Electronic Supplementary Material (ESI) for Chemical Communications

Supporting Information accompanying

DNA-Based Catalytic Enantioselective Intermolecular Oxa-Michael Addition Reactions

R.P. Megens, G. Roelfes

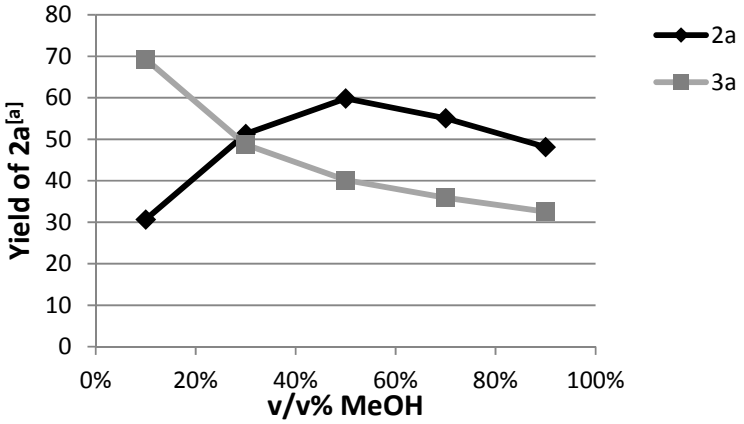


Figure S 1. Yield of the oxa-Michael product as function of methanol content. [a] Determined by NMR. Conditions: 0.15 mM [$Cu(NO_3)_2 \cdot 3\ H_2O$], 20 mM MOPS pH 6.5, 1 mM **1a**, RT, 1d.

Table S 1. Screening of reaction conditions

20 mM MES pH 5.5

MeOH (v/v%)	Conv.	Ratio **2**/**3**	ee **2a**	ee **3a**
10%	Full	24/76	55%	57%
20%	Full	41/59	56%	58%
30%	Full	43/57	49%	54%
40%	Full	45/55	49%	53%
20 mM MOPS pH 6.5				
MeOH (v/v%)	Conv.	Ratio **2**/**3**	ee **2a**	ee **3a**
10%	80%	26/74	49%	53%
20%	86%	41/59	50%	55%
30%	83%	1/1	53%	57%
40%	82%	59/41	64%	66%
20 mM MOPS pH 7.5				
MeOH (v/v%)	Conv.	Ratio **2**/**3**	ee **2a**	ee **3a**
10%	50%	4/6	27%	43%
20%	52%	6/4	42%	52%
30%	55%	64/36	42%	52%
40%	61%	6/4	42%	52%

General conditions: 0.66 mg/ml st-DNA, 1 mM **1a**, 0.15 mM $Cu(NO_3)_2$, 0.165 mM **L1**, 4°C, 1d

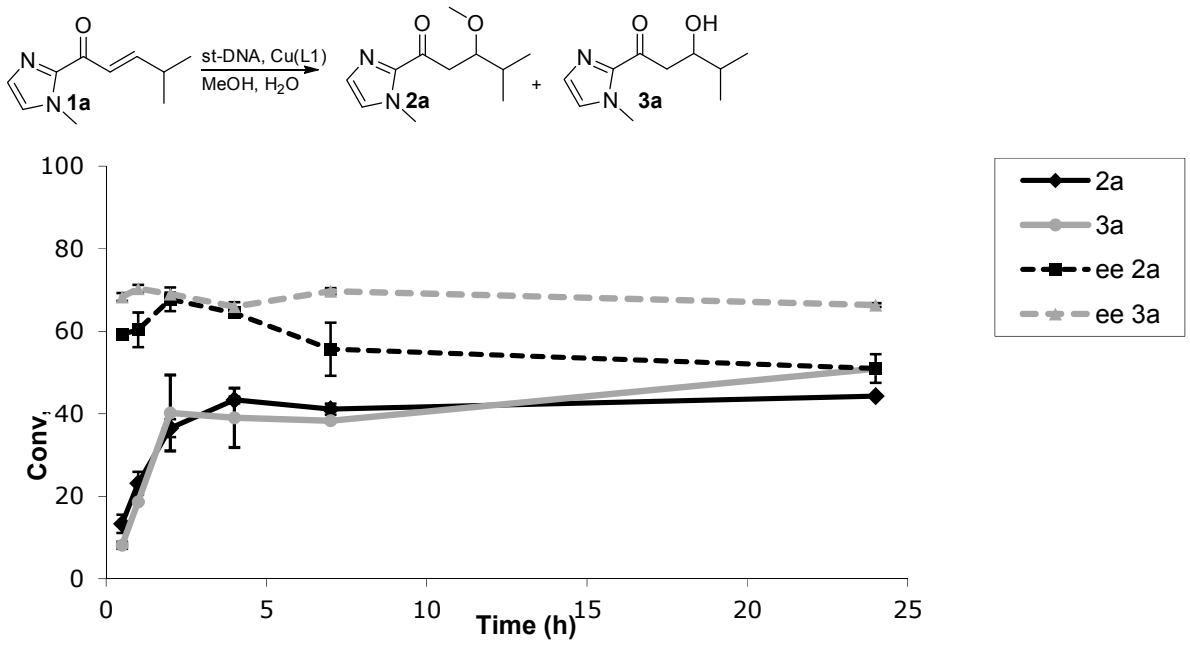


Figure S 2. Time profile for the reaction of **1a**.

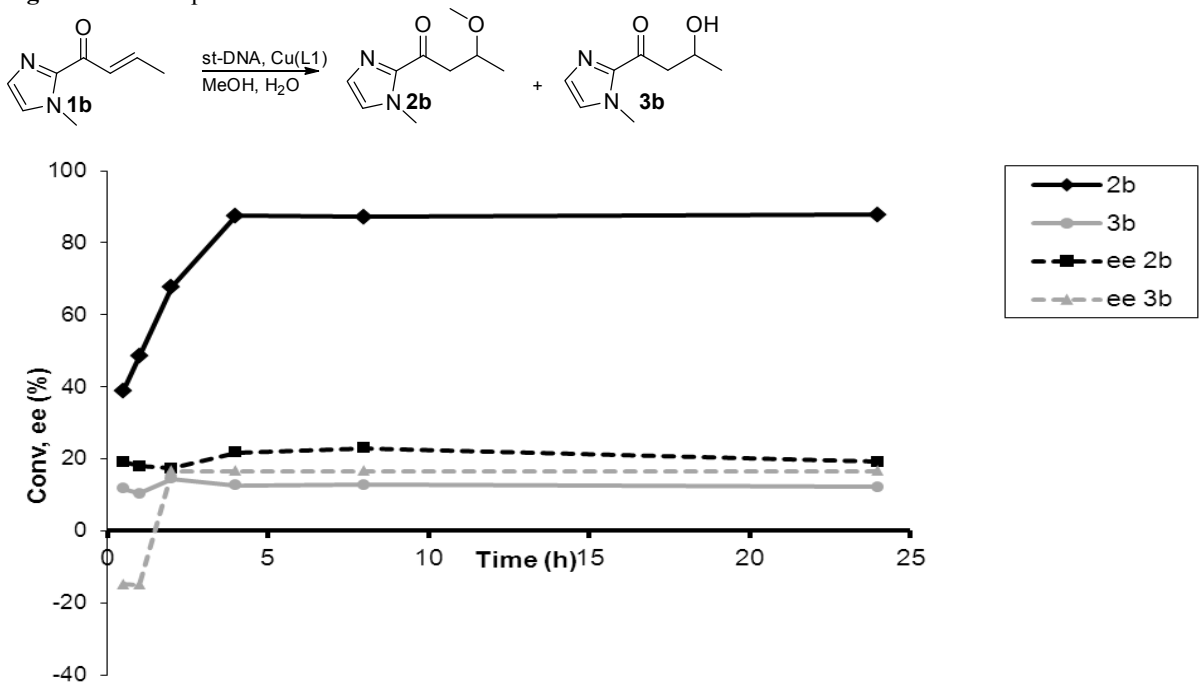


Figure S 3. Time profile for the reaction of **1b**.

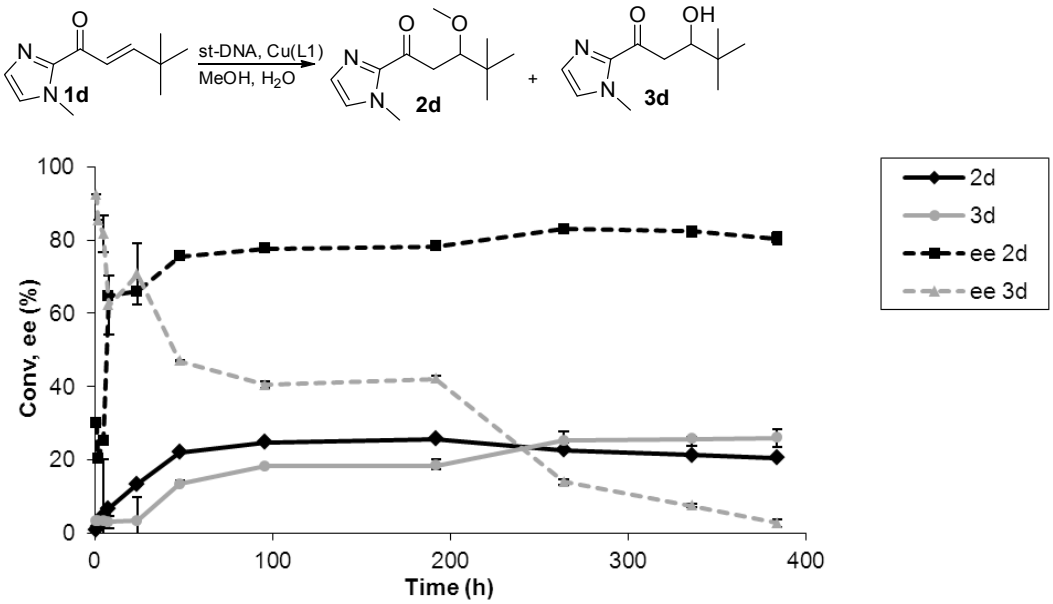


Figure S 4. Time profile for the reaction of **1d**.

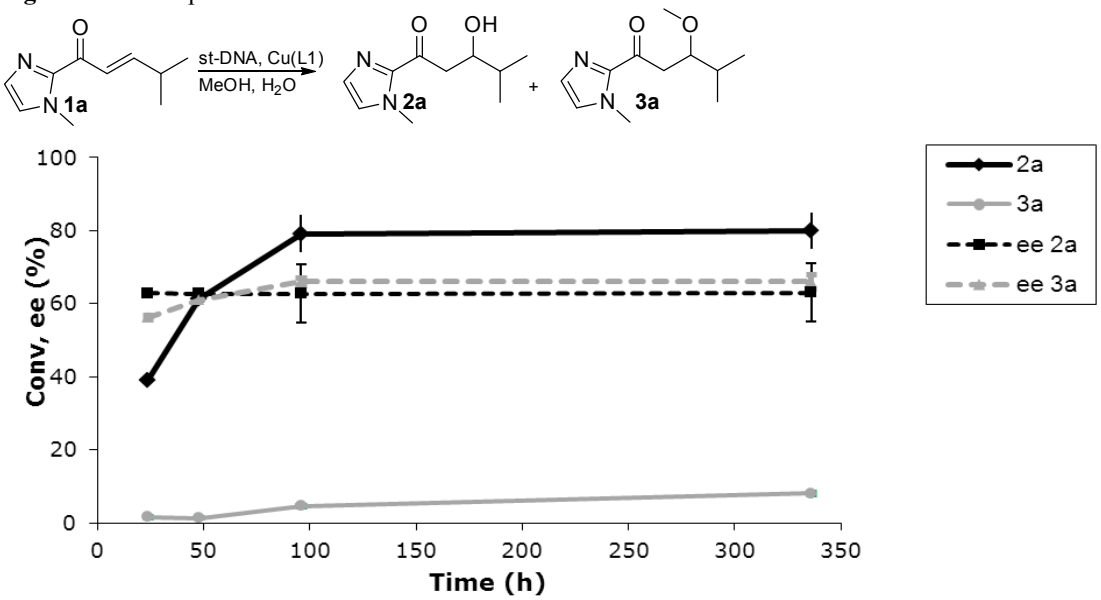


Figure S 5. Time profile for the reaction of **1a** at -18˚C.

Experimental section:

General remarks.

Salmon testes DNA was obtained from Sigma. Ligands **L1-4** and 2-acyl imidazole substrates were synthesized according to published procedures.[1, 2] Enantiomeric excess determination was performed by HPLC analysis on a Shimadzu 10AD-VP system. ^{1}H-NMR and ^{13}C-NMR were recorded on a Varian 400 (400 MHz). Chemical shifts (δ) are quoted in ppm using residual solvent as internal standard (δ_H 7.26 and δ_C 77.0 for $CDCl_3$). Mass spectra were recorded on a LTQ ORBITRAP XL.

Catalytic Oxa-Michael addition, representative procedure.

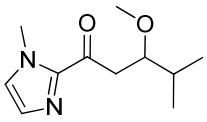
A buffered solution (20 mM MOPS, pH 6.5) of DNA bound catalyst (0.67 mg/ml salmon testes DNA, 0.165 mM **L1** and 0.15 mM $[Cu(NO_3)_2]\cdot 3\ H_2O$ was prepared by mixing a solution of salmon testes DNA (5 ml of a 2 mg/ml solution in 60 mM MOPS, prepared 24 h in advance) with an aqueous solution of catalyst (2.5 ml of a 0.90 mM solution of $[Cu(NO_3)_2]\cdot 3\ H_2O$ and 0.99 mM **L1** in water) and adding water and alcohol to a total volume of 15 ml. The mixture was cooled to 4 °C and 15 µmol of the appropriate α,β unsaturated 2-acyl imidazole dissolved in 10 µL MeCN was added. The reaction was mixed by continuous inversion at 4 °C, followed by extraction of the product with Et_2O. After drying (Na_2SO_4) and removal of the solvent the crude product was analyzed by NMR and HPLC using a chiral stationary phase.

Oxa-michael addition general synthesis of racemates:
A buffered solution (20 mM MOPS, pH 6.5) containing 40% alcohol and 0.15 mM $[Cu(NO_3)_2]\cdot 3\ H_2O$ was prepared. To this mixture 15 µmol of enone dissolved in 10 µL MeCN was added. The reaction was mixed by continuous inversion at RT, followed by extraction of the product with Et_2O. After drying (Na_2SO_4) and removal of the solvent the crude product was purified by column chromatography (EtOAc/heptanes 1:4).

References:

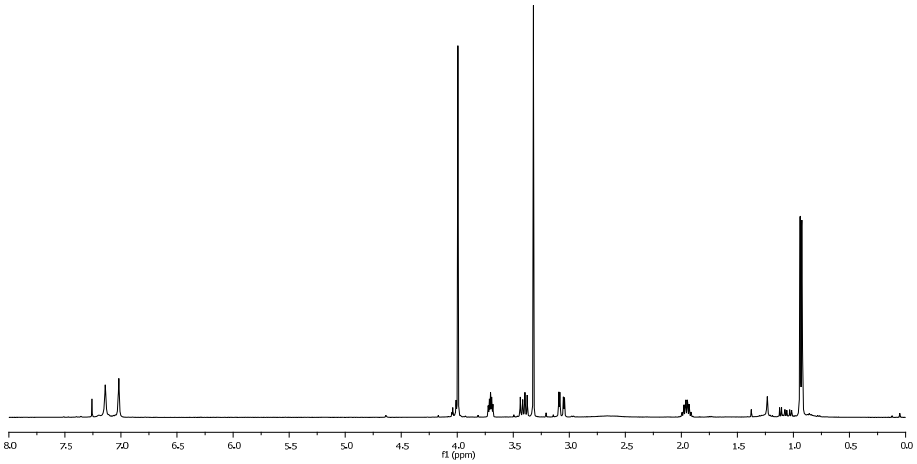
1 A. J. Boersma, D. Coquière, D. Geerdink, F. Rosati, B. L. Feringa, G. Roelfes, *Nat. Chem.* 2010, **2**, 991-995.

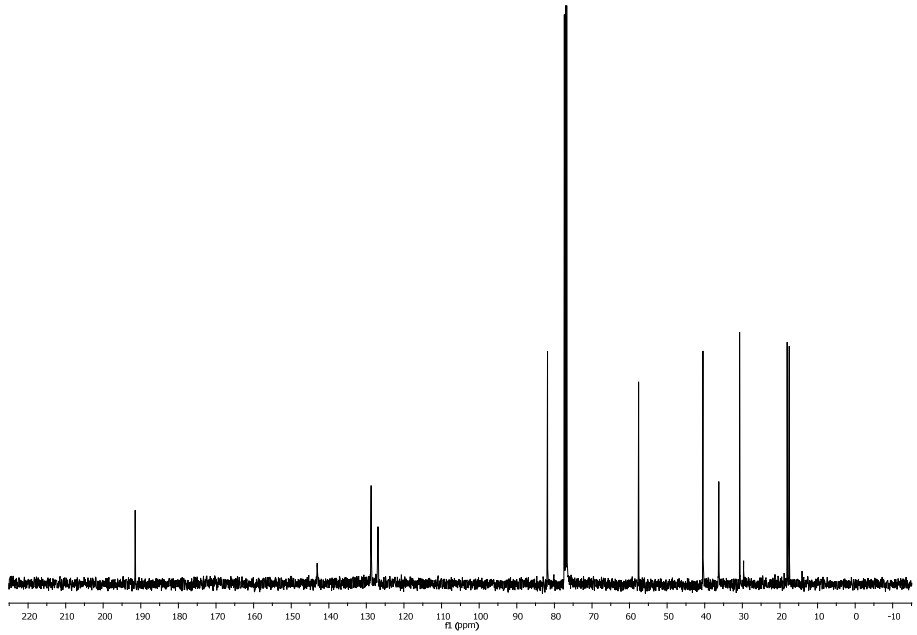
2 D. A. Evans, K. R. Fandrick, H. J. Song, *J. Am. Chem. Soc.* 2005, **127**, 8942-8943.

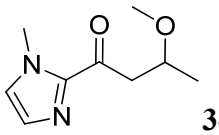


3-methoxy-4-methyl-1-(1-methyl-1H-imidazol-2-yl)pentan-1-one (2a)

After column chromatography the product was obtained as a slighly yellow oil.
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.14 (s, 1H), 7.02 (s, 1H), 3.99 (s, 3H), 3.70 (dt, *J* = 8.4, 4.2 Hz, 1H), 3.41 (dd, *J* = 16.4, 8.4 Hz, 1H), 3.32 (s, 3H), 3.07 (dd, *J* = 16.3, 3.7 Hz, 1H), 1.95 (dq, *J* = 6.7, 1.9 Hz, 1H), 0.93 (dd, *J* = 6.8, 1.7 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 191.5 , 143.1, 128.7, 126.9, 81.8, 57.6, 40.5, 36.3, 30.7, 18.1, 17.5. HRMS: m/z :211.14377 (M+1) , (Calcd. 211.14410; M+1)

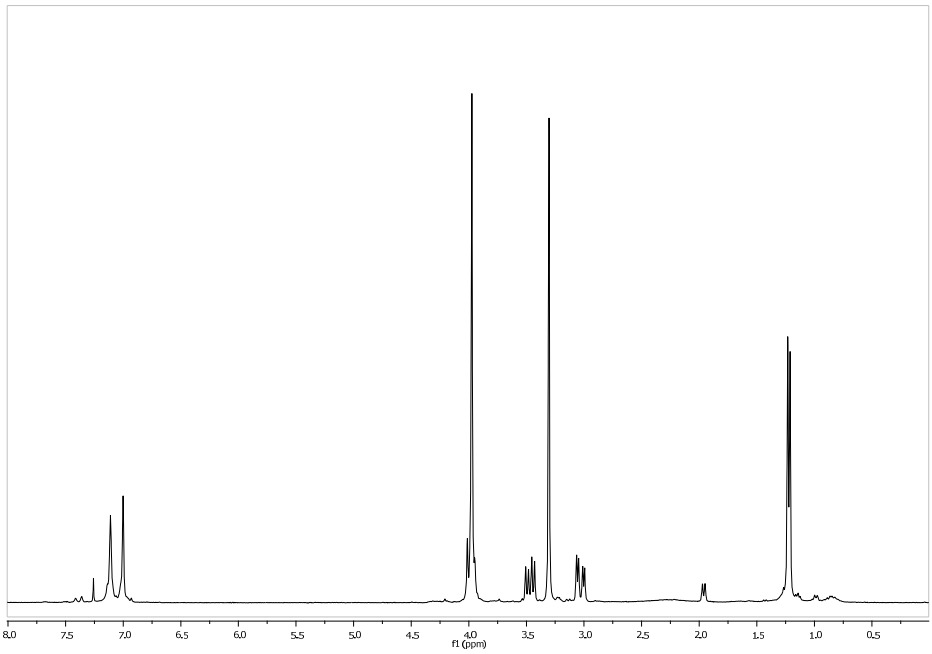


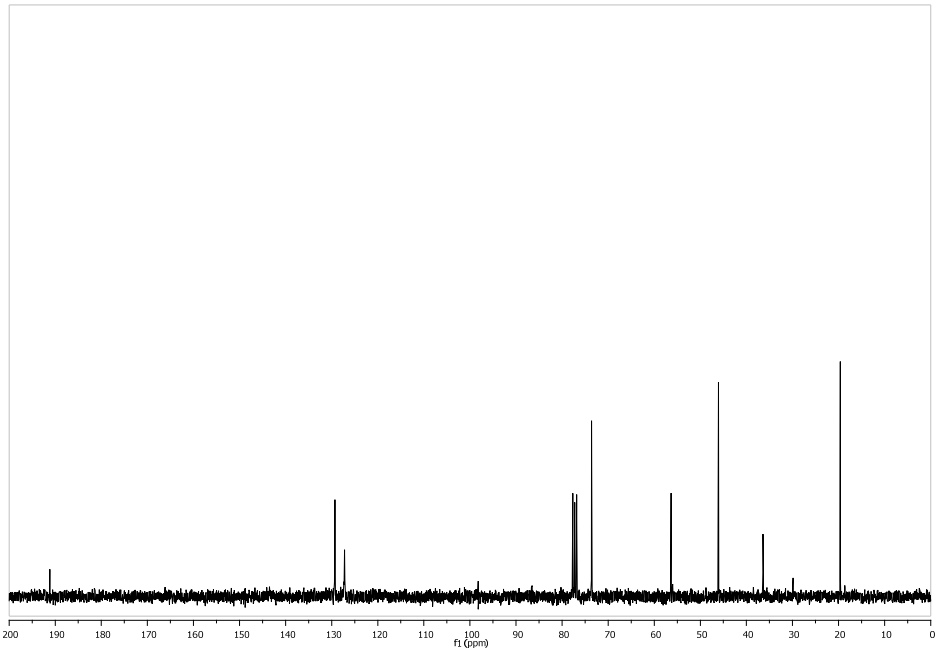


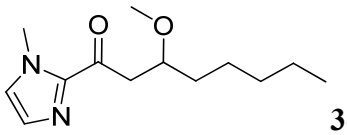


3-methoxy-1-(1-methyl-1H-imidazol-2-yl)butan-1-one (2b)

After column chromatography the product was obtained as a slighly yellow oil.
^{1}H -NMR (400 MHz, $CDCl_3$) δ 7.12 (d, *J* = 0.8 Hz, 1H), 7.01 (s, 1H), 3.99 (s, 3H), 3.99 (dd, *J* = 18.0, 5.3 Hz, 1H), 3.48 (dd, *J* = 15.7, 7.5 Hz, 1H), 3.32 (s, 3H), 3.05 (dd, *J* = 15.7, 5.3 Hz, 1H), 1.24 (d, *J* = 6.2 Hz, 3H). ^{13}C- NMR (75 MHz, $CDCl_3$) 191.2, 143.9, 129.3, 127.2, 73.6, 56.4, 46.1, 36.4, 19.6. HRMS: m/z :183.11288 (M+1) , (Calcd. 183.11280; M+1)

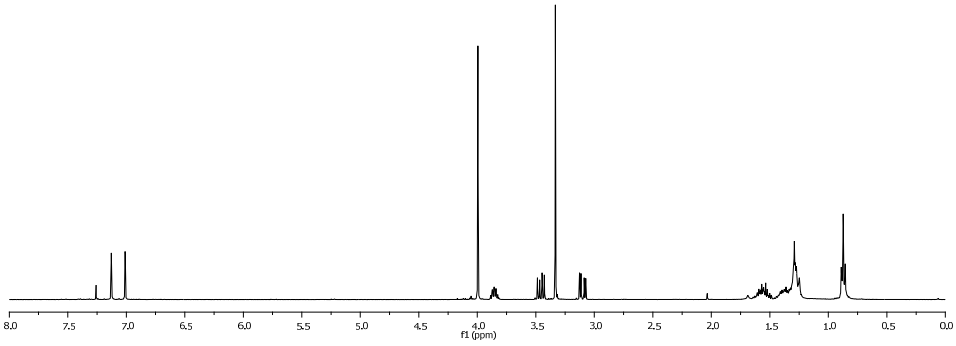


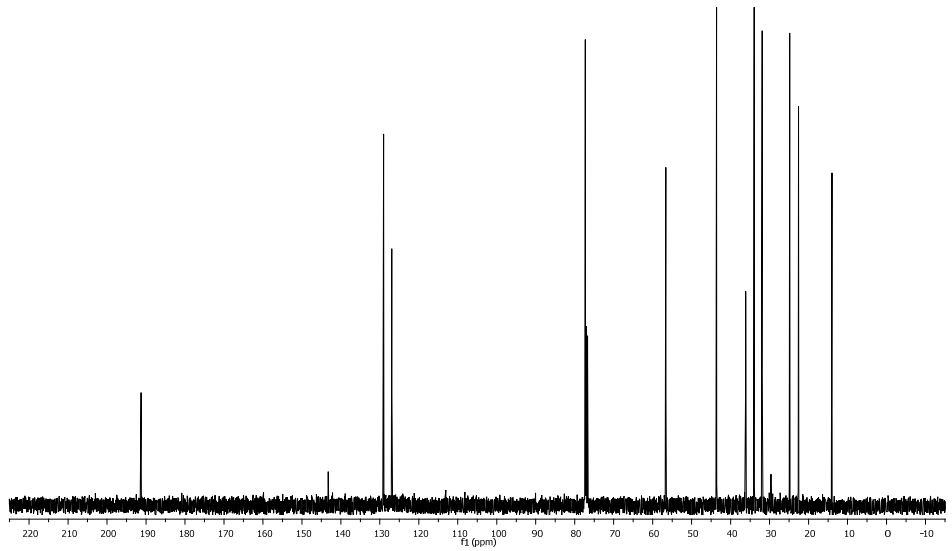


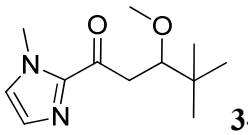


3-methoxy-1-(1-methyl-1H-imidazol-2-yl)octan-1-one (2c)

After column chromatography the product was obtained as a slighly yellow oil.
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.13 (s, 1H), 7.01 (s, 1H), 4.00 (s, 3H), 3.85 (m, 1H), 3.46 (dd, *J* = 16.0, 7.5 Hz, 1H), 3.33 (s, 3H), 3.10 (dd, *J* = 16.0, 4.9 Hz, 1H), 1.68 – 1.47 (m, 2H), 1.46 – 1.32 (m, 2H), 1.47 – 1.20 (m, 6H), 0.87 (t, *J* = 6.9 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 191.27, 143.24 , 129.03, 126.92, 77.29, 56.61, 43.60, 36.15, 33.94, 31.90, 24.82, 22.58, 14.00. HRMS: m/z :239.17589 (M+1) , (Calcd. 239.17540; M+1)

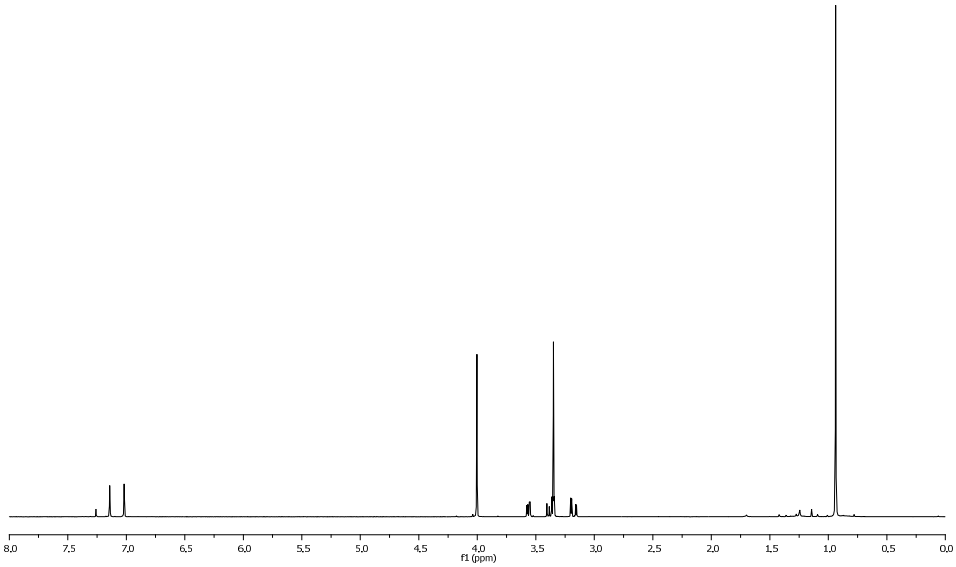


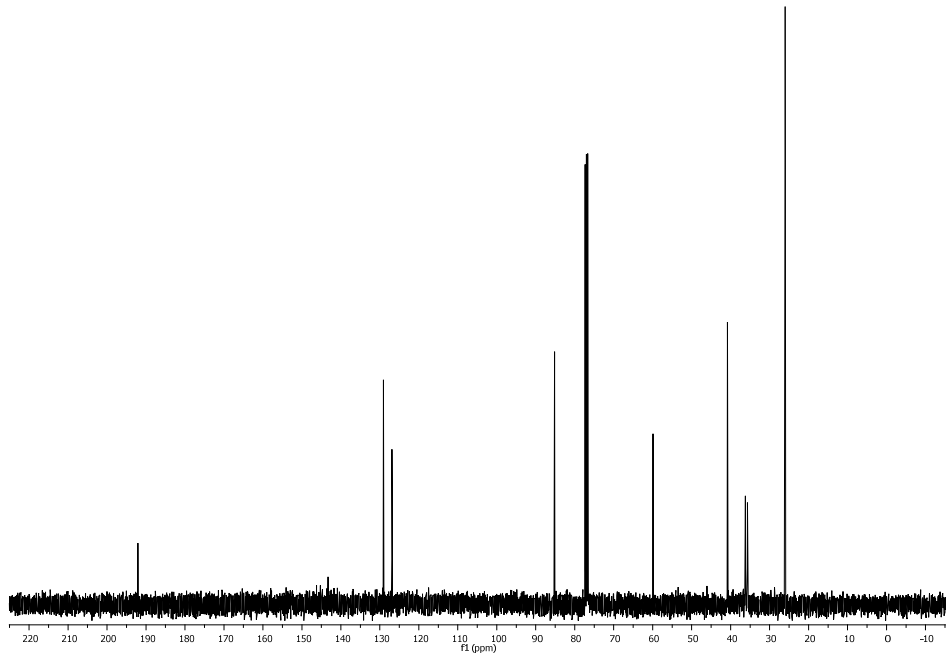


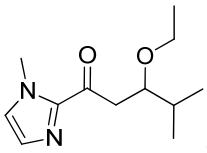


3-methoxy-4,4-dimethyl-1-(1-methyl-1H-imidazol-2-yl)pentan-1-one (2d)

After column chromatography the product was obtained as a slighly yellow oil.
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.14 (s, 1H), 7.02 (s, 1H), 4.00 (s, 3H), 3.56 (dd, J = 8.1, 3.3 Hz, 1H), 3.37 (dd, J = 16.8, 8.1 Hz, 1H), 3.35 (s, 3H), 3.18 (dd, J = 16.8, 3.3 Hz, 1H), 0.94 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 192.1, 143.3, 129.1, 126.9, 85.2, 59.9, 40.8, 36.2, 35.7, 26.0. HRMS: m/z :225.15983 (M+1) , (Calcd. 225.15975; M+1)

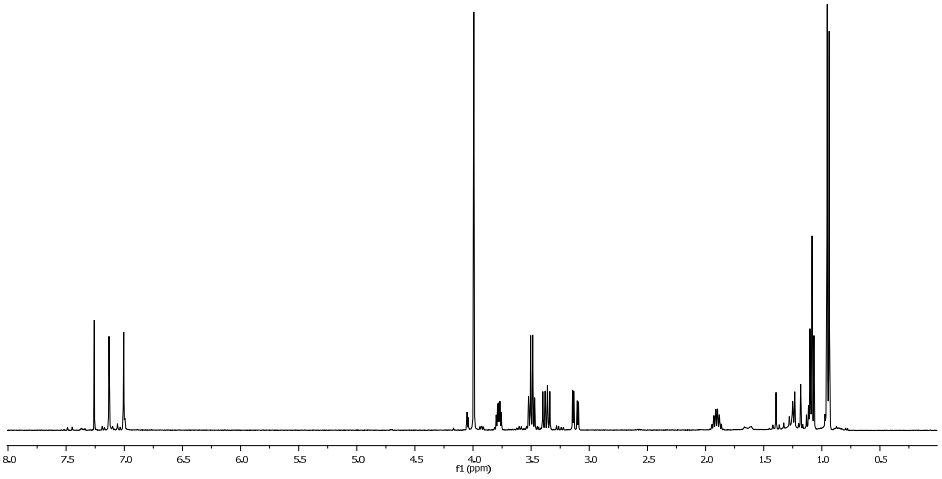


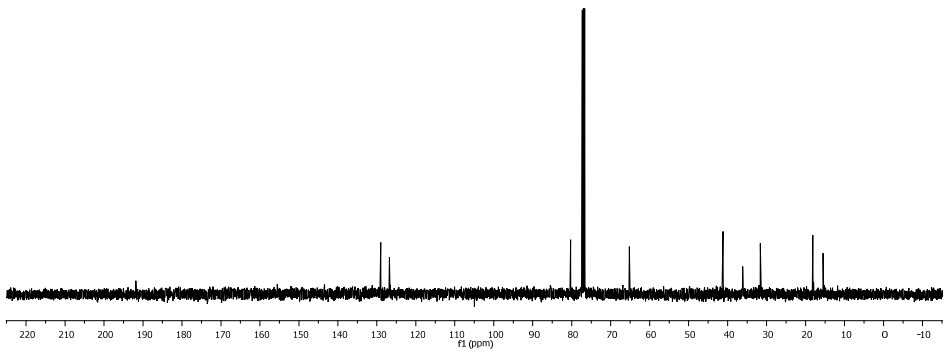


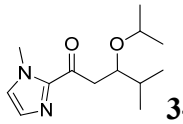


3-ethoxy-4-methyl-1-(1-methyl-1H-imidazol-2-yl)pentan-1-one (2f)

After column chromatography the product was obtained as a slighly yellow oil.
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.13 (s, 1H), 7.01 (s, 1H), 3.99 (s, 3H), 3.78 (dt, *J* = 8.0, 4.6 Hz, 1H), 3.50 (q, *J* = 7.0 Hz, 2H), 3.37 (dd, *J* = 16.1, 7.8 Hz, 1H), 3.12 (dd, *J* = 16.1, 4.1 Hz, 1H), 1.91 (h, *J* = 6.5 Hz, 1H), 1.09 (t, *J* = 7.0 Hz, 3H), 0.95 (d, *J* = 6.8 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 191.8, 143.1, 129.0, 126.8, 80.3, 65.2, 41.2, 36.1, 31.6, 18.1, 18.0, 15.5. HRMS: m/z :183.11288 (M+1) , (Calcd. 183.11280; M+1)







3-isopropoxy-4-methyl-1-(1-methyl-1H-imidazol-2-yl)pentan-1-one (2g)

After column chromatography the product was obtained as a slighly yellow oil.
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.13 (d, *J* = 4.9 Hz, 1H), 7.00 (d, *J* = 6.7 Hz, 1H), 3.99 (s, 3H), 3.93 (t, *J* = 5.9 Hz, 1H), 3.80 (m, 1H), 3.67 (m, 1H), 3.55 (dd, *J* = 15.5, 5.9 Hz, 1H), 3.06 (dd, *J* = 15.4, 6.0 Hz, 1H), 1.12 (d, *J* = 6.1 Hz, 3H), 1.03 (d, *J* = 6.1 Hz, 3H), 0.99 (d, *J* = 6.1 Hz, 3H), 0.81 (d, *J* = 6.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 192.1, 128.8, 126.4, 80.0, 71.0, 63.4, 40.8, 36.1, 24.1, 23.1, 22.2, 20.1. C2-imidazole is missing
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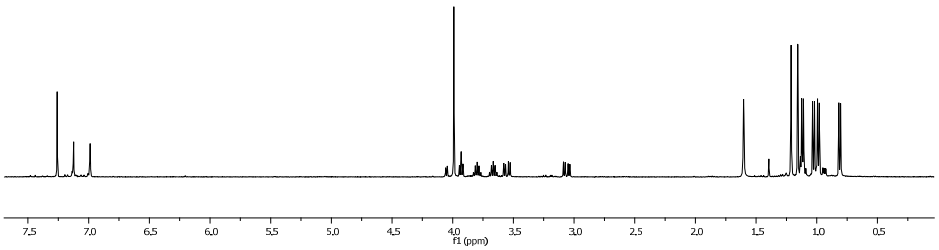

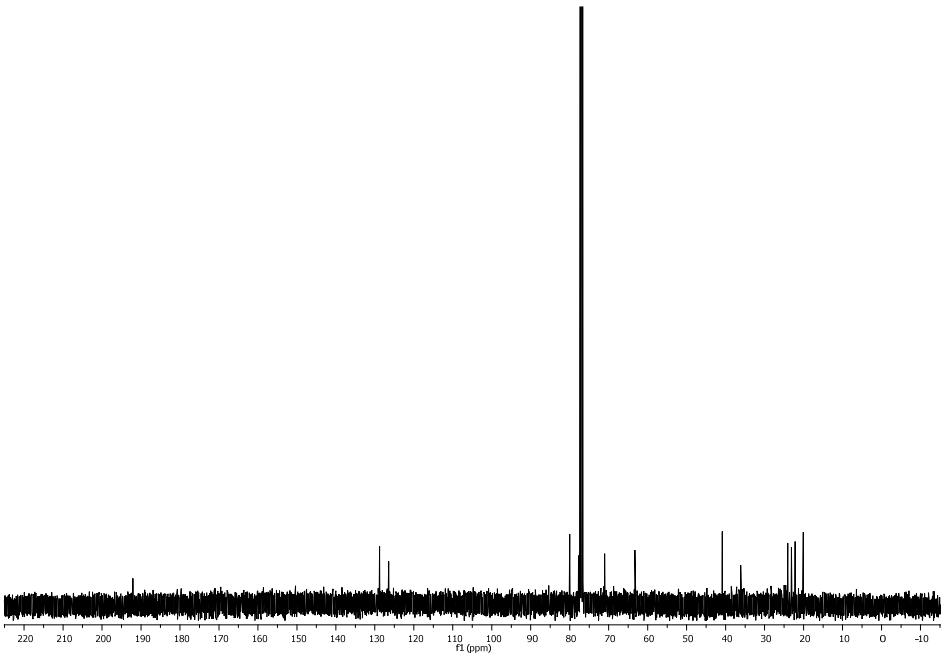

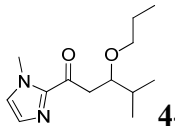

4-methyl-1-(1-methyl-1H-imidazol-2-yl)-3-propoxypentan-1-one (2h)

After column chromatography the product was obtained as a slighly yellow oil.
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.13 (d, *J* = 0.8 Hz, 1H), 7.00 (s, 1H), 3.99 (s, 3H), 3.85 – 3.69 (m, 1H), 3.42 – 3.33 (m, 3H), 3.09 (dd, *J* = 16.0, 4.2 Hz, 1H), 1.92 (dtd, *J* = 13.6, 6.8 Hz, 5.0, 1H), 1.47 (q, *J* = 6.8 Hz, 2H), 0.94 (d, *J* = 6.9 Hz, 6H), 0.82 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 191.8, 143.4, 129.0, 126.8, 80.3, 65.2, 41.2, 36.2, 31.60, 18.1, 18.0, 15.5. HRMS: m/z :239.17602 (M+1) , (Calcd. 239.17595; M+1)