Electronic Supplementary Material (ESI) for Organic Chemistry Frontiers.

Asymmetric cycloisomerization/[3+2] cycloaddition for synthesis of chiral spiroisobenzofuran-1,3'-pyrrolidine derivatives

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Content

(A) General information

^{1}H NMR spectra were recorded on a Bruker ASCEND^{TM} 400M (400MHz) in $CDCl_3$. Chemical shifts were reported in ppm from tetramethylsilane with the solvent resonance as the internal standard ($CDCl_3$, δ = 7.26). Spectra were reported as follows: chemical shift (δ ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constants (Hz), integration and assignment. **^{13}C{^{1}H} NMR** spectra were collected were collected on a Bruker ASCENDTM 400M (100MHz) with complete proton decoupling. Chemical shifts are reported in ppm from the tetramethylsilane with the solvent resonance as internal standard ($CDCl_3$, δ = 77.0). High-resolution mass spectra (**HRMS**) were performed on Thermo Q-Exactive Focus (FTMS+c ESI) and data were reported as (m/z). Enantiomeric excess (ee) was determined by HPLC analysis using the corresponding commercially chiral column as stated in the experimental procedures at 23 °C with UV detector. Infrared spectra (IR) were recorded on Bruker Tensor || spectrometer with Plantium ATR accessory and the peaks are reported as absorption maxima (ν, cm^{-1}). Optical rotations were measured with a Perkin-Elmer model 241 polarimeter and reported as follows: $[\alpha]_{\lambda}^{T}$ (c: g/100 mL, in DCM, λ). Commercially available reagents were used without further purification. Molecular sieves were activated at 500 ℃ for 5 h, then cooled and stored under N_2 atmosphere. All the imines were prepared according to literature.[1] 1,2-dichlorobenzene was dried with $CaCl_2$, and distilled according to *Purification of Laboratory Chemicals* (Fifth Edition). CH_3CCl_3, CH_2ClCH_2Cl, $CHCl_3$, $CHCl_2CHCl_2$, Et_2O, $PhCH_3$ and PhCl were directly distilled before use. Chromatography: Silica gel (HG/T2354-2010) made in Qingdao Haiyang Chemical Co., Ltd.

(B) General procedures for the preparation of Au(I) catalyst and chiral *N*,*N*'-dioxide

1. Preparation of PPh_3AuNTf_2

An oven-dried test tube was charged with PPh_3AuCl (355 mg, 0.5 mmol) and $AgNTf_2$ (1.05 equiv) under N_2 atmosphere, then CH_2Cl_2 (0.25 mL) was added and it was stirred for 5 h at 35 °C. After filtration over celite to remove the silver chloride salt, the PPh_3AuNTf_2 was obtained quantitatively by evaporation of and stored under N_2 atmosphere.

2. Preparation of chiral *N*,*N*'-dioxide

The *N*,*N*'-dioxide ligands were prepared by the similar procedure in the literatures.[2]

(C) General procedures for the preparation of substrates

1. Preparation of aziridines

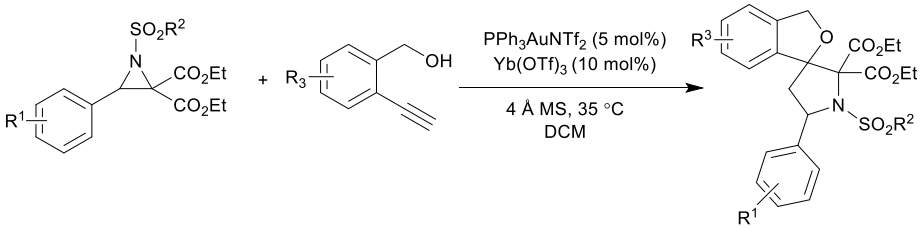
All the aziridines were prepared according to the literature.[3]

2. Preparation of alkynyl alcohols and amides

All the alkynyl alcohols and amides were prepared according to the literature.[4]

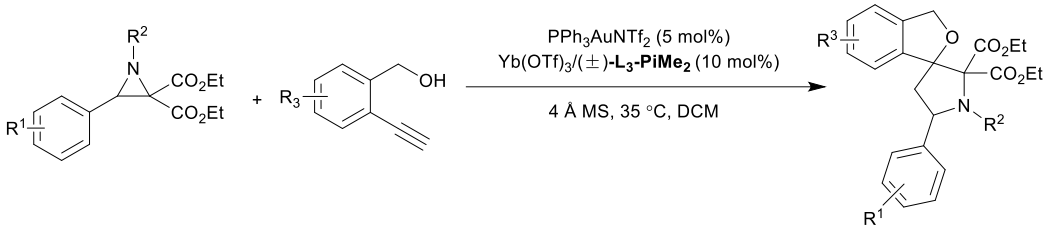
(D) Experimental procedures

1. Preparation of the racemates



1e, 1l, 1p **2** **3e, 3l, 3p**

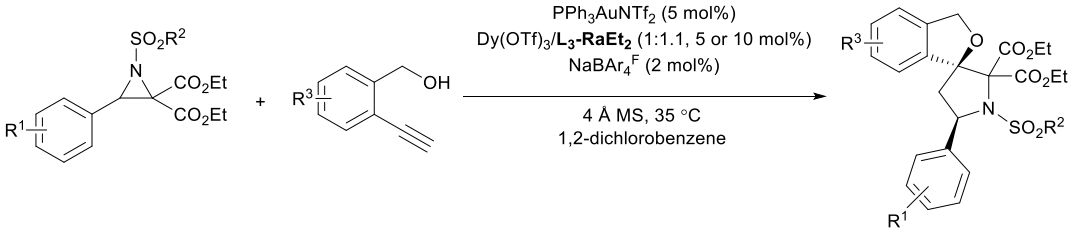
Preparation of the racemates of **3e**, **3l**, **3p**: $Yb(OTf)_3$ (10 mol%, 6.1 mg), PPh_3AuNTf_2 (5 mol%, 3.6 mg) and 4 Å MS (80 mg) were flushed with argon and dissolved in DCM (1.0 mL) at 35 °C, then aziridine **1** (0.1 mmol) and alkynyl alcohol **2** (0.1 mmol) were slowly added and stirred for 2−16 h. The reaction mixture was subjected to flash column chromatography on silica gel and eluted with petroleum ether/ethyl acetate (5:1, v/v) to afford the desired product **3**.



1 **2** **3**

Preparation of other racemates: $Yb(OTf)_3$ (10 mol%, 6.1 mg), (±)-**L_3-PiMe$_2$** (10% mol), PPh_3AuNTf_2 (5 mol%, 3.6 mg) and 4 Å MS (80 mg) were flushed with argon and dissolved in DCM (1.0 mL) at 35 °C for 0.5 h, then aziridine **1** (0.1 mmol) and alkynyl alcohol **2** (0.1 mmol) were slowly added and stirred for 2−16 h. The residue was subjected to flash column chromatography on silica gel and eluted with petroleum ether/ethyl acetate (8:1−4:1, v/v) to afford the desired product.

2. General procedures for the catalytic asymmetric reaction

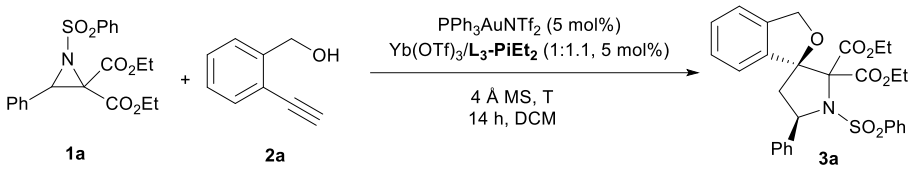


1a-1r **2a-2d** **3a-3u**

PPh_3AuNTf_2 (5 mol%), $Dy(OTf)_3$/**L_3-RaEt$_2$** (5 or 10 mol%), $NaBAr_4^F$ (2% mol) and 4 Å MS (100 mg) were stirred in 1,2-dichlorobenzene (3.0 mL) at 35 °C for 0.5 h under nitrogen atmosphere. Subsequently, aziridine **1** (0.1 mmol) and alkynyl alcohol **2** were added. The reaction was stirred at 35 °C and monitored by TLC. The reaction mixture was directly purified by flash chromatography on silica gel (eluent: petroleum ether/diethyl ether = 4:1−8:1) to afford the desired product **3**. The ee values were determined by high-performance liquid chromatography (HPLC) with Chiralcel AD-H, ASH, IF. The dr values were determined by ^{1}H NMR spectroscopy.

(E) Optimization of the reaction conditions

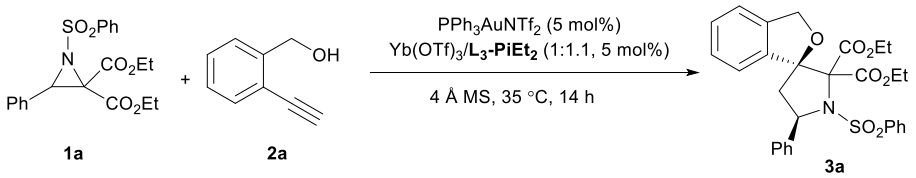
Table S1. Screening of temperature



Entry [a]	t (℃)	Yield (%) [b]	d.r. [c]	ee (%) [c]
1	0	21	60:40	27/31
2	10	30	64:36	31/37
3	20	42	67:34	47/41
4	35	57	75:25	51/47

[a] Unless otherwise noted, all reactions were performed with **1a** (0.1 mmol), **2a** (0.1 mmol), $Ph_3PAuNTf_2$ (2.5 mol %), $Dy(OTf)_3$/**L_3-RaEt$_2$** (1:1, 5 mol %), 4 Å MS (80 mg) in solvent (3.0 mL) at 35 ℃ under N_2 for 14 h. [b] Isolated yield. [c] Determined by HPLC analysis using a chiral stationary phase.

Table S2. Screening of solvents

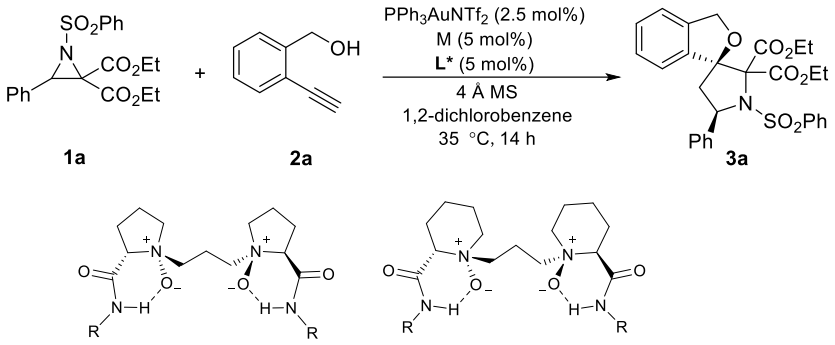


Entry [a]	Solvent	Yield (%) [b]	d.r. [c]	ee (%) [c]
1	Et_2O	53	82:16	34/57
2	EtOAc	77	45:55	23/31
3	THF	28	47:53	52/34
4	toluene	96	71:29	53/32
5	DCM	57	75:25	51/47
6	DCE	67	80:20	47/57
7	1,1,1-trichloroethane	64	78:22-	64/49
8	1,1,2-trichloroethane	68	51:49	58/56
9	1,1,2,2-tetrachloroethane	78	63:37	57/49
10	chlorobenzene	58	75:25	69/69
11	1,2-dichlorobenzene	31	71:29	77/62
12	1,3-dichlorobenzene	41	67:23	71/55
13	1,2,4-trichlorobenzene	43	72:28	77/74

[a] Unless otherwise noted, all reactions were performed with **1a** (0.1 mmol), **2a** (0.10 mmol), $Ph_3PAuNTf_2$ (2.5 mol %), $Dy(OTf)_3$/**L_3-RaEt$_2$** (1:1, 5 mol %), 4 Å MS (80 mg) in solvent (3.0 mL) at 35 ℃ under N_2 for 14 h. [b] Isolated yield. [c]

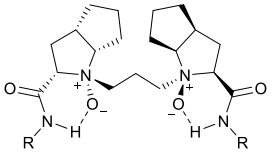
Determined by HPLC analysis using a chiral stationary phase.

Table S3. Screening of metal salts and chiral *N,N′*-dioxide ligands



L3-PrMe2: R = 2,6-$Me_2C_6H_3$
L3-PrEt2: R = 2,6-$Et_2C_6H_3$
L3-PrEt2Me: R = 2,6-Et_2-4-MeC_6H_2

L3-PiMe2: R = 2,6-$Me_2C_6H_3$
L3-PiEt2: R = 2,6-$Et_2C_6H_3$
L3-PiEt2Me: R = 2,6-Et_2-4-MeC_6H_3



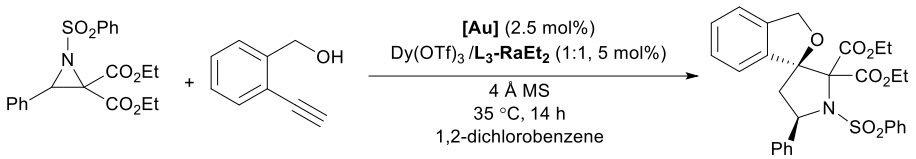
L3-RaMe2: R = 2,6-$Me_2C_6H_3$
L3-RaEt2: R = 2,6-$Et_2C_6H_3$
L3-RaEt2Me: R = 2,6-Et_2-4-MeC_6H_2
L3-RaEt2Bu: R = 2,6-*i*Pr_2-4-*t*BuC_6H_2
L3-RaPr2: R = 2,6-*i*PrC_6H_3
L3-RaEt2Ad: R = 2,6-Et_2-4-(1-adamantyl)C_6H_2

Entry [a]	Metal salt	L*	Yield (%) [b]	d.r. (%) [c]	ee (%) [c]
1	$Sc(OTf)_3$	**L_3-RaEt$_2$**	42	57:43	0/34
2	$Y(OTf)_3$	**L_3-RaEt$_2$**	41	60:40	58/57
3	$La(OTf)_3$	**L_3-RaEt$_2$**	24	51:49	31/-21
4	$Ce(OTf)_3$	**L_3-RaEt$_2$**	23	55:45	30/-10
5	$Pr(OTf)_3$	**L_3-RaEt$_2$**	26	55:45	33/-13
6	$Nd(OTf)_3$	**L_3-RaEt$_2$**	27	68:32	36/26
7	$Sm(OTf)_3$	**L_3-RaEt$_2$**	31	71:29	71/34
8	$Eu(OTf)_3$	**L_3-RaEt$_2$**	33	73:27	71/41
9	$Gd(OTf)_3$	**L_3-RaEt$_2$**	37	75:25	75/47
10	$Tb(OTf)_3$	**L_3-RaEt$_2$**	40	74:26	77/51
11	$Dy(OTf)_3$	**L_3-RaEt$_2$**	47	77:23	81/61
12	$Ho(OTf)_3$	**L_3-RaEt$_2$**	51	75:25	77/62
13	$Er(OTf)_3$	**L_3-RaEt$_2$**	47	74:26	77/60
14	$Tm(OTf)_3$	**L_3-RaEt$_2$**	40	75:25	77/61
15	$Yb(OTf)_3$	**L_3-RaEt$_2$**	31	71:29	77/62
16	$Lu(OTf)_3$	**L_3-RaEt$_2$**	28	67:23	65/49
17	$Dy(OT)_3$	**L_3-RaMe$_2$**	47	65:35	61/42
18	$Dy(OT)_3$	**L_3-RaEt$_2$Me**	51	69:31	67/47
19	$Dy(OT)_3$	**L_3-RaEt$_2$Bu**	28	72:28	51/51
20	$Dy(OT)_3$	**L_3-RaPr$_2$**	52	68:22	70/62
21	$Dy(OT)_3$	**L_3-RaEt$_2$Ad**	51	71:29	57/39
22	$Mg(OTf)_2$	**L_3-RaEt$_2$**	NR	-	-

23	$Ni(OTf)_3$	**L_3-RaEt$_2$**	NR	-	-
24	$Cu(OT)_2$	**L_3-RaEt$_2$**	NR	-	-
25	$Zn(OTf)_2$	**L_3-RaEt$_2$**	NR	-	-
26	$Dy(OT)_3$	**L_3-PrEt$_2$**	41	57:43	54/31
27	$Dy(OT)_3$	**L_3-PiEt$_2$**	45	61:39	59/47

[a] The reactions were performed with **1a** (0.1 mmol), **2a** (0.1 mmol), $Ph_3PAuNTf_2$ (2.5 mol %), M/**L** (1:1, 5 mol %), 4Å MS (80 mg) in 1,2-dichlorobenzene (3.0 mL) at 35 ℃ for 14 h. [b] Isolated yield. [c] Determined by HPLC analysis using a chiral stationary phase.

Table S4. Screening of transition-metal salts

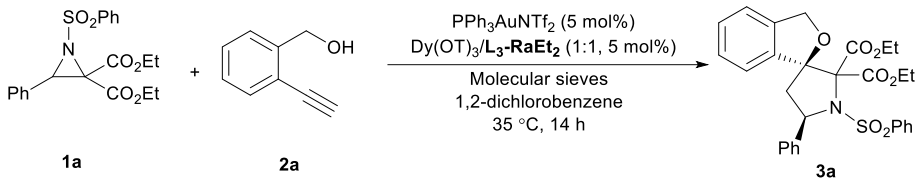


1a **2a** **3a**

Entry [a]	**[Au]**	Yield (%) [b]	d.r. [c]	ee (%) [c]
1	$PPh_3AuCl/AgOAc$	13	-	-
2	$PPh_3AuCl/AgNO_3$	mixture	-	-
3	$PPh_3AuCl/AgBF_4$	mixture	-	-
4	$PPh_3AuCl/AgSbF_6$	31	68:32	65/59
5	$PPh_3AuCl/AgOTf$	49	70:30	71/65
6	$PPh_3AuCl/AgNTf_2$	57	72:28	78/57
7	PPh_3AuNTf_2	47	75:25	81/55
8[d]	PPh_3AuNTf_2	59	74:26	81/55
9	$IPrAuNTf_2$	37	64:36	64/57
10	PPh_3AuCl	31	55:45	57/57
11	$AuCl_3$	15	61:39	47/61
12	$AuCl(CH_3SCH_3)$	17	54:46	31/51
13	CuI	NR	-	

[a] Unless otherwise noted, all reactions were performed with **1a** (0.1 mmol), **2a** (0.1 mmol), PPh_3AuCl/AgX (1:1, 2.5 mol %), $Dy(OTf)_3$/**L_3-RaEt$_2$** (1:1, 5 mol %), 4 Å MS (80 mg) in 1,2-dichlorobenzene (3.0 mL) at 35 ℃ under N_2 for 14 h. [b] Isolated yield. [c] Determined by HPLC analysis using a chiral stationary phase. [d] 5% mol PPh_3AuNTf_2 was used.

Table S5. Screening of molecular sieves

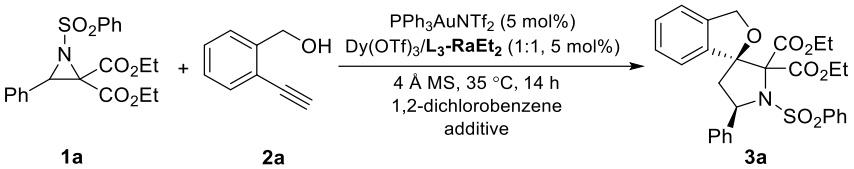


1a **2a** **3a**

Entry [a]	Molecular sieves	Yield (%) [b]	d.r. [c]	ee (%) [c]
1	3Å MS, 80 mg	37	49:51	71/71
2	4Å MS, 80 mg	59	75:25	87/61
3	5Å MS, 80 mg	17	60:40	47/37
4	4Å MS, 40 mg	41	68:32	77/51
5	4Å MS,100 mg	67	72:28	87/55
6	4Å MS, 120 mg	71	67:33	88/61
7	4Å MS,160 mg	44	61:39	77/61
8	4Å MS, 200 mg	31	57:33	71/57

[a] The reactions were performed with **1a** (0.1 mmol), **2a** (0.1 mmol), PPh_3AuNTf_2 (5 mol %), $Dy(OTf)_3$/**L_3-RaEt$_2$** (1:1, 5 mol %), molecular sieves in 1,2-dichlorobenzene (3.0 mL) at 35 ℃ under N_2 for 14 h. [b] Isolated yield. [c] Determined by HPLC analysis using a chiral stationary phase.

Table S6. Screening of additives

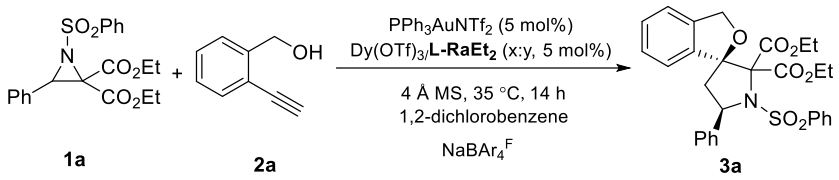


1a **2a** **3a**

Entry [a]	Additives	Yield (%) [b]	d.r. [c]	ee (%) [c]
1	H_2O (10 μL)	36	55:45	67/59
2	EtOAc (10 μL)	77	44:56	61/43
3	1,4-dioxane (10 μL)	41	87:13	67/70
4	Toluene (10 μL)	82	73:27	51/32
5	Et_2O (10 μL)	53	84:16	66/67
6	THF (10 μL)	48	70:30	45/64
7	PhCOOH (10 mol%)	44	40:60	71/59
8	$LiNTf_2$ (10 mol%)	47	81:19	45/38
9	$NaBAr_4^F$ (10 mol%)	31	73:27	87/47
10	$NaBAr_4^F$ (2 mol%)	67	75:25	90/51

[a] The reactions were performed with **1a** (0.1 mmol), **2a** (0.10 mmol), $Ph_3PAuNTf_2$ (5 mol %), $Dy(OTf)_3$/**L_3-RaEt$_2$** (1:1, 5 mol %), 4 Å MS (100 mg) and additive in 1,2-dichlorobenzene (3.0 mL) at 35 ℃ under N_2 for 14 h. [b] Isolated yield. [c] Determined by HPLC analysis using a chiral stationary phase.

Table S7. Screening of the ratio of $Dy(OTf)_3$ and chiral *N, N′*-dioxide ligand

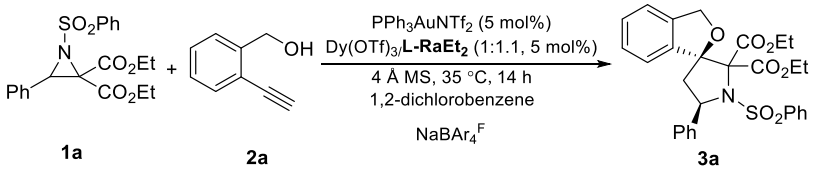


1a **2a** **3a**

Entry [a]	x: y	Yield (%) [b]	d.r. [c]	ee (%) [d]
1	1:1	67	75:25	90/61
2	1:1.1	67	74:26	92/61
3	1:1.2	68	74:26	89/60
4	1:1.5	67	60:40	84/52
5	1:2	trace	-	-
6	1.1:1	68	72:28	87/60
7	1.2:1	77	70:30	79/61
8	1.5:1	71	55:45	77/57
9	2:1	61	53:27	67/61

[a] The reactions were performed with **1a** (0.1 mmol), **2a** (0.1 mmol), $AuPPh_3NTf_2$ (5 mol %), $Dy(OTf)_3$/**L-RaEt$_2$** (x:y, 5 mol %), 4 Å MS (100 mg) and $NaBAr_4^F$ (2 mol %) in 1,2-dichlorobenzene (3.0 mL) at 35 ℃ under N_2 for 14 h. [b] Isolated yield by silica gel chromatography. [c] Determined by ^1H NMR spectroscopy. [d] Determined by HPLC analysis using a chiral stationary phasse.

Table S8. Screening of the ratio of the substrates

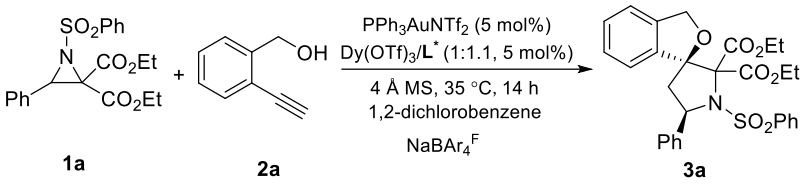


1a **2a** **3a**

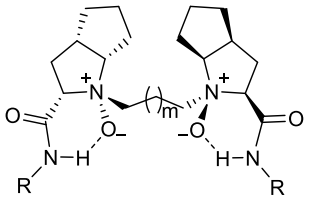
Entry [a]	**1a:2a**	Yield (%) [b]	d.r. [c]	ee (%) [d]
1	1:1	67	75:25	90/56
3	1:1.2	71	74:26	92/55
4	1:1.5	77	60:40	87/52
5	1:2	trace	-	-
7	1.2:1	77	70:30	88/61
8	1.5:1	85	55:45	71/57
9	2:1	61	53:27	67/61

[a] The reactions were performed with **1a**, **2a** at 0.1 mmol scale $AuPPh_3NTf_2$ (5 mol %), $Dy(OTf)_3$/**L-RaEt$_2$** (1:1.1, 5 mol %), 4 Å MS (100 mg) and $NaBAr_4^F$ (2 mol %) in 1,2-dichlorobenzene (3.0 mL) at 35 ℃ under N_2 for 14 h. [b] Isolated yield by silica gel chromatography. [c] Determined by ^1H NMR spectroscopy. [d] Determined by HPLC analysis using a chiral stationary phase.

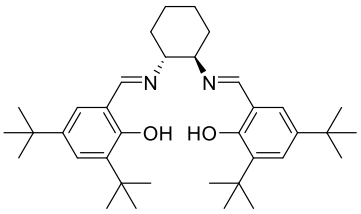
Table S9. Rescreening of the chiral *N,N'*-dioxide ligands and other ligands



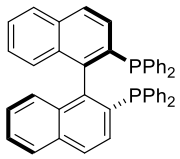
1a **2a** **3a**



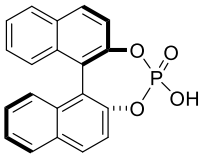
m = 0, **L_2-RaMe$_2$**: R = 2,6-$Me_2C_6H_3$
m = 0, **L_2-RaEt$_2$**: R = 2,6-$Et_2C_6H_3$
m = 1, **L_3-RaMe$_2$**: R = 2,6-$Me_2C_6H_3$
m = 1, **L_3-RaEt$_2$**: R = 2,6-$Et_2C_6H_3$
m = 1, **L_3-RaEt$_2$Me**: R = 2,6-Et_2-4-MeC_6H_2
m = 1, **L_3-RaEt$_2$Br**: R = 2,6-Et_2-4-BrC_6H_2
m = 2, **L_4-RaMe$_2$**: R = 2,6-Me_2-C_6H_3
m = 2, **L_4-RaEt$_2$Me**: R = 2,6-Et-4-MeC_6H_2



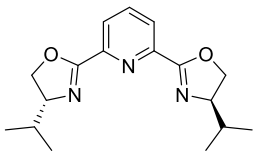
L1: salen



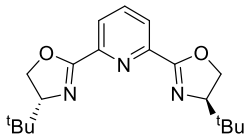
L2: BINAP



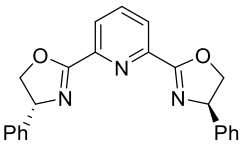
L3: CPA-1



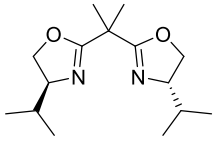
L4: ^{i}Pr-PyBox



L5: ^{t}Bu-Box



L6: Ph-PyBox



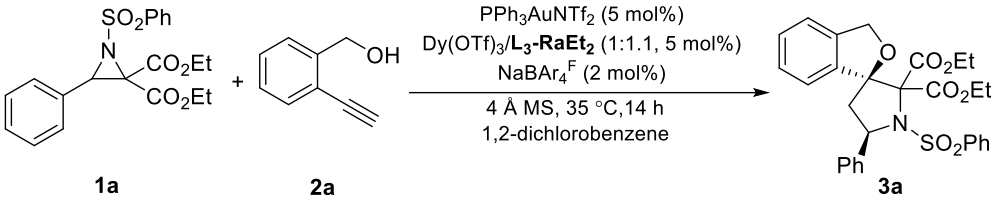
L7: ^{i}Pr-Box

Entry [a]	L*	Yield (%) [b]	d.r. (%) [c]	ee (%) [c]
1	**L_2-RaMe$_2$**	42	70:30	47/21
2	**L_2-RaEt$_2$**	55	71:29	62/33
3	**L_3-RaMe$_2$**	57	67:33	77/42
4	**L_3-RaEt$_2$**	71	74:26	92/55
5	**L_3-RaEt$_2$Me**	68	71:29	77/48
6	**L_3-RaEt$_2$Br**	43	75:25	91/58
7	**L_4-RaMe$_2$**	49	61:29	66/37
8	**L_4-RaEt$_2$Me**	47	66:33	69/44
9	**L1**	trace	--	--
10	**L2**	trace	--	--
11	**L3**	12	57:43	5/3
12	**L4**	37	67:33	31/24
13	**L5**	21	73:27	15/7
14	**L6**	40	63:37	21/10
15	**L7**	37	40:60	0/3

[a] The reactions were performed with **1a** (0.1 mmol), **2a** (0.12 mmol), $Ph_3PAuNTf_2$ (5 mol %), M/**L** (1:1.1, 5

mol %), 4Å MS (100 mg) and $NaBAr_4^F$ (2 mol %) in 1,2-dichlorobenzene (3.0 mL) at 35 °C for 14 h. [b] Isolated yield. [c] Determined by HPLC analysis using a chiral stationary phase.

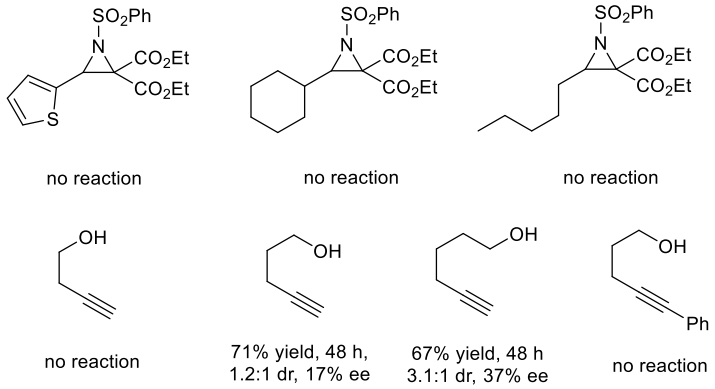
(F) Control experiments

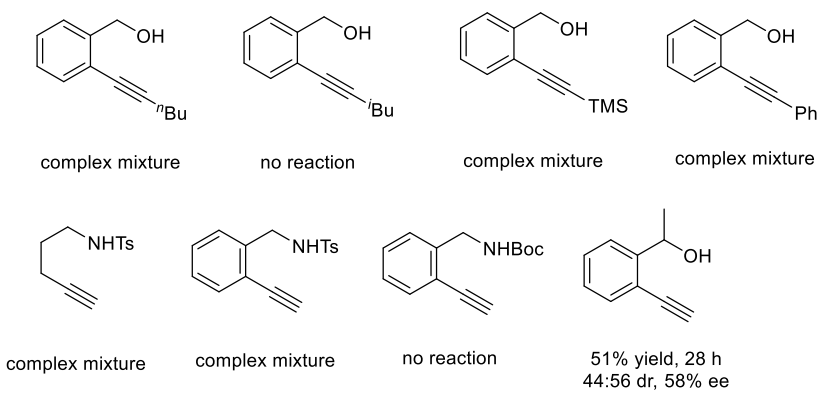


1a **2a** **3a**

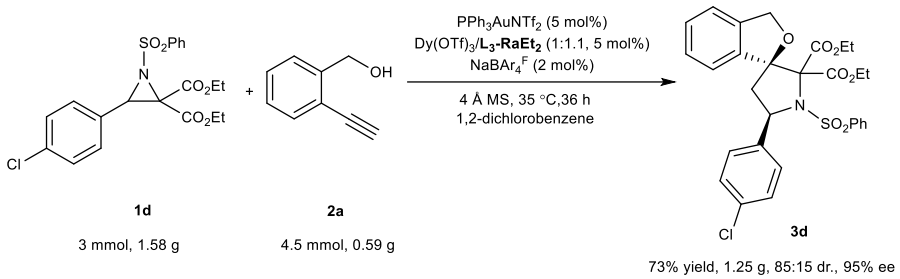
Entey [a]	$Dy(OTf)_3$	**L-RaEt$_2$**	Au (III)	Yield (%) [b]	dr[c]	ee[d] (%)
1	+	+	+	71	74:26	92/55
2	−	−	+	n.r.	--	--
3	−	+	+	n.r.	--	--
4	+	−	+	57	70:30	--
5	+	+	PPh_3AuCl	31	55:45	57/57
6	+	+	$AgNTf_2$	17	75:25	77/42

(G) Unsuccessful substrates





(H) Experimental procedure for the scale-up reaction



An over dried test tube was charged with $Dy(OTf)_3$ (5 mol%, 0.15 mmol, 182.9 mg), **L_3-RaEt$_2$** (5.5 mol%, 0.165 mmol, 106.3 mg), $AuPPh_3NTf_2$ (5% mol, 212.5 mg), $NaBAr_4^F$ (2 mol%, 0.06 mmol, 53.2 mg), 4 Å MS (2.5 g) and 1,2-dichlorobenzene (45 mL) under N_2 atmosphere and the resulting solution was stirred at 35 °C for 2 h. Then, the solution of **1d** (3.0 mmol, 1.58 g) and **2a** (4.5 mmol, 0.59 g) in 45 mL 1,2-dichlorobenzene were slowly added into the tube. Then, the reaction mixture was stirred at 35 °C and detected by TLC. After the reaction was completed, the residue was subjected to column chromatography (SiO_2, eluent: petroleum ether/ethyl acetate = 8:1 to 4:1) to afford the enantioenriched product **3d** (73% yield, 1.25 g, 85:15 dr., 95% ee).

(I) X-ray crystal structure of product

The following single crystal **3d** was recrystallized from DCM/*n*-hexane. The absolute configuration of **3d** was determined as (1*S*,5'*R*) by X-ray diffraction. CCDC 2041898 contains the supplementary crystallographic data which can be obtained free of charge from The Cambrige Crystallographic Data Centere via https://www.ccdc.cam.ac.uk/structures/

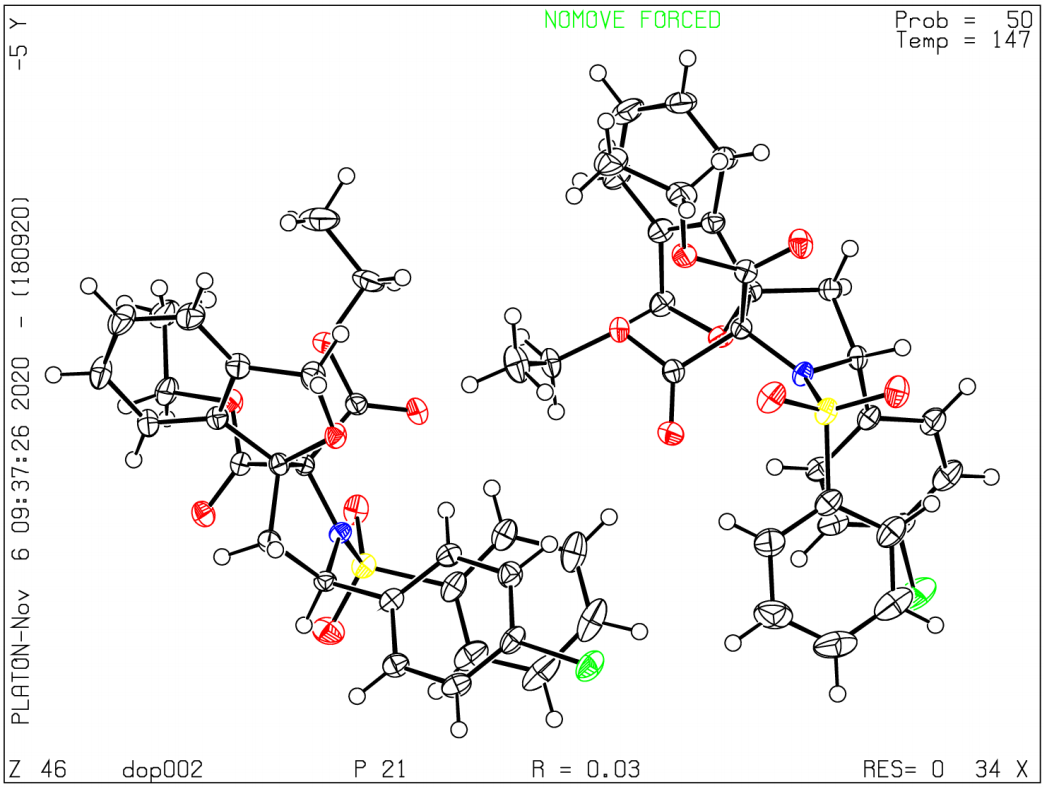
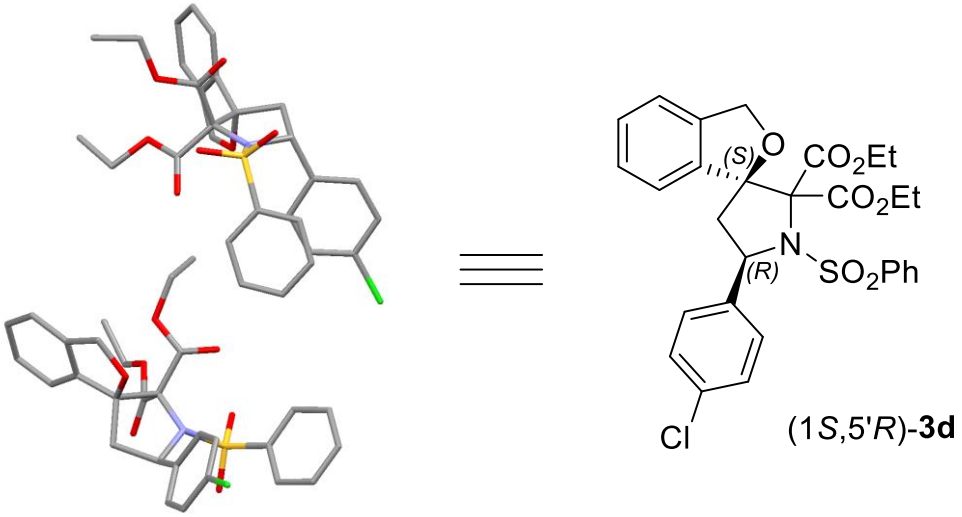


Figure 1. the thermal ellipsoid figure of **3d** with 50% probabilities



Crystallographic Data for **3d**.

Formula	**$C_{29}H_{28}ClNO_7S$ (3d)**
Formula mass (amu)	570.0530
Space group	P 21 21 21
a (Å)	13.2473(6)
c (Å)	12.8427(6)

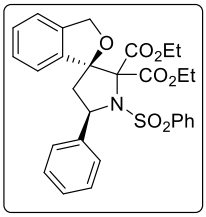
c (Å)	c=16.3970(8)
α (deg)	90
β (deg)	90
γ (deg)	90
V (Å^3)	2787.0(2)
Z	4
λ (Å)	0.71073
T (K)	147
ρ_{calcd} (g cm^{-3})	1.359
μ (mm^{-1})	0.26
Transmission factors	0.916, 0.972
$2\theta_{max}$ (deg)	27.519
No. of unique data, including $F_o^2 < 0$	12801
No. of unique data, with $F_o^2 > 2\sigma(F_o^2)$	12414
No. of variables	707
$R(F)$ for $F_o^2 > 2\sigma(F_o^2)$ [a]	0.0254
$R_w(F_o^2)$ [b]	0.0660
Goodness of fit	1.039

[a] $R(F) = \sum ||F_o| - |F_c|| / \sum |F_o|$.

[b] $R_w(F_o^2) = [\sum [w(F_o^2 - F_c^2)^2] / \sum wF_o^4]^{1/2}$; $w^{-1} = [\sigma^2(F_o^2) + (Ap)^2 + Bp]$, where $p = [\max(F_o^2,0) + 2F_c^2] / 3$.

(J) Spectral characterization data for the products

Diethyl (1*S*,5'*R*)-5'-phenyl-1'-(phenylsulfonyl)-*3H*-spiro[isobenzofuran-1,3'-pyrrolidine]-2',2'-dicarboxylate (3a)



0.1 mmol scale reaction, 14 h, 38.1 mg, 71% yield; white foam. Melting point: 122 – 123 ºC. 74:26 dr., 92% ee for the major isomer and 55% ee for the minor isomer. $[\alpha]_D^{17}$ = +37.4 (c = 1.26 in CH_2Cl_2).

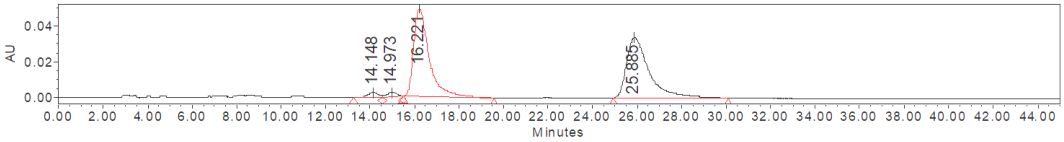
HPLC (Daicel chiralcel ADH, hexane/*i*-PrOH = 90/10, flow rate 1.0 mL/min, λ = 254 nm) t_r (major- major) = 16.70 min, t_r (major-minor) = 26.72 min, t_r (minor-major) = 14.64 min, t_r (minor-minor) = 15.26 min.

^{1}H NMR (400 MHz, Chloroform-*d*) *δ* 7.59 (dd, *J* = 8.4, 1.2 Hz, 2H), 7.50 – 7.36 (m, 5H), 7.35 – 7.27 (m, 2H), 7.25 – 7.19 (m, 3H), 7.16 – 7.06 (m, 2H), 5.82 (d, *J* = 10.4 Hz, 1H), 4.96 (s, 2H), 4.54 – 4.35 (m, 3H), 4.23 – 4.04 (m, 1H), 3.53 (dd, *J* = 13.6, 10.8 Hz, 1H), 2.31 (dd, *J* = 13.6, 1.6 Hz, 1H), 1.42 (t, *J* = 7.2 Hz, 3H), 1.12 (t, *J* = 7.2 Hz, 3H).

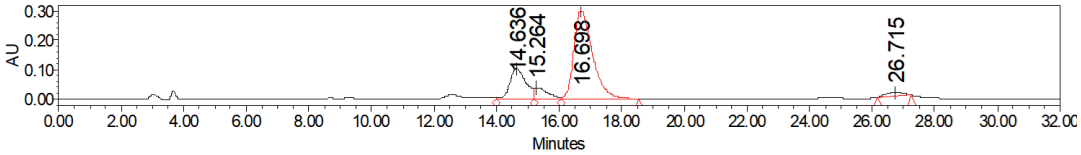
^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*) *δ* 167.73, 165.85, 141.29, 140.73, 136.78, 131.96, 128.95, 128.62, 128.56, 128.21, 127.95, 127.81, 127.74, 127.54, 127.46, 126.8, 122.26, 120.54, 99.78, 73.12, 64.45, 62.52, 61.59, 47.85, 13.89, 13.70.

HR-MS (ESI) calcd for $C_{29}H_{29}NNaO_7S^+$ ([M]+Na^+) = 558.1557, found 558.1558.

IR (neat) ***ν*** (cm^{-1}): 2983, 1753, 1724, 1447, 1365, 1339, 1264, 1227, 1021, 897, 755, 728, 689, 605, 571, 545, 471.

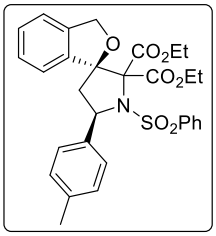


	Retention Time	% Area
1	14.148	1.65
2	14.973	1.58
3	16.221	48.41
4	25.885	48.37

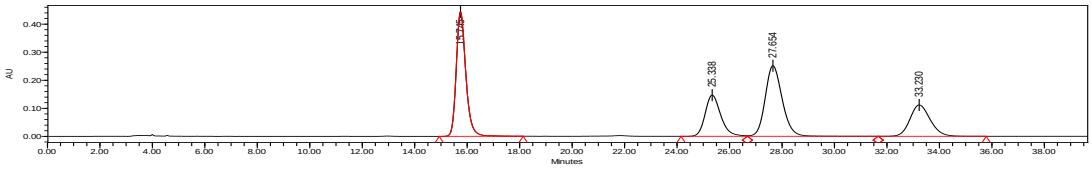


	Retention Time	% Area
1	14.636	20.41
2	15.264	5.91
3	16.698	70.78
4	26.715	2.91

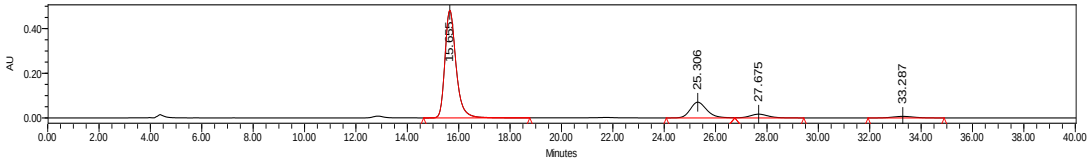
Diethyl (1*S*,5'*R*)-1'-(phenylsulfonyl)-5'-(p-tolyl)-*3H*-spiro[isobenzofuran-1,3'-pyrrolidine]-2',2'-dicarboxylate (3b)



0.1 mmol scale reaction, 14 h, 30.1 mg, 55% yield; white foam. Melting point: 108 – 111 ºC. 80:20 dr., 90% ee for the major isomer and 78% ee for the minor isomer. $[\alpha]_{\lambda}^{17}$ = +5.6 (c = 0.37 in CH_2Cl_2, λ = 405 nm).
HPLC (Daicel chiralcel ADH, hexane/*i*-PrOH = 90/10, flow rate 1.0 mL/min, λ = 254 nm) t_r (major- major) = 15.66 min, t_r (major-minor) = 27.68 min, t_r (minor-major) = 25.31min, t_r (minor-minor) = 33.29 min.
^{1}H NMR (400 MHz, Chloroform-*d*) *δ* 7.50 (d, *J* = 8.2 Hz, 2H), 7.43 – 7.28 (m, 4H), 7.22 (s, 1H), 7.18 – 7.09 (m, 4H), 6.84 (d, *J* = 7.6 Hz, 2H), 5.71 (d, *J* = 10.8 Hz, 1H), 4.91 (s, 2H), 4.46 – 4.26 (m, 3H), 4.13 – 3.98 (m, 1H), 3.43 (dd, *J* = 13.2, 10.8 Hz, 1H), 2.26 (s, 3H), 2.21 (s, 1H), 1.35 (t, *J* = 7.2 Hz, 3H), 1.05 (t, *J* = 7.2 Hz, 3H).
^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*) *δ* 167.76, 165.84, 140.68, 138.38, 136.52, 131.83, 129.01, 128.63, 128.49, 128.22, 127.54, 127.39, 122.28, 120.54, 99.76, 73.13, 64.32, 62.49, 61.57, 47.91, 21.05, 13.90, 13.71.
HR-MS (ESI) calcd for $C_{30}H_{31}NNaO_7S^+$ ([M]+Na^+) = 572.1713, found 572.1714.
IR (neat) ***ν*** (cm^{-1}): 2926, 1756, 1726, 1514, 1447, 1340, 1293, 1231, 1158, 1063, 1025, 899, 815, 760, 727, 689, 604, 576, 547, 466.

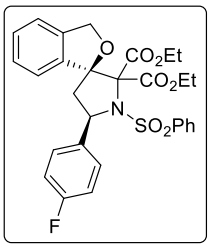


	Retention Time	% Area
1	15.745	32.47
2	25.338	17.53
3	27.654	32.71
4	33.230	17.29



	Retention Time	% Area
1	15.655	76.88
2	25.306	16.75
3	27.675	4.35
4	33.287	2.03

Diethyl (1*S*,5'*R*)-5'-(4-fluorophenyl)-1'-(phenylsulfonyl)-*3H*-spiro[isobenzofuran-1,3'-pyrrolidine]-2',2'-dicarboxylate (3c)



0.1 mmol scale reaction, 28 h, 22.7 mg, 41% yield; white foam. Melting point: 128 – 131 ºC. 80:20 dr., 94% ee for the major isomer and 68% ee for the minor isomer. $[\alpha]_D^{17}$ = +25.7 (c = 0.30 in CH_2Cl_2).

HPLC (Daicel chiralcel ADH, hexane/*i*-PrOH = 90/10, flow rate 1.0 mL/min, λ = 254 nm) t_r (major-major) = 25.87 min, t_r (major-minor) = 31.88 min, t_r (minor-major) = 35.43, t_r (minor-minor) = 44.69.

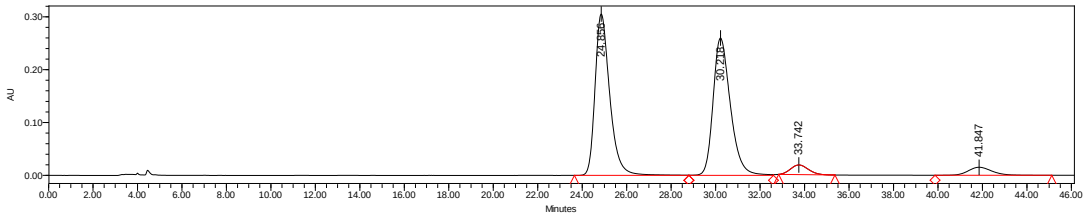
^{1}H NMR (400 MHz, Chloroform-*d*) *δ* 7.67 – 7.43 (m, 2H), 7.41 – 7.25 (m, 5H), 7.19 (q, *J* = 7.6 Hz, 4H), 6.81 – 6.63 (m, 2H), 5.72 (d, *J* = 9.6Hz, 1H), 4.89 (s, 2H), 4.46 – 4.25 (m, 3H), 4.18 – 4.01 (m, 1H), 3.45 (dd, *J* = 13.2, 10.4 Hz, 1H), 2.20 – 2.16 (m, 1H), 1.34 (t, *J* = 7.2 Hz, 3H), 1.05 (t, *J* = 7.2 Hz, 3H).

^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*) *δ* 167.63, 165.86, 163.07, 160.63 (d, *J* = 246.0 Hz), 140.64 (d, *J* = 4.8 Hz), 137.15, 136.61, 132.18, 129.86, 129.78(d, *J* = 8.0 Hz), 129.11, 127.84, 127.57, 122.24, 120.57, 114.62, 114.41(d, *J* = 21.4 Hz), 99.74, 85.32, 73.15, 63.70, 62.58, 61.67, 13.88, 13.69.

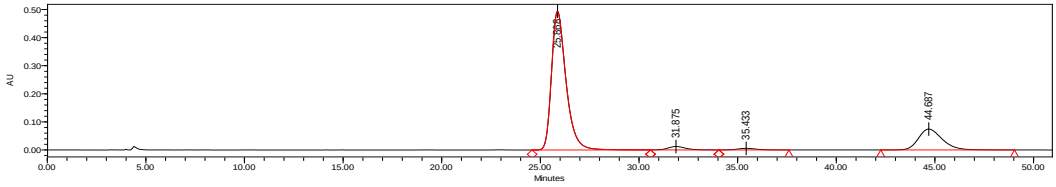
HRMS (ESI) calcd for $C_{29}H_{28}FNNaO_7S^+$ ([M]+Na^+) = 567.1463, found 567.1465.

^{19}F{^{1}H} NMR (376 MHz, Chloroform-*d*) *δ* = –116.11.

IR (neat) ***ν*** (cm^{-1}): 2984, 1754, 1725, 1604, 1510, 1447, 1341, 1295, 1226, 1156, 1063, 1043, 1022, 899, 839, 760, 728, 689, 602, 576, 547, 466.

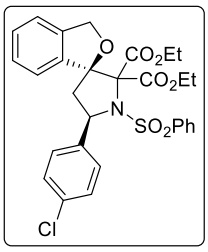


	Retention Time	% Area
1	24.856	46.43
2	30.218	46.41
3	33.742	3.39
4	41.847	3.78



	Retention Time	% Area
1	25.868	77.28
2	31.875	2.42
3	35.433	1.18
4	44.687	19.12

Diethyl (1*S*,5'*R*)-5'-(4-chlorophenyl)-1'-(phenylsulfonyl)-*3H*-spiro[isobenzofuran-1,3'-pyrrolidine]-2',2'-dicarboxylate (3d)



0.1 mmol scale reaction, 36 h, 44.5 mg, 78% yield; white foam. Melting point: 153 – 155 ºC, 85:15 dr., 93% ee for the major isomer and 84% ee for the minor isomer. $[\alpha]_\lambda^{17}$ = +14.8 (c = 1.15 in CH_2Cl_2, λ = 405 nm).

HPLC (Daicel chiralcel ADH, hexane/*i*-PrOH = 85/15, flow rate 1.0 mL/min, λ = 254 nm) t_r (major- major) = 16.22 min, t_r (major-minor) = 32.82 min, t_r (minor-major) = 26.49 min, t_r (minor-minor) = 38.06 min.

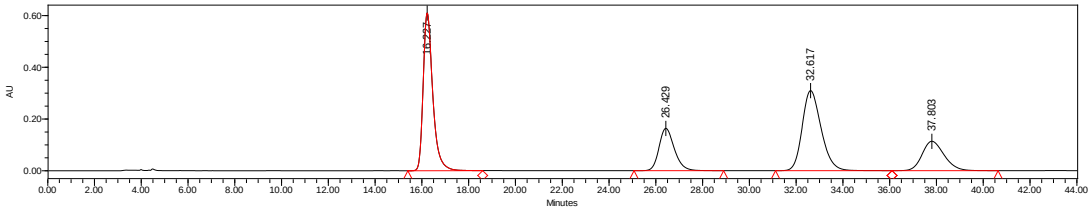
^{1}H NMR (400 MHz, Chloroform-*d*) *δ* 7.55 (d, *J* = 7.2 Hz, 2H), 7.44 – 7.28 (m, 2H), 7.24 – 7.09 (m, 7H), 6.94 (d, *J* = 8.4 Hz, 2H), 5.65 (d, *J* = 10.0 Hz, 1H), 4.83 (s, 2H), 4.41 – 4.23 (m, 3H), 4.12 – 3.94 (m, 1H), 3.40 (dd, *J* = 13.6, 10.8 Hz, 1H), 2.13 (d, *J* = 13.6 Hz, 1H), 1.29 (t, *J* = 7.2 Hz, 3H), 1.01 (t, *J* = 7.2 Hz, 3H).

^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*) *δ* 167.58, 165.84, 140.59, 140.47, 139.96, 136.50, 132.58, 132.27, 130.34, 129.50, 129.14, 128.69, 127.83, 127.63, 122.22, 120.60, 99.76, 85.31, 73.15, 63.69, 62.60, 61.69, 47.76, 13.87, 13.70.

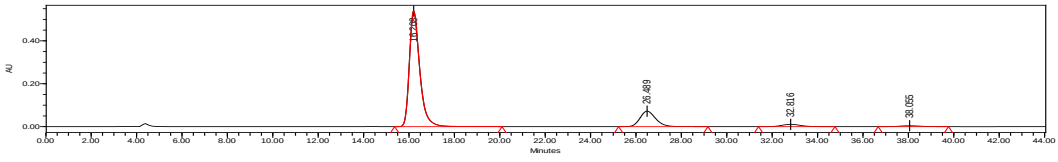
HRMS (ESI) calcd for $C_{29}H_{28}{}^{35}ClNNaO_7S^+$ ([M]+Na^+) = 592.1167, 592.1167.

HRMS (ESI) calcd for $C_{29}H_{28}{}^{37}ClNNaO_7S^+$ ([M]+Na^+) = 594.1138, 592.1137.

IR (neat) ***ν*** (cm^{-1}): 2928, 1754, 1725, 1488, 1447, 1414, 1341, 1294, 1230, 1158, 1091, 1063, 1020, 899, 861, 821, 758, 728, 689, 602, 575, 544, 441.

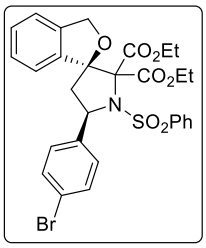


	Retention Time	% Area
1	16.227	34.98
2	26.429	15.01
3	32.617	35.02
4	37.803	14.99

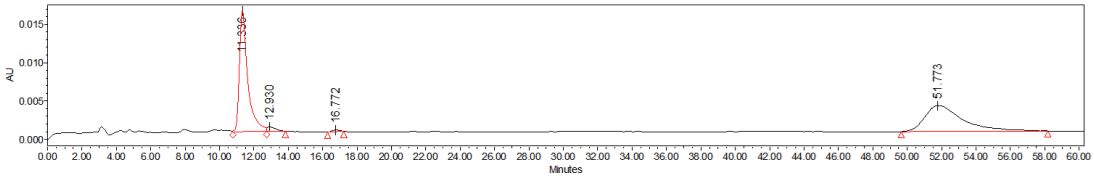


	Retention Time	% Area
1	16.208	79.65
2	26.489	16.13
3	32.816	2.94
4	38.055	1.27

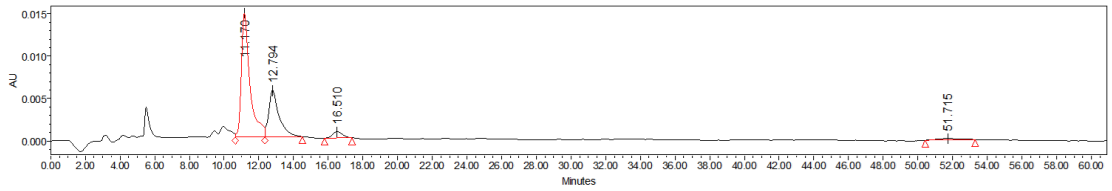
Diethyl (1*S*,5'*R*)-5'-(4-bromophenyl)-1'-(phenylsulfonyl)-*3H*-spiro[isobenzofuran-1,3'-pyrrolidine]-2',2'-dicarboxylate (3e)



0.1 mmol scale reaction, 36 h, 43.6 mg, 71% yield; white foam. Melting point: 161 – 163 ºC. 83:17 dr., 94% ee for the major isomer and 77% ee for the minor isomer. $[\alpha]_{\lambda}^{17}$ = +31.7 (c = 0.82 in CH_2Cl_2, λ = 405 nm).
HPLC (Daicel chiralcel ADH, hexane/*i*-PrOH = 80/20, flow rate 1.0 mL/min, λ = 254 nm) t_r (major- major) = 11.17 min, t_r (major -minor) = 51.72 min, t_r (minor-major) = 12.79 min, t_r (monor-minor) = 16.51 min.
^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.59 (d, *J* = 7.6 Hz, 2H), 7.45 – 7.29 (m, 4H), 7.23 – 7.09 (m, 8H), 5.68 (d, *J* = 9.6 Hz, 1H), 4.87 (s, 2H), 4.37 (dtt, *J* = 18.0, 7.6, 3.2 Hz, 3H), 4.15 – 4.00 (m, 1H), 3.45 (dd, *J* = 13.6, 10.8 Hz, 1H), 2.17 (d, *J* = 13.2 Hz, 1H), 1.34 (t, *J* = 7.2 Hz, 3H), 1.05 (t, *J* = 7.2 Hz, 3H).
^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*) δ 167.58, 165.84, 140.59, 140.47, 140.39, 136.47, 132.31, 130.80, 129.85, 129.16, 127.66, 122.22, 120.76, 120.61, 99.77, 73.18, 63.72, 62.63, 61.72, 47.70, 13.89, 13.72.
HRMS (ESI) calcd for $C_{29}H_{28}{}^{79}BrNNaO_7S^+$ ([M]+Na^+) = 636.0662, found 636.0665.
HRMS (ESI) calcd for $C_{29}H_{28}{}^{81}BrNNaO_7S^+$ ([M]+Na^+) = 638.0641, found 636.0642.
IR (neat): 2983, 1754, 1725, 1484, 1446, 1341, 1294, 1232, 1158, 1093, 1018, 899, 860, 818, 758, 729, 688, 602, 574, 545, 459.

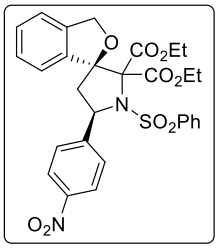


	Retention Time	% Area
1	11.336	49.47
2	12.930	1.76
3	16.772	0.61
4	51.773	48.16



	Retention Time	% Area
1	11.170	65.00
2	12.794	29.30
3	16.510	3.74
4	51.715	1.96

Diethyl (1*S*,5'*R*)-5'-(4-nitrophenyl)-1'-(phenylsulfonyl)-*3H*-spiro[isobenzofuran-1,3'-pyrrolidine]-2',2'-dicarboxylate (3f)



0.1 mmol scale reaction, 60 h, 27.3 mg, 47% yield; white foam. Melting point: 144 – 147 ºC. 85:15 dr., 85% ee for the major isomer and 72% ee for the minor isomer. $[\alpha]_\lambda^{17}$ = +11.8 (c = 1.18 in CH_2Cl_2, λ = 405 nm).

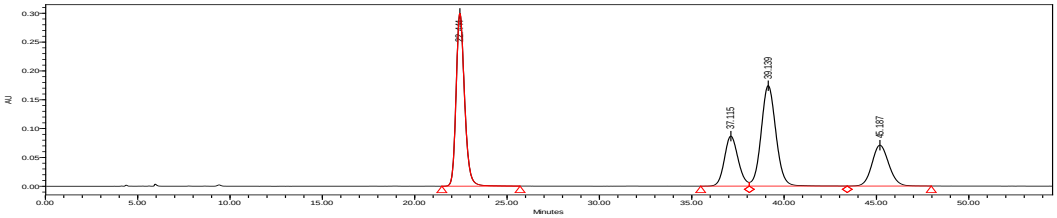
HPLC (Daicel chiralcel ADH, hexane/*i*-PrOH = 85/15, flow rate 1.0 mL/min, λ = 254 nm) t_r (major- major) = 22.49 min, t_r (major -minor) =39.25 min, t_r (minor-major) = 37.20 min, t_r (minor-minor) = 45.35 min.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.81 – 7.68 (m, 2H), 7.64 – 7.45 (m, 2H), 7.43 – 7.26 (m, 3H), 7.24 – 7.13 (m, 2H), 7.05 (m, 4H), 5.66 (d, *J* = 10.4 Hz, 1H), 4.79 – 4.53 (m, 2H), 4.38 – 4.09 (m, 3H), 4.01 – 3.90 (m, 1H), 3.41 (dd, *J* = 13.4, 10.6 Hz, 1H), 2.04 (d, *J* = 13.4 Hz, 1H), 1.21 (t, *J* = 7.2 Hz, 3H), 0.96 (t, *J* = 7.2 Hz, 3H).

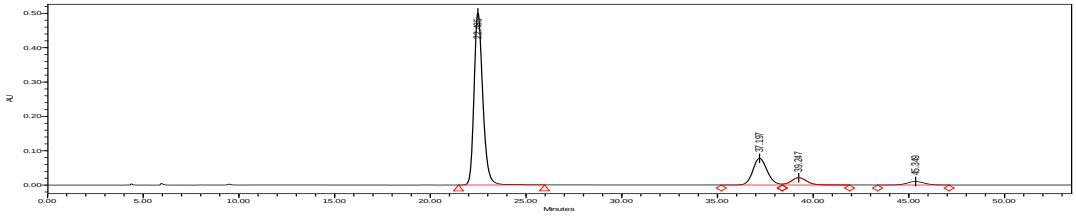
^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*) δ 167.36, 165.88, 146.67, 140.56, 139.98, 132.78, 129.31, 128.81, 128.55, 127.89, 127.70, 122.84, 122.20, 120.67, 73.25, 63.38, 62.80, 61.91, 47.70, 13.87, 13.74.

HRMS (ESI) calcd for $C_{29}H_{28}N2NaO_9S^+$ ([M]+Na^+) = 603.1408, Found 603.1410.

IR (neat) ***ν*** (cm^{-1}): 2984, 1753, 1725, 1602, 1519, 1446, 1343, 1294, 1228, 1159, 1093, 1064, 1020, 901, 853, 755, 729, 689, 601, 575, 548, 440.

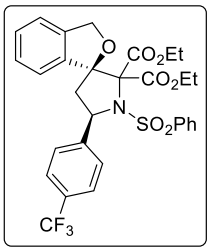


	Retention Time	% Area
1	22.444	33.92
2	37.115	15.86
3	39.139	34.27
4	45.187	15.94



	Retention Time	% Area
1	22.485	72.89
2	37.197	18.50
3	39.247	5.61
4	45.349	2.99

Diethyl (1*S*,5'*R*)-1'-(phenylsulfonyl)-5'-(4-(trifluoromethyl)phenyl)-*3H*-spiro[isobenzofuran-1,3'-pyrrolidine]-2',2'-dicarboxylate (3g)



0.1 mmol scale reaction, 48 h, 36.8 mg, 61% yield; white foam. Melting point: 171 – 173 ºC, 80:20 d.r., 94% ee for the major isomer and 68% ee for the minor isomer. $[\alpha]_{\lambda}^{17}$ = +18.7 (c = 0.978 in CH_2Cl_2, λ = 405 nm). **HPLC** (Daicel chiralcel ADH, hexane/*i*-PrOH = 90/10, flow rate 1.0 mL/min, λ = 254 nm) t_r (major- major) = 22.71 min, t_r (major -minor) = 36.31 min, t_r (minor-major) = 46.64 min, t_r (minor-minor) = 42.28 min

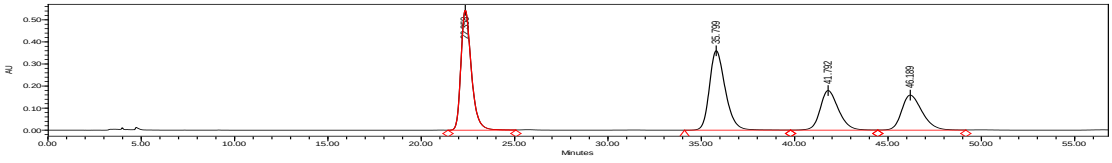
^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.59 (d, *J* = 7.2 Hz, 2H), 7.45 – 7.31 (m, 5H), 7.29 (d, *J* = 8.0 Hz, 2H), 7.24 – 7.11 (m, 5H), 5.72 (d, *J* = 10.4 Hz, 1H), 4.87 (s, 2H), 4.38 (dtq, *J* = 14.4, 7.2, 3.2 Hz, 3H), 4.18 – 4.00 (m, 1H), 3.47 (ddd, *J* = 17.6, 13.4, 10.8 Hz, 1H), 2.20 (d, *J* = 13.6 Hz, 1H), 1.34 (t, *J* = 7.2 Hz, 3H), 1.07 (t, *J* = 7.2 Hz, 3H).

^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*) *δ* 167.53, 165.82, 145.36, 140.59 (d, *J* = 37.4 Hz), 136.34, 132.42, 129.31, 129.22, 129.155, 128.69, 128.35, 127.65, 124.66, 124.62 (d, *J* =3.8 Hz), 122.21, 120.63, 99.82 ((d, *J* =298.2 Hz), 73.22, 63.7, 62.69, 61.78, 47.60, 13.89, 13.74.

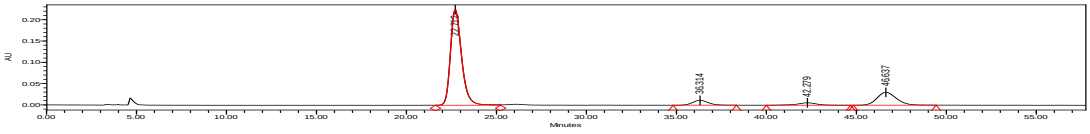
HRMS (ESI) calcd for $C_{30}H_{28}F_3NNaO_7S^+$ ([M]+Na^+) = 626.1431, Found 626.1438.

^{19}F{^{1}H} NMR (376 MHz, Chloroform-*d*) *δ* = –62.70.

IR (neat) ***ν*** (cm^{-1}): 2985, 1755, 1726, 1447, 1421, 1325, 1295, 1232, 1160, 1117, 1065, 1021, 899, 843, 759, 727, 688, 594, 574, 546, 462.

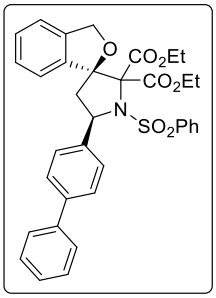


	Retention Time	% Area
1	22.358	31.66
2	35.799	31.78
3	41.792	18.36
4	46.189	18.20



	Retention Time	% Area
1	22.712	74.18
2	36.314	5.35
3	42.279	3.21
4	46.637	17.27

Diethyl (1*S*,5'*R*)-5'-([1,1'-biphenyl]-4-yl)-1'-(phenylsulfonyl)-*3H*-spiro[isobenzofuran-1,3'-pyrrolidine]-2',2'-dicarboxylate (3h)



0.1 mmol scale reaction, 18 h, 39.1 mg, 54% yield; white foam. Melting point: 137 – 141 ºC. 85:15 dr., 93% ee for the major isomer and 87% ee for the minor isomer. $[\alpha]_{\lambda}^{17}$ = +76.8 (c = 0.63 in CH_2Cl_2, λ = 405 nm).

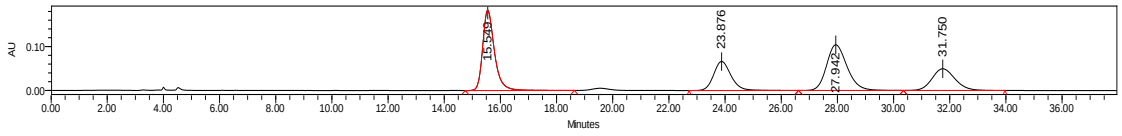
HPLC (Daicel chiralcel ADH, hexane/*i*-PrOH = 90/10, flow rate 1.0 mL/min, λ = 254 nm) t_r (major-major) = 15.52 min, t_r (major-minor) = 28.01 min, t_r (minor-major) = 23.88 min, t_r (minor-minor) = 31.70 min.

^{1}H NMR (400 MHz, Chloroform-*d*) *δ* 7.66 – 7.42 (m, 5H), 7.38 (dd, *J* = 14.0, 7.6 Hz, 4H), 7.33 – 7.27 (m, 3H), 7.25 – 7.18 (m, 2H), 7.14 (t, *J* = 7.6 Hz, 2H), 7.07 (t, *J* = 8.0 Hz, 2H), 5.75 (d, *J* = 9.6 Hz, 1H), 4.92 – 4.82 (m, 2H), 4.34 (dtq, *J* = 18.0, 10.8, 7.2 Hz, 3H), 4.12 – 3.95 (m, 1H), 3.44 (dd, *J* = 13.6, 10.8 Hz, 1H), 2.25 (dd, *J* = 13.6, 1.6 Hz, 1H), 1.32 (t, *J* = 7.2 Hz, 3H), 1.01 (t, *J* = 7.2 Hz, 3H).

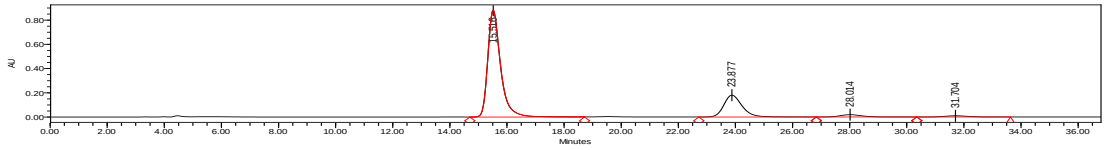
^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*) *δ* 167.73, 165.85, 140.72, 140.67, 140.45, 139.82, 136.75, 131.98, 129.10, 128.76, 128.74, 128.69, 127.61, 127.49, 127.16, 127.00, 126.61, 122.27, 120.59, 99.81, 73.20, 64.21, 62.58, 61.66, 47.79, 13.93, 13.75.

HRMS (ESI) calcd for $C_{35}H_{33}NNaO_7S^+$ ([M]+Na^+) = 634.1870, Found 634.1875.

IR (neat) ***ν*** (cm^{-1}): 2984, 1755, 1725, 1484, 1447, 1340, 1293, 1231, 1158, 1118, 1092, 1064, 1024, 899, 843, 762, 729, 692, 608, 576, 520.

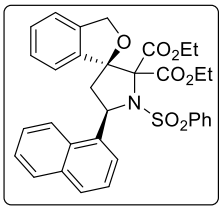


	Retention Time	% Area
1	15.549	32.64
2	23.876	17.56
3	27.942	32.47
4	31.750	17.33



	Retention Time	% Area
1	15.516	73.94
2	23.877	21.75
3	28.014	2.79
4	31.704	1.53

Diethyl (1*S*,5'*R*)-5'-(naphthalen-1-yl)-1'-(phenylsulfonyl)-*3H*-spiro[isobenzofuran-1,3'-pyrrolidine]-2',2'-dicarboxylate (3i)



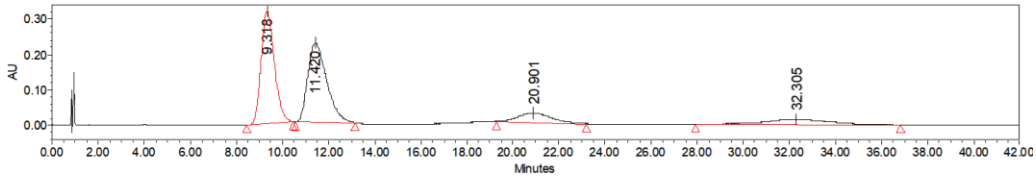
0.1 mmol scale reaction, 18h, 38.7 mg, 51% yield, white foam. Melting point: 123 – 125 ºC. 95:5 dr., 94% ee for the major isomer and 77% ee for the minor isomer. $[\alpha]_{\lambda}^{17}$ = +25.7 (c = 0.66 in CH_2Cl_2, λ = 405 nm). **HPLC** (Daicel chiralcel ADH, hexane/*i*-PrOH = 90/10, flow rate 1.0 mL/min, λ = 254 nm) t_r (major-major) =11.23 min, t_r (major-minor) = 9.32 min, t_r (minor-major) = 20.63 min, t_r (minor-major) = 32.48 min.

^{1}H NMR (400 MHz, Chloroform-*d*) *δ* 8.04 – 7.56 (m, 3H), 7.48 (t, *J* = 7.6 Hz, 3H), 7.34 (dq, *J* = 15.6, 8.0, 7.6 Hz, 2H), 7.22 – 6.95 (m, 6H), 6.94 – 6.51 (m, 2H), 6.47 – 6.30 (m, 1H), 5.26 – 4.77 (m, 1H), 4.71 – 4.53 (m, 1H), 4.48 – 4.22 (m, 3H), 4.11 – 3.72 (m, 1H), 3.62 – 3.24 (m, 1H), 2.20 (d, *J* = 13.2 Hz, 1H), 1.34 (t, *J* = 7.2 Hz, 3H), 0.91 (t, *J* = 7.2 Hz, 3H).

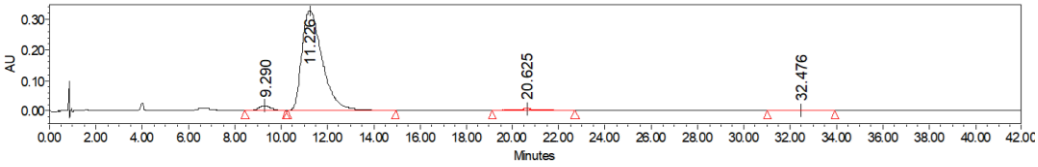
^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*) *δ* 167.75, 166.31, 133.40, 132.44, 129.43, 129.19, 128.25, 127.91, 127.74 127.22, 126.89, 126.36 ,126.01,125.28, 125.01, 124.37, 123.34, 122.79, 122.27, 120.54, 100.05, 85.52, 73.18, 62.68, 62.25, 61.88, 61.18, 59.71, 48.91, 47.27, 14.14, 13.87, 13.51.

HRMS (ESI) calcd for $C_{33}H_{31}NNaO_7S^+$ ([M]+Na^+) = 608.1713, Found 608.1710.

IR (neat) ***ν*** (cm^{-1}): 3063, 2983, 1754, 1511, 1447, 1342, 1297, 1231, 1158, 1120, 1066, 1023, 900, 857, 802, 761, 728, 689, 606, 575, 499.

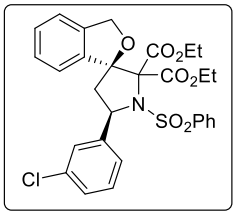


	Retention Time	% Area
1	9.318	41.64
2	11.420	41.52
3	20.901	8.45
4	32.305	8.39



	Retention Time	% Area
1	9.290	2.97
2	11.226	94.78
3	20.625	2.01
4	32.476	0.24

Diethyl (1*S*,5'*R*)-5'-(3-chlorophenyl)-1'-(phenylsulfonyl)-*3H*-spiro[isobenzofuran-1,3'-pyrrolidine]-2',2'-dicarboxylate (3j)



0.1 mmol scale reaction, 36 h, 43.9 mg, 77% yield, white foam. Melting point: 141 – 144 ºC. 72:28 dr., 88% ee for the major isomer and 84% ee for the minor isomer. $[\alpha]_D^{17}$ = +14.7 (c = 1.18 in CH_2Cl_2).

HPLC (Daicel chiralcel ADH, hexane/i-PrOH = 85/15, flow rate 1.0 mL/min, λ = 254 nm) t_r (major- major) = 11.97 min, t_r (major -minor) = 14.71 min, t_r (minor-major) = 19.75 min, t_r (minor-minor) = 16.41 min.

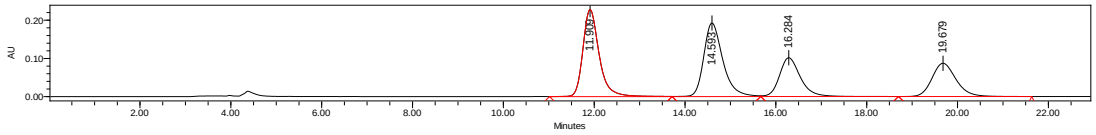
^{1}H NMR (400 MHz, Chloroform-*d*) *δ* 7.71 (d, *J* = 8.0 Hz, 1H), 7.56 (d, *J* = 8.0 Hz, 1H), 7.51 – 7.33 (m, 4H), 7.32 – 7.28 (m, 2H), 7.24 (s, 3H), 7.19 – 7.02 (m, 2H), 5.78 (d, *J* = 10.4 Hz, 1H), 4.95 (s, 2H), 4.45 (td, *J* = 7.2, 2.4 Hz, 3H), 4.23 – 4.07 (m, 1H), 3.54 (dd, *J* = 13.2, 10.4 Hz, 1H), 2.27 (d, *J* = 13.6 Hz, 1H), 1.42 (t, *J* = 7.2 Hz, 3H), 1.17 (t, *J* = 7.2 Hz, 3H).

^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*) *δ* 166.49, 164.61, 142.36, 139.66, 132.63, 131.40, 128.11, 127.97, 127.60, 127.42, 127.18, 126.84, 126.61, 125.92, 125.01, 121.18, 119.60, 98.85, 84.09, 72.19, 62.71, 61.58, 60.67, 49.18, 46.64, 12.92.

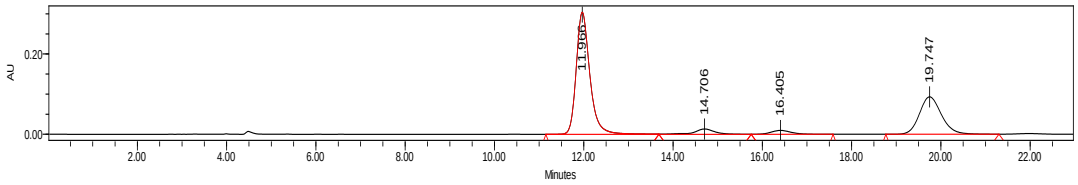
HRMS (ESI) calcd for $C_{29}H_{28}{}^{35}ClNNaO_7S^+$ ([M]+Na$^+$) = 592.1167, found 592.1168.

HRMS (ESI) calcd for $C_{29}H_{28}{}^{37}ClNNaO_7S^+$ ([M]+Na$^+$) = 594.1138, found 594.1138.

IR (neat) ***ν*** (cm^{-1}): 2984, 2361, 1754, 1725, 1587, 146, 1445, 1342, 1264, 1228, 1158, 1118, 1090, 1063, 1023, 900, 790, 759, 729, 688, 612, 579, 440.

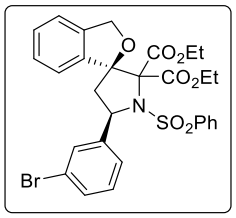


	Retention Time	% Area
1	11.909	31.85
2	14.593	31.66
3	16.284	18.41
4	19.679	18.08



	Retention Time	% Area
1	11.966	62.10
2	14.706	4.11
3	16.405	2.91
4	19.747	30.88

Diethyl (1*S*,5'*R*)-5'-(3-bromophenyl)-1'-(phenylsulfonyl)-*3H*-spiro[isobenzofuran-1,3'-pyrrolidine]-2',2'-dicarboxylate (3k)



0.1 mmol scale reaction, 36 h, 45.4mg, 74% yield, white foam. Melting point: 149 – 152 ºC. 70:30 dr., 92% ee for the major isomer and 66% ee for the minor isomer. $[\alpha]_D^{17}$ = +19.0 (c = 1.14 in CH_2Cl_2).

HPLC (Daicel chiralcel ADH, hexane/*i*-PrOH = 90/10, flow rate 1.0 mL/min, λ = 254 nm) t_r (major- major) =18.02 min, t_r (major -minor) = 20.09 min, t_r (minor-major) = 35.01 min, t_r (minor-minor) = 40.35 min.

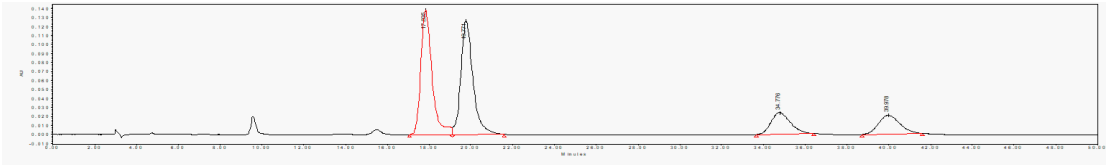
^{1}H NMR (400 MHz, Chloroform-*d*) *δ* 7.59 (d, *J* = 7.6 Hz, 2H), 7.44 (d, *J* = 7.6 Hz, 1H), 7.41 – 7.31 (m, 1H), 7.29 (d, *J* = 7.2 Hz, 1H), 7.16 (dq, *J* = 15.4, 8.0, 8.0 Hz, 7H), 6.89 (q, *J* = 8.0 Hz, 1H), 5.65 (d, *J* = 10.4 Hz, 1H), 4.83 (s, 1H), 4.43 – 4.22 (m, 3H), 4.03 (tq, *J* = 14.4, 7.6 Hz, 1H), 3.41 (dd, *J* = 13.6, 10.8 Hz, 1H), 2.19 – 2.09 (m, 1H), 1.30 (t, *J* = 7.2 Hz, 3H), 1.06 (t, *J* = 7.2 Hz, 3H).

^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*) *δ* 166.47, 164.59, 142.62, 139.66, 139.20, 135.36, 130.73, 130.05, 128.86, 128.48, 128.28, 127.59, 127.40, 126.89, 126.65, 125.48, 121.66, 121.20, 120.89, 119.60, 98.87, 84.07, 72.19, 62.66, 62.03, 60.67, 46.65, 12.93, 12.78.

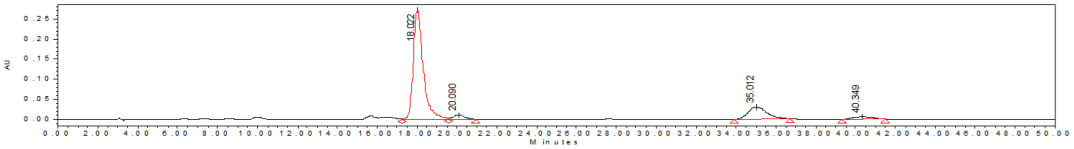
HRMS (ESI) calcd for $C_{29}H_{28}{}^{79}BrNNaO_7S^+$ ([M]+Na$^+$) =636.0662, found 636.0660.

HRMS (ESI) calcd for $C_{29}H_{28}{}^{81}BrNNaO_7S^+$ ([M]+Na$^+$) =638.0642, found 636.0645.

IR (neat) ***ν*** (cm^{-1}): 2983, 1754, 1726, 1570, 1475, 1446, 1342, 1263, 1229, 1157, 1091, 1063, 1023, 898, 860, 788, 759, 730, 688, 610, 577, 437.

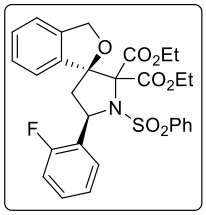


	Retention Time	% Area
1	17.835	38.71
2	19.771	38.43
3	34.776	11.63
4	39.978	11.23



	Retention Time	% Area
1	18.022	77.57
2	20.090	3.23
3	35.012	15.91
4	40.349	3.29

Diethyl (1*S*,5'*R*)-5'-(2-fluorophenyl)-1'-(phenylsulfonyl)-*3H*-spiro[isobenzofuran-1,3'-pyrrolidine]-2',2'-dicarboxylate (3l)



0.1 mmol scale reaction, 40 h, 43.1 mg, 76% yield, white foam. Melting point: 125 – 127 ºC. 82:18 dr., 94% ee for the major isomer and 88% ee for the minor isomer. $[\alpha]_D^{17}$ = +15.5 (c = 1.18 in CH_2Cl_2).

HPLC (Daicel chiralcel ADH, hexane/*i*-PrOH = 90/10, flow rate 1.0 mL/min, λ = 254 nm) t_r (major-major) = 17.73 min, t_r (major-minor) = 8.71 min, t_r (minor-major) = 16.46 min, t_r (minor-minor) = 10.44 min.

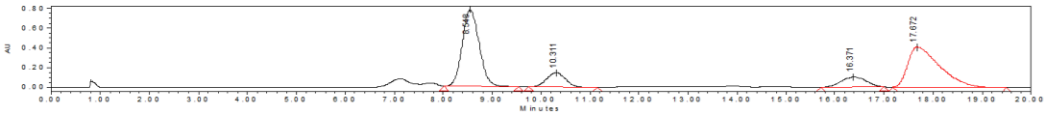
^{1}H NMR (400 MHz, Chloroform-*d*) *δ* 7.65 (d, *J* = 7.2 Hz, 2H), 7.51 (d, *J* = 7.6 Hz, 1H), 7.33 – 7.28 (m, 1H), 7.23 – 7.16 (m, 2H), 7.09 (s, 2H), 7.07 – 6.98 (m, 2H), 6.96 – 6.72 (m, 2H), 6.48 (t, *J* = 7.6 Hz, 1H), 5.92 (d, *J* = 10.4 Hz, 1H), 4.77 – 4.66 (m, 2H), 4.26 (dddd, *J* = 27.2, 11.2, 8.8, 5.6 Hz, 3H), 4.03 – 3.88 (m, 1H), 3.38 (dd, *J* = 13.4, 10.2 Hz, 1H), 2.08 (d, *J* = 13.2 Hz, 1H), 1.25 (t, *J* = 7.2 Hz, 3H), 0.99 (t, *J* = 7.2 Hz, 3H).

^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*) *δ* 167.38, 166.14, 160.91, 158.47 (d, *J* = 244.0 Hz), 140.94, 140.67 (d, J = 15.0 Hz), 140.12, 136.45, 132.43, 130.35 (d, *J* = 3.6 Hz), 129.12, 128.84 (d, *J* = 5.6 Hz), 128.09, 128.01, 127.58, 123.07 (d, J = 3.4 Hz), 122.25, 120.56, 114.27, 114.06, 100.02, 73.21, 62.66, 61.76 (d, J = 4.6 Hz), 57.60, 46.96, 13.89, 13.76.

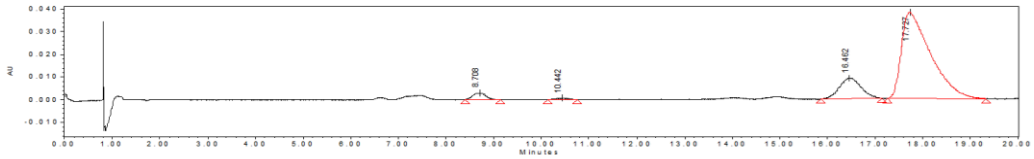
^{19}F{^{1}H} NMR (376 MHz, CDCl3) δ = –119.26.

HRMS (ESI) calcd for $C_{29}H_{28}FNNaO_7S^+$ ([M]+Na^+) = 576.1463, Found 567.1467.

IR (neat) ***ν*** (cm^{-1}): 2984, 1753, 1726, 1616, 1587, 1486, 1453, 1342, 1293, 1233, 1158, 1092, 1065, 1044, 1023, 901, 861, 815, 758, 730, 689, 608, 575, 555, 513.

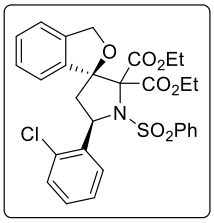


	Retention Time	% Area
1	8.548	42.39
2	10.311	8.53
3	16.371	7.91
4	17.672	41.17



	Retention Time	% Area
1	8.708	2.65
2	10.442	0.42
3	16.462	14.16
4	17.727	82.77

Diethyl (1*S*,5'*R*)-5'-(2-chlorophenyl)-1'-(phenylsulfonyl)-*3H*-spiro[isobenzofuran-1,3'-pyrrolidine]-2',2'-dicarboxylate (3m)



0.1 mmol scale reaction, 40 h, 46.2 mg, 81% yield, white foam. Melting point: 152 – 153 ºC. 56:43 dr., 93% ee for the major isomer and 87% ee for the minor isomer. $[\alpha]_{\lambda}^{26}$ = +31.7 (c = 1.17 in CH_2Cl_2, λ = 405 nm).

HPLC (Daicel chiralcel ASH, hexane/*i*-PrOH = 85/15, flow rate 1.0 mL/min, λ = 254 nm) t_r (major-major) = 9.74 min, t_r (major-minor) = 8.42 min, t_r (minor-major) = 10.58 min, t_r (minor-minor) = 7.21 min.

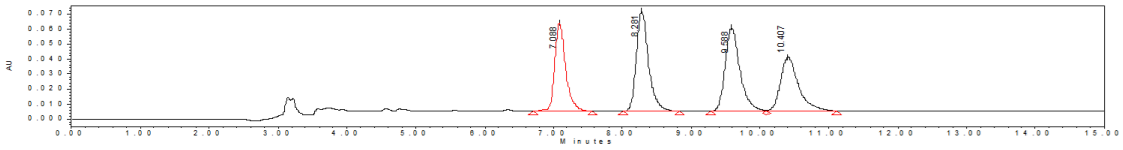
^{1}H NMR (400 MHz, Chloroform-*d*) *δ* 7.73 (d, *J* = 9.6 Hz, 2H), 7.46 – 7.27 (m, 4H), 7.25 – 7.04 (m, 5H), 6.96 (td, *J* = 7.6, 1.6 Hz, 1H), 6.77 – 6.65 (m, 1H), 6.02 (d, *J* = 10 Hz, 1H), 4.79 (q, *J* = 12.4 Hz, 2H), 4.49 – 4.32 (m, 3H), 4.15 – 3.93 (m, 1H), 3.60 – 3.39 (m, 1H), 2.19 (d, *J* = 12.4 Hz, 1H), 1.35 (t, *J* = 7.2 Hz, 3H), 1.10 (t, *J* = 7.2 Hz, 3H).

^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*) *δ* 167.37, 166.20, 140.68, 138.14, 132.46, 130.45, 129.10, 128.89, 128.42, 127.79, 127.72, 127.55, 125.66, 122.28, 120.54, 99.97, 85.49, 73.18, 62.65, 61.75, 61.39, 46.70, 13.88, 13.76.

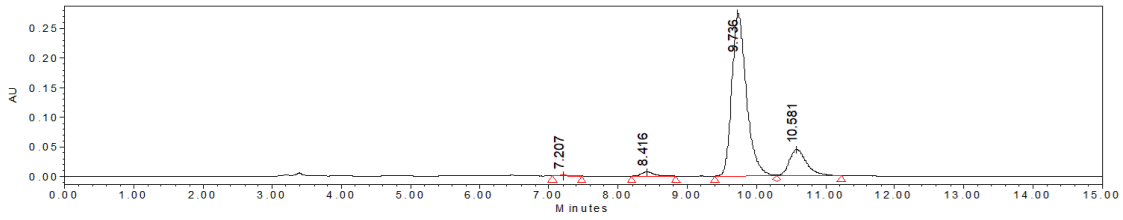
HRMS (ESI) calcd for $C_{29}H_{28}{}^{35}ClNNaO_7S^+$ ([M]+Na$^+$) = 592.1167, found 592.1169.

HRMS (ESI) calcd for $C_{29}H_{28}{}^{37}ClNNaO_7S^+$ ([M]+Na$^+$) = 594.1138, found 594.1141.

IR (neat) ***ν*** (cm^{-1}): 2984, 1753, 1726, 1472, 1446, 1342, 1293, 1232, 1158, 1092, 1052, 1024, 957, 901, 859, 757, 730, 689, 608, 576, 549, 494, 459.

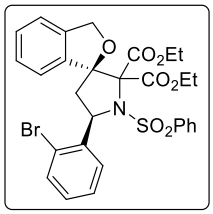


	Retention Time	% Area
1	7.088	21.99
2	8.281	27.90
3	9.588	28.15
4	10.407	21.97



	Retention Time	% Area
1	7.207	1.86
2	8.416	2.07
3	9.736	84.53
4	10.581	11.54

Diethyl (1*S*,5'*R*)-5'-(2-bromophenyl)-1'-(phenylsulfonyl)-*3H*-spiro[isobenzofuran-1,3'-pyrrolidine]-2',2'-dicarboxylate (3n)



0.1 mmol scale reaction, 40 h, 46.0 mg, 75% yield, white foam. Melting point: 142 – 144 ºC. 53:47 dr., 95% ee for the major isomer and 67% ee for the minor isomer. $[\alpha]_{\lambda}^{26}$ = +42.3 (c = 1.01 in CH_2Cl_2, λ = 405 nm). **HPLC** (Daicel chiralcel ASH, hexane/*i*-PrOH = 80/20, flow rate 1.0 mL/min, λ = 254 nm) t_r (major-major) = 8.18 min, t_r (major-minor) = 7.19 min, t_r (minor-major) = 8.78 min, t_r (minor-minor) = 6.36 min.

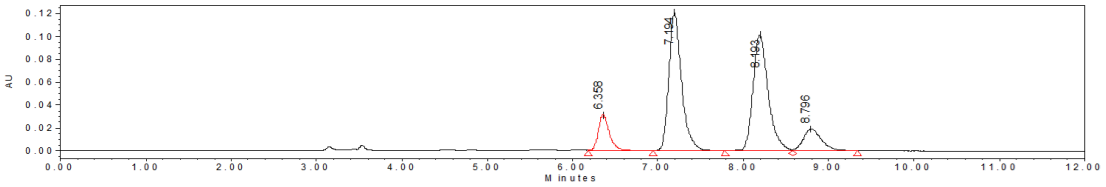
^{1}H NMR (400 MHz, Chloroform-*d*) *δ* 7.76 – 7.61 (m, 2H), 7.49 – 7.29 (m, 4H), 7.25 – 7.11 (m, 4H), 7.01 (t, *J* = 7.6 Hz, 1H), 6.89 (td, *J* = 7.6, 1.6 Hz, 1H), 6.76 (dt, *J* = 22.2, 7.2 Hz, 1H), 5.96 (d, *J* = 10.0 Hz, 1H), 4.79 (q, *J* = 12.4 Hz, 2H), 4.48 – 4.33 (m, 3H), 4.09 (dq, *J* = 10.8, 7.2 Hz, 1H), 3.56 – 3.39 (m, 1H), 2.20 (d, *J* = 14.4 Hz, 1H), 1.34 (t, *J* = 7.2 Hz, 3H), 1.10 (t, *J* = 7.2 Hz, 3H).

^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*) *δ* 167.38, 166.20, 136.46, 132.45, 131.72, 130.78, 129.10, 128.90, 128.05, 127.79, 127.55, 126.26, 122.29, 120.54, 99.89, 73.19, 63.67, 62.66, 61.76, 46.83, 13.88, 13.76.

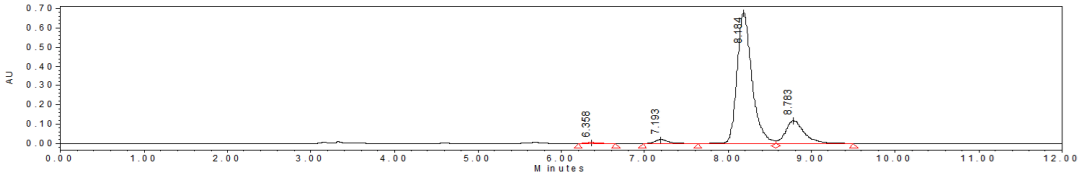
HR-MS (ESI) calcd for $C_{29}H_{28}{}^{79}BrNNaO_7S^+$ ([M]+Na^+) = 636.0662, found 636.0662.

HR-MS (ESI) calcd for $C_{29}H_{28}{}^{81}BrNNaO_7S^+$ ([M]+Na^+) = 638.0642, found 636.0645.

IR (neat) ***ν*** (cm^{-1}): 2983, 1753, 1726, 1466, 1444, 1342, 1293, 1231, 1158, 1021, 900, 858, 802, 730, 607, 574, 548, 489, 443.

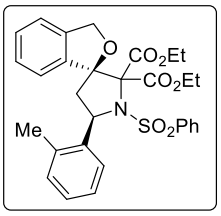


	Retention Time	% Area
1	6.358	9.11
2	7.194	40.80
3	8.193	40.72
4	8.796	9.37



	Retention Time	% Area
1	6.358	0.36
2	7.193	1.85
3	8.184	80.60
4	8.783	17.19

Diethyl (1*S*,5'*R*)-1'-(phenylsulfonyl)-5'-(o-tolyl)-*3H*-spiro[isobenzofuran-1,3'-pyrrolidine]-2',2'-dicarboxylate (3o)



0.1 mmol scale reaction, 28 h, 36.8 mg, 67% yield, white foam. Melting point: 121 – 123 ºC. 61:39 dr., 90% ee for the major isomer and 83% ee for the minor isomer. $[\alpha]_D^{17}$ = +14.8 (c = 0.51 in CH_2Cl_2).

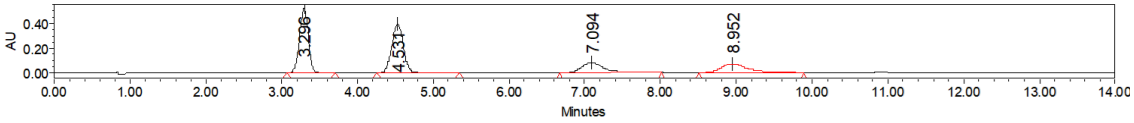
HPLC (Daicel chiralcel ASH, hexane/*i*-PrOH = 80/20, flow rate 1.0 mL/min, λ = 254 nm) t_r (major- major) = 4.52 min, t_r (major-minor) = 3.29 min, t_r (minor-major) = 7.07 min, t_r (minor-minor) = 8.93 min.

^{1}H NMR (400 MHz, Chloroform-*d*) *δ* 7.57 (d, *J* = 7.6 Hz, 2H), 7.42 (d, *J* = 7.6 Hz, 1H), 7.38 – 7.27 (m, 3H), 7.18 (dd, *J* = 11.6, 7.2 Hz, 5H), 7.13 – 7.07 (m, 1H), 7.06 – 6.92 (m, 2H), 6.62 (t, *J* = 7.6 Hz, 1H), 5.95 (d, *J* = 10.4 Hz, 1H), 4.84 (s, 1H), 4.40 (dtt, *J* = 14.4, 11.2, 7.2 Hz, 3H), 4.05 (ddd, *J* = 12.6, 10.8, 7.2 Hz, 1H), 3.60 – 3.42 (m, 1H), 2.42 (m, 3H), 2.13 (d, *J* = 13.2 Hz, 1H), 1.41 (t, *J* = 7.2 Hz, 3H), 1.03 (t, *J* = 7.2 Hz, 3H).

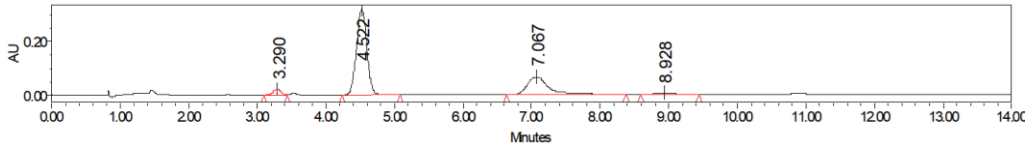
^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*) *δ* 140.75, 138.87, 134.09, 132.14, 130.21, 129.41, 129.03, 128.80, 127.50, 126.50, 125.35, 122.85, 122.28, 120.55, 100.09, 73.17, 62.56, 62.00, 60.97, 59.39, 49.72, 46.72, 13.98, 13.75.

HR-MS (ESI) calcd for $C_{29}H_{29}NNaO_7S^+$ ([M]+Na^+) = 572.1713; found 572.1717.

IR (neat) ***ν*** (cm^{-1}): 2982, 1753, 1725, 1446, 1365, 1339, 1263, 1228, 1156, 1092, 1064, 1023, 898, 860, 803, 757, 728, 688, 607, 574, 551, 460.

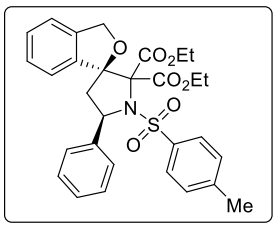


	Retention Time	% Area
1	3.296	35.45
2	4.531	35.26
3	7.094	14.28
4	8.952	15.02



	Retention Time	% Area
1	3.290	3.42
2	4.522	64.99
3	7.067	29.04
4	8.928	2.55

Diethyl (1*S*,5'*R*)-5'-phenyl-1'-tosyl-3*H*-spiro[isobenzofuran-1,3'-pyrrolidine]-2',2'-dicarboxylate (3p)



0.1 mmol scale reaction, 18 h, 33.5 mg, 61% yield; white foam. Melting point: 157 – 160 ºC. 79:21d.r., 93% ee for the major isomer and 46% ee for the minor isomer. $[\alpha]_{\lambda}^{17}$ = +47.7 (c = 0.77 in CH_2Cl_2, λ = 405 nm).

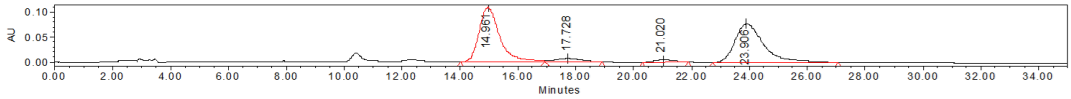
HPLC (Daicel chiralcel ADH, hexane/*i*-PrOH = 90/10, flow rate 1.0 mL/min, λ = 254 nm) t_r (major -major) = 14.94 min, t_r (major-minor) = 23.82 min, t_r (minor-major) = 17.57 min, t_r (minor-minor) = 20.94 min.

^{1}H NMR (400 MHz, Chloroform-*d*) *δ* 7.40 – 7.33 (m, 4H), 7.32 – 7.27 (m, 2H), 7.20 – 7.15 (d, *J* = 8.0 Hz, 2H), 7.11 – 7.00 (m, 3H), 6.93 (t, *J* = 8.0 Hz, 2H), 5.72 (d, *J* = 9.2 Hz, 1H), 4.89 (s, 2H), 4.47 – 4.23 (m, 3H), 4.11 – 3.99 (m, 1H), 3.44 (dd, *J* = 13.6, 10.8 Hz, 1H), 2.32 (s, 1H), 2.30 – 2.21 (m, 3H), 1.35 (t, *J* = 7.2 Hz, 3H), 1.05 (t, *J* = 7.2 Hz, 3H).

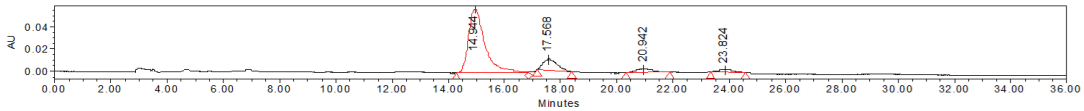
^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*) *δ* 167.80, 165.91, 142.61, 141.49, 140.69, 137.91, 136.84, 129.00, 128.89, 128.64, 128.34, 128.24, 128.07, 127.89, 127.77, 127.52, 126.78, 122.27, 120.52, 99.76, 73.09, 64.40, 62.47, 61.56, 47.85, 21.40, 13.89, 13.69.

HR-MS (ESI) calcd for $C_{30}H_{31}NNaO_7S^+$ ([M]+Na^+) = 572.1713, found 572.1715.

IR (neat) ***ν*** (cm^{-1}): 2983, 1753, 1723, 1451, 1361, 1351, 11264 1211, 1021, 755, 728, 689, 605, 571, 545, 471.

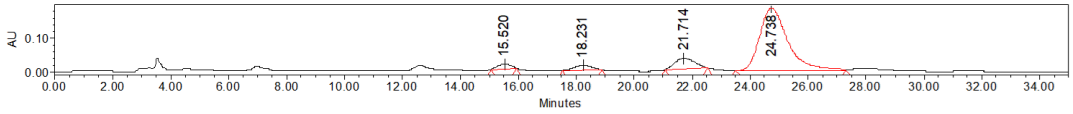


	Retention Time	% Area
1	14.961	47.47
2	17.728	3.62
3	21.020	1.81
4	23.906	47.10



	Retention Time	% Area
1	14.944	80.28
2	17.568	12.22
3	20.942	4.59
4	23.824	2.91

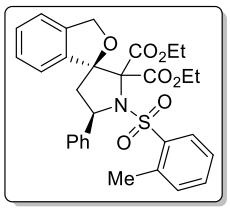
ent-L$_3$-RaEt$_2$ was used. 67% yield, 14:86 d.r., -93/-43% ee. $[\alpha]_{\lambda}^{17}$ = -34.2 (c = 0.56 in CH_2Cl_2, λ = 405 nm).



	Retention Time	% Area
1	15.520	2.80
2	18.231	3.86
3	21.714	9.69

4	24.738	83.66

Diethyl (1*S*,5'*R*)-5'-phenyl-1'-(o-tolylsulfonyl)-3*H*-spiro[isobenzofuran-1,3'-pyrrolidine]-2',2'-dicarboxylate (3q)



0.1 mmol scale reaction, 18 h, 33.5 mg, 77% yield; white foam. Melting point: 132 – 135 ºC. >19:1 dr., 95% ee. $[\alpha]_{\lambda}^{17}$ = +41.4 (c = 0.38 in CH_2Cl_2, λ = 405 nm).

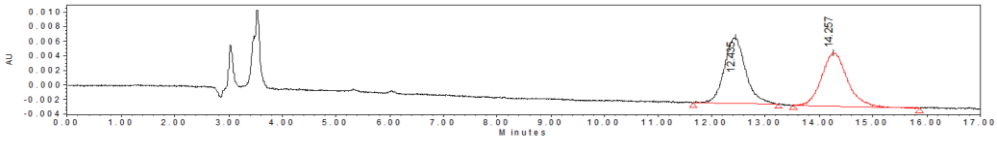
HPLC (Daicel chiralcel ASH, hexane/*i*-PrOH = 85/15, flow rate 1.0 mL/min, λ = 254 nm) t_r (major- major) = 12.43 min, t_r (major-minor) = 14.07 min.

^{1}H NMR (400 MHz, Chloroform-*d*) *δ* 7.77 (d, *J* = 8.0 Hz, 1H), 7.51 (d, *J* = 5.4 Hz, 2H), 7.33 (dt, *J* = 21.6, 7.2 Hz, 2H), 7.18 (dd, *J* = 15.2, 7.6 Hz, 3H), 7.11 (d, *J* = 5.6 Hz, 3H), 7.00 – 6.91 (m, 2H), 5.78 (d, *J* = 10.8 Hz, 1H), 5.00 (q, *J* = 12.0 Hz, 2H), 4.38 (q, *J* = 7.2 Hz, 2H), 4.25 – 4.14 (m, 1H), 4.04 – 3.93 (m, 1H), 3.60 – 3.46 (m, 1H), 2.43 (d, *J* = 13.2 Hz, 1H), 2.38 (s, 3H), 1.34 (t, *J* = 7.2 Hz, 3H), 0.95 (t, *J* = 7.2 Hz, 3H).

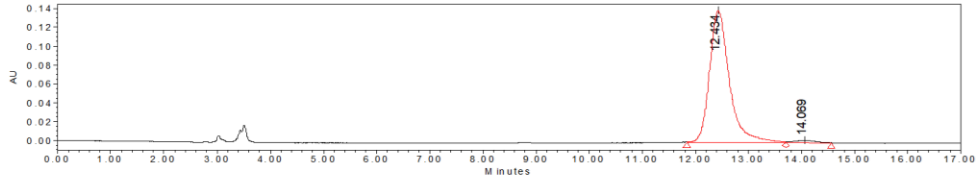
^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*) *δ* 167.77, 165.56, 141.16, 140.78, 137.06, 131.53, 131.43, 129.86, 129.06, 128.73, 127.81, 127.54, 127.12, 124.80, 122.33, 120.61, 99.55, 73.25, 64.23, 62.50, 61.55, 47.42, 20.82, 13.90, 13.56.

HR-MS (ESI) calcd for $C_{30}H_{31}NNaO_7S^+$ ([M]+Na^+) = 572.1713, found 572.1715.

IR (neat) ***ν*** (cm^{-1}): 2983, 1757, 1727, 1459, 1366, 1333, 1233,1159, 1063, 1025, 898, 758, 734, 704, 608.6, 585, 550, 493.

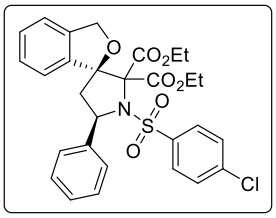


	Retention Time	% Area
2	14.257	49.72
1	12.435	50.28



	Retention Time	% Area
1	12.434	97.63
2	14.069	2.37

Diethyl (1*S*,5'*R*)-1'-((4-chlorophenyl)sulfonyl)-5'-phenyl-3*H*-spiro[isobenzofuran-1,3'-pyrrolidine]-2',2'-dicarboxylate (3r)



0.1 mmol scale reaction, 36 h, 38.8 mg, 68% yield; white foam. Melting point: 172 – 174 ºC. 67:23 dr, 88% ee for the major isomer and 82% ee for the minor isomer. $[\alpha]_{\lambda}^{17}$ = +17.8 (c = 0.67 in CH_2Cl_2, λ = 405 nm).

HPLC (Daicel chiralcel ADH, hexane/*i*-PrOH = 90/10, flow rate 1.0 mL/min, λ = 254 nm) t_r (major -major) = 11.97 min, t_r (major-minor) = 14.71 min, t_r (minor-major) = 19.75 min, t_r (minor-minor) = 16.41 min.

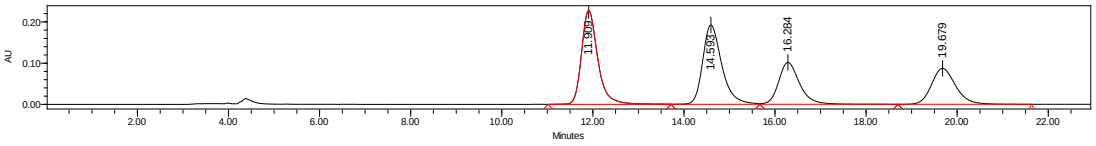
^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.70 – 7.50 (m, 2H), 7.48 – 7.38 (m, 2H), 7.37 – 7.28 (m, 2H), 7.23 (d, *J* = 10.5 Hz, 1H), 7.18 (t, *J* = 8.8 Hz, 5H), 7.10 (s, 1H), 5.68 (d, *J* = 9.6 Hz, 1H), 4.87 (s, 1H), 4.50 – 4.23 (m, 3H), 4.07 (ddt, *J* = 25.0, 10.8, 7.2 Hz, 1H), 3.45 (dd, *J* = 13.2, 10.8 Hz, 1H), 2.81 – 2.59 (m, 1H), 2.17 (d, *J* = 13.2 Hz, 1H), 1.34 (t, *J* = 7.2 Hz, 3H), 1.09 – 1.00 (t, *J* = 7.2 Hz, 3H).

^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*) *δ* 140.59, 140.43, 136.49, 132.27, 130.98, 130.79, 129.85, 129.13, 128.69, 128.46, 127.90, 127.64, 127.60, 99.77, 63.73, 62.61, 61.69, 47.70, 13.87, 13.71.

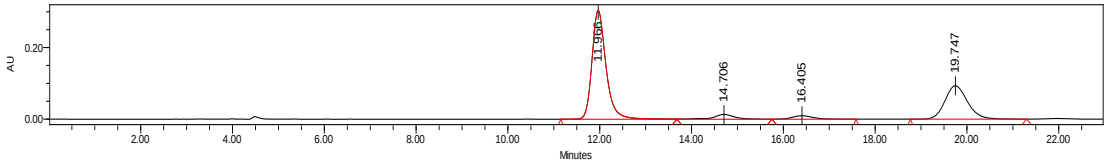
HR-MS (ESI) calcd for $C_{29}H_{28}{}^{35}ClNNaO_7S^+$ ([M]+Na^+) = 592.1167, found 592.1167.

HR-MS (ESI) calcd for $C_{29}H_{28}{}^{37}ClNNaO_7S^+$ ([M]+Na^+) = 594.1138, found 592.1140.

IR (neat) ***ν*** (cm^{-1}): 3273, 2984, 1735, 1583, 1474, 1494, 1370, 1225,1163, 1090, 1025, 856, 754, 620, 552, 481.

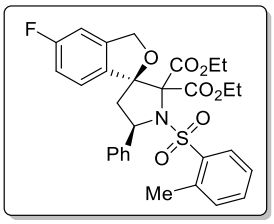


	Retention Time	% Area
1	11.909	31.85
2	14.593	31.66
3	16.284	18.41
4	19.679	18.08



	Retention Time	% Area
1	11.966	62.10
2	14.706	4.11
3	16.405	2.91
4	19.747	30.88

Diethyl (1*S*,5'*R*)-5-fluoro-5'-phenyl-1'-(o-tolylsulfonyl)-3*H*-spiro[isobenzofuran-1,3'-pyrrolidine]-2',2'-dicarboxylate (3s)



0.1 mmol scale reaction, 36 h, 32.3 mg, 57% yield, white foam. Melting point: 128 – 130 ºC. >19:1 dr., 95% ee. $[\alpha]_{\lambda}^{26}$ = +27.33 (c = 0.75 in CH_2Cl_2, λ = 405 nm).

HPLC (Daicel chiralcel IF, hexane/i-PrOH = 90/10, flow rate 1.0 mL/min, λ = 254 nm) t_r (major) = 3.53 min, t_r (minor) =6.05 min.

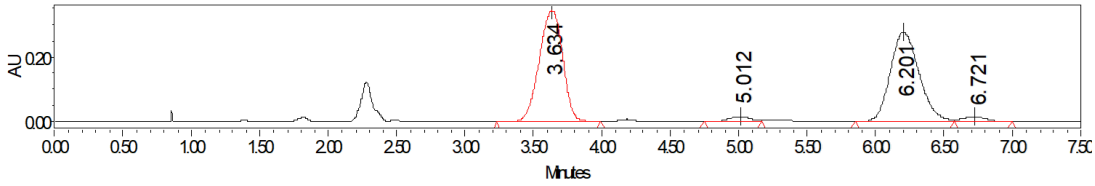
^{1}H NMR (400 MHz, Chloroform-*d*) *δ* 7.75 (d, *J* = 8.0 Hz, 1H), 7.55 – 7.42 (m, 3H), 7.21 – 7.10 (m, 4H), 7.02 – 6.88 (m, 4H), 5.78 (d, *J* = 9.2Hz, 1H), 4.95 (q, *J* = 12.8 Hz, 2H), 4.37 (q, *J* = 7.2 Hz, 2H), 4.26 – 4.15 (m, 1H), 4.02 (dt, *J* = 10.8, 7.2 Hz, 1H), 3.51 (dd, *J* = 13.6, 10.8 Hz, 1H), 2.48 – 2.31 (m, 4H), 1.34 (t, *J* = 7.2 Hz, 3H), 0.99 (t, *J* = 7.2 Hz, 3H).

^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*) 167.83,165.54, 164.83 (d, *J* = 246.2 Hz), 162.37, 143.30(d, *J* = 8.8 Hz), 141.04, 139.74, 137.15, 132.44 (d, *J* = 2.4 Hz), 131.50, 129.87, 128.59, 127.84, 127.16, 123.90 (d, *J* = 9.4 Hz), 123.81, 115.06 (d, *J* = 23.2 Hz), 114.83, 108.12 (d, *J* = 23.8 Hz), 107.88, 99.22, 85.23, 72.74, 64.09, 62.64, 61.67, 47.46, 20.80, 13.91, 13.63.

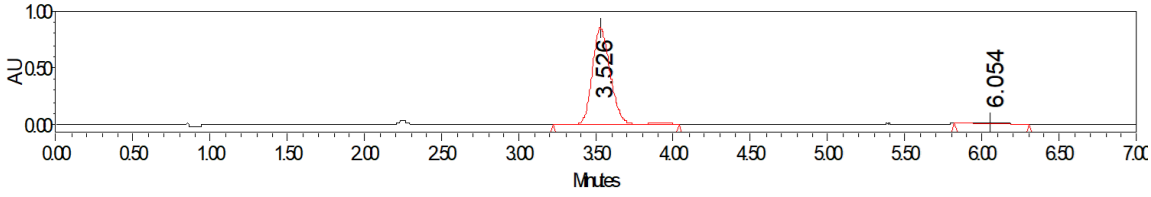
^{19}F{^{1}H} NMR (376 MHz, Chloroform-*d*) *δ* = -113.08.

HR-MS (ESI) calcd for $C_{30}H_{30}FNNaO_7S^+$ ([M]+Na^+) = 590.1619; found 590.1620.

IR (neat) ***ν*** (cm^{-1}): 3061, 2982, 2448, 1750, 1487, 1452, 1340, 1257, 1160, 1036, 941, 870, 757, 700, 608, 579, 464.

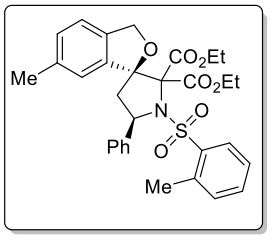


	Retention Time	% Area
1	3.634	47.82
2	5.012	2.36
3	6.201	47.41
4	6.721	2.40



	Retention Time	% Area
1	3.526	97.46
2	6.054	2.54

Diethyl (1*S*,5'*R*)-6-methyl-5'-phenyl-1'-(o-tolylsulfonyl)-3*H*-spiro[isobenzofuran-1,3'-pyrrolidine]-2',2'-dicarboxylate (3t)



0.1 mmol scale reaction, 36 h, 41.0 mg, 73 % yield, white foam. Melting point: 118 – 120 ºC. 55:45 dr., 93% ee for the major isomer and 88% ee for the minor isomer. $[\alpha]_{\lambda}^{26}$ = +32.1 (c = 1.42 in CH_2Cl_2, λ = 405 nm).

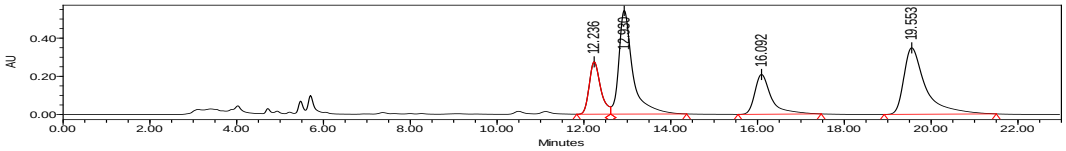
HPLC (Daicel chiralcel ADH, hexane/*i*-PrOH = 85/15, flow rate 1.0 mL/min, λ = 254 nm) t_r (major -major) = 12.93 min, t_r (major-minor) = 19.67 min, t_r (minor-major) = 16.08 min, t_r (minor-minor) = 12.27 min.

^{1}H NMR (400 MHz, Chloroform-*d*) *δ* 7.97 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.72 (dd, *J* = 5.6, 3.2 Hz, 1H), 7.53 (dd, *J* = 5.6, 3.2 Hz, 1H), 7.29 (d, *J* = 7.0 Hz, 3H), 7.25 – 7.21 (m, 1H), 7.16 (s, 1H), 7.12 (dd, *J* = 7.8, 1.8 Hz, 2H), 7.06 (t, *J* = 7.2 Hz, 2H), 7.01 (s, 1H), 6.94 (d, *J* = 7.2 Hz, 2H), 5.56 (t, *J* = 7.6 Hz, 1H), 5.09 (d, *J* = 12.4 Hz, 1H), 4.99 (d, *J* = 12.4 Hz, 1H), 4.39 – 4.25 (m, 3H), 4.12 (dq, *J* = 10.8, 7.2 Hz, 1H), 3.84 (dq, *J* = 10.8, 7.2 Hz, 1H), 2.99 (dd, *J* = 13.2, 7.6 Hz, 1H), 2.81 – 2.76 (m, 1H), 2.19 (s, 3H), 1.30 (t, *J* = 7.2 Hz, 4H), 1.10 (t, *J* = 7.2 Hz, 3H), 0.96 (t, *J* = 7.2 Hz, 2H).

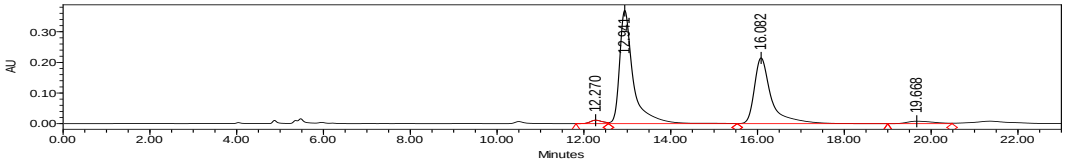
^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*) *δ* 167.80, 165.84, 142.87, 140.32, 138.83, 137.00, 134.98, 132.04, 132.00, 130.94, 130.11, 128.85, 128.12, 127.95, 127.79, 127.74, 125.63, 124.21, 120.97, 97.03, 84.41, 72.52, 64.04, 62.33, 61.99, 49.63, 30.58, 20.95, 19.20, 13.88, 13.73.

HR-MS (ESI) calcd for $C_{31}H_{33}NNaO_7S^+$ ([M]+Na^+) = 585.1870; found 585.1870.

IR (neat) ***ν*** (cm^{-1}): 3267, 2982, 2932, 1753, 1597, 1454, 1338, 1292, 1159, 1036, 816, 699, 608, 556.

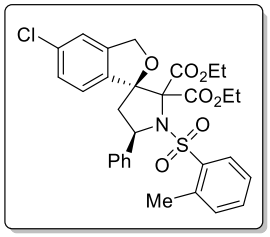


	Retention Time	% Area
1	12.236	14.49
2	12.930	34.75
3	16.092	15.91
4	19.553	34.85



	Retention Time	% Area
1	12.270	1.53
2	12.941	55.83
3	16.082	40.27
4	19.668	2.37

Diethyl (1*S*,5'*R*)-5-chloro-5'-phenyl-1'-(o-tolylsulfonyl)-3*H*-spiro[isobenzofuran-1,3'-pyrrolidine]-2',2'-dicarboxylate (3u)



0.1 mmol scale reaction, 36 h, 47.8 mg, 82% yield, white foam. Melting point: 133 – 135 ºC. 56: 44 dr., 86% ee for the major isomer and 82% ee for the minor isomer. $[\alpha]_{\lambda}^{26}$ = +28.1.1 (c = 0.87 in CH_2Cl_2, λ = 405 nm). **HPLC** (Daicel chiralcel ADH, hexane/*i*-PrOH = 85/15, flow rate 1.0 mL/min, λ = 254 nm) t_r (major -major) = 24.45 min, t_r (major-minor) = 15,52 min, t_r (minor-major) = 19.55 min, t_r (minor-minor) = 8.89 min.

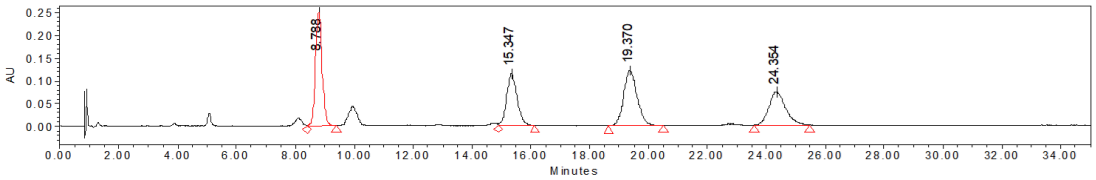
^{1}H NMR (400 MHz, Chloroform-*d*) *δ* 7.98 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.34 – 7.28 (m, 3H), 7.24 – 7.15 (m, 3H), 7.14 – 7.08 (m, 3H), 7.07 – 7.01 (m, 2H), 6.95 (d, *J* = 7.6 Hz, 1H), 5.56 (t, *J* = 7.6 Hz, 1H), 5.11 (d, *J* = 12.4 Hz, 1H), 5.01 (d, *J* = 12.4 Hz, 1H), 4.45 – 4.20 (m, 3H), 4.15 – 4.06 (m, 1H), 3.83 (dt, *J* = 10.8, 7.2 Hz, 1H), 2.99 (dd, *J* = 13.2, 8.0 Hz, 1H), 2.78 (dd, *J* = 13.2, 8.0 Hz, 1H), 2.19 (s, 3H), 1.30 (t, *J* = 7.2 Hz, 3H), 1.10 (t, *J* = 7.2 Hz, 3H).

^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*) *δ* 167.80, 165.83, 142.87, 138.84, 138.24, 137.01, 134.98, 132.04, 132.00, 130.11, 128.13, 127.96, 127.79, 127.74, 125.63, 124.21, 120.97, 97.03, 84.41, 72.53, 64.04, 62.33, 61.99, 49.63, 20.94, 13.89.

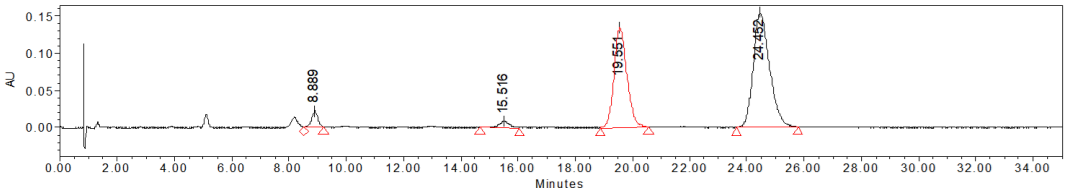
HR-MS (ESI) calcd for $C_{30}H_{30}{}^{35}ClNNaO_7S^+$ ([M]+Na^+) = 606.1324, found 606.1326.

HR-MS (ESI) calcd for $C_{30}H_{30}{}^{37}ClNNaO_7S^+$ ([M]+Na^+) = 608.1294, found 608.1292.

IR (neat) ***ν*** **(cm^{-1})**: 2983, 2933, 1750, 1601, 1465, 1337, 1227, 1158, 1038, 906, 731, 699, 611, 585.



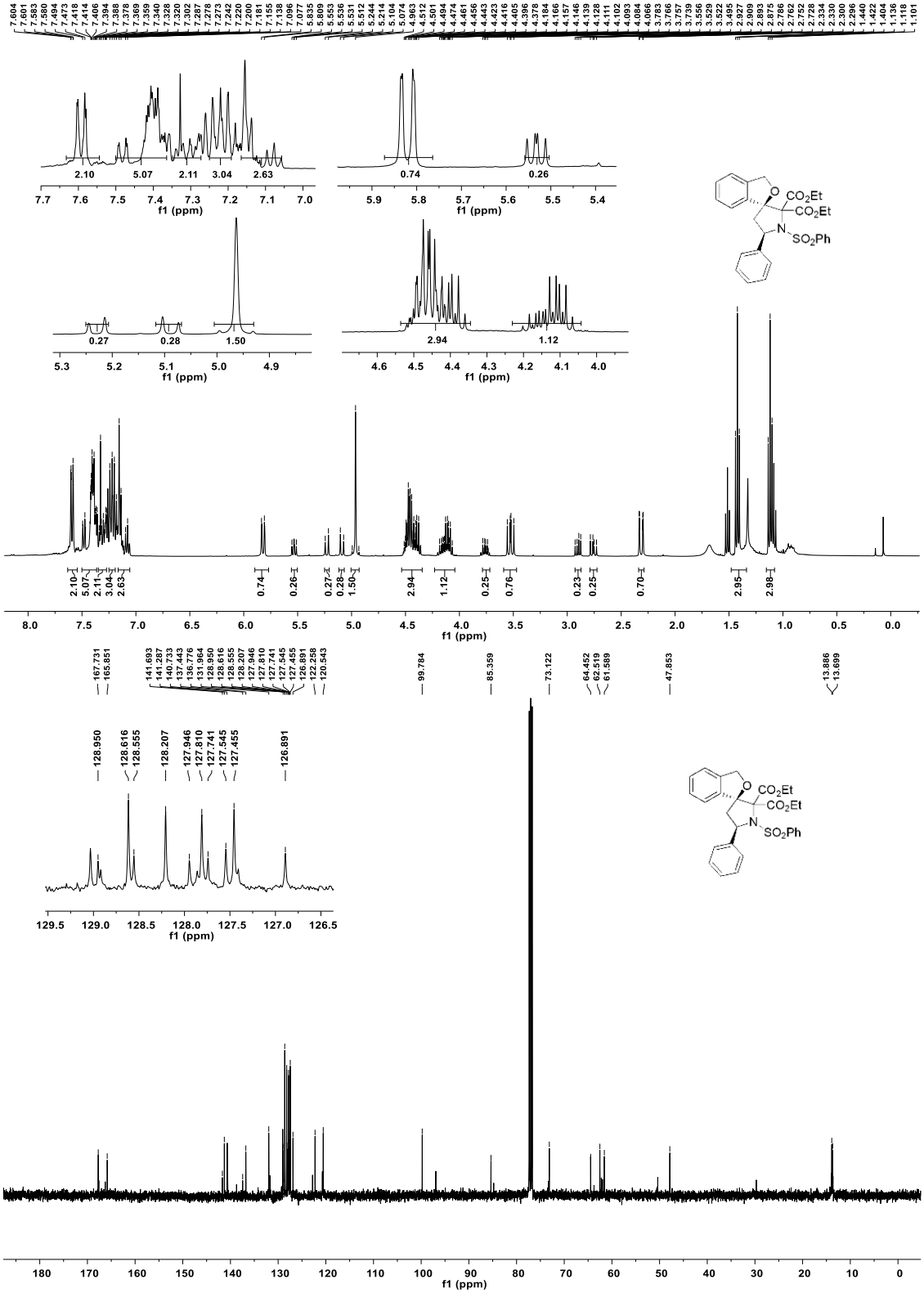
	Retention Time	% Area
1	8.788	28.98
2	15.347	21.07
3	19.370	28.45
4	24.354	21.50



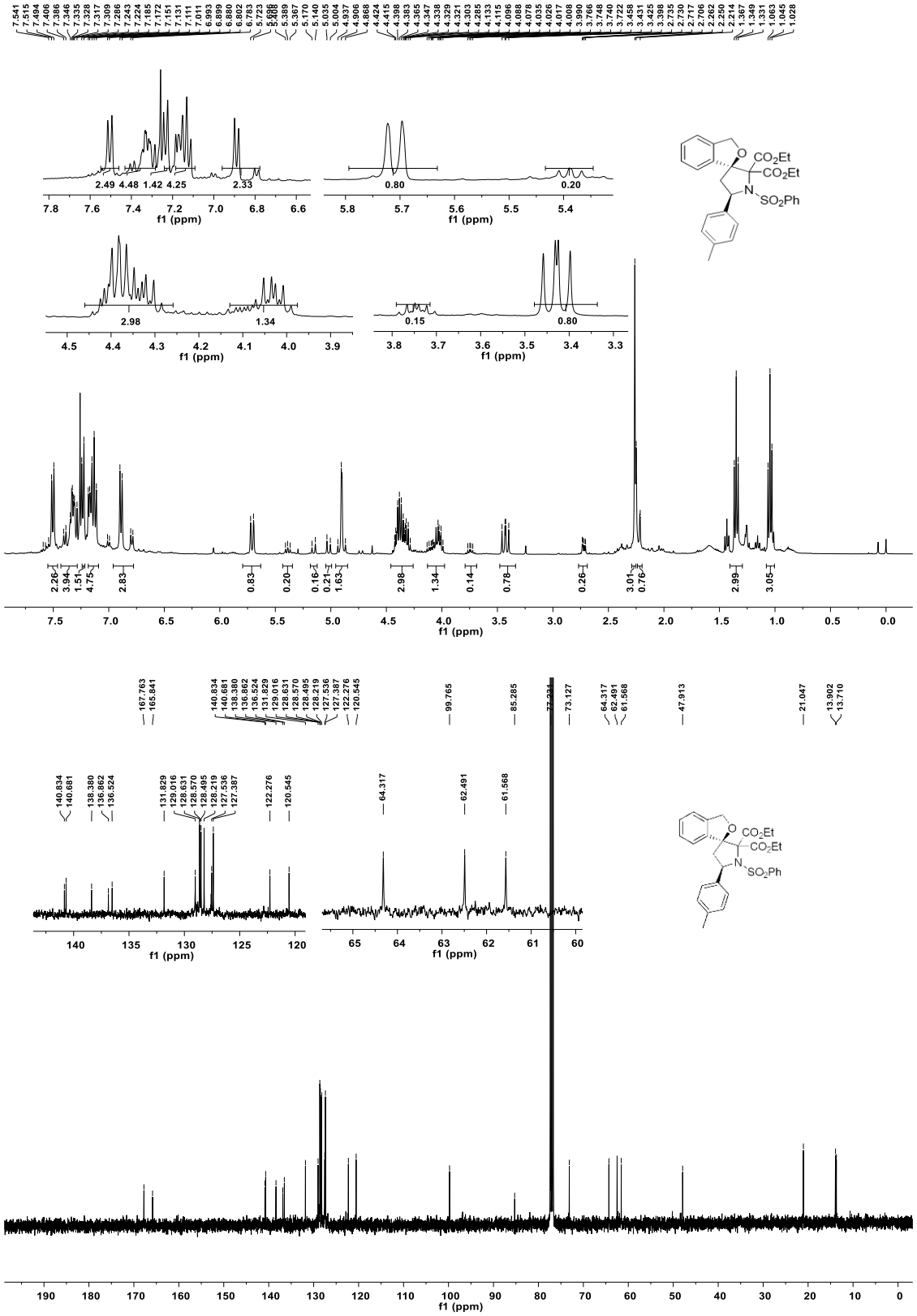
	Retention Time	% Area
1	8.889	3.09
2	15.516	1.98
3	19.551	38.49
4	24.452	56.44

(K) Copies of NMR spectra for the products

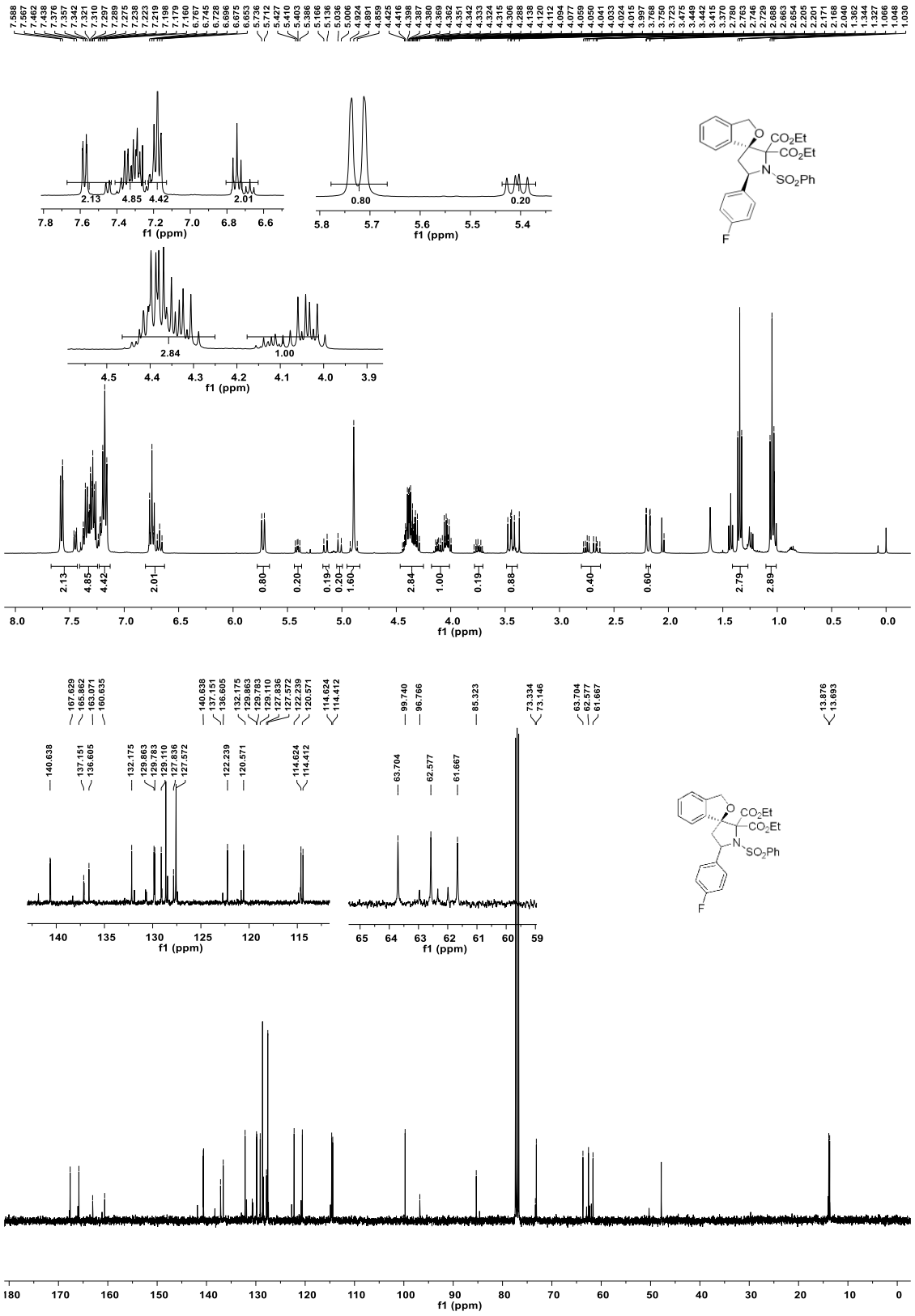
Diethyl (1*S*,5'*R*)-5'-phenyl-1'-(phenylsulfonyl)-3*H*-spiro[isobenzofuran-1,3'-pyrrolidine]-2',2'-dicarboxylate (3a)

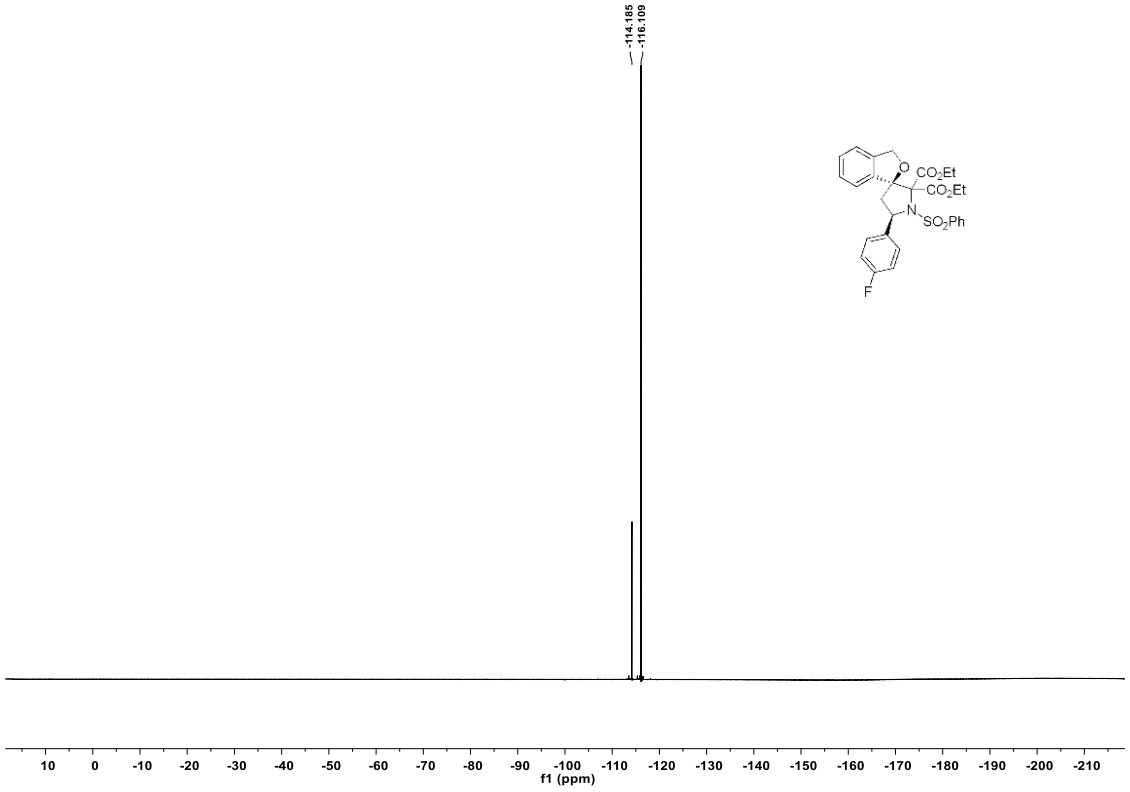


Diethyl (1*S*,5'*R*)-1'-(phenylsulfonyl)-5'-(p-tolyl)-3*H*-spiro[isobenzofuran-1,3'-pyrrolidine]-2',2'-dicarboxylate(3b)

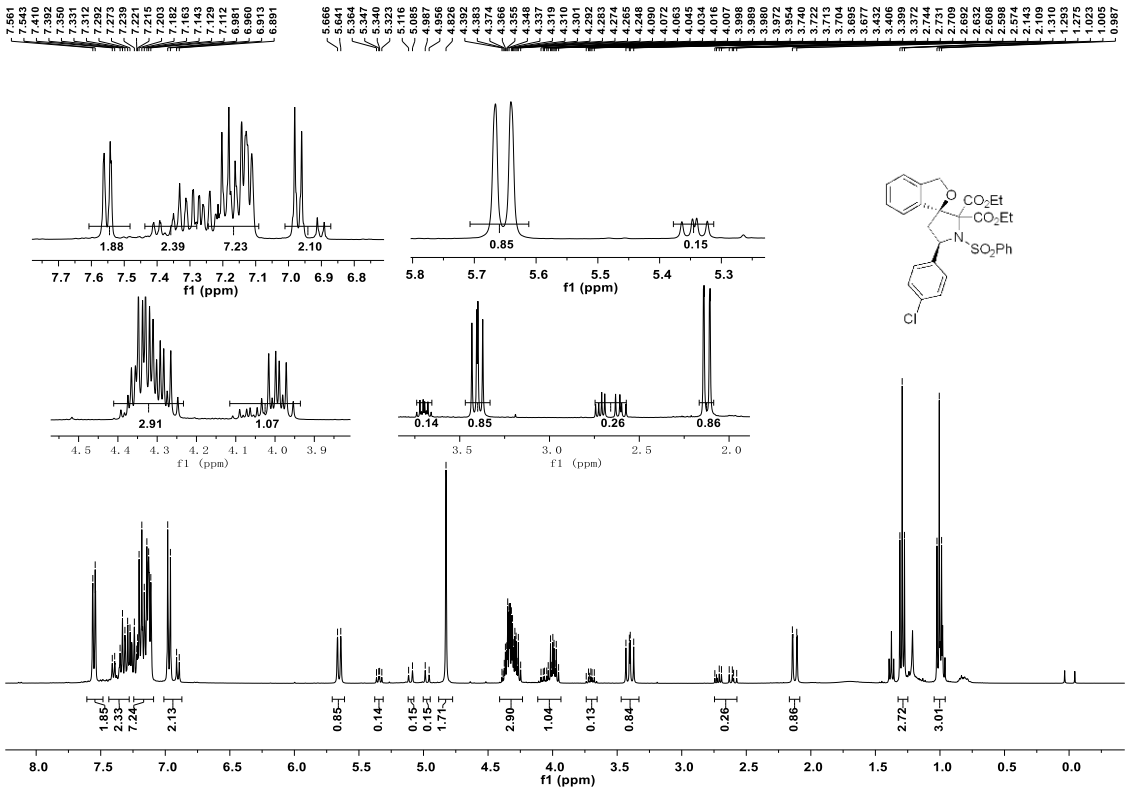


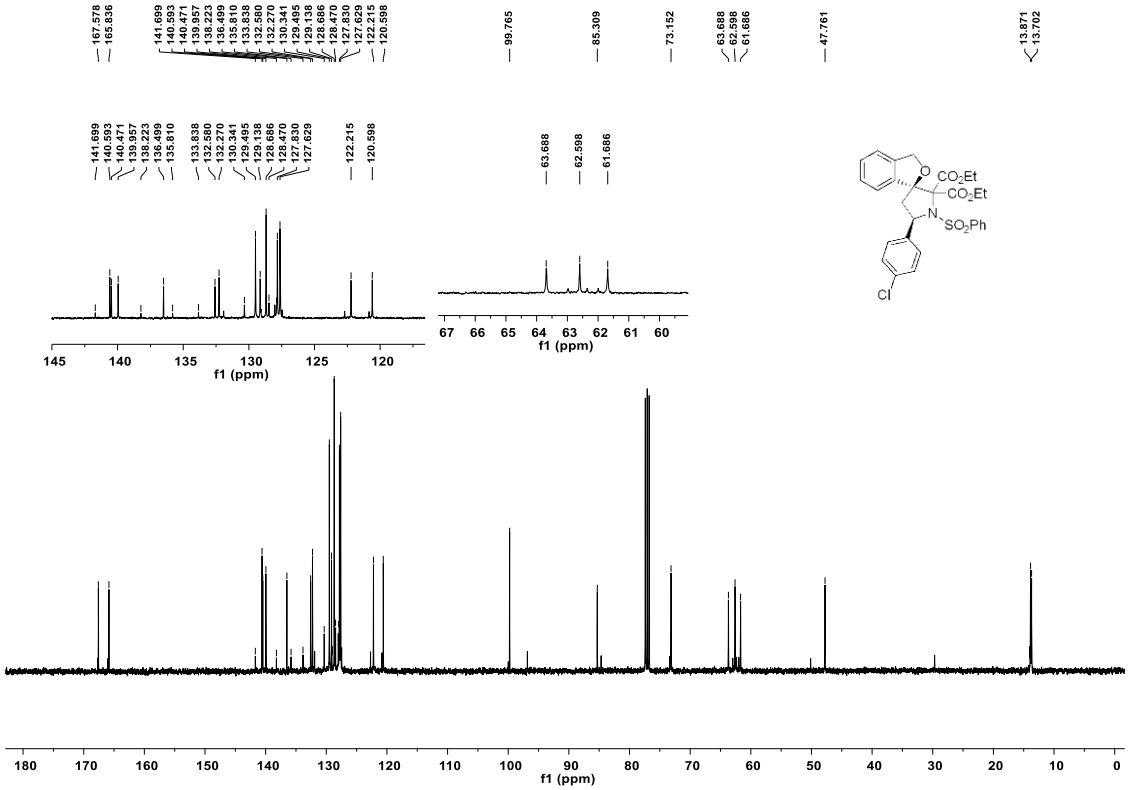
Diethyl (1*S*,5'*R*)-5'-(4-fluorophenyl)-1'-(phenylsulfonyl)-3*H*-spiro[isobenzofuran-1,3'-pyrrolidine]-2',2'-dicarboxylate (3c)



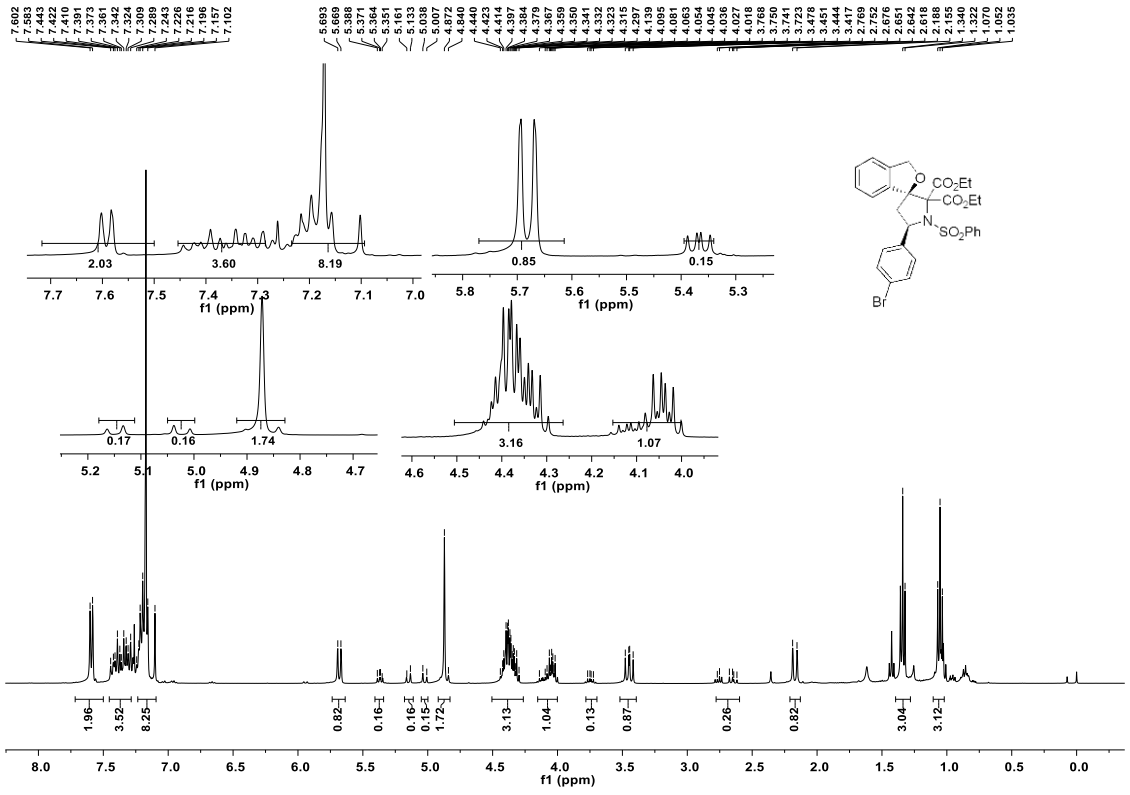


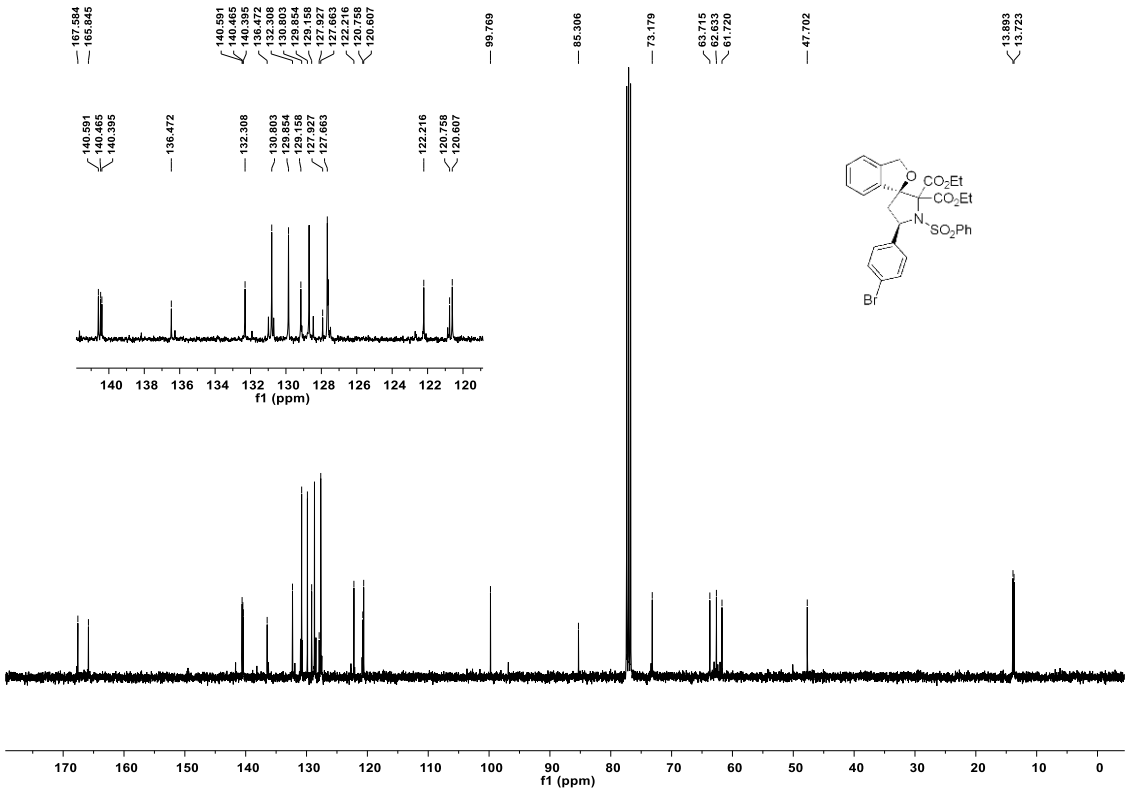
Diethyl (1*S*,5'*R*)-5'-(4-chlorophenyl)-1'-(phenylsulfonyl)-3*H*-spiro[isobenzofuran-1,3'-pyrrolidine]-2',2'-dicarboxylate (3d)



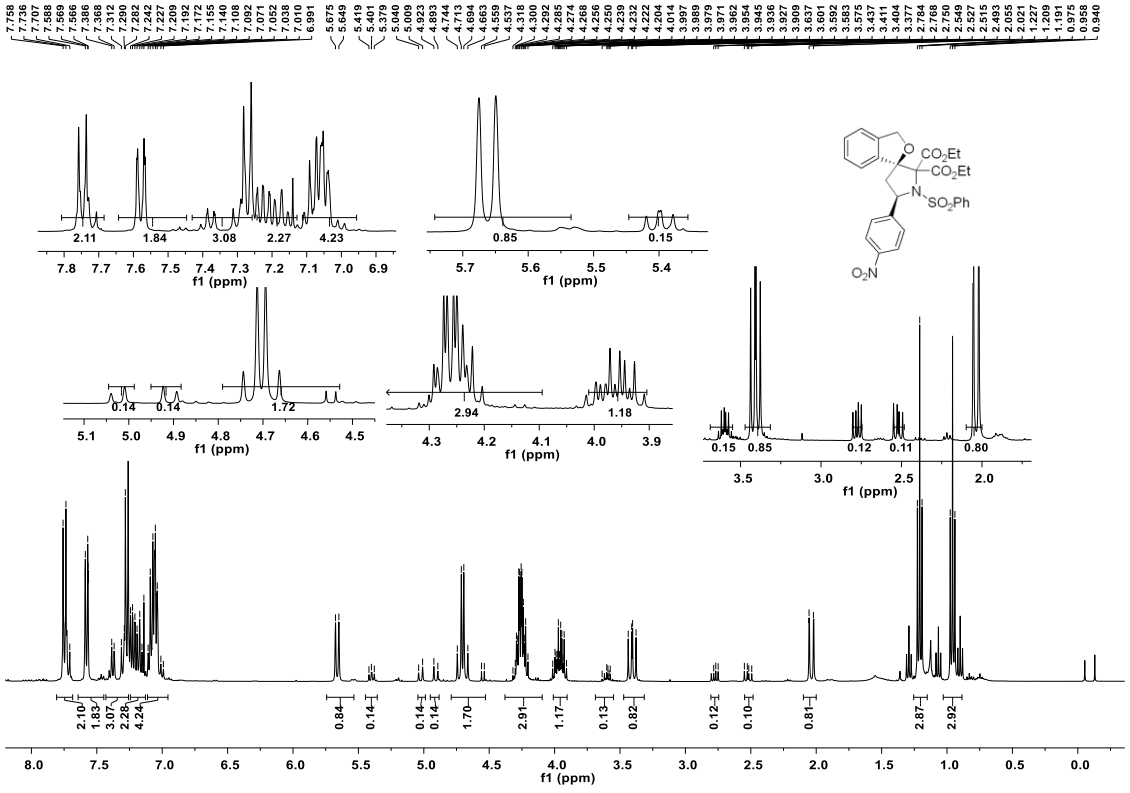


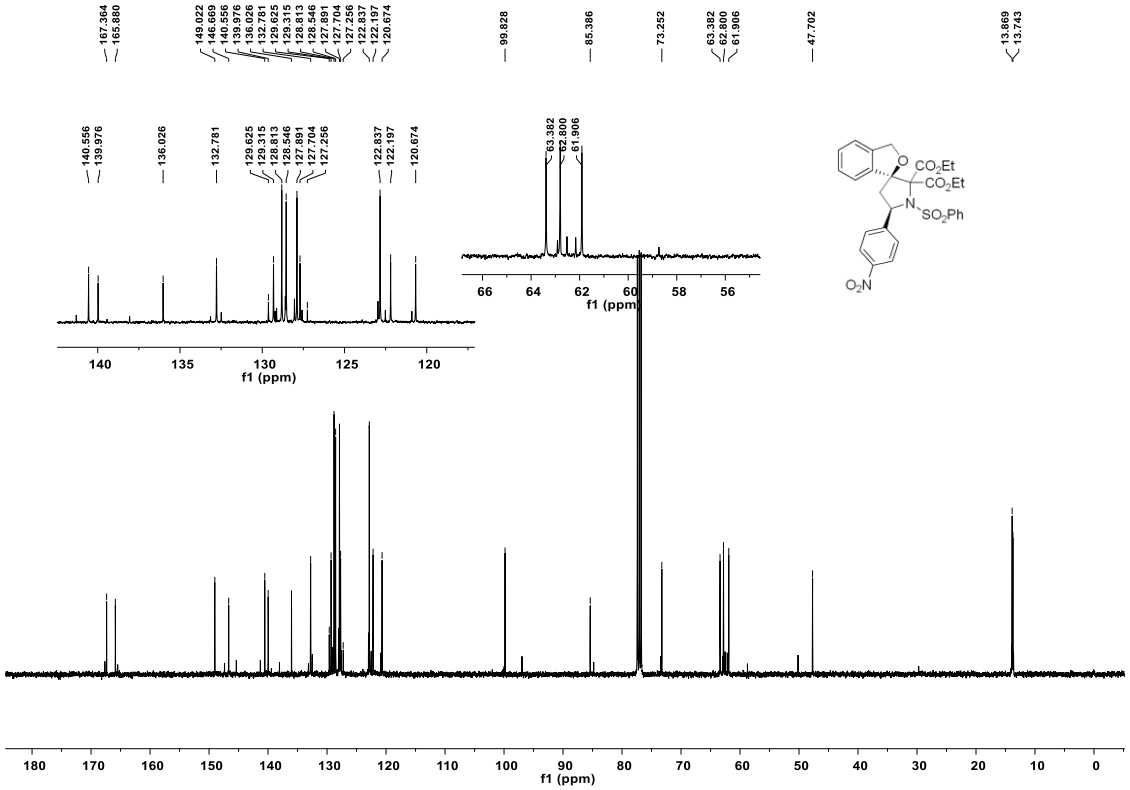
Diethyl (1*S*,5'*R*)-5'-(4-bromophenyl)-1'-(phenylsulfonyl)-3*H*-spiro[isobenzofuran-1,3'-pyrrolidine]-2',2'-dicarboxylate (3e)



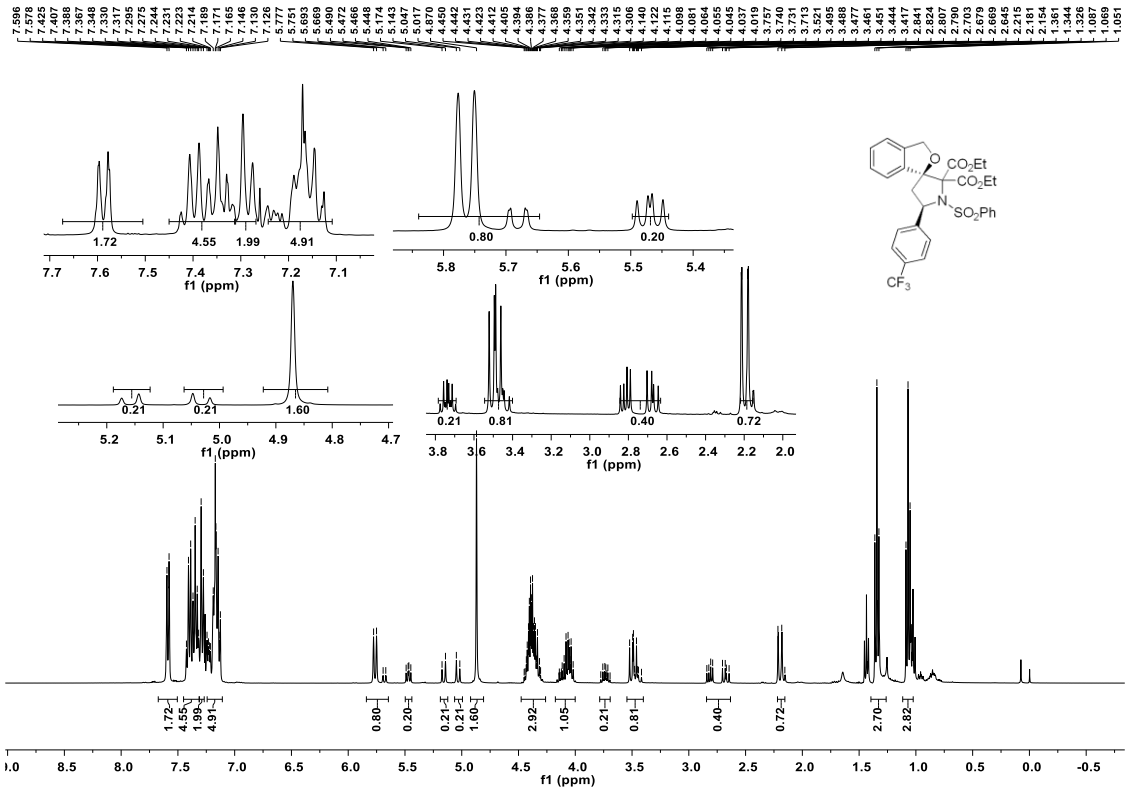


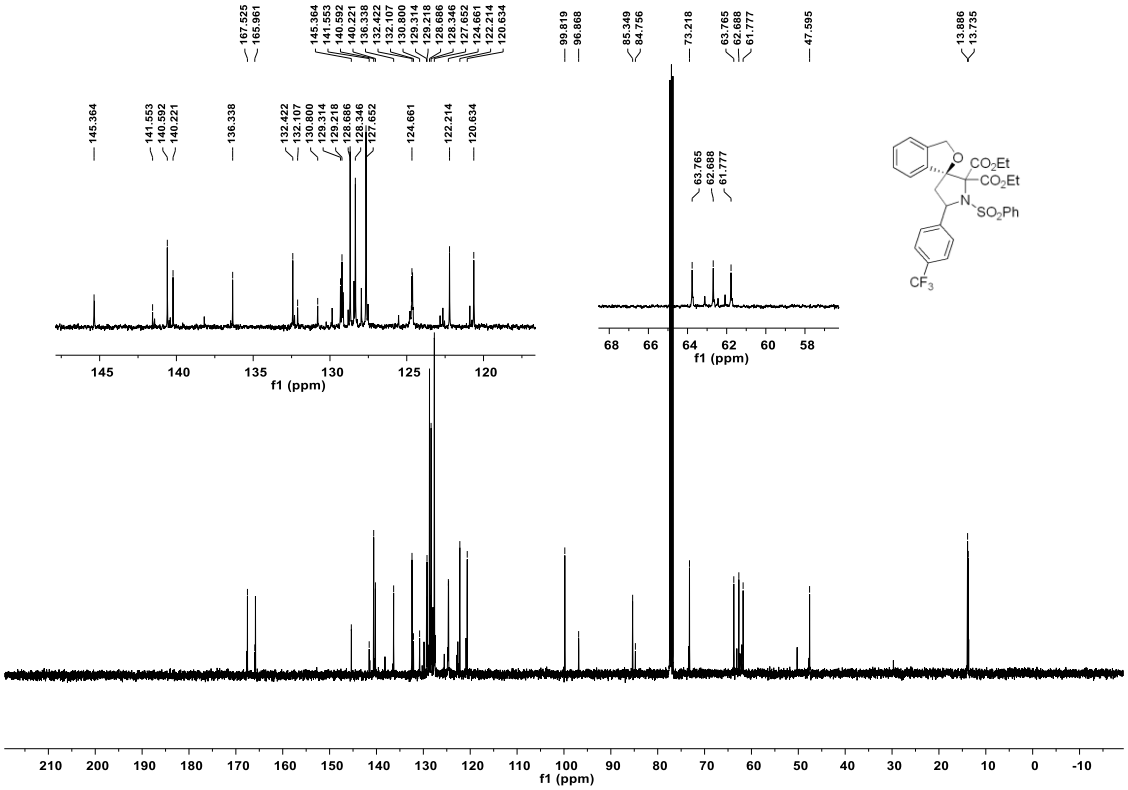
Diethyl (1*S*,5'*R*)-5'-(4-nitrophenyl)-1'-(phenylsulfonyl)-3*H*-spiro[isobenzofuran-1,3'-pyrrolidine]-2',2'-dicarboxylate (3f)





Diethyl (1*S*,5'*R*)-1'-(phenylsulfonyl)-5'-(4-(trifluoromethyl)phenyl)-3*H*-spiro[isobenzofuran-1,3'-pyrrolidine]-2',2'-dicarboxylate (3g)

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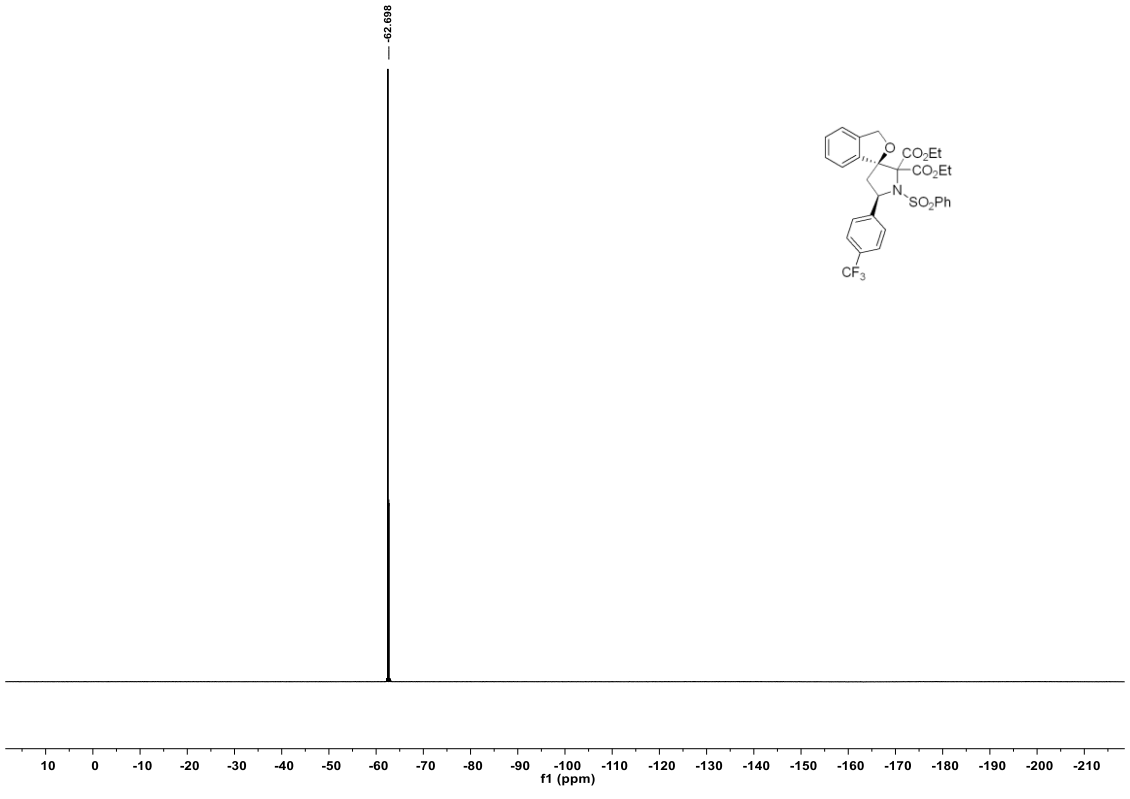
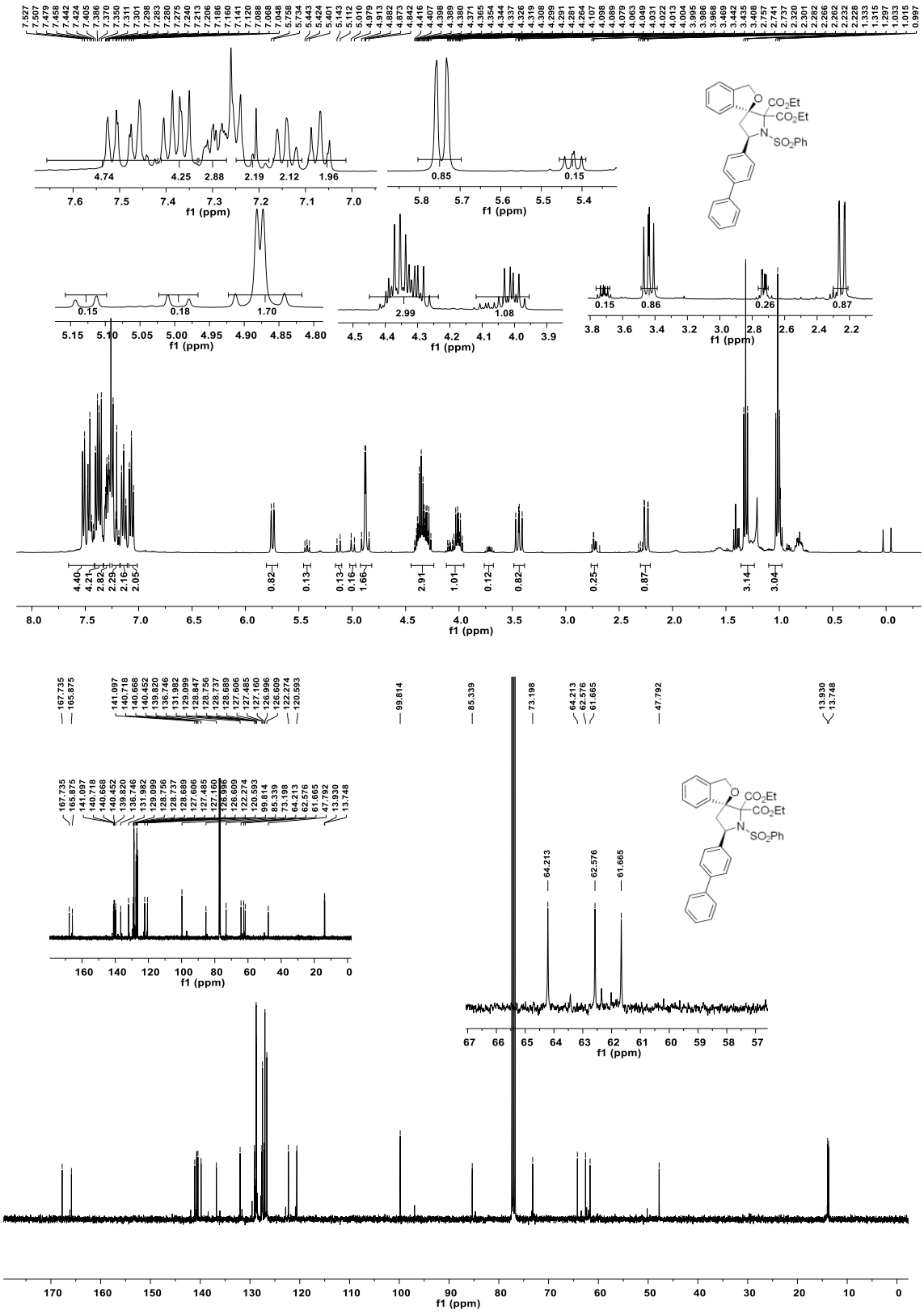
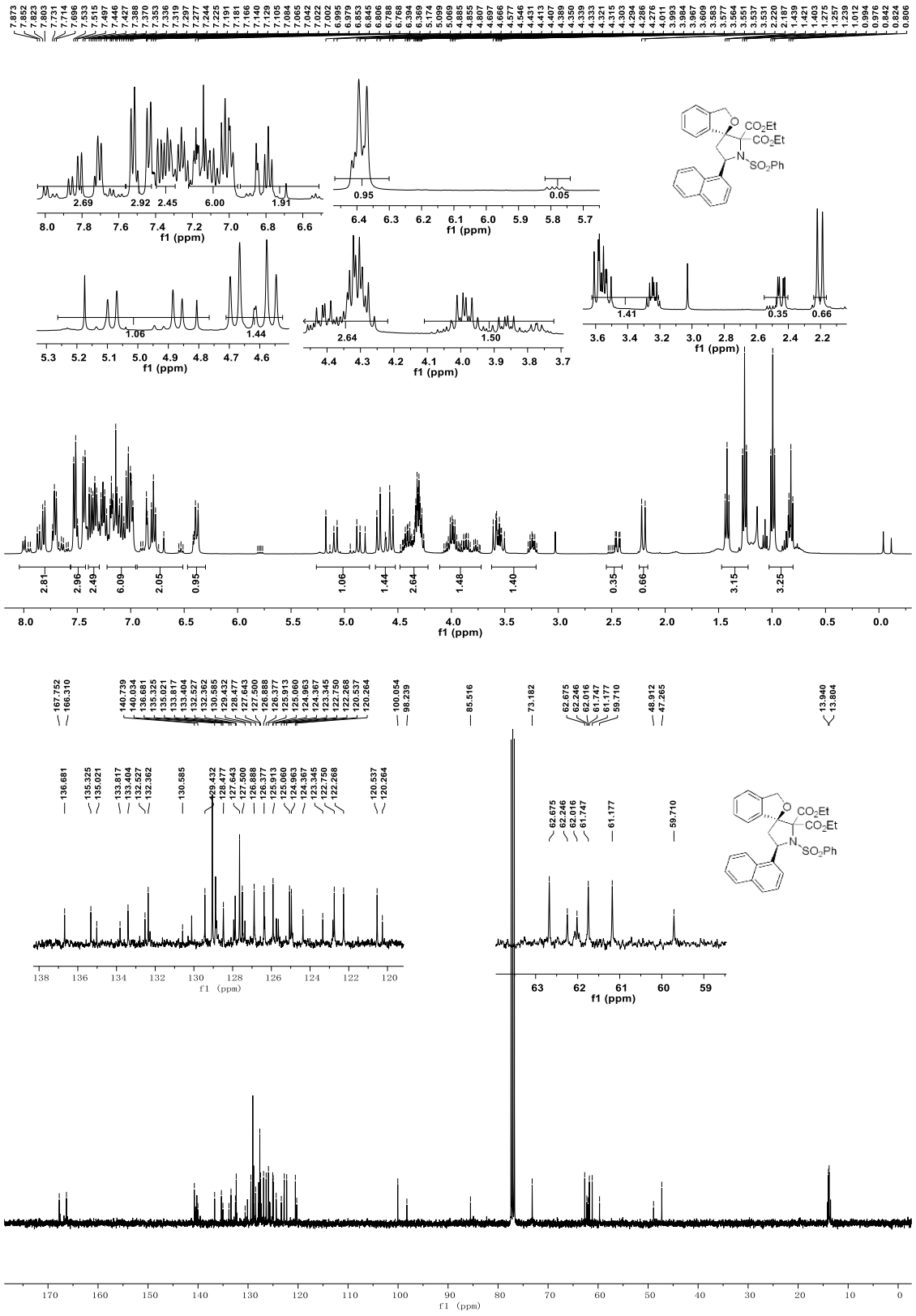
145.364
141.553
140.592
140.221
136.338
132.422
132.107
130.800
129.314
129.218
128.686
128.346
127.652
124.661
122.214
120.634
99.819
96.868
85.349
84.756
73.218
63.765
62.688
61.777
47.595
13.886
13.735
CO2Et
CO2Et
N
SO2Ph
CF3
f1 (ppm)


-62.698
CO2Et
CO2Et
N
SO2Ph
CF3
f1 (ppm)

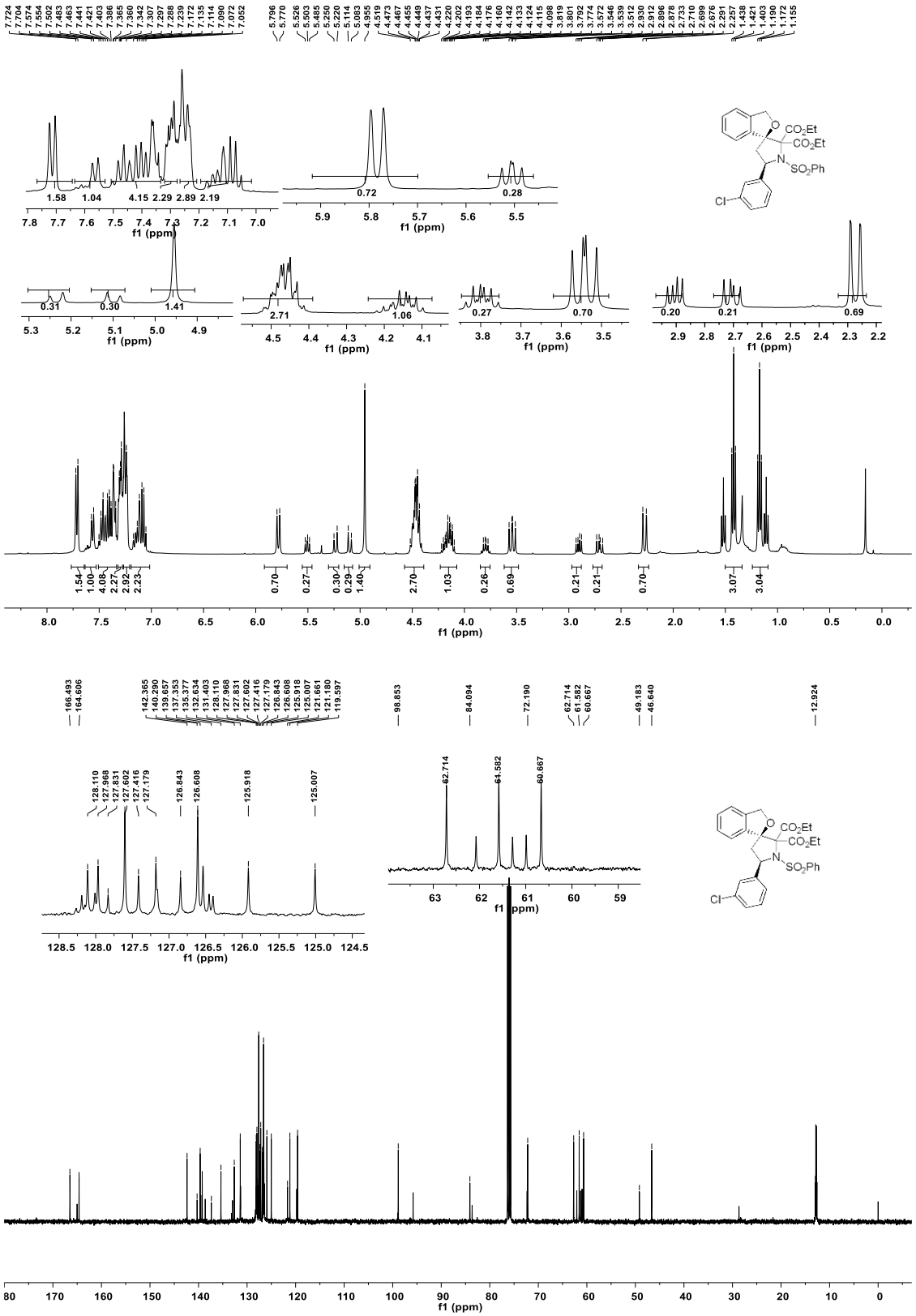
Diethyl (1*S*,5'*R*)-5'-([1,1'-biphenyl]-4-yl)-1'-(phenylsulfonyl)-3*H*-spiro[isobenzofuran-1,3'-pyrrolidine]-2',2'-dicarboxylate (3h)



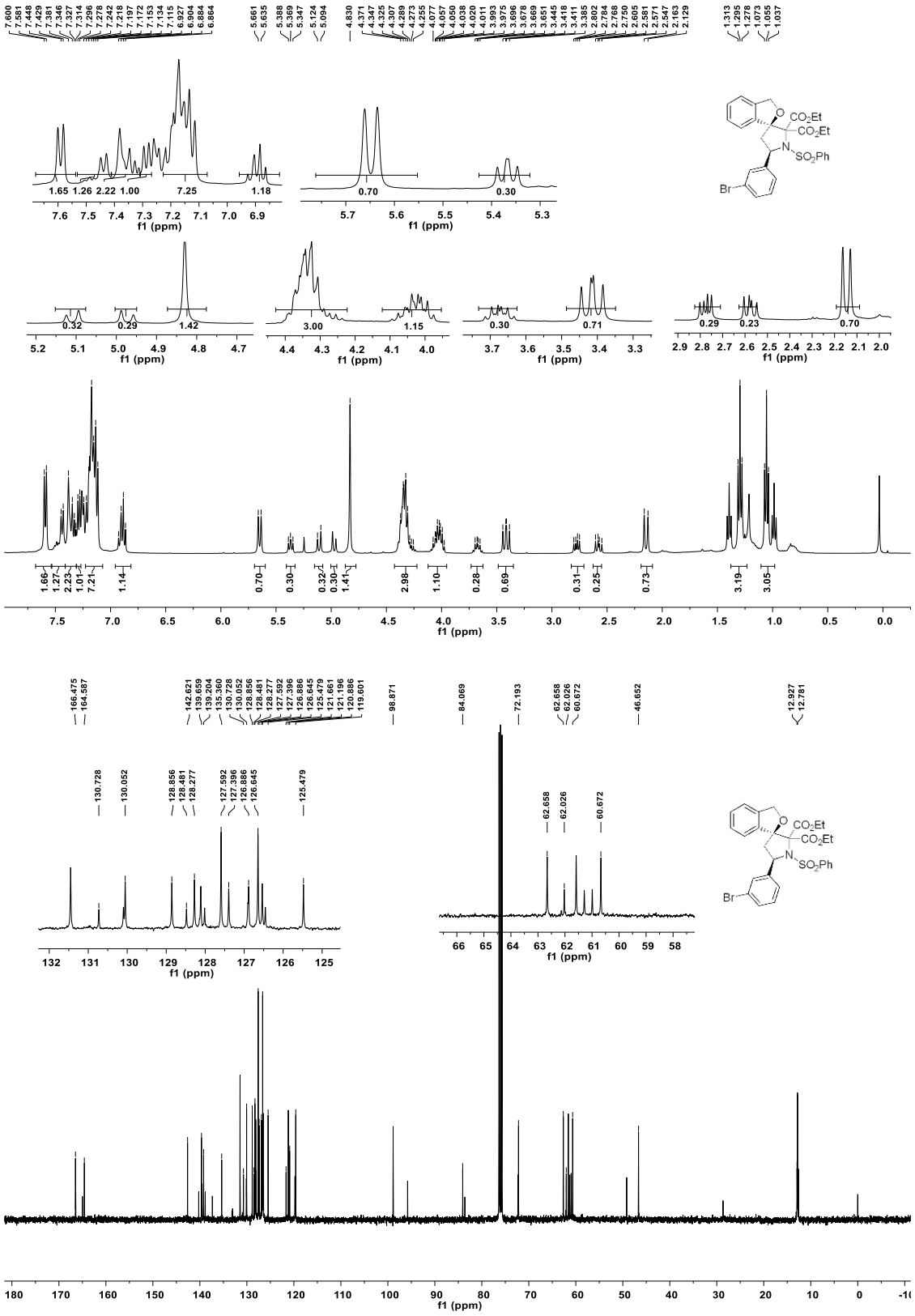
Diethyl (1*S*,5'*R*)-5'-(naphthalen-1-yl)-1'-(phenylsulfonyl)-3*H*-spiro[isobenzofuran-1,3'-pyrrolidine]-2',2'-dicarboxylate (3i)



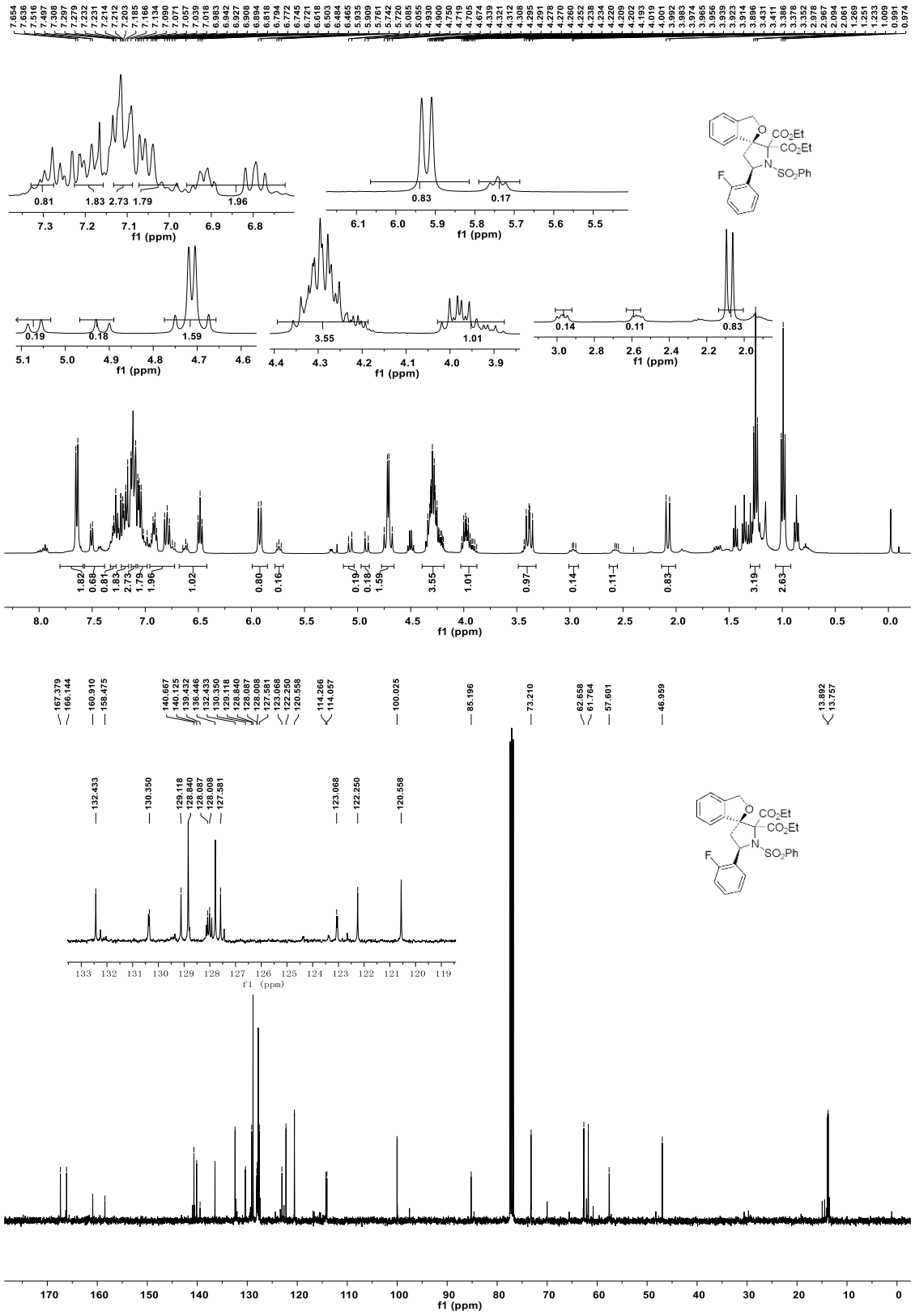
Diethyl (1*S*,5'*R*)-5'-(3-chlorophenyl)-1'-(phenylsulfonyl)-3*H*-spiro[isobenzofuran-1,3'-pyrrolidine]-2',2'-dicarboxylate (3j)

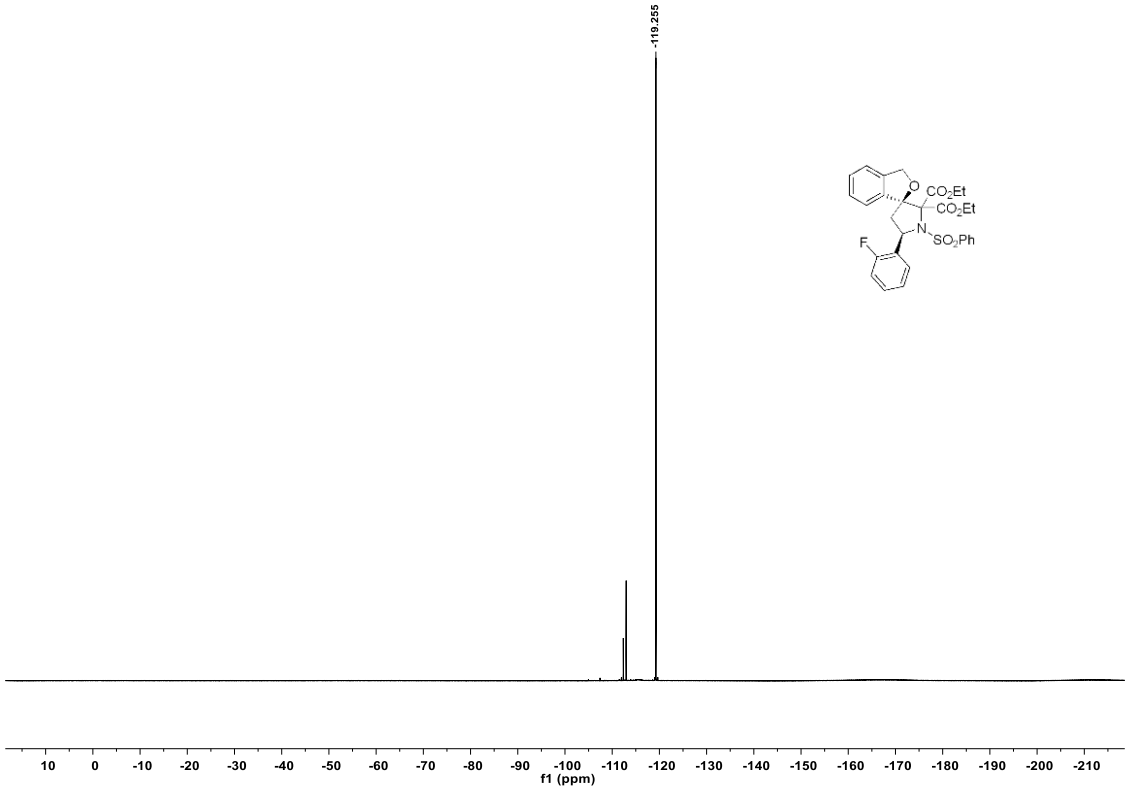


Diethyl (1*S*,5'*R*)-5'-(3-bromophenyl)-1'-(phenylsulfonyl)-3*H*-spiro[isobenzofuran-1,3'-pyrrolidine]-2',2'-dicarboxylate (3k)

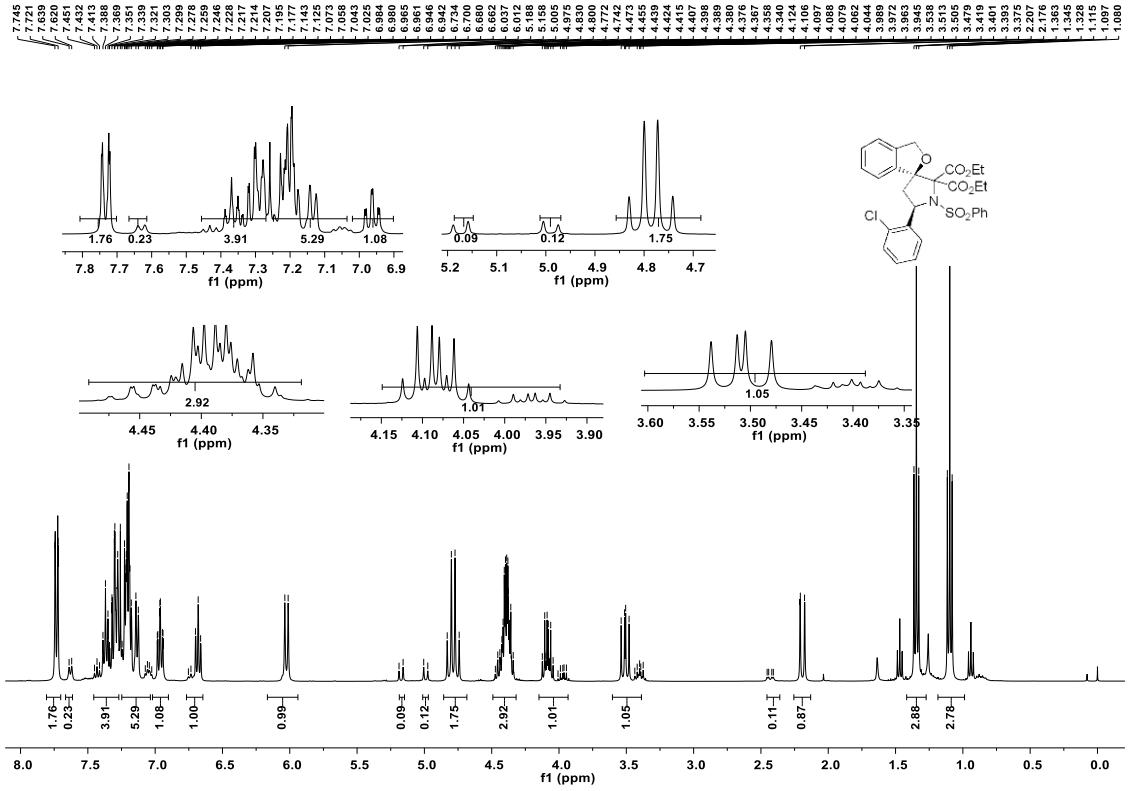


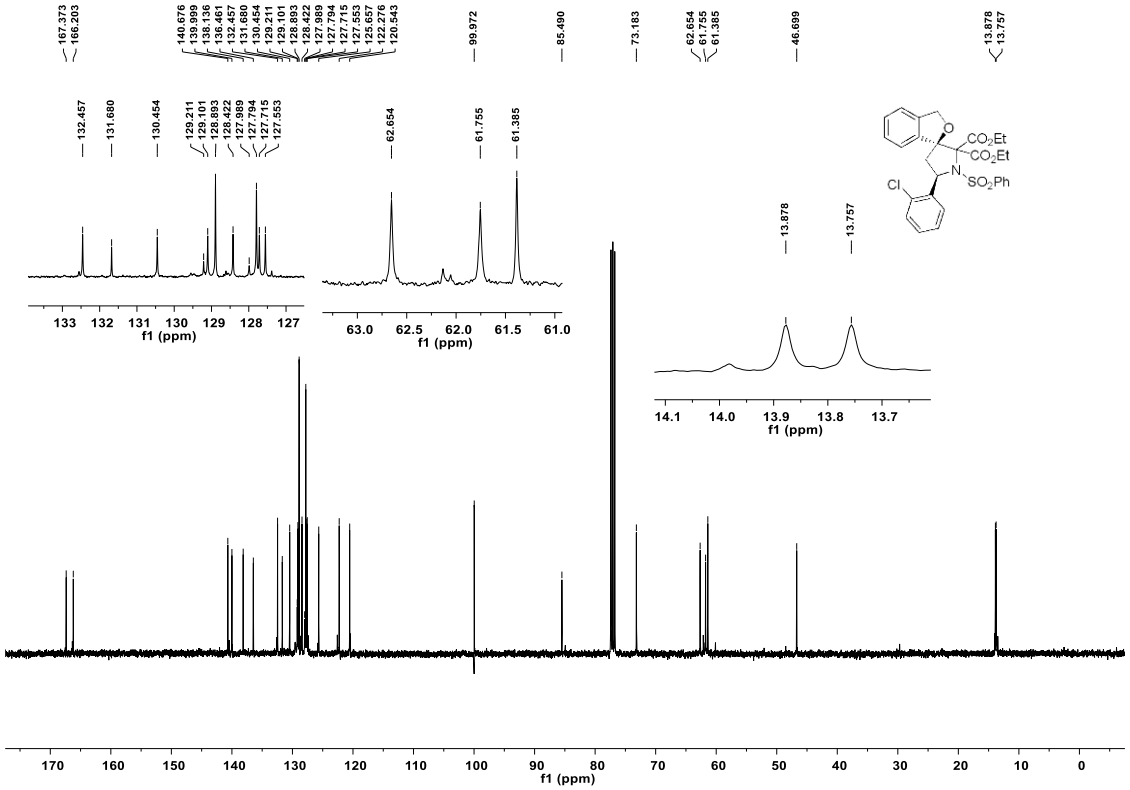
Diethyl (1*S*,5'*R*)-5'-(2-fluorophenyl)-1'-(phenylsulfonyl)-3*H*-spiro[isobenzofuran-1,3'-pyrrolidine]-2',2'-dicarboxylate (3l)



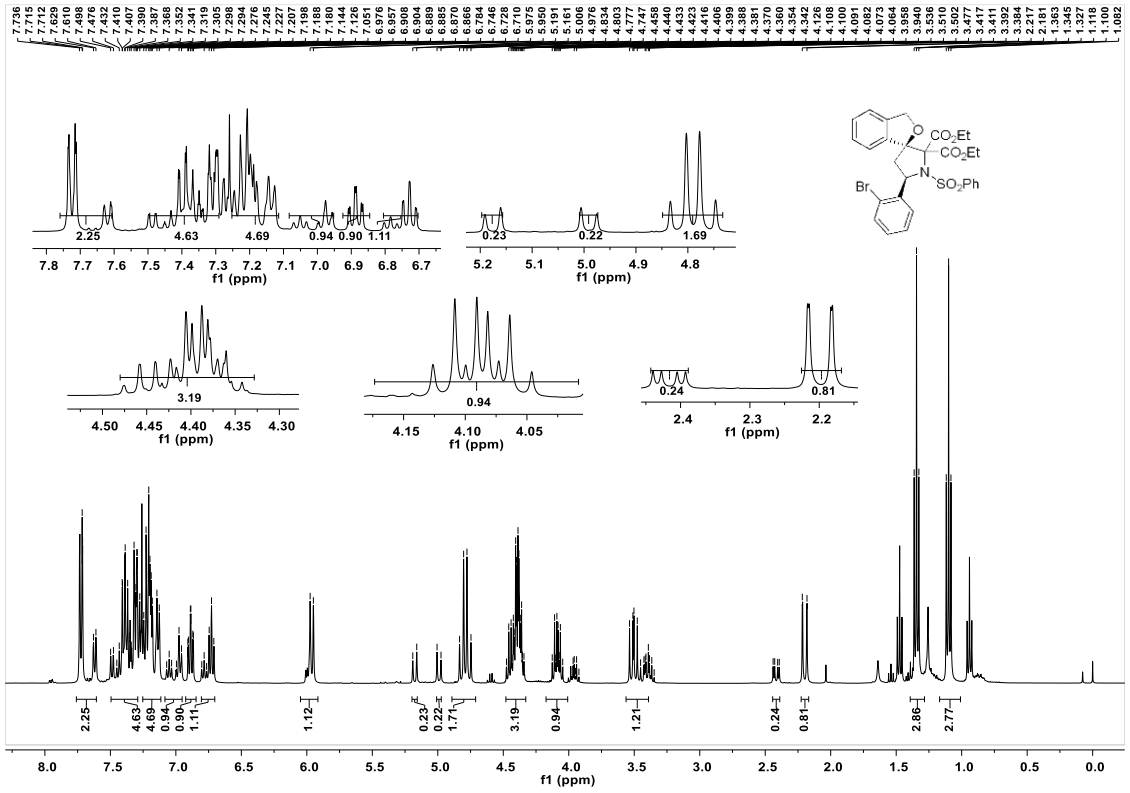


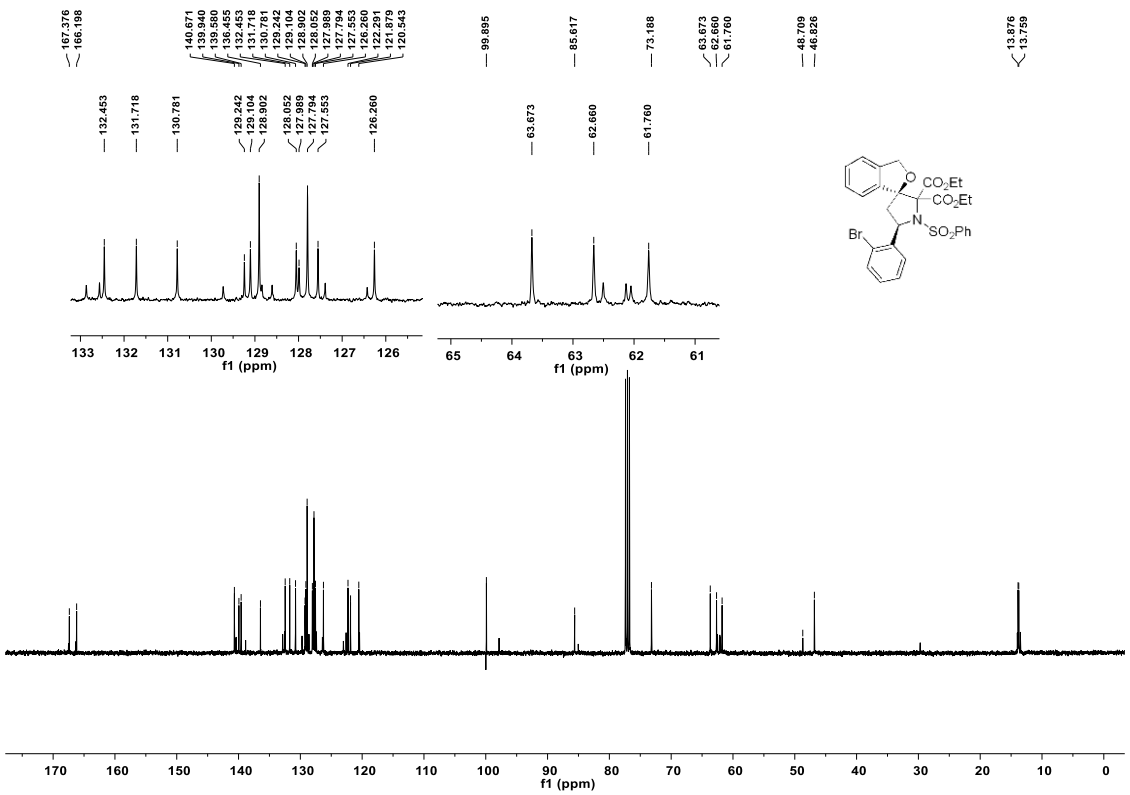
Diethyl (1*S*,5'*R*)-5'-(2-chlorophenyl)-1'-(phenylsulfonyl)-3*H*-spiro[isobenzofuran-1,3'-pyrrolidine]-2',2'-dicarboxylate (3m)



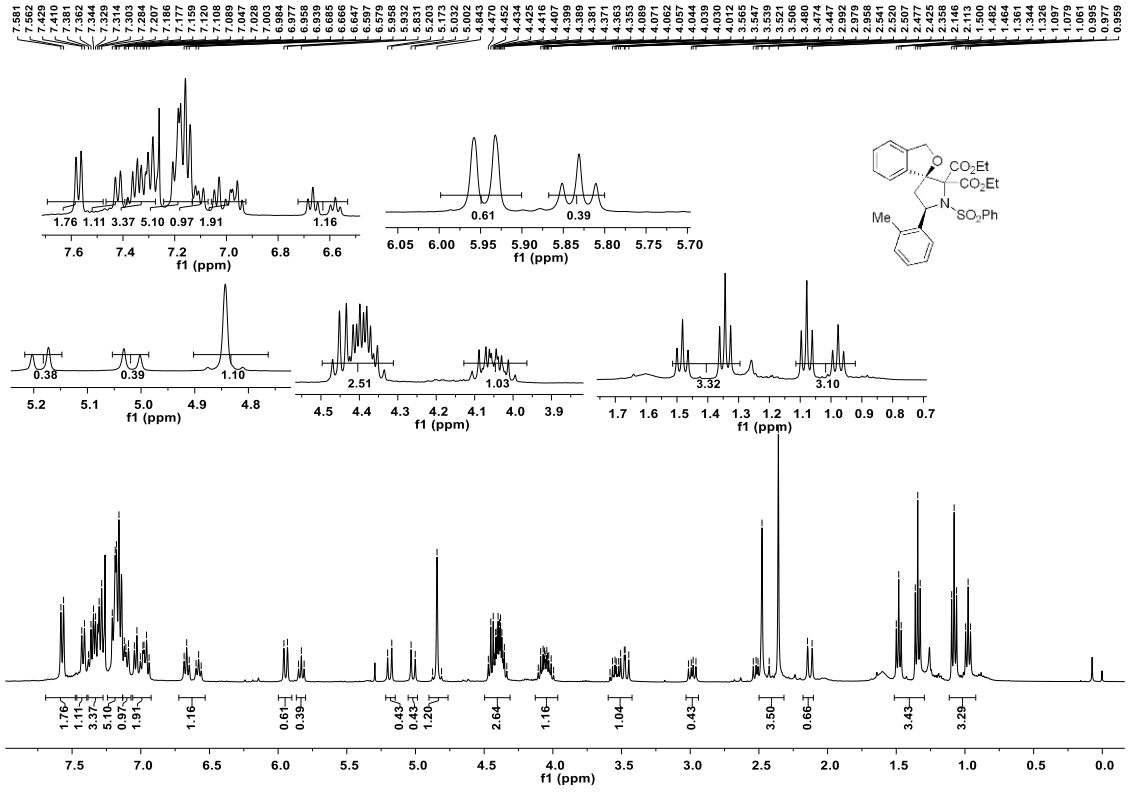


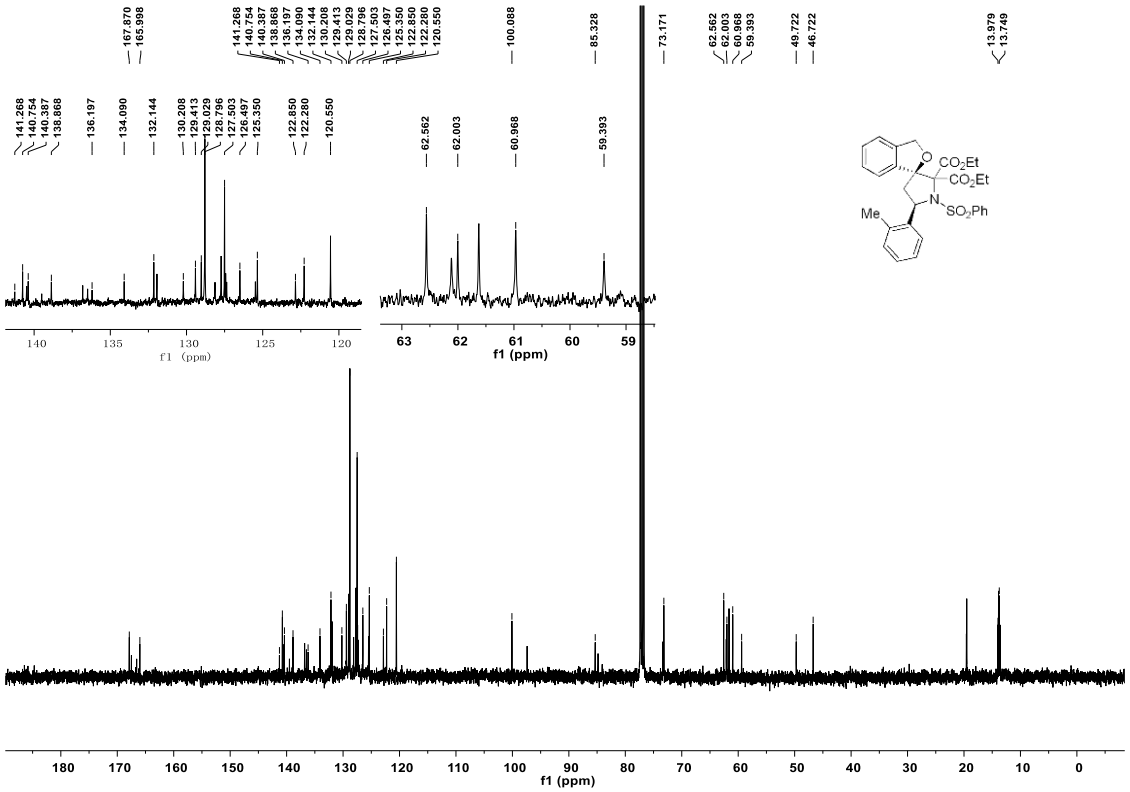
Diethyl (1*S*,5'*R*)-5'-(2-bromophenyl)-1'-(phenylsulfonyl)-3*H*-spiro[isobenzofuran-1,3'-pyrrolidine]-2',2'-dicarboxylate (3n)



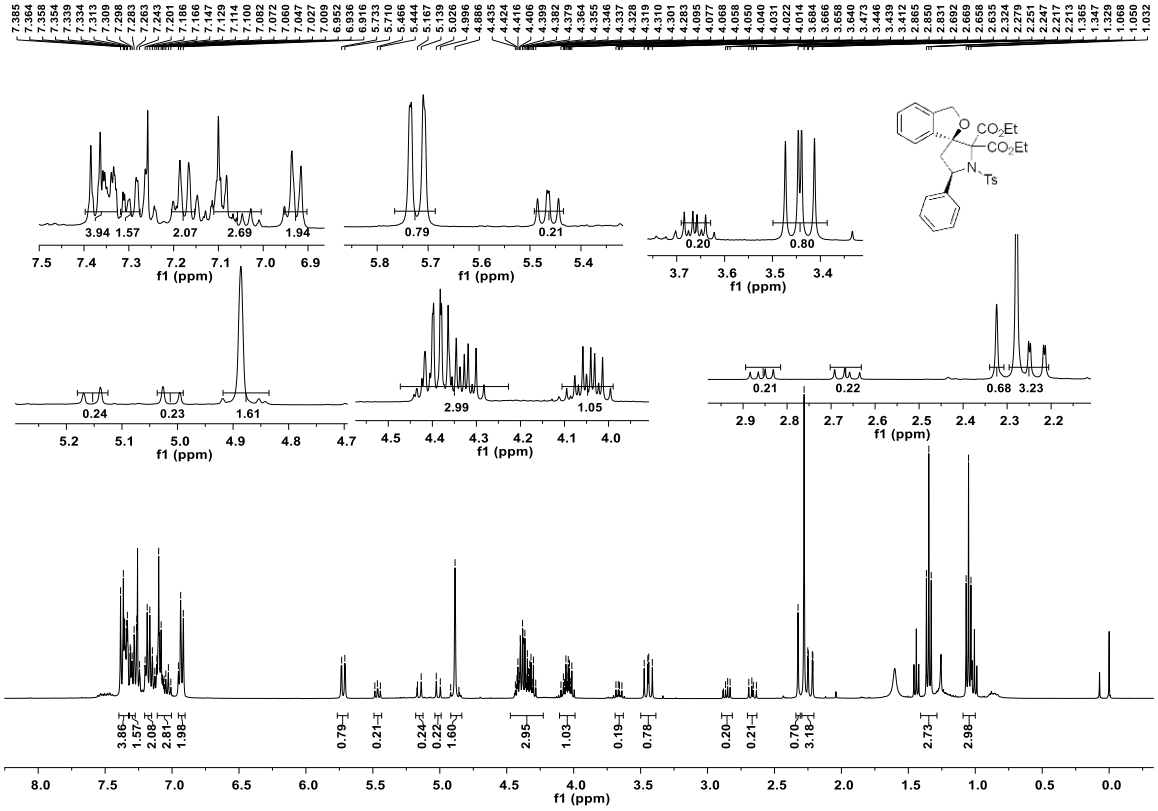


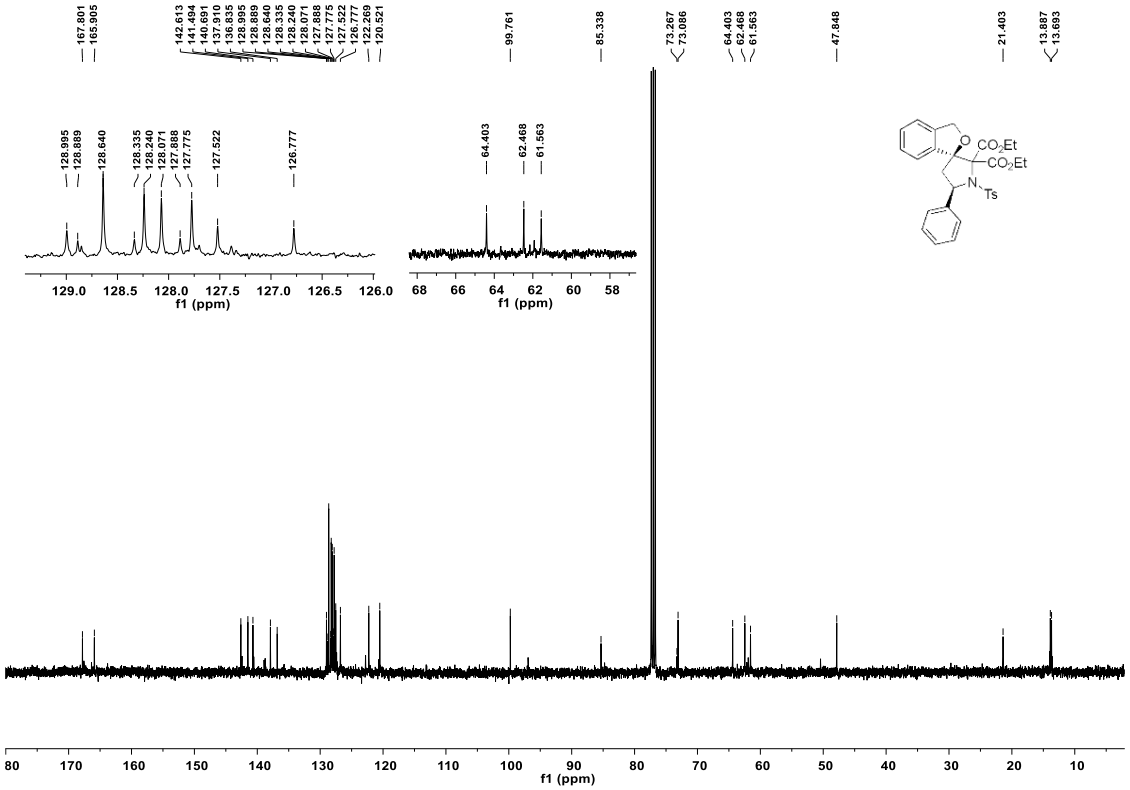
Diethyl (1*S*,5'*R*)-1'-(phenylsulfonyl)-5'-(o-tolyl)-3*H*-spiro[isobenzofuran-1,3'-pyrrolidine]-2',2'-dicarboxylate (3o)



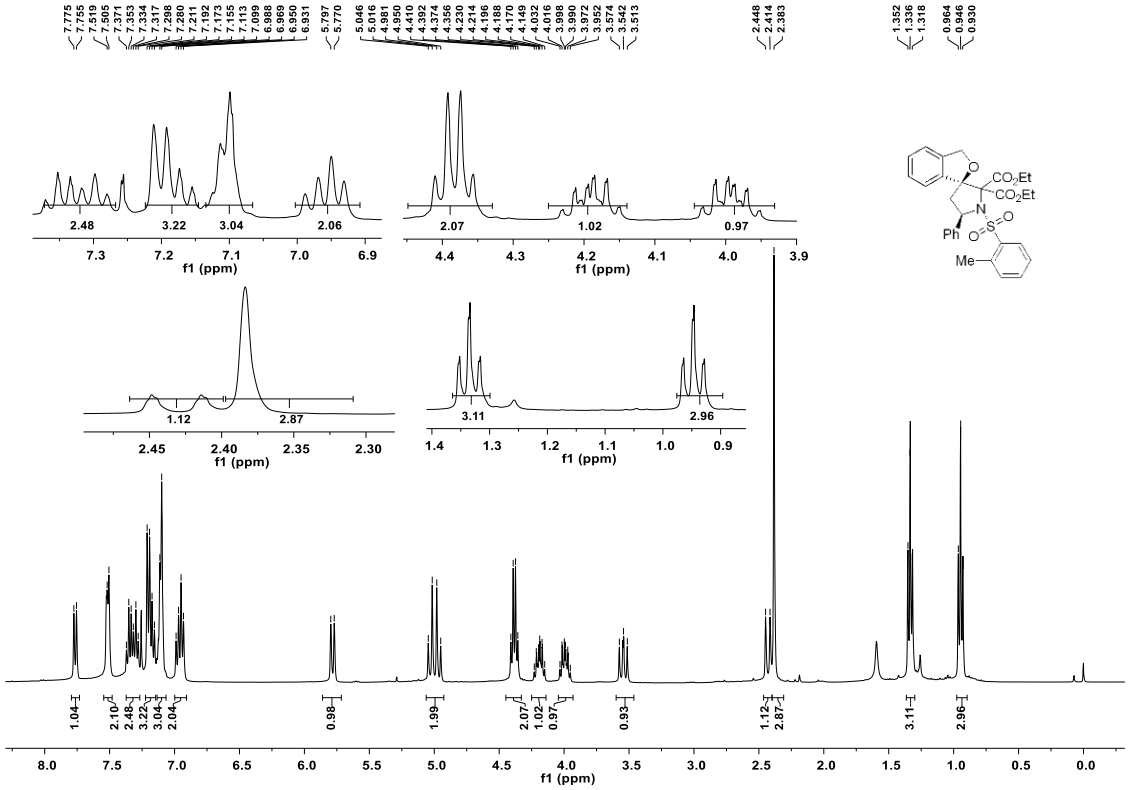


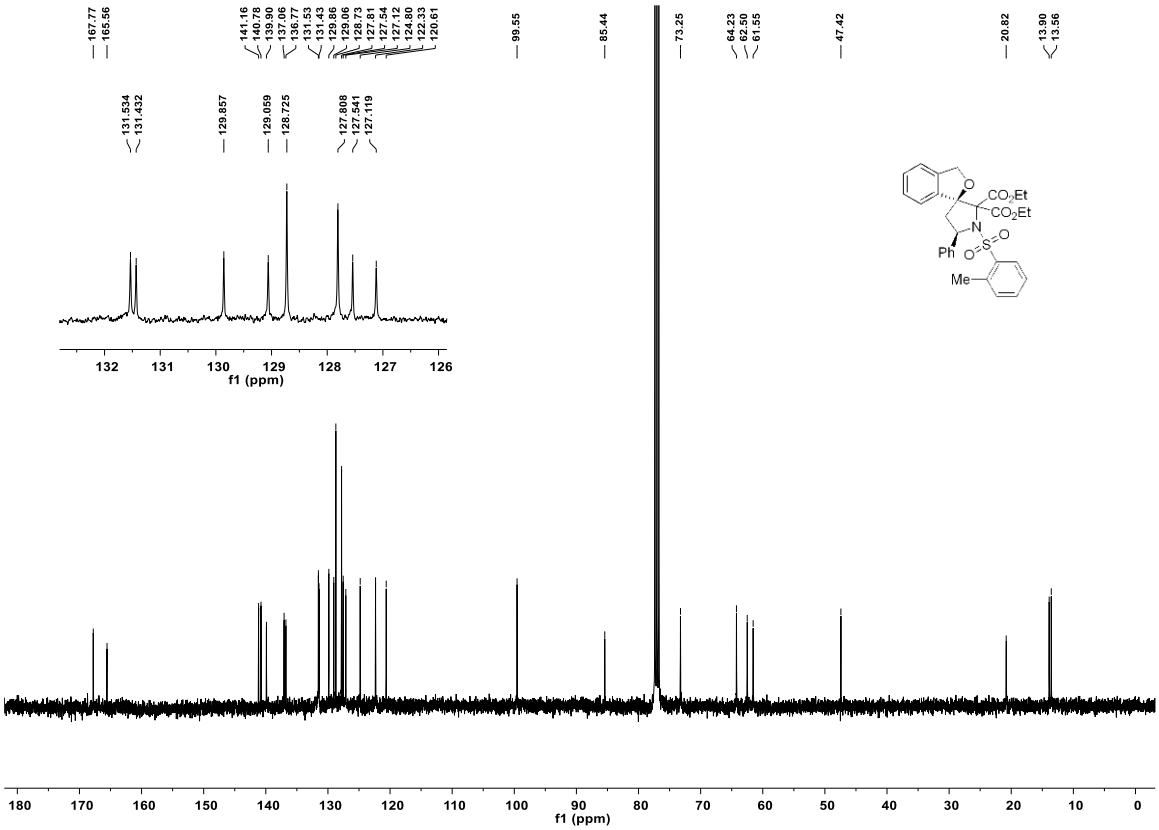
Diethyl (1*S*,5'*R*)-5'-phenyl-1'-(o-tolylsulfonyl)-3*H*-spiro[isobenzofuran-1,3'-pyrrolidine]-2',2'-dicarboxylate (3p)



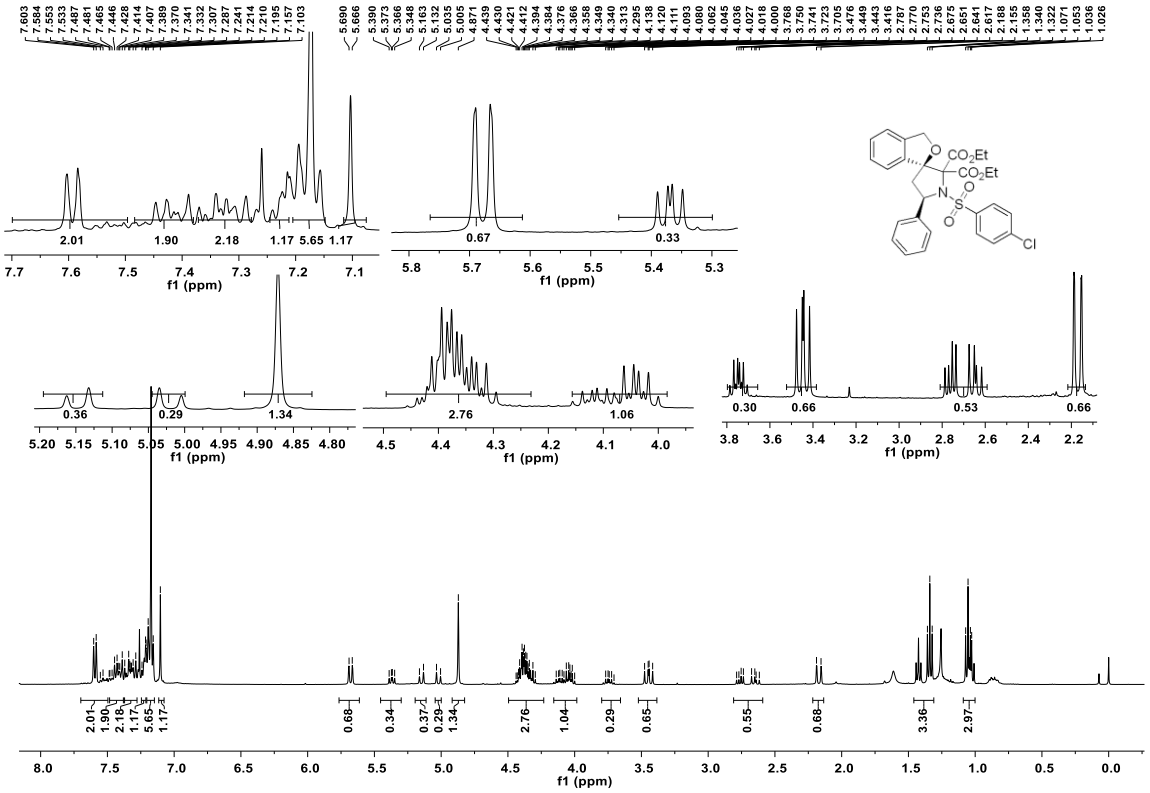


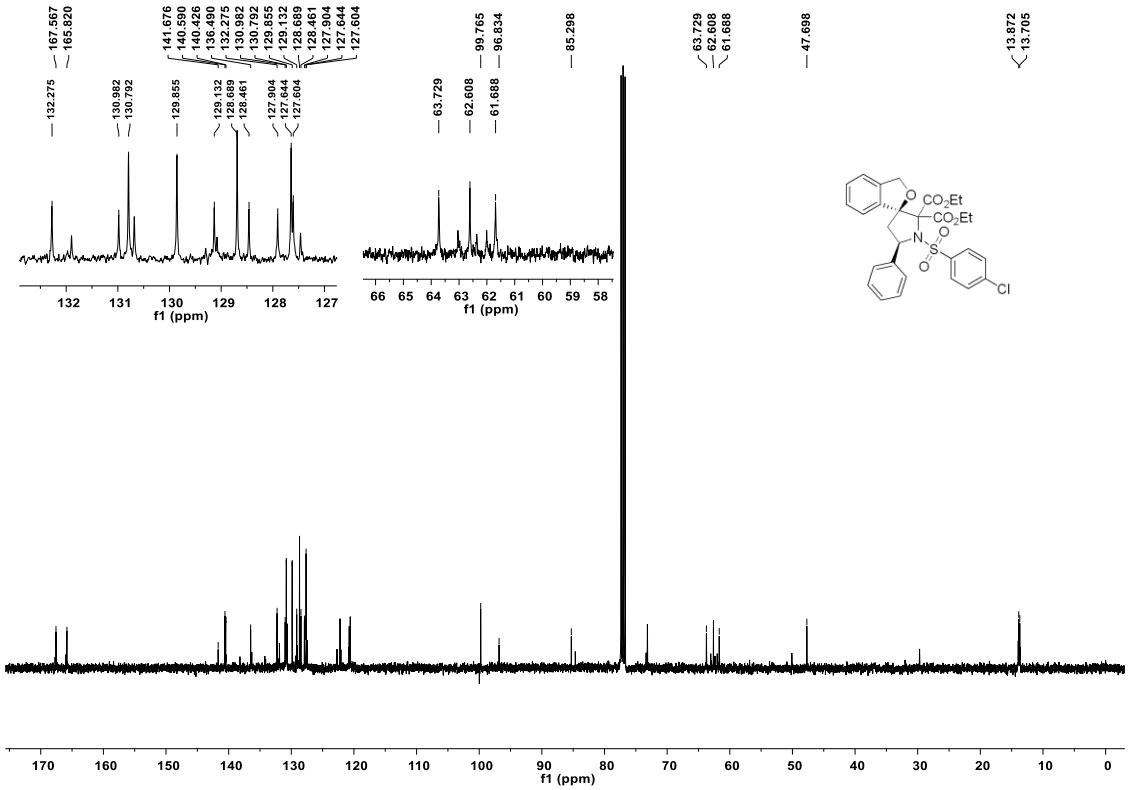
Diethyl (1*S*,5'*R*)-5'-phenyl-1'-(o-tolylsulfonyl)-3*H*-spiro[isobenzofuran-1,3'-pyrrolidine]-2',2'-dicarboxylate (3q)



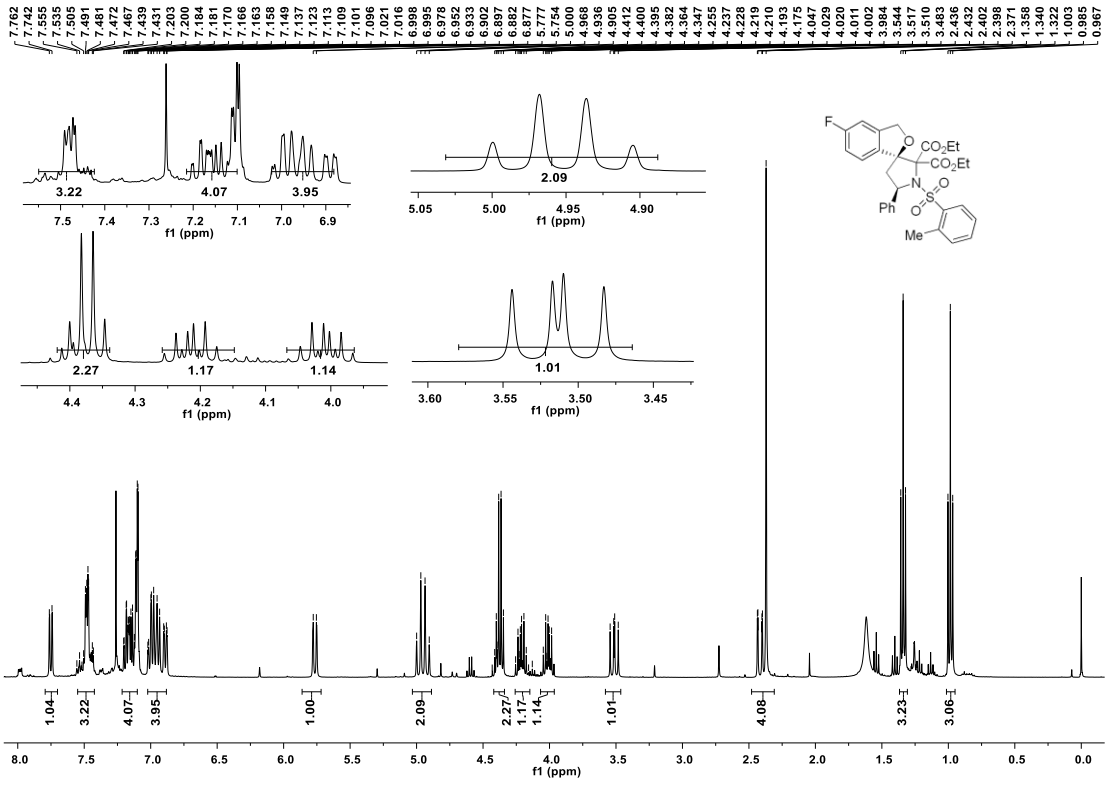


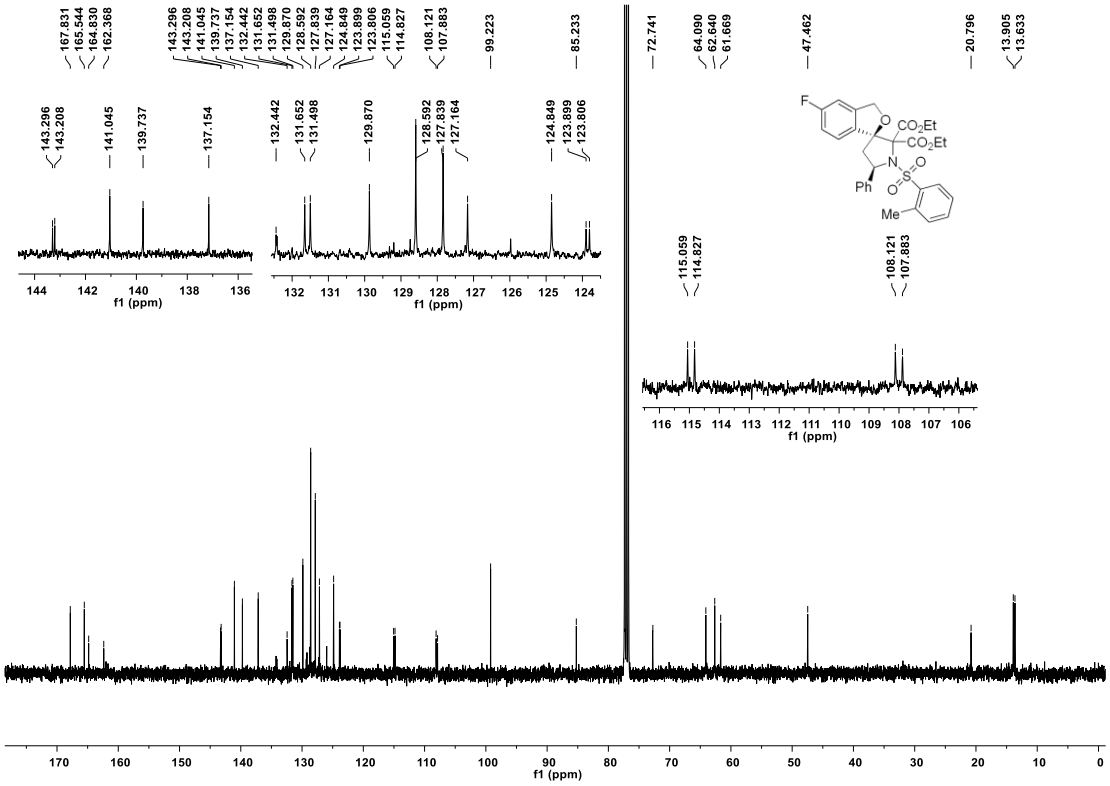
Diethyl (1*S*,5'*R*)-1'-((4-chlorophenyl)sulfonyl)-5'-phenyl-3*H*-spiro[isobenzofuran-1,3'-pyrrolidine]-2',2'-dicarboxylate(3r)





Diethyl (1*S*,5'*R*)-5-fluoro-5'-phenyl-1'-(o-tolylsulfonyl)-3*H*-spiro[isobenzofuran-1,3'-pyrrolidine]-2',2'-dicarboxylate (3s)

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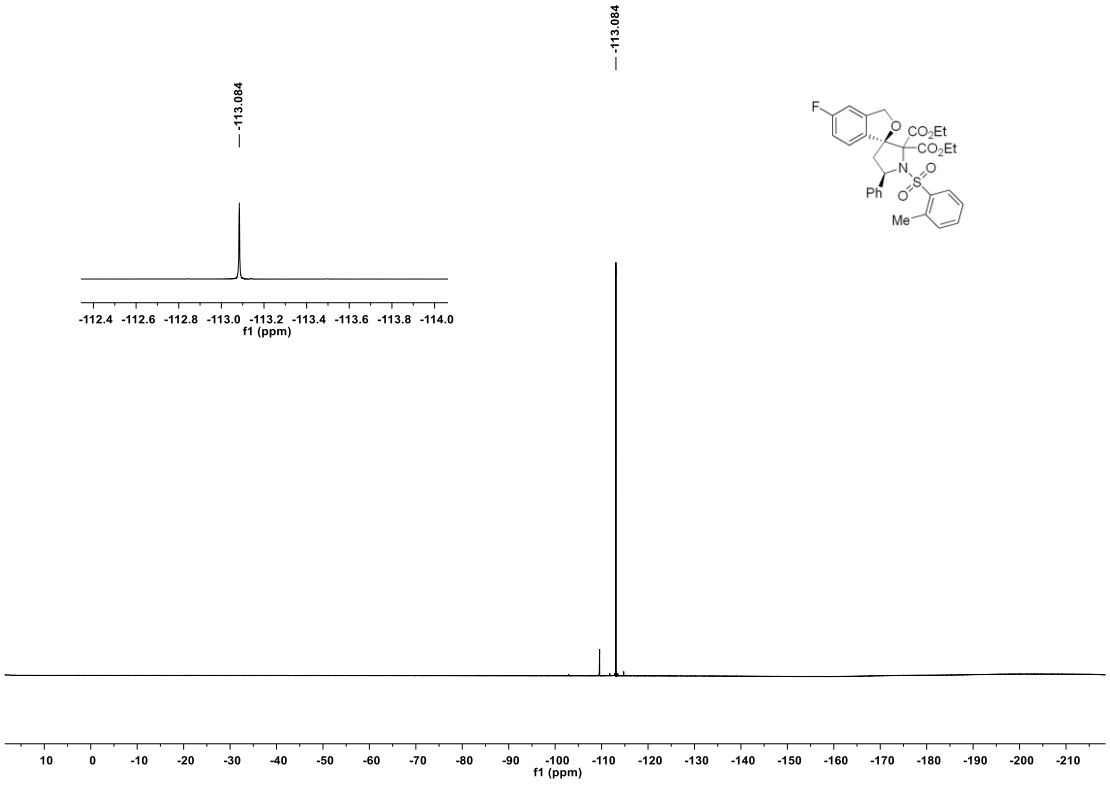
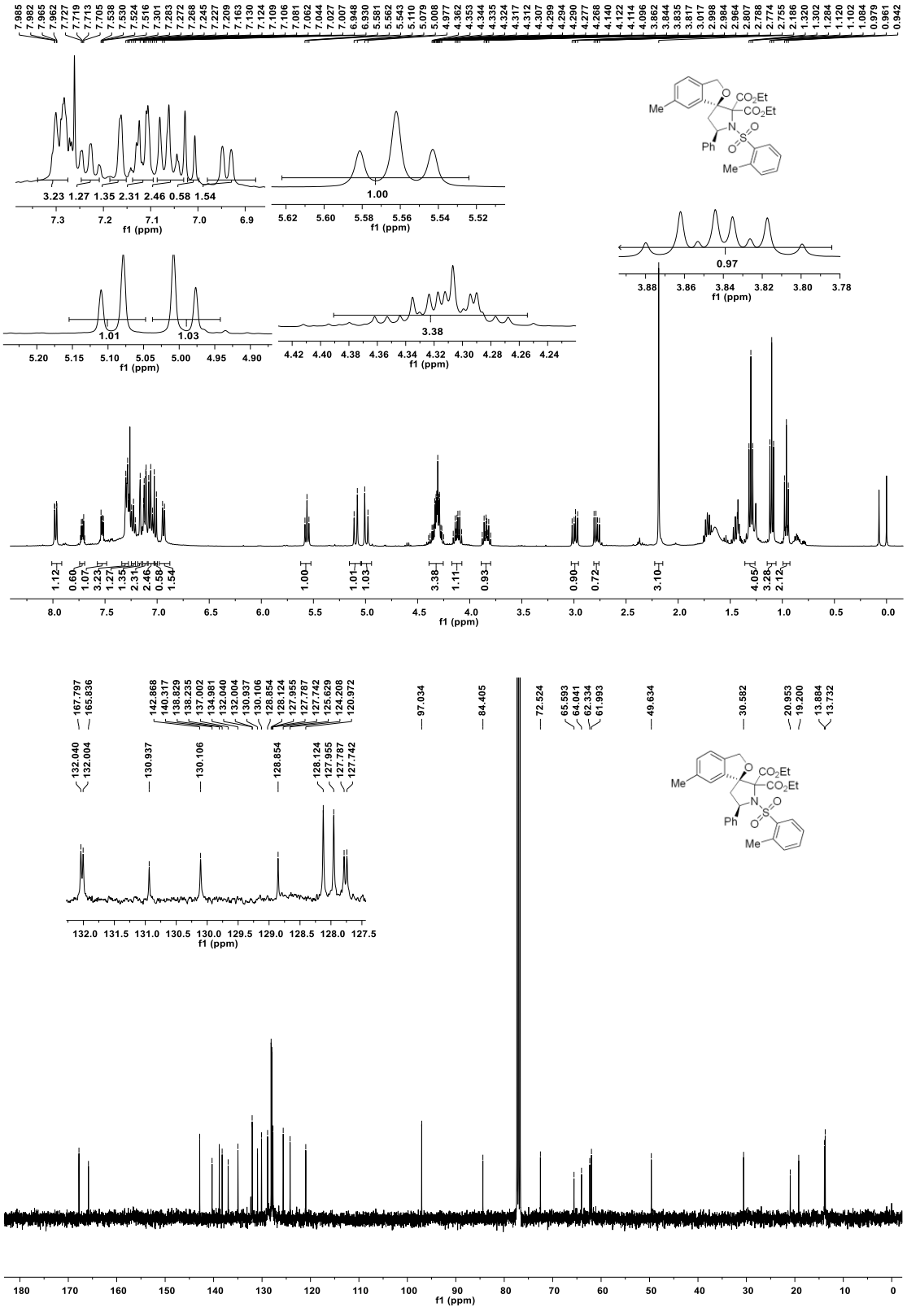
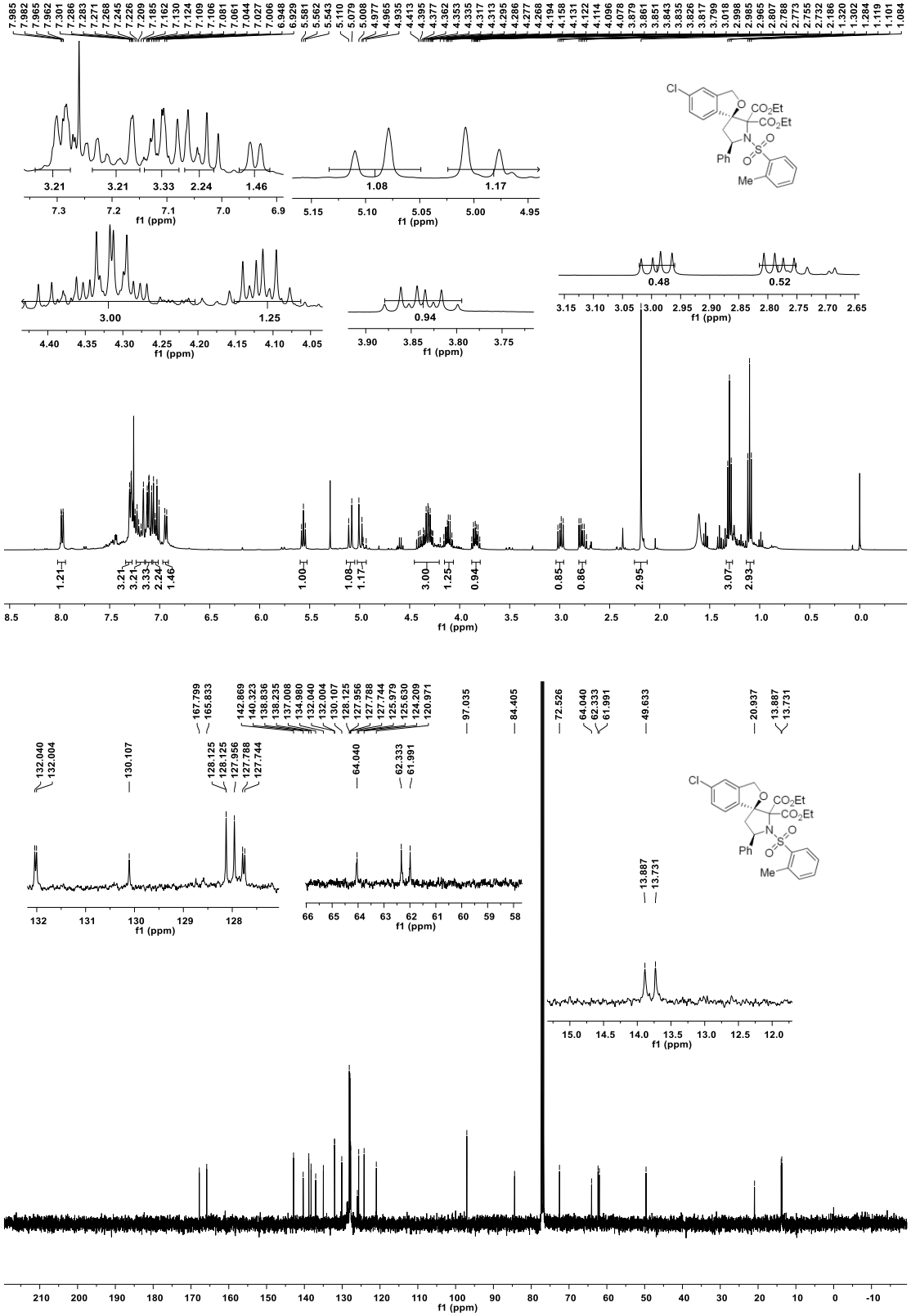
164.830
162.368
143.296
143.208
141.045
139.737
137.154
132.442
131.652
131.498
129.870
128.592
127.839
127.164
124.849
123.899
123.806
115.059
114.827
108.121
107.883
99.223
85.233
72.741
64.090
62.640
61.669
47.462
20.796
13.905
13.633
CO2Et
CO2Et
Ph
Me
f1 (ppm)


-113.084
CO2Et
CO2Et
Ph
Me
f1 (ppm)

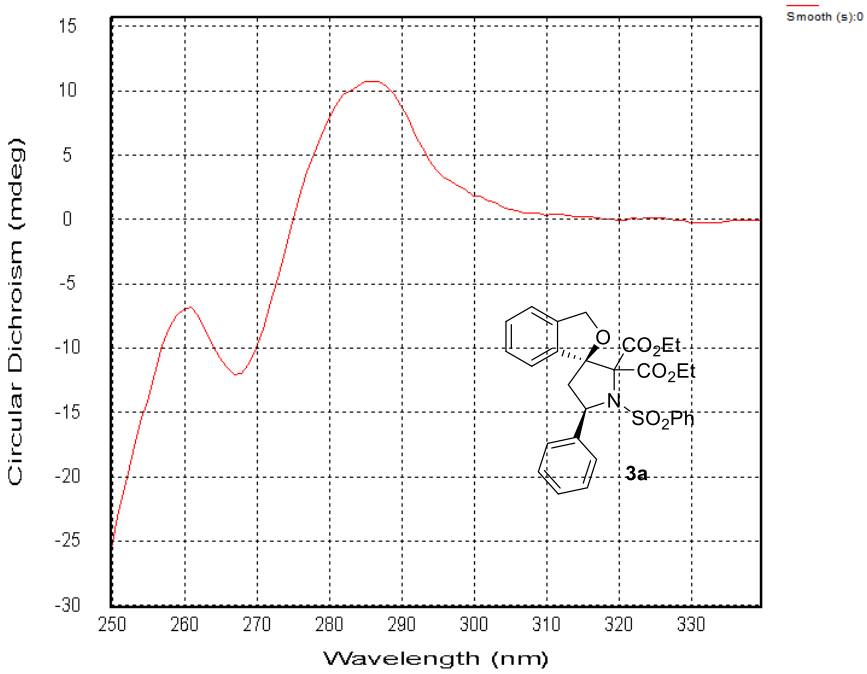
Diethyl (1*S*,5'*R*)-6-methyl-5'-phenyl-1'-(o-tolylsulfonyl)-3H-spiro[isobenzofuran-1,3'-pyrrolidine]-2',2'-dicarboxylate (3t)

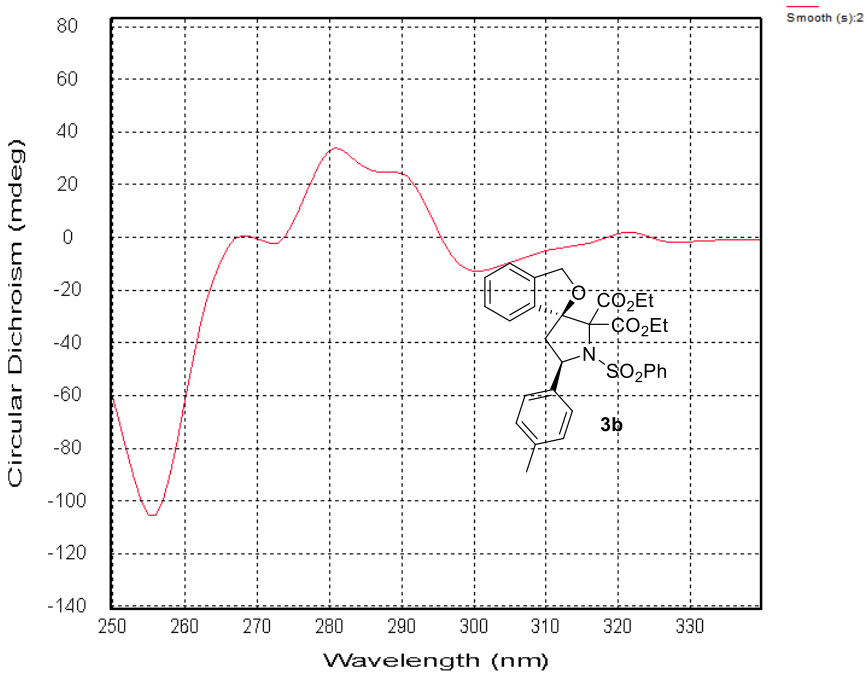


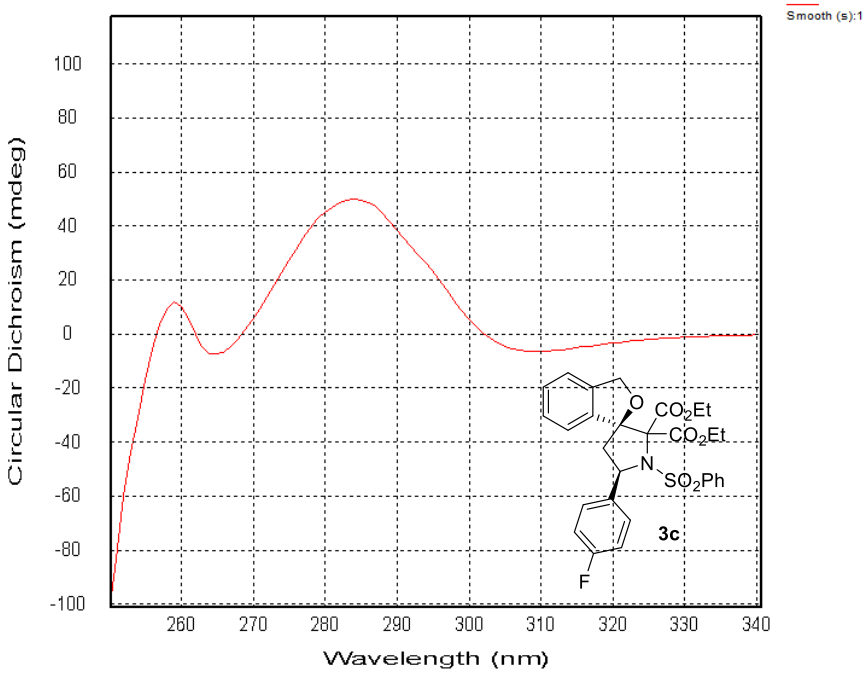
Diethyl (1*S*,5'*R*)-5-chloro-5'-phenyl-1'-(o-tolylsulfonyl)-3*H*-spiro[isobenzofuran-1,3'-pyrrolidine]-2',2'-dicarboxylate (3u)



(L) Copies of CD spectra



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Circular Dichroism (mdeg)
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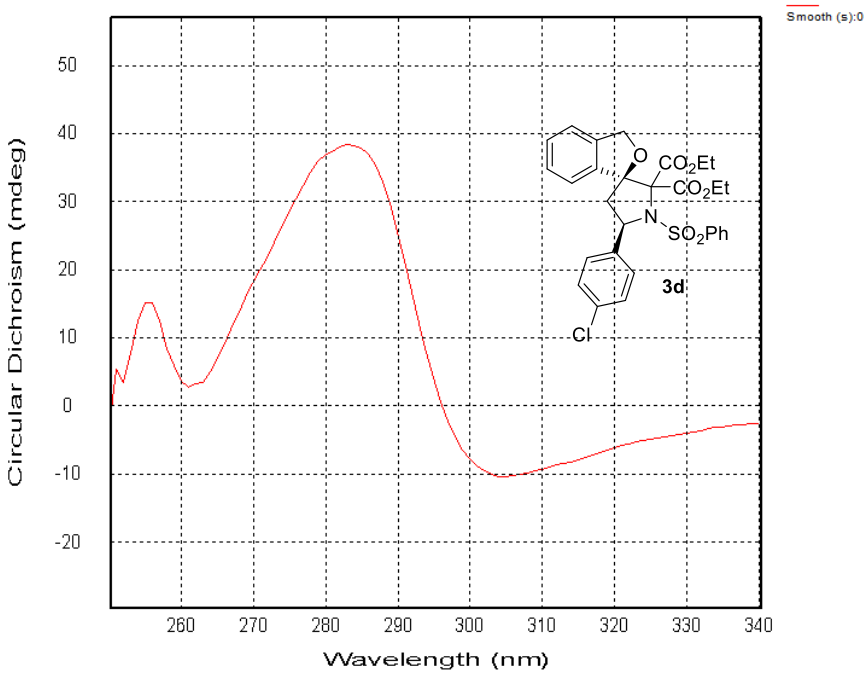
80
60
40
20
0
-20
-40
-60
-80
-100
260
270
280
290
300
310
320
330
340
Wavelength (nm)
O
CO2Et
CO2Et
N
SO2Ph
3c
F


Smooth (s):0
Circular Dichroism (mdeg)
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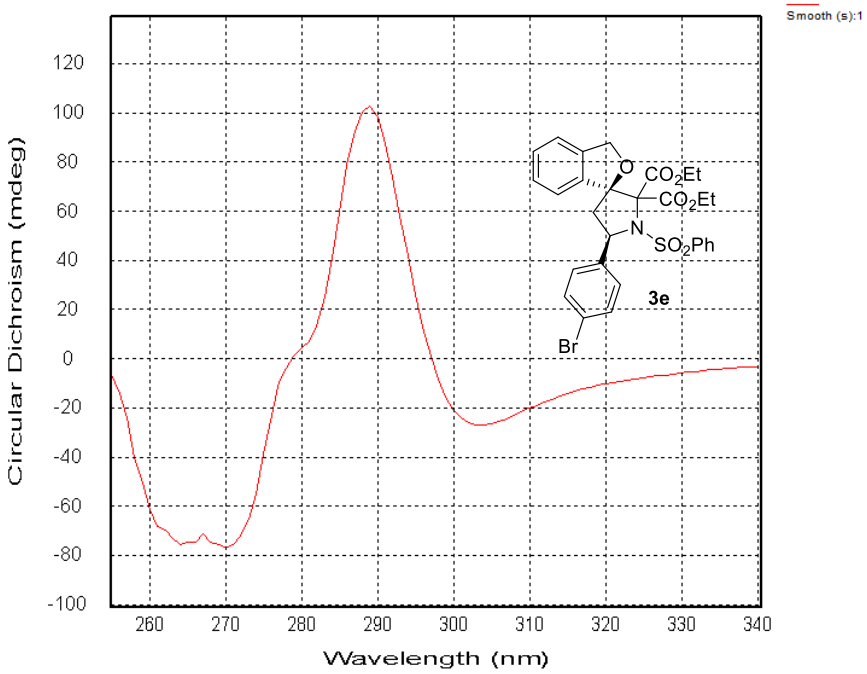
40
30
20
10
0
-10
-20
260
270
280
290
300
310
320
330
340
Wavelength (nm)
O
CO2Et
CO2Et
N
SO2Ph
3d
Cl


Smooth (s):1
Circular Dichroism (mdeg)
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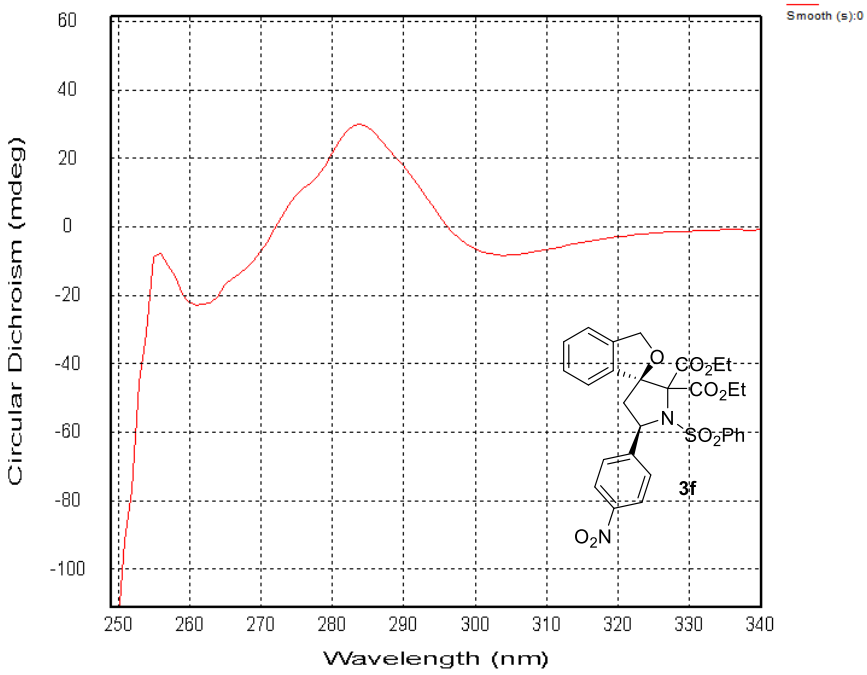
100
80
60
40
20
0
-20
-40
-60
-80
-100
260
270
280
290
300
310
320
330
340
Wavelength (nm)
O
CO2Et
CO2Et
N
SO2Ph
3e
Br


Smooth (s):0
Circular Dichroism (mdeg)
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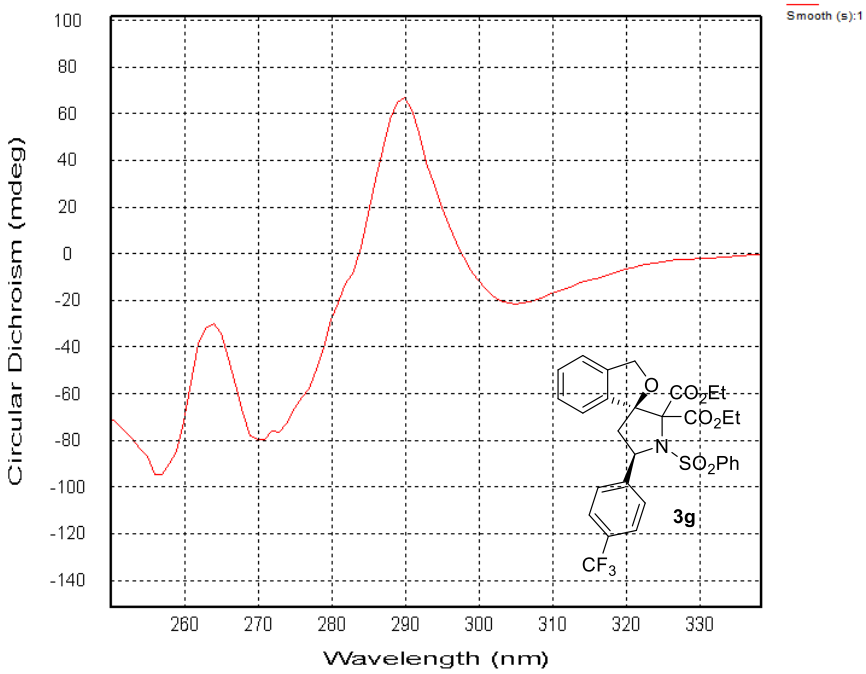
40
20
0
-20
-40
-60
-80
-100
250
260
270
280
290
300
310
320
330
340
Wavelength (nm)
O
CO2Et
CO2Et
N
SO2Ph
3f
O2N


Smooth (s):1
Circular Dichroism (mdeg)
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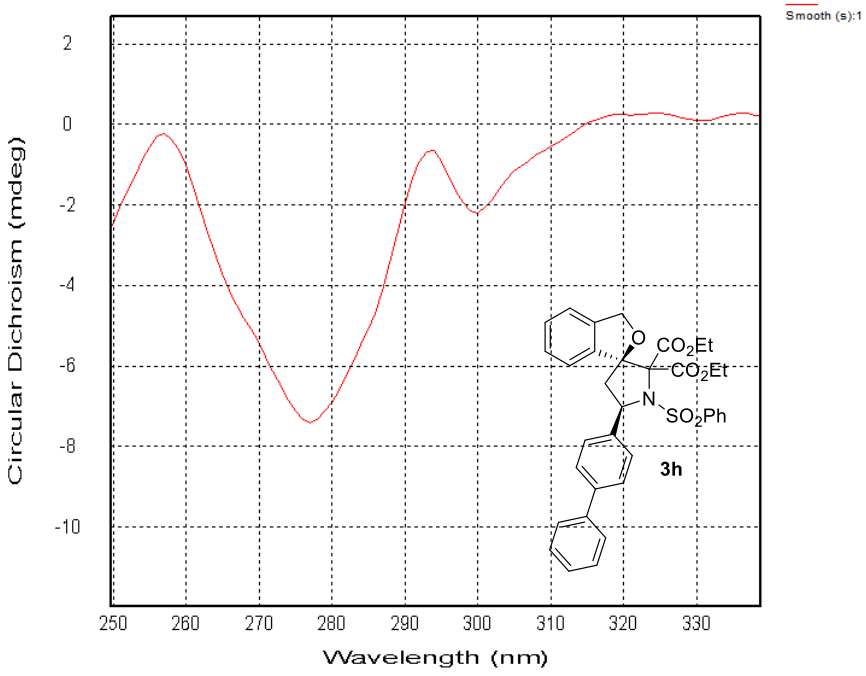
80
60
40
20
0
-20
-40
-60
-80
-100
-120
-140
260
270
280
290
300
310
320
330
Wavelength (nm)
O
CO2Et
CO2Et
N
SO2Ph
3g
CF3


Smooth (s):1
Circular Dichroism (mdeg)
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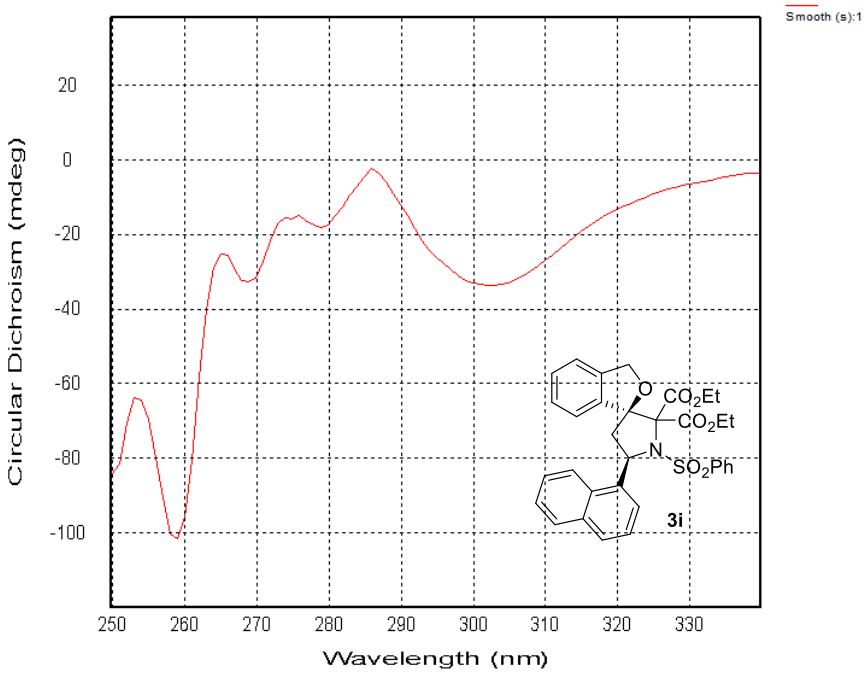
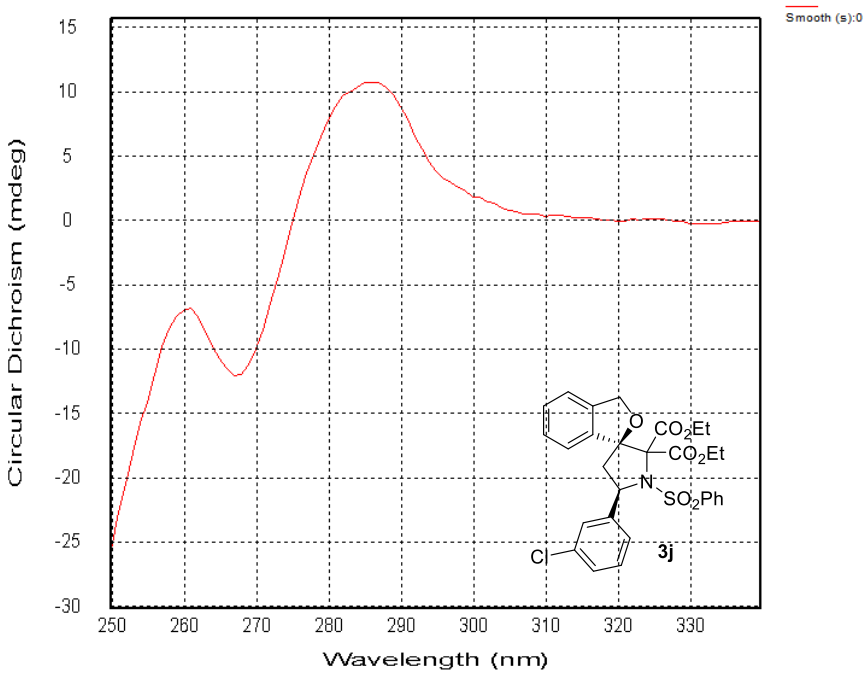
-2
-4
-6
-8
-10
250
260
270
280
290
300
310
320
330
Wavelength (nm)
O
CO2Et
CO2Et
N
SO2Ph
3h


Smooth (s):1
Circular Dichroism (mdeg)
20
0
-20
-40
-60
-80
-100
250
260
270
280
290
300
310
320
330
Wavelength (nm)
O
CO2Et
CO2Et
N
SO2Ph
3i


Smooth (s):0
Circular Dichroism (mdeg)
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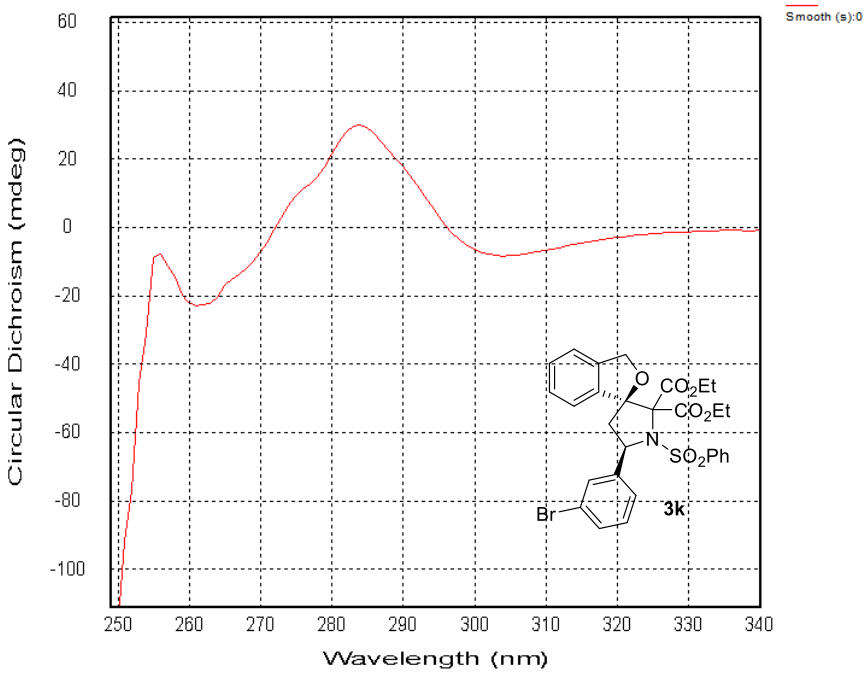
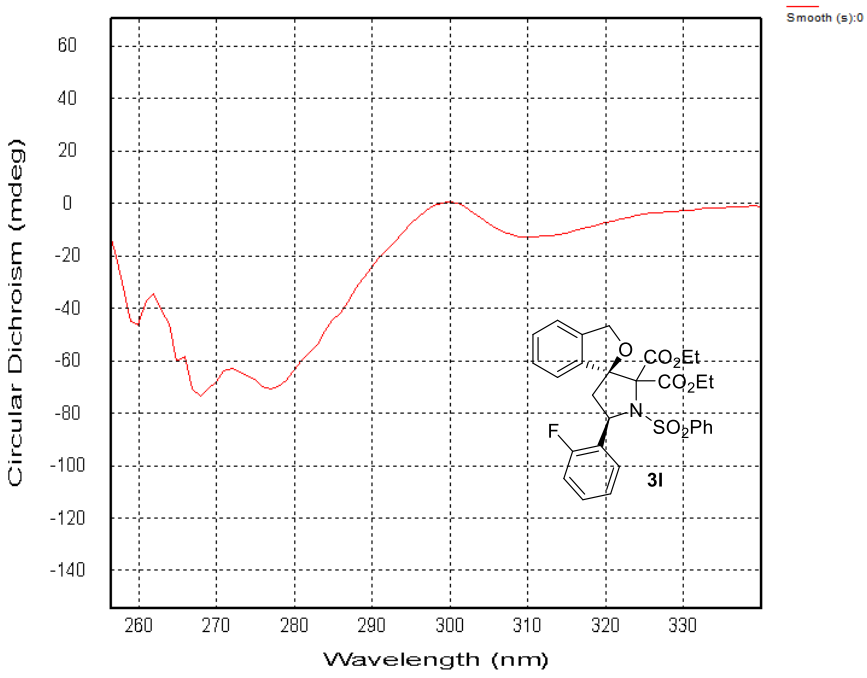
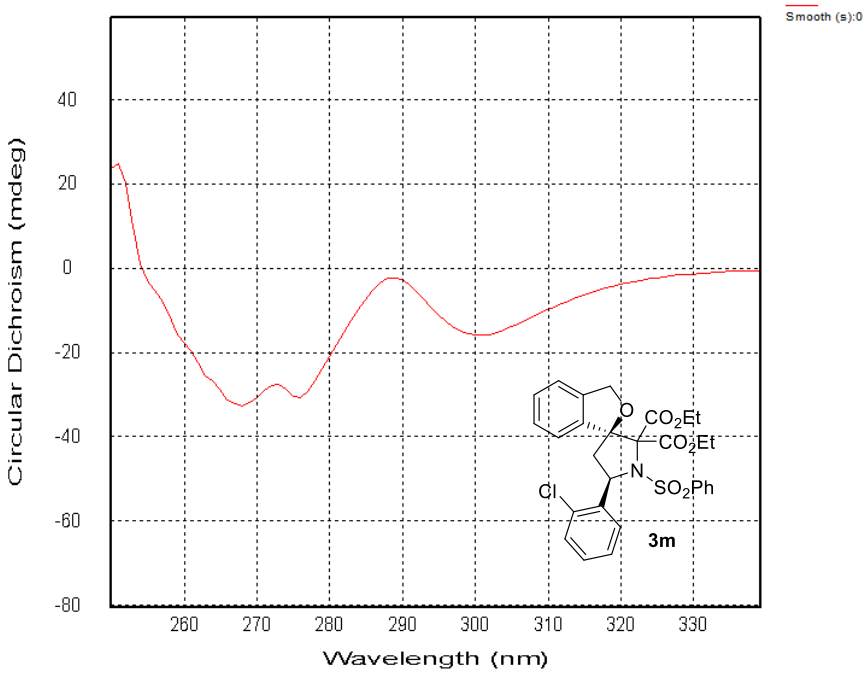
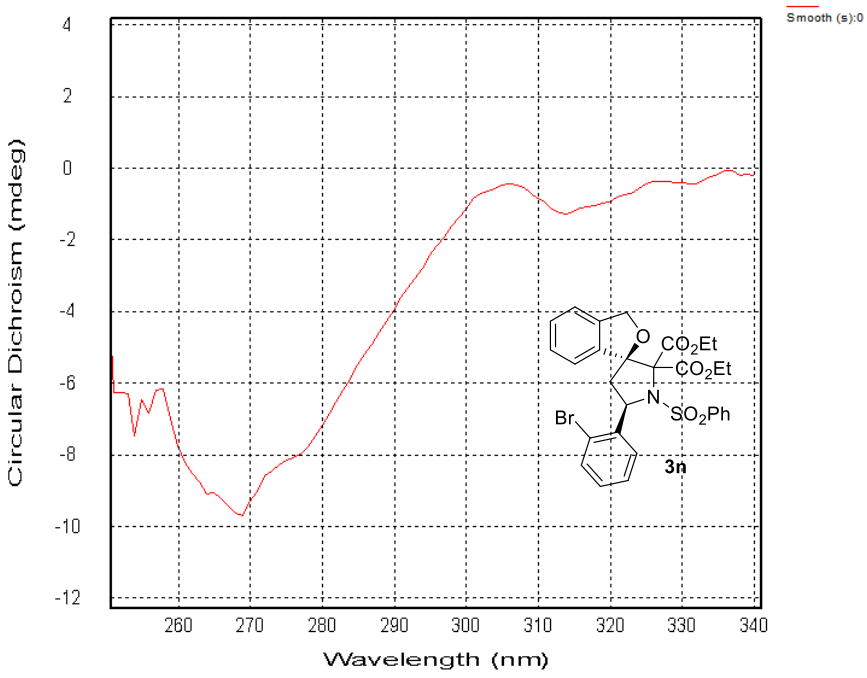
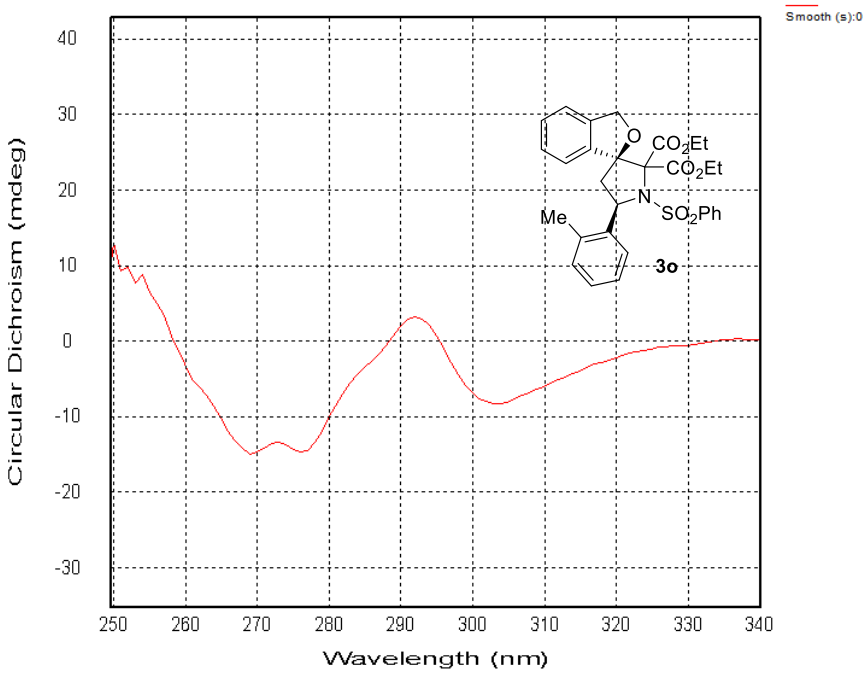
10
5
0
-5
-10
-15
-20
-25
-30
250
260
270
280
290
300
310
320
330
Wavelength (nm)
O
CO2Et
CO2Et
N
SO2Ph
Cl
3j

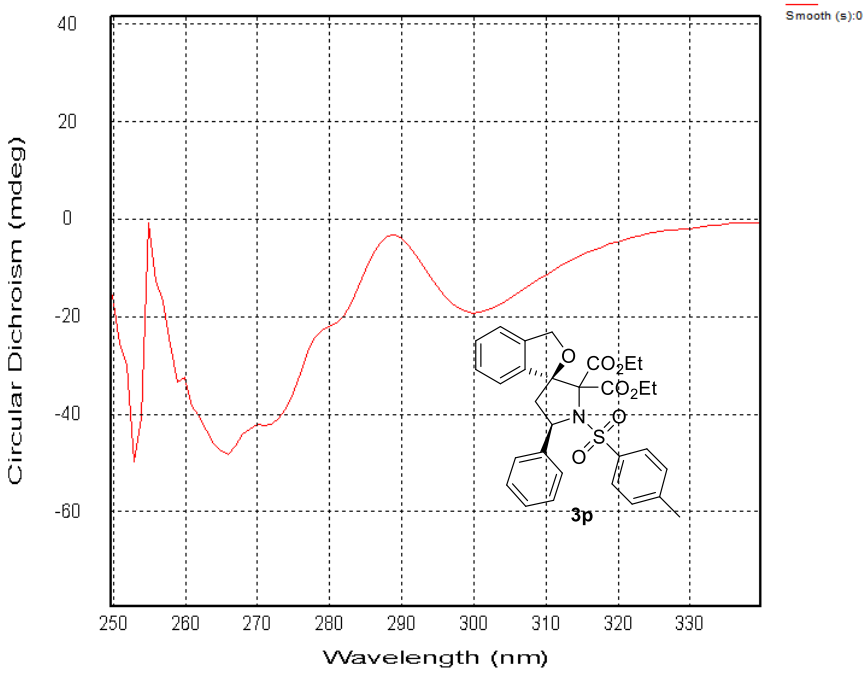

Smooth (s):0
Circular Dichroism (mdeg)
60
40
20
0
-20
-40
-60
-80
-100
250
260
270
280
290
300
310
320
330
340
Wavelength (nm)
O
CO2Et
CO2Et
N
SO2Ph
Br
3k


Smooth (s):0
Circular Dichroism (mdeg)
60
40
20
0
-20
-40
-60
-80
-100
-120
-140
260
270
280
290
300
310
320
330
Wavelength (nm)
O
CO2Et
CO2Et
N
SO2Ph
F
3l


Smooth (s):0
Circular Dichroism (mdeg)
40
20
0
-20
-40
-60
-80
260
270
280
290
300
310
320
330
Wavelength (nm)
O
CO2Et
CO2Et
N
SO2Ph
Cl
3m


Smooth (s):0
Circular Dichroism (mdeg)
4
2
0
-2
-4
-6
-8
-10
-12
260
270
280
290
300
310
320
330
340
Wavelength (nm)
O
CO2Et
CO2Et
N
SO2Ph
Br
3n


Smooth (s):0
Circular Dichroism (mdeg)
40
30
20
10
0
-10
-20
-30
250
260
270
280
290
300
310
320
330
340
Wavelength (nm)
O
CO2Et
CO2Et
N
SO2Ph
Me
3o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Circular Dichroism (mdeg)
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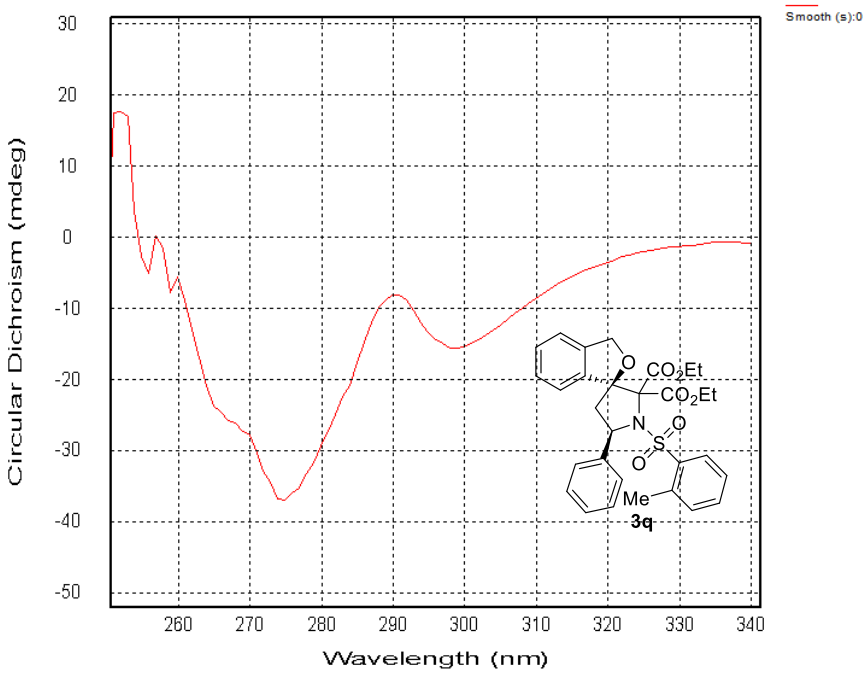
20
0
-20
-40
-60
250
260
270
280
290
300
310
320
330
Wavelength (nm)
O
CO2Et
CO2Et
N
O
S
O
3p


Smooth (s):0
Circular Dichroism (mdeg)
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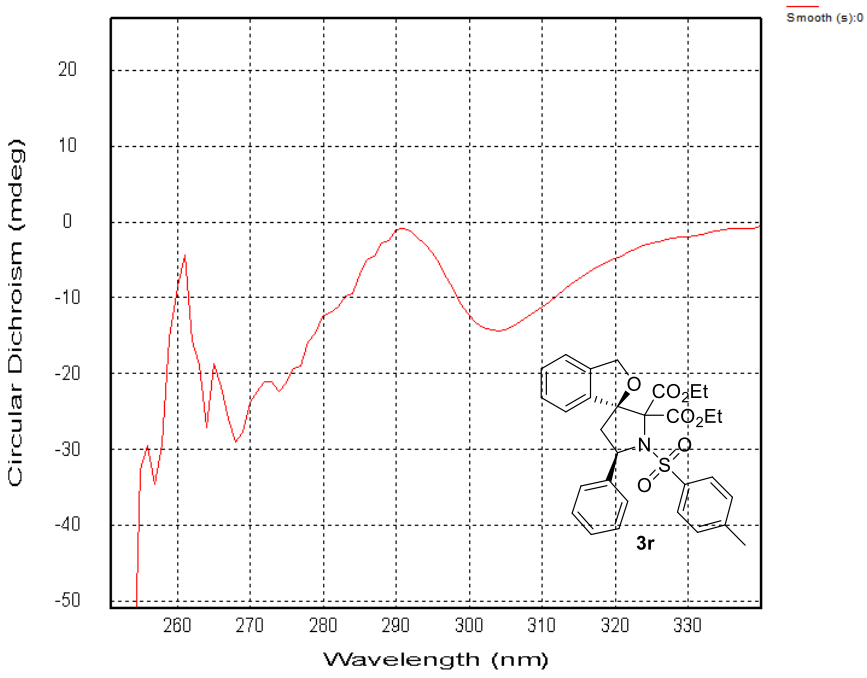
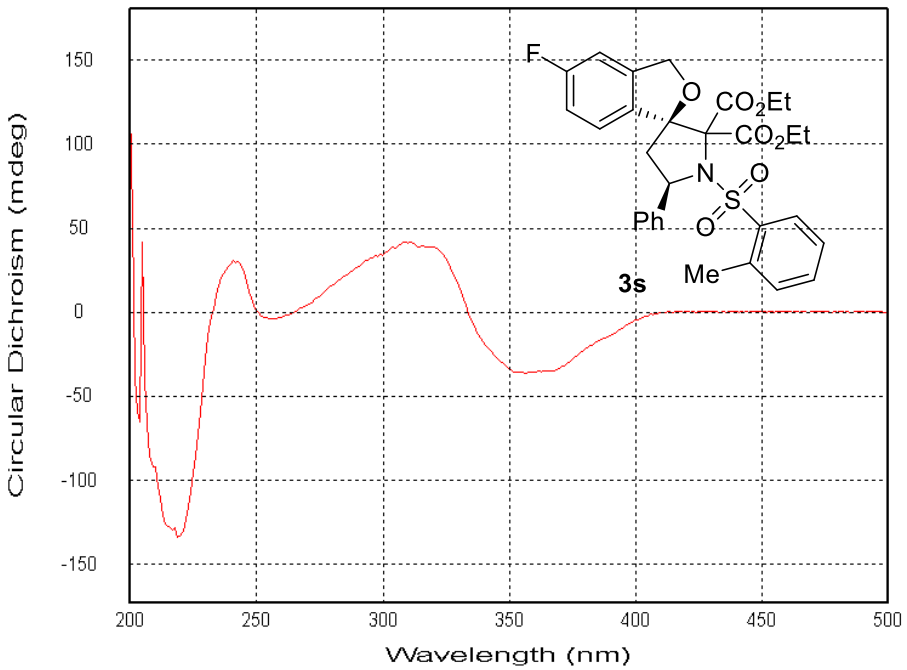
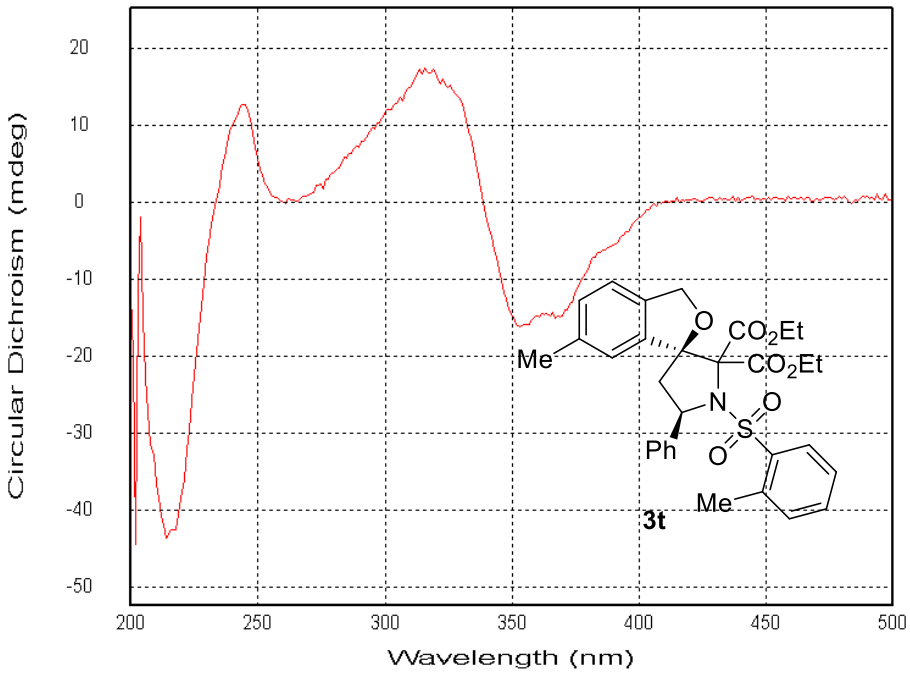
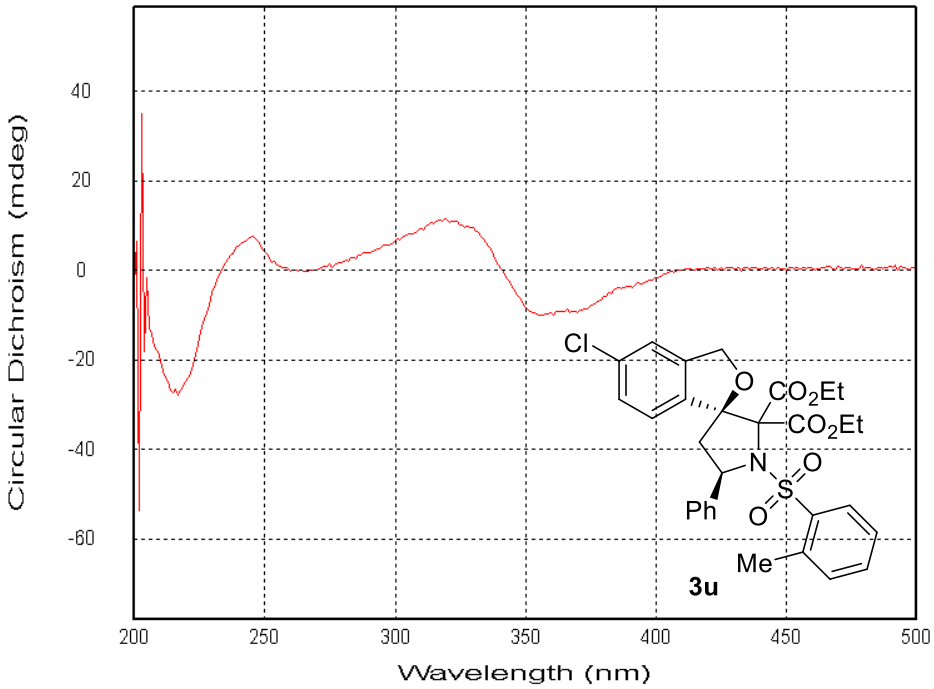
20
10
0
-10
-20
-30
-40
-50
260
270
280
290
300
310
320
330
340
Wavelength (nm)
O
CO2Et
CO2Et
N
S
O
O
Me
3q


Smooth (s):0
Circular Dichroism (mdeg)
20
10
0
-10
-20
-30
-40
-50
260
270
280
290
300
310
320
330
Wavelength (nm)
O
CO2Et
CO2Et
N
S
O
O
3r


Circular Dichroism (mdeg)
150
100
50
0
-50
-100
-150
200
250
300
350
400
450
500
Wavelength (nm)
F
O
CO2Et
CO2Et
N
S
O
O
Ph
Me
3s


Circular Dichroism (mdeg)
20
10
0
-10
-20
-30
-40
-50
200
250
300
350
400
450
500
Wavelength (nm)
Me
O
CO2Et
CO2Et
N
S
O
O
Ph
Me
3t



(M) Supplementary reference

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