Electronic Supplementary Material (ESI) for RSC Advances.

Highly enantioselective tandem enzyme-organocatalyst crossed aldol reactions with acetaldehyde in deep-eutectic-solvents.

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SUPPLEMENTARY INFORMATION

1. Experimental

Chemicals. All chemicals were obtained by Sigma-Aldrich and used without further purification. Immo-CAL-B was delivered by c-LEcta GmbH.

NMR-Spectroscopy. All NMR spectra were measured on a 300 MHz (^{1}H-NMR: 300 MHz, ^{13}C-NMR: 75 MHz) Bruker device from BioSpin GmbH at 23 °C. Chemical shifts are relative to the used solvents ($CDCl_3$: ^{1}H: δ = 7.26 ppm, 13 C: δ = 77.36 ppm), indicated in ppm.

Preparation of glycerol-choline chloride (2:1) DES:

Glycerol (61.3 g, 66.6 mmol) and choline chloride (46.3 g, 33.2 mmol) were mixed and stirred at 60 °C until a clear solution was obtained.

General procedure 1:

The enzyme CAL-B (3.0 mg) was added to a mixture of aromatic aldehyde (1.00 mmol), vinyl acetate (276 µL, 3.00 mmol), 2-propanol (230 µL, 3.00 mmol), DES (glycerol:choline chloride 2:1, 1 mL) and (*S*)-(bis(3,5-bis(trifluoromethyl)phenl)(pyrrolidin-2-yl)methanol (**6**, 105.2 mg, 0.20 mmol). After 48 h of stirring at room temperature, Methanol was added (2.0 mL) and the mixture was cooled down to 0 °C, followed by a slow addition of $NaBH_4$ (227 mg, 6.00 mmol). The reaction was quenched after 1 h at 0 °C by the addition of 2 mL water. The aqueous phase was extracted with ethyl acetate (3 x 2 mL) and the combined organic layers were washed with brine (2 mL). After drying over Na_2SO_4, filtration and removal of the solvent in vacuum, the raw product was obtained. Purification was performed *via* flash chromatography over silica gel.

General procedure 2 - racemates:

The enzyme CAL-B (3.0 mg) was added to a mixture of aromatic aldehyde (1.00 mmol), vinyl acetate (276 µL, 3.00 mmol), 2-propanol (230 µL, 3.00 mmol), DES (glycerol:choline chloride 2:1, 1 mL) and triethylamine (28 µL, 0.20 mmol). After 48 h stirring at room temperature, Methanol was added (2.0 mL) and the mixture was cooled down to 0 °C, followed by a slow addition of $NaBH_4$ (226 mg, 6.0 mmol). The reaction was quenched after 1 h at 0 °C by the addition of 2 mL water. The aqueous phase was extracted with ethyl acetate (3 x 2 mL) and the combined organic layers were washed with brine (2 mL). After drying over Na_2SO_4, filtration and removal of the solvent in vacuum, the raw product was obtained. Purification was performed *via* flash chromatography over silica gel.

(*R*)-1-(4-nitrophenyl)propane-1,3-diol (3a):

By following *general procedure 1*, 4-nitrobenzaldehyde (151.1 mg, 1.00 mmol) was converted. After work-up and purification *via* flash chromatography over silica gel (eluent: 4:1 ethyl acetate/petroleum ether), 137.1 mg (0.70 mmol, 70% yield) of the desired product were obtained as colorless oil.

R_f = 0.33 (eluent: 4:1 ethyl acetate/petroleum ether)

^{1}H-NMR ($CDCl_3$, 300 MHz): δ = 1.97 (q, *J* = 5.8 Hz, 2H), 2.18 (brs, 1H), 3.50 (d, *J* = 2.9 Hz, 1H), 3.90 – 3.95 (m, 2H), 5.10 (t, *J* = 6.00 Hz, 1H), 7.55 (d, *J* = 8.8 Hz, 2H), 8.21 (d, *J* = 8.8 Hz, 2H) ppm.

^{13}C-NMR ($CDCl_3$, 75 MHz): δ = 40.6, 61.7, 73.7, 124.1, 126.8, 147.6, 152.1 ppm.

The analytical data agree with those reported in literature.[1]

HPLC: column: Phenomenex-Lux-Cellulose-3, eluent: hexane/*iso*-propanol 90:10, detection at 270 nm, retention time of (*R*)-1-(4-nitrophenyl)propane-1,3-diol: 40.71 min, (*S*)-1-(4-nitrophenyl)propane-1,3-diol: 50.75 min

(*R*)-1-(3-nitrophenyl)propane-1,3-diol (3b):

By following *general procedure 1*, 3-nitrobenzaldehyde (151.1 mg, 1.00 mmol) was converted. After work-up and purification *via* flash chromatography over silica gel (eluent: 1:1 ethyl acetate/petroleum ether), 45.5 mg (0.23 mmol, 23% yield) of the desired product were obtained as yellowish oil.

R_f = 0.13 (eluent: 1:1 ethyl acetate/petroleum ether)

^{1}H-NMR ($CDCl_3$, 300 MHz): δ = 1.94-2.00(m, 2H), 2.66 (brs, 1H), 3.89 (t, *J* = 5.4 Hz, 2H), 5.08 (t, *J* = 6.2 Hz, 1H), 7.51 (t, *J* = 7.9 Hz, 1H), 7.70 (d, *J* = 7.6 Hz, 1H), 8.09-8.13 (m, 1H), 8.23 (t, *J* = 1.7 Hz, 1H) ppm.

^{13}C-NMR ($CDCl_3$, 75 MHz): δ = 40.6, 61.5, 73.4, 121.0, 122.7, 129.7, 132.1, 146.9, 148.7 ppm.

The analytical data agree with those reported in literature.[1]

HPLC: column: Lux-Cellulose-3, eluent: hexane/*iso*-propanol 95:5, detection at 270 nm, retention time of (*R*)-1-(3-nitrophenyl)propane-1,3-diol: 89.758 min, (*S*)-1-(3-nitrophenyl)propane-1,3-diol: 96.067 min

(*R*)-1-(2-nitrophenyl)propane-1,3-diol (3c):

By following *general procedure 1*, 2-nitrobenzaldehyde (151.1 mg, 1.00 mmol) was converted. After work-up and purification *via* flash chromatography over silica gel (eluent: 1:1 ethyl acetate/petroleum ether), 129.0 mg (0.65 mmol, 65% yield) of the desired product were obtained as yellowish oil.

R_f = 0.27 (eluent: 1:1 ethyl acetate/petroleum ether)

^{1}H-NMR ($CDCl_3$, 300 MHz): δ = 1.88-2.00 (m, 1H), 2.03-2.13 (m, 1H), 2.70 (brs, 1H) 3.87-4.00 (m, 3H), 5.48 (dd, *J* = 8.8 Hz, 1.7 Hz, 1H), 7.38-7.44 (m, 1H), 7.62-7.68 (m, 1H), 7.87-7.93 (m, 2H) ppm.

^{13}C-NMR ($CDCl_3$, 75 MHz): δ = 39.8, 62.1, 70.0, 124.7, 128.4, 128.5, 134.0, 140.2, 147.7 ppm.

The analytical data agree with those reported in literature. [1]

HPLC: column: OJ-H Nov. 2003 without precolumn, eluent: hexane/*iso*-propanol 98:2, flow rate: 0.6 mL/min, detection at 210 nm, retention time of (*R*)-1-(2-nitrophenyl)propane-1,3-diol: 143.133 min, (*S*)-1-(2-nitrophenyl)propane-1,3-diol: 155.133 min

(R)-1-(2-chlorophenyl)propane-1,3-diol (3d):

By following *general procedure 1*, 2-chlorobenzaldehyde (140.6 mg, 1.00 mmol) was converted. After work-up and purification *via* flash chromatography over silica gel (eluent: 1:3 ethyl acetate/petroleum ether), 65.9 mg (0.35 mmol, 35% yield) of the desired product were obtained as yellowish oil.

R_f = 0.19 (eluent: 1:3 ethyl acetate/petroleum ether)

^{1}H-NMR ($CDCl_3$, 300 MHz): δ = 1.87-2.03 (1H, m), 2.07-2.13 (1H, m), 3.01 (1H, br-s), 3.88-3.98 (2H, m), 5.37 (1H, dd, J = 2.9, 8.9 Hz), 7.20-7.24 (1H, m), 7.28-7.35 (2H, m), 7.62-7.66 (1H, m) ppm.

^{13}C-NMR ($CDCl_3$, 75 MHz): δ = 37.2, 62.0, 71.3, 127.2, 127.3, 128.6, 129.5, 131.0 ppm.

The analytical data agree with those reported in literature. [1]

HPLC: column: OJ-H Nov. 2003 without precolumn, eluent: hexane/ethanol 98:2, detection at 215 nm, retention time of (*R*)-1-(2-chlorophenyl)propane-1,3-diol: 68.933 min, (*S*)-1-(2-chlorophenyl)propane-1,3-diol: 72.708 min

(*R*)-1-(2,6-dichlorophenyl)propane-1,3-diol (3e):

By following *general procedure 1*, 2,6-dichlorobenzaldehyde (175,0 mg, 1.00 mmol) was converted. After work-up and purification *via* flash chromatography over silica gel (eluent: 1:2 ethyl acetate/petroleum ether), 116.3 mg (0.53 mmol, 53% yield) of the desired product were obtained as a white solid.

R_f = 0.19 (eluent: 1:2 ethyl acetate/petroleum ether)

^{1}H-NMR ($CDCl_3$, 300 MHz): δ = 1.89-1.99 (1H, m), 2.33 (brs, 1H), 2.39-2.51 (m, 1H), 3.31.(d, J = 8.8 Hz, 1H), 3.91 (t, *J* = 5.8 Hz, 2 H), 5.67 (td, J = 8.8 Hz, 3.71 Hz, 1 H), 7.13 (dd, *J* = 8.7 Hz, 7.4 Hz, 1H), 7.27 -7-31(m, 2H) ppm.

^{13}C-NMR ($CDCl_3$, 75 MHz): δ = 37.4, 61.3, 71.2, 129.3, 129.8, 134.5, 137.7 ppm.

The analytical data agree with those reported in literature. [1]

HPLC: column: OJ-H Nov. 03 without precolumn, eluent: hexane/*iso*-propanol 95:5, detection at 210 nm, retention time of (*R*)-1-(2,6-dichlorophenyl)propane-1,3-diol: 42.947 min, (*S*)-1-(2,6-dichlorophenyl)propane-1,3-diol: 48.080 min

(*R,Z*)-4-bromo-5-phenylpent-4-ene-1,3-diol (3f):

By following *general procedure 1*, α-bromocinnamaldehyde (211.1 mg, 1.00 mmol) was converted. After work-up and purification *via* flash chromatography over silica gel (eluent: 1:2 ethyl acetate/petroleum ether), 36.1 mg (0.14 mmol, 14% yield) of the desired product were obtained as a yellowish oil.

R_f = 0.14 (eluent: 1:2 ethyl acetate/petroleum ether)

^{1}H-NMR ($CDCl_3$, 300 MHz): δ = 2.04-2.11 (m, 2H), 2.20 (br-s, 1H), 3.23 (d, J = 3.2 Hz.), 3.83-3.98 (m, 2H), 4.58 (m, 1H), 7.18 (s, 1H), 7.28-7.40 (m, 3H), 7.60-7.63 (m, 2H) ppm.

^{13}C-NMR ($CDCl_3$, 75 MHz): δ = 37.5, 61.0, 77.2, 77.6, 128.1, 128.5, 129.3, 129.4, 135.4 ppm.

The analytical data agree with those reported in literature. [1]

HPLC: column: OJ-H Nov. 03 without precolumn, eluent: hexane/*iso*-propanol 95:5, detection at 210 nm, retention time of(*R,Z*)-4-bromo-5-phenylpent-4-ene-1,3-diol: 111.083 min, (*S,Z*)-4-bromo-5-phenylpent-4-ene-1,3-diol: 116.558 min

2. Tandem reaction optimization.

2.1. Influence of Solvents

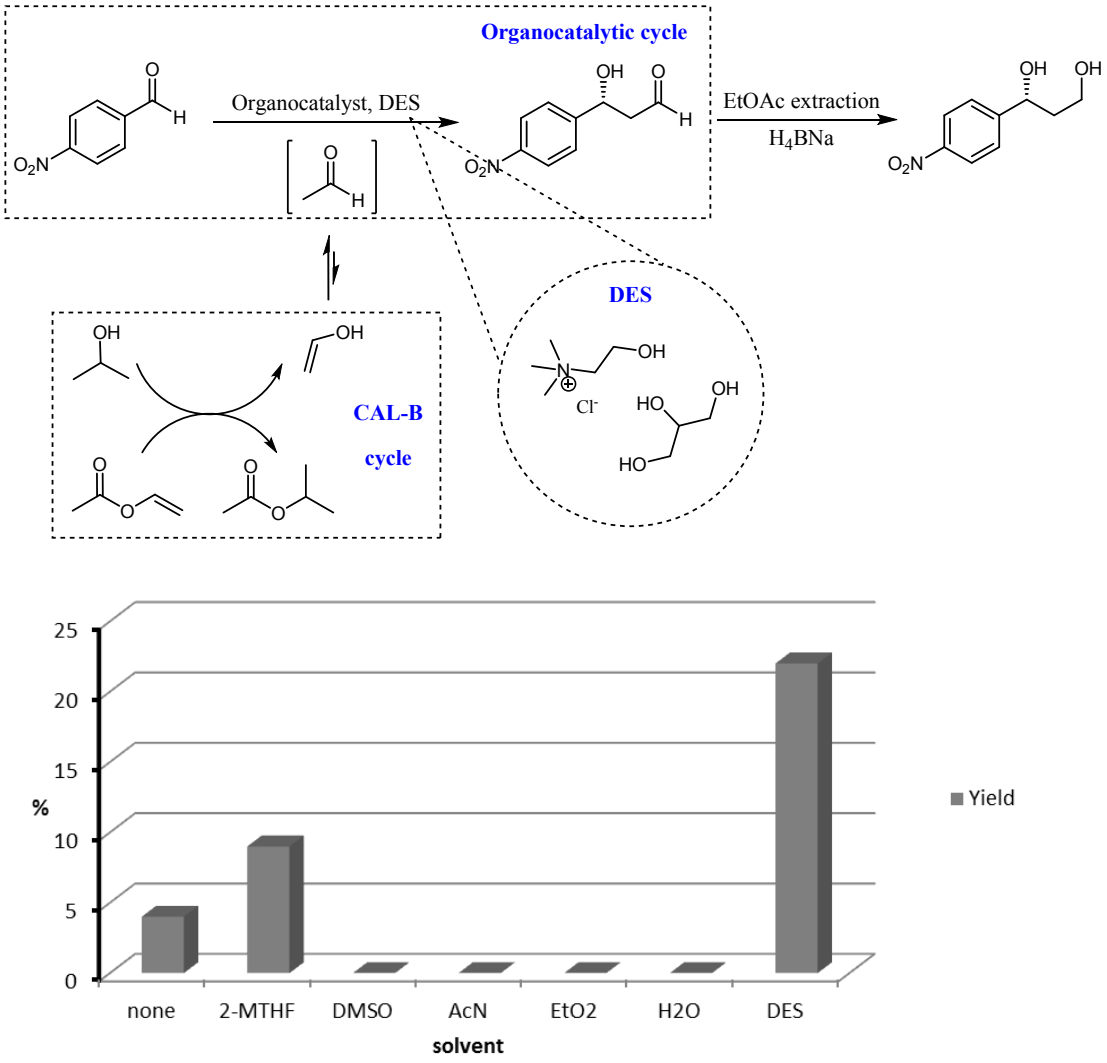


Figure 1. Influence of solvent. Conditions: 1.) 1 mmol *p*-nitrobenaldehyde, 3 mmol vinyl acetate, 3 mmol *iso*-porpanol, 0.2 mmol catalyst **6**, 1 mg CAL-B, 1 mL solvent, 48 h, rt; 2.) 6 mmol $NaBH_4$, 2 mL methanol, 1 h, 0 °C.

2.2. Influence of CAL-B loading

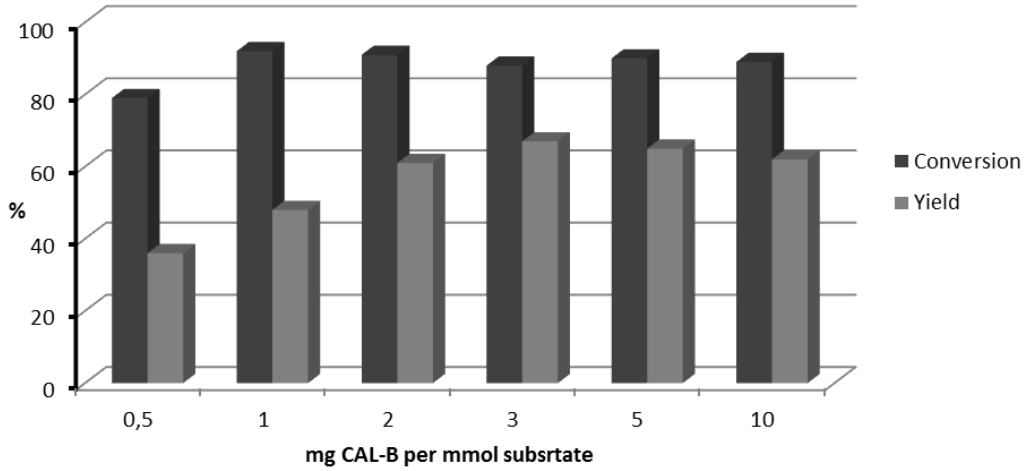


Figure 2. Controlling of *in-situ* available acetaldehyde *via* variation of biocatalyst loading. Conditions: 1.) 1 mmol *p*-nitrobenaldehyde, 3 mmol vinyl acetate, 3 mmol *iso*-porpanol, 0.2 mmol catalyst **6**, CAL-B, 1 mL glycerol-choline chloride (2:1) DES, 48 h, rt; 2.) 6 mmol $NaBH_4$, 2 mL methanol, 1 h, 0 °C.

2.3. Influence of vinyl acetate – isopropanol ratios

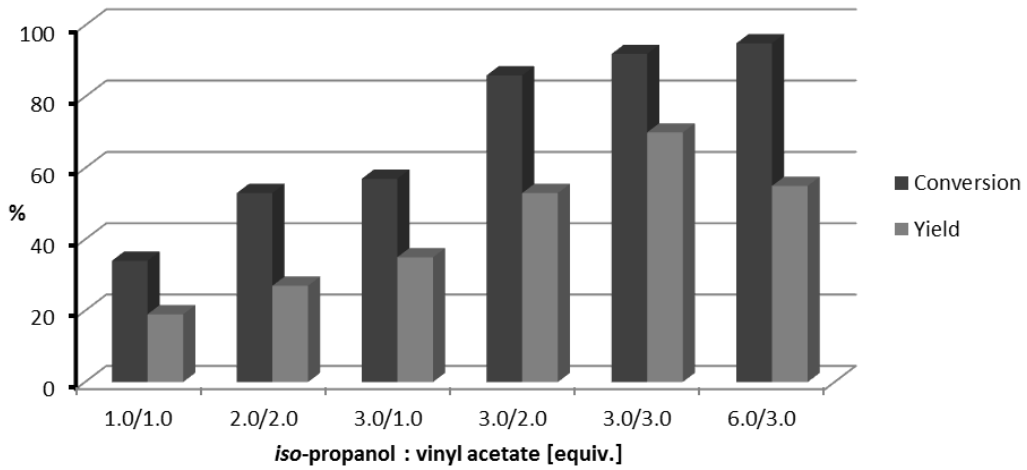


Figure 3. Variation of substrate loadings. Conditions: 1.) 1 mmol *p*-nitrobenaldehyde, vinyl acetate, *iso*-porpanol, 0.2 mmol catalyst **6**, CAL-B, 1 mL glycerol-choline chloride (2:1) DES, 48 h, rt; 2.) 6 mmol $NaBH_4$, 2 mL methanol, 1 h, 0 °C.

2.4. Influence of temperature

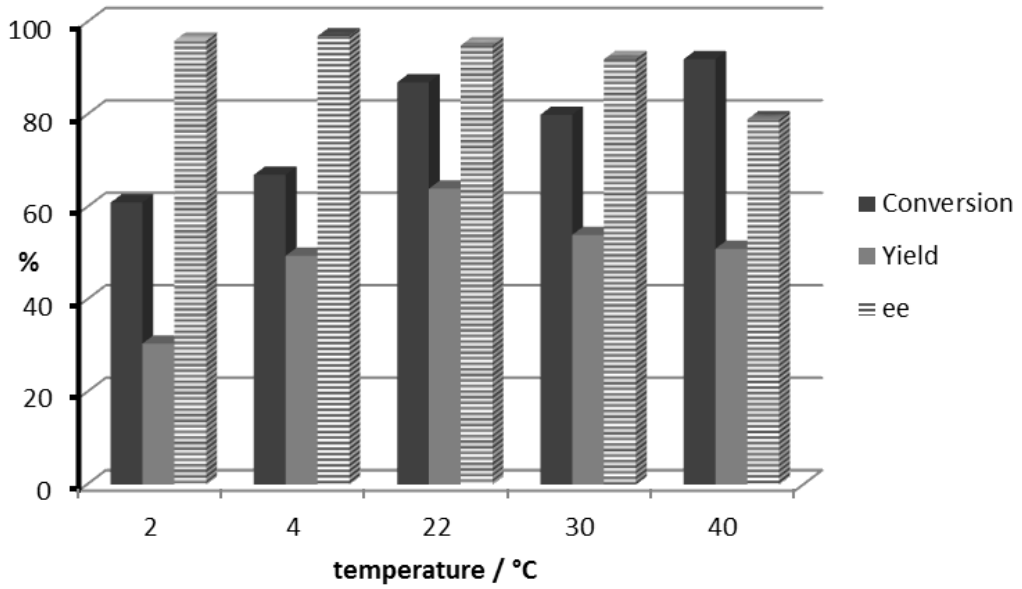


Figure 4. Temperature Screening Conditions: 1.) 1 mmol *p*-nitrobenaldehyde, 3 mmol vinyl acetate, 3 mmol *iso*-porpanol, 0.2 mmol catalyst **6**, 1 mg CAL-B, 1 mL glycerol-choline chloride (2:1) DES, 48 h; 2.) 6 mmol $NaBH_4$, 2 mL methanol, 1 h, 0 °C.

2.5. Influence of organocatalyst

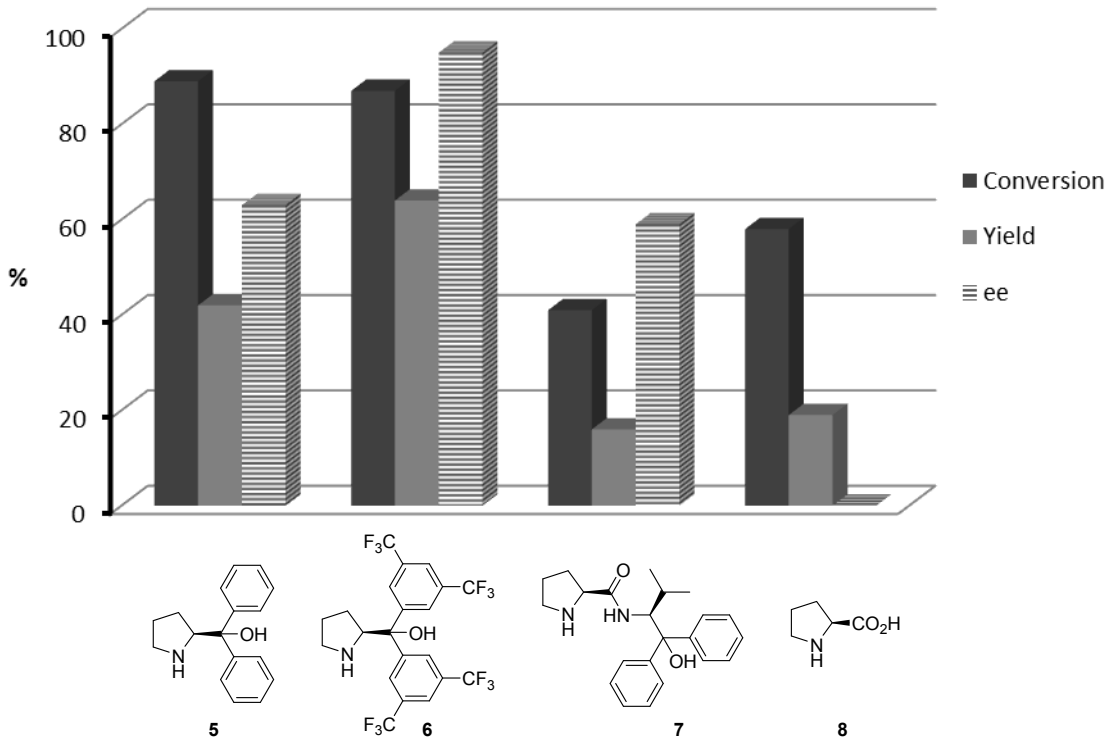
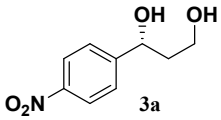


Figure 5. Assessment of different organocatalysts in the tandem reaction in DES media. Conditions: 1.) 1 mmol *p*-nitrobenaldehyde, 3 mmol vinyl acetate, 3 mmol *iso*-porpanol, 0.2 mmol catalyst, 1 mg CAL-B, 1 mL glycerol-choline chloride (2:1) DES, 48 h, rt; 2.) 6 mmol $NaBH_4$, 2 mL methanol, 1 h, 0 °C.

3. Analytics



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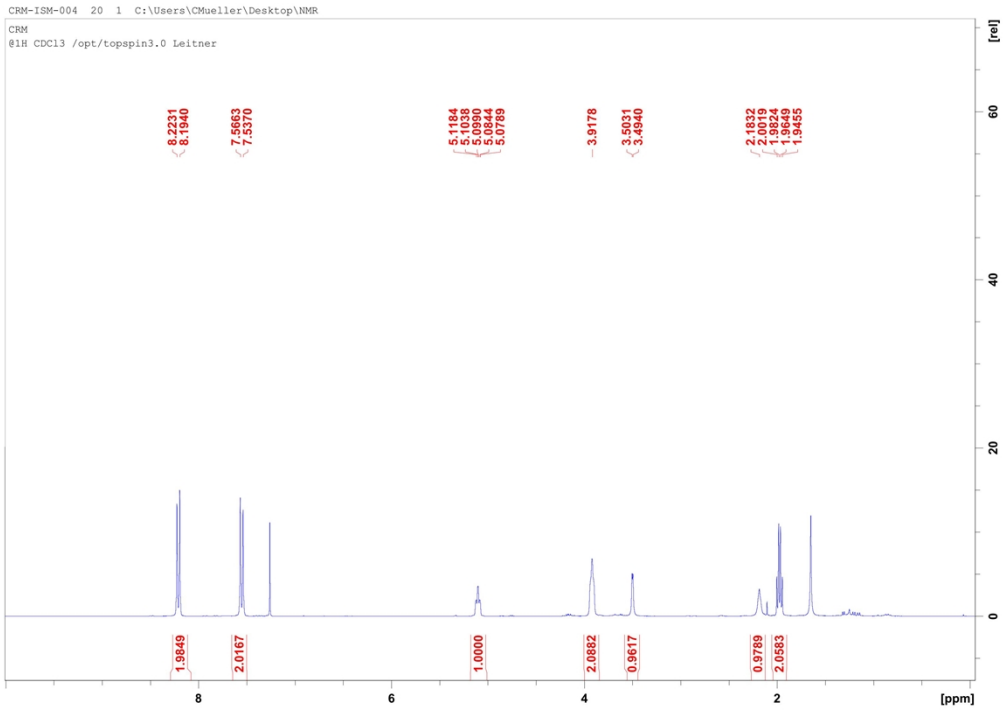

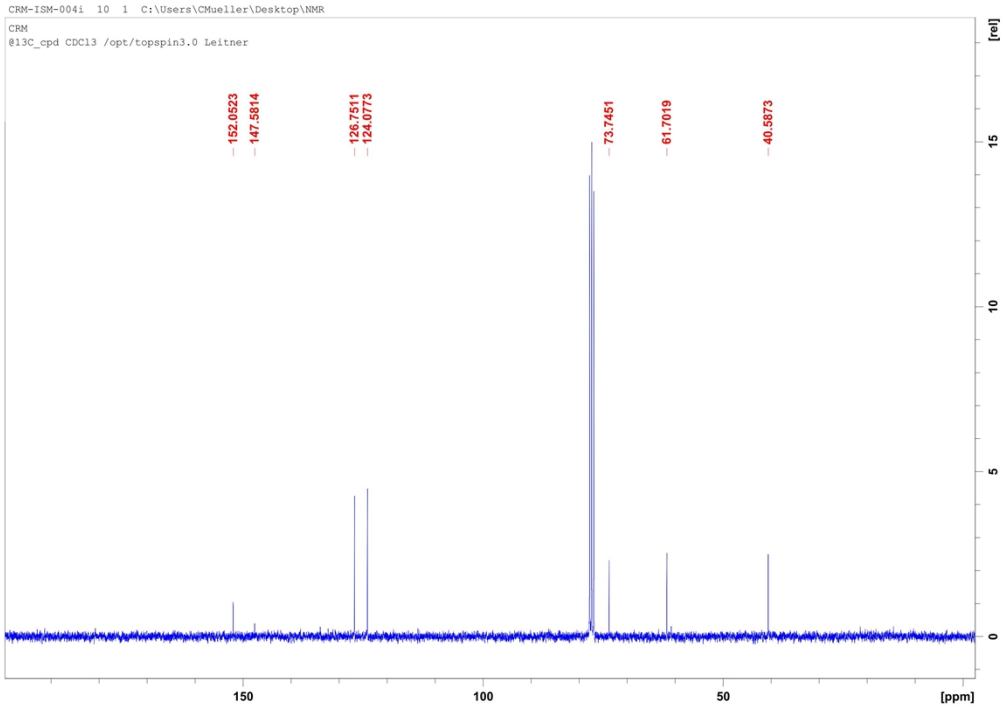

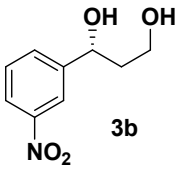
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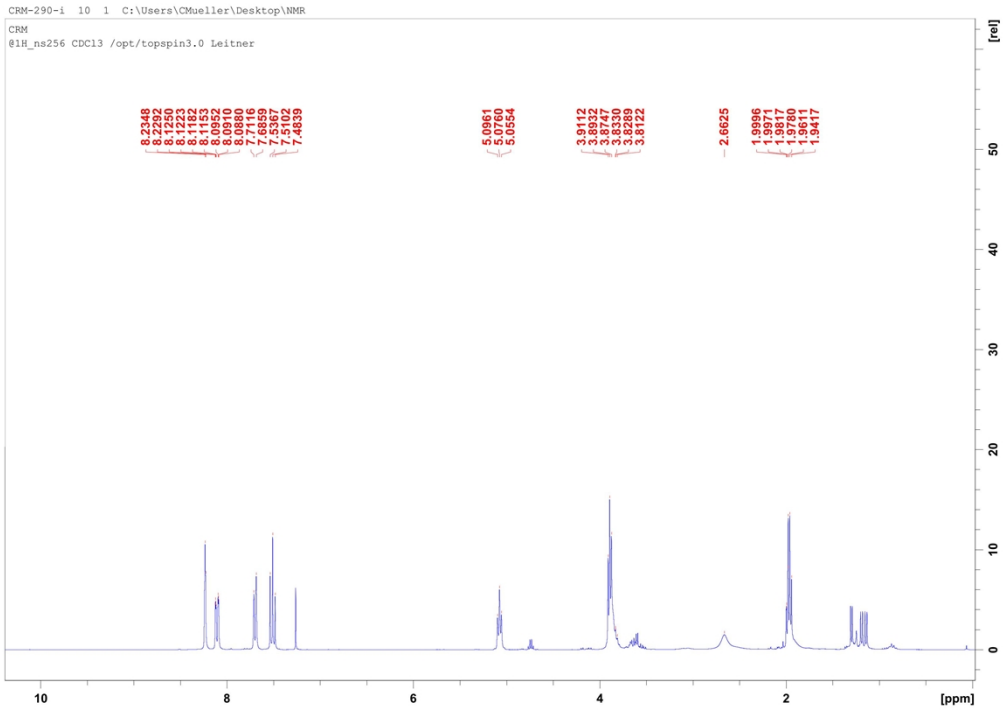
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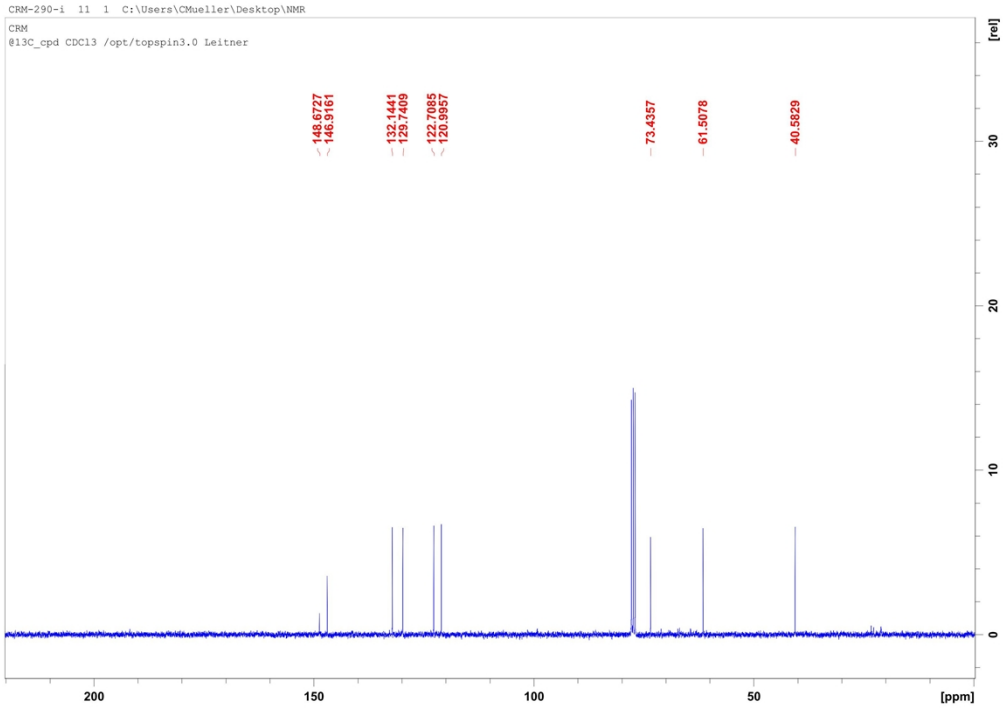
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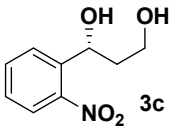
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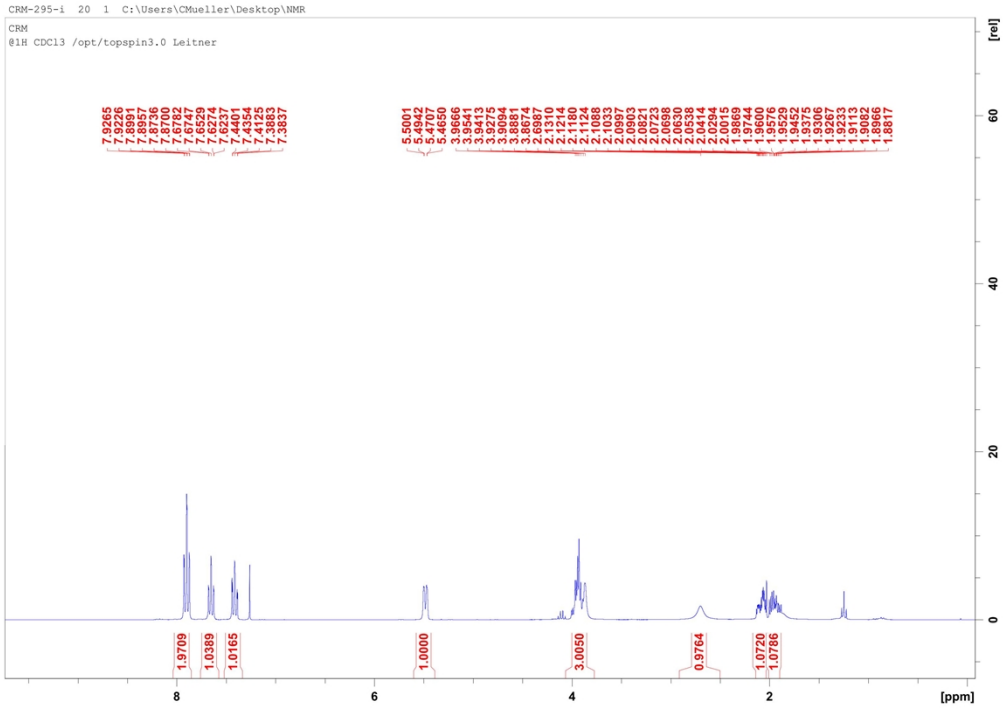
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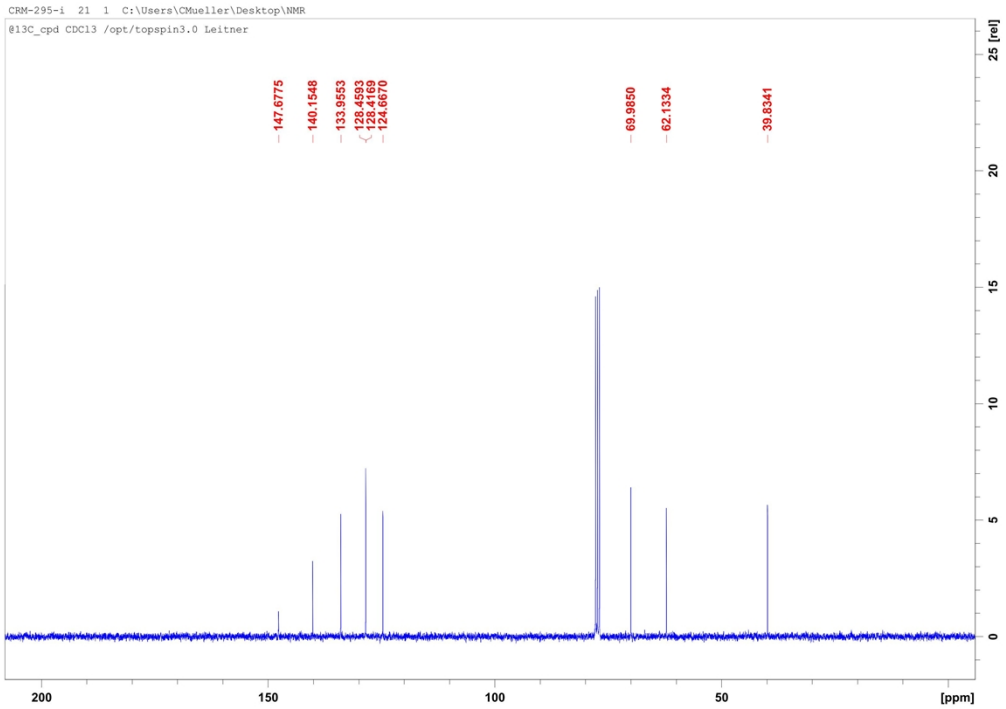
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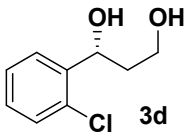
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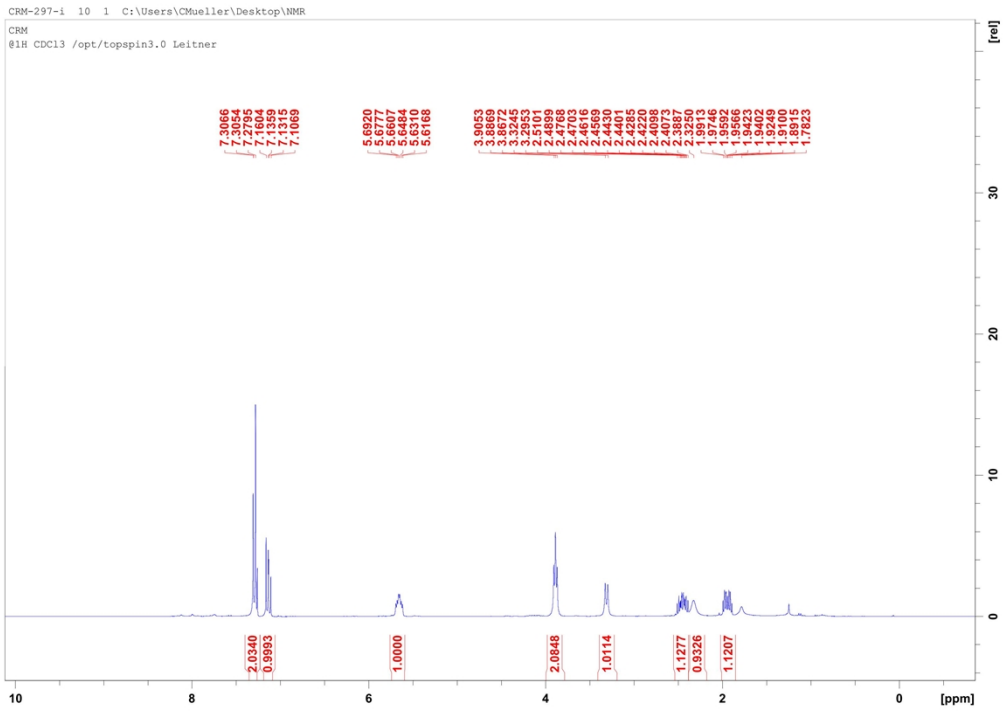
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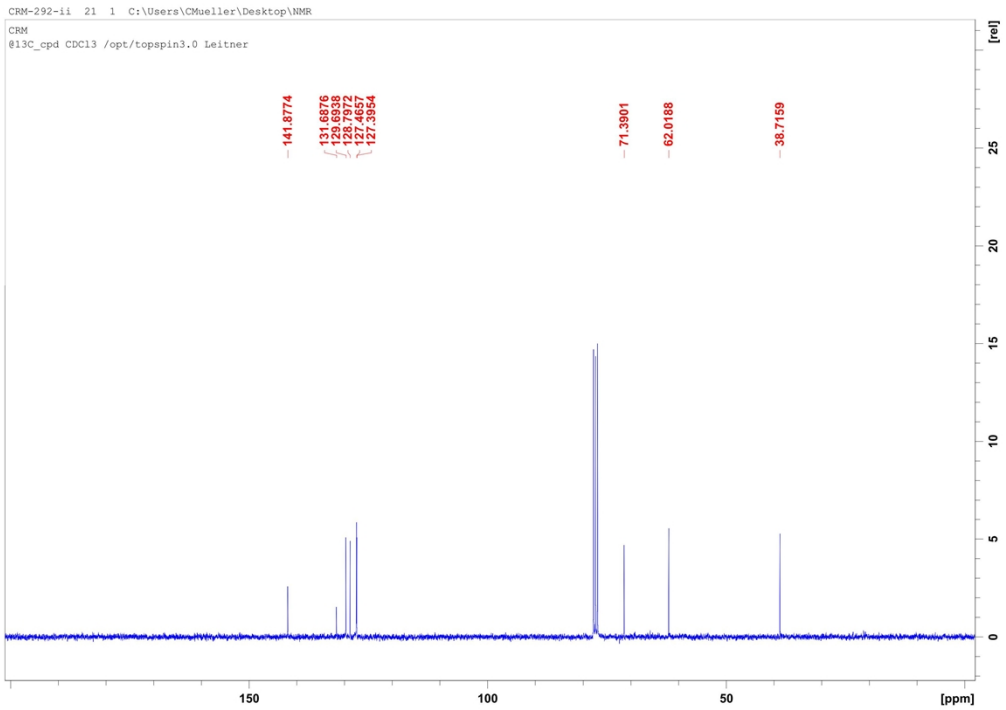
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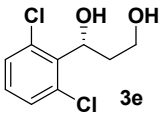
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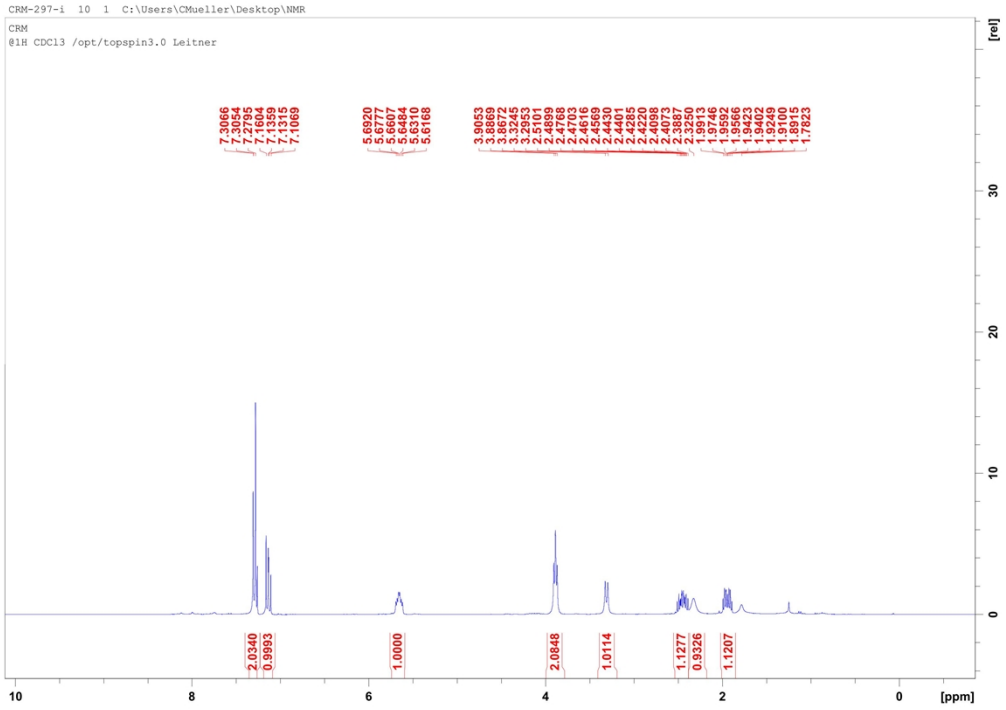
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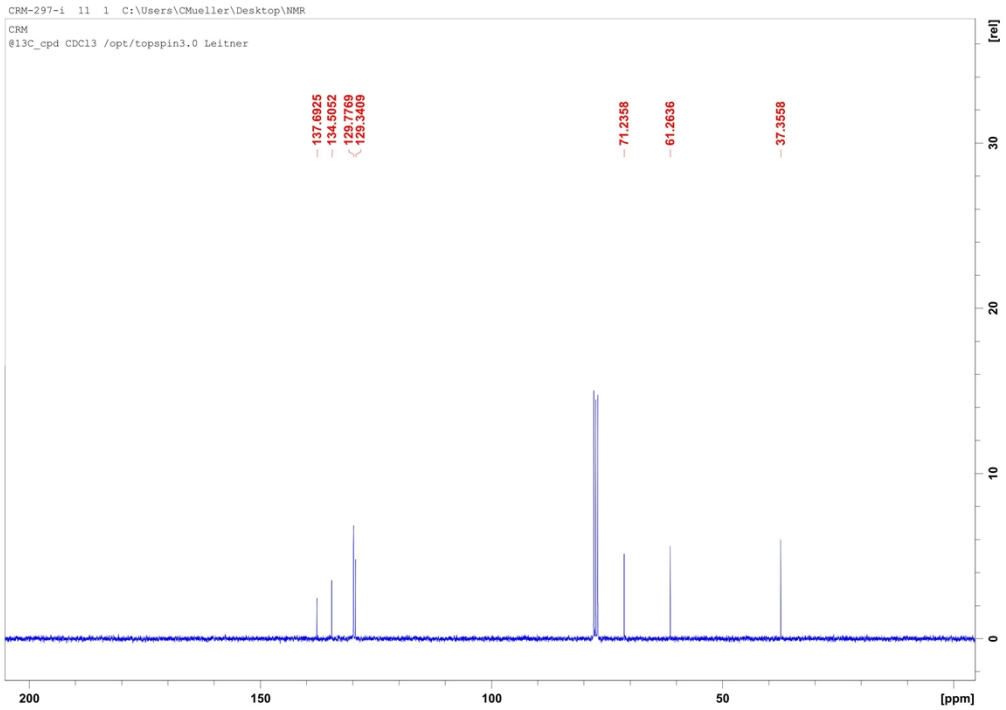
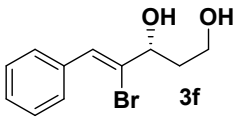
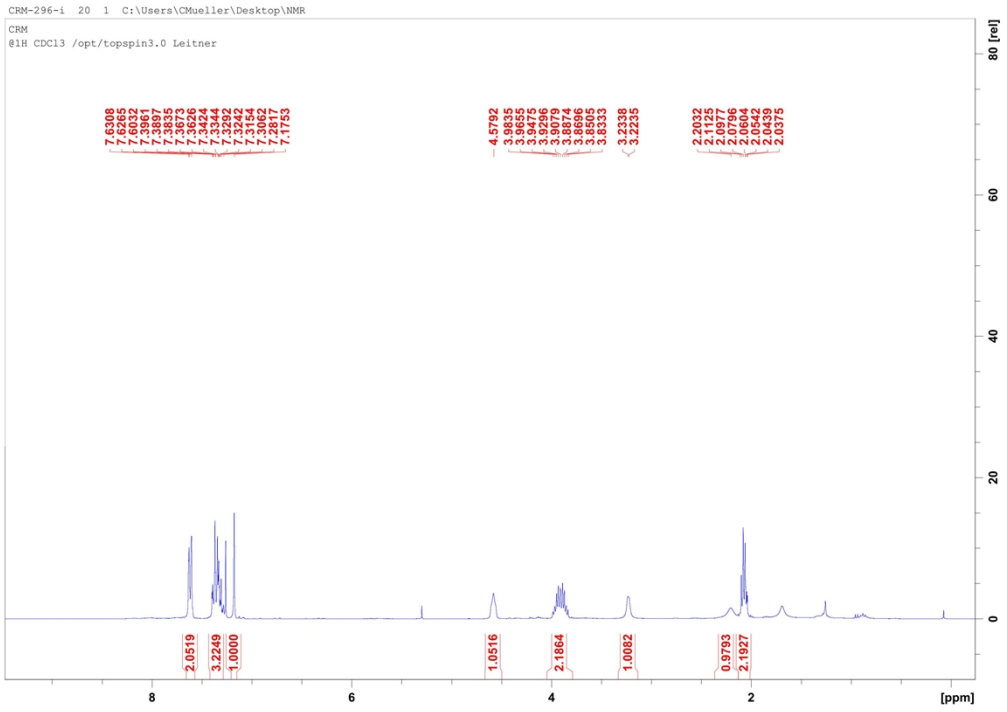
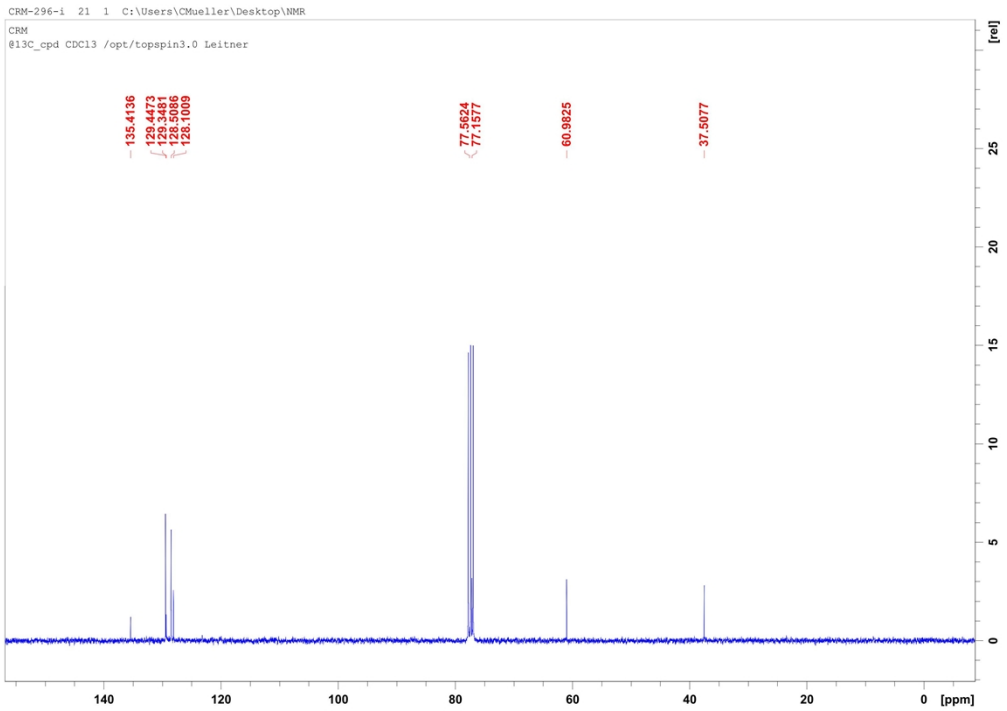
2.4098
2.4073
2.3887
2.3250
2.1913
1.9746
1.9592
1.9566
1.9423
1.9402
1.9249
1.9100
1.8915
1.7823
2.0340
0.9993
1.0000
2.0848
1.0114
1.1277
0.9326
1.1207
[rel]
[ppm]


CRM-297-i 11 1 C:\Users\CMueller\Desktop\NMR
CRM
@13C_cpd CDCl3 /opt/topspin3.0 Leitner
137.6925
134.5052
129.7769
129.3409
71.2358
61.2636
37.3558
[rel]
[ppm]







[1] Y. Hayashi, T. Itoh, S. Aratake, H. Ishikawa, *Angew. Chem. Int. Ed.* **2008**, *47* ,

2082-2084.