Supporting Information

Heterobimetallic dual-catalysts systems for the hydrolytic kinetic resolution of terminal epoxides

Xiang Hong,[a] Mohamed Mellah[a] and Emmanuelle Schulz*[a,b]

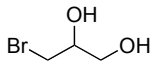
[a]*Equipe de Catalyse Moléculaire, Université Paris Sud, ICMMO, UMR 8182, 91405 Orsay, France*

[b]*CNRS, 91405 Orsay, France.*

e-mail : emmanuelle.schulz@u-psud.fr

Contents

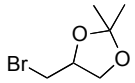
Section 1. Preparation of racemic 3-bromopropane-1,2-diol.



A mixture of epibromohydrin (22.4 g, 163.5 mmol), *p*-toluenesulfonic acid (60 mg, 0.35 mmol) and H_2O (14 mL) was heated to reflux during 7 h, then Na_2CO_3 (74 mg, 0.70 mmol) was added to the mixture with caution. A distillation under reduced pressure (112 °C, 6.7 mbar) afforded the desired product (17.98 g, 71 %) as colourless oil.

^{1}H NMR (250 MHz, $CDCl_3$) δ 3.87-3.96 (m, 1H), 3.76 (dd, J = 3.8, 11.3 Hz, 1H), 3.66 (dd, J = 5.1, 11.3 Hz, 1H), 3.48 (dd, 1H, J = 5.3, 10.5 Hz), 3.44 (dd, J = 6.3, 10.5 Hz, 1H), 2.79 (s, 2H). ^{13}C NMR (90 MHz, $CDCl_3$) δ 71.7 (CH_2), 64.5 (CH), 35.1 (CH_2).

Section 2. Preparation of racemic 4-(bromomethyl)-2,2-dimethyl-1,3-dioxolane.



To a solution of 3-bromopropane-1,2-diol (330 mg, 2.1 mmol) in DCM (13 mL), Amberlyst 15 (26 mg) and 2,2-dimethoxypropane (0.51 mL, 4.2 mmol) were added with continuous stirring. The mixture was stirred at room temperature for 18 h and then filtrated on celite before removal of the solvents under reduced pressure. The resulting residue was purified by chromatography on silica gel (pentane/diethylether 95/5) to afford the product (420 mg, 97 %) as colourless oil.

^{1}H NMR (360 MHz, $CDCl_3$) δ 4.26-4.33 (m, 1H), 4.09 (dd, J = 6.5, 9.0 Hz, 1H), 3.83 (dd, J = 5.0, 9.0 Hz, 1H), 3.39 (dd, 1H, J = 4.7, 10.0 Hz), 3.26 (dd, J = 8.0, 10.0 Hz, 1H), 1.41 (s, 3H), 1.32 (s, 3H). ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 110.4 (C_q), 75.4 (CH_2), 68.4 (CH), 32.9 (CH_2), 27.1 (CH_3), 25.5 (CH_3). IR (NaCl, υ (cm^{-1})) 2988, 2937, 2883, 1381, 1372, 1256, 1214, 1061, 843.

Section 3. Determination of the selectivities in the hydrolysis of epoxides (copies of GC and HPLC chromatograms)

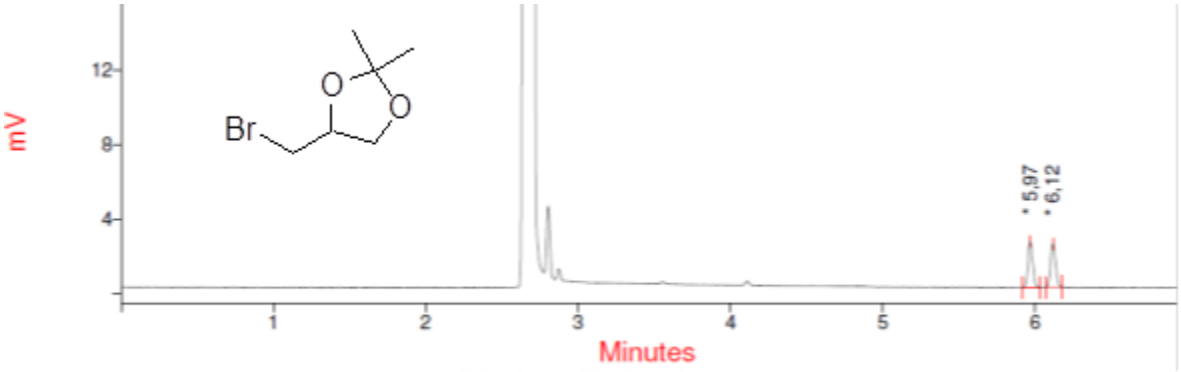
Epibromohydrin.

The absolute stereochemistry of the major enantiomer was consequently assigned according to the reported optical activity of the (*R)*-acetal in the literature[1]

[1] Y. Kawakami, T. Asai, K. Umeyama, Y. Yamashita, *J. Org. Chem.* **1982**, 47, 3581.

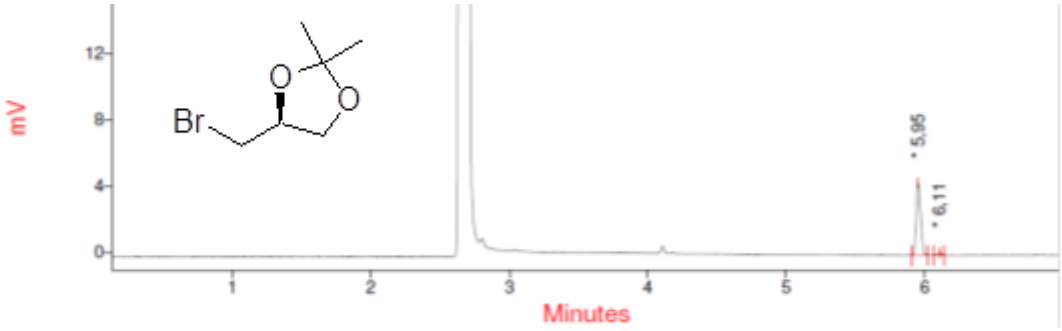
Determination of enantiomeric purity for 4-(bromomethyl)-2,2-dimethyl-1,3-dioxolane.

GC Chromatogram of a racemic sample



Retention time (min.)	Area (%)
5,97	49.99
6,12	50.01

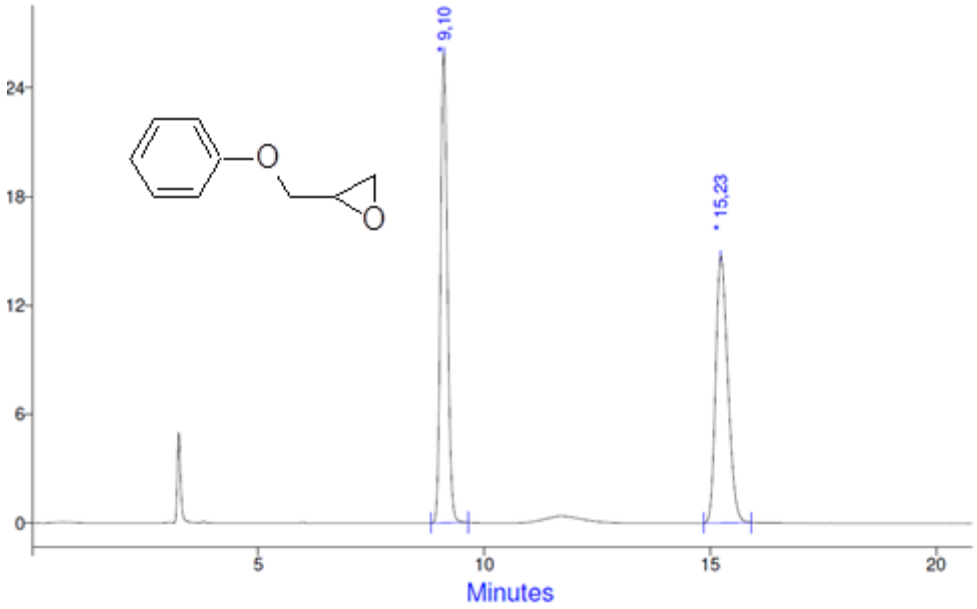
GC Chromatogram of an enantioenriched sample



Retention time (min.)	Area (%)
5,95	96.53
6,11	3.47

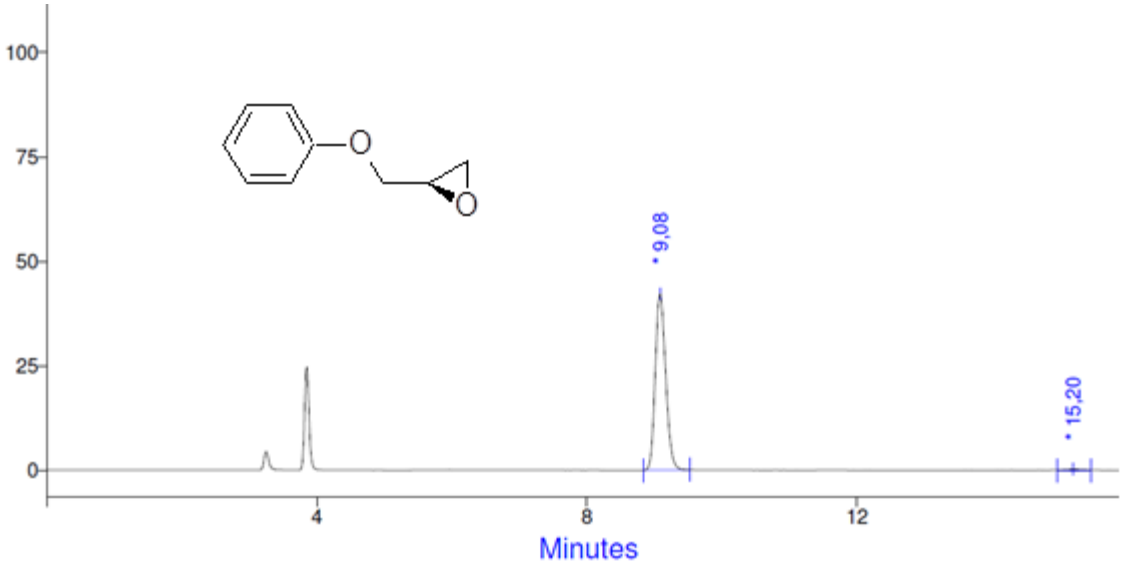
2-phenoxy-methyl-oxirane.

HPLC Chromatogram of a racemic sample of the epoxide



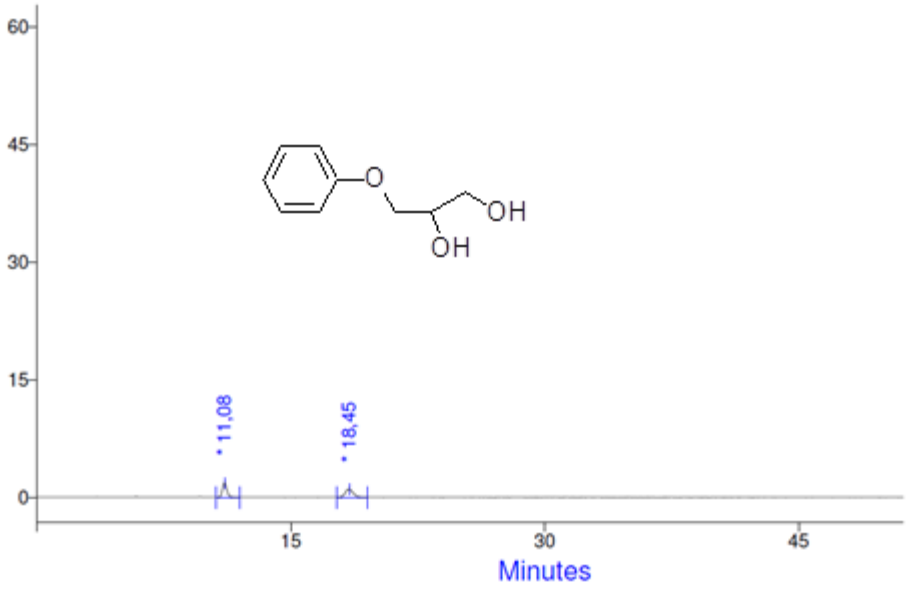
Retention time (min.)	Area (%)
9,10	49.94
15,23	50.06

HPLC Chromatogram of an enantioenriched sample of the epoxide



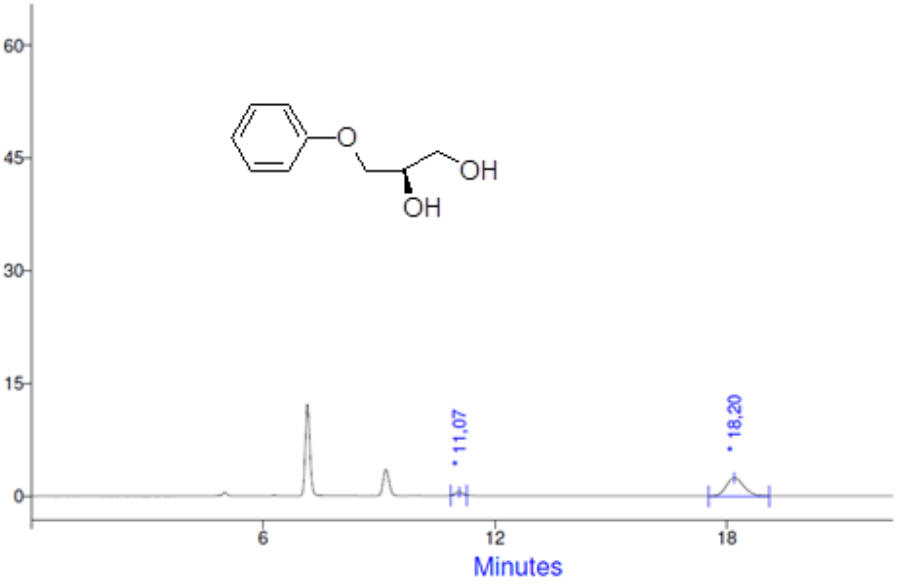
Retention time (min.)	Area (%)
9,08	99.72
15,20	0.28

HPLC Chromatogram of a racemic sample of the diol



Retention time (min.)	Area (%)
11.08	49.67
18.45	50.33

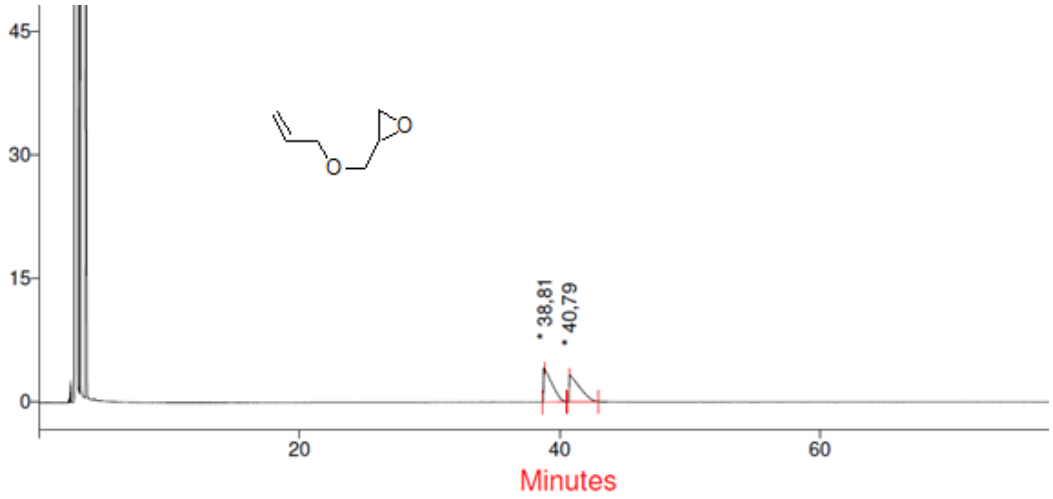
HPLC Chromatogram of an enantioenriched sample of the diol



Retention time (min.)	Area (%)
11.07	7.19
18.20	92.81

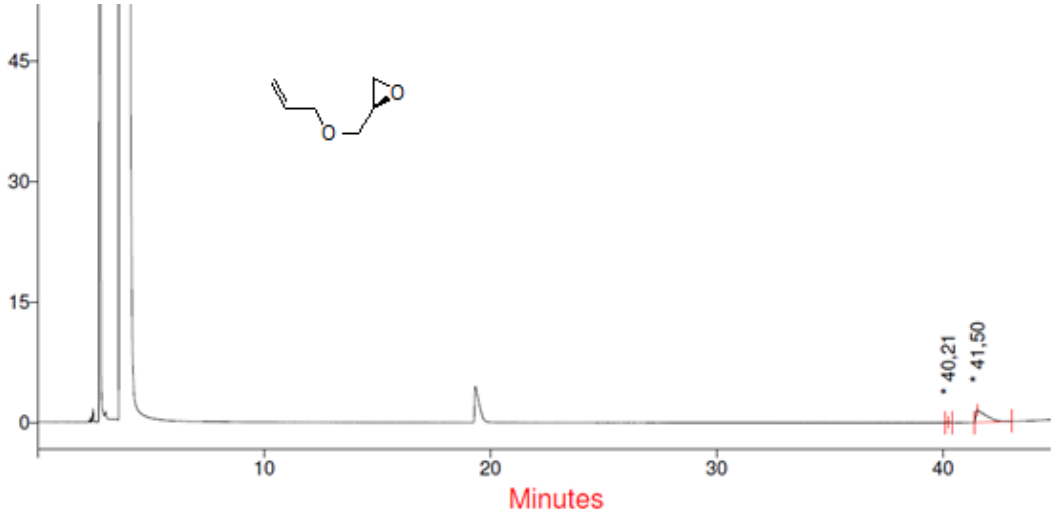
2-Allyloxymethyl-oxirane.

GC Chromatogram of a racemic sample of the epoxide



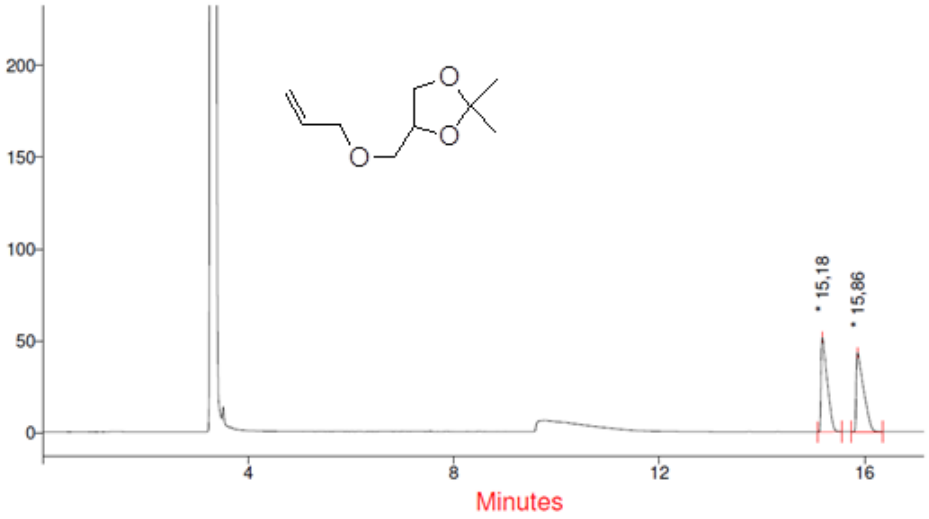
Retention time (min.)	Area (%)
38,81	50.43
40,79	49.57

GC Chromatogram of an enantioenriched sample of the recovered epoxide



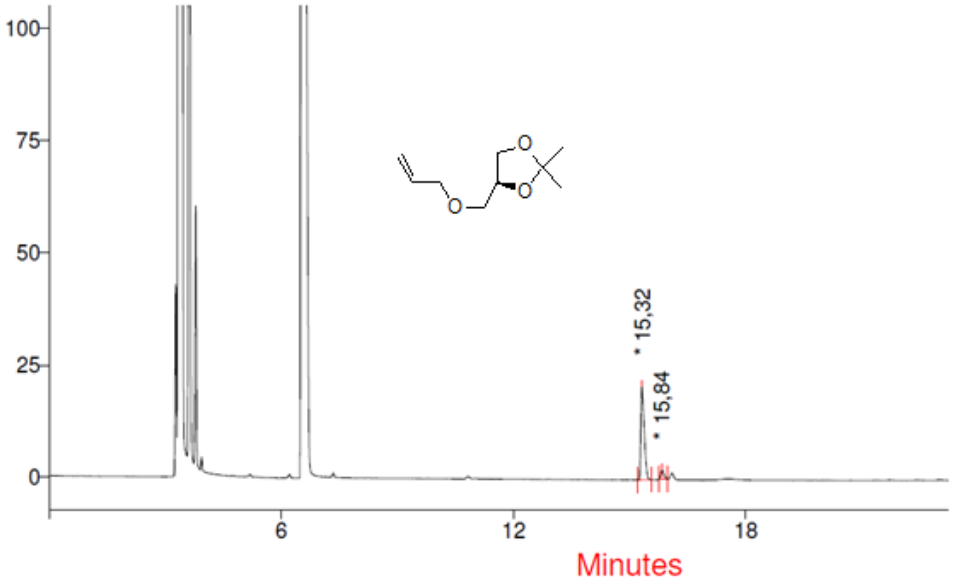
Retention time (min.)	Area (%)
40,21	0.59
41,50	99.41

GC Chromatogram of a racemic sample of the protected diol



Retention time (min.)	Area (%)
15.18	49.87
15.86	50.13

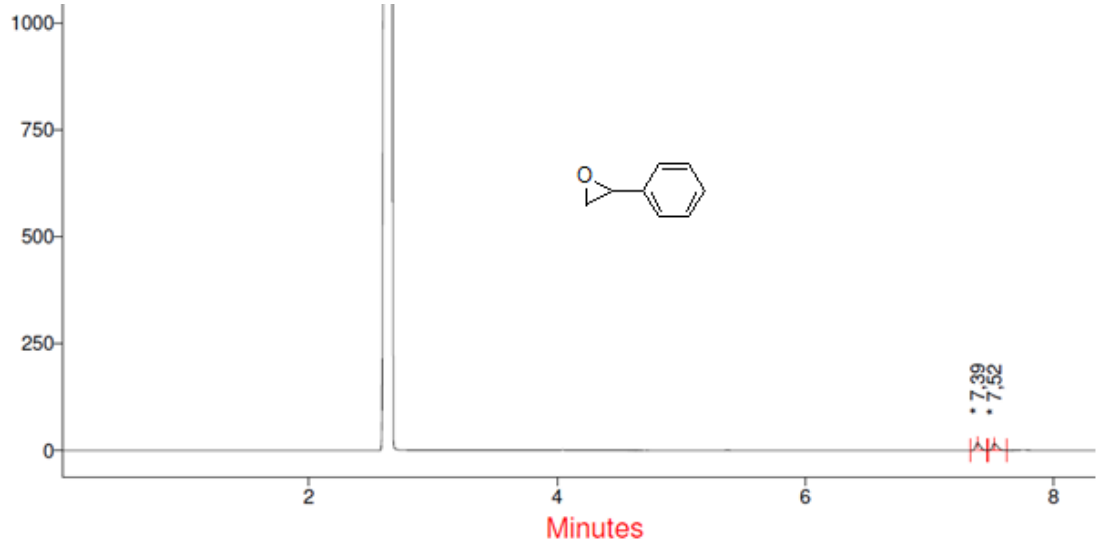
GC Chromatogram of an enantioenriched sample of the protected diol



Retention time (min.)	Area (%)
15.32	7.61
15.86	92.39

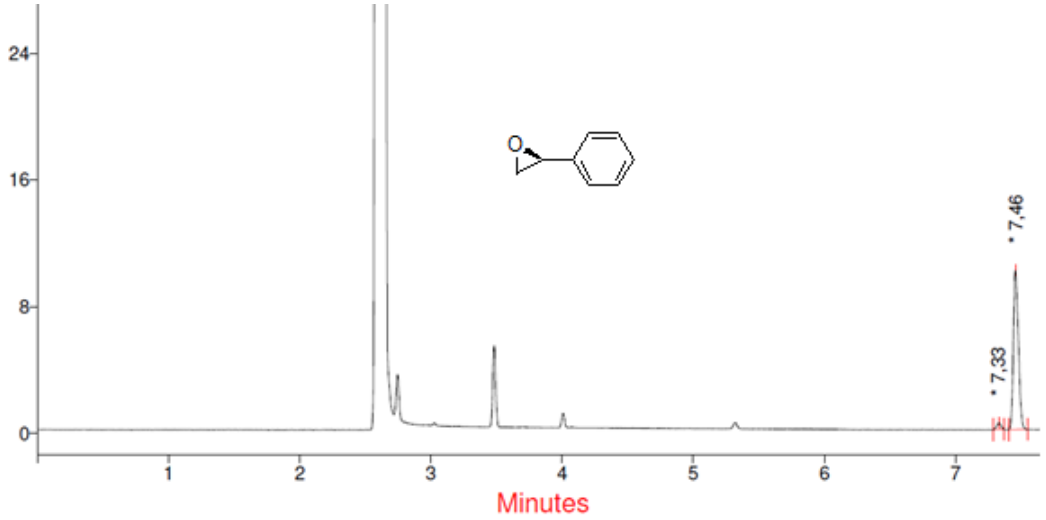
2-phenyl oxirane.

GC Chromatogram of a racemic sample of the recovered epoxide



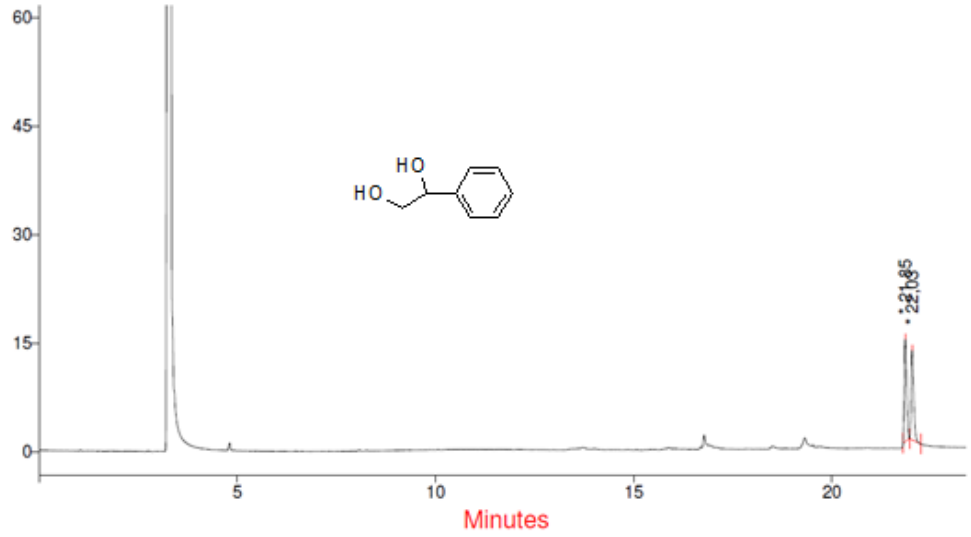
Retention time (min.)	Area (%)
7,39	49.91
7,52	50.09

GC Chromatogram of a enantioenriched sample of the recovered epoxide



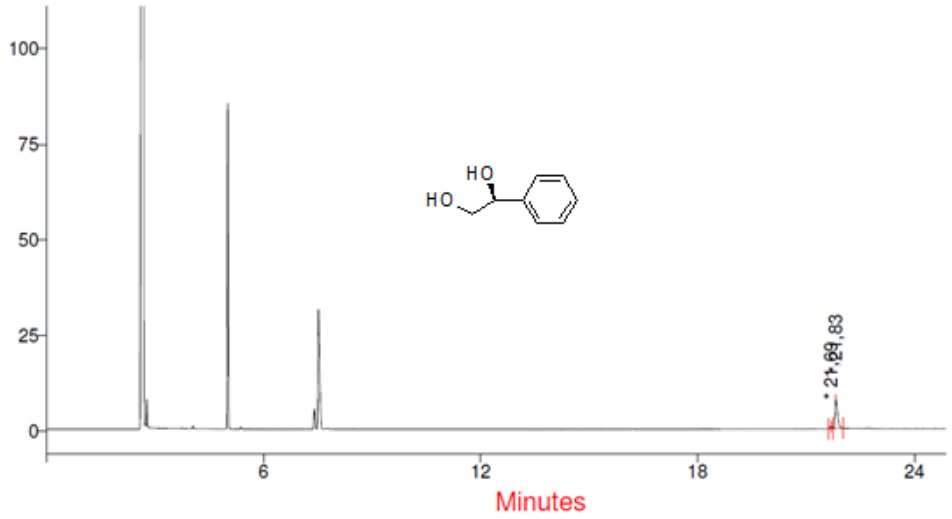
Retention time (min.)	Area (%)
7,33	2.08
7,46	97.92

GC Chromatogram of a racemic sample of the diol



Retention time (min.)	Area (%)
21.85	50.64
22.03	49.36

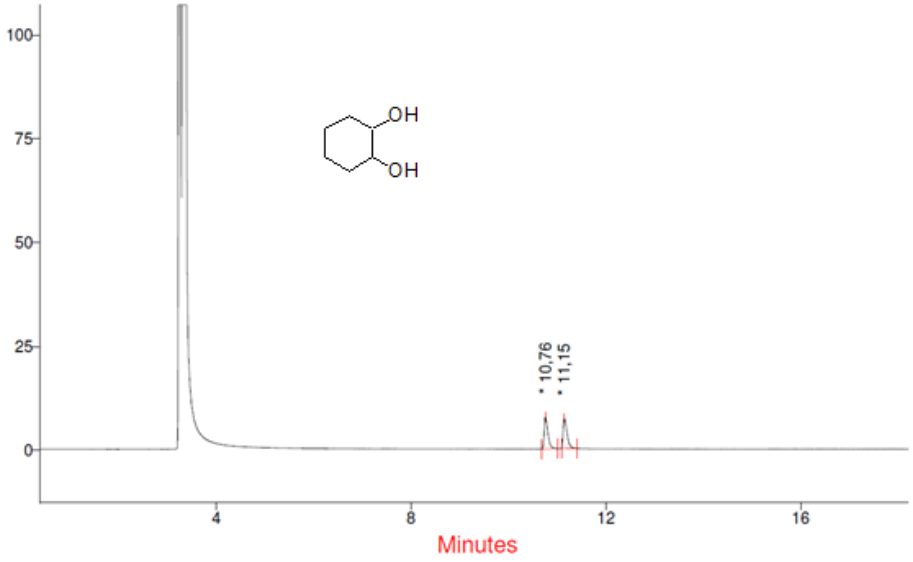
GC Chromatogram of an enantioenriched sample of the diol



Retention time (min.)	Area (%)
21.69	2.56
21.83	97.44

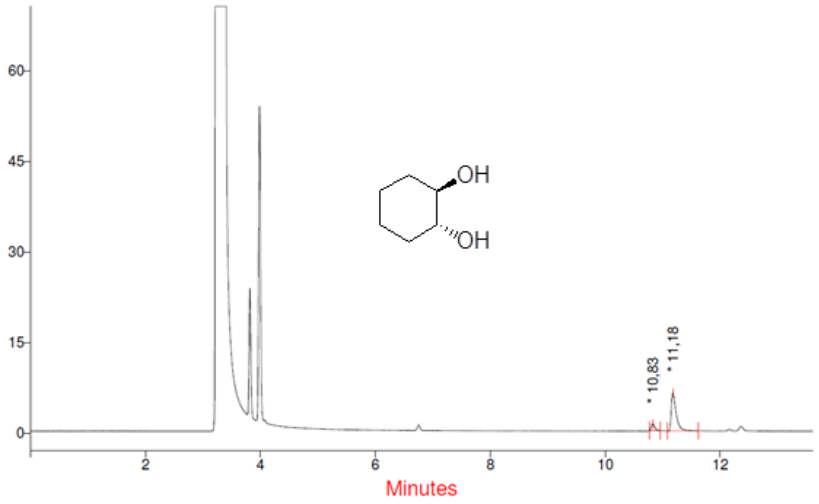
Cyclohexene oxide.

GC Chromatogram of a racemic sample of the diol



Retention time (min.)	Area (%)
10.76	49.86
11,15	50.14

GC Chromatogram of an enantioenriched sample of the diol



Retention time (min.)	Area (%)
10,83	9.11
11,18	90.89

Section 4. Control HKR experiments

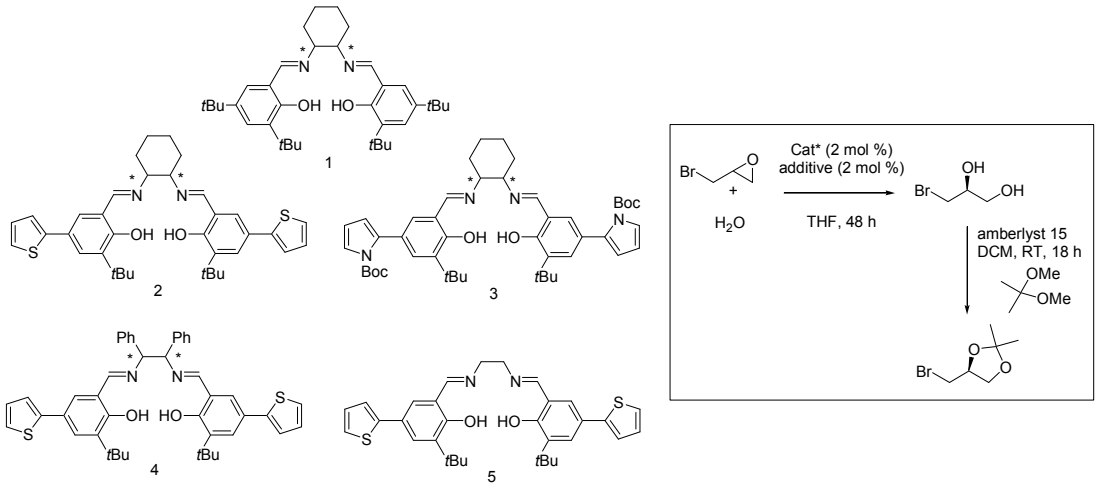


Table 1. *Dynamic HKR of epibromohydrin with additional salen metal complexes – supplementary tests*

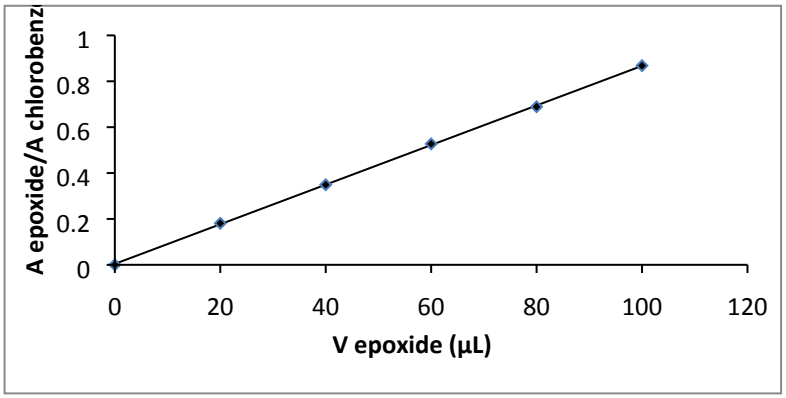
Entry	Cat*	Additive	T (°C)	Conv. (%)	Ee (%)
1	(*S,S*)-**2**-Cr^{III}-Cl	/	20	-	/
2	(*S,S*)-**4**-Cr^{III}-Cl	/	20	-	/
3	(*S,S*)-**2**-Al^{III}-Cl	/	20	-	/
4	(*S,S*)-**1**-Mn^{III}-Cl	/	20	-	/
5	(*S,S*)-**2**-Mn^{III}-Cl	/	20	-	/
6	(*S,S*)-**4**-Mn^{III}-Cl	/	20	-	/
7	(*S,S*)-**2**-V^{IV}=O	/	20	-	/
8	(*S,S*)-**2**-$Ti^{IV}(OiPr)_2$	/	20	-	/
9	(*S,S*)-**4**-$Ti^{IV}(OiPr)_2$	/	20	-	/
10	(*S,S*)-**2**-$V^{IV}O(OiPr)$	/	20	-	/
11	(*S,S*)-**4**-$V^{IV}O(OiPr)$	/	20	-	/
12	(*S,S*)-**2**-Co^{III}-OAc	(*S,S*)-**4**-Cr^{III}-Cl	4	> 99	91 (*S*)
13	(*S,S*)-**2**-Co^{III}-OAc	(*S,S*)-**4**-$Ti^{IV}(OiPr)_2$	4	> 99	90 (*S*)
14	(*S,S*)-**2**-Co^{III}-OAc	(*S,S*)-**4**-$V^{IV}O(OiPr)$	4	> 99	61 (*S*)
15	(*S,S*)-**1**-Co^{III}-OAc	/	4	> 99	96 (*S*)
16	(*S,S*)-**1**-Co^{III}-OAc	(*S,S*)-**1**-Mn^{III}-Cl	4	> 99	98 (*S*)
17	(*S,S*)-**1**-Co^{III}-OAc	(*S,S*)-**2**-Mn^{III}-Cl	4	> 99	98 (*S*)
18	(*S,S*)-**1**-Co^{III}-OAc	(*S,S*)-**4**-Mn^{III}-Cl	4	> 99	98 (*S*)
19	(*S,S*)-**1**-Co^{III}-OAc	(*R,R*)-**4**-Mn^{III}-Cl	4	> 99	96 (*S*)

- Entries 1 to 11, all other tested salen metal complexes are not active catalysts for the HKR.
- Entries 12 to 14, other salen metal complexes with different salen ligands have also different "match" or "mis-match" effects on the HKR catalysed by the same salen Co^{III}-OAc complex
- Entries 15 to 19, similar but less obvious "match" effects were also observed for Jacobsen's salen Co^{III}-OAc complex

Section 5. Kinetic studies

Section 5. 1. Calibration of chlorobenzene as internal standard:

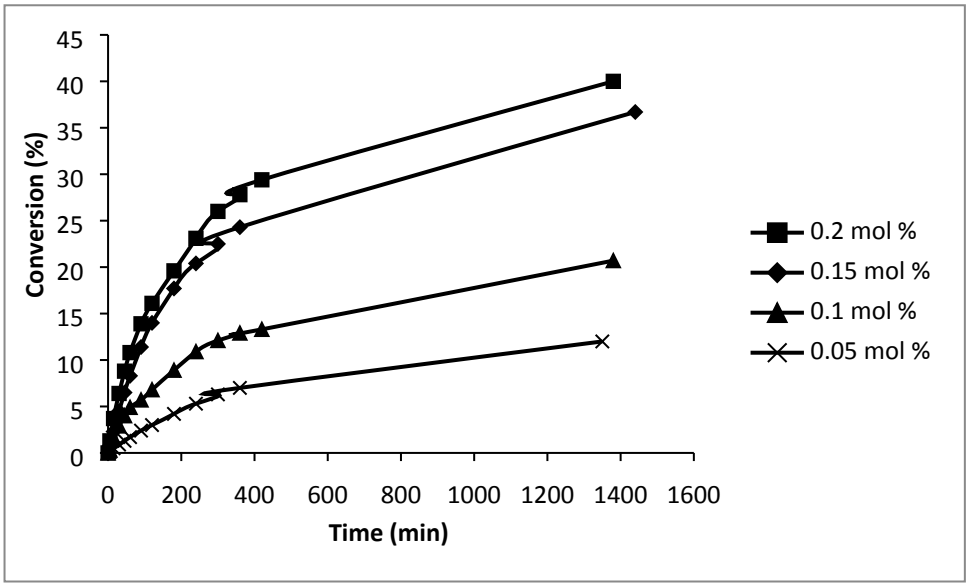
A mixture of epibromohydrin (20 to 100 µL) and chlorobenzene (50 µL) were diluted in THF (3 mL) and then analysed with GC (column VF-1 ms).



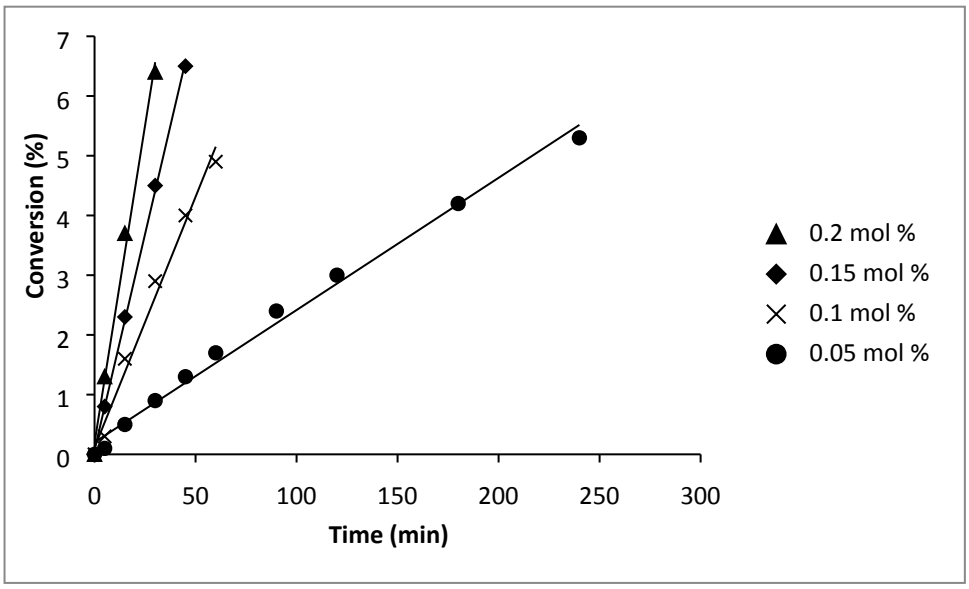
$V_{epoxide}$ (µL)	20	40	60	80	100
$A_{epoxide\ (\%)}$	15.33	25.89	34.52	40.79	46.46
$A_{chlorobenzene\ (\%)}$	84.67	74.11	65.48	59.21	53.54

Section 5.2. Kinetic studies for the dynamic HKR of epibromohydrin catalysed by (S,S)-2-Co^{III}-OAc

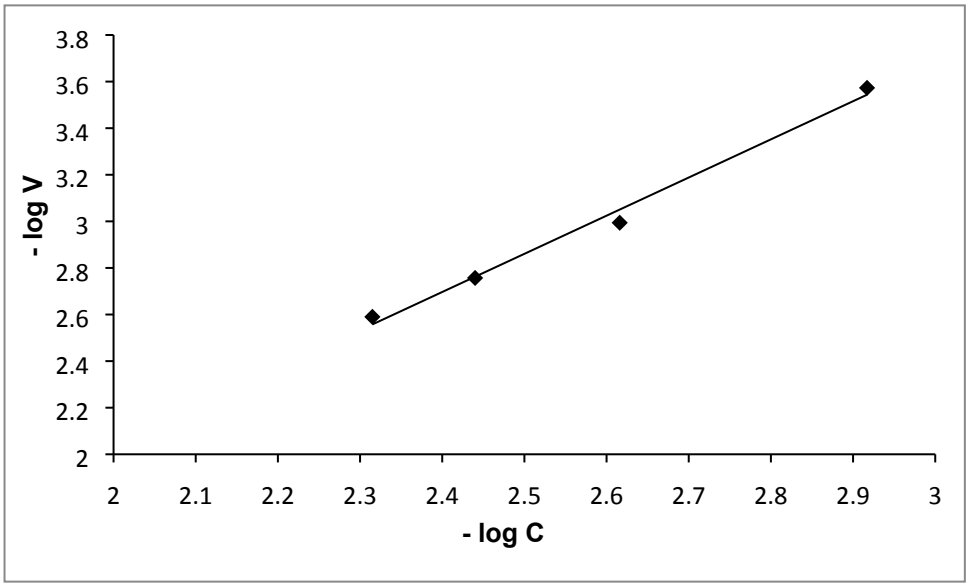
Epibromohydrin (208 µL, 2.42 mmol) was added to a solution of complex *(S,S)*-**2**-Co^{III}-OAc (1 – 4 mg, 0.05 – 0.2 mol %) in THF (1 mL) containing water (67 µL, 3.62 mmol) and chlorobenzene (100 µL) at 20 °C with continuous stirring (1100 rpm). An aliquot of 2 µL was taken from the resulting solution for GC analysis (column VF-1ms) at specified time. Conversions of epibromohydrin were calculated with chlorobenzene as internal standard.



Scheme 1. Conversion/time plots for the dynamic HKR of epibromohydrin catalysed by (*S,S*)-**2**-Co^{III}-OAc under diluted conditions.



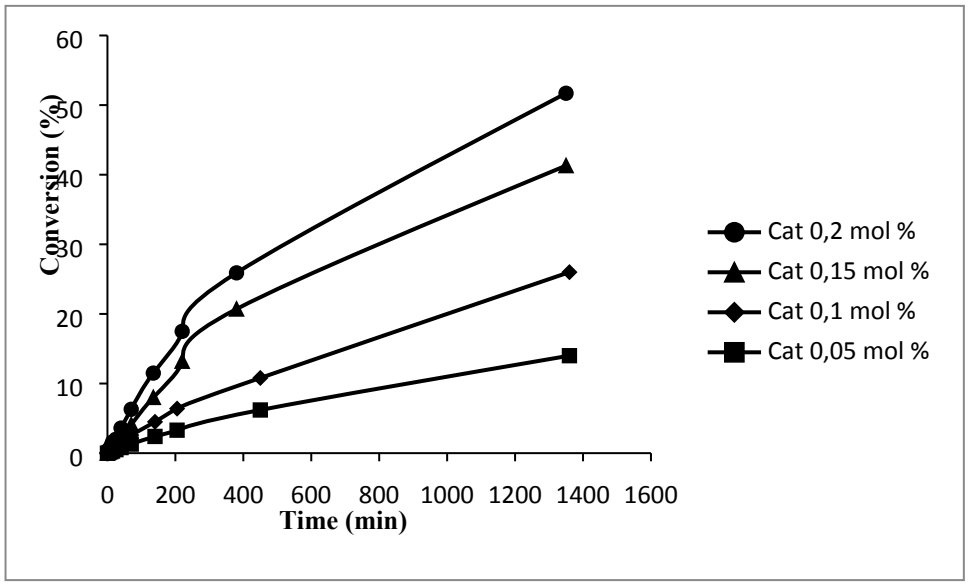
Scheme 2. Conversion/time plots for the dynamic HKR of epibromohydrin catalysed by (*S,S*)-**2**-Co^{III}-OAc under diluted conditions for the first 5 % conversion.



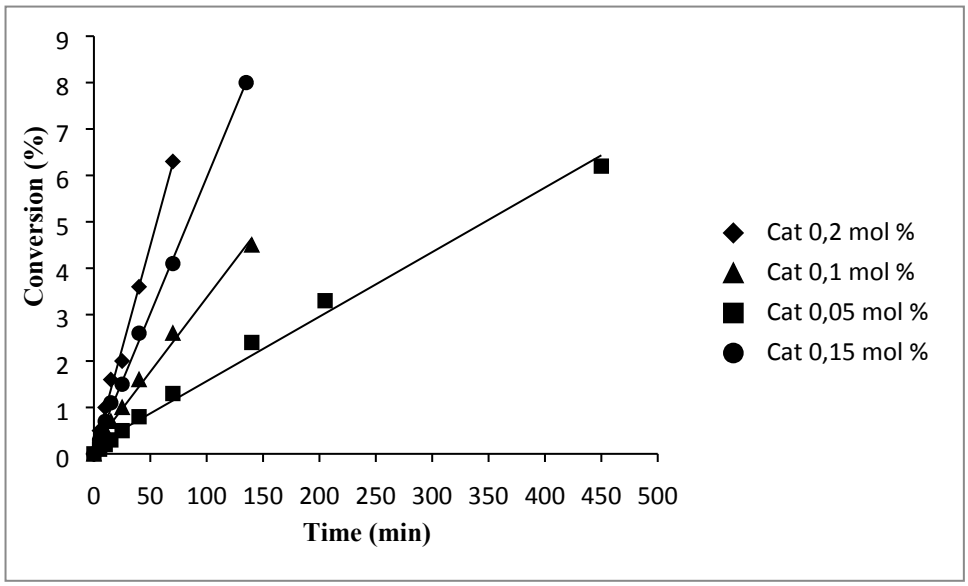
Scheme 3. log *V*/log C plot for the dynamic HKR of epibromohydrin catalysed by (*S,S*)-**2**-Co^{III}-OAc.

Section 5. 3. Kinetic studies for the dynamic HKR of epibromohydrin catalysed by (S,S)-2-Co^{III}-OTs

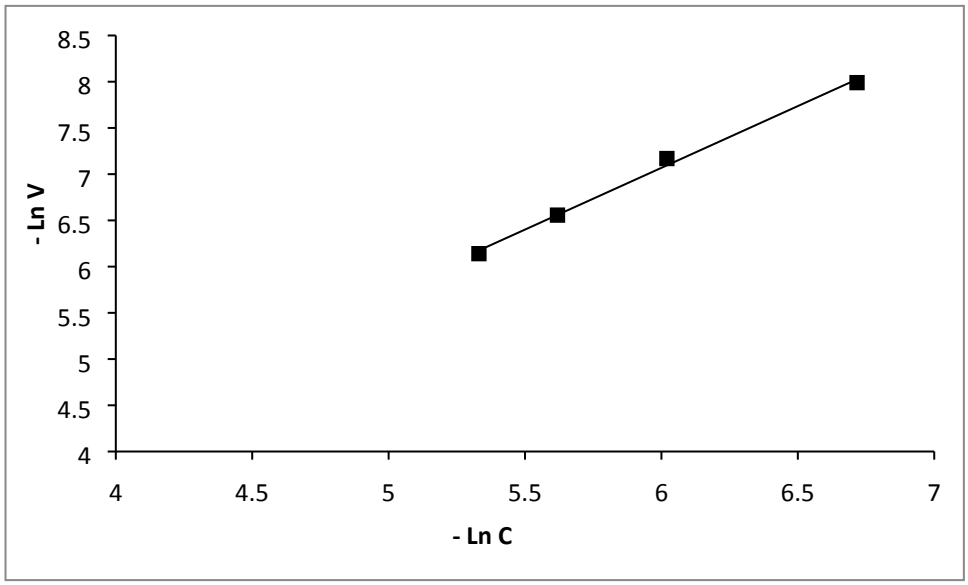
Epibromohydrin (208 µL, 2.42 mmol) was added to a solution of complex (*S,S*)-**2**-Co^{III}-OTs (1 – 4 mg, 0.05 – 0.2 mol %) in THF (1 mL) containing water (67 µL, 3.62 mmol) and chlorobenzene (100 µL) at 20 °C with continuous stirring (1100 rpm). An aliquot of 2 µL was taken from the resulting solution for GC analysis (column VF-1ms) at specified time. Conversions of epibromohydrin were calculated with chlorobenzene as internal standard.



Scheme 4. Conversion/time plots for the dynamic HKR of epibromohydrin catalysed by (*S,S*)-**2**-Co^{III}-OTs under diluted conditions.



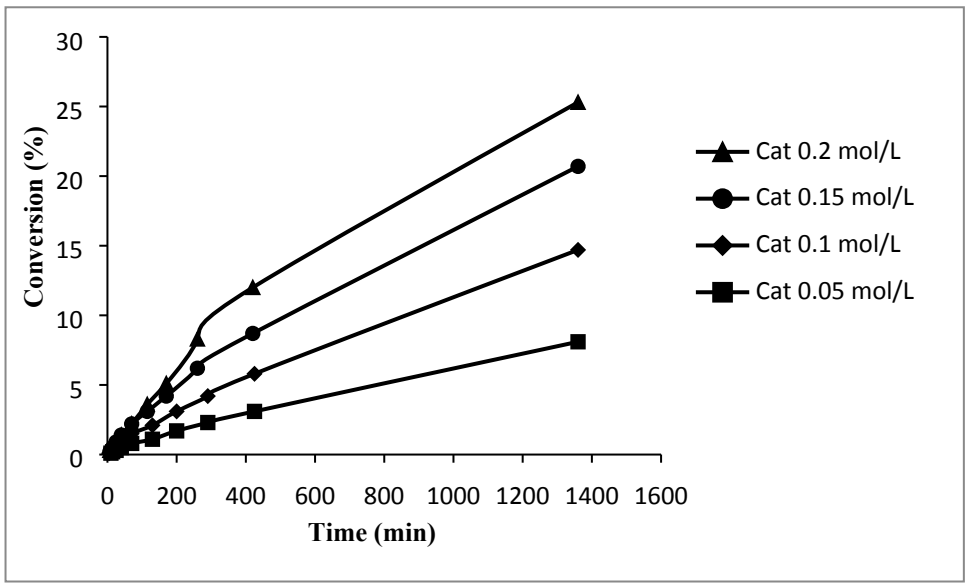
Scheme 5. Conversion/time plots for the dynamic HKR of epibromohydrin catalysed by (*S,S*)-**2**-Co^{III}-OTs under diluted conditions for the first 5 % conversion.



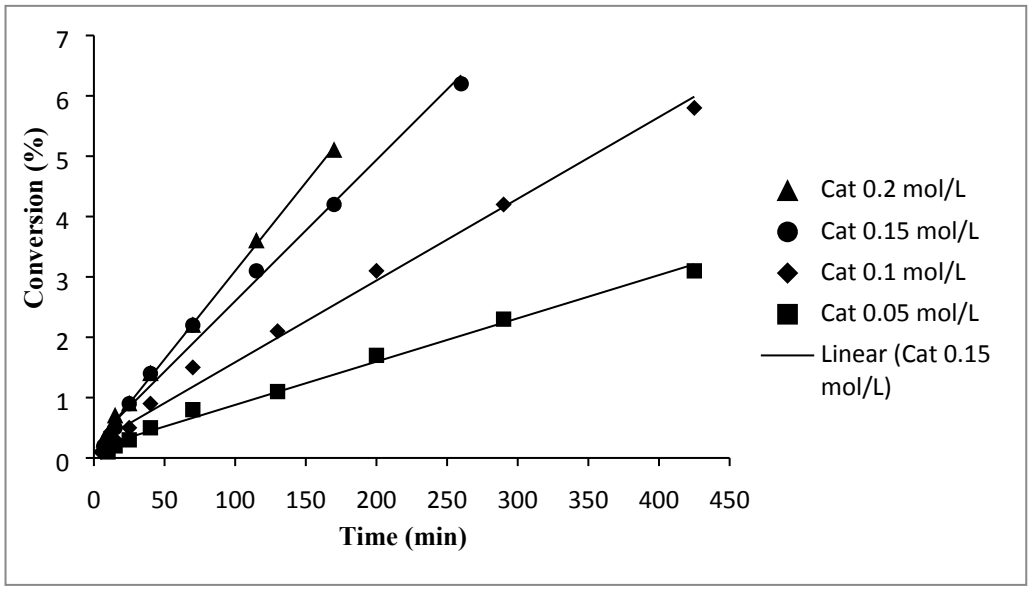
Scheme 6. log *V*/log C plot for the dynamic HKR of epibromohydrin catalysed by (*S,S*)-**2**-Co^{III}-OTs.

Section 5. 4. Kinetic studies for the dynamic HKR of epibromohydrin catalysed by (S,S)-2-Co^{III}-BF_4

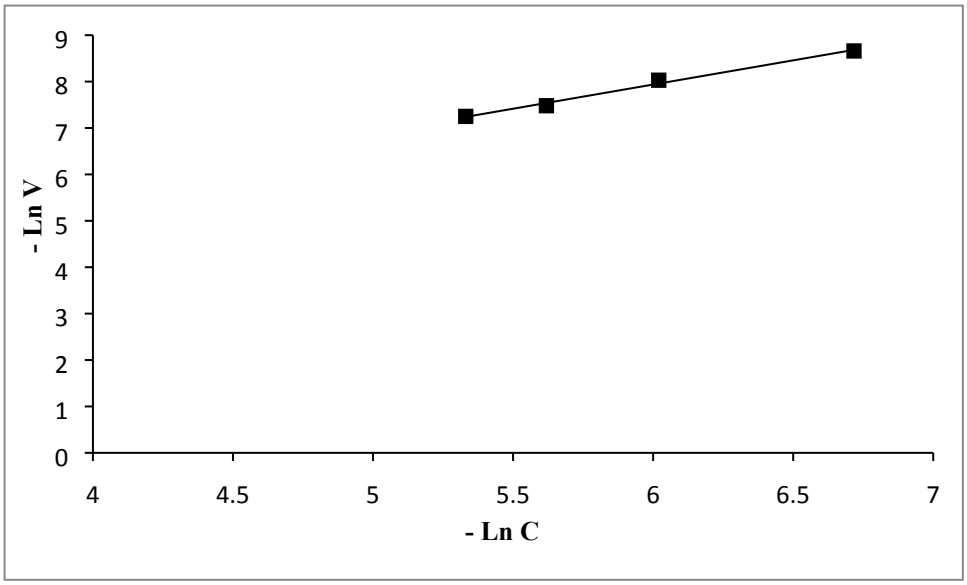
Epibromohydrin (208 µL, 2.42 mmol) was added to a solution of complex (*S,S*)-**2**-Co^{III}-BF_4 (1 – 4 mg, 0.05 – 0.2 mol %) in THF (1 mL) containing water (67 µL, 3.62 mmol) and chlorobenzene (100 µL) at 20 °C with continuous stirring (1100 rpm). An aliquot of 2 µL was taken from the resulting solution for GC analysis (column VF-1ms) at specified time. Conversions of epibromohydrin were calculated with chlorobenzene as internal standard.



Scheme 7. Conversion/time plots for the dynamic HKR of epibromohydrin catalysed by (*S,S*)-**2**-Co^{III}-BF_4 under diluted conditions.



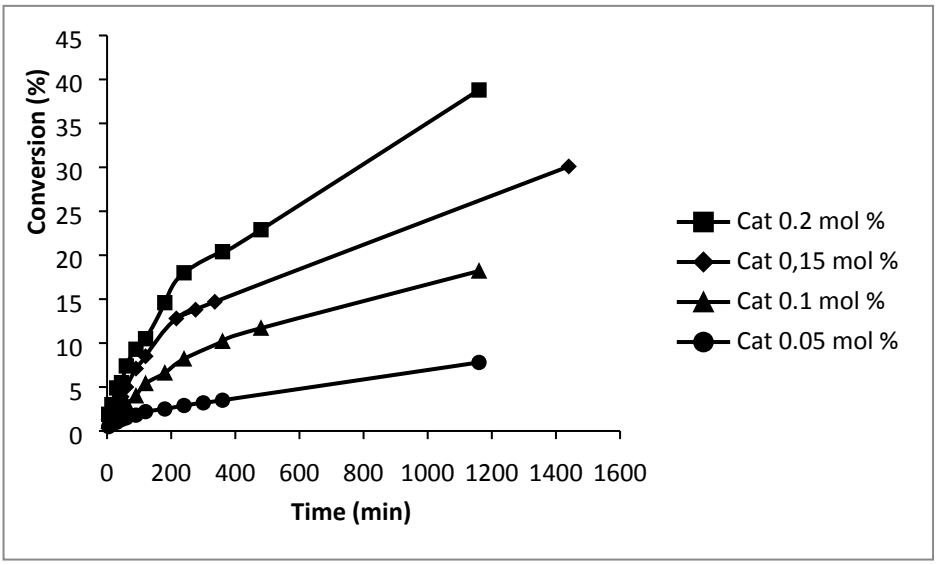
Scheme 8. Conversion/time plots for the dynamic HKR of epibromohydrin catalysed by (*S,S*)-**2**-Co^{III}-BF_4 under diluted conditions for the first 5 % conversion.



Scheme 9. log *V*/log C plot for the dynamic HKR of epibromohydrin catalysed by (*S,S*)-**2**-Co^{III}-BF_4.

Section 5. 5. Kinetic studies for the dynamic HKR of epibromohydrin catalysed by mixtures of (S,S)-2-Co^{III}-OAc and (S,S)-2-Mn^{III}-Cl

Epibromohydrin (208 µL, 2.42 mmol) was added to a solution of complex (*S,S*)-**2**-Mn^{III}-Cl (38 mg, 2 mol %) and complex (*S,S*)-**2**-Co^{III}-OAc (1 – 4 mg, 0.05 – 0.2 mol %) in THF (1 mL) containing water (67 µL, 3.62 mmol) and chlorobenzene (100 µL) at 20 °C under continuous stirring (1100 rpm). An aliquot of 2 µL was taken from the resulting solution for GC analysis (column VF-1ms) at specified time. Conversions of epibromohydrin were calculated with chlorobenzene as internal standard.

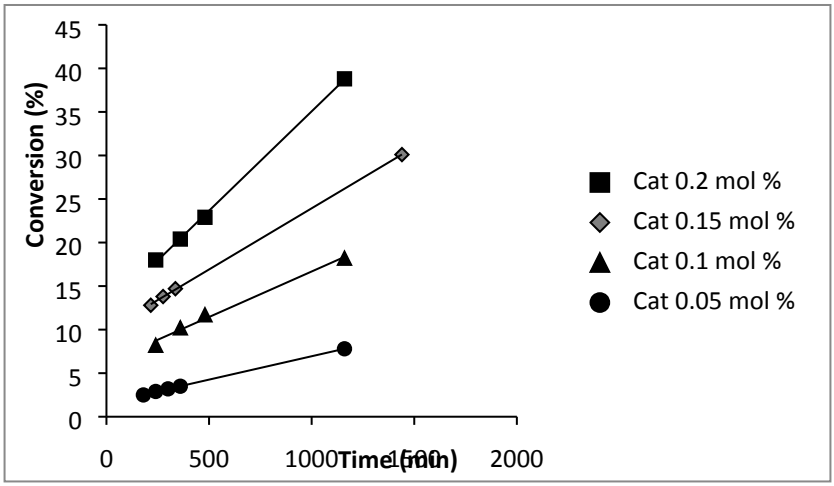


Scheme 10. Conversion/time plots for the dynamic HKR of epibromohydrin catalysed by mixtures of (*S,S*)-**2**-Co^{III}-OAc (0.05 – 0.2 mol %) and (*S,S*)-**2**-Mn^{III}-Cl (2 mol %).

The rate equation for the dynamic HKR of epibromohydrin catalysed by mixtures of two complexes could be represented as:

$$V = k_1[Co^{III}\text{-}OH][Co^{III}\text{-}X] + k_2[Co^{III}_{tot}]^n[Mn^{III}\text{-}Cl]^m$$

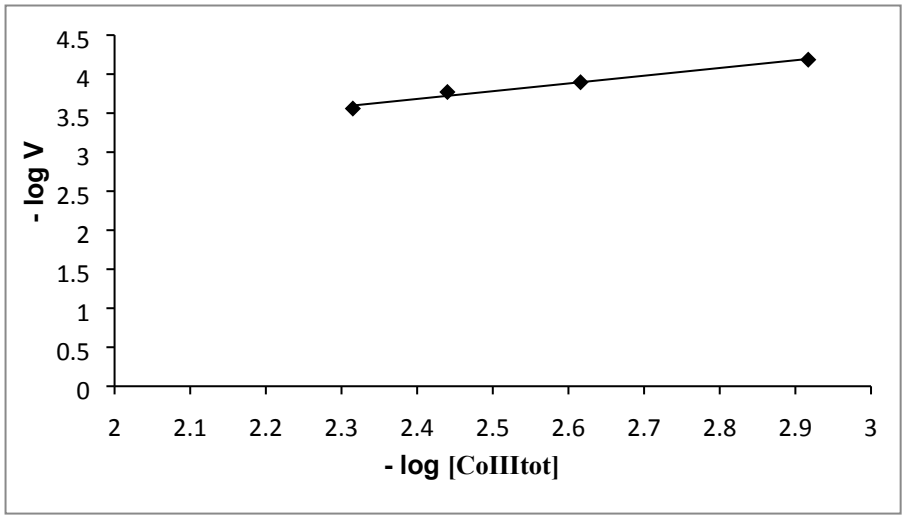
$$\text{With } [Co^{III}_{tot}] = [Co^{III}\text{-}OH] + [Co^{III}\text{-}X]$$



Scheme 11. Conversion/time plots for the dynamic HKR of epibromohydrin catalysed by mixtures of (*S,S*)-**2**-Mn^{III}-Cl and (*S,S*)-**2**-Co^{III}-OAc after an induction time of 4 hours.

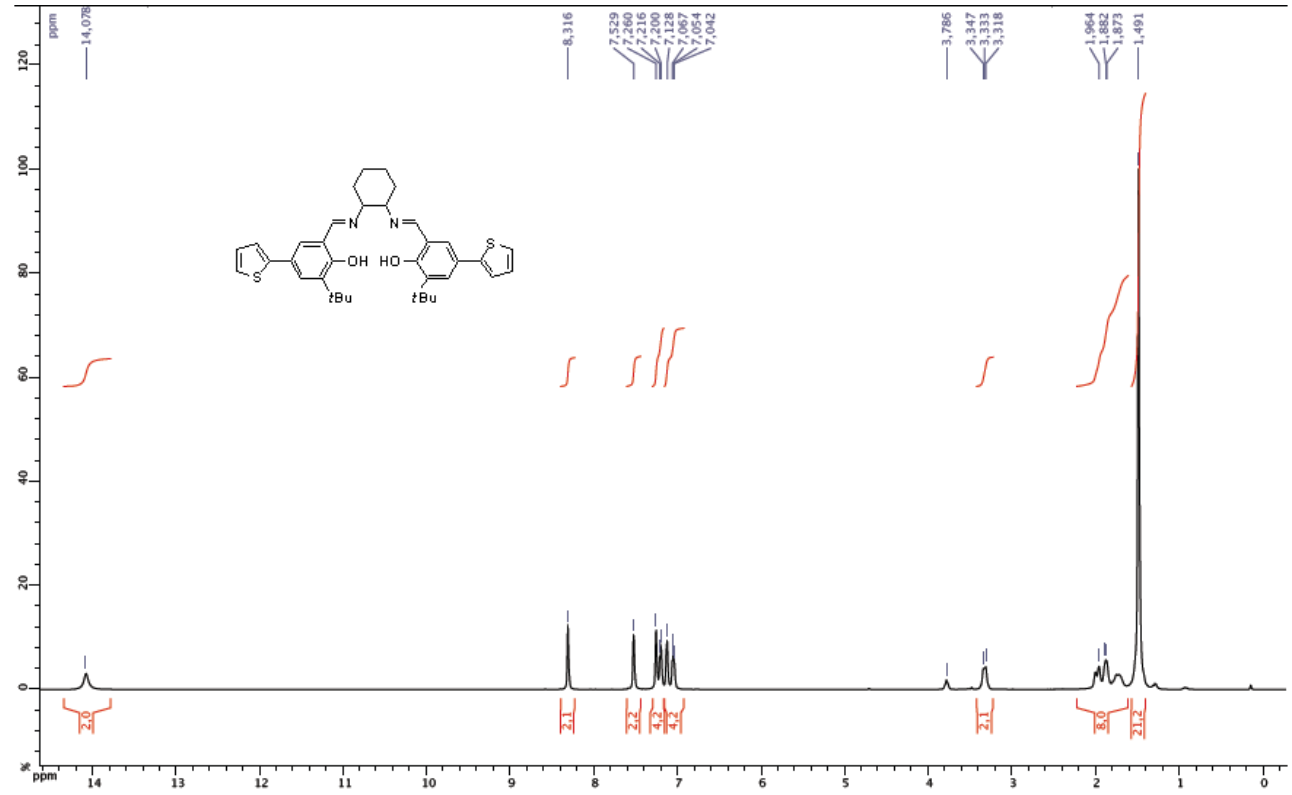
With $[Mn^{III}\text{-}Cl] > [Co^{III}_{tot}]$ the first part of the equation rate can be neglected to yield $V = K[Co^{III}_{tot}]^n$. The conversion vs time plots obtained in these conditions is reported in Scheme 11, after an induction period of 4 h.[2] The rate of each reactions could be calculated from the above plots, and value of n has been determined by log *V*/log $[Co^{III}_{tot}]$ plot.

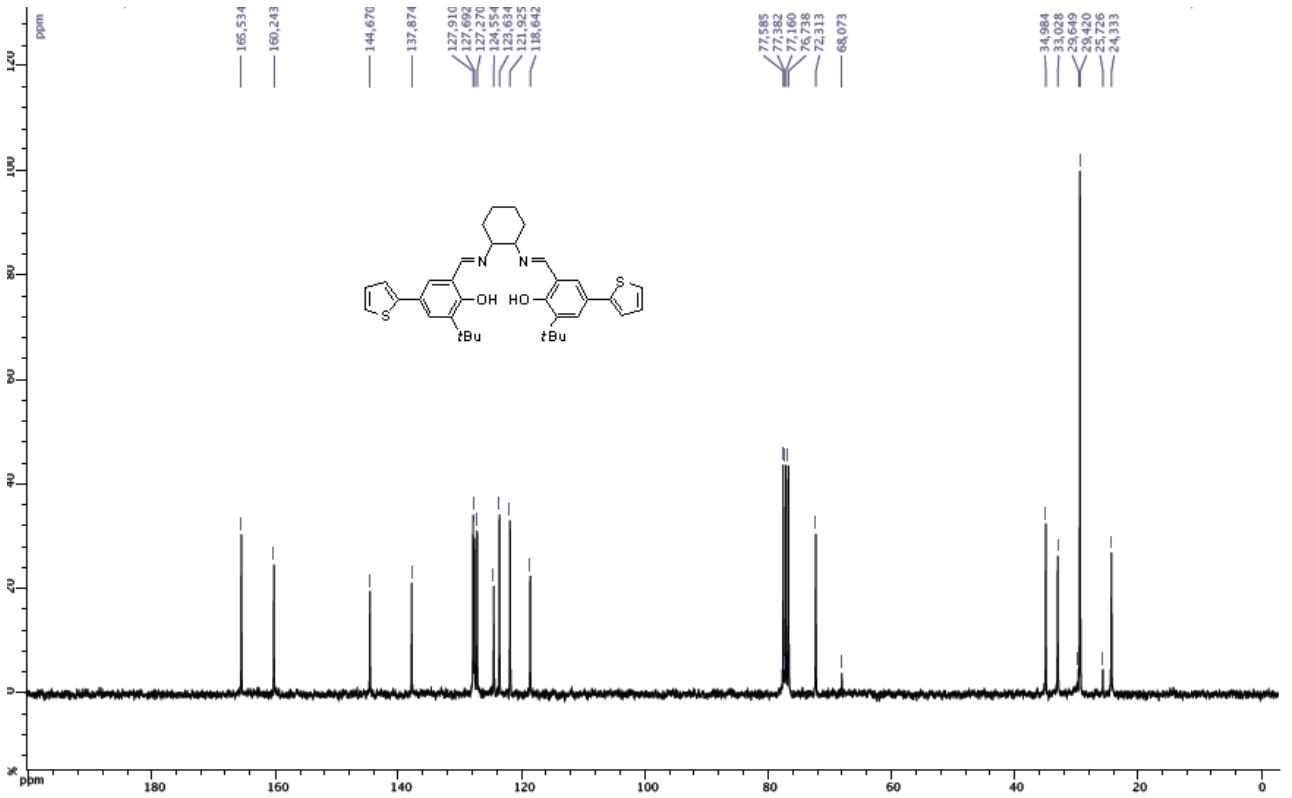
[2] The existence of induction time for the HKR catalyzed by a salen Co^{III}-OAc complex has been reported: Nielsen, L. P. C.; Zuend, S. J.; Ford, D. D.; Jacobsen, E. N. *J. Org. Chem.* **2012**, *77,* 2486.

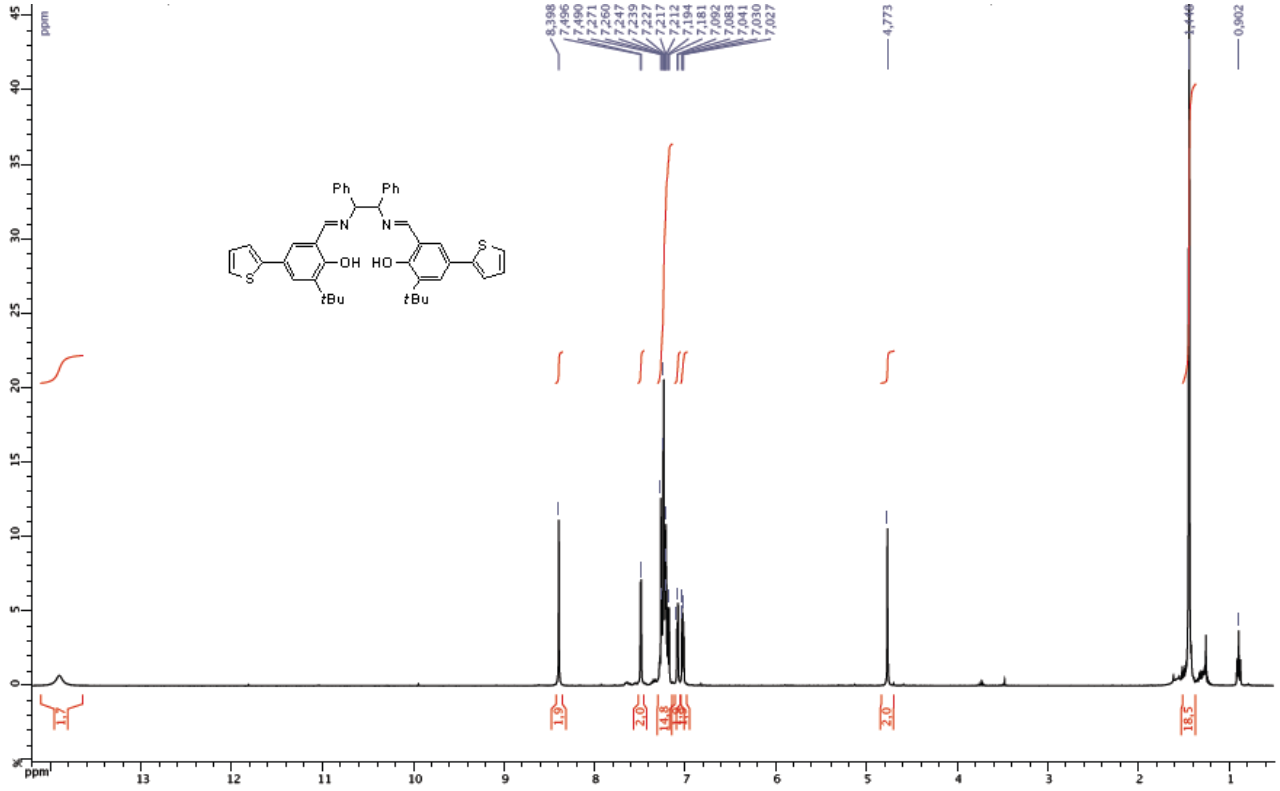


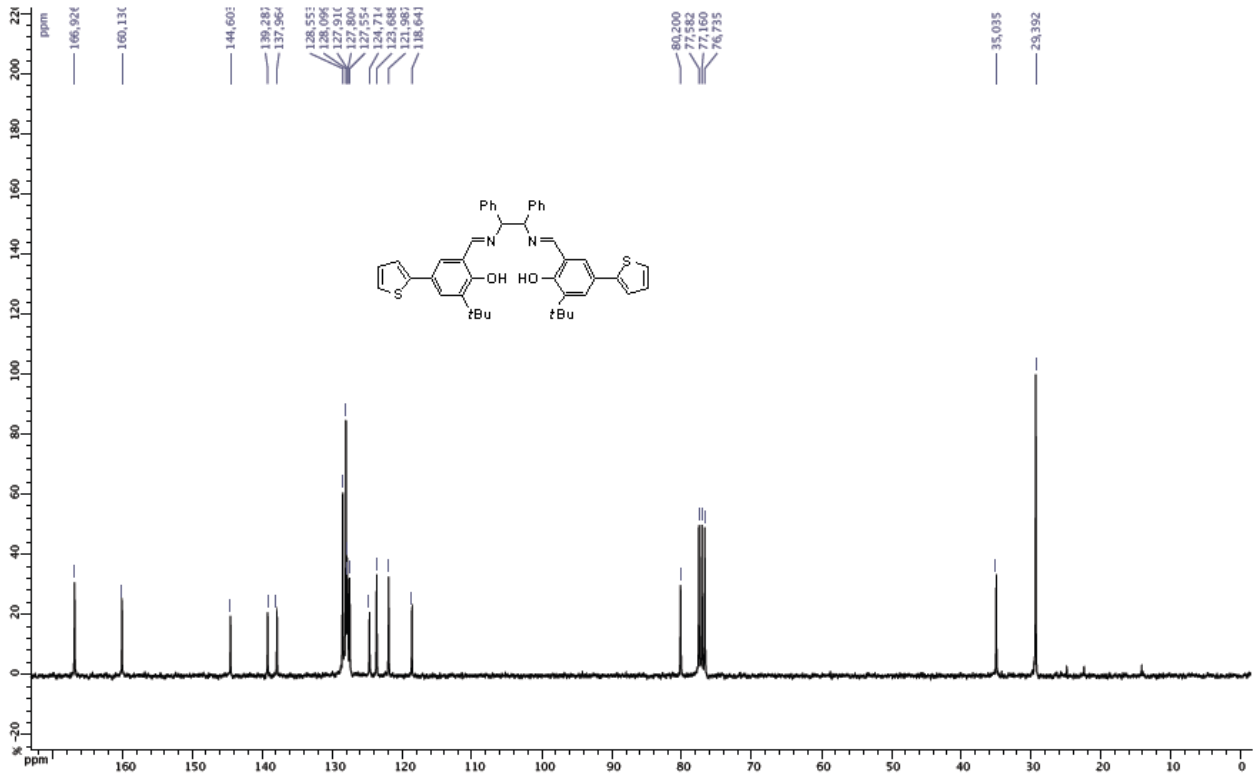
Scheme 12. log *V*/log [Co^{III}_{tot}] plot for the dynamic HKR of epibromohydrin catalysed by mixtures of (*S,S*)-**2**-Mn^{III}-Cl and (*S,S*)-**2**-Co^{III}-OAc.

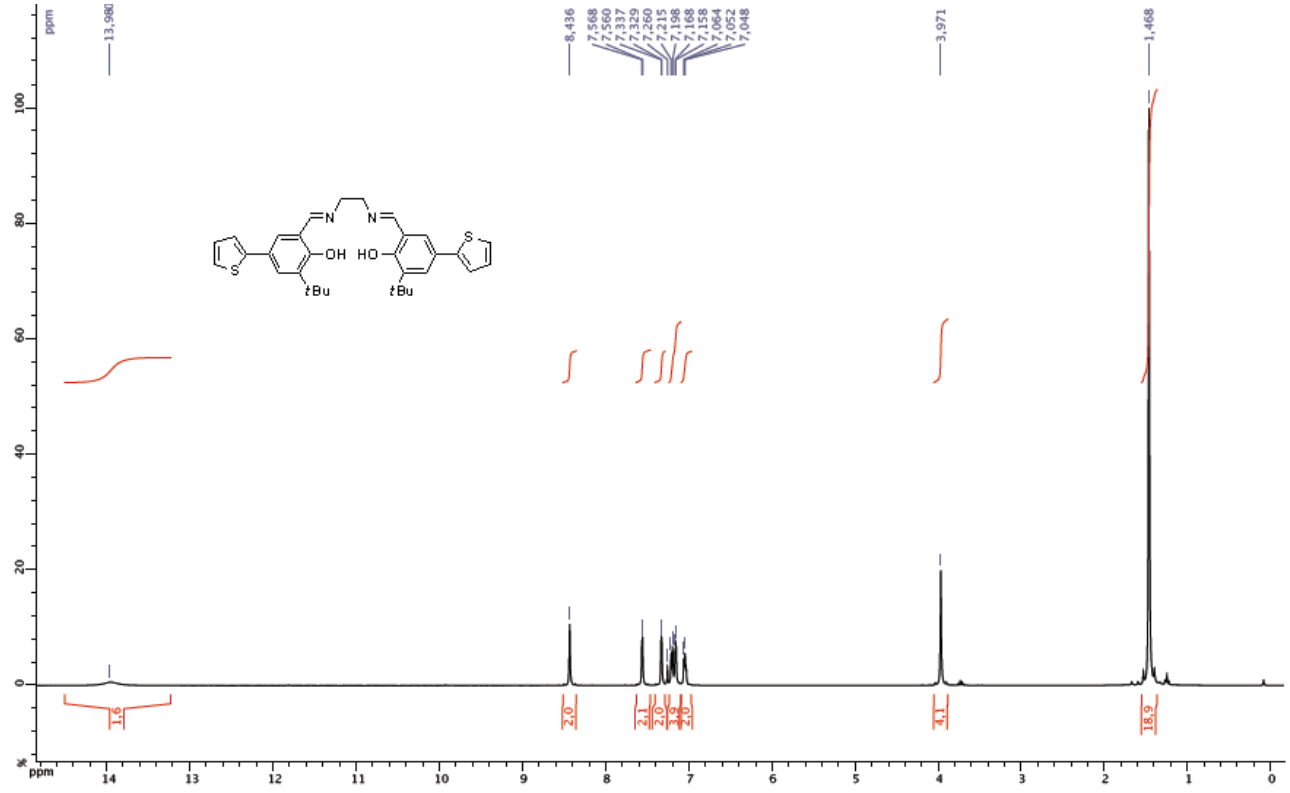
Section 6. NMR spectra

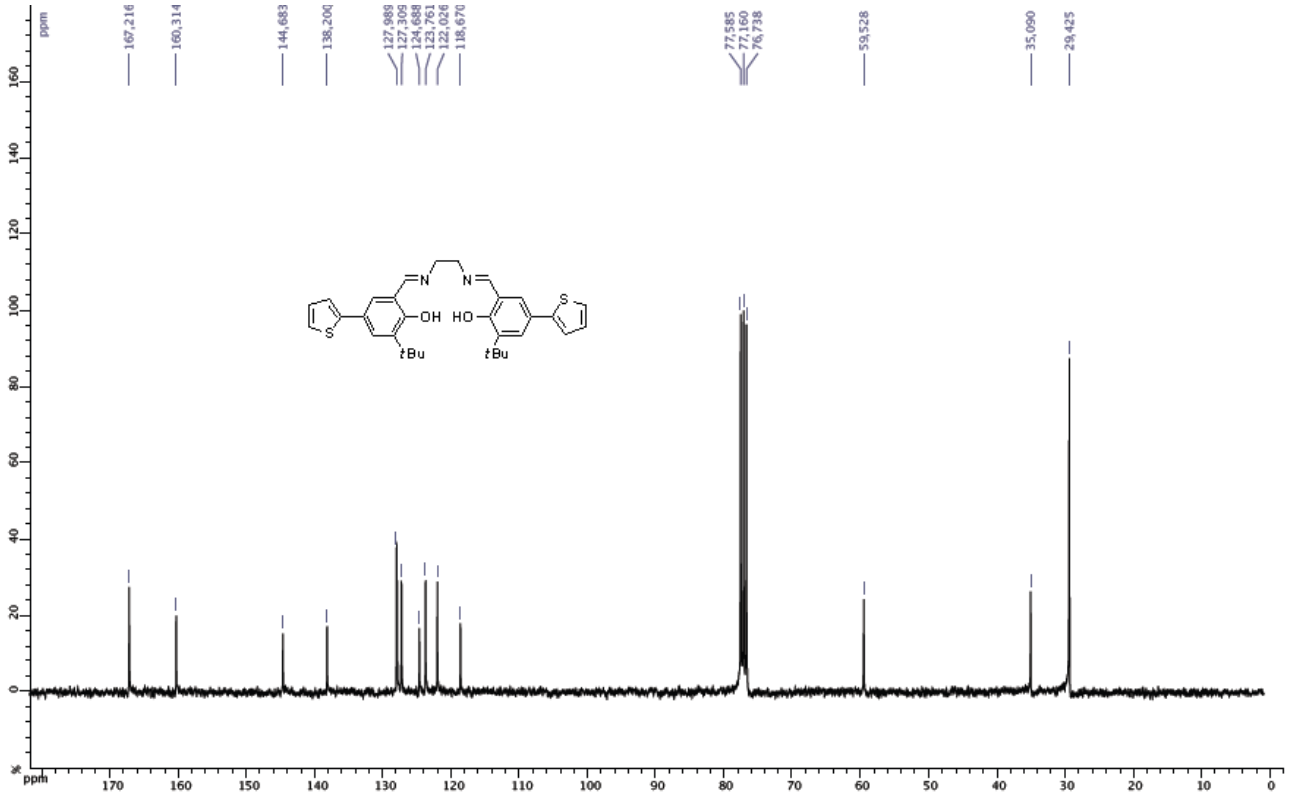


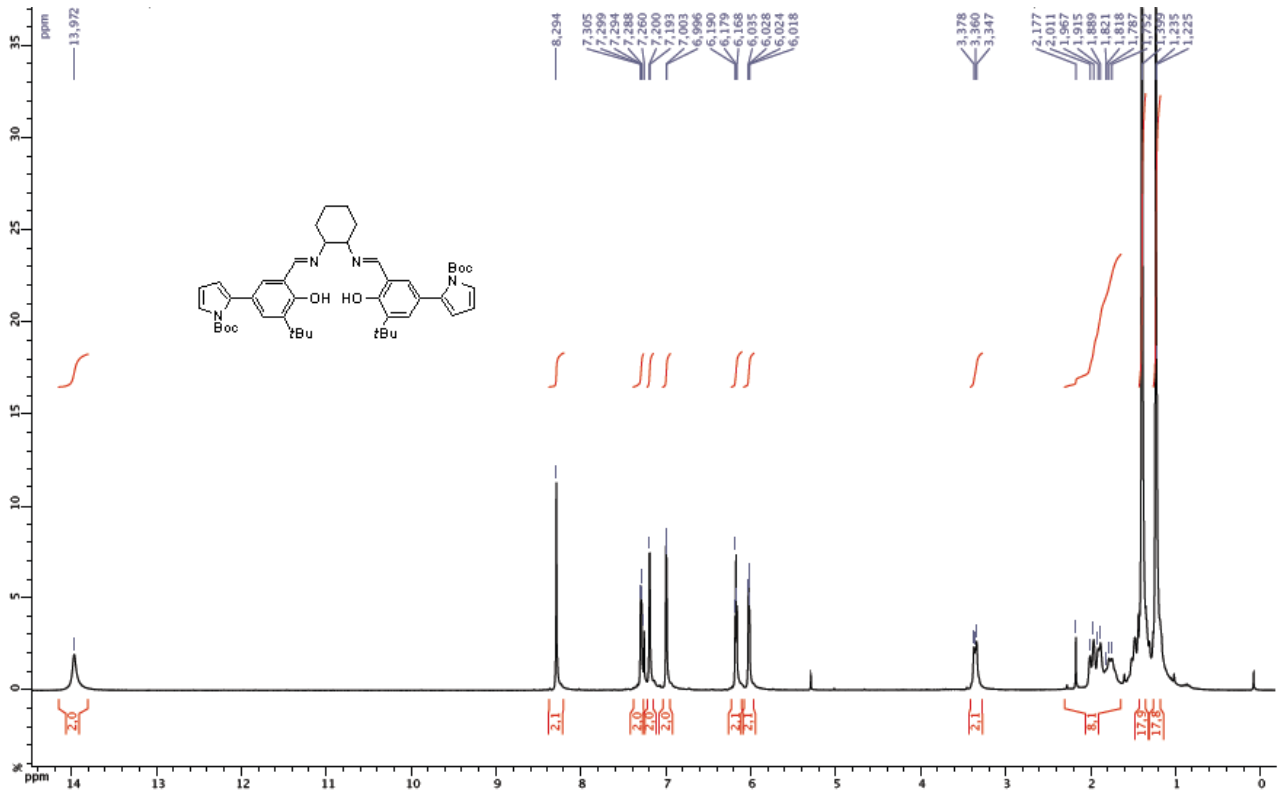


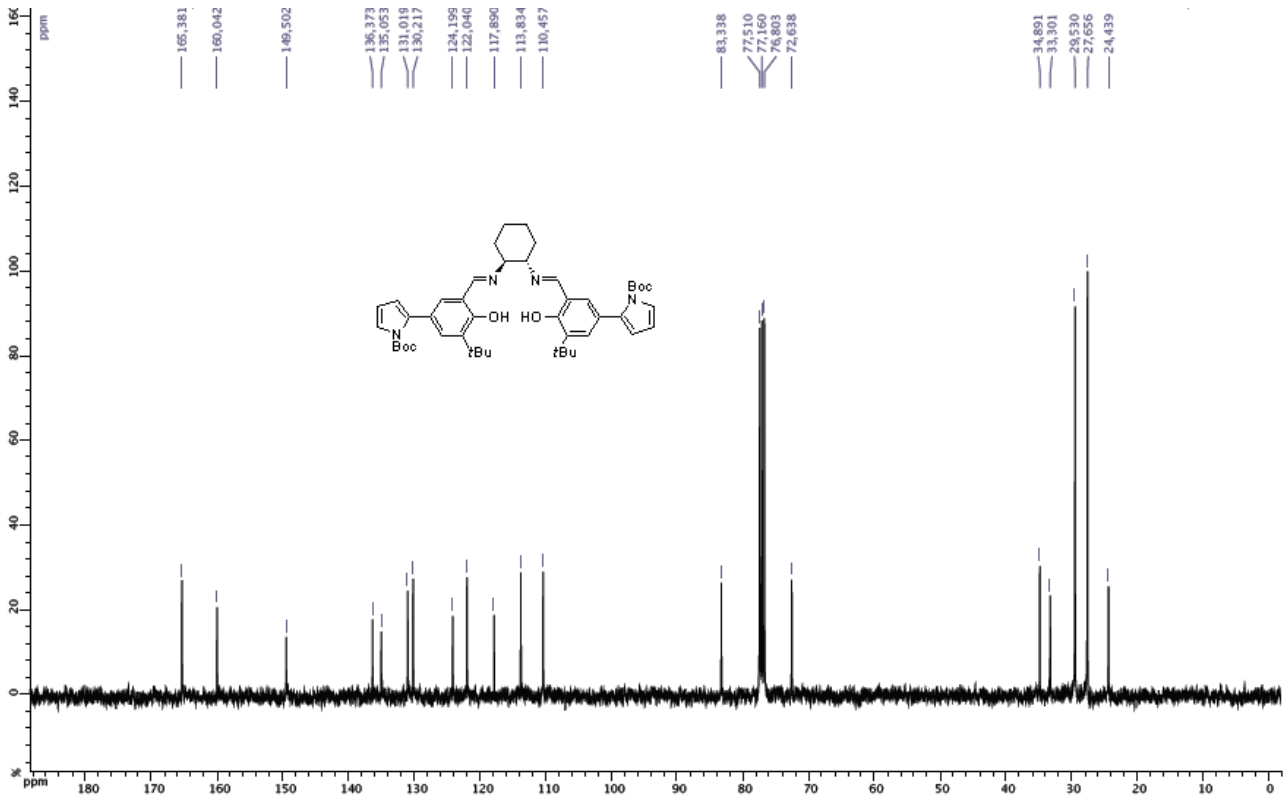

ppm
8,398
7,496
7,490
7,271
7,260
7,247
7,239
7,227
7,217
7,212
7,194
7,181
7,092
7,083
7,041
7,030
7,027
4,773
1,446
0,902
Ph
Ph
N
N
OH
HO
S
S
tBu
tBu
1,7
1,9
2,0
14,8
2,0
18,5

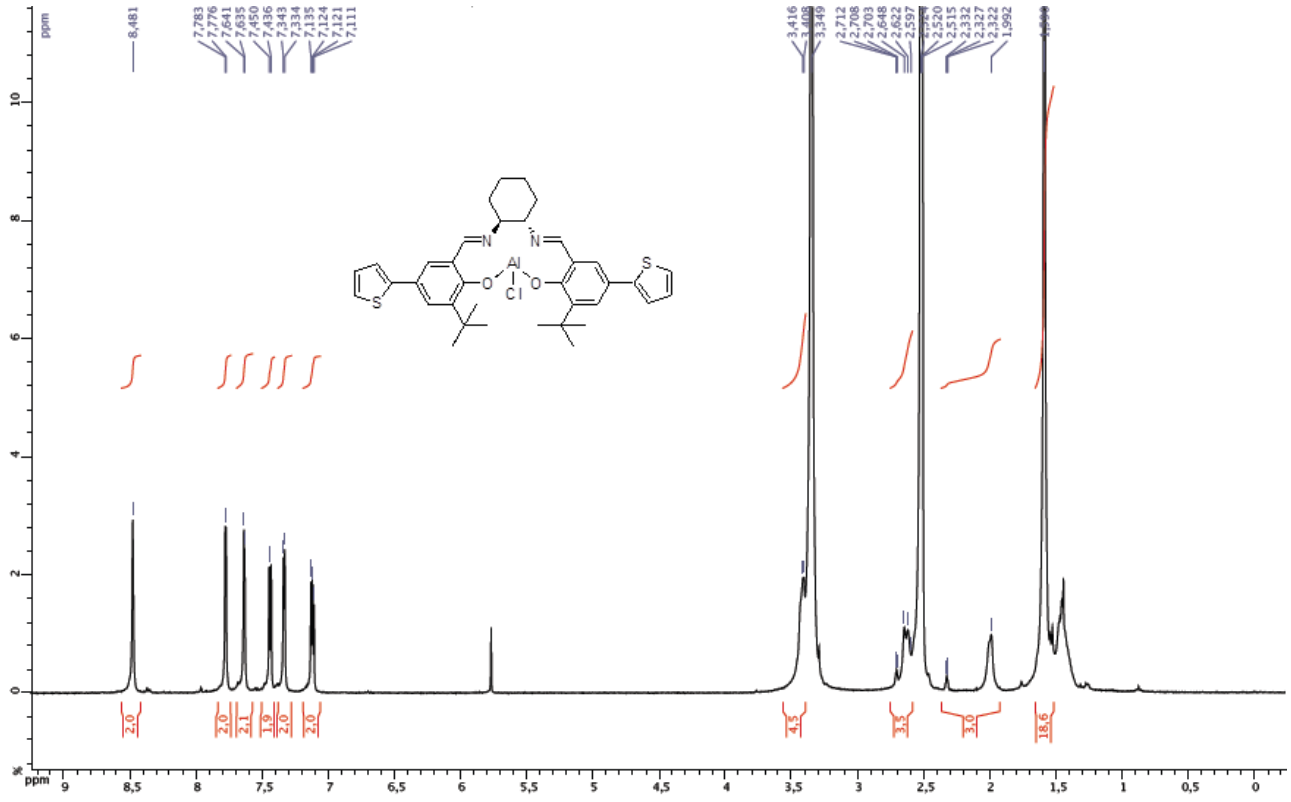

ppm
166,92
160,13
144,60
139,28
137,96
128,55
128,09
127,91
127,80
127,55
124,71
123,68
121,98
118,64
80,200
77,582
77,160
76,735
35,035
29,392
Ph
Ph
N
N
OH
HO
S
S
tBu
tBu

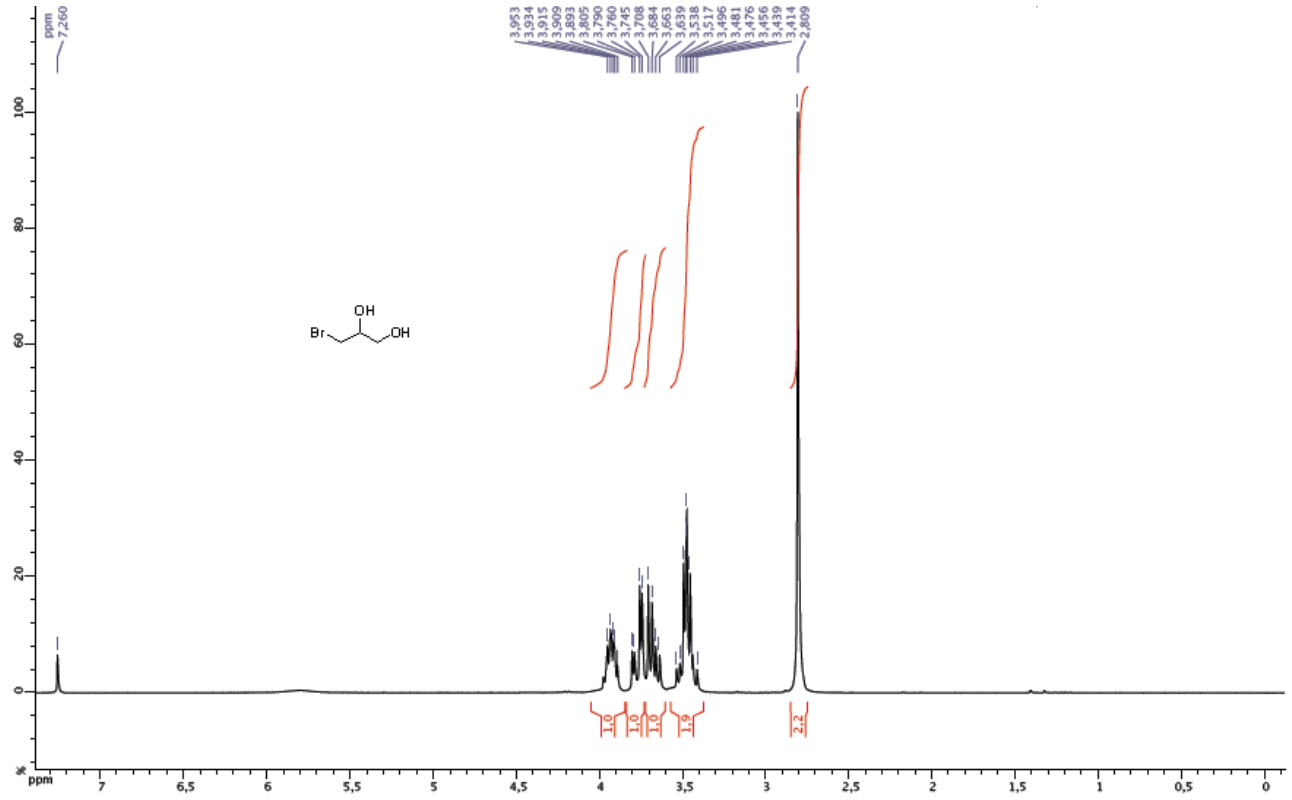

ppm
13,980
8,436
7,568
7,560
7,337
7,329
7,260
7,215
7,198
7,168
7,158
7,064
7,052
7,048
3,971
1,468
OH
HO
tBu
tBu
1,6
2,0
2,1
2,0
3,9
4,0
4,1
18,9

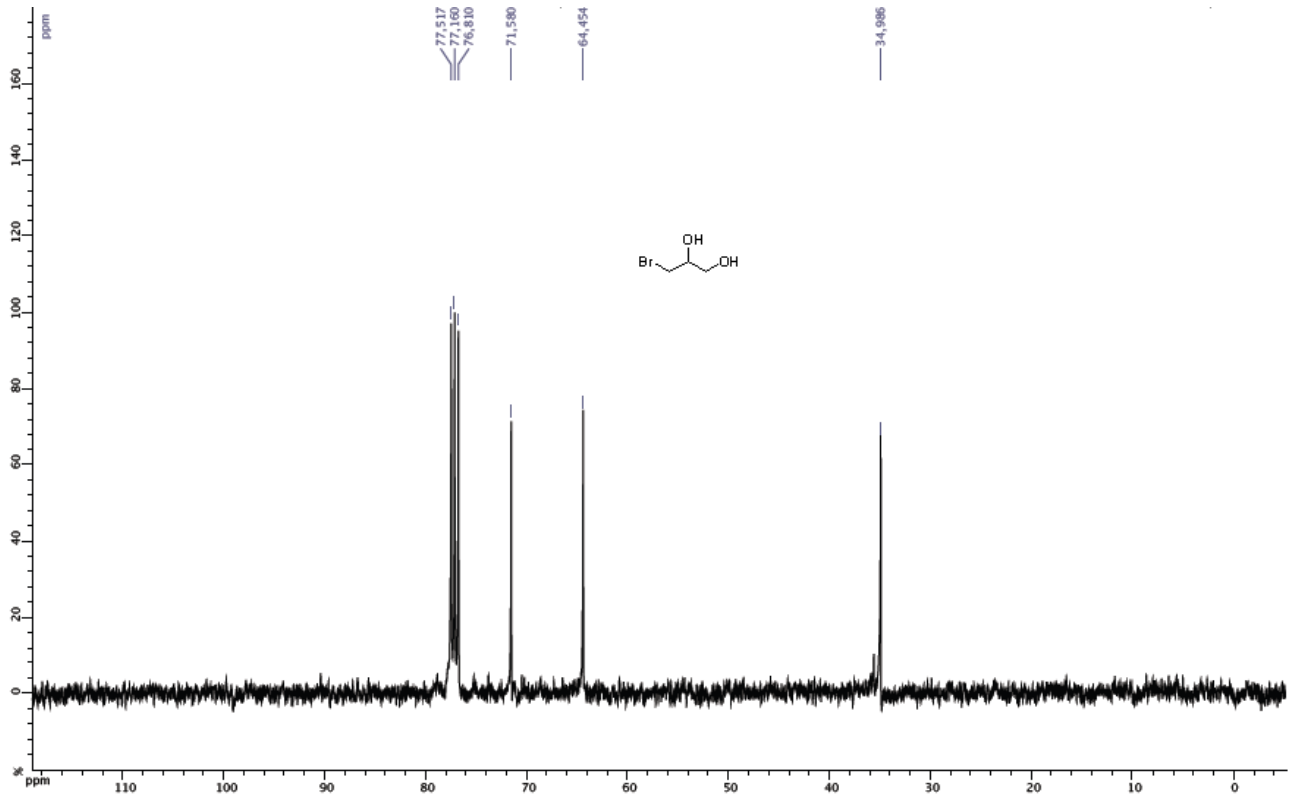

ppm
167,216
160,314
144,683
138,200
127,989
127,309
124,688
123,761
122,026
118,670
77,585
77,160
76,738
59,528
35,090
29,425
OH
HO
tBu
tBu

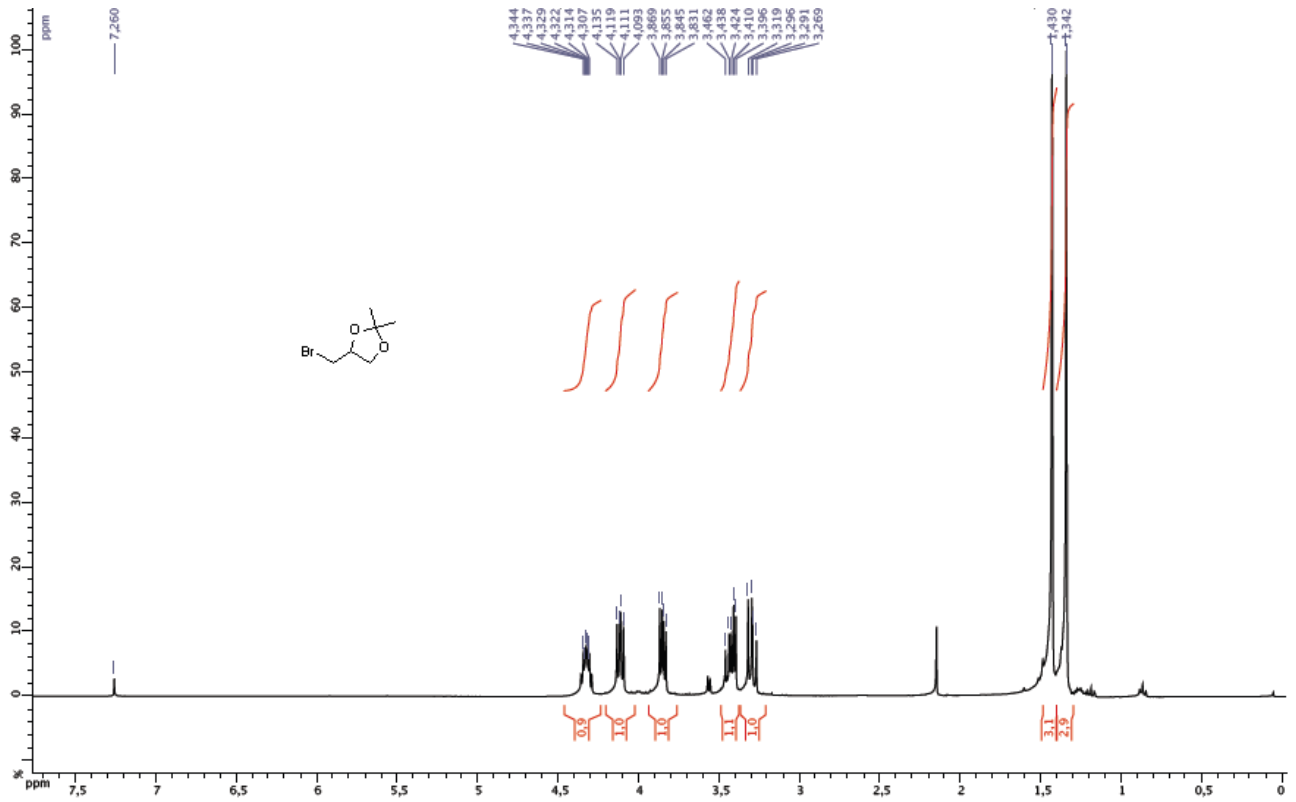

ppm
13,972
8,294
7,305
7,299
7,294
7,288
7,260
7,200
7,193
7,003
6,996
6,190
6,179
6,168
6,035
6,028
6,024
6,018
3,378
3,360
3,347
2,177
2,011
1,967
1,915
1,889
1,821
1,818
1,787
1,752
1,399
1,235
1,225
OH
HO
Boc
tBu

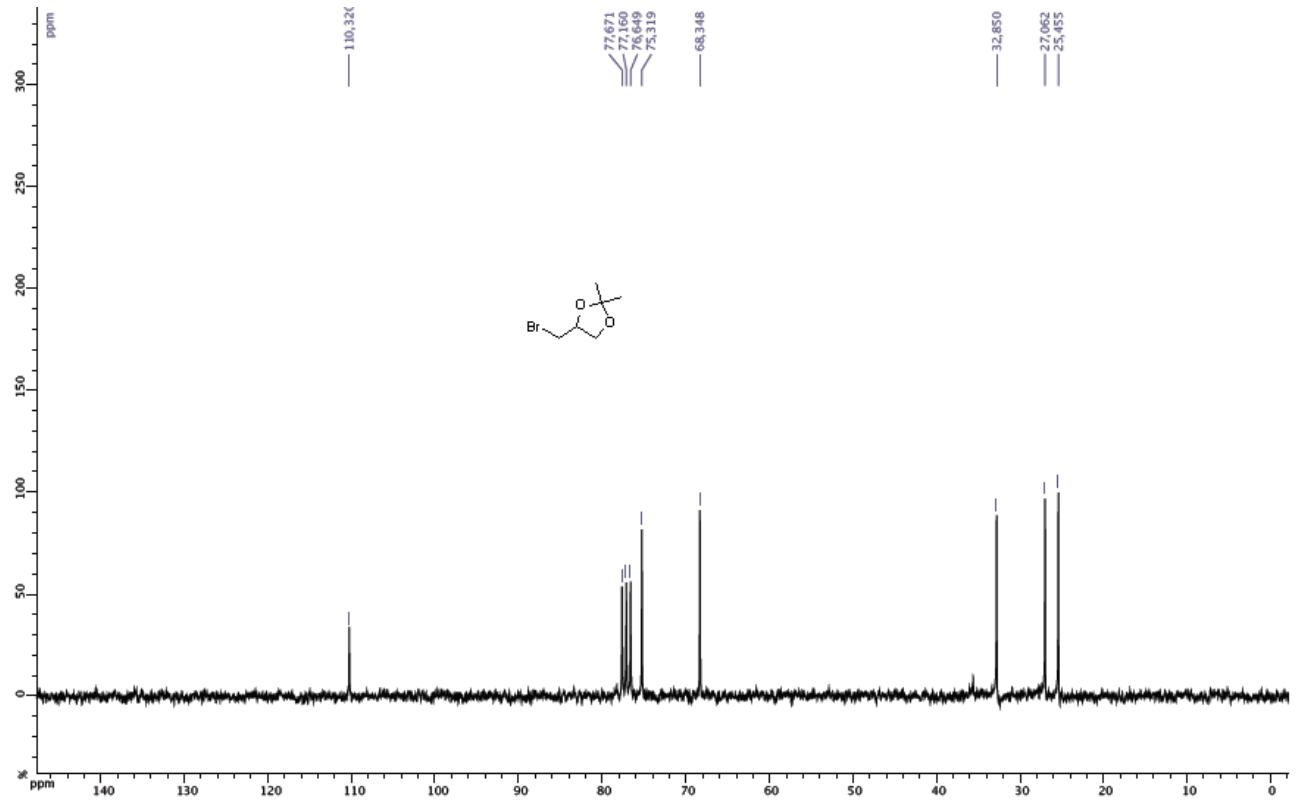

ppm
165,381
160,042
149,502
136,373
135,053
131,019
130,217
124,195
122,040
117,890
113,834
110,457
83,338
77,510
77,160
76,803
72,638
34,891
33,301
29,530
27,656
24,439
OH
HO
Boc
tBu

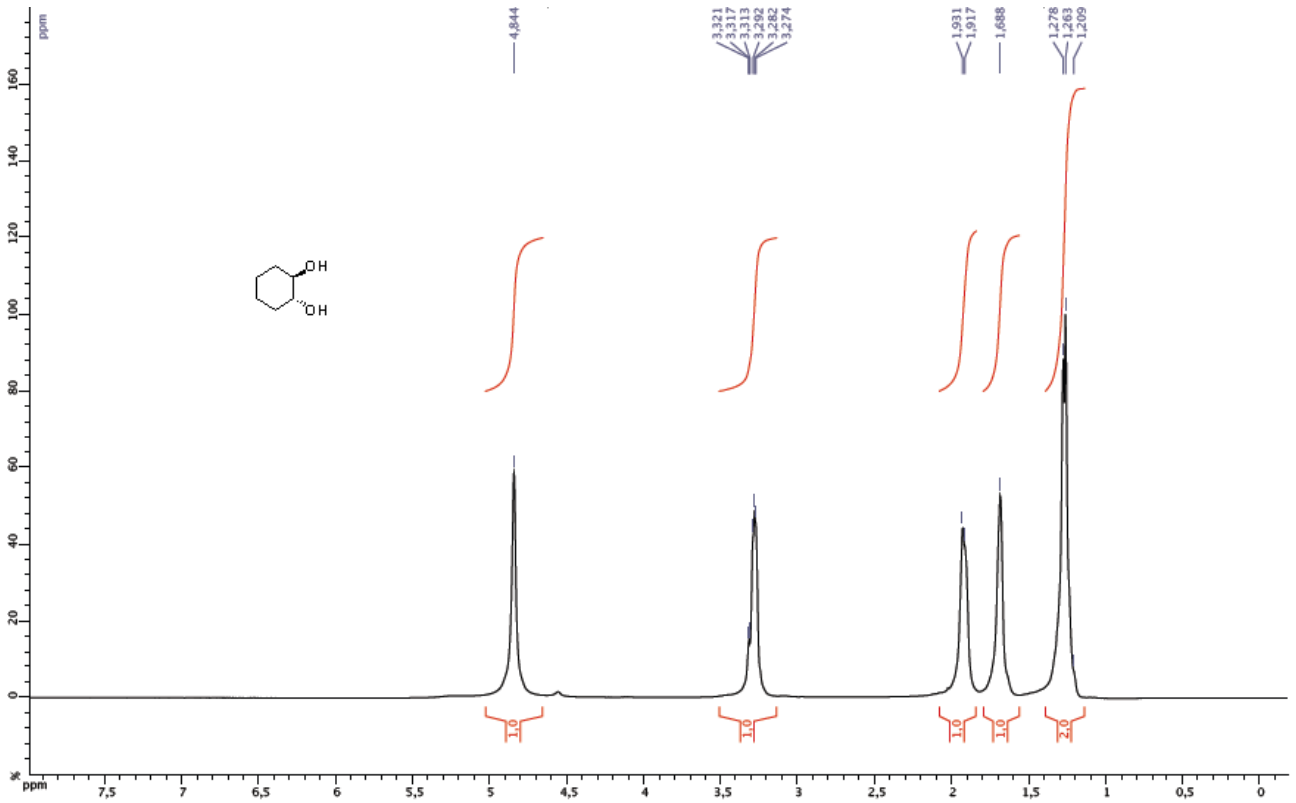

ppm
8,481
7,783
7,776
7,641
7,635
7,450
7,436
7,343
7,334
7,135
7,124
7,121
7,111
3,416
3,406
3,349
2,712
2,708
2,703
2,648
2,622
2,597
2,520
2,515
2,332
2,327
2,322
1,992
N
N
Al
Cl
O
O
S
S
2,0
2,0
2,1
1,9
2,0
2,0
4,5
3,5
3,0
18,6
ppm

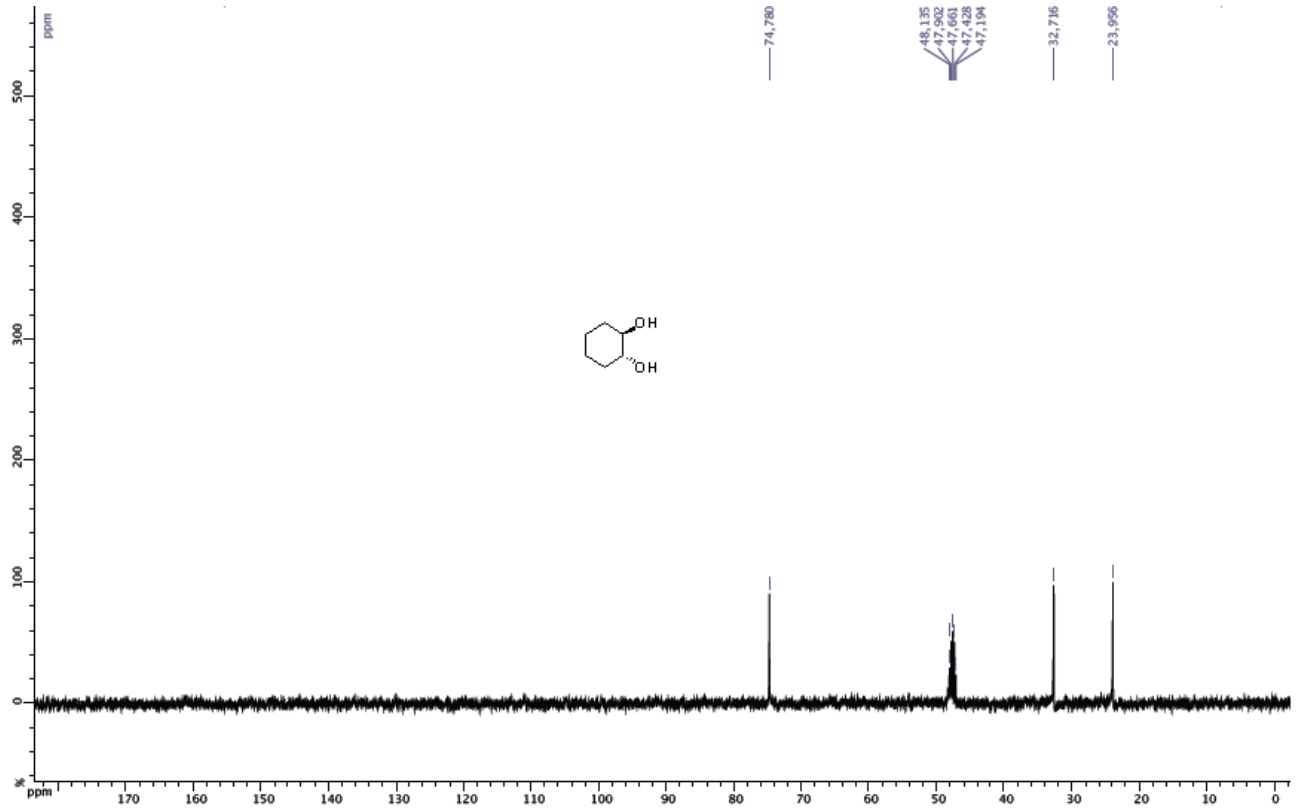

ppm
7,260
3,953
3,934
3,915
3,969
3,893
3,865
3,790
3,760
3,745
3,708
3,684
3,663
3,639
3,538
3,517
3,496
3,481
3,476
3,456
3,439
3,414
2,809
OH
Br
OH
1,0
1,0
1,0
1,9
2,2
ppm


ppm
77,517
77,160
76,810
71,580
64,454
34,986
OH
Br
OH
ppm


ppm
7,260
4,344
4,337
4,329
4,322
4,314
4,307
4,135
4,119
4,111
4,093
3,869
3,855
3,845
3,831
3,462
3,438
3,424
3,410
3,396
3,319
3,296
3,291
3,269
1,430
1,342
Br
O
O
0,9
1,0
1,0
1,1
1,0
3,1
2,9
ppm
7,5
7
6,5
6
5,5
5
4,5
4
3,5
3
2,5
2
1,5
1
0,5
0


ppm
110,326
77,671
77,160
76,649
75,319
68,348
32,850
27,062
25,455
Br
O
O
ppm
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0


ppm
4,844
3,321
3,317
3,313
3,292
3,282
3,274
1,931
1,917
1,688
1,278
1,263
1,209
OH
OH
1,0
1,0
1,0
1,0
2,0
%
ppm


ppm
74,780
48,135
47,902
47,661
47,428
47,194
32,716
23,956
OH
OH
%
ppm