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Ionic liquid supported 4-HO-Pro-Val derived organocatalysts for asymmetric aldol reactions in the presence of water

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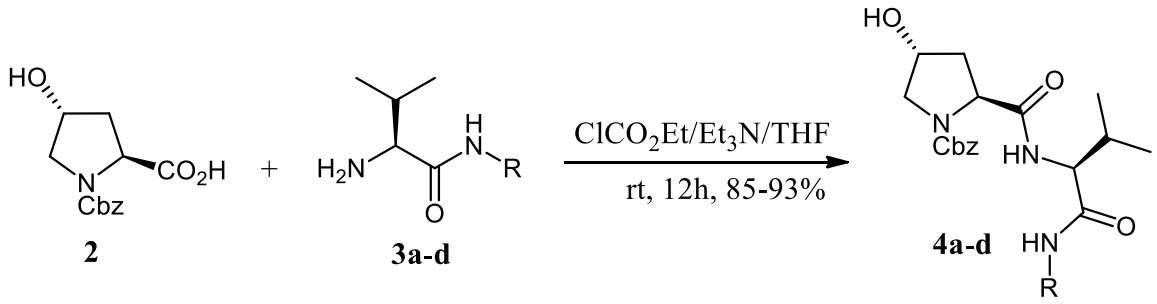
General Information:

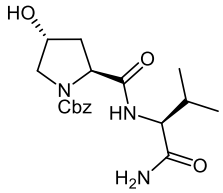
The ^{1}H and ^{13}C NMR spectra were recorded by Bruker AM 300-500 in $CDCI_3$ and DMSO-d_6. The chemical shifts of ^{1}H and ^{13}C were measured relative to Me_4Si or $CDCl_3$, respectively. The high-resolution mass spectra (HRMS) were measured with a Bruker microTOF II spectrometer by using electrospray ionization (ESI). The measurements were taken either in the positive ion mode (interface capillary voltage 4500 V) or in the negative ion mode (3200 V) in the mass range from m/z = 50–3000 Da; external or internal calibration was done with electrospray calibrant solution (Fluka). Syringe injection was used for solution in methanol (flow rate 3 μL/min). Nitrogen was applied as a dry gas and the interface temperature was set at 180°C. Specific angles of rotation $[\alpha]_D^{20}$ were measured on a Jasco DIP-360 polarimeter at 589 nm. Silica gel 0.060–0.200 (Acros) was used for column chromatography. The solvents were purified by standard procedures.

1. Preparation of amides 4a-d



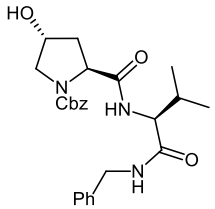
A solution of ethyl chloroformate (2.00 ml, 21.0 mmol) in THF (10 ml) was added dropwise to a stirred solution of (2*S*) -*N* - benzyloxycarbonyl-4-hydroxyproline **2** (5.56 g, 21.0 mmol) and Et_3N (2.93 ml, 21.0 mmol) in THF (100 ml) at 0°C for 15 min. After 30 min, (*S*)-2-amino-*N*-R-3-methylbutanamide **3** (21.0 mmol) was added to the mixture and the resulting solution was stirred at ambient temperature for 12 h. The precipitate was filtered off and washed successively with water (3 × 30 ml) and Et_2O (3 × 30 ml). The resulting white solid was dried under reduced pressure (0.5 Torr) at 50 °C for 2 h to afford amide **4a-d.**

Benzyl (2*S*,4*R*)-2-[*N*-((*S*)-1-amino-3-methyl-1-oxobutan-2-yl)carbamoyl]-4-hydroxy-pyrrolidine-1-carboxylate (4a).



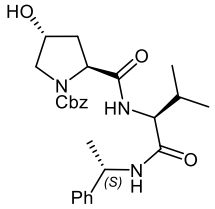
Colorless oil, yield 7.10 g (93%). ^{1}H NMR (500 MHz, DMSO-d_6): δ = 9.08 (s, 1H), 7.90 (dd, *J* = 26.3, 8.7 Hz, 1H),6.99 (d, *J* = 26.1 Hz, 2H),7.36-7.32(m, 6 H), 7.90 (dd, *J* = 26.3, 8.7 Hz, 1H), 7.71 (d, *J* = 26.1 Hz, 2H), 6.99 (d, *J* = 7.0 Hz, 1H), 5.03 (dd, *J* = 45.7, 12.7 Hz, 2H), 4.49 (dt, *J* = 36.4, 7.2 Hz, 1H), 4.14 (dt, *J* = 14.8, 7.7 Hz, 3H), 3.85 (s, 3H), 3.52 (d, *J* = 11.8 Hz, 1H), 3.31 (s, 2H), 2.51 (s, 1H), 2.37 (d, *J* = 5.2 Hz, 2H), 2.11 (dd, *J* = 12.5, 5.9 Hz, 1H), 2.02 – 1.85 (m, 1H), 1.86 – 1.74 (m, 2H), 1.51 (s, 2H), 0.96 – 0.68 (m, 6H). ^{13}C NMR (DMSO-d_6): δ = 16.6, 18.3, 30.0, 39.8, 55.1, 56.1, 58.0, 65.3, 72.5, 127.2-129.2 (Ar), 135.8, 156.5, 172.4, 176.3 ppm. HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{18}H_{26}N_3O_5$: 364.1867; found 364.1861.

Benzyl (2*S*,4*R*)-2-[*N*-((*S*)-1-benzylamino-3-methyl-1-oxobutan-2-yl)carbamoyl]-4-hydroxy-pyrrolidine-1-carboxylate (4b).



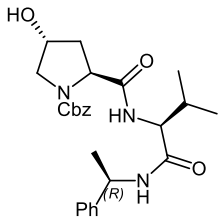
Colorless oil, yield 8.50 g (89%). ^{1}H NMR (300 MHz, DMSO-d_6) δ = 8.53 – 8.32 (m, 1H), 8.03 (dd, *J* = 21.2, 8.8 Hz, 1H), 7.42 – 7.14 (m, 9H), 5.16 – 4.84 (m, 3H), 4.44 (dt, *J* = 23.0, 7.6 Hz, 1H), 4.14 (dd, *J* = 7.8 Hz, 1H), 3.57 – 3.41 (m, 1H), 2.18 – 1.71 (m, *J* = 54.5, 18.9 Hz, 3H), 0.86 (dd, *J* = 6.3, 3.5 Hz, 2H), 0.75 (t, *J* = 6.8 Hz, 3H) ppm. ^{13}C NMR (DMSO-d_6): δ = 17.8, 18.9, 30.2, 39.6, 55.2, 57.4, 58.5, 68.1, 71.6, 127.8-129.0 (Ar), 136.4, 137.1, 156.4, 173.3 ppm. HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{25}H_{32}N_3O_5$: 454.2336; found 454.2330.

Benzyl (2*S*,4*R*)-4-hydroxy-2-(*N*-{(*S*)-3-methyl-1-oxo-1-[((*S*)-1-phenylethyl)amino]butan-2-yl}carbamoyl)pyrrolidine-1-carboxylate (4c).



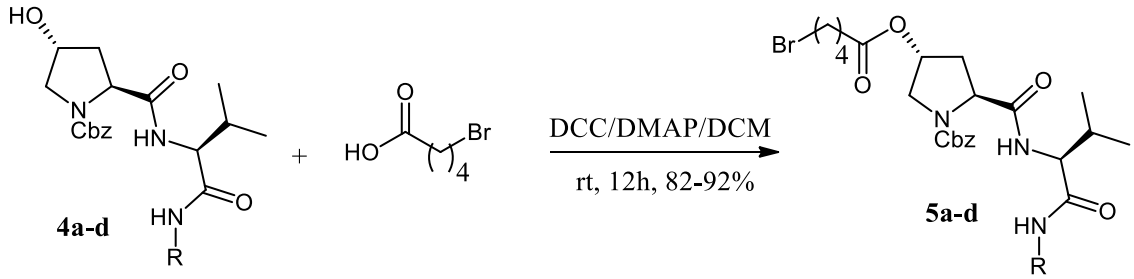
Colorless solid, yield 8.4 g (85%), mp 92-94°C. ^{1}H NMR (300 MHz, DMSO-d_6): δ = 8.34 (dd, *J* = 13.7, 8.0 Hz, 1H), 7.89 (dd, *J* = 16.5, 8.9 Hz, 1H), 7.45 – 7.11 (m, 9H), 5.16 – 4.80 (m, 4H), 4.43 (dt, *J* = 22.3, 7.5 Hz, 1H), 4.25 (s, 1H), 4.15 (t, *J* = 7.7 Hz, 1H), 3.47 (td, *J* = 10.1, 4.0 Hz, 1H), 2.19 – 1.74 (m, 3H), 1.32 (t, *J* = 7.4 Hz, 3H), 0.77 (d, *J* = 6.6 Hz, 2H), 0.65 (t, *J* = 5.8 Hz, 3H) ppm. ^{13}C NMR (DMSO-d_6) δ = 18.9, 19.6, 21.6, 30.3, 39.0, 48.2, 55.2, 56.7, 58.4, 59.2, 67.1, 68.8, 126.6-128.5 (Ar), 137.4, 144.6, 170.6, 172.4, 172.0 ppm. HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{26}H_{34}N_3O_5$: 468.2493; found 468.2487.

Benzyl (2*S*,4*R*)-4-hydroxy-2-(*N*-{(*S*)-3-methyl-1-oxo-1-[((*R*)-1-phenylethyl)amino]butan-2-yl}carbamoyl)pyrrolidine-1-carboxylate (4d).



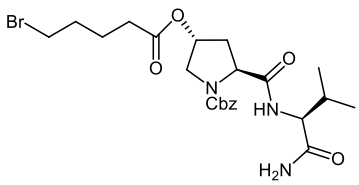
Colorless solid, yield 8.5 g (87%), mp 89-91°C. ^{1}H NMR (300 MHz, DMSO-d_6) δ = 8.30 (dd, *J* = 17.8, 7.9 Hz, 1H), 7.97 (dd, *J* = 20.4, 8.8 Hz, 1H), 7.40 – 7.13 (m, 9H), 5.16 – 4.79 (m, 4H), 4.40 (dt, *J* = 22.5, 7.6 Hz, 1H), 4.24 (s, 1H), 4.18 – 4.05 (m, 1H), 3.47 (td, *J* = 11.0, 4.3 Hz, 1H), 2.12 – 1.70 (m, 3H), 1.32 (dd, *J* = 6.5, 4.8 Hz, 3H), 0.86 (d, *J* = 6.7 Hz, 2H), 0.76 (dd, *J* = 15.3, 6.7 Hz, 3H) ppm. ^{13}C NMR (DMSO-d_6) δ = 18.9, 19.6, 22.9, 30.8, 48.2, 55.4, 55.9, 58.6, 59.3, 66.3, 68.3, 126.5-128.9 (Ar), 137.5, 144.8, 170.5, 172.1, 172.5 ppm. HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{26}H_{34}N_3O_5$: 468.2493; found 468.2489.

2. Preparation of esters 5a-d.



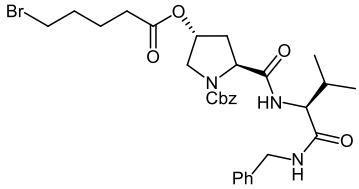
Hydroxy amide **4** (7.2 mmol), 5-bromovaleric acid (1.32 g, 7.2 mmol), DCC (1.50 g, 7.2 mmol), and DMAP (cat.) in CH_2Cl_2 (100 ml) were stirred at 25 °C for 12 h. The precipitate was filtered off and washed with CH_2Cl_2 (3 × 25 ml). The combined organic washings were evaporated and the residue was purified by column chromatography on silica gel (eluent: hexane-EtOAc 2:1 – 1:1) to afford the esters **5**.

Benzyl (2*S*,4*R*)-2-[*N*-((*S*)-1-amino-3-methyl-1-oxobutan-2-yl)carbamoyl]-4-(5-bromo-pentanoyloxy)pyrrolidine-1-carboxylate (5a).



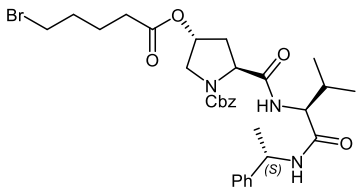
Colorless oil, yield 3.50 g (92%). ^{1}H NMR (DMSO-d_6): δ = 0.85-0.91 (dd, *J* = 12.5, 6.7 Hz, 6H), 1.70-1.88 (m, 5H), 2.16-2.40 (m, 5H), 3.35-3,40 (t, *J* = 6.4 Hz), 3.70 (m, 2H), 4.27-4.29 (m, 1H), 4.47-4.52 (m, 1H), 5.14 (s, 2H), 5.20-5.29 (m, 1H), 6.01 (m, 1H), 6.50 (m, 1H), 7.15 (d, *J* = 8.3 Hz, 1H), 7.20-7.33 (m, 5H, Ph) ppm. ^{13}C NMR (DMSO-d_6) δ = 16.5, 18.4, 23.0, 31.2, 32.1, 33.5, 35.2, 38.0, 55.2, 59.0, 68.1, 72.0, 217.8-129.0 (Ar), 135.8, 155.7, 172.2, 173.9, 176.3 ppm. HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{23}H_{33}BrN_3O_6$: 526.1547; found 526.1541.

Benzyl (2*S*,4*R*)-2-[*N*-((*S*)-1-benzylamino-3-methyl-1-oxobutan-2-yl)carbamoyl]-4-(5-bromo-pentanoyloxy)pyrrolidine-1-carboxylate (5b).



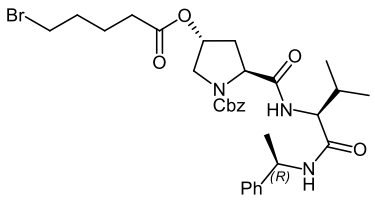
Colorless solid, yield 3.6 g (82%), mp 78-80°C. $[\alpha]_D^{20}$ -36.92° (*c* 1.0; MeOH). ^{1}H NMR (300 MHz, DMSO-d_6) δ = 8.45 (dd, *J* = 4.0, 2.0 Hz, 1H), 8.08 (dd, *J* = 15.3, 8.9 Hz, 1H), 7.42 – 7.15 (m, 9H), 5.19 (s, 1H), 5.12 – 4.90 (m, 2H), 4.57 – 4.41 (m, 1H), 4.28 (s, 2H), 4.19 – 4.08 (m, 1H), 3.66 (d, *J* = 7.4 Hz, 1H), 3.58 – 3.45 (m, 3H), 2.40 – 2.29 (m, 2H), 2.29 – 2.18 (m, 1H), 2.12 – 1.90 (m, *J* = 21.9 Hz, 2H), 1.93 – 1.43 (m, *J* = 52.5, 17.1, 6.9 Hz, 5H), 1.34 – 1.01 (m, 1H), 0.86 -0.75 (m, 6H) ppm. ^{13}C NMR (DMSO-d_6) δ = 16.2, 18.8, 23.4, 31.3, 31.9, 33.2, 35.0, 37.9, 43.1, 53.1, 56.9, 68.3, 71.6, 217.6-128.5 (Ar), 136.6, 137.5, 156.2, 173.2, 173.8 ppm. HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{30}H_{39}BrN_3O_6$: 616.2017; found 616.2021.

Benzyl (2*S*,4*R*)-4-(5-bromopentanoyloxy)-2-(*N*-{(*S*)-3-methyl-1-oxo-1-[((*S*)-1-phenylethyl)-amino]butan-2-yl}carbamoyl)pyrrolidine-1-carboxylate (5c).



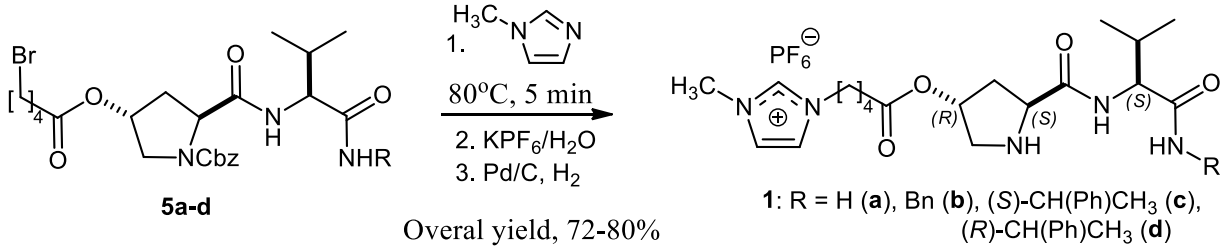
Colorless solid, yield 3.8 g (85%), mp 82-84°C. $[\alpha]_D^{20}$ -66.49° (*c* 1.0; MeOH). ^{1}H NMR (300 MHz, DMSO-d_6) δ = 8.38 (t, *J* = 9.0 Hz, 1H), 7.96 (dd, *J* = 13.4, 8.9 Hz, 1H), 7.38 – 7.23 (m, 8H), 7.22 – 7.12 (m, 1H), 5.17 (s, 1H), 5.08 – 5.01 (m, 1H), 4.93 – 4.82 (m, 1H), 4.55 – 4.40 (m, 1H), 4.01 (q, *J* = 7.2 Hz, 1H), 3.64 (td, *J* = 14.7, 7.3 Hz, 1H), 3.50 (t, *J* = 6.6 Hz, 3H), 2.33 (td, *J* = 7.2, 3.5 Hz, 2H), 2.10 – 1.99 (m, 1H), 1.98 – 1.85 (m, 1H), 1.85 – 1.54 (m, *J* = 29.8, 14.7, 7.2 Hz, 5H), 1.31 (t, *J* = 6.3 Hz, 3H), 1.16 (t, *J* = 7.1 Hz, 1H), 0.76 (d, *J* = 6.5 Hz, 2H), 0.64 (t, *J* = 6.3 Hz, 3H). ^{13}C NMR (75 MHz, DMSO-d_6) δ = 172.7, 171.6, 171.3, 170.1, 154.3, 144.7, 144.7, 137.2, 137.2, 128.8, 128.6, 128.5, 128.2, 127.9, 127.8, 127.4, 127.0, 126.3, 72.9, 72.2, 66.5, 66.4, 58.6, 58.4, 53.1, 53.0, 52.5, 48.1, 39.1, 37.1, 35.8, 34.9, 33.8, 32.9, 31.8, 31.0, 30.8, 24.9, 23.4, 22.7, 19.6, 19.5, 18.8 ppm. HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{31}H_{41}BrN_3O_6$: 630.2173; found 630.2165.

Benzyl (2*S*,4*R*)-4-(5-bromopentanoyloxy)-2-(*N*-{(*S*)-3-methyl-1-oxo-1-[((*R*)-1-phenylethyl)-amino]butan-2-yl}carbamoyl)pyrrolidine-1-carboxylate (5d).



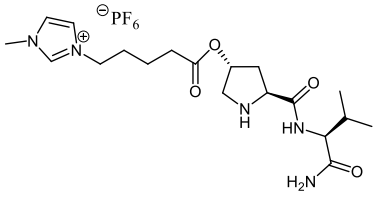
Colorless solid, yield 3.9 g (86%), mp 68-70°C. $[\alpha]_D^{20}$ -17.0° (*c* 1.04; MeOH). ^{1}H NMR (300 MHz, DMSO-d_6) δ = 8.34 (dd, *J* = 13.1, 8.0 Hz, 1H), 8.02 (dd, *J* = 15.9, 8.9 Hz, 1H), 7.41 – 7.13 (m, 9H), 5.10 – 4.84 (m, 3H), 4.45 (dt, *J* = 19.7, 7.7 Hz, 1H), 4.19 – 4.08 (m, 1H), 3.66 (td, *J* = 11.5, 4.5 Hz, 1H), 3.56 – 3.42 (m, 3H), 2.39 – 2.12 (m, 3H), 2.07 – 1.87 (m, 2H), 1.86 – 1.48 (m, 5H), 1.39 – 1.21 (m, 3H), 0.87-0.76 (m, *J* = 6.6 Hz, 6H), ppm. ^{13}C NMR (75 MHz, DMSO-d_6) δ = 172.72, 171.69, 171.32, 170.31, 154.31, 144.74, 144.70, 137.24, 137.20, 128.81, 128.61, 128.57, 128.24, 127.95, 127.87, 127.47, 127.01, 126.39, 72.99, 72.29, 66.50, 66.46, 58.66, 58.49, 53.11, 53.09, 52.57, 48.18, 40.85, 40.57, 40.29, 40.01, 39.74, 39.46, 39.18, 37.13, 35.80, 34.91, 33.80, 32.96, 31.86, 31.06, 30.82, 24.91, 23.43, 22.76, 19.65, 19.50, 18.77 ppm. HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{31}H_{41}BrN_3O_6$: 630.2173; found 630.2168.

3. Preparation of catalysts 1a-d.



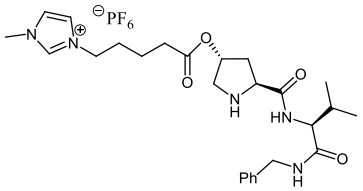
A mixture of **5** (4.0 mmol) and 1-methylimidazole (1.0 g, 0.96 ml, 12.0 mmol) was heated at 80°C for 5 min. After cooling to ambient temperature, the mixture was washed with Et_2O (10 x 30 ml). The residue was dissolved in water (10 ml) and aqueous KPF_6 (0.92 g, 5.0 mmol) was added to the resulting solution. The precipitated salt was filtered, washed with water (3 x 20 mL) and dried *in vacuo* (15 Torr) at 60°C for 2 h. Then, the suspension of thus obtained hexafluorophosphate salt, 5% Pd/C (200 mg) and MeOH (100 ml) was stirred under H_2 (1 bar) at ambient temperature for 1 h. The catalyst was filtered off and washed with MeOH (50 ml). The combined methanol phase was evaporated and the residue was dried *in vacuo* (15 Torr) at 40°C for 2 h to afford **1** as colorless solid.

3-(5-{(3*R*,5*S*)-5-[*N*-((*S*)-1-Amino-3-methyl-1-oxobutan-2-yl)carbamoyl)pyrrolidin-3-yl]oxy}-5-oxopentyl)-1-methyl-1*H*-imidazol-3-ium hexafluorophosphate (1a).



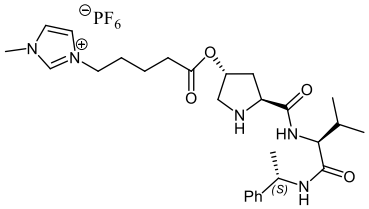
Colorless solid, yield 1.70 g (80%). mp 65-70°C. ^{1}H NMR (300 MHz, DMSO-d_6) δ = 9.08 (s, 1H), 7.90 (dd, *J* = 26.3, 8.7 Hz, 1H), 6.99 (d, *J* = 26.1 Hz, 2H),7.36-7.32 (m, 6H), 7.90 (dd, *J* = 26.3, 8.7 Hz, 1H), 7.71 (d, *J* = 26.1 Hz, 2H), 6.99 (d, *J* = 7.0 Hz, 1H), 5.03 (dd, *J* = 45.7, 12.7 Hz, 2H), 4.49 (dt, *J* = 36.4, 7.2 Hz, 1H), 4.14 (dt, *J* = 14.8, 7.7 Hz, 3H), 3.85 (s, 3H), 3.52 (d, *J* = 11.8 Hz, 1H), 3.31 (s, 2H), 2.51 (s, 1H), 2.37 (d, *J* = 5.2 Hz, 2H), 2.11 (dd, *J* = 12.5, 5.9 Hz, 1H), 2.02 – 1.85 (m, 1H), 1.86 – 1.74 (m, 2H), 1.51 (s, 2H), 0.96 – 0.68 (m, 6H) ppm.^{13}C NMR (75 MHz, DMSO-d_6) δ 16.6, 18.4, 23.0, 31.2, 32.1, 33.5, 35.2, 38.0, 55.2, 59.0, 68.1, 72.0, 217.8-130.0 (Ar), 135.8, 155.7, 172.2, 173.4, 176.1 ppm. HRMS (ESI): *m/z* $[M]^+$ calcd for $C_{19}H_{32}N_5O_4$: 394.2449; found 394.2453.

3-(5-{(3R,5S)-5-[((S)-1-Benzylamino-3-methyl-1-oxobutan-2-yl)carbamoyl]pyrrolidin-3-yl)oxy}-5-oxopentyl)-1-methyl-1H-imidazol-3-ium hexafluorophosphate (1b).



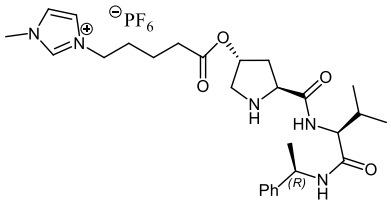
Colorless solid, yield 1.90 g (75%), mp 72-74°C. $[\alpha]_D^{20}$ -11,85° (*c* 1.0; MeOH). ^{1}H NMR (300 MHz, DMSO-d_6) δ = 9.07 (s, 1H), 8.48 (s, 1H), 8.09 (s, 1H), 7.69 (s, 2H), 7.30 (s, 8H), 5.19 (s, 1H), 5.05 (s, 2H), 4.50 (s, 1H), 4.28 (s, 2H), 4.15 (s, 2H), 3.84 (s, 2H), 3.68 (s, 1H), 3.52 (s, 1H), 2.36 (s, 2H), 2.08 (s, 1H), 1.79 (s, 2H), 1.49 (s, 2H), 0.85 (s, 3H), 0.75 (s, 3H) ppm. ^{13}C NMR (75 MHz, DMSO-d_6) δ = 18.2, 19.7, 21.4, 29.2, 31.8, 33.3, 36.2, 37.3, 48.9, 52.8, 57.3, 59.9, 76.4, 122.7, 124.1, 127.3, 127.7, 128.7, 137.0, 139.7, 171.1, 172.7, 173.4 ppm. HRMS (ESI): *m/z* $[M]^+$ calcd for $C_{26}H_{38}N_5O_4$: 484.2918; found 484.2923.

1-Methyl-3-{5-[(3R,5S)-5-((S)-3-methyl-1-oxo-1-((S)-1-phenylethylamino)butan-2-ylcarbamoyl)pyrrolidin-3-yloxy]-5-oxopentyl}-1H-imidazol-3-ium hexafluorophosphate (1c).



Colorless solid, yield 1.98 g (77%), mp 72-75°C. $[\alpha]_D^{20}$ -39,76° (*c* 1.0; MeOH). ^{1}H NMR (300 MHz, DMSO-d_6) δ = 9.12 (s, 1H), 8.59 (d, *J* = 8.1 Hz, 1H), 8.08 (d, *J* = 9.4 Hz, 1H), 7.73 (d, *J* = 18.1 Hz, 3H), 7.30 (d, *J* = 3.8 Hz, 5H), 7.24 – 7.17 (m, 1H), 5.12 (s, 1H), 4.97 – 4.83 (m, 1H), 4.29 – 4.08 (m, 4H), 3.90 – 3.79 (m, 4H), 2.98 (s, 2H), 2.40 – 2.25 (m, 3H), 2.19 – 2.00 (m, 2H), 2.00 – 1.70 (m, 5H), 1.60 – 1.40 (m, 3H), 1.34 (d, *J* = 7.0 Hz, 4H), 0.80 – 0.65 (m, 7H) ppm. ^{13}C NMR (75 MHz, DMSO-d_6) δ = 18.1, 19.7, 21.3, 22.9, 29.2, 32.1, 33.3, 36.2, 37.3, 48.4, 48.9, 52.8, 56.9, 59.8, 76.3, 122.7, 124.1, 126.4, 127.1, 128.6, 137.0, 145.0, 170.2, 172.7, 173.2 ppm. HRMS (ESI): *m/z* $[M]^+$ calcd for $C_{27}H_{40}N_5O_4$: 498.3075; found 498.3080.

1-Methyl-3-{5-[(3R,5S)-5-((S)-3-methyl-1-oxo-1-((R)-1-phenylethylamino)butan-2-ylcarbamoyl)pyrrolidin-3-yloxy]-5-oxopentyl}-1H-imidazol-3-ium hexafluorophosphate (1d).



Colorless solid, yield 1.85 g (72%), mp 77-80°C. $[\alpha]_D^{20}$ +10,84° (*c* 1.0; MeOH). ^{1}H NMR (300 MHz, DMSO-d6) δ = 9.08 (s, 1H), 8.51 (d, *J* = 7.8 Hz, 1H), 8.04 (d, *J* = 9.4 Hz, 1H), 7.70 (d, *J* = 17.7 Hz, 2H), 7.29(s,4H), 7.22(s,1H), 5.07 (s, 1H), 4.92 (t, *J* = 7.6 Hz, 1H), 4.7-4.08 (m, 3H), 3.82 (s, 3H), 3.72 (t, *J* = 9Hz, 1H), 2.93 (s, 2H), 2.31 (t, *J* = 7.1 Hz, 2H), 2.13-2.01 (m,1H) 2.00-1.69 (m, 4H), 1.56-1.39 (m, 2H), 1.33 (d, *J* = 7.0 Hz, 3H), 0.82 (dd, *J* = 11.5, 6.7 Hz, 6H) ppm.^{13}C NMR (75 MHz, DMSO-d_6) δ = 18.8, 19.5, 21.3, 22.8, 29.1, 30.8, 33.1, 36.1, 37.3, 48.2, 48.8, 52.7, 58.5, 59.1, 63.2, 73.5, 122.7, 124.1, 126.4, 127.5, 128.6, 137.0, 144.7, 170.1, 172.6, 173.3 ppm. HRMS (ESI): *m/z* $[M]^+$ calcd for $C_{27}H_{40}N_5O_4$: 498.3075; found 498.3080.

4. General procedure for asymmetric aldol reaction.

A mixture of catalyst **1c** (8.5 mg, 0.013 mmol), ketone **6** (0.40 mmol), aldehyde **7** (0.13 mmol) and water (0.23 ml, 13 mmol, 100 equiv. with respect to **7**) was stirred for 20-48 h. Aldol **8** was extracted with Et_2O (2×5 ml), the combined extracts were passed through a silica gel pad (1 g) and evaporated under reduced pressure (15 Torr). The *dr* ratio of aldols **8** was determined from the ^{1}H NMR spectra of crude reaction mixture. The mixtures of *syn* and *anti* isomers of aldols **8** were purified on a column with silica gel (eluent hexane - ethyl acetate 3:1-1:1)). ^{1}H NMR spectra of compounds **8** correspond to reported data [1-3]. The *ee* values of **8** were determined by HPLC on Chiralcel OD-H and OJ-H or Chiralpak AD chiral phases.

5. Recycling of catalyst 1c.

After extraction of aldol **8ad**, fresh portions of reagents **6a** (0.40 mmol) and **7d** (0.13 mmol) were added to the remaining suspension of catalyst **1c** in water and the reaction was re-performed as described above.

6. References.

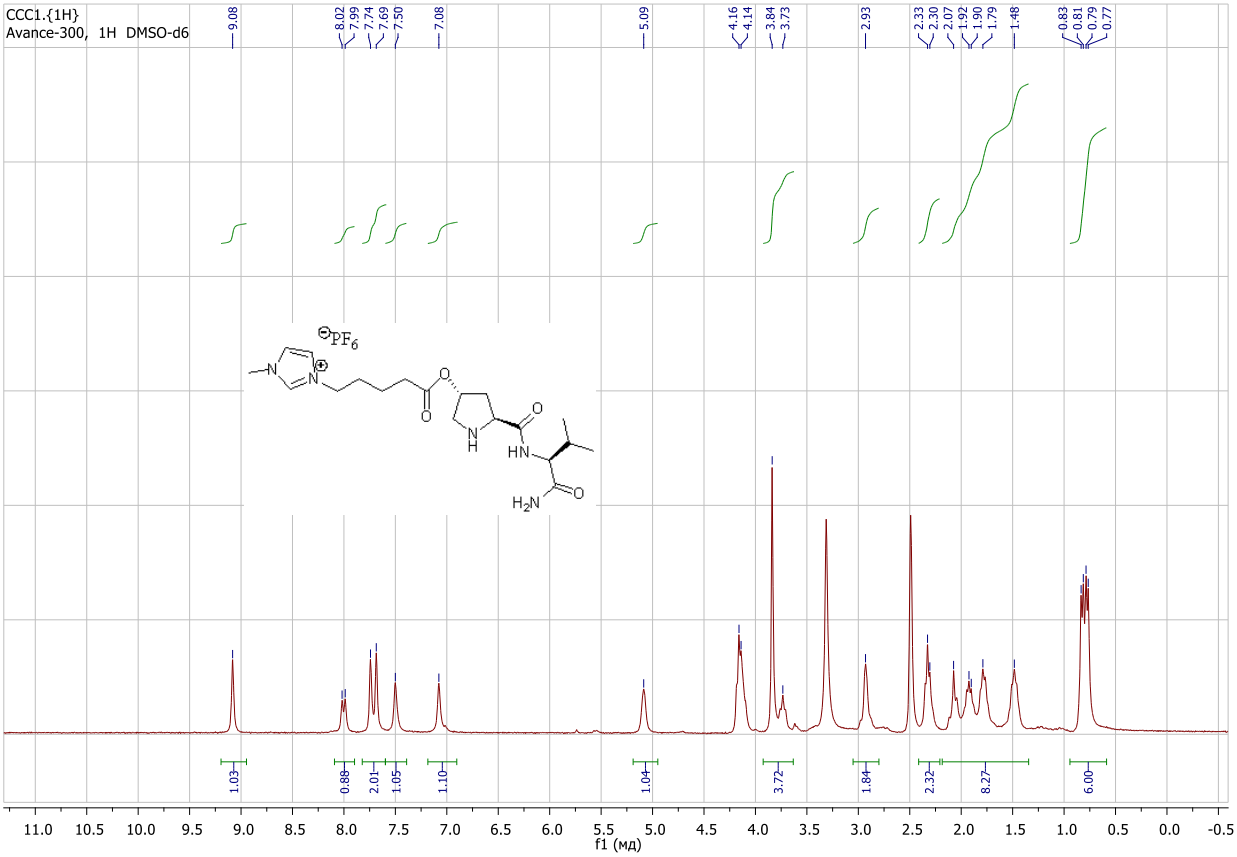
1. Y. Xu and A. Cordova, *Chem*. *Commun*., 2006, 460.

2. D. Font, C. Jimeno and M. A. Pericas, *Org*. *Lett*., 2006, **8**, 4653.

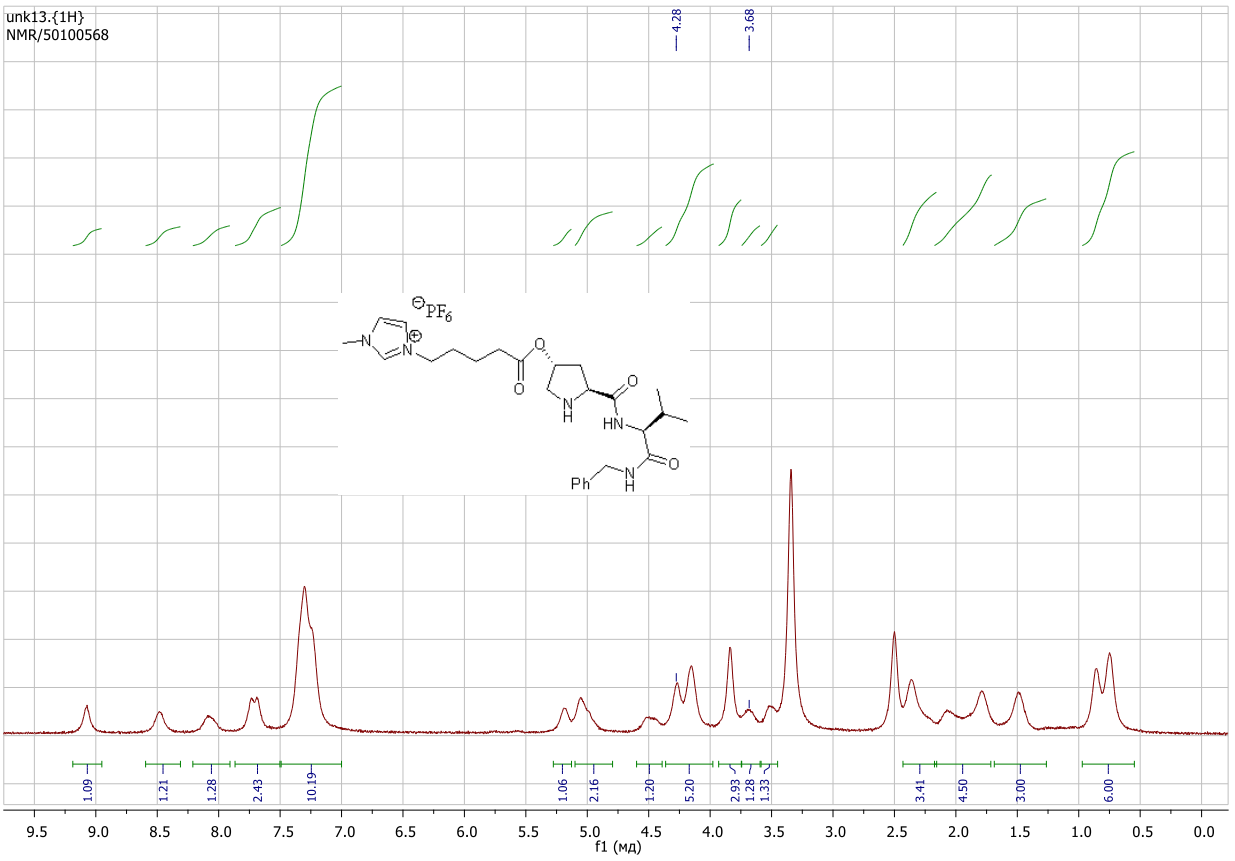
3. J. R. Chen, H. H. Lu, X. Y. Li, L. Cheng, J. Wan and W. J. Xiao, *Org*. *Lett*., 2005, **7**, 4543.

Pictures of ^{1}H and ^{13}C NMR spectra for compounds **1a-d**.

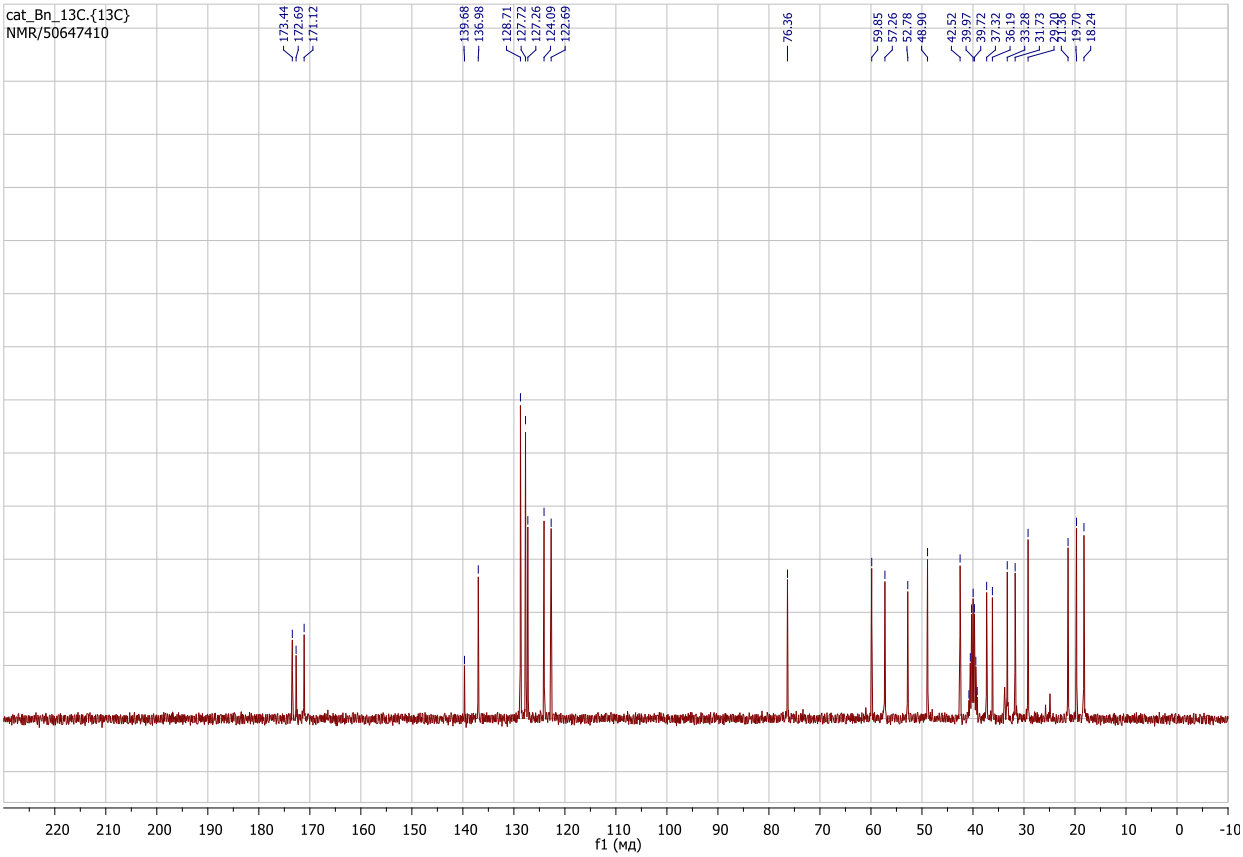
Catalyst **1a**:



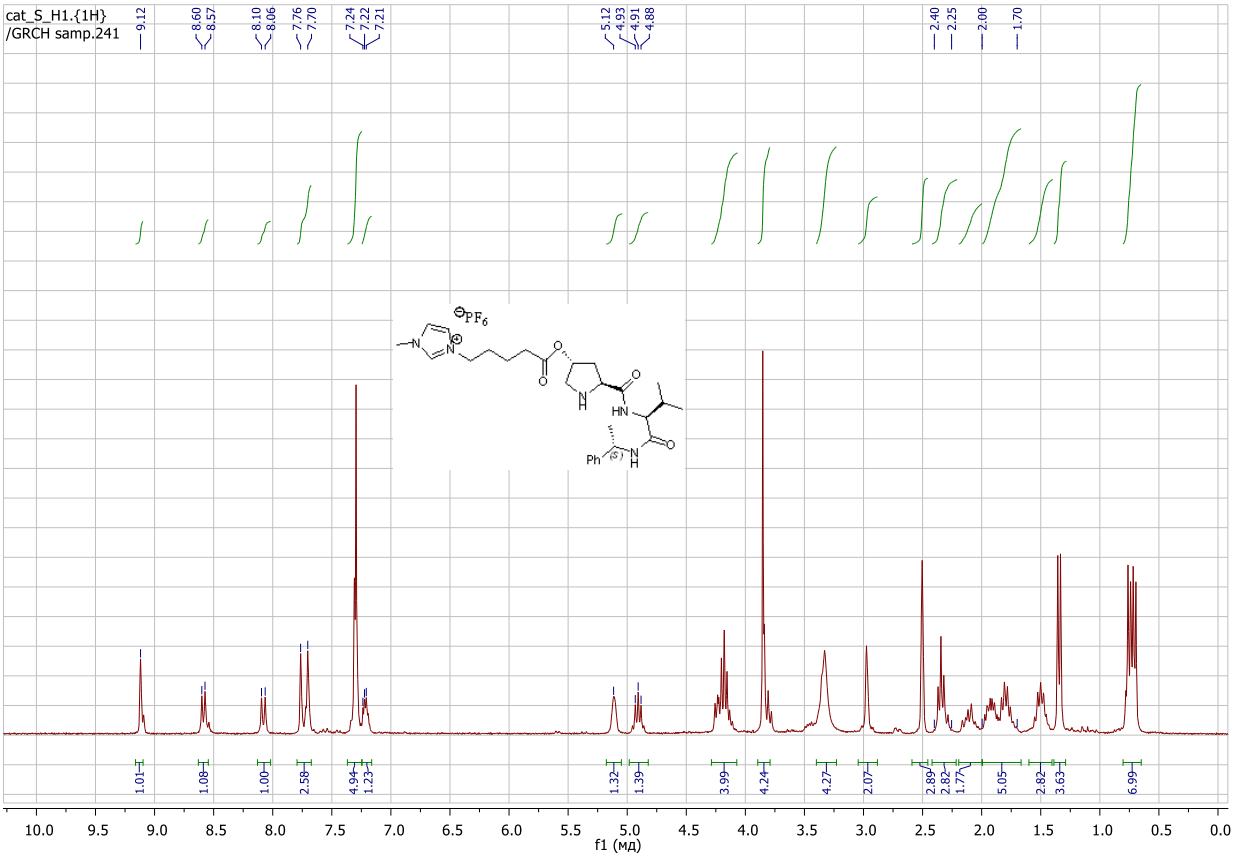
Catalyst **1b**:



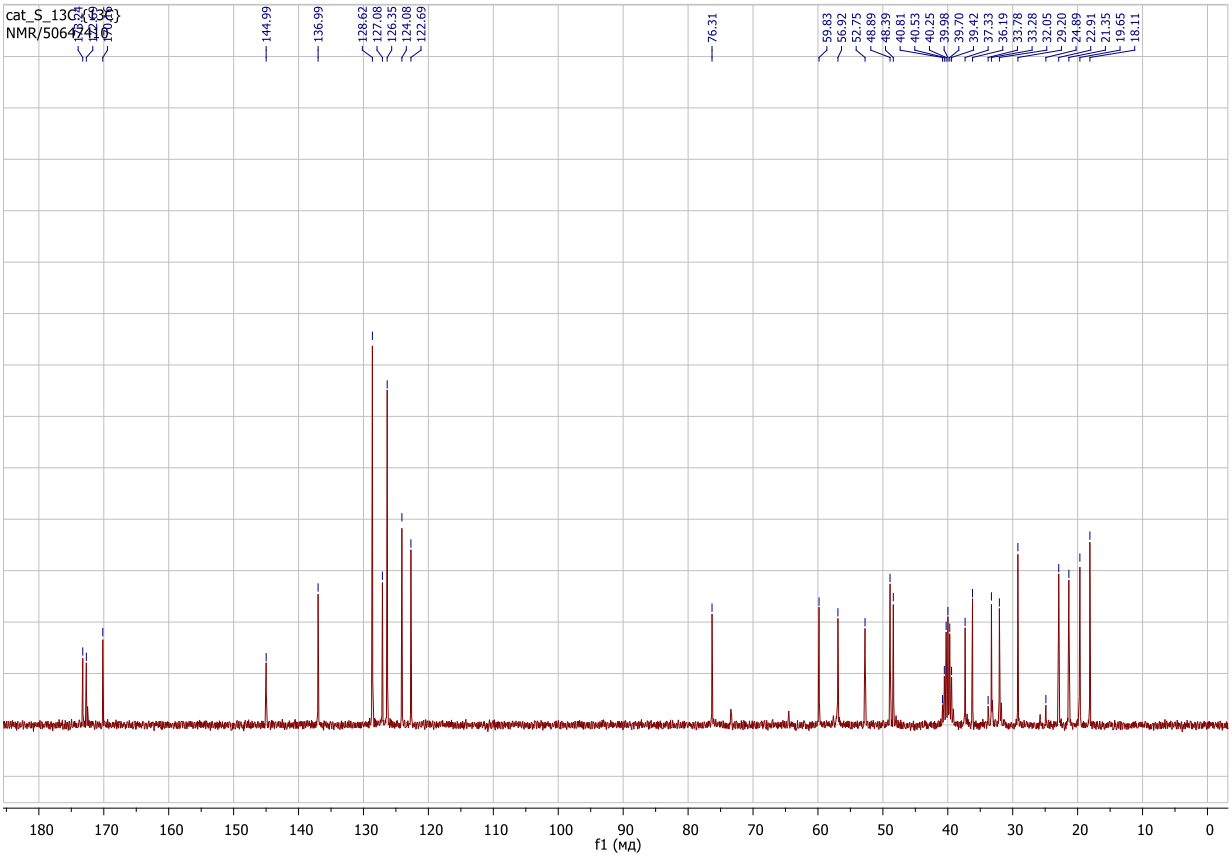
Catalyst **1b**:



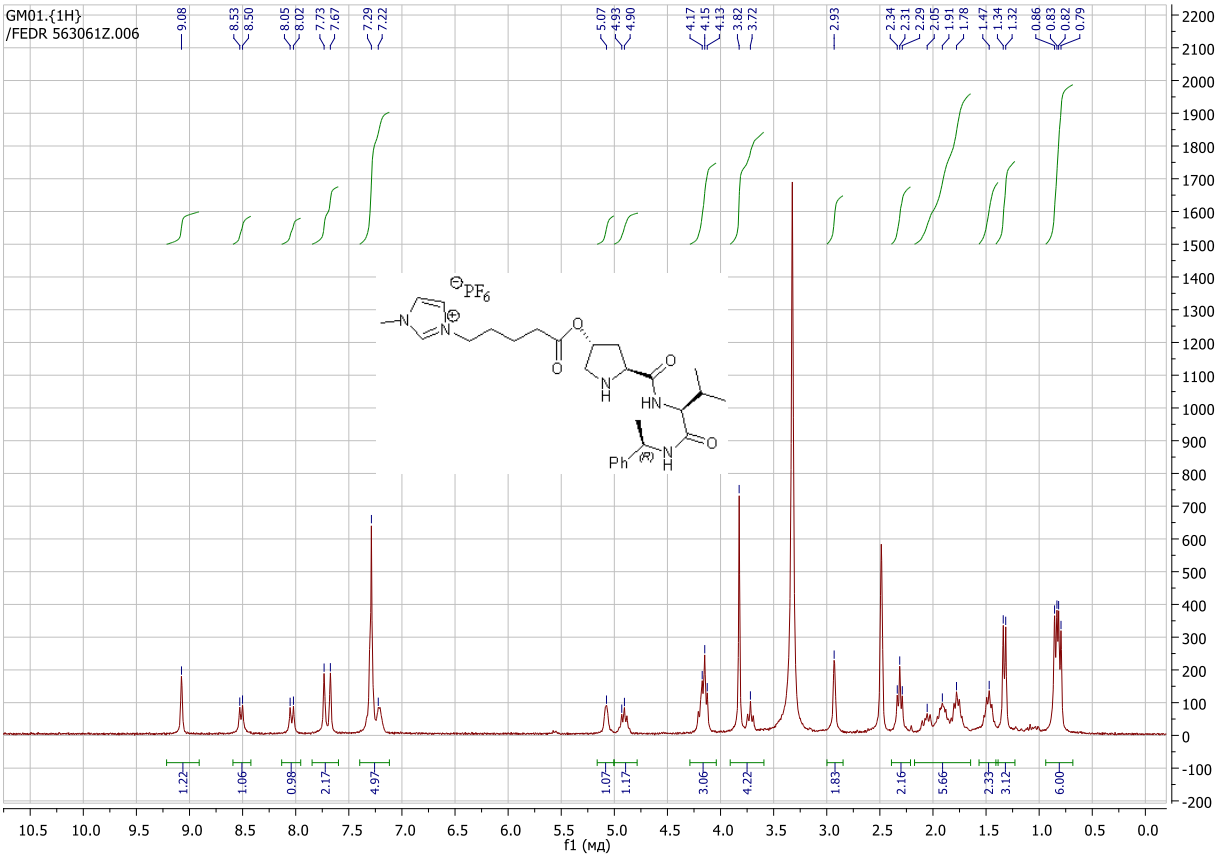
Catalyst **1c**:



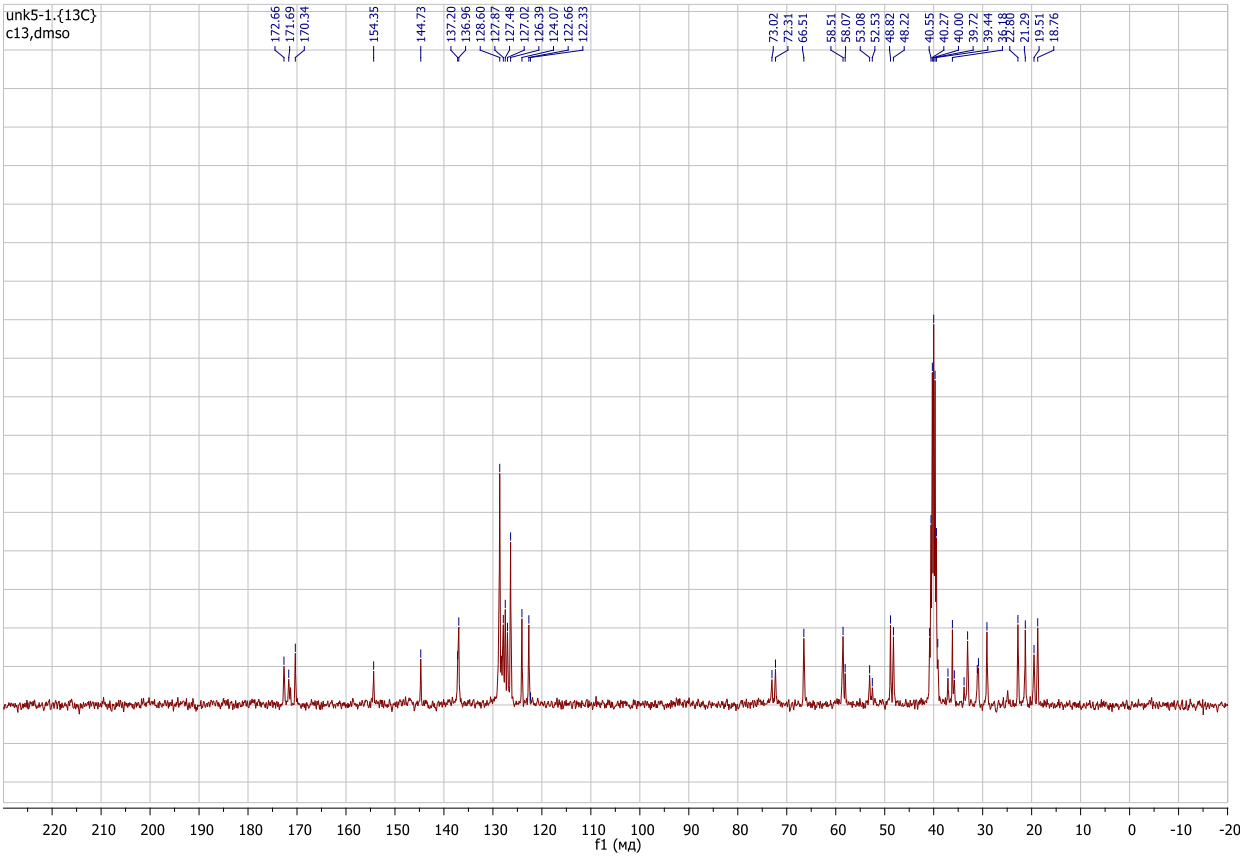
Catalyst **1c**:



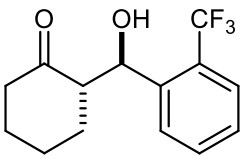
Catalyst **1d**:

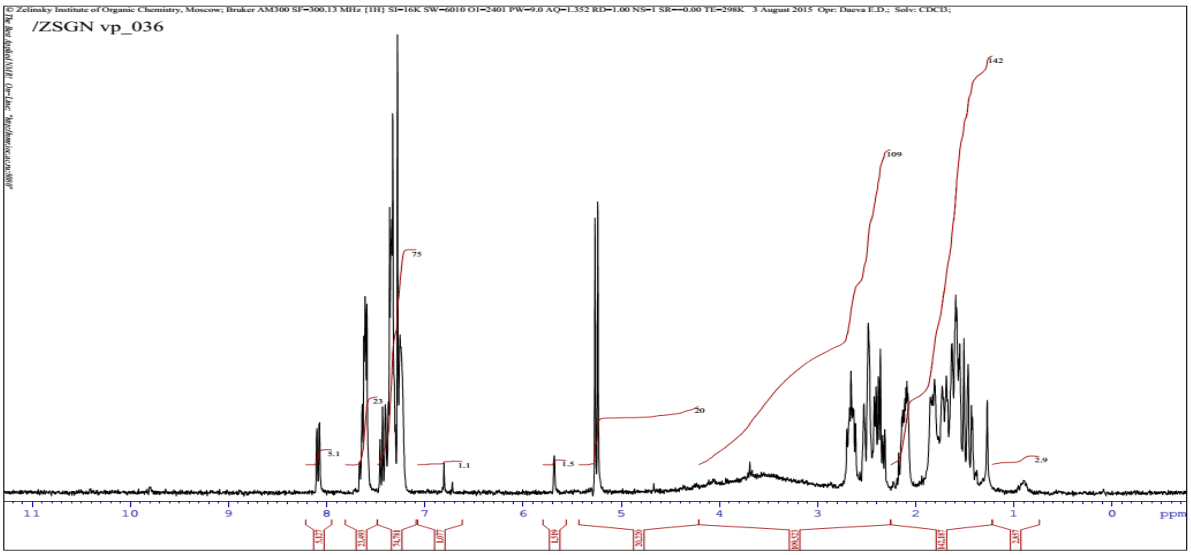


Catalyst **1d**:

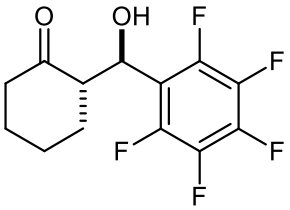


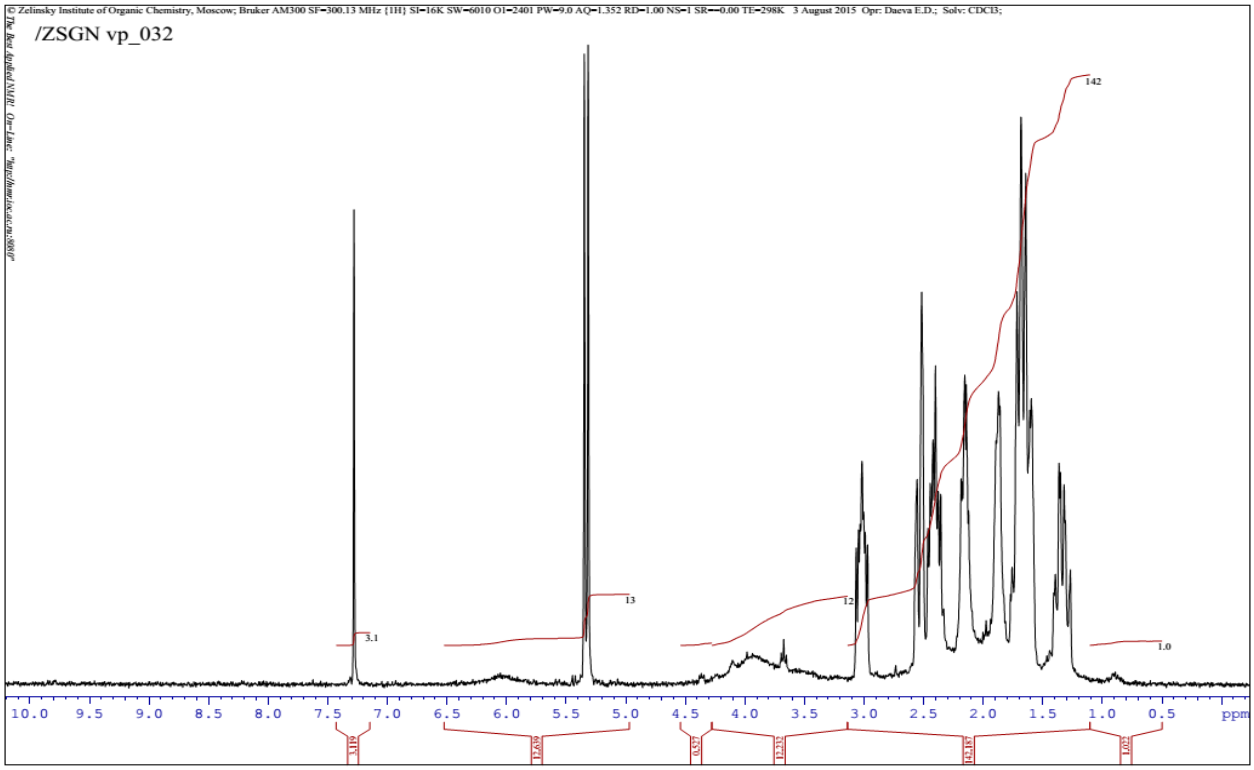
Compound **8ab**:



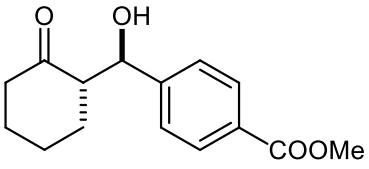


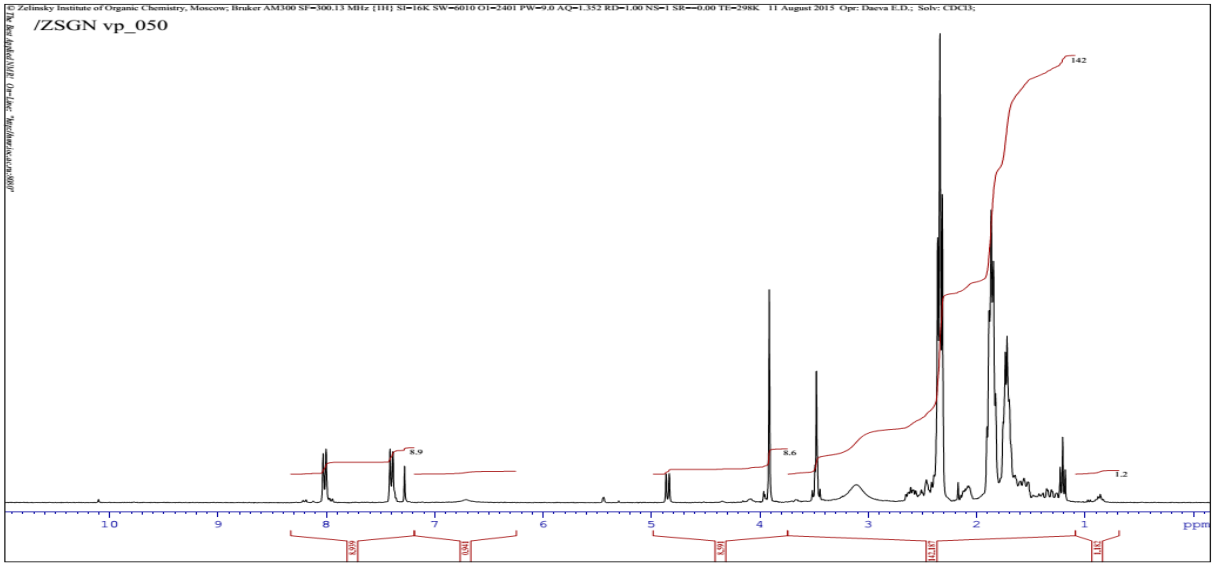
Compound **8ac**:



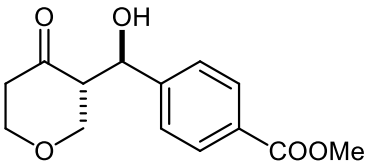


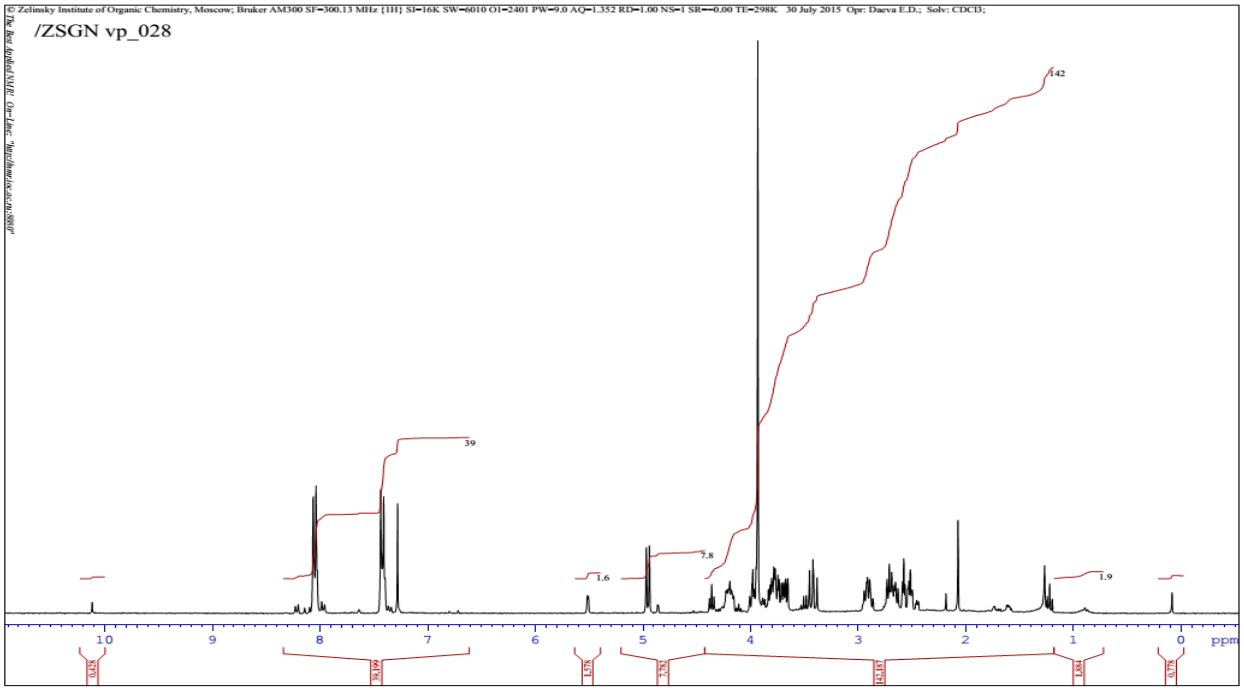
Compound **8ad**:



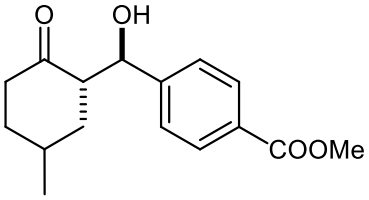


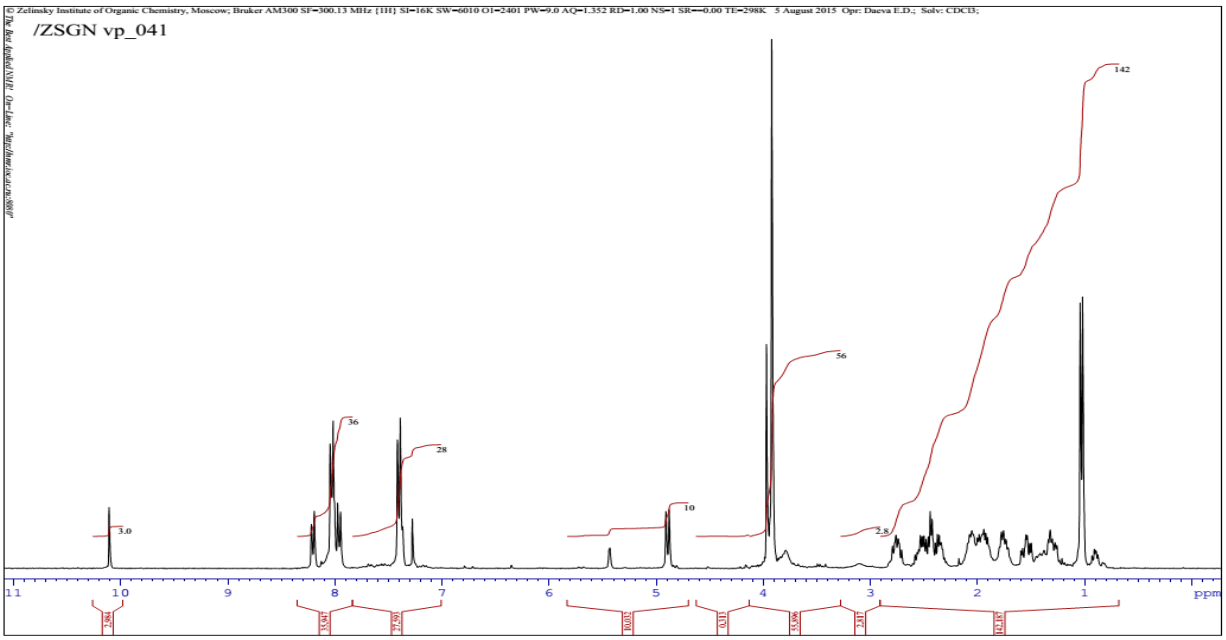
Compound **8bd**:





Compound **8cd**:





Compound **8dd**: