Supporting Information (Experimental Part)

Confined Acid-Catalyzed Asymmetric Carbonyl–Ene Cyclization

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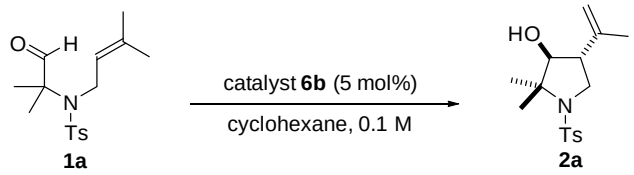
General information

Unless otherwise stated, all reagents were purchased from commercial suppliers and used without further purification. All solvents used in the reactions were distilled from appropriate drying agents prior to use. Reactions were monitored by thin layer chromatography (TLC) on silica gel pre-coated plastic sheets (0.2 mm, Macherey-Nagel). Visualization was accomplished by irradiation with UV light at 254 nm and/or phosphomolybdic acid (PMA) stain. Column chromatography was performed on Merck silica gel (60, particle size 0.040-0.063 mm). Proton and carbon NMR spectra were recorded on Bruker AV-500, Bruker AV-400 or Bruker AV-300 spectrometer in deuterated solvents. Proton chemical shifts are reported in ppm (δ) relative to tetramethylsilane (TMS) with the solvent resonance employed as the internal standard ($CDCl_3$ δ 7.26 ppm; CD_2Cl_2 δ 5.32 ppm). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, s = sextet, h = heptet, m = multiplet, br = broad), coupling constants (Hz) and integration. ^{13}C chemical shifts are reported in ppm from tetramethylsilane (TMS) with the solvent resonance as the internal standard ($CDCl_3$ δ 77.16 ppm; CD_2Cl_2 δ 53.84 ppm). Proton and carbon NMR spectra of the major diastereomer of the product **2** are reported. High resolution mass spectra were determined on a Bruker APEX III FTMS (7 T magnet). Optical rotations were determined with Autopol IV polarimeter (Rudolph Research Analytical) at 589 nm and 25 °C. Data are reported as follows: $[\alpha]_{\lambda}^{temp}$, concentration (c in g/100 mL), and solvent. Enantiomeric ratios (e.r.) of the cyclic homoallylic alcohols were determined by GC or HPLC analysis employing a chiral stationary phase column specified in the individual experiment, by comparing the samples with the appropriate racemic mixtures.

1.ESI-MS Studies

In order to elucidate the reaction mechanism, we performed Electrospray Ionization Mass Spectroscopy (ESI-MS) studies using the cyclization of olefinic aldehyde **1a** as a model reaction. For this purpose, we carried out two reactions: One experiment was the cyclization of **1a** in the presence of catalytic amounts of catalyst **6b** under the optimized reaction conditions, and the other experiment was performed in the presence of catalytic amounts of catalyst **6c**. General procesure: substrate **1a** (15.5 mg, 0.05mmol) and dry cyclohexane (0.5 mL) were added to a vial, then catalyst **6b** (2.45 mg, 0.0025 mmol) or **6c** (3.3 mg, 0.0025 mmol) were added at 22 °C. Samples of the reaction mixtures were monitored at different time during the initial 24h. The selected spectra Figure S1 and Figure S2, and the HRMS data of the catalyst **6b**, **6c**, and intermediate **7b**, **7c** were sumerized in Table S1 and Table S2. The ESI-MS obtained revealed the characteristic signals of free catalysts **6b** and **6c**. As soon as substrate **1a**, catalyst **6b** were combined under the optimized reaction conditions, the new peak at *m/z* 1291.3 could be detected which matches the mass of the covalent the intermediate [**7b** + H]$^+$ generated from substrate **1a** and the corresponding catalyst **6b**. Interestingly, the fact that the intermediate **7b** could be easily detected under the reaction conditions, while the catalyst **6b** remained below the detection limit, suggested that the elimination of catalyst **6b** from **7b** could be the rate-limiting step of the whole reaction.



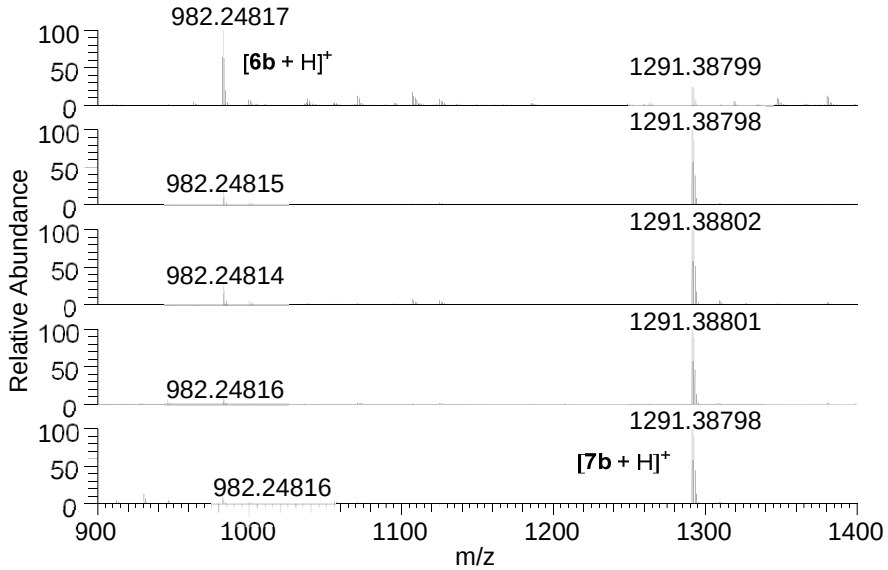


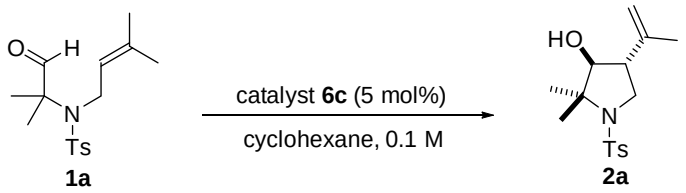
Figure S1. ESI-MS study: The reaction was performed using catalyst **6b** (2.45 mg, 0.0025 mmol), **1a** (15.5 mg, 0.05mmol) in dry cyclohexane (0.5 mL) at room temperature, and samples of the reaction mixtures were monitored at different time during the initial 24 h.

Table S1. High-Resolution Mass Data[a]

species	formula	HRMS calcd	HRMS found	deviation [ppm]
	$C_{64}H_{42}NO_6P_2$	982.24819	982.24816	0.03
	$C_{80}H_{65}N_2O_9P_2S$	1291.38805	1291.38801	0.03

[a]The reaction was performed using catalyst **6b** (2.45 mg, 0.0025 mmol), **1a** (15.5 mg, 0.05mmol) in dry cyclohexane (0.5 mL) at room temperature and samples of the reaction mixtures were monitored at different time during the initial 24h

As soon as substrate **1a**, catalyst **6c** were combined under the optimized reaction conditions, the new peak at *m/z* 1627.7 could be detected which match the masses of the covalent the intermediate $[\mathbf{7c} + H]^+$ generated from substrate **1a** and the corresponding catalyst **6c**.



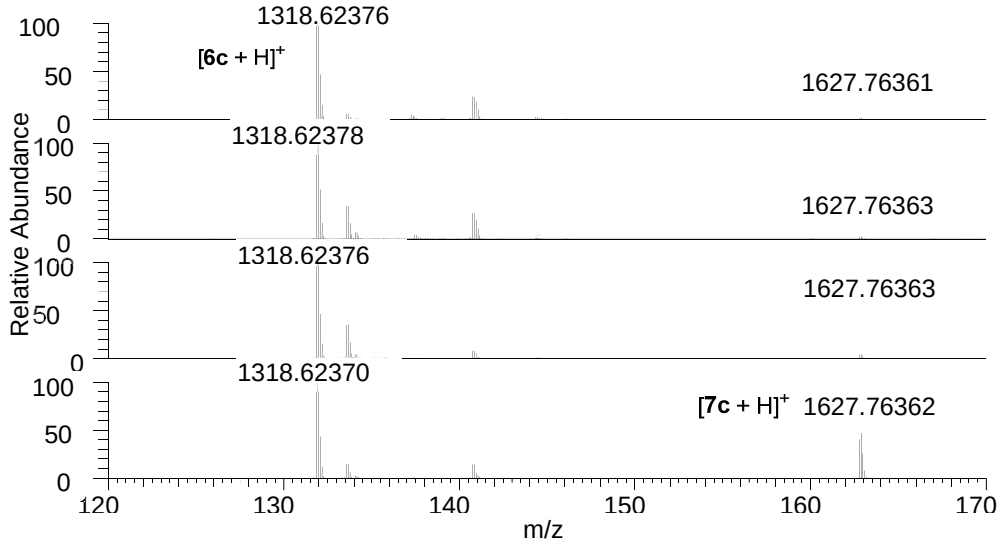
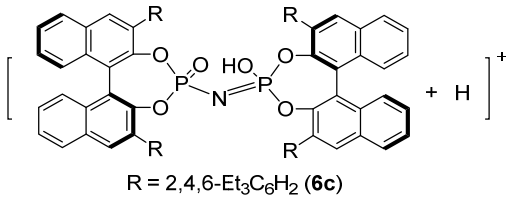
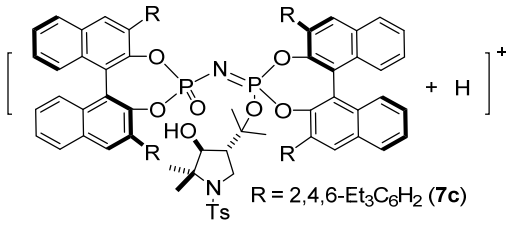


Figure S2. ESI-MS study: The reaction was performed using catalyst **6c** (3.3 mg, 0.0025 mmol), **1a** (15.5 mg, 0.05mmol) in dry cyclohexane (0.5 mL) at room temperature and samples of the reaction mixtures were monitored at different time during the initial 24h.

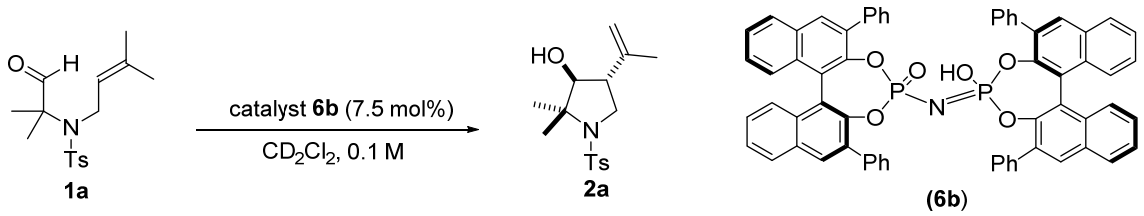
Table S2. High-Resolution Mass Data[a]

species	formula	HRMS calcd	HRMS found	deviation [ppm]
 R = 2,4,6-$Et_3C_6H_2$ (**6c**)	$C_{88}H_{90}NO_6P_2$	1318.62379	1318.62370	0.07
 R = 2,4,6-$Et_3C_6H_2$ (**7c**)	$C_{104}H_{113}N_2O_9P_2S$	1627.76365	1627.76362	0.02

[a]The reaction was performed using catalyst **6c** (3.3 mg, 0.0025 mmol), **1a** (15.5 mg, 0.05mmol) in dry cyclohexane (0.5 mL) at room temperature and samples of the reaction mixtures were monitored at different time during the initial 24 h.

2. NMR Kinetic Studies

To further support the covalent compound **7** as catalytic intermediate, we carried out NMR kinetic studies. In the beginning, we investigated the following reaction: Substrate **1a** (15.5 mg, 0.05mmol) and dry CD_2Cl_2 (0.5 mL) were added to a dry NMR tube, then catalyst **6b** (3.93 mg, 0.004 mmol) was added at 22 °C. ^{1}H NMR spectra of the reaction mixtures were monitored at various time until full conversion was reached (Figure S3). Selected ^{31}P NMR spectra were shown in Figure S3. In accordance with the ESI-MS studies, new species **7b** was generated as soon as substrate **1a**, catalyst **6b** and solvent CD_2Cl_2 were combined (Figure S3, S4), which were fully consistent with the compounds **7b** which was carefully characterized in the next section. On the basis of the fact that catalyst **6b** remained below the detection limit in both of ^{1}H NMR spectra and ^{31}P NMR spectra for a long period in the reaction, suggested that the reaction of Figure S3 apparently proceeded through a covalent intermediate **7b** and the elimination of **6b** from **7b** could be the rate-determining step which consisted with the results of previous ESI-MS studies. Remarkably, the ^{31}P NMR spectra of the reaction mixtures shown in Figure S4 were in accordance with stereoselectivities of the reaction. 8 peaks were detected in the ^{31}P NMR spectra of reaction mixture, which consisted with the poor enantioselectivity and high diastereoselectivity (53.5:46.5 e.r. and >20:1 d.r.).



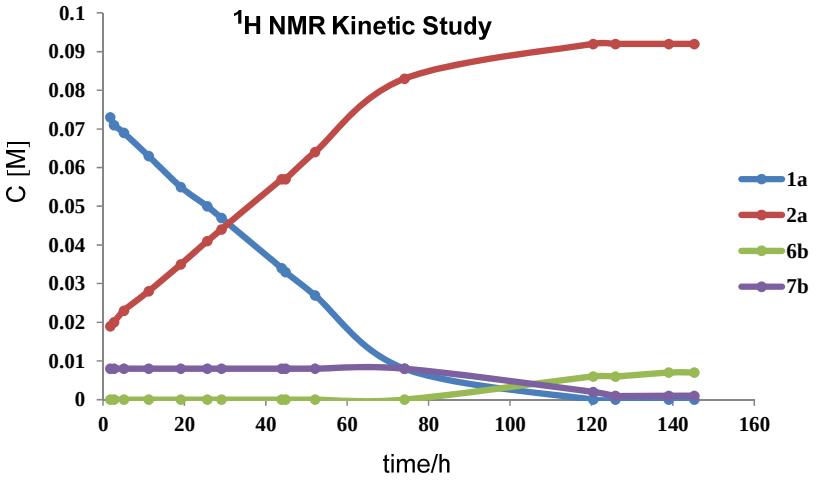


Figure S3. ^{1}H NMR kinetic study: The reaction was performed using catalyst **6b**.

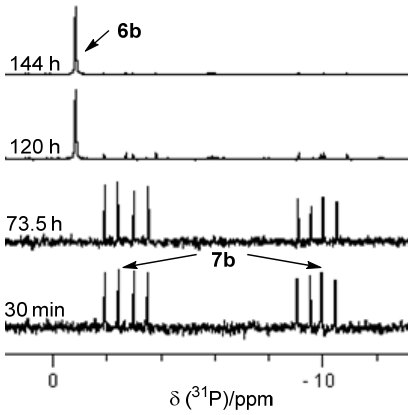
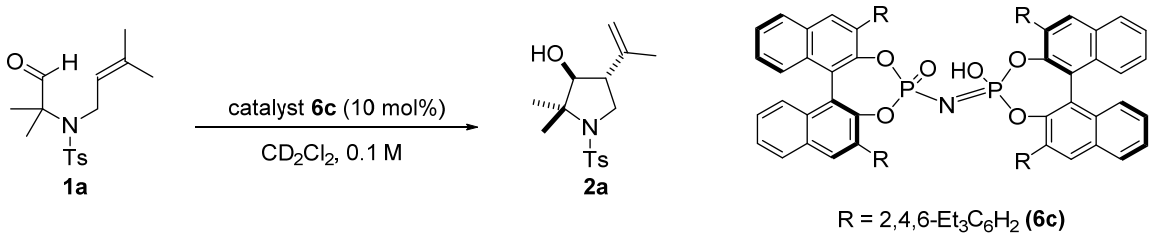


Figure S4. ^{31}P NMR Spectra of Reaction Mixtures using catalyst **6b** taken at various time.

In the next, we carried out another reaction substrate **1a** (15.5 mg, 0.05mmol) and dry CD_2Cl_2 (0.5 mL), were added to a dry NMR tube, then catalyst **6c** (6.59 mg, 0.005 mmol) was added at 22 °C. ^1H NMR spectra of the reaction mixtures were monitored at various time until full conversion was reached (Figure S5). The selected ^{31}P NMR spectra were selectively measured (Figure S6). Similar to previous observations, **7c** was generated as soon as substrate **1a**, catalyst **6c** and CD_2Cl_2 were combined (Figure S5, S6), which were fully consistent with the compounds **7c** which was also carefully characterized later. At the same time, 4 peaks were detected in the ^{31}P NMR spectra of reaction mixture of Figure S5, which were in accordance with excellent enantioselectivity and diastereoselectivity (97.5:2.5 e.r. and >20:1 d.r.). Obviously, according to the ^1H and ^{31}P NMR data, the continual transformation of compound **7c** allowed accomplishing the regeneration of catalyst **6c** and affording product. Intermediate **7c** could not be detected after completion the reaction, ruling out the possibility that compound **7c** was formed from product **2a** and catalyst **6c**. Also, if product **2a** (0.1M, CD2Cl2) was mixed with catalyst **6c** (10 mol%), adduct **7c** could not be detected within 48h.



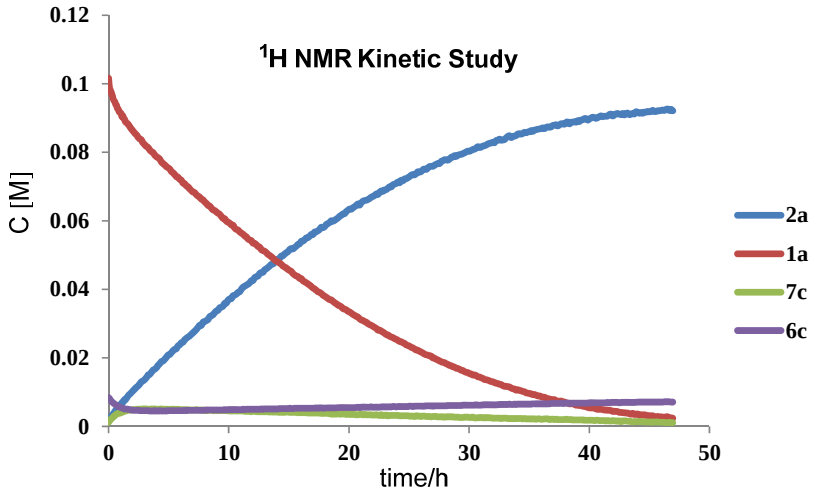


Figure S5. ^{1}H NMR Kinetic Study

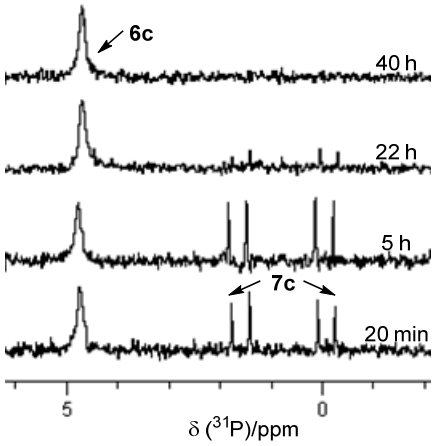


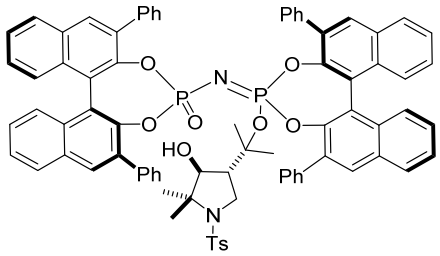
Figure S6. ^{31}P NMR Spectra of Reaction Mixtures taken at various time using catalyst **6c**.

3. Characterization of Intermediate 7

3.1. Characterization of Intermediate 7b

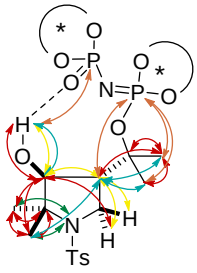
The detected intermediate **7b** were futher characterized by ^{1}H, ^{13}C, ^{1}H-^{1}H NOESY, ^{1}H-^{13}C HMBC, ^{1}H-^{31}P HMBC and ^{1}H-^{15}N HMBC NMR experiments of reaction mixture. The ^{15}N-, ^{13}C- and ^{31}P spectra of intermediate **7b** were referenced indirectly to the referenced proton frequency with the Ξ-scale[1,2] with the factors 0.10136767 for ^{15}N ($\delta(MeNO_2)$ = 0 ppm), 0.25145020 for ^{13}C ($\delta(Me_4Si)$ = 0 ppm)) and 0.40480742 for ^{31}P ($\delta(H_3PO_0)$ = 0 ppm)). The ^{15}N chemical shifts were determined from the indirect dimension of a ^{1}H,^{15}N-HMBC. The abosolute configuration of two diastereomers of **7b** was not determined.

HRMS *m/z* (ESI): calcd. for $C_{80}H_{65}N_2O_9P_2S$ [M+H]: 1291.38805; found: 1291.38801.



Intermediate **7b**

Diastereomer I of **7b**



Connections showing J-couplings

^{1}H-^{1}H-COSY

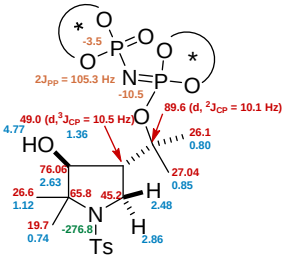
^{1}H-^{31}P-HMBC

^{1}H-^{15}N-HMBC

^{1}H-^{13}C-HMBC

Connections showing close distances of atoms

^{1}H-^{1}H-NOESY



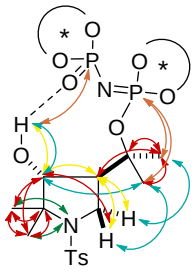
^{1}H (ppm)

^{13}C (ppm)

^{15}N (ppm)

^{31}P (ppm)

Diastereomer II of **7b**



Connections showing J-couplings

^{1}H-^{1}H-COSY

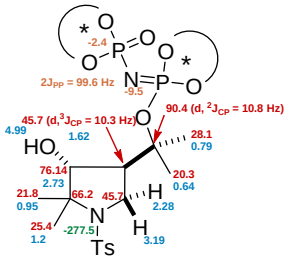
^{1}H-^{31}P-HMBC

^{1}H-^{15}N-HMBC

^{1}H-^{13}C-HMBC

Connections showing close distances of atoms

^{1}H-^{1}H-NOESY



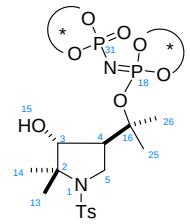
^{1}H (ppm)

^{13}C (ppm)

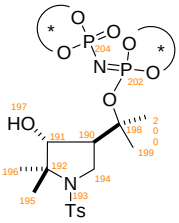
^{15}N (ppm)

^{31}P (ppm)

Selected NMR spectra of Intermediate 7b

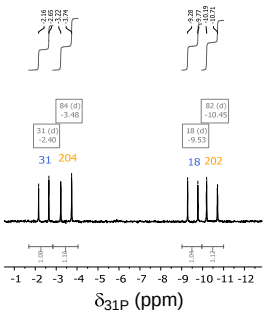


Diastereomer I of **7b**

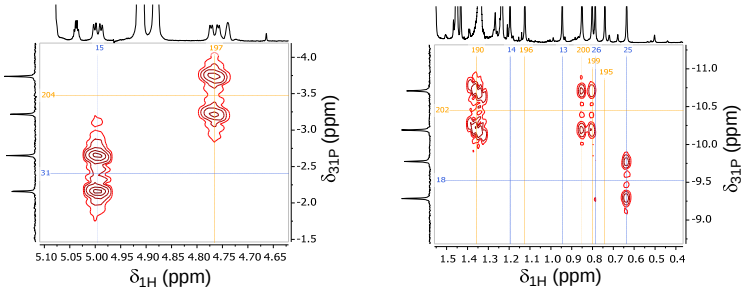


Diastereomer II of **7b**

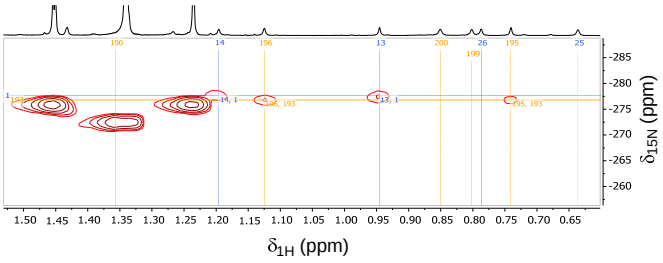
^{31}P NMR Spectrum



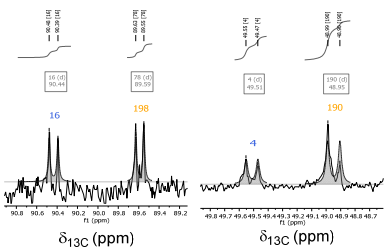
^{1}H-^{31}P-HMBC NMR Spectrum



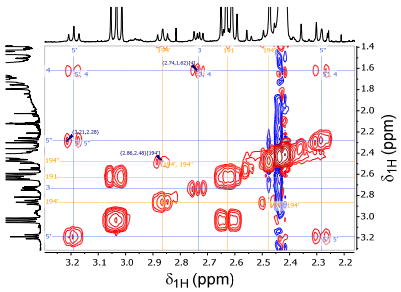
^{1}H-^{15}N-HMBC NMR Spectrum



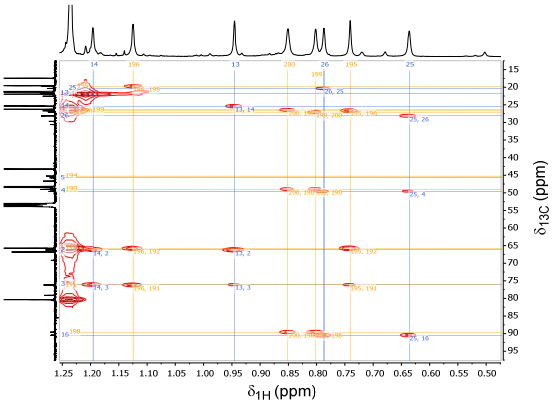
^{13}C NMR Spectrum



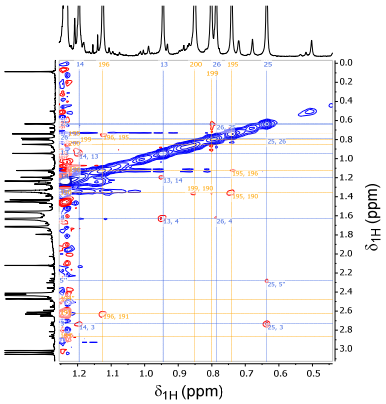
^{1}H-^{1}H-COSY NMR Spectrum



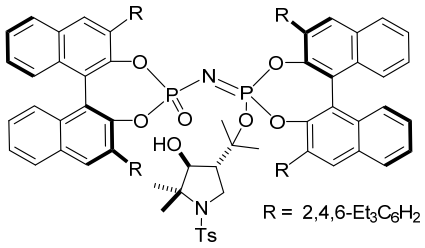
^{1}H-^{13}C-HMBC NMR Spectrum



^{1}H-^{1}H-NOESY NMR Spectrum



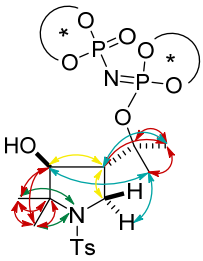
3. 2. Characterization of Intermediate 7c



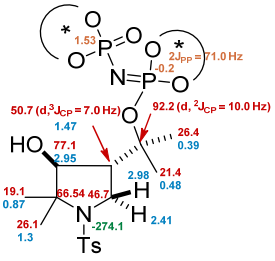
Intermediate **7c**

The detected intermediate **7c** were futher characterized by ^{1}H, ^{13}C, ^{1}H-^{1}H NOESY, ^{1}H-^{13}C HMBC, ^{1}H-^{31}P HMBC and ^{1}H-^{15}N HMBC NMR experiments of reaction mixture. The ^{15}N-, ^{13}C- and ^{31}P spectra of intermediate **7c** were referenced indirectly to the referenced proton frequency with the Ξ-scale[1,2] with the factors 0.10136767 for ^{15}N (δ(Me**N**O$_2$) = 0 ppm), 0.25145020 for ^{13}C (δ(Me$_4$Si) = 0 ppm)) and 0.40480742 for ^{31}P (δ(H$_3$PO$_0$) = 0 ppm)). The ^{15}N chemical shifts were determined from the indirect dimension of a ^{1}H,^{15}N-HMBC. The abosolute configuration of two diastereomers of **7c** was not determined.

HRMS *m/z* (ESI): calcd. for $C_{104}H_{113}N_2O_9P_2S$ [M+H]: 1627.76365; found: 1627.76362.



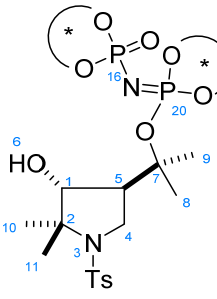
Connections showing J-couplings
^{1}H-^{1}H-COSY
^{1}H-^{15}N-HMBC
^{1}H-^{13}C-HMBC
Connections showing close distances of atoms
^{1}H-^{1}H-NOESY

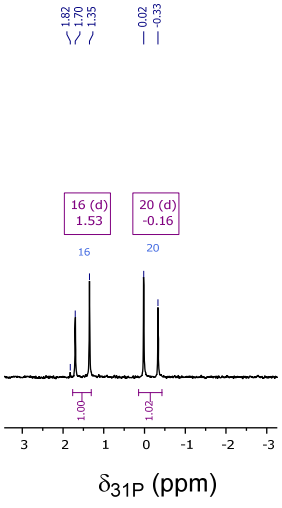


^{1}H (ppm)
^{13}C (ppm)
^{15}N (ppm)
^{31}P (ppm)

Selected NMR spectra of Intermediate 7c

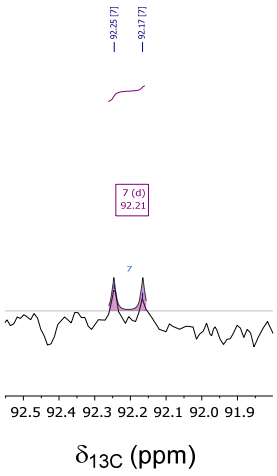
^{31}P NMR Spectrum





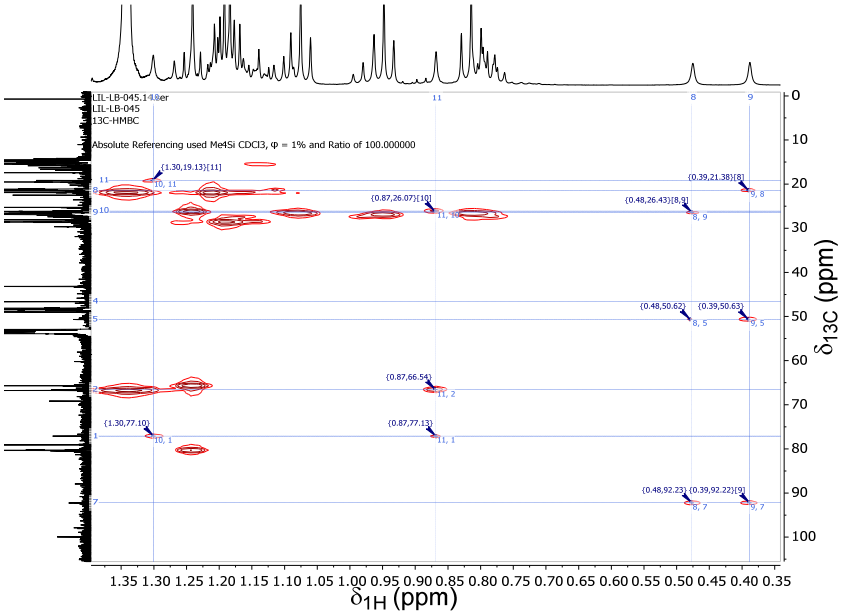
δ_{31P} (ppm)

^{13}C NMR Spectrum

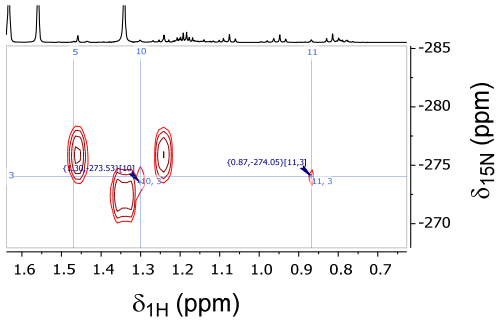


δ_{13C} (ppm)

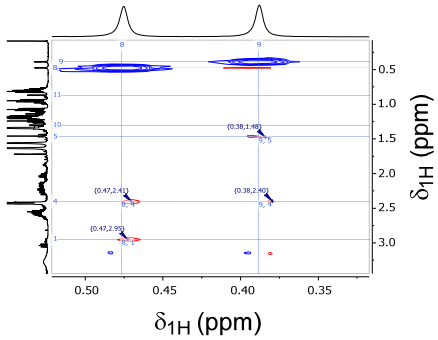
^{1}H-^{13}C-HMBC NMR Spectrum



^{1}H-^{15}N-HMBC NMR Spectrum

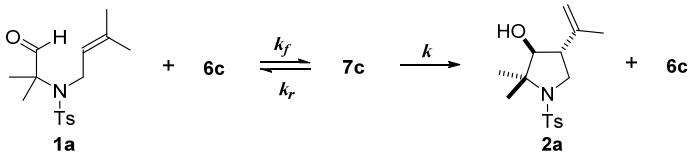


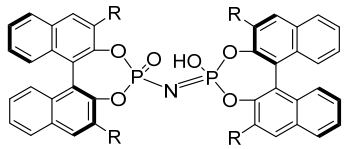
^{1}H-^{1}H-NOESY NMR Spectrum



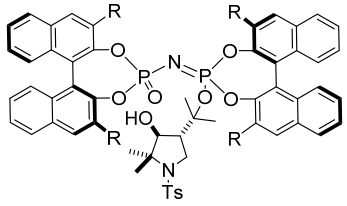
4. Eyring Equation Studies

The activation parameters of the elimination of catalyst **6c** from **7c** were determined by measuring the rate constant as a function of temperatures on the basis of Eyring equation. By reducing the loading of the catalyst **6c** to 1 mol%, all the catalyst **6c** could be saturated to the intermediate **7c**. Subsequently, the concentration of **7c** did not change in the beginning of the reaction, so the reaction rate to generate the product **2a** reached V_{max} in the beginning of the reaction($d[\mathbf{2a}] = \mathbf{k}\,[\mathbf{7c}]\,dt$). We carried out the following reactions: substrate **1a** (235.2 mg, 0.76 mmol) and dry CD_2Cl_2 (0.5 mL) were added to a dry NMR tube, then catalyst **6c** (10 mg, 0.0076 mmol) was added at -78°C. Then the reaction was performed at various temperatures. The total volume of sample was 0.7 ml at 22°C and we ignored the changes of volume at different temperatures. ^{1}H and ^{31}P NMR spectra of the reaction mixtures were monitored at various time. The kinetic data of time versus ***[2a]*** were provided, and the ***[2a]*** was determined by several different signals. $V_{max} = k\,[\mathbf{7c}]$, ***[7c]*** = 0.01086 M. The obtained NMR data was analyzed with the reaction monitoring plugin of MestReNova 9.1 and Origin 2015G 32Bit.





R = 2,4,6-$Et_3C_6H_2$ **(6c)**



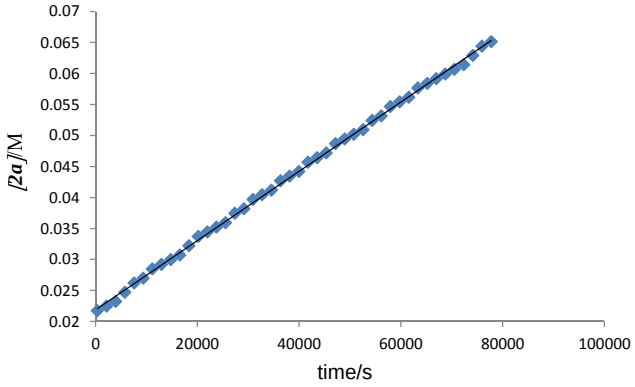
R = 2,4,6-$Et_3C_6H_2$ **(7c)**

Temperature 280.6 K:

Substrate **1a** (235.2 mg, 0.76 mmol) and dry CD_2Cl_2 (0.5 mL) were added to a dry NMR tube, then catalyst **6c** (10 mg, 0.0076 mmol) was added at -78°C. The reaction was conducted at 280.6 K as internally monitored.[3] ^1H NMR spectra of the reaction mixtures were monitored at various time. The kinetic datas of time versus ***[2a]*** were provided, and the ***[2a]*** was determined by several different signals. $V_{max} = k$ ***[7c]***^{2}, ***[7c]*** = 0.01086 M.

k = 5.17372E-05 s^{-1}

	1	2	3	average
V_m	5.69E-07	5.57E-07	5.59E-07	5.61718E-07
R^2	0.99524	0.99024	0.99921	0.994897



time/s	*[2a]*/M		
	1	**2**	**3**
383	0.026207	0.028453	0.021714
2183	0.026207	0.028453	0.022463
3983	0.026207	0.029202	0.023212
5783	0.028453	0.029951	0.024709
7583	0.0307	0.031448	0.026207
9383	0.029951	0.031448	0.026956
11183	0.032197	0.034443	0.028453
12983	0.032946	0.035192	0.029202
14783	0.032946	0.035192	0.029951
16583	0.032946	0.037438	0.0307
18383	0.03669	0.038187	0.032197
20183	0.037438	0.040433	0.033695
21983	0.038187	0.041931	0.034443
23783	0.038187	0.040433	0.035192
25583	0.038936	0.041931	0.035941
27383	0.041182	0.04268	0.037438
29183	0.041182	0.044177	0.038187
30983	0.043429	0.045675	0.039685
32783	0.043429	0.045675	0.040433
34583	0.044177	0.049419	0.041182
36383	0.047172	0.050167	0.04268
38183	0.047172	0.049419	0.043429
39983	0.04867	0.050916	0.044177
41783	0.049419	0.051665	0.045675
43583	0.050167	0.051665	0.046424

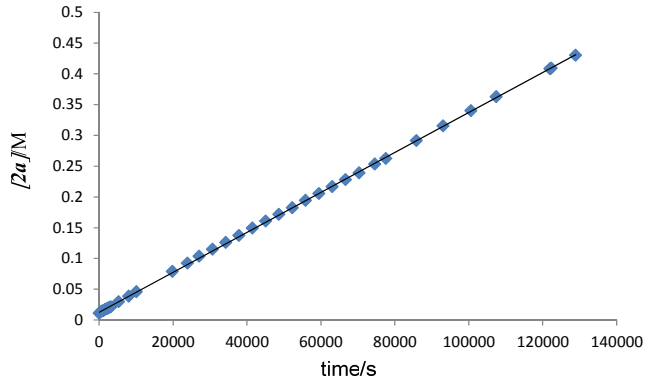
45383	0.051665	0.053163	0.047172
47183	0.052414	0.056158	0.04867
48983	0.052414	0.055409	0.049419
50783	0.053911	0.058404	0.050167
52583	0.05466	0.058404	0.050916
54383	0.056906	0.056158	0.052414
56183	0.056906	0.06065	0.053163
57983	0.059901	0.062148	0.05466
59783	0.06065	0.06065	0.055409
61583	0.06065	0.062897	0.056158
63383	0.061399	0.062148	0.057655
65183	0.062897	0.065143	0.058404
66983	0.064394	0.065143	0.059153
68783	0.064394	0.067389	0.059901
70583	0.062897	0.064394	0.06065
72383	0.064394	0.065892	0.061399
74183	0.067389	0.068138	0.062897
75983	0.069635	0.068138	0.064394
77783	0.068887	0.072631	0.065143

Temperature 294.2 K:

Substrate **1a** (235.2 mg, 0.76 mmol) and dry CD_2Cl_2 (0.5 mL) were added to a dry NMR tube, then catalyst **6c** (10 mg, 0.0076 mmol) was added at -78°C. The reaction was conducted at 294.2 K measured by thermometer. ^{1}H NMR spectra of the reaction mixtures were monitored at various time. The kinetic datas of time versus ***[2a]*** were provided, and the ***[2a]*** was determined by several different signals. $V_{max} = k$ ***[7c]***, ***[7c]*** = 0.01086 M. ^{1}H NMR kinetics study also followed.

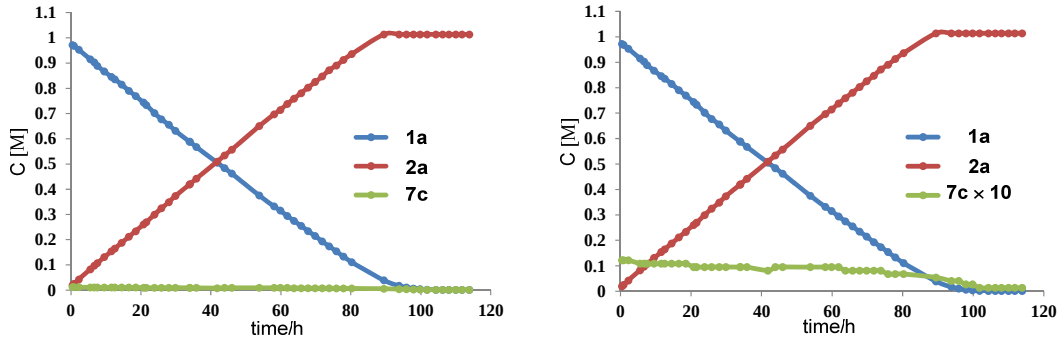
k = 0.000301 s^{-1}

	1	2	3	average
V_m	3.25E-06	3.29E-06	3.27E-06	3.26883E-06
R^2	0.99988	0.9999	0.99988	0.999887



time/s	*[2a]*/M		
	1	**2**	**3**
0	0.010483	0.013478	2.097E-02
360	0.012729	0.015724	2.471E-02
780	0.014227	0.016473	2.471E-02
1200	0.014975	0.01797	2.621E-02
1560	0.016473	0.018719	2.621E-02
1980	0.01797	0.020217	2.845E-02
2340	0.018719	0.020966	2.920E-02
2760	0.020217	0.022463	3.070E-02
3120	0.020966	0.023212	3.145E-02
5280	0.029202	0.031448	4.043E-02
8040	0.038187	0.040433	4.867E-02
10080	0.045675	0.047921	5.616E-02
19830	0.078621	0.081616	8.985E-02
23880	0.092099	0.094345	1.026E-01
27060	0.10333	0.105576	1.138E-01
30660	0.114562	0.117557	1.250E-01
34260	0.125793	0.129537	1.363E-01
37860	0.137025	0.14002	1.475E-01
41460	0.149005	0.152749	1.595E-01
45060	0.160236	0.163232	1.707E-01
48660	0.171468	0.175212	1.820E-01
52260	0.181951	0.185695	1.924E-01

55860	0.193931	0.198424	2.044E-01
59460	0.205163	0.209655	2.164E-01
63060	0.216394	0.220887	2.276E-01
66660	0.227626	0.232118	2.381E-01
70320	0.238857	0.244099	2.508E-01
74580	0.253084	0.258325	2.643E-01
77580	0.262069	0.266562	2.733E-01
85860	0.291271	0.297261	3.033E-01
93060	0.315232	0.32197	3.280E-01
100620	0.339941	0.34668	3.527E-01
107460	0.362404	0.369892	3.751E-01
121980	0.408079	0.416315	4.208E-01
122340	0.408828	0.417064	4.223E-01



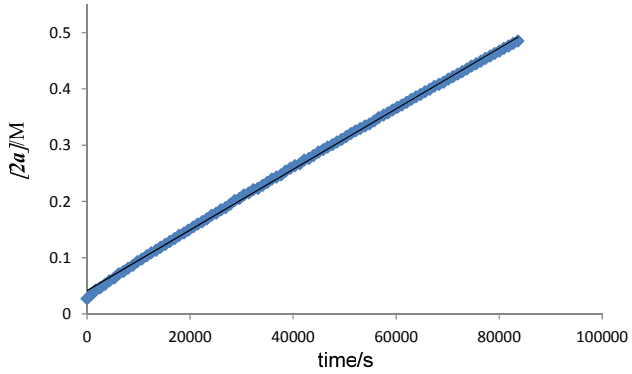
^{1}H NMR kinetics of the conversion of **1a** to **2a**.

Temperature 301.2 K:

Substrate **1a** (235.2 mg, 0.76 mmol) and dry CD_2Cl_2 (0.5 mL) were added to a dry NMR tube, then catalyst **6c** (10 mg, 0.0076 mmol) was added at -78°C. The reaction was conducted at 301.2 K as internally monitored.[4] ^1H NMR spectra of the reaction mixtures were monitored at various time. The kinetic datas of time versus ***[2a]*** were provided, and the ***[2a]*** was determined by several different signals. $V_{max} = k$ ***[7c]***^{2}, ***[7c]*** = 0.01086 M.

k = 0.000493541 s^{-1}

	1	2	3	average
V_m	5.38E-06	5.38E-06	5.31E-06	5.35845E-06
R^2	0.99904	0.99888	0.99867	0.998863



time/s	*[2a]*/M		
	1	**2**	**3**
0	0.026956	0.014975	0.013478
780	0.033695	0.021714	0.019468
1680	0.041931	0.028453	0.026207
2580	0.046424	0.034443	0.032946
3480	0.052414	0.040433	0.038936
4380	0.059153	0.046424	0.044926
5280	0.063645	0.051665	0.050167
6180	0.071133	0.057655	0.056158
7080	0.075626	0.063645	0.062148
7980	0.080867	0.068887	0.067389
8880	0.086108	0.074877	0.072631
9780	0.092847	0.080118	0.078621
10680	0.09734	0.086857	0.084611
11580	0.10333	0.090601	0.089103
12480	0.108571	0.096591	0.095094
13380	0.113064	0.101833	0.100335
14280	0.118305	0.106325	0.105576
15180	0.123547	0.112315	0.110818
16080	0.128788	0.117557	0.116059
16980	0.13403	0.122798	0.1213
17880	0.139271	0.128039	0.126542
18780	0.143764	0.132532	0.131034
19680	0.149005	0.137773	0.136276
20580	0.154246	0.143015	0.141517

21480	0.159488	0.148256	0.14601
22380	0.16398	0.153498	0.151251
23280	0.169222	0.158739	0.156493
24180	0.175212	0.165478	0.161734
25080	0.178956	0.168473	0.166227
25980	0.184946	0.175212	0.171468
26880	0.18869	0.178207	0.175961
27780	0.19468	0.183448	0.181202
28680	0.201419	0.189438	0.186443
29580	0.205163	0.193931	0.190936
30480	0.211153	0.199172	0.196177
31380	0.214897	0.204414	0.20067
32280	0.220887	0.208906	0.205911
33180	0.223133	0.21265	0.210404
34080	0.228374	0.217143	0.214897
34980	0.233616	0.222384	0.220138
35880	0.239606	0.226877	0.224631
36780	0.24335	0.232118	0.229872
37680	0.247094	0.236611	0.233616
38580	0.253833	0.241103	0.238857
39480	0.259074	0.246345	0.24335
40380	0.263567	0.250837	0.248591
41340	0.266562	0.256079	0.253084
42180	0.2733	0.260571	0.257576
43080	0.276296	0.265813	0.262069
43980	0.281537	0.270305	0.26731
44940	0.287527	0.275547	0.271803
45840	0.29202	0.280039	0.276296
46680	0.296512	0.284532	0.281537
47640	0.301005	0.289773	0.28603
48540	0.305498	0.294266	0.290522
49440	0.30999	0.299507	0.295015
50340	0.315232	0.304	0.299507
51240	0.320473	0.308493	0.304749
52140	0.324966	0.312985	0.308493
53040	0.329458	0.318227	0.313734
53940	0.333951	0.322719	0.318227
54840	0.337695	0.327212	0.322719
55740	0.342936	0.331704	0.327212
56640	0.348926	0.336946	0.332453
57540	0.353419	0.341438	0.336197
58440	0.357163	0.345931	0.34069
59340	0.362404	0.350424	0.345931
60240	0.366897	0.354916	0.350424
61140	0.371389	0.359409	0.354167
62040	0.375882	0.36465	0.359409
62940	0.381123	0.369892	0.363901
63840	0.385616	0.372887	0.368394
64740	0.390108	0.377379	0.372138
65640	0.394601	0.382621	0.377379
66540	0.399094	0.387113	0.381872
67440	0.404335	0.391606	0.386365
68340	0.408079	0.396099	0.390857
69240	0.411823	0.400591	0.394601
70140	0.417064	0.406581	0.399842
71040	0.421557	0.410325	0.404335
71940	0.426049	0.414818	0.408828
72840	0.430542	0.41931	0.41332
73740	0.435034	0.423054	0.417064

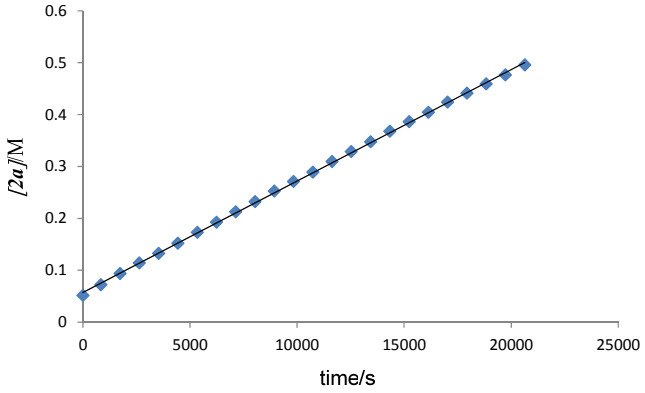
74640	0.440276	0.428296	0.421557
75540	0.444768	0.432788	0.426798
76440	0.449261	0.436532	0.430542
77340	0.453754	0.441773	0.435034
78240	0.458246	0.446266	0.439527
79140	0.462739	0.450759	0.44402
80040	0.467232	0.455251	0.448512
80940	0.471724	0.458995	0.452256
81840	0.476217	0.463488	0.456749
82740	0.480709	0.46798	0.461241
83640	0.485202	0.473222	0.465734

Temperature 312.3 K:

Substrate **1a** (235.2 mg, 0.76 mmol) and dry CD_2Cl_2 (0.5 mL) were added to a dry NMR tube, then catalyst **6c** (10 mg, 0.0076 mmol) was added at -78°C. The reaction was conducted at 312.3 K.[4] ^{1}H NMR spectra of the reaction mixtures were monitored at various time. The kinetic datas of time versus ***[2a]*** were provided, and the ***[2a]*** was determined by several different signals. $V_{max} = k$ ***[7c]***, ***[7c]*** = 0.01086 M.

k = 0.001958173 s^{-1}

	1	2	3	average
V_m	2.15E-5	2.13E-05	2.10E-05	0.0000212602
R^2	0.99963	0.99967	0.99964	0.999647



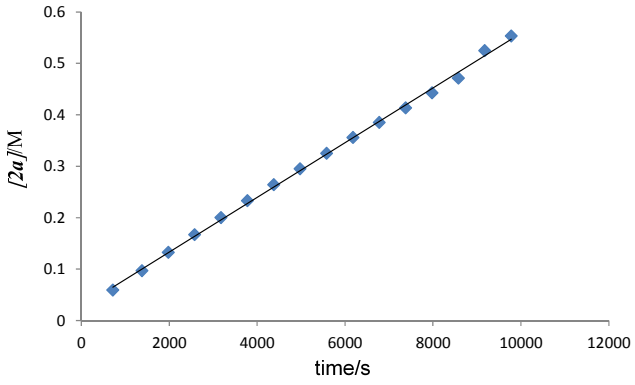
time/s	*[2a]*/M		
	1	2	3
0	0.051665	0.068887	0.050916
840	0.071882	0.087606	0.071133
1740	0.093596	0.107074	0.092099
2640	0.113813	0.128039	0.111567
3540	0.132532	0.149005	0.131034
4440	0.152	0.166975	0.150502
5340	0.172966	0.187192	0.170719
6240	0.192433	0.207409	0.190187
7140	0.21265	0.226877	0.208906
8040	0.232118	0.245596	0.228374
8940	0.252335	0.265813	0.247094
9840	0.271054	0.284532	0.265813
10740	0.289025	0.304	0.284532
11640	0.309241	0.323468	0.304
12540	0.328709	0.342187	0.322719
13440	0.347429	0.361655	0.341438
14340	0.367645	0.379626	0.359409
15240	0.386365	0.399842	0.378128
16140	0.404335	0.417813	0.396099
17040	0.423803	0.435783	0.414818
17940	0.441025	0.453754	0.432788
18840	0.458995	0.473222	0.450759
19740	0.476217	0.488946	0.46798
20640	0.495685	0.507665	0.485951

Temperature 323.4 K:

Substrate **1a** (235.2 mg, 0.76 mmol) and dry CD_2Cl_2 (0.5 mL) were added to a dry NMR tube, then catalyst **6c** (10 mg, 0.0076 mmol) was added at -78°C.[4] ^1H NMR spectra of the reaction mixtures were monitored at various time. The kinetic datas of time versus ***[2a]*** were provided, and the ***[2a]*** was determined by several different signals. $V_{max} = k$ ***[7c]***, ***[7c]*** = 0.01086 M.

k = 0.004711654 s^{-1}

	1	2	3	average
V_m	5.32E-05	5.03E-05	5.00E-05	5.11551E-05
R^2	0.99835	0.99831	1	0.998887



time/s	*[2a]*/M		
	1	2	3
720	0.059153	0.04867	0.059153
1380	0.096591	0.083862	0.092099
1980	0.132532	0.117557	0.122049
2580	0.166975	0.149754	0.152
3180	0.199921	0.181202	0.181951
3780	0.232867	0.211901	0.211901
4380	0.264315	0.241852	0.241852
4980	0.295015	0.271054	0.271803
5580	0.324966	0.299507	0.301754
6180	0.355665	0.327961	0.331704
6780	0.384867	0.355665	0.361655
7380	0.41332	0.383369	0.392355
7980	0.442522	0.410325	0.422305
8580	0.470975	0.437281	0.452256
9180	0.524887	0.489695	0.482207
9780	0.55334	0.515153	0.512158

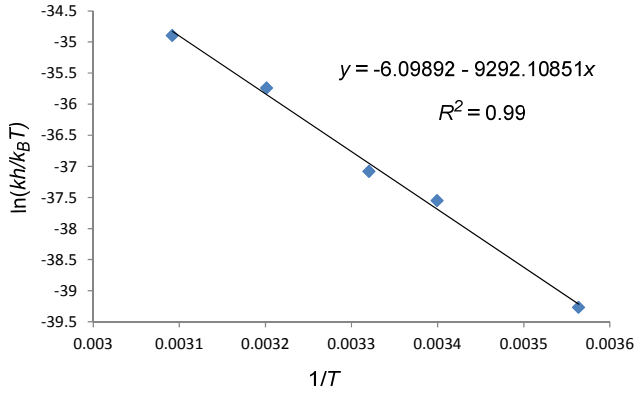
Eyring Plot

$\ln(kh/k_BT) = -\Delta H/RT + \Delta S/R$

Boltzmann Constant $k_B = 1.3806488 \times 10^{-23}$ J/K, Planck Constant $h = 6.62606957 \times 10^{-34}$ J·s.

1 $kcal_{th}$ = 4184 J, R = 8.314462175 J/(K· mol).

T (K)	280.6	294.2	301.2	312.3	323.4
$1/T$ (K^{-1})	0.003564	0.0034	0.00332	0.003202	0.003092
k (s^{-1})	5.17372E-05	0.000301076	0.000493541	0.001958173	0.004711654
$\ln(kh/k_BT)$	-39.2662417	-37.5522139	-37.0815238	-35.7398133	-34.896584



slope = $-\Delta H/R$ = -9292.10851 ± 369.50685, intercept = $\Delta S/R$ = -6.09892 ± 1.22658.

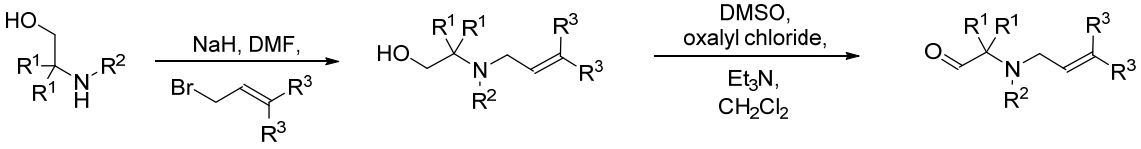
Calculation of activation parameters at 298.15 K

ΔH	77258.88 ± 3072.25 J/mol	18.47 ± 0.73 kcal/mol
ΔS	-50.71 ± 10.20 J/(K·mol)	-0.0121 ± 0.0024 kcal/(K·mol)
ΔG	92377.84 ± 6112.89 J/mol	22.08 ± 1.46 kcal/mol

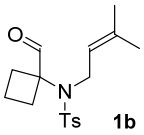
5. Substrates Synthesis

Substrates **1a**, **1g**, **1i**, **1j** have been previously reported.[5,6]

Synthesis of 1b-1f and 1h



The reactions were carried out according to a literature method.[1, 2] General procedure: The corresponding aminoalcohol compound (1 equiv) was dissolved in DMF (0.5 M) and NaH (60% dispersion in mineral oil, 1 equiv) was added portionwise at 0 °C under an argon atmosphere. The bubbling solution was stirred for 30 minutes at room temperature before allyl bromide (1.1 equiv) was added. The solution was stirred at room temperature until full consumption of the starting material. After addition of H_2O, the aqueous phase was extracted with CH_2Cl_2. The combined organic layers were washed with H_2O, brine and dried over Na_2SO_4, then concentrated with a rotary evaporator. The crude mixture was purified by column chromatography on silica gel using EtOAc/hexane as the eluent. The obtained alcohol was used for the next Swern oxidation step. To a solution of dimethyl sulfoxide (2.6 equiv) in CH_2Cl_2 (0.5 M) at -78°C was added oxalyl chloride (1.3 equiv). After 30 minutes, the alcohol (1 equiv) was added using CH_2Cl_2 (1.0 M). After 30 minutes, triethylamine (6 equiv) was added and the reaction was taken off of the cold bath. After addition of H_2O, the aqueous phase was extracted with CH_2Cl_2. The combined organic layers were washed with H_2O, brine and dried over Na_2SO_4, then concentrated with a rotary evaporator. The desired aldehyde was purified by column chromatography on silica gel using EtOAc/hexane as the eluent.



1b

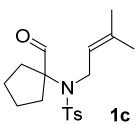
***N*-(1-Formylcyclobutyl)-4-methyl-*N*-(3-methylbut-2-en-1-yl)benzenesulfonamide**.

Prepared according to general procedure. White solid, 54%.

^{1}H NMR (300 MHz, CD_2Cl_2): δ 9.68 (s, 1H), 7.70 (d, *J* = 8.3 Hz, 2H), 7.34 (d, *J* = 8.0 Hz, 2H), 7.30 (d, *J* = 8.0 Hz, 2H), 5.11 (app. t, *J* = 6.8 Hz, 1H), 3.91 (d, *J* = 6.8 Hz, 2H), 2.43 (s, 3H), 2.37-2.20 (m, 4H), 1.88-1.68 (m, 2H), 1.67 (d, *J* = 1.1 Hz, 3H), 1.60 (s, 3H).

^{13}C NMR (75 MHz, CD_2Cl_2): δ 199.8, 144.0, 139.7, 136.8, 130.1, 127.4, 121.4, 68.6, 44.7, 29.3, 25.8, 21.7, 18.0, 14.3.

HRMS *m/z* (ESI): calcd. for $C_{17}H_{23}N_1O_3S_1Na$ [M+Na]: 344.129085; found: 344.129100.



1c

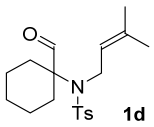
***N*-(1-Formylcyclopentyl)-4-methyl-*N*-(3-methylbut-2-en-1-yl)benzenesulfonamide**.

Prepared according to general procedure. White solid, 50%.

^{1}H NMR (500 MHz, CD_2Cl_2): δ 9.60 (s, 1H), 7.70 (d, *J* = 8.3 Hz, 2H), 7.32 (d, *J* = 8.1 Hz, 2H), 5.15 (app. t, *J* = 6.2 Hz, 1H), 3.90 (d, *J* = 6.2 Hz, 2H), 2.42 (s, 3H), 2.10-2.05 (m, 2H), 1.78-1.73 (m, 2H), 1.67 (d, *J* = 1.1 Hz, 3H), 1.59 (s, 3H), 1.57-1.51 (m, 4H).

^{13}C NMR (126 MHz, CD_2Cl_2): δ 198.0, 144.2, 138.3, 134.9, 130.0, 128.0, 122.5, 77.1, 45.1, 32.5, 25.7, 24.0, 21.6, 18.0.

HRMS *m/z* (ESI): calcd. for $C_{18}H_{25}N_1O_3S_1Na$ [M+Na]: 358.144735; found: 358.144700.



1d

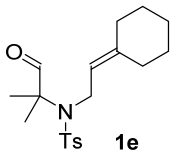
***N*-(1-Formylcyclohexyl)-4-methyl-*N*-(3-methylbut-2-en-1-yl)benzenesulfonamide**.

Prepared according to general procedure. White solid, 73%.

^{1}H NMR (500 MHz, $CDCl_3$): δ 9.69 (s, 1H), 7.72 (d, *J* = 8.3 Hz, 2H), 7.28 (d, *J* = 8.3 Hz, 2H), 5.15 (app. t, *J* = 6.2 Hz, 1H), 3.84 (d, *J* = 6.2 Hz, 2H), 2.41 (s, 3H), 2.17 (d, *J* = 13.4 Hz, 2H), 1.69 (td, *J* = 12.6, 3.8 Hz, 2H), 1.64 (s, 3H), 1.60-1.49 (m, 8H), 1.17-1.07 (m, 1H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 200.0, 143.4, 138.1, 133.8, 129.5, 127.8, 122.6, 68.8, 43.4, 31.1, 25.6, 24.8, 22.5, 21.5, 17.8.

HRMS *m/z* (ESI): calcd. for $C_{19}H_{27}N_1O_3S_1Na$ [M+Na]: 372.160386; found: 372.160520.



1e

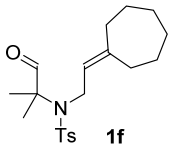
***N*-(2-Cyclohexylideneethyl)-4-methyl-*N*-(2-methyl-1-oxopropan-2-yl)benzenesulfonamide**.

Prepared according to general procedure. White solid, 41%.

^{1}H NMR (500 MHz, CD_2Cl_2): δ 9.60 (s, 1H), 7.75 (d, *J* = 8.3 Hz, 2H), 7.34 (d, *J* = 8.0 Hz, 2H), 5.05 (app. t, *J* = 6.5 Hz, 1H), 3.83 (d, *J* = 6.5 Hz, 2H), 2.42 (s, 3H), 2.05 (td, *J* = 24, 6.1 Hz, 4H), 1.52-1.43 (m, 6H), 1.36 (s, 6H).

^{13}C NMR (126 MHz, CD_2Cl_2): δ 198.8, 144.4, 142.3, 137.8, 130.0, 128.3, 119.1, 67.3, 42.8, 37.2, 29.0, 28.5, 27.5, 26.9, 22.4, 21.6.

HRMS *m/z* (ESI): calcd. for $C_{19}H_{27}N_1O_3S_1Na$ [M+Na]: 372.160385; found: 372.160090.



1f

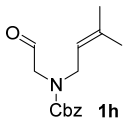
***N*-(2-Cycloheptylideneethyl)-4-methyl-*N*-(2-methyl-1-oxopropan-2-yl)benzenesulfonamide**.

Prepared according to general procedure. White solid, 42%.

^{1}H NMR (500 MHz, CD_2Cl_2): δ 9.63 (s, 1H), 7.77 (d, *J* = 8.3 Hz, 2H), 7.36 (d, *J* = 8.0 Hz, 2H), 5.10 (app. t, *J* = 6.0 Hz, 1H), 3.83 (d, *J* = 6.0 Hz, 2H), 2.45 (s, 3H), 2.16-2.12 (m, 4H), 1.52-1.47 (m, 8H), 1.36 (s, 6H).

^{13}C NMR (126 MHz, CD_2Cl_2): δ 198.8, 144.4, 143.9, 137.7, 130.0, 128.3, 122.7, 67.3, 43.2, 37.8, 30.5, 30.1, 29.7, 29.4, 27.0, 22.4, 21.6.

HRMS *m/z* (ESI): calcd. for $C_{20}H_{29}N_1O_3S_1Na$ [M+Na]: 386.176035; found: 386.176120.



1h

Benzyl (3-methylbut-2-en-1-yl)(2-oxoethyl)carbamate.

Prepared according to general procedure. White oil, 46%.

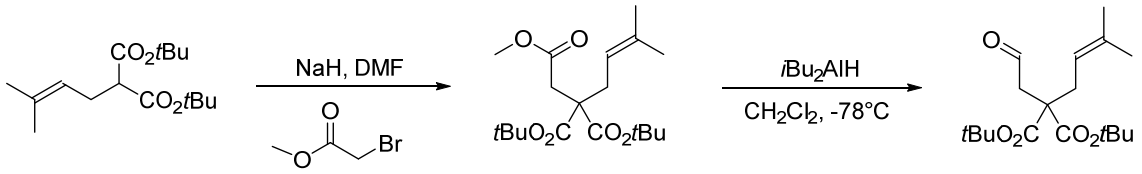
The NMR signals are reported as observed . The signals belong to two different rotamers.

^{1}H NMR (500 MHz, CD_2Cl_2): δ 9.53-9.52 (m, 1H), 7.38-7.29 (m, 5H), 5.16-5.10 (m, 3H), 3.99-3.91 (m, 4H), 1.72 (m, 3H), 1.64-1.57 (m, 3H).

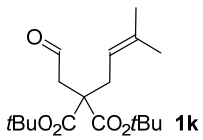
^{13}C NMR (75 MHz, CD_2Cl_2): δ 199.2, 156.8, 156.1, 138.1, 137.5, 137.2, 136.2, 128.9, 128.4, 128.2, 120.5, 119.7, 119.6, 67.8, 57.0, 56.3, 46.2, 25.8, 18.0, 17.9.

HRMS *m/z* (ESI): calcd. for $C_{15}H_{19}N_1O_3Na$ [M+Na]: 284.125713; found: 284.125770.

Synthesis of 1k



The reactions were carried out according to a literature method.[6] General procedure: To a solution of di-*tert*-butyl-malonat (4ml, 15 mmol) in DMF (75 mL), sodium hydride (719mg, 18mmol) was added at 0 °C. After stirring for one hour, 10mmol of methylbromacetate was added to this reaction mixture.The reaction was stirred at r.t. for 6 h, then was diluted with 30 mL a.q. $NaHCO_3$ and extracted by 2 x 90 mL MTBE. The organic layer was rinsed with H_2O (2 x 150 mL) and brine (2 x 150 mL), then dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The product was isolated by flash chromatography (2-5% ethyl acetate/hexanes) as a clear, viscous oil (780mg, 2.19 mmol, 44% yield). To a solution of 2,2-di-*tert*-butyl 1-methyl 5-methylhex-4-ene-1,2,2-tricarboxylate (749mg, 2.1 mmol) in CH_2Cl_2 (20 ml, 0.1 M), diisobutylaluminum hydride (4.6 mL, 4.6 mmol, 1M in hexane) was added at -78°C. The reaction mixture was stirred for 4h at -78°C. The reaction was quenched by adding 0.1 mL H_2O, 0.1 mL 15% aqueous NaOH, and 0.4 mL H_2O waiting 5 minutes between each addition. The resulting suspension was carefully dried over Mg_2SO_4 and filtered, rinsed with CH_2Cl_2 then concentrated with a rotary evaporator. The product was obtained by flash chromatography (Hexane:Ether 95:5) as an clear oil (200 mg, 0.612 mmol, 29% yield).



1k

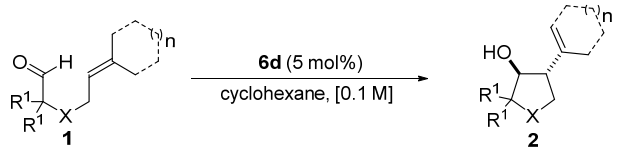
Di-*tert*-butyl 2-(3-methylbut-2-en-1-yl)-2-(2-oxoethyl)malonate.

^{1}H NMR (500 MHz, CD_2Cl_2): δ 9.68 (t, *J* = 2.0 Hz, 1H), 5.0 (app. t, *J* = 7.8 Hz, 1H), 2.72 (d, *J* = 2.0 Hz, 2H), 2.59 (d, *J* = 7.7 Hz, 2H), 1.69 (d, *J* = 0.9 Hz, 3H), 1.59 (s, 3H), 1.43 (s, 18H).

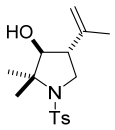
^{13}C NMR (126 MHz, CD_2Cl_2): δ 200.3, 169.8, 136.5, 118.3, 82.4, 56.5, 46.7, 33.0, 27.9, 26.1, 18.2.

HRMS *m/z* (ESI): calcd. for $C_{18}H_{30}O_5Na$ [M+Na]: 349.198544; found: 349.198410

6.General Procedure for the Asymmetric Carbonyl-Ene Reaction



Unless specified otherwise, aldehyde **1** (0.1 mmol) was added to catalyst **6d** (0.005 mmol, 5 mol%) in anhydrous cyclohexane (0.1 M). The mixture was stirred vigorously at room temperature. Purification was performed by column chromatography or preparative thin layer chromatography on silica gel using EtOAc/hexanes as the eluents.



2a

(3*S*,4*R*)-2,2-Dimethyl-4-(prop-1-en-2-yl)-1-tosylpyrrolidin-3-ol.

Prepared according to general procedure. 30.0 mg white solid, 97%.

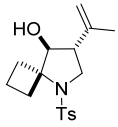
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.73 (d, *J* = 8.3 Hz, 2H), 7.29 (d, *J* = 8.1 Hz, 2H), 4.92 (t, *J* = 1.4 Hz, 1H), 4.89 (s, 1H), 3.63 (d, *J* = 10.4 Hz, 1H), 3.57 (t, *J* = 9.1 Hz, 1H), 3.06 (t, *J* = 10.1 Hz, 1H), 2.62 (q, *J* = 10.2 Hz, 1H), 2.41 (s, 3H), 1.71 (s, 3H), 1.50 (s, 3H), 1.27 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 143.0, 141.3, 138.2, 129.5, 127.2, 113.9, 80.4, 65.9, 48.6, 48.1, 26.5, 21.6, 21.5, 19.8.

HRMS *m/z* (ESI): calcd. for $C_{16}H_{23}N_1O_3S_1Na$ [M+Na]: 332.129130; found: 332.129085.

The enantiomeric ratio was measured by HPLC analysis using Chiralpak AS-3R, CH_3CN/ H_2O = 35:65, Flow rate = 1.0 mL/min, λ = 220 nm, t_R = 17.7 min (minor) and t_R= 18.9 min (major). er = 97.5:2.5.

$[\alpha]_D^{25}$ = -19.1 (*c* 0.70, CH_2Cl_2).



2b

(7*R*,8*S*)-7-(prop-1-en-2-yl)-5-tosyl-5-azaspiro[3.4]octan-8-ol.

Prepared according to general procedure. 26 mg white solid, 81%.

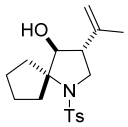
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.73 (d, *J* = 8.3 Hz, 2H), 7.30 (d, *J* = 7.5 Hz, 2H), 4.92-4.90 (m, 2H), 3.84 (d, *J* = 8.7 Hz, 1H), 3.60 (dd, *J* = 9.6, 8.2 Hz, 1H), 3.19-3.13 (m, 2H), 2.61 (m, 1H), 2.52 (q, *J* = 8.6 Hz, 1H), 2.42 (s, 3H), 2.29-2.23 (m, 1H), 2.09-2.03 (m, 1H), 1.82 (tq, *J* = 10.8, 3.6 Hz, 1H), 1.72 (s, 3H), 1,70-1,64 (m, 1H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 143.1, 141.1, 138.2, 129.7, 126.9, 113.7, 79.8, 67.7, 49.3, 49.0, 32.5, 29.9, 21.5, 20.3, 13.5.

HRMS *m/z* (ESI): calcd. for $C_{17}H_{23}N_1O_3S_1Na$ [M+Na]: 344.129085; found: 344.128960.

The enantiomeric ratio was measured by Heart-Cut HPLC analysis using Chiralpak OJ-3R , CH_3CN/ H_2O = 40:60, Flow rate = 1.0 mL/min, λ = 220 nm, t_R = 9.3 min (major) and t_R= 10.8 min (minor). er = 97:3.

$[\alpha]_D^{25}$ = -8.8 (*c* 0.80, CH_2Cl_2).



2c

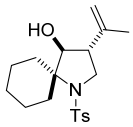
(3*R*,4*S*)-3-(Prop-1-en-2-yl)-1-tosyl-1-azaspiro[4.4]nonan-4-ol.

Prepared according to general procedure. 27.8 mg white solid, 83%.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.72 (d, *J* = 8.3 Hz, 2H), 7.30 (d, *J* = 8.1 Hz, 2H), 4.92-4.91 (m, 1H), 4.89-4.88 (m, 1H), 3.78 (d, *J* = 10.0 Hz, 1H), 3.58 (t, *J* = 9.1 Hz, 1H), 3.10 (t, *J* = 9.9 Hz, 1H), 2.62-2.52 (m, 2H), 2.42 (s, 3H), 2.02-1.89 (m, 3H), 1.86-1.79 (m, 1H), 1.71 (s, 3H), 1.69-1.58 (m, 3H), 1.53-1.45 (m, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$): δ 143.0, 141.3, 138.3, 129.6, 127.1, 113.9, 81.2, 75.7, 49.6, 48.7, 36.7, 33.3, 25.9, 25.3, 21.5, 19.9.

HRMS *m/z* (ESI): calcd. for $C_{18}H_{25}N_1O_3S_1Na$ [M+Na]: 358.144735; found: 358.144700. The enantiomeric ratio was measured by Heart-Cut HPLC analysis using Chiralpak OJ-3R , CH_3CN/ H_2O = 40:60, Flow rate = 1.0 mL/min, λ = 220 nm, t_R = 15.2 min (minor) and t_R= 15.5 min (major). er = 95.5:4.5.

$[\alpha]_D^{25}$ = -11.6 (*c* 0.78, CH_2Cl_2).



2d

(3R,4S)-3-(prop-1-en-2-yl)-1-tosyl-1-azaspiro[4.5]decan-4-ol.

The reaction was performed at 10°C for 5 days. 27.0 mg white solid, 77%.

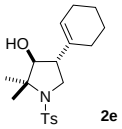
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.73 (d, *J* = 8.3 Hz, 2H), 7.28 (d, *J* = 8.0 Hz, 2H), 4.91-4,89 (m, 1H), 4.89-4,88 (m, 1H), 4.00 (d, *J* = 7.0 Hz, 1H), 3.55 (dd, *J* = 9.7, 7.8 Hz, 1H), 3.24 (dd, *J* = 9.7, 8.9 Hz, 1H), 2.62 (q, *J* = 7.9 Hz, 1H), 2.41 (s, 3H), 2.27-2.39 (m, 2H), 1.91 (d, *J* = 12.1 Hz, 1H), 1.74 (s, 3H), 1.70-1.61 (m, 6H), 1.44 (tq, *J* = 13.4, 3.2 Hz, 1H), 1.33-1.27 (m, 1H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 142.8, 141.7, 138.7, 129.5, 127.2, 113.2, 81.1, 70.2, 51.2, 48.4, 36.4, 31.7, 24.7, 23.9, 23.7, 21.5, 20.7.

HRMS *m/z* (ESI): calcd. for $C_{19}H_{27}N_1O_3S_1Na$ [M+Na]: 372.160386; found: 372.160520.

The enantiomeric ratio was measured by Heart-Cut HPLC analysis using Chiralpak OJ-3R , CH_3CN/ H_2O = 50:50, Flow rate = 1.0 mL/min, λ = 220 nm, t_R = 38.4 min (minor) and t_R= 38.9 min (major). er = 95:5.

$[\alpha]_D^{25}$ = -1.8 (*c* 0.33, CH_2Cl_2).



2e

(3*S*,4*R*)-4-(Cyclohex-1-en-1-yl)-2,2-dimethyl-1-tosylpyrrolidin-3-ol.

Prepared according to general procedure. 28.0 mg white solid, 80%.

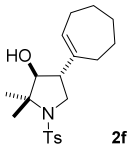
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.72 (d, *J* = 7.0 Hz, 2H), 7.28 (d, *J* = 8.5 Hz, 2H), 5.61 (br. s, 1H), 3.63 (d, *J* = 10.4 Hz, 1H), 3.55 (t, *J* = 9.5 Hz, 1H), 3.01 (dt, *J* = 10.6, 1.2 Hz, 1H), 2.51 (q, *J* = 9.8 Hz, 1H), 2.41 (s, 3H), 2.00 (d, *J* = 1.6 Hz, 2H), 1.89 (br. s, 2H), 1.72 (br. s, 1H), 1.64-1.55 (m, 4H), 1.49 (s, 3H), 1.27 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 142.8, 138.3, 133.3, 129.5, 127.2, 125.3, 79.9, 65.8, 49.0, 48.1, 26.6, 25.6, 25.2, 22.7, 22.3, 21.5, 21.4.

HRMS *m/z* (ESI): calcd. for $C_{19}H_{27}N_1O_3S_1Na$ [M+Na]: 372.160385; found: 372.160500.

The enantiomeric ratio was measured by HPLC analysis using Chiralpak AS-3R, CH_3CN/H_2O = 70:30, Flow rate = 1.0 mL/min, λ = 220 nm, t_R = 3.4 min (major) and t_R= 3.7 min (minor). er = 92:8.

$[\alpha]_D^{25}$ = -15.3 (*c* 0.34, CH_2Cl_2).



2f

(3*S*,4*R*)-4-(Cyclohept-1-en-1-yl)-2,2-dimethyl-1-tosylpyrrolidin-3-ol.

Prepared according to general procedure. 35.0 mg white solid, 96%.

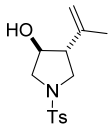
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.73 (d, *J* = 8.3 Hz, 2H), 7.29 (d, *J* = 8.0 Hz, 2H), 5.77 (t, *J* = 6.6 Hz, 1H), 3.55 (d, *J* = 10.2 Hz, 1H), 3.48 (t, *J* = 9.3 Hz, 1H), 3.02 (t, *J* = 9.9 Hz, 1H), 2.52 (q, *J* = 9.8 Hz, 1H), 2.42 (s, 3H), 2.11 (q, *J* = 6.5 Hz, 2H), 2.05 (dd, *J* = 5.8, 4.1 Hz, 2H), 1.77-1.72 (m, 3H), 1.63 (br. s, 1H), 1.50 (s, 3H), 1.48-1.40 (m, 4H), 1.23 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 142.9, 140.0, 138.3, 131.5, 129.5, 127.2, 79.8, 65.6, 51.0, 47.9, 32.7, 28.8, 28.3, 27.1, 26.9, 26.7, 21.5, 21.1.

HRMS *m/z* (ESI): calcd. for $C_{20}H_{29}N_1O_3S_1Na$ [M+Na]: 386.176035; found: 386.175930.

The enantiomeric ratio was measured by HPLC analysis using Chiralpak OJ-3R, CH_3CN/H_2O = 50:50, Flow rate = 1.0 mL/min, λ = 220 nm, t_R = 9.2 min (major) and t_R= 9.9 min (minor). er = 95.5:4.5.

$[\alpha]_D^{25}$ = -23.4 (*c* 1.0, CH_2Cl_2).



2g

(3*S*,4*R*)-4-(Prop-1-en-2-yl)-1-tosylpyrrolidin-3-ol.

The reaction was performed at room temperature for 3 days then at 50 °C for 2 days in the presence of **6d** (7.5 mol%). 24.0 mg white solid, 85%. Running the reaction at 50 °C from the start gave lower enantioselectivity.

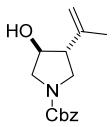
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.74 (d, *J* = 8.3 Hz, 2H), 7.34 (d, *J* = 7.9 Hz, 2H), 4.84-4.83 (m, 1H), 4.75-4.73 (m, 1H), 4.10 (p, *J* = 5.0 Hz, 1H), 3.60 (dd, *J* = 10.4, 6.1 Hz, 1H), 3.52 (dd, *J* = 10.1, 8.1 Hz, 1H), 3.21 (dd, *J* = 10.1, 7.4 Hz, 1H), 3.12 (dd, *J* = 10.4, 5.5 Hz, 1H), 2.55 (q, *J* = 7.3 Hz, 1H), 2.44 (s, 3H), 1.69 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$): δ143.7, 141.6, 133.6, 129.74, 129.73, 127.6, 112.9, 73.1, 54.0, 53.4, 49.7, 21.5, 20.7.

HRMS *m/z* (ESI): calcd. for $C_{14}H_{19}N_1O_3S_1Na$ [M+Na]: 304.097786; found: 304.097580.

The enantiomeric ratio was measured by HPLC analysis using Chiralpak OJ-3R, CH_3CN/H_2O = 25:75, Flow rate = 1.0 mL/min, λ = 220 nm, t_R = 22.8 min (major) and t_R= 25.4 min (minor). er = 98:2.

$[\alpha]_D^{25}$ = -13.0 (*c* 1.0, CH_2Cl_2).



2h

Benzyl (3*S*,4*R*)-3-hydroxy-4-(prop-1-en-2-yl)pyrrolidine-1-carboxylate.

The reaction was performed at room temperature for 3 days then at 50 °C for 8 days in the presence of **6d** (7.5 mol%). 19.0 mg White solid, 73%.

The NMR signals of major diastereomer are reported as observed . The signals belong to two different rotamers (ratio ~ 1:1).

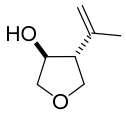
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.36-7.31 (m, 5H), 5.13 (s, 2H), 4.90 (d, *J* = 3.6 Hz, 1H), 4.84 (d, *J* = 11.8 Hz, 1H), 4.23 (ddd, *J* = 12.1, 6.1, 2.2 Hz, 1H), 3.77-3.86 (m, 2H), 3.42-3.36 (m, 1H), 3.33-3.27 (m, 1H), 2.68 (s, *J* = 8.8 Hz, 1H), 2.30 (br. s, 1H), 1.76 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$): δ154.9, 142.3, 142.2, 136.8, 128.5, 128.0, 127.9, 127.8, 112.6, 112.5, 73.1, 72.4, 66.9, 66.8, 53.1, 52.6, 52.5, 52.2, 48.2, 48.0, 23.0, 21.0, 20.9.

HRMS *m/z* (ESI): calcd. for $C_{15}H_{19}N_1O_3Na$ [M+Na]: 284.125713; found: 284.125710.

The enantiomeric ratio was measured by Heart-Cut HPLC analysis using Chiralpak OJ-3R , CH_3CN/ H_2O = 70:30, Flow rate = 1.0 mL/min, λ = 220 nm, t_R = 17.1 min (major) and t_R= 17.8 min (minor). er = 98:2.

$[\alpha]_D^{25}$ = -8.6 (*c* 0.95, CH_2Cl_2).



2i

(3*S*,4*R*)-4-(Prop-1-en-2-yl)tetrahydrofuran-3-ol.

The reaction was performed under neat condition. White oil, 78% NMR yield using 1,1,2,2-tetrachloroethane used as internal standard.

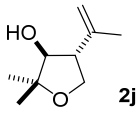
^{1}H NMR (500 MHz, CD_2Cl_2): δ 4.84 (m, 1H), 4.80 (m, 1H), 4.29-4.26 (m, 1H), 4.05 (dd, *J* = 9.2, 7.5 Hz, 1H), 3.90 (dd, *J* = 9.6, 5.3 Hz, 1H), 3.68 (dd, *J* = 8.8, 6.3 Hz, 1H), 3.65 (dd, *J* = 9.5, 3.2 Hz, 1H), 2.69 (dt, *J* = 6.8, 3.8 Hz, 1H), 1.93 (d, *J* = 5.0 Hz, 1H), 1.77 (t, *J* = 1.1 Hz, 3H).

^{13}C NMR (126 MHz, CD_2Cl_2): δ144.1, 111.5, 76.4, 75.1, 71.3, 56.2, 21.5.

HRMS *m/z* (ESI): calcd. for $C_7H_{12}O_2Na$ [M+Na]: 151.072949; found: 151.073020.

The enantiomeric ratio was measured by GC analysis on Hydrodex-gamma-TBDAc-CD column: t_R = 11.1 min (major) and t_R= 12.1 min (minor). er = 97:3.

$[\alpha]_D^{25}$ = -20 (*c* 0.33, CH_2Cl_2).



2j

(3*S*,4*R*)-2,2-Dimethyl-4-(prop-1-en-2-yl)tetrahydrofuran-3-ol.

The reaction was performed under neat condition. 14mg white oil, 90%.

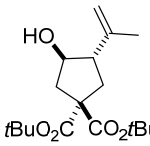
^{1}H NMR (500 MHz, $CDCl_3$): δ 4.89-4.87 (m, 2H), 3.96 (t, *J* = 8.9 Hz, 1H), 3.80 (dd, *J* = 8.6, 5.1 Hz, 1H), 3.65 (t, *J* = 9.1 Hz, 1H), 2.83 (q, *J* = 9.0 Hz, 1H), 1.77 (s, 3H), 1.75 (d, *J* = 5.4 Hz, 1H), 1.29 (s, 3H), 1.18 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 142.6, 112.6, 81.1, 80.9, 66.7, 54.1, 26.6, 21.4, 19.9.

HRMS *m/z* (ESI): calcd. for $C_9H_{16}O_2Na$ [M+Na]: 179.104249; found: 179.104430.

The enantiomeric ratio was measured by GC analysis on Hydrodex-BTBDAC-G-589 column: t_R = 33.0 min (minor) and t_R= 36.0 min (major).

$[\alpha]_D^{25}$ = -30.5 (*c* 0.42, CH_2Cl_2). er = 98:2.



2k

Di-*tert*-butyl (3*R*,4*S*)-3-hydroxy-4-(prop-1-en-2-yl)cyclopentane-1,1-dicarboxylate.

The reaction was performed at room temperature for 3 days then at 50 °C for 2 days in the presence of **6d** (7.5 mol%). 26.5 mg white oil, 81%.

^{1}H NMR (500 MHz, $CDCl_3$): δ 4.81 (m, 2H), 4.04 (q, *J* = 7.1 Hz, 1H), 2.52-2.38 (m, 3H), 2.23 (br. s, 1H), 2.09 (dd, *J* = 13.3, 10.8 Hz, 1H), 2.02-1.98(m, 1H), 1.75 (t, *J* = 0.9 Hz, 3H), 1.46 (s, 9H), 1.44 (s, 9H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 172.2, 171.1, 144.4, 111.5, 81.6, 81.3, 74.9, 58.3, 54.8, 41.2, 35.9, 27.8, 20.3.

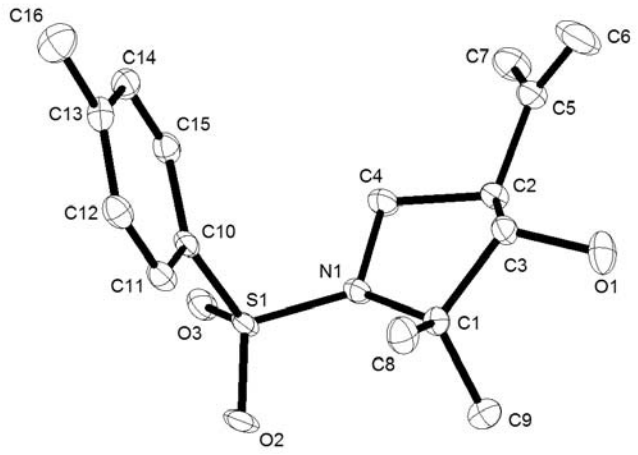
HRMS *m/z* (ESI): calcd. for $C_{18}H_{30}O_5Na$ [M+Na]: 349.198544; found: 349.198320.

The enantiomeric ratio was measured by GC analysis on BGB-176/BGB-15-G-618 column: t_R = 53.3 min (minor) and t_R= 53.8 min (major). er = 98:2.

$[\alpha]_D^{25}$ = -6.0 (*c* 0.6, CH_2Cl_2).

7.Crystal structure

X-Ray structural analysis parameter for 2a:



Crystal data and structure refinement.

Identification code	9037sadabs	
Empirical formula	C_{13} H^{23} N O_3 S	
Color	colourless	
Formula weight	309.41 $g \cdot mol^{-1}$	
Temperature	100 K	
Wavelength	1.54178 Å	
Crystal system	TRICLINIC	
Space group	p 1, (no. 1)	
Unit cell dimensions	a = 8.8573(4) Å	α= 100.3631(12)°.
	b = 11.7268(5) Å	β= 92.9867(11)°.
	c = 15.6313(7) Å	γ = 90.2474(12)°.
Volume	1594.78(12) $Å^3$	
Z	4	
Density (calculated)	1.289 $Mg \cdot m^{-3}$	
Absorption coefficient	1.883 mm^{-1}	
F(000)	664 e	
Crystal size	0.8 x 0.2 x 0.16 mm^3	
θ range for data collection	3.832 to 67.596°.	
Index ranges	$-10 \le \eta \le 10, -13 \le \kappa \le 14, -18 \le \lambda \le 18$	
Reflections collected	72019	
Independent reflections	9536 [R_{int} = 0.0369]	
Reflections with I>2□(I)	9493	
Completeness to □ = 67.596°	96.7 %	
Absorption correction	Gaussian	

Max. and min. transmission	0.80136 and 0.36318	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	9536 / 3 / 809	
Goodness-of-fit on F^2	1.020	
Final R indices [I>2σ(I)]	$R_1 = 0.0402$	$wR^2 = 0.1049$
R indices (all data)	$R_1 = 0.0403$	$wR^2 = 0.1050$
Absolute structure parameter	0.010(12)	
Extinction coefficient	0	
Largest diff. peak and hole	0.493 and -0.435 $e \cdot Å^{-3}$	

Selected bond lengths [Å] and angles [°].

C(1)-C(2)	1.559(4)	C(1)-C(8)	1.523(5)
C(1)-C(9)	1.517(5)	C(1)-N(1)	1.506(4)
C(2)-C(3)	1.522(4)	C(2)-O(1)	1.418(4)
C(3)-C(4)	1.535(4)	C(3)-C(5)	1.511(4)
C(4)-N(1)	1.480(4)	C(5)-C(6)	1.314(6)
C(5)-C(7)	1.511(5)	C(6)-H(6A)	0.89(5)
C(6)-H(6B)	0.95(6)	C(10)-C(11)	1.396(4)
C(10)-C(15)	1.398(5)	C(10)-S(1)	1.761(4)
C(11)-C(12)	1.381(5)	C(12)-C(13)	1.398(5)
C(13)-C(14)	1.401(5)	C(13)-C(16)	1.506(6)
C(14)-C(15)	1.376(5)	N(1)-S(1)	1.613(3)
O(2)-S(1)	1.432(2)	O(3)-S(1)	1.442(2)
C(33)-C(34)	1.544(5)	C(33)-C(40)	1.532(4)
C(33)-C(41)	1.525(4)	C(33)-N(3)	1.503(4)
C(34)-C(35)	1.528(4)	C(34)-O(7)	1.415(4)
C(35)-C(36)	1.528(5)	C(35)-C(37)	1.504(5)
C(36)-N(3)	1.483(4)	C(37)-C(38)	1.505(5)
C(37)-C(39)	1.313(6)	C(39)-H(39A)	0.93(5)
C(39)-H(39B)	1.02(7)	C(42)-C(43)	1.398(4)
C(42)-C(47)	1.397(5)	C(42)-S(3)	1.765(3)
C(43)-C(44)	1.381(5)	C(44)-C(45)	1.400(5)
C(45)-C(46)	1.397(4)	C(45)-C(48)	1.508(5)
C(46)-C(47)	1.379(5)	N(3)-S(3)	1.611(3)
O(8)-S(3)	1.443(2)	O(9)-S(3)	1.431(2)
C(17)-C(18)	1.564(5)	C(17)-C(24)	1.519(5)
C(17)-C(25)	1.521(4)	C(17)-N(2)	1.509(4)
C(18)-C(19)	1.521(5)	C(18)-O(4)	1.409(4)
C(19)-C(20)	1.537(4)	C(19)-C(21)	1.512(5)
C(20)-N(2)	1.484(4)	C(21)-C(22)	1.324(6)
C(21)-C(23)	1.501(5)	C(22)-H(22A)	0.98(5)
C(22)-H(22B)	0.97(7)	C(26)-C(27)	1.397(4)
C(26)-C(31)	1.393(5)	C(26)-S(2)	1.772(3)
C(27)-C(28)	1.380(5)	C(28)-C(29)	1.403(5)
C(29)-C(30)	1.393(5)	C(29)-C(32)	1.505(5)
C(30)-C(31)	1.386(5)	N(2)-S(2)	1.622(3)
O(5)-S(2)	1.444(2)	O(6)-S(2)	1.430(3)
C(49)-C(50)	1.565(4)	C(49)-C(56)	1.522(5)

C(49)-C(57)	1.521(4)	C(49)-N(4)	1.508(4)
C(50)-C(51)	1.516(4)	C(50)-O(10)	1.412(4)
C(51)-C(52)	1.534(5)	C(51)-C(53)	1.517(4)
C(52)-N(4)	1.486(4)	C(53)-C(54)	1.324(5)
C(53)-C(55)	1.490(5)	C(54)-H(54A)	0.95(5)
C(54)-H(54B)	0.98(5)	C(58)-C(59)	1.391(5)
C(58)-C(63)	1.395(4)	C(58)-S(4)	1.775(3)
C(59)-C(60)	1.381(5)	C(60)-C(61)	1.404(4)
C(61)-C(62)	1.387(5)	C(61)-C(64)	1.510(5)
C(62)-C(63)	1.383(5)	N(4)-S(4)	1.615(3)
O(11)-S(4)	1.433(2)	O(12)-S(4)	1.446(3)

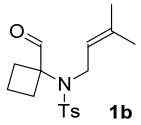
C(8)-C(1)-C(2)	110.1(3)	C(9)-C(1)-C(2)	112.7(3)
C(9)-C(1)-C(8)	110.6(3)	N(1)-C(1)-C(2)	99.8(2)
N(1)-C(1)-C(8)	114.8(3)	N(1)-C(1)-C(9)	108.5(3)
C(3)-C(2)-C(1)	104.8(2)	O(1)-C(2)-C(1)	111.6(3)
O(1)-C(2)-C(3)	113.5(3)	C(2)-C(3)-C(4)	100.7(2)
C(5)-C(3)-C(2)	118.1(3)	C(5)-C(3)-C(4)	111.2(3)
N(1)-C(4)-C(3)	102.9(2)	C(3)-C(5)-C(7)	114.0(3)
C(6)-C(5)-C(3)	123.9(4)	C(6)-C(5)-C(7)	122.1(4)
C(5)-C(6)-H(6A)	119(3)	C(5)-C(6)-H(6B)	128(4)
H(6A)-C(6)-H(6B)	113(5)	C(11)-C(10)-C(15)	120.1(3)
C(11)-C(10)-S(1)	120.4(3)	C(15)-C(10)-S(1)	119.5(2)
C(12)-C(11)-C(10)	119.3(3)	C(11)-C(12)-C(13)	121.5(3)
C(12)-C(13)-C(14)	118.1(3)	C(12)-C(13)-C(16)	121.5(3)
C(14)-C(13)-C(16)	120.4(3)	C(15)-C(14)-C(13)	121.2(3)
C(14)-C(15)-C(10)	119.8(3)	C(1)-N(1)-S(1)	125.1(2)
C(4)-N(1)-C(1)	112.4(2)	C(4)-N(1)-S(1)	119.1(2)
N(1)-S(1)-C(10)	107.83(15)	O(2)-S(1)-C(10)	108.57(15)
O(2)-S(1)-N(1)	108.06(14)	O(2)-S(1)-O(3)	119.10(14)
O(3)-S(1)-C(10)	106.38(15)	O(3)-S(1)-N(1)	106.45(13)
C(40)-C(33)-C(34)	113.1(3)	C(41)-C(33)-C(34)	110.0(3)
C(41)-C(33)-C(40)	110.0(3)	N(3)-C(33)-C(34)	100.3(2)
N(3)-C(33)-C(40)	108.4(3)	N(3)-C(33)-C(41)	114.9(3)
C(35)-C(34)-C(33)	104.6(3)	O(7)-C(34)-C(33)	111.7(3)
O(7)-C(34)-C(35)	113.8(3)	C(36)-C(35)-C(34)	100.6(2)
C(37)-C(35)-C(34)	118.4(3)	C(37)-C(35)-C(36)	112.0(3)
N(3)-C(36)-C(35)	103.1(3)	C(35)-C(37)-C(38)	114.1(3)
C(39)-C(37)-C(35)	123.9(3)	C(39)-C(37)-C(38)	122.0(4)
C(37)-C(39)-H(39A)	123(3)	C(37)-C(39)-H(39B)	125(4)
H(39A)-C(39)-H(39B)	111(5)	C(43)-C(42)-S(3)	120.3(2)

C(47)-C(42)-C(43)	120.1(3)	C(47)-C(42)-S(3)	119.5(2)
C(44)-C(43)-C(42)	119.5(3)	C(43)-C(44)-C(45)	121.1(3)
C(44)-C(45)-C(48)	121.2(3)	C(46)-C(45)-C(44)	118.3(3)
C(46)-C(45)-C(48)	120.4(3)	C(47)-C(46)-C(45)	121.4(3)
C(46)-C(47)-C(42)	119.5(3)	C(33)-N(3)-S(3)	125.5(2)
C(36)-N(3)-C(33)	111.9(3)	C(36)-N(3)-S(3)	119.1(2)
N(3)-S(3)-C(42)	108.05(16)	O(8)-S(3)-C(42)	106.21(15)
O(8)-S(3)-N(3)	106.32(14)	O(9)-S(3)-C(42)	108.41(14)
O(9)-S(3)-N(3)	107.90(15)	O(9)-S(3)-O(8)	119.49(15)
C(24)-C(17)-C(18)	109.8(3)	C(24)-C(17)-C(25)	110.3(3)
C(25)-C(17)-C(18)	112.6(3)	N(2)-C(17)-C(18)	99.0(2)
N(2)-C(17)-C(24)	111.0(3)	N(2)-C(17)-C(25)	113.7(3)
C(19)-C(18)-C(17)	105.8(3)	O(4)-C(18)-C(17)	113.8(3)
O(4)-C(18)-C(19)	114.8(3)	C(18)-C(19)-C(20)	101.7(3)
C(21)-C(19)-C(18)	115.8(3)	C(21)-C(19)-C(20)	113.1(3)
N(2)-C(20)-C(19)	104.0(3)	C(22)-C(21)-C(19)	119.2(3)
C(22)-C(21)-C(23)	121.1(3)	C(23)-C(21)-C(19)	119.7(3)
C(21)-C(22)-H(22A)	124(3)	C(21)-C(22)-H(22B)	126(4)
H(22A)-C(22)-H(22B)	111(5)	C(27)-C(26)-S(2)	119.4(3)
C(31)-C(26)-C(27)	120.6(3)	C(31)-C(26)-S(2)	120.0(2)
C(28)-C(27)-C(26)	119.3(3)	C(27)-C(28)-C(29)	121.2(3)
C(28)-C(29)-C(32)	120.5(3)	C(30)-C(29)-C(28)	118.3(3)
C(30)-C(29)-C(32)	121.3(3)	C(31)-C(30)-C(29)	121.4(3)
C(30)-C(31)-C(26)	119.1(3)	C(17)-N(2)-S(2)	125.2(2)
C(20)-N(2)-C(17)	113.0(2)	C(20)-N(2)-S(2)	117.6(2)
N(2)-S(2)-C(26)	108.65(15)	O(5)-S(2)-C(26)	105.82(15)
O(5)-S(2)-N(2)	106.10(13)	O(6)-S(2)-C(26)	108.45(15)
O(6)-S(2)-N(2)	108.06(15)	O(6)-S(2)-O(5)	119.38(15)
C(56)-C(49)-C(50)	112.2(3)	C(57)-C(49)-C(50)	109.4(3)
C(57)-C(49)-C(56)	110.4(3)	N(4)-C(49)-C(50)	99.3(2)
N(4)-C(49)-C(56)	113.9(3)	N(4)-C(49)-C(57)	111.2(3)
C(51)-C(50)-C(49)	105.3(3)	O(10)-C(50)-C(49)	113.7(3)
O(10)-C(50)-C(51)	114.7(3)	C(50)-C(51)-C(52)	102.1(3)
C(50)-C(51)-C(53)	116.4(3)	C(53)-C(51)-C(52)	112.5(3)
N(4)-C(52)-C(51)	103.8(3)	C(54)-C(53)-C(51)	119.0(3)
C(54)-C(53)-C(55)	122.0(3)	C(55)-C(53)-C(51)	118.9(3)
C(53)-C(54)-H(54A)	120(3)	C(53)-C(54)-H(54B)	121(3)
H(54A)-C(54)-H(54B)	120(4)	C(59)-C(58)-C(63)	120.6(3)
C(59)-C(58)-S(4)	119.2(2)	C(63)-C(58)-S(4)	120.1(3)
C(60)-C(59)-C(58)	119.5(3)	C(59)-C(60)-C(61)	120.8(3)
C(60)-C(61)-C(64)	119.9(3)	C(62)-C(61)-C(60)	118.5(3)

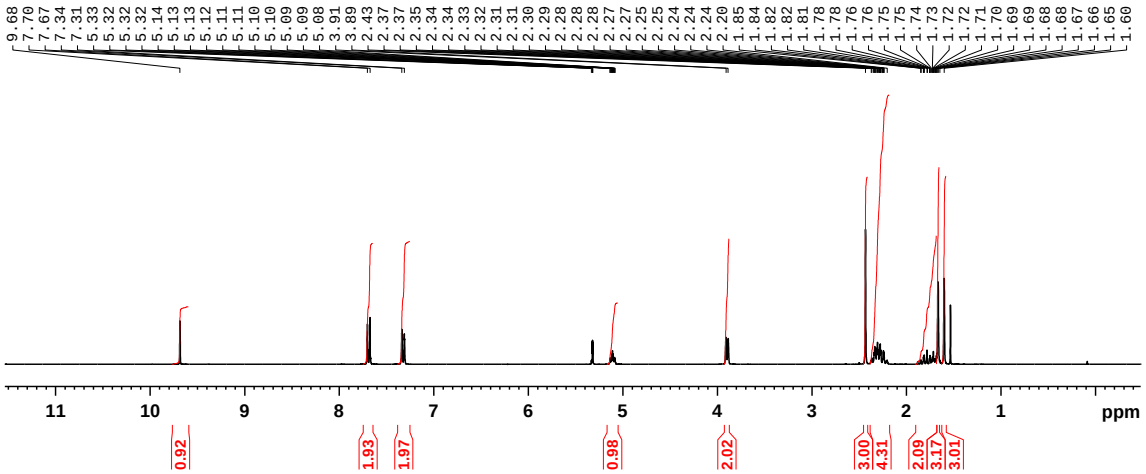
C(62)-C(61)-C(64)	121.6(3)	C(63)-C(62)-C(61)	121.6(3)
C(62)-C(63)-C(58)	118.9(3)	C(49)-N(4)-S(4)	125.8(2)
C(52)-N(4)-C(49)	112.7(3)	C(52)-N(4)-S(4)	117.4(2)
N(4)-S(4)-C(58)	108.42(15)	O(11)-S(4)-C(58)	108.40(15)
O(11)-S(4)-N(4)	107.89(14)	O(11)-S(4)-O(12)	119.51(15)
O(12)-S(4)-C(58)	106.07(15)	O(12)-S(4)-N(4)	106.14(14)

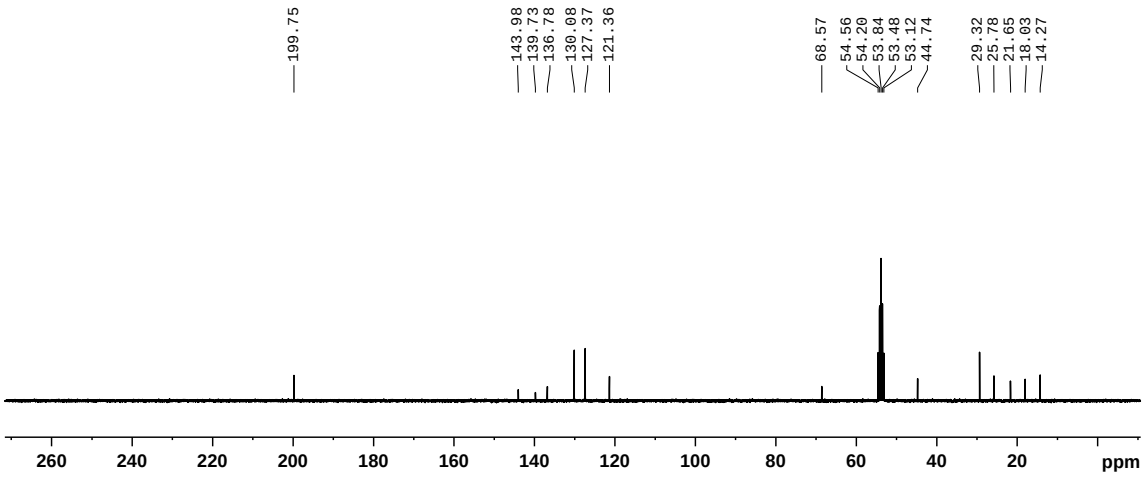
Symmetry transformations used to generate equivalent atoms

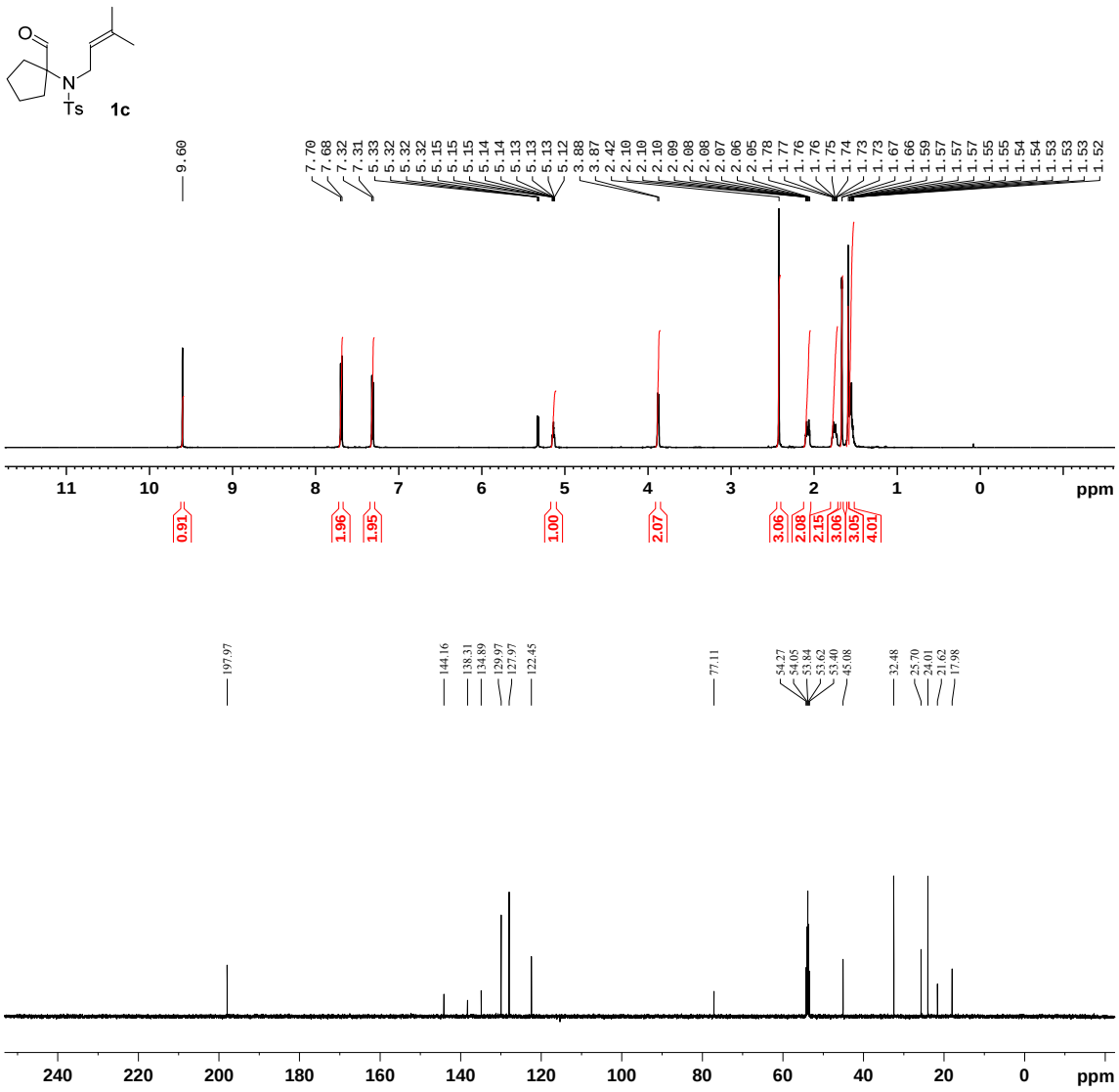
8. ^{1}H and ^{13}C NMR Spectra



1b



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5.15
5.15
5.14
5.14
5.13
5.13
5.13
5.12
3.88
3.87
2.42
2.10
2.10
2.10
2.09
2.08
2.08
2.07
2.06
2.05
1.78
1.77
1.76
1.76
1.75
1.74
1.73
1.73
1.67
1.66
1.59
1.57
1.57
1.57
1.55
1.55
1.54
1.54
1.53
1.53
1.53
1.52
11
10
9
8
7
6
5
4
3
2
1
0
ppm
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1.96
1.95
1.00
2.07
3.06
2.08
2.15
3.06
3.05
4.01
197.97
144.16
138.31
134.89
129.97
127.97
122.45
77.11
54.27
54.05
53.84
53.62
53.40
45.08
32.48
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120
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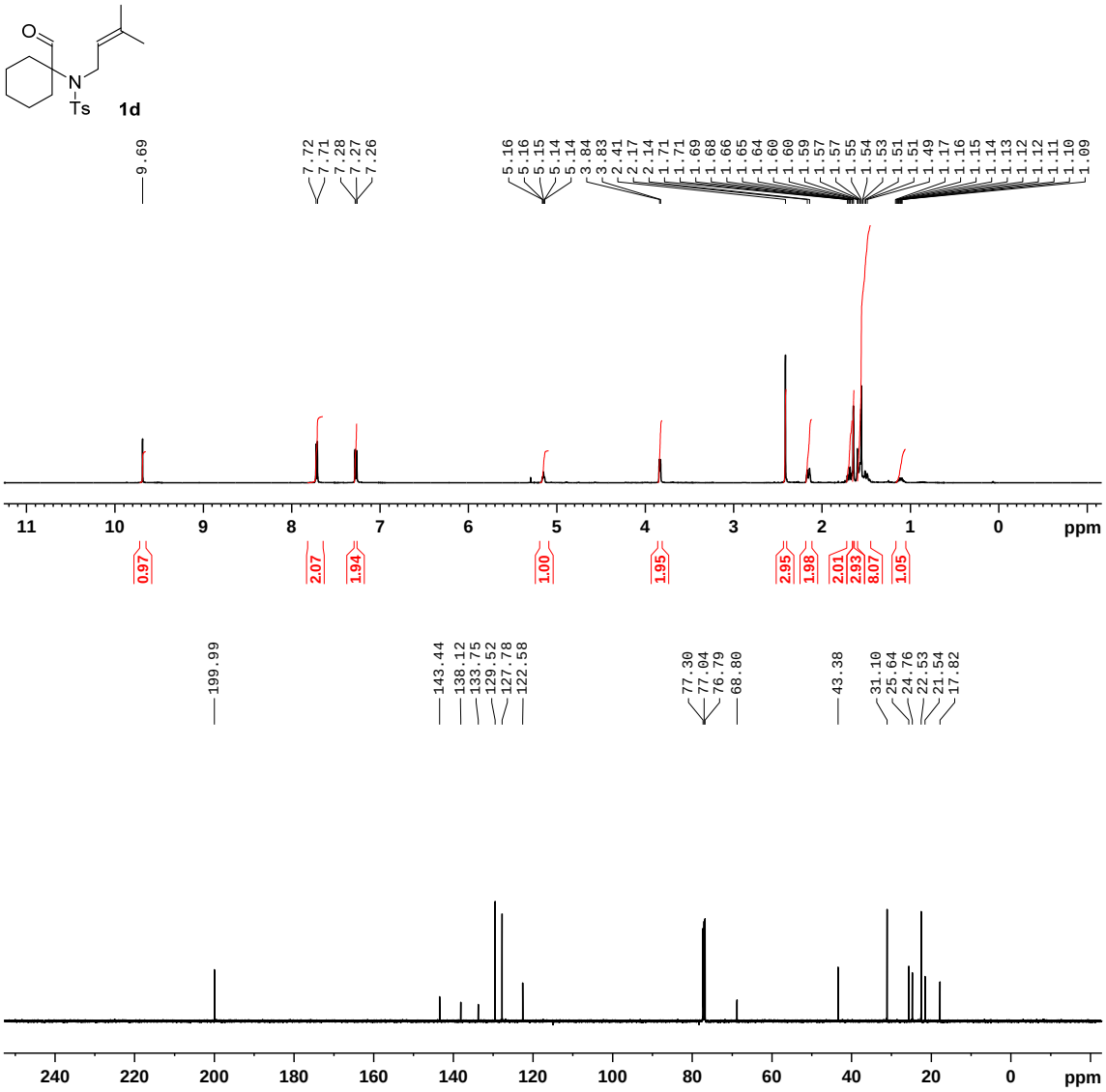
ppm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N
Ts
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5.14
3.84
3.83
2.41
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2.14
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1.71
1.69
1.68
1.66
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1.12
1.11
1.10
1.09
11
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6
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1.98
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127.78
122.58
77.30
77.04
76.79
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43.38
31.10
25.64
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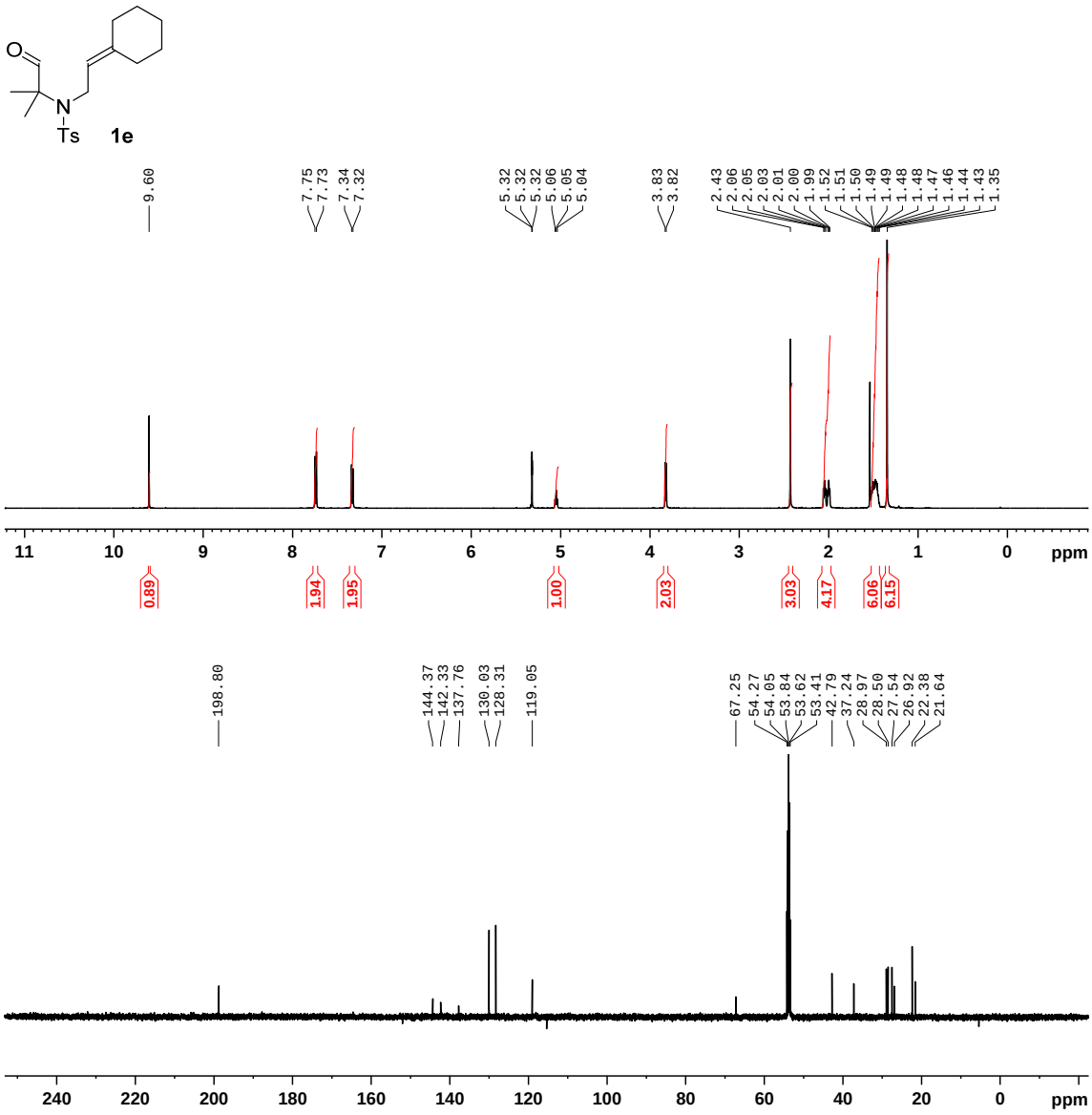
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Ts
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5.32
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5.05
5.04
3.83
3.82
2.43
2.06
2.05
2.03
2.01
2.00
1.99
1.52
1.51
1.50
1.49
1.49
1.48
1.48
1.47
1.46
1.44
1.43
1.35
11
10
9
8
7
6
5
4
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1.95
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3.03
4.17
6.06
6.15
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144.37
142.33
137.76
130.03
128.31
119.05
67.25
54.27
54.05
53.84
53.62
53.41
42.79
37.24
28.97
28.50
27.54
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22.38
21.64
240
220
200
180
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120
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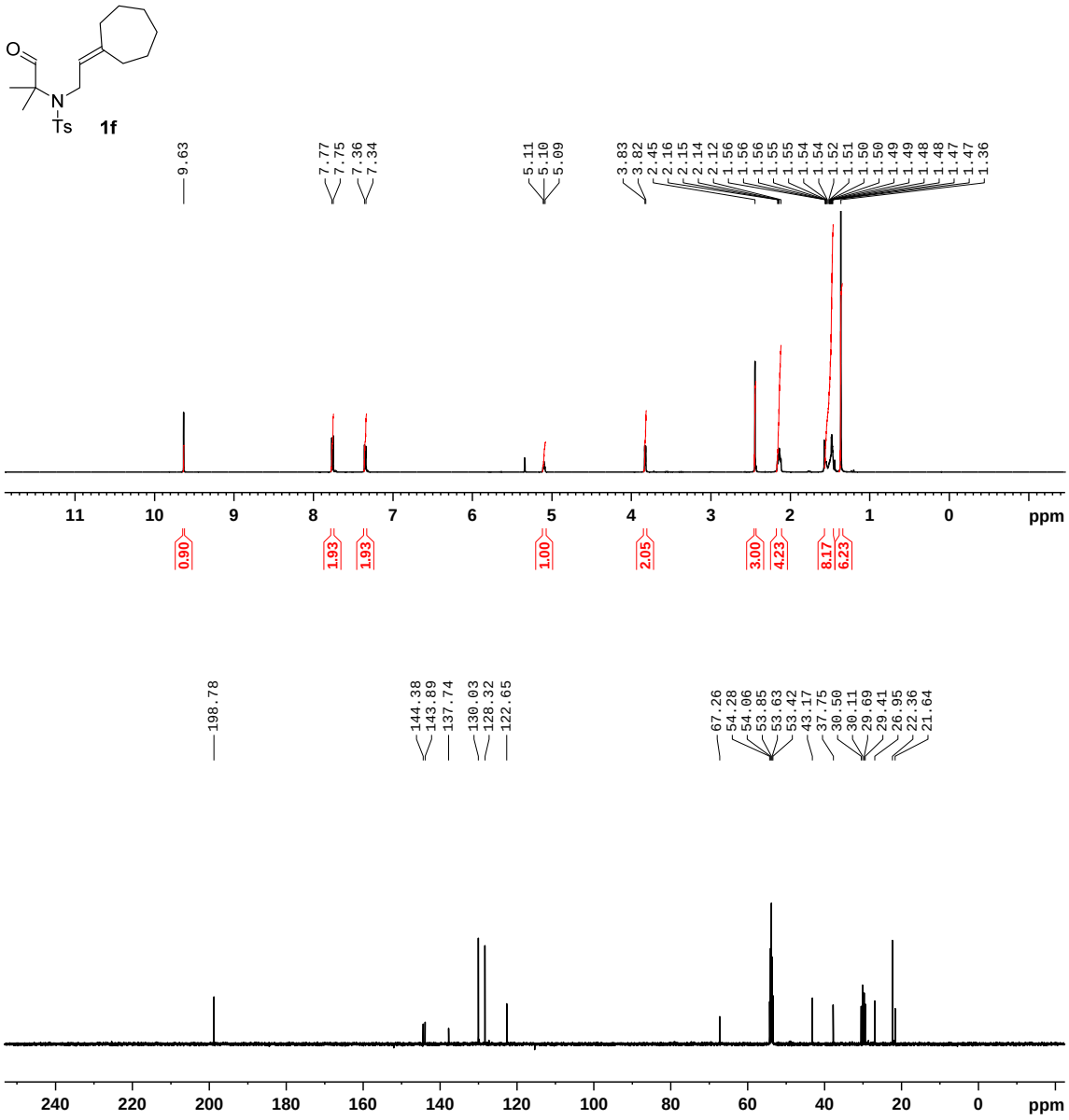
80
60
40
20
0
ppm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Ts
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5.09
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3.82
2.45
2.16
2.15
2.14
2.12
1.56
1.56
1.55
1.55
1.54
1.54
1.52
1.51
1.50
1.50
1.49
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1.48
1.47
1.47
1.36
11
10
9
8
7
6
5
4
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ppm
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1.00
2.05
3.00
4.23
8.17
6.23
198.78
144.38
143.89
137.74
130.03
128.32
122.65
67.26
54.28
54.06
53.85
53.63
53.42
43.17
37.75
30.50
30.11
29.69
29.41
26.95
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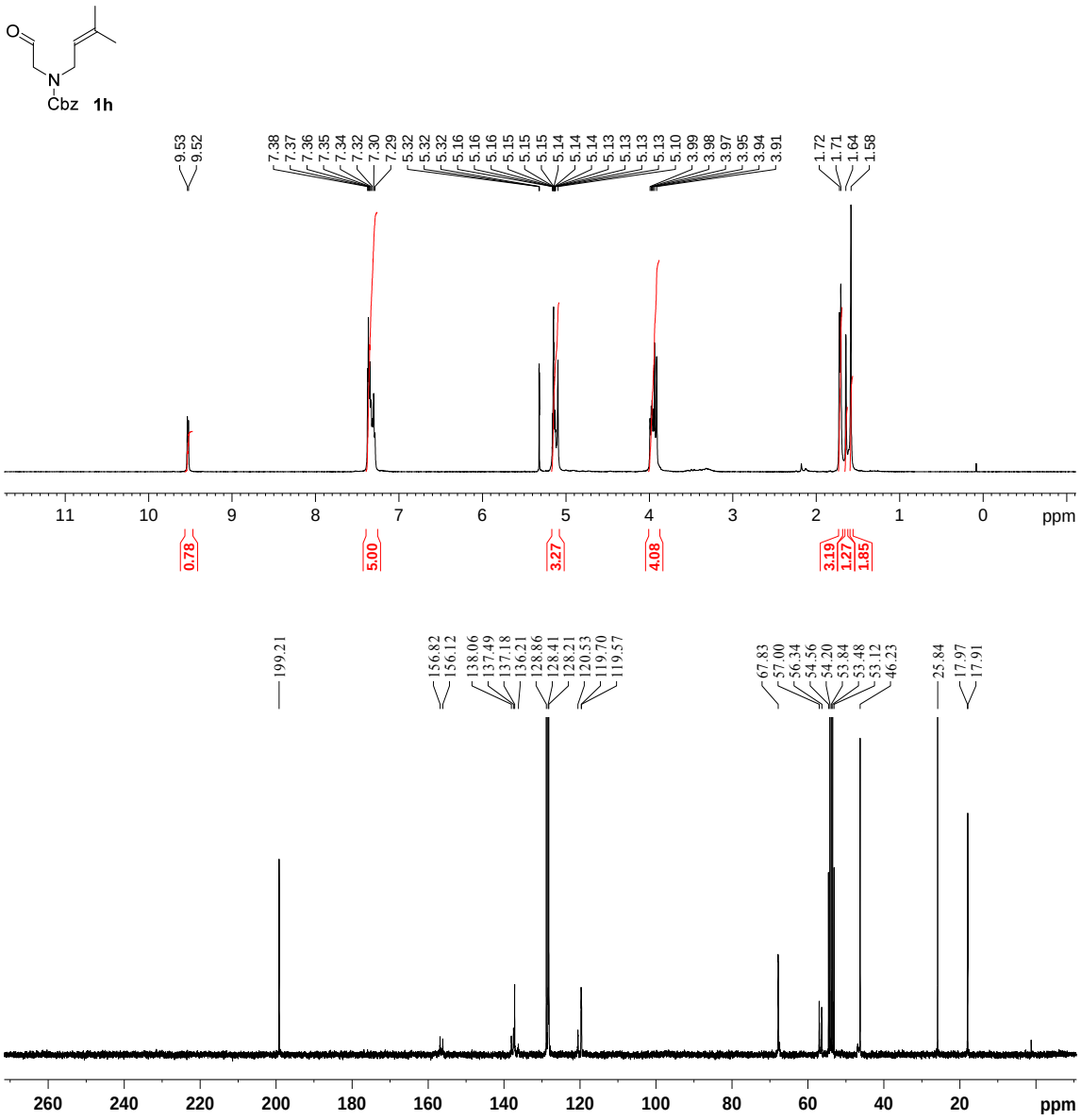
21.64
240
220
200
180
160
140
120
100
80
60
40
20
0
ppm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N
Cbz
1h
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7.38
7.37
7.36
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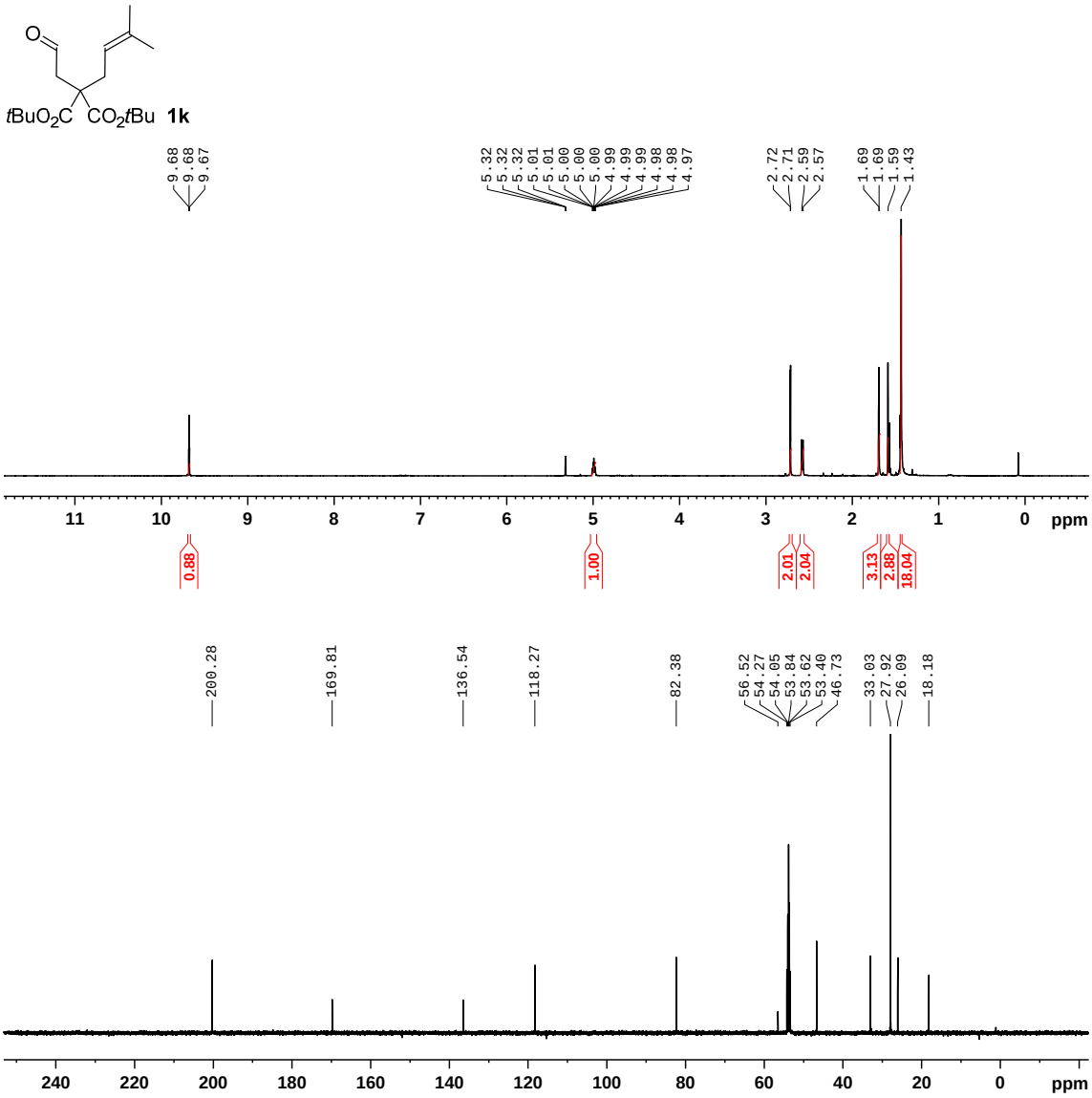
7.34
7.32
7.30
7.29
5.32
5.32
5.32
5.16
5.16
5.16
5.15
5.15
5.15
5.14
5.14
5.14
5.13
5.13
5.13
5.13
5.10
3.99
3.98
3.97
3.95
3.94
3.91
1.72
1.71
1.64
1.58
11
10
9
8
7
6
5
4
3
2
1
0
ppm
0.78
5.00
3.27
4.08
3.19
1.27
1.85
199.21
156.82
156.12
138.06
137.49
137.18
136.21
128.86
128.41
128.21
120.53
119.70
119.57
67.83
57.00
56.34
54.56
54.20
53.84
53.48
53.12
46.23
25.84
17.97
17.91
260
240
220
200
180
160
140
120
100
80
60
40
20
ppm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5.32
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5.01
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5.00
5.00
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4.99
4.99
4.98
4.98
4.97
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1.69
1.69
1.59
1.43
11
10
9
8
7
6
5
4
3
2
1
0
ppm
0.88
1.00
2.01
2.04
3.13
2.88
18.04
200.28
169.81
136.54
118.27
82.38
56.52
54.27
54.05
53.84
53.62
53.40
46.73
33.03
27.92
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18.18
240
220
200
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160
140
120
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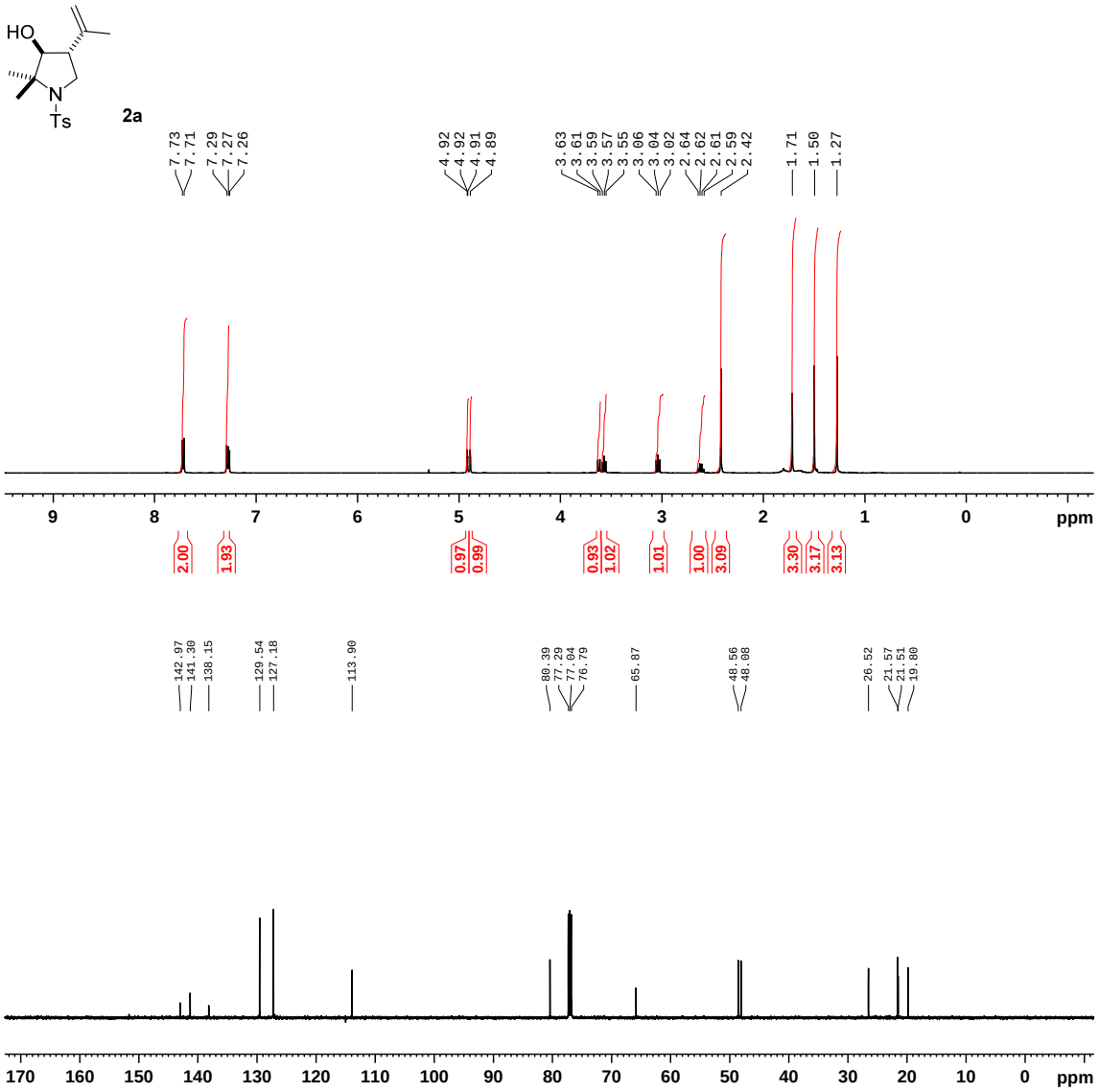
60
40
20
0
ppm


HO
N
Ts
2a
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7.71
7.29
7.27
7.26
4.92
4.92
4.91
4.89
3.63
3.61
3.59
3.57
3.55
3.06
3.04
3.02
2.64
2.62
2.61
2.59
2.42
1.71
1.50
1.27
2.00
1.93
0.97
0.99
0.93
1.02
1.01
1.00
3.09
3.30
3.17
3.13
142.97
141.30
138.15
129.54
127.18
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76.79
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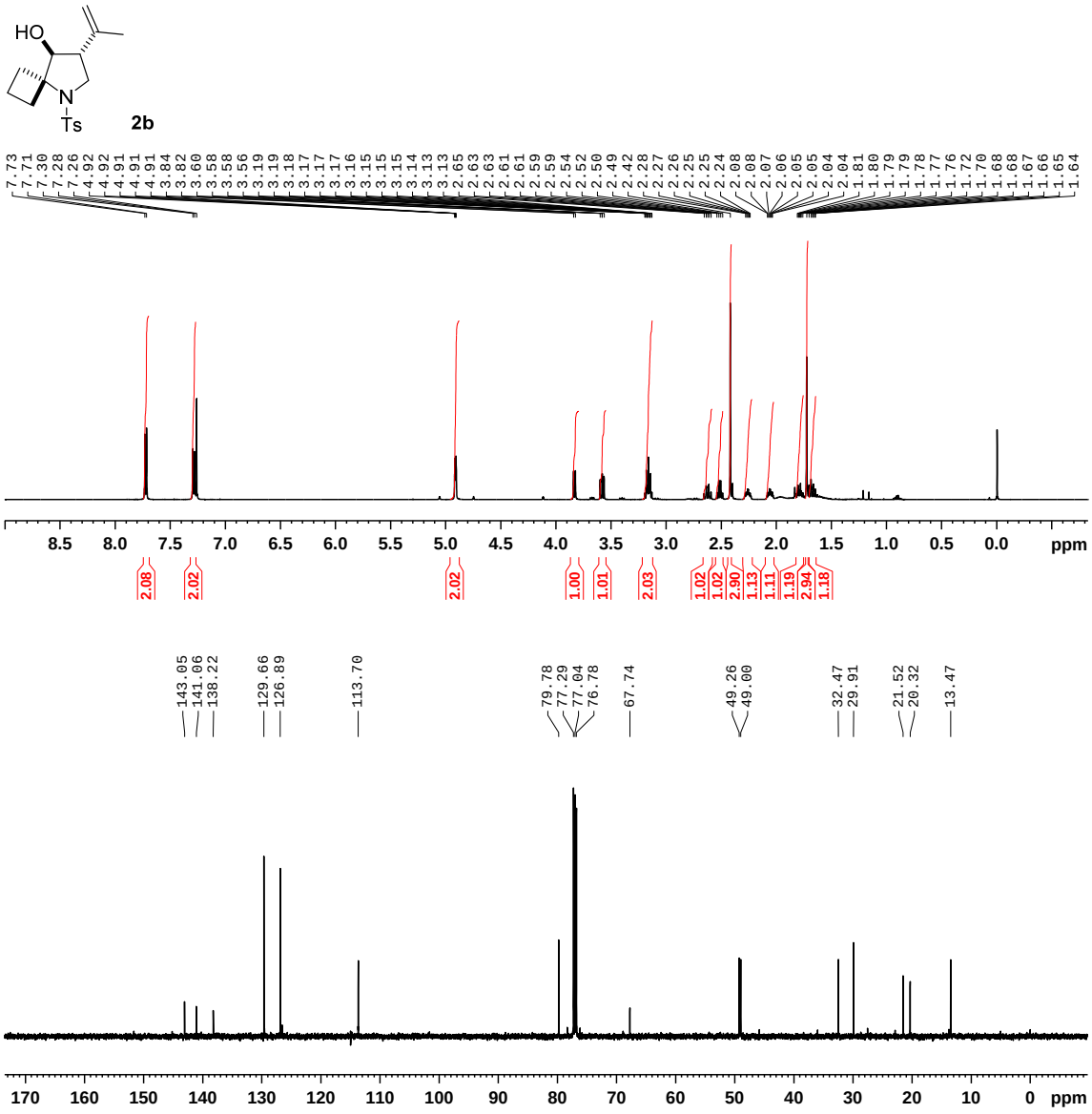
48.08
26.52
21.57
21.51
19.80
ppm


HO
N
Ts
2b
7.73 7.71 7.30 7.28 7.26 4.92 4.92 4.91 4.91 4.91 3.84 3.82 3.60 3.58 3.58 3.56 3.19 3.19 3.18 3.17 3.17 3.17 3.16 3.15 3.15 3.15 3.14 3.13 3.13 2.65 2.63 2.63 2.61 2.61 2.59 2.59 2.54 2.52 2.50 2.49 2.42 2.28 2.27 2.26 2.25 2.25 2.24 2.08 2.08 2.07 2.06 2.05 2.05 2.04 2.04 1.81 1.80 1.79 1.79 1.78 1.77 1.76 1.72 1.70 1.68 1.68 1.67 1.66 1.65 1.64
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 ppm
2.08 2.02 2.02 1.00 1.01 2.03 1.02 1.02 2.90 1.13 1.11 1.19 2.94 1.18
143.05 141.06 138.22 129.66 126.89 113.70 79.78 77.29 77.04 76.78 67.74 49.26 49.00 32.47 29.91 21.52 20.32 13.47
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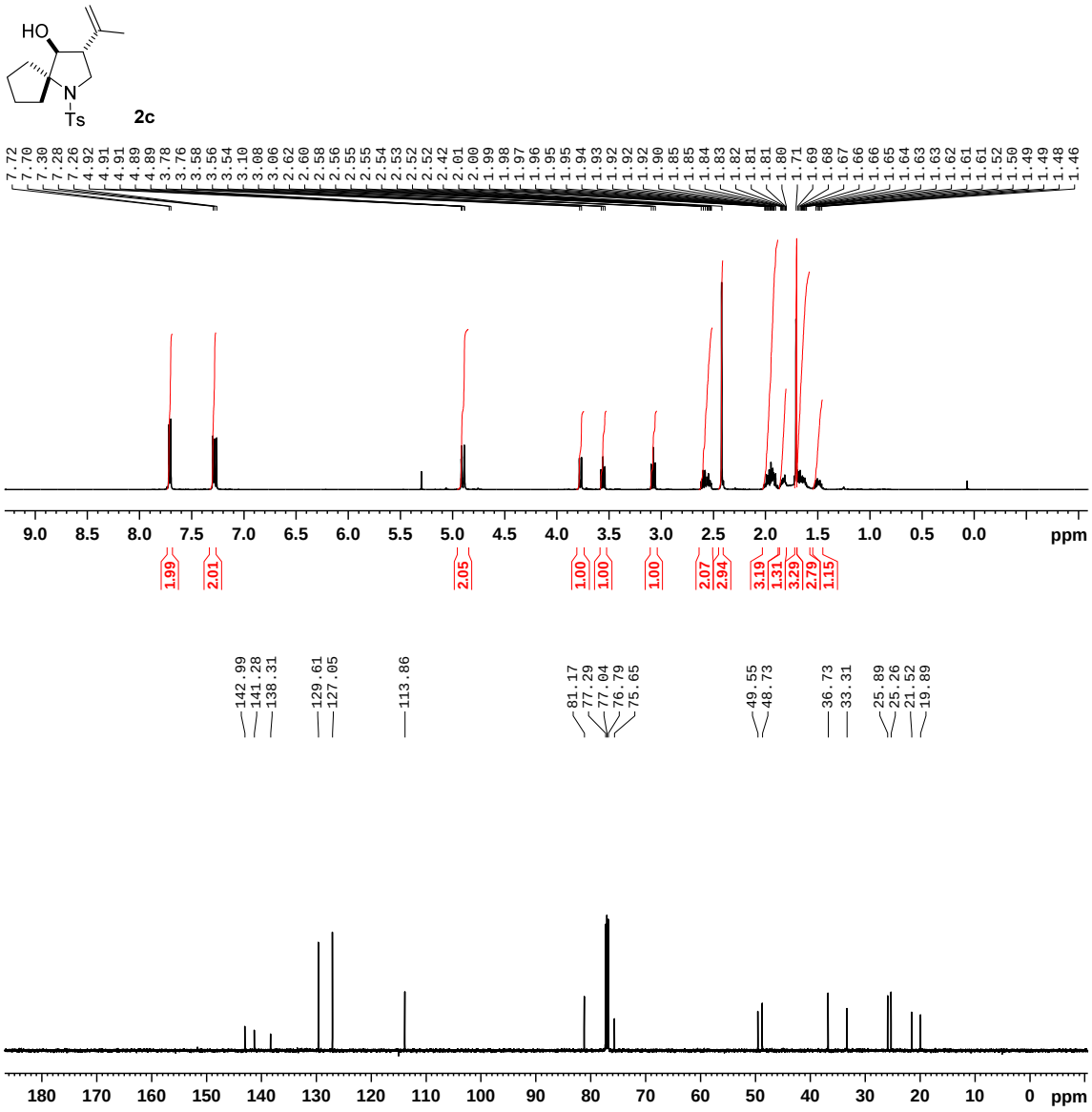
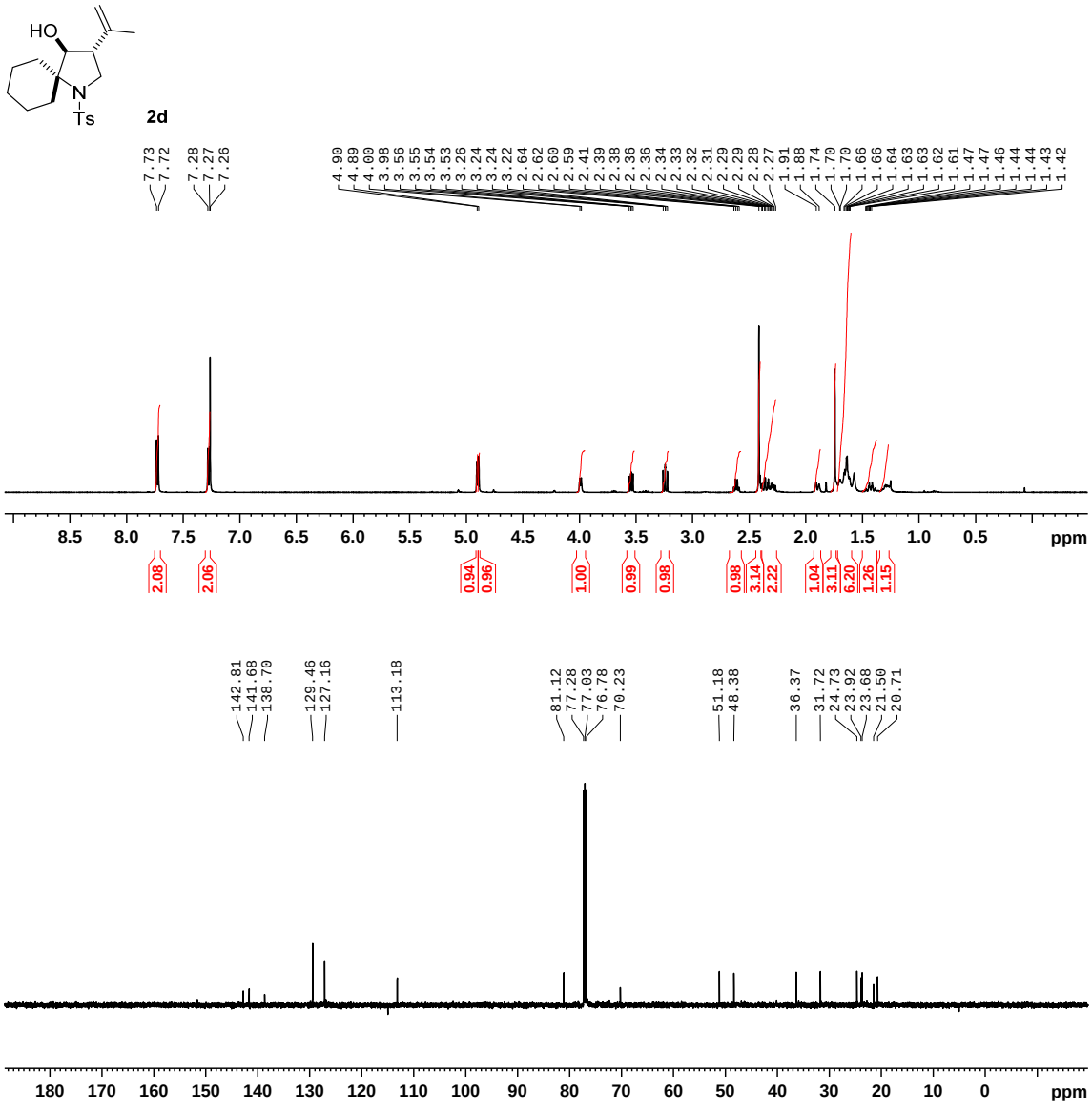

HO
N
Ts
2c
7.72 7.70 7.30 7.28 7.26 4.92 4.91 4.89 4.89 3.78 3.76 3.58 3.56 3.54 3.10 3.08 3.06 2.62 2.60 2.58 2.56 2.55 2.54 2.53 2.52 2.52 2.42 2.01 2.00 1.99 1.98 1.97 1.96 1.95 1.95 1.94 1.93 1.92 1.92 1.92 1.90 1.85 1.85 1.84 1.83 1.82 1.81 1.81 1.80 1.71 1.69 1.68 1.67 1.66 1.65 1.64 1.63 1.63 1.62 1.61 1.61 1.52 1.50 1.49 1.49 1.48 1.46
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 ppm
1.99 2.01 2.05 1.00 1.00 1.00 2.07 2.94 3.19 1.31 3.29 2.79 1.15
142.99 141.28 138.31 129.61 127.05 113.86 81.17 77.29 77.04 76.79 75.65 49.55 48.73 36.73 33.31 25.89 25.26 21.52 19.89
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm


HO
N
Ts
2d
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7.72
7.28
7.27
7.26
4.90
4.89
4.00
3.98
3.56
3.55
3.54
3.53
3.26
3.24
3.24
3.22
2.64
2.62
2.60
2.59
2.41
2.39
2.38
2.36
2.36
2.34
2.33
2.32
2.31
2.29
2.29
2.28
2.27
1.91
1.88
1.74
1.70
1.70
1.66
1.66
1.64
1.63
1.63
1.62
1.61
1.47
1.47
1.46
1.44
1.44
1.43
1.42
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
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2.0
1.5
1.0
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ppm
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2.06
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0.96
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0.99
0.98
0.98
3.14
2.22
1.04
3.11
6.20
1.26
1.15
142.81
141.68
138.70
129.46
127.16
113.18
81.12
77.28
77.03
76.78
70.23
51.18
48.38
36.37
31.72
24.73
23.92
23.68
21.50
20.71
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130
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100
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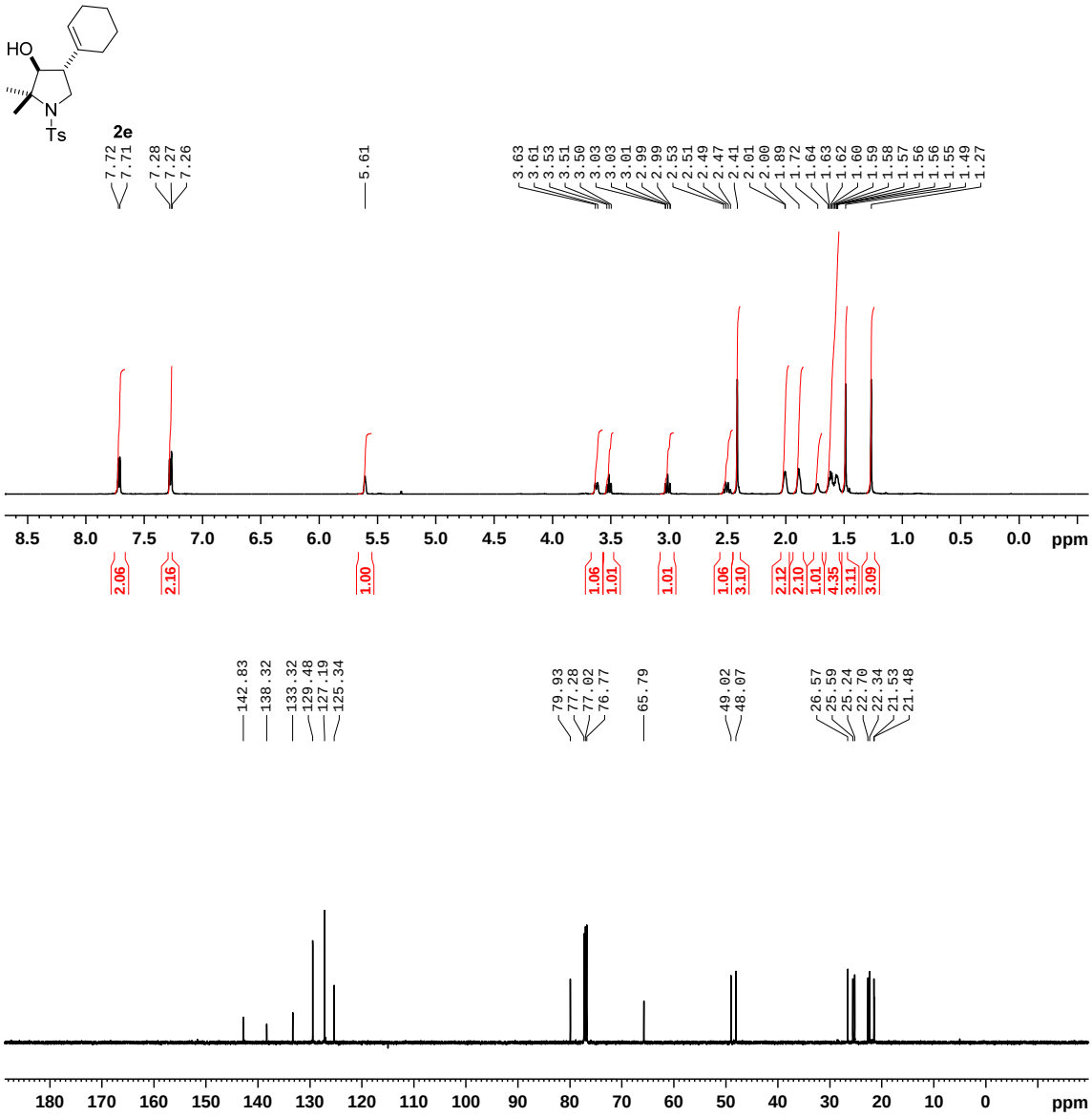
ppm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N
Ts
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7.27
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3.61
3.53
3.51
3.50
3.03
3.03
3.01
2.99
2.99
2.53
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1.63
1.62
1.60
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1.49
1.27
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 ppm
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1.06
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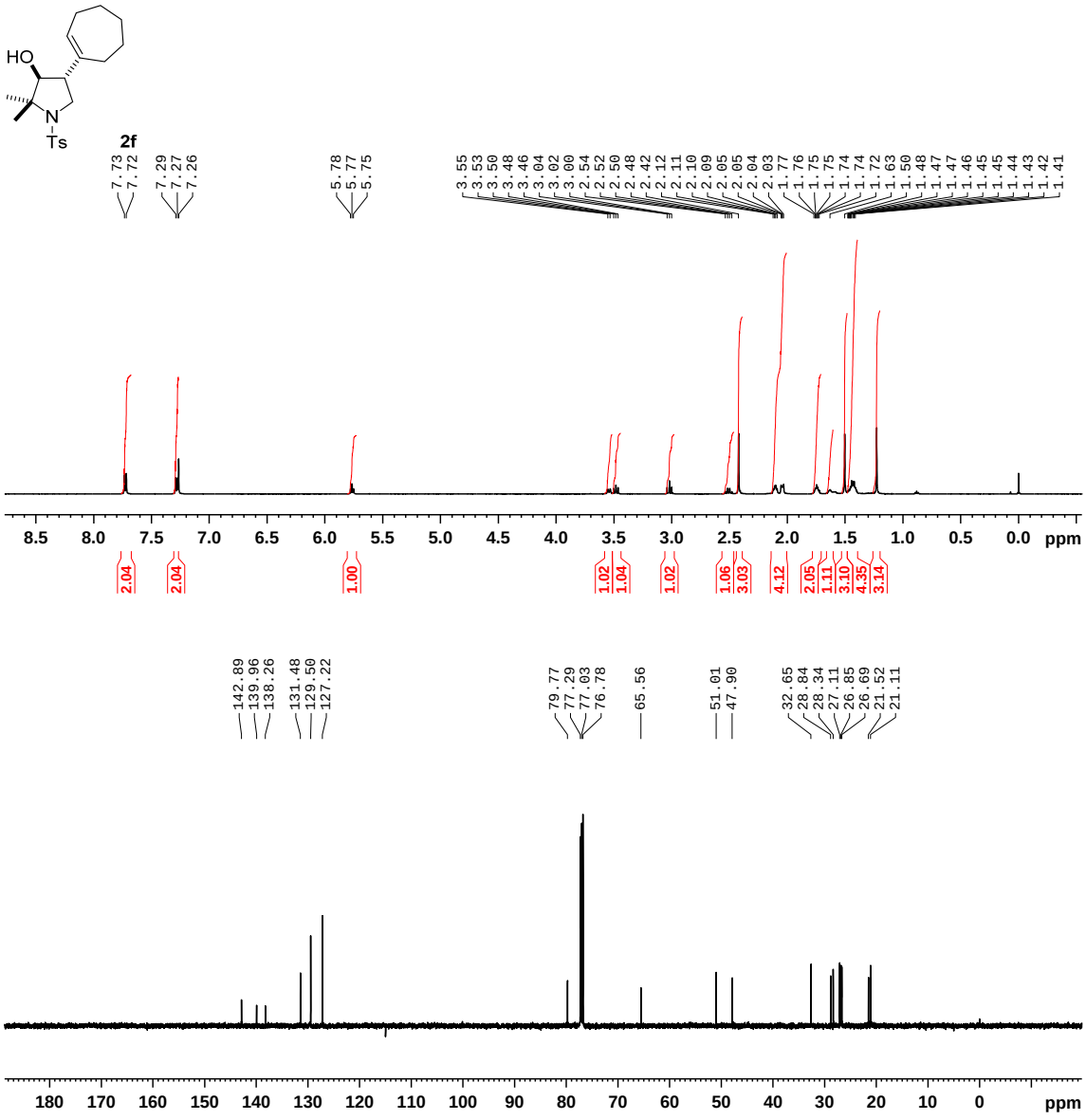
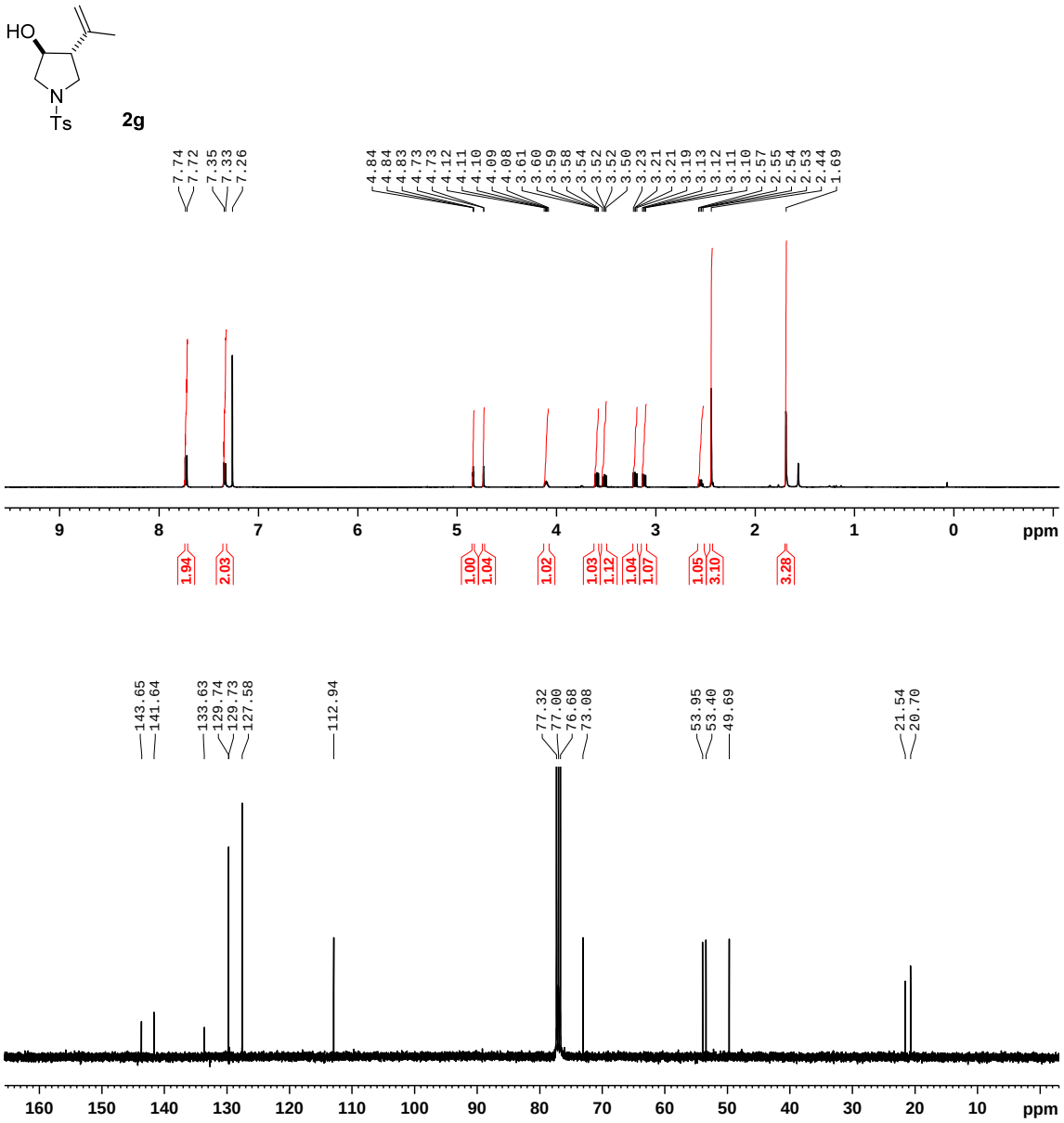
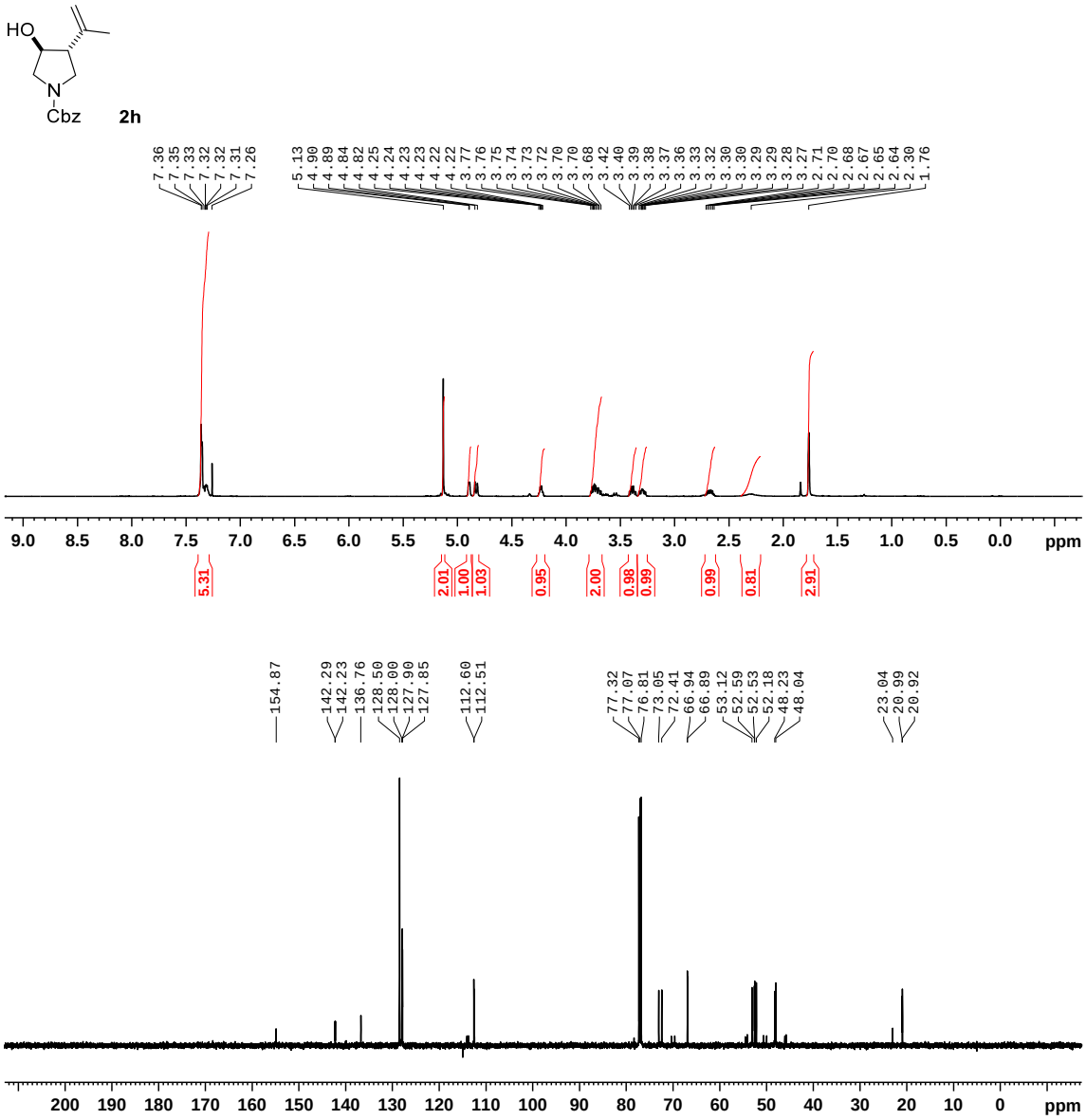
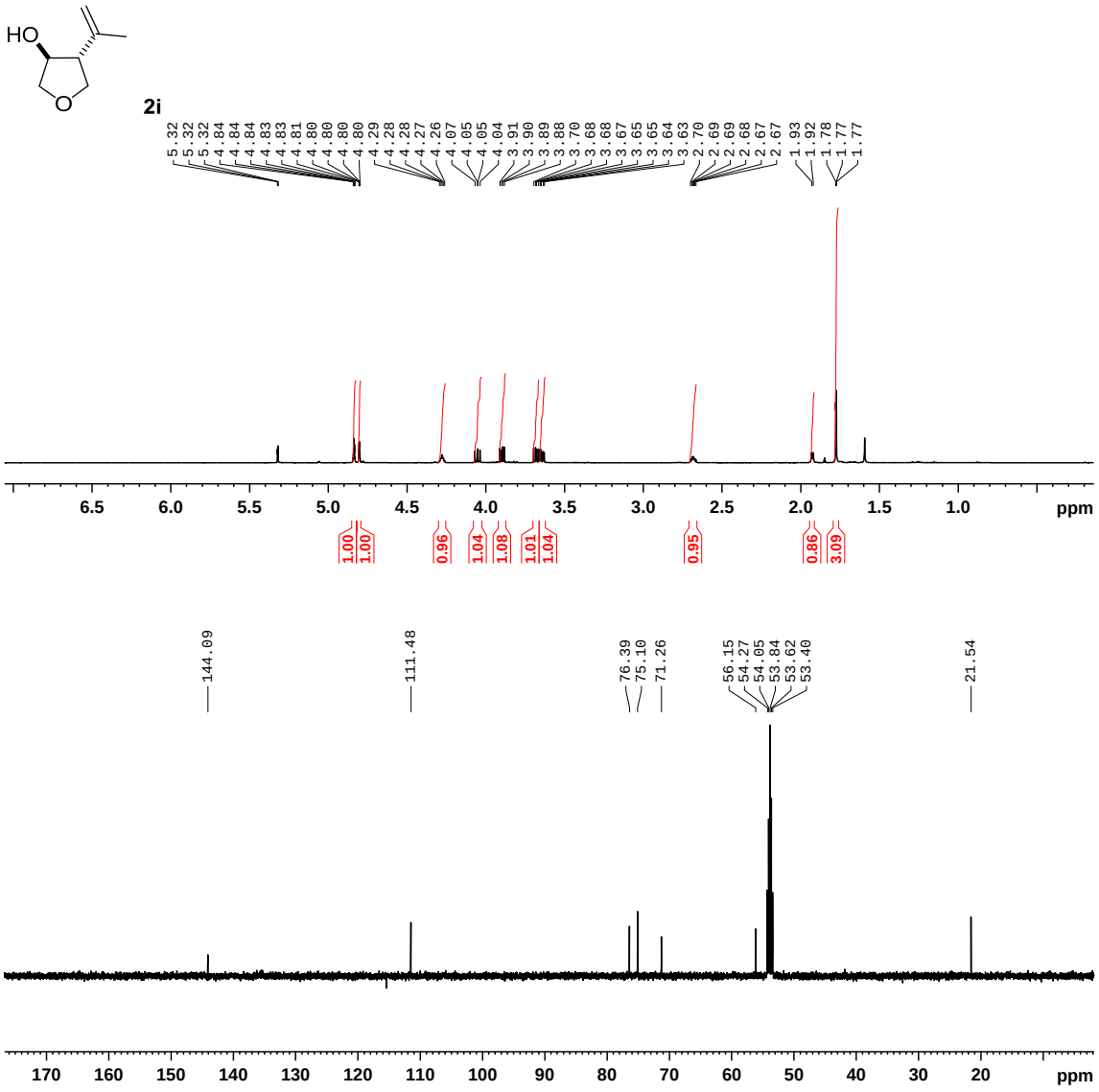
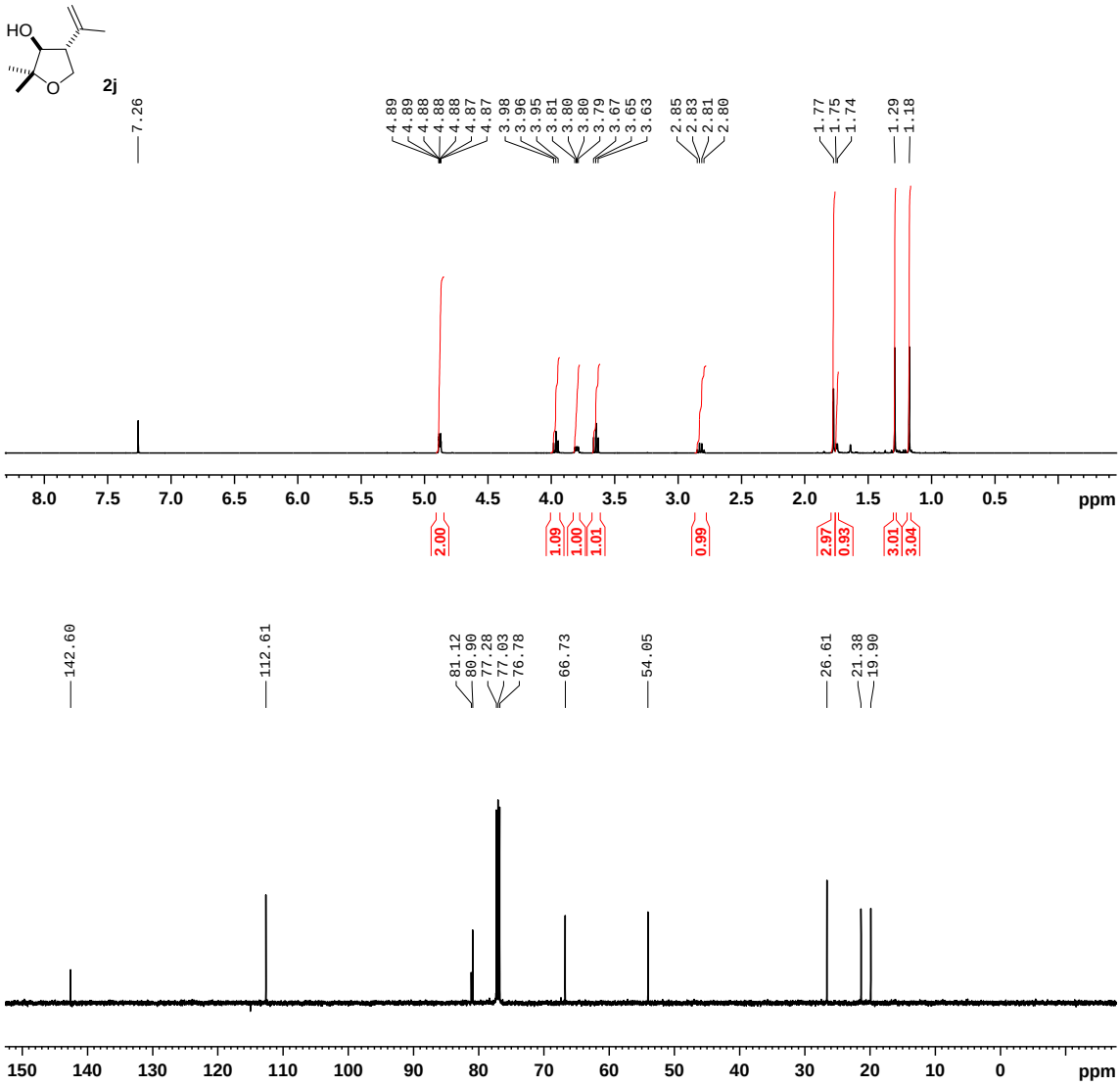
1.01
1.06
3.10
2.12
2.10
1.01
4.35
3.11
3.09
142.83
138.32
133.32
129.48
127.19
125.34
79.93
77.28
77.02
76.77
65.79
49.02
48.07
26.57
25.59
25.24
22.76
22.34
21.53
21.48
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

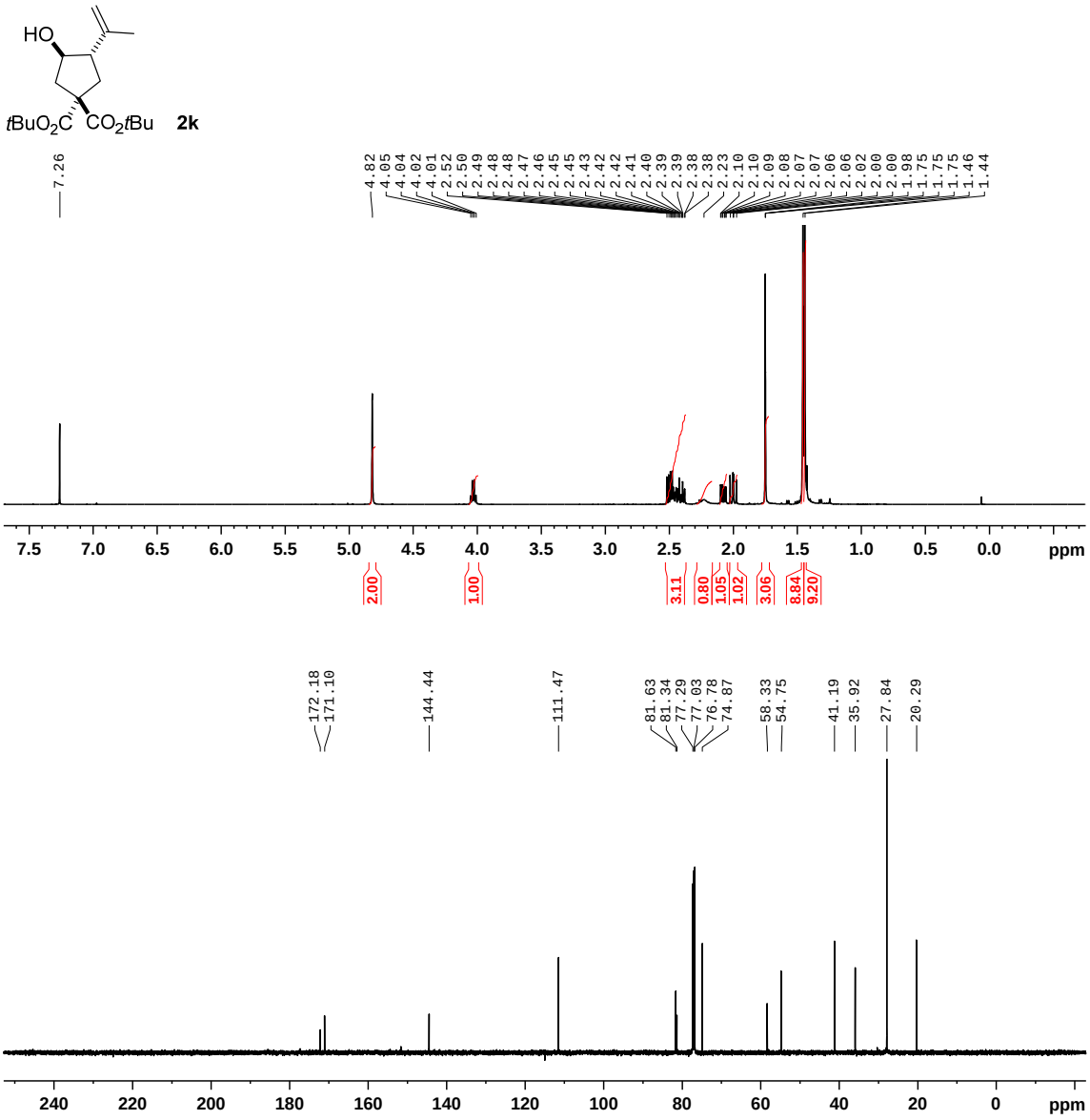

HO
N
Ts
2f
7.73
7.72
7.29
7.27
7.26
5.78
5.77
5.75
3.55
3.53
3.50
3.48
3.46
3.04
3.02
3.00
2.54
2.52
2.50
2.48
2.42
2.12
2.11
2.10
2.09
2.05
2.05
2.04
2.03
1.77
1.76
1.75
1.75
1.74
1.74
1.72
1.63
1.50
1.48
1.47
1.47
1.46
1.45
1.45
1.44
1.43
1.42
1.41
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 ppm
2.04
2.04
1.00
1.02
1.04
1.02
1.06
3.03
4.12
2.05
1.11
3.10
4.35
3.14
142.89
139.96
138.26
131.48
129.50
127.22
79.77
77.29
77.03
76.78
65.56
51.01
47.90
32.65
28.84
28.34
27.11
26.85
26.69
21.52
21.11
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm


HO
N
Ts
2g
7.74
7.72
7.35
7.33
7.26
4.84
4.84
4.83
4.73
4.73
4.12
4.11
4.10
4.09
4.08
3.61
3.60
3.59
3.58
3.54
3.52
3.52
3.50
3.23
3.21
3.21
3.19
3.13
3.12
3.11
3.10
2.57
2.55
2.54
2.53
2.44
1.69
9
8
7
6
5
4
3
2
1
0
ppm
1.94
2.03
1.00
1.04
1.02
1.03
1.12
1.04
1.07
1.05
3.10
3.28
143.65
141.64
133.63
129.74
129.73
127.58
112.94
77.32
77.00
76.68
73.08
53.95
53.40
49.69
21.54
20.70
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

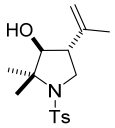

HO
N
Cbz
2h
7.36
7.35
7.33
7.32
7.32
7.31
7.26
5.13
4.90
4.89
4.84
4.82
4.25
4.24
4.23
4.23
4.22
4.22
3.77
3.76
3.75
3.74
3.73
3.72
3.70
3.70
3.68
3.42
3.40
3.39
3.38
3.37
3.36
3.33
3.32
3.30
3.30
3.29
3.29
3.28
3.27
2.71
2.70
2.68
2.67
2.65
2.64
2.30
1.76
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 ppm
5.31
2.01
1.00
1.03
0.95
2.00
0.98
0.99
0.99
0.81
2.91
154.87
142.29
142.23
136.76
128.50
128.00
127.90
127.85
112.60
112.51
77.32
77.07
76.81
73.05
72.41
66.94
66.89
53.12
52.59
52.53
52.18
48.23
48.04
23.04
20.99
20.92
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm


HO
O
2i
5.32
5.32
5.32
4.84
4.84
4.84
4.83
4.83
4.81
4.80
4.80
4.80
4.80
4.29
4.28
4.28
4.27
4.26
4.07
4.05
4.05
4.04
3.91
3.90
3.89
3.88
3.70
3.68
3.68
3.67
3.65
3.65
3.64
3.63
2.70
2.69
2.69
2.68
2.67
2.67
1.93
1.92
1.78
1.77
1.77
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm
1.00
1.00
0.96
1.04
1.08
1.01
1.04
0.95
0.86
3.09
144.09
111.48
76.39
75.10
71.26
56.15
54.27
54.05
53.84
53.62
53.40
21.54
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm

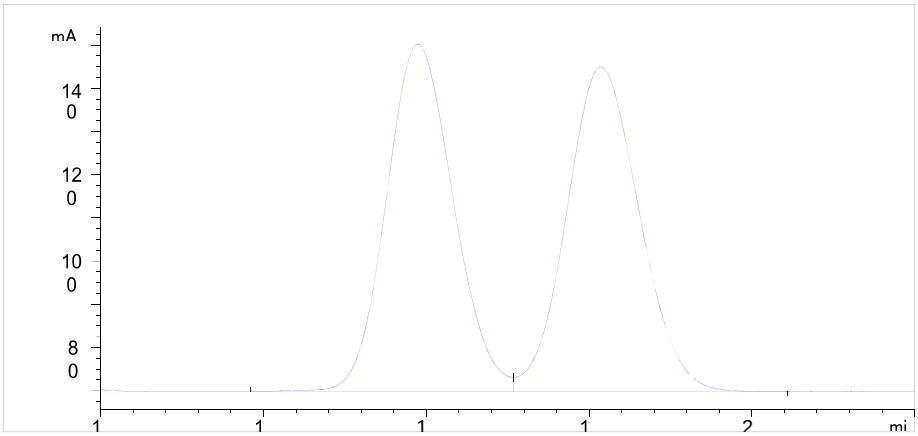

HO
O
2j
7.26
4.89
4.89
4.88
4.88
4.88
4.87
4.87
3.98
3.96
3.95
3.81
3.80
3.80
3.79
3.67
3.65
3.63
2.85
2.83
2.81
2.80
1.77
1.75
1.74
1.29
1.18
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
2.00
1.09
1.00
1.01
0.99
2.97
0.93
3.01
3.04
142.60
112.61
81.12
80.90
77.28
77.03
76.78
66.73
54.05
26.61
21.38
19.90
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm


HO
tBuO2C CO2tBu
2k
7.26
4.82
4.05
4.04
4.02
4.01
2.52
2.50
2.49
2.48
2.48
2.47
2.46
2.45
2.45
2.43
2.42
2.42
2.41
2.40
2.39
2.39
2.38
2.38
2.23
2.10
2.10
2.09
2.08
2.07
2.07
2.06
2.06
2.02
2.00
2.00
1.98
1.75
1.75
1.46
1.44
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 ppm
2.00
1.00
3.11
0.80
1.05
1.02
3.06
8.84
9.20
172.18
171.10
144.44
111.47
81.63
81.34
77.29
77.03
76.78
74.87
58.33
54.75
41.19
35.92
27.84
20.29
240 220 200 180 160 140 120 100 80 60 40 20 0 ppm

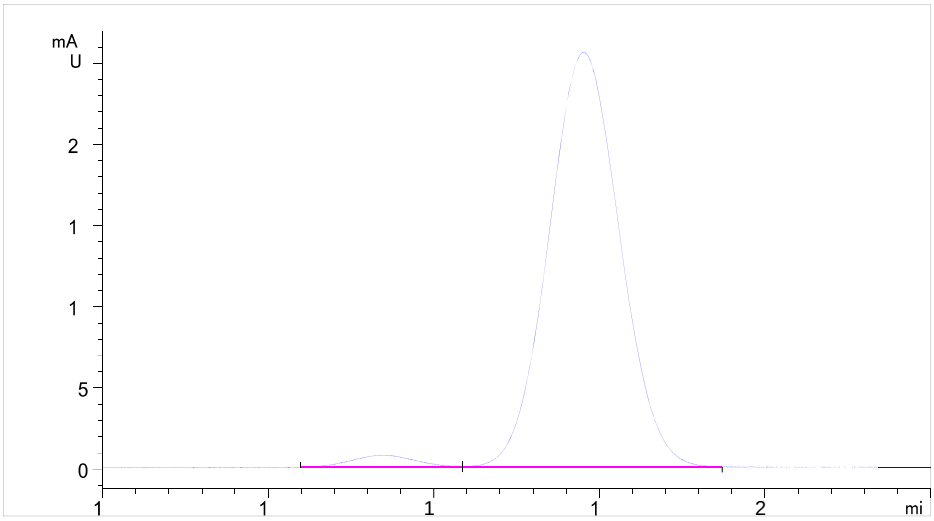
9. HPLC and GC Traces



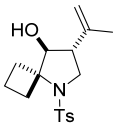
2a



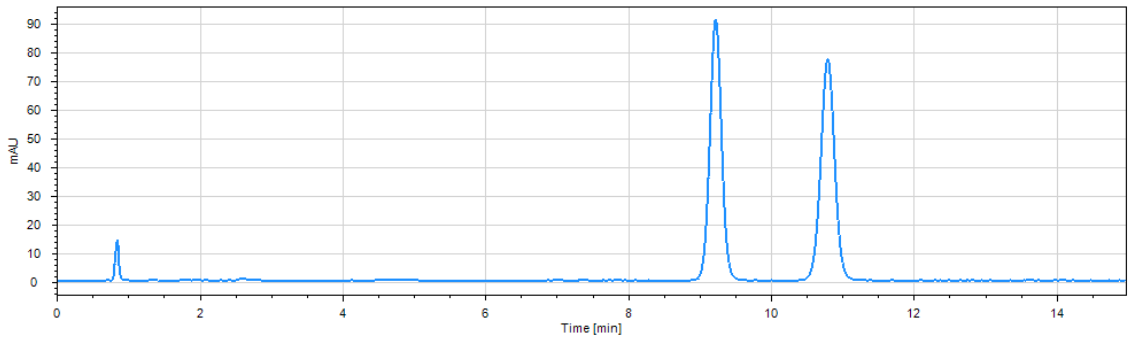
Peak #	RT [min]	Area %	Name
	17.95	49.69	Enantiomer
	19.07	50.31	Enantiomer



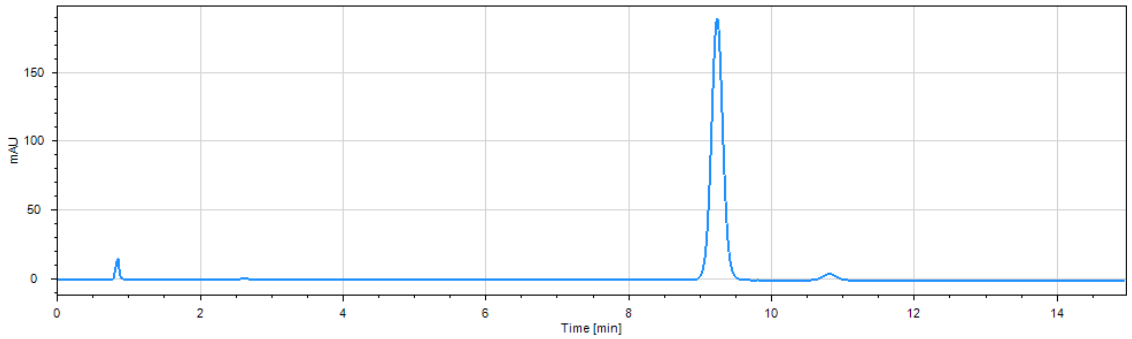
Peak #	RT [min]	Area %	Name
	17.69	2.59	Enantiomer
	18.90	97.41	Enantiomer



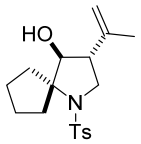
2b



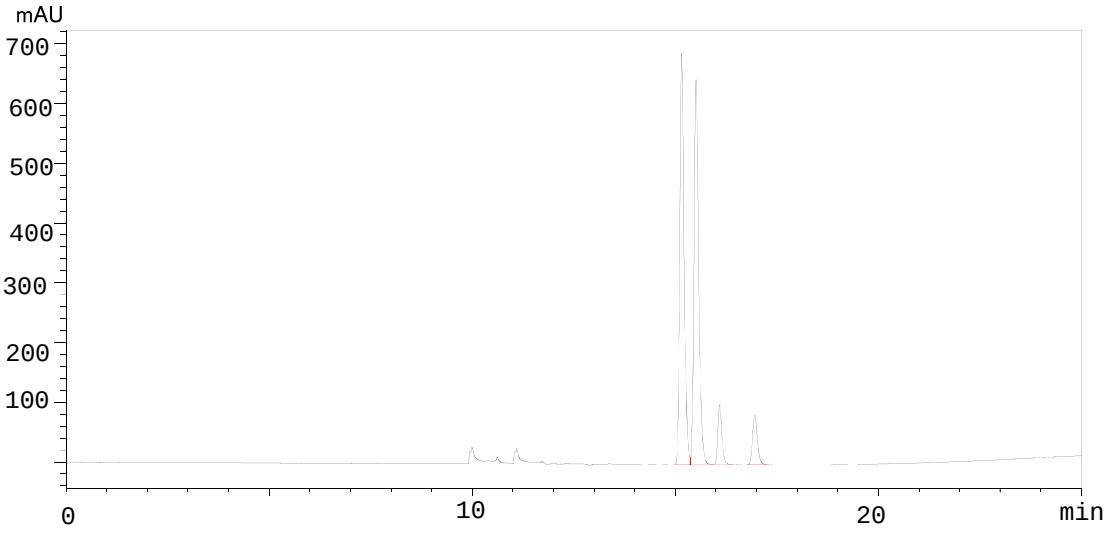
Peak #	RT [min]	Area %	Name
	9.24	50.02	Enantiomer
	10.81	49.98	Enantiomer



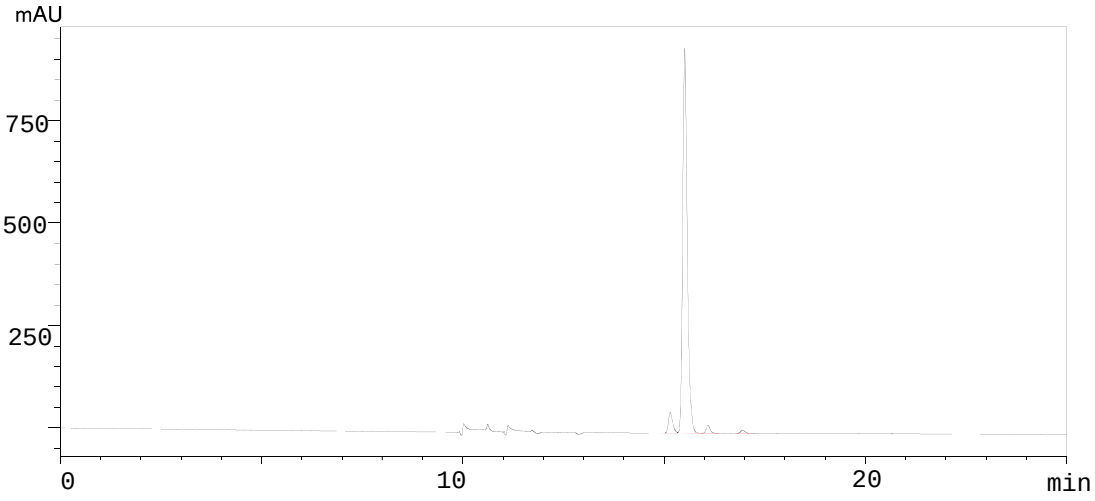
Peak #	RT [min]	Area %	Name
	9.26	97.39	Enantiomer
	10.83	2.61	Enantiomer



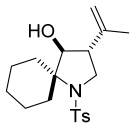
2c



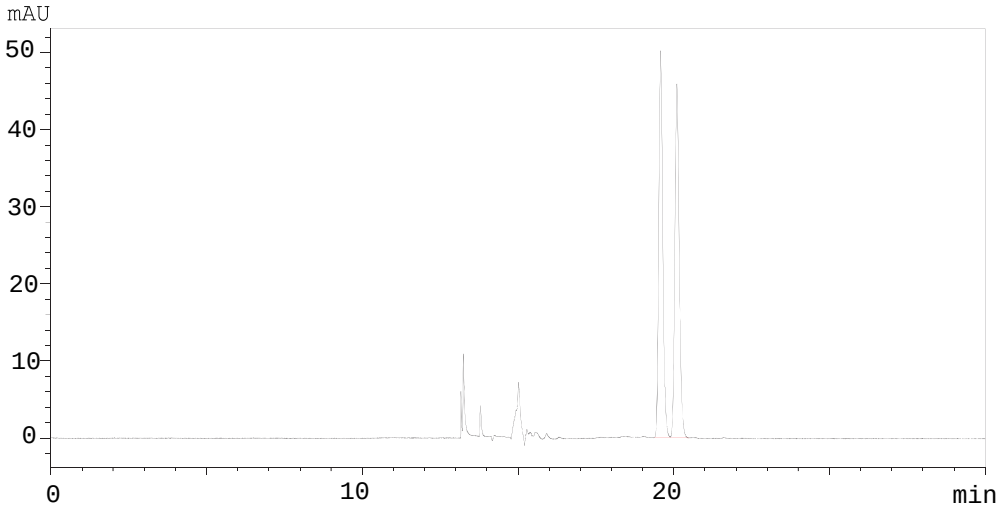
Peak #	RT [min]	Area %	Name
	15.16	44.05	Enantiomer diastereomer1
	15.51	44.25	Enantiomer diastereomer1
	16.09	5.85	Enantiomer diastereomer2
	16.96	5.84	Enantiomer diastereomer2



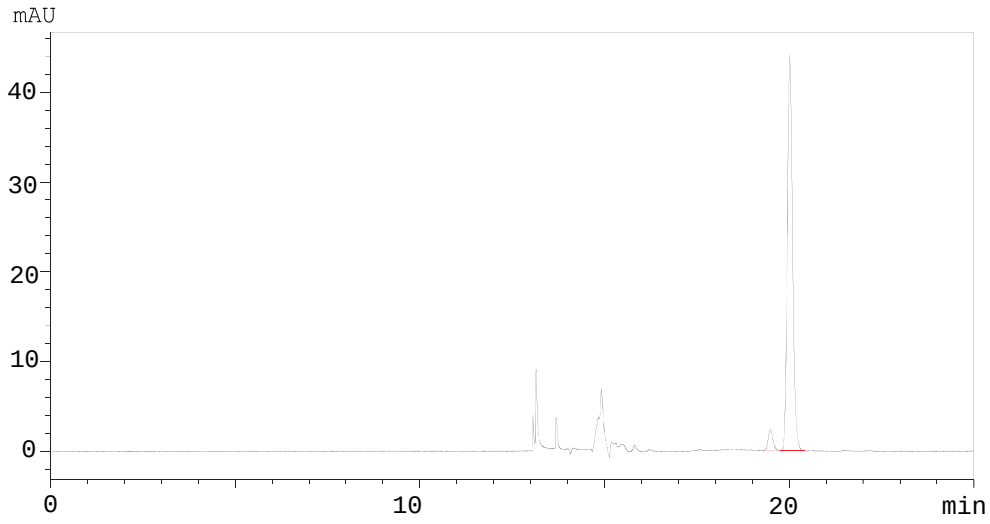
Peak #	RT [min]	Area %	Name
	15.16	4.62	Enantiomer diastereomer1
	15.51	92.89	Enantiomer diastereomer1
	16.09	1.70	Enantiomer diastereomer2
	16.96	0.79	Enantiomer diastereomer2



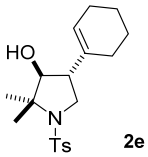
2d



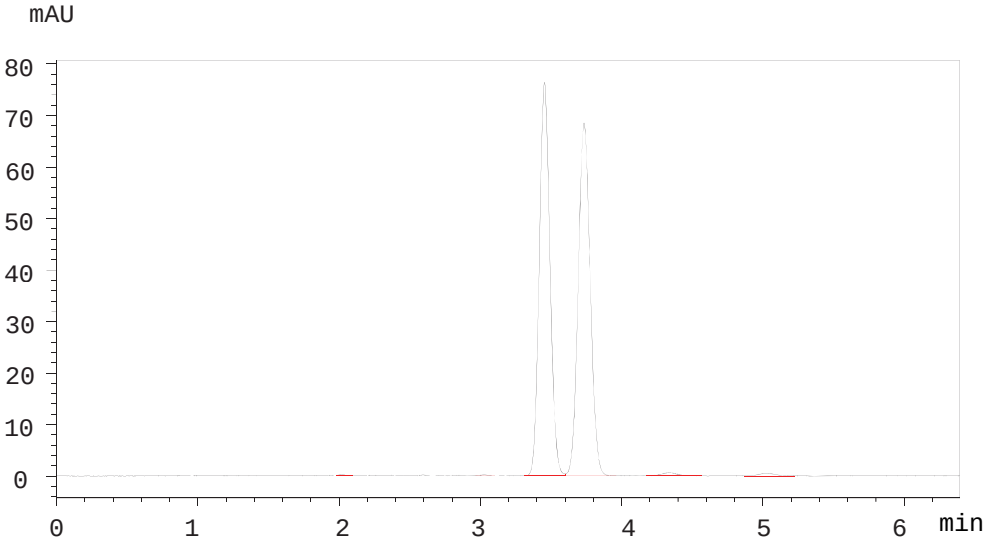
Peak #	RT [min]	Area %	Name
	19.58	50.00	Enantiomer
	20.10	50.00	Enantiomer



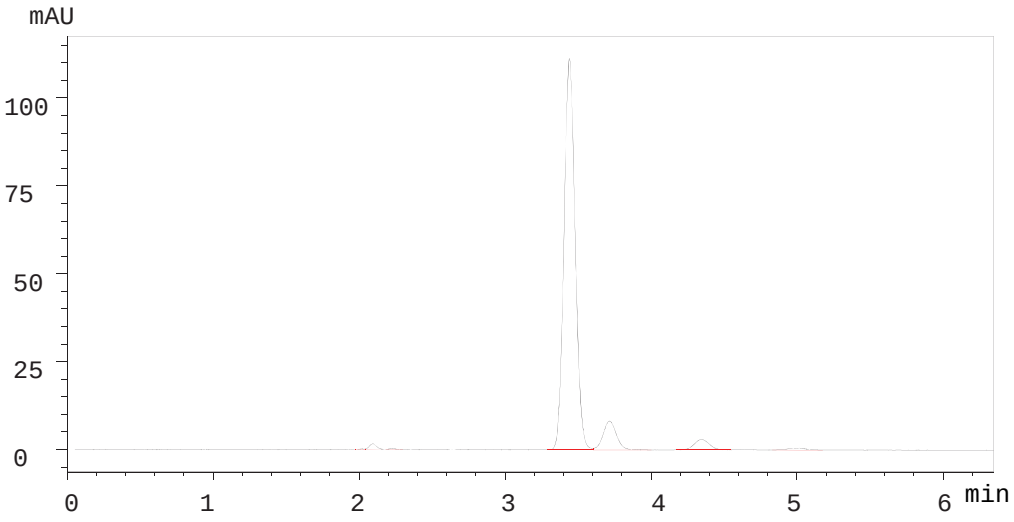
Peak #	RT [min]	Area %	Name
	19.49	4.65	Enantiomer
	20.02	95.35	Enantiomer



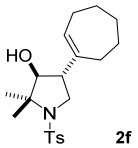
2e



Peak #	RT [min]	Area %	Name
	3.45	49.46	Enantiomer diastereomer1
	3.73	49.47	Enantiomer diastereomer1
	4.34	0.61	Enantiomer diastereomer2
	5.03	0.46	Enantiomer diastereomer2



Peak #	RT [min]	Area %	Name
	3.44	88.35	Enantiomer diastereomer1
	3.72	7.74	Enantiomer diastereomer1
	4.35	3.19	Enantiomer diastereomer2
	4.99	0.72	Enantiomer diastereomer2



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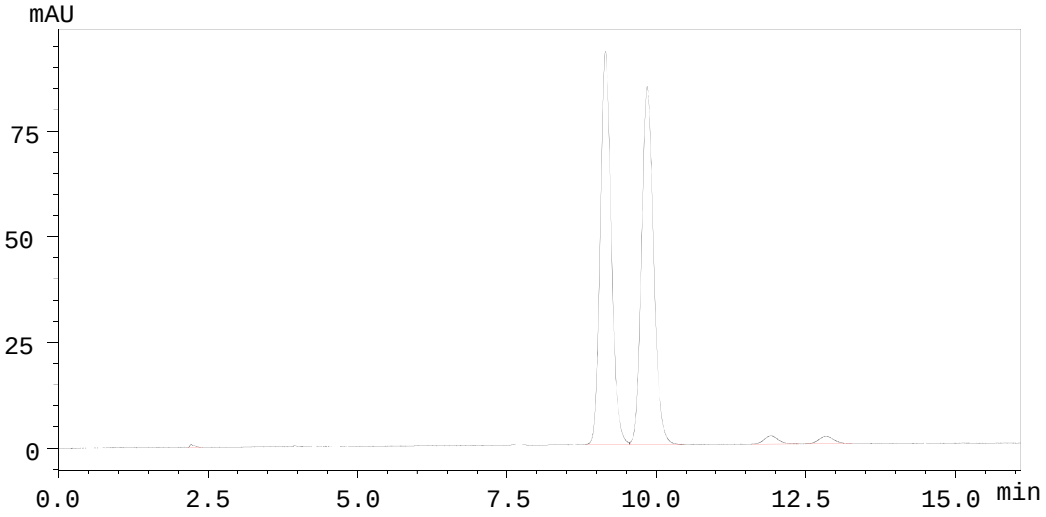
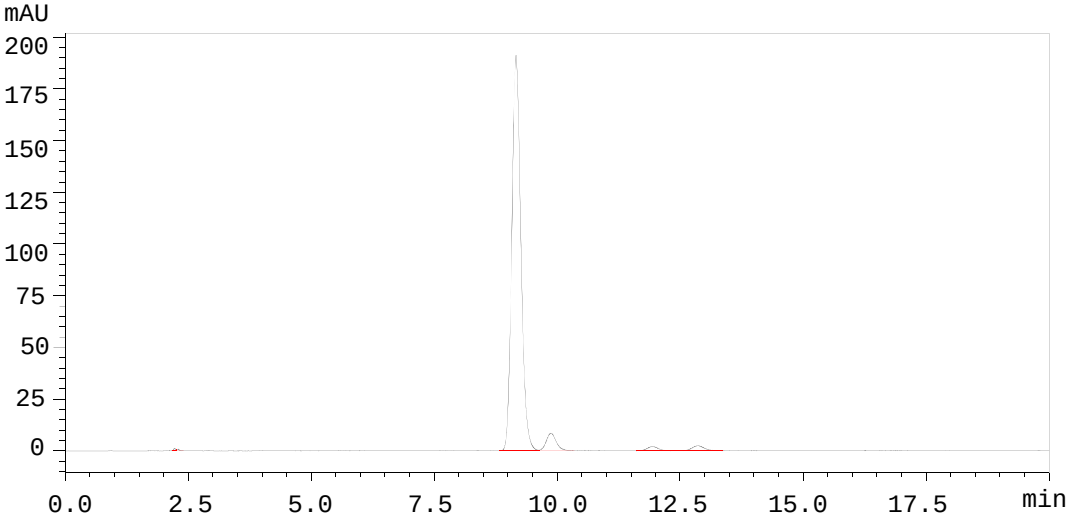
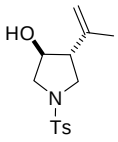


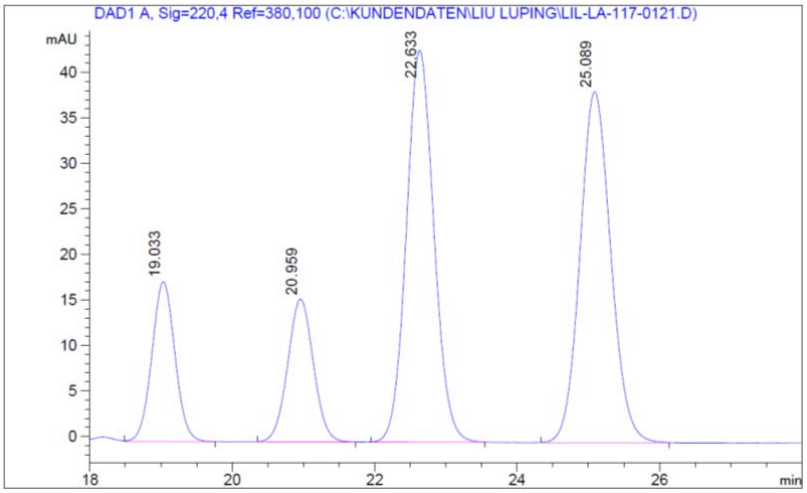
Peak #	RT [min]	Area %	Name
	9.15	48.83	Enantiomer diastereomer1
	9.85	48.65	Enantiomer diastereomer1
	11.92	1.27	Enantiomer diastereomer2
	12.84	1.25	Enantiomer diastereomer2



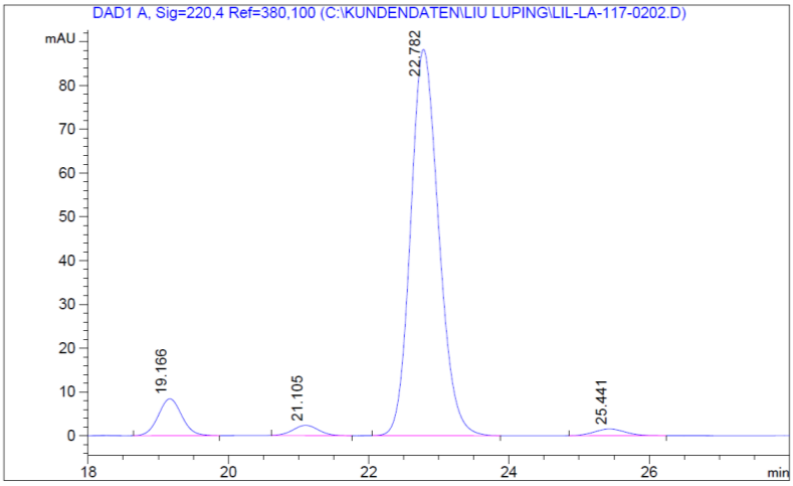
Peak #	RT [min]	Area %	Name
2	9.17	92.63	Enantiomer diastereomer1
3	9.87	4.53	Enantiomer diastereomer1
4	11.94	1.23	Enantiomer diastereomer2
5	12.86	1.61	Enantiomer diastereomer2



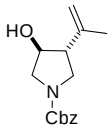
2g



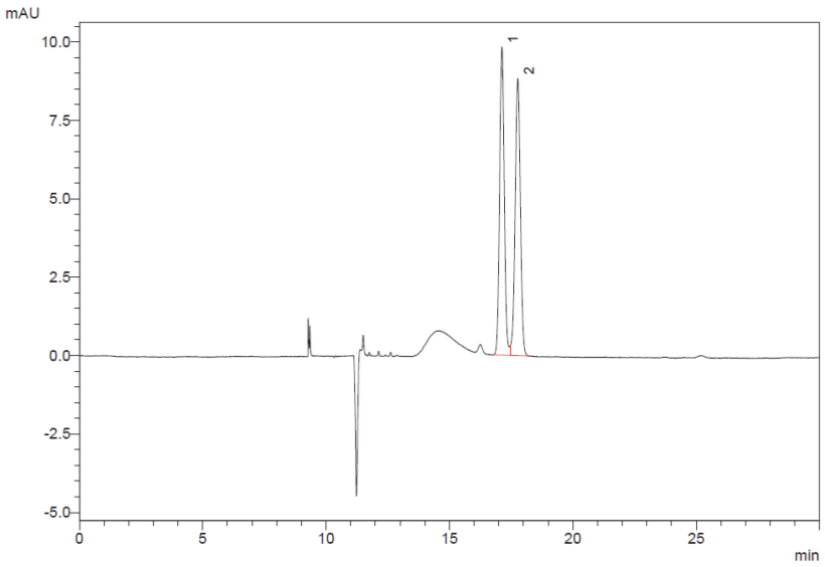
Peak #	RT [min]	Area %	Name
	19.03	12.73	Enantiomer diastereomer1
	20.96	12.71	Enantiomer diastereomer1
	22.63	37.25	Enantiomer diastereomer2
	25.09	37.30	Enantiomer diastereomer2



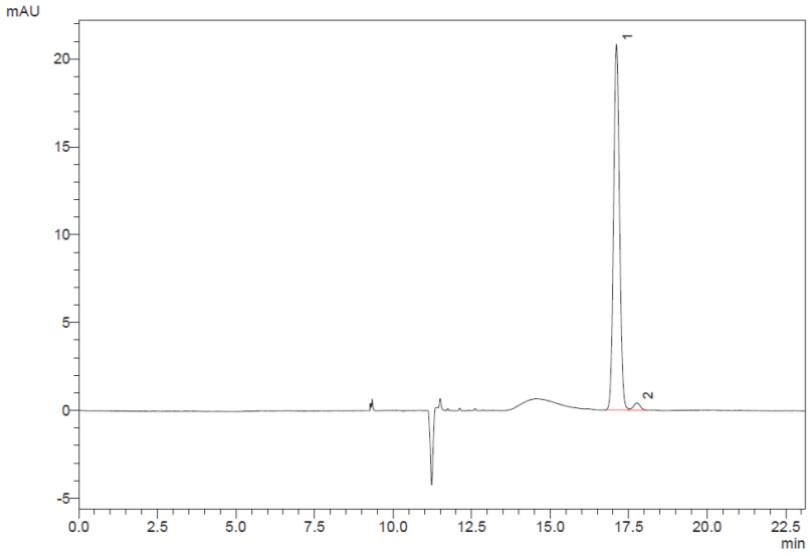
Peak #	RT [min]	Area %	Name
	19.17	7.11	Enantiomer diastereomer1
	21.10	2.14	Enantiomer diastereomer1
	22.78	89.04	Enantiomer diastereomer2
	25.44	1.71	Enantiomer diastereomer2



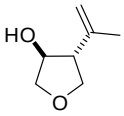
2h



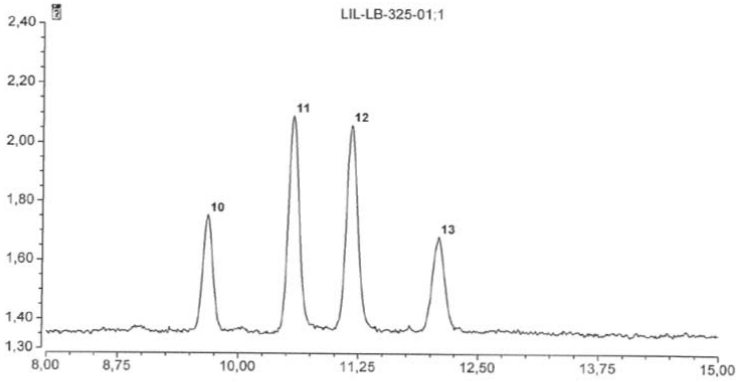
Peak #	RT [min]	Area %	Name
	17.12	49.90	Enantiomer
	17.77	50.10	Enantiomer



Peak #	RT [min]	Area %	Name
	17.11	97.96	Enantiomer
	17.76	2.24	Enantiomer



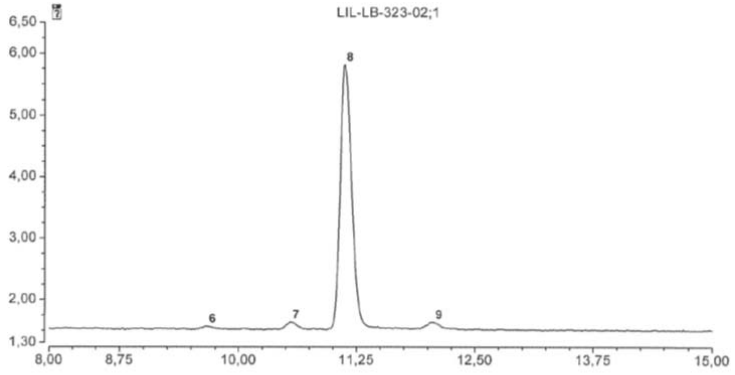
2i



Sample: **LIL-LB-325-01;1**
Sequenz: **94907 LIL-LB Ru_569**
Sequenz date: **11.06.15**

Instrument: **GC_413**
Measured: **12.06.15 10:51**
Processing M.: ee-Verhältnis;1
Report-File: ee- Verhältnis 325-01;1

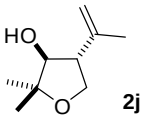
No.	Ret.Time min	Rel.Area %
10	9,68	16,23
11	10,57	33,69
12	11,18	33,59
13	12,09	16,48



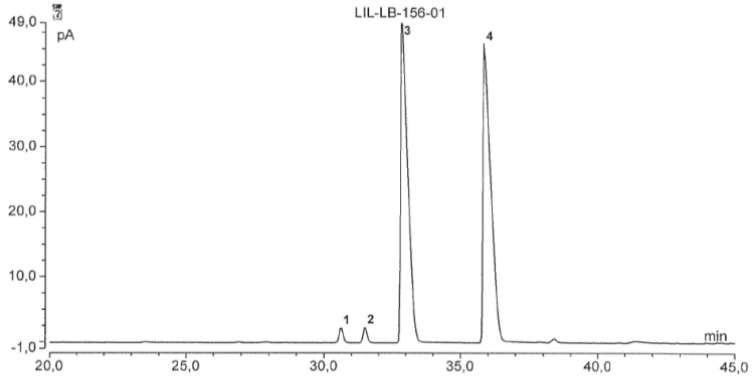
Sample: **LIL-LB-323-02;1**
Sequenz: **94928 LIL-LB Ru_581**
Sequenz date: **17.06.15**

Instrument: **GC_413**
Measured: **17.06.15 11:58**
Processing M.: ee- Verhältnis 323-02;1
Report-File: ee-Verhältnis 323-02;1

No.	Ret.Time min	Rel.Area %
6	9,66	1,17
7	10,55	2,41
8	11,12	93,50
9	12,06	2,93



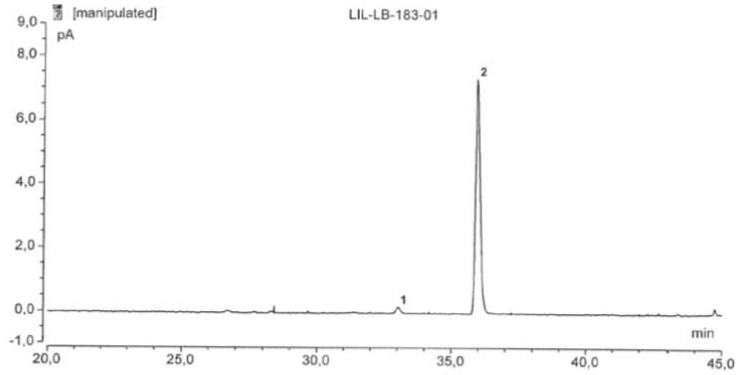
2j



Sample: **LIL-LB-156-01**
Sequenz: **94554 LIL-LB RO_380**
Sequenz date: **02.03.15**

Instrument: **GC_121**
Measured: **03.03.15 11:26**
Processing M.: **MPI**
Report-File: **Übersichtsanalyse**

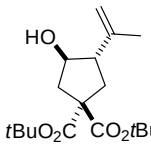
No.	Ret.Time min	area-% %
1	30,62	1,26
2	31,50	1,29
3	32,85	48,62
4	35,86	48,83



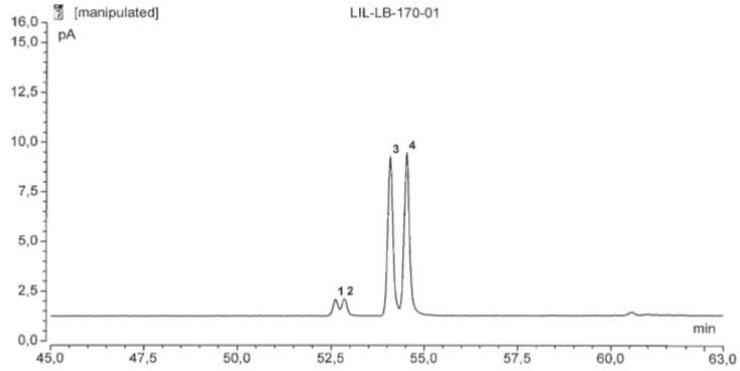
Sample: **LIL-LB-183-01**
Sequenz: **94642 LIL-LB RO_432**
Sequenz date: **19.03.15**

Instrument: **GC_122**
Measured: **19.03.15 13:55**
Processing M.: **MPI**
Report-File: **Übersichtsanalyse**

No.	Ret.Time min	area-% %
1	33,04	2,22
2	35,95	97,78

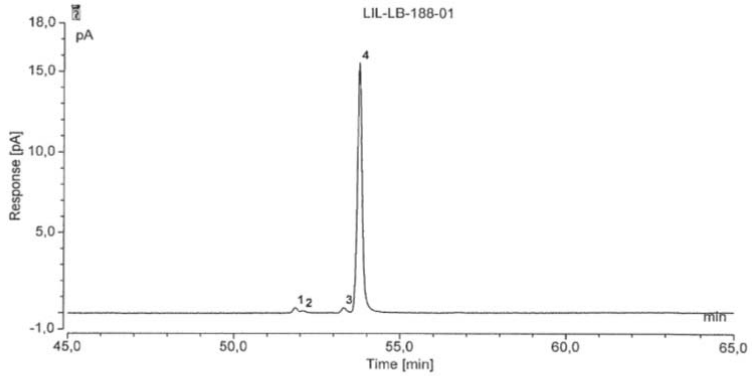


2k



Sample:	LIL-LB-170-01	Instrument:	GC_221
Sequenz:	94576 LIL-LB RO_391	Measured:	13.03.15 11:39
Sequenz date:	12.03.15	Processing M.:	MPI
		Report-File:	Übersichtsanalyse

No.	Ret.Time min	area-% %
1	52,62	4,48
2	52,86	4,27
3	54,09	46,03
4	54,54	45,22



Sample:	LIL-LB-188-01	Instrument:	GC_121
Sequenz:	94655 LIL-LB RO_444	Measured:	23.03.15 08:26
Sequenz date:	23.03.15	Processing M.:	MPI
		Report-File:	Übersichtsanalyse

No.	Ret.Time min	area-% %
1	51,86	1,96
2	52,09	0,83
3	53,31	2,07
4	53,78	95,14

10. References

[1] Harris, R. K.; Becker, E. D.; Cabral de Menezes, S. M.; Granger, P.; Hoffman, R. E.; Zilm, K. W. *Pure Appl. Chem.* **2008**, *80*, 59–84.

[2] Findeisen, M.; Berger, S.; *50 and More Essential NMR Experiments: A Detailed Guide*, Wiley-VCH, 2013.

[3] The temperatures were determined with the 'calctemp' macro of Bruker Topspin 2.1 and 4% MeOH in MeOD was used as sample to determine the temperature: Findeisen, M.; Brand,T.; Berger, S. *Magn. Reson. Chem.*, **2007**, *45*, 175.

[4] The temperatures were determined with the 'calctemp' macro of Bruker Topspin 2.1 and 80% glycol in DMSO was used as sample to determine the temperature: Hoffman,R.E., Becker,D.B. *J. Magn. Reson.* **2005**, *176*, 87.

[5] Grachan, M. L.; Tudge, M. T.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2008**, *47*, 1469.

[6] Comito, R. J.; Finelli, F. G.; MacMillan, D. W. C. *J. Am. Chem. Soc*. **2013**, *135*, 9358.