbene (24.78 mg, 0.138 mmol) was added to the reaction after the work-up (prior to removal of the solvent) due to poor solubility of the internal standard in toluene.

3.0 Characterisation Data

Synthesis of catalysts 15a-h and 16

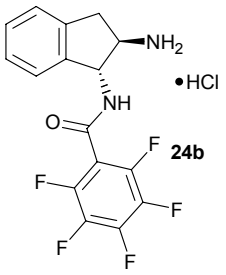
(1*R*,2*R*)-*trans*-*N*-(2-Azido-indan-1-yl)-2,3,4,5,6-pentafluoro-benzamide 23b



Prepared as per the synthesis of **23a** using **21** (0.762 g, 3.615 mmol) in CH_2Cl_2 (6.0 cm^3), triethylamine (2.51 cm^3, 18.033 mmol) and a solution of **22b** (0.60 cm^3, 4.338 mmol) in CH_2Cl_2 (8 cm^3). Purification by column chromatography (1:1 CH_2Cl_2-hexane, R_f 0.2) gave **23b** (1.237 g, 93%) as a white solid, mp 211-212 ^oC. $[\alpha]_D^{20} = -27.9$ (*c* 0.63 in $CHCl_3$).

δ_H (600 MHz, DMSO-d_6) 2.87 (1H, dd, *J* 15.4, 8.4), 3.29 (1H, m, (under H_2O resonance)), 4.30-4.34 (1H, app. q) 5.43-5.45 (1H, app. t), 7.21 (1H, d, *J* 7.3), 7.31-7.32 (3H, m), 9.59 (1H, d, *J* 8.1). δ_C (150 MHz, DMSO-d_6) 35.3, 59.4, 66.7, 112.0 (t, *J* 20.8), 123.4, 124.8, 127.3, 128.5, 136.0 (d of t, *J* 250.5, 14.7), 139.0, 139.5, 140.4 (d of m, *J* 257.7), 142.2 (d of m, *J* 251.7), 157.0. ν_{max} (neat)/cm^{-1} 3266, 2968, 2934, 2105, 1655, 1499, 1077, 988, 752. *m/z* (ES) 391.0579 (M^+ + Na. $C_{16}H_9N_4OF_5Na$ requires 391.0594).

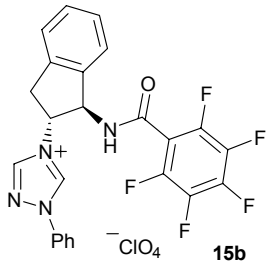
(1*R*,2*R*)-*trans*-1-Pentafluorobenzoylamino-indan-2-yl ammonium; chloride 24b



Prepared as per **24a** using **23b** (1.137 g, 3.089 mmol), triphenylphosphine (0.810 g, 3.089 mmol) in THF (28 cm^3) and addition of water (4 cm^3). Concentration of the aqueous layer produced a white solid which was purified by washing with ether to yield **24b** (1.060 g, 91%) as a white solid, mp 277-279 °C. $[\alpha]_D^{20}$ = -26.7 (*c* 0.99 in MeOH).

δ_H (600 MHz, DMSO-d_6) 3.04 (1H, dd, *J* 15.8, 7.5), 3.39 (1H, dd, *J* 15.8, 8.3), 3.87-3.91 (1H, app. q), 5.62-5.65 (1H, app.t), 7.27 (1H, d, *J* 4.9), 7.32-7.36 (3H, m), 8.69 (3H, s (broad)), 9.66 (1H, d, *J* 7.9). δ_C (150 MHz, DMSO-d_6) 35.3, 56.3, 58.5, 112.1 (t, *J* 20.1), 124.1, 125.3, 127.9, 129.0, 136.5 (d of t, *J* 249.9, 16.2), 139.2, 140.0, 140.7 (d of m, *J* 254.1), 142.7 (d of m, *J* 250.7), 157.5. ν_{max} (neat)/cm^{-1} 3299, 2856, 1661, 1552, 1518, 1496, 994, 768, 738, 713. *m/z* (ES) 343.0858 (M^+ - Cl. $C_{16}H_{12}N_2OF_5$ requires 343.0870.

(1*R*,2*R*)-*trans*-4-(1-Pentafluorobenzoylamino-indan-2-yl)-1-phenyl-4*H*-[*1,2,4*]triazol-1-ium; perchlorate 15b



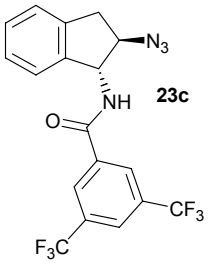
15b

Prepared as per **15a** using **25** (0.330 g, 1.338 mmol), oven-dried molecular sieves (4Å, 1.30 g) and **24b** (free-based amine, 0.458 g, 1.338 mmol) in CH_3CN (7 cm^3). The reaction was heated under reflux for 4 d under an atmosphere of Ar. Filtration under a stream of Ar followed by removal of the filtrate *in vacuo* yielded a red-brown residue. Purification by column chromatography (1:1 EtOAc-hexane, R_f 0.2) gave **15b** (0.321 g, 42%) as a yellow solid, mp 101-102 °C. $[\alpha]_D^{20}$ = -40.8 (c 2.42 in $CHCl_3$).

δ_H (600 MHz, DMSO-d_6) 3.66 (1H, dd, *J* 15.8, 9.4), 3.71 (1H, dd, *J* 15.8, 8.7), 5.28 (1H, ddd, *J* 9.4, 8.7, 8.3), 6.09 (1H, dd, *J* 8.3, 7.9), 7.33-7.34 (1H, m), 7.44-7.47 (3H, m), 7.69 (1H, t, *J* 7.5), 7.75-7.77 (2H, app. t), 7.96 (2H, d, *J* 7.9), 9.70 (1H, s), 9.85 (1H, d, *J* 7.9), 11.29 (1H, s). δ_C (150 MHz, DMSO-d_6) 36.1, 60.6, 65.3, 111.4 (t, *J* 33.6), 120.5, 123.6, 125.0, 127.9, 129.1,

130.3, 130.7, 134.9, 136.1 (d of m, *J* 250.9), 137.7, 137.9, 140.6 (d of m, *J* 252.1), 141.3, 142.4 (d of m, *J* 247.6), 144.6, 157.8. ν_{max} (neat)/cm^{-1} 3290, 3127, 3077, 2925, 1657, 1570, 1542, 1516, 1501, 1461, 1072, 990, 756, 686. *m/z* (ES) 471.1238 (M^+ -ClO_4. $C_{24}H_{16}N_4OF_5$ requires 471.1244).

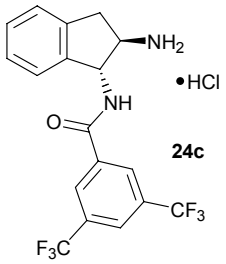
(1*R*,2*R*)-*trans*-*N*-(2-Azido-indan-1-yl)-3,5-bis-trifluoromethyl-benzamide 23c



Prepared as per the synthesis of **23a** using **21** (1.200 g, 5.696 mmol) in CH_2Cl_2 (10 cm^3), triethylamine (2.38 cm^3, 17.089 mmol) and a solution of **22c** (1.23 cm^3, 6.836 mmol) in CH_2Cl_2 (8 cm^3). Purification by column chromatography (6:4 CH_2Cl_2-hexane, R_f 0.3) gave **23c** (2.161 g, 92%) as a white solid, mp 207-208 ^oC. $[\alpha]_D^{20}$ = -20.7 (*c* 0.97 in $CHCl_3$).

δ_H (600 MHz, DMSO-d_6) 2.89 (1H, dd, *J* 15.6, 7.3), 3.37 (1H, dd, *J* 15.6, 7.7), 4.39-4.43 (1H, m), 5.54-5.57 (1H, m), 7.26-7.33 (4H, m), 8.35 (1H, s), 8.60 (2H, s), 9.49 (1H, d, *J* 8.4). δ_C (150 MHz, DMSO-d_6) 35.4, 59.7, 66.9, 120.4 (q, *J* 272.9), 124.2, 124.7, 125.1 (septet, *J* 3.3), 127.2, 128.2 (q, *J* 3.0), 128.4, 130.2 (q, *J* 33.2), 136.1, 139.3, 140.0, 163.6. ν_{max} (neat)/cm^{-1} 3257, 3094, 2928, 2105, 1645, 1547, 1272, 1124, 910, 847, 701, 680. *m/z* (ES) 437.0807 (M^+ + Na. $C_{18}H_{12}N_4OF_6Na$ requires 437.0813).

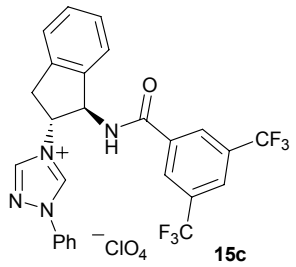
(1*R*,2*R*)-*trans*-1-(3,5-Bis-trifluoromethyl-benzoylamino)-indan-2-yl-ammonium; chloride 24c



Prepared as per **24a** using **23c** (2.161 g, 5.215 mmol), triphenylphosphine (1.368 g, 5.215 mmol) in THF (44 cm^3) and addition of water (6 cm^3). Concentration of the aqueous layer produced a white solid which was purified by washing with ether to yield **24c** (2.105 g, 95%) as a white solid, mp 301-303 °C. $[\alpha]_D^{20} = -4.7$ (*c* 1.11 in MeOH).

δ_H (600 MHz, DMSO-d_6) 3.06 (1H, dd, *J* 15.7, 9.2), 3.37 (1H, dd, *J* 15.7, 7.9), 3.97-4.03 (1H, m), 5.75-5.77 (1H, app. t), 7.26-7.40 (4H, m), 8.36 (1H, s), 8.63 (2H, s), 8.74 (3H, broad s), 9.57 (1H, d, *J* 8.3). δ_C (150 MHz, DMSO-d_6) 34.4, 56.6, 57.8, 120.4 (q, *J* 273.7), 123.9, 124.8, 124.9 (septet, *J* 3.3), 127.4, 128.4, 128.5 (q, *J* 3.8), 130.1 (q, *J* 33.1), 136.5, 138.5, 140.2, 164.2. ν_{max} (neat)/cm^{-1} 3280, 2861, 1646, 1621, 1544, 1278, 1124, 847, 742, 682. *m/z* (ES) 389.1071 (M^+ - Cl. $C_{18}H_{15}N_2OF_6$ requires 389.1089).

(1*R*,2*R*)-*trans*-4-[1-(3,5-Bistrifluoromethyl-benzoylamino)-indan-2-yl]-1-phenyl-4*H*-[*1,2,4*]triazol-1-ium; perchlorate 15c

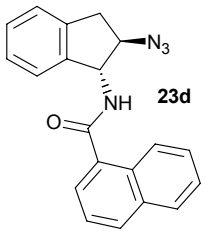


Prepared as per **15a** using **25** (0.285 g, 1.155 mmol), oven-dried molecular sieves (4Å, 1.10 g) and **24c** (free-based amine, 0.427 g, 1.100 mmol) in CH_3CN (10 cm^3). The reaction was heated under reflux for 7 d under an atmosphere of Ar. Filtration under a stream of Ar followed by removal of the filtrate *in vacuo* yielded a red-brown residue. Purification by column

chromatography (7:3 EtOAc-hexane, R_f 0.3) gave **15c** (0.597 g, 88%) as a yellow solid, mp 127-128 °C. $[\alpha]_D^{20}$ = -78.9 (c 1.62 in $CHCl_3$).

δ_H (600 MHz, DMSO-d_6) 3.64 (1H, dd, *J* 15.8, 9.2), 3.75 (1H, dd, *J* 15.8, 8.8), 5.34 (1H, ddd, *J* 9.2, 8.8, 8.1), 6.18 (1H, dd, *J* 8.1, 7.3), 7.40-7.48 (4H, m), 7.66 (1H, t, *J* 7.3), 7.73-7.76 (2H, app. t), 7.96 (2H, d, *J* 8.1), 8.37 (1H, s), 8.57 (2H, s), 9.74 (1H, d, *J* 7.3), 9.78 (1H, s) 11.20 (1H, s). δ_C (150 MHz, DMSO-d_6) 36.7, 60.8, 65.9, 120.7 (q, *J* 273.1), 120.9, 124.6, 125.1, 125.5 (septet, *J* 2.7), 128.1, 128.8 (q, *J* 4.1), 129.2, 130.4 (q, *J* 33.3), 130.6, 131.0, 135.3, 136.3, 138.3, 138.9, 141.8, 145.1, 164.9. ν_{max} (neat)/cm^{-1} 3318, 3133, 3076, 1655, 1621, 1570, 1534, 1461, 1277, 1128, 1069, 759, 681. *m/z* (ES) 517.1473 (M^+ -ClO_4. $C_{26}H_{19}N_4OF_6$ requires 517.1463).

(1*R*,2*R*)-*trans*-Naphthalene-1-carboxylic acid (2-azido-indan-1-yl)-amide 23d

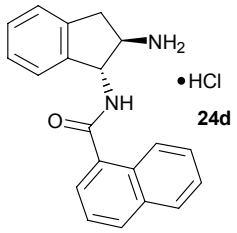


23d

Prepared as per the synthesis of **23a** using **21** (1.500 g, 7.120 mmol) in CH_2Cl_2 (10 cm^3), triethylamine (2.97 cm^3, 21.361 mmol) and a solution of **22d** (1.28 cm^3, 8.545 mmol) in CH_2Cl_2 (15 cm^3). Purification by column chromatography (CH_2Cl_2, R_f 0.4) gave **23d** (2.086 g, 89%) as an off-white solid, mp 204-205 °C. $[\alpha]_D^{20}$ = -41.3 (*c* 0.93 in $CHCl_3$).

δ_H (600 MHz, DMSO-d_6) 2.87 (1H, dd, *J* 15.4, 8.4), 3.32-3.36 (1H, m, (under H_2O resonance)), 4.40-4.44 (1H, app. q), 5.60-5.63 (1H, app. t), 7.29-7.33 (3H, m), 7.36 (1H, d, *J* 7.2), 7.58-7.64 (3H, m), 7.71 (1H, d, *J* 7.0), 8.00 (1H, d, *J* 8.1), 8.06 (1H, d, *J* 8.4), 8.33 (1H, d, *J* 8.4), 9.16 (1H, d, *J* 8.4). δ_C (150 MHz, DMSO-d_6) 35.3, 59.3, 66.7, 123.6, 124.7, 124.9, 125.25, 125.29, 126.3, 126.8, 127.2, 128.1, 128.2, 129.7, 130.0, 133.1, 134.2, 138.8, 140.8, 168.9. ν_{max} (neat)/cm^{-1} 3238, 3047, 2926, 2888, 2098, 1646, 1527, 1519, 773, 753. *m/z* (ES) 351.1210 (M^+ + Na. $C_{20}H_{16}N_4ONa$ requires 351.1222).

(1*R*,2*R*)-*trans*-1-[(Naphthalene-1-carbonyl)-amino]-indan-2-yl-ammonium; chloride 24d

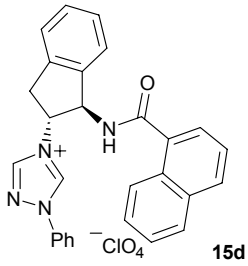


24d

Prepared as per **24a** using **23d** (1.986 g, 6.048 mmol), triphenylphosphine (1.586 g, 6.048 mmol) in THF (50 cm^3) and addition of water (5 cm^3). Concentration of the aqueous layer produced a white solid which was purified by washing with ether to yield **24d** (1.915 g, 93%) as a white solid, mp 293-295 °C. $[\alpha]_D^{20} = -72.2$ (*c* 1.68 in MeOH).

δ_H (600 MHz, DMSO-d_6) 3.03 (1H, dd, *J* 15.8, 8.7), 3.38 (1H, dd, *J* 15.8, 8.3), 3.94-4.01 (1H, app. q,), 5.76-5.79 (1H, app. t), 7.33-7.36 (4H, m), 7.59-7.65 (3H, m), 7.88 (1H, d, *J* 6.4), 8.01 (1H, d, *J* 7.9), 8.07 (1H, d, *J* 8.3), 8.43 (1H, d, *J* 8.3), 8.66 (3H, s (broad)), 9.12 (1H, d, *J* 8.3). δ_C (150 MHz, DMSO-d_6) 35.1, 56.7, 58.0, 124.1, 125.1, 125.2, 126.0, 126.4, 126.6, 127.1, 127.8, 128.6, 128.7, 130.1, 130.6, 133.5, 134.2, 138.8, 141.1, 169.5. ν_{max} (neat)/cm^{-1} 3290, 2981, 2857, 1633, 1522, 1329, 1305, 1260, 1169, 783, 734. *m/z* (ES) 303.1493 (M^+ - Cl. $C_{20}H_{19}N_2O$ requires 303.1497).

(1*R*,2*R*)-*trans*-4-{1-[(Naphthalene-1-carbonyl)-amino]-indan-2-yl}-1-phenyl-4*H*-[*1,2,4*]triazol-1-ium; perchlorate 15d



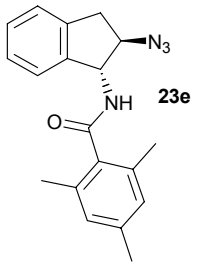
15d

Prepared as per **15a** using **25** (0.582 g, 2.360 mmol), oven-dried molecular sieves (4Å, 2.20 g) and **24d** (free-based amine, 0.680 g, 2.248 mmol) in CH_3CN (30 cm^3). The reaction was heated under reflux for 7 d under an atmosphere of Ar. Filtration under a stream of Ar followed by removal of the filtrate *in vacuo* yielded a red-brown residue. Purification by column

chromatography (7:3 hexane-EtOAc, R_f 0.1) gave **15d** (0.616 g, 52%) as an off-white solid, mp 159-160 ^oC. $[\alpha]_D^{20}$ = -113.2 (c 0.71 in MeOH).

δ_H (600 MHz, DMSO-d_6) 3.67 (1H, dd, *J* 15.6, 9.4), 3.73 (1H, dd, *J* 15.6, 8.3), 5.32-5.37 (1H, app. q), 6.18-6.21 (1H, app. t), 7.42-7.51 (5H, m), 7.56-7.61 (2H, m), 7.69 (1H, t, *J* 7.5), 7.76-7.79 (2H, app. t), 7.85 (1H, d, *J* 6.8), 7.99-8.02 (3H, m), 8.07 (1H, d, *J* 8.3), 8.12 (1H, d, *J* 8.3), 9.38 (1H, d, *J* 7.9), 9.86 (1H, s), 11.35 (1H, s). δ_C (150 MHz, DMSO-d_6) 36.5, 60.6, 65.9, 120.9, 124.3, 125.15, 125.19, 125.5, 126.5, 126.6, 127.1, 128.1, 128.6, 129.0, 130.0, 130.7, 130.9, 131.1, 133.47, 133.52, 135.3, 138.1, 139.3, 141.9, 145.2, 170.1. ν_{max} (neat)/cm^{-1} 3294, 3136, 3104, 1640, 1593, 1569, 1530, 1505, 1485, 1078, 769. *m/z* (ES) 431.1863 (M^+ -ClO_4. $C_{28}H_{23}N_4O$ requires 431.1872).

(1*R*,2*R*)-*trans*-*N*-(2-Azido-indan-1-yl)-2,4,6-trimethyl-benzamide 23e

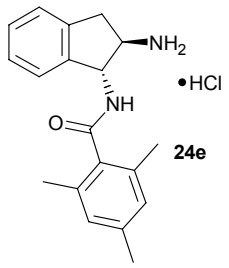


23e

Prepared as per the synthesis of **23a** using **21** (1.000 g, 4.747 mmol) in CH_2Cl_2 (8 cm^3), triethylamine (3.96 cm^3, 28.482 mmol) and a solution of **22e** (2.670 g, 14.618 mmol) in CH_2Cl_2 (10 cm^3). Purification by column chromatography (1:1 CH_2Cl_2-hexane, R_f 0.1) gave **23e** (1.116 g, 73%) as a red-brown solid, mp 149-150 ^oC. $[\alpha]_D^{20}$ = -61.3 (*c* 1.03 in $CHCl_3$).

δ_H (400 MHz, $CDCl_3$) 2.29 (3H, s), 2.39 (6H, s), 2.98 (1H, dd, *J* 15.7, 7.0), 3.32 (1H, dd, *J* 15.7, 7.5), 4.12 (1H, ddd, *J* 7.5, 7.0, 6.5), 5.60 (1H, dd, *J* 8.0, 6.5), 5.92 (1H, d, *J* 8.0), 6.87 (2H, s), 7.26-7.33 (4H, m). δ_C (100 MHz, $CDCl_3$) 18.9, 20.7, 35.8, 59.3, 67.9, 123.7, 124.6, 127.3, 127.8, 128.5, 133.7, 133.9, 138.3, 138.9, 139.3, 170.1. ν_{max} (neat)/cm^{-1} 3242, 2951, 2912, 2099, 1639, 1518, 1458, 1260, 856, 748, 704, 682. *m/z* (ES) 321.1725 (M^+ + H. $C_{19}H_{21}N_4O$ requires 321.1715).

(1*R*,2*R*)-*trans*-1-(2,4,6-Trimethyl-benzoylamino)-indan-2-yl-ammonium chloride 24e

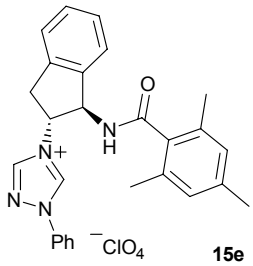


24e

Prepared as per **24a** using **23e** (1.116 g, 3.483 mmol), triphenylphosphine (0.914 g, 3.483 mmol) in THF (29 cm^3) and addition of water (4 cm^3). Concentration of the aqueous layer produced a pale brown solid which was purified by washing with ether to yield **24e** (0.641 g, 56%) as a white solid, mp 278-280 °C. $[\alpha]_D^{20} = -37.5$ (*c* 0.70 in MeOH).

δ_H (600 MHz, DMSO-d_6) 2.24 (3H, s), 2.27 (6H, s), 2.99 (1H, dd, *J* 16.6, 6.4), 3.42 (1H, dd, *J* 16.6, 8.1), 3.87-3.90 (1H, app. q), 5.57-5.59 (1H, app. t), 6.87 (2H, s), 7.30-7.32 (3H, m), 7.37 (1H, d, *J* 6.4), 8.53 (3H, s (broad)), 8.85 (1H, d, *J* 7.5). δ_C (150 MHz, DMSO-d_6) 19.1, 20.6, 35.4, 56.1, 58.2, 124.4, 124.8, 127.3, 127.7, 128.4, 133.8, 134.9, 137.4, 139.0, 140.5, 169.7. ν_{max} (neat)/cm^{-1} 3251, 2915, 1634, 1612, 1517, 1477, 1375, 848, 746. *m/z* (ES) 295.1815 (M^+ - Cl. $C_{19}H_{23}N_2O$ requires 295.1810).

(1*R*,2*R*)-*trans*-1-phenyl-4-[1-(2,4,6-trimethyl-benzoylamino)-indan-2-yl]-4*H*-[*1,2,4*]triazol-1-ium; perchlorate 15e



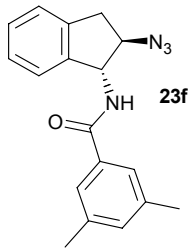
15e

Prepared as per **15a** using **25** (0.416 g, 1.687 mmol), oven-dried molecular sieves (4Å, 1.60 g) and **24e** (free-based amine, 0.473 g, 1.606 mmol) in CH_3CN (15 cm^3). The reaction was heated under reflux for 5 d under an atmosphere of Ar. Filtration under a stream of Ar followed by

removal of the filtrate *in vacuo* yielded a red-brown residue. Purification by column chromatography (7:3 hexane-EtOAc, R_f 0.2) gave **15e** (0.403 g, 48%) as a pale green solid, mp 143-144 ^oC. $[\alpha]_D^{20}$ = -94.1 (c 2.22 in $CHCl_3$).

δ_H (600 MHz, DMSO-d_6) 2.18 (6H, s), 2.24 (3H, s), 3.57 (1H, dd, *J* 15.7, 9.6), 3.68 (1H, dd, *J* 15.7, 8.3), 5.24-5.29 (1H, app. q), 6.18-6.21 (1H, app. t), 6.88 (2H, s), 7.35-7.36 (1H, m), 7.40-7.43 (3H, m), 7.68 (1H, t, *J* 7.5), 7.75-7.78 (2H, app. t), 7.96 (2H, d, *J* 7.9), 9.13 (1H, d, *J* 7.9), 9.77 (1H, s) 11.38 (1H, s). δ_C (150 MHz, DMSO-d_6) 18.9, 20.6, 36.5, 59.6, 65.4, 120.5, 123.6, 124.9, 127.7, 127.8, 128.7, 130.3, 130.8, 133.4, 134.7, 134.8, 137.57, 137.60, 138.8, 141.5, 144.9, 170.3. ν_{max} (neat)/cm^{-1} 3284, 3128, 3029, 2922, 1639, 1610, 1569, 1501, 1487, 1460, 1379, 1084, 852, 755. *m/z* (ES) 423.2195 (M^+ -ClO_4. $C_{27}H_{27}N_4O$ requires 423.2185).

(1*R*,2*R*)-*trans*-*N*-(2-Azido-indan-1-yl)-3,5-dimethyl-benzamide 23f

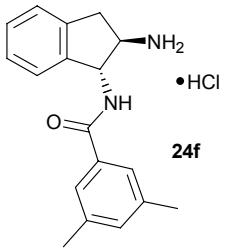


23f

Prepared as per the synthesis of **23a** using **21** (1.100 g, 5.222 mmol) in CH_2Cl_2 (10 cm^3), triethylamine (4.36 cm^3, 31.330 mmol) and a solution of **22f** (2.807 g, 16.637 mmol) in CH_2Cl_2 (10 cm^3). Purification by column chromatography (CH_2Cl_2, R_f 0.1) gave **23f** (1.469 g, 92%) as a yellow solid, mp 178-180 ^oC. $[\alpha]_D^{20}$ = -20.5 (*c* 0.74 in $CHCl_3$).

δ_H (400 MHz, $CDCl_3$) 2.38 (6H, s), 2.96 (1H, dd, *J* 16.1, 6.5), 3.34 (1H, dd, *J* 16.1, 7.5), 4.20-4.25 (1H, app. q), 5.62-5.66 (1H, app. t), 6.35 (1H, d, *J* 7.5), 7.18 (1H, s), 7.29-7.33 (4H, m), 7.43 (2H, s). δ_C (100 MHz, $CDCl_3$) 20.8, 35.8, 59.8, 67.7, 123.9, 124.4, 124.6, 127.3, 128.5, 133.0, 133.4, 138.0, 139.3, 139.5, 167.4. ν_{max} (neat)/cm^{-1} 3248, 3044, 2914, 2100, 1640, 1601, 1532, 1459, 861, 744, 683. *m/z* (ES) 307.1559 (M^+ + H. $C_{18}H_{19}N_4O$ requires 307.1559).

(1*R*,2*R*)-*trans*-1-(3,5-Dimethyl-benzoylamino)-indan-2-yl-ammonium; chloride 24f

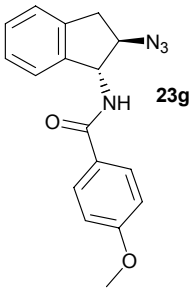


24f

Prepared as per **24a** using **23f** (1.386 g, 4.525 mmol), triphenylphosphine (1.187 g, 4.525 mmol) in THF (38 cm^3) and addition of water (5 cm^3). Concentration of the aqueous layer produced a yellow solid which was purified by washing with ether to yield **24f** (1.427 g, 99%) as a pale yellow solid, mp 265-266 °C (dec). $[\alpha]_D^{20} = -31.9$ (*c* 0.91 in MeOH).

δ_H (600 MHz, DMSO-d_6) 2.33 (6H, s), 3.02 (1H, dd, *J* 15.4, 8.7), 3.34-3.39 (1H, m, (under H_2O resonance)), 3.97-3.99 (1H, app. q), 5.67-5.70 (1H, app. t), 7.16 (1H, d, *J* 7.2), 7.20 (1H, s), 7.24-7.31 (3H, m), 7.59 (2H, s), 8.64 (3H, broad s), 8.90 (1H, d, *J* 8.3). δ_C (150 MHz, DMSO-d_6) 20.8, 34.5, 56.3, 57.5, 123.6, 124.6, 125.2, 127.3, 128.0, 132.6, 134.0, 137.2, 138.3, 140.9, 167.1. ν_{max} (neat)/cm^{-1} 3306, 2947, 2920, 2838, 1641, 1601, 1521, 1475, 1343, 863, 769, 750, 691. *m/z* (ES) 281.1662 (M^+ - Cl. $C_{18}H_{21}N_2O$ requires 281.1654).

(1*R*,2*R*)-*trans*-*N*-(2-Azido-indan-1-yl)-4-methoxy-benzamide 23g

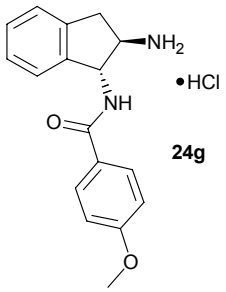


23g

Prepared as per the synthesis of **23a** using **21** (1.200 g, 5.696 mmol) in THF (10 cm^3), triethylamine (2.38 cm^3, 17.089 mmol), DMAP (0.035 g, 0.285 mmol) and a solution of **22g** (0.93 cm^3, 6.836 mmol) in THF (13 cm^3). Purification by column chromatography (CH_2Cl_2, R_f 0.3) gave **23g** (1.038 g, 59%) as an off-white solid, mp 174-175 ^oC. $[\alpha]_D^{20} = -26.1$ (*c* 0.76 in $CHCl_3$).

δ_H (600 MHz, DMSO-d_6) 2.84 (1H, dd, *J* 15.4, 8.4), 3.28 (1H, m, (under H_2O resonance)), 3.83 (3H, s), 4.38-4.42 (1H, app. q), 5.50-5.53 (1H, app. t), 7.03 (2H, d, *J* 8.8), 7.16 (1H, d, *J* 7.7), 7.24-7.29 (3H, m), 7.92 (2H, d, *J* 8.8), 8.83 (1H, d, *J* 8.4). δ_C (150 MHz, DMSO-d_6) 35.2, 55.4, 59.2, 66.7, 113.5, 123.7, 124.6, 126.2, 127.1, 128.0, 129.2, 138.9, 141.1, 161.8, 166.1. ν_{max} (neat)/cm^{-1} 3279, 3025, 2913, 2847, 2097, 1634, 1507, 1259, 844, 750. *m/z* (ES) 331.1164 (M^+ + Na. $C_{17}H_{16}N_4O_2Na$ requires 331.1171).

(1*R*,2*R*)-*trans*-1-(4-Methoxy-benzoylamino)-indan-2-yl-ammonium; chloride 24g

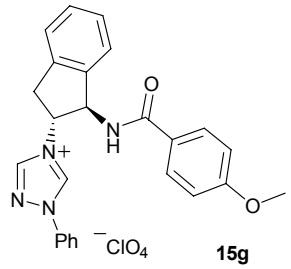


24g

Prepared as per **24a** using **23g** (0.938 g, 3.043 mmol), triphenylphosphine (0.798 g, 3.043 mmol) in THF (25 cm^3) and addition of water (4 cm^3). Concentration of the aqueous layer produced a white solid which was purified by washing with ether to yield **24g** (0.925 g, 95%) as a white solid, mp 272-273 °C. $[\alpha]_D^{20}$ = -10.5 (*c* 0.87 in MeOH).

δ_H (600 MHz, DMSO-d_6) 2.99 (1H, dd, *J* 14.7, 7.9), 3.28-3.39 (1H, m (under H_2O resonance)), 3.84 (3H, s), 3.94-3.97 (1H, app. q,), 5.68-5.71 (1H, app. t), 7.04 (2H, d *J* 7.7), 7.18 (1H, d, *J* 6.4), 7.27-7.31 (3H, m), 7.95 (2H, d, *J* 7.7), 8.49 (3H, s (broad)), 8.87 (1H, d, *J* 7.2). δ_C (150 MHz, DMSO-d_6) 34.6, 55.4, 56.7, 57.7, 113.5, 123.8, 124.7, 126.2, 127.4, 128.2, 129.4, 138.4, 141.0, 161.8, 166.4. ν_{max} (neat)/cm^{-1} 3323, 2933, 2866, 1629, 1608, 1533, 1505, 1251, 842, 742. *m/z* (ES) 283.1450 (M^+ - Cl. $C_{17}H_{19}N_2O_2$ requires 283.1447).

(1*R*,2*R*)-*trans*-4-[1-(4-Methoxy-benzoylamino)-indan-2-yl]-1-phenyl-4*H*-[*1,2,4*]triazol-1-ium; perchlorate 15g

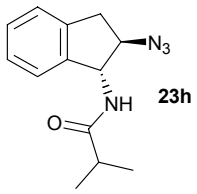


15g

Prepared as per **15a** using **25** (0.355 g, 1.441 mmol), oven-dried molecular sieves (4Å, 1.40 g) and **24g** (free-based amine, 0.388 g, 1.373 mmol) in CH_3CN (14 cm^3). The reaction was heated under reflux for 7 d under an atmosphere of Ar. Filtration under a stream of Ar followed by removal of the filtrate *in vacuo* yielded a red-brown residue. Purification by column chromatography (7:3 EtOAc-hexane, R_f 0.2) gave **15g** (0.533 g, 76%) as a pink solid, mp 123-124 ^oC. $[\alpha]_D^{20}$ = -88.9 (c 0.72 in $CHCl_3$).

δ_H (600 MHz, DMSO-d_6) 3.59 (1H, dd, *J* 16.1, 9.6), 3.72 (1H, dd, *J* 16.1, 8.3), 3.82 (3H, s), 5.31 (1H, ddd, *J* 9.6, 8.7, 8.3), 6.11 (1H, dd, *J* 8.7, 8.3), 7.02 (2H, d, *J* 8.7), 7.32 (1H, d, *J* 7.2), 7.37-7.44 (3H, m), 7.66 (1H, t, *J* 7.3), 7.73-7.75 (2H, app. t), 7.90 (2H, d, *J* 8.7), 7.95 (2H, d, *J* 7.5), 9.09 (1H, d, *J* 8.3), 9.74 (1H, s), 11.21 (1H, s). δ_C (150 MHz, DMSO-d_6) 36.4, 55.4, 60.1, 65.6, 113.5, 120.6, 123.9, 124.7, 125.7, 127.7, 128.6, 129.5, 130.3, 130.7, 135.0, 137.7, 139.4, 141.4, 144.7, 162.0, 166.9. ν_{max} (neat)/cm^{-1} 3363, 3123, 3074, 2841, 1640, 1605, 1571, 1498, 1460, 1253, 1075, 757, 687. *m/z* (ES) 411.1822 (M^+ -ClO_4. $C_{25}H_{23}N_4O_2$ requires 411.1821).

(1*R*,2*R*)-*trans*-*N*-(2-Azido-indan-1-yl)-isobutyramide 23h

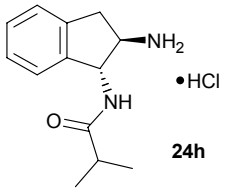


23h

Prepared as per the synthesis of **23a** using **21** (1.000 g, 4.747 mmol) in CH_2Cl_2 (8 cm^3), triethylamine (1.98 cm^3, 14.241 mmol) and a solution of **22h** (0.60 cm^3, 5.696 mmol) in CH_2Cl_2 (8 cm^3). Purification by column chromatography (0.95:0.05 CH_2Cl_2-hexane, R_f 0.2) gave **23h** (1.137 g, 98%) as a white solid, mp 177-178 ^oC. $[\alpha]_D^{20}$ = -15.3 (*c* 0.87 in $CHCl_3$).

δ_H (600 MHz, DMSO-d_6) 1.07 (3H, d, *J* 6.6), 1.11 (3H, d, *J* 7.0), 2.44-2.48 (1H, m), 2.77 (1H, dd, *J* 15.5, 8.4), 3.24 (1H, dd, *J* 15.5, 7.5), 4.17-4.21 (1H, app. q), 5.25-5.27 (1H, app. t), 7.10 (1H, d, *J* 7.0), 7.24-7.28 (3H, m), 8.32 (1H, d, *J* 8.4). δ_C (150 MHz, DMSO-d_6) 19.2, 19.6, 34.1, 35.2, 58.6, 66.7, 123.5, 124.6, 127.1, 128.0, 138.8, 141.0, 176.5. ν_{max} (neat)/cm^{-1} 3269, 2973, 2877, 2100, 1644, 1524, 1460, 745. *m/z* (ES) 267.1209 (M^+ + Na. $C_{13}H_{16}N_4ONa$ requires 267.1222).

(1*R*,2*R*)-*trans*-1-(Isobutyrylamino)-indan-2-yl-ammonium; chloride 24h

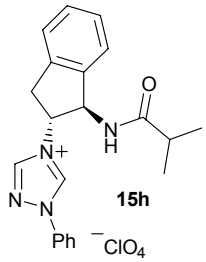


24h

Prepared as per **24a** using **23h** (0.979 g, 4.009 mmol), triphenylphosphine (1.052 g, 4.009 mmol) in THF (33 cm^3) and addition of water (5 cm^3). Concentration of the aqueous layer produced a white solid which was purified by washing with ether to yield **24h** (0.878 g, 86%) as a white solid, mp 274-276 °C. $[\alpha]_D^{20}$ = -28.1 (*c* 0.76 in MeOH).

δ_H (600 MHz, DMSO-d_6) 1.10 (3H, d, *J* 6.8), 1.12 (3H, d, *J* 6.8) 2.46-2.51 (1H, m), 2.99 (1H, dd, *J* 15.8, 8.7), 3.30 (1H, dd, *J* 15.8, 8.3), 3.74 (1H, ddd, *J* 8.7, 8.3, 7.9), 5.39 (1H, dd, *J* 7.9, 7.9), 7.11 (1H, d, *J* 6.0), 7.26-7.28 (3H, m), 8.41 (1H, d, *J* 7.9), 8.65 (3H, s (broad)). δ_C (150 MHz, DMSO-d_6) 19.5, 20.3, 34.4, 34.9, 56.9, 57.4, 124.0, 125.0, 127.7, 128.5, 138.8, 141.3, 177.4. ν_{max} (neat)/cm^{-1} 3301, 2966, 2831, 1643, 1596, 1522, 1474, 1354, 746. *m/z* (ES) 219.1488 (M^+ - Cl. $C_{13}H_{19}N_2O$ requires 219.1497).

(1*R*,2*R*)-*trans*-4-(1-Isobutyrylamino)-indan-2-yl]-1-phenyl-4*H*-[*1,2,4*]triazol-1-ium; perchlorate 15h

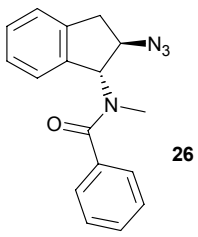


15h

Prepared as per **15a** using **25** (0.420 g, 1.705 mmol), oven-dried molecular sieves (4Å, 1.60 g) and **24h** (free-based amine, 0.354 g, 1.624 mmol) in CH_3CN (11 cm^3). The reaction was heated under reflux for 7 d under an atmosphere of Ar. Filtration under a stream of Ar followed by removal of the filtrate *in vacuo* yielded a red-brown residue. Purification by column chromatography (7:3 EtOAc-hexane, R_f 0.3) gave **15h** (0.515 g, 71%) as a pale brown solid, mp 86-87 ^oC. $[\alpha]_D^{20} = -2.3$ (c 0.53 in $CHCl_3$).

δ_H (600 MHz, DMSO-d_6) 1.02 (3H, d, *J* 6.6), 1.07 (3H, d, *J* 6.6), 2.47-2.51 (1H, m, (under DMSO resonance)), 3.56 (1H, dd, *J* 16.0, 9.5), 3.66 (1H, dd, *J* 16.0, 8.4), 5.09-5.13 (1H, app. q), 5.82-5.85 (1H, app. t), 7.27 (1H, d, *J* 7.3), 7.38-7.42 (3H, m), 7.67 (1H, t, *J* 7.3), 7.74-7.76 (2H, app. t,), 7.95 (2H, d, *J* 7.3), 8.62 (1H, d, *J* 8.1), 9.67 (1H, s), 11.20 (1H, s). δ_C (150 MHz, DMSO-d_6) 19.3, 19.6, 33.9, 36.0, 59.5, 66.0, 120.5, 123.7, 124.8, 127.7, 128.7, 130.0, 130.7, 134.9, 137.7, 138.9, 141.3, 144.6, 177.7. ν_{max} (neat)/cm^{-1} 3349, 3125, 2972, 1649, 1570, 1520, 1487, 1460, 1386, 1070, 756, 687. *m/z* (ES) 347.1875 (M^+ -ClO_4. $C_{21}H_{23}N_4O$ requires 347.1872).

(1*R*,2*R*)-*trans*-*N*-(2-Azido-indan-1-yl)-*N*-methyl-benzamide 26



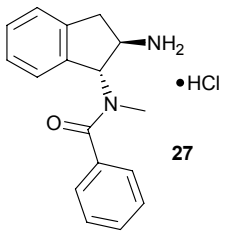
26

An oven-dried 25 cm^3 round bottomed flask equipped with a magnetic stirring bar was charged with **23a** (1.200 g, 4.312 mmol) and put under an atmosphere of Ar (balloon). THF (6.5 cm^3) was charged *via* syringe and the reaction was cooled to 0 ^oC. NaH (60% suspension, 0.198 g, 4.959 mmol) was added quickly from a clock glass, the reaction was returned to an atmosphere

of Ar and stirred for 30 min at 0 °C. Methyl iodide (0.30 cm^3, 4.743 mmol) was added *via* syringe and the reaction left to return to ambient temperature overnight. Deionised water (15 cm^3) and EtOAc (40 cm^3) were added and the organic layer removed. The aqueous layer was washed with EtOAc (4 x 10 cm^3) and the organic extracts combined, dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (8:2 CH_2Cl_2-hexane, R_f 0.2) gave **26** (0.850 g, 67%) as a yellow oil, $[\alpha]_D^{20}$ = -92.6 (*c* 1.10 in $CHCl_3$).

The ^1H and ^{13}C NMR spectra of this compound indicate the presence of 2 rotameric species at rt in DMSO-d_6 - the ratio of these was found to be 0.40:0.60; δ_H (400 MHz, DMSO-d_6) 2.67 (1.2H, s), 2.69 (0.6H, dd, *J* 15.6, 9.5), 2.79 (1.8H, s), 2.84 (0.4H, dd, *J* 15.6, 9.5), 3.21 (0.6H, dd, *J* 15.6, 8.0), 3.39-3.36 (0.4H, m, (under H_2O resonance)), 4.60-4.66 (1H, m), 5.09 (0.6H, d, *J* 7.8), 6.15 (0.4H, d, *J* 7.8), 7.25-7.35 (4H, m), 7.44-7.55 (5H, m). δ_C (100 MHz, DMSO-d_6) 28.2, 32.9, 34.5, 35.5, 63.0, 63.2, 64.0, 69.1, 123.3, 123.7, 125.1, 125.2, 126.4, 126.8, 127.3, 127.6, 128.4, 128.5, 128.67, 128.71, 129.6, 129.7, 136.2, 136.4, 137.4, 137.8, 138.7, 139.7, 171.5, 171.6. ν_{max} (neat)/cm^{-1} 3026, 2921, 2097, 1635, 1396, 1263, 748, 700. *m/z* (ES) 293.1404 (M^+ + H. $C_{17}H_{17}N_4O$ requires 293.1402).

(1*R*,2*R*)-*trans*-1-(Benzoyl-methyl-amino)-indan-2-yl-ammonium, chloride 27



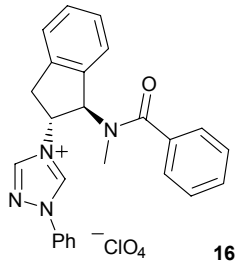
27

Prepared as per **24a** using **26** (0.850 g, 2.907 mmol), triphenylphosphine (0.763 g, 2.907 mmol) in THF (24 cm^3) and addition of water (4 cm^3). Concentration of the aqueous layer produced an off-white solid which was purified by washing with ether to yield **27** (0.814 g, 93%) as an off-white solid, mp 254-255 °C. $[\alpha]_D^{20}$ = -66.4 (*c* 1.15 in MeOH).

The ^1H and ^{13}C NMR spectra of this compound indicate the presence of 2 rotameric species at rt in DMSO-d_6 - the ratio of these was found to be 0.33:0.67. δ_H (600 MHz, DMSO-d_6) 2.68 (2.01H, s), 2.77 (0.99H, s), 2.85 (0.33H, dd, *J* 14.4, 8.0), 3.01 (0.67H, dd, *J* 14.4, 8.0), 3.24

(0.33H, dd, *J* 14.4, 7.5), 3.34-3.40 (0.66H, m, under H_2O resonance)), 4.09-4.14 (1H, m), 5.33 (0.33H, d, *J* 8.0), 6.27 (0.67H, d, *J* 8.0), 7.22-7.70 (9H, m), 8.68 (0.99H, s (broad)), 8.83 (2.01H, s (broad)). δ_C (150 MHz, DMSO-d_6) 28.5, 33.4, 34.3, 34.8, 53.0, 53.2, 62.5, 67.3, 123.5, 123.7, 125.4, 125.5, 126.90, 126.93, 127.8, 128.0, 128.5, 128.7, 129.0, 129.1, 129.5, 130.0, 136.7, 136.9, 138.0, 138.2, 138.8, 139.5, 171.8, 172.5. ν_{max} (neat)/cm^{-1} 2924, 2851, 1622, 1598, 1481, 1386, 751, 731, 697. *m/z* (ES) 267.1506 (M^+ - Cl. $C_{17}H_{19}N_2O$ requires 267.1497).

(1*R*,2*R*)-*trans*-4-[1-(Benzoyl-methyl-amino)-indan-2-yl]-1-phenyl-4*H*-[*1,2,4*]triazol-1-ium; perchlorate 16



16

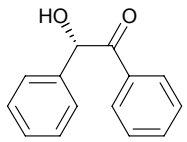
Prepared as per **15a** using **25** (0.476 g, 1.932 mmol), oven-dried molecular sieves (4Å, 1.80 g) and **27** (free-based amine, 0.490 g, 1.840 mmol) in CH_3CN (5 cm^3). The reaction was heated under reflux for 7 d under an atmosphere of Ar. Filtration under a stream of Ar followed by removal of the filtrate *in vacuo* yielded a red-brown residue. Purification by preparative thin layer chromatography (7:3 EtOAc-hexane, R_f 0.2) gave **16** (0.182 g, 20%) as an orange solid, mp 155-156 ^oC. $[\alpha]_D^{20}$ = -53.0 (c 0.82 in $CHCl_3$).

The ^1H NMR spectrum of this compound indicates the presence of 2 rotameric species at rt in CD_3CN - the ratio of these was found to be 0.20:0.80, the ^{13}C spectrum indicates the major rotamer only. δ_H (600 MHz, CD_3CN) 2.83-2.97 (3H, m), 3.31 (0.20H, s (broad)), 3.55 (0.80H, s (broad)), 3.67 (0.20H, s (broad)), 3.90 (0.80H, s (broad)), 5.43-5.47 (1H, app. q), 5.88 (0.20H, s (broad)), 6.65 (0.80H, s (broad)), 7.16-7.62 (9H, m), 7.73-7.88 (5H, m), 8.80 (0.20H, s (broad)), 9.16 (0.80H, s (broad)), 9.78 (0.20H, s (broad)), 10.25 (0.80H, s (broad)). δ_C (150 MHz, CD_3CN) 34.2, 37.7, 63.4, 66.0, 122.0, 125.6, 126.4, 128.4, 129.1, 129.4, 130.3, 131.2, 131.4, 132.1, 136.0, 136.6, 137.0, 139.7, 141.4, 145.4, 174.6. ν_{max} (neat)/cm^{-1} 3131, 3068, 1623, 1600,

1571, 1479, 1403, 1084, 760, 689. *m/z* (ES) 395.1873 (M^+ -ClO_4. $C_{25}H_{23}N_4O$ requires 395.1872).

Synthesis of acyloins 6 and 43-51

(*S*)-2-Hydroxy-1,2-diphenyl-ethanone (*S*)-6 (Table 2, entry 19)



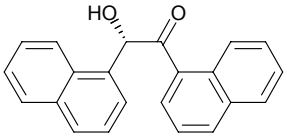
(*S*)-6

Prepared as per reaction condition set C using catalyst **15a** (52.90 mg, 0.11 mmol), with addition of toluene (0.67 cm^3) and KHMDS (220 μL, 0.110 mmol, 0.5M solution in toluene) over 7 min. Benzaldehyde (111.7 μL, 1.100 mmol) was added dropwise over 5 min and the reaction was stirred at room temperature for 18 h. Purification by column chromatography (6:4 CH_2Cl_2:hexane, R_f 0.2) gave **(*S*)-6** (13.6 mg, 12%) as a white solid, mp 131-132 °C, lit.,[1] 132-133 °C, 62% *ee*. $[\alpha]_D^{20}$ = +62.8 (c 0.20 in MeOH), lit.,[2] $[\alpha]_D^{20}$: +146.5 (c 1.0 in MeOH), for *S* enantiomer with 90% *ee*.

CSP-HPLC analysis. Chiralpak AD (4.6 mm x 25 cm), hexane/IPA: 9/1, 1.0 mL min^{-1}, RT, UV detection at 220 nm, retention times: 21.4 min (minor enantiomer) and 29.1 (major enantiomer).

δ_H (400 MHz, $CDCl_3$) 4.58 (1H, d, *J* 5.8), 5.98 (1H, d, *J* 5.8), 7.29-7.44 (5H, m (overlapping with $CHCl_3$ resonance)), 7.41-7.44 (2H, app. t), 7.53 (1H, t, *J* 7.0), 7.93 (2H, d, *J* 7.1)

(*S*)-2-Hydroxy-1,2-di-naphthalen-2-yl-ethanone (*S*)-43 (Table 3, entry 1)



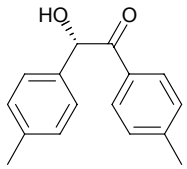
(*S*)-43

Prepared as per reaction condition set C using catalyst **15a** (52.90 mg, 0.11 mmol), with addition of toluene (0.40 cm^3) and KHMDS (220 μL, 0.110 mmol, 0.5M solution in toluene) over 7 min. Aldehyde **34** (171.80 mg, 1.100 mmol) in toluene (0.38 cm^3) was added dropwise over 5 min and the reaction was stirred at room temperature for 16 h. Purification by column chromatography (6:4 CH_2Cl_2:hexane, R_f 0.1) gave **(*S*)-43** (62.6 mg, 36%) as a pale yellow solid, mp 127-128 ^oC, lit.,[3] 127 ^oC, 35% *ee*. $[\alpha]_D^{20}$ = -6.8 (c 0.63 in $CHCl_3$), lit.,[4] $[\alpha]_D^{20}$: +21.0 (c 1.1 in $CHCl_3$), for *R* enantiomer with 99% *ee*.

CSP-HPLC analysis. Chiralpak AD (4.6 mm x 25 cm), hexane/IPA: 8/2, 1.0 mL min^{-1}, RT, UV detection at 254 nm, retention times: 28.1 min (minor enantiomer) and 47.7 (major enantiomer).

δ_H (400 MHz, $CDCl_3$) 4.75 (1H, s (broad)), 6.30 (1H, s), 7.45-7.61 (5H, m), 7.78-7.85 (5H, m), 7.89 (1H, d, *J* 8,5), 7.94 (1H, s), 8.01 (1H, d, *J* 8.5), 8.53 (1H, s)

(*S*)-2-Hydroxy-1,2-bis-(4-methylphenyl)ethanone (*S*)-45 (Table 3, entry 3)



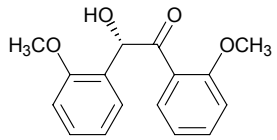
(*S*)-45

Prepared as per reaction condition set C using catalyst **15a** (52.90 mg, 0.11 mmol), with addition of toluene (0.65 cm^3) and KHMDS (220 μL, 0.110 mmol, 0.5M solution in toluene) over 7 min. Substrate **36** (129.7 μL, 1.100 mmol) was added dropwise over 5 min and the reaction was stirred at room temperature for 18 h. Purification by column chromatography (6:4 CH_2Cl_2:hexane, R_f 0.1) gave **(*S*)-45** (12.8 mg, 10%) as a yellow solid, mp 90-91 ^oC, lit.,[5] 89-90 ^oC, 45% *ee*. $[\alpha]_D^{20}$ = +51.3 (c 0.18 in MeOH), lit.,[6] $[\alpha]_D^{20}$: -130.8 (c 1.0 in MeOH), for *R* enantiomer with 82% *ee*.

CSP-HPLC analysis. Chiralpak AD (4.6 mm x 25 cm), hexane/IPA: 9/1, 0.8 mL min^{-1}, RT, UV detection at 254 nm, retention times: 29.3 min (minor enantiomer) and 33.8 (major enantiomer).

δ_H (400 MHz, $CDCl_3$) 2.31 (3H, s), 2.38 (3H, s), 4.60 (1H, s, (broad)), 5.92 (1H, s (broad)), 7.13-7.34 (6H, m (overlapping with $CHCl_3$ resonance)), 7.83 (2H, d, *J* 8.0)

(*S*)-2-Hydroxy-1,2-bis-(2-methoxy-phenyl)ethanone (*S*)-46 (Table 3, entry 4)



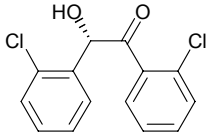
(*S*)-46

Prepared as per reaction condition set C using catalyst **15a** (52.90 mg, 0.11 mmol), with addition of toluene (0.48 cm^3) and KHMDS (220 µL, 0.110 mmol, 0.5M solution in toluene) over 7 min. Substrate **37** (149.77 mg, 1.100 mmol) in toluene (0.30 cm^3) was added dropwise over 5 min and the reaction was stirred at room temperature for 24 h. Purification by column chromatography (CH_2Cl_2, R_f 0.2) gave **(*S*)-46** (42.9 mg, 29%) as an off-white solid, mp 98-99 ^oC, lit.,[7] 98-99 ^oC, 54% *ee*. $[\alpha]_D^{20}$ = +39.1 (c 0.43 in $CHCl_3$), lit.,[8] $[\alpha]_D^{20}$: +123.0 (c 1.0 in $CHCl_3$), for *S* enantiomer with 98% *ee*.

CSP-HPLC analysis. Chiralpak OD-H (4.6 mm x 25 cm), hexane/IPA: 85/15, 0.5 mL min^{-1}, RT, UV detection at 254 nm, retention times: 30.8 min (major enantiomer) and 43.7 (minor enantiomer).

δ_H (400 MHz, $CDCl_3$) 3.74 (3H, s), 3.75 (3H, s), 4.50 (1H, s (broad)), 6.13 (1H, s), 6.76-6.81 (2H, app. t), 6.84-6.88 (1H, app. t), 6.93-6.97 (1H, app. t), 7.17-7.22 (2H, m (overlapping with $CHCl_3$ resonance)), 7.37-7.41 (1H, app. t), 7.70 (1H, d, *J* 7.5)

(*S*)-1,2-Bis-(2-chloro-phenyl)-2-hydroxy-ethanone (*S*)-48 (Table 3, entry 6)



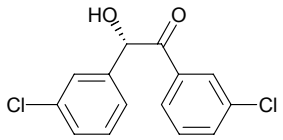
(*S*)-48

Prepared as per reaction condition set C using catalyst **15a** (52.90 mg, 0.11 mmol), with addition of toluene (0.66 cm^3) and KHMDS (220 μL, 0.110 mmol, 0.5M solution in toluene) over 7 min. Substrate **39** (123.9 μL, 1.100 mmol) was added dropwise over 5 min and the reaction was stirred at room temperature for 16 h. Purification by column chromatography (6:4 CH_2Cl_2:hexane, R_f 0.2) gave **(*S*)-48** (11.6 mg, 8%) as a colourless solid, mp 61-62 ^oC, lit.,[5] 63-64 ^oC, 28% *ee*. $[\alpha]_D^{20}$ = +9.3 (c 0.17 in $CHCl_3$), lit.,[4] $[\alpha]_D^{20}$: -46.0 (c 1.0 in $CHCl_3$), for *R* enantiomer with 97% *ee*.

CSP-HPLC analysis. Chiralpak AD (4.6 mm x 25 cm), hexane/IPA: 9/1, 0.8 mL min^{-1}, RT, UV detection at 254 nm, retention times: 22.8 min (major enantiomer) and 25.8 (minor enantiomer).

δ_H (400 MHz, $CDCl_3$) 3.30 (1H, s (broad)), 6.31 (1H, s), 7.15-7.23 (5H, m (overlapping with $CHCl_3$ resonance)), 7.31-7.34 (3H, m)

(*S*)-1,2-Bis-(3-chloro-phenyl)-2-hydroxy-ethanone (*S*)-49 (Table 3, entry 7)



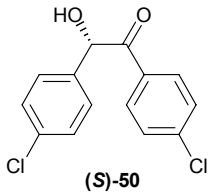
(*S*)-49

Prepared as per reaction condition set C using catalyst **15a** (52.90 mg, 0.11 mmol), with addition of toluene (0.66 cm^3) and KHMDS (220 μL, 0.110 mmol, 0.5M solution in toluene) over 7 min. Substrate **40** (124.60 μL, 1.100 mmol) was added dropwise over 5 min and the reaction was stirred at room temperature for 16 h. Purification by column chromatography (6:4 CH_2Cl_2:hexane, R_f 0.3) gave **(*S*)-49** (73.1 mg, 47%) as an off-white solid, mp 75-76 ^oC, lit.,[5] 76-77 ^oC, 1% *ee*. $[\alpha]_D^{20}$ = +2.4 (c 0.73 in $CHCl_3$), lit.,[4] $[\alpha]_D^{20}$: -31.0 (c 1.2 in $CHCl_3$), for *R* enantiomer with 99% *ee*.

CSP-HPLC analysis. Chiralpak AD (4.6 mm x 25 cm), hexane/IPA: 9/1, 0.8 mL min^{-1}, RT, UV detection at 254 nm, retention times: 19.7 min (minor enantiomer) and 26.9 (major enantiomer).

δ_H (400 MHz, $CDCl_3$) 4.50 (1H, d, *J* 5.5), 5.90 (1H, d, *J* 5.5), 7.23-7.41 (5H, m), 7.53 (1H, d, *J* 8.0), 7.76 (1H, d, *J* 7.5), 7.93 (1H, s)

(*S*)-1,2-Bis-(4-chloro-phenyl)-2-hydroxy-ethanone (*S*)-50 (Table 3, entry 8)



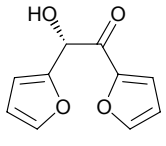
(*S*)-50

Prepared as per reaction condition set C using catalyst **15a** (52.90 mg, 0.11 mmol), with addition of toluene (0.40 cm^3) and KHMDS (220 µL, 0.110 mmol, 0.5M solution in toluene) over 7 min. Substrate **41** (154.63 mg, 1.100 mmol) in toluene (0.38 cm^3) was added dropwise over 5 min and the reaction was stirred at room temperature for 16 h. Purification by column chromatography (6:4 CH_2Cl_2:hexane, R_f 0.3) gave **(*S*)-50** (48.8 mg, 32%) as an off-white solid, mp 88-89 ^oC, lit.,[5] 87-88 ^oC, 6% *ee*. $[\alpha]_D^{20}$ = +1.4 (c 0.49 in MeOH), lit.,[9] $[\alpha]_D^{20}$: -12.3 (c 1.0 in MeOH), for *R* enantiomer with 29% *ee*.

CSP-HPLC analysis. Chiralpak OJ-H (4.6 mm x 25 cm), hexane/IPA: 95/5, 0.6 mL min^{-1}, RT, UV detection at 220 nm, retention times: 34.7 min (major enantiomer) and 37.8 (minor enantiomer).

δ_H (400 MHz, $CDCl_3$) 4.49 (1H, s (broad)), 5.90 (1H, s), 7.26-7.27 (2H, d, (overlapping with $CHCl_3$ resonance)), 7.32 (2H, d, *J* 8.0), 7.40 (2H, d, *J* 7.8), 7.84 (2H, d, *J* 7.8)

(*S*)-1,2-Di-furan-2-yl-2-hydroxy-ethanone (*S*)-51 (Table 3, entry 9)



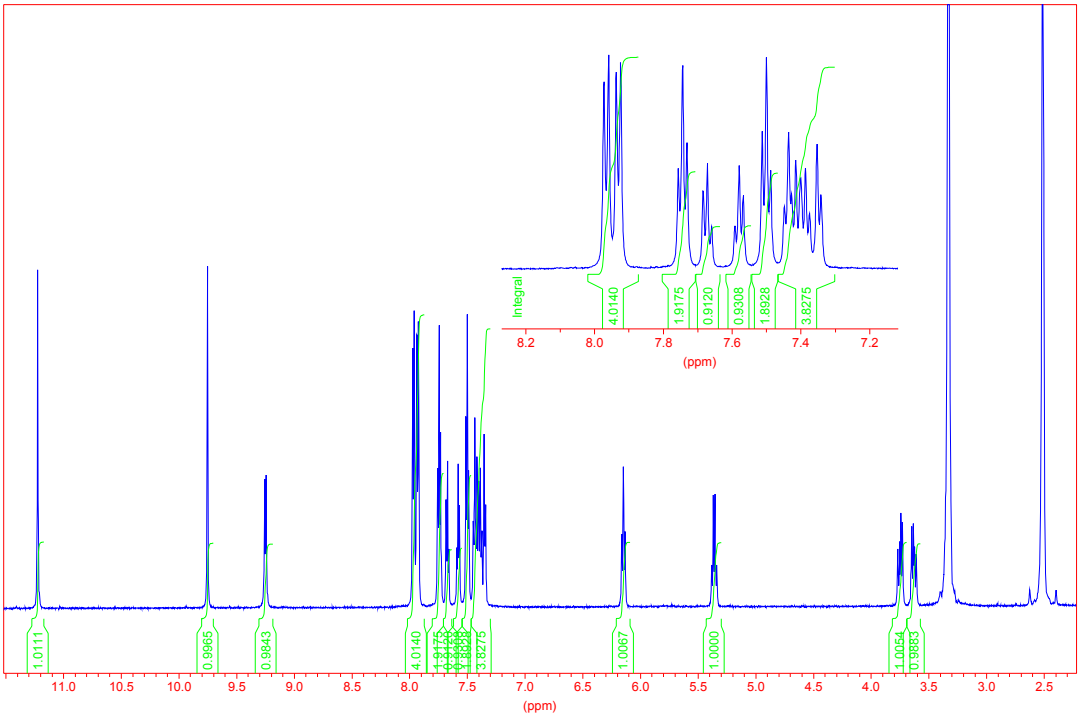
(*S*)-51

Prepared as per reaction condition set C using catalyst **15a** (52.90 mg, 0.11 mmol), with addition of toluene (0.69 cm^3) and KHMDS (220 μL, 0.110 mmol, 0.5M solution in toluene) over 7 min. Substrate **42** (90.72 μL, 1.100 mmol) was added dropwise over 5 min and the reaction was stirred at room temperature for 18 h. Purification by column chromatography (CH_2Cl_2, R_f 0.2) gave **(*S*)-51** (51.3 mg, 49%) as a pale yellow solid, mp 134-135 ^oC, lit.,[10] 135-136 ^oC, 1% *ee*. $[\alpha]_D^{20}$ = +0.6 (c 0.51 in MeOH), lit.,[4] $[\alpha]_D^{20}$: -21.6 (c 0.1 in MeOH), for *R* enantiomer with 92% *ee*.

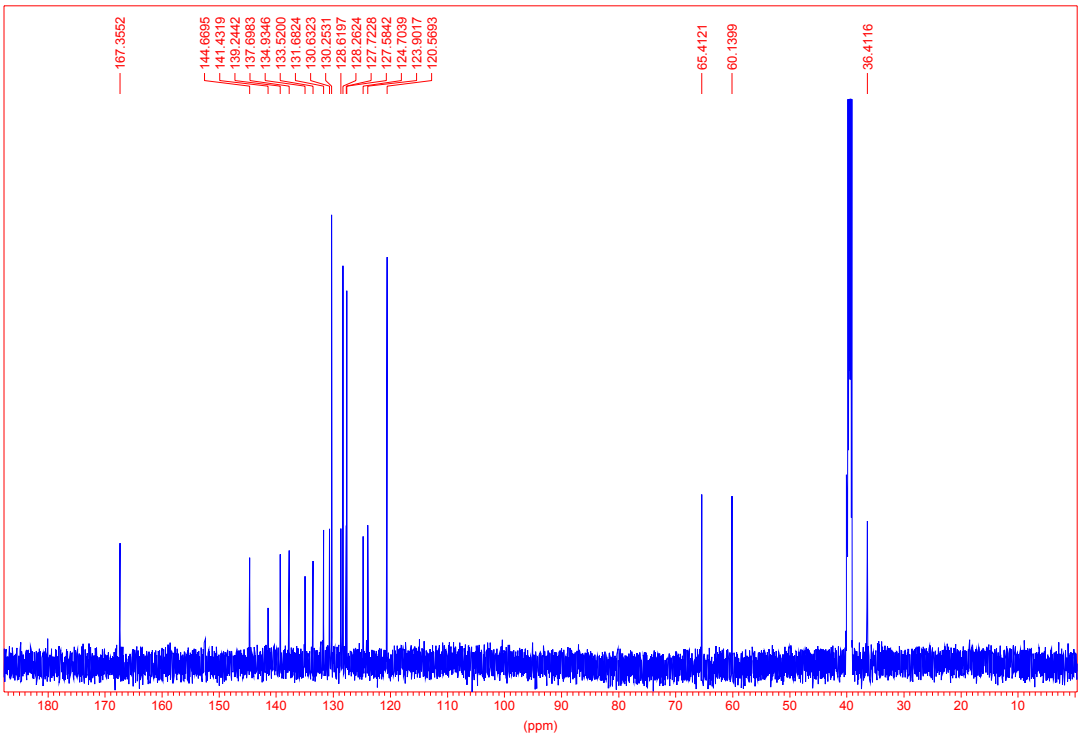
CSP-HPLC analysis. Chiralpak AD (4.6 mm x 25 cm), hexane/IPA: 9/1, 0.8 mL min^{-1}, RT, UV detection at 254 nm, retention times: 33.3 min (major enantiomer) and 40.9 (minor enantiomer).

δ_H (400 MHz, $CDCl_3$) 4.22 (1H, s (broad)), 5.82 (1H, s, (broad)), 6.37 (1H, dd, *J* 3.3, 1.5), 6.42 (1H, d, *J* 3.5), 6.56 (1H, dd, *J*, 3.5, 1.5), 7.27 (1H, m (overlapping with $CHCl_3$ resonance)), 7.40 (1H, d, *J* 1.5), 7.64 (1H, app. s)

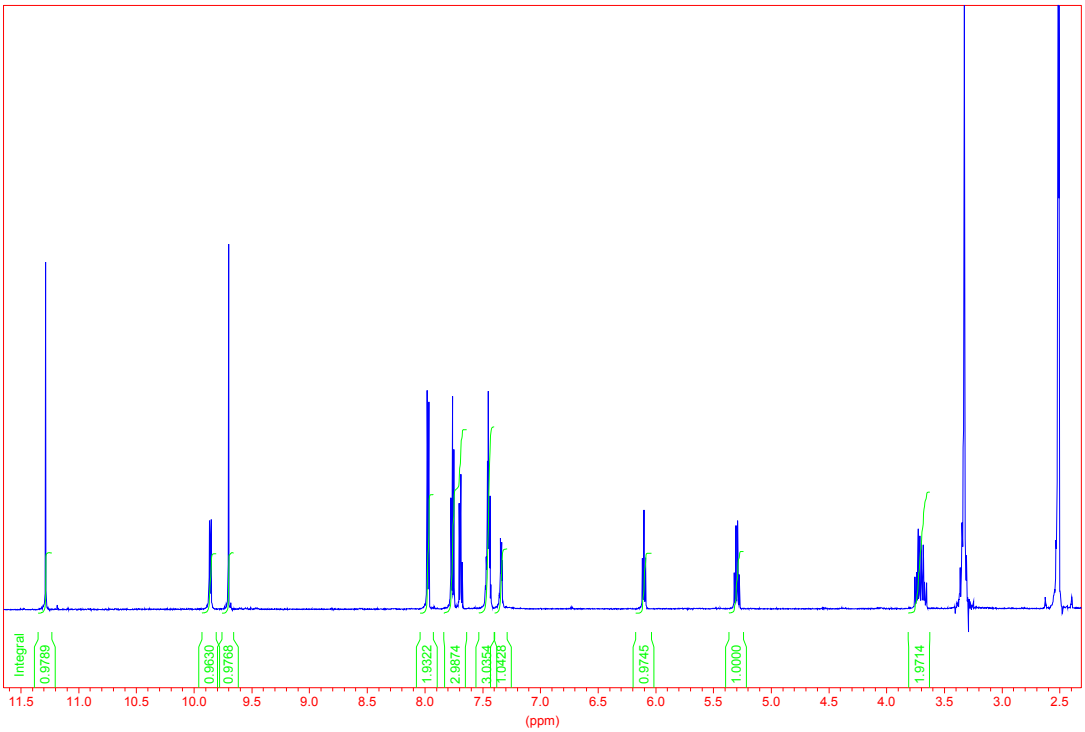
4.0 NMR spectra



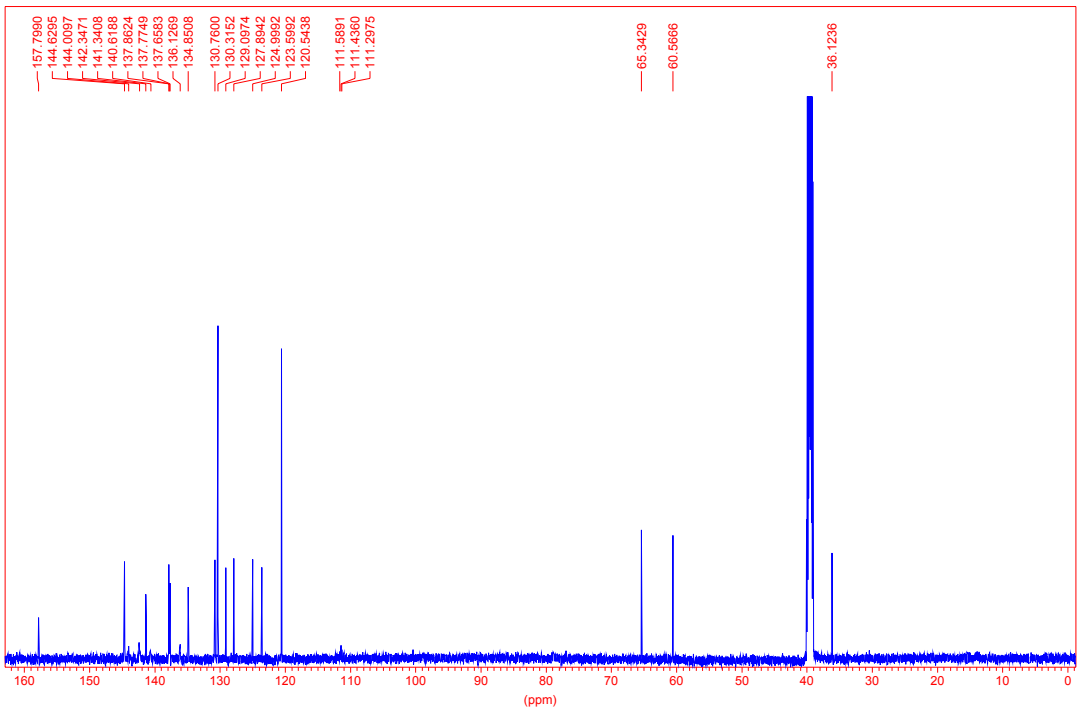
^{1}H NMR spectrum (600 MHz, DMSO) of catalyst **15a**



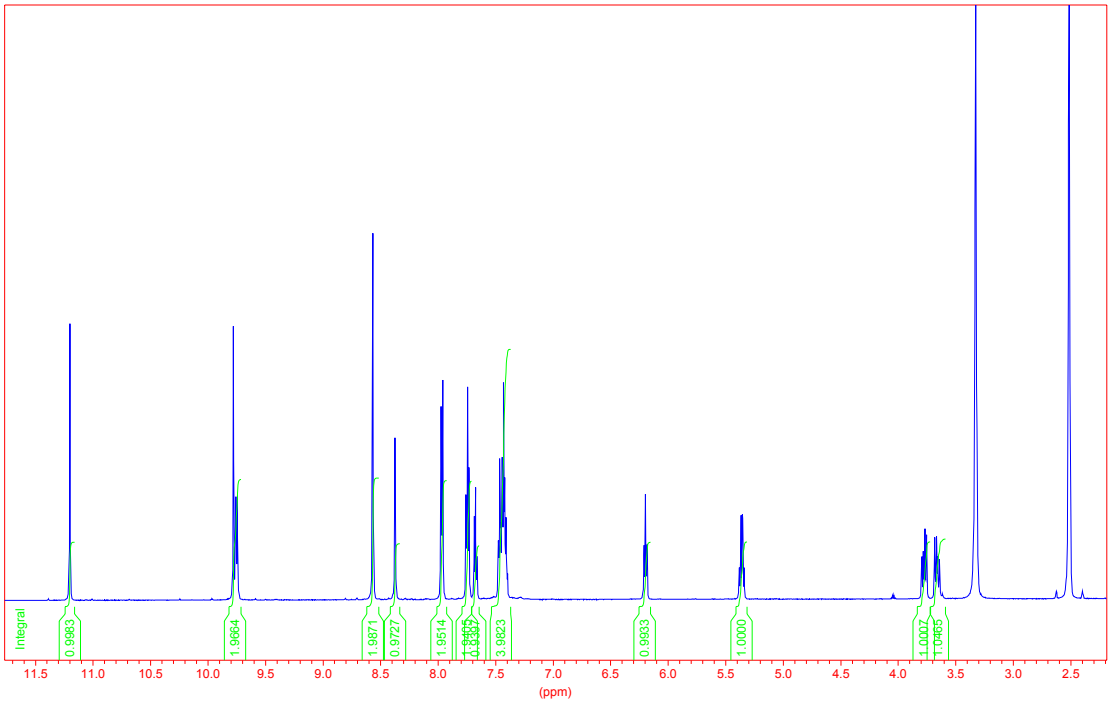
^{13}C NMR spectrum (150 MHz, $CDCl_3$) of catalyst **15a**



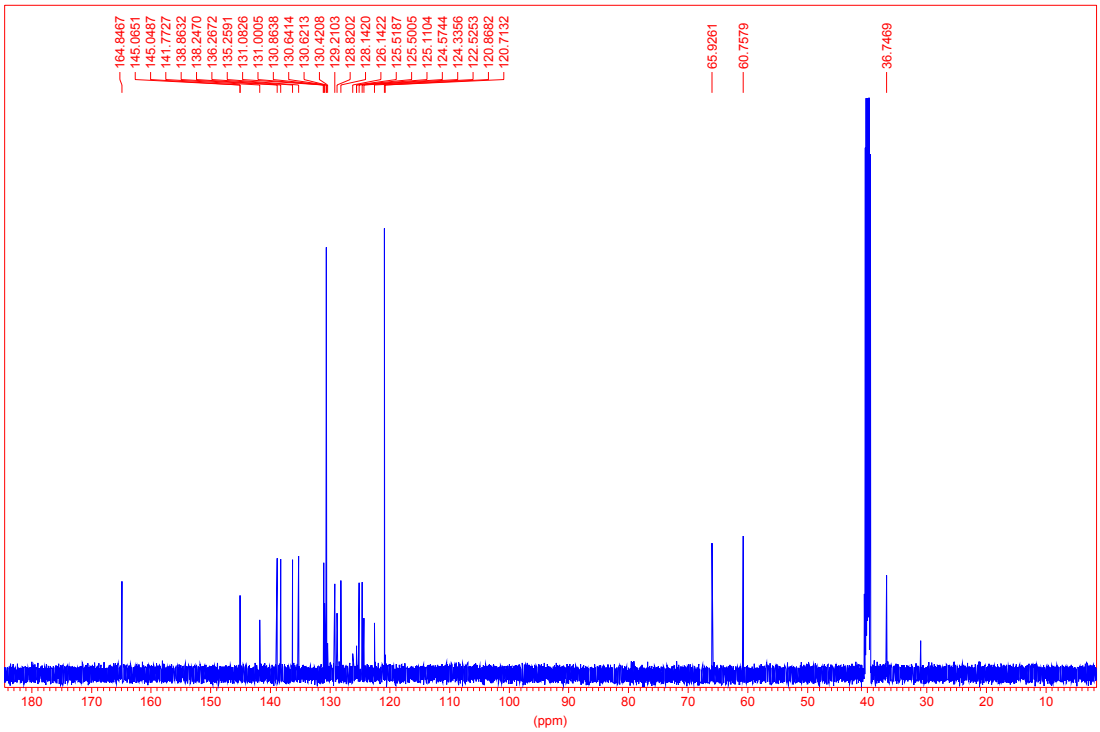
^{1}H NMR spectrum (600 MHz, DMSO) of catalyst **15b**



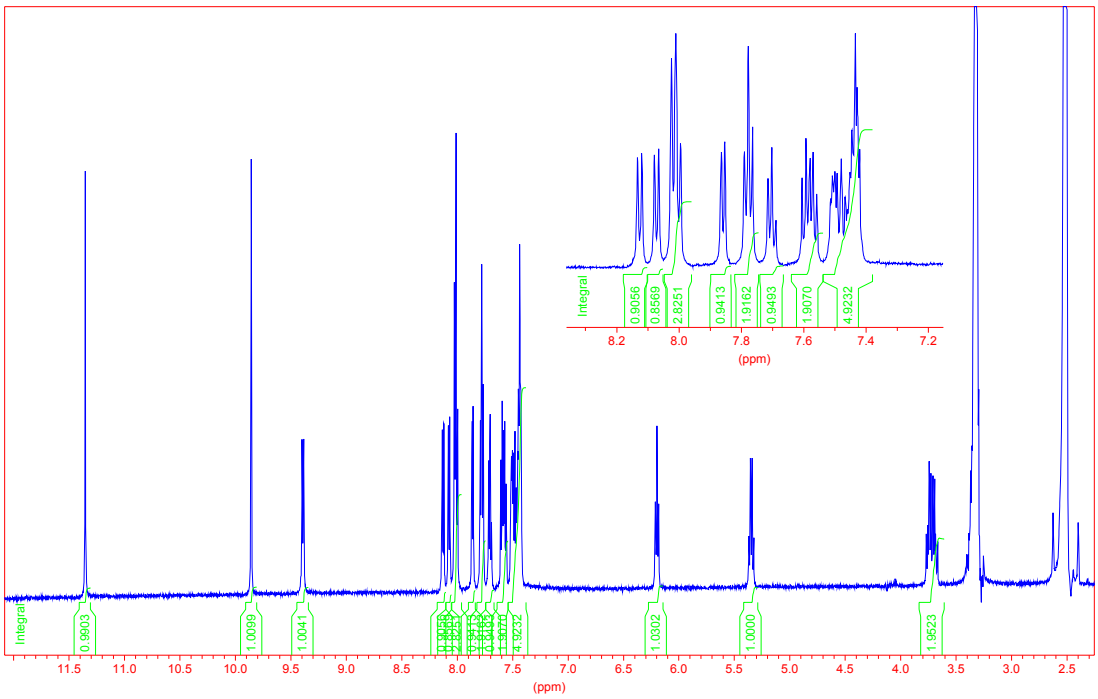
^{13}C NMR spectrum (150 MHz, DMSO) of catalyst **15b**



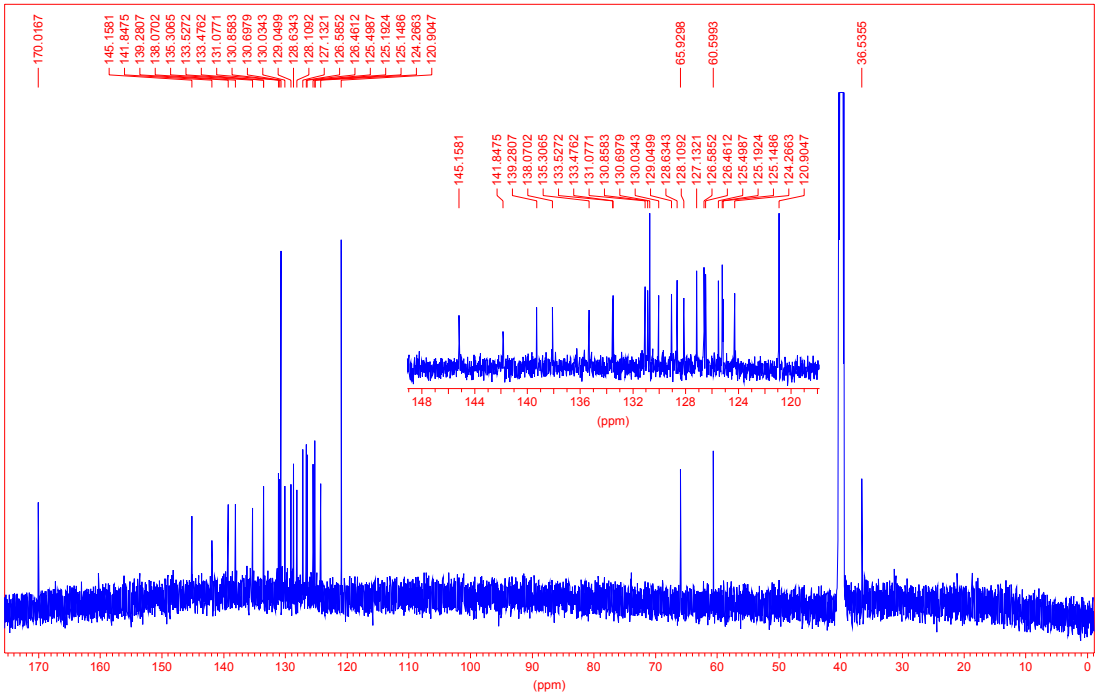
^{1}H NMR spectrum (600 MHz, DMSO) of catalyst **15c**



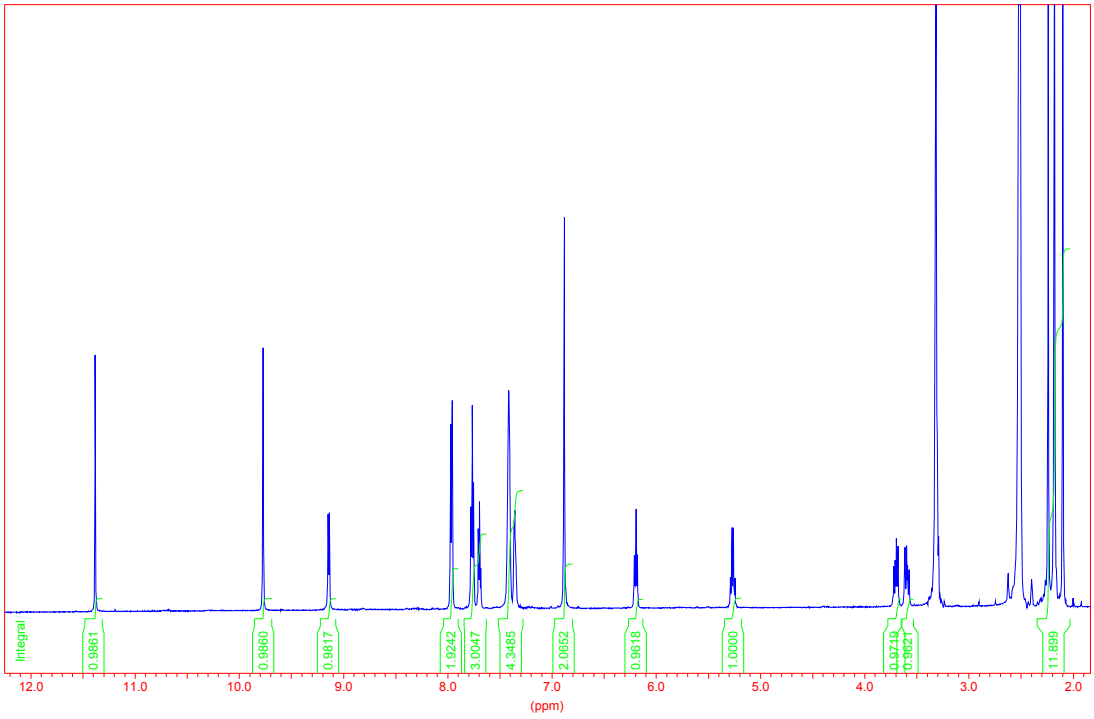
^{13}C NMR spectrum (150 MHz, DMSO) of catalyst **15c**



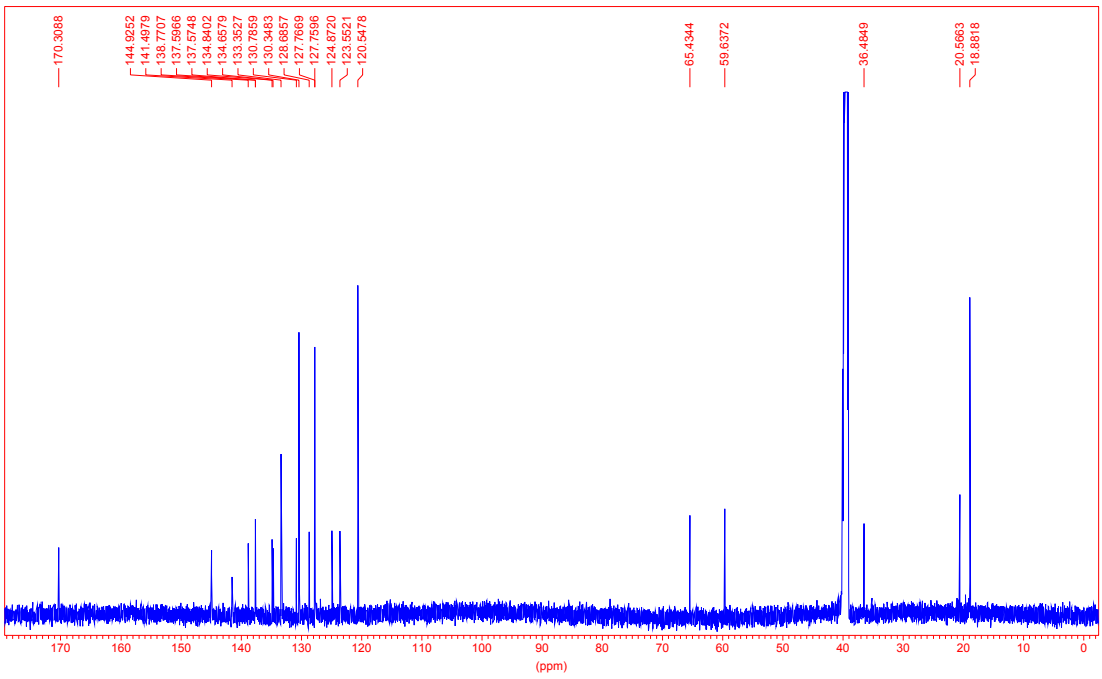
^{1}H NMR spectrum (600 MHz, DMSO) of catalyst **15d**



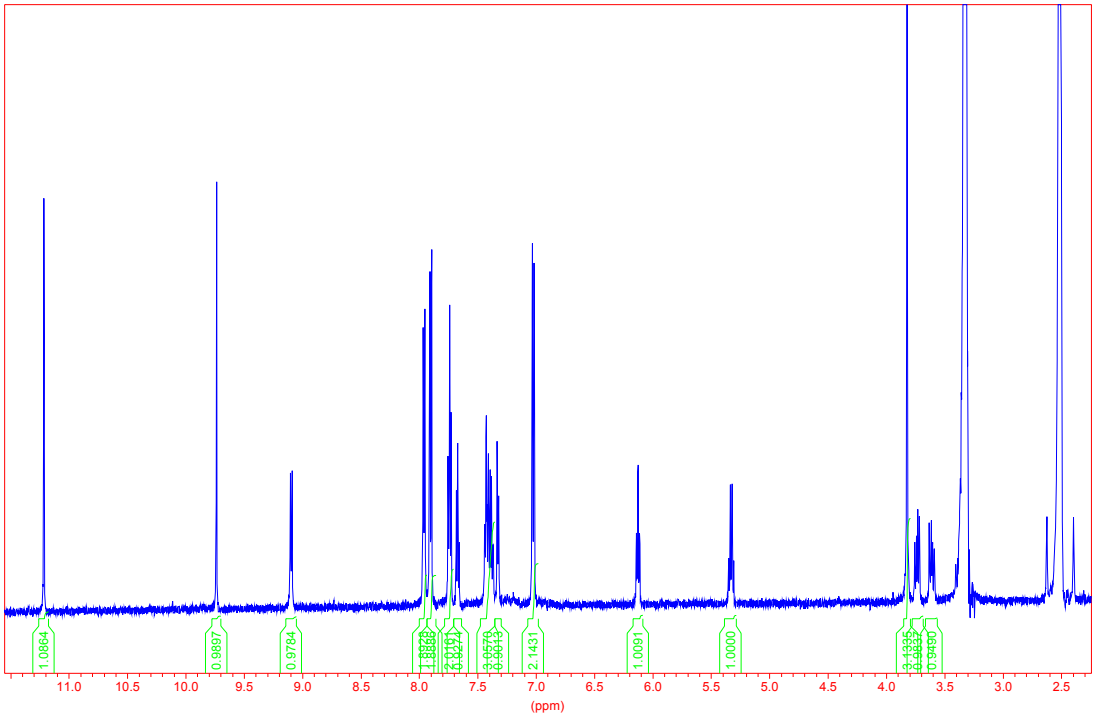
^{13}C NMR spectrum (150 MHz, DMSO) of catalyst **15d**



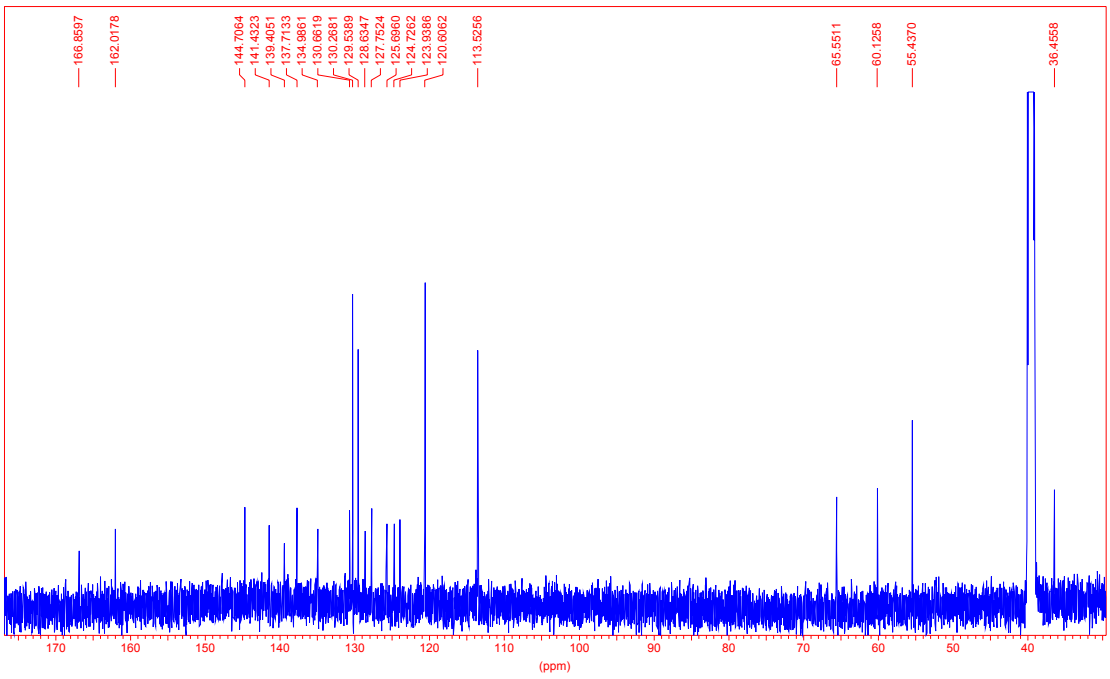
^{1}H NMR spectrum (600 MHz, DMSO) of catalyst **15e**



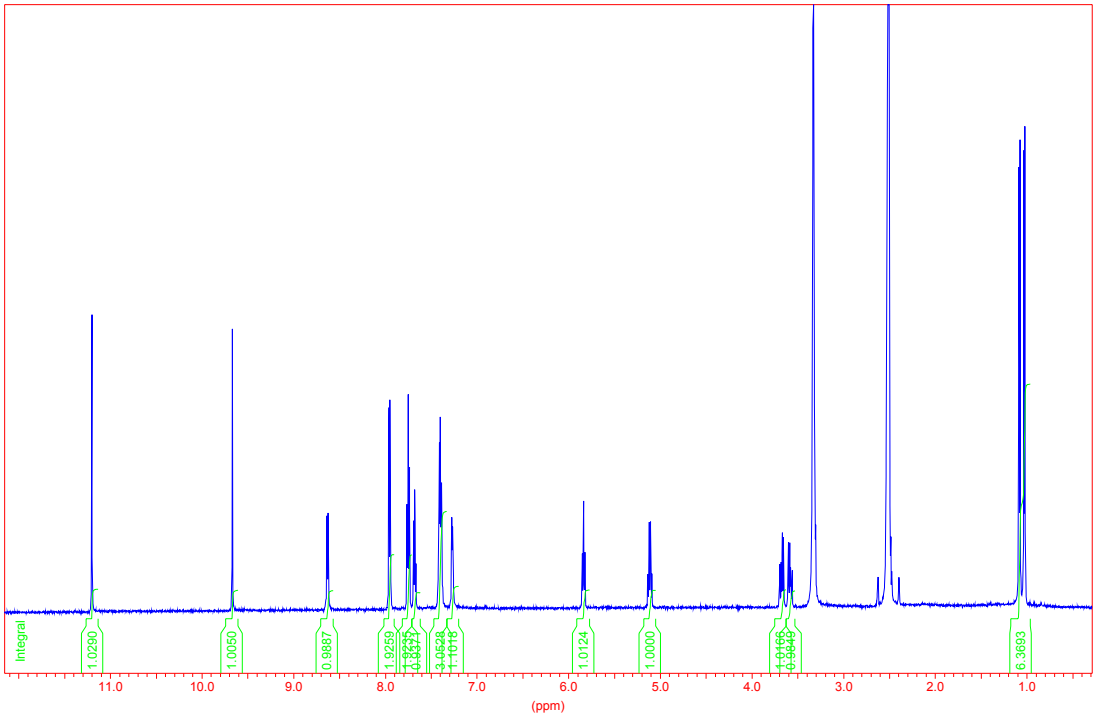
^{13}C NMR spectrum (150 MHz, DMSO) of catalyst **15e**



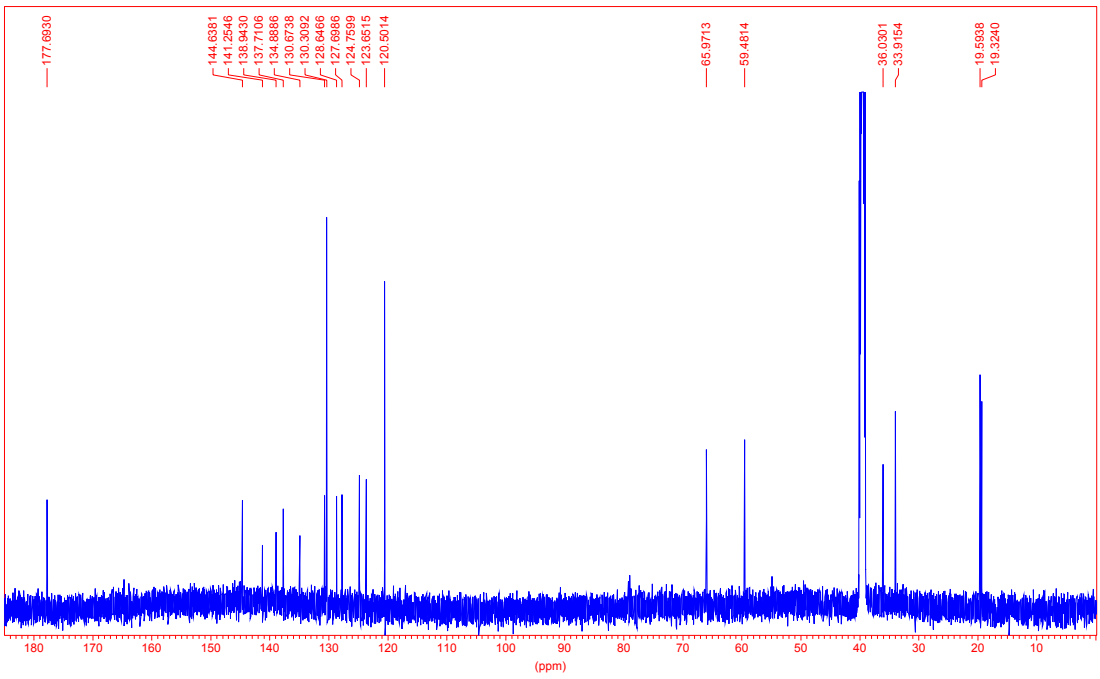
^{1}H NMR spectrum (600 MHz, DMSO) of catalyst **15g**



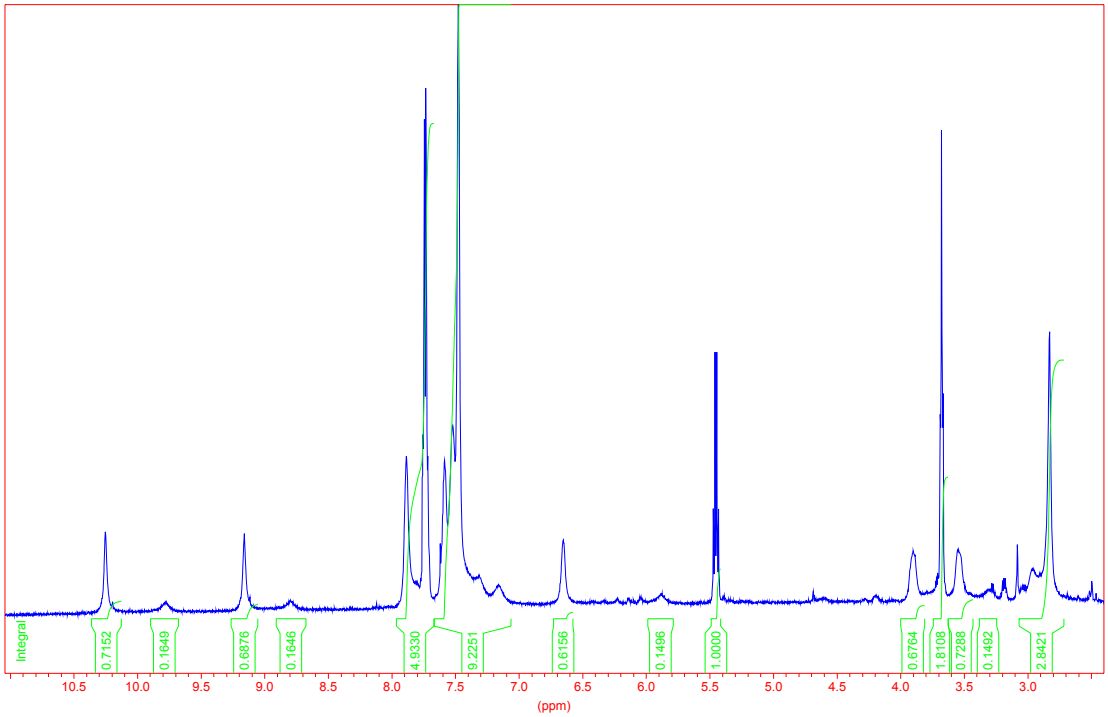
^{13}C NMR spectrum (150 MHz, DMSO) of catalyst **15g**



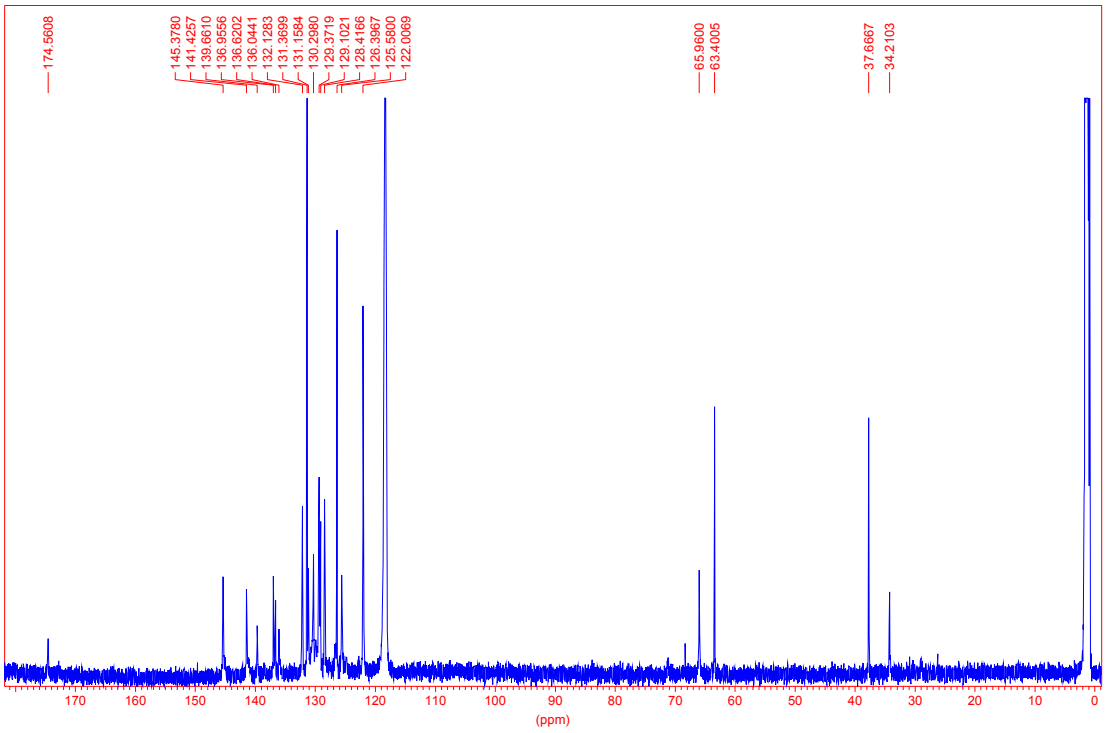
^{1}H NMR spectrum (600 MHz, DMSO) of catalyst **15h**



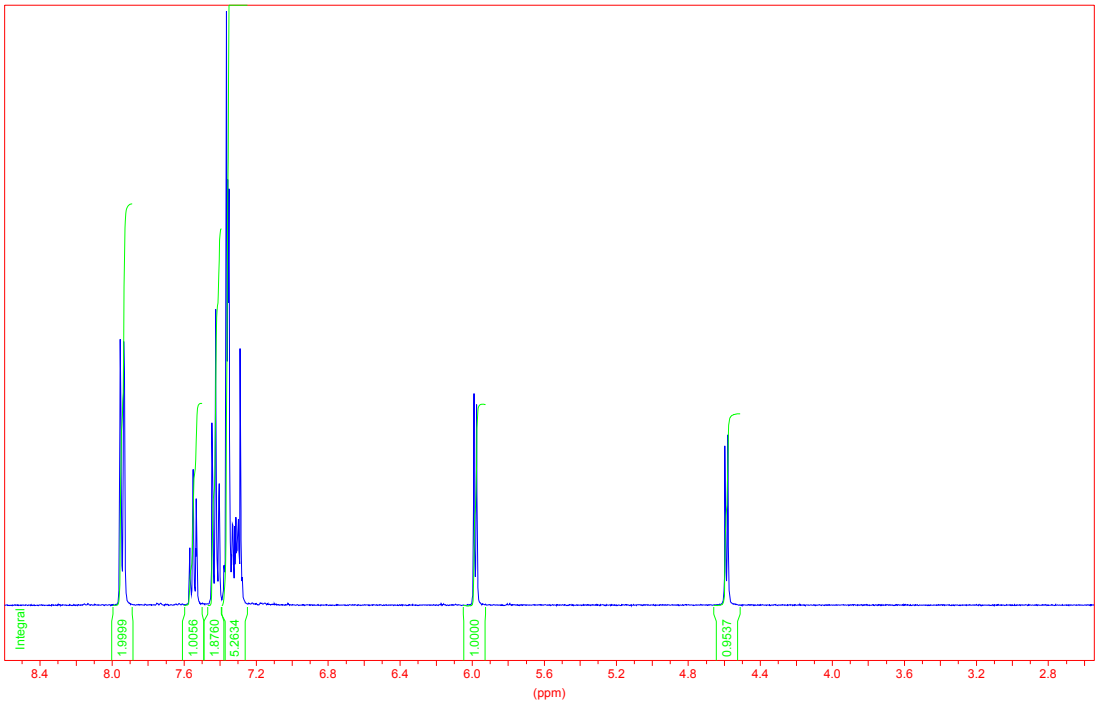
^{13}C NMR spectrum (150 MHz, DMSO) of catalyst **15h**



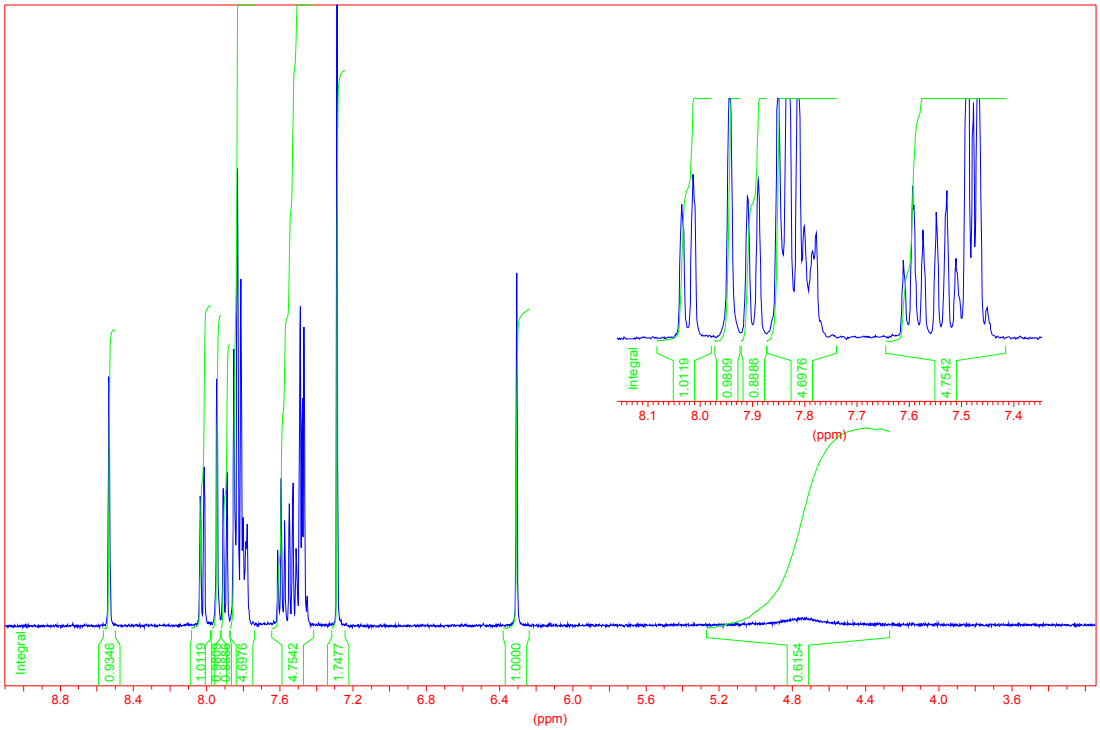
^{1}H NMR spectrum (600 MHz, CD_3CN) of catalyst **16**



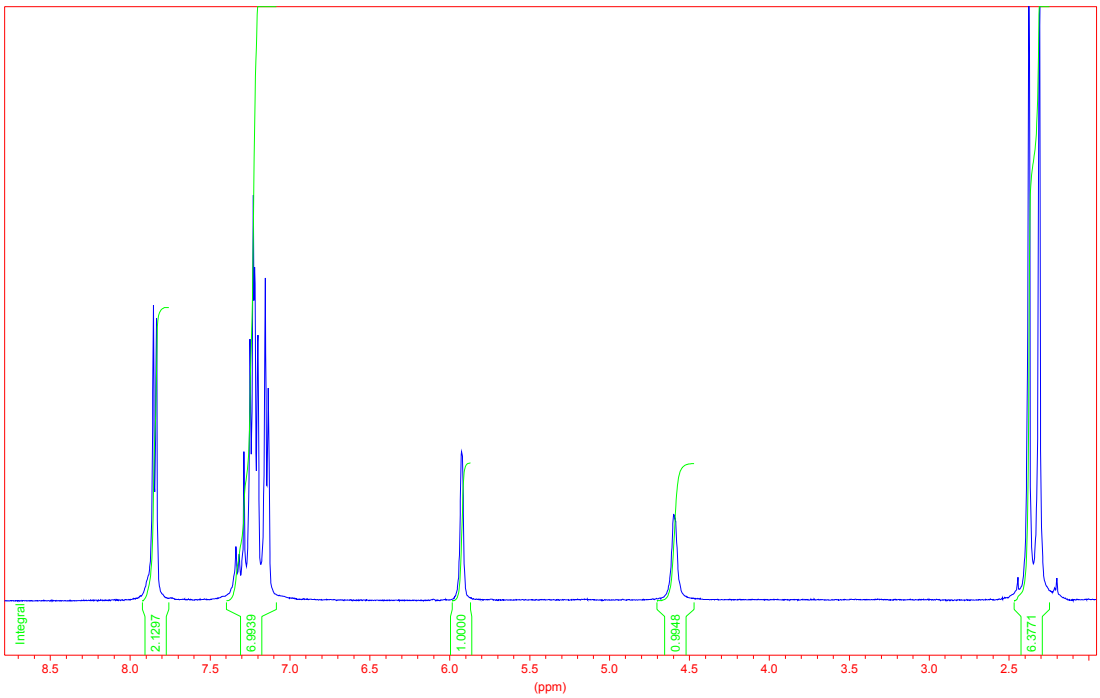
^{13}C NMR spectrum (150 MHz, CD_3CN) of catalyst **16**



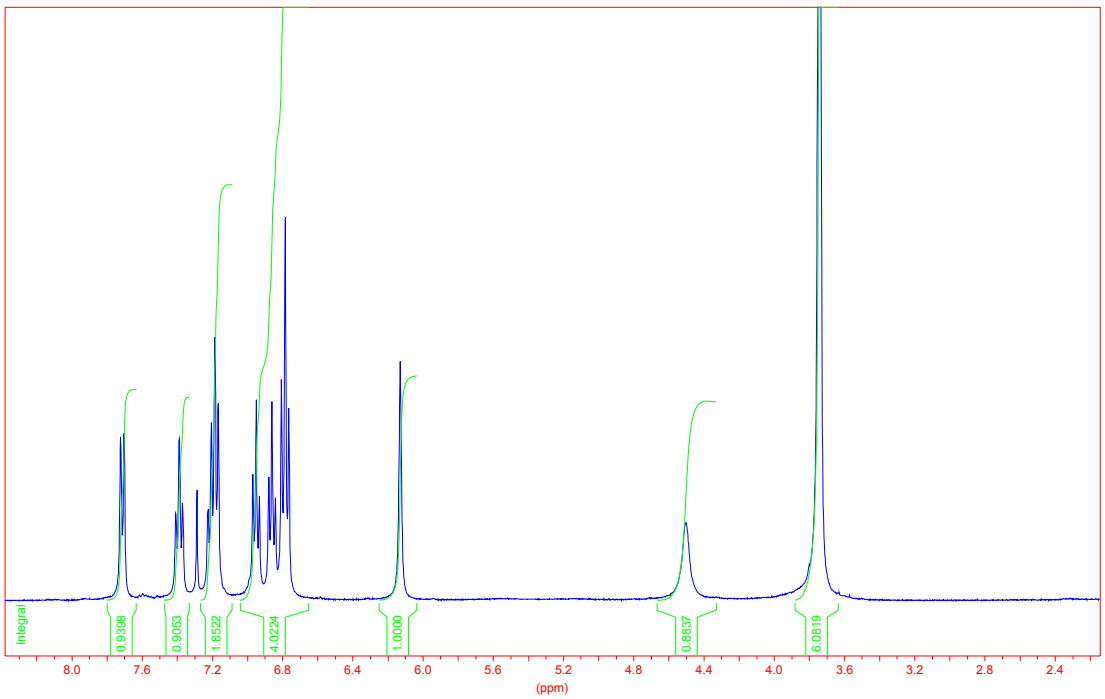
^{1}H NMR spectrum (400 MHz, $CHCl_3$) of benzoin **(*S*)-6**



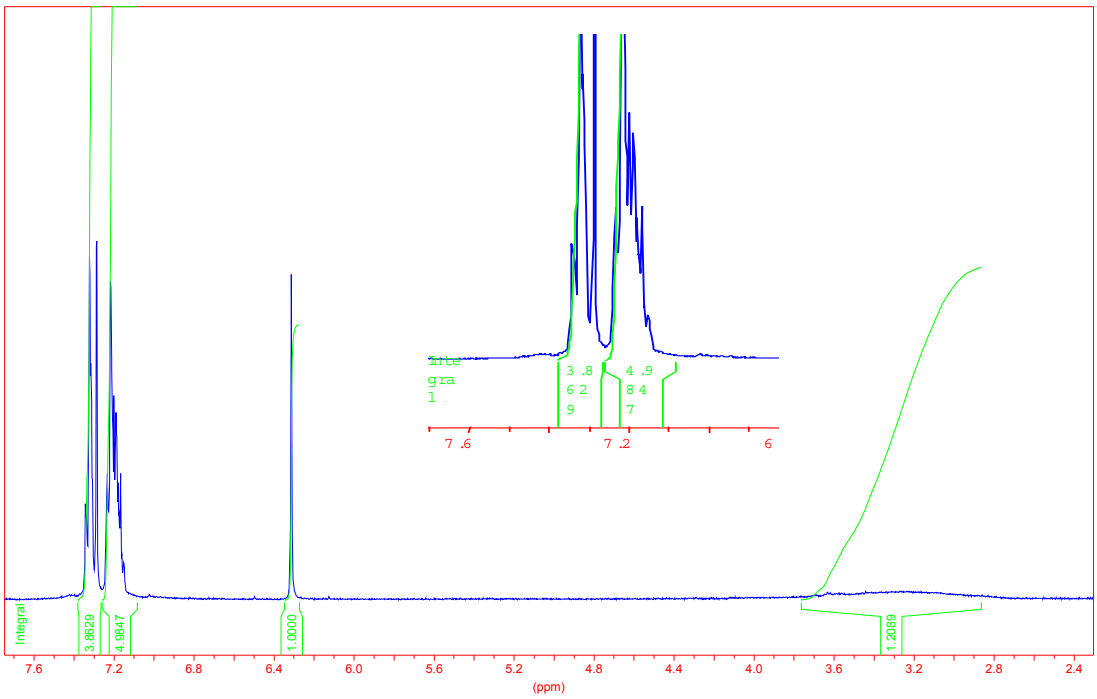
^{1}H NMR spectrum (400 MHz, $CHCl_3$) of acyloin **(*S*)-43**



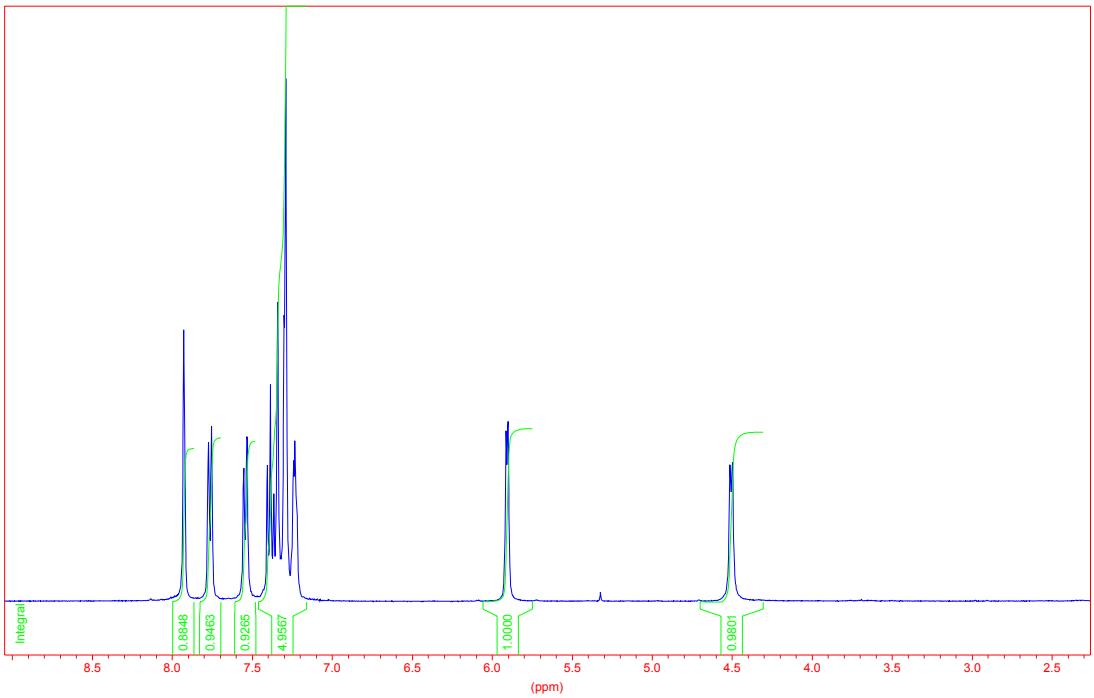
^{1}H NMR spectrum (400 MHz, $CHCl_3$) of acyloin **(*S*)-45**



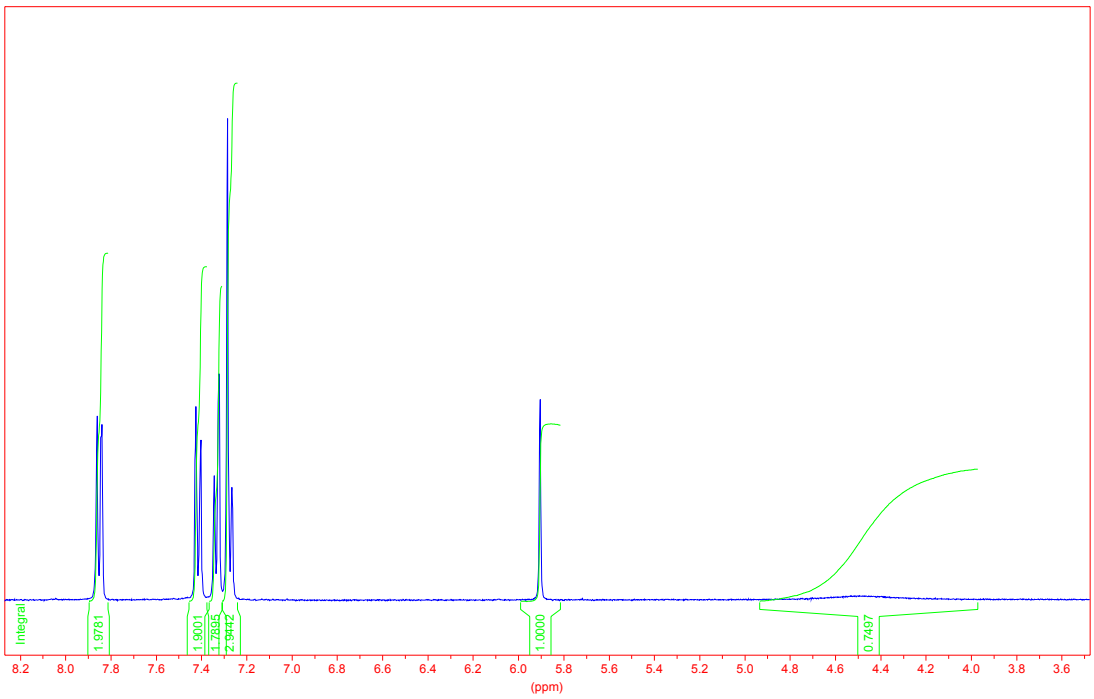
^{1}H NMR spectrum (400 MHz, $CHCl_3$) of acyloin **(*S*)-46**



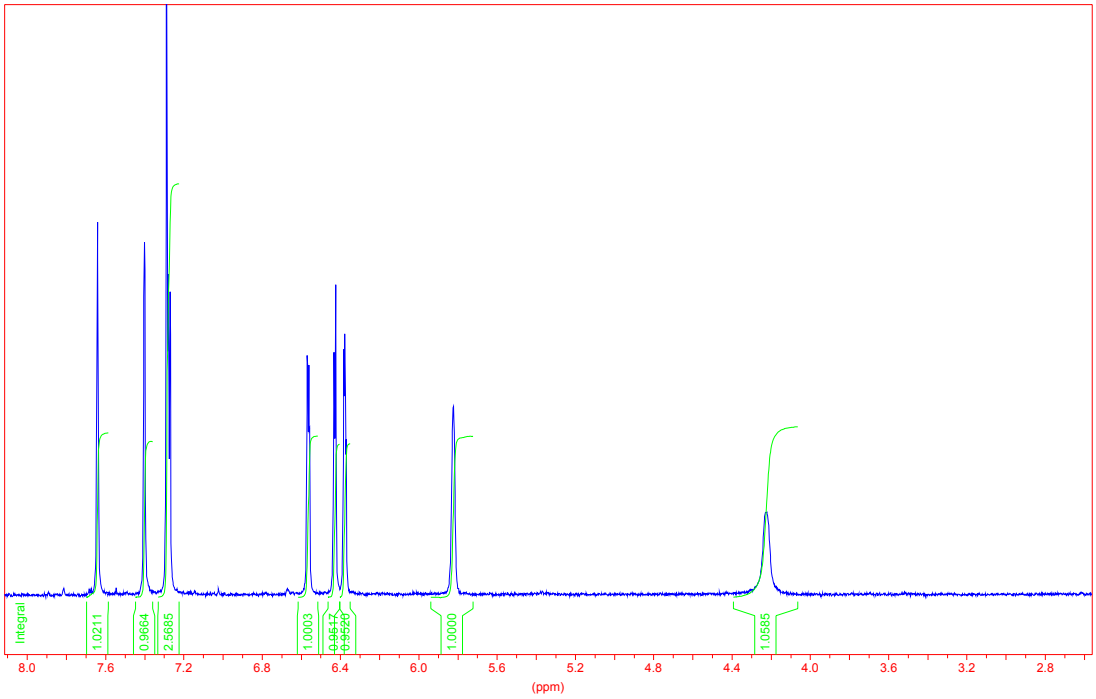
^{1}H NMR spectrum (400 MHz, $CHCl_3$) of acyloin **(*S*)-48**



^{1}H NMR spectrum (400 MHz, $CHCl_3$) of acyloin **(*S*)-49**



^{1}H NMR spectrum (400 MHz, $CHCl_3$) of acyloin **(*S*)-50**



^{1}H NMR spectrum (400 MHz, $CHCl_3$) of acyloin **(*S*)-51**

5.0 HPLC Chromatograms – acyloin products

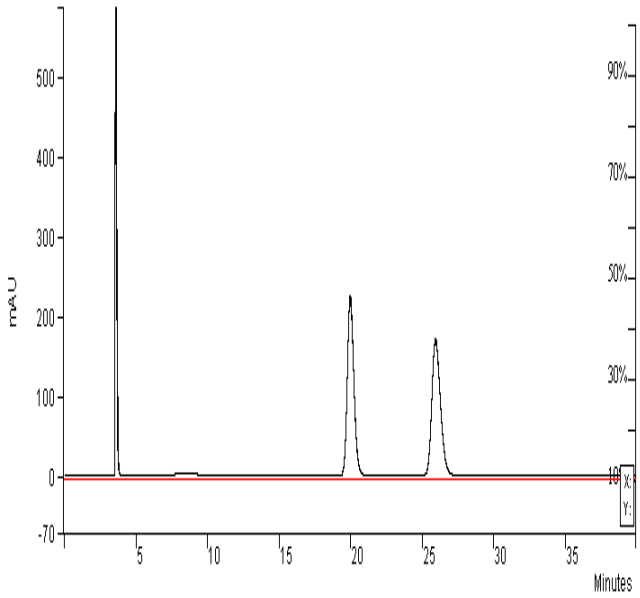
HPLC Chromatograms of benzoin **6**

Chiralpak AD (4.6 mm x 25 cm),

Hexane/IPA: 90/10, 1.0 mL min^{-1},

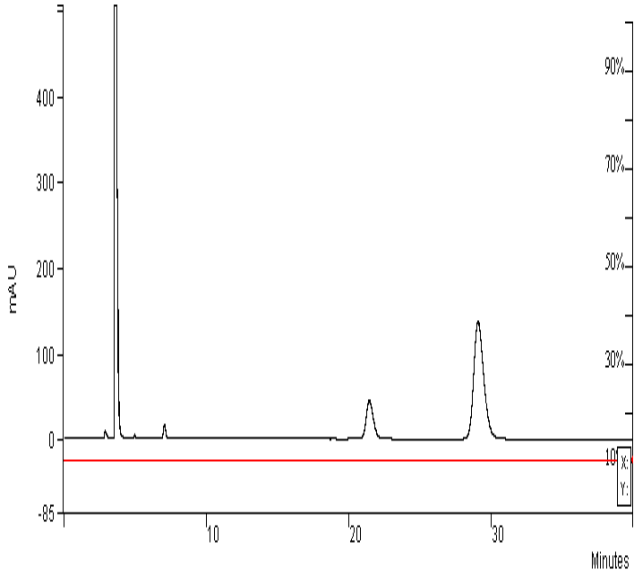
RT, UV detection at 220 nm

Peak No	Result	Ret. Time (min)	Area (counts)
1	26.9502	3.563	55210724
2	35.4223	19.962	72566776
3	35.5037	25.923	72733568



Resolved HPLC chromatogram for benzoin **6** – racemate

Peak No	Result	Ret. Time (min)	Area (counts)
1	59.5478	3.567	130113328
2	7.3227	21.420	16000226
3	30.9034	29.050	67524552



Resolved HPLC chromatogram for enantioenriched benzoin **(*S*)-6**

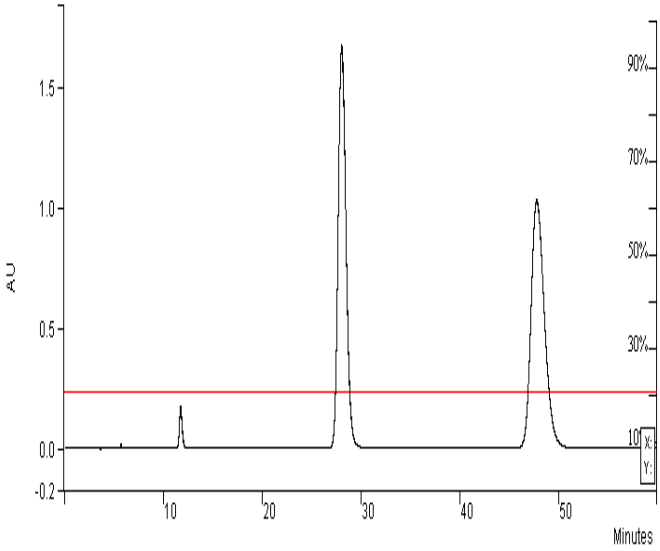
HPLC Chromatograms of acyloin **43**

Chiralpak AD (4.6 mm x 25 cm),

Hexane/IPA: 80/20, 1.0 mL min^{-1},

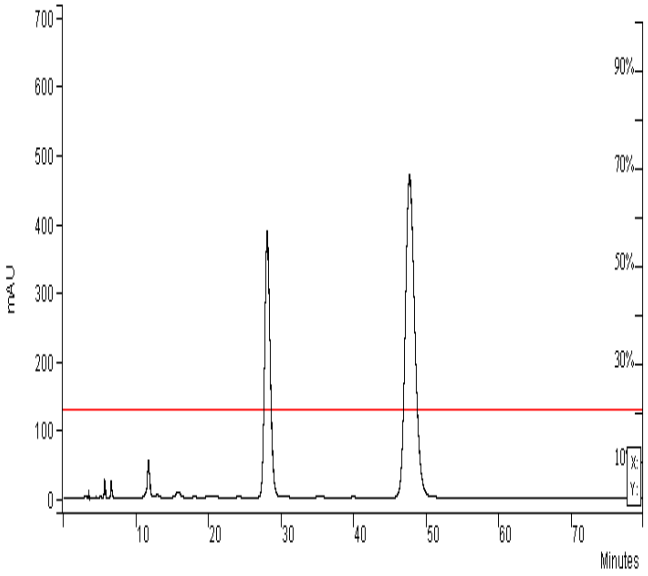
RT, UV detection at 254 nm

Peak No	Result	Ret. Time (min)	Area (counts)
1	2.6624	11.693	52989984
2	46.8965	28.002	933370496
3	49.0492	47.737	976215360



Resolved HPLC chromatogram for acyloin **43** – racemate

Peak No	Result	Ret. Time (min)	Area (counts)
1	2.6721	11.685	18404882
2	29.9990	28.057	206630688
3	62.2526	47.686	428791392



Resolved HPLC chromatogram for enantioenriched **(*S*)-43**

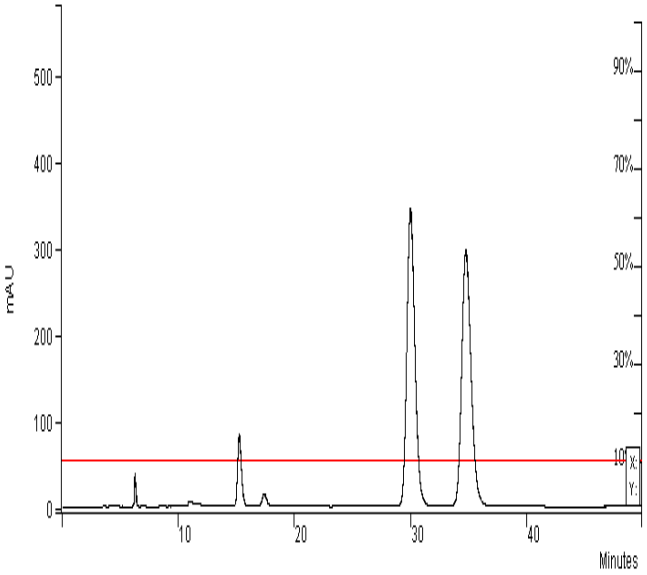
HPLC Chromatograms of acyloin **45**

Chiralpak AD (4.6 mm x 25 cm),

Hexane/IPA: 90/10, 0.8 mL min^{-1},

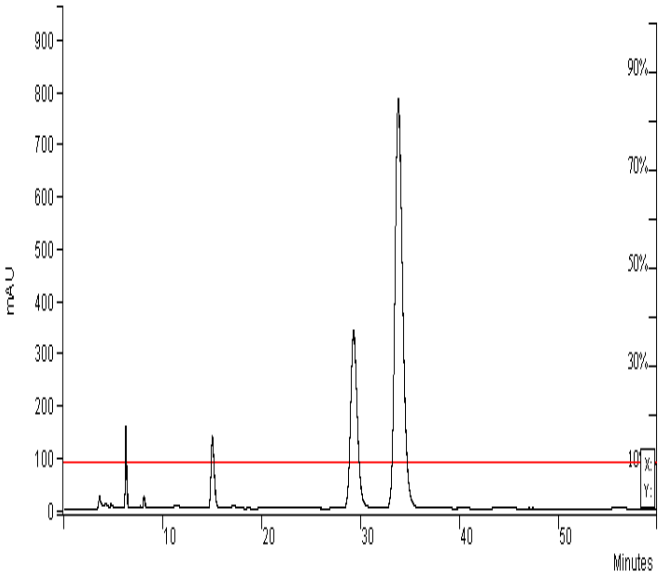
RT, UV detection at 254 nm

Peak No	Result	Ret. Time (min)	Area (counts)
1	5.3822	15.218	20315480
2	44.7063	29.974	168748384
3	44.7916	34.745	169070336



Resolved HPLC chromatogram for acyloin **45** – racemate

Peak No	Result	Ret. Time (min)	Area (counts)
1	5.1507	14.978	34403052
2	24.3999	29.248	162974368
3	64.5106	33.766	430885536



Resolved HPLC chromatogram for enantioenriched acyloin **(*S*)-45**

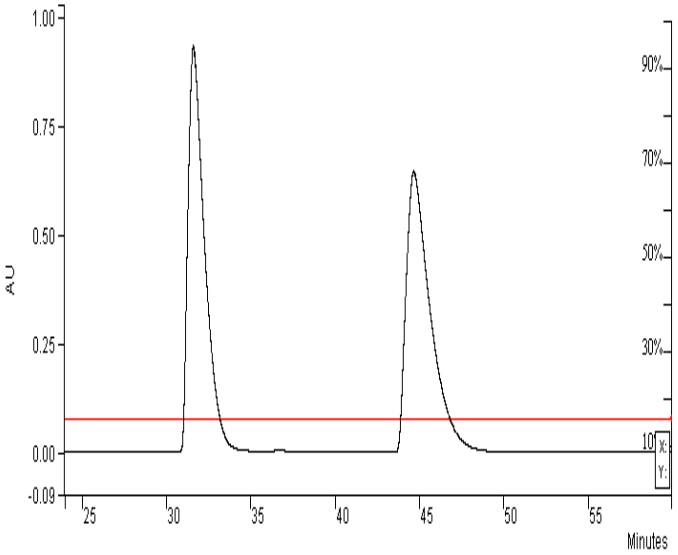
HPLC Chromatograms of acyloin **46**

Chiralpak OD-H (4.6 mm x 25 cm),

Hexane/IPA: 85/15, 0.5 mL min^{-1},

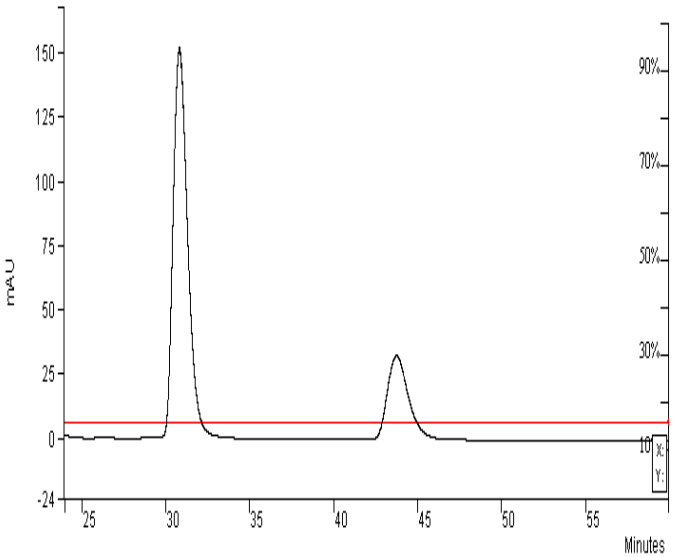
RT, UV detection at 254 nm

Peak No	Result	Ret. Time (min)	Area (counts)
1	47.5720	31.573	647311424
2	47.7258	44.635	649404352



Resolved HPLC chromatogram for acyloin **46** – racemate

Peak No	Result	Ret. Time (min)	Area (counts)
1	75.4243	30.795	97125208
2	22.2516	43.716	28653682



Resolved HPLC chromatogram for enantioenriched acyloin **(*S*)-46**

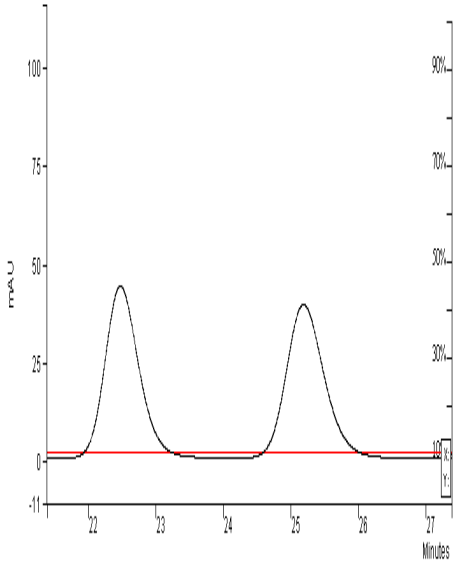
HPLC Chromatograms of acyloin **48**

Chiralpak AD (4.6 mm x 25 cm),

Hexane/IPA: 90/10, 0.8 mL min^{-1},

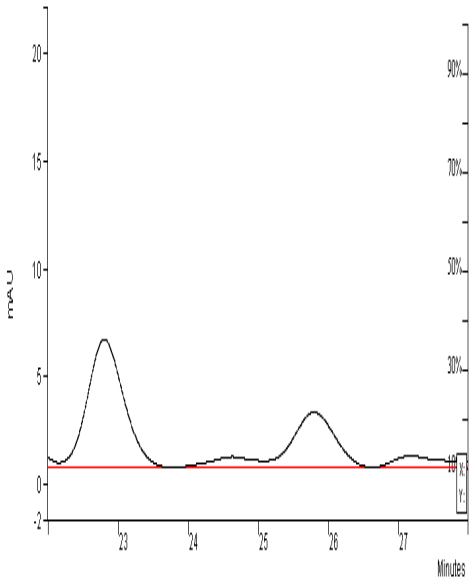
RT, UV detection at 254 nm

Peak No	Result	Ret. Time (min)	Area (counts)
1	48.3036	22.475	15873804
2	48.9320	25.187	16002846



Resolved HPLC chromatogram for acyloin **48** – racemate

Peak No	Result	Ret. Time (min)	Area (counts)
1	59.5268	22.796	2578769
2	33.2922	25.782	1442275



Resolved HPLC chromatogram for enantioenriched acyloin **(*S*)-48**

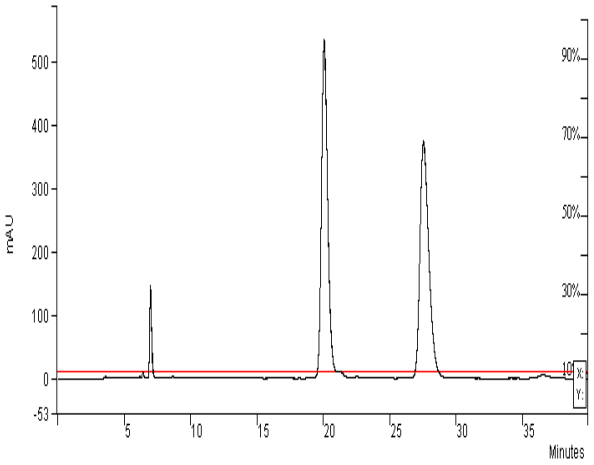
HPLC Chromatograms of acyloin **49**

Chiralpak AD (4.6 mm x 25 cm),

Hexane/IPA: 90/10, 0.8 mL min^{-1},

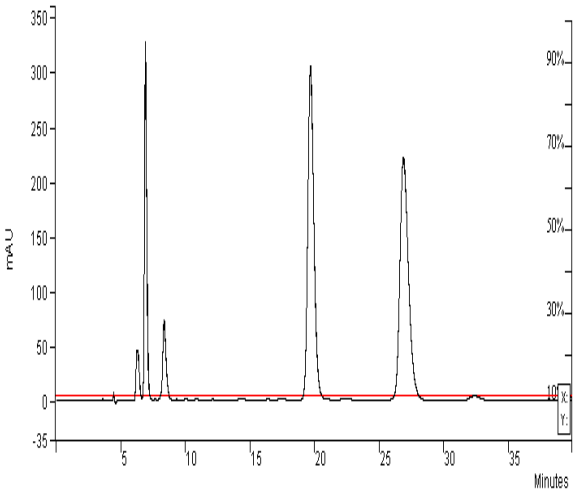
RT, UV detection at 254 nm

Peak No	Result	Ret. Time (min)	Area (counts)
1	4.2522	6.964	16089827
2	47.5049	20.053	179751856
3	46.4197	27.534	175645760



Resolved HPLC chromatogram for acyloin **49** – racemate

Peak No	Result	Ret. Time (min)	Area (counts)
1	13.6230	6.893	40922868
2	35.2856	19.675	105996464
3	35.9107	26.878	107874448



Resolved HPLC chromatogram for enantioenriched acyloin **(*S*)-49**

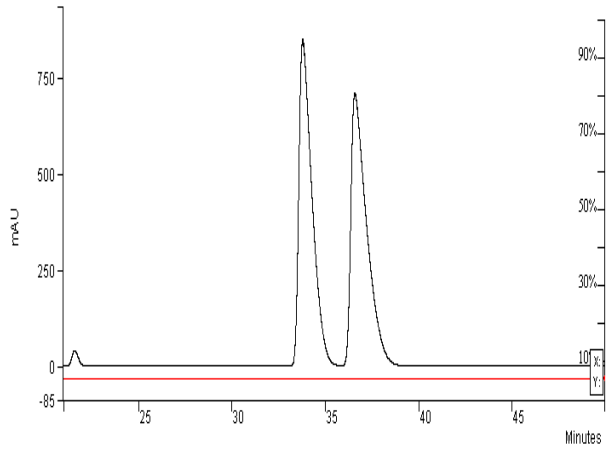
HPLC Chromatograms of acyloin **50**

Chiralpak OJ-H (4.6 mm x 25 cm),

Hexane/IPA: 95/5, 0.6 mL min^{-1},

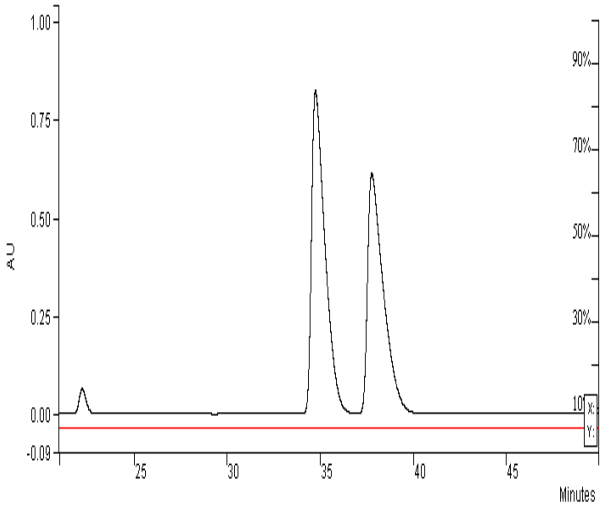
RT, UV detection at 220 nm

Peak No	Result	Ret. Time (min)	Area (counts)
1	1.3207	21.565	11785942
2	46.6360	33.767	416180544
3	46.9019	36.564	418554016



Resolved HPLC chromatogram for acyloin **50** – racemate

Peak No	Result	Ret. Time (min)	Area (counts)
1	1.8564	22.192	19732320
2	49.8431	34.721	415292192
3	43.8779	37.747	365590048



Resolved HPLC chromatogram for enantioenriched acyloin **(*S*)-50**

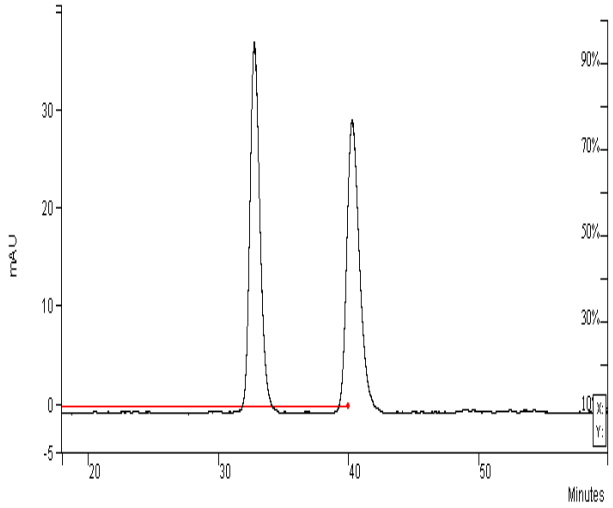
HPLC Chromatograms of acyloin **51**

Chiralpak AD (4.6 mm x 25 cm),

Hexane/IPA: 90/10, 0.8 mL min^{-1},

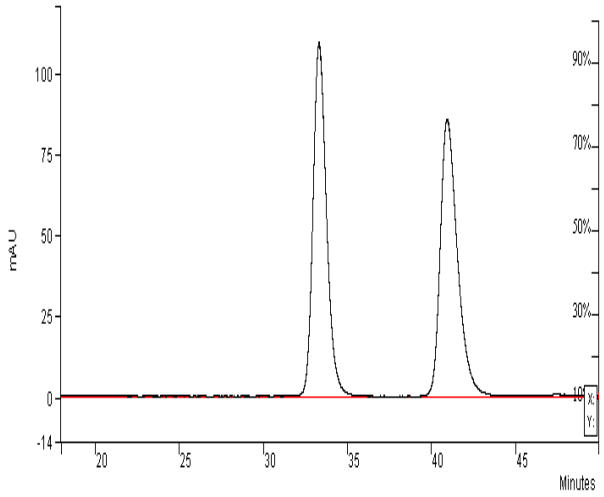
RT, UV detection at 254 nm

Peak No	Result	Ret. Time (min)	Area (counts)
1	48.4271	32.735	20961732
2	48.5545	40.254	21066802



Resolved HPLC chromatogram for acyloin **51** – racemate

Peak No	Result	Ret. Time (min)	Area (counts)
1	47.2647	33.297	63945848
2	46.1670	40.920	62158180



Resolved HPLC chromatogram for enantioenriched acyloin **(*S*)-51**

5.0 References

1. J. Kenyon and R. L. Patel, *J. Chem. Soc.*, 1965, 435.
2. H. G. Rule and J. Crawford, *J. Chem. Soc.*, 1937, 138.
3. R. Fulton, *J. Chem. Soc.*, 1939, 200.
4. A. S. Demir, Ö. Şeşengolu, E. Eren, B. Hosrik, M. Pohl, E. Janzen, R. Feldman, P. Dunkelmann and M. Müller, *Adv. Synth. Catal.*, 2002, **344**, 96.
5. C. W. N. Cumper, and A. P. Thurston, *J. Chem. Soc. Perkin Trans. 2*, 1972, 106.
6. R. L. Knight and F. J. Leeper, *J. Chem. Soc. Perkin Trans. 1*, 1998, 1891.
7. N. J. Clecak and R. J. Cox, *Chem. Abstr.*, 1970, **73**, 89166.
8. J. Pesch, K. Harms and T. Bach, *Eur. J. Org. Chem.*, 2004, 2025.
9. D. Enders, K. Breuer and J. H. Teles, *Helv. Chim. Acta*, 1996, **79**, 1217.
10. H. Stetter, Y. Rämsch and H. Kuhlmann, *Synthesis*, 1976, 733.