Practical Synthetic Procedures of the Iron-Catalyzed Intermolecular Olefin Aminohydroxylation Using Functionalized Hydroxylamines

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Supporting Material

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A. General Information

General Procedures. All reactions were performed in oven-dried or flame-dried round-bottom flasks and vials. Stainless steel syringes and cannula were used to transfer air- and moisture-sensitive liquids. Flash chromatography was performed using silica gel 60 (230-400 mesh) from Sigma–Aldrich.

Materials. Commercial reagents were purchased from Sigma Aldrich, Fluka, EM Science, and Lancaster and used as received. All solvents were used after being freshly distilled unless otherwise noted.

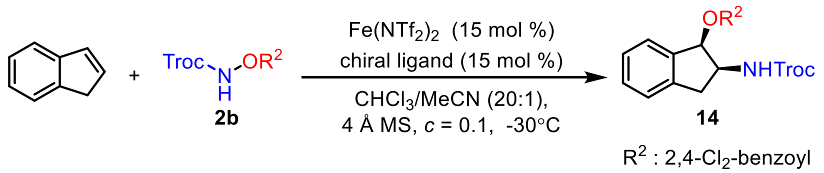
Instrumentation. Proton nuclear magnetic resonance (^{1}H NMR) spectra， carbon nuclear magnetic resonance (^{13}C NMR) spectra and fluorine nuclear magnetic resonance (^{19}F NMR) were recorded on Bruker UltraShield-400 (400 MHz). Chemical shifts for protons are reported in parts per million downfield from tetramethylsilane and are referenced to the NMR solvent residual peak ($CHCl_3$: δ 7.26). Chemical shifts for carbons are reported in parts per million downfield from tetramethylsilane and are referenced to the carbon resonances of the NMR solvent ($CDCl_3$: δ 77.0). Chemical shifts for fluorine are reported in parts per million downfield and are referenced to the fluorine resonances of $CFCl_3$. Data are represented as follows: chemical shift, multiplicity (br = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constants in Hertz (Hz), and integration.

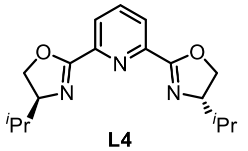
The mass spectroscopic data were obtained at the Georgia State University mass spectrometry facility using a Micromass Platform II single quadruple instrument. Infrared (IR) spectra were obtained using a Perkin Elmer Spectrum 100 FT-IR spectrometer. Data are represented as follows: frequency of absorption (cm^{-1}) and absorption strength (s = strong, m = medium, w = weak).

Abbreviations used: EtOH–ethanol, EtOAc–ethyl acetate, THF–tetrahydrofuran, MeOH–methanol, Et_2O–diethyl ether, CH_2Cl_2–dichloromethane, TEA–triethylamine, MeCN–acetonitrile, MS–molecular sieves, CDI–1,1′-carbonyldiimidazole, Troc–2,2,2-trichloroethoxycarbonyl, DCC–*N*,*N*′- dicyclohexylcarbodiimide, TLC–thin layer chromatography， Boc_2O–di-*tert*-butyl dicarbonate, DMAP−4-dimethylaminopyridine.

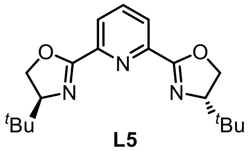
B. Procedure for the Iron-Catalyzed Asymmetric Indene Amino-Oxygenation

a. Discovery of Chiral Ligands for Asymmetric Induction

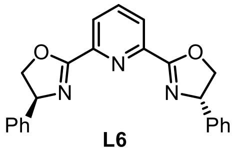




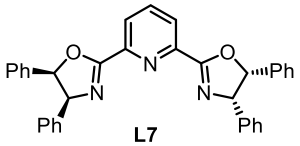
L4



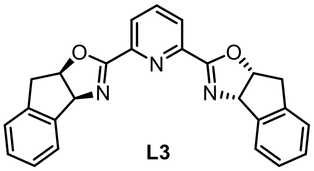
L5



L6



L7



L3

entry	ligand	isolated yield	ee
1	**L4**	39%	33%
2	**L5**	35%	40%
3	**L6**	42%	56%
4	**L7**	48%	51%
5	**L3**	71%	81%

Ligand **L3** was synthesized according to a known procedure.[1]

To a flame-dried sealable 2-dram vial (vial **A**) equipped with a stir bar were added $Fe(NTf_2)_2$ (36.9 mg, 0.06 mmol) and a chiral ligand (0.06 mmol). After the vial was evacuated and backfilled with N_2 for three times, anhydrous $CHCl_3$ (0.8 mL) and MeCN (0.2 mL) were added via a syringe and the mixture was stirred at room temperature for 20 min. To another flame dried 2-dram vial (vial **B**) equipped with a stir bar were added activated 4Å molecular sieves (100 mg) and **2b** (152.4 mg, 0.40 mmol). The vial was also was evacuated and backfilled with N_2 for three times and then anhydrous $CHCl_3$ (3.0 mL) was added via a syringe. Both solutions were degassed with brief evacuation and backfilling with N_2 twice. Then indene (55.9 µL, 0.48 mmol) was added to vial **B** and the catalyst solution (vial **A)** was added by a syringe pump over 30 min to vial **B** at -30 °C. The reaction was kept stirring at the same temperature for another 30 min. The reaction was quenched with saturated $NaHCO_3$ aqueous solution (2 mL) and stirred vigorously for additional 10 min. The organic layer was separated and the aqueous phase was extracted with CH_2Cl_2 (2 mL × 2) and EtOAc (2 mL× 2). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The product **14** was isolated through a silica gel flash column and analyzed through chiral HPLC columns. The results are listed in the table.

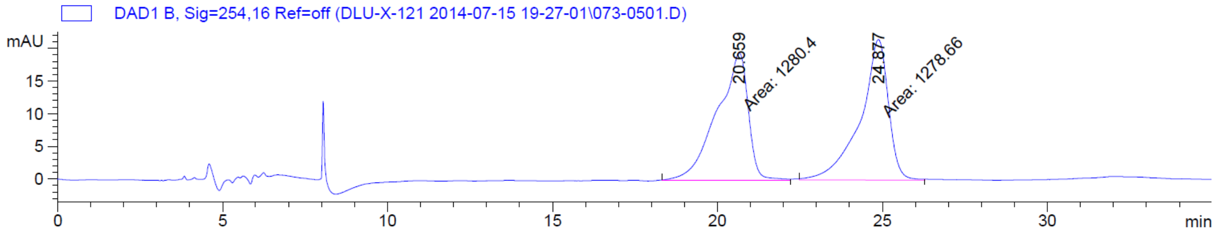
When chiral Ligand **L3** was applied, the product **14** was isolated through a silica gel flash column (hexanes/acetone: from 50:1 to 6:1) as a white solid.

14, yield: 141.3 mg (71%).

$[\alpha]_D^{20}$ = -60.1 (*c* 1.0, $CHCl_3$).

The *ee* was measured by Chiral HPLC analysis (Chiral *S.S.* Whelk, 1.0 mL/min, 254 nm, 5% EtOH in hexanes, t_r (minor) = 20.66 min, t_r (major) = 24.88 min, 81% *ee*).

Racemic sample



```
Peak RetTime Type  Width     Area       Height      Area
  #   [min]        [min]   [mAU*s]      [mAU]        %
----|-------|----|-------|----------|----------|--------|
   1  20.659 MM    1.0946 1280.40137   19.49595  50.0340
   2  24.877 MM    0.9894 1278.66064   21.53968  49.9660

Totals :                  2559.06201   41.03563
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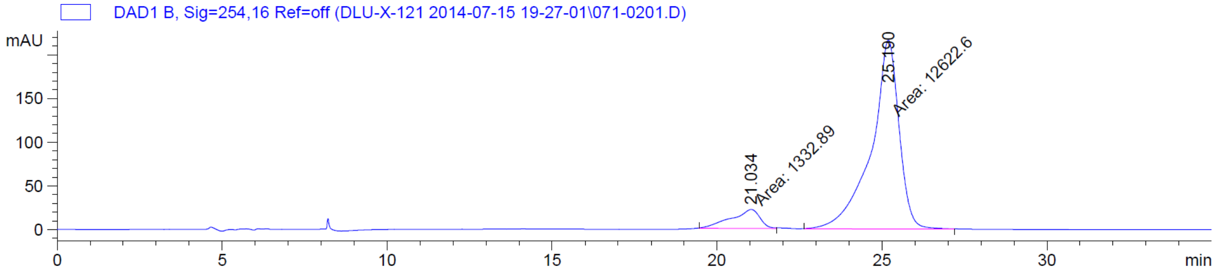
Enantio-enriched sample (81% *ee*)



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Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]        %
----|-------|----|-------|----------|----------|--------|
   1  21.034 MM    1.0183 1332.88940   21.81666   9.5510
   2  25.190 MM    0.9740 1.26226e4   216.00296  90.4490

Totals :                  1.39555e4   237.81962
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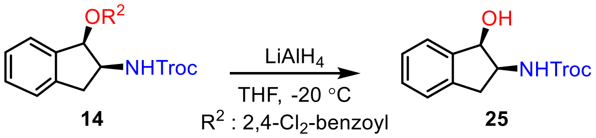
b. Derivatization of 14



14 **25**

dr > 20:1
81% *ee*

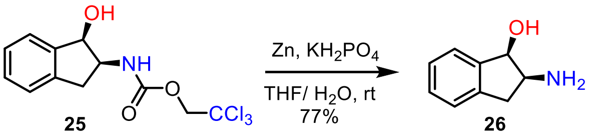
85% yield, *dr* > 20:1
81% *ee*

By following the aforementioned $LiAlH_4$ reductive procedure, compound **14** can be selectively converted to 2-amino-1-indanol **25** without erosion of its *dr* and *ee* (85% yield).

$[\alpha]_D^{20}$ = +23.2 (*c* 1.0, $CHCl_3$).

The *ee* was determined by Chiral HPLC analysis (Chiral *S.S.* Whelk, 1.0 mL/min, 265 nm, 15% EtOH in hexanes, t_r (major) = 12.24 min, t_r (minor) = 16.74 min (81% *ee*).

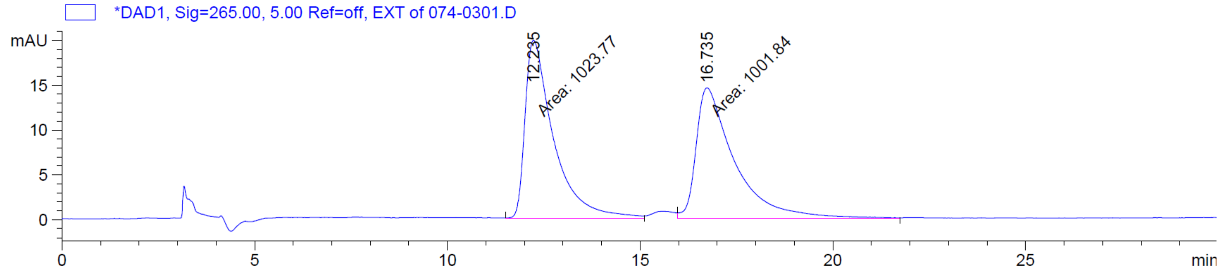
The absolute chemistry was determined by comparison of the rotation data of 2-amino indanol obtained after zinc dust reduction with literature precedent.[2]



25 **26**

$[\alpha]_D^{20}$ = +40.2 (*c* 1.0, $CHCl_3$)

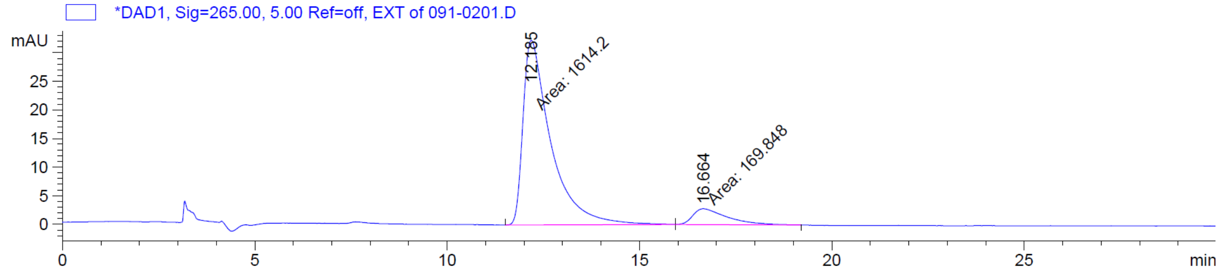
Racemic sample



```
Peak RetTime Type  Width     Area       Height      Area
  #   [min]         [min]   [mAU*s]     [mAU]        %
----|-------|----|-------|----------|----------|--------|
   1  12.235 MF     0.8602 1023.76611   19.83623  50.5412
   2  16.735 FM     1.1484 1001.84143   14.53924  49.4588

Totals :                   2025.60754   34.37547
```

Enantio-enriched sample (81% *ee*)



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Peak RetTime Type  Width     Area       Height      Area
  #   [min]         [min]   [mAU*s]     [mAU]        %
----|-------|----|-------|----------|----------|--------|
   1  12.185 MM     0.8342 1614.19958   32.24887  90.4796
   2  16.664 MM     1.0289  169.84776    2.75140   9.5204

Totals :                   1784.04735   35.00026
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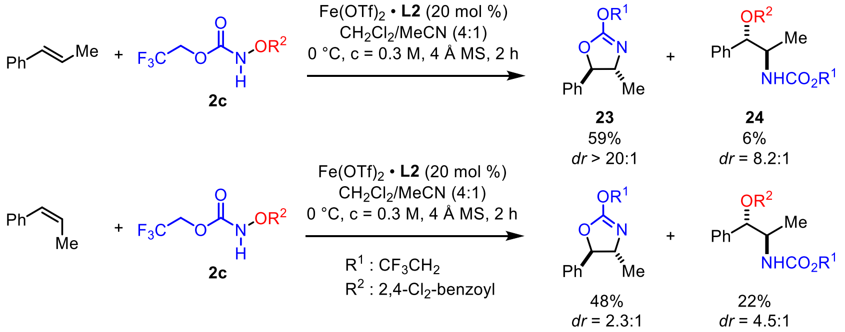
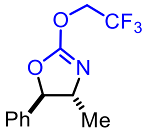
C. Iron-Catalyzed Amino-Oxygenation of Isomeric β-Methyl Styrenes



Both *trans* and *cis* *β*-methylstyrene are commercially available and they were distilled before usage.

To a flame-dried sealable 2-dram vial (vial **A**) equipped with a stir bar were added Fe(OTf)$_2$ (28.3 mg, 0.08 mmol) and **L2** (22.2 mg, 0.08 mmol). After the vial was evacuated and backfilled with N$_2$ for three times, anhydrous CH$_2$Cl$_2$ (0.7 mL) and MeCN (0.5 mL) were added via a syringe and the mixture was stirred at room temperature for 20 min. To another flame dried 2-dram vial (vial **B**) equipped with a stir bar were added activated 4Å molecular sieves (100 mg) and **2c** (132.8 mg, 0.40 mmol). The vial was also was evacuated and backfilled with N$_2$ for three times and then anhydrous CH$_2$Cl$_2$ (0.8 mL) was added via a syringe. Both solutions were degassed with brief evacuation and backfilling with N$_2$ twice. Then, *trans*- or *cis*-β-methyl styrene (94.6 mg, 0.8 mmol) was added to vial **B** and the catalyst solution (vial **A)** was added by a syringe pump over 30 min to vial **B** at 0 °C. The reaction was kept stirring at the same temperature until it was completed (another 1.5 h for *trans* and 2.5 h for *cis*). The reaction was quenched with saturated NaHCO$_3$ aqueous solution (2 mL) and stirred vigorously for additional 10 min. The organic layer was separated and the aqueous phase was extracted with CH$_2$Cl$_2$ (2 mL × 2) and EtOAc (2 mL× 2). The combined organic layers were dried over anhydrous Na$_2$SO$_4$ and concentrated *in vacuo*.

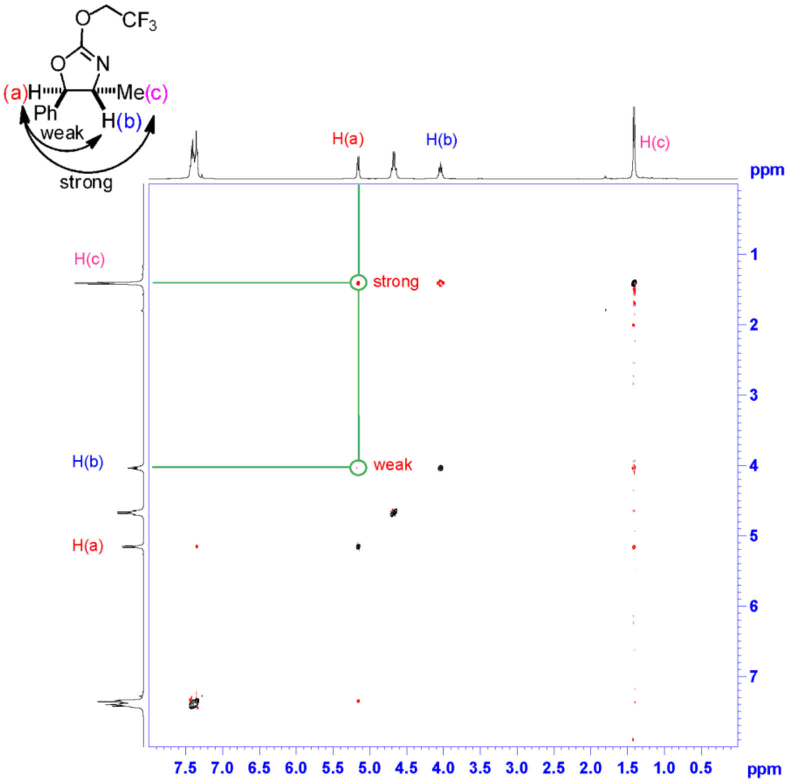


23

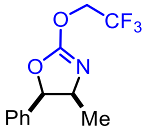
***anti*-4-Methyl-5-phenyl-2-(2,2,2-trifluoroethoxy)-4,5-dihydrooxazole** (**23**): compound **23** was isolated through a silica gel flash column (hexanes (buffered with 1% TEA)/acetone: from 50:1 to 10:1) from the reaction of *trans*-*β*-methyl styrene as colorless oil (61.2 mg, 59% yield); IR

ν_{max} (neat)/cm^{-1}: 2967 (w), 1761 (s), 1421 (m), 1345 (m), 1264 (s), 1166 (s); ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.48 – 7.30 (m, 5H), 5.16 (d, *J* = 7.5 Hz, 1H), 4.67 (q, *J* = 8.0 Hz, 2H), 4.04 (p, *J* = 6.7 Hz, 1H), 1.41 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR (101 MHz, CDCl$_3$) δ 160.5, 138.8, 128.9, 126.7, 125.6, 122.5 (q, *J* = 277.6 Hz), 90.5, 67.7, 66.2 (q, *J* = 37.1 Hz), 21.6; ^{19}F NMR (377 MHz, CDCl$_3$) δ -74.26 (t, *J* = 8.2 Hz); HRMS (ESI, m/z): calcd for $C_{12}H_{13}F_3NO_2^+$ [M + H$^+$], 260.0893, found 260.0882.

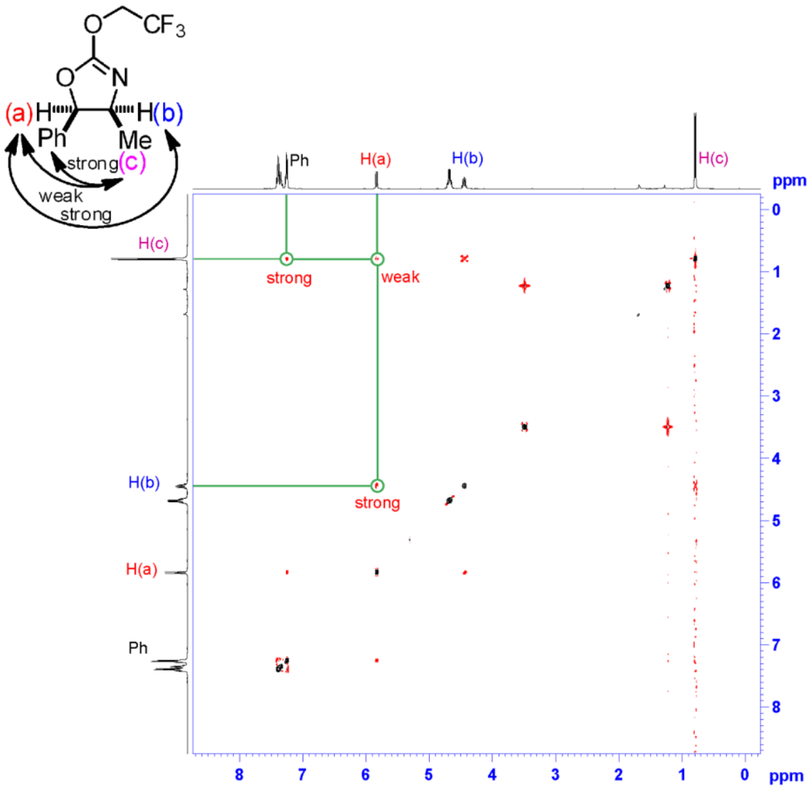
The relative stereochemistry of **23** and **23-*syn*** was determined through *NOE* analysis for both diastereomers.



For the major (*anti*) diastereomer **23**: H(a) demonstrates a strong *NOE* with H(c), while it has a very weak *NOE* with H(b).

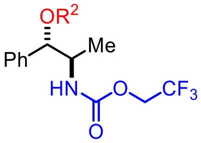


23-*syn*



syn*-4-Methyl-5-phenyl-2-(2,2,2-trifluoroethoxy)-4,5-dihydrooxazole** (**23-*syn): compound **23-*syn*** was isolated through a silica gel flash column (hexanes (buffered with 1% TEA)/EtOAc: 50:1 to 5:1) from the reaction of *cis-β*-methyl styrene as colorless oil (15.1 mg, 14% yield); IR ν_{max} (neat)/cm^{-1}: 2968 (w), 1761 (s), 1421 (m), 1343 (m), 1264 (s), 1167 (s); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 – 7.31 (m, 3H), 7.31 – 7.19 (m, 2H), 5.84 (d, *J* = 9.1 Hz, 1H), 4.76 – 4.59 (m, 2H), 4.45 (dq, *J* = 13.9, 6.9 Hz, 1H), 0.79 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 161.2, 135.7, 128.4, 128.2, 125.8, 122.5 (d, *J* = 277.3 Hz), 86.3, 66.2 (q, *J* = 37.1 Hz), 62.7, 18.2; ^{19}F NMR (377 MHz, $CDCl_3$) δ -74.25 (t, *J* = 8.2 Hz; HRMS (ESI, m/z): calcd for $C_{12}H_{13}F_3NO_2^+$ [M + Na$^+$], 260.0893, found 260.0887;

For the minor (*syn*) diastereomer **23-*syn***: H(a) has a strong *NOE* with H(b), while the effect between it and H(c) is relatively weak. In addition, strong *NOE* is also observed between H(c) and protons in the aromatic region.



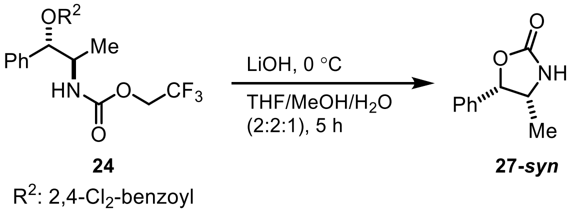
24

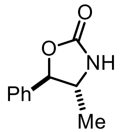
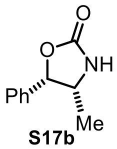
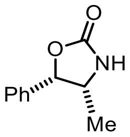
R^2: 2,4-Cl$_2$-benzoyl

anti**-1-Phenyl-2-(((2,2,2-trifluoroethoxy)carbonyl)amino)propyl 2,4-dichlorobenzoate** (**24**): compound **24** was isolated through a silica gel flash column (hexanes (buffered with 1% TEA)/acetone: from 50:1 to 10:1) from the reaction of *trans-β*-methyl styrene as colorless oil (*anti*-diastereomer, 32.0 mg, 16% yield). IR ν_{max} (neat)/cm^{-1}: 3352 (w), 2977 (w), 1719 (s), 1585 (m), 1520 (m), 1279 (m), 1163 (s); ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.93 (d, *J* = 8.4 Hz, 1H), 7.52 (d, *J* = 1.6 Hz, 1H), 7.44 – 7.29 (m, 6H), 6.13 (d, *J* = 3.3 Hz, 1H), 5.12 (d, *J* = 9.0 Hz, 1H), 4.57 – 4.39 (m, 2H), 4.39 – 4.24 (m, 1H), 1.21 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (101 MHz, CDCl$_3$) δ 163.9, 153.8, 138.8, 136.0, 134.9, 133.1, 131.2, 128.6, 128.5, 127.8, 127.2, 126.6, 79.0, 50.9, 15.7; ^{19}F NMR (377 MHz, CDCl$_3$) δ -74.25 (t, *J* = 8.5 Hz); HRMS (ESI, m/z): calcd for $C_{19}H_{16}Cl_2F_3NNaO_4^+$ [M + H$^+$], 472.0301, found 472.0281.

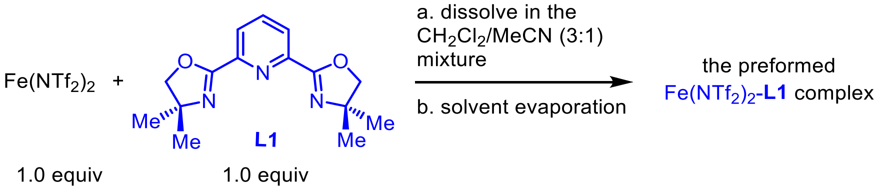
Determination of the Relative Stereochemistry of 24

The relative stereochemistry of **24** was determined by comparison of the ^{1}H NMR data of its derivative with known compounds **27-*anti*** and **27-*syn***.[3,4] The oxazolidinone derived from **24** fits **27-*syn*** through ^{1}H NMR analysis; therefore, the relative stereochemistry of **24** was determined to be *anti*.

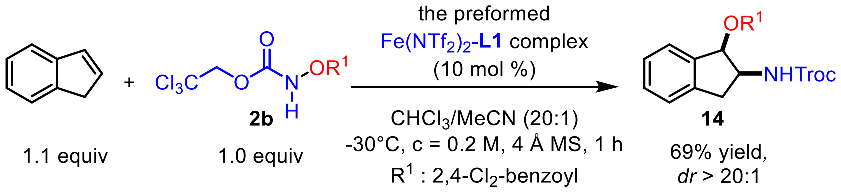


	 **S17a** (Literature Data)[3]	 **S17b** (Literature Data)[4]	 (hydrolysis product obtained from **24**
^{1}H NMR (400 MHz, $CDCl_3$)	δ 7.5-7.3 (m, 5H), 6.41 (br s, 1H), 5.04 (d, *J* = 7.3 Hz, 1H), 3.84 (p, *J* = 4 × 6.3 Hz, 1H), 1.39 (d, *J* = 6.2 Hz, 3H)	δ 7.35 (m, 5H), 6.40 (bs, 1H), 5.71 (d, *J* = 8.0, 1H), 4.21 (m, 1H), 0.81 (d, *J* = 6.5, 3H).	δ 7.43 – 7.27 (m, 5H), 5.72 (d, *J* = 7.9 Hz, 1H), 5.50 (br s, 1H), 4.20 (p, *J* = 6.7 Hz, 1H), 0.81 (d, *J* = 6.5 Hz, 1H).

D. Catalytic Indene Aminohydroxylation Using the Preformed Iron Catalyst



To a flame-dried sealable 3-dram vial equipped with a stir bar were added $Fe(NTf_2)_2$ (307.5 mg, 0.5 mmol) and **L1** (136.5 mg, 0.5 mmol). After the vial was evacuated and backfilled with N_2 three times, anhydrous CH_2Cl_2 (6 mL) and MeCN (2 mL) were added and the mixture was stirred at room temperature for 1 h. The resulting solution was filtered through a cotton wool under N_2 and the filtrate was concentrated and dried *in vacuo* to afford foam. The residue was suspended in anhydrous hexanes and sonicated. After removal of hexanes *in vacuo*, the orange solid can be used directly as the catalyst. Attempts were made to obtain the X-ray crystallographic analysis of the preformed $Fe(NTf_2)_2$–**L1** complex; however, it proved challenging.



Indene aminohydroxylation using the pre-formed $Fe(NTf_2)_2$–**L1** complex affords **14** (69% yield).

E. References

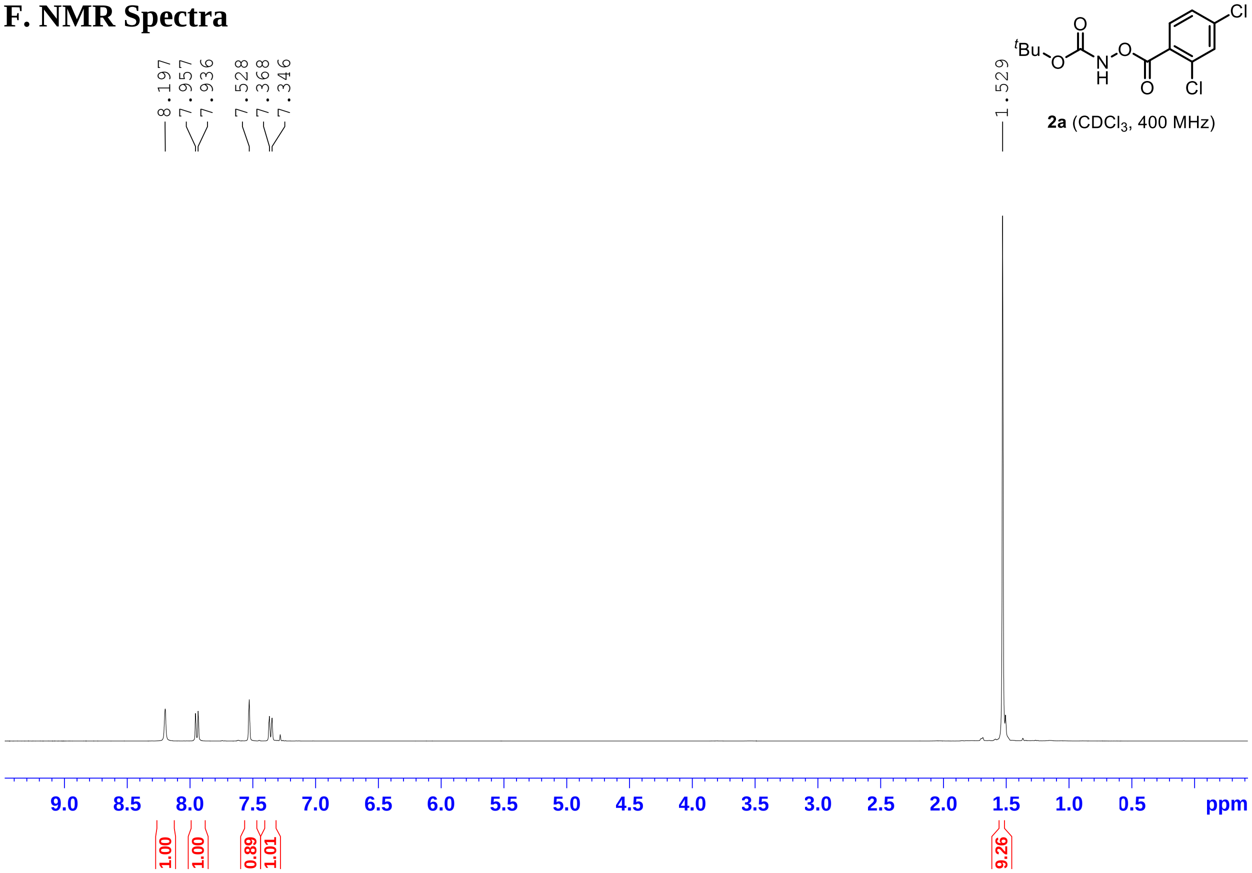
(1) Gutierrez, E. G.; Wong, C. J.; Sahin, A. H.; Franz, A. K. *Org. Lett.* **2011**, *13*, 5754.

(2) Corey, E. J.; Roper, T. D.; Ishihara, K.; Sarakinos, G. *Tetrahedron Lett.* **1993**, *34*, 8399.

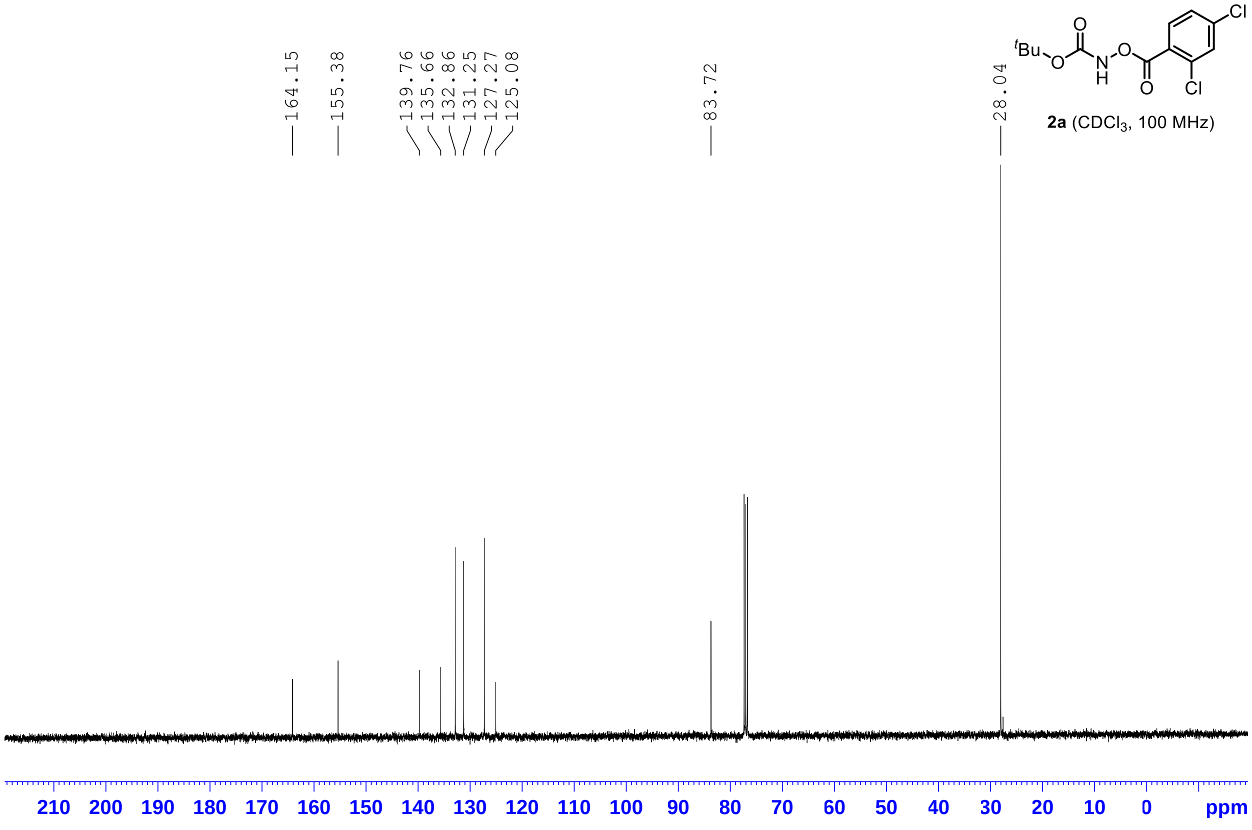
(3) Johannes, M.; Altmann, K.-H. *Org. Lett.* **2012**, *14*, 3752.

(4) Paz, J.; Pérez-Balado, C.; Iglesias, B.; Muñoz, L. *J. Org. Chem.* **2010**, *75*, 3037.

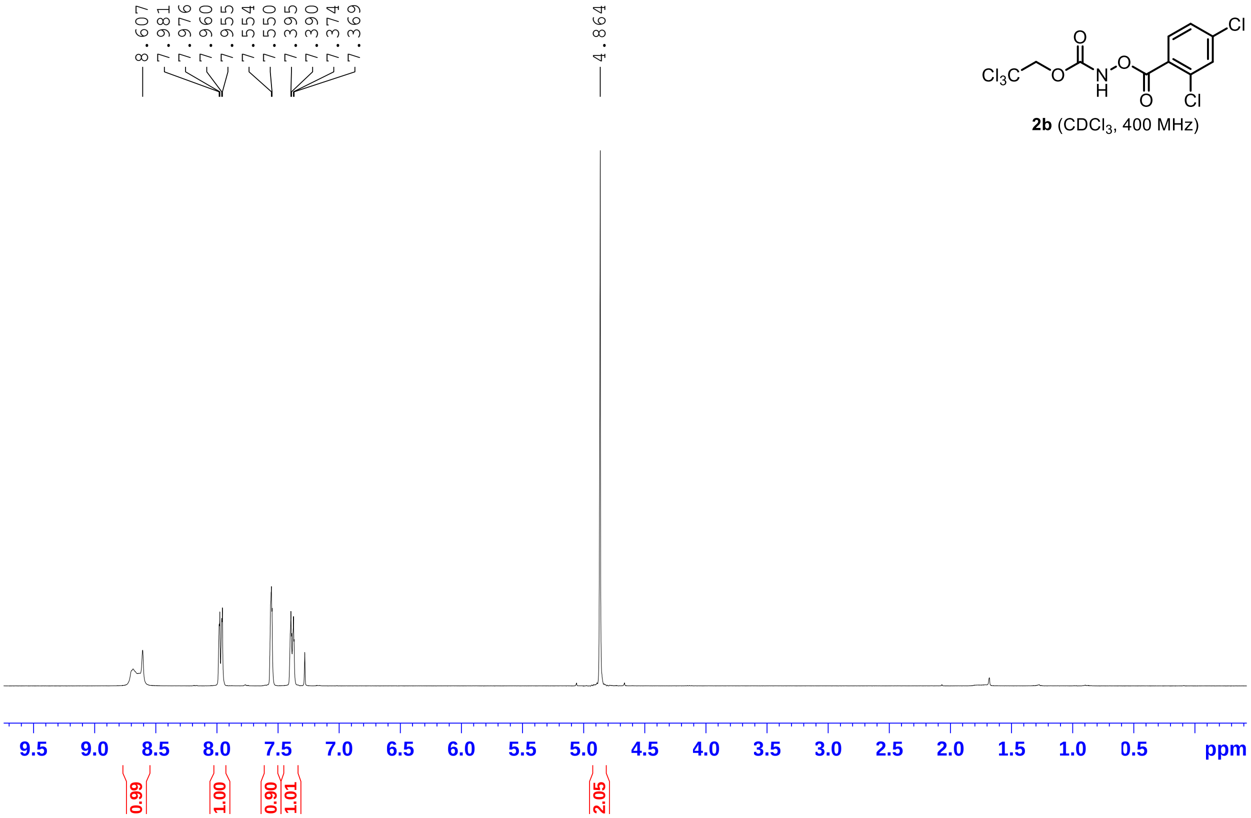
F. NMR Spectra



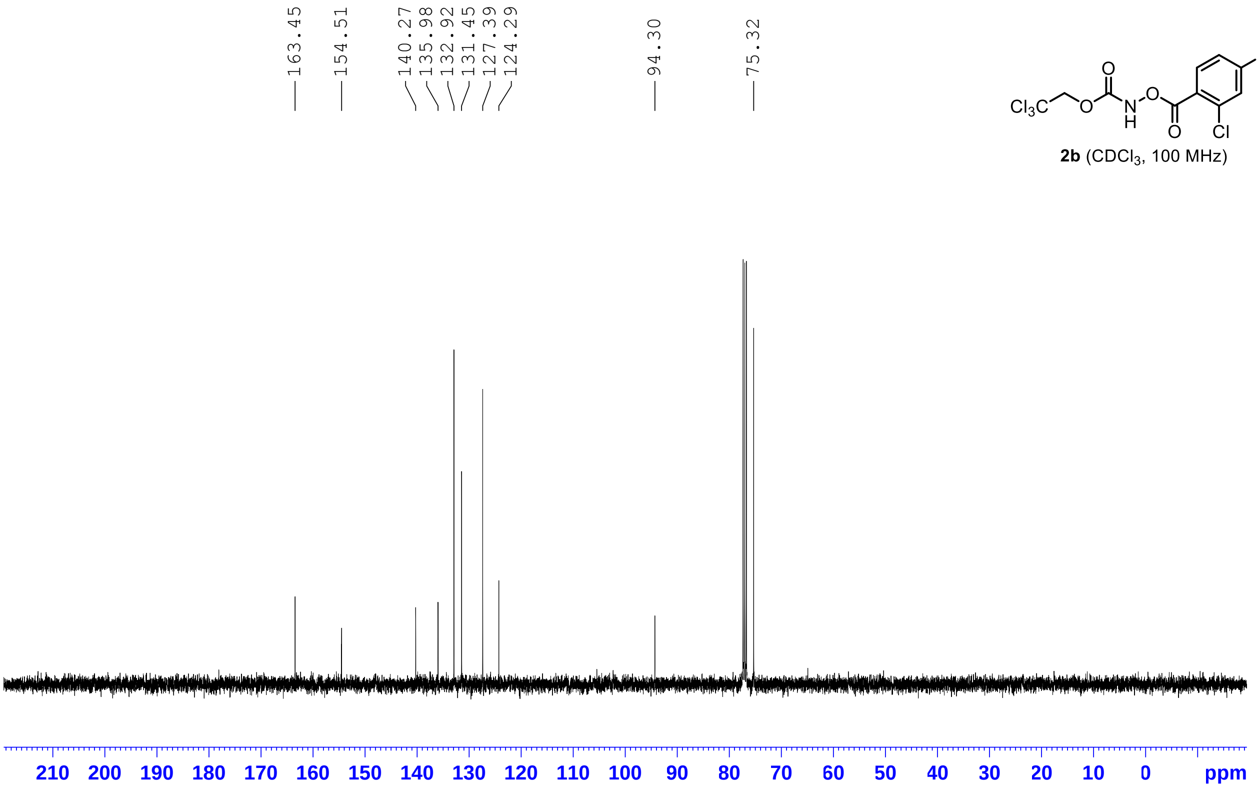
2a (CDCl$_3$, 400 MHz)



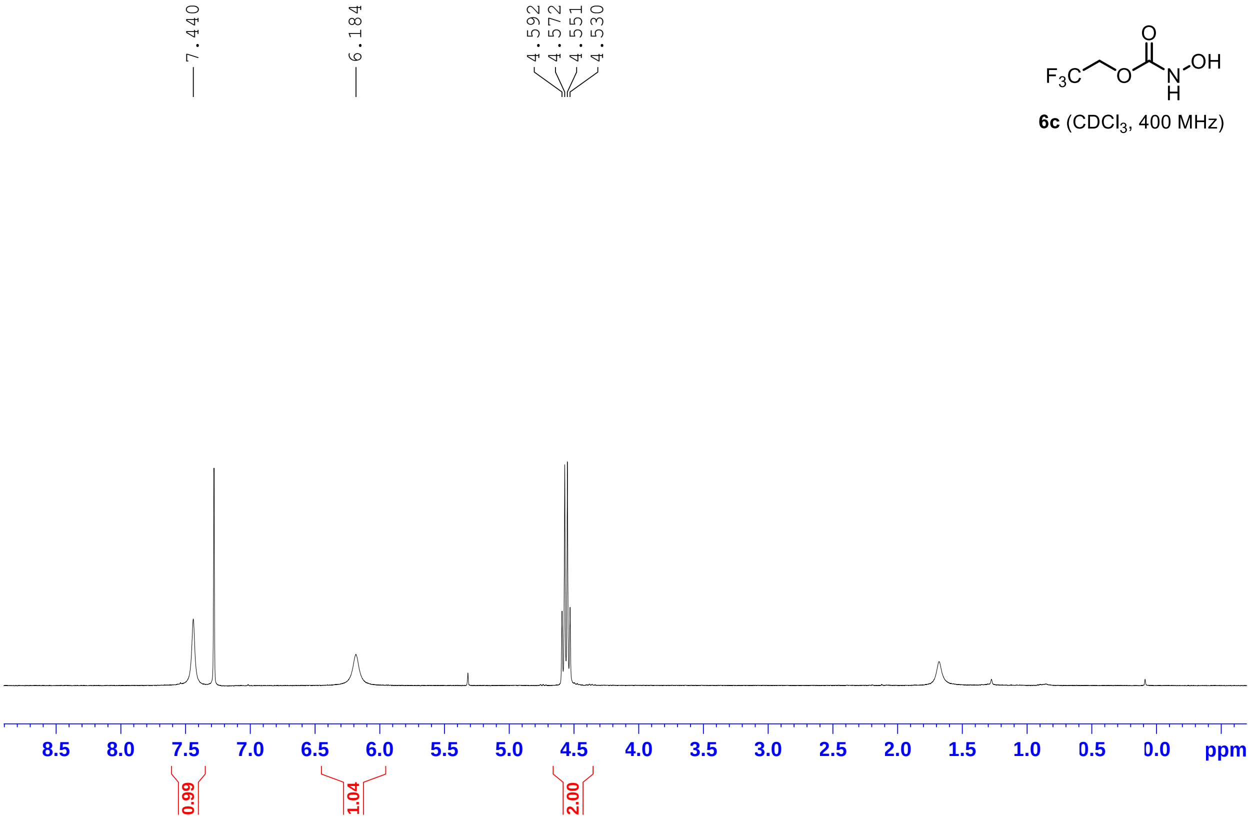
2a (CDCl$_3$, 100 MHz)



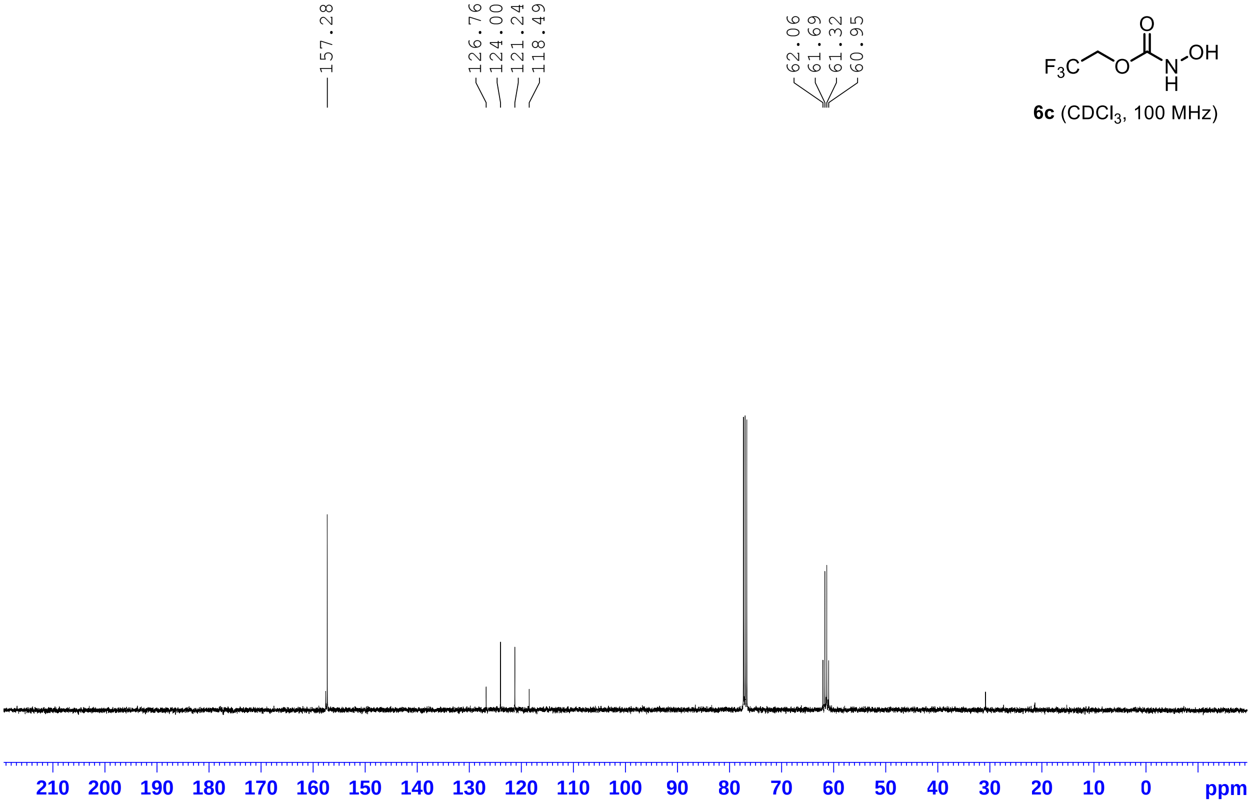
2b ($CDCl_3$, 400 MHz)



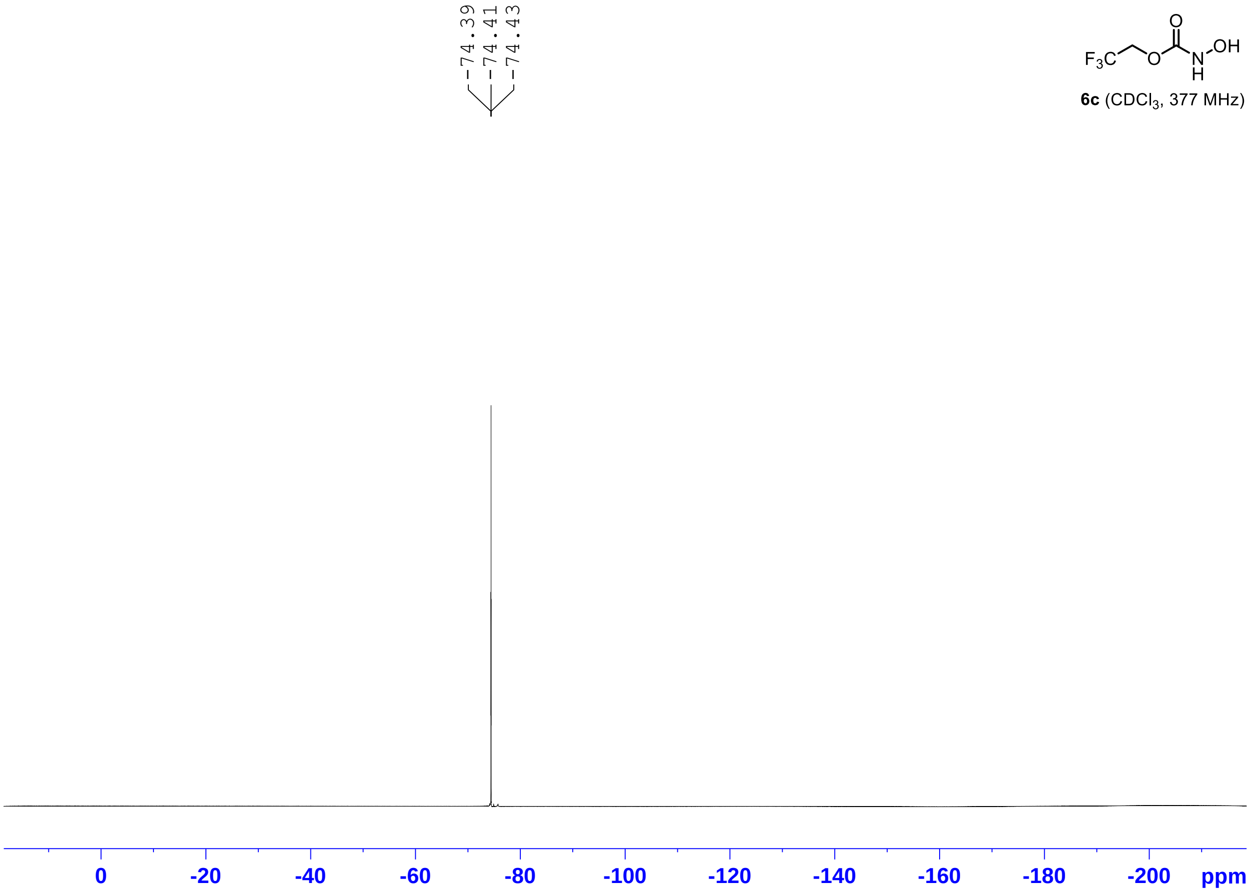
2b ($CDCl_3$, 100 MHz)



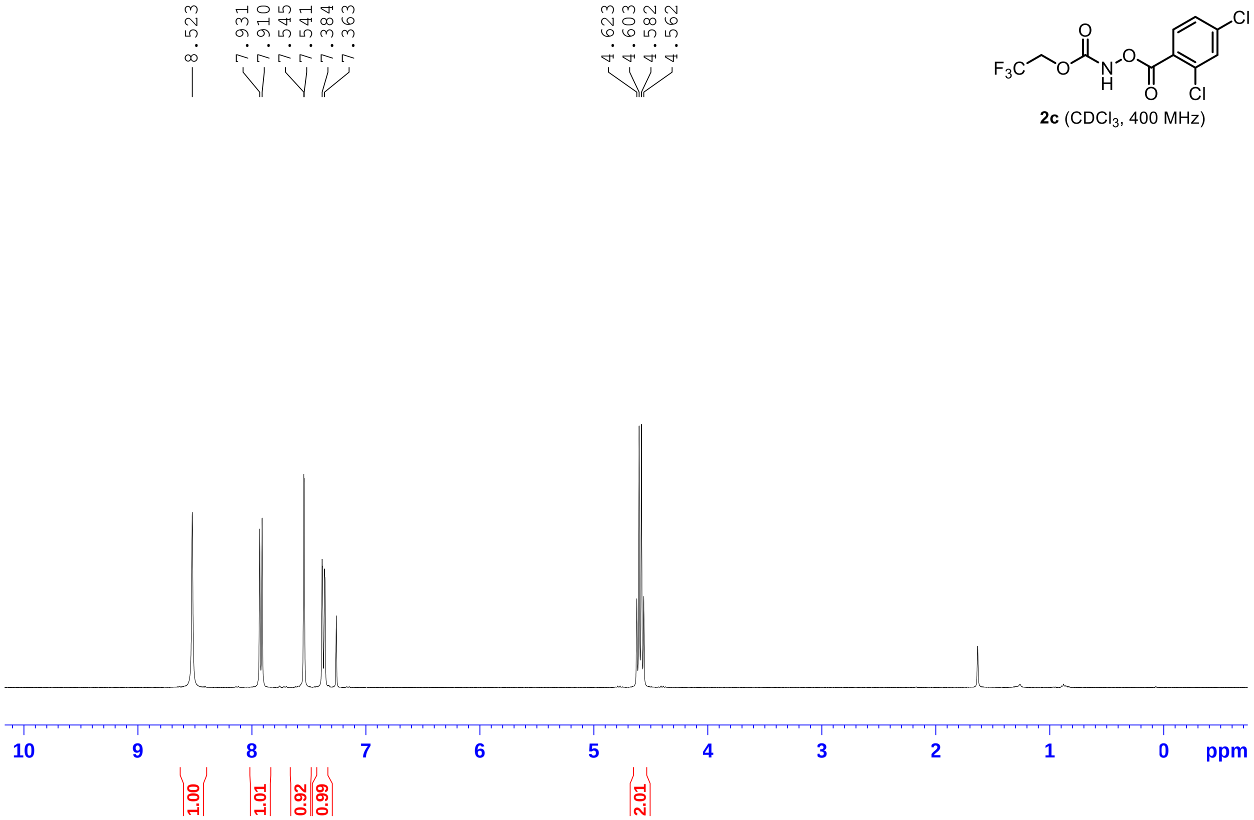
6c ($CDCl_3$, 400 MHz)



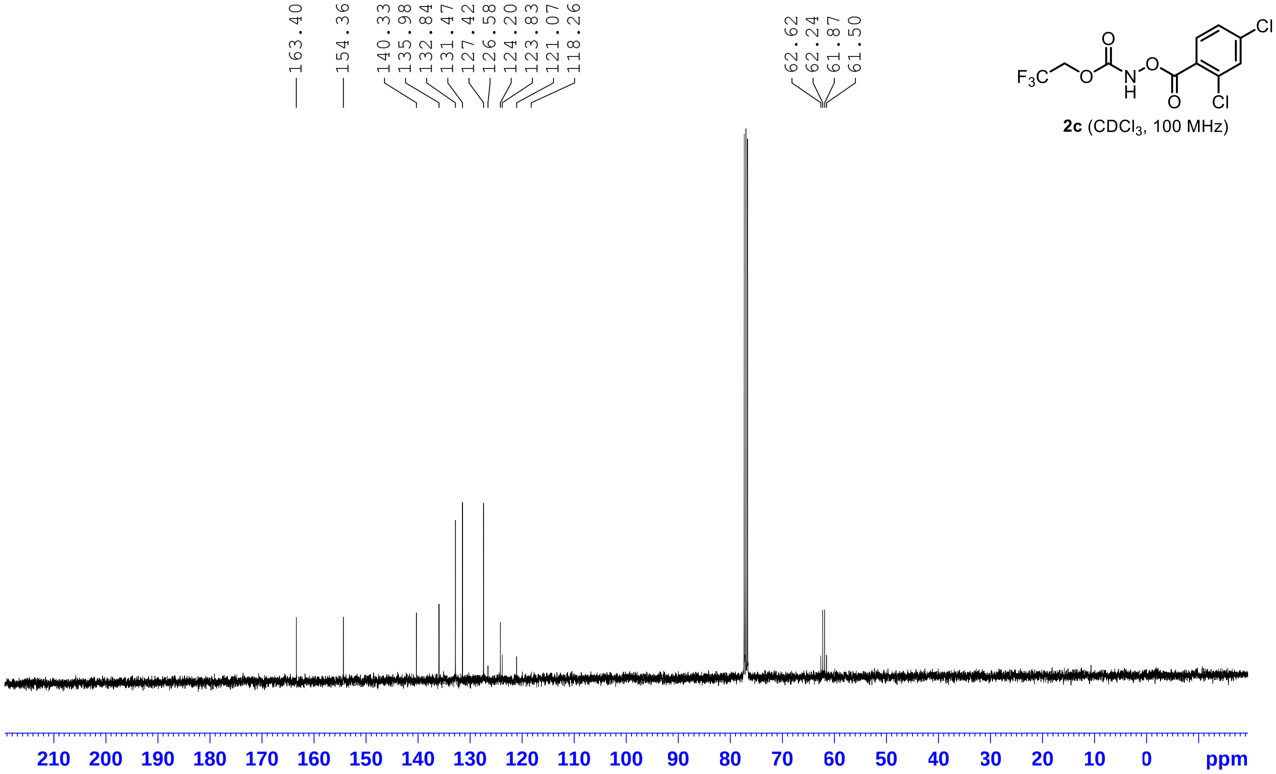
6c ($CDCl_3$, 100 MHz)



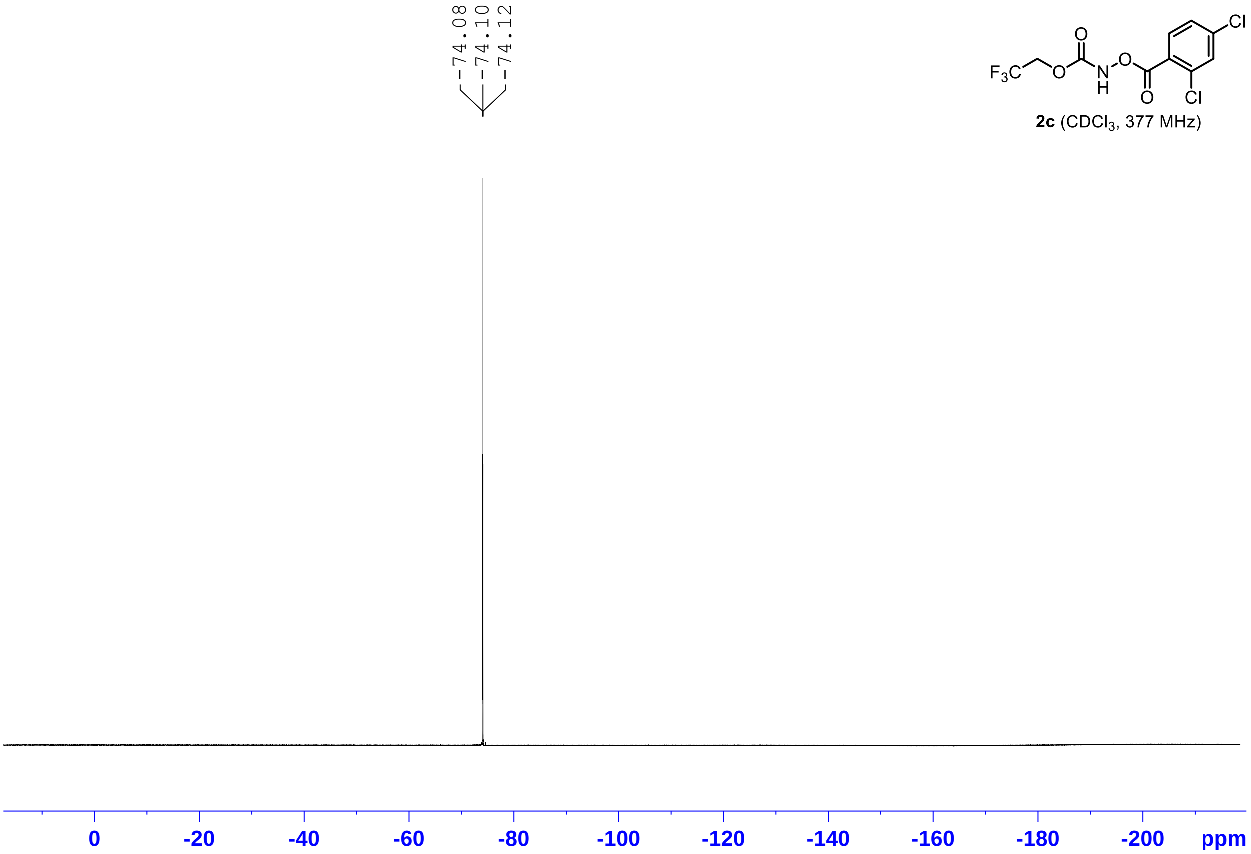
6c (CDCl$_3$, 377 MHz)



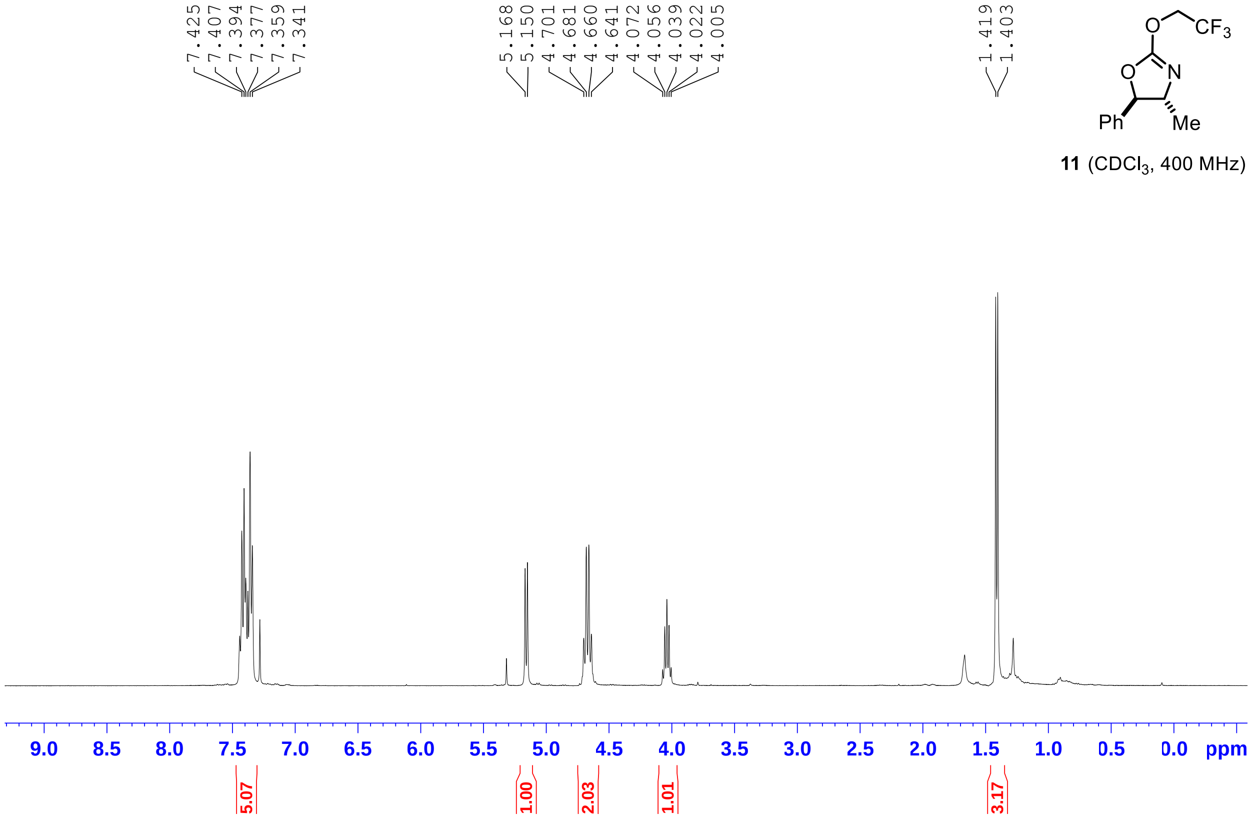
2c (CDCl$_3$, 400 MHz)

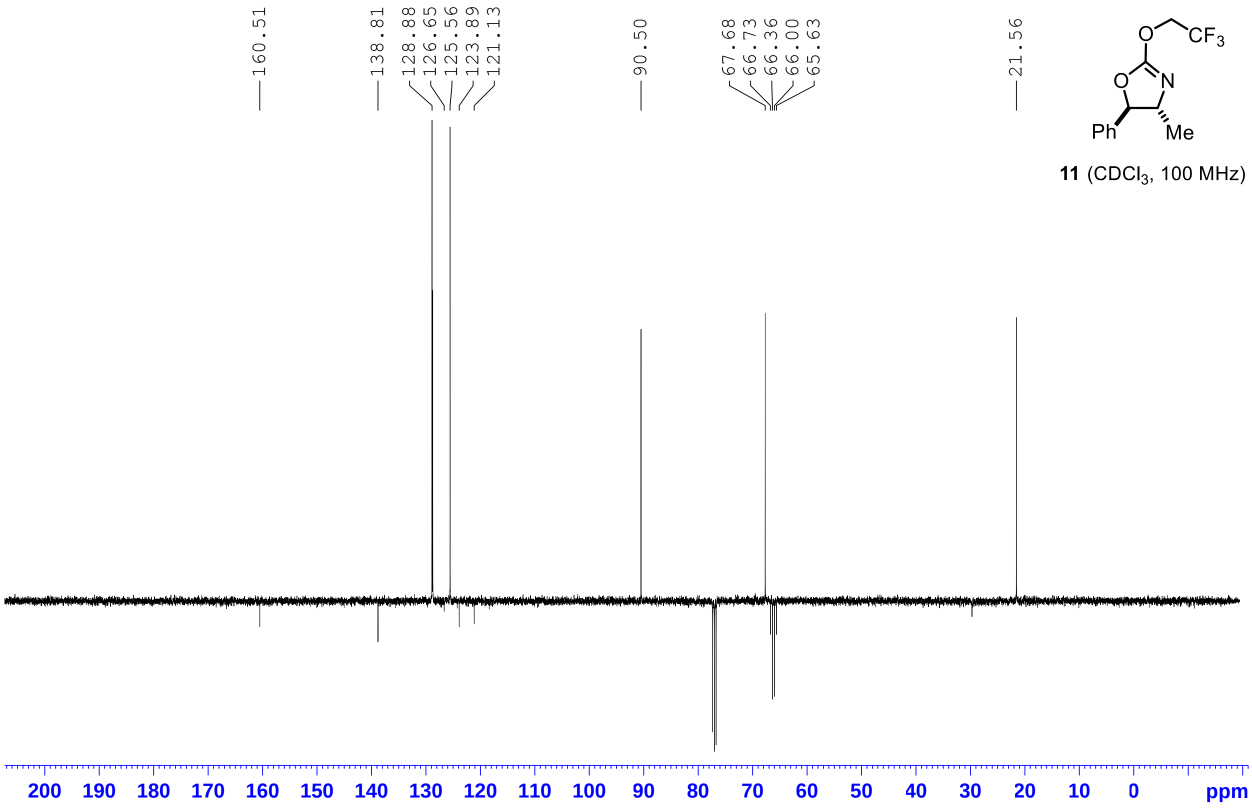


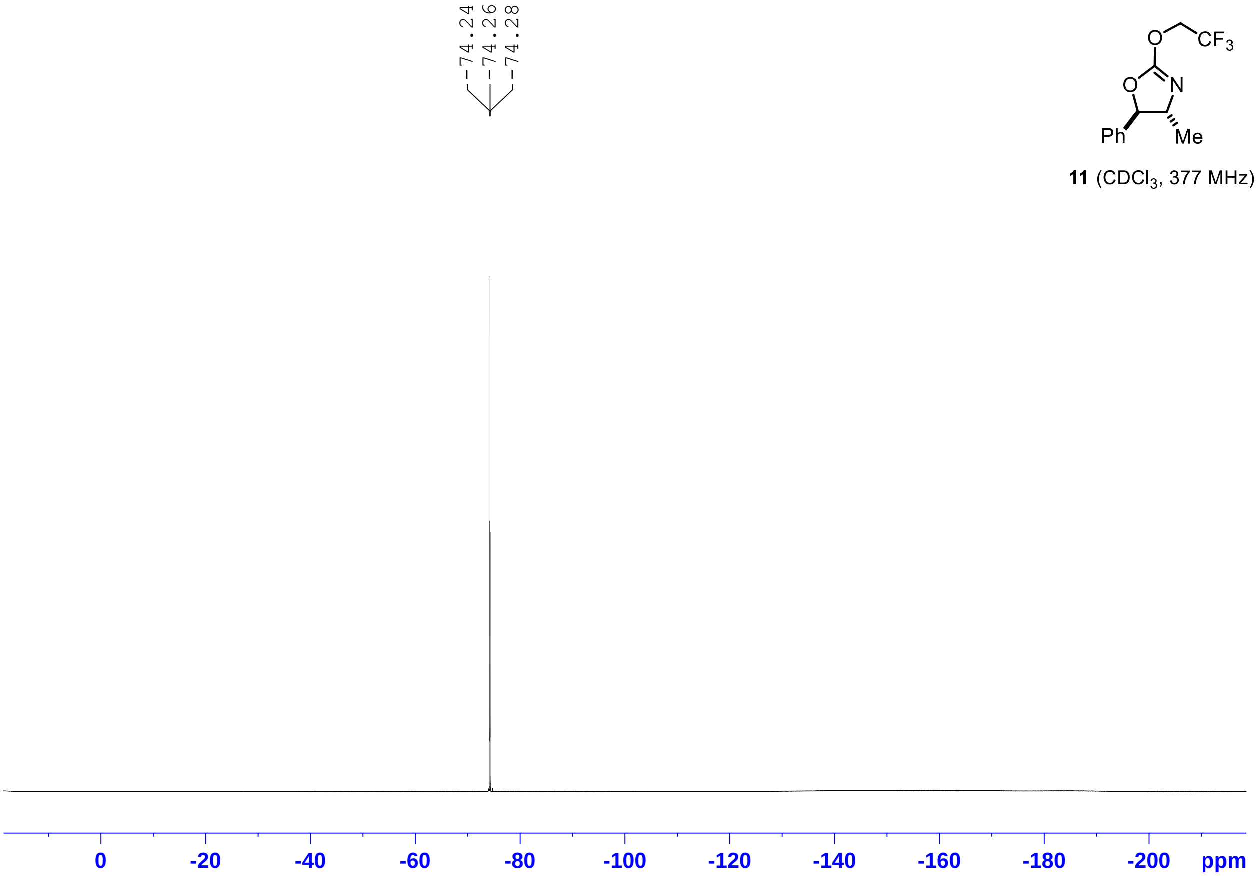
2c (CDCl$_3$, 100 MHz)



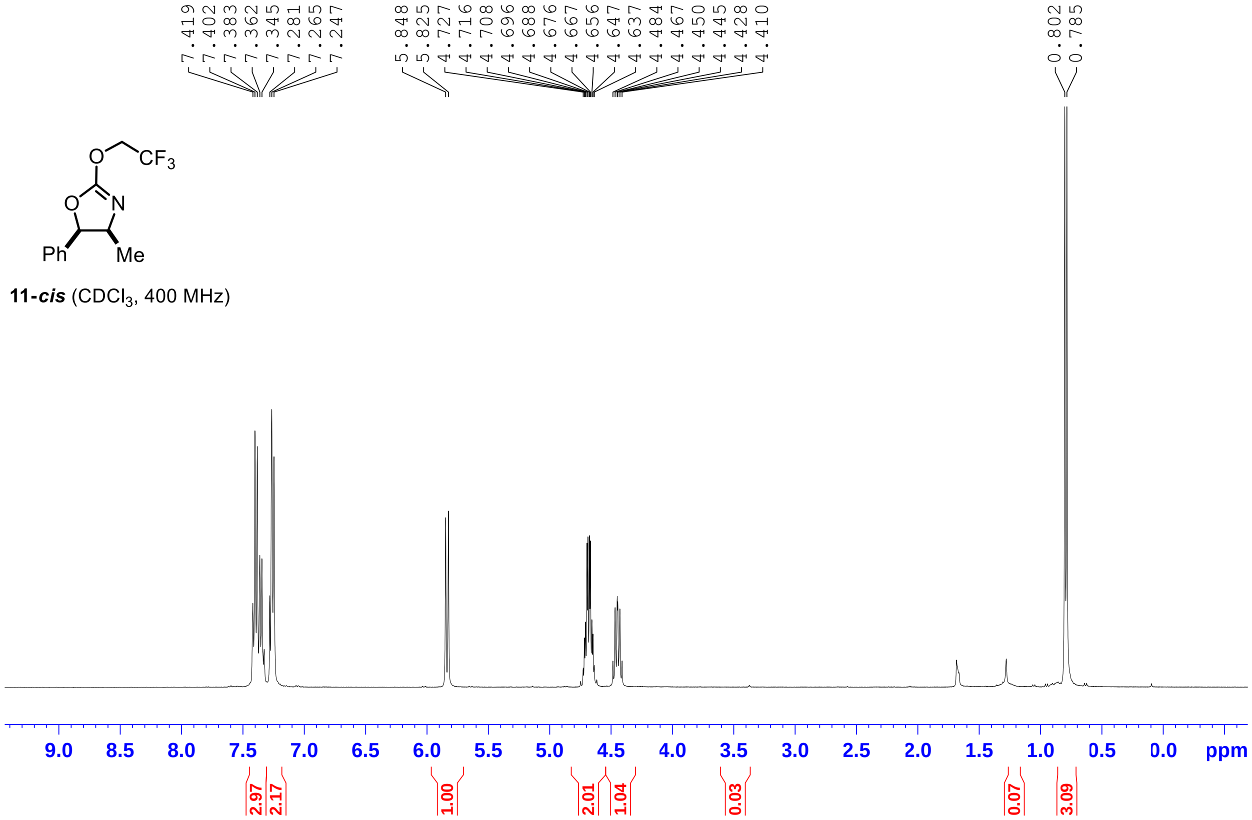
2c ($CDCl_3$, 377 MHz)


11 (CDCl$_3$, 400 MHz)

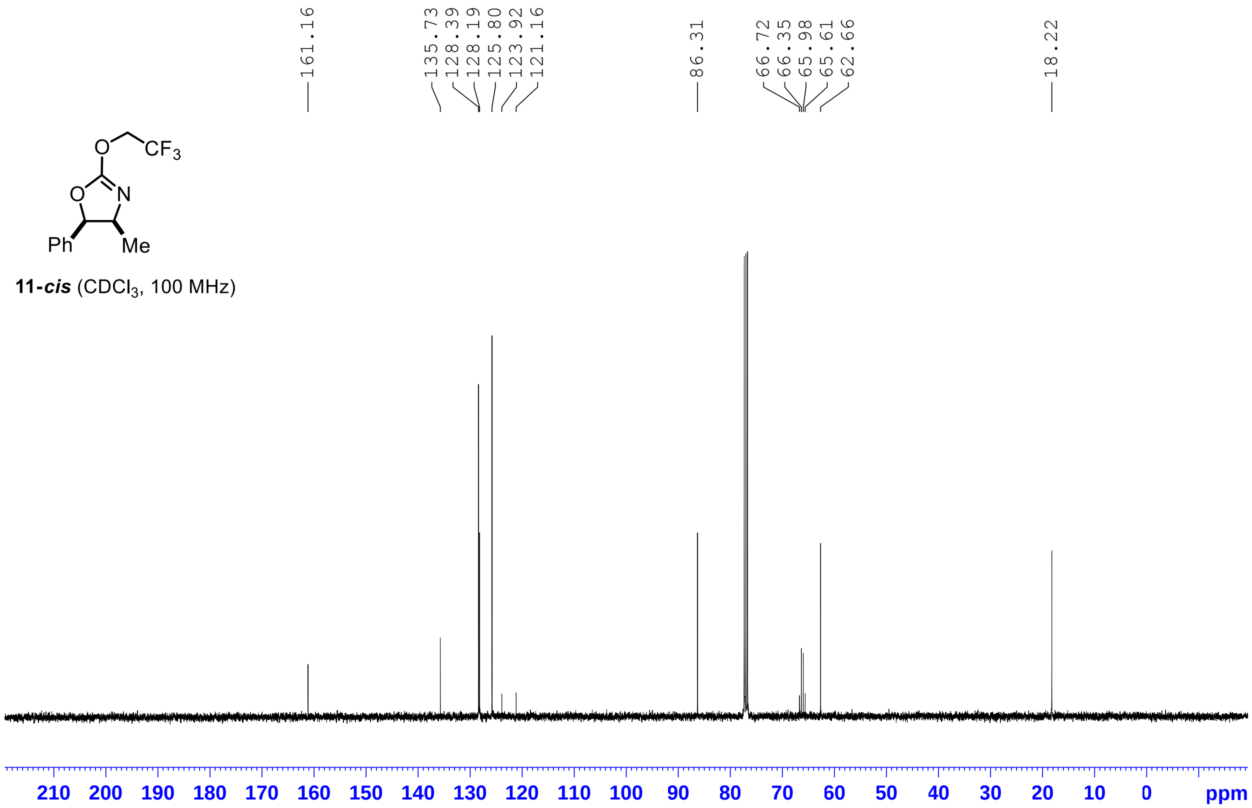

11 (CDCl$_3$, 100 MHz)



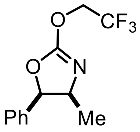
11 (CDCl$_3$, 377 MHz)



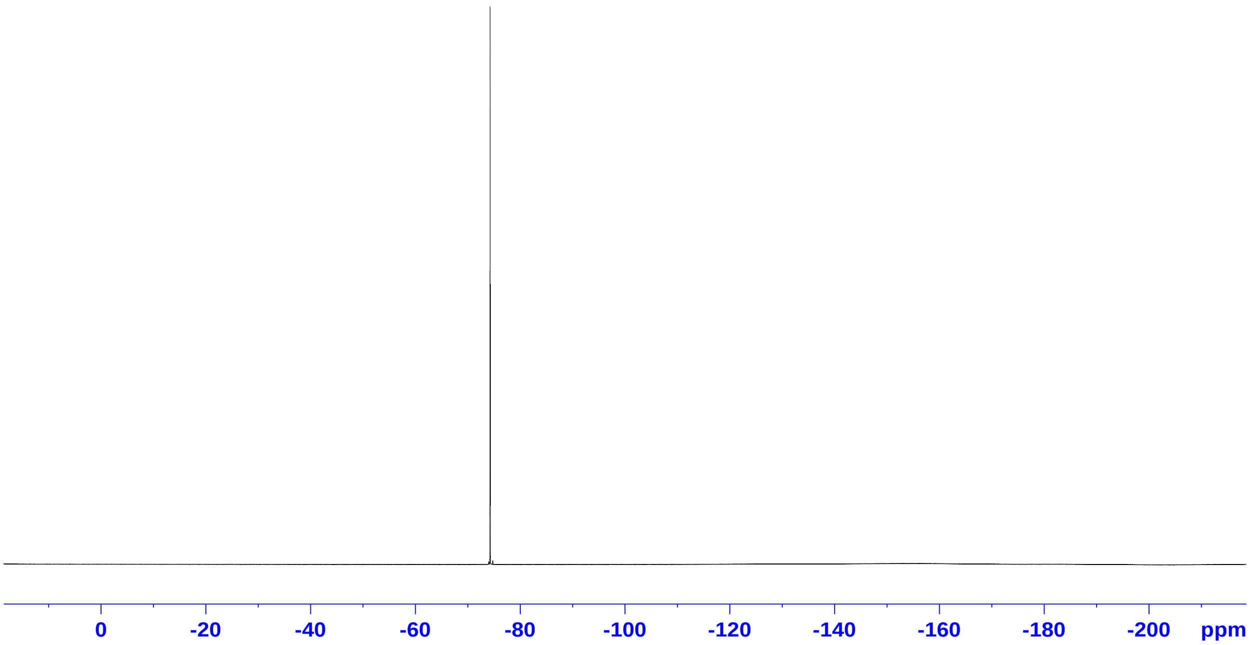
11-*cis* ($CDCl_3$, 400 MHz)

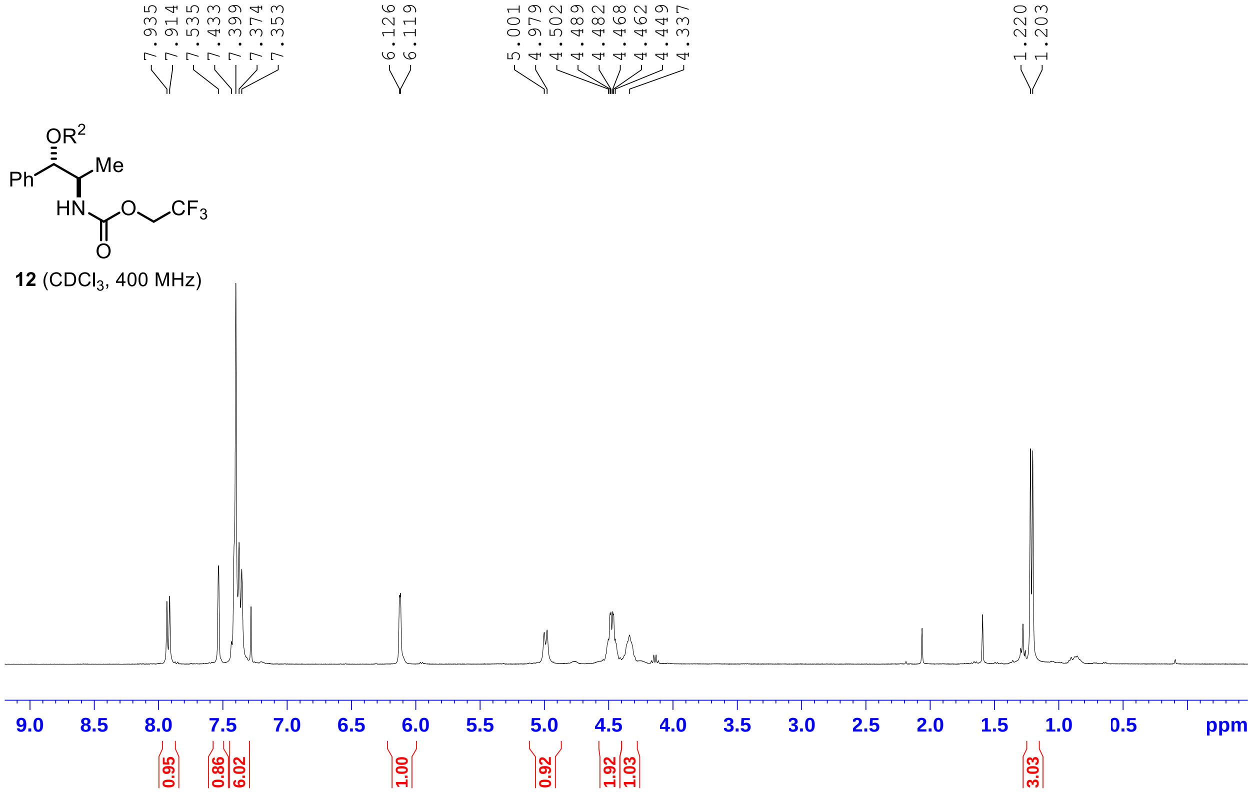


11-*cis* ($CDCl_3$, 100 MHz)

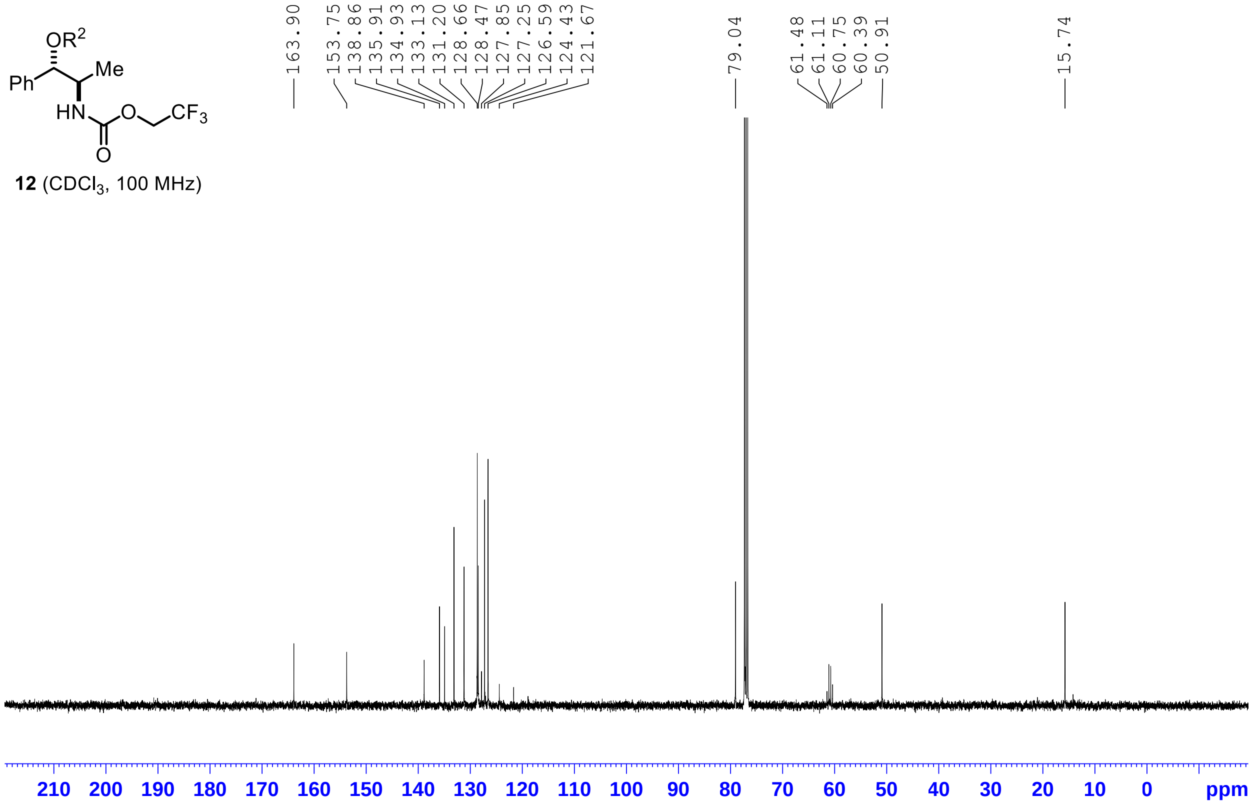


11-*cis* ($CDCl_3$, 377 MHz)

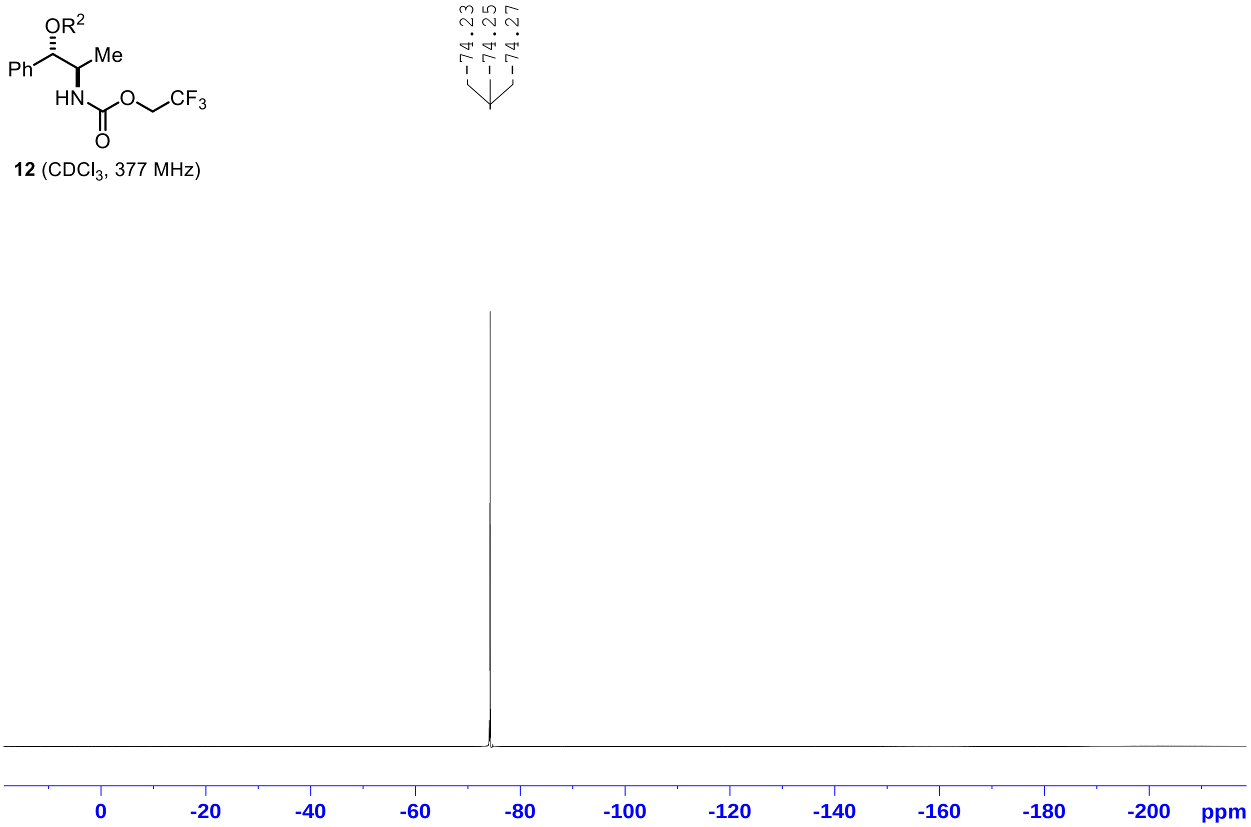




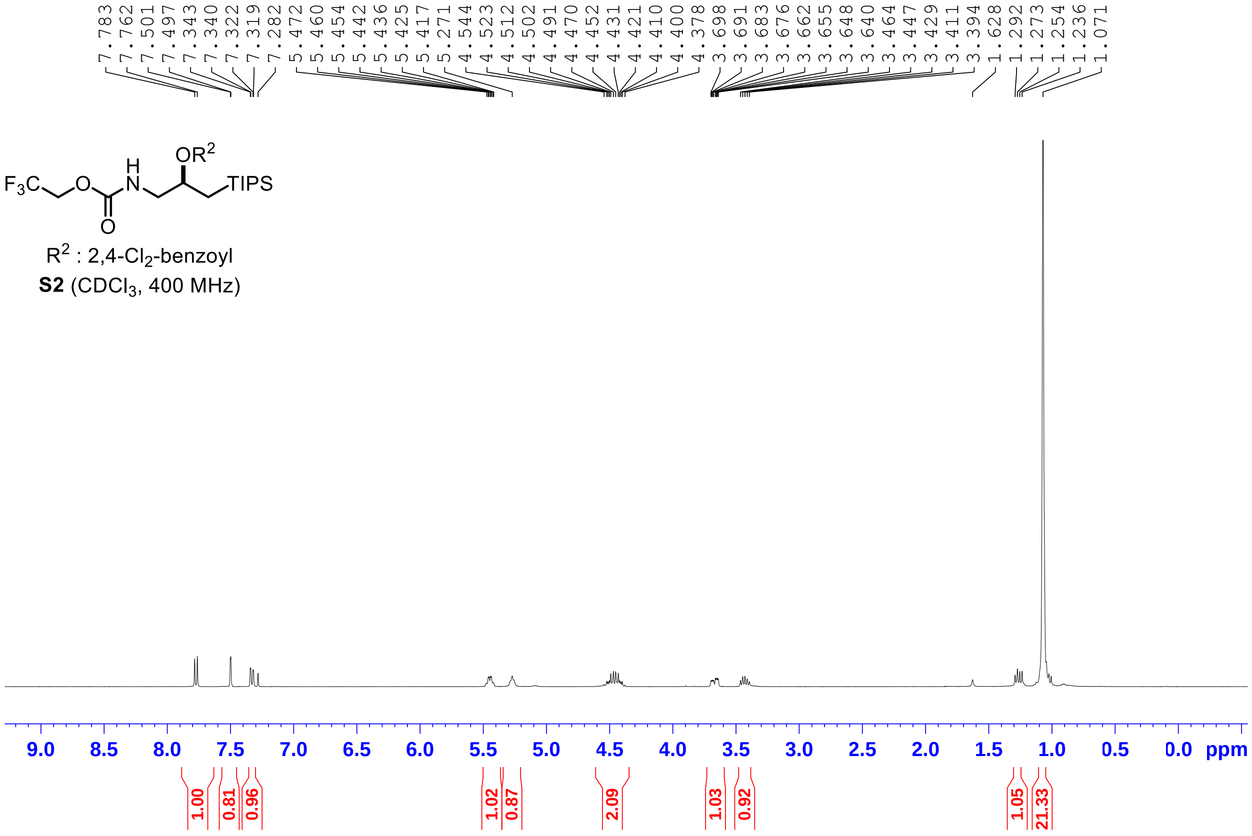
12 (CDCl$_3$, 400 MHz)



12 (CDCl$_3$, 100 MHz)

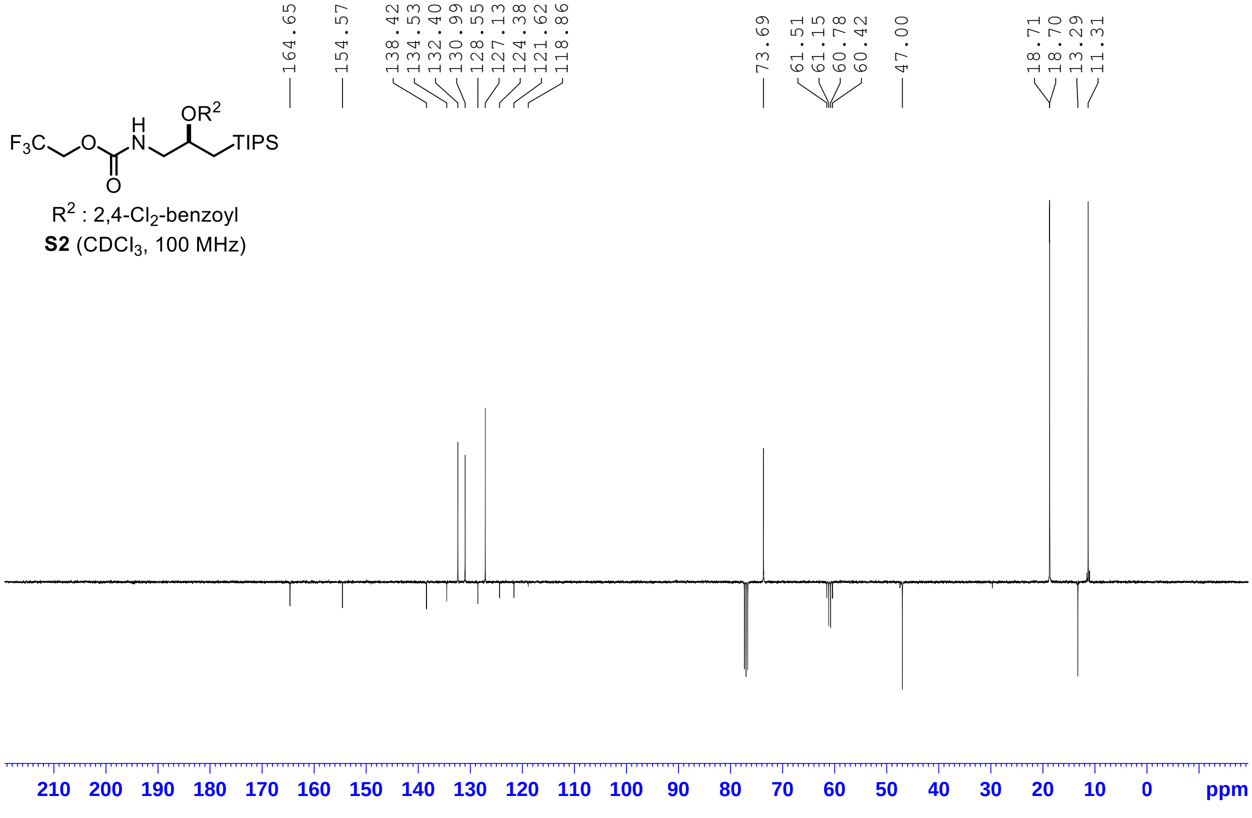


12 (CDCl$_3$, 377 MHz)



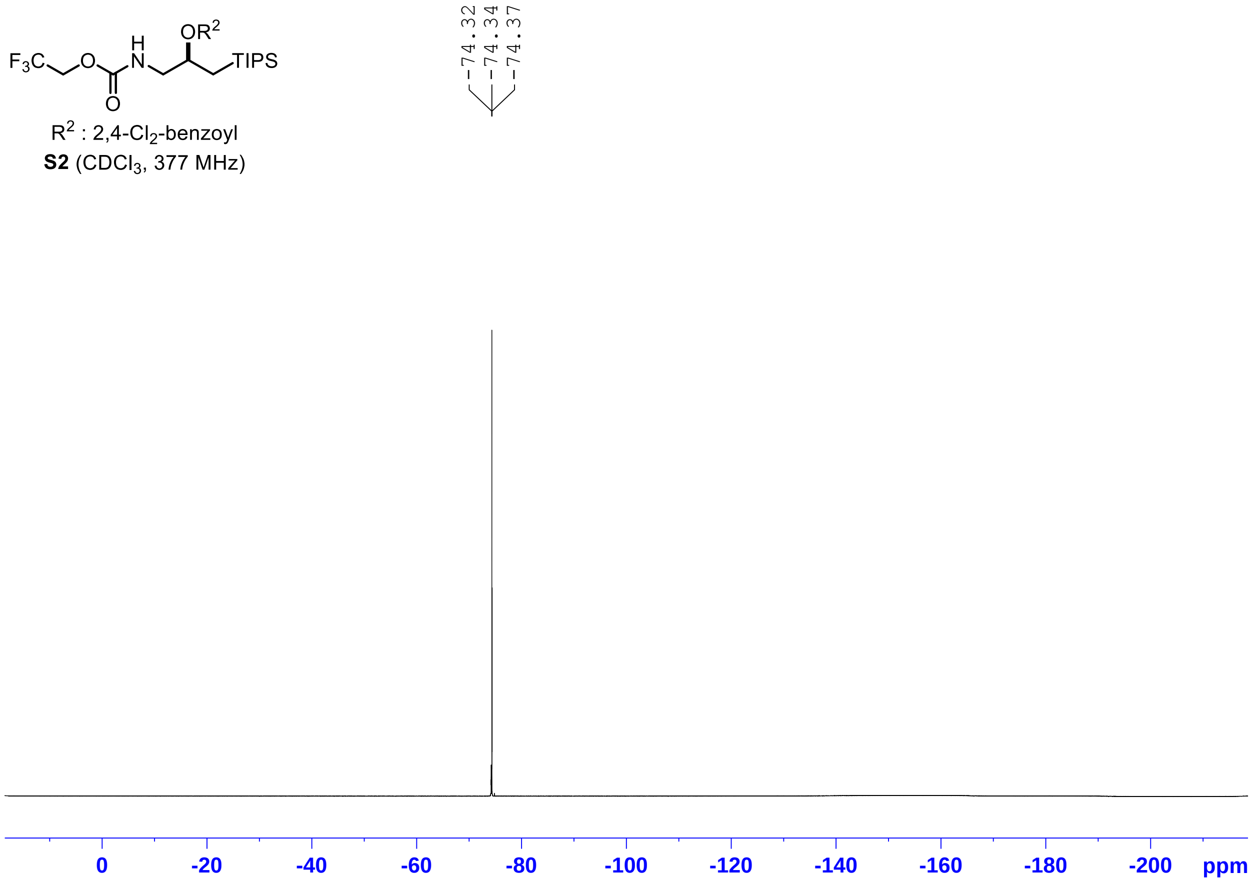
R^2 : 2,4-Cl_2-benzoyl

S2 ($CDCl_3$, 400 MHz)



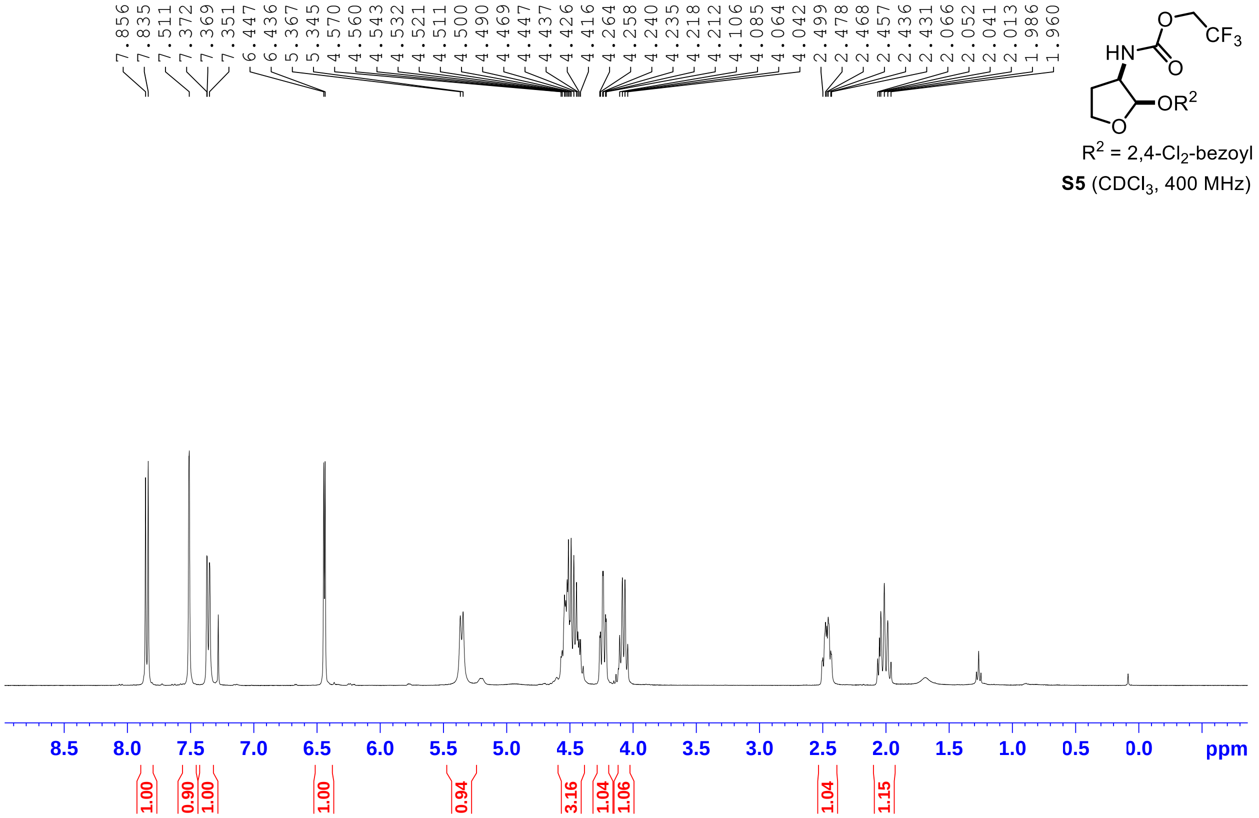
R^2 : 2,4-Cl_2-benzoyl

S2 ($CDCl_3$, 100 MHz)



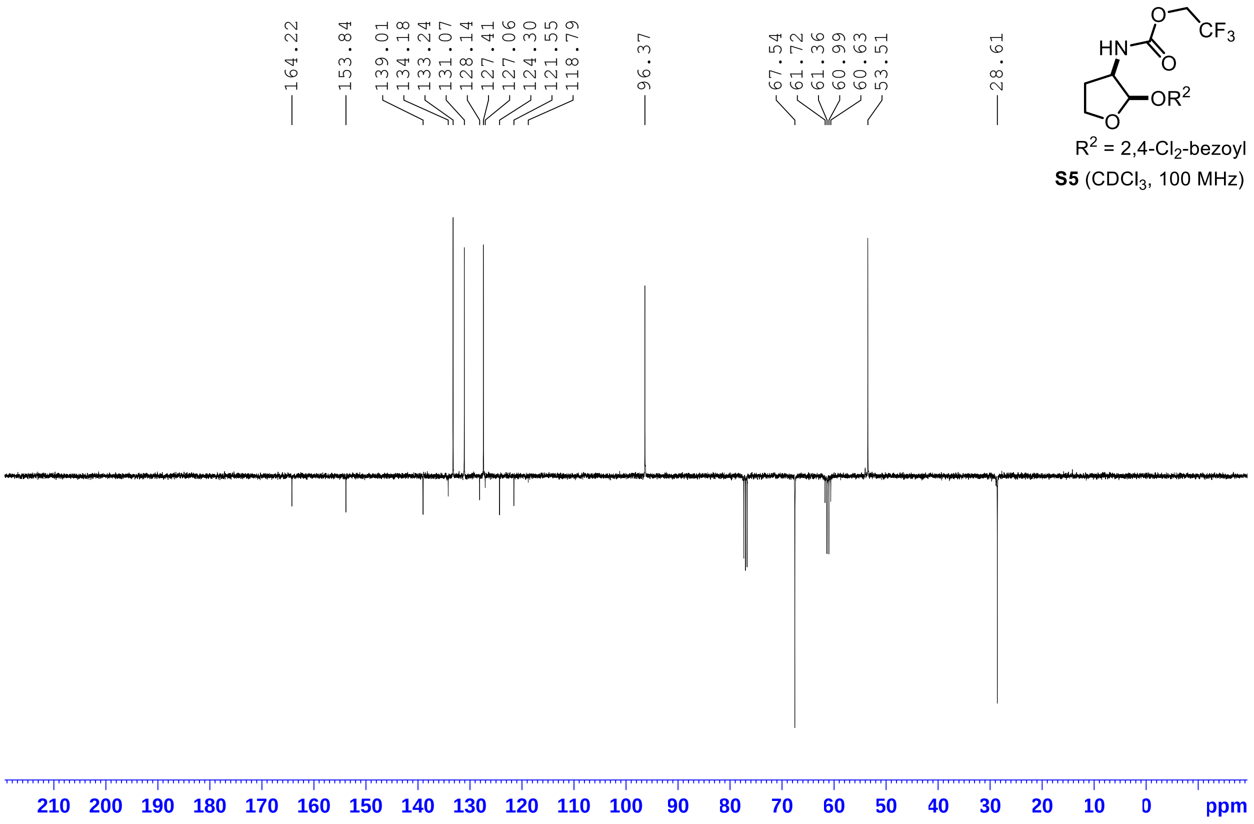
R^2 : 2,4-Cl_2-benzoyl

S2 ($CDCl_3$, 377 MHz)



R^2 = 2,4-Cl_2-bezoyl

S5 ($CDCl_3$, 400 MHz)

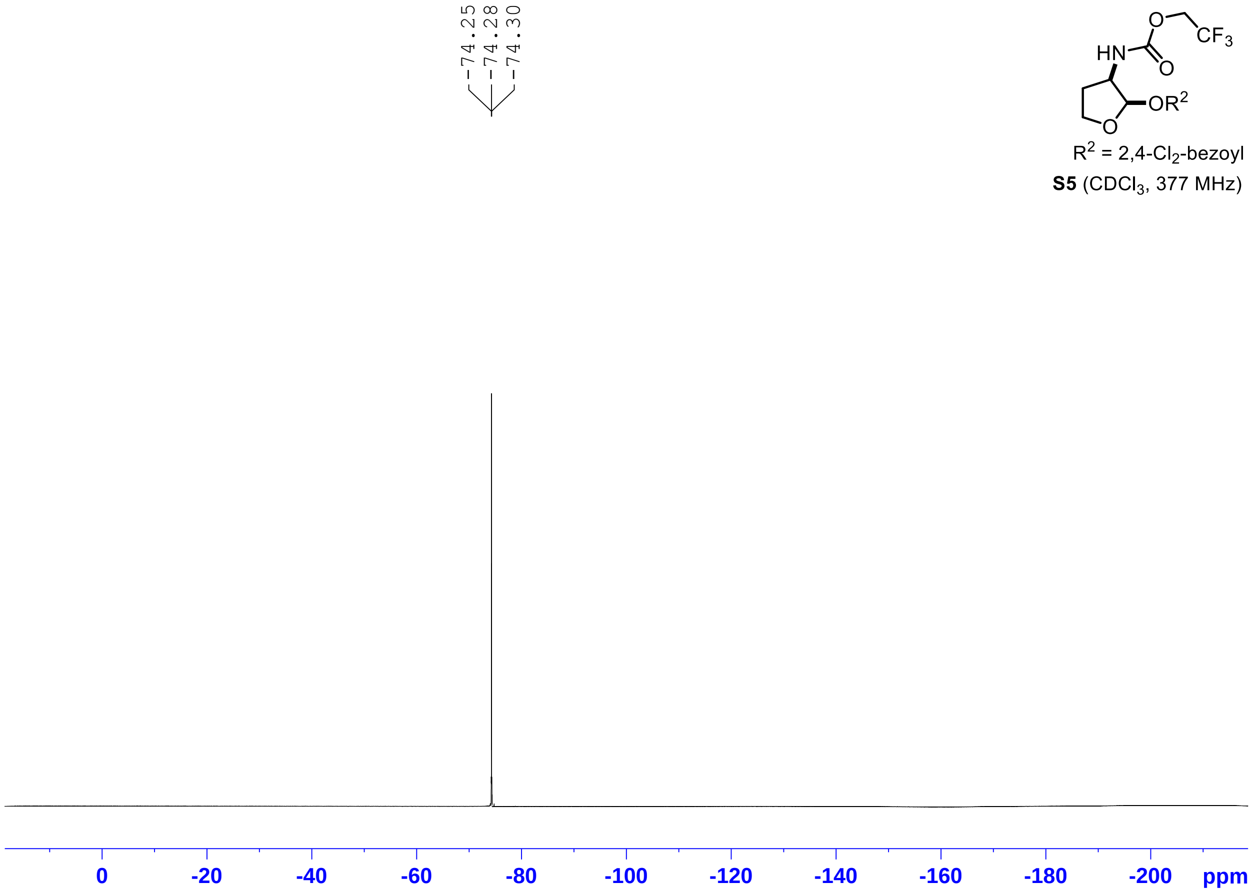


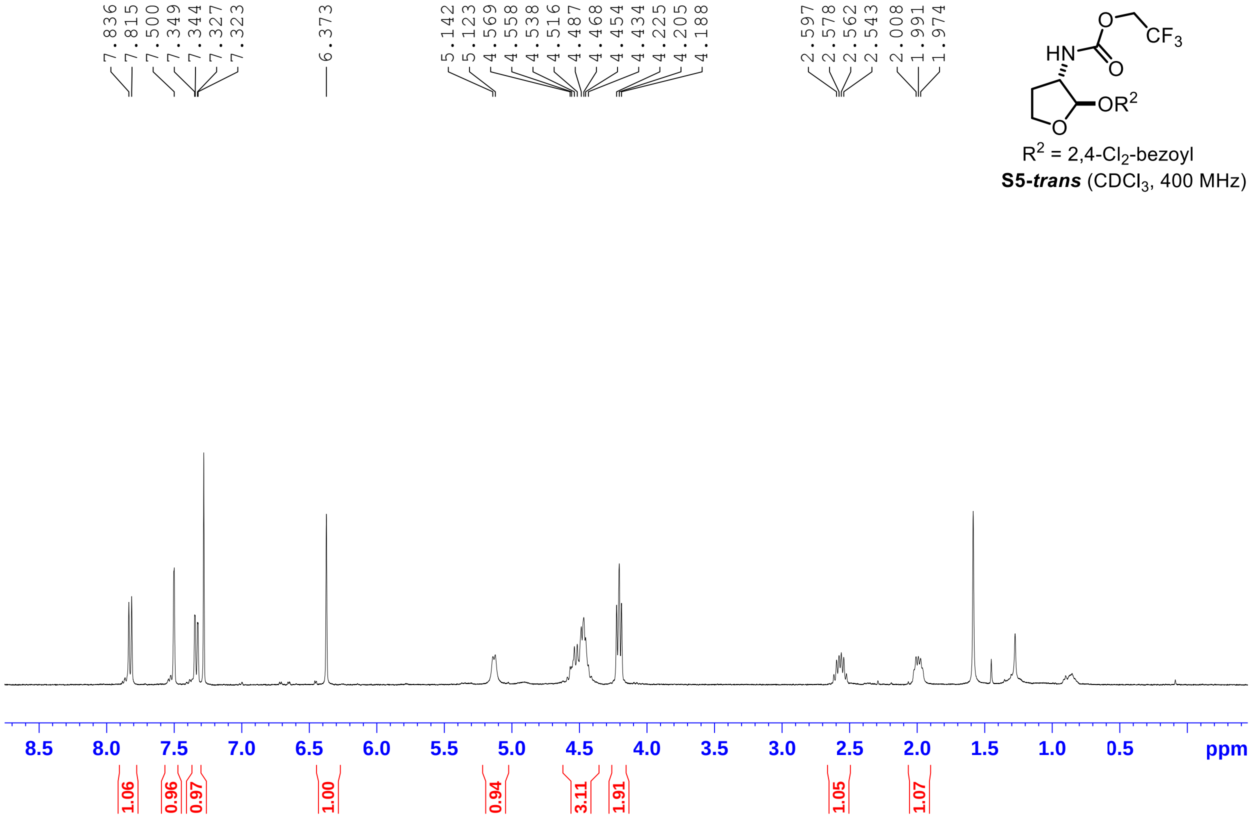
R^2 = 2,4-Cl_2-bezoyl

S5 ($CDCl_3$, 100 MHz)

R^2 = 2,4-Cl_2-bezoyl

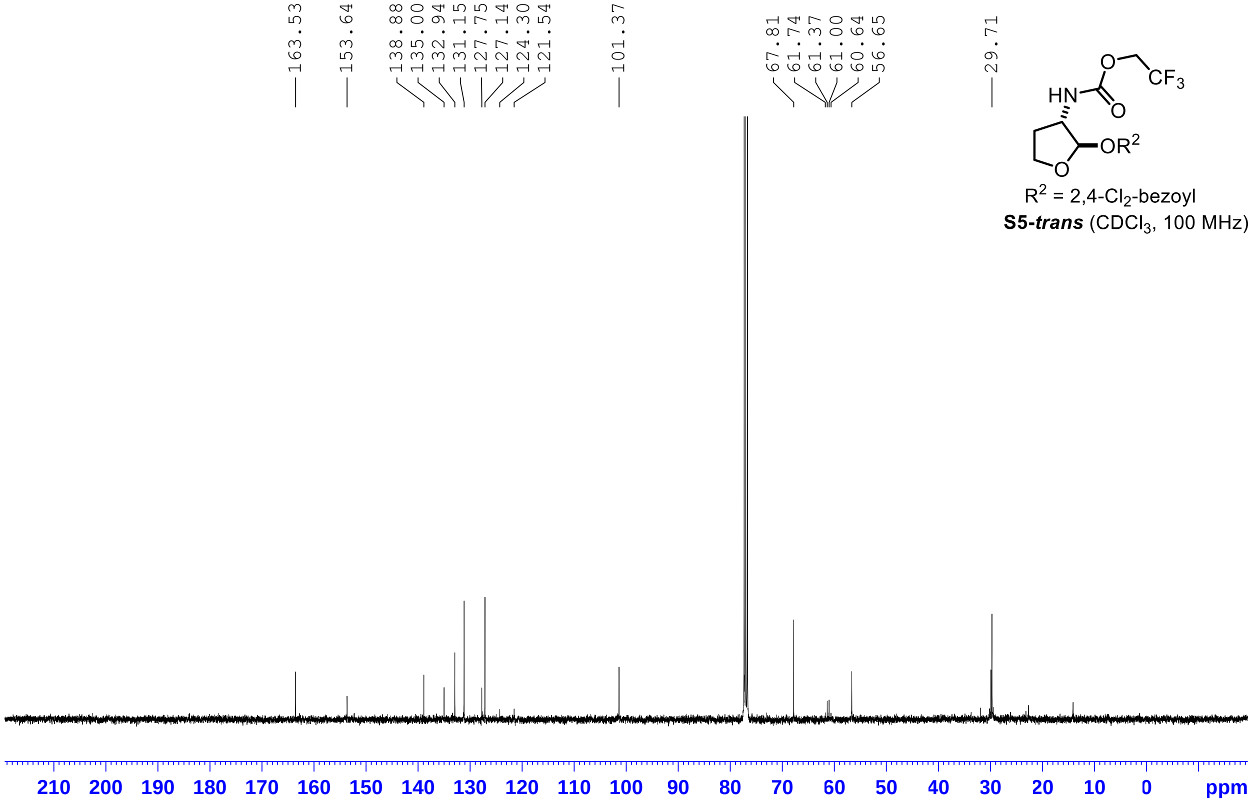
S5 ($CDCl_3$, 377 MHz)





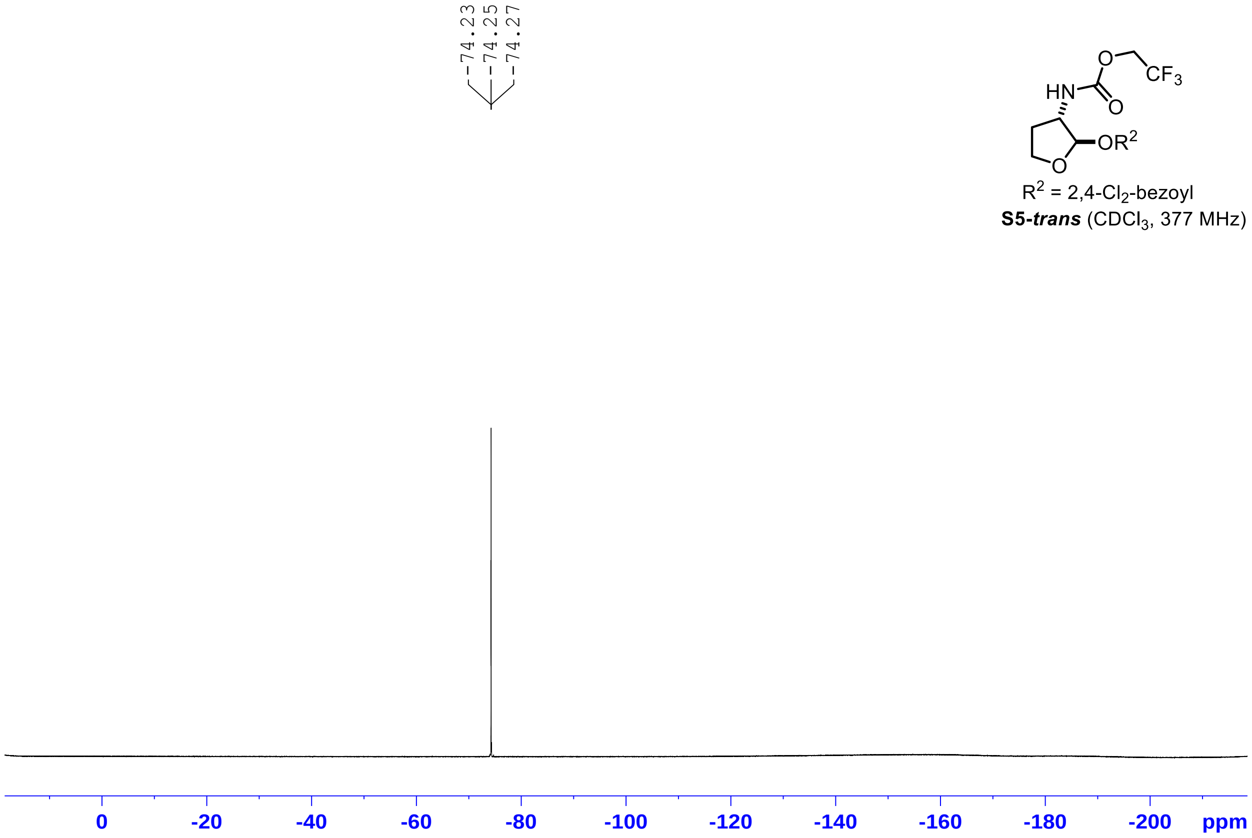
R^2 = 2,4-Cl_2-bezoyl

S5-*trans* ($CDCl_3$, 400 MHz)



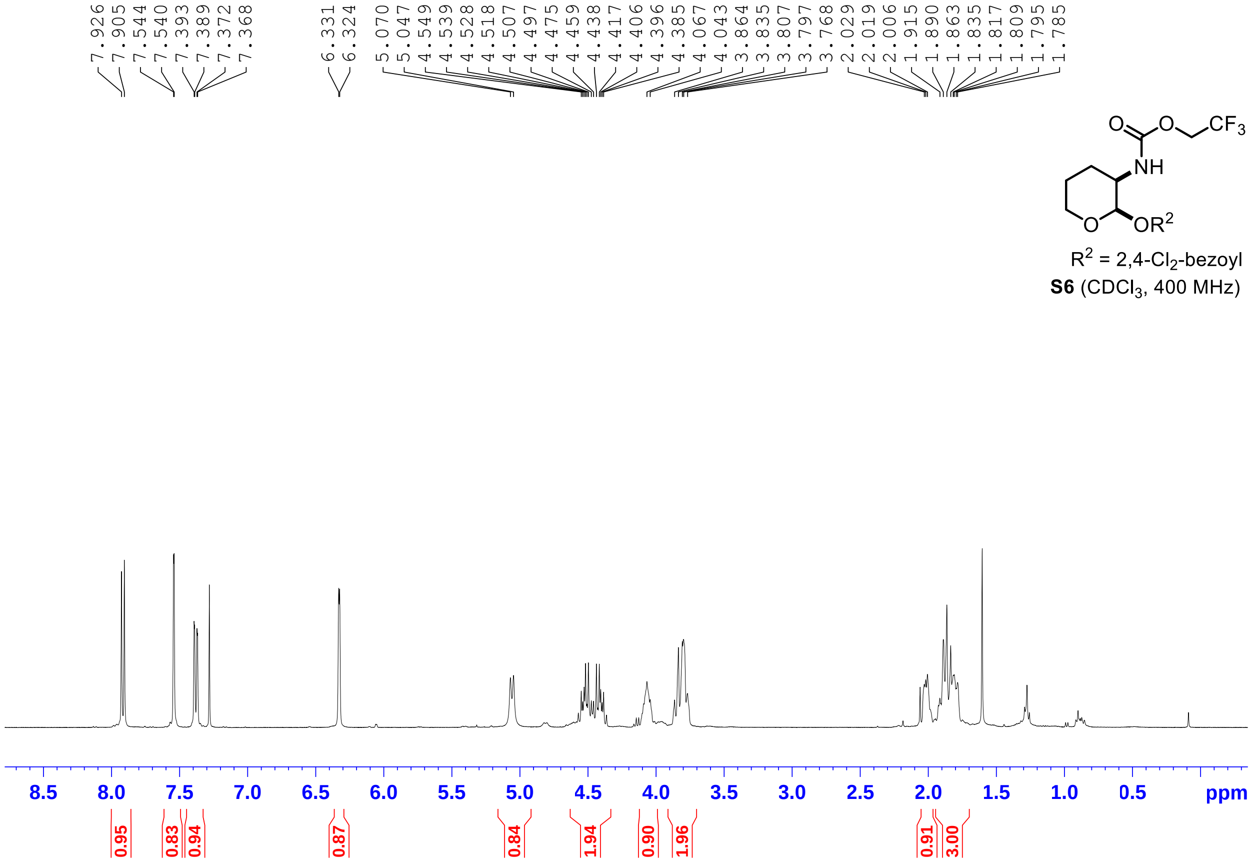
R^2 = 2,4-Cl_2-bezoyl

S5-*trans* ($CDCl_3$, 100 MHz)



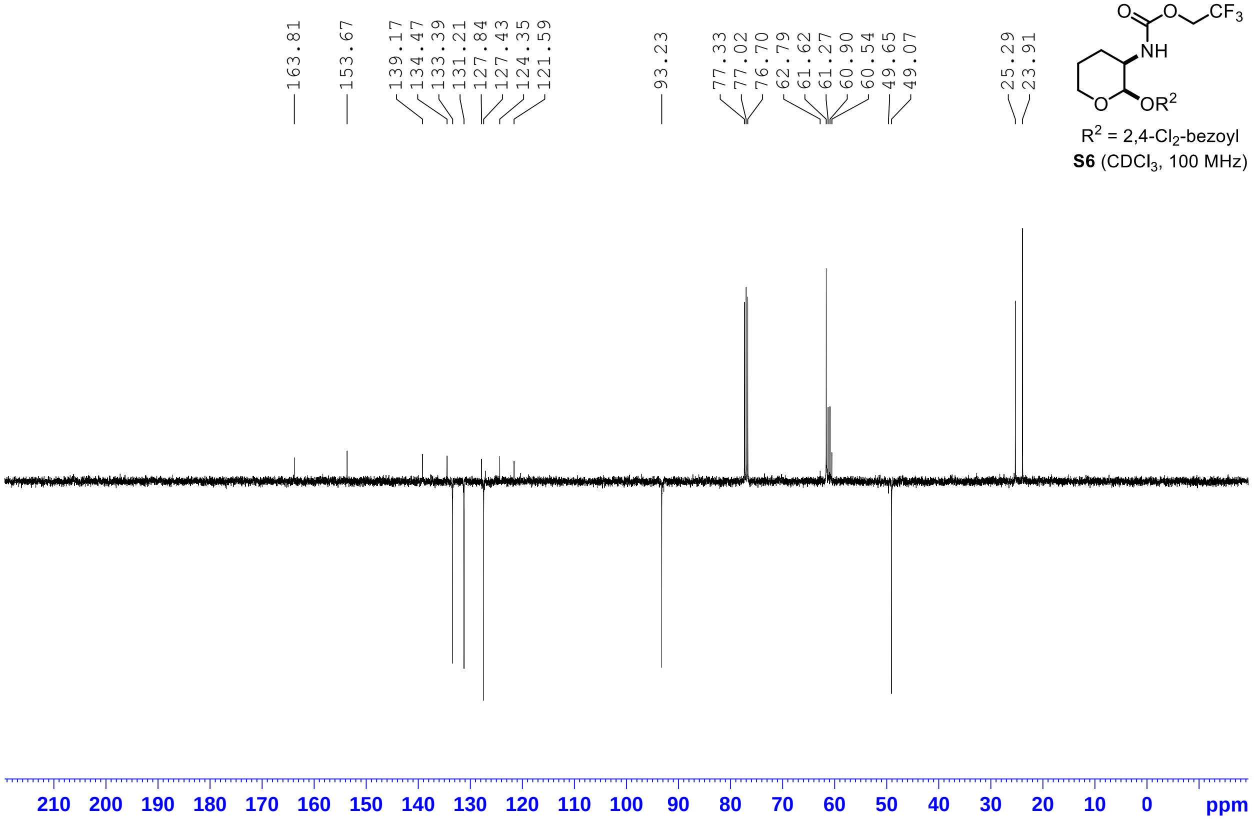
R^2 = 2,4-Cl_2-bezoyl

S5-*trans* ($CDCl_3$, 377 MHz)



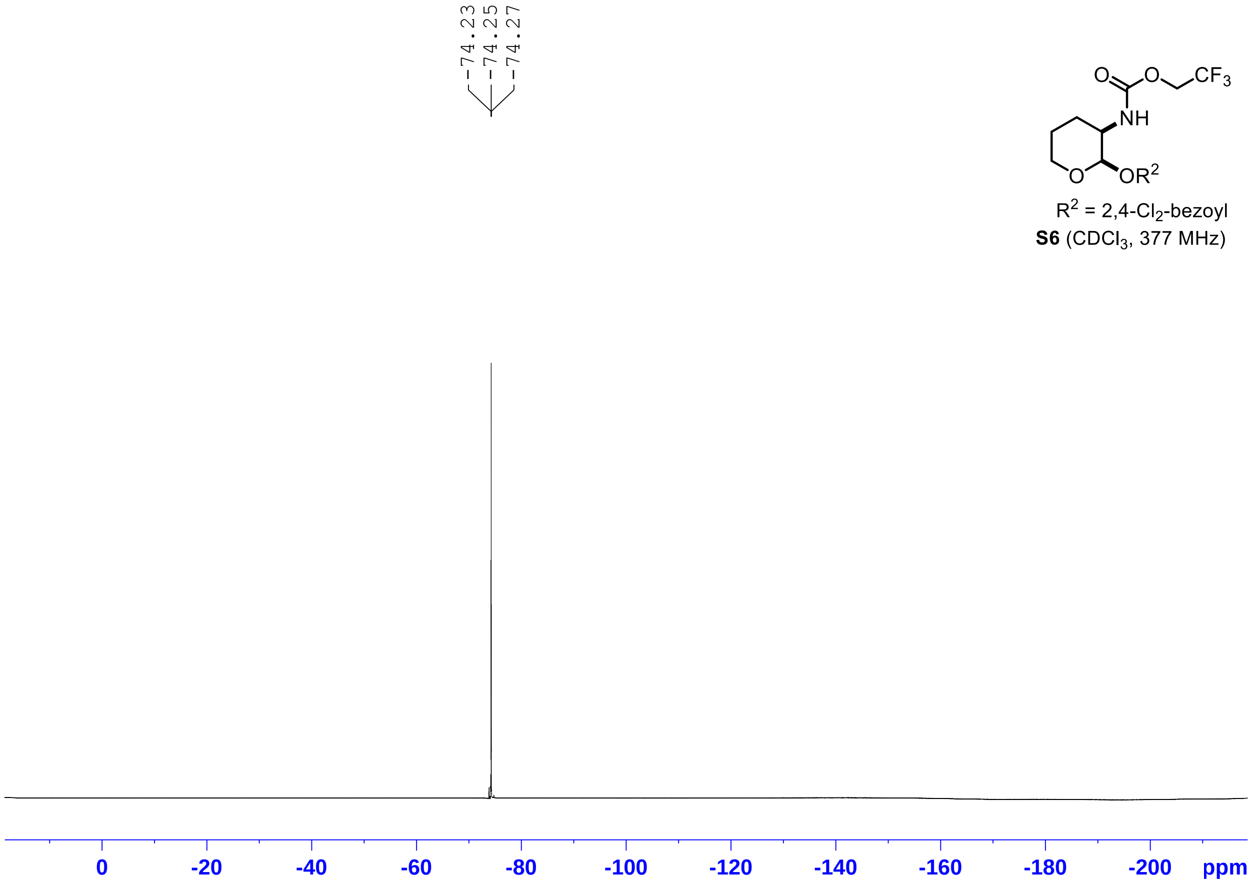
R^2 = 2,4-Cl_2-bezoyl

S6 ($CDCl_3$, 400 MHz)



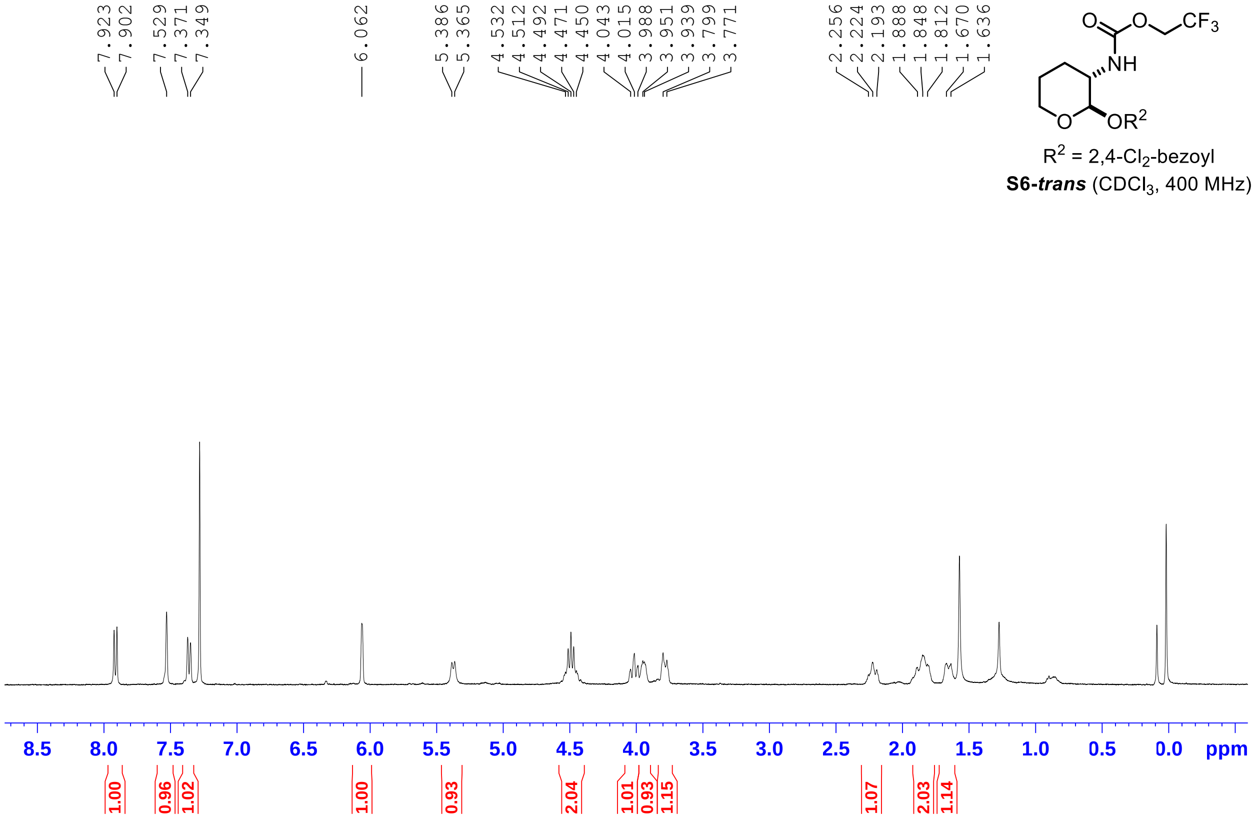
R^2 = 2,4-Cl_2-bezoyl

S6 ($CDCl_3$, 100 MHz)

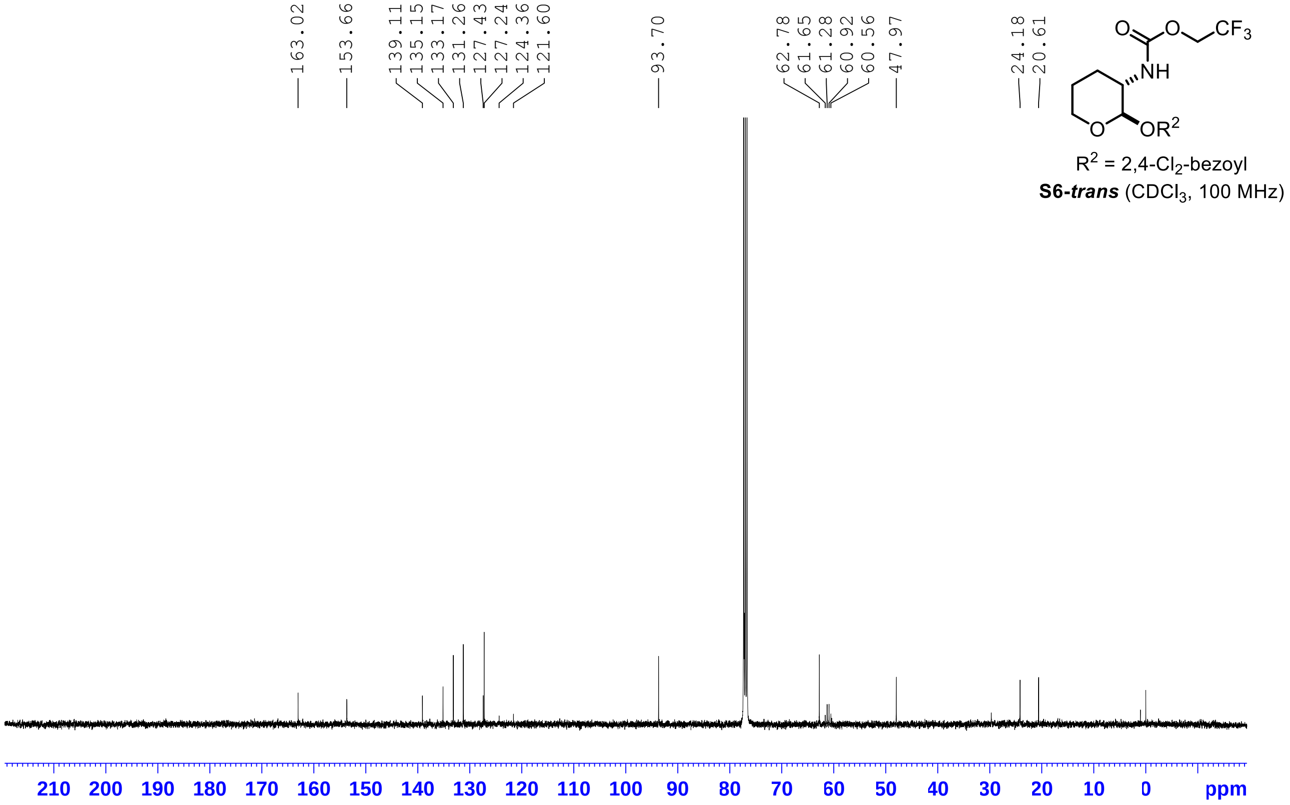


R^2 = 2,4-Cl_2-bezoyl

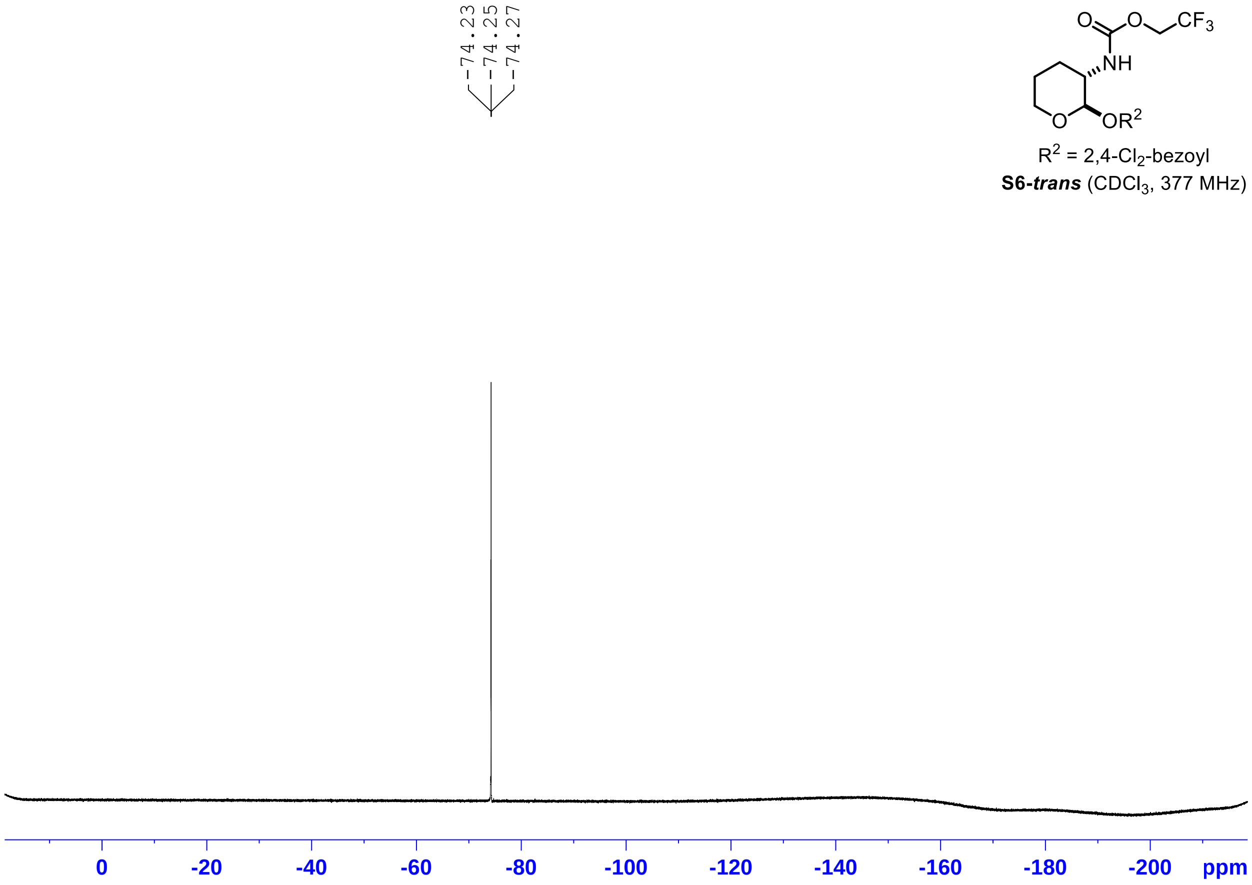
S6 ($CDCl_3$, 377 MHz)



R^2 = 2,4-Cl_2-bezoyl
S6-*trans* ($CDCl_3$, 400 MHz)

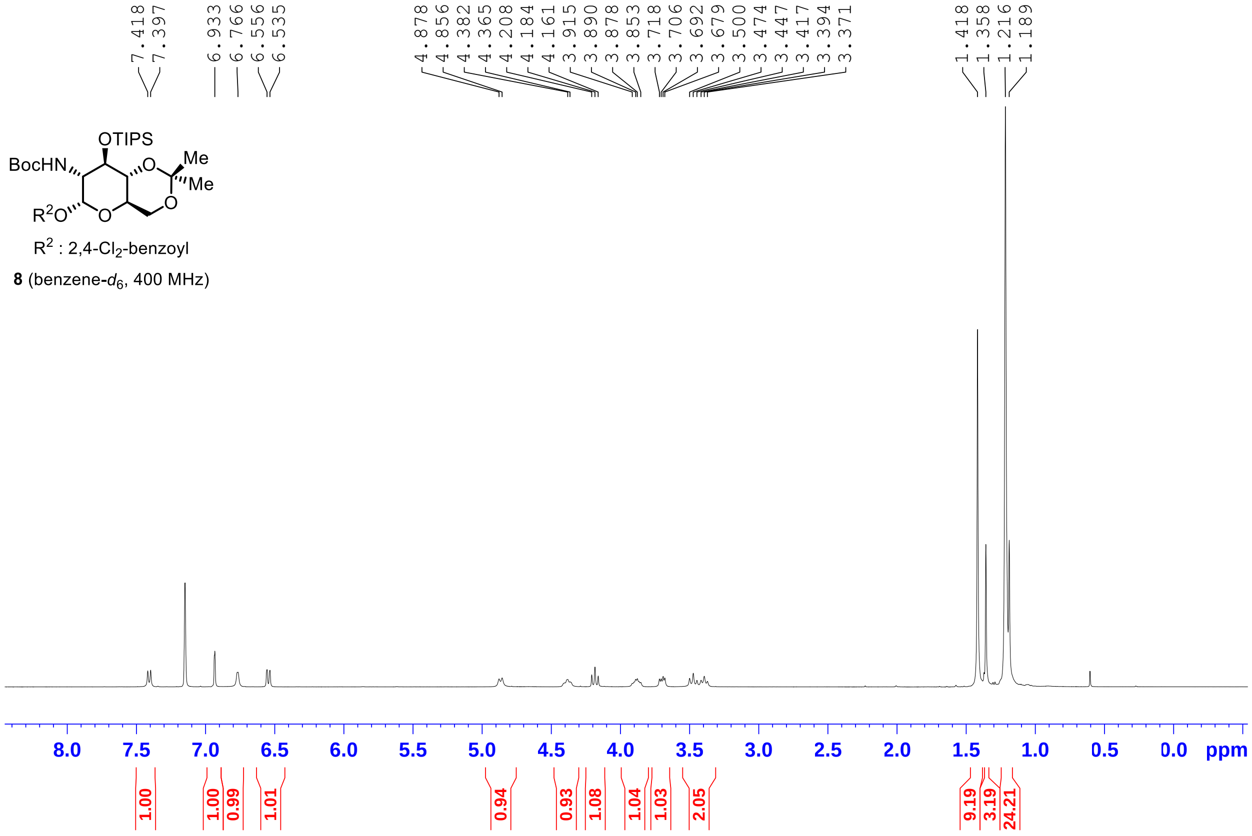


R^2 = 2,4-Cl_2-bezoyl
S6-*trans* ($CDCl_3$, 100 MHz)



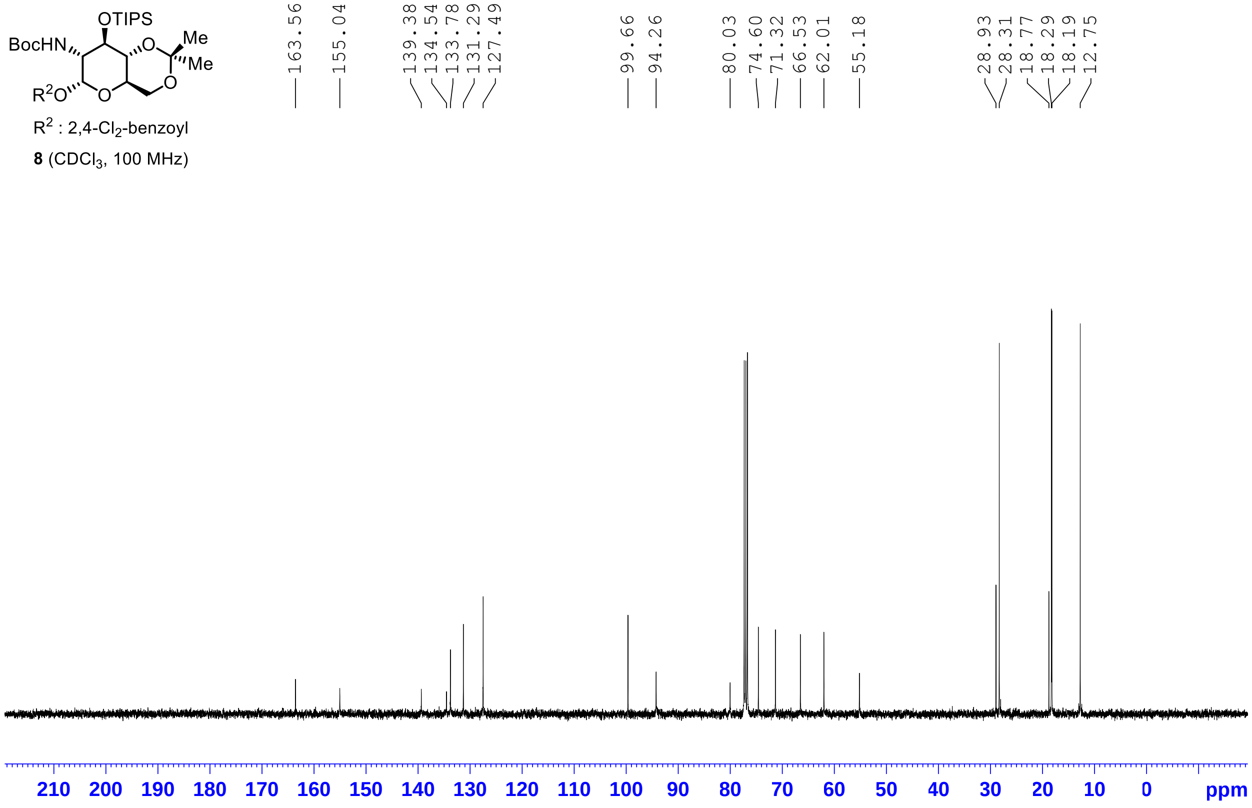
R^2 = 2,4-Cl_2-bezoyl

S6-*trans* ($CDCl_3$, 377 MHz)



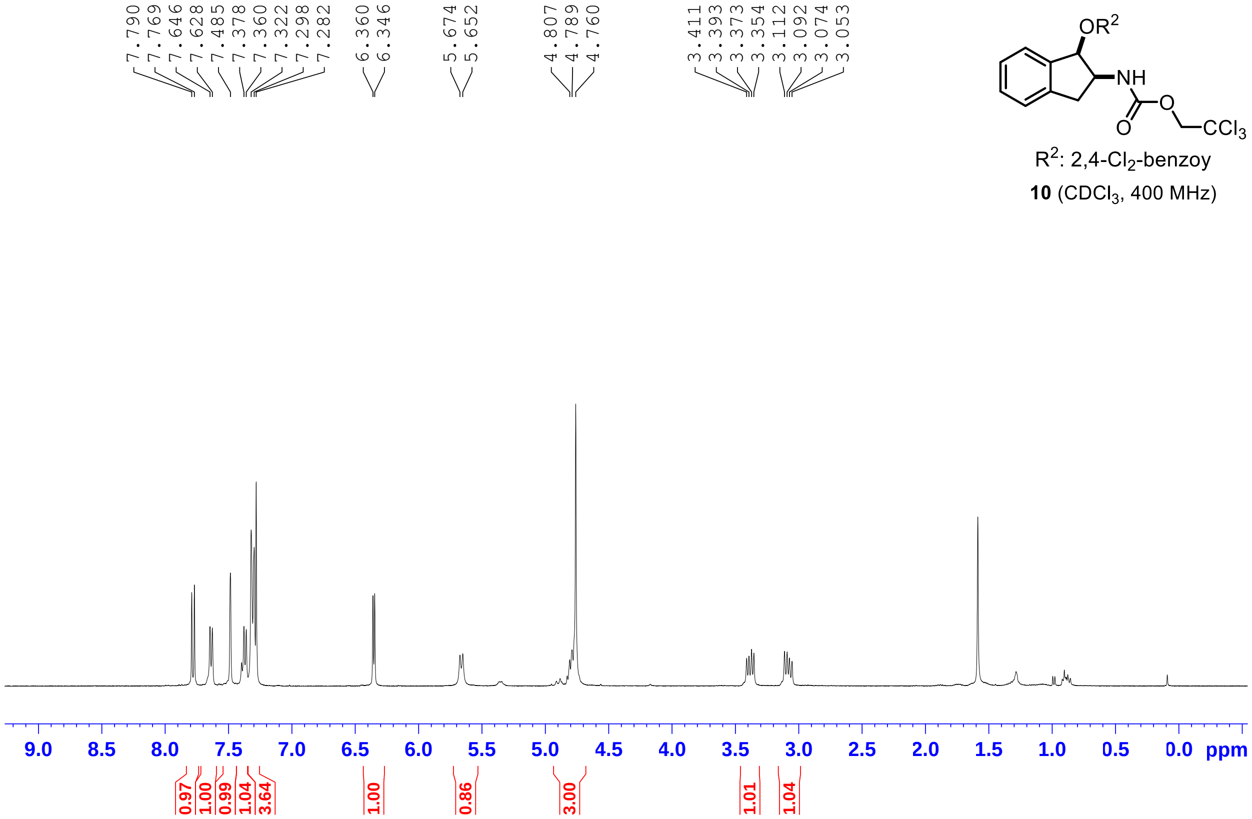
R^2 : 2,4-Cl_2-benzoyl

8 (benzene-d_6, 400 MHz)



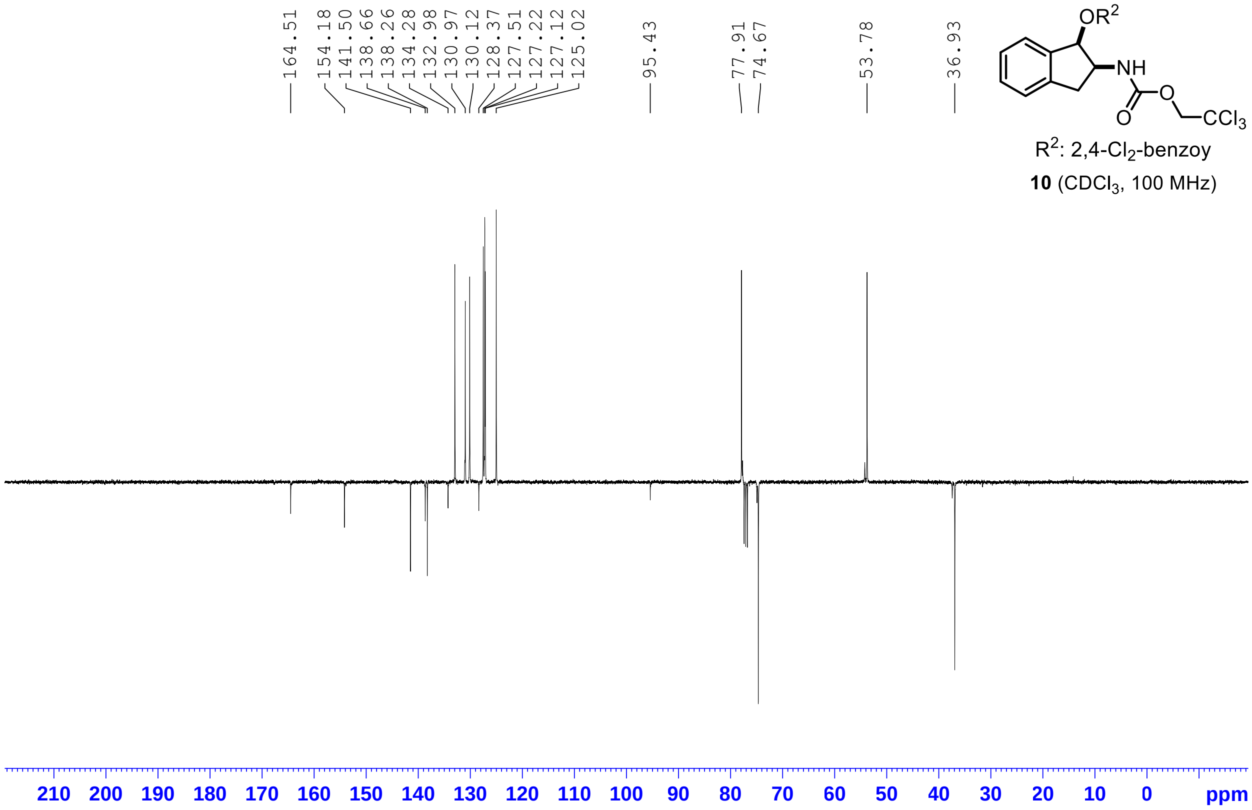
R^2 : 2,4-Cl_2-benzoyl

8 ($CDCl_3$, 100 MHz)



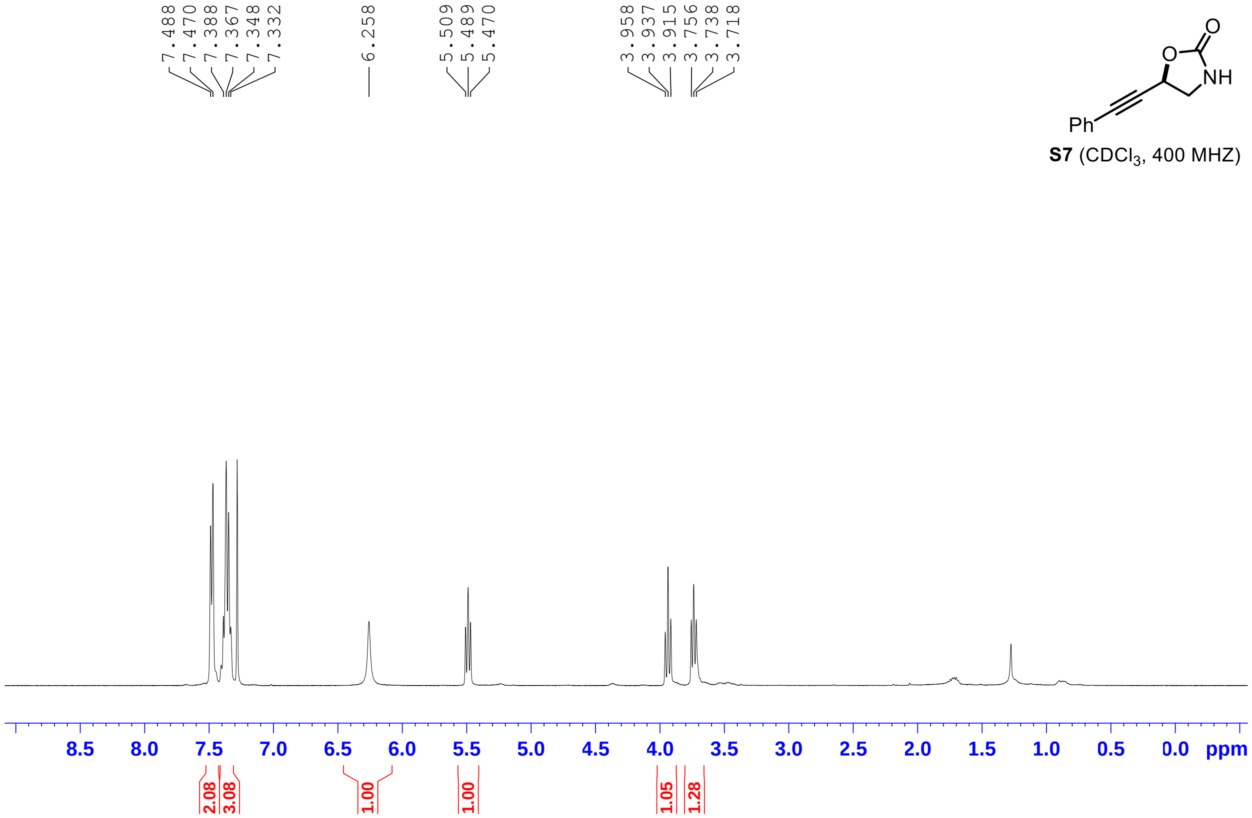
R^2: 2,4-Cl$_2$-benzoy

10 (CDCl$_3$, 400 MHz)

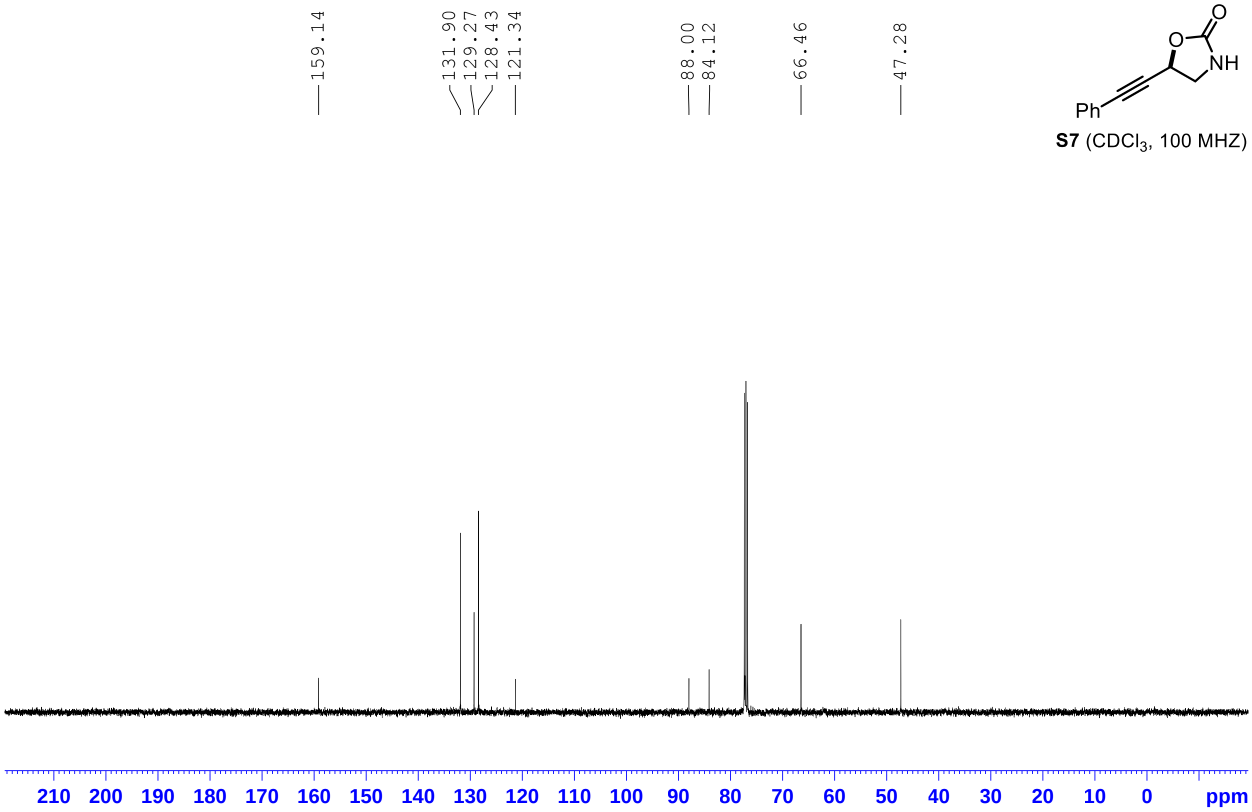


R^2: 2,4-Cl$_2$-benzoy

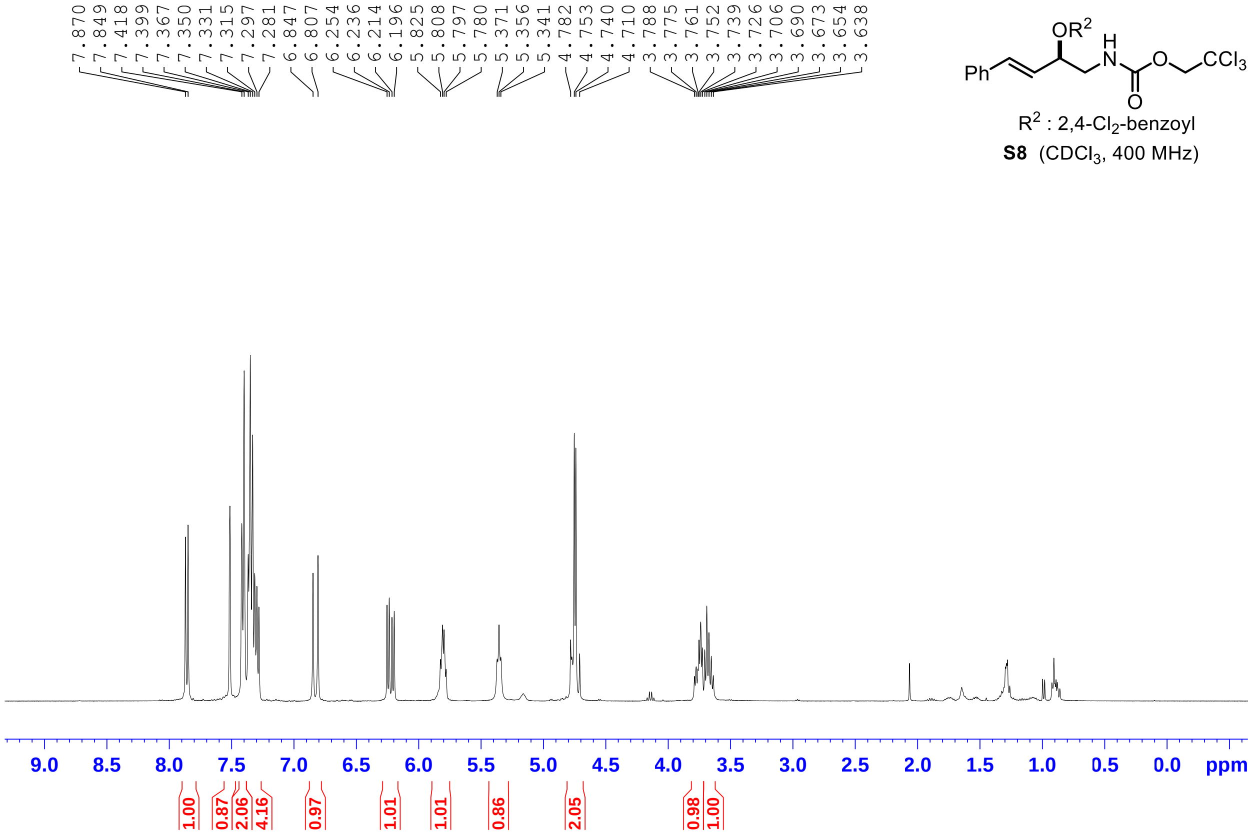
10 (CDCl$_3$, 100 MHz)



S7 ($CDCl_3$, 400 MHZ)

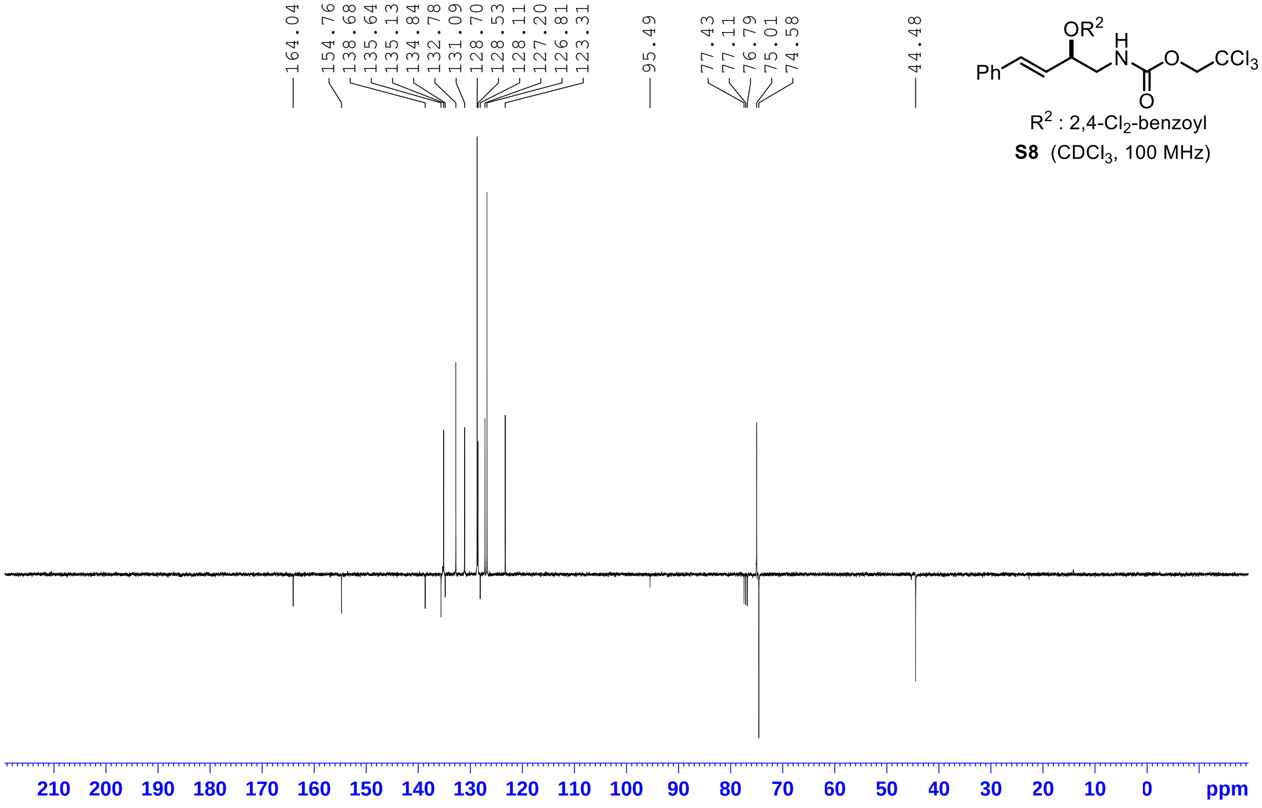


S7 ($CDCl_3$, 100 MHZ)



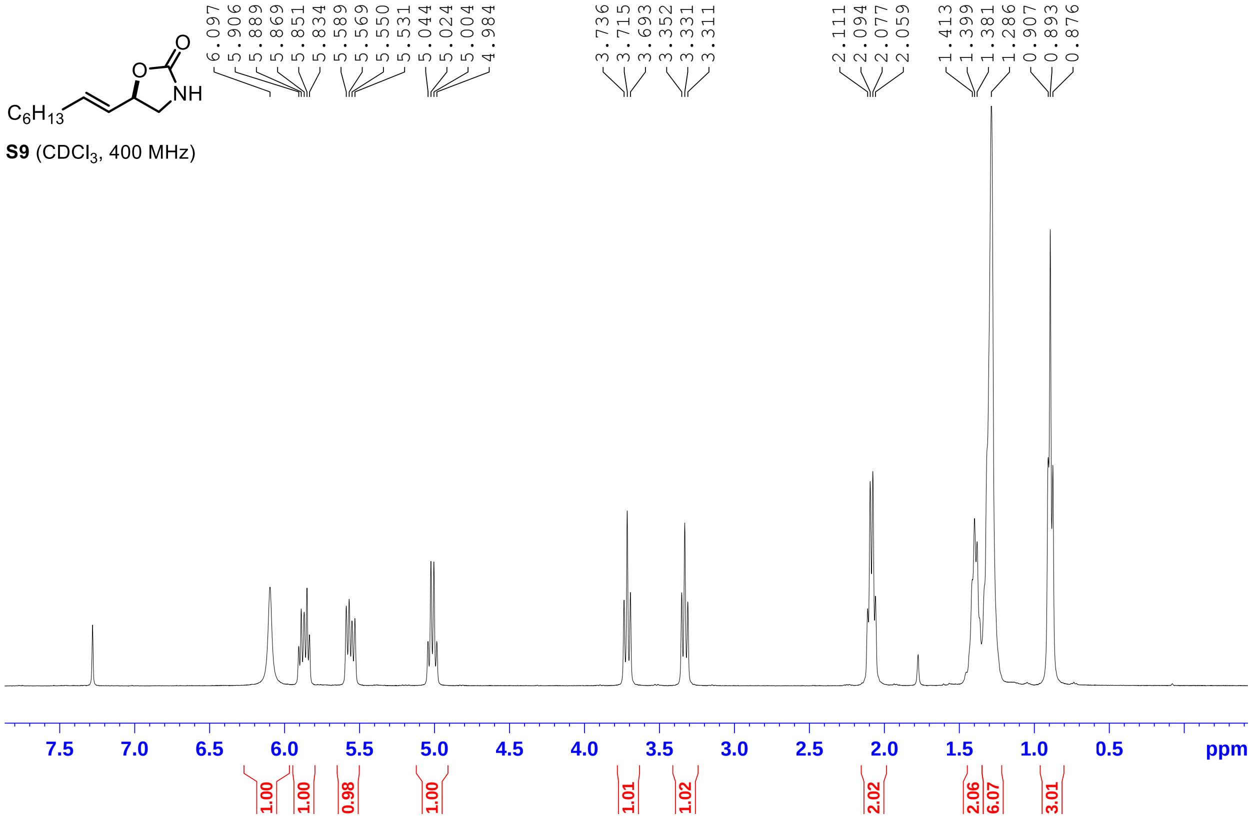
R^2 : 2,4-Cl_2-benzoyl

S8 ($CDCl_3$, 400 MHz)

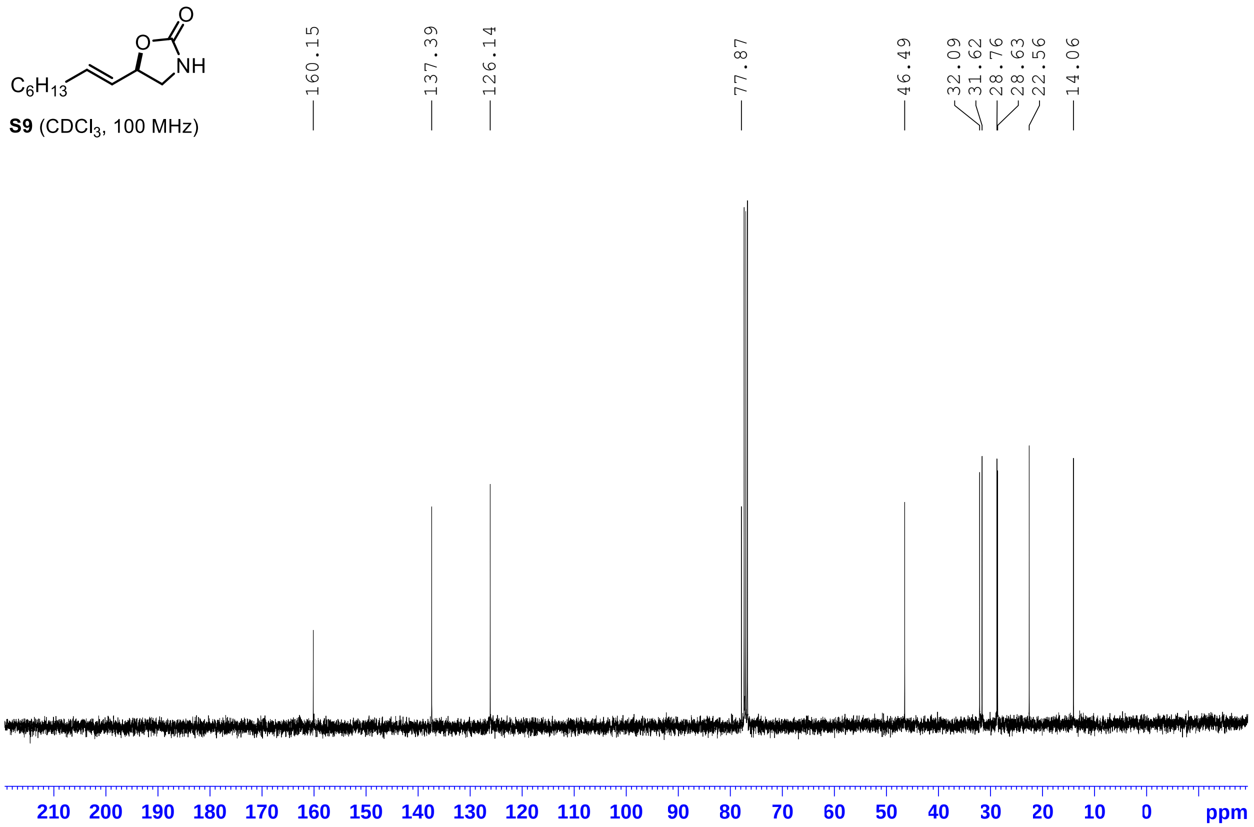


R^2 : 2,4-Cl_2-benzoyl

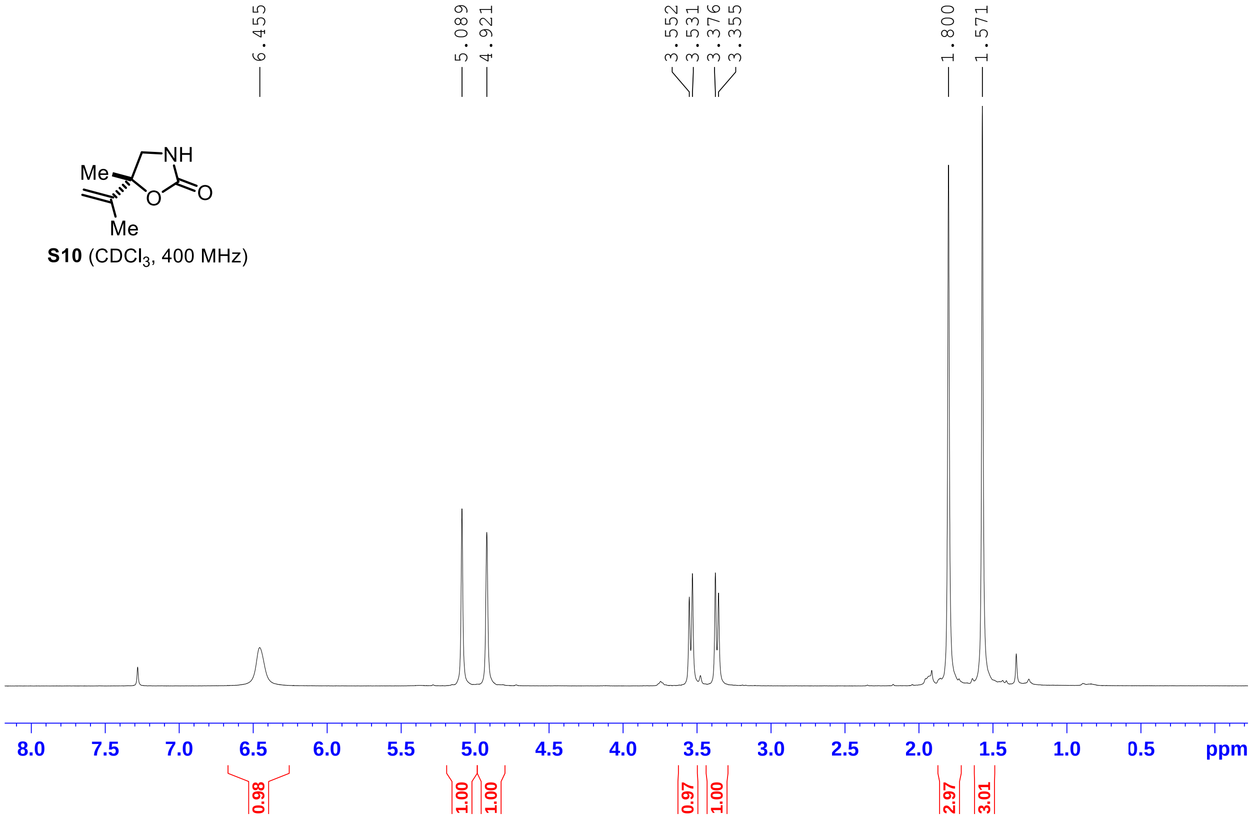
S8 ($CDCl_3$, 100 MHz)

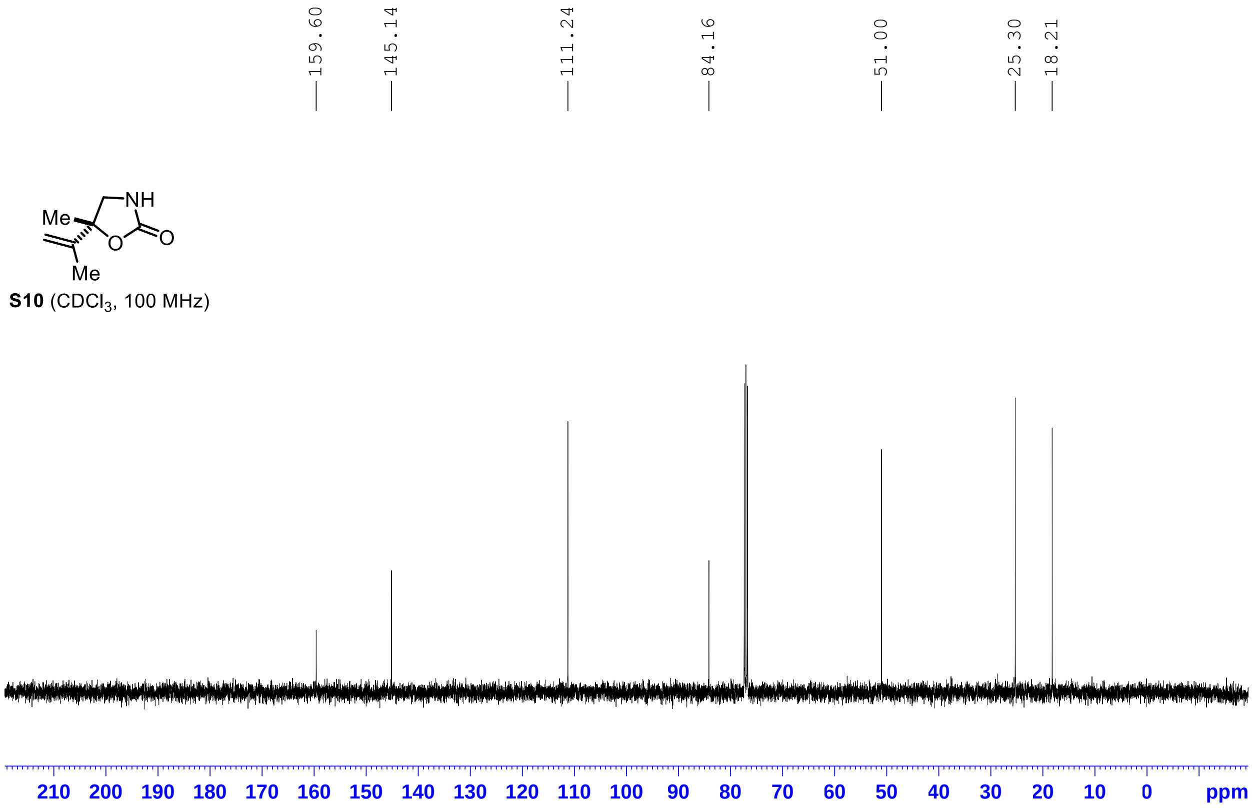


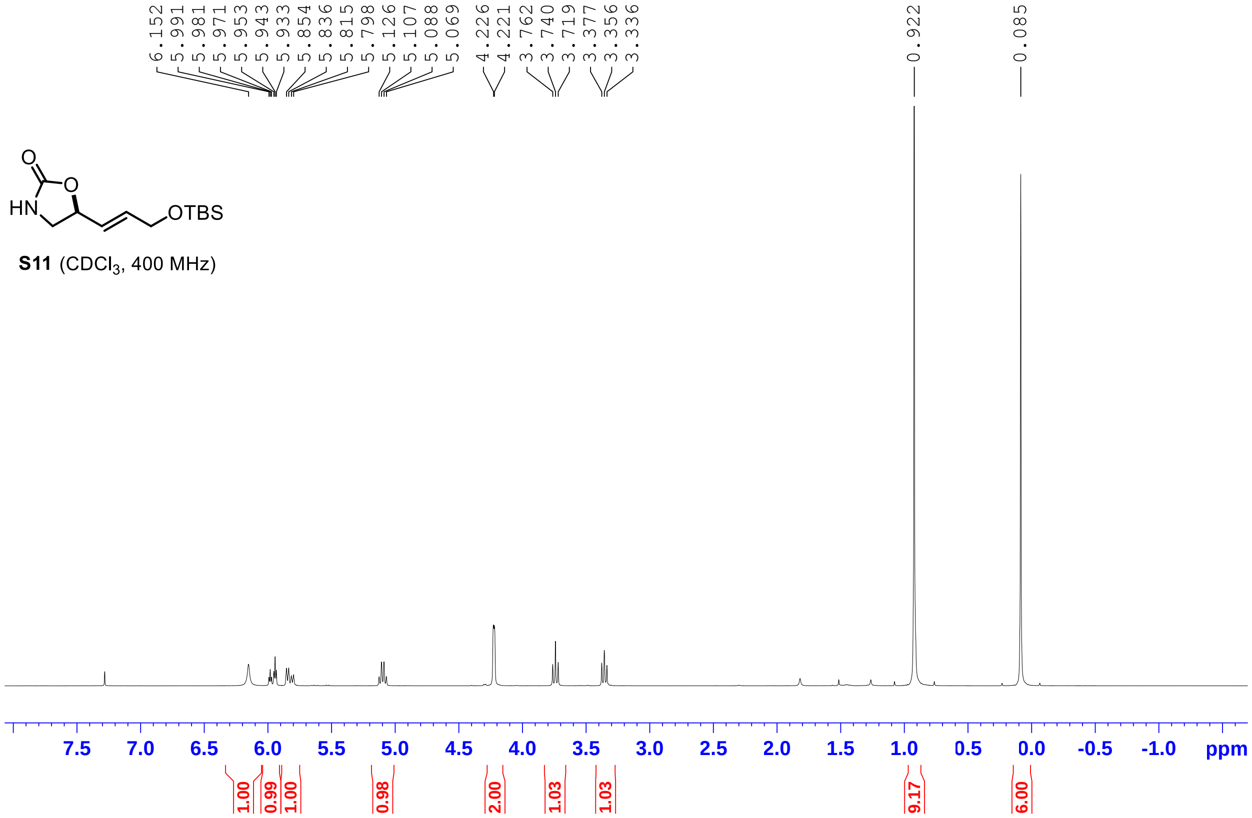
S9 (CDCl$_3$, 400 MHz)



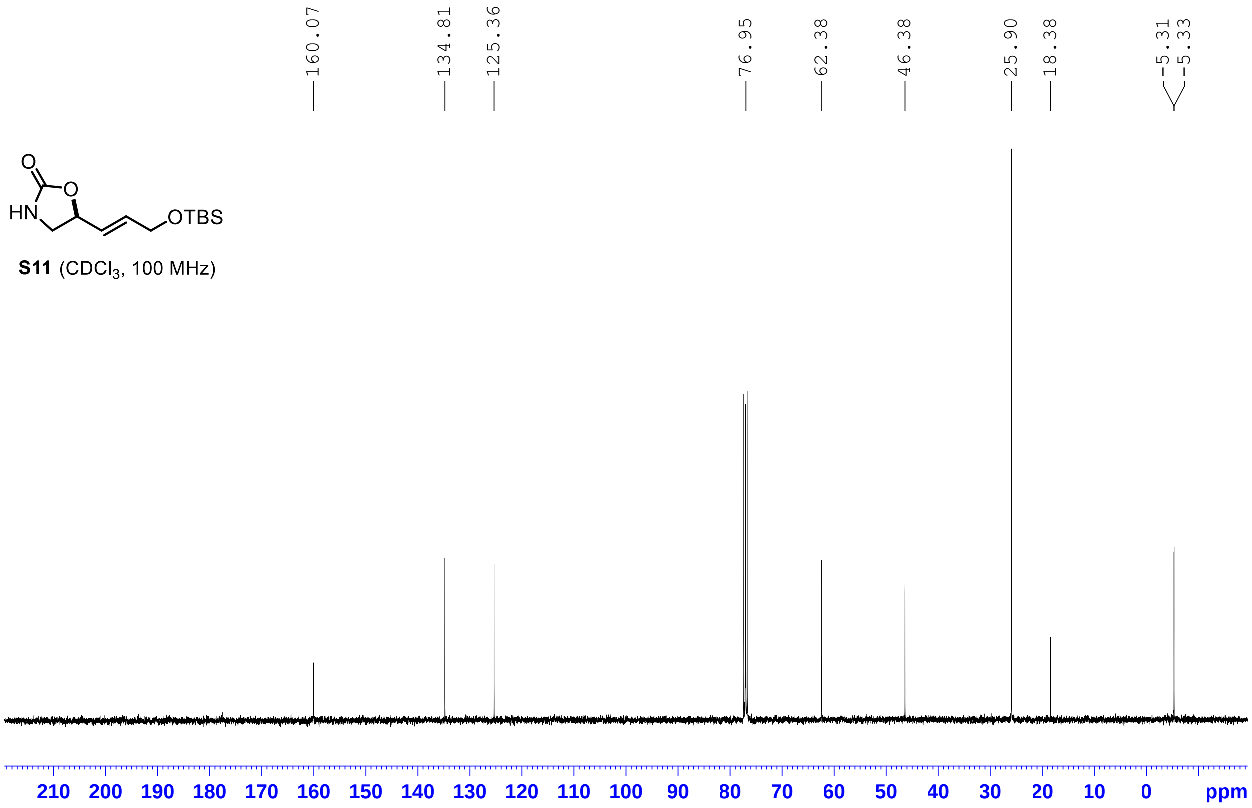
S9 (CDCl$_3$, 100 MHz)


6.455
5.089
4.921
3.552
3.531
3.376
3.355
1.800
1.571
Me
NH
O
O
Me
S10 (CDCl3, 400 MHz)
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
0.98
1.00
1.00
0.97
1.00
2.97
3.01

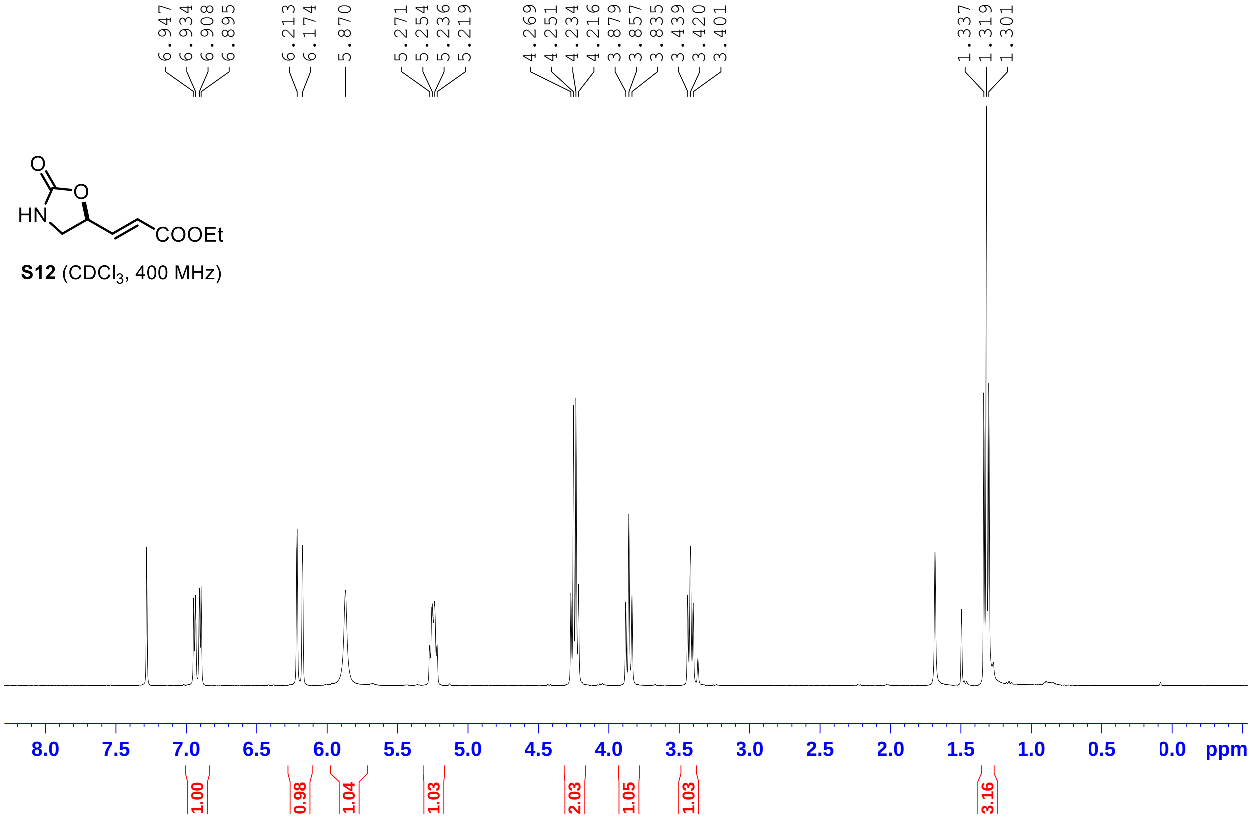

159.60
145.14
111.24
84.16
51.00
25.30
18.21
Me
NH
O
O
Me
S10 (CDCl3, 100 MHz)
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm



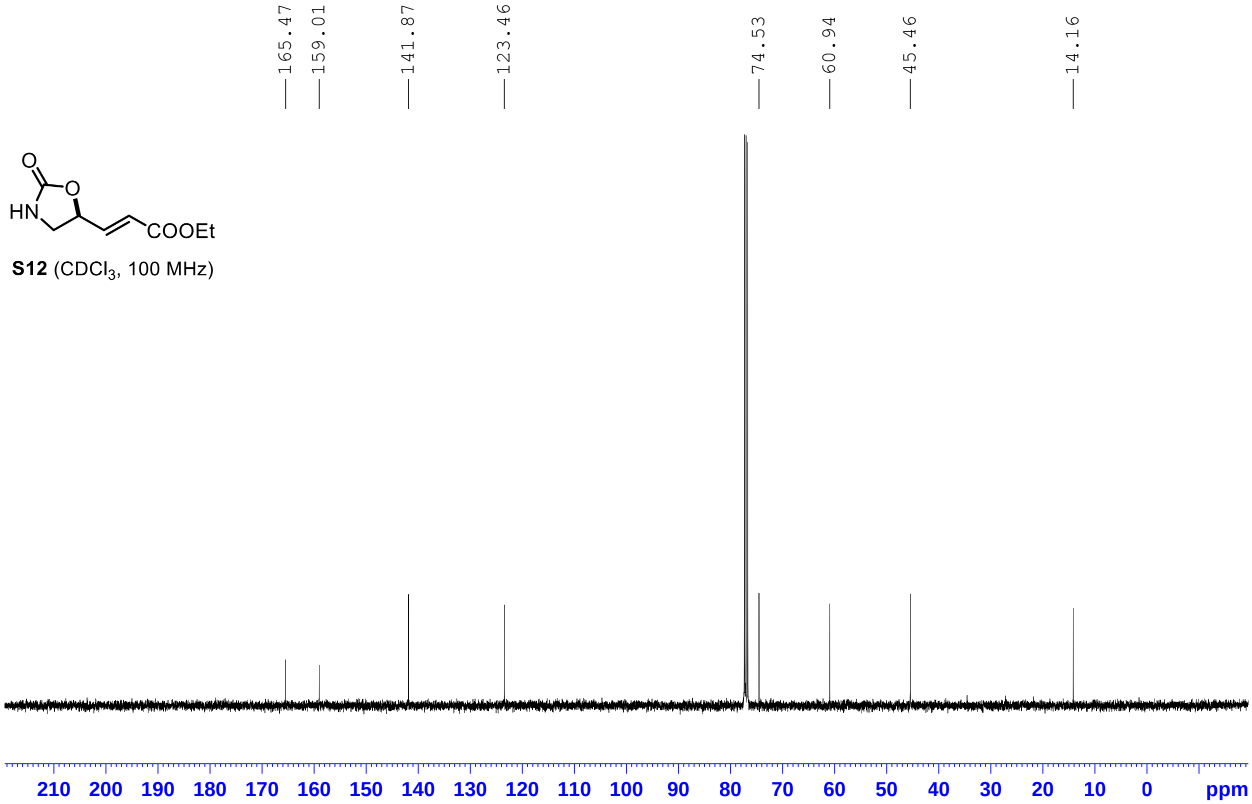
S11 (CDCl$_3$, 400 MHz)



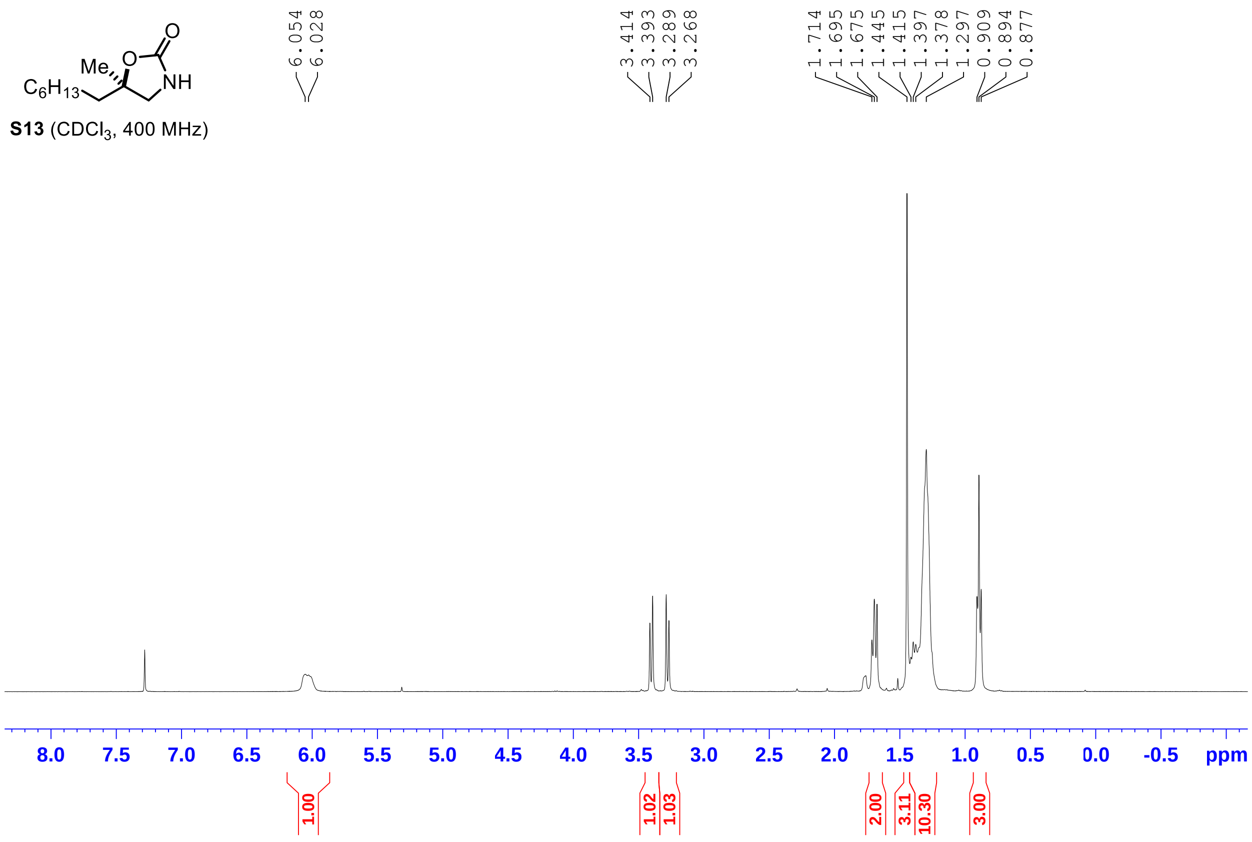
S11 (CDCl$_3$, 100 MHz)



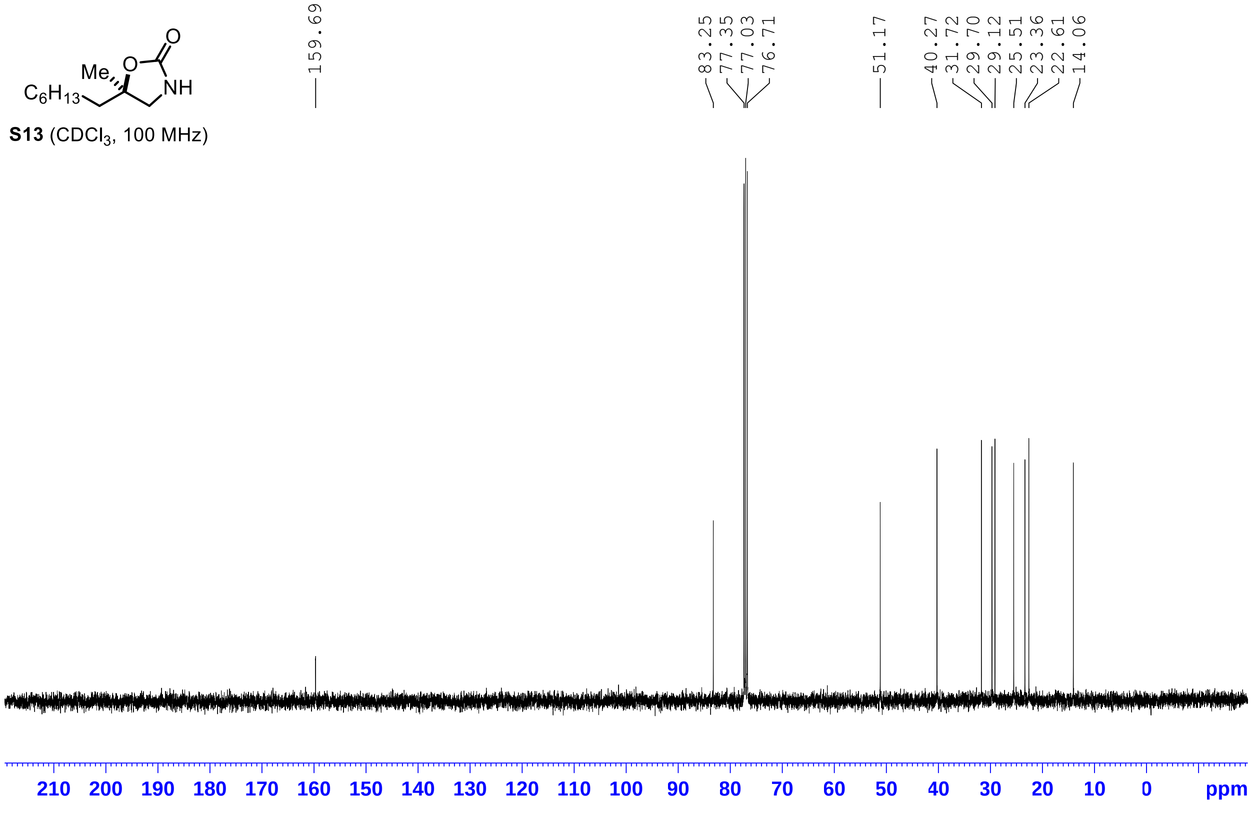
S12 ($CDCl_3$, 400 MHz)



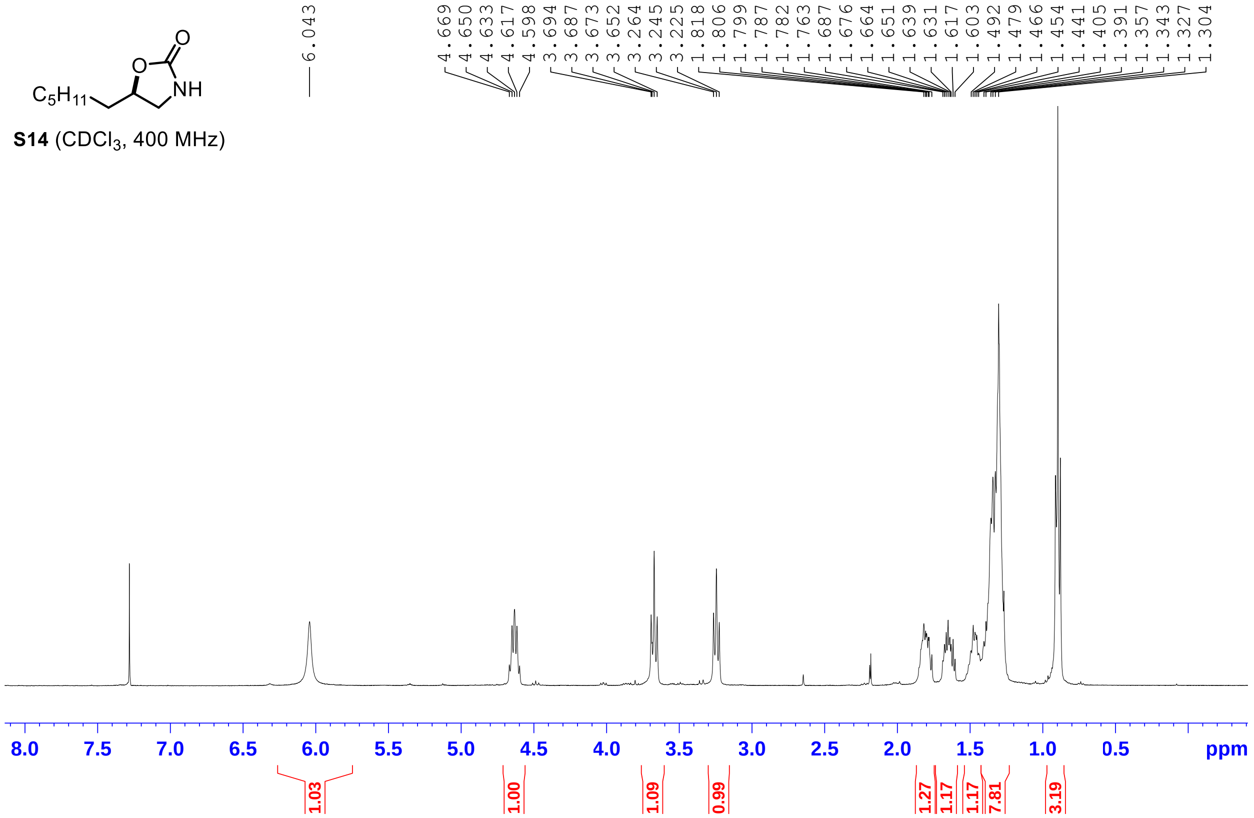
S12 ($CDCl_3$, 100 MHz)



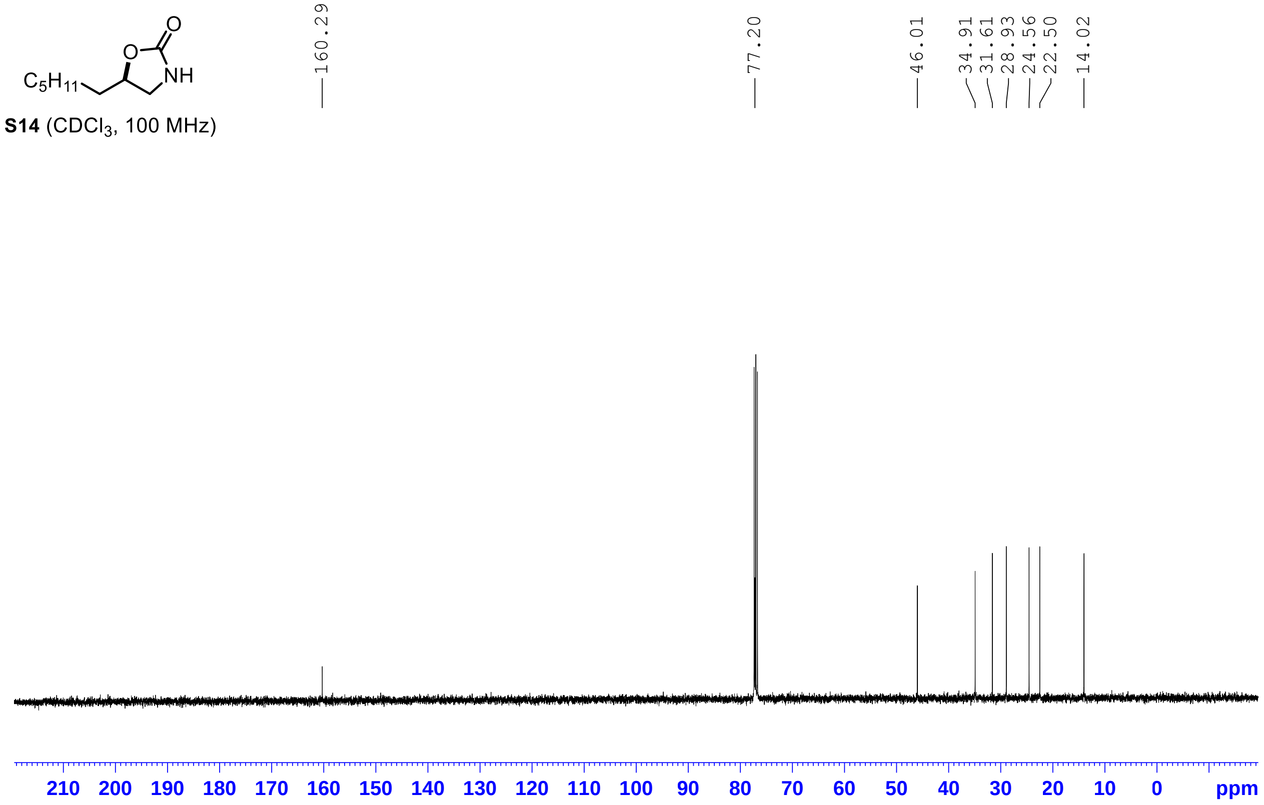
S13 ($CDCl_3$, 400 MHz)



S13 ($CDCl_3$, 100 MHz)



S14 (CDCl$_3$, 400 MHz)



S14 (CDCl$_3$, 100 MHz)