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Supporting Information

69451 Weinheim, Germany

Regio- and Enantioselective Direct Oxyamination Reaction of Aldehydes Catalyzed by α,α-Diphenylprolinol Trimethylsilyl Ether

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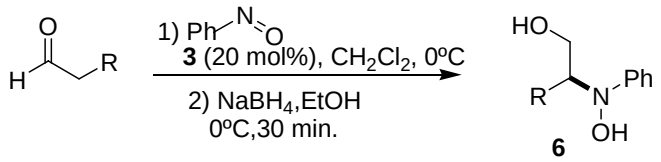
A) General information:

All reactions were carried out under nitrogen atmosphere in flame dried glassware with efficient magnetic stirring. Methylene chloride (CH_2Cl_2) was distilled from CaH_2, toluene was dried in the presence of sodium metal. Isopropanol, ethyl acetate, DMF and dimethyl sulphoxide were used as reagent grade. Purification of reaction products was carried out by flash column chromatography using silica gel 60(0.040-0.063mm, 230-400 mesh). Analytical thin layer chomatography (TLC) was performed on 0.25mm silica gel 60-F plates. Visualization was accomplished with UV Light and a solution obtained by admixing in 470 ml of water ammonium molybdate (21g), cerium sulphate (1g) and concentrated sulphuric acid (31 ml), followed by heating. Melting points were measured

with a Buchi SMP-20 melting point apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on Bruker Advance-500 and are reported in ppm from internal tetramethylsilane (TMS). Analytical high performance liquid chromatography (HPLC) was performed on waters-600E, waters-2996 and Hewlett Packard series 1050 chromatographs, equipped with diode array UV detector, using Daicel Chiralpak AD, IB and IA columns. Optical rotations were recorded on a Perkin Elmer polarimeter. MS spectra were recorded on an ESI-ion trap Mass spectrometer (Agilent 1100 series LC/MSD, SL model). Diphenylprolinol trimethylsilylether catalyst **3** was purchased from Aldrich and used without further purification.

B) General procedure for the oxyamination reaction:

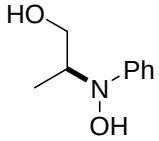
B,1) General Procedure A:



To a greenish solution of the aldehyde (6 mmol, 3 equiv.) and nitrosobenzene (2 mmol, 1 equiv.) in CH_2Cl_2 (2mL) at 0ºC was added the catalyst (0.4 mmol, 20 mol%) wherein an almost instantaneous decoloration was observed. The resulting solution was stirred at 0ºC for 30 min. EtOH (2 mL) and $NaBH_4$ (8 mmol) were successively added at the same temperature, and after stirring for 30 min. the reaction was quenched with sat. NaCl (3 ml), and allowed to reach room temperature. After extraction with CH_2Cl_2 (3 x 4ml), the combined organic phases were dried over $MgSO_4$, concentrated under reduced pressure and purified over silicagel by flash column chromatography to afford the expected adducts. The regioselectivity of the process was determined by ^{1}H-NMR analysis of the crude products and was found to be >99/1 in all cases. In addition, for the reaction of propionaldehyde **4a** the regioselectivity was also corroborated by HPLC analysis of the crude product (see HPLC chromatograms on page S15).

B,2) General Procedure B: The reaction was carried out at -20ºC. For the procedure, see Experimental Section of the paper.

(S)-2-(Hydroxy(phenyl)amino)propan-1-ol (6a)[1]

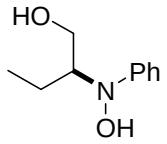


Prepared according to the general procedure with propanal (0.47 mL, 6 mmol). The crude material was purified by column chromatography on silica gel (eluting with hexane/ ethyl acetate 90/10) to give the compound as a pale yellow oil). 70% yield, (231.2mg).
Spectroscopic data are in agreement with published data. The

[1] T. Kano, M. Ueda, J. Takai, K. Maruoka *J. Am. Chem. Soc.* **2006**, *128*, 6046-6947.

enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak AD-H, hexane/ethanol 90/10, flow rate=1 mL/min, retention time; 14.5 min (min), and 15.4 min (major).

(S)-2-(Hydroxy(phenyl)amino)butan-1-ol (6b)

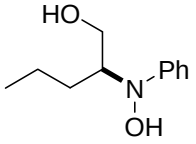


Prepared according to the general procedure with butanal (0.5 mL, 6 mmol). The crude material was purified by column chromatography on silica gel (eluting with hexane/ ethyl acetate 90/10) to give the compound as a pale yellow oil [65% yield, (235.6 mg)].

The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak IA, hexane/ethanol 98/2, flow rate=0.5 mL/min, retention time; 37.8 min (min), and 42.2 min (major). $[\alpha]_D^{25}$ = -2.8 (c=1, CH_2Cl_2).

^{1}H-RMN (500MHz, CD_3OD) δ: 7.19 (app t, 2H, J=7.6, Ar-H); δ: 7.02 (d, 2H, J=7.9, Ar-H); δ: 6.76 (app t; 1H, J=7.6, Ar-H); δ: 4.28 (t, 1H, J=5.4, CH_2-OH); δ: 3.54-3.52 (m, 1H, CH-CH_2-OH); δ: 3.46-3.40 (m, 2H, CH_2-OH); δ: 1.60-1.53 (m, 2H, CH_3-CH_2); δ: 0.90 (t, 3H, J=7.4, CH_3-CH_2). ^{13}C-RMN (75MHz, $CDCl_3$) δ: 153.14, 128.23, 120.06, 115.41, 68.61, 61.58, 48.65, 48.36, 48.08, 47.79, 47.51, 47.22, 46,94, 19.82, 10.67.

(S)-2-(Hydroxy(phenyl)amino)pentan-1-ol (6c)

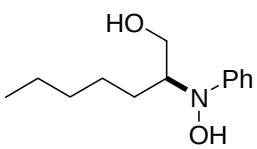


Prepared according to the general procedure with pentanal (0.6 mL, 6 mmol). The crude material was purified by column chromatography on silica gel (eluting with hexane/ ethyl acetate 90/10) to give the compound as a pale yellow oil [66% yield, (257.7mg].

The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak AD-H, hexane/ethanol 95/5, flow rate=0.5 mL/min, retention time; 10.4 min (min), and 12.7min (major). $[\alpha]_D^{25}$ = +8.6 (c=0.9, CH_2Cl_2)

^{1}H-RMN (500MHz, CD_3OD) δ: 7.19 (app t, 2H, J=7.5 Hz, Ar-H); δ: 7.02 (d, 2H, J=7.9Hz, Ar-H); δ: 6.76 (app t, 1H, J=7.5Hz, Ar-H); δ: 4.28 (t, 1H, J=5.0Hz, CH_2-OH); δ: 3.55-3.34 (m, 3H, CH-CH_2-OH); δ: 1.38-1.21(m, 4H, CH_2-CH_2); δ: 0.926 (t, 3H, J=7.3Hz, CH_2-CH_3). ^{13}C-RMN (75MHz, CD_3OD) δ: 153.11, 128.17, 120.00, 115.37, 66.70, 61.82, 29.23, 19.71, 13.24. MS (ESI, m/z): calcd for $C_{11}H_{17}NO_2$ ($M + H^+$), 196.26; found, 197.00.

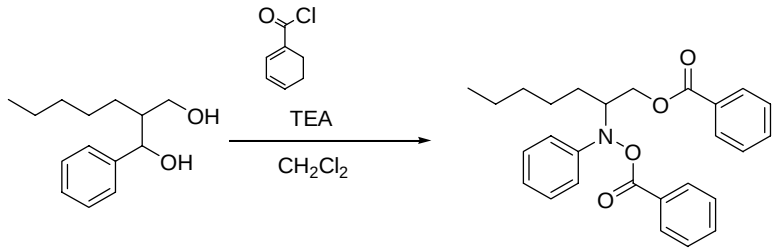
(S)-2-(Hydroxy(phenyl)amino)heptan-1-ol (6d)



Prepared according to the general procedure with heptanal (0.83 ml, 6 mmol). The crude material was purified by column chromatography on silica gel (eluting with hexane/ ethyl acetate 90/10) to give the compound as a pale yellow oil [75% yield, (334.97mg)].

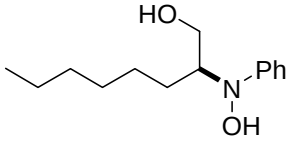
The enantiomeric purity was determined by HPLC analysis the benzoyl derivative (Daicel Chiralpak IB, hexane/ethanol 95/5, flow rate=0.5 mL/min, retention time; 13.5 min (min), and 15.6min (major).

Derivatization of 2-(*N*-phenylhydroxyamino)heptan-1-ol (6d) with benzoyl cloride



223 mg (1mmol) of 2-(*N*-phenylhydroxyamino)heptan-1-ol were solved in 2ml of anhydrous methylenechloride and triethylamine (0.8 mL, 6 mmol, 6eq) was added at room temperature. Benzoyl chloride (0.30 ml, 2.6 mmol, 2.6 eq) was dropped at the same temperature and the mixture was stirred at room temperature for 1h and then quenched with 2ml of distilled water. The product was extracted with 3x10ml of methylenechloride and the organic phase was washed with NH_4Cl (sat. sol.) and $NaHCO_3$ (sat. sol.). The organic phase was then dried over magnesium sulphate and evaporated under reduced pressure. The crude material was purified by column chromatography on silica gel (eluting with hexane / ethyl acetate = 90:10) to afford the title compound as a pale yellow solid (74%yield). MS (ESI, m/z): calcd for $C_{27}H_{29}NO_4$ ($M + H^+$), 432.21; found, 432.1.

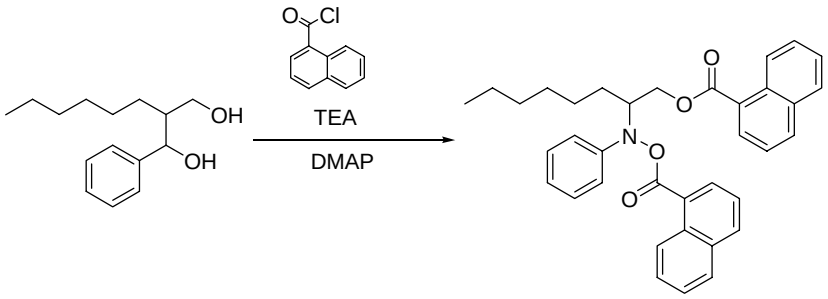
(S)-2-(Hydroxy(phenyl)amino)octan-1-ol (6e)



Prepared according to the general procedure with octanal (0.94 mL, 6 mmol). The crude material was purified by column chromatography on silica gel (eluting with hexane/ ethyl acetate 95/5) to give the compound as a pale yellow oil 75% yield.

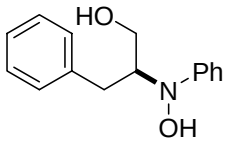
The enantiomeric was determined by HPLC analysis the naphthoyl derivative (Daicel chiralpak IA, hexane/ethanol 98/2, flow rate=0.5 mL/min, retention time; 35.8 min (min), and 39. 5min (major).

Derivatization of 2-(*N*-phenylhydroxyamino)octan-1-ol (6e) with naphthoyl cloride



118mg (0.50mmol) of 2-(*N*-phenylhydroxyamino)octan-1-ol were solved in 2ml of anhydrous dichloromethane and triethylamine (0.42 mL, 3 mmol, 6 eq) was added at room temperature. 1-Naphthoyl chloride (0.30 mL, 2 mmol, 4 eq) was dropped followed of 6 mg (0.05 mmol, 10%) of dimethylaminopyridine. The mixture was stirred at room temperature for 3h and then quenched with 2ml of distilled water. The product was extracted with 3x10ml of dichloromethane and the organic phase was washed with NH_4Cl (sat. sol.) and $NaHCO_3$ (sat. sol.). The organic phase was then dried over magnesium sulphate and evaporated under reduced pressure. The crude material was purified by column chromatography on silica gel (eluting with hexane / ethyl acetate = 90:10) to afford the title compound as a pale yellow solid [87%yield (237mg)]. MS (ESI, m/z): calcd for $C_{36}H_{37}NO_4$ ($M + H^+$), 546.26; found, 546.20.

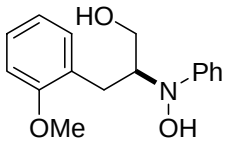
(S)-2-(Hydroxy(phenyl)amino)-3-phenylpropan-1-ol (6f)[1]



Prepared according to the general procedure with 3-phenylpropanal (0.98 mL, 6 mmol). The crude material was purified by column chromatography on silica gel (eluting with hexane/ ethyl acetate 80/20) to give the compound as a pale yellow oil[(70% yield, (340.62mg)].

Spectroscopic data are in agreement with published data. The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak AD, hexane/ethanol 60/40, flow rate=0.5 mL/min, retention time; 14.2 min (min), and 15.7 min (major).

(S)-2-(Hydroxy(phenyl)amino)-3-(2-methoxyphenyl)propan-1-ol (6g)

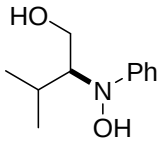


Prepared according to the general procedure with 2-methoxiphenylpropanal (0.98 mL, 6 mmol). The crude material was purified by column chromatography on silica gel (eluting with hexane/ ethyl acetate 80/20) to give the compound as a pale yellow oil [40% yield, (218.6mg)].

The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak AD, hexane/ethanol 80/20, flow rate=0.5 mL/min, retention time; 14.2 min (min), and 15.7 min (major).

^{1}H RMN (200MHZ, CD_3OD), δ: 7.20-7.13 (m, 4H, Ar-H); δ: 7.07 (appt, 1H, J=6.6Hz, Ar-H); δ: 6.94-6.82 (m, 5H, Ar-H); δ: 3.82 (s, 3H, CH_3-O-Ar); δ: 3.71-3.65 (m, 1H, Ph-HCH-CH-); δ: 3.64-3.58 (m, 1H, Ph-HCH-CH-)δ: 2.83-2.76(m, 1H, CH_2-OH); δ: 2.69-2.60 (m, 1H, CH_2-OH). ^{13}C-RMN (75MHz, CD_3OD) δ: 157.70, 157.50, 130.72, 129.51, 127.07, 126.75, 120.09, 118.70, 110.24, 72.67, 61.76, 54.45, 28.89.

(S)-2-(Hydroxy(phenyl)amino)-4-methylpentan-1-ol (6h)[1]

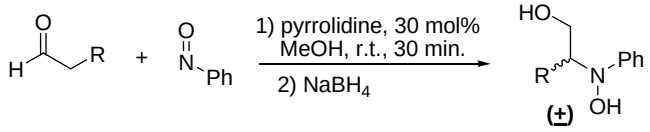


Prepared according to the general procedure with isovaleraldehyde (0.96 mL, 6 mmol). The crude material was purified by column chromatography on silica gel (eluting with hexane/ ethyl acetate 95/5) to give the compound as a pale yellow oil[(60% yield, (175.74mg)].

The enantiomeric purity was determined by HPLC analysis (Daicel Chiralpak OJ, hexane/ethanol 80/20, flow rate=0.5 mL/min, retention time; 12.1 min (major), and 13.5 min (min).

C) Preparation of racemic samples:

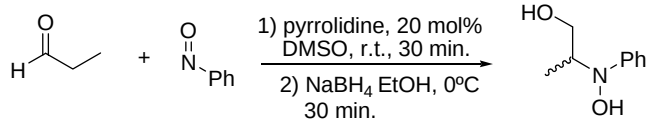
C,1) Racemic oxyaminated compounds (6a-h):



6a-h

Pyrrolidine (30 mol%, 1.2 mmol, 0.1 mL) was added to a solution of the aldehyde (12 mmol, 3 eq.) and nitrosobenzene (4mmol, 428.4 mg) in MeOH (12 mL). The mixture was stirred for 30 min. at room temperature and the cooled to 0ºC. $NaBH_4$ (16 mmol, 605 mg) was added and after 30 min. of stirring at 0ºC NaCl (sat. sol.) was dropped and the mixture extracted with CH_2Cl_2 (3 x 10 mL). The combined organic extracts were dried over $MgSO_4$, and evaporation of the solvents under vacuum afforded the expected adducts which were purified by flash column chromatography on silicagel (eluent: mixtures of hexane / ethyl acetate).

C,2) Racemic aminoxylated compound (7a)[2]:

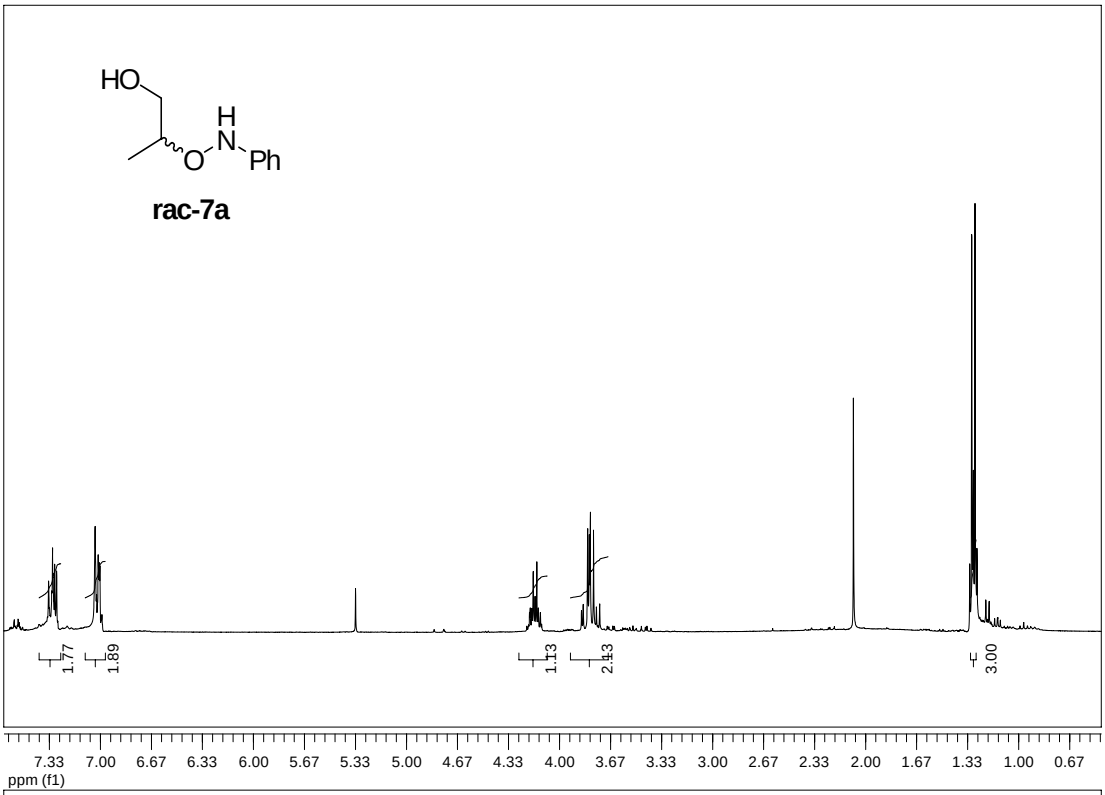


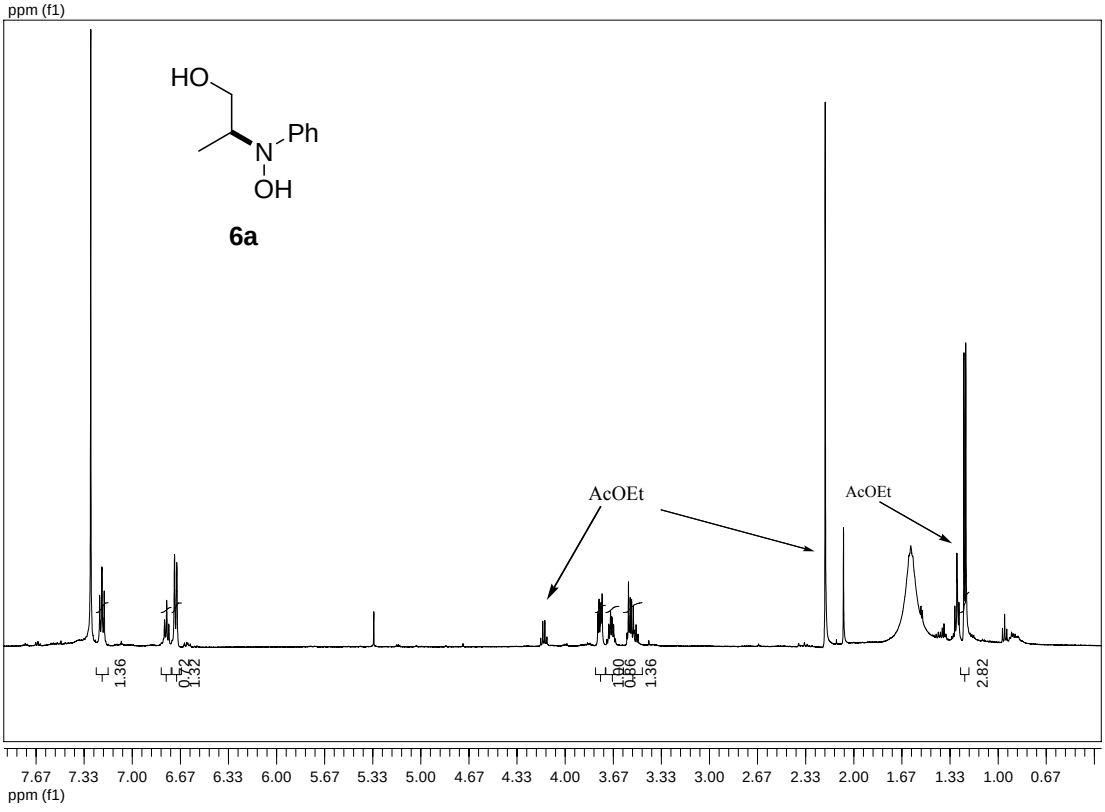
(±)-7a

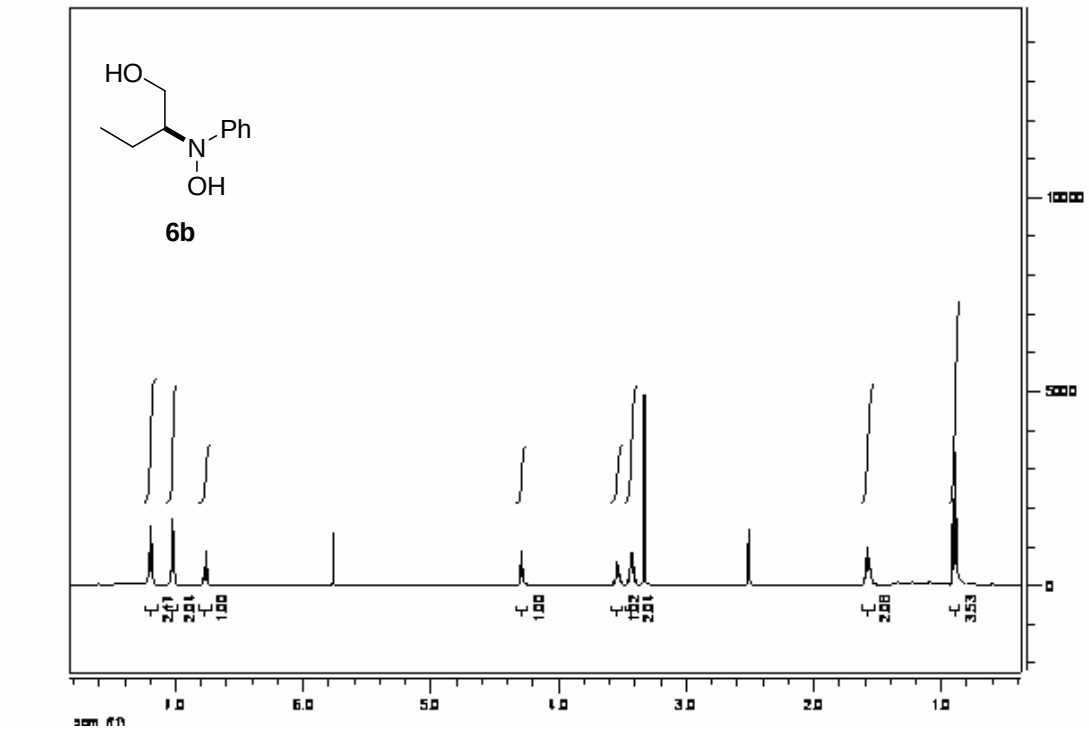
Racemic proline (0.8 mmol, 20 mol%) was added to a solution of propionaldehyde (4.8 mL, 0.34 mL) and nitrosobenzene (4 mL, 428,4 mg) in anhydrous DMSO (8 mL). The mixture was stirred for 10 min. at room temperature and then cooled to 0ºC. EtOH (4 mL) and $NaBH_4$ (16 mmol, 608 mg) were successively added and after 30 min. of stirring the reaction was quenched with sat. NaCl (10 ml), and allowed to reach room temperature. After extraction with CH_2Cl_2 (3 x 10ml), the combined organic phases were dried over $MgSO_4$, concentrated under reduced pressure and purified over silicagel by flash column chromatography to afford the expected adducts (eluent: mixtures of hexane / ethyl acetate).

[2] G. Zhong *Angew. Chem.* **2003**, *115*, 4379-4382; *Angew. Chem. Int. Ed.* **2003**, *42*, 4247-4250.

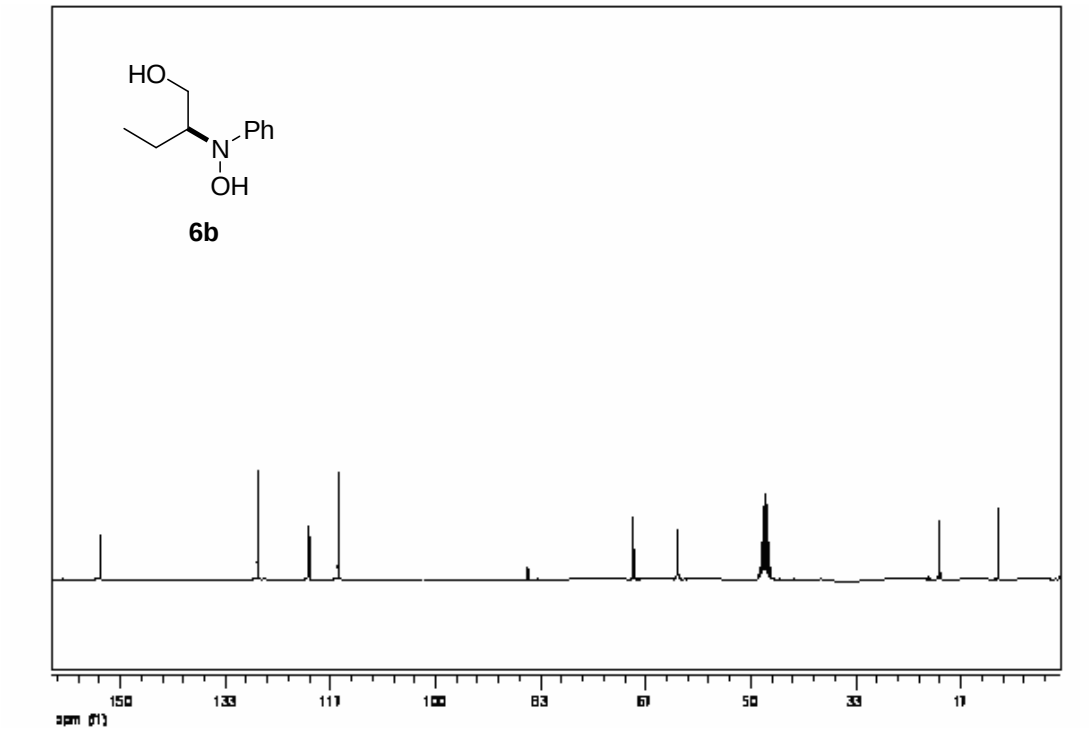
D) ^{1}H, ^{13}C-NMR and Mass spectra of some representative compounds:



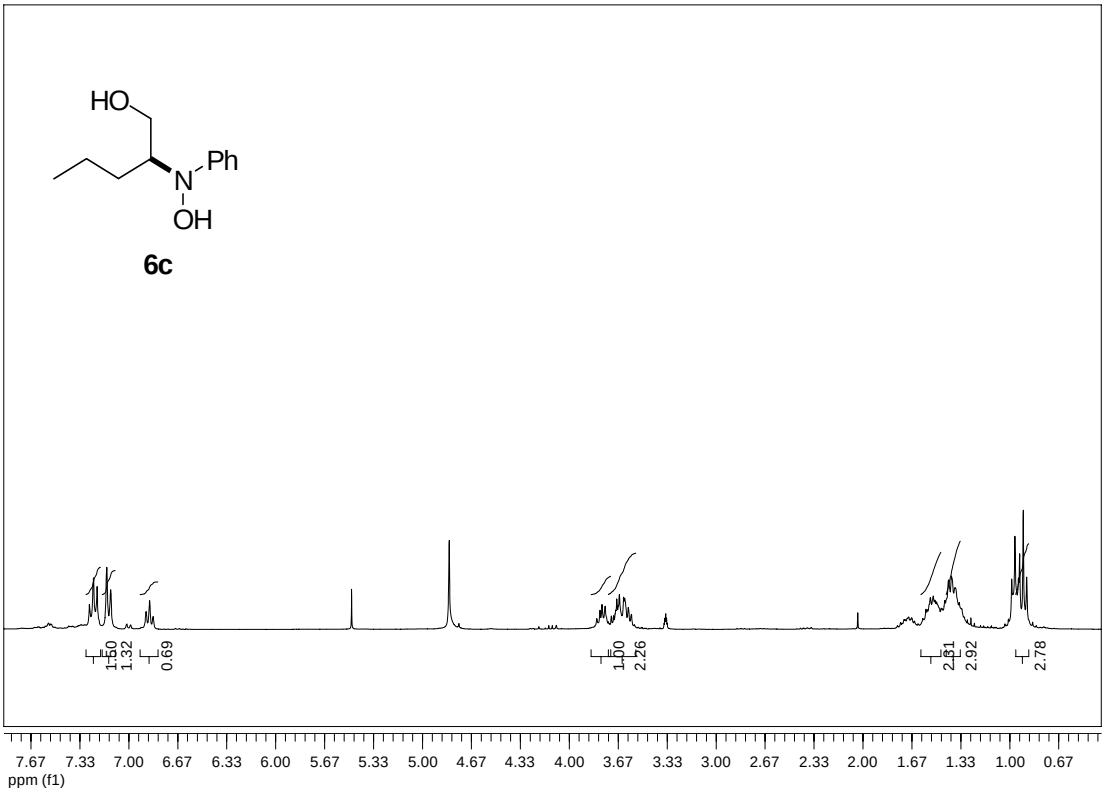




6b



6b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6c
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2.92
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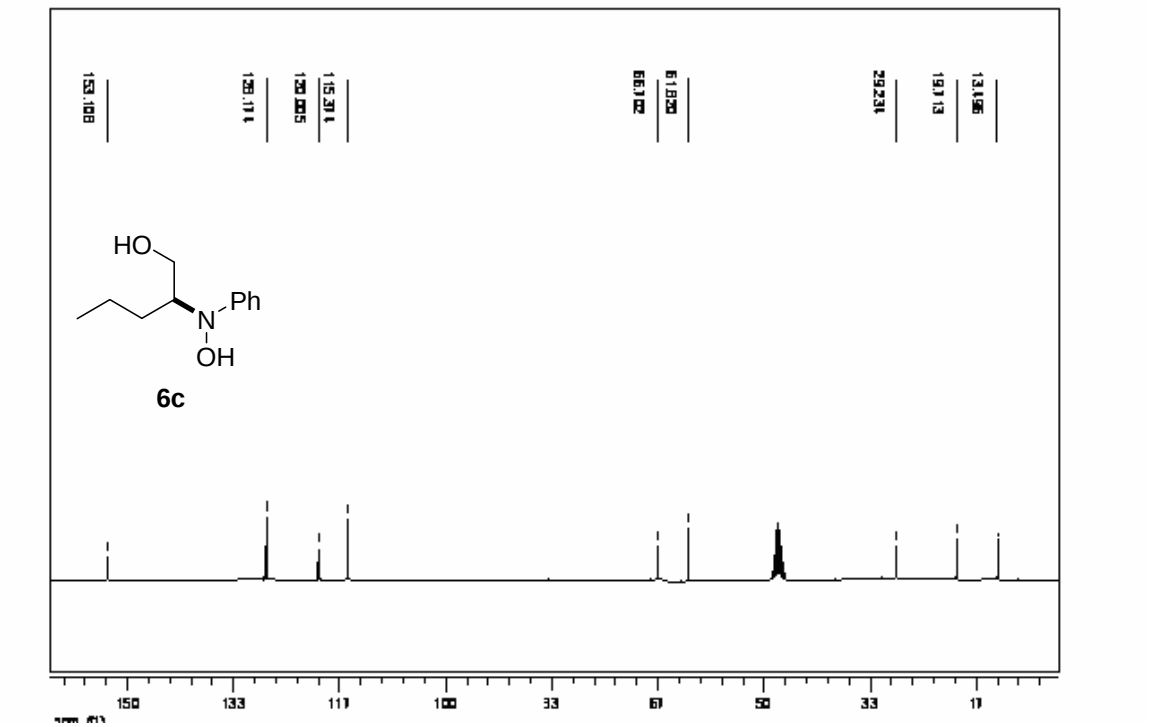
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Ph
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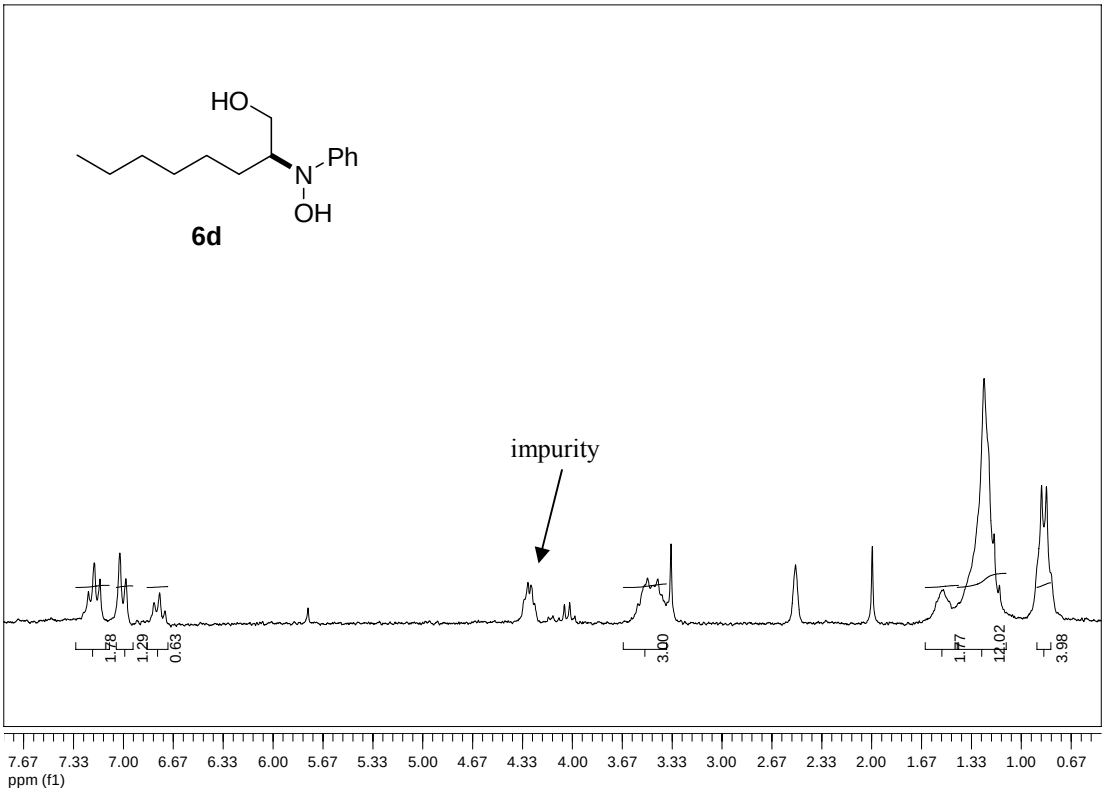
OH
6c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N
Ph
OH
6d
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3.98
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ppm (f1)

Mass Calibration Check Report - MS

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Method: REGINA.MS **Operator:** Regina **Acq. Date:** 04/16/07 13:36:37
Analysis Info: SV7.105P en MeOH/HCOOH

Acquisition Parameter:

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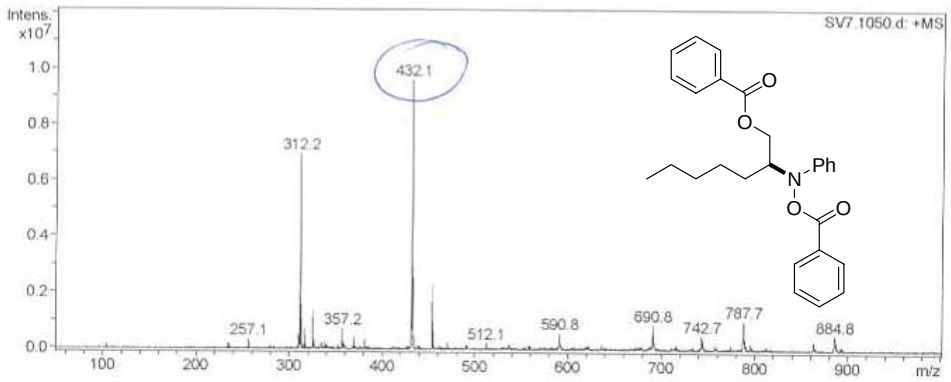
+MS



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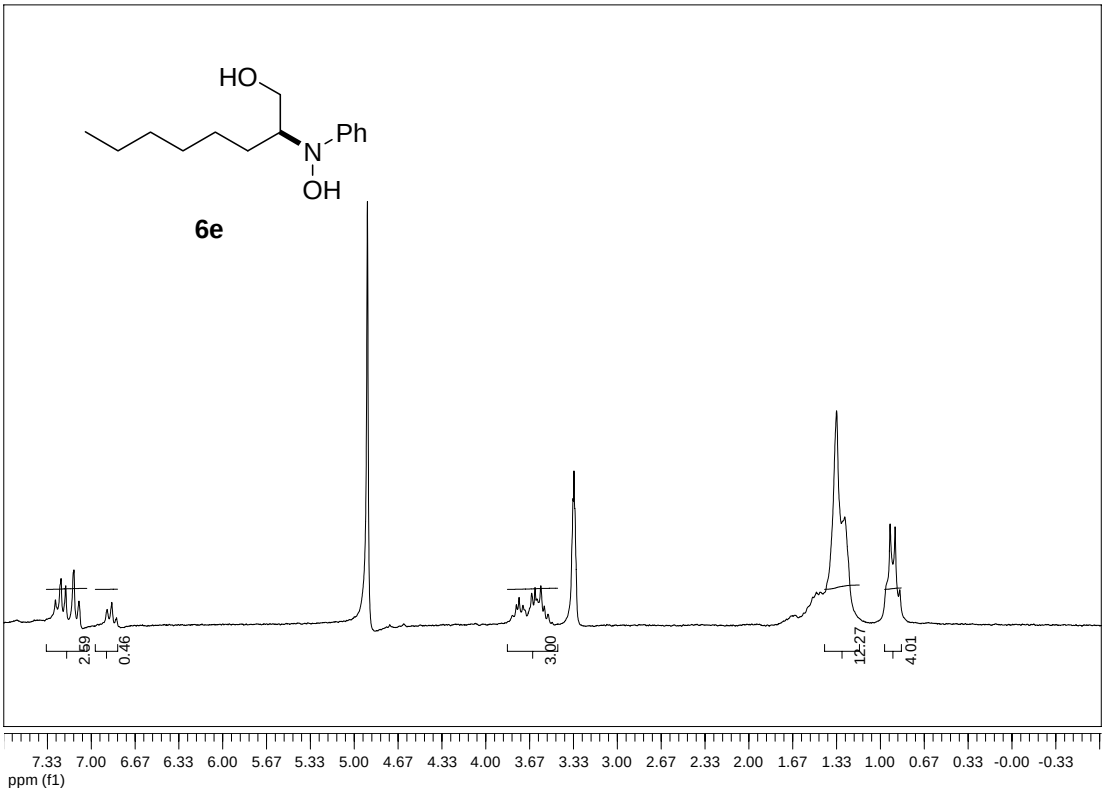
9	690.8	9
10	787.7	11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ppm (f1)

Mass Calibration Check Report - MS

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Analysis Info: IV1.81P en MeOH/HCOOH

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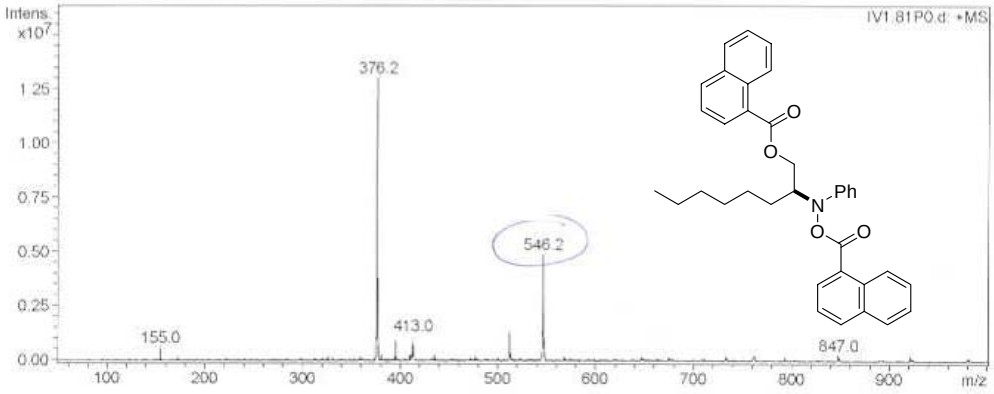
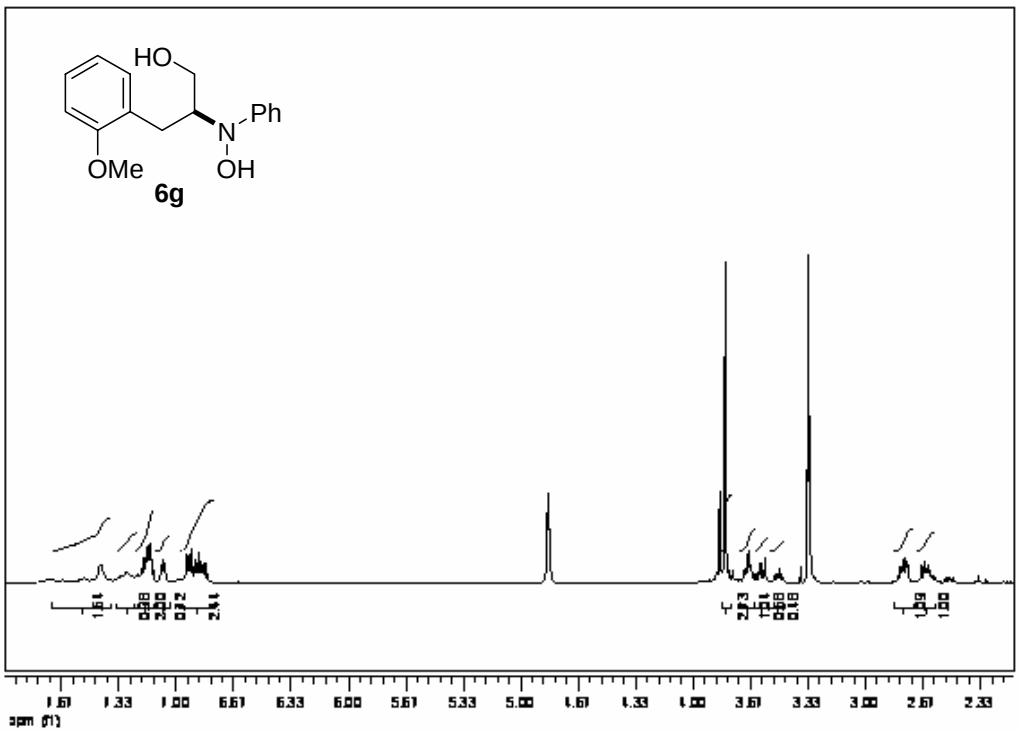
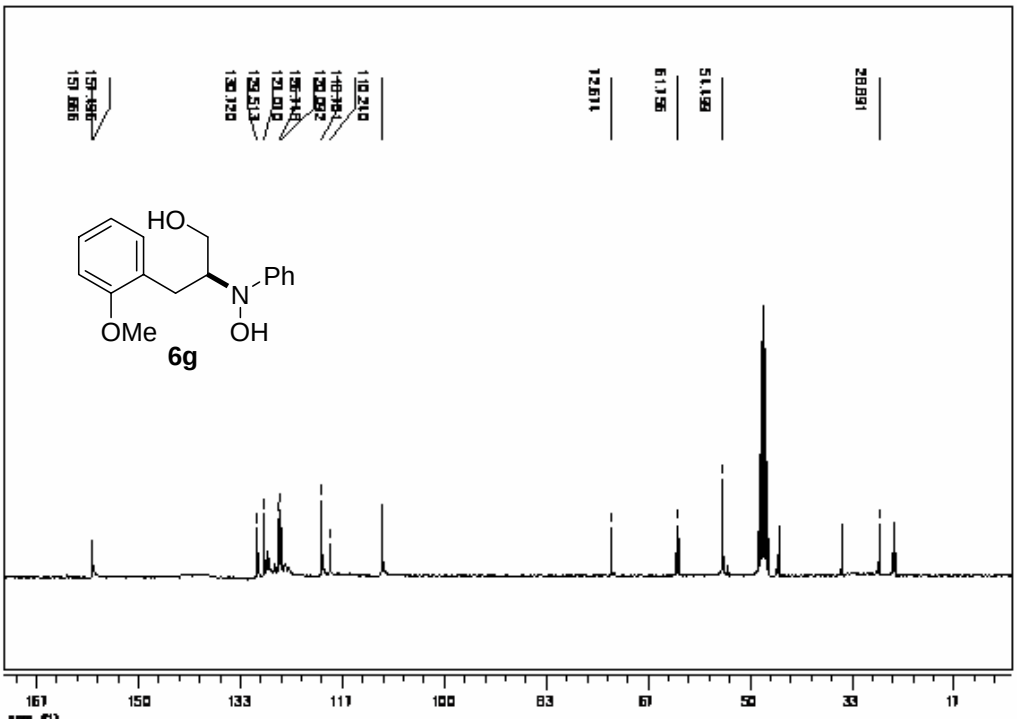
+MS



MS Peak List:

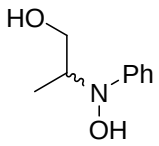
#	m/z	I %
1	155.0	5
2	376.2	100
3	377.1	29
4	378.1	5
5	395.2	8
6	413.0	9
7	512.1	10
8	513.1	3
9	546.2	38
10	547.1	16


HO
Ph
N
OMe
OH
6g


HO
Ph
N
OMe
OH
6g

E) HPLC-chromatograms of selected compounds:

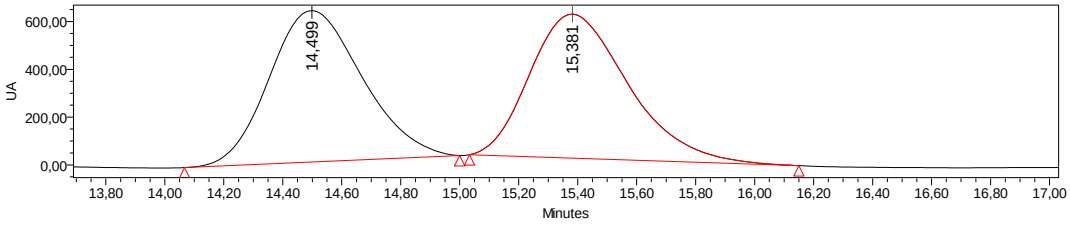
Chiralpak AD-H, 1ml/min, hexane/ethanol 90:10, λ= 254nm



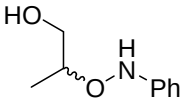
rac-6a

Processed Channel Descr.: 210nm

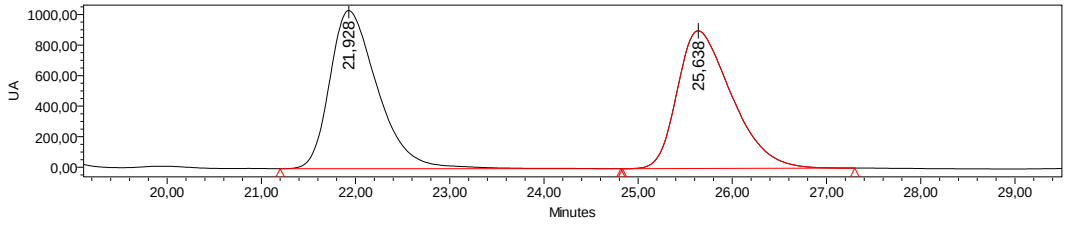
	Processed Channel Descr.	RT	Area	% Area	Height
1	210nm	14,499	4110156	49,70	196042
2	210nm	15,381	4160100	50,30	186813



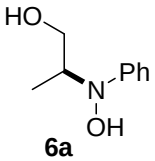
Chiralpak AD-H, 1ml/min, hexane/ethanol 90:10, λ= 254nm



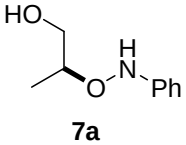
rac-7a



Chiralpak AD-H, 1ml/min, hexane/ethanol 90:10, λ= 254nm



6a

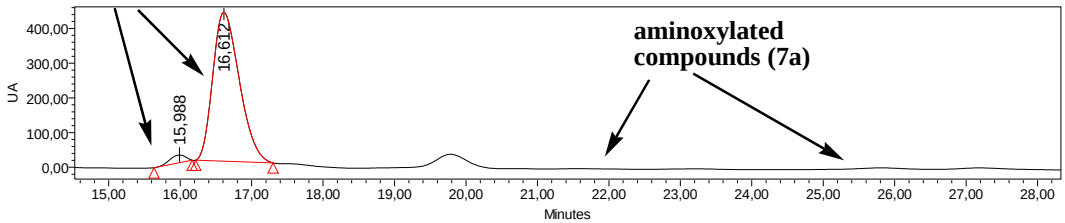


7a

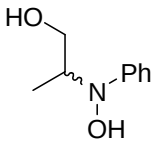
crude reaction of **4a** and **5**

oxyaminated compounds (6a)

aminoxylated compounds (7a)



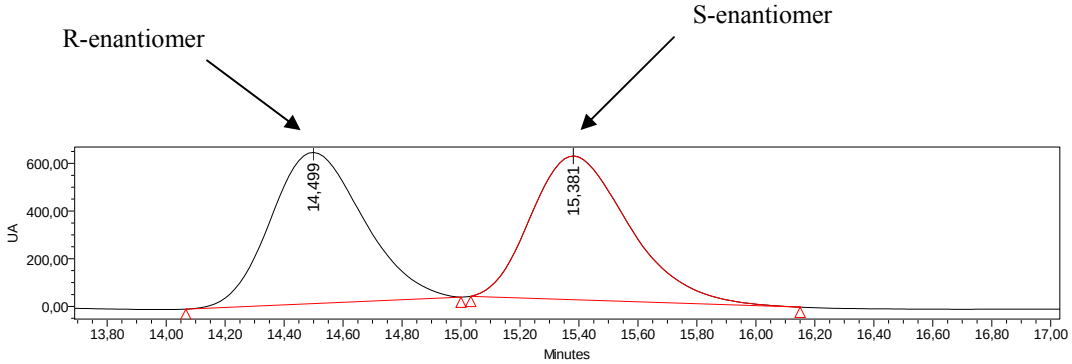
Chiralpak AD-H, 1ml/min, hexane/ethanol 90:10, λ= 254nm

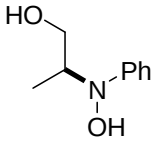


rac-6a

Processed Channel Descr.: 210nm

	Processed Channel Descr.	RT	Area	% Area	Height
1	210nm	14,499	4110156	49,70	196042
2	210nm	15,381	4160100	50,30	186813

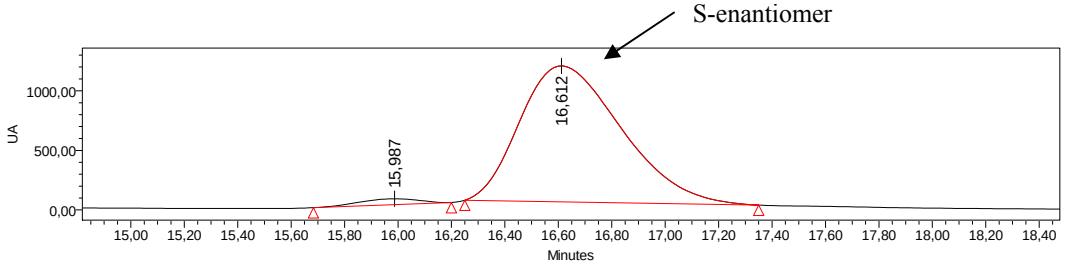




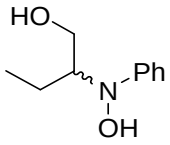
6a

Processed Channel Descr.: 210nm

	Processed Channel Descr.	RT	Area	% Area	Height
1	210nm	15,988	343789	3,00	22147
2	210nm	16,612	11131387	97,00	430271



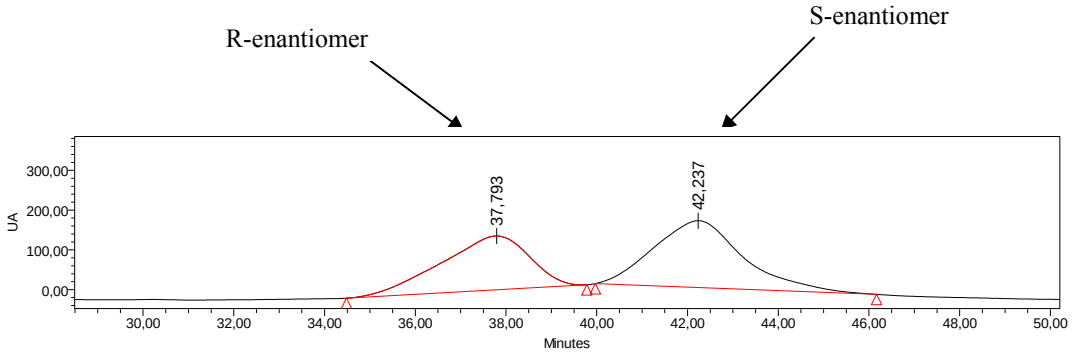
Chiralpak IA, 0.5ml/min, hexane/ethanol 98:2, λ= 210nm

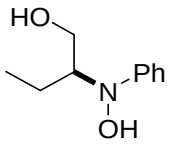


rac-6b

Processed Channel Descr.: 210nm

	Processed Channel Descr.	RT	Area	% Area	Height
1	210nm	37,793	18323686	44,38	135114
2	210nm	42,237	22964465	55,62	168012

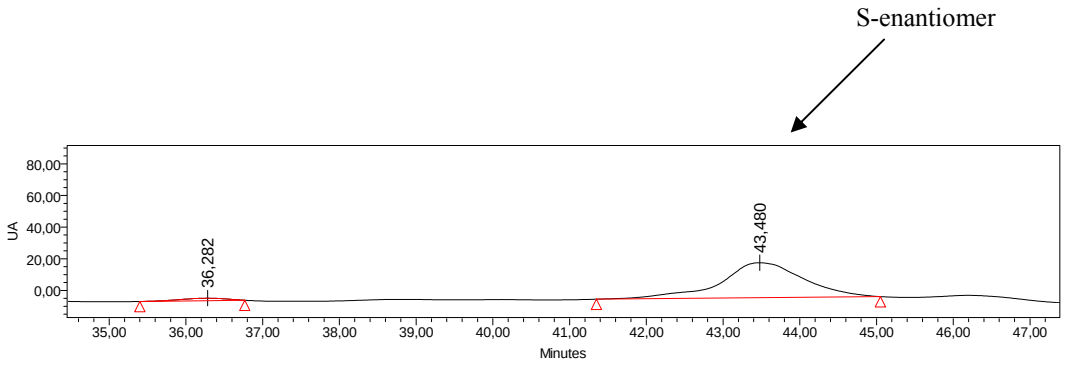




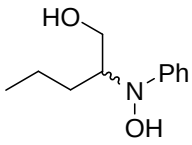
6b

Processed Channel Descr.: 210nm

	Processed Channel Descr.	RT	Area	% Area	Height
1	210nm	36,282	66075	3,81	1583
2	210nm	43,480	1666197	96,19	22095



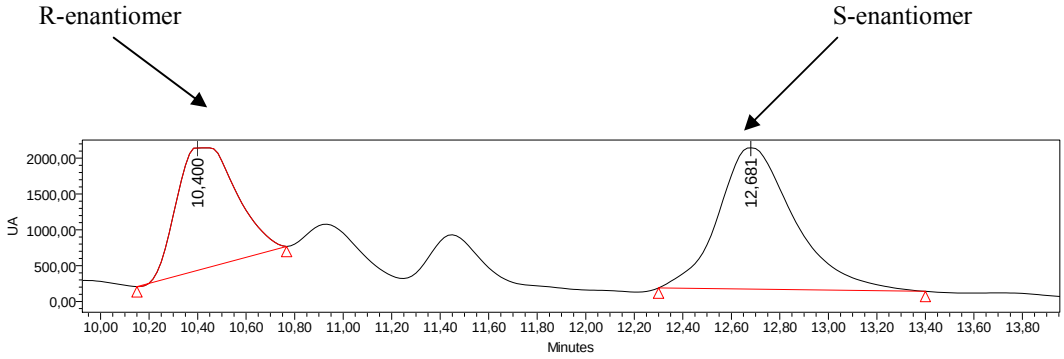
Chiralpak AD-H, 0.5ml/min, hexane/ethanol 95:5, λ= 254nm

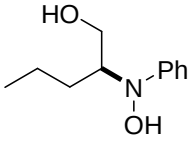


rac-6c

Processed Channel Descr.: 254nm

	Processed Channel Descr.	RT	Area	% Area	Height
1	254nm	10,400	29078556	40,24	1727361
2	254nm	12,681	43183408	59,76	1974686

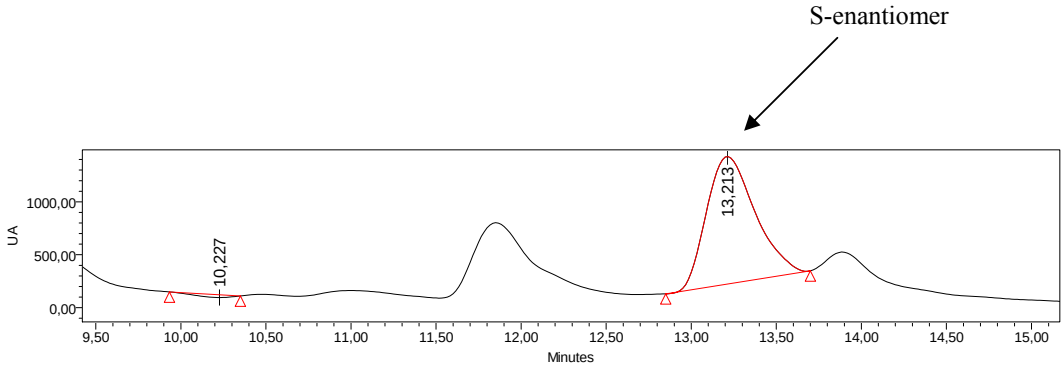




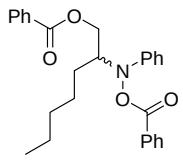
6c

Processed Channel Descr.: 254nm

	Processed Channel Descr.	RT	Area	% Area	Height
1	254nm	10,227	392285	1,62	-26024
2	254nm	13,213	23883775	98,38	1205036



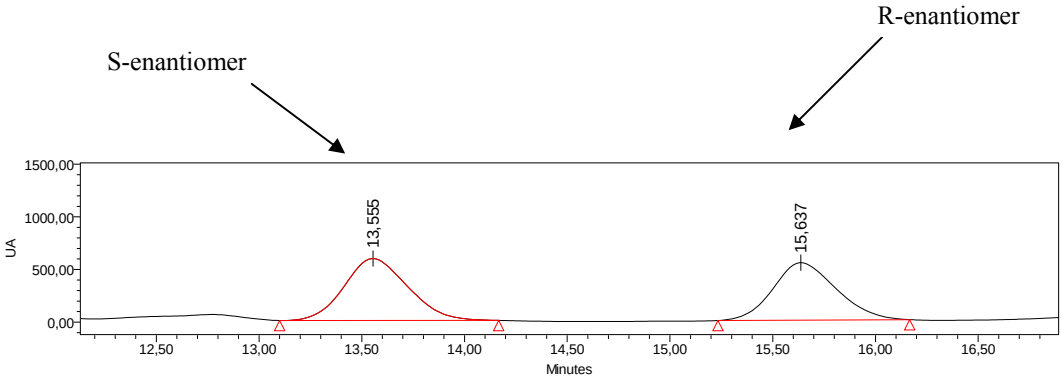
Chiralpak IB, 0.5ml/min, hexane/ethanol 95:5, λ= 210nm

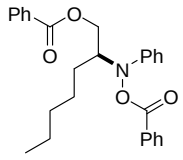


From rac-6d

Processed Channel Descr.: 210nm

	Processed Channel Descr.	RT	Area	% Area	Height
1	210nm	13,555	12649898	52,02	588381
2	210nm	15,637	11667089	47,98	546147

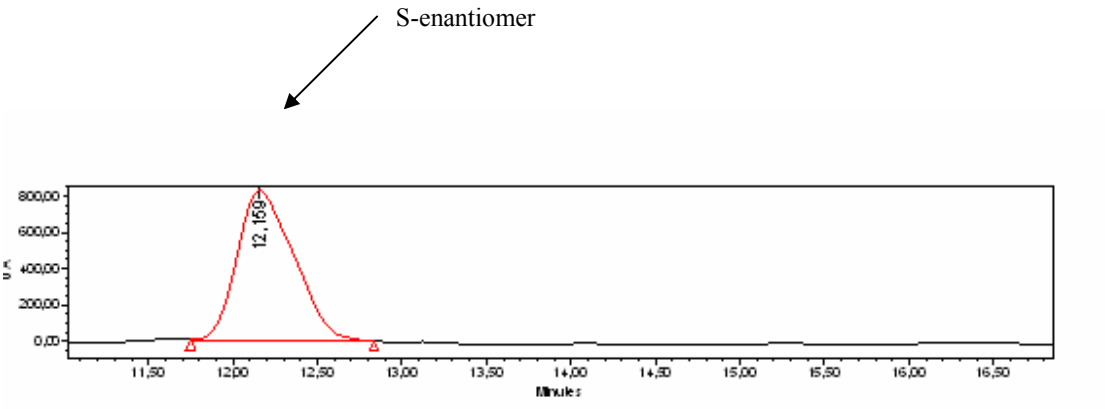




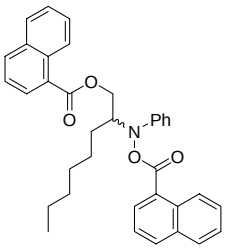
From 6d

Processed Channel Descr.: 210nm

	Processed Channel Descr.	RT	Area	% Area	Height
1	210nm	12,159	19112161	100,00	822464



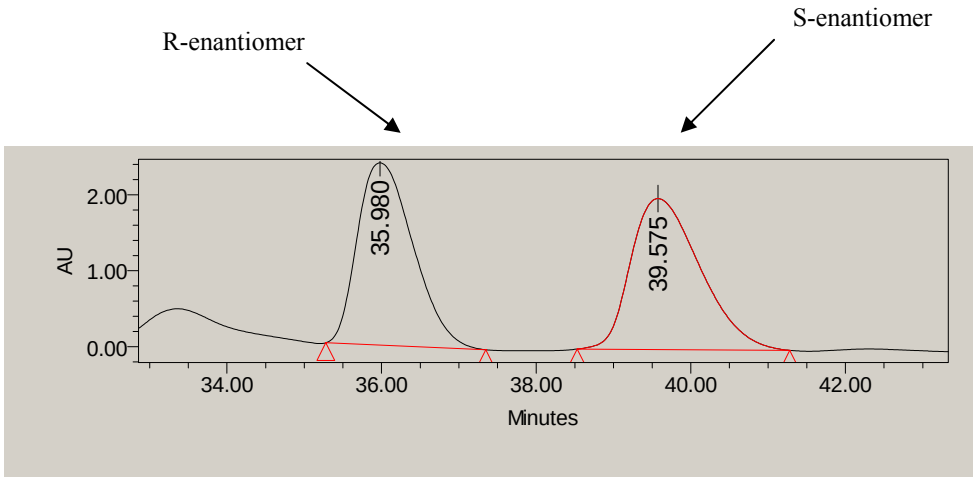
Chiralpak IA, 0.5ml/min, hexane/ethanol 98:2, λ= 241nm

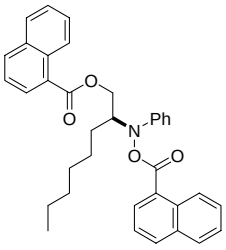


From rac-6c

Processed Channel Descr.: PDA 241.3 nm

	Processed Channel Descr.	RT	Area	% Area	Height
1	PDA 241.3 nm	35.980	119973107	49.25	2398904
2	PDA 241.3 nm	39.575	123617932	50.75	1987556

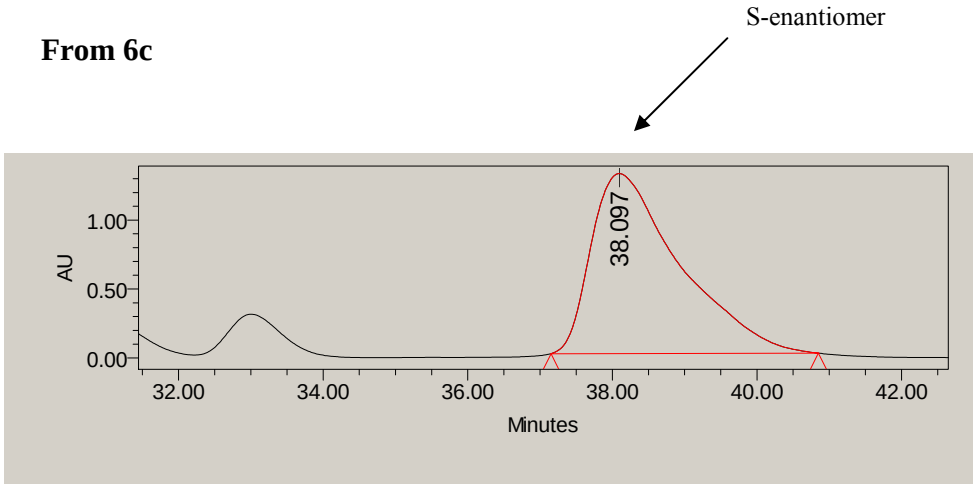




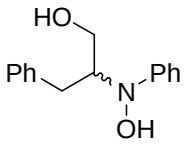
From 6c

Processed Channel Descr.: PDA 241.3 nm

	Processed Channel Descr.	RT	Area	% Area	Height
1	PDA 241.3 nm	38.097	114184533	100.00	1321137



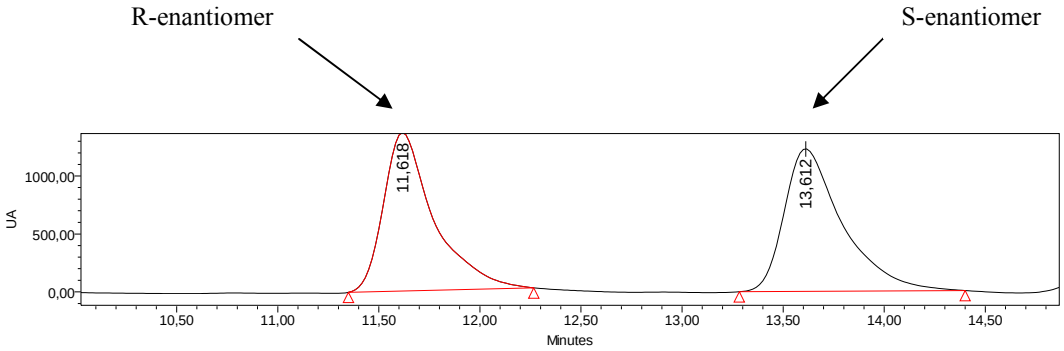
Chiralpak AD 0.5ml/min, hex/etanol 60:40, λ= 210nm

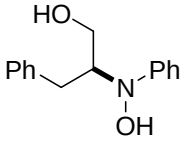


rac-6f

Processed Channel Descr.: 210nm

	Processed Channel Descr.	RT	Area	% Area	Height
1	210nm	11,618	23871251	49,67	1370743
2	210nm	13,612	24184319	50,33	1225824

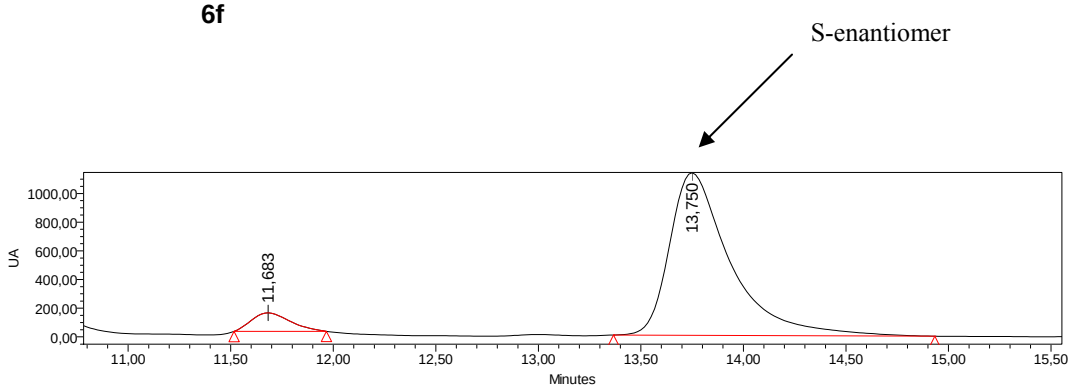




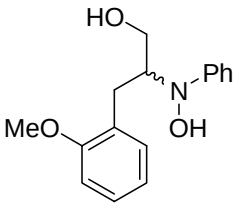
6f

Processed Channel Descr.: 210nm

	Processed Channel Descr.	RT	Area	% Area	Height
1	210nm	11,683	1252184	5,09	109700
2	210nm	13,750	23329693	94,91	1134737



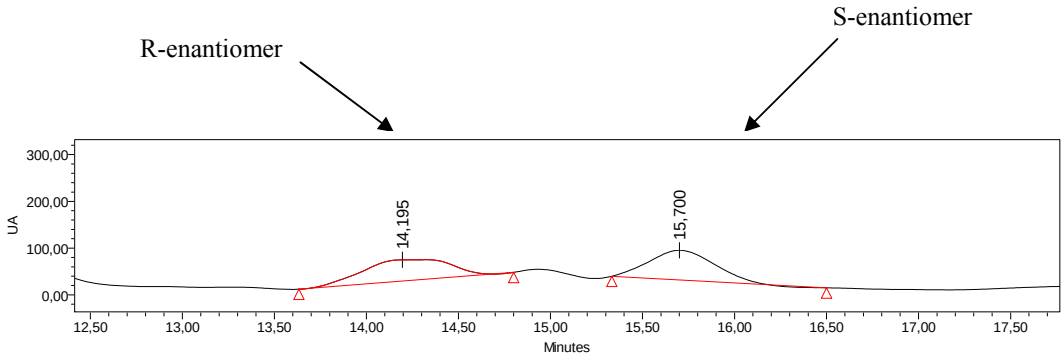
Chiralpak AD 0.5ml/min, hexane/ethanol 80:20, λ= 210nm

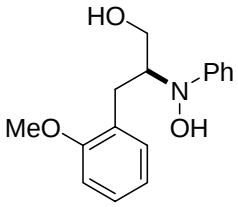


rac-6g

Processed Channel Descr.: 210nm

	Processed Channel Descr.	RT	Area	% Area	Height
1	210nm	14,195	1500365	48,35	45521
2	210nm	15,700	1602711	51,65	63227

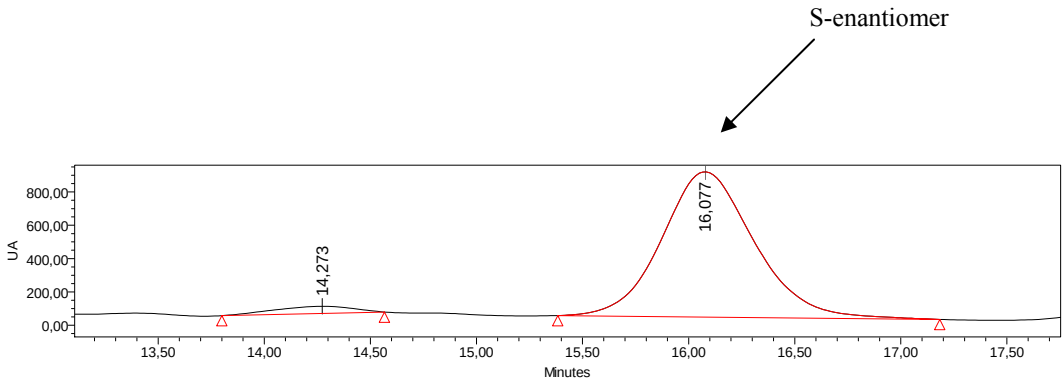




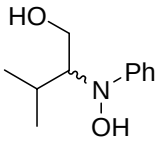
6g

Processed Channel Descr.: 210nm

	Processed Channel Descr.	RT	Area	% Area	Height
1	210nm	14,273	1107300	4,02	42609
2	210nm	16,077	26470545	95,98	871766



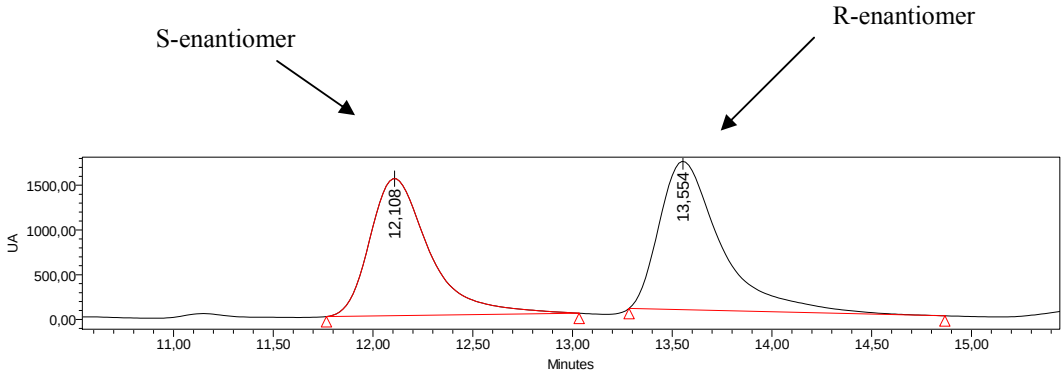
Chiralcell OJ, 0.5ml/min, hexane/ethanol 80:20, λ= 210nm

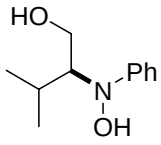


rac-6h

Processed Channel Descr.: 210nm

	Processed Channel Descr.	RT	Area	% Area	Height
1	210nm	12,108	31917157	47,12	1534417
2	210nm	13,554	35819862	52,88	1659941

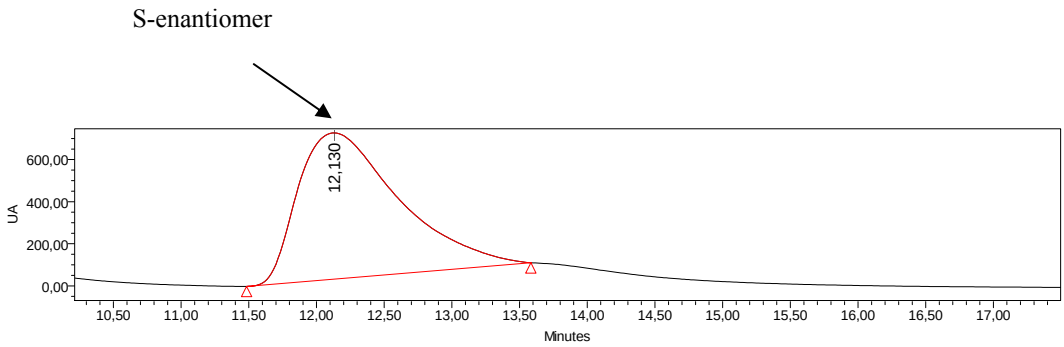




6h

Processed Channel Descr.: 210nm

	Processed Channel Descr.	RT	Area	% Area	Height
1	210nm	12,130	35998747	100,00	694706



F) Preliminary mechanistic observations by computational methods

All structures were computed using the functional B3LYP[3] and the 6-31G* basis sets as implemented in Gaussian 03.[4,5] All energy minima and transition structures were characterized by frequency analysis. The energies reported in this work include the zero-point vibrational energy corrections (ZPVE). The stationary points were characterized by frequency calculations in order to verify that they have the right number of negative eigenvalues. The intrinsic reaction coordinates (IRC)[6] were followed in order to verify the energy profiles connecting each TS to the correct associated local minima. As a model reaction, we chose the addition of propionaldehyde to nitrosobenzene catalyzed by naked pyrrolidine.

We assumed that the oxyamination and aminoxylation occur through a similar mechanism to that of the proline catalyzed aldol reactions, involving initial formation of the enamine between the aldehyde and pyrrolidine with concomitant loosing of a molecule of water.[7] This step should not interfere in neither the reactivity nor the stereoselectivity of the final process. Our catalytic system does not include any additive capable to activate the reaction through hydrogen bonding. We hypothesized that either the molecule of water liberated during the enamine formation step or the final product of the reaction could act as hydrogen bonding promoters, as they possess hydrogen donor sites to bind either the nitrogen or the oxygen of nitrosobenzene. To check this possibility and get some insight into the origin of the activation and the regioselectivity of the reaction, we computed and compared the activation energies for the non-catalyzed, the water catalyzed reaction and the catalysis by one molecule of *N*,*N*-dimethyl hydroxylamine **8**, a model molecule that mimics **6**, the final product of the addition.
As found by others,[5a] the non-catalyzed reaction is regioselective, and there is a net preference for formation of the C-N (oxyamination, TS_N) bond against the C-O bond (aminoxylation, TS_O) ($\Delta\Delta G^{\ddagger}$ = 3.0 kcal/mol).

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[3] Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648-5652. Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev. B* **1988**, *37*, 785-789

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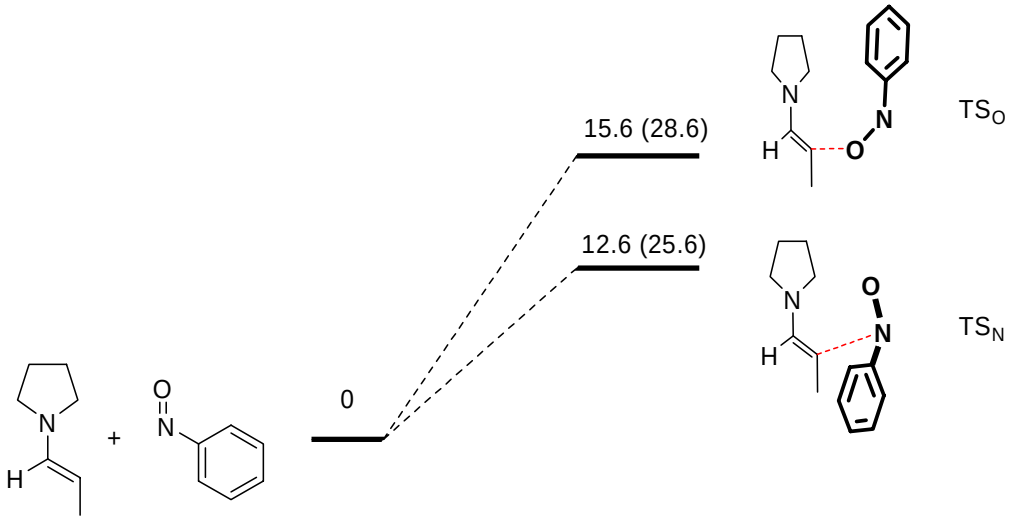

Figure S1. Activation barriers for the non-catalyzed reaction between propionaldehyde-enamine and nitrosobenzene. $\Delta E^{\ddagger}$ values are given in kcal/mol and $\Delta G^{\ddagger}$ are shown in parenthesis.

We also computed the reaction in the presence of 1 molecule of water. The oxygen in nitrosobenzene has two possible hydrogen bonding sites, the lone pairs *syn* and *anti* to the phenyl ring. It leads to two possible transition states for the water catalyzed oxyamination reaction, namely TS$_N$**water**syn and TS$_N$**water**anti. In the aminooxylation, coordination of water to nitrogen has only one possibility (TS$_O$**water**). The free energy activation barriers are lowered in ca. 5 kcal/mol for the three cases in comparison to the non-catalyzed reaction, the lowest ones corresponding to TS$_N$**water**syn and TS$_N$**water**anti (20.9 kcal/mol). In this transition structure, the water-hydrogen binds the nitrosobenzene-oxygen through a strong hydrogen bond (1.8 Å). Besides, water-oxygen forms two weak hydrogen bonds, with one H-C of the pyrrolidine ring (2.41 Å)[8] and with a H-C of the phenyl ring[9] (2.38 Å in *syn* approach).

[8] For precedents on the participation of methylene hydrogens of the pyrrolidine ring in intramolecular hydrogen bonding in a related aldol reaction, see ref 5b. For computational studies on related R_3N^+-C-H···O hydrogen bonding, see: Cannizzaro, C. E.; Houk, K. N. *J. Am. Chem. Soc.* **2002**, *124*, 7163-7169.

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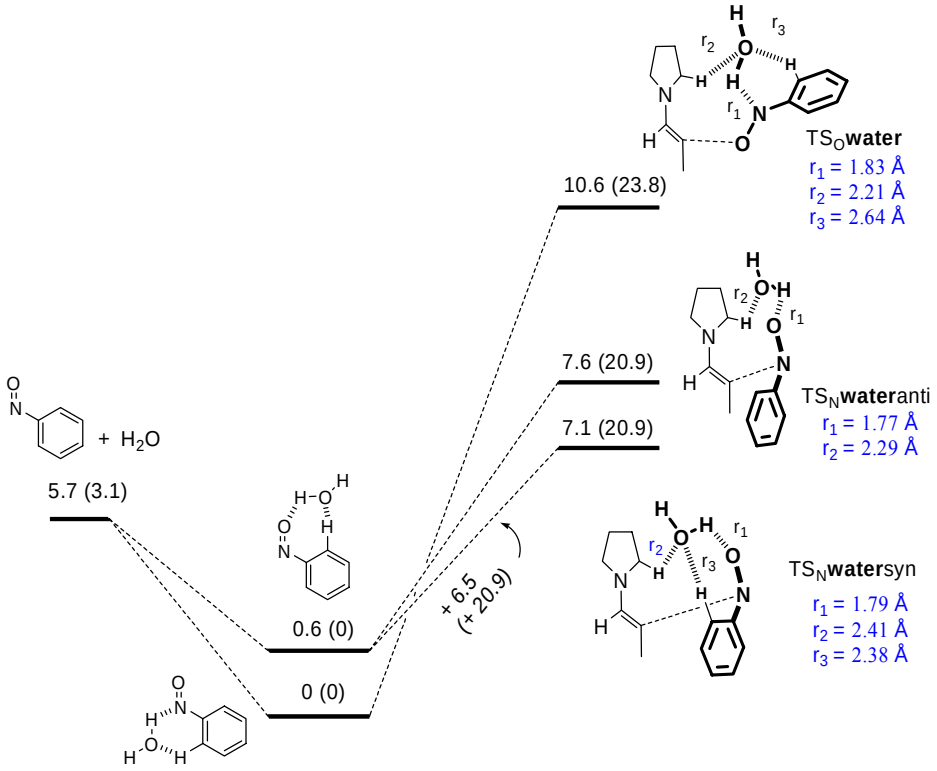

Figure S2. Activation barriers for the oxyamination and aminoxylation reactions between propionaldehyde-enamine and nitrosobenzene in the presence of one molecule of water. $\Delta E^{\ddagger}$ values are given in kcal/mol and $\Delta G^{\ddagger}$ are shown in parenthesis.

A similar scenario was found when we computed the reaction in the presence of 1 molecule of *N*,*N*-dimethylhydroxylamine **8**. The same reasoning as before leads to the formation of three different transition states, two for the aminooxylation (TS_N**8**syn and TS_N**8**anti) and one for the oxyamination (TS_O**8**).

The activation barriers are lowered in ca. 4 kcal/mol for the three cases, indicating a similar activation properties of water and **8**. The lowest transition state corresponds to TS_N**8**anti (21.4 kcal/mol), slightly more favourable than TS_N**8**syn (22.8 kcal/mol). The order of preference between both gets switched in favour of the anti approach, if compared to the water promoted system. This is probably due to the relatively greater steric bulkiness of **8**, which provokes some steric repulsion between **8** and the pyrrolidine ring in TS_N**8**syn. These transition structures present again the same type of weak interactions (r_2 and r_3) as those mentioned for water.

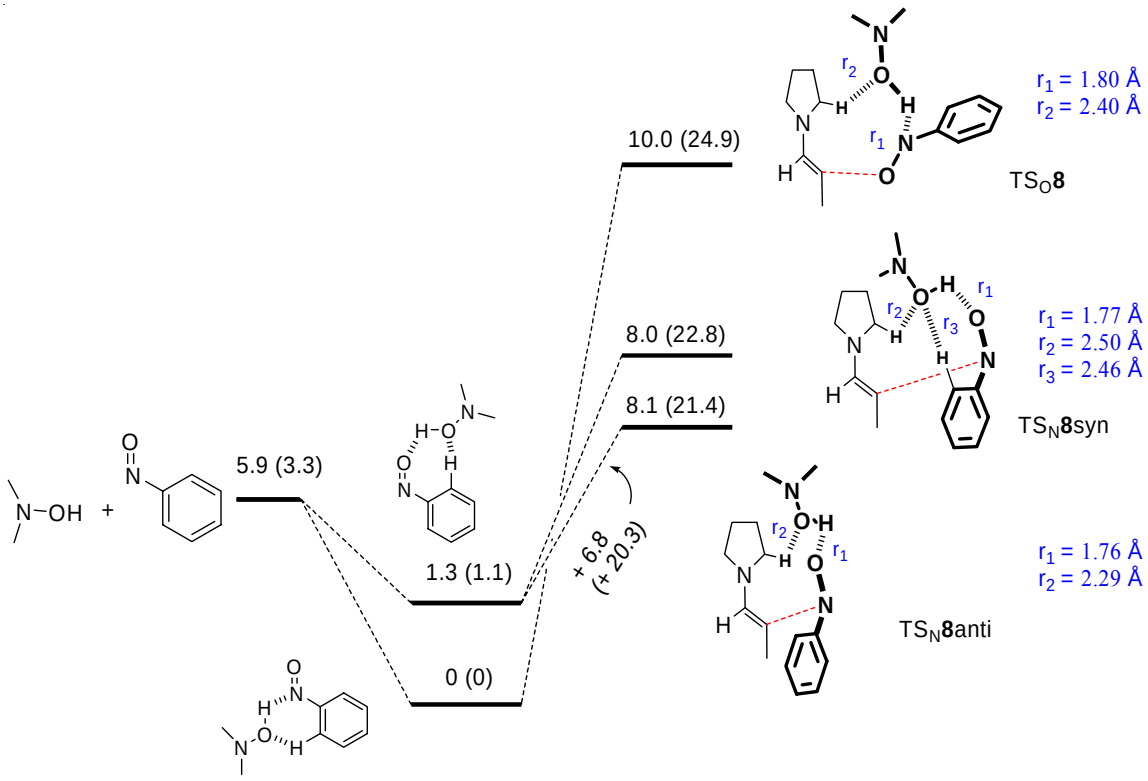

Figure S3. Activation barriers for the oxyamination and aminoxylation reactions between propionaldehyde-enamine and nitrosobenzene catalyzed by **8**. $\Delta E^{\ddagger}$ values are given in kcal/mol and $\Delta G^{\ddagger}$ are shown in parenthesis.

The IRC calculation proofs the connection between transition structures, initial reactants and zwitterionic intermediates, as outlined in Figure S4 for the most favourable reaction coordinate in the case of the water-promoted reaction (TS_N**water**syn). As the reaction proceeds, the increase in the charge in the oxygen of the nitrosobenzene induces a shortening of the H···O=N bond, with distances of 2.04 Å in the starting reactant, 1.79 Å in the transition structure and 1.74 Å in the zwitterionic intermediate. The transition structure is quite late (forming C-C bond distance: 1.84 Å) and presents great similarity with the reaction product. The highly energetic zwitterionic intermediate should lead to the final product by protonation and hydrolysis.

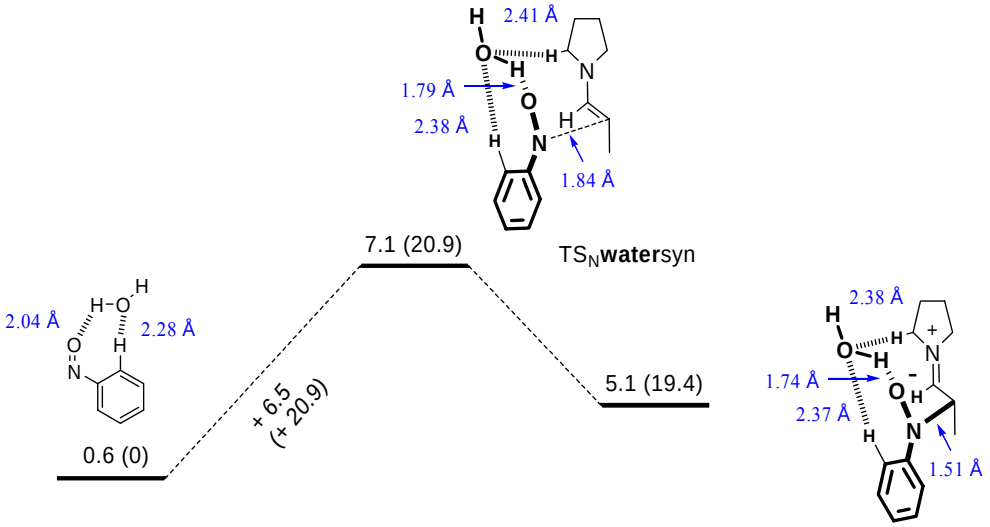

Figure S4. Reaction coordinate for the enamine addition to nitrosobenzene in the presence of one molecule of water.

Cartesian coordinates of the Stationary points of the aminooxylation and oxyamination reactions between propionaldehyde and nitrosobenzene catalyzed by pyrrolidine. HF energies correspond to the corrected energy + ZPVE and to the free energy of activation in hartrees.

TS_N

HF= -690.532480, -690.574811
Freq: -325.6

Atom	X	Y	Z
C	-2.1844	-1.4007	-0.9030
H	-2.1463	-1.2805	-1.9928
N	-1.8744	-0.1210	-0.2324
C	-0.8867	0.6803	-0.6631
C	-0.3234	1.6935	0.1494
H	-0.9920	2.1414	0.8820
N	0.4967	0.6456	1.3424
O	-0.3836	-0.0136	1.9928
C	1.5349	-0.2124	0.7597
C	2.7406	0.3613	0.3390
H	2.8754	1.4357	0.4029
C	3.7753	-0.4509	-0.1270
H	4.7087	0.0027	-0.4514
C	3.6251	-1.8389	-0.1551
H	4.4361	-2.4700	-0.5087
C	2.4332	-2.4113	0.3013
H	2.3170	-3.4928	0.3017
C	1.3967	-1.6051	0.7651
H	0.4740	-2.0183	1.1575
C	-2.9563	0.2745	0.6934
H	-2.5378	0.7200	1.5933
H	-3.6210	0.9971	0.1930
C	-3.6789	-1.0473	0.9603
H	-3.1378	-1.6045	1.7326
H	-4.7087	-0.8985	1.2981
C	-3.5860	-1.7732	-0.3929
H	-3.7209	-2.8558	-0.3144
H	-4.3515	-1.3906	-1.0785
C	0.6123	2.6957	-0.4850
H	0.0421	3.4928	-0.9777
H	1.2602	2.2322	-1.2356
H	1.2433	3.1595	0.2803
H	-0.3305	0.3191	-1.5241
H	-1.4353	-2.1478	-0.6204

TS_O

HF= -690.527765, -690.569957
Freq: -402.5

Atom	X	Y	Z
C	-0.4571	2.6518	0.4470
C	-0.8455	1.4474	1.3120
C	-2.1753	1.4451	-0.7426
C	-2.2244	-0.5289	0.7990
C	-3.3029	-2.7471	0.2504
C	-2.6244	-1.4731	-0.1832
C	-1.7030	2.8725	-0.4270
H	-3.2639	1.3687	-0.8437
H	-1.4940	3.4443	-1.3359
H	-1.9790	-0.8670	1.8015
H	-3.1208	-3.5262	-0.4964
H	-4.3855	-2.6059	0.3449
H	-2.9140	-3.0976	1.2122
H	-3.0076	-1.0593	-1.1153
H	-2.4728	3.4112	0.1390
H	-0.1906	3.5262	1.0479
H	0.4046	2.3867	-0.1749
H	-1.3853	1.7529	2.2205
H	0.0127	0.8313	1.6026
H	-1.7068	1.0432	-1.6439
N	-1.7292	0.6632	0.4362
O	-1.1038	-1.9976	-0.6831
N	-0.3686	-1.0669	-1.2828
C	0.8539	-0.8970	-0.6433
C	3.4037	-0.4097	0.4817
C	1.7801	-0.0330	-1.2786
C	1.2407	-1.5146	0.5704
C	2.4983	-1.2627	1.1179
C	3.0318	0.2003	-0.7246
H	1.4882	0.4242	-2.2205
H	0.5539	-2.2053	1.0453
H	2.7795	-1.7504	2.0492
H	3.7295	0.8601	-1.2357
H	4.3855	-0.2287	0.9104

TS_N**water**anti

HF= -766.937312, -766.983438
Freq: -308.5

Atom	X	Y	Z
C	1.8790	-2.0860	0.4327
C	-0.4139	2.2125	1.4329
C	0.4822	1.4063	0.5254
C	3.2696	-2.4494	-0.1168
C	3.6277	-1.2558	-1.0204
C	3.0578	-0.0643	-0.2520
C	0.8318	0.0910	0.9001
H	1.0748	-2.5317	-0.1603
H	1.7403	-2.3931	1.4767
H	2.8747	0.8133	-0.8671
H	3.7236	0.2204	0.5783
H	3.1222	-1.3377	-1.9885
H	4.7025	-1.1596	-1.1978
H	3.2626	-3.4069	-0.6452
H	1.2502	1.9950	0.0296
H	3.9914	-2.5282	0.7047
H	0.1774	2.7018	2.2169
H	-1.1716	1.5920	1.9223
H	-0.9225	2.9962	0.8615
H	0.1328	-0.4877	1.4999
N	1.8047	-0.6122	0.3147
C	-1.4966	0.0806	-0.8582
C	-2.6721	0.5778	-0.2819
C	-3.7942	-0.2431	-0.1636
C	-3.7616	-1.5557	-0.6390
C	-2.5988	-2.0378	-1.2488
C	-1.4747	-1.2241	-1.3666
H	-2.7123	1.6111	0.0453
H	-2.5735	-3.0515	-1.6419
H	-4.7025	0.1515	0.2847
H	-0.5720	-1.5596	-1.8646
H	-4.6399	-2.1901	-0.5552
N	-0.3683	0.9885	-1.0502
O	0.5021	0.5073	-1.8748
H	1.5833	1.8692	-2.2169
O	2.2420	2.6046	-2.1396
H	1.7025	3.4069	-2.1947

TS_N**water**syn

HF= -766.938066, -766.983445
Freq: -322.1

Atom	X	Y	Z
C	-2.3122	-1.1026	-1.0991
C	0.8440	2.5932	0.0203
C	-0.7602	0.7129	-0.4639
C	-0.1457	1.5543	0.4872
C	-2.8772	0.3295	0.8010
C	-3.9460	-0.7568	0.6208
C	-3.8270	-1.1330	-0.8661
H	-2.0266	-0.8727	-2.1310
H	-1.8566	-2.0509	-0.7994
H	1.4788	2.9103	0.8539
H	0.3210	3.4808	-0.3572
H	1.4878	2.2155	-0.7805
H	-0.2231	0.4547	-1.3734
H	-0.7804	1.8928	1.3025
H	-2.4475	0.3523	1.8015
H	-3.2671	1.3273	0.5509
H	-3.6920	-1.6223	1.2395
H	-4.9421	-0.3991	0.8977
H	-4.2556	-2.1126	-1.0951
H	-4.3259	-0.3856	-1.4957
N	-1.8352	-0.0328	-0.1935
C	1.7044	-0.4614	0.7710
C	2.9342	0.1860	0.5896
C	3.9929	-0.4726	-0.0355
C	3.8418	-1.7916	-0.4668
C	2.6258	-2.4483	-0.2549
C	1.5626	-1.7957	0.3665
H	3.0617	1.1948	0.9674
H	4.9421	0.0404	-0.1683
H	4.6679	-2.3092	-0.9470
H	2.5053	-3.4808	-0.5742
H	0.6291	-2.3163	0.5470
N	0.6735	0.2670	1.5094
O	-0.2327	-0.4829	2.0318
H	-1.1888	-3.4698	2.1310
H	-1.0470	-2.0258	1.6190
O	-1.5115	-2.8780	1.4347

TS_O**water**

HF= -766.932436, -766.978741
Freq: -373.4

Atom	X	Y	Z
C	0.9201	2.7276	-1.6200
C	2.6179	-1.5564	-0.6424
C	1.0266	1.3751	-2.3321
C	3.1422	-2.9258	-0.9925
C	2.6331	1.4655	-0.4830
C	2.3003	2.8868	-0.9617
C	2.1974	-0.6886	-1.6900
H	3.0364	3.2275	-1.7004
H	0.6729	3.5396	-2.3098
H	0.1374	2.6753	-0.8558
H	1.4684	1.4740	-3.3341
H	0.0691	0.8505	-2.4184
H	2.2678	1.2946	0.5325
H	3.7052	1.2421	-0.5181
H	2.2976	3.5979	-0.1314
H	1.7824	-1.1162	-2.5986
H	2.9965	-3.5979	-0.1412
H	4.2117	-2.8912	-1.2280
H	2.6109	-3.3446	-1.8534
H	3.1391	-1.0769	0.1854
N	1.9247	0.5959	-1.4616
C	-0.7393	-0.6429	-0.0539
C	-3.2453	-0.0163	-1.2005
C	-1.5468	0.3919	0.4839
C	-1.2183	-1.3561	-1.1781
C	-2.4557	-1.0347	-1.7377
C	-2.7777	0.6913	-0.0832
H	-1.1759	0.9362	1.3484
H	-0.6284	-2.1765	-1.5692
H	-2.8122	-1.5988	-2.5972
H	-3.3842	1.4846	0.3477
H	-4.2117	0.2202	-1.6368
N	0.4716	-0.8797	0.5817
O	1.1322	-1.9088	0.0526
H	0.9768	0.2747	1.9070
O	1.2102	1.0622	2.4633
H	1.4169	0.6916	3.3341

TS_N**8**syn

HF= -900.785336, -900.837210
Freq: -322.1

Atom	X	Y	Z
C	-1.9260	-1.7030	1.6810
C	2.1850	-2.9460	-0.8560
C	0.0760	-2.3030	0.3620
C	0.7720	-2.4190	-0.8600
C	-2.2200	-2.6100	-0.5690
C	-3.5840	-2.2830	0.0540
C	-3.3130	-2.3440	1.5670
H	-1.3480	-2.0430	2.5470
H	-2.0070	-0.6120	1.7090
H	2.7000	-2.6500	-1.7750
H	2.1870	-4.0420	-0.8100
H	2.7600	-2.5720	-0.0020
H	0.6310	-2.1060	1.2760
H	0.1840	-2.7570	-1.7100
H	-2.0560	-2.1260	-1.5300
H	-2.0740	-3.6950	-0.6790
H	-3.8760	-1.2670	-0.2270
H	-4.3610	-2.9800	-0.2750
H	-4.0620	-1.8100	2.1590
H	-3.2820	-3.3850	1.9130
N	-1.2450	-2.1030	0.4310
C	1.4680	0.2030	-0.4610
C	2.8620	0.2180	-0.5940
C	3.6350	1.0780	0.1870
C	3.0220	1.9440	1.0930
C	1.6280	1.9500	1.2030
C	0.8510	1.0930	0.4280
H	3.3310	-0.4250	-1.3310
H	4.7160	1.0820	0.0730
H	3.6220	2.6200	1.6970
H	1.1420	2.6340	1.8960
H	-0.2300	1.1130	0.4980
N	0.7210	-0.6650	-1.3700
O	-0.5070	-0.3230	-1.5410
C	-3.1970	3.0070	0.4800
C	-3.7560	2.2040	-1.7240
H	-2.4160	3.0000	1.2450
H	-3.3850	1.5880	-2.5470
H	-4.1270	2.6010	0.9180
H	-3.3750	4.0420	0.1690
H	-3.9200	3.2210	-2.0970
H	-4.7160	1.7900	-1.3690
N	-2.7410	2.2490	-0.6760
H	-1.7650	0.5720	-0.6740
O	-2.5750	0.8910	-0.2010

TS_N**8**anti

HF= -900.785120, -900.839440
Freq: -310.8

Atom	X	Y	Z
C	0.8514	2.4003	-0.4251
C	0.6271	-1.8388	2.1604
C	0.0607	-0.9648	1.0689
C	-0.2040	3.4156	-0.8913
C	-1.4327	2.5403	-1.1931
C	-1.3869	1.4898	-0.0827
C	0.6270	0.3082	0.8469
H	1.4811	2.0586	-1.2525
H	1.5086	2.7954	0.3590
H	-1.9195	0.5743	-0.3299
H	-1.7939	1.8947	0.8572
H	-1.3240	2.0465	-2.1650
H	-2.3711	3.1020	-1.1938
H	0.1383	3.9967	-1.7523
H	-1.0173	-1.0530	0.9607
H	-0.4345	4.1198	-0.0832
H	0.1671	-1.5913	3.1252
H	1.7105	-1.7198	2.2648
H	0.4095	-2.8906	1.9477
H	1.6796	0.4597	1.0755
N	0.0654	1.2565	0.0898
C	1.8326	-1.6653	-0.9254
C	2.6794	-2.5796	-0.2866
C	4.0257	-2.6531	-0.6459
C	4.5315	-1.8347	-1.6581
C	3.6749	-0.9495	-2.3205
C	2.3311	-0.8688	-1.9637
H	2.2752	-3.2468	0.4668
H	4.0573	-0.3257	-3.1252
H	4.6762	-3.3662	-0.1458
H	1.6370	-0.2160	-2.4809
H	5.5779	-1.9013	-1.9436
N	0.4101	-1.6735	-0.5927
O	-0.2924	-1.0374	-1.4682
H	-1.9531	-1.4751	-1.1023
O	-2.8130	-1.5118	-0.6074
N	-3.6881	-2.2997	-1.4439
C	-4.0128	-3.4957	-0.6757
H	-4.6928	-4.1198	-1.2668
H	-4.4883	-3.2636	0.2936
H	-3.0931	-4.0569	-0.4913
C	-4.8671	-1.4766	-1.6787
H	-4.5705	-0.5812	-2.2316
H	-5.3655	-1.1673	-0.7427
H	-5.5779	-2.0462	-2.2882

TS_O**8**

HF= -900.782166, -900.833990
Freq: -374.7

Atom	X	Y	Z
C	1.2860	2.0712	-1.1951
C	-1.2513	-0.9087	1.4515
C	1.3886	1.4303	0.1935
C	-1.6570	-1.5513	2.7523
C	-0.9133	1.2593	-0.6287
C	-0.2023	2.4422	-1.3024
C	-0.2127	0.0601	1.4581
H	-0.4026	3.3717	-0.7553
H	1.9552	2.9293	-1.3055
H	1.5510	1.3306	-1.9573
H	1.5627	2.1799	0.9787
H	2.1668	0.6622	0.2603
H	-1.1390	0.4592	-1.3362
H	-1.8428	1.5443	-0.1251
H	-0.5361	2.5808	-2.3346
H	0.5570	0.0138	2.2240
H	-2.0662	-2.5462	2.5512
H	-2.4275	-0.9595	3.2598
H	-0.8035	-1.6620	3.4297
H	-2.0666	-0.7571	0.7433
N	0.0710	0.7994	0.3850
C	1.3100	-1.9562	-0.7823
C	4.0741	-1.9812	-1.3783
C	1.7701	-1.7967	-2.1130
C	2.2695	-2.1333	0.2426
C	3.6307	-2.1393	-0.0636
C	3.1284	-1.8130	-2.3998
H	1.0340	-1.6760	-2.9037
H	1.9256	-2.2991	1.2566
H	4.3536	-2.2843	0.7367
H	3.4583	-1.6967	-3.4297
H	5.1357	-1.9977	-1.6083
N	-0.0636	-1.9385	-0.5882
O	-0.4089	-2.1720	0.6737
H	-1.4262	-1.6704	-1.7401
O	-2.2179	-1.4533	-2.3094
N	-3.2914	-1.3727	-1.3424
C	-4.2678	-0.4749	-1.9458
H	-3.8220	0.5169	-2.0607
H	-5.1357	-0.4003	-1.2815
H	-4.6025	-0.8255	-2.9368
C	-3.8327	-2.7252	-1.2019
H	-3.0553	-3.3717	-0.7863
H	-4.1684	-3.1418	-2.1655
H	-4.6772	-2.6987	-0.5030