Electronic Supplementary Material (ESI) for Organic & Biomolecular Chemistry

Electronic Supporting Information of the Manuscript:

"SULFOLEFIN": Highly Modular Mixed S/Olefin Ligands for Enantioselective Rh-Catalyzed 1,4 Addition.

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Table of contents

General Methods

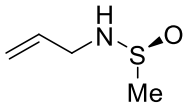
All reactions were run under an atmosphere of dry argon using oven-dried glassware and freshly distilled and dried solvents. Toluene, CH_2Cl_2 and diethyl ether were dried on an Innovative technology drying system. The metallic precursors were purchased from Strem Chemicals and the rest of the chemicals were obtained from Sigma-Aldrich and used without further purification. TLC was performed on Silica Gel GF254 (Merck) with detection by charring with phosphomolybdic acid/EtOH. For flash chromatography, silica Gel (Merck 230-400 mesh) was used. Chromatographic columns were eluted with positive air pressure and eluents are given as volume to volume ratios (v/v). NMR spectra were recorded with a Bruker Avance DPX400 (^{1}H, 400 MHz) and Bruker Avance DRX500 (^{1}H, 500 MHz), spectrometers. Chemical shifts are reported in ppm, and coupling constants are reported in Hz. Routine spectra were referenced to the residual proton or carbon signals of the solvent. High Resolution mass spectra (HRMS) were recorded in "Centro de Investigación, Tecnología e Innovación de la Universidad de Sevilla" with a Kratos MS-80RFA 241-MC apparatus. Optical rotations were determined with a Perkin-Elmer 341 polarimeter. Elemental analysis were measured in a LECO TruSpec® CHNS-932 apparatus. Melting points were measured in STUART SMP3 apparatus in open end capillary tubes. Enantiomeric excesses were measured on a Waters alliance 2695 and Agilent Technologies 1200 series apparatus with stationary chiral phase columns (Chiralcel® AD, OD, OD-H, AS-H).

Synthesis of sulfinamido-olefin ("sulfolefin") ligands[1]

General method for the synthesis of DAG-derived ligands

A solution of allylamine (375 µL, 5 mmol) in THF (7 mL) is cooled to -78 ºC for 15 min, then a commercial solution of *n*-BuLi (3.2 mL, 5 mmol) is added dropwise and the reaction is stirred for 2 hours at -78 ºC. This solution is added *via cannula* over a solution of the corresponding DAG-sulfinylating agent (2.5 mmol). The reaction is stirred at -78 ºC for 5 min, then H_2O (10 mL) is added carefully. The phases are separated, the aqueous layer is extracted with EtOAc (2x10 mL) and the organic extracts are collected and dried over anhydrous $MgSO_4$. The solvent is eliminated under vacuum and the residue is purified by flash chromatography. Eluents are detailed for each case.

(*S*)-*N*-allyl-methanesulfinamide (1)



Flash chromatography (EtOAc), yellow oil. Yield: 500 mg, 78%.

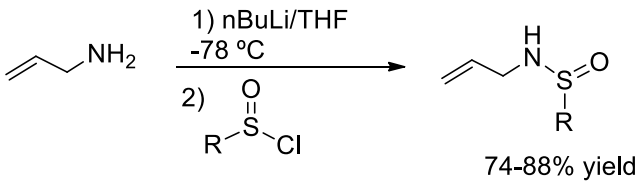
$[\alpha]^{D}_{20}$= -3.0 (*c* 0.7, $CHCl_3$).

HPLC: Chiralcel ®AD column (*n*-hexane/2-propanol, 94:6, 0.5 mL/min); t_R: 33.1 min. (*S*-isomer), 34.9 min. (*R*-isomer).

^{1}H NMR (500 MHz, $CDCl_3$): δ 5.95-5.86 (m, 1H), 5.26 (d, *J*= 17.1 Hz, 1H), 5.16 (d, *J*= 10.2 Hz, 1H), 4.11 (bs, 1H), 3.76-3.65 (m, 2H), 2.63 (s, 3H).

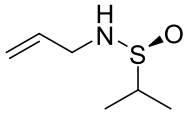
^{13}C NMR (125 MHz, $CDCl_3$): δ 134.7, 117.4, 44.9, 41.9.

[1]For the synthesis of the racemic ligands for HPLC studies, allylamine was treated with 2 eq. of *n*BuLi followed by quenching with the corresponding racemic sulfinyl chloride according to the following scheme.



Elemental analysis: Calcd. for C_4H_9NOS: C, 40.31%; H,7.61 %; N, 11.75%; S, 26.90%. Found: C, 40.48; H, 7.89%; N, 11.58%; S, 26.92%.

(*S*)-*N*-allyl-isopropanesulfinamide (2)



Flash chromatography (EtOAc), yellow oil. Yield: 315 mg, 87%

$[\alpha]^{D}_{20}$ = -10.5 (*c* 0.6, $CHCl_3$).

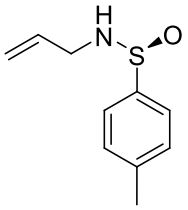
HPLC: Chiralcel® AD column (*n*-hexane/2-propanol, 90:10, 0.5 mL/min); t_R: 30.5 min. (*S*-isomer), 34.0 min. (*R*-isomer).

^{1}H NMR (500 MHz, $CDCl_3$): δ 5.94-5.88 (m, 1H), 5.27 (d, *J* = 17.4 Hz, 1H), 5.17 (d, *J* = 9.0 Hz, 1H), 3.80-3.50 (m, 3H), 2.78 (sep, *J* = 6.3 Hz, 1H), 1.24 (d, *J* = 6.8 Hz, 3H), 1.22 (d, *J* = 6.7 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 135.0, 117.2, 53.6, 46.3, 15.6.

Elemental analysis: Calcd. for $C_6H_{13}NOS$: C, 48.94%; H,8.90 %; N, 9.51%; S, 21.78%. Found: C, 49.05; H, 8.91%; N, 9.31%; S, 21.96%.

(*S*)-*N*-allyl-*p*-toluenesulfinamide (3)



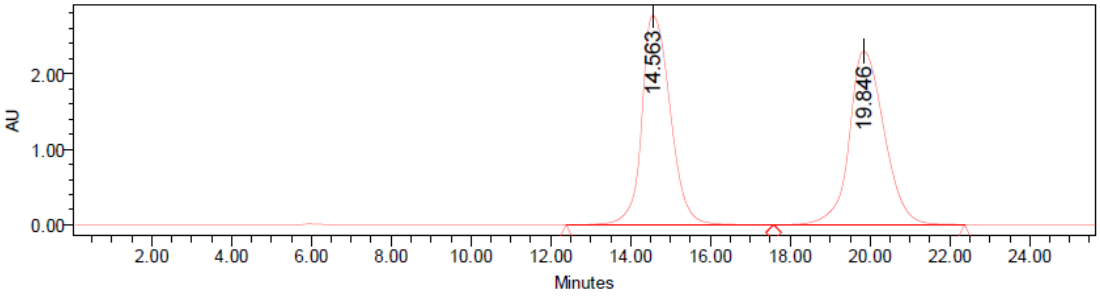
Flash chromatography (Hexane:EtOAc,1:1), white solid. Yield: 430 mg, 67%

$[\alpha]^{D}_{20}$= -24 (*c* 0.5, $CHCl_3$).

HPLC: Chiralcel® AD column (*n*-hexane/2-propanol, 90:10, 0.5 mL/min); t_R: 14.5 min. (*S*-isomer), 19.8 min. (*R*-isomer).

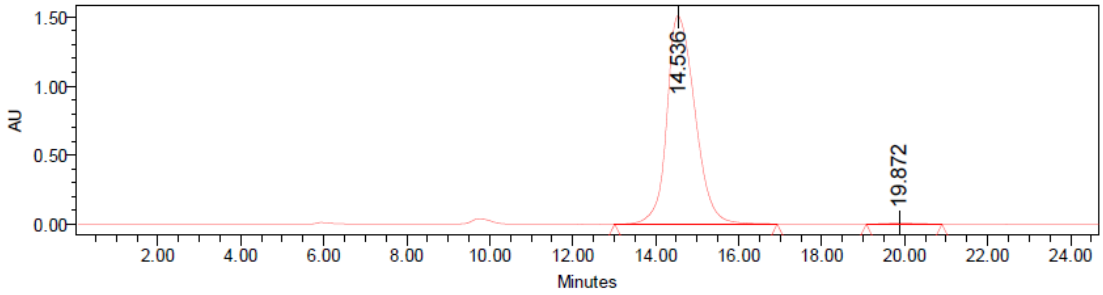
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.58 (d, *J* = 8.6 Hz, 2H), 7.29 (d, *J* = 7.7 Hz, 2H), 5.87-5.80 (m, 1H), 5.20 (d, *J* = 17.1 Hz, 1H), 5.11 (d, *J* = 10.1 Hz, 1H), 4.17 (bs, 1H), 3.80 (dd, *J* = 5.7 and 14.8 Hz, 1H), 3.70 (dd, *J* = 4.3 and 14.9 Hz, 1H), 2.40 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$):δ 141.3, 134.7, 129.5, 125.9, 117.3, 43.6, 21.3



Peak Results

	Name	RT	% Area
1		14.563	49.61
2		19.846	50.39



Peak Results

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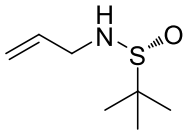
1		14.536	99.56
2		19.872	0.44

(*R*)-*N*-allyl-*tert*-butanesulfinamide (4)



Flash chromatography (Hexane:EtOAc, 1:1),yellow oil. Yield: 669 mg, 83%

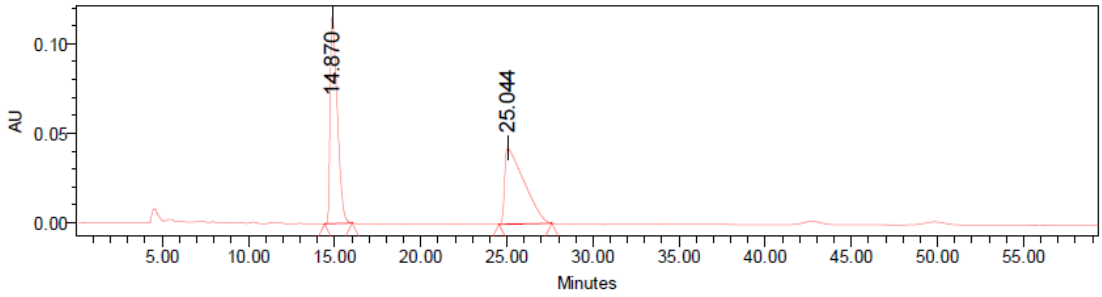
$[\alpha]^{D}_{20}$= +12.3 (*c* 0.6, $CHCl_3$).

HPLC: Chiralcel® AS-H column (*n*-hexane/2-propanol, 90:10, 0.7 mL/min); t_R: 13.8 min. (*S*-isomer), 24.7 min. (*R*-isomer).

^{1}H NMR (500 MHz, $CDCl_3$): δ 5.95-5.86 (m, 1H), 5.26 (d, *J* = 17.1 Hz, 1H), 5.16 (d, *J* = 10.2 Hz, 1H), 3.74-3.65 (m, 1H), 3.47-3.39 (m, 1H), 1.22 (s, 9H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 135.2, 117.0, 55.7, 48.1, 22.5.

Elemental analysis: Calcd. for $C_7H_{15}NOS$: C, 52.13%; H,9.38 %; N, 8.69%; S, 19.88%. Found: C, 52.36; H, 9.26%; N, 8.39%; S, 20.10%.



Peak Results

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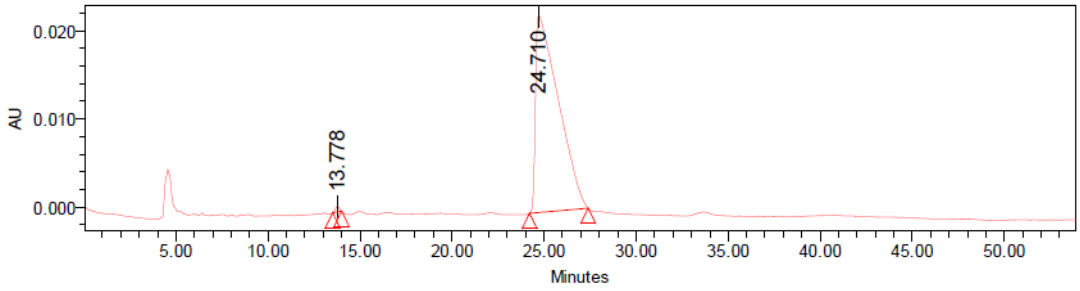
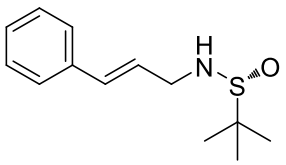
1		14.870	50.06
2		25.044	49.94



Peak Results

	Name	RT	% Area
1		13.778	0.48
2		24.710	99.52

(*R*)-*N*-cinammyl-*tert*-butanesulfinamide (5)



Flash chromatography (Hexane:EtOAc, 1:1) Light yellow solid.

Mp (ºC): 58-59 ºC

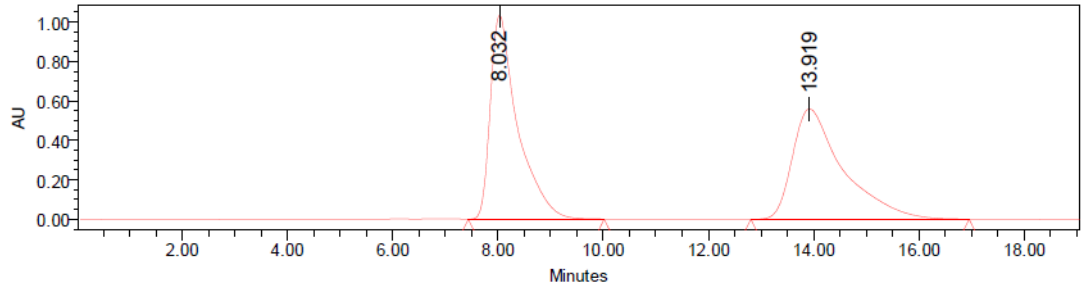
$[\alpha]^{D}_{20}$= - 36.1 (*c* 0.5, $CHCl_3$)

HPLC: Chiralcel® OD column (*n*-hexane/2-propanol, 90:10, 1 mL/min); t_R: 8.0 min. (*S*-isomer), 13.8 min. (*R*-isomer).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.37 (d, *J* = 7.7 Hz, 2H), 7.31 (t, *J* =7.7 Hz, 2H), 7.24 (t, *J* = 7.2 Hz, 1H), 6.57 (d, *J* = 15.8 Hz, 1H), 6.24 (dt, *J*= 6.2, 15.8 Hz, 1H), 4.02-3.94 (m, 1H), 3.93-3.84 (m, 1H), 3.34 (t, *J* = 5.5 Hz, 1H), 1.24 (s, 9H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 136.4, 132.5, 128.5, 127.7, 126.4, 55.7, 47.8, 22.6.

Elemental analysis: Calcd. for $C_{13}H_{19}NOS$: C, 65.78%; H,8.07 %; N, 5.90%; S, 13.51%. Found: C, 65.66; H, 7.94%; N, 6.15%; S, 13.79%.



Peak Results

	Name	RT	% Area
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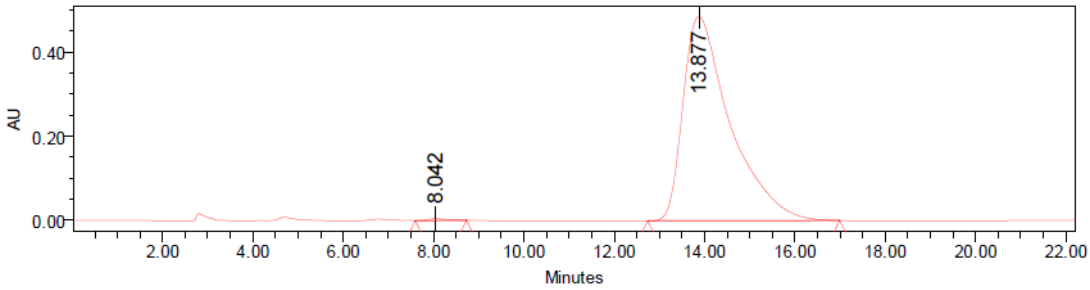
2		13.919	50.01



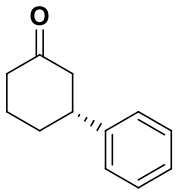
Peak Results

	Name	RT	% Area
1		8.042	0.37
2		13.877	99.63

Representative procedure for the Rh(I) catalyzed 1,4-addition of boronic acids to enones

A mixture of sulfolefin ligand **5** (7.1 mg, 0.03 mmol) and $[Rh(C_2H_4)_2Cl]_2$ (6.0 mg, 0.015 mmol) is stirred for 0.5 hours in 1.2 mL of degassed solvent. $PhB(OH)_2$ (146 mg, 1.2 mmol) is added over the catalyst and sequentially the α,β-unsaturated carbonyl compound (0.6 mmol) and 2.5 M KOH aqueous solution (120 µL, 2.5 M). The reaction is followed by TLC, and once the starting material is consumed, the crude reaction mixture is purified by flash chromatography. The eluents are detailed for each case.

(*R*)-3-Phenyl-cyclohexanone (8)



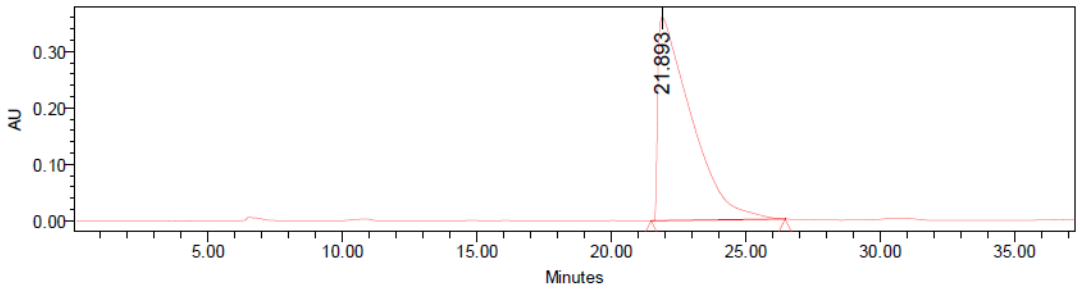
Following the typical procedure for the 1,4-addition, the reaction of cyclohexenone **6** (58µL, 0.6 mmol) and phenyl boronic acid **7** (146 mg, 1.2 mmol) gave, after flash chromatography (Hexane:Et_2O, 9:1), the product **8** as a colourless oil. Yield: 97.2 mg, 93%

$[\alpha]^{D}_{20}$ = -18.3 (*c* 0.9, $CHCl_3$).

HPLC: 99 % ee, Chiralcel® OD-H column (*n*-hexane/2-propanol, 90:10, 0.5 mL/min); t_R: 21.8 min (major), 23.7 min (minor).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.33-7.36 (m, 2H), 7.21-7.26 (m, 3H), 3.01(m, 1H), 2.37-2.59 (m, 4H), 2.07-2.16 (m, 2H), 1.80-1.89 (m, 2H).

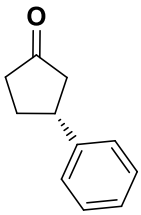
^{13}C NMR (125 MHz, $CDCl_3$): δ, 210.9, 144.3, 128.6, 126.6, 126.5, 48.9, 44.7, 41.1, 32.7, 25.5



Peak Results

	Name	RT	% Area
1		21.893	100.00

(*R*)-3-Phenyl-cyclopentanone (12)



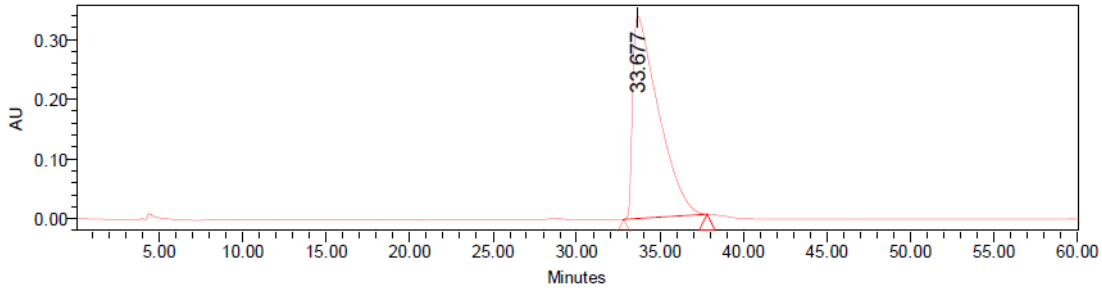
Following the typical procedure for the 1,4-addition, the reaction of 2-cyclopentenone **9** (50µL, 0.6 mmol) and phenyl boronic acid **7** (146 mg, 1.2 mmol) gave the product **12**, after flash chromatography (Hexane:Et_2O, 9:1), as a colorless oil. Yield: 89.4 mg, 93%.

$[\alpha]^{D}_{20}$ = -123.6 (*c* 0.5, $CHCl_3$)

HPLC: 99 % ee, Chiralcel® OB column (*n*-hexane/2-propanol, 90:10, 0.5 mL/min); t_R: 30.5 min. (minor), 34.0 min. (major).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.33-7.38 (m, 2H), 7.23-7.28 (m, 3H), 3.40-3.48 (m, 1H), 2.62-2.71(m, 1H), 2.30-2.49 (m, 4H), 1.98-2.02 (m, 1H) ppm.

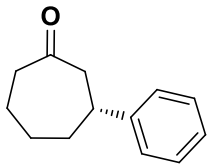
^{13}C NMR (125 MHz, $CDCl_3$): δ 218.1, 142.9, 128.5, 126.5, 126.5, 45.6, 42.0, 38.7, 31.0. ppm



Peak Results

	Name	RT	% Area
1		33.677	100.00

(*R*)-3-Phenyl-cycloheptanone (13)



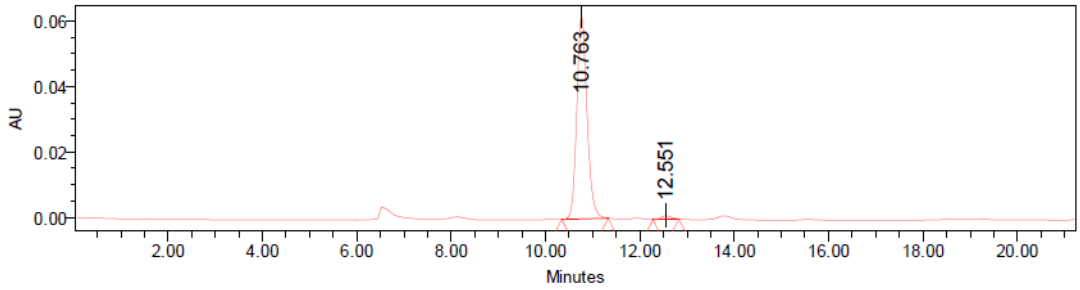
Following the typical procedure for the 1,4-addition, the reaction of 2-cycloheptenone **10** (66.8 µL, 0.6 mmol) and phenyl boronic acid **7** (146 mg, 1.2 mmol) gave the product **13**, after flash chromatography (Hexane:Et_2O, 9:1), as a colorless oil. Yield: 103.9 mg, 92%.

$[\alpha]^{D}_{20}$= -72.6 (*c* 0.8, $CHCl_3$).

HPLC: 96% ee, Chiralcel® OD-H column (n-hexane/2-propanol, 90:10, 0.5 mL/min); t_R: 10.7min. (major), 12.5 min. (minor).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.26-7.32 (m, 2H), 7.16-7.22 (m, 3H), 2.90-2.94 (m, 2H), 2.57-2.67 (m, 3H), 2.03-2.07 (m, 3H), 1.72-1.75 (m, 2H), 1.51 (m, 1H) ppm.

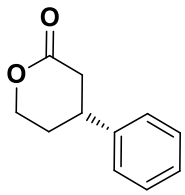
^{13}C NMR (125 MHz, $CDCl_3$): δ 213.3, 146.8, 128.5, 126.3, 126.2, 51.2, 43.8, 42.6, 39.1, 29.1, 24.1 ppm.



Peak Results

	Name	RT	% Area
1		10.763	98.32
2		12.551	1.68

(*R*)-4-phenyl-tetrahydro-2H-pyran-2-one (14)



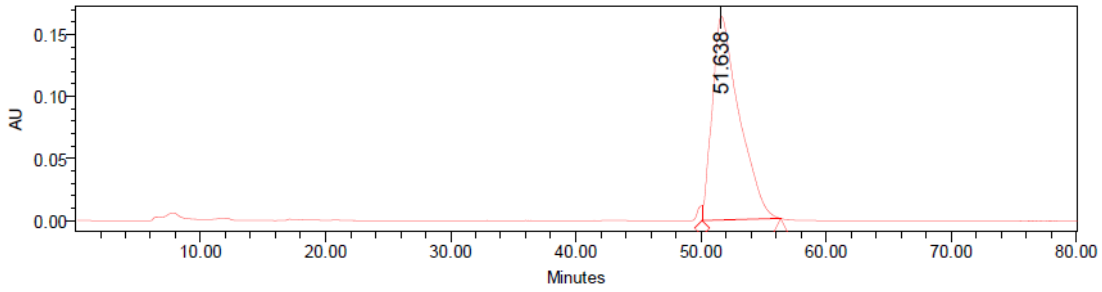
Following the typical procedure for the 1,4-addition, the reaction of 5,6-dihydro-2*H*-pyran-2-one **11** (58.8 µL, 0.6 mmol) and phenyl boronic acid **7** (146 mg, 1.2 mmol) gave the product **14**, after flash chromatography (Hexane:Et_2O, 9:1), as a colorless oil. Yield: 101.5 mg, 96%.

$[\alpha]^{D}_{20}$= -8.3 (*c* 0.7, $CHCl_3$)

HPLC: 99% ee, Chiralcel® OD-H column (n-hexane/2-propanol, 90:10, 0.5 mL/min); t_R: 51.6 min. (mayor), 61.4 min. (minor).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.20-7.39 (m, 5H), 4.38-4.52 (m, 2H), 3.22-3.26 (m, 1H),2.88-2.96 (m, 1H), 2.64 (dd, *J* = 10.6 Hz, *J* =17.6 Hz, 1H), 2.00-2.16 (m, 2H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 170.6, 142.8, 128.9, 127.2, 126.4, 68.6, 37.4, 30.3 ppm.



Peak Results

	Name	RT	% Area
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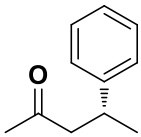
(*R*)-4-phenylpentan-2-one (16)

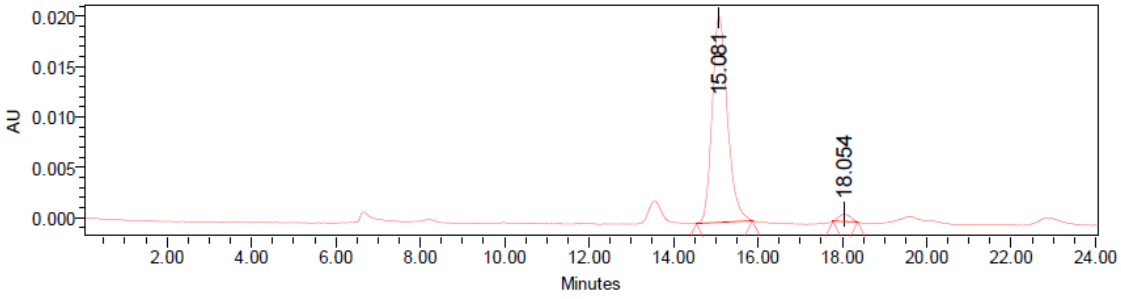


Following the typical procedure for the 1,4-addition, the reaction of 3-penten-2-one **15** (83.1µL, 0.6 mmol) and phenyl boronic acid **7** (146 mg, 1.2 mmol) gave the product **16**, after flash chromatography (Hexane:Et_2O, 9:1), as a colorless oil. Yield: 75.9 mg, 78%. $[\alpha]^{D}_{20}$ = -20.8 (*c* 0.8, $CHCl_3$).

HPLC: 94% ee, Chiralcel® AS-H column (n-hexane/2-propanol, 98:2, 0.5 mL/min); t_R: 15.1 min. (mayor), 18.1 min (minor).

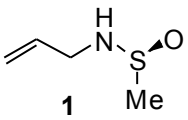
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.17-7.32 (m, 5H), 3.28-3.34 (m, 1H), 2.61- 2.80 (m, 2H), 2.06 (s, 3H), 2.01(d, *J* = 6.9Hz, 3H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 207.7, 146.1, 128.5, 126.7, 126.2,51.9,35.4, 30.5, 21.9 ppm.

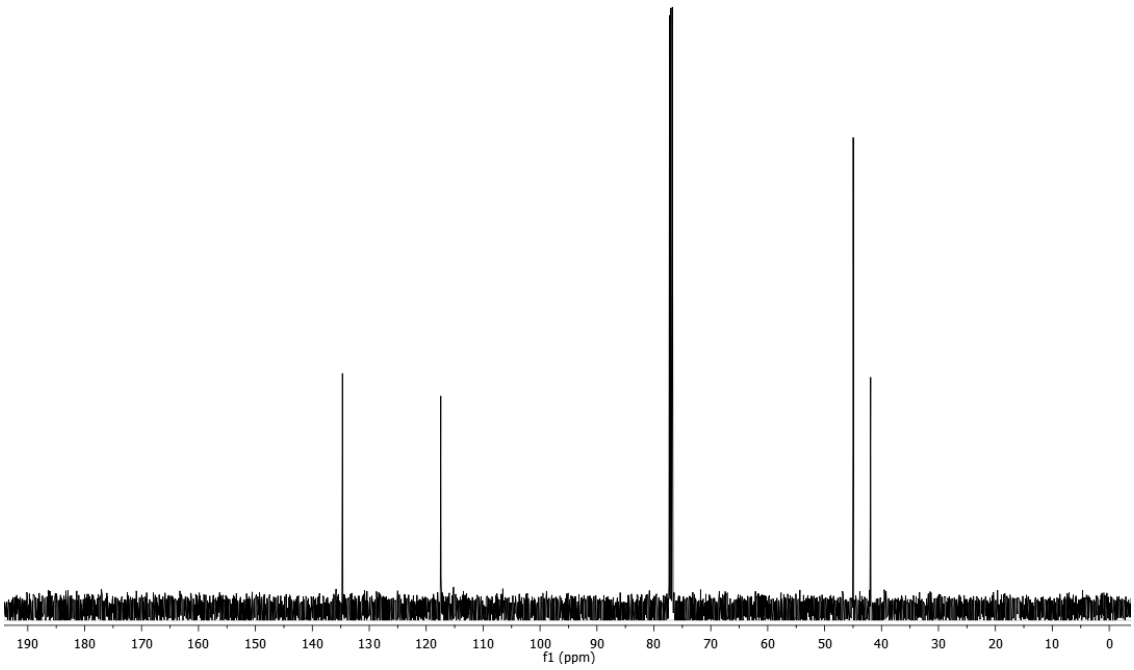


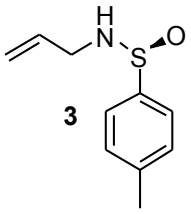
Peak Results

	Name	RT	% Area
1		15.081	97.35
2		18.054	2.65



1





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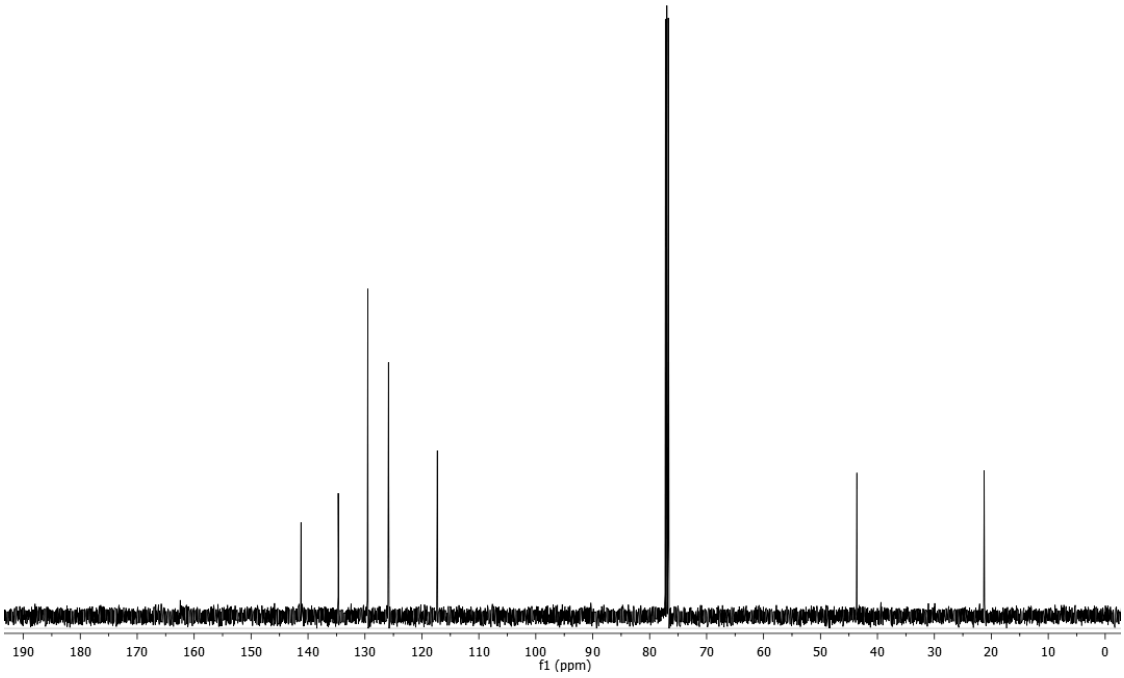

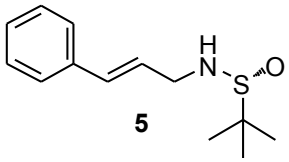

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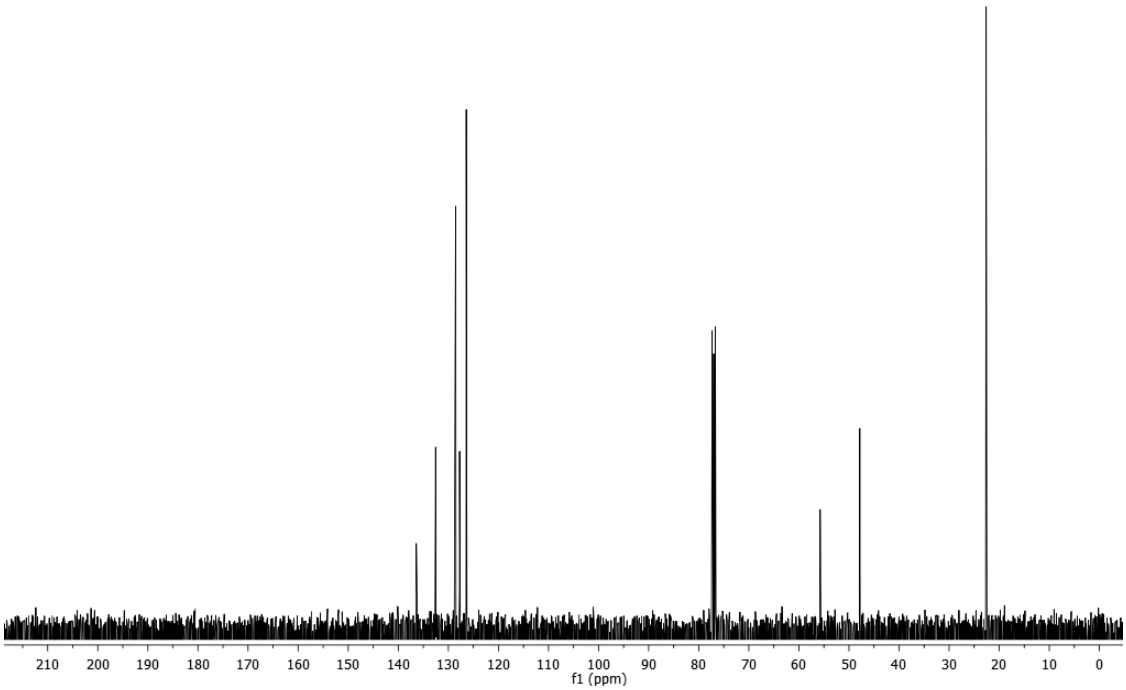
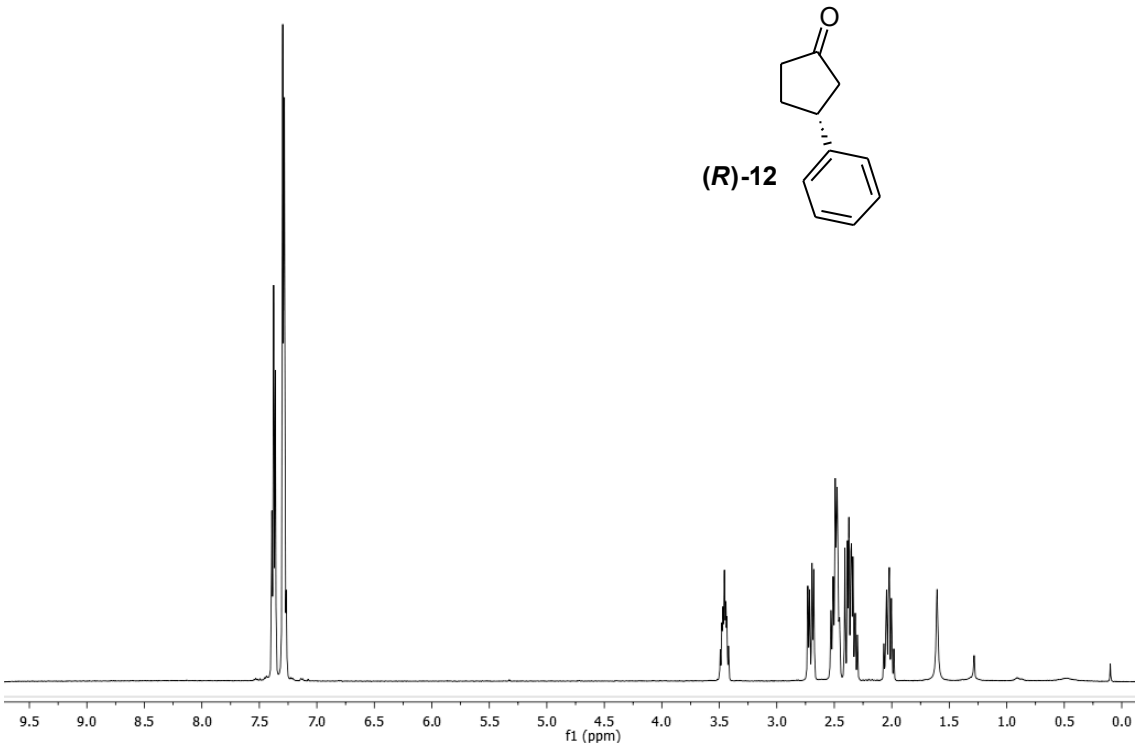
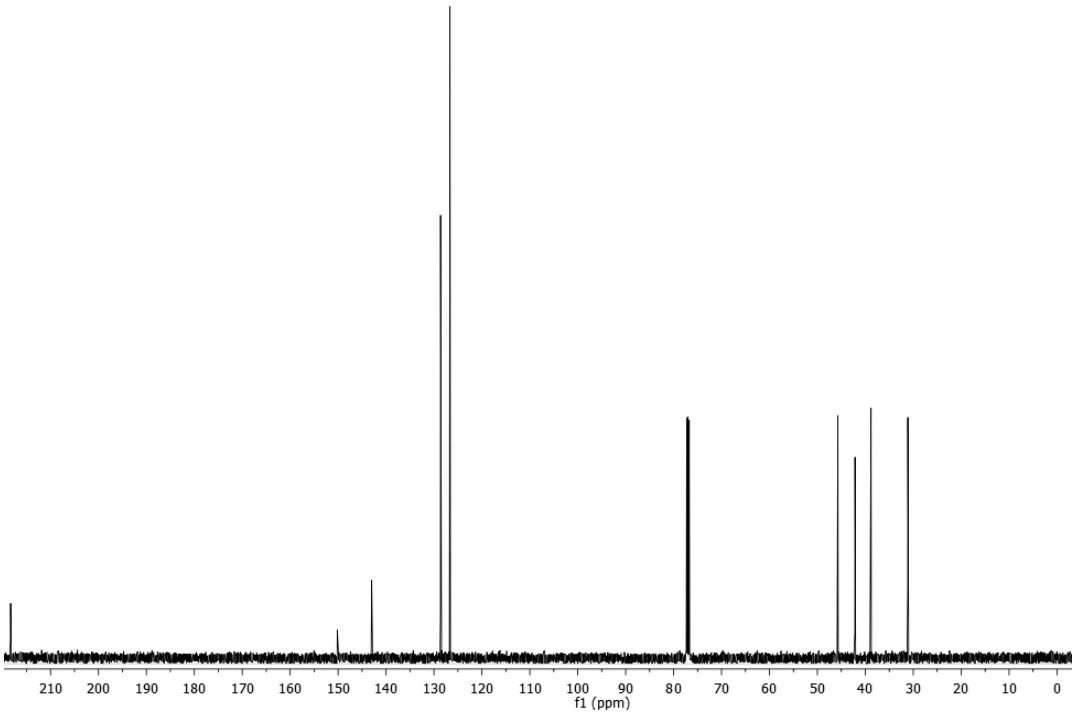
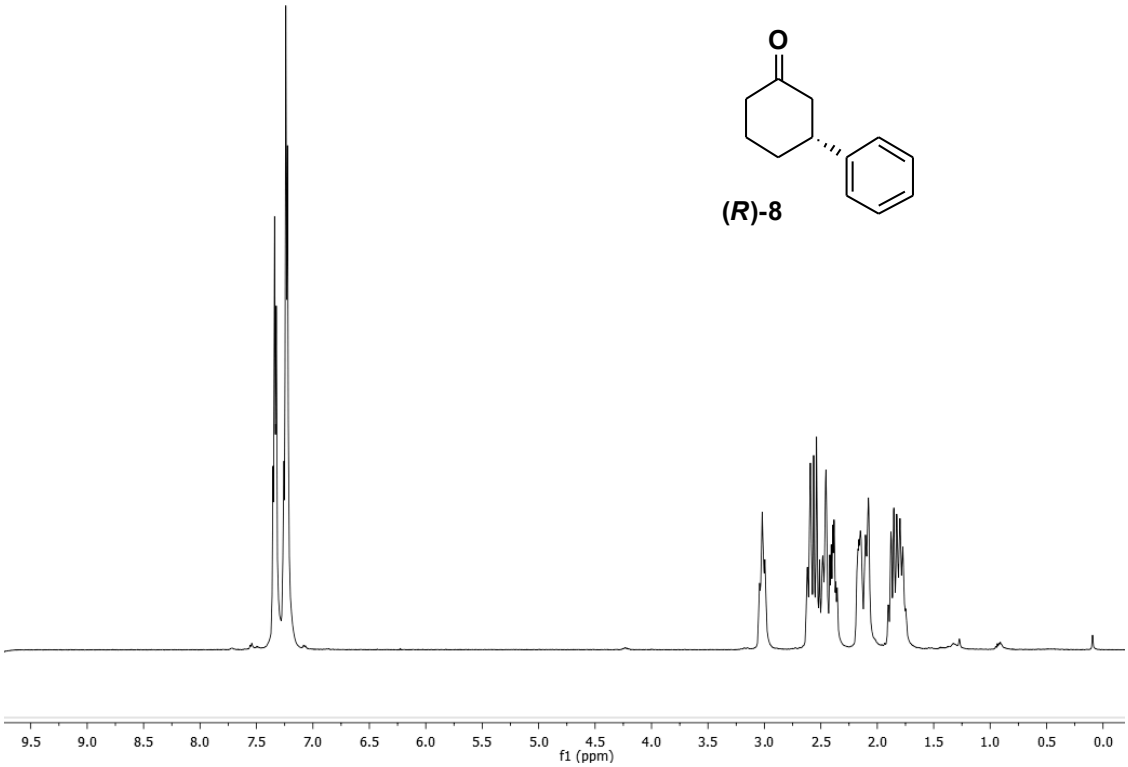
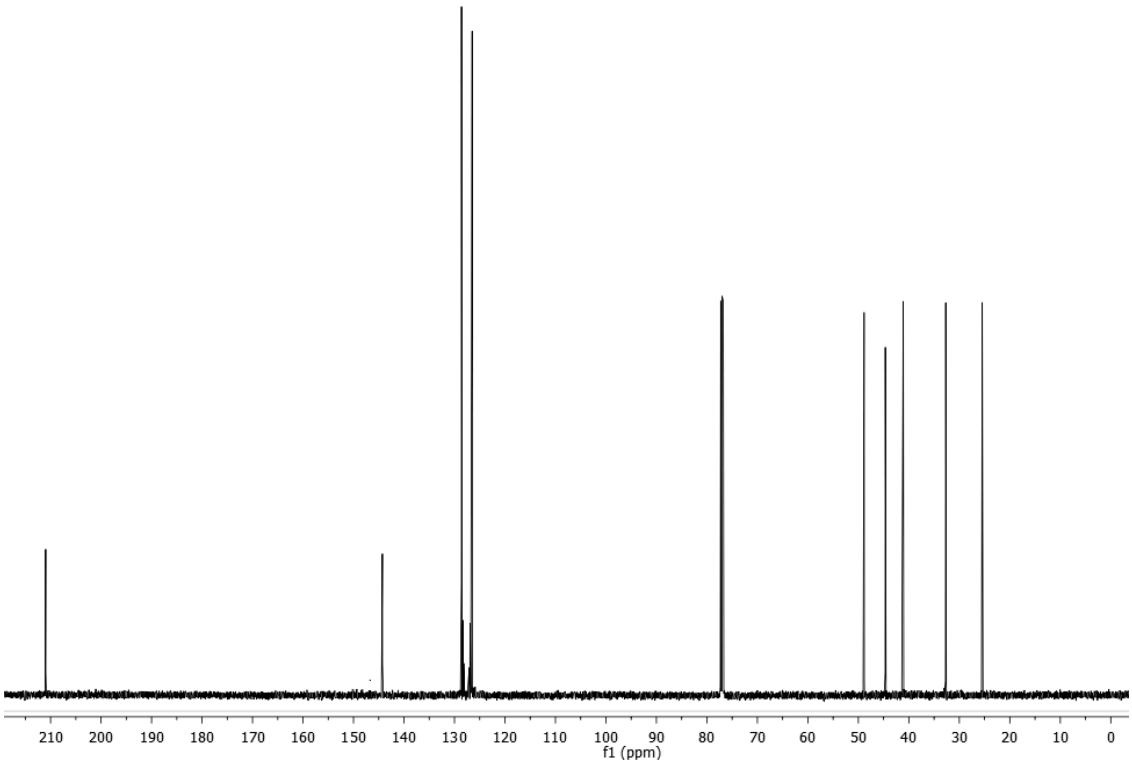







O
(R)-8
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)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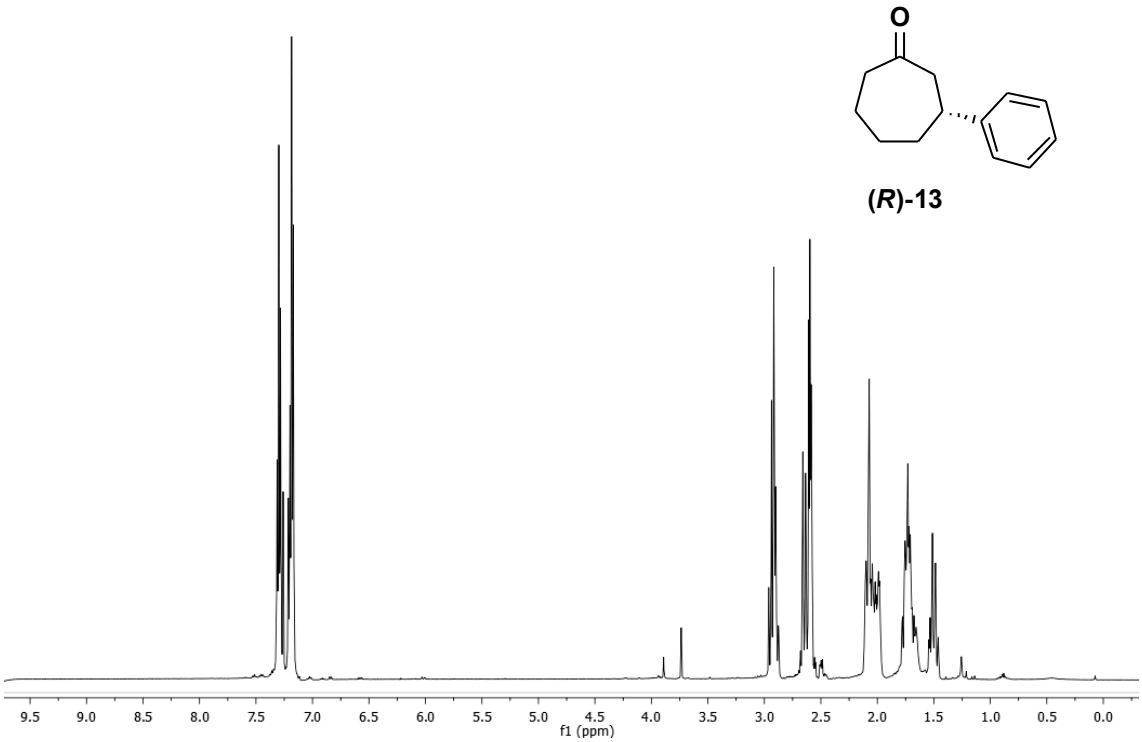
f1 (ppm)


O
(R)-13
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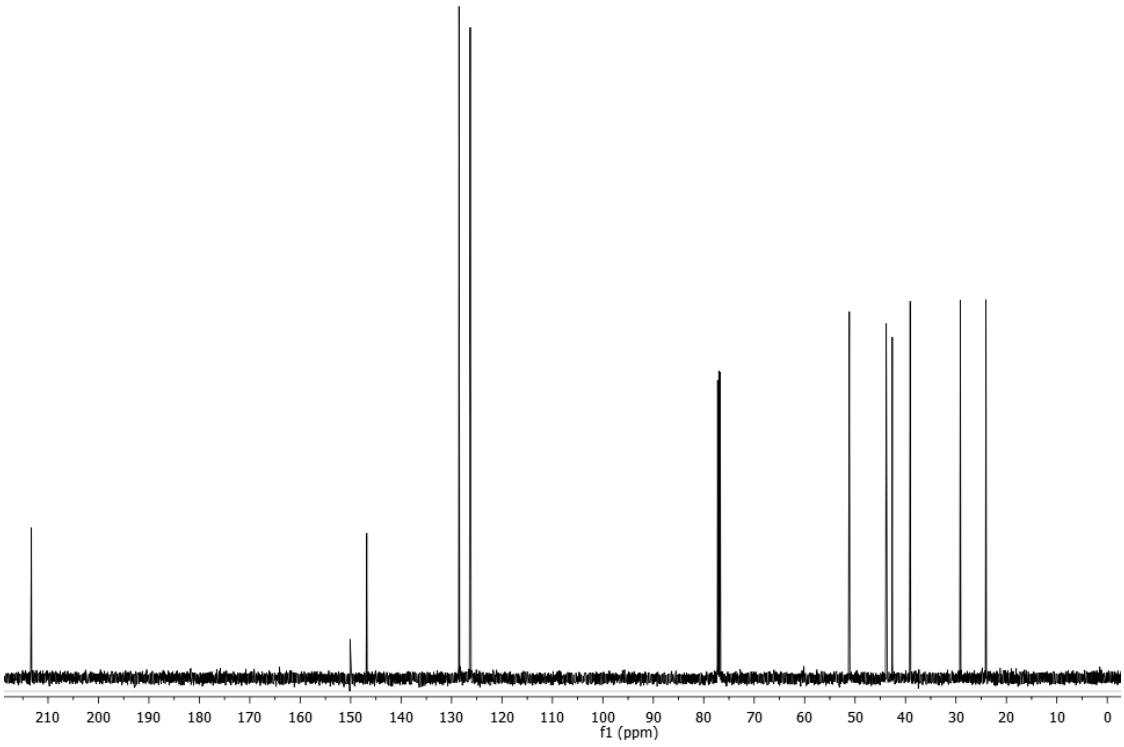
f1 (ppm)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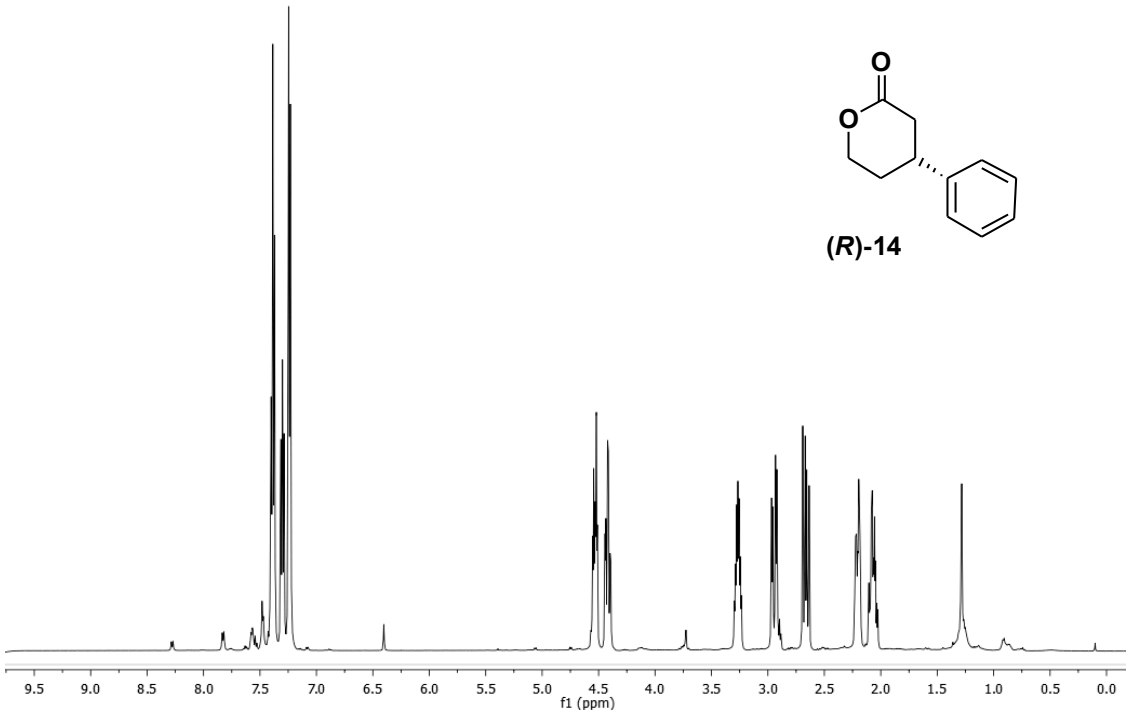

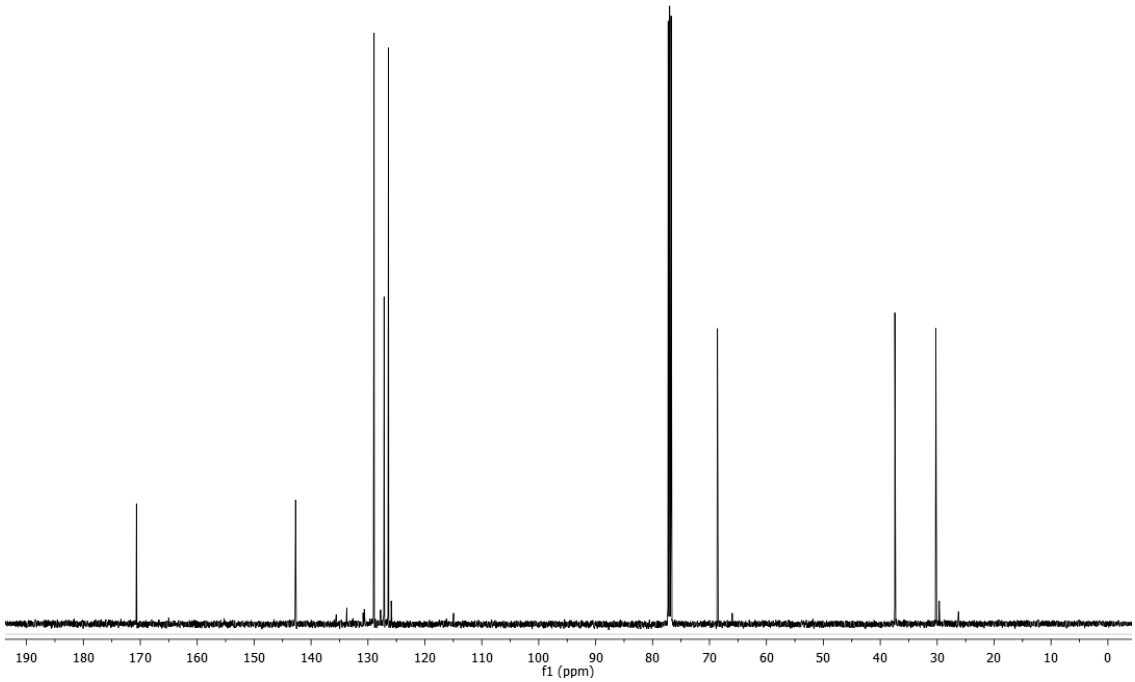

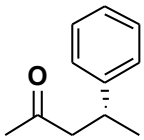

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