Non-enzymatic Acylative Kinetic Resolution of Baylis-Hillman Adducts

Ciarán Ó Dálaigh and Stephen J. Connon[*]

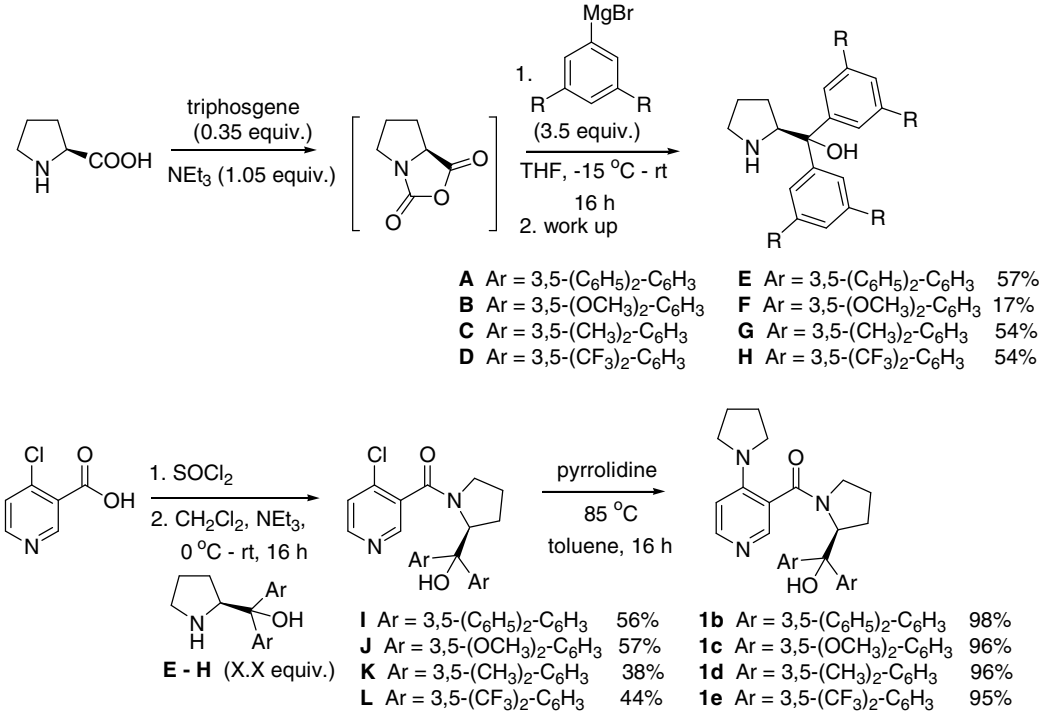
Table of Contents

1.0 General

Proton Nuclear Magnetic Resonance spectra were recorded on a 400 MHz spectrometer in $CDCl_3$ referenced relative to residual $CHCl_3$ (δ = 7.26 ppm). Chemical shifts are reported in ppm and coupling constants in Hertz. Carbon NMR spectra were recorded on the same instrument (100 MHz) with total proton decoupling. All melting points are uncorrected. 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 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 CHIRALCEL OD-H (4.6 mm x 25 cm) and CHIRALCEL AS-H (4.6 mm x 25 cm) columns. Unless otherwise stated, all chemicals were obtained from commercial sources and used as received. *m*-terphenylmagnesium bromide,[1] 3,5-dimethoxyphenylmagnesium bromide,[2] 3,5-*bis*(trifluromethyl)phenylmagnesium bromide,[3] were synthesized according to literature procedures. Unless otherwise specified, all reactions were carried out in oven-dried glassware with magnetic stirrers under an atmosphere of argon.

2.0 Synthesis of catalysts 1a-1e

General outline



Prolinol E

A 25 mL three-necked round bottom flask fitted with an Ar inlet tube, 10 mL addition funnel and a Teflon-coated thermocouple probe, containing dry THF (5 mL) was charged with (*S*)-proline (187 mg, 1.627 mmol). To the well-stirred, cooled (15-20 ^{o}C) suspension was added a solution of tri-phosgene (160 mg, 0.542 mmol) in THF (5 mL) over a 30 min period, maintaining the internal temperature at 15-20 ^{o}C. The mixture was warmed to 30-40 ^{o}C and aged for 1 h. Once homogeneous, the reaction mixture was allowed stir for an additional 0.5 h at 30-35 ^{o}C and then cooled to 15-20 ^{o}C. While maintaining the internal temperature at 15-20 ^{o}C, the reaction mixture was concentrated *in vacuo* to a volume of 2 mL. The residue was dissolved in dry THF (8 mL) and the solution was cooled to 0-5 ^{o}C. With good agitation, dry NEt_3 (237 µL, 1.71 mmol) was added over 15 min while maintaining the internal temperature at 0-5 ^{o}C. After the addition was

complete, the mixture was aged for 30 min at 0 ^{o}C and then filtered through a medium frit, sintered-glass funnel. The resultant cake of NEt_3.HCl was washed with THF (5 mL x 2). The filtrate and THF washes were combined to afford a solution containing (*S*)-pyrrolo-oxazole product that was used immediately without further purification.

A 50 mL three-necked flask fitted with a 25 mL addition funnel containing the THF solution of the pyrrolo-oxazole (1.6 mmol in 20 mL) and a stirrer was charged with a solution of *m*-terphenyl magnesium bromide (5.7 mmol) in THF (10 mL) and cooled to -15 ^{o}C. The THF solution of pyrrolo-oxazole was added over a 30 min period while maintaining the internal temperature at -10 to -15 ^{o}C. After the addition was complete, the mixture was allowed warm to room temperature and aged for 16 h. The reaction was quenched with the addition of 2 M aqueous H_2SO_4 (2 mL), over a 0.5 h period, while maintaining the internal temperature below 20 ^{o}C. During the quench a thick white precipitate of $MgSO_4$ formed. The mixture was agitated for 1 h at 0 ^{o}C and filtered through a medium-frit, sintered-glass funnel. The $MgSO_4$ cake was washed free of residual product with THF (3 x 10 mL). The filtrate and THF washes were combined and concentrated at atmospheric pressure to 10% of the original volume. The product as its sulfate salt failed to precipitate from solution. The crude mixture was basified with 2M NaOH (4 mL, 8 mmol) and diluted with CH_2Cl_2 (25 mL). The organic layer was washed with H_2O (2 x 25 mL), dried with $MgSO_4$ and concentrated *in vacuo*. Purification by column chromatography (99:1 CH_2Cl_2-NEt_3) gave **prolinol E** (512 mg, 57 %) as a white solid, m.p.: 92-94 °C. $[\alpha]_D^{20}$ = -62.2 (c 0.143, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ 7.90 (s, 2H), 7.80 (s, 2H), 7.74 -7.60 (m, 10H), 7.49-7.41 (m, 8H), 7.40-7.36 (m, 4H), 4.56 (m, 1H), 2.96 (m, 2H), 1.92-1.70 (m, 4H). ^{13}C NMR ($CDCl_3$) δ 145.9, 144.3, 141.8, 141.4, 141.2, 141.0, 128.6, 128.5, 128.4, 128.3, 127.3,

127.2, 124.7, 124.4, 123.7, 123.3, 77.4, 64.7, 46.6, 26.5, 25.2. IR (film) 3356, 2968, 2869, 2299, 1594, 1428, 1264 cm^{-1}. HRMS (ESI, m/z) calcd for $C_{41}H_{36}NO$ $(M+H)^+$ 558.2797, found 558.2791.

Prolinol F

Prepared as per the synthesis of **prolinol E** using (*S*)-pyrrolo-oxazole (2.88 mmol in 20 mL) and 3,5-dimethoxyphenylmagnesium bromide (8.64 mmol) in THF (40 mL). Purification by column chromatography (99:1, EtOAc-NEt_3, R_f 0.2) gave **prolinol F** (185 mg, 17%) as a clear oil. $[\alpha]_D^{20}$ = -81 (c 0.12, $CHCl_3$). ^1H NMR ($CDCl_3$) δ 6.77 (s, 2H), 6.69 (s, 2H), 6.30 (s, 2H), 4.19 (dd, 1H, J = 7.5, 7.5 Hz), 3.79 (s, 6H), 3.78 (s, 6H), 2.98 (m, 2H), 1.78-1.57 (m, 4H). ^{13}C NMR ($CDCl_3$) δ 160.2, 159.9, 103.8, 103.3, 98.0, 97.8, 76.8, 64.2, 54.9, 54.8, 46.2, 25.8, 24.8. IR (film) 3344, 2936, 2837, 1592, 1425, 1203, 1152 cm^{-1}. HRMS (ESI, m/z) calcd for $C_{21}H_{27}NO_5Na$ $(M+Na)^+$ 396.1923, found 396.1927.

Prolinol G

Prepared as per the synthesis of **prolinol E** using (*S*)-pyrrolo-oxazole (6.52 mmol in 20 mL) and (3,5-dimethylphenyl)magnesium bromide (19.55 mmol) in THF (40 mL). Purification by column chromatography (98:2, CH_2Cl_2-NEt_3 R_f 0.3) gave **prolinol G** (1.100 g, 54%) as a white solid, m.p. 96-98 ^oC (lit.[4] 97.5-98 ^oC). ^1H NMR ($CDCl_3$) δ 7.19 (s, 2H), 7.12 (s, 2H), 6.81 (s, 2H), 4.24 (dd, 1H, J = 8.0, 7.5 Hz), 3.08-2.92 (m, 2H), 2.30 (s, 6H), 2.29 (s, 6H), 1.78-1.55 (m, 4H).

Prolinol H

Prepared as per the synthesis of **prolinol E** using (*S*)-pyrrolo-oxazole (8.68 mmol in 20 mL) and 3,5-[*bis*(trifluromethyl)phenyl]magnesium bromide (33 mmol) in THF (30 mL). Purification by column chromatography (99:1 EtOAc-NEt_3, R_f 0.3) gave **prolinol H** (2.45 g, 54%) as a white solid, m.p. 102-104 ^oC. ^1H NMR ($CDCl_3$) δ 8.06 (s, 2H), 7.98 (s, 2H), 7.79 (s, 2H), 4.37 (dd, 1H, J = 7.5, 7.5 Hz), 3.09 (m, 2H), 1.86-1.77 (m, 2H), 1.72 (m, 1H, NH), 1.61-1.51 (m, 2H). Spectral data for this compound is consistent with that in the literature.[5]

Chloropyridine I

A 10 mL round bottom flask charged with 4-chloronicotinic acid (68 mg, 0.431 mmol) and $SOCl_2$ (1.0 mL) was fitted with a reflux condenser and heated at 90 ^oC for 1 hour. Removal of $SOCl_2$ by distillation gave 4-chloronicotinic acid chloride hydrochloride as a yellow solid, which was placed under an atmosphere of Ar, cooled to 0 ^oC and suspended in CH_2Cl_2 (3 mL) added *via* syringe. Subsequently a solution of **prolinol E** (200 mg, 0.359 mmol) and NEt_3 (200 µL, 1.44 mmol) in CH_2Cl_2 (5 mL), was added *via* syringe. The yellow solution was left to stir overnight. CH_2Cl_2 (30 mL) was then added and the resulting solution washed with $NaHCO_3$ (2 x 40 mL), and brine (2 x 40 mL). The organic extracts were separated, dried ($MgSO_4$) and the solvent removed *in vacuo*. Purification by column chromatography (9:1 CH_2Cl_2-EtOAc, R_f 0.3) gave **chloropyridine I** (141 mg, 56%) as a white solid, m.p. 136-137 ^oC. $[\alpha]_D^{20}$ = -117.5 (c 0.143, $CHCl_3$). ^1H NMR ($CDCl_3$) δ 8.50 (bs, 1H), 7.92 (s, 2H), 7.85-7.80 (m, 4H), 7.67 (m, 8H), 7.49-7.45 (m, 9H), 7.41-7.30 (m, 5H), 6.72 (s, 1H, OH), 5.57 (dd, 1H, J = 7.0, 7.0 Hz), 3.12-2.91 (m, 2H), 2.40-2.28 (m, 2H), 1.78-1.62 (m, 1H), 1.59-1.38 (m, 1H). ^{13}C NMR ($CDCl_3$) δ 167.5, 150.5, 150.4, 147.8, 146.2, 143.8, 141.6, 141.4, 141.2, 141.0, 129.0, 128.9, 128.8, 127.6, 127.5,

127.4, 127.3, 127.2, 125.8, 125.7, 125.6, 125.5, 82.2, 68.4, 50.4, 30.4, 23.9. IR (film) 3275, 2962, 2245, 1575, 1427, 1185, 1030 cm^{-1}. HRMS (ESI, m/z) calcd for $C_{47}H_{38}N_2O_2Cl$ $(M+H)^+$ 697.2622, found 697.2640

Chloropyridine J

Prepared as per the synthesis of **chloropyridine I** using 4-chloronicotinic acid (86 mg, 0.547 mmol), $SOCl_2$ (1.0 mL), CH_2Cl_2 (3 + 5 mL), **prolinol F** (170 mg, 0.456 mmol) and NEt_3 (253 µL, 1.82 mmol). Purification by column chromatography (1:1 $CHCl_2$-EtOAc, R_f 0.3) gave **chloropyridine J** (132 mg, 57%) as a white solid, m.p. 70-72 ^oC. $[\alpha]_D^{20}$ = -98(c 0.126, $CHCl_3$). ^1H NMR ($CDCl_3$) δ 8.53 (d, 1H, J = 5.5 Hz), 8.30-8.15 (bs, 1H), 7.37 (d, 1H, J = 5.5 Hz), 6.78 (s, 2H), 6.67 (s, 2H), 6.61 (s, 1H), 6.46 (s, 1H), 6.41 (s, 1H), 5.19 (dd, 1H, J = 7.5, 8.0 Hz), 3.80 (s, 6H), 3.79 (s, 6H), 3.17 (m, 2H), 2.14 (m, 2H), 1.73-1.48 (m, 2H). ^{13}C NMR ($CDCl_3$) δ: 166.4, 159.9, 159.8, 149.7, 147.0, 146.8, 144.6, 139.1, 131.4, 124.5, 105.9, 105.7, 98.7, 98.6, 81.2, 68.4, 55.0, 54.9, 49.2, 29.9, 23.5. IR (film): 3275, 2938, 2837, 1594, 1425, 1203, 1060 cm^{-1}. HRMS (ESI, m/z) calcd for $C_{27}H_{30}ClN_2O_6$ $(M+H)^+$ 513.1792, found 513.1805

Chloropyridine K

Prepared as per the synthesis of **chloropyridine I** using 4-chloronicotinic acid (440 mg, 2.79 mmol), $SOCl_2$ (2.0 mL), CH_2Cl_2 (6 + 10 mL), **prolinol G** (720 mg, 2.32 mmol) and NEt_3 (1.29 mL, 9.28 mmol). Purification by column chromatography (1:1 CH_2Cl_2-EtOAc, R_f 0.4) gave **chloropyridine K** (394 mg, 38%) as a white solid, m.p. 73-75^oC. $[\alpha]_D^{20}$ = -117.5 (c 0.143, $CHCl_3$). ^1H NMR ($CDCl_3$) δ 8.52 (d, 1H, J = 5.5 Hz), 8.30-8.10 (bs, 1H), 7.37 (d, 1H, J = 5.5 Hz), 7.21 (s, 2H), 7.08 (s, 2H), 6.99 (s, 1H), 6.95 (s, 1H), 6.20 (s, 1H), 5.35 (dd, 1H, J = 6.5, 6.5

Hz), 3.08 (m, 1H), 2.85 (m, 1H), 2.35 (s, 6H), 2.32 (s, 6H), 2.25 (m, 1H), 2.11 (m, 1H), 1.60 (m, 1H), 1.34 (m, 1H). ^{13}C NMR ($CDCl_3$) δ 166.5, 150.5, 147.7, 144.9, 142.4, 139.8, 139.7, 136.9, 136.6, 132.5, 128.6, 125.3, 125.0, 124.2, 81.4, 67.3, 49.9, 29.5, 23.4, 21.2, 21.1. IR (film) 3303, 2917, 2245, 1619, 1576, 1435, 1156. HRMS (ESI, m/z) calcd for $C_{27}H_{29}N_2O_2NaCl$ $(M+Na)^+$ 471.1815, found 471.1824.

Chloropyridine L

Prepared as per the synthesis of chloropyridine I using 4-chloronicotinic acid (144 mg, 0.914 mmol), $SOCl_2$ (1.0 mL), CH_2Cl_2 (3 + 5 mL), **prolinol H** (400 mg, 0.762 mmol) and NEt_3 (540 µL, 3.90 mmol). Purification by column chromatography (1:1 CH_2Cl_2-EtOAc, Rf 0.3) gave **chloropyridine L** (222 mg, 44%) as a white solid, m.p. 78-80 ^oC. $[\alpha]_D^{20}$ = -67.5 (c 0.157, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ 8.55 (d, 1H, J = 5.5 Hz), 8.40-8.22 (bs, 1H), 8.08 (s, 2H), 7.96 (s, 1H), 7.89 (s, 3H), 7.37 (d, 1H, J = 5.5 Hz), 7.17 (s, 1H), 5.31 (dd, 1H, J = 8.0, 8.0 Hz), 3.28 (m, 1H), 3.08 (m, 1H), 2.20 (m, 1H), 1.97 (m, 1H), 1.76 (m, 1H), 1.50 (m, 1H). ^{13}C NMR ($CDCl_3$) δ 167.9, 151.1, 147.4, 146.0, 144.2, 139.6, 131.4, 131.3 (J = 34.0 Hz), 131.2 (J = 34.0 Hz), 127.4, 127.0, 124.2, 122.7 (J = 271.4 Hz), 122.6 (J = 271.4 Hz), 121.9, 121.8, 80.1, 67.7, 50.0, 29.7, 23.5. IR (film) 3368, 2923, 2853, 1623, 1462, 1277, 1130 cm^{-1}. HRMS (ESI, m/z) calcd for $C_{27}H_{18}N_2O_2F_{12}Cl$ $(M+H)^+$ 665.0865, found 665.0881.

Catalyst 1b

A 10 mL round bottom flask was charged with **chloropyridine I** (121 mg, 0.17 mmol) and toluene (2 mL) with stirring. To this was added pyrrolidine (145 µL, 1.7 mmol) *via* syringe. The flask was fitted with a reflux condenser and heated at 85 °C for 16 h. CH_2Cl_2 (20 mL) was then

added and the solution washed with $NaHCO_3$ (2 x 30 mL) and brine (2 x 30 mL). The organic extracts were separated, dried ($MgSO_4$) and the solvent removed *in vacuo*. Purification by column chromatography (1:1 Hex-CH_2Cl_2, R_f 0.2) gave **catalyst 1b** (124 mg, 98%) as a white solid, m.p. 253-254 ^oC. $[\alpha]_D^{20}$ = -37 (c 0.1, $CHCl_3$). ^1H NMR ($CDCl_3$) δ (Major rotamer): 8.10 (d, 1H, J = 3.0 Hz), 8.02-7.32 (m, 27H), 6.43 (d, 1H J = 3.0 Hz), 5.32 (m, 1H), 3.51 (m, 3H), 3.11 (m, 3H), 2.32 (m, 2H), 2.08 (m, 2H), 1.96 (m, 2H), 1.70-1.50 (m, 2H). (Major and minor rotamer together): 8.12 (m, 0.25H), 8.10 (d, 1H, J = 3.0 Hz), 8.02-7.32 (m, 26.75H), 6.43 (d, 1H, J = 3.0 Hz), 5.47 (m, 0.25H), 5.32 (m,).75H), 3.63 (m, 0.25H), 3.51 (m, 2.25H), 3.27 (m, 0.5H), 3.16-3.01 (m, 3H), 2.32 (m, 2H), 2.08 (m, 1.5H), 1.96 (m, 1.5H), 1.70-1.50 (m, 2.5H), 1.43-1.30 (m, 0.5H). ^{13}C NMR ($CDCl_3$) δ 171.8, 149.7, 148.4, 148.3, 146.0, 143.4, 141.5, 141.3, 141.2, 141.0, 128.7, 128.6, 127.4, 127.3, 127.2, 127.1, 125.8, 125.6, 125.4, 125.3, 116.5, 108.3, 82.1, 69.6, 52.1, 48.9, 31.4, 25.5, 23.7; Rotamer resonances: 172.7, 149.4, 148.1, 147.3, 144.9, 81.5, 69.2, 50.9, 30.4, 23.5. IR (film) 3210, 2972, 1589, 1412, 1144, 696 cm^{-1}. HRMS (ESI, m/z) calcd for $C_{51}H_{46}N_3O_2$ $(M+H)^+$ 732.3590, found 732.3610. *Anal.* calcd. for $C_{51}H_{45}N_3O_2$: C, 83.69; H, 6.20; N, 5.74. Found: C, 83.50; H, 6.23; N, 5.78.

Catalyst 1c

Prepared as per the synthesis of **1b** using **chloropyridine J** (77 mg, 0.150 mmol), toluene (2 mL) and pyrrolidine (125 μL, 1.50 mmol). Purification of the resulting product by column chromatography (1:1 Hex-CH_2Cl_2, R_f 0.1) gave **1c** (79 mg, 96%) as a white solid, m.p. 227-229 ^oC. $[\alpha]_D^{20}$ = -78.3 (c 0.143, $CHCl_3$). ^1H NMR ($CDCl_3$) δ (Major rotamer): 8.15 (d, 1H, J = 4.0 Hz), 7.54 (s, 1H), 7.21 (s, 1H), 6.82 (s, 2H), 6.70 (s, 2H), 6.52-6.39 (m, 3H), 5.07 (dd, 1H, J = 5.0, 5.5 Hz), 3.82 (s, 6H), 3.80 (s, 6H), 3.50 (m, 3H), 3.28-3.09 (m, 3H), 2.28-1.58 (m, 8H).

(Major and minor rotamer together): 8.15 (d, 1H, J = 4.0 Hz), 7.58-7.54 (m, 1H), 7.21 (s, 1H), 6.82 (s, 2H), 6.70 (s, 2H), 6.52-6.39 (m, 3H), 5.07 (dd, 1H, J = 5.0, 5.5 Hz), 3.82 (s, 6H), 3.80 (s, 6H), 3.65 (m, 0.15H), 3.50 (m, 2.55H), 3.28-3.09 (m, 3H), 2.91 (m, 0.3H), 2.28-1.58 (m, 8H). ^{13}C NMR ($CDCl_3$) δ 171.7, 160.3, 160.1, 149.6, 148.5, 148.4, 147.3, 144.8, 116.7, 108.3, 106.2, 106.1, 99.1, 99.0, 81.7, 68.9, 55.3, 55.2, 52.1, 48.8, 30.7, 25.5, 23.6; Rotamer resonances: 172.9, 149.2, 146.9, 145.1, 105.8, 98.8, 80.9, 70.4, 51.4, 31.4, 22.5. IR (film) 3217, 2955, 2332, 1592, 1424, 1153 cm^{-1}. HRMS (ESI, m/z) calcd for $C_{31}H_{38}N_3O_6$ $(M+H)^+$ 548.2761, found 548.2775. *Anal.* calcd. for $C_{31}H_{37}N_3O_6$: C, 67.99; H, 6.81; N, 7.67. Found: C, 67.78; H, 6.78; N, 7.48.

Catalyst 1d

Prepared as per the synthesis of **1b** using **chloropyridine K** (80 mg, 0.179 mmol), toluene (2 mL) and pyrrolidine (149 μL, 1.79 mmol). Purification of the resulting product by column chromatography (1:1 CH_2Cl_2-EtOAc, R_f 0.2) gave **1d** (83 mg, 96%) as a white solid, m.p. 179-180 °C. $[\alpha]_D^{20}$ = -50.3 (c 0.171, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ (Major rotamer):8.14 (d, 1H, J = 4.0 Hz), 7.45 (s, 1H), 7.25 (s, 2H), 7.11 (s, 2H), 7.06 (s, 1H), 6.94 (s, 1H), 6.86 (s, 1H), 6.45 (d, 1H, J = 4.0 Hz), 5.20 (dd, 1H, J = 5.3 Hz), 3.50 (m, 3H), 3.11 (m, 2H), 2.94 (m, 1H), 2.39 (s, 6H), 2.32 (s, 6H), 2.26-1.52 (m, 8H). (Major and minor rotamer together): 8.14 (d, 1H, J = 3.5 Hz), 7.45 (s, 1H), 7.25 (s, 2H), 7.16-7.06 (m, 3H), 6.96-6.85 (m, 2H), 6.45 (d, 1H, J = 4.0 Hz), 5.26-5.20 (dd, 1H, J = 5.3, 5.3 Hz), 3.50 (m, 2.8H), 3.33 (m, 0.2H), 3.11 (m, 2H), 2.94 (m, 1H), 2.39 (s, 6H), 2.32 (s, 6H), 2.26-1.52 (m, 8H). ^{13}C NMR ($CDCl_3$) δ 171.2, 149.4, 148.4, 148.3, 145.0, 142.5, 137.2, 136.9, 128.9, 128.8, 125.5, 125.4, 116.7, 108.3, 82.1, 68.2, 51.8, 48.8, 30.4, 25.5, 23.6, 21.5, 21.4; Rotamer resonances: 171.5, 125.7, 82.1, 68.8, 49.0, 29.9, 25.6, 22.5. IR (film) 3244, 2970, 1587, 1415, 749 cm^{-1}. HRMS (ESI, m/z) calcd for $C_{31}H_{38}N_3O_2$ $(M+H)^+$ 484.2964,

found 484.2964. *Anal.* calcd. for $C_{31}H_{37}N_3O_2$: C, 76.98; H, 7.71; N, 8.69. Found: C, 76.84; H, 7.73; N, 8.53.

Catalyst 1e

Prepared as per the synthesis of **1b** using **chloropyridine L** (55 mg, 0.083 mmol), toluene (2 mL) and pyrrolidine (70 µL, 0.828 mmol). Purification of the resulting product by column chromatography (1:1 CH_2Cl_2, R_f 0.2) gave **1e** (55 mg, 95%) as a white solid, m.p. 120-122 ^oC. $[\alpha]_D^{20}$ = -54 (c 0.1, $CHCl_3$). ^1H NMR ($CDCl_3$) δ (Major and minor rotamers): 8.22-7.83 (m, 7H), 7.44 (s, 1H), 6.49 (d, 1H, J = 5.5 Hz), 5.24-5.05 (m, 1H), 3.68 (m, 1H), 3.49 (m, 2H), 3.28-2.91 (m, 3H), 2.28-1.65 (m, 8H). ^{13}C NMR ($CDCl_3$) δ 172.4, 149.9, 148.6, 147.9, 146.3, 144.5, 131.7, 131.6, 127.5, 127.4, 123.1, 123.0, 122.1, 122.0, 115.6, 108.6, 80.4, 68.9, 52.2, 49.1, 31.2, 25.4, 23.7. Rotamer resonances: 173.1, 149.6, 147.3, 80.2, 68.7, 50.9, 30.4, 29.5, 22.5. IR (film) 3240, 2928, 2298, 1642, 1371, 1132, 682 cm^{-1}. HRMS (ESI, m/z) calcd for $C_{31}H_{26}F_{12}N_3O_2$ $(M+H)^+$ 700.1833, found 700.1835. *Anal.* calcd. for $C_{31}H_{25}F_{12}N_3O_2$: C, 53.23; H, 3.60; F, 32.59, N, 6.01. Found: C, 53.07; H, 3.71; F, 32.29, N, 5.72.

One pot synthesis and resolution of **9**

A 1 mL reaction vessel charged with **1e** (12.7 mg, 18.2 µmol) and a small magnetic stirring bar was placed under an atmosphere of Ar. To this was added benzaldehyde (370 µL, 0.364 mmol), DBU (380 µL, 0.255 mmol) and methyl acrylate (985 µL, 1.09 mmol) *via* syringe and the resulting homogeneous solution stirred at room temperature for 24 h. CH_2Cl_2 (500 µL) was then added *via* syringe and the solution was cooled to -78 ^oC and left to stir for 30 minutes. *Iso*-butyric anhydride (91 µL, 0.546 mmol) was subsequently added *via* syringe. After 24 h at -78 ^oC

the reaction was quenched by the addition of MeOH (200 μL) and allowed to warm to ambient temperature. Solvents were removed *in vacuo*. The alcohol and its ester were separated from the catalyst by passing a concentrated solution of the crude (CH_2Cl_2) through a pad of silica gel. The selectivity of the kinetic resolution (s = 4.3) was then established by CSP-HPLC on a Chiralcel AS-H column (4.6 x 250 mm), hexanes/*i*-PrOH, 90/10, 1 mL min^{-1}, RT, UV detection at 220 nm for **9a** and a Chiralcel OD-H column (4.6 x 250 mm), hexanes/*i*-PrOH, 90/10, 1 mL min^{-1}, RT, UV detection at 220 nm for **9b**. Retention times: **9a** (75% *ee*): 7.8 min, (*R*)-isomer (minor) and 14.9 min, (*S*)-isomer (major),[6] **9b** (35% *ee*): 6.0 min, (*S*)-isomer (minor) and 6.9 min (*R*)-isomer (major). The alcohol was then isolated by column chromatography (CH_2Cl_2) to give **(*S*)-9a** (17.6 mg, 25%, 75% *ee*) as a colorless oil.$[\alpha]_D^{20}$ = +47.3 (c 0.1, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ 7.41-7.31 (m, 5H), 6.37 (s, 1H), 5.85 (s, 1H), 5.59 (s, 1H), 3.76 (s, 3H), 3.02 (bs, 1H). Absolute configuration of the major isomer determined by comparision of optical rotation[7] and CSP-HPLC data[6] with that in the literature.

One pot synthesis and resolution of **10**

A 1 mL reaction vessel charged with **1e** (4.3 mg, 6.14 μmol) and a small magnetic stirring bar was placed under an atmosphere of Ar. To this was added *o*-anisaldehyde (50 mg, 0.368 mmol), DBU (18 μL, 0.123 mmol) and methyl acrylate (11 μL, 0.123 mmol) *via* syringe and the resulting homogeneous solution stirred at rt for 96 h. CH_2Cl_2 (500 μL) was then added *via* syringe and the solution was cooled to -78 ^oC and left to stir for 30 min. *Iso*butyric anhydride (16 μL, 0.98 mmol) was subsequently added *via* syringe. After 24 h at -78 ^oC the reaction was quenched by the addition of MeOH (200 μL) and allowed to warm to ambient temperature. Solvents were removed *in vacuo*. The alcohol and its ester were separated from the catalyst by

passing a concentrated solution of the crude (CH_2Cl_2) through a pad of silica gel. The selectivity of the kinetic resolution (*s* = 7.6) was then established by CSP-HPLC on a Chiralcel OD-H column (4.6 x 250 mm), hexanes/*i*-PrOH, 98/2, 1 mL min^{-1}, RT, UV detection at 220 nm. Retention times: **10a** (89% *ee*): 34.8 min, (*S*)-isomer (major) and 45.0 min, (*R*)-isomer (minor), **10b** (47% *ee*): 8.5 min, (*S*)-isomer (minor) and 22.3 min (*R*)-isomer (major). The alcohol was then isolated by column chromatography (CH_2Cl_2) to give **(*S*)-10a** (6.9 mg, 25%, 89% *ee*) as a colorless oil $[\alpha]_D^{20}$ = +83 (c 0.1, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ 7.36 (d, 1H, J = 7.5 Hz), 7.28 (t, 1H, J 8.0 Hz), 6.97 (app. t, 1H, J = 7.5 Hz), 6.89 (d, 1H, J = 8.0 Hz), 6.31 (s, 1H), 5.88 (s, 1H), 5.73 (s, 1H), 3.84 (s, 3H), 3.75 (s, 3H). Absolute configuration is tentatively assigned based on a comparison of CSP-HPLC retention times and optical rotation data with that of **(*S*)-9a**.

3.0 Spectral data for previously uncharacterized esters

Isobutyric ester 9b: Isolated (47.3 mg, 49.5%, 35% *ee*) as a colorless oil. $[\alpha]_D^{20}$ = -33 (c 0.16, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ 7.42-7.30 (m, 5H), 6.69 (s, 1H), 6.41 (s, 1H), 5.86 (s, 1H), 3.74 (s, 3H), 2.63 (app. hept, 1H, J = 7.0 Hz), 1.22-1.17 (m, 6H). ^{13}C NMR ($CDCl_3$) δ 175.2, 165.4, 139.9, 137.9, 128.3, 128.1, 127.4, 125.6, 72.6, 51.8, 33.9, 18.8, 18.6. IR (film) 2975, 1729, 1495, 1249, 1140 cm^{-1}. HRMS (ESI, m/z) calcd for $C_{15}H_{18}O_4Na$ $(M+Na)^+$ 285.1103, found 285.1115.

Isobutyric ester 10b: Isolated (16.2 mg, 45.1%, 47% *ee*) as a colorless oil. $[\alpha]_D^{20}$ = -62 (c 0.1, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ 7.34-7.27 (m, 2H), 7.05 (s, 1H), 6.96(app.dd, 1H, J = 7.5 Hz), 6.90 (d, 1H, J = 8.0 Hz), 6.41 (s, 1H), 5.61 (s, 1H), 3.84 (s, 3H), 3.76 (s, 3H), 2.63 (app. hept, 1H, J = 7.0 Hz), 1.22-1.18 (m, 6H). ^{13}C NMR ($CDCl_3$) δ: 175.0, 165.4, 156.5, 138.8, 129.0, 127.1, 126.8,

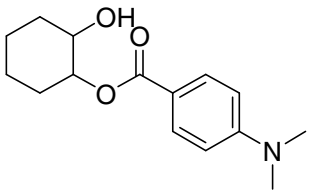
125.7, 119.9, 110.3, 67.2, 56.0, 51.5, 33.6, 18.5, 18.4. IR (film) 2973, 2840, 1725, 1492, 1246 cm^{-1}. HRMS (ESI, m/z) calcd for $C_{16}H_{20}O_5Na$ $(M+Na)^+$ 315.1208, found 315.1216.

Isobutyric ester 11b: Isolated (40.1 mg, 75%) as a colorless oil. $[\alpha]_D^{20}$ = -14.2 (c 0.29, $CHCl_3$). ^1H NMR ($CDCl_3$) δ 7.42-7.30 (m, 5H), 6.35 (s, 1H), 6.10 (s, 1H), 6.01 (s, 1H), 2.71 (app. hept, 1H, J = 7.0 Hz), 1.28-1.22 (m, 6H). ^{13}C NMR ($CDCl_3$) δ: 174.9, 135.3, 131.5, 128.7, 128.5, 126.4, 123.0, 115.7, 73.6, 33.5, 18.4, 18.3. IR (film) 2976, 2228, 1739, 1496, 1243 cm^{-1}. HRMS (ESI, m/z) calcd for $C_{14}H_{15}NO_2Na$ $(M+Na)^+$ 252.1000, found 252.1009.

Isobutyric ester 12b: Isolated (36 mg, 59.3%) as a colorless oil. $[\alpha]_D^{20}$ = -11.9 (c 0.26, $CHCl_3$). ^1H NMR ($CDCl_3$) δ 7.48 (d, 1H, J =7.5 Hz), 7.35 (app.dd, 1H, J = 8.0 Hz), 7.04 (app.dd, 1H, J = 7.5 Hz), 6.92 (d, 1H, J = 8.0 Hz), 6.73 (s, 1H), 6.03 (s, 1H), 6.00 (s, 1H), 3.87 (s, 3H), 2.71 (app. hept, 1H, J = 7.0 Hz), 1.28-1.23 (m, 6H). ^{13}C NMR ($CDCl_3$) δ: 174.9, 155.8, 131.5, 129.7, 126.4, 123.9, 122.2, 120.5, 115.9, 110.2, 68.2, 55.0, 33.6, 18.5, 18.4. IR (film) 2975, 2841, 2228, 1740, 1492, 1247, 1142 cm^{-1}. HRMS (ESI, m/z) calcd for $C_{15}H_{17}NO_3Na$ $(M+Na)^+$ 282.1106, found 282.1118.

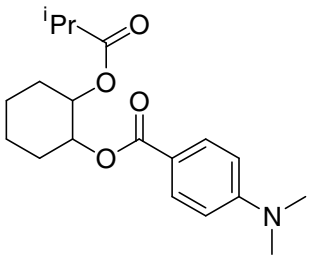
4.0 HPLC conditions/retention times and optical rotation data

(*cis*)-4-Dimethylamino-benzoic acid 2-hydroxy-cyclohexyl ester (2)



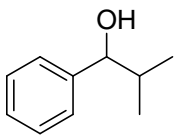
Chiralcel OD-H (4.6 mm x 25 cm), hexanes/*i*-PrOH, 90/10, 1 mL min^{-1}, RT, UV detection at 220 nm. Retention times: 17.3 min (1*R*, 2*S*) minor and 34.4 min (1*S*, 2*R*) major.[8]

(*cis*)-4-Dimethylamino-benzoic acid 2-isobutyryloxy-cyclohexyl ester



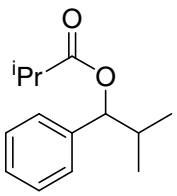
Chiralcel OD-H column (4.6 x 250 mm), hexanes/*i*-PrOH, 90/10, 1 mL min^{-1}, RT, UV detection at 220 nm. Retention times: 8.4 min (1*S*, 2*R*) minor and 9.9 min (1*R*, 2*S*) major.[8]

2-Methyl-1-phenyl-propan-1-ol



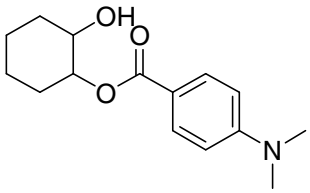
Chiralcel OD-H (4.6 mm x 25 cm), hexanes/*i*-PrOH, 99/1, 1 mL min^{-1}, RT, UV detection at 220 nm. Retention times: 21.2 min (*R*) major and 22.8 min (*S*) minor.[9]

Isobutyric acid 2-methyl-1-phenyl-propyl ester



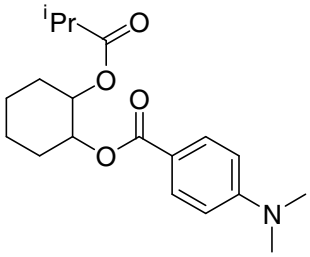
Chiralcel OD-H (4.6 mm x 25 cm), hexanes/*i*-PrOH, 99.6/0.4, 1 mL min^{-1}, RT, UV detection at 220 nm. Retention times: 5.4 min (*R*) minor and 5.9 min (*S*) major.[9]

(*trans*)-4-Dimethylamino-benzoic acid 2-hydroxy-cyclohexyl ester (8)



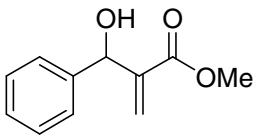
Chiralcel AS-H (4.6 mm x 25 cm), hexanes/*i*-PrOH, 90/10, 1 mL min^{-1}, RT, UV detection at 220 nm. Retention times: 12.2 min (minor) and 25.8 min (major).

(*trans*)-4-Dimethylamino-benzoic acid 2-isobutyryloxy-cyclohexyl ester



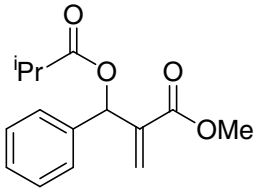
Chiralcel OD-H (4.6 mm x 25 cm), hexanes/*i*-PrOH, 90/10, 1 mL min^{-1}, RT, UV detection at 220 nm. Retention times: 11.9 min (major) and 14.7 min (minor).

2-(Hydroxy-phenyl-methyl)-acrylic acid methyl ester (9a)



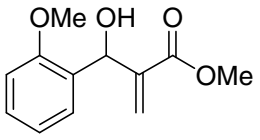
Chiralcel AS-H column (4.6 x 250 mm), hexanes/*i*-PrOH, 90/10, 1 mL min^{-1}, RT, UV detection at 220 nm. Retention times: 7.8 min, (*R*)-isomer (minor) and 14.9 min, (*S*)-isomer (major).[6]

2-(Isobutyryloxy-phenyl-methyl)-acrylic acid methyl ester (9b)



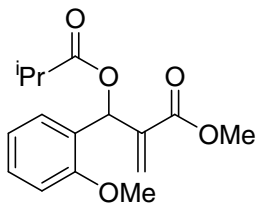
Chiralcel OD-H column (4.6 x 250 mm), hexanes/*i*-PrOH, 90/10, 1 mL min^{-1}, RT, UV detection at 220 nm. Retention times: 6.0 min, (*S*)-isomer (minor) and 6.7 min, (*R*)-isomer (major). $[\alpha]_D^{20}$ = -33 (c 0.16, $CHCl_3$).

2-[Hydroxy-(2-methoxy-phenyl)-methyl]-acrylic acid methyl ester (10a)



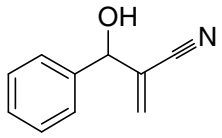
Chiralcel OD-H column (4.6 x 250 mm), hexanes/*i*-PrOH, 98/2, 1 mL min^{-1}, RT, UV detection at 220 nm. Retention times: 34.8 min, (*S*)-isomer (major) and 45.0 min, (*R*)-isomer (minor).

2-[Isobutyryloxy-(2-methoxy-phenyl)-methyl]-acrylic acid methyl ester (10b)



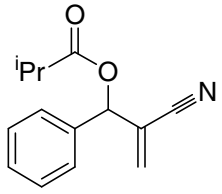
Chiralcel OD-H column (4.6 x 250 mm), hexanes/*i*-PrOH, 98/2, 1 mL min^{-1}, RT, UV detection at 220 nm. Retention times: 8.5 min, (*S*)-isomer (minor) and 22.3 min, (*R*)-isomer (major). $[\alpha]_D^{20}$ = -62 (c 0.1, $CHCl_3$).

2-(Hydroxy-phenyl-methyl)-acrylonitrile (11a)



Chiralcel OD-H column (4.6 x 250 mm), hexanes/*i*-PrOH, 90/10, 1 mL min^{-1}, RT, UV detection at 220 nm. Retention times: 13.2 min (minor) and 14.0 min (major). $[\alpha]_D^{20}$ = +77 (c .04, $CHCl_3$).

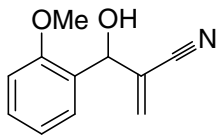
2-(Isobutyryloxy-phenyl-methyl)-acrylonitrile (11b)



Could not be resolved by CSP-HPLC using Chiralcel OD-H, Chiralcel AS-H or Chiralpak AD-H columns.

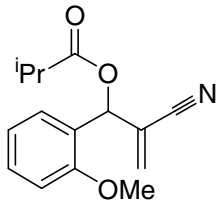
$[\alpha]_D^{20}$ = -14.2 (c 0.29, $CHCl_3$).

2-[Hydroxy-(2-methoxy-phenyl)-methyl]-acrylonitrile (12a)



Chiralcel OD-H column (4.6 x 250 mm), hexanes/*i*-PrOH, 90/10, 1 mL min^{-1}, RT, UV detection at 220 nm. Retention times: 11.3 min, (*R*)-isomer (major) and 12.6 min, (*S*)-isomer (minor).[10] Note that due to a priority change, the label of the stereogenic centre changes in **(+)-12a** from (*S*) to (*R*). $[\alpha]_D^{20}$ = +31.8 (c 0.08, $CHCl_3$). Absolute configuration of the major isomer determined by comparision of optical rotation data with that in the literature.[10]

2-[Isobutyryloxy-(2-methoxy-phenyl)-methyl]-acrylonitrile (12b)

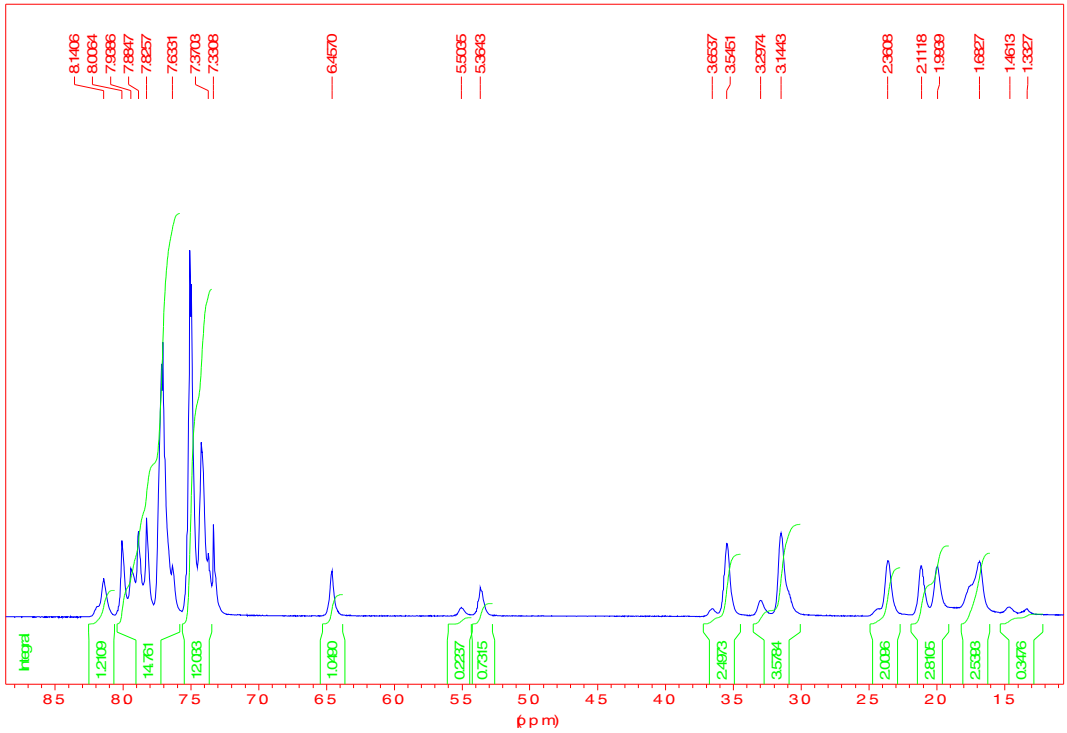


Could not be resolved by CSP-HPLC using Chiralcel OD-H, Chiralcel AS-H or Chiralpak AD-H columns.

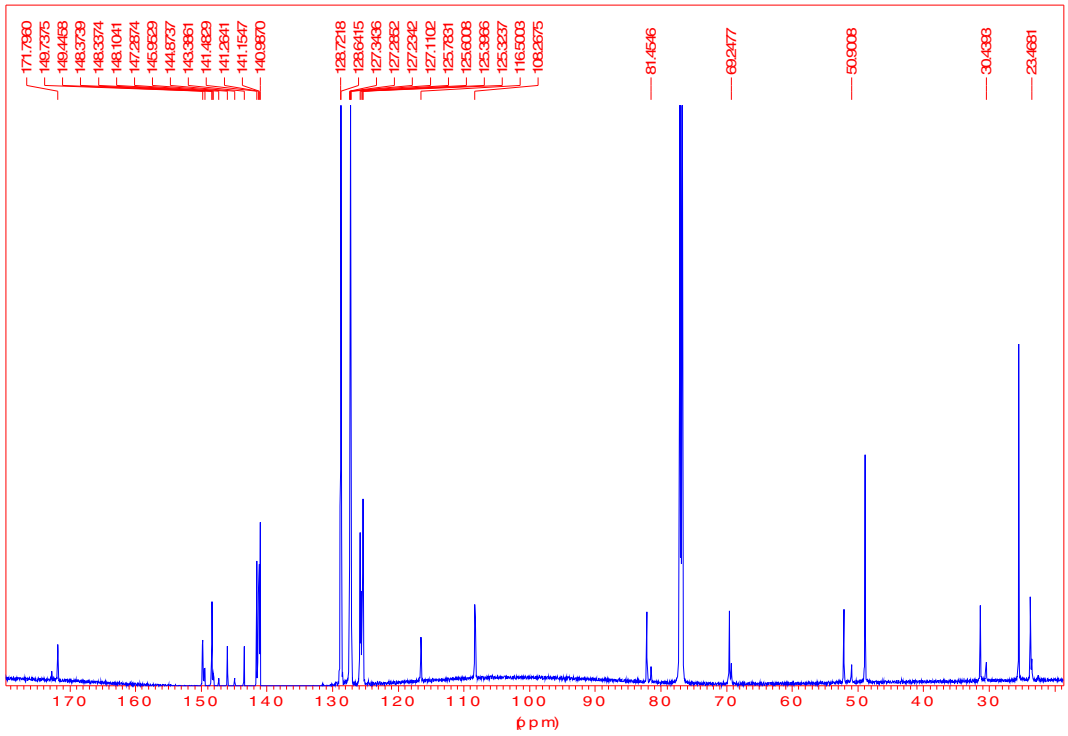
$[\alpha]_D^{20}$ = -11.9 (c 0.26, $CHCl_3$).

5.0 NMR spectra

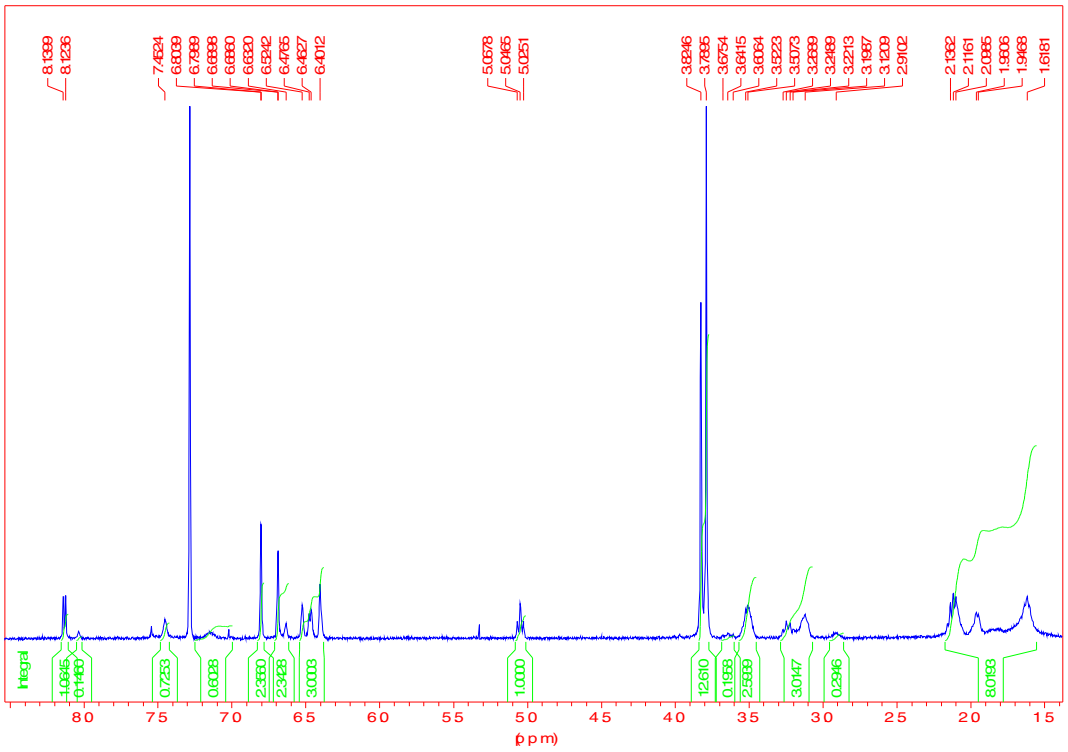
^{1}H NMR spectrum (400 MHz, $CDCl_3$) of catalyst **1b**



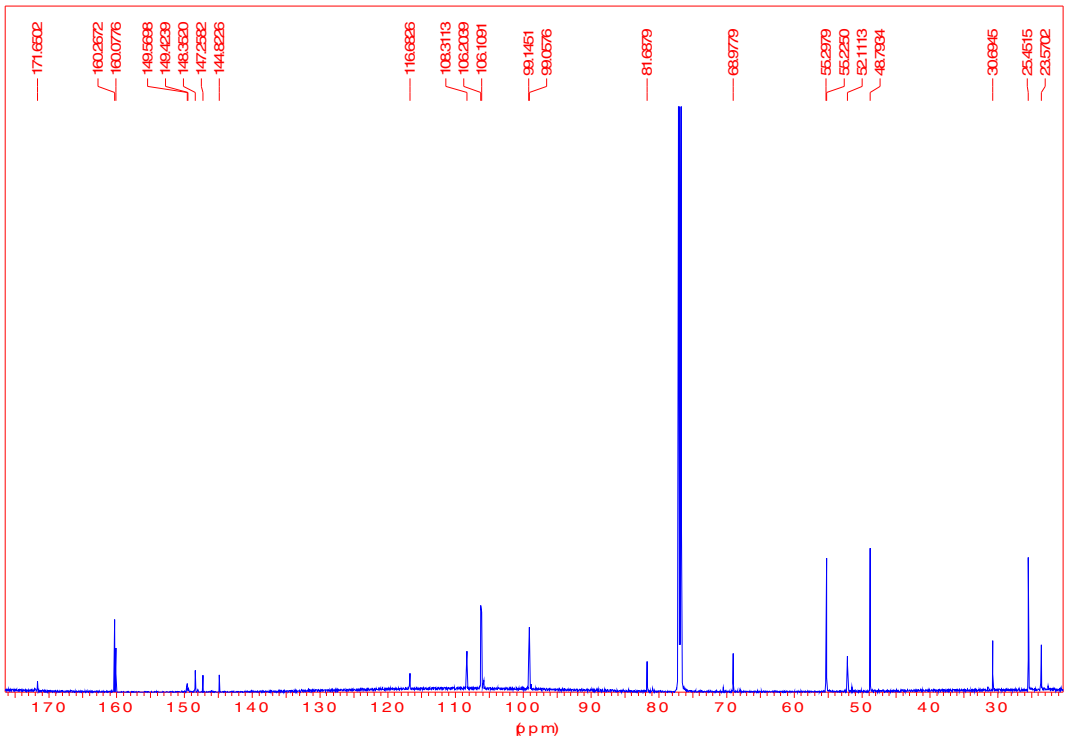
^{13}C NMR spectrum (100 MHz, $CDCl_3$) of catalyst **1b**



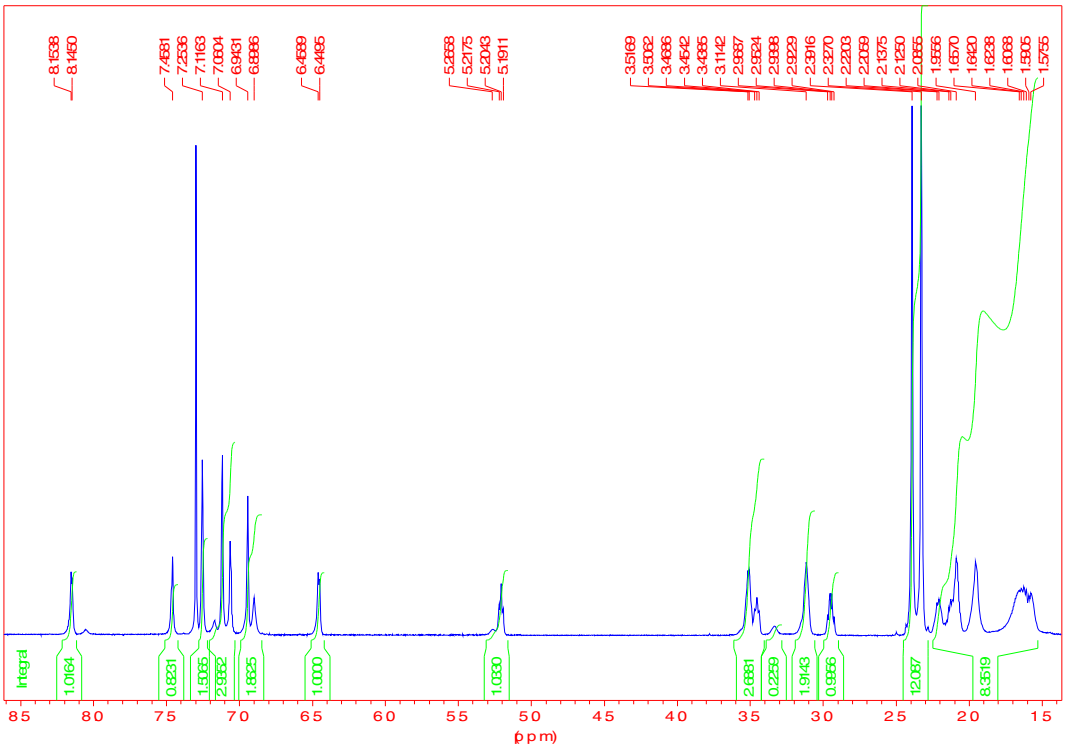
^{1}H NMR spectrum (400 MHz, $CDCl_3$) of catalyst **1c**



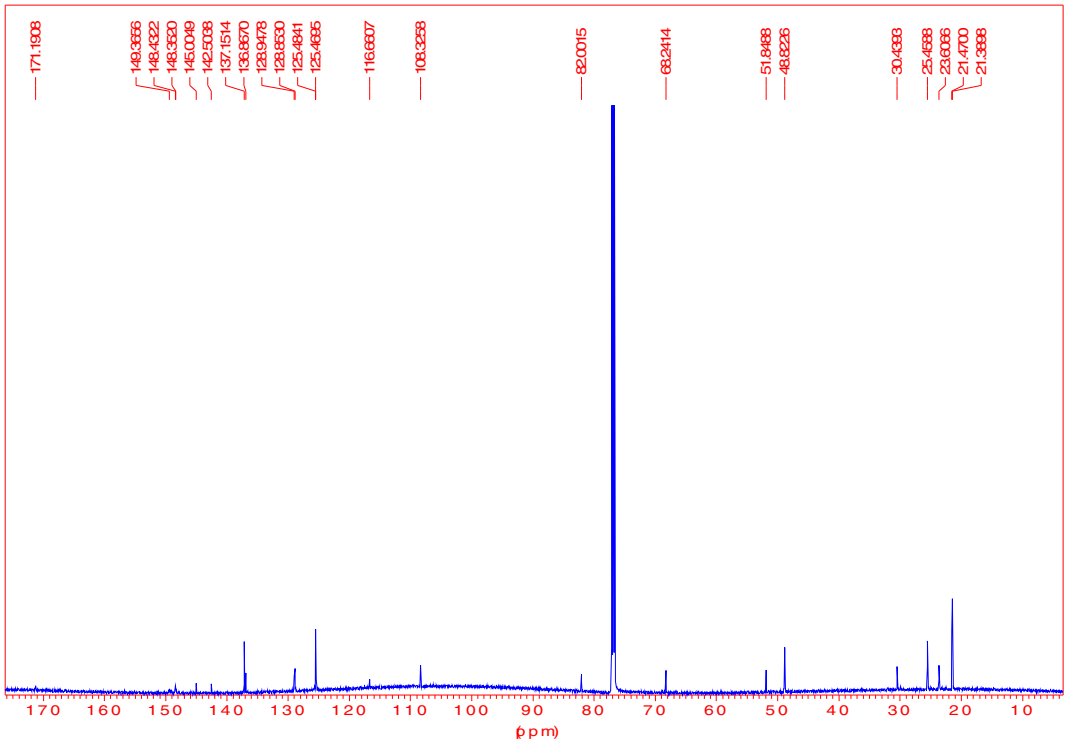
^{13}C NMR spectrum (100 MHz, $CDCl_3$) of catalyst **1c**



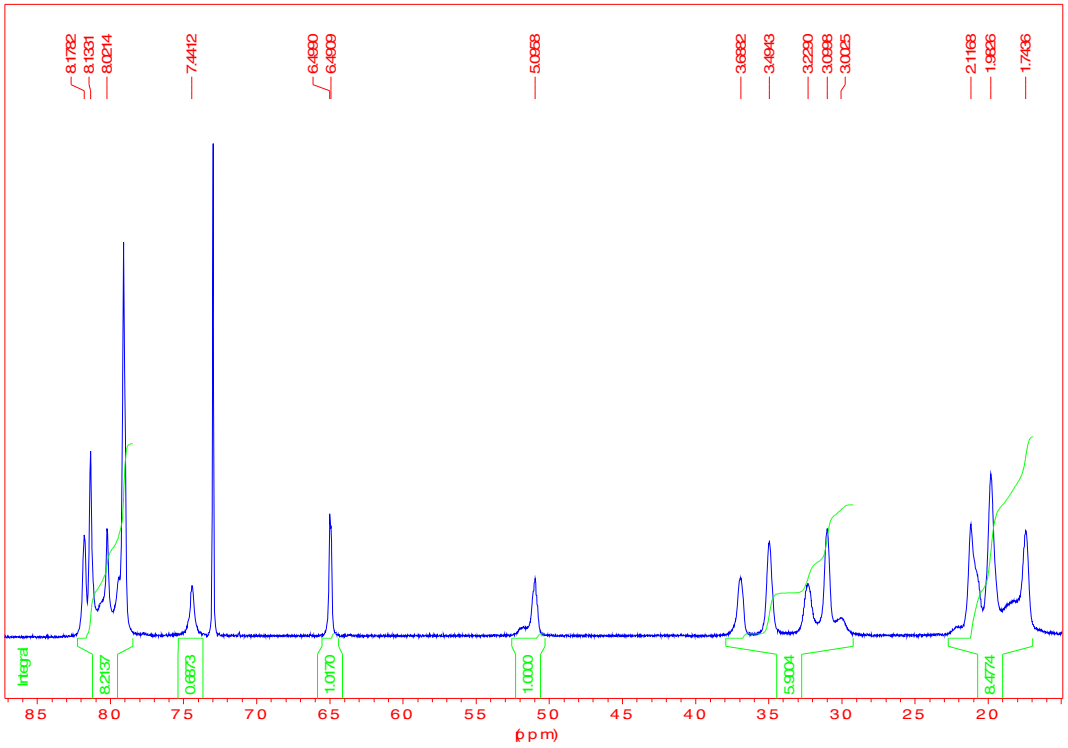
^{1}H NMR spectrum (400 MHz, $CDCl_3$) of catalyst **1d**



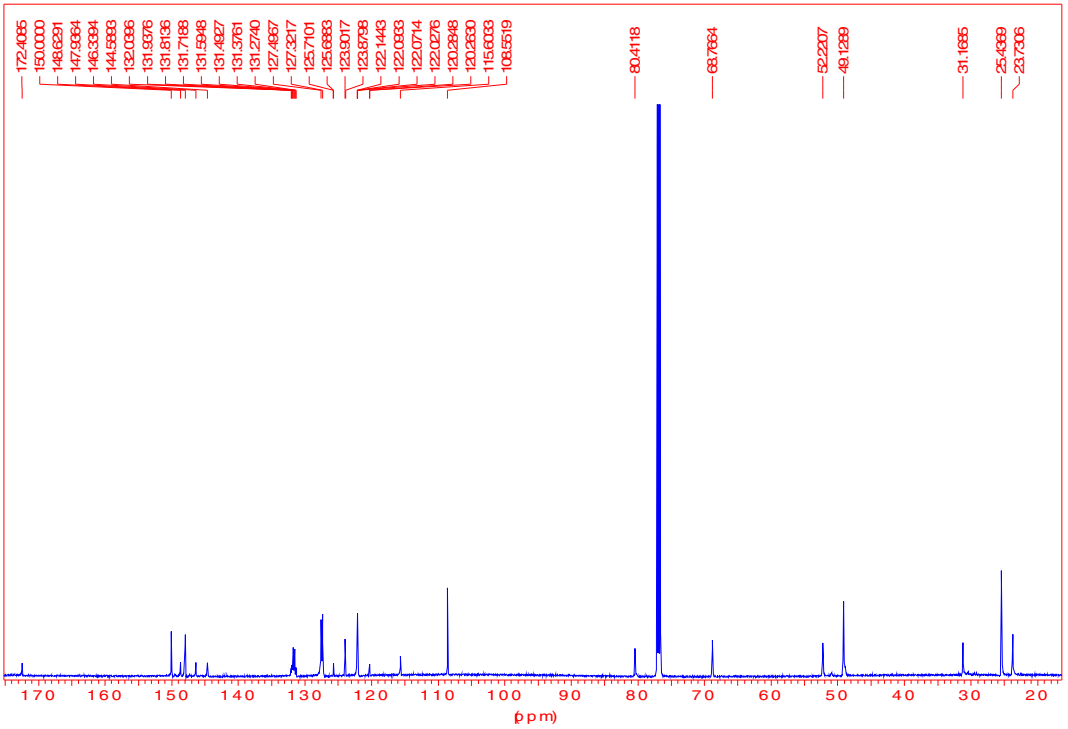
^{13}C NMR spectrum (100 MHz,$CDCl_3$) of catalyst **1d**



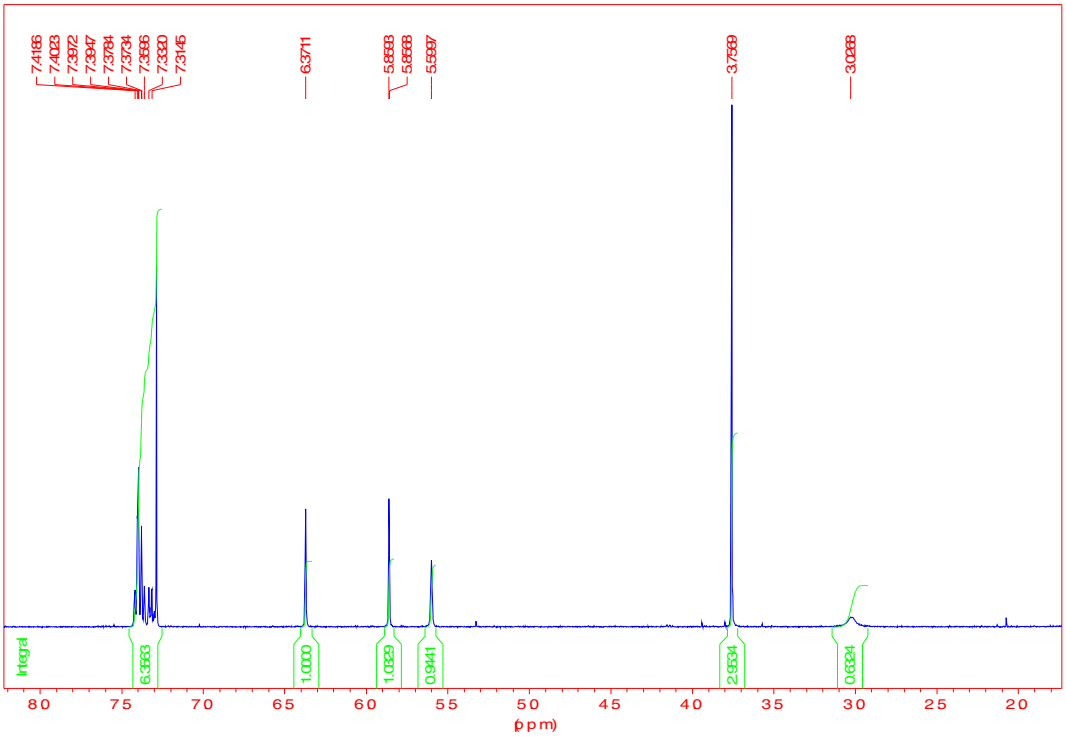
^{1}H NMR spectrum (400 MHz, $CDCl_3$) of catalyst **1e**



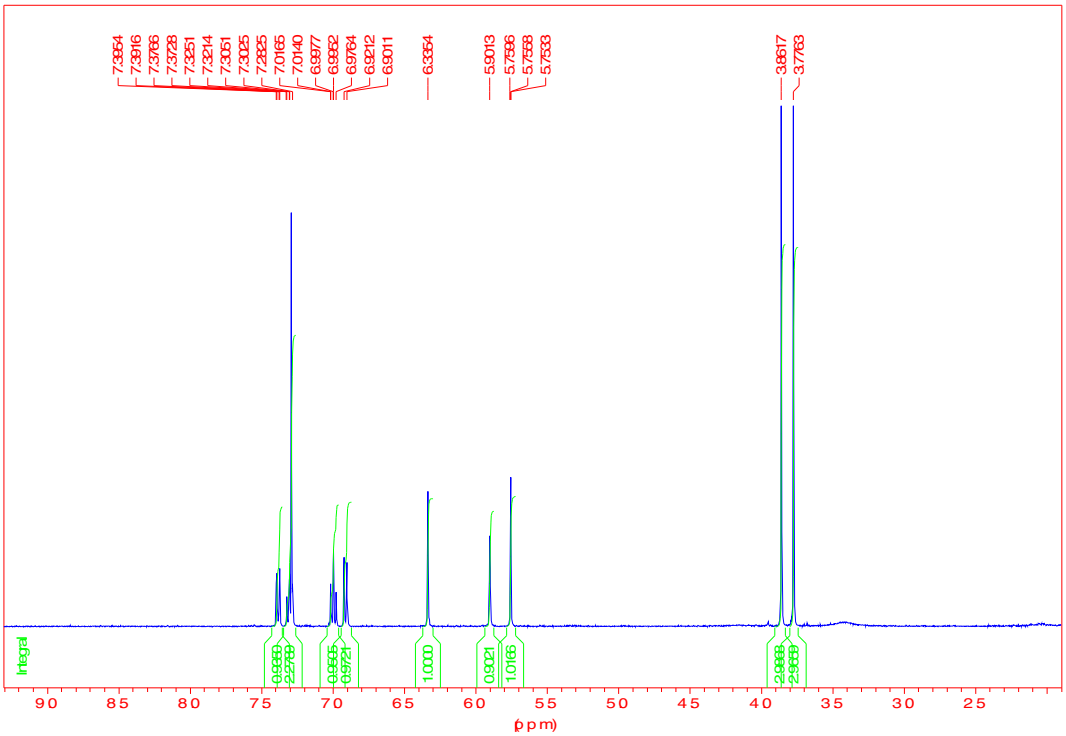
^{13}C NMR spectrum (100 MHz, $CDCl_3$) of catalyst **1e**



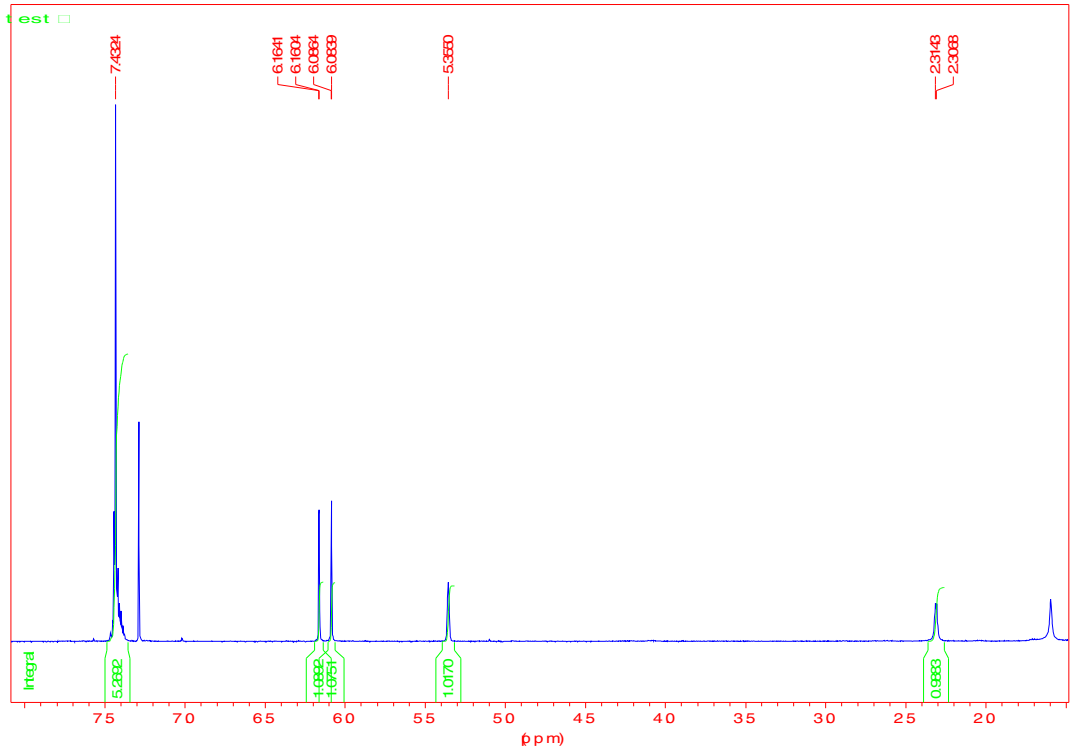
^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **9a**



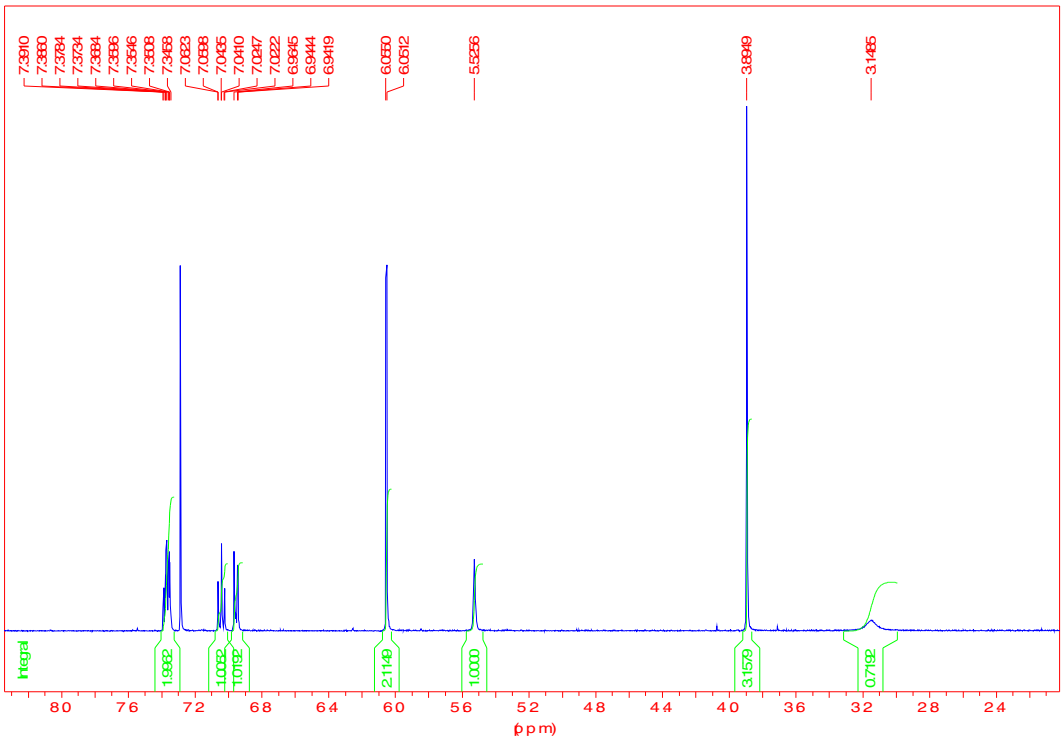
^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **10a**



^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **11a**



^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **12a**



6.0 References

1. Matsumoto, K.; Hatano, K.; Umezawa, N.; Higuchi, T. *Synthesis* **2004**, *13*, 2181.

2. Coleman, M. P.; Boyd, M. K. *J. Org. Chem.* **2002**, *67*, 7641.

3. Leazer Jr., J. L.; Cvetovich, R.; Tsay, F.-R.; Dolling, U.; Vickery, T.; Bachert, D. *J. Org. Chem.* **2003**, *68*, 3695.

4. Mathre, D. J.;Jones, T. K.; Xavier, L. C.; Blacklock, T. J.; Reamer, R. A.; Mohan, J. J.; Turner-Jones, E. T.; Hoogsteen, K.; Baum, M. W.; Grabowski, E. J. J. *J. Org. Chem.* **1991**, *56*, 751.

5. Marigo, M.; Wabnitz, T. C.; Fielenbach, D.; Jørgensen, K. A. *Angew. Chem. Int. Ed.* **2005**, *44*, 794.

6. Shiina, I.; Yamai, Y.-S.; Shimazaki, T. *J. Org. Chem.* **2005**, *70*, 8103.

7 Drewes, S. E.; Emslie, N. D.; Field, J. S.; Khan, A. A.; Ramesar, N. *Tetrahedron Asymm.* **1992**, *3*, 255.

8. Priem, G.; Pelotier, B.; Macdonald, S. J. F.; Anson, M. S.; Campbell, I. B. *J. Org. Chem.* **2003**, *68*, 3844.

9. Birman, V. B.; Jiang, H.; *Org. Lett.* **2005**, *7*, 3445.

10. Kundig, E. P.; Xu, L. H.; Romanens, P.; Bernardinelli, G. *Tetrahedron Lett.* **1993**, *34*, 7049.