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DNA-Based asymmetric catalysis as a synthetic tool

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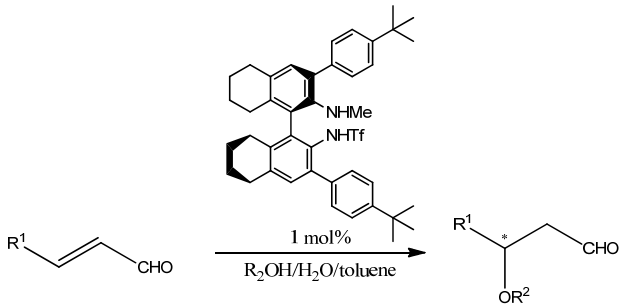
Chapter 4
DNA-Based Catalytic Enantioselective Intermolecular Oxa-Michael Addition Reactions

DNA-based asymmetric catalysis has been used for a wide variety of reactions in water (chapter 1); furthermore, it has been described in chapter 3 that organic co-solvents can be used in combination with DNA-based catalysis. However some of these co-solvents can also be used as reactant. In this chapter a novel Cu(II)-catalyzed enantioselective oxa-Michael addition of alcohols to enones using the DNA-based catalysis concept is described. Enantioselectivities of up to 86% can be obtained. The presence of water proved to be important for the reactivity, possibly by reverting unwanted side reactions such as 1,2-additions.

Parts of this chapter have been published: R.P. Megens, G. Roelfes, *Chem. Commun.*, **2012**, 48, 6366.

4.1 Introduction

The catalytic enantioselective conjugate addition of alcohols, also known as the oxa-Michael reaction, is a reaction of great potential in organic synthesis.[1,2] Yet, the development of this reaction, and in particular the intermolecular variant, has been complicated by the inherently low reactivity of most alcohols in such reactions and the fact that the conjugate addition step is generally reversible. As a result, reports about catalytic enantioselective intermolecular oxa-Michael reactions of simple achiral alcohols to enones, are scarce.[1,2] Most examples either involve intramolecular oxa-Michael additions,[3-7] or make use of alcohol analogues.[8-11] One of the few examples of such reactions is the organocatalytic oxa-Michael addition developed by Maruoka (Scheme 4.1).[12] A chiral octahydrobinal based diamine is used to catalyze the asymmetric addition of alcohols to α,β-unsaturated aldehydes. The reaction required water, probably for the hydrolysis of the intermediate iminium species, in the absence of water the reaction was significantly slower. By the addition of toluene, which was added to solubilize the catalyst, the yield of the reaction was significantly improved, however at the expense of the enantioselectivity (Entry 1 and 2). A variety of substrates and alcohols were used giving the product with moderate enantioselectivities (Entry 3-6).

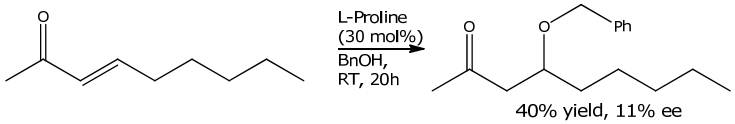


entry	R^1	R^2	Time (h)	Yield (%)	Ee (%)
1	Bu	Me	48	65	51
2[a]	Bu	Me	24	29	68
3	Pr	Me	48	66	46
4	$BnCH_2$	Me	48	83	53
5	Bu	Et	24	55	48
6	Bu	Allyl	48	60	16

Conditions: α,β-unsaturated aldehydes 0.25 mmol, 1 mol% catalyst in MeOH (950 μl), H_2O (50 μl) and toluene (100 μl). a; without toluene.

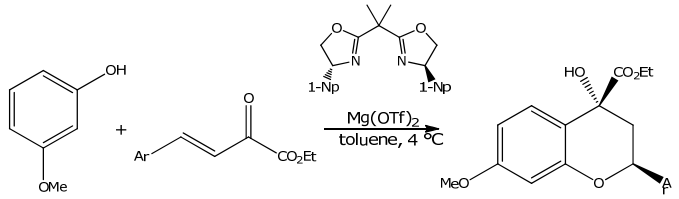
Scheme 4.1. Organocatalytic oxa-Michael addition of alcohols to α,β-unsaturated aldehydes.

The only other example is an isolated case of a proline catalyzed oxa-Michael addition of benzylalcohol to an α,β-unsaturated ketone.[13] T he oxa-Michael addition product was obtained in 40% yield and only 11% ee (Scheme 4.2).



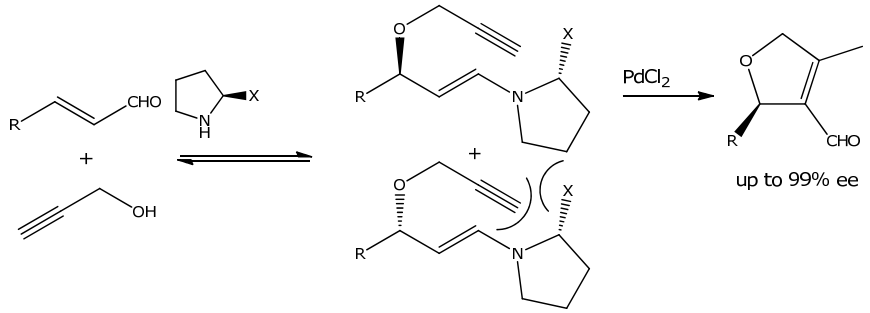
Scheme 4.2. Proline catalyzed oxa-Michael addition of benzylalcohol to an α,β-unsaturated ketone.

The intermolecular oxa-Michael addition has also been reported as the first step of an enantioselective tandem reaction. In both published cases a subsequent reaction was used to push the unfavorable equilibrium of the C-O bond formation by a follow up reaction of the product.[14,15] The first example is an oxa-Michael addition of phenol to an β,γ-unsaturated α-ketoester followed by a Friedel-Crafts alkylation catalyzed by a bisoxazoline-$Mg(OTf)_2$ complex. After optimization of the reaction conditions diastereometrically pure chromans could be obtained with reasonable yields and up to 81% ee (Scheme 4.3).[15]



Scheme 4.3. Oxa-Michael addition followed by Friedel-Crafts alkylation of phenol to β,γ-unsaturated α-ketoesters.

The second and last example comes from the group of Córdova, who developed a dynamic kinetic asymmetric domino oxa-Michael/carbocyclization catalyzed by a combination of a transition-metal and a proline derivative (Scheme 4.4).[14] By combining these catalysts substituted furans could be synthesized with excellent enantioselectivities. It is thought that the enantioselectivity in this domino reaction originates from the carbocyclization since one of the enantiomers would react faster. However, the enantioselectivity of the oxa-Michael reaction itself has not be determined because the reaction without palladium gave only trace amounts of the oxa-Michael product.



Scheme 4.4. Dynamic kinetic asymmetric domino oxa-Michael/carbocyclization cascade reaction.

4.2 DNA-based catalytic enantioselective intermolecular oxa-Michael addition reactions

Recently, DNA-based catalysis was used to achieve the first catalytic enantioselective *syn*-hydration of enones.[16] This remarkable reaction, which has no equivalent in homogeneous catalysis, demonstrated the power of the DNA-based catalysis concept and suggested the possibility of achieving enantioselective intermolecular oxa-Michael addition reaction of alcohols to enones. In this study, as a benchmark reaction the addition of methanol to α,β-unsaturated 2-acyl imidazole **1a** was investigated (Figure 4.1).

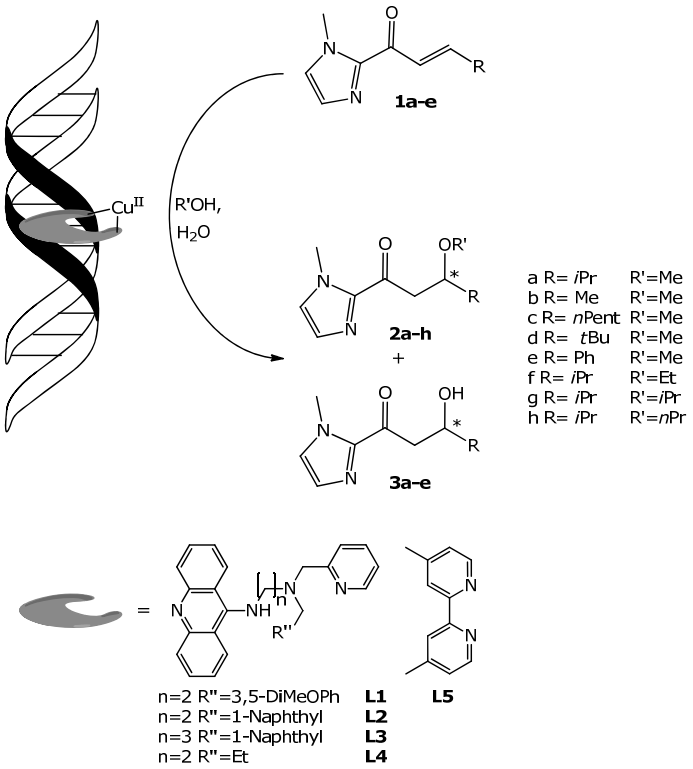
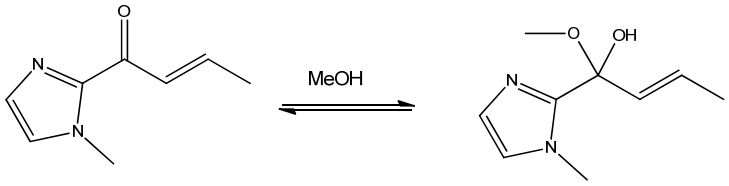


Figure 4.1. DNA-based catalytic enantioselective intermolecular oxa-Michael addition reaction in water.

Since the DNA-based catalyst requires aqueous conditions, first the optimal water/methanol mixture was investigated in the reaction catalyzed by $Cu(NO_3)_2$ in the absence of DNA. Interestingly, it was observed that the highest yield of the methanol addition product **2a** was obtained when the catalyzed reaction was performed in a 50:50 water/ methanol mixture; further increasing the fraction of methanol led to a lower yield of **2a** (Figure 4.2). This surprising observation suggests that water plays an important role in the reaction, possibly by reverting unwanted side reactions such as 1,2-additions of the alcohol, which

would give rise to (hemi-)acetals (Scheme 4.5). For the DNA-based reactions 40% v/v methanol was selected, since it was found before that this methanol content can be used without causing precipitation of DNA (chapter 3).



Scheme 4.5. 1,2-addition of alcohol.

4.2.1 Optimization of conditions of DNA-based catalysis

The pH and MeOH contents were varied in order to find the best conditions for the enantioselectivity and conversion (Table 4.1). In the optimization pH 6.5 was found to be the pH at which the highest ee's could be obtained with high yields.

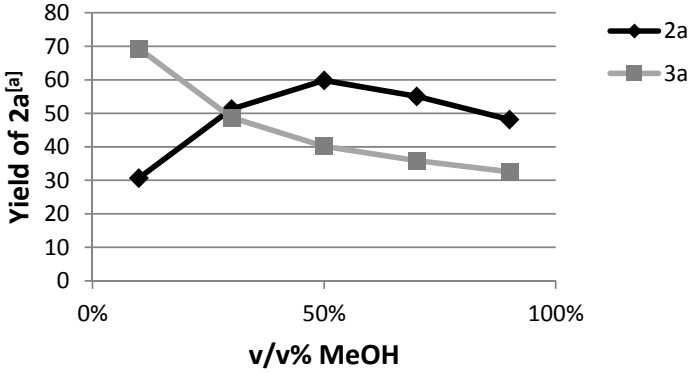


Figure 4.2. Conversion towards oxa-Michael product as function of methanol content. a; Determined by ^{1}H-NMR. Conditions: 0.15 mM [$Cu(NO_3)_2 \cdot 3\ H_2O$], 20 mM MOPS pH 6.5, 1 mM **1a**, RT, 1d.

Next, bidentate nitrogen ligands **L1-L5** were evaluated in the catalytic reaction in the presence of salmon testes DNA (st-DNA) at pH 6.5. In addition to the methanol addition product **2a**, ~30 % of the hydration product **3a** was obtained as a side-product, with ee's similar to the methanol addition product. The highest enantioselectivities for the methanol addition product **2a** were achieved with the ligands **L1** and **L2**: 64 and 57 % ee, respectively (Table 4.2). This trend is consistent with what was observed before in the catalytic hydration reaction.[16] Since also the highest conversions of **1a** were obtained with **L1**, this ligand was selected for further study.

Table 4.1. 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%	50/50	53%	57%
40%	83%	59/41	64%	66%
20 mM MOPS pH 7.5				
MeOH (v/v%)	Conv.	Ratio **2**/**3**	ee **2a**	ee **3a**
10%	50%	40/60	27%	43%
20%	52%	60/40	42%	52%
30%	55%	64/36	42%	52%
40%	61%	60/40	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.

Table 4.2. Screening of ligands.

Entry	Ligand	Time	Conv.	Ratio **2**/**3**	Ee **2**	Ee **3**
1	**L1**	4h	82%	59/41	64%	66%
2	**L2**	1d	69%	70/30	57%	59%
3	**L3**	1d	34%	58/42	4%	21%
4	**L4**	1d	26%	62/38	13%	46%
5a	**L5**	1d	28%	54/46	-5%	5%

Conditions: 0.66 mg/ml st-DNA, 20 mM MOPS pH 6.5, 0.165 mM **L**, 0.15 mM $Cu(NO_3)_2$, 1 mM **1a**, 40 v/v% MeOH, 4 °C. a; 0.15 mM Cu(dmbipy)$(NO_3)_2$. All conversions and enantioselectivities are the average of triplicate experiments; all values are reproducible within +/- 2%.

4.2.2 Substrate scope

Using Cu-**L1**/st-DNA and the optimized conditions, the substrate scope of the reaction was investigated. It was found that the maximum conversion of the enone and the ratio of **2**/**3** decreased with increasing

steric bulk of the substituent R at the β position (Table 4.3). The opposite trend was observed for the ee of **2**, namely, an increase in enantioselectivity upon going from R= methyl (24% ee, Entry 3) to R= *t*-butyl (81% ee; Entry 7). In case of R= phenyl, no conversion was observed. Most likely, the addition to this highly conjugated substrate is thermodynamically unfavorable.

Table 4.3. Substrate scope.

Entry	Substrate	Time	Conv.	Product	Ratio **2**/**3**	ee **2**	ee **3**
1	**1a**	4h	82%	**2a**	59/41	64%	66%
2[a]	**1a**	4d	85%	**2a**	94/6	63%	66%
3	**1b**	4h	Full	**2b**	87/13	24%	17%
4[a]	**1b**	1d	Full	**2b**	99/1	25%	n.d.
5	**1c**	1d	76%	**2c**	76/24	35%	51%
6[a]	**1c**	1d	70%	**2c**	93/7	58%	82%
7	**1d**	4d	43%	**2d**	58/42	81%	40% (*R*)
8[a]	**1d**	7d	21%	**2d**	63/37	83%	85%
9	**1e**	1d	-	**2e**	-	nd.	nd.

Conditions: 0.66 mg/ml st-DNA, 20 mM MOPS pH 6.5, 0.165 mM **L1**, 0.15 mM $Cu(NO_3)_2$, 1 mM substrate, 40 v/v% MeOH, 4 °C. a; Reaction performed at -18 °C. All conversions, product **2**/**3** ratios and enantioselectivities are the average of at least duplicate experiments; all values are reproducible within ±2%.

The reaction of **1a–d** with methanol was also performed at -18 °C, which is possible due to the high methanol content in the reaction mixture (Chapter 3). This resulted in a similar ee of the alcohol addition products, with exception of **2c** for which the ee increased from 35% to 58%. Interestingly, at -18 °C, the hydration side reaction was suppressed. The ratio **2**/**3** was increased moderately in the case of **1d** (Entry 8), but almost complete selectivity towards the alcohol addition product **2** was found for **1a–c** (Entries **2**, **4**, and **6**). Apparently, the rate of the hydration reaction depends much stronger on temperature than the alcohol addition reaction. Hence, even though the requirement for aqueous conditions causes the formation of a side product resulting from hydration of the enone, the reaction can be made chemoselective by lowering the reaction temperature.

Several of these reactions were followed in time (Figure 4.3). In contrast to the hydration product **3**, which in several cases racemizes in time,[16] the ee of the alcohol addition product **2** was found to be constant over time; no significant racemization occured in the time investigated.[17]

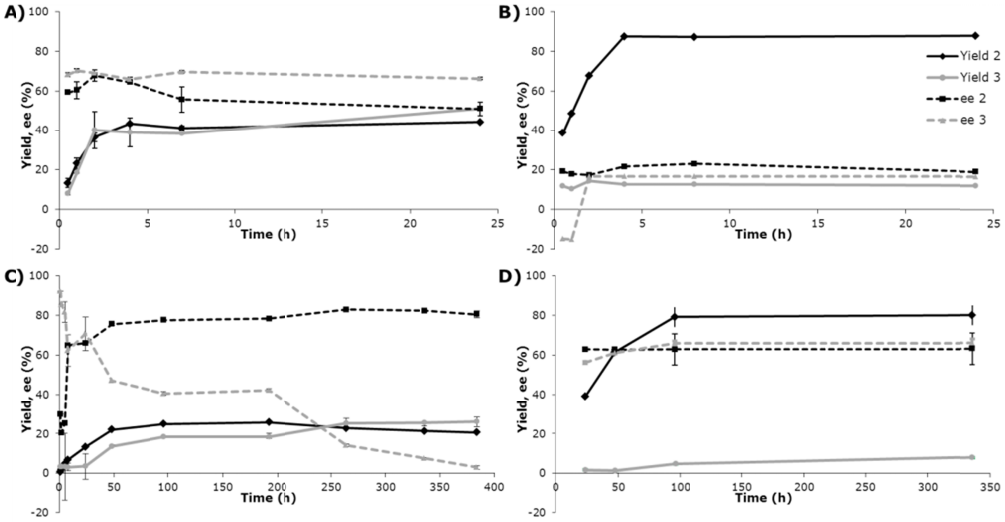


Figure 4.3. Time profile for the reaction of A; **1a**, B; **1b**, C; **1d**, D; **1a** at -18 °C.

4.2.3 Nucleophile scope.

The nucleophile scope was examined by using various alcohols. (Table 4.4). It was found that the reaction rate decreased dramatically with increasing steric bulk of the alcohol. As a consequence also the ratio of **2**/**3** decreased. A clear illustration for this are the results obtained for the addition of *i*PrOH to **1a**: after 16 days 60% of conversion of **1a** was achieved, of which only a minor fraction, i.e. 7%, was towards the alcohol addition product **2g** (Entry 3). This indicates that *i*-propanol is too large to attack the β position of the enone and the hydration reaction becomes dominant. The highest ee for the alcohol addition was obtained using *n*-propanol, that is, 86% (Entry 4).

Table 4.4. Nucleophile scope.

Entry	R'OH	Time	Conv.	Product	Ratio **2**/**3**	Ee **2**	Ee **3**
1	MeOH	4h	82%	**2a**	59/41	64%	66%
2	EtOH	11d	74%	**2f**	51/49	52%	28%
3	*i*PrOH	16d	60%	**2g**	7/93	57%	36%
4	*n*PrOH	11d	65%	**2h**	32/68	86%	36%

Conditions: 0.66 mg/ml st-DNA, 20 mM MOPS pH 6.5, 0.165 mM **L1**, 0.15 mM $Cu(NO_3)_2$, 1 mM **1a**, 40% v/v R'OH, 4 °C. All conversions and enantioselectivities are the average of triplicate experiments; all values are reproducible within +/- 2%.

A preliminary study of the DNA sequence dependence of the oxa-Michael addition, using self-complementary oligonucleotides as catalyst scaffold, showed that sequences containing a central AT segment give

rise to higher ee's than GC rich sequences (Table 4.5), a pattern that was also observed for the hydration reaction. However, the ee's obtained are lower than what is obtained with salmon testes DNA. This indicates that the optimal DNA sequence has most likely not been found to date. However, it can also not be excluded that the high methanol content of the reaction mixture affects the structure of small duplex DNAs and, hence, the enantioselectivity of the catalyzed reaction.[18] The decrease of stability of the duplexes in the presence of MeOH is obvious from the lowering of the melting temperature (T_m).

Table 4.5. DNA-sequence dependence.

Sequence	T_m (water)	T_m (40 v/v% MeOH)	Conv.	Ratio **2**/**3**	ee **2a**	ee **3a**
TCAGGGCCCTGA	41 °C	31 °C	68%	50/50	19%	25%
GCGCGCGCGCGC	50 °C	33 °C	71%	58/42	14%	31%
GCGCTATAGCGC	32 °C	21 °C	85%	53/47	36%	40%
CAAAAATTTTTG	21 °C	13 °C	82%	40/60	43%	39%

Conditions: DNA (1 mM in bp), 20 mM MOPS pH 6.5, 0.165 mM **L1**, 0.15 mM $Cu(NO_3)_2$, 1 mM **1a**, 40% v/v MeOH, 4 °C, 1d.

4.3 Conclusions

In conclusion, using the DNA-based catalysis concept, we have achieved the catalytic enantioselective intermolecular oxa-Michael addition reactions of simple achiral alcohols to enones mediated by a transition metal complex. Up to 81% ee was achieved for the addition of methanol to enones and up to 86% ee could be obtained when using *n*-propanol as nucleophile. These ee values represent the highest enantioselectivities achieved for the catalytic asymmetric intermolecular oxa-Michael addition reaction to date.

4.4 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[16,19] 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, at 400 MHz and 100 MHz, respectively. Chemical shifts (δ) are quoted in ppm using residual solvent as internal standard (δH 7.26 and δC 77.0 for CDCl3). Mass spectra were recorded on a LTQ ORBITRAP XL.

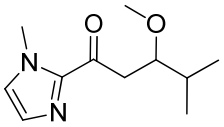
Catalytic Oxa-Michael addition, representative procedure

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 $Cu(NO_3)_2$) 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 $Cu(NO_3)_2$ 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 enone 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 ^{1}H-NMR and HPLC using a chiral stationary phase. Reaction was followed in time by taking samples at specific time points and analyzing them by NMR and HPLC

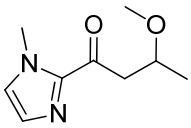
Oxa-Michael addition general synthesis of racemates

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).



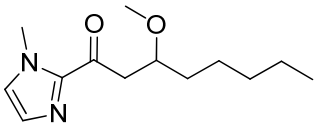
3-Methoxy-4-methyl-1-(1-methyl-1H-imidazol-2-yl) pentan-1-one (2a)

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, 1H), 3.41 (dd, *J* = 16.4, 8.4, 1H), 3.32 (s, 3H), 3.07 (dd, *J* = 16.3, 3.7, 1H), 1.95 (dq, *J* = 6.7, 1.9, 1H), 0.93 (dd, *J* = 6.8, 1.7, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 191.52 , 143.10, 128.74, 126.90, 81.82, 57.59, 40.48, 36.27, 30.71, 18.08, 17.54. HRMS: m/z: 211.14377 (M+1), (Calcd. 211.14410; M+1)



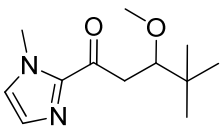
3-Methoxy-1-(1-methyl-1H-imidazol-2-yl)butan-1-one (2b)

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, 1H), 7.01 (s, 1H), 3.99 (s, 3H), 3.99 (dd, *J* = 18.0, 5.3, 1H), 3.48 (dd, *J* = 15.7, 7.5, 1H), 3.32 (s, 3H), 3.05 (dd, *J* = 15.7, 5.3, 1H), 1.24 (d, *J* = 6.2, 3H). ^{13}C- NMR (75 MHz, $CDCl_3$) 191.17, 143.87, 129.28, 127.21, 73.60, 56.35, 46.07, 36.38, 19.63. HRMS: m/z: 183.11288 (M+1), (Calcd. 183.11280; M+1)



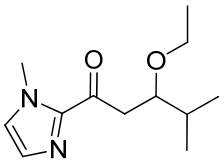
3-Methoxy-1-(1-methyl-1H-imidazol-2-yl) octan-1-one (2c)

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 (tt, *J* = 9.8, 4.8, 1H), 3.46 (dd, *J* = 16.0, 7.5, 1H), 3.33 (s, 3H), 3.10 (dd, *J* = 16.0, 4.9, 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, 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)



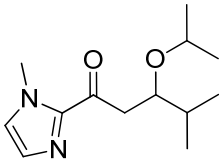
3-Methoxy-4,4-dimethyl-1-(1-methyl-1H-imidazol-2-yl)pentan-1-one (2d)

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, 1H), 3.37 (dd, *J* = 16.8, 8.1, 1H), 3.35 (s, 3H), 3.18 (dd, *J* = 16.8, 3.3, 1H), 0.94 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 192.10, 143.29, 129.07, 126.89, 85.17, 59.93, 40.81, 36.20, 35.70, 26.04. HRMS: m/z: 225.15983 (M+1), (Calcd. 225.15975; M+1)



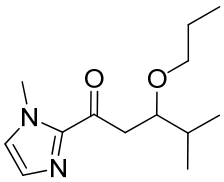
3-Ethoxy-4-methyl-1-(1-methyl-1H-imidazol-2-yl) pentan-1-one (2f)

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, 1H), 3.50 (q, *J* = 7.0, 2H), 3.37 (dd, *J* = 16.1, 7.8, 1H), 3.12 (dd, *J* = 16.1, 4.1, 1H), 1.91 (h, *J* = 6.5, 1H), 1.09 (t, *J* = 7.0, 3H), 0.95 (d, *J* = 6.8, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 191.84, 143.12, 129.00, 126.76, 80.31, 65.22, 41.21, 36.14, 31.60, 18.14, 17.98, 15.52. 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 signal is missing. HRMS: m/z: 239.17602 (M+1), (Calcd. 239.17531; M+1)



4-Methyl-1-(1-methyl-1H-imidazol-2-yl)-3-propoxy pentan-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)

4.5 References

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