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Secondary-sphere modification in proline catalysis: Old friend, new connection

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Supporting Information

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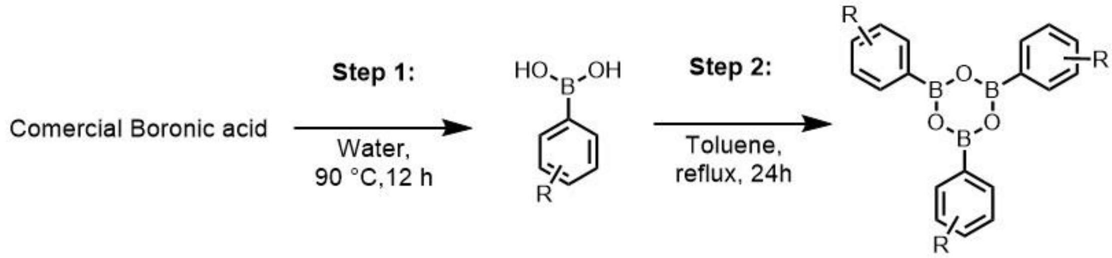
1. General Information

Reagents were purchased from commercial suppliers and used without further purification, unless otherwise stated. All the aldehydes were distilled before use. Anhydrous solvents were prepared from commercial grade (AR), added to molecular sieves (3Å) that were activated by microwave (20% m/v) for 6-7 minutes and then under vacuum with flame. The solvent with molecular sieves was kept under argon for at least 48h before use. For catalytic reactions, the molecular sieves (3, 4 and 5Å) were crushed to powder, weighed and kept in the oven in the reaction vial overnight at 200 ºC, they were then activated by heat gun and cooled to room temperature under argon before use. Thin-layer chromatography (TLC) analysis of reaction mixtures was performed using Merck silica gel 60 F254 TLC plates and visualized under UV or by staining with anisaldehyde stain. Column chromatography was performed on Merck Silica Gel 60 Å, 230 X 400 mesh. Nuclear magnetic resonance (NMR) spectra were recorded using a Bruker DPX400 instrument. ^{1}H and ^{13}C chemical shifts are reported in ppm downfield of tetramethylsilane and referenced to residual solvent peak ($CHCl_3$; $\delta H = 7.26$ ppm and $\delta C = 77.0$ ppm, DMSO; $\delta H = 2.50$ ppm and $\delta C = 39.5$ ppm, ACN; $\delta H = 1.96$ ppm). Multiplicities are reported using the following abbreviations: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet. Solvent abbreviations are reported as follows: EtOAc = ethyl acetate, Hex = hexanes, DCM = dichloromethane, Et_2O = diethyl ether, MeOH = methanol, THF = tetrahydrofuran. Enantiomeric excess was measured on a Shimadzu high performance liquid chromatography, LC-20A series chiral HPLC using Chiralpak IB, IA, IC, AD-H, and AS-H columns.

All raw files for HPLC, Mass spectrometry and NMR analyses presented in this work are provided online:

https://github.com/Milo-group/ChemComm2021

2. Synthesis of Aryl boroxine



Step 1: Synthesis of boronic acid

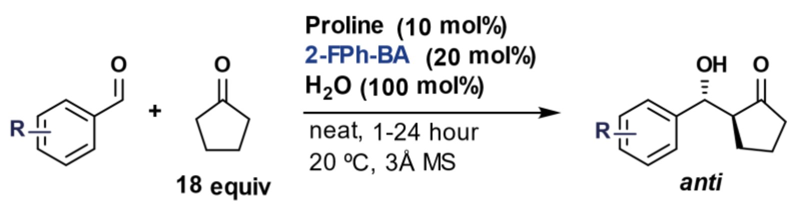
Commercial aryl boroxines are available as a mixture of boronic acid, its dimer and boroxine. To better control the addition of boronic acid to our reaction, we converted the purchased mixture completely to the respective boroxine. This was accomplished by first heating the mixture in water (distilled) for 12 h, at 90 ºC. This yielded the boronic acid as a solid, after filtration. The solid was then brought into a sealed box (or a desiccator) containing Drierite and left to dry for 12 h. Next, the boronic acid was converted to boroxine, following the procedure presented in step 2

Step 2: Boroxine synthesis

In a dry Dean-Stark apparatus equipped with a magnetic stir bar and under argon, the aryl boronic acid prepared in step 1 (16.4 mmol) and anhydrous toluene (70 mL) were added. The mixture was refluxed for 24 h and was allowed to cool to room temperature, followed by evaporation under reduced pressure to furnish boroxine.[1]

3. General Procedure for the Enantioselective Direct Aldol Reaction

Proline (0.05 mmol, 5.8 mg), 2-F-phenyl boroxine (0.0333 mmol, 12.1 mg), 1,3,5-trimethoxybenzene (20 mg, 0.119 mmol), 25 mg of molecular sieves 3 Å, 0.8 mL cyclopentanone and 9 µL H_2O were placed in a screw capped vial under argon. The mixture was stirred for 15 min at ambient temperature followed by addition of aldehyde (0.5 mmol). After completion of the reaction, the reaction mixture was treated with saturated aqueous ammonium chloride solution and the whole mixture was extracted 3 times with $CHCl_3$. The organic layer was dried over sodium-sulfate and concentrated to give a crude residue which was then purified via column chromatography over silica gel using hexane-ethyl acetate or hexane-DCM as an eluent to afford pure product. Diastereoselectivity and yield were determined by 1H NMR analysis of the crude aldol product. The enantiomeric excess (ee) of the aldol product was determined by chiral-phase HPLC analysis. The absolute configuration of aldol products was determined by comparing the values with those previously reported in the literature.[6-9]



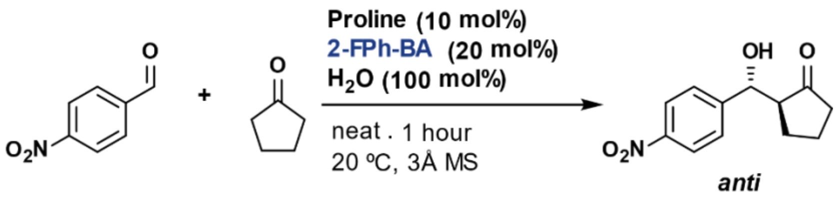
Scheme S1. General aldol Reaction scheme

Lastly, solvent was removed under reduced pressure and the reaction crude was then dissolved in CDCl3 and directly analyzed via 1H NMR for yield and diastereoselectivity determination. From this solution, 0.05 mL was sampled into HPLC vials. The solvent was again removed under high vacuum and the remaining crude was diluted with 1 mL of isopropanol and analyzed via chiral-HPLC for determination of enantioselectivity.

4. Control experiments

These reactions were performed according to the general procedure above, all NMR spectra and HPLC traces are presented below.

Table S1. Control experiments



Deviation from conditions	Yield[a]%		d.r[a]		ee[b]%	
No boronic acid, no H_2O[c]	10	14	0.4:1	0.3:1	n.d	n.d
No boronic acid[d]	36	39	0.6:1	0.7:1	35	37
No proline[f]	0	0	--	--	--	--
No molecular sieves[e]	75	75	11.1:1	11.5:1	97	96
No molecular sieves[e], 77 mol% H_2O	57	57	7.5:1	8.2:1	98	98
No molecular sieves[e], 55 mol% H_2O	40	48	6.2:1	7.2:1	97	97
No molecular sieves[e], 22 mol% H_2O	25	29	4.8:1	6.5:1	96	96
4 Å molecular sieves	86	86	10.1:1	11.0:1	97	96
5 Å molecular sieves	56	59	8.6:1	6.4:1	96	97
No molecular sieves[e], 100 mol% $KCl_{(S)}$	76	79	11.1:1	11.9:1	98	98
No molecular sieves[e],10 mol% 2,6-lutidine	78	80	9.1:1	9.9:1	98	98
No molecular sieves[e], 10 mol% $KHCO_{3(S)}$	69	67	1.3:1	1.2:1	30	37

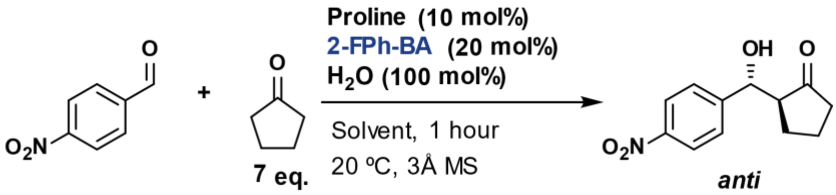
Reaction conditions: Proline (0.05 mmol, 5.8 mg), 2-F-phenyl boroxine (0.0333 mmol, 12.1 mg), 1,3,5-trimethoxybenzene (20 mg, 0.119 mmol), 25 mg of molecular sieves 3 Å, 0.8 mL cyclopentanone, 9 μL H_2O were first mixed together and stirred for 15 min, followed by addition of 0.5 mmol of *p*-nitro benzaldehyde; [a]determined by the crude H^1 NMR; [b]determined by chiral HPLC; [c]Neither water nor boronic acid were added; [d]no boronic acid was added; [e]no molecular sieves were added; [f]no proline

Figure S1. Reaction with addition of boronic acid (left) vs. reaction without boronic acid

5. Solvent screening

A set of 4 different solvent have been tested as a part of the optimization. Results shown below (all NMR spectra and HPLC traces are presented bellow).

Table S2. Reaction Optimization: Solvent screening

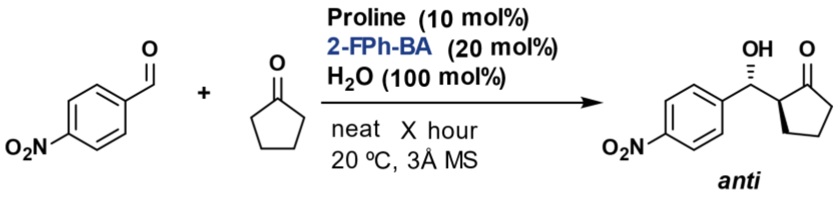


Solvent	Yield[a]%		d.r[a]		ee[b]%	
CH_3CN	17	19	n.d[c]	19.3:1	n.d	n.d
$CHCl_3$	25	32	6.9:1	7.1:1	89	90
MeOH	57	70	5.5	4.0	20	20
Hexane	67	78	3.7	3.9	65	67

Reaction conditions: Proline (0.05 mmol, 5.8 mg), 2-F-phenyl boroxine (0.0333 mmol, 12.1 mg), 1,3,5-trimethoxybenzene (20 mg, 0.119 mmol), 25 mg of molecular sieves 3 Å, 0.2 mL cyclopentanone, 0.6 mL solvent, 9 µL H_2O and 0.5 mmol of *p*-nitro benzaldehyde.; [a]determined by the crude H^1 NMR.; [b]determined by chiral HPLC.; [c] d.r couldn't be determined accurately in the crude mixture.

6. Time optimization

Table S3. Reaction optimization: Time screening

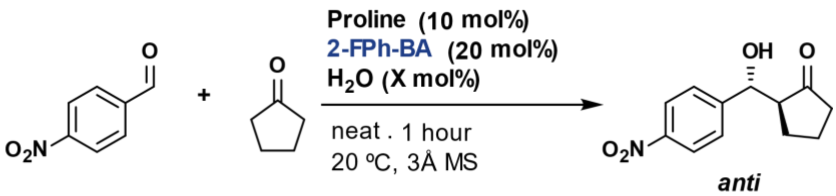


Time (hours)	**Yield[a]%**		**d.r[a]**		**ee[b]%**	
0.5	81	86	9.4:1	9.7:1	96	96
1	98	99	10.6:1	12.8:1	96	96
2	88	93	11.9:1	11.8:1	96	96
4	86	87	8.7:1	8.1:1	96	96
20	87	92	5.9:1	6.3:1	96	96

Reaction conditions: Proline (0.05 mmol, 5.8 mg), 2-F-phenyl boroxine (0.0333 mmol, 12.1 mg), 1,3,5-trimethoxybenzene (20 mg, 0.119 mmol), 25 mg of molecular sieves 3 Å, 0.8 mL cyclopentanone, 9 µL H_2O and 0.5 mmol of *p*-nitro benzaldehyde**.;** [b] determined by the crude H^1 NMR.; [c]determined by chiral HPLC.

7. **Water optimization**

Table S4. Reaction optimization: Screening of amount of water (0-200 mol%)

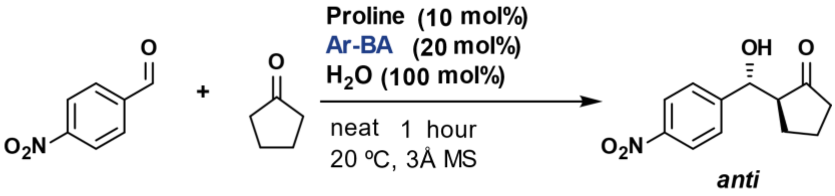


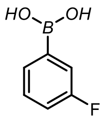
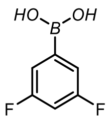
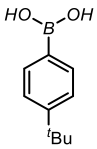
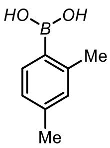
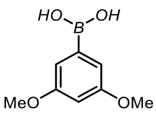
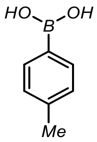
H_2O (mol%)	**Yield[a] %**		**d.r[b]**		**ee[c] %**	
0	31	26	5.1:1	5.2:1	89	90
50	46	47	6.8:1	8.2:1	96	96
100	98	99	10.6:1	12.8:1	96	96
200	98	99	10.0:1	11.2:1	88	90

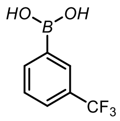
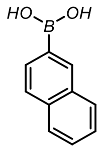
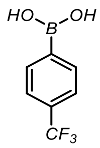
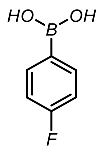
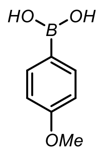
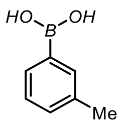
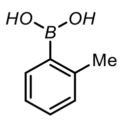
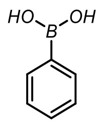
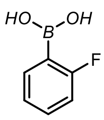
Reaction conditions: Proline (0.05 mmol, 5.8 mg), 2-F-phenyl boroxine (0.0333 mmol, 12.1 mg), 1,3,5-trimethoxybenzene (20 mg, 0.119 mmol), 25 mg of molecular sieves 3 Å, 0.8 mL cyclopentanone, 9 μL H_2O and 0.5 mmol of *p*-nitro benzaldehyde**.;** [a]determined by the crude H^1 NMR; [c]determined by chiral HPLC.

8. Boronic acid screening

Table S5. Reaction optimization: Boronic acid screening



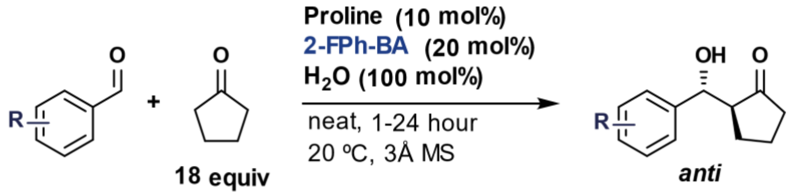
Boronic acid	Yield[a]%		d.r[a]		ee[b]%	
	78	81	10.1:1	10.8:1	96	96
	89	88	11.3:1	9.9:1	98	97
	93	89	3.6:1	3.4:1	90	90
	90	91	3.3:1	3.4:1	92	90
	90	95	6.4:1	6.3:1	92	92
	76	76	3.6:1	3.9:1	90	90

	73	78	9.9:1	10.4:1	96	96
	94	98	6.1:1	6.2:1	92	92
	70	76	3.3:1	3.8:1	92	92
	76	78	6.6:1	6.9:1	94	94
	71	72	3.2:1	3.3:1	90	90
	88	87	4.7:1	5.6:1	90	90
	89	90	4.4:1	4.6:1	98	98
	73	73	5.5:1	5.7:1	92	
	98	99	10.6:1	12.8:1	96	96

Reaction conditions: Proline (0.05 mmol, 5.8 mg), aryl boroxine (0.0333 mmol), 1,3,5-trimethoxybenzene (20 mg, 0.119 mmol), 25 mg of molecular sieves 3 Å, 0.8 mL cyclopentanone, 9 µL H_2O and 0.5 mmol of *p*-nitro benzaldehyde**.** [a]determined by the crude H^1 NMR; [b]determined by chiral HPLC.

9. **Aldehyde scope**

Table S6. Reaction scope

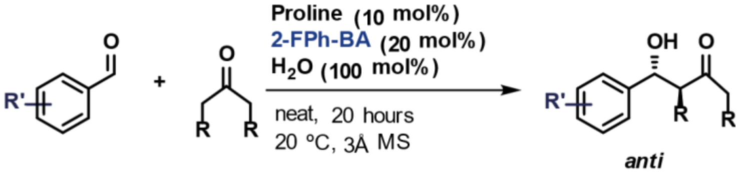


Benzaldehyde	Reaction Time (hours)	Yield[a]%		ee [c]%		d.r[b]	
4-NO_2	1	99	98	96	96	12.7:1	11.7:1
4-I	1	92	89	94	94	10.1:1	9.7:1
4-Cl	24	78	78	93	94	6.34:1	6.14:1
2-F	1	85	83	97	98	17.2:1	17.9:1
2-Cl	1	91	93	96	96	9.7:1	9.2:1
2-Br	1	78	75	92	94	10.1:1	9.0:1
4-CF_3	1	86	88	95	94	9.5:1	8.5:1
-H	24	90	89	89	90	5.5:1	5.3:1
3-Ome	24	81	82	92	92	6:1	6.4:1
4-Me	24	83	81	88	90	6.4:1	5.4:1
2-Ome	24	87	88	89	89	4.8:1	4.8:1
3-Cl	1	89	88	94	95	7.5:1	6.2:1
Thiophene	24	81	83	92	92	6.5:1	6.3:1
Furfural	24	88	88	88	86	4.6:1	4.5:1

Reaction conditions: Proline (0.05 mmol, 5.8 mg), 2-F-phenyl boroxine (0.0333 mmol, 12.1 mg), 1,3,5-trimethoxybenzene (20 mg, 0.119 mmol), 25 mg of molecular sieves 3 Å, 0.8 mL cyclopentanone, 9 µL H_2O and 0.5 mmol of aryl aldehyde; [a]isolated yield; [b]determined by the crude H[1] NMR; [c]determined by chiral HPLC.

10. Additional ketones as donors

Table S7. Ketone scope



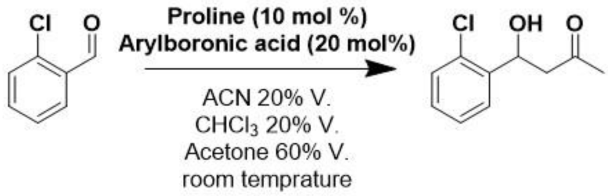
Ketone donor	Benzaldehyde	Yield[a]%		ee [c]%		d.r[b]	
Cyclo-hexanone	**4-NO_2**	90	88	98	98	12.3:1	14.3:1
	4-CF_3	>99	>99	98	98	15.1:1	18.5:1
	4-CN	90	97	98	98	18.5:1	20.0:1
	2-OMe	71	71	98	98	3.3:1	4.6:1
	4-Cl	81	84	93	93	11.8:1	13.4:1
Acetone	**4-NO_2**	63	64	68	66	--	--
	4-CN	60	59	67	68	--	--
	2-OMe	24	21	68	67	--	--
Cyclo-heptanone	**4-NO_2**	n.d	n.d	--	--	--	--

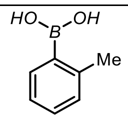
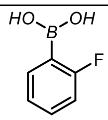
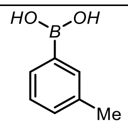
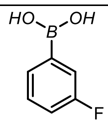
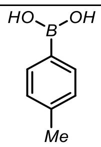
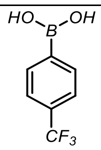
Reaction conditions: Proline (0.05 mmol, 5.8 mg), 2-F-phenyl boroxine (0.0333 mmol, 12.1 mg), 1,3,5-trimethoxybenzene (20 mg, 0.119 mmol), 25 mg of molecular sieves 3 Å, 0.8 mL ketone, 9 µL H_2O and 0.5 mmol of aryl aldehyde; [a]isolated yield; [b]determined by the crude H^1 NMR; [c]determined by chiral HPLC. n.d = no product detected.

11. Boronic acid screening for acetone as aldol donor

The selection of 2-fluoroboronic acid as secondary sphere modifier was made on the basis of the optimization presented below. In this optimization, acetone was used as aldol donor and it was part of our preliminary investigation on the feasibility of this project. As seen bellow, both 2-F and 4-CF_3 were good candidates to proceed with our reaction optimization.

Table S8. Preliminary results: Boronic acid screening.



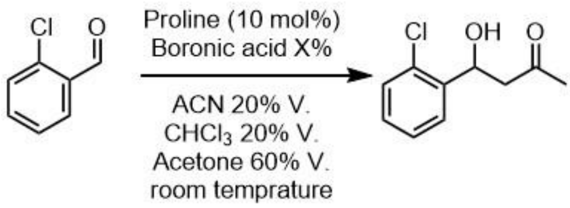
Boronic Acid	Yield[a] %		ee[b] %	
	83	83	57	55
	90	92	60	62
	78	79	53	56
	88	88	57	59
	84	81	55	56
	87	93	61	60

Reaction conditions: Proline (0.05 mmol, 5.8 mg), phenyl boroxine (0.0333 mmol, 12.1 mg), 0.8 mL of a solvent mixture (20%DMSO / 20% CHCl / ;60% acetone), 0.5 mmol of aryl aldehyde; [a]isolated yield; [b]determined by chiral HPLC.

12. Screening of boronic acid / proline ratio using acetone as a substrate

The selection of the ratio of 2:1 of 2-fluoroboronic acid to proline was made on the basis of the optimization presented below. In this optimization, acetone was used as aldol donor and it was part of our preliminary investigation on the feasibility of this project. As seen bellow, a ratio of 1:1 led to a slight decrease in e.e., whereas a ratio higher than 2:1boronic acid to proline led to decreased yields. In all cases when the yield was lower unreacted aldehyde accounts for >95% of the remaining mass balance.

Table S9. Preliminary results: Boronic acid / proline ratio screening.



Boronic Acid	**Yield^a %**		**ee^b %**	
1 eq	91	91	56	60
2 eq	88	89	66	68
4 eq	66	61	62	66
6 eq	45	33	66	70

Reaction conditions: Proline (0.05 mmol, 5.8 mg), phenyl boroxine (xx mmol, xx mg), 0.8 mL of a solvent mixture (20%DMSO / 20% CHCl / 60% acetone), 0.5 mmol of aryl aldehyde; [a]isolated yield; [b]determined by chiral HPLC.

13. Mechanistic investigation

13.1 NMR studies

CD_3CN was used as NMR solvent. The following measurements were performed with a D1= 50, at 20 ºC and with the same concentration as used in the general procedure.

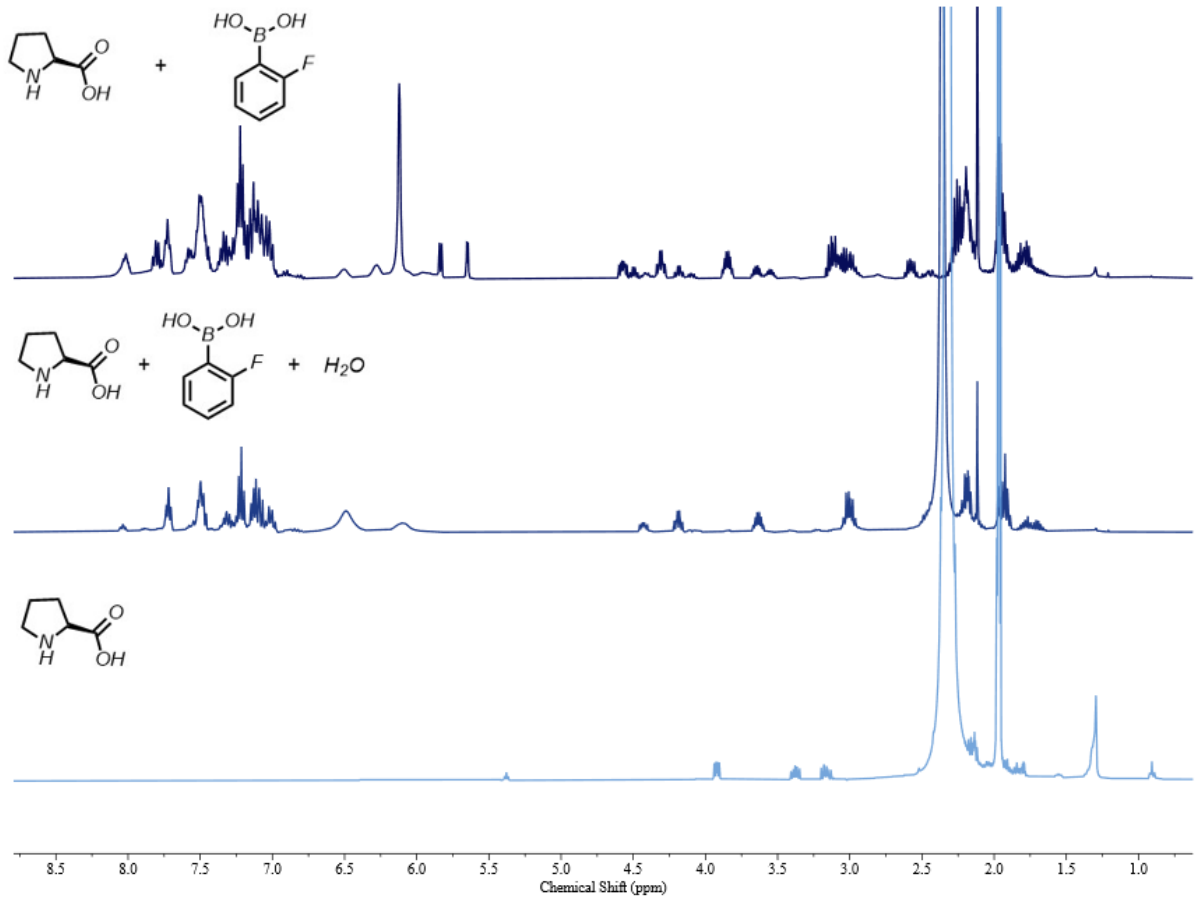


Figure S2. NMR studies (full spectra): **Bottom** - Proline + H_2O; **Middle** - Proline + 2-Fluorophenyl boroxine + H_2O; **Top** - Proline + 2-Fluorophenyl boroxine

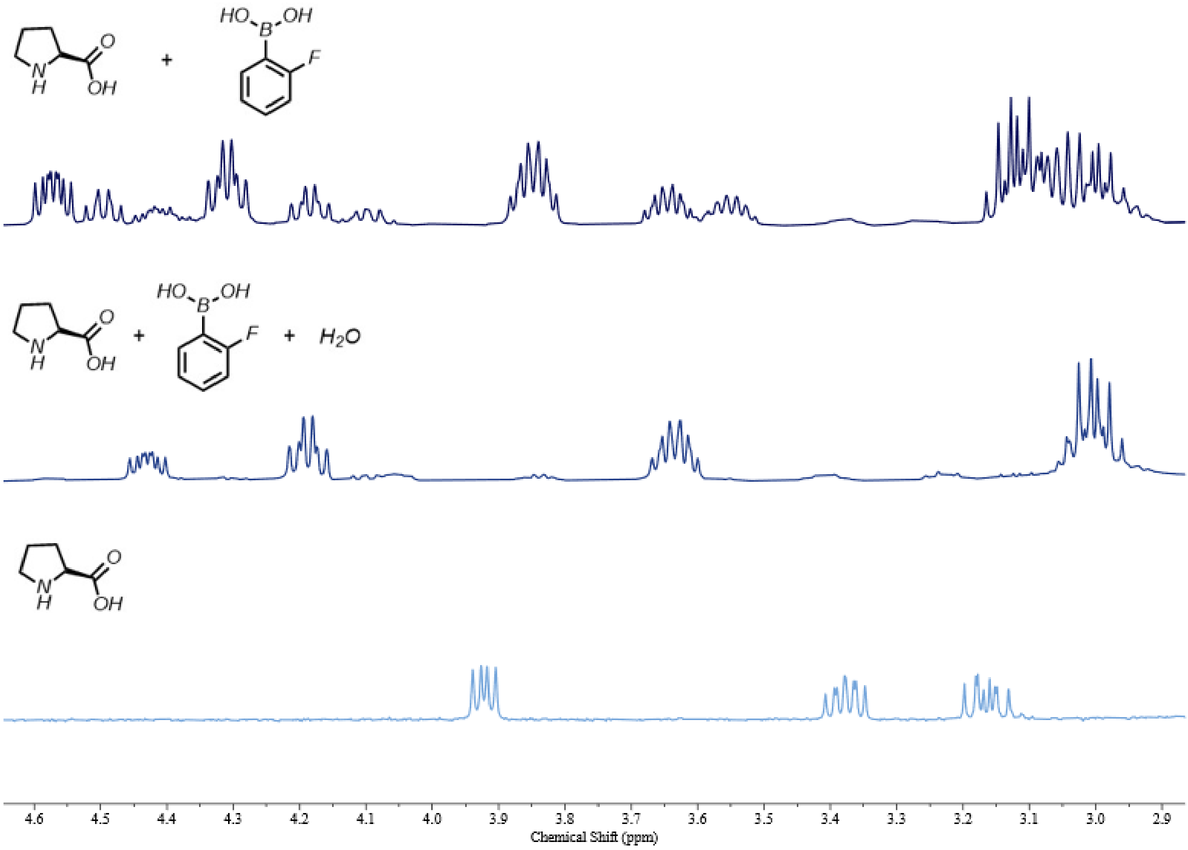


Figure S3. NMR studies (zoom in between 2.8 and 4.7 ppm): **Bottom** - Proline + H_2O; **Middle** - Proline + 2-Fluorophenyl boroxine + H_2O; **Top** - Proline + 2-Fluorophenyl boroxine

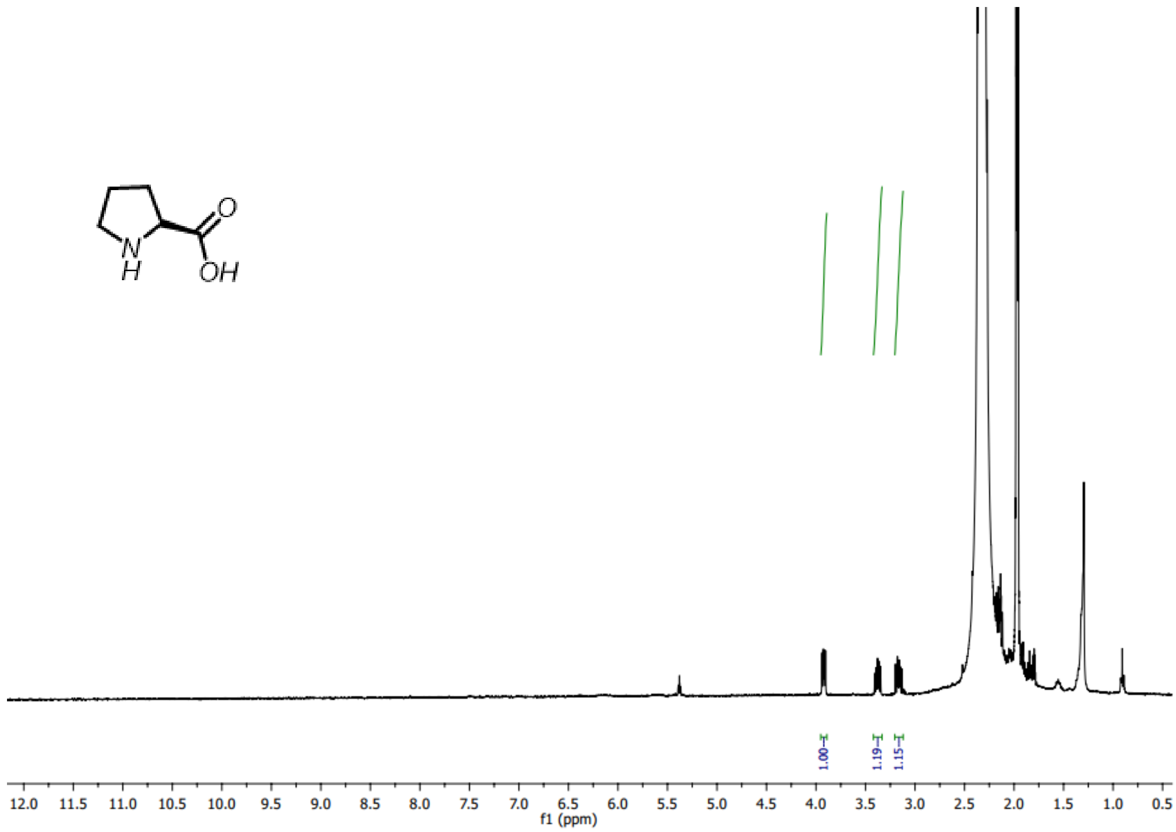


Figure S4. NMR studies (full spectra): Proline + H_2O.

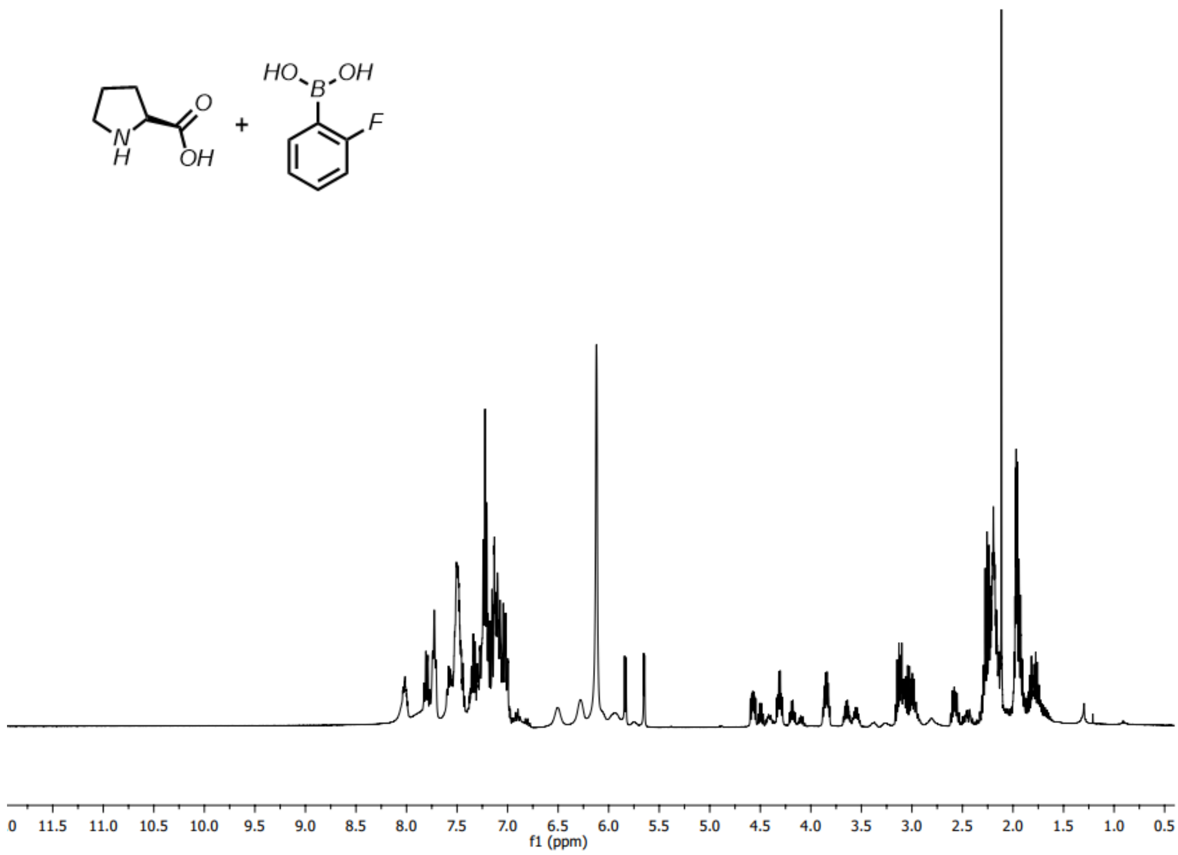


Figure S5. NMR studies (full spectra): Proline + 2-fluorophenylboronic acid.

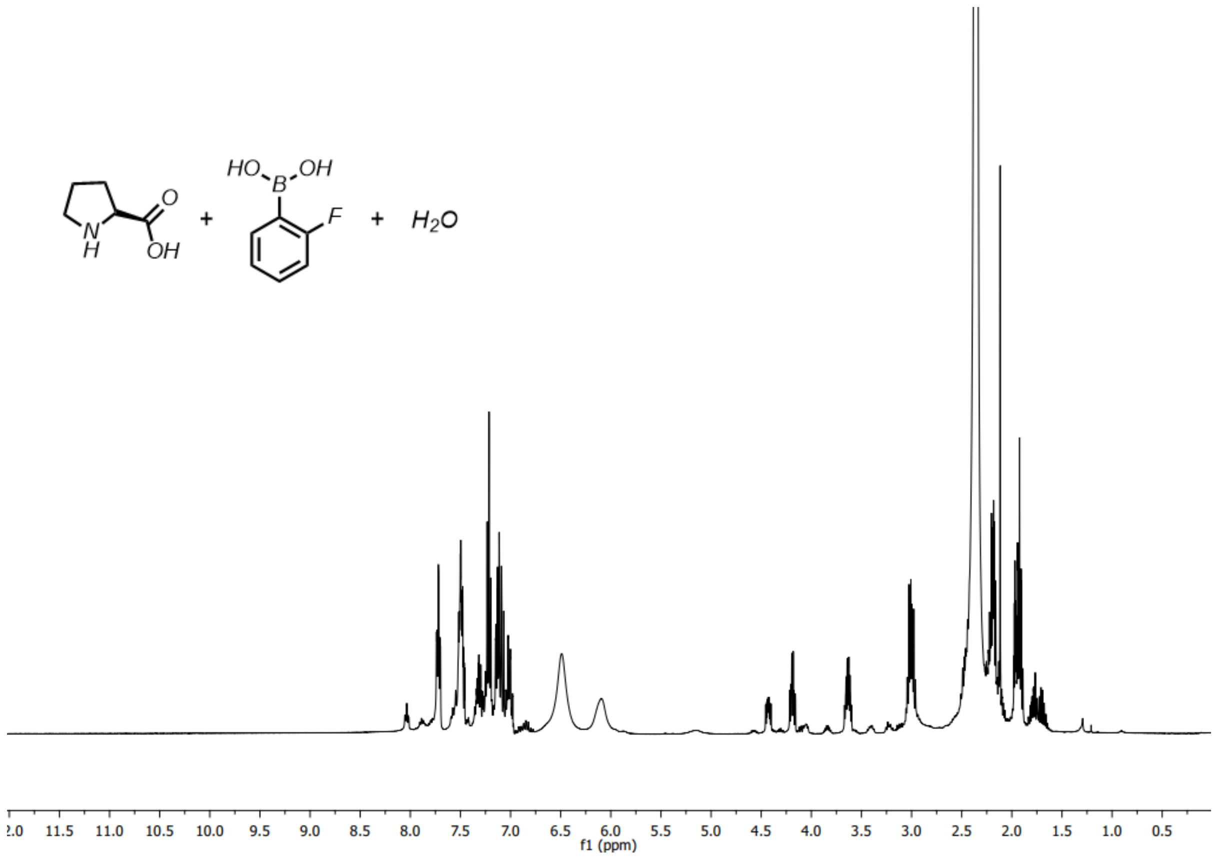
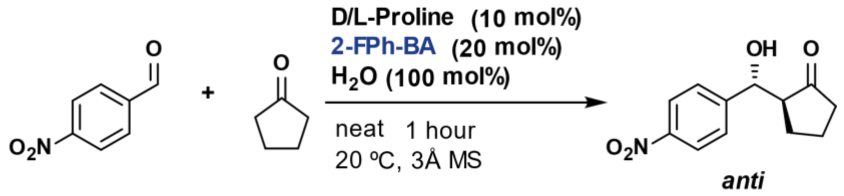


Figure S6. NMR studies (full spectra): Proline + 2-fluorophenylboronic acid + water.

13.2 Non-linear experiments (NLE)

These reactions were performed according to the general procedure. Reactions were run with a scalemic mixture of catalyst. A graph was plotted of the average %ee of the product versus the $\%ee_{cat}$. A non-linear effect was not observed in this system.

Table S10. Non-linear experiments



D-proline (mg)	L-proline (mg)	$\%ee_{cat}$	ee [a] %
0	5.8	99	96
0.725	5.075	75	74.4
1.45	4.35	50	51
2.175	3.625	25	29
2.9	2.9	0	1

Reaction conditions: Proline (0.05 mmol, 5.8 mg), 2-F-phenyl boroxine (0.0333 mmol, 12.1 mg), 1,3,5-trimethoxybenzene (20 mg, 0.119 mmol), 25 mg of molecular sieves 3 Å, 0.8 mL cyclopentanone, 9 μL H_2O and 0.5 mmol of aryl aldehyde; [a]determined by chiral HPLC.

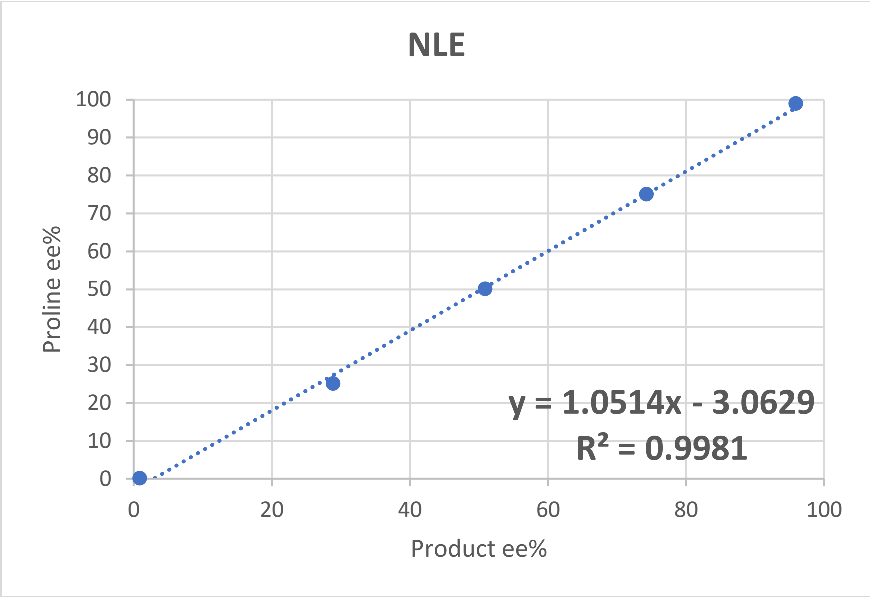
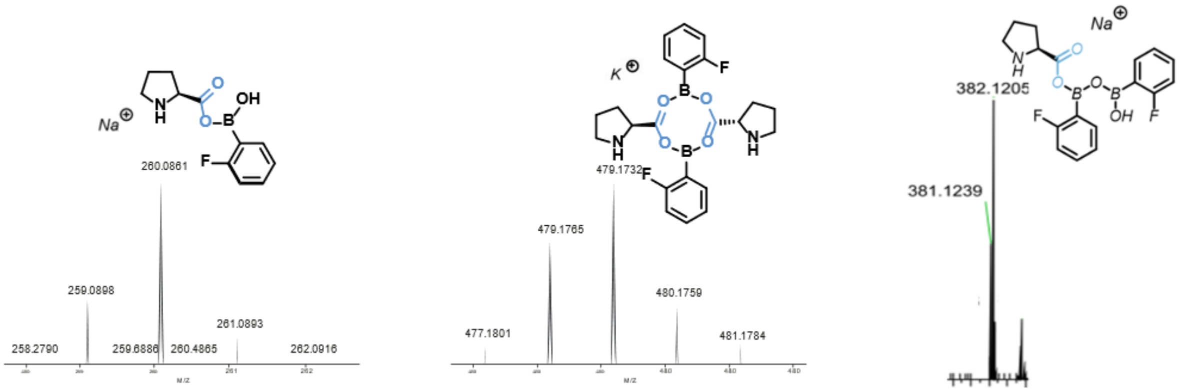


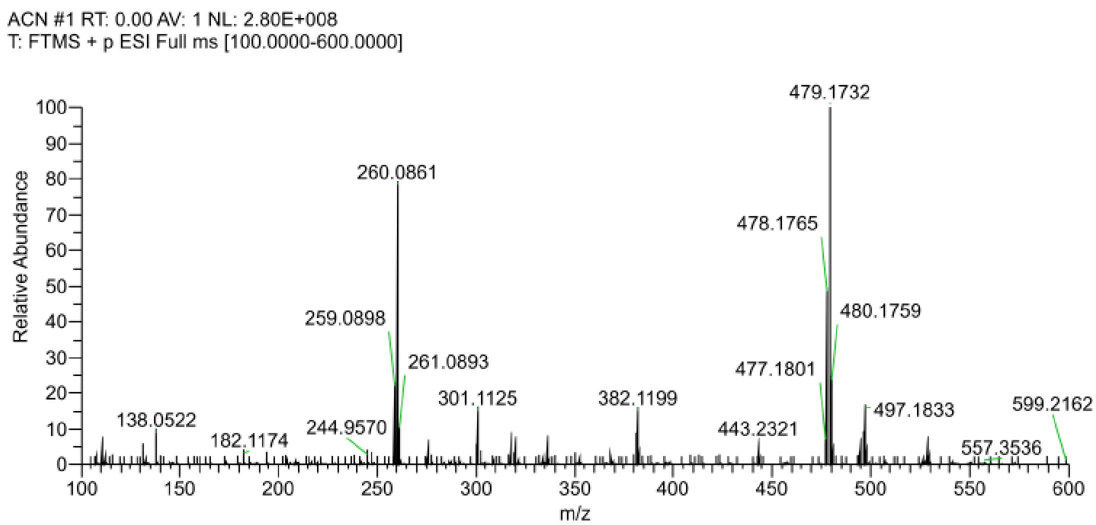
Figure S7. Non-linear experiment plot

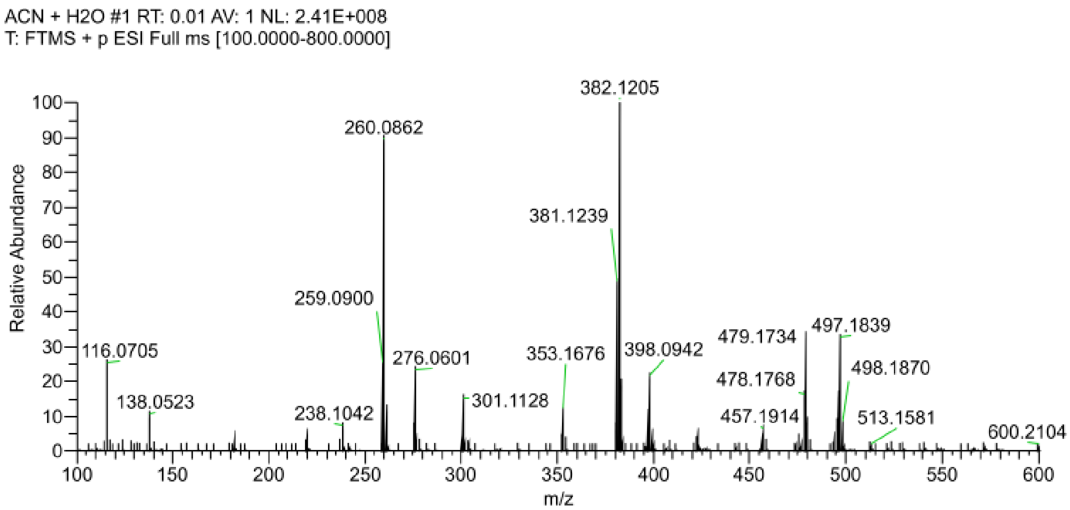
13.3 High-resolution MS experiments

CH_3CN used as a solvent. A mixture of 1 to 1 proline and 2-Fluorophenyl boroxine diluted with the solvent and injected to the machine. In addition, a similar sample made but with stochiometric amount of H_2O.
a. without water

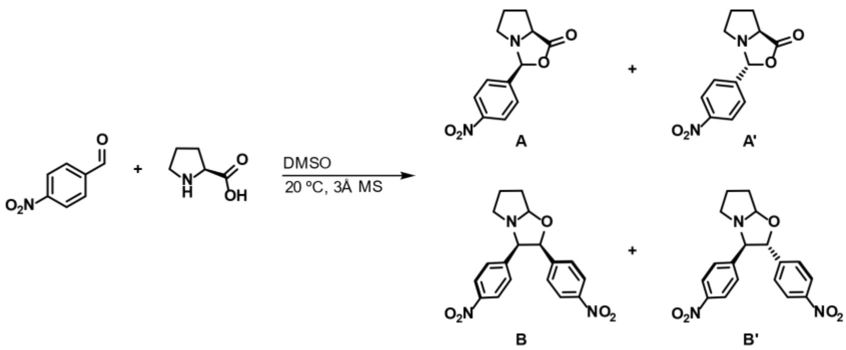


b. with water





13.4 Influence of boronic acid and water on the reaction intermediates



In previous work,[2–4] several reaction intermediates that are considered unreactive have been identified, of those, the main ones are oxazolidinones that can decompose reversibly back to proline (A and A') and oxapyrrolizidines (B and B') that are formed irreversibly. To probe the influence of our reaction conditions on the formation of these intermediates we conducted the following experiments.

We first performed a stoichiometric experiment between proline and *p*-nitro benzaldehyde at a 1:1 ratio to isolate the different products. **Procedure:** proline (58 mg, 0.5 mmol), and *p*-nitro benzaldehyde (76 mg, 0.5 mmol) were placed in screw capped vial loaded with a magnetic stir bar. 3 ml of DMSO were added and the mixture was stirred for 24 hours. Upon aqueous work-up and column chromatography we isolated B and B' (clean on pages S112-S115), while A and A' could not be purified. This procedure was based on previous literature.[4]

At the second step we conducted a set of 4 NMR experiments to probe the influence of each reaction component on the formation of the different intermediates:

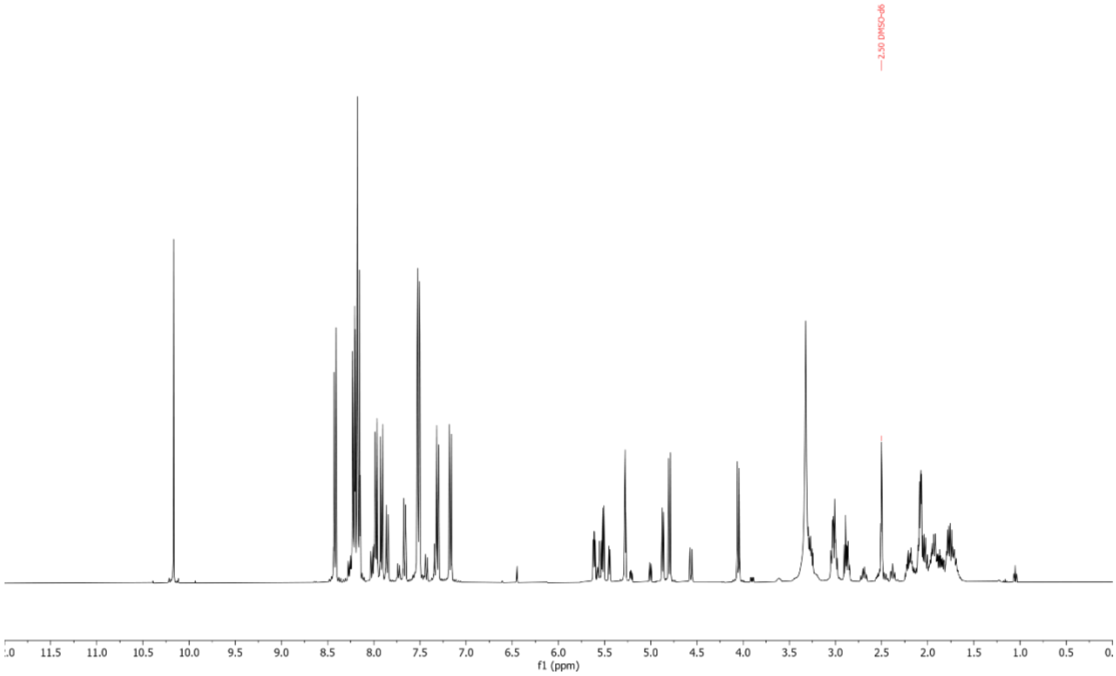
1. To a 1:1 mixture of proline and aldehyde we added 2 equiv of boronic acid. This was followed by adding 10 equiv of water
2. To a 1:2 mixture of proline and boronic acid (respectively) we added 1 equiv of aldehyde
3. To a 1:2:10 mixture of proline, boronic acid and water (respectively) we added 1 equiv of aldehyde
4. To a 1:10 mixture of proline and water (respectively) we added 1 equiv of aldehyde

In the next pages we will provide the procedure and NMR spectra for each of these experiment.

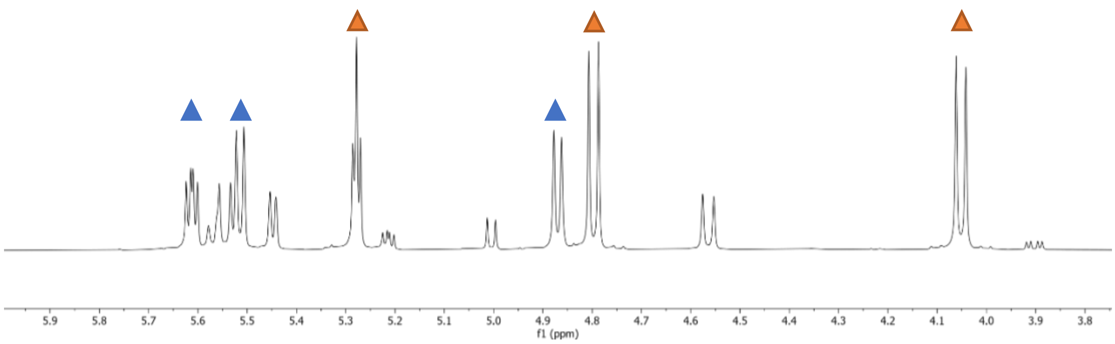
1. **(a)** 1:1 proline (0.03 mmol) to *p*-nitro benzaldehyde (0.03 mmol) in 0.5 ml of $DMSO_{d6}$ were mixed for 5 minutes and then NMR spectrum was recorded. **(b)** 2 equivalent of 2-F phenylboronic acid was added and an NMR spectrum was recorded after 5 minutes. **(c)** 10 equivalent of H_2O was added and again an NMR spectrum was recorded after 5 minutes.

Crude NMR spectra:

Figure S8. 1(a) proline and aldehyde (1:1)



Zoom-in

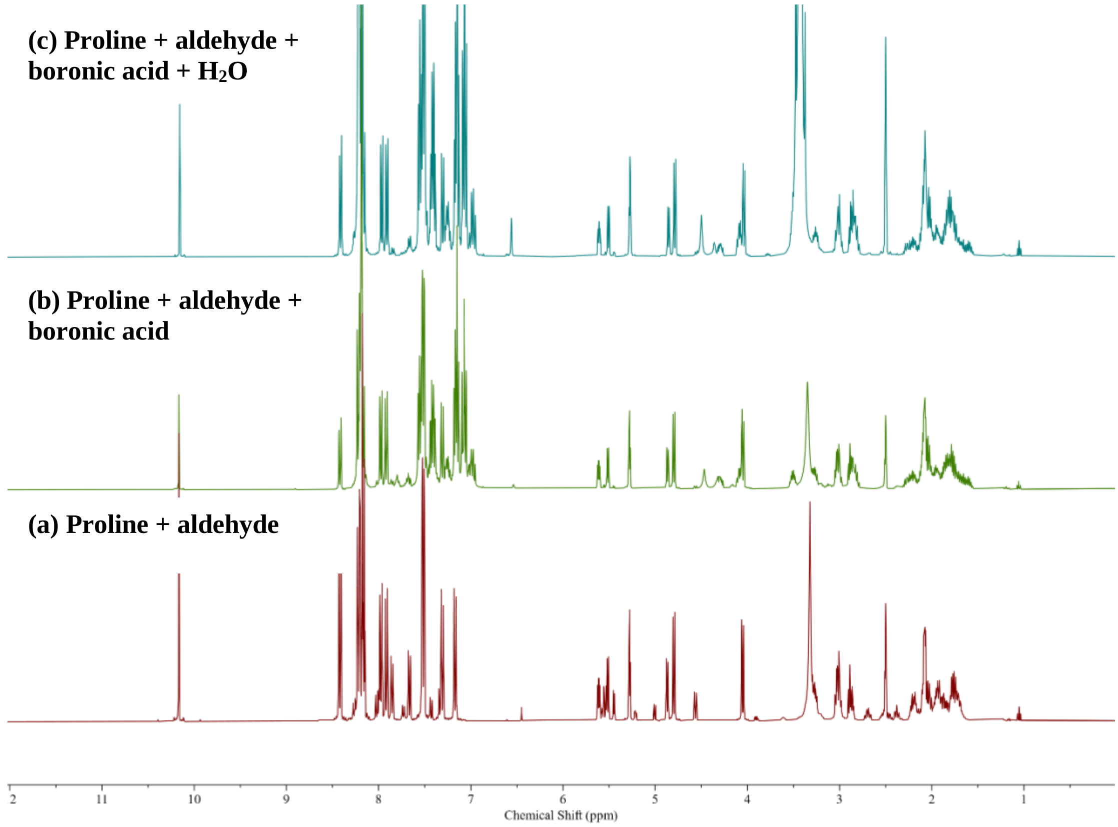


Peaks marked with ▲ corresponded to the *anti* **oxapyrrolizidine (B).**

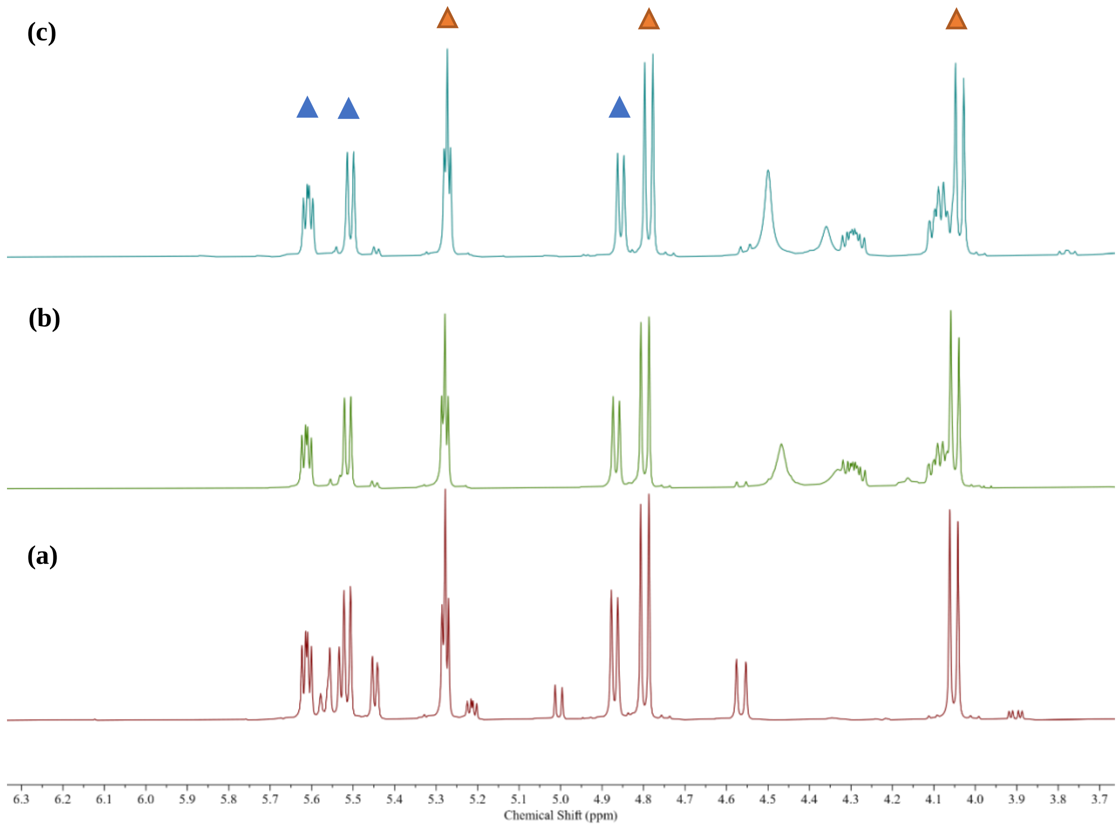
Peaks marked with ▲ corresponded to the *syn* **oxapyrrolizidine (B').**

The rest of the peaks are assumed to be the reversible oxazolidinones based on similarity to literature.[4] As shown in the following figure, these peaks disappeared after the addition of boronic acid, while the irreversible peaks were not affected even after the addition of H_2O, as expected. The additional peaks between 4.1 to 4.5 ppm correspond to the species forming between the boronic acid and proline.

Figure S9. 1(a-c)



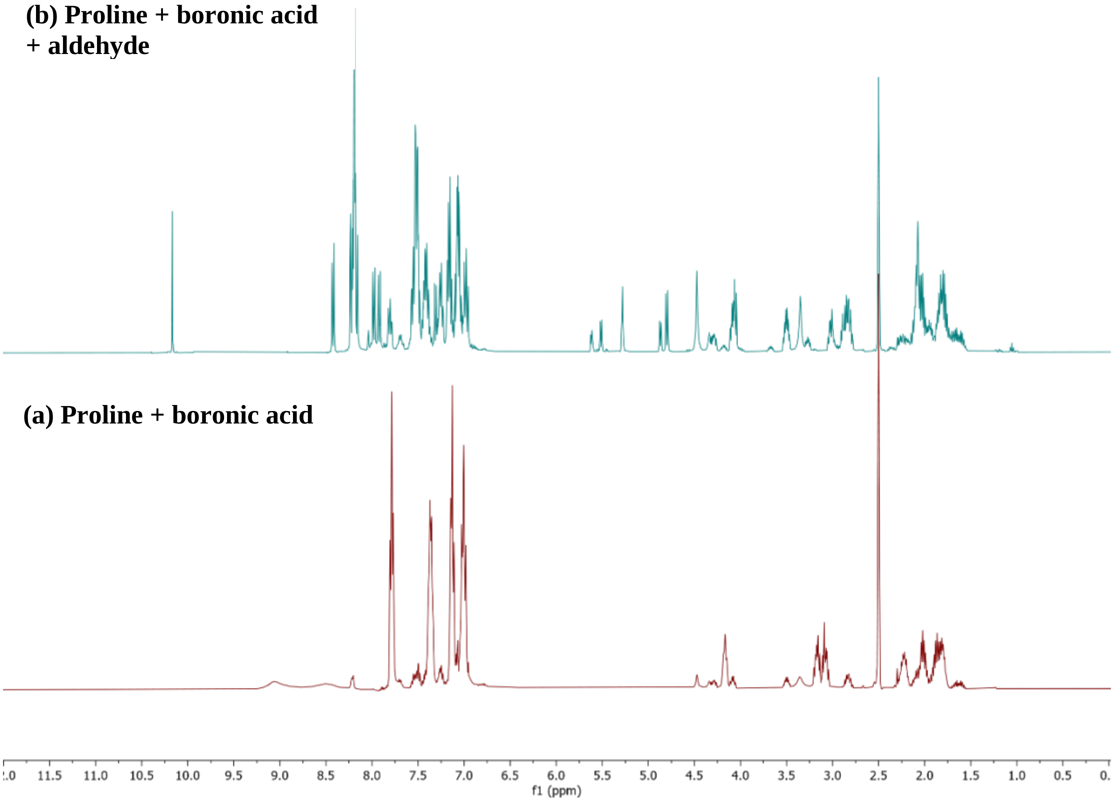
Zoom-in



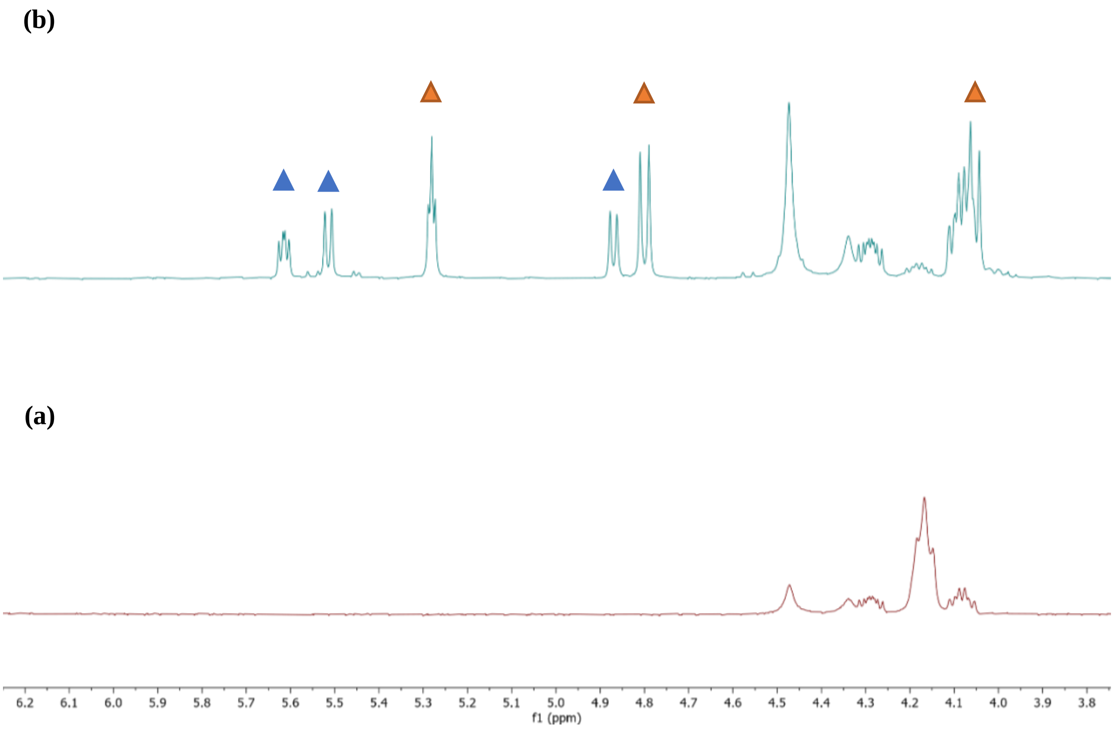
2. **(a)** 1:2 proline to 2-FPh boronic acid in $DMSO_{d6}$ for 5 minutes then NMR spectrum was recorded. **(b)** 1 equivalent of p-nitro benzaldehyde was added and an NMR spectrum was recorded after 5 minutes.

From this experiment we see that the change in the order of addition does not affect the formation of the irreversible side product.

Figure S10. 2(a-b)



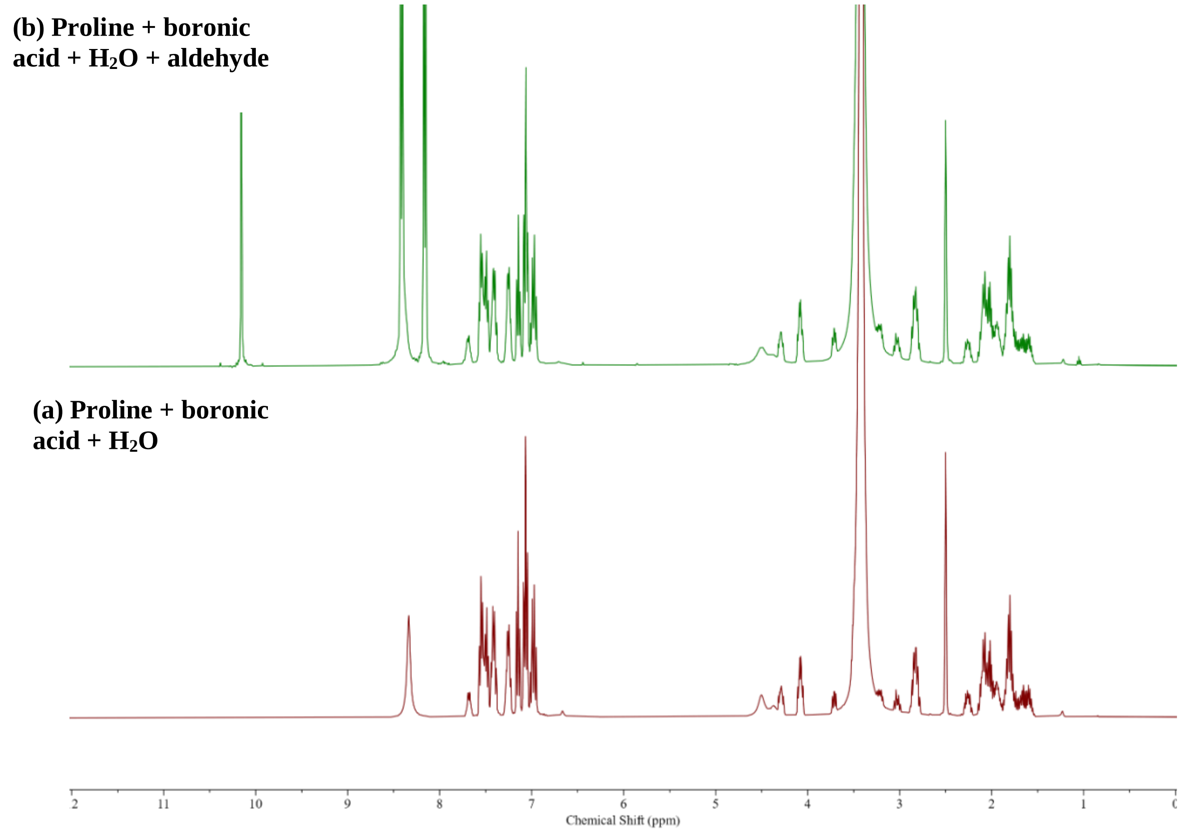
Zoom-in



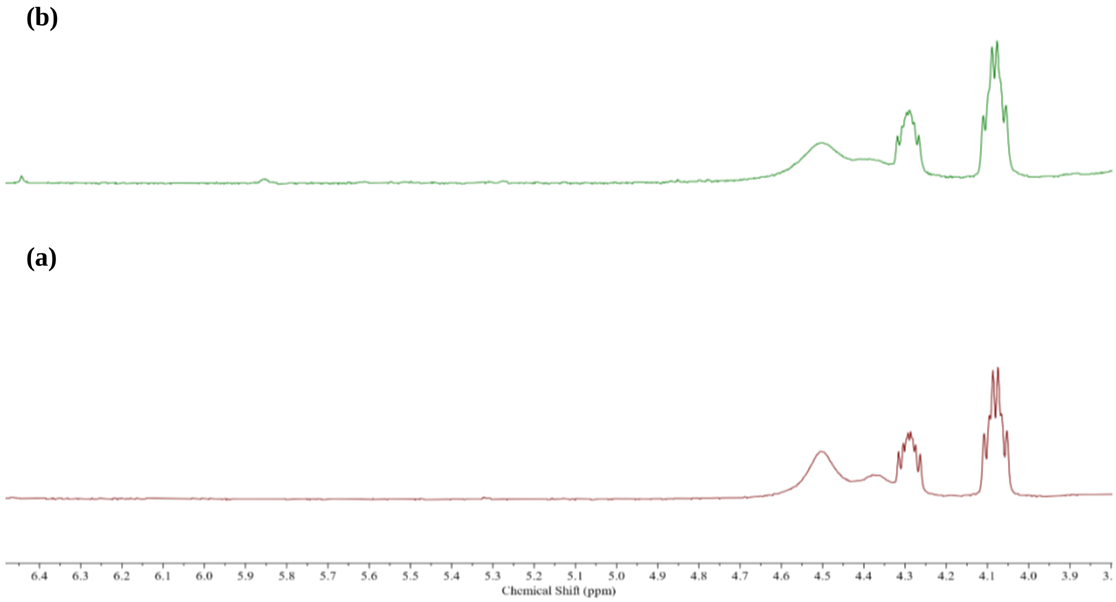
3. **(a)** 1:2:10 of proline, 2-FPh boronic acid, and H_2O were mixed in $DMSO_{d6}$ for 5 minutes then an NMR spectrum was recorded. **(b)** 1 equivalent of *p*-nitro benzaldehyde was added, and then an NMR spectrum was recorded after 5 minutes.

These results showed that upon prior addition of boronic acid and water no formation of both reversible and irreversible side products.

Figure S11. 3(a-b)



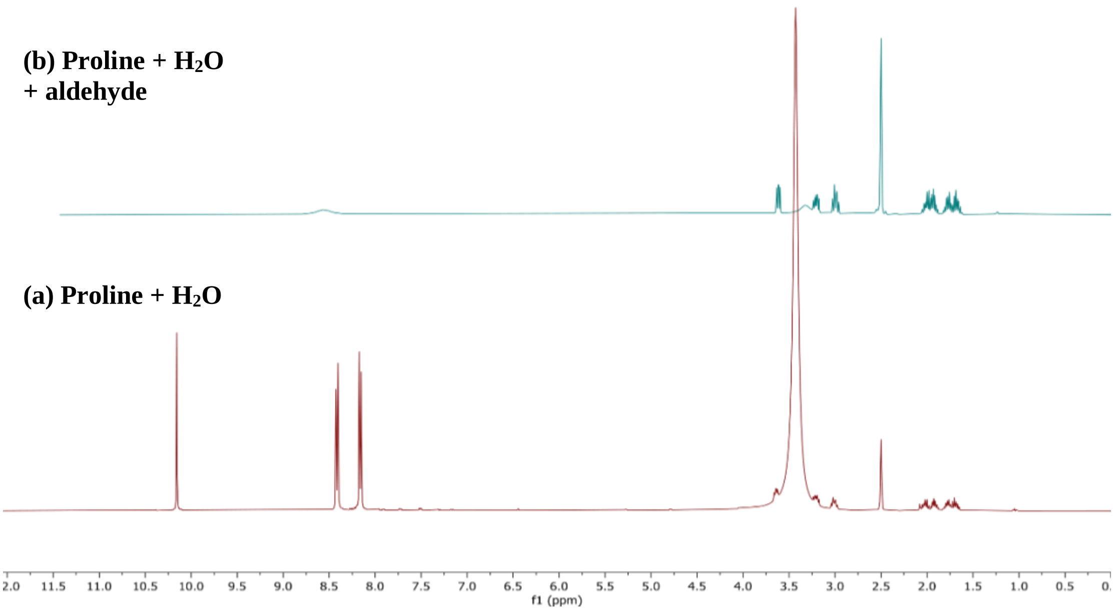
Zoom-in



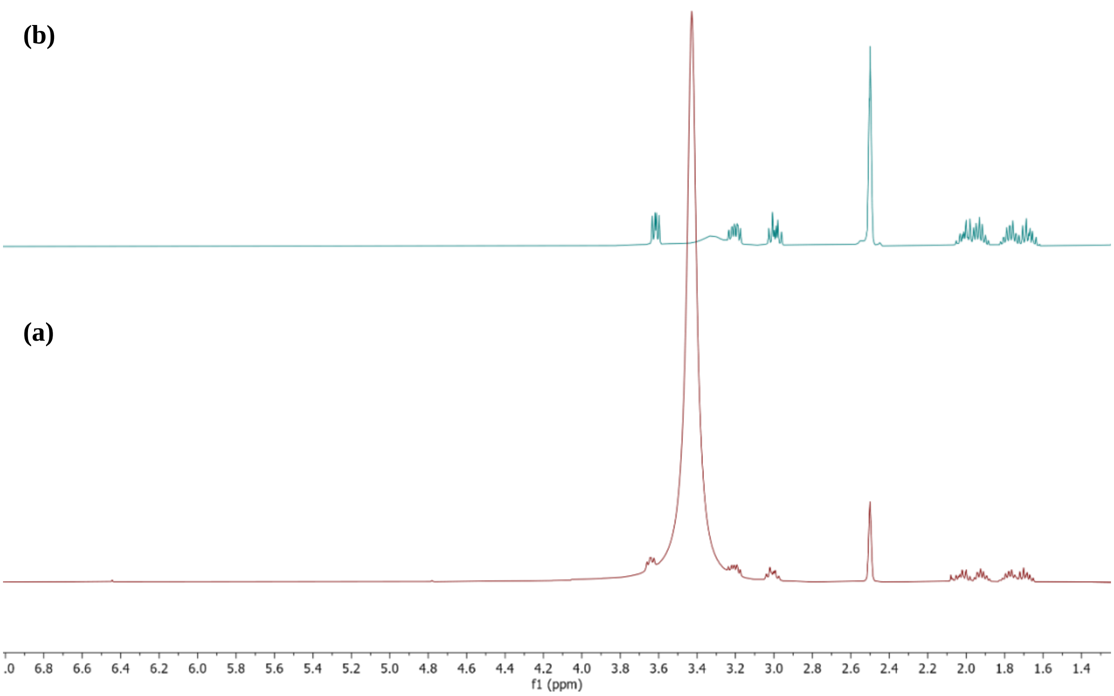
4. **(a)** 1:10 proline and H_2O was mixed in $DMSO_{d6}$ for 5 minutes then an NMR spectrum was recorded. **(b)** 1 equivalent of *p*-nitro benzaldehyde was added, and an NMR was spectrum recorded after 5 minutes.

The results from this control experiment show that water alone can suppress the formation of both reversible and irreversible side-product. This conclusion fits with previous work by Blackmond and coworkers[4] which also observed the suppression of side products when adding water to the catalytic proline system.

Figure S12. 4(a-b)



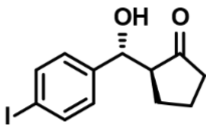
Zoom-in



14. Characterization

All of the compound prepared according to the procedure mentioned below and compared to literature[5–8].

<u>*p*-iodo benzaldehyde</u>

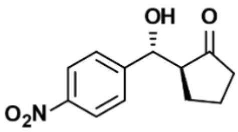


The resulting pure product was examined by ^{1}H and ^{13}C NMR. The spectroscopic NMR data agree with the previously reported ones.

^{1}H NMR (400 MHz, CDCl3) δ 7.61 (d, J = 8.3 Hz, 2H), 7.03 (d, J = 8.3 Hz, 2H), 4.59 (d, J = 9.1 Hz, 1H), 4.49 (s, 1H), 2.45 – 2.25 (m, 2H), 2.17 (ddd, J = 19.5, 10.8, 9.0 Hz, 1H), 1.96 – 1.84 (m, 1H), 1.66 (dddd, J = 14.3, 8.4, 7.3, 3.5 Hz, 2H), 1.47 – 1.34 (m, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 141.21, 137.55, 128.52, 93.51, 74.74, 55.24, 38.71, 26.93, 20.41.

<u>*p*-nitro benzaldehyde</u>



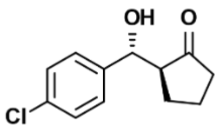
anti

The resulting pure product was examined by ^{1}H and ^{13}C NMR. The spectroscopic NMR data agree with the previously reported ones.

^{1}H NMR (400 MHz, CDCl3) δ 8.15 (d, J = 8.6 Hz, 2H), 7.47 (d, J = 8.7 Hz, 2H), 4.78 (d, J = 9.2 Hz, 1H), 4.67 (s, 1H), 2.47 – 2.15 (m, 2H), 2.01 – 1.90 (m, 1H), 1.72 – 1.60 (m, 2H), 1.48 (q, J = 6.7 Hz, 2H).

^{13}C NMR (101 MHz, CDCl3) δ 148.65, 127.36, 123.74, 74.47, 55.11, 38.60, 26.88, 20.38.

<u>*p*-chloro benzaldehyde</u>



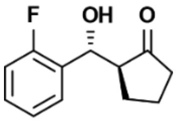
anti

The resulting pure product was examined by ^{1}H and ^{13}C NMR. The spectroscopic NMR data agree with the previously reported ones.

^{1}H NMR (400 MHz, CDCl3) δ 7.54 – 6.96 (m, 4H), 4.62 (d, J = 9.1 Hz, 1H), 4.51 (s, 1H), 2.46 – 2.26 (m, 2H), 2.17 (ddd, J = 19.5, 10.7, 9.0 Hz, 1H), 1.96 – 1.86 (m, 1H), 1.72 – 1.61 (m, 2H), 1.48 – 1.36 (m, 1H).

^{13}C NMR (101 MHz, CDCl3) δ 140.01, 133.71, 128.64, 127.94, 74.63, 55.31, 38.71, 26.94, 20.41.

_o-_fluoro benzaldehyde



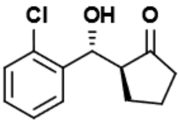
anti

The resulting pure product was examined by ^{1}H and ^{13}C NMR. The spectroscopic NMR data agree with the previously reported ones.

^{1}H NMR (400 MHz, CDCl3) δ 7.44 (td, J = 7.5, 1.9 Hz, 1H), 7.17 (ddd, J = 7.4, 5.5, 2.1 Hz, 1H), 7.09 (td, J = 7.5, 1.3 Hz, 1H), 6.93 (ddd, J = 9.7, 8.2, 1.3 Hz, 1H), 5.02 (d, J = 9.5 Hz, 1H), 4.52 (s, 1H), 2.44 – 2.30 (m, 2H), 2.20 (ddd, J = 19.3, 10.3, 8.7 Hz, 1H), 1.92 (dddd, J = 12.5, 10.3, 7.3, 2.2 Hz, 1H), 1.76 – 1.60 (m, 2H), 1.54 (dddd, J = 12.6, 7.7, 5.7, 2.1 Hz, 1H).

^{13}C NMR (101 MHz, CDCl3) δ 161.07, 158.62, 129.33, 128.20, 124.55, 68.12, 55.09, 38.64, 26.45, 20.42.

_o-_chloro benzaldehyde



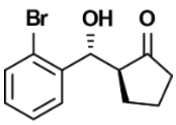
anti

The resulting pure product was examined by ^{1}H and ^{13}C NMR. The spectroscopic NMR data agree with the previously reported ones.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 (dd, *J* = 7.7, 1.7 Hz, 1H), 7.36 – 7.27 (m, 2H), 7.21 (td, *J* = 7.6, 1.8 Hz, 1H), 5.30 (d, *J* = 9.3 Hz, 1H), 4.52 (s, 1H), 2.53 – 2.36 (m, 2H), 2.37 – 2.23 (m, 1H), 2.06 – 1.95 (m, 1H), 1.83 – 1.60 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 139.18, 132.44, 129.34, 128.93, 128.38, 127.39, 70.37, 55.56, 38.68, 26.43, 20.55.

_o-_bromo benzaldehyde



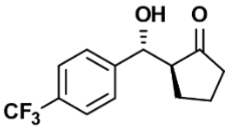
anti

The resulting pure product was examined by ^{1}H and ^{13}C NMR. The spectroscopic NMR data agree with the previously reported ones.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (ddd, *J* = 13.4, 7.9, 1.5 Hz, 2H), 7.36 (td, *J* = 7.6, 1.3 Hz, 1H), 7.15 (td, *J* = 7.7, 1.8 Hz, 1H), 5.27 (d, *J* = 9.3 Hz, 1H), 4.50 (s, 1H), 2.51 – 2.39 (m, 2H), 2.36 – 2.26 (m, 1H), 2.02 (tdt, *J* = 8.0, 5.5, 3.2 Hz, 1H), 1.79 – 1.66 (m, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 140.75, 132.64, 129.34, 128.67, 128.02, 122.77, 72.76, 55.65, 38.71, 26.53, 20.60.

p-trifluoromethyl benzaldehyde



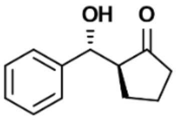
anti

The resulting pure product was examined by ^1H and ^{13}C NMR. The spectroscopic NMR data agree with the previously reported ones.

^1H NMR (400 MHz, $CDCl_3$) δ 7.54 (d, *J* = 8.1 Hz, 2H), 7.40 (d, *J* = 8.1 Hz, 2H), 4.71 (d, *J* = 9.2 Hz, 1H), 4.60 (s, 1H), 2.46 – 2.28 (m, 2H), 2.19 (ddd, *J* = 19.5, 10.7, 8.9 Hz, 1H), 1.93 (dddd, *J* = 16.0, 8.8, 5.8, 2.6 Hz, 1H), 1.74 – 1.58 (m, 2H), 1.45 (qt, *J* = 11.5, 5.5 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 145.44, 126.89, 125.41, 74.71, 55.22, 38.66, 26.90, 20.39.

Benzaldehyde



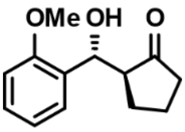
anti

The resulting pure product was examined by ^1H and ^{13}C NMR. The spectroscopic NMR data agree with the previously reported ones.

^1H NMR (400 MHz, $CDCl_3$) δ 7.27 (d, *J* = 4.4 Hz, 4H), 7.25 – 7.20 (m, 1H), 4.64 (d, *J* = 9.2 Hz, 1H), 2.44 – 2.30 (m, 2H), 2.25 – 2.09 (m, 1H), 1.89 (dddd, *J* = 16.3, 8.9, 4.2, 2.1 Hz, 1H), 1.74 – 1.56 (m, 2H), 1.51 – 1.37 (m, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 141.45, 128.47, 128.03, 126.59, 75.27, 55.37, 38.77, 27.03, 20.43.

o-methoxy benzaldehyde

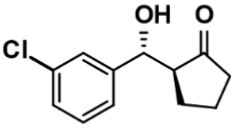


The resulting pure product was examined by ^1H and ^{13}C NMR. The spectroscopic NMR data agree with the previously reported ones.

^1H NMR (400 MHz, $CDCl_3$) δ 7.43 (dd, *J* = 7.6, 1.8 Hz, 1H), 7.27 – 7.21 (m, 1H), 6.98 (td, *J* = 7.5, 1.1 Hz, 1H), 6.86 (dd, *J* = 8.3, 1.1 Hz, 1H), 5.19 (d, *J* = 9.1 Hz, 1H), 4.37 (s, 1H), 3.81 (s, 3H), 2.57 – 2.46 (m, 1H), 2.45 – 2.34 (m, 1H), 2.25 (ddd, *J* = 19.0, 10.0, 8.7 Hz, 1H), 2.00 – 1.91 (m, 1H), 1.79 – 1.57 (m, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 156.52, 129.86, 128.73, 127.68, 121.00, 110.57, 68.48, 55.39, 38.71, 26.55, 20.52.

m-chloro benzaldehyde

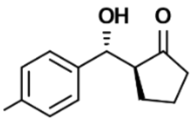


The resulting pure product was examined by ^{1}H and ^{13}C NMR. The spectroscopic NMR data agree with the previously reported ones.

^{1}H NMR (400 MHz, CDCl$_3$) δ 7.29 (q, *J* = 1.5 Hz, 1H), 7.21 – 7.19 (m, 2H), 7.14 (dtd, *J* = 5.4, 3.9, 1.4 Hz, 1H), 4.61 (d, *J* = 9.2 Hz, 1H), 4.55 (s, 0H), 2.43 – 2.24 (m, 2H), 2.24 – 2.11 (m, 1H), 1.99 – 1.83 (m, 1H), 1.76 – 1.57 (m, 2H), 1.49 – 1.38 (m, 1H).

^{13}C NMR (101 MHz, CDCl$_3$) δ 143.57, 134.41, 129.73, 128.17, 126.73, 124.79, 74.69, 55.24, 38.69, 26.95, 20.40.

p-methyl benzaldehyde



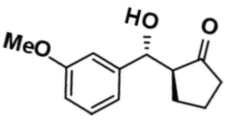
anti

The resulting pure product was examined by ^{1}H and ^{13}C NMR. The spectroscopic NMR data agree with the previously reported ones.

^{1}H NMR (400 MHz, CDCl$_3$) δ 7.24 – 7.20 (m, 2H), 7.15 (d, *J* = 7.9 Hz, 2H), 4.67 (d, *J* = 9.1 Hz, 1H), 2.48 – 2.37 (m, 2H), 2.34 (s, 3H), 2.29 – 2.17 (m, 1H), 1.95 (dddd, *J* = 12.6, 8.5, 6.6, 2.2 Hz, 1H), 1.79 – 1.65 (m, 2H), 1.56 – 1.42 (m, 1H).

^{13}C NMR (101 MHz, CDCl$_3$) δ 138.53, 137.66, 129.12, 126.52, 75.04, 55.35, 38.79, 27.04, 21.17, 20.43.

m-methoxy benzaldehyde

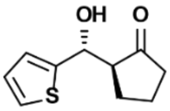


The resulting pure product was examined by ^{1}H and ^{13}C NMR. The spectroscopic NMR data agree with the previously reported ones.

^{1}H NMR (400 MHz, CDCl$_3$) δ 7.28 – 7.22 (m, 1H), 6.94 – 6.88 (m, 2H), 6.83 (ddd, *J* = 8.2, 2.6, 1.1 Hz, 1H), 4.68 (d, *J* = 9.1 Hz, 1H), 4.53 (s, 1H), 3.81 (s, 3H), 2.48 – 2.36 (m, 2H), 2.25 (ddd, *J* = 19.4, 10.5, 8.7 Hz, 1H), 2.04 – 1.89 (m, 1H), 1.84 – 1.64 (m, 2H), 1.56 – 1.43 (m, 1H).

^{13}C NMR (101 MHz, CDCl$_3$) δ 159.78, 143.08, 129.44, 118.97, 113.57, 111.96, 75.18, 55.35, 55.26, 38.77, 27.06, 20.43.

Thiophene-2-carbaldehyde



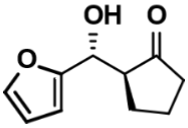
anti

The resulting pure product was examined by ^{1}H and ^{13}C NMR. The spectroscopic NMR data agree with the previously reported ones.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20 (dd, *J* = 4.7, 1.5 Hz, 1H), 6.91 – 6.85 (m, 2H), 4.94 (d, *J* = 9.0 Hz, 1H), 4.57 (d, *J* = 1.3 Hz, 1H), 2.48 – 2.32 (m, 2H), 2.17 (ddd, *J* = 19.4, 10.9, 8.7 Hz, 1H), 1.96 – 1.80 (m, 2H), 1.70 (dddd, *J* = 17.7, 8.5, 4.6, 2.6 Hz, 1H), 1.49 (qd, *J* = 11.8, 6.8 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 145.28, 126.39, 125.14, 124.41, 71.28, 55.85, 38.74, 27.01, 20.30.

Furfural

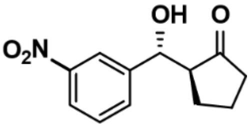


The resulting pure product was examined by ^{1}H and ^{13}C NMR. The spectroscopic NMR data agree with the previously reported ones.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 (dd, *J* = 1.9, 0.8 Hz, 1H), 6.31 (ddd, *J* = 16.0, 3.2, 1.3 Hz, 2H), 4.78 (d, *J* = 9.1 Hz, 1H), 4.33 (s, 1H), 2.75 – 2.65 (m, 1H), 2.44 (ddd, *J* = 19.2, 8.5, 2.1 Hz, 1H), 2.24 (ddd, *J* = 19.3, 10.8, 8.8 Hz, 1H), 2.06 – 1.89 (m, 2H), 1.86 – 1.76 (m, 1H), 1.52 (qd, *J* = 11.8, 7.0 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 142.39, 110.14, 107.53, 68.54, 52.86, 38.51, 26.55, 20.40.

m-nitro benzaldehyde

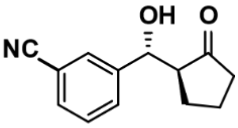


The resulting pure product was examined by ^{1}H and ^{13}C NMR. The spectroscopic NMR data agree with the previously reported ones.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24 (t, *J* = 2.1 Hz, 1H), 8.17 (ddd, *J* = 8.1, 2.4, 1.1 Hz, 1H), 7.72 – 7.69 (m, 1H), 7.54 (t, *J* = 7.9 Hz, 1H), 4.83 (d, *J* = 9.3 Hz, 1H), 4.78 (d, *J* = 1.0 Hz, 1H), 2.53 – 2.37 (m, 2H), 2.35 – 2.18 (m, 1H), 2.08 – 1.94 (m, 1H), 1.82 – 1.69 (m, 2H), 1.57 (s, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 143.69, 132.66, 129.48, 123.03, 121.63, 74.49, 55.10, 38.61, 29.70, 26.94, 20.38.

m-cyano benzaldehyde

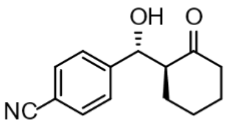


The resulting pure product was examined by ^{1}H and ^{13}C NMR. The spectroscopic NMR data agree with the previously reported ones.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 (d, *J* = 1.8 Hz, 1H), 7.60 (dd, *J* = 7.8, 1.7 Hz, 2H), 7.49 – 7.44 (m, 1H), 4.75 (d, *J* = 9.3 Hz, 1H), 4.72 (d, *J* = 1.1 Hz, 1H), 2.52 – 2.21 (m, 3H), 2.11 – 1.91 (m, 1H), 1.84 – 1.66 (m, 2H), 1.61 – 1.44 (m, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 143.08, 131.68, 130.99, 130.26, 129.31, 118.68, 112.63, 74.46, 55.14, 38.61, 29.70, 26.91, 20.37.

p-cyano benzaldehyde

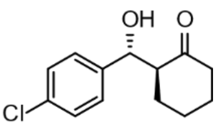


The resulting pure product was examined by ^{1}H and ^{13}C NMR. The spectroscopic NMR data agree with the previously reported ones.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 – 7.60 (m, 2H), 7.46 – 7.41 (m, 2H), 4.83 (dd, *J* = 8.5, 3.1 Hz, 1H), 4.04 (d, *J* = 3.1 Hz, 1H), 2.62 – 2.44 (m, 2H), 2.40 – 2.31 (m, 1H), 2.11 (ddt, *J* = 12.1, 5.7, 2.9 Hz, 1H), 1.89 – 1.79 (m, 1H), 1.76 – 1.47 (m, 2H), 1.43 – 1.28 (m, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 215.01, 146.47, 132.35, 127.92, 118.87, 77.48, 77.16, 76.84, 74.40, 57.29, 42.83, 30.88, 27.79, 24.84.

p-chloro benzaldehyde

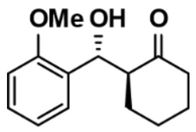


The resulting pure product was examined by ^{1}H and ^{13}C NMR. The spectroscopic NMR data agree with the previously reported ones.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 – 7.29 (m, 2H), 7.29 – 7.21 (m, 2H), 4.76 (dd, *J* = 8.7, 2.8 Hz, 1H), 3.98 (d, *J* = 2.8 Hz, 1H), 2.60 – 2.44 (m, 2H), 2.35 (tdd, *J* = 13.6, 6.2, 1.3 Hz, 1H), 2.09 (ddt, *J* = 12.2, 5.8, 2.8 Hz, 1H), 1.79 (dqd, *J* = 10.4, 3.3, 1.7 Hz, 1H), 1.74 – 1.46 (m, 2H), 1.32 – 1.26 (m, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 214.93, 139.08, 128.15, 127.99, 126.76, 73.75, 56.97, 42.28, 30.36, 27.33, 24.32.

<u>*o*-methoxy benzaldehyde</u>

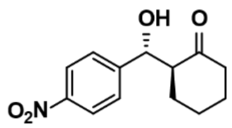


The resulting pure product was examined by ^{1}H and ^{13}C NMR. The spectroscopic NMR data agree with the previously reported ones.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 (dd, *J* = 7.6, 1.8 Hz, 1H), 7.25 (ddd, *J* = 8.3, 7.4, 1.8 Hz, 1H), 6.98 (td, *J* = 7.5, 1.1 Hz, 1H), 6.86 (dd, *J* = 8.3, 1.1 Hz, 1H), 5.26 (dd, *J* = 8.5, 4.5 Hz, 1H), 3.83 (d, *J* = 4.5 Hz, 1H), 3.81 (s, 3H), 2.79 – 2.68 (m, 1H), 2.52 – 2.42 (m, 1H), 2.35 (dddd, *J* = 13.6, 12.4, 5.9, 1.3 Hz, 1H), 2.10 – 1.96 (m, 1H), 1.92 – 1.37 (m, 4H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 215.57, 154.70, 129.62, 128.63, 127.80, 120.92, 110.50, 68.62, 57.32, 42.60, 30.52, 27.96, 24.74.

<u>*p*-nitro benzaldehyde</u>

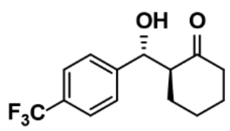


The resulting pure product was examined by ^{1}H and ^{13}C NMR. The spectroscopic NMR data agree with the previously reported ones.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.36 – 8.09 (m, 2H), 7.59 – 7.42 (m, 2H), 4.90 (dd, *J* = 8.4, 3.1 Hz, 1H), 4.07 (d, *J* = 3.2 Hz, 1H), 2.68 – 2.45 (m, 2H), 2.36 (tdd, *J* = 13.6, 6.1, 1.2 Hz, 1H), 2.12 (ddt, *J* = 12.1, 5.8, 2.8 Hz, 1H), 1.88 – 1.77 (m, 1H), 1.78 – 1.48 (m, 3H), 1.46 – 1.29 (m, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 214.35, 148.35, 147.16, 127.47, 123.18, 73.63, 56.79, 42.28, 30.36, 27.24, 24.29.

<u>*p*-trifluoromethyl benzaldehyde</u>



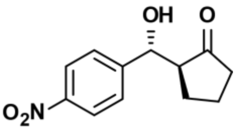
The resulting pure product was examined by ^{1}H and ^{13}C NMR. The spectroscopic NMR data agree with the previously reported ones.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 – 7.58 (m, 2H), 7.52 – 7.39 (m, 2H), 4.85 (dd, *J* = 8.6, 3.0 Hz, 1H), 4.03 (d, *J* = 3.0 Hz, 1H), 2.65 – 2.44 (m, 2H), 2.36 (tdd, *J* = 13.5, 6.1, 1.2 Hz, 1H), 2.10 (ddt, *J* = 12.2, 5.8, 3.0 Hz, 1H), 1.87 – 1.75 (m, 1H), 1.74 – 1.47 (m, 3H), 1.40 – 1.28 (m, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 215.23, 145.12, 127.51, 125.45, 122.89, 74.43, 57.42, 42.83, 30.91, 27.85, 24.87.

15. Chiral HPLC of the scope

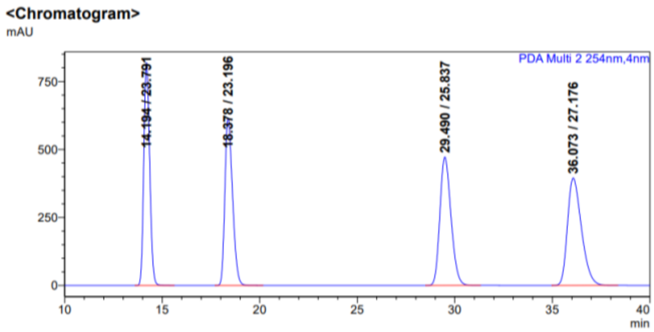
All the reactions were performed in duplicate and HPLC traces are provided. The absolute configuration of Aldol product for the L-proline was determined by comparison to literature[6–9] and by analogy for new substrates. The retention time and peak area (in %) appear on each peak of the HPLC traces (table S6 and S7).



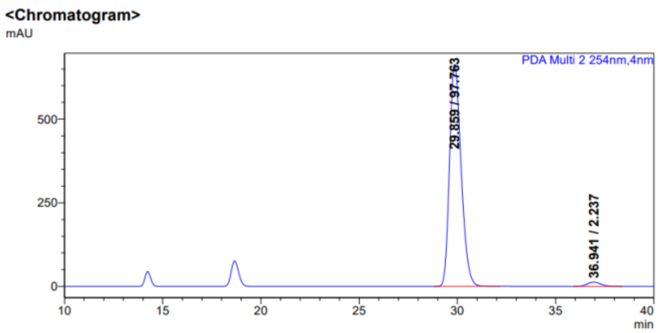
anti

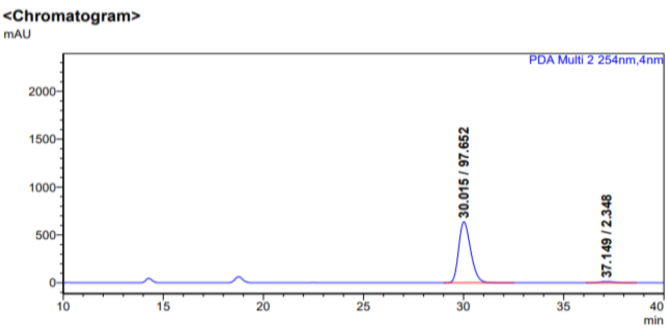
HPLC conditions: IC 10% IPA in Hexane. 1 ml/min. 254.

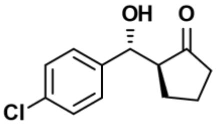
HPLC traces for racemic:



HPLC traces for chiral (reaction and duplicate) (reaction and duplicate)



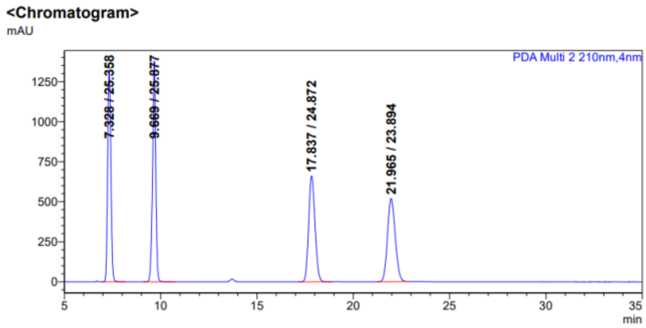




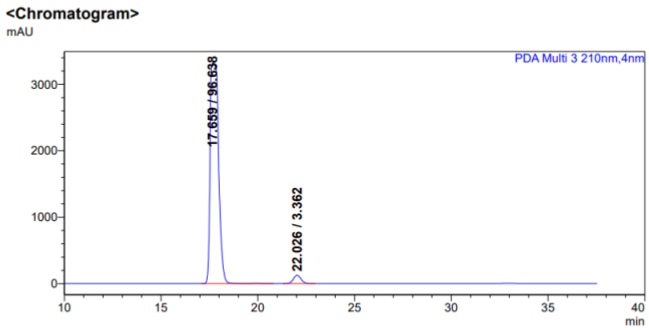
anti

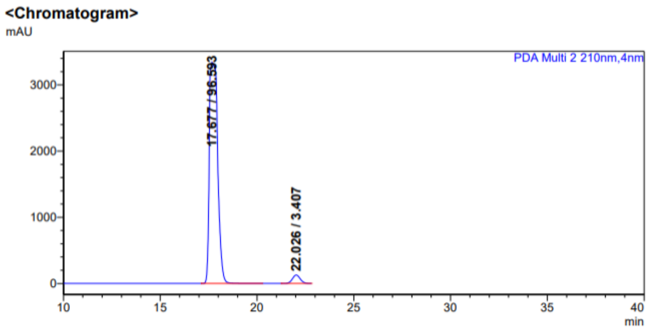
<u>HPLC conditions:</u> IC 10% IPA in Hexane. 1 ml/min. 210 nm.

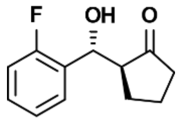
HPLC traces for racemic



HPLC traces for chiral (reaction and duplicate)



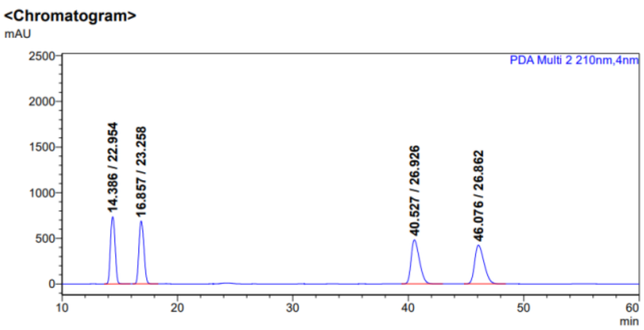




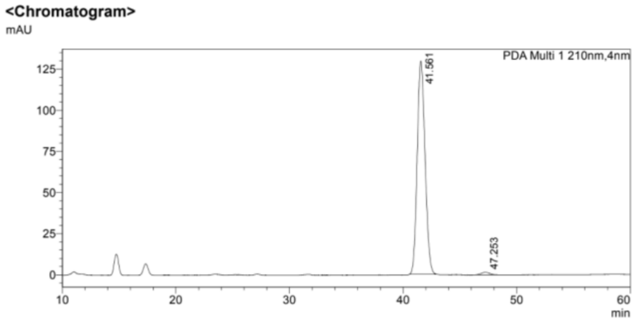
anti

<u>HPLC conditions:</u> IC 3% IPA in Hexane. 1 ml/min. 210 nm.

HPLC traces for racemic



HPLC traces for chiral (reaction and duplicate)



<Peak Table>

PDA Ch1 210nm

Peak#	Ret. Time	Area	Height	Conc.	Unit	Mark	Name
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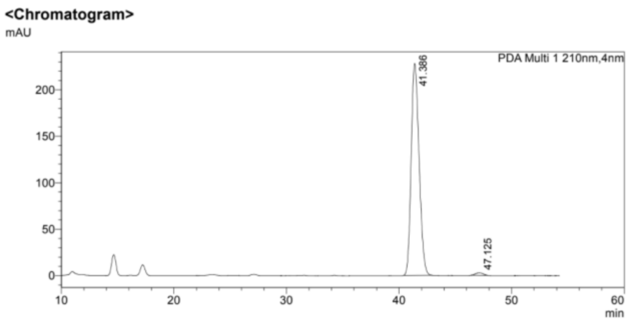
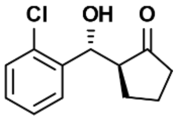
2	47.253	79699	1557	0.000		M	
Total		6309921	131110				



<Peak Table>

PDA Ch1 210nm

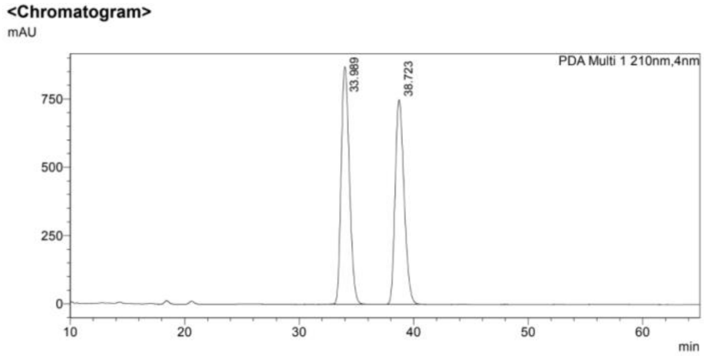
Peak#	Ret. Time	Area	Height	Conc.	Unit	Mark	Name
1	41.386	11140852	228124	0.000			
2	47.125	125796	2685	0.000		M	
Total		11266649	230809				



anti

<u>HPLC conditions:</u> IC 10% IPA in Hexane. 1 ml/min. 210 nm.

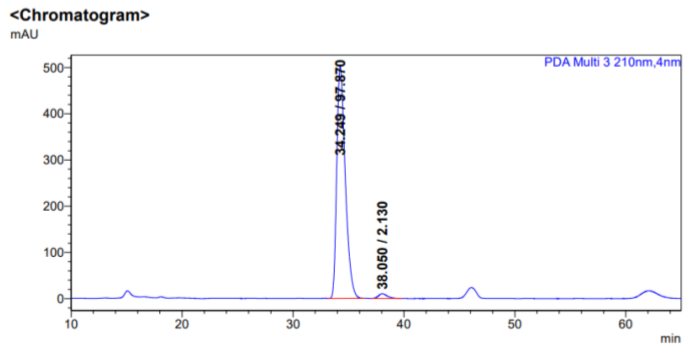
HPLC traces for racemic

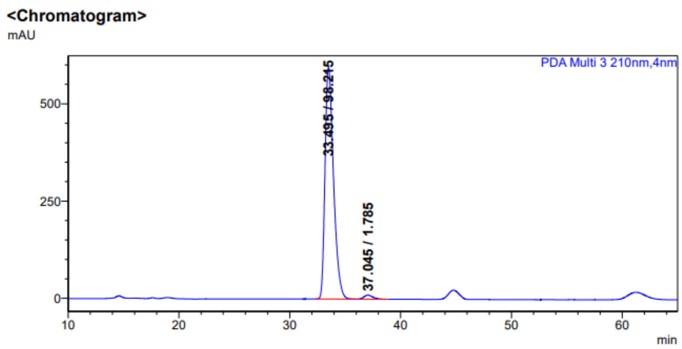


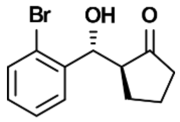
<Peak Table>
PDA Ch1 210nm

Peak#	Ret. Time	Area	Height	Conc.	Unit	Mark	Name
1	33.989	43446910	868293	0.000		M	
2	38.723	40689789	748104	0.000			
Total		84136699	1616397				

HPLC traces for chiral (reaction and duplicate)



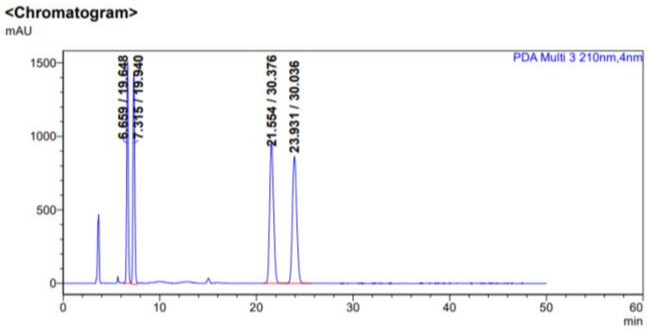




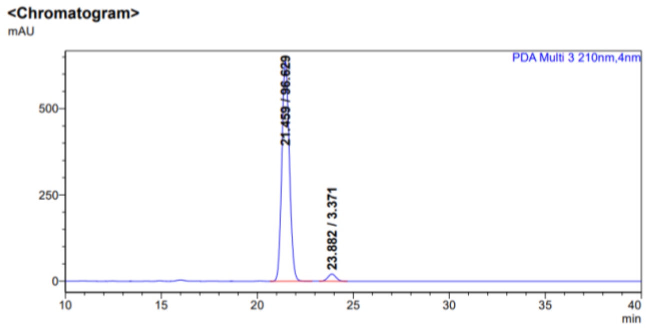
anti

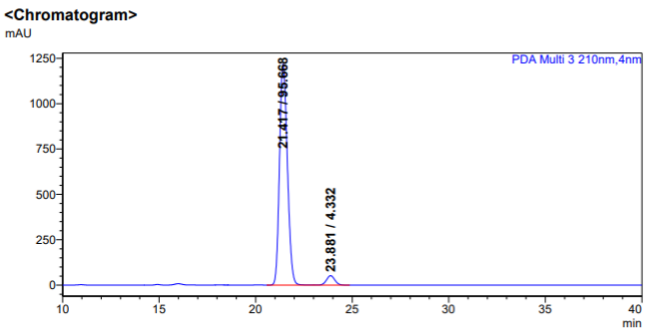
HPLC conditions: IC 10% IPA in Hexane. 1 ml/min. 210 nm.

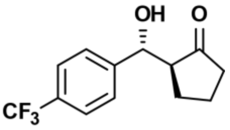
HPLC traces for racemic



HPLC traces for chiral (reaction and duplicate)



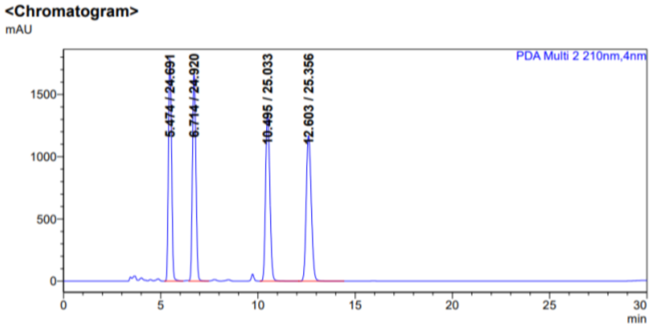




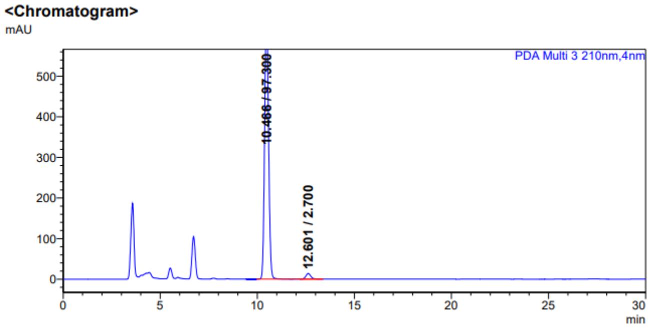
anti

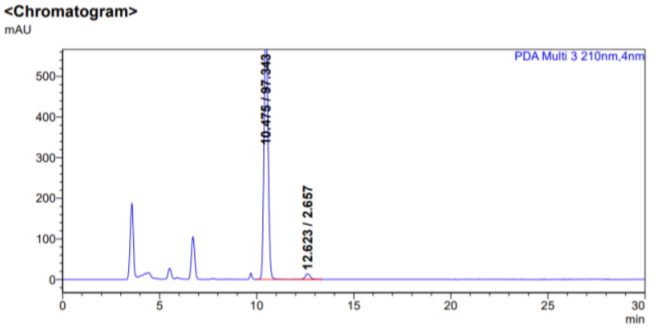
HPLC conditions: IC 10% IPA in Hexane. 1 ml/min. 210 nm.

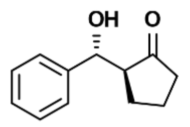
HPLC traces for racemic



HPLC traces for chiral (reaction and duplicate)



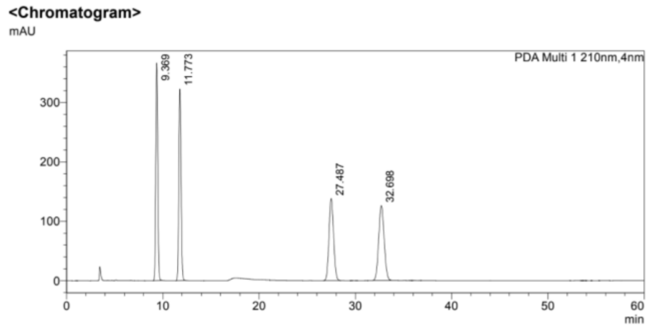




anti

<u>HPLC conditions:</u> IC 10% IPA in Hexane. 1 ml/min. 210 nm.

HPLC traces for racemic



<Peak Table>

PDA Ch1 210nm

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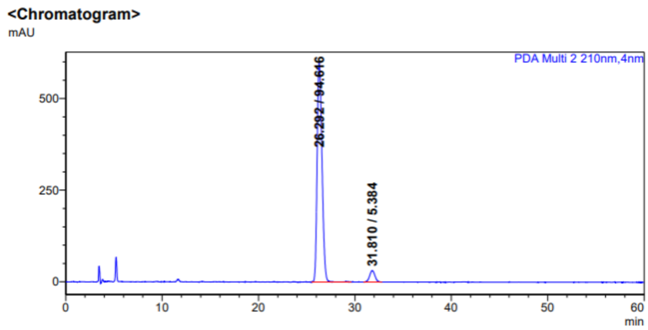
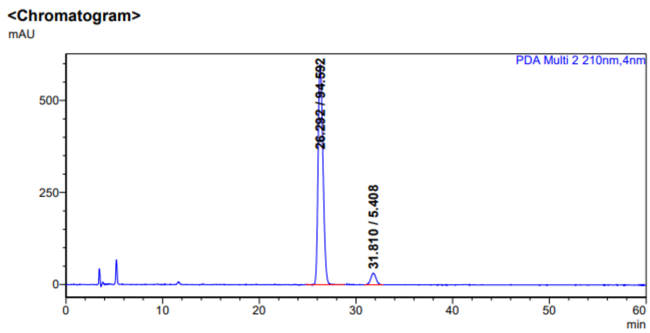
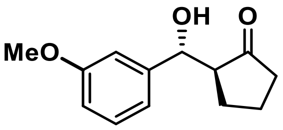
2	11.773	5182903	322761	0.000			
3	27.487	4584706	138085	0.000			
4	32.698	4980465	125961	0.000			
Total		20146523	953298				

HPLC traces for chiral (reaction and duplicate)



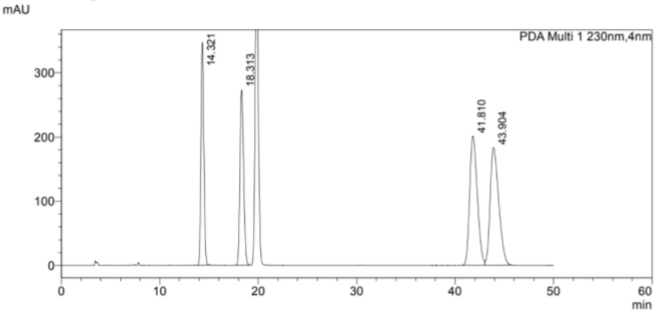




<u>HPLC conditions:</u> IC 10% IPA in Hexane. 1 ml/min. 210 nm.

HPLC traces for racemic

<Chromatogram>



<Peak Table>

PDA Ch1 230nm

Peak#	Ret. Time	Area	Height	Conc.	Unit	Mark	Name
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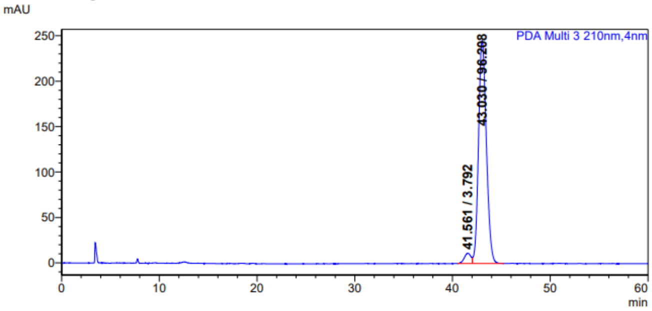
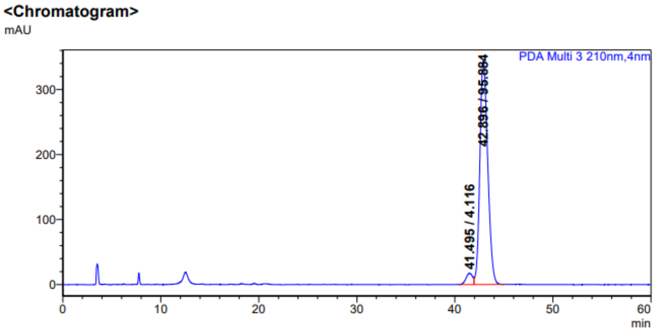
2	18.313	7065614	272871	0.000			
3	41.810	10789824	201105	0.000			
4	43.904	11112362	183022	0.000		V	
Total		36041160	1004274				

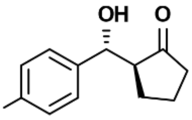
HPLC traces for chiral (reaction and duplicate)

<Chromatogram>



<Chromatogram>



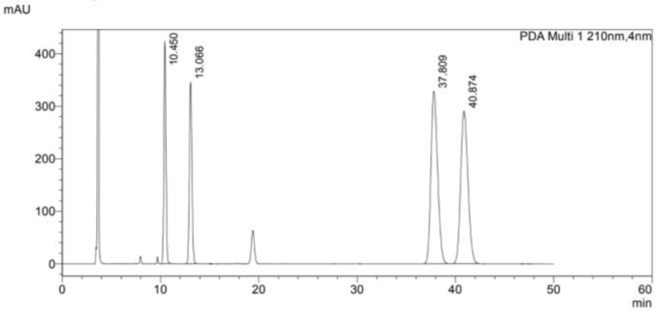


anti

<u>HPLC conditions:</u> IC 10% IPA in Hexane. 1 ml/min. 210 nm.

HPLC traces for racemic

<Chromatogram>



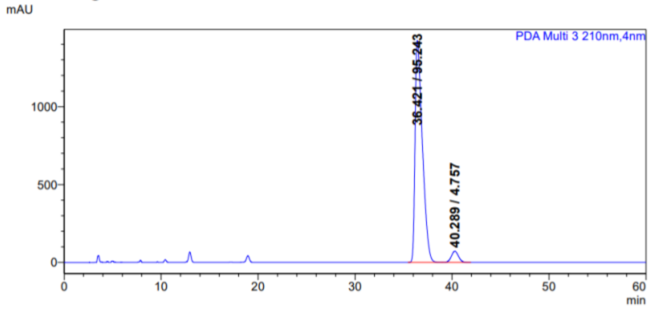
<Peak Table>

PDA Ch1 210nm

Peak#	Ret. Time	Area	Height	Conc.	Unit	Mark	Name
1	10.450	6185642	422194	2.091	mg/L		Binol R
2	13.066	6193100	345079	0.000			
3	37.809	15457760	328018	0.000			
4	40.874	14936524	290364	0.000			
Total		42773026	1385655				

HPLC traces for chiral (reaction and duplicate)

<Chromatogram>



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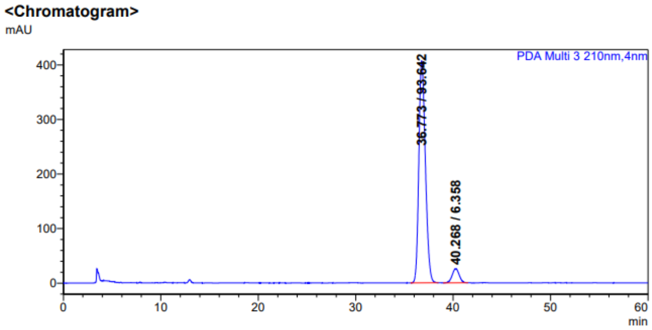
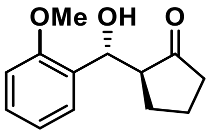
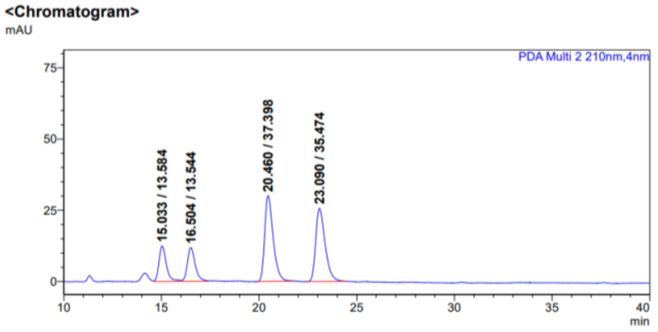


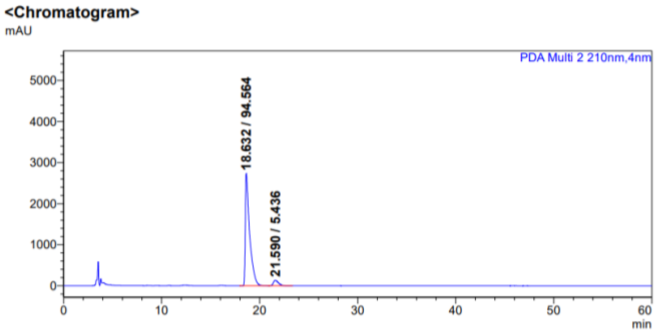


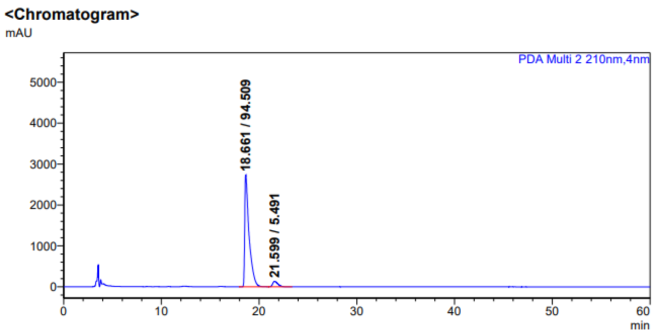
<u>HPLC conditions:</u> IB 5% IPA in Hexane. 1 ml/min. 210 nm.

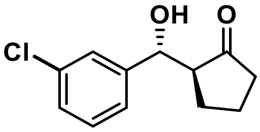
HPLC traces for racemic



HPLC traces for chiral (reaction and duplicate)

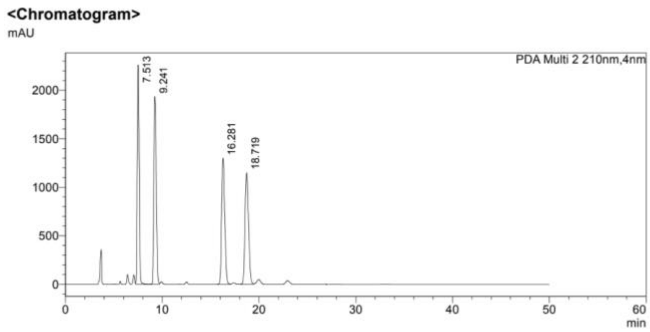






<u>HPLC conditions:</u> IC 10% IPA in Hexane. 1 ml/min. 210 nm.

HPLC traces for racemic

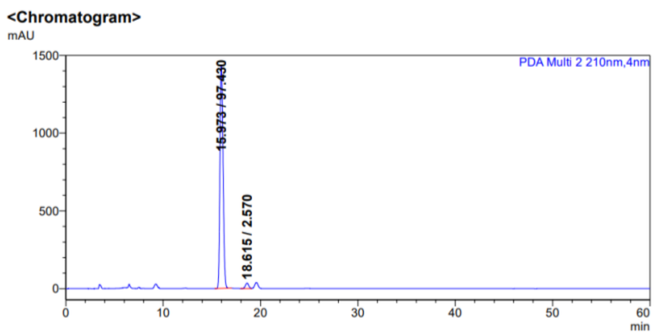


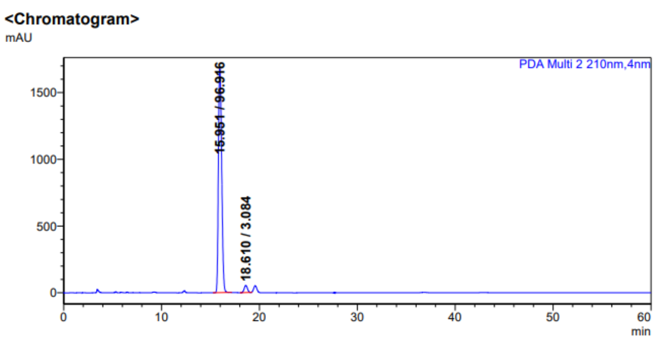
<Peak Table>

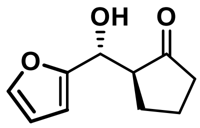
PDA Ch2 210nm

Peak#	Ret. Time	Area	Height	Conc.	Unit	Mark	Name
1	7.513	31679459	2260595	0.000			
2	9.241	33699073	1935032	0.000		V	
3	16.281	29168656	1299848	0.000			
4	18.719	29237831	1148979	0.000			
Total		123785018	6644456				

HPLC traces for chiral (reaction and duplicate)

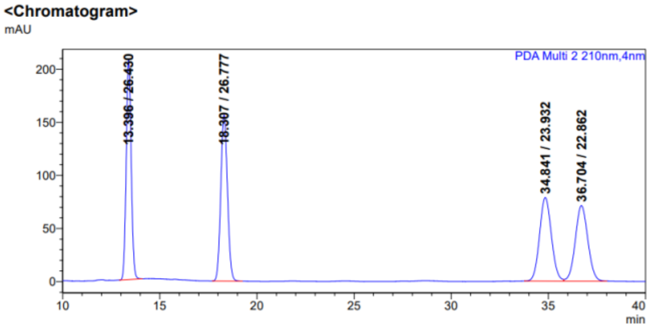




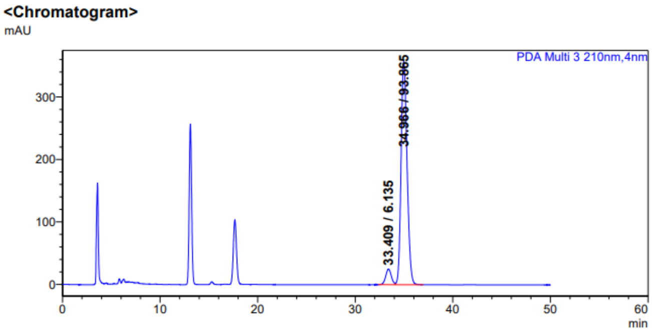


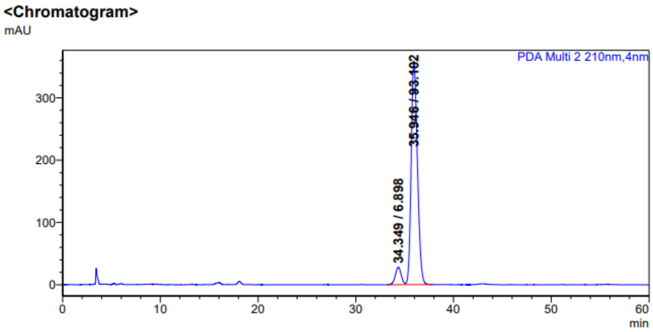
<u>HPLC conditions:</u> IC 10% IPA in Hexane. 1 ml/min. 210 nm.

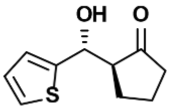
HPLC traces for racemic



HPLC traces for chiral (reaction and duplicate)





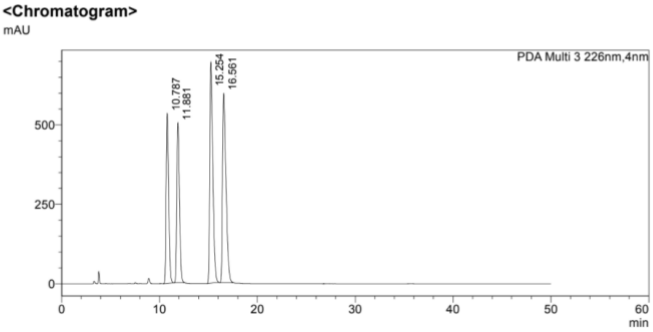


anti

HPLC conditions: IB 5% IPA in Hexane. 1 ml/min. 226 nm.

HPLC traces for racemic

<Chromatogram>



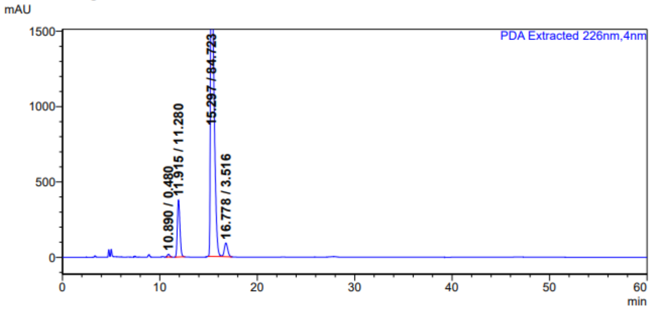
<Peak Table>

PDA Ch3 226nm

Peak#	Ret. Time	Area	Height	Conc.	Unit	Mark	Name
1	10.787	9593148	534647	0.000		M	
2	11.881	9591144	502868	0.000		M	
3	15.254	14942671	694912	0.000		M	
4	16.561	14827314	597010	0.000		M	
Total		48954278	2329437				

HPLC traces for chiral (reaction and duplicate)

<Chromatogram>



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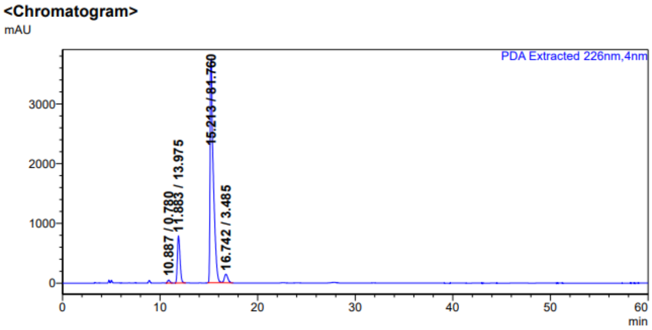
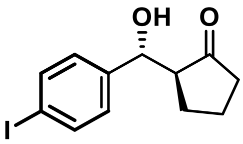
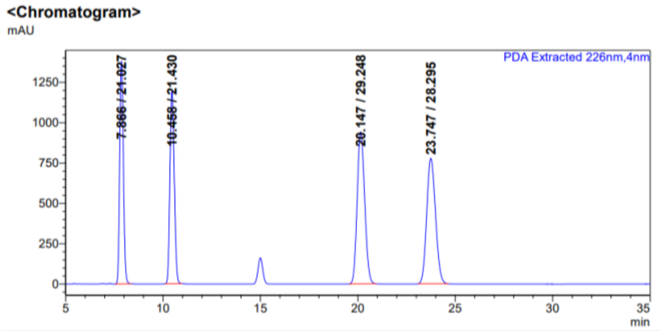


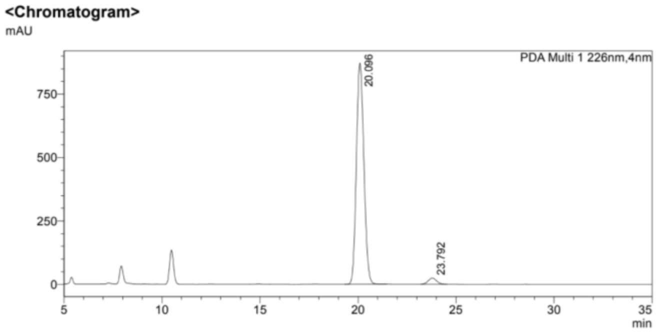


HPLC conditions: IC 10% IPA in Hexane. 1 ml/min. 226 nm.

HPLC traces for racemic



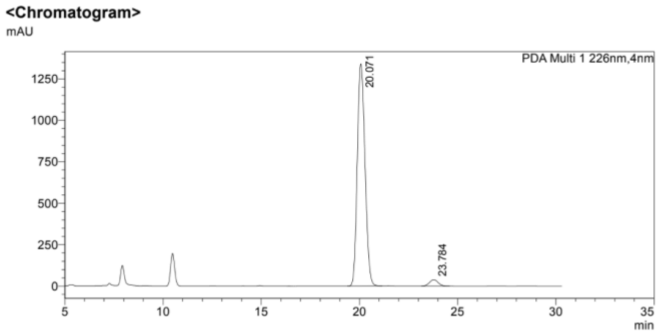
HPLC traces for chiral (reaction and duplicate)



<Peak Table>

PDA Ch1 226nm

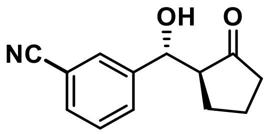
Peak#	Ret. Time	Area	Height	Conc.	Unit	Mark	Name
1	20.096	23249260	871743	0.000		M	
2	23.792	728320	24160	0.000			
Total		23977580	895903				



<Peak Table>

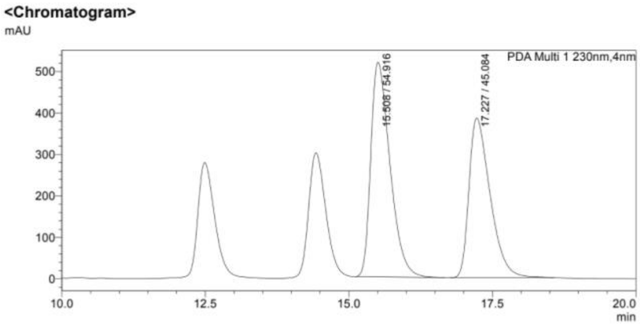
PDA Ch1 226nm

Peak#	Ret. Time	Area	Height	Conc.	Unit	Mark	Name
1	20.071	36647735	1340107	0.000			
2	23.784	1168767	38533	0.000			
Total		37816502	1378640				

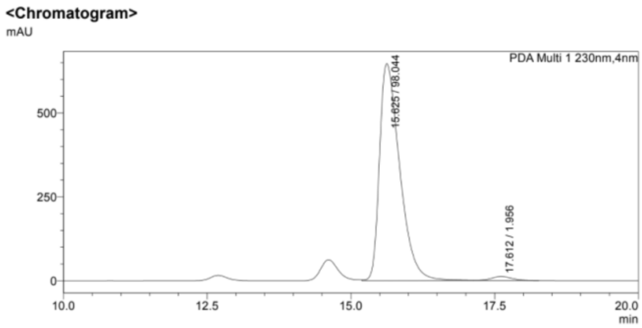


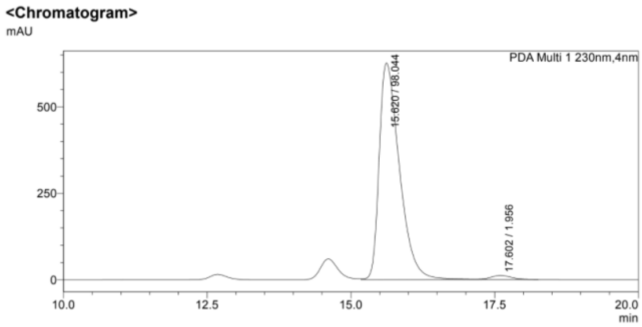
<u>HPLC conditions</u>: IB 10% IPA in Hexane. 1 ml/min. 226 nm.

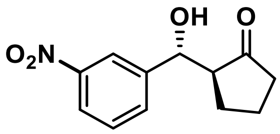
HPLC traces for racemic



HPLC traces for chiral (reaction and duplicate)

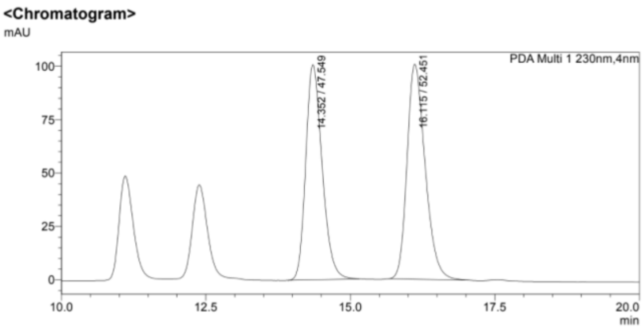




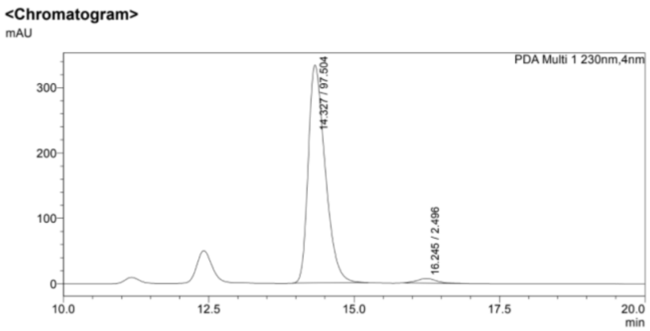


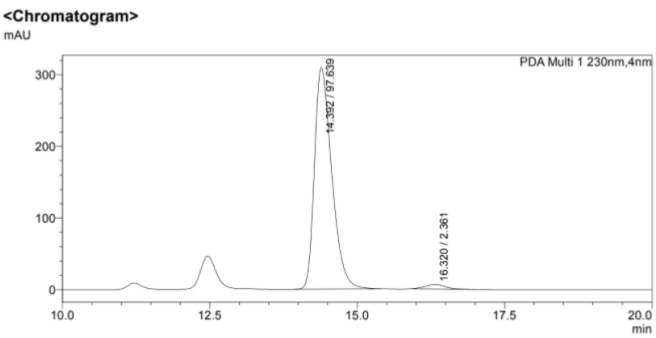
<u>HPLC conditions</u>: IB 10% IPA in Hexane. 1 ml/min. 226 nm.

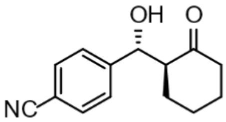
HPLC traces for racemic



HPLC traces for chiral (reaction and duplicate)

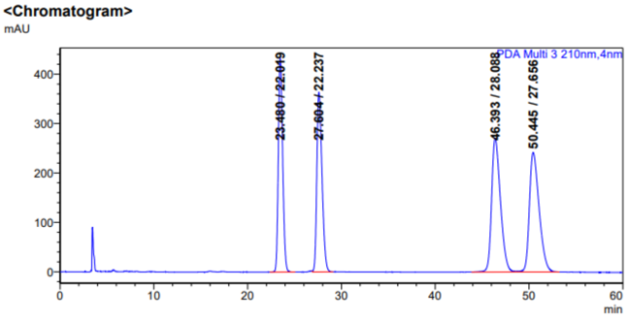




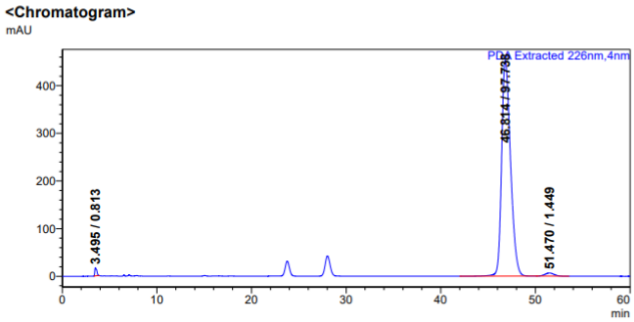


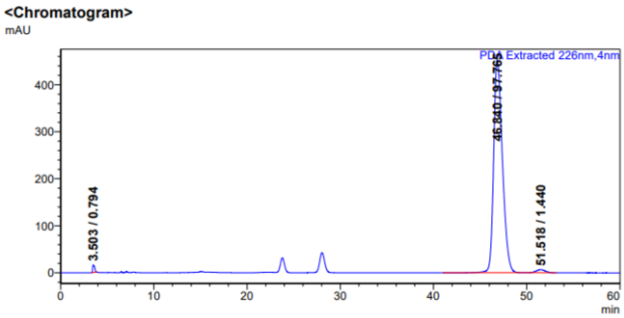
HPLC conditions: IC 10% IPA in Hexane. 1 ml/min. 226 nm.

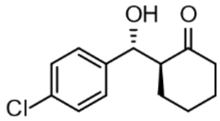
HPLC traces for racemic



HPLC traces for chiral (reaction and duplicate)

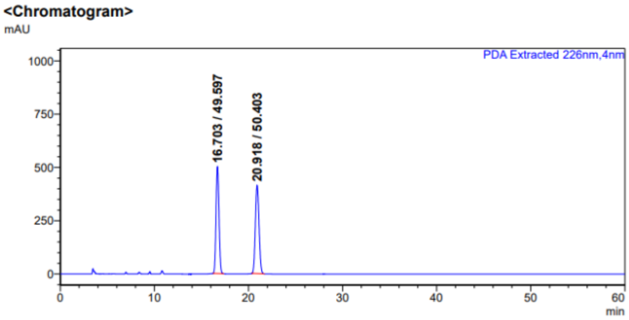




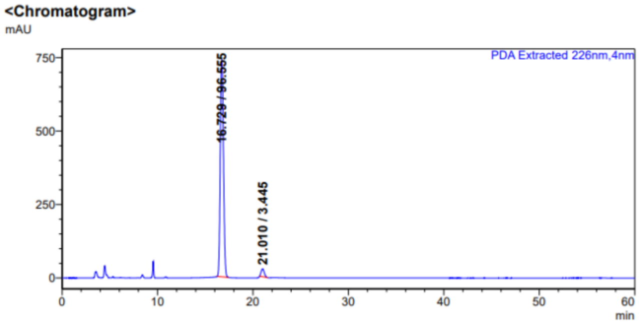


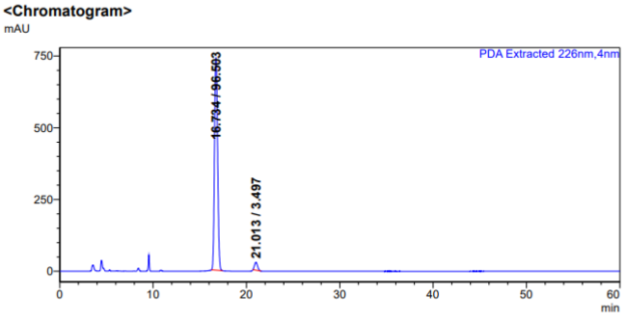
HPLC conditions: IC 10% IPA in Hexane. 1 ml/min. 226 nm.

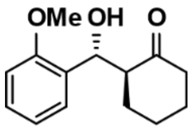
HPLC traces for racemic



HPLC traces for chiral (reaction and duplicate)

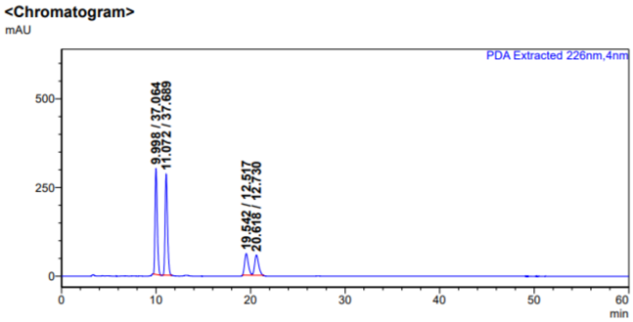




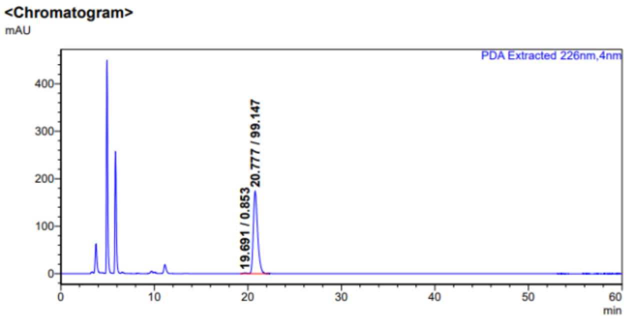


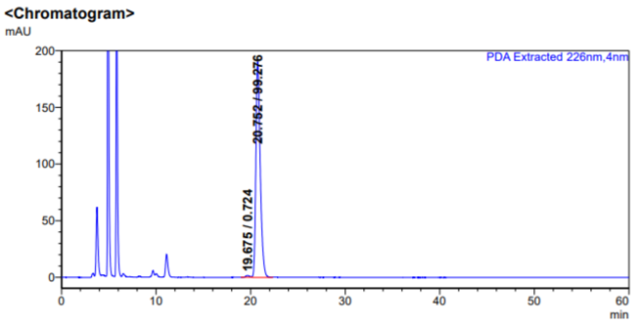
HPLC conditions: AS-H 9% IPA in Hexane. 1 ml/min. 226 nm.

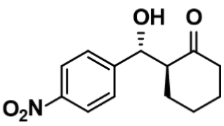
HPLC traces for racemic



HPLC traces for chiral (reaction and duplicate)

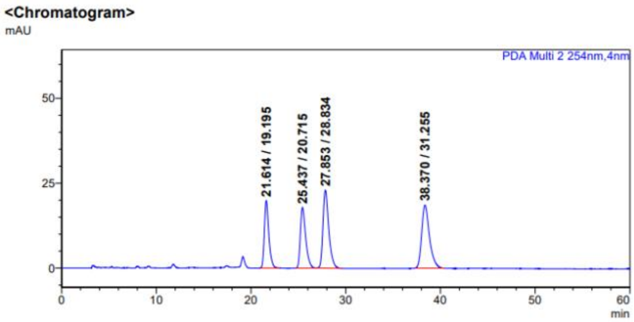




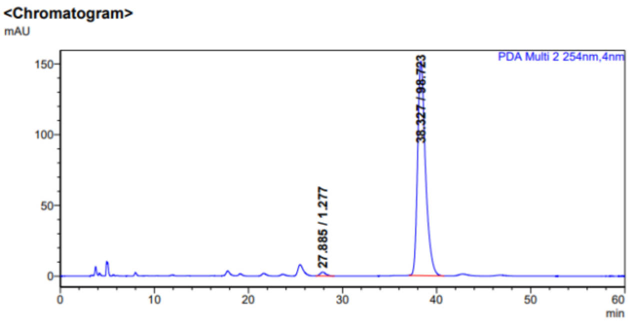


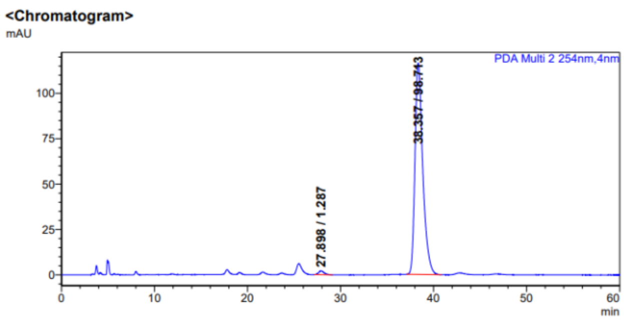
HPLC conditions: AS-H 9% IPA in Hexane. 1 ml/min. 254 nm.

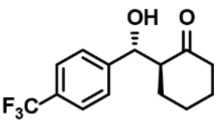
HPLC traces for racemic



HPLC traces for chiral (reaction and duplicate)

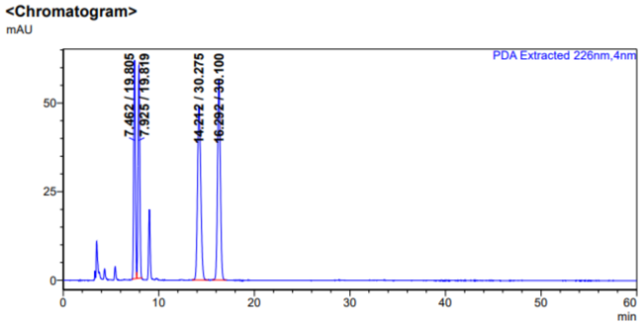




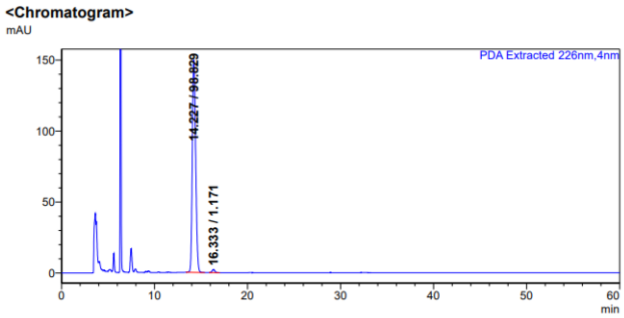


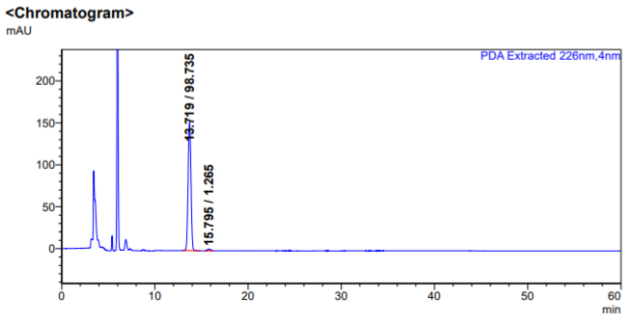
HPLC conditions: IA 9% IPA in Hexane. 1 ml/min. 226 nm.

HPLC traces for racemic



HPLC traces for chiral (reaction and duplicate)

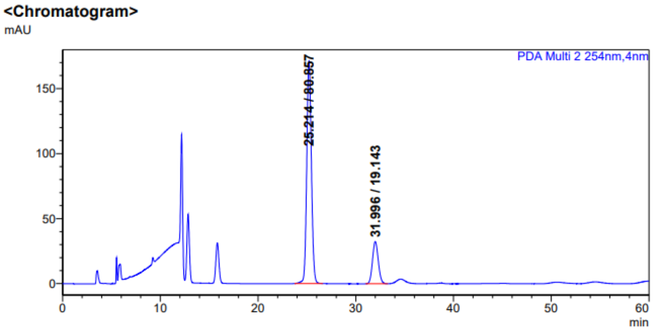


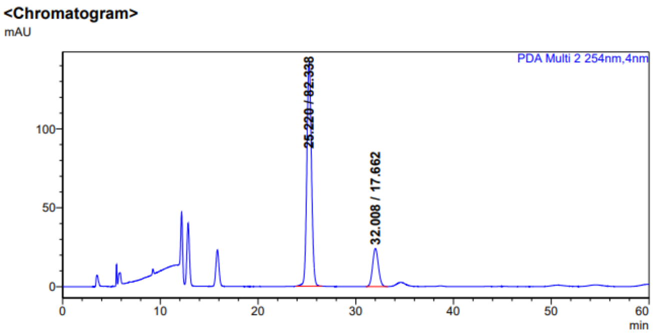


16. Chiral HPLC of optimization and control experiments

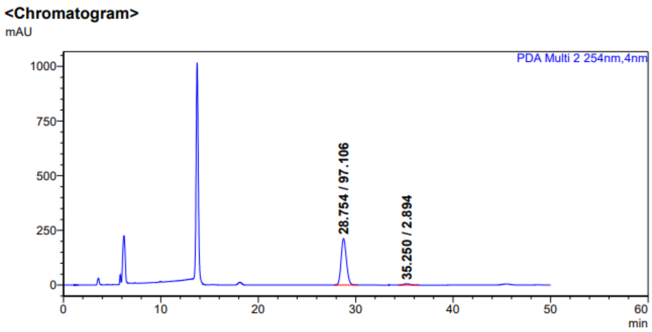
16.1 Solvent screening (table S2)

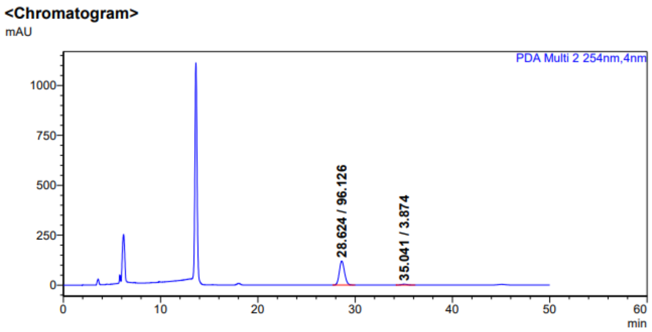
With hexane as a solvent:



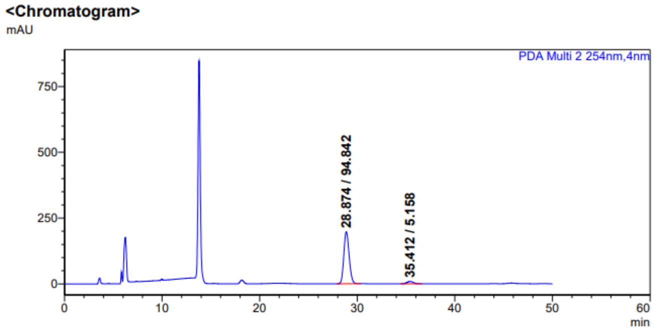


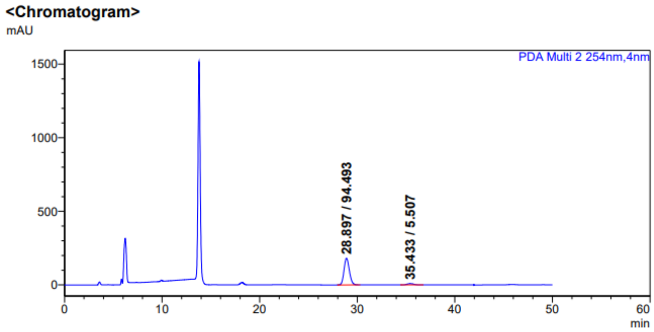
With CH_3CN as a solvent:



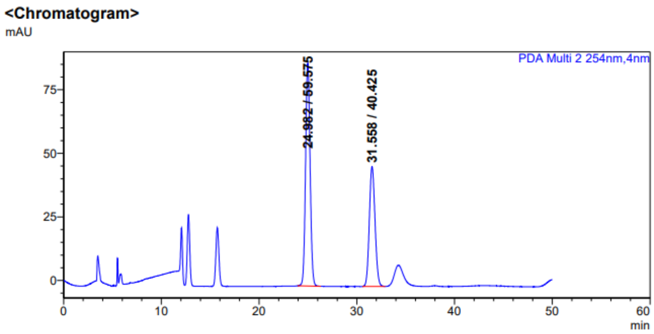


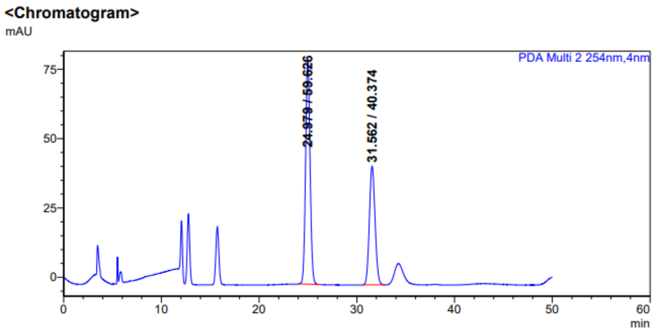
With $CHCl_3$ as a solvent:





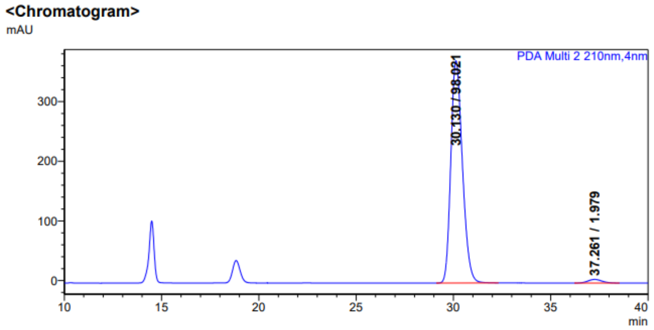
With MeOH as a solvent:

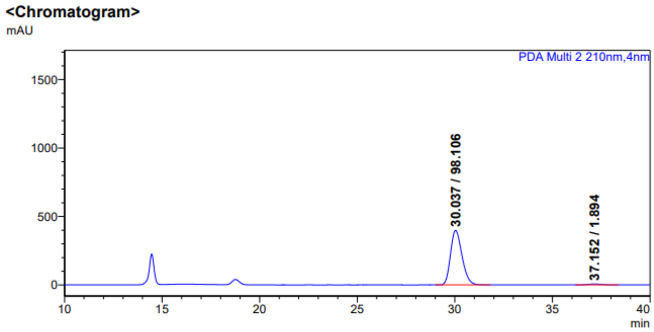




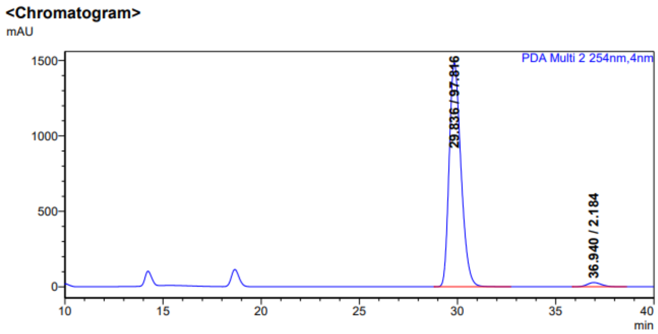
16.2 Time optimization (table S3)

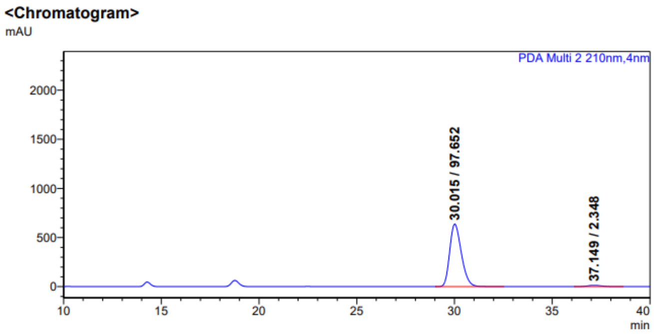
0.5 hour with boronic acid



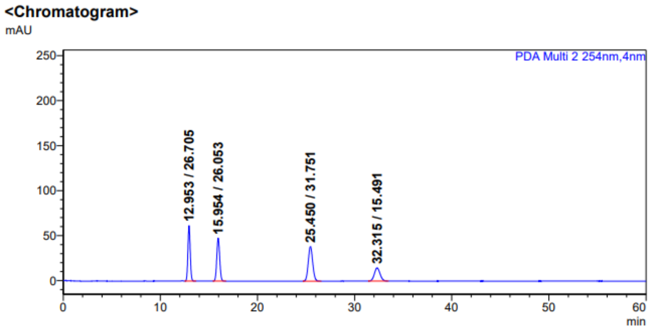


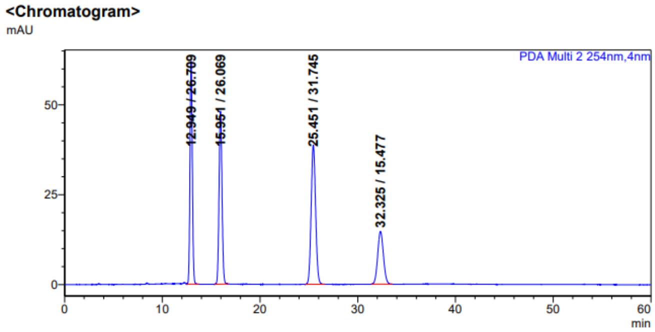
1 hour with boronic acid



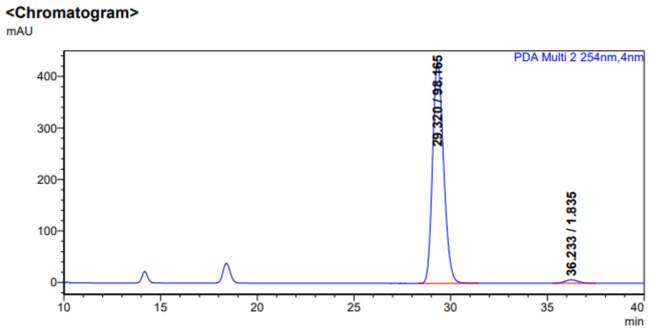


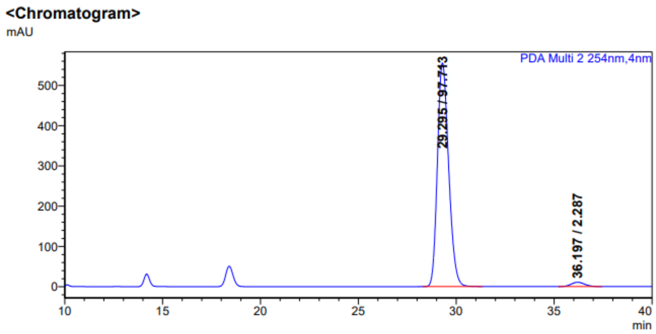
1 hour without boronic acid



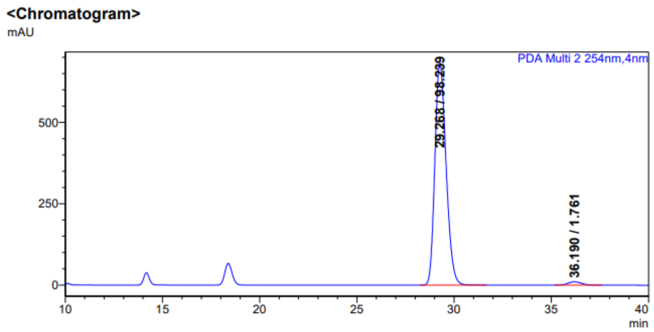


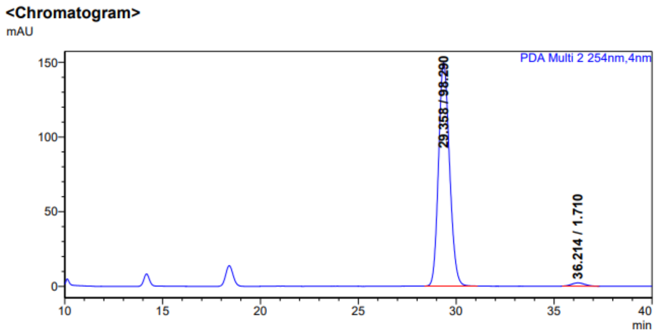
2 hours with boronic acid



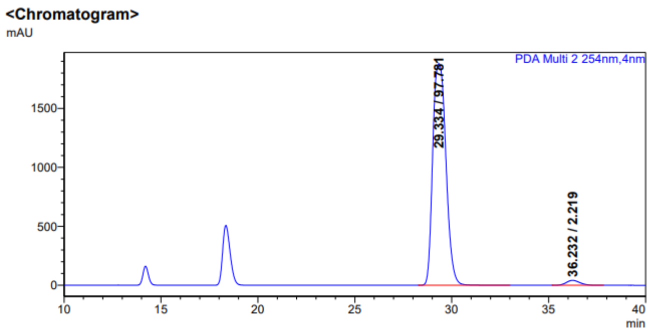


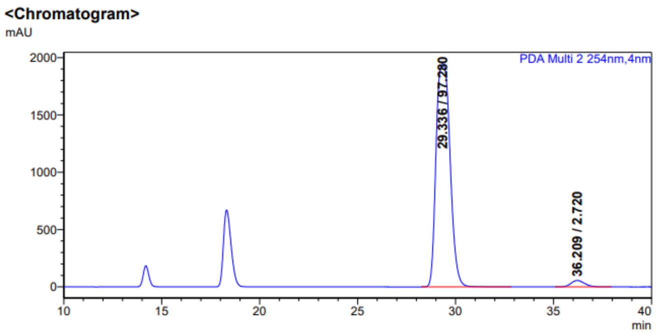
4 hours with boronic acid



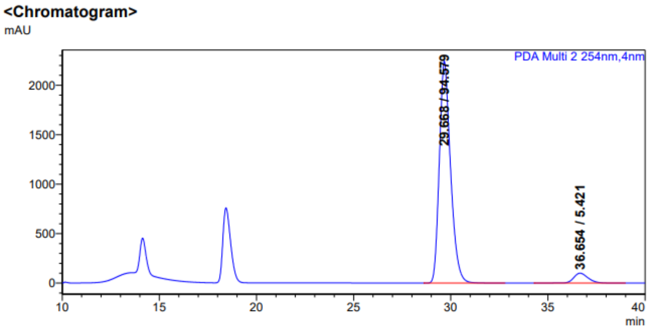


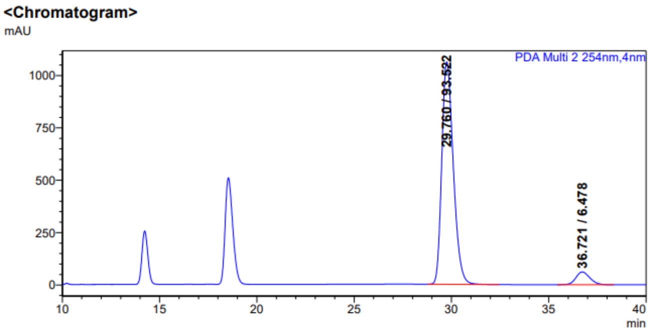
20 hours with boronic acid





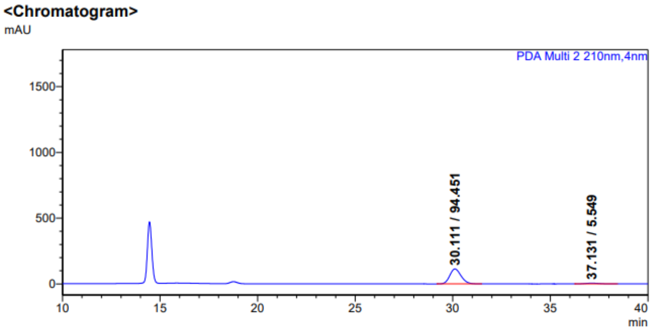
20 hours without boronic acid

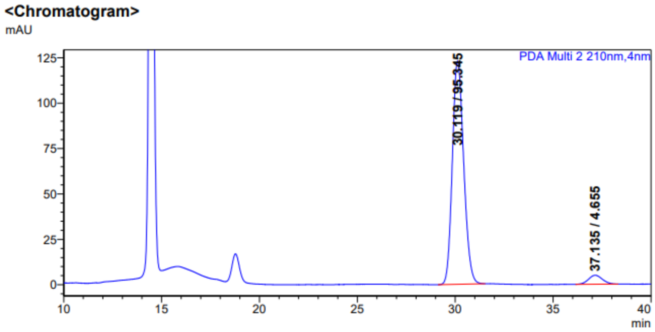




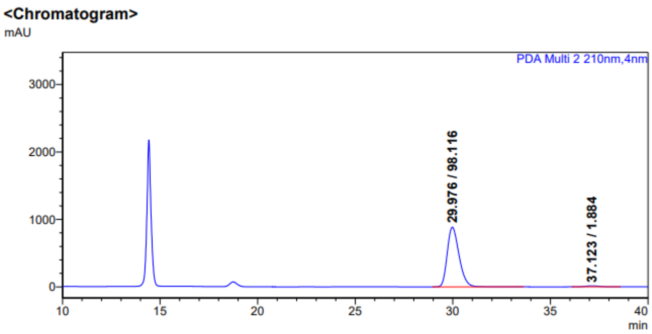
16.3 Water optimization (table S4)

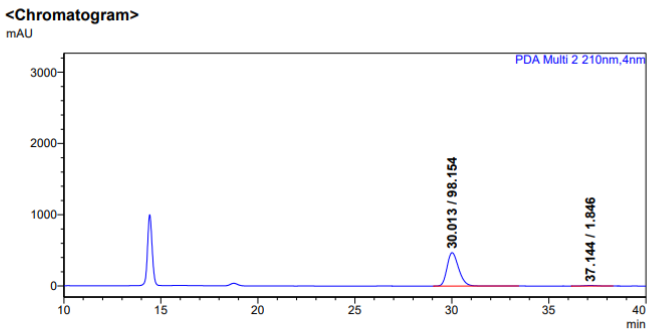
0 mol% H_2O



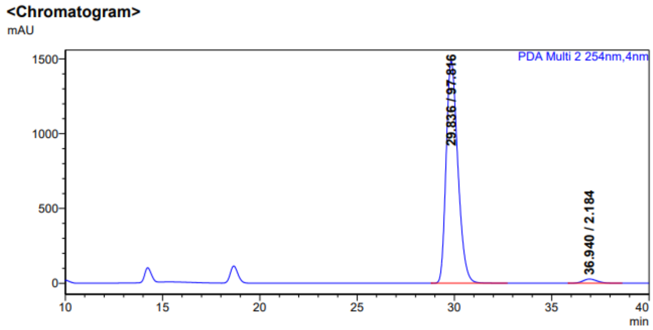


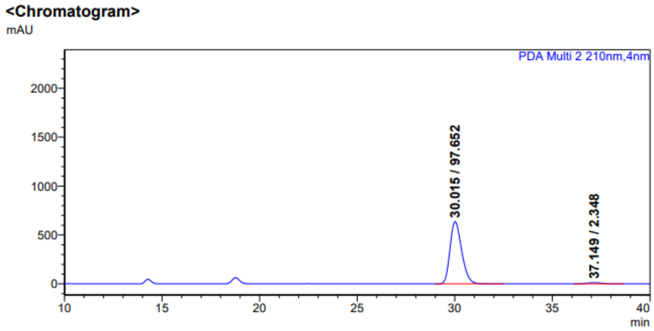
50 mol%



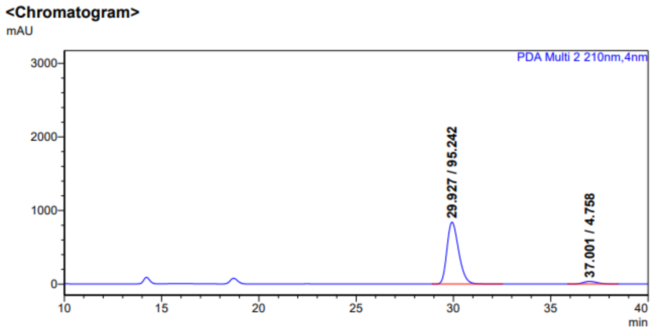


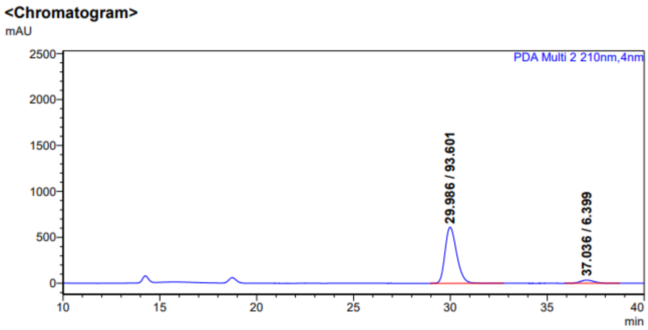
100 mol%





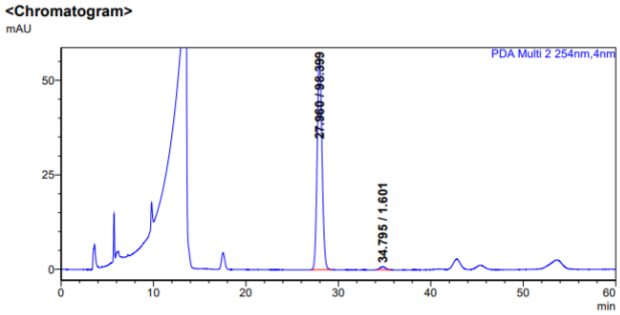
200 mol%

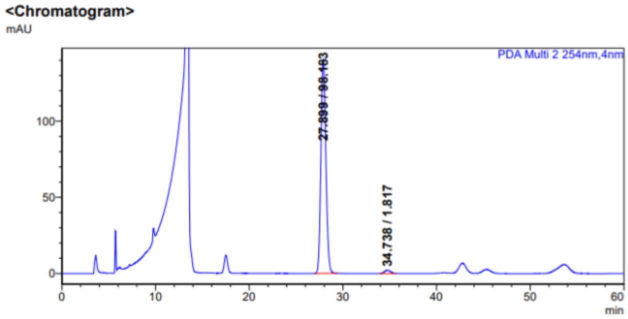




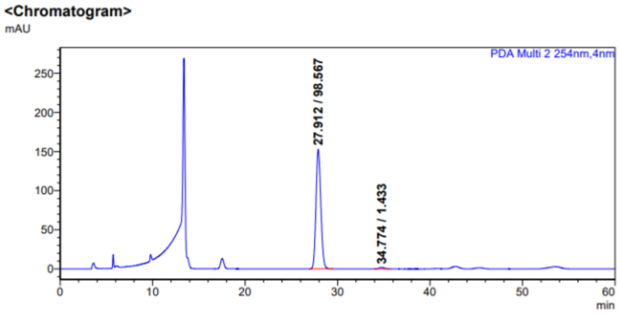
16.4 Water screening without molecular sieves (table S1)

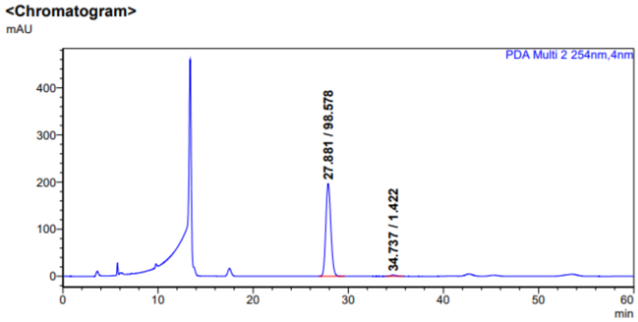
22 mol%



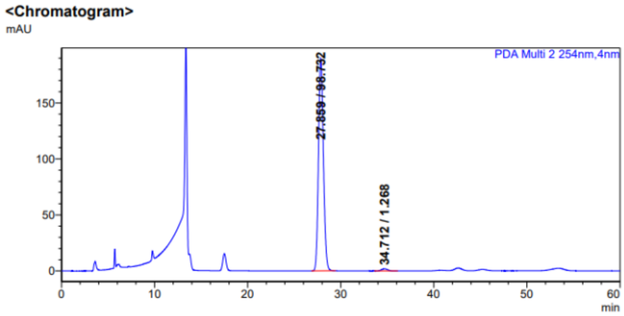


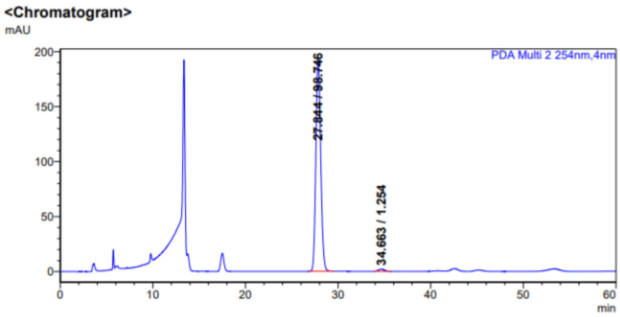
55 mol%





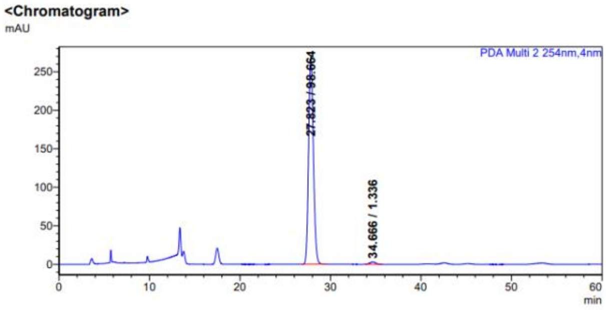
77 mol%

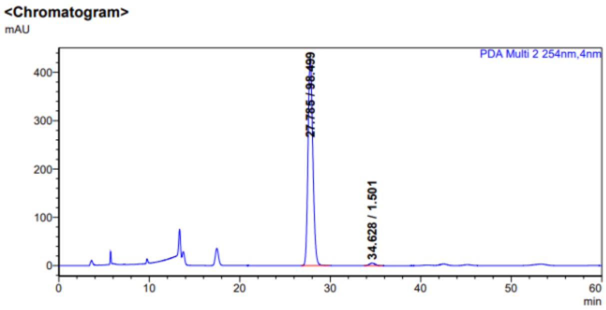

<Chromatogram>
mAU
PDA Multi 2 254nm,4nm
27.859 / 98.732
34.712 / 1.268
min


<Chromatogram>
mAU
PDA Multi 2 254nm,4nm
27.844 / 98.746
34.663 / 1.254
min

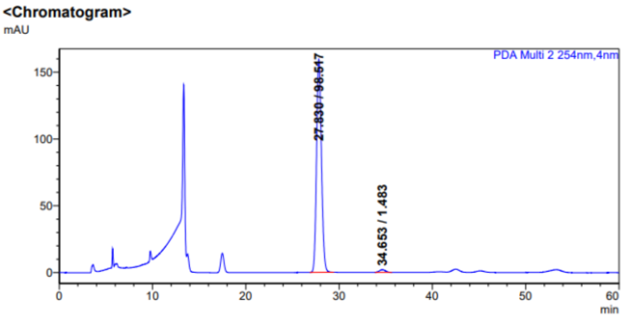
16.5 additional molecular sieves sizes (table S1)

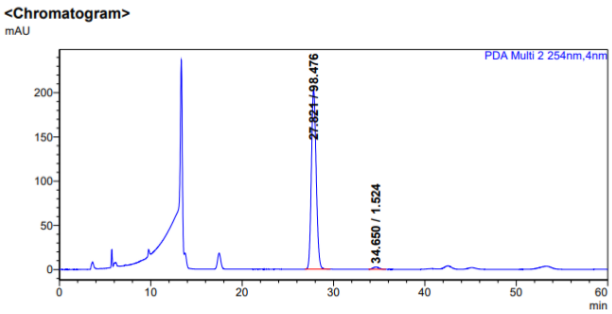
4 angstrom molecular sieves





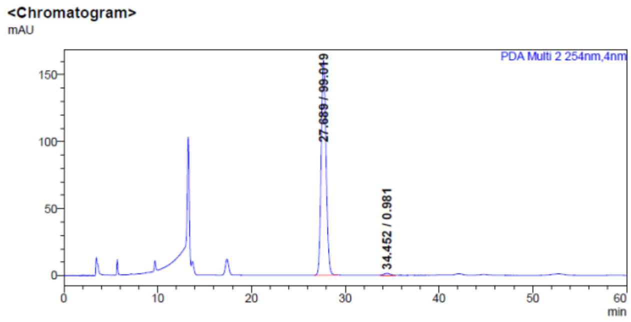
5 angstrom molecular sieves

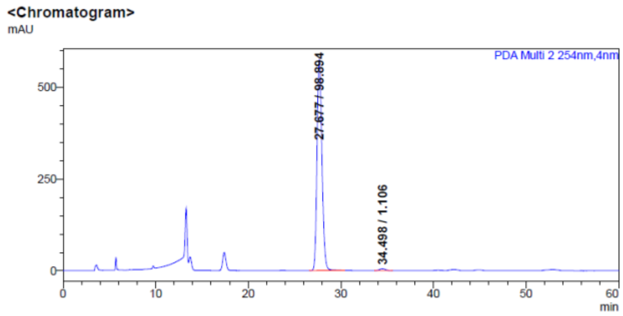




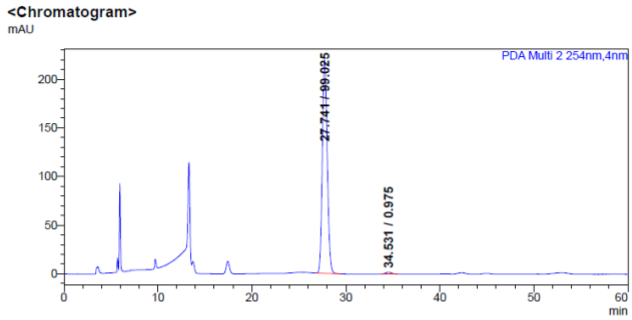
16.6 additional control experiments (table S1)

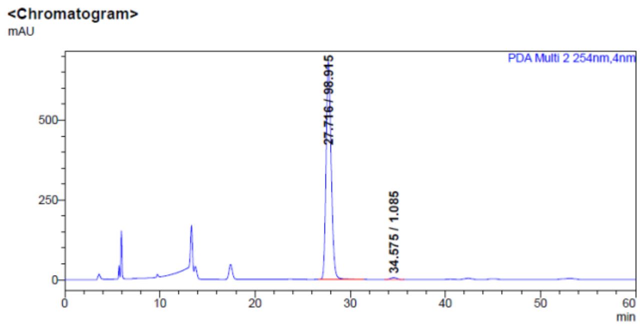
No molecular sieves, 100 mol% H_2O, 100 mol% $KCl_{(S)}$



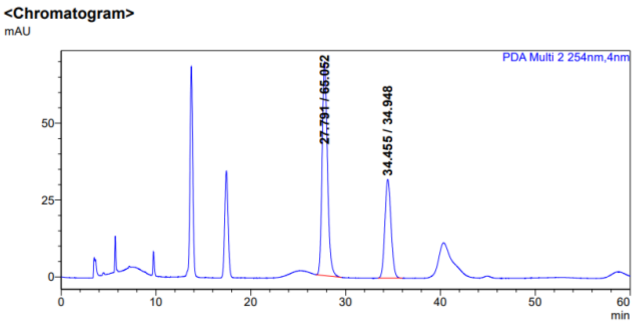


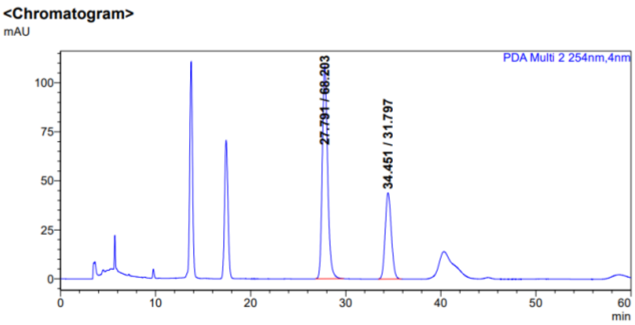
No molecular sieves, 100 mol% H_2O, 10 mol% 2,6-lutidine





No molecular sieves, 100 mol% H_2O, 10 mol% $KHCO_{3(S)}$

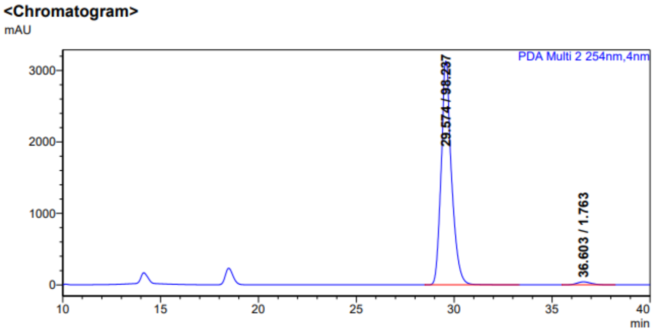




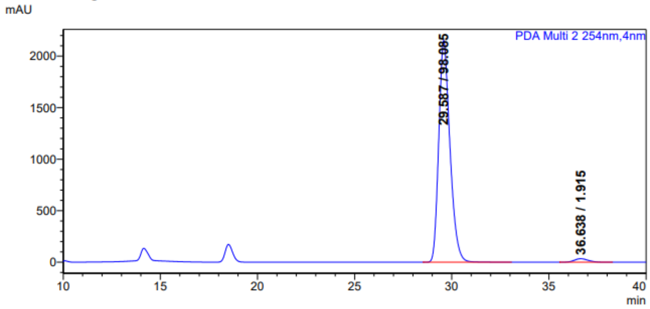
16.7 Boronic acid screening (table S5)

3-F phenylboronic acid

<Chromatogram>

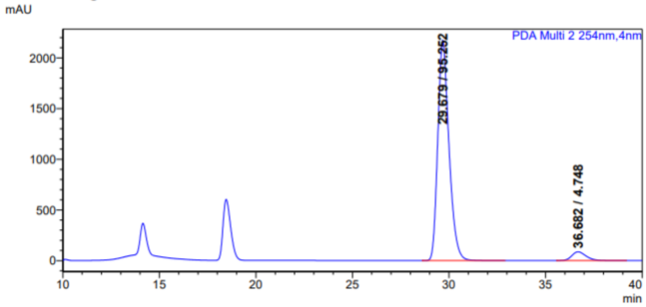


<Chromatogram>

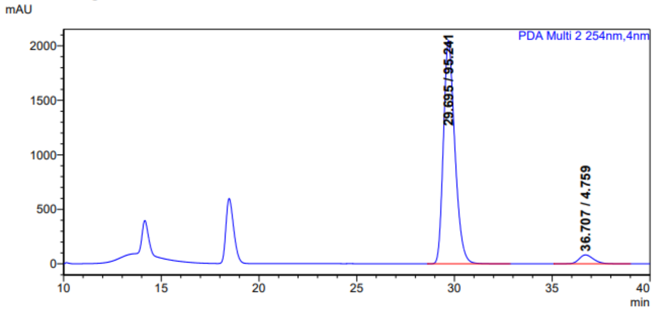


4-*t*Bu phenylboronic acid

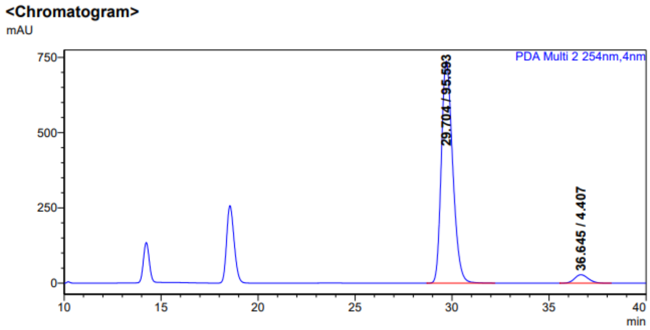
<Chromatogram>

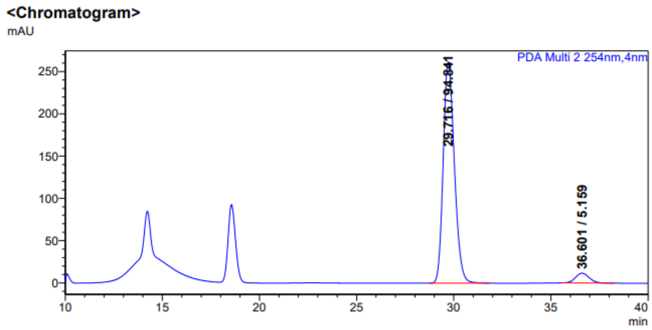


<Chromatogram>

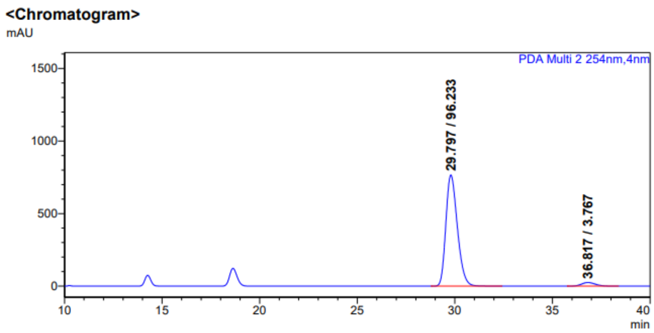


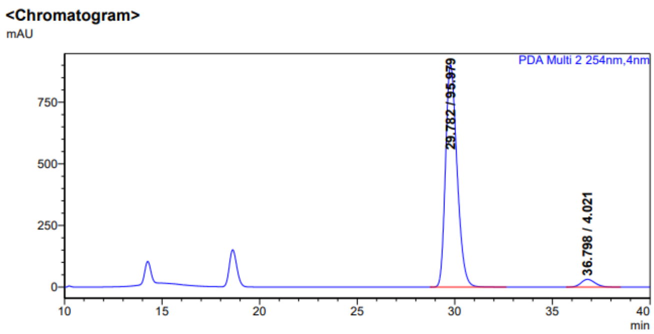
2,4-Me phenylboronic acid



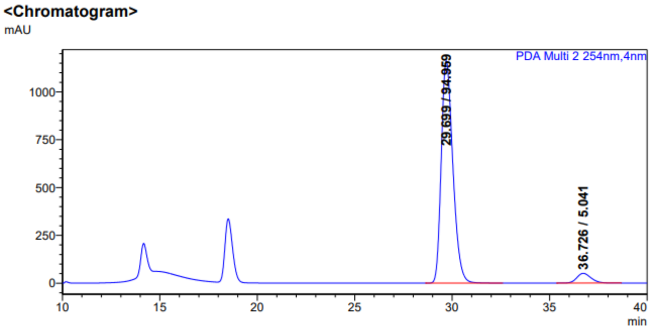


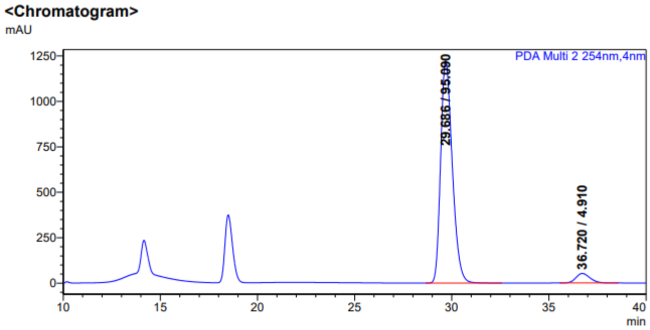
3,5-OMe phenylboronic acid



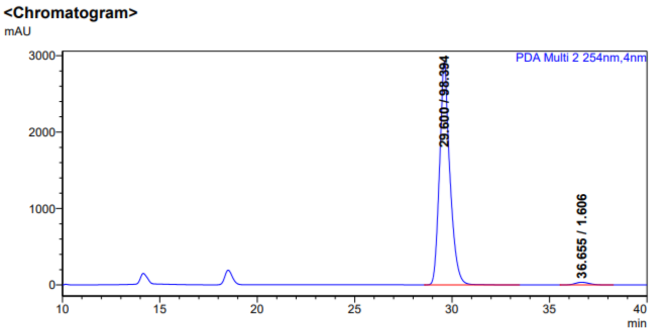


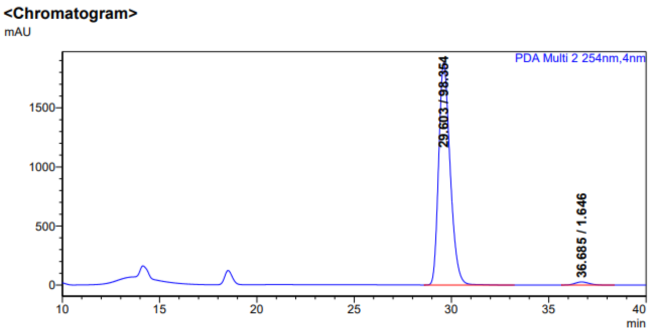
4-Me phenylboronic acid



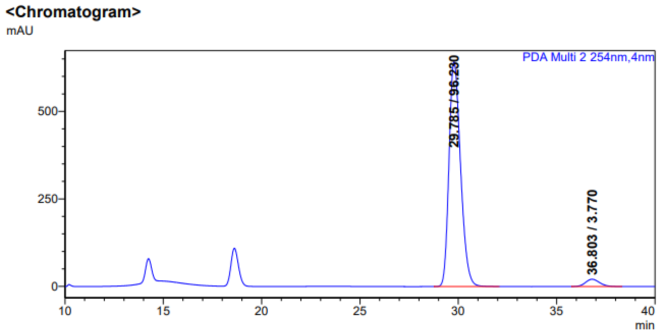


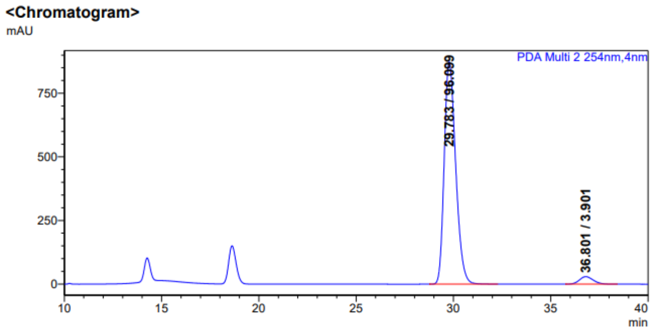
3-CF_3 phenylboronic acid



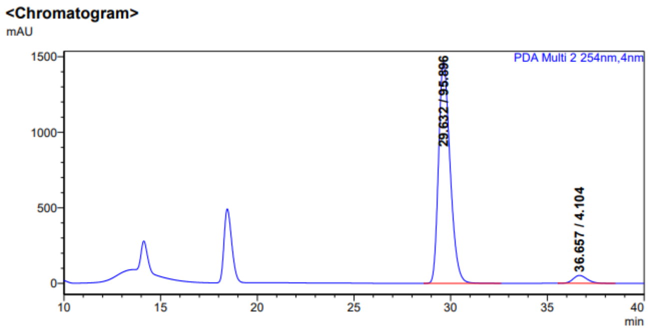


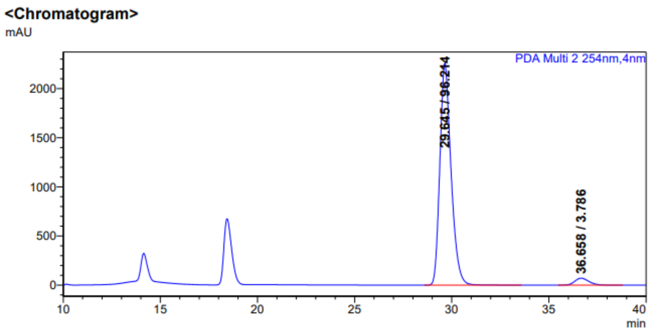
Naphthalene boronic acid



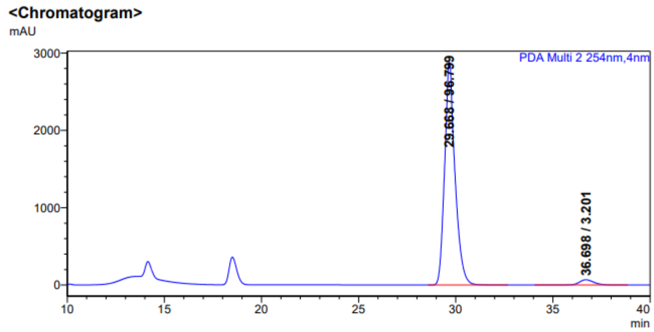


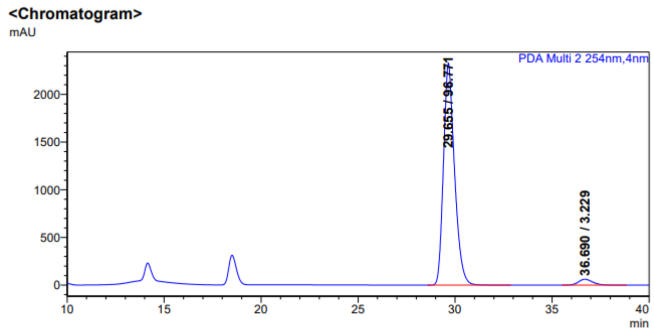
4-CF_3 phenylboronic acid



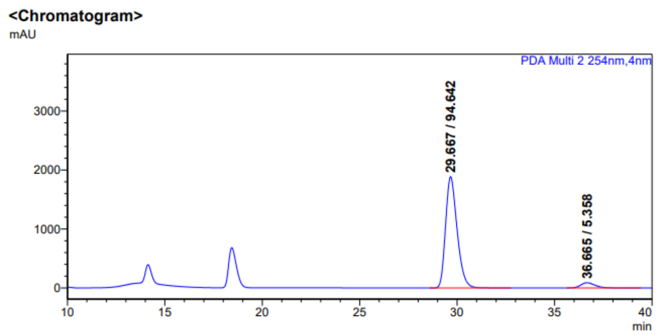


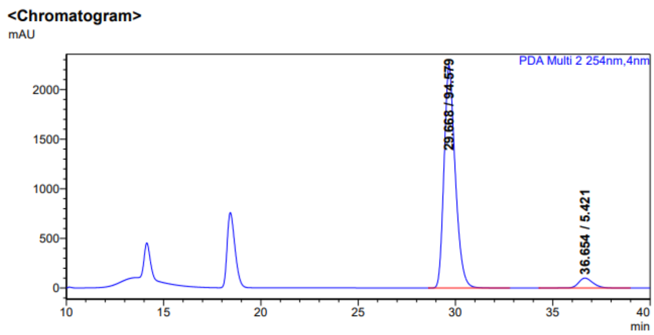
4-F phenylboronic acid



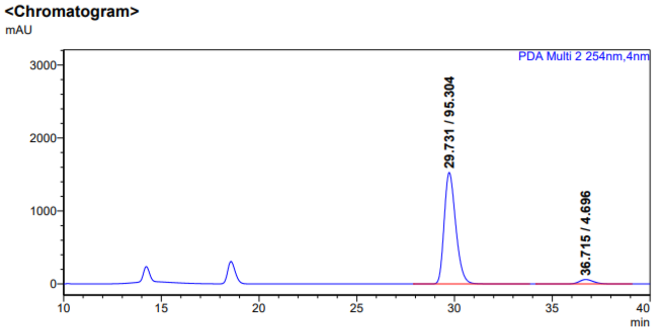


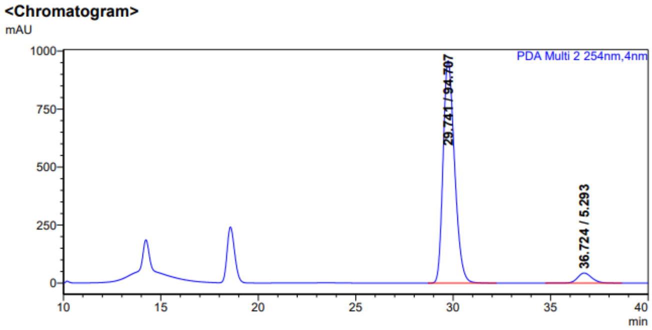
4-OMe phenylboronic acid



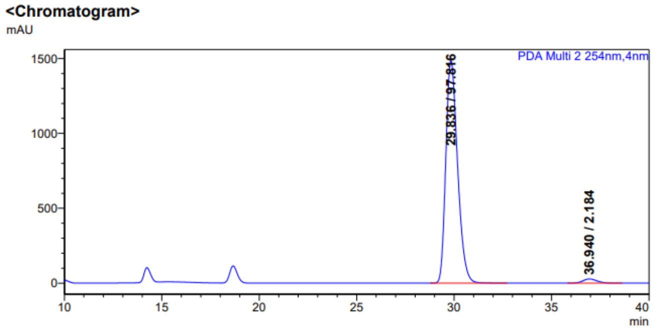


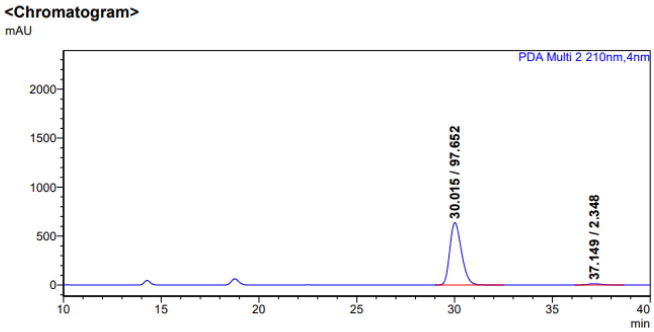
3-Me phenylboronic acid



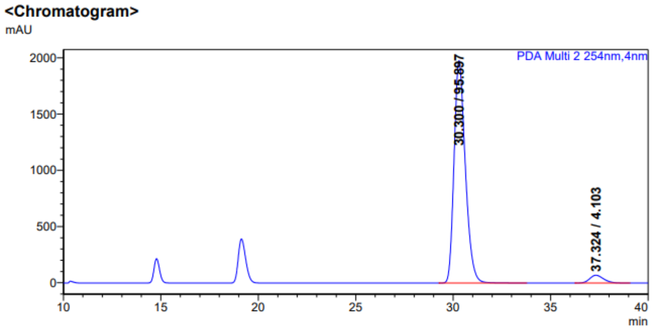


2-F phenylboronic acid

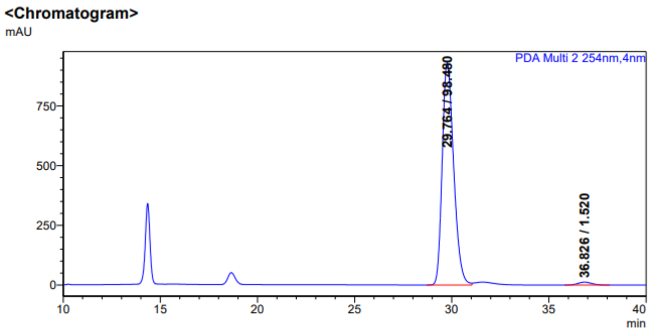


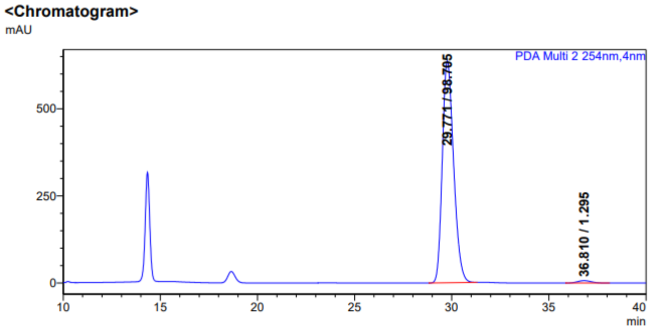


Phenylboronic acid

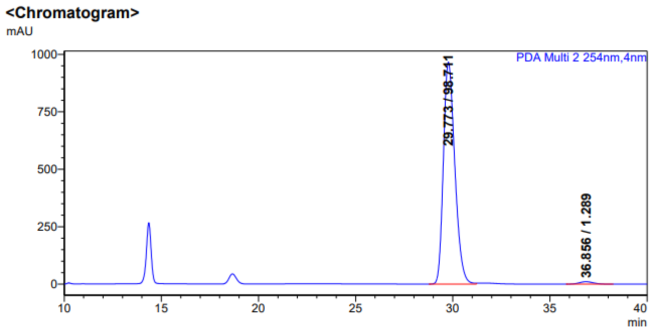


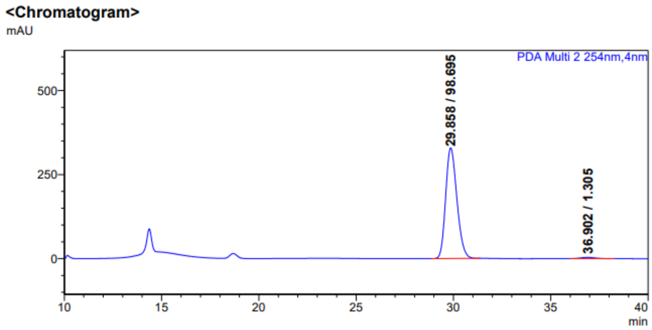
3,5-F phenylboronic acid





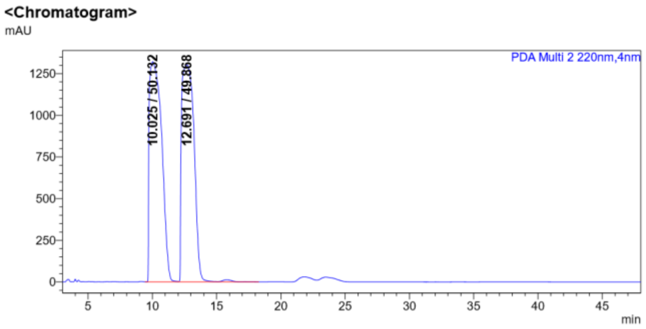
2-Me phenylboronic acid



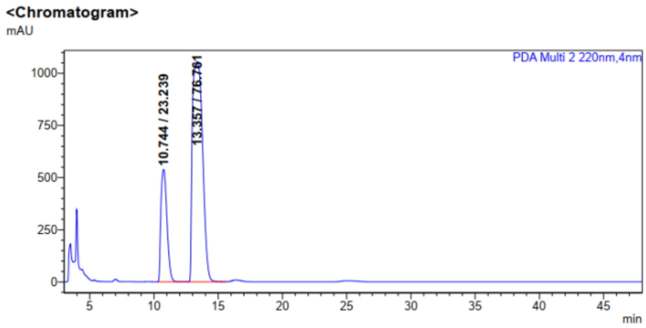


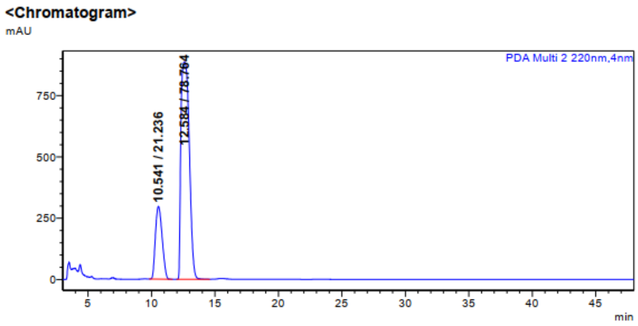
16.8 Boronic acid screening using acetone as aldol donor (table S8)

Racemic

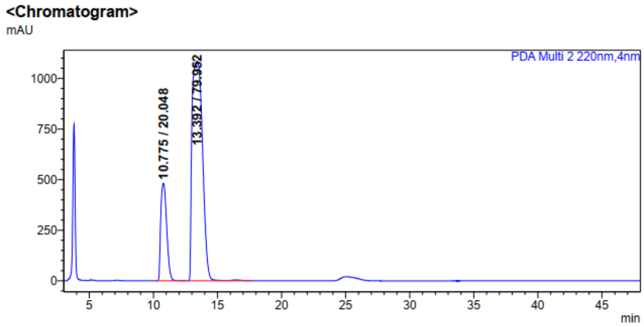


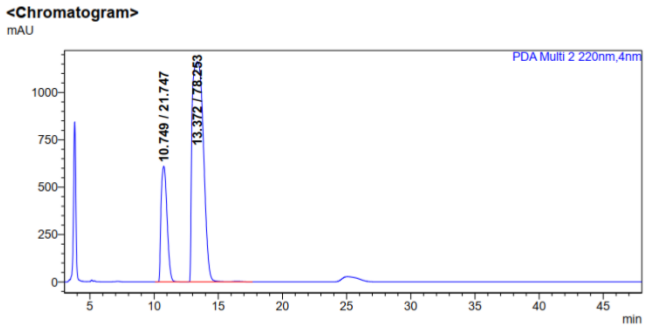
2-Me phenylboronic acid



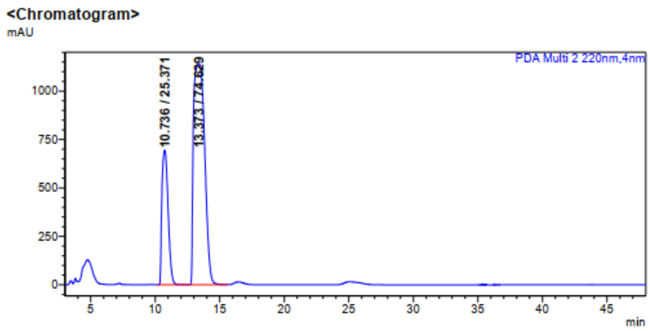


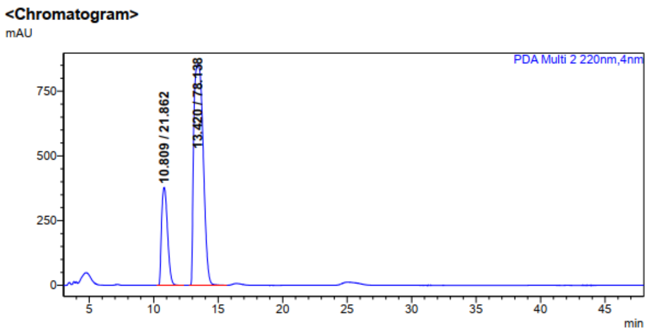
2-F phenylboronic acid



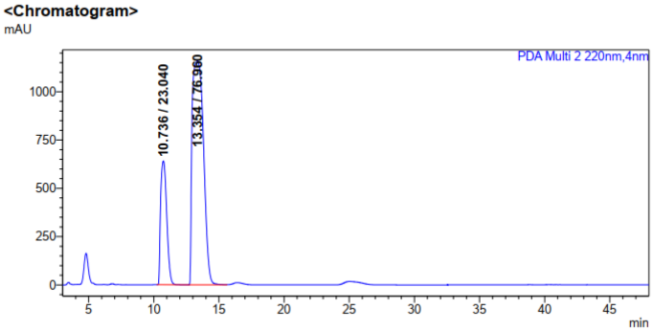


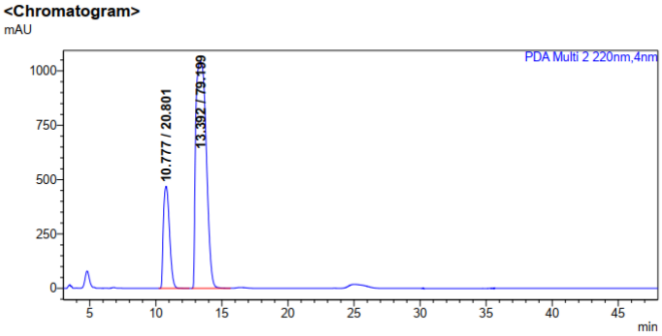
3-Me phenylboronic acid



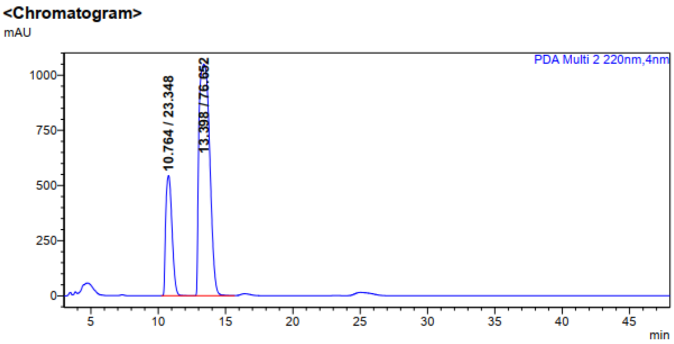


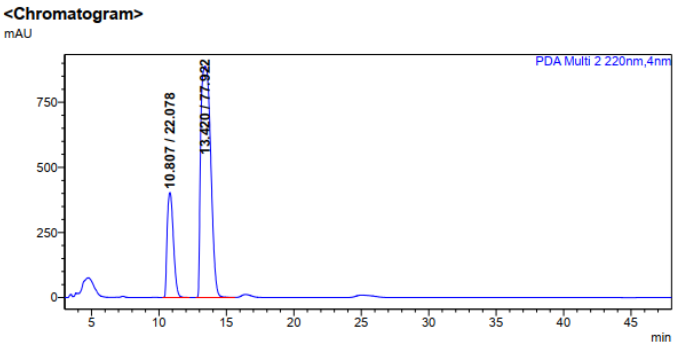
3-F phenylboronic acid



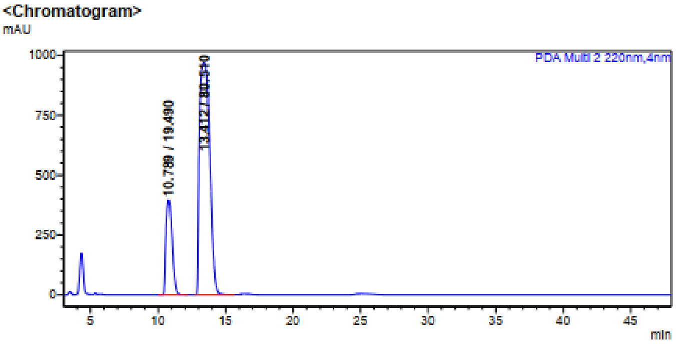


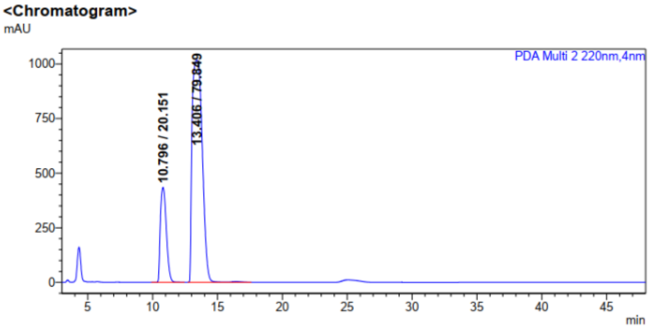
4-Me phenylboronic acid





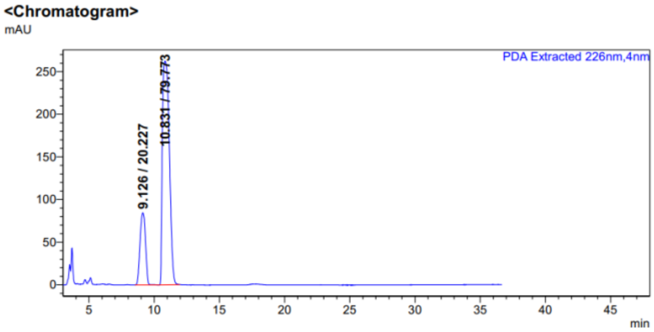
4-CF_3 phenylboronic acid

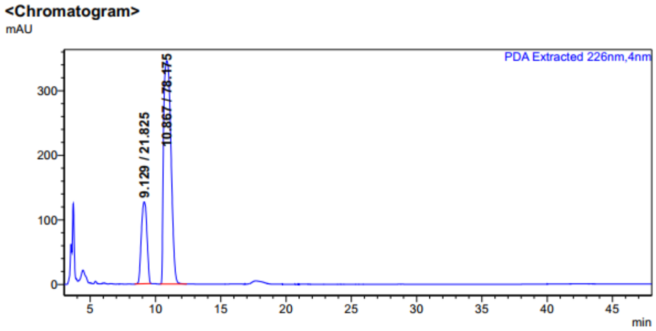




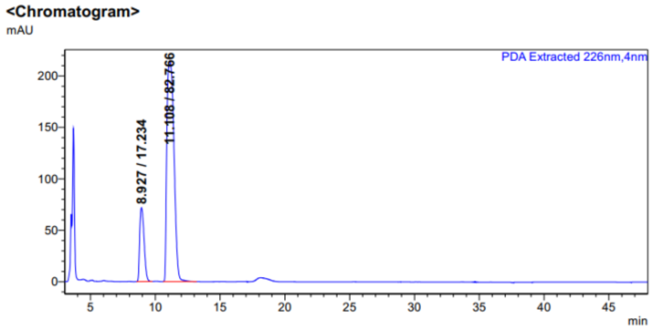
16.9 Boronic acid / proline ratio screening using acetone as aldol donor (table S9)

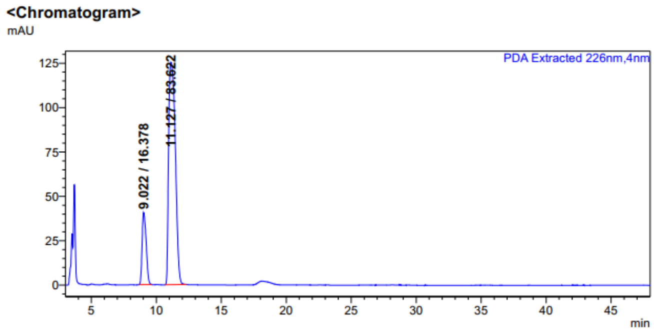
1:1



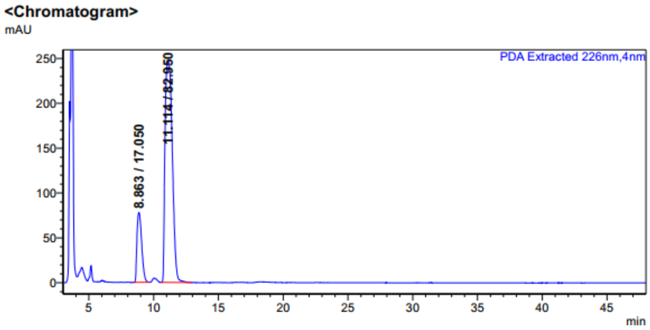


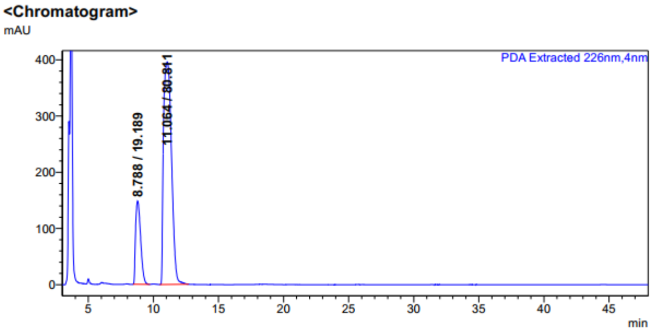
2:1



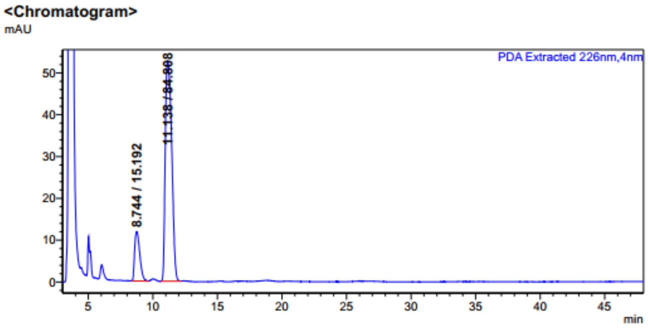


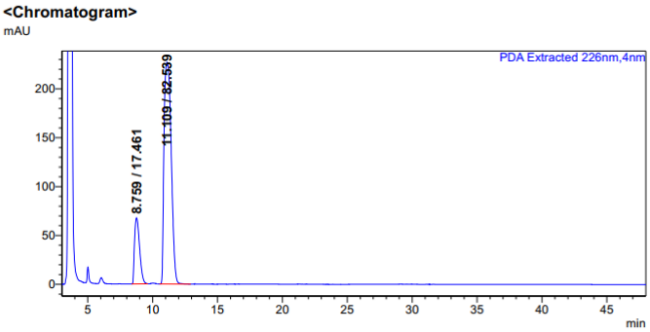
4:1


<Chromatogram>
mAU
PDA Extracted 226nm,4nm
8.863 / 17.050
11.114 / 82.950
min


<Chromatogram>
mAU
PDA Extracted 226nm,4nm
8.788 / 19.189
11.064 / 80.811
min

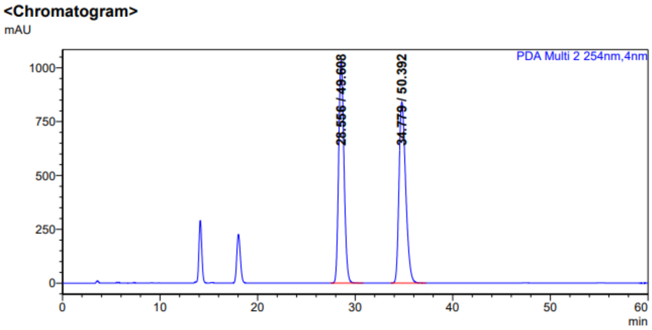
6:1

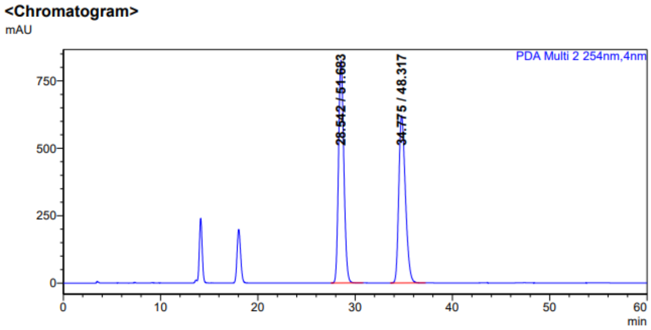

<Chromatogram>
mAU
PDA Extracted 226nm,4nm
8.744 / 15.192
11.138 / 84.808
min


<Chromatogram>
mAU
PDA Extracted 226nm,4nm
8.759 / 17.461
11.109 / 82.539
min

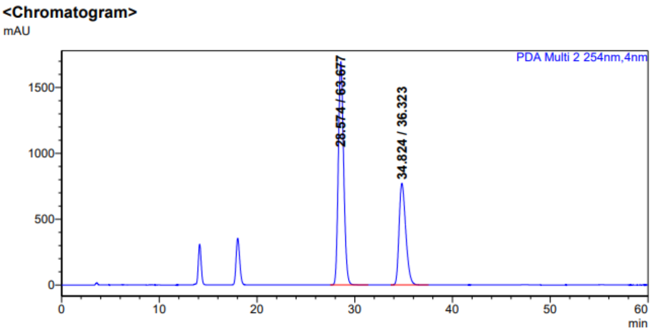
16.10 Non-linear experiments (table S10)

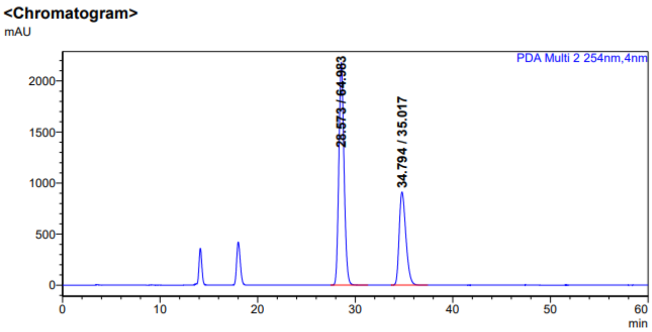
0 mol%



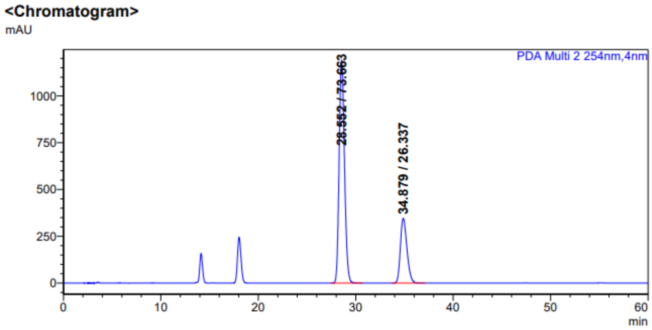


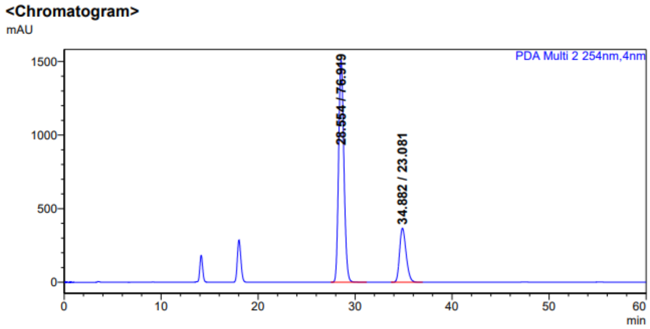
25% ee



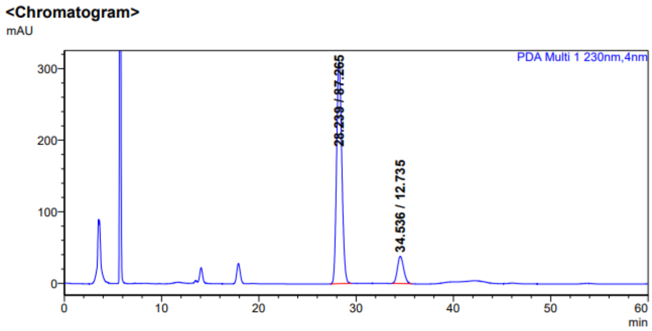


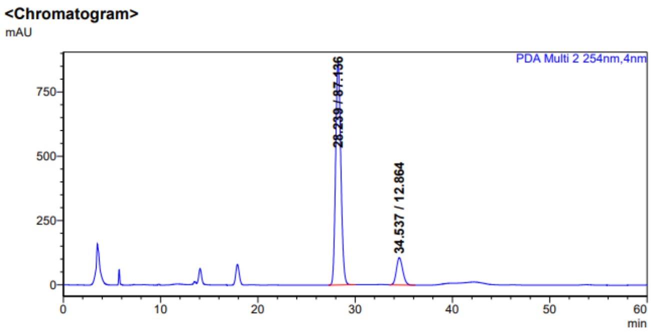
50% ee


<Chromatogram>
mAU
PDA Multi 2 254nm,4nm
28.552 / 73.663
34.879 / 26.337
0
250
500
750
1000
10
20
30
40
50
60
min

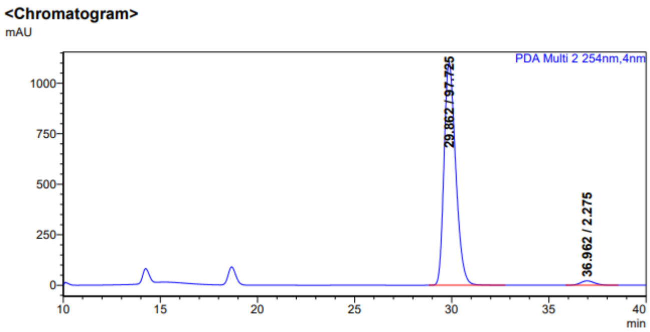

<Chromatogram>
mAU
PDA Multi 2 254nm,4nm
28.554 / 76.919
34.882 / 23.081
0
500
1000
1500
10
20
30
40
50
60
min

75% ee

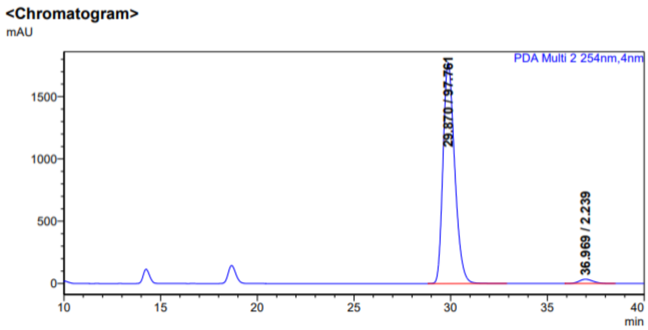

<Chromatogram>
mAU
PDA Multi 1 230nm,4nm
28.239 / 87.265
34.536 / 12.735
0
100
200
300
10
20
30
40
50
60
min


<Chromatogram>
mAU
PDA Multi 2 254nm,4nm
28.239 / 87.136
34.537 / 12.864
0
250
500
750
10
20
30
40
50
60
min

99% ee



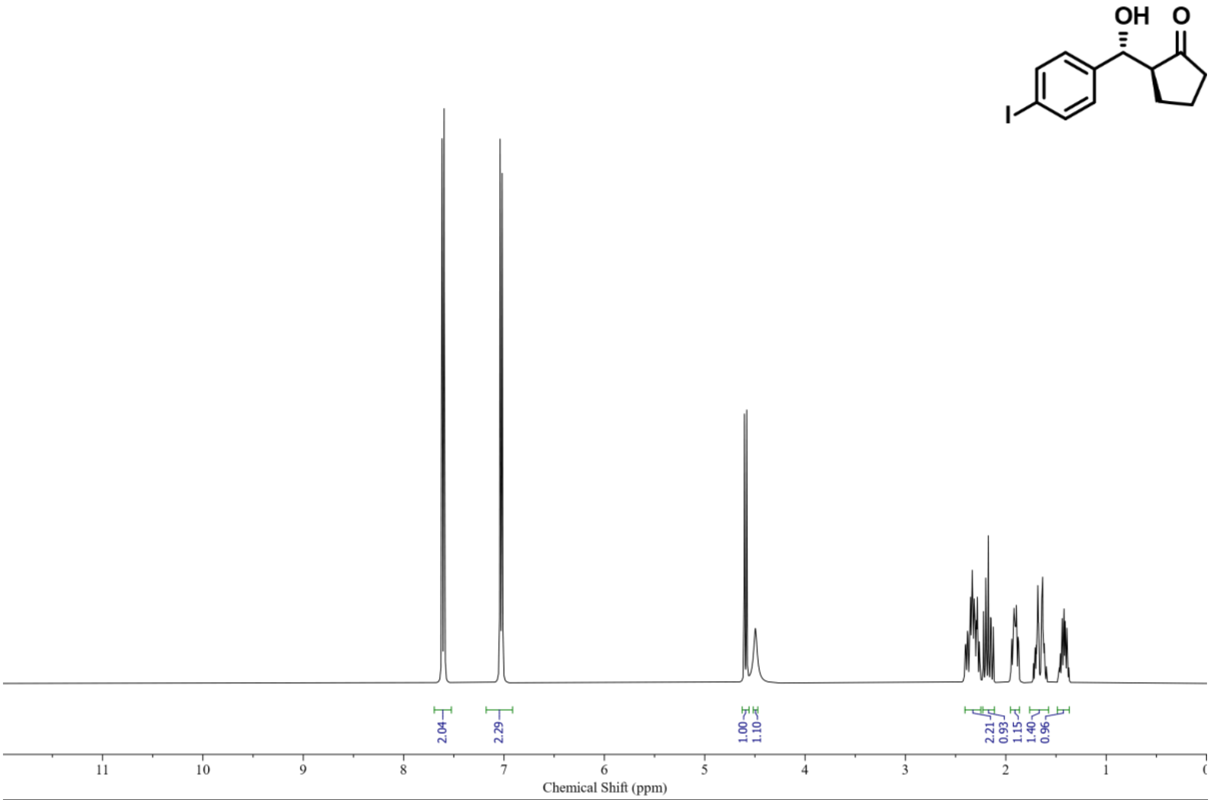
<Chromatogram>
mAU
PDA Multi 2 254nm,4nm
29.862 / 97.725
36.962 / 2.275
min



<Chromatogram>
mAU
PDA Multi 2 254nm,4nm
29.870 / 97.761
36.969 / 2.239
min

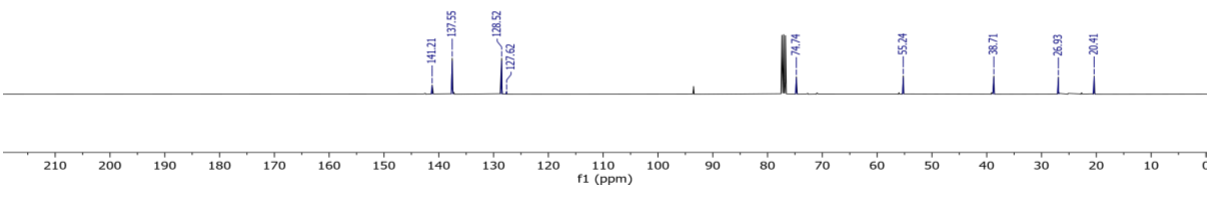
17. NMR spectra of aldol adducts after purification

^{1}H-NMR



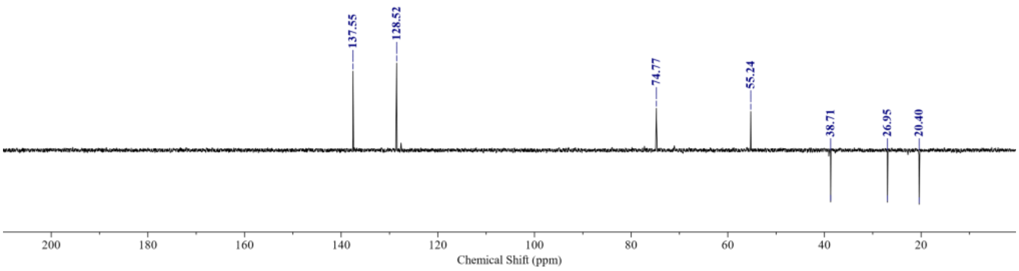
1H NMR (400 MHz, CDCl3) δ 7.61 (d, J = 8.3 Hz, 2H), 7.03 (d, J = 8.3 Hz, 2H), 4.59 (d, J = 9.1 Hz, 1H), 4.49 (s, 1H), 2.45 – 2.25 (m, 2H), 2.17 (ddd, J = 19.5, 10.8, 9.0 Hz, 1H), 1.96 – 1.84 (m, 1H), 1.66 (dddd, J = 14.3, 8.4, 7.3, 3.5 Hz, 2H), 1.47 – 1.34 (m, 1H).

^{13}C-NMR



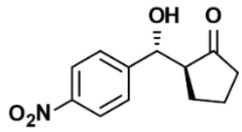
^{13}C NMR (101 MHz, $CDCl_3$) δ 141.21, 137.55, 128.52, 93.51, 74.74, 55.24, 38.71, 26.93, 20.41.

^{13}C-DEPT NMR

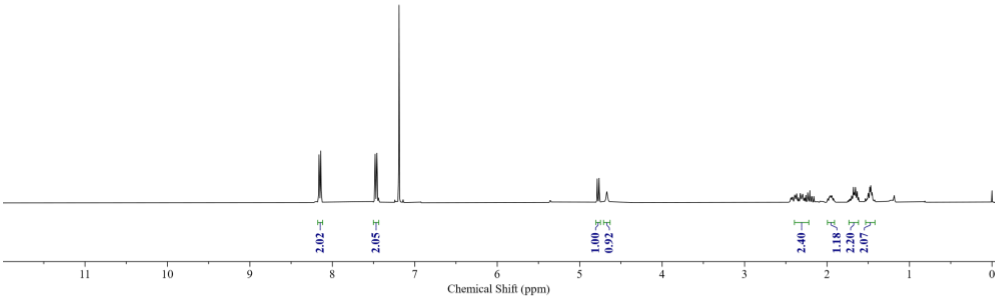


^{13}C NMR (101 MHz, $CDCl_3$) δ 137.55, 128.52, 74.77, 55.24, 38.71, 26.95, 20.40.

^{1}H-NMR

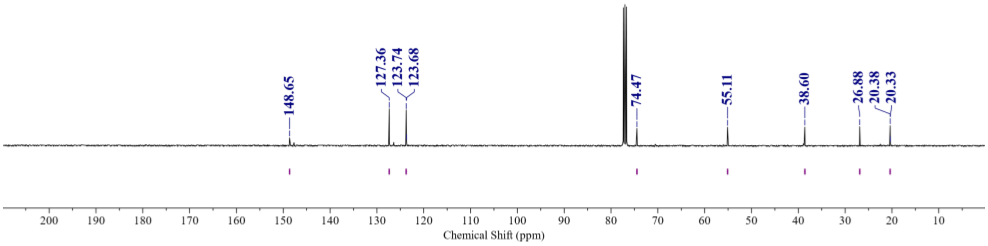


anti



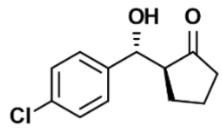
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15 (d, *J* = 8.6 Hz, 2H), 7.47 (d, *J* = 8.7 Hz, 2H), 4.78 (d, *J* = 9.2 Hz, 1H), 4.67 (s, 1H), 2.47 – 2.15 (m, 2H), 2.01 – 1.90 (m, 1H), 1.72 – 1.60 (m, 2H), 1.48 (q, *J* = 6.7 Hz, 2H).

^{13}C-NMR

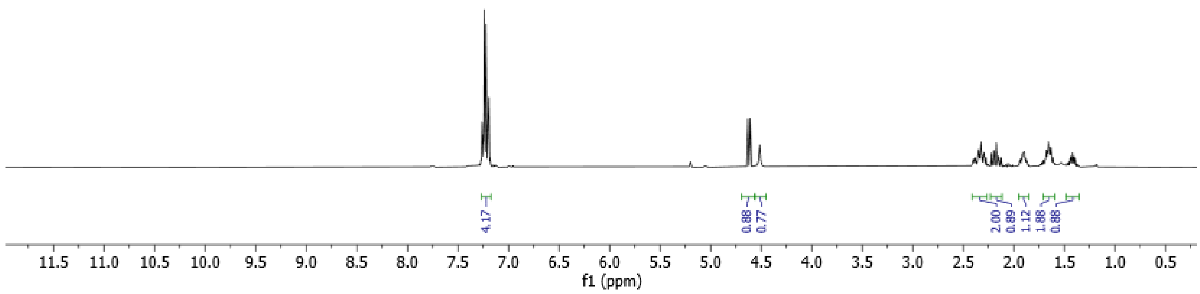


^{13}C NMR (101 MHz, $CDCl_3$) δ 148.65, 127.36, 123.74, 74.47, 55.11, 38.60, 26.88, 20.38.

[1]H-NMR

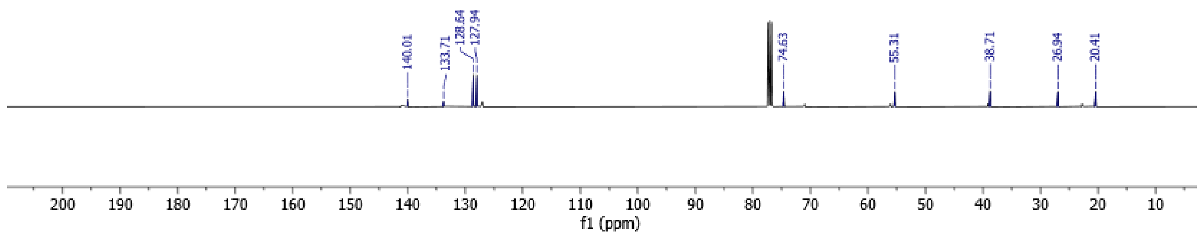


anti



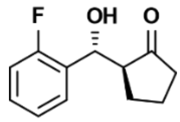
[1]H NMR (400 MHz, $CDCl_3$) δ 7.54 – 6.96 (m, 4H), 4.62 (d, *J* = 9.1 Hz, 1H), 4.51 (s, 1H), 2.46 – 2.26 (m, 2H), 2.17 (ddd, *J* = 19.5, 10.7, 9.0 Hz, 1H), 1.96 – 1.86 (m, 1H), 1.72 – 1.61 (m, 2H), 1.48 – 1.36 (m, 1H).

[13]C-NMR

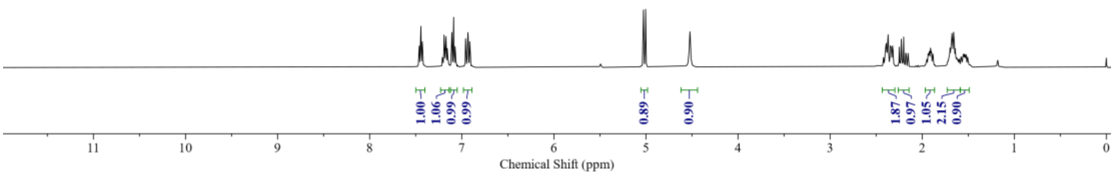


[13]C NMR (101 MHz, $CDCl_3$) δ 140.01, 133.71, 128.64, 127.94, 74.63, 55.31, 38.71, 26.94, 20.41.

^{1}H-NMR

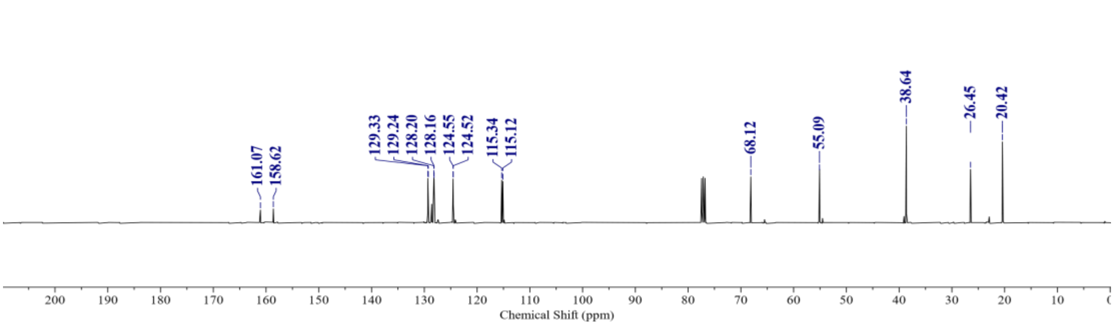


anti



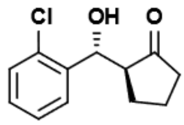
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 (td, *J* = 7.5, 1.9 Hz, 1H), 7.17 (ddd, *J* = 7.4, 5.5, 2.1 Hz, 1H), 7.09 (td, *J* = 7.5, 1.3 Hz, 1H), 6.93 (ddd, *J* = 9.7, 8.2, 1.3 Hz, 1H), 5.02 (d, *J* = 9.5 Hz, 1H), 4.52 (s, 1H), 2.44 – 2.30 (m, 2H), 2.20 (ddd, *J* = 19.3, 10.3, 8.7 Hz, 1H), 1.92 (dddd, *J* = 12.5, 10.3, 7.3, 2.2 Hz, 1H), 1.76 – 1.60 (m, 2H), 1.54 (dddd, *J* = 12.6, 7.7, 5.7, 2.1 Hz, 1H).

^{13}C-NMR

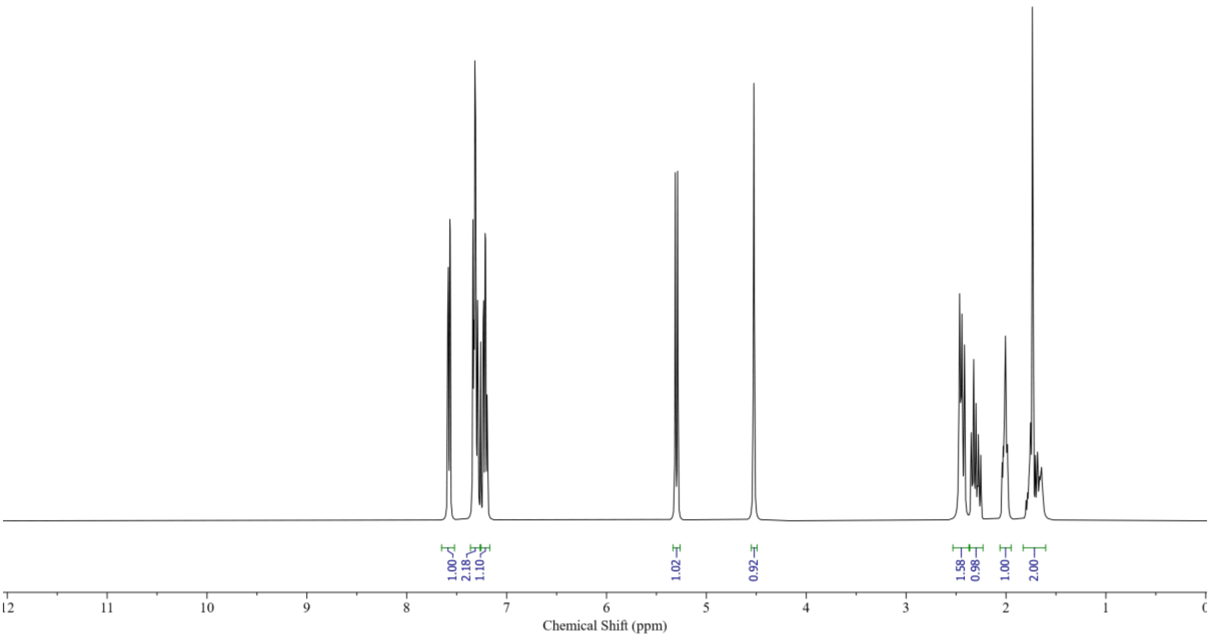


^{13}C NMR (101 MHz, $CDCl_3$) δ 161.07, 158.62, 129.33, 128.20, 124.55, 68.12, 55.09, 38.64, 26.45, 20.42.

[1]H-NMR

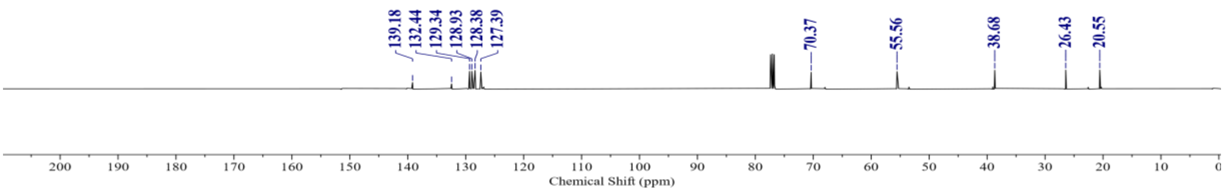


anti



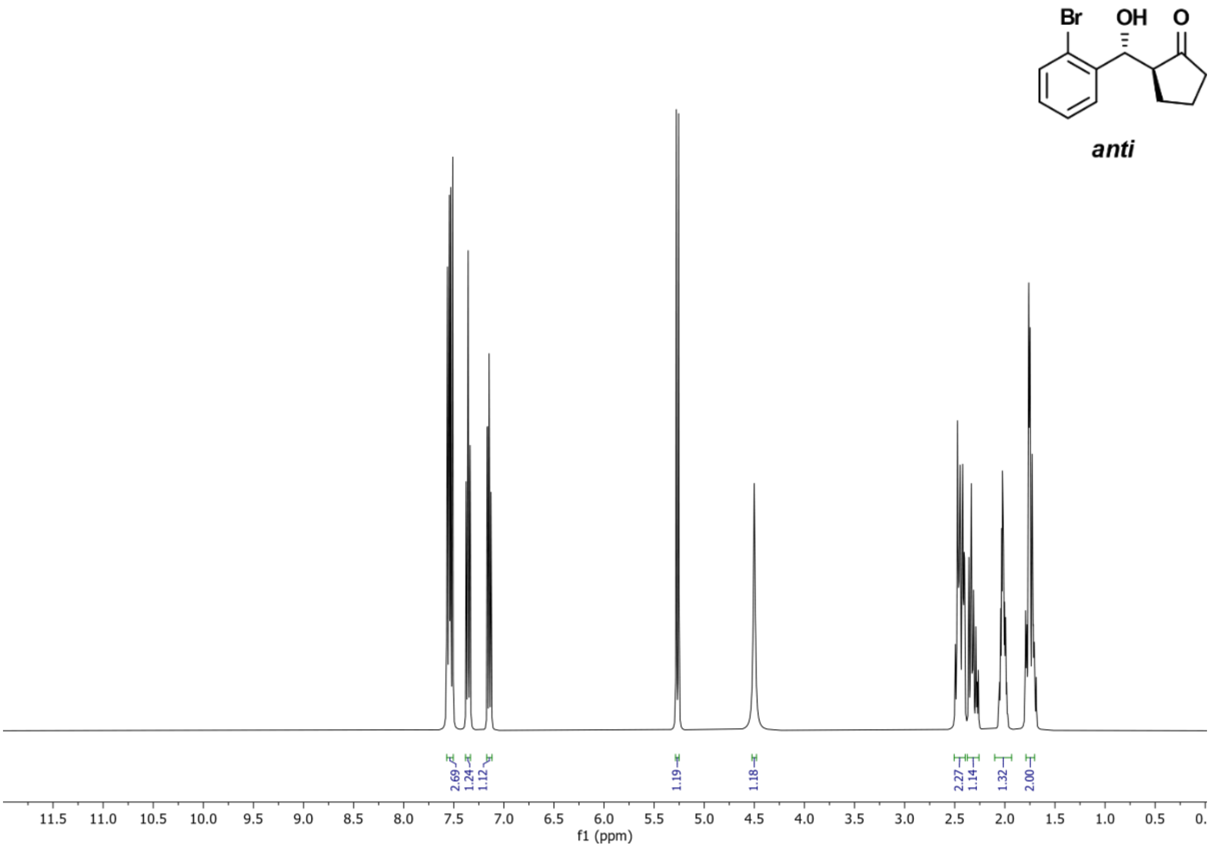
[1]H NMR (400 MHz, CDCl$_3$) δ 7.58 (dd, *J* = 7.7, 1.7 Hz, 1H), 7.36 – 7.27 (m, 2H), 7.21 (td, *J* = 7.6, 1.8 Hz, 1H), 5.30 (d, *J* = 9.3 Hz, 1H), 4.52 (s, 1H), 2.53 – 2.36 (m, 2H), 2.37 – 2.23 (m, 1H), 2.06 – 1.95 (m, 1H), 1.83 – 1.60 (m, 2H).

[13]C-NMR



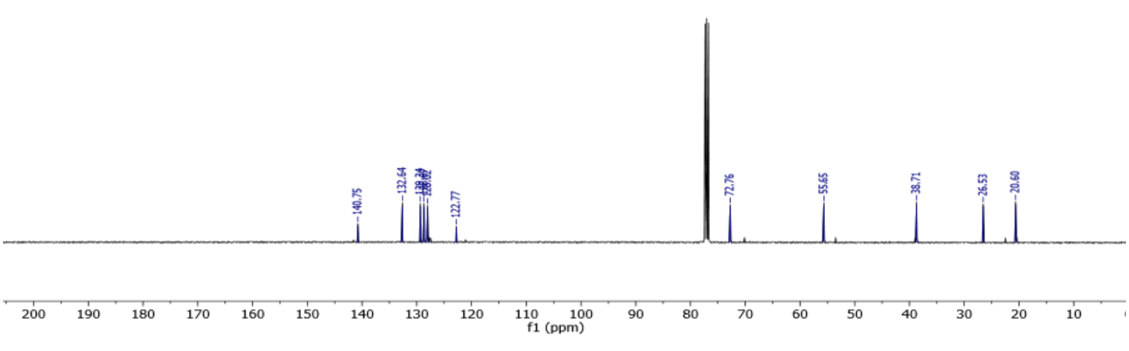
[13]C NMR (101 MHz, CDCl$_3$) δ 139.18, 132.44, 129.34, 128.93, 128.38, 127.39, 70.37, 55.56, 38.68, 26.43, 20.55.

[1]H-NMR



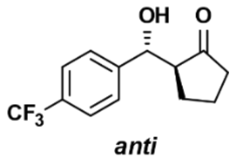
[1]H NMR (400 MHz, CDCl$_3$) δ 7.54 (ddd, *J* = 13.4, 7.9, 1.5 Hz, 2H), 7.36 (td, *J* = 7.6, 1.3 Hz, 1H), 7.15 (td, *J* = 7.7, 1.8 Hz, 1H), 5.27 (d, *J* = 9.3 Hz, 1H), 4.50 (s, 1H), 2.51 – 2.39 (m, 2H), 2.36 – 2.26 (m, 1H), 2.02 (tdt, *J* = 8.0, 5.5, 3.2 Hz, 1H), 1.79 – 1.66 (m, 3H).

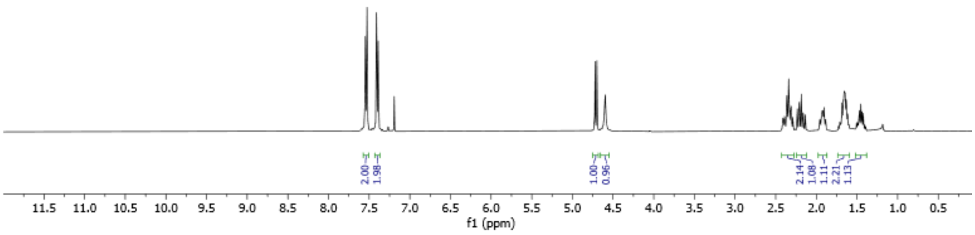
[13]C-NMR



[13]C NMR (101 MHz, CDCl$_3$) δ 140.75, 132.64, 129.34, 128.67, 128.02, 122.77, 72.76, 55.65, 38.71, 26.53, 20.60.

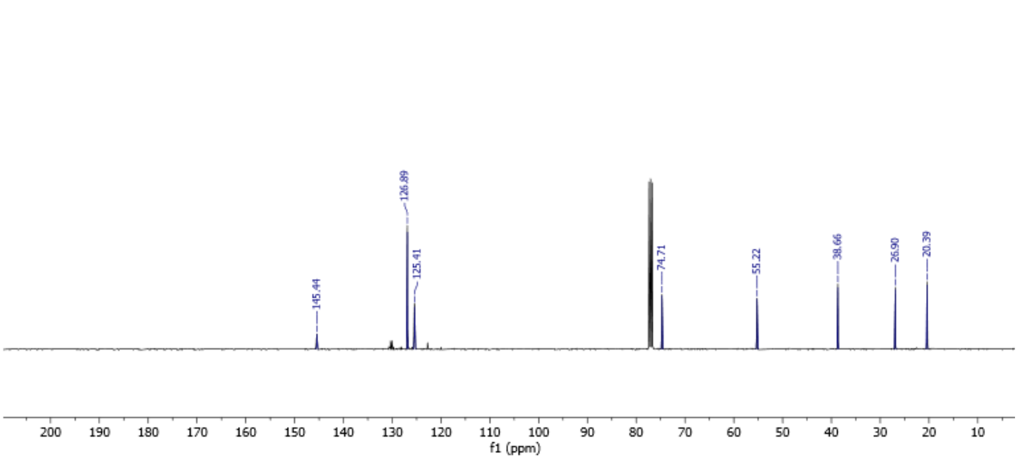
^{1}H-NMR





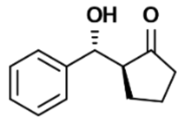
^{1}H NMR (400 MHz, CDCl$_3$) δ 7.54 (d, *J* = 8.1 Hz, 2H), 7.40 (d, *J* = 8.1 Hz, 2H), 4.71 (d, *J* = 9.2 Hz, 1H), 4.60 (s, 1H), 2.46 – 2.28 (m, 2H), 2.19 (ddd, *J* = 19.5, 10.7, 8.9 Hz, 1H), 1.93 (dddd, *J* = 16.0, 8.8, 5.8, 2.6 Hz, 1H), 1.74 – 1.58 (m, 2H), 1.45 (qt, *J* = 11.5, 5.5 Hz, 1H).

^{13}C-NMR

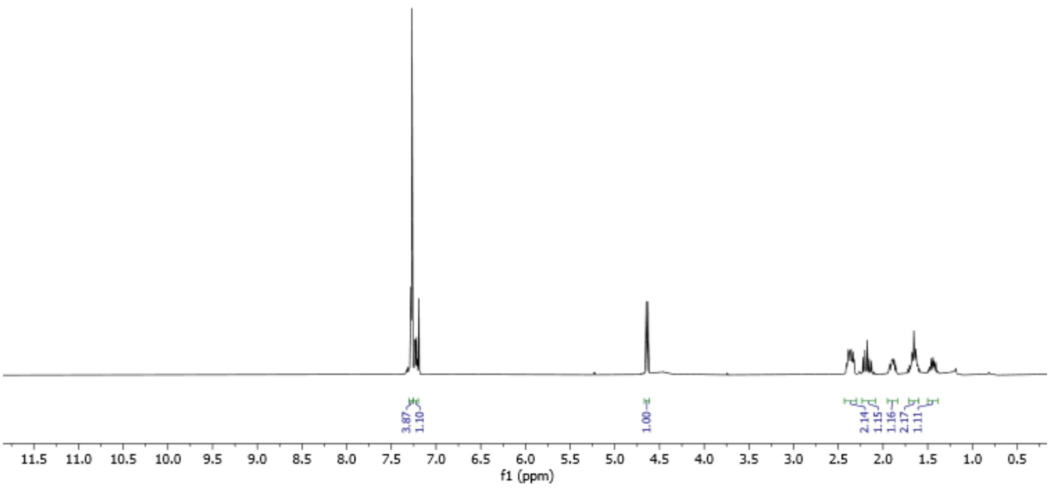


^{13}C NMR (101 MHz, CDCl$_3$) δ 145.44, 126.89, 125.41, 74.71, 55.22, 38.66, 26.90, 20.39.

^{1}H-NMR

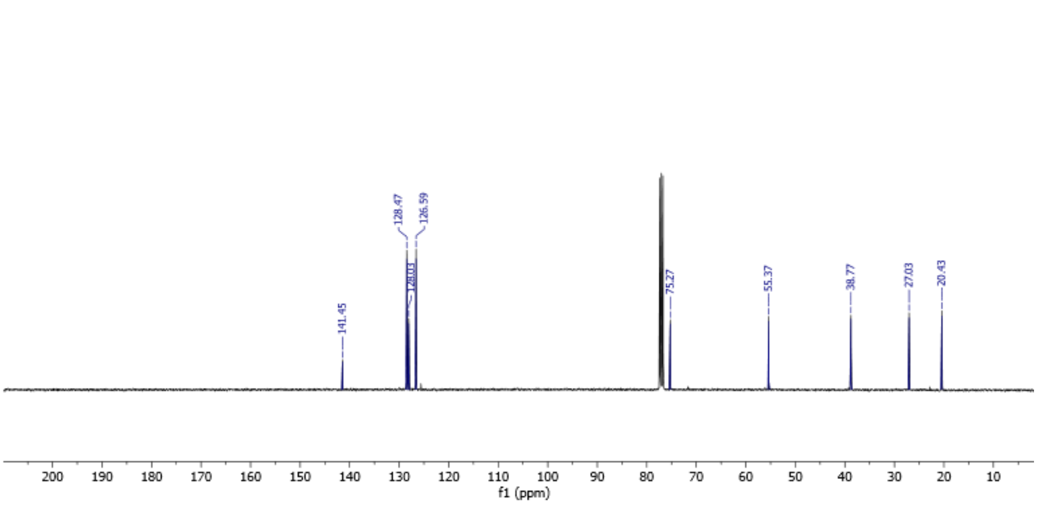


anti



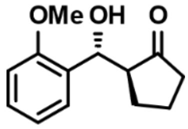
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 (d, *J* = 4.4 Hz, 4H), 7.25 – 7.20 (m, 1H), 4.64 (d, *J* = 9.2 Hz, 1H), 2.44 – 2.30 (m, 2H), 2.25 – 2.09 (m, 1H), 1.89 (dddd, *J* = 16.3, 8.9, 4.2, 2.1 Hz, 1H), 1.74 – 1.56 (m, 2H), 1.51 – 1.37 (m, 1H).

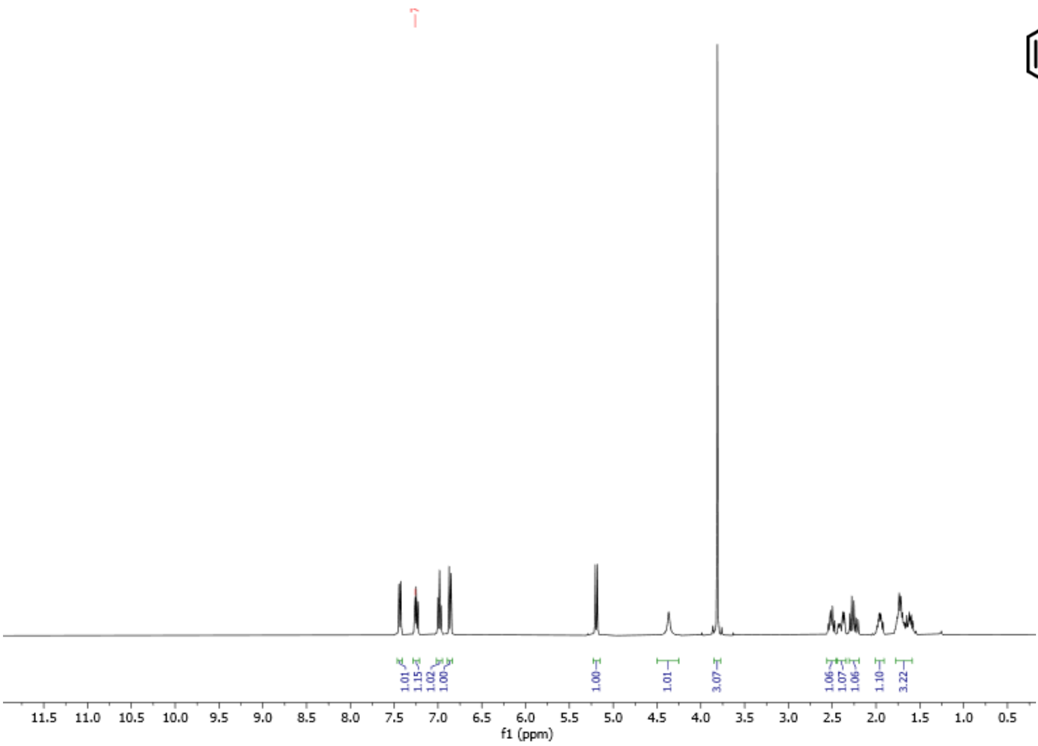
^{13}C-NMR



^{13}C NMR (101 MHz, $CDCl_3$) δ 141.45, 128.47, 128.03, 126.59, 75.27, 55.37, 38.77, 27.03, 20.43.

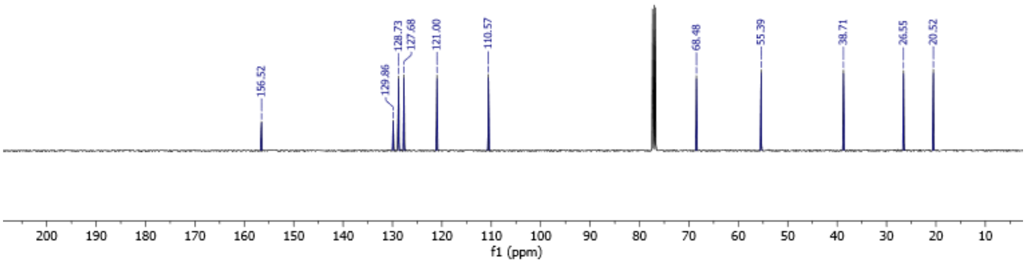
^{1}H-NMR





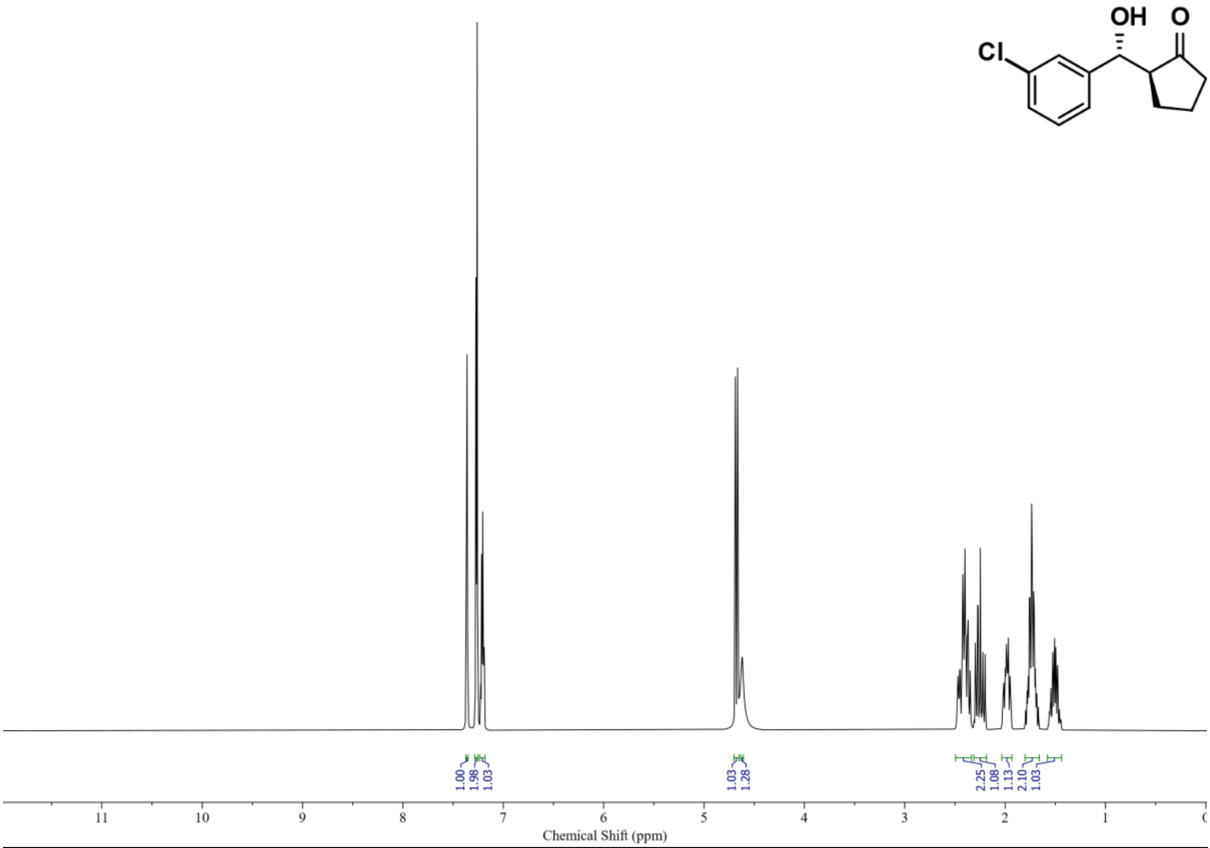
^{1}H NMR (400 MHz, CDCl$_3$) δ 7.43 (dd, *J* = 7.6, 1.8 Hz, 1H), 7.27 – 7.21 (m, 1H), 6.98 (td, *J* = 7.5, 1.1 Hz, 1H), 6.86 (dd, *J* = 8.3, 1.1 Hz, 1H), 5.19 (d, *J* = 9.1 Hz, 1H), 4.37 (s, 1H), 3.81 (s, 3H), 2.57 – 2.46 (m, 1H), 2.45 – 2.34 (m, 1H), 2.25 (ddd, *J* = 19.0, 10.0, 8.7 Hz, 1H), 2.00 – 1.91 (m, 1H), 1.79 – 1.57 (m, 3H).

^{13}C-NMR

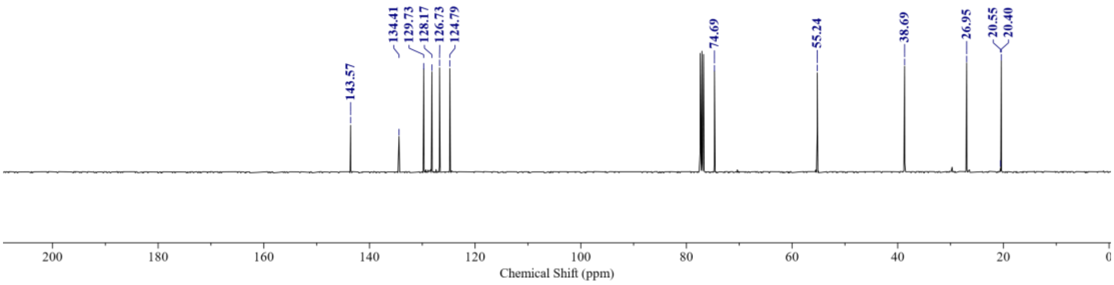


^{13}C NMR (101 MHz, CDCl$_3$) δ 156.52, 129.86, 128.73, 127.68, 121.00, 110.57, 68.48, 55.39, 38.71, 26.55, 20.52.

^{1}H-NMR

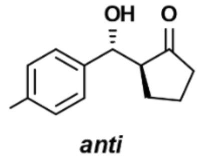


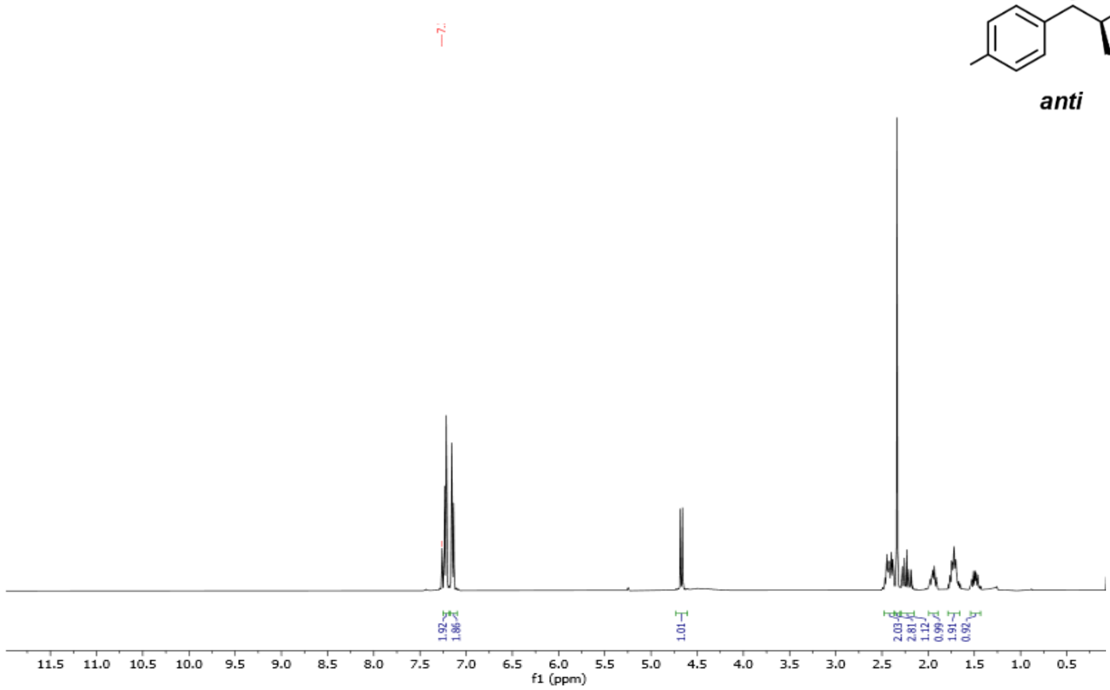
^{13}C-NMR



^{13}C NMR (101 MHz, $CDCl_3$) δ 143.57, 134.41, 129.73, 128.17, 126.73, 124.79, 74.69, 55.24, 38.69, 26.95, 20.40.

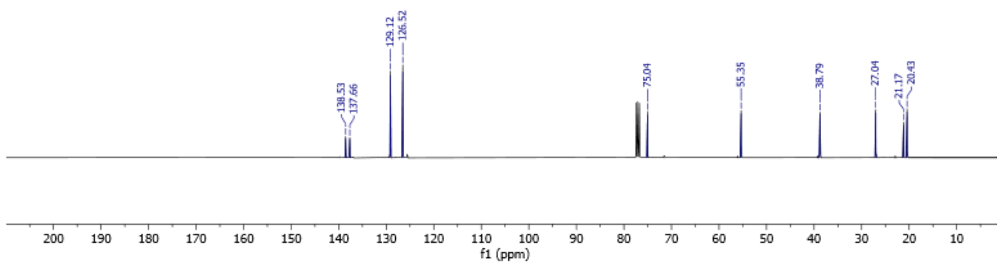
[1]H-NMR





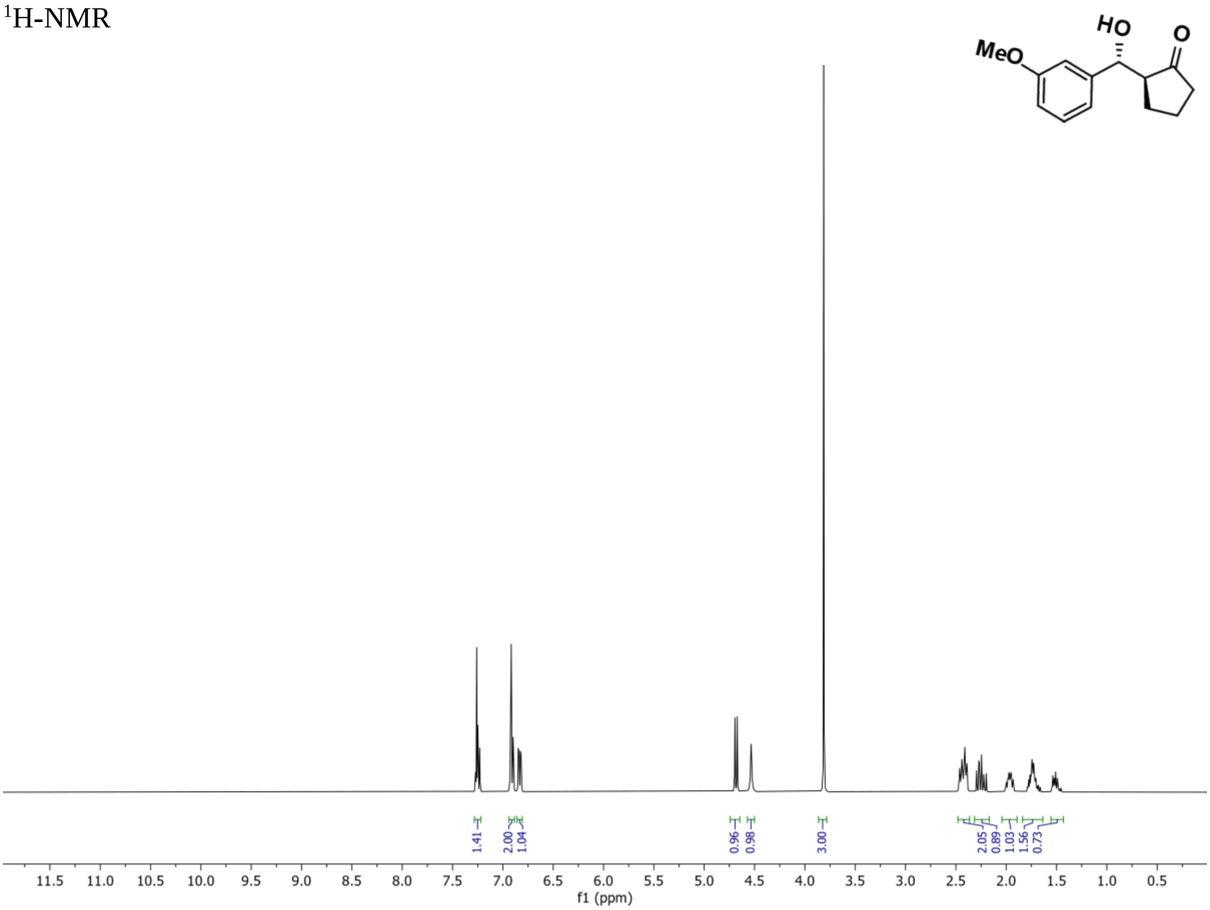
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24 – 7.20 (m, 2H), 7.15 (d, *J* = 7.9 Hz, 2H), 4.67 (d, *J* = 9.1 Hz, 1H), 2.48 – 2.37 (m, 2H), 2.34 (s, 3H), 2.29 – 2.17 (m, 1H), 1.95 (dddd, *J* = 12.6, 8.5, 6.6, 2.2 Hz, 1H), 1.79 – 1.65 (m, 2H), 1.56 – 1.42 (m, 1H).

^{13}C-NMR



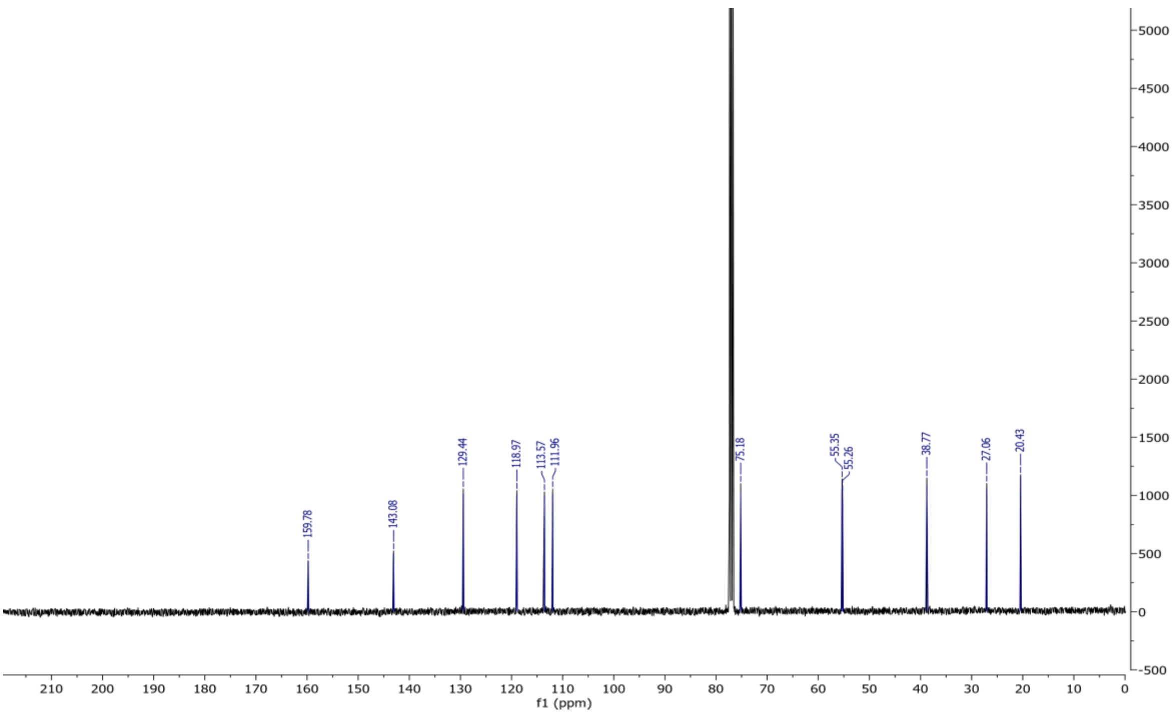
^{13}C NMR (101 MHz, $CDCl_3$) δ 138.53, 137.66, 129.12, 126.52, 75.04, 55.35, 38.79, 27.04, 21.17, 20.43.

^{1}H-NMR



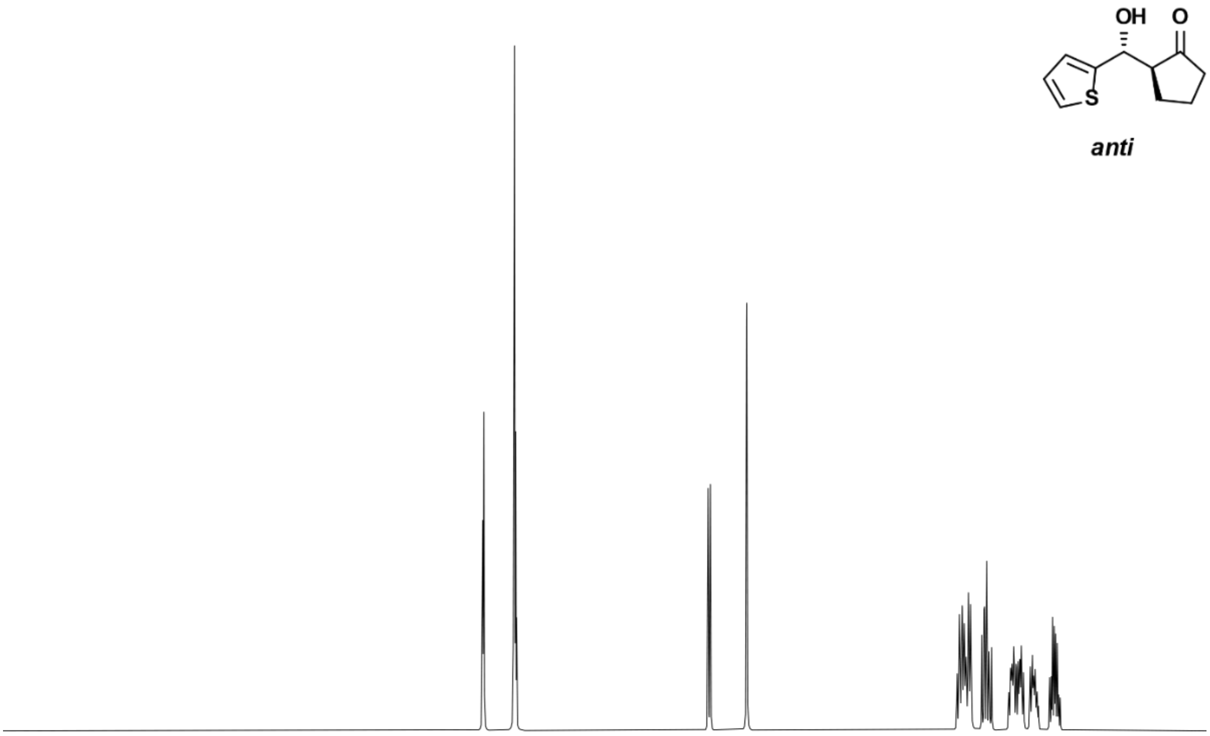
^{1}H NMR (400 MHz, CDCl$_3$) δ 7.28 – 7.22 (m, 1H), 6.94 – 6.88 (m, 2H), 6.83 (ddd, *J* = 8.2, 2.6, 1.1 Hz, 1H), 4.68 (d, *J* = 9.1 Hz, 1H), 4.53 (s, 1H), 3.81 (s, 3H), 2.48 – 2.36 (m, 2H), 2.25 (ddd, *J* = 19.4, 10.5, 8.7 Hz, 1H), 2.04 – 1.89 (m, 1H), 1.84 – 1.64 (m, 2H), 1.56 – 1.43 (m, 1H).

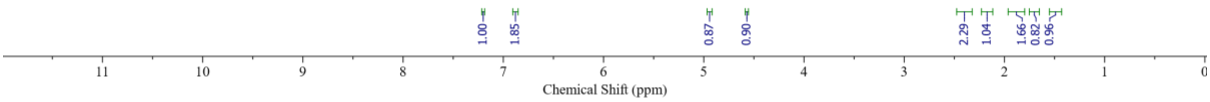
^{13}C-NMR



^{13}C NMR (101 MHz, CDCl$_3$) δ 159.78, 143.08, 129.44, 118.97, 113.57, 111.96, 75.18, 55.35, 55.26, 38.77, 27.06, 20.43.

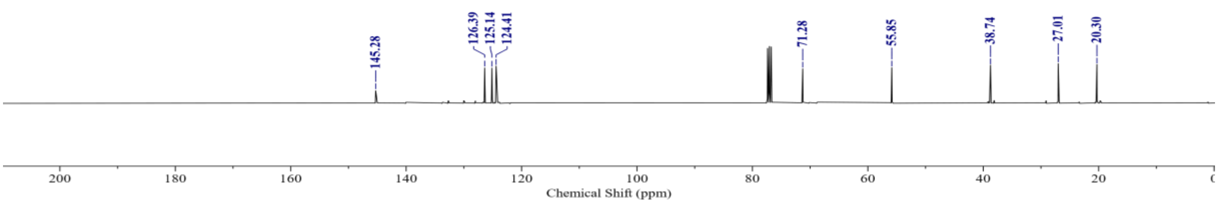
^{1}H-NMR





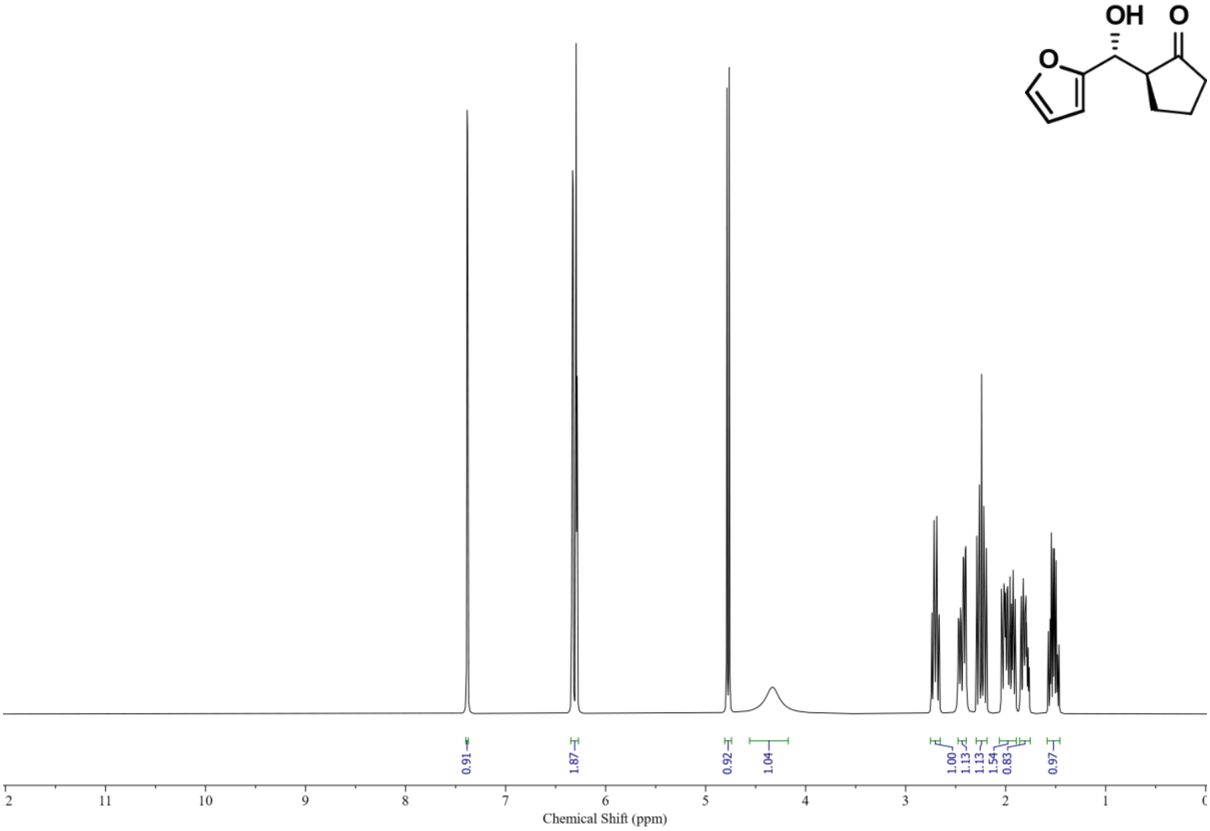
^{1}H NMR (400 MHz, CDCl$_3$) δ 7.20 (dd, *J* = 4.7, 1.5 Hz, 1H), 6.91 – 6.85 (m, 2H), 4.94 (d, *J* = 9.0 Hz, 1H), 4.57 (d, *J* = 1.3 Hz, 1H), 2.48 – 2.32 (m, 2H), 2.17 (ddd, *J* = 19.4, 10.9, 8.7 Hz, 1H), 1.96 – 1.80 (m, 2H), 1.70 (dddd, *J* = 17.7, 8.5, 4.6, 2.6 Hz, 1H), 1.49 (qd, *J* = 11.8, 6.8 Hz, 1H).

^{13}C-NMR



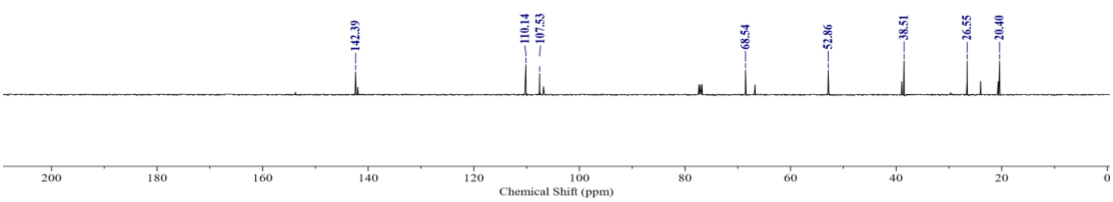
^{13}C NMR (101 MHz, CDCl$_3$) δ 145.28, 126.39, 125.14, 124.41, 71.28, 55.85, 38.74, 27.01, 20.30.

^{1}H-NMR



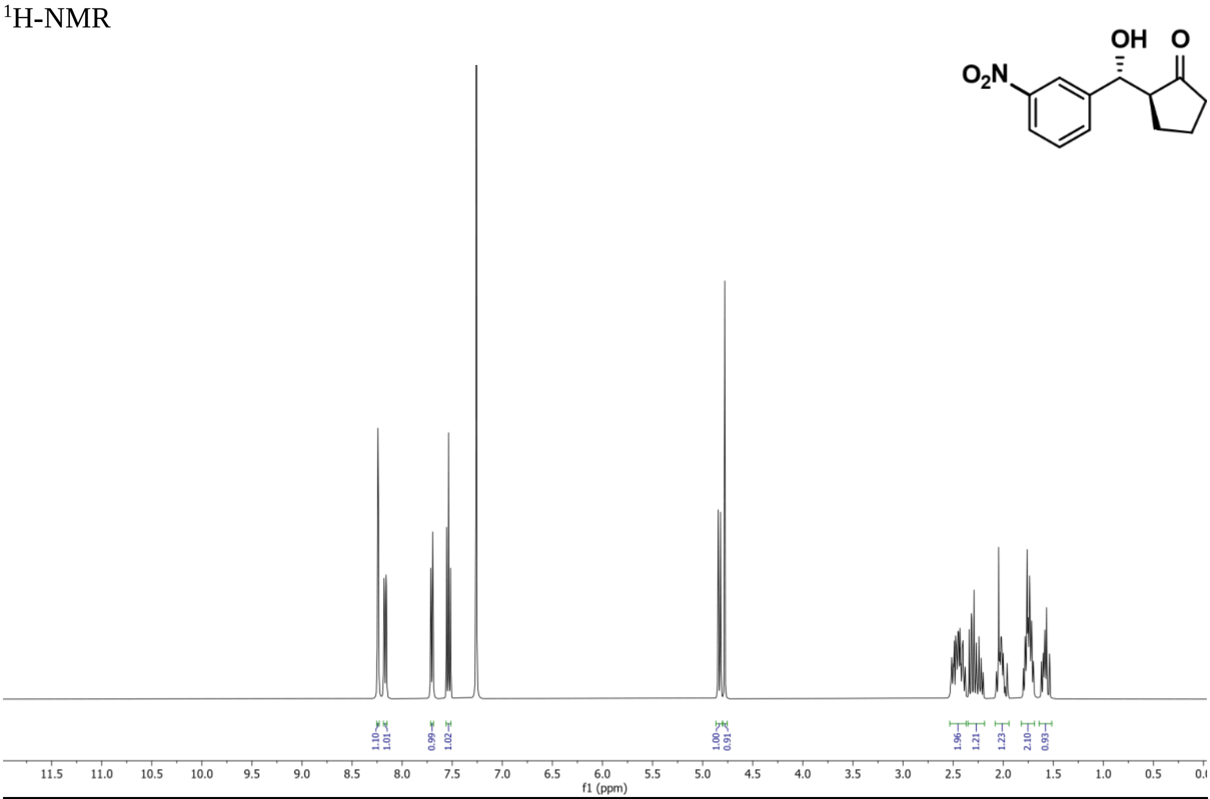
^{1}H NMR (400 MHz, CDCl$_3$) δ 7.38 (dd, *J* = 1.9, 0.8 Hz, 1H), 6.31 (ddd, *J* = 16.0, 3.2, 1.3 Hz, 2H), 4.78 (d, *J* = 9.1 Hz, 1H), 4.33 (s, 1H), 2.75 – 2.65 (m, 1H), 2.44 (ddd, *J* = 19.2, 8.5, 2.1 Hz, 1H), 2.24 (ddd, *J* = 19.3, 10.8, 8.8 Hz, 1H), 2.06 – 1.89 (m, 2H), 1.86 – 1.76 (m, 1H), 1.52 (qd, *J* = 11.8, 7.0 Hz, 1H).

^{13}C-NMR



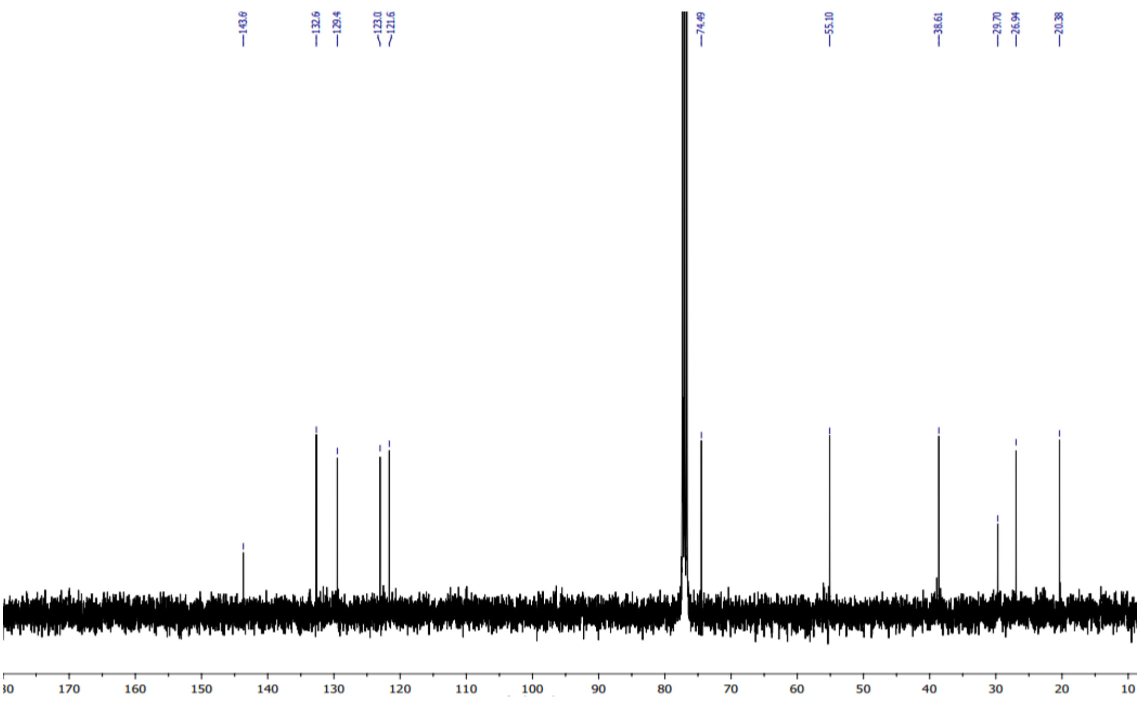
^{13}C NMR (101 MHz, CDCl$_3$) δ 142.39, 110.14, 107.53, 68.54, 52.86, 38.51, 26.55, 20.40.

^{1}H-NMR



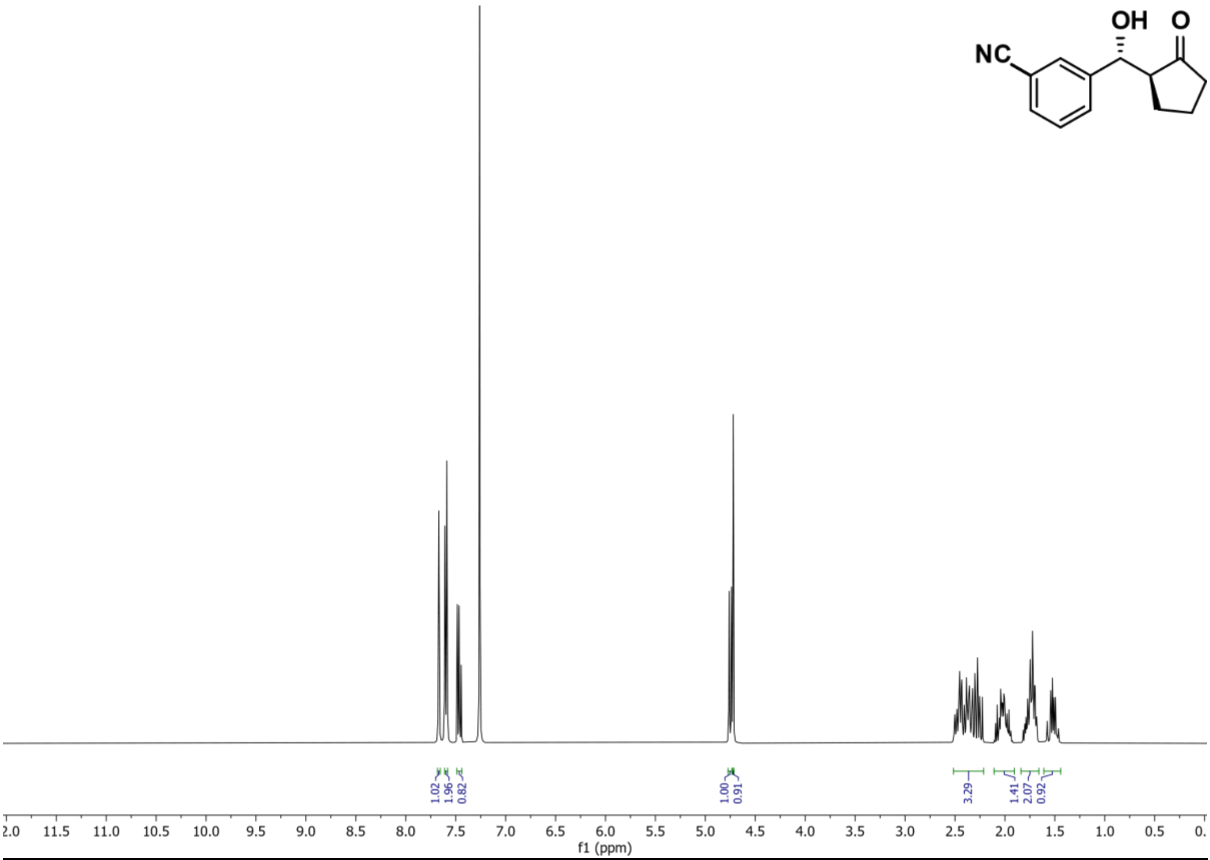
^{1}H NMR (400 MHz, CDCl$_3$) δ 8.24 (t, *J* = 2.1 Hz, 1H), 8.17 (ddd, *J* = 8.1, 2.4, 1.1 Hz, 1H), 7.72 – 7.69 (m, 1H), 7.54 (t, *J* = 7.9 Hz, 1H), 4.83 (d, *J* = 9.3 Hz, 1H), 4.78 (d, *J* = 1.0 Hz, 1H), 2.53 – 2.37 (m, 2H), 2.35 – 2.18 (m, 1H), 2.08 – 1.94 (m, 1H), 1.82 – 1.69 (m, 2H), 1.57 (s, 1H).

^{13}C-NMR



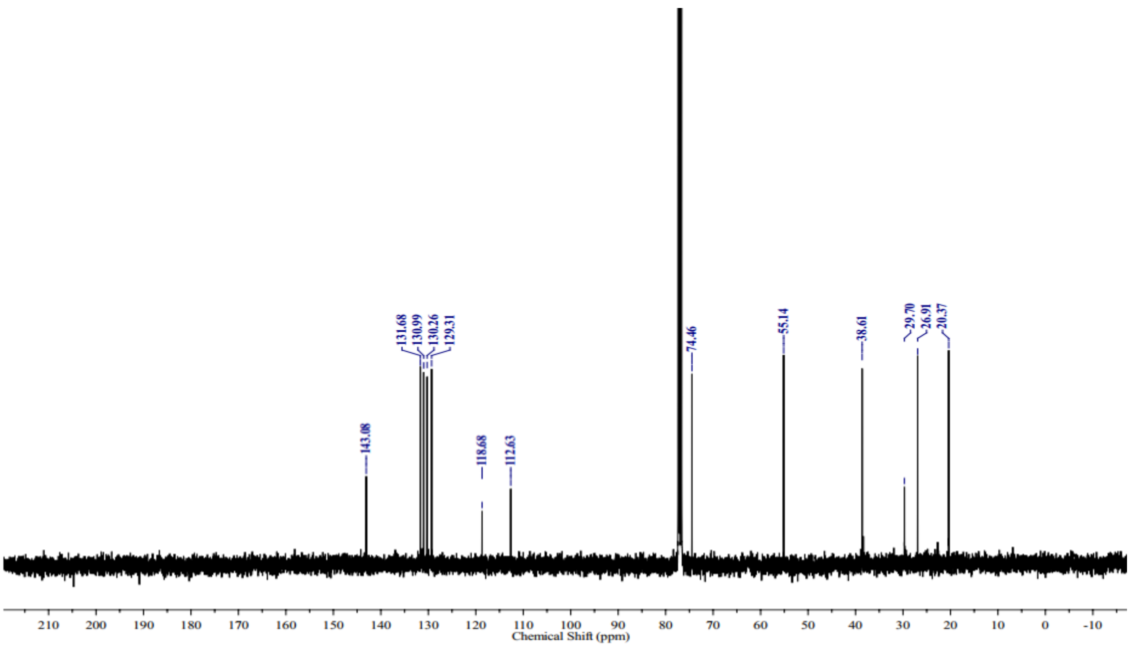
^{13}C NMR (101 MHz, CDCl$_3$) δ 143.69, 132.66, 129.48, 123.03, 121.63, 74.49, 55.10, 38.61, 29.70, 26.94, 20.38.

[1]H-NMR



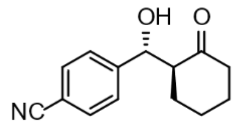
[1]H NMR (400 MHz, $CDCl_3$) δ 7.67 (d, *J* = 1.8 Hz, 1H), 7.60 (dd, *J* = 7.8, 1.7 Hz, 2H), 7.49 – 7.44 (m, 1H), 4.75 (d, *J* = 9.3 Hz, 1H), 4.72 (d, *J* = 1.1 Hz, 1H), 2.52 – 2.21 (m, 3H), 2.11 – 1.91 (m, 1H), 1.84 – 1.66 (m, 2H), 1.61 – 1.44 (m, 1H).

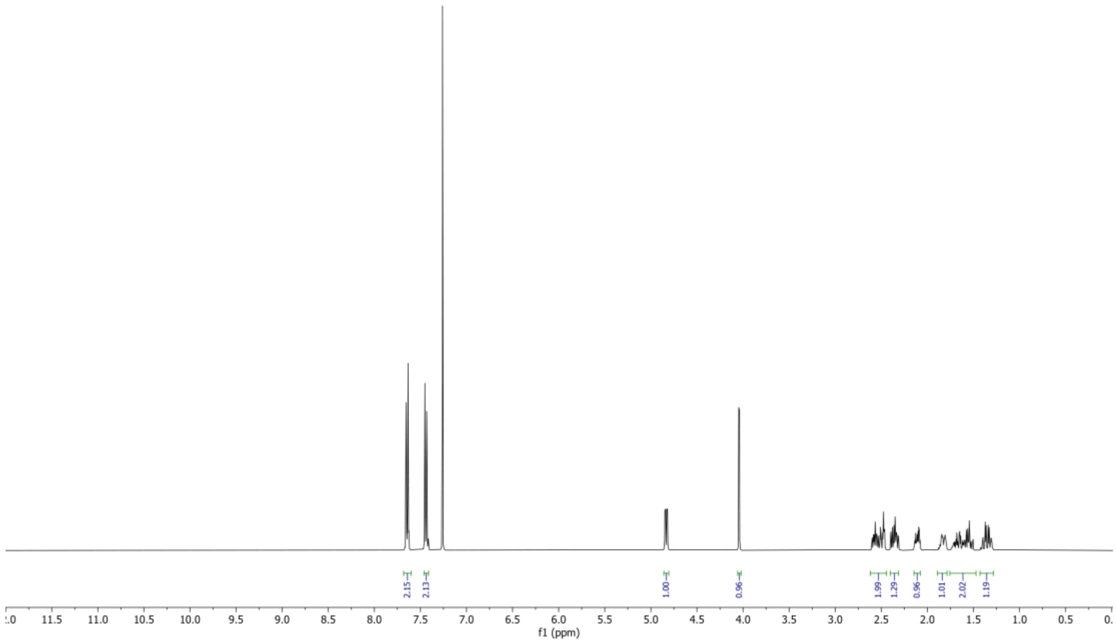
[13]C-NMR



[13]C NMR (101 MHz, $CDCl_3$) δ 143.08, 131.68, 130.99, 130.26, 129.31, 118.68, 112.63, 74.46, 55.14, 38.61, 29.70, 26.91, 20.37.

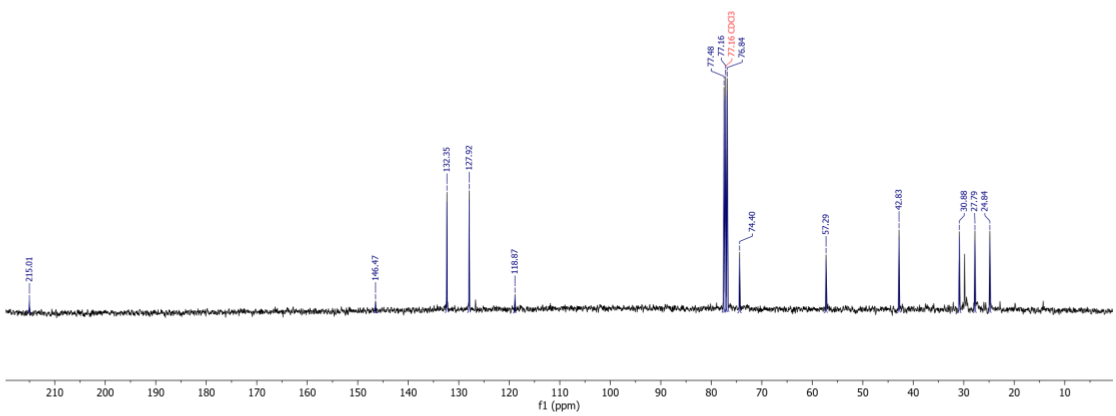
H-NMR[1]





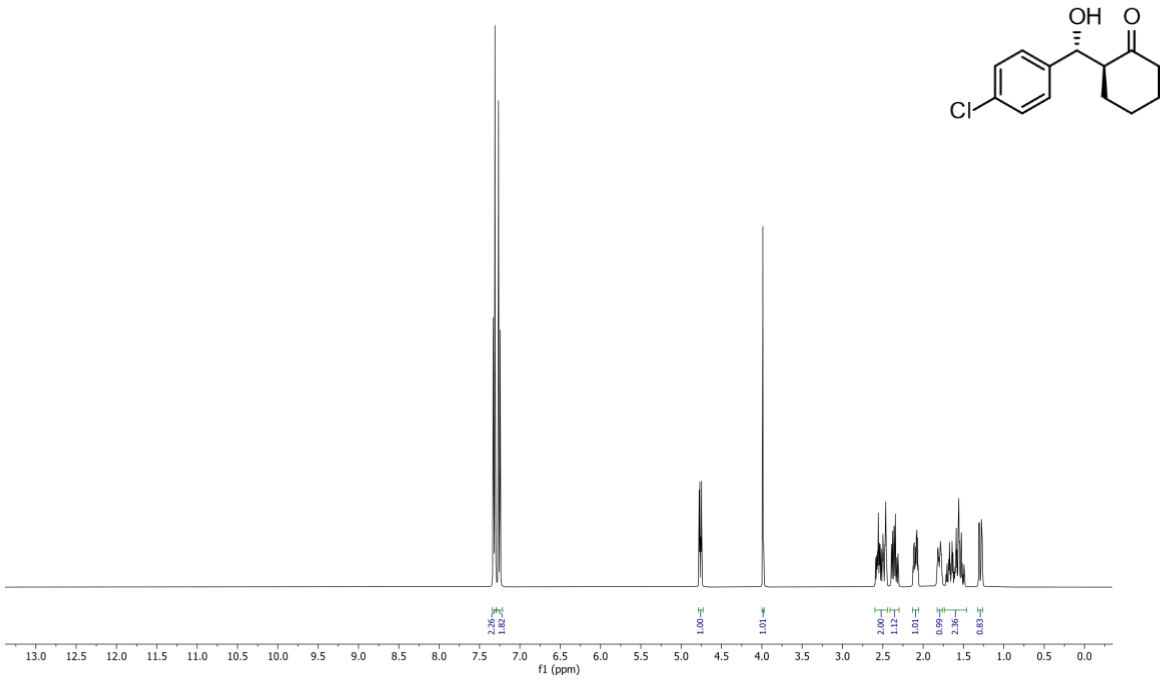
[1]H NMR (400 MHz, $CDCl_3$) δ 7.68 – 7.60 (m, 2H), 7.46 – 7.41 (m, 2H), 4.83 (dd, *J* = 8.5, 3.1 Hz, 1H), 4.04 (d, *J* = 3.1 Hz, 1H), 2.62 – 2.44 (m, 2H), 2.40 – 2.31 (m, 1H), 2.11 (ddt, *J* = 12.1, 5.7, 2.9 Hz, 1H), 1.89 – 1.79 (m, 1H), 1.76 – 1.47 (m, 2H), 1.43 – 1.28 (m, 1H).

C-NMR[13]



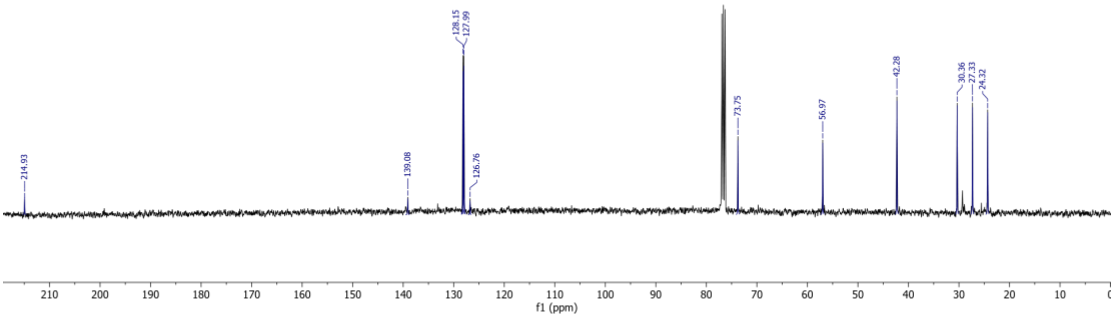
[13]C NMR (101 MHz, $CDCl_3$) δ 215.01, 146.47, 132.35, 127.92, 118.87, 77.48, 77.16, 76.84, 74.40, 57.29, 42.83, 30.88, 27.79, 24.84.

^{1}H-NMR



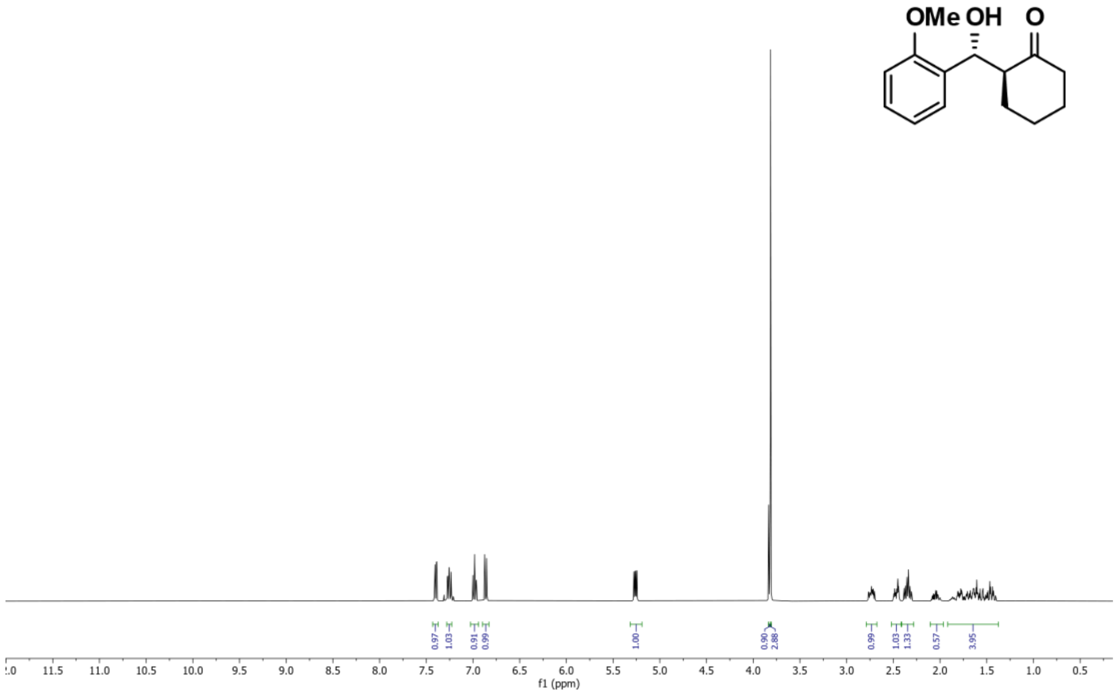
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 – 7.29 (m, 2H), 7.29 – 7.21 (m, 2H), 4.76 (dd, *J* = 8.7, 2.8 Hz, 1H), 3.98 (d, *J* = 2.8 Hz, 1H), 2.60 – 2.44 (m, 2H), 2.35 (tdd, *J* = 13.6, 6.2, 1.3 Hz, 1H), 2.09 (ddt, *J* = 12.2, 5.8, 2.8 Hz, 1H), 1.79 (dqd, *J* = 10.4, 3.3, 1.7 Hz, 1H), 1.74 – 1.46 (m, 2H), 1.32 – 1.26 (m, 1H).

C-NMR^{13}



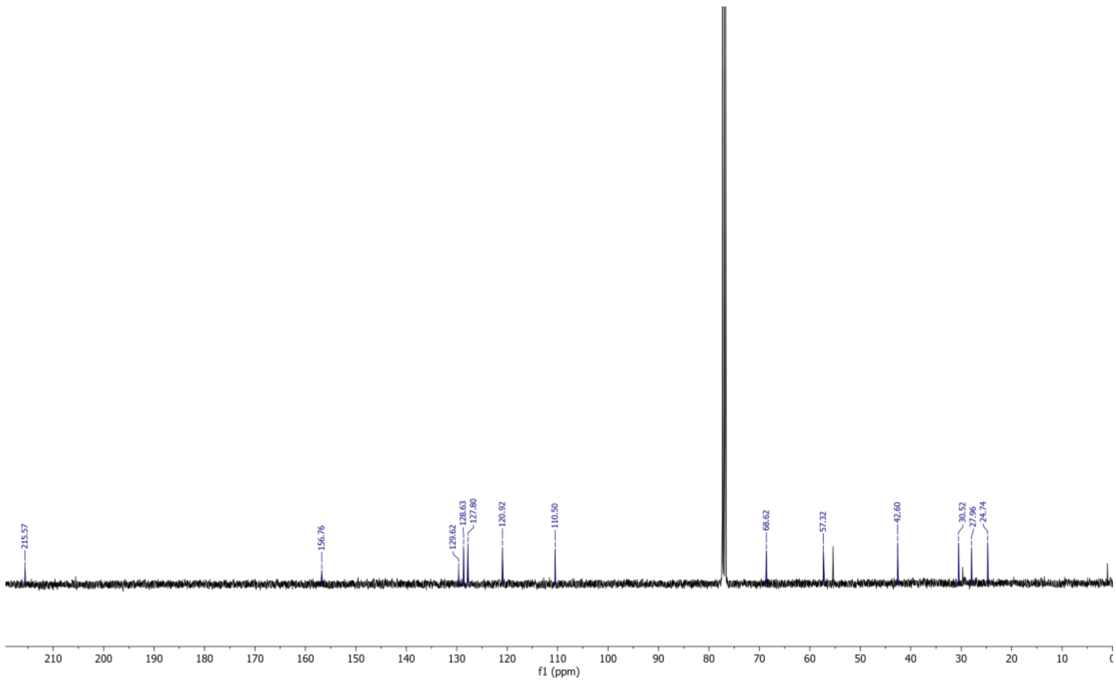
^{13}C NMR (101 MHz, $CDCl_3$) δ 214.93, 139.08, 128.15, 127.99, 126.76, 73.75, 56.97, 42.28, 30.36, 27.33, 24.32.

^{1}H-NMR



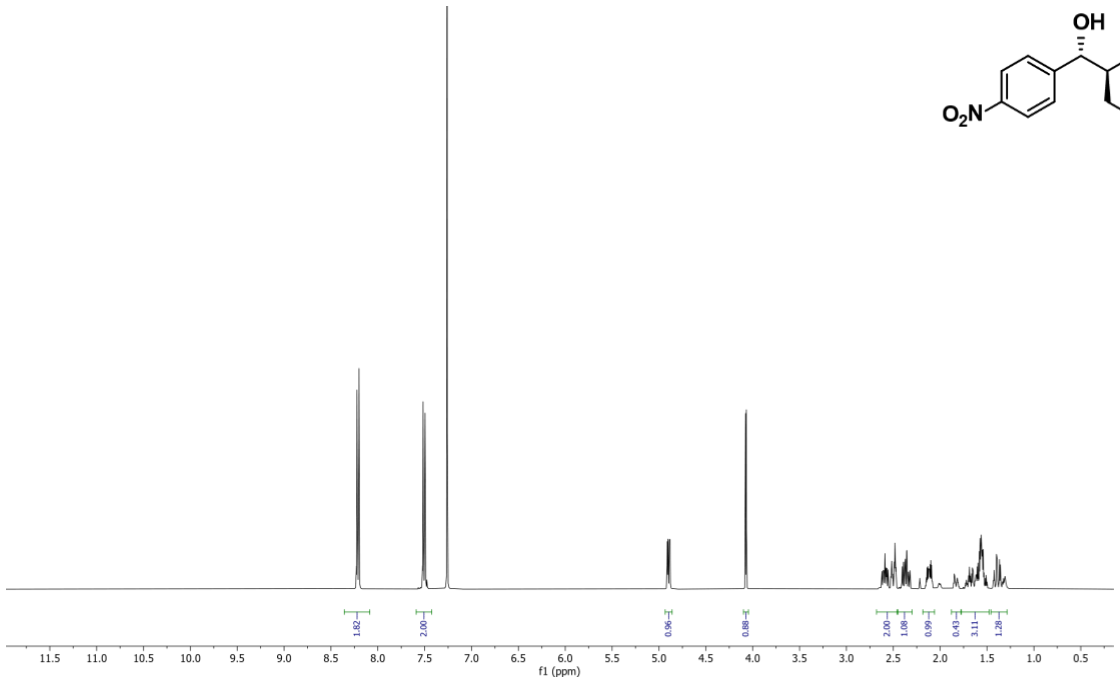
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 (dd, *J* = 7.6, 1.8 Hz, 1H), 7.25 (ddd, *J* = 8.3, 7.4, 1.8 Hz, 1H), 6.98 (td, *J* = 7.5, 1.1 Hz, 1H), 6.86 (dd, *J* = 8.3, 1.1 Hz, 1H), 5.26 (dd, *J* = 8.5, 4.5 Hz, 1H), 3.83 (d, *J* = 4.5 Hz, 1H), 3.81 (s, 3H), 2.79 – 2.68 (m, 1H), 2.52 – 2.42 (m, 1H), 2.35 (dddd, *J* = 13.6, 12.4, 5.9, 1.3 Hz, 1H), 2.10 – 1.96 (m, 1H), 1.92 – 1.37 (m, 4H).

C-NMR[13]



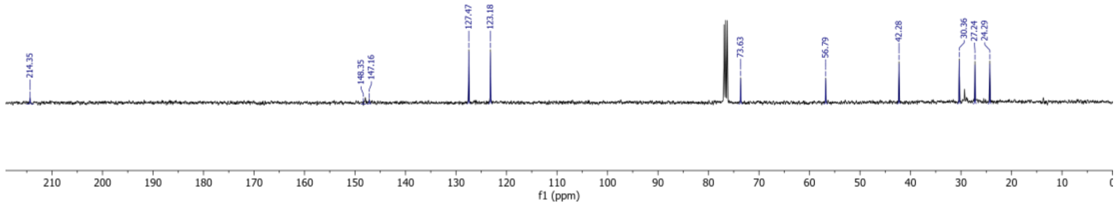
^{13}C NMR (101 MHz, $CDCl_3$) δ 215.57, 154.70, 129.62, 128.63, 127.80, 120.92, 110.50, 68.62, 57.32, 42.60, 30.52, 27.96, 24.74.

[1]H-NMR



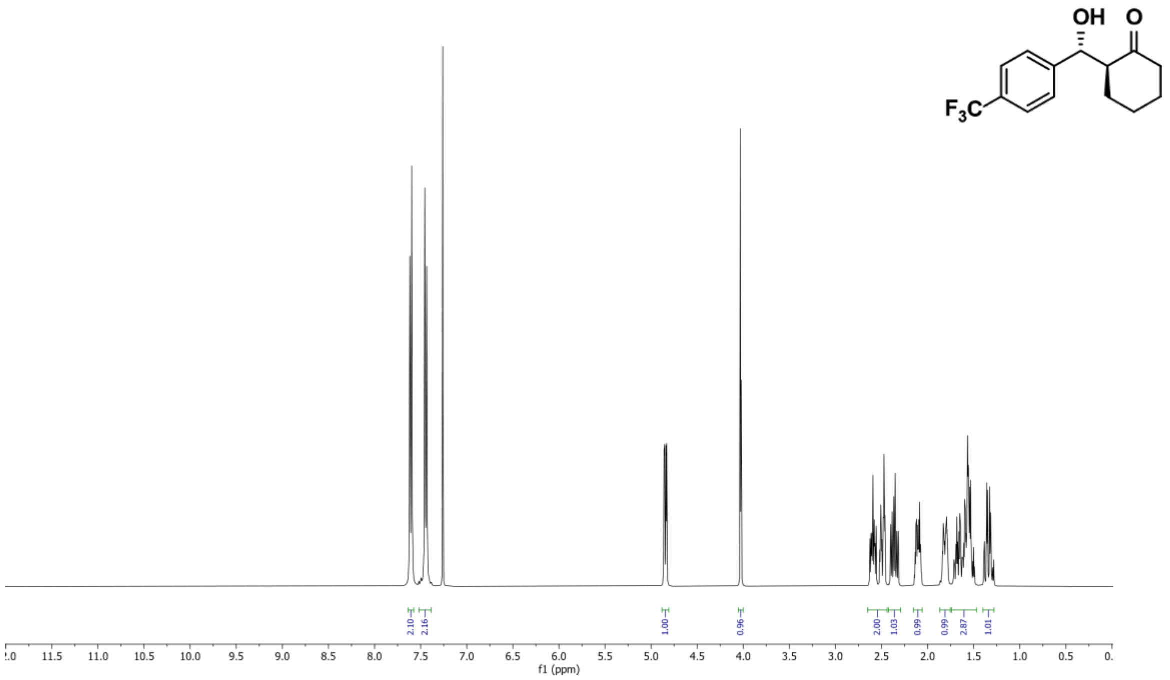
[1]H NMR (400 MHz, $CDCl_3$) δ 8.36 – 8.09 (m, 2H), 7.59 – 7.42 (m, 2H), 4.90 (dd, *J* = 8.4, 3.1 Hz, 1H), 4.07 (d, *J* = 3.2 Hz, 1H), 2.68 – 2.45 (m, 2H), 2.36 (tdd, *J* = 13.6, 6.1, 1.2 Hz, 1H), 2.12 (ddt, *J* = 12.1, 5.8, 2.8 Hz, 1H), 1.88 – 1.77 (m, 1H), 1.78 – 1.48 (m, 3H), 1.46 – 1.29 (m, 1H).

C-NMR[13]



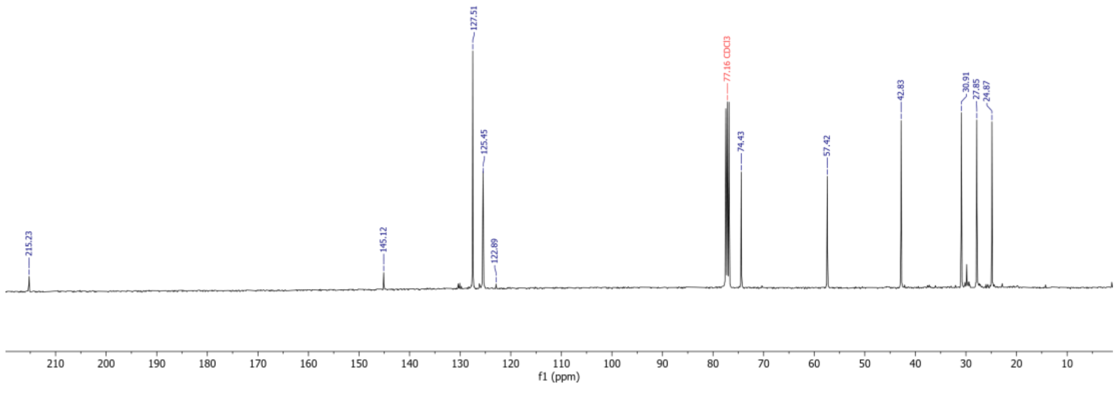
[13]C NMR (101 MHz, $CDCl_3$) δ 214.35, 148.35, 147.16, 127.47, 123.18, 73.63, 56.79, 42.28, 30.36, 27.24, 24.29.

[1]H-NMR



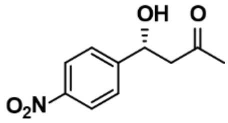
[1]H NMR (400 MHz, CDCl$_3$) δ 7.64 – 7.58 (m, 2H), 7.52 – 7.39 (m, 2H), 4.85 (dd, *J* = 8.6, 3.0 Hz, 1H), 4.03 (d, *J* = 3.0 Hz, 1H), 2.65 – 2.44 (m, 2H), 2.36 (tdd, *J* = 13.5, 6.1, 1.2 Hz, 1H), 2.10 (ddt, *J* = 12.2, 5.8, 3.0 Hz, 1H), 1.87 – 1.75 (m, 1H), 1.74 – 1.47 (m, 3H), 1.40 – 1.28 (m, 1H).

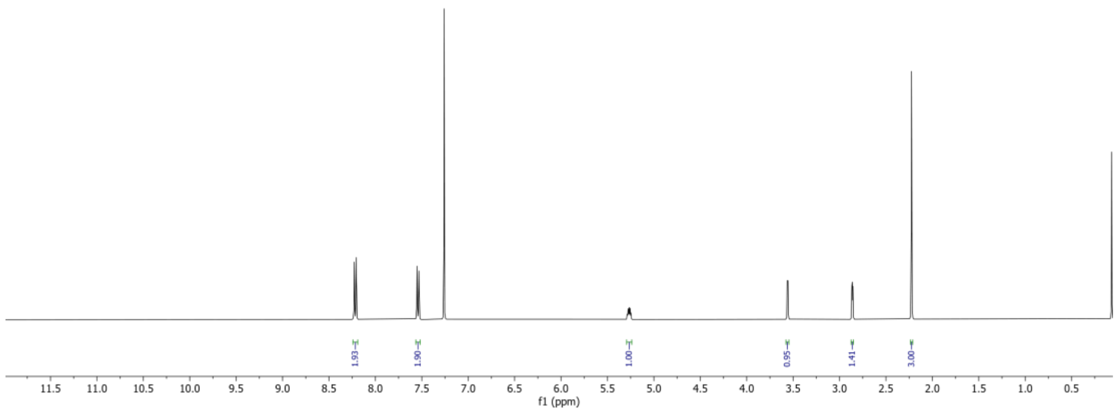
C-NMR[13]



[13]C NMR (101 MHz, CDCl$_3$) δ 215.23, 145.12, 127.51, 125.45, 122.89, 74.43, 57.42, 42.83, 30.91, 27.85, 24.87.

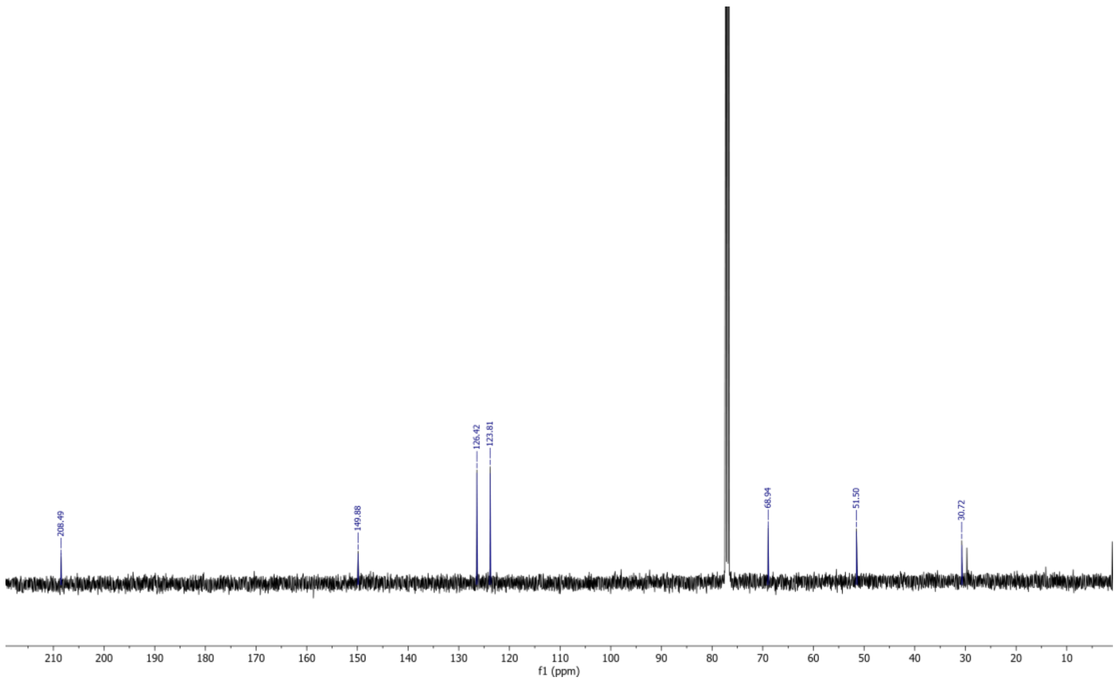
^{1}H-NMR





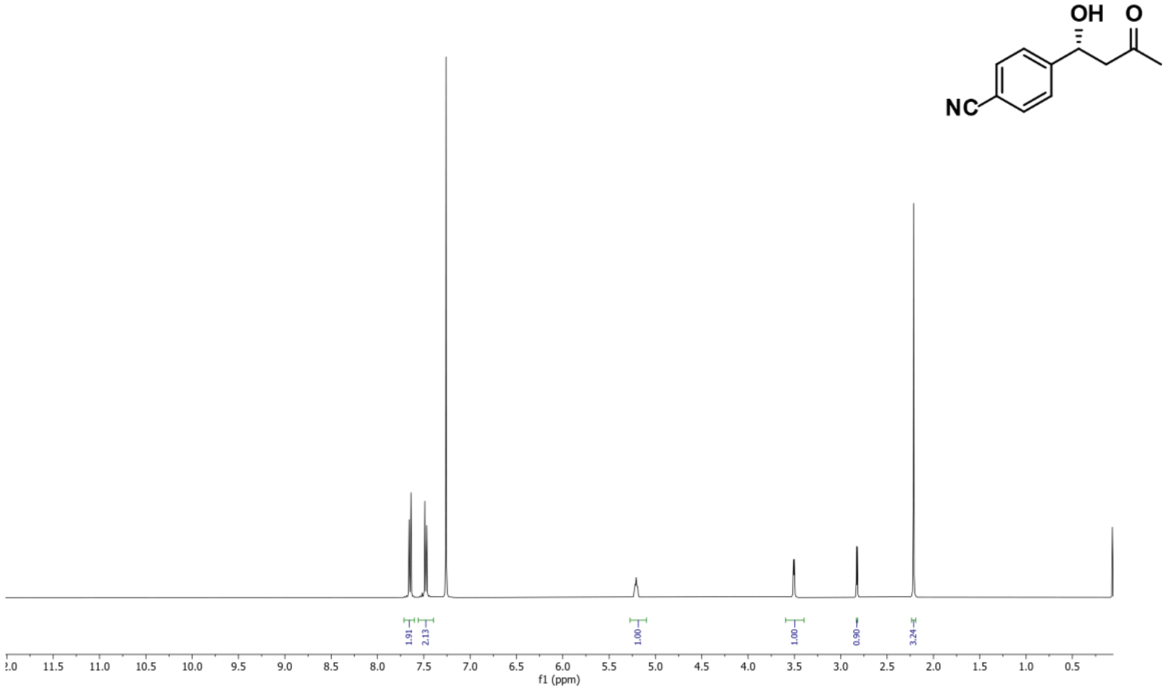
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24 – 8.19 (m, 2H), 7.56 – 7.52 (m, 2H), 5.27 (dt, *J* = 7.7, 3.7 Hz, 1H), 3.56 (d, *J* = 3.3 Hz, 1H), 2.88 – 2.85 (m, 1H), 2.22 (s, 3H).

C-NMR^{13}



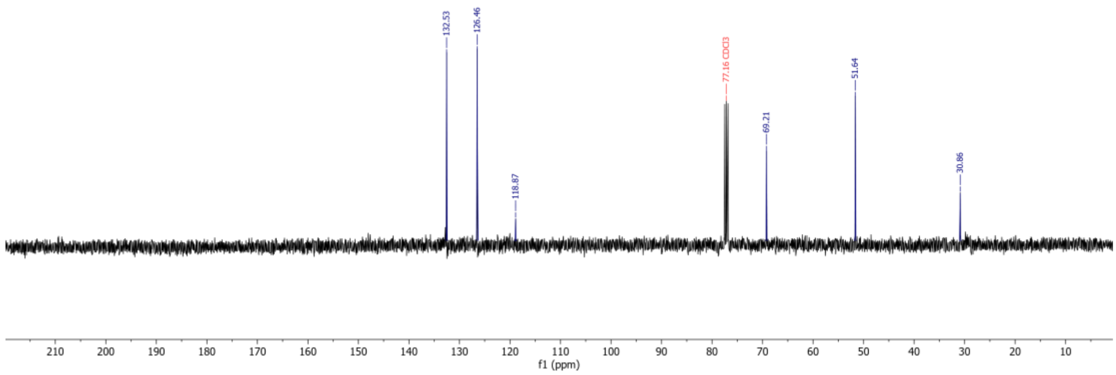
^{13}C NMR (101 MHz, $CDCl_3$) δ 208.49, 149.88, 126.42, 123.81, 68.94, 51.50, 30.72.

[1]H-NMR



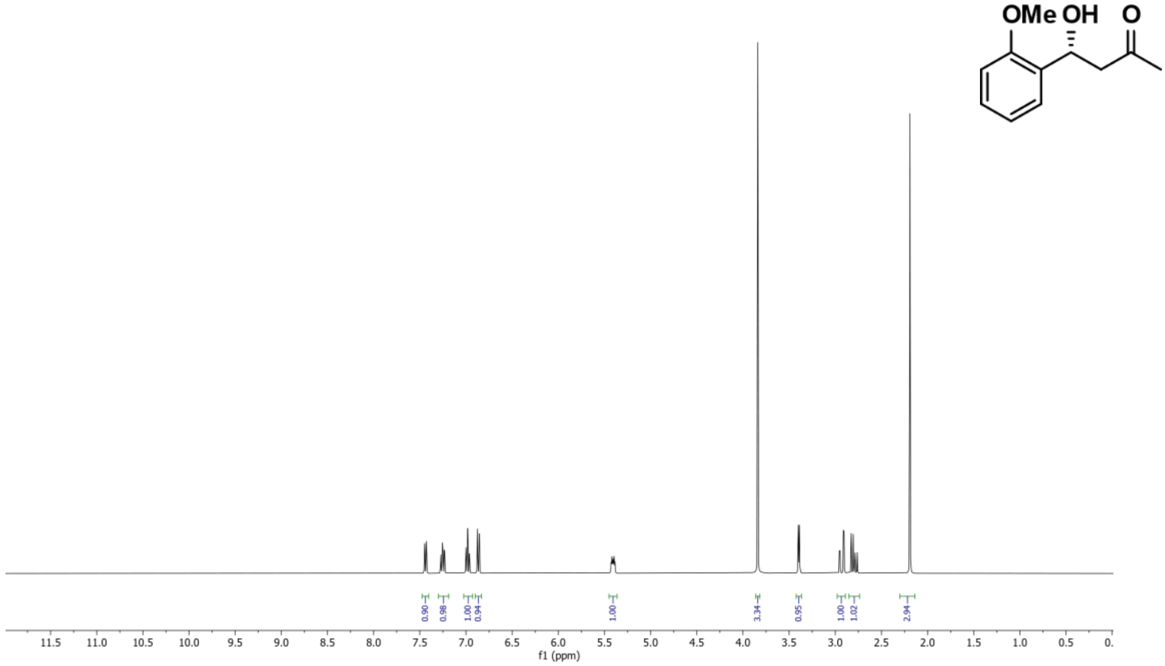
[1]H NMR (400 MHz, $CDCl_3$) δ 7.71 – 7.60 (m, 2H), 7.56 – 7.39 (m, 2H), 5.21 (dt, *J* = 7.7, 3.8 Hz, 1H), 3.51 (d, *J* = 3.2 Hz, 1H), 2.82 (d, *J* = 3.5 Hz, 1H), 2.21 (s, 3H).

C-NMR[13]



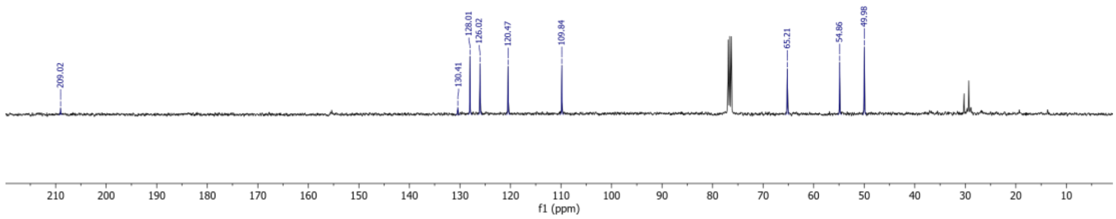
[13]C NMR (101 MHz, $CDCl_3$) δ 132.53, 126.46, 118.87, 69.21, 51.64, 30.86.

^{1}H-NMR



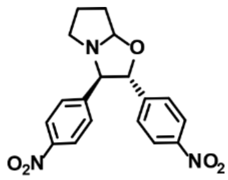
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 (ddd, *J* = 7.6, 1.8, 0.7 Hz, 1H), 7.25 (ddd, *J* = 8.2, 7.4, 1.8 Hz, 1H), 6.98 (td, *J* = 7.5, 1.1 Hz, 1H), 6.87 (dd, *J* = 8.2, 1.1 Hz, 1H), 5.41 (dt, *J* = 9.3, 3.7 Hz, 1H), 3.84 (s, 3H), 3.39 (d, *J* = 4.5 Hz, 1H), 2.98 – 2.89 (m, 1H), 2.85 – 2.74 (m, 1H), 2.19 (s, 3H).

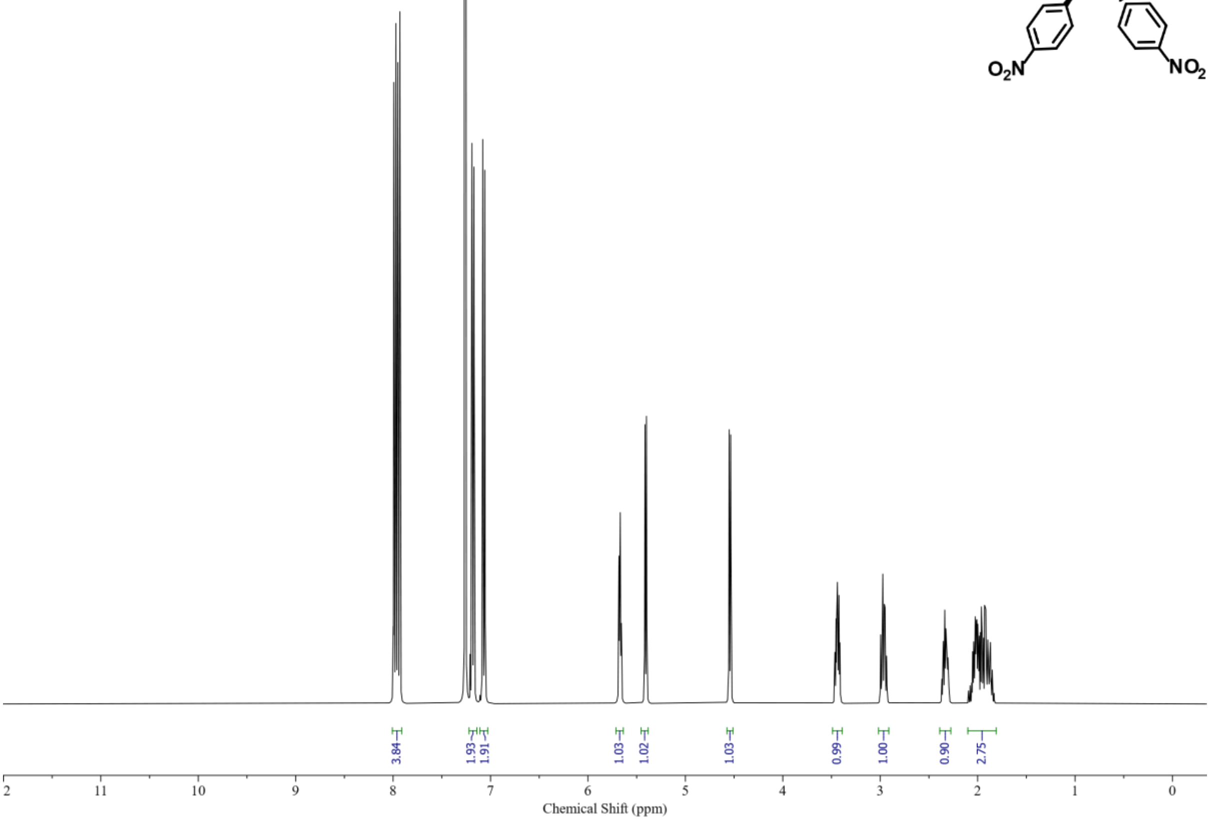
C-NMR^{13}



^{13}C NMR (101 MHz, $CDCl_3$) δ 209.02, 130.41, 128.01, 126.02, 120.47, 109.84, 65.21, 54.86, 49.98.

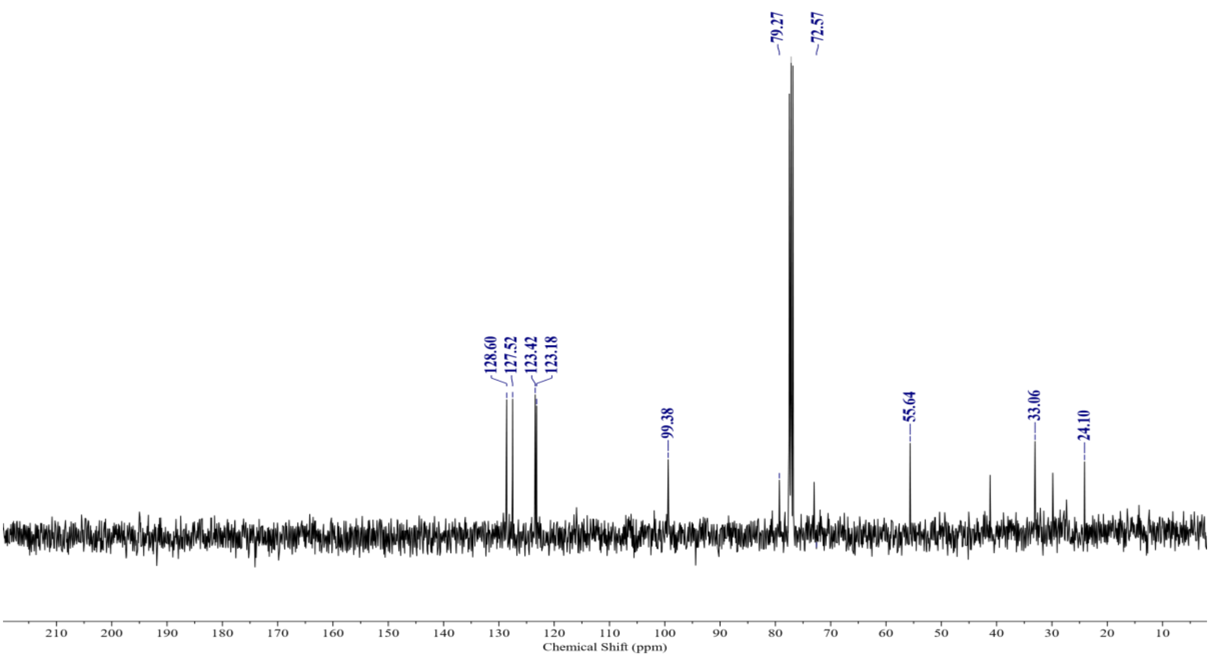
In $CDCl_3$ - ^{1}H-NMR





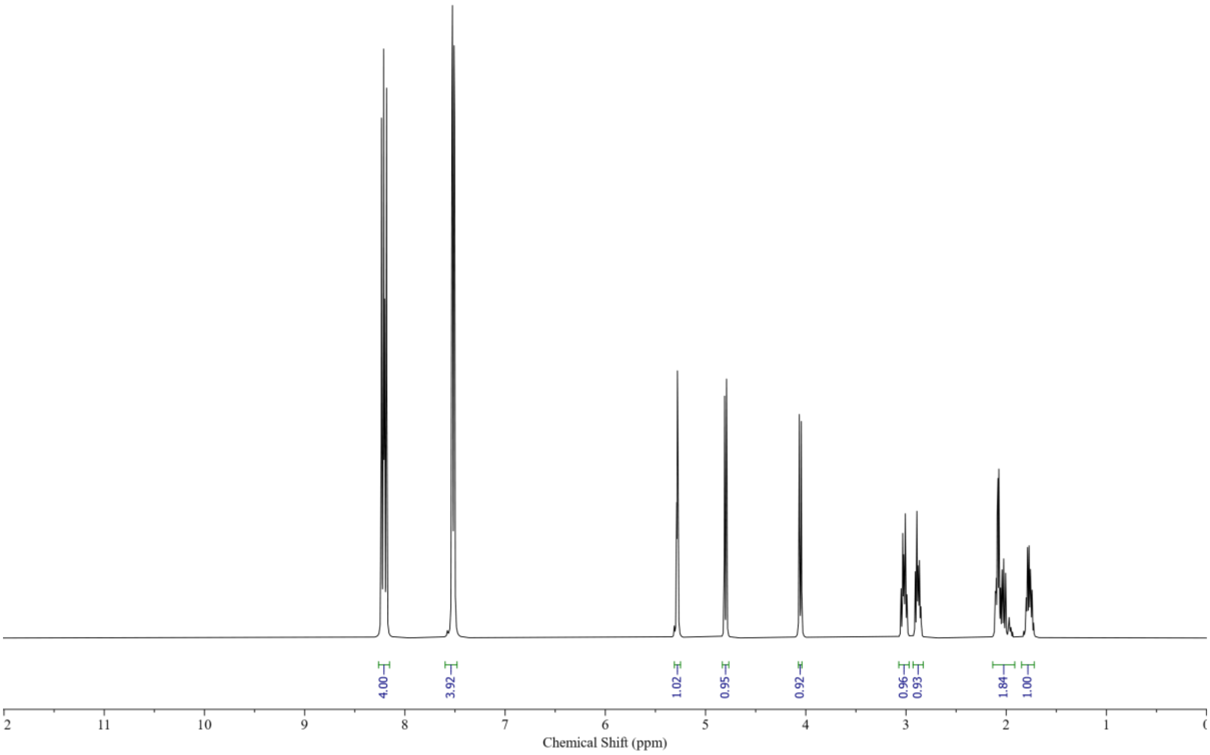
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.23 – 8.16 (m, 4H), 7.47 – 7.32 (m, 4H), 5.34 (dd, *J* = 4.7, 2.2 Hz, 1H), 4.69 (d, *J* = 7.9 Hz, 1H), 3.84 (d, *J* = 7.9 Hz, 1H), 3.16 (dt, *J* = 10.3, 6.5 Hz, 1H), 2.85 (dt, *J* = 10.3, 6.3 Hz, 1H), 2.28 – 2.16 (m, 2H), 2.14 – 2.07 (m, 1H), 1.91 (dtd, *J* = 12.3, 6.1, 1.1 Hz, 1H).

C-NMR^{13}



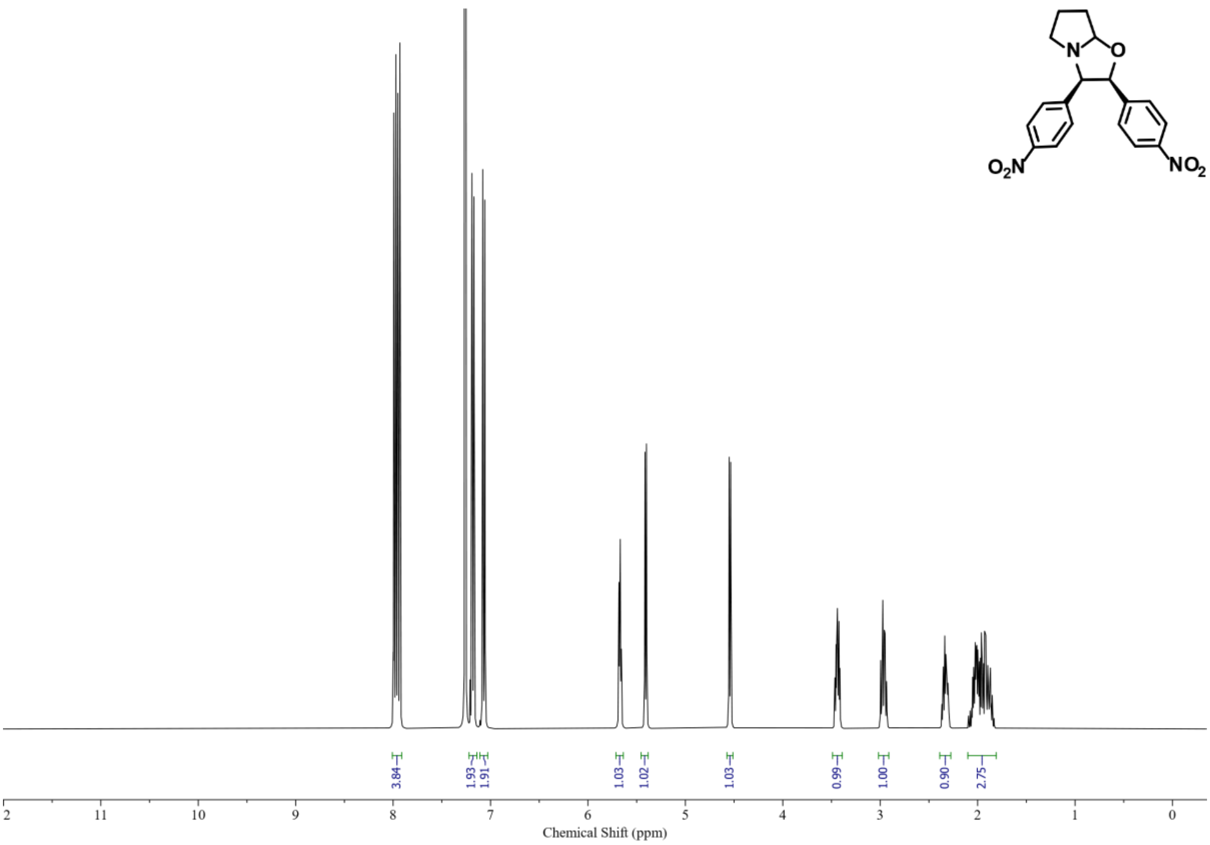
^{13}C NMR (101 MHz, $CDCl_3$) δ 128.15, 127.21, 124.11, 124.05, 99.48, 87.59, 78.64, 56.02, 31.72, 24.24.

In DMSO-d_6 - ^{1}H-NMR



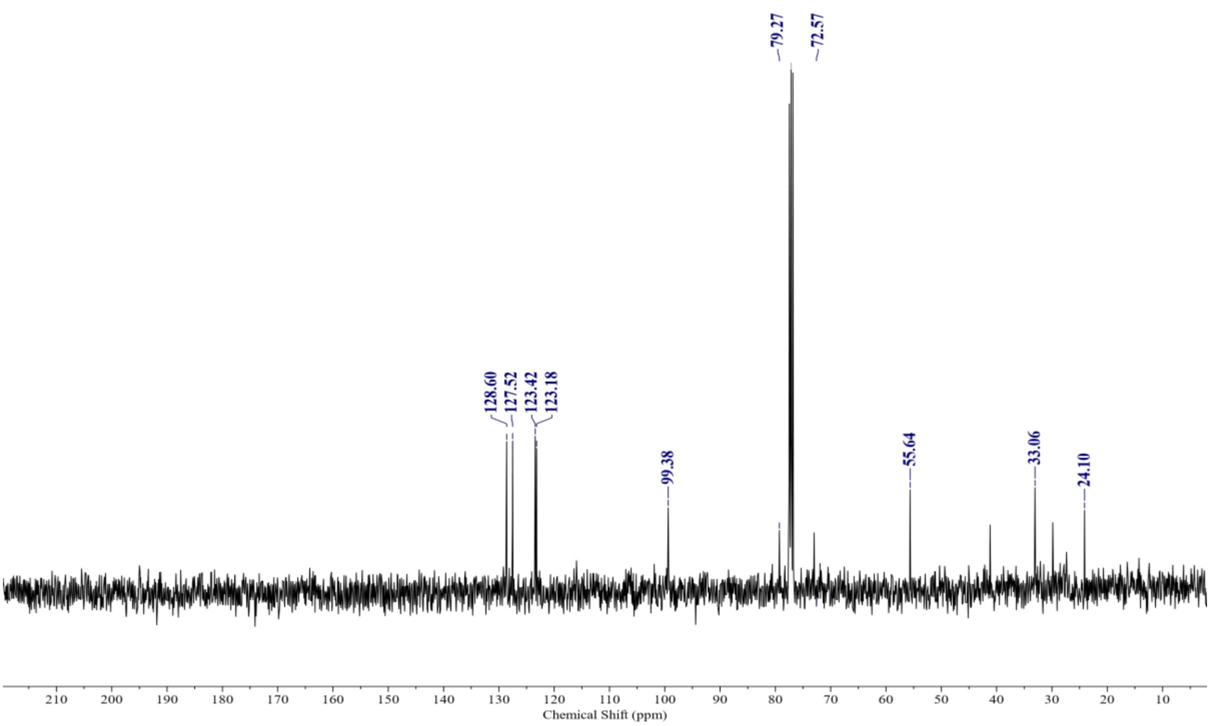
^{1}H NMR (400 MHz, DMSO) δ 8.26 – 8.15 (m, 4H), 7.60 – 7.48 (m, 4H), 5.28 (t, *J* = 3.2 Hz, 1H), 4.80 (d, *J* = 7.9 Hz, 1H), 4.05 (d, *J* = 7.9 Hz, 1H), 3.02 (dt, *J* = 10.2, 6.4 Hz, 1H), 2.88 (dt, *J* = 10.0, 6.1 Hz, 1H), 2.13 – 1.91 (m, 2H), 1.77 (dt, *J* = 11.9, 5.9 Hz, 1H).

In $CDCl_3$ - ^1H-NMR



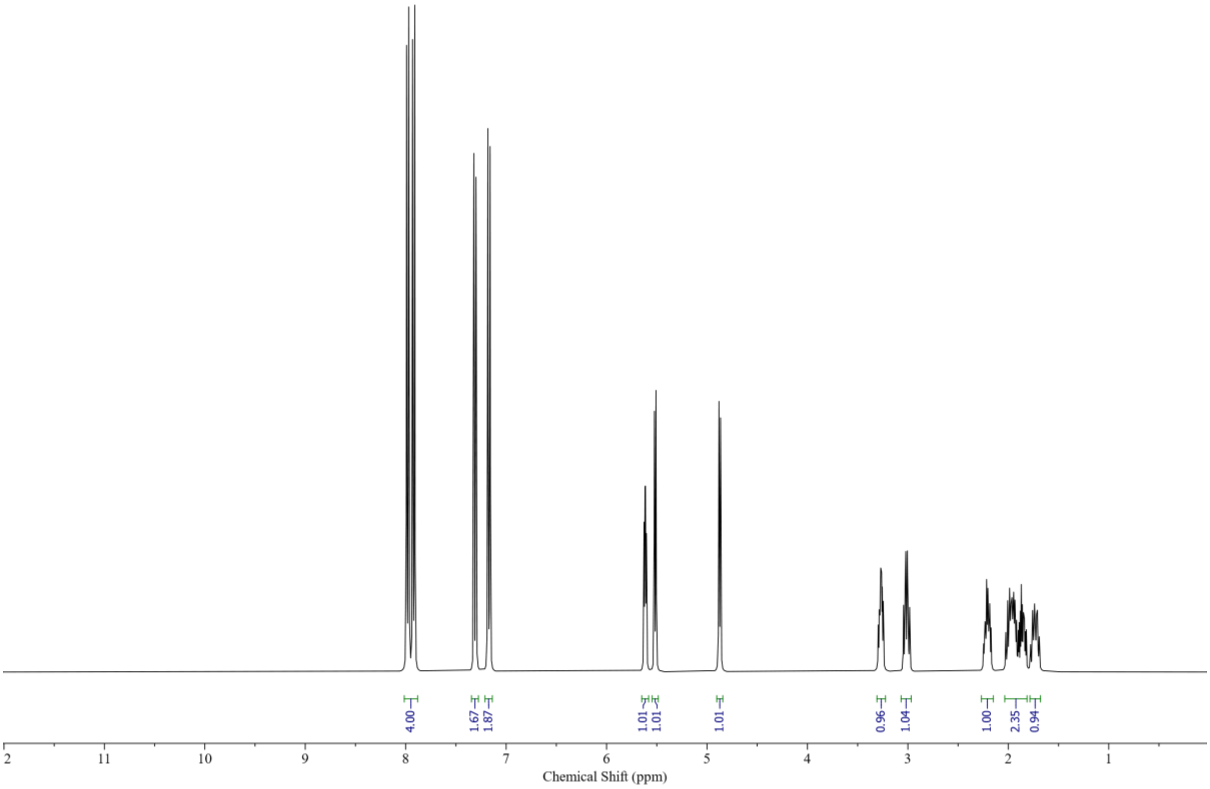
^1H NMR (400 MHz, $CDCl_3$) δ 8.01 – 7.91 (m, 4H), 7.22 – 7.14 (m, 2H), 7.11 – 7.03 (m, 2H), 5.67 (dd, *J* = 5.6, 3.6 Hz, 1H), 5.41 (d, *J* = 6.1 Hz, 1H), 4.54 (d, *J* = 6.1 Hz, 1H), 3.44 (ddd, *J* = 10.1, 6.4, 3.9 Hz, 1H), 3.02 – 2.91 (m, 1H), 2.39 – 2.28 (m, 1H), 2.10 – 1.81 (m, 3H).

C-NMR[13]



^{13}C NMR (101 MHz, $CDCl_3$) δ 128.60, 127.52, 123.42, 123.18, 99.38, 79.27, 72.57, 55.64, 33.06, 24.10.

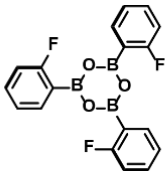
In DMSO-d_6 - ^{1}H-NMR

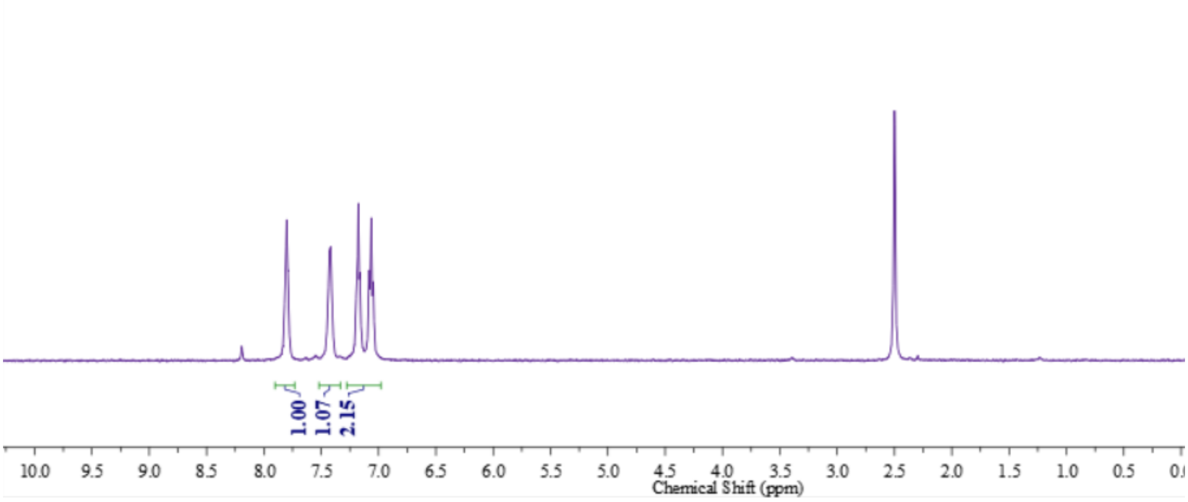


^{1}H NMR (400 MHz, DMSO) δ 8.01 – 7.88 (m, 4H), 7.34 – 7.28 (m, 2H), 7.21 – 7.14 (m, 2H), 5.62 (dd, *J* = 5.6, 3.6 Hz, 1H), 5.52 (d, *J* = 6.2 Hz, 1H), 4.87 (d, *J* = 6.2 Hz, 1H), 3.31 – 3.22 (m, 1H), 3.01 (td, *J* = 9.0, 6.2 Hz, 1H), 2.27 – 2.15 (m, 1H), 2.04 – 1.81 (m, 2H), 1.78 – 1.68 (m, 1H).

NMRs in agreement to the literature.[3-9]

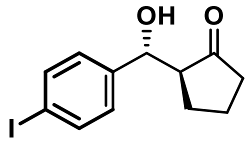
^{1}H-NMR


F
O
B
O
B
F
O
B
F

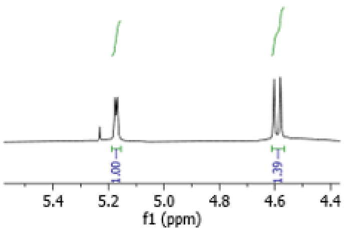

1.00
1.07
2.15
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
Chemical Shift (ppm)

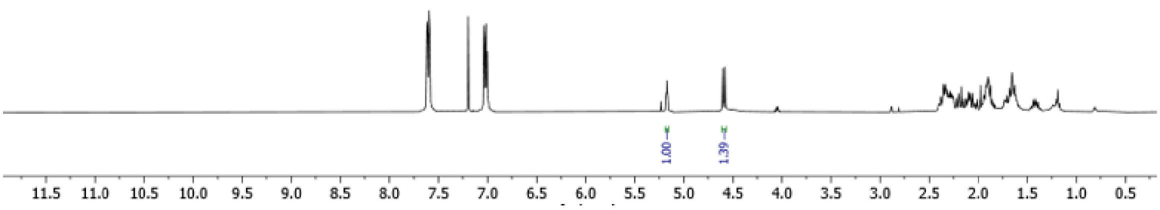
18. Crude NMR spectra

18.1 Scope (table S6 and S7)

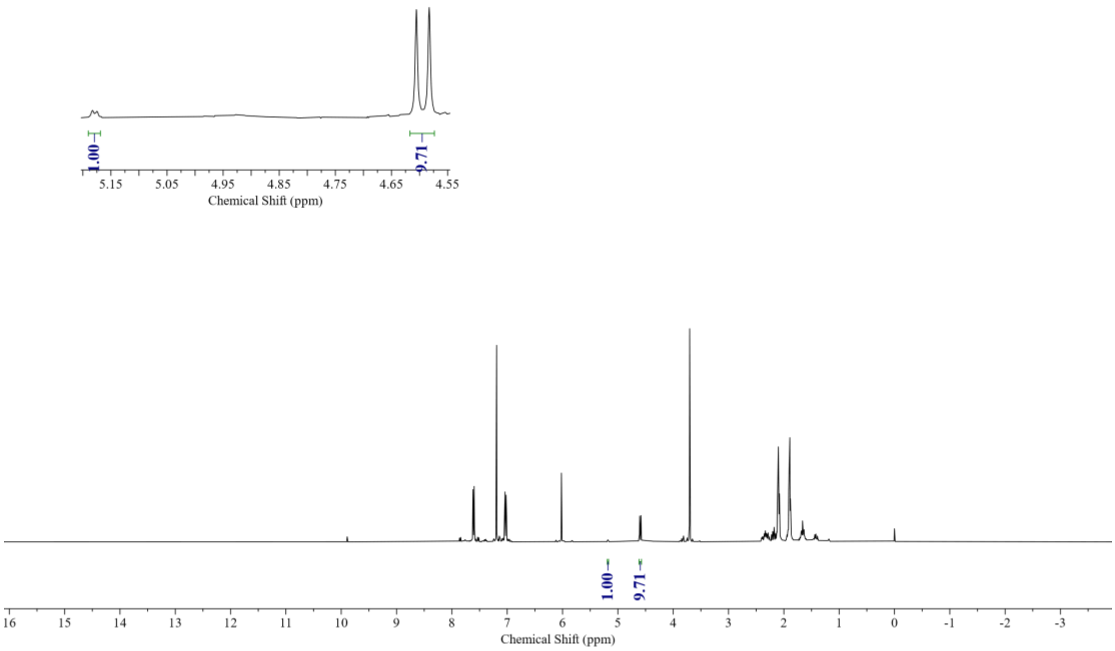


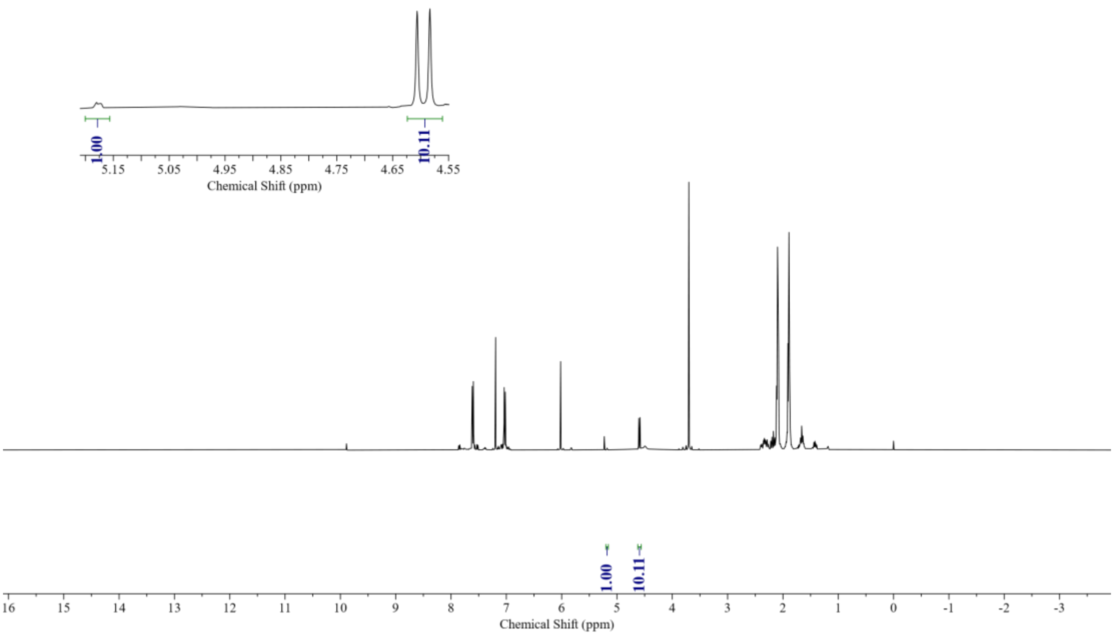
~1:1 Syn:Anti (racemic)

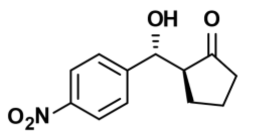




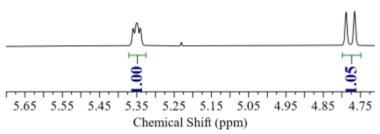
Crude (chiral sample)

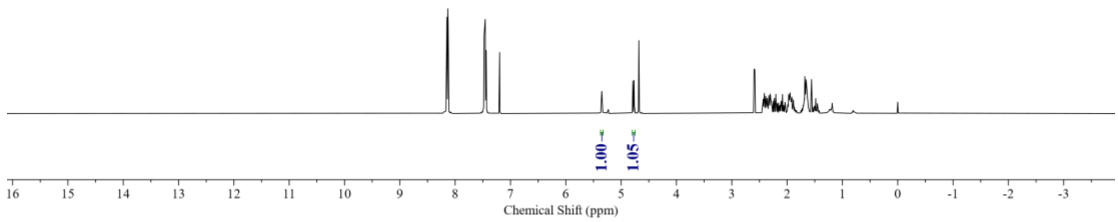




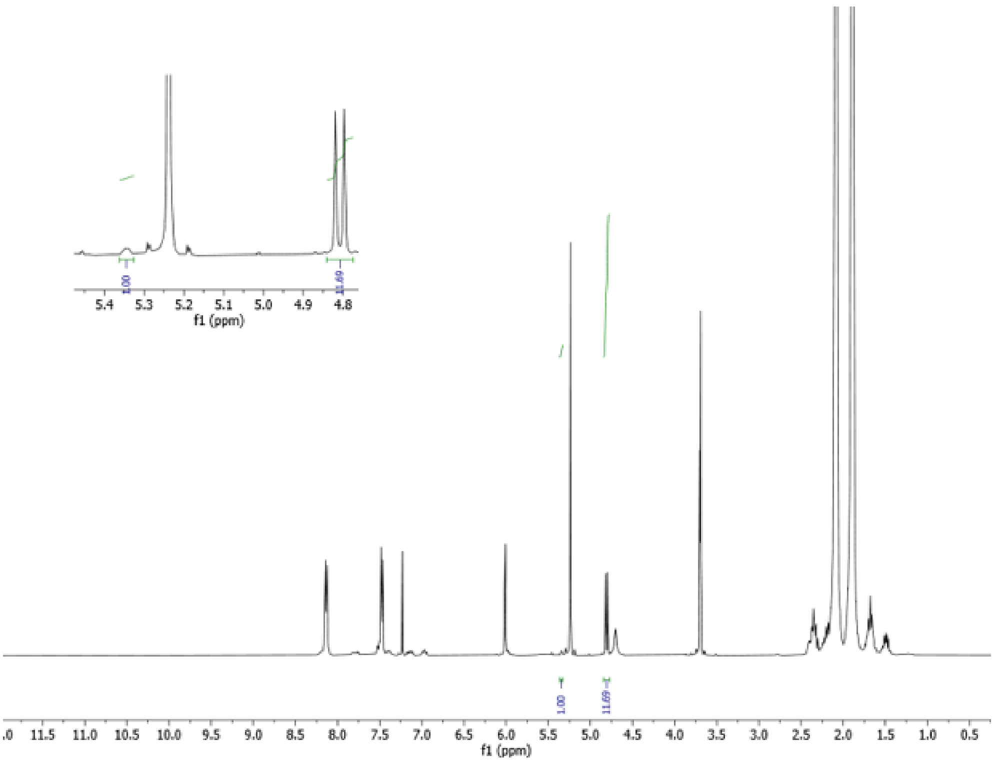


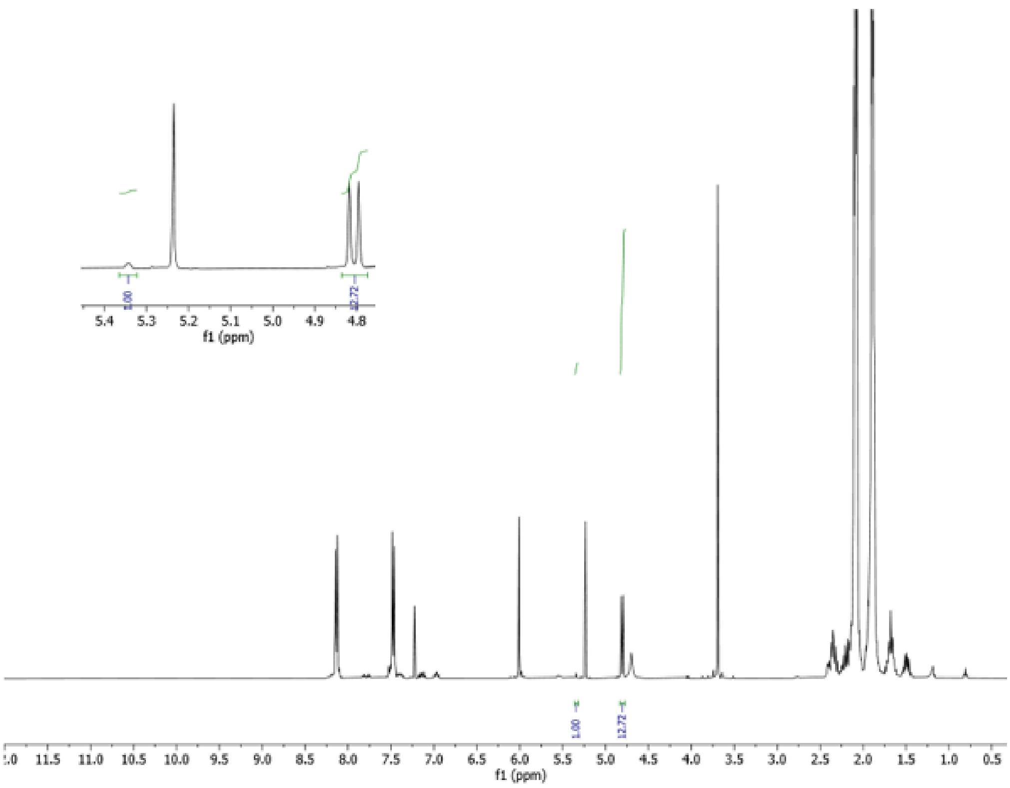
Syn:Anti ~ 1:1 (racemic)

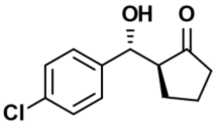




Crude (chiral sample)

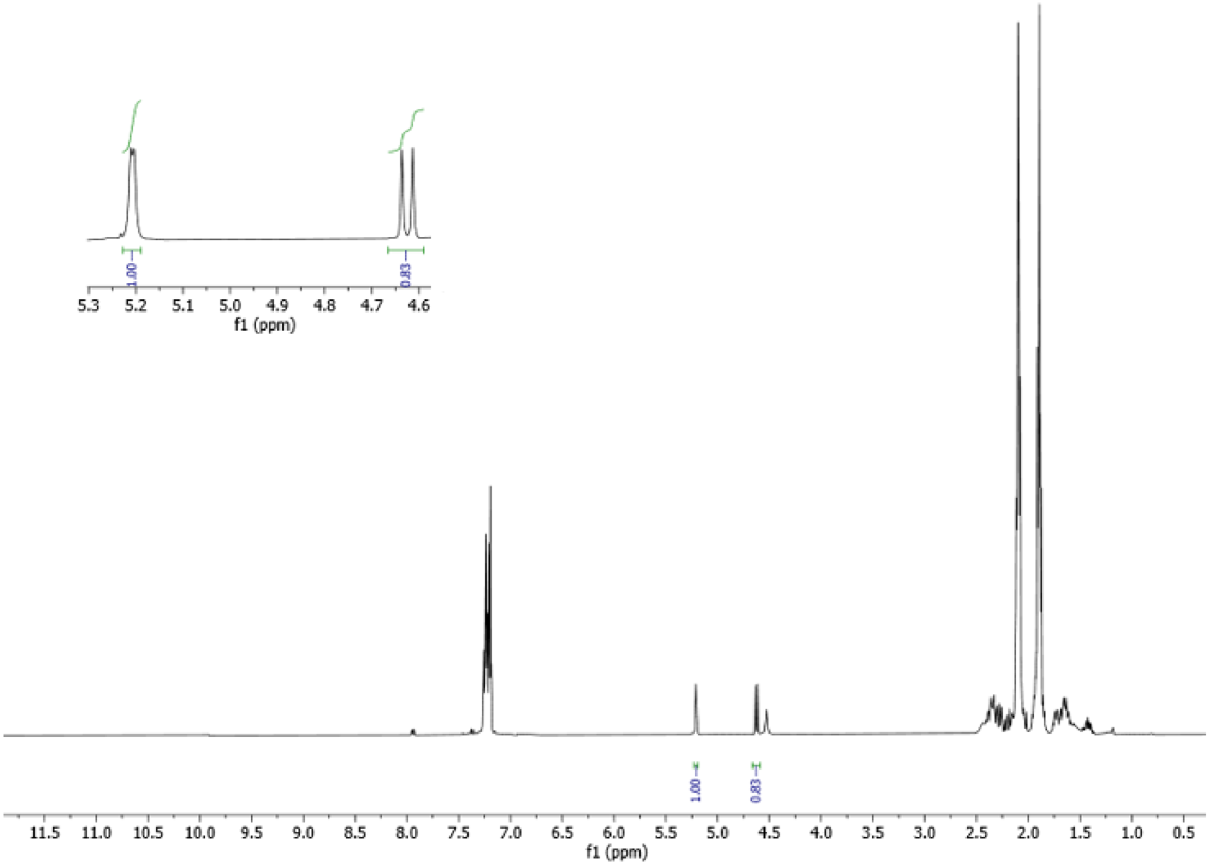




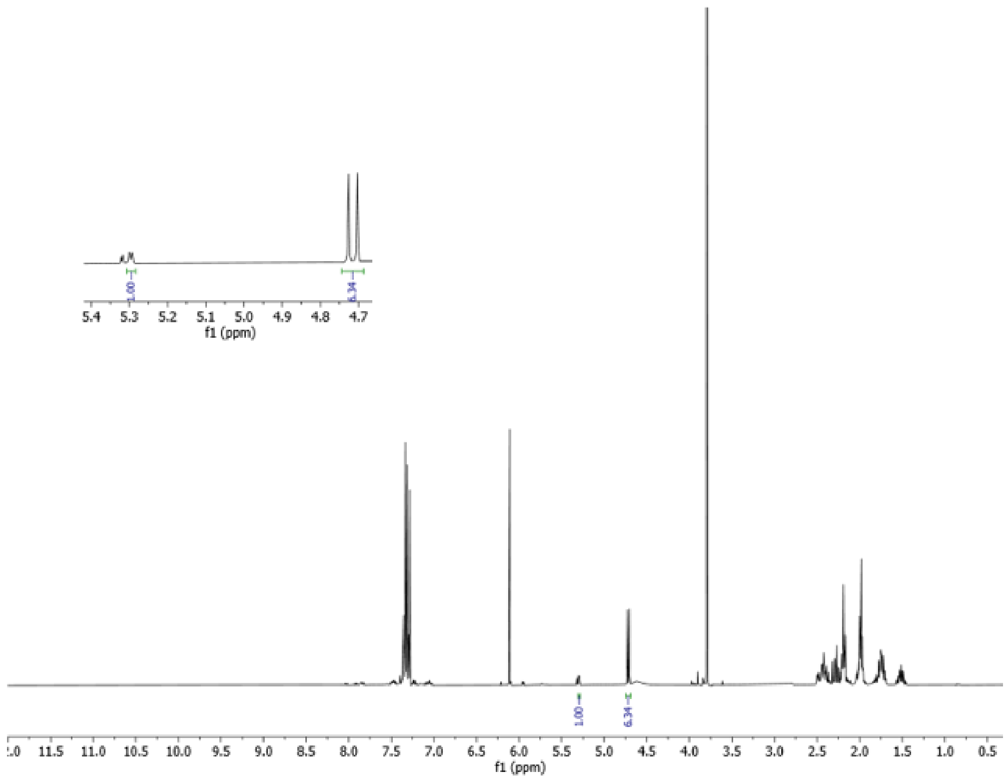


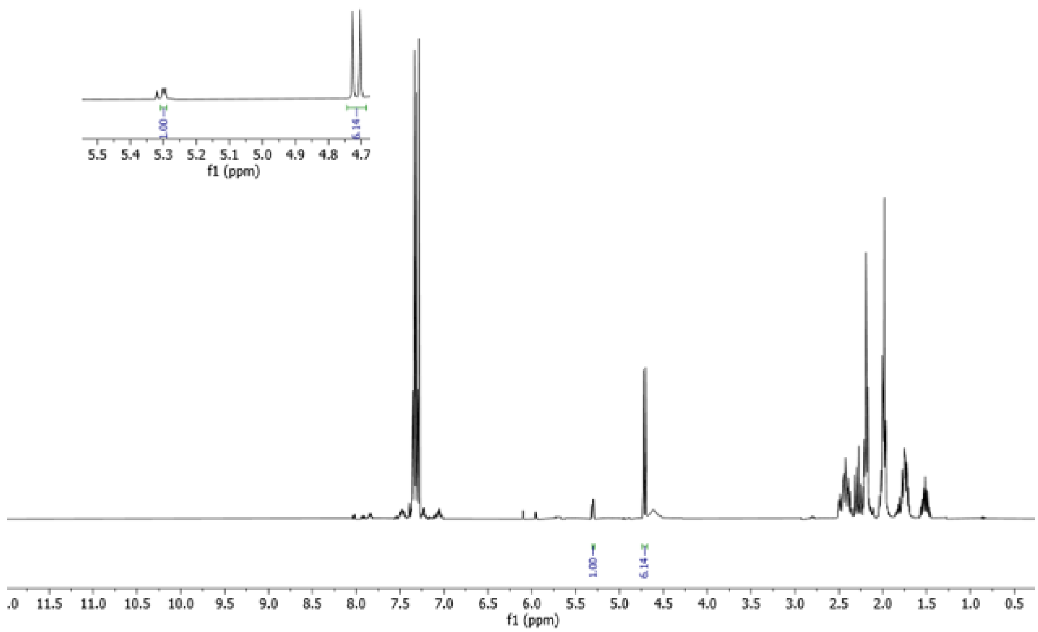
anti

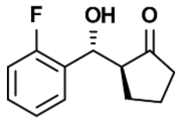
1:1 Syn:Anti~(racemic)



Crude NMR (chiral sample)

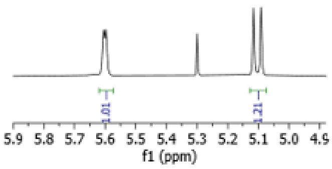


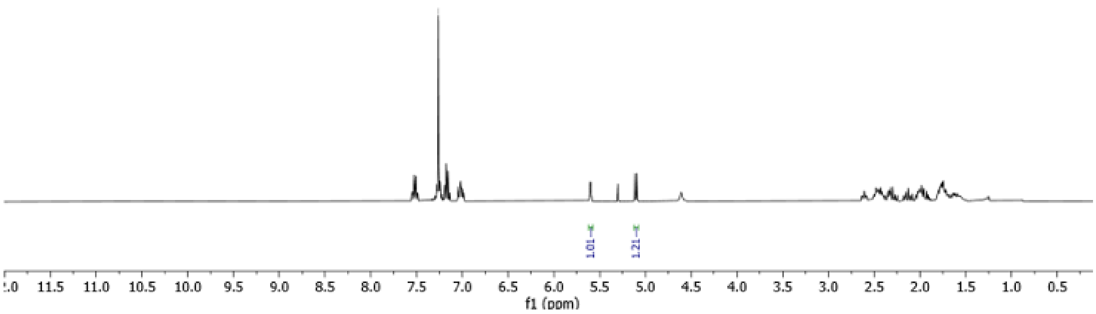




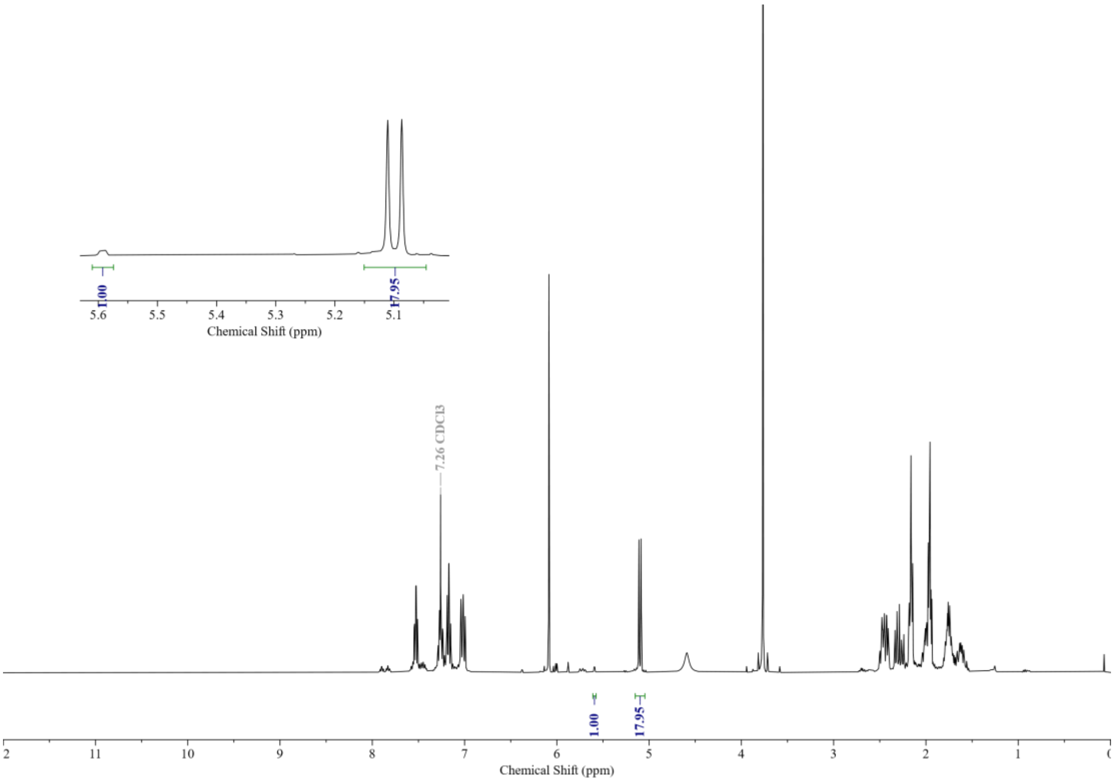
anti

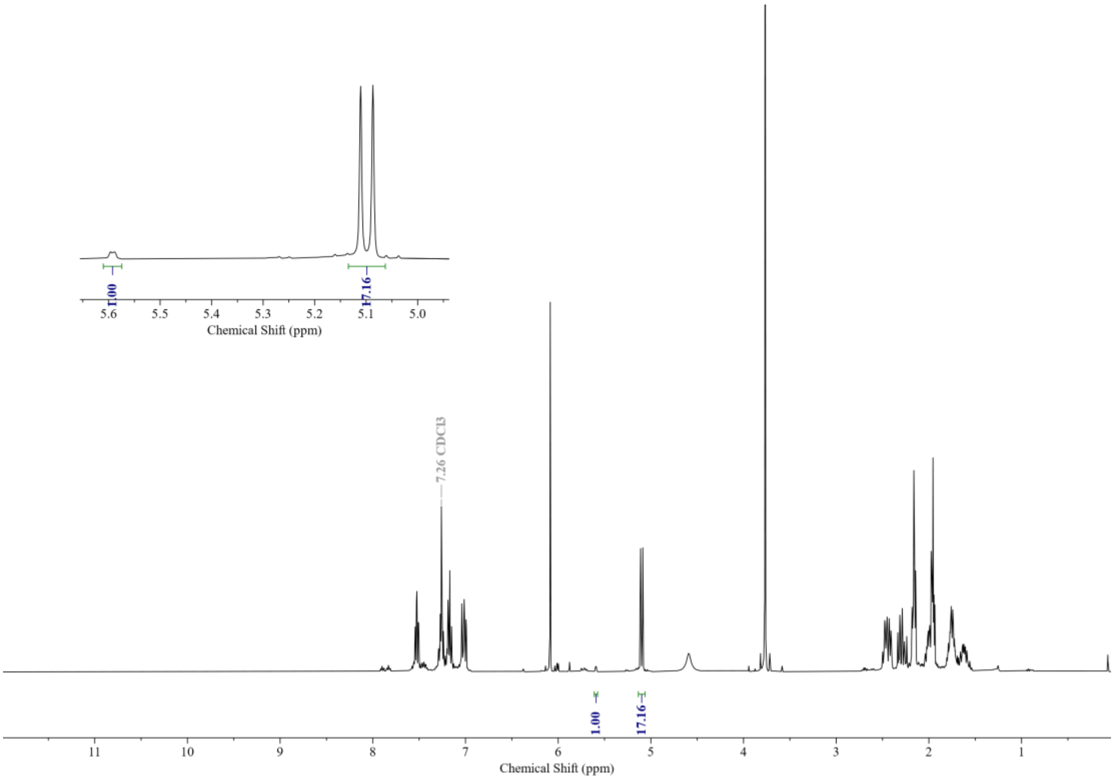
1:1 Syn:Anti~ (racemic)

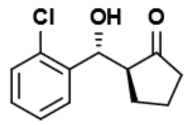




Crude NMR (chiral sample)

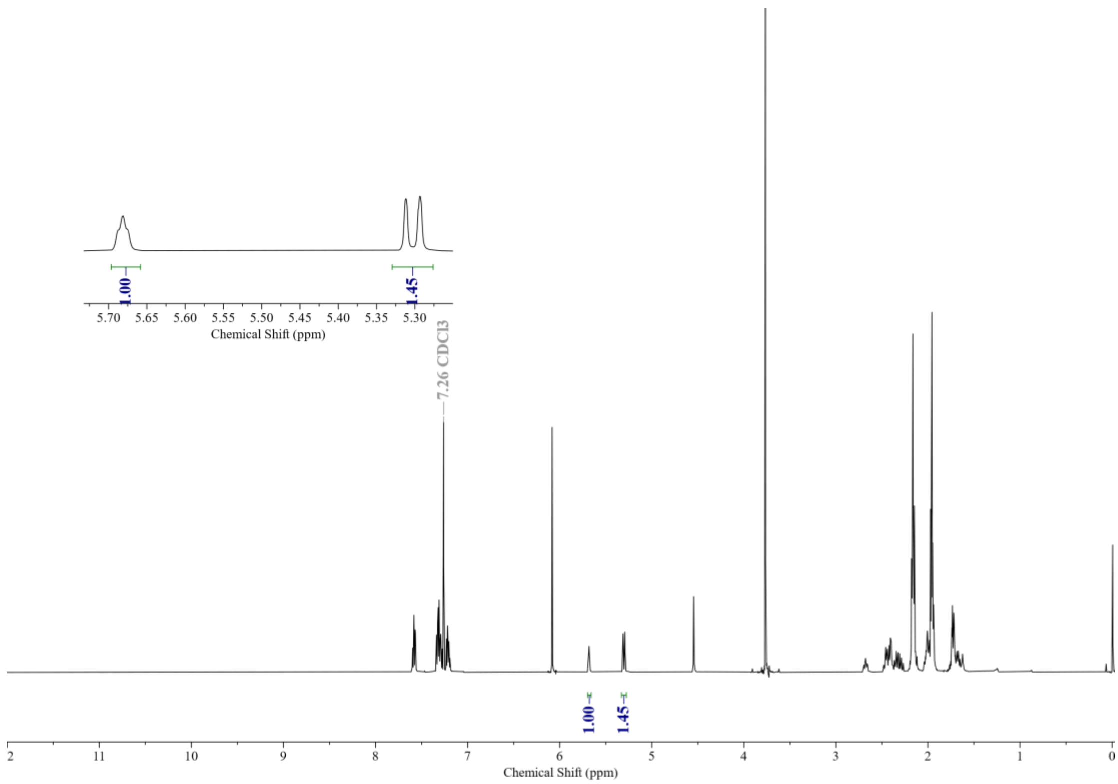




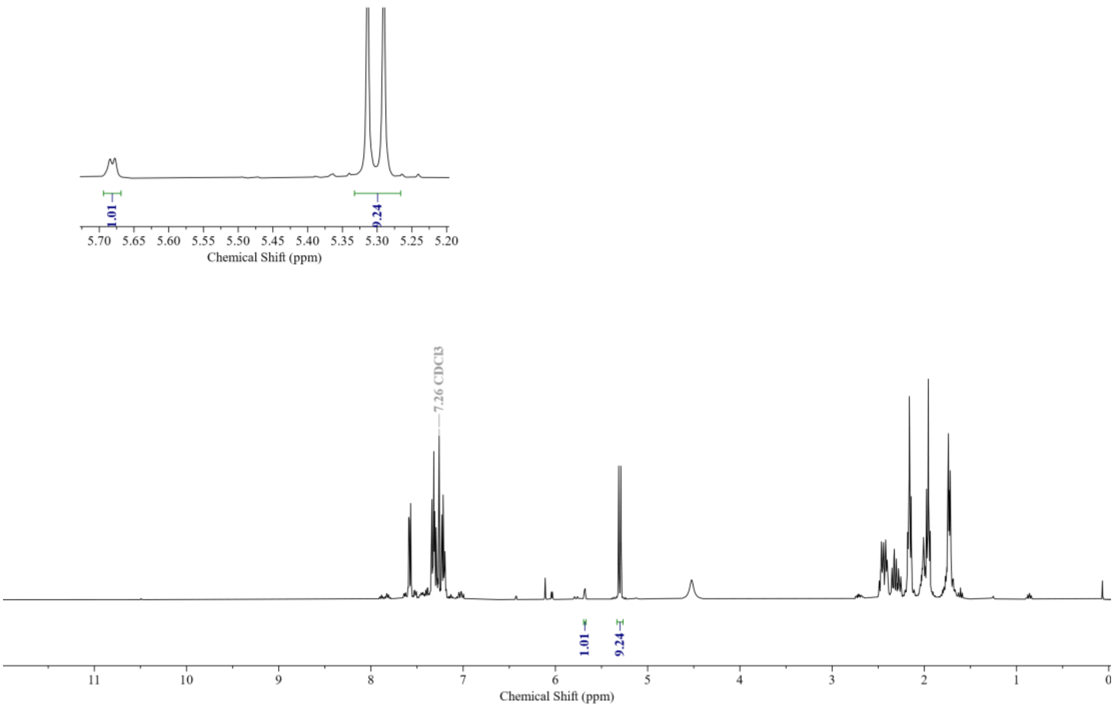


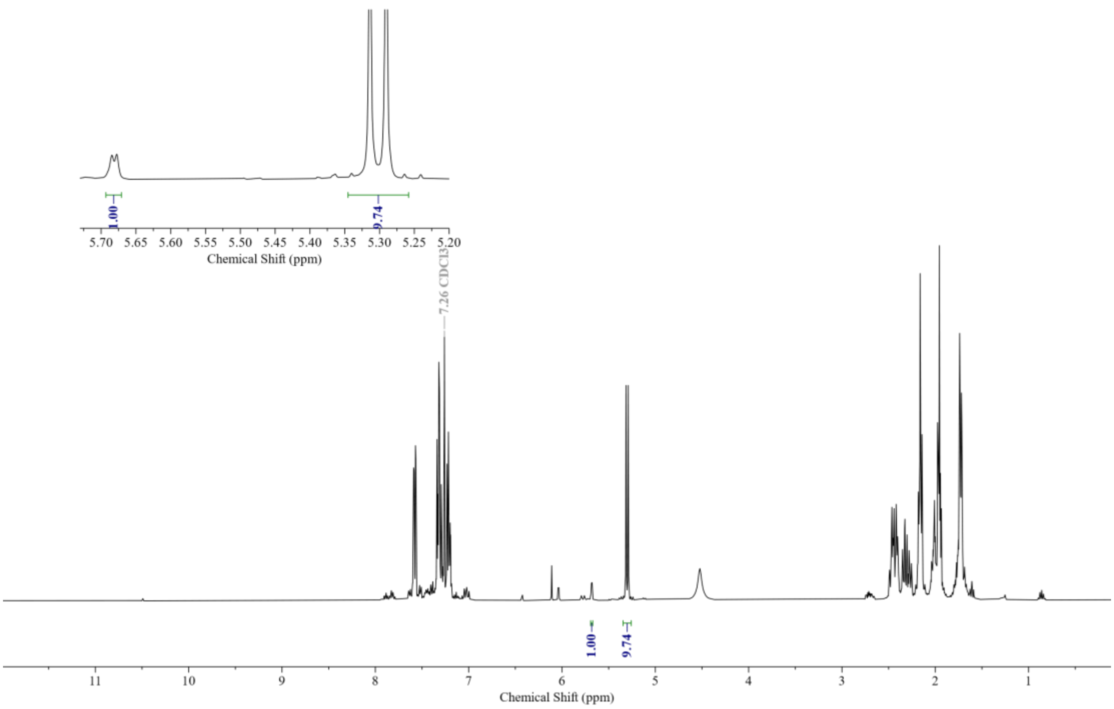
anti

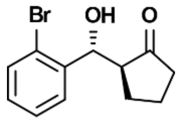
1:1 Syn:Anti~ (racemic)



Crude NMR (chiral sample)

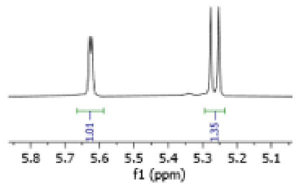


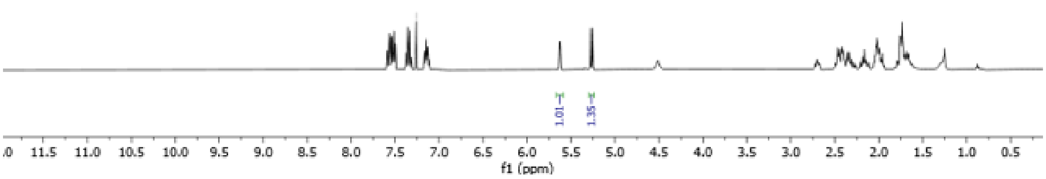




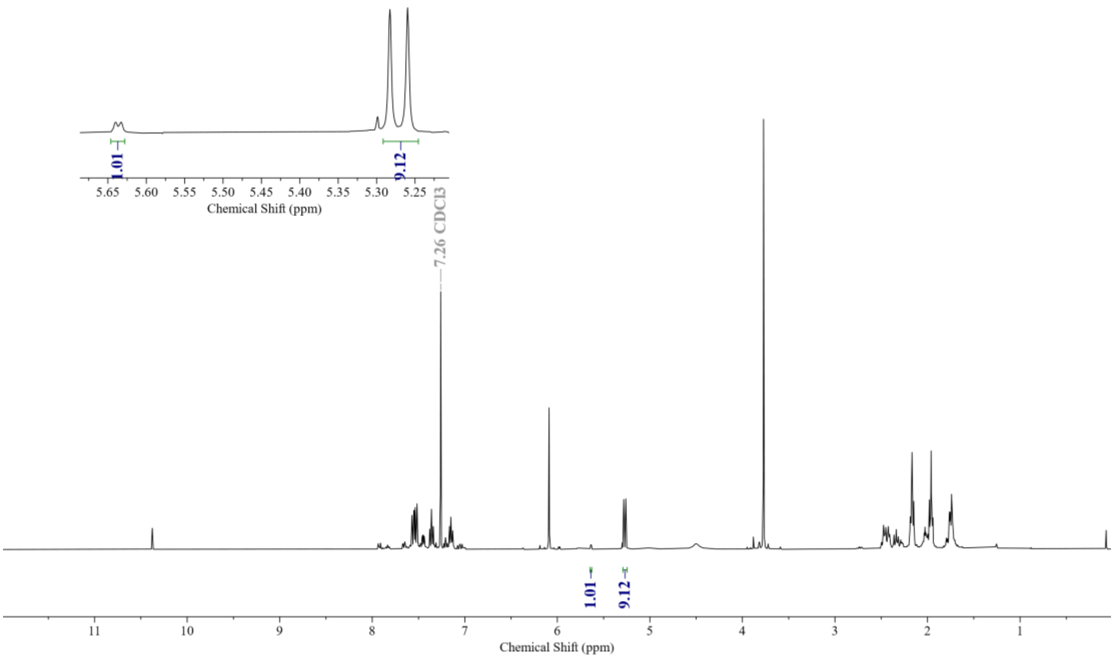
anti

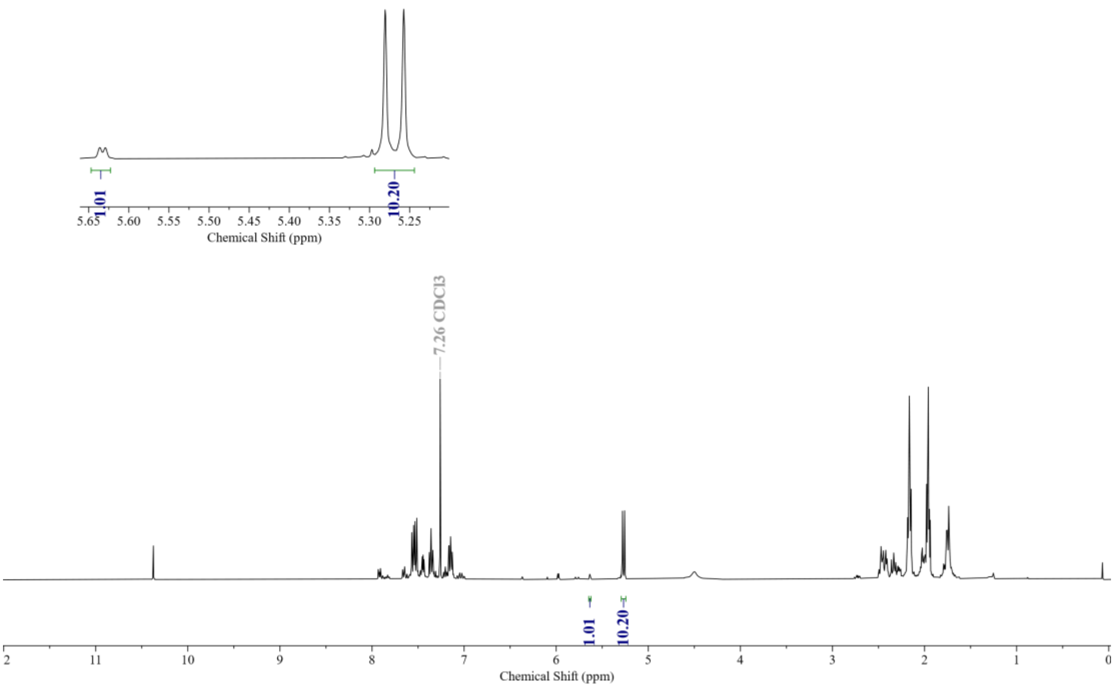
~1:1 anti : syn (racemic)

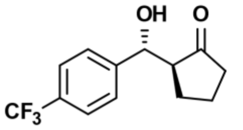




Crude nmr (chiral sample)

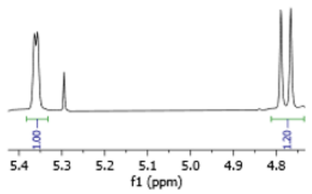


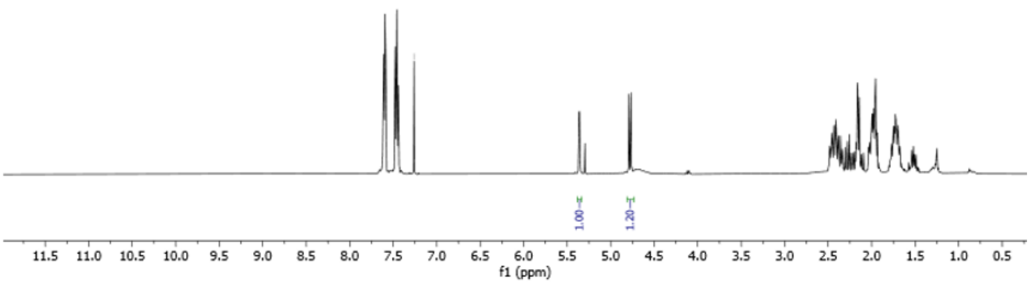




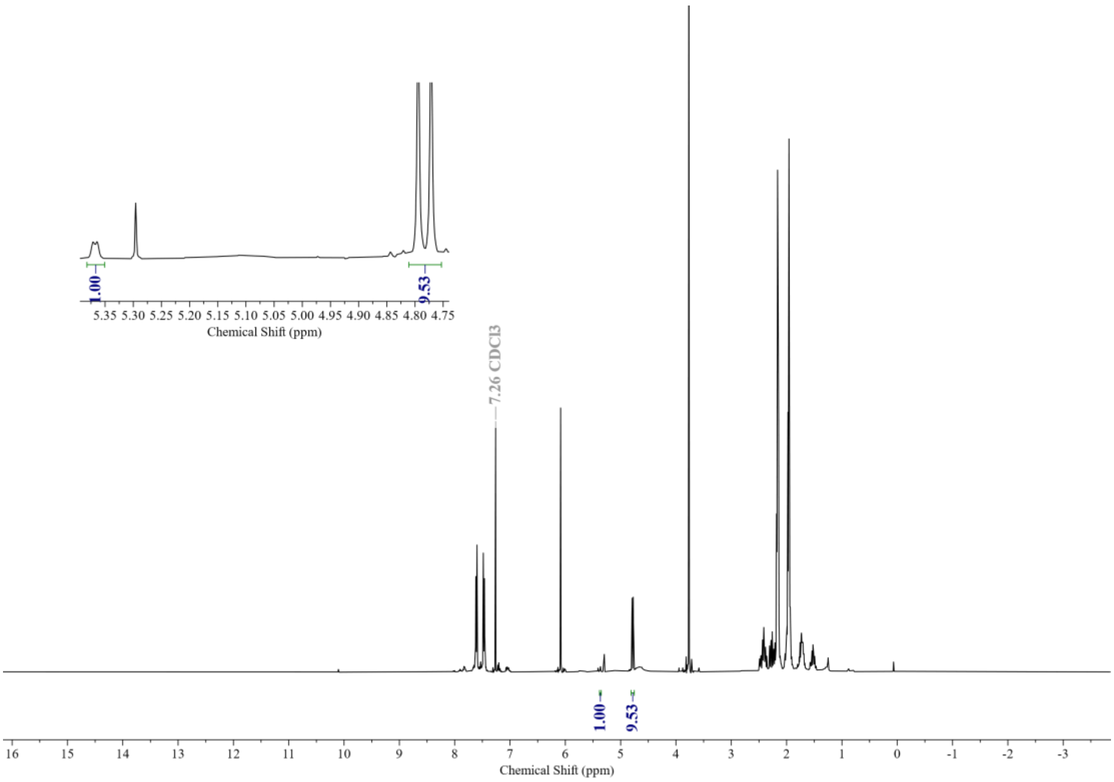
anti

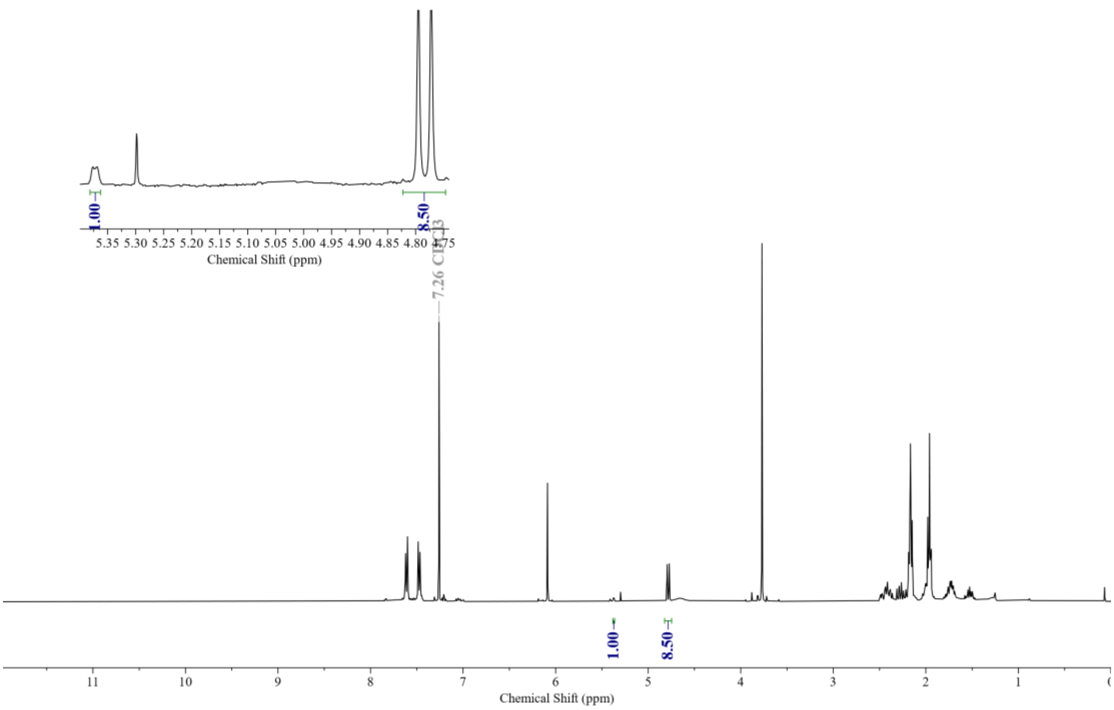
~1:1 anti : syn (racemic)

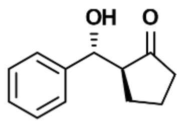




Crude (chiral sample)

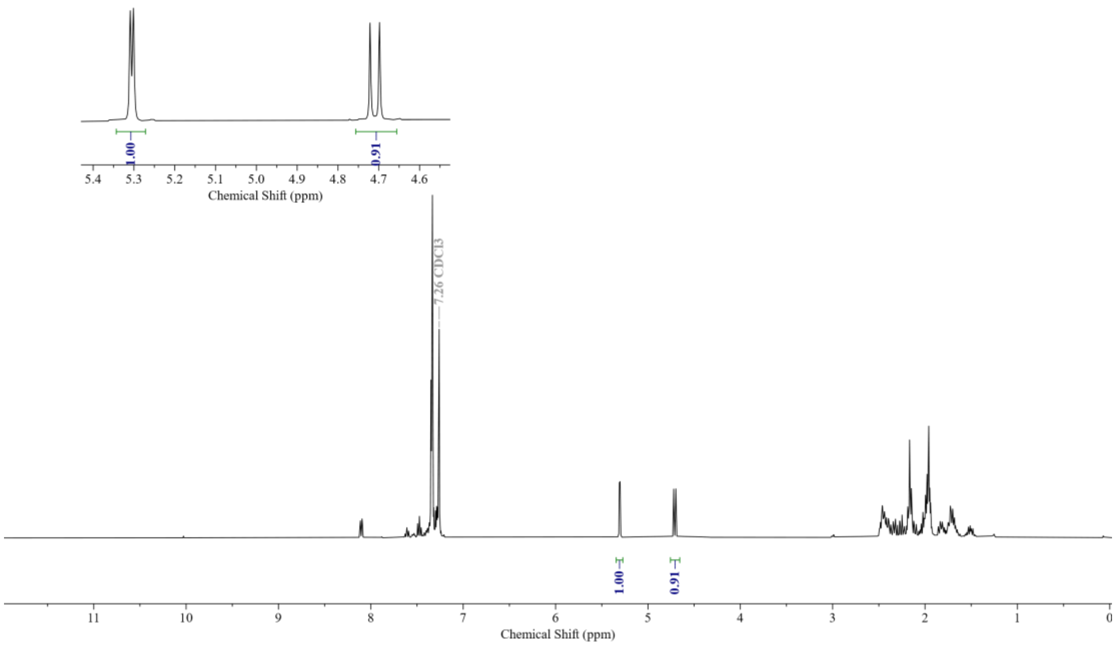




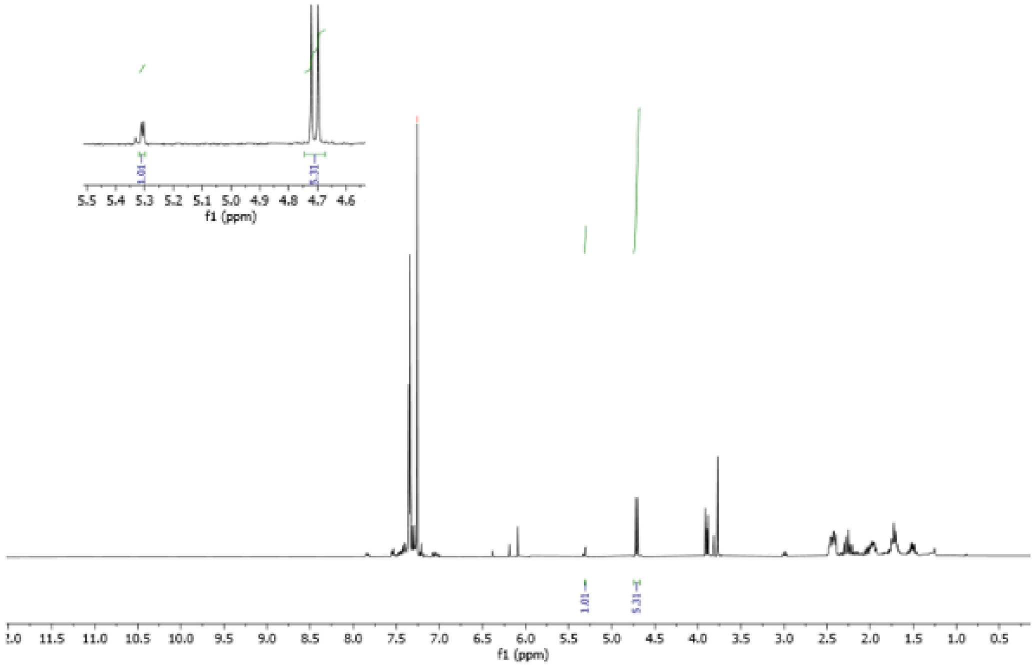


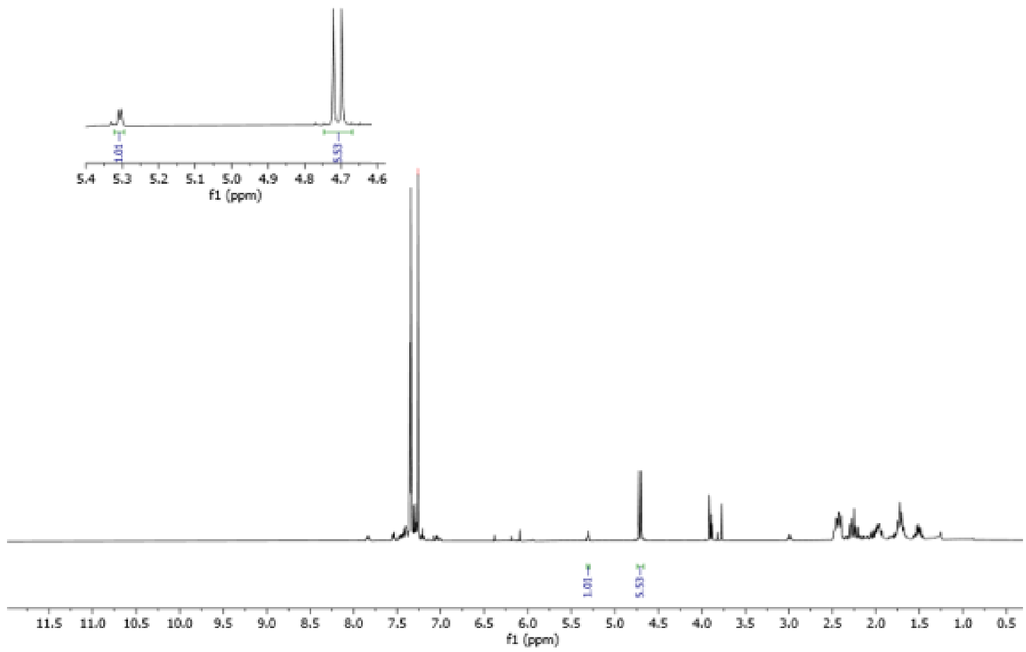
anti

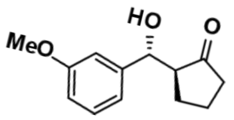
~1:1 anti : syn (racemic)



Crude (chiral sample)







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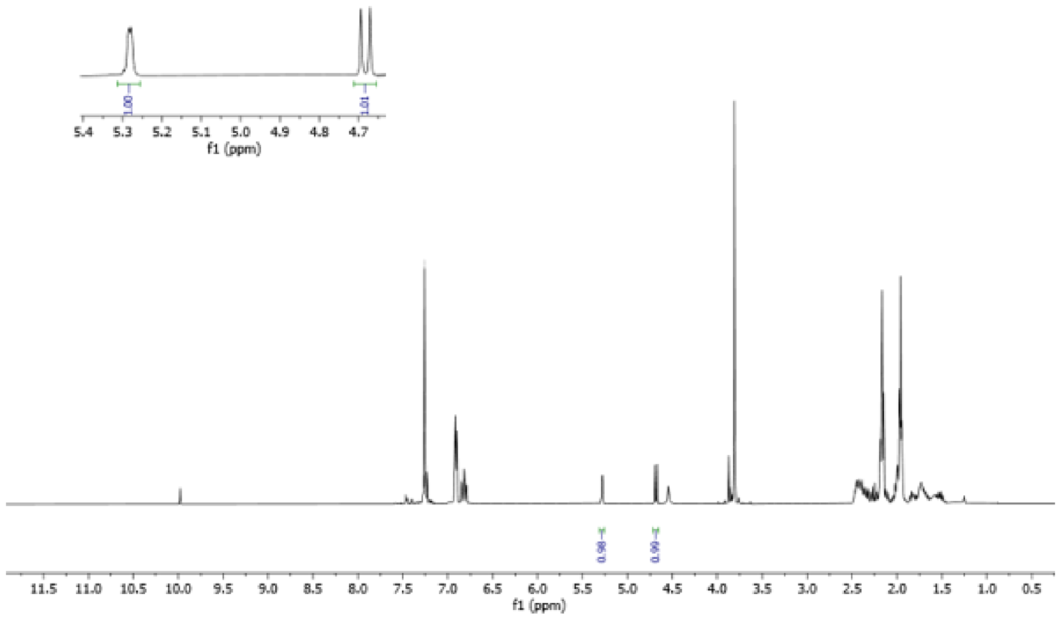
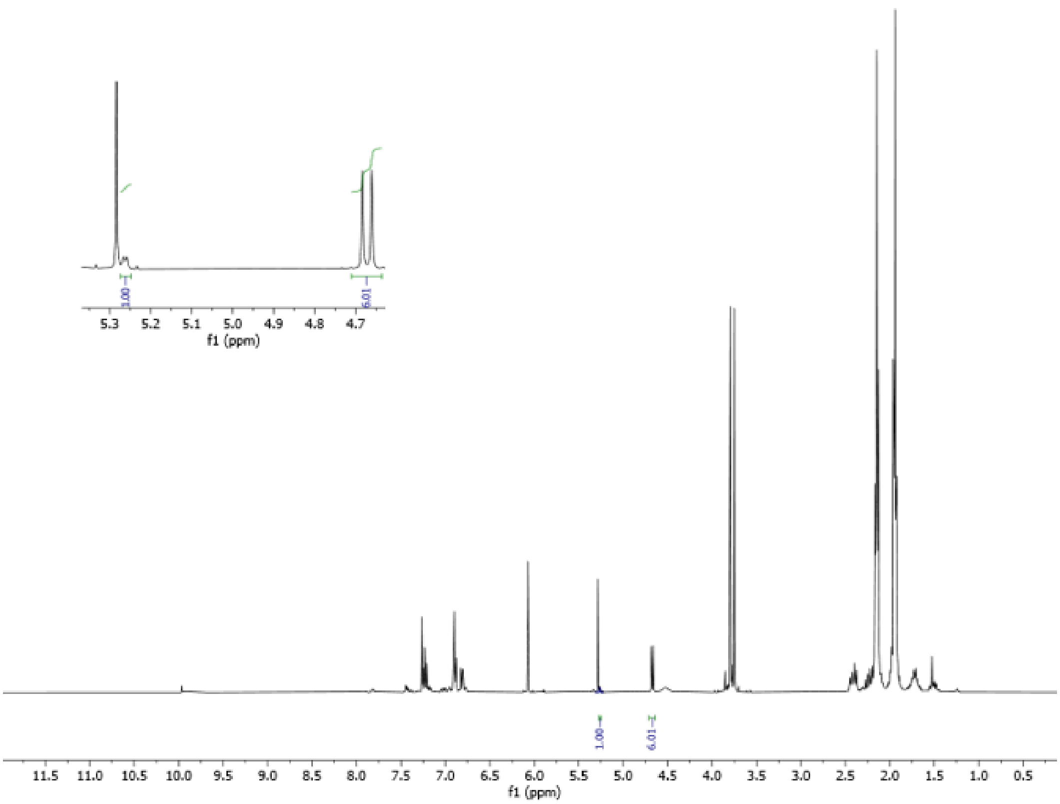
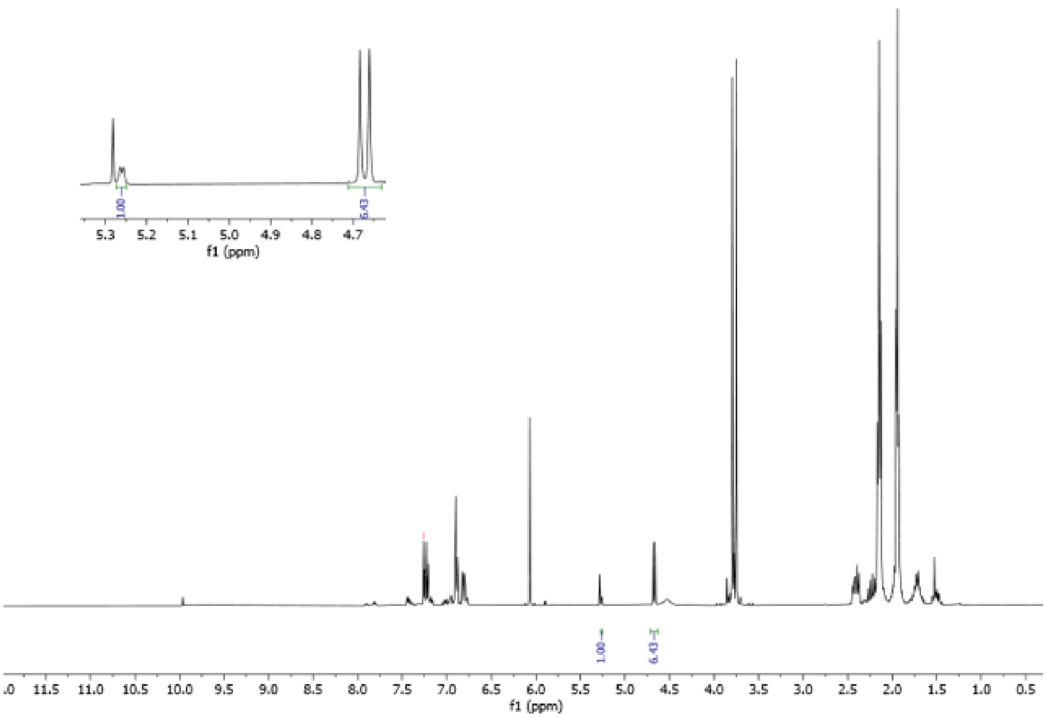
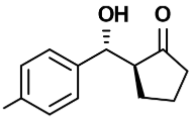


Crude (chiral sample)







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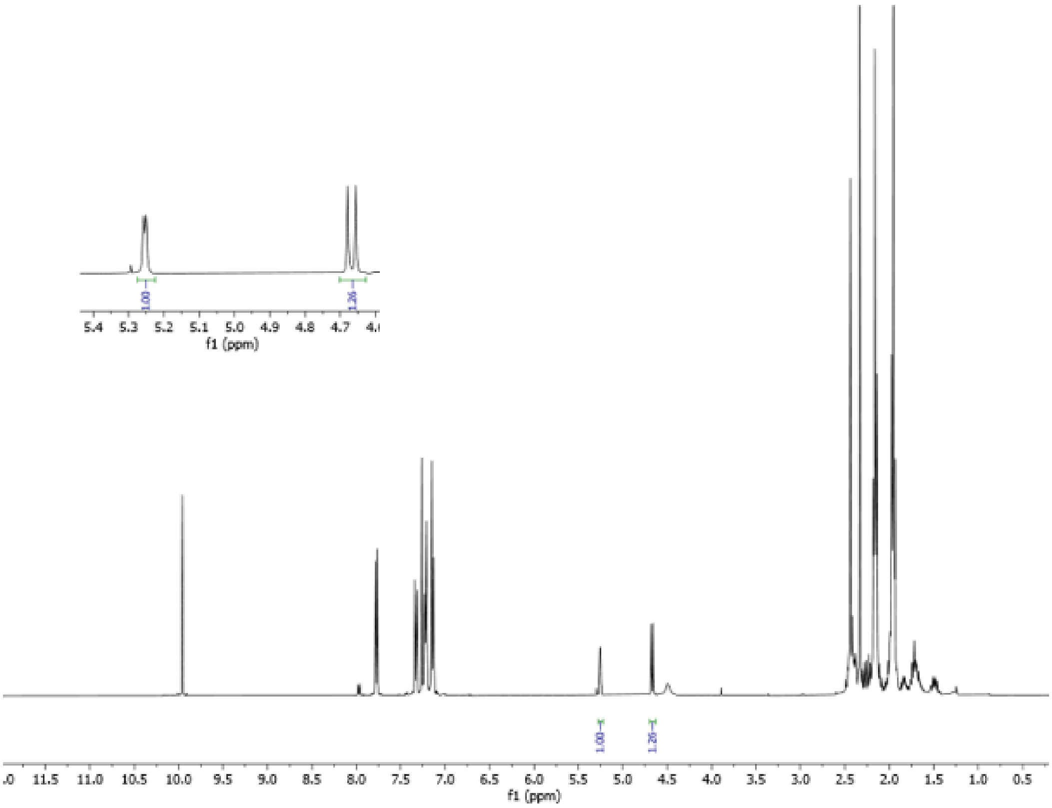
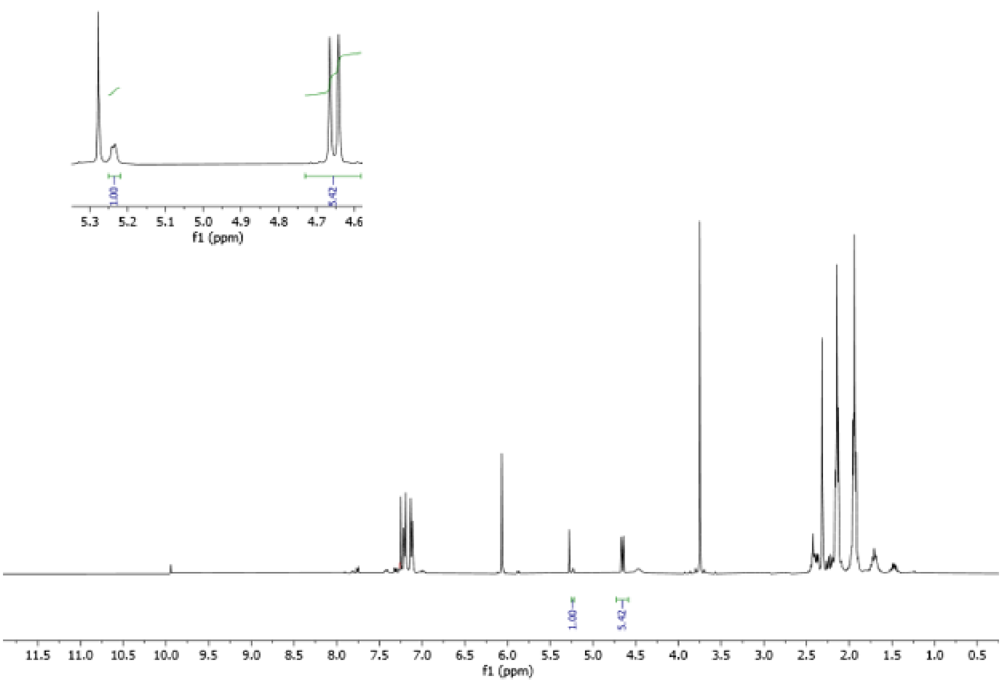
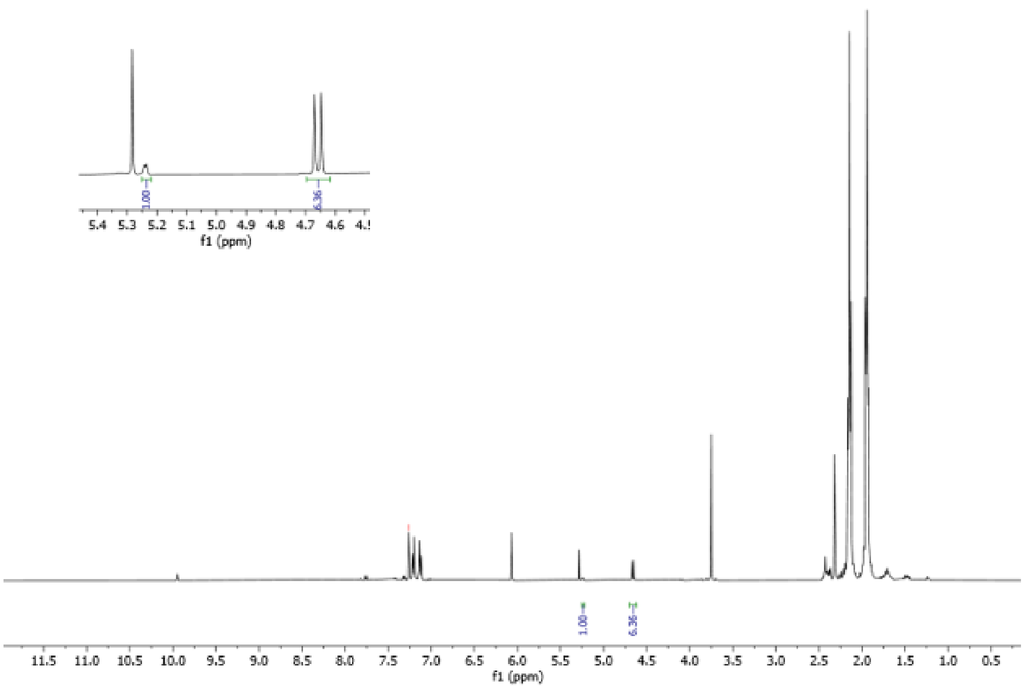
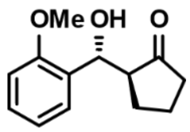


Crude (chiral sample)







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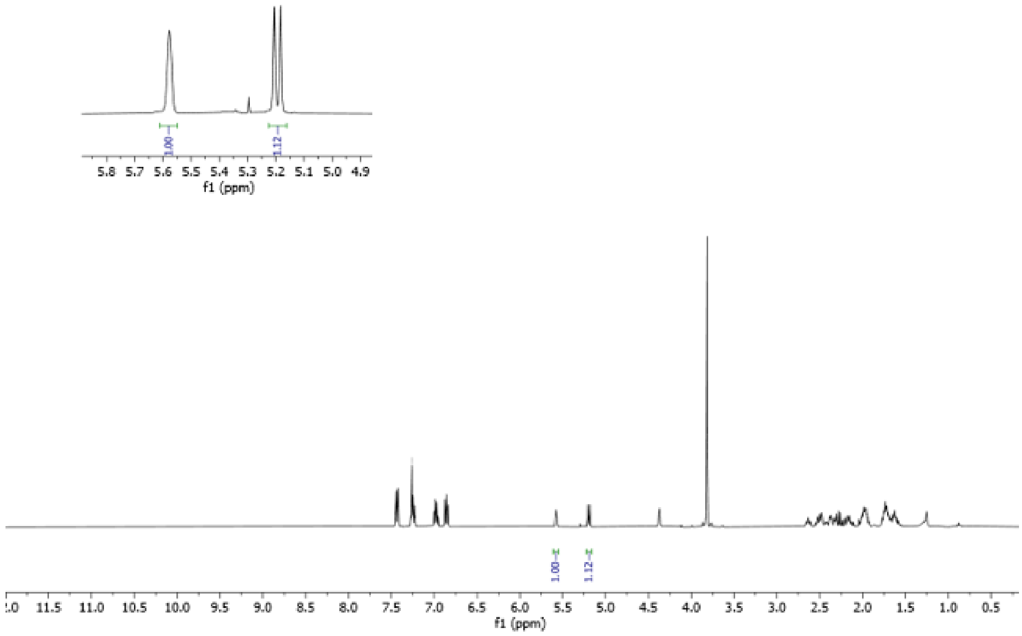

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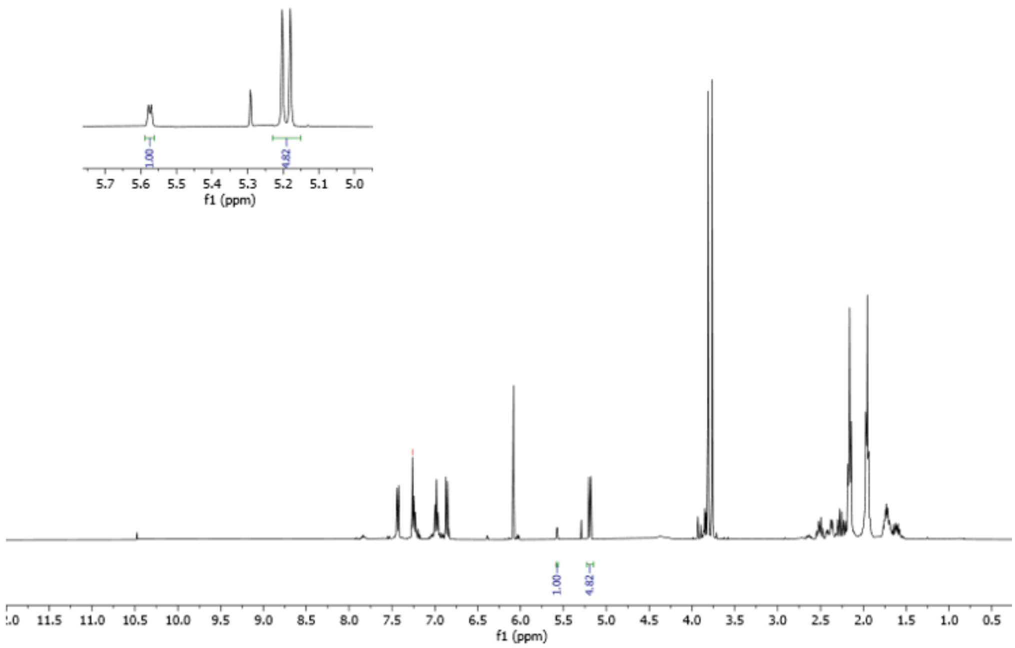

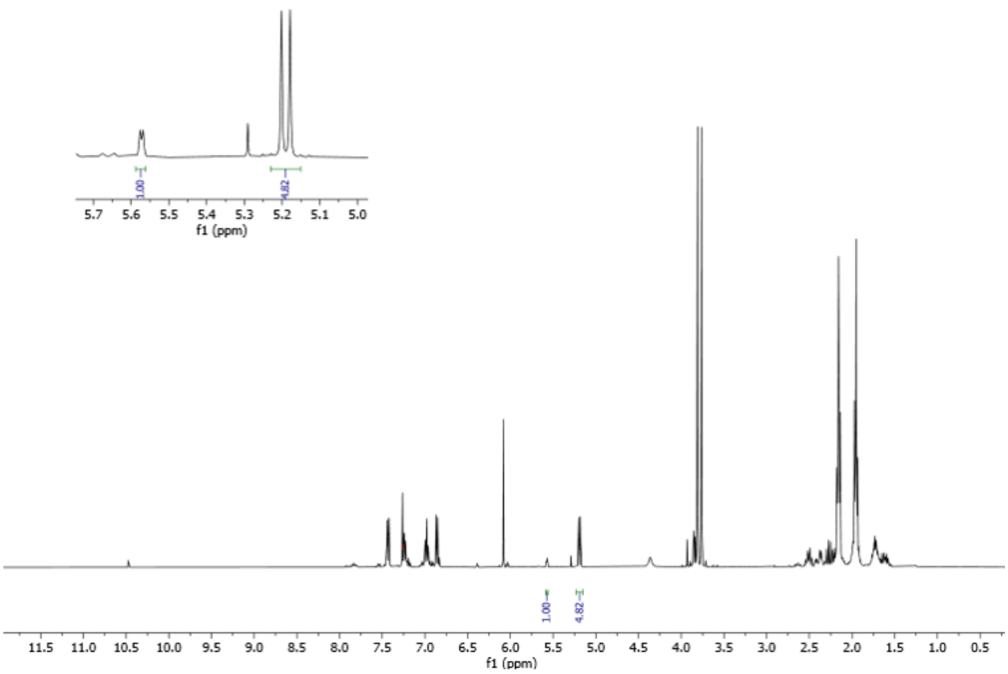

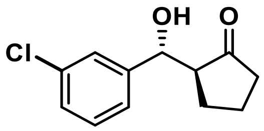

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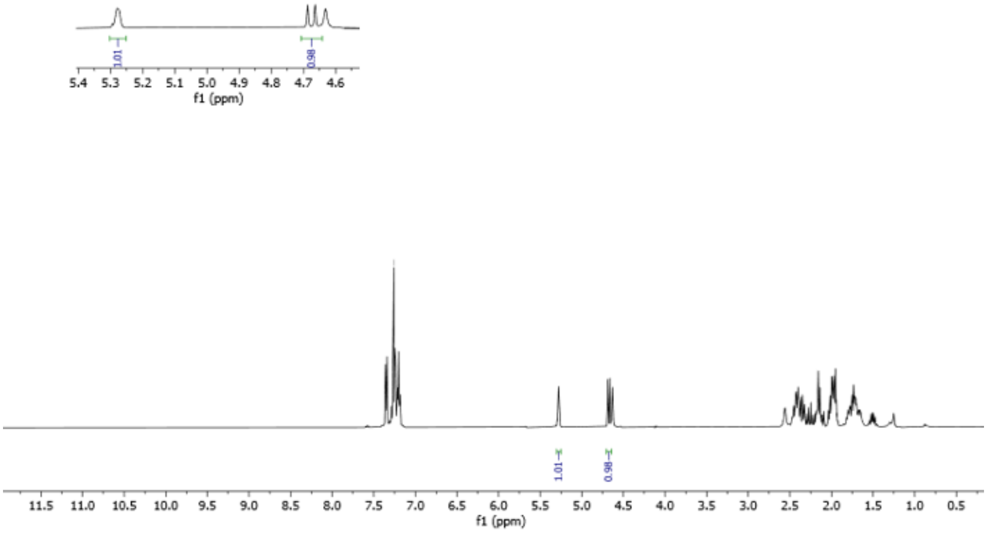

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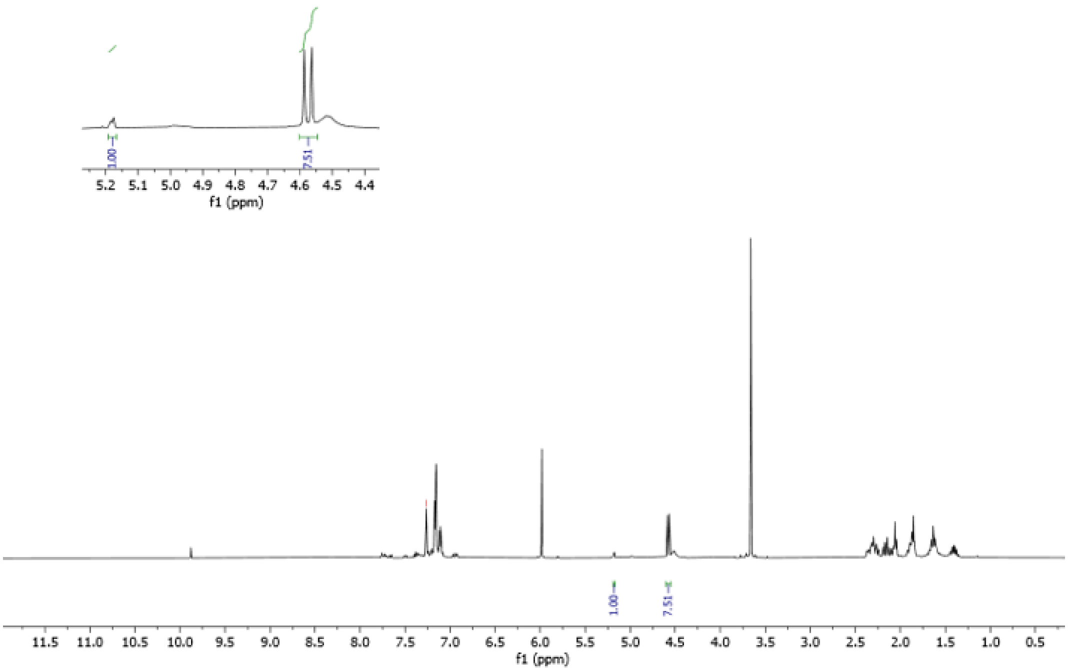
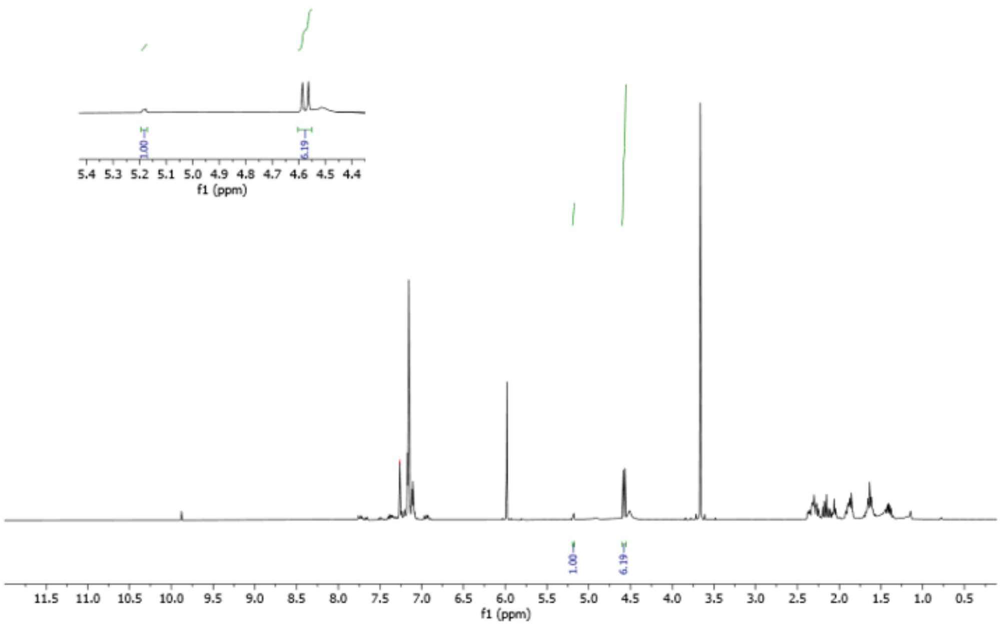
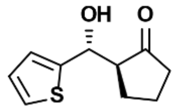
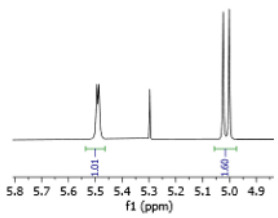


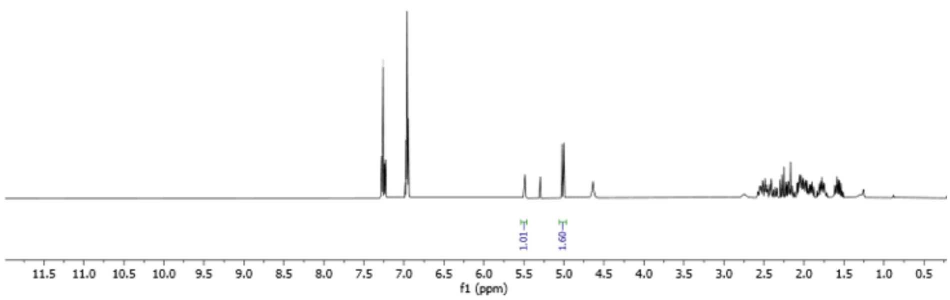




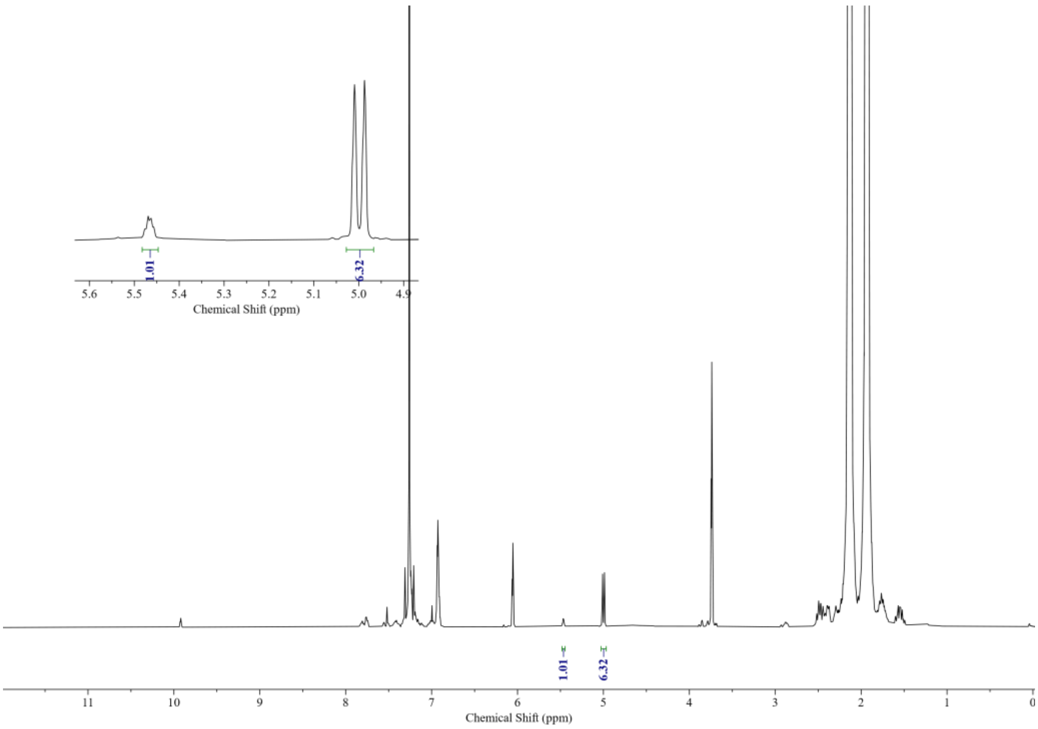
anti

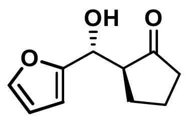
~1:1 anti:syn (racemic)



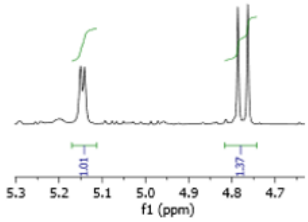


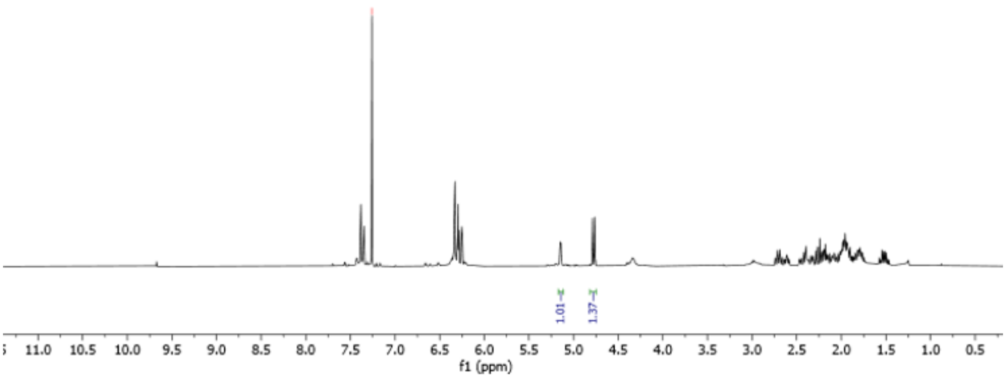
Crude (chiral sample)



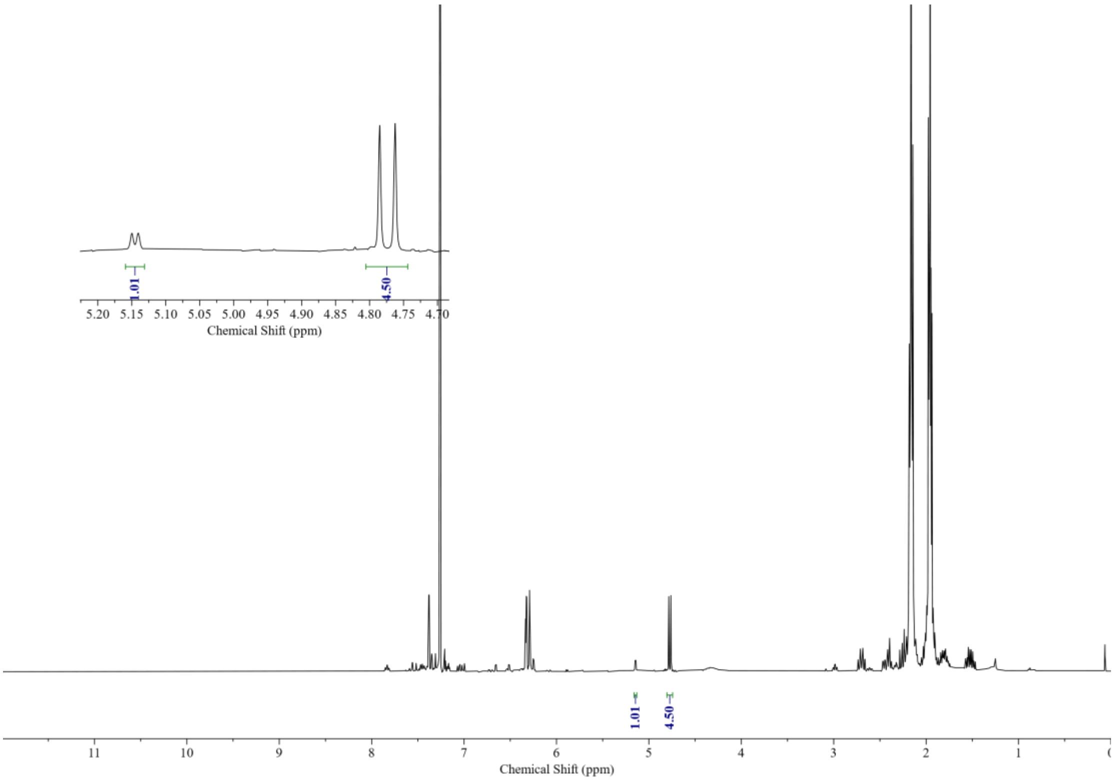


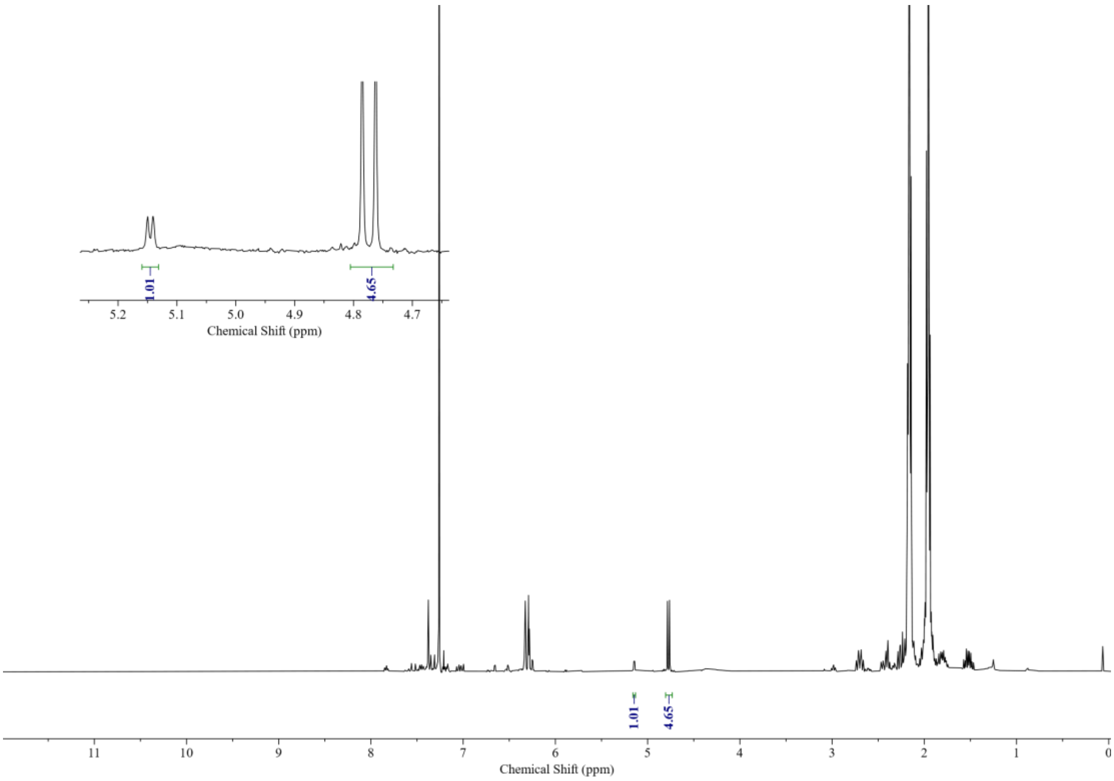
~1:1 anti:syn (racemic)

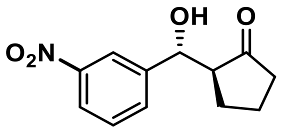




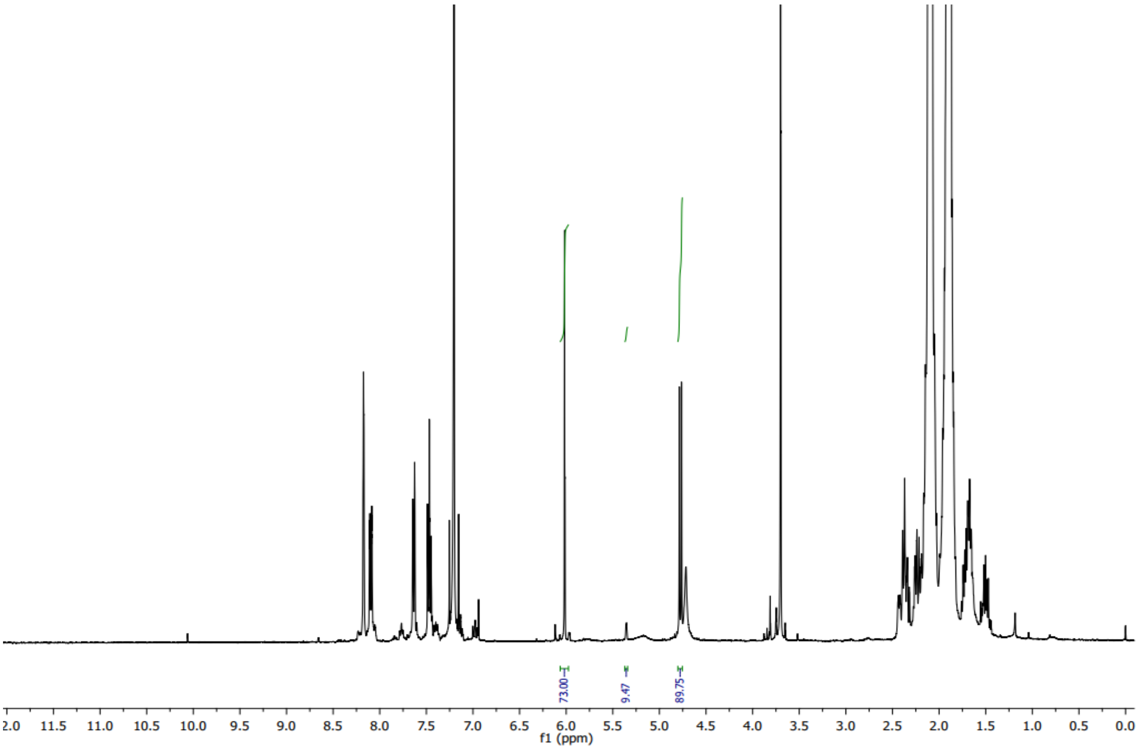
Crude (chiral sample)

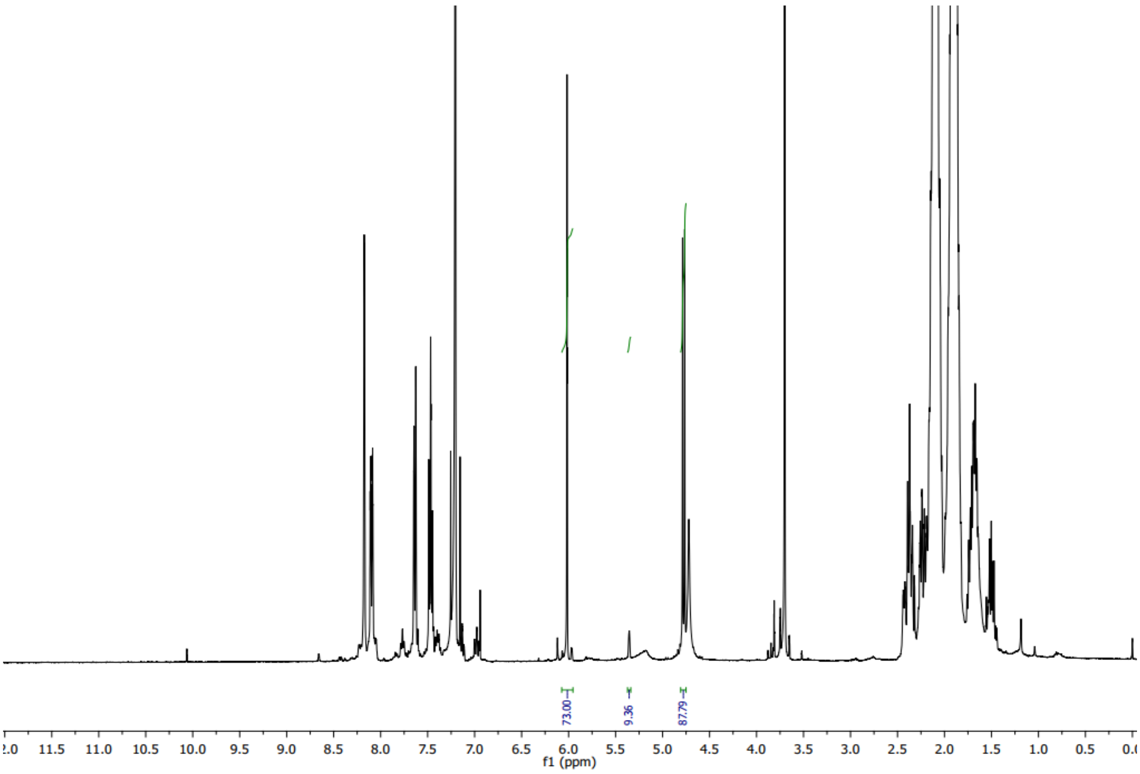


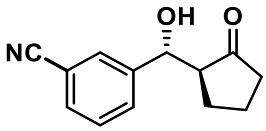




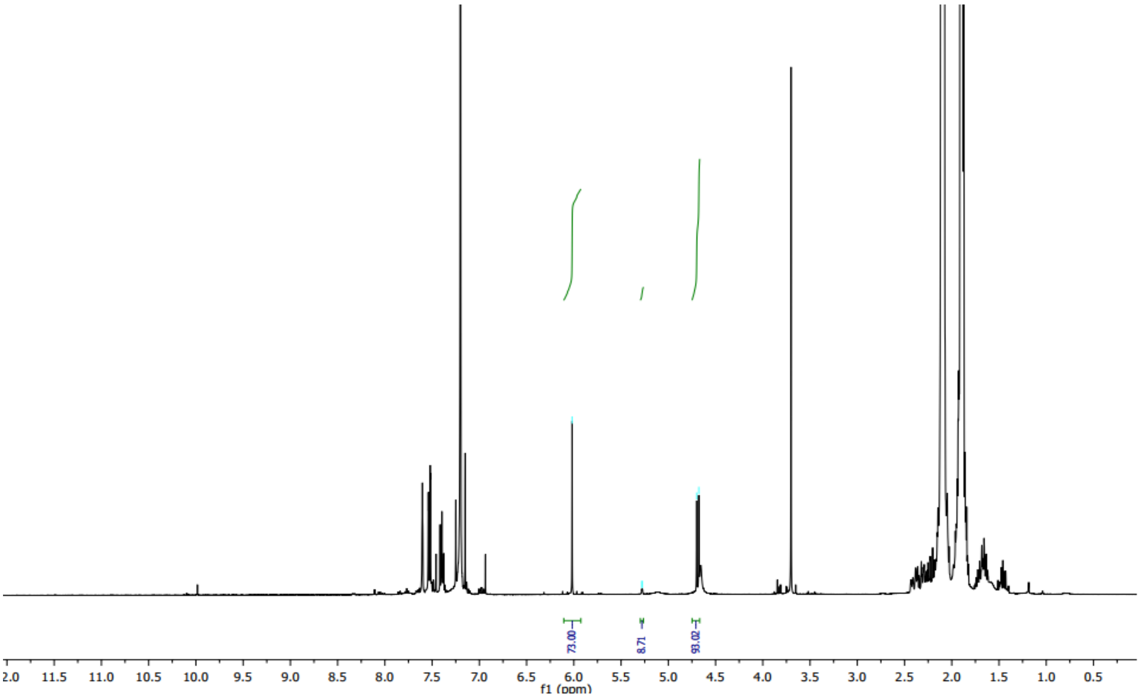
Crude (chiral sample)

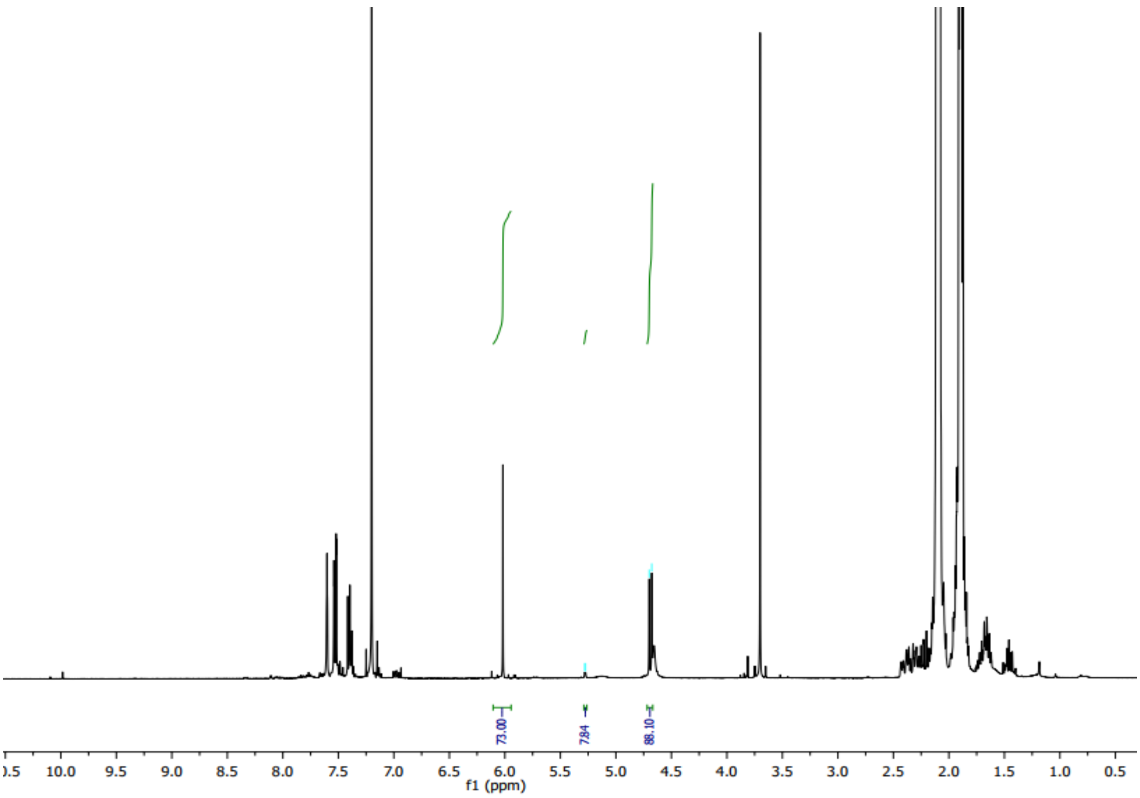






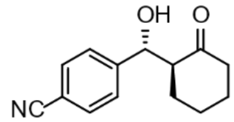
Crude (chiral sample)

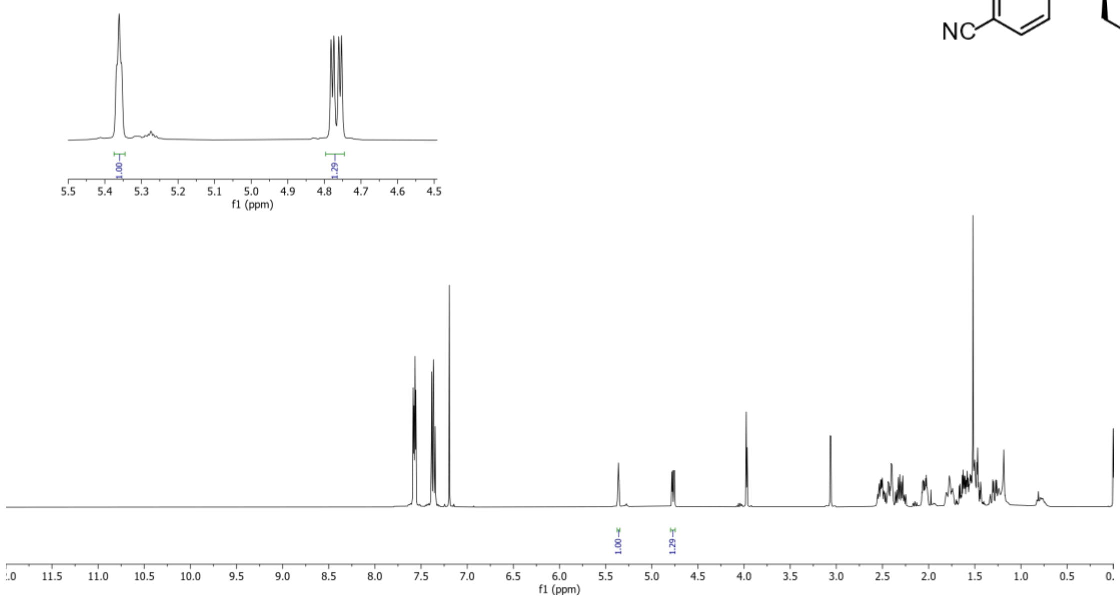




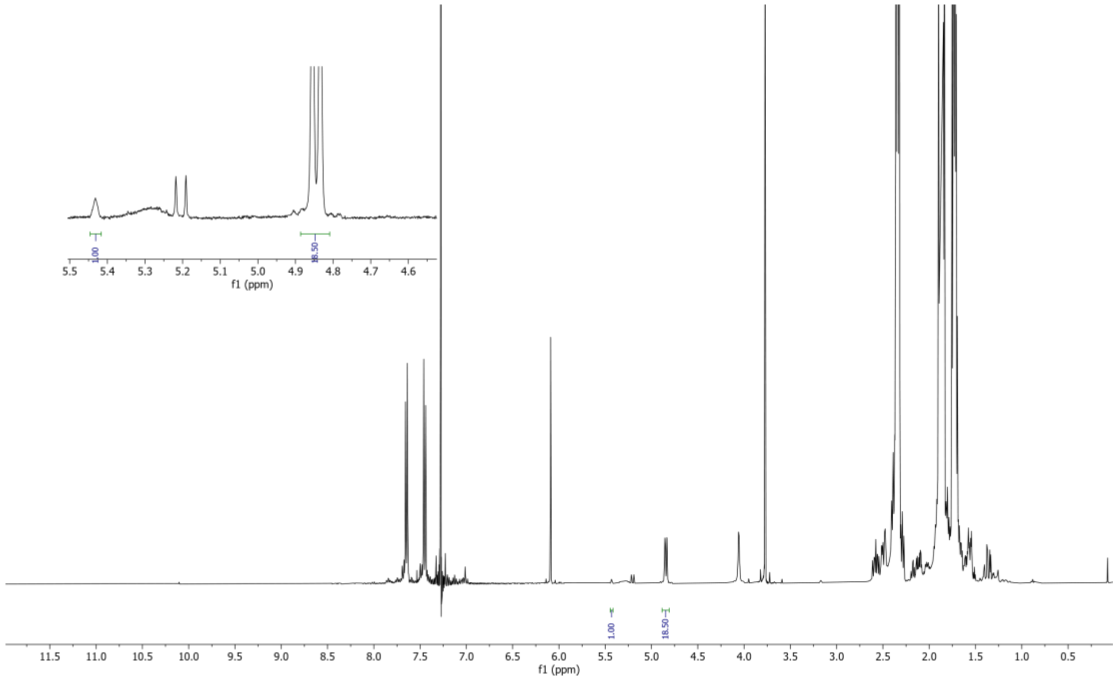
H-NMR[1]

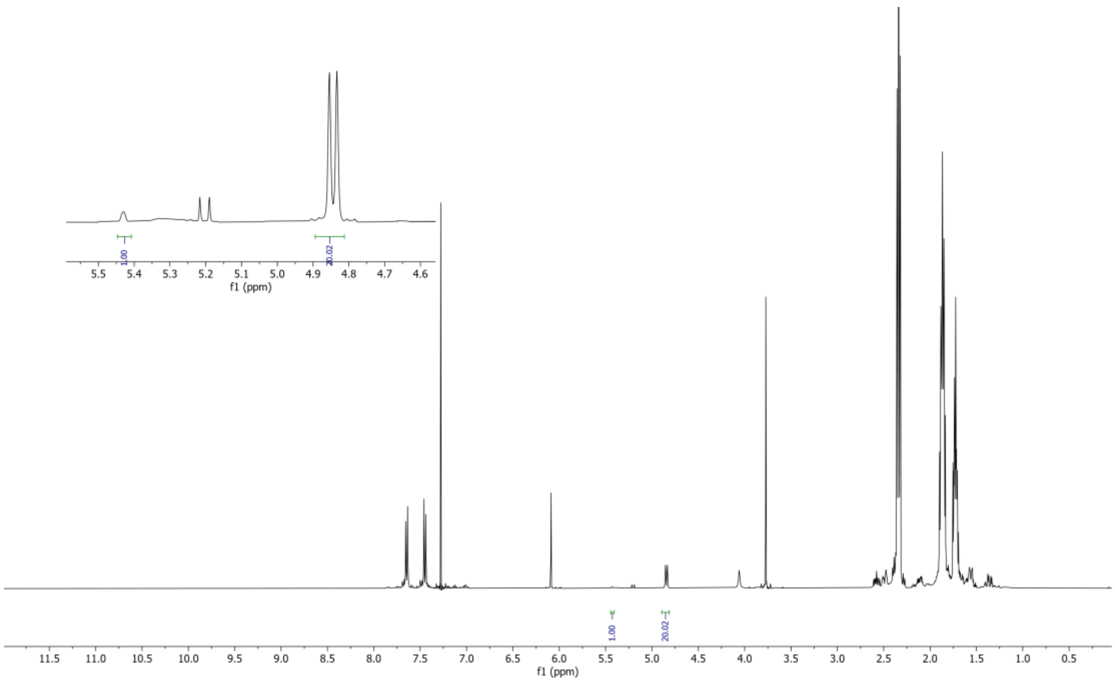
~1:1 anti:syn (racemic)





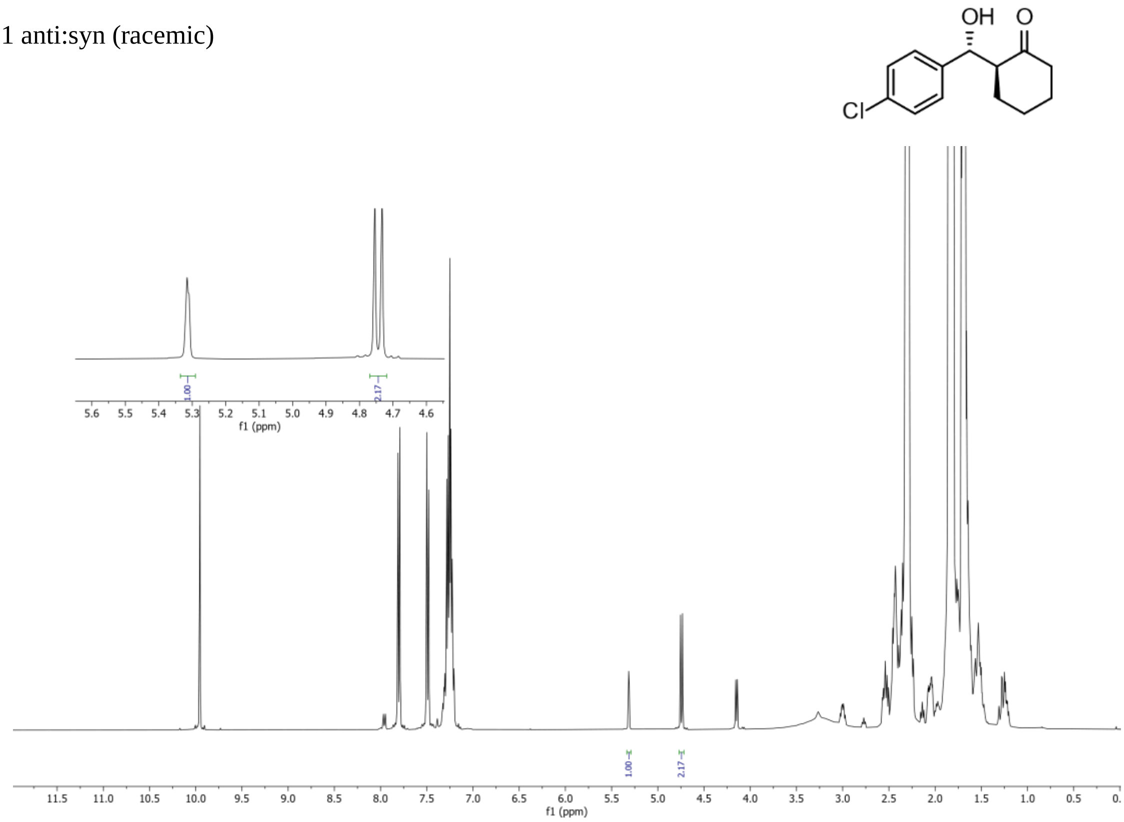
Crude (chiral sample)



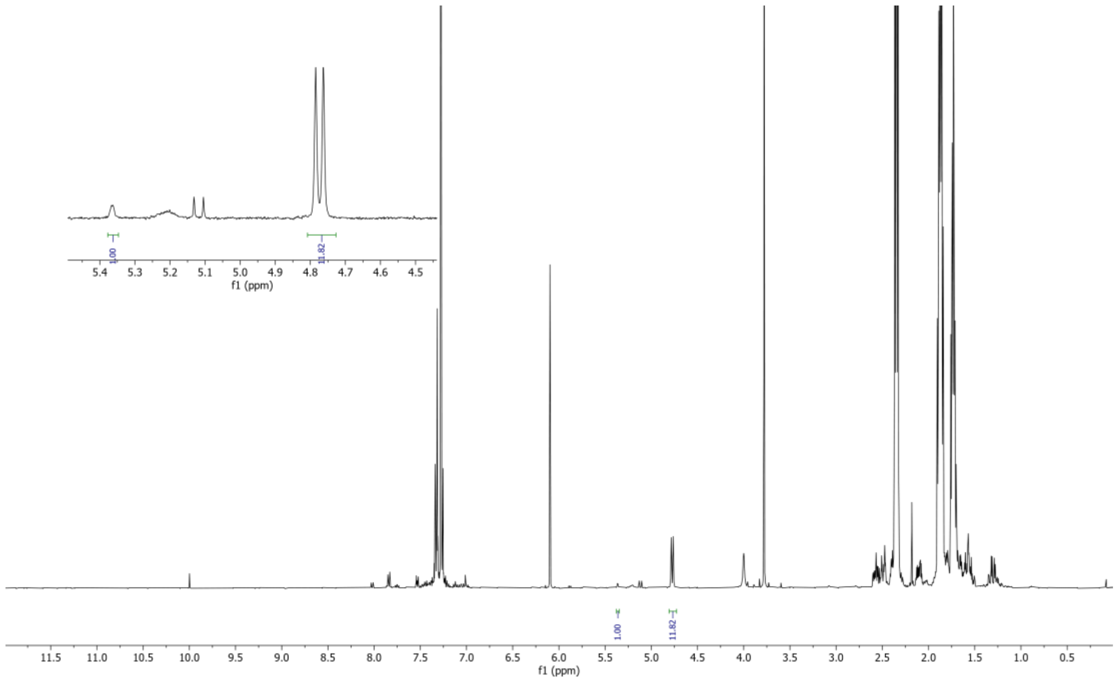


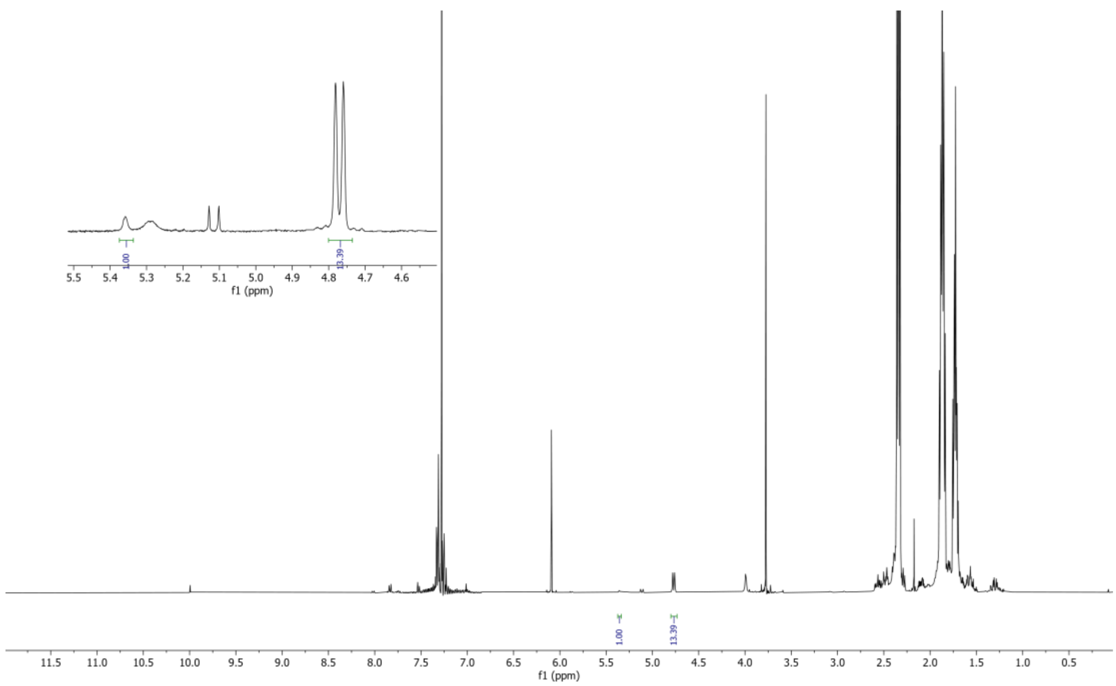
H-NMR[1]

~1:1 anti:syn (racemic)



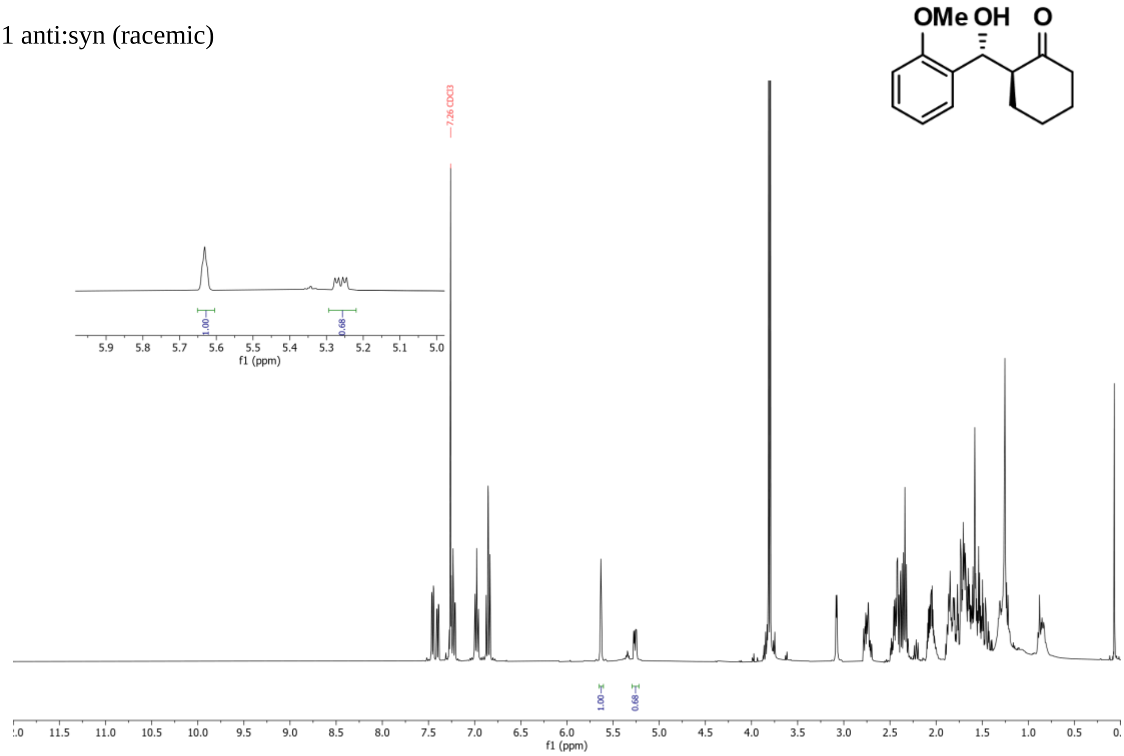
Crude (chiral sample)



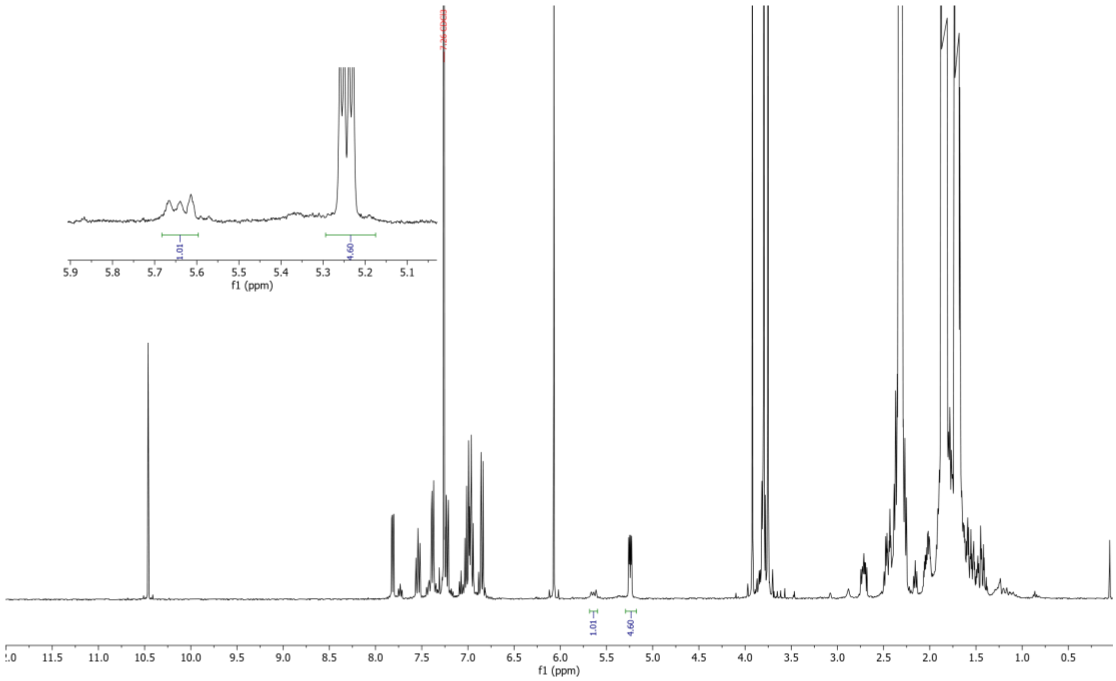


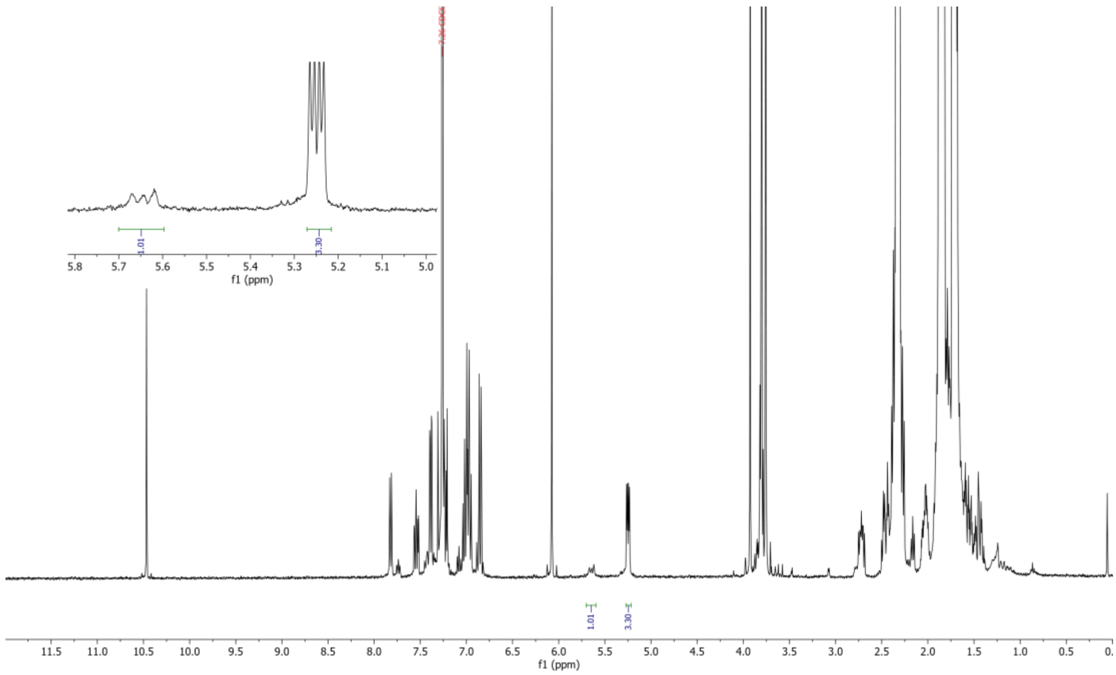
^{1}H-NMR

~1:1 anti:syn (racemic)



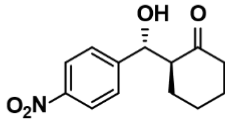
Crude (chiral sample)

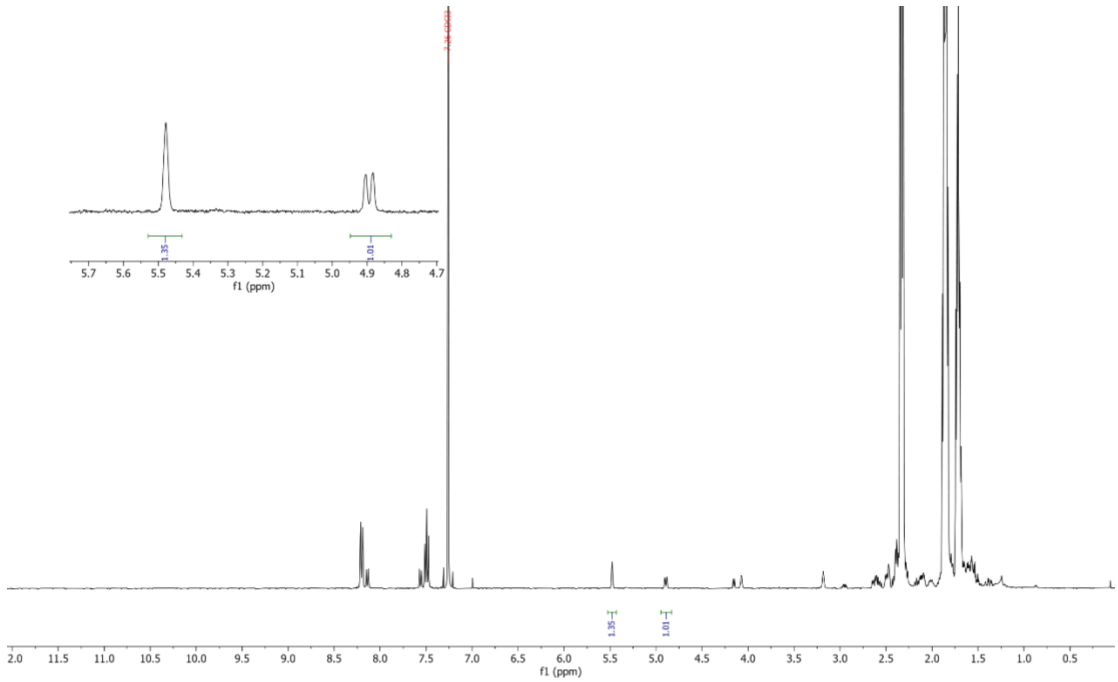




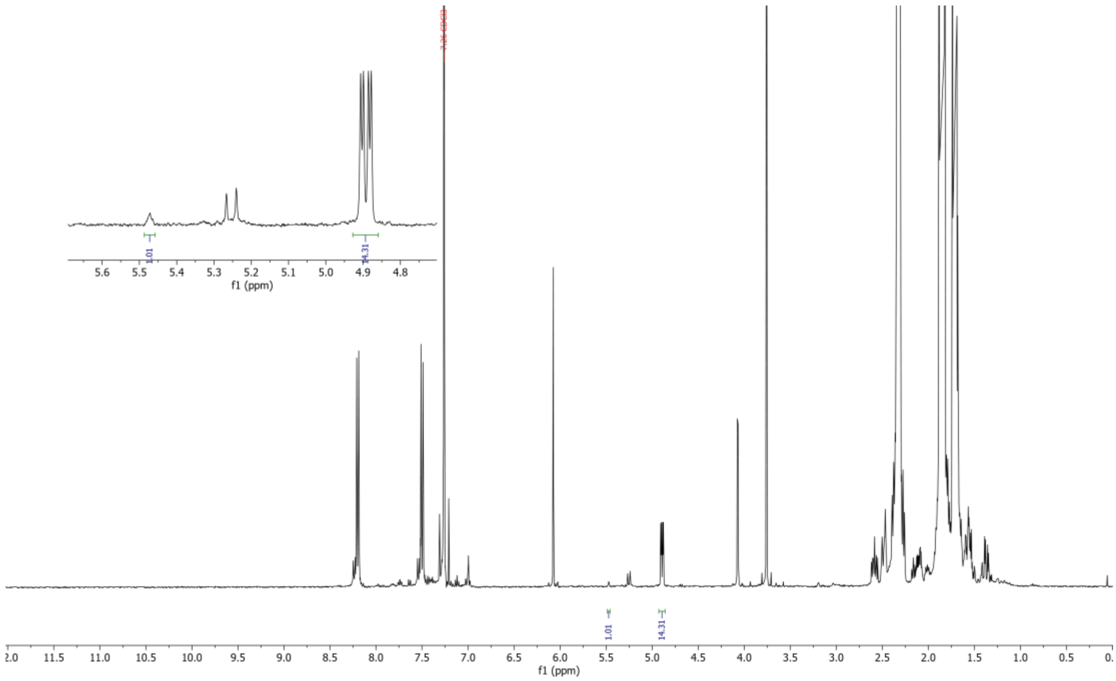
^{1}H-NMR

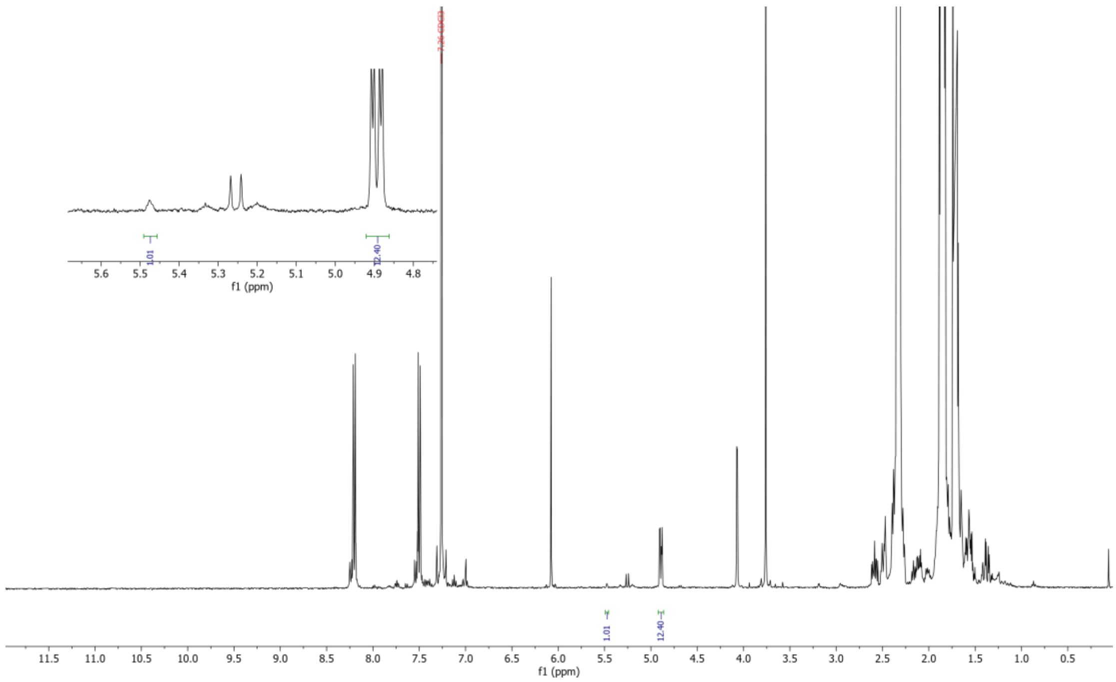
~1:1 anti:syn (racemic)





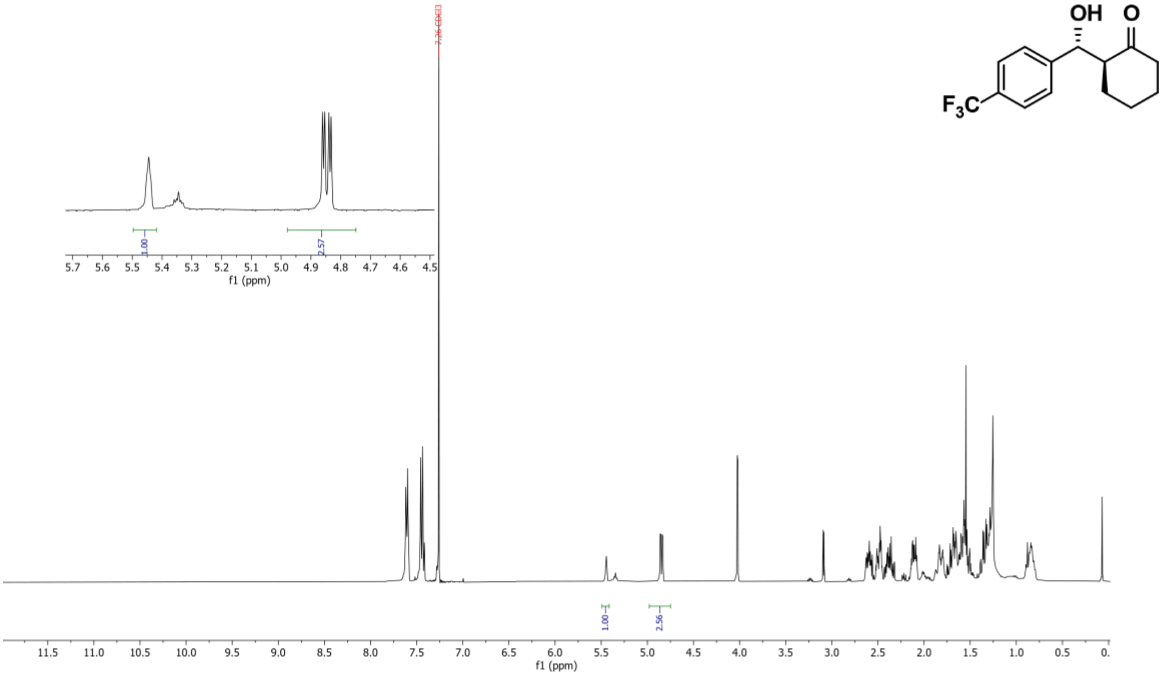
Crude (chiral sample)



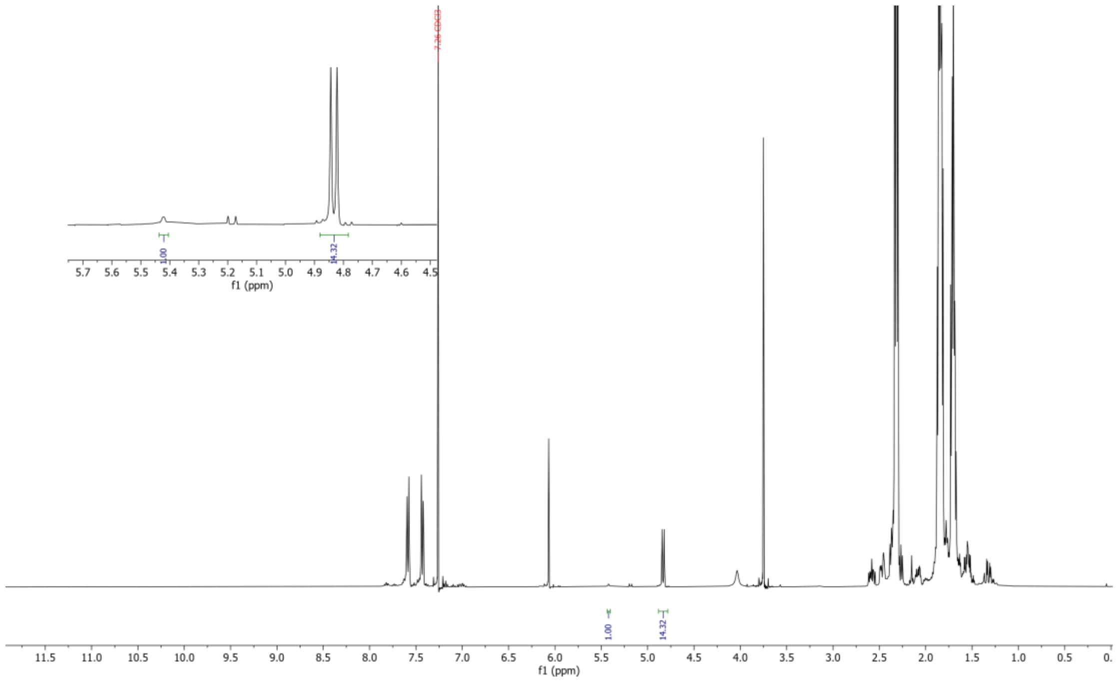


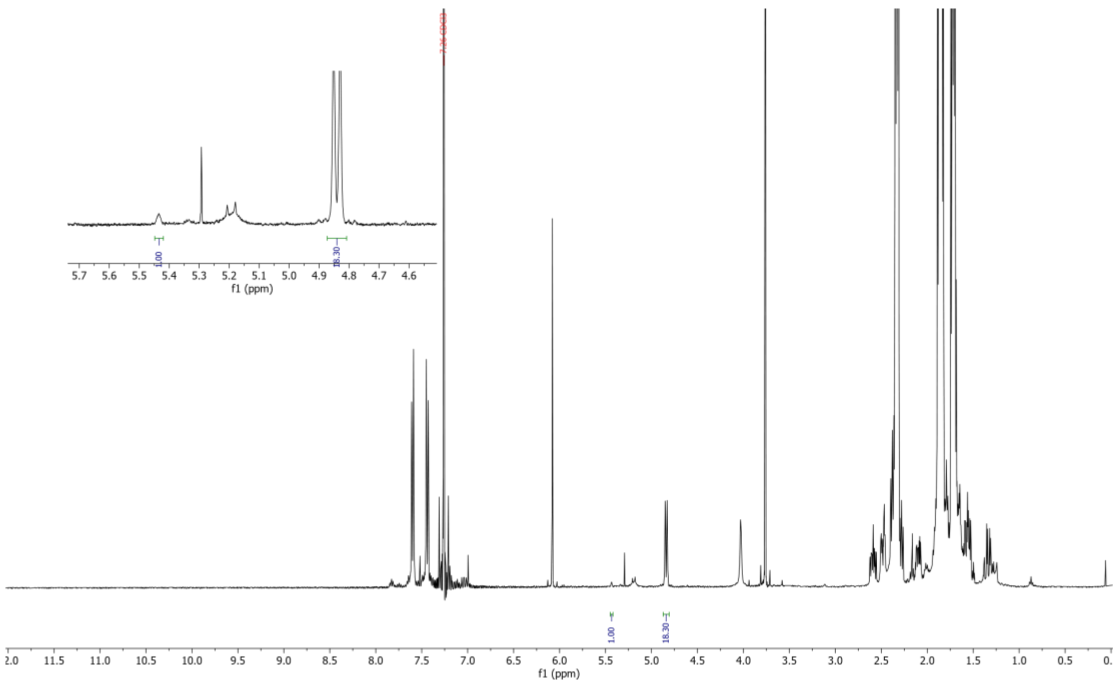
[1]H-NMR

~1:1 anti:syn (racemic)



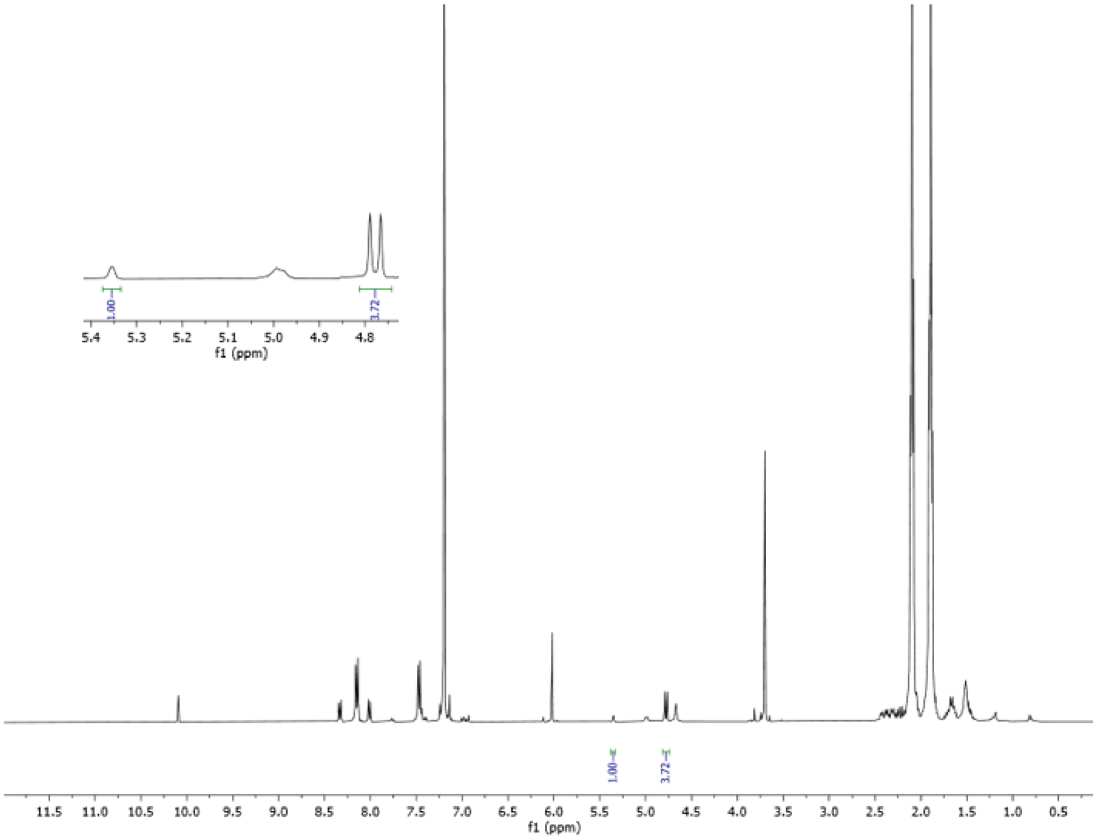
Crude (chiral sample)

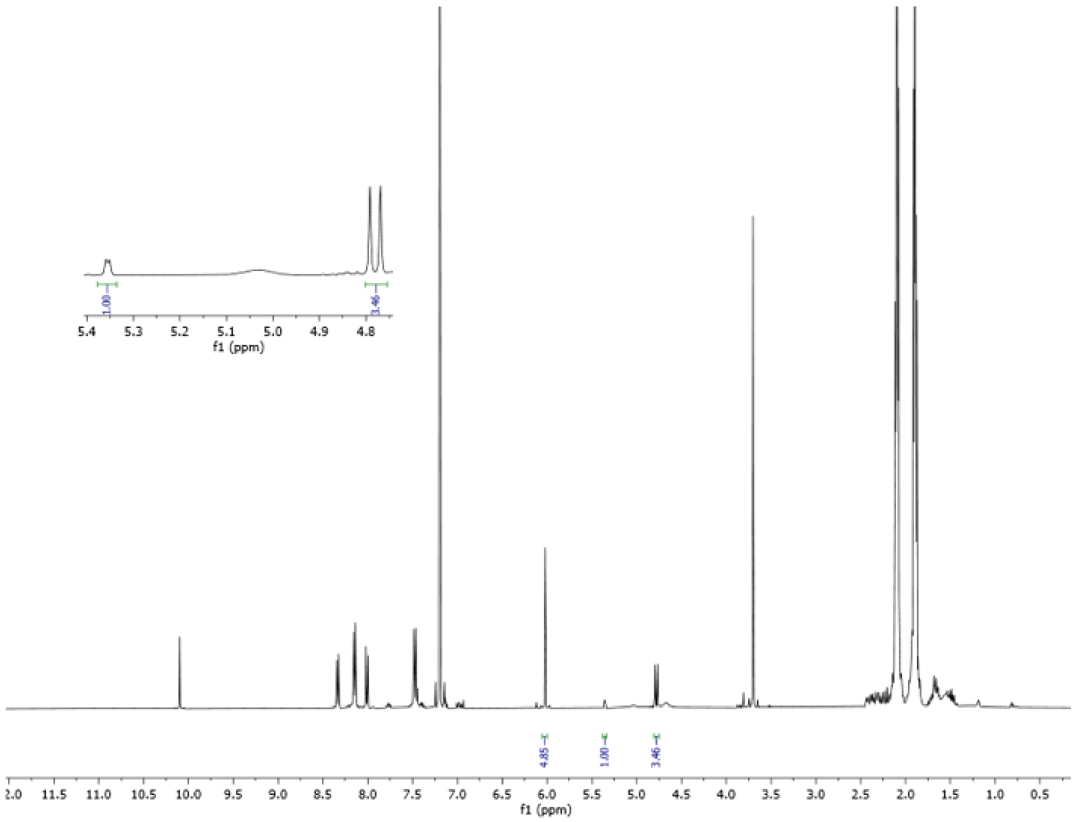




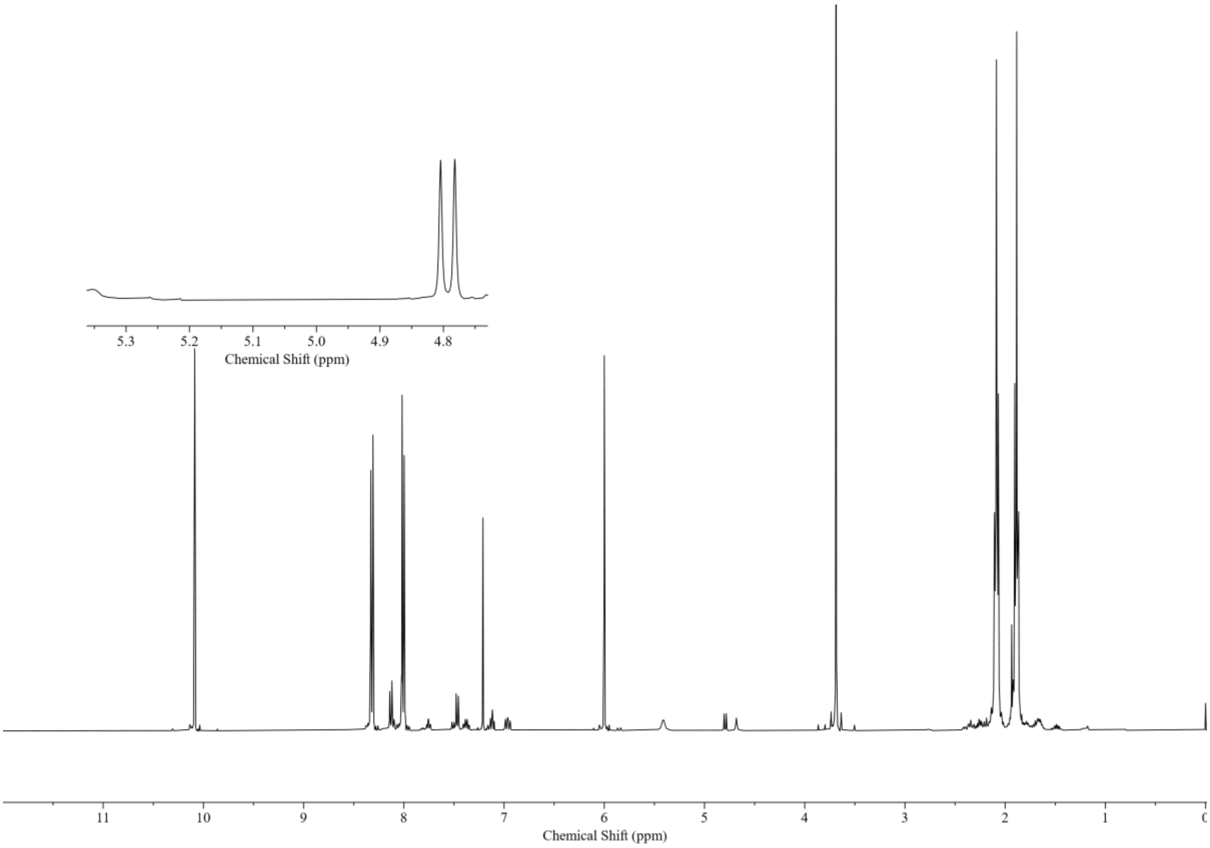
18.2 Solvent screening (table S2)

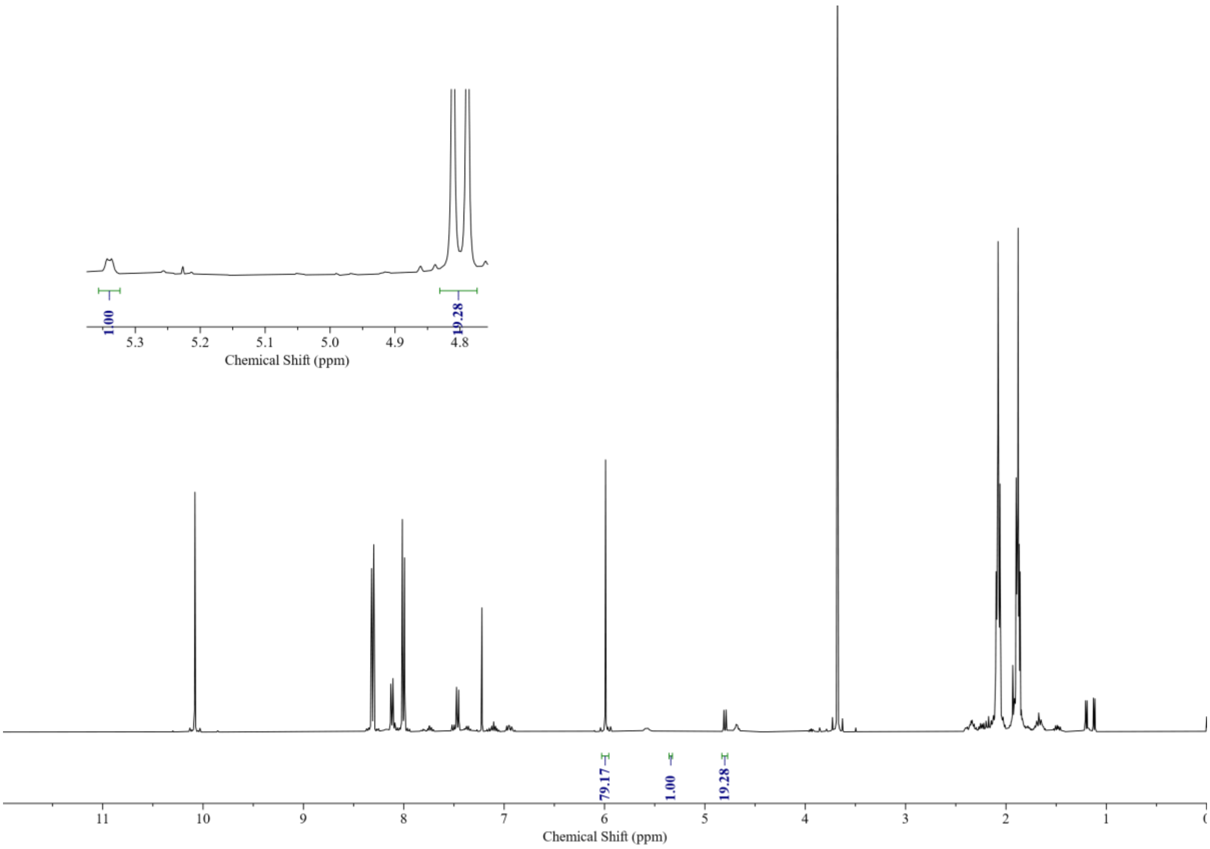
Hexane as a solvent:



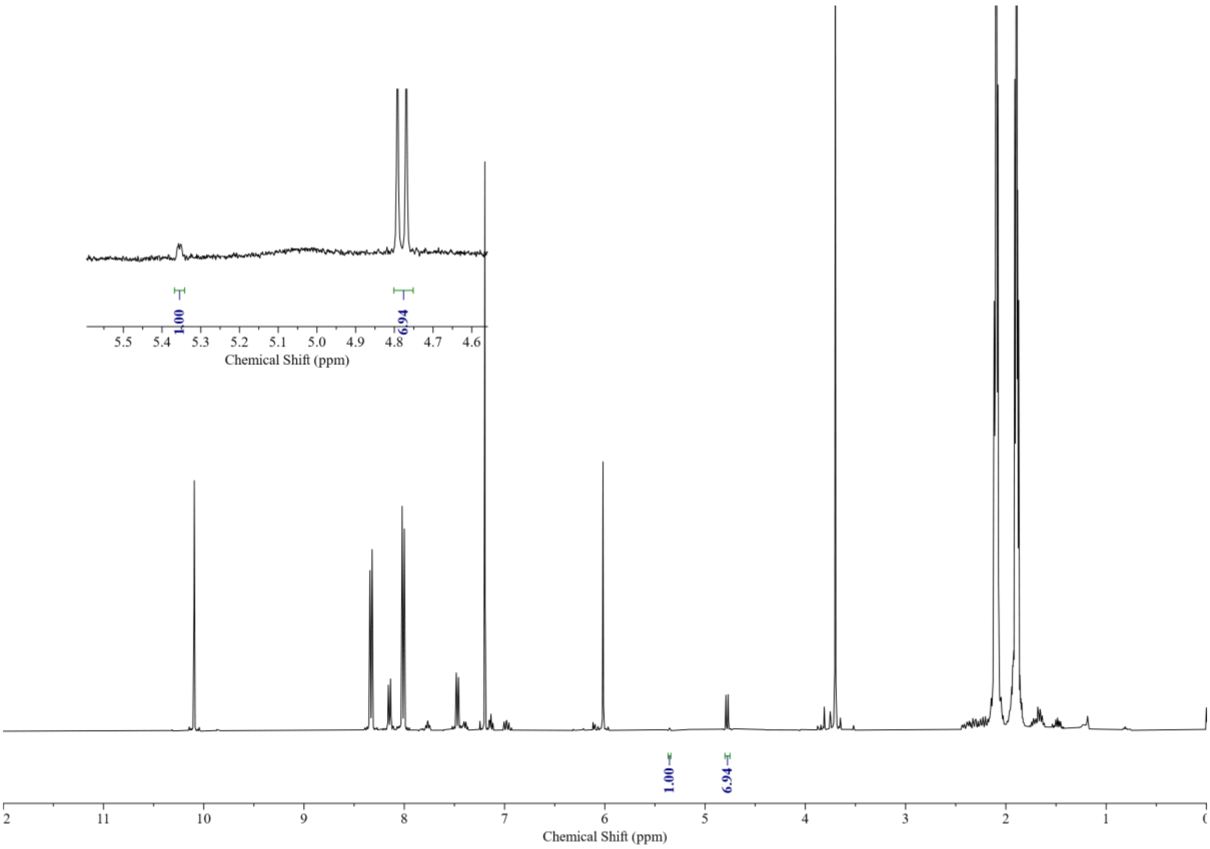


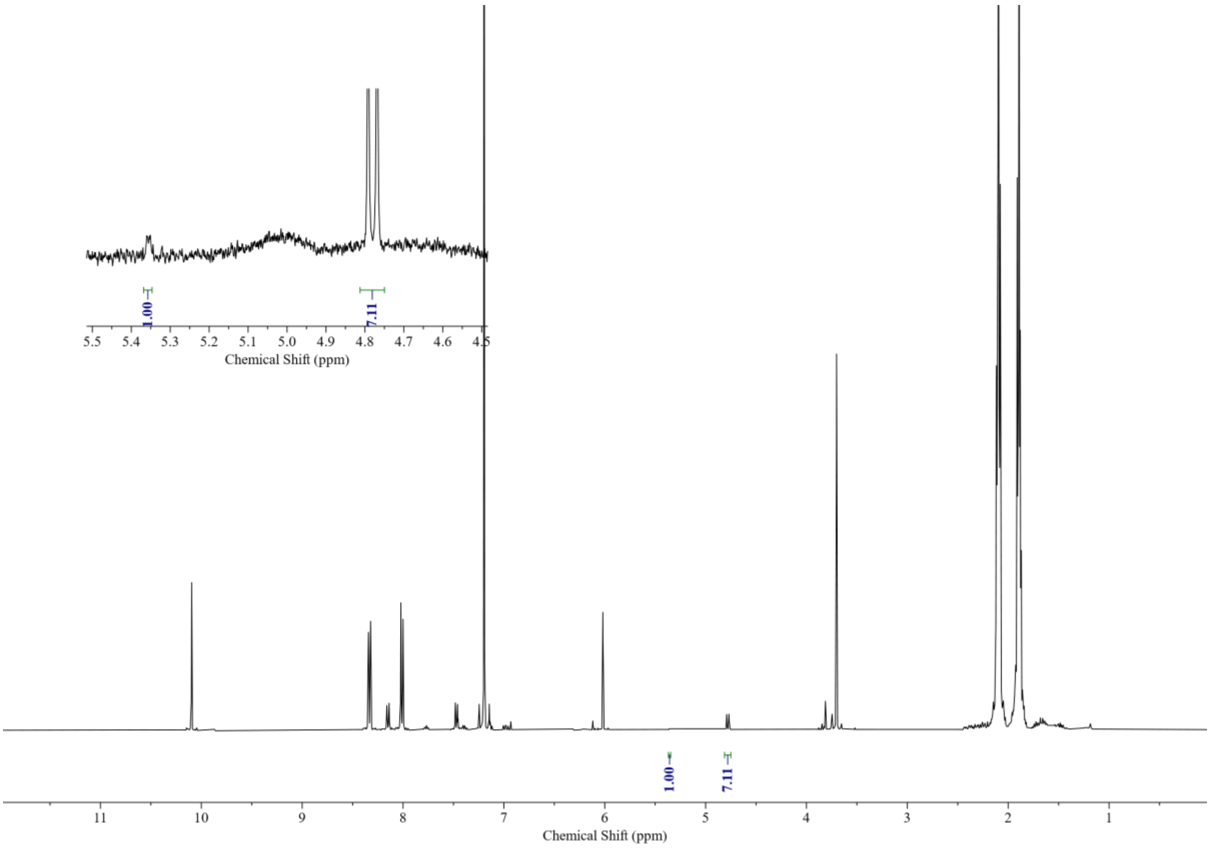
CH_3CN as a solvent:



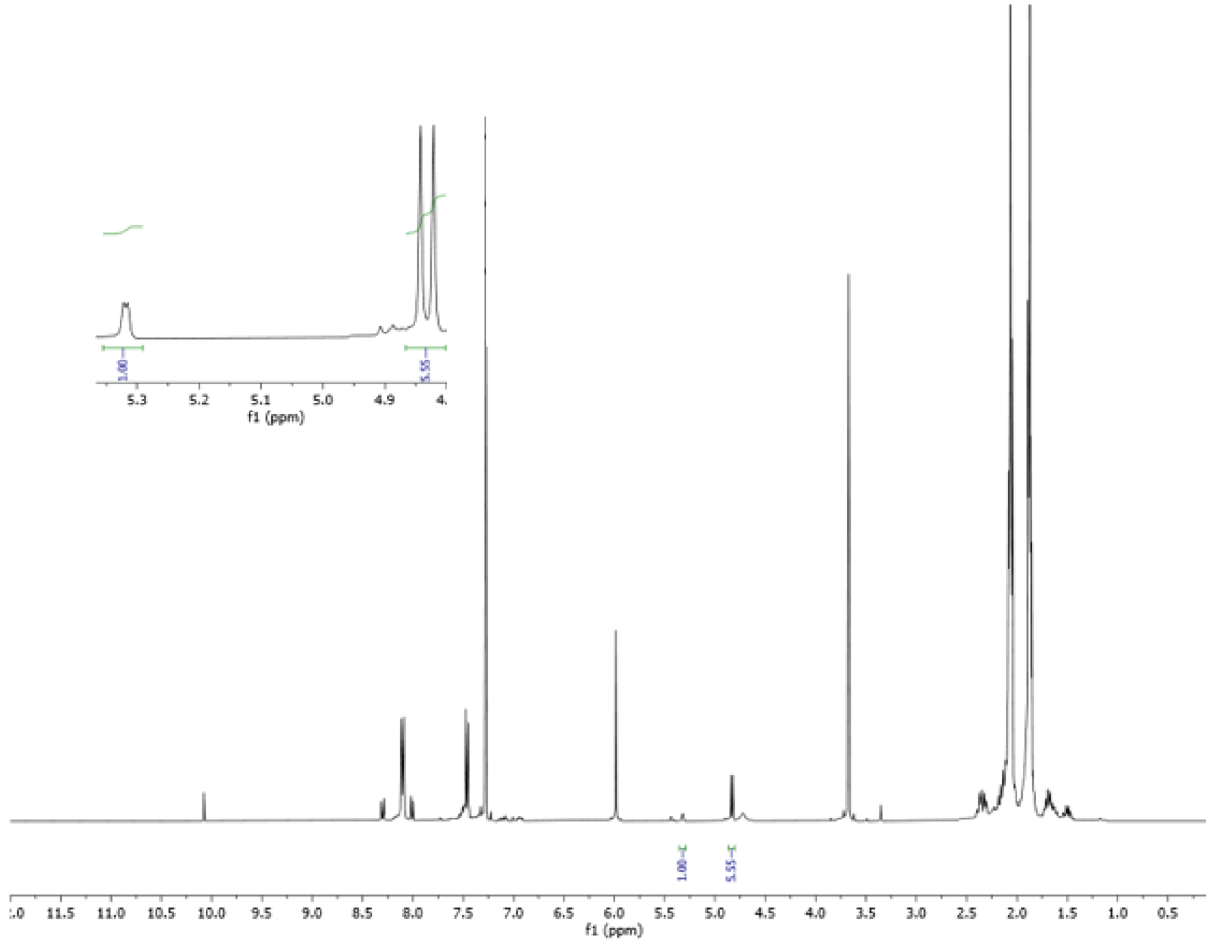


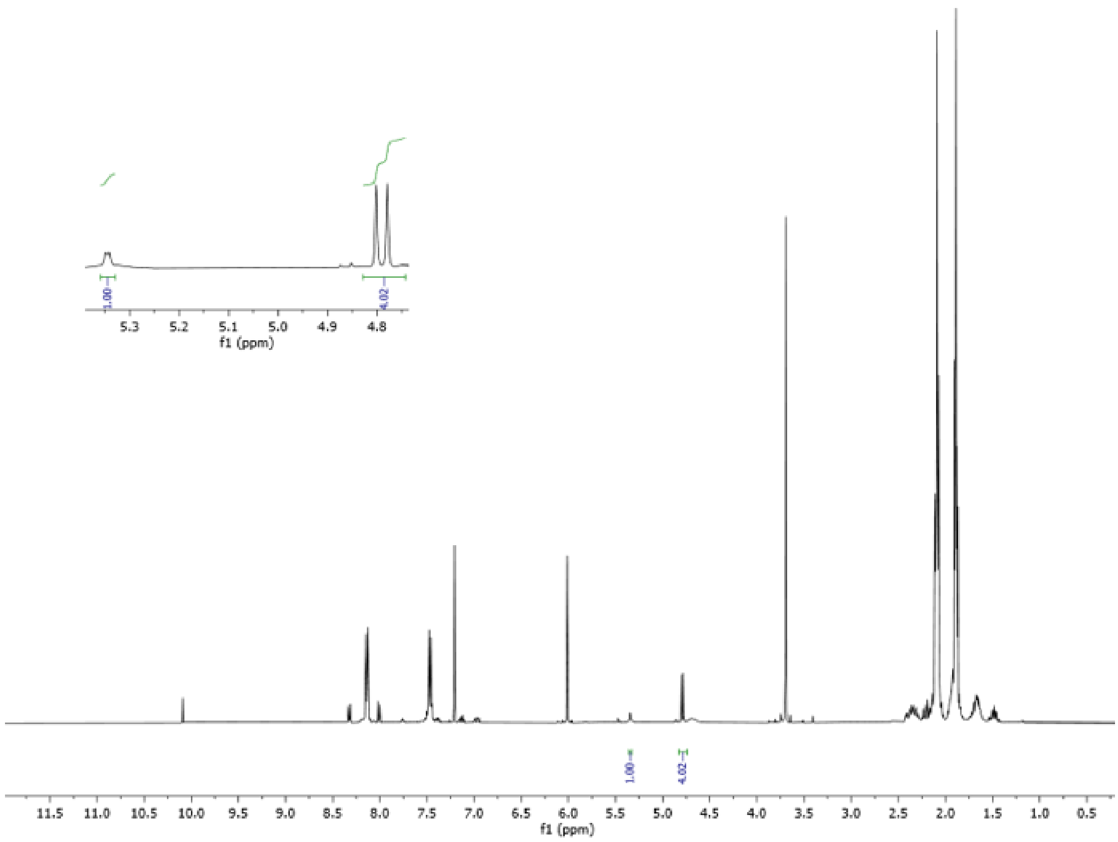
$CHCl_3$ as a solvent:





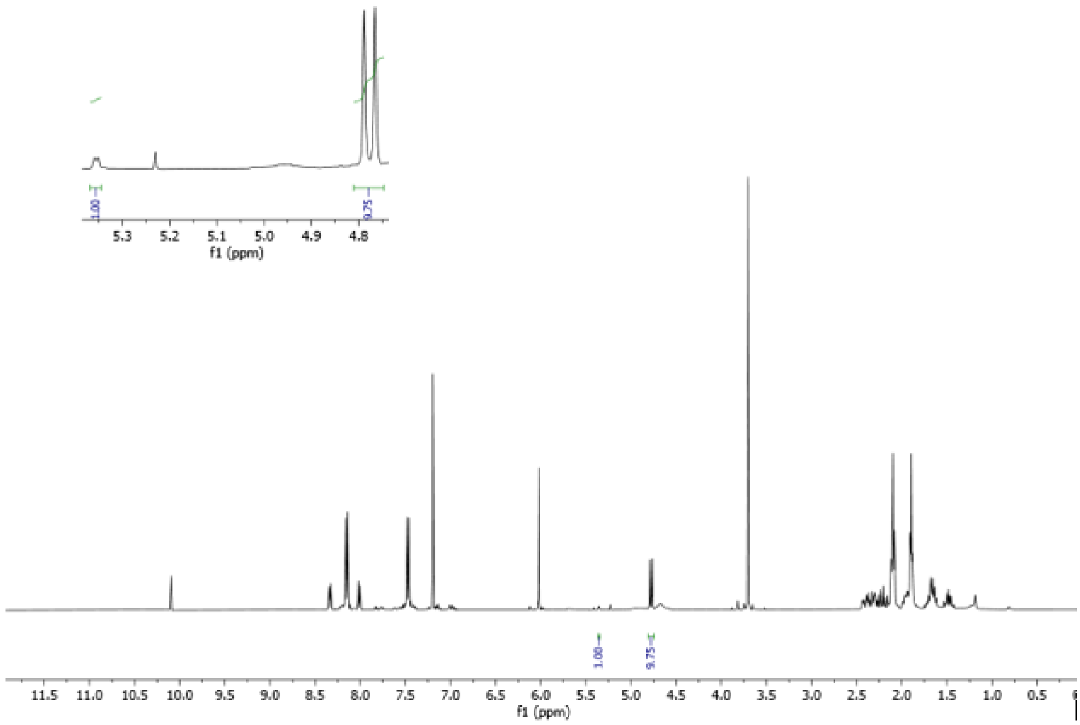
MeOH as a solvent:

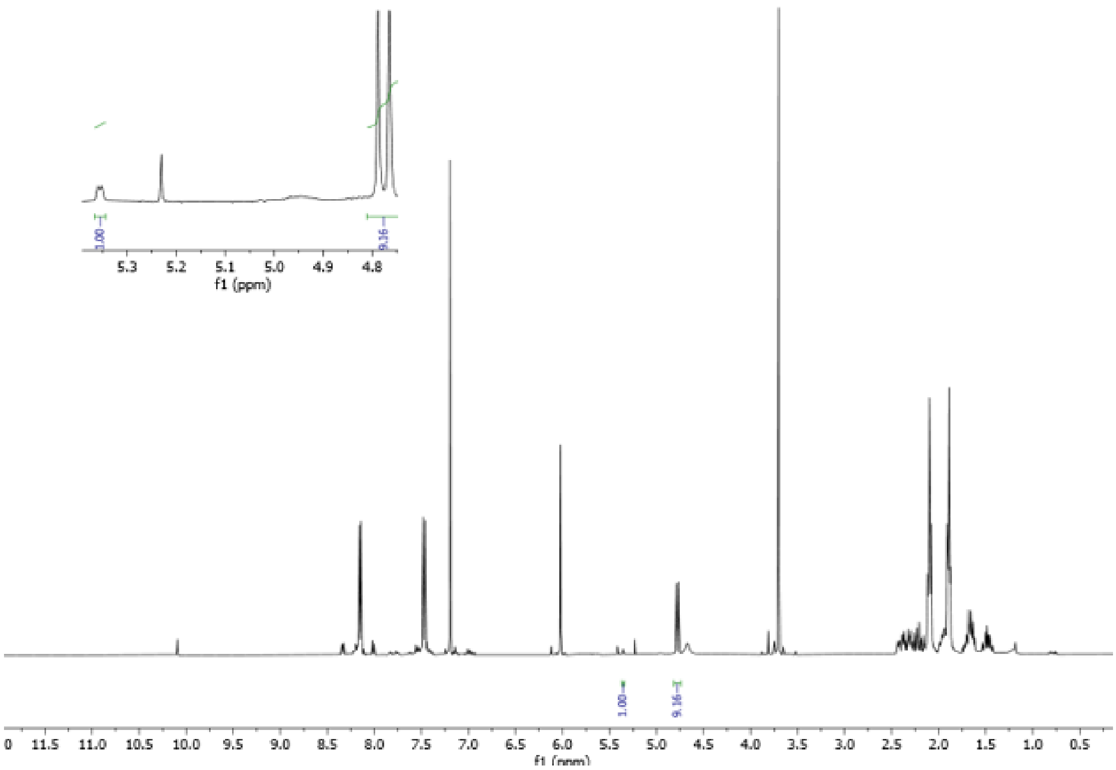




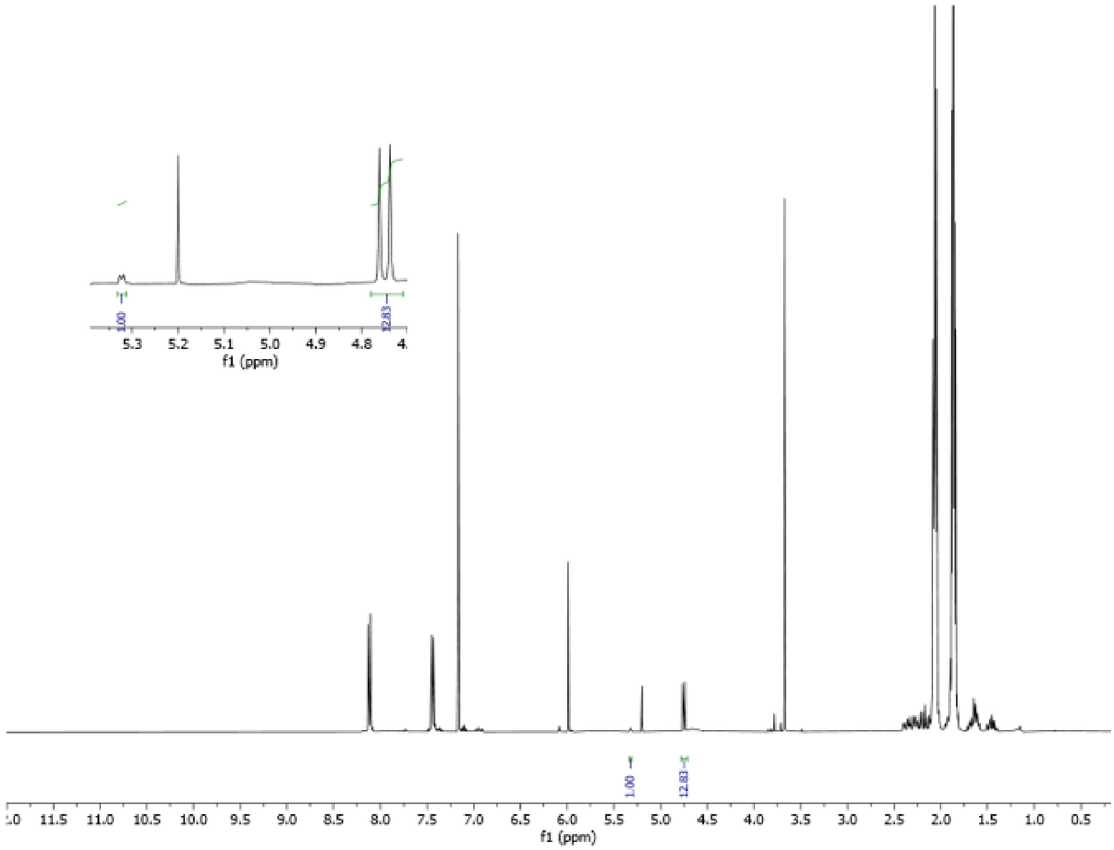
18.4 Time screening (table S3)

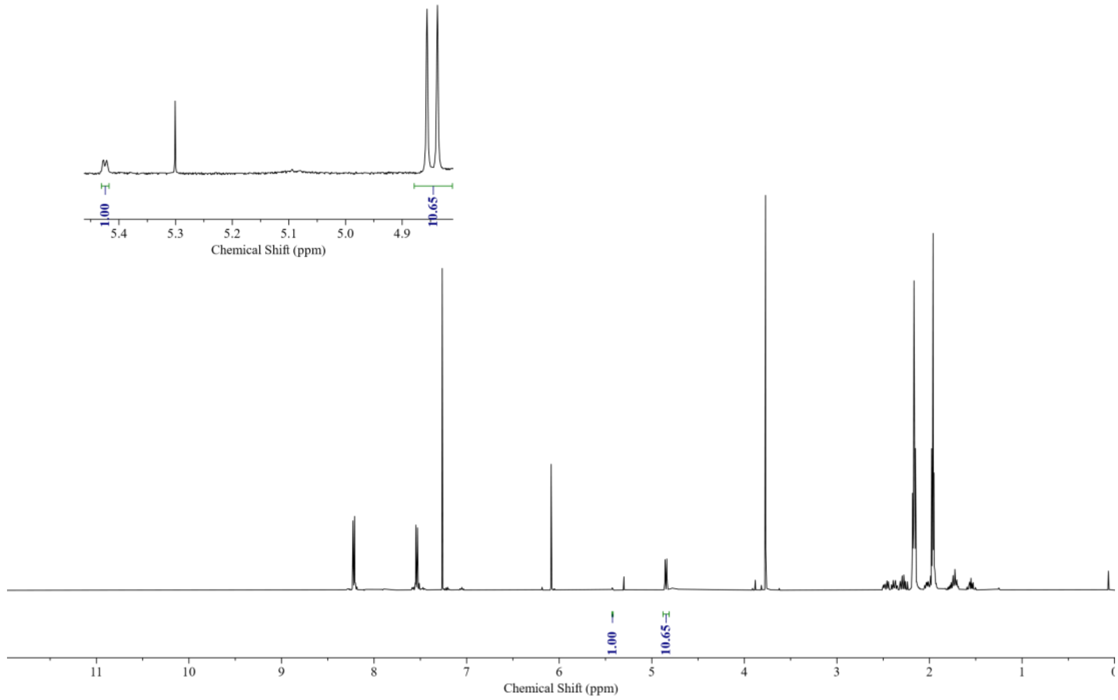
0.5 hour



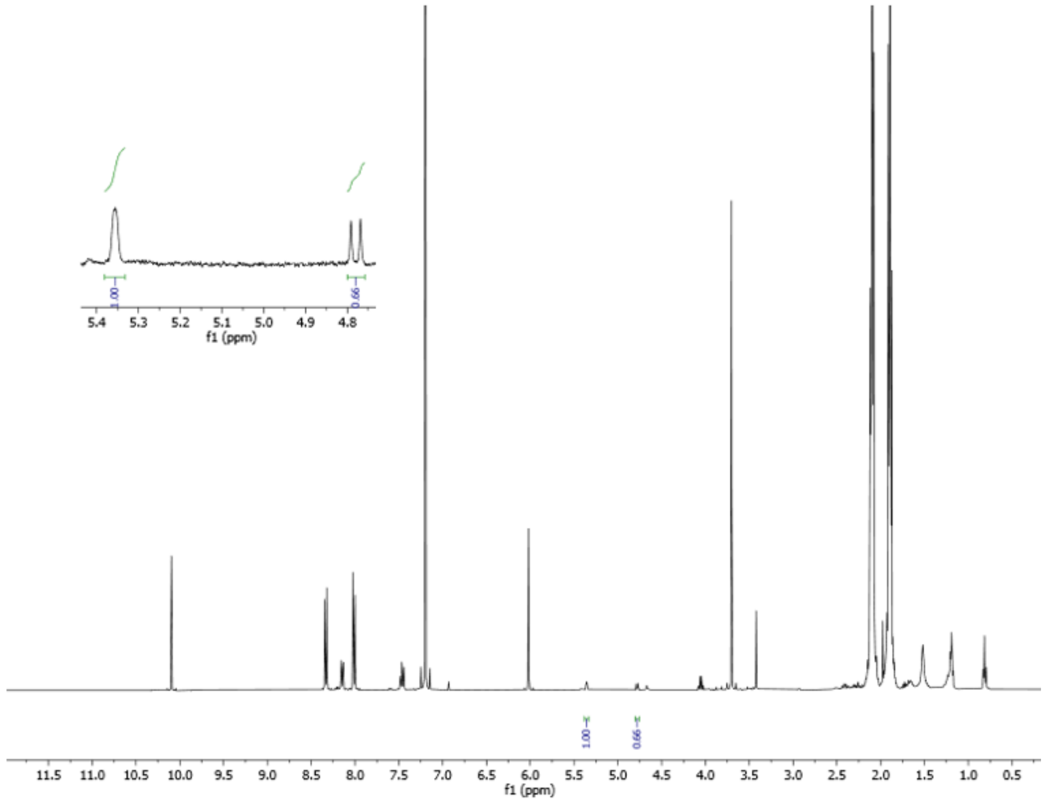


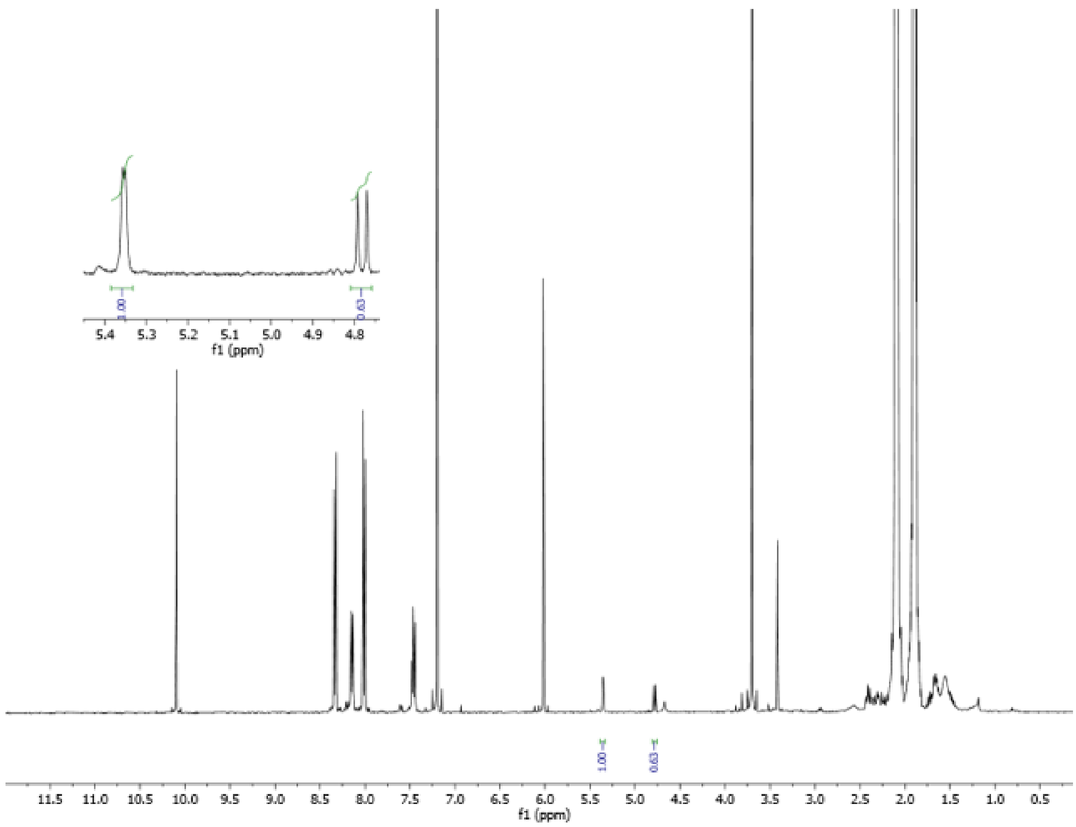
1 hour


1.00
12.83
f1 (ppm)
f1 (ppm)

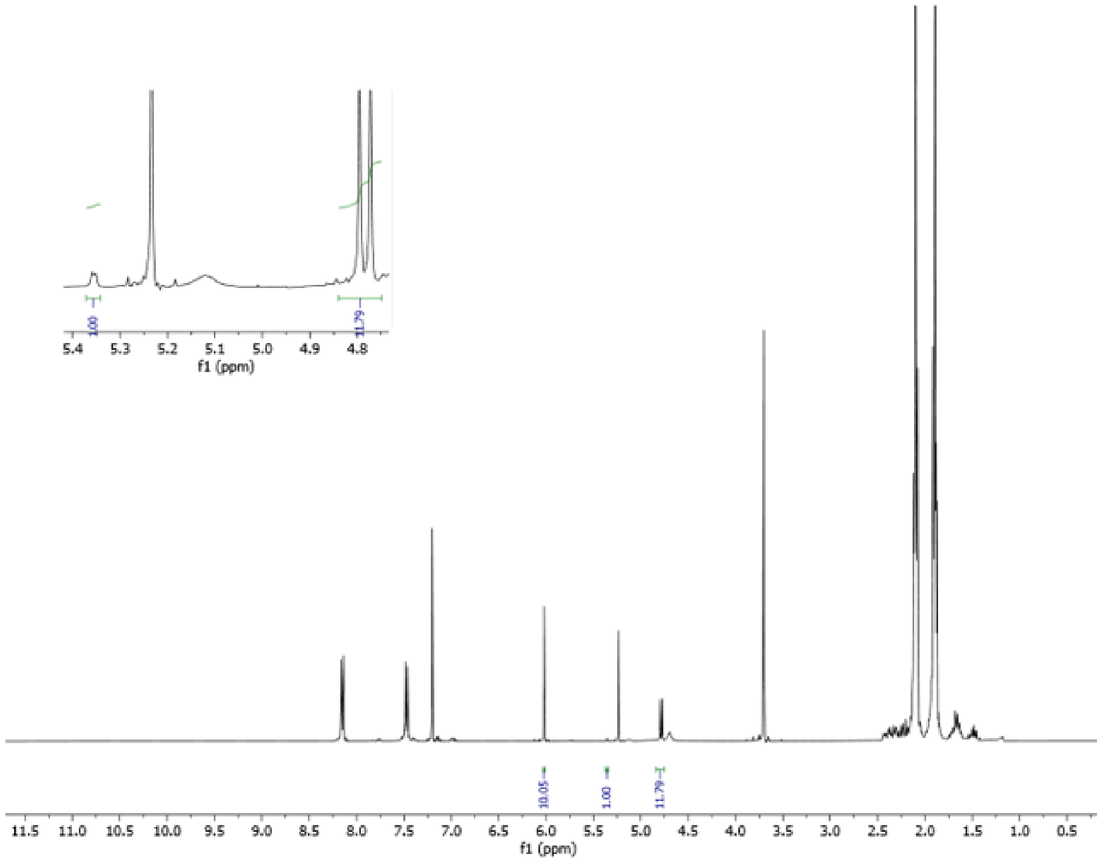

1.00
10.65
Chemical Shift (ppm)
Chemical Shift (ppm)

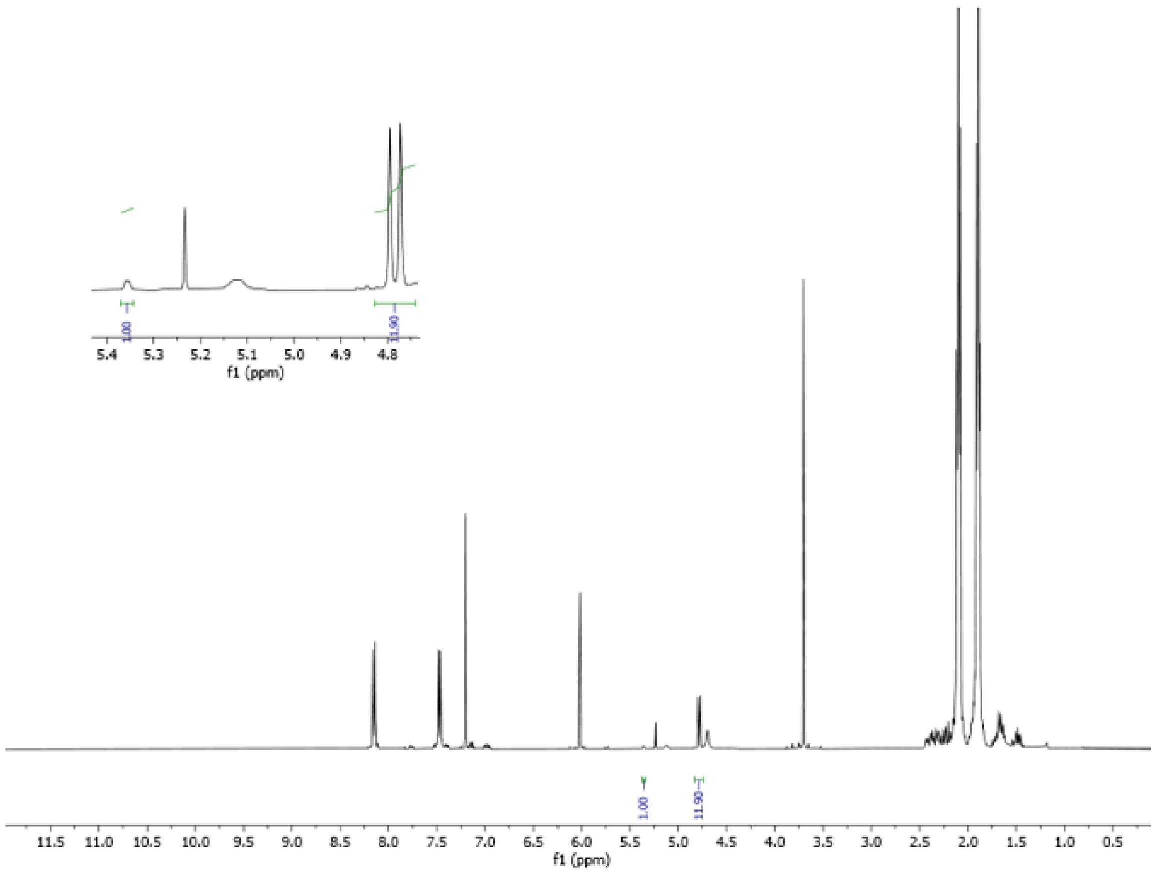
1 hour – No boronic acid



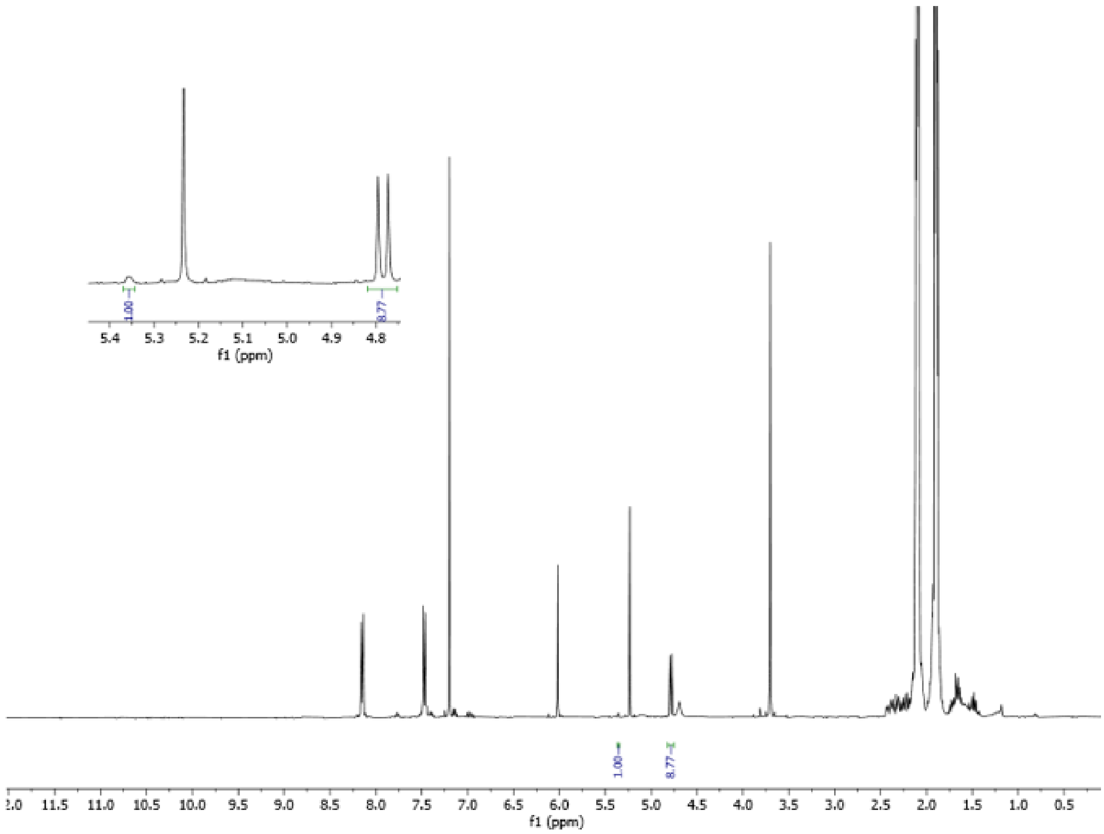


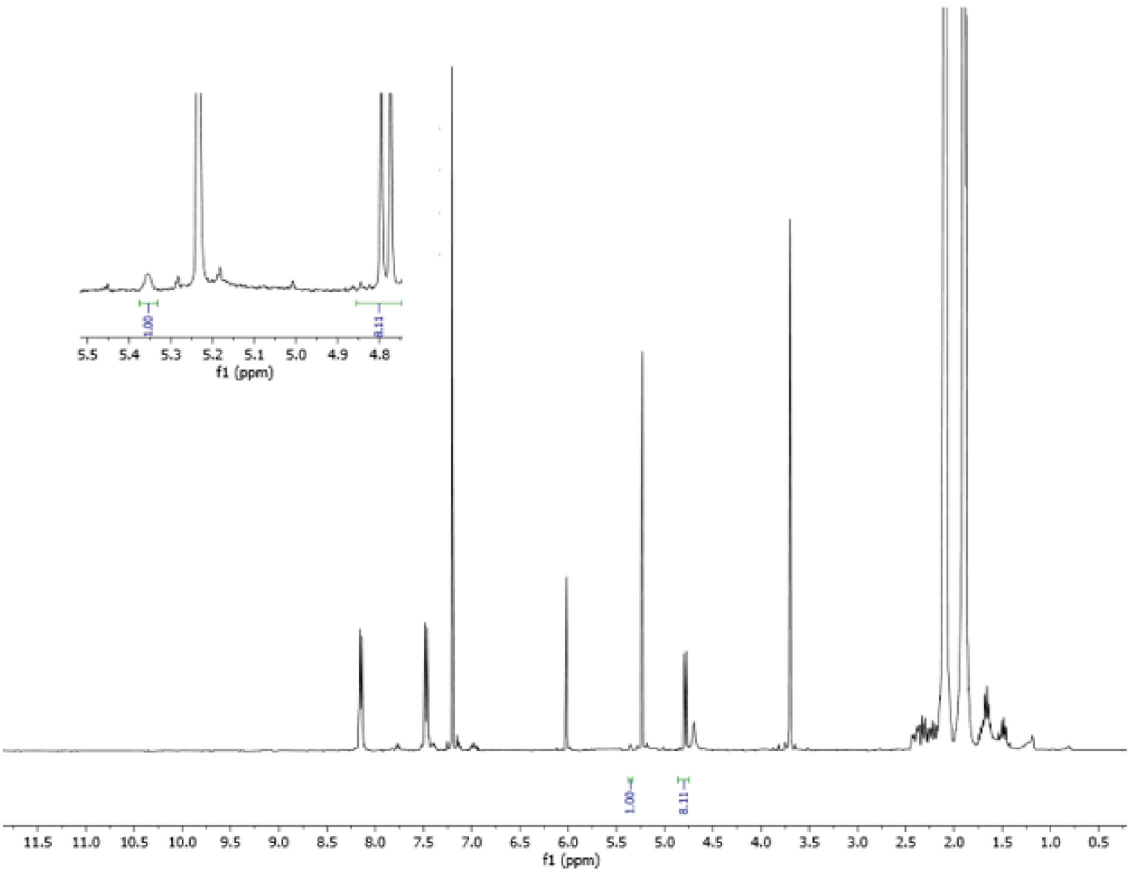
2 hours – with boronic acid



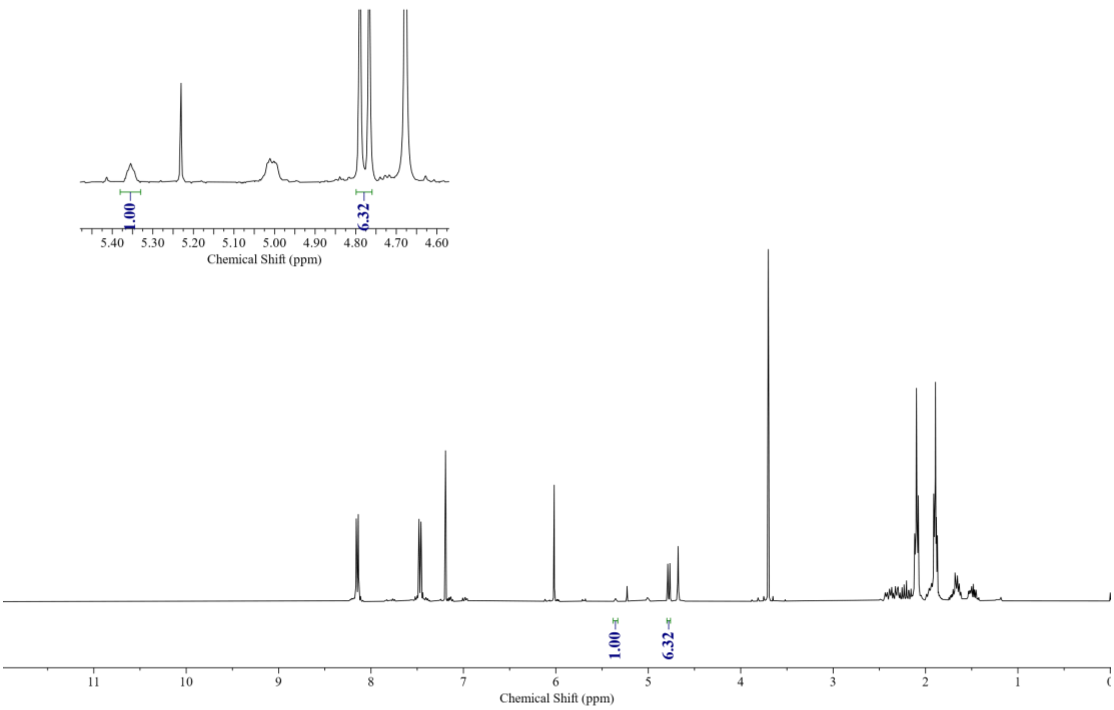


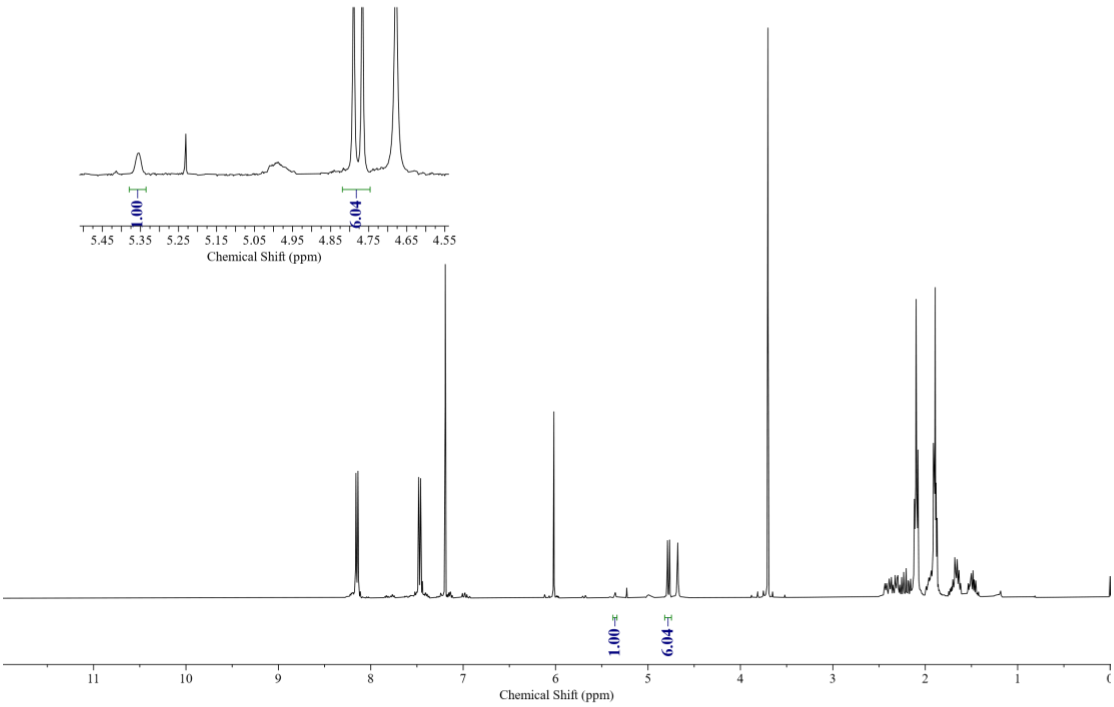
4 hours – with boronic acid



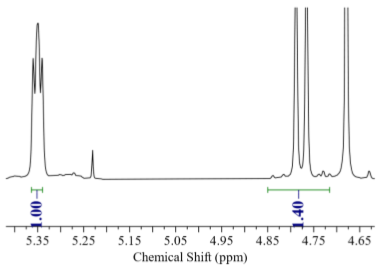


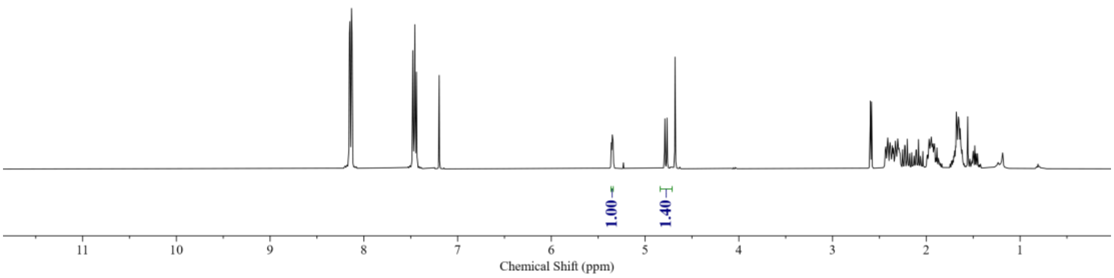
20 hours – with boronic acid

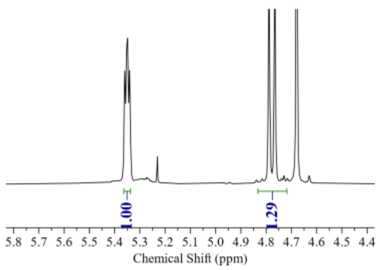


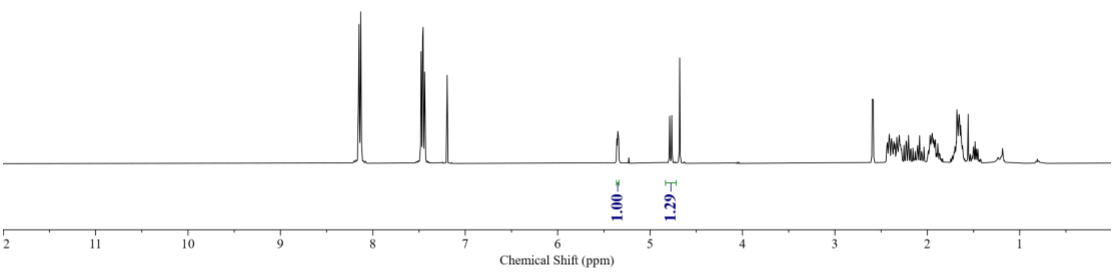


20 hours – without boronic acid



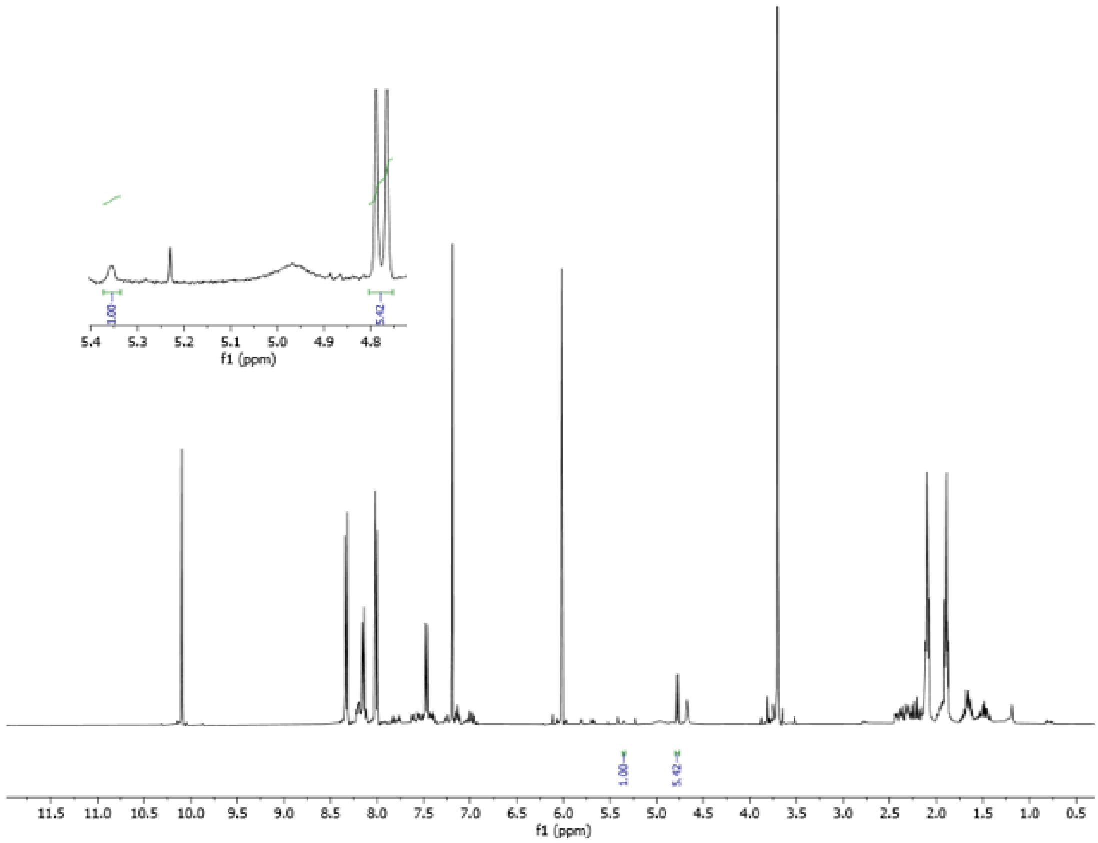


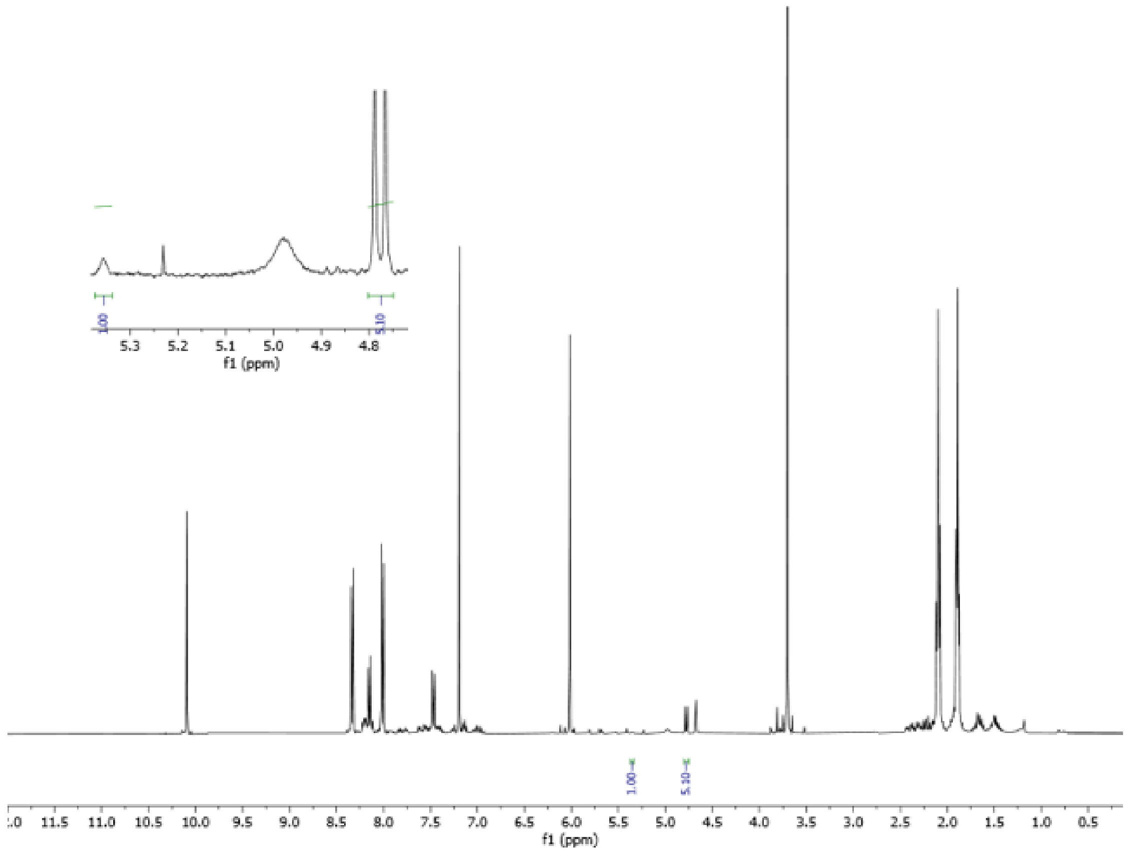




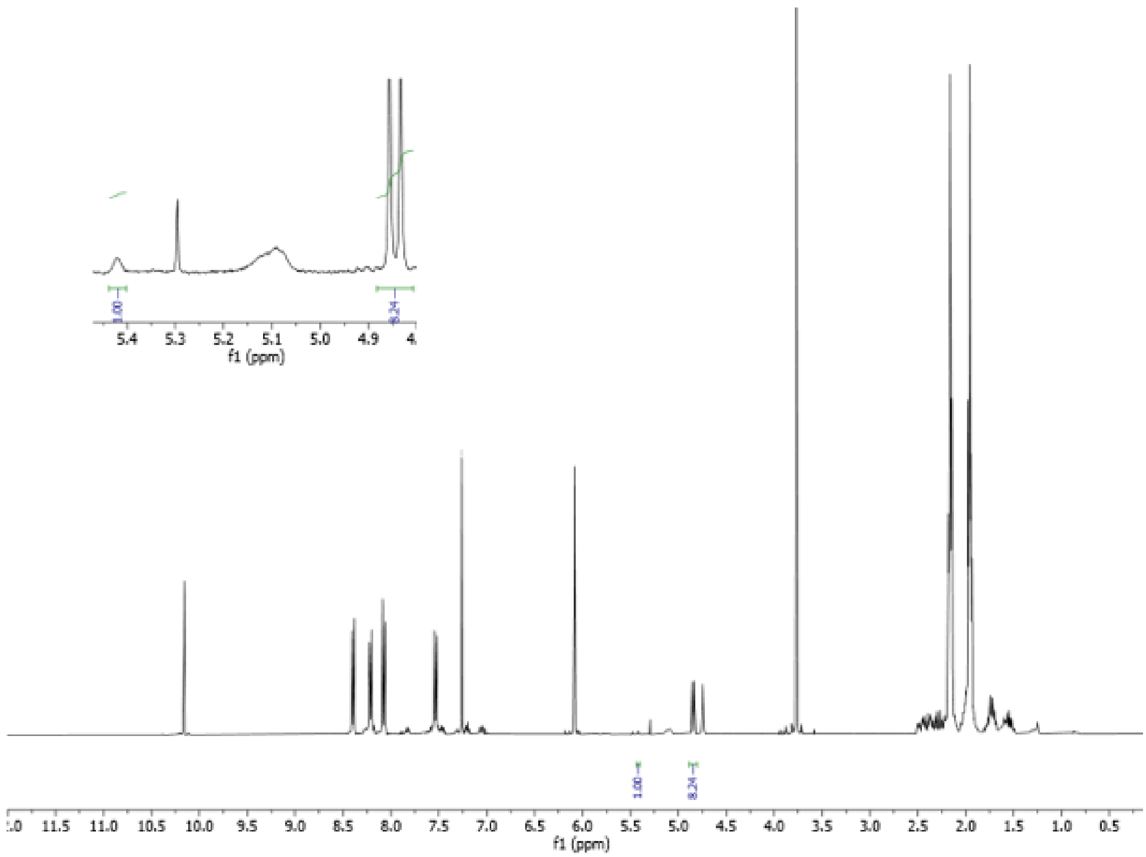
18.5 Water optimization (table S4)

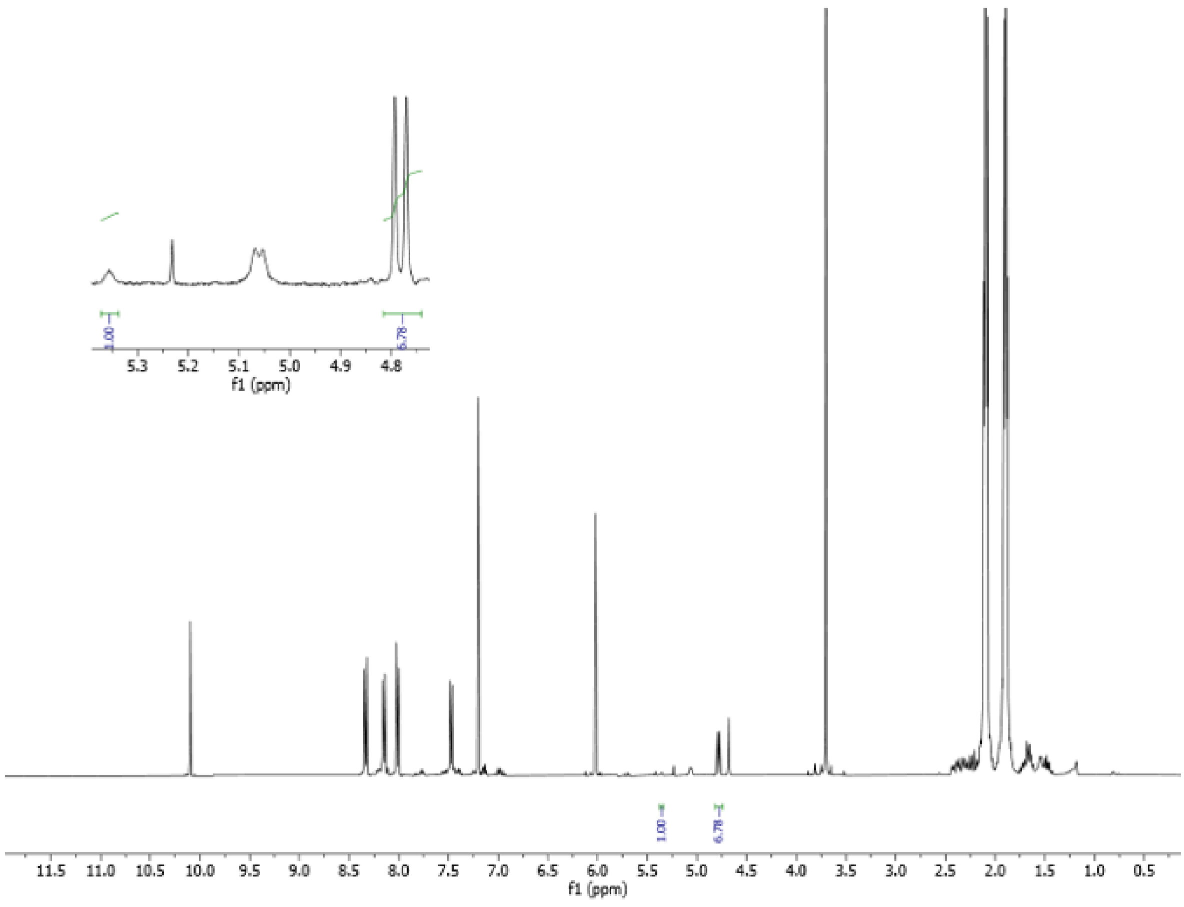
0 mol%



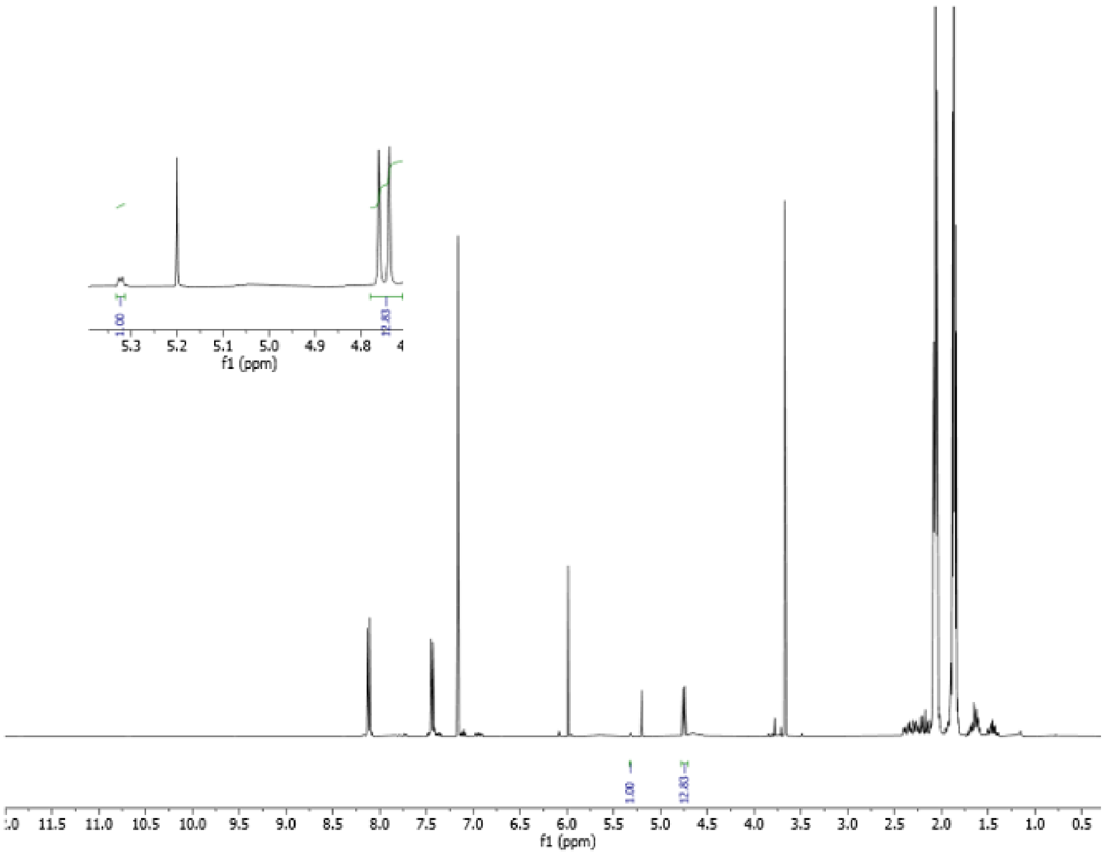


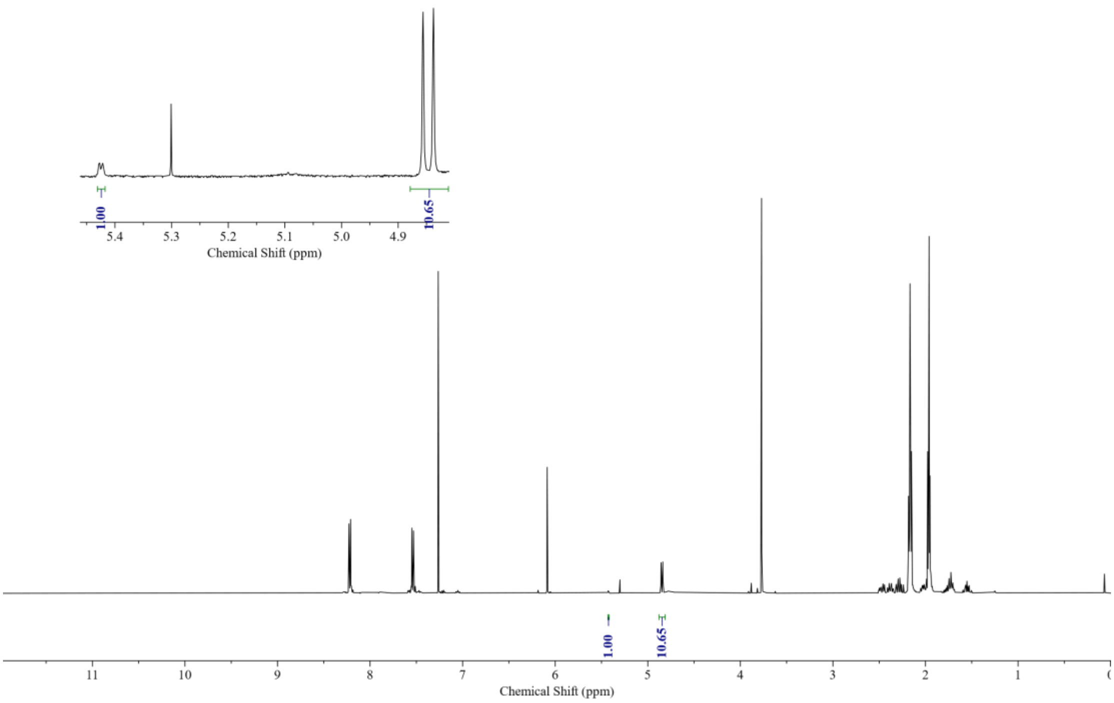
50 mol%



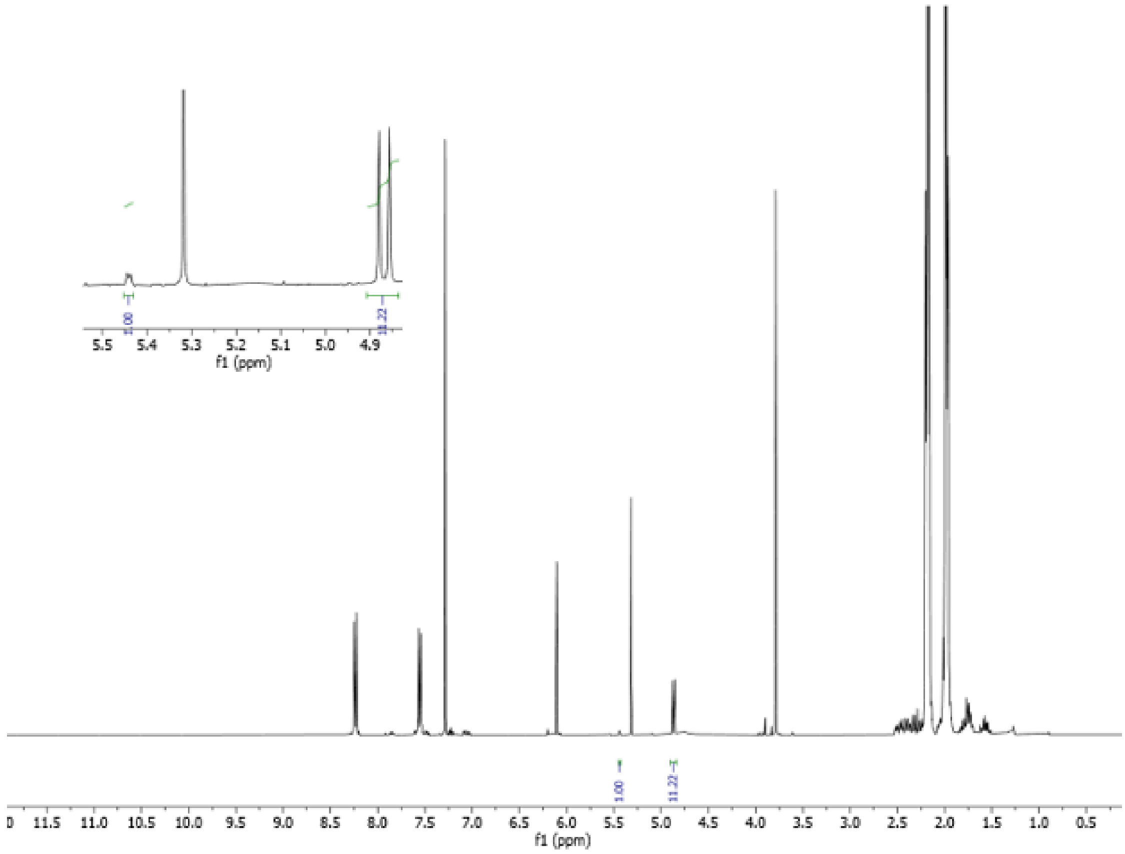


100 mol%

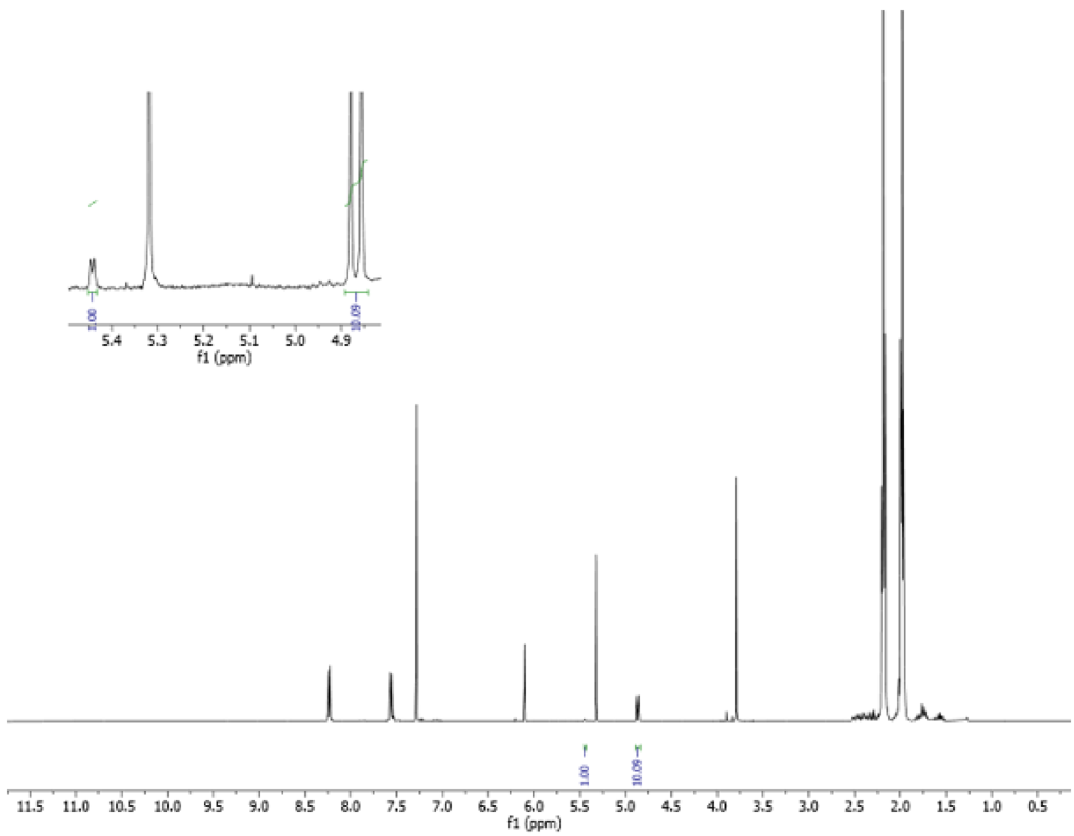

1.00
12.83
5.3
5.2
5.1
5.0
4.9
4.8
f1 (ppm)
1.00
12.83
11.5
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)


1.00
10.65
5.4
5.3
5.2
5.1
5.0
4.9
Chemical Shift (ppm)
1.00
10.65
11
10
9
8
7
6
5
4
3
2
1
Chemical Shift (ppm)

200 mol%



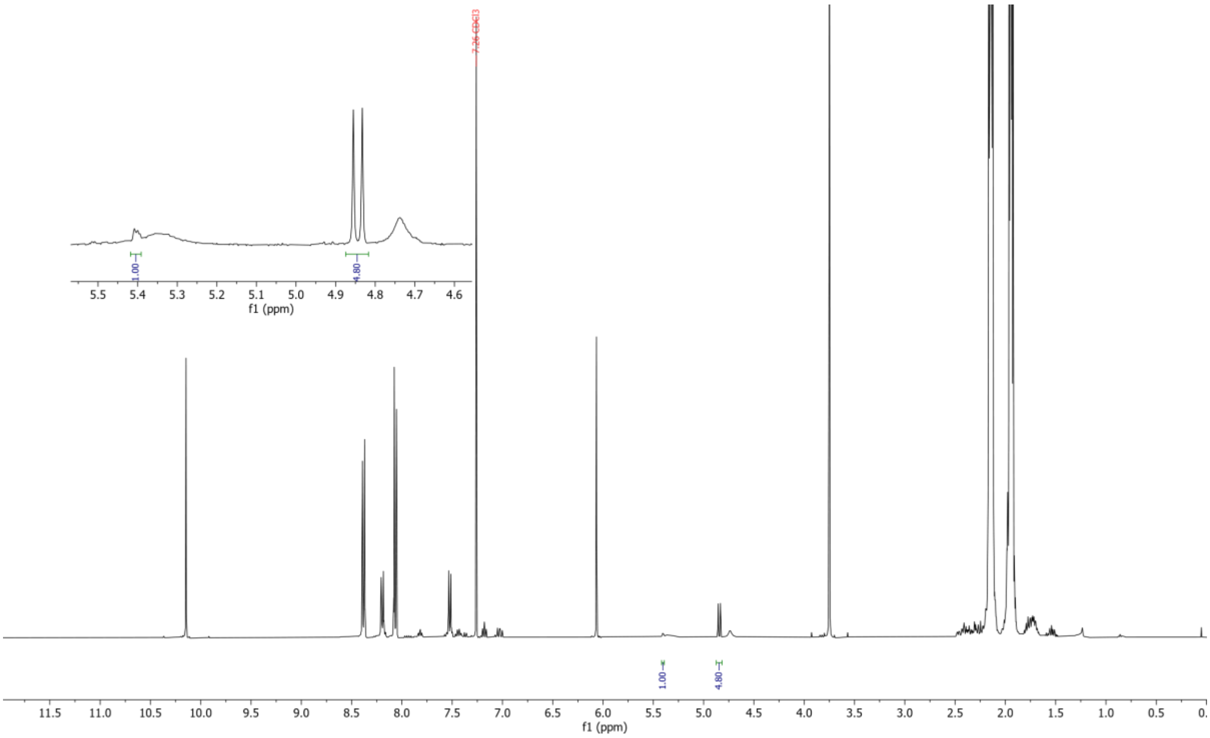
1.00
11.22
5.5
5.4
5.3
5.2
5.1
5.0
4.9
f1 (ppm)
11.5
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

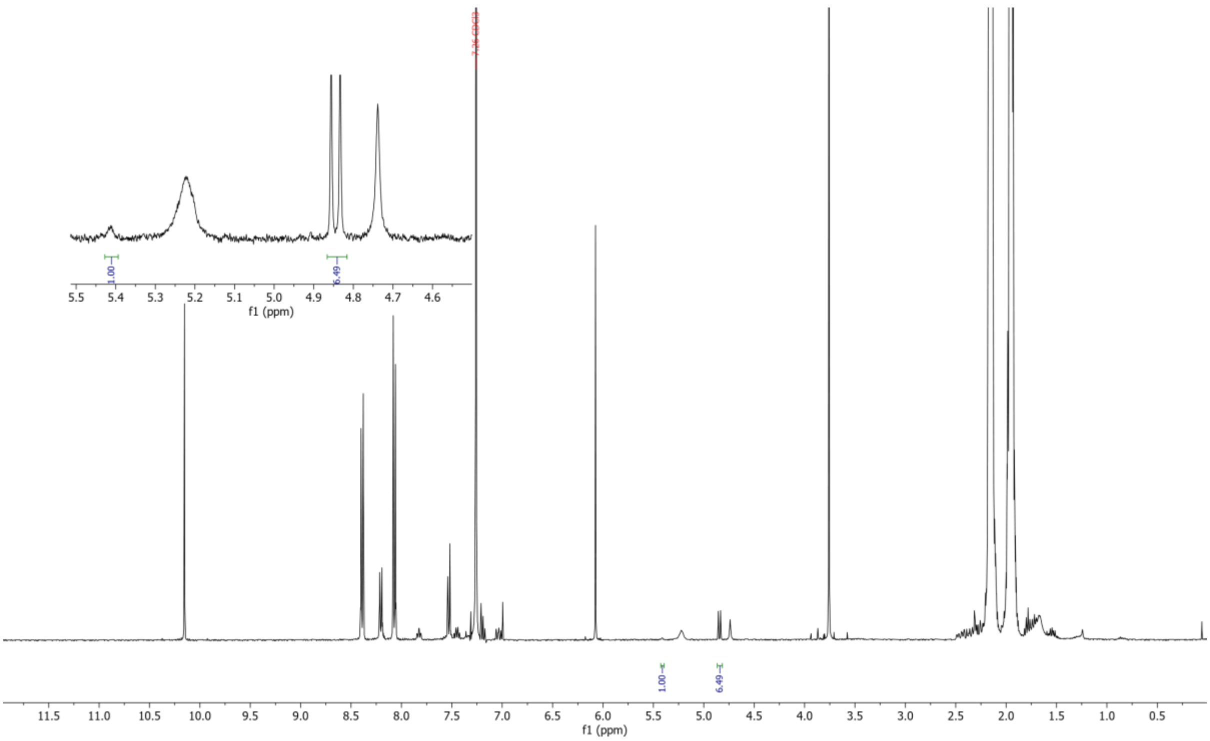


1.00
10.09
5.4
5.3
5.2
5.1
5.0
4.9
f1 (ppm)
11.5
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

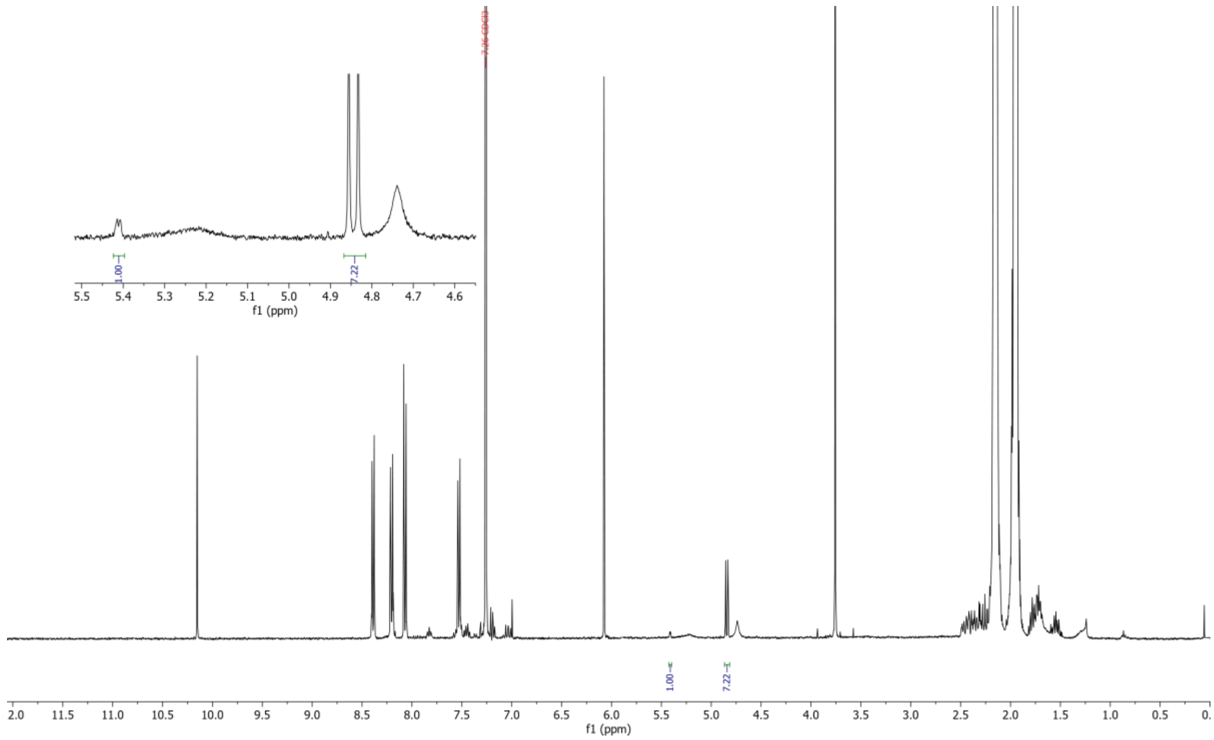
18.6 Water screening without molecular sieves (table S1)

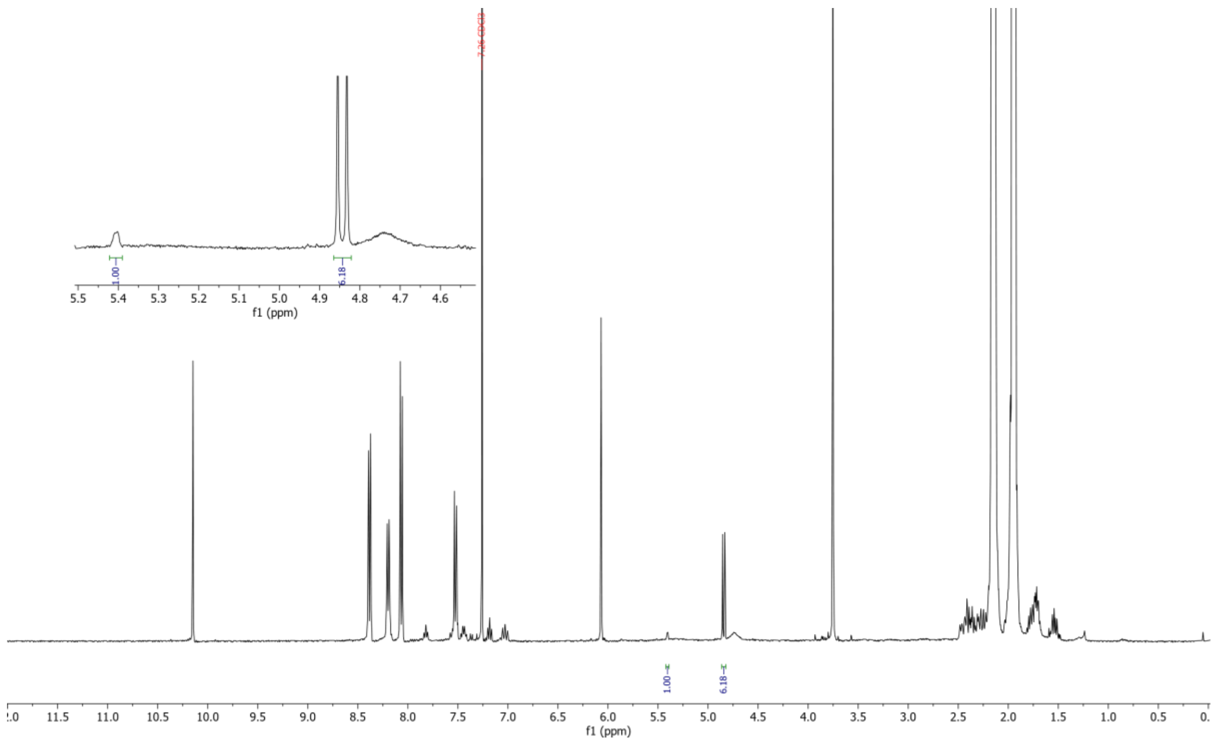
22 mol%



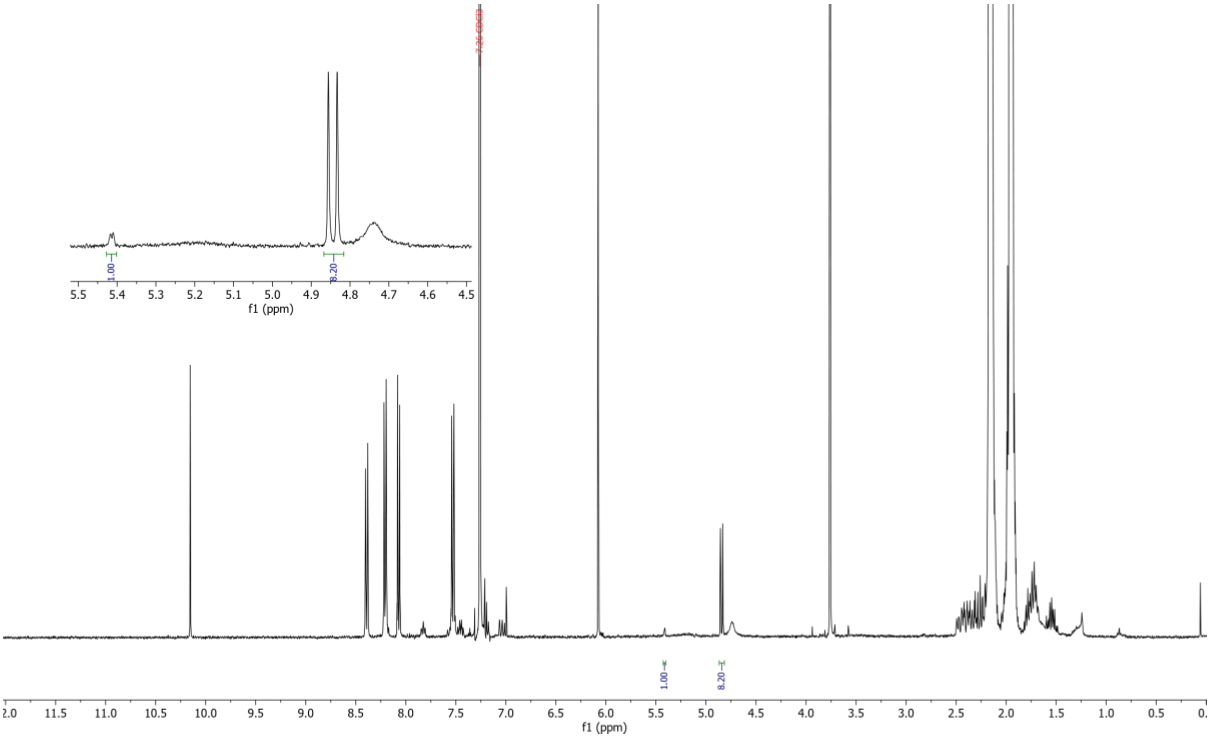


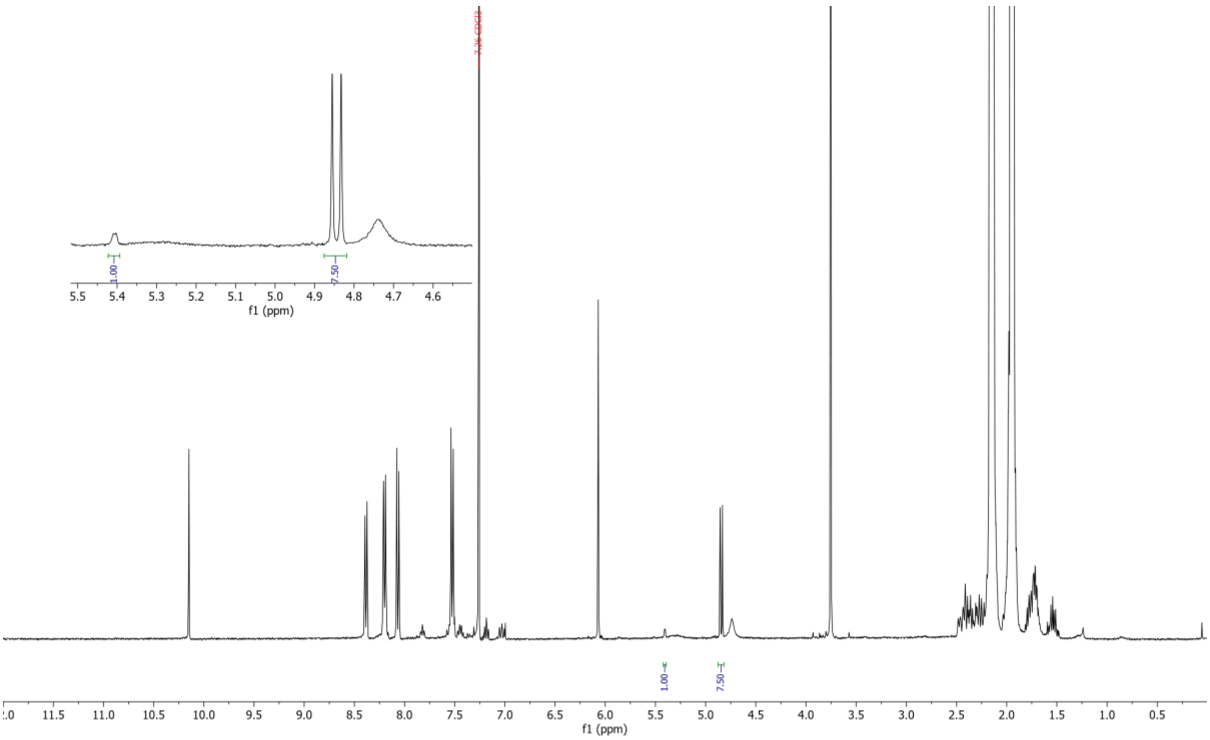
55 mol%





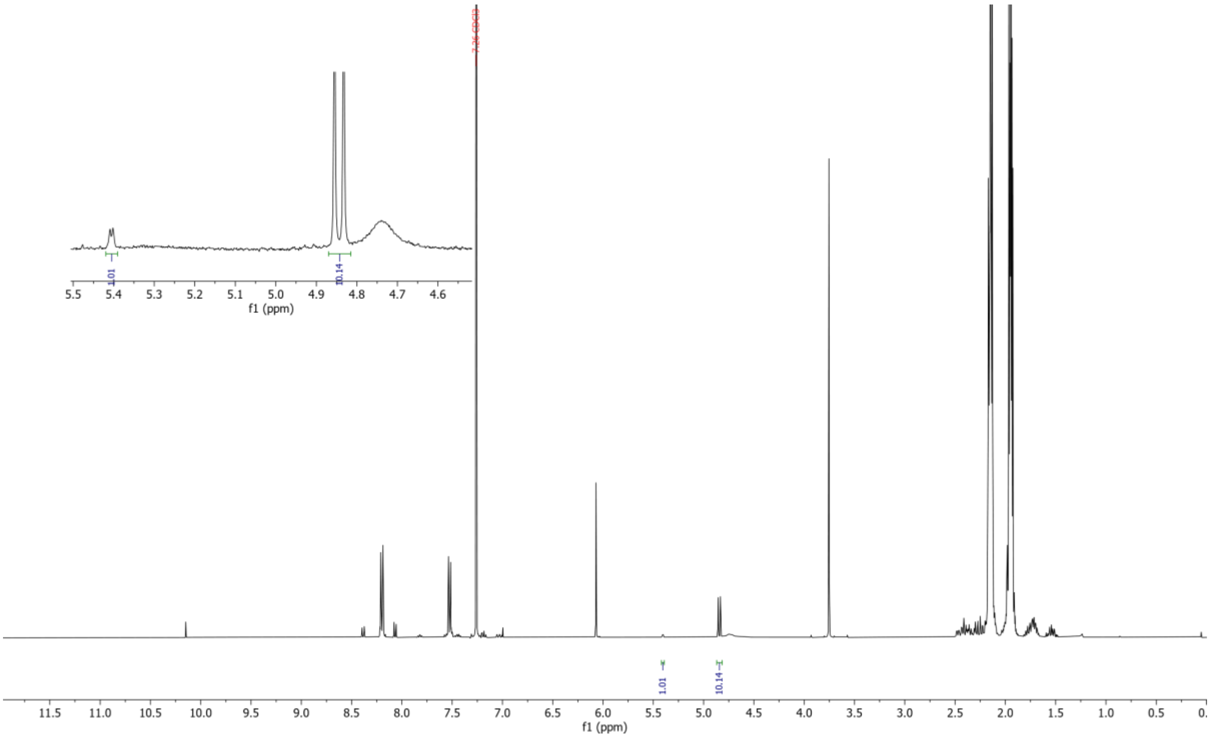
77 mol%

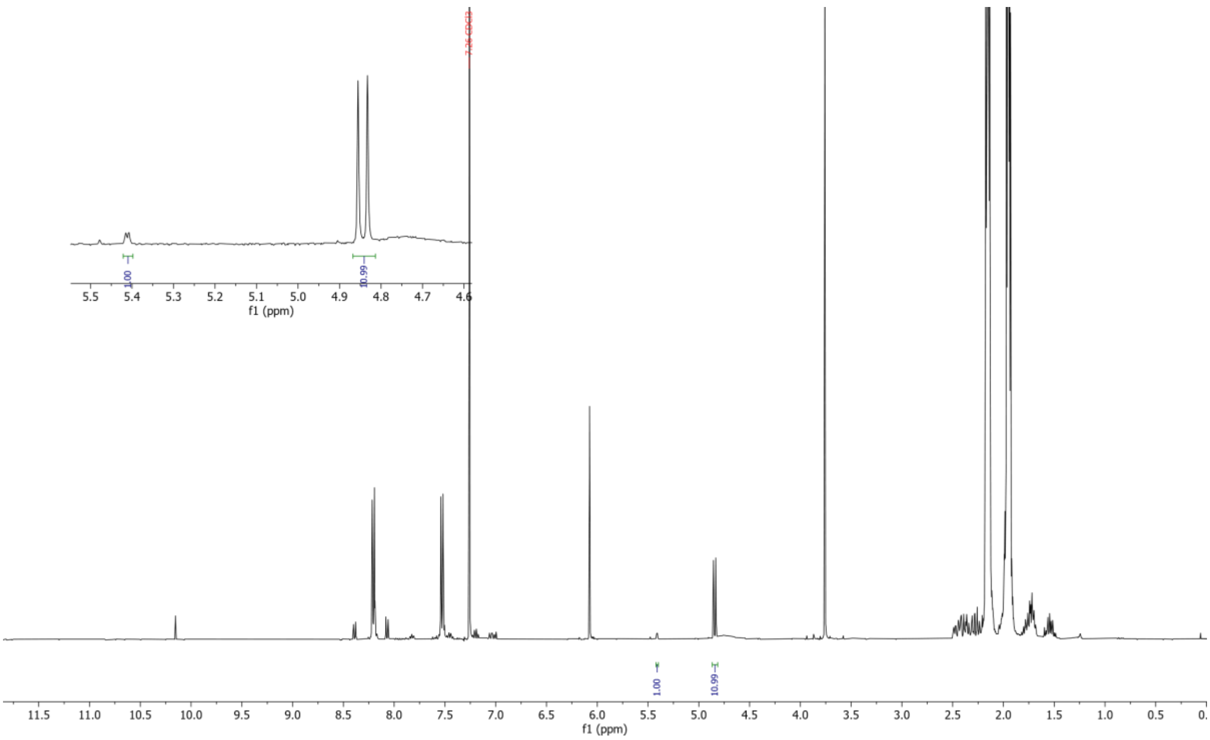




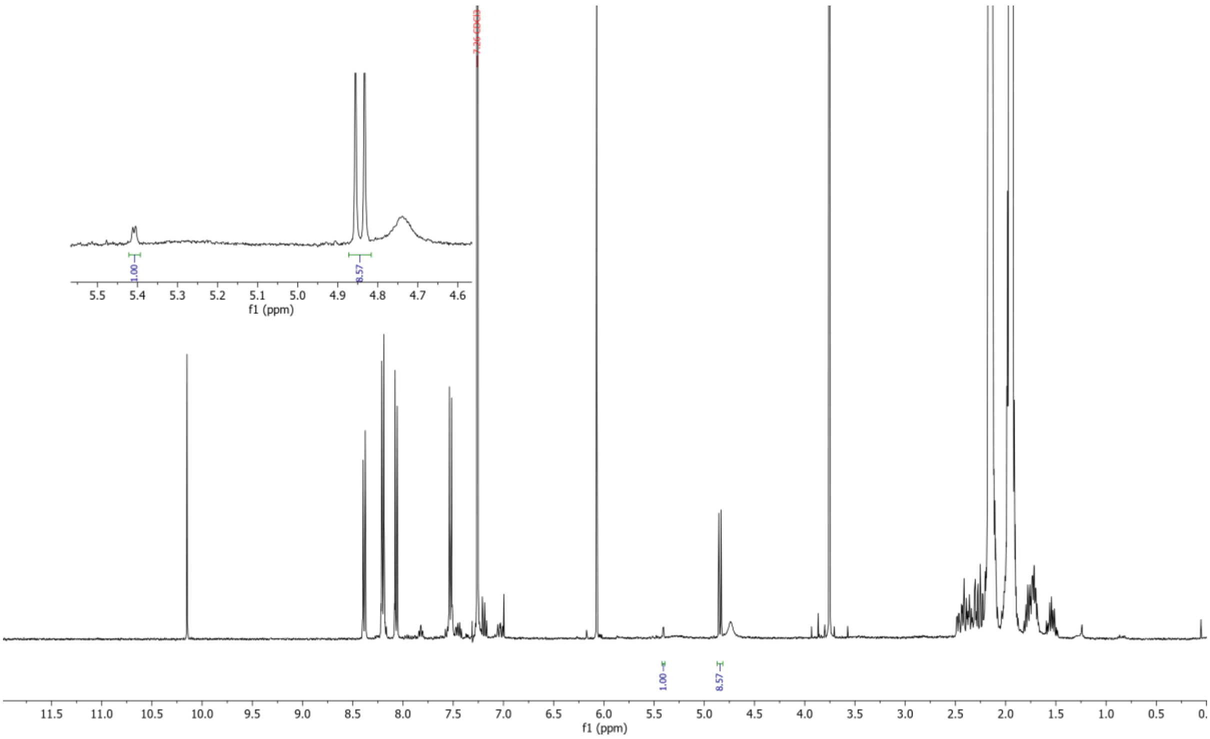
18.7 Screening molecular sieves size (table S1)

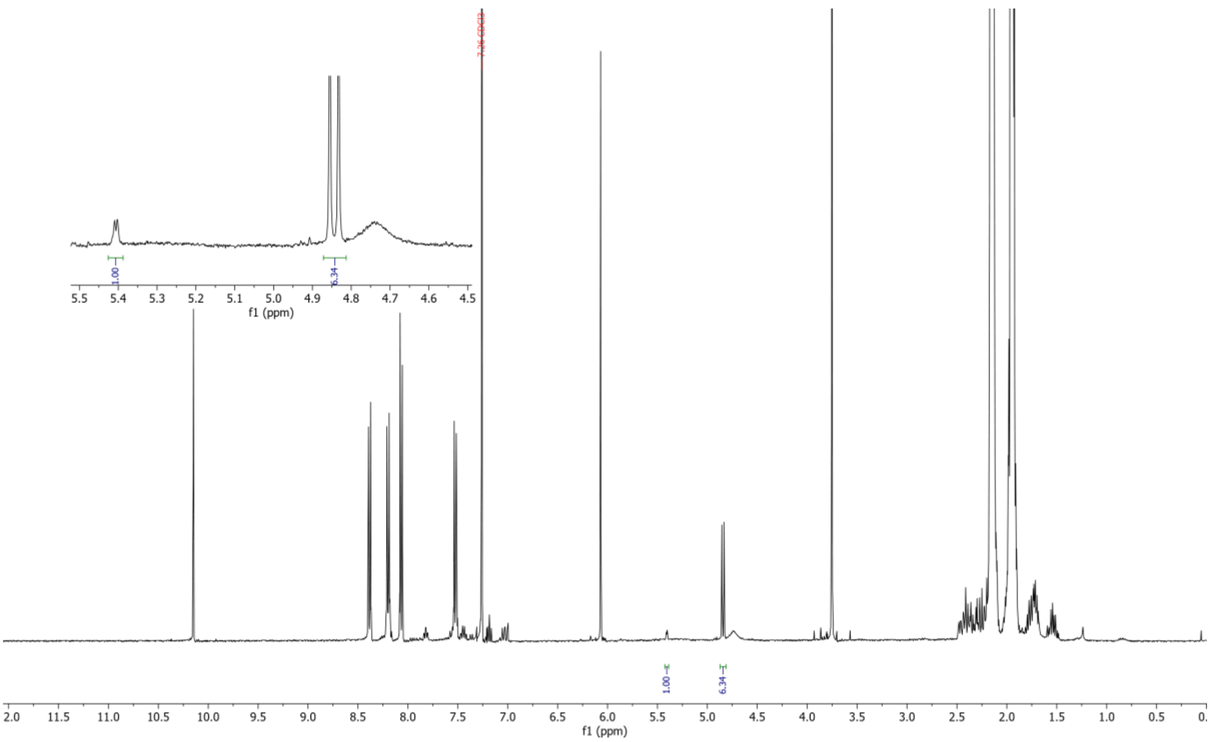
4 angstrom molecular sieves





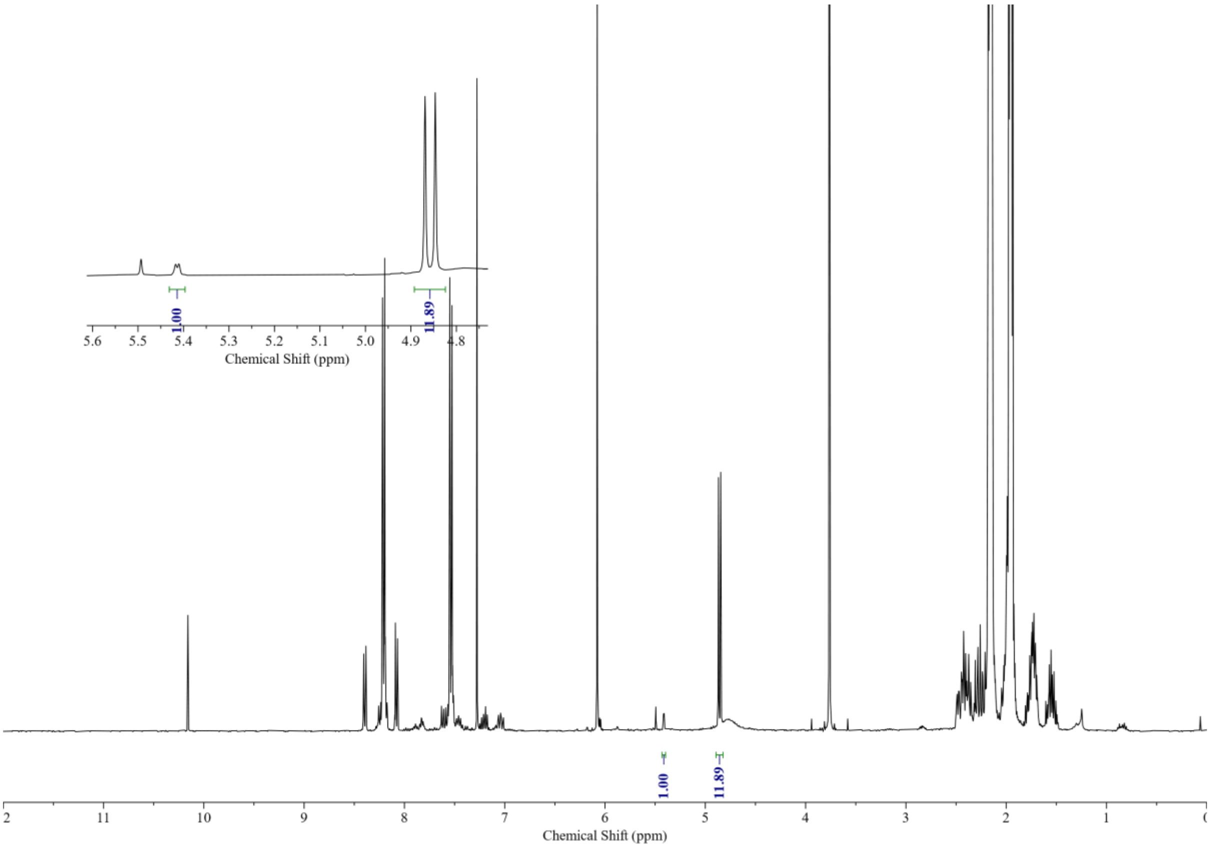
5 angstrom molecular sieves

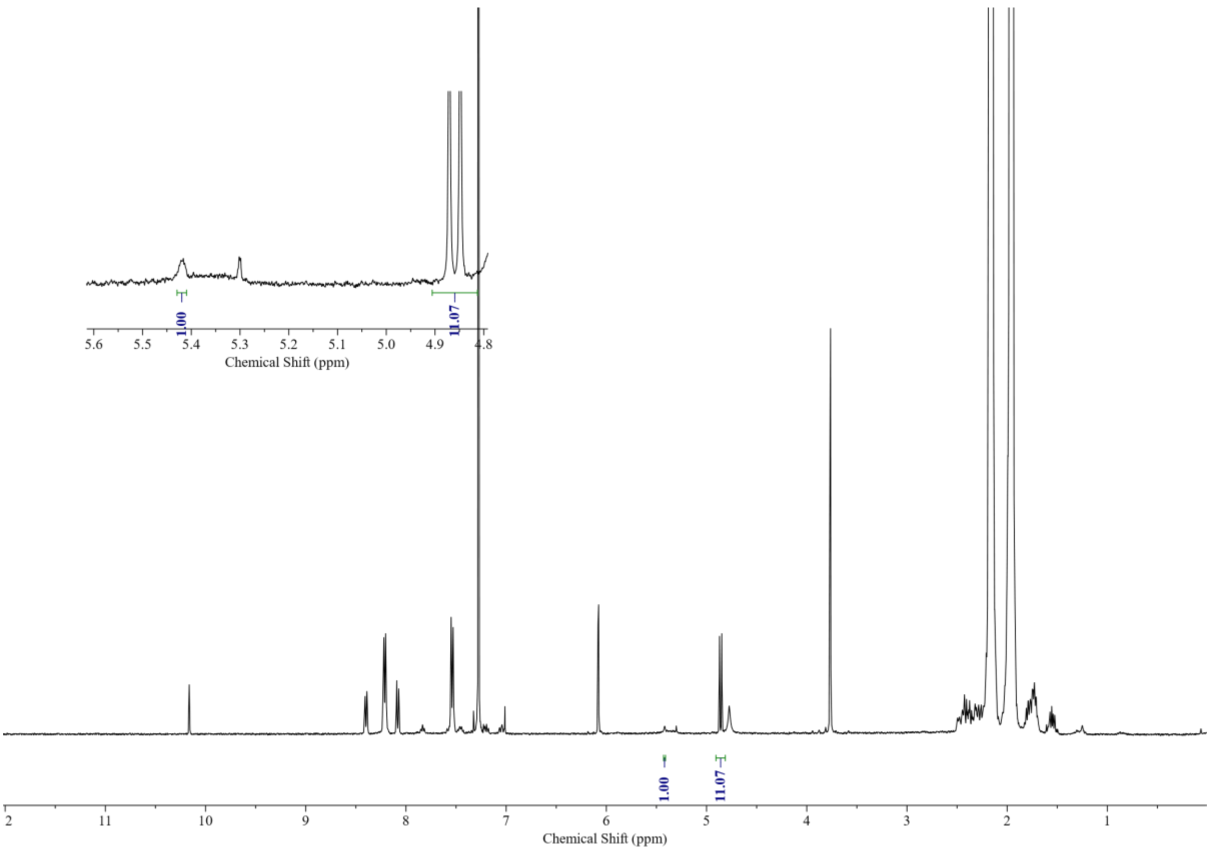




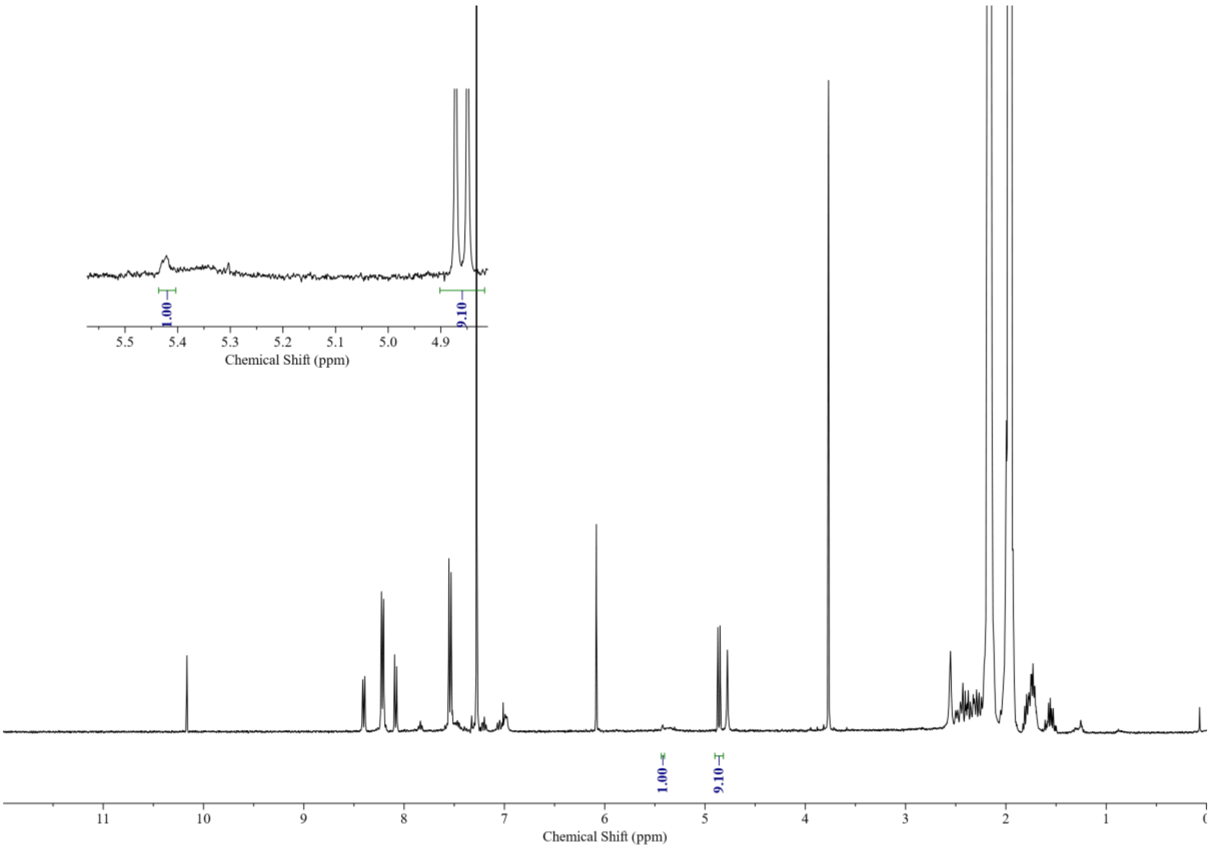
18.8 additional control experiments (table S1)

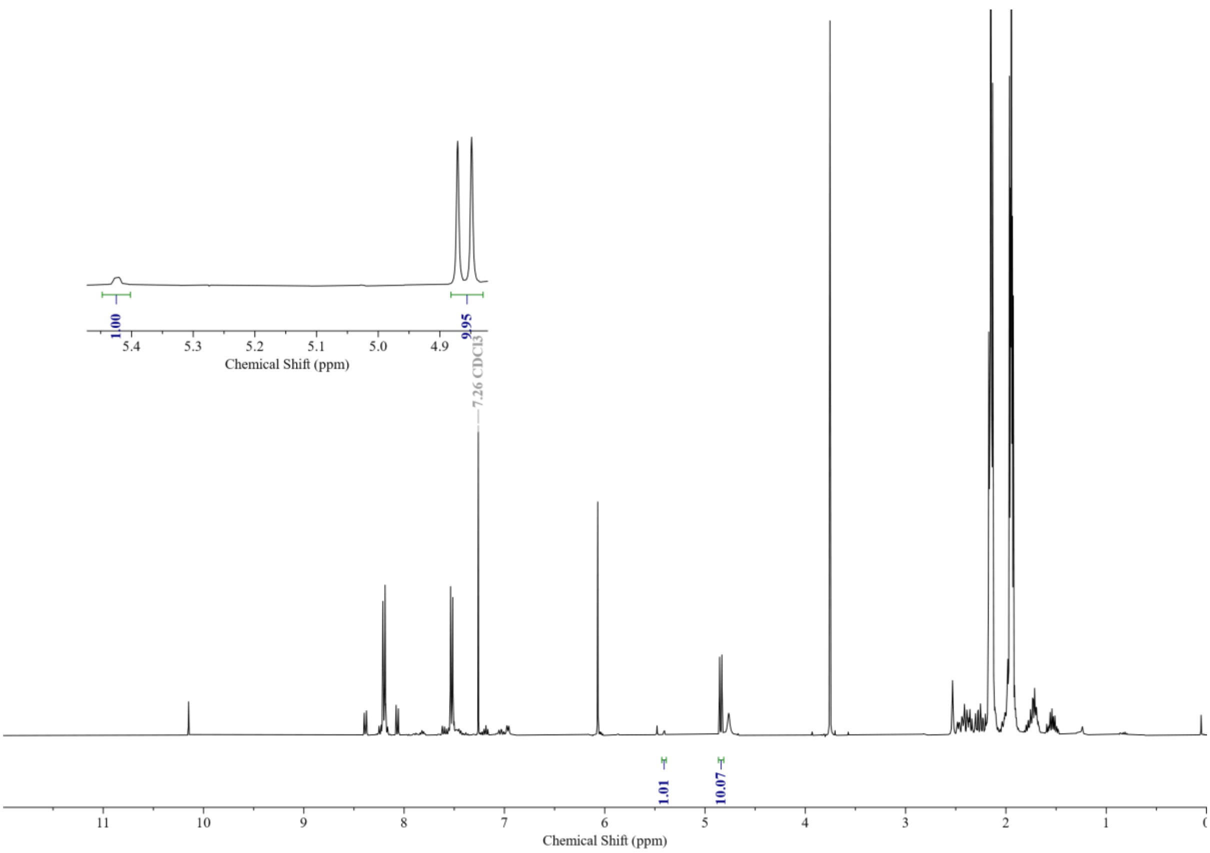
No molecular sieves, 100 mol% H_2O, 100 mol% $KCl_{(S)}$



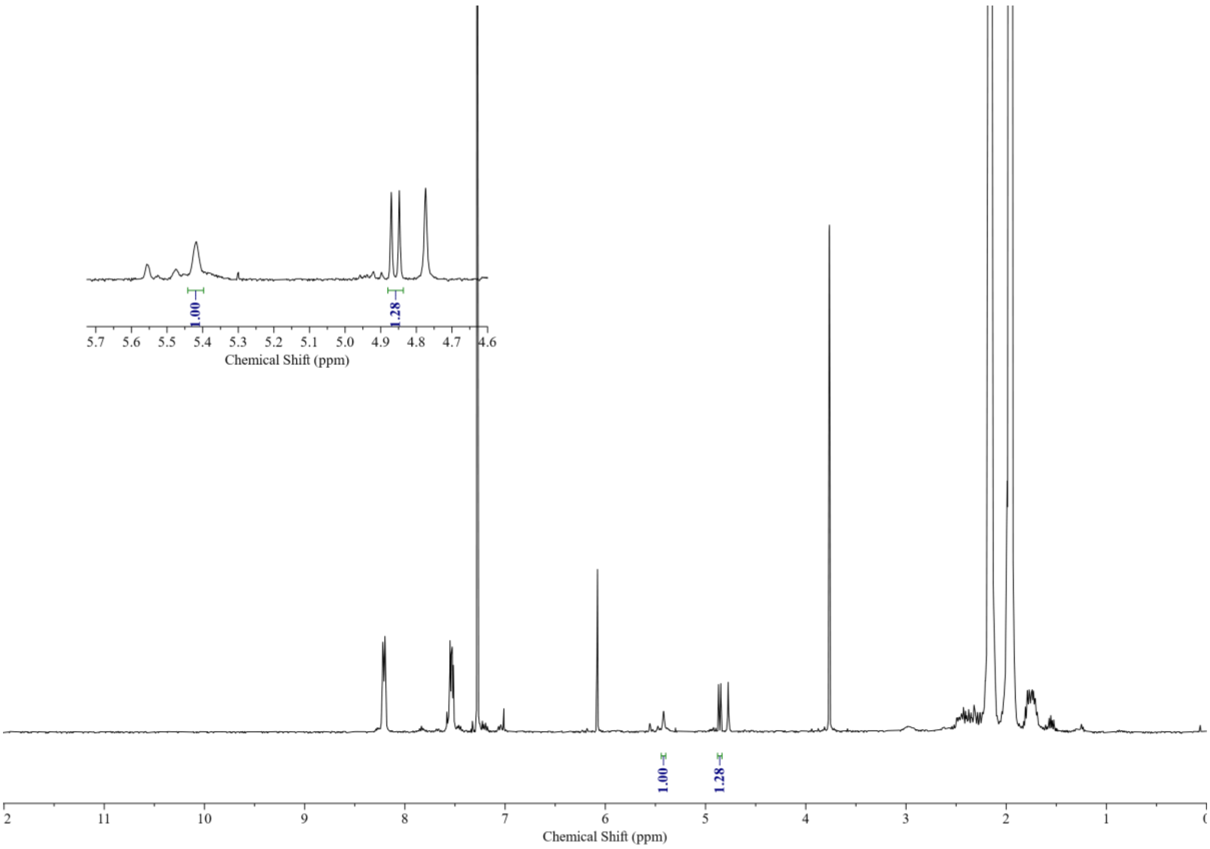


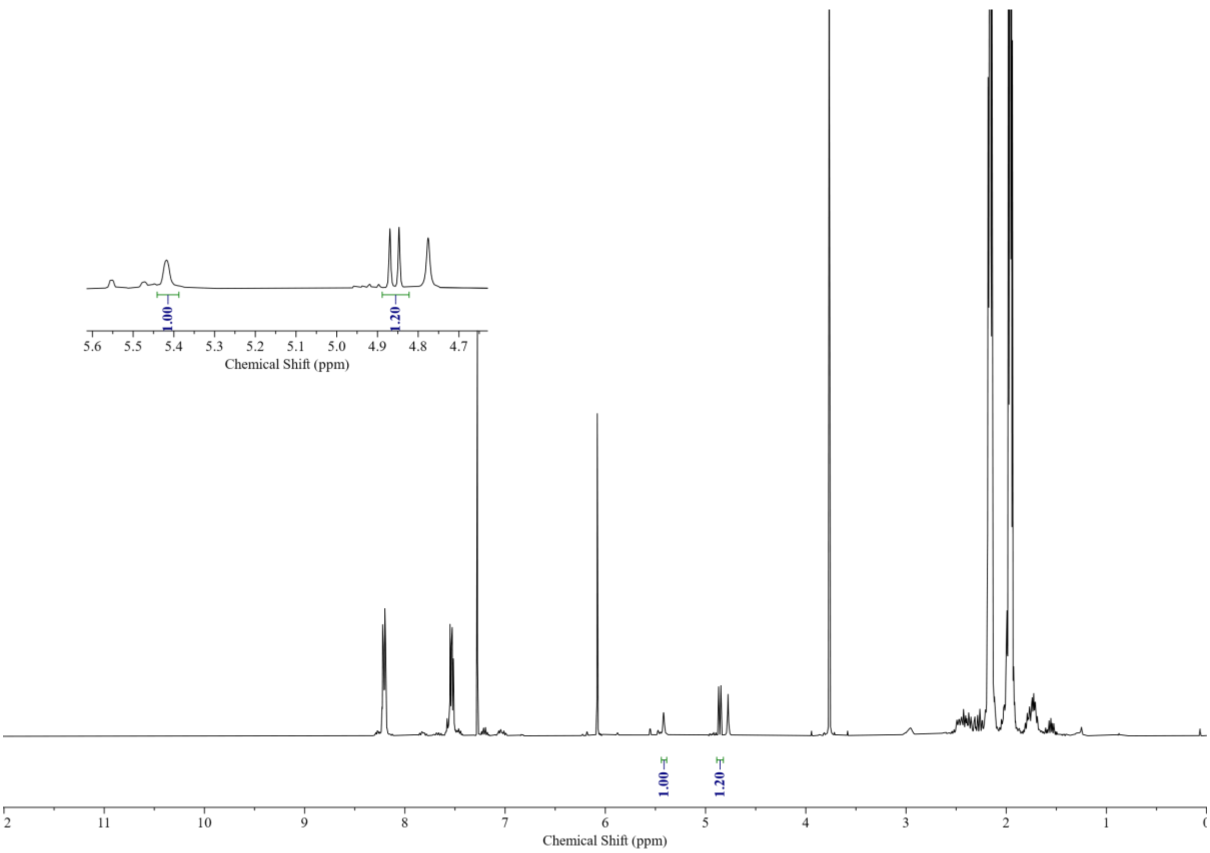
No molecular sieves, 100 mol% H_2O, 10 mol% 2,6-lutidine





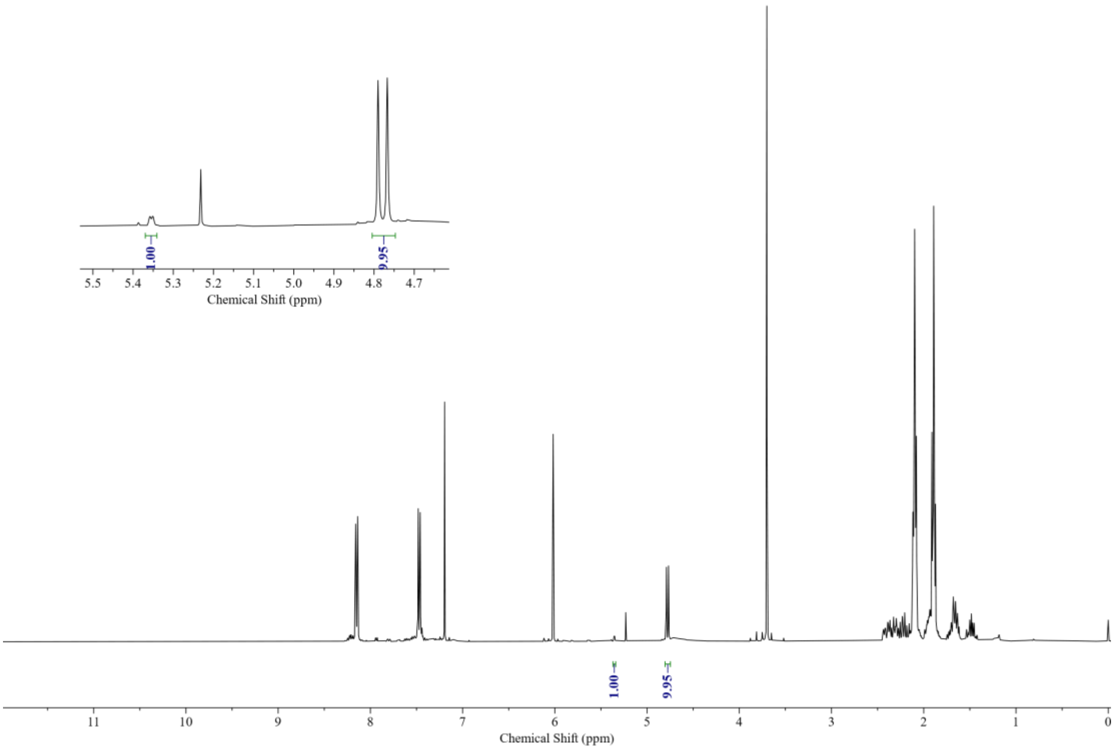
No molecular sieves, 100 mol% H_2O, 10 mol% $KHCO_{3(S)}$

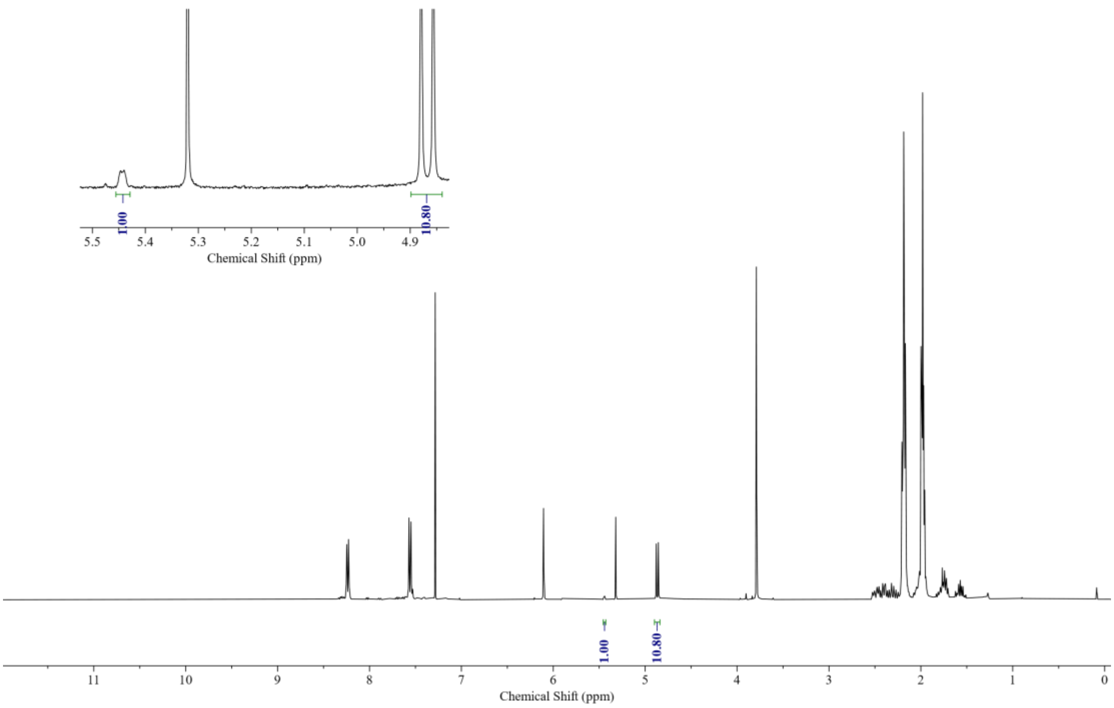




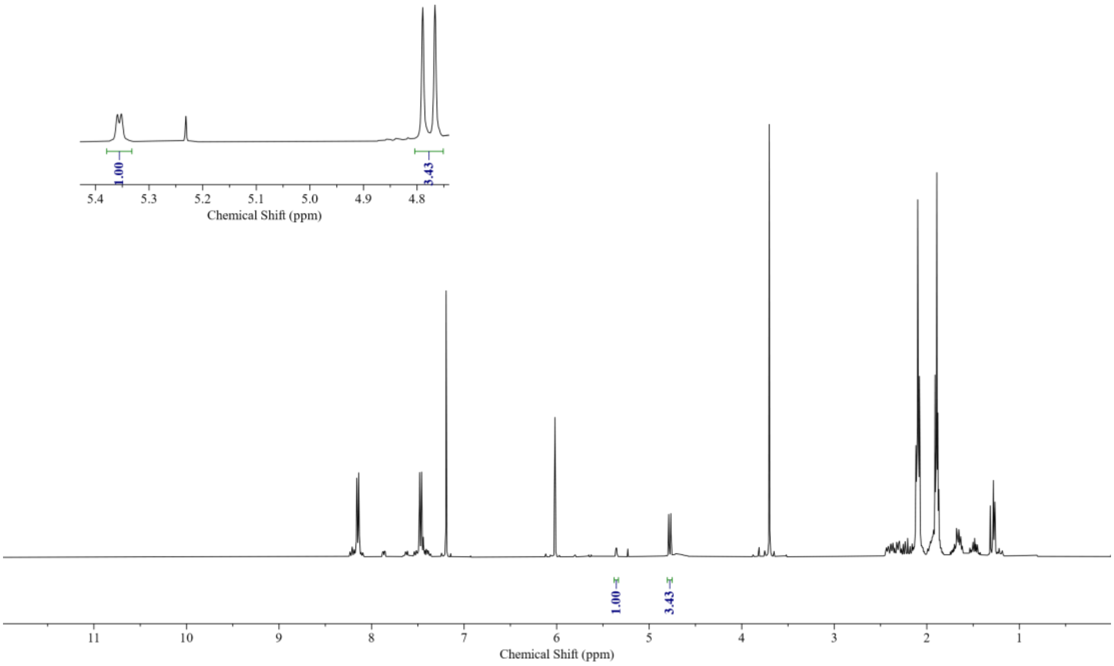
18.9 boronic acid screening (table S5)

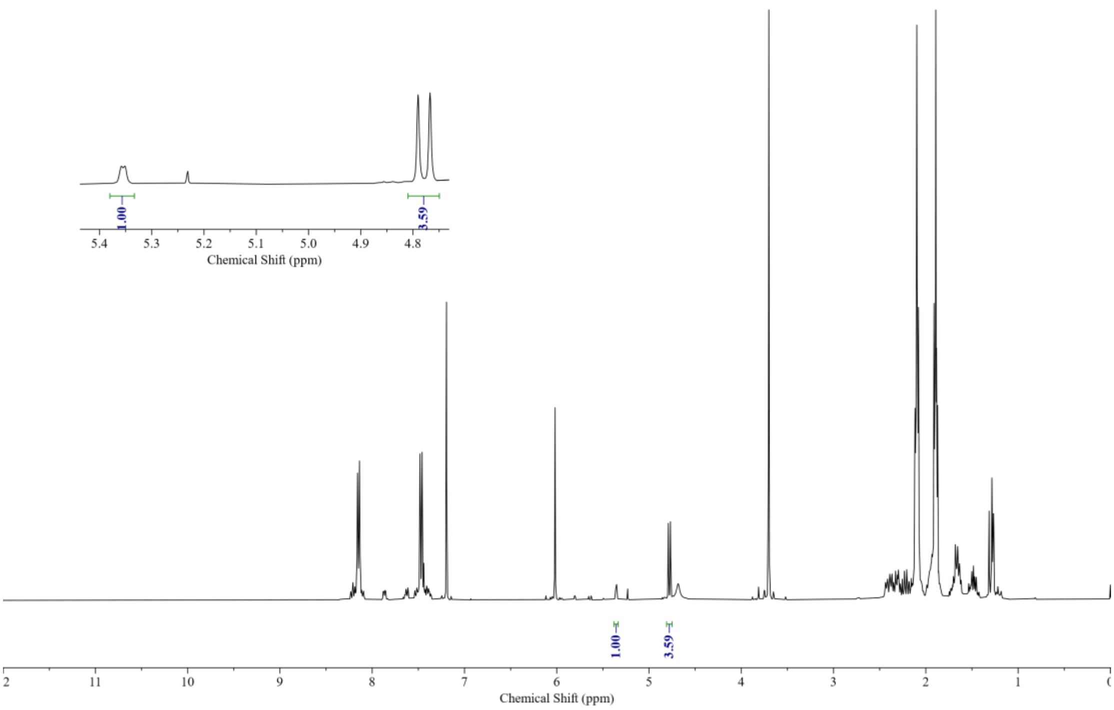
3-F phenylboronic acid



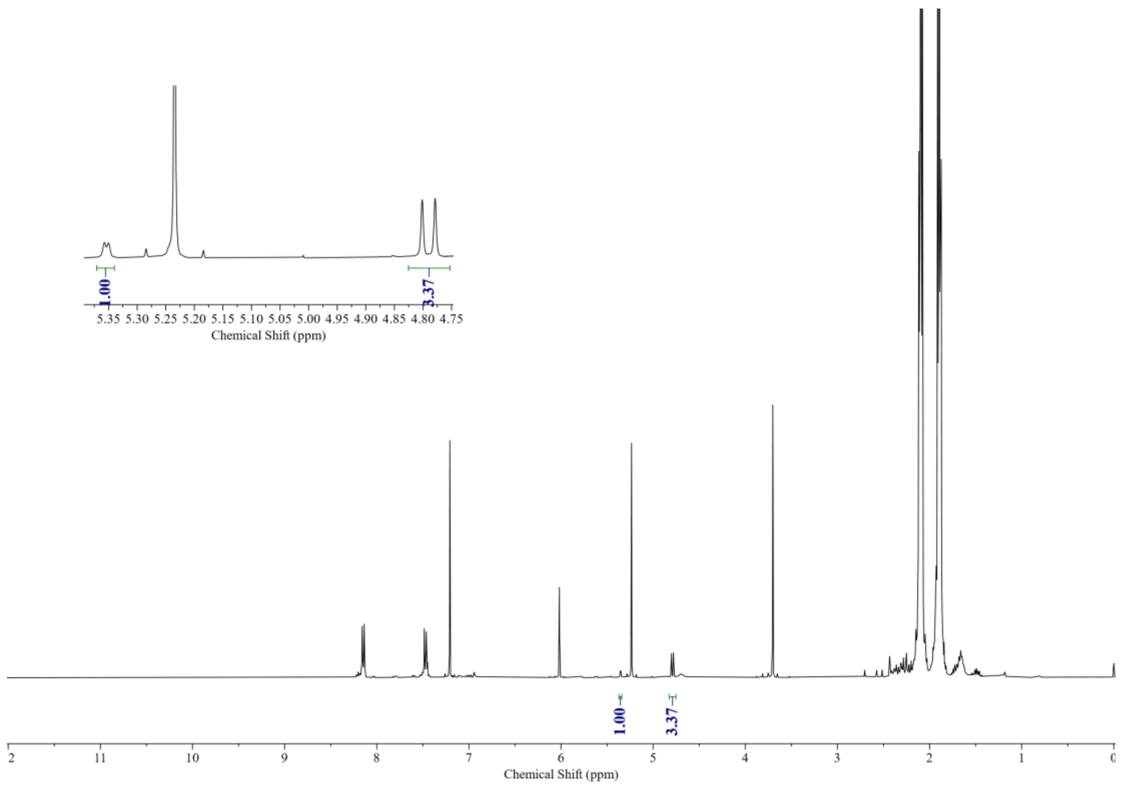


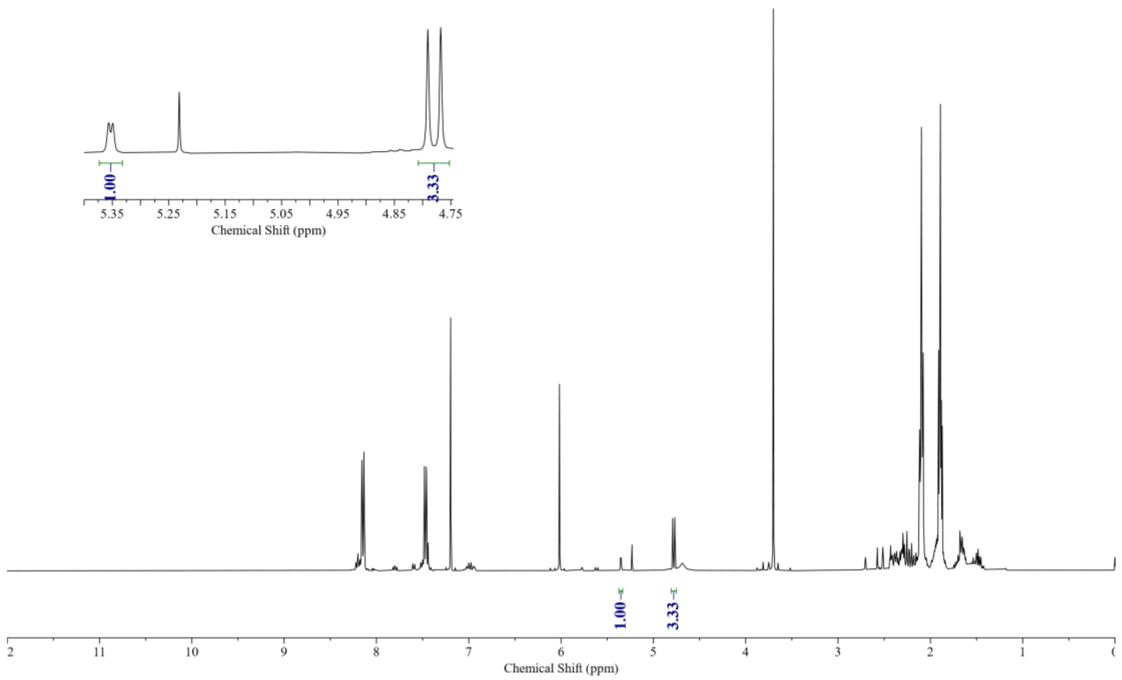
4-tBu phenylboronic acid



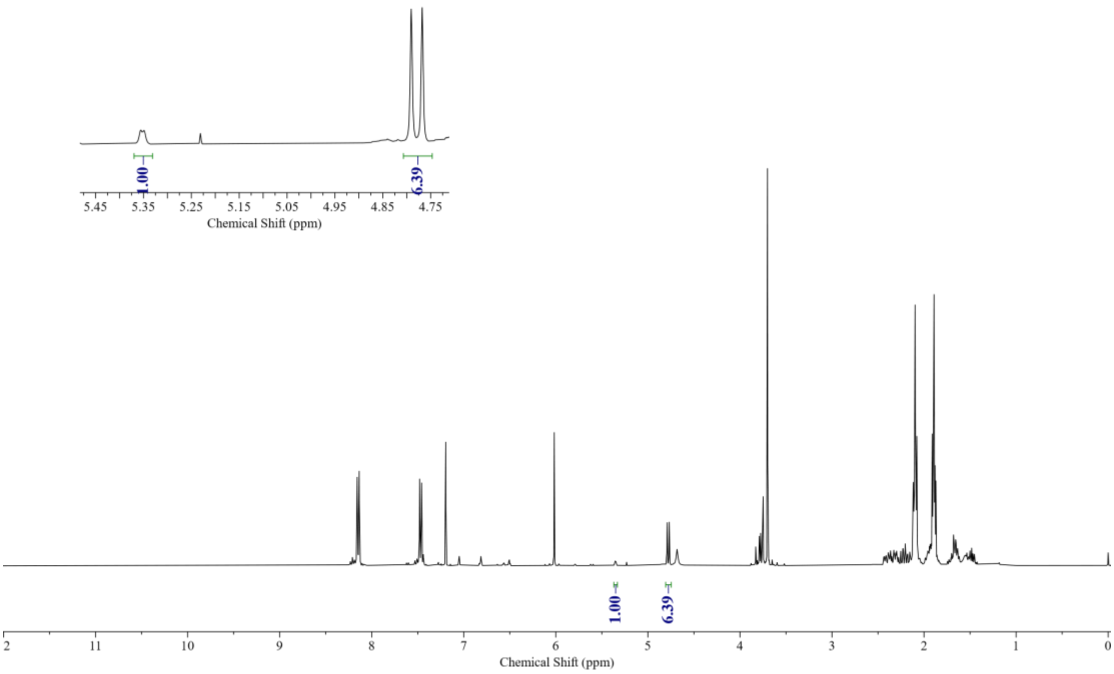


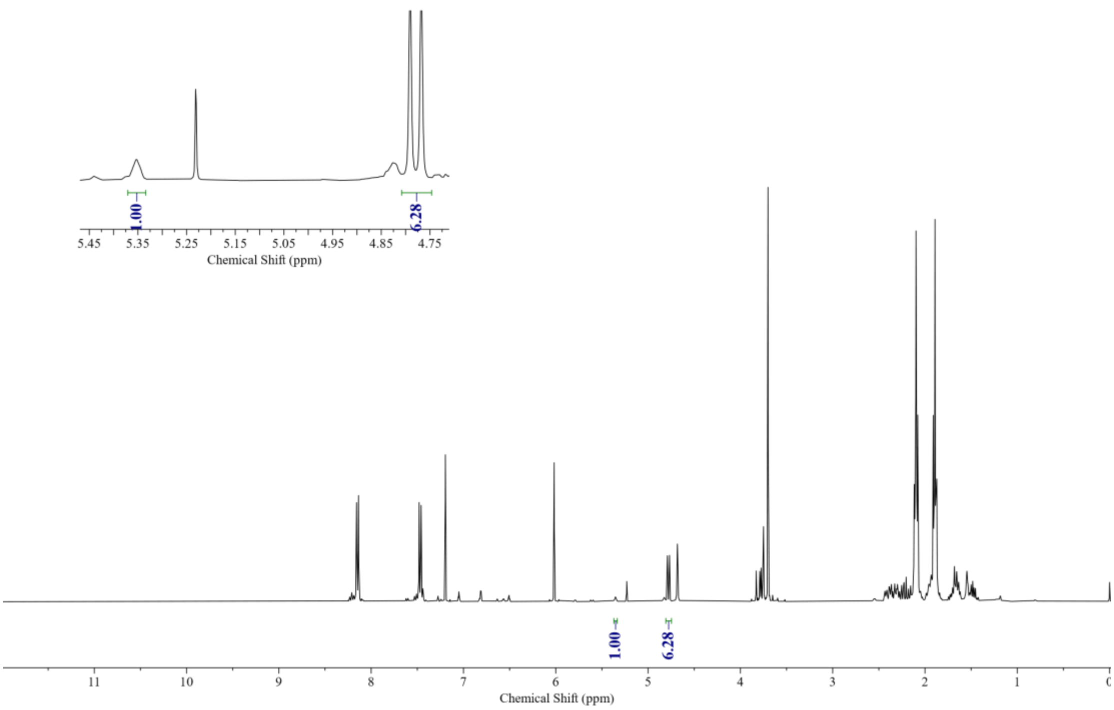
2,4-Me phenylboronic acid



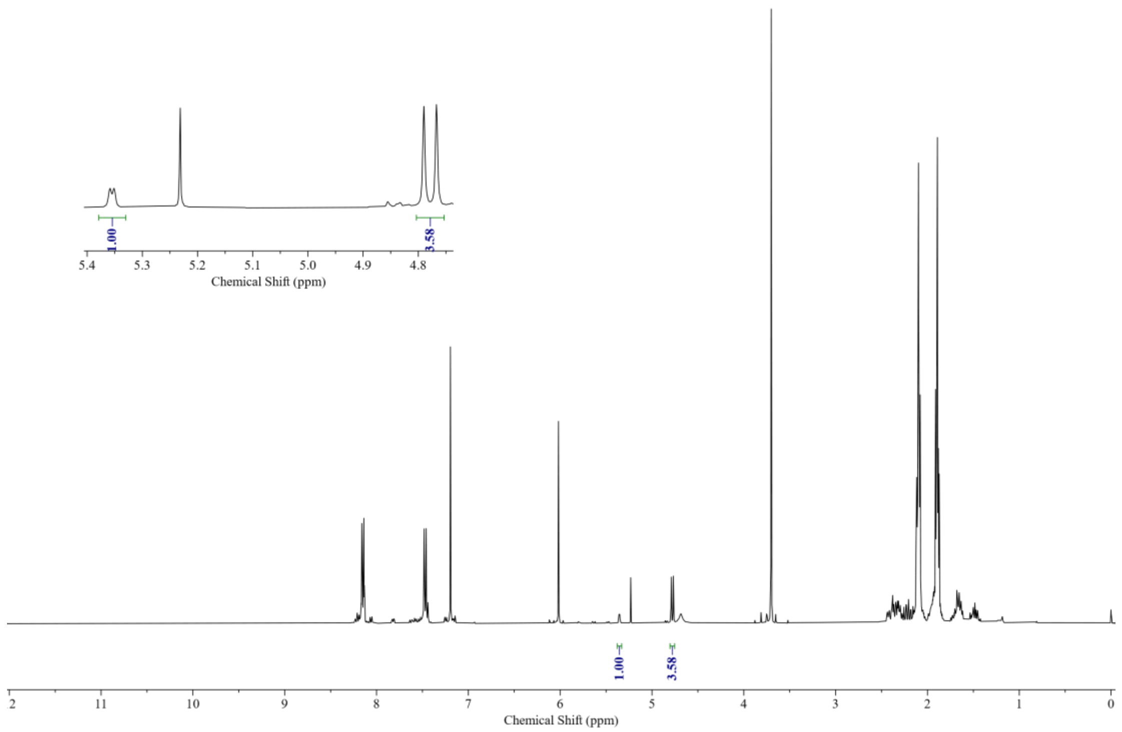


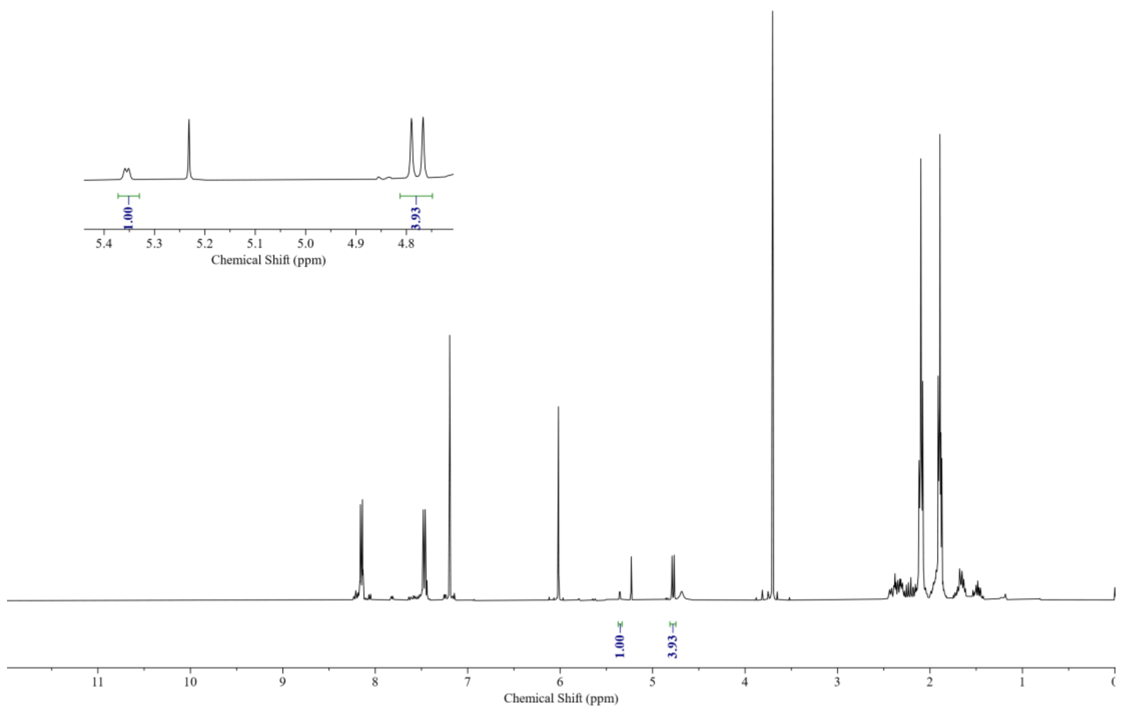
3,5-OMe phenylboronic acid



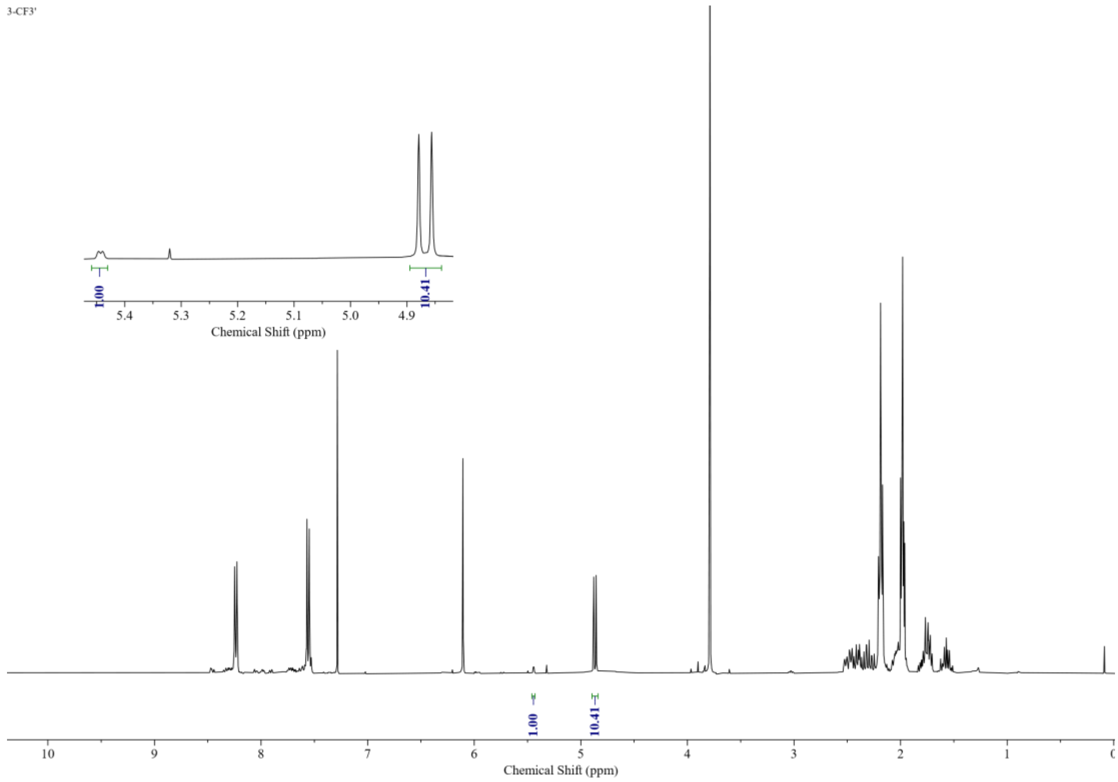


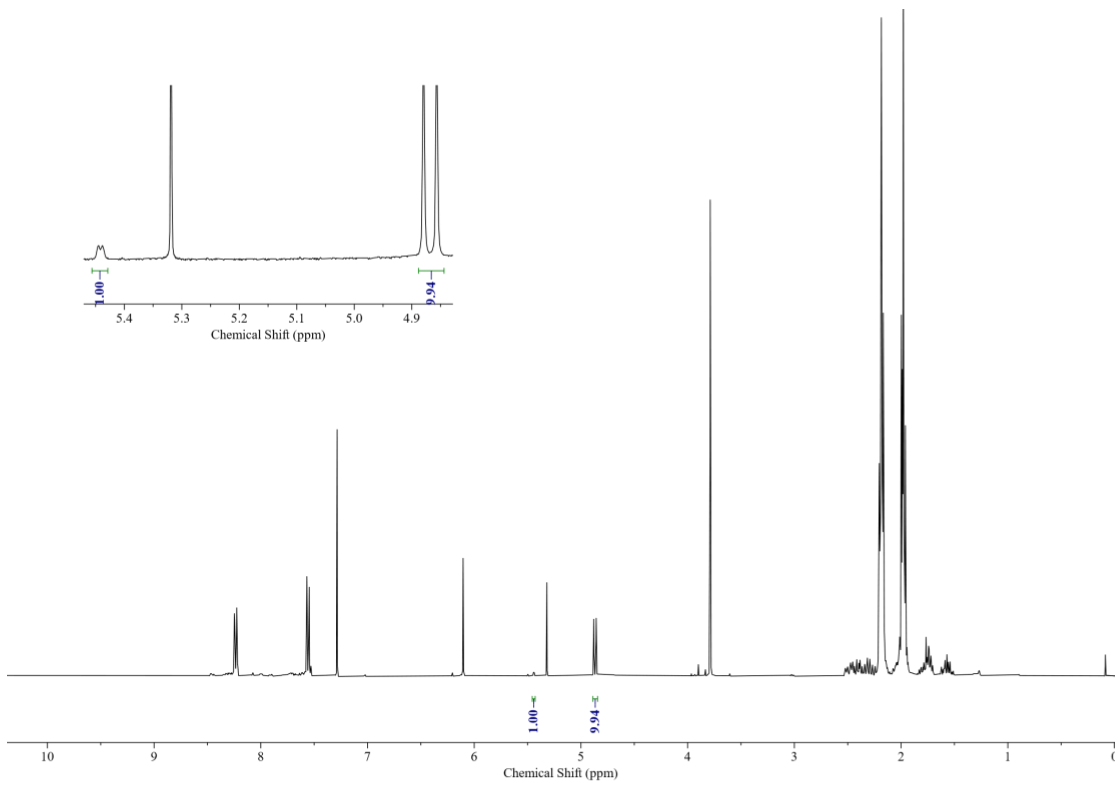
4-Me phenylboronic acid



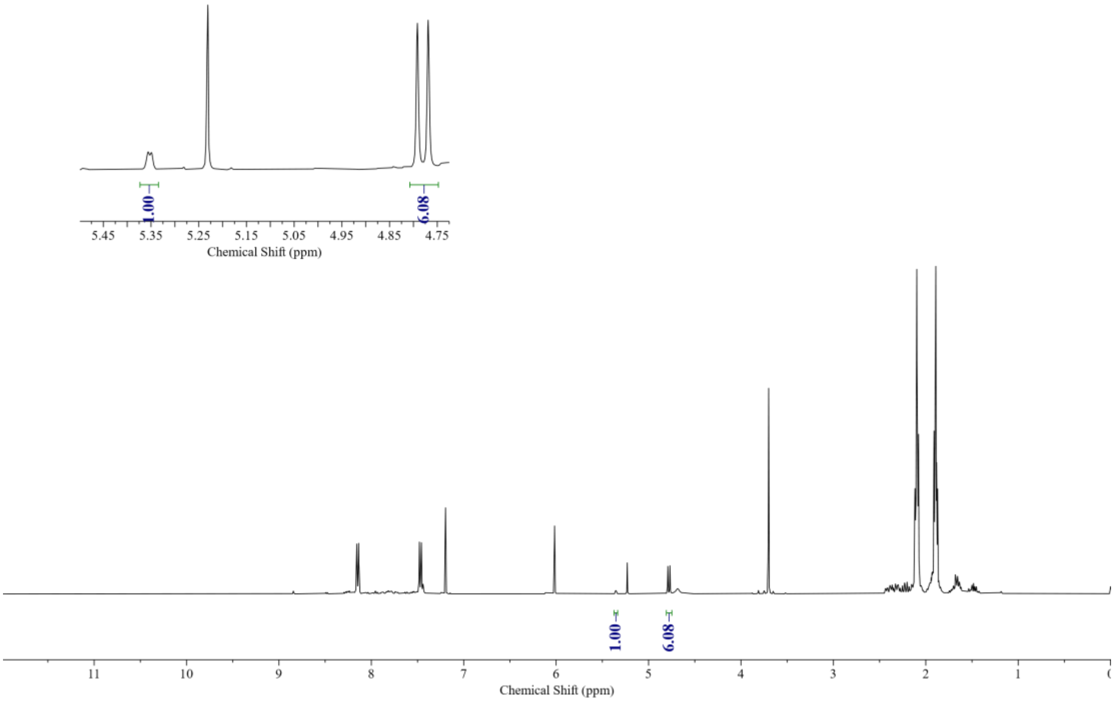


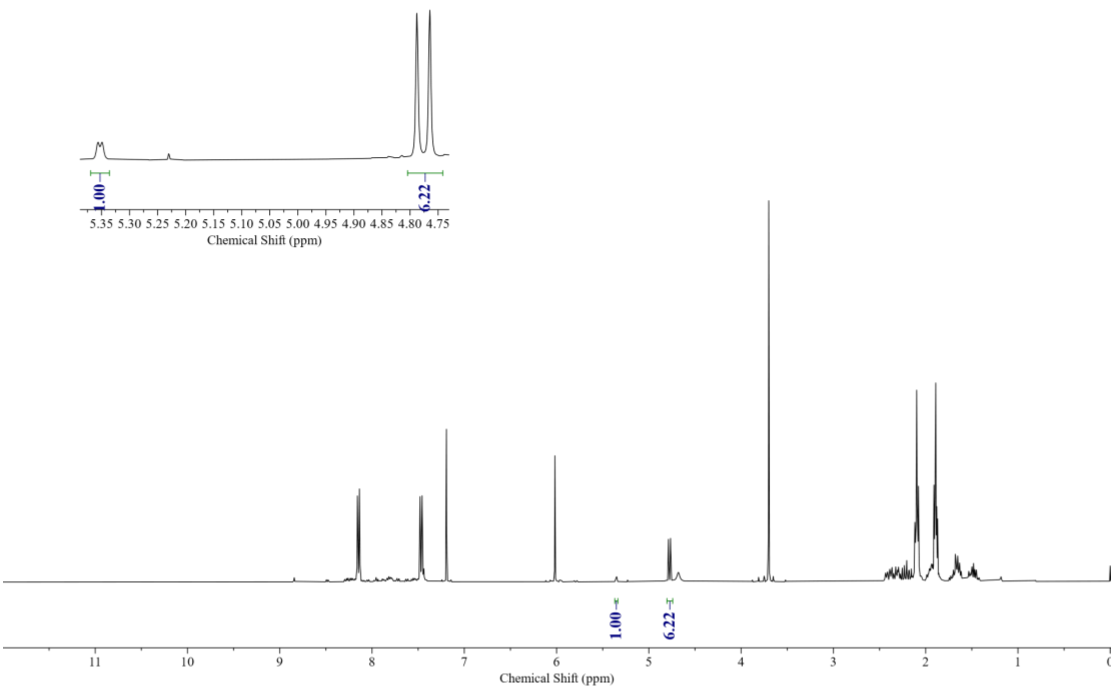
3-CF_3 phenylboronic acid



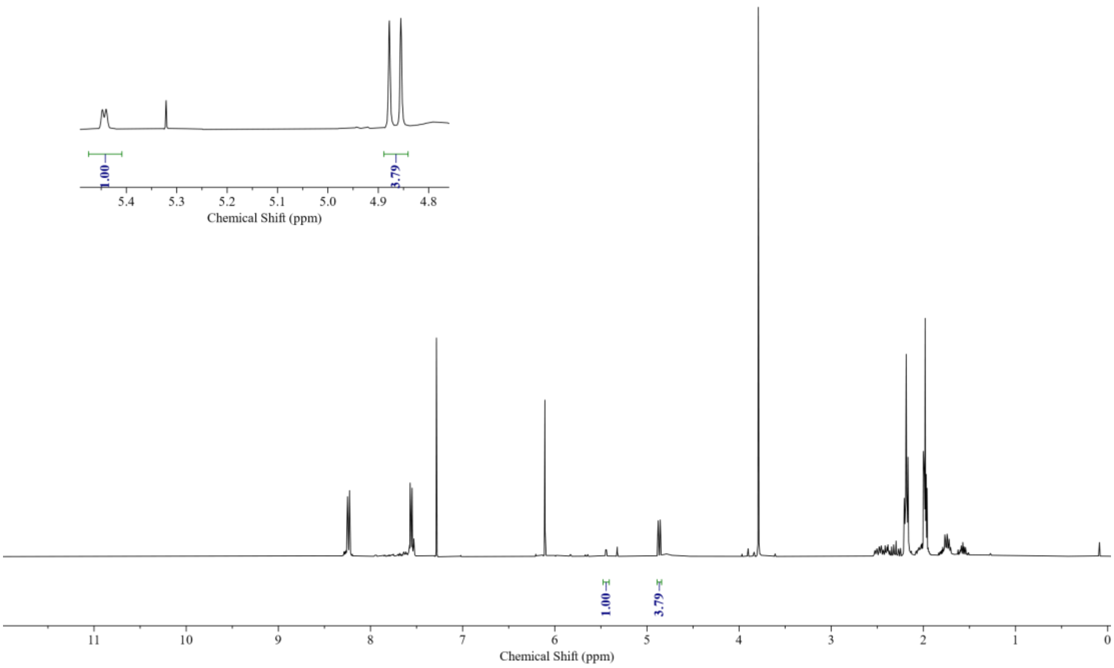


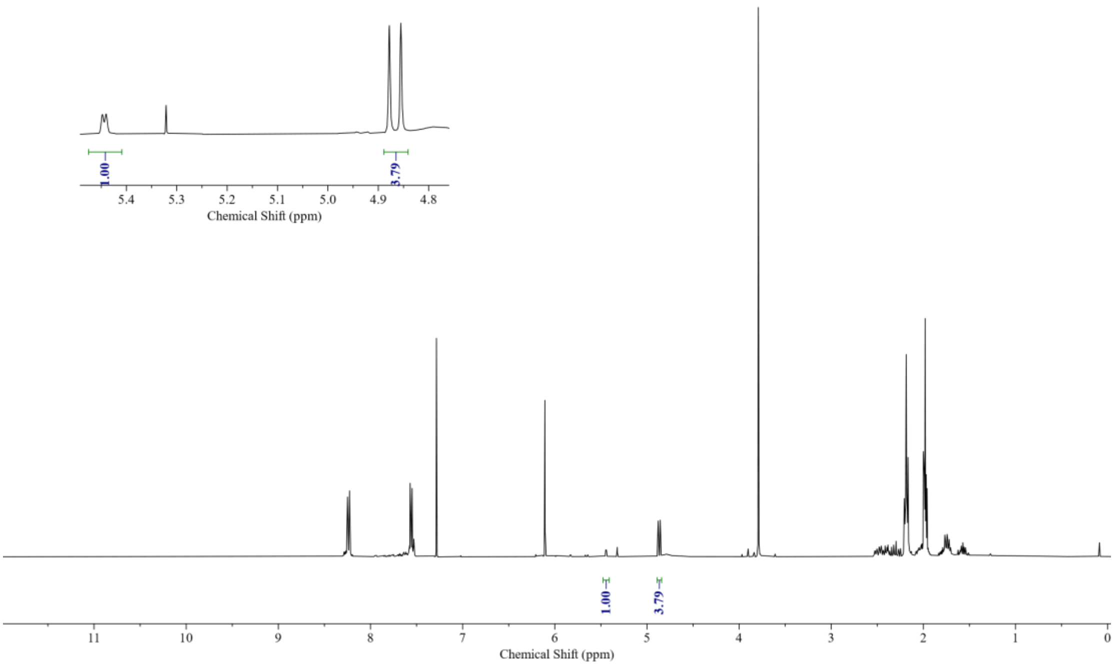
Naphthalen boronic acid



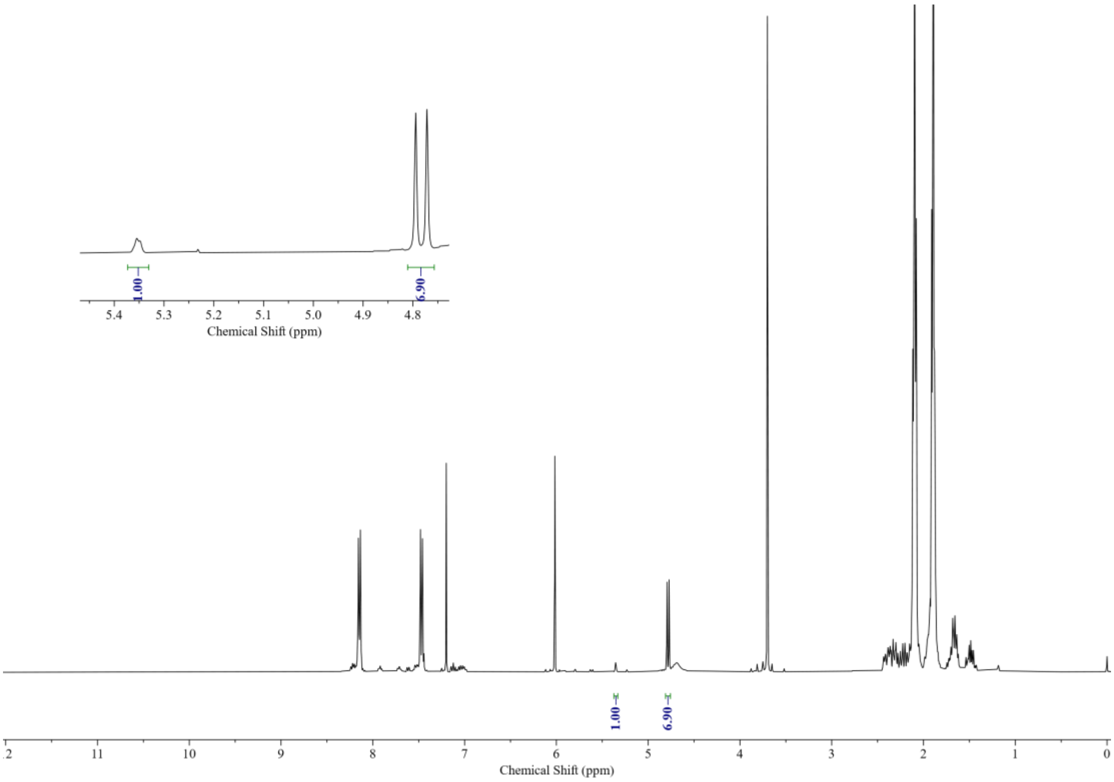


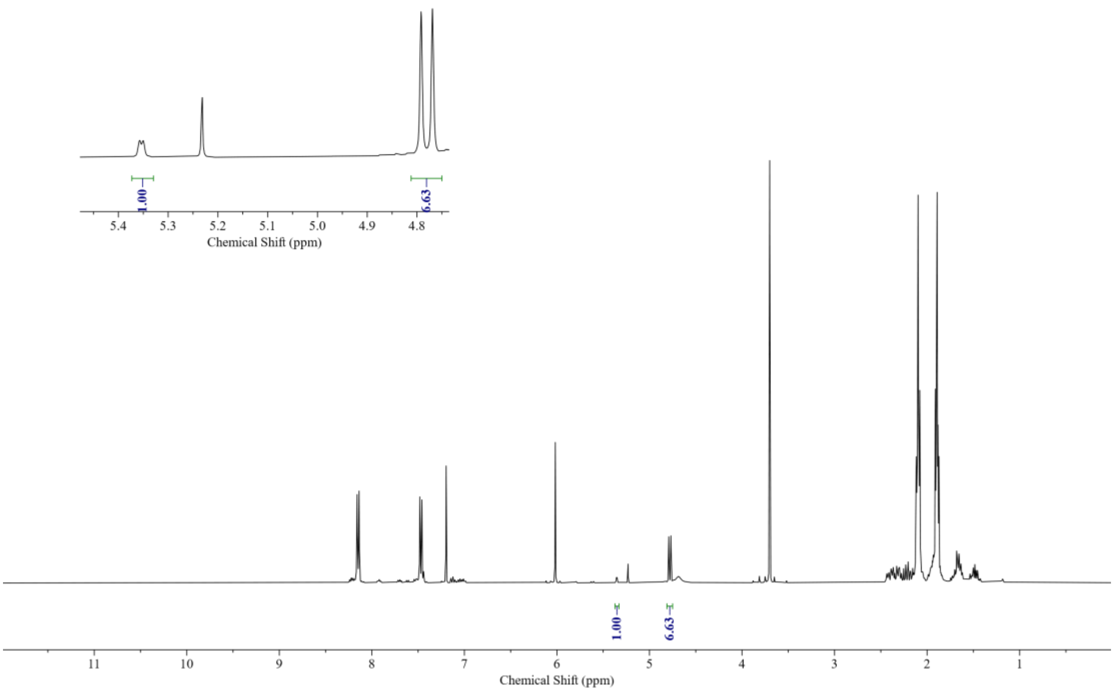
4-CF_3 phenylboronic acid



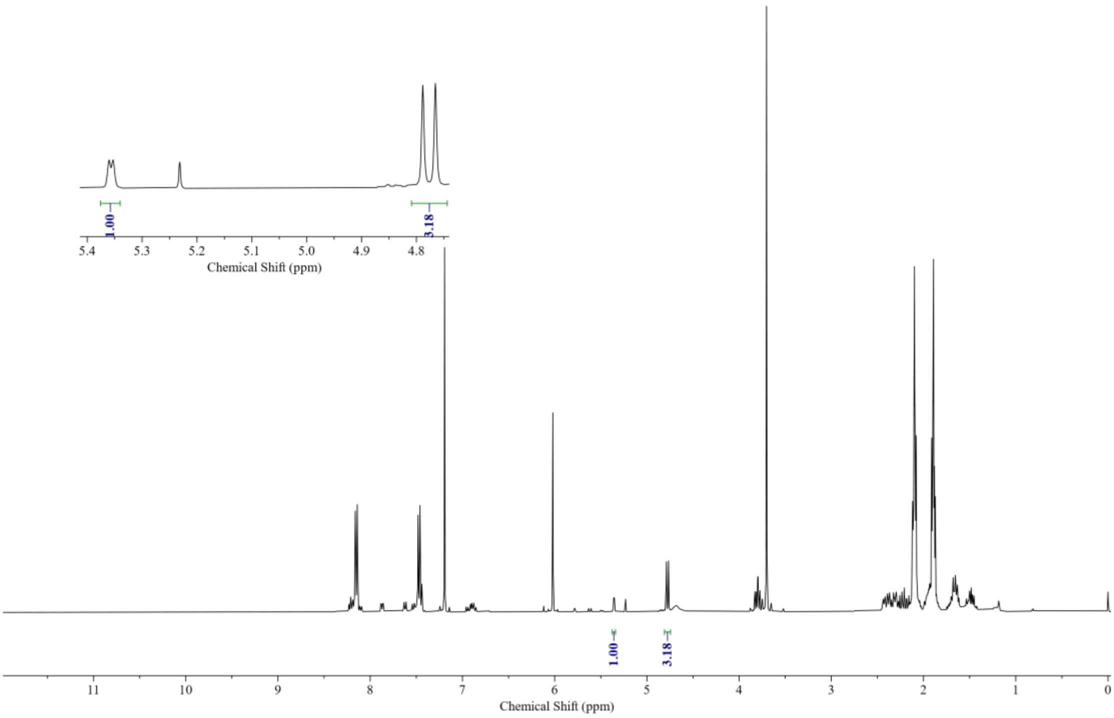


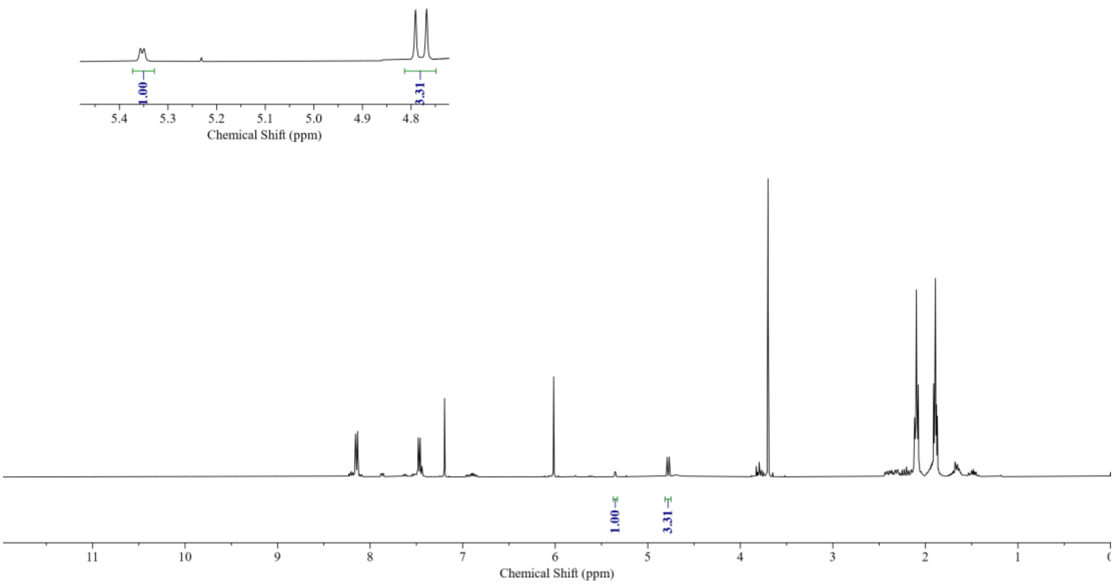
4-F phenylboronic acid



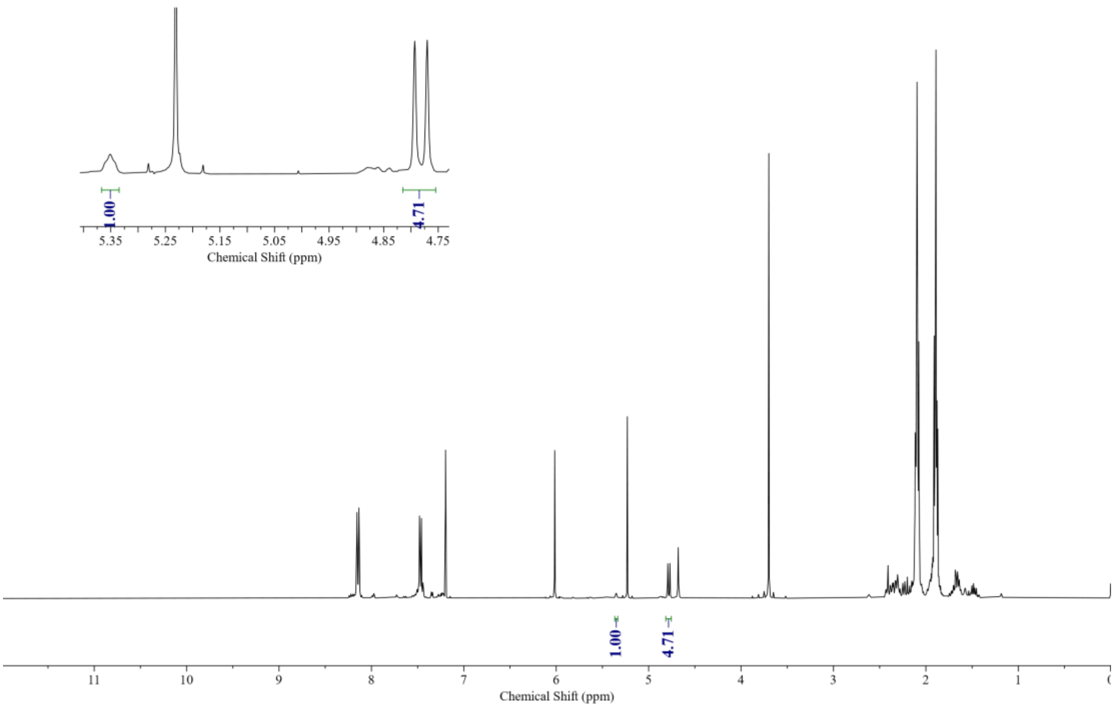


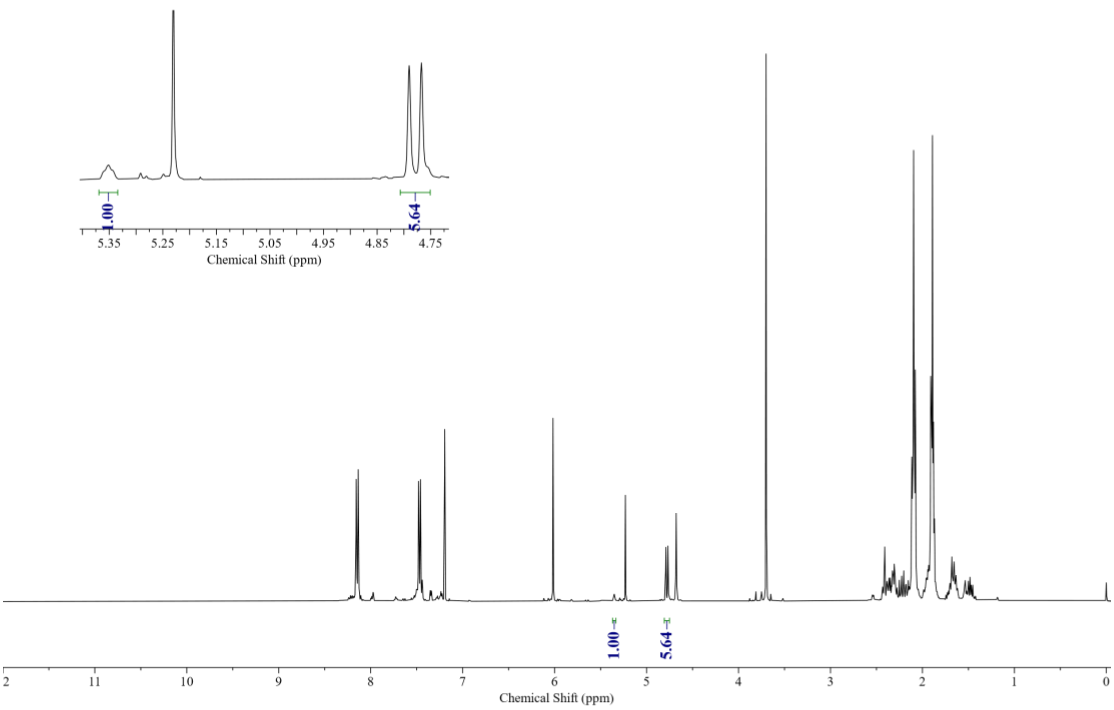
4-OMe phenylboronic acid



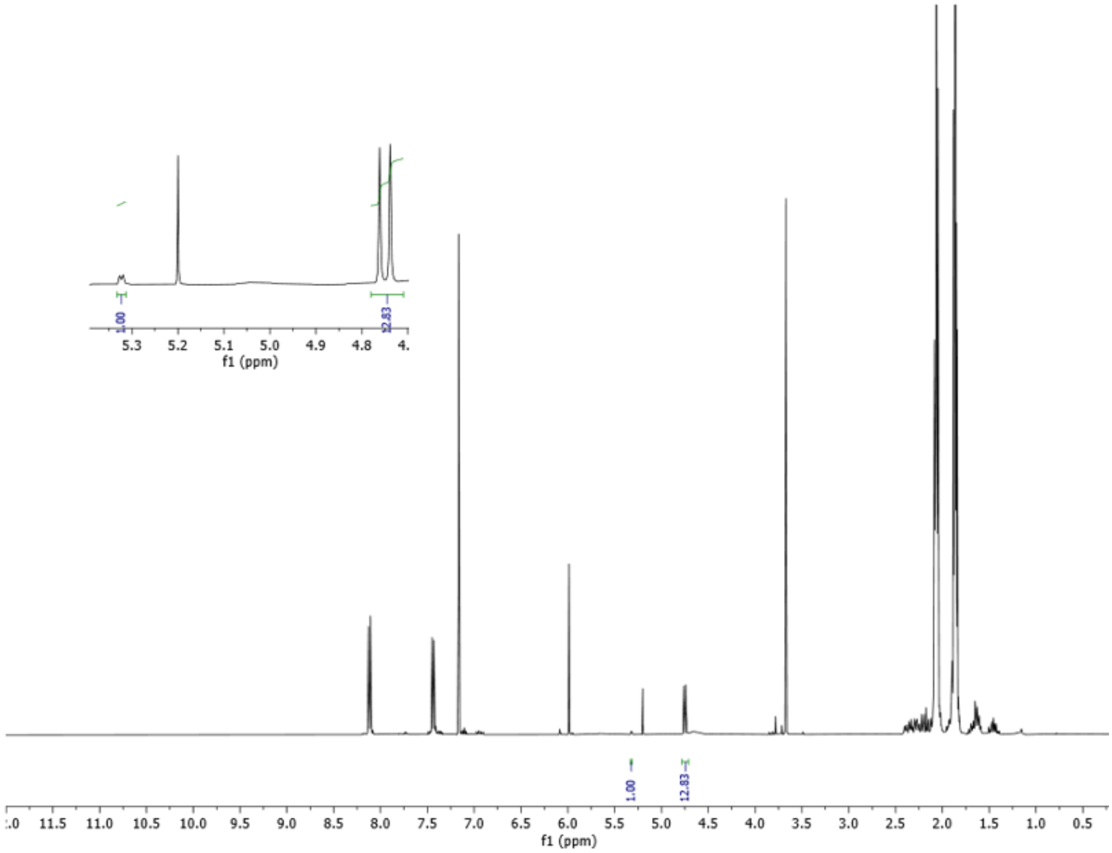


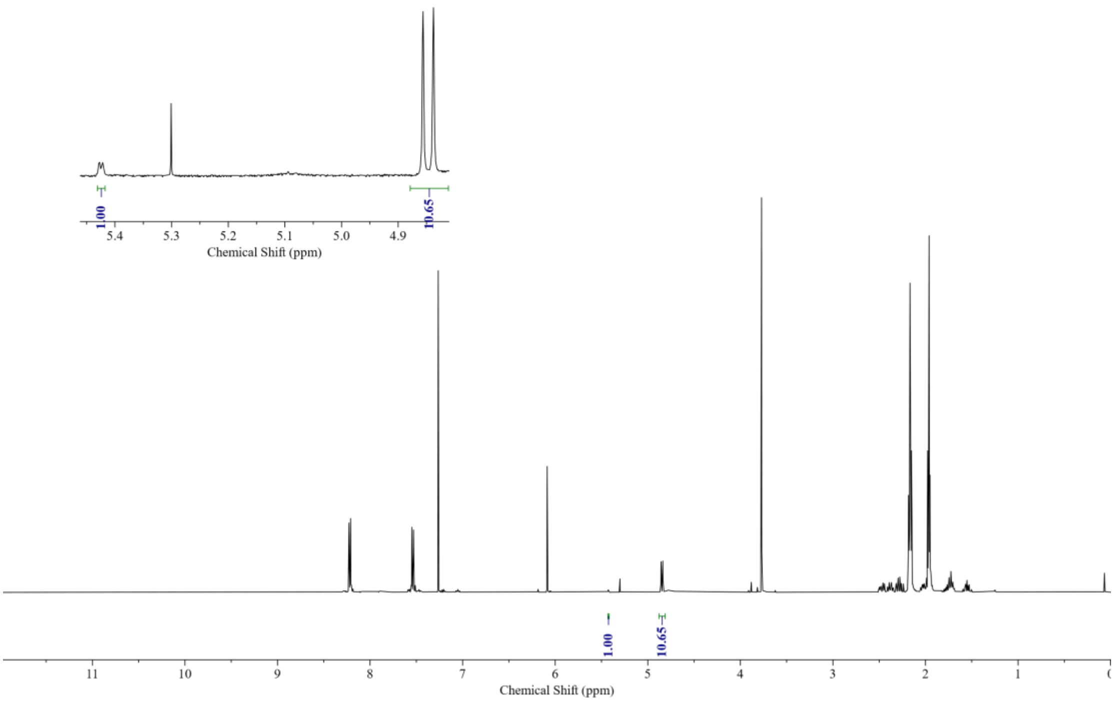
3-Me phenylboronic acid



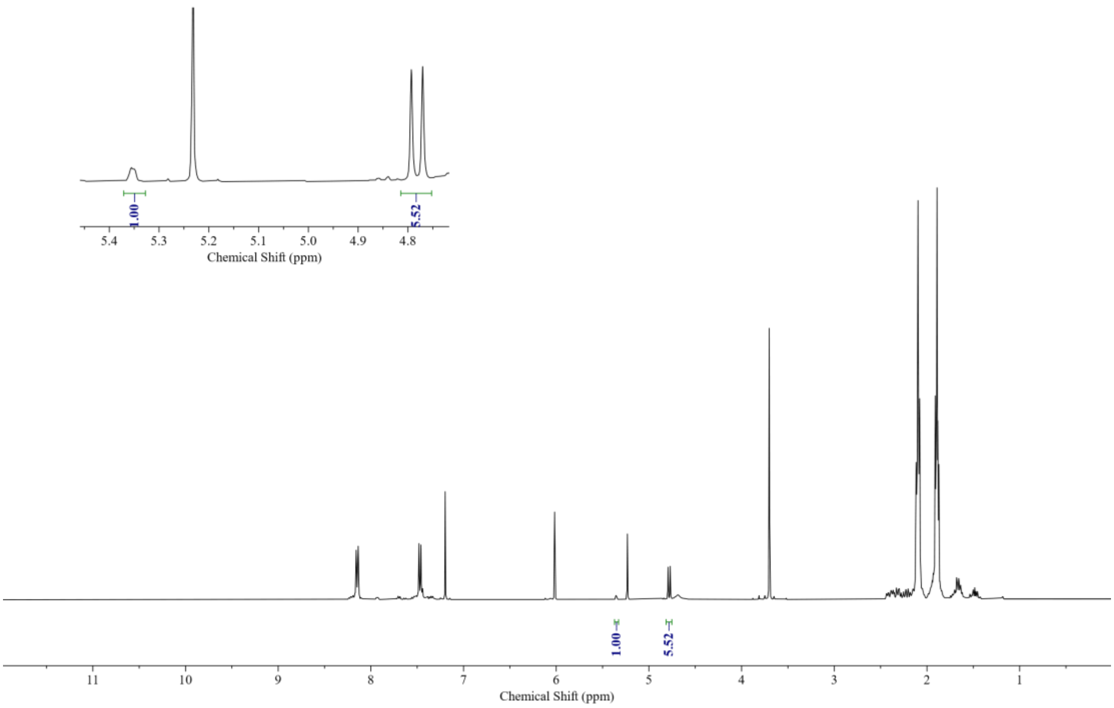


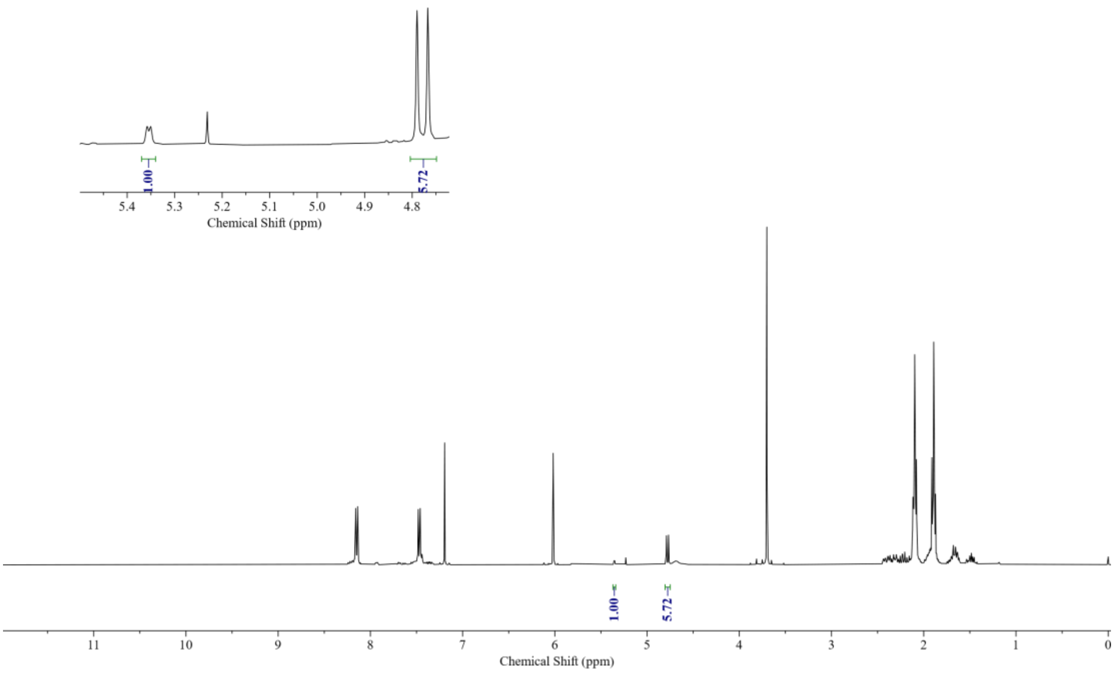
2-F phenylboronic acid



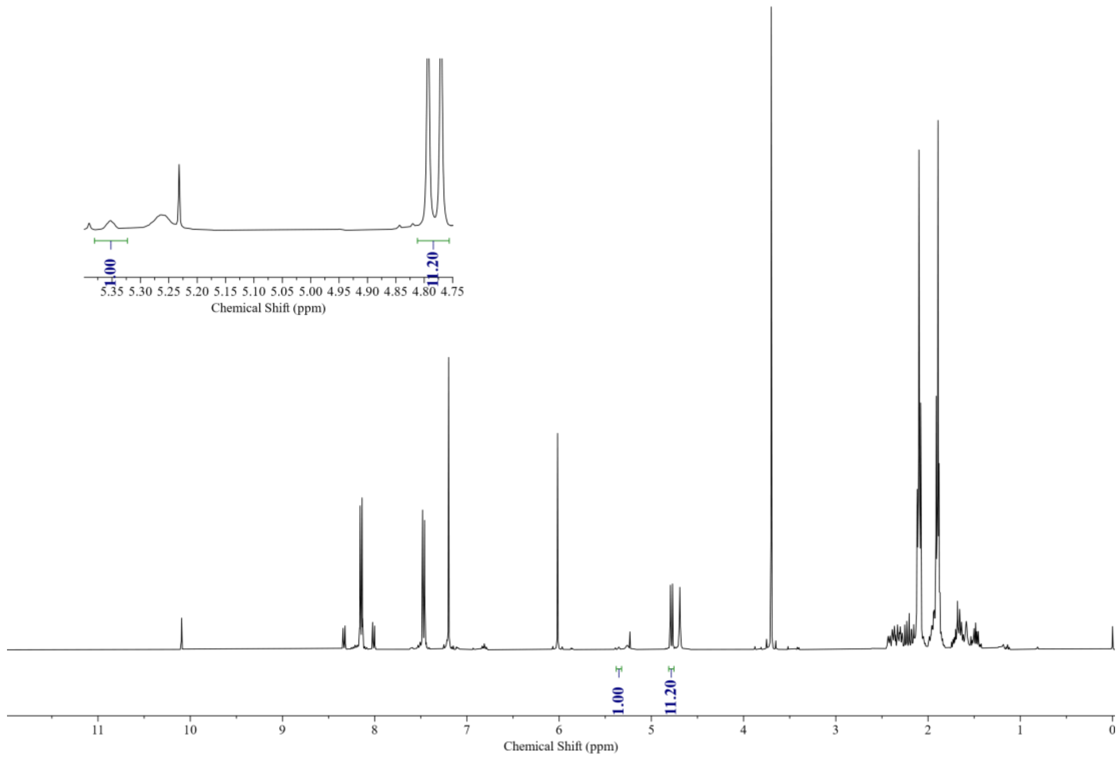


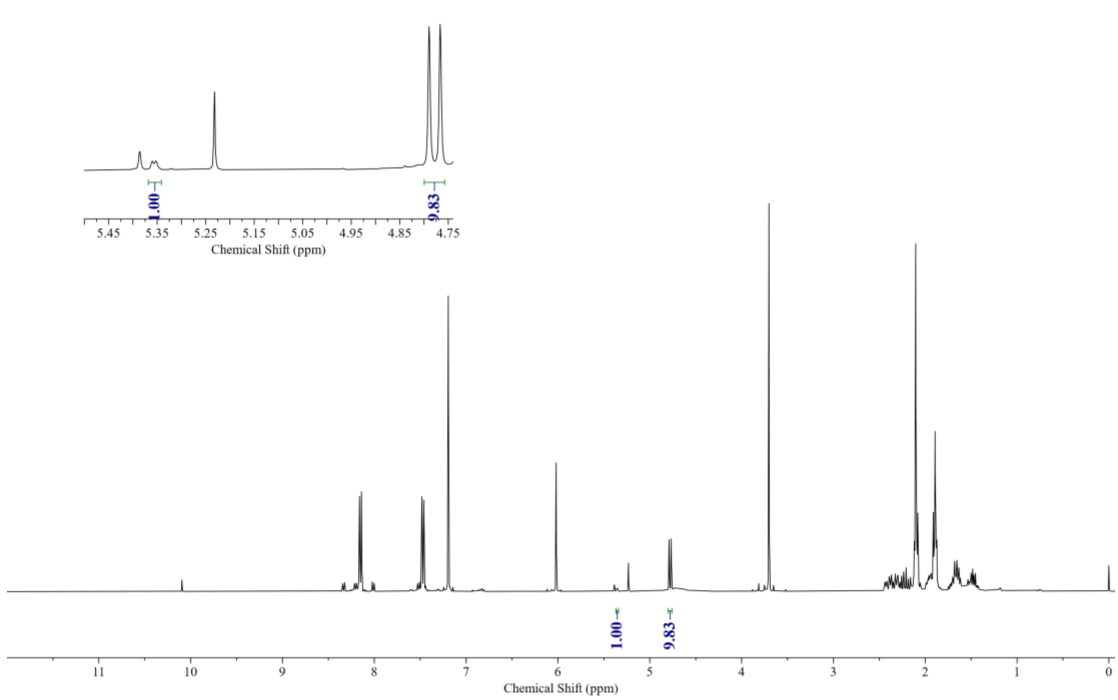
Phenylboronic acid



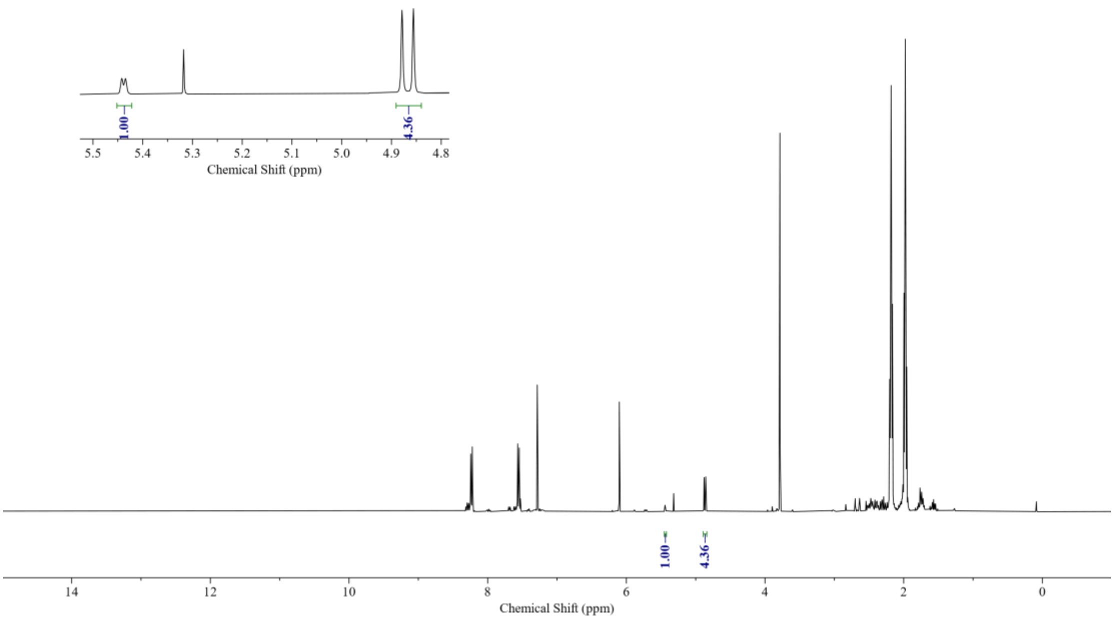


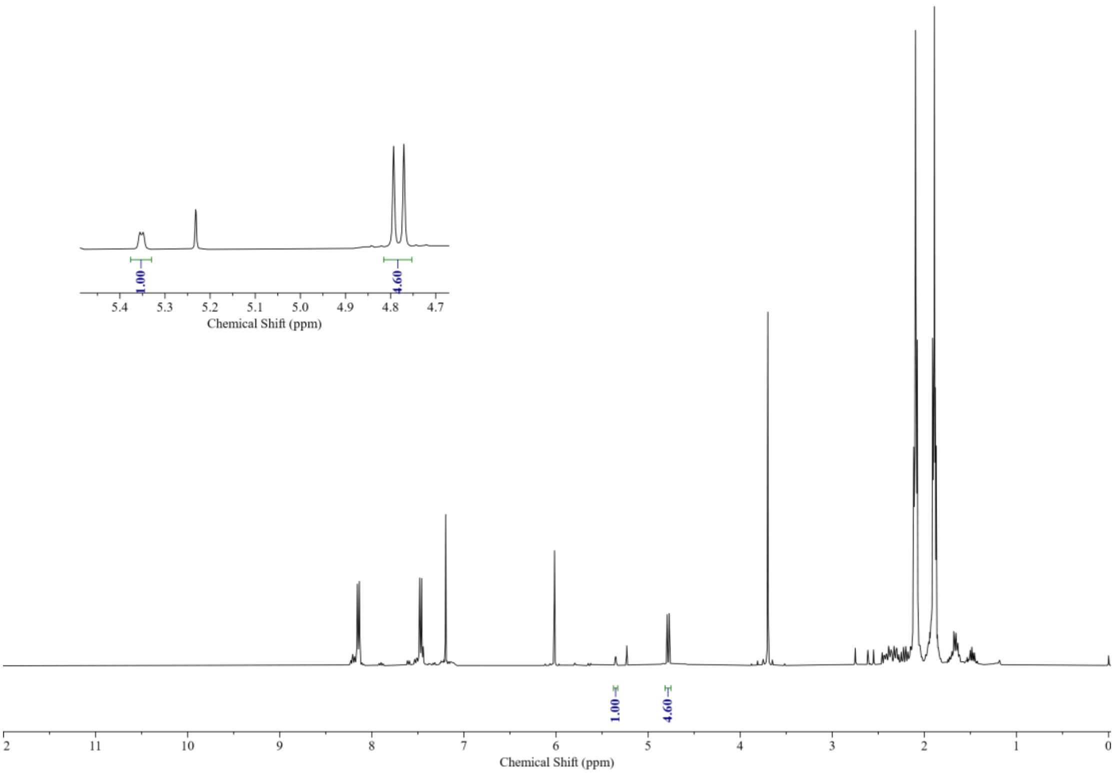
3,5-F phenylboronic acid





2-Me phenylboronic acid





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