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Published in:
Nature Chemistry

DOI:
10.1038/NCHEM.819

Publication date:
2010

nature chemistry

SUPPLEMENTARY INFORMATION

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Catalytic enantioselective *syn* hydration of enones in water using a DNA based catalyst.

Arnold J. Boersma, David Coquière, Danny Geerdink, Fiora Rosati, Ben L. Feringa* and Gerard Roelfes*

Control experiments

A number of control experiments were performed to establish that the observed ee indeed is the result of an enantioselective hydration and not from an alternative process, such as for example an enantioselective retro-aldol/aldol sequence. A retro-aldol reaction of the β-hydroxy ketone would yield pivaldehyde and 2-acetyl imidazole, which could lead to R-enriched **2a** via a kinetic resolution. However, no trace of 2-acetyl-(1-methyl)imidazole was detected by reversed phase hplc during the reaction. Moreover, scrambling experiments by addition of benzaldehyde or valeraldehyde to the reaction did not give rise to any other products than **1a** and **2a**, Moreover, the conversion and enantioselectivity obtained were also the same as before. Finally, the labelling experiments using D_2O are inconsistent with such a pathway.

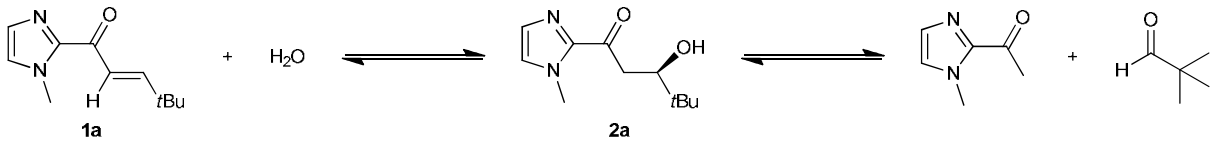

Table S1: Control experiments. Reaction time 24 h, 5 °C, 20 mM MES buffer pH 5.5, 15 µmol **1a** (1 mM), 1.3 mg/mL st-DNA (2 mM base pairs), 0.39 mM L1, 0.30 mM $Cu(NO_3)_2$.

Entry	**1**	**2**	L	Reaction time (h)	Conversion[a] (%)	ee[b] (%)
1	**1a**	**2a**	-	24	20	42 (*S*)
2[c]	**1a**	**2a**	L2	24	-	-
3[d]	**1a**	**2a**	L2	24	-	-
4[e]	**1a**	**2a**	L2	72	10	35 (*R*)
5[f]	**1a**	**2a**	L2	24	48	62 (*R*)

[a] determined by ^{1}H-NMR. [b] determined by HPLC. [c] in the absence of copper. [d] in the absence of copper and DNA. [e] 14 µg/mL st-DNA, 3.9 µM ligand, 3.0 µM $Cu(NO_3)_2$. [f] calf-thymus DNA used as DNA source.

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Table S2: Sequence dependence of the hydration of **1a** catalyzed by DNA/Cu-L2 in deuterium oxide.[a]

Entry	DNA Sequence	Conversion (%)[b]	Ee (%)[c]
1	d(CAAAAATTTTTG)$_2$	16	82
2	d(GCGCTATAGCGC)$_2$	14	82
3	d(TCG CTATAG CGA)$_2$	20	80
4	d(TCA GTATAC TGA)$_2$	19	80
5	Salmon testes DNA[d]	39[e]	79
6	d(CGT CTATAG ACG)$_2$	16	79
7	d(TCGAGTATACTCGA)$_2$	26	79
8	d(CGCGATATCGCG)$_2$	41	78
9	d(CGCGTATACGCG)$_2$	40	78
10	d(AGTACTATAGTACT)$_2$	23	78
11	d(CGCAAATTTGCG)$_2$	40	77
12	d(AGTAGTATACTACT)$_2$	22	77
13	d(ATATATATATAT)$_2$	41	76
14	d(TAAAAATTTTTA)$_2$	22	76
15	d(TCGACTATAGTCGA)$_2$	18	76
16	d(CGCGAATTCGCG)$_2$	29	73
17	d(CGCATATATGCG)$_2$	15	72
18	d(CCCAAATTTGGG)$_2$	12	68
19	d(TATATATATATA)$_2$	66	67
20	d(CGCGCGCGCGCG)$_2$	42	59
21	d(GAAAAATTTTTC)$_2$	16	59

[a] Reactions performed with 1 mM **1a**, 1.3 mg/mL DNA, 0.3 mM $Cu(NO_3)_2$, and 0.39 mM L2, in 20 mM MES pD 5.5, in 0.6 mL D_2O, for 1 d at 5 °C. [b] Conversions are determined by HPLC, and corrected for the differences in extinction coefficient. [c] Ee's are determined by chiral HPLC. [d] Reaction performed in 15 mL D_2O with same concentration of reactants for 3 days. [e] Conversion determined by ^{1}H-NMR.

Figure S3: HPLC analysis of enantioenriched **2a** (Chiralpak-AD, heptane:iPrOH 90:10, flow 1 mL/min).

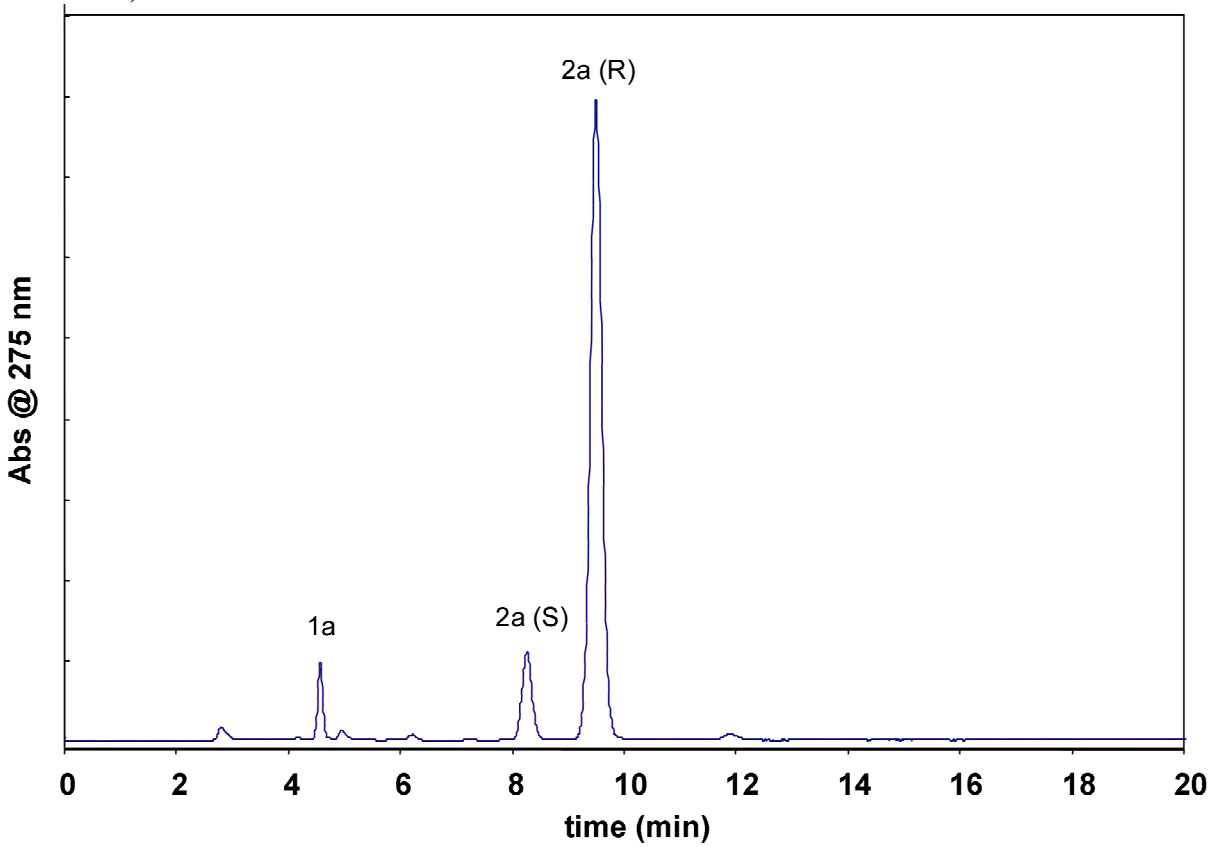

Figure S4: RP-HPLC trace of the reaction mixture of the DNA/CuL1 catalyzed hydration of **1a** (Chiralpak-AD-RH eluent water(A)/acetonitrile(B), 70% A: 0 to12 min, 40% A: 12 to 30 min, flow 0.5 mL/min). IS = Internal Standard (caffeine)

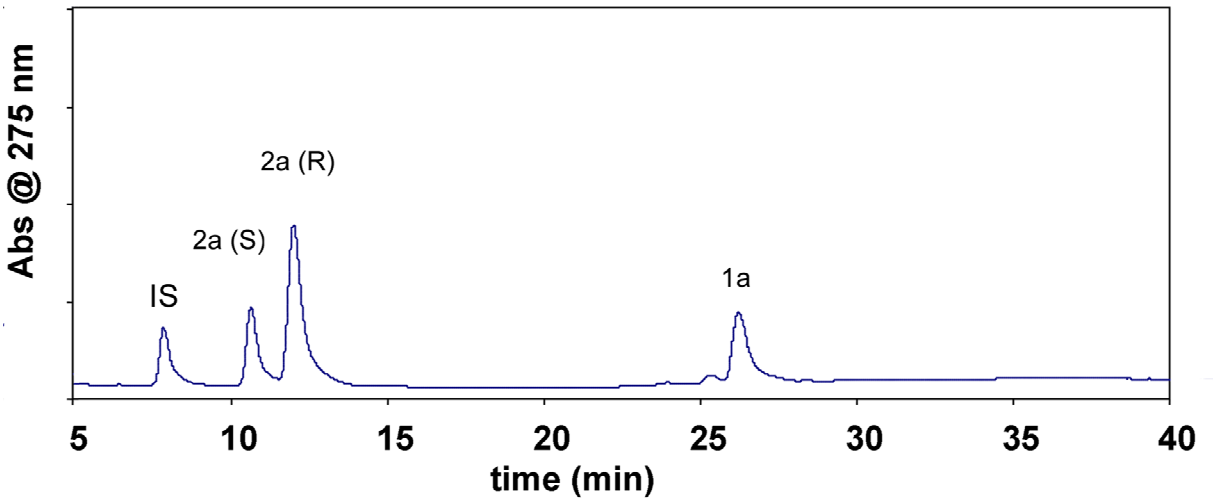

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Figure S5: Eantiomeric excess of the product of the asymmetric hydration of **1d** under standard conditions followed in time by RP-HPLC.

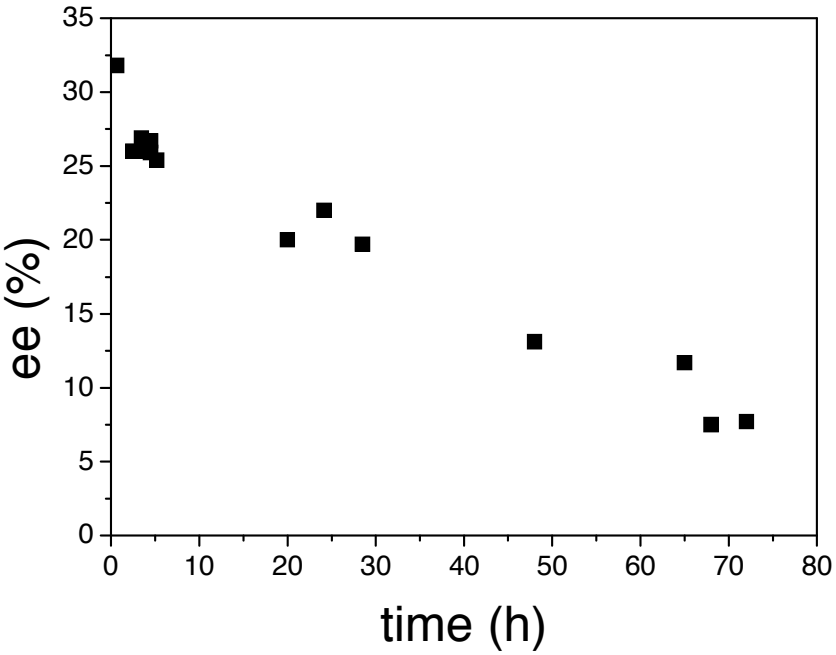

Figure S6: Enantiomeric excess of the product of the asymmetric hydration of **1d** under standard conditions followed in time by RP-HPLC.

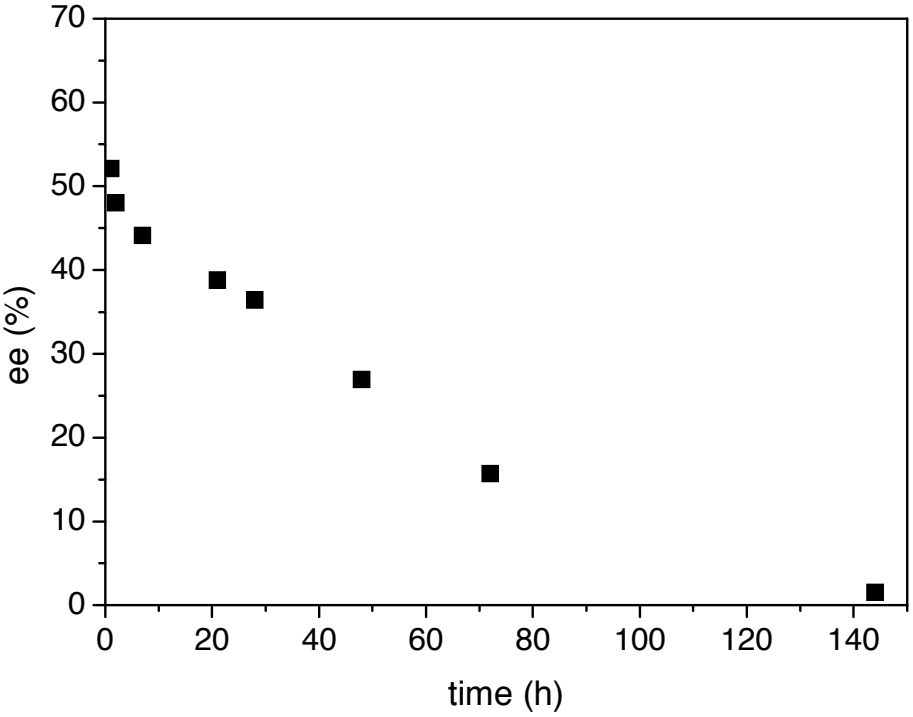

Figure S7: Ee of the product of the asymmetric hydration of **1e** under standard conditions followed in time by RP-HPLC.

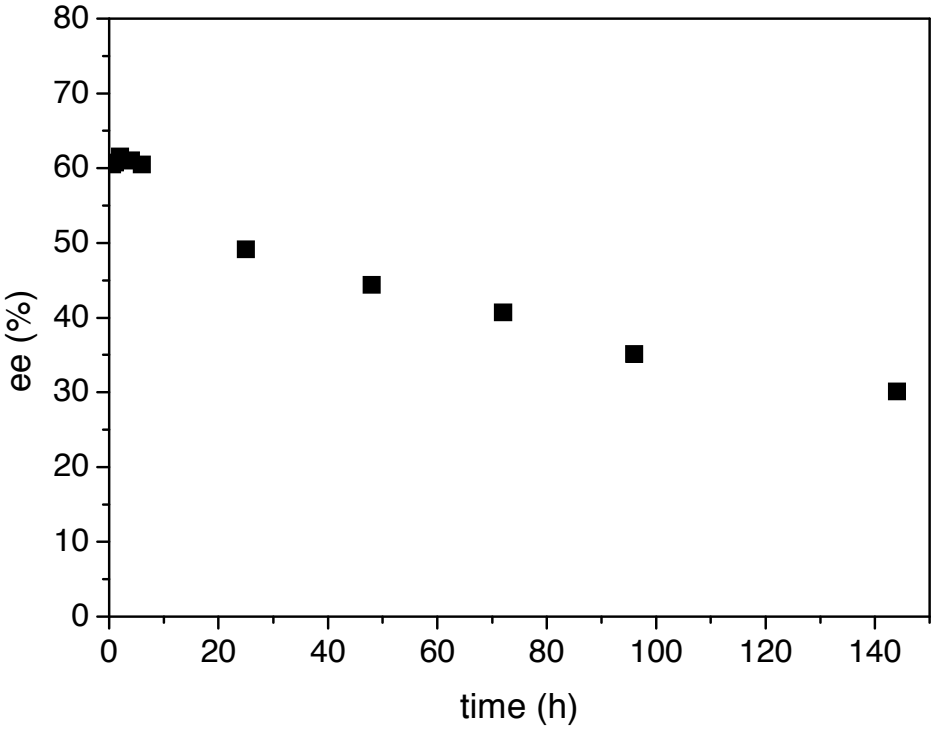

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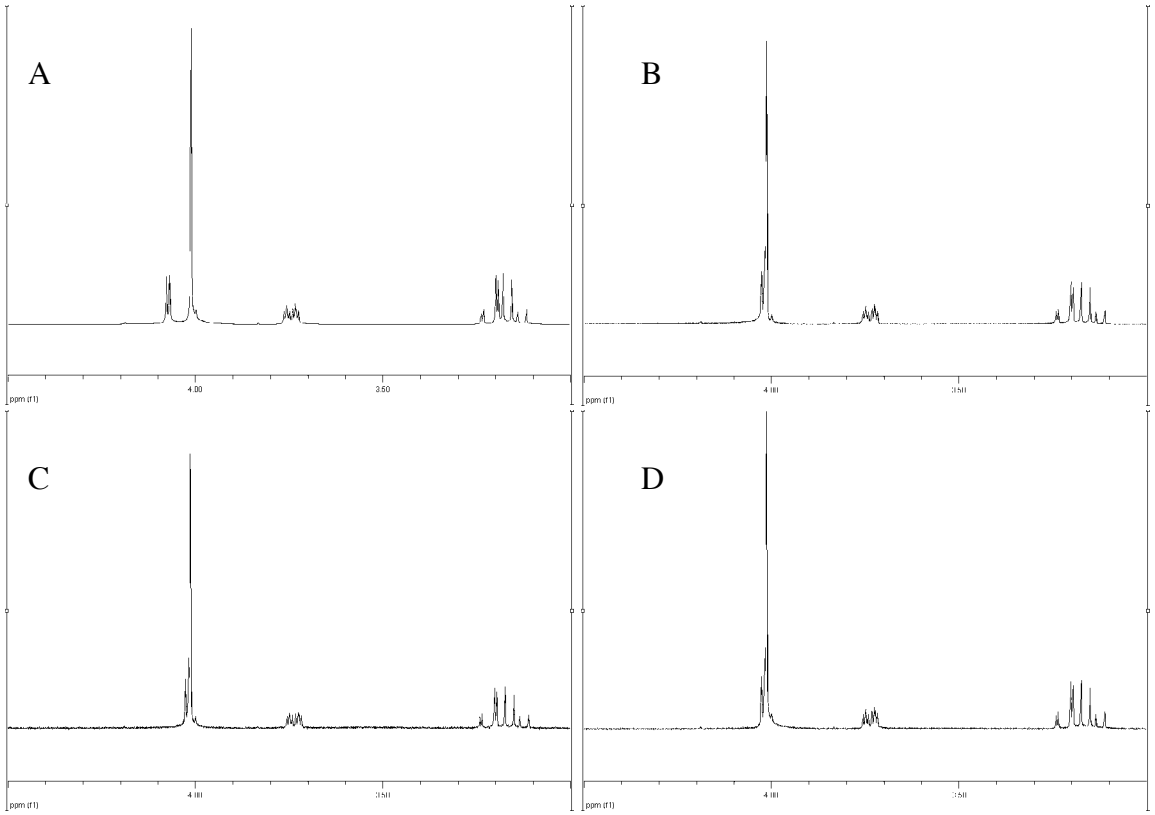
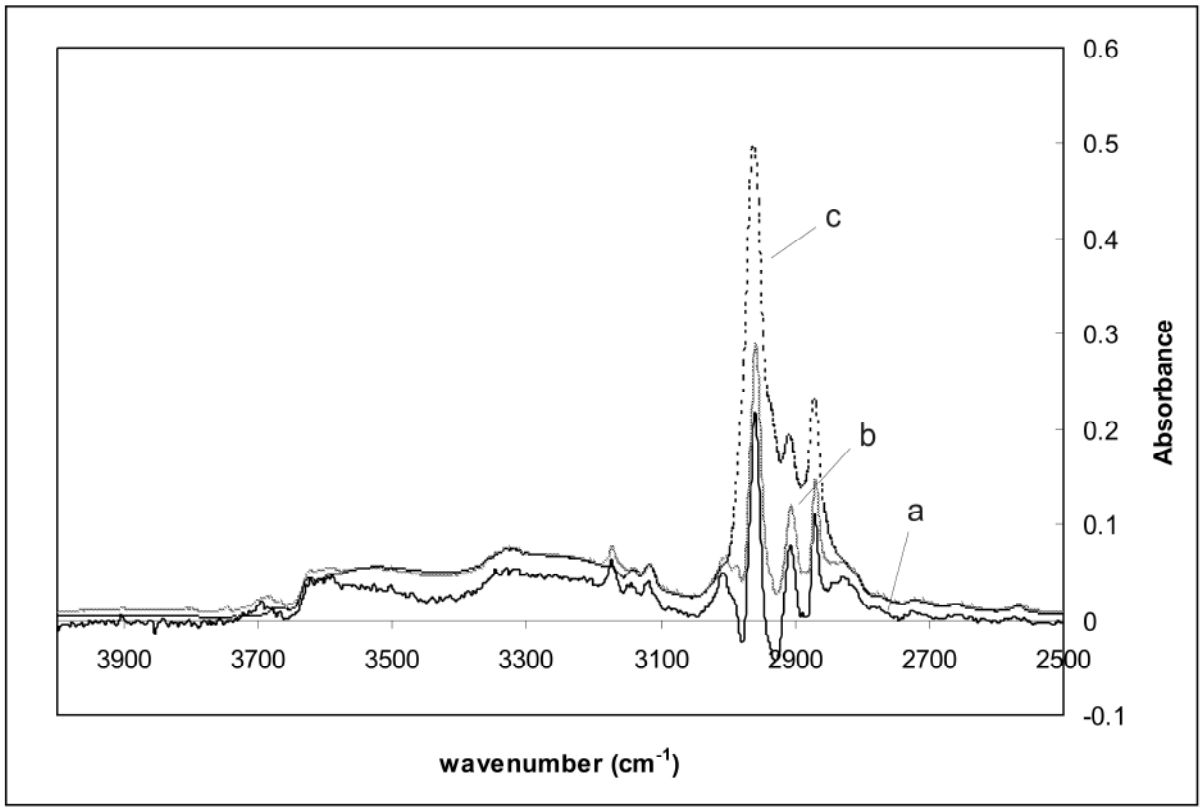
Figure S8: Dependence of the shift of the O-H proton of **2a** on the concentration in $CDCl_3$. A: 500 mM. B: 10 mM. C: 5 mM. D: 2 mM. No shift of the OH proton was observed in the range between 2-10 mM, which demonstrates that intermolecular hydrogen bonds are not formed at these concentrations. Only at very high concentrations of **2a** a small shift of the OH proton was observed.



Concentration **2a** in $CDCl_3$	δ (ppm) –O-H
500 mM	4.08
10 mM	4.02
5 mM	4.02
2 mM	4.02

Figure S9: Normalized IR spectra of **2a** in $CDCl_3$. a) 10 mM. b) 40 mM. c) 500 mM. Peaks in the region 2800 – 3050 cm^{-1} originate from the imidazole ring. Peaks at 3133, 3144, and 3151 cm^{-1} are artefacts due to solvent subtraction. The broad peaks at 3322 and 3523 cm^{-1} can be assigned to vibrations from hydrogen bonded O-H groups. Hence, a vibration due to a free O-H group is not observed. The peak at 3700 cm^{-1} originates from water.

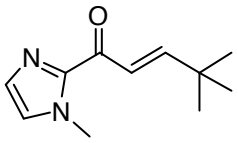


General Remarks

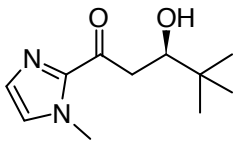
Salmon testes and calf thymus DNA were obtained from Sigma. Ligands L1 – L4,[1] complex Cu–L5,[2] α,β-unsaturated 2-acyl imidazoles **1b**, **1c**, and **1e**,[3] **1d**,[4] were prepared following published procedures. ^{1}H-NMR and ^{13}C-NMR spectra were recorded on a Varian 400 (400 and 100 MHz), Varian 300 (300 and 75 MHz) or Varian 200 (200 and 50 MHz) in $CDCl_3$. Chemical shifts (δ) are denoted in ppm using residual solvent peaks as internal standard (δ_C = 77.0 and δ_H = 7.26 for $CDCl_3$). Mass spectra (HRMS) were recorded on an AEI MS-902. Optical rotations were measured on a Schmidt and Haensch Polartronic MH8. FT-IR spectra were measured on a PerkinElmer Spectrum 400 equipped with a PerkinElmer liquid sipper sampling accessory, and a 0.1 mm path length cell. Enantiomeric excess determinations were performed by HPLC analysis using UV-detection. Reactions were followed in time by HPLC and RP-HPLC analysis using caffeine as an internal standard and UV-detection. Flash chromatography was performed using silica gel 60 Å (Merck, 200-400 mesh).

[1] G. Roelfes, B. L. Feringa, *Angew. Chem. Int. Ed.* **2005**, *44*, 3230-3232
[2] G. Roelfes, A. J. Boersma, B. Feringa, *Chem. Commun.* **2006**, 635-637.
[3] D. A. Evans, K. R. Fandrick, H.-J. Song, *J. Am. Chem. Soc.* **2005**, *127*, 8942-8943.
[4] A. J. Boersma, B. L. Feringa, G. Roelfes, *Angew. Chem. Int. Ed.*. **2009**, *48*, 3346-3348.

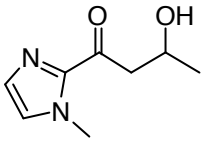
DOI: 10.1038/NCHEM.819



(E)-4,4-dimethyl-1-(1-methyl-1H-imidazol-2-yl)-2-penten-1-one (1a)
To a 100 ml round bottomed flask filled with 20 ml THF was added 1.44 g 1-(1-methyl-1*H*-imidazol-2-yl)-1-ethanone[5] (11.6 mmol), 2 pellets of KOH (dissolved in minimal amount of EtOH), and 1.00 g of pivaldehyde (11.6 mmol). After stirring for two days the solvent was evaporated. The crude product was dissolved in ethyl acetate (50 mL), washed with brine (30 mL), and dried over Na_2SO_4. Concentration in vacuo, and purification by column chromatography (SiO_2, EtOAc:pentane 1:4), yielded **1a** (604 mg, 27%) as a colorless oil. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ = 1.15 (s, 9H), 4.05 (s, 3H), 7.04 (s, 1H), 7.12 (d, 1H, J = 15.8 Hz), 7.18 (s, 1H), 7.33 (d, 1H, J = 15.8 Hz). ^{13}C-NMR ($CDCl_3$, 75 MHz) δ = 29.0, 34.3, 36.5, 121.5, 127.3, 129.4, 144.1, 158.6, 181.5. HRMS calcd for MH^+ $C_{11}H_{17}N_2O$ 193.1335, found 193.1332.

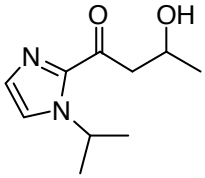


(*R*) - 3-hydroxy-4,4-dimethyl-1-(1-methyl-1H-imidazol-2-yl)pentan-1-one (2a)
Purified by column chromatography (SiO_2, EtOAc:heptane 1:4) to give a colourless oil that slowly solidfies in the fridge. $[\alpha]_D^{25}$ = +37.3 ° (c = 15.8 mg/mL in $CHCl_3$). ^{1}H-NMR ($CDCl_3$, 400 MHz) δ = 0.98 (s, 9H), 3,14 (dd, 1H, J = 9.4, J = 15.7 Hz), 3.22 (dd, 1H, J = 2.3 Hz, J = 15.7 Hz), 3.73 (dt, 1H, J = 2.3 Hz, J = 9.4 Hz), 4.01 (s, 3H), 4.02 (d, 1H, J = 3.2 Hz), 7.04 (s, 1H), 7.15 (s, 1H). ^{13}C-NMR ($CDCl_3$, 100 MHz): δ = 25.9, 35.1, 36.5, 42.9, 75.9, 127.4, 129.4, 143.5, 193.5. Exact mass (HRMS) calcd for MH^+ $C_{11}H_{19}N_2O_2$ 221.1441, found 221.1441. The ee was determined by HPLC analysis (Chiralpak-AD, n-heptane:iPrOH 90:10, 1 ml/min). Retention times: 8.2 (*S*-**2a**) and 9.3 min (*R*-**2a**).

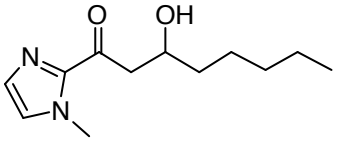


3-hydroxy-1-(1-methyl-1H-imidazol-2-yl)butan-1-one (2b)
Pure product was obtained as a colourless oil and the compound was analyzed without further purification since **2b** appeared to be unstable during column chromatography. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ = 1.28 (d, 3H, J = 6.4 Hz), 3.13 (dd, 1H, J = 8.9 Hz, J = 16.2 Hz), 3.30 (dd, 1H, J = 2.4 Hz, J = 16.2 Hz), 4.01 (s, 3H), 4.14 (s, 1H), 4.30 (m, 1H, J = 6.4 Hz), 7.05 (s, 1H), 7.15 (s, 1H). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ = 192.7, 143.2, 129.4, 127.4, 64.6, 48.8, 36.5, 23.3. NMR in accordance with literature.[6] The ee was determined by HPLC analysis (Chiralpak-AS, n-heptane/iPrOH 97:3, 1 ml/min). Retention times: 31.4 and 36.7 min.

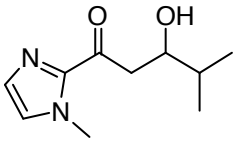
[5] Myers, M. C.; Bharadwaj, A. R.; Milgram, B. C.; Scheidt, K. A. *J. Am. Chem. Soc.*, **2005**, *127*, 14675.
[6] Davies, D. H.; Hall, J.; Smith, E. H. *J. Chem. Soc. Perkin Trans. 1*, **1991**, 2691.



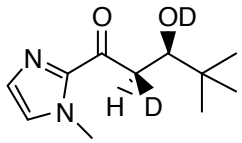
3-hydroxy-1-(1-isopropyl-1H-imidazol-2-yl)-1-butanone (2c)
Purified by column chromatography (SiO_2, EtOAc:heptane 1:4) to give a colorless oil. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ = 1.28 (d, 3H, J = 6.6 Hz), 1.45 (d, 6H, J = 6.6 Hz), 3.15 (dd, 1H, J = 7.9 Hz, J = 15.2 Hz), 3.30 (dd, 1H, J = 2.4, J = 16.2 Hz), 4.24 (s, 1H), 4.29 (m, 1H), 5.53 (m, 1H), 7.17 (s, 1H), 7.28 (s, 1H). ^{13}C-NMR ($CDCl_3$, 100 MHz): δ = 23.0, 23.6, 49.1, 49.3, 64.5, 121.4, 129.6, 142.3, 192.6. HRMS calcd for MH^+ $C_{10}H_{17}N_2O_2$ 197.1285, found 197.1285. The ee was determined by HPLC analysis (Chiralpak-AD, n-heptane/iPrOH 95:5, 1 ml/min). Retention times: 16.6 and 19.5 min.



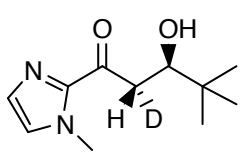
3-hydroxy-1-(1-methyl-1H-imidazol-2-yl)octan-1-one (2d)
Purified by column chromatography (SiO_2, EtOAc:heptane 1:4) to give a colourless oil. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ = 0.88 (t, 3H, J = 6.2 Hz), 1.30-1.64 (m, 8H), 3,14 (dd, 1H, J = 8.8 Hz, J = 16.1 Hz), 3.27 (dd, 1H, J = 2.44 Hz, J = 16.1 Hz), 4.01 (s, 3H), 4.08 (s, 1H), 4.15 (s, 1H), 7.04 (s, 1H), 7.15 (s, 1H). ^{13}C-NMR ($CDCl_3$, 100 MHz): δ = 192.8, 159.3, 129.3, 127.4, 68.6, 47.4, 37.7,36.0, 32.0, 25.4, 22.8, 14.2.HRMS calcd for MH^+ $C_{12}H_{21}N_2O_2$: 225.1597, found 225.1596. The ee was determined by HPLC analysis (Chiracel-OBH, n-heptane/iPrOH 99:1, 0.5 ml/min). Retention times: 55.9 and 58.7 min.



3-hydroxy-4-methyl-1-(1-methyl-1H-imidazol-2-yl)pentan-1-one (2e)
Purified by column chromatography (SiO_2, EtOAc:heptane 1:4) to give a colourless oil. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ = 0.99 (dd, 6H, J = 3.6 Hz, J = 6.8 Hz), 1.78 (m, 1H), 3.17 (d, 1H, J = 3.1 Hz), 3.19 (s, 1H), 3.85 (m, 1H), 4.01 (s, 3H), 4.15 (s, 1H), 7.04 (s, 1H), 7.14 (s, 1H). ^{13}C-NMR ($CDCl_3$, 100 MHz): δ = 193.2, 143.4, 129.4, 127.5, 73.1, 44.7, 36.5, 33.9, 18.6, 17.9. HRMS calcd for MH^+ $C_{10}H_{17}N_2O_2$ 197.1285, found 197.1285. The ee was determined by HPLC analysis (Chiralpak-AD, n-heptane/iPrOH 95:5, 1 ml/min). Retention times: 18.3 and 21.7 min.

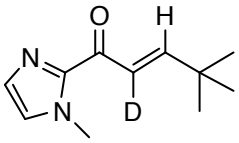


***R*,*R*-2-deutero-3-hydroxy-4,4-dimethyl-1-(1-methyl-1H-imidazol-2-yl)pentan-1-one (3a)**
Prepared following general catalysis procedure in D_2O as solvent, with a reaction time of 7 d. Purified by column chromatography (SiO_2, heptane:EtOAc 4:1). ^{1}H-NMR ($CDCl_3$, 400 MHz) δ = 0.98 (s, 9H), 3,18 (d, 1H, J = 2.0 Hz), 3.73 (s, 1H), 4.01 (s, 3H), 7.05 (s, 1H), 7.15 (s, 1H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ = 193.5, 143.5, 129.4, 127.4, 75.9, 42.8 (t, J = 19.6 Hz), 36.5, 35.1, 25.9. HRMS (dissolved in MeOH) calcd for MH^+ $C_{11}H_{18}DN_2O_2$: 212.1504. Found: 212.1504.



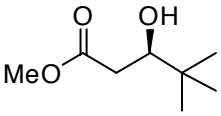
***S*,*R*-2-deutero-3-hydroxy-4,4-dimethyl-1-(1-methyl-1H-imidazol-2-yl)pentan-1-one (3b)**
Purified by column chromatography (SiO_2 heptane:EtOAc 4:1). ^{1}H-NMR ($CDCl_3$, 400 MHz) δ = 0.98 (s, 9H), 3.11 (dt, 1H, J = 10.0, J = 2.0 Hz), 3.72 (d, 1H, J = 10.0 Hz), 4.01 Hz (s, 3H), 4.07 (s, 1H), 7.04 (s, 1H), 7.15 (s, 1H). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ = 193.3, 143.3, 129.1, 127.1, 75.7, 42.4 (t, J = 19.5 Hz), 36.2, 34.9, 25.6.

DOI: 10.1038/NCHEM.819



(E)-4,4-dimethyl-1-(1-methyl-1H-imidazol-2-yl)-2-deutero-2-penten-1-one (4)

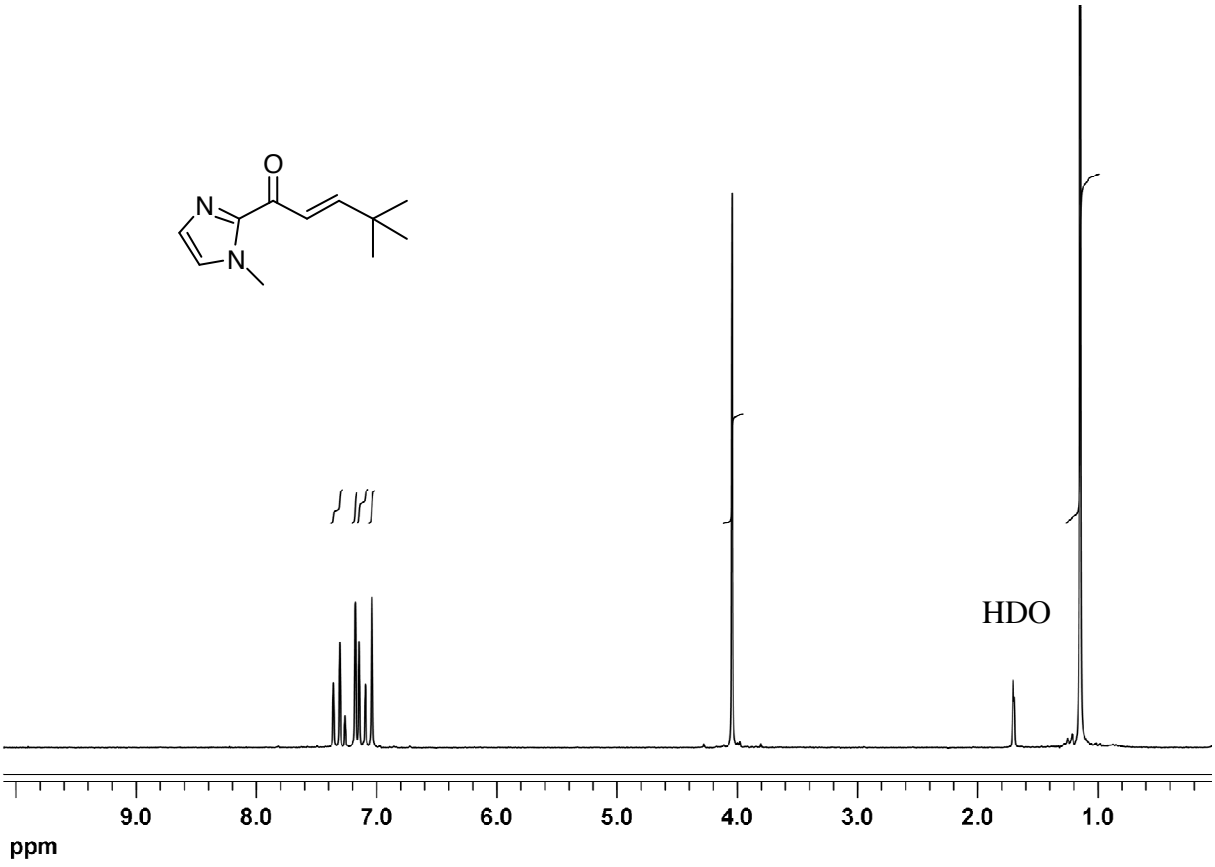
A 100 mL round bottomed flask was loaded with 20 mL CH_2CH_3OD, and 100 mg KOH. 2-Acetyl N-methyl imidazole[6] (1.24 g) was added, and the reaction was stirred overnight at room temperature. Pivaldehyde (0.86 g) was added and the mixture was left stirring for 24 h. The layers were separated after addition of 30 mL brine, 10 mL H_2O, and 3 x 30 mL EtOAc. After drying over Na_2SO_4, and concentration in vacuo, the residue was purified by column chromatography (SiO_2, EtOAc:pentane 1:4), yielded **4** (350 mg, 18 %). From ^{1}H-NMR it was determined that a ratio of 85:15 of **4**:**1a** was obtained. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ = 1.16 (s, 9H), 4.05 (s, 3H), 7.08 (s, 1H), 7.13 (m, 1H), 7.18 (s, 1H). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ = 180.8, 157.9, 143.5, 128.8, 126.8, 121.0, 36.0, 33.8, 28.5. HRMS calcd for MH^+ $C_{11}H_{16}DN_2O$ 194.1398, found 194.1397.

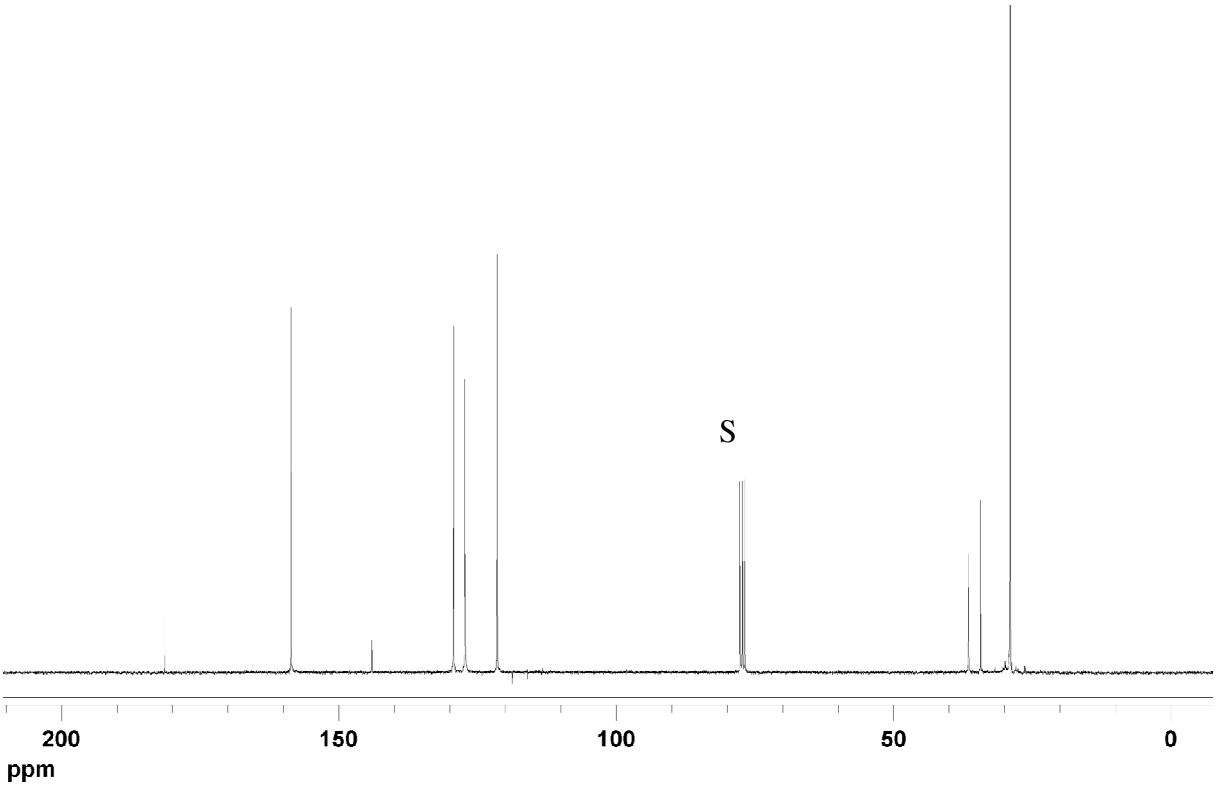


(*R*)-Methyl 3-hydroxy-4,4-dimethylpentanoate (5)

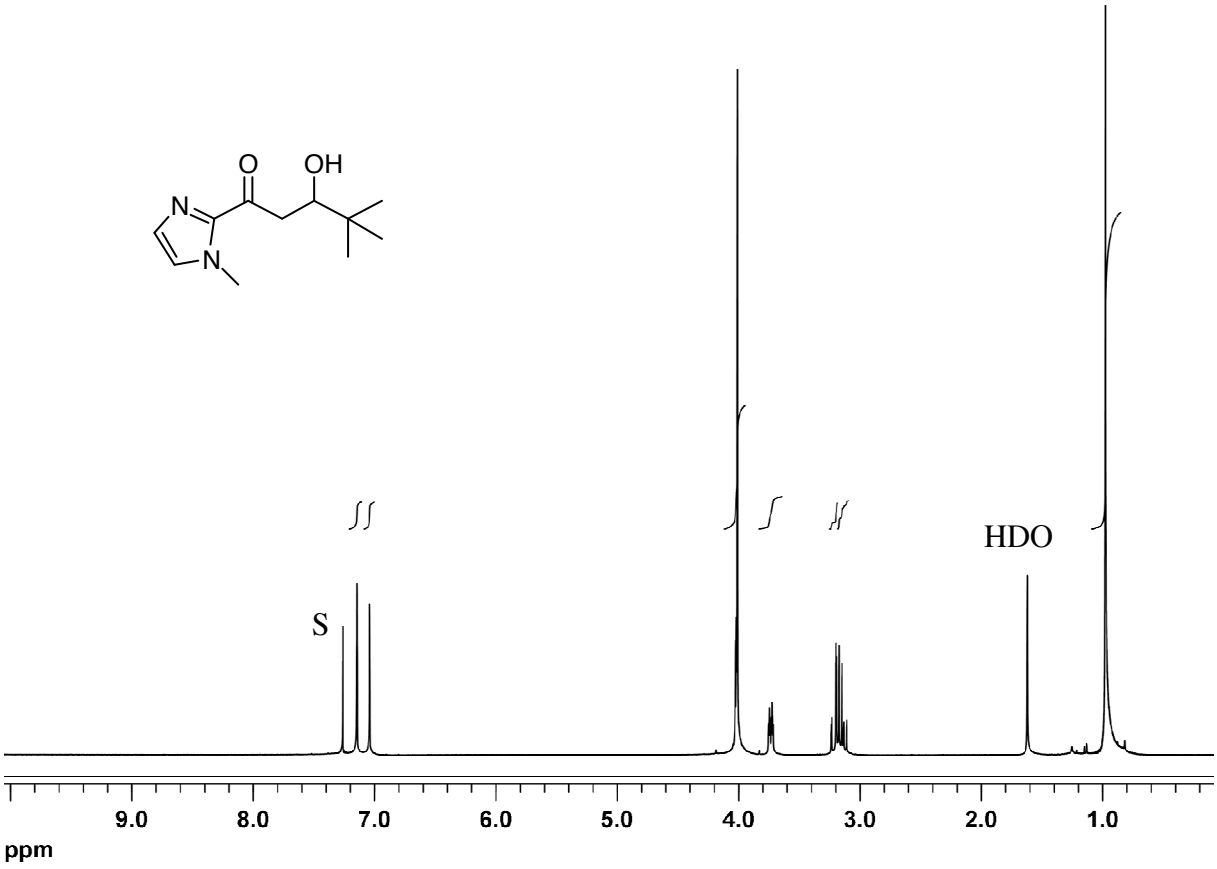
A 25 mL round bottomed flask under N_2 atmosphere was loaded with 1 mL dry dichoromethane, 30.3 mg **2a** (0.144 mmol), and 17.4 µL methyl triflate (0.158 mmol, 1.1 eq). After stirring for 3h at r.t. 0.5 mL MeOH and 0.2 mL DBU were added, and the mixture was left stirring for another 0.5h. The reaction mixture was subjected to column chromatography (SiO_2, pentane:Et_2O 1:1), yielding 8.5 mg (37%) **5** as a colourless oil. $[\alpha]_D^{25}$ = 19.2 ° (c = 4.25 mg/mL in EtOH). ^{1}H-NMR ($CDCl_3$, 400 MHz) δ = 0.92 (s, 9H), 2.36 (dd, 1H, J = 10.6 Hz, J = 16.1 Hz), 2.54 (dd, 1H, J = 2.1, J = 16.1 Hz), 2.79 (d, 1H, J = 3.7 Hz), 3.72 (s, 3H). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ = 174.5, 75.7, 52.1, 36.6, 34.6, 25.8. NMR in accordance with literature.[7]

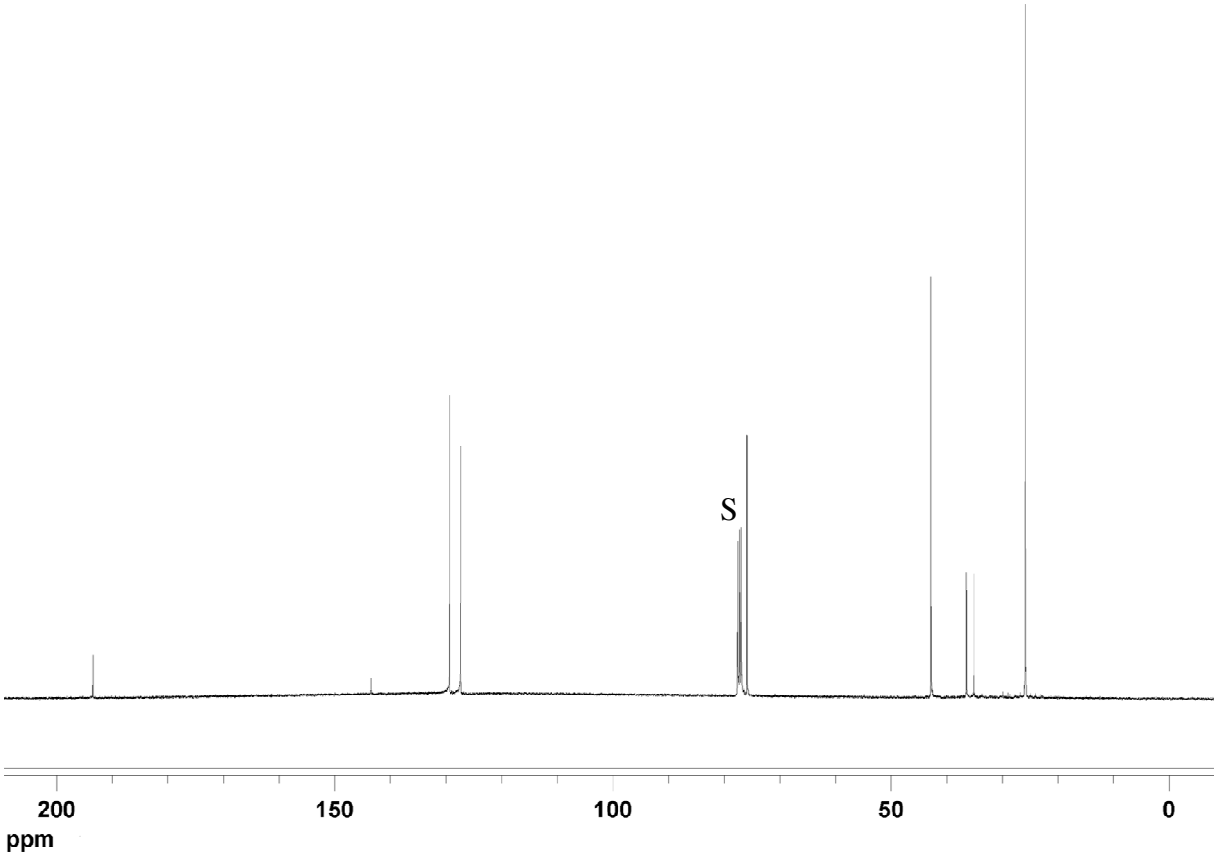
[7] Denmark, S. E.; Winter, S. B. D.; Su, X.; Wong, K.-T. *J. Am. Chem. Soc.*, **1996**, *118*, 7404.

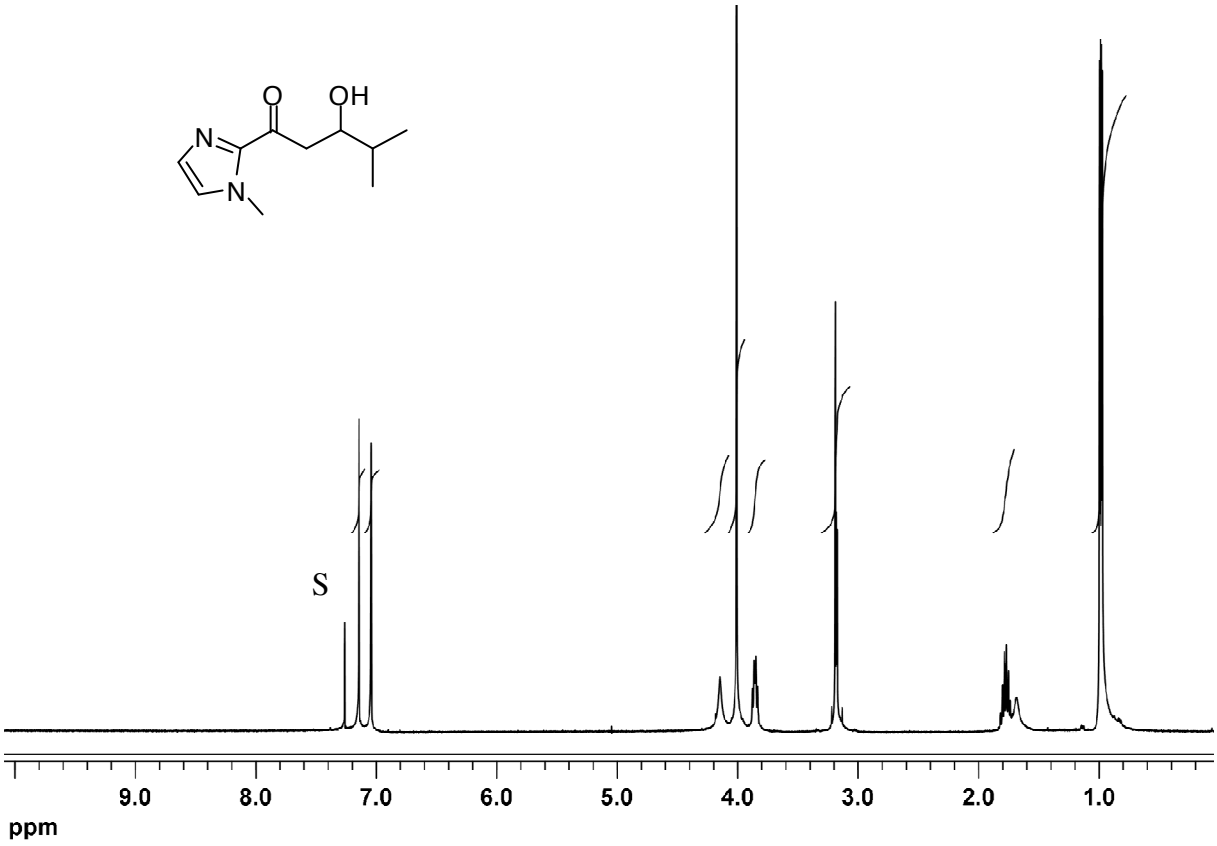


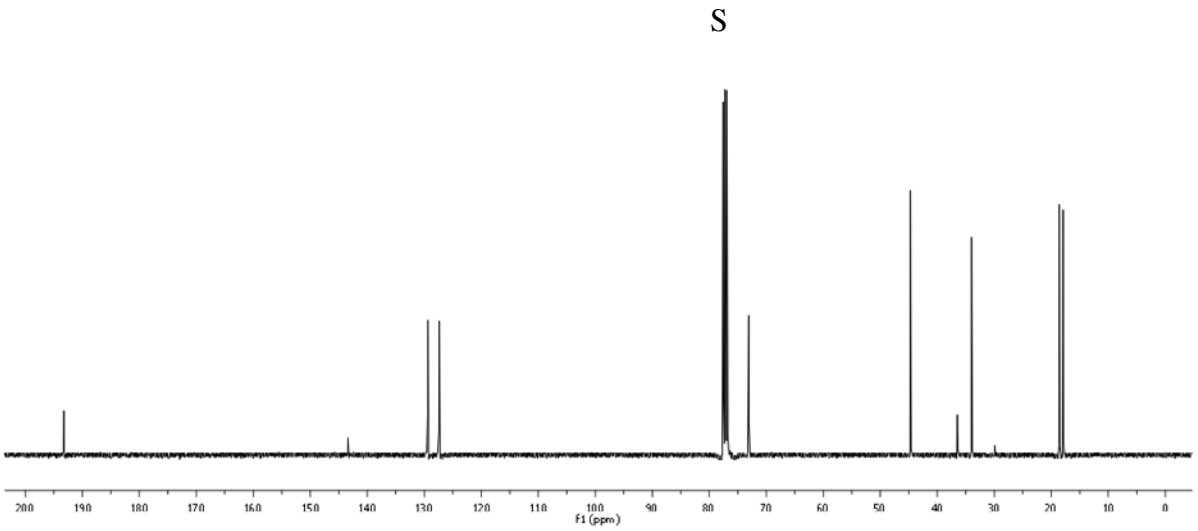


DOI: 10.1038/NCHEM.819









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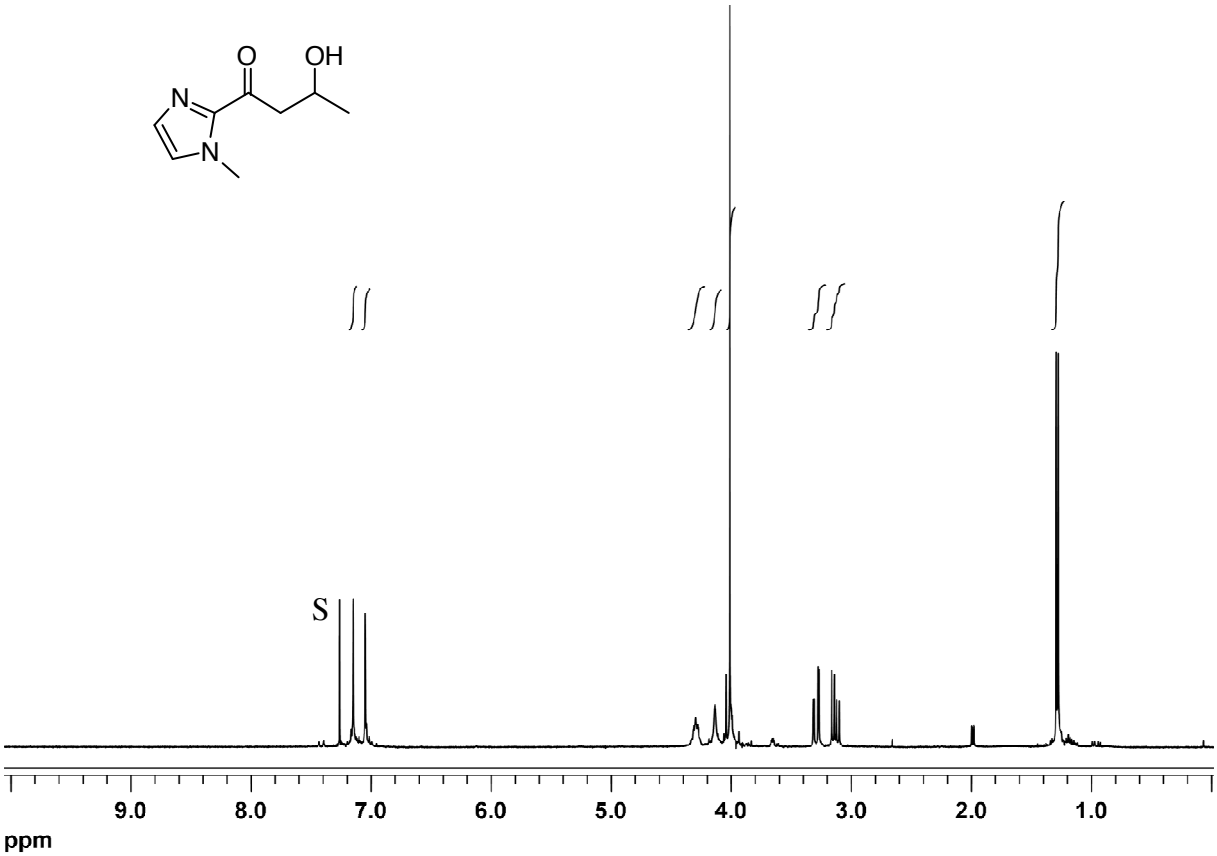

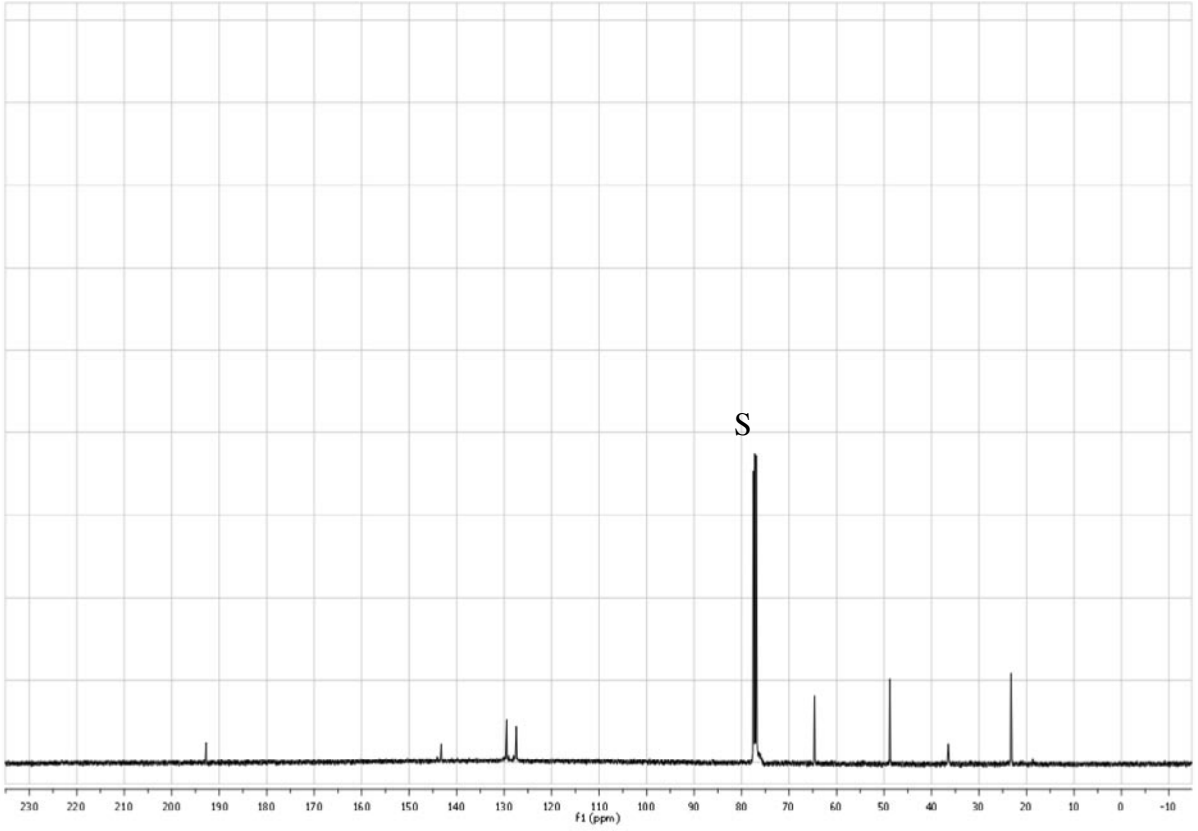

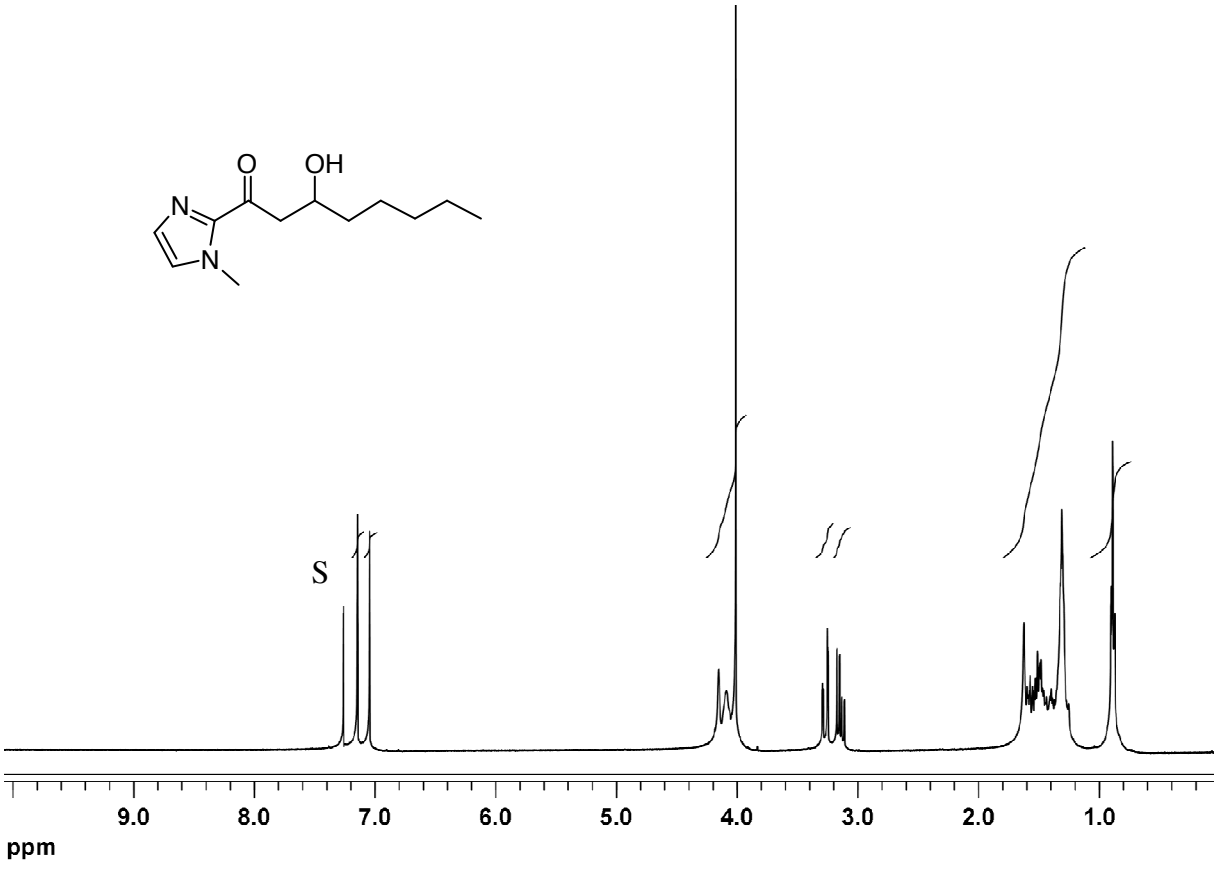

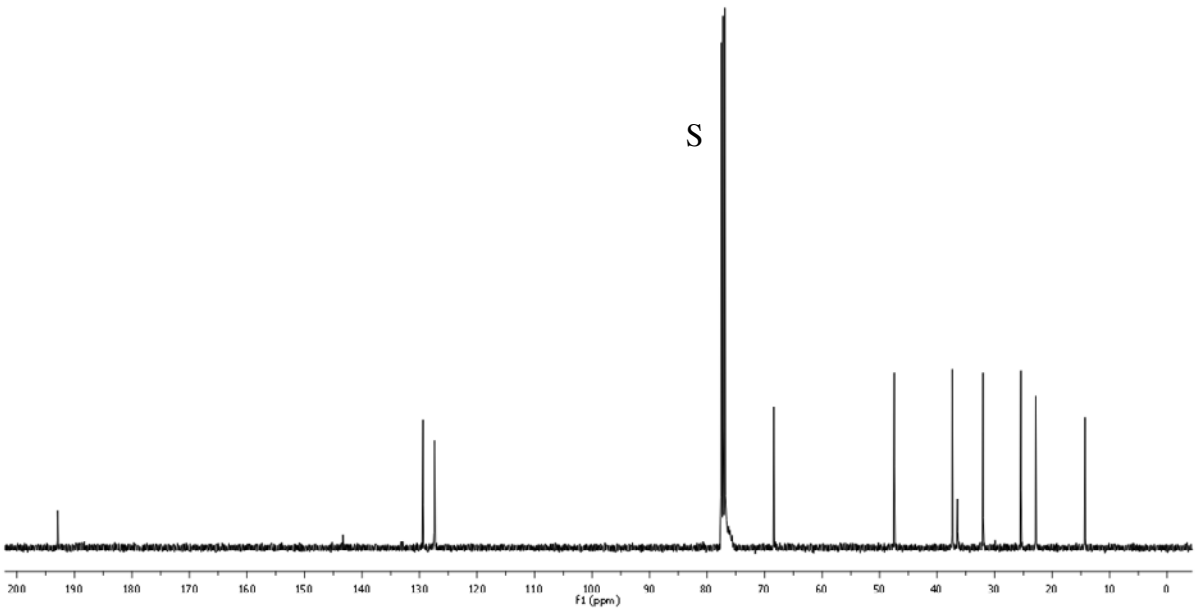

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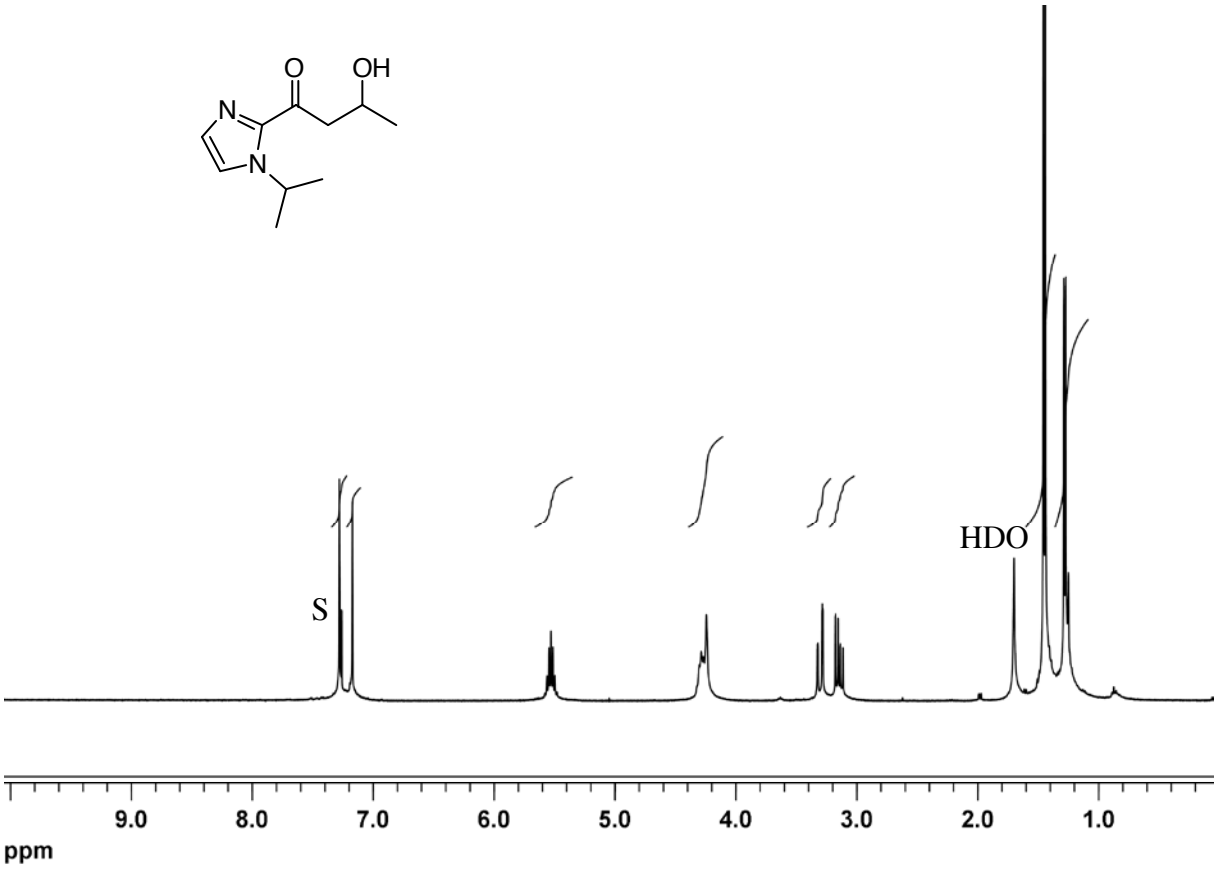

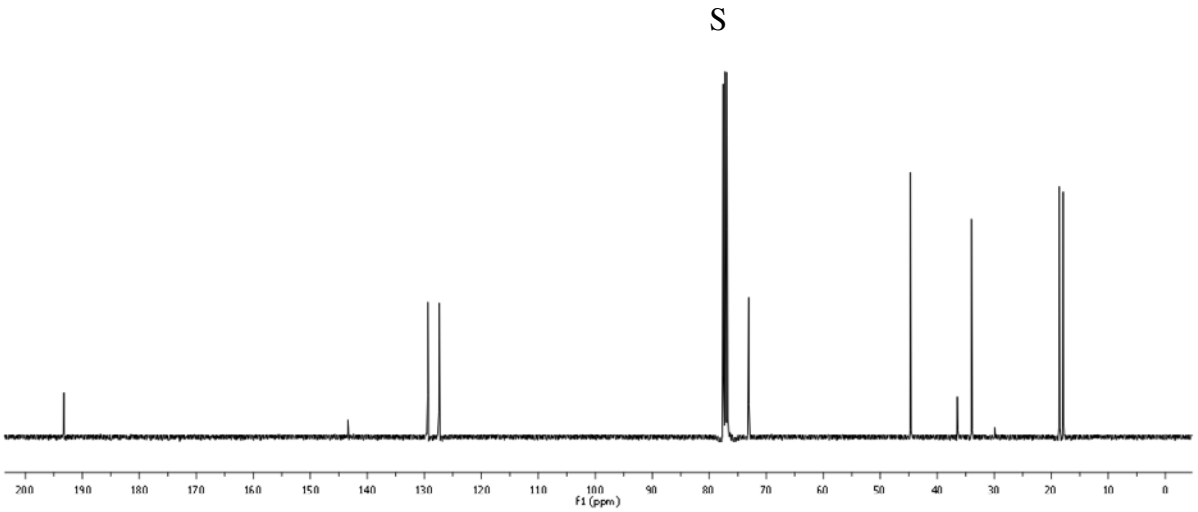

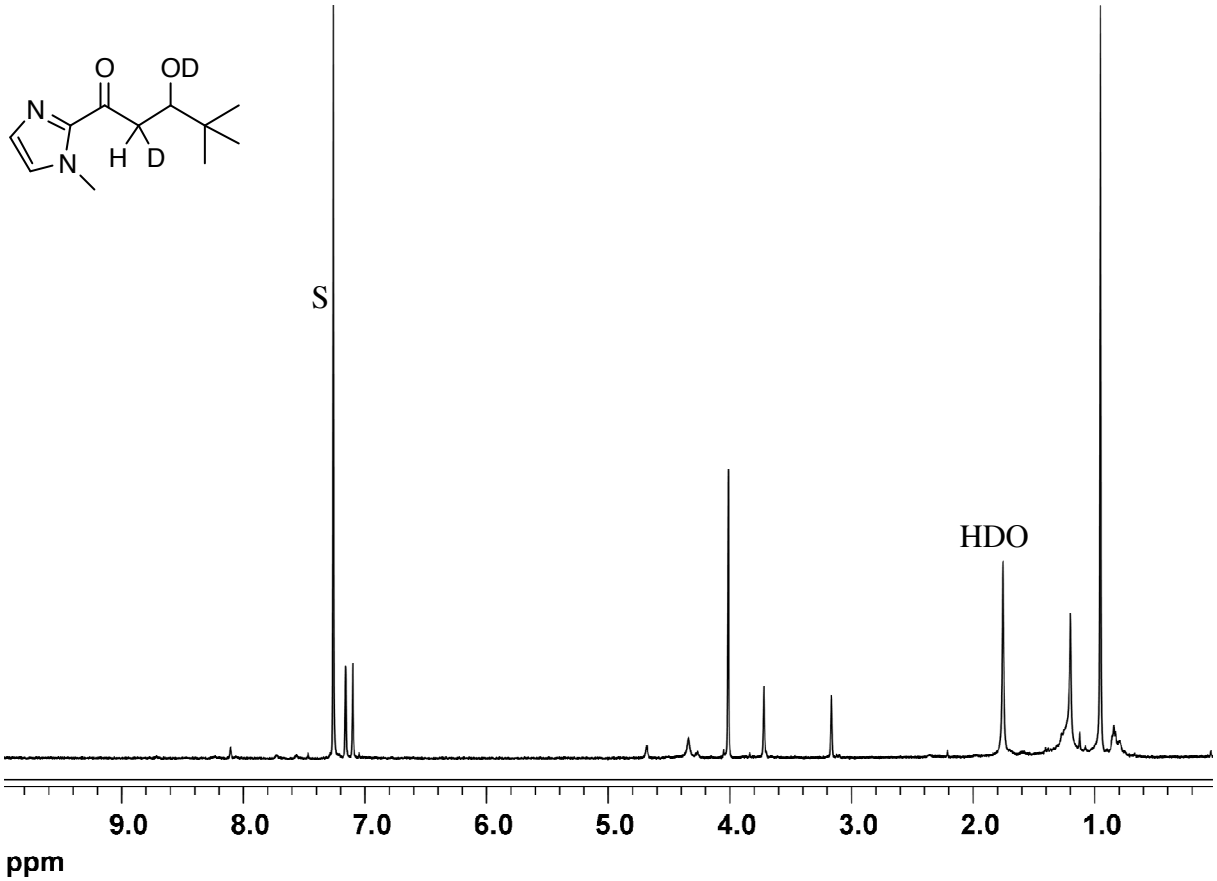

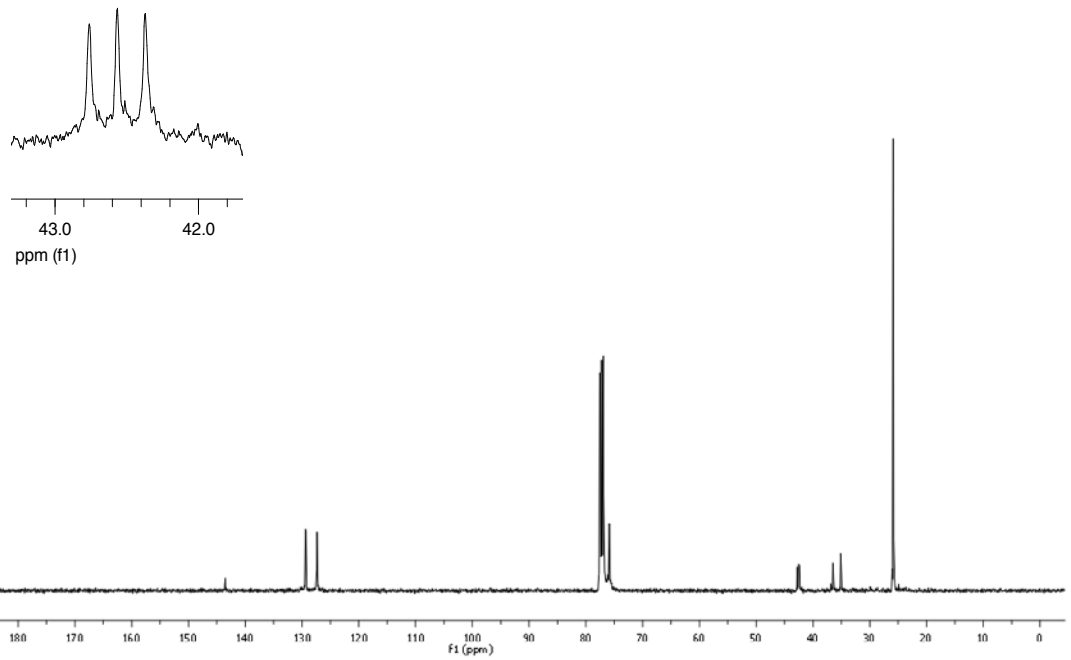

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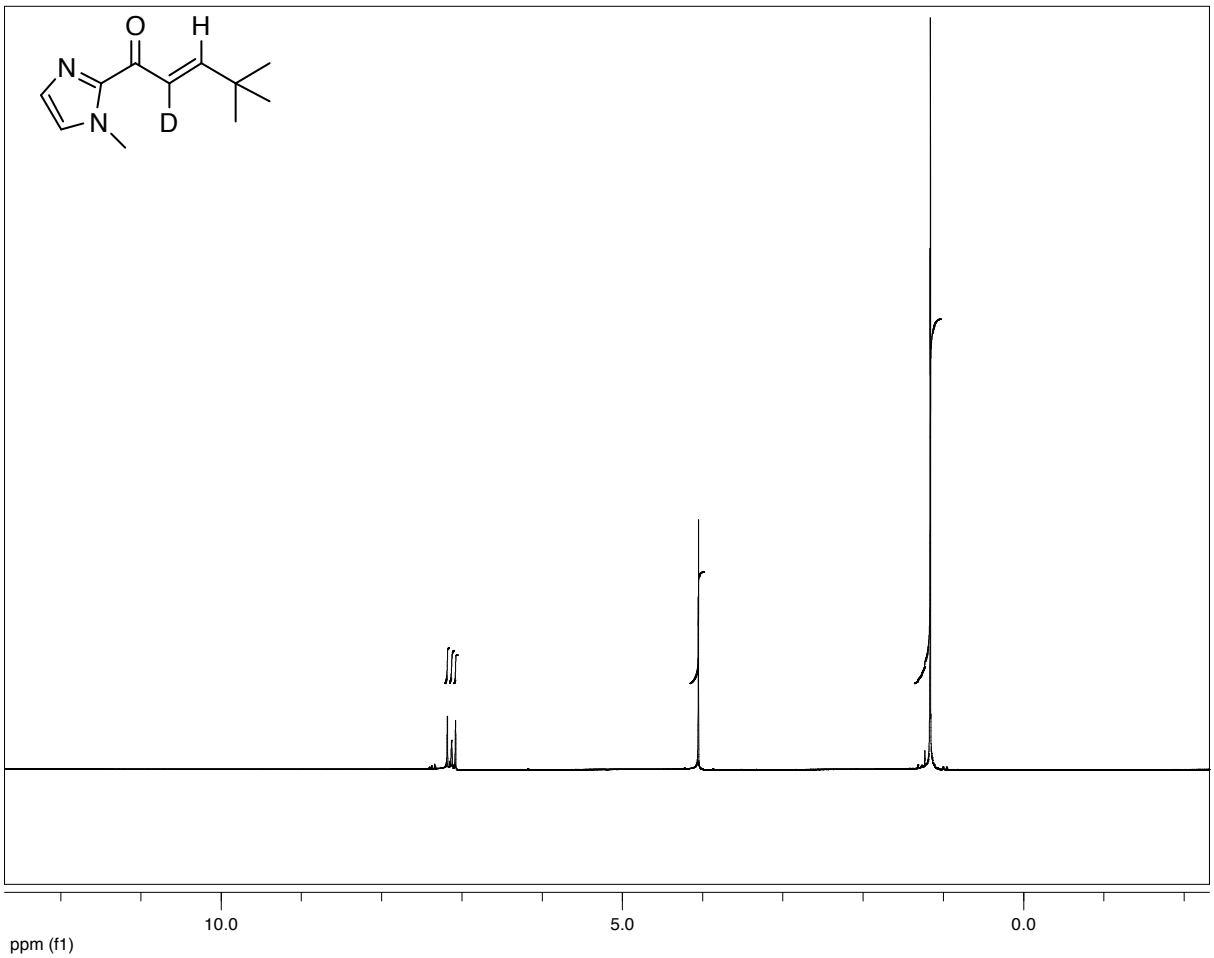

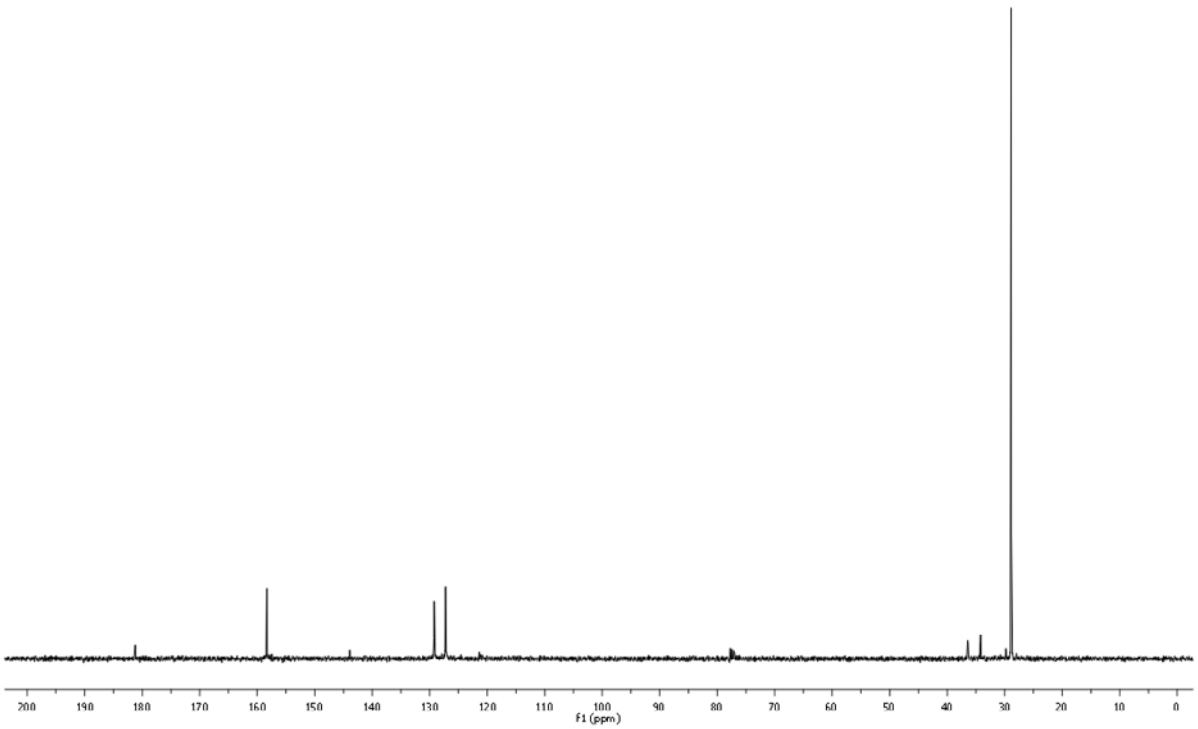

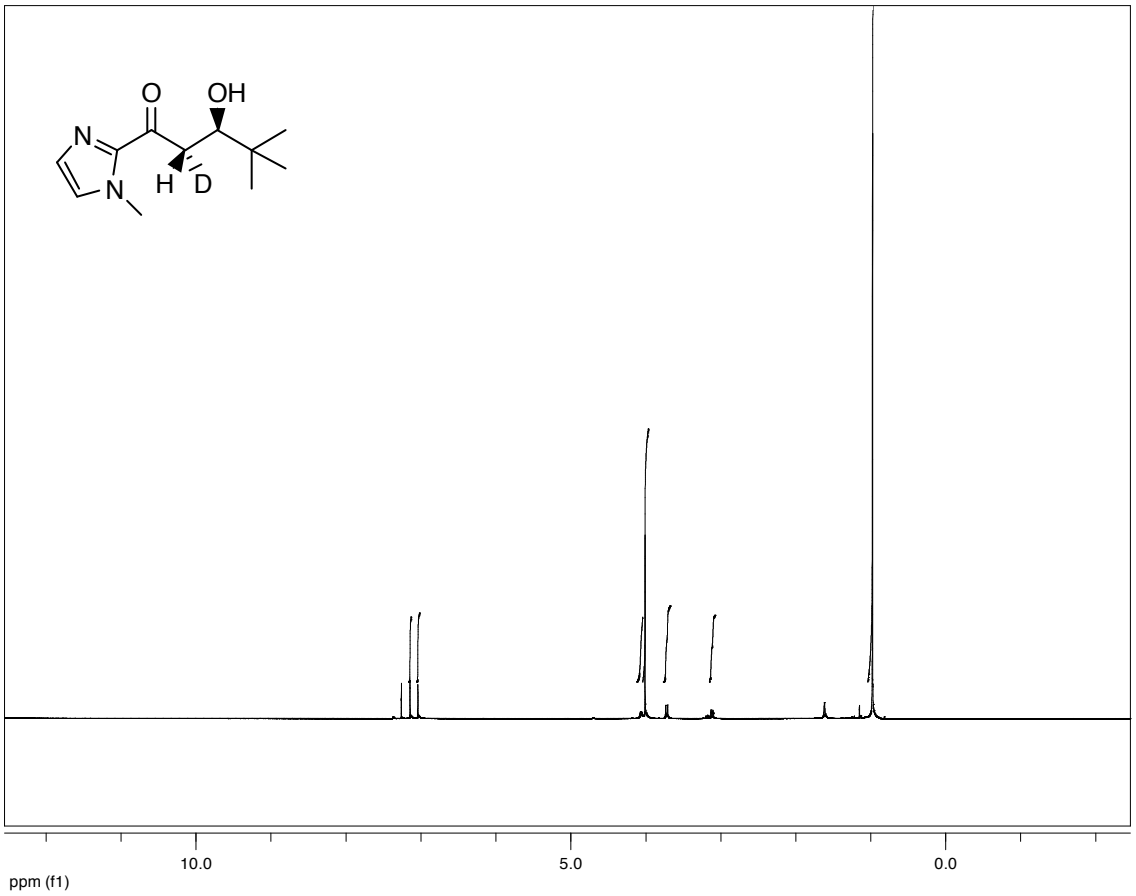

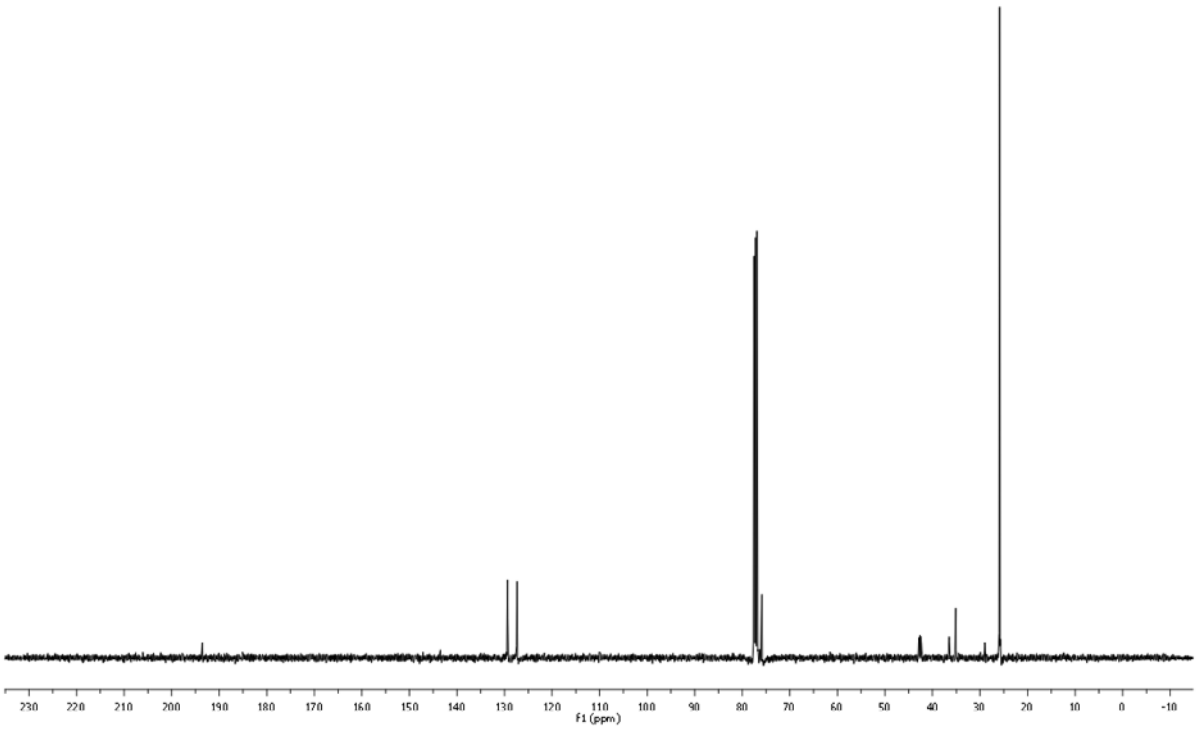

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