A Robust Heterogeneous Chiral Phosphoric Acid Enables Multi Decagram Scale Production of Optically Active N,S-Ketals

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General Experimental Information

All solvents and chemicals were obtained from typical commercial vendors and were used as received, without any further purification.

When required, column chromatographic purification was performed by using a Biotage Isolera automated flash chromatography system with cartridges packed with KP-SIL, 60 Å (32–63 µm particle size). Analytical thin-layer chromatography (TLC) was carried out using Merck silica gel 60 GF254 plates. Compounds were visualized by means of UV or by using KMnO4.

^{1}H, ^{19}F and ^{13}C-NMR spectra were recorded on a Bruker Avance III 300 MHz instrument at room temperature, in CDCl3 as solvent, at 300 MHz and 75 MHz, respectively. Chemical shifts (δ) are reported in ppm relative to the residual solvent peak ($CDCl_3$, ^{1}H: 7.26 ppm; ^{13}C: 77.16 ppm). Coupling constants are reported in Hertz. Multiplicity is reported with the usual abbreviations.

Analytical HPLC analysis was carried out on a C18 reversed-phase (RP) analytical column (150 × 4.6 mm, particle size 5 mm) at 37 °C by using mobile phases A [water/acetonitrile 90:10 (v/v) + 0.1% TFA] and B (acetonitrile + 0.1% TFA) at a flow rate of 1.5 mL/min. The following gradient was applied: Linear increase from 3% solution B to 5% B over 3 min, linear increase from 5% B to 30% B over 4 min, linear increase from 30% B to 100% B over 3 min, hold at 100% B for 2 min, linear decrease from 100% B to 3% B over 0.5 min, hold at 3% B for 2.5 min.

Chiral HPLC analysis was performed on a Shimadzu HPLC system (DGU-403 degassing unit, CTO-40S column oven, CBM20 system controller, SPD-40 UV-VIS detector, LC-20AT pumps).

Optical rotation was measured in $CHCl_3$ (HPLC-grade) at 25 °C against the sodium D-line (λ= 589 nm) on a Perkin Elmer Polarimeter 341 using a 10-cm pathlength cell. The specific rotation was calculated with the following equation, where T is the temperature in °C, D is the sodium D-line emission, α is the angle of rotation, c is the concentration of the solution in g per 100 mL and d is the length of the polarimeter tube in dm (here 1 dm). The given data was calculated as the average of three measurements.

$$[\alpha]_D^T = \frac{100 \times \alpha}{c \times d}$$

The absolute configuration was determined by comparison of the optical rotation for compound **3a**, and the absolute configurations of other compounds were assigned by analogy.[S1]

High-resolution mass spectra were recorded in either negative or positive mode on an Agilent 6230 TOF LC/MS (G6230B) by flow injections on an Agilent 1260 Infinity Series HPLC (HiP Degasser G4225A, Binary Pump G1312B, ALS Autosampler G1329B, TCC Column thermostat G1316A, DAD Detector G4212B).

Equipment for the continuous flow reactions was assembled using commercially available components. Liquid streams were pumped by using Syrris® Asia syringe pumps. Reaction coils were heated by means of a conventional oil bath. Reagent feeds were either streamed directly or by using injection valves and sample loops. Sample loops and reactor coils were made by using perfluoroalkoxy alkane (PFA) tubings (1/16" OD, 0.80 mm ID or 1/8" OD, 1.58 mm ID). Details of reaction setups as well as general procedures can be found in the following sections.

Infrared spectra (IR) were taken in a Bruker Alpha spectrometer with an ATR unit.

PS-TRIP samples were imaged on a Zeiss Gemini DSM982 field-emission scanning electron microscope at the University of Graz, Department of Earth Sciences, NAWI Graz Geocenter.

For SEM imaging, aliquots of **PS-TRIP** were transferred to an standard aluminium SEM stub using conductive graphite tape and coated with C/Pt (0.5 nm and 3 nm, respectively) using a Leica EM ACE600 Sputtercoater. Samples were imaged using combined external and in-lens secondary electron (SE) detectors. The detector signals were dynamically combined to increase structural resolution using the DISS5 SEM software (point electronic GmbH).

Elemental analysis was perfomed using a EDWIN energy-dispersive X-ray spectroscope (EDS; RÖNTEC GmbH), using 10kV acceleration voltage. Peak identification was performed using the RÖNTEC WinShell und WinTool software (RÖNTEC GmbH).

Reactor design

The design was performed with Autodesk Fusion-360. All the units are shown in mm. All the parts were cut from PTFE pieces. 1.5 mm OD / 0.8 mm ID tubes were connected into the bottom part with cyanoacrylate glue. Once the catalyst was filled into the packed bed reactor, it was covered with glass wool to prevent the catalyst beads to clog the outlet.

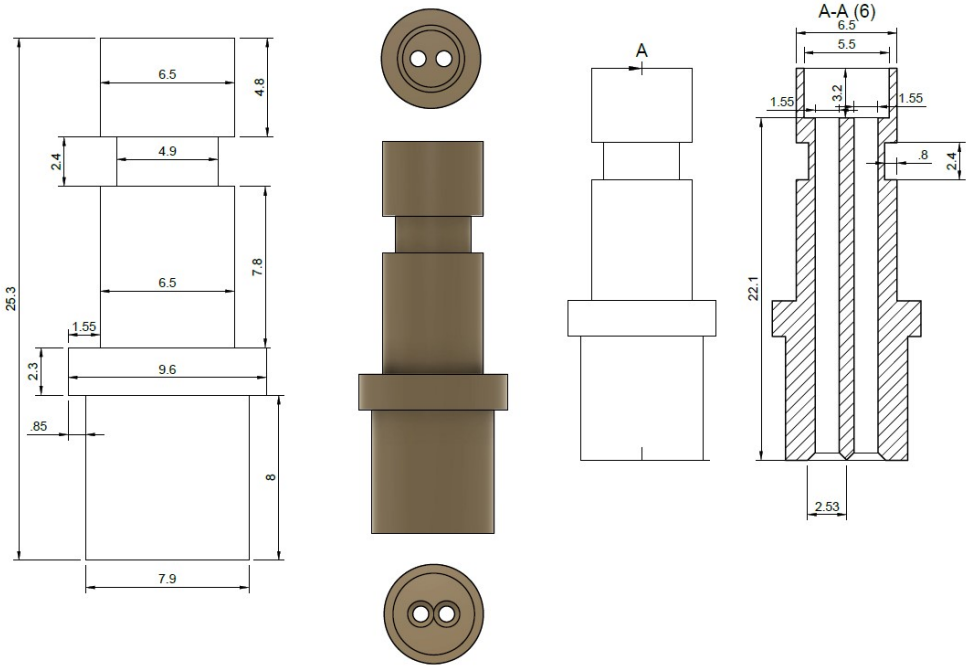


Figure S1. Bottom conector.

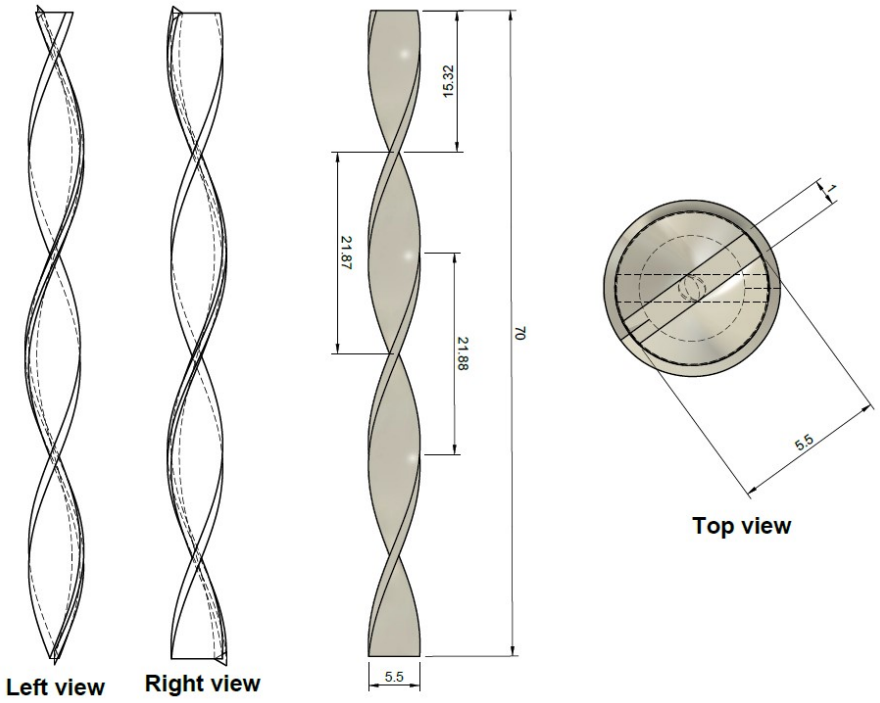


Figure S2. Spiral mixer.

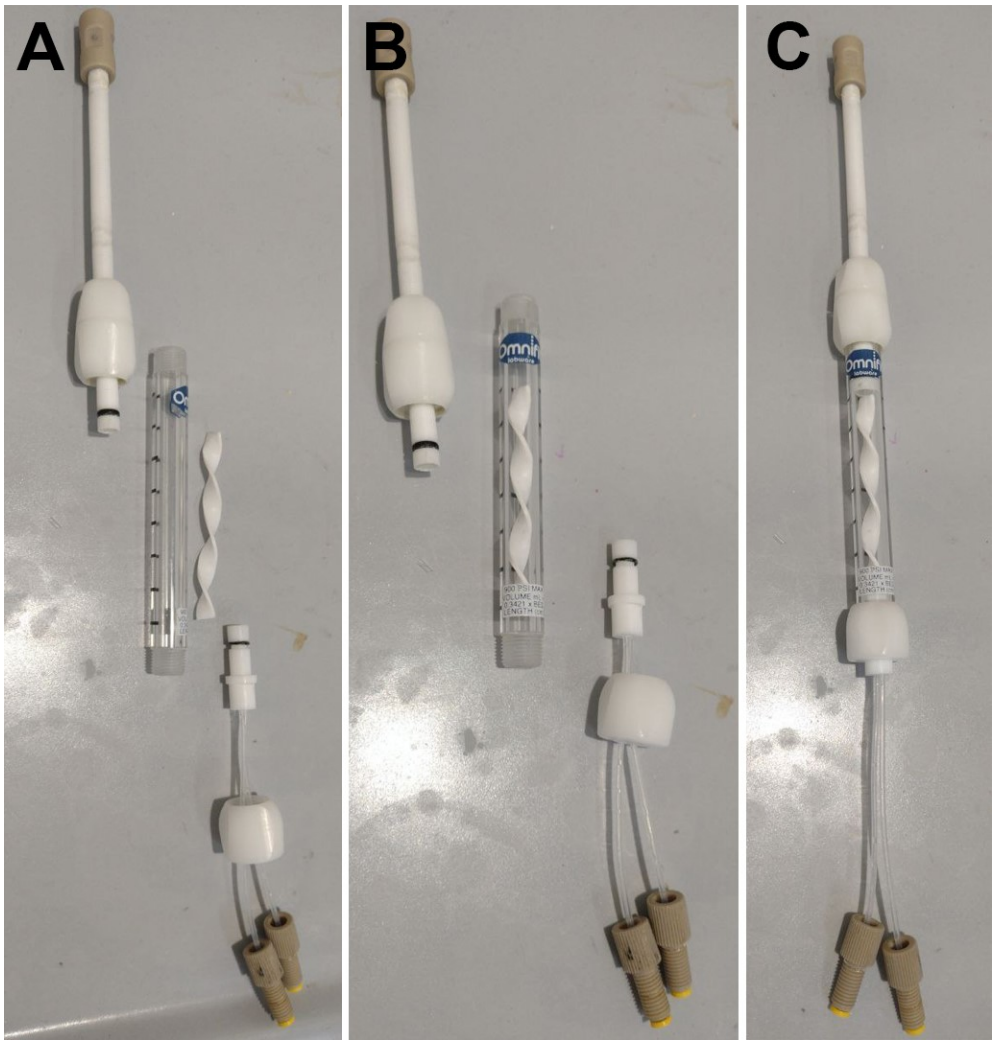
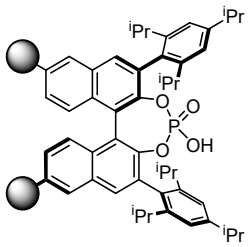


Figure S3. *Reactor assembly:* ***A)*** *Fully disassembled.* ***B)*** *Mixer inside the glass column.* ***C)*** *Fully assembled.*

Synthesis and characterization of PS-TRIP catalyst



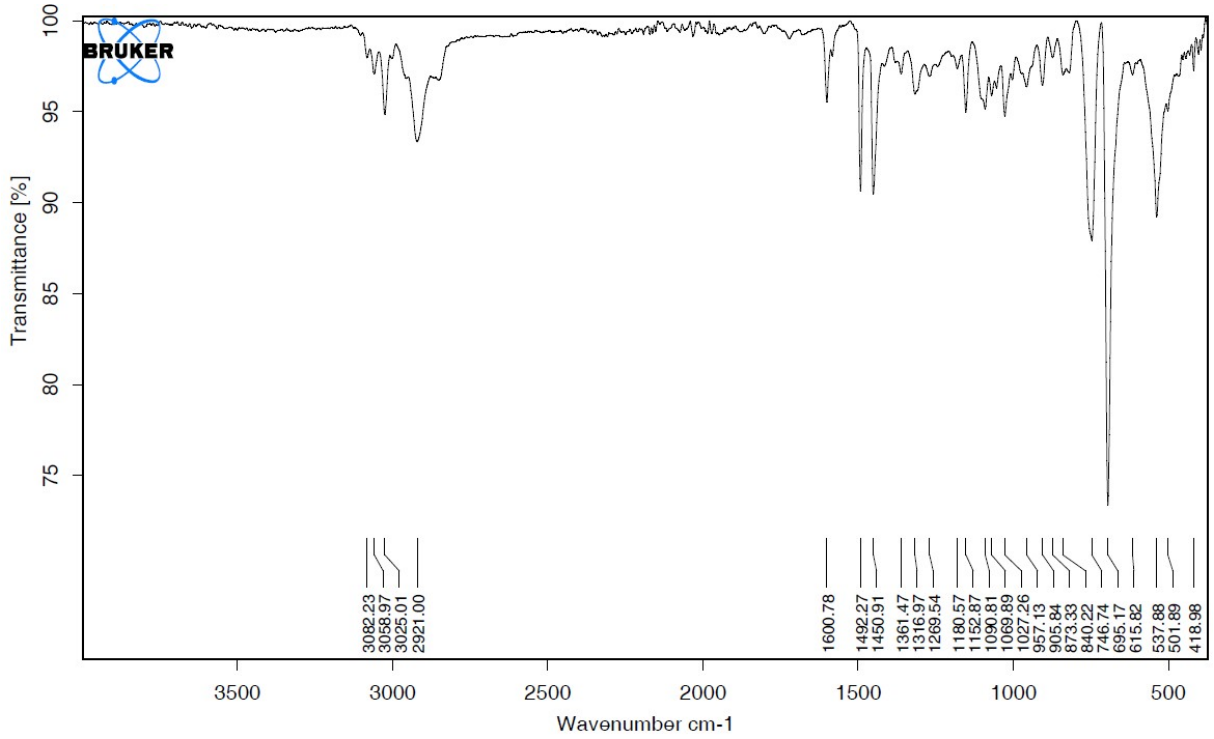
The synthesis of **PS-TRIP** catalysts was performed following Pericàs´s procedure. [S2, S3]
The catalyst loading of the resin was calculated based on the P elemental analysis by using the following formula:

$$f\left(\frac{mmol}{g}\right) = \frac{\%P\ x\ 1000}{number\ of\ P\ atoms\ x\ MW(P) x\ 100}$$

Elem. Anal. P: 0.48%.
f = 0.15 mmol/g

IR

As prepared catalyst



Used catalyst

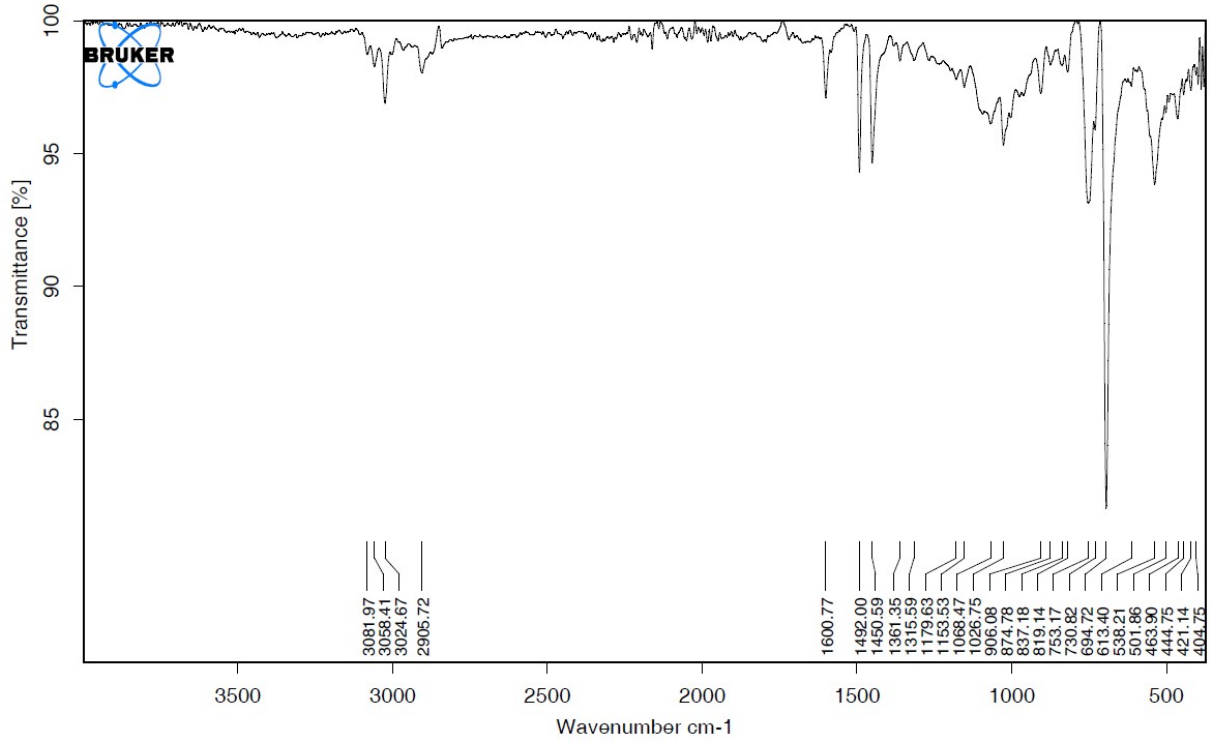


Figure S4. *IR of as prepared and used PS-TRIP catalyst.*

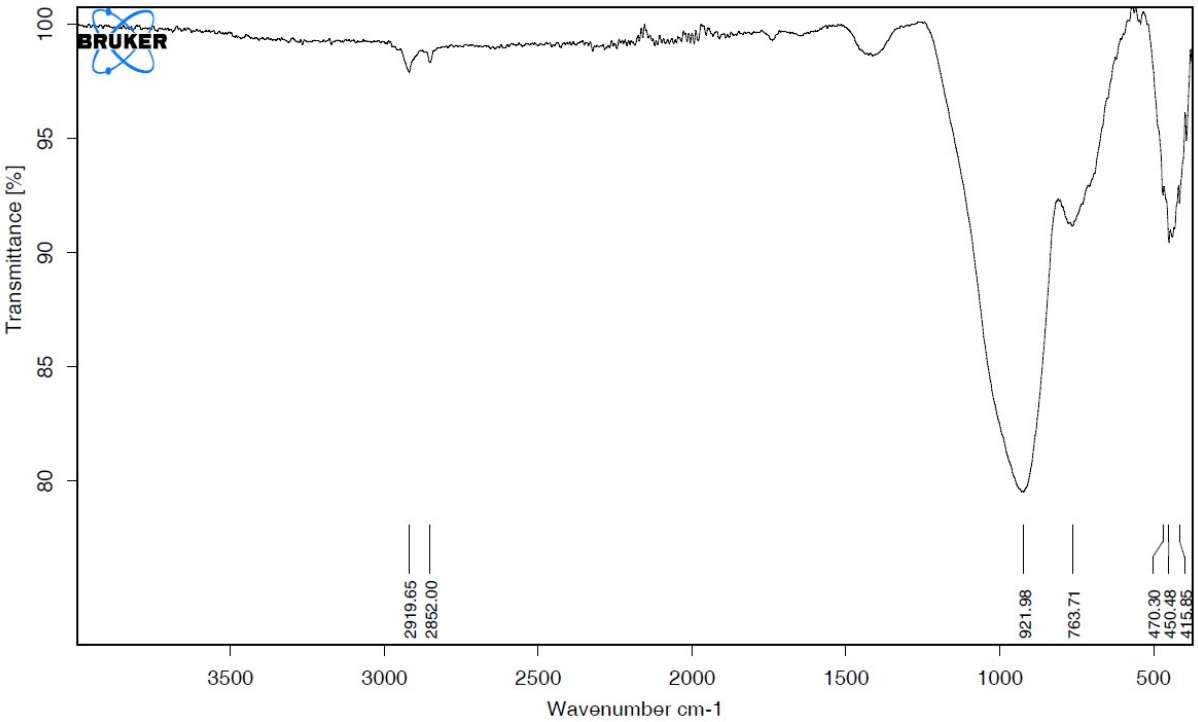
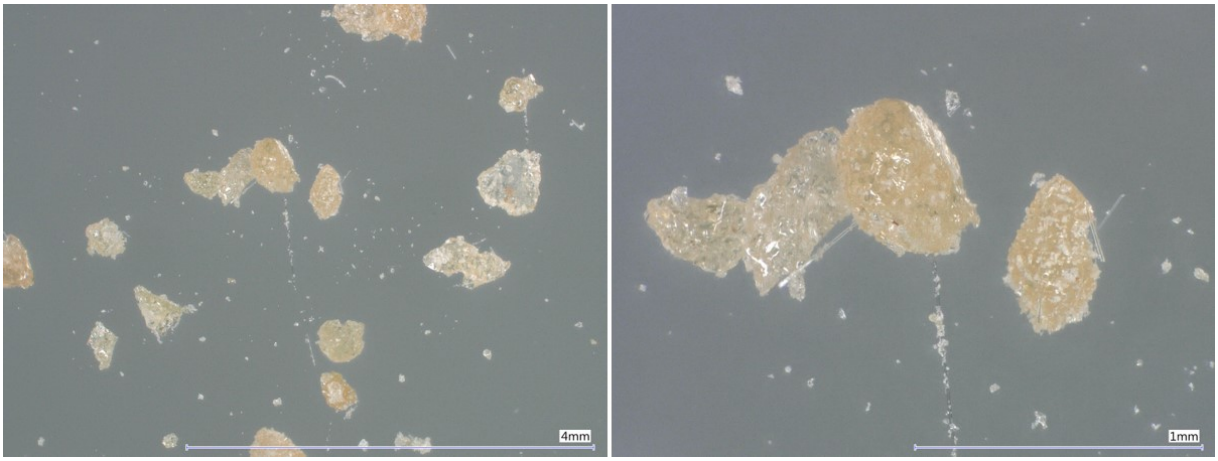


Figure S5. Reference IR of the glass wool.

Optical microscopy

As prepared catalyst



Used catalyst

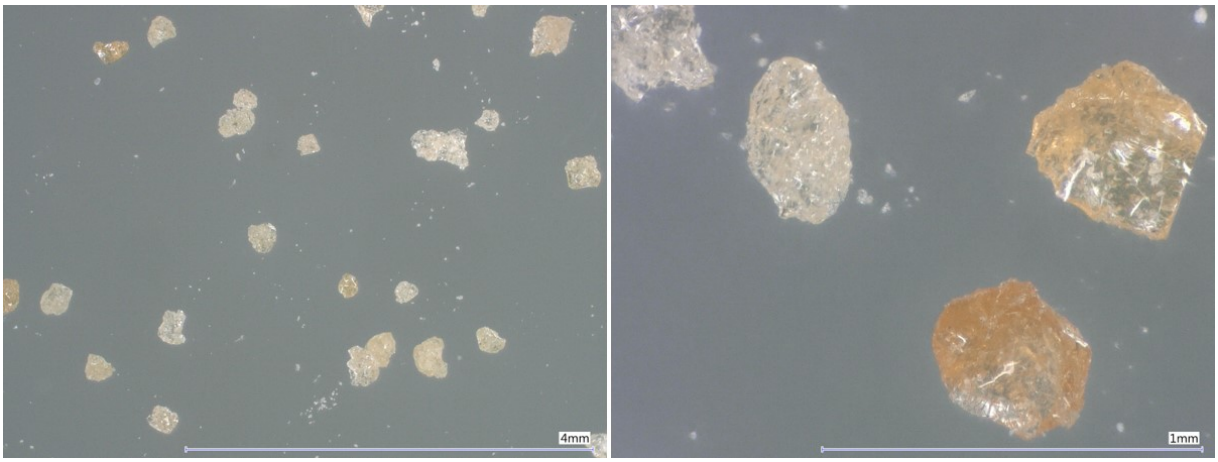


Figure S6. *Optical microscopy of as prepared and used PS-TRIP catalyst.*

SEM

As prepared catalyst

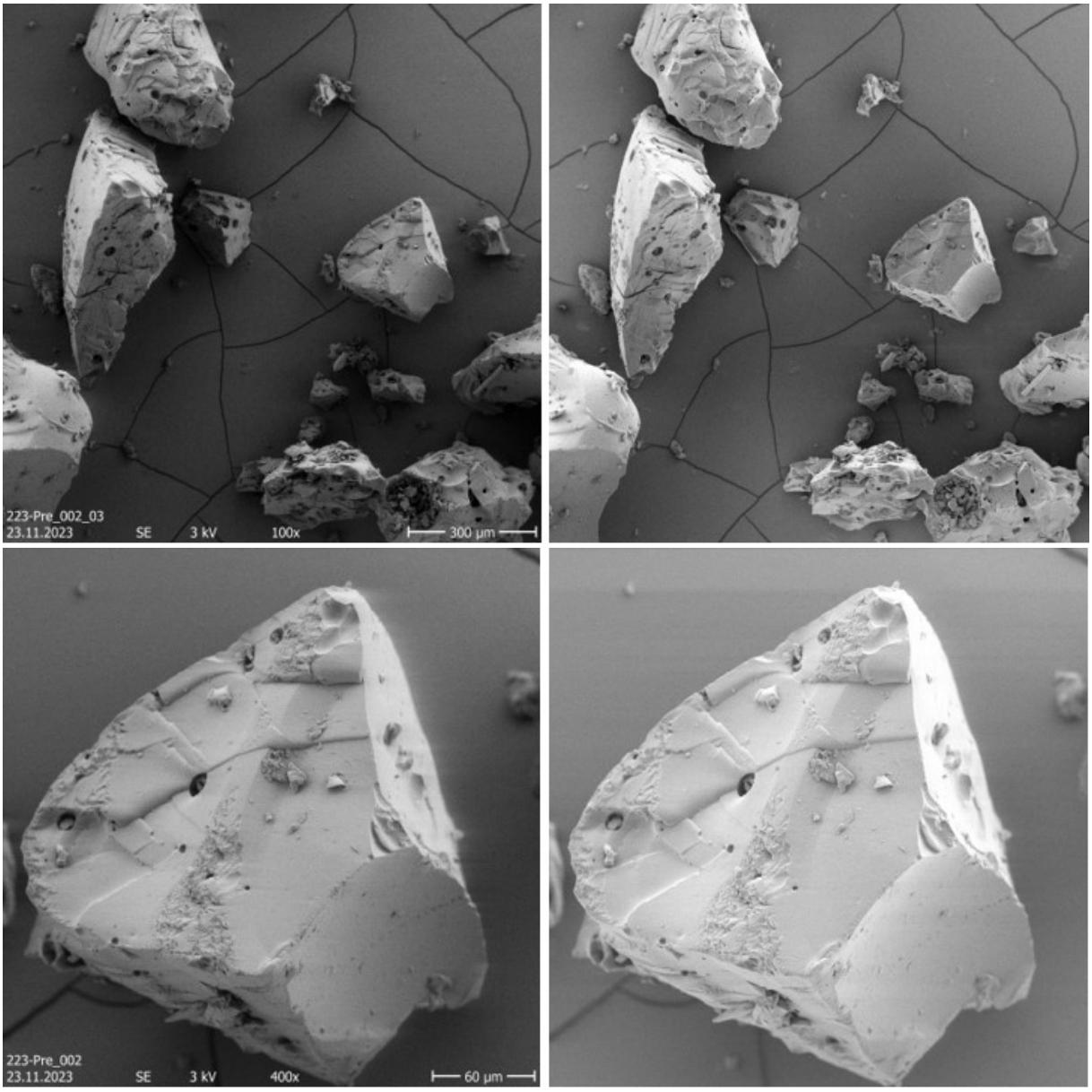


Figure S7.1 *SEM of as prepared PS-TRIP catalyst.*

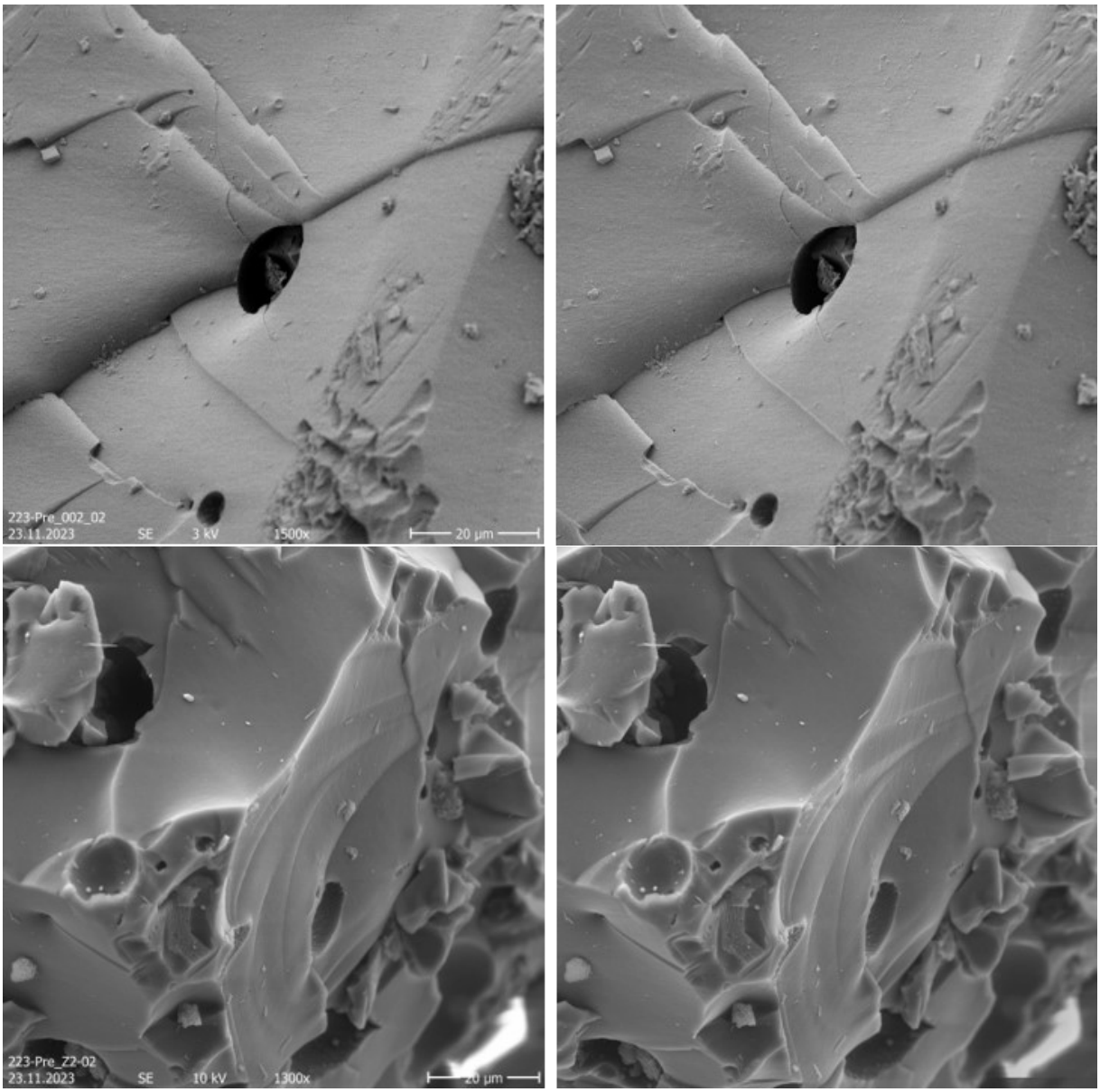


Figure S7.2 *SEM of as prepared PS-TRIP catalyst.*

Used catalyst

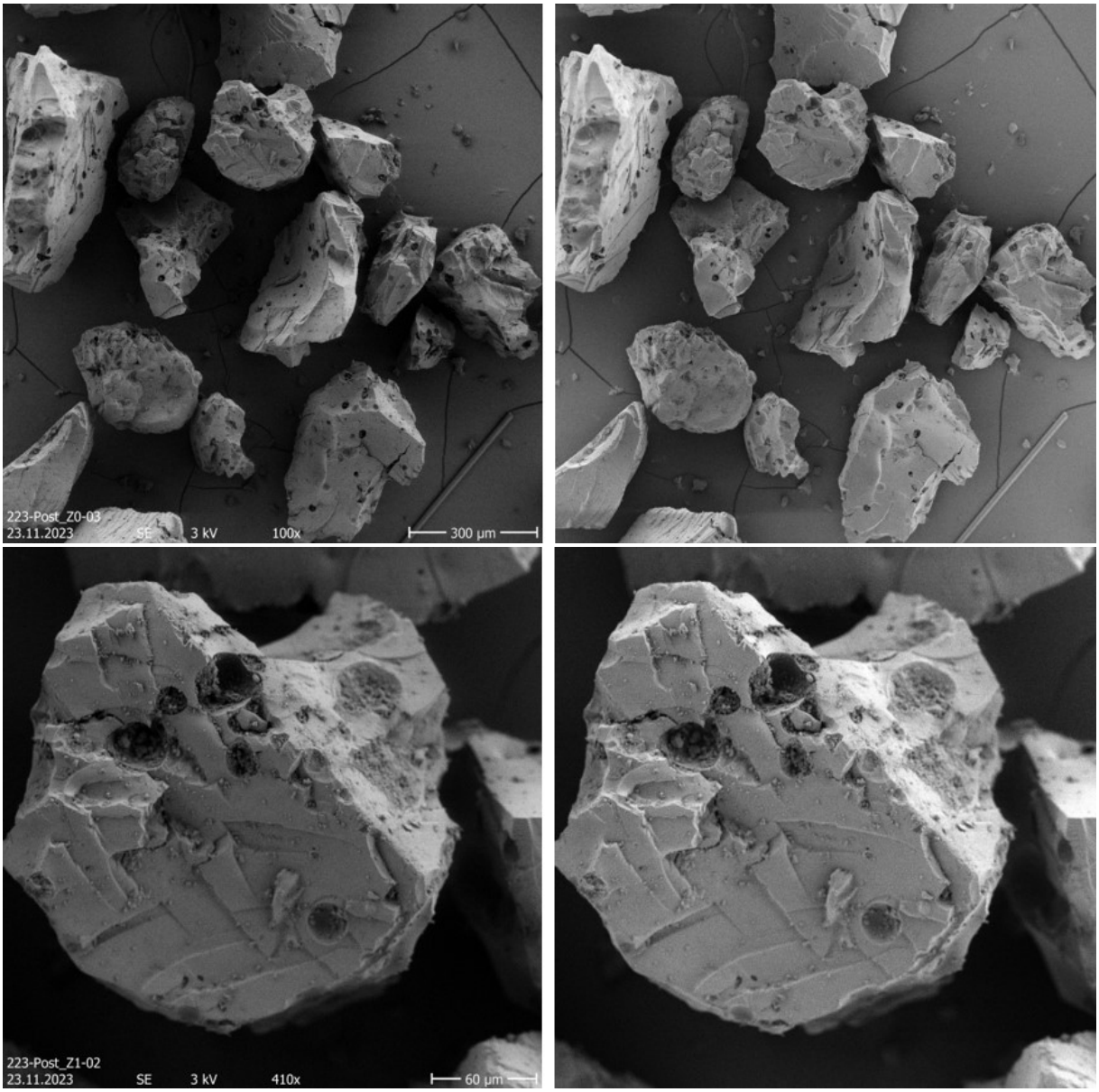


Figure S8.1 *SEM of used PS-TRIP catalyst.*

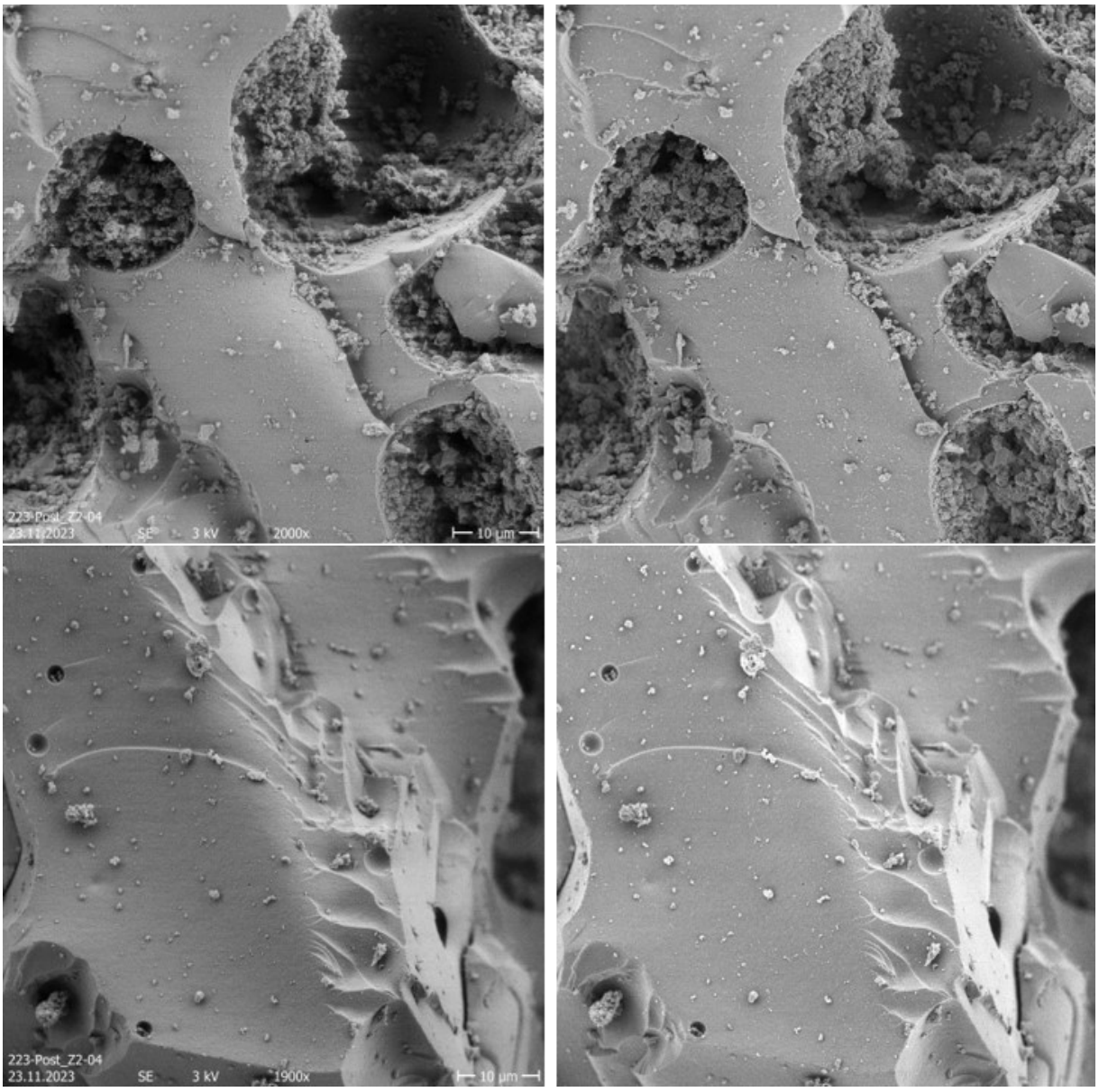


Figure S8.2 *SEM of used PS-TRIP catalyst.*

SEM-EDX

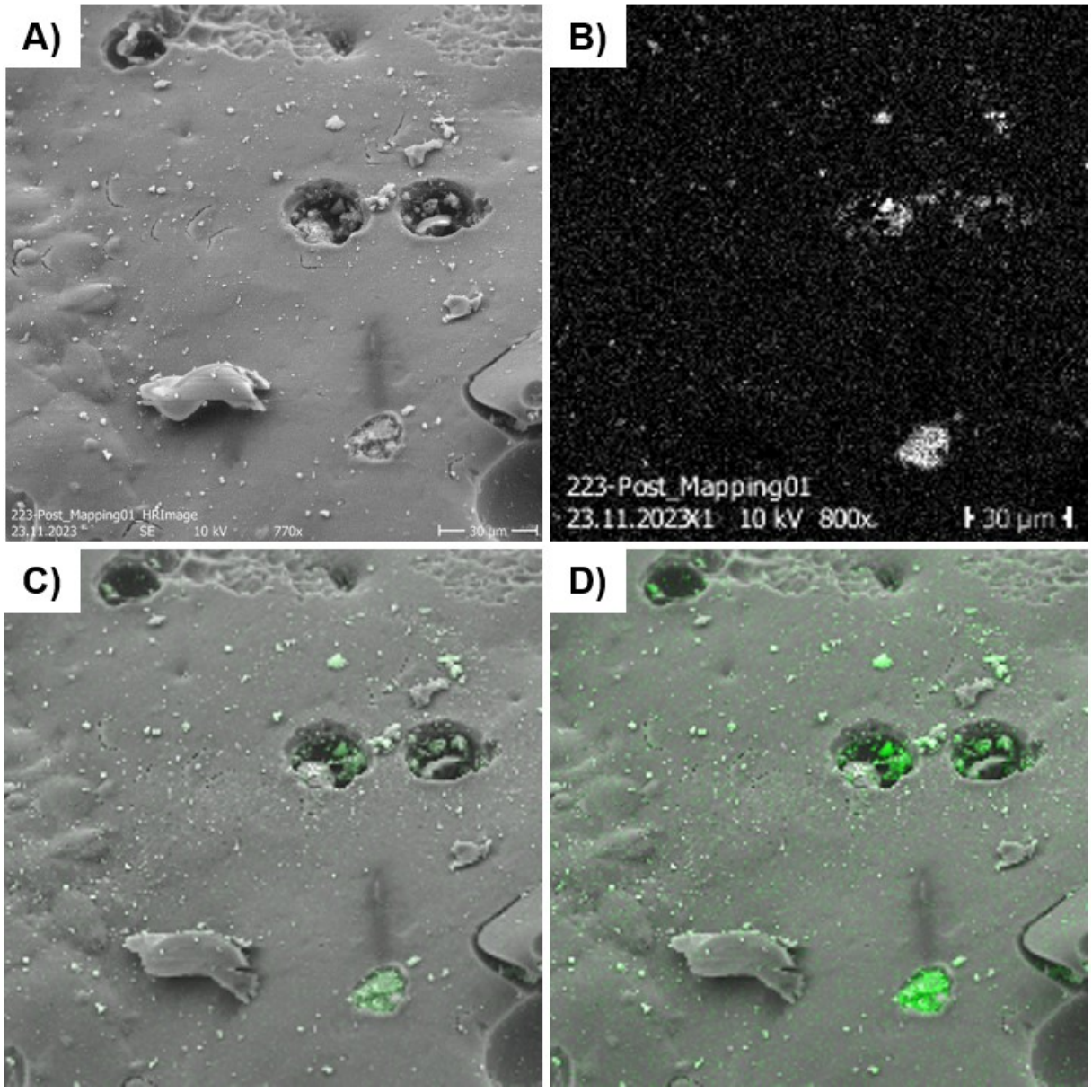


Figure S9. A) *SEM picture of the used PS-TRIP catalyst.* ***B)*** *SEM-EDX.* ***C)*** *Overlapped pictures, Si-containing particles are highlighted in green.* ***D)*** *Color saturation of C increased for clear visualization.*

SEM-EDX

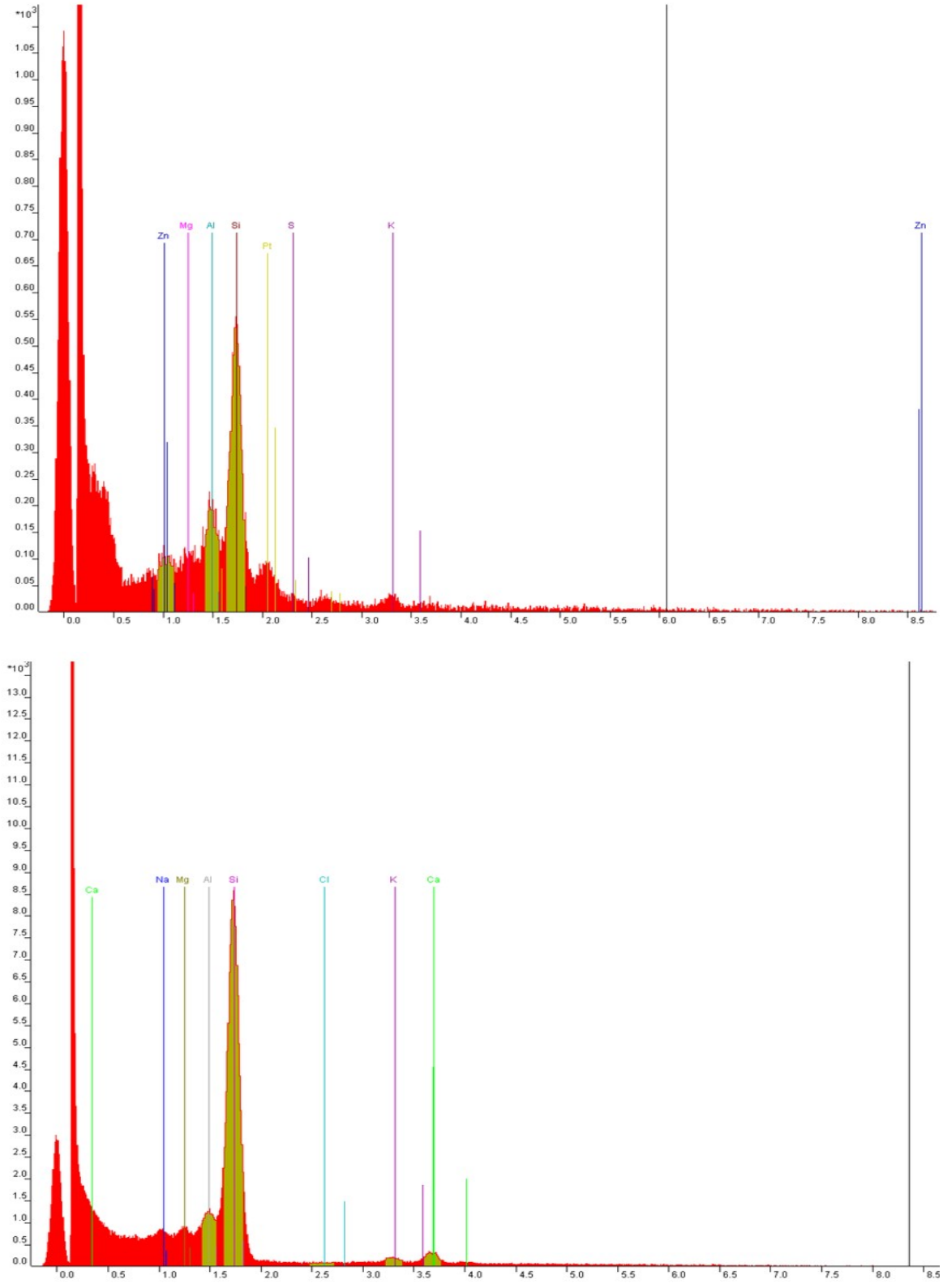
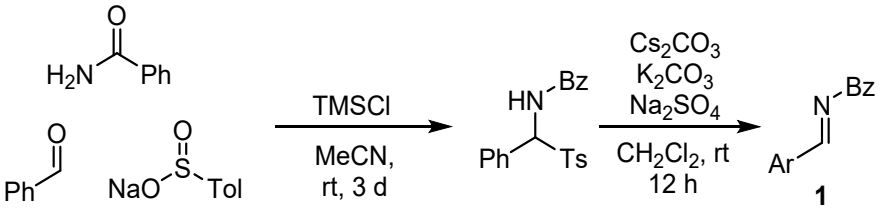


Figure S10. *SEM-EDX element mapping: Deposition of the used PS-TRIP catalyst (Top). Glass wool reference sample (Bottom).*

General procedures for the batch synthesis of 3

General procedure for the synthesis of imine 1:

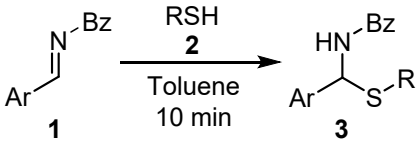


Imine **1** was synthesized at 100 mmol scale by a modified literature procedure:[S4]

Step 1: A 500 mL round-bottomed flask fitted with a dropping funnel and a magnetic stirrer was charged with sodium *p*-toluenesulfinate (26.7 g, 150 mmol, 1.5 equiv.) and benzamide (18.2 g, 150 mmol, 1.5 equiv.). The flask was then charged with acetonitrile (100 mL). To the resulting slurry was added benzaldehyde (10.2 mL, 100 mmol, 1.0 equiv.) in one portion. To this resulting mixture was slowly added TMSCl (25.4 mL, 200 mmol, 2.0 equiv.) using dropping funnel (15-30 min). The reaction was then monitored by TLC until reaction completion (2-3 days). Then, water (150 mL) was added and the resulting suspension was stirred for additional 30 min. The solids were isolated by filtration and the filter cake was washed with additional water (150 mL) and hexane (200 mL). The cake was dried in a vacuum oven at 50 ºC at 1 torr for 12 h to give the product as a fine white solid in quantitative yield.

Step 2: To a 500 mL round bottom flask equipped with a magnetic stir bar was added Cs_2CO_3 (16.3 g, 50 mmol, 0.5 equiv.) K_2CO_3 (34.5 g, 250 mmol, 2.5 equiv.) and Na_2SO_4 (42.6 g, 300 mmol, 3.0 equiv.). It was dried in a vacuum oven at 50 ºC at 1 torr for 12 h and cooled down under nitrogen atmosphere. Then, the α-amido sulfone was added in one portion and suspended in anhydrous CH_2Cl_2 (300 mL). The resulting slurry was vigorously stirred under nitrogen atmosphere for 3-5h and followed by NMR. Once the reaction was complete, the solids were filtered through oven-dried celite under vacuum. Removal of the filtrate in a vacuum provided 18.14 g (86%) of the pure imine as a yellowish liquid, which solidified as a crystaline white solid after 2 h under high vacuum.

General procedure for the synthesis of racemic 3:[S1]



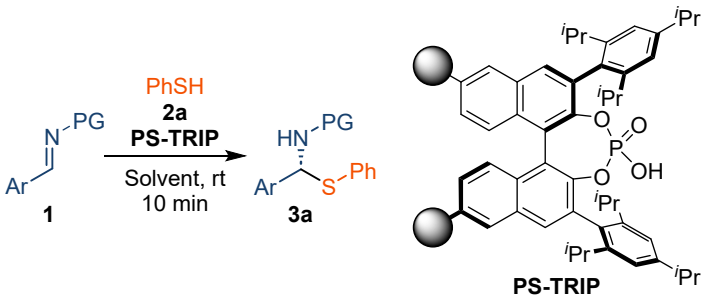
To a solution of imine (1.0 mmol, 1.0 equiv.) in toluene (5.0 mL) was added the corresponding thiol (1.0 mmol, 1.0 equiv.) at room temperature. The reaction was stirred for 10 min and then quenched with 0.25 M NaOCl solution (1.0 mL). The formed precipitate was filtered and washed with distilled water (5 mL) and cyclohexane (5 mL). The cake was dried in a vacuum oven at 50 ºC at 1 torr for 12 h to give the pure product.

Reaction optimization in batch

Imine **1** (20.9 mg, 0.1 mmol, 1.0 equiv.) was dissolved in the corresponding solvent (1.0 mL) and added to a screw-cap vial containing the **PS-TRIP** catalyst (33.3 mg, 0.005 mol, 0.005 equiv.). To the resulting mixture was added thiophenol **2a** (12.3 µL, 0.12 mmol, 1.2 equiv.) at room temperature. The reaction was shaken for 10 min and then filtered, diluted in iPrOH and analyzed by HPLC.

The reaction was analyzed in several solvents to obtain the optimal ratio of enantioselecitvity and solubility. Fast precipitation of the reaction product in the reaction mixture would make the process unsuitable in flow.

Table S1. *Solvent optimization in batch (solubility test).*



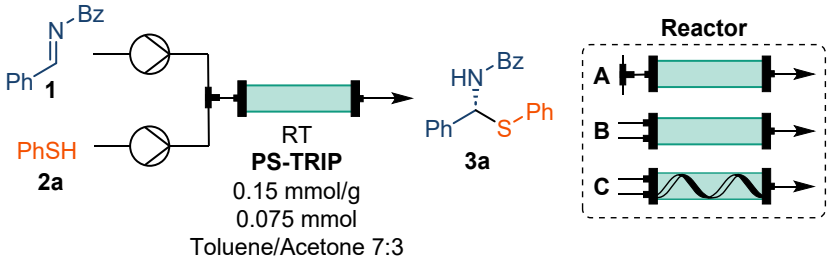
Entry	Solvent	Conv. (%)[a]	ee (%)[b]	Notes
1	Toluene	>98	94	Product precipitation
2	CHCl3	>98	0	Soluble
3	DMSO	>98	0	Soluble
4	Acetone	>98	10	Soluble
5	MeCN	>98	10	Product precipitation
6	MTBE	>98	0	Product precipitation
7	Tol/Acetone 9:1	>98	93	Product precipitation
8	Tol/Acetone 7:3	>98	91	Soluble
9	Tol/Acetone 1:1	>98	87	Soluble

a) Conversion was determined by HPLC Area %.
b) ee was determined by chiral HPLC.

Reaction optimization in flow

Prior to the reactions, the system was filled with toluene/acetone 7:3 mixture. The stock solutions of **1** (1.0 equiv.) and **2a** were pumped independently and combined just before the packed bed reactor (Entries 1-6) or mixed directly into the packed bed (Entries 7-17) using a Syrris® Asia syringe pump. In each run, the product stream was collected for 30 s after reaching steady state. Between each experiment, the reactor was washed with toluene/acetone 7:3. The resulting material was diluted in iPrOH analyzed by HPLC.

***Table S2**. Reaction optimization in flow.*



Entry	2a (equiv.)	Flow rate (mL/min)		Reactor	Conv. (%)[a]	ee (%)[b]
		Pump 1 (1)	Pump 2 (2a)			
1	1.00	0.1	0.1	A	>98	0
2	1.00	0.25	0.25	A	>98	10
3	1.00	0.5	0.5	A	>98	25
4	1.00	0.75	0.75	A	>98	43
5	1.00	1.0	1.0	A	>98	52
6	1.00	1.5	1.5	A	>98	51
7	1.00	0.5	0.5	B	>98	79
8	1.00	1.0	1.0	B	>98	80
9	1.00	1.5	1.5	B	>98	75
10	1.00	2.0	2.0	B	>98	70
11	1.11	1.9	2.1	B	>98	78
12	1.22	1.8	2.2	B	>98	82
13	1.35	1.7	2.3	B	>98	90
14	1.50	1.6	2.4	B	>98	93
15	1.50	1.6	2.4	C	>98	92
16	1.22	1.8	2.2	C	>98	92
17	1.11	1.9	2.1	C	>98	90

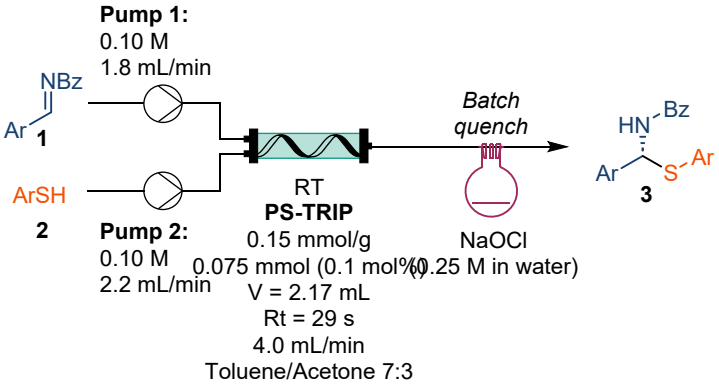
a) Conversion was determined by HPLC Area %.
b) ee was determined by chiral HPLC.

Procedure for filling the packed-bed reactor

The packed bed reactor was prepared as shown in Figure S3. The adjustable end of the Omnifit® glass column (10 mm ID) was opened and 0.5 g of dry catalyst was loaded (dried overnight at 40ºC in a vacuum oven). The reactor was then filled with toluene to swell the resin, closed and adjusted as required. Both ends were closed with glass wool to prevent the catalyst particles from clogging the system.

General procedure for the synthesis of **3** in continuous flow

0.5 g of **PS-TRIP** catalyst (0.075 mmol, 0.1 mol%) was loaded into a modified adjustable Omnifit® glass column (10 mm ID). Before the reactions, the catalyst bed was swollen by pumping toluene/acetone 7:3 at 4.0 mL/min for 5 min. The stock solutions (in toluene/acetone 7:3) of imine **1** (0.10 M, 1.80 mL/min, 1.0 equiv.) and **2a** (0.1 M, 2.20 mL/min, 1.2 equiv.) were pumped independently (4.0 mL/min overall flow rate) and combined in the modified Omnifit column containing the **PS-TRIP** catalyst by using a Syrris® Asia syringe pump. The pressure of the system generated by the packed bed reactor during the long run was 0.8 bar. The reaction outcome was quenched by pumping directly into an aqueous solution of 0.25 M NaClO.



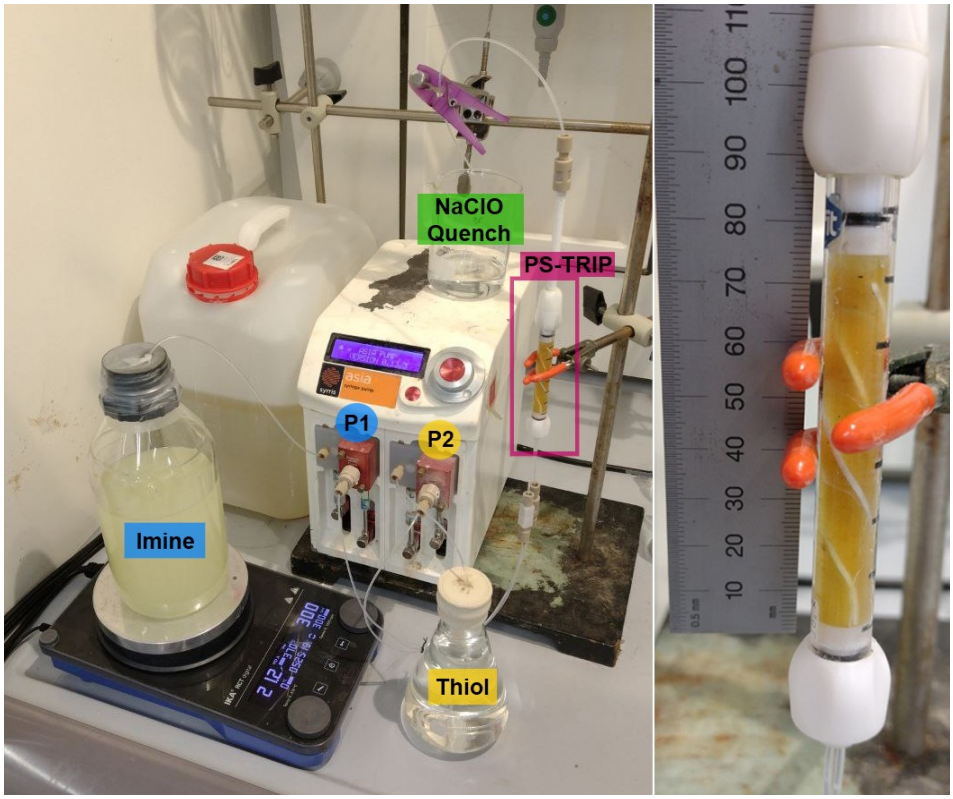


Figure S11. *Optimal flow set up.*

Quenching for 30 min of reaction in continuous flow: For analysis purposes, 30 min fractions were independently collected. The reaction mixture was pumped through a 0.25 M solution of NaClO (30 mL) After 1h precipitation of the product was observed and the crude was allowed to further precipitate for 6 h to ensure complete precipitation of the product.

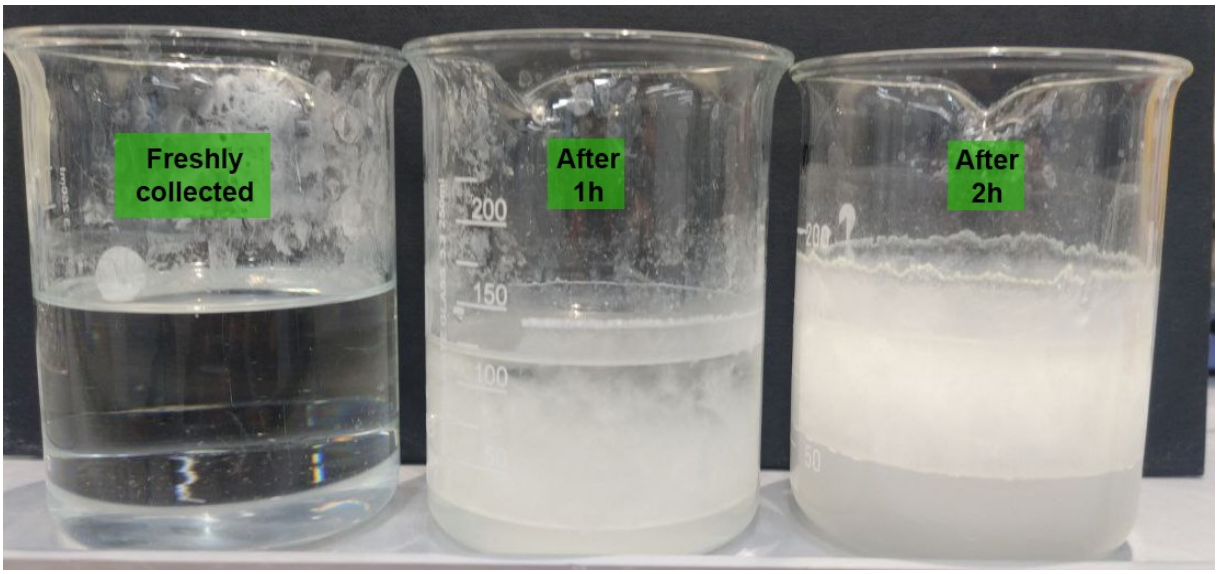


Figure S12. *Precipitation of the product over time.*

Work up for 6 h reaction: The combined fractions were filtered and washed with water (3x 200 mL) and cyclohexane (3x 250 mL). The cake was dried in a vacuum oven at 50 ºC at 1 torr for 12 h to give the pure product (19.44 g, 94% yield, 92% ee).

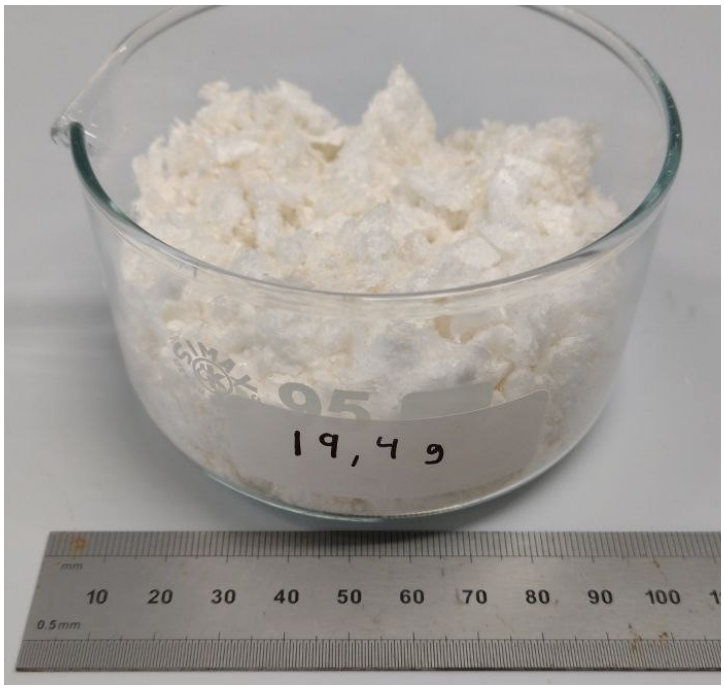


Figure S13. *Isolated product from the 6 h run.*

Green metrics, TRIP vs PS-TRIP comparison

Table S3. Homogeneous TRIP vs PS-TRIP and process comparation. Green flag: preferred; amber flag: some issues; red flag: undesirable.

Entry		TRIP (homogeneous)[S1]		PS-TRIP	
1	Batch/Flow	Batch		Flow	
2	Catalyst recovery	No		Yes	
3	Workup	Chromatography		Filtration	
4	Solvent	Toluene		Toluene	Acetone
5	Solvents workup	Hexane	EtOAc	Water	Cyclohexane
6	Health concerns	PhSH: H300, H310, H330			
7	Environmental implications	Hexane: H411		Cyclohexane: H410 NaClO solution: H410	
		PhSH: H410			
8	Yield (%)	98		94	
9	PMI	1373.3		143.3	
10	TON	49.0		812.2	
11	STY (kg m^{-3} h^{-1})	-		1493	
12	Atom Economy (%)	100		100	
13	Reaction Mass Efficiency (%)	91.7		87.9	
14	Optimum Efficiency (%)	91.7		87.9	
15	E factor	1183.7		78.4	

For the Batch process metrics, 5.0 g of silica gel and 10 column volumes of EtOAc/Hexane 1:2 were considered, since no precise information was provided in the literature.[S1]

Catalyst metrics

Turnover number (TON) and space time yield (STY) were calculated for the 6h long run following the literature formulas.[S5]

$$TON = \frac{mmoles\ limiting\ reactant}{mmoles\ catalyst} \times yield = \frac{64.8}{0.075} \times 0.94 = 812.2$$

$$STY = \frac{mass\ of\ product}{volume\ of\ reactor\ \times reaction\ time} = \frac{1.944\ e^{-2} kg}{2.17e^{-6}\ m^3\ \times 6\ h} = 1493.0\ kg\ m^{-3}\ h^{-1}$$

The reactor volume used for the STY was calculated using the packed bed reactor volume. It was calculated according to the indications from the vendor and the volume corresponding to the spiral mixer (0.4 mL) was substracted.

$$Bed\ volume\ (mL) = 0.3421 \times bed\ height\ (cm) - spiral\ volume\ (mL) = 0.3421 \times 7.5 - 0.4 = 2.16575\ mL$$

Experimental residence time and steady state

Ferrocene 0.01 M solution was prepared by dissolving 186 mg of Ferrocene in 100 mL of Toluene/Acetone 7:3 mixture. The observed wavelength range was 438-443 nm. At time t=0, pure solvent was switched with Ferrocene solution and the flow rates were kept the same. UV/Vis spectra were recorded using a fibre-coupled Avantes Starline AvaSpec-2048 spectrometer, with an Avantes AvaLight-DHc lamp as the light source. These spectra were processed using Avasoft 8.7 software. Each experiment was done by duplicate and the shown data represent the average of both measurements.

Flow rate	4 mL/min	2 mL/min	1 mL/min
Residence time (R_T)	29 s	52 s	80 s
Steady state	80 s	140 s	270 s

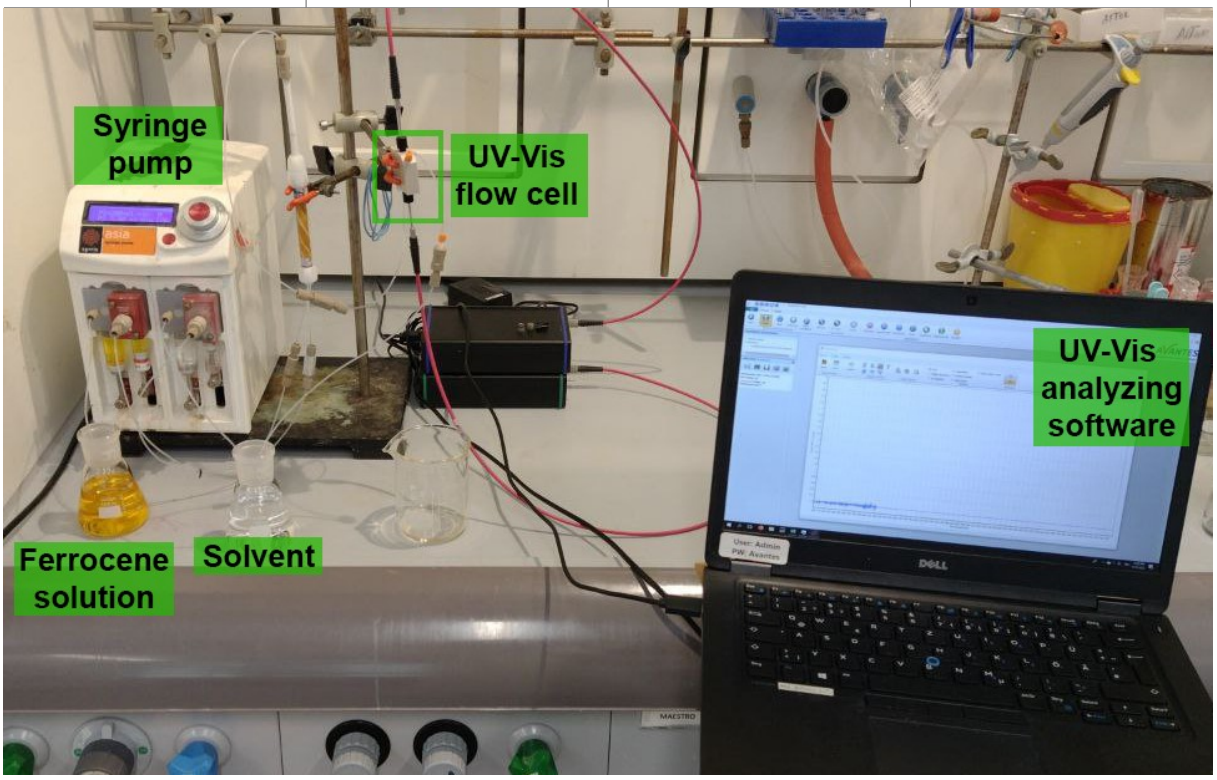


Figure S14. *Set up for measuring the residence time and steady state.*

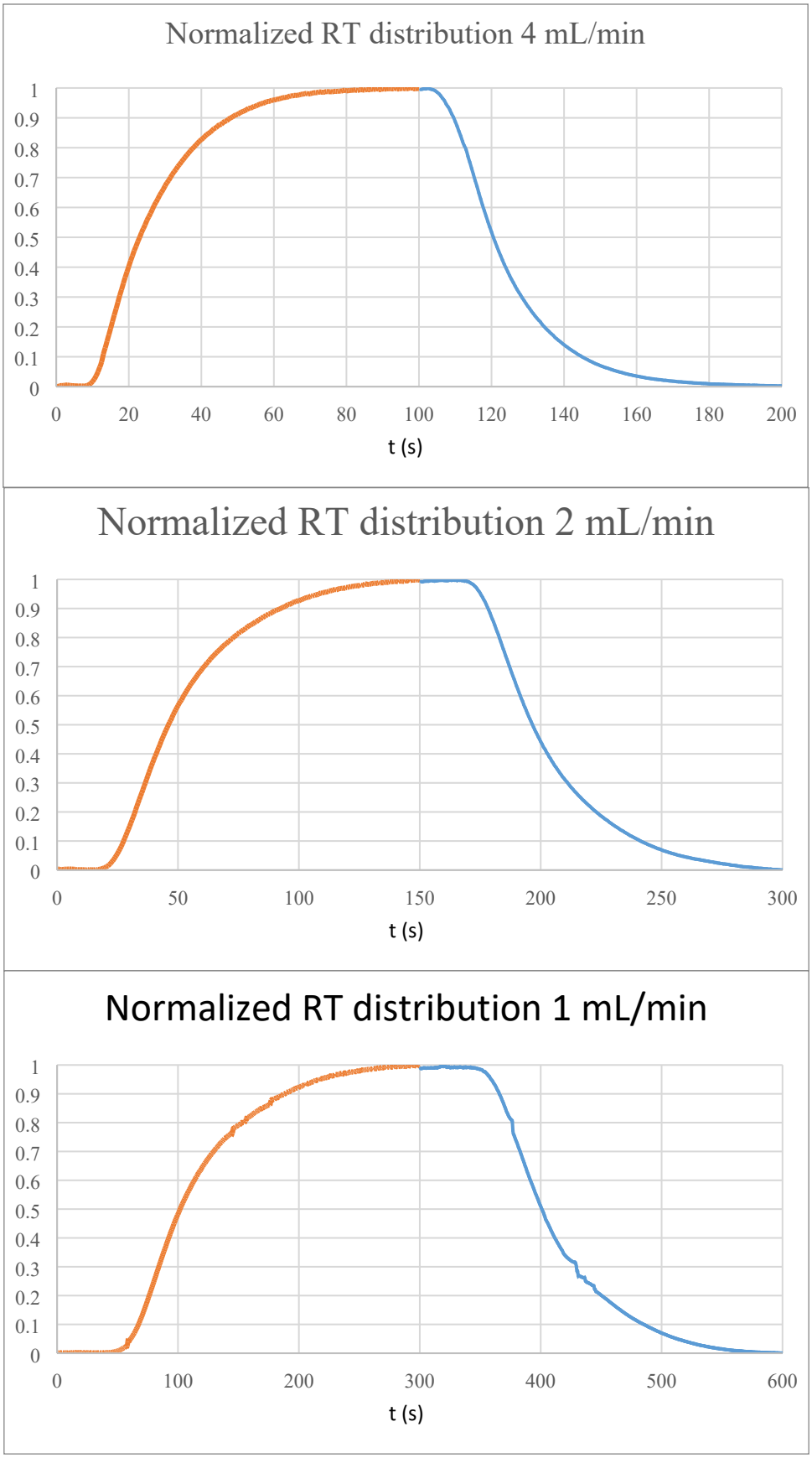
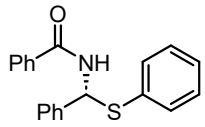


Figure S15. *Normalized RT distribution graphs. Colour change indicates the point where the tracer was switched to solvent.*

Characterization data of 3

(*R*)-N-(phenyl(phenylthio)methyl)benzamide (3a)



The general procedure was followed.

Optimal flow rates: 1.8 mL/min of **1** and 2.2 mL/min **2** (4.0 mL/min in total).

The product was collected for 6h after the steady state, affording 19.44 g (94%) of the product as a white solid. The reported data match the literature.[S1]

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.68 – 7.61 (m, 2H), 7.54 – 7.45 (m, 5H), 7.43 – 7.32 (m, 5H), 7.29 – 7.26 (m, 3H), 6.83 – 6.68 (m, 2H).

^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$) δ 166.5, 138.7, 134.0, 133.0, 132.5, 132.0, 129.3, 128.9, 128.8, 128.6, 128.1, 127.0, 126.8, 59.8.

HRMS (TOF+, m/Z): calcd for $C_{20}H_{17}NOSNa$ $[M+Na]^+$: 342.0923, found: 342.0930.

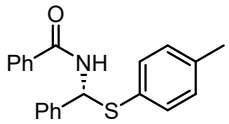
$[\alpha]_{589}^{25} = \frac{100 \times -0.0193}{0.5 \times 1} = -3.86$, measured in $CHCl_3$.

Literature data for (*S*)-**3a** (99% ee), c=0.5 (in CHCl3): -4.0.[S1]

HPLC (chiral): Chiralcel-IC, n-heptane/i-PrOH 80:20, 1.0 mL/min, 25 °C, detection at 254 nm.

Residence time: 7.1 min (major), 8.0 (minor). 92% ee.

(*R*)-N-(phenyl(p-tolylthio)methyl)benzamide (3b)



The general procedure was followed.

Optimal flow rates: 1.8 mL/min of **1** and 2.2 mL/min **2** (4.0 mL/min in total).

The product was collected for 5 min after the steady state, affording 279 mg (93%) of the product as a white solid.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.66 (d, *J* = 6.9 Hz, 2H), 7.53 – 7.43 (m, 3H), 7.43 – 7.29 (m, 7H), 7.08 (d, *J* = 7.8 Hz, 2H), 6.77 (d, *J* = 9.1 Hz, 1H), 6.69 (d, *J* = 9.1 Hz, 1H), 2.30 (s, 3H).

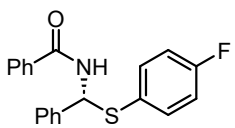
^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$) δ 166.4, 138.9, 138.5, 134.0, 133.3, 131.9, 130.0, 129.1, 128.9, 128.7, 128.4, 127.0, 126.8, 60.1, 21.3.

HRMS (TOF+, m/Z): calcd for $C_{21}H_{19}NOSNa$ $[M+Na]^+$: 356.1079, found: 356.1092.

HPLC (chiral): Chiralcel-IC, n-heptane/i-PrOH 80:20, 1.0 mL/min, 25 °C, detection at 254 nm.

Residence time: 8.1 min (major), 9.0 (minor). 88% ee.

(*R*)-N-(((4-fluorophenyl)thio)(phenyl)methyl)benzamide (3c)



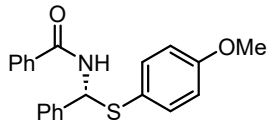
The general procedure was followed.

Optimal flow rates: 1.8 mL/min of **1** and 2.2 mL/min **2** (4.0 mL/min in total).

The product was collected for 5 min after the steady state, affording 273 mg (90%) of the product as a white solid.

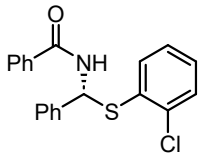
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.66 (d, *J* = 8.5 Hz, 2H), 7.54 – 7.30 (m, 10H), 6.96 (t, *J* = 8.7 Hz, 2H), 6.70 (s, 2H).
^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$) δ 166.3, 163.1 (d, *J* = 248.9 Hz), 138.6, 135.8 (d, *J* = 8.3 Hz), 133.9, 132.1, 129.0, 128.8, 128.7, 127.9 (d, *J* = 3.4 Hz), 127.0, 126.8, 116.4 (d, *J* = 21.9 Hz), 60.5.
^{19}F NMR (282 MHz, $CDCl_3$) δ -112.5.
HRMS (TOF+, m/Z): calcd for $C_{20}H_{16}FNOSNa$ [M+Na]$^+$: 360.0829, found: 360.0843.
HPLC (chiral): Chiralcel-IC, n-heptane/i-PrOH 80:20, 1.0 mL/min, 25 °C, detection at 254 nm.
Residence time: 6.2 min (major), 7.1 (minor). 86% ee.

(*R*)-N-(((4-methoxyphenyl)thio)(phenyl)methyl)benzamide (3d)



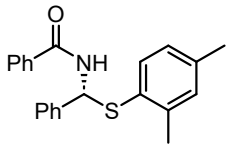
The general procedure was followed.
Optimal flow rates: 1.8 mL/min of **1** and 2.2 mL/min **2** (4.0 mL/min in total).
The product was collected for 5 min after the steady state, affording 286 mg (91%) of the product as a white solid. The reported data match the literature. [S1]
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.66 (d, *J* = 8.4 Hz, 2H), 7.52 – 7.28 (m, 10H), 6.80 (d, *J* = 8.8 Hz, 2H), 6.68 (d, *J* = 9.2 Hz, 1H), 6.59 (d, *J* = 9.2 Hz, 1H), 3.76 (s, 3H).
^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$) δ 166.3, 160.3, 139.0, 136.2, 134.1, 131.9, 128.9, 128.8, 128.4, 127.0, 126.8, 122.9, 114.8, 60.8, 55.5.
HRMS (TOF+, m/Z): calcd for $C_{21}H_{19}NO_2SNa$ [M+Na]$^+$: 372.1029, found: 372.1047.
HPLC (chiral): Chiralcel-IC, n-heptane/i-PrOH 80:20, 1.0 mL/min, 25 °C, detection at 254 nm.
Residence time: 10.3 min (major), 11.2 (minor). 87% ee.

(*R*)-N-(((2-chlorophenyl)thio)(phenyl)methyl)benzamide (3e)



The general procedure was followed.
Optimal flow rates: 1.8 mL/min of **1** and 2.2 mL/min **2** (4.0 mL/min in total).
The product was collected for 5 min after the steady state, affording 312 mg (98%) of the product as a white solid.
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.68 (d, *J* = 8.4 Hz, 2H), 7.59 – 7.52 (m, 3H), 7.52 – 7.45 (m, 1H), 7.44 – 7.29 (m, 6H), 7.22 – 7.13 (m, 2H), 6.92 (d, *J* = 9.2 Hz, 1H), 6.87 (d, *J* = 9.2 Hz, 1H).
^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$) δ 166.5, 138.1, 136.0, 133.7, 133.1, 132.7, 132.0, 130.1, 129.0, 129.0 (2), 128.8, 128.7, 127.6, 127.1, 126.8, 59.1.
HRMS (TOF+, m/Z): calcd for $C_{20}H_{16}ClNOSNa$ [M+Na]$^+$: 376.0533, found: 376.0551.
HPLC (chiral): Chiralcel-IC, n-heptane/i-PrOH 80:20, 1.0 mL/min, 25 °C, detection at 254 nm.
Residence time: 6.2 min (major), 7.5 (minor). 88% ee.

(*R*)-N-(((2,4-dimethylphenyl)thio)(phenyl)methyl)benzamide (3f)



The general procedure was followed.

Optimal flow rates: 1.8 mL/min of **1** and 2.2 mL/min **2** (4.0 mL/min in total).

The product was collected for 5 min after the steady state, affording 295 mg (94%) of the product as a white solid.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.65 (d, *J* = 8.4 Hz, 2H), 7.51 – 7.45 (m, 3H), 7.44 – 7.30 (m, 6H), 7.03 (d, *J* = 2.0 Hz, 1H), 6.90 (dd, *J* = 7.8, 2.0 Hz, 1H), 6.69 (d, *J* = 9.0 Hz, 1H), 6.61 (d, *J* = 9.0 Hz, 1H), 2.42 (s, 3H), 2.27 (s, 3H).

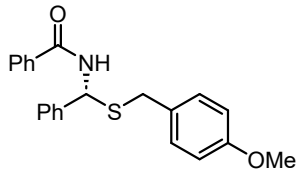
^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$) δ 166.4, 140.8, 139.1, 138.7, 134.1, 134.0, 131.9, 131.6, 128.9, 128.7, 128.5, 127.5, 127.0, 126.7, 59.2, 21.2, 20.8.

HRMS (TOF+, m/Z): calcd for $C_{22}H_{21}NOSNa$ $[M+Na]^+$: 370.1236 , found: 370.1259.

HPLC (chiral): Chiralcel-IC, n-heptane/i-PrOH 90:10, 1.0 mL/min, 25 °C, detection at 254 nm.

Residence time: 11.3 min (major), 13.7 (minor). 85% ee.

(*R*)-N-(((4-methoxybenzyl)thio)(phenyl)methyl)benzamide (3g)



The general procedure was followed.

Optimal flow rates: 0.9 mL/min of **1** and 1.1 mL/min **2** (2.0 mL/min in total).

The product was collected for 10 min after the steady state, affording 281 mg (86%) of the product as a white solid.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.65 (d, *J* = 8.6 Hz, 2H), 7.56 – 7.48 (m, 1H), 7.47 – 7.38 (m, 4H), 7.38 – 7.25 (m, 5H), 6.81 (d, *J* = 8.6 Hz, 2H), 6.57 (d, *J* = 9.0 Hz, 1H), 6.42 (d, *J* = 9.0 Hz, 1H), 3.88 (d, *J* = 13.7 Hz, 1H), 3.80 (d, *J* = 13.7 Hz, 1H), 3.75 (s, 3H).

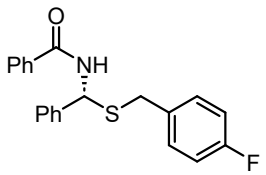
^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$) δ 166.2, 158.9, 139.1, 133.7, 132.0, 130.4, 130.1, 128.9, 128.7, 128.3, 127.1, 126.7, 114.2, 57.6, 55.4, 35.9.

HRMS (TOF+, m/Z): calcd for $C_{22}H_{21}NO_2SNa$ $[M+Na]^+$: 386.1185, found: 386.1197.

HPLC (chiral): Chiralcel-IC, n-heptane/i-PrOH 80:20, 1.0 mL/min, 25 °C, detection at 254 nm.

Residence time: 10.4 min (major), 11.4 (minor). 81% ee.

(*R*)-N-(((4-fluorobenzyl)thio)(phenyl)methyl)benzamide (3h)



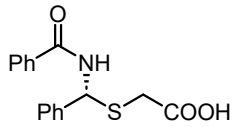
The general procedure was followed.

Optimal flow rates: 0.45 mL/min of **1** and 0.55 mL/min **2** (1.0 mL/min in total).

The product was collected for 20 min after the steady state, affording 275 mg (87%) of the product as a white solid.

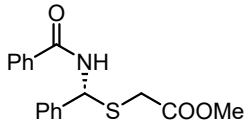
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.70 (d, *J* = 8.5 Hz, 2H), 7.53 (ddt, *J* = 8.3, 6.5, 1.4 Hz, 1H), 7.44 – 7.42 (m, 4H), 7.34 – 7.31 (m, 5H), 6.97 (t, *J* = 8.7 Hz, 2H), 6.64 (d, *J* = 9.3 Hz, 1H), 6.45 (d, *J* = 9.3 Hz, 1H), 3.91 (d, *J* = 13.8 Hz, 1H), 3.80 (d, *J* = 13.8 Hz, 1H).
^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$) δ 166.35, 162.1 (d, *J* = 245.8 Hz), 138.9, 134.1 (d, *J* = 3.2 Hz), 133.6, 132.1, 130.6 (d, *J* = 8.1 Hz), 129.0, 128.8, 128.5, 127.1, 126.6, 115.7 (d, *J* = 21.5 Hz), 57.5, 35.8.
^{19}F NMR (282 MHz, $CDCl_3$) δ -115.28.
HRMS (TOF+, m/Z): calcd for $C_{21}H_{18}FNOSNa$ $[M+Na]^+$: 374.0985, found: 374.0995.
HPLC (chiral): Chiralcel-IE, n-heptane/i-PrOH 80:20, 1.0 mL/min, 25 °C, detection at 254 nm.
Residence time: 11.5 min (major), 13.3 (minor). 86% ee.

(*R*)-2-((benzamido(phenyl)methyl)thio)acetic acid (3i)



The general procedure was followed.
Optimal flow rates: 0.45 mL/min of **1** and 0.55 mL/min **2** (1.0 mL/min in total).
The product was collected for 20 min after the steady state, affording 211 mg (78%) of the product as a white solid.
^{1}H NMR (300 MHz, DMSO-d6) δ 9.36 (d, *J* = 9.1 Hz, 1H), 7.91 (d, *J* = 8.5 Hz, 2H), 7.59 – 7.52 (m, 3H), 7.51 – 7.45 (m, 2H), 7.41 – 7.29 (m, 3H), 6.51 (d, *J* = 9.1 Hz, 1H), 3.47 (d, *J* = 15.7 Hz, 1H), 3.34 (d, *J* = 15.7 Hz, 1H).
*The doublet at 3.34 ppm is overlapped with the water present in the DMSO.
^{13}C {^{1}H} NMR (75 MHz, DMSO-d6) δ 171.2, 166.2, 139.5, 133.8, 131.6, 128.5, 128.3, 128.0, 127.7, 127.0, 56.7, 33.4.
HRMS (TOF+, m/Z): calcd for $C_{16}H_{15}NO_3SNa$ $[M+Na]^+$: 324.0665, found: 324.0675.
HPLC (chiral): Chiralcel-IC, n-heptane/i-PrOH 80:20, 1.0 mL/min, 25 °C, detection at 254 nm.
Residence time: 7.9 min (major), 9.3 (minor). 54% ee.

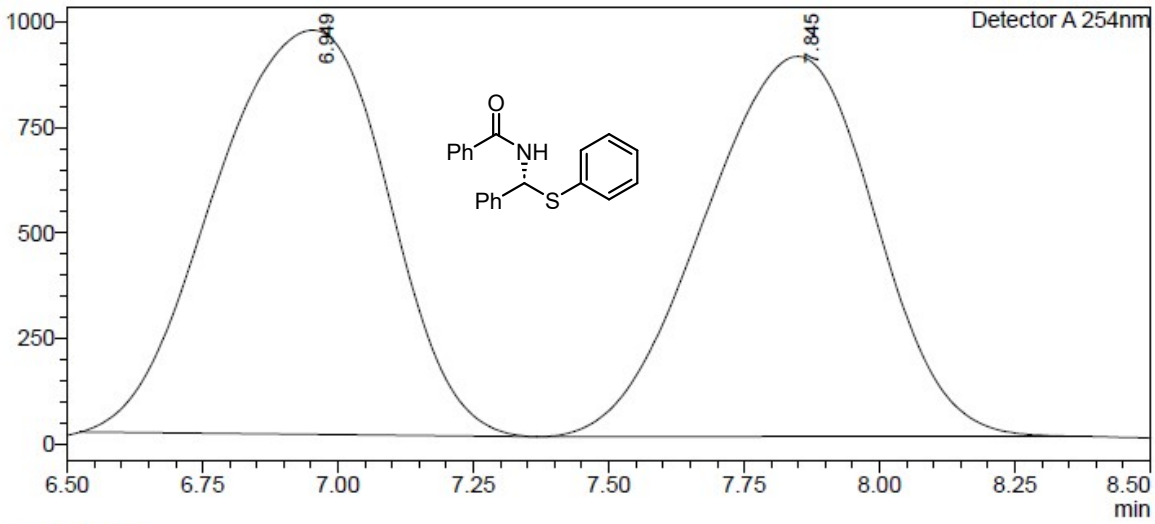
methyl (*R*)-2-((benzamido(phenyl)methyl)thio)acetate (3j)



The general procedure was followed.
Optimal flow rates: 0.45 mL/min of **1** and 0.55 mL/min **2** (1.0 mL/min in total).
The product was collected for 20 min after the steady state, affording 235 mg (83%) of the product as a white solid.
^{1}H NMR (300 MHz, $CDCl_3$) δ 8.07 (d, *J* = 8.7 Hz, 1H), 7.92 (d, *J* = 8.4 Hz, 2H), 7.55 – 7.42 (m, 5H), 7.38 – 7.27 (m, 3H), 6.62 (d, *J* = 8.7 Hz, 1H), 3.68 (s, 3H), 3.30 (d, *J* = 16.3 Hz, 1H), 3.23 (d, *J* = 16.3 Hz, 1H).
^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$) δ 172.7, 166.1, 138.0, 133.6, 131.9, 128.8, 128.7, 128.3, 127.3, 126.7, 57.5, 53.0, 32.4.
HRMS (TOF+, m/Z): calcd for $C_{17}H_{17}NO_3SNa$ $[M+Na]^+$: 338.0821, found: 338.0846.
HPLC (chiral): Chiralcel-IC, n-heptane/i-PrOH 80:20, 1.0 mL/min, 25 °C, detection at 254 nm.
Residence time: 14.8 min (major), 17.0 (minor). 89% ee.

Chiral HPLC chromatograms of 3

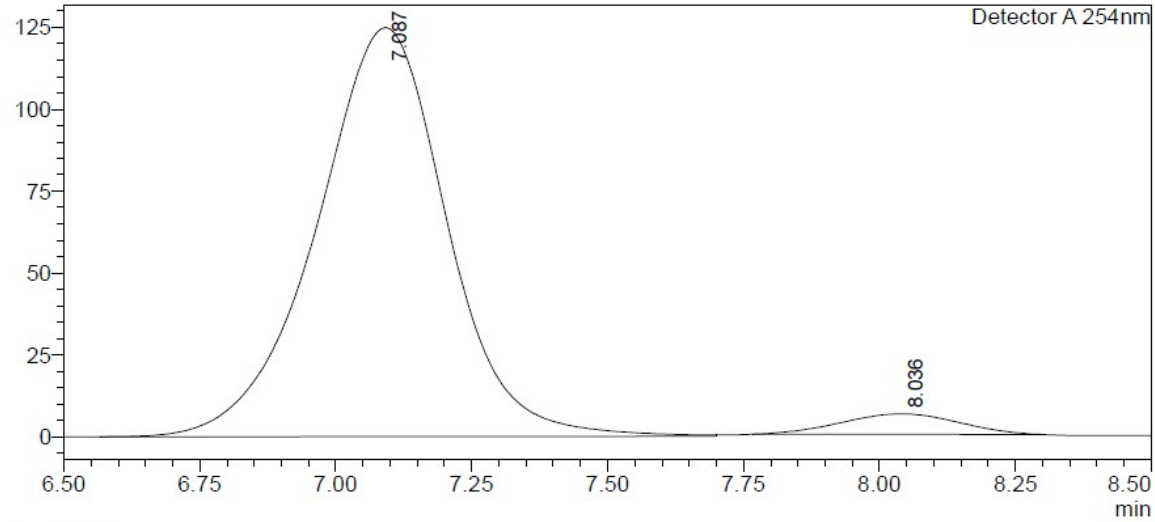
(*R*)-N-(phenyl(phenylthio)methyl)benzamide (4a)



<Peak Table>

Detector A 254nm

Peak#	Ret. Time	Area	Height	Conc.	Name	Area%
1	6.949	21335632	958173	51.943		51.943
2	7.845	19739096	900850	48.057		48.057
Total		41074728	1859023			100.000

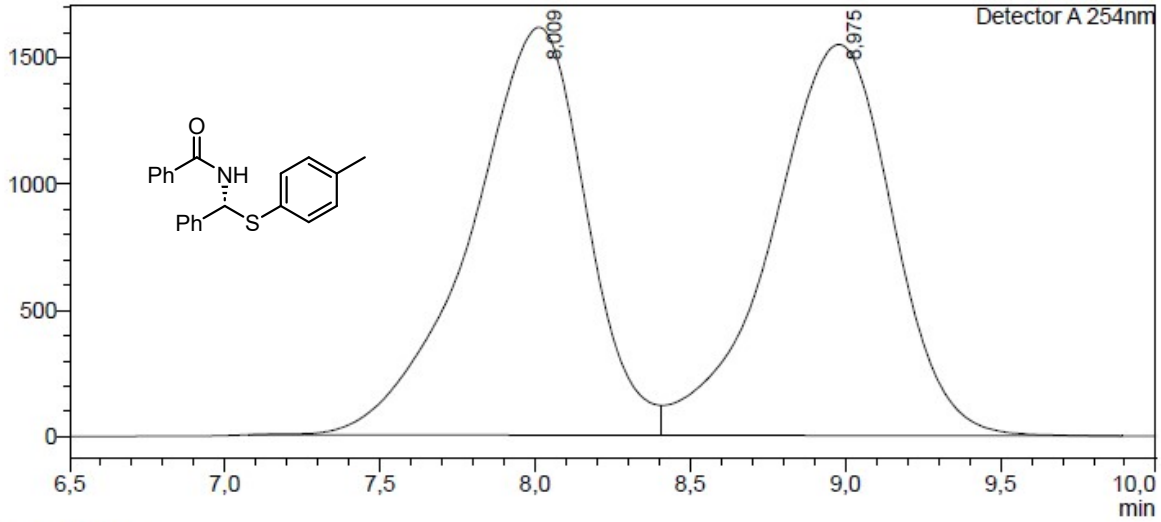


<Peak Table>

Detector A 254nm

Peak#	Ret. Time	Area	Height	Conc.	Name	Area%
1	7.087	2077350	124874	95.646		95.646
2	8.036	94555	6267	4.354		4.354
Total		2171905	131141			100.000

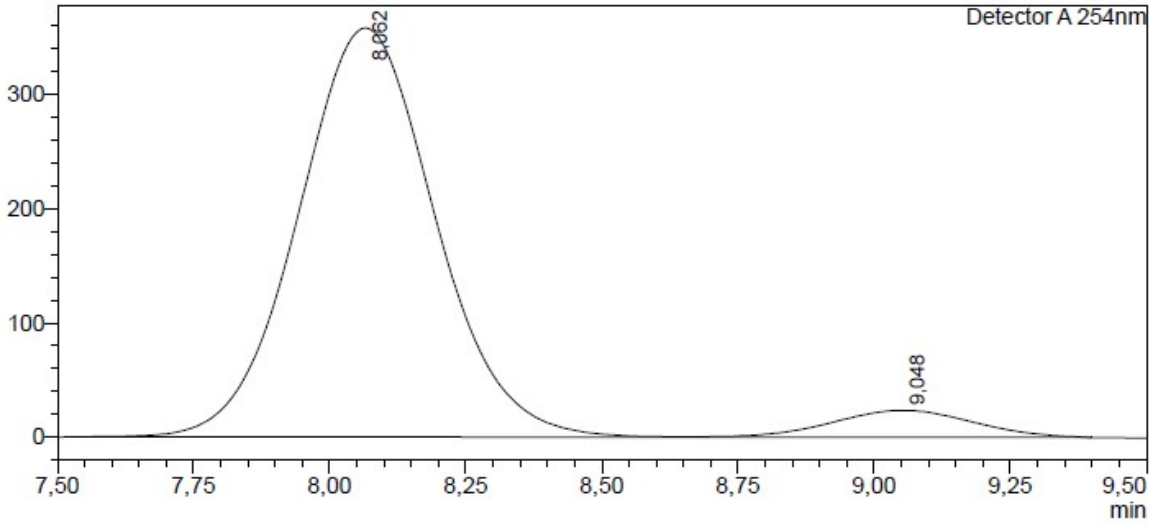
(*R*)-N-(phenyl(p-tolylthio)methyl)benzamide (3b)



<Peak Table>

Detector A 254nm

Peak#	Ret. Time	Area	Height	Conc.	Unit	Mark	Name
1	8,009	42057579	1615780	49,886		M	
2	8,975	42250261	1550476	50,114		V M	
Total		84307840	3166257				

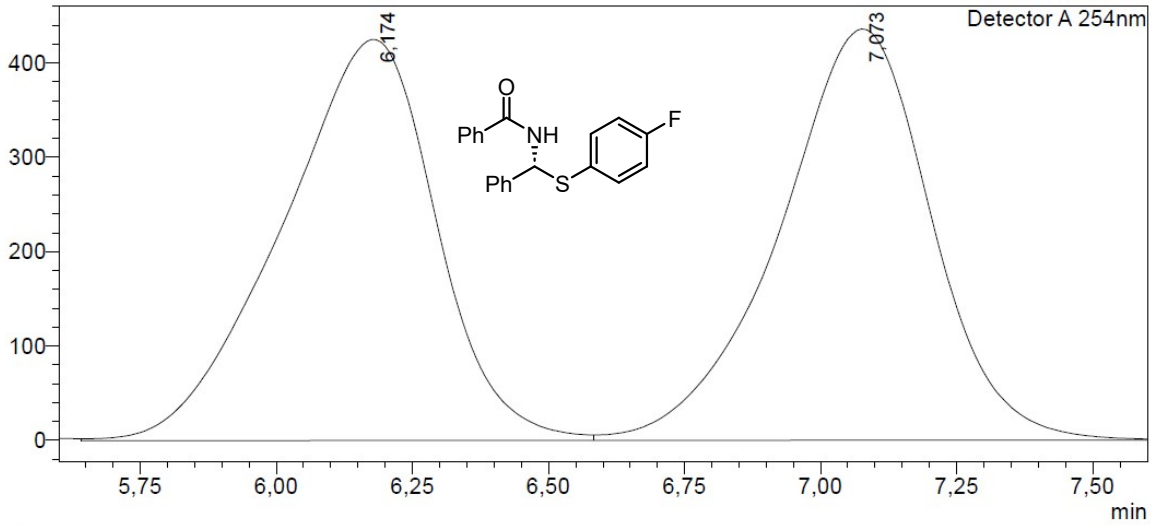


<Peak Table>

Detector A 254nm

Peak#	Ret. Time	Area	Height	Conc.	Unit	Mark	Name
1	8,062	6247234	358044	93,663		M	
2	9,048	422705	23577	6,337		V M	
Total		6669939	381621				

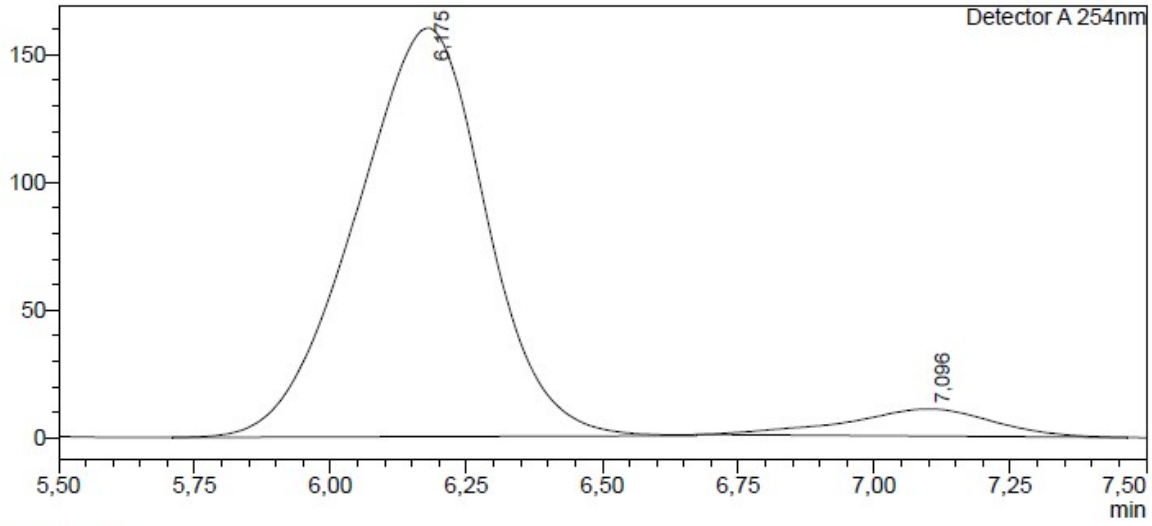
(*R*)-N-(((4-fluorophenyl)thio)(phenyl)methyl)benzamide (3c)



<Peak Table>

Detector A 254nm

Peak#	Ret. Time	Area	Height	Conc.	Unit	Mark	Name
1	6,174	8389895	424969	49,760			
2	7,073	8470984	435905	50,240		V	
Total		16860879	860874				

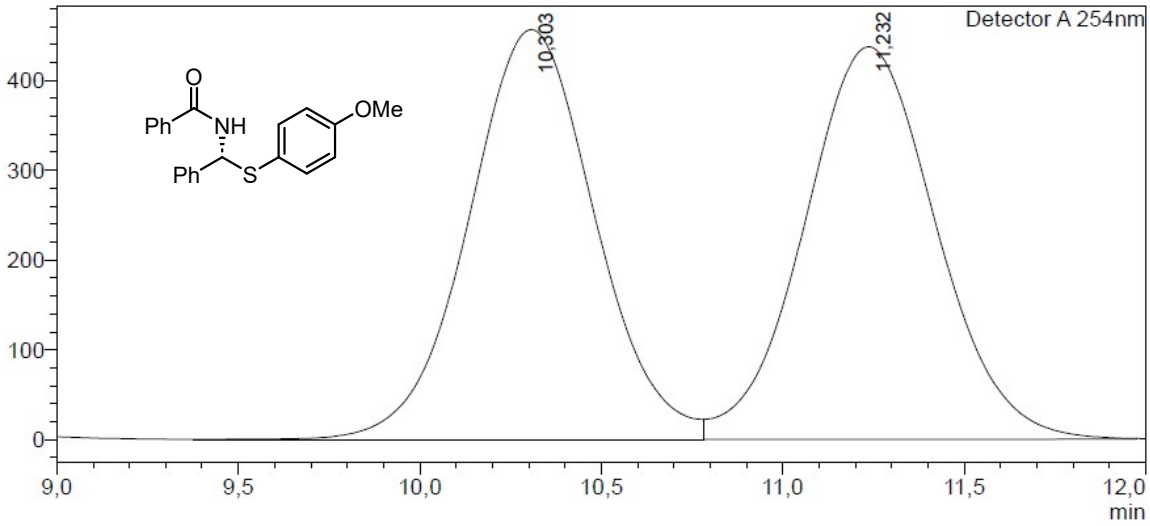


<Peak Table>

Detector A 254nm

Peak#	Ret. Time	Area	Height	Conc.	Unit	Mark	Name
1	6,175	2669811	159766	93,033		M	
2	7,096	199935	10639	6,967		M	
Total		2869746	170405				

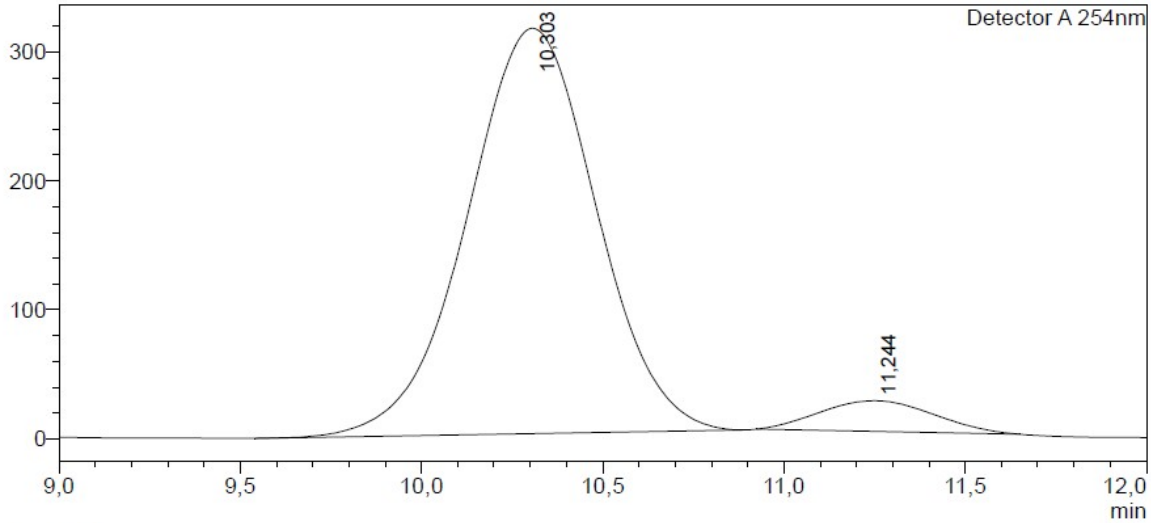
(*R*)-N-(((4-methoxyphenyl)thio)(phenyl)methyl)benzamide (3d)



<Peak Table>

Detector A 254nm

Peak#	Ret. Time	Area	Height	Conc.	Unit	Mark	Name
1	10,303	11024352	456603	49,963			
2	11,232	11040687	437245	50,037		V M	
Total		22065039	893848				

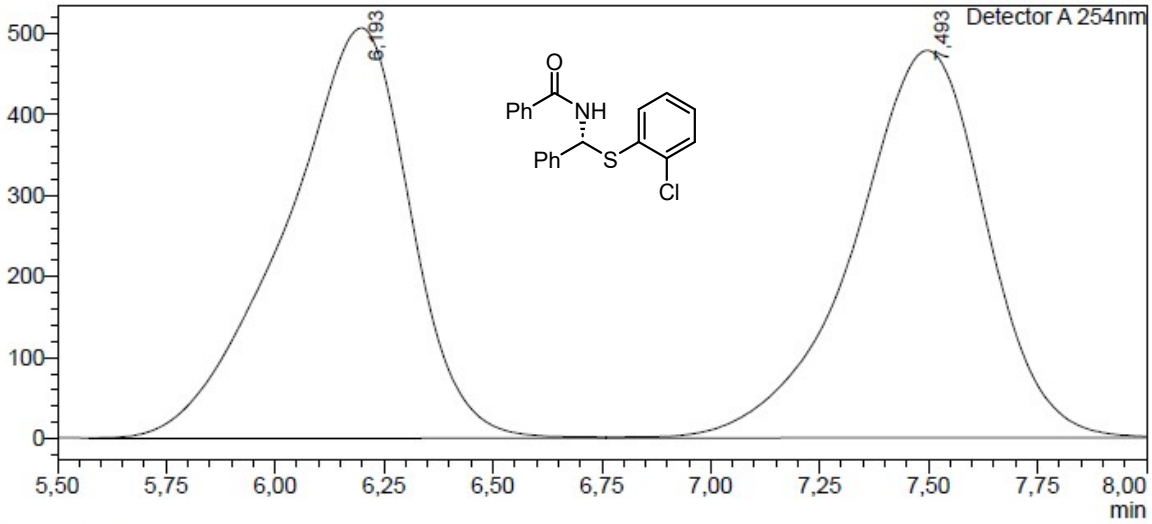


<Peak Table>

Detector A 254nm

Peak#	Ret. Time	Area	Height	Conc.	Unit	Mark	Name
1	10,303	7774044	314159	93,741		M	
2	11,244	519059	23768	6,259		M	
Total		8293102	337927				

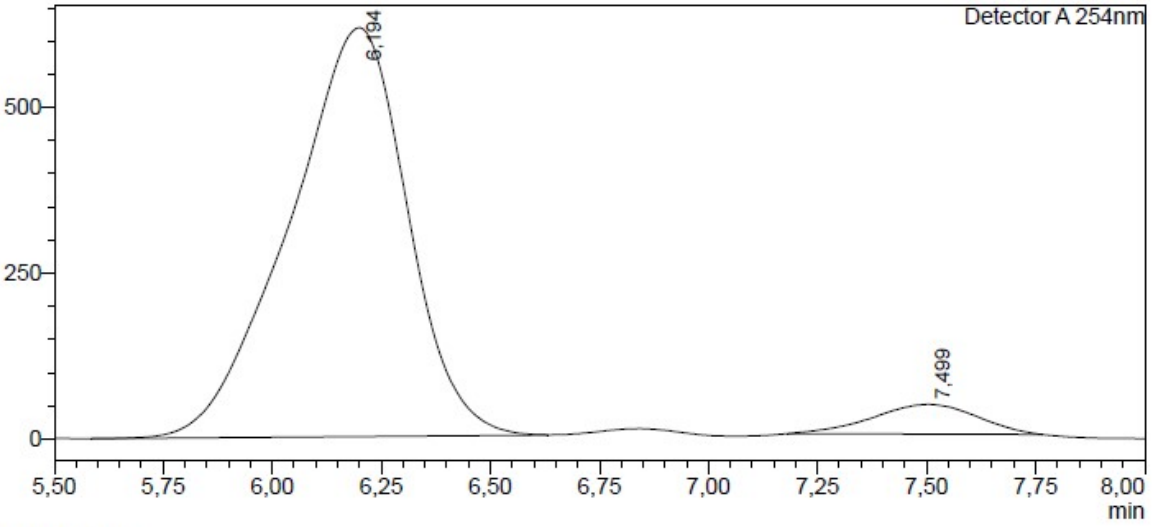
(*R*)-N-(((2-chlorophenyl)thio)(phenyl)methyl)benzamide (3e)



<Peak Table>

Detector A 254nm

Peak#	Ret. Time	Area	Height	Conc.	Unit	Mark	Name
1	6,193	10233871	506858	50,211			
2	7,493	10147873	478380	49,789		V	
Total		20381744	985238				

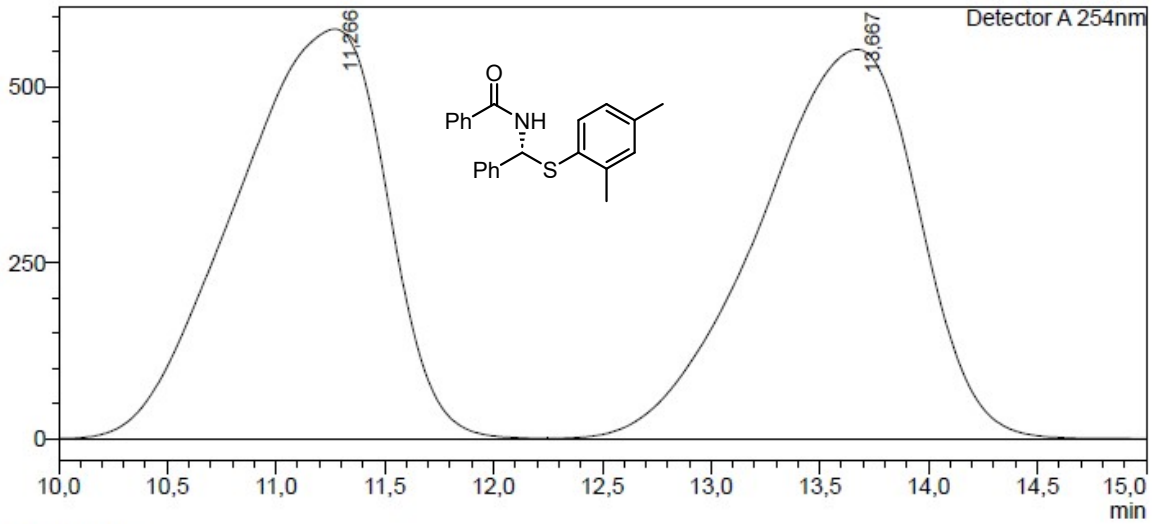


<Peak Table>

Detector A 254nm

Peak#	Ret. Time	Area	Height	Conc.	Unit	Mark	Name
1	6,194	11577198	615978	93,945		M	
2	7,499	746155	44602	6,055		M	
Total		12323353	660580				

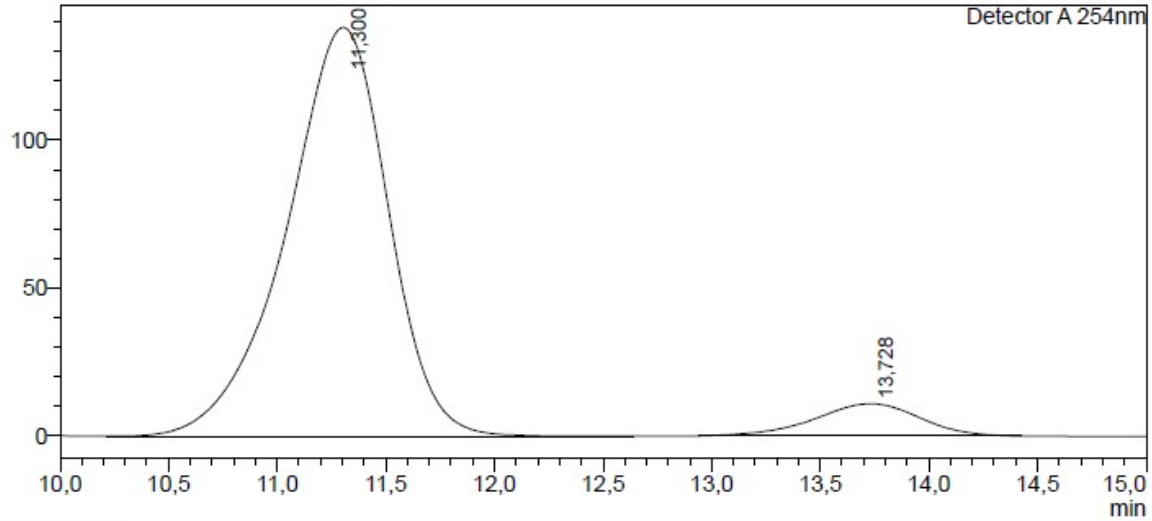
(*R*)-N-(((2,4-dimethylphenyl)thio)(phenyl)methyl)benzamide (3f)



<Peak Table>

Detector A 254nm

Peak#	Ret. Time	Area	Height	Conc.	Unit	Mark	Name
1	11,266	28331342	581766	49,973			
2	13,667	28361391	552847	50,027		V	
Total		56692733	1134613				

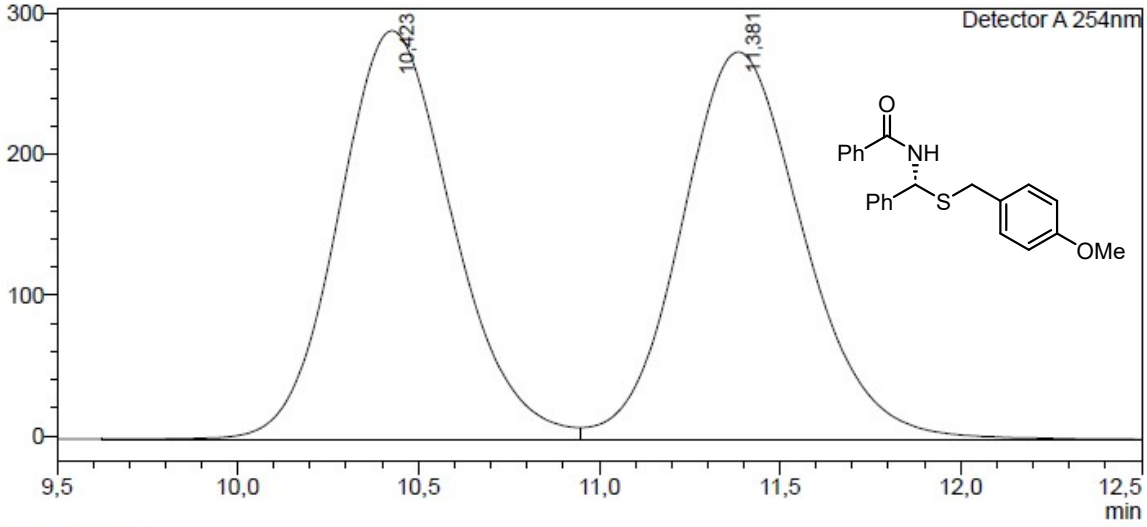


<Peak Table>

Detector A 254nm

Peak#	Ret. Time	Area	Height	Conc.	Unit	Mark	Name
1	11,300	4516232	138156	92,512		M	
2	13,728	365554	10887	7,488		M	
Total		4881786	149043				

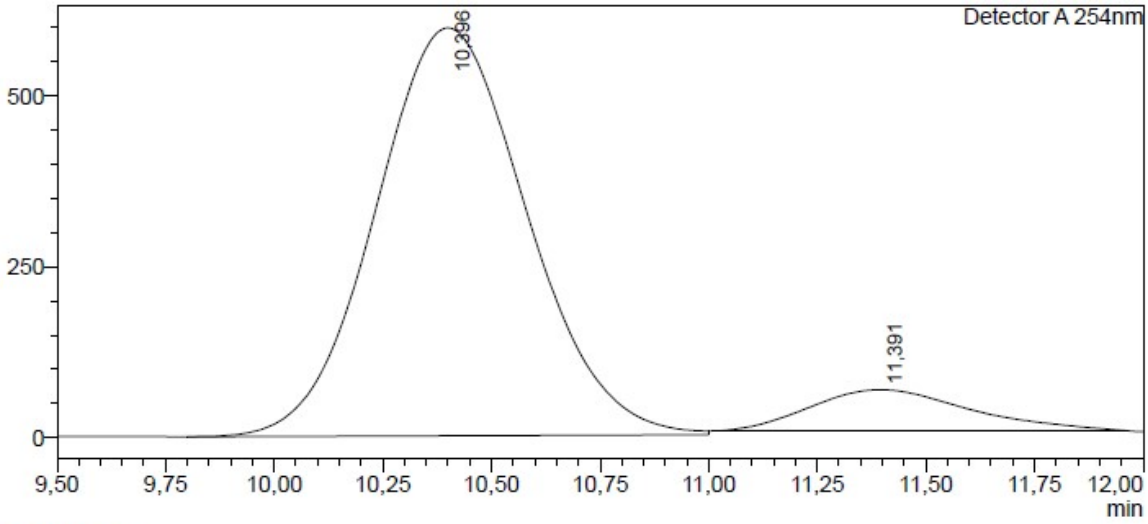
(*R*)-N-(((4-methoxybenzyl)thio)(phenyl)methyl)benzamide (3g)



<Peak Table>

Detector A 254nm

Peak#	Ret. Time	Area	Height	Conc.	Unit	Mark	Name
1	10,423	6416199	289999	49,606			
2	11,381	6518118	275063	50,394		V M	
Total		12934317	565062				

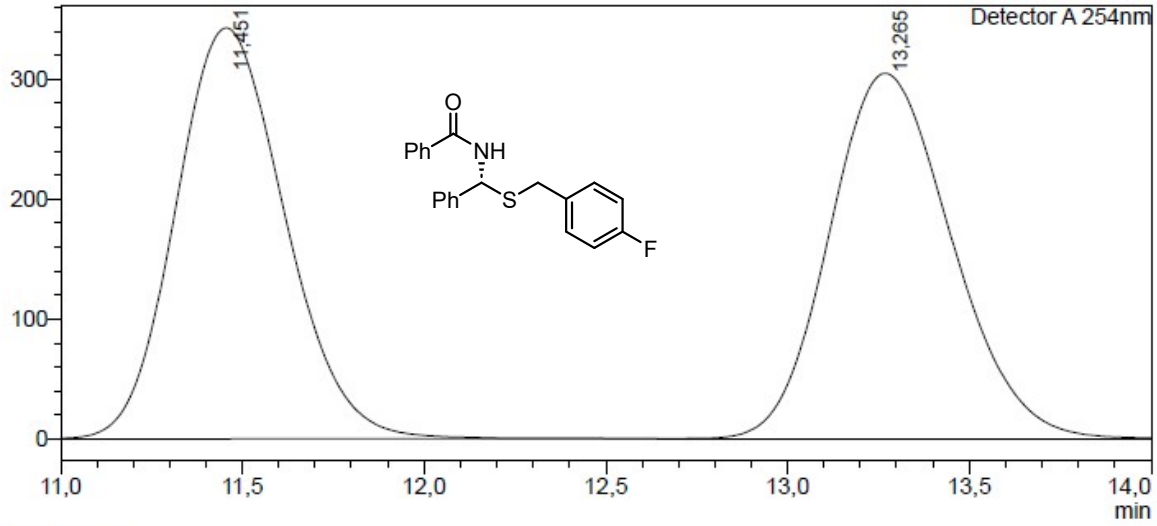


<Peak Table>

Detector A 254nm

Peak#	Ret. Time	Area	Height	Conc.	Unit	Mark	Name
1	10,396	14426387	596827	90,442			
2	11,391	1524634	60082	9,558		M	
Total		15951021	656908				

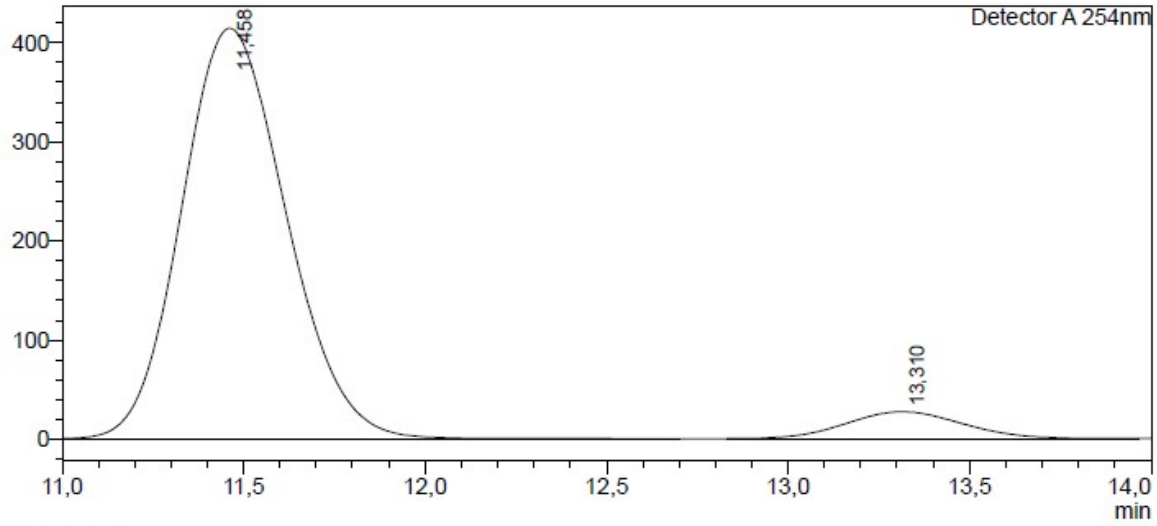
(*R*)-N-(((4-fluorobenzyl)thio)(phenyl)methyl)benzamide (3h)



<Peak Table>

Detector A 254nm

Peak#	Ret. Time	Area	Height	Conc.	Unit	Mark	Name
1	11,451	7171417	342332	50,134			
2	13,265	7133095	304516	49,866		V	
Total		14304512	646848				

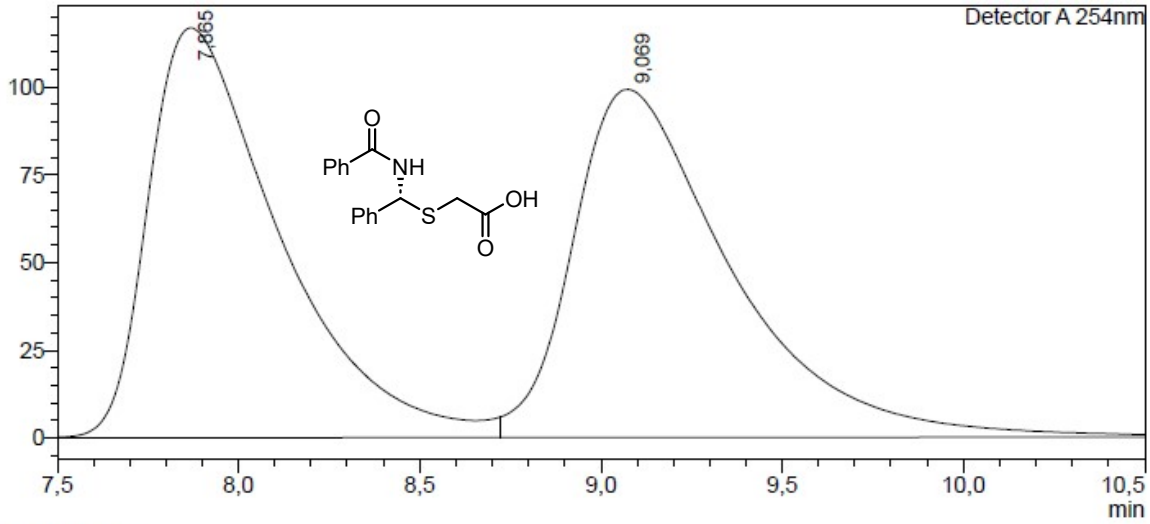


<Peak Table>

Detector A 254nm

Peak#	Ret. Time	Area	Height	Conc.	Unit	Mark	Name
1	11,458	8322735	414220	93,186			
2	13,310	608601	27156	6,814		M	
Total		8931336	441376				

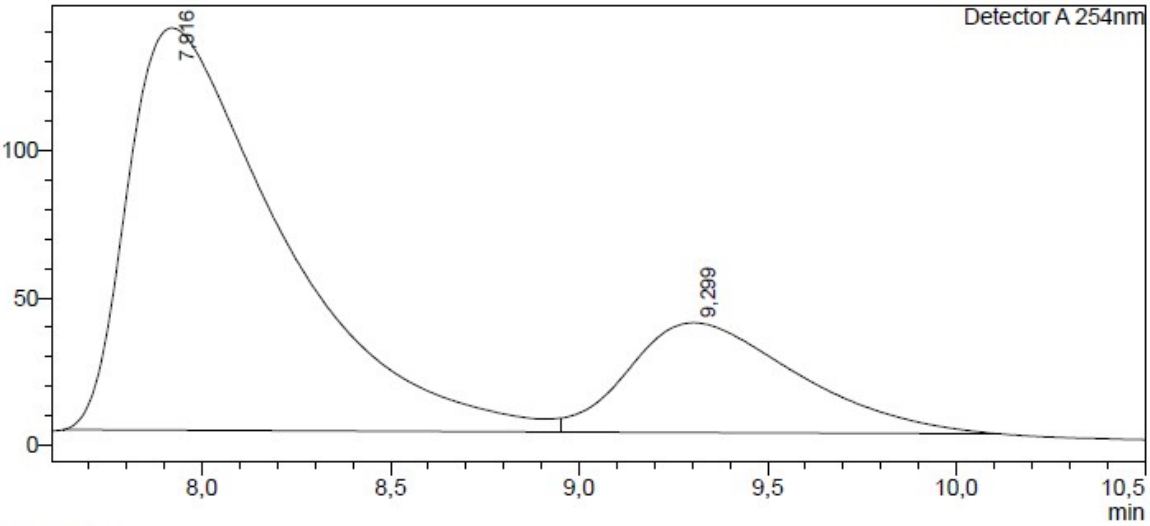
(*R*)-2-((benzamido(phenyl)methyl)thio)acetic acid (3i)



<Peak Table>

Detector A 254nm

Peak#	Ret. Time	Area	Height	Conc.	Unit	Mark	Name
1	7,865	2954853	116736	49,331		M	
2	9,069	3035033	99167	50,669		V M	
Total		5989885	215903				

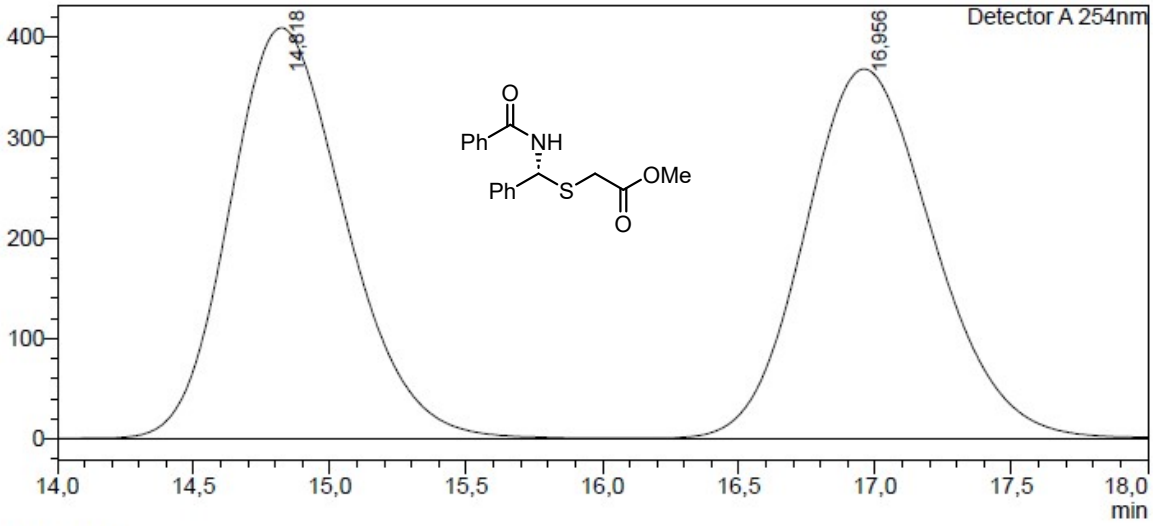


<Peak Table>

Detector A 254nm

Peak#	Ret. Time	Area	Height	Conc.	Unit	Mark	Name
1	7,916	3892716	136383	76,930		M	
2	9,299	1167370	37213	23,070		V M	
Total		5060086	173596				

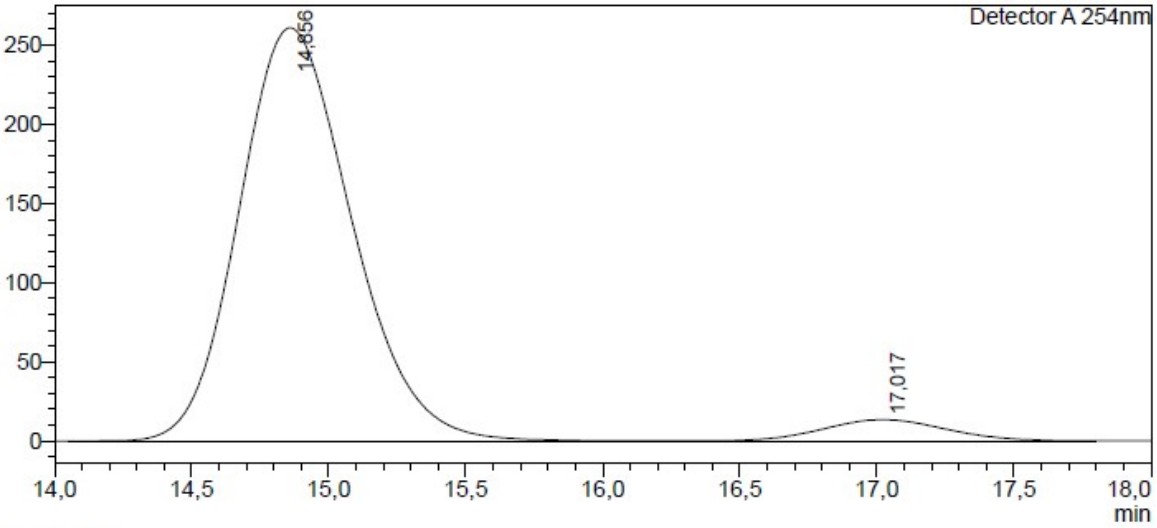
methyl (*R*)-2-((benzamido(phenyl)methyl)thio)acetate (3j)



<Peak Table>

Detector A 254nm

Peak#	Ret. Time	Area	Height	Conc.	Unit	Mark	Name
1	14,818	12141650	409018	49,954			
2	16,956	12163777	368084	50,046		V	
Total		24305426	777102				



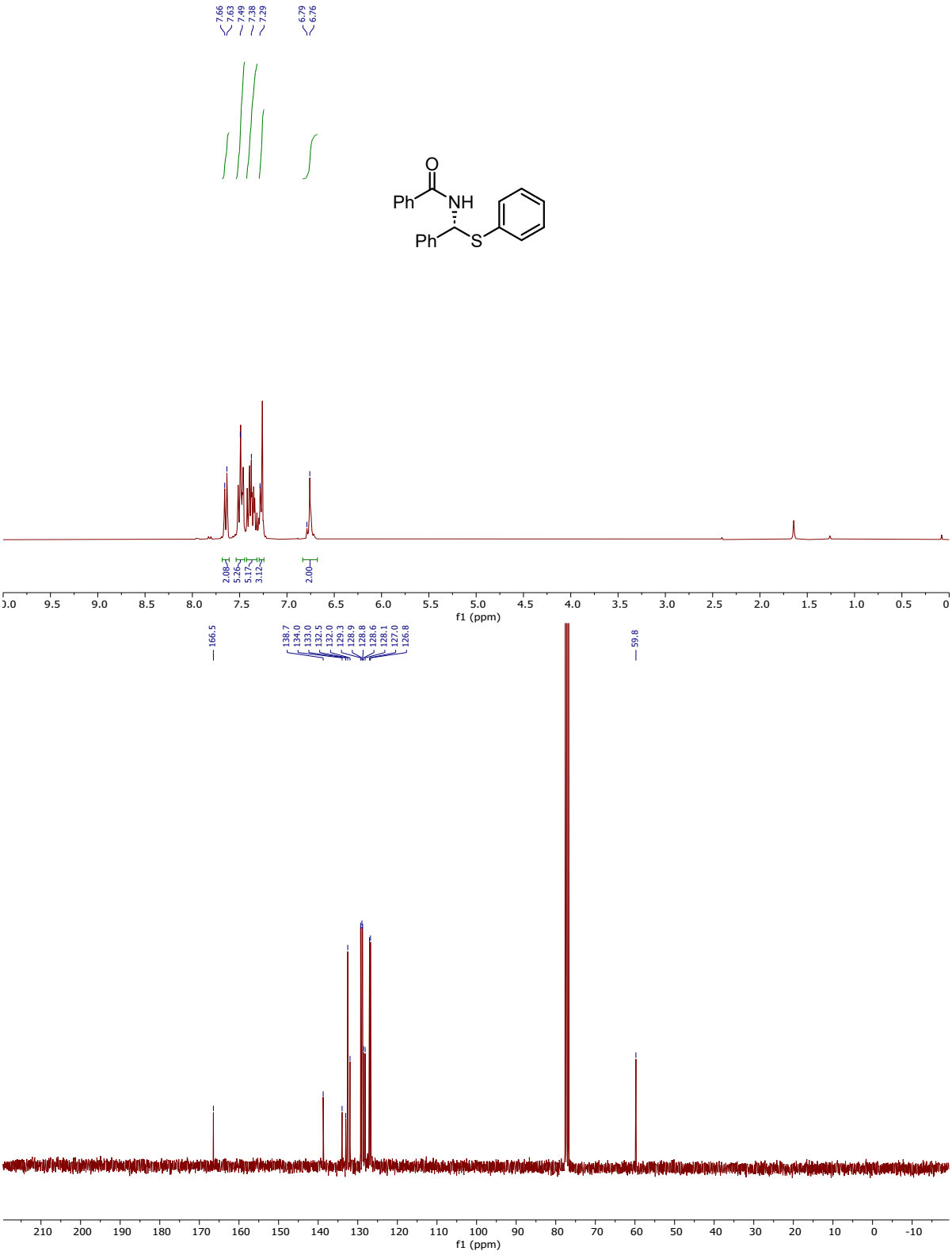
<Peak Table>

Detector A 254nm

Peak#	Ret. Time	Area	Height	Conc.	Unit	Mark	Name
1	14,856	7460528	260853	94,531			
2	17,017	431624	13531	5,469		V	
Total		7892152	274384				

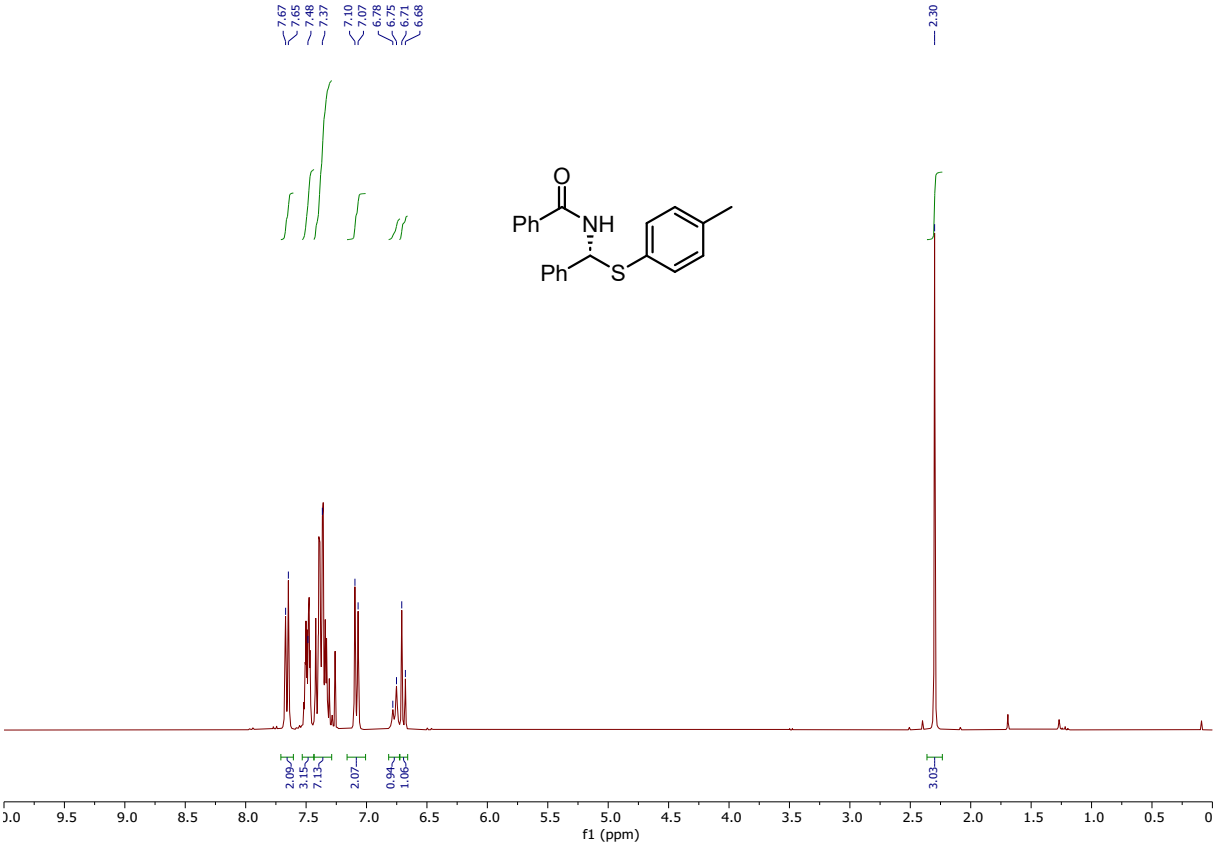
NMR spectra of **3** [1]

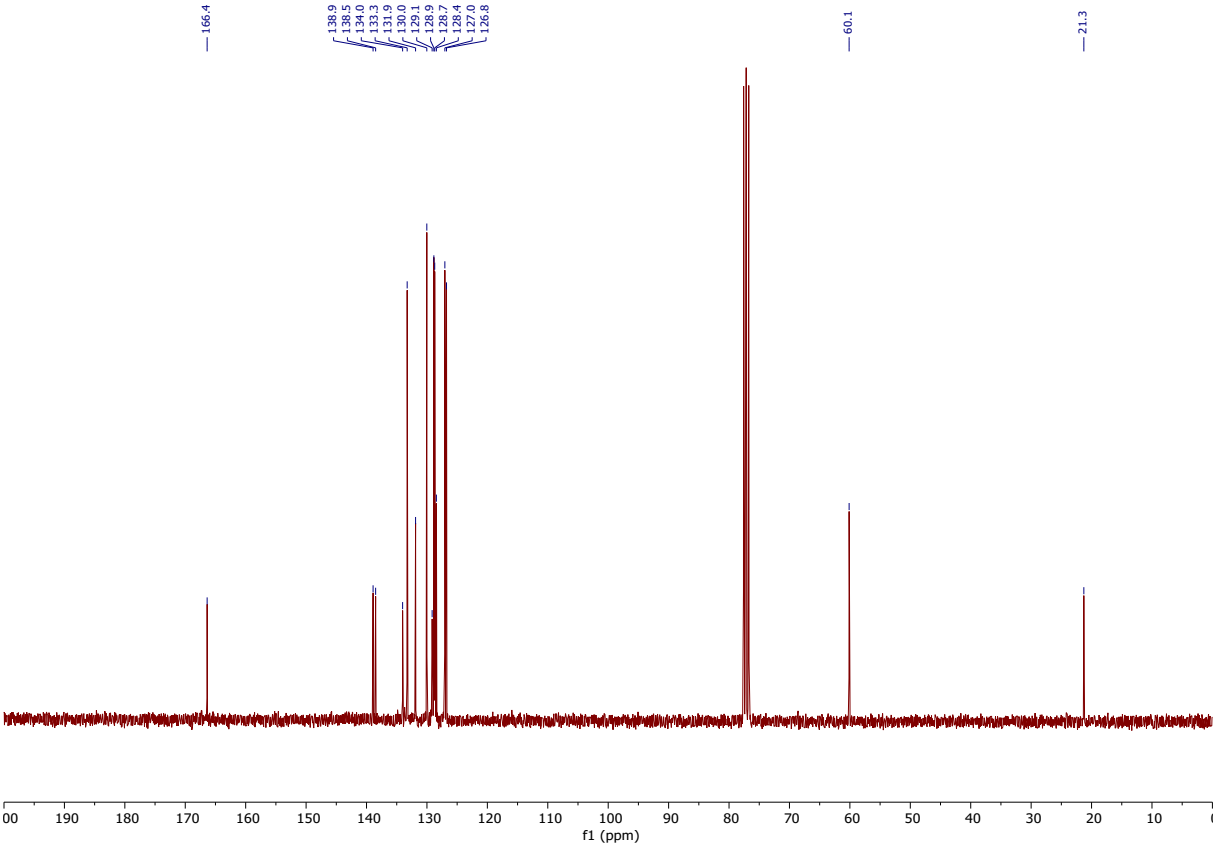
(*R*)-N-(phenyl(phenylthio)methyl)benzamide (3a) ($CDCl_3$, ^1H 300 MHz, ^{13}C 75 MHz)



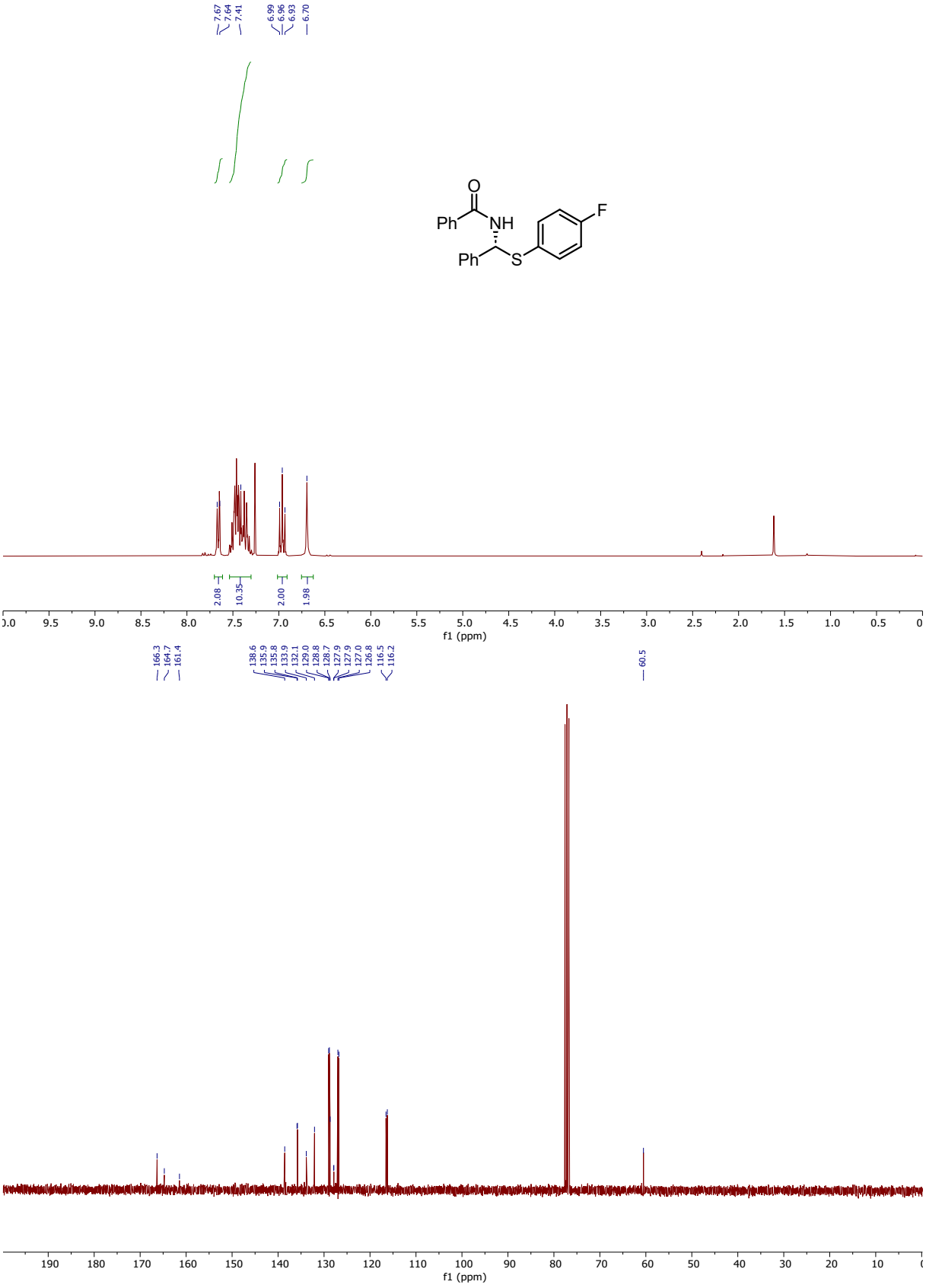
(*R*)-N-(phenyl(p-tolylthio)methyl)benzamide (3b) ($CDCl_3$, ^1H 300 MHz, ^{13}C 75 MHz)

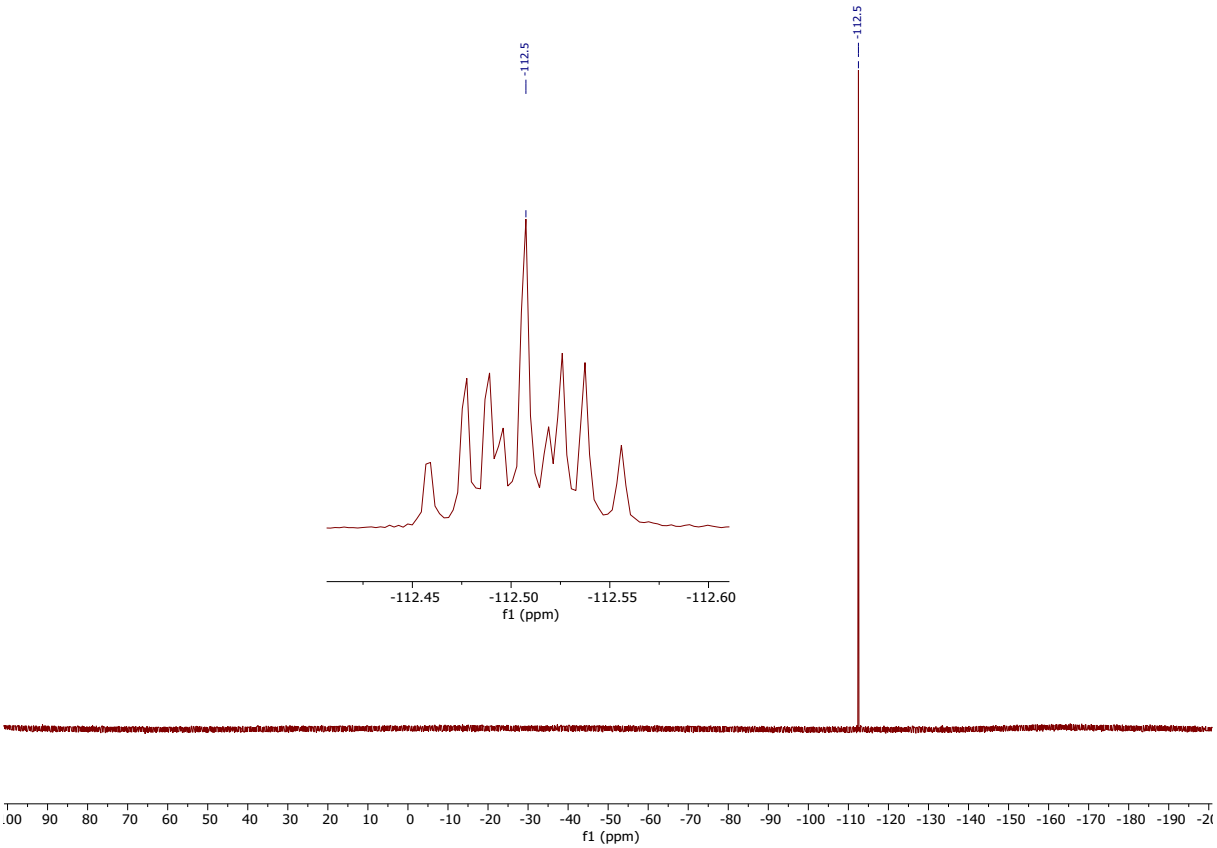
[1] All the NMR spectra correspond to the crude products after simple filtration. No additional crystallization or chromatography was performed.


7.67
7.65
7.48
7.37
7.10
7.07
6.78
6.75
6.71
6.68
2.30
O
Ph
NH
Ph
S
2.09
3.15
7.13
2.07
0.94
1.06
3.03
f1 (ppm)

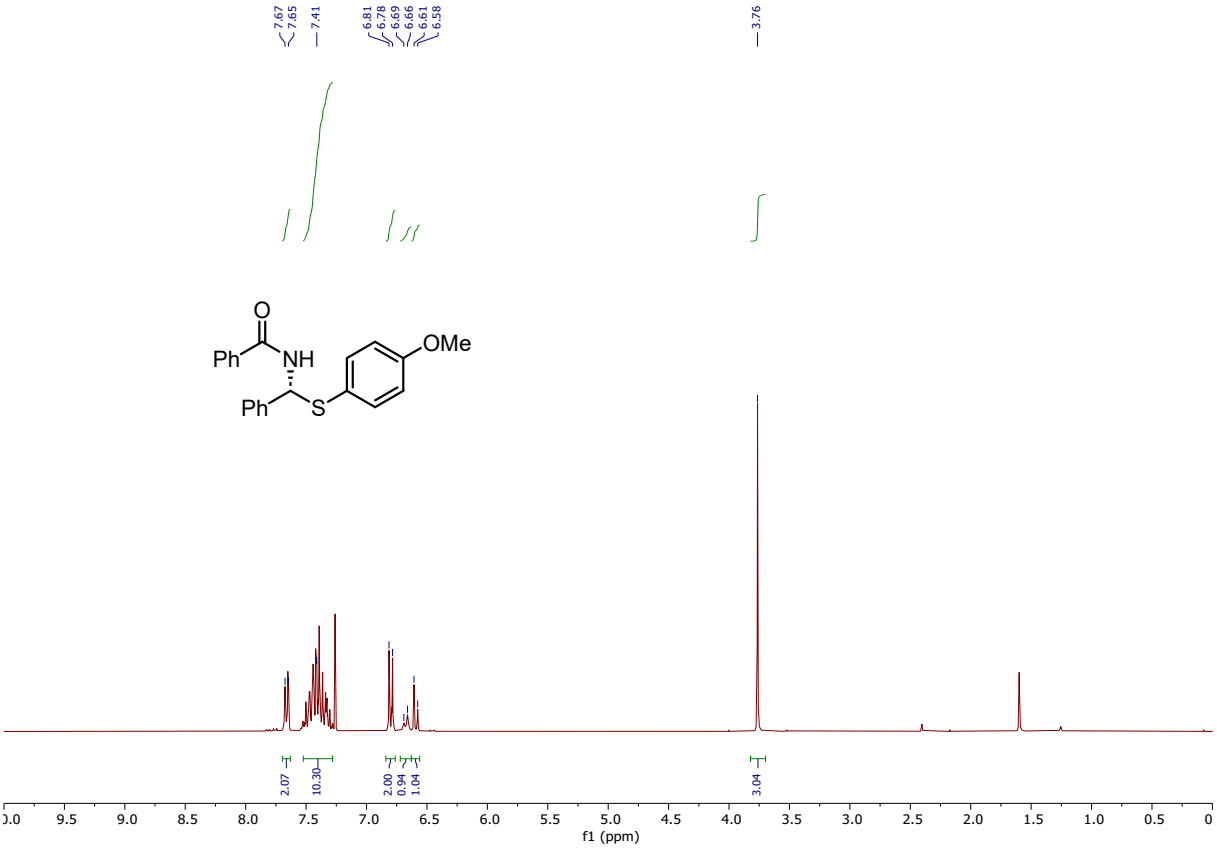

166.4
138.9
138.5
134.0
133.3
131.9
130.0
129.1
128.9
128.7
128.4
127.0
126.8
60.1
21.3
f1 (ppm)

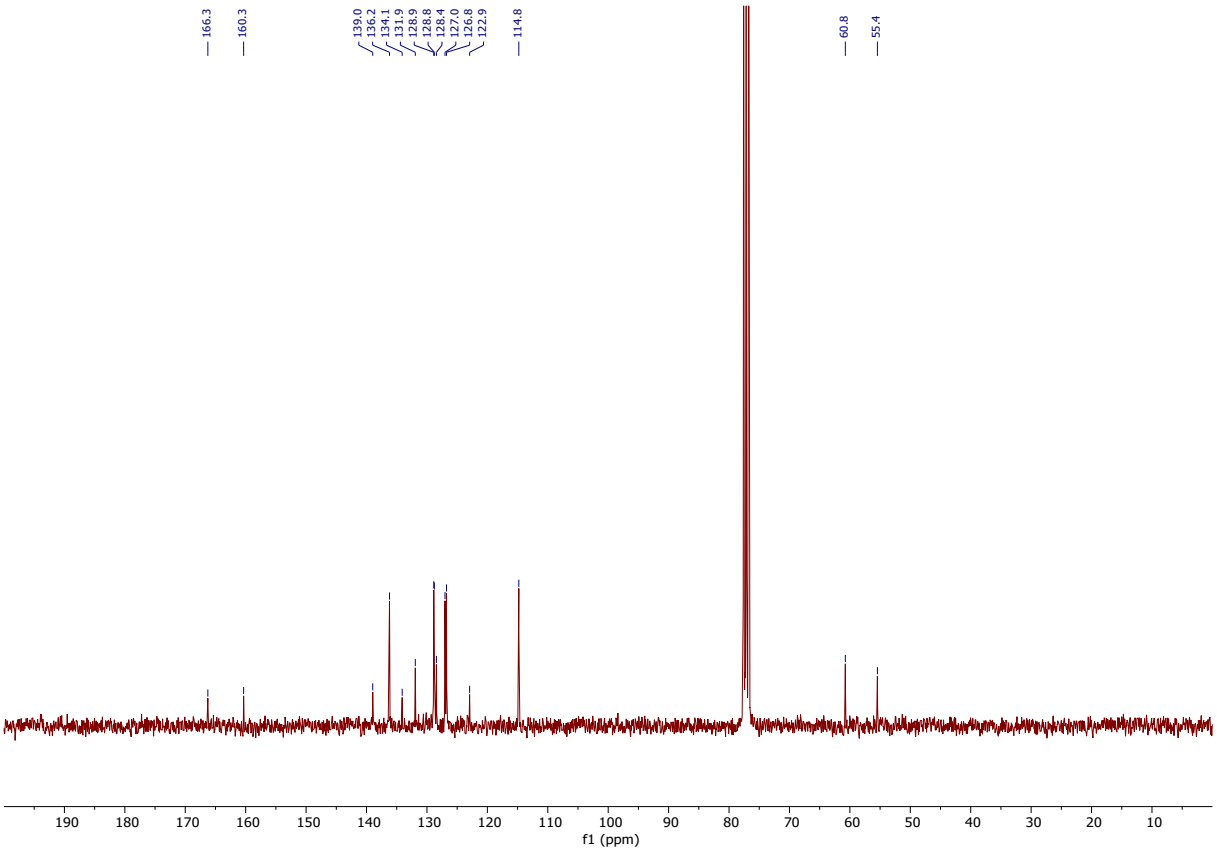
(*R*)-N-(((4-fluorophenyl)thio)(phenyl)methyl)benzamide (3c) ($CDCl_3$, ^1H 300 MHz, ^{13}C 75 MHz, ^{19}F 282 MHz)



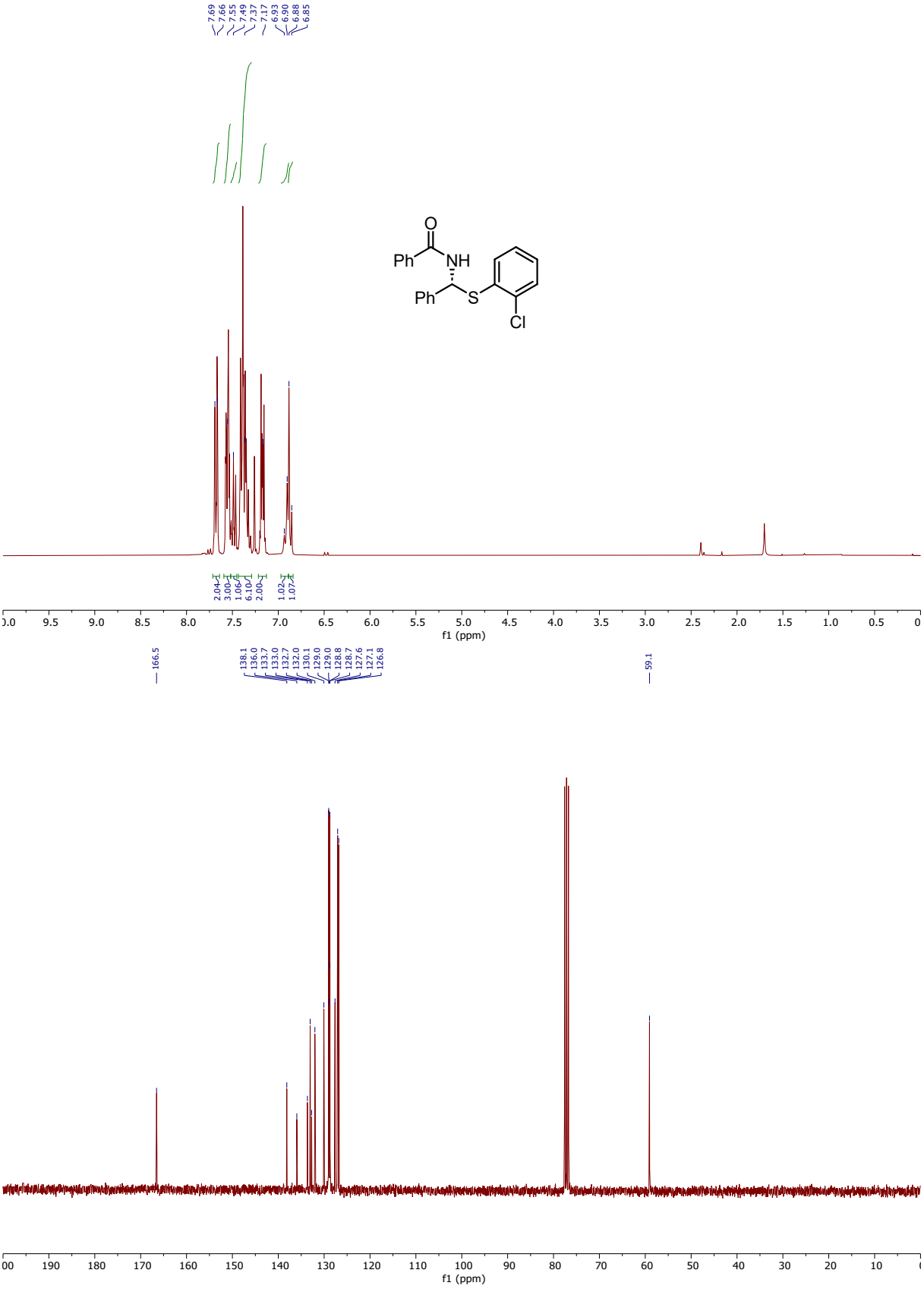

-112.5
-112.5
-112.45
-112.50
-112.55
-112.60
f1 (ppm)
.00 90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190
f1 (ppm)

(*R*)-N-(((4-methoxyphenyl)thio)(phenyl)methyl)benzamide (3d) ($CDCl_3$, ^1H 300 MHz, ^{13}C 75 MHz)

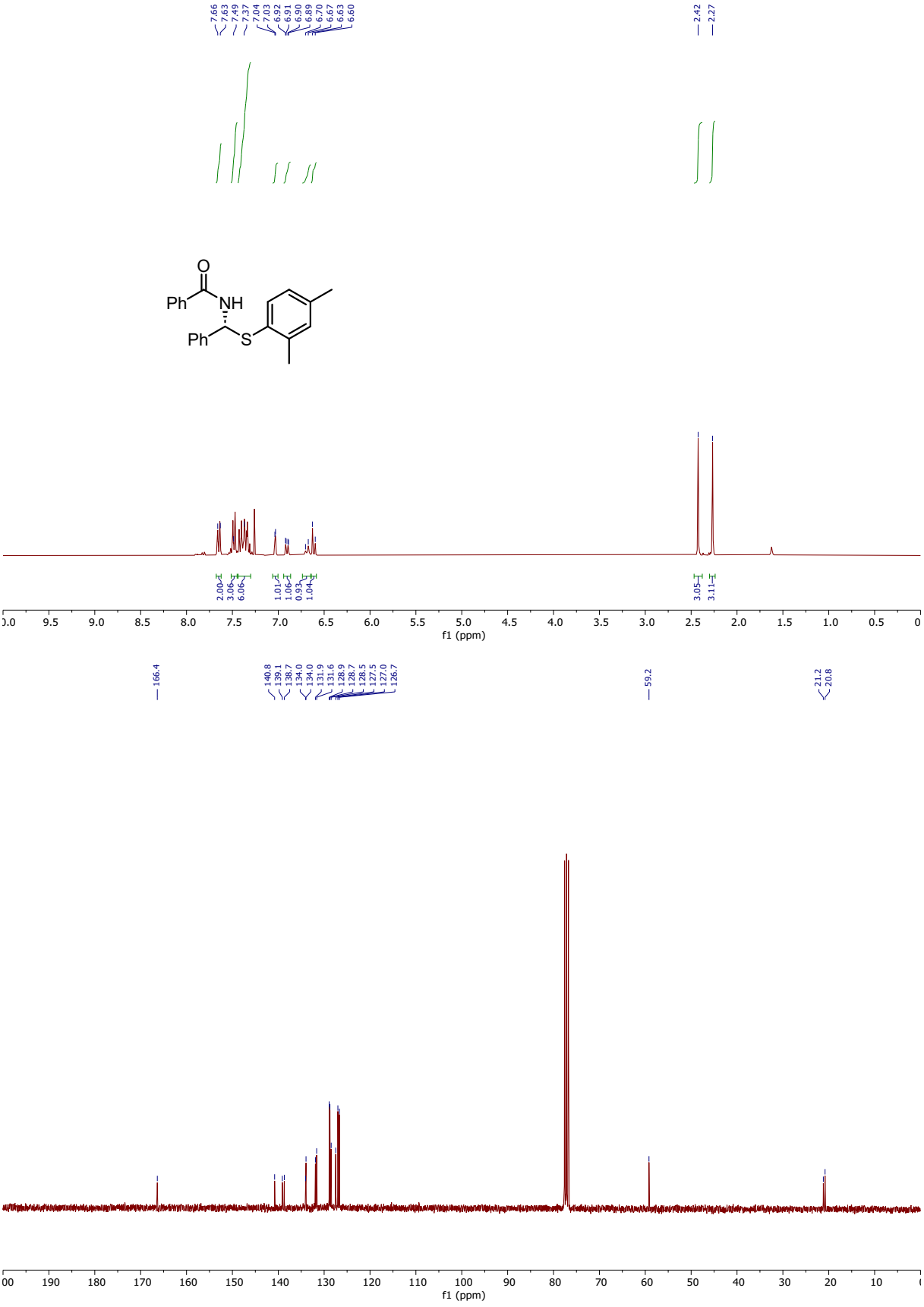




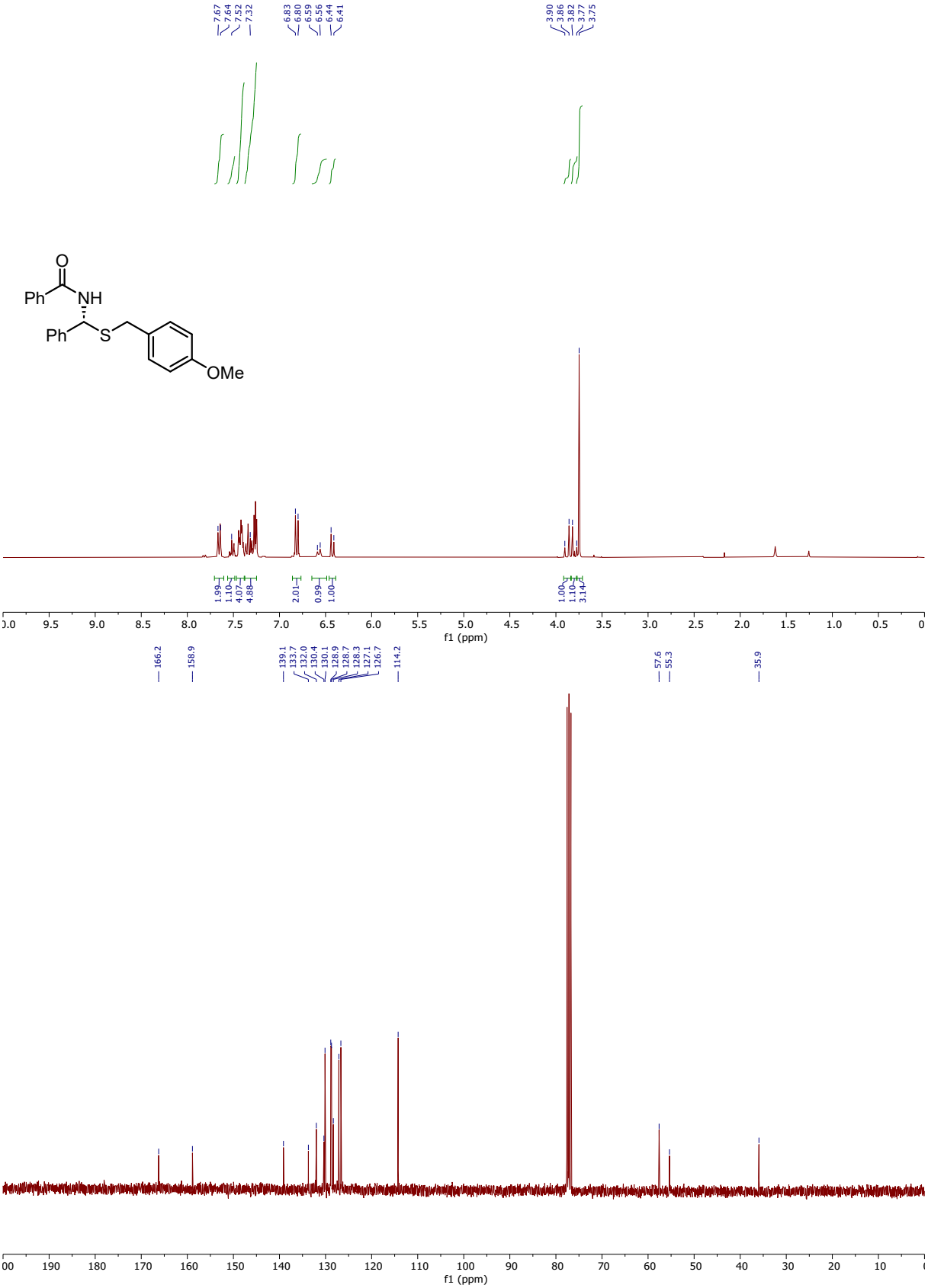
(*R*)-N-(((2-chlorophenyl)thio)(phenyl)methyl)benzamide (3e) ($CDCl_3$, ^1H 300 MHz, ^{13}C 75 MHz)



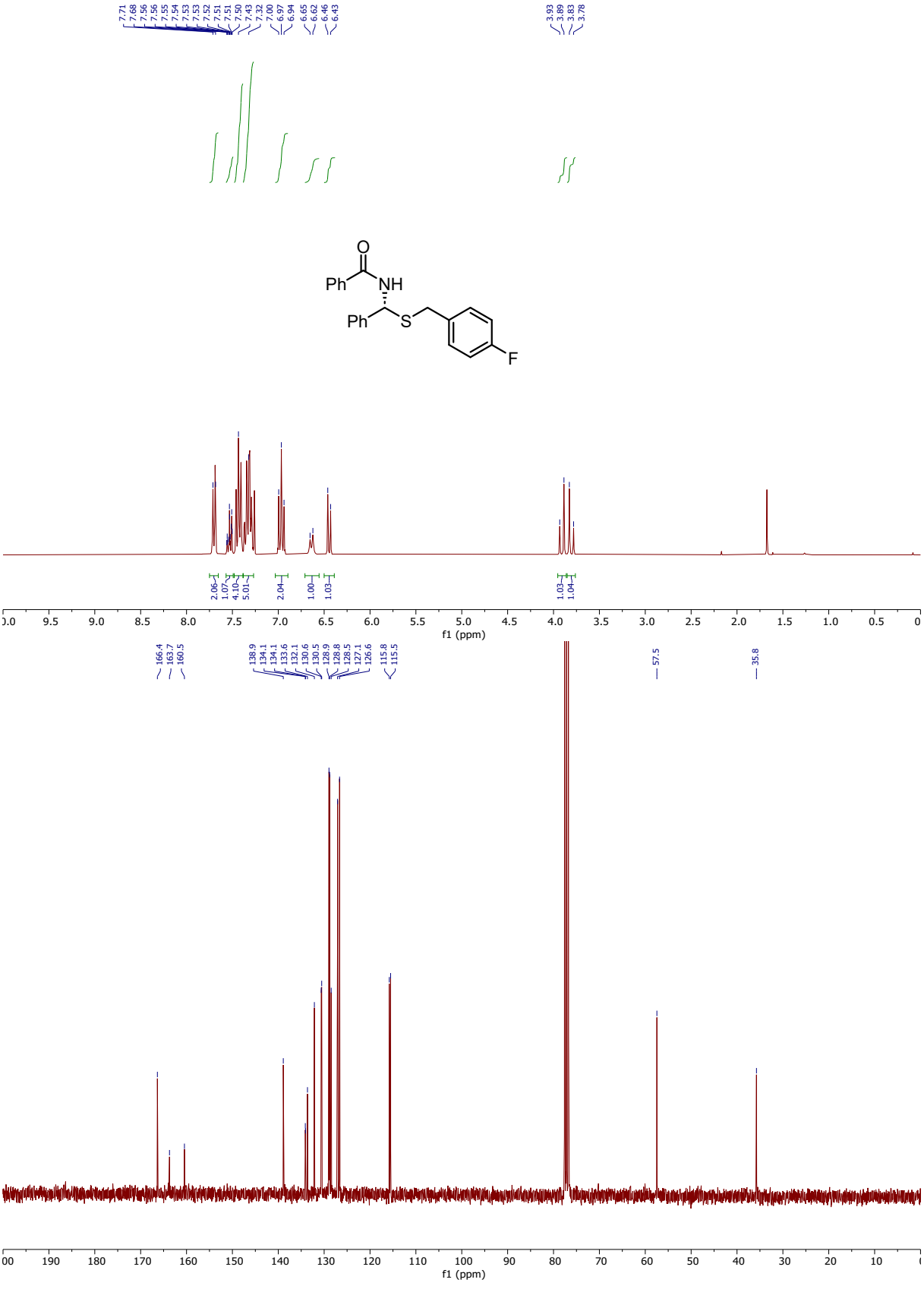
(*R*)-N-(((2,4-dimethylphenyl)thio)(phenyl)methyl)benzamide (3f) ($CDCl_3$, ^1H 300 MHz, ^{13}C 75 MHz)

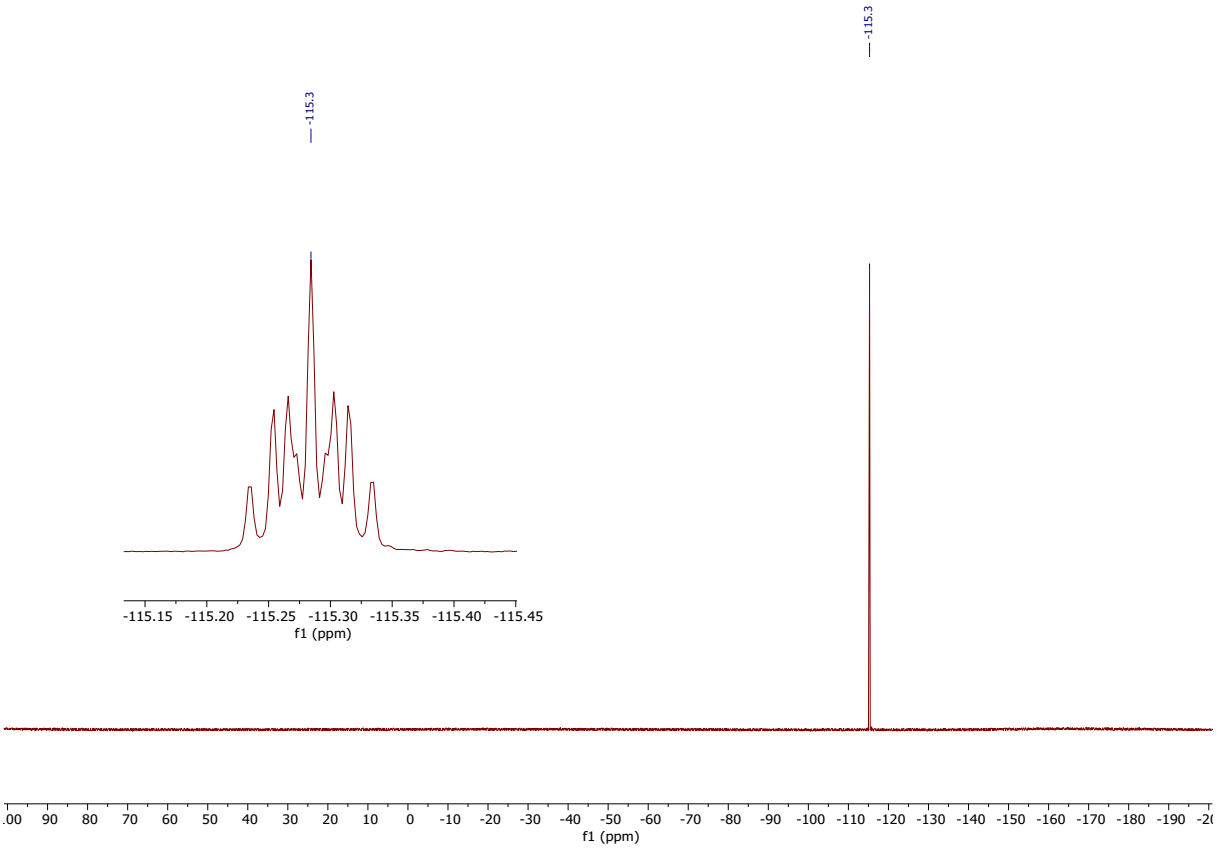


(*R*)-N-(((4-methoxybenzyl)thio)(phenyl)methyl)benzamide (3g) ($CDCl_3$, ^1H 300 MHz, ^{13}C 75 MHz)

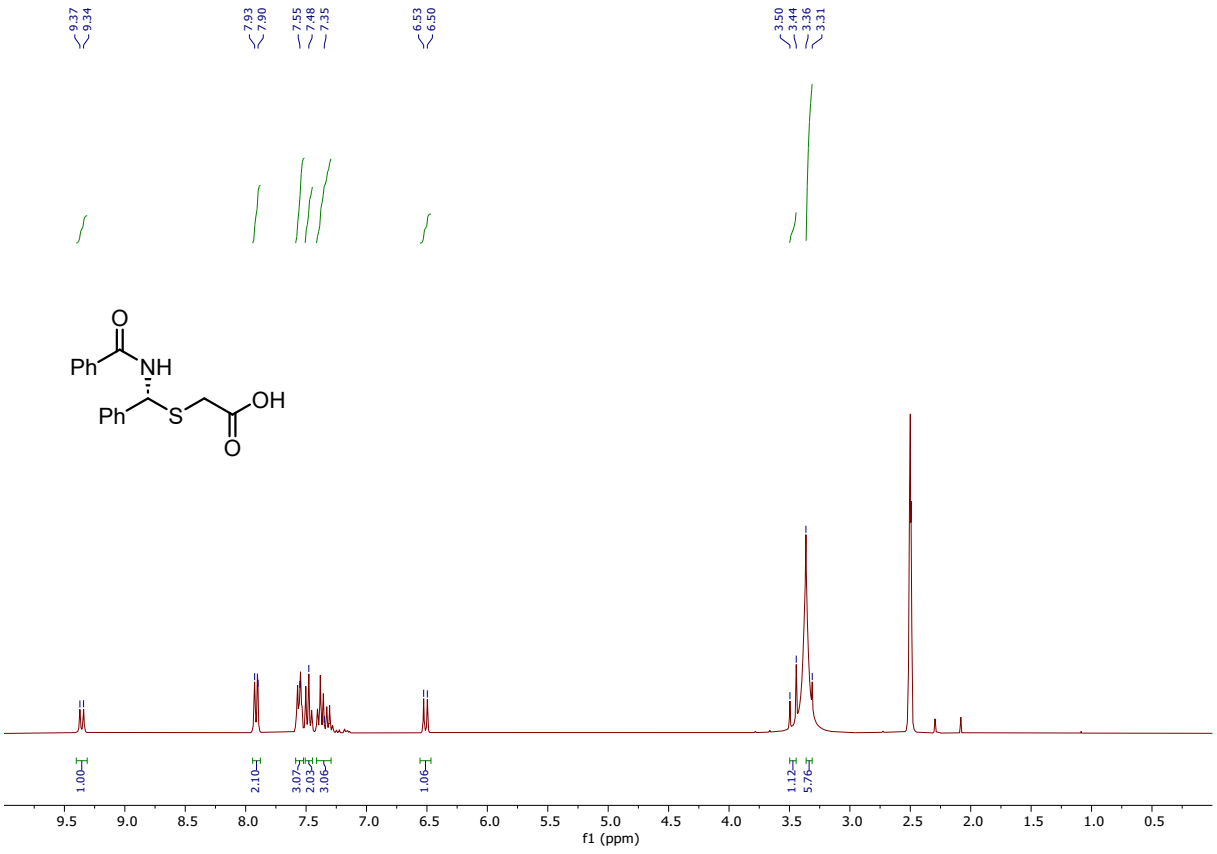


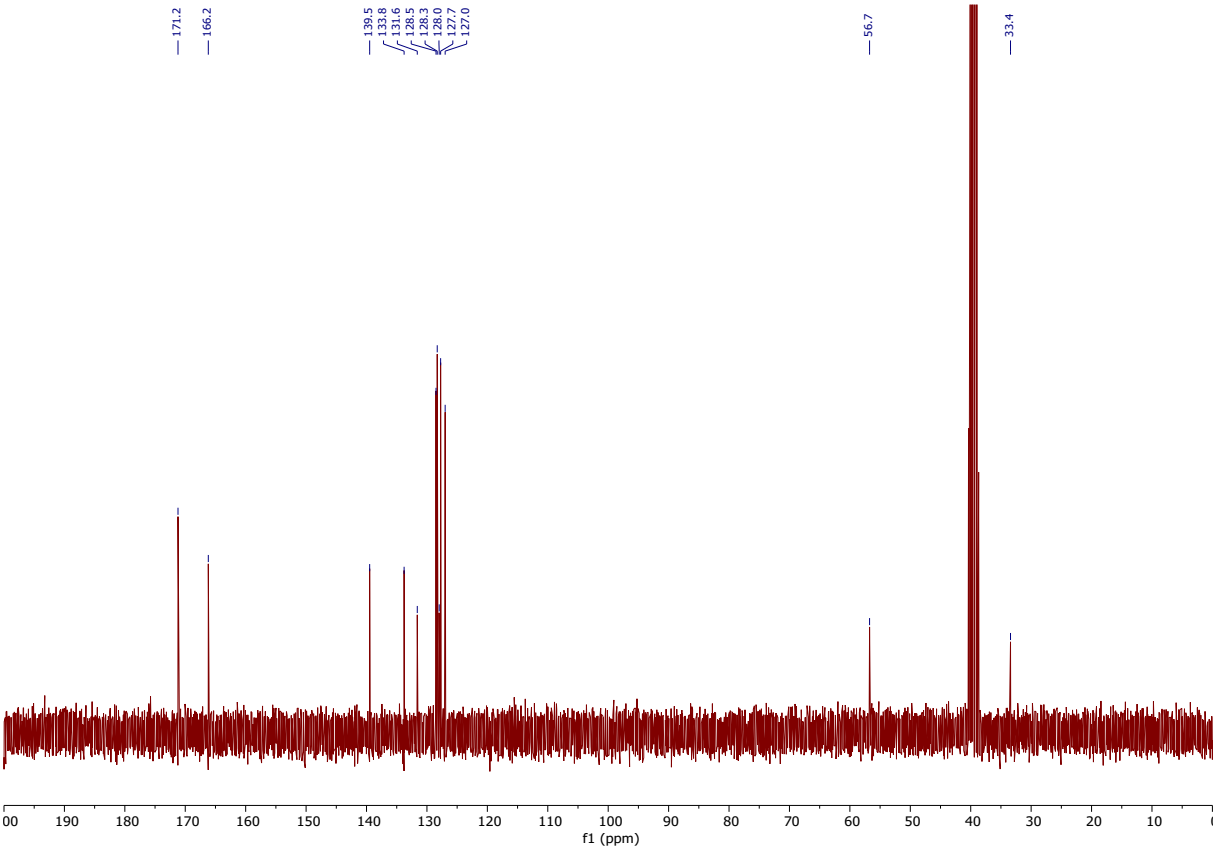
(*R*)-N-(((4-fluorobenzyl)thio)(phenyl)methyl)benzamide (3h) ($CDCl_3$, ^1H 300 MHz, ^{13}C 75 MHz, ^{19}F 282 MHz)



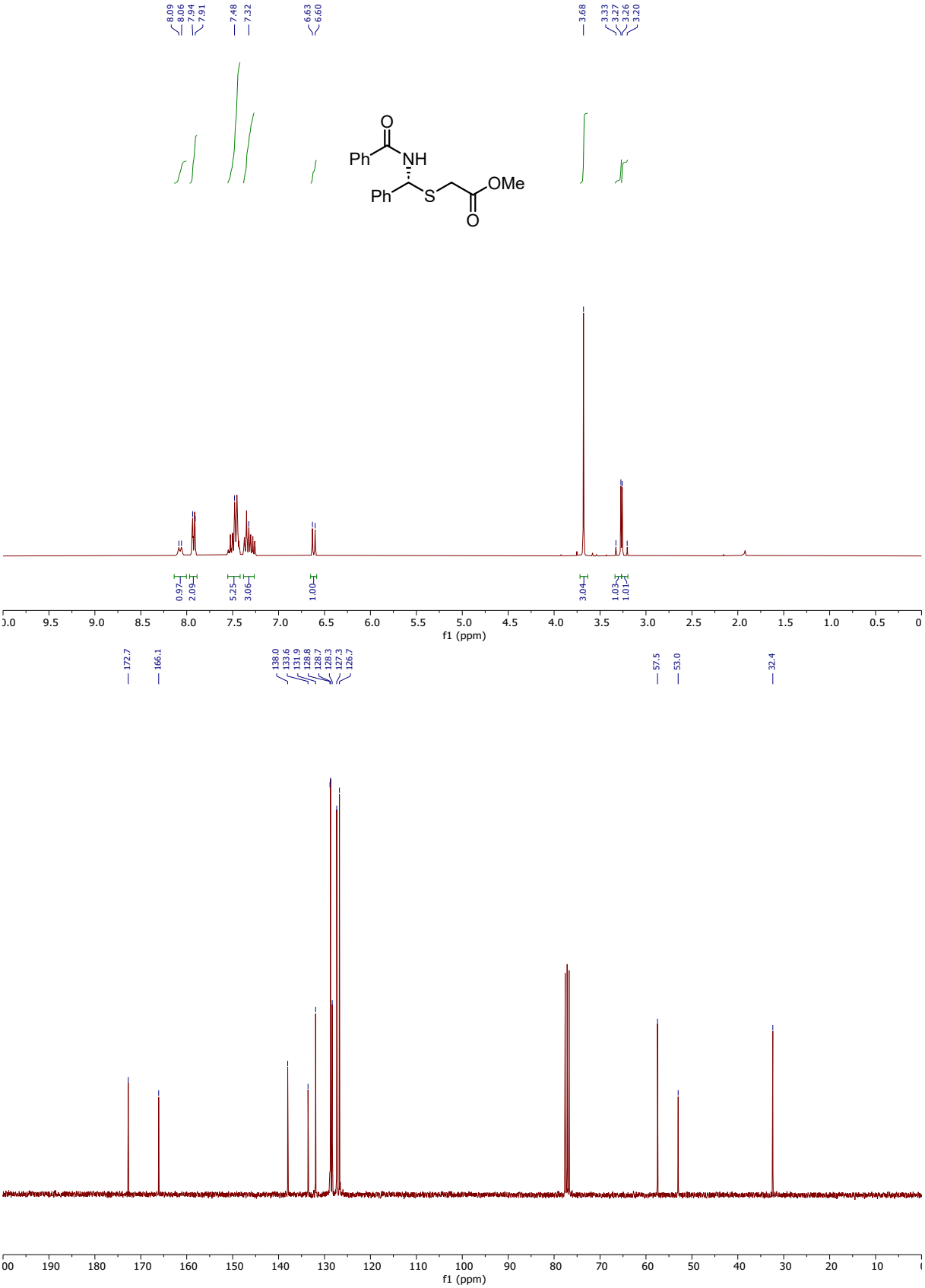

-115.3
-115.3
-115.15 -115.20 -115.25 -115.30 -115.35 -115.40 -115.45
f1 (ppm)
.00 90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190
f1 (ppm)

(*R*)-2-((benzamido(phenyl)methyl)thio)acetic acid (3i) (DMSO-d6, ^{1}H 300 MHz, ^{13}C 75 MHz)





methyl (*R*)-2-((benzamido(phenyl)methyl)thio)acetate (3j) ($CDCl_3$, ^1H 300 MHz, ^{13}C 75 MHz)



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